[DESCRIPTION]

[Title of Invention] CYCLIC COMPOUND HAVING SELECTIVE KRAS INHIBITORY EFFECT ON HRAS AND NRAS

[Technical Field]

[0001]

The present invention in one aspect relates to cyclic compounds.

[Background Art]

[0002]

RAS is a protein belonging to the small GTPase family, and KRAS, NRAS, and HRAS are known. RAS is in an active state or an inactive state according to whether it is bound to GTP or GDP. It is activated by the exchange reaction from GDP to GTP by GEFs (guanine nucleotide exchange factors) and inactivated by the hydrolysis reaction of GTP by GAPs (GTPase-activating proteins) (NPL 1). Activated RAS induces cell proliferation, survival, and differentiation by activating various downstream signals in the MAPK pathway, PI3K/Akt pathway, RAL pathway, and such, and the constitutive activation of RAS plays an important role in the development and progression of cancer. In cancer, it is known that the RAS-RAF-MEK-ERK pathway is activated by the activation of an upstream signal of RAS, constitutive activation of RAS, and/or activating mutations of RAS (NPL 2). These activating mutations of RAS have been found in numerous cancer types. G12, G13, and Q61 are known as hot spots of RAS mutation, and G12 is frequently found mutated in KRAS and Q61 in NRAS. These mutations are also known to be associated with the prognosis of patients (NPL 3).

[0003]

Meanwhile, when it comes to access to a tough target, as typified by inhibition of a protein-protein interaction, medium sized molecules (having a molecular weight of 500 to 2000 g/mol) may be superior to low molecular weight compounds. Also, medium sized molecules may be superior to antibodies in that they can migrate into cells. Among biologically active medium sized molecules, peptide drugs are highly valuable molecular species, with more than 40 peptide drugs being already commercially available (NPL 4). Representative examples of such peptide drugs include cyclosporin A and polymyxin B, which are peptides containing some non-natural amino acids. A non-natural amino acid refers to an amino acid that is not naturally encoded on mRNA. It is highly interesting that non-natural amino acids are contained in naturally-occurring cyclosporin A and polymyxin B.

[0004]

Since the discovery of the pharmaceutical utility of naturally-occurring peptides, peptides having pharmacological activity and bioabsorbability have been attracting attention, and those having a molecular weight of about 500 to 2000 g/mol have been actively researched (NPL 5).

[0005]

There is a report on conditions for medium molecular weight peptides to have increased membrane permeability and metabolic stability, which may contribute to improving their biokinetics (conditions necessary for satisfying drug-likeness) (PTL 1).

[0006]

Moreover, as for the conditions that may contribute to improving the biokinetics of medium molecular weight peptides, conditions necessary for cyclic peptides to satisfy drug-likeness have been shown (PTL 2).

[0007]

Peptides that bind to RAS have been found, and the binding site between a cyclic peptide and RAS has been studied by X-ray structural analysis (NPL 6, NPL 7, and NPL 8). Also, cyclic peptides that apparently inhibit binding between RAS and SOS have been found (PTL 3). Moreover, a competition assay for binding with RAS has suggested that some cyclic peptides inhibit binding between a particular compound and RAS (PTL 4).

[Citation List]

[Patent Literature]

[0008]

[PTL 1] WO 2013/100132

[PTL 2] WO 2018/225864

[PTL 3] WO 2012/122059

[PTL 4] WO 2017/181061

[Non-Patent Literature]

[0009]

[NPL 1] Nat. Rev. Drug Discov. 2014 Nov;13(11):828-851.

[NPL 2] Nat. Rev. Drug Discov. 2014 Dec;13(12):928-942.

[NPL 3] Nat. Rev. Drug Discov. 2016 Nov;15(11):771-785.

[NPL 4] Future Med. Chem. 2009, 1, 1289-1310.

[NPL 5] Current Topics in Medicinal Chemistry, 2013, Vol. 13, No. 7, 821-836.

[NPL 6] Biochem. Biophys. Res. Commun. 2017, 484, 605-611.

[NPL 7] Bioorg. Med. Chem. Lett. 2017, 27, 2757-2761.

[NPL 8] ACS Med. Chem. Lett. 2017, 8, 732-736.

[Summary of Invention]

[Technical Problem]

[0010]

The present invention relates to cyclic compounds effective for RAS-mutant cancer and non-natural amino acids and peptide compounds useful for the production thereof.

PTL 1 and PTL 2 describe drug-like peptides, but do not describe a peptide having an antitumor effect on cancers including RAS-mutant cancer.

PTL 3 describes the inhibition of binding between RAS and SOS, and PTL 4 describes a peptide competing with a compound that binds to RAS. However, none of these documents shows any pharmacological action, especially action on tumor cells. These documents do not describe drug-like peptides, either.

[0011]

NPL 1 shows the relationship between RAS and cancer in detail. This document describes molecules that bind to RAS. Although their efficacy was shown in preclinical studies, no compound was shown to be effective as a drug specifically on RAS-mutant cancer. Also, no drug-like cyclic peptide is disclosed.

NPL 2 provides detailed descriptions about RAS and the RAF-MEK-ERK pathway, which is downstream of RAS. Although this document suggests the possibility of treating RAS-mutant cancer with RAF, MEK, and ERK inhibitors, it does not show any compound that directly inhibits RAS.

NPL 3 describes a compound that binds to the GTP/GDP binding site of RAS and inhibits the function of RAS, and the mechanism thereof. This document describes the interaction with the GTP/GDP binding site in detail, but does not show pharmacological action, especially action on tumor cells.

NPL 4 describes peptides that are used as drugs, but does not describe a drug-like peptide or a peptide useful for RAS-mutant cancer.

NPL 5 describes the molecular form and pharmacokinetics of cyclic peptides, but does not describe a compound useful for RAS-mutant cancer.

NPLs 6 to 8 describe peptides that bind to RAS, but their action on tumor cells is limited, and, in addition, a drug-like peptide is not described.

[0012]

Moreover, to the present inventors' knowledge, there is no report of a compound having sufficiently selective inhibitory action on KRAS over HRAS and NRAS.

[Solution to Problem]

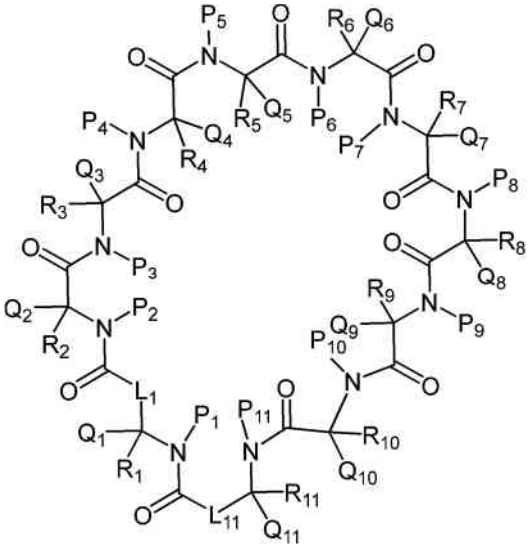
[0013]

As a result of dedicated research to search for cyclic compounds having selective inhibitory action on KRAS over HRAS and NRAS, the present inventors found cyclic compounds that interact with KRAS selectively as compared to HRAS and NRAS. In addition, the inventors found that the cyclic compounds have pharmacological action of inhibiting the growth of tumor cells having a RAS mutation.

[0014]

In a specific non-limiting embodiment, the present invention encompasses the following:

[1] A cyclic compound represented by formula (1):

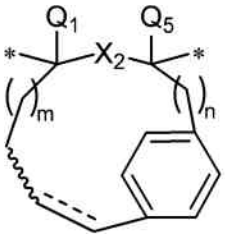


(1)

wherein

L_1 is a single bond;

R_1 is a C_1 to C_7 alkyl, or R_1 joins together with R_5 to form a divalent group, wherein a partial structure: *-CR_1Q_1-L_1-CO-NP_2-CR_2Q_2-CO-NP_3-CR_3Q_3-CO-NP_4-CR_4Q_4-CO-NP_5-CR_5Q_5-* in the cyclic compound represented by formula (1) is represented by the following formula:



wherein:

X_2 is -L_1-CO-NP_2-CR_2Q_2-CO-NP_3-CR_3Q_3-CO-NP_4-CR_4Q_4-CO-NP_5-,

---- is a single bond or a double bond,

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may take *E* or *Z* configuration, if

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is a double bond,

n is 0, 1 or 2,

m is 0, 1, 2, 3 or 4,

* represents an attachment point to an adjacent atom;

P_1 is a C_1 to C_6 alkyl;

Q_1 is a hydrogen atom;

R_2 is a C_1 to C_6 alkyl;

P_2 is a hydrogen atom;

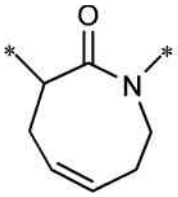
Q_2 is a hydrogen atom;

R_3 is a hydrogen atom or R_3 joins together with a carbon atom to which P_3 and R_3 are attached and a nitrogen atom to which P_3 is attached, to form a 4 to 7-membered saturated heterocycle;

P_3 is a C_1 to C_6 alkyl or a C_3 to C_8 cycloalkyl except the case where R_3 and P_3 form a 4 to 7-membered saturated heterocycle;

Q_3 is a hydrogen atom;

R_4 joins together with P_5 to form a divalent group, wherein a partial structure *-CR_4Q_4-CO-NP_5-* in the cyclic compound represented by formula (1) is represented by the following formula:



;

P_4 is a C_1 to C_6 alkyl;

Q_4 is a hydrogen atom,

R_5 is a benzyl optionally substituted with one or more groups selected from the group consisting of a C_1 to C_6 alkyl, a C_1 to C_6 haloalkyl, and a C_3 to C_8 cycloalkyl except the case where R_1 and R_5 form a divalent group;

Q_5 is a hydrogen atom,

R_6 is a hydrogen atom;

P_6 is a C_1 to C_6 alkyl,

Q_6 is a hydrogen atom,

R_7 is a phenethyl optionally substituted with one or more groups selected from the group consisting of a halogen atom, a C_1 to C_6 haloalkyl and a C_1 to C_6 alkoxy;

P_7 is a hydrogen atom,

Q_7 is a hydrogen atom,

R_8 joins together with a carbon atom to which P_8 and R_8 are attached and a nitrogen atom to which P_8 is attached, to form a 4 to 7-membered saturated heterocycle, wherein the 4 to 7-membered saturated heterocycle is optionally substituted with a C_1 to C_6 alkoxy;

Q_8 is a hydrogen atom,

R_9 joins together with Q_9 and a carbon atom to which R_9 and Q_9 are attached to form a 3 to 8-membered alicyclic ring, wherein the 3 to 8-membered alicyclic ring is optionally substituted with one or more C_1 to C_6 alkyls;

P_9 is a hydrogen atom or a C_1 to C_6 alkyl,

R_{10} is a C_1 to C_6 alkyl or a C_3 to C_8 cycloalkyl;

P_{10} is a C_1 to C_6 alkyl,

Q_{10} is a hydrogen atom, and

L_{11} is $-CH_2-$,

R_{11} is a di-C_1 to C_6 alkylaminocarbonyl or a 4 to 8-membered cyclic aminocarbonyl;

P_{11} is a C_1 to C_6 alkyl, and

Q_{11} is a hydrogen atom,

or a salt thereof, or a solvate thereof, wherein

the cyclic compound represented by formula (1) is selected from the group consisting of:

PP1574: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-N-ethyl-27-isobutyl-N,4,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclopentane]-23-carboxamide,

PP1650: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-27-isobutyl-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP1827: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-N-ethyl-N,3,18,21,25,31,34-heptamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,

PP1830: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-

1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,

PP2093: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-N,N,3',3',4,19,22,26,35-nonamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2260: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-22-carboxamide,

PP2316: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,4,16,19,22,26,35-octamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2320: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,2,14,18,21,24,36-octamethyl-10-[(1S)-1-methylpropyl]-3,9,12,15,19,22,25,31,34,37,45-undecaoxo-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-17-carboxamide,

PP2328: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,4,16,19,22,26,35-octamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2574: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP2576: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-

undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,
PP2583: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,34-heptamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,
PP2687: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-2-[(4-ethylphenyl)methyl]-27-isobutyl-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,
PP2691: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-2-[(4-cyclopropylphenyl)methyl]-12-ethoxy-27-isobutyl-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,
PP2957: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,34-pentamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,
PP3033: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone,
PP3034: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone,
PP3036: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-

undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP3037: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP3047: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-7-[2-(3,4-dichlorophenyl)ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone,

PP3093: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.9.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tripentaconta-37,43(52),44,46(51)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,53-undecone,

PP3094: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-11-propoxy-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.9.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tripentaconta-37,43(52),44,46(51)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,53-undecone,

PP3095: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3096: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3097: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-

(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3098: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3099: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3100: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-(p-tolylmethyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3101: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-17-(pyrrolidine-1-carbonyl)-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3102: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-38-(p-tolylmethyl)-17-(pyrrolidine-1-carbonyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3103: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-

undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3104: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3105: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3106: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3110: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3111: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3112: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3113: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3114: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3115: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-(p-tolylmethyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3116: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-17-(pyrrolidine-1-carbonyl)-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3117: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-38-(p-tolylmethyl)-17-(pyrrolidine-1-carbonyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3118: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3119: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3120: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3121: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-N-ethyl-N,3,18,21,25,31,34-heptamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

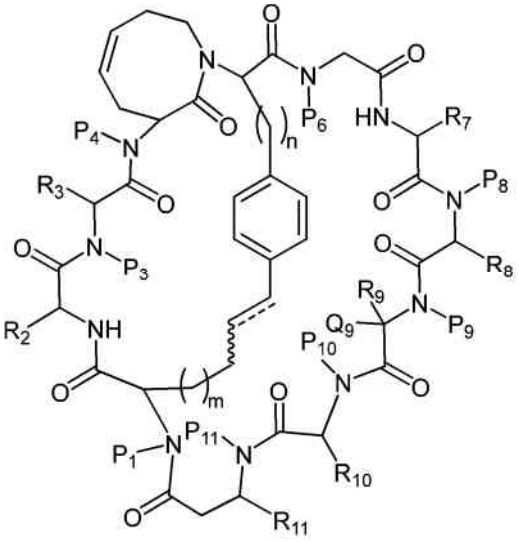
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,34-heptamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,34-pentamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, and

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-7-[2-(3,4-dichlorophenyl)ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone.

[2] The cyclic compound or a salt thereof, or a solvate thereof according to [1], wherein the formula (1) is expressed by formula (2):



(2)

wherein

,

n, m, P_1, R_2, R_3, P_3, P_4, P_6, R_7, R_8, P_8, R_9, P_9, Q_9, R_{10}, P_{10}, R_{11} and P_{11} are the same as defined in [1],

the cyclic compound represented by formula (2) is selected from the group consisting of:

PP1827: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-N-ethyl-N,3,18,21,25,31,34-heptamethyl-29-[(1S)-1-

methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,

PP1830: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,

PP2260: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-22-carboxamide,

PP2574: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP2576: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP2583: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,34-heptamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP2957: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,34-pentamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP3033: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-

undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone,

PP3034: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone,

PP3036: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP3037: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP3047: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-7-[2-(3,4-dichlorophenyl)ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone,

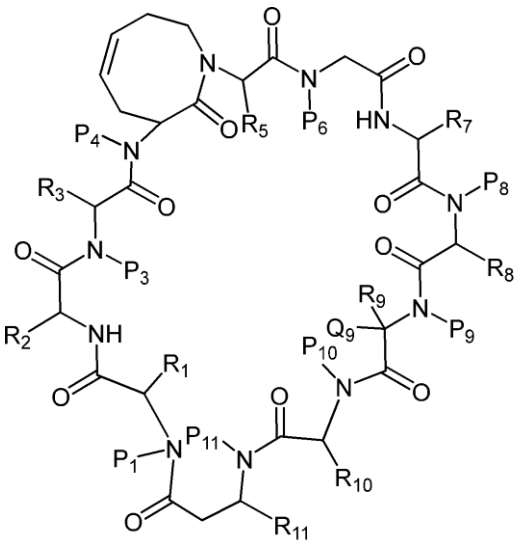
PP3093: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.9.2^{43,46}.1^{35,41}.0^{9,13}]tripentaconta-37,43(52),44,46(51)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,53-undecone,

PP3094: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-11-propoxy-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.9.2^{43,46}.1^{35,41}.0^{9,13}]tripentaconta-37,43(52),44,46(51)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,53-undecone,

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-N-ethyl-N,3,18,21,25,31,34-heptamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-

undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,34-heptamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,34-pentamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, and
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-7-[2-(3,4-dichlorophenyl)ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone.

[3] The cyclic compound or a salt thereof, or a solvate thereof according to [1], wherein the formula (1) is expressed by formula (3):



（3）

wherein,

R_1 is a C_1 to C_7 alkyl;

R_5 is benzyl optionally substituted with one or more groups selected from the group consisting of a C_1 to C_6 alkyl, a C_1 to C_6 haloalkyl and a C_3 to C_8 cycloalkyl;

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n, m, P_1, R_2, R_3, P_3, P_4, P_6, R_7, R_8, P_8, R_9, P_9, Q_9, R_{10}, P_{10}, R_{11} and P_{11} are the same as defined in [1], wherein

the cyclic compound represented by formula (3) is selected from the group consisting of:

PP1574: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-N-ethyl-27-isobutyl-N,4,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclopentane]-23-carboxamide,

PP1650: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-27-isobutyl-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2093: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-N,N,3',3',4,19,22,26,35-nonamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2316: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,4,16,19,22,26,35-octamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2320: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,2,14,18,21,24,36-octamethyl-10-[(1S)-1-methylpropyl]-3,9,12,15,19,22,25,31,34,37,45-undecaoxo-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-17-carboxamide,

PP2328: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,4,16,19,22,26,35-octamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2687: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-2-[(4-ethylphenyl)methyl]-27-isobutyl-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2691: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-2-[(4-cyclopropylphenyl)methyl]-12-ethoxy-27-isobutyl-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP3095: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3096: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3097: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3098: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3099: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3100: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-(p-tolylmethyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3101: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-17-(pyrrolidine-1-carbonyl)-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3102: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-38-(p-tolylmethyl)-17-(pyrrolidine-1-carbonyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3103: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3104: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3105: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3106: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3110: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3111: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3112: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-

(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3113: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3114: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3115: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-(p-tolylmethyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3116: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-17-(pyrrolidine-1-carbonyl)-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3117: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-38-(p-tolylmethyl)-17-(pyrrolidine-1-carbonyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3118: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-

undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,
PP3119: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,
PP3120: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, and
PP3121: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone.

[4-1] A cyclic compound which is PP1574: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-N-ethyl-27-isobutyl-N,4,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclopentane]-23-carboxamide, or a salt thereof, or a solvate thereof.

[4-2] A cyclic compound which is PP1650: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-27-isobutyl-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide, or a salt thereof, or a solvate thereof.

[4-3] A cyclic compound which is PP1827: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-N-ethyl-N,3,18,21,25,31,34-heptamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide, or a salt thereof, or a solvate thereof.

[4-4] A cyclic compound which is PP1830: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide, or a salt thereof, or a solvate thereof.

[4-5] A cyclic compound which is PP2093: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-N,N,3',3',4,19,22,26,35-nonamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide, or a salt thereof, or a solvate thereof.

[4-6] A cyclic compound which is PP2260: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-22-carboxamide, or a salt thereof, or a solvate thereof.

[4-7] A cyclic compound which is PP2316: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,4,16,19,22,26,35-octamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide, or a salt thereof, or a solvate thereof.

[4-8] A cyclic compound which is PP2320: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,2,14,18,21,24,36-octamethyl-10-[(1S)-1-methylpropyl]-3,9,12,15,19,22,25,31,34,37,45-undecaoxo-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-17-carboxamide, or a salt thereof, or a solvate thereof.

[4-9] A cyclic compound which is PP2328: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,4,16,19,22,26,35-octamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-

undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide, or a salt thereof, or a solvate thereof.

[4-10] A cyclic compound which is PP2574: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, or a salt thereof, or a solvate thereof.

[4-11] A cyclic compound which is PP2576: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, or a salt thereof, or a solvate thereof.

[4-12] A cyclic compound which is PP2583: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,34-heptamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, or a salt thereof, or a solvate thereof.

[4-13] A cyclic compound which is PP2687: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-2-[(4-ethylphenyl)methyl]-27-isobutyl-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide, or a salt thereof, or a solvate thereof.

[4-14] A cyclic compound which is PP2691: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-2-[(4-cyclopropylphenyl)methyl]-12-ethoxy-27-isobutyl-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide, or a salt thereof, or a solvate thereof.

[4-15] A cyclic compound which is PP2957: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,34-pentamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, or a salt thereof, or a solvate thereof.

[4-16] A cyclic compound which is PP3033: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone, or a salt thereof, or a solvate thereof.

[4-17] A cyclic compound which is PP3034: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone, or a salt thereof, or a solvate thereof.

[4-18] A cyclic compound which is PP3036: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, or a salt thereof, or a solvate thereof.

[4-19] A cyclic compound which is PP3037: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, or a salt thereof, or a solvate thereof.

[4-20] A cyclic compound which is PP3047: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-7-[2-(3,4-dichlorophenyl)ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone, or a salt thereof, or a solvate thereof.

[4-21] A cyclic compound which is PP3093: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.9.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tripentaconta-37,43(52),44,46(51)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,53-undecone, or a salt thereof, or a solvate thereof.

[4-22] A cyclic compound which is PP3094: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-11-propoxy-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.9.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tripentaconta-37,43(52),44,46(51)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,53-undecone, or a salt thereof, or a solvate thereof.

[4-23] A cyclic compound which is PP3095: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-24] A cyclic compound which is PP3096: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-25] A cyclic compound which is PP3097: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-26] A cyclic compound which is PP3098: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-27] A cyclic compound which is PP3099: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone, or a salt thereof, or a solvate thereof.

[4-28] A cyclic compound which is PP3100: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-(p-tolylmethyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone, or a salt thereof, or a solvate thereof.

[4-29] A cyclic compound which is PP3101: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-17-(pyrrolidine-1-carbonyl)-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone, or a salt thereof, or a solvate thereof.

[4-30] A cyclic compound which is PP3102: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-38-(p-tolylmethyl)-17-(pyrrolidine-1-carbonyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone, or a salt thereof, or a solvate thereof.

[4-31] A cyclic compound which is PP3103: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-32] A cyclic compound which is PP3104: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-33] A cyclic compound which is PP3105: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-34] A cyclic compound which is PP3106: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-35] A cyclic compound which is PP3110: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-36] A cyclic compound which is PP3111: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-37] A cyclic compound which is PP3112: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-38] A cyclic compound which is PP3113: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-39] A cyclic compound which is PP3114: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone, or a salt thereof, or a solvate thereof.

[4-40] A cyclic compound which is PP3115: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-(p-tolylmethyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone, or a salt thereof, or a solvate thereof.

[4-41] A cyclic compound which is PP3116: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-17-(pyrrolidine-1-carbonyl)-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone, or a salt thereof, or a solvate thereof.

[4-42] A cyclic compound which is PP3117: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-38-(p-tolylmethyl)-17-(pyrrolidine-1-carbonyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone, or a salt thereof, or a solvate thereof.

[4-43] A cyclic compound which is PP3118: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-44] A cyclic compound which is PP3119: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-45] A cyclic compound which is PP3120: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-46] A cyclic compound which is PP3121: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone, or a salt thereof, or a solvate thereof.

[4-47] A cyclic compound which is (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-N-ethyl-N,3,18,21,25,31,34-heptamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide, or a salt thereof, or a solvate thereof.

[4-48] A cyclic compound which is (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide, or a salt thereof, or a solvate thereof.

[4-49] A cyclic compound which is (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-

16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, or a salt thereof, or a solvate thereof.

[4-50] A cyclic compound which is (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, or a salt thereof, or a solvate thereof.

[4-51] A cyclic compound which is (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,34-heptamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, or a salt thereof, or a solvate thereof.

[4-52] A cyclic compound which is (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,34-pentamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, or a salt thereof, or a solvate thereof.

[4-53] A cyclic compound which is (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-7-[2-(3,4-dichlorophenyl)ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone, or a salt thereof, or a solvate thereof.

[5] The cyclic compound or a salt thereof according to any one of [1] to [4-53].

[6] The cyclic compound or a solvate thereof according to any one of [1] to [4-53].

[7] A solvate of the cyclic compound or a salt thereof according to any one of [1] to [4-53].

[8] The cyclic compound according to any one of [1] to [4-53].

[9] The cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53], which binds to KRAS.

[10] The cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53], which inhibits KRAS.

[11] The cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53], which has high selectivity for KRAS.

[12] The cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53], having KRAS selectivity (KRAS selectivity to NRAS and/or KRAS selectivity to HRAS) higher than PP1820: ((3S,9S,12S,17S,20S,23S,27S,30S,36S)-3-[2-[3-chloro-4-(trifluoromethyl)phenyl]ethyl]30-cyclopentyl-23-isobutyl-9-(isopentyloxymethyl)-N,N,7,17,18,24,28,31-octamethyl-20-[(1S)-1-methylpropyl]-2,5,8,11,16,19,22,25,29,32,35-undecaoxo-10-propyl-spiro [1,4,7,10,15,18,21,24,28,31,34-undecazatricyclo[34.3.0.012,15]nonatriacontane-33,1'-cyclobutane]-27-carboxamide).

[13] The cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53], which selectively binds to KRAS.

[14] The cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53], which selectively inhibits KRAS.

[15] The cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53], which has KRAS binding activity that is 3 times or more higher than NRAS binding activity and HRAS binding activity.

[16] The cyclic compound or a salt thereof, or a solvate thereof according to [15], which has KRAS binding activity that is is 5 times, 7 times, 10 times, 15 times, or 20 times or more higher than NRAS binding activity and HRAS binding activity.

[17] The cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53], which has KRAS inhibitory activity that is 3 times or more higher than NRAS inhibitory activity and HRAS inhibitory activity.

[18] The cyclic compound or a salt thereof, or a solvate thereof according to [17], which has KRAS inhibitory activity that is is 5 times, 7 times, 10 times, 15 times, or 20 times or more higher than NRAS inhibitory activity and HRAS inhibitory activity.

[19] A pharmaceutical composition comprising the cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53].

[20] A pharmaceutical composition for selectively inhibiting KRAS in a subject, the composition comprising the cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53].

[21] The pharmaceutical composition according to [20], wherein KRAS inhibitory activity of the compound is 3 times or more higher than NRAS inhibitory activity and HRAS inhibitory activity of the compound.

[22] The pharmaceutical composition according to [21], wherein KRAS inhibitory activity of the compound is 5 times, 7 times, 10 times, 15 times, or 20 times or more higher than NRAS inhibitory activity and HRAS inhibitory activity of the compound.

[23] A pharmaceutical composition for treating or preventing cancer in a subject, the composition comprising an effective amount of the cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53].

[24] The pharmaceutical composition according to [23], wherein the cancer is lung cancer.

[25] The pharmaceutical composition of any one of [20] to [24], wherein the subject is a human.

[26] The cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53] for use in treatment or prevention of cancer in a subject.

[27] The cyclic compound or a salt thereof, or a solvate thereof according to [26], wherein the cancer is lung cancer.

[28] The cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53] for use in selectively inhibiting KRAS in a subject.

[29] The cyclic compound or a salt thereof, or a solvate thereof according to any one of [26] to [28], wherein the subject is a human.

[30] Use of the cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53] in the manufacture of a medicament for treating or preventing cancer in a subject.

[31] The use according to [30], wherein the cancer is lung cancer.

[32] Use of the cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53] in the manufacture of a medicament for selectively inhibiting KRAS in a subject.

[33] The use according to any one of [30] to [32], wherein the subject is a human.

[34] A method for treating or preventing cancer in a subject, the method comprising administering an effective amount of the cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53] to a subject in need thereof.

[35] The method according to [34], wherein the cancer is lung cancer.

[36] A method for selectively inhibiting KRAS in a subject, the method comprising administering an effective amount of the cyclic compound or a salt thereof, or a solvate thereof according to any one of [1] to [4-53] to a subject in need thereof.

[37] The method according to any one of [34] to [36], wherein the subject is a human.

[Effects of the Invention]

[0015]

The present invention can provide novel cyclic compounds having selective KRAS inhibitory action.

[Description of Embodiments]

[0016]

(Abbreviations)

The abbreviations used herein are as follows.

AA: Ammonium acetate

Boc: tert-Butoxycarbonyl

CSA: (+)-10-Camphorsulfonic acid

CPME: Cyclopentyl methyl ether

DAST: (Diethylamino)sulfur trifluoride

DBU: 1,8-Diazabicyclo[5.4.0]-7-undecene

DCM: Dichloromethane

DCE: 1,2-Dichloroethane

DEAD: Diethyl azodicarboxylate

DEPBT: 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one

DIAD: Diisopropyl azodicarboxylate

DIC: N,N'-Diisopropylcarbodiimide

DIPEA: N,N-Diisopropylethylamine

DHP: 3,4-Dihydro-2H-pyran

DMA: N,N-Dimethylacetamide

DMAP: N,N-Dimethyl-4-aminopyridine

DMF: N,N-Dimethylformamide

dtbbpy: 4,4'-Di-tert-butyl-2,2'-bipyridine

EDTA: Ethylenediaminetetraacetic acid

FA: Formic acid

Fmoc: 9-Fluorenylmethyloxycarbonyl

NMP: N-Methyl-2-pyrrolidone

TBME: t-Butyl methyl ether

TES: Triethylsilane

TFA: Trifluoroacetic acid

TFE: 2,2,2-Trifluoroethanol

THF: Tetrahydrofuran

THP: Tetrahydropyranyl

TMSCl: Chlorotrimethylsilane

HFIP: 1,1,1,3,3,3-Hexafluoroisopropyl alcohol

HOAt: 1-Hydroxy-7-azabenzotriazole

HOBt: 1-Hydroxybenzotriazole

HOOBt: 3,4-Dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine

IPAC: Isopropyl acetate

oxyma: Ethyl cyano(hydroxyimino)acetate

PPTS: Pyridinium p-toluenesulfonate

Pis: 2-Phenylisopropyl

WSCI·HCl, WSCDI: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

TIPS: Triisopropylsilane

TfOH: Trifluoromethanesulfonic acid

HATU: O-(7-Aza-1H-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

DMSO: Dimethylsulfoxide

Fmoc-Cl: (9H-Fluoren-9-yl)methyl carbonochloridate

Fmoc-OSu: 9-Fluorenylmethyl N-succinimidyl carbonate

Ns: o-Nitrobenzenesulfonyl

Trt: Triphenylmethyl

9-BBN: 9-Borabicyclo[3.3.1]nonane

HMDS: 1,1,1,3,3,3-Hexamethyldisilazane

LDA: Lithium diisopropylamide

TMSOTf: Trimethylsilyl trifluoromethanesulfonate

PPA: Polyphosphoric acid

[0017]

Herein, the term "about" when used in combination with a numerical value means a numerical range of +10% and -10% of that numerical value.

[0018]

Herein, "-" indicating a range includes values at opposite ends of the range. For example, "A-B" means a range of A or more and B or less.

[0019]

The unit of molecular weight herein is "g/mol" (hereinafter, the unit of molecular weight may be omitted).

[0020]

The use of the articles "a", "an", and "the" in both the description and the claims are to be construed as covering both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context.

[0021]

(Definitions of functional groups and the like)

Examples of "halogen atoms" herein include F, Cl, Br, and I.

[0022]

"Alkyl" herein means a monovalent group derived by removing any one hydrogen atom from an aliphatic hydrocarbon, and has a subset of hydrocarbyl or hydrocarbon group

structures not containing either a heteroatom (which refers to an atom other than carbon and hydrogen atoms) or an unsaturated carbon-carbon bond but containing hydrogen and carbon atoms in its backbone. The alkyl includes linear and branched alkyls. Specifically, the alkyl has 1 to 20 carbon atoms (C_1-C_{20}, hereinafter "C_p-C_q" means that the number of carbon atoms is p to q), and is preferably C_1-C_{10} alkyl, and more preferably C_1-C_6 alkyl. Specific examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, isobutyl (2-methylpropyl), n-pentyl, s-pentyl (1-methylbutyl), t-pentyl (1,1-dimethylpropyl), neopentyl (2,2-dimethylpropyl), isopentyl (3-methylbutyl), 3-pentyl (1-ethylpropyl), 1,2-dimethylpropyl, 2-methylbutyl, n-hexyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1,1,2,2-tetramethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, and 2-ethylbutyl.

[0023]

"Alkenyl" herein means a monovalent group having at least one double bond (two adjacent SP^2 carbon atoms). Depending on the configuration of a double bond and a substituent (if present), the geometrical form of the double bond can be entgegen (E) or zusammen (Z) as well as cis or trans configuration. The alkenyl includes linear and branched alkenyls. The alkenyl is preferably C_2-C_{10} alkenyl, and more preferably C_2-C_7 alkenyl or C_2-C_6 alkenyl, and specific examples include vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl (including cis and trans forms), 3-butenyl, pentenyl, 3-methyl-2-butenyl, hexenyl, and 6-heptenyl.

[0024]

"Alkynyl" herein means a monovalent group having at least one triple bond (two adjacent SP carbon atoms). The alkynyl includes linear and branched alkynyls. The alkynyl is preferably C_2-C_{10} alkynyl, and more preferably C_2-C_6 alkynyl, and specific examples include ethynyl, 1-propynyl, propargyl, 3-butynyl, pentynyl, hexynyl, 3-phenyl-2-propynyl, 3-(2'-fluorophenyl)-2-propynyl, 2-hydroxy-2-propynyl, 3-(3-fluorophenyl)-2-propynyl, and 3-methyl-(5-phenyl)-4-pentynyl.

[0025]

"Cycloalkyl" herein means a saturated or partially saturated cyclic monovalent aliphatic hydrocarbon group and includes a monocyclic ring, a bicyclo ring, and a spiro ring. The cycloalkyl is preferably C_3-C_8 cycloalkyl, and specific examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, and spiro[3.3]heptyl.

[0026]

"Aryl" herein means a monovalent aromatic hydrocarbon ring, and is preferably C_6-C_{10} aryl. Specific examples of the aryl include phenyl and naphthyl (e.g., 1-naphthyl and 2-naphthyl). Aryl herein includes bicyclic aryl in which the aromatic hydrocarbon ring is

condensed with another saturated ring or unsaturated ring, and, for example, includes aryl having a condensed ring structure in which the aromatic hydrocarbon ring is a benzene ring and the saturated ring is a 5-, 6-, or 7-membered saturated hydrocarbon ring or saturated heterocyclic ring. Specific examples include indanyl, 1,2,3,4-tetrahydronaphthyl, and 2,3-dihydrobenzofuran.

[0027]

"Heterocyclyl" herein means a non-aromatic cyclic monovalent group containing 1 to 5 hetero atoms in addition to carbon atoms. The heterocyclyl may have a double and/or triple bond within the ring, a carbon atom within the ring may be oxidized to form carbonyl, and heterocyclyl may be a monocyclic ring or a condensed ring. The number of atoms constituting the ring is preferably 3 to 10 (3- to 10-membered heterocyclyl) or 4 to 10 (4- to 10-membered heterocyclyl), and more preferably 3 to 7 (3- to 7-membered heterocyclyl) or 4 to 7 (4- to 7-membered heterocyclyl). Specific examples of the heterocyclyl include azetidinyl, oxiranyl, oxetanyl, azetidinyl, dihydrofuryl, tetrahydrofuryl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridyl, tetrahydropyrimidyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, 1,2-thiazinane, thiadiazolidinyl, azetidinyl, oxazolidone, benzodioxanyl, benzoxazolyl, dioxolanyl, dioxanyl, tetrahydropyrrolo[1,2-c]imidazole, thietanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, sultam, and 2-oxaspiro[3.3]heptyl.

[0028]

"Protected heterocyclyl" herein means a group in which one or more functional groups, such as an amino group, contained in the above-defined "heterocyclyl" are protected with a protecting group, and is preferably 4- to 7-membered protected heterocyclyl. Specific examples of the protecting group include Boc, Fmoc, Cbz, Troc, and Alloc, and specific examples of the protected heterocyclyl include Boc-protected azetidine.

[0029]

"Heterocycloalkylidene" herein means a divalent group obtained by removing two hydrogen atoms from one carbon atom of the above-defined "heterocyclyl", in which a free valence forms a part of a double bond. The heterocycloalkylidene is preferably 4- to 7-membered heterocycloalkylidene, and specific examples include tetrahydropyran-4-ylidene and azetidin-3-ylidene.

[0030]

"Protected heterocycloalkylidene" herein means a group in which one or more functional groups, such as an amino group, contained in the above-defined "heterocycloalkylidene" are protected with a protecting group, and is preferably 4- to 7-

membered protected heterocycloalkylidene. Specific examples of the protecting group include Boc, Fmoc, Cbz, Troc, and Alloc, and specific examples of the protected heterocycloalkylidene include Boc-protected azetidin-3-ylidene.

[0031]

"Heteroaryl" herein means an aromatic cyclic monovalent group containing 1 to 5 heteroatoms in addition to carbon atoms. The ring may be a monocyclic ring, may be a condensed ring formed with another ring, or may be partially saturated. The number of atoms constituting the ring is preferably 5 to 10 (5- to 10-membered heteroaryl) and more preferably 5 to 7 (5- to 7-membered heteroaryl). Specific examples of the heteroaryl include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, benzofuranyl, benzothienyl, benzothiadiazolyl, benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzoimidazolyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, benzodioxolyl, indolizinyl, and imidazopyridyl.

[0032]

"Alkoxy" herein means an oxy group to which the above-defined "alkyl" is bonded, and is preferably C_1-C_6 alkoxy. Specific examples of the alkoxy include methoxy, ethoxy, 1-propoxy, 2-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, and 3-methylbutoxy.

[0033]

"Alkylthio" herein means a thiol group to which the above-defined "alkyl" is bonded, and is preferably C_1-C_6 alkylthio. Specific examples of alkylthio include methylthio, ethylthio, 1-propylthio, 2-propylthio, n-butylthio, i-butylthio, s-butylthio, and t-butylthio.

[0034]

"Alkenyloxy" herein means an oxy group to which the above-defined "alkenyl" is bonded, and is preferably C_2-C_6 alkenyloxy. Specific examples of the alkenyloxy include vinyloxy, allyloxy, 1-propenyloxy, 2-propenyloxy, 1-butenyloxy, 2-butenyloxy (including cis and trans forms), 3-butenyloxy, pentenyloxy, and hexenyloxy.

[0035]

"Cycloalkoxy" herein means an oxy group to which the above-defined "cycloalkyl" is bonded, and is preferably C_3-C_8 cycloalkoxy. Specific examples of the cycloalkoxy include cyclopropoxy, cyclobutoxy, and cyclopentyloxy.

[0036]

"Aryloxy" herein means an oxy group to which the above-defined "aryl" is bonded, and is preferably C_6-C_{10} aryloxy. Specific examples of the aryloxy include phenoxy, 1-naphthyloxy, and 2-naphthyloxy.

[0037]

"Amino" herein means -NH_2 in a narrow sense and -NRR' in a broad sense, wherein R and R' are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, or R and R', together with the nitrogen atom to which they are attached, form a ring. The amino is preferably -NH_2, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, 4- to 8-membered cyclic amino, or the like.

[0038]

"Monoalkylamino" herein means a group corresponding to the above-defined "amino" wherein R is hydrogen and R' is the above-defined "alkyl", and is preferably mono-C_1-C_6 alkylamino. Specific examples of the monoalkylamino include methylamino, ethylamino, n-propylamino, i-propylamino, n-butylamino, s-butylamino, and t-butylamino.

[0039]

"Dialkylamino" herein means a group corresponding to the above-defined "amino" wherein R and R' are independently the above-defined "alkyl", and is preferably di-C_1-C_6 alkylamino. Specific examples of the dialkylamino include dimethylamino and diethylamino.

[0040]

"Cyclic amino" herein means a group corresponding to the above-defined "amino" wherein R and R', together with the nitrogen atom to which they are attached, form a ring, and is preferably 4- to 8-membered cyclic amino. Specific examples of the cyclic amino include 1-azetidyl, 1-pyrrolidyl, 1-piperidyl, 1-piperazyl, 4-morpholinyl, 3-oxazolidyl, 1,1-dioxidethiomorpholinyl-4-yl, and 3-oxa-8-azabicyclo[3.2.1]octan-8-yl.

[0041]

"Protected amino" herein means an amino group protected with any protecting group. Specific examples of the protected amino include amino protected with a protecting group such as Boc, Fmoc, Cbz, Troc, or Alloc.

[0042]

"Alkylcarbonyl" herein means a carbonyl group to which the above-defined "alkyl" is bonded, and is preferably C_1-C_6 alkylcarbonyl. Specific examples of alkylcarbonyl include acetyl, propionyl, and butyryl. The number of carbon atoms set forth in the above definition indicates the number of carbon atoms in the alkyl moiety. For example, "C_1-C_6" in "C_1-C_6 alkylcarbonyl" indicates that the alkyl moiety has 1 to 6 carbon atoms.

[0043]

"Aminocarbonyl" herein means a carbonyl group to which the above-defined "amino" is bonded, and is preferably -$CONH_2$, mono-C_1-C_6 alkylaminocarbonyl, di-C_1-C_6 alkylaminocarbonyl, and 4- to 8-membered cyclic aminocarbonyl. Specific examples of the aminocarbonyl include -$CONH_2$, dimethylaminocarbonyl, 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, 1-piperazinylcarbonyl, 4-morpholinylcarbonyl, 3-

oxazolidinylcarbonyl, 1,1-dioxidethiomorpholinyl-4-ylcarbonyl, and 3-oxa-8-azabicyclo[3.2.1]octan-8-ylcarbonyl.

[0044]

"Alkenyloxycarbonyl" herein means a carbonyl group to which the above-defined "alkenyloxy" is bonded, and is preferably C_2-C_6 alkenyloxycarbonyl. Specific examples of the alkenyloxycarbonyl include vinyloxycarbonyl, allyloxycarbonyl, 1-propenyloxycarbonyl, 2-propenyloxycarbonyl, 1-butenyloxycarbonyl, 2-butenyloxycarbonyl (including cis and trans forms), 3-butenyloxycarbonyl, pentenyloxycarbonyl, and hexenyloxycarbonyl.

[0045]

"Alkylsulfonyl" herein means a sulfonyl group to which the above-defined "alkyl" is bonded, and is preferably C_1-C_6 alkylsulfonyl. Specific examples of the alkylsulfonyl include methylsulfonyl.

[0046]

"Hydroxyalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with hydroxyl groups, and is preferably C_1-C_6 hydroxyalkyl. Specific examples of the hydroxyalkyl include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl, and 5-hydroxypentyl.

[0047]

"Haloalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with halogen, and is preferably C_1-C_6 haloalkyl, and more preferably C_1-C_6 fluoroalkyl. Specific examples of the haloalkyl include difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3-difluoropropyl, 4,4-difluorobutyl, 5,5-difluoropentyl, and 1,1-difluoroethyl.

[0048]

"Cyanoalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with cyano, and is preferably C_1-C_6 cyanoalkyl. Specific examples of the cyanoalkyl include cyanomethyl and 2-cyanoethyl.

[0049]

"Aminoalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "amino", and is preferably C_1-C_6 aminoalkyl. Specific examples of the aminoalkyl include 1-pyridylmethyl, 2-(1-piperidyl)ethyl, 3-(1-piperidyl)propyl, 4-aminobutyl, and 2-aminoethyl.

[0050]

"Carboxyalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with carboxy, and is preferably C_1-C_6 carboxyalkyl or C_2-C_6 carboxyalkyl. Specific examples of the carboxyalkyl include carboxymethyl. The number of

carbon atoms set forth in the above definition indicates the number of carbon atoms in the alkyl moiety. For example, "C_1-C_6" in "C_1-C_6 carboxyalkyl" indicates that the alkyl moiety has 1 to 6 carbon atoms.

[0051]

"Alkenyloxycarbonylalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "alkenyloxycarbonyl", and is preferably C_2-C_6 alkenyloxycarbonyl C_1-C_6 alkyl, and more preferably C_2-C_6 alkenyloxycarbonyl C_1-C_2 alkyl. Specific examples of the alkenyloxycarbonylalkyl include allyloxycarbonylmethyl and 2-(allyloxycarbonyl)ethyl.

[0052]

"Alkoxyalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "alkoxy", and is preferably C_1-C_6 alkoxy C_1-C_6 alkyl, and more preferably C_1-C_6 alkoxy C_1-C_2 alkyl. Specific examples of the alkoxyalkyl include methoxymethyl, ethoxymethyl, 1-propoxymethyl, 2-propoxymethyl, n-butoxymethyl, i-butoxymethyl, s-butoxymethyl, t-butoxymethyl, pentyloxymethyl, 3-methylbutoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 1-ethoxyethyl, and 1-n-propyloxyethyl.

[0053]

"Alkylthioalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "alkylthio", and is preferably C_1-C_6 alkylthioC_1-C_6 alkyl, and more preferably C_1-C_6 alkylthioC_1-C_2 alkyl. Specific examples of alkylthioalkyl include methylthiomethyl, ethylthiomethyl, 1-propylthiomethyl, 2-propylthiomethyl, n-butylthiomethyl, i-butylthiomethyl, s-butylthiomethyl, and t-butylthiomethyl.

[0054]

"Alkenyloxyalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "alkenyloxy", and is preferably C_2-C_6 alkenyloxyC_1-C_6 alkyl, and more preferably C_1-C_6 alkenyloxyC_1-C_2 alkyl. Specific examples of alkenyloxyalkyl include vinyloxymethyl and allyloxymethyl.

[0055]

"Cycloalkylalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "cycloalkyl", and is preferably C_3-C_8 cycloalkyl C_1-C_6 alkyl, and more preferably C_3-C_6 cycloalkyl C_1-C_2 alkyl. Specific examples of the cycloalkylalkyl include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, and cyclohexylmethyl.

[0056]

"Cycloalkoxylalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "cycloalkoxy", and is preferably C_3-C_8 cycloalkoxy C_1-C_6 alkyl, and more preferably C_3-C_6 cycloalkoxy C_1-C_2 alkyl. Specific examples of the cycloalkoxyalkyl include cyclopropoxymethyl and cyclobutoxymethyl.

[0057]

"Heterocyclylalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "heterocyclyl", and is preferably 4- to 7-membered heterocyclyl C_1-C_6 alkyl, and more preferably 4- to 7-membered heterocyclyl C_1-C_2 alkyl. Specific examples of the heterocyclylalkyl include 2-(tetrahydro-2H-pyran-4-yl)ethyl and 2-(azetidin-3-yl)ethyl.

[0058]

"Alkylsulfonylalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "alkylsulfonyl", and is preferably C_1-C_6 alkylsulfonyl C_1-C_6 alkyl, and more preferably C_1-C_6 alkylsulfonyl C_1-C_2 alkyl. Specific examples of the alkylsulfonylalkyl include methylsulfonylmethyl and 2-(methylsulfonyl)ethyl.

[0059]

"Aminocarbonylalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "aminocarbonyl", and is preferably aminocarbonyl C_1-C_6 alkyl, and more preferably aminocarbonyl C_1-C_4 alkyl. Specific examples of the aminocarbonylalkyl include methylaminocarbonylmethyl, dimethylaminocarbonylmethyl, t-butylaminocarbonylmethyl, 1-azetidinylcarbonylmethyl, 1-pyrrolidinylcarbonylmethyl, 1-piperidinylcarbonylmethyl, 4-morpholinylcarbonylmethyl, 2-(methylaminocarbonyl)ethyl,2-(dimethylaminocarbonyl)ethyl, 2-(1-azetidinylcarbonyl)ethyl, 2-(1-pyrrolidinylcarbonyl)ethyl, 2-(4-morpholinylcarbonyl)ethyl, 3-(dimethylaminocarbonyl)propyl, and 4-(dimethylaminocarbonyl)butyl.

[0060]

"Aryloxyalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "aryloxy", and is preferably C_6-C_{10} aryloxy C_1-C_6 alkyl, and more preferably C_6-C_{10} aryloxy C_1-C_2 alkyl. Specific examples of the aryloxyalkyl include phenoxymethyl and 2-phenoxyethyl.

[0061]

"Aralkyl (arylalkyl)" herein means a group in which one or more hydrogen atoms of the above-defined "alkyl" are replaced with the above-defined "aryl", and is preferably C_7-C_{14} aralkyl, and more preferably C_7-C_{10} aralkyl. Specific examples of the aralkyl include benzyl, phenethyl, and 3-phenylpropyl.

[0062]

"Aralkoxy" herein means an oxy group to which the above-defined "aralkyl" is bonded, and is preferably C_7-C_{14} aralkoxy, and more preferably C_7-C_{10} aralkoxy. Specific examples of the aralkoxy include benzyloxy, phenethyloxy, and 3-phenylpropoxy.

[0063]

"Aralkoxyalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "aralkoxy", and is preferably C_7-C_{14} aralkoxy C_1-C_6 alkyl, and more preferably C_7-C_{14} aralkoxy C_1-C_2 alkyl. Specific examples of the aralkoxyalkyl include benzyloxymethyl and 1-(benzyloxy)ethyl.

[0064]

"Heteroarylalkyl" herein means a group in which one or more hydrogen atoms of the above-defined "alkyl" are replaced with the above-defined "heteroaryl", and is preferably 5- to 10-membered heteroaryl C_1-C_6 alkyl, and more preferably 5- to 10-membered heteroaryl C_1-C_2 alkyl. Specific examples of the heteroarylalkyl include 3-thienylmethyl, 4-thiazolylmethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-(2-pyridyl)ethyl, 2-(3-pyridyl)ethyl, 2-(4-pyridyl)ethyl, 2-(6-quinolyl)ethyl, 2-(7-quinolyl)ethyl, 2-(6-indolyl)ethyl, 2-(5-indolyl)ethyl, and 2-(5-benzofuranyl)ethyl.

[0065]

"Heteroarylalkoxy" herein means an oxy group to which the above-defined "heteroarylalkyl" is bonded, and is preferably 5- to 10-membered heteroaryl C_1-C_6 alkoxy, and more preferably 5- to 10-membered heteroarylC_1-C_2 alkoxy. Specific examples of the heteroarylalkoxy include 3-thienylmethoxy and 3-pyridylmethoxy.

[0066]

"Heteroarylalkoxyalkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "heteroarylalkoxy", and is preferably 5- to 10-membered heteroaryl C_1-C_6 alkoxy C_1-C_6 alkyl, and more preferably 5- to 10-membered heteroaryl C_1-C_2 alkoxy C_1-C_2 alkyl. Specific examples of the heteroarylalkoxyalkyl include 3-pyridylmethoxymethyl.

[0067]

"Heterocycloalkylidenealkyl" herein means a group in which one or more hydrogens of the above-defined "alkyl" are replaced with the above-defined "heterocycloalkylidene", and is preferably 4- to 7-membered heterocycloalkylidene C_1-C_6 alkyl, and more preferably 4- to 7-membered heterocycloalkylidene C_1-C_2 alkyl. Specific examples of the heterocycloalkylidenealkyl include tetrahydro-4H-pyran-4-ylidenemethyl and azetidin-3-ylidenemethyl.

[0068]

"Alkoxyalkenyl" herein means a group in which one or more hydrogens of the above-defined "alkenyl" are replaced with the above-defined "alkoxy", and is preferably C_1-C_6 alkoxy C_2-C_6 alkenyl. Specific examples of the alkoxyalkenyl include (E)-4-methoxybut-2-en-1-yl.

[0069]

"Aminocarbonylalkenyl" herein means a group in which one or more hydrogens of the above-defined "alkenyl" are replaced with the above-defined "aminocarbonyl", and is preferably aminocarbonyl C_2-C_6 alkenyl. Specific examples of the aminocarbonylalkenyl include (E)-3-(dimethylaminocarbonylcarbonyl)-prop-2-en-1-yl.

[0070]

"Haloalkoxy" herein means a group in which one or more hydrogens of the above-defined "alkoxy" are replaced with halogen, and is preferably C_1-C_6 haloalkoxy. Specific examples of the haloalkoxy include difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, and 2,2,2-trifluoroethoxy.

[0071]

"Alkylene" herein means a divalent group derived by further removing any one hydrogen atom from the above "alkyl", and is preferably C_4-C_8 alkylene. Specific examples of the alkylene include $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH(CH_3)CH_2-$, $-C(CH_3)_2-$, $-(CH_2)_4-$, $-CH(CH_3)CH_2CH_2-$, $-C(CH_3)_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2C(CH_3)_2-$, $-CH_2CH_2CH(CH_3)-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, and $-(CH_2)_8-$.

[0072]

"Cycloalkylene" herein means a divalent group derived by further removing any one hydrogen atom from the above "cycloalkyl", and is preferably C_3-C_8 cycloalkylene. Specific examples of cycloalkylene include cyclopropane-1,2-diyl, cyclobutane-1,2-diyl, cyclopentane-1,2-diyl, and cyclohexane-1,2-diyl.

[0073]

"Heterocyclylene" herein means a divalent group derived by removing any one hydrogen atom from the above "heterocyclyl", and is preferably 3- to 7-membered heterocyclylene. Specific examples of heterocyclylene include oxylan-2,3-diyl, oxetan-2,3-diyl, tetrahydrofuran-2,5-diyl, and tetrahydropyran-2,6-diyl.

[0074]

"Alkenylene" herein means a divalent group derived by further removing any one hydrogen atom from the above "alkenyl". Depending on the configuration of a double bond and a substituent (if present), the geometrical form of the double bond can be entgegen (E) or zusammen (Z) as well as cis or trans configuration. Alkenylene may be linear or branched, and is preferably C_2-C_{10} alkenylene and more preferably C_2-C_6 alkenylene.

[0075]

"Alkynylene" herein means a divalent group derived by further removing any one hydrogen atom from the above "alkynyl". Alkynylene may be linear or branched, and is preferably C_2-C_{10} alkynylene and more preferably C_2-C_6 alkynylene.

[0076]

"Arylene" herein means a divalent group derived by further removing any one hydrogen atom from the above "aryl". Arylene may be a monocyclic ring or a condensed ring. The number of atoms constituting the ring is not particularly limited, and is preferably 6 to 10 (C_{6-10} arylene). Specific examples of arylene include 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene, 1,3-naphthylene, and 1,4-naphthylene.

[0077]

"Spirocycloalkyl" herein means a group formed by sharing of one carbon atom constituting a cycloalkane ring with a carbon atom present in a group to be bonded. Spirocycloalkyl is preferably C_3-C_8 spirocycloalkyl, and specific examples include spirocyclopropyl, spirocyclobutyl, spirocyclopentyl, spirocyclohexyl, spirocycloheptyl, and spirocyclooctyl.

[0078]

"Spiroheterocyclyl" herein means a group obtained by replacing one or more carbon atoms in the above "spirocycloalkyl" with heteroatoms. Heterospirocycloalkyl is preferably 4- to 10-membered spiroheterocyclyl.

[0079]

"Alicyclic ring" herein means a non-aromatic hydrocarbon ring. The alicyclic ring may have an unsaturated bond within the ring, and may be a polycyclic ring having two or more rings. A carbon atom constituting the ring may be oxidized to form carbonyl. The alicyclic ring is preferably a 3- to 8-membered alicyclic ring, and specific examples include a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, a cyclohexane ring, a cycloheptane ring, a cyclooctane ring, and a bicyclo[2.2.1]heptane ring.

[0080]

"Saturated heterocyclic ring" herein means a non-aromatic heterocyclic ring containing 1 to 5 hetero atoms in addition to carbon atoms and not containing a double bond and/or a triple bond within the ring. The saturated heterocyclic ring may be a monocyclic ring, or may form a condensed ring with another ring, e.g., an aromatic ring such as a benzene ring. The saturated heterocyclic ring is preferably a 4- to 7-membered saturated heterocyclic ring, and specific examples include an azetidine ring, an oxetane ring, a tetrahydrofuran ring, a tetrahydropyran ring, a morpholine ring, a thiomorpholine ring, a pyrrolidine ring, a 4-oxopyrrolidine ring, a piperidine ring, a 4-oxopiperidine ring, a piperazine ring, a pyrazolidine ring, an imidazolidine ring, an oxazolidine ring, an isoxazolidine ring, a thiazolidine ring, an isothiazolidine ring, a

thiadiazolidine ring, an oxazolidone ring, a dioxolane ring, a dioxane ring, a thietane ring, an octahydroindole ring, an indoline ring, and an azepane ring.

[0081]

"Peptide chain" herein refers to a peptide chain in which 1, 2, 3, 4, or more natural amino acids and/or non-natural amino acids are connected by an amide bond and/or an ester bond. The peptide chain is preferably a peptide chain comprising 1 to 4 amino acid residues, and more preferably a peptide chain consisting of 1 to 4 amino acid residues.

[0082]

"Optionally substituted" herein means that a group may be substituted with any substituent.

[0083]

"Optionally protected" herein means that a group may be protected with any protecting group.

[0084]

"One or more" herein means one or two or more. When "one or more" is used in a context relating to the substituent of a group, the phrase means a number encompassing one to the maximum number of substituents permitted by that group. Specific examples of "one or more" include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and/or a greater number.

[0085]

The wavy line in the structural formulae herein can mean that any stereochemistry is permitted. For example, when the asymmetric center is provided with a wavy line, the stereochemistry of the asymmetric center may be in the S configuration or in the R configuration. When a double bond is provided with a wavy line, the stereochemistry of the double bond may be in the E configuration or in the Z configuration.

[0086]

As used herein, a symbol represented by "PPn^{1}n^{2}n^{3}n^4, where n^1, n^2, n^3 and n^4 each independently represent an integer of 0 to 9", for example, PP1574 and PP1640, represents the number of a compound.

[0087]

The compound of the present invention can be a salt thereof, and preferably a chemically or pharmaceutically acceptable salt thereof. Also, the compound of the present invention or a salt thereof can be a solvate thereof, and preferably a chemically or pharmaceutically acceptable solvate thereof. Examples of salts of the compound of the present invention include hydrochloride; hydrobromide; hydroiodide; phosphate; phosphonate; sulfate; sulfonates such as methanesulfonate and p-toluenesulfonate; carboxylates such as acetate, citrate, malate, tartrate, succinate, and salicylate; alkali metal salts such as a sodium salt and a potassium

salt; alkaline earth metal salts such as a magnesium salt and a calcium salt; and ammonium salts such as an ammonium salt, an alkylammonium salt, a dialkylammonium salt, a trialkylammonium salt, and a tetraalkylammonium salt. These salts are produced by, for example, bringing the compound into contact with an acid or a base usable in the production of pharmaceutical products. In the present invention, a solvate of a compound refers to one molecular group formed by the compound together with a solvent, and is called a hydrate when the solvent is water. The solvate of the compound of the present invention is preferably a hydrate, and specific examples of such hydrates include mono- to deca-hydrates, preferably mono- to penta-hydrates, and more preferably mono- to tri-hydrates. The solvate of the compound of the present invention includes not only a solvate formed of a single solvent such as water, alcohol (e.g., methanol, ethanol, 1-propanol, or 2-propanol), or dimethylformamide, but also a solvate formed of a plurality of solvents.

[0088]

The term "amino acid" as used herein includes natural and unnatural amino acids. The term "natural amino acid" as used herein refers to Gly, Ala, Ser, Thr, Val, Leu, Ile, Phe, Tyr, Trp, His, Glu, Asp, Gln, Asn, Cys, Met, Lys, Arg, or Pro. Examples of the unnatural amino acid include, but are not particularly limited to, β-amino acids, □-amino acids, D-amino acids, N-substituted amino acids, α, α-disubstituted amino acids, amino acids having side chains that are different from those of natural amino acids, and hydroxycarboxylic acids. Amino acids herein may have any conformation. There is no particular limitation on the selection of amino acid side chain, but in addition to a hydrogen atom, it can be freely selected from, for example, an alkyl group, an alkenyl group, an alkynyl group, an aryl group, a heteroaryl group, an aralkyl group, and a cycloalkyl group. One or two non-adjacent methylene groups in such a group are optionally substituted with an oxygen atom, a carbonyl group (-CO-), or a sulfonyl group (-SO_2-). Each group may have a substituent, and there are no limitations on the substituent. For example, one or more substituents may be freely and independently selected from any substituents including a halogen atom, an O atom, an S atom, an N atom, a B atom, an Si atom, or a P atom. Examples include an optionally substituted alkyl group, alkenyl group, alkynyl group, aryl group, heteroaryl group, aralkyl group, and cycloalkyl group. In a non-limiting embodiment, amino acids herein may be compounds having a carboxy group and an amino group in the same molecule (even in this case, imino acids such as proline and hydroxyproline are also included in amino acids).

[0089]

The main chain amino group of an amino acid may be unsubstituted (an NH_2 group) or substituted (i.e., an -NHR group, where R represents alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, or cycloalkyl which may have a substituent, one or two non-adjacent methylene groups

in such a group may be substituted with an oxygen atom, a carbonyl group (-CO-), or a sulfonyl group (-SO_2-), and the carbon chain bonded to the N atom and the carbon atom at the position α may form a ring, as in proline). The R substituent is selected as the substituent in the aforementioned amino acid side chain is selected. When the main chain amino group is substituted, the R is included in the "amino acid side chain" as used herein. Such amino acids in which the main chain amino group is substituted are herein called "N-substituted amino acids." Preferred examples of the "N-substituted amino acids" as used herein include, but are not limited to, N-alkylamino acids, N-C_1-C_6 alkylamino acids, N-C_1-C_4 alkylamino acids, and N-methylamino acids.

[0090]

"Amino acids" as used herein which constitute a peptide compound include all isotopes corresponding to each amino acid. The isotope of the “amino acid” refers to one having at least one atom replaced with an atom of the same atomic number (number of protons) and different mass number (total number of protons and neutrons). Examples of isotopes contained in the "amino acid" constituting the peptide compounds of the present invention include a hydrogen atom, a carbon atom, a nitrogen atom, an oxygen atom, a phosphorus atom, a sulfur atom, a fluorine atom, and a chlorine atom, which respectively include ^{2}H and ^{3}H; ^{13}C and ^{14}C; ^{15}N; ^{17}O and ^{18}O; ^{31}P and ^{32}P; ^{35}S; ^{18}F; and ^{36}Cl.

[0091]

Substituents containing a halogen atom as used herein include include a halogen-substituted alkyl group, cycloalkyl group, alkenyl group, alkynyl group, aryl group, heteroaryl group, or aralkyl group. More specific examples include fluoroalkyl, difluoroalkyl, and trifluoroalkyl.

[0092]

Substituents containing an O atom include groups such as hydroxy (-OH), oxy (-OR), carbonyl (-C(=O)-R), carboxy (-CO_2H), oxycarbonyl (-C(=O)-OR), carbonyloxy (-O-C(=O)-R), thiocarbonyl (-C(=O)-SR), carbonylthio (-S-C(=O)-R), aminocarbonyl (-C(=O)-NHR), carbonylamino (-NH-C(=O)-R), oxycarbonylamino (-NH-C(=O)-OR), sulfonylamino (-NH-SO_2-R), aminosulfonyl (-SO_2-NHR), sulfamoylamino (-NH-SO_2-NHR), thiocarboxy (-C(=O)-SH), and carboxycarbonyl (-C(=O)-CO_2H).

[0093]

Examples of oxy (-OR) include alkoxy, cycloalkoxy, alkenyloxy, alkynyloxy, aryloxy, heteroaryloxy, and aralkyloxy. Alkoxy is preferably C_1-C_4 alkoxy or C_1-C_2 alkoxy, and particularly preferably methoxy or ethoxy.

[0094]

Examples of carbonyl (-C(=O)-R) include formyl (-C(=O)-H), alkylcarbonyl, cycloalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, arylcarbonyl, heteroarylcarbonyl, and aralkylcarbonyl.

[0095]

Examples of oxycarbonyl (-C(=O)-OR) include alkyloxycarbonyl, cycloalkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, and aralkyloxycarbonyl.

[0096]

Examples of carbonyloxy (-O-C(=O)-R) include alkylcarbonyloxy, cycloalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, and aralkylcarbonyloxy.

[0097]

Examples of thiocarbonyl (-C(=O)-SR) include alkylthiocarbonyl, cycloalkylthiocarbonyl, alkenylthiocarbonyl, alkynylthiocarbonyl, arylthiocarbonyl, heteroarylthiocarbonyl, and aralkylthiocarbonyl.

[0098]

Examples of carbonylthio (-S-C(=O)-R) include alkylcarbonylthio, cycloalkylcarbonylthio, alkenylcarbonylthio, alkynylcarbonylthio, arylcarbonylthio, heteroarylcarbonylthio, and aralkylcarbonylthio.

[0099]

Examples of aminocarbonyl (-C(=O)-NHR) include alkylaminocarbonyl (such as C_1-C_6 or C_1-C_4 alkylaminocarbonyl and, in particular, ethylaminocarbonyl and methylaminocarbonyl), cycloalkylaminocarbonyl, alkenylaminocarbonyl, alkynylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, and aralkylaminocarbonyl. In addition, examples further include compounds obtained by replacing the H atom bonded to the N atom in -C(=O)-NHR with alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl.

[0100]

Examples of carbonylamino (-NH-C(=O)-R) include alkylcarbonylamino, cycloalkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, and aralkylcarbonylamino. In addition, examples further include compounds obtained by replacing the H atom bonded to the N atom in -NH-C(=O)-R with alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl.

[0101]

Examples of oxycarbonylamino (-NH-C(=O)-OR) include alkoxycarbonylamino, cycloalkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, and aralkyloxycarbonylamino. In

addition, examples further include compounds obtained by replacing the H atom bonded to the N atom in -NH-C(=O)-OR with alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl.

[0102]

Examples of sulfonylamino (-NH-SO_2-R) include alkylsulfonylamino, cycloalkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, and aralkylsulfonylamino. In addition, examples further include compounds obtained by replacing the H atom bonded to the N atom in -NH-SO_2-R with alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl.

[0103]

Examples of aminosulfonyl (-SO_2-NHR) include alkylaminosulfonyl, cycloalkylaminosulfonyl, alkenylaminosulfonyl, alkynylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, and aralkylaminosulfonyl. In addition, examples further include compounds obtained by replacing the H atom bonded to the N atom in -SO_2-NHR with alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl.

[0104]

Examples of sulfamoylamino (-NH-SO_2-NHR) include alkylsulfamoylamino, cycloalkylsulfamoylamino, alkenylsulfamoylamino, alkynylsulfamoylamino, arylsulfamoylamino, heteroarylsulfamoylamino, and aralkylsulfamoylamino. Moreover, two H atoms bonded to the N atoms in -NH-SO_2-NHR may be replaced with substituents independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and aralkyl, and these two substituents may form a ring.

[0105]

Substituents containing an S atom include groups such as thiol (-SH), thio (-S-R), sulfinyl (-S(=O)-R), sulfonyl (-SO_2-R), and sulfo (-SO_3H).

[0106]

Examples of thio (-S-R) are selected from alkylthio, cycloalkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, aralkylthio, and the like.

[0107]

Examples of sulfonyl (-SO_2-R) include alkylsulfonyl, cycloalkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and aralkylsulfonyl.

[0108]

Substituents containing an N atom include groups such as azide (-N_3, also referred to as an "azido group"), cyano (-CN), primary amino (-NH_2), secondary amino (-NH-R; also referred to as mono-substituted amino), tertiary amino (-NR(R'); also referred to as di-substituted amino), amidino (-C(=NH)-NH_2), substituted amidino (-C(=NR)-NR'R"), guanidino (-NH-

C(=NH)-NH_2), substituted guanidino (-NR-C(=NR'")-NR'R"), aminocarbonylamino (-NR-CO-NR'R"), pyridyl, piperidino, morpholino, and azetidinyl.

[0109]

Examples of secondary amino (-NH-R; mono-substituted amino) include alkylamino, cycloalkylamino, alkenylamino, alkynylamino, arylamino, heteroarylamino, and aralkylamino.

[0110]

Examples of tertiary amino (-NR(R'); di-substituted amino) include amino groups that have any two substituents each independently selected from alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and aralkyl, such as alkyl(aralkyl)amino, and these two substituents may form a ring. Specific examples include dialkylamino, in particular, C_1-C_6 dialkylamino, C_1-C_4 dialkylamino, dimethylamino, and diethylamino. The "C_p-C_q dialkylamino group" herein refers to an amino group substituted with two C_p-C_q alkyl groups, and the C_p-C_q alkyl groups may be the same or different.

[0111]

Examples of substituted amidino (-C(=NR)-NR'R") include groups in which three substituents R, R', and R" on the N atoms are each independently selected from alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and aralkyl, such as alkyl(aralkyl)(aryl)amidino.

[0112]

Examples of substituted guanidino (-NR-C(=NR'")-NR'R") include groups in which R, R', R", and R'" are each independently selected from alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and aralkyl, and groups in which these substituents form a ring.

[0113]

Examples of aminocarbonylamino (-NR-CO-NR'R") include groups in which R, R', and R" are each independently selected from a hydrogen atom, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and aralkyl, or groups in which these substituents form a ring.

[0114]

Herein, a “peptide residue” or an "amino acid residue" constituting the peptide compound may be simply referred to as a “peptide” or an "amino acid", respectively.

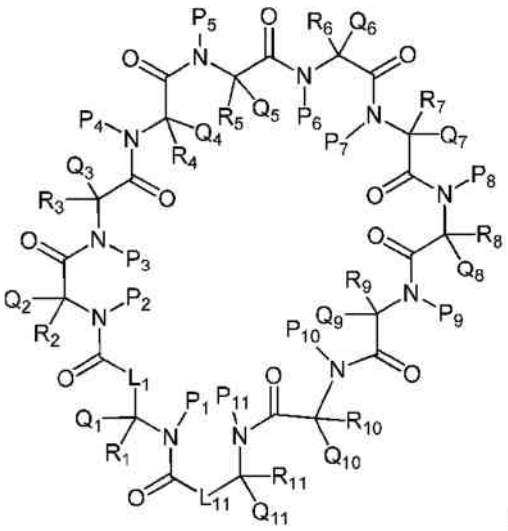
[0115]

In the present invention, the meaning of the term "and/or" includes any combination attained by suitably combining "and" and "or". Specifically, for example, "A, B, and/or C" includes the following 7 variations:

(i) A, (ii) B, (iii) C, (iv) A and B, (v) A and C, (vi) B and C, (vii) A, B, and C.

[0116]

In an embodiment, the present invention relates to a cyclic compound represented by formula (1) below or a salt thereof, or a solvate thereof.



(1)

In the cyclic compound of formula (1), the ring is composed of 11 amino acid residues. Herein, the amino acid residue having P_1, Q_1, R_1, and L_1 in the formula may be referred to as core 1, the amino acid residue having P_2, Q_2, and R_2 as core 2, the amino acid residue having P_3, Q_3, and R_3 as core 3, the amino acid residue having P_4, Q_4, and R_4 as core 4, the amino acid residue having P_5, Q_5, and R_5 as core 5, the amino acid residue having P_6, Q_6, and R_6 as core 6, the amino acid residue having P_7, Q_7, and R_7 as core 7, the amino acid residue having P_8, Q_8, and R_8 as core 8, the amino acid residue having P_9, Q_9, and R_9 as core 9, the amino acid residue having P_{10}, Q_{10}, and R_{10} as core 10, and the amino acid residue having P_{11}, Q_{11}, R_{11}, and L_{11} as core 11.

[0117]

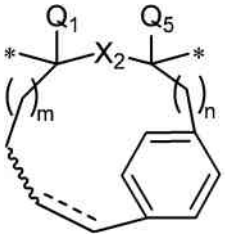
In an embodiment, in formula (1), L_1 is a single bond.

[0118]

In an embodiment, in formula (1), R_1 is a C_1 to C_7 alkyl, and preferably, a 2-methylpropyl or a n-propyl.

[0119]

In an embodiment, R_1 joins together with R_5 to form a divalent group, wherein a partial structure: *-CR_1Q_1-L_1-CO-NP_2-CR_2Q_2-CO-NP_3-CR_3Q_3-CO-NP_4-CR_4Q_4-CO-NP_5-CR_5Q_5-* in the cyclic compound represented by formula (1) is represented by the following formula:



,

wherein:

X_2 is -L_1-CO-NP_2-CR_2Q_2-CO-NP_3-CR_3Q_3-CO-NP_4-CR_4Q_4-CO-NP_5-,

---

is a single bond or a double bond,

n is 0, 1 or 2,

m is 0, 1, 2, 3 or 4,

* represents an attachment point to an adjacent atom;

wherein

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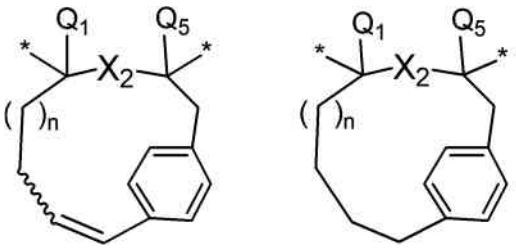
may take *E* or *Z* configuration, if

---

is a double bond.

[0120]

The formula is preferably a formula:



.

[0121]

In an embodiment, P_1 is a C_1 to C_6 alkyl, and preferably methyl.

[0122]

In an embodiment, Q_1 is a hydrogen atom.

[0123]

The amino acid residue of core 1 is, for example, MeLeu or MeNva except the case where a side chain (R_1) of core 1 and a side chain (R_5) of core 5 join together to form a divalent group.

If a side chain (R_1) of core 1 and a side chain (R_5) of core 5 join together to form a divalent group, the group at the position corresponding to R_1 of MeAhpe (2), MeAocte (2) or MeAhxe (2) and the group at the position corresponding to side chain (R_5) of core 5 can be linked by use of a method described, for example, in the "common process" later described.

[0124]

In an embodiment, in formula (1), R_2 is a C_1 to C_6 alkyl, and preferably 1-methylpropyl.

[0125]

In an embodiment, P_2 is a hydrogen atom.

[0126]

In an embodiment, Q_2 is a hydrogen atom.

[0127]

The amino acid residue of core 2 is, for example, Ile.
~~~

[0128]

In an embodiment, in formula (1), R_3 is a hydrogen atom.

[0129]

In an embodiment, R_3 joins together with a carbon atom to which P_3 and R_3 are attached and a nitrogen atom to which P_3 is attached, to form a 4 to 7-membered saturated heterocycle. The 4 to 7-membered saturated heterocycle is, for example, a pyrrolidine ring.

[0130]

In an embodiment, P_3 is a C_1 to C_6 alkyl or a C_3 to C_8 cycloalkyl, and preferably a methyl or a cyclopropyl.

[0131]

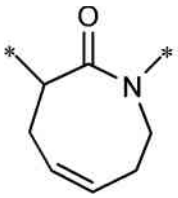
In an embodiment, Q_3 is a hydrogen atom.

[0132]

The amino acid residue of core 3 is, for example, MeGly, Pro or cPrGly.

[0133]

In an embodiment, R_4 joins together with P_5 to form a divalent group, wherein a partial structure: *-CR_4Q_4-CO-NP_5-* of a cyclic compound represented by formula (1) is expressed by the following formula:



.

[0134]

In an embodiment, P_4 is a C_1 to C_6 alkyl, and preferably methyl.

[0135]

In an embodiment, Q_4 is a hydrogen atom.

[0136]

If a side chain (R_4) of core 4 and N substituent (P_5) of core 5 join together to form a divalent group, preferably, a group at the position corresponding to R_4 of MeAlgly and a group at the position corresponding to N substituent (P_5) of core 5 can be linked by use of a method described, for example, in the "common process" later described.

[0137]

In an embodiment, in formula (1), R_5 is a benzyl optionally substituted with one or more groups independently selected from the group consisting of a C_1 to C_6 alkyl, a C_1 to C_6 haloalkyl, and a C_3 to C_8 cycloalkyl, and preferably, 4-cyclopropylbenzyl, 4-(trifluoromethyl)benzyl, 4-methylbenzyl or 4-ethylbenzyl.

[0138]

In an embodiment, in formula (1), R_5 joins together with R_1 to form a divalent group. The details of this group are the same as defined in the above.

[0139]

In an embodiment, P_5 joins together with R_4 to form a divalent group. The details of this group are the same as defined in the above.

[0140]

In an embodiment, Q_5 is a hydrogen atom.

[0141]

If a side chain (R_5) of core 5 and a side chain (R_1) of core 1 join together to form a divalent group, and a N substituent (P_5) of core 5 and side chain (R_4) of core 4 join together to form a divalent group, more specifically, R_5 of ButenylPhe (4-CH=CH2) and a group at the position corresponding to P_5, and a side chain (R_1) of core 1 and a group at the position corresponding to a side chain (R_4) of core 4, can be linked respectively, by use of a method described, for example, in the "common process" later described.

In the case where a side chain (R_5) of core 5 and a side chain (R_1) of core 1 do not form a divalent group, and a N substituent (P_5) of core 5 and a side chain (R_4) of core 4 form a divalent group, more specifically, a group at the position corresponding to P_5 of ButenylPhe (4-Et), ButenylPhe (4-cPr) or AllylPhe (4-CF3) and a group at the position corresponding to side chain (R_4) of core 4 can be linked by use of a method described, for example, in the "common process" later described.

[0142]

In an embodiment, in formula (1), R_6 is a hydrogen atom.

[0143]

In an embodiment, P_6 is a C_1 to C_6 alkyl, and preferably methyl.

[0144]

In an embodiment, Q_6 is a hydrogen atom.

[0145]

The amino acid residue of core 6 is, for example, MeGly.

[0146]

In an embodiment, in formula (1), phenethyl optionally substituted with one or more groups independently selected from the group consisting of halogen, a C_1 to C_6 haloalkyl and a C_1 to C_6 alkoxy, is preferably, 3,5-difluoro-4-(trifluoromethyl)phenethyl, 3,4-dichlorophenethyl or 3-methoxy-4-(trifluoromethyl)phenethyl.

[0147]

In an embodiment, P_7 is a hydrogen atom.

[0148]

In an embodiment, Q_7 is a hydrogen atom.

[0149]

The amino acid residue of core 7 is, for example, Hph(4-CF3-35-F2), Hph(34-Cl2) or Hph(4-CF3-3-OMe).

[0150]

In an embodiment, in formula (1), R_8 joins together with a carbon atom to which P_8 and R_8 are attached and a nitrogen atom to which P_8 is attached, to form a 4 to 7-membered saturated heterocycle. The 4 to 7-membered saturated heterocycle is optionally substituted with a C_1 to C_6 alkoxy, and preferably ethoxy or n-propoxy. The 4 to 7-membered saturated heterocycle is, for example, a pyrrolidine ring.

[0151]

In an embodiment, Q_8 is a hydrogen atom.

[0152]

The amino acid residue of core 8 is, for example, Hyp (Et) or Hyp (nPr).

[0153]

In an embodiment, in formula (1), R_9 joins together with Q_9 and a carbon atom to which R_9 and Q_9 are attached to form a 3 to 8-membered alicyclic ring. The 3 to 8-membered alicyclic ring is optionally substituted with one or more C_1 to C_6 alkyls, for example, two methyl groups. The 3 to 8-membered alicyclic ring is, for example, a cyclobutane ring or a cyclopentane ring.

[0154]

In an embodiment, P_9 is a hydrogen atom or a C_1 to C_6 alkyl, and preferably a hydrogen atom or a methyl.

[0155]

The amino acid residue of core 9 is, for example, cLeu, cVal, cVal (3-Me2) or MecVal.

[0156]

In an embodiment, in formula (1), R_{10} is a C_1 to C_6 alkyl or a C_3 to C_8 cycloalkyl, and preferably, a pentan-3-yl or cyclopentyl.

[0157]

In an embodiment, P_{10} is a C_1 to C_6 alkyl, and preferably methyl.

[0158]

In an embodiment, Q_{10} is a hydrogen atom.

[0159]

The amino acid residue of core 10 is, for example, MeGly (cPent) or MeNva (3-Et).

[0160]

In an embodiment, in formula (1), L_{11} is $-CH_2-$.

[0161]

In an embodiment, in formula (1), R_{11} is a di-C_1 to C_6 alkylaminocarbonyl or a 4 to 8-membered cyclic aminocarbonyl, and preferably, a dimethylaminocarbonyl, a N-ethyl-N-methylaminocarbonyl, a pyrrolidinylcarbonyl or a piperidinylcarbonyl.

[0162]

In an embodiment, P_{11} is a C_1 to C_6 alkyl, and preferably, a methyl.

[0163]

In an embodiment, Q_{11} is a hydrogen atom.

[0164]

In an embodiment, the compound of the present invention can be one or more compounds selected from the following:

PP1574: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-N-ethyl-27-isobutyl-N,4,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclopentane]-23-carboxamide,

PP1650: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-27-isobutyl-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP1827: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-N-ethyl-N,3,18,21,25,31,34-heptamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,

PP1830: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,

PP2093: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-N,N,3',3',4,19,22,26,35-nonamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2260: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-22-carboxamide,

PP2316: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,4,16,19,22,26,35-octamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2320: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,2,14,18,21,24,36-octamethyl-10-[(1S)-1-methylpropyl]-3,9,12,15,19,22,25,31,34,37,45-undecaoxo-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-17-carboxamide,

PP2328: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,4,16,19,22,26,35-octamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2574: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP2576: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP2583: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-19-cyclopentyl-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,34-heptamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP2687: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-2-[(4-ethylphenyl)methyl]-27-isobutyl-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2691: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-2-[(4-cyclopropylphenyl)methyl]-12-ethoxy-27-isobutyl-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,3',3',4,19,22,26,32,35-decamethyl-30-[(1S)-1-methylpropyl]-3,6,9,15,18,21,25,28,31,34,42-undecaoxo-spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-23-carboxamide,

PP2957: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,34-pentamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP3033: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone,

PP3034: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone,

PP3036: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP3037: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

PP3047: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47E)-7-[2-(3,4-dichlorophenyl)ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone,

PP3093: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-11-ethoxy-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(piperidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.9.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tripentaconta-37,43(52),44,46(51)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,53-undecone,

PP3094: (1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z)-19-cyclopentyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-11-propoxy-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.9.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tripentaconta-37,43(52),44,46(51)-tetraene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,53-undecone,

PP3095: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3096: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3097: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3098: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-

carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,
PP3099: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,
PP3100: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-(p-tolylmethyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,
PP3101: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-17-(pyrrolidine-1-carbonyl)-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,
PP3102: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-38-(p-tolylmethyl)-17-(pyrrolidine-1-carbonyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.0^{4,8}.0^{26,30}]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,
PP3103: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,
PP3104: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-

tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,
PP3105: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,
PP3106: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-12-ethoxy-8-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,
PP3110: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,
PP3111: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,
PP3112: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,
PP3113: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-32-cyclopropyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,35-hexamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.0^{10,14}]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3114: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3115: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-17-(piperidine-1-carbonyl)-13-propyl-38-(p-tolylmethyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3116: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-17-(pyrrolidine-1-carbonyl)-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3117: (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-32-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-28-ethoxy-2,14,18,21,24,36-hexamethyl-10-[(1S)-1-methylpropyl]-13-propyl-38-(p-tolylmethyl)-17-(pyrrolidine-1-carbonyl)spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-3,9,12,15,19,22,25,31,34,37,45-undecone,

PP3118: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3119: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-23-(piperidine-1-carbonyl)-27-propyl-2-(p-tolylmethyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3120: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-23-(pyrrolidine-1-carbonyl)-2-[[4-(trifluoromethyl)phenyl]methyl]spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

PP3121: (2S,8S,12R,14S,20S,23S,27S,30S,36S,38Z)-20-cyclopentyl-8-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-12-ethoxy-4,16,19,22,26,32,35-heptamethyl-30-[(1S)-1-methylpropyl]-27-propyl-2-(p-tolylmethyl)-23-(pyrrolidine-1-carbonyl)spiro[1,4,7,10,16,19,22,26,29,32,35-undecazatricyclo[34.5.1.$0^{10,14}$]dotetracont-38-ene-17,1'-cyclobutane]-3,6,9,15,18,21,25,28,31,34,42-undecone,

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-N-ethyl-N,3,18,21,25,31,34-heptamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

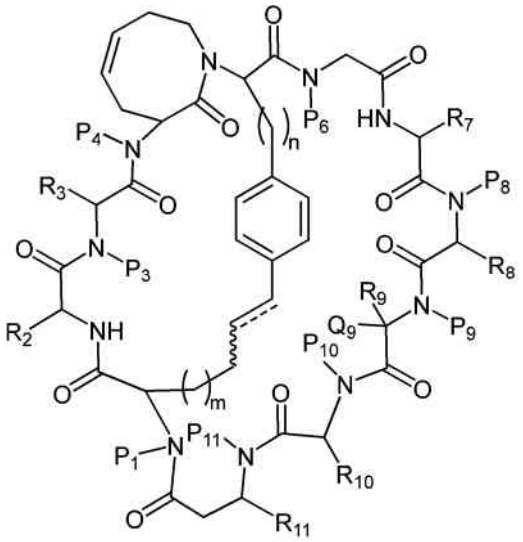
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,34-heptamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,34-pentamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, and
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-7-[2-(3,4-dichlorophenyl)ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.$2^{43,46}$.$1^{35,41}$.$0^{9,13}$]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone
or a salt thereof, or a solvate thereof. These compounds are included in the formula represented by the formula (1).

[0165]

In an embodiment, the compound of the present invention is preferably a compound represented by formula (2):



(2)

wherein

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n, m, P_1, R_2, R_3, P_3, P_4, P_6, R_7, R_8, P_8, R_9, P_9, Q_9, R_{10}, P_{10}, R_{11} and P_{11} are the same as defined in formula (1).

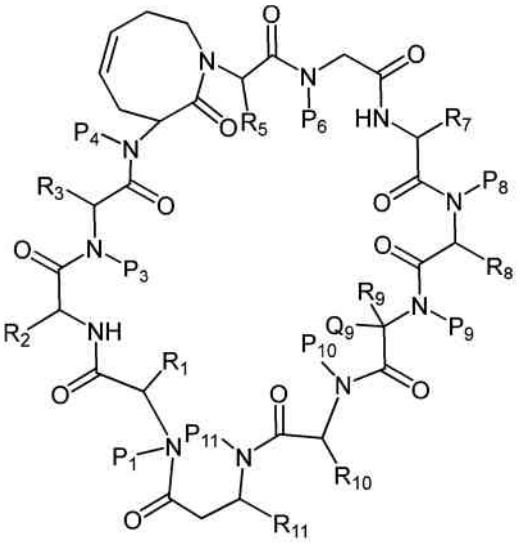
For example, compounds PP1827, PP1830, PP2260, PP2574, PP2576, PP2583, PP2957, PP3033, PP3034, PP3036, PP3037, PP3047, PP3093 and PP3094 and the following compounds can be included in the formula (2).

(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-N-ethyl-N,3,18,21,25,31,34-heptamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-

undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-11-ethoxy-N-ethyl-7-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,3,3',3',18,21,25,31,34-nonamethyl-29-[(1S)-1-methylpropyl]-2,5,8,14,17,20,24,27,30,33,55-undecaoxo-spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-22-carboxamide,
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,3',3',18,21,25,31,34-octamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-19-cyclopentyl-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-3,3',3',18,21,25,34-heptamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone,
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-31-cyclopropyl-7-[2-[3,5-difluoro-4-(trifluoromethyl)phenyl]ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,34-pentamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.10.2^{43,46}.1^{35,41}.0^{9,13}]tetrapentaconta-37,43(53),44,46(52),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,54-undecone, and
(1S,7S,11R,13S,19S,22S,26S,29S,35S,37Z,47Z)-7-[2-(3,4-dichlorophenyl)ethyl]-11-ethoxy-19-(1-ethylpropyl)-3,18,21,25,31,34-hexamethyl-29-[(1S)-1-methylpropyl]-22-(pyrrolidine-1-carbonyl)spiro[3,6,9,15,18,21,25,28,31,34,41-undecazapentacyclo[24.15.11.2^{43,46}.1^{35,41}.0^{9,13}]pentapentaconta-37,43(54),44,46(53),47-pentaene-16,1'-cyclobutane]-2,5,8,14,17,20,24,27,30,33,55-undecone.

[0166]

In an embodiment, the compound of the present invention is preferably a compound represented by formula (3):



(3)

In formula (3), R_1 is a C_1 to C_7 alkyl;

R_5 is a benzyl optionally substituted with one or more groups selected from the group consisting of a C_1 to C_6 alkyl, a C_1 to C_6 haloalkyl and a C_3 to C_8 cycloalkyl;

, n, m, P_1, R_2, R_3, P_3, P_4, P_6, R_7, R_8, P_8, R_9, P_9, Q_9, R_{10}, P_{10}, R_{11} and P_{11} are the same as defined in formula (1).

For example, compounds PP1574, PP1650, PP2093, PP2316, PP2320, PP2328, PP2687, PP2691, PP3095, PP3096, PP3097, PP3098, PP3099, PP3100, PP3101, PP3102, PP3103, PP3104, PP3105, PP3106, PP3110, PP3111, PP3112, PP3113, PP3114, PP3115, PP3116, PP3117, PP3118, PP3119, PP3120, and PP3121 can be included in formula (3).

[0167]

In an embodiment, the cyclic compound of the present invention has high selectivity for KRAS. In an embodiment, the cyclic compound of the present invention selectively inhibits KRAS. Without wishing to be bound by a particular theory, the divalent group that R_4 and P_5 together form interacts with His95 of KRAS, and thereby high selectivity for KRAS can be achieved. While it is known that there are three isotypes of RAS protein, i.e., HRAS, KRAS, and NRAS, His95 exists only in KRAS. Accordingly, a compound that specifically interacts with His95 of KRAS can inhibit KRAS with high selectivity over NRAS and/or HRAS.

[0168]

In the present invention, the origin of NRAS, HRAS, and KRAS is not particularly limited, and may encompass those derived from a variety of animals such as human, mouse, rat, rabbit, dog, cat, cattle, horse, pig, goat, rhesus monkey, cynomolgus monkey, chimpanzee, and chicken, but human-derived HRAS, KRAS, and NRAS are preferable. The amino acid sequence of human-derived NRAS is shown in SEQ ID NO: 1, the amino acid sequence of

human-derived HRAS is shown in SEQ ID NO: 2, and the amino acid sequence of human-derived KRAS is shown in SEQ ID NO: 3.

[0169]

In an embodiment, the cyclic compound of the present invention has KRAS inhibitory activity that is 3 times or more higher than NRAS inhibitory activity and/or HRAS inhibitory activity. In an embodiment, the cyclic compound of the present invention has KRAS binding activity that is 3 times or more higher than NRAS binding activity and/or HRAS binding activity.

[0170]

In an embodiment, the cyclic compound of the present invention has KRAS inhibitory activity that is 5 times, 7 times, 10 times, 15 times, or 20 times or more higher than NRAS inhibitory activity and/or HRAS inhibitory activity. In an embodiment, the cyclic compound of the present invention has KRAS binding activity that is 5 times, 7 times, 10 times, 15 times, or 20 times or more higher than NRAS binding activity and/or HRAS binding activity.

[0171]

In the present invention, the KRAS inhibitory activity relative to the NRAS inhibitory activity and/or the HRAS inhibitory activity can be determined from the ratio of the KRAS inhibitory activity of the cyclic compound of the present invention to the NRAS inhibitory activity and/or the HRAS inhibitory activity of the cyclic compound of the present invention. For example, when this ratio is defined as [IC_{50} value of cyclic compound of present invention with respect to NRAS and/or HRAS] divided by [IC_{50} value of cyclic compound of present invention with respect to KRAS], a larger value of this ratio means that the KRAS inhibitory activity is higher than the NRAS inhibitory activity and/or the HRAS inhibitory activity, or in other words, the KRAS selective inhibitory activity of the cyclic compound of the present invention is high. On the other hand, a smaller value of this ratio means that the KRAS inhibitory activity is lower than the NRAS inhibitory activity and/or the HRAS inhibitory activity, or in other words, the KRAS selective inhibitory activity of the cyclic compound of the present invention is low.

[0172]

In the present invention, the KRAS binding activity relative to the NRAS binding activity and/or the HRAS binding activity can be determined from the ratio of the KRAS binding activity of the cyclic compound of the present invention to the NRAS binding activity and/or the HRAS binding activity of the cyclic compound of the present invention. For example, when this ratio is defined as [KD value with respect to NRAS and HRAS] divided by [KD with respect to KRAS], a larger value means that the KRAS binding activity is higher than the NRAS binding activity and/or the HRAS binding activity, or in other words, the binding selectivity for KRAS

over NRAS and/or HRAS is high. On the other hand, a smaller value means that the KRAS binding activity is lower than the NRAS binding activity and/or the HRAS binding activity, or in other words, the binding selectivity for KRAS over NRAS and/or HRAS is low.

[0173]

In the present invention, the "interaction" means non-covalent interaction as exemplified by electrostatic interaction (including ionic bonding, hydrogen bonding, and dipole interaction), van der Waals interaction (including hydrophobic interaction), and the like. For example, it means CH-π interaction, NH-π interaction, S-π interaction, cation-π interaction, or halogen-π interaction. The interaction in the present invention may or may not be mediated by another molecule such as a water molecule, but is preferably not mediated by another molecule such as a water molecule.

[0174]

In the present invention, whether the 95th amino acid residue histidine (denoted as His95 or H95) in the human KRAS wild-type protein interacts with the cyclic compound can be determined by the interatomic distance of their non-hydrogen atoms (in the case of bonding via another molecule such as a water molecule, the interatomic distance between their non-hydrogen atoms taking no account of such another molecule). When the interatomic distanceis 5.1 angstroms (Å) or less, it can be determined that their non-hydrogen atoms interact with each other. In some embodiments, the interatomic distance between two interacting non-hydrogen atoms may be, for example, 5.1 Å or less, 4.8 Å or less, 4.5 Å or less, 4.3 Å or less, 4.2 Å or less, 4.1 Å or less, 4.0 Å or less, 3.9 Å or less, or 3.7 Å or less. Also, the interatomic distance may be 2.0 Å or more, 2.1 Å or more, or 2.5 Å or more.

[0175]

In the present invention, the interatomic distance can be measured, for example, through an analysis of the three-dimensional structure of a complex of the human KRAS wild-type protein and the cyclic compound of the present invention. Specifically, a crystal of the complex of the human KRAS wild-type protein and the cyclic compound of the present invention is prepared. The crystal is subjected to X-ray diffractometry to obtain X-ray diffraction intensity data of space groups, unit cells, and the like. The obtained X-ray diffraction intensity data is applied to a program for initial structure or refined structure determination well known to those skilled in the art, such as Coot (Emsley, P. et al., 2010), Phenix (Adams, P.D. et al., 2010), Phaser (J. Appl. Cryst. 40: 658-674 (2007)), Refmac5 (Acta Cryst. D67: 355-467 (2011)), and ARP/wARP (Cohen, S.X. et al., 2008), and thereby the three-dimensional structure of the complex of the human KRAS wild-type protein and the cyclic compound of the present invention can be determined.

[0176]

Once the three-dimensional structure of the complex of the human KRAS wild-type protein and the cyclic compound of the present invention is determined, the interatomic distance can be measured by a method well known to those skilled in the art. For example, the interatomic distance can be measured by allowing a software program for use in molecular modeling or molecular simulation, such as Discovery Studio 2020 Client, MOE (Molecular Operating Environment), or Maestro, to read the structural information of the complex of the cyclic compound of the present invention and the human KRAS wild-type protein, and using a function incorporated in the software program (such as the Distance Monitor function in the case of Discovery Studio 2020 Client). The details of conditions and criteria used by the software to determine the presence or absence of interactions can be viewed in a manual, specification, or the like appended to the software (e.g., in the case of Discovery Studio 2020 Client, the details of conditions and criteria for determining the presence or absence of interactions can be viewed by opening the web page of the specification from the Help button, selecting "Receptor-Ligand Interactions tools", then selecting "Theory-Receptor-Ligand Interactions", and further selecting "Non-bond Interactions").

[0177]

The crystal of the complex of the human KRAS wild-type protein and the cyclic compound of the present invention can also be obtained by a method well known to those skilled in the art. For example, a solution containing the cyclic compound of the present invention is mixed with a solution containing the human KRAS wild-type protein to obtain the complex of the human KRAS wild-type protein and the cyclic compound of the present invention. By subjecting the resulting complex to a crystallization method well known to those skilled in the art such as a vapor diffusion method, a batch method (a bulk batch method or a microbatch method), a dialysis method, or a counter-diffusion method, the crystal of the complex of the human KRAS wild-type protein and the cyclic compound of the present invention can be prepared. Known vapor diffusion methods are a sitting drop method, a hanging drop method, and a sandwich drop method.

[0178]

The human KRAS wild-type protein can also be obtained by a method known to those skilled in the art. For example, the human KRAS wild-type protein can be prepared by a recombinant polypeptide expressing method in which cells are used, but the method is not limited thereto. In one embodiment, a nucleic acid that encodes the human KRAS wild-type protein of the present invention is inserted into a suitable expression vector, the vector is introduced into a suitable cell, the transformed cell is cultured, and the expressed protein is isolated and purified. Such a protein can also be expressed as a fusion protein with another protein to facilitate purification. For example, it is possible to use a method of preparing a

fusion protein with a maltose binding protein using *Escherichia coli* as a host (vector pMAL series sold by New England BioLabs, USA), a method of preparing a fusion protein with glutathione-S-transferase (GST) (vector pGEX series sold by Amersham Pharmacia Biotech), a method of preparing a protein to which a histidine tag is added (pET series of Novagen), and a method of preparing a protein to which an HAT tag is added. The host cell is not particularly limited as long as it is a cell suitable for expressing a recombinant protein, and, in addition to *E. coli* mentioned above, for example, yeast, various animal and plant cells, insect cells, and the like can be used. Various methods known to those skilled in the art can be used to introduce a vector into a host cell. For example, for introduction into *Escherichia coli*, introduction methods involving calcium ions (Mandel, M., Higa, A. (1970) Journal of Molecular Biology, 53, 158-162, and Hanahan, D. (1983) Journal of Molecular Biology, 166, 557-580) can be used. The protein expressed in the host cell can be purified and recovered from the host cell or its cell culture or culture supernatant by a method known to those skilled in the art. When a protein is expressed as a fusion protein with the above maltose binding protein, HAT tag, or the like, affinity purification and gel filtration chromatography (size exclusion chromatography, SEC) purification can be easily performed. In affinity chromatography purification and SEC purification, AKTAxpress™ apparatus (GE Healthcare), NGC™ Chromatography System (Bio-Rad), BioLogic DuoFlow™ Chromatography System (Bio-Rad), or the like can be used.

[0179]

Interatomic energy can also be measured by a method well known to those skilled in the art. For example, interatomic energy can be easily calculated by allowing a molecular simulation program well known to those skilled in the art, such as Discovery Studio 2020 Client, MOE (Molecular Operating Environment), or Maestro, to read the three-dimensional structure of a substance to be measured, and, according to the instructions of the program, selecting a force field (such as Amber or CHARM) to be used in calculation and atoms for which energy calculation is performed. For example, in the case of Discovery Studio 2020 Client, interatomic energy can be calculated using the Calculate Interaction Energy function.

[0180]

In one non-limiting embodiment, in a complex of the cyclic compound of the present invention and the human KRAS wild-type protein, the cyclic compound of the present invention interacts with His95 in the human KRAS wild-type protein.

[0181]

Without wishing to be bound by a specific theory, it is considered that the formation of a complex by the cyclic compound of the present invention and the human KRAS wild-type protein in this manner is associated with contribution to the high binding activity of the cyclic

compound of the present invention to the human KRAS wild-type protein and, moreover, with the binding selectivity over HRAS and NRAS.

[0182]

The present invention also relates to a non-natural amino acid for use in the production of the cyclic compound of the present invention. In an embodiment, the non-natural amino acid of the present invention is an N-protected non-natural amino acid for use in the production of the peptide compound using a solid-phase synthesis method, and in another embodiment, the non-natural amino acid of the present invention is a non-natural amino acid having a free amino group obtained by removing the protecting group from the N-protected non-natural amino acid. Examples of the protecting group of the N-protected non-natural amino acid include an Fmoc group, a Boc group, a Cbz group, an Alloc group, a nosyl group, a dinitronosyl group, a t-Bu group, a trityl group, and a cumyl group. Of these, an Fmoc group, a Boc group, a Cbz group, and an Alloc group are preferable, and an Fmoc group is more preferable.

[0183]

In an embodiment, examples of the N-protected non-natural amino acid having an Fmoc group as a protecting group in the present invention include the following amino acids listed in Table 4 or salts thereof, or solvates thereof.

aa004: (2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]octanoic acid,

aa013: (2R)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-methylsulfanyl-propanoic acid,

aa019: (2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4,4-difluoro-butanoic acid,

aa023: (2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-(3-thienyl)propanoic acid,

aa028: (2S)-3-(3,4-dichlorophenyl)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid,

aa043: (2S)-5,5-dichloro-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]pentanoic acid,

aa056: (2R)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-2-methyl-propanoic acid,

aa098: (2S,3S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-3-methyl-azetidine-2-carboxylic acid,

aa099: (2S,3R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-3-methyl-azetidine-2-carboxylic acid,

aa100: (2S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-3,3-dimethyl-azetidine-2-carboxylic acid,

aa111: (2R)-3-allyloxy-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid,

aa136: (2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(propyl)amino]-3-[4-(trifluoromethyl)phenyl]propanoic acid,

aa174: (2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(propyl)amino]-3-(p-tolyl)propanoic acid,

aa210: (2S)-2-cyclopentyl-2-[ethyl(9H-fluoren-9-ylmethoxycarbonyl)amino]acetic acid,

aa220: (2S)-4-(4-chloro-3,5-difluoro-phenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid,

aa229: (2S)-4-(benzothiophen-5-yl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid,
aa233: (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-[3-methyl-4-(trifluoromethyl)phenyl]butanoic acid,
aa235: (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-[3-methoxy-4-(trifluoromethyl)phenyl]butanoic acid,
aa239: (2S,4S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-methyl-pyrrolidine-2-carboxylic acid,
aa244: (2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-5,5-difluoro-pentanoic acid,
aa246: (2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-propoxy-pyrrolidine-2-carboxylic acid,
aa250: (2R)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-propoxy-propanoic acid,
aa264: (2S,3R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-3-tetrahydropyran-2-yloxy-pyrrolidine-2-carboxylic acid,
aa265: (2S,3S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-3-tetrahydropyran-2-yloxy-pyrrolidine-2-carboxylic acid,
aa268: (1S,2S,5R)-3-(9H-fluoren-9-ylmethoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid,
aa279: (2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-tetrahydropyran-2-yloxy-pyrrolidine-2-carboxylic acid,
aa281: (2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-methoxy-pyrrolidine-2-carboxylic acid,
aa331: (2S)-3-ethyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]pentanoic acid,
aa389: (2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(propyl)amino]-4-methyl-pentanoic acid,
aa391: (2S,3R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-propoxy-butanoic acid,
aa397: (2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(propyl)amino]-3-isopentyloxy-propanoic acid,
aa398: (2S)-3-(cyclobutoxy)-2-[9H-fluoren-9-ylmethoxycarbonyl(propyl)amino]propanoic acid,
aa399: (2S)-4-(7-chloro-1-methyl-indol-5-yl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid,
aa400: (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-(2-fluoro-3-methyl-benzothiophen-5-yl)butanoic acid,
aa401: (2S)-4-(7-chlorobenzothiophen-5-yl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid,
aa402: (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-(1-methyl indol-6-yl)butanoic acid,
aa403: (2S)-4-(1,3-dimethyl indol-6-yl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid,
aa404: (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-(1,2,3-trimethyl indol-6-yl)butanoic acid,
aa405: (2S)-4-(2,3-dimethyl benzothiophen-5-yl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid,

aa406: (2S)-4-(3-chloro-4-ethyl-phenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid,
aa407: (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-[4-(methoxymethyl)-3,5-dimethyl-phenyl]butanoic acid,
aa408: (2S)-4-(4-chloro-3-methoxy-phenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid,
aa409: (2S)-4-[4-chloro-3-(trifluoromethyl)phenyl]-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid,
aa410: (2S)-4-[4-(difluoromethyl)-3,5-difluoro-phenyl]-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid,
aa411: (2S)-4-(4-chloro-3,5-dimethyl-phenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid,
aa414: (2S,4R)-4-(cyclopentoxy)-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-carboxylic acid,
aa415: (2S,4R)-4-(cyclobutoxy)-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-carboxylic acid,
aa423: (3S)-3-cyclobutyl-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid,
aa424: (3R)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]pentanoic acid,
aa425: (3S)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-methyl-pentanoic acid,
aa426: (3S)-3-cyclohexyl-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid, and
aa443: (2S)-2-[but-3-enyl(9H-fluoren-9-ylmethoxycarbonyl)amino]-3-(p-tolyl)propanoic acid.

[0184]

(General production method)

General production methods for the cyclic compound of the present invention, and the oligopeptide compound and the non-natural amino acid for use in the production of these compounds will be described below. Herein, the cyclic compound may be referred to as “cyclic peptide compound”. Herein, the “cyclic moiety” of a peptide compound means a cyclic portion formed by connection of two or more amino acid residues.

[0185]

<u>Chemical synthesis methods for peptide compounds</u>

Examples of chemical synthesis methods for the peptide compounds or the cyclic compounds herein include a liquid-phase synthesis method, a solid-phase synthesis method using Fmoc synthesis, Boc synthesis, or the like, and a combination thereof. In Fmoc synthesis, a basic unit is an amino acid in which a main-chain amino group is protected with an Fmoc group, and a side-chain functional group is protected as necessary with a protecting group that is not

cleaved by piperidine or such bases, such as a t-Bu group, a THP group, or a Trt group, and a main-chain carboxylic acid is not protected. The basic unit is not particularly limited as long as it is a combination having an Fmoc-protected amino group and a carboxyl group. For example, dipeptide or tripeptide may be a basic unit, and a cyclic structure may be formed between substituents on nitrogen atoms and/or side chains contained in the dipepetide or tripeptide. The basic unit disposed at the N terminus may be a unit other than the Fmoc amino acid. For example, it may be a Boc amino acid or a Tfa group or Ns group, or a carboxylic acid analog which does not have an amino group. The main-chain carboxyl group, or a side-chain carboxyl group of an amino acid that has a carboxyl group in a side chain and in which the main-chain carboxyl group is protected with a suitable protecting group, is supported on a solid phase by a chemical reaction with the functional group of a solid-phase carrier. Subsequently, the Fmoc group is deprotected by a base such as piperidine or DBU, and a newly produced amino group and a subsequently added, basic-unit protected amino acid having a carboxyl group are subjected to a condensation reaction to produce a peptide bond. In the condensation reaction, various combinations such as a combination of DIC and HOBt, a combination of DIC and HOAt, and a combination of HATU and DIPEA are possible as activating agents for the carboxyl group. The desired peptide sequence can be produced by repeating the Fmoc group deprotection and the subsequent peptide bond forming reaction. After the desired sequence is obtained, cleavage from the solid phase and deprotection of the optionally introduced protecting group of the side-chain functional group are conducted. Further, conformational conversion and cyclization of the peptide can be performed before cleaving from the solid phase. Cleaving from the solid phase and deprotection may be performed under the same conditions, e.g., in 90:10 TFA/H_2O, or deprotection may be performed under different conditions as necessary. Cleaving from the solid phase may be achieved using a weak acid such as 1% TFA in some cases, and a protecting group that can be deprotected with a Pd-containing catalyst or the like may be used to utilize the orthogonality of both chemical reactions. During or at the end of these steps, a step such as cyclization can also be performed. For example, a side-chain carboxylic acid and an N-terminal main-chain amino group can be condensed, and a side-chain amino group and a C-terminal main-chain carboxylic acid can be condensed. In addition, an olefin can be introduced into two or more sites of the side chains and/or the substituents of nitrogen atoms, and cyclized by metathesis reaction. Moreover, a double bond produced by cyclization can be reduced to a single bond. Also, a double bond produced by cyclization can be converted to a cyclopropane ring under conditions involving diiodomethane-diethylzinc or the like. These steps of cyclization, reduction, conversion to a cyclopropane ring, and the like may be carried out during the course of synthesizing a basic unit such as dipeptide or tripeptide. In the meantime, reaction orthogonality is required between the carboxylic acid on the C-terminal side and the

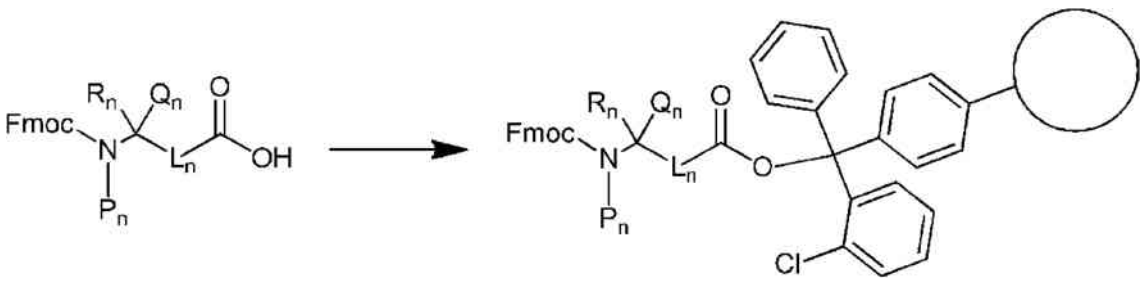
side-chain carboxylic acid to be cyclized, between the main-chain amino group or hydroxy group on the N-terminal side and the side-chain amino group to be cyclized, or between the olefins of side chains and/or substituents of nitrogen atoms and the olefins to be cyclized. As described above, the protecting group is selected in consideration of the orthogonality of the protecting group. In addition, by placing a chloroacetyl group at the N-terminus, cyclization can also be performed between the thiol groups of side chains of cysteine residues. The reaction product thus obtained can be purified by a reverse-phase column, a molecular sieve column, or the like. Details of these procedures are described in, for example, the Solid-Phase Synthesis Handbook published by Merck on May 1, 2002. Commercially available resins for solid phase synthesis are usable, and examples include CTC resin, Wang resin, and SASRIN resin.

[0186]

A general method for synthesizing an amino acid-supported resin for use in peptide synthesis by a peptide synthesizer will be described below.

[0187]

An Fmoc amino acid can be supported on a resin by the method described in WO2013/100132 or WO2018/225864. Specifically, for example, 2-chlorotrityl chloride resin and a solvent (e.g., dehydrated dichloromethane) are introduced into a filter-equipped reaction vessel to swell the resin. Next, the solvent and the resin are separated, and then a mixture of the resin, a C-terminal free Fmoc amino acid dissolved in a solvent (e.g., dehydrated dichloromethane), a solvent (e.g., dehydrated methanol), and a base (e.g., diisopropylethylamine) is added to the reaction vessel and mixed to support the Fmoc amino acid on the resin. After the resin and the reaction solution are separated, the resin is mixed with a mixture of one or more solvents and a base (e.g., a mixture of dehydrated dichloromethane, dehydrated methanol, and diisopropylethylamine) to wash the resin. After the resin is washed with a solvent (e.g., dichloromethane) multiple times as necessary, the resin and the reaction solution are separated. By drying the resulting resin under reduced pressure overnight, an Fmoc amino acid-supported resin can be obtained.



(wherein n represents an integer of 1 to 11; P_1 to P_{11}, Q_1 to Q_{11}, and R_1 to R_{11} mean P_1 to P_{11}, Q_1 to Q_{11}, and R_1 to R_{11} as defined herein, respectively; L_1 and L_{11} mean L_1 and L_{11} as described herein, respectively; L_2 to L_{10} are single bonds; and ○ (circle) means a resin portion.)

The above structure shows that in the Fmoc-amino acid, the 2-chlorotrityl group on the resin is bonded to the carboxylic acid of the Fmoc amino acid via an ester bond.

[0188]

In the production of the compound described herein, when the defined group undergoes undesired chemical conversion under the conditions of the performed method, the compound can be produced by means of, for example, protection and deprotection of a functional group. Selection and introduction/removal procedures of a protecting group can be performed according to, for example, the methods described in Greene's "Protective Groups in Organic Synthesis" (5th Ed., John Wiley & Sons, 2014), which may be suitably used depending on the reaction conditions. Further, the order of reaction steps such as introduction of a substituent can be changed as necessary. For example, the protecting group for an amino group is an Fmoc, Boc, Cbz, or Alloc group. These carbamate groups can be introduced by reacting an amino group with a carbamating agent in the presence of a basic catalyst. Examples of the carbamating agent include Boc_2O, BocOPh, FmocOSu, FmocCl, CbzCl, and AllocCl. Examples of the basic catalyst include lithium carbonate, sodium carbonate, sodium hydrogen carbonate, potassium carbonate, potassium hydrogen carbonate, cesium carbonate, cesium hydrogen carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, cesium hydroxide, sodium phosphate, potassium phosphate, N-methylmorpholine, triethylamine, diisopropylethylamine, and N,N-dimethylaminopyridine. A carbamate group which is a protecting group for an amino group can be removed under basic conditions, acidic conditions, hydrogenolysis reaction conditions, or the like.

[0189]

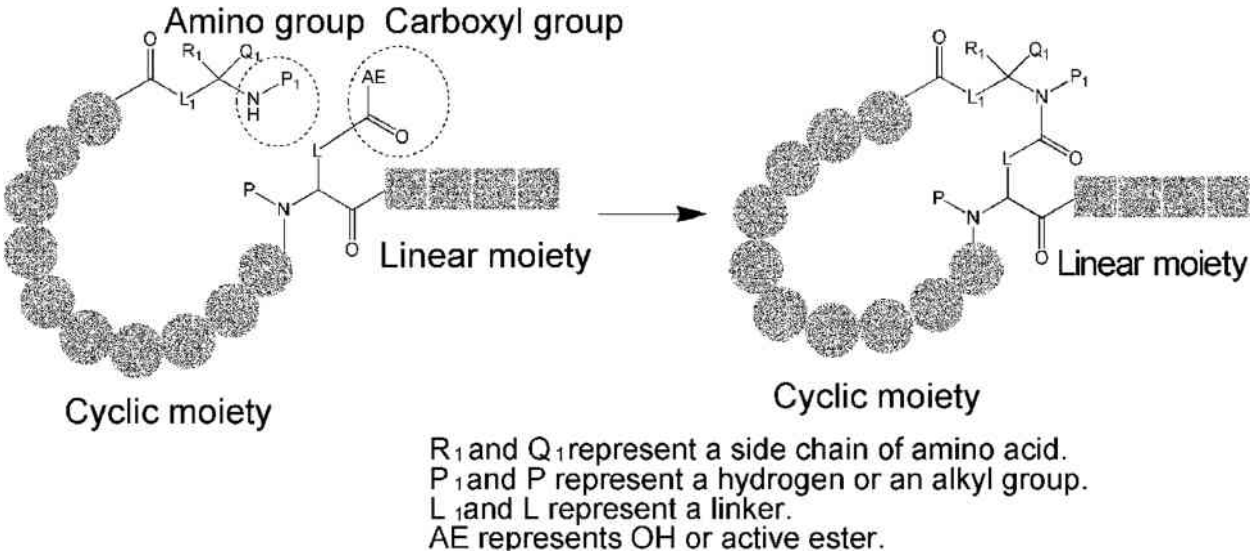
(Synthesis methods for cyclic compounds by cyclization of peptide compounds)

A method for transforming a linear peptide compound into a cyclic peptide compound can be performed by carrying out a bond forming reaction within the molecule according to, for example, the method described in Comprehensive Organic Transformations, A Guide to Functional Group Preparations, 3rd Edition by R.C. Larock, or March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 7th Edition by M.B. March. After the bond forming reaction, further, a functional group transforming reaction can also be performed. Examples of the bond forming reaction include a C(O)-N bond formed from carboxylic acid and amine; a C-O-C bond, a C(O)-O bond, and a C(S)-O bond using an oxygen atom; a C(O)-S bond, a C(S)-S bond, a C-S-S-C bond, a C-S-C bond, a C-S(O)-C bond, and a C-S(O_2)-C bond using a sulfur atom; and a C-N-C bond, a C=N-C bond, an N-C(O)-N bond, an N-C(S)N bond, and a C(S)-N bond using a nitrogen atom. Furthermore, examples include C-C bond forming reactions catalyzed by a transition metal, such as Suzuki reaction, Heck reaction, Sonogashira reaction, and metathesis reaction. Examples of the functional group transforming reaction

further performed after the bond forming reaction include an oxidation reaction and a reduction reaction. A specific example is a reaction for oxidizing a sulfur atom to transform it into a sulfoxide group or a sulfone group. Another example is a reduction reaction for reducing a triple bond or a double bond of carbon-carbon bonds to a double bond or a single bond. While a closed ring structure is formed by a peptide bond when two amino acids are bonded with the amino acid main chain, a covalent bond between two amino acids may be formed by bonding between side chains of two amino acids, bonding between a side chain and a main chain, or the like. A black circle or a black square below indicates an amino acid residue, and connected black circles or black squares represent a peptide chain connected by an amide bond. The number of amino acid residues constituting a peptide chain are not particularly limited, and the number of amino acid residues is not limited to the number of black circles or black squares exemplified below.

[0190]

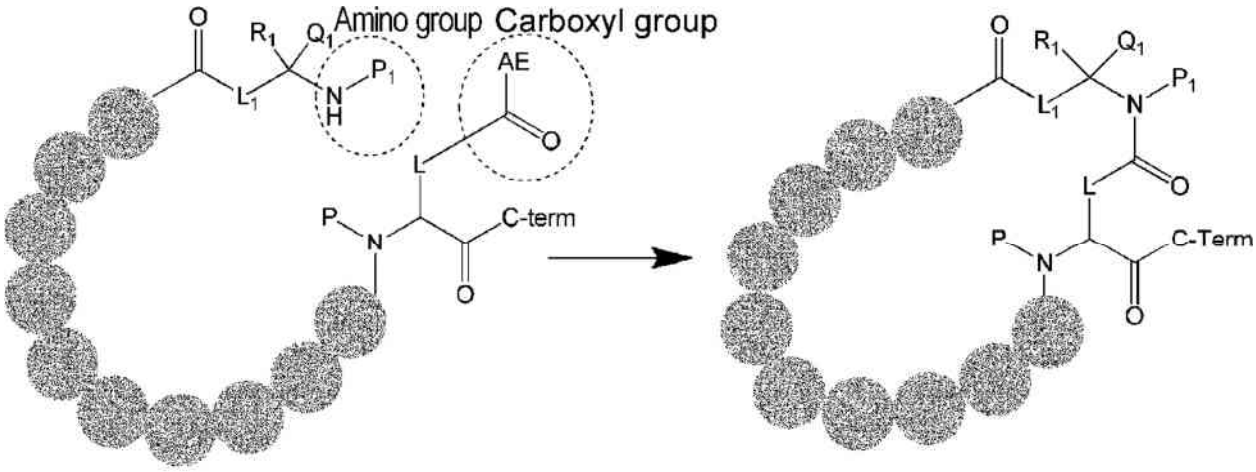
(General preparation method 1 for cyclic compounds)



Cyclic moieties of cyclic compounds having linear moieties can be cyclized by activating the N-terminal amino group and the C-terminal side chain carboxyl group (e.g., L = -CH_2- in the case of aspartic acid or its derivative, and L = -CH_2CH_2- in the case of glutamic acid or its derivative) with an activating reagent or converting them to active esters, and then condensing them in the molecule to form a C(O)-N bond.

[0191]

(General preparation method 2 for cyclic compounds)



R_1 and Q_1 represent a side chain of amino acid.
P_1 and P represent a hydrogen or an alkyl group.
L_1 and L represent a linker.
AE represents OH or active ester.
C-Term represents OH, an alkoxy group, or an optionally substituted amino group.

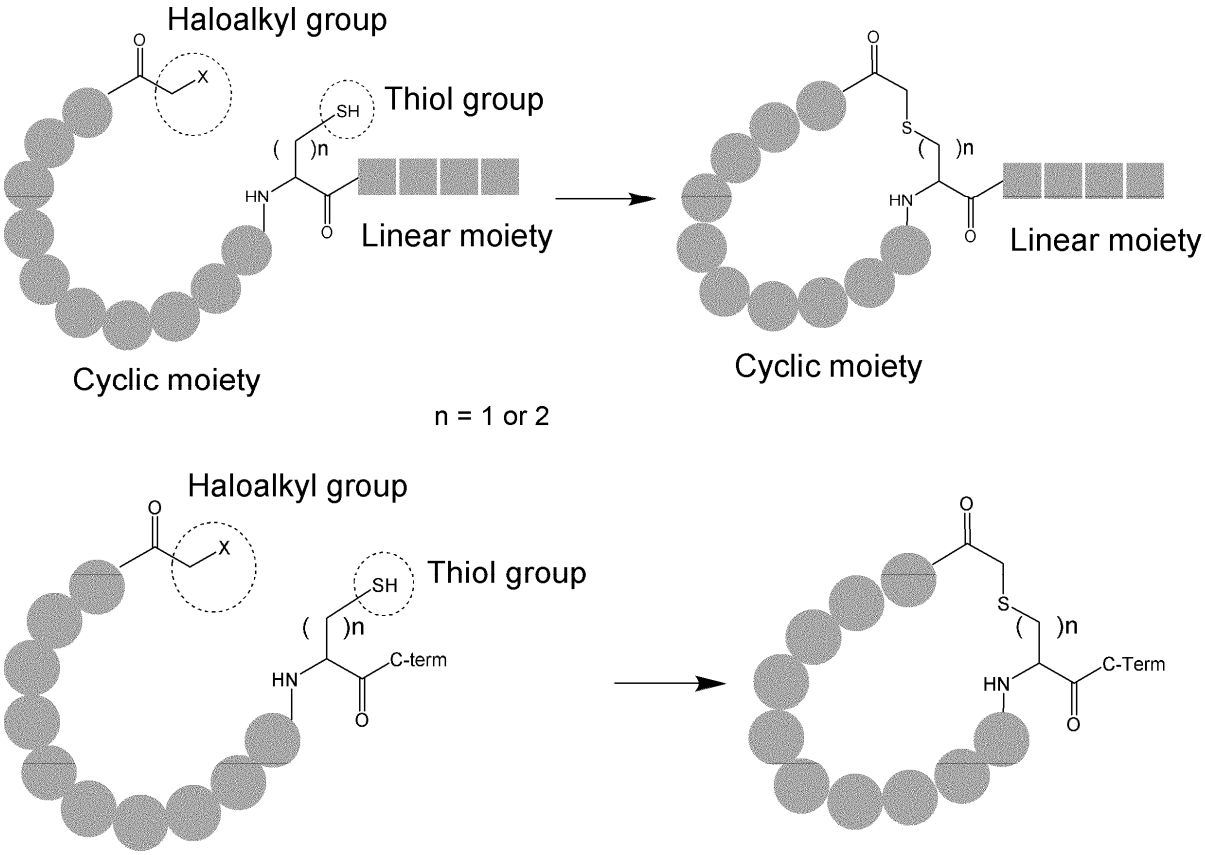
[0192]

Cyclic compounds described in "General preparation method 1 for cyclic compounds" in which the linear moiety is C-Term can be cyclized by activating the N-terminal amino group and the C-terminal side chain carboxyl group (e.g., L = $-CH_2-$ in the case of aspartic acid or its derivative, and L = $-CH_2CH_2-$ in the case of glutamic acid or its derivative) with an activating reagent or converting them to active esters, and then condensing them in the molecule to form a C(O)-N bond.

[0193]

(General preparation method 3 for cyclic compounds)

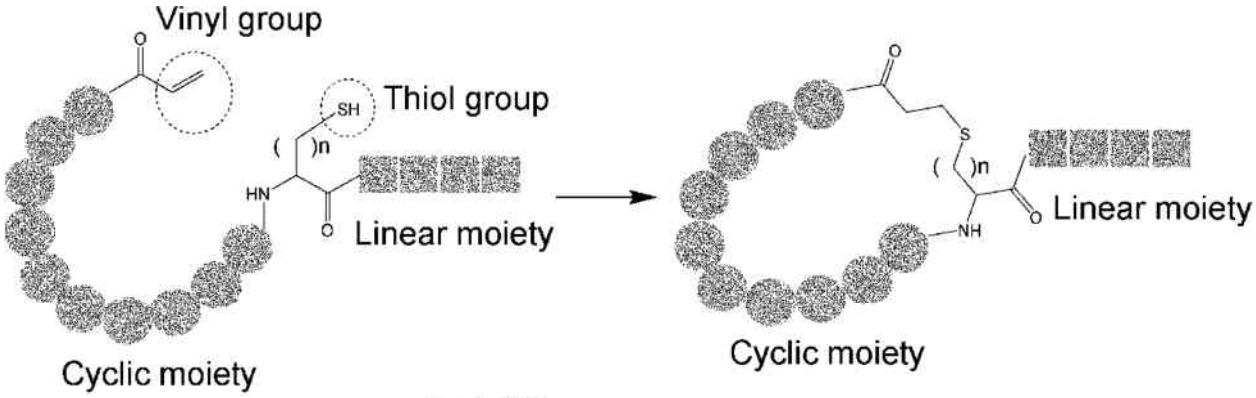
(Method of cyclizing with haloalkyl and SH groups)

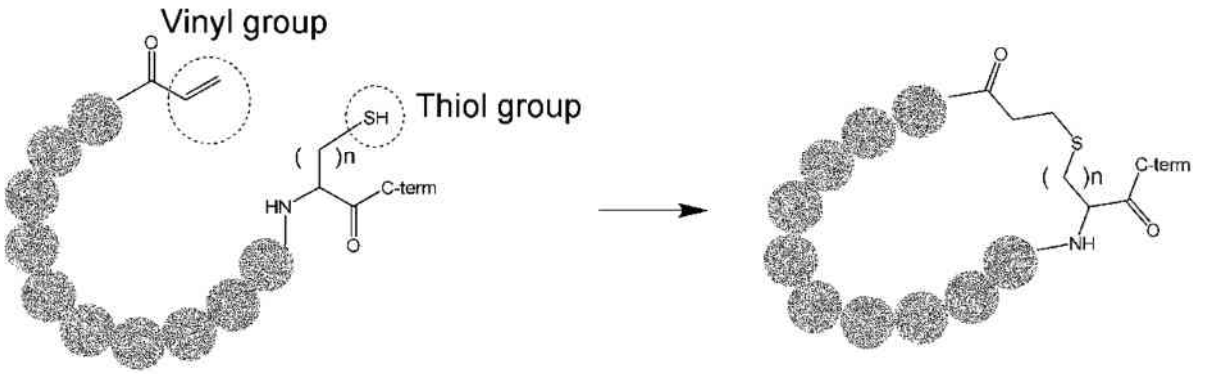


Cyclic moieties of cyclic compounds having linear moieties can be cyclized by reacting the haloalkyl group of an amino acid residue with the thiol group of an amino acid residue in the molecule to form a C-S-C bond. Cyclic compounds described in "General preparation method 1 for cyclic compounds" in which the linear moiety is C-Term can also be similarly cyclized by reacting the haloalkyl group of an amino acid residue with the thiol group of an amino acid residue in the molecule to form a C-S-C bond. Further, a C-S(O)-C or C-$S(O_2)$-C bond can also be formed by oxidizing and converting a sulfur atom to a sulfoxide or sulfone.

[0194]

(Method of cyclizing with vinyl and SH groups)



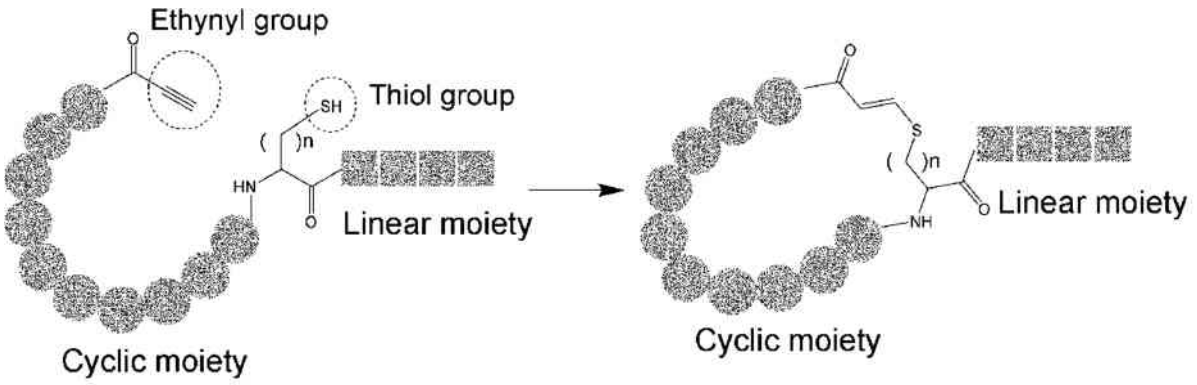


n = 1 or 2
C-Term represents OH, an alkoxy group, or an optionally substituted amino group.

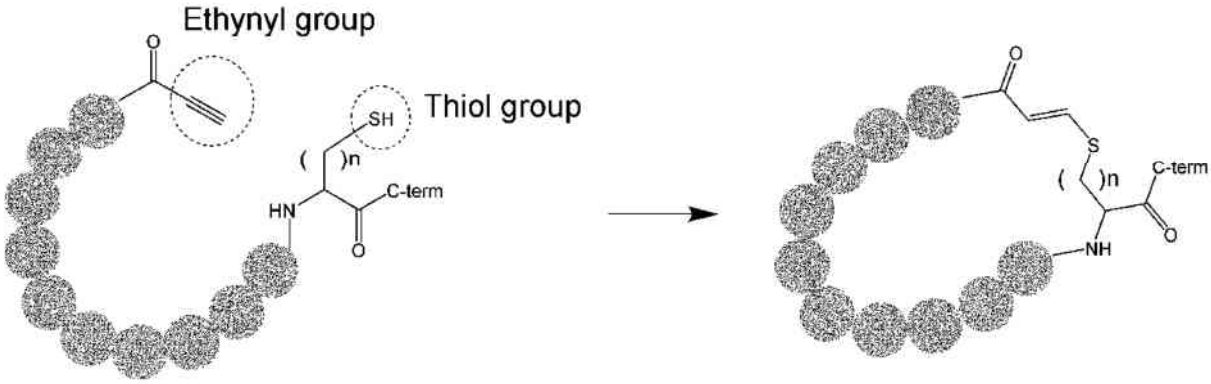
Cyclic moieties of cyclic compounds having linear moieties can be cyclized by reacting the vinyl group of an amino acid residue with the thiol group of an amino acid residue in the molecule to form a C-S-C bond. Cyclic compounds described in "General preparation method 1 for cyclic compounds" in which the linear moiety is C-Term can also be similarly cyclized by reacting the vinyl group of an amino acid residue with the thiol group of an amino acid residue in the molecule to form a C-S-C bond. Further, a C-S(O)-C or C-S(O_2)-C bond can also be formed by oxidizing and converting a sulfur atom to a sulfoxide or sulfone.

[0195]

(Method of cyclizing with ethynyl and SH groups)



n = 1 or 2

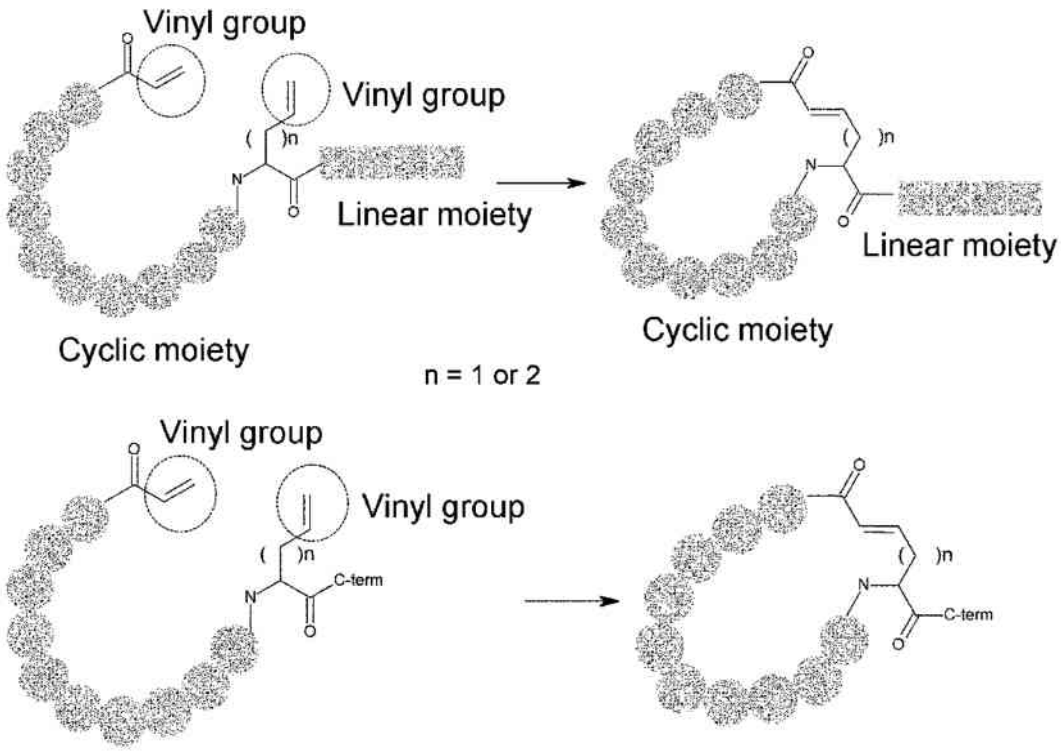


n = 1 or 2
C-Term represents OH, an alkoxy group, or an optionally substituted amino group.

Cyclic moieties of cyclic compounds having linear moieties can be cyclized by reacting the ethynyl group of an amino acid residue with the thiol group of an amino acid residue in the molecule to form a C-S-C bond. Cyclic compounds described in "General preparation method 1 for cyclic compounds" in which the linear moiety is C-Term can also be similarly cyclized by reacting the ethynyl group of an amino acid residue with the thiol group of an amino acid residue in the molecule to form a C-S-C bond. Further, a C-S(O)-C or C-S(O_2)-C bond can also be formed by oxidizing and converting a sulfur atom to a sulfoxide or sulfone. The double bond site can also be reduced and converted to a single bond.

[0196]

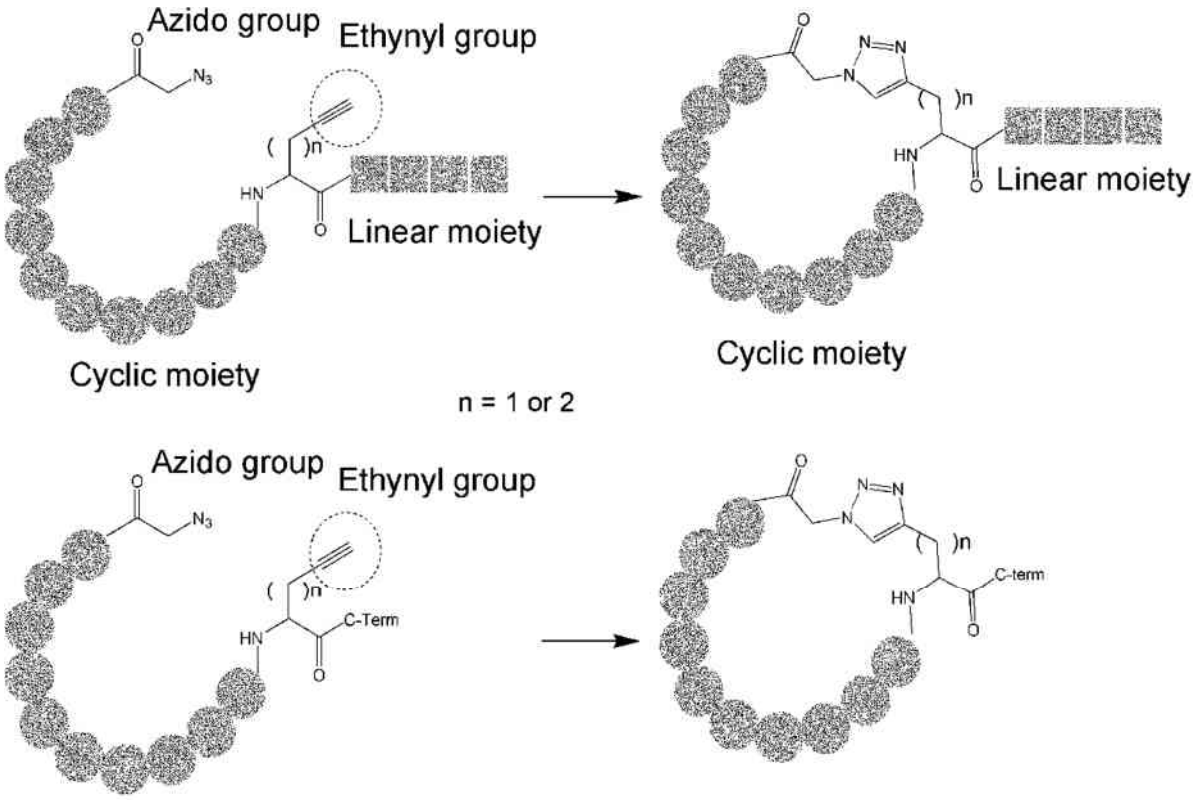
(Method of cyclizing with vinyl and vinyl groups)



Cyclic moieties of cyclic compounds having linear moieties can be cyclized by reacting different vinyl groups of amino acid residues with each other in the molecule to form a C-C bond. Cyclic compounds described in "General preparation method 1 for cyclic compounds" in which the linear moiety is C-Term can also be similarly cyclized by reacting different vinyl groups of amino acid residues with each other in the molecule to form a C-C bond.

[0197]

(Method of cyclizing by forming a triazole ring with azido and ethynyl groups)



n = 1 or 2
C-Term represents OH, an alkoxy group, or an optionally substituted amino group.

Cyclic moieties of cyclic compounds having linear moieties can be cyclized by reacting the azido group of an amino acid residue with the ethynyl group of an amino acid residue in the molecule to form a triazole ring. Cyclic compounds described in "General preparation method 1 for cyclic compounds" in which the linear moiety is C-Term can also be similarly cyclized by reacting the azido group of an amino acid residue with the ethynyl group of an amino acid residue in the molecule to form a triazole ring.

[0198]

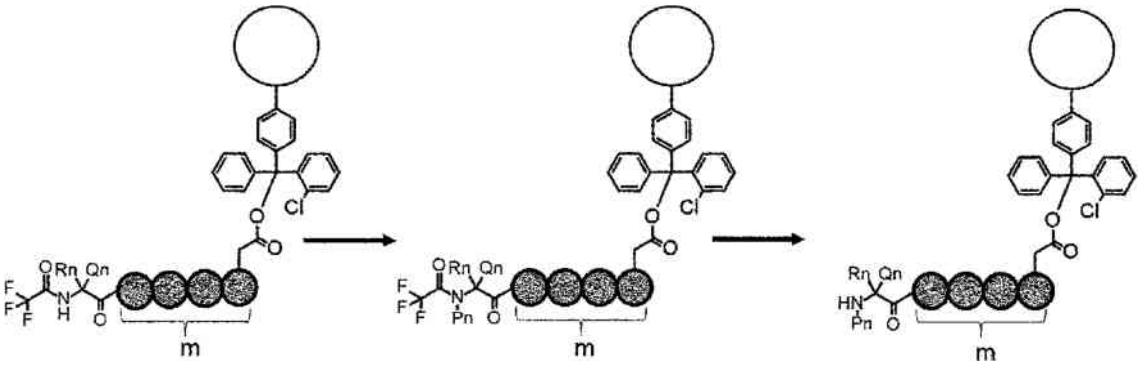
General preparation methods for peptide compounds by peptide modification are shown below. In the following schemes, P_n represents a substituent for a nitrogen atom, R_n and Q_n each represent an amino acid side chain, a black circle represents an amino acid residue, linked black circles represent a peptide chain linked by amide bonds, and m represents the number of amino acid residues and may be any integer of 1 or more.

[0199]

(Method of preparing peptides containing N-alkylamino acids)

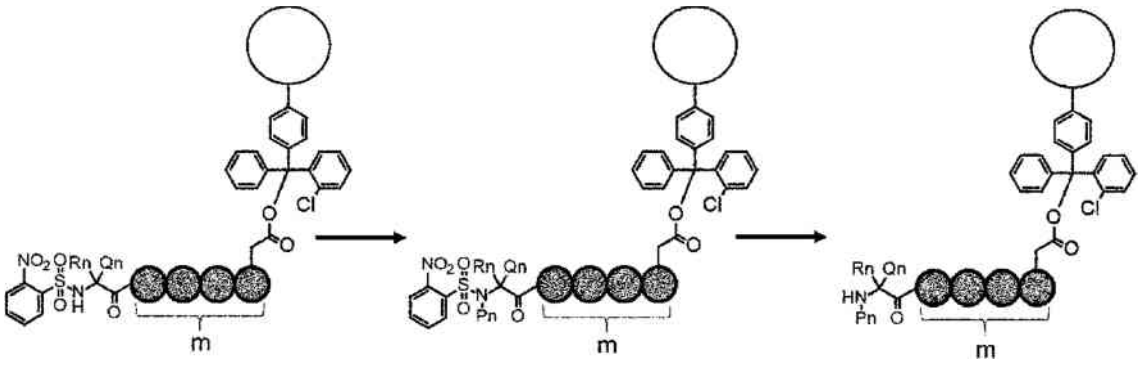
Peptides containing N-alkylamino acids can be synthesized according to the general peptide synthesis method described in the present Examples using an Fmoc-protected N-alkylamino acid as a raw material, or alternatively can be prepared by alkylating the N-terminal nitrogen on a resin as illustrated below. Specifically, the target peptides having an N-

alkylamino acid at the N-terminus can be prepared by reacting the nitrogen of the N-terminal Tfa amide (trifluoroacetamide) of a resin-loaded peptide with an alkyl halide under basic conditions, and then treating the peptide with a reducing agent by referring to Organic Letters, 2008, 10, 4815-4818 or the like. Further, cyclic compounds can be prepared by elongating, cleaving from the resin, cyclizing, deprotecting, and purifying the peptide according to the general peptide synthesis method described in the present Examples.



[0200]

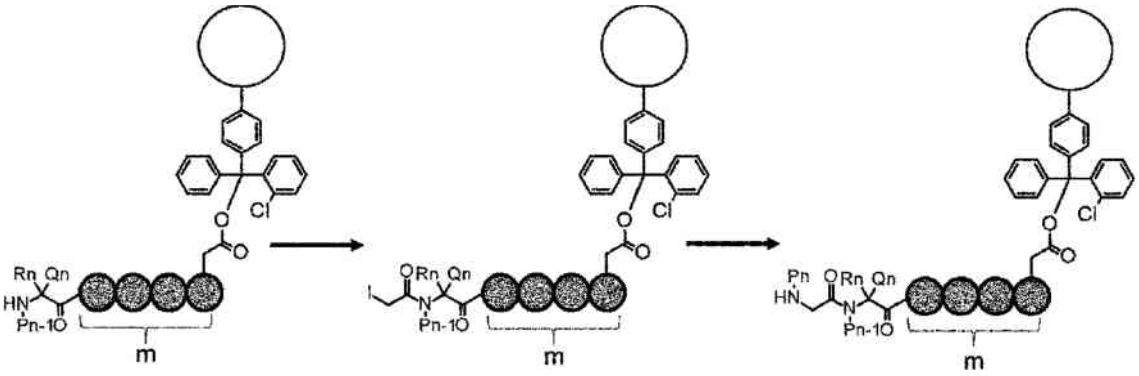
The method described in Nature Protocols, 2012, 7, 432-444 which is shown below can also be used as another method of introducing P_n onto the N-terminal nitrogen. Specifically, the target peptides having P_n at the N-terminus can be obtained by converting the N-terminal amine of a resin-loaded peptide to an Ns-substituted form, introducing P_n by Mitsunobu reaction, and then deprotecting the Ns group. Further, cyclic compounds can be prepared by elongating, cleaving from the resin, cyclizing, deprotecting, and purifying the peptide according to the general peptide synthesis method described in the present Examples.



[0201]

Peptides containing glycine with P_n introduced onto the nitrogen atom can be synthesized according to the general peptide synthesis method described in the present Examples using glycine with P_n introduced onto the Fmoc-protected nitrogen atom as a raw material, or alternatively can be prepared by substitution reaction between the N-terminal halogenated carbon and an amine as illustrated below. Specifically, the target peptides having N-terminal glycine

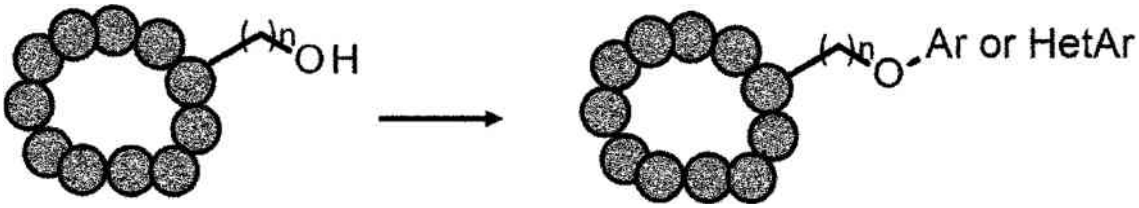
with P_n introduced onto the nitrogen atom can be obtained by reacting the N-terminal amine with iodoacetic acid and then reacting it with any primary amine by referring to Organic Letters, 2010, 12, 4928-4931 or the like. Further, cyclic compounds can be prepared by elongating, cleaving from the resin, cyclizing, deprotecting, and purifying the peptide according to the general peptide synthesis method described in the present Examples.



[0202]

(Method of preparing peptides containing an aryloxy or heteroaryloxy group on the side chain)

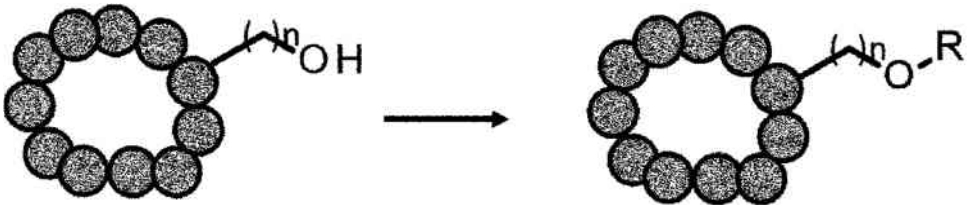
Peptides containing an aryloxy or heteroaryloxy group on a side chain can be prepared according to the general peptide synthesis method described in the present Examples using an Fmoc amino acid having the target aryloxy or heteroaryloxy group on the side chain as a raw material, or alternatively can be prepared using a peptide having an alcohol on the side chain as a precursor by referring to Organic Letters, 2014, 16, 4944-4947, Tetrahedron Letters, 2003, 44, 3863-3865, or the like, as illustrated below. Specifically, peptides having an aryloxy or heteroaryloxy group on the side chain can be prepared by reacting a peptide having an alcohol on the side chain with triarylboroxane-pyridine complex in the presence of copper(II) acetate.



[0203]

Peptides having an ether group excluding an aryloxy or heteroaryloxy group on a side chain can be prepared according to the general peptide synthesis method described in the present Examples using an Fmoc amino acid having the target ether group on the side chain as a raw material, or alternatively can be prepared using a peptide having an alcohol on the side chain as a precursor by referring to the method described in Journal of Medicinal Chemistry, 2011, 54, 4815-4830 or Journal of Medicinal Chemistry, 2014, 57, 159-170, as illustrated below. Specifically, the peptides having the target ether group on the side chain can be prepared by reacting a peptide having an alcohol with an alkyl halide in the presence of silver(I) oxide, or by

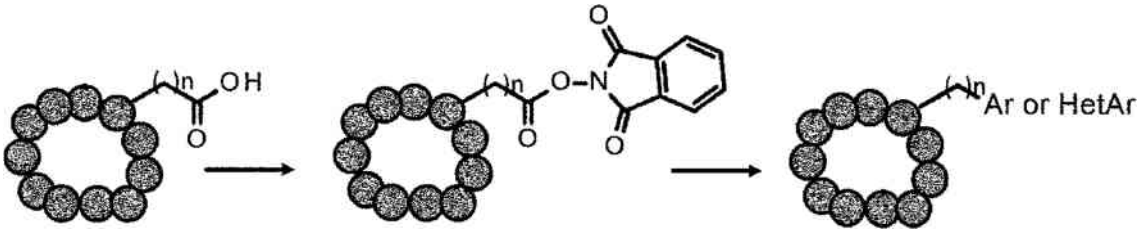
reacting a peptide having an alcohol with an alkyl halide using an aqueous sodium hydroxide solution as a base in the presence of a phase transfer catalyst such as a tetraalkylammonium salt.



[0204]

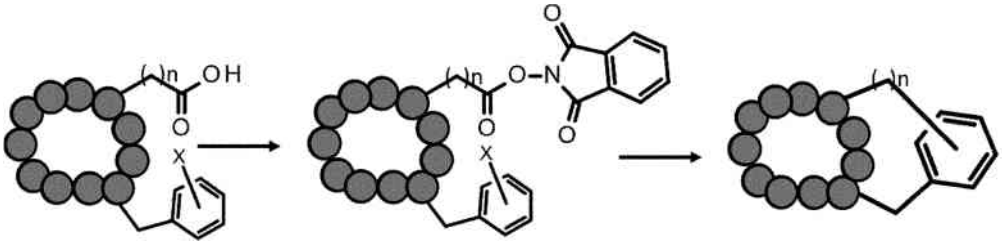
(Method of preparing peptides containing an aryl or heteroaryl group on the side chain)

Peptides having an aryl or heteroaryl group on a side chain can be prepared according to the general peptide synthesis method described in the present Examples using an Fmoc amino acid having the target aryl or heteroaryl group on the side chain as a raw material, or alternatively can be prepared using a peptide having a carboxylic acid on the side chain as a precursor by referring to the method described in J. Am. Chem. Soc., 2016, 138, 5016-5019 or the like, as illustrated below. Specifically, the peptides having the target aryl or heteroaryl group on the side chain can be prepared by activating a peptide having a carboxylic acid on the side chain with N-hydroxyphthalimide, and reacting it with any aryl halide or heteroaryl halide.



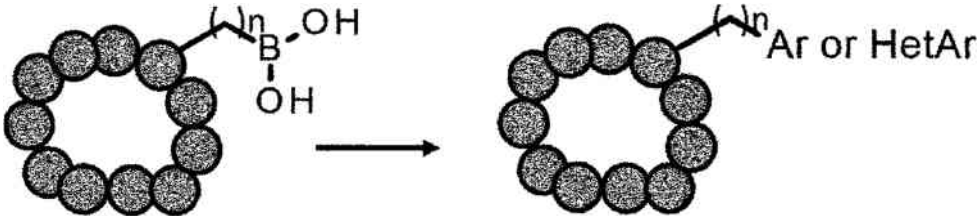
[0205]

A peptide having carboxylic acid in a substituent of a nitrogen atom and/or in a side chain and having aryl halide or heteroaryl halide in a substituent of another nitrogen atom and/or in another side chain within the molecule can be used to produce a peptide compound in which the peptide main chain is crosslinked. Specifically, a crosslinked compound can be produced by activating a peptide having carboxylic acid with N-hydroxyphthalimide and crosslinking it by reaction with aryl halide or heteroaryl halide within the molecule.



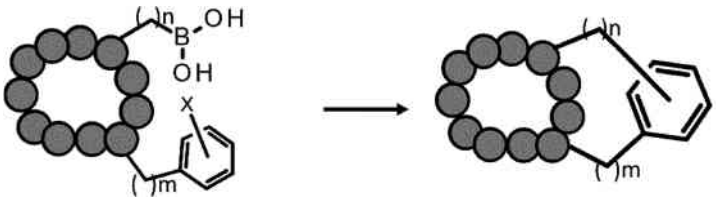
[0206]

Alternatively, peptides having an aryl or heteroaryl group on a side chain can also be synthesized by Suzuki coupling using a peptide having a boronic acid on the side chain as a precursor, as illustrated below. Specifically, the target peptides having an aromatic ring on the side chain can be prepared by synthesizing a precursor peptide using an Fmoc amino acid having a boronic acid on the side chain as a raw material, and reacting it with any aryl halide in the presence of a palladium catalyst.



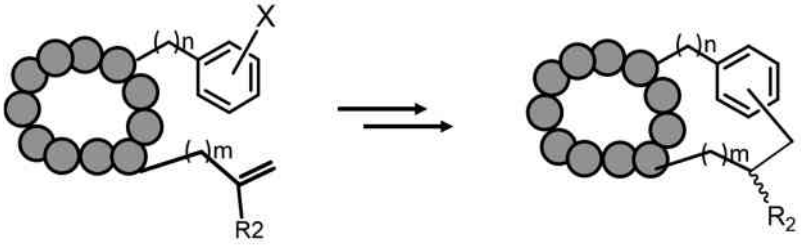
[0207]

A peptide having boronic acid in a substituent of a nitrogen atom and/or in a side chain and having aryl halide in a substituent of another nitrogen atom and/or in another side chain within the molecule can be used to produce a peptide compound in which the peptide main chain is crosslinked. Specifically, a crosslinked compound can be produced by allowing a peptide having boronic acid to react and thereby crosslink with aryl halide within the molecule in the presence of a palladium catalyst.



[0208]

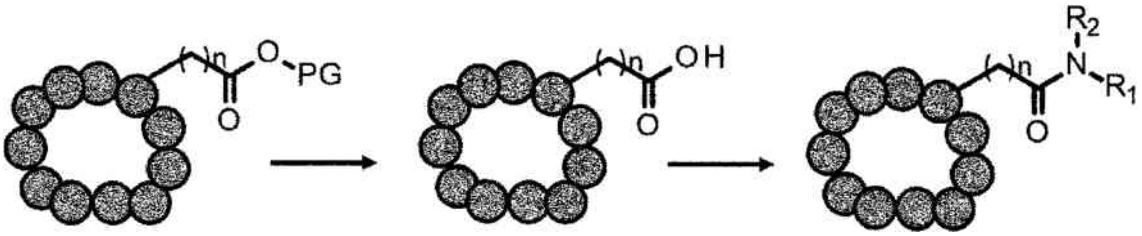
A peptide having olefin in the substituent of a nitrogen atom and/or in a side chain and having aryl halide in the substituent of another nitrogen atom and/or in another side chain within the molecule can be used to produce a peptide compound that is crosslinked by arylene-containing alkylene. Specifically, the crosslinked compound can be produced by conversion to a boron compound by a hydroboration reaction on olefin, and then causing the boron compound to be reacted, and thereby crosslinked, with the intramolecular aryl halide in the presence of a palladium catalyst.



[0209]

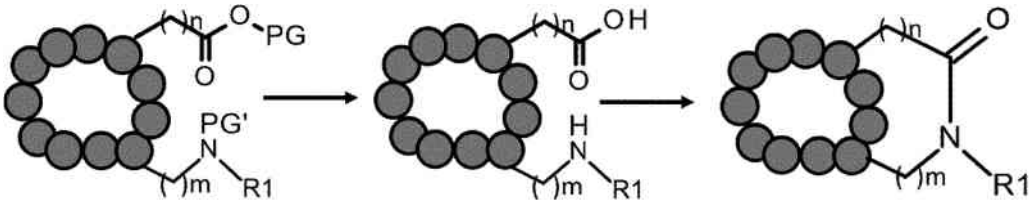
(Method of preparing peptides containing an amide group on the side chain)

Peptides having an amide group on the side chain can be synthesized using an Fmoc amino acid having the target amide group on the side chain as a raw material, or alternatively can be synthesized by amidation of a peptide having a carboxylic acid on the side chain as a precursor, as illustrated below. Specifically, the target peptides having an amide group on the side chain can be obtained by deprotecting a peptide having a protected carboxylic acid on the side chain to synthesize a precursor peptide having a carboxylic acid on the side chain, and condensing it with any amine using a condensing agent such as HATU.



[0210]

A peptide having carboxylic acid in a substituent of a nitrogen atom and/or in a side chain and having an amino group in a substituent of another nitrogen atom and/or in another side chain within the molecule can be used to produce a peptide compound in which the peptide main chain is crosslinked. Specifically, a crosslinked compound can be produced by synthesizing a precursor peptide having carboxylic acid and an amino group by deprotection, and condensing them using a condensing agent such as HATU for crosslinking by intramolecular amidation reaction.

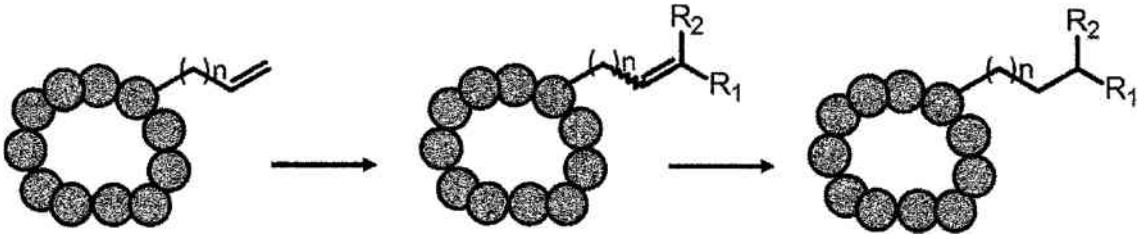


[0211]

(Synthesis of peptides containing a structure that is highly substituted and may contain a double bond on the side chain)

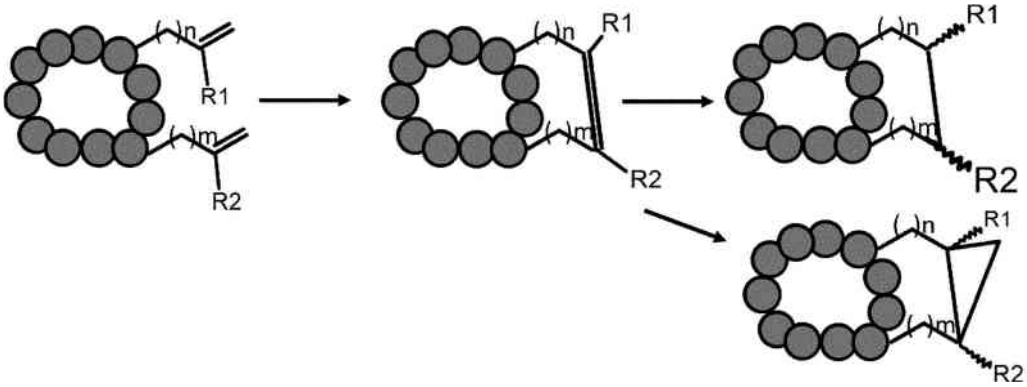
Peptides having a structure that is highly substituted and may contain a double bond on the side chain can be synthesized using an Fmoc amino acid having the target double bond on the side chain as a raw material, or alternatively can be prepared by functionalization of a terminal olefin. Specifically, a peptide having a terminal olefin on the side chain can be synthesized according to the general peptide synthesis method described in the present Examples, and the side chain can be further converted to a side chain having a highly substituted olefin by coupling with a substrate having any terminal olefin by olefin metathesis reaction. Further, the side

chain can be converted to a corresponding side chain by reducing the olefin by hydrogenation reaction.



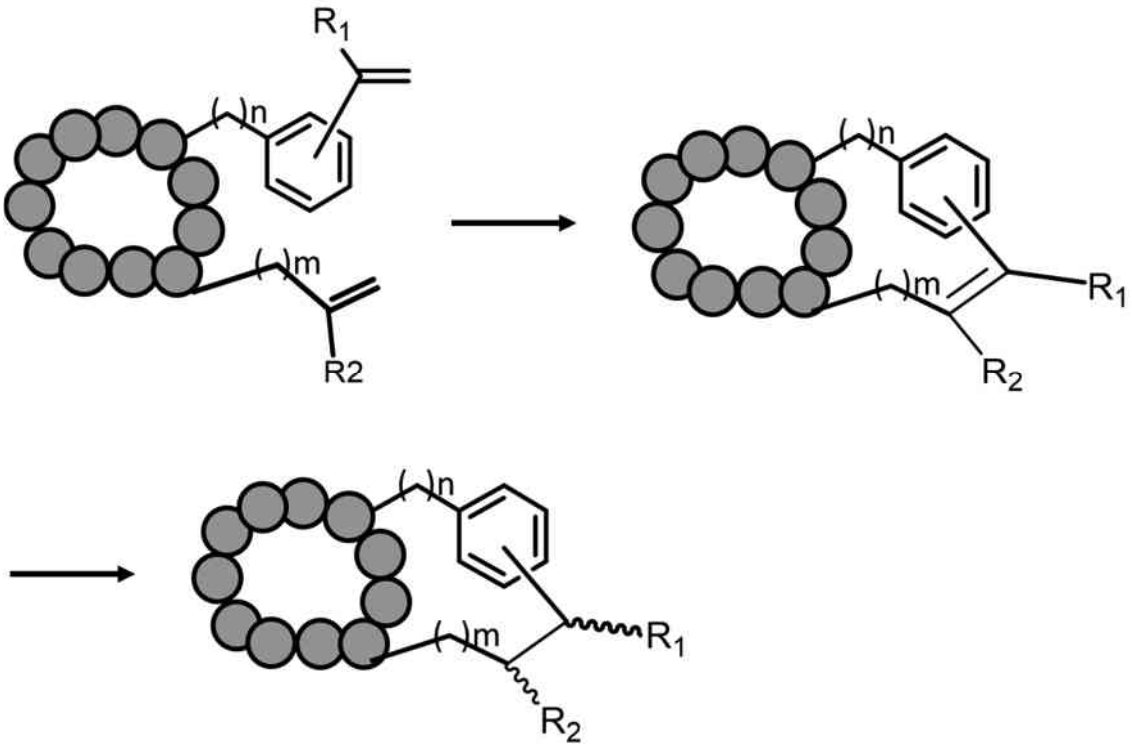
[0212]

Peptide compounds with a peptide backbone crosslinked can also be prepared using a peptide having multiple double bonds in substituents of nitrogen atoms and/or in side chains. Specifically, crosslinked compounds can be prepared by synthesizing a peptide having an olefin at two sites of the substituents of nitrogen atoms and/or the side chains according to the general peptide synthesis method described in the present Examples, and further crosslinking the two olefins by olefin metathesis reaction by referring to Nature Protocols, 2011, 6, 761-771. Further, compounds crosslinked with saturated alkylenes can be prepared by reducing the olefins by hydrogenation reaction.



[0213]

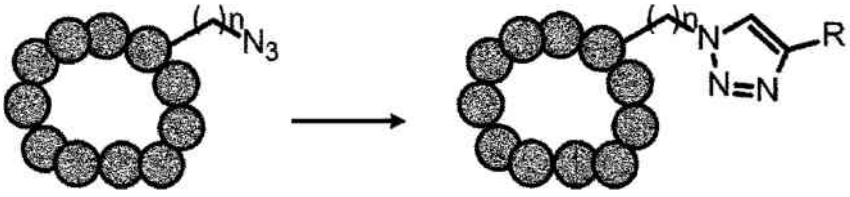
A peptide that contains aryl having an olefin-containing substituent in the substituent of a nitrogen atom and/or in a side chain can be used to produce, as the crosslinked compound, a peptide compound that is crosslinked by arylene and a divalent group containing a double bond. Specifically, the crosslinked compound can be produced by synthesizing a peptide having an aryl containing an olefin in the substituent of a nitrogen atom and/or in a side chain and having olefin in the substituent of another nitrogen atom and/or in another side chain within the molecule according to the general peptide synthesis method described in the Examples, and crosslinking the two olefins by an olefin metathesis reaction. Moreover, a compound crosslinked by arylene-containing alkylene can be produced by reducing olefin by a hydrogenation reaction.



[0214]

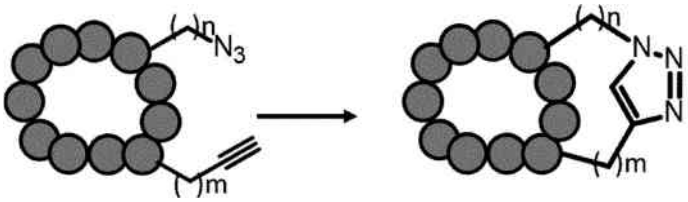
(Synthesis of peptides containing a triazole on the side chain)

Peptides having a triazole on the side chain can be prepared by click reaction with an azido group. Specifically, peptide compounds having an azido group on the side chain can be prepared by synthesizing a peptide having an azido group on the side chain according to the general peptide synthesis method described in the present Examples, and coupling the peptide with any acetylene in the presence of copper(I) iodide by referring to Bioorganic & Medicinal Chemistry Letters, 2009, 19, 4130-4133 or the like.



[0215]

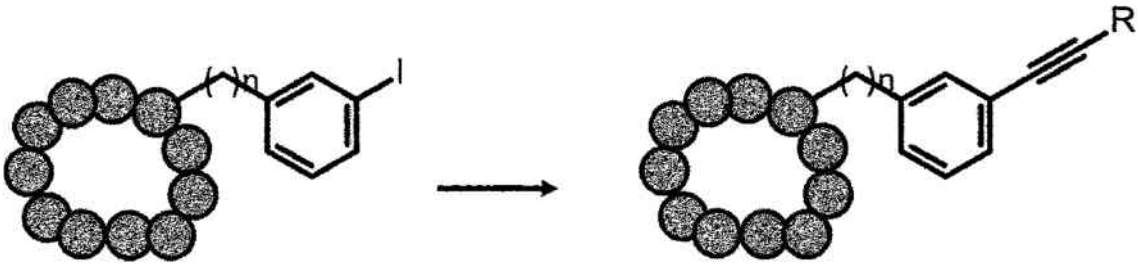
A peptide having an azide group in a substituent of a nitrogen atom and/or in a side chain and having acetylene in a substituent of another nitrogen atom and/or in another side chain within the molecule can be used to produce a peptide compound in which the peptide main chain is crosslinked. Specifically, a crosslinked compound can be produced by allowing a peptide having an azide group to react and thereby crosslink with acetylene within the molecule in the presence of a palladium catalyst.



[0216]

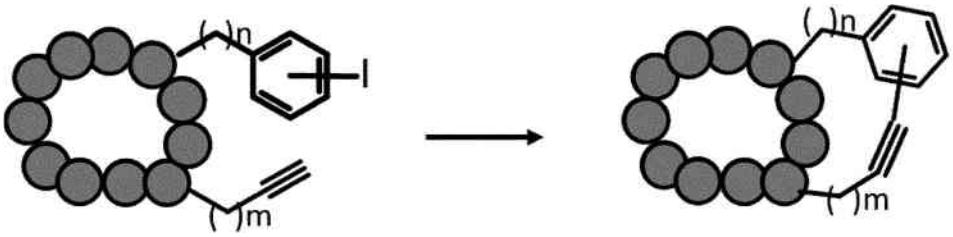
(Synthesis of peptides containing an aryl group substituted with an alkynyl group on the side chain)

Peptides containing an aryl group substituted with an alkynyl group on the side chain can be synthesized by Sonogashira coupling reaction with an aryl halide group. Specifically, the conversion to peptide compounds having an aryl group substituted with an alkynyl group on the side chain can be conducted by synthesizing a peptide having an aryl iodide group on the side chain according to the general peptide synthesis method described in the present Examples, and coupling the peptide with any acetylene in the presence of copper(I) iodide.



[0217]

A peptide having an aryl halide in a substituent of a nitrogen atom and/or in a side chain and having acetylene in a substituent of another nitrogen atom and/or in another side chain within the molecule can be used to produce a peptide compound in which the peptide main chain is crosslinked. Specifically, a crosslinked compound can be produced by allowing a peptide having aryl iodide to be couple and thus crosslink with acetylene within the molecule in the presence of copper(I) iodide.



[0218]

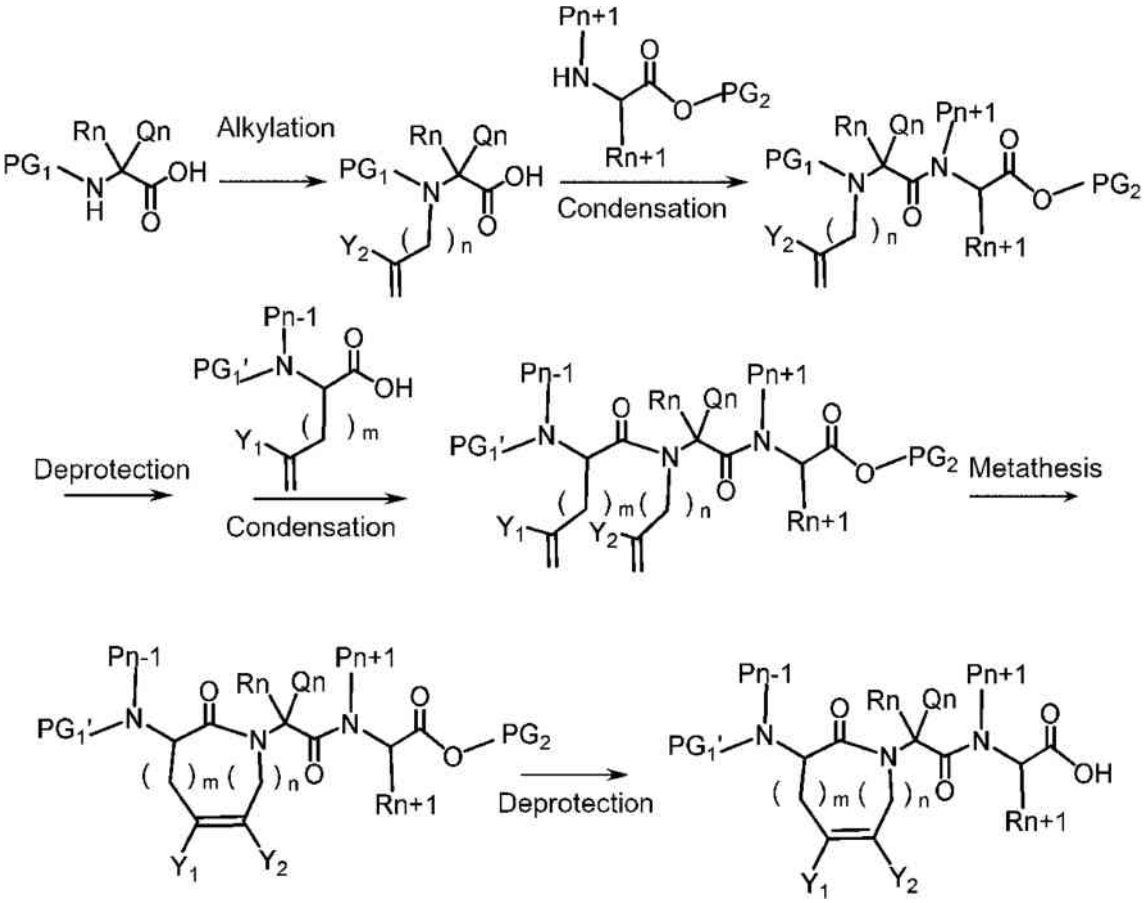
(General method for producing oligopeptide compounds)

Provided belowis a general method for producing an oligopeptide having a cyclic structure formed between a substituent of a nitrogen atom and a side chain. In the following scheme, PG_1 and PG_1' represent protecting groups of a nitrogen atom, PG_2 and PG_2' represent

protecting groups of an oxygen atom, R_{n-1}, R_n, R_{n+1}, and Q_n represent side chains of an amino acid, P_{n-1}, P_n, and P_{n+1} represent substituents of a nitrogen atom, and Y_1 and Y_2 each represent hydrogen, halogen, or alkyl. In the method for producing an amino acid provided below, groups other than the intended functional group may undergo chemical reaction. In such a case, introducing a protecting group to the unintended functional groups enables only the desired reaction to proceed. The reactions for attaching and detaching such a protecting group may be performed, for example, by the methods described in Greene's, "Protective Groups in Organic Synthesis" (5th edition, John Wiley & Sons 2014). As for the conversion reaction of functional groups of a compound, Comprehensive Organic Transformations: A Guide to Functional Group Preparations (5th edition) by Larock or March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (8th edition) by Smith can be referred to.

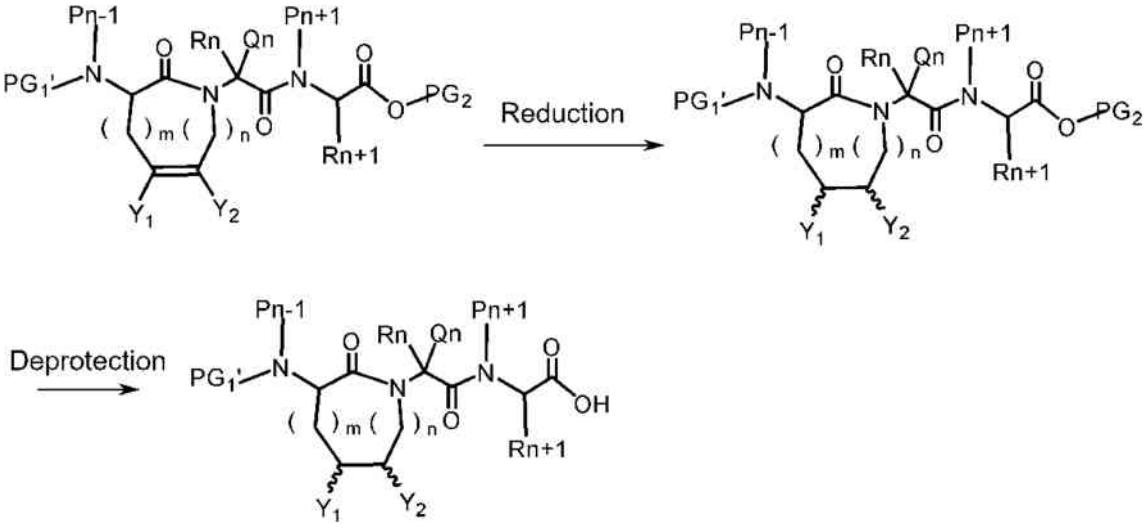
[0219]

An oligopeptide compound with a cyclic structure formed between a substituent of a nitrogen atom of an amino acid and a side chain of another amino acid can be synthesized using the following method. A protected amino acid can be reacted with an alkylating agent having an olefin in the presence of a base to introduce an alkyl group having an olefin. Then, the C-terminus can be elongated with an amino acid by condensation with a C-terminally protected amino acid. The condensation reaction can be carried out using various combinations of carboxyl-activating agents, such as the combination of DIC and HOBt, the combination of DIC and HOAt, and the combination of HATU and DIPEA. Subsequently, the protected nitrogen atom can be deprotected and then elongated with a protected amino acid having an olefin in the side chain. Then, the olefins within the molecule can be cyclized by metathesis reaction. Then, the C-terminal protecting group can be deprotected to produce an oligopeptide compound that has a free C-terminus and a double bond-containing cyclic structure formed between a substituent of a nitrogen atom and a side chain.



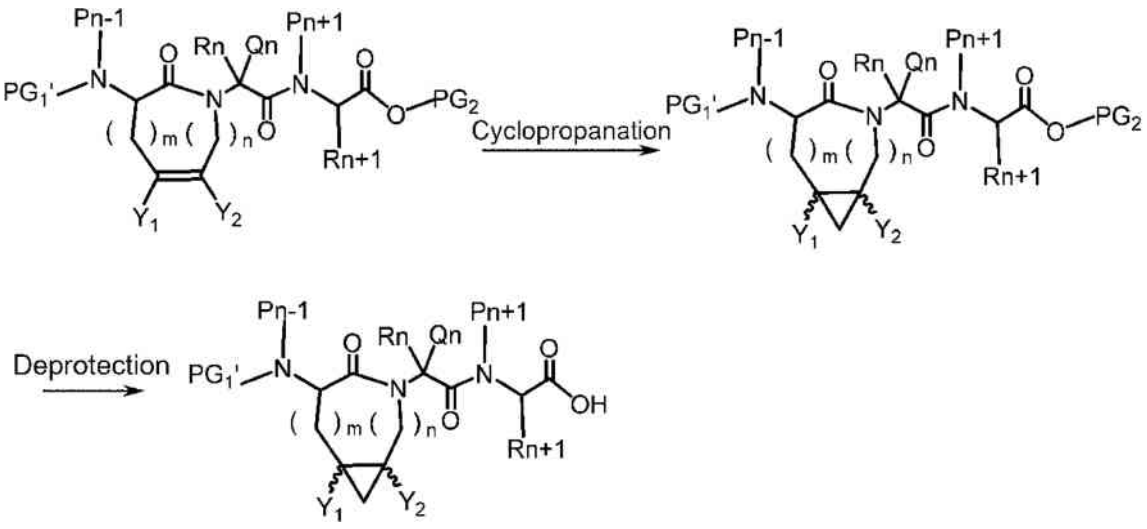
[0220]

Also, an oligopeptide compound having a double bond-containing cyclic structure can be used to produce an oligopeptide compound having a cyclic structure in which the double bond is converted to a single bond. Specifically, a C-terminally protected compound having a double bond-containing cyclic structure is reduced by hydrogenation reaction and then the C-terminal protecting group is deprotected, whereby an oligopeptide compound having a free C-terminus and a cyclic structure formed with alkylene between a substituent of a nitrogen atom and a side chain can be produced.



[0221]

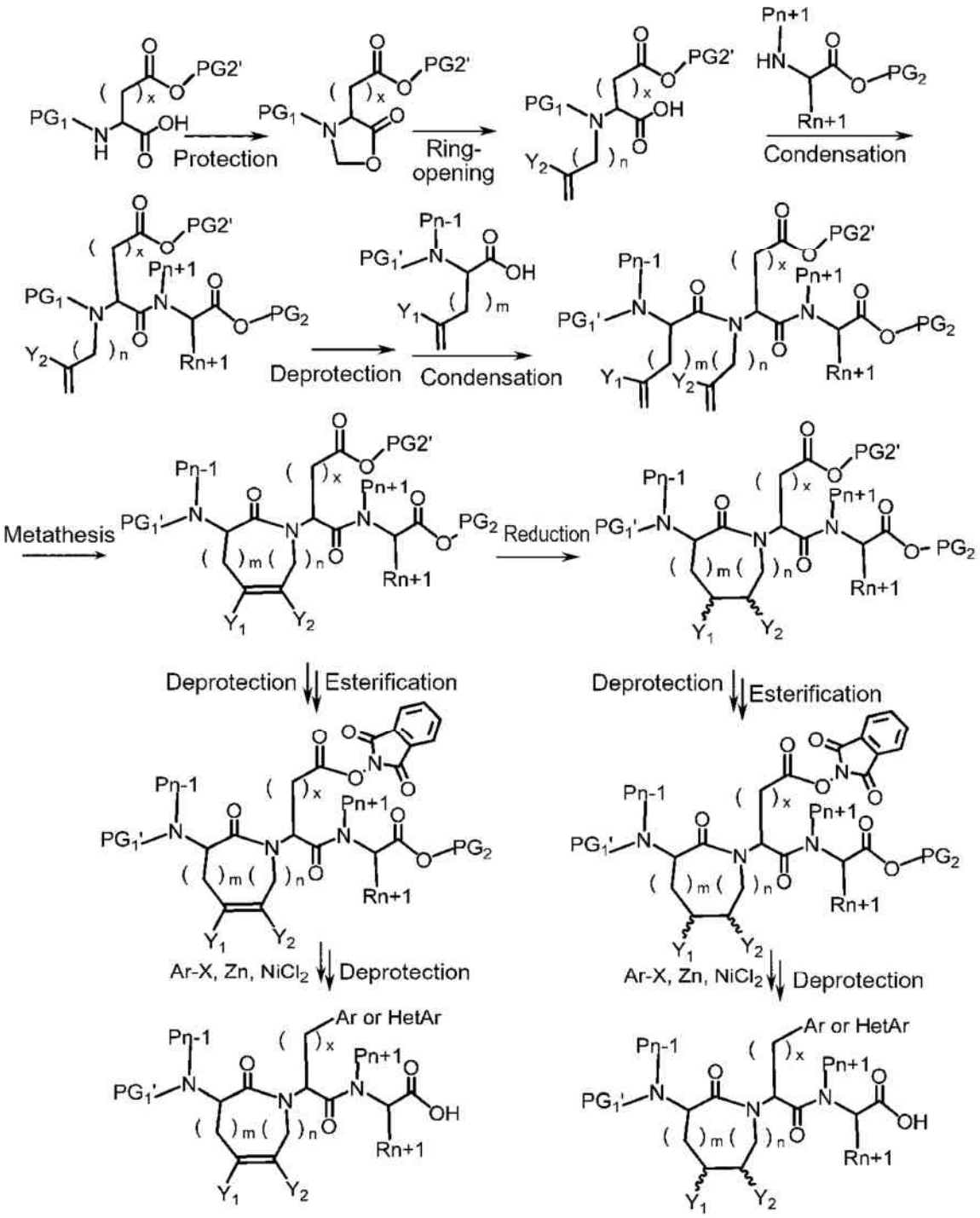
Moreover, an oligopeptide compound having a double bond-containig cyclic structure can be used to produce an oligopeptide compound having a crosslinked structure in which the double bond is converted to a cyclopropane ring. Specifically, a C-terminally protected compound having a double bond-containing cyclic structure can be subjected to conditions such as diiodomethane-diethylzinc to convert the double bond to a cyclopropane ring. Then, the C-terminal protecting group is deprotected, whereby an oligopeptide compound having a crosslinked structure in which the double bond is converted to a cyclopropane ring can be produced.



[0222]

An oligopeptide compound having a cyclic structure formed between a substituent of a nitrogen atom of an amino acid and a side chain of another amino acid can also be synthesized by the following method. By allowing an aldehyde to act on a protected amino acid according to the method of Freidinger et al. (J. Org. Chem., 1983, 48(1), 77-81), an oxazolidinone

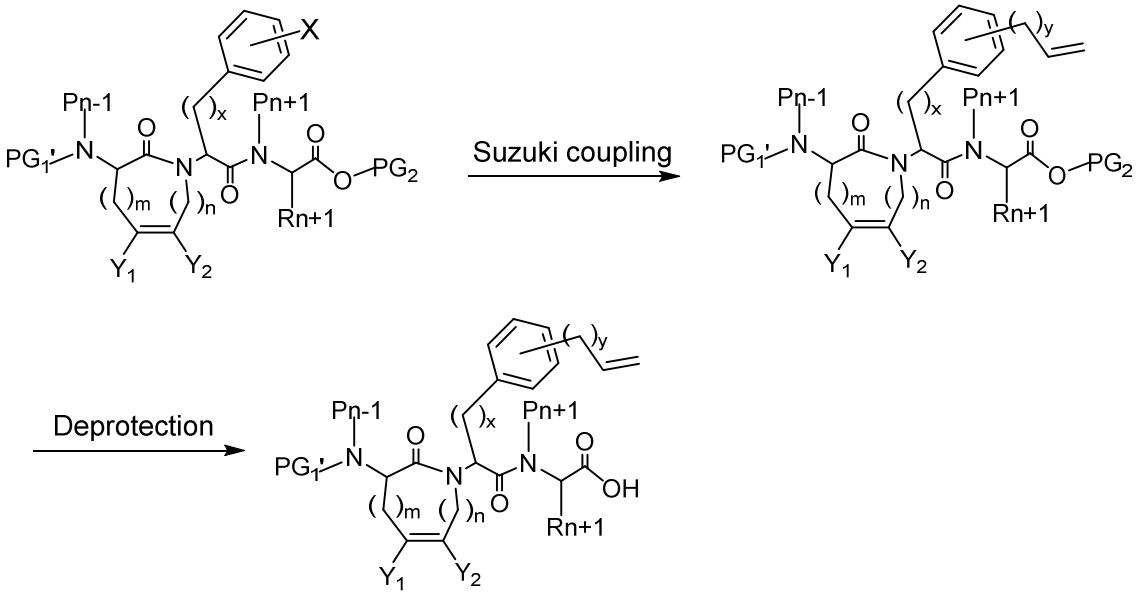
compound to which a cyclic protecting group is introduced can be obtained. Then, by carrying out a ring-opening reaction using a silicon compound having an olefin according to the method of Nguyen et al. (Synthesis, 2009, 12, 1991), an alkyl group having an olefin can be introduced to the nitrogen atom. The C-terminus can then be elongated with an amino acid by condensation with a C-terminally protected amino acid. Subsequently, the protected nitrogen atom can be deprotected and then elongated with a protected amino acid having an olefin in the side chain. Then, the olefins within the molecule can be cyclized by metathesis reaction. Then, the C-terminal protecting group is deprotected, whereby an oligopeptide compound having a free C-terminal and a cyclic structure containing a double bond between a substituent of a nitrogen atom and a side chain is formed can be produced.



[0223]

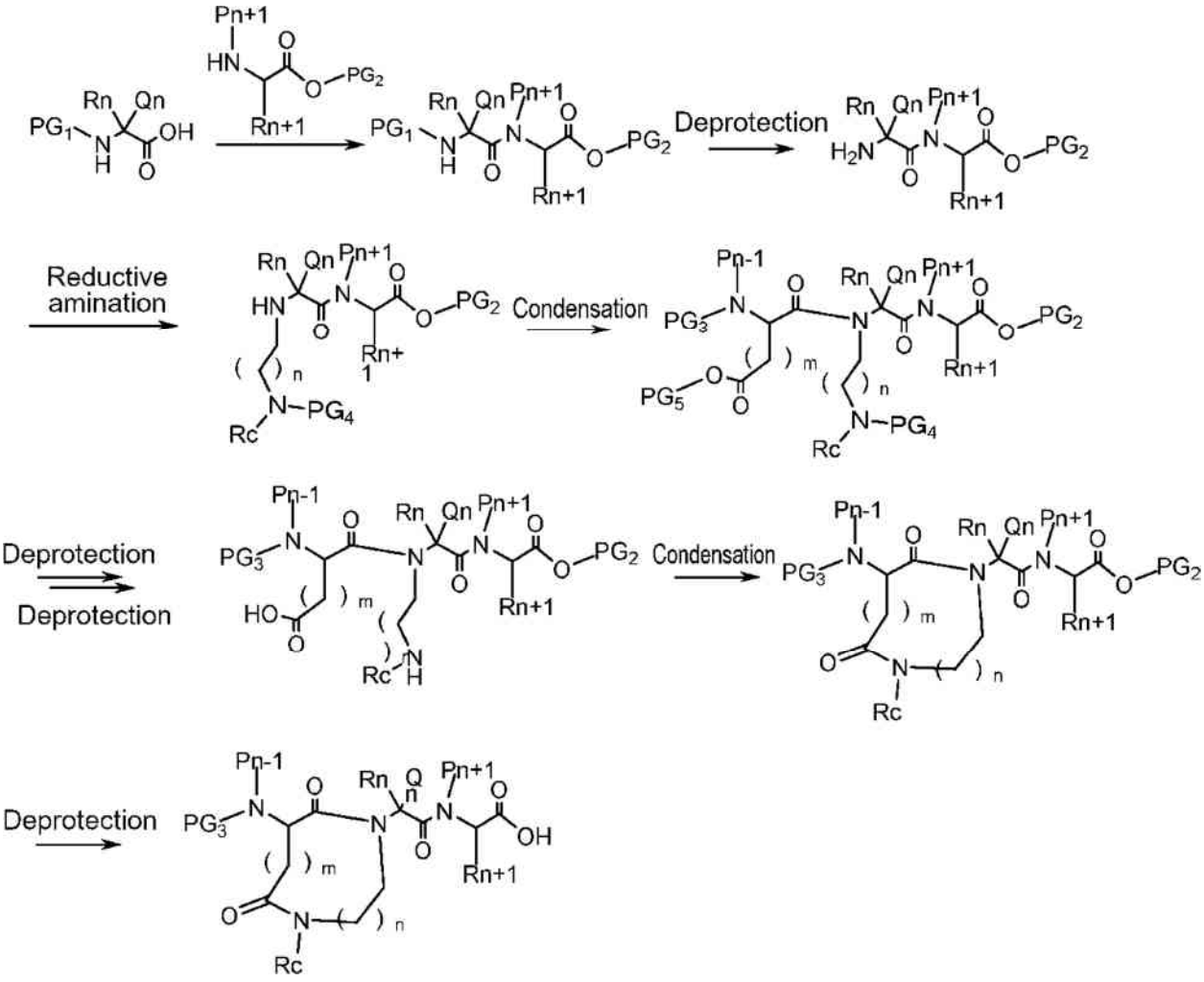
An oligopeptide containing an aryl group substituted with an alkenyl group (y = 0 to 2) in a side chain can be produced by a Suzuki coupling reaction between an aryl halide group and a boron compound having an alkenyl group. Specifically, a peptide having an aryl iodide group in a side chain can be synthesized according to the general oligopeptide synthesis method described in the Examples, and then coupled with a boron compound having an alkenyl group in

the presence of a palladium catalyst for conversion to an oligopeptide compound having an aryl group that is substituted with an alkenyl group (y = 0 to 2) in a side chain.



[0224]

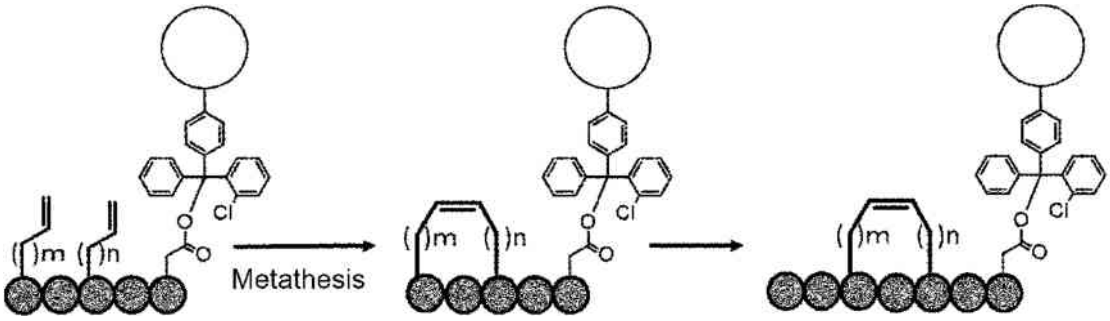
An oligopeptide compound in which a substituent for the nitrogen atom of an amino acid and the side chain of another amino acid form a cyclic structure by an amide bond can be synthesized using the following method. Specifically, a C-terminally protected peptide is synthesized according to the general synthesis method described in the Examples, then deprotected at the N-terminal, and subjected to a reductive amination reaction with an aldehyde compound containing an amino group having a protecting group to introduce an amino group having a protecting group in the N-substituent. This is then condensed with a protected amino acid that contains a carboxy group having a protecting group in a side chain. After the protecting groups for the carboxy group and the amino group are removed, the molecule is condensed intramolecularly and deprotected at the C-terminal, thereby achieving conversion to an oligopeptide compound in which a substituent for the nitrogen atom of an amino acid and the side chain of another amino acid form a cyclic structure by an amide bond.



[0225]

(Method for cyclizing peptide compound on resin)

Cyclic compounds and oligopeptide compounds having a cyclic structure can be cyclized by, in addition to cyclization according to the method described in the present Examples, metathesis reaction on a resin as shown in the following method. Specifically, as a resin-supported peptide, a peptide having an olefin in two sites of the substituents of nitrogen atoms and/or the side chains is synthesized according to the common peptide synthesis method described in the present Examples, then the two olefins can be cyclized by metathesis reaction to produce a compound having a cyclic structure. Moreover, peptide elongation, cleavage from resin, cyclization, deprotection, and purification can be performed according to the common peptide synthesis method described in the present Examples to produce a cyclic compound and an oligopeptide compound having a cyclic structure.



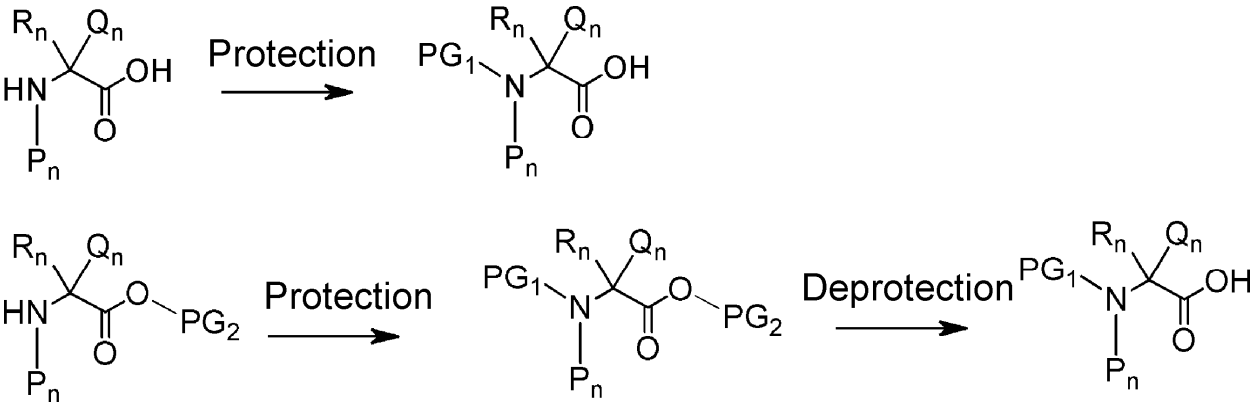
[0226]

(General preparation methods for non-natural amino acids)

General preparation methods for C-terminal-free non-natural amino acids where the nitrogen atoms of the amino acids are protected are shown below. In the following schemes, PG_1 and PG_1' each represent a protecting group for a nitrogen atom, PG_2 and PG_2' each represent a protecting group for an oxygen atom, PG_3 and PG_4 each represent a protecting group for an amino acid side chain, R_n and Q_n each represent an amino acid side chain, P_n represents a substituent for a nitrogen atom, P' represents C_1-C_5 alkyl, and R, R', R", and R'" each represent a substituent for a hydrogen or amino group. In the methods of preparing amino acids shown below, a functional group other than the target functional group may cause chemical reaction. In such a case, only the desired reaction can be allowed to proceed by introducing a protecting group onto a non-target functional group. Examples of such protecting group introduction and removal reactions include methods described in Greene's "Protective Groups in Organic Synthesis" (5th ed., John Wiley & Sons 2014). For conversion reactions of compound functional groups, one can refer to Larock's "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" (5th ed.) or Smith's "March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" (8th ed.).

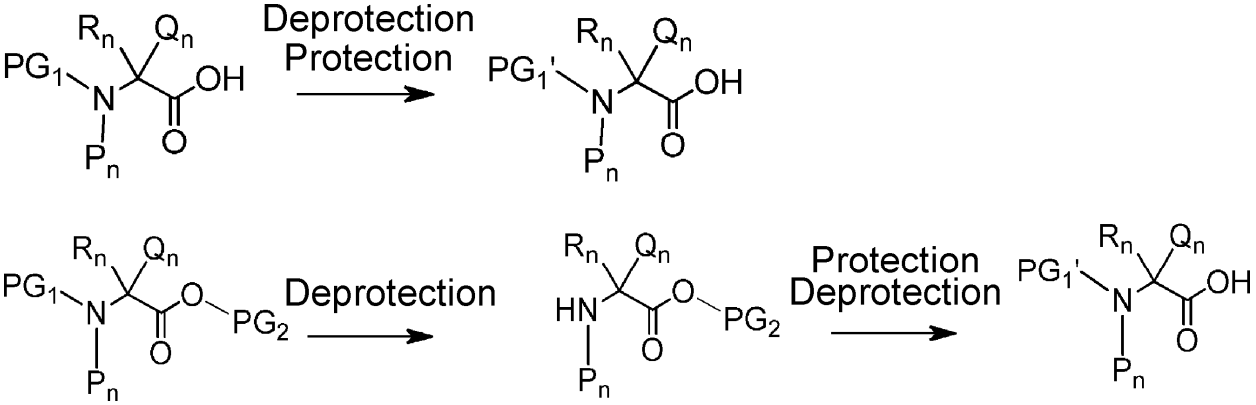
[0227]

Non-natural amino acids having a protecting group (PG_1) introduced onto the amino acid nitrogen atom can be prepared using the following method. The target C-terminal-free non-natural amino acids can be prepared by introducing a protecting group onto an N-terminal-free amino acid available from a commercial supplier and deprotecting it as necessary according to conventional methods.



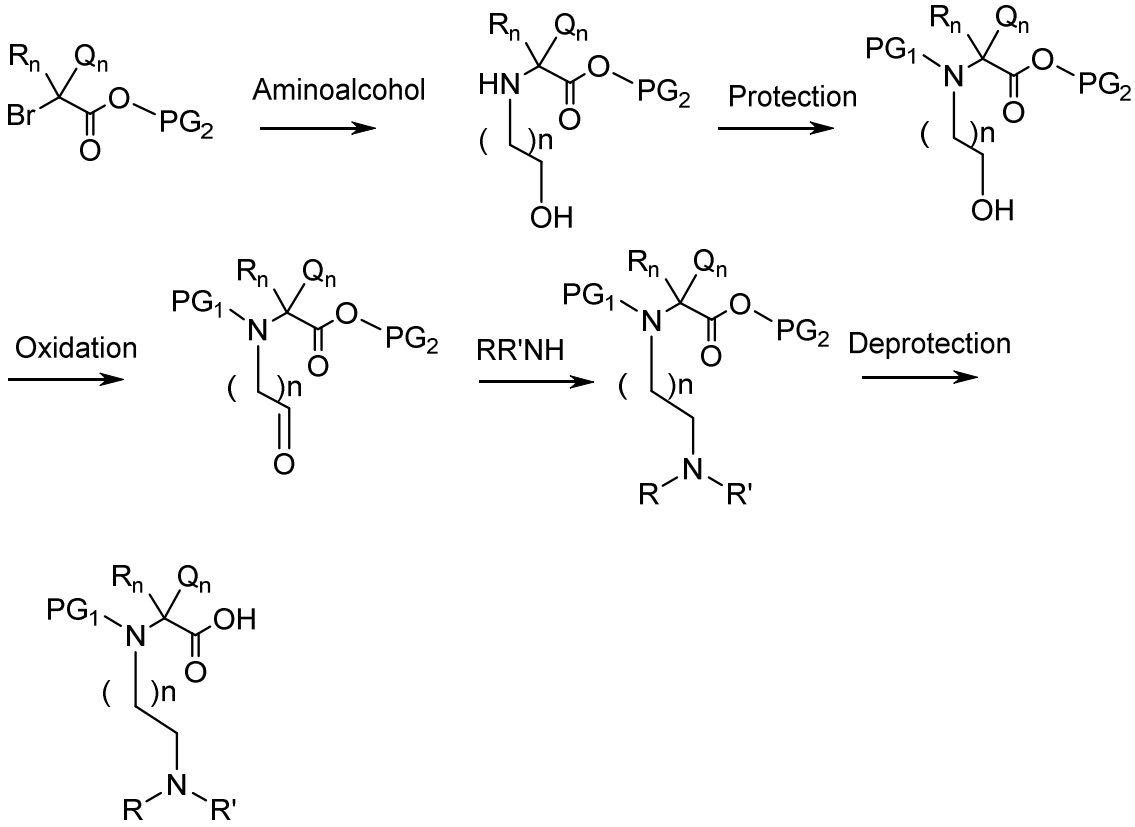
[0228]

Non-natural amino acids having a protecting group (PG_1') introduced onto the amino acid nitrogen atom can be prepared using the following method. The target C-terminal-free non-natural amino acids can be prepared by deprotecting an amino acid that has a protecting group (PG_1) introduced onto the N-terminus which is available from a commercial supplier, and introducing a protecting group, according to conventional methods.



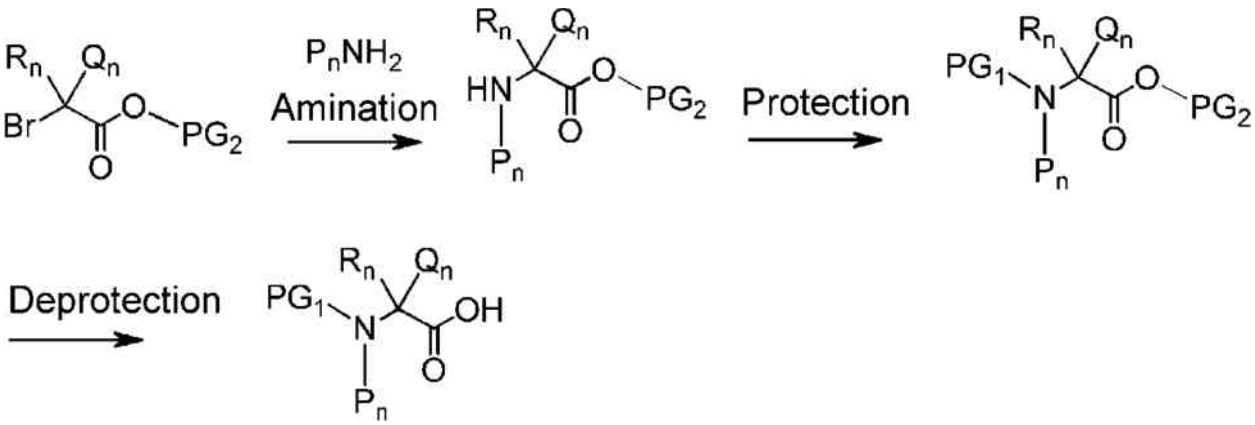
[0229]

Non-natural amino acids having an aminoalkyl group introduced onto the substituent (P_n) of the amino acid nitrogen atom can be prepared using the following method. A bromoacetic acid ester derivative available from a commercial supplier is reacted with an amino alcohol according to the method of King et al. (Tetrahedron Letters, 2002, 43(11), 1987-1990), and then a protecting group (PG_1) is introduced onto the nitrogen atom. Next, the hydroxyl group is oxidized according to the method of Dess et al. (J. Org. Chem., 1983, 48(22), 4155-4156), and the aldehyde group is reductively aminated according to the method of Borch et al. (J. Org. Chem. 1972, 37(10), 1673-1674) to introduce an amino group. Next, the target C-terminal-free non-natural amino acid can be prepared by deprotecting the protecting group for the oxygen atom.



[0230]

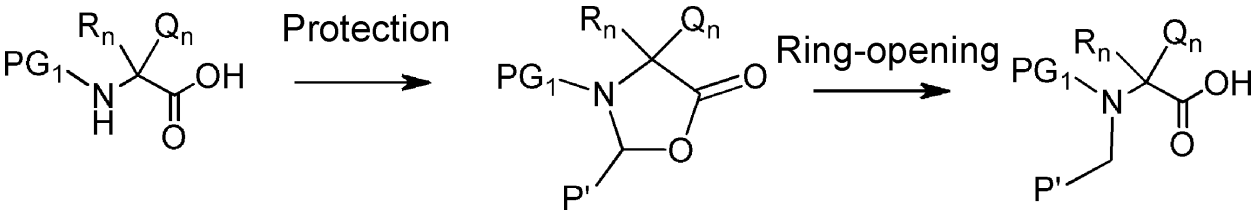
N-substituted amino acids can also be prepared by the following scheme of introducing a substituent (P_n) onto the amino acid nitrogen atom. A bromoacetic acid ester derivative available from a commercial supplier is reacted with an amine (P_nNH_2) in the presence of a base, and then a protecting group (PG_1) is introduced onto the nitrogen atom. Next, the target C-terminal-free non-natural amino acid can be prepared by deprotecting the protecting group for the oxygen atom.



[0231]

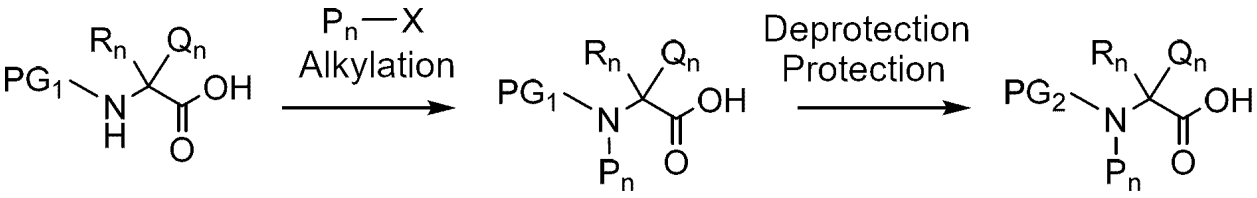
Non-natural amino acids having a -CH_2-P' group introduced onto the amino acid nitrogen atom can be prepared according to the following scheme. An oxazolidinone

compound having an introduced cyclic protecting group can be obtained by allowing an aldehyde to act on a C-terminal-free amino acid available from a commercial supplier according to the method of Freidinger et al. (J. Org. Chem., 1983, 48(1), 77-81). Next, the target C-terminal-free non-natural amino acid can be prepared by ring-opening reaction.



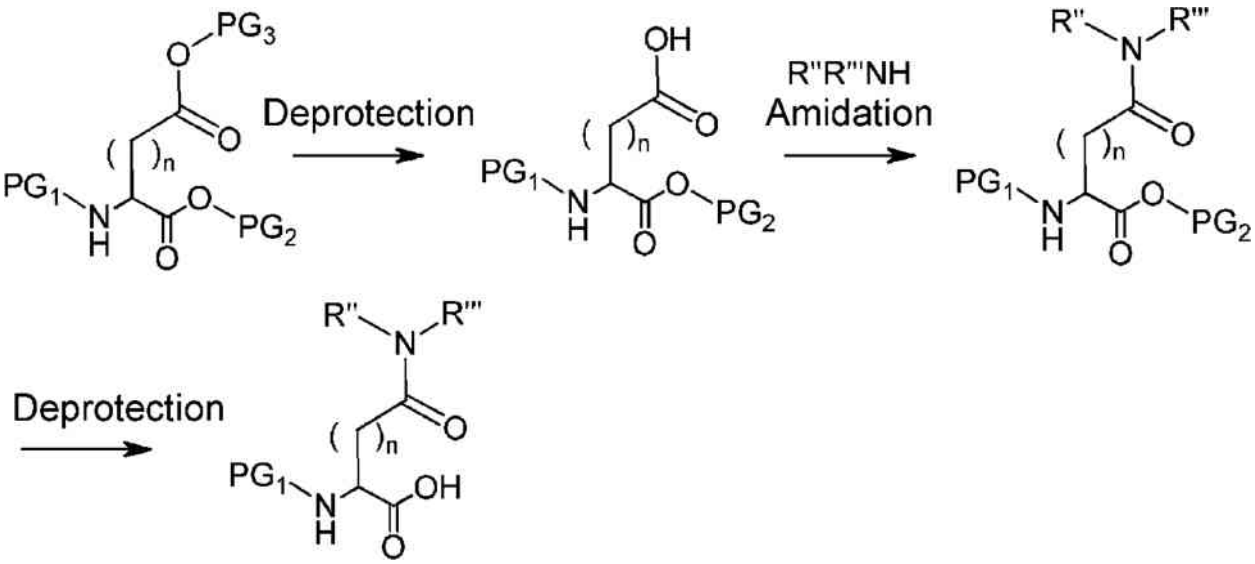
[0232]

Non-natural amino acids having a P_n group introduced onto the amino acid nitrogen atom can be produced according to the following scheme. The P_n group can be introduced onto a commercially available C-terminal-free amino acid by allowing an alkylating agent (P_n-X) to act on it in the presence of a base. Then, a C-terminal-free non-natural amino acid can be produced by carrying out deprotection reaction and protecting group-introducing reaction by conventional methods.



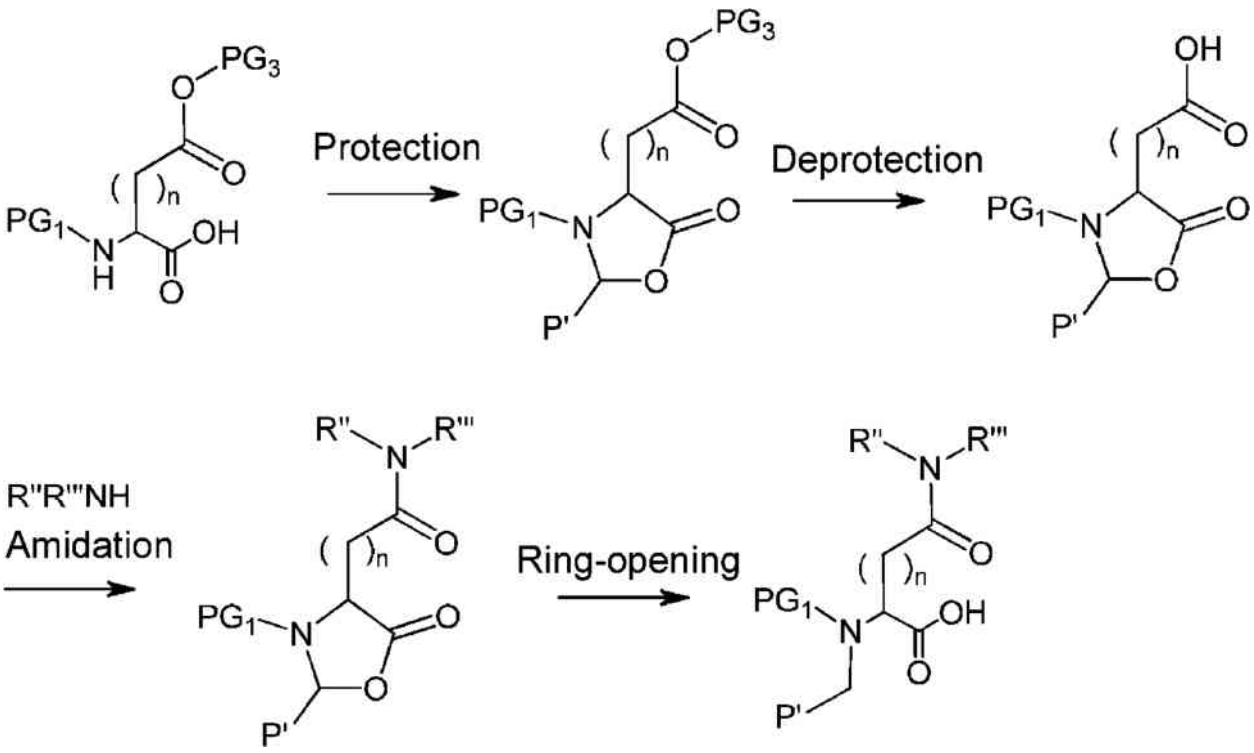
[0233]

Non-natural amino acids having an amide group introduced onto the amino acid side chain can be prepared according to the following scheme. An amide group can be introduced onto the side chain by deprotecting a commercially available protected amino acid (n = 1 or 2) and allowing an amine (R"R'"NH) to act on the resulting carboxylic acid. Next, a C-terminal-free non-natural amino acid can be prepared by deprotecting the C-terminal protecting group.



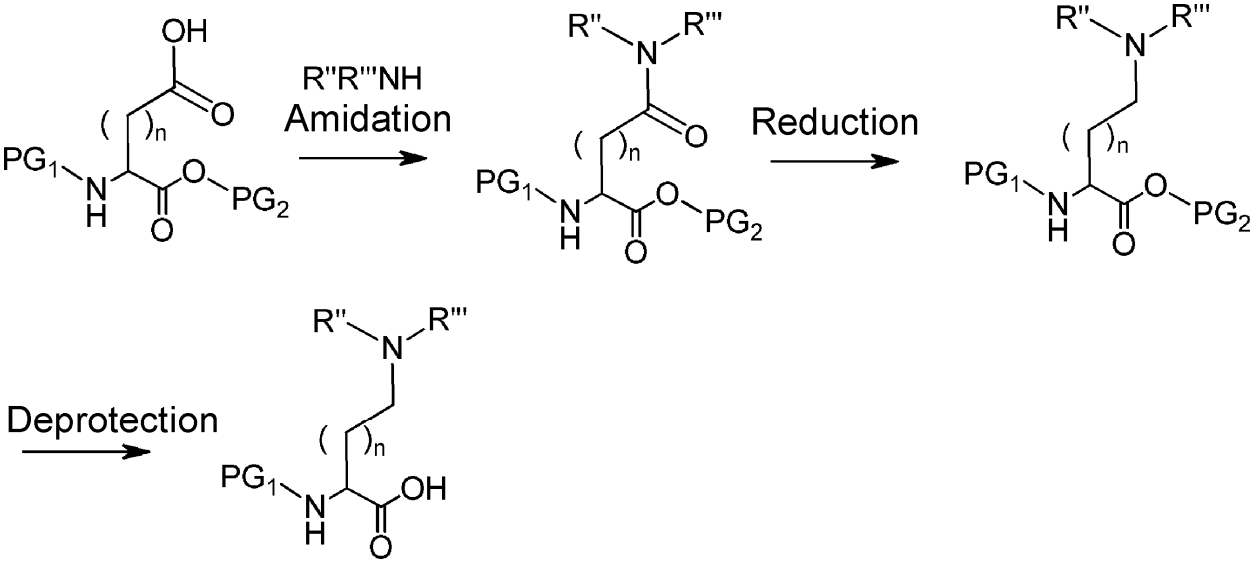
[0234]

Non-natural amino acids having an amide group introduced onto the amino acid side chain and a -CH_2-P' group introduced onto the amino acid nitrogen atom can be prepared according to the following scheme. An oxazolidinone compound having an introduced cyclic protecting group can be obtained by allowing an aldehyde to act on a commercially available protected amino acid (n = 1 or 2) according to the method of Freidinger et al. (J. Org. Chem., 1983, 48(1), 77-81). Next, an amide compound can be obtained by deprotecting the side-chain protecting group and then allowing an amine (R''R'''NH) to act on it. Next, the target C-terminal-free non-natural amino acid can be prepared by ring-opening reaction.



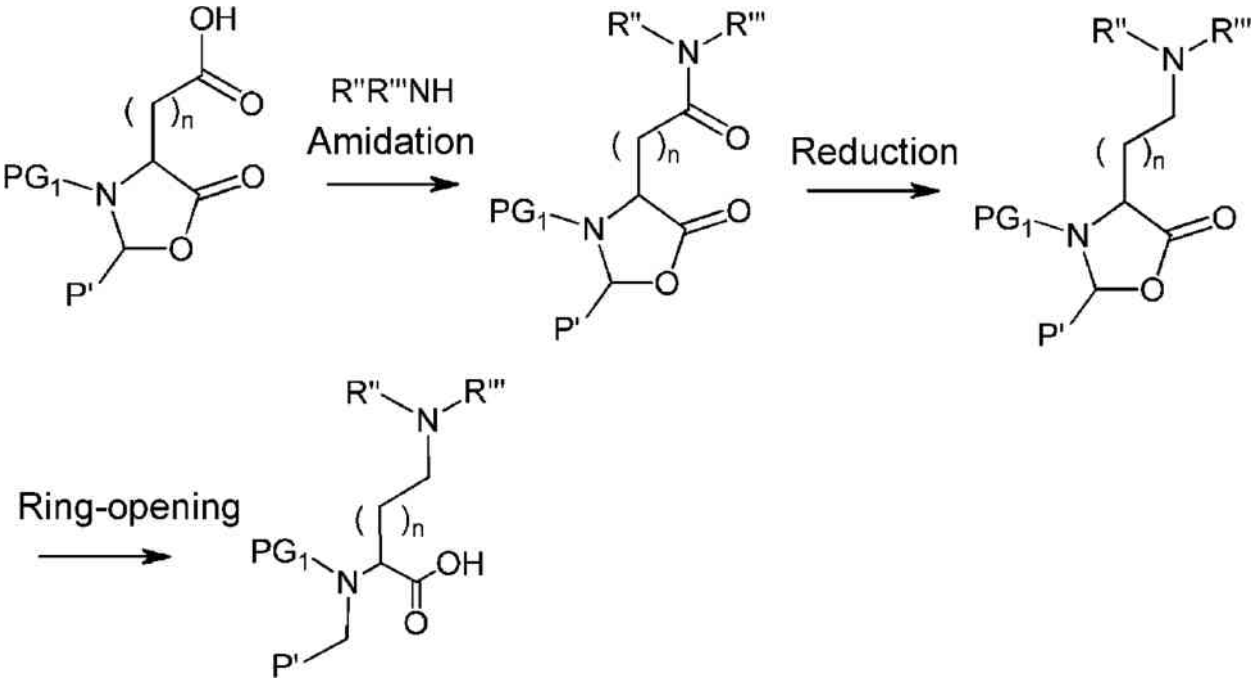
[0235]

Non-natural amino acids having an amino group introduced onto the amino acid side chain can be prepared according to the following scheme. An amide group can be introduced onto the side chain by allowing an amine (R"R'"NH) to act on the carboxyl group of a commercially available protected amino acid (n = 1 or 2). Next, a C-terminal-free non-natural amino acid can be prepared by conducting reduction reaction according to the method of Reeves et al. (Advanced Synthesis & Catalysis, 2013, 355(1), 47-52) and then deprotecting the C-terminal protecting group.



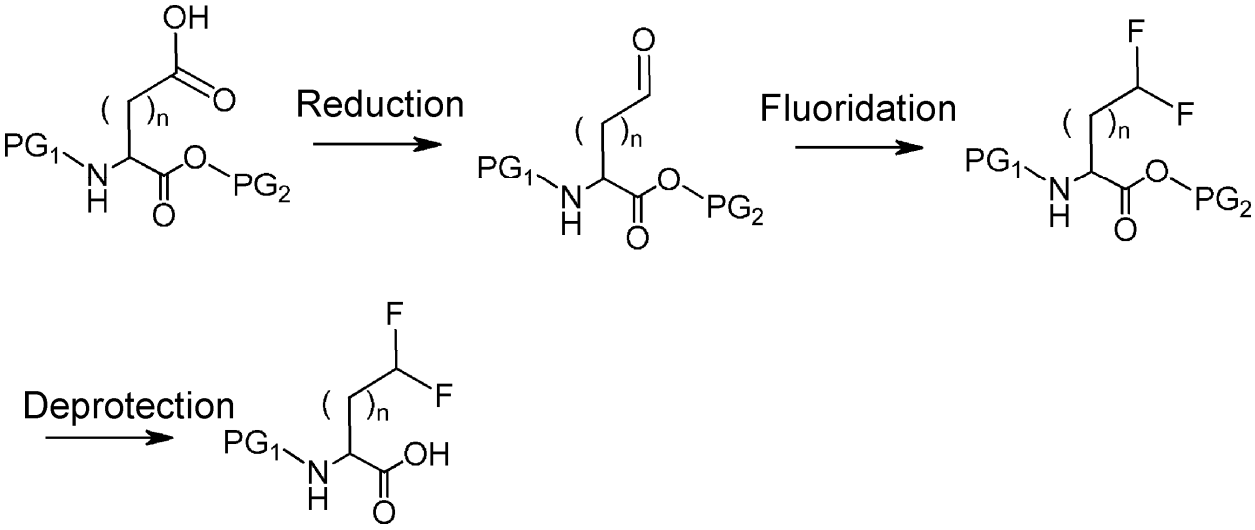
[0236]

Non-natural amino acids having an amino group introduced onto the amino acid side chain and a -CH_2-P' group introduced onto the amino acid nitrogen atom can be prepared according to the following scheme. An amide group can be introduced onto the side chain by allowing an amine (R"R'"NH) to act on the carboxyl group of an amino acid protected by a cyclic protecting group (n = 1 or 2). Next, the target C-terminal-free non-natural amino acid can be prepared by conducting reduction reaction according to the method of Reeves et al. (Advanced Synthesis & Catalysis, 2013, 355(1), 47-52) and then performing ring-opening reaction.



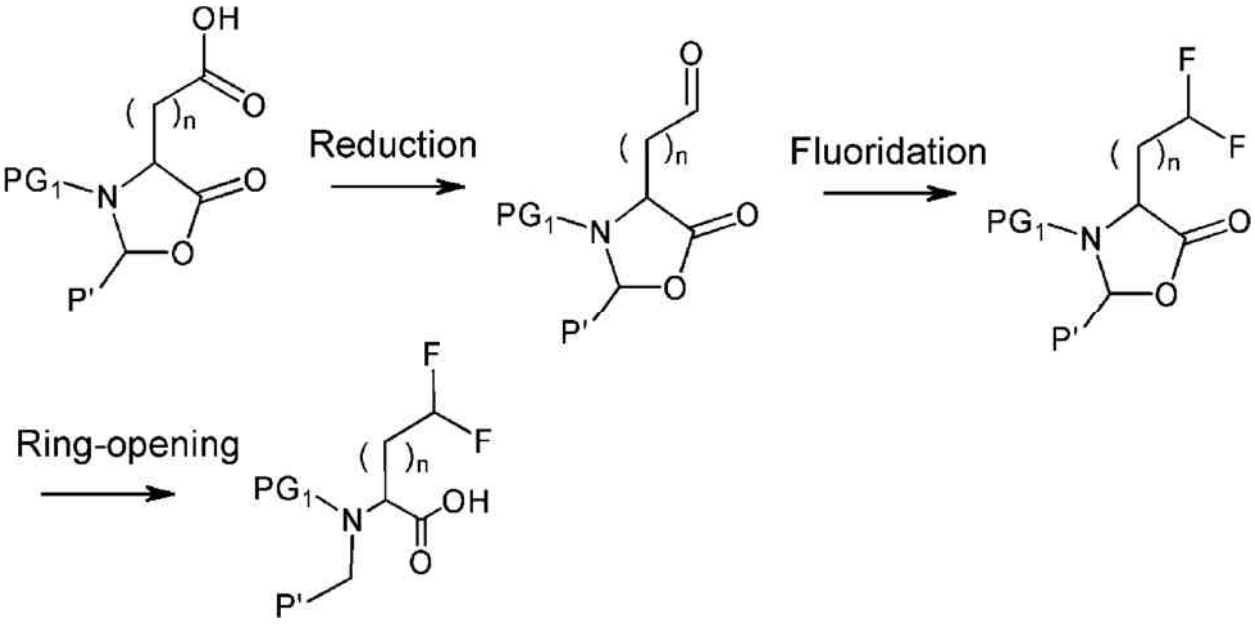
[0237]

Non-natural amino acids having a fluoroalkyl group introduced onto the amino acid side chain can be prepared according to the following scheme. The carboxyl group of a commercially available protected amino acid (n = 1 or 2) can be reduced and converted to an aldehyde group according to a conventional method, and the aldehyde group can be converted to a difluoromethyl group by introducing a fluorine atom according to a conventional method. Next, a C-terminal-free non-natural amino acid can be prepared by deprotecting the C-terminal protecting group.



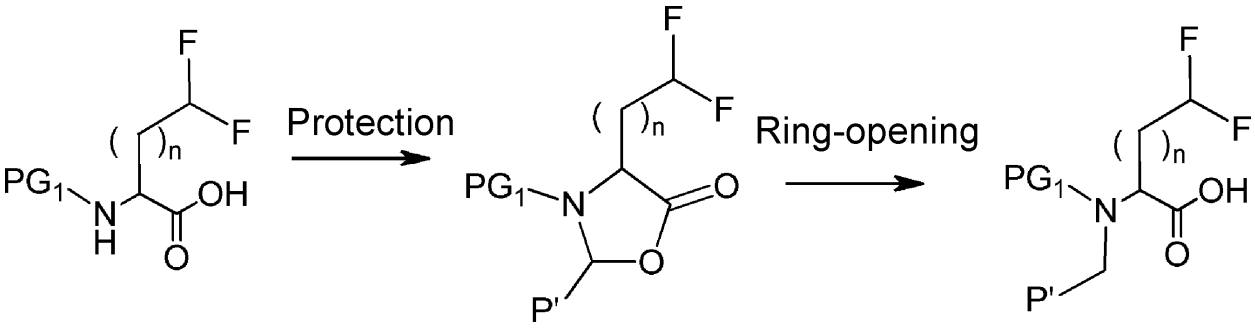
[0238]

Non-natural amino acids having a halogenated alkyl group introduced onto the amino acid side chain and a -CH_2-P' group introduced onto the amino acid nitrogen atom can be prepared according to the following scheme. The carboxyl group of an amino acid protected by a cyclic protecting group (n = 1 or 2) can be reduced and converted to an aldehyde group according to a conventional method, and the aldehyde group can be converted to a dihalogenated methyl group by introducing a halogen atom according to a conventional method. Next, a C-terminal-free non-natural amino acid can be prepared by ring-opening of the C-terminal cyclic protecting group.



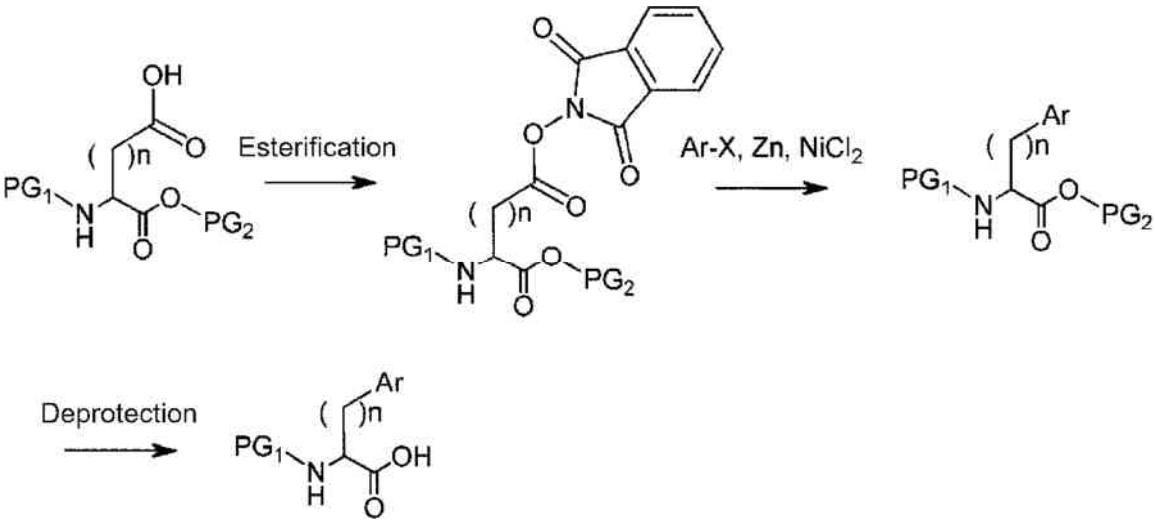
[0239]

C-terminal-free non-natural amino acids having a halogenated alkyl group introduced onto the amino acid side chain and a -CH_2-P' group introduced onto the amino acid nitrogen atom can also be prepared by the method shown below.



[0240]

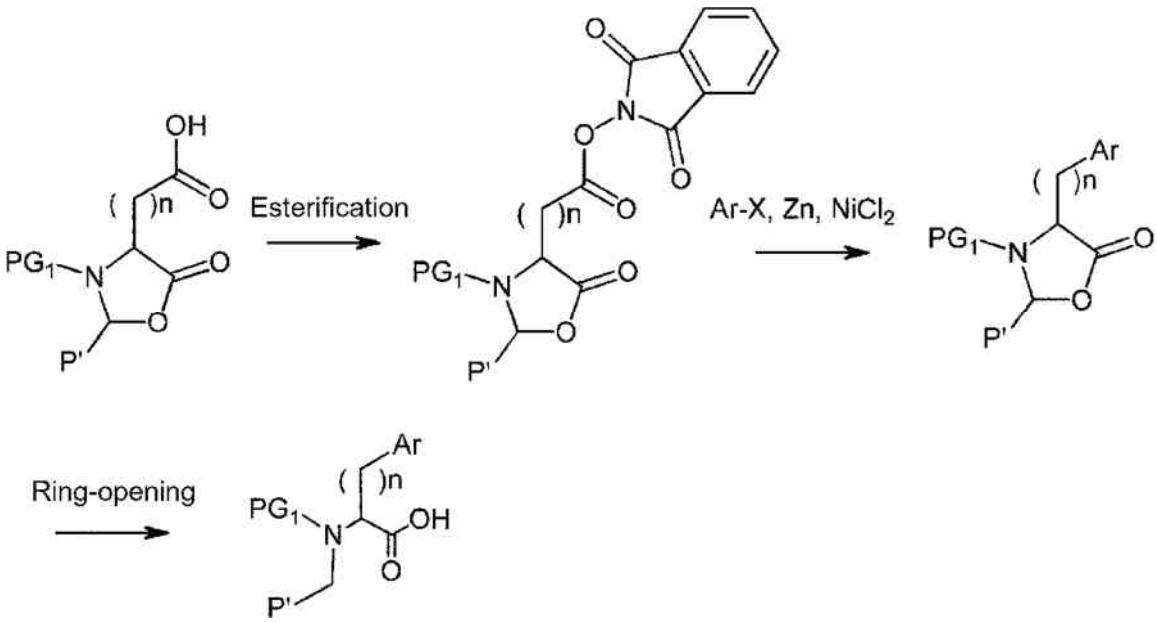
Non-natural amino acids having an aryl or heteroaryl group (such groups are referred to as "Ar" in the scheme) introduced onto the amino acid side chain can be prepared according to the following scheme. An N-hydroxyphthalimide (NHPI) group can be introduced onto the side chain by allowing NHPI to act on the carboxyl group of a protected amino acid (n = 1 or 2). A non-natural amino acid having an aryl or heteroaryl group introduced and possessing an aralkyl or heteroaralkyl group on the side chain can be prepared by allowing an aryl halide or heteroaryl halide to react according to the method of Huihui et al. (J. Am. Chem. Soc., 2016, 138(15), 5016-5019). Next, a C-terminal-free non-natural amino acid can be prepared by deprotecting the C-terminal protecting group.



[0241]

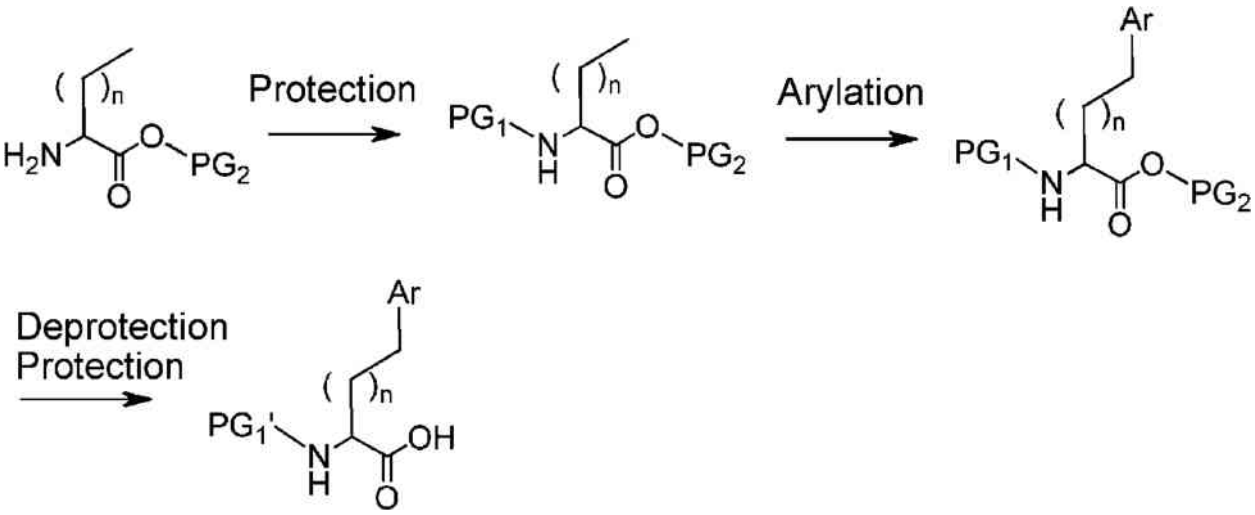
Non-natural amino acids having an aryl or heteroaryl group (such groups are referred to as "Ar" in the scheme) introduced onto the amino acid side chain and having a -CH_2-P' group introduced onto the amino acid nitrogen atom can be prepared according to the following scheme. An N-hydroxyphthalimide (NHPI) group can be introduced onto the side chain by

allowing NHPI to act on the carboxyl group of an amino acid protected by a cyclic protecting group (n = 1 or 2). A non-natural amino acid which has an aryl or heteroaryl group introduced, and has an aralkyl or heteroarylalkyl group on the side chain, and is protected by a cyclic protecting group, can be prepared by allowing an aryl halide or heteroaryl halide to react according to the method of Huihui et al. (J. Am. Chem. Soc., 2016, 138(15), 5016-5019). Next, the target C-terminal-free non-natural amino acid can be prepared by ring-opening reaction.

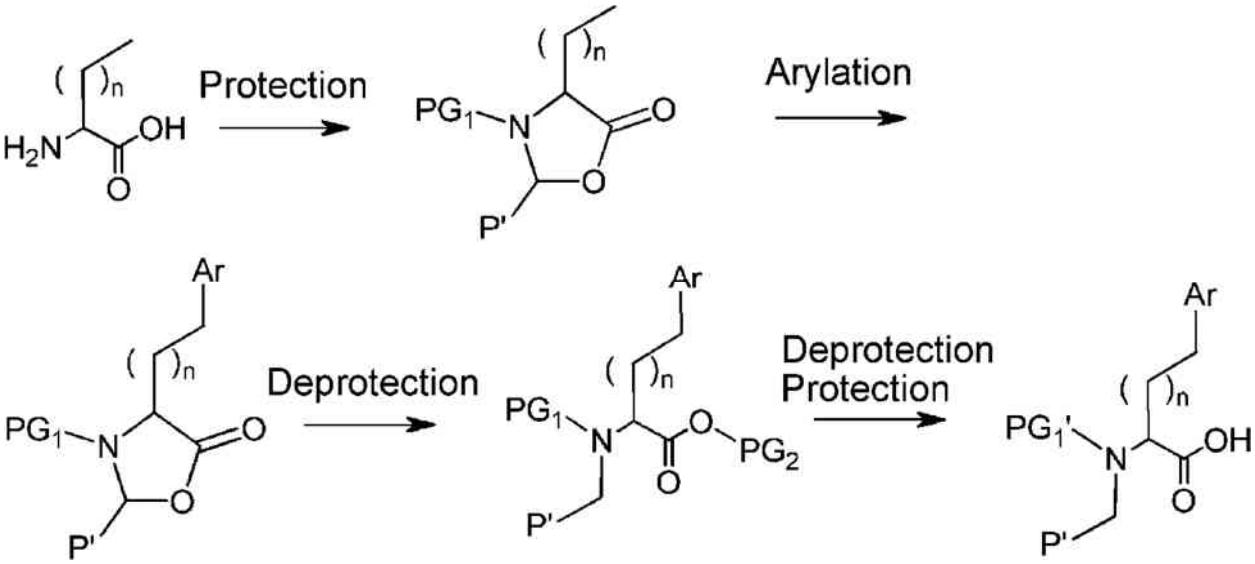


[0242]

Non-natural amino acids having an aryl or heteroaryl group (such groups are referred to as "Ar" in the scheme) introduced onto the amino acid side chain can be prepared according to the following scheme. A non-natural amino acid having an aryl or heteroaryl group introduced and possessing an aralkyl or heteroaralkyl group on the side chain can be prepared by introducing a protecting group onto a commercially available protected amino group (n = 0 or 1) and then allowing an aryl halide or heteroaryl halide to react according to the method of He et al. (Org. Lett. 2014, 16(24), 6488-6491). Next, the target C-terminal-free non-natural amino acid can be prepared by deprotection reaction and protecting group introduction reaction.

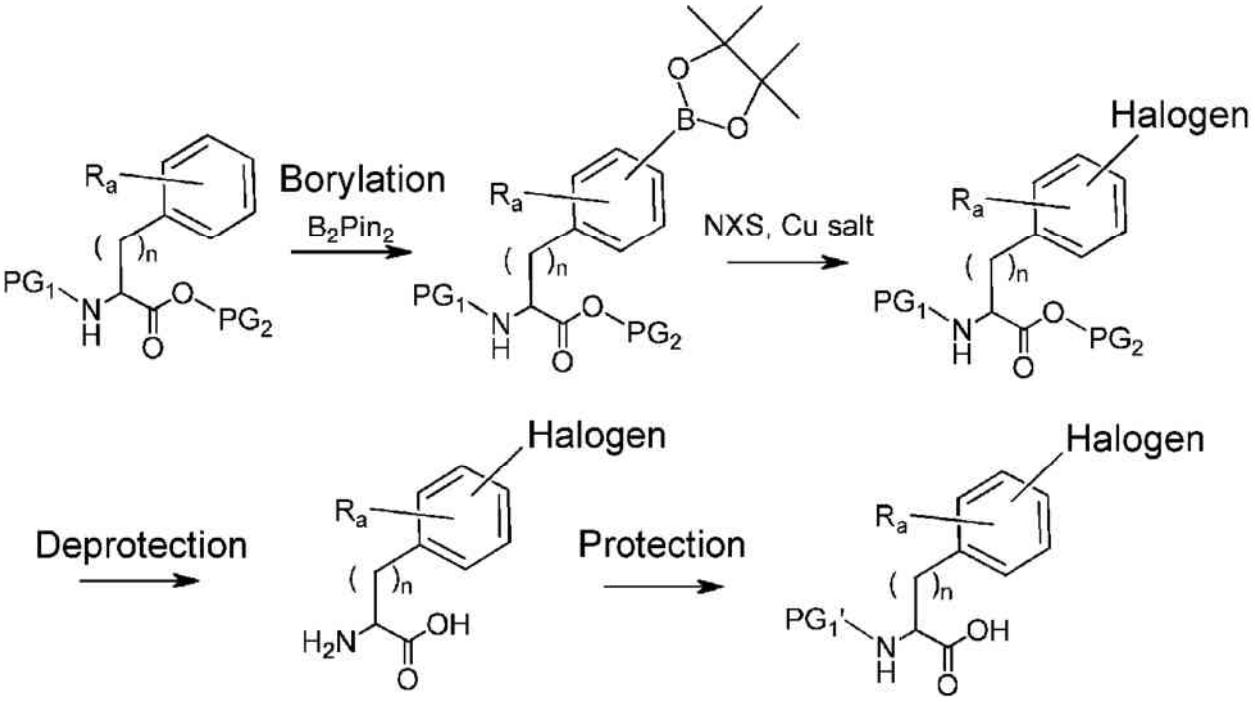


[0243]



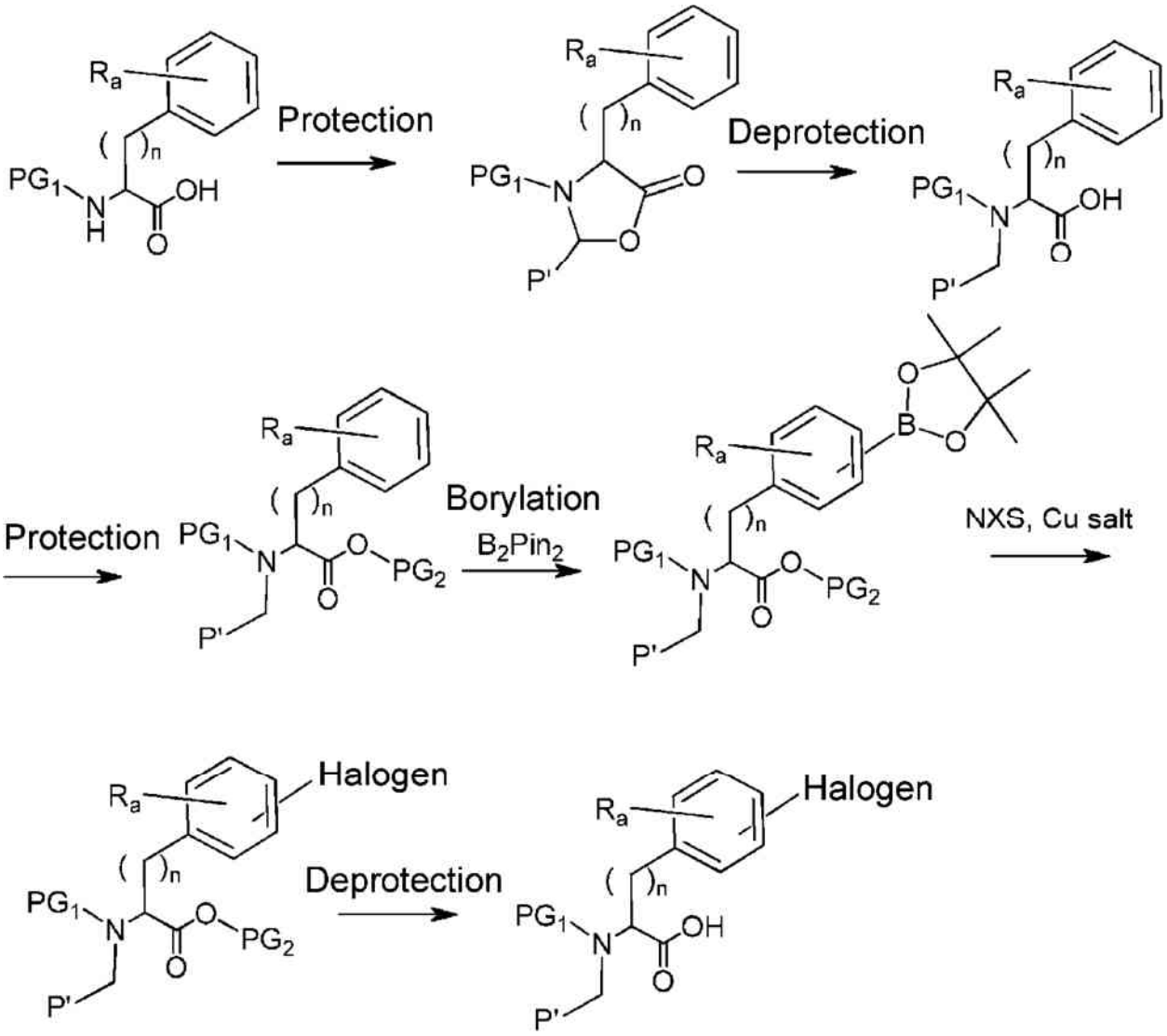
[0244]

Non-natural amino acids having a halogen atom introduced onto the aralkyl group on the amino acid side chain can be prepared according to the following scheme. A boronic acid ester can be introduced onto the aralkyl group which may have a substituent (R_a) on the amino acid side chain according to the method of Ishiyama et al. (J. Am. Chem. Soc. 2002, 124(3), 390-391). A halogen atom can be introduced onto the introduced boryl group using N-halosuccinimide according to the method of Lindner et al. (Chem. Eur. J., 2016, 22, 13218-13235). The target C-terminal-free non-natural amino acid can be prepared by appropriately introducing/removing a protecting group onto/from the obtained non-natural amino acid as necessary.



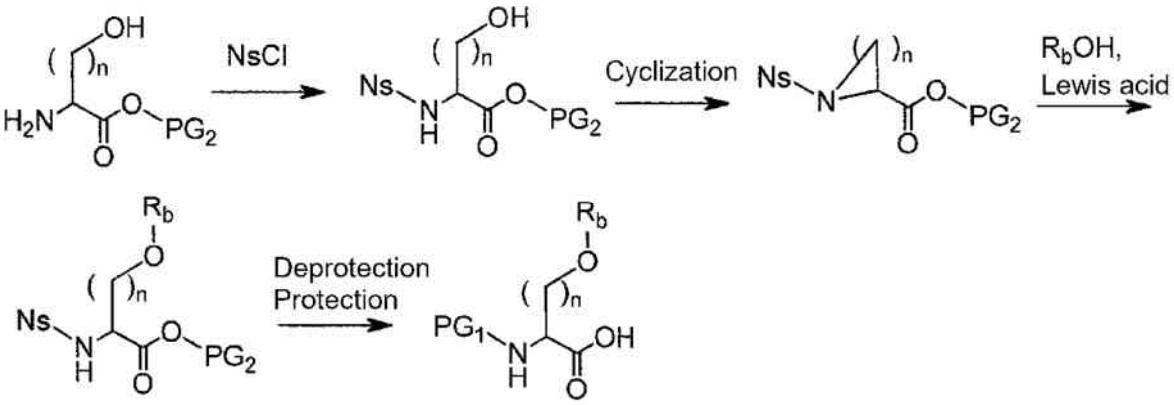
[0245]

Non-natural amino acids having a halogen atom introduced onto the aralkyl group of the amino acid side chain and a -CH_2-P' group introduced onto the amino acid nitrogen atom can be prepared according to the following scheme. A boronic acid ester can be introduced onto the aryl group of the amino acid having an aralkyl group which may have a substituent (R_a) on the amino acid side chain according to the method of Ishiyama et al. (J. Am. Chem. Soc. 2002, 124(3), 390-391). A halogen atom can be introduced onto the introduced boryl group using N-halosuccinimide according to the method of Lindner et al. (Chem. Eur. J., 2016, 22, 13218-13235). The target C-terminal-free non-natural amino acid can be prepared by appropriately introducing/removing a protecting group onto/from the obtained non-natural amino acid as necessary.



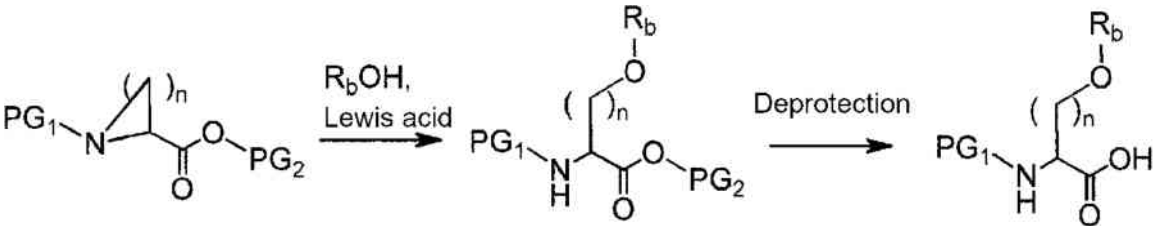
[0246]

Non-natural amino acids having an optionally substituted alkoxy or aralkoxy (R_bO) group on the amino acid side chain can be prepared according to the following scheme. A cyclized compound can be obtained according to the method of Mitsunobu et al. (Synthesis, 1981, 1, 1-28) after introducing a nosyl (Ns) group onto a commercially available serine derivative (n = 1 or 2) according to a conventional method. A serine ether compound can be obtained by ring-opening of the cyclized compound with a suitable alcohol (R_bOH) in the presence of a Lewis acid such as $BF_3 \cdot OEt_2$. The target C-terminal-free non-natural amino acid can be prepared by appropriately introducing/removing a protecting group onto/from the obtained non-natural amino acid as necessary.



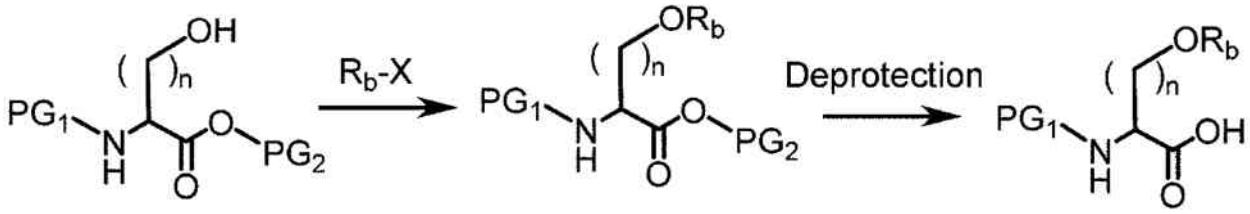
[0247]

Non-natural amino acids having an optionally substituted alkoxy or aralkoxy (R_bO) group on the amino acid side chain can be prepared according to the following scheme. A serine ether compound can be obtained by ring-opening of a commercially available cyclic compound (n = 1 or 2) with a suitable alcohol (R_bOH) in the presence of a Lewis acid such as $BF_3 \cdot OEt_2$ according to a conventional method. The target C-terminal-free non-natural amino acid can be prepared by appropriately introducing/removing a protecting group onto/from the obtained non-natural amino acid as necessary.



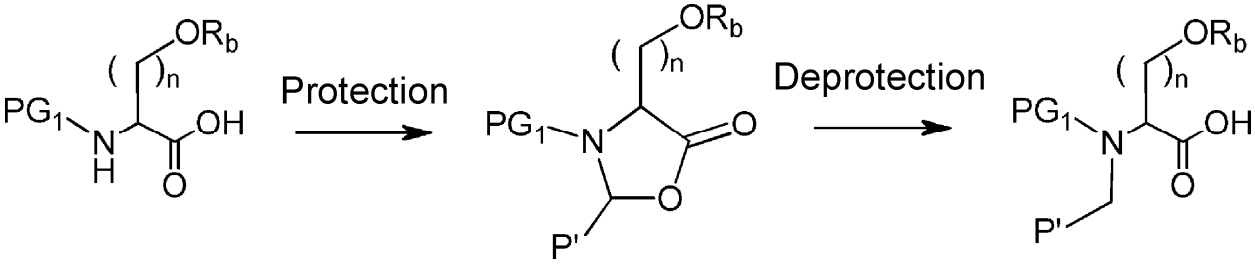
[0248]

Non-natural amino acids having an optionally substituted alkoxy or aralkoxy (R_bO) group on the amino acid side chain can be prepared according to the following scheme. A serine ether compound can be obtained by allowing an alkylating agent (R_b-X) to act on a commercially available serine derivative (n = 1 or 2) in the presence of a suitable base according to the method of Williamson et al. (Liebigs Ann. Chem. 1851, 77, 37-49). When R_b has a further convertible functional group, R_b can be converted to a target functional group by additional functional group conversion. Examples of such additional functional group conversion include multiple bond reduction reaction. Next, the target C-terminal-free non-natural amino acid can be prepared by deprotecting the obtained non-natural amino acid.



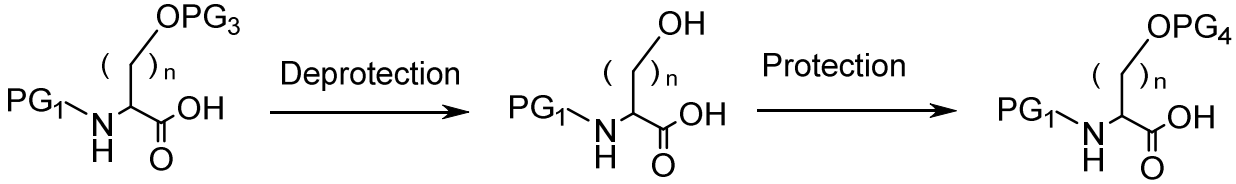
[0249]

Non-natural amino acids having an optionally substituted alkoxy or aralkoxy (R_bO) group on the amino acid side chain and having a -CH_2-P' group introduced onto the amino acid nitrogen atom can be prepared according to the following scheme. An oxazolidinone compound having a cyclic protecting group introduced can be obtained by allowing an aldehyde to act on a commercially available serine derivative or a serine derivative prepared by the above-described method (n = 1 or 2) according to the method of Freidinger et al. (J. Org. Chem., 1983, 48(1), 77-81). Next, the target C-terminal-free non-natural amino acid can be prepared by ring-opening reaction.



[0250]

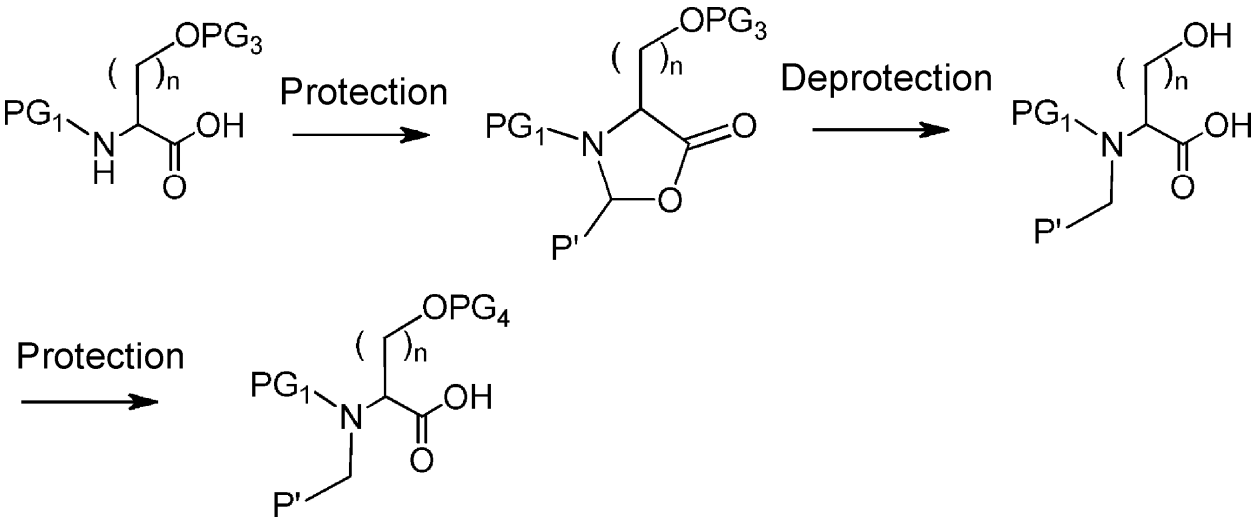
Non-natural amino acids having a protected hydroxy group on the amino acid side chain can be prepared according to the following scheme. The target C-terminal-free non-natural amino acid can be prepared by appropriately introducing/removing a protecting group onto/from a commercially available serine derivative or a serine derivative prepared by the above-described method (n = 1 or 2).



[0251]

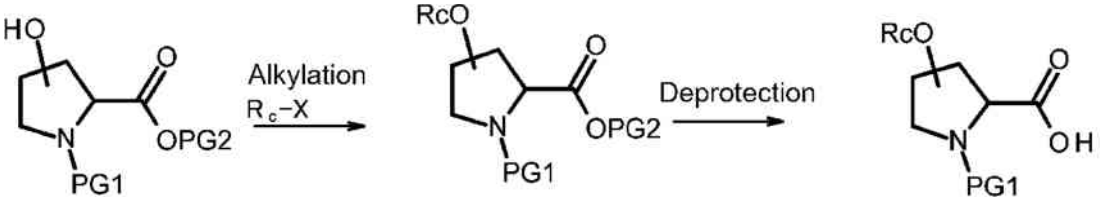
Non-natural amino acids having a protected hydroxy group on the amino acid side chain and a -CH_2-P' group introduced onto the amino acid nitrogen atom can be prepared according to the following scheme. An oxazolidinone compound having a cyclic protecting group introduced can be obtained by allowing an aldehyde to act on a commercially available serine derivative or a serine derivative prepared by the above-described method (n = 1 or 2)

according to the method of Freidinger et al. (J. Org. Chem., 1983, 48(1), 77-81). Next, the target C-terminal-free non-natural amino acid can be prepared by ring-opening reaction and protecting group introduction reaction.



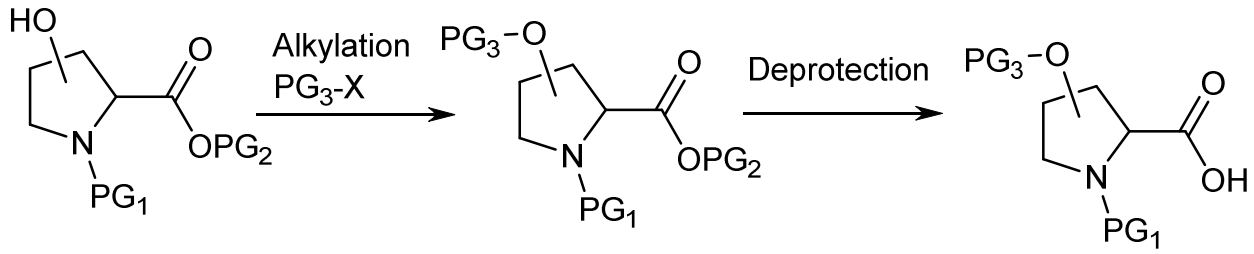
[0252]

Cyclic non-natural amino acids having a substituent (R_c) introduced onto the hydroxyl group of the cyclic amino acid can be prepared according to the following scheme. The hydroxy group of a commercially available cyclic amino acid can be converted to the target -OR_c group by appropriately introducing a functional group. As a reaction of converting the functional group, an ether bond can be produced by allowing an alkylating agent (R_c-X) to react in the presence of a suitable base according to the method of Williamson et al. (Liebigs Ann. Chem. 1851, 77, 37-49). When R_c has a further convertible functional group, R_c can be converted to a target functional group by additional functional group conversion. Next, the target C-terminal-free non-natural amino acid can be prepared by deprotection reaction.



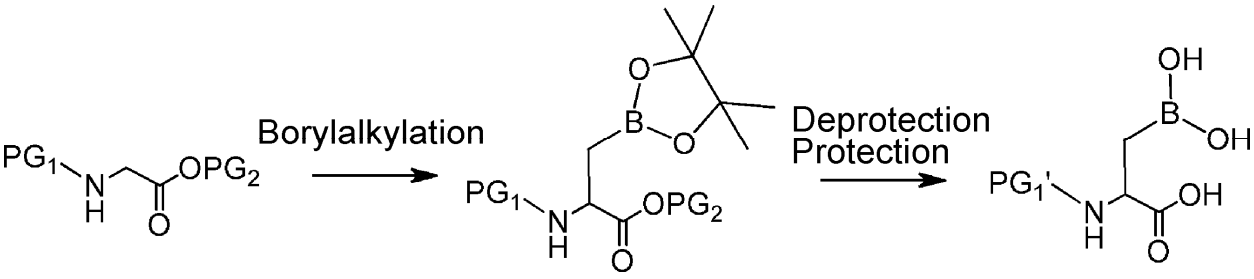
[0253]

Cyclic non-natural amino acids having a protecting group (PG_3) introduced onto the hydroxyl group of the cyclic amino acid can be prepared according to the following scheme. The target C-terminal-free non-natural amino acid can be prepared by appropriately introducing/removing a protecting group onto/from a commercially available cyclic amino acid.



[0254]

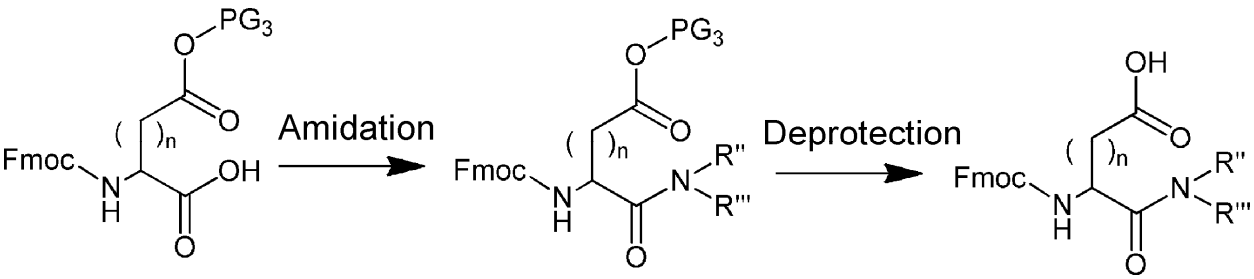
Non-natural amino acids having a boronic acid introduced onto the amino acid side chain can be prepared according to the following scheme. A non-natural amino acid having a boronic acid ester introduced can be obtained by allowing an aldehyde to act on a commercially available glycine derivative according to the method of Lee et al. (Bioorg. Med. Chem. Lett., 2009, 19(17), 4887-5274). Next, the target C-terminal-free non-natural amino acid can be prepared by appropriately introducing or removing a protecting group.



[0255]

(Synthesis 1 of Fmoc non-natural amino acids having a carboxyl group on the side chain)

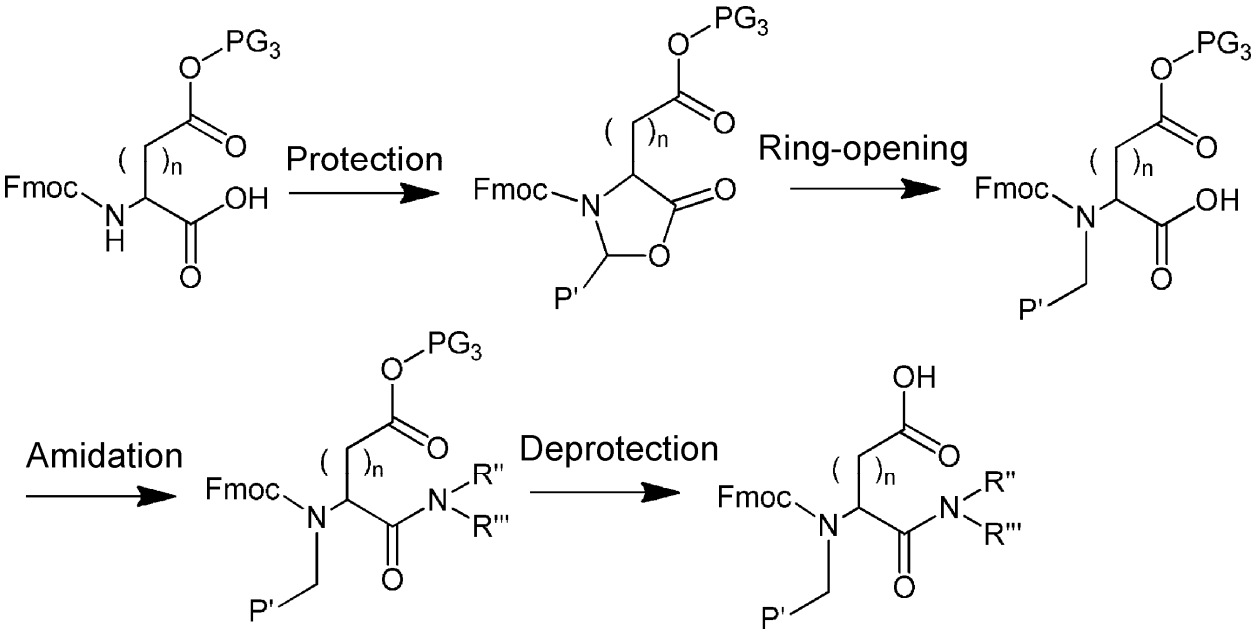
Fmoc non-natural amino acids having a carboxyl group on the side chain can be prepared according to the following scheme. The main chain carboxyl group of a starting material which is available from a commercial supplier and has a side chain carboxyl group protected by PG_3 (n = 1 or 2) can be converted to an amide group by condensing it with an amine (R"R'"NH) in the presence of a condensing agent such as DIC. Next, the target Fmoc non-natural amino acid having a carboxyl group on the side chain can be prepared by deprotecting PG_3.



[0256]

(Synthesis 2 of Fmoc non-natural amino acids having a carboxyl group on the side chain)

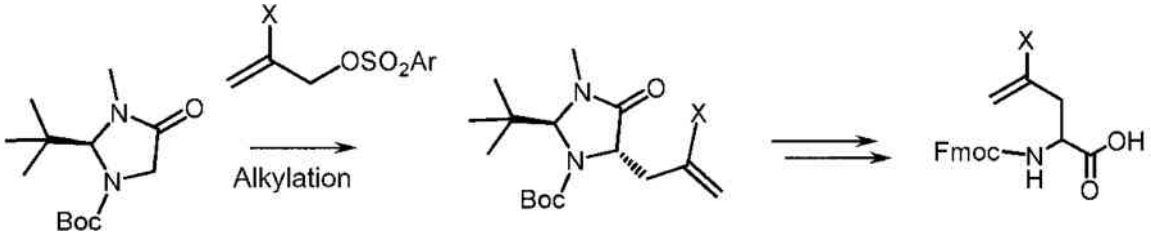
Fmoc non-natural amino acids having a carboxyl group on the side chain and a -CH_2-P' group introduced onto the amino acid nitrogen atom can be prepared according to the following scheme. The main chain carboxyl group of a starting material which is available from a commercial supplier and has a side chain carboxyl group protected by PG_3 (n = 1 or 2) can be converted to an amide group by condensing it with an amine (R"R'"NH) in the presence of a condensing agent such as DIC. Next, the target Fmoc non-natural amino acid having a carboxyl group on the side chain can be prepared by deprotecting PG_3.



[0257]

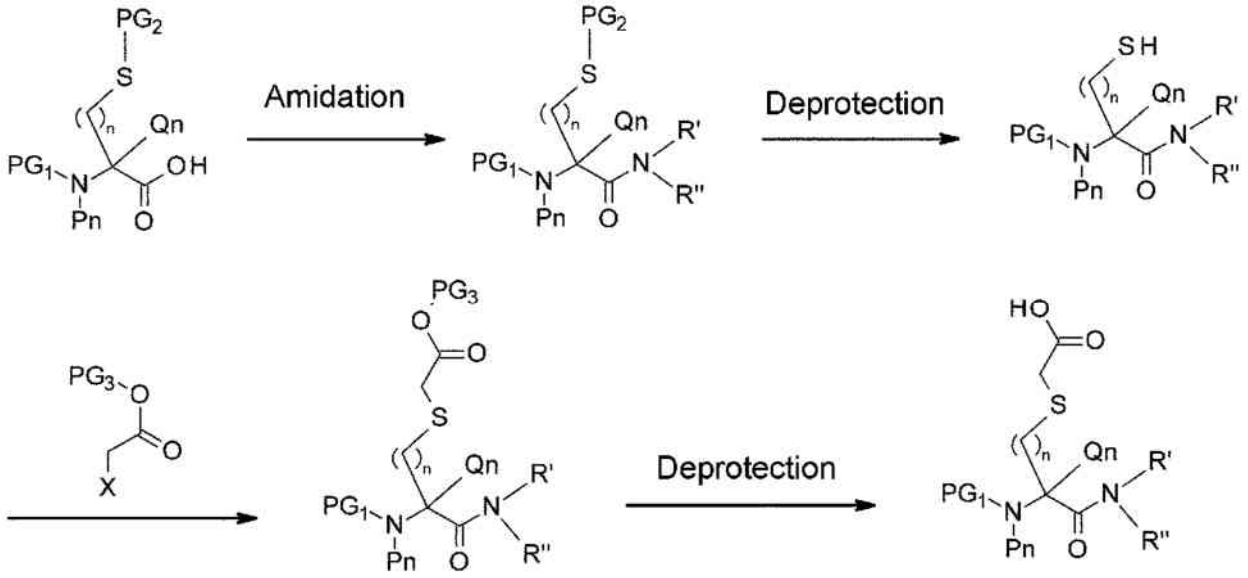
(Synthesis of Fmoc non-natural amino acids having vinyl halide on the side chain)

Fmoc non-natural amino acids having vinyl halide in the side chain can be synthesized by the following scheme according to the method of Shendage et al. (Eur. J. Org. Chem., 2005, 719-727). Boc-2-t-butyl-3-methylimidazolidin-4-one available from a commercial supplier is reacted with an alkylating agent having vinyl halide in the side chain in the presence of a base, and the intended Fmoc non-natural amino acid having vinyl halide in the side chain can be produced by the method described in the literature.



[0258]

Non-natural amino acids containing a thioether group on the side chain (n = 1 or 2) can be produced according to the following scheme. An amino acid having a protected side chain thiol group was subjected to carboxylic acid amidation, and following deprotection of the thiol group, halogenated acetic acid having a protected carboxylic acid was allowed to react to form a thioether bond. Next, the amino acid having a thioether group on the side chain can be produced by deprotecting the side chain carboxylic acid.



[0259]

Peptides containing a thioether group on the peptide main chain can be produced by using as a raw material the aforementioned amino acid having a thioether group on the side chain, but alternatively, they can also be produced by the method of Roberts *et al.* in which an N-terminal bromoacetamide is reacted with a cysteine side chain (Tetrahedron Letters, 1998, 39, 8357-8360), or the method of Robey *et al.* in which an N-terminal chloroacetamide is reacted with a cysteine side chain (Journal of Peptide Research, 2000, 56, 115-120).

[0260]

The compounds of the present invention and salts thereof, and solvates thereof include all stereoisomers (such as enantiomers and diastereomers (including cis and trans geometric isomers)) of the target compounds obtained through the above-described reaction steps, and racemates and other mixtures of such isomers. For example, the compounds of the present invention may have one or more asymmetric points, and the present invention encompasses racemic mixtures, diastereomeric mixtures, and enantiomers of such compounds.

[0261]

When the compounds according to the present invention are obtained as free forms, they can be converted to salts that may be formed by such compounds, or hydrates or solvates thereof, according to conventional methods.

[0262]

When the compounds according to the present invention are obtained as salts, hydrates, or solvates of such compounds, they can be converted to free forms of such compounds according to conventional methods.

[0263]

<Pharmaceutical compositions>

The present invention provides pharmaceutical compositions containing a cyclic compound of the present invention.

The pharmaceutical compositions of the present invention can be formulated by introducing a pharmaceutically acceptable carrier, in addition to a compound of the present invention, a salt thereof, or a solvate thereof by conventional methods. Commonly used excipients, binders, lubricants, colorants, correctives, and as necessary, stabilizers, emulsifiers, absorption promoters, surfactants, pH adjusters, preservatives, antioxidants, and the like can be used for formulation, and they are blended with ingredients generally used as raw materials of pharmaceutical formulations, and formulated by conventional methods.

For example, oral formulations are prepared by adding the compound of the present invention or a salt thereof, and an excipient, and as necessary, a binder, a disintegrant, a lubricant, a colorant, a corrective, and the like, and then formulating them into powder, fine granules, granules, tablets, coated tablets, capsules, and the like by a conventional method.

[0264]

Examples of these ingredients include animal and vegetable oils such as soybean oil, beef tallow, and synthetic glyceride; hydrocarbons such as liquid paraffin, squalane, and solid paraffin; ester oils such as octyldodecyl myristate and isopropyl myristate; higher alcohols such as cetostearyl alcohol and behenyl alcohol; silicone resin; silicone oil; surfactants such as polyoxyethylene fatty acid ester, sorbitan fatty acid ester, glycerol fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene hydrogenated castor oil, and polyoxyethylene-polyoxypropylene block copolymer; water-soluble polymers such as hydroxyethylcellulose, polyacrylic acid, carboxyvinyl polymer, polyethylene glycol, polyvinylpyrrolidone, and methylcellulose; lower alcohols such as ethanol and isopropanol; polyhydric alcohols such as glycerol, propylene glycol, dipropylene glycol, and sorbitol; sugars such as glucose and sucrose; inorganic powders such as silicic anhydride, magnesium aluminum silicate, and aluminum silicate; and purified water.

[0265]

Examples of the excipients include lactose, corn starch, white soft sugar, glucose, mannitol, sorbitol, microcrystalline cellulose, and silicon dioxide.

[0266]

Examples of the binders include polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, polypropylene glycol-polyoxyethylene block polymer, and meglumine.

[0267]

Examples of the disintegrants include starch, agar, gelatin powder, microcrystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, dextrin, pectin, and carboxymethylcellulose calcium.

[0268]

Examples of the lubricants include magnesium stearate, talc, polyethylene glycol, silica, and hydrogenated vegetable oil.

[0269]

For colorants, those approved as additives to pharmaceuticals are used. For correctives, cocoa powder, peppermint camphor, empasm, mentha oil, borneol, powdered cinnamon bark, and the like are used.

[0270]

Obviously, these tablets and granules may be sugar-coated or otherwise coated appropriately as necessary. When liquid formulations such as syrups and injectable formulations are prepared, they are formulated by adding pH adjusters, solubilizers, tonicity adjusting agents, and the like, and as necessary, solubilizing agents, stabilizers, and the like to the compounds according to the present invention or pharmacologically acceptable salts thereof using conventional methods.

[0271]

For example, the pharmaceutical compositions can be parenterally used in the form of injectable sterile solutions or suspensions with water or other pharmaceutically acceptable liquids. For example, they would be formulated by appropriately combining with pharmacologically acceptable carriers or media, specifically, sterile water, saline, vegetable oils, emulsifiers, suspending agents, surfactants, stabilizers, flavoring agents, excipients, vehicles, preservatives, or binders, and blending in unit dosage forms required in generally approved formulation. Specifically, carriers may include light anhydrous silicic acid, lactose, microcrystalline cellulose, mannitol, starch, carmellose calcium, carmellose sodium, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinyl acetal diethylaminoacetate, polyvinylpyrrolidone, gelatin, medium chain fatty acid triglyceride, polyoxyethylene

hydrogenated castor oil 60, white soft sugar, carboxymethylcellulose, corn starch, and inorganic salts. The amount of the active ingredient in such a formulation is designed to provide a suitable dose within an indicated range.

Sterile compositions for injection can be formulated in a conventional formulation manner using a vehicle such as distilled water for injection.

[0272]

Aqueous solutions for injection include, for example, isotonic solutions containing saline, glucose, and other adjuvants, such as D-sorbitol, D-mannose, D-mannitol, and sodium chloride, and may be used in combination with appropriate solubilizers, for example, alcohols, specifically, ethanol, polyalcohols, e.g., propylene glycol or polyethylene glycol, and nonionic surfactants, e.g., polysorbate 80 (registered trademark) or HCO-50.

[0273]

Oily liquids include sesame oil and soybean oil, and may be used in combination with benzyl benzoate and benzyl alcohol as solubilizers. They may also be blended with buffering agents such as phosphate buffer and sodium acetate buffer; analgesics such as procaine hydrochloride; stabilizers such as benzyl alcohol and phenol; and antioxidants. Prepared injections are usually packed in suitable ampoules.

[0274]

The administration method is preferably oral administration, but is not limited thereto. Specific examples of parenteral administration include dosage forms of injection, nasal administration, pulmonary administration, and transdermal administration. Examples of injection dosage forms include systemic or local administration by intravenous injection, intramuscular injection, intraperitoneal injection, subcutaneous injection, etc.

[0275]

The administration method can also be selected according to the age and symptom of the patient. The dosage of the pharmaceutical composition containing the peptide compound prepared by the method of the present invention can be selected, for example, in the range of 0.0001 mg to 1000 mg per kg body weight per dose. Alternatively, the dosage can be selected, for example, in the range of 0.001 to 100000 mg/body per patient; however, it is not necessarily limited to such values. The dosage and the administration method vary according to the body weight, the age, the symptom, and the like of the patient, but can be appropriately selected by those skilled in the art.

[0276]

In an embodiment, a cyclic compound of the present invention or a salt thereof, or a solvate thereof; or a pharmaceutical composition containing a cyclic compound of the present

invention or a salt thereof, or a solvate thereof can bind or selectively bind to KRAS in a subject and can be used for selectively inhibiting KRAS.

[0277]

In an embodiment, a cyclic compound of the present invention or a salt thereof, or a solvate thereof can bind or selectively bind to KRAS in a subject, and can be used for producing a medical drug for selectively inhibiting KRAS.

[0278]

In an embodiment, the present invention relates to a method for binding or selectively binding a cyclic compound of the present invention or a salt thereof, or a solvate thereof to KRAS in a subject, or a method for selectively inhibiting KRAS in a subject, including a step of administering an effective amount of a cyclic compound of the present invention or a salt thereof, or a solvate thereof to a subject who needs it.

[0279]

A cyclic compound of the present invention or a salt thereof, or a solvate thereof as mentioned above has high selectivity to KRAS in a subject. For example, a cyclic compound of the present invention has selectivity to KRAS (KRAS selectivity to NRAS and/or KRAS selectivity to HRAS) higher than PP1820: ((3S,9S,12S,17S,20S,23S,27S,30S,36S)-3-[2-[3-chloro-4-(trifluoromethyl)phenyl]ethyl]30-cyclopentyl-23-isobutyl-9-(isopentyloxymethyl)-N,N,7,17,18,24,28,31-octamethyl-20-[(1S)-1-methylpropyl]-2,5,8,11,16,19,22,25,29,32,35-undecaoxo-10-propyl-spiro [1,4,7,10,15,18,21,24,28,31,34-undecazatricyclo[34.3.0.012,15]nonatriacontane-33,1'-cyclobutane]-27-carboxamide).

[0280]

In an embodiment, the pharmaceutical composition of the present invention has KRAS inhibitory activity that is 3 times or more higher than NRAS inhibitory activity and HRAS inhibitory activity.

[0281]

In an embodiment, the pharmaceutical composition of the present invention has KRAS inhibitory activity that is 5 times, 7 times, 10 times, 15 times, or 20 times or more higher than NRAS inhibitory activity and HRAS inhibitory activity.

[0282]

In an embodiment, the cyclic compound of the present invention, or a salt thereof, or a solvate thereof, or a pharmaceutical composition containing the cyclic compound of the present invention, or a salt thereof, or a solvate thereof, can be used to treat and/or prevent cancer in a subject.

[0283]

In an embodiment, the cyclic compound of the present invention, or a salt thereof, or a solvate thereof, can be used in the manufacture of a medicament for treating and/or preventing cancer in a subject.

[0284]

In an embodiment, the present invention relates to a method for treating and/or preventing cancer in a subject, comprising the step of administering an effective amount of the cyclic compound of the present invention, or a salt thereof, or a solvate thereof, to a subject in need thereof.

[0285]

Specific examples of the cancer include lung cancer.

[0286]

The term "subject" herein includes mammals, and mammals are preferably humans.

[0287]

All prior art documents cited in the present specification are incorporated herein by reference.

[Example]

[0288]

The scope of the present invention will now be further described by way of Examples and Reference Examples below, but the present invention is not limited thereto. When production methods are not described, starting materials and reagents were obtained from commercial suppliers or synthesized using known methods. The analytical conditions of LC/MS are provided in Table 1.

[0289]

[Table 1]

Analytical conditions	Apparatus	Column (I.D.xlength)(mm)	Mobile phase	Gradient (A/B)	Flow rate (mL/Min)	Column temperature (°C)	Wave length
SQDFA05	Acquity UPLC/SQD	Ascentis Express C18 (2.1x50)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=> 0/100(1.0 Min) => 0/100(0.4 Min)	1.0	35	210-400nm PDA total
SQDFA50	Acquity UPLC/SQD	Ascentis Express C18 (2.1x50)	A)0.1% FA,H_2O B)0.1% FA,MeCN	50/50=> 0/100(0.7 Min) => 0/100(0.7 Min)	1.0	35	210-400nm PDA total
SQDFA50_2	Acquity UPLC/SQD	Ascentis Express C18 (2.1x50)	A)0.1% FA,H_2O B)0.1% FA,MeCN	50/50=> 0/100(1 Min) => 0/100(0.4 Min)	1.0	35	210-400nm PDA total
SQDFA40	Acquity UPLC/SQD	Ascentis Express C18 (2.1x50)	A)0.1% FA,H_2O B)0.1% FA,MeCN	60/40=> 0/100(1 Min) => 0/100(0.4 Min)	1.0	35	210-400nm PDA total
SQDFA05long	Acquity UPLC/SQD	Ascentis Express C18 (2.1x50)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=> 0/100(4.5 Min) => 0/100(0.5 Min)	1.0	35	210-400nm PDA total
SQDFA50long	Acquity UPLC/SQD	Ascentis Express C18 (2.1x50)	A)0.1% FA,H_2O B)0.1% FA,MeCN	50/50=> 0/100(4.5 Min) => 0/100(0.5 Min)	1.0	35	210-400nm PDA total
SQDAA05	Acquity UPLC/SQD	Ascentis Express C18 (2.1x50)	A)10mM $AcONH_4$,H_2O B)MeOH	95/5=> 0/100(1.0 Min) => 0/100(0.4 Min)	1.0	35	210-400nm PDA total
SQDAA50	Acquity UPLC/SQD	Ascentis Express C18 (2.1x50)	A)10mM $AcONH_4$,H_2O B)MeOH	50/50=> 0/100(0.7 Min) => 0/100(0.7 Min)	1.0	35	210-400nm PDA total
SQDAA50_2	Acquity UPLC/SQD	Ascentis Express C18 (2.1x50)	A)10mM $AcONH_4$,H_2O B)MeOH	50/50=> 0/100(0.7 Min) => 0/100(0.7 Min)	0.9	35	210-400nm PDA total

SMD method_02	Shimazu LCMS-2020	Shim-Pack XR-ODS (3.0x50)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	60/40=> 5/95(3 **Min**)=> 5/95(0.7 **Min**)	1.2	40	190-400 PDA total
SMD method_03	Nexera/2020	Ascentis Express C18 (2.1x50)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=> 0/100(4.5 **Min**) => 0/100(0.5 **Min**)	1.0	35	210-400nm PDA total
SMD method_04	Nexera/2020	Ascentis Express C18 (2.1x50)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=> 0/100(1.5 **Min**) => 0/100(0.5 **Min**)	1.0	35	210-400nm PDA total
SMD method_05	Nexera/2020	Ascentis Express RP-Amide (2.1x50)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=>0/100(1.5 **Min**) =>0/100(0.5 **Min**)	1.0	35	210-400nm PDA total
SMD method_06	Nexera/2020	Ascentis Express C18 (2.1x50)	A)0.1% FA,H_2O B)0.1% FA,MeCN	50/50=>0/100(1 **Min**) =>0/100(1 **Min**)	1.0	35	210-400nm PDA total
SMD method_07	Nexera/2020	Ascentis Express RP-Amide (2.1x50)	A)0.1% FA,H_2O B)0.1% FA,MeCN	50/50=>0/100(1 **Min**) =>0/100(1 **Min**)	1.0	35	210-400nm PDA total
SMD method_08	Nexera/2020	Accucore C18 (2.1x50)	A) 10mM NH4HCO3 in H2O B) MeCN	95/5=>5/95(1.5 **Min**) =>5/95(0.5 **Min**)	1.0	35	210-400nm PDA total
SMD method_10	Nexera/2020	Kinetex EVO C18 (2.1x50)	A) 10mM NH4HCO3 in H2O B) MeCN	95/5=>5/95(1.5 **Min**) =>5/95(0.5 **Min**)	1.0	35	210-400nm PDA total
SMD method_11	Shimazu LCMS-2020	Shim-Pack XR-ODS-C18 (3.0x50)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 5/95(2 **Min**)=> 5/95(0.7 **Min**)	1.2	40	190-400nm PDA total
SMD method_12	Shimazu LCMS-2020	Shim-Pack XR-ODS (3.0x50)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 0/100(1.2 **Min**)=> 0/100(1 **Min**)	1.0	40	190-800nm PDA total

SMD method_13	Shimazu LCMS-2020	Shim-Pack XR-ODS (3.0x50)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 0/100(2.2 **Min**)=> 0/100(1 **Min**)	1.0	40	190-800nm PDA total
SMD method_14	Shimazu LCMS-2020	Shim-Pack XR-ODS (3.0x50)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 0/100(1.1 **Min**)=> 0/100(0.6 **Min**)	1.2	40	190-400nm PDA total
SMD method_15	Shimazu LCMS-2020	Shim-Pack XR-ODS-C18 (3.0x50)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	70/30=> 5/95(3.8 **Min**)=> 5/95(0.8 **Min**)	1.2	40	190-400nm PDA total
SMD method_16	Shimazu LCMS-2020	Shim-Pack XR-ODS-C18 (3.0x50)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 5/95(3.0 **Min**)=> 5/95(0.7 **Min**)	1.2	40	190-400nm PDA total
SMD method_17	Shimadzu LCMS-2020 LC-20ADXR	kinetex XB-C18(3.0x50)	A)0.1% FA,H2O B)0.1% FA,MeCN	90/10=> 0/100(1.2 **Min**)=> 0/100(0.5 **Min**) =>90/10(0.1 **Min**)	1.5	40	190-400nm PDA total
SMD method_18	Shimadzu LCMS-2020 LC-20AD	Shim-Pack XR-ODS (3.0x50)	A)0.05% TFA,H2O B)0.05% TFA,MeCN	95/5=> 0/100(2.2 **Min**)=> 0/100(1.0 **Min**) =>95/5(0.1 **Min**)	1.0	40	190-400nm PDA total
SMD method_19	Shimadzu LCMS-2020	ACQUITY BEH C18 (2.1x50)	A)0.15% FA,H_2O B)0.15% FA,MeCN	90/10=> 30/70(3.6 **Min**)=> 30/70(1.0 **Min**)	0.7	45	190-600nm PDA total
SMD method_20	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 5/95(1.2 **Min**)=> 5/95(0.6 分間)=> 95/5(0.02 **Min**)	1.5	40	190-400nm PDA total
SMD method_21	Shimadzu LCMS-2020 LC-20AD	Ascentis Express C18 (4.6x100)	A)0.1% FA,H2O B)0.1% FA,MeCN	95/5=> 70/30(15.0 **Min**)=> 70/30(3.0 **Min**) =>5/95(2.0 **Min**)	1.0	40	190-400nm PDA total
SSC-AA-02/03	Nexera UC/2020	Ascentis Express C18 (2.1x50)	A)10mM $AcONH_4$,H_2O B)MeOH	70/30=> 0/100(8.75 **Min**)=> 0/100(1.25 **Min**)	0.5	50	210-400nm PDA total
SSC-FA-02/03	Nexera UC/2020	Ascentis Express C18 (2.1x50)	A)0.1% FA,H2O B)0.1% FA,MeCN	70/30=> 10/90(7.5 **Min**) => 0/100(0.01 **Min**) => 0/100(2.49 **Min**)	0.5	50	210-400nm PDA total

SMD method_22	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 5/95(0.7Min)=> 5/95(0.4Min)	1.5	40	190-400nm PDA total
SMD method_23	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	60/40=> 0/100(2.0Min)=> 0/100(0.7Min)	1.2	40	190-400nm PDA total
SMD method_24	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 0/100(1.1Min)=> 0/100(0.6Min)	1.5	40	190-400nm PDA total
SMD method_25	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 0/100(1.1Min)=> 0/100(0.6Min)	1.2	40	190-400nm PDA total
SMD method_26	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=> 5/95(1.1Min)=> 5/95(0.6Min)	1.5	40	190-400nm PDA total
SMD method_27	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	50/50=> 0/100(2.0Min)=> 0/100(0.7Min)	1.2	40	190-400nm PDA total
SMD method_28	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=> 5/95(0.7Min)=> 5/95(0.4Min)	1.2	40	190-400nm PDA total
SMD method_29	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 5/95(1.1Min)=> 5/95(0.6Min)	1.3	40	190-400nm PDA total
SMD method_30	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 0/100(0.7Min)=> 0/100(0.4Min)	1.5	40	190-400nm PDA total
SMD method_31	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 5/95(0.7Min)=> 5/95(0.4Min)	1.2	40	190-400nm PDA total

SMD method_32	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	70/30=> 30/70(1.7Min)=> 0/100(0.6Min)=> 0/100(0.5Min)	1.2	40	190-400nm PDA total
SMD method_33	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 0/100(0.7Min)=> 0/100(0.4Min)	1.3	40	190-400nm PDA total
SMD method_34	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	60/40=> 0/100(2.0Min)=> 0/100(0.7Min)	1.3	40	190-400nm PDA total
SMD method_35	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=> 0/100(0.7Min)=> 0/100(0.4Min)	1.0	40	190-400nm PDA total
SMD method_36	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=> 5/95(0.7Min)=> 5/95(0.4Min)	1.0	40	190-400nm PDA total
SMD method_37	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.1% FA,H_2O B)0.1% FA,MeCN	60/40=> 5/95(2.3Min)=> 5/95(0.5Min)	1.2	40	190-400nm PDA total
SMD method_38	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=> 5/95(1.1Min)=> 5/95(0.6Min)	1.2	40	190-400nm PDA total
SMD method_39	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=> 5/95(0.7Min)=> 5/95(0.4Min)	1.5	40	190-400nm PDA total
SMD method_40	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.1% FA,H_2O B)0.1% FA,MeCN	95/5=> 0/100(0.7Min)=> 0/100(0.4Min)	1.2	40	190-400nm PDA total
SMD method_41	Shimazu LCMS-2020	Halo C18 (3.0x30)	A)0.05% TFA,H_2O B)0.05% TFA,MeCN	95/5=> 5/95(1.1Min)=> 5/95(0.6Min)	1.5	40	190-400nm PDA total

[0290]

Example 1 Solid-phase synthesis of peptide compound

Peptide elongation was performed through the following basic route (also called the basic peptide synthesis method) according to the peptide synthesis method by the Fmoc method described in WO2013/100132 or WO2018/225864. That is to say, it included the five steps of:

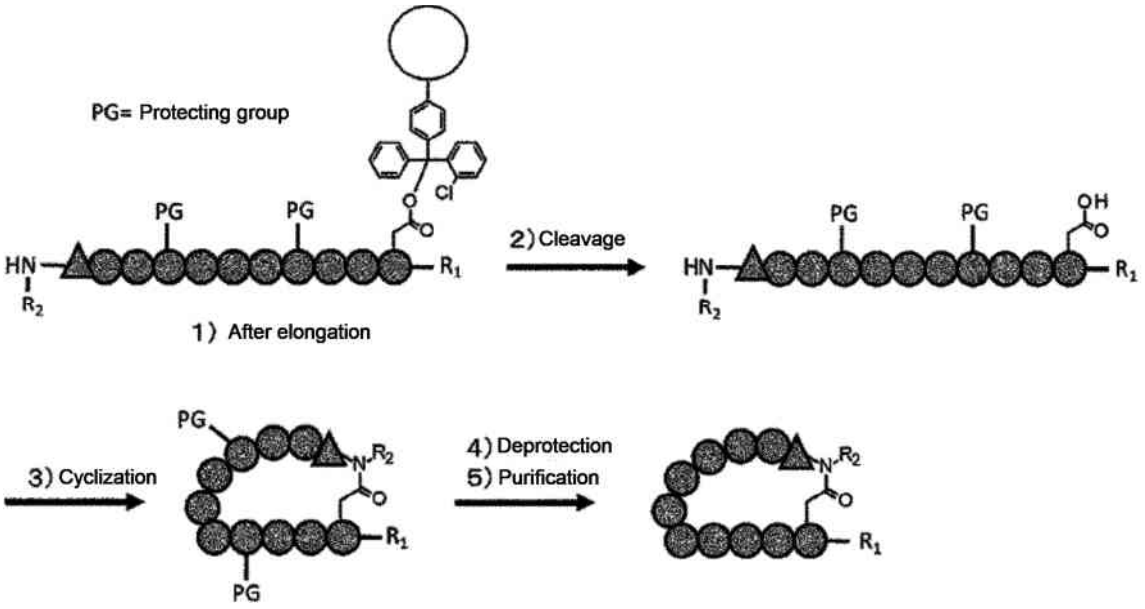
1) a peptide elongation reaction by the Fmoc method from the N-terminal of an amino acid in which the Asp side-chain carboxylic acid or the peptide main-chain carboxylic acid was supported on 2-chlorotrityl resin,

2) a process of cleaving a peptide from 2-chlorotrityl resin,

3) amide cyclization by condensation between the Asp side-chain carboxylic acid or the peptide main-chain carboxylic acid resulting from removal from 2-chlorotrityl resin by the cleaving process and the amino group at the peptide chain N-terminal (a triangular unit),

4) optional deprotection of the protecting group of a side-chain functional group contained in the peptide chain, and

5) purification of a compound by preparative HPLC. In the present Examples, peptide compounds were synthesized through this basic route unless specified otherwise.



[0291]

1-1. Fmoc-amino acid used in peptide synthesis by peptide synthesizer

In the peptide synthesis described herein, the Fmoc-amino acids listed in Table 2 to Table 4 were used in synthesis by a peptide synthesizer.

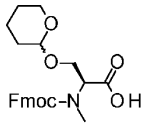
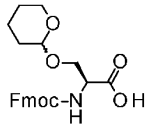
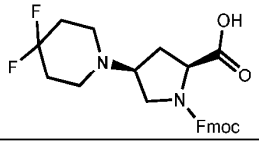
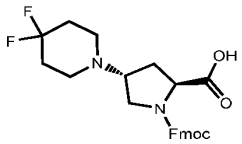
The Fmoc-amino acids listed in Table 2 were synthesized according to the method described in WO2018/225851 or WO2018/225864.

The Fmoc-amino acids listed in Table 3 were purchased from commercial suppliers.

The Fmoc-amino acids listed in Table 4 were synthesized according to the scheme shown below.

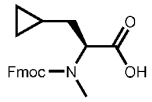
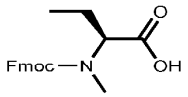
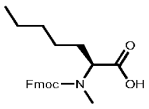
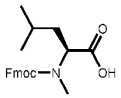
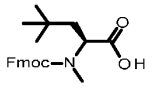
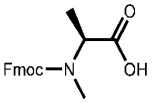
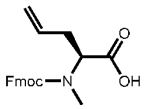
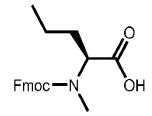
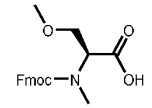
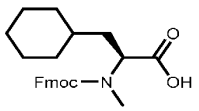
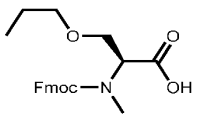
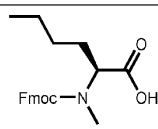
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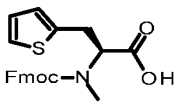
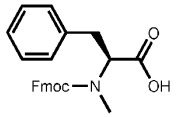
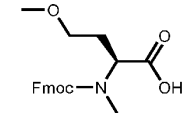
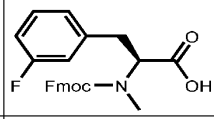
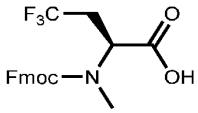
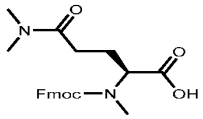
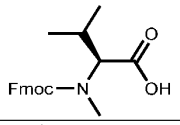
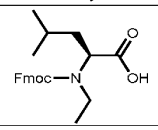
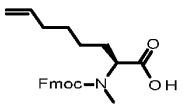
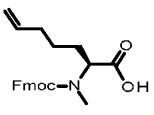
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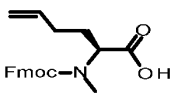
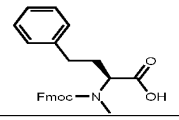
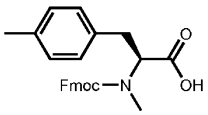
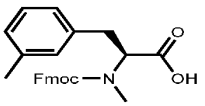
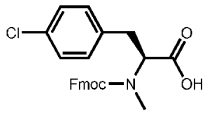
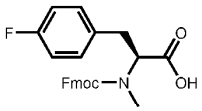
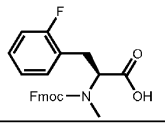
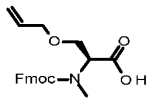
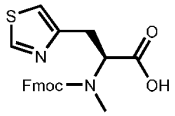
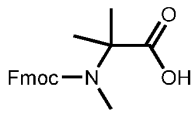
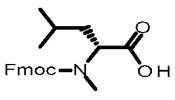
Compound No.	Abbreviation	Structural Formula	Name
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aa073	Fmoc-Ser(THP)-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-tetrahydropyran-2-yloxy-propanoic acid
aa270	Fmoc-cisPro(4-pip-4-F2)-OH		(2S,4S)-4-(4,4-difluoro-1-piperidyl)-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidine-2-carboxylic acid
aa271	Fmoc-Pro(4-pip-4-F2)-OH		(2S,4R)-4-(4,4-difluoro-1-piperidyl)-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidine-2-carboxylic acid

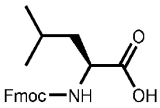
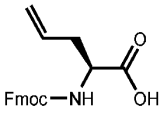
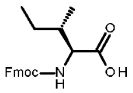
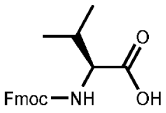
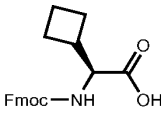
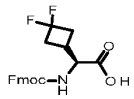
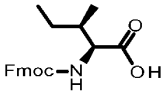
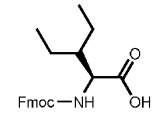
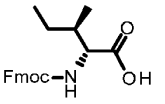
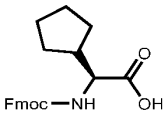
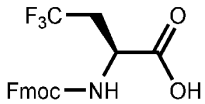
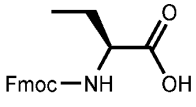
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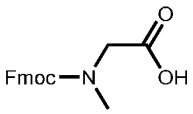
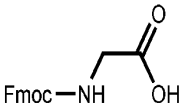
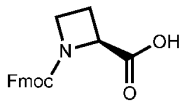
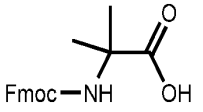
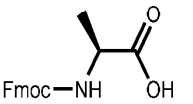
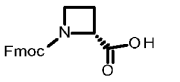
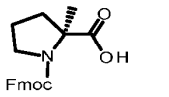
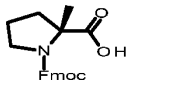
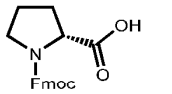
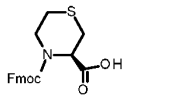
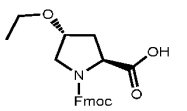
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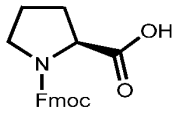
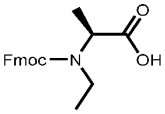
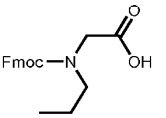
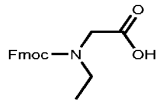
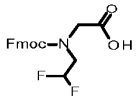
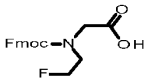
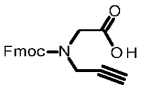
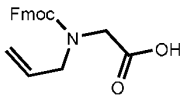
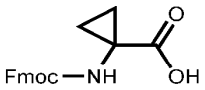
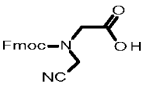
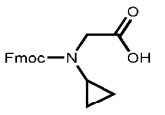
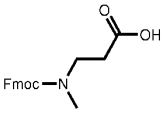
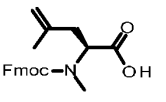
Compound No.	Abbreviation	Structural Formula	Name	CAS No.
aa001	Fmoc-MeAla(cPr)-OH		(2S)-3-cyclopropyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid	2304413-31-6
aa002	Fmoc-MeAbu-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]butanoic acid	1310575-53-1
aa003	Fmoc-MeHnl-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]heptanoic acid	
aa007	Fmoc-MeLeu-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-methyl-pentanoic acid	103478-62-2
aa008	Fmoc-MeAla(tBu)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4,4-dimethyl-pentanoic acid	1357308-53-2
aa009	Fmoc-MeAla-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid	84000-07-7
aa011	Fmoc-MeAlgly-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]pent-4-enoic acid	2606012-88-6
aa012	Fmoc-MeNva-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]pentanoic acid	252049-05-1
aa014	Fmoc-MeSer(Me)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-methoxy-propanoic acid	1569103-64-5
aa015	Fmoc-MeCha-OH		(2S)-3-cyclohexyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid	148983-03-3
aa016	Fmoc-MeSer(nPr)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-propoxy-propanoic acid	2255321-10-7
aa017	Fmoc-MeNle-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]hexanoic acid	112883-42-8

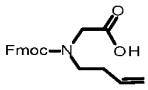
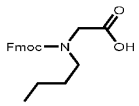
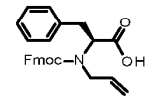
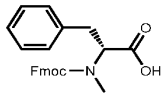
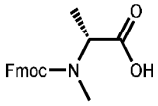
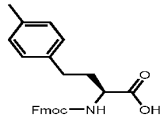
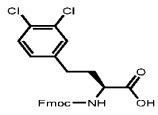
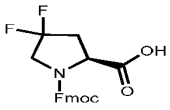
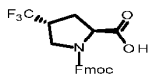
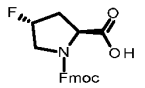
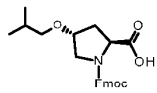
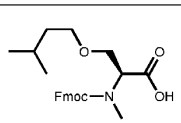
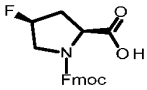
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aa025	Fmoc-MeAla(3-Pyr)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-(3-pyridyl)propanoic acid	1979173-93-7
aa026	Fmoc-MePhe-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-phenyl-propanoic acid	77128-73-5
aa027	Fmoc-MeHse(Me)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-methoxy-butanoic acid	1979169-11-3
aa032	Fmoc-MePhe(3-Cl)-OH		(2S)-3-(3-chlorophenyl)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid	1446478-28-9
aa033	Fmoc-MePhe(3-F)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-(3-fluorophenyl)propanoic acid	1820567-10-9
aa034	Fmoc-MeAbu(4-F3)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4,4,4-trifluoro-butanoic acid	
aa035	Fmoc-MeGln(Me2)-OH		(2S)-5-(dimethylamino)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-5-oxo-pentanoic acid	2255321-26-5
aa037	Fmoc-MeVal-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-methyl-butanoic acid	84000-11-3
aa038	Fmoc-EtLeu-OH		(2S)-2-[ethyl(9H-fluoren-9-ylmethoxycarbonyl)amino]-4-methyl-pentanoic acid	
aa039	Fmoc-MeAocte(2)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]oct-7-enoic acid	1808268-11-2
aa040	Fmoc-MeAhpe(2)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]hept-6-enoic acid	856412-24-3

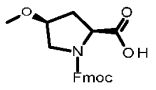
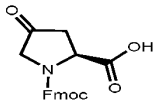
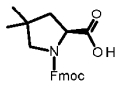
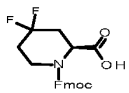
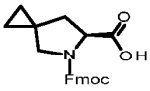
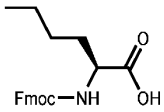
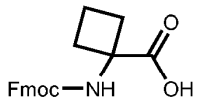
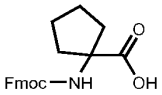
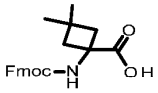
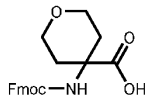
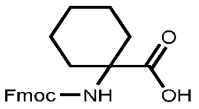
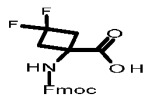
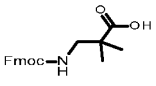
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aa042	Fmoc-MeHph-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-phenyl-butanoic acid	1065076-30-3
aa045	Fmoc-MePhe(4-Me)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-(p-tolyl)propanoic acid	227616-20-8
aa046	Fmoc-MePhe(3-Me)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-(m-tolyl)propanoic acid	
aa048	Fmoc-MePhe(4-Cl)-OH		(2S)-3-(4-chlorophenyl)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid	1217716-50-1
aa051	Fmoc-MePhe(4-F)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-(4-fluorophenyl)propanoic acid	1979176-87-8
aa052	Fmoc-MePhe(2-F)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-(2-fluorophenyl)propanoic acid	2109724-64-1
aa053	Fmoc-MeSer(Al)-OH		(2S)-3-allyloxy-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid	
aa054	Fmoc-MeAla(4-Thz)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-thiazol-4-yl-propanoic acid	1446478-22-3
aa055	Fmoc-MeAib-OH		2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-2-methyl-propanoic acid	400779-65-9
aa057	Fmoc-Azp(2)-OH		(2S)-1-(9H-fluoren-9-ylmethoxycarbonyl)azepane-2-carboxylic acid	2322925-11-9
aa058	Fmoc-D-MeLeu-OH		(2R)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-methyl-pentanoic acid	103478-63-3

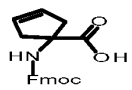
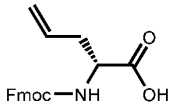
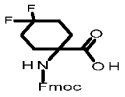
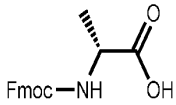
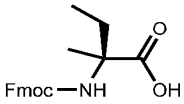
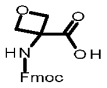
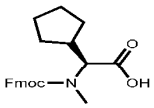
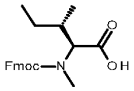
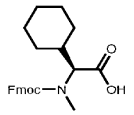
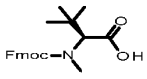
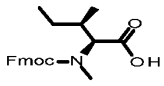
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aa062	Fmoc-Ile-OH		(2S,3S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-methyl-pentanoic acid	71989-23-6
aa063	Fmoc-Val-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-methyl-butanoic acid	68858-20-8
aa064	Fmoc-Gly(cBu)-OH		(2S)-2-cyclobutyl-2-(9H-fluoren-9-ylmethoxycarbonylamino)acetic acid	1391630-31-1
aa065	Fmoc-Gly(cBu-3-F2)-OH		(2S)-2-(3,3-difluorocyclobutyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)acetic acid	2349734-08-1
aa066	Fmoc-alle-OH		(2S,3R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-methyl-pentanoic acid	251316-98-0
aa067	Fmoc-Nva(3-Et)-OH		(2S)-3-ethyl-2-(9H-fluoren-9-ylmethoxycarbonylamino)pentanoic acid	1310680-47-7
aa068	Fmoc-D-Ile-OH		(2R,3R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-methyl-pentanoic acid	143688-83-9
aa069	Fmoc-Gly(cPent)-OH		(2S)-2-cyclopentyl-2-(9H-fluoren-9-ylmethoxycarbonylamino)acetic acid	220497-61-0
aa070	Fmoc-Abu(4-F3)-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4,4-trifluoro-butanoic acid	181128-48-3
aa071	Fmoc-Abu-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid	135112-27-5

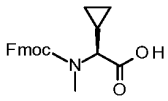
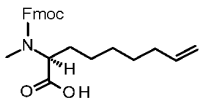
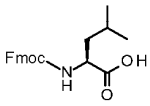
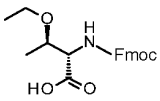
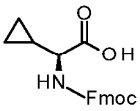
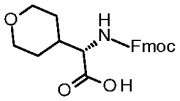
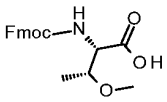
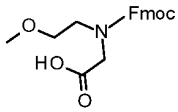
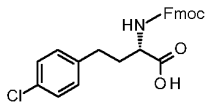
aa074	Fmoc-MeGly-OH		2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetic acid	77128-70-2
aa075	Fmoc-Gly-OH		2-(9H-fluoren-9-ylmethoxycarbonylamino)acetic acid	29022-11-5
aa076	Fmoc-Aze(2)-OH		(2S)-1-(9H-fluoren-9-ylmethoxycarbonyl)azetidine-2-carboxylic acid	136552-06-2
aa077	Fmoc-Aib-OH		2-(9H-fluoren-9-ylmethoxycarbonylamino)-2-methyl-propanoic acid	94744-50-0
aa078	Fmoc-Ala-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)propanoic acid	35661-39-3
aa079	Fmoc-D-Aze(2)-OH		(2R)-1-(9H-fluoren-9-ylmethoxycarbonyl)azetidine-2-carboxylic acid	374791-02-3
aa080	Fmoc-(Me)Pro-OH		(2S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-2-methyl-pyrrolidine-2-carboxylic acid	167275-47-0
aa081	Fmoc-D-(Me)Pro-OH		(2R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-2-methyl-pyrrolidine-2-carboxylic acid	1286768-33-9
aa082	Fmoc-D-Pro-OH		(2R)-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidine-2-carboxylic acid	101555-62-8
aa083	Fmoc-Tmo(2)-OH		(3R)-4-(9H-fluoren-9-ylmethoxycarbonyl)thiomorpholine-3-carboxylic acid	959572-96-4
aa084	Fmoc-Mor(3)-OH		(3S)-4-(9H-fluoren-9-ylmethoxycarbonyl)morpholine-3-carboxylic acid	281655-37-6
aa085	Fmoc-Pic(2)-OH		(2S)-1-(9H-fluoren-9-ylmethoxycarbonyl)piperidine-2-carboxylic acid	86069-86-5
aa086	Fmoc-Hyp(Et)-OH		(2S,4R)-4-ethoxy-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidine-2-carboxylic acid	1446478-31-4

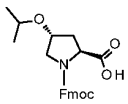
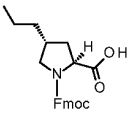
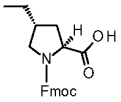
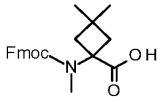
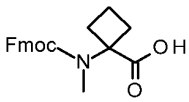
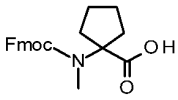
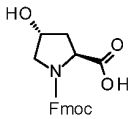
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aa088	Fmoc-EtAla-OH		(2S)-2-[ethyl(9H-fluoren-9-ylmethoxycarbonyl)amino]propanoic acid	84000-09-9
aa090	Fmoc-nPrGly-OH		2-[9H-fluoren-9-ylmethoxycarbonyl(propyl)amino]acetic acid	1310680-42-2
aa091	Fmoc-EtGly-OH		2-[ethyl(9H-fluoren-9-ylmethoxycarbonyl)amino]acetic acid	162545-29-1
aa092	Fmoc-DfeGly-OH		2-[2,2-difluoroethyl(9H-fluoren-9-ylmethoxycarbonyl)amino]acetic acid	2172536-70-6
aa093	Fmoc-MfeGly-OH		2-[9H-fluoren-9-ylmethoxycarbonyl(2-fluoroethyl)amino]acetic acid	
aa094	Fmoc-PraGly-OH		2-[9H-fluoren-9-ylmethoxycarbonyl(prop-2-ynyl)amino]acetic acid	1033622-38-6
aa095	Fmoc-AllylGly-OH		2-[allyl(9H-fluoren-9-ylmethoxycarbonyl)amino]acetic acid	222725-35-1
aa101	Fmoc-1-ACPrC-OH		1-(9H-fluoren-9-ylmethoxycarbonylamino)cyclopropanecarboxylic acid	126705-22-4
aa102	Fmoc-NCMeGly-OH		2-[cyanomethyl(9H-fluoren-9-ylmethoxycarbonyl)amino]acetic acid	2172570-83-9
aa103	Fmoc-cPrGly-OH		2-[cyclopropyl(9H-fluoren-9-ylmethoxycarbonyl)amino]acetic acid	1342767-08-1
aa104	Fmoc-bMeAla-OH		3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid	172965-84-3
aa106	Fmoc-MeMethagly-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-methyl-pent-4-enoic acid	145615-72-1

aa113	Fmoc-ButenylGly-OH		2-[but-3-enyl(9H-fluoren-9-ylmethoxycarbonyl)amino]acetic acid	227006-55-5
aa123	Fmoc-nBuGly-OH		2-[butyl(9H-fluoren-9-ylmethoxycarbonyl)amino]acetic acid	234442-58-1
aa155	Fmoc-AllylPhe-OH		(2S)-2-[allyl(9H-fluoren-9-ylmethoxycarbonyl)amino]-3-phenyl-propanoic acid	1054548-99-0
aa208	Fmoc-D-MePhe-OH		(2R)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-phenyl-propanoic acid	138775-05-0
aa212	Fmoc-D-MeAla-OH		(2R)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid	138774-92-2
aa221	Fmoc-Hph(4-Me)-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-(p-tolyl)butanoic acid	1260587-57-2
aa231	Fmoc-Hph(34-Cl2)-OH		(2S)-4-(3,4-dichlorophenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid	1260616-12-3
aa238	Fmoc-Pro(4-F2)-OH		(2S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4,4-difluoro-pyrrolidine-2-carboxylic acid	203866-21-1
aa240	Fmoc-Pro(4R-CF3)-OH		(2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-(trifluoromethyl)pyrrolidine-2-carboxylic acid	2549171-72-2
aa241	Fmoc-Pro(4R-F)-OH		(2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-fluoro-pyrrolidine-2-carboxylic acid	203866-20-0
aa245	Fmoc-Hyp(iBu)-OH		(2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-isobutoxy-pyrrolidine-2-carboxylic acid	865353-14-6
aa249	Fmoc-MeSer(iPen)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-isopentyloxy-propanoic acid	2255321-12-9
aa262	Fmoc-Pro(4S-F)-OH		(2S,4S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-fluoro-pyrrolidine-2-carboxylic acid	203866-19-7

aa263	Fmoc-cisHyp(Me)-OH		(2S,4S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-methoxy-pyrrolidine-2-carboxylic acid	1190617-97-0
aa274	Fmoc-Pro(4-keto)-OH		(2S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-oxo-pyrrolidine-2-carboxylic acid	223581-83-7
aa275	Fmoc-Pro(4-Me2)-OH		(2S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic acid	1380336-01-5
aa277	Fmoc-Pic(2)(4-F2)-OH		(2S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4,4-difluoro-piperidine-2-carboxylic acid	1221793-52-7
aa278	Fmoc-Pro(4-cPr)-OH		(6S)-5-(9H-fluoren-9-ylmethoxycarbonyl)-5-azaspiro[2.4]heptane-6-carboxylic acid	2170726-27-7
aa280	Fmoc-Nle-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)hexanoic acid	77284-32-3
aa301	Fmoc-cVal-OH		1-(9H-fluoren-9-ylmethoxycarbonylamino)cyclobutanecarboxylic acid	885951-77-9
aa302	Fmoc-cLeu-OH		1-(9H-fluoren-9-ylmethoxycarbonylamino)cyclopentanecarboxylic acid	117322-30-2
aa303	Fmoc-cVal(3-Me2)-OH		1-(9H-fluoren-9-ylmethoxycarbonylamino)-3,3-dimethyl-cyclobutanecarboxylic acid	1936161-54-4
aa305	Fmoc-Athpc-OH		4-(9H-fluoren-9-ylmethoxycarbonylamino)tetrahydropyran-4-carboxylic acid	285996-72-7
aa306	Fmoc-cHex-OH		1-(9H-fluoren-9-ylmethoxycarbonylamino)cyclohexanecarboxylic acid	162648-54-6
aa307	Fmoc-cVal(3-F2)-OH		1-(9H-fluoren-9-ylmethoxycarbonylamino)-3,3-difluoro-cyclobutanecarboxylic acid	1936532-04-5
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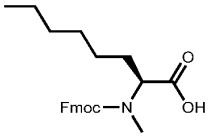
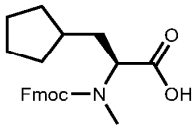
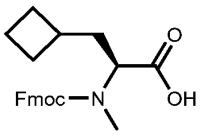
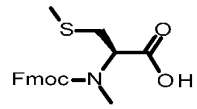
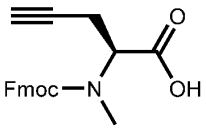
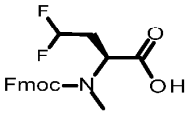
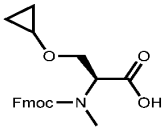
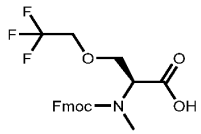
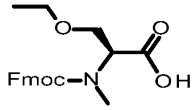
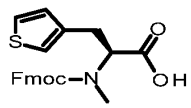
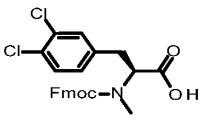
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aa311	Fmoc-D-Algly-OH		(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)pent-4-enoic acid	170642-28-1
aa312	Fmoc-cHex(4-F2)-OH		1-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-difluoro-cyclohexanecarboxylic acid	1986905-26-3
aa314	Fmoc-D-Ala-OH		(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)propanoic acid	79990-15-1
aa316	Fmoc-(Me)Abu-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-2-methyl-butanoic acid	857478-30-9
aa318	Fmoc-AoxeC-OH		3-(9H-fluoren-9-ylmethoxycarbonylamino)oxetane-3-carboxylic acid	1380327-56-9
aa330	Fmoc-MeGly(cPent)-OH		(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetic acid	187475-29-2
aa336	Fmoc-MeIle-OH		(2S,3S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-methyl-pentanoic acid	138775-22-1
aa337	Fmoc-MeChg-OH		(2S)-2-cyclohexyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetic acid	925240-97-7
aa338	Fmoc-MeTle-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3,3-dimethyl-butanoic acid	1172579-62-2
aa340	Fmoc-MeAlle-OH		(2S,3R)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-methyl-pentanoic acid	1821797-58-3

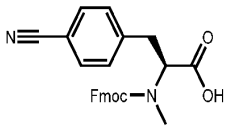
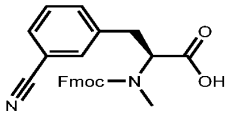
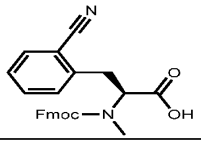
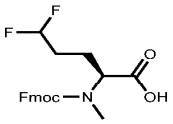
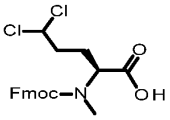
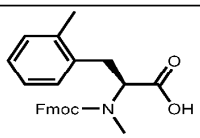
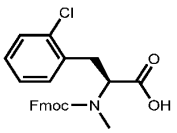
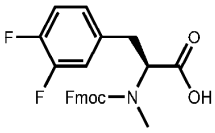
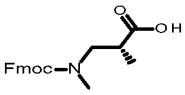
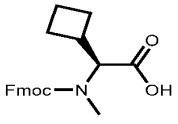
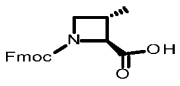
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aa388	Fmoc-MeAnone(2)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]non-8-enoic acid	1808268-51-0
aa390	Fmoc-Leu-OH		(2S)-2-([(9H-fluoren-9-ylmethoxy)carbonyl]amino)-4-methyl-pentanoic acid	35661-60-0
aa392	Fmoc-Thr(Et)-OH		(2S,3R)-3-ethoxy-2-(9H-fluoren-9-ylmethoxycarbonyl amino)butanoic acid	2108708-74-1
aa393	Fmoc-Gly(cPr)-OH		(2S)-2-cyclopropyl-2-(9H-fluoren-9-ylmethoxycarbonyl amino)acetic acid	1212257-18-5
aa394	Fmoc-Gly(4-THP)-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonyl amino)-2-tetrahydropyran-4-yl-acetic acid	368866-31-3
aa395	Fmoc-Thr(Me)-OH		(2S,3R)-2-(9H-fluoren-9-ylmethoxycarbonyl amino)-3-methoxy-butanoic acid	928063-81-4
aa396	Fmoc-(MeOEt)Gly-OH		2-[9H-fluoren-9-ylmethoxycarbonyl(2-methoxyethyl)amino]acetic acid	1341969-00-3
aa412	Fmoc-Hph(4-Cl)-OH		(2S)-4-(4-chlorophenyl)-2-(9H-fluoren-9-ylmethoxycarbonyl amino)butanoic acid	1260608-62-5

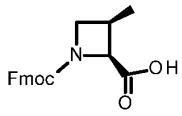
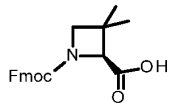
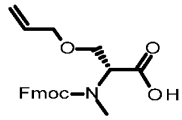
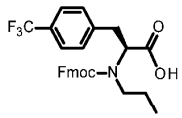
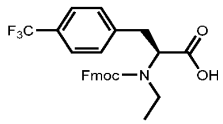
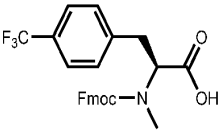
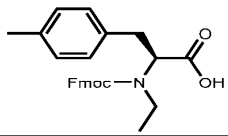
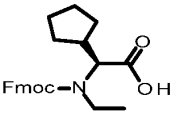
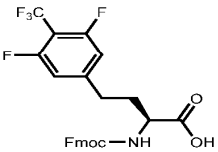
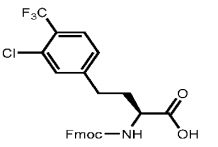
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aa417	Fmoc-Pro(4R-Me)-OH		(2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-methyl-pyrrolidine-2-carboxylic acid	333777-34-7
aa418	Fmoc-Pro(4R-nPr)-OH		(2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-propyl-pyrrolidine-2-carboxylic acid	
aa419	Fmoc-Pro(4R-Et)-OH		(2S,4R)-4-ethyl-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidine-2-carboxylic acid	
aa420	Fmoc-MecVal(3-Me2)-OH		1-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3,3-dimethyl-cyclobutane-carboxylic acid	2025106-27-6
aa421	Fmoc-MecVal-OH		1-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]cyclobutane-carboxylic acid	1700368-07-5
aa422	Fmoc-MecLeu-OH		1-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]cyclopentane-carboxylic acid	1694050-88-8
aa427	Fmoc-Hyp-OH		(2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-hydroxy-pyrrolidine-2-carboxylic acid	88050-17-3

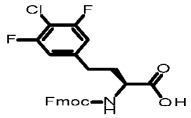
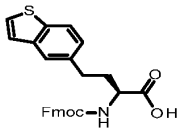
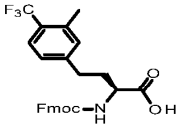
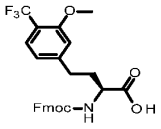
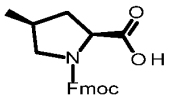
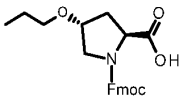
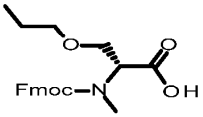
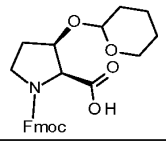
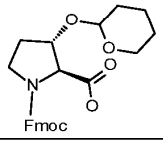
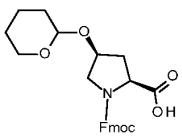
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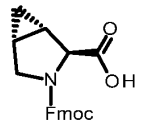
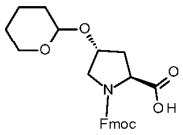
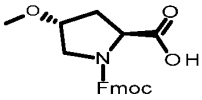
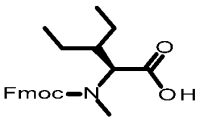
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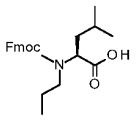
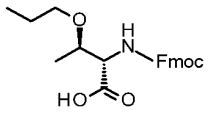
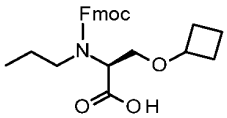
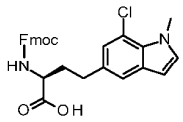
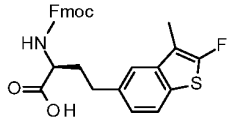
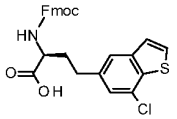
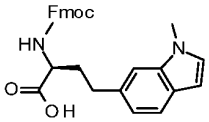
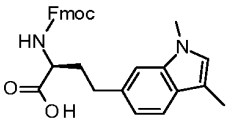
Compound No.	Abbreviation	Structural Formula	Name
aa004	Fmoc-MeAOC(2)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]octanoic acid
aa006	Fmoc-MeAla(cPent)-OH		(2S)-3-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid
aa010	Fmoc-MeAla(cBu)-OH		(2S)-3-cyclobutyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid
aa013	Fmoc-MeCys(Me)-OH		(2R)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-methylsulfanyl-propanoic acid
aa018	Fmoc-MePRA-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]pent-4-ynoic acid
aa019	Fmoc-MeAbu(4-F2)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4,4-difluoro-butanoic acid
aa020	Fmoc-MeSer(cPr)-OH		(2S)-3-(cyclopropoxy)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid
aa021	Fmoc-MeSer(Tfe)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-(2,2,2-trifluoroethoxy)propanoic acid
aa022	Fmoc-MeSer(Et)-OH		(2S)-3-ethoxy-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid
aa023	Fmoc-MeAla(3-Thie)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-(3-thienyl)propanoic acid
aa028	Fmoc-MePhe(34-Cl2)-OH		(2S)-3-(3,4-dichlorophenyl)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid

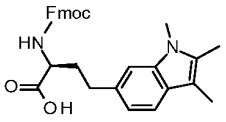
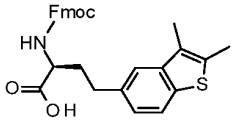
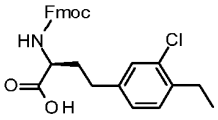
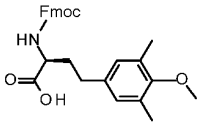
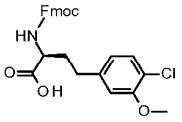
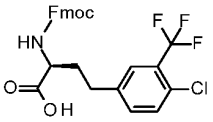
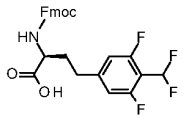
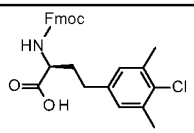
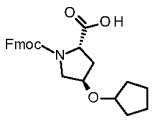
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aa030	Fmoc-MePhe(3-CN)-OH		(2S)-3-(3-cyanophenyl)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid
aa031	Fmoc-MePhe(2-CN)-OH		(2S)-3-(2-cyanophenyl)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid
aa244	Fmoc-MeNva(5-F2)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-5,5-difluoro-pentanoic acid
aa043	Fmoc-MeNva(5-Cl2)-OH		(2S)-5,5-dichloro-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]pentanoic acid
aa047	Fmoc-MePhe(2-Me)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-(o-tolyl)propanoic acid
aa049	Fmoc-MePhe(2-Cl)-OH		(2S)-3-(2-chlorophenyl)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid
aa050	Fmoc-MePhe(34-F2)-OH		(2S)-3-(3,4-difluorophenyl)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid
aa056	Fmoc-R-MeAMPA-OH		(2R)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-2-methyl-propanoic acid
aa060	Fmoc-MeGly(cBu)-OH		(2S)-2-cyclobutyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetic acid
aa098	Fmoc-Aze(2)(3S-Me)-OH		(2S,3S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-3-methyl-azetidine-2-carboxylic acid

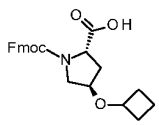
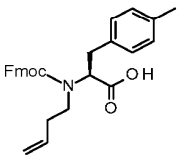
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aa100	Fmoc-Aze(2)(3-Me2)-OH		(2S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-3,3-dimethyl-azetidine-2-carboxylic acid
aa111	Fmoc-D-MeSer(Al)-OH		(2R)-3-allyloxy-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid
aa136	Fmoc-nPrPhe(4-CF3)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(propyl)amino]-3-[4-(trifluoromethyl)phenyl]propanoic acid
aa164	Fmoc-EtPhe(4-CF3)-OH		(2S)-2-[ethyl(9H-fluoren-9-ylmethoxycarbonyl)amino]-3-[4-(trifluoromethyl)phenyl]propanoic acid
aa174	Fmoc-nPrPhe(4-Me)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(propyl)amino]-3-(p-tolyl)propanoic acid
aa199	Fmoc-MePhe(4-CF3)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-[4-(trifluoromethyl)phenyl]propanoic acid
aa201	Fmoc-EtPhe(4-Me)-OH		(2S)-2-[ethyl(9H-fluoren-9-ylmethoxycarbonyl)amino]-3-(p-tolyl)propanoic acid
aa210	Fmoc-EtGly(cPent)-OH		(2S)-2-cyclopentyl-2-[ethyl(9H-fluoren-9-ylmethoxycarbonyl)amino]acetic acid
aa217	Fmoc-Hph(4-CF3-35-F2)-OH		(2S)-4-[3,5-difluoro-4-(trifluoromethyl)phenyl]-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa218	Fmoc-Hph(4-CF3-3-Cl)-OH		(2S)-4-[3-chloro-4-(trifluoromethyl)phenyl]-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid

aa219	Fmoc-Hph(4-CF3-3-F)-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-[3-fluoro-4-(trifluoromethyl)phenyl]butanoic acid
aa220	Fmoc-Hph(4-Cl-35-F2)-OH		(2S)-4-(4-chloro-3,5-difluoro-phenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa229	Fmoc-Abu(5-Bzt)-OH		(2S)-4-(benzothiophen-5-yl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa233	Fmoc-Hph(4-CF3-3-Me)-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-[3-methyl-4-(trifluoromethyl)phenyl]butanoic acid
aa235	Fmoc-Hph(4-CF3-3-OMe)-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-[3-methoxy-4-(trifluoromethyl)phenyl]butanoic acid
aa239	Fmoc-Pro(4S-Me)-OH		(2S,4S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-methyl-pyrrolidine-2-carboxylic acid
aa246	Fmoc-Hyp(nPr)-OH		(2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-propoxy-pyrrolidine-2-carboxylic acid
aa250	Fmoc-D-MeSer(nPr)-OH		(2R)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-propoxy-propanoic acid
aa264	Fmoc-cisHyp(3)(THP)-OH		(2S,3R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-3-tetrahydropyran-2-yloxy-pyrrolidine-2-carboxylic acid
aa265	Fmoc-Hyp(3)(THP)-OH		(2S,3S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-3-tetrahydropyran-2-yloxy-pyrrolidine-2-carboxylic acid
aa267	Fmoc-cisHyp(THP)-OH		(2S,4S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-tetrahydropyran-2-yloxy-pyrrolidine-2-carboxylic acid

aa268	Fmoc-Pro(3S4-C1)-OH		(1S,2S,5R)-3-(9H-fluoren-9-ylmethoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid
aa279	Fmoc-Hyp(THP)-OH		(2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-tetrahydropyran-2-yloxy-pyrrolidine-2-carboxylic acid
aa281	Fmoc-Hyp(Me)-OH		(2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-methoxy-pyrrolidine-2-carboxylic acid
aa331	Fmoc-MeNva(3-Et)-OH		(2S)-3-ethyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]pentanoic acid

aa389	Fmoc-nPrLeu-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(propyl)amino]-4-methyl-pentanoic acid
aa391	Fmoc-Thr(nPr)-OH		(2S,3R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-propoxy-butanoic acid
aa397	Fmoc-nPrSer(iPen)-OH		(2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(propyl)amino]-3-isopentyloxy-propanoic acid
aa398	Fmoc-nPrSer(cBu)-OH		(2S)-3-(cyclobutoxy)-2-[9H-fluoren-9-ylmethoxycarbonyl(propyl)amino]propanoic acid
aa399	Fmoc-Abu(1-Me-7-Cl-5-Indo)-OH		(2S)-4-(7-chloro-1-methyl-indol-5-yl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa400	Fmoc-Abu(5-Bzt-2-F-3-Me)-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-(2-fluoro-3-methyl-benzothiophen-5-yl)butanoic acid
aa401	Fmoc-Abu(5-Bzt-7-Cl)-OH		(2S)-4-(7-chlorobenzothiophen-5-yl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa402	Fmoc-Abu(1-Me-6-Indo)-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-(1-methyl indol-6-yl)butanoic acid
aa403	Fmoc-Abu(13-Me2-6-Indo)-OH		(2S)-4-(1,3-dimethyl indol-6-yl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid

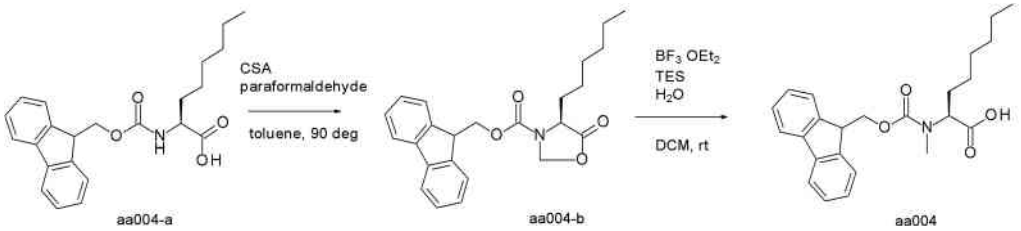
aa404	Fmoc-Abu(123-Me3-6-Indo)-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-(1,2,3-trimethyl indol-6-yl)butanoic acid
aa405	Fmoc-Abu(5-Bzt-23-Me2)-OH		(2S)-4-(2,3-dimethyl benzothiophen-5-yl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa406	Fmoc-Hph(3-Cl-4-Et)-OH		(2S)-4-(3-chloro-4-ethyl-phenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa407	Fmoc-Hph(4-OMe-35-Me2)-OH		(2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-[4-(methoxymethyl)-3,5-dimethyl-phenyl]butanoic acid
aa408	Fmoc-Hph(4-Cl-3-OMe)-OH		(2S)-4-(4-chloro-3-methoxy-phenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa409	Fmoc-Hph(4-Cl-3-CF3)-OH		(2S)-4-[4-chloro-3-(trifluoromethyl)phenyl]-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa410	Fmoc-Hph(4-CHF2-35-F2)-OH		(2S)-4-[4-(difluoromethyl)-3,5-difluoro-phenyl]-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa411	Fmoc-Hph(4-Cl-35-Me2)-OH		(2S)-4-(4-chloro-3,5-dimethyl-phenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa414	Fmoc-Hyp(cPent)-OH		(2S,4R)-4-(cyclopentoxy)-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-carboxylic acid

aa415	Fmoc-Hyp(cBu)-OH		(2S,4R)-4-(cyclobutoxy)-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-carboxylic acid
aa443	Fmoc-ButenylPhe(4-Me)-OH		(2S)-2-[but-3-enyl(9H-fluoren-9-ylmethoxycarbonyl)amino]-3-(p-tolyl)propanoic acid

[0295]

Synthesis of Fmoc-amino acids

Synthesis of Compound aa004



[0296]

Compound aa004-a (3.00 g, 7.86 mmol) was dissolved in toluene (79 mL), paraformaldehyde (708 mg, 23.6 mmol) and CSA (91 mg, 0.393 mmol) were added, and the mixture was stirred at 90°C for 5 hours. After cooling the mixture to room temperature, paraformaldehyde (236 mg, 7.86 mmol) and CSA (46 mg, 0.197 mmol) were added, and the mixture was further stirred at 90°C for 30 minutes. After being cooled to room temperature, the mixture was filtered through Celite, and the residue was washed with ethyl acetate (50 mL). The filtrate was washed twice with a saturated aqueous sodium hydrogen carbonate solution (50 mL) and washed with 50% brine (50 mL). This was dried over sodium sulfate and filtered off, and the solvent was distilled off under reduced pressure to give Compound aa004-b as a crude product.

LCMS (ESI) m/z = 394 (M+H)+

Retention time: 1.08 min (Analytical condition SQDFA05)

[0297]

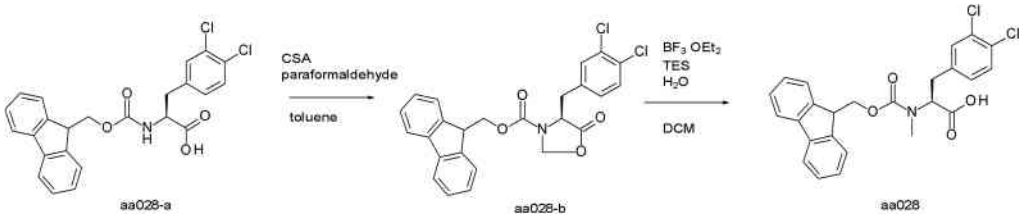
The crude product (7.86 mmol) of Compound aa004-b was dissolved in DCM (39 mL), then a boron trifluoride diethyl ether complex ($BF_3 \cdot OEt_2$) (2.96 mL, 23.6 mmol), TES (1.95 mL, 23.6 mmol), and water (0.142 mL, 7.86 mmol) were added, and the mixture was stirred at room temperature for 1 hour. The reaction solution was washed with a saturated ammonium chloride solution (40 mL), washed with 50% brine (40 mL), then dried over sodium sulfate, and filtered off, and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in acetonitrile (40 mL) and washed twice with n-hexane (40 mL). The solvent was distilled off under reduced pressure to give Compound aa004 (3.04 g, 98%).

LCMS (ESI) m/z = 396 (M+H)+

Retention time: 1.00 min (Analytical condition SQDFA05)

[0298]

<u>Synthesis of Compound aa028</u>



[0299]

Using aa028-a as a starting material, aa028-b (9.61 g, 94%) was obtained as a crude product in the same manner as the synthesis of Compound aa004-b.

[0300]

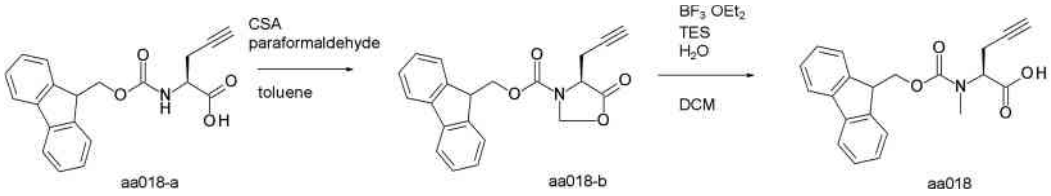
Using aa028-b as a starting material, aa028 (8.10 g, 84%) was obtained in the same manner as the synthesis of Compound aa004.

LCMS (ESI) m/z = 470 (M+H)+

Retention time: 0.99 min (Analytical condition SQDFA05)

[0301]

Synthesis of Compound aa018



[0302]

Using Compound aa018-a, ((2S)-2-[9H-fluoren-9-ylmethoxycarbonylamino]pent-4-ynoic acid, Fmoc-PRA-OH) (3 g, 8.95 mmol) as a starting material, Compound aa018-b (2.71 g, 87%) was obtained in the same manner as the synthesis of Compound aa004-b.

LCMS (ESI) m/z = 348 (M+H)+

Retention time: 0.87 min (Analytical condition SQDFA05)

[0303]

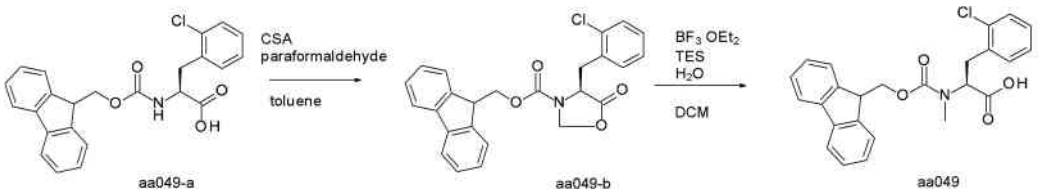
Using the resulting Compound aa018-b (989 mg, 2.85 mmol), Compound aa018 (986 mg, 99%) was obtained in the same manner as the synthesis of Compound aa004.

LCMS (ESI) m/z = 350 (M+H)+

Retention time: 0.79 min (Analytical condition SQDFA05)

[0304]

Synthesis of Compound aa049



[0305]

Using Compound aa049-a, ((2S)-3-(2-chlorophenyl)-2-[9H-fluoren-9-ylmethoxycarbonylamino]propanoic acid, Fmoc-Phe(2-Cl)-OH) (5 g, 11.85 mmol) as a starting material, Compound aa049-b (4.2 g, 82%) was obtained in the same manner as the synthesis of Compound aa004-b.

LCMS (ESI) m/z = 434 (M+H)+

Retention time: 1.01 min (Analytical condition SQDFA05)

[0306]

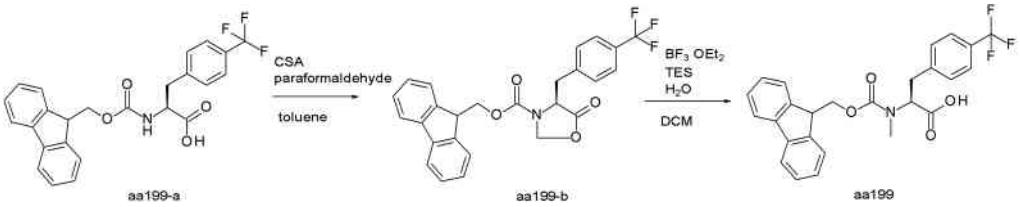
Using the resulting Compound aa049-b (4.2 g), Compound aa049 (3.32 g, 79%) was obtained in the same manner as the synthesis of Compound aa004.

LCMS (ESI) m/z = 436 (M+H)+

Retention time: 0.94 min (Analytical condition SQDFA05)

[0307]

Synthesis of Compound aa199



[0308]

Using Compound aa199-a, ((2S)-2-[9H-fluoren-9-ylmethoxycarbonylamino]-3-[4-(trifluoromethyl)phenyl]propanoic acid, Fmoc-Phe(4-CF3)-OH) (200 g, 439 mmol) as a starting material, Compound aa199-b (206.8 g) was obtained as a crude product in the same manner as the synthesis of Compound aa004-b.

LCMS (ESI) m/z = 469 (M+H)+

Retention time: 3.30 min (Analytical condition SMD method_03)

[0309]

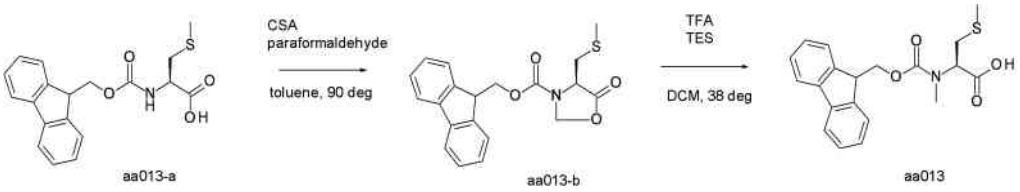
Using the resulting Compound aa199-b (205 g), Compound aa199 (195 g, 2 steps, 95%) was obtained in the same manner as the synthesis of Compound aa004.

LCMS (ESI) m/z = 470 (M+H)+

Retention time: 2.96 min (Analytical condition SMD Method_03)

[0310]

Synthesis of Compound aa013



[0311]

Using aa013-a as a starting material, aa013-b (5.29 g, 102%) was obtained as a crude product in the same manner as the synthesis of Compound aa004-b.

LCMS (ESI) m/z = 370 (M+H)+

Retention time: 0.89 min (Analytical condition SQDFA05)

[0312]

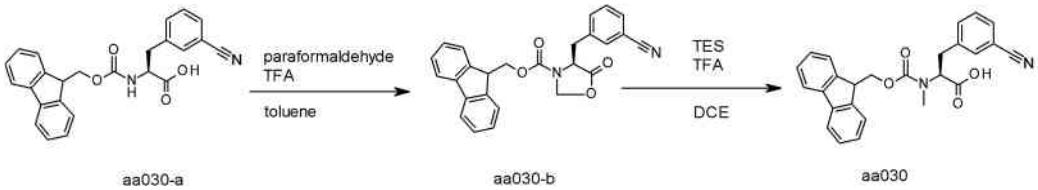
Compound aa013-b (5.29 g, 14.3 mmol) was dissolved in DCM (125 mL), TES (22.9 mL, 143 mmol) and TFA (36.4 mL, 473 mmol) were added, and the mixture was stirred at 38°C for 8 hours. The solvent was distilled off under reduced pressure, and the residue was dissolved in TBME (100 mL) and washed with a 1 M aqueous dipotassium hydrogen phosphate solution (50 mL). The aqueous layer was extracted 3 times with TBME, the organic layers were combined, and the solvent was distilled off under reduced pressure. Acetonitrile/n-hexane = 1/2 (100 mL) was added, and the mixture was extracted with a 5% aqueous potassium hydrogen carbonate solution (100 mL). The aqueous layer was acidified with 6 M hydrochloric acid, and extracted twice with TBME (30 mL). The organic layer was dried over sodium sulfate and filtered off, and the solvent was distilled off under reduced pressure. Acetonitrile (100 mL) was added, the mixture was washed with n-hexane (50 mL), and the solvent was distilled off under reduced pressure to give Compound aa013 (4.06 g, 76%).

LCMS (ESI) m/z = 372 (M+H)+

Retention time: 0.83 min (Analytical condition SQDFA05)

[0313]

Synthesis of Compound aa030



[0314]

In a nitrogen atmosphere, paraformaldehyde (172 mg, 5.74 mmol) and TFA (1.326 mL, 17.22 mmol) were added to a toluene solution (5.7 mL) of (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(3-cyanophenyl)propanoic acid (aa030-a, Fmoc-Phe(3-CN)-OH) (789 mg, 1.913 mmol), and the mixture was stirred at room temperature for 5 hours and 30 minutes. The reaction solution was concentrated under reduced pressure, diluted with DCM, then washed with a saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, and filtered. The resulting solution was concentrated under reduced pressure to give Compound aa030-b (859 mg) as a crude product. The compound was used in the next reaction without further purification.

[0315]

In a nitrogen atmosphere, TES (2.75 mL, 17.22 mmol) and TFA (3.98 mL, 51.7 mmol) were added to a DCE (10 mL) solution of Compound aa030-b (853 mg) at room temperature, and the mixture was stirred at 60°C for 5 hours. The reaction solution was cooled to room temperature, the solvent was distilled off under reduced pressure, t-butyl methyl ether/n-hexane

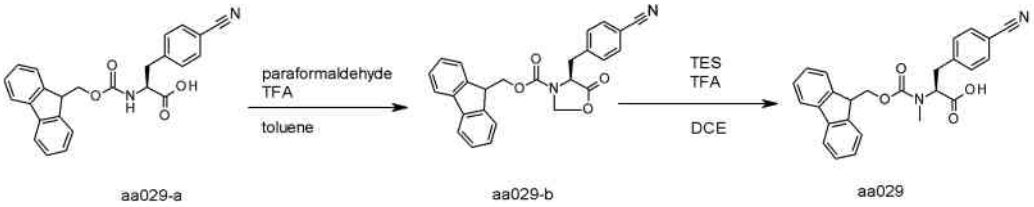
(1/1) was added to the resulting crude product, and the mixture was extracted 5 times with a saturated aqueous sodium hydrogen carbonate solution. The pH of the resulting aqueous layer was acidified with concentrated hydrochloric acid, and then the mixture was extracted with ethyl acetate 3 times. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtered, and then the solvent was distilled off under reduced pressure to give Compound aa030 (811 mg, 2 steps, 99%). The resulting Compound aa060 was used in peptide synthesis without further purification.

LCMS (ESI) m/z = 427 (M+H)+

Retention time: 0.83 min (Analytical condition SQDFA05)

[0316]

Synthesis of Compound aa029



[0317]

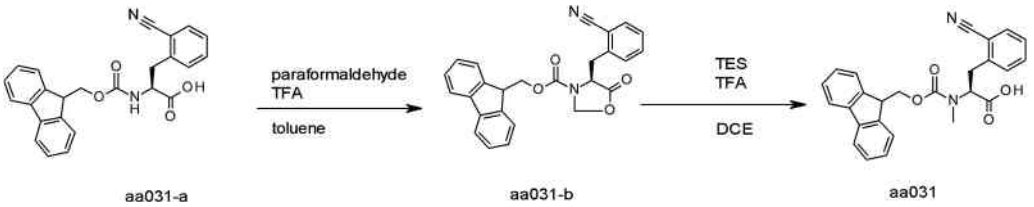
Using Compound aa029-a, ((2S)-3-(4-cyanophenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)propanoic acid, Fmoc-Phe(4-CN)-OH) (1 g, 2.425 mmol) as a starting material, Compound aa029 (1.14 g, 2 steps, 108%) was obtained as a crude product in the same manner as the synthesis of Compound aa030. The resulting Compound aa029 was used in peptide synthesis without further purification.

LCMS (ESI) m/z = 427 (M+H)+

Retention time: 0.82 min (Analytical condition SQDFA05)

[0318]

Synthesis of Compound aa031



[0319]

Using Compound aa031-a, ((2S)-3-(2-cyanophenyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)propanoic acid, Fmoc-Phe(2-CN)-OH) (1 g, 2.425 mmol) as a starting material, Compound aa031-b was obtained as a crude product in the same manner as the synthesis of Compound aa030-b. Using the resulting Compound aa031-b, the crude product obtained in the same manner as the synthesis of Compound aa030 was purified by reverse phase

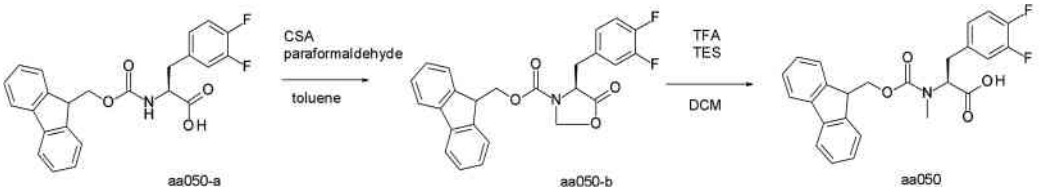
column chromatography (0.1% aqueous formic acid solution/0.1% formic acid acetonitrile solution) to give Compound aa031 (529 mg, 2 steps, 51%).

LCMS (ESI) m/z = 427 (M+H)+

Retention time: 0.85 min (Analytical condition SQDFA05)

[0320]

Synthesis of Compound aa050



[0321]

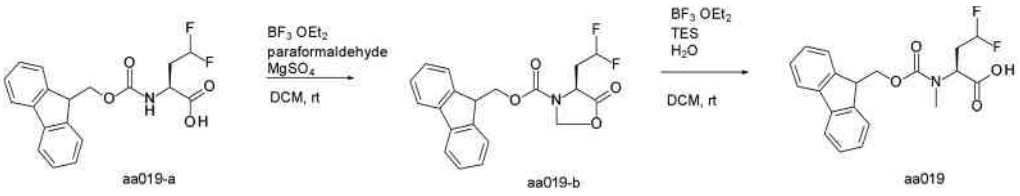
Using Compound aa050-a, ((2S)-3-(3,4-difluorophenyl)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid, Fmoc-Phe(34-F2)-OH) (105 mg, 0.247 mmol) as a starting material, Compound aa050-b was obtained as a crude product in the same manner as the synthesis of Compound aa004-b. Furthermore, using aa050-b, Compound aa050 (74.4 mg, 2 steps, 69%) was obtained in the same manner as the synthesis of Compound aa030.

LCMS (ESI) m/z = 438 (M+H)+

Retention time: 0.88 min (Analytical condition SQDFA05)

[0322]

Synthesis of Compound aa019



[0323]

Compound aa019-a (5.00 g, 13.8 mmol) was suspended in DCM (46 mL), and paraformaldehyde (2.08 g, 69 mmol) and magnesium sulfate (4.16 g, 34.6 mmol) were added. A boron trifluoride diethyl ether complex ($BF_3 \cdot OEt_2$) (2.10 mL, 16.6 mmol) was added dropwise thereto, and the mixture was stirred at room temperature for 1 hour. Solids were filtered off, and TES (5.51 mL, 34.6 mmol) and water (0.249 mL, 13.8 mmol) were added. $BF_3 \cdot OEt_2$ (2.63 mL, 20.8 mmol) was added dropwise thereto at 0°C, and the mixture was stirred at room temperature for 1 hour. TES (1.10 mL, 6.92 mmol) was added, the mixture was stirred at room temperature for 40 minutes, $BF_3 \cdot OEt_2$ (0.877 mL, 6.92 mmmol) was added, and the mixture was stirred at room temperature. The reaction solution was washed with a saturated aqueous sodium chloride solution (25 mL) and washed with saturated brine (50 mL). The organic layer was dried over sodium sulfate and filtered off, and the solvent was distilled off under reduced

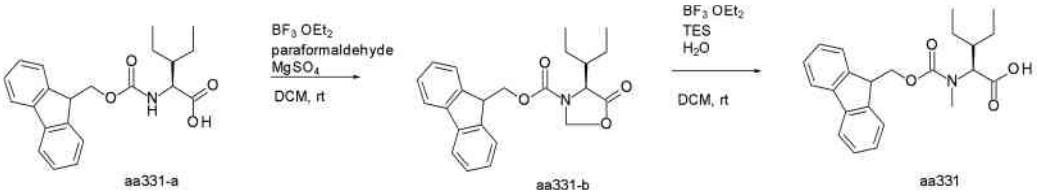
pressure. The resulting solids were pulverized and washed 3 times with n-hexane (50 mL) to give Compound aa019 (4.93 g, 95%).

LCMS (ESI) m/z = 376 (M+H)+

Retention time: 0.80 min (Analytical condition SQDFA05)

[0324]

Synthesis of Compound aa331



[0325]

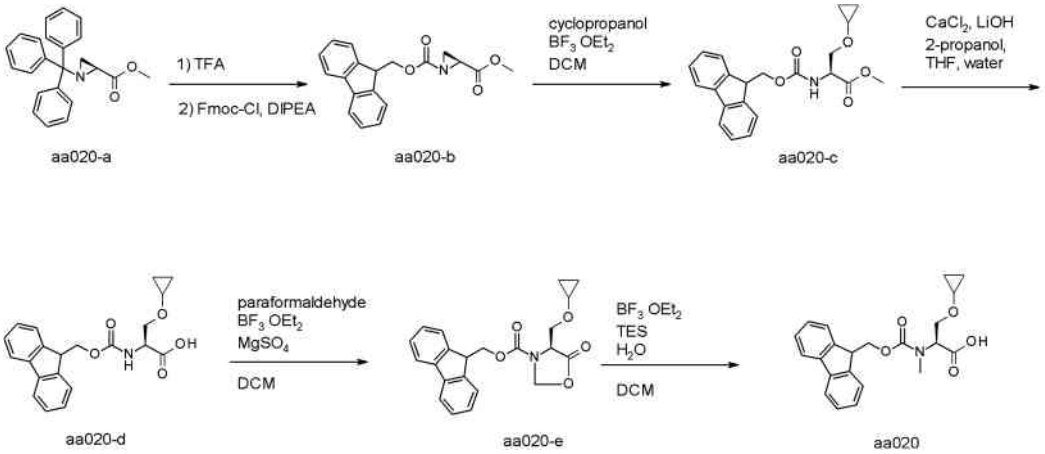
Using aa331-a as a starting material, aa331 (9.09 g, 86%) was obtained in the same manner as the synthesis of Compound aa019.

LCMS (ESI) m/z = 382 (M+H)+

Retention time: 0.94 min (Analytical condition SQDFA05)

[0326]

Synthesis of Compound aa020



[0327]

(S)-Methyl N-tritylaziridine-2-carboxylate (aa020-a, CAS No. 75154-68-6) (50 g, 146 mmol) was added to a mixed solution of chloroform (145 mL) and methanol (145 mL), then TFA (33 mL, 3 eq) was added dropwise at 0°C in a nitrogen atmosphere, and the mixture was stirred for 7 hours. DIPEA (127 mL, 5 eq) was added to this reaction solution at 0°C, and further, a 1,4-dioxane (145 mL) solution of Fmoc-Cl (36 g, 139 mmol) was added dropwise, and the mixture was stirred at 0°C for 90 minutes in a nitrogen atmosphere. The reaction solution was concentrated under reduced pressure, diluted with ethyl acetate, and then washed sequentially with water, an aqueous ammonium chloride solution, an aqueous sodium hydrogen carbonate solution, and saturated brine. After the resulting organic layer was dried with

anhydrous sodium sulfate, the residue obtained by distilling off the solvent under reduced pressure was purified by silica gel column chromatography (ethyl acetate/petroleum ether, 0/100 to 10/90) to give Compound aa020-b (1-O-(9H-fluoren-9-ylmethyl) 2-O-methyl (2S)-aziridine-1,2-dicarboxylate) (40 g, 85%).

LCMS (ESI) m/z = 324 (M+H)+

Retention time: 2.631 min (Analytical condition SMD method_10)

[0328]

In a nitrogen atmosphere, Compound aa020-b, (1-O-(9H-fluoren-9-ylmethyl) 2-O-methyl (2S)-aziridine-1,2-dicarboxylate) (5 g, 15.46 mmol) was dissolved in DCM (30.9 mL), cyclopropanol (1.665 mL, 26.3 mmol) was added, and then a boron trifluoride diethyl ether complex ($BF_3 \cdot OEt_2$) (0.291 mL, 2.319 mmol) was added while the mixture was ice-cooled. After the mixture was reacted for 2 hours while being ice-cooled, water and a saturated aqueous sodium hydrogen carbonate solution were added to the reaction solution to quench the reaction, the aqueous layer was removed by a phase separator, and then the organic layer was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 4/1) to give Compound aa020-c (4.6 g, 78%).

LCMS (ESI) m/z = 382 (M+H)+

Retention time: 0.89 min (Analytical condition SQDFA05)

[0329]

Calcium chloride (20.08 g, 181 mmol) was dissolved in water (50.2 mL), lithium hydroxide monohydrate (2.024 g, 48.2 mmol) was added thereto, and the mixture was stirred at room temperature for 5 minutes to prepare Aqueous Solution A. Compound aa020-c (4.6 g, 12.06 mmol) was dissolved in isopropanol (201 mL) and THF (50.2 mL), Aqueous Solution A prepared in advance was added, and the mixture was stirred at room temperature for 5 hours. Then, 1 N hydrochloric acid (72 mL) was added to the reaction solution, and then isopropanol and THF were removed by concentration under reduced pressure. The resulting aqueous layer was diluted with water (50.2 mL), and extracted 3 times with ethyl acetate (total amount 100 mL). The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was washed with ethyl acetate/n-hexane (1/2, 20 v/w) to give aa020-d, ((2S)-3-cyclopropyloxy-2-(9H-fluoren-9-ylmethoxycarbonylamino)propanoic acid, Fmoc-Ser(cPr)-OH) (3.5 g, 79%).

LCMS (ESI) m/z = 368 (M+H)+

Retention time: 0.78 min (Analytical condition SQDFA05)

[0330]

Paraformaldehyde (1.815 g, 60.5 mmol), magnesium sulfate (2.36 g, 19.63 mmol), and a boron trifluoride diethyl ether complex ($BF_3 \cdot OEt_2$) (1.184 mL, 9.42 mmol) were added in a nitrogen atmosphere to a DCM (87 mL) solution of Compound aa020-d, ((2S)-3-cyclopropyloxy-2-(9H-fluoren-9-ylmethoxycarbonylamino)propanoic acid, Fmoc-Ser(cPr)-OH) (2.89 g, 7.85 mmol), and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction solution to separate the organic layer and the aqueous layer. The aqueous layer was extracted twice with DCM, the combined organic layer was washed with saturated brine and dried over sodium sulfate, and the solvent was distilled off under reduced pressure to give Compound aa020-e as a crude product (3.1 g, quant.).

LCMS (ESI) m/z = 380 (M+H)+

Retention time: 0.93 min (Analytical condition SQDFA05)

[0331]

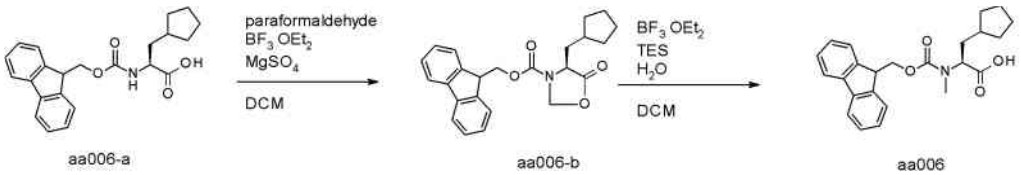
Triethylsilane (3.13 mL, 19.64 mmol), water (0.141 mL, 7.85 mmol), and a boron trifluoride diethyl ether complex ($BF_3 \cdot OEt_2$) (2.49 mL, 19.6 mmol) were added to DCM (26.2 mL) solution of the resulting Compound aa020-e (2.98 g, 7.85 mmol) under an ice-cold condition in a nitrogen atmosphere, and the mixture was stirred for 2 hours. A saturated aqueous ammonium chloride solution was added to the reaction solution to separate the organic layer. The organic layer was washed with a saturated aqueous ammonium chloride solution, then washed with saturated brine, and concentrated under reduced pressure to give a crude product. The resulting crude product was dissolved in acetonitrile, washed with n-hexane, and the acetonitrile layer was concentrated under reduced pressure to give Compound aa020 (2.71 g, 90%).

LCMS (ESI) m/z = 382 (M+H)+

Retention time: 0.83 min (Analytical condition SQDFA05)

[0332]

Synthesis of Compound aa006



[0333]

Using Compound aa006-a, ((2S)-3-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonylamino]propanoic acid, Fmoc-Ala(cPent)-OH) (10 g, 26.4 mmol) as a starting material, Compound aa006-b (10.5 g) was obtained as a crude product in the same manner as the synthesis of Compound aa020-e.

LCMS (ESI) m/z = 392 (M+H)+

Retention time: 1.05 min (Analytical condition SQDFA05)

[0334]

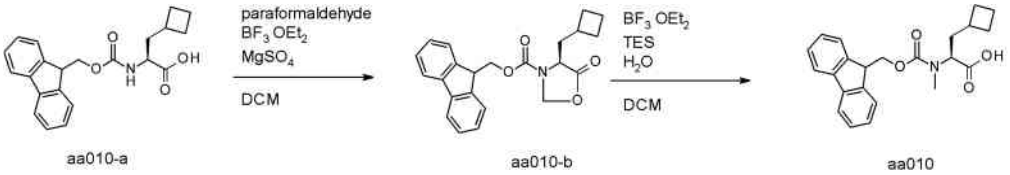
The resulting Compound aa006-b (10.5 g) was reacted in the same manner as the synthesis of Compound aa020, and then the resulting crude product was purified by reverse phase column chromatography (0.1% aqueous formic acid solution/0.1% formic acid acetonitrile solution) to give Compound aa006 (10.11 g, 2 steps, 96%).

LCMS (ESI) m/z = 394 (M+H)+

Retention time: 0.98 min (Analytical condition SQDFA05)

[0335]

Synthesis of Compound aa010



[0336]

Using Compound aa010-a, ((2S)-3-cyclobutyl-2-[9H-fluoren-9-ylmethoxycarbonylamino]propanoic acid, Fmoc-Ala(cBu)-OH) (3.36 g, 9.19 mmol) as a starting material, Compound aa010-b (3.63 g) was obtained as a crude product in the same manner as the synthesis of Compound aa020-e.

LCMS (ESI) m/z = 378 (M+H)+

Retention time: 1.01 min (Analytical condition SQDFA05)

[0337]

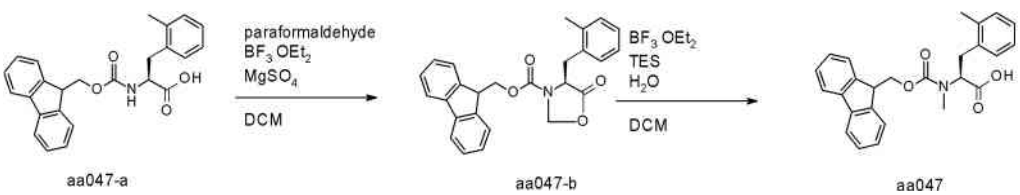
The resulting Compound aa010-b (3.63 g) was reacted in the same manner as the synthesis of Compound aa020, and then the resulting crude product was purified by reverse phase column chromatography (0.1% formic acid-water/0.1% formic acid-acetonitrile) to give Compound aa010 (3.18 g, 2 steps, 91%).

LCMS (ESI) m/z = 380 (M+H)+

Retention time: 0.94 min (Analytical condition SQDFA05)

[0338]

Synthesis of Compound aa047



[0339]

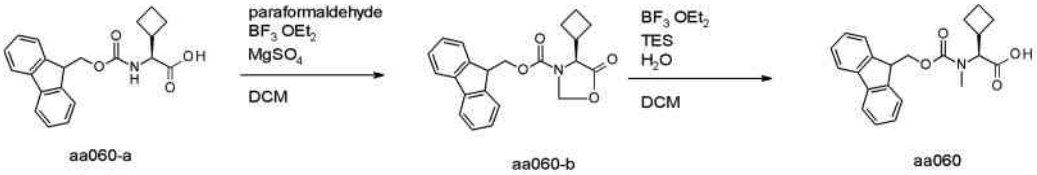
Using Compound aa047-a, ((2S)-2-[9H-fluoren-9-ylmethoxycarbonylamino]-3-(2-methylphenyl)propanoic acid, Fmoc-Phe(2-Me)-OH) (2 g, 4.98 mmol) as a starting material, a saturated aqueous sodium hydrogen carbonate solution was added to the reaction solution obtained in the same manner as the synthesis of Compound aa020-e, a silica gel column (2 v/w) was charged with the mixture, and this was eluted with DCM to give Compound aa047-b as a crude product (1.45 g). Using the resulting Compound aa047-b, Compound aa047 (1.21 g, 2 steps, 58%) was obtained in the same manner as the synthesis of Compound aa020.

LCMS (ESI) m/z = 416 (M+H)+

Retention time: 0.94 min (Analytical condition SQDFA05)

[0340]

Synthesis of Compound aa060



[0341]

Using Compound aa060-a, ((2S)-2-cyclobutyl-2-[9H-fluoren-9-ylmethoxycarbonylamino]acetic acid, Fmoc-Gly(cBu)-OH) (2.5 g, 7.11 mmol) as a starting material, Compound aa075-b was obtained as a crude product in the same manner as the synthesis of Compound aa020-e.

LCMS (ESI) m/z = 364 (M+H)+

Retention time: 0.97 min (Analytical condition SQDFA05)

[0342]

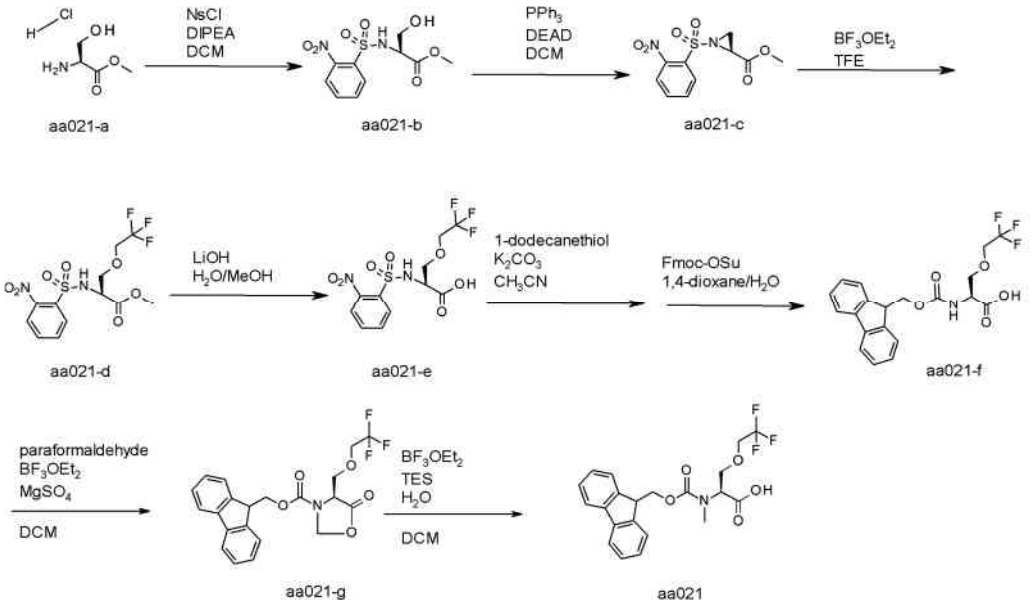
The entire amount of Compound aa060-b obtained as mentioned above was reacted in the same manner as the synthesis of Compound aa020, and then the resulting crude product was purified by reverse phase column chromatography (0.1% aqueous formic acid solution/0.1% formic acid acetonitrile solution) to give Compound aa060 (2.32 g, 2 steps, 89%).

LCMS (ESI) m/z = 366 (M+H)+

Retention time: 0.88 min (Analytical condition SQDFA05)

[0343]

Synthesis of Compound aa021



[0344]

2-Nitrobenzenesulfonyl chloride (NsCl) (32.37 g, 146 mmol) and L-serine methyl ester hydrochloride (aa021-a, 25 g, 161 mmol, CAS No. 5680-80-8) were dissolved in DCM (874 mL), and DIPEA (51 mL, 292 mmol) was added at 5°C. The mixture was stirred at room temperature for 1 hour, then washed twice with water (440 mL), washed once with saturated brine/water (1/1, 440 mL), and then dried over magnesium sulfate. Magnesium sulfate was filtered off, and then the filtrate was concentrated under reduced pressure to give Compound aa021-b as a crude product (39.4 g, 89%).

LCMS (ESI) m/z = 302.9 (M-H)-

Retention time: 0.729 min (Analytical condition SMD method_06)

[0345]

Compound aa021-b (23 g, 75.6 mmol) was dissolved in DCM (598 mL), and triphenylphosphine (31.7 g, 121 mmol) was added at room temperature. After the mixture was cooled to -14°C, DEAD (55.0 mL, 121 mmol) was added over 10 minutes, and then the mixture was stirred at -5°C for 50 minutes. n-Hexane (300 mL) was added, and the precipitate was filtered off. The filtrate was purified by silica gel column chromatography (n-hexane/DCM = 50:50 to 0:100) to give Compound aa021-c (13.3 g, 62%).

LCMS (ESI) m/z = 287 (M+H)+

Retention time: 0.872 min (Analytical condition SMD method_06)

[0346]

Compound aa021-c (10.7 g, 37.3 mmol) was dissolved in TFE (75 mL), a boron trifluoride diethyl ether complex ($BF_3 \cdot OEt_2$) (0.469 mL, 3.73 mmol) was added, and then the mixture was stirred at 70°C for 30 minutes. TFE was distilled off under reduced pressure, and the resulting crude product was purified by reverse phase column chromatography (0.1% formic

acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound aa021-d (12.3 g, 85%).

LCMS (ESI) m/z = 387 (M+H)+

Retention time: 0.72 min (Analytical condition SQDFA05)

[0347]

Compound aa021-d (12 g, 31.1 mmol) was dissolved in methanol (47 mL), and an aqueous solution (31 mL) of lithium hydroxide monohydrate (5.21 g, 124 mmol) was added. The mixture was stirred at room temperature for 90 minutes, then formic acid (11.7 mL, 311 mmol) was added, and the mixture was diluted with water (30 mL) and then purified by reverse phase column chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound aa021-e (7.90 g, 68%).

LCMS (ESI) m/z = 373 (M+H)+

Retention time: 0.63 min (Analytical condition SQDFA05)

[0348]

Compound aa021-e (7.72 g, 20.7 mmol) was dissolved in acetonitrile (104 mL), potassium carbonate (7.17 g, 51.8 mmol) and dodecanethiol (7.44 mL, 31.1 mmol) were added, and then the mixture was stirred at room temperature for 74 hours. This was diluted with water (100 mL), and washed twice with TBME (200 mL). A 1,4-dioxane (150 mL) solution of Fmoc-OSu (3.5 g) was added to the resulting aqueous solution, and the mixture was stirred for 25 minutes. Further, a 1,4-dioxane (10 mL) solution of Fmoc-OSu (700 mg) was added, and the mixture was stirred for 5 minutes. Furthermore, a 1,4-dioxane (5 mL) solution of Fmoc-OSu (350 mg) was added, and the mixture was stirred for 5 minutes. Further, a 1,4-dioxane (5 mL) solution of Fmoc-OSu (350 mg) was added, the mixture was stirred for 5 minutes, then formic acid (3.9 mL) was added, and the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase column chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound aa021-f, ((2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(2,2,2-trifluoroethoxy)propanoic acid, Fmoc-Ser(Tfe)-OH) (5.67 g, 67%).

LCMS (ESI) m/z = 410 (M+H)+

Retention time: 2.35 min (Analytical condition SQDFA05 long)

[0349]

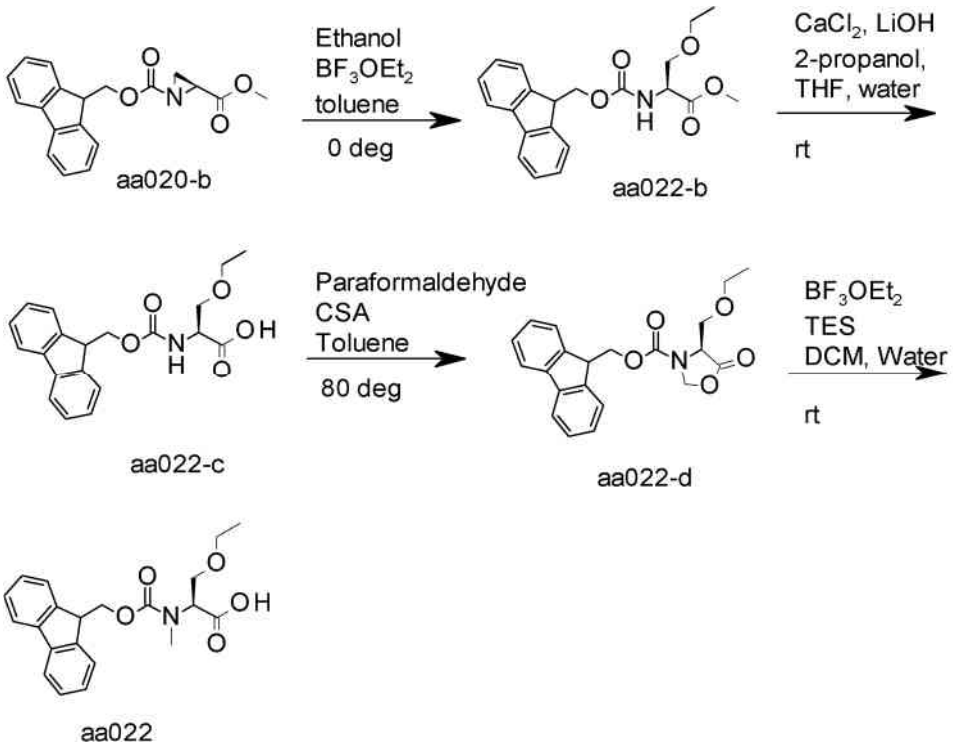
Using Compound aa021-f (2.00 g, 4.89 mmol) as a starting material, Compound aa021-g was obtained as a crude product in the same manner as the synthesis of Compound aa020-e. Furthermore, Compound aa021 (1.80 g, 2 steps, 87%) was obtained in the same manner as the synthesis of Compound aa020.

LCMS (ESI) m/z = 424 (M+H)+

Retention time: 0.84 min (Analytical condition SQDFA05)

[0350]

Synthesis of Compound aa022



[0351]

In a nitrogen atmosphere, Compound aa020-b (1 g, 3.09 mmol) was dissolved in toluene (6.2 mL), ethanol (0.542 mL, 9.28 mmol) was added, and then $BF_3 \cdot OEt_2$ (0.059 mL, 0.464 mmol) was added dropwise over 5 minutes while being ice-cooled. This was stirred for 2.5 hours while being brought back to room temperature. The reaction was quenched by adding a saturated aqueous $NaHCO_3$ solution, and the aqueous layer was removed by a phase separator. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. Ethyl acetate/hexane (3/1, 24 mL) was added to the resulting residue, and the solvent was distilled off under reduced pressure. Hexane/TBME (85/15, 24 mL) was added to the resulting solids, and the mixture was stirred for 30 minutes, and then the solvent was filtered off to give Compound aa022-b (787 mg, 69%).

LCMS (ESI) m/z = 370 (M+H)+

Retention time: 0.86 min (Analytical condition SQDFA05)

[0352]

Calcium chloride (2.25 g, 20.3 mmol) was dissolved in H_2O (5.7 mL), lithium hydroxide monohydrate (227 mg, 5.41 mmol) was added thereto, and the mixture was stirred at room temperature for 5 minutes to prepare Aqueous Solution A.

[0353]

Compound aa022-b was dissolved in isopropanol (22.6 mL) and THF (57 mL), Aqueous Solution A prepared in advance was added, and the mixture was stirred at room temperature for 7 hours. Then, 1 N hydrochloric acid (8.1 mL) was added to the reaction solution, and then isopropanol and THF were removed by concentration under reduced pressure. The resulting aqueous layer was diluted with H_2O and extracted 3 times with ethyl acetate. The organic layer was washed with H_2O and saturated brine, dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure. The residue residue was triturated with ethyl acetate/n-hexane (1/5, 20 v/w) to give Compound aa022-c (3.5 g, 79%).

LCMS (ESI) m/z = 356 (M+H)+

Retention time: 0.78 min (Analytical condition SQDFA05)

[0354]

Using aa022-c as a starting material, aa022-d (871 mg, 84%) was obtained as a crude product in the same manner as the synthesis of Compound aa004-b.

LCMS (ESI) m/z = 368 (M+H)+

Retention time: 0.84 min (Analytical condition SQDFA05)

[0355]

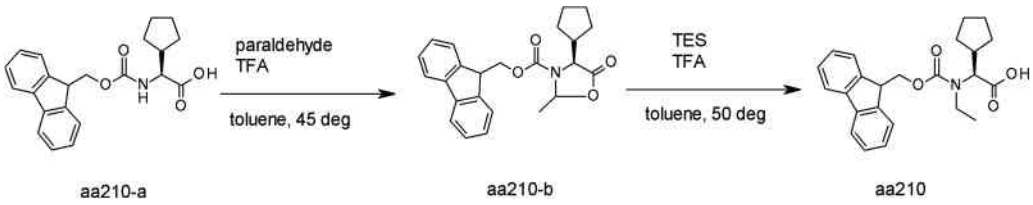
Using aa022-d as a starting material, aa022 (254 mg, 90%) was obtained in the same manner as the synthesis of Compound aa004.

LCMS (ESI) m/z = 370 (M+H)+

Retention time: 0.80 min (Analytical condition SQDFA05)

[0356]

Synthesis of Compound aa210



[0357]

Compound aa210-a (5.00 g, 13.7 mmol) was dissolved in toluene (17 mL), TFA (9.49 mL, 123 mmol) and paraldehyde (5.42 mL, 41.0 mmol) were added, and the mixture was stirred at 45°C for 24 hours. The mixture was cooled to 0°C, toluene (17 mL), TFA (19.0 mL, 246 mmol), and TES (19.6 mL, 123 mmol) were added, and the mixture was stirred at 50°C overnight. The solvent was distilled off under reduced pressure, ethyl acetate was added, and the mixture was washed with a saturated aqueous sodium hydrogen carbonate solution and washed with saturated brine. The organic layer was dried over sodium sulfate and filtered off, and the solvent was distilled off under reduced pressure. Purification by reverse phase column

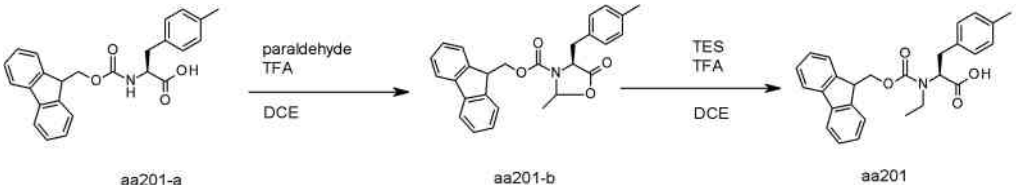
chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) gave Compound aa210 (2.17 g, 40%).

LCMS (ESI) m/z = 394 (M+H)+

Retention time: 0.94 min (Analytical condition SQDFA05)

[0358]

Synthesis of Compound aa201



[0359]

In a nitrogen atmosphere, Compound aa201-a, ((2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(4-methylphenyl)propanoic acid, Fmoc-Phe(4-Me)-OH) (5.62 g, 14.0 mmol, CAS No. 199006-54-7) was suspended in DCE (17.5 mL), then paraldehyde (5.61 mL, 42.0 mmol) and TFA (9.65 mL, 126 mmol) were added, and the mixture was stirred at 60°C for 6 hours. The resulting reaction solution containing Compound aa201-b was directly used in the next step.

LCMS (ESI) m/z = 428 (M+H)+

Retention time: 1.03 min (Analytical condition SQDFA05)

[0360]

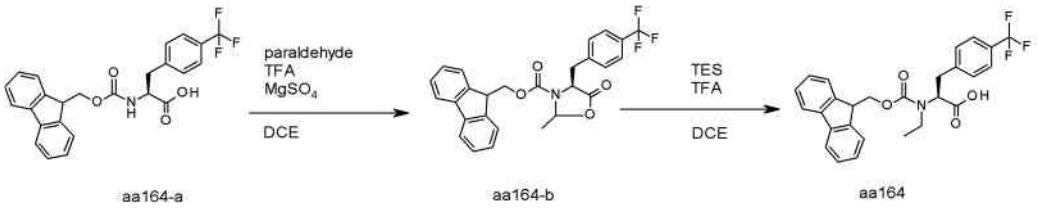
DCE (17.5 mL), TFA (19.3 mL, 252 mmol), and TES (20.1 mL, 126 mmol) were added to the resulting reaction solution of Compound aa201-b, and the mixture was stirred at 60°C for 17 hours. After the mixture was cooled to room temperature and concentrated under reduced pressure, the resulting residue was dissolved in ethyl acetate (40 mL). The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution (40 mL) and saturated brine (40 mL) and dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure. The resulting residue was dissolved in acetonitrile (30 mL) and washed twice with hexane (15 mL), and the solvent was distilled off under reduced pressure. The resulting residue was purified by reverse phase column chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compounds aa201, ((2S)-2-[ethyl(9H-fluoren-9-ylmethoxycarbonyl)amino]-3-(4-methylphenyl)propanoic acid, Fmoc-EtPhe(4-Me)-OH) (4.4 g, 2 steps, 73%).

LCMS (ESI) m/z = 430 (M+H)+

Retention time: 0.95 min (Analytical condition SQDFA05)

[0361]

Synthesis of Compound aa164



[0362]

In a nitrogen atmosphere, Compound aa164-a, ((2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-[4-(trifluoromethyl)phenyl]propanoic acid, Fmoc-Phe(4-CF3)-OH (4.04 g, 8.87 mmol, CAS No. 247113-86-6) was suspended in DCE (11.1 mL), then anhydrous magnesium sulfate (4.27 g, 35.4 mmol), paraldehyde (3.55 mL, 26.6 mmol), and TFA (6.11 mL, 80 mmol) were added, and the mixture was stirred at 60°C for 3 hours. Furthermore, anhydrous magnesium sulfate (2.14 g, 17.7 mmol) was added, and the mixture was stirred at 60°C for 1 hour. The resulting reaction solution containing Compound aa164-b was directly used in the next reaction.

LCMS (ESI) m/z = 482 (M+H)+

Retention time: 1.04 min (Analytical condition SQDFA05)

[0363]

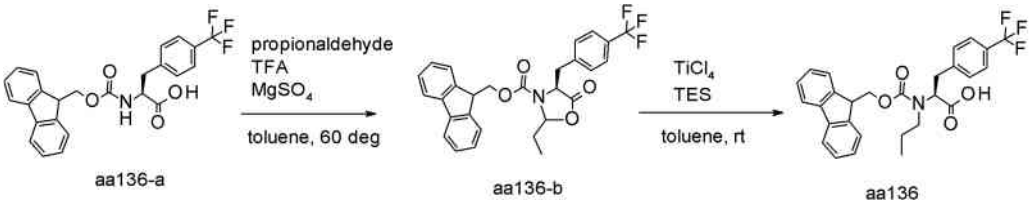
DCE (11.1 mL), TFA (12.2 mL, 159 mmol), and triethylsilane (12.7 mL, 80 mmol) were added to the resulting reaction solution containing Compound aa164-b, and the mixture was stirred at 60°C for 10 hours. The mixture was cooled to room temperature, magnesium sulfate was filtered off, and the mixture was concentrated under reduced pressure. Since the intended reaction was not complete, the resulting residue was dissolved in DCE (22.2 mL), then TFA (18.3 mL, 239 mmol) and triethylsilane (12.7 mL, 80 mmol) were added, and the mixture was stirred at 60°C for 8 hours. After the mixture was cooled to room temperature and concentrated under reduced pressure, the resulting residue was dissolved in ethyl acetate (40 mL). The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution (40 mL) and saturated brine (40 mL) and dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure. The resulting residue was dissolved in acetonitrile (30 mL) and washed twice with hexane (15 mL), and the solvent was distilled off under reduced pressure. The resulting residue was purified by reverse phase column chromatography (0.1% formic acid-containing water/acetonitrile) to give Compound aa164 (1.90 g, 2 steps, 44%).

LCMS (ESI) m/z = 484 (M+H)+

Retention time: 0.97 min (Analytical condition SQDFA05)

[0364]

<u>Synthesis of Compound aa136</u>



[0365]

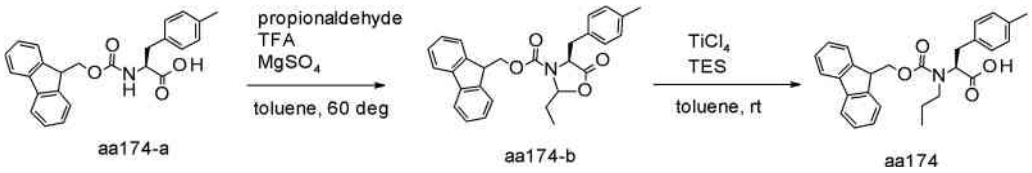
Compound aa136-a (10.1 g, 22.1 mmol) was dissolved in toluene (28 mL), then propionaldehyde (14.3 mL, 199 mmol), TFA (15.3 mL, 199 mmol), and magnesium sulfate (7.99 g, 66.4 mmol) were added, and the mixture was stirred at 60°C for 3 hours. Solids were filtered off with a silica gel pad, and the filtrate was washed twice with water (100 mL). Acetonitrile (20 mL) was added thereto, and the mixture was washed with a 1 M aqueous dipotassium hydrogen phosphate solution (30 mL), washed 3 times with a 3.5% aqueous potassium hydrogen carbonate solution (40 mL), and washed with saturated brine (100 mL). The mixture was dried over anhydrous magnesium sulfate and filtered off, and the solvent was distilled off under reduced pressure to give Compound aa136-b as a crude product. The crude product of Compound aa136-b was dissolved in toluene (28 mL), and TES (7.07 mL, 44.3 mmol) was added. The mixture was cooled to 0°C, $TiCl_4$ (4.88 mL, 44.3 mmol) was added, and the mixture was stirred at room temperature for 15 minutes. Water (50 mL) was added dropwise, and the organic layer was washed with water (100 mL) and washed with a 1 M aqueous dipotassium hydrogen phosphate solution (50 mL). n-Hexane (90 mL) was added, and the mixture was extracted 3 times with a mixed solvent of acetonitrile (15 mL) and a 1% aqueous potassium hydrogen carbonate solution (30 mL). Furthermore, the mixture was extracted twice with a mixed solvent of acetonitrile (20 mL) and a 1% aqueous potassium hydrogen carbonate solution (30 mL). n-Hexane (90 mL) was added to the organic layer, and the mixture was extracted twice with a mixed solvent of acetonitrile (20 mL) and a 1% aqueous potassium hydrogen carbonate solution (30 mL). The aqueous layers were combined, n-hexane (80 mL) was added, phosphoric acid was added to adjust pH to 3, and then the mixture was extracted 3 times with TBME (150 mL). The organic layer was washed with saturated brine (50 mL), dried over anhydrous magnesium sulfate, and filtered off, and the solvent was distilled off under reduced pressure to give Compound aa136 (5.03 g, 46%).

LCMS (ESI) m/z = 498 (M+H)+

Retention time: 1.02 min (Analytical condition SQDFA05)

[0366]

Synthesis of Compound aa174



[0367]

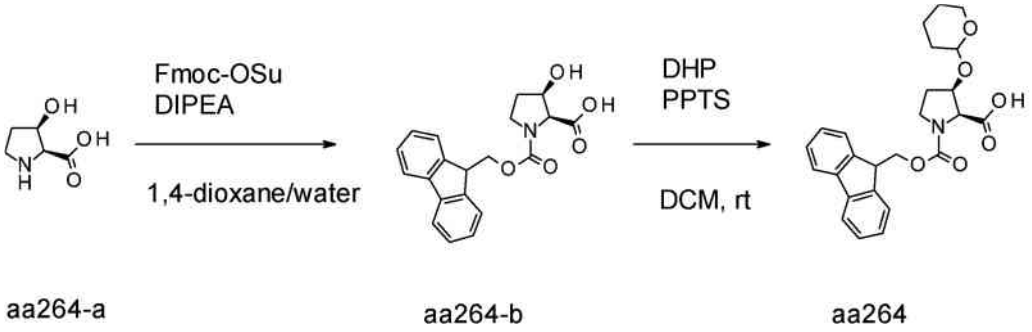
Using aa174-a as a starting material, aa174 (18.6 g, 84%) was obtained in the same manner as the synthesis of Compound aa136.

LCMS (ESI) m/z = 460 (M+NH4)+

Retention time: 1.41 min (Analytical condition SMD method_04)

[0368]

Synthesis of Compound aa264



[0369]

Compound aa264-a (H-cisHyp(3)-OH, 950 mg, 7.24 mmol) was dissolved in water (22 mL), and DIPEA (3.47 mL, 19.9 mmol) was added. A 1,4-dioxane solution (14.5 mL) of Fmoc-OSu (2.44 g, 7.24 mmol) was added thereto. The resulting solids were crushed with a spatula, and irradiated with ultrasonic waves for further pulverization. 1,4-Dioxane (15 mL) was added to and dissolve the solids, and the solution was stirred at room temperature for 40 minutes. Washing was performed twice with n-hexane/CPME (3/1, 10 mL), and potassium hydrogen sulfate (3.70 g, 27.2 mmol) was added. The mixture was extracted 3 times with isopropyl acetate (30 mL), the organic layer was washed with 50% brine (30 mL), dried over anhydrous sodium sulfate, filtered off, and the solvent was distilled off under reduced pressure to give Compound aa264-b (2.39 g, 93%).

LCMS (ESI) m/z = 355 (M+H)+

Retention time: 0.64 min (Analytical condition SQDFA05)

[0370]

Compound 264-b (2.39 g, 6.76 mmol) and PPTS (0.170 g, 0.676 mmol) were suspended in DCM (23 mL), then DHP (1.39 mL, 15.2 mmol) was added, and the mixture was stirred at room temperature for 19 hours. PPTS (0.085 g, 0.338 mmol) and DHP (0.741 mL, 8.11 mmol) were added, and the mixture was stirred at room temperature for 3 hours. This was

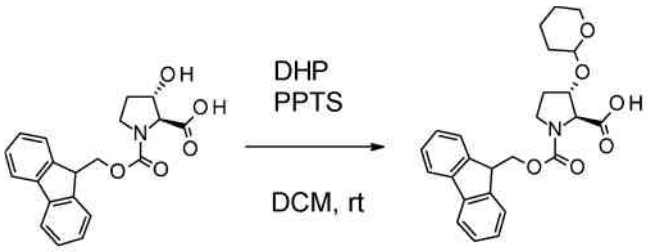
washed with water, and washed with saturated brine. The mixture was dried over anhydrous sodium sulfate and filtered off, and the solvent was distilled off under reduced pressure. This was dissolved in THF (25 mL), a phosphate buffer (pH = 8.2, 25 mL) was added, and the mixture was stirred at 50°C for 11 hours. Ethyl acetate (25 mL) was added to remove the aqueous layer, and the aqueous layer was extracted twice with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered off, and the solvent was distilled off under reduced pressure. This was dissolved in DCM (30 mL), and n-hexane (30 mL) was added. Only DCM was distilled off under reduced pressure, and further, n-hexane was distilled off under reduced pressure. n-Hexane was added to the resulting solids, and this was irradiated with ultrasonic waves, and n-hexane was removed by decantation, and this was dried under reduced pressure to give Compound aa264 as a sodium salt. This was dissolved in isopropyl acetate (50 mL), a 0.05 M aqueous phosphoric acid solution (pH = 2, 90 mL) was added, the mixture was stirred at room temperature for 10 minutes, and then the aqueous layer was removed. The aqueous layer was extracted with isopropyl acetate, the organic layer was dried over anhydrous sodium sulfate and filtered off, and the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound aa264 (2.33 g, 79%).

LCMS (ESI) m/z = 456 $(M+NH_3)+$

Retention time: 0.81 min (Analytical condition SQDFA05)

[0371]

Synthesis of Compound aa265



aa265-a aa265

[0372]

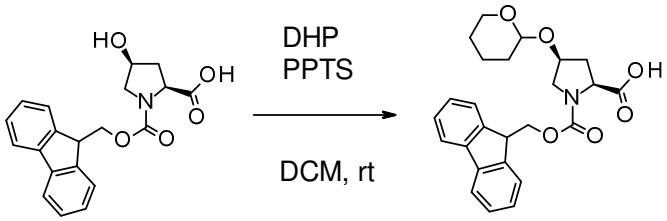
Using aa265-a as a starting material, aa265 (1.38 g, 78%) was obtained in the same manner as the synthesis of Compound aa264.

LCMS (ESI) m/z = 439 (M+H)+

Retention time: 0.85 min (Analytical condition SQDFA05)

[0373]

Synthesis of Compound aa267



aa267-a aa267

[0374]

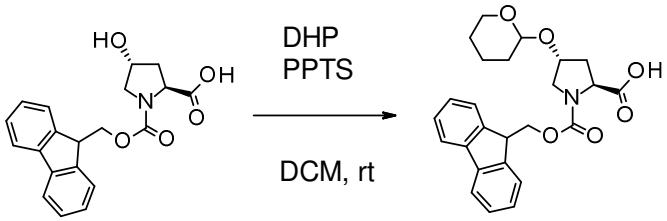
Using aa267-a as a starting material, aa267 (9.04 g, quant) was obtained in the same manner as the synthesis of Compound aa264.

LCMS (ESI) m/z = 460 (M+Na)+

Retention time: 0.81 min (Analytical condition SQDFA05)

[0375]

Synthesis of Compound aa279



aa279-a aa279

[0376]

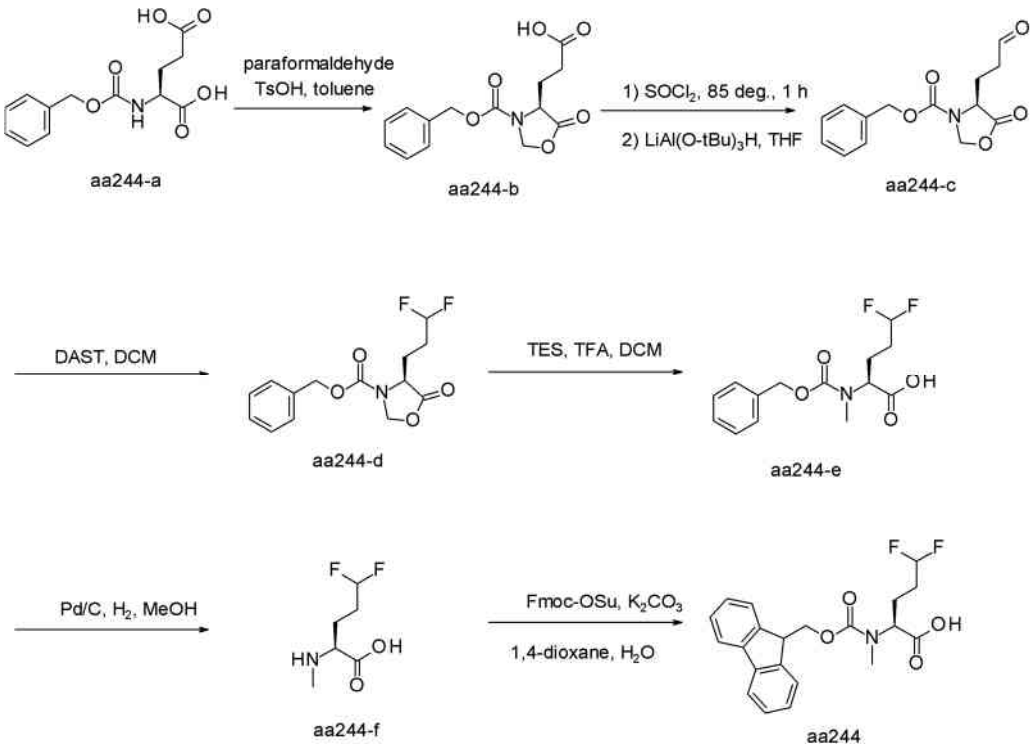
Using aa279-a as a starting material, aa279 (5.15 g, 83%) was obtained in the same manner as the synthesis of Compound aa264.

LCMS (ESI) m/z = 460 (M+Na)+

Retention time: 0.85 min (Analytical condition SQDFA05)

[0377]

Synthesis of Compound aa244



aa244-a aa244-b aa244-c aa244-d aa244-e aa244-f aa244

[0378]

A toluene (500 mL) mixed solution of Compound aa244-a, ((2S)-2-(phenylmethoxycarbonylamino)pentanedioic acid) (50 g, 177.8 mmol), paraformaldehyde (11.87g), and p-toluenesulfonic acid (1.84 g, 10.69 mmol) was stirred at 120°C for 16 hours. The reaction solution was cooled to room temperature, diluted with ethyl acetate, washed with saturated brine, and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give Compound aa244-b as a crude product (52 g, 96%). This crude product was used in the next reaction without purification.

[0379]

After a thionyl chloride (50 mL) solution of Compound aa244-b (4 g, 13.64 mmol) was stirred at 85°C for 1 hour, the solvent was distilled off under reduced pressure. The residue was dissolved in THF (20 mL), and cooled to -78°C in a nitrogen atmosphere. A THF (20 mL) solution of lithium tri-tert-butoxyaluminum hydride (2.76 g, 10.87 mmol) was added dropwise thereto over 2.5 hours. After the mixture was stirred at -78°C for 3 hours, water was added to the reaction solution, and the precipitate was removed by filtration. The filtrate was extracted with ethyl acetate, the organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give Compound aa244-c (2 g).

^{1}H-NMR (400-MHz, $CDCl_3$) δ 7.41-7.32 (m, 5H), 5.49 (br.s, 1H), 5.27-5.11 (m, 3H), 4.38-4.33 (m, 1H), 2.58-2.19 (m, 4H)

[0380]

In a nitrogen atmosphere, (diethylamino)sulfur trifluoride (DAST) (780 mg, 4.84 mmol) was added to a DCM (20 mL) solution of Compound aa244-c (450 mg, 1.62 mmol) at 0°C, and the mixture was stirred at room temperature for 16 hours. After water was added to the reaction solution, the reaction solution was diluted with DCM, and washed successively with an aqueous sodium hydrogen carbonate solution and saturated brine. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give Compound aa244-d (0.35 g, 72%). The compound was mixed with another similarly synthesized lot, and subjected to the next reaction.

^{1}H-NMR (400-MHz, $CDCl_3$) δ 7.42-7.35 (m, 5H), 5.97-5.58 (m, 2H), 5.25-5.16 (m, 3H), 4.50-4.35 (m, 1H), 2.14-1.68 (m, 4H)

^{19}F-NMR (400 MHz, $CDCl_3$) δ-116.562

[0381]

Compound aa244-d (1 g, 3.34 mmol) and TES (12.63 g, 109 mmol) were dissolved in TFA/DCM (10/10 mL), stirred at room temperature for 4 days, and then the solvent was distilled off under reduced pressure. The residue was diluted with an aqueous sodium hydrogen carbonate solution, washed with ether, and adjusted to pH 3 with 2 N hydrochloric acid. Extraction was performed with DCM, the organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give Compound aa244-e (0.6 g) as a crude product. This crude product was used in the next reaction without purification.

[0382]

A methanol (10 mL) mixed solution of Compound aa244-e (0.6 g) and palladium carbon (10%, 60 mg) was stirred for 16 hours in a hydrogen atmosphere of about 3 atm. Palladium carbon was removed by filtration, and the solvent was distilled off from the filtrate under reduced pressure to give Compound aa244-f (0.23 g) as a crude product. This crude product was mixed with another similarly synthesized lot without purification, and subjected to the next reaction.

[0383]

Fmoc-OSu (0.9 g, 1.5 eq) was added to a 1,4-dioxane/water (5/5 mL) mixed solution of Compound aa244-f (0.3 g, 1.79 mmol) and potassium carbonate (745 mg, 5.4 mmol), and the mixture was stirred for 2 hours. The reaction solution was diluted with water, washed with diethyl ether, and adjusted to pH 3 with 2 N hydrochloric acid. The reaction solution was extracted 3 times with ethyl acetate, the combined organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced

pressure. The resulting residue was purified by reverse phase column chromatography (0.05% TFA-containing acetonitrile/0.05% TFA-containing distilled water) to give Compound aa244 (0.2 g, 29%). Another similarly synthesized lot was also used in the peptide synthesis in the present Examples.

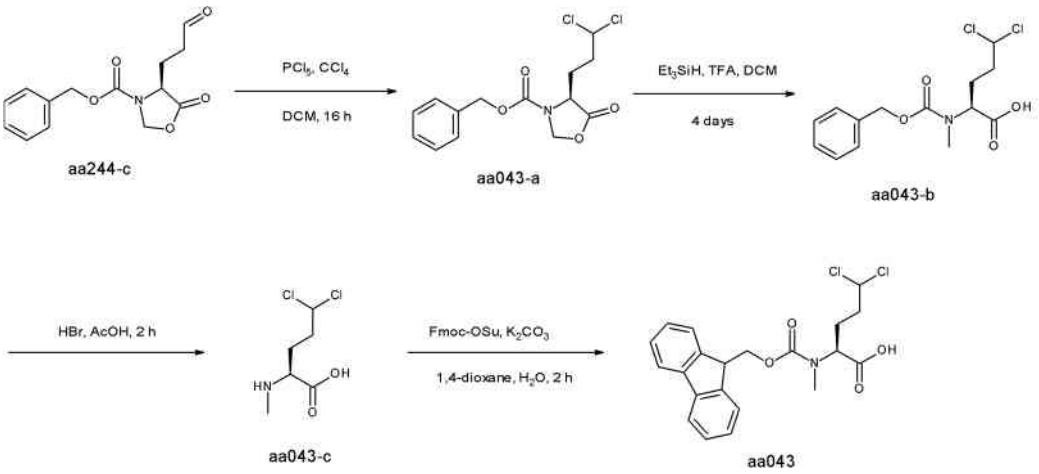
Retention time: 3.153 min (Analytical condition SMD method_19)

^{1}H-NMR (300-MHz, DMSO-d_6) δ 12.94 (br.s, 1H), 7.92-7.88 (d, J = 7.2 Hz, 2H), 7.66-7.61 (m, 2H), 7.44-7.31 (m, 4H), 6.35-5.75 (m, 1H), 4.49-4.26 (m,4H), 2.72 (s, 3H), 1.78-1.65 (m, 4H)

^{19}F-NMR (300 MHz, DMSO-d_6) δ-115.730

[0384]

Synthesis of Compound aa043



[0385]

In a nitrogen atmosphere, aa244-c (18 g, 64.98 mmol) was dissolved in dichloromethane (50 mL), and a carbon tetrachloride (550 mL) solution of phosphorus pentachloride (27 g, 130 mmol) was slowly added dropwise at 0°C. The reaction solution was stirred at room temperature for 16 hours, and then dichloromethane was added for dilution. The resulting solution was washed with water, the aqueous phase was extracted twice with dichloromethane, and then the organic phases were combined and washed with an aqueous sodium hydrogen carbonate solution. The resulting solution was dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure. The resulting crude product was purified by normal phase column chromatography (hexane/ethyl acetate) to give aa043-a (7.2 g, 33%).

[0386]

aa043-a (7.2 g, 21.75 mmol) was dissolved in dichloromethane (150 mL), then triethylsilane (83.2 g, 718 mmol) and trifluoroacetic acid (24.8 g, 218 mmol) were added, and the mixture was stirred at room temperature for 4 days. The reaction solution was concentrated

under reduced pressure, the resulting residue was dissolved in an aqueous sodium hydrogen carbonate solution, and the aqueous phase was washed with diethyl ether. Subsequently, the resulting solution was adjusted to pH 3 with 2 N hydrochloric acid. The mixed solution was extracted twice with dichloromethane, the organic phase was washed with saturated brine and dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure. The resulting crude product aa043-b (5.5 g) was directly used in the next step.

[0387]

A solution obtained by diluting an acetic acid solution (10 mL) of 33% hydrogen bromide with acetic acid (10 mL) was added to the crude product aa043-b (1.1 g), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with water. The resulting solution was washed with diethyl ether, and the solvent was distilled off under reduced pressure to give a crude product (1.0 g) of aa043-c. Crude product aa043-b was directly used in the next reaction.

LCMS (ESI) m/z = 200 (M+H)+

Retention time: 0.88 min (Analytical condition SMD method_12)

[0388]

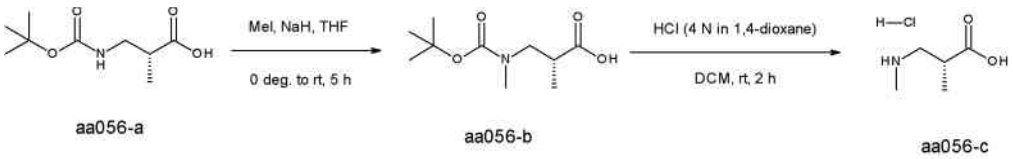
Crude product aa043-c (1.00 g) and potassium carbonate (1.48 g, 10.7 mmol) were dissolved in water (10 mL), and a 1,4-dioxane solution (10 mL) of Fmoc-OSu (1.8 g, 5.36 mmol) was added. After being stirred at room temperature for 2 hours, the reaction solution was diluted with water. The resulting solution was washed with diethyl ether (30 mL), and 2 N hydrochloric acid was added to adjust pH to 3. Subsequently, the mixed solution was extracted 3 times with ethyl acetate, the organic phase was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting concentrate was purified by reverse phase column chromatography (water-acetonitrile) to give aa043 (0.5 g, 27%, 3 steps).

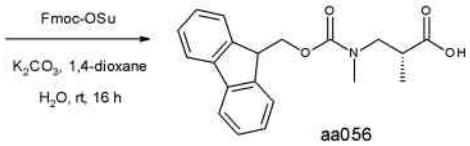
LCMS (ESI) m/z = 422 (M+H)+

Retention time: 2.3 min (Analytical condition SMD method_13)

[0389]

<u>Synthesis of Compound aa056</u>





[0390]

In a nitrogen atmosphere, aa056-a (90 g, 443 mmol) and methyl iodide (314 g, 2.21 mol) were dissolved in tetrahydrofuran (3.15 L). The mixed solution was cooled to 0°C, and sodium hydride (60%, 77.56 g, 2.21 mol) was added while stirring the mixed solution. The reaction solution was stirred at 25°C for 3 hours, and then added to ice water. The resulting solution was washed 3 times with t-butyl methyl ether/n-hexane (1/3). Then, 1 N hydrochloric acid was added to the aqueous phase to adjust pH to 2-3, and the mixture was extracted 3 times with ethyl acetate. The resulting organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give aa056-b (94 g) as a crude product. The resulting crude product was directly used in the next reaction.

LCMS (ESI) m/z = 240 (M+Na)+

Retention time: 1.1 min (Analytical condition SMD method_14)

[0391]

The crude product (94 g) of aa056-b was dissolved in dichloromethane (600 mL). This solution was cooled to 0°C, and 4 N HCl/1,4-dioxane (660 mL) was added. The reaction solution was stirred at 25°C for 3 hours and concentrated under reduced pressure to give a crude product (90 g) of aa056-c.

LCMS (ESI) m/z = 118 (M+H)+

Retention time: 0.25 min (Analytical condition SMD method_14)

[0392]

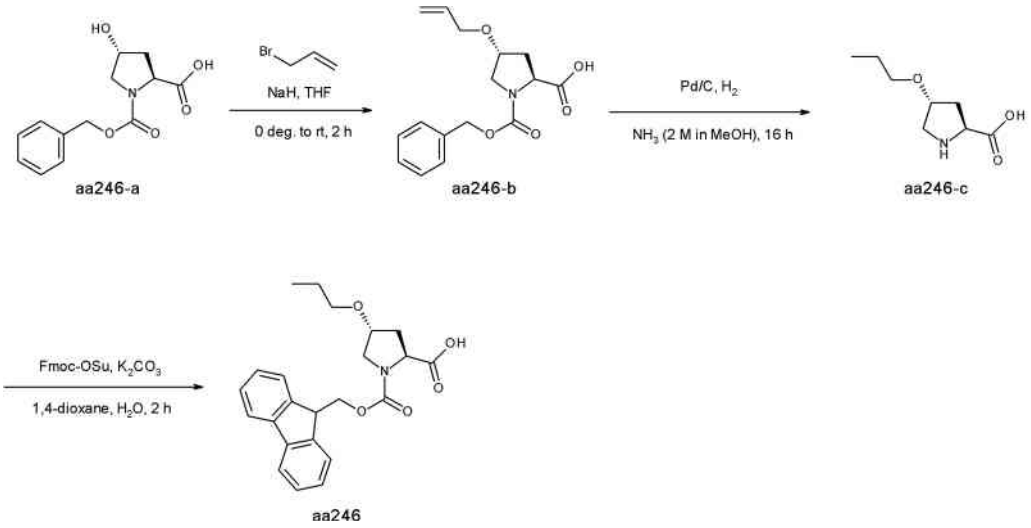
The crude product (90 g) of aa056-c was dissolved in water (560 mL), and potassium carbonate was added to adjust pH to 7. Subsequently, potassium carbonate (149 g, 1.08 mol), Fmoc-OSu (131 g, 389 mmol), and 1,4-dioxane (560 mL) were added to the reaction solution, and the mixture was stirred at 25°C for 3 hours. Next, the reaction solution was washed with t-butyl methyl ether/n-hexane (1/3), then 1 N hydrochloric acid was added to adjust pH to 2 to 3, and solids were collected by filtration. The resulting solids were washed with water and dried under reduced pressure at 50°C for 16 hours to give aa056 (130 g, 86% (3 steps)).

LCMS (ESI) m/z = 362 (M+Na)+

Retention time: 2.0 min (Analytical condition SMD method_15)

[0393]

Synthesis of Compound aa246



[0394]

In a nitrogen atmosphere, aa246-a (30 g, 113 mmol) was dissolved in tetrahydrofuran (300 mL), and sodium hydride (in oil, 60%, 5.97 g, 249 mmol) was added at 0°C. The reaction solution was stirred at room temperature for 4 hours and then cooled to 0°C, and 3-bromo-1-propene (15.73 g, 130 mmol) was added dropwise. Then, the reaction solution was stirred at room temperature for 2 hours, and ice water was added to quench the reaction. The pH of the resulting mixture was adjusted to 2 with concentrated hydrochloric acid, and then the mixture was extracted with ethyl acetate twice. The organic phase was washed with saturated brine, and dried over anhydrous sodium sulfate. The organic phase was concentrated under reduced pressure to give a crude product (27.3 g) of aa246-b.

LCMS (ESI) m/z = 306 (M+H)+

Retention time: 2.0 min (Analytical condition SMD method_16)

[0395]

The crude product (26 g) of aa246-b was dissolved in methanol (260 mL), and a 2 M ammonia-methanol solution (63.9 mL) and 10% palladium carbon (3.3 g) were added. The reaction solution was stirred at room temperature for 16 hours in a hydrogen atmosphere and then filtered. The resulting filtrate was concentrated under reduced pressure to give a crude product (14.2 g) of aa246-c.

LCMS (ESI) m/z = 174 (M+H)+

Retention time: 0.84 min (Analytical condition SMD method_16)

[0396]

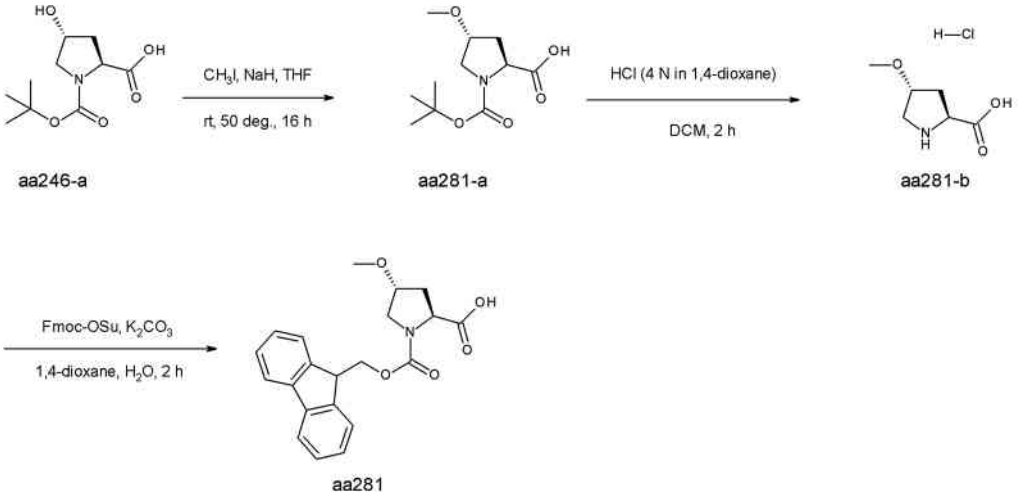
The crude product (10 g) of aa246-c was dissolved in 1,4-dioxane (100 mL) and water (100 mL), and potassium carbonate (23.9 g, 172 mmol) was added. Fmoc-OSu (17.4 g, 51.7 mmol) was added to the reaction solution, and the mixture was stirred at room temperature for 16 hours and then filtered. The resulting filtrate was washed 5 times with t-butyl methyl ether/hexane (1/3), and the aqueous phase was adjusted to pH 2 with concentrated hydrochloric acid. The resulting solution was extracted twice with ethyl acetate. Subsequently, the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give aa246 (15.3 g, 58%, 3 steps).

LCMS (ESI) m/z = 396 (M+H)+

Retention time: 2.0 min (Analytical condition SMD method_11)

[0397]

Synthesis of Compound aa281



[0398]

In a nitrogen atmosphere, aa246-a (10 g, 43.2 mmol) was dissolved in tetrahydrofuran (150 mL) and cooled to -10°C, and then sodium hydride (60%, 3.8 g, 95.1 mmol) was added. The reaction solution was stirred at room temperature for 1 hour. Subsequently, methyl iodide (7.4 g, 51.9 mmol) was added dropwise at room temperature. The reaction solution was heated to 50°C, and stirred at 50°C for 16 hours. Then, a saturated aqueous sodium hydrogen carbonate solution was added to the reaction solution. The aqueous phase was washed with diethyl ether (150 mL), and 1 N hydrochloric acid was added to adjust pH to 3. The resulting mixture was extracted twice with ethyl acetate (200 mL). The organic phase was washed with saturated brine and a 5 % aqueous sodium thiosulfate solution, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure to give a crude product (11.1 g) of aa281-a.

LCMS (ESI) m/z = 268 (M+Na)+

Retention time: 0.75 min (Analytical condition SQDFA05)

[0399]

The crude product (11.1 g) of aa281-a was dissolved in dichloromethane (110 mL), and 4 N HCl/1,4-dioxane (56.6 mL, 227 mL) was added. The reaction solution was stirred at room temperature for 2 hours, and then the solvent was distilled off under reduced pressure. The resulting residue was suspended in diethyl ether (110 mL), and solids were collected by filtration to give aa281-b (7.4 g, 94%, 2 steps).

LCMS (ESI) m/z = 146 (M+H)+

Retention time: 0.14 min (Analytical condition SQDFA05)

[0400]

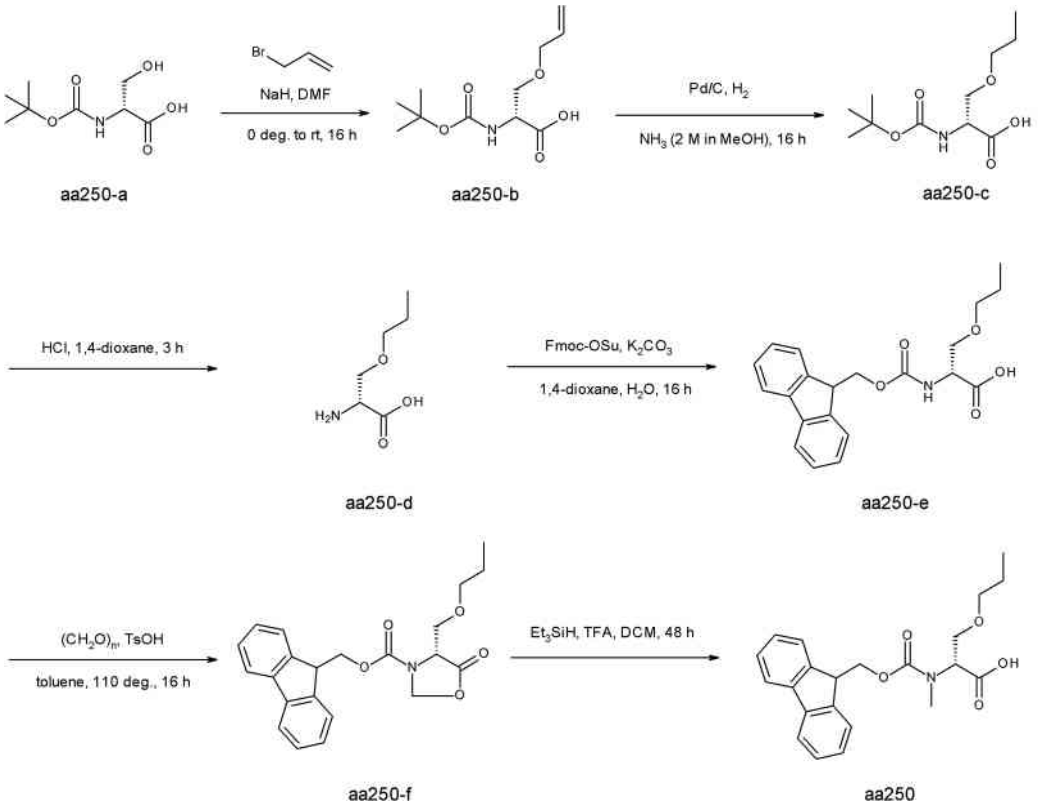
aa281-b (7.4 g, 40.7 mmol) was dissolved in water (70 mL), and potassium carbonate was added to adjust pH to 7. Then, 1,4-dioxane (70 mL), potassium carbonate (11.3 g, 81.5 mmol), and Fmoc-OSu (12.4 g, 36.7 mmol) were added thereto at room temperature. After the reaction solution was stirred at room temperature for 2 hours, the aqueous phase was washed 3 times with t-butyl methyl ether-n-hexane (1/3, 70 mL). Subsequently, 1 N hydrochloric acid was added to the aqueous phase to adjust pH to 3, and the mixture was extracted with t-butyl methyl ether (140 mL). The organic phase was washed with saturated brine (70 mL), and dried over anhydrous sodium sulfate. The resulting organic phase was concentrated under reduced pressure to give aa281 (15 g, 98%).

LCMS (ESI) m/z = 368 (M+H)+

Retention time: 1.79 min (Analytical condition SMD method_11)

[0401]

<u>Synthesis of Compound aa250</u>



[0402]

In a nitrogen atmosphere, aa250-a (233 g, 1.14 mol) was dissolved in DMF (1500 mL), and NaH (in oil, 60%, 100 g, 4.17 mol) was added while ice-cooling the mixture. The reaction solution was stirred at room temperature for 3 hours and cooled to 0°C, and a DMF (500 mL) solution of 3-bromo-1-propene (130 g, 1.07 mol) was added dropwise. Subsequently, the reaction solution was stirred at room temperature for 16 hours, and ice water was added to quench the reaction. The resulting solution was adjusted to pH 2 with concentrated hydrochloric acid. The mixed solution was extracted twice with ethyl acetate, the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate-n-hexane) to give aa250-b (200 g, 72%).

LCMS (ESI) m/z = 246 (M+H)+

Retention time: 1.2 min (Analytical condition SMD method_14)

[0403]

aa250-b (300 g, 1.22 mol) was dissolved in methanol (2 L) and dissolved in a 2 M ammonia-methanol solution (918 mL) and methanol (2000 mL), and 10% palladium carbon (60 g) was added. The reaction solution was stirred at room temperature for 16 hours in a hydrogen atmosphere at 10 atm. The reaction solution was filtered and then concentrated under reduced pressure to give a crude product (290 g) of aa250-c.

LCMS (ESI) m/z = 248 (M+H)+

Retention time: 1.2 min (Analytical condition SMD method_14)

[0404]

The crude product (100 g) of aa250-c was dissolved in 1,4-dioxane (1500 mL), and 12 N hydrochloric acid (200 mL) was added. The reaction solution was stirred at room temperature for 4 hours, and then the volatile organic solvent was distilled off under reduced pressure to give an aqueous solution of aa250-d. The resulting aqueous solution was adjusted to pH 7 with potassium carbonate, and then 1,4-dioxane (500 mL), Fmoc-OSu (115 g, 0.34 mmol), and potassium carbonate (104.5 g, 0.76 mol) were added. The reaction solution was stirred at room temperature for 16 hours and then filtered. The filtrate was washed 5 times with t-butyl methyl ether/hexane (1/3), and then concentrated hydrochloric acid was added to adjust pH to 1. The resulting solution was extracted twice with ethyl acetate, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give aa250-e (90 g, 58%, 3 steps).

LCMS (ESI) m/z = 370 (M+H)+

Retention time: 1.3 min (Analytical condition SMD method_14)

[0405]

aa250-e (110 g, 298 mmol) was dissolved in toluene (1000 mL), and p-toluenesulfonic acid (3 g, 17.4 mmol) and paraformaldehyde (27 g, 893 mmol) were added. The reaction solution was stirred at 110°C for 16 hours. The reaction solution was cooled, washed 4 times with an aqueous sodium hydrogen carbonate solution, and dried over anhydrous sodium sulfate. The resulting organic phase was concentrated under reduced pressure to give a crude product (90 g) of aa250-f.

LCMS (ESI) m/z = 382 (M+H)+

Retention time: 2.9 min (Analytical condition SMD method_16)

[0406]

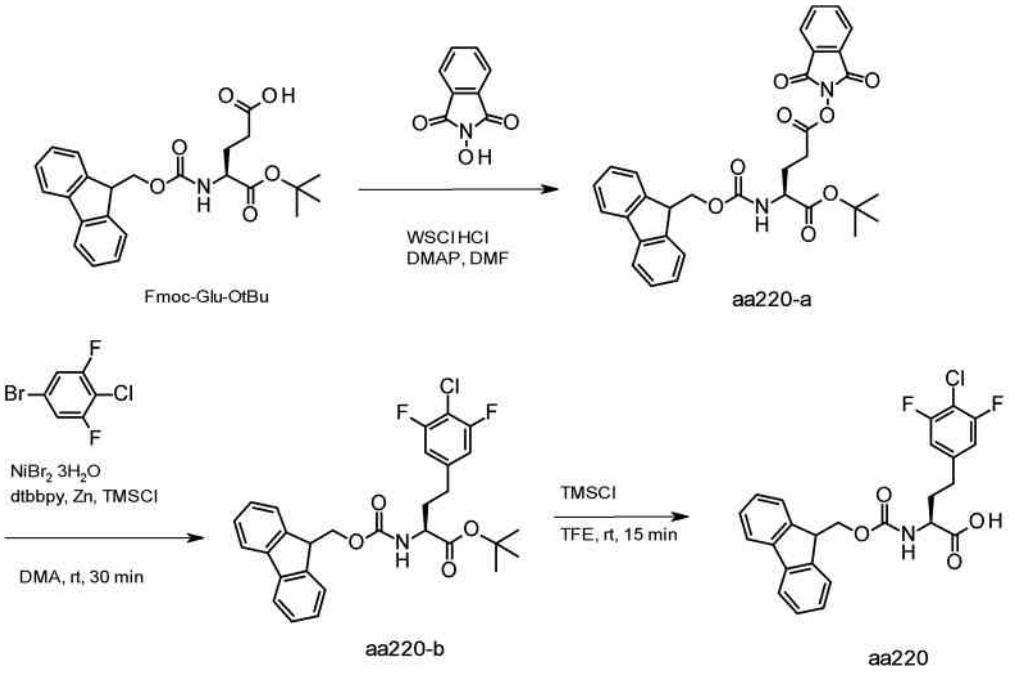
The crude product (60 g) of aa250-f was dissolved in dichloromethane (700 mL), then triethylsilane (59 g, 507 mmol) and trifluoroacetic acid (700 mL, 1.41 mol) were added, and the mixture was stirred at room temperature for 48 hours. Then, the reaction solution was concentrated, and the resulting concentrate was dissolved in water (50 mL). The resulting aqueous solution was neutralized with a saturated aqueous potassium carbonate solution to adjust pH to 8. Subsequently, the mixture was washed 4 times with n-hexane, the resulting solution was adjusted to pH 2 with concentrated hydrochloric acid, and extracted twice with t-butyl methyl ether. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give aa250 (50 g, 66%, 2 steps).

LCMS (ESI) m/z = 384 (M+H)+

Retention time: 2.0 min (Analytical condition SMD method_11)

[0407]

Synthesis of Compound aa220



[0408]

Fmoc-Glu-OtBu ((4S)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-5-[(2-methylpropan-2-yl)oxy]-5-oxopentanoic acid, CAS No. 84793-07-7) (175 g, 411 mmol), N-hydroxyphthalimide (67.1 g, 411 mmol), WSCI·HCl (78.85 g, 411 mmol), and DMAP (2.51 g, 20.6 mmol) were added to DMF (2 L), and the mixture was stirred at room temperature for 16 hours. A 1 N hydrochloric acid solution was added to the reaction solution, and the reaction mixture was extracted with TBME. The organic layers were combined, sequentially washed with water, saturated aqueous sodium hydrogen carbonate solution/water (1/1), and saturated brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether, 0/100 to 30/70) to give Compound aa220-a (1-O-tert-butyl 5-O-(1,3-dioxoisoindol-2-yl) (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)pentanedioate) (105 g, 45%).

LCMS (ESI) m/z = 593.5 (M+Na)+

Retention time: 2.374 min (Analytical condition SMD method_09)

^{1}H-NMR (300-MHz, DMSO-d_6) δ 8.00-7.91 (m, 4H), 7.85 (dd, J =23.0, 7.6Hz, 3H), 7.75 (d, J =7.4Hz, 2H), 7.75-7.32 (m, 4H), 4.60-4.31 (m, 2H), 4.30-4.02 (m, 2H), 3.01-2.74 (m, 2H), 2.26-1.86 (m, 2H), 1.41 (s, 9H)

[0409]

In a nitrogen atmosphere, N,N-dimethylacetamide (35.1 mL) was added to nickel(II) bromide trihydrate (0.76 g, 2.8 mmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (0.75 g, 2.8 mmol), and the mixture was stirred at room temperature for 10 minutes (sol A). Then, sol A and chlorotrimethylsilane (0.9 mL, 7.0 mmol) were added to an N,N-dimethylacetamide (35.1 mL) solution of aa220-a (8.0 g, 14.0 mmol), 5-bromo-2-chloro-1,3-difluorobenzene (4.5 mL, 35.1 mmol), and zinc (4.6 g, 70.1 mmol), and the mixture was stirred at room temperature for 30 minutes. tert-Butyl methyl ether (250 mL) was added, the mixture was passed through a filter obtained by coating Celite with sodium sulfate, and then a 5 wt% aqueous disodium ethylenediaminetetraacetate solution (250 mL) was added for extraction. The organic layer was washed twice with a 5 wt% aqueous sodium carbonate solution (150 mL), washed with a saturated aqueous ammonium chloride solution (150 mL), dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure. The resulting concentrate was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give aa220-b (4.75 g, 64%).

Retention time: 1.18 min (Analytical condition SQDFA05)

[0410]

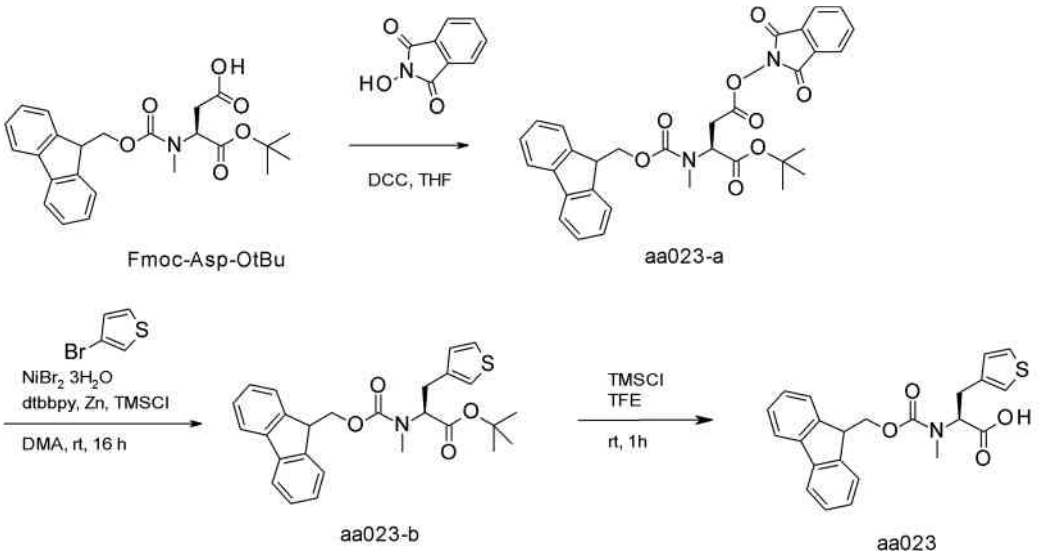
aa220-b (4.75 g, 9.0 mmol) was dissolved in 2,2,2-trifluoroethanol (90.0 mL), chlorotrimethylsilane (3.4 mL, 27.0 mmol) was added at room temperature, the mixture was stirred for 15 minutes, and then the solvent was distilled off under reduced pressure. A 20:1 mixed solution (100 mL) of n-hexane and tert-butyl methyl ether was added to the resulting concentrate, then the mixture was filtered under reduced pressure, and the resulting residue was washed twice with a 40:1 mixed solution (100 mL) of n-hexane and tert-butyl methyl ether and dried under reduced pressure to give aa220 (3.92 g, 92%).

LCMS (ESI) m/z = 470 (M-H)-

Retention time: 0.99 min (Analytical condition SQDFA05)

[0411]

Synthesis of Compound aa023



[0412]

Fmoc-MeAsp-OtBu ((3S)-4-tert-butoxy-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-butanoic acid, CAS No. 2271413-88-6) (300 g, 729 mmol) and N-hydroxyphthalimide (130.8 g, 801.8 mmol) were added to THF (3 L), and further, DCC (181.8 g, 1.1 mol) was added, and the mixture was stirred at room temperature for 3 hours. The solvent was distilled off from the reaction solution under reduced pressure, toluene was added to the residue, and solids were removed by filtration. The solvent was distilled off from the filtrate under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give Compound aa023-a (272g, 67%).

LCMS (ESI) m/z = 578.7 (M+Na)+

Retention time: 1.728 min (Analytical condition SMD method_08)

[0413]

Using the resulting aa023-a, aa023-b (12.0 g, 51%) was obtained in the same manner as the synthesis of Compound aa220-b using 3-bromothiophene in place of 5-bromo-2-chloro-1,3-difluorobenzene.

LCMS (ESI) m/z = 486 (M+Na)+

Retention time: 1.23 min (Analytical condition SMD method_20)

[0414]

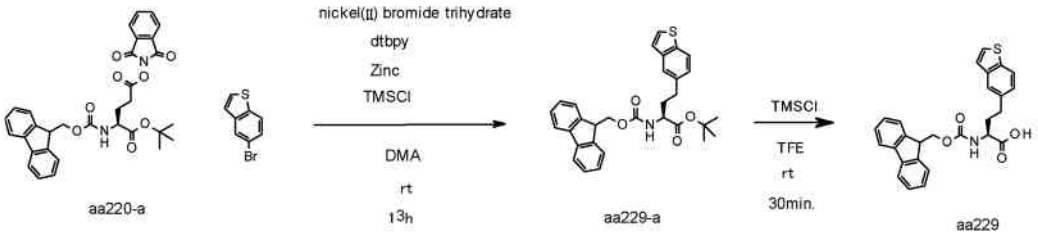
Using the resulting aa023-b, aa023 (8.8 g, 84%) was obtained under the same reaction conditions as the synthesis of Compound aa220.

LCMS (ESI) m/z = 408 (M+H)+

Retention time: 0.86 min (Analytical condition SQDFA05)

[0415]

Synthesis of Compound aa229



[0416]

Using aa220-a as a starting material, aa229-a (3.83 g, 43%) was obtained in the same manner as the synthesis of Compound aa220-b using 5-bromobenzothiophene in place of 5-bromo-2-chloro-1,3-difluorobenzene.

LCMS (ESI) m/z = 515 (M+H)+

Retention time: 1.17 min (Analytical condition SQDFA05)

[0417]

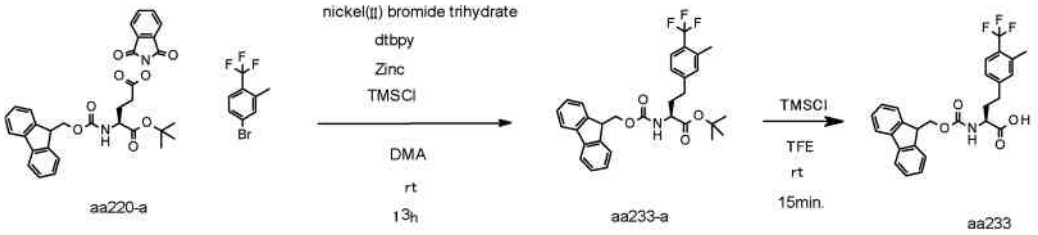
Using the resulting aa229-a, aa229 (3.05 g, 89%) was obtained under the same reaction conditions as the synthesis of Compound aa220.

LCMS (ESI) m/z = 458 (M+H)+

Retention time: 0.96 min (Analytical condition SQDFA05)

[0418]

Synthesis of Compound aa233



[0419]

Using aa220-a as a starting material, aa233-a (1.08 g, 67%) was obtained in the same manner as the synthesis of Compound aa220-b using 4-bromo-2-methyl-1-(trifluoromethyl)benzene in place of 5-bromo-2-chloro-1,3-difluorobenzene.

LCMS (ESI) m/z = 541 (M+H)+

Retention time: 1.20 min (Analytical condition SQDFA05)

[0420]

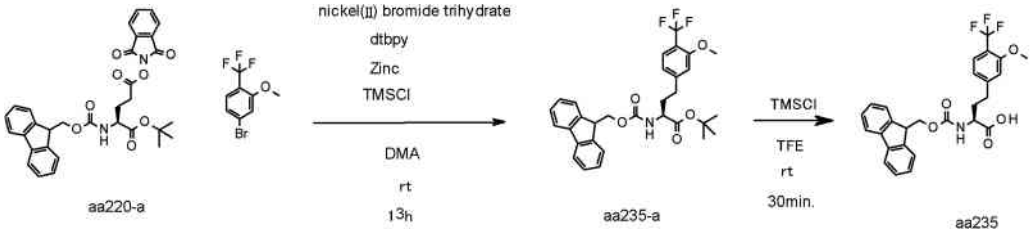
Using the resulting aa233-a, aa233 (0.65 g, 67%) was obtained under the same reaction conditions as the synthesis of Compound aa220.

LCMS (ESI) m/z = 484 (M+H)+

Retention time: 1.01 min (Analytical condition SQDFA05)

[0421]

Synthesis of Compound aa235



[0422]

Using aa220-a as a starting material, aa235-a (4.73 g, 69%) was obtained in the same manner as the synthesis of Compound aa220-b using 4-bromo-2-methoxy-1-(trifluoromethyl)benzene in place of 5-bromo-2-chloro-1,3-difluorobenzene.

Retention time: 1.15 min (Analytical condition SQDFA05)

[0423]

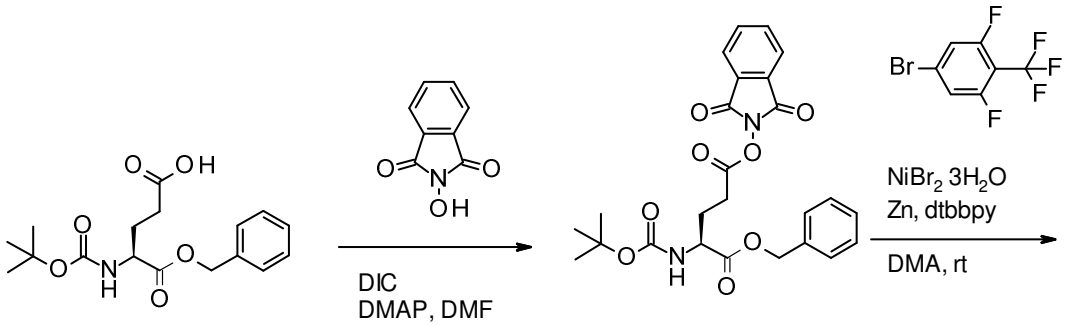
Using the resulting aa235-a, aa235 (3.91 g, 92%) was obtained under the same reaction conditions as the synthesis of Compound aa220.

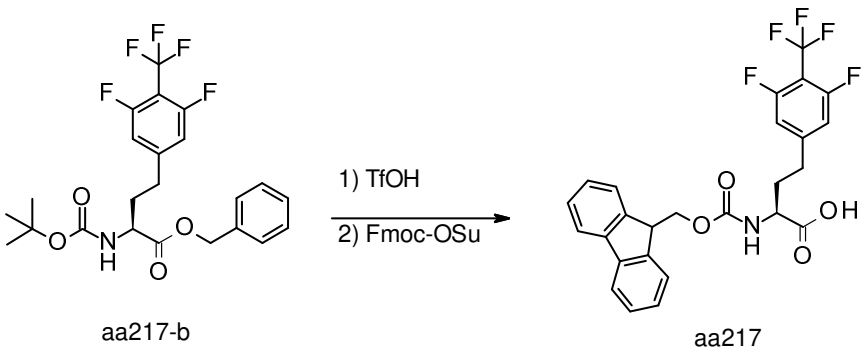
LCMS (ESI) m/z = 500 (M+H)+

Retention time: 0.96 min (Analytical condition SQDFA05)

[0424]

Synthesis of Compound aa217





[0425]

DIC (138 mL, 1.54 eq) was added dropwise at 0°C in a nitrogen atmosphere to a THF (2 L) solution of (4S)-4-[(2-methylpropan-2-yl)oxycarbonylamino]-5-oxo-5-phenylmethoxypentanoic acid (Boc-Glu-OBn, CAS number 30924-93-7) (200 g, 592.82 mmol), N-hydroxyphthalimide (106 g, 649.78 mmol, 1.10 eq), and DMAP (3.6 g, 29.47 mmol, 0.05 eq). The reaction solution was stirred at 25°C for 16 hours, solid matter was removed by filtration, and the solvent was distilled off from the filtrate under reduced pressure. The residue was diluted with toluene, the resulting solids were removed by filtration, and the solvent was distilled off from the filtrate under reduced pressure. The residue was purified by recrystallization (acetone/heptane) to give Compound aa217-a (1-O-benzyl 5-O-(1,3-dioxoisoindol-2-yl) (2S)-2-[(2-methylpropan-2-yl)oxycarbonylamino]pentanedioate) (230 g, 80%).

LCMS (ESI) m/z = 505.2 (M+Na)+

Retention time: 0.992 min (Analytical condition SMD method_16)

[0426]

Nickel bromide trihydrate ($NiBr_2 \cdot 3H_2O$) (13.5 g, 49.7 mmol, 0.3 eq) and 4,4'-di-tert-butyl-2,2'-bipyridyl (dtbbpy, CAS No. 72914-19-3) (13.3 g, 49.7 mmol, 0.3 eq) were added to DMA (400 mL), and the mixture was stirred at 50°C for 3 hours in a nitrogen atmosphere to prepare a Ni solution.

[0427]

A DMA (400 mL) mixed solution of Compound aa217-a, (1-O-benzyl 5-O-(1,3-dioxoisoindol-2-yl) (2S)-2-[(2-methylpropan-2-yl)oxycarbonylamino]pentandioate) (80 g, 166 mmol), zinc powder (54.2 g, 829 mmol, 5 eq), and 4-bromo-1,3-difluoro-2-(trifluoromethyl)benzene (CAS No. 156243-64-0, 86.6 g, 332 mmol, 2 eq) was stirred at room temperature for 1 hour in a nitrogen atmosphere, the Ni solution prepared in advance was added, and the mixture was stirred at room temperature for 16 hours. An aqueous EDTA·2Na solution (800 mL, 10%) was added to the reaction solution, and solids were removed by filtration. The filtrate was extracted with ethyl acetate, the combined organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give Compound aa217-b (57.2 g, 69%).

LCMS (ESI) m/z = 496 (M+Na)+

Retention time: 1.544 min (Analytical condition SMD method_15)

[0428]

A toluene mixture (690 mL) of Compound aa217-b (57.2 g, 121 mmol) was cooled to 0°C, and trifluoromethanesulfonic acid (TfOH) (54.4 g, 362 mmol, 3 eq) was added dropwise. After 1 hour of stirring at room temperature, water (58 mL) was added. The mixed solution was extracted with water, and the combined aqueous layer was extracted with ethyl acetate.

The combined organic layer was washed with water and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give 60 g of a residue. Acetonitrile/water (400/400 mL) was added to the residue, and pH was adjusted to 7 with an aqueous sodium hydroxide solution (48%). Fmoc-OSu (36.6 g, 108.6 mmol, 0.9 eq) was added to this solution, and pH was adjusted to 8.0 with an aqueous sodium hydroxide solution (48%), and then the mixture was stirred at room temperature for 16 hours. The reaction solution was filtered while being washed with acetonitrile/water (1/1) to remove solid components. The filtrate was diluted with acetonitrile and acidified with 6 N hydrochloric acid, and precipitated solids were collected by filtration to give Compound aa217 (52 g, 83%).

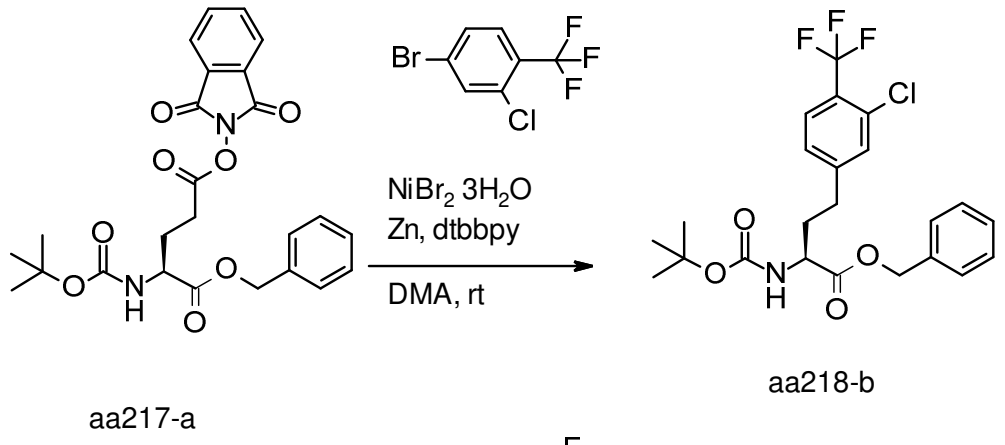
LCMS (ESI) m/z = 528 (M+Na)+

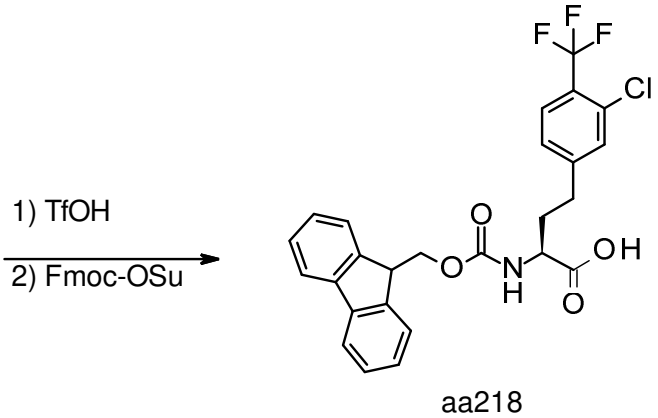
Retention time: 3.538 min (Analytical condition SMD method_14)

^{1}H-NMR (300-MHz, DMSO-d_6) δ 12.69 (s, 1H), 7.90 (d, J =7.5 Hz, 2H), 7.78-7.54 (m, 3H), 7.48-7.20 (m, 6H), 4.33 (d, J =6.3 Hz, 2H), 4.24 (t, J =6.9 Hz, 1H), 3.97-3.84 (m, 1H), 2.79-2.65 (m, 2H), 2.15-2.00 (m, 1H), 2.00-1.83 (m, 1H)

[0429]

Synthesis of Compound aa218





[0430]

Nickel bromide trihydrate ($NiBr_2 \cdot 3H_2O$) (4 g, 0.07 eq) and 4,4'-di-tert-butyl-2,2'-bipyridyl (dtbbpy, CAS No. 72914-19-3) (3.9 g, 14.55 mmol, 0.07 eq) were added to DMA (500 mL), and the mixture was stirred at 50°C for 2 hours in a nitrogen atmosphere to prepare a Ni solution.

[0431]

The Ni solution prepared in advance was added to a DMA (500 mL) mixed solution of Compound aa217-a (100 g, 207.3 mmol), zinc powder (70 g, 5 eq), and 4-bromo-2-chloro-1-(trifluoromethyl)benzene (CAS No. 467435-07-0, 160 g, 617 mmol, 3 eq), and the mixture was stirred at 25°C for 16 hours. An aqueous EDTA·2Na solution (10%) was added to the reaction solution, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give Compound aa218-b (75 g, 77%).

LCMS (ESI) m/z = 494 (M+Na)+

Retention time: 2.863 min (Analytical condition SMD method_17)

[0432]

A toluene solution (900 mL) of Compound aa218-b (75 g, 158.93 mmol) was cooled to 0°C, and trifluoromethanesulfonic acid (TfOH) (42 mL, 3.00 eq) was added dropwise. After 1 hour of stirring at room temperature, water (75 mL) was added. The mixed solution was extracted with water, and the combined aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. Acetonitrile/water (900/900 mL) was added to the residue, and pH was adjusted to 7 with an aqueous sodium hydroxide solution (48%). Fmoc-OSu (51.2 g, 151.93 mmol, 0.95 eq) was added to this solution, and the mixture was stirred at room temperature for 16 hours while maintaining pH at 7.8 to 8.0. The reaction solution was filtered, and the filtrate was adjusted to pH 2 with 6 N hydrochloric acid. The precipitated solids were collected and dried at 50°C to give Compound aa218 (70 g, 87%).

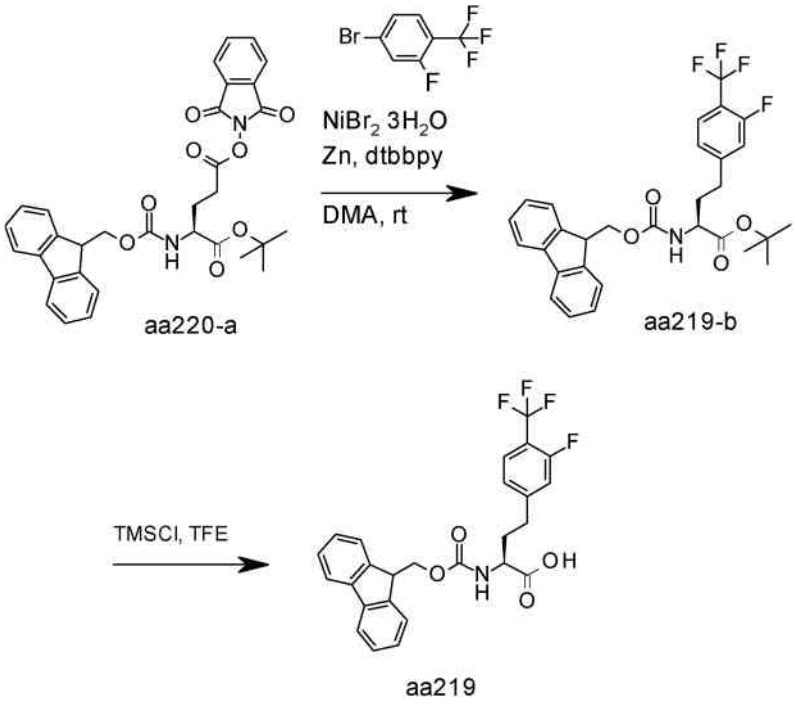
LCMS (ESI) m/z = 526 (M+Na)+

Retention time: 2.180 min (Analytical condition SMD method_21)

^{1}H-NMR (300-MHz, DMSO-d_6) δ 12.70 (s, 1H), 7.91 (d, J =7.5 Hz, 2H), 7.79-7.59 (m, 5H), 7.45-7.28 (m, 5H), 4.40-4.19 (m, 3H), 3.96-3.88 (m,1H), 2.82-2.60 (m, 2H), 2.11-1.77 (m, 2H)

[0433]

<u>Synthesis of Compound aa219</u>



[0434]

Nickel bromide trihydrate ($NiBr_2 \cdot 3H_2O$) (71.5 g, 263 mmol, 0.3 eq) and 4,4'-di-tert-butyl-2,2'-bipyridyl (dtbbpy, CAS Number 72914-19-3) (70.56 g, 263 mmol, 0.3 eq) were added to DMA (2 L), and the mixture was stirred at 50°C for 3 hours in a nitrogen atmosphere to prepare a Ni solution.

[0435]

A DMA (2 L) mixed solution of Compound aa220-a (1-O-tert-butyl 5-O-(1,3-dioxoisoindol-2-yl) (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)pentanedioate) (500 g, 876 mmol), zinc powder (287 g, 4.38 mol, 5 eq), and 4-bromo-2-fluoro-1-(trifluoromethyl)benzene (CAS No. 142808-15-9, 425.87 g, 1.753 mol, 2 eq) was stirred at room temperature for 1 hour in a nitrogen atmosphere. The Ni solution prepared in advance was added to this mixed solution, and the mixture was stirred at room temperature for 16 hours. An aqueous EDTA·2Na solution (4 L, 10%) was added to the reaction solution, and solids were removed by filtration while being washed with ethyl acetate. The filtrate was washed with saturated brine and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give Compound aa219-b (230 g, 43%).

LCMS (ESI) m/z = 566 (M+Na)+

Retention time: 1.317 min (Analytical condition SMD method_18)

[0436]

A trifluoroethanol (TFE) (2.3 L) mixed solution of the resulting Compound aa219-b (230 g, 423 mmol) and chlorotrimethylsilane (TMSCl) (137.9 g, 1.269 mol) was stirred at room

temperature for 1 hour, and the precipitated solids were collected by filtration. The operation of dissolving the resulting solids in TBME and distilling off the solvent under reduced pressure was repeated several times to give the intended Compound aa219 (190 g, 90%).

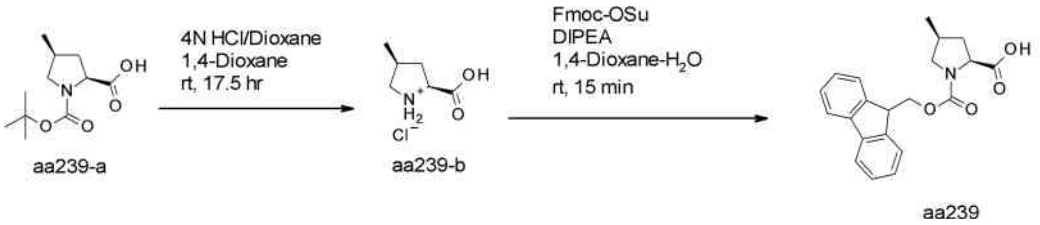
LCMS (ESI) m/z = 510 (M+Na)+

Retention time: 1.585 min (Analytical condition SMD method_13)

^{1}H-NMR (300-MHz, DMSO-d_6) δ 12.69 (s, 1H), 7.90 (d, J =7.5 Hz, 2H), 7.81-7.66 (m, 4H), 7.47-7.37 (m, 3H), 7.37-7.29 (m, 2H), 7.25 (d, J = 8.1 Hz, 1 H), 4.44-4.14 (m, 3H), 3.97-3.84 (m, 1H), 2.80-2.63 (m, 2H), 2.12-1.81 (m, 2H)

[0437]

Synthesis of Compound aa239



[0438]

aa239-a (2 g, 8.72 mmol) was dissolved in 1,4-dioxane (2 mL) at room temperature, and 4 N HCl/dioxane (4.36 mL, 17.45 mmol) was added. The reaction mixture was stirred at room temperature for 17.5 hours, the solvent was distilled off under reduced pressure, and the resulting crude product was dissolved in water and freeze-dried to give aa239-a (1.49 g, quant.).

[0439]

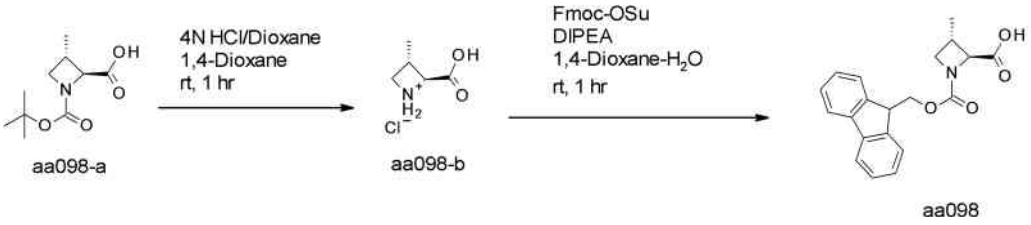
Water (22.5 mL) and DIPEA (5.89 mL, 33.7 mmol) were added to aa239-a (1.49 g, 9 mmol) at room temperature to dissolve it, 1,4-dioxane (15 mL) was added, then N-(9-fluorenylmethoxycarbonyloxy)succinimide (3.03 g, 9 mmol) was added, and the mixture was stirred at room temperature for 15 minutes. Hexane-CPME (3:1) (10 mL) was added to the reaction mixture, and the separated aqueous phase was washed twice with hexane-CPME (3:1) (10 mL). Potassium hydrogen sulfate (4.59 g, 33.7 mmol) and ethyl acetate were added to the aqueous phase, the separated organic phase (about 60 mL) was washed twice with brine (10 mL) and dried over anhydrous sodium sulfate, then the solvent was distilled off under reduced pressure, and the resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give aa239 (2.89 g, 91%).

LCMS (ESI) m/z = 352 (M+H)+

Retention time: 0.81 min (Analytical condition SQDFA05)

[0440]

Synthesis of Compound aa098



[0441]

Using aa098-a as a starting material, aa098-b (2.30 g, quant.) was obtained in the same manner as the synthesis of Compound aa239-b.

LCMS (ESI) m/z = 116 (M+H)+

Retention time: 0.16 min (Analytical condition SQDFA05) (retention time of MS peak is described)

[0442]

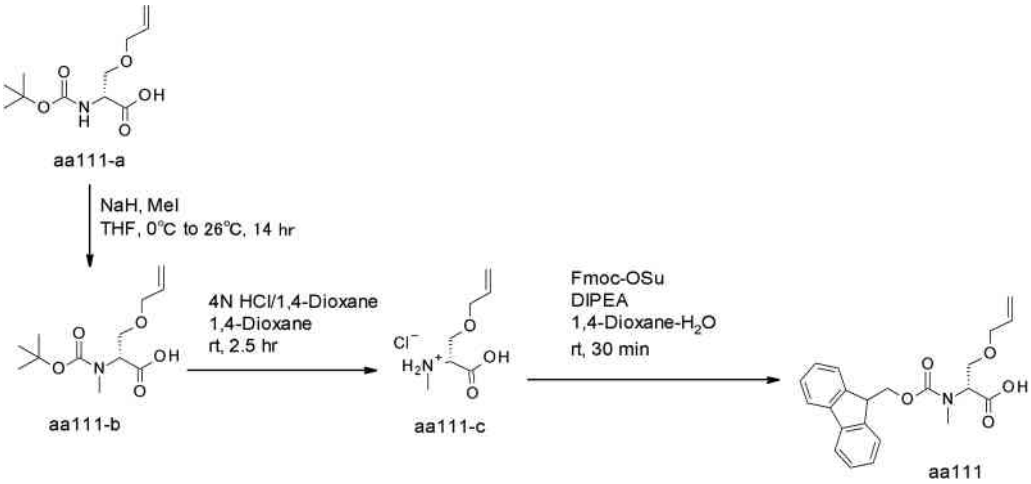
Using the resulting aa098-b, aa098 (2.73 g, 87%) was obtained under the same reaction conditions as the synthesis of Compound aa239.

LCMS (ESI) m/z = 338 (M+H)+

Retention time: 0.73 min (Analytical condition SQDFA05)

[0443]

Synthesis of Compound aa111



[0444]

In a nitrogen atmosphere, dehydrated THF (40 mL) was added to sodium hydride (1.47 g, 36.7 mmol: calculated as having 60 wt%) cooled in an ice bath. A dehydrated THF (10 mL) solution of aa111-a (3 g, 12.23 mmol) and methyl iodide (4.59 mL, 73.4 mmol) was added dropwise to the resulting suspension. The reaction mixture was stirred for 14 hours from an ice-cooled temperature to 26°C, and then water (2 mL) was added while the mixture was ice-cooled. The resulting mixture was stirred at room temperature for 10 minutes, and then the solvent was distilled off under reduced pressure. Hexane-CPME (20:1) (20 mL) and water (20

mL) were added to the concentrated residue for extraction, and the aqueous phase (about 30 mL) was washed twice with hexane-CPME (20:1) (20 mL). Potassium hydrogen sulfate (4.1 g, 30.1 mmol) and ethyl acetate were added to the aqueous phase, the separated organic phase (about 50 mL) was washed twice with brine (20 mL) and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give aa111-b (2.66 g, 84%).

LCMS (ESI) m/z = 282 (M+H)+

Retention time: 0.62 min (Analytical condition SQDFA05)

[0445]

Using aa111-b as a starting material, aa111-c (1.55 g, 77%) was obtained in the same manner as the synthesis of Compound aa239-b.

LCMS (ESI) m/z = 160 (M+H)+

Retention time: 0.17 min (Analytical condition SQDFA05) (retention time of MS peak is described)

[0446]

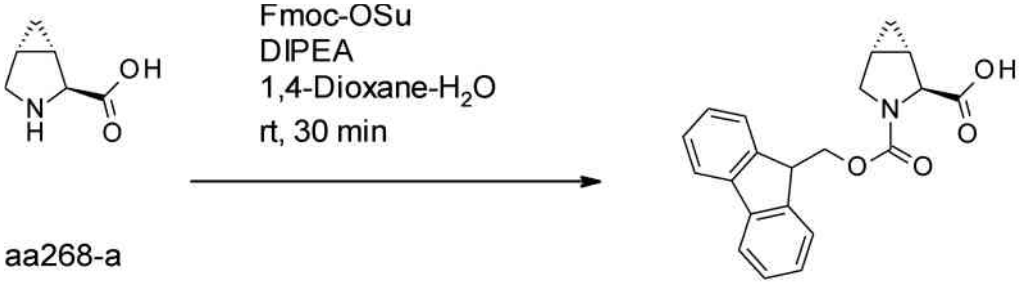
Using the resulting aa111-c, aa111 (0.837 g, 28%) was obtained under the same reaction conditions as the synthesis of Compound aa239.

LCMS (ESI) m/z = 383 (M+H)+

Retention time: 0.82 min (Analytical condition SQDFA05)

[0447]

Synthesis of Compound aa268



aa268-a

aa268

[0448]

Water (10 mL) and DIPEA (4.81 mL, 27.5 mmol) were added to aa268-a (1 g, 7.87 mmol) at room temperature to dissolve it, 1,4-dioxane (15 mL) was added, then N-(9-fluorenylmethoxycarbonyloxy)succinimide (2.65 g, 7.87 mmol) was added, and the mixture was stirred at room temperature for 30 minutes. Water (15 ml) and hexane (10 mL) were added to the reaction mixture, and the separated aqueous phase was washed twice with hexane-CPME (3:1) (15 mL). Potassium hydrogen sulfate (3.75 g, 27.5 mmol) and ethyl acetate were added to the aqueous phase, the separated organic phase (about 60 mL) was washed twice with brine (15

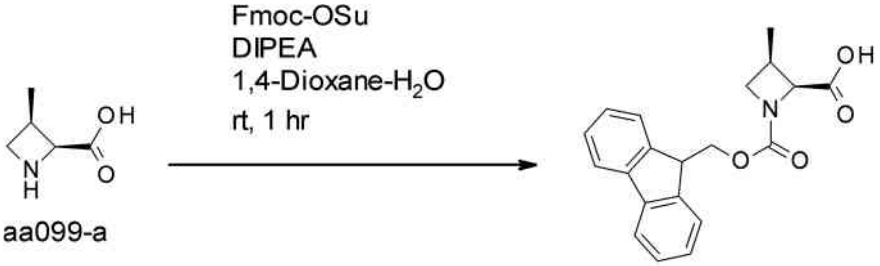
mL) and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give aa268 (2.85 g, quant).

LCMS (ESI) m/z = 350 (M+H)+

Retention time: 0.78 min (Analytical condition SQDFA05)

[0449]

Synthesis of Compound aa099



[0450]

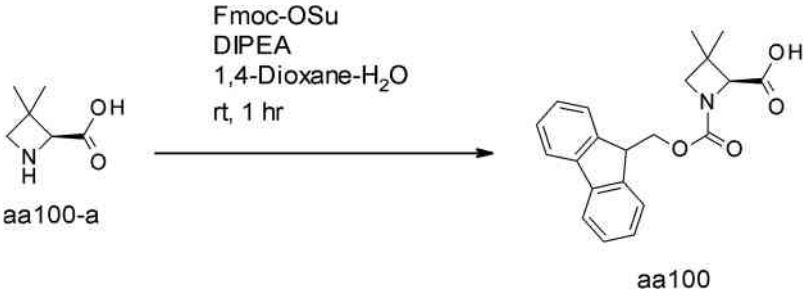
Using aa099-a, aa099 (9.91 g, 75%) was obtained under the same reaction conditions as the synthesis of Compound aa268.

LCMS (ESI) m/z = 338 (M+H)+

Retention time: 0.72 min (Analytical condition SQDFA05)

[0451]

Synthesis of Compound aa100



[0452]

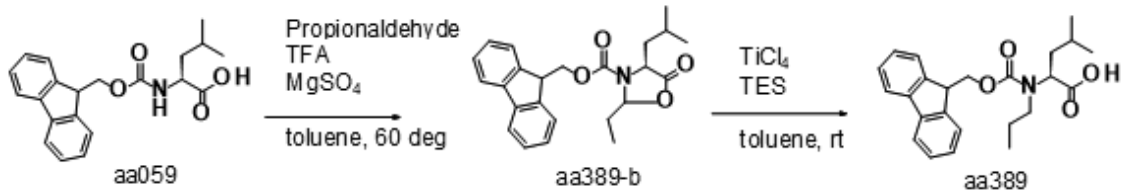
Using aa100-a, aa100 (2.15 g, 80%) was obtained under the same reaction conditions as the synthesis of Compound aa268.

LCMS (ESI) m/z = 352 (M+H)+

Retention time: 0.76 min (Analytical condition SQDFA05)

[0453]

Synthesis of Compound aa389



[0454]

Using aa059 (Fmoc-Leu-OH) as a starting material, a crude product of aa389-b was obtained in the same manner as synthesis of Compound aa136-b.

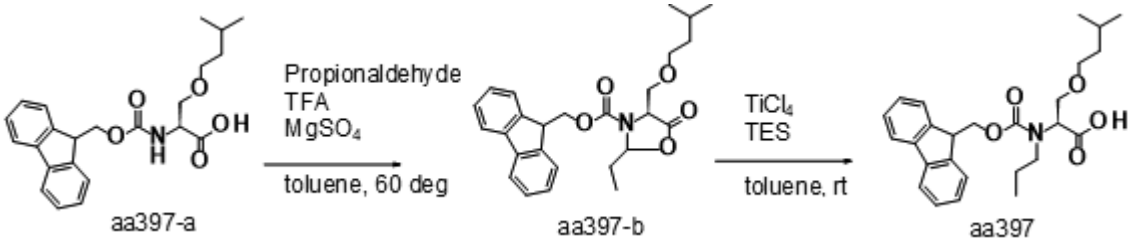
Using the resulting aa389-b, aa389 (7.7 g, 69% in 2 steps) was obtained in the same manner as Compound aa136.

LCMS (ESI) m/z = 396 (M+H)+

Retention time: 0.99 min (Analytical condition SQDFA05)

[0455]

Synthesis of Compound aa397



[0456]

Using aa397-a (N-(((9H-fluoren-9-yl)methoxy)carbonyl)-O-isopentyl-L-serine, Fmoc-Ser(iPen)-OH, CAS No. 2255321-11-8) as a starting material, aa397-b was obtained in the same manner as synthesis of Compound aa136-b.

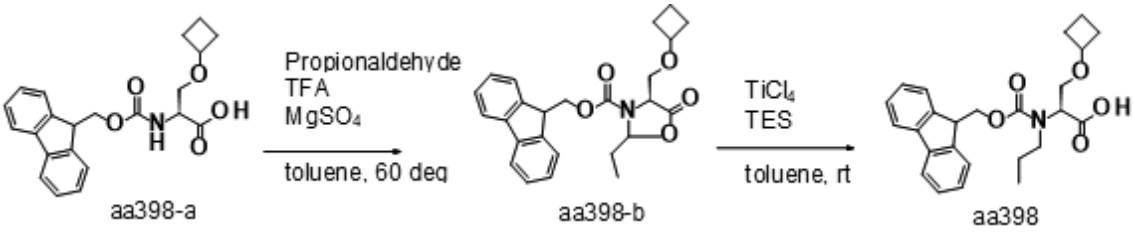
Using the resulting aa397-b, aa397 (8.1 g, 73% in 2 steps) was obtained in the same manner as synthesis of Compound aa136.

LCMS (ESI) m/z = 440 (M+H)+

Retention time: 1.04 min (Analytical condition SQDFA05)

[0457]

Synthesis of Compound aa398



[0458]

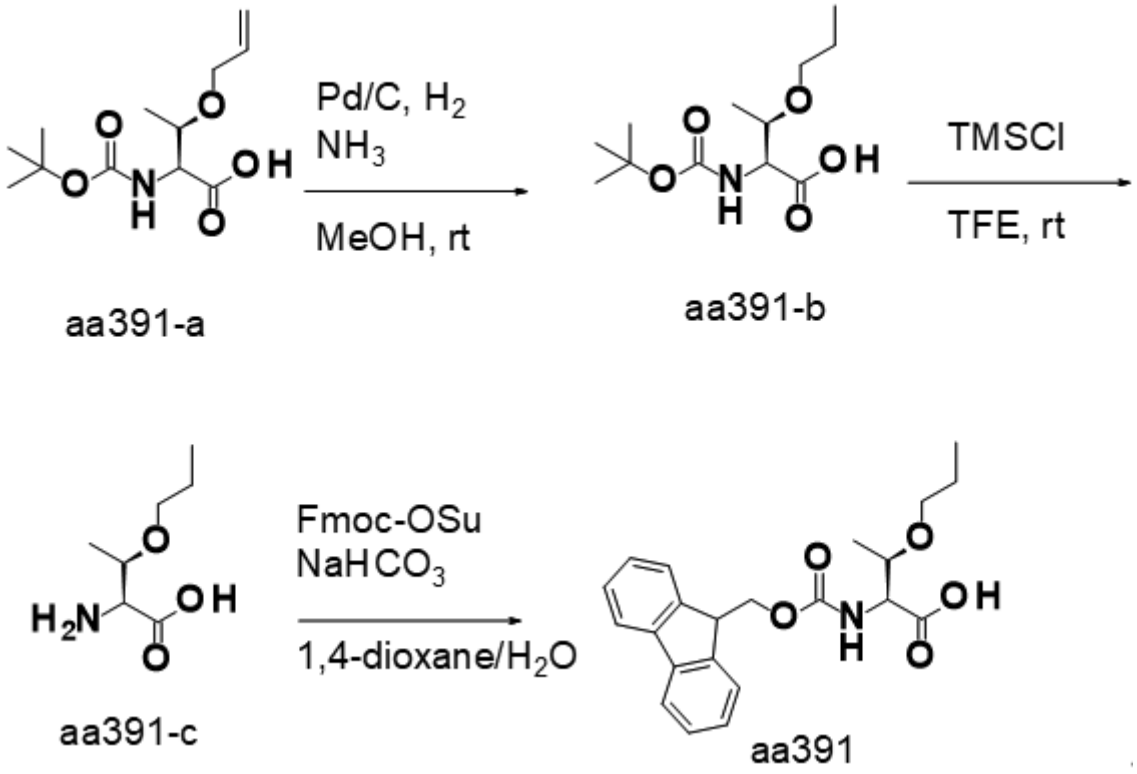
Using aa398-a (N-(((9H-fluoren-9-yl)methoxy)carbonyl)-O-cyclobutyl-L-serine, Fmoc-Ser(cBu)-OH, CAS No. 2642331-49-3) as a starting material, aa398-b was obtained in the same manner as synthesis of Compound aa136-b. Using the resulting aa398-b, aa398 (5.3 g, 48% in 2 steps) was obtained in the same manner as synthesis of Compound aa136.

LCMS (ESI) m/z = 424 (M+H)+

Retention time: 0.95 min (Analytical condition SQDFA05)

[0459]

Synthesis of Compound aa391



[0460]

aa391-a (O-allyl-N-(tert-butoxycarbonyl)-L-threonine, CAS No. 300831-37-2) (5.00 g, 19.3 mmol) was dissolved in methanol (60 mL), and palladium on carbon (5%, 492 mg) and a 7 M ammonia methanol solution (4.13 mL) were added in a nitrogen atmosphere. The mixture was stirred at room temperature for 1.5 hours in a hydrogen atmosphere. Palladium on carbon was removed by filtration, and the solvent was distilled off from the filtrate under reduced pressure to give aa391-b as a crude product. The crude product was used in the next reaction without purification.

aa391-b was dissolved in TFE (89 mL), TMSCl (6.16 mL, 48.2 mmol) was added, and the mixture was stirred at room temperature for 30 minutes. The solvent was distilled off from

the mixture under reduced pressure to give aa391-c as a crude product. The crude product was used in the next reaction without purification.

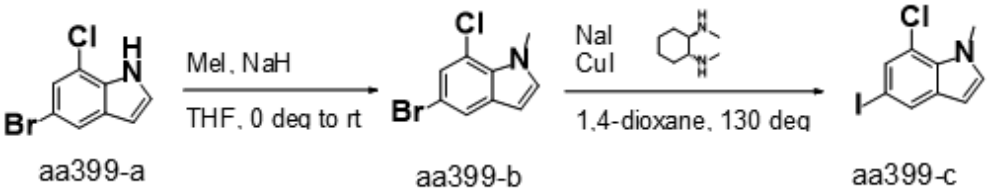
aa391-c was dissolved in water (54 mL), and sodium hydrogen carbonate (6.48 g, 77 mmol) and 1,4-dioxane (54 mL) were added. Fmoc-OSu (6.18 g, 18.3 mmol) was added to the mixture, and the mixture was stirred at room temperature for 4.5 hours. The reaction solution was washed with TBME (100 mL), and 2 N HCl (108 mL) was added to the aqueous layer, followed by extraction with DCM (40 mL) 3 times. The organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the resulting residue was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water). The resulting crude product was dissolved in TBME (100 mL), extracted with a 3.5% aqueous sodium hydrogen carbonate solution (100 mL), and further extracted with a 3.5% aqueous sodium hydrogen carbonate solution (50 mL). After 2 M phosphoric acid was added to the aqueous layer to adjust the pH to 2, the mixture was extracted with ethyl acetate. The mixture was dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure to give 391 (4.07 g, 55% in 3 steps).

LCMS (ESI) m/z = 384 (M+H)+

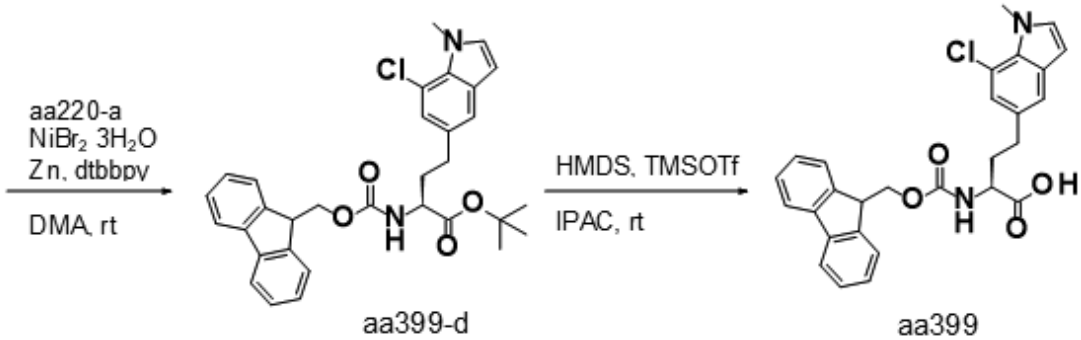
Retention time: 0.84 min (Analytical condition SQDFA05)

[0461]

Synthesis of Compound aa399



aa399-a aa399-b aa399-c



aa399-d aa399

[0462]

399-a (5-bromo-7-chloro-1H-indole, CAS No. 180623-89-6, 15.0 g, 65.1 mmol) was added to a THF solution (150 mL) of NaH (2.86 g, 71.6 mmol, 60%) under ice cooling, and the

mixture was stirred at room temperature for 30 minutes. Iodomethane (10.2 g, 71.6 mmol) was added dropwise thereto under ice cooling, and the mixture was stirred at room temperature for 16 hours. Water was added thereto, followed by extraction with ethyl acetate 3 times. The solvent was distilled off from the organic layer under reduced pressure to give aa399-b as a crude product (17.2 g).

[0463]

1,4-Dioxane solution (70 mL) of the crude product of aa399-b (6.10 g, 24.9 mmol), sodium iodide (18.7 g, 125 mmol), copper(I) iodide (0.48 g, 2.50 mmol), and trans-N^1,N^2-dimethylcyclohexane-1,2-diamine (0.71 g, 4.99 mmol) was stirred at 130°C for 16 hours in a nitrogen atmosphere. After being cooled to room temperature, the mixture was diluted with water and extracted twice with ethyl acetate. The organic layer was washed twice with brine, dried over anhydrous sodium sulfate, and filtered off, and the solvent was distilled off under reduced pressure to give aa399-c as a crude product (6.1 g).

[0464]

Using aa220-a (17.7 g, 31.0 mmol), aa399-d (10.5 g, 31%) was obtained in the same manner as Compound aa219-b except that aa399-c was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 567 (M+Na)+

Retention time: 0.95 min (Analytical condition SMD method_22)

[0465]

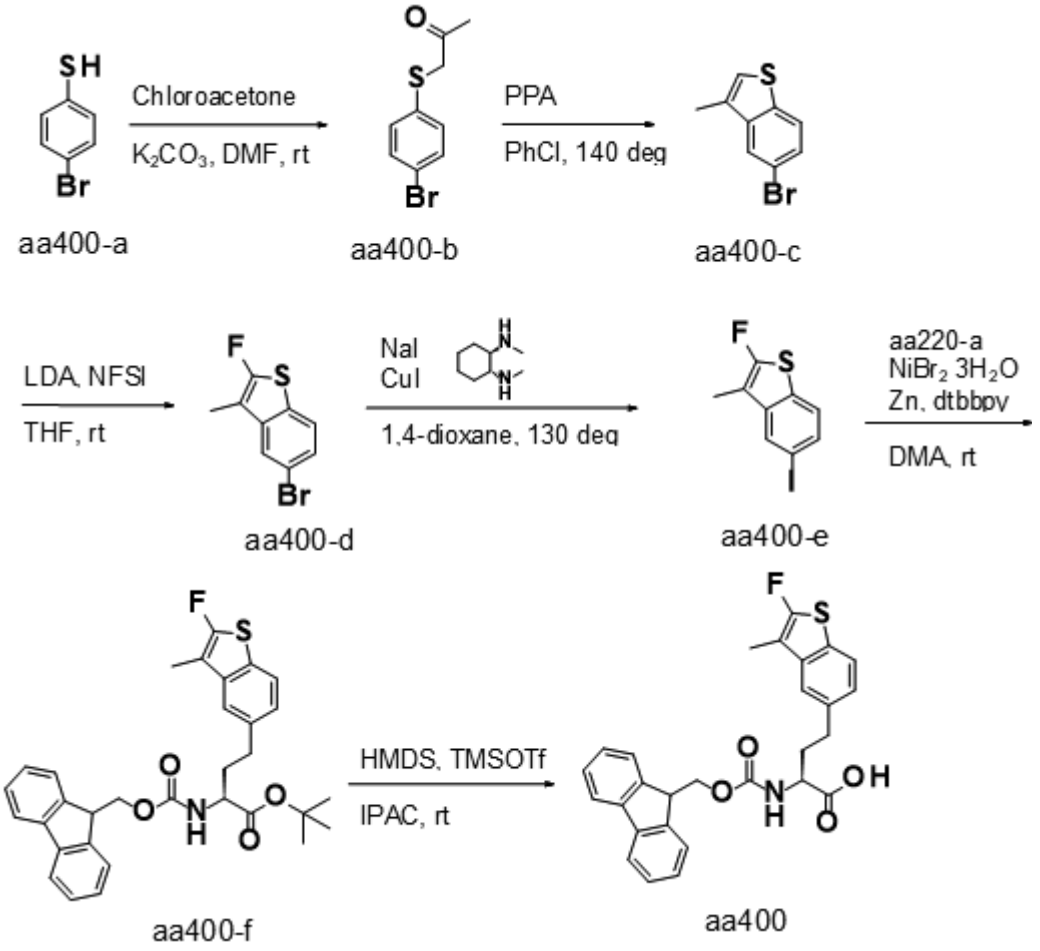
TMSOTf (8.56 g, 38.5 mmol) was added to an IPAC solution (110 mL) of aa399-d (10.5 g, 19.3 mmol) and HMDS (6.22 g, 38.5 mmol) in a nitrogen atmosphere. The mixture was stirred at room temperature for 16 hours. After a 5% aqueous disodium hydrogen phosphate solution was added, the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with a 2% aqueous phosphoric acid solution and washed with 15% brine. The organic layer was dried over sodium sulfate and filtered off, and the solvent was distilled off under reduced pressure. The resultant was purified by reverse phase chromatography (acetonitrile-water) and then washed with hexane/TBME (5/1) to give aa399 (7 g, 74%).

LCMS (ESI) m/z = 489 (M+H)+

Retention time: 1.36 min (Analytical condition SMD method_23)

[0466]

<u>Synthesis of Compound aa400</u>



[0467]

A DMF solution (500 mL) of aa400-a (4-bromobenzenethiol, CAS No. 106-53-6, 50 g, 264 mmol), potassium carbonate (73.1 g, 529 mmol), and chloroacetone (26.9 g, 291 mmol) was stirred at room temperature for 16 hours in a nitrogen atmosphere. Water was added, solids were filtered off, and the solvent was distilled off from the filtrate under reduced pressure to give aa400-b as a crude product (61.0 g).

[0468]

A chlorobenzene solution (700 mL) of the crude product of aa400-b (84 g, 342 mmol) and PPA (250 g, 2.17 mmol) was stirred at 140°C for 16 hours in a nitrogen atmosphere. After this solution was cooled to room temperature, the upper layer was added to ethyl acetate to be diluted, and washed with water, and then the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give aa400-c (42.5 g, 54%).

Retention time: 1.13 min (Analytical condition SMD method_24)

[0469]

A THF solution (300 mL) of aa400-c (40 g, 176 mmol) was cooled to -78°C, and LDA (2 M THF solution, 96 mL, 194 mmol) was added dropwise in a nitrogen atmosphere. The mixture was stirred at -78°C for 30 minutes, and N-fluorobenzenesulfonimide (NFSI, 100 g, 317 mmol) was added dropwise at -78°C. After stirring this mixture at room temperature for 16 hours, an aqueous ammonium chloride solution was added, followed by extraction with ethyl acetate twice. The organic layer was washed twice with water, dried over anhydrous sodium sulfate, and filtered off, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give aa400-d (20 g, 43%).

Retention time: 1.31 min (Analytical condition SMD method_26)

[0470]

aa400-e was obtained as a crude product (25.0 g) in the same manner as Compound 399-c except that aa400-d (19 g, 77.5 mmol) was used in place of aa399-b.

[0471]

Using aa220-a (19.0 g, 33.3 mmol), aa400-f (13.8 g, 73%) was obtained in the same manner as Compound aa219-b except that aa400-e was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 568 (M+Na)+

Retention time: 1.31 min (Analytical condition SMD method_26)

[0472]

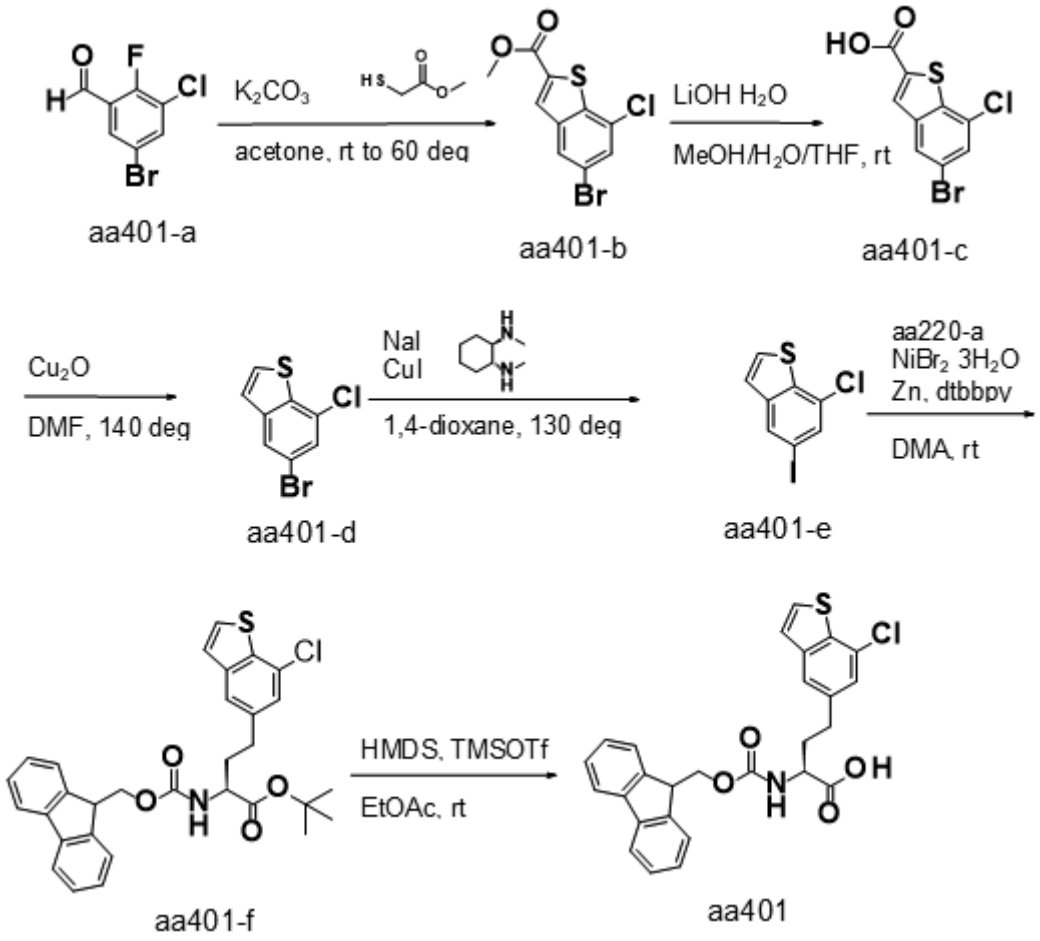
aa400 (8 g, 81%) was obtained in the same manner as Compound 399 except that aa400-f (3.0 g, 5.50 mmol) was used in place of aa399-d, and ethyl acetate was used as a solvent in place of IPAC.

LCMS (ESI) m/z = 490 (M+H)+

Retention time: 1.31 min (Analytical condition SMD method_27)

[0473]

Synthesis of Compound aa401



[0474]

Methyl thioglycolate (10.2 g, 96.0 mmol) and potassium carbonate (22.1 g, 160 mmol) were added to an acetone solution (300 mL) of aa401-a (5-bromo-3-chloro-2-fluorobenzaldehyde, CAS No. 1280786-80-2, 19 g, 80 mmol) at room temperature, and the mixture was stirred at 60°C for 2 hours in a nitrogen atmosphere. After the mixture was cooled to room temperature, solids were filtered off, and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in ethyl acetate, dried over anhydrous sodium sulfate, and filtered off, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give aa401-b (16.4 g, 67%).

Retention time: 0.89 min (Analytical condition SMD method_22)

[0475]

Lithium hydroxide monohydrate (6.43 g, 268 mmol) was added to a THF (102 mL)/methanol (34 mL)/water (34 mL) solution of aa401-b (16.4 g, 53.7 mmol) at room temperature. After stirring this mixture at room temperature for 1 hour, the solvent was distilled off under reduced pressure. The resulting residue was dissolved in water, and 2 M

hydrochloric acid was added to adjust the pH to 3, followed by extraction with ethyl acetate 3 times. The organic layer was washed with water, dried over anhydrous sodium sulfate, and filtered off, and the solvent was distilled off under reduced pressure to give aa401-c as a crude product (15.9 g).

[0476]

Copper(I) oxide (31.2 g, 218 mmol) was added to a DMF solution (160 mL) of the crude product of 401-c (15.9 g, 54.5 mmol), and the mixture was stirred at 140°C for 16 hours. After solids were filtered off, the filtrate was washed with water, dried over anhydrous sodium sulfate, and filtered off, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give aa401-d (11.7 g, 87%).

Retention time: 0.99 min (Analytical condition SMD method_28)

[0477]

aa401-e was obtained as a crude product (12.5 g) in the same manner as Compound 399-c except that aa401-d (11.7 g, 47.3 mmol) was used in place of aa399-b.

[0478]

Using aa220-a (12.1 g, 21.2 mmol), aa401-f (8.6 g, 74%) was obtained in the same manner as Compound aa219-b except that aa401-e was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 570 (M+Na)+

Retention time: 0.96 min (Analytical condition SMD method_22)

[0479]

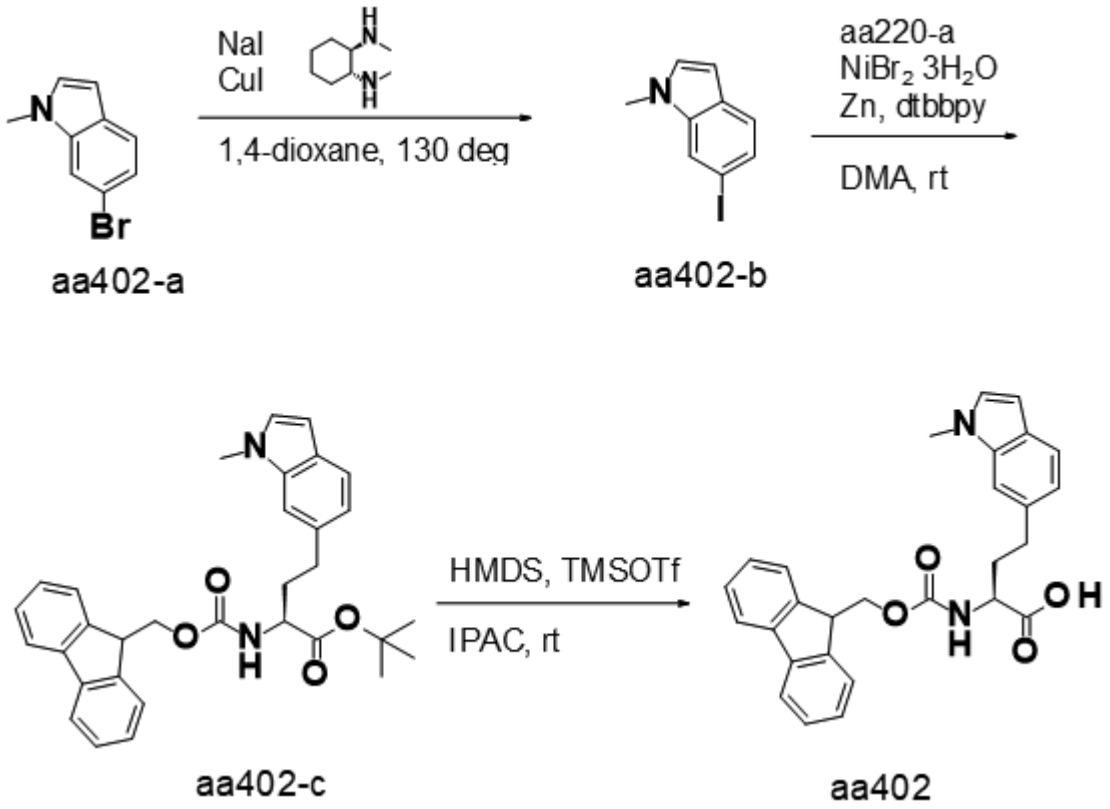
aa401 (4.4 g, 57%) was obtained in the same manner as Compound 399 except that aa401-f (8.6 g) was used in place of aa399-d, and ethyl acetate was used as a solvent in place of IPAC.

LCMS (ESI) m/z = 492 (M+H)+

Retention time: 1.33 min (Analytical condition SMD method_29)

[0480]

<u>Synthesis of Compound aa402</u>



aa402-a aa402-b aa402-c aa402

[0481]

aa402-b was obtained as a crude product (23 g) in the same manner as Compound 399-c except that aa402-a (6-bromo-1-methyl-1H-indole, CAS No. 125872-95-9, 20 g, 95.2 mmol) was used in place of aa399-b.

[0482]

Using aa220-a (9.00 g, 15.8 mmol), aa402-c (3.6 g, 44%) was obtained in the same manner as Compound aa219-b except that aa402-b was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 511 (M+H)+

Retention time: 0.92 min (Analytical condition SMD method_30)

[0483]

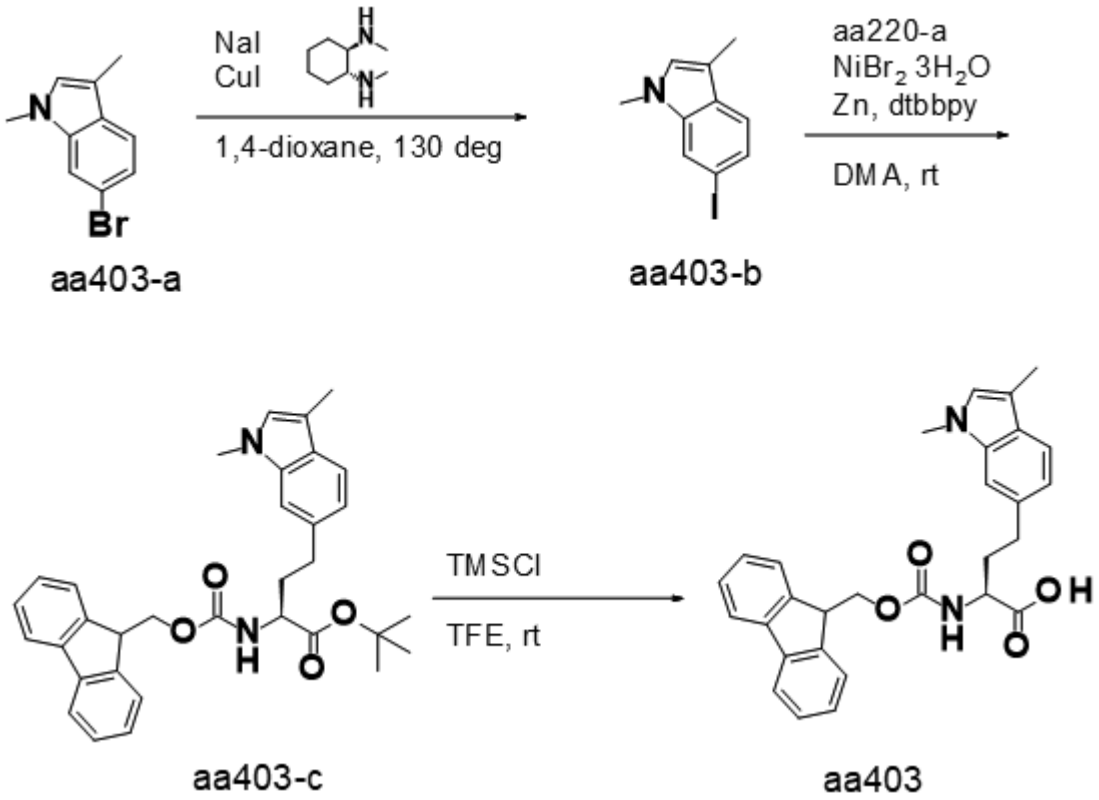
aa402 (5 g, 70%) was obtained in the same manner as Compound 399 except that aa402-c (8.00 g, 15.7 mmol) was used in place of aa399-d.

LCMS (ESI) m/z = 455 (M+H)+

Retention time: 1.04 min (Analytical condition SMD method_24)

[0484]

Synthesis of Compound aa403



[0485]

aa403-b was obtained as a crude product (18.1 g) in the same manner as Compound 399-c except that aa403-a (6-bromo-1,3-dimethyl-1H-indole, CAS No. 1616099-24-1, 15.3 g, 68.3 mmol) was used in place of aa399-b.

[0486]

Using aa220-a (19.1 g, 33.4 mmol), aa403-c (9.5 g, 54%) was obtained in the same manner as Compound aa219-b except that aa403-b was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 525 (M+H)+

Retention time: 0.97 min (Analytical condition SMD method_31)

[0487]

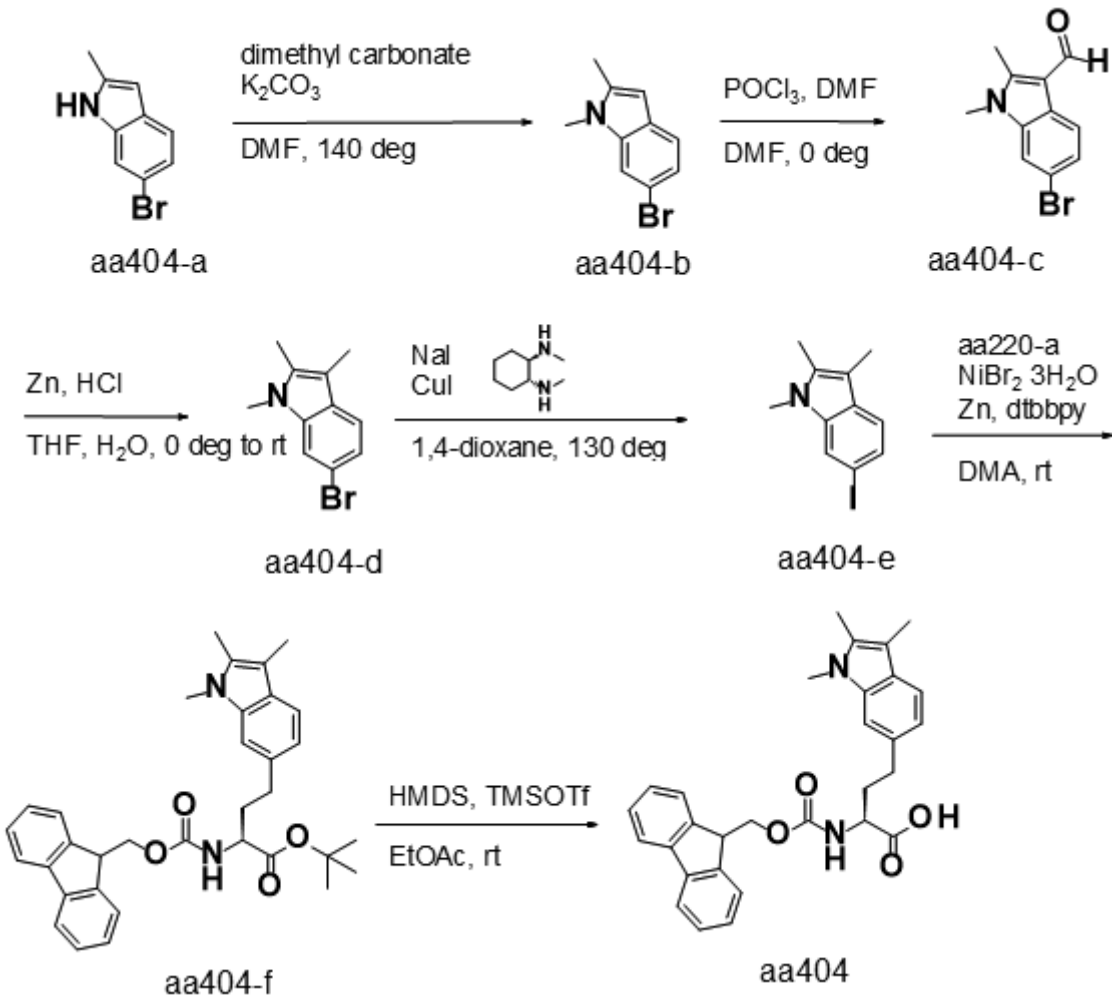
A crude product of aa403 was obtained in the same manner as Compound 219 except that aa403-c (9.5 g, 18.1 mmol) was used in place of aa219-b. The crude product was purified by reverse phase chromatography (acetonitrile-water) to give aa403 (4.5 g, 53%).

LCMS (ESI) m/z = 469 (M+H)+

Retention time: 1.82 min (Analytical condition SMD method_32)

[0488]

Synthesis of Compound aa404



[0489]

A DMF solution (100 mL) of aa404-a (6-bromo-2-methyl-1H-indole, CAS No. 6127-19-1, 19 g, 90.4 mmol), potassium carbonate (18.9 g, 137 mmol), and dimethyl carbonate (24.4 g, 271 mmol) was stirred at 140°C for 16 hours in a nitrogen atmosphere. After being cooled to room temperature, the solution was diluted with 1 M hydrochloric acid and extracted twice with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and filtered off, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give aa404-b (25 g, quant.).

LCMS (ESI) m/z = 224 (M+H)+

Retention time: 0.98 min (Analytical condition SMD method_33)

[0490]

Phosphorus oxychloride (16.6 mL, 179 mmol) was added dropwise to DMF (200 mL) under ice cooling in a nitrogen atmosphere. The mixture was stirred for 10 minutes under ice cooling, and a DMF solution (50 mL) of aa404-b (20 g, 89.2 mmol) was added dropwise over 10

minutes under ice cooling. The mixture was stirred at room temperature for 40 minutes, and treated with an aqueous sodium hydrogen carbonate solution. The mixture was stirred for 10 minutes and then extracted twice with ethyl acetate, the organic layer was washed with brine, dried over sodium sulfate, and filtered off, and the solvent was distilled off under reduced pressure to give aa404-c as a crude product (19 g).

[0491]

Hydrochloric acid (12 M, 21.5 mL, 377 mmol) was added dropwise to a THF solution (500 mL) of the crude product of aa404-c (19 g, 75.4 mmol) and zinc powder (14.8 g, 226 mmol) under ice cooling in a nitrogen atmosphere. The mixture was stirred at room temperature for 16 hours and then diluted with water. The mixture was extracted twice with ethyl acetate, the organic layer was washed with brine, dried over sodium sulfate, and filtered off, and the solvent was distilled off under reduced pressure to give aa404-d as a crude product (13 g).

[0492]

aa404-e was obtained as a crude product (16 g) in the same manner as Compound 399-c except that aa404-d (13 g, 54.6 mmol) was used in place of aa399-b.

[0493]

Using aa220-a (16.5 g, 28.9 mmol), Compound aa404-f (7.9 g, 45%) was obtained in the same manner as Compound aa219-b except that aa404-e was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 539 (M+H)+

Retention time: 1.08 min (Analytical condition SMD method_33)

[0494]

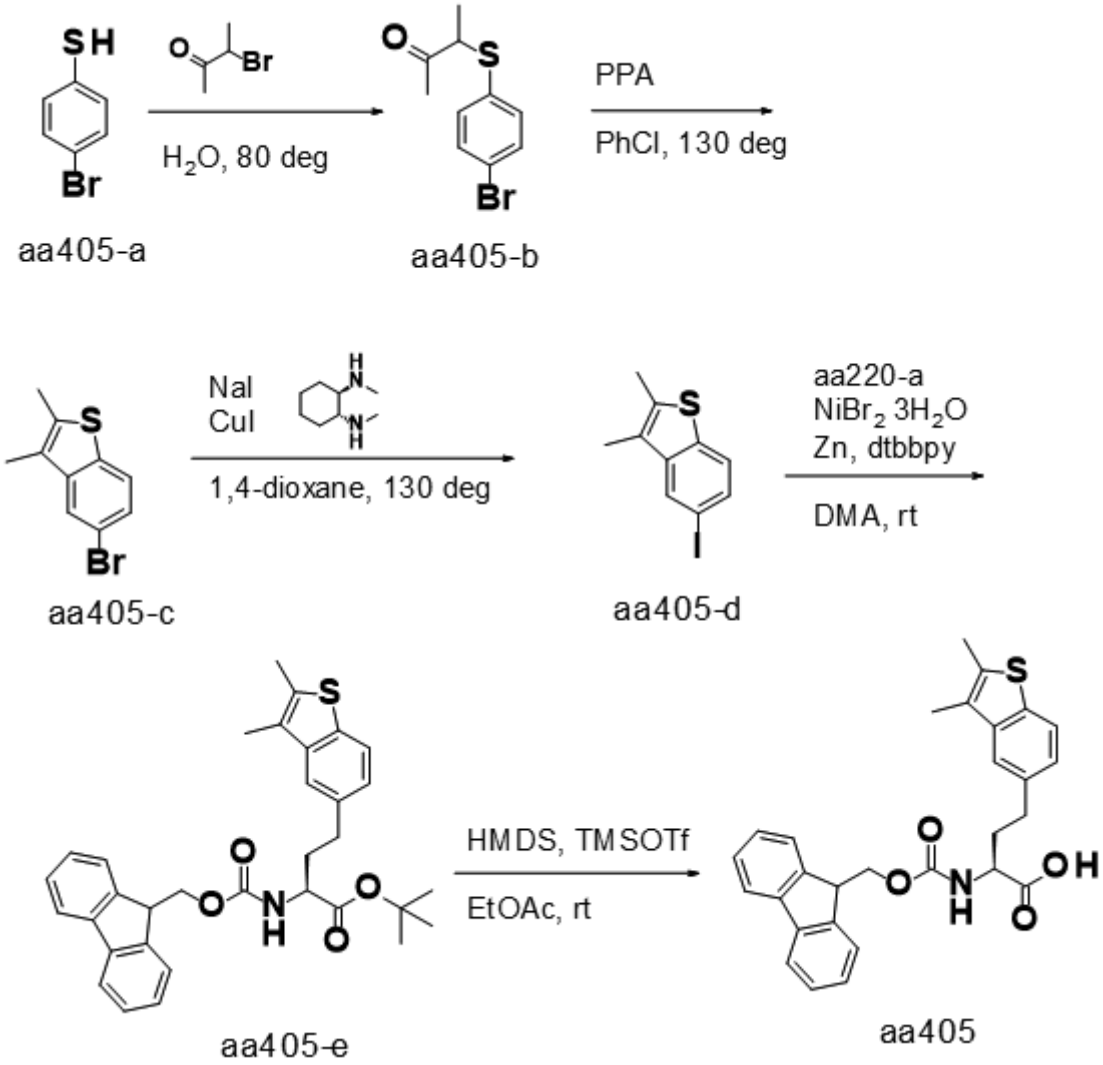
aa404 (4.5 g, 62%) was obtained in the same manner as Compound 399 except that aa404-f (7.9 g, 14.7 mmol) was used in place of aa399-d, and ethyl acetate was used as a solvent in place of IPAC.

LCMS (ESI) m/z = 483 (M+H)+

Retention time: 1.35 min (Analytical condition SMD method_34)

[0495]

<u>Synthesis of Compound aa405</u>



[0496]

3-Bromo-2-butanone (28.8 g, 190 mmol) was added to an aqueous solution (300 mL) of aa405-a (4-bromobenzenethiol, CAS No. 106-53-6, 30 g, 159 mmol), and the mixture was stirred at 80°C for 1 hour. The mixture was extracted 3 times with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate and filtered off, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give aa405-b (40 g, 85%).

LCMS (ESI) m/z = 259 (M+H)+

Retention time: 0.71 min (Analytical condition SMD method_35)

[0497]

aa405-c (13.7 g, 70%) was obtained in the same manner as Compound aa400-c except that aa405-b (20 g, 77.1 mmol) was used in place of aa400-b.

Retention time: 0.88 min (Analytical condition SMD method_36)

[0498]

aa405-d was obtained as a crude product (15.4 g) in the same manner as Compound 399-c except that aa405-c (13.7 g, 56.8 mmol) was used in place of aa399-b.

[0499]

Using aa220-a (15.3 g, 26.7 mmol), aa405-e (9.06 g, 61%) was obtained in the same manner as Compound aa219-b except that aa405-d was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 564 (M+Na)+

Retention time: 0.99 min (Analytical condition SMD method_36)

[0500]

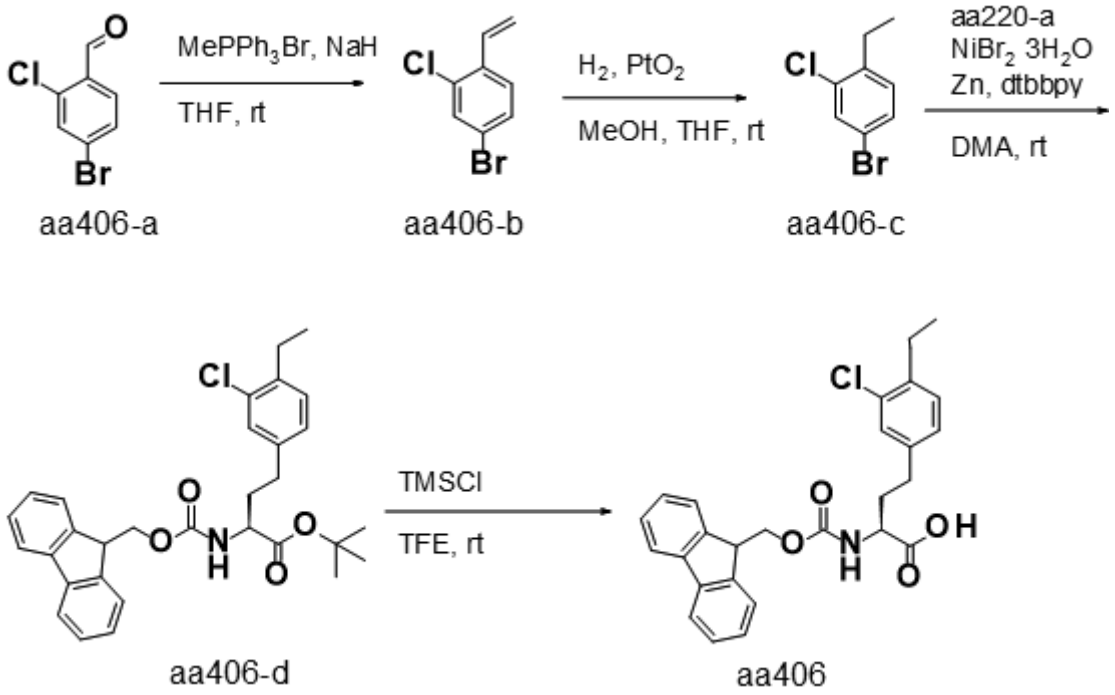
aa405 (5.03 g, 61%) was obtained in the same manner as Compound 399 except that aa405-e (9.06 g, 16.7 mmol) was used in place of aa399-d, and ethyl acetate was used as a solvent in place of IPAC.

LCMS (ESI) m/z = 486 (M+H)+

Retention time: 1.47 min (Analytical condition SMD method_37)

[0501]

Synthesis of Compound aa406



[0502]

NaH (5.03 g, 210 mmol) was added in small devided portions to a THF solution (100 mL) of (bromomethyl)triphenylphosphonium bromide (49.9 g, 140 mmol) at 55°C in a nitrogen atmosphere. The mixture was stirred at 55°C for 30 minutes and then cooled to room temperature, and a THF solution (50 mL) of aa406-a (2-chloro-4-bromobenzaldehyde, CAS No. 158435-41-7, 15.3 g, 70 mmol) was added dropwise. After stirring this mixture at room

temperature for 16 hours, water was added. The mixture was extracted 3 times with ethyl acetate, the organic layer was washed with water, dried over sodium sulfate, and filtered off, and the solvent was distilled off under reduced pressure to give aa406-b as a crude product (43 g).

[0503]

A methanol (10 mL)/THF (10 mL) solution of aa406-b (2.5 g, 11.5 mmol) and platinum(IV) oxide (0.25 g, 1.10 mmol) was stirred at room temperature for 2 hours in a hydrogen atmosphere. Solids were filtered off, and the solvent was distilled off from the filtrate under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give aa406-c (1.2 g, 42%).

Retention time: 1.41 min (Analytical condition SMD method_38)

[0504]

Using aa220-a (17 g, 30.0 mmol), Compound aa406-d (4.8 g, 31%) was obtained in the same manner as Compound aa219-b except that aa406-c was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 542 (M+Na)+

Retention time: 1.53 min (Analytical condition SMD method_38)

[0505]

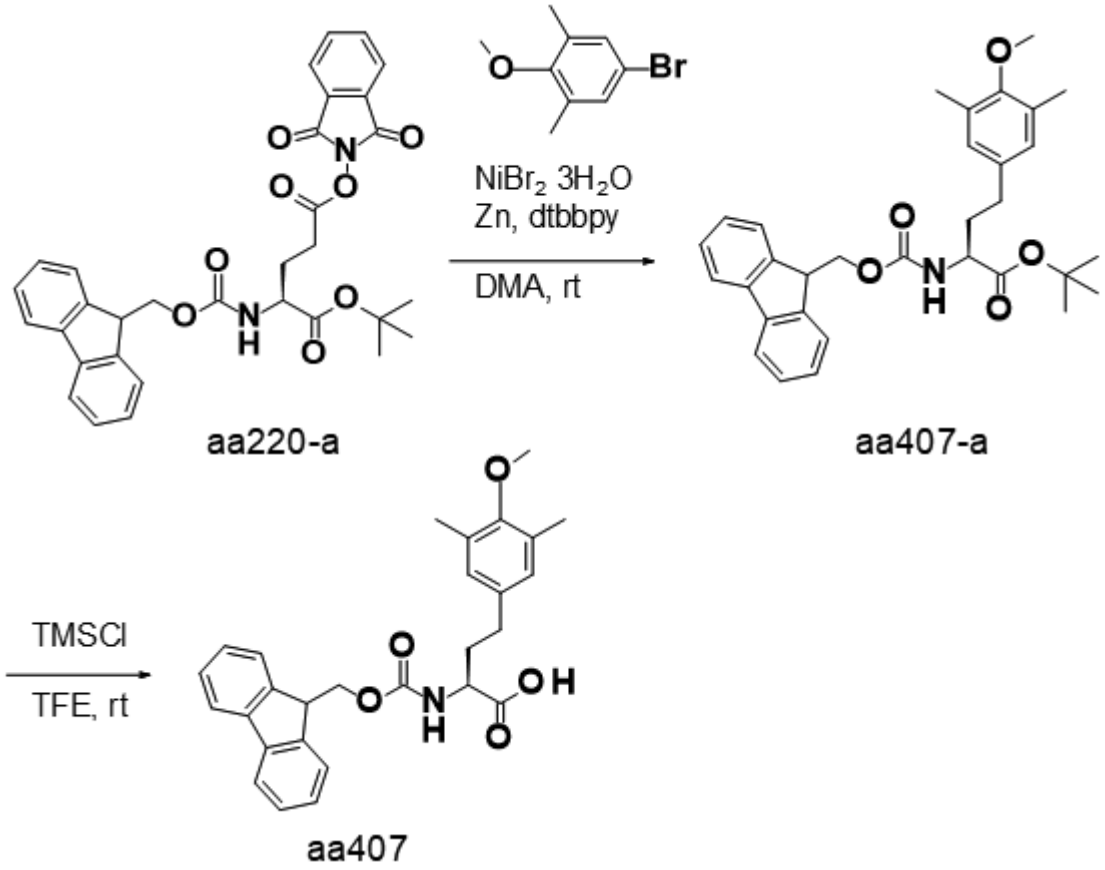
aa406 (4.3 g, 95%) was obtained in the same manner as Compound 219 except that aa406-d (5 g, 9.61 mmol) was used in place of aa219-b.

LCMS (ESI) m/z = 486 (M+Na)+

Retention time: 1.32 min (Analytical condition SMD method_38)

[0506]

<u>Synthesis of Compound aa407</u>



[0507]

Using aa220-a (21 g, 36.8 mmol), aa407-a (9.84 g, 52%) was obtained in the same manner as Compound aa219-b except that 4-bromo-2,6-dimethylanisole (CAS No. 14804-38-7) was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 538 (M+Na)+

Retention time: 1.44 min (Analytical condition SMD method_38)

[0508]

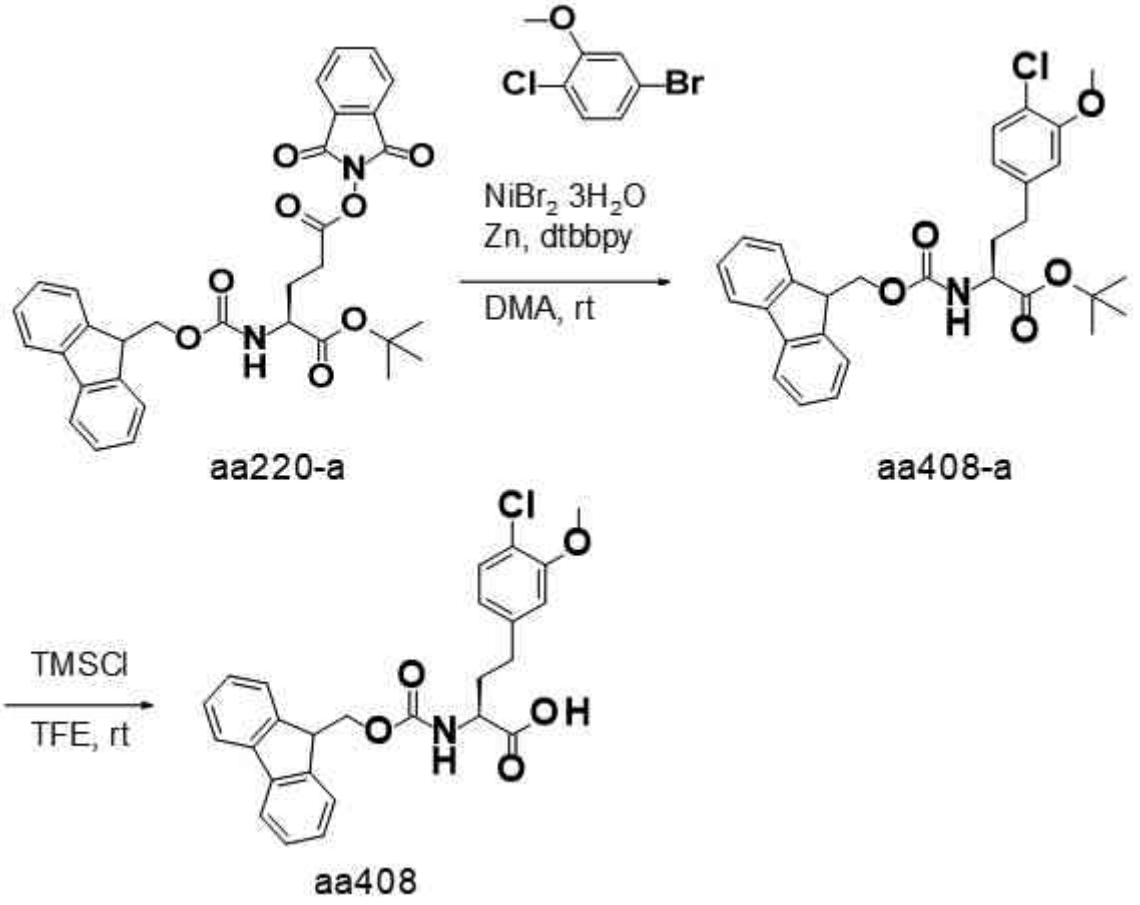
aa407 (4.3 g, 95%) was obtained in the same manner as Compound 219 except that aa407-a (9.84 g, 19.1 mmol) was used in place of aa219-b.

LCMS (ESI) m/z = 460 (M+H)+

Retention time: 1.23 min (Analytical condition SMD method_38)

[0509]

Synthesis of Compound aa408



[0510]

Using aa220-a (15 g, 26.3 mmol), aa408-a (6.4 g, 46%) was obtained in the same manner as Compound aa219-b except that 5-bromo-2-chloroanisole (CAS No. 16817-43-9) was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 544 (M+Na)+

Retention time: 0.89 min (Analytical condition SMD method_39)

[0511]

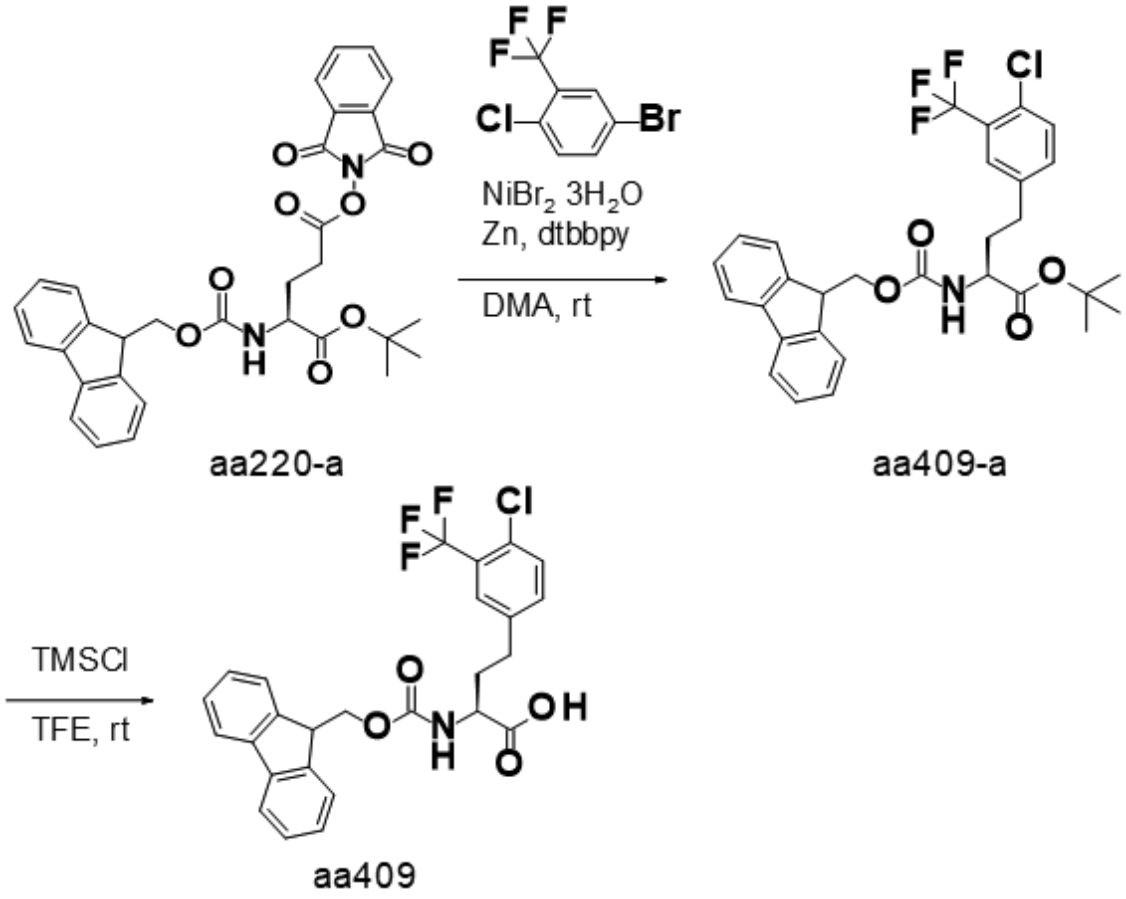
aa408 (3.5 g, 62%) was obtained in the same manner as Compound 219 except that aa408-a (6.4 g, 12.3 mmol) was used in place of aa219-b.

LCMS (ESI) m/z = 488 (M+Na)+

Retention time: 1.00 min (Analytical condition SMD method_26)

[0512]

Synthesis of Compound aa409



[0513]

Using aa220-a (5 g, 8.76 mmol), aa409-a (3.8 g, 77%) was obtained in the same manner as Compound aa219-b except that 5-bromo-2-chlorobenzotrifluoride (CAS No. 445-01-2) was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 582 (M+Na)+

Retention time: 0.93 min (Analytical condition SMD method_40)

[0514]

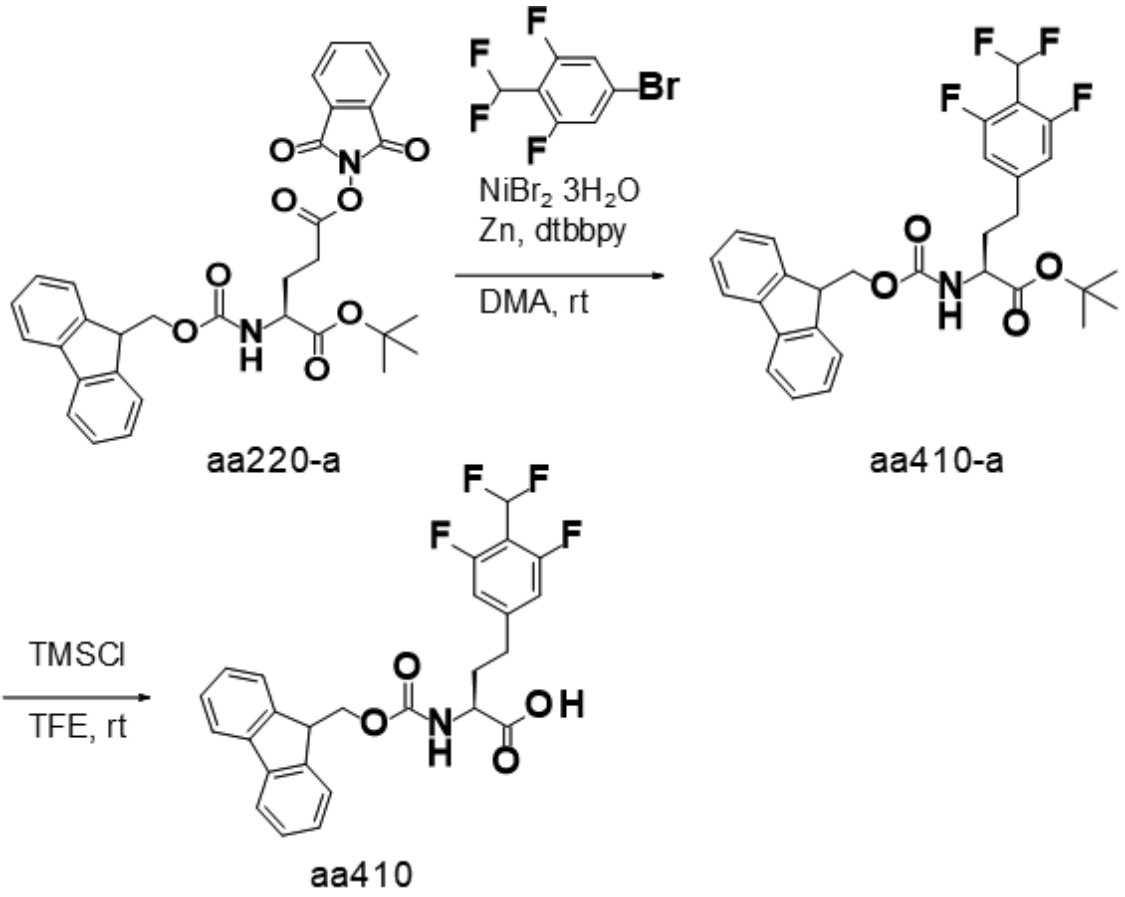
aa409 (3 g, 88%) was obtained in the same manner as Compound 219 except that aa409-a (3.8 g, 6.79 mmol) was used in place of aa219-b.

LCMS (ESI) m/z = 526 (M+Na)+

Retention time: 1.08 min (Analytical condition SMD method_26)

[0515]

Synthesis of Compound aa410



[0516]

Using aa220-a (5 g, 8.76 mmol), aa410-a (3.5 g, 73%) was obtained in the same manner as Compound aa219-b except that 5-bromo-2-(difluoromethyl)-1,3-difluorobenzene (CAS No. 1221272-77-0) was used in place of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene.

LCMS (ESI) m/z = 566 (M+Na)+

Retention time: 1.21 min (Analytical condition SMD method_24)

[0517]

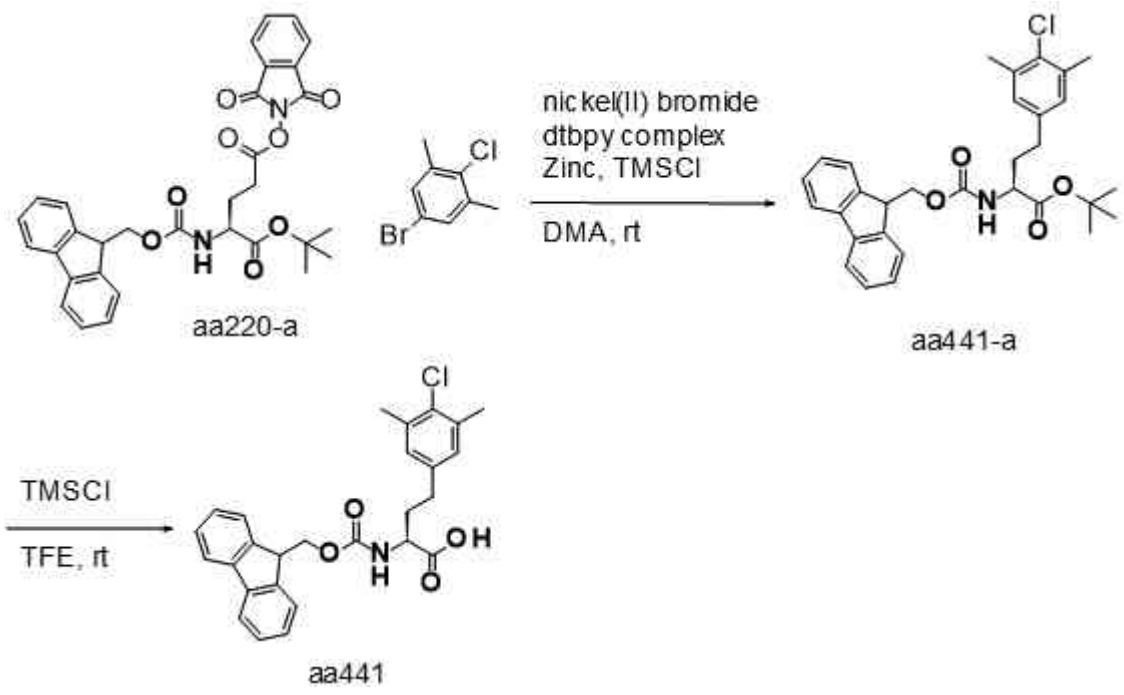
aa410 (1.9 g, 60%) was obtained in the same manner as Compound 219 except that aa410-a (3.5 g, 6.44 mmol) was used in place of aa219-b.

LCMS (ESI) m/z = 488 (M+H)+

Retention time: 0.99 min (Analytical condition SMD method_41)

[0518]

Synthesis of Compound aa411



[0519]

An N,N-dimethylacetamide (2.92 mL) solution of a nickel(II) bromide 4,4'-di-tert-butyl-2,2'-bipyridine complex (85 mg, 0.175 mmol) and chlorotrimethylsilane (0.111 mL, 0.876 mmol) were added to an N,N-dimethylacetamide (5.84 mL) solution of aa220-a (1.00 g, 1.75 mmol), 5-bromo-2-chloro-1,3-dimethylbenzene (577 mg, 2.63 mmol), and zinc (573 mg, 8.76 mmol), and the mixture was stirred at room temperature for 23 hours in a nitrogen atmosphere. tert-Butyl methyl ether (10 mL) was added, the mixture was passed through a Celite filter covered with sodium sulfate, and then a 5 wt% aqueous disodium ethylenediaminetetraacetate solution (40 mL) was added for extraction. The organic layer was washed with a 5 wt% aqueous sodium carbonate solution (20 mL), washed with a saturated aqueous ammonium chloride solution (20 mL), washed with brine (20 mL), and dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure to give aa441-a as a crude product.

[0520]

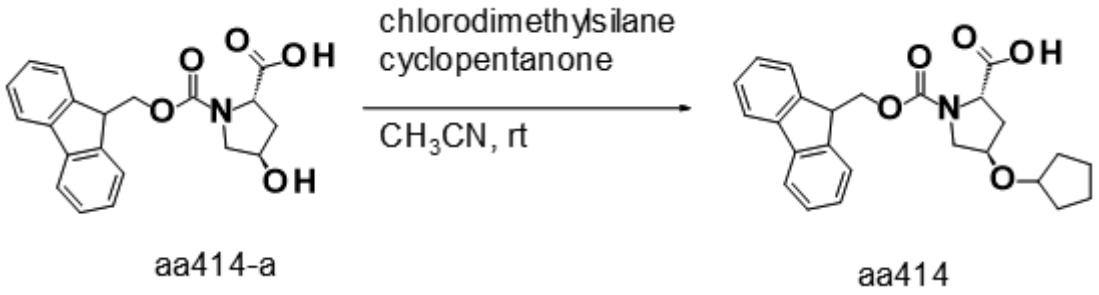
The crude product of aa441-a was dissolved in TFE (8.76 mL), TMSCl (0.667 mL, 5.26 mmol) was added, and the mixture was stirred at room temperature for 30 minutes. The solvent was distilled off from the mixture under reduced pressure, the resulting crude product was purified by reverse phase column chromatography (0.1% aqueous formic acid solution/0.1% formic acid acetonitrile solution) to give aa441 (364 mg, 45% in 2 steps).

LCMS (ESI) m/z = 462 (M-H)-

Retention time: 1.01 min (Analytical condition SQDFA05)

[0521]

Synthesis of Compound aa414



aa414-a aa414

[0522]

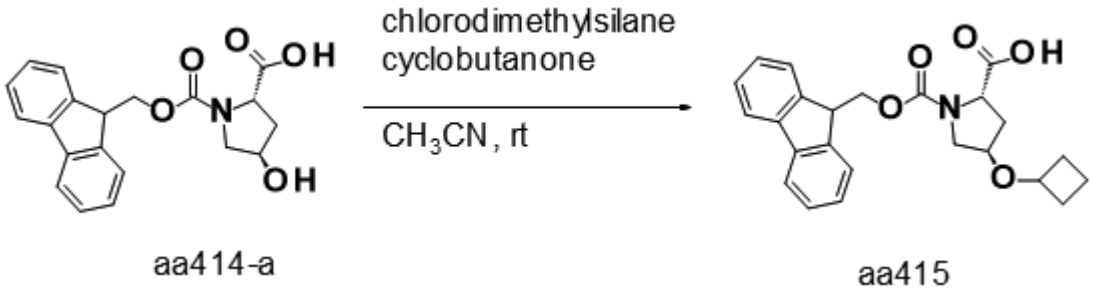
Chlorodimethylsilane (18.5 mL, 170 mmol) was added to an acetonitrile (51.5 mL) solution of aa414-a ((2S,4R)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-hydroxypyrrolidine-2-carboxylic acid, Fmoc-Hyp-OH, CAS No. 88050-17-3) (10.0 g, 28.3 mmol) and cyclopentanone (15.0 mL, 170 mmol), and the mixture was stirred at room temperature for 28 hours. A 2 N aqueous sodium hydroxide solution (85 mL) was slowly added dropwise thereto under ice cooling so as not to exceed 30°C. A 2 N aqueous sodium hydroxide solution (14 mL) was further added to adjust the pH to 11. Phosphoric acid was added thereto to adjust the pH to 7 to 8, and the mixture was washed with TBME/hexane (1/3, 150 mL). Phosphoric acid was added to the aqueous layer to adjust the pH to 3, followed by extraction with TBME (150 mL) and further extraction with TBME (100 mL). After the resulting organic layer was washed with brine and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to give aa414 (11.7 g, 98%).

LCMS (ESI) m/z = 422 (M+H)+

Retention time: 0.91 min (Analytical condition SQDFA05)

[0523]

Synthesis of Compound aa415



aa414-a aa415

[0524]

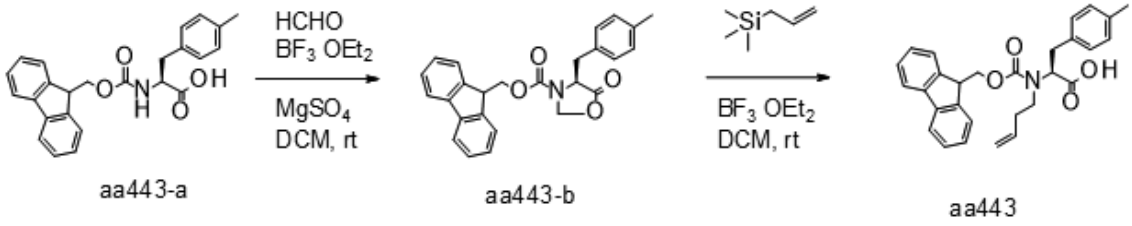
aa415 (10.8 g, 94%) was obtained in the same manner as Compound 414 except that cyclobutanone was used in place of cyclopentanone.

LCMS (ESI) m/z = 408 (M+H)+

Retention time: 0.86 min (Analytical condition SQDFA05)

[0525]

Synthesis of Compound aa443



Using Compound aa443-a (N-([(9H-fluoren-9-yl)methoxy]carbonyl)-4-(methyl)-L-phenylalanine) as a starting material, a crude product of aa443-b (2.39 g, 93%) was obtained in the same manner as synthesis of Compound tp006-b.

LCMS (ESI) m/z = 414.5 (M+H)+

Retention time: 1.01 min (Analytical condition SQDFA05)

[0526]

Using the resulting crude product of Compound aa443-b, Compound aa443 (2.23 g, 85%) was obtained in the same manner as synthesis of Compound tp006-c.

LCMS (ESI) m/z = 454 (M-H)+

Retention time: 0.99 min (Analytical condition SQDFA05)

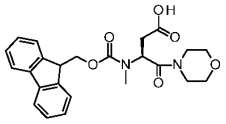
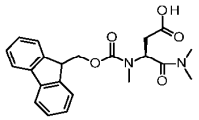
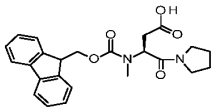
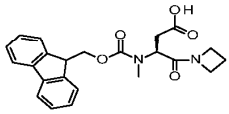
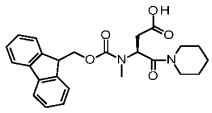
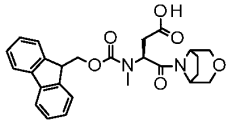
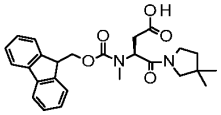
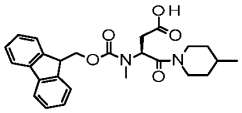
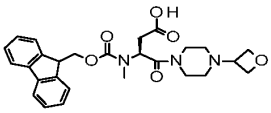
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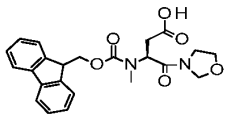
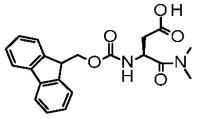
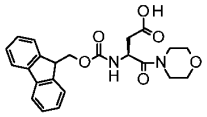
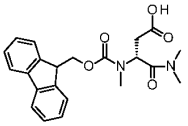
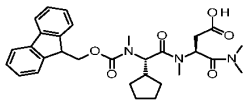
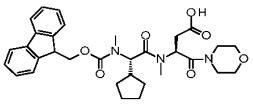
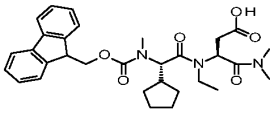
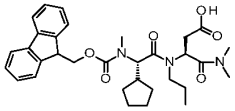
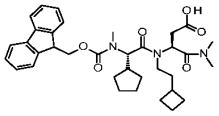
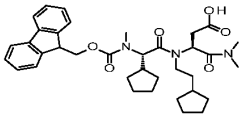
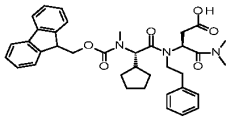
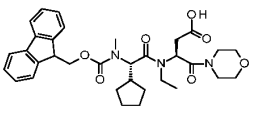
1-2. Synthesis of amino acid-supporting resin used in solid-phase peptide synthesis by peptide synthesizer

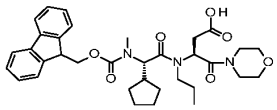
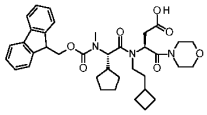
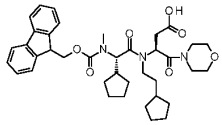
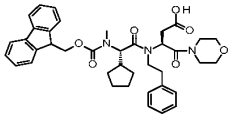
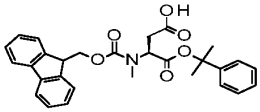
Amino acids listed in Table 5 were synthesized by the method shown below, supported on a resin, and used in peptide synthesis by a peptide synthesizer. Resins on which Compound aa427 to Compound aa438 were supported were synthesized by the following method using resins on which the amino acids shown in Table 5 were supported as raw materials, and used in peptide synthesis with a peptide synthesizer. Amino acids listed in Table 6 were purchased from commercial suppliers, supported on a resin, and used in peptide synthesis by a peptide synthesizer. The reaction for causing Fmoc amino acid to be supported on a resin was carried out according to the method described in WO2013/100132 or WO2018/225864. 2-Chlorotrityl chloride resin (100 to 200 mesh, 1% DVB) was purchased from Watanabe Chemical Industries Ltd., and Chem-Impex.

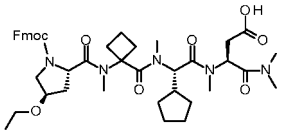
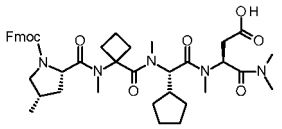
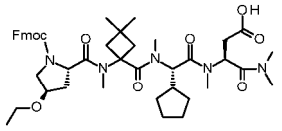
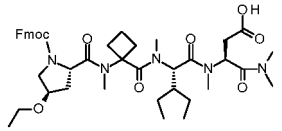
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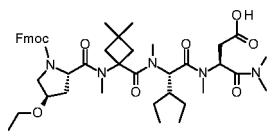
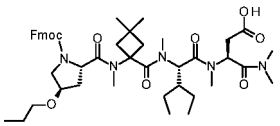
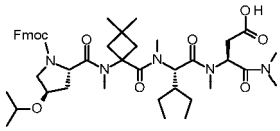
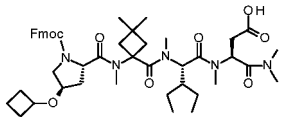
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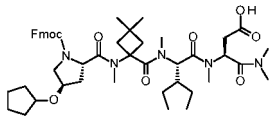
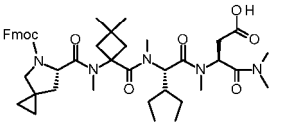
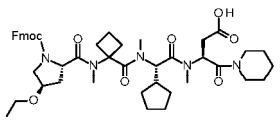
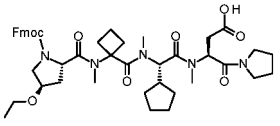
Compound No.	Abbreviation	Structural Formula	Name
aa358	Fmoc-MeAsp-mor		(3S)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-morpholin-4-yl-4-oxobutanoic acid
aa359	Fmoc-MeAsp-NMe2		(3S)-4-(dimethylamino)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxobutanoic acid
aa360	Fmoc-MeAsp-pyrro		(3S)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-4-pyrrolidin-1-ylbutanoic acid
aa361	Fmoc-MeAsp-aze		(3S)-4-(azetidin-1-yl)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxobutanoic acid
aa362	Fmoc-MeAsp-pip		(3S)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-4-piperidin-1-ylbutanoic acid
aa363	Fmoc-MeAsp-mor(26-bicyc)		(3S)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-4-oxobutanoic acid
aa364	Fmoc-MeAsp-pyrro(3-Me2)		(3S)-4-(3,3-dimethylpyrrolidin-1-yl)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxobutanoic acid
aa365	Fmoc-MeAsp-pip(4-Me)		(3S)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-(4-methylpiperidin-1-yl)-4-oxobutanoic acid
aa366	Fmoc-MeAsp-piz(oxe)		(3S)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-[4-(oxetan-3-yl)piperazin-1-yl]-4-oxobutanoic acid

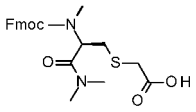
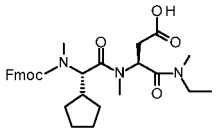
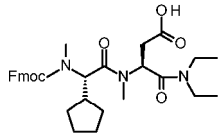
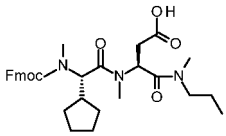
aa367	Fmoc-MeAsp-oxz		(3S)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-(1,3-oxazolidin-3-yl)-4-oxobutanoic acid
aa368	Fmoc-Asp-NMe2		(3S)-4-(dimethylamino)-3-(9H-fluoren-9-ylmethoxycarbonylamino)-4-oxobutanoic acid
aa369	Fmoc-Asp-mor		(3S)-3-(9H-fluoren-9-ylmethoxycarbonylamino)-4-morpholin-4-yl-4-oxobutanoic acid
aa373	Fmoc-D-MeAsp-NMe2		(R)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-4-(dimethylamino)-4-oxobutanoic acid
aa374	Fmoc-MeGly(cPent)-MeAsp-NMe2		(S)-3-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-cyclopentyl-N-methylacetamido)-4-(dimethylamino)-4-oxobutanoic acid
aa375	Fmoc-MeGly(cPent)-MeAsp-mor		(S)-3-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-cyclopentyl-N-methylacetamido)-4-morpholino-4-oxobutanoic acid
aa376	Fmoc-MeGly(cPent)-EtAsp-NMe2		(3S)-3-[[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]-ethyl-amino]-4-(dimethylamino)-4-oxo-butanoic acid
aa377	Fmoc-MeGly(cPent)-nPrAsp-NMe2		(3S)-3-[[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]-propyl-amino]-4-(dimethylamino)-4-oxo-butanoic acid
aa378	Fmoc-MeGly(cPent)-cBuEtAsp-NMe2		(3S)-3-[2-cyclobutylethyl-[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]amino]-4-(dimethylamino)-4-oxo-butanoic acid
aa379	Fmoc-MeGly(cPent)-cPentEtAsp-NMe2		(3S)-3-[2-cyclopentylethyl-[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]amino]-4-(dimethylamino)-4-oxo-butanoic acid
aa380	Fmoc-MeGly(cPent)-PhenethylAsp-NMe2		(3S)-3-[[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]-(2-phenylethyl)amino]-4-(dimethylamino)-4-oxo-butanoic acid
aa381	Fmoc-MeGly(cPent)-EtAsp-mor		(3S)-3-[[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]-ethyl-amino]-4-morpholino-4-oxo-butanoic acid

aa382	Fmoc-MeGly(cPent)-nPrAsp-mor		(3S)-3-[[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]-propyl-amino]-4-morpholino-4-oxo-butanoic acid
aa383	Fmoc-MeGly(cPent)-cBuEtAsp-mor		(3S)-3-[2-cyclobutylethyl-[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]amino]-4-morpholino-4-oxo-butanoic acid
aa384	Fmoc-MeGly(cPent)-cPentEtAsp-mor		(3S)-3-[2-cyclopentylethyl-[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]amino]-4-morpholino-4-oxo-butanoic acid
aa385	Fmoc-MeGly(cPent)-PhenethylAsp-mor		(3S)-3-[[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]-(2-phenylethyl)amino]-4-morpholino-4-oxo-butanoic acid
aa386	Fmoc-MeAsp(OPis)		(3S)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-(1-methyl-1-phenyl-ethoxy)-4-oxo-butanoic acid

aa427	Fmoc-Hyp(Et)-MecVal-MeGly(cPent)-MeAsp-NMe2		(3S)-3-[[(2S)-2-cyclopentyl-2-[[1-[[(2S,4R)-4-ethoxy-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-carbonyl]-methyl-amino]cyclobutan carbonyl]-methyl-amino]acetyl]-methyl-amino]-4-(dimethyl amino)-4-oxo-butanoic acid
aa428	Fmoc-Pro(4S-Me)-MecVal-MeGly(cPent)-MeAsp-NMe2		(3S)-3-[[(2S)-2-cyclopentyl-2-[[1-[[(2S,4S)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-methyl-pyrrolidin-2-carbonyl]-methyl-amino]cyclobutan carbonyl]-methyl-amino]acetyl]-methyl-amino]-4-(dimethyl amino)-4-oxo-butanoic acid
aa429	Fmoc-Hyp(Et)-MecVal(3-Me2)-MeGly(cPent)-MeAsp-NMe2		(3S)-3-[[(2S)-2-cyclopentyl-2-[[1-[[(2S,4R)-4-ethoxy-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-carbonyl]-methyl-amino]-3,3-dimethyl-cyclobutan carbonyl]-methyl-amino]acetyl]-methyl-amino]-4-(dimethyl amino)-4-oxo-butanoic acid
aa430	Fmoc-Hyp(Et)-MecVal-MeNva(3-Et)-MeAsp-NMe2		(3S)-4-(dimethyl amino)-3-[[(2S)-2-[[1-[[(2S,4R)-4-ethoxy-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-carbonyl]-methyl-amino]cyclobutan carbonyl]-methyl-amino]-3-ethyl-pentanoyl]-methyl-amino]-4-oxo-butanoic acid

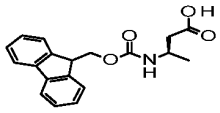
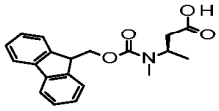
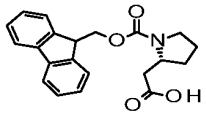
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aa432	Fmoc-Hyp(nPr)-MecVal(3-Me2)-MeNva(3-Et)-MeAsp-NMe2		(3S)-4-(dimethyl amino)-3-[[(2S)-3-ethyl-2-[[1-[[(2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-propoxy-pyrrolidin-2-carbonyl]-methyl-amino]-3,3-dimethyl-cyclobutan carbonyl]-methyl-amino]pentanoyl]-methyl-amino]-4-oxo-butanoic acid
aa433	Fmoc-Hyp(iPr)-MecVal(3-Me2)-MeNva(3-Et)-MeAsp-NMe2		(3S)-4-(dimethyl amino)-3-[[(2S)-3-ethyl-2-[[1-[[(2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)-4-isopropoxy-pyrrolidin-2-carbonyl]-methyl-amino]-3,3-dimethyl-cyclobutan carbonyl]-methyl-amino]pentanoyl]-methyl-amino]-4-oxo-butanoic acid
aa434	Fmoc-Hyp(cBu)-MecVal(3-Me2)-MeNva(3-Et)-MeAsp-NMe2		(3S)-3-[[(2S)-2-[[1-[[(2S,4R)-4-(cyclobutoxy)-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-carbonyl]-methyl-amino]-3,3-dimethyl-cyclobutan carbonyl]-methyl-amino]-3-ethyl-pentanoyl]-methyl-amino]-4-(dimethyl amino)-4-oxo-butanoic acid

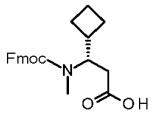
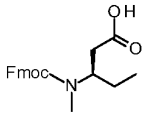
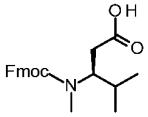
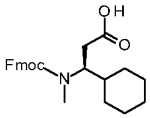
aa435	Fmoc-Hyp(cPent)-MecVal(3-Me2)-MeNva(3-Et)-MeAsp-NMe2		(3S)-3-[[(2S)-2-[[1-[[(2S,4R)-4-(cyclopentoxy)-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-carbonyl]-methyl-amino]-3,3-dimethyl-cyclobutan carbonyl]-methyl-amino]-3-ethyl-pentanoyl]-methyl-amino]-4-(dimethyl amino)-4-oxo-butanoic acid
aa436	Fmoc-Pro(4-cPr)-MecVal(3-Me2)-MeNva(3-Et)-MeAsp-NMe2		(3S)-4-(dimethyl amino)-3-[[(2S)-3-ethyl-2-[[1-[[(6S)-5-(9H-fluoren-9-ylmethoxycarbonyl)-5-azaspiro[2.4]heptan-6-carbonyl]-methyl-amino]-3,3-dimethyl-cyclobutan carbonyl]-methyl-amino]pentanoyl]-methyl-amino]-4-oxo-butanoic acid
aa437	Fmoc-Hyp(Et)-MecVal-MeGly(cPent)-MeAsp-pip		(3S)-3-[[(2S)-2-cyclopentyl-2-[[1-[[(2S,4R)-4-ethoxy-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-carbonyl]-methyl-amino]cyclobutan carbonyl]-methyl-amino]acetyl]-methyl-amino]-4-oxo-4-(1-piperidyl)butanoic acid
aa438	Fmoc-Hyp(Et)-MecVal-MeGly(cPent)-MeAsp-pyrro		(3S)-3-[[(2S)-2-cyclopentyl-2-[[1-[[(2S,4R)-4-ethoxy-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-carbonyl]-methyl-amino]cyclobutan carbonyl]-methyl-amino]acetyl]-methyl-amino]-4-oxo-4-pyrrolidin-1-yl-butanoic acid

aa439	Fmoc-MeCys(AcOH)-NMe2		2-[(2R)-3-(dimethyl amino)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-3-oxo-propyl]sulfanyl-acetic acid
aa440	Fmoc-MeGly(cPent)-MeAsp-MeNEt		(3S)-3-[[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]-methyl-amino]-4-[ethyl(methyl)amino]-4-oxo-butanoic acid
aa441	Fmoc-MeGly(cPent)-MeAsp-NEt2		(3S)-3-[[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]-methyl-amino]-4-(diethyl amino)-4-oxo-butanoic acid
aa442	Fmoc-MeGly(cPent)-MeAsp-MeNnPr		(3S)-3-[[(2S)-2-cyclopentyl-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]acetyl]-methyl-amino]-4-[methyl(propyl)amino]-4-oxo-butanoic acid

[0529]

[Table 6]

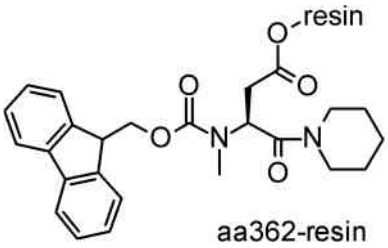
Compound No.	Abbreviation	Structural Formula	Name
aa370	Fmoc-D-3-Abu-OH		(3R)-3-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid
aa371	Fmoc-D-3-MeAbu-OH		(3R)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]butanoic acid
aa372	Fmoc-D-Pro-(C#CH2)-OH		2-[(2R)-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-yl]acetic acid

aa423	Fmoc-MebAla(3S-cBu)-OH		(3S)-3-cyclobutyl-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid
aa424	Fmoc-MebAla(3R-Et)-OH		(3R)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]pentanoic acid
aa425	Fmoc-D-MeVal-(C#CH2)-OH		(3S)-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-methyl-pentanoic acid
aa426	Fmoc-MebAla(3S-cHex)-OH		(3S)-3-cyclohexyl-3-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanoic acid

[0530]

Synthesis of resin

Synthesis of Compound aa362-resin



aa362-resin

[0531]

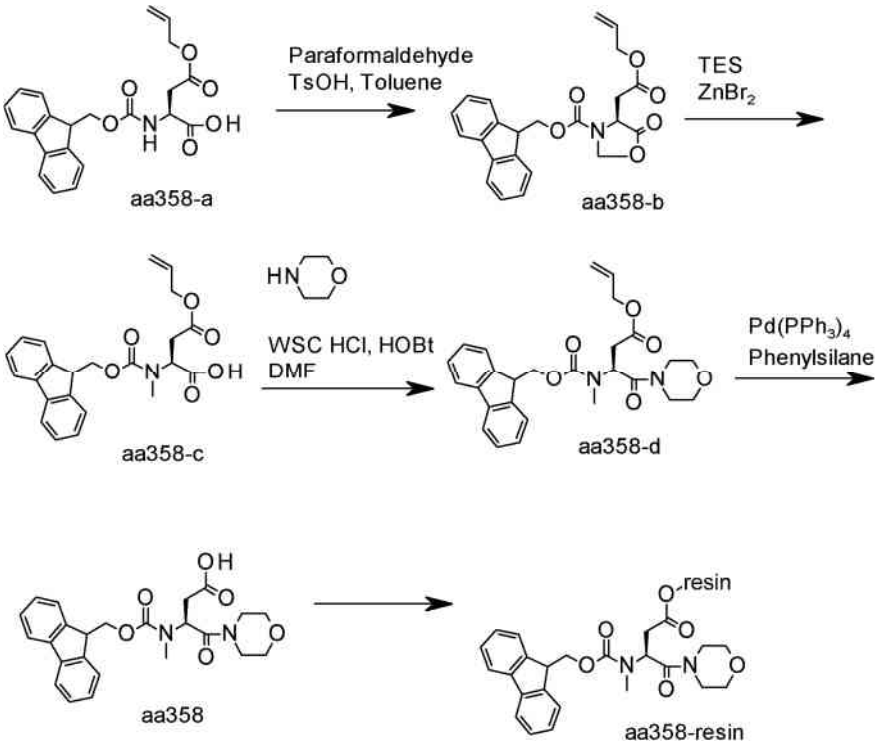
Compound aa362-resin was synthesized by the method described in WO2018/225864.

[0532]

Herein, when a resin and a compound are bonded, the resin moiety may be indicated as "○" (circle) or "resin". The 2-chlorotrityl group may be omitted. Further, to clarify the reaction point of the resin moiety, the chemical structure of the reaction moiety may be indicated in connection with "○" (circle) or "resin". In the above structure of Compound aa362-resin, the 2-chlorotrityl group on the resin is bonded to the side-chain carboxylic acid of MeAsp via an ester bond.

[0533]

Synthesis of Compound aa358-resin



[0534]

Fmoc-Asp(OAl)-OH (Compound aa358-a, (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-oxo-4-prop-2-enoxybutanoic acid, CAS No. 146982-24-3) (200 g, 506 mmol), p-toluenesulfonic acid (5.7 g, 0.05 eq), and paraformaldehyde (45.6 g, 3 eq) were mixed with toluene (2000 mL), and the mixture was stirred at 110°C for 16 hours. The solvent was distilled off from the reaction solution under reduced pressure, the residue was dissolved in ethyl acetate, and the mixture was washed twice with an aqueous sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether, 0/100 to 30/70) to give Compound aa358-b (9H-fluoren-9-ylmethyl (4S)-5-oxo-4-(2-oxo-2-prop-2-enoxyethyl)-1,3-oxazolidine-3-carboxylate) (175 g, 85%). The compound was mixed with another similarly synthesized batch, and used in the following reaction.

LCMS (ESI) m/z = 408 (M+H)+

Retention time: 1.407 min (Analytical condition SMD method_20)

[0535]

A DCM (1 L) mixed solution of Compound aa358-b (100 g, 245 mmol), zinc bromide ($ZnBr_2$) (110 g, 496 mmol), and TES (56 g, 481.6 mmol) was stirred at room temperature for 48 hours in a nitrogen atmosphere. Four batches of the same scale of the reaction solution were mixed, and the solvent was distilled off under reduced pressure. The residue was dissolved in TBME and extracted 10 times with 0.5 M phosphate buffer (pH = about 7.5). The aqueous

layers were combined, adjusted to pH 2 with 5 N hydrochloric acid, and extracted twice with isopropyl acetate (IPAC). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. To remove IPAC, the procedure of adding TBME to the resulting residue and distilling off solvent under reduced pressure was repeated 6 times, and thus Compounds aa358-c ((2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-4-prop-2-enoxybutanoic acid) was obtained (270 g, 54%).

LCMS (ESI) m/z = 410 (M+H)+

Retention time: 1.956 min (Analytical condition SMD method_05)

[0536]

WSCI·HCl (0.506 g, 2.64 mmol) was dissolved in DMF (4.4 mL), then HOBt (0.356 g, 2.64 mmol), Compound aa358-c ((2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-4-prop-2-enoxybutanoic acid), Fmoc-MeAsp(OAl)-OH) (0.9 g, 2.2 mmol) were added, and the mixture was stirred at 0°C for 10 minutes. Morpholine (0.23 mL, 2.64 mmol) was added dropwise to the reaction solution, and the mixture was stirred at 0°C for 1 hour. Ethyl acetate (9 mL) was added to the reaction solution, the mixture was washed with 0.5 N hydrochloric acid, water, a saturated aqueous sodium hydrogen carbonate solution/water (1/1), and saturated brine/water (1/1), and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give Compound aa358-d as a crude product (522 mg, 50%).

LCMS (ESI) m/z = 479 (M+H)+

Retention time: 0.87 min (Analytical condition SQDFA05)

[0537]

Tetrakis(triphenylphosphine)palladium(0) (10.8 mg, 0.0093 mmol) was added to a DCM (1.86 mL) solution of Compound aa358-d (446 mg, 0.932 mmol), and further, phenylsilane (0.081 mL, 0.653 mmol) was added dropwise, and the mixture was stirred at room temperature for 30 minutes. The reaction solution was diluted with TBME, and a 5% aqueous sodium hydrogen carbonate solution was added. The organic layer was removed, phosphoric acid (548 mg) was added to the aqueous layer, and the mixture was extracted with TBME. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give Compound aa358 (321 mg, 79%).

LCMS (ESI) m/z = 439 (M+H)+

Retention time: 0.69 min (Analytical condition SQDFA05)

[0538]

The reaction for causing the Fmoc amino acid to be supported on a resin was performed according to the method described in WO2013/100132 or WO2018/225864.

2-Chlorotrityl chloride resin (1.60 mmol/g, 100-200 mesh, 1% DVB, 1 g, 1.6 mmol) and dehydrated dichloromethane (13.3 mL) were placed in a filter-equipped reaction vessel, and shaken at room temperature for 10 minutes. After dichloromethane was removed by applying nitrogen pressure, a mixed solution obtained by adding dehydrated methanol (0.259 mL, 6.4 mmol) and DIPEA (0.671 mL, 3.84 mmol) to a dehydrated dichloromethane (13.3 mL) solution of Compound aa358 (317 mg, 0.723 mmol) was added to the reaction vessel, and the reaction vessel was shaken for 30 minutes. After the reaction solution was removed by applying nitrogen pressure, a mixed solution obtained by adding dehydrated methanol (1.99 mL) and DIPEA (0.671 mL) to dehydrated dichloromethane (13.3 mL) were added to the reaction vessel, and the reaction vessel was shaken for 1 hour and 30 minutes. After the reaction solution was removed by applying nitrogen pressure, dichloromethane was added to the reaction vessel, the reaction vessel was shaken for 5 minutes, and then the reaction solution was removed by applying nitrogen pressure. This resin washing operation with dichloromethane was repeated 2 more times, and the resulting resin was dried under reduced pressure overnight to give Compound aa358-resin (1.22 g, 0.37 mmol/g).

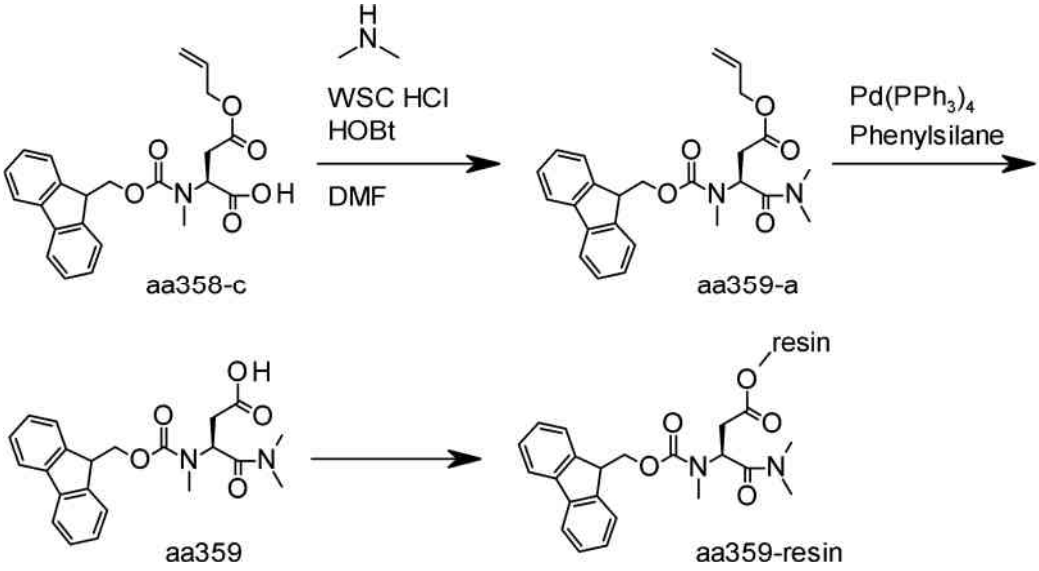
[0539]

The amount of amino acid supported on the resin was calculated as follows. The resulting Compound aa358-resin (10.4 mg) was placed in the reaction vessel, DMF (2 mL) was added, and the reaction vessel was shaken at room temperature for 1 hour. Then, DBU (40 μL) was added, and the reaction vessel was shaken at 30°C for 30 minutes. Then, DMF (8 mL) was added to the reaction mixture, and 1 mL of the solution was diluted with DMF (11.5 mL). The absorbance (294 nm) of the resulting diluted solution was measured (measured with Shimadzu UV-1600PC (cell length 1.0 cm)), and thus the calculated amount of supported Compound aa358-resin was 0.370 mmol/g.

Another similarly synthesized lot having a different supported amount was also used in the peptide synthesis.

[0540]

Synthesis of Compound aa359-resin



[0541]

Using Compound aa358-c ((2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-4-prop-2-enoxybutanoic acid) (1.5 g, 3.66 mmol) as a starting material, Compound aa359-a (1.47 g, 92%) was obtained in the same manner as the synthesis of Compound aa358-d using a THF solution (2 mol/L) of dimethylamine in place of morpholine.

LCMS (ESI) m/z = 437 (M+H)+

Retention time: 0.88 min (Analytical condition SQDFA05)

[0542]

Using the resulting Compound aa359-a (1.4 g, 3.21 mmol), Compound aa359 (1.30 g, quant.) was obtained in the same manner as the synthesis of Compound aa358.

LCMS (ESI) m/z = 397 (M+H)+

Retention time: 0.70 min (Analytical condition SQDFA05)

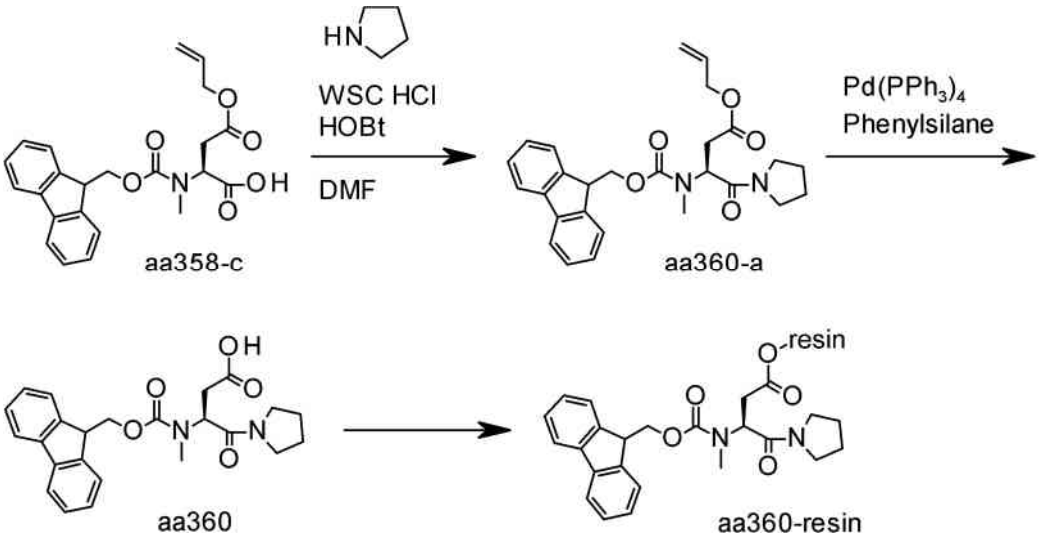
[0543]

Using the resulting Compound aa359 (1.21 g, 3.05 mmol), Compound aa359-resin (4.45 g, supported amount 0.318 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

Another similarly synthesized lot having a different supported amount was also used in the peptide synthesis in the present Example.

[0544]

Synthesis of Compound aa360-resin



[0545]

Using Compound aa358-c ((2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-4-prop-2-enoxybutanoic acid) (30 g, 73.3 mmol) as a starting material, Compound aa360-a (30.7 g, 91%) was obtained in the same manner as the synthesis of Compound aa358-d using pyrrolidine in place of morpholine.

LCMS (ESI) m/z = 463 (M+H)+

Retention time: 0.88 min (Analytical condition SQDFA05)

[0546]

Using the resulting Compound aa360-a (30.7 g, 66.4 mmol), Compound aa360 (26.2 g, 93%) was obtained in the same manner as the synthesis of Compound aa358.

LCMS (ESI) m/z = 423 (M+H)+

Retention time: 0.71 min (Analytical condition SQDFA05)

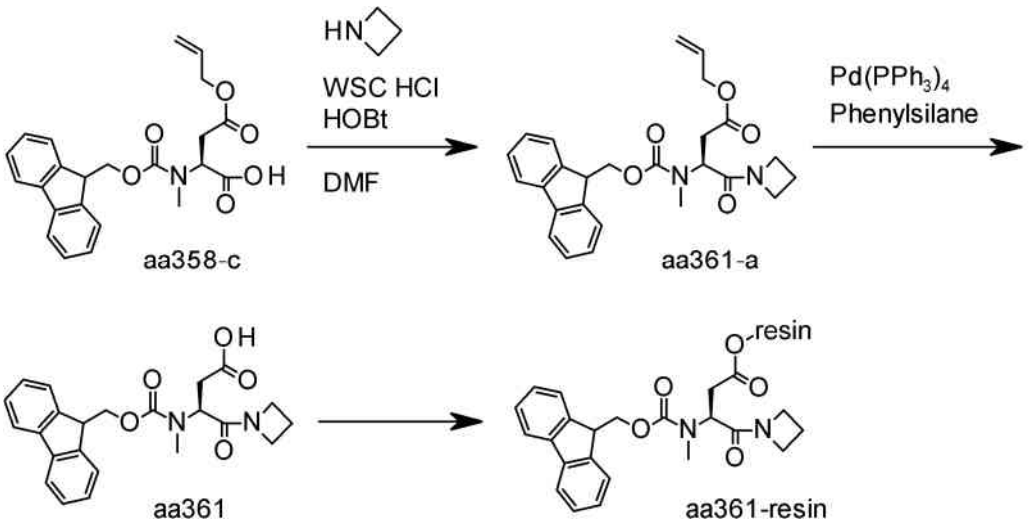
[0547]

Using the resulting Compound aa360 (24.6 g, 58.2 mmol), Compound aa360-resin was obtained in the same manner as the synthesis of Compound aa358-resin (84.1 g, supported amount 0.5216 mmol/g).

Another similarly synthesized lot having a different supported amount was also used in the peptide synthesis in the present Example.

[0548]

Synthesis of Compound aa361-resin



[0549]

Using Compound aa358-c ((2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-4-prop-2-enoxybutanoic acid) (1.5 g, 3.66 mmol) as a starting material, Compound aa361-a (1.41 g, 86%) was obtained in the same manner as the synthesis of Compound aa358-a using azetidine in place of morpholine.

LCMS (ESI) m/z = 449 (M+H)+

Retention time: 0.86 min (Analytical condition SQDFA05)

[0550]

Using the resulting Compound aa361-a (1.4 g, 3.12 mmol), Compound aa361 (1.14 g, 89%.) was obtained in the same manner as the synthesis of Compound aa358.

LCMS (ESI) m/z = 409 (M+H)+

Retention time: 0.69 min (Analytical condition SQDFA05)

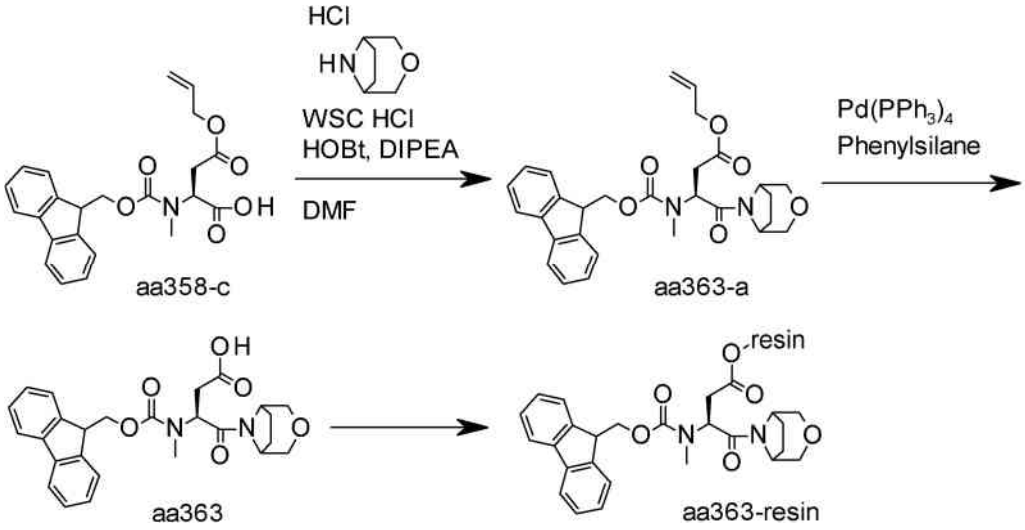
[0551]

Using the resulting Compound aa361 (1.05 g, 2.57 mmol), Compound aa361-resin (3.64 g, supported amount 0.2984 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

Another similarly synthesized lot having a different supported amount was also used in the peptide synthesis in the present Example.

[0552]

Synthesis of Compound aa363-resin



[0553]

Using Compound aa358-c ((2S)-2-[9H-fluoren-9-ylmethoxycarbonyl (methyl)amino]-4-oxo-4-prop-2-enoxybutanoic acid) (5 g, 12.21 mmol) as a starting material, Compound aa363-a (5.8 g, 94%) was obtained in the same manner as the synthesis of Compound aa358-d using (1R,5S)-3-oxa-8-azabicyclo[3.2.1]octane hydrochloride and 1 eq of DIPEA based on amine, in place of morpholine.

LCMS (ESI) m/z = 505 (M+H)+

Retention time: 0.87 min (Analytical condition SQDFA05)

[0554]

Using the resulting Compound aa363-a (5.8 g, 11.49 mmol), Compound aa363 (5.1 g, 96%) was obtained in the same manner as the synthesis of Compound aa358.

LCMS (ESI) m/z = 465 (M+H)+

Retention time: 0.69 min (Analytical condition SQDFA05)

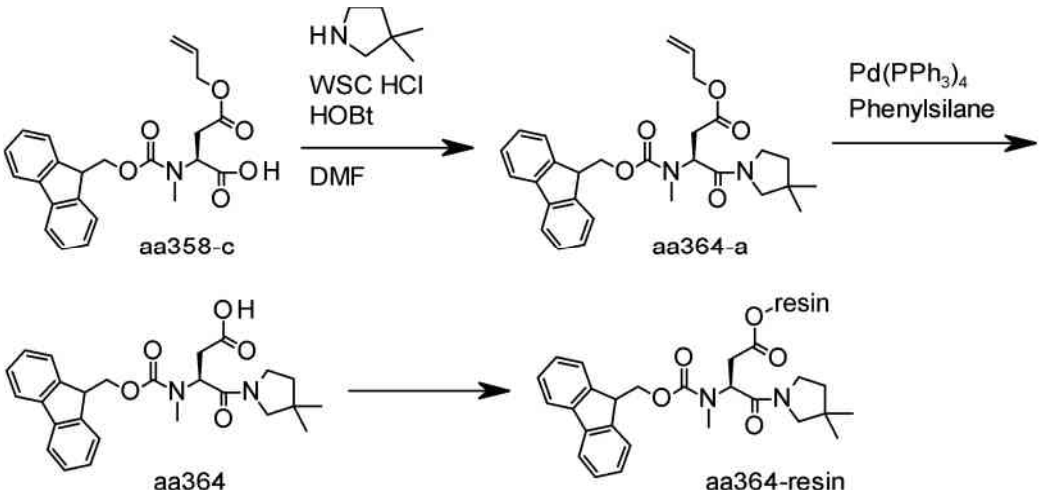
[0555]

Using the resulting Compound aa363 (5.1 g, 10.98 mmol), Compound aa363-resin (18.3 g, supported amount 0.419 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

Another similarly synthesized lot having a different supported amount was also used in the peptide synthesis in the present Example.

[0556]

Synthesis of Compound aa364-resin



[0557]

Using Compound aa358-c ((2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-4-prop-2-enoxybutanoic acid) (0.5 g, 1.221 mmol) as a starting material, Compound aa364-a (359.6 mg, 60%) was obtained in the same manner as the synthesis of Compound aa358-d using 3,3-dimethylpyrrolidine in place of morpholine.

LCMS (ESI) m/z = 491 (M+H)+

Retention time: 0.98 min (Analytical condition SQDFA05)

[0558]

Using the resulting Compound aa364-a (338 mg, 0.689 mmol), Compound aa364 (226.2 mg, 73%) was obtained in the same manner as the synthesis of Compound aa358.

LCMS (ESI) m/z = 451 (M+H)+

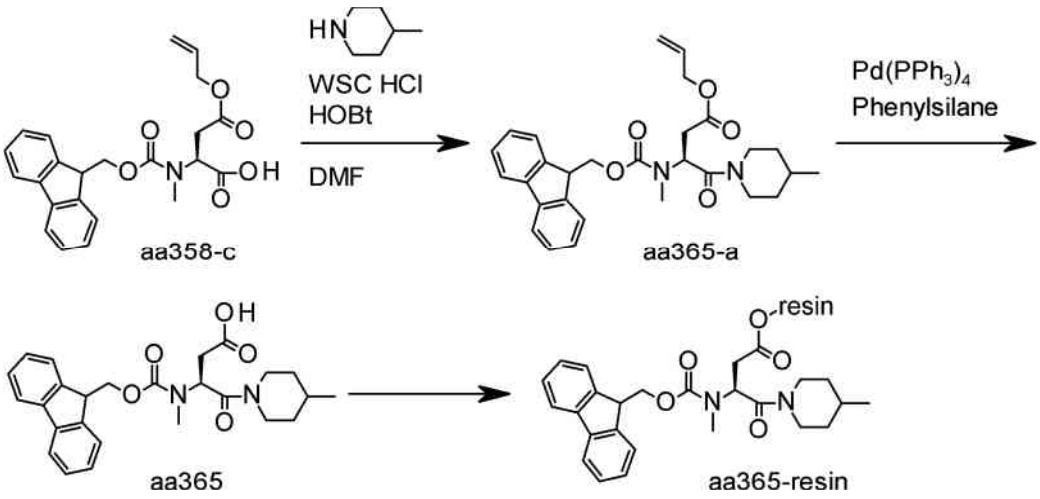
Retention time: 0.84 min (Analytical condition SQDFA05)

[0559]

Using the resulting Compound aa364 (226 mg, 0.502 mmol), Compound aa364-resin (731 mg, supported amount 0.455 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

[0560]

Synthesis of Compound aa365-resin



[0561]

Using Compound aa358-c ((2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-4-prop-2-enoxybutanoic acid) (0.9 g, 2.198 mmol) as a starting material, a crude material of Compound aa365-a was obtained in the same manner as the synthesis of Compound aa358-d using 4-methylpiperidine in place of morpholine. The resulting crude product was purified by reverse phase column chromatography (0.1% formic acid-containing water-acetonitrile), and further, dissolved in 20% ethyl acetate-hexane, then washed twice with a saturated aqueous sodium hydrogen carbonate solution and once with a saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give Compound aa365-a (0.587 g, 54%).

LCMS (ESI) m/z = 491 (M+H)+

Retention time: 1.02 min (Analytical condition SQDFA05)

[0562]

Using the resulting Compound aa365-a (535 mg, 1.09 mmol), Compound aa365 (376.6 mg, 77%) was obtained in the same manner as the synthesis of Compound aa358.

LCMS (ESI) m/z = 451 (M+H)+

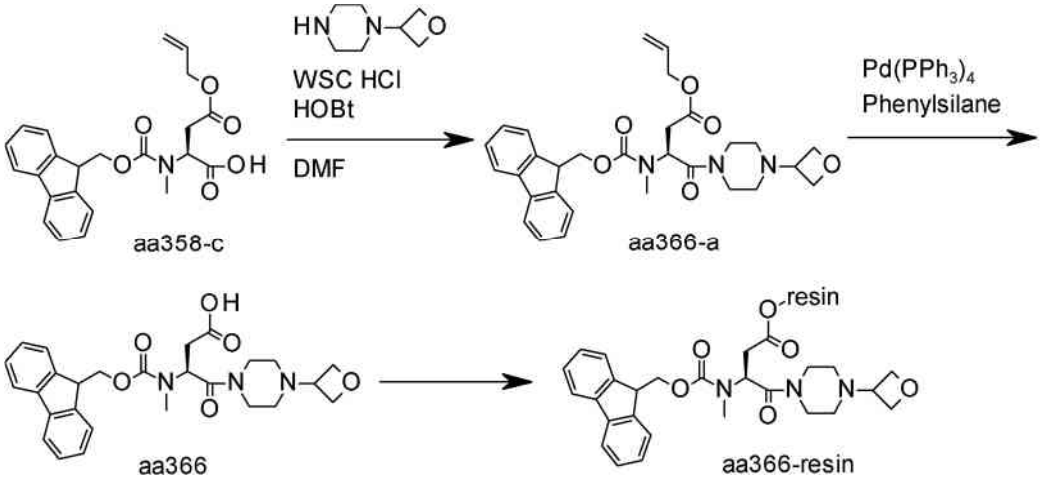
Retention time: 0.85 min (Analytical condition SQDFA05)

[0563]

Using the resulting Compound aa365 (364 mg, 0.808 mmol), Compound aa365-resin (1.2 g, supported amount 0.403 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

[0564]

Synthesis of Compound aa366-resin



[0565]

Using Compound aa358-c ((2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-4-prop-2-enoxybutanoic acid) (0.4 g, 0.977 mmol) as a starting material, Compound aa366-a (466 mg, 89%) was obtained in the same manner as the synthesis of Compound aa358-d using 1-(oxetan-3-yl)piperazine in place of morpholine.

LCMS (ESI) m/z = 534 (M+H)+

Retention time: 0.64 min (Analytical condition SQDFA05)

[0566]

A crude product obtained in the same manner as the synthesis of Compound aa358 using the resulting Compound aa366-a (466 mg, 0.873 mmol), was purified by reverse phase column chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound aa366 (385 mg, 89%).

LCMS (ESI) m/z = 494 (M+H)+

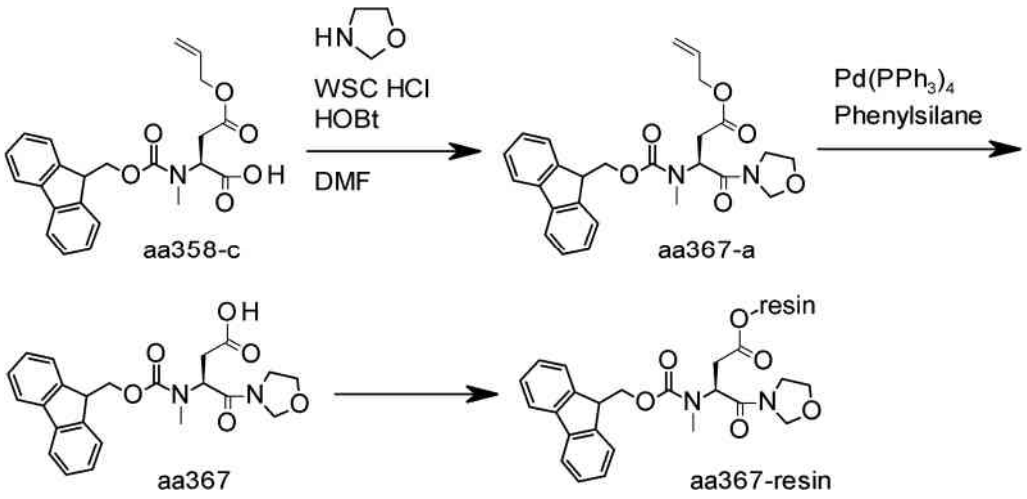
Retention time: 0.50 min (Analytical condition SQDFA05)

[0567]

Using the resulting Compound aa366 (385 mg, 0.78 mmol), Compound aa366-resin (1.49 g, supported amount 0.266 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

[0568]

Synthesis of Compound aa367-resin



[0569]

Using Compound aa358-c ((2S)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]-4-oxo-4-prop-2-enoxybutanoic acid) (725 mg, 1.77 mmol) as a starting material, Compound aa367-a (164 mg, 20%) was obtained in the same manner as the synthesis of Compound aa358-d.

LCMS (ESI) m/z = 465 (M+H)+

Retention time: 0.86 min (Analytical condition SQDFA05)

[0570]

Using the resulting Compound aa367-a (146.4 mg, 0.315 mmol), Compound aa367 (111 mg, 83%) was obtained in the same manner as the synthesis of Compound aa358. Another similarly synthesized lot was also added, and the following reaction was carried out.

LCMS (ESI) m/z = 425 (M+H)+

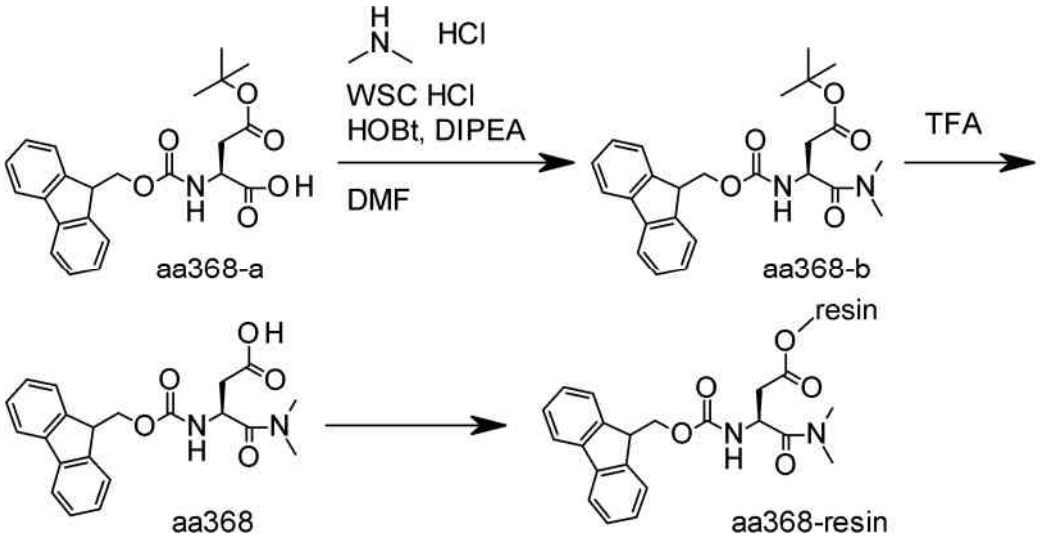
Retention time: 0.69 min (Analytical condition SQDFA05)

[0571]

Using the resulting Compound aa367 (0.25 g, 0.589 mmol), Compound aa367-resin (1.06 g, supported amount 0.283 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

[0572]

Synthesis of Compound aa368-resin



[0573]

In a nitrogen atmosphere, dimethylamine hydrochloride (0.991 g, 12.15 mmol), WSCI·HCl (2.8 g, 14.58 mmol), and DIPEA (2.117 mL, 12.15 mmol) were successively added at 0°C to a DMF (24.3 mL) solution of Fmoc-Asp(OtBu)-OH (Compound aa368-a), 4-tert-butyl N-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-aspartate, CAS No. 71989-14-5) (5 g, 12.15 mmol), and HOBt monohydrate (2.047 g, 13.37 mmol), and the mixture was stirred at 0°C for 50 minutes. Ethyl acetate/hexane (1/1, 100 mL) and saturated brine/water (1/1, 50 mL) were added to the reaction solution, and the organic layer was separated. The resulting organic layer was succesively washed with a saturated aqueous ammonium chloride solution, water, and saturated brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give Compound aa368-b (5.02 g, 94%).

LCMS (ESI) m/z = 439 (M+H)+

Retention time: 1.03 min (Analytical condition SQDAA05)

[0574]

The operation of adding toluene (150 mL) to Compound aa368-b (5 g, 11.4 mmol) and distilling off the solvent under reduced pressure was performed three times. The residue was dissolved in DCM (5.06 mL), TFA (10.13 mL, 137 mmol) was added dropwise at 0°C in a nitrogen atmosphere, and the mixture was stirred at room temperature for 1 hour. The reaction solution was cooled to 0°C, diethyl ether (10.1 mL) was added, and an 8 N aqueous sodium hydroxide solution (17.1 mL) was added dropwise. Furthermore, a saturated aqueous sodium dihydrogen phosphate solution (7.6 mL) and water (5 mL) were added. This solution was extracted with ethyl acetate, the resulting organic layer was washed with a saturated aqueous sodium dihydrogen phosphate solution/water (1/1), dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure to give Compound aa368 (2.63 g, 60%).

The compound was used in the next reaction without further purification.

LCMS (ESI) m/z = 383 (M+H)+

Retention time: 0.80 min (Analytical condition SQDAA05)

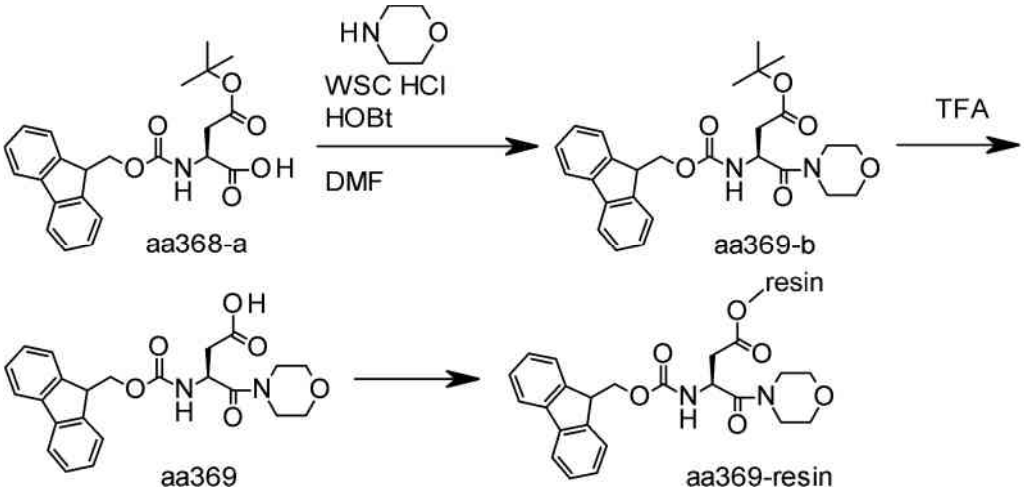
[0575]

Using the resulting Compound aa368 (2.367 g, 6.19 mmol), Compound aa368-resin (9.07 g, supported amount 0.399 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

Another similarly synthesized lot having a different supported amount was also used in the peptide synthesis in the present Example.

[0576]

Synthesis of Compound aa369-resin



[0577]

Using Compound aa368-a (1 g, 2.43 mmol) as a starting material, Compound aa369-b (713 mg, 61%) was obtained in the same manner as the synthesis of Compound aa368-b using morpholine in place of dimethylamine hydrochloride and DIPEA.

LCMS (ESI) m/z = 481 (M+H)+

Retention time: 0.88 min (Analytical condition SQDFA05)

[0578]

Using the resulting Compound aa369-b (400 mg, 0.832 mmol), Compound aa369 (353.4 mg, 100%) was obtained in the same manner as the synthesis of Compound aa368, provided that triethylamine was used in place of an 8 N aqueous sodium hydroxide solution for work-up.

LCMS (ESI) m/z = 425 (M+H)+

Retention time: 0.66 min (Analytical condition SQDFA05)

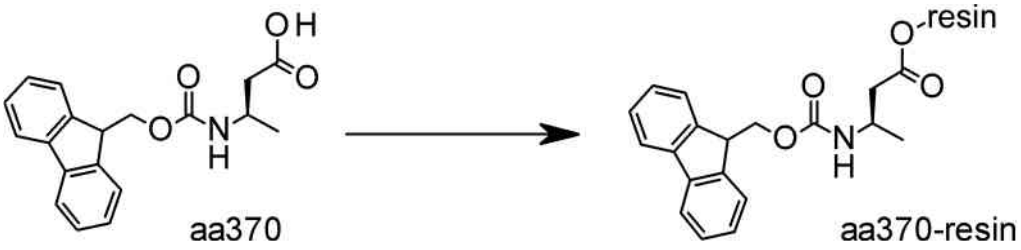
[0579]

Using the resulting Compound aa369 (326 mg, 0.768 mmol), Compound aa369-resin (1.21 g, supported amount 0.415 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

Another similarly synthesized lot having a different supported amount was also used in the peptide synthesis in the present Example.

[0580]

Synthesis of Compound aa370-resin



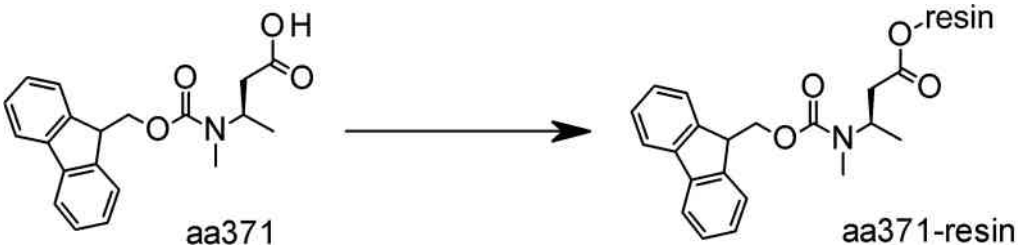
[0581]

Using Compound aa370 (7.1 g, 21.82 mmol) and 2-chlorotrityl chloride resin (1.6 mmol/g, 100-200 mesh, 1% DVB, 27.25 g, 43.6 mmol) purchased from a commercial supplier, Compound aa370-resin (33.44 g, supported amount 0.598 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

Another similarly synthesized lot having a different supported amount was also used in the peptide synthesis in the present Example.

[0582]

Synthesis of Compound aa371-resin



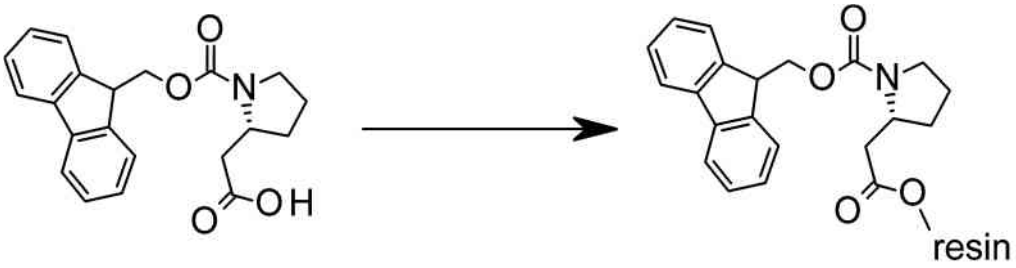
[0583]

Using Compound aa371 (11.5 g, 33.9 mmol) and 2-chlorotrityl chloride resin (1.69 mmol/g, 100-200 mesh, 1% DVB, 50 g, 84.5 mmol) purchased from a commercial supplier, Compound aa371-resin (58.95 g, supported amount 0.536 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

Another similarly synthesized lot having a different supported amount was also used in the peptide synthesis in the present Example.

[0584]

Synthesis of Compound aa372-resin



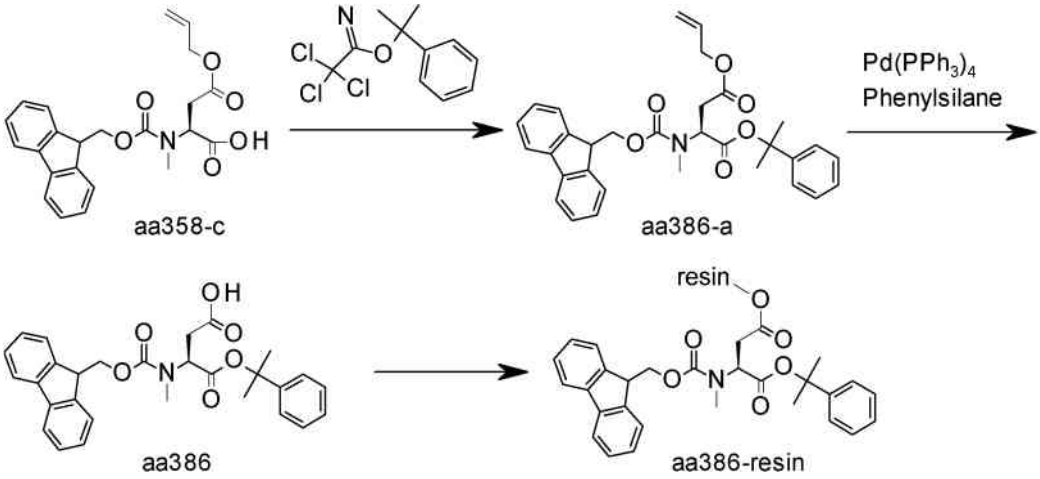
aa372 aa372-resin

[0585]

Using Compound aa372 (1 g, 2.85 mmol) and 2-chlorotrityl chloride resin (1.6 mmol/g, 100-200 mesh, 1% DVB, 7 g, 21.39 mmol) purchased from a commercial supplier, Compound aa372-resin (7.19 g, supported amount 0.377 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

[0586]

Synthesis of Compound aa386



aa358-c aa386-a aa386 aa386-resin

[0587]

A DCM solution of 2-phenylpropan-2-yl 2,2,2-trichloroacetoimidate (2.74 g, 9.77 mmol) was added to a DCM (15 mL) solution of Compound aa358-c (2 g, 4.88 mmol), and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off from the reaction solution under reduced pressure, and the resulting residue was purified by reverse phase column chromatography to give Compound aa386-a (2.10 g, 81%).

LCMS (ESI) m/z = 550.3 (M+Na)+

Retention time: 0.76 min (Analytical condition SQDAA50)

[0588]

In a nitrogen atmosphere, tetrakis(triphenylphosphine)palladium(0) (0.046 g, 0.04 mmol) and phenylsilane (0.343 mL, 2.79 mmol) were added to a DCM (15 mL) solution of Compound aa386-a (2.1 g, 3.98 mmol) at room temperature, and the mixture was stirred for 1

hour. The reaction solution was diluted with TBME and a 5% aqueous sodium hydrogen carbonate solution, the solvent was distilled off under reduced pressure, and the resulting residue was purified by reverse phase column chromatography to give Compound aa386 (1.67 g, 86%).

LCMS (ESI) m/z = 510 (M+Na)+

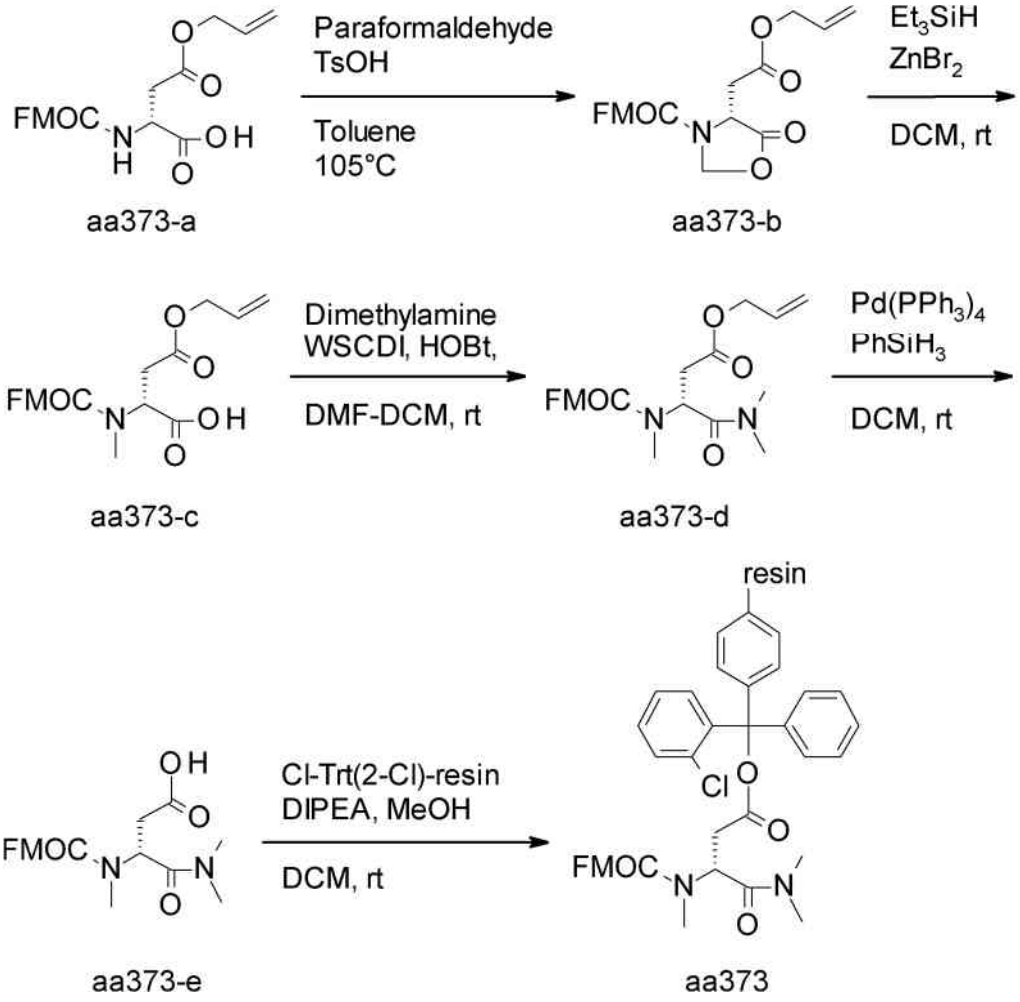
Retention time: 0.94 min (Analytical condition SQDFA05)

[0589]

Using the resulting Compound aa386 (1.17 g, 2.4 mmol), Compound aa386-resin (3.6 g, 0.377 mmol/g) was obtained in the same manner as the synthesis of Compound aa358-resin.

[0590]

Synthesis of Compound aa373-resin



aa373-a aa373-b aa373-c aa373-d aa373-e aa373

[0591]

In a nitrogen atmosphere, a toluene (500 mL) suspension of aa373-a (20 g, 50.58 mmol), paraformaldehyde (4.56 g, 151.74 mmol), and p-toluenesulfonic acid (0.09 g, 0.5 mmol) was stirred at 105°C for 16 hours. After the reaction mixture was cooled to room temperature, the solvent was distilled off under reduced pressure. The resulting residue was dissolved in tert-butyl methyl ether, washed with an aqueous sodium carbonate solution, and the organic

phase was dried over sodium sulfate. The solvent was distilled off under reduced pressure to give aa373-b (20 g, 90%).

LCMS (ESI) m/z = 408 (M+H)+

Retention time: 1.05 min (Analytical condition SMD method_02)

[0592]

In a nitrogen atmosphere, zinc bromide (11.06 g, 49.09 mmol) was added to a DCM (200 mL) solution of aa373-b (20 g, 49.09 mmol) and triethylsilane (11.42 g, 98.18 mmol). The reaction mixture was stirred at room temperature for 48 hours, and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in an aqueous potassium carbonate solution and washed twice with hexane. The aqueous phase was adjusted to pH 2 with hydrochloric acid, and then extracted with ethyl acetate 3 times. After the organic phase was dried over sodium sulfate, the solvent was distilled off under reduced pressure to give aa373-c (15 g, 93%).

LCMS (ESI) m/z = 410 (M+H)+

Retention time: 0.98 min (Analytical condition SMD method_02)

[0593]

HOBt (5.7 g, 42.18 mmol) was added to a DMF (110 mL)-DCM (32 mL) solution of aa373-c (15.7 g, 38.35 mmol), and then WSCDI (8.82 g, 46.01 mmol) was added. The reaction mixture was stirred at room temperature for 15 minutes, and then cooled in an ice bath. Dimethylamine (1,90 g, 42.18 mmol) was added dropwise over 5 minutes. The reaction mixture was stirred while being ice-cooled until the reaction was complete, and then ethyl acetate was added. The resulting mixture was washed with 1 N hydrochloric acid, water, an aqueous sodium hydrogen carbonate solution, and brine. After the organic phase was dried over sodium sulfate, the solvent was distilled off under reduced pressure to give aa373-d (13 g, 78%).

LCMS (ESI) m/z = 437 (M+H)+

Retention time: 1.86 min (Analytical condition SMD method_02)

[0594]

In a nitrogen atmosphere, phenylsilane (0.343 mL, 2.72 mmol) was added dropwise to a DCM (7.8 mL) solution of aa373-d (1.70 g, 3.88 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.045 g, 0.039 mmol). The reaction mixture was stirred at room temperature for 30 minutes, and then diluted with tert-butyl methyl ether (17 mL). An aqueous sodium hydrogen carbonate solution (17 mL) was added to the resulting mixture to quench the reaction. The separated organic phase was extracted with water (8.5 mL), and DCM (17 mL) was added to the combined aqueous phase. Phosphoric acid (1.36 mL, 23.31 mmol) was added dropwise to the resulting mixture. After the organic phase was

separated, the aqueous phase was extracted with DCM (17 mL), and the combined organic phase was washed with brine (17 mL). After the organic phase was dried over sodium sulfate, the solvent was distilled off under reduced pressure to give aa373 (1.31 g, 85%).

LCMS (ESI) m/z = 397 (M+H)+

Retention time: 0.71 min (Analytical condition SQDFA05)

[0595]

2-Chlorotrityl chloride resin (1.25 mmol/g, 5.3 g, 6.62 mmol) and DCM (37 mL) were placed in a filter-equipped reaction vessel (60 mL), and left to stand still at room temperature for 45 minutes. After DCM was removed by applying nitrogen pressure, a DCM (37 mL) solution of Compound aa373 (1.31 g, 3.31 mmol), DIPEA (2.77 mL, 15.9 mmol), and methanol (1.07 mL, 26.5 mmol) was added to the reaction vessel, and the reaction vessel was shaken at room temperature for 60 minutes. After the reaction solution was removed by applying nitrogen pressure, a DCM (37 mL) solution of DIPEA (2.77 mL, 15.9 mmol) and methanol (7.5 mL, 185 mmol) was added to the reaction vessel, and the reaction vessel was shaken at room temperature for 90 minutes. After the reaction solution was removed by applying nitrogen pressure, DCM (37 mL) was added, mixed, and then discharged by applying nitrogen pressure. This resin washing operation using DCM was repeated 5 times in total, and the resulting resin was dried under reduced pressure overnight to give aa373-resin (6.07 g).

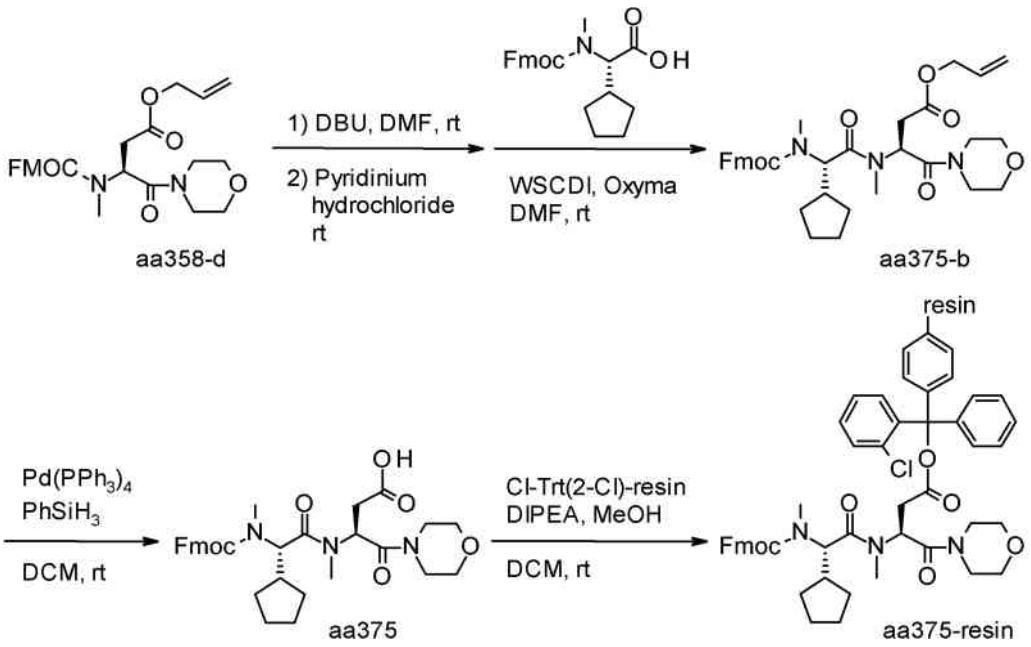
[0596]

The amount of supported amino acid on the resin was calculated as follows.

The resulting Compound aa373-resin (10 mg) was placed in a reaction vessel, DMF (4 mL) was added, and the reaction vessel was shaken at room temperature for 30 minutes. Then, DBU (40 μL) was added, and the reaction vessel was shaken at 30°C for 15 minutes. Then, DMF was added to the reaction mixture to 10 mL, and 80 μL of this solution was diluted with DMF so as to have a liquid volume of 1 mL. The resulting diluted solution was analyzed by LC/MS (injection volume: 5 μL), and the amount of supported aa373 was calculated to be 0.404 mmol/g from the UV area value of dibenzofulvene (294 nm: 4211.62; 304 nm: 3791.08). Using a calibration curve created based on the UV area values of dibenzofulvene at wavelengths of 294 nm and 304 nm on each measurement day utilizing, as a standard substance, a mixed solution of Fmoc-Gly-OH (purchased from a commercial supplier) having a known concentration and DBU, the average value of the supported amounts calculated for each wavelength was regarded as the amount of supported resin.

[0597]

Synthesis of Compound aa375-resin



[0598]

In a nitrogen atmosphere, DBU (3.15 mL, 20.90 mmol) was added dropwise to a dehydrated DMF (50 mL) solution of aa358-d (10 g, 20.90 mmol) at room temperature, and the mixture was stirred for 10 minutes. Pyridine hydrochloride (2.66 g, 22.99 mmol) was added to the reaction mixture at room temperature, and the mixture was stirred for 10 minutes. A separately prepared active ester solution (as described below) was added to the reaction mixture at room temperature, and then DIPEA (4.01 mL, 22.99 mmol) was added dropwise. After the resulting reaction mixture was stirred at room temperature for 4 hours and 15 minutes, ethyl acetate (100 mL), hexane (20 mL), and 1 N hydrochloric acid (100 mL) were added. The resulting mixture was extracted with ethyl acetate-hexane (5:1) (total amount of organic phase of about 300 mL), the organic phase was washed with 1 N hydrochloric acid (100 mL), water (100 mL), an aqueous sodium hydrogen carbonate solution (100 mL x 2), and brine (100 mL), dried over sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting crude product was purified by normal phase silica gel chromatography (hexane/ethyl acetate). This was dissolved in TBME (100 mL) and washed with an aqueous potassium carbonate solution (1 w/v%, 50 mL). The organic phase was washed with saturated brine/water (1/1, 50 mL) and dried over sodium sulfate, and the solvent was distilled off under reduced pressure to give aa375-b (9.98 g, 81%).

[0599]

The active ester solution was prepared as follows.

In a nitrogen atmosphere, dehydrated DMF (55 mL) was added to a mixture of (αS)-α-[[(9H-fluoren-9-ylmethoxy)carbonyl]methylamino]cyclopentaneacetic acid (7.53 g, 19.85 mmol), WSCI·HCl (5.21 g, 27.2 mmol), and Oxyma (3.56 g, 25.08 mmol) at room temperature

and stirred for 40 minutes, and the resulting reaction mixture was used as an active ester solution.

LCMS (ESI) m/z = 618 (M+H)+

Retention time: 0.96 min (Analytical condition SQDFA05)

[0600]

In a nitrogen atmosphere, dehydrated DCM (15 mL) was added to a mixture of aa375-b (9.90 g, 16.03 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.185 g, 0.16 mmol), and the mixture was stirred at room temperature. Phenylsilane (1.38 mL, 11.22 mmol) was added dropwise to the resulting solution. The resulting reaction mixture was stirred for 30 minutes, TBME (100 mL) was added, and then an aqueous sodium hydrogen carbonate solution (obtained by diluting a saturated aqueous solution by 2-fold) (100 mL) was slowly added dropwise to quench the reaction. The resulting mixture was extracted twice with water (total amount of aqueous phase of about 150 mL), and then DCM (100 mL) and phosphoric acid (5.6 mL) were added to the aqueous phase. The resulting mixture was extracted twice with DCM (total amount of organic phase of about 200 mL), the organic phase was washed with brine (80 mL x 2) and dried over sodium sulfate, the solvent was distilled off under reduced pressure, and the resulting aa375 (9.57 g, quant.) was used in the next reaction.

LCMS (ESI) m/z = 578 (M+H)+

Retention time: 0.79 min (Analytical condition SQDFA05)

[0601]

2-Chlorotrityl chloride resin (1.36 mmol/g, 20.5 g, 15.07 mmol) and DCM (140 mL) were placed in a filter-equipped reaction vessel, and left to stand still at room temperature for 1 hour. After DCM was removed by applying nitrogen pressure, a DCM (140 mL) solution of Compound aa375 (9.50 g, 16.45 mmol), methanol (5.32 mL, 132 mmol), and DIPEA (13.8 mL, 79 mmol) was added to the reaction vessel, and the reaction vessel was shaken at 25°C at 60 rpm for 60 minutes. After the reaction solution was removed by applying nitrogen pressure, a DCM (140 mL) solution of methanol (20 mL, 493 mmol) and DIPEA (13.8 mL, 79 mmol) was added to the reaction vessel, and the reaction vessel was shaken at 25°C at 60 rpm for 60 minutes. After the reaction solution was removed by applying nitrogen pressure, DCM (140 mL) was added, mixed, and then discharged by applying nitrogen pressure. This resin washing operation with DCM was repeated 5 times in total, and the resulting resin was dried under reduced pressure for 1 day to give aa375-resin (26.89 g).

[0602]

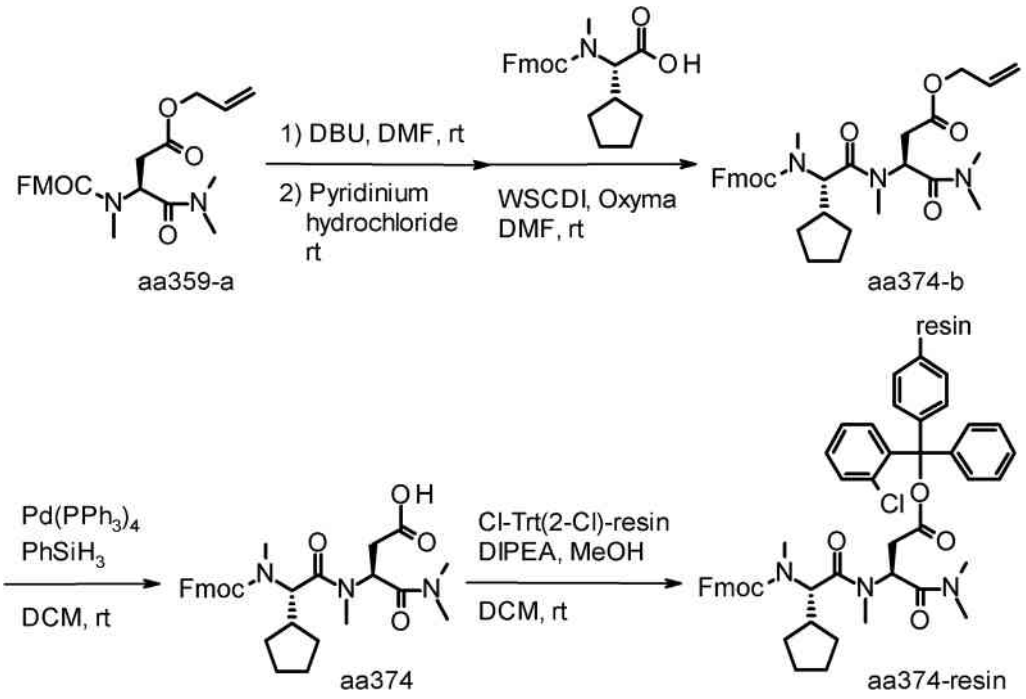
The amount of suppored amino acid on the resin was calculated as follows.

The resulting compound aa375-resin (10 mg) was placed in a reaction vessel, DMF (2 mL) was added, and the mixture was left to stand still at room temperature for 1 hour. Then,

DBU (40 μL) was added, and the reaction vessel was shaken at 25°C for 30 minutes. Then, DMF (8 mL) was added to the reaction mixture, and 1 mL of this solution was diluted with DMF (11.5 mL). The absorbance (294 nm) of the resulting diluted solution was measured (measured with Shimadzu UV-1600PC (cell length 1.0 cm)), and thus the amount of supported Compound aa375 was calculated to be 0.415 mmol/g.

[0603]

Synthesis of Compound aa374-resin



[0604]

Using aa359-a as a starting material, aa074-b (5.0 g, 43%) was obtained in the same manner as the synthesis of Compound aa0375-b.

LCMS (ESI) m/z = 576.5 (M+H)+

Retention time: 1.02 min (Analytical condition SQDFA05)

[0605]

Using the resulting aa374-b, aa074 (0.786 g, 92%) was obtained under the same reaction conditions as the synthesis of Compound aa375.

LCMS (ESI) m/z = 536 (M+H)+

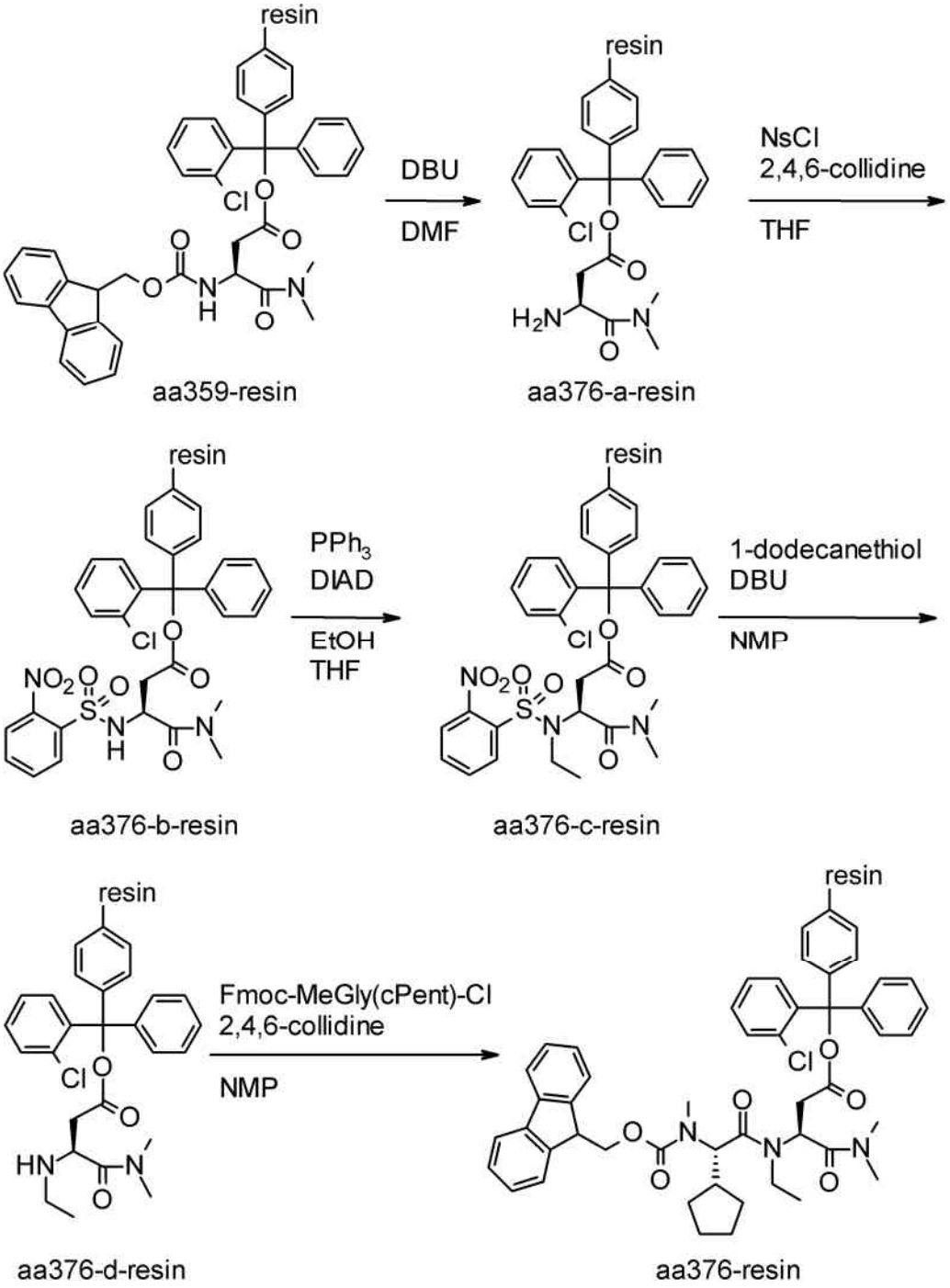
Retention time: 0.85 min (Analytical condition SQDFA05)

[0606]

Using the resulting aa374, aa374-resin (2.72 g) was obtained under the same reaction conditions as the synthesis of Compound aa375-resin. The supported amount calculated in the same manner as aa375-resin was 0.345 mmol/g.

[0607]

Synthesis of Compound aa376-resin



[0608]

Compound aa359-resin (10 g, 0.362 mmol/g, 3.62 mmol) and DCM (100 mL) were added to a filter-equipped reaction vessel to swell the resin. After DCM was removed, the resin was washed 4 times with DMF (100 mL). A DMF solution of DBU (2% v/v, 60 mL) was added, the mixture was shaken for 5 minutes at room temperature, and then the reaction solution was removed. The resin was washed 4 times with NMP (100 mL), and washed with a DCM solution (100 mL) of triethylamine hydrochloride (1.57 g, 11.4 mmol). The resin was washed 4

times with DCM (100 mL) and 4 times with THF (100 mL) to give the resin-supported Compound aa376-a.

[0609]

A THF solution (100 mL) of nosyl chloride (3.66 g, 16.5 mmol) and 2,4,6-cholidine (6.60 mL, 49.6 mmol) were added thereto, and the mixture was shaken at room temperature for 3 hours. Then, the reaction solution was removed, and the resin was washed 4 times with THF (100 mL) and washed 4 times with DCM (100 mL) to give the resin-supported Compound aa376-b. The amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of the resin-supported Compound aa376-b, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 347 (M+H)+

Retention time: 0.45 min (Analytical condition SQDFA05)

[0610]

Then, 6 g of this Compound 376-b-resin was weighed out, and swelled by adding DCM (60 mL). After DCM was removed, the resin was washed 3 times with THF (42 mL). A THF solution (20 mL) of DIAD (2.11 mL, 10.9 mmol) was added to a THF solution (20 mL) of triphenylphosphine (2.85 g, 10.9 mmol), and the mixture was shaken for 15 minutes. Ethanol (1.27 mL, 21.7 mmol) was added thereto, and the mixture was left to stand still for 5 minutes. This was added to the resin, the mixture was shaken at room temperature for 1 hour, and then the reaction solution was removed. The resin was washed 4 times with THF (42 mL) and washed 4 times with DCM (42 mL) to give the resin-supported Compound aa376-c. The amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of the resin-supported Compound aa376-c, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 375 (M+H)+

Retention time: 0.56 min (Analytical condition SQDFA05)

[0611]

DCM (60 mL) was added to swell this Compound aa376-c-resin. After DCM was removed, the resin was washed 3 times with NMP (42 mL). An NMP solution of DBU (1.64 mL, 10.9 mmol) and an NMP solution (20 mL) of 1-dodecanethiol (4.93 mL, 21.7 mmol) were added, and the mixture was shaken at 40°C for 1 hour. Then, the reaction solution was removed, and the resin was washed 4 times with NMP (42 mL) and washed 4 times with DCM (42 mL). This was washed 8 times with DMF (42 mL) and washed 4 times with DCM (42 mL) to give the resin-supported Compound aa376-d. The amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of the resin-supported Compound aa376-d, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 189 (M+H)+

Retention time: 0.14 min (Analytical condition SQDFA05)

[0612]

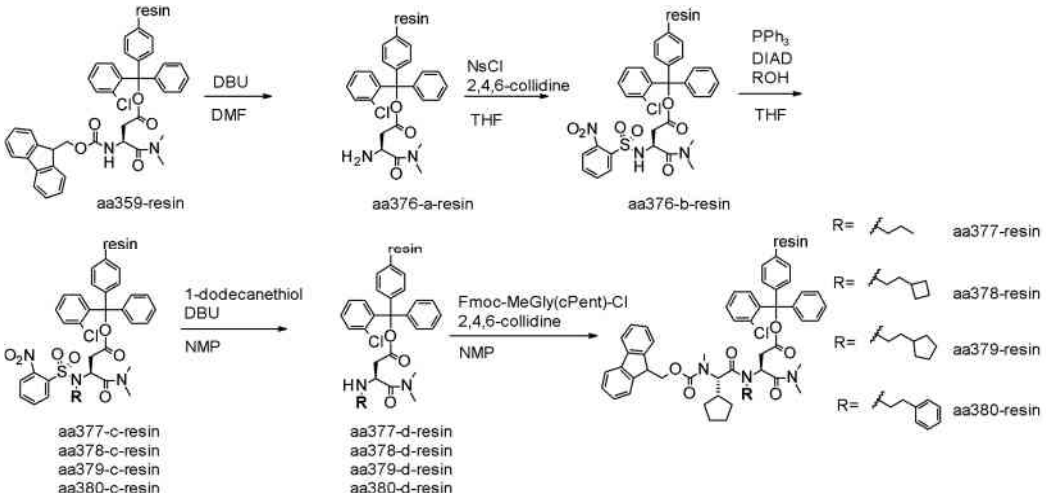
Then, 5 g of this Compound 376-d-resin was weighed out, and swelled by adding DCM (50 mL). After DCM was removed, the resin was washed 4 times with NMP (50 mL). Compound aa330 (Fmoc-MeGly(cPent)-OH, 2.75 g, 7.24 mmol) was dissolved in DCM (72 mL), thionyl chloride (1.32 mL, 18.1 mmol) and DMF (0.056 mL, 0.724 mmol) were added thereto, and the mixture was stirred at room temperature for 2 hours. After the solvent was distilled off from this under reduced pressure, NMP (70 mL) and 2,4,6-cholidine (2.4 mL, 18.1 mmol) were added. This was added to the resin, and the mixture was shaken at 40°C for 1.5 hours. Then, the reaction solution was removed, and the resin was washed 4 times with NMP (50 mL) and washed 4 times with DCM (50 mL) to give the resin-supported Compound aa376. The amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of the resin-supported Compound aa376, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 551 (M+H)+

Retention time: 0.86 min (Analytical condition SQDFA05)

[0613]

Synthesis of Compounds aa377-resin, aa378-resin, aa379-resin, and aa380-resin



[0614]

In place of ethanol, the alcohols shown in Table 7 below were reacted with aa376-b-resin in the same manner as aa376-c-resin, and thus resin-supported aa377-c to aa380-c were obtained. Using them, resin-supported aa377-d to aa380-d were obtained in the same manner as aa376-d-resin. Using them, resin-supported aa377 to aa380 were synthesized in the same manner as aa376-resin. The amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of the resin-supported Compounds aa377 to aa380, and the structure was verified by LC/MS.

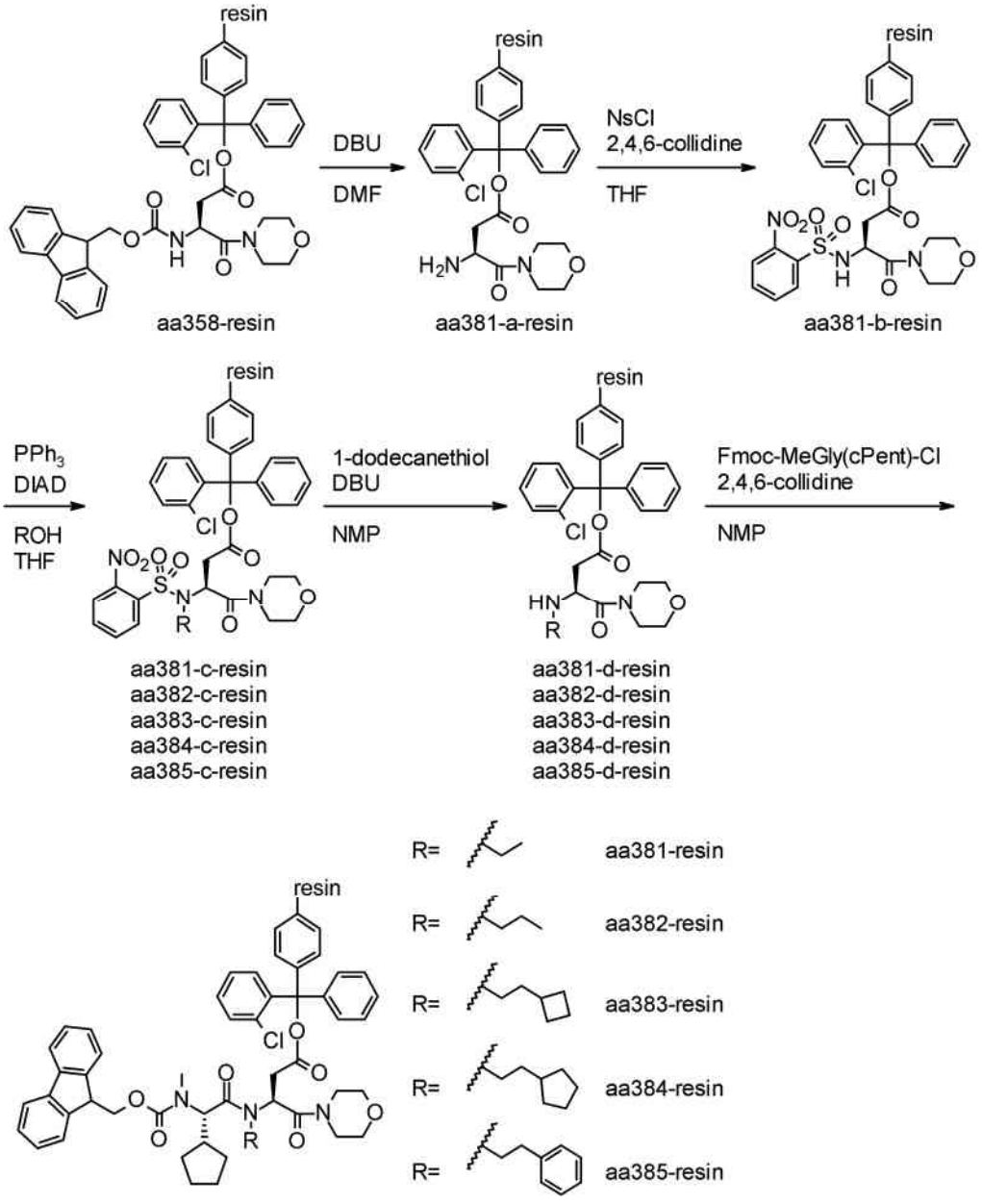
[0615]

[Table 7]

Intended product	Alcohol	LCMS (ESI) m/z (M+H)+	Retention time (Analytical condition SQDFA05)
Compound aa377-resin	1-propanol	565	0.92 Min
Compound aa378-resin	2-Cyclobutylethanol	605	1.03 Min
Compound aa379-resin	2-Cyclopentylethanol	619	1.07 Min
Compound aa380-resin	2-Phenylethanol	627	1.01 Min

[0616]

Synthesis of Compounds aa381-resin, aa382-resin, aa383-resin, aa384-resin, and aa385-resin



[0617]

Using aa358-resin in place of aa359-resin, resin-supported aa381-a was obtained in the same manner as aa376-a-resin. Using this compound, resin-supported aa381-b was obtained in the same manner as aa376-b-resin. Using this compound, resin-supported aa381-c to aa385-c were obtained in the same manner as aa376-c-resin or using alcohols shown in Table 8 below to react with the compound in place of ethanol. Using these compounds, resin-supported aa381-d to aa385-d were obtained in the same manner as aa376-d-resin. Using these compounds, resin-supported aa381 to aa385 were synthesized in the same manner as aa376-resin. The amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compounds aa381 to aa385, and the structure was verified by LC/MS.

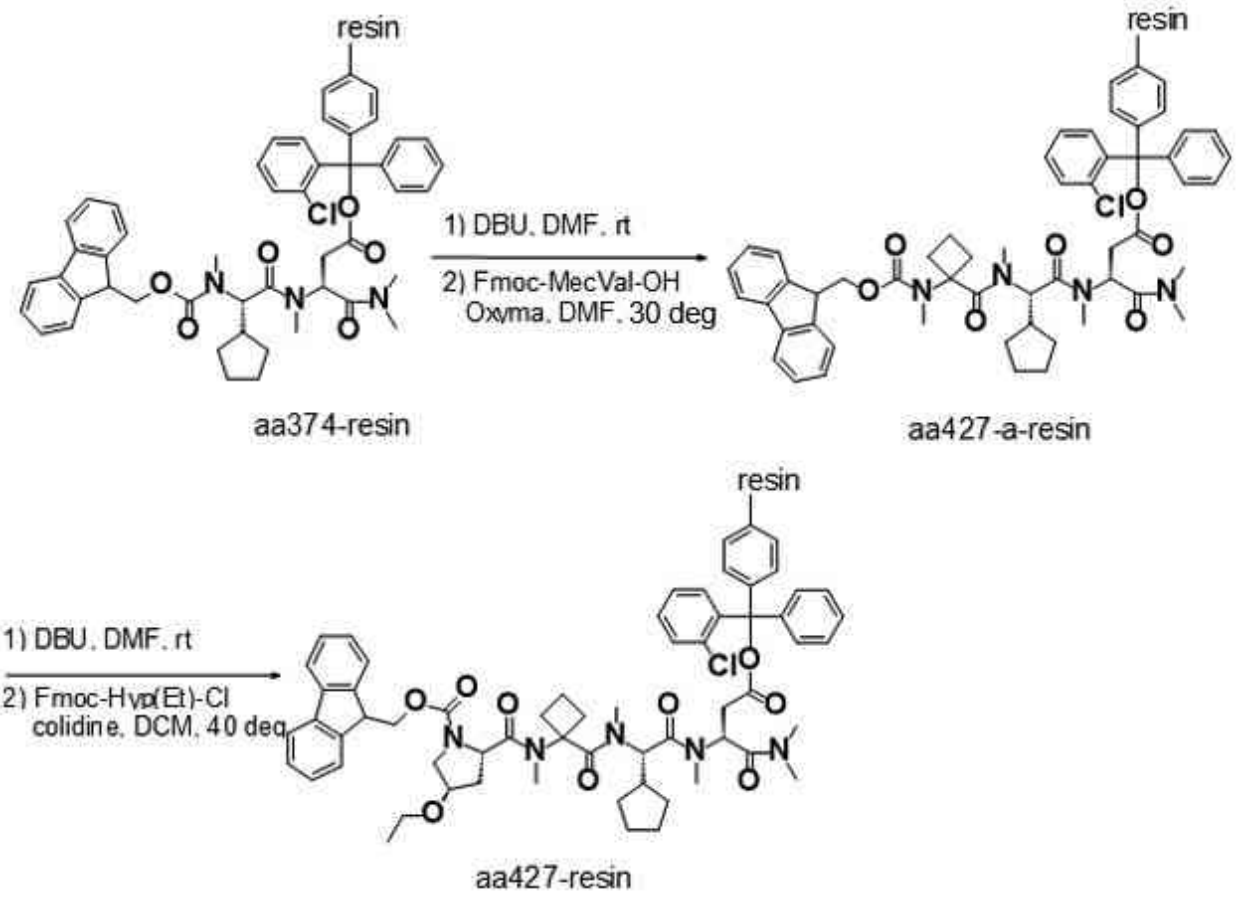
[0618]

[Table 8]

Intended product	Alcohol	LCMS(ESI) m/z (M+H)+	Retention time (Analytical condition SQDFA05)
Compound aa381-resin	ethanol	593	0.85
Compound aa382-resin	1-propanol	607	0.91
Compound aa383-resin	2-Cyclobutylethanol	647	1.02
Compound aa384-resin	2-Cyclopentylethanol	661	1.06
Compound aa385-resin	2-Phynylethanol	669	1.00

[0619]

Synthesis of Compound aa427-resin



[0620]

aa374-resin (0.420 mmol/g, 10 g) was placed in a filter-equipped reaction vessel, dichloromethane (100 mL) was added, and the mixture was shaken at room temperature for 5 minutes to swell the resin. After dichloromethane was removed with a filter, the resin was washed 4 times with DMF (100 mL). Subsequently, a 2% DBU/DMF solution (de-Fmoc solution: 60 mL) was added to the resin, and the mixture was shaken at room temperature for 10 minutes to carry out an Fmoc-removal reaction. After the de-Fmoc solution was removed, the resin was washed 6 times with DMF (100 mL). An Fmoc-MecVal-OH (Compound aa421) elongation reaction was carried out on the resulting resin. The elongation reaction was carried out by adding a solution obtained by mixing DIC (2.63 mL, 16.8 mmol) with a DMF solution (40 mL) of Fmoc-MecVal-OH (Compound aa421, 2.95 g, 8.40 mmol) and oxyma (597 mg, 4.20 mmol) to the resin, and shaking the mixture at 30°C for 86 hours. After the liquid phase of the elongation reaction was removed with a filter, the resin was washed 6 times with DMF (100 mL) and 6 times with dichloromethane (100 mL) and dried to give aa427-a-resin.

[0621]

Dichloromethane (100 mL) was added to the resulting aa427-a-resin, and the mixture was shaken at room temperature for 5 minutes to swell the resin. After dichloromethane was

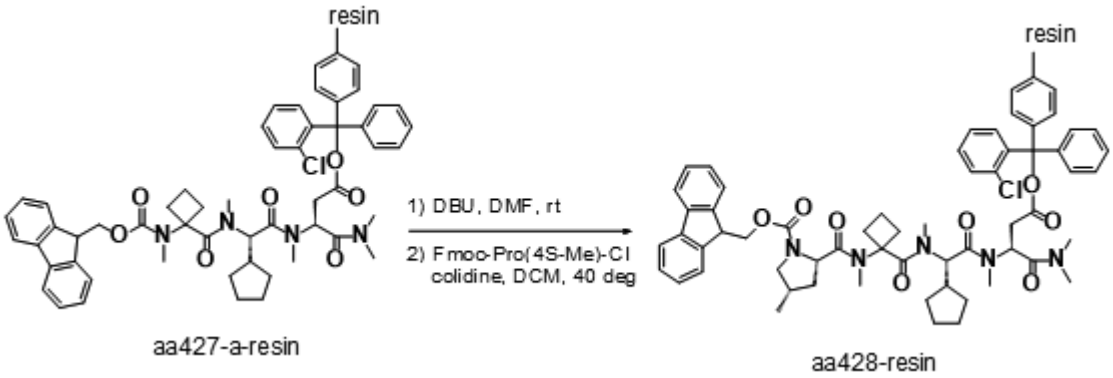
removed with a filter, the resin was washed 4 times with DMF (100 mL). Subsequently, a 2% DBU/DMF solution (de-Fmoc solution: 60 mL) was added to the resin, and the mixture was shaken at room temperature for 10 minutes to carry out an Fmoc-removal reaction. After the de-Fmoc solution was removed, the resin was washed 6 times with DMF (100 mL) and 6 times with dichloromethane (100 mL). An Fmoc-Hyp(Et)-OH (Compound aa086) elongation reaction was carried out on the resulting resin. The elongation reaction was carried out by, first, adding thionyl chloride (3.07 mL, 42.0 mmol) and DMF (0.131 mL, 1.68 mmol) to a DCM solution (84 mL) of Fmoc-Hyp(Et)-OH (Compound aa086, 6.41 g, 16.8 mmol), and stirring the mixture at room temperature for 4 hours in a nitrogen atmosphere. The solvent and thionyl chloride were distilled off under reduced pressure to give an acid chloride of Fmoc-Hyp(Et)-OH. This acid chloride was dissolved in DCM (100 mL) and mixed with collidine (5.59 mL, 42.0 mmol), the resulting solution was added to the resin, and the mixture was shaken at 40°C for 13 hours. After the liquid phase of the elongation reaction was removed with a filter, the resin was washed 6 times with DMF (100 mL) and 6 times with dichloromethane (100 mL) and dried to give aa427-resin. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa427, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 789 (M+H)+

Retention time: 0.84 min (Analytical condition SQDFA05)

[0622]

Synthesis of Compound aa428-resin



[0623]

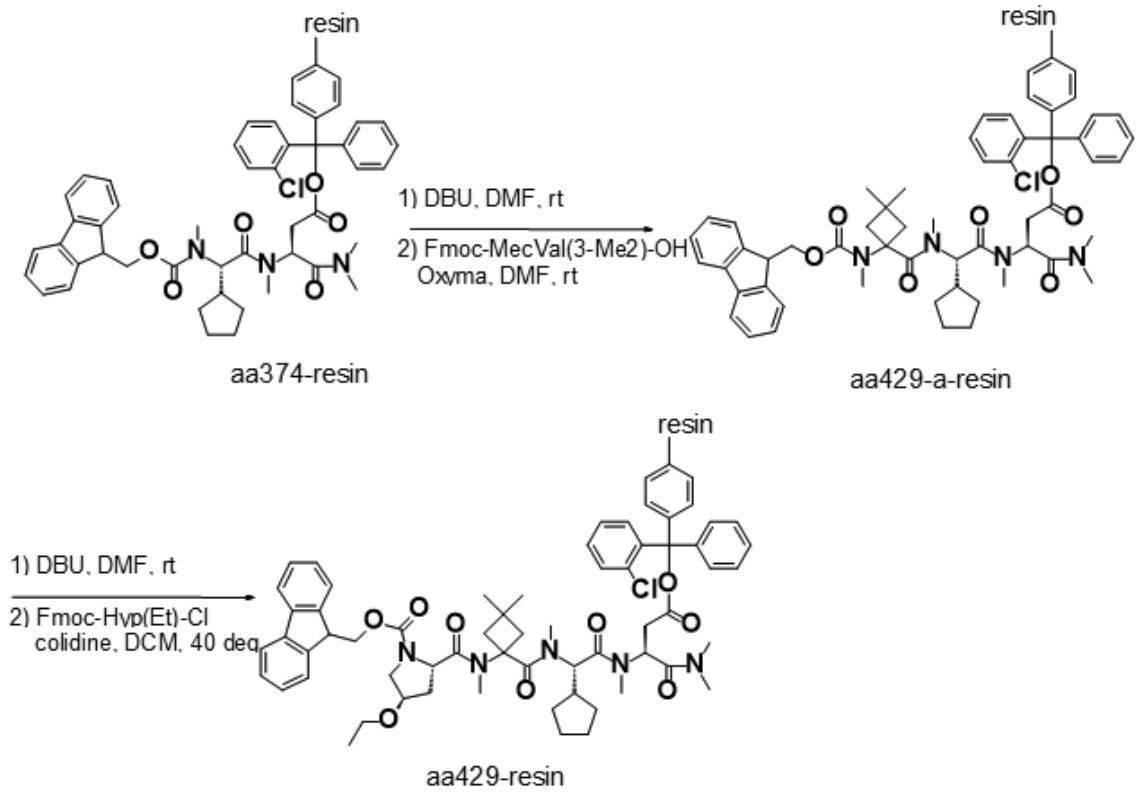
Using aa427-a-resin, aa428-resin was obtained in the same manner as Compound aa427-resin except that Fmoc-Pro(4S-Me)-OH (Compound aa239) was used in place of Fmoc-Hyp(Et)-OH. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa428, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 759 (M+H)+

Retention time: 0.85 min (Analytical condition SQDFA05)

[0624]

Synthesis of Compound aa429-resin



[0625]

Using aa374-resin, aa429-a-resin was obtained in the same manner as Compound aa427-a-resin except that Fmoc-MecVal(3-Me2)-OH (Compound aa420) was used in place of Fmoc-MecVal-OH.

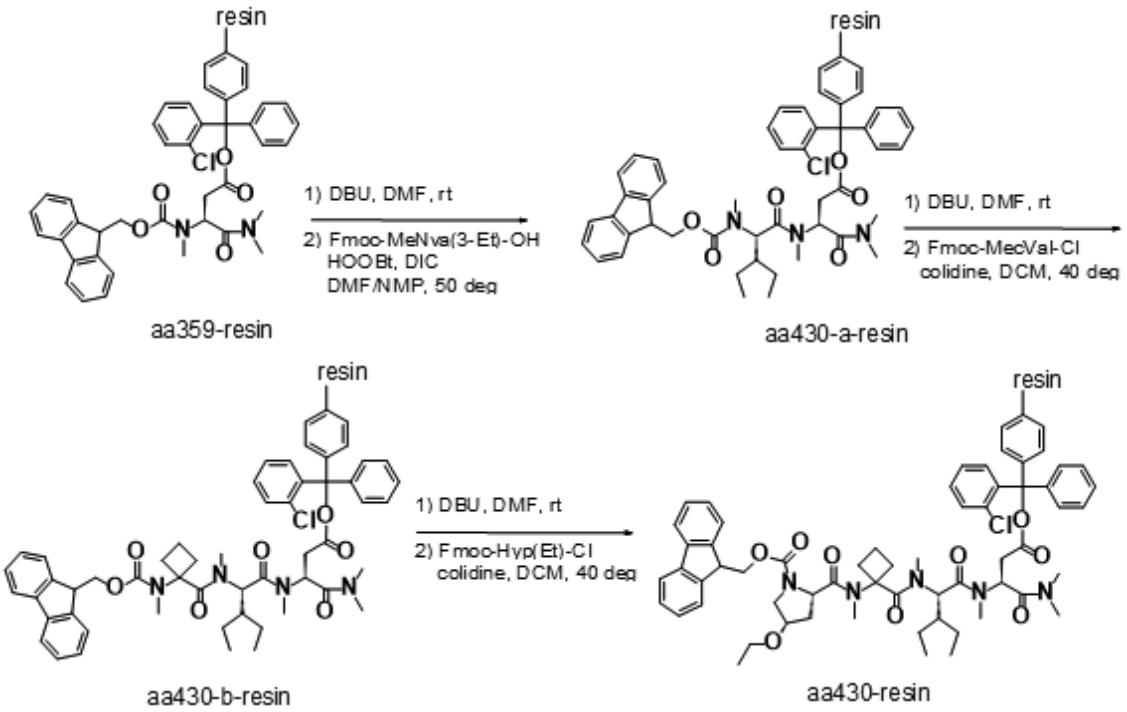
Using the resulting aa429-a-resin, aa429-resin was obtained in the same manner as Compound aa427-resin. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa429, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 817 (M+H)+

Retention time: 0.94 min (Analytical condition SQDFA05)

[0626]

Synthesis of Compound aa430-resin



[0627]

aa359-resin (0.320 mmol/g, 5 g) was placed in a filter-equipped reaction vessel, dichloromethane (50 mL) was added, and the mixture was shaken at room temperature for 5 minutes to swell the resin. After dichloromethane was removed with a filter, the resin was washed 4 times with DMF (50 mL). Subsequently, a 2% DBU/DMF solution (de-Fmoc solution: 30 mL) was added to the resin, and the mixture was shaken at room temperature for 10 minutes to carry out an Fmoc-removal reaction. After the de-Fmoc solution was removed, the resin was washed 6 times with DMF (50 mL). An Fmoc-MeNva(3-Et)-OH (Compound aa331) elongation reaction was carried out on the resulting resin. The elongation reaction was carried out by adding to the resin a solution obtained by mixing an NMP solution (15 mL) of Fmoc-MeNva(3-Et)-OH (Compound aa331, 2.44 g, 6.40 mmol) and HOOBt (653 mg, 4.00 mmol) with a DMF solution (15 mL) of DIC (1.50 mL, 9.60 mmol), shaking the mixture at 50°C for 14 hours, removing the liquid phase of the elongation reaction with a filter, again adding to the resin a solution obtained by mixing an NMP solution (15 mL) of Fmoc-MeNva(3-Et)-OH (Compound aa331, 2.44 g, 6.40 mmol) and HOOBt (653 mg, 4.00 mmol) with a DMF solution (15 mL) of DIC (1.50 mL, 9.60 mmol), and shaking the mixture at 50°C for 14 hours. After the liquid phase of the elongation reaction was removed with a filter, the resin was washed 4 times with DMF (100 mL) and 4 times with dichloromethane (100 mL) and dried to give aa430-a-resin.

[0628]

Using the resulting aa430-a-resin, aa430-b-resin was obtained in the same manner as Compound aa427-resin except that Fmoc-MecVal-OH was used in place of Fmoc-Hyp(Et)-OH.

[0629]

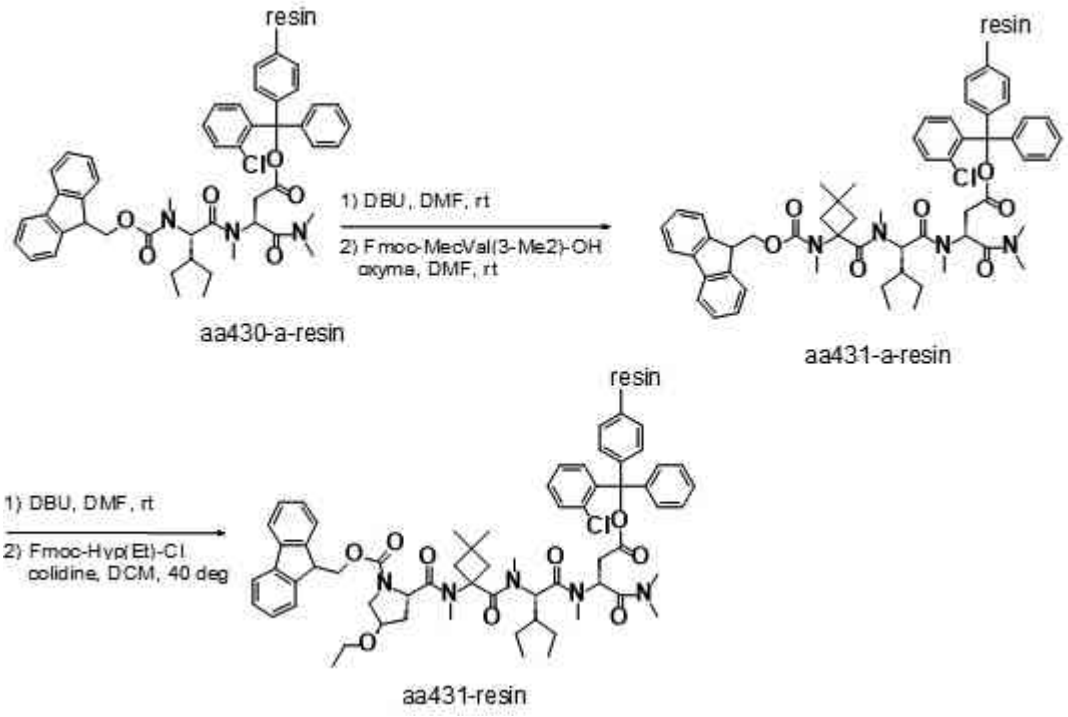
Using the resulting aa430-b-resin, aa430-resin was obtained in the same manner as Compound aa427-resin. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa430, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 791 (M+H)+

Retention time: 0.88 min (Analytical condition SQDFA05)

[0630]

Synthesis of Compound aa431-resin



[0631]

Using aa430-a-resin, aa431-a-resin was obtained in the same manner as Compound aa427-a-resin except that Fmoc-MecVal(3-Me2)-OH (Compound aa420) was used in place of Fmoc-MecVal-OH.

[0632]

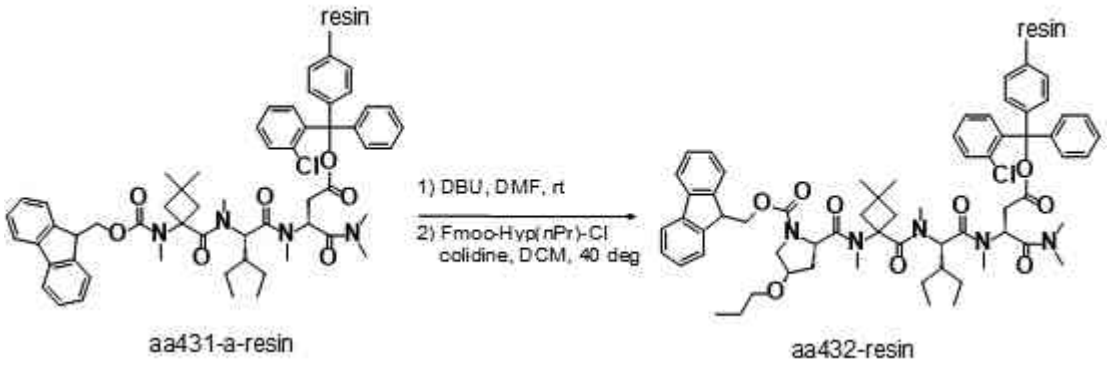
Using the resulting aa431-a-resin, aa431-resin was obtained in the same manner as Compound aa427-resin. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa431, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 819 (M+H)+

Retention time: 0.98 min (Analytical condition SQDFA05)

[0633]

Synthesis of Compound aa432-resin



aa431-a-resin aa432-resin

[0634]

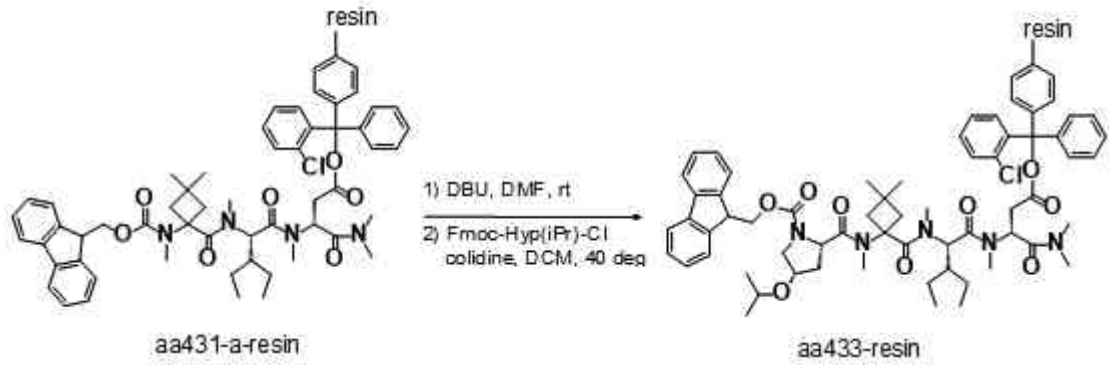
Using aa431-a-resin, aa432-resin was obtained in the same manner as Compound aa427-resin except that Fmoc-Hyp(nPr)-OH (Compound aa246) was used in place of Fmoc-Hyp(Et)-OH. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa432, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 833 (M+H)+

Retention time: 1.03 min (Analytical condition SQDFA05)

[0635]

Synthesis of Compound aa433-resin



aa431-a-resin aa433-resin

[0636]

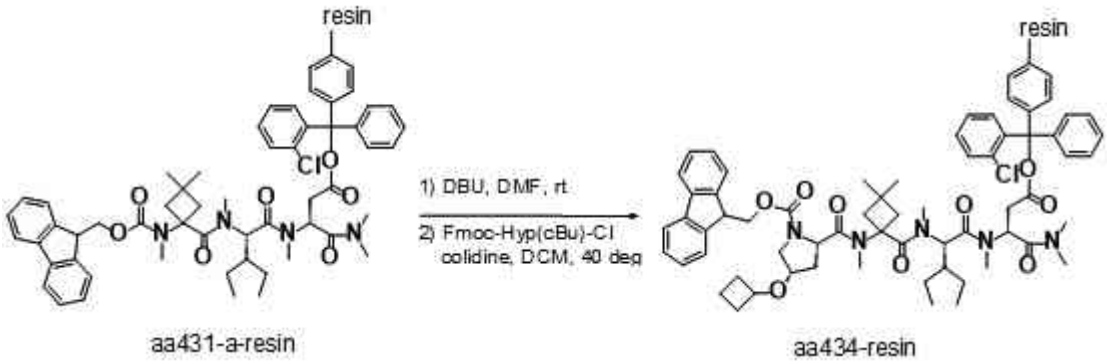
Using aa431-a-resin, aa433-resin was obtained in the same manner as Compound aa427-resin except that Fmoc-Hyp(iPr)-OH (Compound aa416) was used in place of Fmoc-Hyp(Et)-OH. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa433, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 833 (M+H)+

Retention time: 1.01 min (Analytical condition SQDFA05)

[0637]

Synthesis of Compound aa434-resin



aa431-a-resin aa434-resin

[0638]

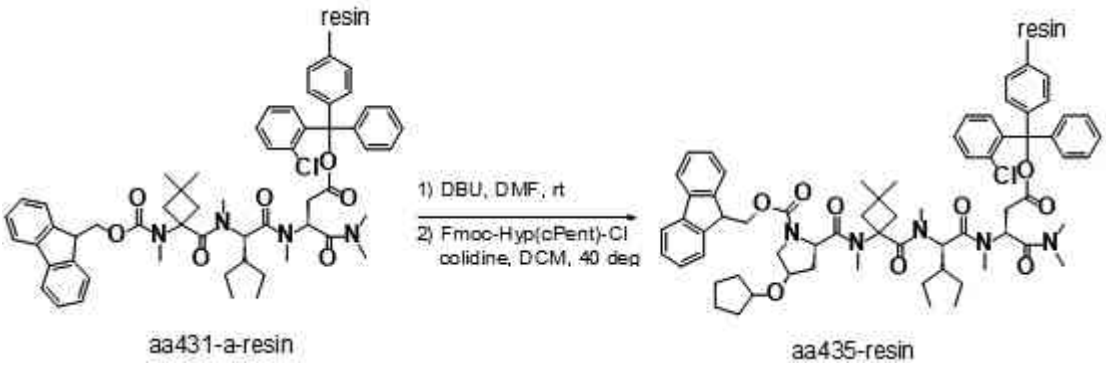
Using aa431-a-resin, aa434-resin was obtained in the same manner as Compound aa427-resin except that Fmoc-Hyp(cBu)-OH (Compound aa415) was used in place of Fmoc-Hyp(Et)-OH. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa434, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 845 (M+H)+

Retention time: 1.04 min (Analytical condition SQDFA05)

[0639]

Synthesis of Compound aa435-resin



aa431-a-resin aa435-resin

[0640]

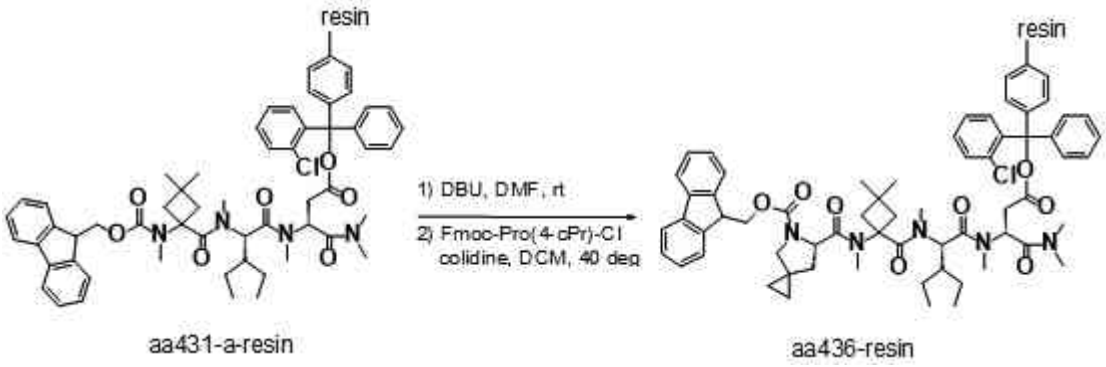
Using aa431-a-resin, aa435-resin was obtained in the same manner as Compound aa427-resin except that Fmoc-Hyp(cPent)-OH (Compound aa414) was used in place of Fmoc-Hyp(Et)-OH. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa435, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 859 (M+H)+

Retention time: 1.08 min (Analytical condition SQDFA05)

[0641]

Synthesis of Compound aa436-resin



aa431-a-resin aa436-resin

[0642]

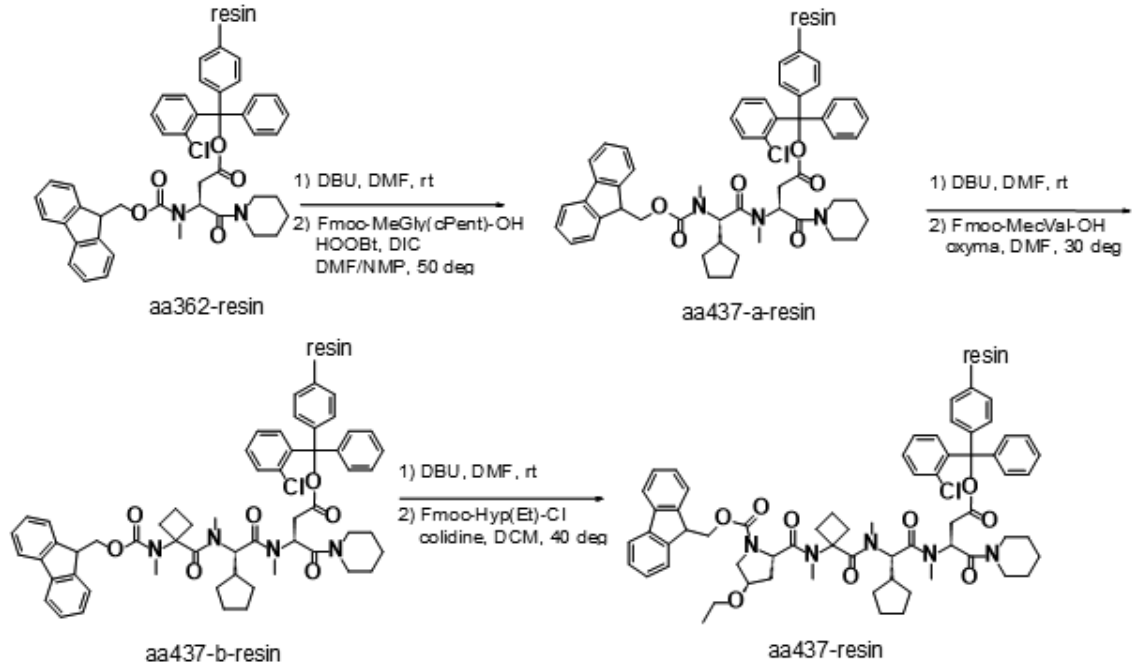
Using aa431-a-resin, aa436-resin was obtained in the same manner as Compound aa427-resin except that Fmoc-Pro(4-cPr)-OH (Compound aa278) was used in place of Fmoc-Hyp(Et)-OH. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa436, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 801 (M+H)+

Retention time: 0.99 min (Analytical condition SQDFA05)

[0643]

Synthesis of Compound aa437-resin



aa362-resin aa437-a-resin aa437-b-resin aa437-resin

[0644]

Using aa362-resin as a starting material, aa437-a-resin was obtained in the same manner as Compound aa430-a-resin except that Fmoc-MeGly(cPent)-OH (Compound aa330) was used in place of Fmoc-MeNva(3-Et)-OH.

[0645]

Using the resulting aa437-a-resin, aa437-b-resin was obtained in the same manner as Compound aa427-a-resin.

[0646]

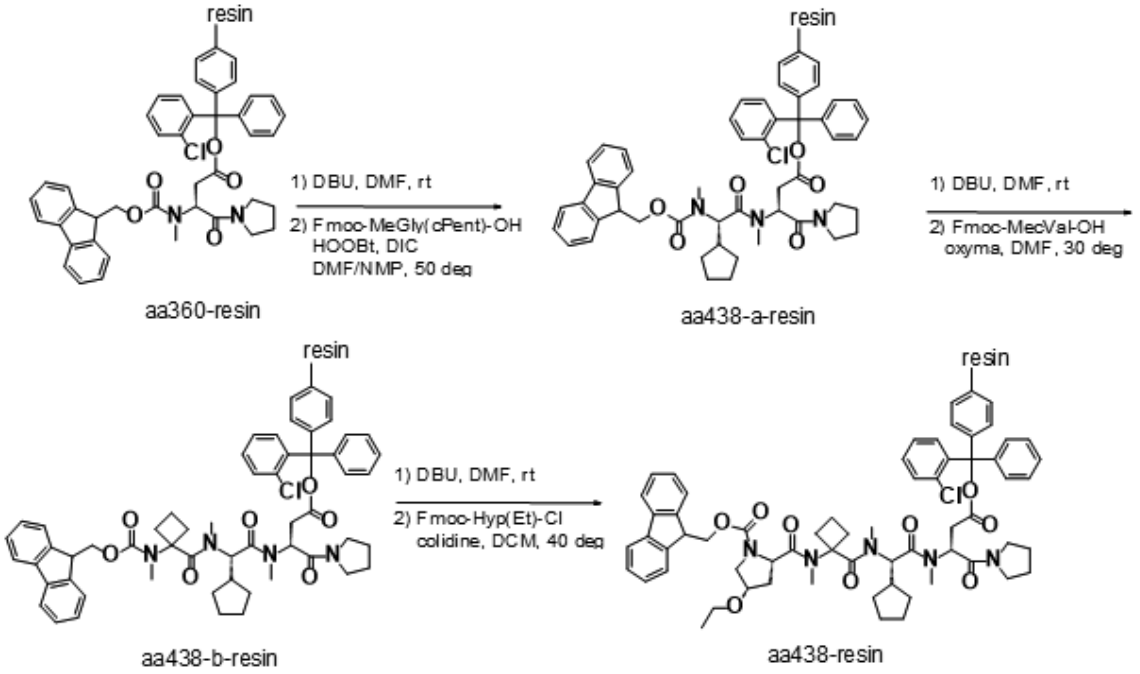
Using the resulting aa437-b-resin, aa437-resin was obtained in the same manner as Compound aa427-resin. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa437, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 829 (M+H)+

Retention time: 0.93 min (Analytical condition SQDFA05)

[0647]

Synthesis of Compound aa438-resin



[0648]

Using aa360-resin as a starting material, aa438-a-resin was obtained in the same manner as Compound aa430-a-resin except that Fmoc-MeGly(cPent)-OH (Compound aa330) was used in place of Fmoc-MeNva(3-Et)-OH.

[0649]

Using the resulting aa438-a-resin, aa438-b-resin was obtained in the same manner as Compound aa427-a-resin.

[0650]

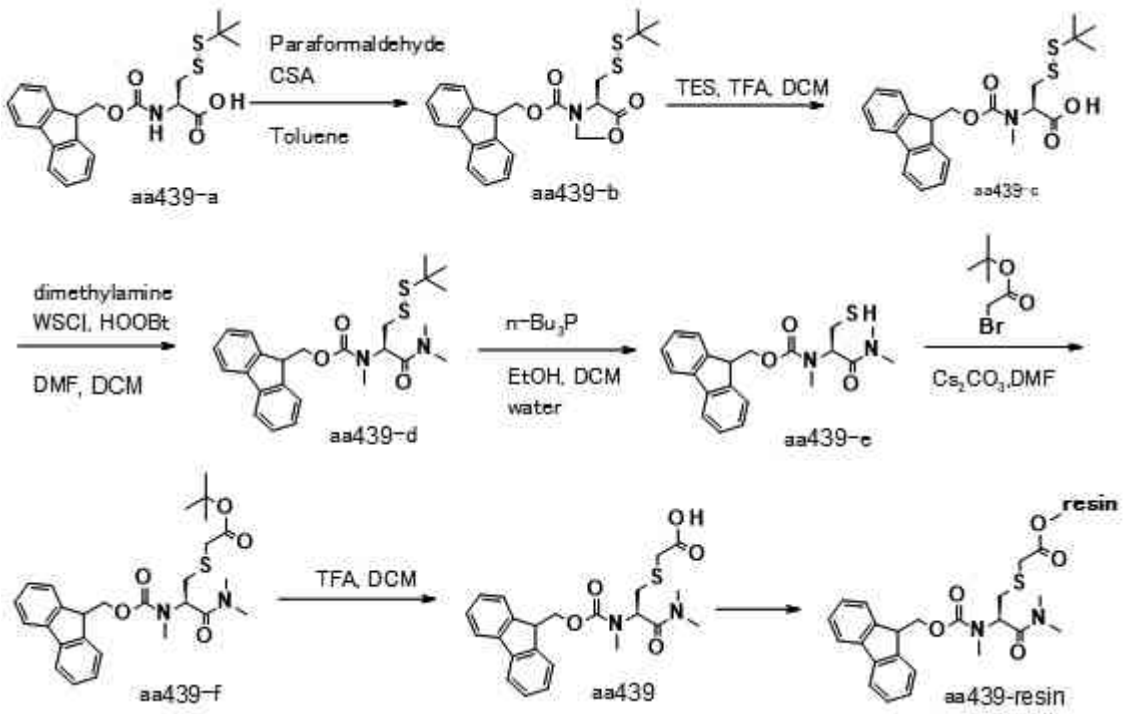
Using the resulting aa438-b-resin, aa438-resin was obtained in the same manner as Compound aa427-resin. Amino acid was cleaved from the resin by TFE/DCM (1/1) using a small amount of resin-supported Compound aa438, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 815 (M+H)+

Retention time: 0.87 min (Analytical condition SQDFA05)

[0651]

Synthesis of Compound aa439-resin



[0652]

A toluene (200 mL) mixture of (2R)-3-(tert-butyldisulfanyl)-2-[9H-fluoren-9-ylmethoxycarbonyl(methyl)amino]propanonic acid (20.0 g, 46.3 mmol), (+)-camphorsulfonic acid (752.6 mg, 3.2 mmol, 0.07 eq), and paraformaldehyde (13.9 g, 463.4 mmol, 10.0 eq) was stirred at room temperature for 1 hour in a nitrogen atmosphere. The reaction solution was diluted with ethyl acetate, washed 3 times with an aqueous sodium hydrogen carbonate solution, and then washed with brine. The resulting organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give Compound aa439-b (23 g) as a crude product.

LCMS (ESI) m/z = 466.1 (M+Na)+

Retention time: 1.560 min (Analytical condition SMD method_20)

[0653]

Trifluoroacetic acid (120 mL) was added to a mixed solution of Compound aa439-b (23 g) obtained above and triethylsilane (60.2 g, 518 mmol) in dichloromethane (120 mL) at room temperature in a nitrogen atmosphere, and the mixture was stirred for 40 hours. The solvent was distilled off from the reaction solution under reduced pressure, the resulting residue was purified by reverse phase column chromatography (C18, acetonitrile/water) to give Compound aa439-c (13 g, 63% in 2 steps).

LCMS (ESI) m/z = 446.1 (M+H)+

Retention time: 0.852 min (Analytical condition SMD method_30)

[0654]

Compound aa439-c (13.0 g, 29.2 mmol), WSCI·HCl (6.49 g, 33.84 mmol, 1.2 eq), and 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HOOBt) (5.23 g, 32.09 mmol, 1.1 eq) were added to a mixed solution of DMF (26 mL) and DCM (90 mL) at room temperature in a nitrogen atmosphere, and the mixture was stirred for 5 minutes. The resulting reaction solution was cooled to 0°C, dimethylamine (2 mol/L of THF solution, 15.60 mL, 31.2 mmol, 1.07 eq) was added dropwise, and the mixture was stirred at 0°C for 1 hour. The reaction solution was diluted with ethyl acetate, washed twice with hydrochloric acid (1 mol/L, 130 mL), washed once with water (130 mL), washed twice with an aqueous sodium hydrogen carbonate solution (130 mL), and washed once with brine (130 mL). The resulting organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by normal phase chromatography (petroleum ether/ethyl acetate) to give Compound aa439-d (12.1 g, 88%).

LCMS (ESI) m/z = 495.2 (M+Na)+

Retention time: 1.546 min (Analytical condition SMD method_20)

[0655]

Tri-n-butylphosphine (6.0 g, 29.7 mmol, 1.2 eq) was added dropwise to a mixed solution of Compound aa439-d (11.7 g, 24.7 mmol), ethanol (100 mL), DCM (150mL), and water (25 mL) at room temperature in a nitrogen atmosphere, and the mixture was stirred at room temperature for 3 hours. The reaction solution was extracted with dichloromethane (DCM), the resulting organic layer was washed with brine and dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure. The resulting residue was purified by normal phase chromatography (petroleum ether/ethyl acetate), and the resulting mixture was purified by reverse phase column chromatography (C18, acetonitrile/water) to give Compound aa439-e (3.03 g, 32%).

LCMS (ESI) m/z = 407.2 (M+Na)+

Retention time: 1.326 min (Analytical condition SMD method_20)

[0656]

A mixed solution of Compound aa439-e (2.80 g, 7.29 mmol) and tert-butyl bromoacetate (2.10 g, 10.77 mmol, 1.5 eq) in DMF (40 mL) was stirred at room temperature for 5 minutes, cesium carbonate (2.80 g, 8.59 mmol, 1.2 eq) was added thereto, and the mixture was stirred for 1 hour. The reaction solution was diluted with ethyl acetate, and washed with water. The resulting organic layer was dried over anhydrous sodium sulfate, and the solvent was

distilled off under reduced pressure to give Compound aa439-f (3.1 g) as a crude product. The resulting crude product was used in the next reaction without further purification.

LCMS (ESI) m/z = 499.3 (M+H)+

Retention time: 1.467 min (Analytical condition SMD method_20)

[0657]

Compound aa439-f (3.1 g) obtained above was dissolved in a mixed solution of trifluoroacetic acid (TFA) (30 mL) and dichloromethane (DCM) (30 mL), and stirred at room temperature for 2 hours in a nitrogen atmosphere. The solvent was distilled off from the reaction solution under reduced pressure, the resulting residue was purified by reverse phase column chromatography (C18, acetonitrile/water), and the resulting mixture was further purified by reverse phase high performance column chromatography (acetonitrile/water, containing TFA), and the resulting eluate was extracted with DCM. The resulting organic layer was washed successively with water and hydrochloric acid (1 mol/L), and the solvent was distilled off under reduced pressure to give Compound aa439 (1.79 g, 55% in 2 steps).

LCMS (ESI) m/z = 443.2 (M+H)+

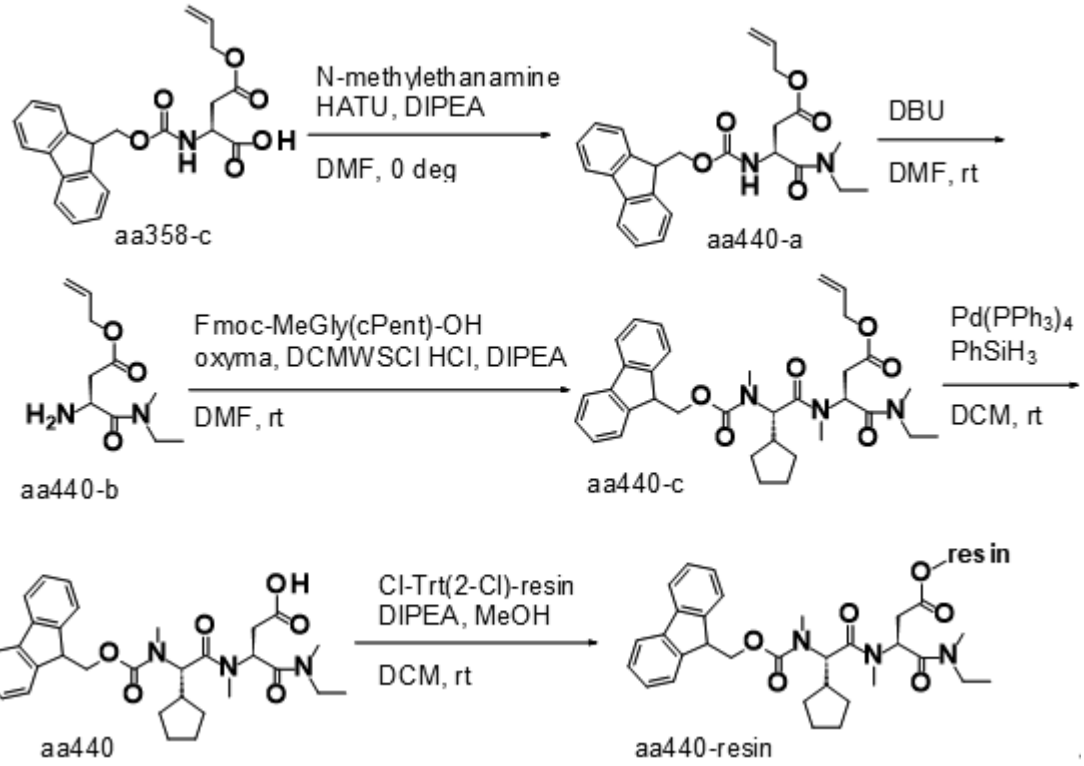
Retention time: 1.383 min (Analytical condition SMD method_31)

[0658]

Using Compound aa439 (0.46 g, 1.04 mmol), Compound aa439-resin (1.54 g, supported amount 0.336 mmol/g) was obtained in the same manner as synthesis of Compound aa358-resin.

[0659]

<u>Synthesis of Compound aa440-resin</u>



[0660]

After DIPEA (26.3 mL, 148 mmol) was added to a DMF solution (211 mL) of aa358-c (30.3 g, 74.0 mmol) at 0°C, HATU (30.9 g, 81.0 mmol) and N-methylethaneamine (6.97 mL, 81.0 mmol) were added. After being stirred at 0°C for 30 minutes, the mixture was diluted with toluene (300 mL), and 1 N hydrochloric acid (600 mL) was added. The organic layer was separated, washed with water (300 mL), washed with a 50% aqueous sodium hydrogen carbonate solution (300 mL), and washed with half brine (300 mL). The organic layer was dried over anhydrous sodium sulfate and filtered off, and the solvent was distilled off under reduced pressure to give Compound aa440-a as a crude product (36.6 g). The crude product was dissolved in toluene (211 mL), and DBU (11.0 mL, 74 mmol) was added at 0°C. After stirring at room temperature for 5 minutes, 1 N hydrochloric acid (333 mL) was added to separate the aqueous layer. After the aqueous layer was washed with toluene (333 mL), a 50% aqueous sodium hydroxide solution (7.5 mL) was added to adjust the pH to 8 to 9. The mixture was extracted 5 times with ethyl acetate (200 mL), and the organic layer was washed with half brine (333 mL). The organic layer was dried over anhydrous sodium sulfate and filtered off, and the solvent was distilled off under reduced pressure to give aa440-b as a crude product (12.6 g).

[0661]

Oxyma (9.41 g, 66.2 mmol) was added to a DMF solution (158 mL) of Fmoc-MeGly(cPent)-OH (Compound aa330, 21 g, 55.2 mmol) at 0°C. WSCI·HCl (14.8 g, 77 mmol)

was added thereto, and the mixture was stirred at room temperature for 30 minutes. A DMF solution (31 mL) of aa440-b (12.6 g, 55.2 mmol) and DIPEA (10.8 mL, 60.7 mmol) were added thereto, and the mixture was stirred at room temperature for 15 hours. Toluene (250 mL) and 0.5 N hydrochloric acid (250 mL) were added, and the organic layer was washed with a 50% aqueous sodium hydrogen carbonate solution (250 mL) and washed with half brine (250 mL). The organic layer was dried over anhydrous sodium sulfate and filtered off, the solvent was distilled off under reduced pressure, and the resulting residue was purified by silica gel chromatography (hexane-ethyl acetate) to give aa440-c (25.6 g, 59% in 3 steps).

LCMS (ESI) m/z = 612 (M+Na)+

Retention time: 3.27 min (Analytical condition SMD method_03)

[0662]

Phenylsilane (3.69 mL, 30.0 mmol) was added to a DCM solution (86 mL) of aa440-c (25.3 g, 42.9 mmol). Tetrakis(triphenylphosphine)palladium(0) (496 mg, 0.429 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. The mixture was diluted with TBME (250 mL), and extracted with a 50% aqueous sodium hydrogen carbonate solution (250 mL). The organic layer was further extracted with a 50% aqueous sodium hydrogen carbonate solution (125 mL), and phosphoric acid (17.9 mL, 323 mmol) was added to the combined aqueous layer to adjust the pH to 2 to 3. The mixture was extracted with DCM (250 mL), the organic layer was washed with half brine (250 mL), and the solvent was distilled off under reduced pressure to give aa440 as a crude product (23.6 g).

LCMS (ESI) m/z = 572 (M+Na)+

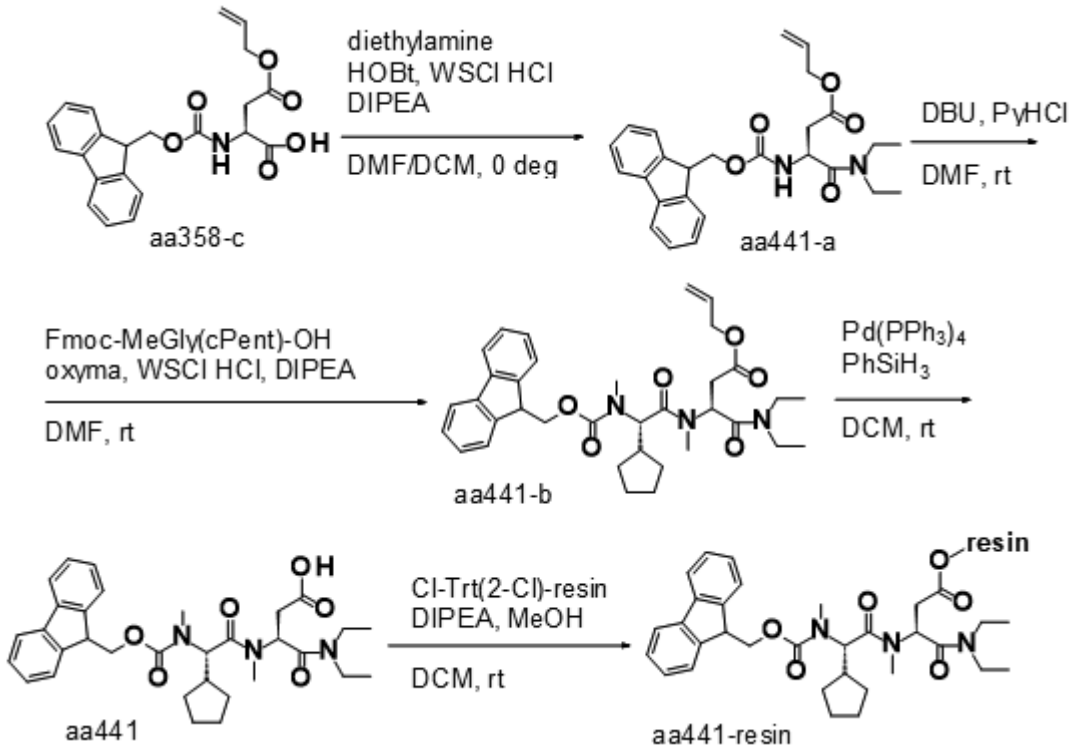
Retention time: 2.64 min (Analytical condition SMD method_03)

[0663]

Using the resulting aa440 (23.5 g, 42.8 mmol), aa440-resin (79.2 g) was obtained under the same reaction conditions as synthesis of Compound aa373-resin. The supported amount calculated in the same manner as aa373-resin was 0.333 mmol/g.

[0664]

Synthesis of Compound aa441-resin



[0665]

HOBt (7.30 g, 54.0 mmol) was added to a DMF solution (89 mL) of WSCI·HCl (11.3 g, 58.9 mmol) at 0°C in a nitrogen atmosphere, and the mixture was stirred for 5 minutes. A DMF/DCM solution (1/1, 74 mL) of aa358-c (20.1 g, 49.1 mmol) was added thereto, and the mixture was stirred at 0°C for 30 minutes. After diethylamine (5.60 mL, 54.0 mmol) was added thereto, the mixture was stirred at room temperature for 2 hours. The mixture was diluted with ethyl acetate (200 mL), washed with 1 N hydrochloric acid (160 mL), and washed with water (200 mL). The mixture was further washed twice with a 50% aqueous sodium hydrogen carbonate solution (200 mL) and washed with half brine (200 mL). The organic layer was dried over anhydrous sodium sulfate and filtered off, and the solvent was distilled off under reduced pressure to give aa441-a as a crude product (23.3 g).

[0666]

DBU (6.61 mL, 44.2 mmol) was added dropwise to a DMF solution (147 mL) of aa441-a (20.5 g, 44.2 mmol) in a nitrogen atmosphere, and the mixture was stirred at room temperature for 5 minutes. Pyridine hydrochloride (5.62 g, 48.6 mmol) was added thereto, and the mixture was stirred at room temperature for 10 minutes. To this mixture was added a solution that is obtained by adding WSCI·HCl (11.9 g, 61.9 mmol) to a DMF solution (147 mL) of Fmoc-MeGly(cPent)-OH (Compound aa330, 15.9 g, 42.0 mmol) and oxyma (7.54 g, 53.0 mmol). The resulting mixture was stireed at room temperature for 30 minutes. Moreover, DIPEA (8.47 mL, 48.6 mL) was added, and then the mixture was stirred at room temperature for

17 hours. The mixture was diluted with ethyl acetate (200 mL), and washed twice with 1 N hydrochloric acid (200 mL). The aqueous layer was extracted with ethyl acetate (200 mL), and the combined organic layer was washed with water (200 ml), washed twice with a 50% aqueous sodium hydrogen carbonate solution (200 mL), and washed with half brine (200 mL). The organic layer was dried over magnesium sulfate and filtered off, the solvent was distilled off under reduced pressure, and the resulting residue was purified twice by silica gel chromatography (hexane-ethyl acetate) to give aa441-b (13.7 g, 52%).

LCMS (ESI) m/z = 626 (M+Na)+

Retention time: 1.50 min (Analytical condition SMD method_04)

[0667]

aa441 was obtained as a crude product (10.5 g) in the same manner as Compound aa440 except that aa441-b (13.7 g, 22.7 mmol) was used in place of aa440-c.

LCMS (ESI) m/z = 586 (M+Na)+

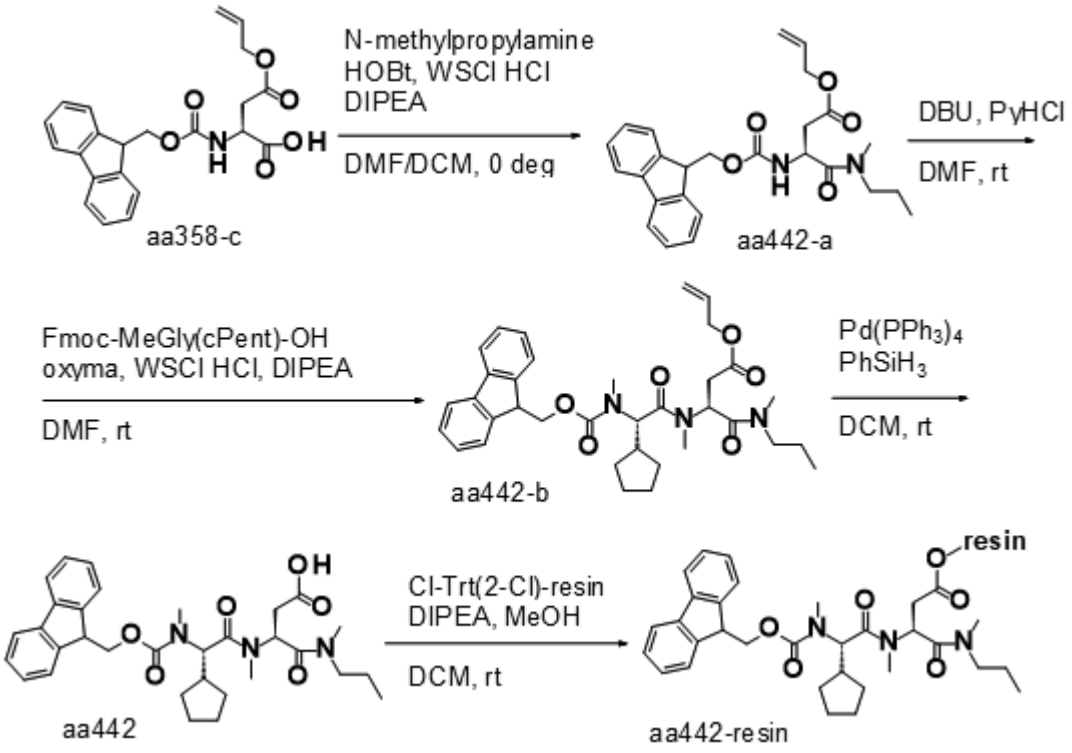
Retention time: 1.17 min (Analytical condition SMD method_05)

[0668]

Using the resulting Compound aa441 (10.5 g, 18.6 mmol), aa441-resin (36.3 g) was obtained under the same reaction conditions as synthesis of Compound aa373-resin. The supported amount calculated in the same manner as aa373-resin was 0.362 mmol/g.

[0669]

Synthesis of Compound aa442-resin



[0670]

aa442-a was obtained as a crude product (23.6 g) in the same manner as Compound aa441-a except that N-methylpropylamine was used in place of diethylamine.

[0671]

aa442-b (15.9 g, 53%) was obtained in the same manner as Compound aa441-b except that aa442-a (22.9 g, 49.4 mmol) was used in place of aa441-a.

LCMS (ESI) m/z = 626 (M+Na)+

Retention time: 1.51 min (Analytical condition SMD method_04)

[0672]

aa442 (13.7 g, 92%) was obtained in the same manner as Compound aa441 except that 442-b (15.9 g, 26.4 mmol) was used in place of aa441-b.

LCMS (ESI) m/z = 564 (M+H)+

Retention time: 1.28 min (Analytical condition SMD method_04)

[0673]

Using the resulting aa442 (13.6 g, 24.2 mmol), aa442-resin (47.1 g) was obtained under the same reaction conditions as synthesis of Compound aa373-resin. The supported amount calculated in the same manner as aa373-resin was 0.348 mmol/g.

[0674]

1-3. Solid-phase peptide synthesis by peptide synthesizer

Cyclic peptide compounds (Table 38) were synthesized by the method described in WO2013/100132 or WO2018/225864. Peptides were synthesized by the Fmoc method, which is described in more detail below, using a peptide synthesizer (Multipep RS and RSi; manufactured by Intavis). The detailed operational procedure was according to the manual appended to the synthesizer. The relationship between the formal name, structure, and abbreviation of each amino acid residues and oligo peptides constituting the cyclic peptides provided in Table 38 can be understood from Tables 2 to 6 above, and Table 9, Table 10, Table 9-1, Table 17-1, and Table 29-1 below.

[0675]

A peptide synthesis method (a basic peptide synthesis method) by the Fmoc method is described in detail in 1-3-1 to 1-3-5 below.

[0676]

1-3-1. Peptide elongation reaction by Fmoc method from N-terminal of amino acid

A peptide compound was synthesized by a solid-phase synthesis method involving an Fmoc-protected amino acid using a peptide synthesizer (Multipep RS or Multipep RSi) manufactured by Intavis. The detailed operational procedure was according to the manual appended to the synthesizer.

[0677]

The Fmoc-protected amino acid (0.3 to 0.6 mol/L) constituting the intended peptide, and HOAt, oxyma, or HOOBt (0.375 mol/L) as a carboxyl group activator, were dissolved in NMP or NMP/DMF (1/1) to prepare Solution 1. When the Fmoc-protected amino acid was poorly soluble in the above solvents, DMSO was added so as to have a concentration of 20 to 30% (v/v) to prepare Solution 1. When, for example, Fmoc-Ser(THP)-OH or Fmoc-MeSer(THP)-OH was used as an Fmoc-protected amino acid having a THP-protecting group in a side chain, Solution 1 was prepared using oxyma as a carboxyl group activator, and Molecular Sieves 4A1/8 (Wako Pure Chemical Industries, Ltd.) or Molecular Sieves 4A1/16 (Wako Pure Chemical Industries, Ltd.) was added and then used in peptide synthesis. When the α,α-di-substituted Fmoc amino acid used was, for example, Fmoc-cVal-OH (Compound aa301), Fmoc-cLeu-OH (Compound aa302), Fmoc-cHex-OH (Compound aa306), Fmoc-cVal(3-Me2)-OH (Compound aa303), Fmoc-cVal(3-F2)-OH) (Compound aa307), Fmoc-AoxeC-OH (Compound aa318), Fmoc-Aib-OH (Compound aa315), or Fmoc-(Me)Abu-OH (Compound aa316), oxyma was used as a carboxyl group activator to prepare Solution 1. When the serin derivative used was, for example, Fmoc-MeSer(nPr)-OH (Compound aa016), Fmoc-MeSer(cPr)-OH (Compound aa020), Fmoc-MeSer(Tfe)-OH (Compound aa021), Fmoc-MeSer(Et)-OH (Compound aa022), Fmoc-MeSer(iPen)-OH (Compound aa249), Fmoc-D-MeSer(nPr)-OH (Compound aa250), or Fmoc-MeSer(Me)-OH (Compound aa252), HOAt or HOOBt was used as a carboxyl group activator to prepare Solution 1. When the azetidine or a derivative thereof used was, for example, Fmoc-Aze(2)-OH (Compound 076), Fmoc-D-Aze(2)-OH (Compound aa079), Fmoc-Aze(2)(3S-Me)-OH (Compound aa098), Fmoc-Aze(2)(3R-Me)-OH (Compound aa099), or Fmoc-Aze(2)(3-Me2)-OH (Compound aa100), HOOBt was used as a carboxyl group activator to prepare Solution 1. N,N'-diisopropylcarbodiimide (DIC) (10% v/v) and N,N-dimethylformamide (DMF) were mixed to prepare Solution 2.

[0678]

2-Chlorotrityl resin (100 mg), which is bound to the side-chain carboxylic acid moiety of N-terminal Fmoc-protected aspartic acid or the main-chain carboxylic acid moiety of an N-terminal Fmoc-protected amino acid , was added to a solid-phase reaction vessel, and the reaction vessel was placed in a peptide synthesizer. Dichloromethane (DCM) (0.8 mL) was added to this resin (100 mg), and the mixture was left to stand still for 1 hour to swell the resin. The solution was then discharged from the frit. Solution 1 and Solution 2 were placed in the peptide synthesizer, and automatic synthesis by the peptide synthesizer was started.

[0679]

A DMF solution (2% v/v, 0.7 mL) of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) was added to a solid-phase reaction vessel containing the resin to deprotect the N-terminal Fmoc

group at room temperature. Reaction was carried out for 4.5 minutes in the deprotection of the first residue, and for 10 minutes in the deprotection of the second and subsequent residues, and then the solution was discharged from the frit. DMF (0.7 mL) was added thereto, and after being left to stand still for 5 minutes, the solution was discharged from the frit. By repeating this resin washing step 3 more times, an amino acid bonded to the resin, or the resin in which the Fmoc group at the N-terminal of the peptide was removed to yield an amino group, was obtained. The washing step may be carried out in such a manner that the resin is washed once with DMF (0.7 mL), then washed once with a toluene solution (0.7 mL) of DIPEA·HOAt (2 eq based on resin), and further washed 3 times with DMF (0.7 mL).

[0680]

Subsequently, Solution 1 (0.3 mL) and Solution 2 (0.36 mL) were mixed in the mixing vial of the synthesizer and then added to the resin that had undergone the above deprotection treatment, and the solid-phase reaction vessel was heated to 40°C. In the case of a poorly elongatable sequence, the temperature was increased to 60°C as necessary. The condensation reaction of the amino group on the resin and the Fmoc-protected amino acid was carried out for 2.5 hours. In the case of a poorly elongatable sequence, the reaction was carried out for 20 hours as necessary. In the case of α,α-di-substituted Fmoc amino acid, the temperature was increased to 60°C and the reaction was carried out for 16 hours, as necessary. In the case of Fmoc-protected amino acid of azetidine or a derivative thereof, the temperature was increased to 50°C and the reaction was carried out for 10 hours, as necessary, then Solution 2 (0.36 mL) was added again, and the reaction was further carried out at 50°C for 10 hours. After reaction, the solution was discharged from the frit. When the elongation efficiency was poor, this condensation reaction of the Fmoc-protected amino acid was repeated one or two more times. For example, this corresponds to the condensation reaction of an N-alkylated Fmoc-protected amino acid on Compound aa358-resin (Fmoc-MeAsp(O-Trt(2-Cl)resin)-mor) and Compound aa359-resin (Fmoc-MeAsp(O-Trt (2-Cl)resin)-NMe2). In the case of Fmoc-protected amino acids of MecVal and MecLeu, the mixture was heated to 60°C and reacted for 6 hours if necessary, then Solution 2 (0.36 mL) was added again, and the reaction was further carried out at 60°C for 6 hours. This operation was repeated, so the reaction was carried out for a total of 24 hours. When elongating Fmoc protected proline or its derivative following MecVal and MecLeu, the operation of heating the mixture to 60°C to be reacted for 6 hours, then adding again Solution 2 (0.36 mL), further reacting the mixture at 60°C for 6 hours, and discharging the solution from the frit was carried out 3 times. Then, the resin was washed 3 times with DMF (0.7 mL). This Fmoc group deprotection reaction and the subsequent Fmoc amino acid condensation reaction were regarded as constituting one cycle, and a peptide was elongated on the resin surface by repeating this cycle. After completion of peptide elongation, a DMF

solution (2% v/v, 0.7 mL) of DBU was added to the resin, and a reaction was carried out for 15 minutes to perform a deprotection reaction of the Fmoc group, and then the solution was discharged from the frit. The resulting resin was washed 4 times with DMF (0.7 mL), and then washed 4 times with DCM (0.7 mL).

[0681]

1-3-2. Cleaving of elongated peptide from resin

To the resin obtained by the method described in WO2013/100132 or WO2018/225864 or by the above method was added 2,2,2-trifluoroethanol (TFE)/DCM (1/1, v/v, 2 mL) containing 0.75% (v/v) DIPEA, and the resin was reacted for 2 hours at room temperature to carry out the reaction of cleaving a peptide chain from the resin. After reaction, the solution in the tube was recovered from the frit. 2,2,2-Trifluoroethanol (TFE)/DCM (1/1, v/v, 1 mL) was added to the remaining resin, and the operation of recovering the solution from the frit was performed twice. The entirety of the resulting cleaved solutions was combined and mixed with DMF (4 mL) or 1,2-dichloroethane (4 mL), and then the solvent was distilled off under reduced pressure using a high-throughput centrifugal evaporator (HT-12) manufactured by Genevac.

[0682]

1-3-3. Method of cyclizing cleaved peptide

The residue obtained by the above method was dissolved in a mixed solution of DMF (4 mL) and DCM (4 mL), a DMF solution (0.5 M, 1.5 eq) of (1-cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) or a DMF solution (0.5 M, 1.5 eq) of O-(7-aza-1H-benzotriazol-1-yl)-N,N,N,N-tetramethyluronium hexafluorophosphate (HATU) and DIPEA (1.8 eq) were added, and the mixture was stirred at room temperature for 2 hours to carry out a condensation cyclization reaction of the N-terminal amino group and the C-terminal carboxyl group. The equivalent number was calculated based on the product of multiplying the amino acid supporting ratio (mmol/g) of the resin used as a raw material by the amount of the resin used (usually 100 mg). Production of the intended cyclic peptide was verified by LC/MS measurement (SQ Detector 2 manufactured by Waters), and then the solvent was distilled off from the reaction solution under reduced pressure by a high-throughput centrifugal evaporator (HT-12) manufactured by Genevac.

[0683]

1-3-4. Deprotection of protecting group of side-chain functional group contained in cyclic peptide

In the sequences synthesized using Fmoc-protected amino acids having a THP-protected hydroxyl group in a side chain, such as Fmoc-Ser(THP)-OH (Compound aa073),

Fmoc-MeSer(THP)-OH (Compound aa044), Fmoc-Hyp(THP)-OH (Compound aa279), Fmoc-Hyp(3)(THP)-OH (Compound aa265), Fmoc-cisHyp(THP)-OH (Compound 267), and Fmoc-cisHyp(3)(THP)-OH (Compound aa264), and in the sequences synthesized using Fmoc-MeAsp(O-Trt(2-Cl)resin)-OPis (Compound aa386-resin), 4 mL of a 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) solution (containing 2% (v/v) triisopropylsilane (TIPS) and 1% (v/v) 1,2-dichloroethane) of tetramethylammonium hydrogen sulfate (0.05 M) was added to the residue obtained above to dissolve the residue, and then the mixture was left to stand at room temperature for 4 hours to deprotect the THP protecting group or Pis protecting group. After completion of the reaction was confirmed with LC/MS (SQ Detector 2 manufactured by Waters), diisopropylethylamine (DIPEA) (70 μL) was added to the reaction solution, and the solvent was distilled off under reduced pressure with a high-throughput centrifugal evaporator (HT-12) manufactured by Genevac. In this deprotection reaction, another fluoroalcohol such as 2,2,2-trifluoroethanol (TFE) can be used in place of HFIP.

[0684]

1-3-5. Cyclic peptide purification method

DMSO or DMF and acetonitrile were added to the residue obtained by the above method, insoluble matter was removed by filter filtration, and then the solution was purified by preparative-HPLC. The purification apparatus used was Waters Auto Purification System, the column used was YMC-Actus Triart C18 (inner diameter 20 mm, length 100 mm) or YMC-Actus Triart Phenyl (inner diameter 20 mm, length 100 mm), and the mobile phase used was an aqueous methanol-ammonium acetate solution (50 mmol/L) or acetonitrile-water containing 0.1% formic acid. Fractions containing a compound as the main component were selected, the same amount of DMSO as the amount of the solution of each fraction was added, and the solvent was distilled off under reduced pressure with a high-throughput centrifugal evaporator (HT-12) manufactured by Genevac. The resulting residue was dissolved in DMSO, fractions were integrated as necessary, and again the solvent was distilled off under reduced pressure with a high-throughput centrifugal evaporator (HT-12) manufactured by Genevac to give the intended cyclic peptide.

[0685]

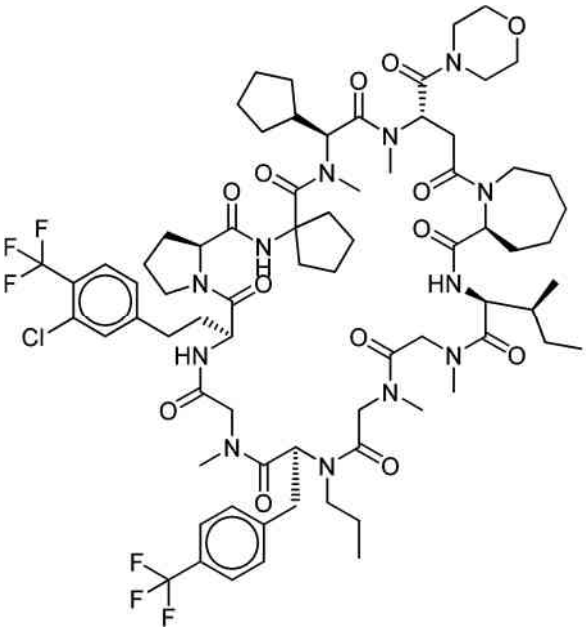
Synthesis of Compound PP0247

Compound aa375-resin (0.448 mmol/g, 100 mg) was used as a raw material, and Fmoc-cLeu-OH, Fmoc-Pro-OH, Fmoc-Hph(4-CF3-3-Cl)-OH, Fmoc-MeGly-OH, Fmoc-nPrPhe(4-CF3)-OH, Fmoc-Ile-OH, and Fmoc-Azp(2)-OH were used as Fmoc-protected amino acids. The above-described peptide elongation reaction by the Fmoc method, cleaving of an elongated peptide from resin, cyclization of a cleaved peptide (using (1-cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU)

as a cyclization reagent), and purification of a cyclic peptide were performed to give the intended compound PP0247 (12.7 mg, 19%).

[0686]

Compound PP0247



LCMS (ESI) m/z = 1517.6 (M+H)+

Retention time: 7.775 min (Analytical condition SSC-AA-02/03)

[0687]

Using the resins, on which amino acid shown in Table 5 and Table 6 was supported, as raw materials, the following compounds were produced according to the above-described Fmoc method in the same manner as the production method of Compound PP0247. A deprotection reaction was added as necessary.

Compounds PP0001, PP0002, PP0003, PP0004, PP0006, PP0007, PP0011, PP0013, PP0014, PP0015, PP0016, PP0018, PP0019, PP0020, PP0021, PP0022, PP0023, PP0024, PP0025, PP0027, PP0028, PP0029, PP0030, PP0031, PP0032, PP0037, PP0039, PP0041, PP0042, PP0043, PP0044, PP0045, PP0047, PP0048, PP0049, PP0050, PP0051, PP0067, PP0068, PP0070, PP0071, PP0076, PP0077, PP0078, PP0138, PP0141, PP0144, PP0145, PP0146, PP0148, PP0149, PP0150, PP0151, PP0152, PP0153, PP0154, PP0155, PP0156, PP0158, PP0162, PP0165, PP0166, PP0168, PP0169, PP0170, PP0171, PP0172, PP0173, PP0174, PP0175, PP0176, PP0177, PP0178, PP0179, PP0180, PP0181, PP0182, PP0183, PP0184, PP0185, PP0186, PP0187, PP0188, PP0189, PP0190, PP0191, PP0192, PP0193, PP0194, PP0195, PP0196, PP0197, PP0198, PP0199, PP0200, PP0201, PP0202, PP0203, PP0204, PP0205, PP0206, PP0207, PP0208, PP0209, PP0212, PP0217, PP0220, PP0221, PP0222, PP0223, PP0224, PP0225, PP0226, PP0227, PP0228, PP0229, PP0230, PP0231, PP0232,

PP0233, PP0234, PP0235, PP0236, PP0237, PP0238, PP0239, PP0240, PP0241, PP0247, PP0248, PP0249, PP0250, PP0251, PP0252, PP0253, PP0254, PP0256, PP0257, PP0258, PP0259, PP0260, PP0261, PP0262, PP0263, PP0264, PP0265, PP0266, PP0267, PP0268, PP0269, PP0270, PP0271, PP0272, PP0273, PP0274, PP0275, PP0276, PP0277, PP0278, PP0279, PP0281, PP0282, PP0283, PP0284, PP0285, PP0286, PP0287, PP0288, PP0289, PP0290, PP0291, PP0292, PP0293, PP0294, PP0295, PP0296, PP0297, PP0298, PP0299, PP0300, PP0301, PP0302, PP0303, PP0304, PP0305, PP0306, PP0307, PP0308, PP0309, PP0310, PP0311, PP0312, PP0313, PP0314, PP0315, PP0320, PP0321, PP0322, PP0323, PP0324, PP0325, PP0326, PP0327, PP0328, PP0329, PP0330, PP0331, PP0332, PP0333, PP0334, PP0335, PP0336, PP0337, PP0338, PP0339, PP0340, PP0341, PP0342, PP0343, PP0344, PP0345, PP0346, PP0347, PP0348, PP0349, PP0350, PP0351, PP0352, PP0353, PP0354, PP0355, PP0356, PP0357, PP0358, PP0359, PP0360, PP0361, PP0362, PP0363, PP0364, PP0365, PP0366, PP0367, PP0368, PP0369, PP0370, PP0371, PP0372, PP0373, PP0374, PP0375, PP0376, PP0377, PP0378, PP0379, PP0380, PP0381, PP0382, PP0383, PP0384, PP0385, PP0386, PP0387, PP0388, PP0389, PP0390, PP0392, PP0393, PP0394, PP0395, PP0396, PP0397, PP0398, PP0399, PP0400, PP0401, PP0402, PP0403, PP0404, PP0405, PP0406, PP0407, PP0408, PP0409, PP0410, PP0411, PP0412, PP0413, PP0414, PP0415, PP0416, PP0417, PP0418, PP0419, PP0420, PP0421, PP0422, PP0423, PP0424, PP0425, PP0426, PP0427, PP0428, PP0429, PP0430, PP0431, PP0432, PP0433, PP0434, PP0435, PP0436, PP0437, PP0438, PP0439, PP0440, PP0441, PP0442, PP0443, PP0444, PP0445, PP0446, PP0447, PP0448, PP0449, PP0450, PP0451, PP0452, PP0453, PP0454, PP0455, PP0456, PP0457, PP0745, PP0746, PP0747, PP0748, PP0749, PP0750, PP0751, PP0752, PP0753, PP0766, PP0767, PP0768, PP0769, PP0770, PP0783, PP0784, PP0785, PP0786, PP0787, PP0788, PP0789, PP0802, PP0803, PP0804, PP1815, PP1816, PP1817, PP1818, PP1819, PP1820, PP1914, PP1916, PP1918, PP1920, PP1922, PP1926, PP1928, PP1930, PP1946, PP1947, PP1948, PP1949, PP1950, PP1952, PP1953, PP1954, PP1955, PP1956, PP1957, PP1958, PP1959, PP1960, PP1961, PP1963, PP1964, PP1965, PP1967, PP1968, PP1969, PP1970, and PP1971.

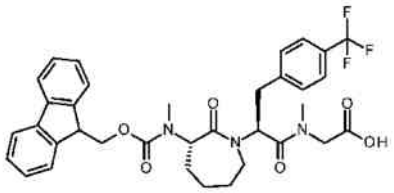
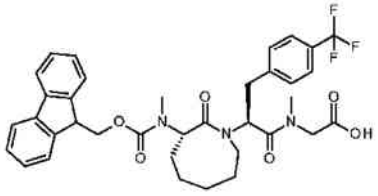
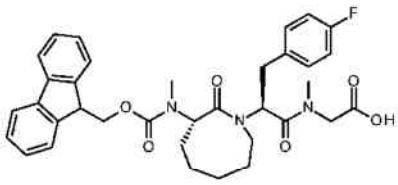
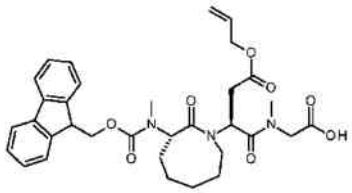
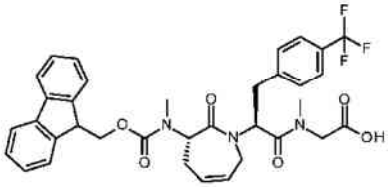
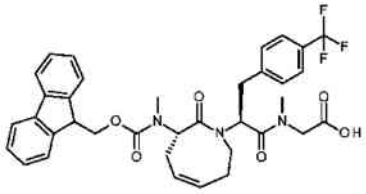
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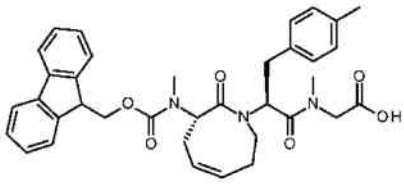
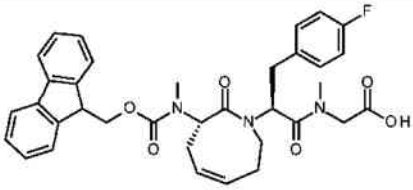
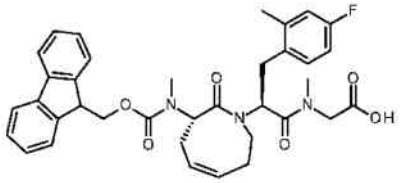
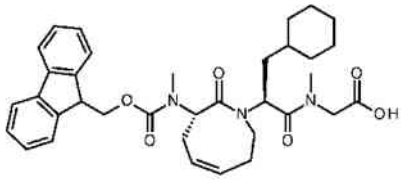
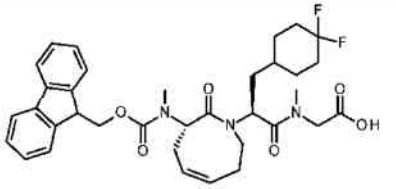
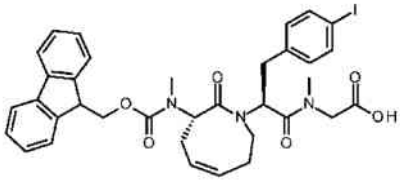
1-4. Cyclic peptide synthesis using Fmoc-protected tripeptide as reagent

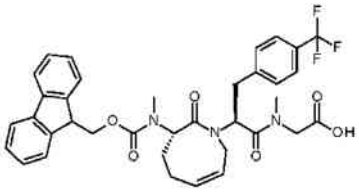
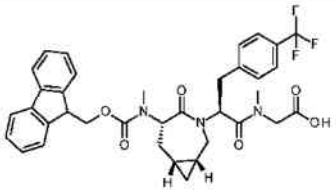
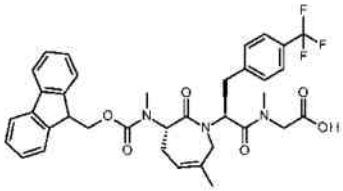
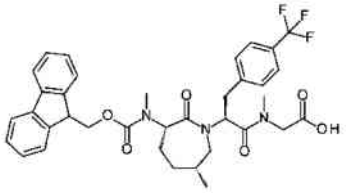
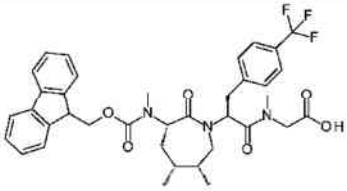
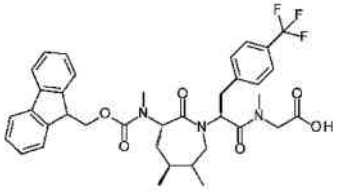
Synthesis of Fmoc-protected tripeptides

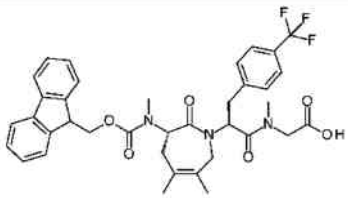
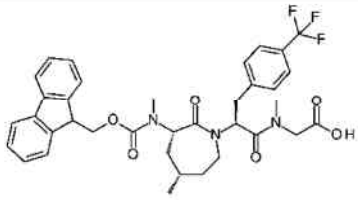
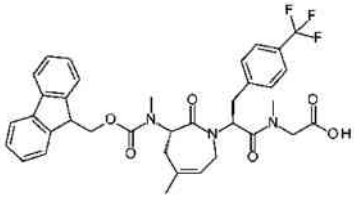
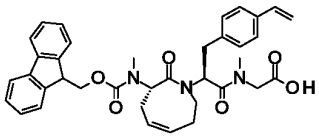
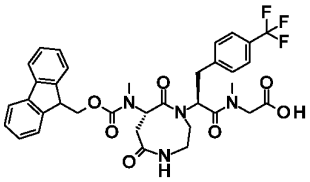
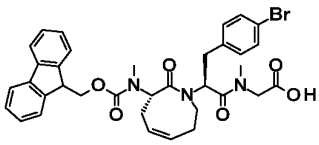
The tripeptides shown in Table 9 were synthesized by the following method and used in peptide synthesis by a peptide synthesizer.

[Table 9]

Compound No.	Structural Formula	Name
tp001		N-((S)-2-((S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxoazepan-1-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp002		N-((S)-2-((S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxoazocan-1-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp003		N-((S)-2-((S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxoazocan-1-yl)-3-(4-fluorophenyl)propanoyl)-N-methylglycine
tp004		N-((S)-2-((S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxoazocan-1-yl)-4-(allyloxy)-4-oxobutanoyl)-N-methylglycine
tp005		N-((S)-2-((S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-1-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp006		N-((S)-2-((S,Z)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine

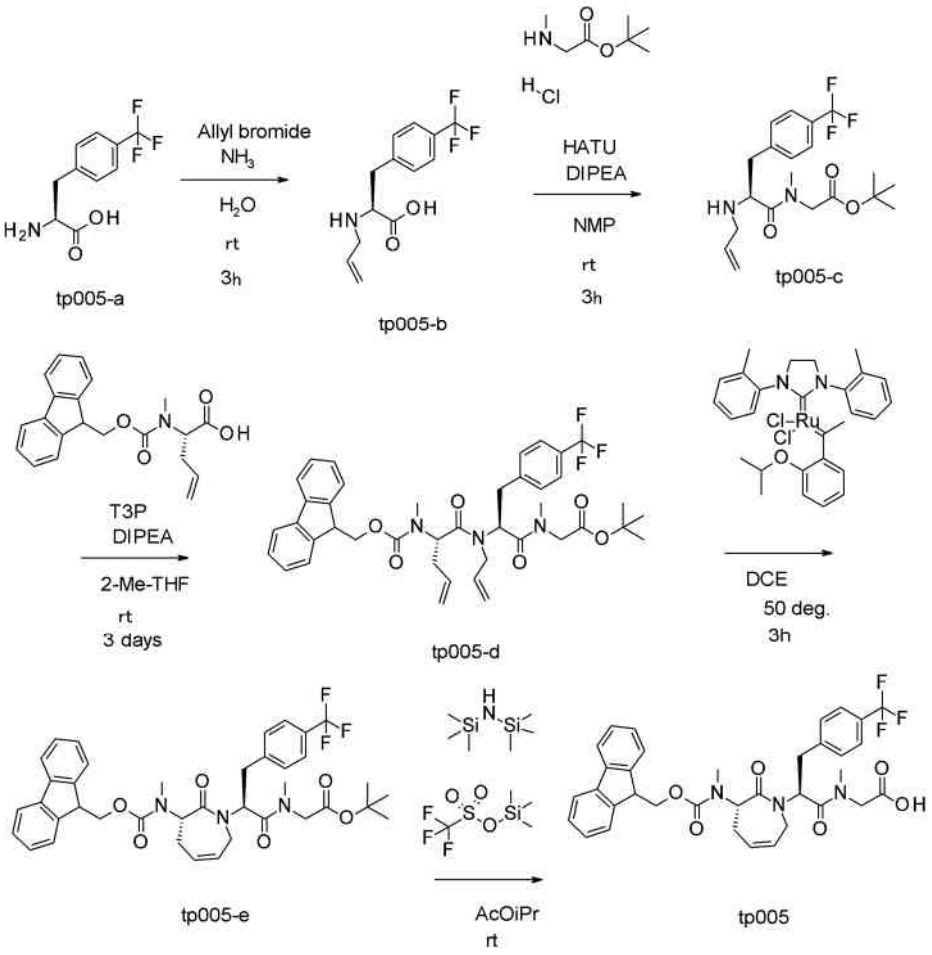
tp007		N-((S)-2-((S,Z)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)-3-(p-tolyl)propanoyl)-N-methylglycine
tp008		N-((S)-2-((S,Z)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)-3-(4-fluorophenyl)propanoyl)-N-methylglycine
tp009		N-((S)-2-((S,Z)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)-3-(4-fluoro-2-methylphenyl)propanoyl)-N-methylglycine
tp010		N-((S)-2-((S,Z)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)-3-cyclohexylpropanoyl)-N-methylglycine
tp011		N-((S)-2-((S,Z)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)-3-(4,4-difluorocyclohexyl)propanoyl)-N-methylglycine
tp012		N-((S)-2-((S,Z)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)-3-(4-iodophenyl)propanoyl)-N-methylglycine

tp013		N-((S)-2-((S,Z)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxo-3,4,5,8-tetrahydroazocin-1(2H)-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp014		N-((S)-2-((1R,5S,7R)-5-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-4-oxo-3-azabicyclo[5.1.0]octan-3-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp015		N-((S)-2-((S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-6-methyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-1-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp016		N-((S)-2-((3S,6R)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-6-methyl-2-oxoazepan-1-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp017		N-((S)-2-((3S,5R,6R)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-5,6-dimethyl-2-oxoazepan-1-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp018		N-((2S)-2-((3S,5S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-5,6-dimethyl-2-oxoazepan-1-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine

tp019		N-((S)-2-((S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-5,6-dimethyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-1-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp020		N-((S)-2-((3S,5S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-5-methyl-2-oxoazepan-1-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp021		N-((S)-2-((S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-5-methyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-1-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp022		N-((S)-2-((S,Z)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)-3-(4-vinyl phenyl)propanoyl)-N-methylglycine
tp023		N-((S)-2-((S)-7-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-5,8-dioxo-1,4-diazocan-1-yl)-3-(4-(trifluoromethyl)phenyl)propanoyl)-N-methylglycine
tp024		N-((S)-2-((S,Z)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)-3-(4-bromophenyl)propanoyl)-N-methylglycine

[0689]

Synthesis of Compound tp005



[0690]

In a nitrogen atmosphere, water (257.0 mL) and a 28% aqueous ammonia solution (94.0 g, 1544.0 mmol) were added to tp005-a (30.0 g, 129.0 mmol), allyl bromide (65.3 mL, 772. 0 mmol) was added dropwise, and the mixture was stirred at room temperature for 3 hours. Ethanol (290.0 mL) was added to the reaction solution, and the mixture was stirred at room temperature for 30 minutes. The mixture was filtered, and the resulting residue was washed with water (300 mL) and dried under reduced pressure to give tp005-b (30.4 g, 86%).

LCMS (ESI) m/z = 274 (M+H)+

Retention time: 0.64 min (Analytical condition SMD method_04)

[0691]

In a nitrogen atmosphere, N-methyl-2-pyrrolidinone (209.0 mL) was added to a reaction vessel containing tp005-b (20.0 g, 73.2 mmol) and tert-butyl methyl glycinate hydrochloride (26.6 g, 146.0 mmol), N,N-diisopropylethylamine (51.1 mL, 293.0 mmol) was added dropwise, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxidehexafluorophosphate (55.7 g, 146.0 mmol) was added in several times. After the mixture was stirred at room temperature for 3 hours, ethyl acetate (400 mL), water (200 mL), and a 5 wt% aqueous sodium carbonate solution (200 mL) were added for extraction. The organic

layer was washed with a 5 wt% aqueous sodium carbonate solution (400 mL), washed twice with potassium hydrogen sulfate (400 mL), washed with 15 wt% brine (400 mL), and passed through a filter provided with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to give tp005-c as a crude product (44.5 g).

LCMS (ESI) m/z = 401 (M+H)+

Retention time: 0.77 min (Analytical condition SMD method_04)

[0692]

2-Methyltetrahydrofuran (293.0 ml) was added to a reaction vessel containing tp005-c (29.3 g, 73.2 mmol) and (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pent-4-enoic acid (33.4 g, 95.0 mmol), N,N-diisopropylethylamine (63.7 mL, 366.0 mmol) was added, and a 50% propylphosphonic anhydride·ethyl acetate solution (93.0 g, 146.0 mmol) and a 50% propylphosphonic anhydride·toluene solution (23.3 g, 36.6 mmol) were added dropwise. After the mixture was stirred at room temperature for 3 days, ethyl acetate (300 mL) and a 5 wt% aqueous sodium carbonate solution (200 mL) were added for extraction. The organic layer was washed twice with 5 wt% potassium hydrogen sulfate (600 mL), washed twice with a 5 wt% aqueous sodium carbonate solution (600 ml), washed with 15 wt% brine (600 mL), and passed through a filter provided with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate) to give tp005-d (39.1 g, 73%). Moreover, ethyl acetate (37.0 ml) was added to tp005-d (23.1 g, 31.5 mmol), the mixture was heated to 50°C to be dissolved, and then returned to room temperature, and n-hexane (220.0 ml) was gradually added. The resulting precipitate was filtered, washed with a 95:5 mixed solution of n-hexane and ethyl acetate, and dried under reduced pressure to give tp005-d (19.8 g, 85%).

LCMS (ESI) m/z = 734 (M+H)+

Retention time: 1.68 min (Analytical condition SMD method_04)

[0693]

In a nitrogen atmosphere, 1,2-Dichloroethane (467.0 ml) was added to a reaction vessel containing tp005-d (10.3 g, 14.0 mmol) and dichloro[1,3-bis(2-methylphenyl)-2-imidazolidinilidene](2-isopropoxyphenylmethylene)ruthenium(II) (0.4 g, 0.7 mmol), and the mixture was stirred at 50°C for 3 hours. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate) to give tp005-e (8.6 g, 87%).

LCMS (ESI) m/z = 706 (M+H)+

Retention time: 0.70 min (Analytical condition SQDFA50)

[0694]

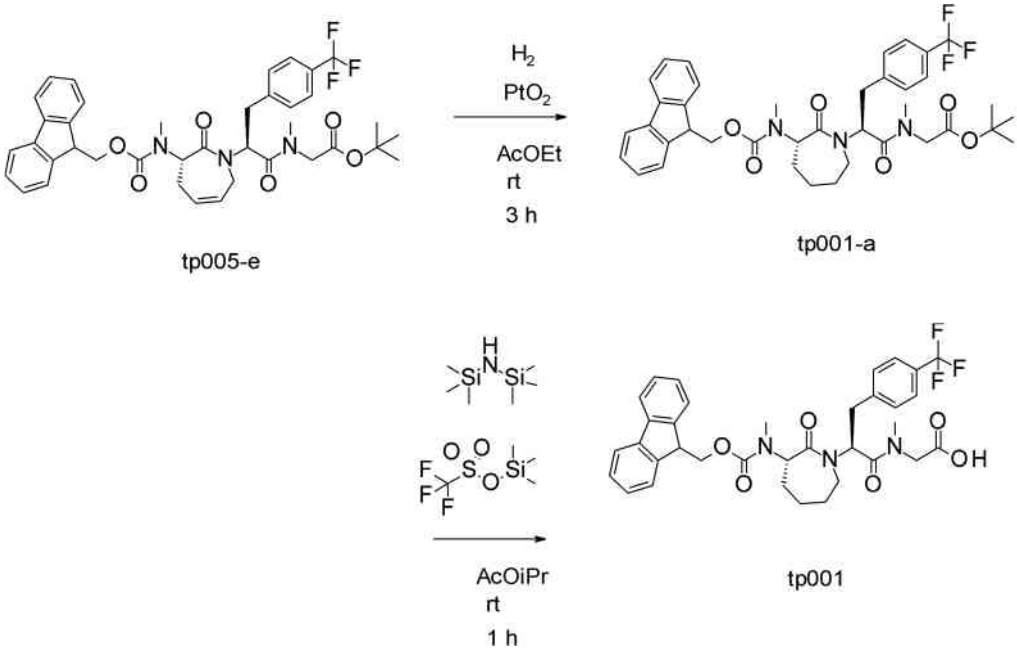
In a nitrogen atmosphere, tp005-e (2.0 g, 2.8 mmol) was dissolved in isopropyl acetate (11.3 ml), then bis(trimethylsilyl)amine (1.5 ml, 7.1 mmol) and trimethylsilyltrifluoromethanesulfonic acid (1.0 ml, 5.7 mmol) were added dropwise at room temperature, and the mixture was stirred for 1 hour. A 1.0 M aqueous disodium hydrogen phosphate solution (15.0 ml) was added, and the mixture was extracted with ethyl acetate (15.0 ml). The organic layer was concentrated under reduced pressure, and the resulting residue was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give tp005 (1.2 g, 64%).

LCMS (ESI) m/z = 650 (M+H)+

Retention time: 0.48 min (Analytical condition SQDFA50)

[0695]

Synthesis of Compound tp001



[0696]

tp005-e (13.1 g, 18.6 mmol) was dissolved in ethyl acetate (124.0 ml), platinum(IV) oxide (844.0 mg, 3.7 mmol) was added, and the mixture was stirred at room temperature for 3 hours in a hydrogen atmosphere. After the solvent was distilled off under reduced pressure, the resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate) to give tp001-a (11.4 g, 87%).

LCMS (ESI) m/z = 708 (M+H)+

Retention time: 0.73 min (Analytical condition SQDFA50)

[0697]

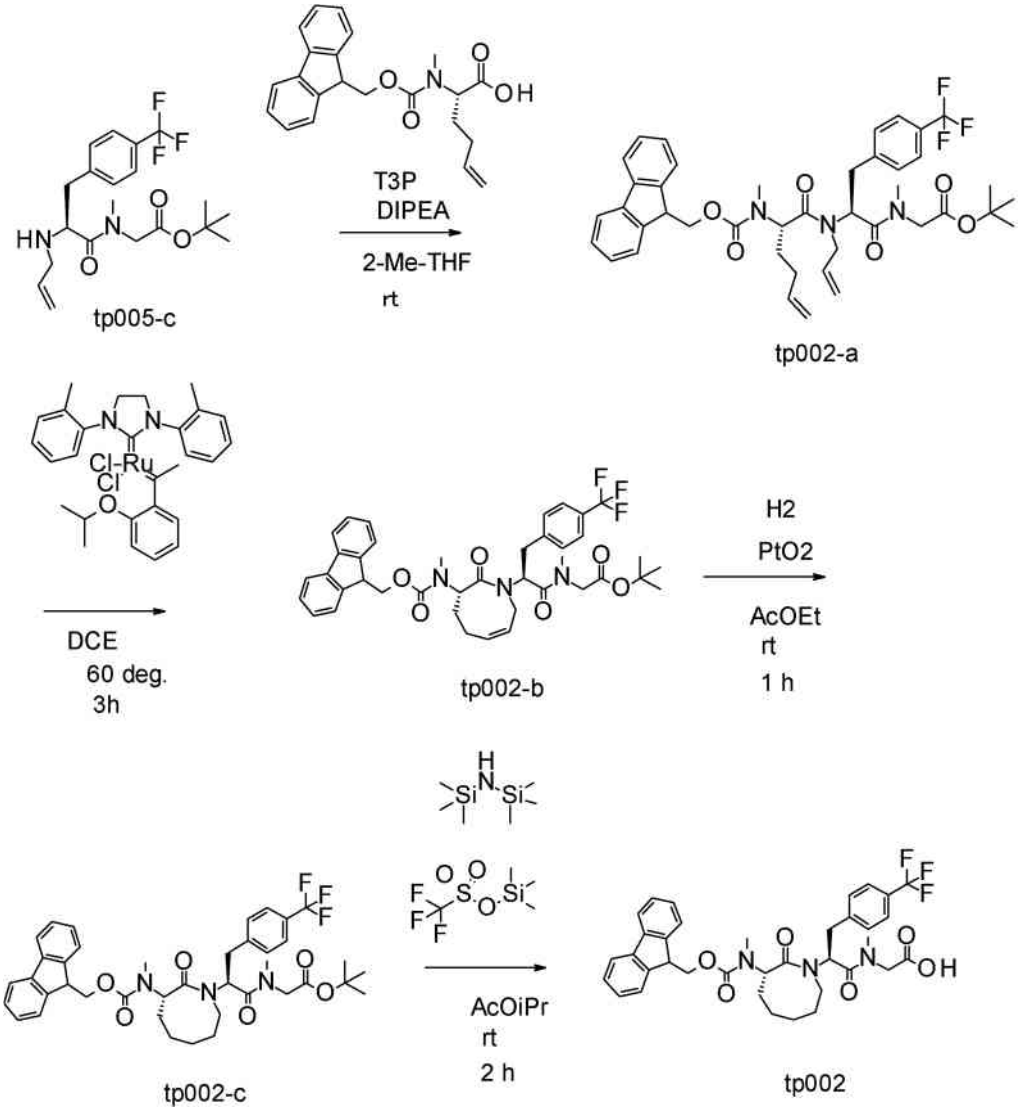
Using tp001-a as a starting material, tp001 (9.6 g, 91%) was obtained in the same manner as synthesis of Compound tp005.

LCMS (ESI) m/z = 652 (M+H)+

Retention time: 0.46 min (Analytical condition SQDFA50)

[0698]

Synthesis of Compound tp002



[0699]

Using tp005-c as a starting material, tp002-a (26.3 g, 65%) was obtained in the same manner as synthesis of Compound tp005-d.

LCMS (ESI) m/z = 748 (M+H)+

Retention time: 1.70 min (Analytical condition SMD method_04)

[0700]

Using tp002-a as a starting material, tp002-b (2.9 g, 60%) was obtained in the same manner as synthesis of Compound tp005-e.

LCMS (ESI) m/z = 720 (M+H)+

Retention time: 1.02 min (Analytical condition SMD method_06)

[0701]

Using tp002-b as a starting material, tp002-c (9.1 g, 99%) was obtained in the same manner as synthesis of Compound tp001-a.

LCMS (ESI) m/z = 722 (M+H)+

Retention time: 1.01 min (Analytical condition SMD method_06)

[0702]

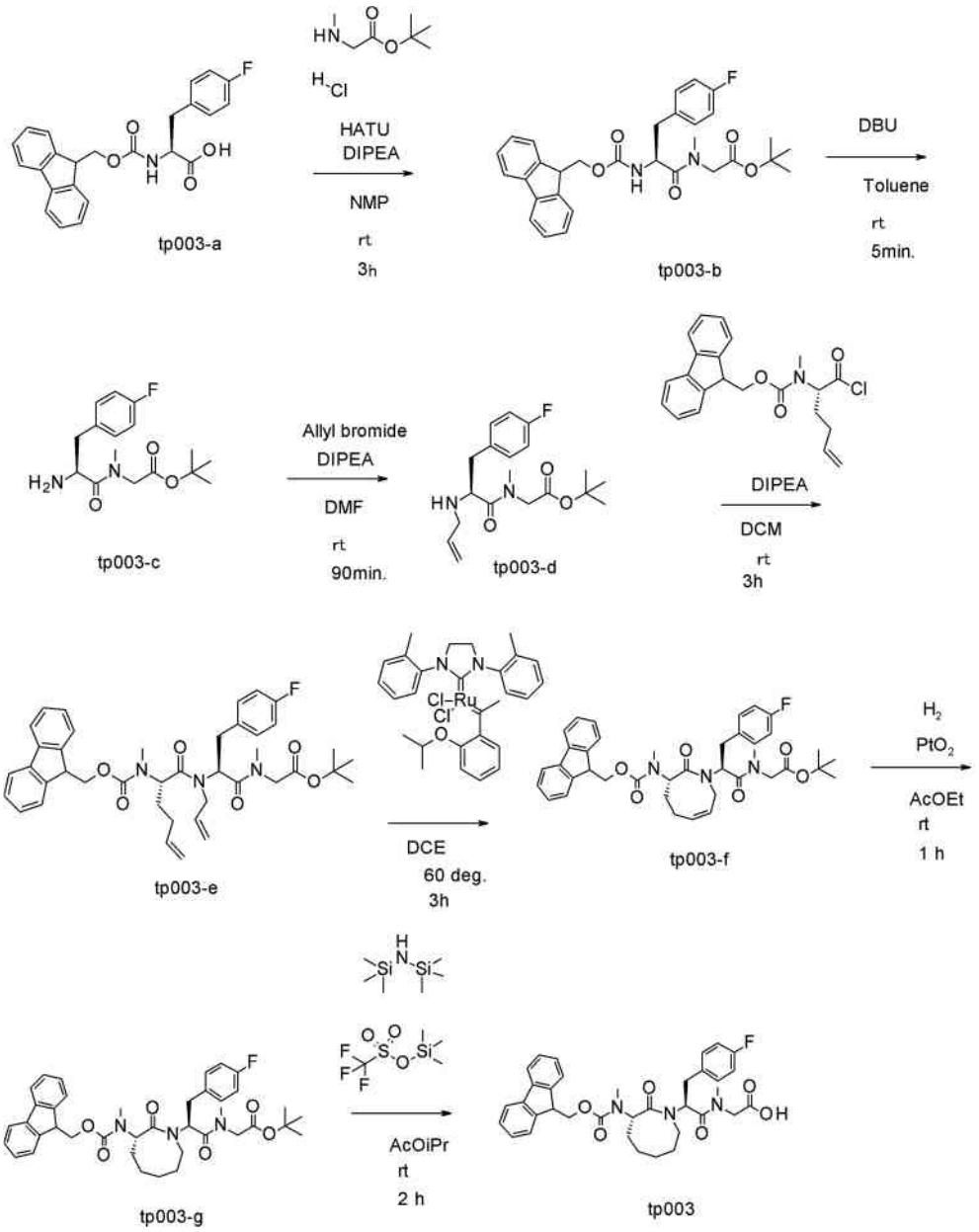
Using tp002-c as a starting material, tp002 (15.6 g, 90%) was obtained in the same manner as synthesis of Compound tp005.

LCMS (ESI) m/z = 666 (M+H)+

Retention time: 1.30 min (Analytical condition SMD method_04)

[0703]

Synthesis of Compound tp003



[0704]

Using tp003-a as a starting material, tp003-b (24.6 g, 93%) was obtained in the same manner as synthesis of Compound tp005-c.

LCMS (ESI) m/z = 533 (M+H)+

Retention time: 1.42 min (Analytical condition SMD method_04)

[0705]

tp003-b (24.6 g, 46.2 mmol) and toluene (161.0 ml) were added to a reaction vessel, 1,8-diazabicyclo[5.4.0]-7-undecene (7.0 ml, 46.2 mmol) was added, and the mixture was stirred at room temperature for 5 minutes. Ethyl acetate (75 ml) was added, and the organic layer was washed with a 1.0 mmol/L aqueous potassium dihydrogen phosphate solution (150 ml). n-Hexane (225 ml) was added to the organic layer, and the mixture was extracted with a mixed

solution of 2 N hydrochloric acid (35 ml) and water (300 ml). The resulting aqueous layer was adjusted to pH 8.01 with a 3.3 mmol/L aqueous potassium phosphate solution. The mixture was extracted with ethyl acetate (200 ml), and the organic layer was dried over magnesium sulfate. After filtration, the solvent was distilled off under reduced pressure to give tp003-c (9.7 g, 68%).

LCMS (ESI) m/z = 311 (M+H)+

Retention time: 0.66 min (Analytical condition SMD method_04)

[0706]

tp003-c (9.7 g, 31.2 mmol), N,N-dimethylformamide (208.0 ml), and N,N-diisopropylethylamine (5.7 ml, 32.8 mmol) were added to the reaction vessel, allyl bromide (6.8 ml, 78.0 mmol) was added dropwise, and the mixture was stirred at room temperature for 90 minutes. Ethyl acetate (200 ml) was added, and the mixture was washed with water (200 ml) and then washed with a 1.0 mmol/L aqueous potassium dihydrogen phosphate solution (200 ml). n-Hexane (400 ml) was added to the organic layer, and the mixture was extracted with a mixed solution of 2 N hydrochloric acid (15.6 ml) and water (200 ml). The resulting aqueous layer was adjusted to pH 8.15 with a 3.3 mmol/L aqueous potassium phosphate solution. The mixture was extracted with ethyl acetate (200 ml), and the organic layer was dried over magnesium sulfate. After filtration, the solvent was distilled off under reduced pressure to give tp003-d (7.6 g, 69%).

LCMS (ESI) m/z = 351 (M+H)+

Retention time: 0.68 min (Analytical condition SMD method_04)

[0707]

(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)(methyl)amino)hex-5-enoic acid (26.1 g, 71.3 mmol), dichloromethane (184. 0 ml), and N,N-dimethylformamide (0.6 ml, 7.1 mmol) were added to the reaction vessel, thionyl chloride (13.0 ml, 178.0 mmol) was added, the mixture was stirred at room temperature for 1 hour, and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in dichloromethane (81.0 ml), and this was added by cannulation to a reaction vessel containing tp003-d (22.7 g, 64.8 mmol), N,N-diisopropylethylamine (39.5 ml, 227.0 mmol), and dichloromethane (243.0 ml). After the mixture was stirred at room temperature for 3 hours, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate) to give tp003-e (38.3 g, 85%).

LCMS (ESI) m/z = 698 (M+H)+

Retention time: 1.65 min (Analytical condition SMD method_04)

[0708]

Using tp003-e as a starting material, tp003-f (17.4 g, 58%) was obtained in the same manner as synthesis of Compound tp005-e.

LCMS (ESI) m/z = 670 (M+H)+

Retention time: 0.93 min (Analytical condition SMD method_06)

[0709]

Using tp003-f as a starting material, tp003-g (17.9 g, 100%) was obtained in the same manner as synthesis of Compound tp001-a.

LCMS (ESI) m/z = 672 (M+H)+

Retention time: 0.91 min (Analytical condition SMD method_06)

[0710]

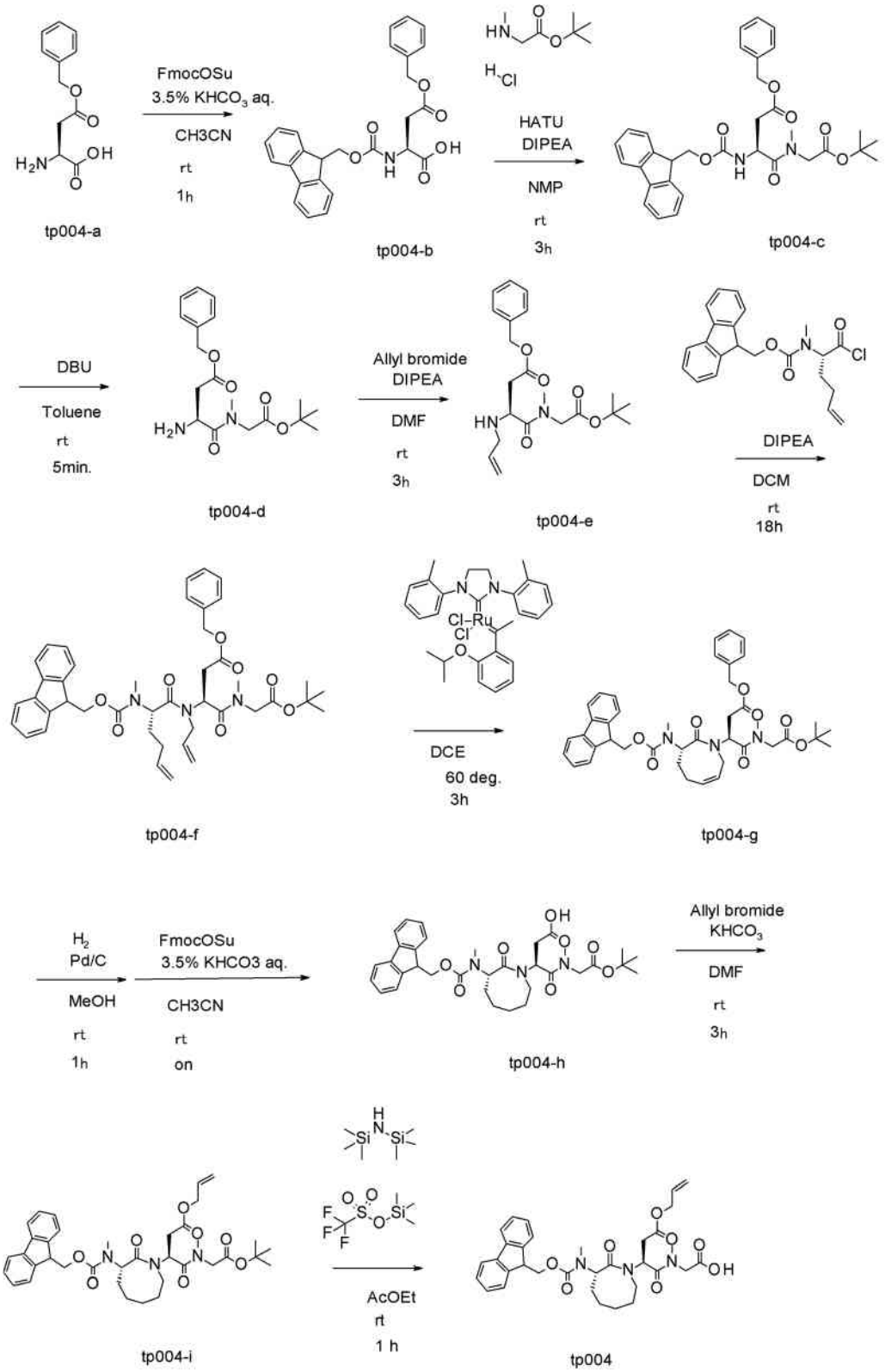
Using tp003-g as a starting material, tp003 (16.7 g, 82%) was obtained in the same manner as synthesis of Compound tp005.

LCMS (ESI) m/z = 616 (M+H)+

Retention time: 1.21 min (Analytical condition SMD method_04)

[0711]

Synthesis of Compound tp004



[0712]

A 3.5 wt% aqueous potassium hydrogen carbonate solution (194 ml) and acetonitrile (194 ml) were added to tp004-a (13.0 g, 58.2 mmol), then (2,5-dioxopyrrolidin-1-yl) (9H-fluoren-9-yl)methyl carbonate (19.6 g, 58.2 mmol) was added, and then the mixture was

vigorously stirred at room temperature for 1 hour. A 3.5 wt% aqueous potassium hydrogen carbonate solution (195 ml) was added, and the mixture was stirred at room temperature for 30 minutes. The reaction solution was washed with a 1:2 mixed solution (390 ml) of tert-butyl methyl ether and n-hexane, and then adjusted to pH 3 with phosphoric acid. The mixture was extracted with tert-butyl methyl ether (195 ml), and the organic layer was washed with a saturated aqueous sodium chloride solution (130 ml). The organic layer was dried over magnesium sulfate and filtered, and then the solvent was distilled off under reduced pressure to give tp004-b (25.9 g, 100%).

LCMS (ESI) m/z = 446 (M+H)+

Retention time: 1.22 min (Analytical condition SMD method_04)

[0713]

Using tp004-b as a starting material, tp004-c (32.1 g, 96%) was obtained in the same manner as synthesis of Compound tp005-c.

LCMS (ESI) m/z = 573 (M+H)+

Retention time: 1.43 min (Analytical condition SMD method_04)

[0714]

Using tp004-c as a starting material, tp004-d (17.7 g, 90%) was obtained in the same manner as synthesis of Compound tp003-c.

LCMS (ESI) m/z = 351 (M+H)+

Retention time: 0.95 min (Analytical condition SMD method_08)

[0715]

Using tp004-d as a starting material, tp004-e (13.6 g, 69%) was obtained in the same manner as synthesis of Compound tp003-d.

LCMS (ESI) m/z = 391 (M+H)+

Retention time: 1.15 min (Analytical condition SMD method_08)

[0716]

Using tp004-e as a starting material, tp004-f (1.4 g, 76%) was obtained in the same manner as synthesis of Compound tp003-e.

LCMS (ESI) m/z = 760 (M+Na)+

Retention time: 1.65 min (Analytical condition SMD method_04)

[0717]

Using tp004-f as a starting material, tp004-g (6.4 g, 59%) was obtained in the same manner as synthesis of Compound tp005-e.

LCMS (ESI) m/z = 732 (M+Na)+

Retention time: 1.56 min (Analytical condition SMD method_04)

[0718]

tp004-g (6.4 g, 9.0 mmol) was dissolved in methanol (299 ml), 10% palladium carbon (636.0 mg) was added, and the mixture was stirred in a hydrogen atmosphere for 1 hour. After filtration, the solvent was distilled off under reduced pressure. Acetonitrile (128 ml) and a 3.5 wt% aqueous potassium hydrogen carbonate solution (128 ml) were added, then (2,5-dioxopyrrolidin-1-yl) (9H-fluoren-9-yl)methyl carbonate (5.4 g, 16.0 mmol) was added, and then the mixture was stirred at room temperature for 30 minutes. Moreover, (2,5-dioxopyrrolidin-1-yl) (9H-fluoren-9-yl)methyl carboxylate (5.4 g, 16.0 mmol) was added, and then the mixture was stirred overnight at room temperature. A 3.5 wt% aqueous potassium hydrogen carbonate solution (128 ml) and water (128 ml) were added, and the mixture was washed with a 1:2 mixed solution of ethyl acetate and n-hexane (384 ml) and adjusted to pH 3 with phosphoric acid. The mixture was extracted with ethyl acetate (128 ml), and the organic layer was washed with a saturated aqueous sodium chloride solution (64 ml). The organic layer was dried over magnesium sulfate and filtered, and then the solvent was distilled off under reduced pressure to give tp004-h (12.3 g, 100%).

LCMS (ESI) m/z = 622 (M+H)+

Retention time: 1.28 min (Analytical condition SMD method_04)

[0719]

tp004-h (11.4 g, 18.3 mmol) was dissolved in N,N-dimethylformamide (183.0 ml), and after potassium hydrogen carbonate (4.6 g, 45.8 mmol) and then allyl bromide (10.6 ml, 122.0 mmol) were added, the mixture was vigorously stirred at room temperature for 3 hours. Ethyl acetate (200 ml) and n-hexane (200 ml) were added, the organic layer was washed with a 3.5 wt% aqueous potassium hydrogen carbonate solution (200 ml) and then water (200 ml), and the organic layer was dried over anhydrous magnesium sulfate. After filtration, the solvent was distilled off under reduced pressure, and the resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate) to give tp004-i (11.4 g, 92%).

LCMS (ESI) m/z = 684 (M+Na)+

Retention time: 1.49 min (Analytical condition SMD method_04)

[0720]

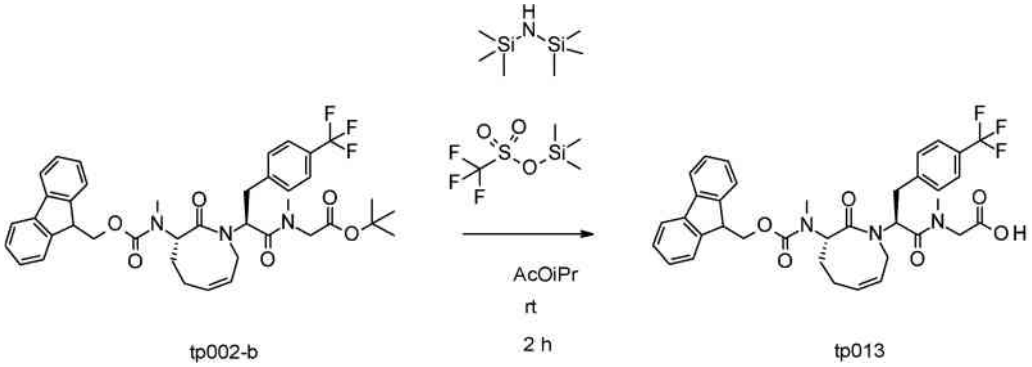
Using tp004-i as a starting material, tp004 (5.3 g, 94%) was obtained in the same manner as synthesis of Compound tp005.

LCMS (ESI) m/z = 628 (M+Na)+

Retention time: 1.16 min (Analytical condition SMD method_04)

[0721]

<u>Synthesis of Compound tp013</u>



[0722]

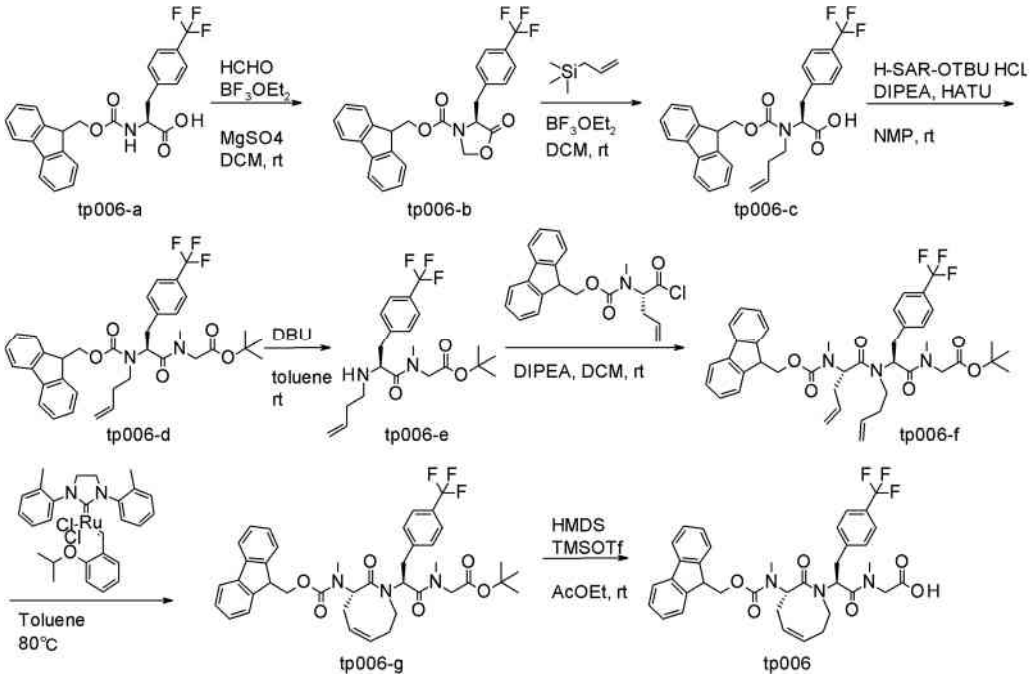
Using tp002-b as a starting material, tp013 (760.7 mg, 94%) was obtained in the same manner as synthesis of Compound tp005.

LCMS (ESI) m/z = 664 (M+H)+

Retention time: 1.32 min (Analytical condition SMD method_04)

[0723]

Synthesis of Compound tp006



[0724]

Magnesium sulfate (6.61 g, 54.9 mmol) and paraformaldehyde (1.98 g, 65.9 mmol) were added at room temperature to a dichloromethane (200 mL) solution of Compound tp006-a (N-([(9H-fluoren-9-yl)methoxy]carbonyl)-4-(trifluoromethyl)-L-phenylalanine) (10.0 g, 22.0 mmol), and then a boron trifluoride diethyl ether complex (2.78 mL, 22.0 mmol) was added dropwise. After the reaction mixture was stirred at room temperature for 1 hour, the reaction

solution was filtered through silica gel (24 g) and then concentrated under reduced pressure to give a crude product tp006-b (10.5 g, quant.).

LCMS (ESI) m/z = 468 (M+H)+

Retention time: 1.45 min (Analytical condition SMD method_04)

[0725]

The resulting crude product tp006-b (10.3 g, 22.0 mmol) was dissolved in dichloromethane (200 mL), and allyltrimethylsilane (12.2 mL, 77.0 mmol) was added in a nitrogen atmosphere, and a boron trifluoride diethyl ether complex (7.0 mL, 54.9 mmol) was added dropwise. After the reaction mixture was stirred at room temperature for 6 hours, allyltrimethylsilane (12.2 mL, 77.0 mmol) and a boron trifluoride diethyl ether complex (7.0 mL, 54.9 mmol) were added, and the mixture was stirred for 3 days. Water (40 mL) was added to the reaction solution, the mixture was stirred at room temperature for 10 minutes, filtered through Celite, the filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in toluene (24 mL). The organic layer was washed with water (48 mL), hexane (100 mL) was added, and the mixture was extracted with a mixed solution (2:1, 300 mL) of a 3.5% aqueous potassium hydrogen carbonate solution and acetonitrile. Phosphoric acid was added to the resulting aqueous layer until pH 3, and then the mixture was extracted with ethyl acetate (200 mL). The organic layer was washed with saturated brine (100 mL), dried over anhydrous magnesium sulfate, and then filtered. The resulting solution was concentrated under reduced pressure to give Compound tp006-c (10.3 g, 92%).

LCMS (ESI) m/z = 510 (M+H)+

Retention time: 1.00 min (Analytical condition SMD method_08)

[0726]

After HATU (60.4 g, 159 mmol) was added to an NMP (379 mL) solution of Compound tp006-c (67.5 g, 132 mmol) and sarcosine tert-butyl ester hydrochloride (25.3 g, 139 mmol), DIPEA (69. 2 mL, 397 mmol) was added dropwise. After the reaction mixture was stirred at room temperature for 1.5 hours, toluene (1.0 L, 15 v/w) was added, and the organic layer was washed with water (473 mL, 7 v/w), a 3.5% aqueous potassium hydrogen carbonate solution (473 mL, 7 v/w), and a 1 M aqueous potassium dihydrogen phosphate solution (473 mL, 7 v/w). The organic layer was dried by being passed through an anhydrous magnesium sulfate pad and washed with toluene (67.5 mL, 1 v/w), and the resulting filtrate and washing solution were combined to give Compound tp006-d, which was directly used in the next reaction as a solution.

LCMS (ESI) m/z = 637 (M+H)+

Retention time: 1.66 min (Analytical condition SMD method_10)

[0727]

DBU (1.97 mL, 13.2 mmol) was added to a toluene solution of the above Compound tp-006-d (132 mmol) at room temperature. The reaction mixture was stirred at room temperature for 17 hours and then washed with a 1 M aqueous potassium dihydrogen phosphate solution (420 mL, 5 v/w). The resulting organic layer was diluted with n-hexane (840 mL, 10 v/w), and then extracted twice with a mixed solution of 2 N hydrochloric acid (99 mL, 198 mmol), water (840 mL, 10 v/w), and acetonitrile (588 mL, 7 v/w). A 3.3 M aqueous potassium phosphate solution was added to the resulting aqueous layer to adjust the pH to 9.5, and the mixture was extracted with ethyl acetate (840 mL, 10 v/w). The organic layer was concentrated under reduced pressure, the resulting residue was dissolved in ethyl acetate (840 mL, 10 v/w), washed with brine (420 mL, 5 v/w), dried over anhydrous magnesium sulfate, and then filtered. The resulting solution was concentrated under reduced pressure to give Compound tp006-e (49.0 g, 90%).

LCMS (ESI) m/z = 415 (M+H)+

Retention time: 1.31 min (Analytical condition SMD method_10)

[0728]

DIPEA (72.3 mL, 414 mmol) was added to a dichloromethane (276 mL) solution of Compound tp006-e (49.0 g, 118 mmol). The resulting mixture was added dropwise to a separately prepared dichloromethane (276 mL) solution of (9H-fluoren-9-yl)methyl (S)-(1-chloro-1-oxopent-4-en-2-yl)(methyl)carbamate (described below) over 30 minutes. After the resulting reaction mixture was stirred at room temperature for 17 hours, the organic layer was washed with a 5% aqueous sodium dihydrogen phosphate solution (500 mL, 10 v/w), dried over anhydrous magnesium sulfate, and then filtered, and the solution was concentrated under reduced pressure. The resulting crude product was purified by normal phase silica gel chromatography (n-hexane/ethyl acetate) to give Compound tp006-f (45.0 g, 51%).

[0729]

(9H-Fluoren-9-yl)methyl (S)-(1-chloro-1-oxopent-4-en-2-yl)(methyl)carbamate was prepared as follows. After thionyl chloride (21.6 mL, 296 mmol) was added to a dichloromethane (296 mL) solution of (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pent-4-enoic acid (41.6 g, 118 mmol), DMF (0.92 mL, 11.8 mmol) was added dropwise. The resulting reaction mixture was stirred at room temperature for 15 minutes and then concentrated under reduced pressure. Toluene (20 mL, 5 v/w) was added to the resulting residue, and the mixture was concentrated under reduced pressure. The resulting crude product was dissolved in dichloromethane (276 mL) and used in the above-described reaction.

LCMS (ESI) m/z = 748 (M+H)+

Retention time: 1.71 min (Analytical condition SMD method_10)

[0730]

A dichloroethane (891 mL) solution of Compound tp006-f (16.7 g, 22.3 mmol), benzoquinone (0.24 g, 2.23 mmol), and a Stewart-Grubbs catalyst (0.51 g, 0.89 mmol) was degassed 5 times, and stirred at 80°C for 4 hours in a nitrogen atmosphere. The reaction mixture was cooled to room temperature, and then concentrated under reduced pressure, and the resulting crude product was purified by normal phase silica gel column chromatography (hexane/ethyl acetate) to give Compound tp006-g (33.9 g, 39%).

LCMS (ESI) m/z = 720 (M+H)+

Retention time: 1.00 min (Analytical condition SMD method_07)

[0731]

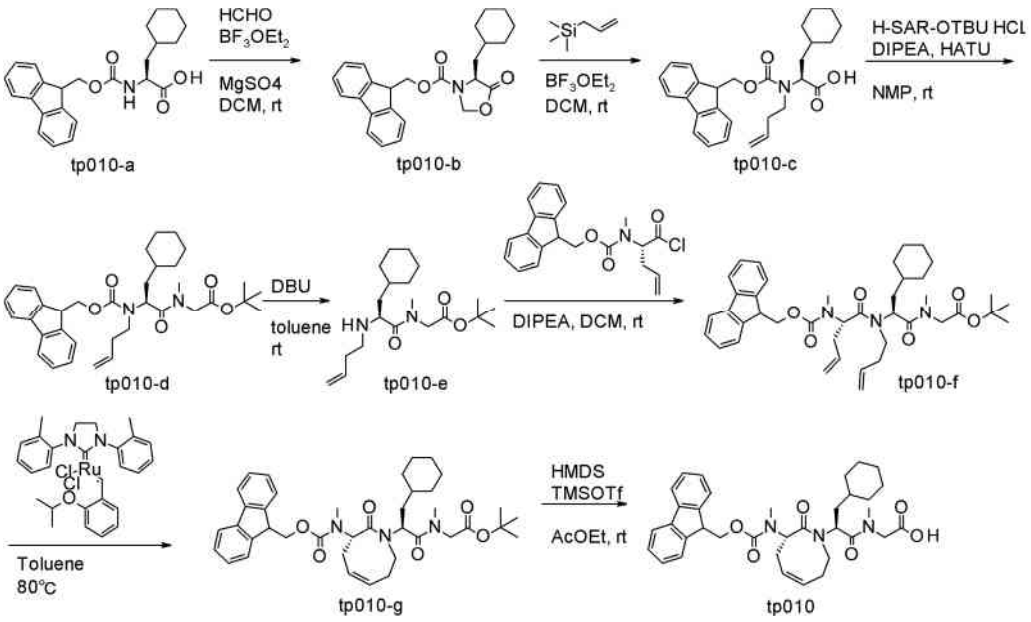
After hexamethyldisilazane (24.7 mL, 118 mmol) was added to an ethyl acetate (236 mL) solution of tp006-g (33.9 g, 47.1 mmol) in a nitrogen atmosphere, trimethylsilyl trifluoromethanesulfonate (17.0 mL, 94 mmol) was added dropwise while cooling the mixture in a water bath (25°C). After the reaction mixture was stirred at room temperature for 1.5 hours, a 5% aqueous disodium hydrogen phosphate solution (340 mL, 10 v/w) was added while cooling the mixture in an ice bath to quench the reaction. Water (170 mL, 5 v/w) and phosphoric acid were added to the resulting mixture to adjust the pH to 3. The separated organic layer was washed with saturated brine (340 mL, 10 v/w), dried over anhydrous magnesium sulfate, and filtered, and the solution was concentrated under reduced pressure. The resulting crude product was purified by reverse phase column chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water), and collected fractions were purified by reverse phase column chromatography (acetonitrile/distilled water) to give Compound tp006 (22.4 g, 72%).

LCMS (ESI) m/z = 664 (M+H)+

Retention time: 0.63 min (Analytical condition SMD method_06)

[0732]

Synthesis of Compound tp010



[0733]

Using Compound tp010-a ((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-cyclohexylpropanoic acid) (14.0 g, 35.6 mmol) as a starting material, a crude product tp010-b (14.4 g, quant.) was obtained in the same manner as synthesis of Compound tp006-b.

LCMS (ESI) m/z = 406 (M+H)+

Retention time: 0.78 min (Analytical condition SQDAA50_2)

[0734]

Using the resulting crude product tp010-b (14.4 g, 35.6 mmol), Compound tp010-c (12.6 g, 79%) was obtained in the same manner as synthesis of Compound tp006-c.

LCMS (ESI) m/z = 448 (M+H)+

Retention time: 0.71 min (Analytical condition SQDAA50_2)

[0735]

Using Compound tp010-c (12.6 g, 28.3 mmol), a toluene solution of Compound tp010-d was obtained in the same manner as synthesis of Compound tp006-d. The resulting solution of Compound tp010-d was directly used in the next reaction.

LCMS (ESI) m/z = 575 (M+H)+

Retention time: 0.88 min (Analytical condition SQDAA50_2)

[0736]

Using a toluene solution of the above Compound tp010-d (28.3 mmol), Compound tp010-e (9.0 g, 91%) was obtained in the same manner as synthesis of Compound tp006-e.

LCMS (ESI) m/z = 353 (M+H)+

Retention time: 0.66 min (Analytical condition SQDAA50_2)

[0737]

Using Compound tp010-e (4.5 g, 12.8 mmol), Compound tp010-f (8.6 g, 98%) was obtained in the same manner as synthesis of Compound tp006-f.

LCMS (ESI) m/z = 708 (M+Na)+

Retention time: 0.91 min (Analytical condition SQDAA50_2)

[0738]

After nitrogen bubbling in a dichloroethane (469 mL) solution of Compound tp010-f (8.0 g, 11.7 mmol) and a Stewart-Grubbs catalyst (0.17 g, 0.29 mmol), the mixture was stirred at 80°C for 16 hours in a nitrogen atmosphere. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure, and the resulting crude product was purified by normal phase silica gel column chromatography (n-hexane/ethyl acetate) to give Compound tp010-g (5.7 g, 73%).

LCMS (ESI) m/z = 680 (M+Na)+

Retention time: 0.84 min (Analytical condition SQDAA50_2)

[0739]

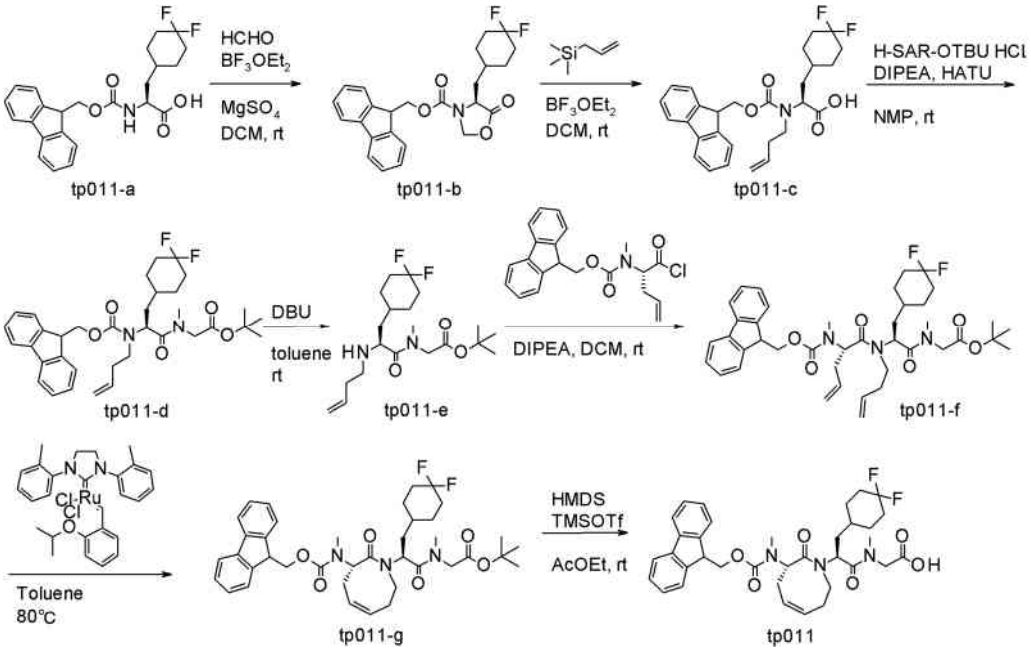
Using Compound tp010-g (5.7 g, 8.6 mmol), Compound tp010 (3.8 g, 74%) was obtained in the same manner as synthesis of Compound tp006.

LCMS (ESI) m/z = 624 (M+Na)+

Retention time: 0.69 min (Analytical condition SQDFA40)

[0740]

Synthesis of Compound tp011



[0741]

Using Compound tp011-a ((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4,4-difluorocyclohexyl)propanoic acid) (14.0 g, 32. 6 mmol) as a starting material, a crude

product tp011-b (14.4 g, quant.) was obtained in the same manner as synthesis of Compound tp006-b.

LCMS (ESI) m/z = 464 (M+Na)+

Retention time: 0.69 min (Analytical condition SQDAA50_2)

[0742]

Using the resulting crude product tp011-b (14.4 g, 32.6 mmol), Compound tp011-c (11.6 g, 73%) was obtained in the same manner as synthesis of Compound tp006-c.

LCMS (ESI) m/z = 484 (M+H)+

Retention time: 0.65 min (Analytical condition SQDAA50_2)

[0743]

Using Compound tp011-c (11.6 g, 23.9 mmol), a toluene solution of Compound tp011-d was obtained in the same manner as synthesis of Compound tp006-d. The resulting solution of Compound tp011-d was directly used in the next reaction.

LCMS (ESI) m/z = 611 (M+H)+

Retention time: 0.82 min (Analytical condition SQDAA50_2)

[0744]

Using a toluene solution of the above Compound tp011-d (23.9 mmol), Compound tp011-e (8.6 g, 92%) was obtained in the same manner as synthesis of Compound tp-006-e.

LCMS (ESI) m/z = 389 (M+H)+

Retention time: 0.58 min (Analytical condition SQDAA50_2)

[0745]

Using Compound tp011-e (4.3 g, 11.0 mmol), Compound tp011-f (6.9 g, 87%) was obtained in the same manner as synthesis of Compound tp006-f.

LCMS (ESI) m/z = 744 (M+Na)+

Retention time: 0.86 min (Analytical condition SQDAA50_2)

[0746]

Using Compound tp011-f (6.9 g, 9.6 mmol), Compound tp011-g (4.8 g, 72%) was obtained in the same manner as synthesis of Compound tp010-g.

LCMS (ESI) m/z = 716 (M+Na)+

Retention time: 0.79 min (Analytical condition SQDAA50_2)

[0747]

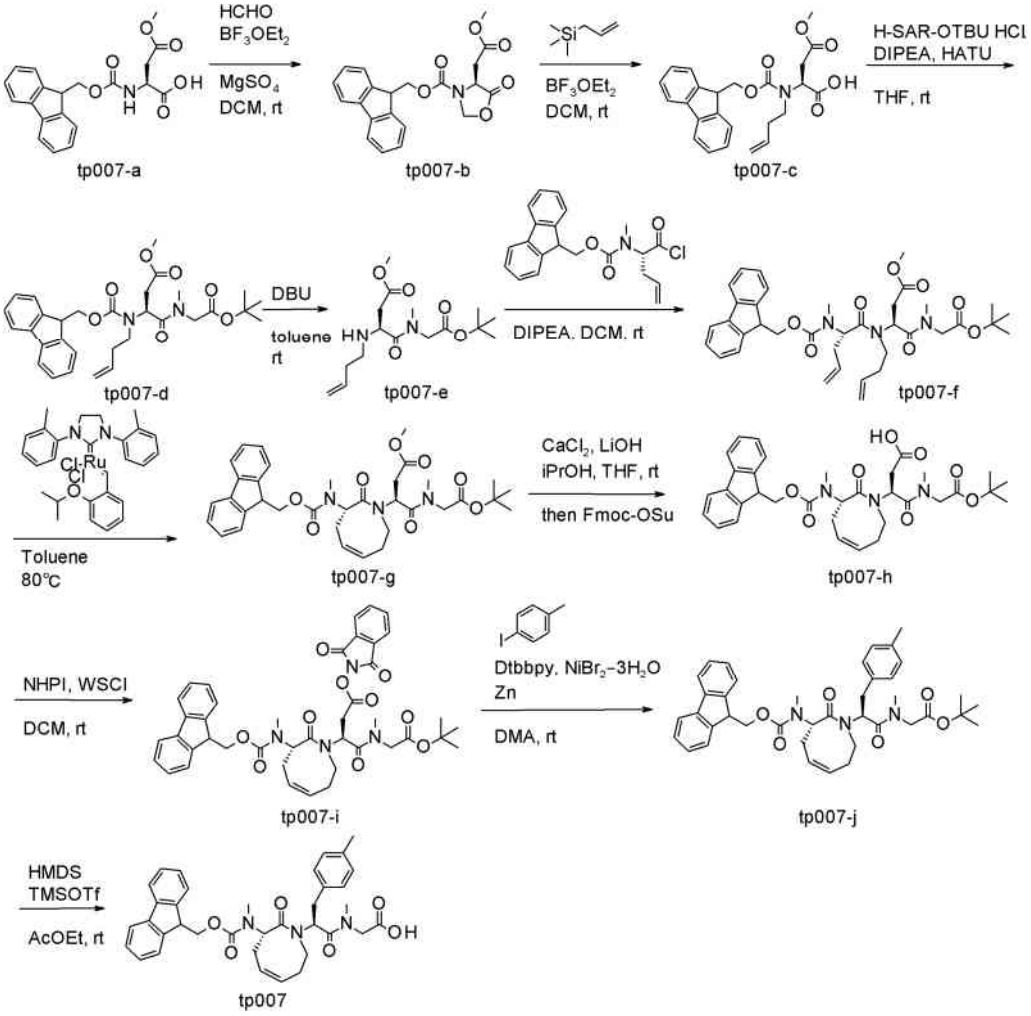
Using Compound tp011-g (4.8 g, 7.0 mmol), Compound tp011 (2.8 g, 64%) was obtained in the same manner as synthesis of Compound tp006.

LCMS (ESI) m/z = 660 (M+Na)+

Retention time: 0.63 min (Analytical condition SQDFA40)

[0748]

Synthesis of Compound tp007



[0749]

Compound tp007-a ((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-methoxy-4-oxobutanoic acid) (30.0 g, 81.0 mmol) as a starting material was reacted in the same manner as synthesis of Compound tp006-b, and the filtrate obtained by Celite-filtering the reaction solution was regarded as Compound tp007-b and directly used in the next reaction.

LCMS (ESI) m/z = 382 (M+H)+

Retention time: 1.22 min (Analytical condition SMD method_04)

[0750]

Using a dichloromethane solution of the above Compound tp007-b (81.0 mmol), Compound tp007-c (35.9 g, quant.) was obtained in the same manner as synthesis of Compound tp006-c.

LCMS (ESI) m/z = 424 (M+H)+

Retention time: 0.85 min (Analytical condition SMD method_10)

[0751]

Compound tp007-c (34.3 g, 81.0 mmol) was dissolved in tetrahydrofuran (231 mL), reacted in the same manner as synthesis of tp006-d, and then purified by normal phase column chromatography (hexane/ethyl acetate) to give Compound tp007-d (44.4 g, 100%).

LCMS (ESI) m/z = 551 (M+H)+

Retention time: 1.45 min (Analytical condition SMD method_04)

[0752]

Using Compound tp007-d (44.4 g, 81.0 mmol), Compound tp007-e (23.3 g, 88%) was obtained in the same manner as synthesis of tp006-e.

LCMS (ESI) m/z = 329 (M+H)+

Retention time: 0.58 min (Analytical condition SMD method_04)

[0753]

Using Compound tp007-e (23.3 g, 71.0 mmol), Compound tp007-f (43.5 g, 93%) was obtained in the same manner as synthesis of tp006-f.

LCMS (ESI) m/z = 662 (M+H)+

Retention time: 1.54 min (Analytical condition SMD method_04)

[0754]

After a dichloroethane (996 mL) solution of a Stewart-Grubbs catalyst (0.47 g, 0.82 mmol) was degassed 4 times, a dichloroethane (100 mL) solution of Compound tp007-f (21.8 g, 32.9 mmol) was added dropwise over 1 hour while being stirred at 80°C in a nitrogen atmosphere. The reaction mixture was stirred at 80°C for 1 hour and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure, and the resulting crude product was purified by reverse phase column chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound tp007-g (20.8 g, 50%).

LCMS (ESI) m/z = 634 (M+H)+

Retention time: 1.39 min (Analytical condition SMD method_04)

[0755]

After calcium chloride (61.1 g, 551 mmol) was dissolved in water (153 mL), lithium hydroxide monohydrate (6.16 g, 147 mmol) was added at room temperature. After the mixture was stirred for 5 minutes, isopropanol (612 mL) and a tetrahydrofuran solution (153 mL) of Compound tp007-g (23.3 g, 36.7 mmol) were added and stirred overnight at room temperature. Fmoc-OSu (12.4 g, 36.7 mmol) was added, the mixture was stirred for 2 hours, then water (460 mL, 20 v/w) was added, 2 N hydrochloric acid was added to adjust the pH to 2.5, and the mixture was extracted with ethyl acetate (460 mL, 20 v/w). The organic layer was washed with saturated brine (230 mL, 10 v/w) and concentrated under reduced pressure. Ethyl acetate (115 mL, 5 v/w), acetonitrile (115 mL, 5 v/w), and hexane (230 mL, 10 v/w) were added to and

dissolve the resulting residue, and the mixture was extracted with a 3.5% aqueous potassium hydrogen carbonate solution (230 mL, 10 v/w). Phosphoric acid was added to the resulting aqueous layer to adjust the pH to 3, and then the mixture was extracted with ethyl acetate (115 mL, 5 v/w). The organic layer was washed with saturated brine (70 mL, 3 v/w) and concentrated under reduced pressure, and the resulting crude product was purified by reverse phase column chromatography (0.1%-formic acid containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound tp007-h (12.6 g, 56%).

LCMS (ESI) m/z = 620 (M+H)+

Retention time: 0.94 min (Analytical condition SMD method_10)

[0756]

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.87 g, 30.6 mmol) was added to a dichloromethane (93 ml) suspension of Compound tp007-h (12.6 g, 20.4 mmol) and N-hydroxyphthalimide (3.66 g, 22.4 mmol), and the mixture was stirred at room temperature for 2.5 hours. The reaction mixture was washed with water, then the organic layer was concentrated under reduced pressure, and the resulting crude product was purified by normal phase column chromatography (hexane/ethyl acetate) to give Compound tp007-i (15.1 g, 97%).

LCMS (ESI) m/z = 765 (M+H)+

Retention time: 1.35 min (Analytical condition SMD method_05)

[0757]

Nickel(II) bromide trihydrate (2.47 g, 6.46 mmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (1.73 g, 6.46 mmol) were dissolved in DMA (20 mL) to prepare a nickel solution. The nickel solution prepared in advance and chlorotrimethylsilane (0.41 mL, 3.23 mmol) were added to a DMA (110 mL) suspension of Compound tp007-i (4.94 g, 6.46 mmol), zinc powder (6.33 g, 97.0 mmol), and 1-iodo-4-methylbenzene (14.1 g, 64.6 mmol), and the mixture was stirred at room temperature for 2 hours. The resulting reaction mixture was purified by reverse phase column chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound tp007-j (2.7 g, 63%).

LCMS (ESI) m/z = 666 (M+H)+

Retention time: 1.57 min (Analytical condition SMD method_04)

[0758]

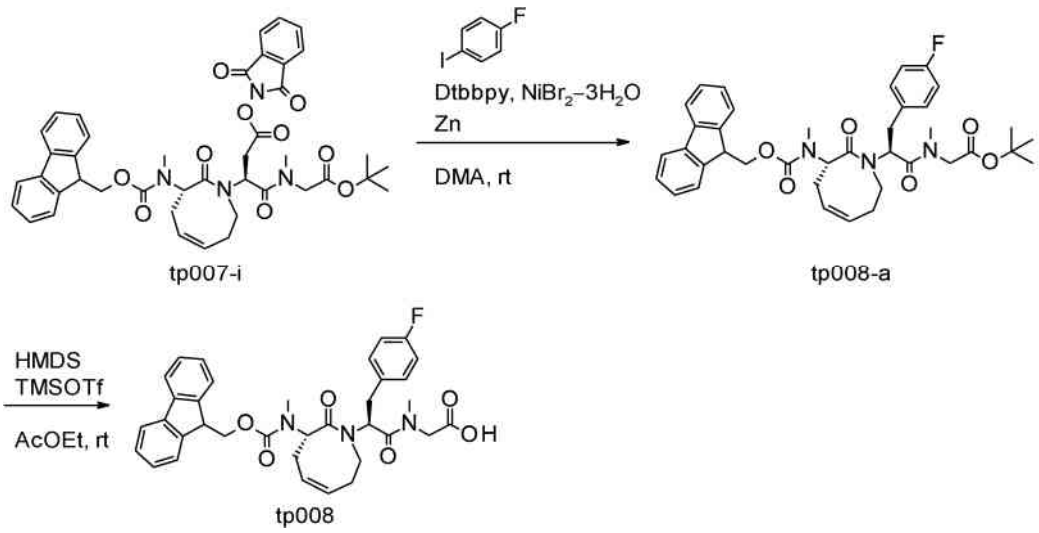
Using Compound tp007-j (2.6 g, 3.90 mmol), Compound tp007 (1.78 g, 45%) was obtained in the same manner as synthesis of tp006.

LCMS (ESI) m/z = 610 (M+H)+

Retention time: 1.26 min (Analytical condition SMD method_04)

[0759]

Synthesis of Compound tp008



[0760]

In a nitrogen atmosphere, nickel(II) bromide trihydrate (1.33 g, 4.89 mmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (1.31 g, 4.89 mmol) were dissolved in DMA (48.9 mL), and the mixture was stirred at room temperature for 30 minutes to prepare a nickel solution. The nickel solution prepared in advance and chlorotrimethylsilane (0.31 mL, 2.45 mmol) were added to a DMA (48.9 mL) suspension of Compound tp007-i (3.74 g, 4.89 mmol), zinc powder (4.80 g, 73.3 mmol), and 1-fluoro-4-iodobenzene (10.2 mL, 88.0 mmol), and the mixture was stirred at room temperature for 1 hour. The resulting reaction mixture was filtered through Celite, and the filtrate was washed with an aqueous ammonium chloride solution (37 mL, 10 v/w). The organic layer was dried over anhydrous magnesium sulfate and then filtered, and the solution was concentrated under reduced pressure. The resulting crude product was purified by normal phase silica gel chromatography (hexane/ethyl acetate) to give Compound tp008-a (2.97 g, 72%).

LCMS (ESI) m/z = 670 (M+H)+

Retention time: 1.39 min (Analytical condition SMD method_05)

[0761]

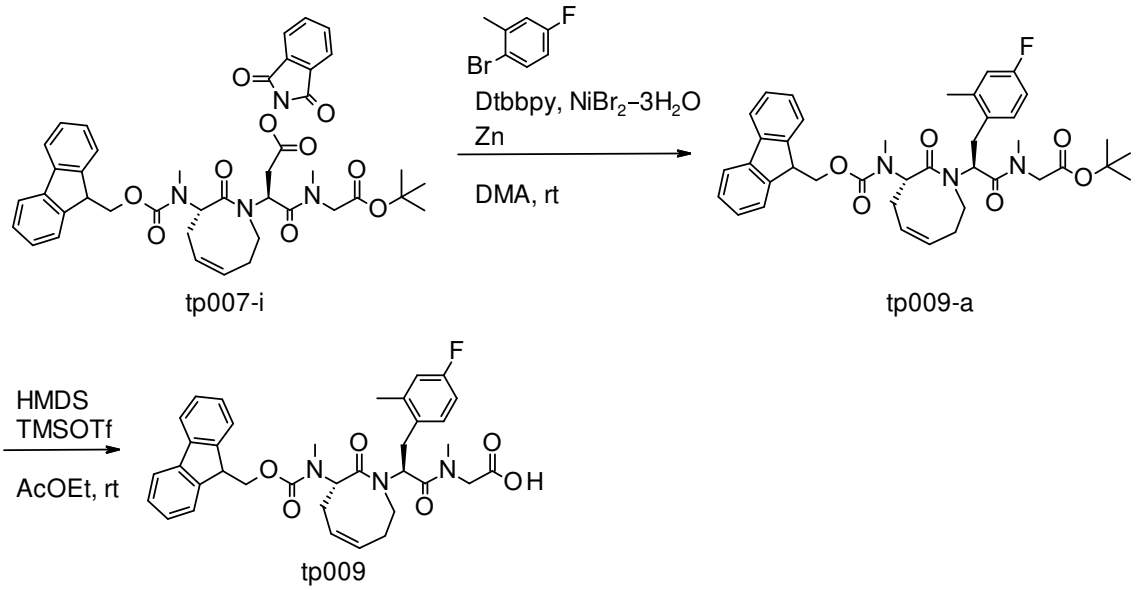
Using Compound tp008-a (2.97 g, 4.43 mmol), Compound tp008 (2.36 g, 87%) was obtained in the same manner as synthesis of tp006.

LCMS (ESI) m/z = 614 (M+H)+

Retention time: 1.22 min (Analytical condition SMD method_04)

[0762]

Synthesis of Compound tp009



[0763]

In a nitrogen atmosphere, nickel(II) bromide trihydrate (1.76 g, 6.41 mmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (1.72 g, 6.41 mmol) were dissolved in DMA (64.1 mL) to prepare a nickel solution. The nickel solution prepared in advance and chlorotrimethylsilane (0.41 mL, 3.20 mmol) were added to a DMA (64.1 mL) suspension of Compound tp007-i (4.90 g, 6.41 mmol), zinc powder (6.28 g, 96.0 mmol), and 1-bromo-4-fluoro-2-methylbenzene (16.2 mL, 128 mmol), and the mixture was stirred at room temperature for 2 hours. The resulting reaction mixture was filtered through Celite, and a 15% aqueous ammonium chloride solution (150 mL, 30 v/w) was added to the filtrate to separate the organic layer. After the organic layer was washed with an 8% aqueous EDTA disodium solution (150 mL, 30 v/w) and 10% brine (150 mL, 30 v/w), the organic layer was dried over anhydrous magnesium sulfate and then filtered, and the solution was concentrated under reduced pressure. The resulting crude product was purified by normal phase silica gel chromatography (hexane/ethyl acetate) to give Compound tp009-a (2.43 g, 55%).

LCMS (ESI) m/z = 684 (M+H)+

Retention time: 1.42 min (Analytical condition SMD method_05)

[0764]

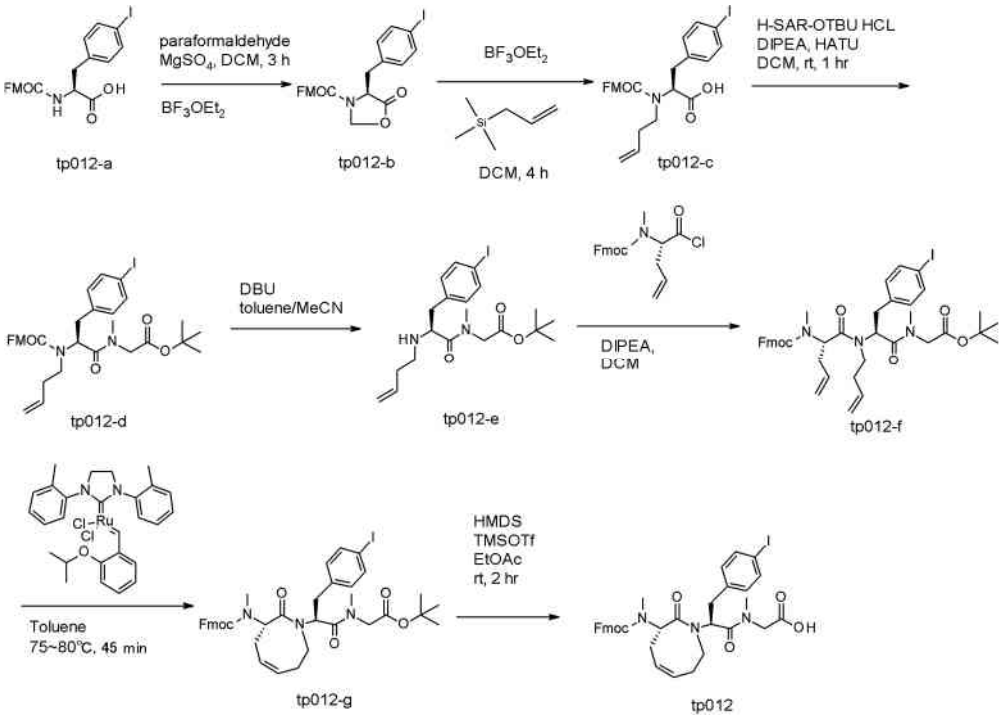
Using Compound tp009-a (2.42 g, 3.54 mmol), Compound tp009 (1.76 g, 79%) was obtained in the same manner as synthesis of tp006.

LCMS (ESI) m/z = 628 (M+H)+

Retention time: 1.26 min (Analytical condition SMD method_04)

[0765]

Synthesis of Compound tp012



[0766]

tp012-a (4.88 g, 9.51 mmol) was dissolved in dichloromethane (95 mL), then anhydrous magnesium sulfate (2.86 g, 23.8 mmol), paraformaldehyde (856 mg, 28.5 mmol), and a boron trifluoride diethyl ether complex (1.2 mL, 9.51 mmol) were added, and the mixture was stirred at room temperature for 3 hours. The reaction solution was filtered through silica gel, silica gel was washed with dichloromethane (100 mL), and the filtrate was concentrated under reduced pressure to give a crude product (4.50 g) of tp012-b.

LCMS (ESI) m/z = 548 (M+Na)+

Retention time: 1.10 min (Analytical condition SQDAA05)

[0767]

In a nitrogen atmosphere, the above tp012-b (9.51 mmol) was dissolved in dichloromethane (95 mL), then allyltrimethylsilane (10.6 mL, 66.6 mmol) and a boron trifluoride diethyl ether complex (6.0 mL, 47.6 mmol) were added, and the mixture was stirred at room temperature for 88 hours. The reaction solution was cooled to 0°C, and water (20 mL) was added. The mixed solution was filtered through Celite, and Celite was washed with dichloromethane (100 mL). The resulting filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in toluene (50 mL) and washed with water (24 mL) and a 1 M aqueous dipotassium hydrogen phosphate solution (24 mL). Hexane (100 mL) was added to the organic phase, and the mixture was extracted 5 times with a 3.5% aqueous potassium hydrogen carbonate solution/acetonitrile (2/1, 42 mL). The aqueous phase was washed twice

with hexane (40 mL), 2 N hydrochloric acid was added to adjust the pH to 2, and then the mixture was extracted 3 times with ethyl acetate (50 mL). The organic phase was washed with brine (24 mL) and concentrated under reduced pressure to give tp012-c (4.09 g, 76%).

LCMS (ESI) m/z = 568 (M+H)+

Retention time: 1.03 min (Analytical condition SQDFA05)

[0768]

In a nitrogen atmosphere, tp012-c (3.09 g, 5.45 mmol) and sarcosine tert-butyl ester hydrochloride (989 mg, 5.45 mmol) were dissolved in dichloromethane (16 mL), then DIPEA (2.85 ml, 16.34 mmol) and HATU (2.49 g, 6.53 mmol) were added, and the mixture was stirred at room temperature for 1 hour. Subsequently, the reaction solution was successively washed with water (30 mL), a 3.5% aqueous potassium hydrogen carbonate solution (30 mL), and a 1 M aqueous dipotassium hydrogen phosphate solution (30 mL), and the organic phase was dried over anhydrous sodium sulfate. The resulting solution was concentrated under reduced pressure to give a crude product of tp012-d. The resulting tp012-d was directly used in the next step.

LCMS (ESI) m/z = 695 (M+H)+

Retention time: 0.82 min (Analytical condition SQDFA50)

[0769]

The crude product (5.45 mmol) of tp012-d was dissolved in toluene (32.7 mL) and acetonitrile (3.63 mL), DBU (0.81 mL) was added, and the mixture was stirred at room temperature for 20 minutes. A 1 M aqueous potassium dihydrogen phosphate solution (30 mL), n-hexane (60 mL), water (40 mL), acetonitrile (20 mL), and 2 N hydrochloric acid (4.2 mL) were added to the reaction solution and shaken, then the mixture separated into three layers. Water (40 mL), acetonitrile (20 mL), and toluene (20 mL) were further added, but the three-layer separation did not disappear, thus the upper-layer organic phase was discarded, and an aqueous 3 M potassium phosphate solution (4 mL) was added to the remaining lower two layers to adjust the pH to 8. The resulting mixed solution was extracted twice with ethyl acetate (30 mL), and the organic phase was washed with saturated brine (20 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give tp012-e (2.74 g, 85%, 2 steps).

LCMS (ESI) m/z = 473.6 (M+H)+

Retention time: 0.57 min (Analytical condition SQDFA05)

[0770]

In a nitrogen atmosphere, (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pent-4-enoic acid (2.80 g, 7.96 mmol) was dissolved in DCM (20 ml) at room temperature, DMF (0.062 ml, 0.796 mmol) was added, and then thionyl

chloride (1.45 ml, 19.9 mmol) was added dropwise. The resulting reaction mixture was stirred for 20 minutes and then concentrated under reduced pressure. Toluene (7 ml) was added to the resulting residue, and the mixture was concentrated under reduced pressure. This operation was performed twice in total, and the resulting crude product was dissolved in DCM (16 mL) and used in the subsequent reaction.

[0771]

In a nitrogen atmosphere, a DCM (20 mL) solution of tp012-e (3.42 g, 7.24 mmol) and DIPEA (4.41 mL, 25.3 mmol) was added to the prepared DCM (16 ml) solution of (9H-fluoren-9-yl)methyl (S)-(1-chloro-1-oxopent-4-en-2-yl)(methyl)carbamate. The reaction solution was stirred at room temperature for 3 hours, and then washed with a 1 M aqueous potassium dihydrogen phosphate solution (35 mL). Subsequently, the organic phase was washed with a 3.5% aqueous potassium hydrogen carbonate solution (35 mL) and concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography (n-hexane/ethyl acetate) to give tp012-f (4.45 g, 76%).

LCMS (ESI) m/z = 806.5 (M+H)+

Retention time: 0.88 min (Analytical condition SQDAA50)

[0772]

In a nitrogen atmosphere, tp012-f (2.79 g, 3.46 mmol) was dissolved in 1,2-dichloroethane (115 mL) in a three-neck flask, and a first-generation Grubbs catalyst (60 mg, 0.0715 mmol) was added. While warming to 80°C and stirring the reaction solution, a 1,2-dichloroethane (15 mL) solution of a first-generation Grubbs catalyst (60 mg, 0.0715 mmol) was added dropwise over 2 hours with a syringe pump. Subsequently, the reaction solution was stirred at 80°C for 1 hour, cooled to room temperature, and then concentrated under reduced pressure. To complete the reaction, the resulting crude product was again dissolved in 1,2-dichloroethane (115 mL) in a nitrogen atmosphere, a first-generation Grubbs catalyst (240 mg, 0.286 mmol) was added, and the mixture was stirred at 80°C for 90 minutes. The reaction solution was cooled to room temperature, and then concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography (n-hexane/ethyl acetate) to give tp012-g (1.57 g, 58%).

LCMS (ESI) m/z = 778.5 (M+H)+

Retention time: 0.74 min (Analytical condition SQDFA50)

[0773]

In a nitrogen atmosphere, tp012-g (1.57 g, 2.02 mmol) was dissolved in ethyl acetate (24 mL), hexamethyldisilazane (1.481 mL, 7.07 mmol) was added, and then trimethylsilyl trifluoromethanesulfonate (1.02 mL, 5.65 mmol) was added dropwise. The resulting reaction mixture was stirred for 150 minutes, then the reaction solution was diluted with ethyl acetate (20

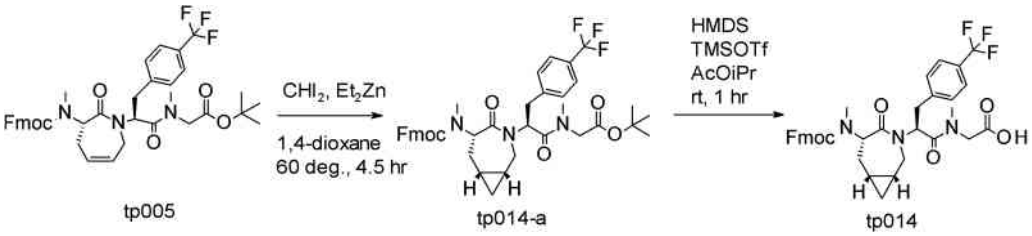
mL), and a 1 M aqueous disodium hydrogen phosphate solution (40 ml) was added to quench the reaction. The organic phase was separated, and the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give tp012 (1.02 g, 70%).

LCMS (ESI) m/z = 722 (M+H)+

Retention time: 0.47 min (Analytical condition SQDFA50)

[0774]

Synthesis of Compound tp014



tp005 tp014-a tp014

[0775]

In a nitrogen atmosphere, tp005 (0.75 g, 1.06 mmol) was dissolved in 1,4-dioxane (5.3 mL), a 1 M diethylzinc toluene solution (5.31 mL, 5.31 mmol) was added, and then diiodomethane (0.856 mL, 10.63 mmol) was added dropwise. The reaction solution was heated to 60°C, stirred at 60°C for 4 and a half hours and cooled to room temperature, and a saturated aqueous ammonium chloride solution was added to quench the reaction. The organic phase was separated, the aqueous phase was extracted with ethyl acetate, and the resulting organic phases were combined and concentrated under reduced pressure.

[0776]

The same operation was repeated using tp005 (0.75 g, 1.06 mmol), and the resulting crude products were combined and purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give tp014-a (0.21 g, 14%). At this time, the raw-material tp005 (0.58 g, 39%) and a mixture of tp005 and tp014-a (3/2, 0.18 g, 12%) were also recovered.

LCMS (ESI) m/z = 720.5 (M+H)+

Retention time: 0.74 min (Analytical condition SQDFA50)

[0777]

In a nitrogen atmosphere, tp014-a (264 mg, 0.367 mmol) was dissolved in ethyl acetate (2.0 mL), hexamethyldisilazane (0.269 mL, 1.28 mmol) was added, and then trimethylsilyl trifluoromethanesulfonate (0.186 mL, 1.03 mmol) was added dropwise. The resulting reaction mixture was stirred for 1 hour, then the reaction solution was diluted with ethyl acetate (5 mL), and a 1 M aqueous disodium hydrogen phosphate solution (5 ml) was added to quench the

reaction. The organic phase was separated, and the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water).

[0778]

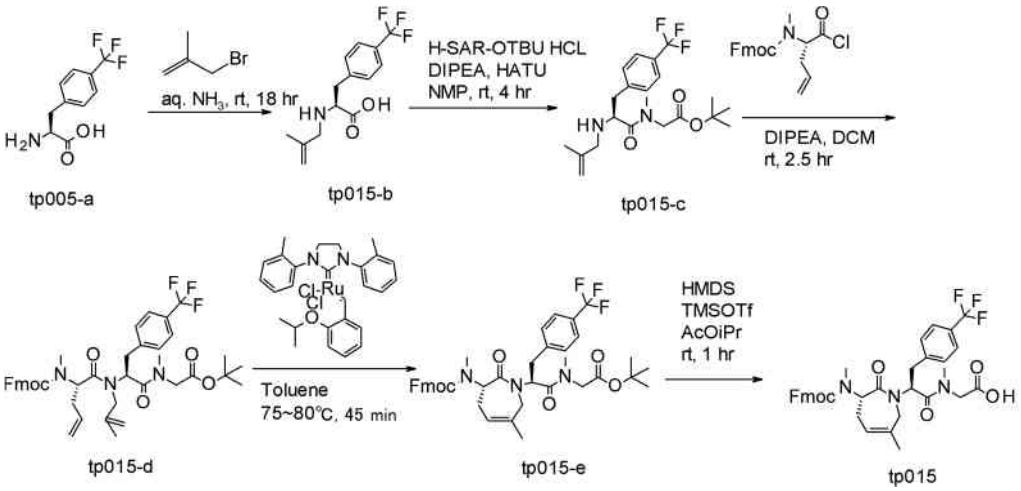
The same operation was repeated using tp014-a (142 mg, 0.197 mmol), hexamethyldisilazane (0.145 mL, 0.690 mmol), and trimethylsilyl trifluoromethanesulfonate (0.100 mL, 0.552 mmol), and, after reverse phase chromatography, the resulting products were combined to give tp014 (274 mg, 73%).

LCMS (ESI) m/z = 664.5 (M+H)+

Retention time: 0.97 min (Analytical condition SQDFA50 long)

[0779]

Synthesis of Compound tp015



[0780]

Aqueous ammonia (7.8 ml, 13.2 mmol) was added to a water (17.15 ml) suspension of tp005-a (2 g, 8.58 mmol) at room temperature to dissolve tp005-a, and then 3-bromo-2-methylpropene (5.19 ml, 51.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 18 hours, ethanol (6 ml) was added, and the mixture was further stirred at room temperature for 2 hours. The resulting white solids were collected by filtration, washed with water, and the vacuum-dried to give tp015-b (2.61 g, quant.).

LCMS (ESI) m/z = 289 (M+H)+

Retention time: 0.47 min (Analytical condition SQDFA05)

[0781]

In a nitrogen atmosphere, dehydrated NMP (10 ml) was added to a mixture of tp015-b (1 g, 3.48 mmol) and sarcosine tert-butyl ester hydrochloride (1.26 g, 6.96 mmol). DIPEA (2.43 ml, 13.92 mmol) was added dropwise to the resulting suspension, the mixture was stirred for about 3 minutes, and then HATU (2.65 g, 6.96 mmol) was added. After the reaction

mixture was stirred at room temperature for 4 hours, ethyl acetate (20 ml), water (10 ml), and a 5% aqueous sodium carbonate solution (10 ml) were added. The separated organic phase was washed with a 5% aqueous sodium carbonate solution (20 ml), a 5% aqueous potassium hydrogen sulfate solution (20 ml × 2), and brine (20 ml), and dried over sodium sulfate. The crude product obtained by distilling off the solvent under reduced pressure was dissolved in TBME (5 ml), then hexane (5 ml) was added to precipitate the product, and the supernatant was removed. The operation of adding hexane (5 ml) and removing the supernatant was performed 2 more times, and vacuum drying was performed to give tp015-c (1.30 g, 90%).

LCMS (ESI) m/z = 415 (M+H)+

Retention time: 0.55 min (Analytical condition SQDFA05)

[0782]

In a nitrogen atmosphere, DIPEA (3,79 ml, 21.71 mmol) was added to a dehydrated DCM (20 ml) solution of tp015-c (3.0 g, 7.24 mmol). The resulting mixture was stirred while being cooled in a water bath (25°C), and a separately prepared DCM (5 ml) solution of (9H-fluoren-9-yl)methyl (S)-(1-chloro-1-oxopent-4-en-2-yl) (methyl)carbamate (described below) was added dropwise over 5 minutes. The resulting reaction mixture was stirred at room temperature for 2.5 hours, and then the solvent was distilled off under reduced pressure. Ethyl acetate (30 ml) and water (12 ml) were added to the resulting residue. The separated organic phase was washed with brine (12 ml × 2) and dried over sodium sulfate, and then the solvent was distilled off under reduced pressure. The resulting crude product was purified by normal phase silica gel chromatography (hexane/ethyl acetate) to give tp015-d (4.56 g, 84%).

[0783]

(9H-Fluoren-9-yl)methyl (S)-(1-chloro-1-oxopent-4-en-2-yl)(methyl)carbamate was prepared as follows.

In a nitrogen atmosphere, (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pent-4-enoic acid (2.8 g, 7.97 mmol) was dissolved in DCM (15 ml) at room temperature, DMF (0.031 ml, 0.398 mmol) was added, and then thionyl chloride (1.45 ml, 19.92 mmol) was added dropwise. The resulting reaction mixture was stirred for 20 minutes and then concentrated under reduced pressure. Toluene (5 ml) was added to the resulting residue, and the mixture was concentrated under reduced pressure. This operation was performed 3 times in total, and the resulting crude product was dissolved in DCM and used in the above-described reaction.

LCMS (ESI) m/z = 749 (M+H)+

Retention time: 0.84 min (Analytical condition SQDFA05)

[0784]

In a nitrogen atmosphere, tp015-d (1.1 g, 1.47 mmol) and a Stewart-Grubbs catalyst (0.042 g, 0.074 mmol) were dissolved in degassed dehydrated toluene (45 ml), and the mixture was stirred at 75°C to 80°C for 45 minutes. After cooling to room temperature, the solvent was distilled off under reduced pressure, and the resulting crude product was purified by normal phase silica gel chromatography (hexane/ethyl acetate) to give tp015-e (1.22 g, 94%).

LCMS (ESI) m/z = 721 (M+H)+

Retention time: 0.75 min (Analytical condition SQDFA05)

[0785]

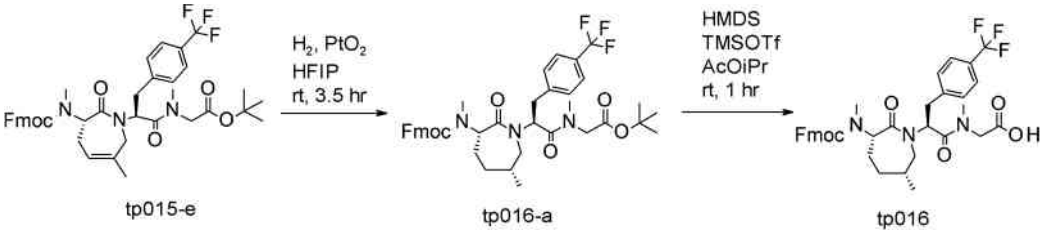
In a nitrogen atmosphere, tp015-e (1.0 g, 1.39 mmol) was dissolved in isopropyl acetate (5 ml), hexamethyldisilazane (0.728 ml, 3.47 mmol) was added, and then trimethylsilyl trifluoromethanesulfonate (0.5 ml, 2.78 mmol) was added dropwise. The resulting reaction mixture was stirred for 1 hour, and then 1 M dipotassium hydrogen phosphate (5 ml) was added to quench the reaction. The resulting mixture was extracted with ethyl acetate, the organic phase was washed with brine (10 ml × 2) and dried over sodium sulfate, and then the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give tp015 (1.0 g, 90%).

LCMS (ESI) m/z = 665 (M+H)+

Retention time: 0.91 min (Analytical condition SQDFA05)

[0786]

Synthesis of Compound tp016



tp015-e tp016-a tp016

[0787]

In a nitrogen atmosphere, 1,1,1,3,3,3-hexafluoropropan-2-ol (100 ml) was added to a mixture of tp015-e (4 g, 5.56 mmol) and platinum oxide (0.379 g, 1.67 mmol). The resulting mixture was depressurized while being stirred, and substituted with hydrogen. This hydrogen substitution operation was performed 3 times in total, and the mixture was stirred at room temperature for 3.5 hours in a hydrogen atmosphere. The reaction mixture was filtered through Celite and washed with ethyl acetate, and the solvent was distilled off under reduced pressure. The resulting crude product was purified by normal phase silica gel chromatography (hexane/ethyl acetate) to give tp016-a (3.05 g, 76%).

LCMS (ESI) m/z = 723 (M+H)+

Retention time: 2.30 min (Analytical condition SQDFA50 long)

[0788]

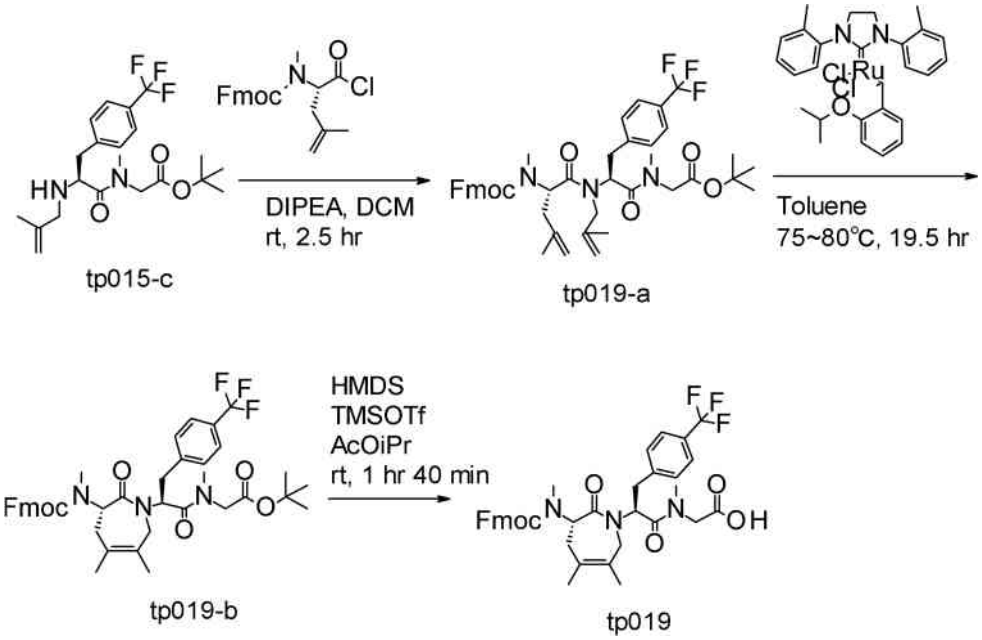
Using the resulting tp016-a, tp016 (2.61 g, 94%) was obtained under the same reaction conditions as synthesis of Compound tp015.

LCMS (ESI) m/z = 666 (M+H)+

Retention time: 2.92 min (Analytical condition SQDFA05 long)

[0789]

Synthesis of Compound tp019



[0790]

Using tp015-c as a starting material, tp0019-a (1.28 g, 70%) was obtained in the same manner as synthesis of Compound tp015-d.

LCMS (ESI) m/z = 763 (M+H)+

Retention time: 3.13 min (Analytical condition SQDFA50 long)

[0791]

Using the resulting tp019-a, tp019-b (0.667 g, 62%) was obtained under the same reaction conditions as synthesis of Compound tp015-e.

LCMS (ESI) m/z = 735 (M+H)+

Retention time: 3.66 min (Analytical condition SQDFA05 long)

[0792]

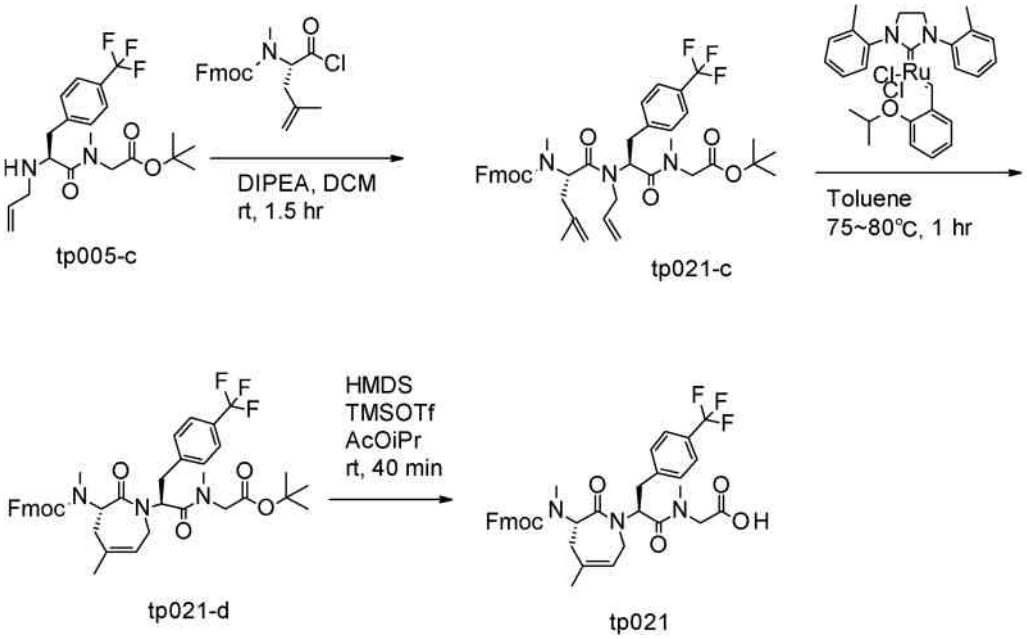
Using the resulting tp019-b, tp019 (0.54 g, 88%) was obtained under the same reaction conditions as synthesis of Compound tp015.

LCMS (ESI) m/z = 679 (M+H)+

Retention time: 2.82 min (Analytical condition SQDFA05 long)

[0793]

Synthesis of Compound tp021



[0794]

Using tp005-c, tp021-c (3.87 g, 72%) was obtained under the same reaction conditions as synthesis of Compound tp015-d .

LCMS (ESI) m/z = 749 (M+H)+

Retention time: 2.88 min (Analytical condition SQDFA50 long)

[0795]

Using the resulting tp021-c, tp021-d (3.35 g, 90%) was obtained under the same reaction conditions as synthesis of Compound tp015-e.

LCMS (ESI) m/z = 720 (M+H)+

Retention time: 2.19 min (Analytical condition SQDFA50 long)

[0796]

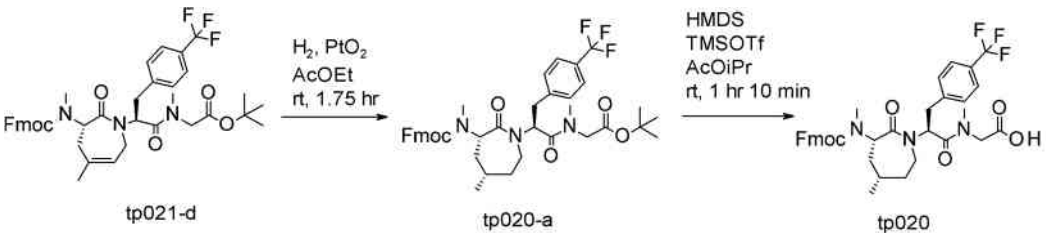
Using the resulting tp021-d, tp021 was obtained under the same reaction conditions as synthesis of Compound tp015 (1.13 g, 82%).

LCMS (ESI) m/z = 664 (M+H)+

Retention time: 2.80 min (Analytical condition SQDFA05 long)

[0797]

Synthesis of Compound tp020



tp021-d tp020-a tp020

[0798]

Using tp021-d as a starting material, tp0020-a (1.69 g, quant.) was obtained in the same manner as synthesis of Compound tp016-a.

LCMS (ESI) m/z = 723 (M+H)+

Retention time: 2.35 min (Analytical condition SQDFA50 long)

[0799]

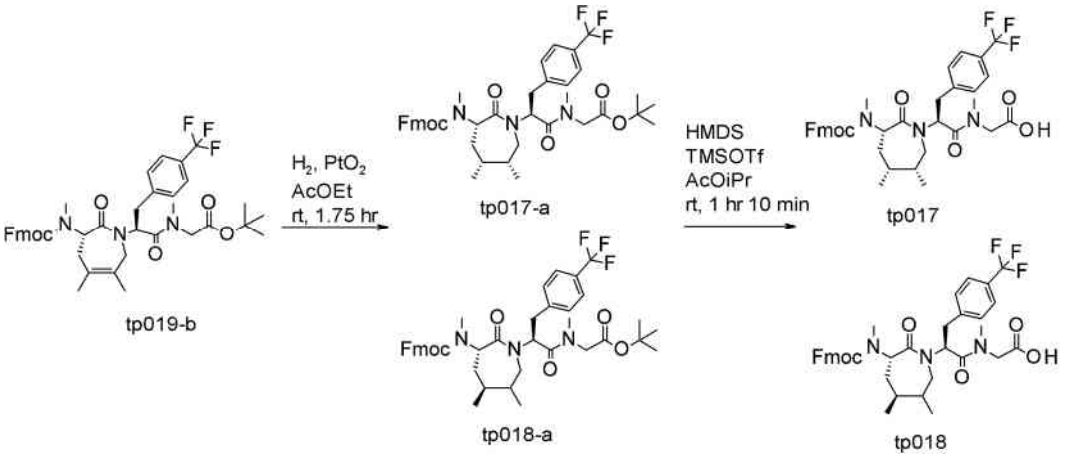
Using the resulting tp020-a, tp020 (1.25 g, 77%) was obtained under the same reaction conditions as synthesis of Compound tp016.

LCMS (ESI) m/z = 666 (M+H)+

Retention time: 2.91 min (Analytical condition SQDFA05 long)

[0800]

Synthesis of Compounds tp017 and tp018



tp019-b tp017-a tp017 tp018-a tp018

[0801]

Using tp019-b as a starting material, a mixture of tp0017-a and tp018-a (2.3:1) was obtained (1.56 g, 58%) in the same manner as synthesis of Compound tp016-a.

LCMS (ESI) m/z = 737 (M+H)+

Retention time: 2.51 min, 2.59 min (Analytical condition SQDFA50 long)

[0802]

Using the resulting mixture of tp0017-a and tp018-a (2.3:1), a mixture of tp017 and tp018 (1.31 g, 91%) was obtained under the same reaction conditions as synthesis of Compound tp016.

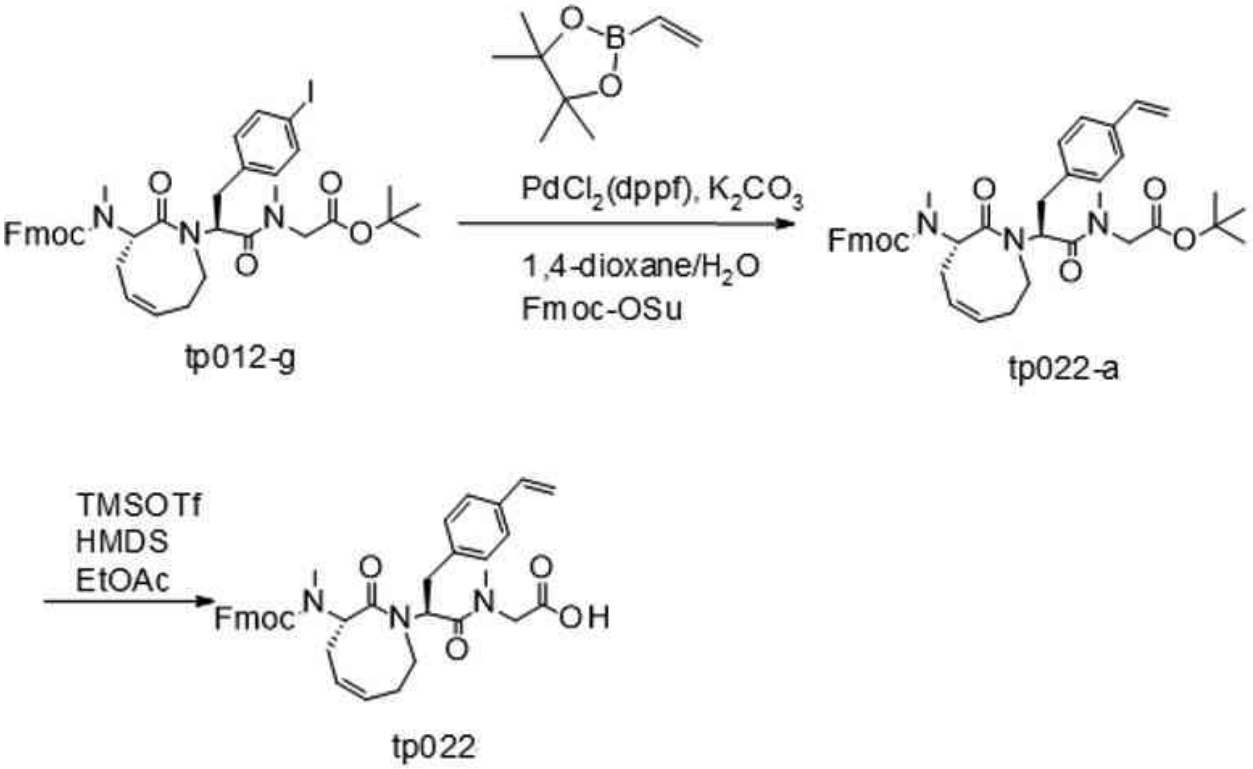
LCMS (ESI) m/z = 680 (M+H)+

Retention time: 3.04 min (Analytical condition SQDFA05 long)

tp017 and tp018 were not separated.

[0803]

Synthesis of Compound tp022



tp012-g

tp022-a

tp022

[0804]

In a nitrogen atmosphere, tp012-g (20.1 g, 25.8 mmol) was dissolved in 1,4-dioxane (86 mL) and water (43 mL), and then potassium carbonate (10.7 g, 78.0 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (1.06 g, 1.29 mmol), and vinylboronic acid pinacol ester (5.97 g, 38.8 mmol) were added. The reaction solution was heated to 90°C and stirred for 4 hours. The reaction solution was cooled to room temperature and left to stand still overnight, then Fmoc-OSu (4.36 g, 12.9 mmol) was added, and the mixture was stirred at room temperature for 1 hour. Ethyl acetate (200 mL) and half brine (200 mL) were added to the reaction solution and subjected to Celite filtration to isolate the organic phase. The organic phase was washed with half brine and dried over magnesium sulfate, and the resulting solution was concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography (n-hexane-ethyl acetate) to give a crude product of tp022-a (17.43 g).

LCMS (ESI) m/z = 678 (M+H)+

Retention time: 0.97 min (Analytical condition SMDFA50)

[0805]

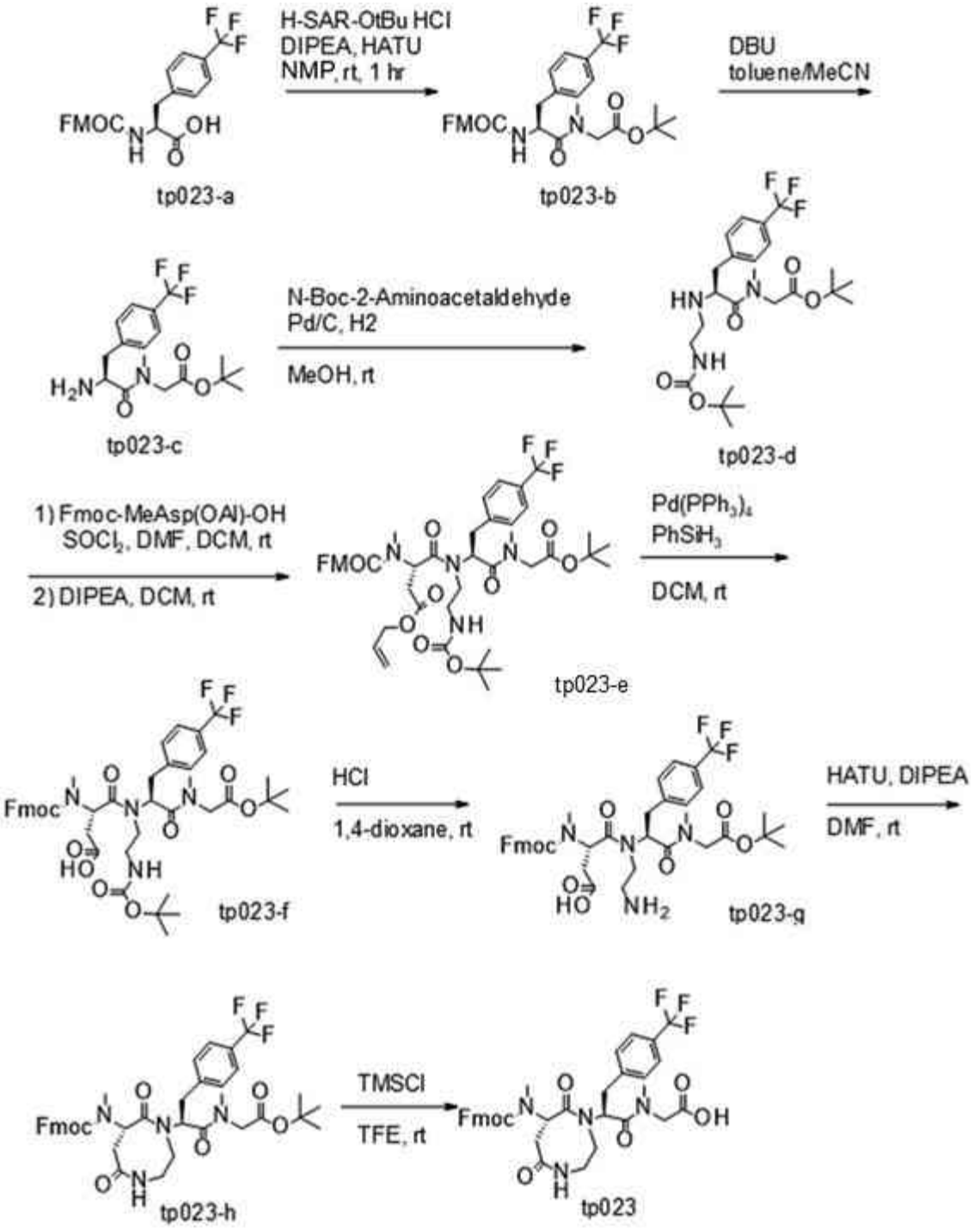
In a nitrogen atmosphere, the above tp022-a (17.43 g) was dissolved in ethyl acetate (129 mL), then hexamethyldisilazane (13.5 mL, 64.3 mmol) was added, and trimethylsilyl trifluoromethanesulfonate (9.29 mL, 51.4 mmol) was added dropwise over 3 minutes. After the resulting reaction mixture was stirred for 1 hour, a 5% aqueous disodium hydrogen phosphate solution (170 ml) was added to the reaction solution under ice cooling to quench the reaction. After the reaction solution was warmed to room temperature, water (85 mL) was added, and phosphoric acid was added to adjust the pH to 3. The organic phase was separated, and the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give tp022 (7.60 g, 48%, 2 steps).

LCMS (ESI) m/z = 622 (M+H)+

Retention time: 0.60 min (Analytical condition SMDFA50)

[0806]

Synthesis of Compound tp023



[0807]

In a nitrogen atmosphere, tp023-a (10.1 g, 22.2 mmol) and sarcosine tert-butyl ester hydrochloride (4.11 g, 22.6 mmol) were dissolved in NMP (55 mL), then DIPEA (11.6 ml, 66.5 mmol) and HATU (10.1 g, 26.6 mmol) were added, and the mixture was stirred at room temperature for 1.5 hours. Subsequently, the reaction solution was diluted with toluene (200 mL) and sequentially washed with water (100 mL), a 3.5% aqueous potassium hydrogen carbonate solution (100 mL), and a 1 M aqueous sodium dihydrogen phosphate solution (100

mL), and the organic phase was dried over anhydrous sodium sulfate. The resulting solution was concentrated under reduced pressure to give a crude product of tp023-b. The resulting tp023-b was directly used in the next step.

LCMS (ESI) m/z = 583 (M+H)+

Retention time: 1.03 min (Analytical condition SQDFA05)

[0808]

The above crude product of tp023-b (22.2 mmol) was dissolved in toluene (130 mL), DBU (3.34 mL, 22.2 mmol) was added at 0°C in a nitrogen atmosphere, and the mixture was stirred at 0°C for 20 minutes. A 1 M aqueous sodium dihydrogen phosphate solution (100 mL) was added to the reaction solution, and the resulting precipitate was collected by filtration. The resulting precipitate was washed with toluene/n-hexane and water, and dried under reduced pressure to give the desired product. At this time, the organic phase was recovered from the filtrate and the washing solution, and extracted with 0.2 N hydrochloric acid/acetonitrile (113 mL/50 mL) and water/acetonitrile (80 mL/40 mL). The aqueous phase was recovered, the pH was adjusted to 11 with a 3 N aqueous phosphoric acid solution, and this was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The solids collected by filtration and the extract were combined to give tp023-c (7.56 g, 95%, 2 steps).

LCMS (ESI) m/z = 361 (M+H)+

Retention time: 0.50 min (Analytical condition SQDFA05)

[0809]

In a nitrogen atmosphere, N-BOC-2-aminoacetaldehyde (3.34 g, 21.0 mmol) was dissolved in methanol (210 mL) and ice-cooled to 0°C. 10% palladium carbon (1.67 g, 50 wt%) was added thereto, and then a methanol solution (6 mL) of tp023-c (7.56 g, 21.0 mmol) was added. The reaction solution was stirred at 0°C for 2.5 hours at 1 atm of a hydrogen atmosphere, then heated to room temperature, and stirred for 1.5 hours. The reaction solution was subjected to Celite filtration, and the Celite was washed with ethyl acetate, followed by concentration under reduced pressure. The resulting crude product was purified by reverse phase chromatography (10 mM aqueous ammonium acetate solution-methanol) to give tp023-d (7.03 g, 67%).

LCMS (ESI) m/z = 505 (M+H)+

Retention time: 0.64 min (Analytical condition SQDFA05)

[0810]

In a nitrogen atmosphere, Fmoc-MeAsp(OAl)-OH (Compound 358-c, 4.27 g, 10.4 mmol) was dissolved in DCM (26 ml) at room temperature, DMF (0.081 ml, 1.04 mmol) was added, and then thionyl chloride (2.08 ml, 28.7 mmol) was added dropwise. The resulting

reaction mixture was stirred for 30 minutes, and then concentrated under reduced pressure. Toluene (30 ml) was added to the resulting residue, and the mixture was concentrated under reduced pressure. This operation was carried out twice in total, and the resulting crude product of Fmoc-MeAsp(OAl)-Cl was dissolved in DCM (10 mL) and used in the subsequent reaction.

[0811]

In a nitrogen atmosphere, a DCM (30 mL) solution of tp023-d (3.07 g, 6.10 mmol) and DIPEA (6.05 mL, 34.7 mmol) was added to the prepared DCM (10 ml) solution of Fmoc-MeAsp(OAl)-Cl. After the reaction solution was stirred at room temperature for 3 hours, a 3.5% aqueous potassium hydrogen carbonate solution (30 mL) was added. The organic phase was recovered and concentrated under reduced pressure. The resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give tp023-e (4.72 g, 87%).

LCMS (ESI) m/z = 896 (M+H)+

Retention time: 1.16 min (Analytical condition SQDFA50)

[0812]

In a nitrogen atmosphere, tp023-e (4.72 g, 5.27 mmol) was dissolved in dichloromethane (53 mL), tetrakistriphenylphosphine palladium (183 mg, 0.158 mmol) was added, and then phenylsilane (0.454 mL, 3.69 mmol) was slowly added dropwise. The reaction solution was stirred at room temperature for 2.5 hours, and TBME (94 mL) was added. The organic phase was washed with 50% aqueous sodium hydrogen carbonate solution/acetonitrile (47 mL/9.4 mL), and the organic phase was concentrated under reduced pressure. The resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give tp023-f (3.99 g, 88%).

LCMS (ESI) m/z = 856 (M+H)+

Retention time: 1.04 min (Analytical condition SQDFA05)

[0813]

tp023-f (1.96 g, 2.29 mmol) was dissolved in 1,4-dioxane (40 mL), a 4 N hydrochloric acid/1,4-dioxane solution (20 mL) was added, and the mixture was stirred at room temperature for 4.5 hours. The reaction solution was concentrated under reduced pressure to give a crude product of tp023-g. The resulting crude product was directly used in the next step.

[0814]

HATU (2.66 g, 7.00 mmol) was dissolved in DMF (75 mL), and a DMF solution (100 mL) of the above crude product of tp023-g and DIPEA (1.46 mL, 8.40 mmol) was added dropwise over 100 minutes. Thereafter, a saturated aqueous ammonium chloride solution (200 mL) was added to the reaction solution, and the resulting mixed solution was extracted twice with ethyl acetate (100 mL). The organic phases were combined and washed twice with water

(100 mL) and once with brine (100 mL). The resulting organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give tp023-h (0.56 g, 33%, 2 steps).

LCMS (ESI) m/z = 738 (M+H)+

Retention time: 1.04 min (Analytical condition SQDFA50)

[0815]

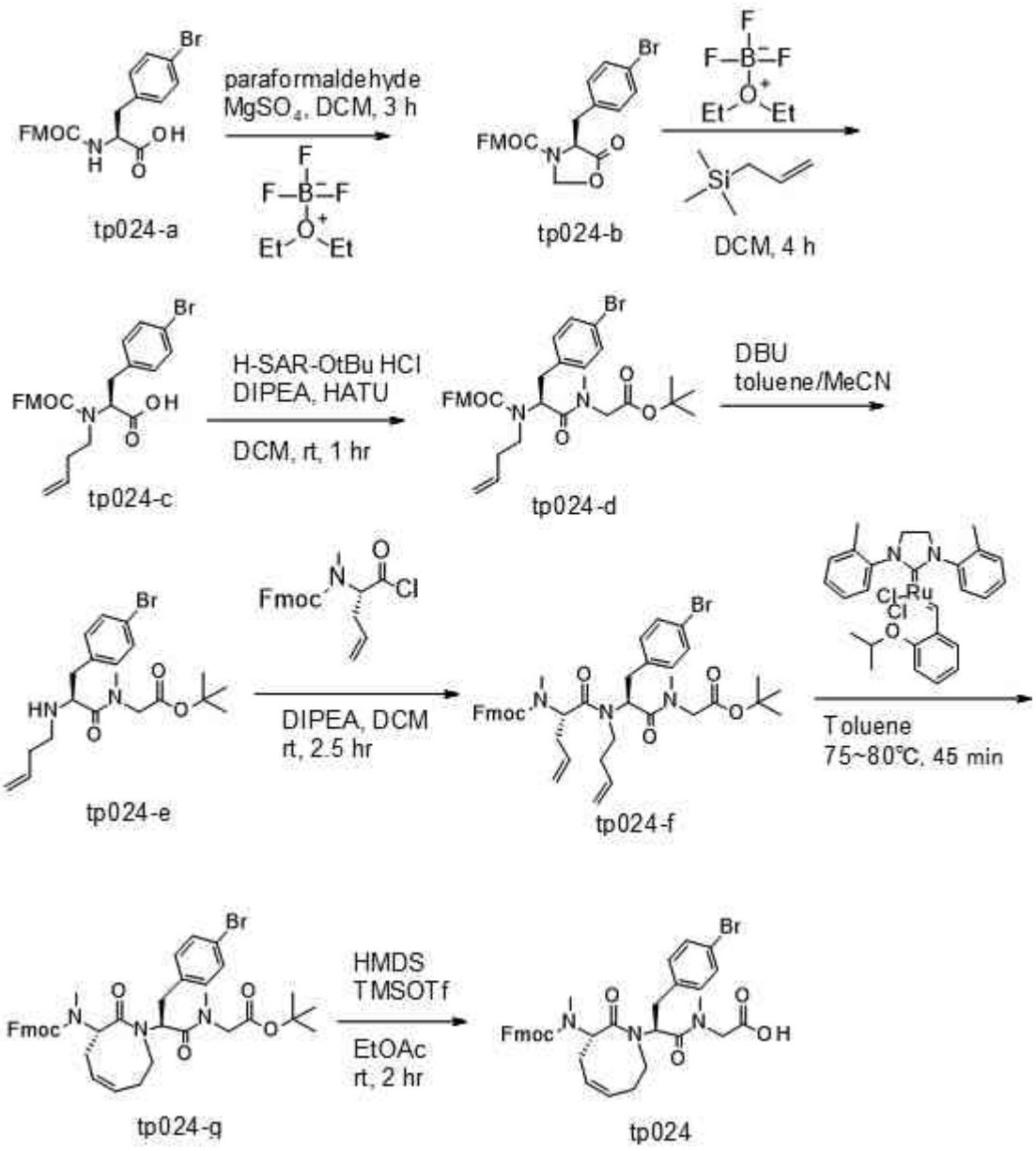
tp023-h (0.56 g, 0.760 mmol) was dissolved in 2,2,2-trifluoroethanol (10 mL), chlorotrimethylsilane (0.288 mL, 2.28 mmol) was added, and the mixture was stirred at room temperature for 1 hour. Chlorotrimethylsilane (0.15 mL, 1.19 mmol) was added to the reaction solution, then the mixture was stirred for 2.5 hours, chlorotrimethylsilane (0.05 mL, 0.396 mmol) was added, and the mixture was further stirred for 1.5 hours. The reaction solution was concentrated under reduced pressure, and the resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give tp023 (0.28 g, 54%).

LCMS (ESI) m/z = 682 (M+H)+

Retention time: 0.80 min (Analytical condition SQDFA50)

[0816]

Synthesis of Compound tp024



[0817]

tp024-a (15.0 g, 32.2 mmol) was dissolved in dichloromethane (214 mL), then anhydrous magnesium sulfate (9.68 g, 80.0 mmol), paraformaldehyde (2.90 g, 96.0 mmol), and a boron trifluoride diethyl ether complex (4.08 mL, 32.2 mmol) were added, and the mixture was stirred at room temperature for 3 hours. The reaction solution was filtered through silica gel, the silica gel was washed with dichloromethane (200 mL), and the filtrate was concentrated under reduced pressure. The resulting crude product of tp024-b was directly used in the next reaction.

Retention time: 1.472 min (Analytical condition SMD method_04)

[0818]

In a nitrogen atmosphere, the above crude product of tp024-b (32.2 mmol) was dissolved in dichloromethane (322 mL), then allyltrimethylsilane (35.8 mL, 225 mmol) and a boron trifluoride diethyl ether complex (20.2 mL, 161 mmol) were added, and the mixture was stirred at room temperature for 89 hours. The reaction solution was cooled to 0°C, and water (25 mL) was added. The mixed solution was subjected to Celite filtration, and the Celite was washed with dichloromethane (100 mL). The resulting filtrate was washed with a 1 N aqueous dipotassium hydrogen phosphate solution (200 mL) and half brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to give tp024-c (16.4 g, 98%, 2 steps).

LCMS (ESI) m/z = 520 (M+H)+

Retention time: 1.563 min (Analytical condition SMD method_04)

[0819]

In a nitrogen atmosphere, tp024-c (16.4 g, 31.5 mmol) and sarcosine tert-butyl ester hydrochloride (5.72 g, 31.5 mmol) were dissolved in dichloromethane (100 mL), then DIPEA (16.5 ml, 95.0 mmol) and HATU (14.4 g, 37.8 mmol) were added, and the mixture was stirred at room temperature for 1 hour. Subsequently, the reaction solution was sequentially washed with water (100 mL), a 3.5% aqueous potassium hydrogen carbonate solution (100 mL), and a 1 M aqueous dipotassium hydrogen phosphate solution (100 mL), and the organic phase was dried over anhydrous sodium sulfate. The resulting solution was concentrated under reduced pressure to give a crude product of tp024-d. The resulting crude product was purified by silica gel chromatography (ethyl acetate-n-hexane) to give tp024-d (13.1 g, 64%).

LCMS (ESI) m/z = 647 (M+Na)+

Retention time: 1.680 min (Analytical condition SMD method_04)

[0820]

tp024-d (13.1 g, 20.2 mmol) was dissolved in toluene (135 mL), DBU (3.02 mL, 20.2 mmol) was added, and the mixture was stirred at room temperature for 20 minutes. The reaction solution was washed with a 1 M aqueous potassium dihydrogen phosphate solution (80 mL), then n-hexane (140 mL), water (140 mL), acetonitrile (70 mL), and 2 N hydrochloric acid (12 mL) were added to the organic phase, and the mixture was shaken. The aqueous phase was recovered, and the organic phase was extracted with water/acetonitrile/2 N hydrochloric acid (30 mL/15 mL/3 mL). The resulting aqueous phases were combined, and 3 N phosphoric acid (12 mL) was added to adjust the pH to 8. The resulting mixed solution was extracted twice with ethyl acetate (100 mL, 50 mL), and the organic phase was washed with brine (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give tp024-e (8.20 g, 95%).

LCMS (ESI) m/z = 425 (M+H)+

Retention time: 0.849 min (Analytical condition SMD method_04)

[0821]

In a nitrogen atmosphere, (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pent-4-enoic acid (7.45 g, 21.2 mmol) was dissolved in DCM (85 ml) at room temperature, DMF (0.164 ml, 2.12 mmol) was added, and then thionyl chloride (3.85 ml, 53.0 mmol) was added dropwise. The resulting reaction mixture was stirred for 20 minutes and then concentrated under reduced pressure. Toluene (20 ml) was added to the resulting residue, and the mixture was concentrated under reduced pressure. This operation was carried out twice in total, and the resulting crude product was dissolved in DCM (23 mL) and used in the subsequent reaction.

[0822]

In a nitrogen atmosphere, a DCM (72 mL) solution of tp024-e (8.20 g, 19.3 mmol) and DIPEA (11.8 mL, 67.5 mmol) was added to the prepared DCM (23 ml) solution of (S)-(9H-fluoren-9-yl)methyl (1-chloro-1-oxopent-4-en-2-yl)(methyl)carbamate. The reaction solution was stirred at room temperature for 2 hours, and then washed with a 1 M aqueous potassium dihydrogen phosphate solution (82 mL). Subsequently, the organic phase was washed with a 3.5% aqueous potassium hydrogen carbonate solution (82 mL), and concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography (n-hexane-ethyl acetate) to give a crude product of tp024-f (14.0 g, 96%).

LCMS (ESI) m/z = 758 (M+H)+

Retention time: 1.737 min (Analytical condition SMD method_04)

[0823]

In a nitrogen atmosphere, tp024-f (1.00 g, 1.32 mmol) and 1,4-benzoquinone were dissolved in 1,2-dichloroethane (40 mL) in a three-necked flask, and the reaction solution was heated to 80°C. A 1,2-dichloromethane solution (4 mL) of the first-generation Grubbs catalyst (55 mg, 0.066 mmol) was added dropwise over 1 hour to the reaction solution stirred at 80°C. Subsequently, the reaction solution was stirred at 80°C for one more hour, cooled to room temperature, and then concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography (n-hexane-ethyl acetate) to give tp024-g (0.65 g, 68%).

LCMS (ESI) m/z = 730 (M+H)+

Retention time: 1.002 min (Analytical condition SMD method_06)

[0824]

In a nitrogen atmosphere, tp024-g (1.80 g, 2.46 mmol) was dissolved in ethyl acetate (20 mL), hexamethyldisilazane (1.29 mL, 6.16 mmol) was added, and then trimethylsilyl trifluoromethanesulfonate (0.89 mL, 4.93 mmol) was added dropwise. After the resulting reaction mixture was stirred for 150 minutes, the reaction solution was diluted with n-hexane (50 mL), and extracted once with a 3.5% aqueous potassium hydrogen carbonate

solution/acetonitrile (2/1, 40 mL). The pH of the aqueous phase was adjusted to 3 with phosphoric acid, and this was extracted with ethyl acetate (30 mL). The resulting organic phase was dried over sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give tp024 (0.92 g, 55%).

LCMS (ESI) m/z = 674 (M+H)+

Retention time: 0.625 min (Analytical condition SMD method_06)

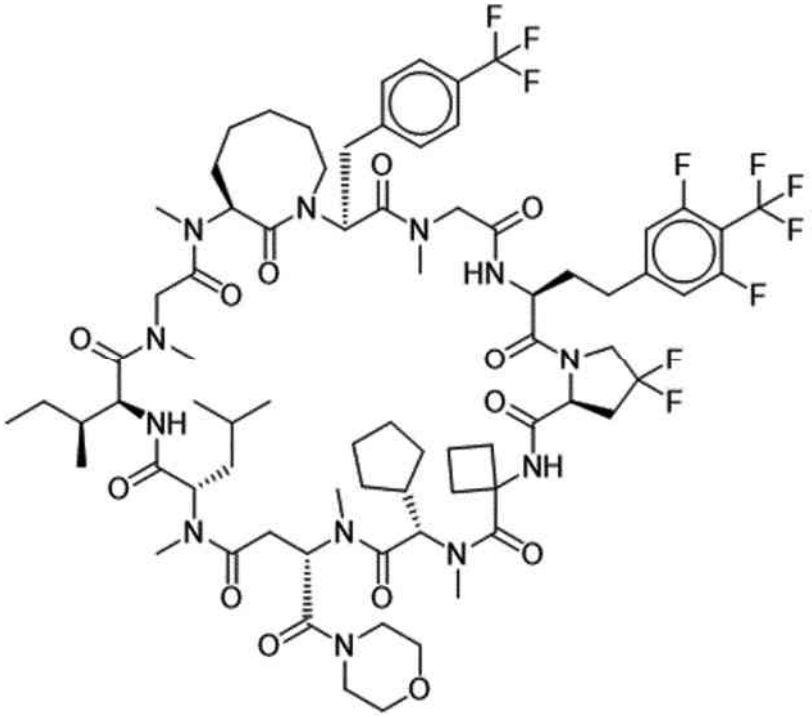
[0825]

Synthesis of Compound PP0464

Using Compound aa375-resin (0.426 mmol/g, 100 mg) as a raw material, Fmoc-cVal-OH, Fmoc-Pro(4-F2)-OH, Fmoc-Hph(4-CF3-35-F2)-OH, Compound tp002, Fmoc-MeGly-OH, Fmoc-Ile-OH, and Fmoc-MeLeu-OH were used. Peptide elongation reaction by the basic Fmoc method described in the present Examples, cleaving of an elongated peptide from resin, cyclization of a cleaved peptide (using (1-cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) as a cyclization reagent), and purification of a cyclic peptide were performed to give the intended Compound PP0464 (17.2 mg, 26%).

[0826]

Compound PP0464



LCMS (ESI) m/z = 1568.2 (M-H)-

Retention time: 7.979 min (Analytical condition SSC-AA-02/03)

[0827]

Using the resins, on which amino acid shown in Table 5 and Table 6 was supported, as raw materials, the following compounds were produced according to the above-described Fmoc method in the same manner as the production method of Compound PP0464. A deprotection reaction was added as necessary.

Compounds PP0464, PP0465, PP0466, PP0467, PP0468, PP0469, PP0470, PP0471, PP0472, PP0473, PP0474, PP0475, PP0476, PP0477, PP0478, PP0479, PP0480, PP0481, PP0483, PP0484, PP0485, PP0487, PP0488, PP0490, PP0491, PP0492, PP0493, PP0494, PP0495, PP0496, PP0497, PP0498, PP0499, PP0500, PP0501, PP0502, PP0503, PP0504, PP0505, PP0506, PP0507, PP0508, PP0509, PP0510, PP0511, PP0512, PP0513, PP0514, PP0515, PP0516, PP0520, PP0521, PP0522, PP0523, PP0538, PP0539, PP0540, PP0541, PP0542, PP0543, PP0544, PP0545, PP0546, PP0547, PP0548, PP0549, PP0550, PP0551, PP0552, PP0553, PP0554, PP0555, PP0556, PP0557, PP0558, PP0559, PP0560, PP0561, PP0562, PP0563, PP0564, PP0565, PP0566, PP0567, PP0568, PP0569, PP0570, PP0571, PP0572, PP0573, PP0574, PP0575, PP0576, PP0577, PP0578, PP0579, PP0580, PP0581, PP0582, PP0583, PP0584, PP0585, PP0586, PP0587, PP0588, PP0589, PP0590, PP0591, PP0594, PP0595, PP0596, PP0597, PP0598, PP0630, PP0631, PP0632, PP0633, PP0634, PP0635, PP0636, PP0637, PP0638, PP0639, PP0640, PP0641, PP0642, PP0643, PP0644, PP0645, PP0646, PP0647, PP0648, PP0649, PP0650, PP0651, PP0652, PP0653, PP0654, PP0655, PP0656, PP0657, PP0658, PP0659, PP0660, PP0661, PP0662, PP0663, PP0664, PP0665, PP0666, PP0667, PP0668, PP0669, PP0670, PP0671, PP0672, PP0673, PP0674, PP0675, PP0678, PP0679, PP0680, PP0681, PP0682, PP0683, PP0684, PP0685, PP0686, PP0687, PP0688, PP0689, PP0690, PP0693, PP0694, PP0695, PP0696, PP0697, PP0698, PP0699, PP0700, PP0701, PP0702, PP0703, PP0704, PP0705, PP0706, PP0708, PP0709, PP0710, PP0711, PP0712, PP0713, PP0714, PP0715, PP0716, PP0717, PP0718, PP0719, PP0720, PP0721, PP0722, PP0723, PP0724, PP0725, PP0726, PP0727, PP0728, PP0729, PP0730, PP0731, PP0732, PP0733, PP0806, PP0807, PP0808, PP0809, PP0810, PP0811, PP0812, PP0813, PP0814, PP0815, PP0816, PP0817, PP0818, PP0819, PP0820, PP0821, PP0822, PP0823, PP0824, PP0825, PP0826, PP0827, PP0828, PP0829, PP0830, PP0831, PP0832, PP0833, PP0834, PP0835, PP0836, PP0837, PP0838, PP0839, PP0840, PP0841, PP0842, PP0843, PP0844, PP0845, PP0846, PP0847, PP0848, PP0849, PP0850, PP0851, PP0852, PP0853, PP0854, PP0855, PP0856, PP0857, PP0858, PP0859, PP0860, PP0861, PP0862, PP0863, PP0864, PP0865, PP0866, PP0867, PP0868, PP0869, PP0870, PP0871, PP0872, PP0873, PP0926, PP0927, PP0928, PP0929, PP0930, PP0931, PP0932, PP0933, PP0934, PP0935, PP0936, PP0937, PP0938, PP0939, PP0940, PP0941, PP0942, PP0943, PP0944, PP0945, PP0946, PP0947, PP0948, PP0949, PP0950, PP0951, PP0952, PP0953, PP0954,

PP0955, PP0956, PP0958, PP0959, PP0960, PP0961, PP0962, PP0963, PP0964, PP0965, PP0966, PP0967, PP0968, PP0969, PP0970, PP0971, PP0972, PP0973, PP0975, PP0976, PP0977, PP0978, PP0979, PP0980, PP0981, PP0982, PP0983, PP0984, PP1017, PP1018, PP1019, PP1020, PP1021, PP1022, PP1024, PP1025, PP1026, PP1027, PP1028, PP1029, PP1030, PP1031, PP1032, PP1033, PP1034, PP1035, PP1036, PP1037, PP1038, PP1039, PP1040, PP1041, PP1042, PP1043, PP1044, PP1045, PP1046, PP1047, PP1048, PP1049, PP1050, PP1051, PP1052, PP1053, PP1054, PP1056, PP1057, PP1058, PP1059, PP1060, PP1063, PP1064, PP1065, PP1086, PP1087, PP1088, PP1089, PP1090, PP1091, PP1092, PP1093, PP1094, PP1095, PP1096, PP1097, PP1098, PP1099, PP1100, PP1101, PP1102, PP1103, PP1104, PP1105, PP1106, PP1107, PP1108, PP1109, PP1110, PP1111, PP1112, PP1113, PP1114, PP1115, PP1116, PP1117, PP1118, PP1119, PP1120, PP1121, PP1122, PP1123, PP1124, PP1125, PP1126, PP1127, PP1128, PP1129, PP1130, PP1131, PP1132, PP1133, PP1134, PP1135, PP1136, PP1137, PP1138, PP1139, PP1140, PP1141, PP1142, PP1143, PP1144, PP1145, PP1146, PP1147, PP1148, PP1149, PP1150, PP1155, PP1156, PP1157, PP1158, PP1159, PP1160, PP1161, PP1162, PP1163, PP1164, PP1165, PP1166, PP1167, PP1168, PP1169, PP1170, PP1171, PP1172, PP1173, PP1174, PP1175, PP1176, PP1177, PP1178, PP1179, PP1180, PP1181, PP1182, PP1183, PP1184, PP1185, PP1186, PP1187, PP1188, PP1189, PP1190, PP1191, PP1192, PP1193, PP1194, PP1195, PP1196, PP1197, PP1198, PP1199, PP1200, PP1201, PP1202, PP1203, PP1204, PP1205, PP1206, PP1207, PP1208, PP1209, PP1210, PP1211, PP1212, PP1213, PP1214, PP1215, PP1216, PP1217, PP1218, PP1219, PP1220, PP1221, PP1222, PP1223, PP1224, PP1225, PP1226, PP1227, PP1228, PP1229, PP1230, PP1231, PP1232, PP1233, PP1234, PP1235, PP1242, PP1243, PP1244, PP1245, PP1246, PP1247, PP1248, PP1249, PP1250, PP1251, PP1252, PP1253, PP1254, PP1255, PP1256, PP1257, PP1258, PP1259, PP1260, PP1261, PP1262, PP1263, PP1264, PP1265, PP1266, PP1267, PP1268, PP1269, PP1270, PP1271, PP1272, PP1273, PP1274, PP1275, PP1276, PP1277, PP1278, PP1279, PP1280, PP1281, PP1282, PP1283, PP1284, PP1285, PP1286, PP1287, PP1288, PP1289, PP1290, PP1291, PP1292, PP1293, PP1294, PP1295, PP1296, PP1297, PP1298, PP1299, PP1336, PP1337, PP1338, PP1339, PP1340, PP1341, PP1342, PP1343, PP1344, PP1345, PP1346, PP1347, PP1348, PP1349, PP1350, PP1351, PP1352, PP1353, PP1354, PP1355, PP1356, PP1357, PP1358, PP1359, PP1360, PP1361, PP1362, PP1363, PP1364, PP1365, PP1366, PP1367, PP1368, PP1369, PP1370, PP1371, PP1372, PP1373, PP1374, PP1375, PP1376, PP1377, PP1378, PP1379, PP1380, PP1381, PP1382, PP1383, PP1384, PP1385, PP1386, PP1390, PP1391, PP1392, PP1393, PP1394, PP1395, PP1396, PP1397, PP1398, PP1399, PP1400, PP1401, PP1402, PP1403, PP1404, PP1405, PP1406, PP1407, PP1408, PP1409, PP1410, PP1411, PP1412, PP1413, PP1414, PP1415, PP1416, PP1417, PP1418, PP1419, PP1420, PP1421,

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PP2995, PP2996, PP2997, PP2998, PP2999, PP3000, PP3001, PP3002, PP3003, PP3004, PP3005, PP3006, PP3007, PP3008, PP3009, PP3010, PP3011, PP3012, PP3013, PP3014, PP3015, PP3017, PP3018, PP3019, PP3021, PP3022, PP3026, PP3030, and PP3031.

[0828]

The following compounds were produced according to the above-described Fmoc method in the same manner as the production method of Compound PP0464 using aa427-resin to aa438-resin as raw materials:

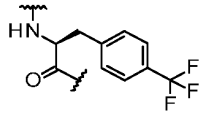
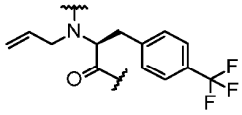
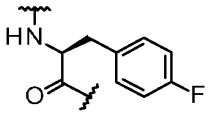
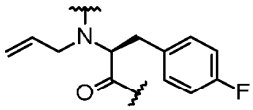
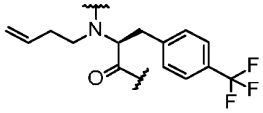
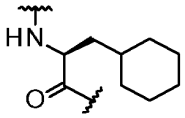
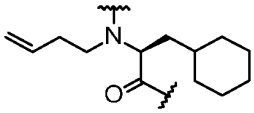
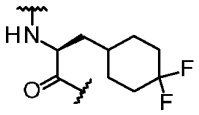
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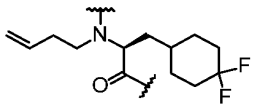
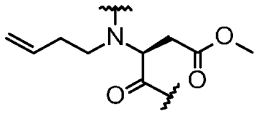
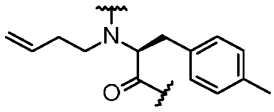
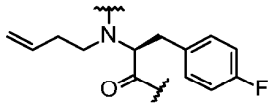
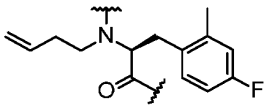
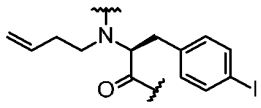
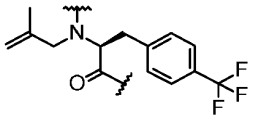
[0829]

In a cyclic compound and an oligopeptide compound synthesized with a tripeptide, abbreviations and structures of amino acids contained as partial structures are provided below.

[0830]

[Table 9-1]

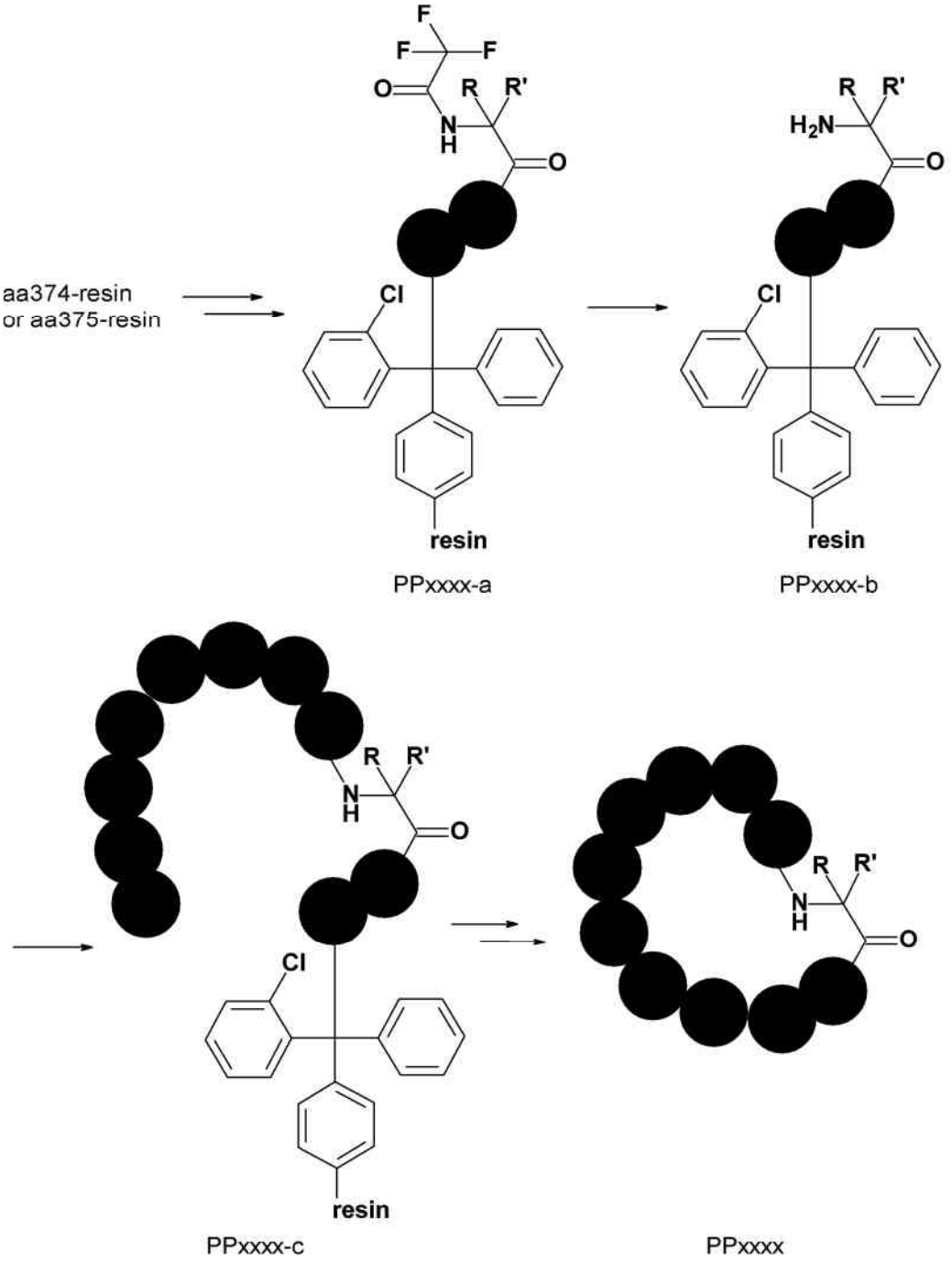
Compound No.	Abbreviation	Amino acid Structural Formula
bb001	Phe(4-CF3)	
bb002	AllylPhe(4-CF3)	
bb003	Phe(4-F)	
bb004	AllylPhe(4-F)	
bb005	ButenylPhe(4-CF3)	
bb006	Cha	
bb007	ButenylCha	
bb008	Cha(4-F2)	

Compound No.	Abbreviation	Amino acid Structural Formula
bb009	ButenylCha(4-F2)	
bb010	BuetnylAsp(OMe)	
bb011	ButenylPhe(4-Me)	
bb012	ButenylPhe(4-F)	
bb013	ButenylPhe(4-F-2-Me)	
bb014	ButenylPhe(4-I)	
bb015	MethaPhe(4-CF3)	

[0831]

1-5. Cyclic peptide synthesis using Tfa-protected amino acid as reagent

According to the general reaction scheme provided below, PP0734 to PP0744, PP0754 to PP0765, PP0771 to PP0776, PP0778 to PP0782, PP0790 to PP0801, PP0805, and PP0874 to PP0881 were synthesized (● indicates an amino acid unit).



[0832]

Peptide elongation was performed according to the basic route up to the N-terminal before a Tfa-protected amino acid was elongated. Next, Tfa-protected amino acid was elongated through 3 steps of 1) Fmoc deprotection of peptide chain N-terminal, 2) Condensation reaction using Tfa-protected amino acid, and 3) Tfa deprotection. Subsequent peptide elongation, cleaving from resin, and synthesis of a cyclized peptide were performed according to the basic route.

[0833]

Synthesis of Compound PP0754

1) Fmoc deprotection of peptide chain N-terminal

Compound aa375-resin (0.276 mmol/g, 1 g) was placed in a filter-equipped reaction vessel, dichloromethane (10 mL) was added, and the mixture was shaken at room temperature for 5 minutes to swell the resin. After dichloromethane was removed with the filter, the resin was washed twice with DMF (7 mL). Subsequently, a 2% DBU/DMF solution (de-Fmoc solution: 7 mL) was added to the resin, and the mixture was shaken at room temperature for 10 minutes to carry out a de-Fmoc reaction. After the de-Fmoc solution was removed, the resin was washed 4 times with DMF (7 mL).

[0834]

2) Condensation reaction using Tfa-protected amino acid

An elongation reaction of Tfa-(Me)Abu-OH (Compound aa317) was performed on the resulting resin. The elongation reaction was performed by adding a mixed solution of a 0.6 M Tfa-(Me)Abu-OH (Compound aa317)/DMF solution (3 mL) and a 10% DIC/DMF solution (3.6 mL) to the resin and shaking the mixture at 60°C for 24 hours. After the liquid phase of the elongation reaction was removed with a filter, the resin was washed 4 times with DMF (7 mL) and 4 times with dichloromethane (7 mL) and dried to give Compound PP0754-a (Tfa-(Me)Abu-MeGly(cPent)-MeAsp(O-Trt(2-Cl)-resin)-mor).

[0835]

3) Tfa Deprotection

NaBH4 (0.5 g, 13.2 mmol) was placed in a flask, pumped up, then dissolved in trigrim (6.6 mL) under nitrogen atmosphere to give Solution A. The resulting resin PP0754-a (100 mg) was swollen with dichloromethane (1 mL) and then washed twice with tetrahydrofuran (0.7 mL). Tetrahydrofuran (0.5 mL), methanol (0.25 mL), and Solution A (0.25 mL) were added, and the mixture was left to stand still in an open system at room temperature for 2 hours. After the reaction solution was removed, tetrahydrofuran (0.5 mL), methanol (0.25 mL), and Solution A (0.25 mL) were added, and the mixture was left to stand still in an open system at room temperature for 30 minutes. After the reaction solution was removed, the operation of adding methanol (0.7 mL) and washing the mixture for 1 minute was repeated 4 times, and the mixture was further washed with dichloromethane (0.7 mL) 4 times. The amino acid was cleaved from the resin with TFE/DCM (1/1 (v/v)) containing DIPEA (0.045 mmol/L) using a small amount of resin-supported Compound PP0754-b, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 455 (M+H)+

Retention time: 0.39 min (Analytical condition SQDFA05)

[0836]

Subsequent peptide chain elongation, cleaving from resin, and synthesis of a cyclized peptide were performed according to the basic peptide synthesis method described in the present Examples. LC/MS data is provided in Table 36.

[0837]

Using aa374-resin and aa375-resin as raw materials, PP0734-a to PP0744-a, PP0754-a to PP0765-a, PP0771-a to PP0776-a, PP0778-a to PP0782-a, PP0790-a to PP0801-a, PP0805-a, and PP0874-a to PP0881-a were obtained in the same manner as synthesis of Compound PP0754-a using the Tfa-protected amino acids listed in Table 10 in place of Tfa-(Me)Abu-OH. Then, PP0734-b to PP0744-b, PP0754-b to PP0765-b, PP0771-b to PP0776-b, PP0778-b to PP0782-b, PP0790-b to PP0801-b, PP0805-b, and PP0874-b to PP0881-b were obtained in the same manner as synthesis of PP0754-b. Subsequent peptide chain elongation, cleaving from resin, and synthesis of a cyclized peptide were performed according to the basic peptide synthesis method described in the present Examples to give Compounds PP0734 to PP0744, PP0754 to PP0765, PP0771 to PP077, PP0778 to PP0782, PP0790 to PP0801, PP0805, and PP0874 to PP0881. LC/MS data is provided in Table 36.

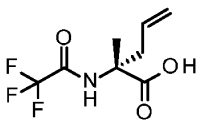
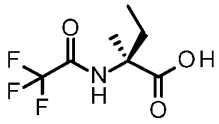
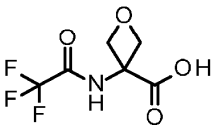
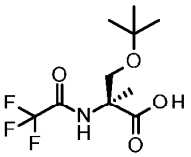
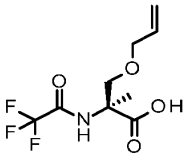
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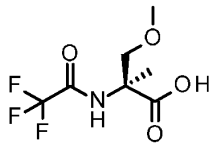
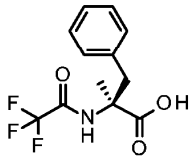
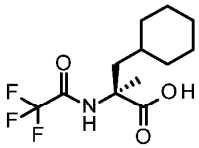
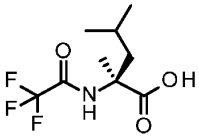
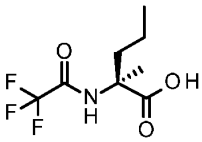
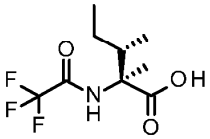
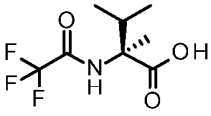
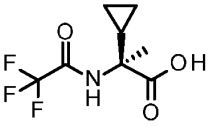
Synthesis of Tfa-protected amino acids

The amino acids listed in Table 10 were synthesized by the following method and used in a peptide elongation reaction.

[0839]

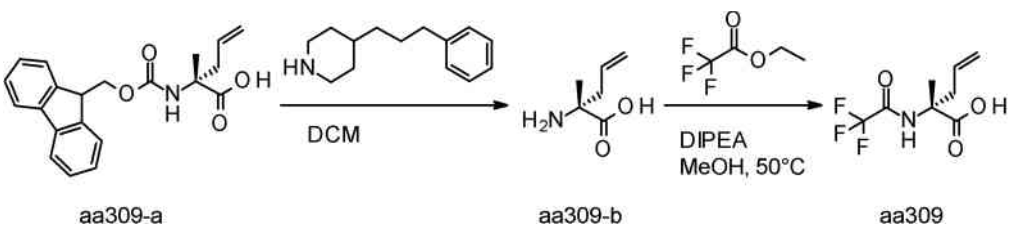
[Table 10]

Compound No.	Abbreviation	Structural Formula	Name
aa309	Tfa-D-(Me)Algly-OH		(R)-2-methyl-2-(2,2,2-trifluoroacetamido)pent-4-enoic acid
aa317	Tfa-(Me)Abu-OH		(S)-2-methyl-2-(2,2,2-trifluoroacetamido)butanoic acid
aa319	Tfa-AoxeC-OH		3-(2,2,2-trifluoroacetamido)oxetane-3-carboxylic acid
aa320	Tfa-(Me)Ser(tBu)-OH		(S)-3-(tert-butoxy)-2-methyl-2-(2,2,2-trifluoroacetamido)propanoic acid
aa321	Tfa-(Me)Ser(Al)-OH		(S)-3-(allyloxy)-2-methyl-2-(2,2,2-trifluoroacetamido)propanoic acid

aa322	Tfa-(Me)Ser(Me)-OH		(S)-3-methoxy-2-methyl-2-(2,2,2-trifluoroacetamido)propanoic acid
aa323	Tfa-(Me)Phe-OH		(S)-2-methyl-3-phenyl-2-(2,2,2-trifluoroacetamido)propanoic acid
aa324	Tfa-(Me)Cha-OH		(S)-3-cyclohexyl-2-methyl-2-(2,2,2-trifluoroacetamido)propanoic acid
aa325	Tfa-(Me)Leu-OH		(S)-2,4-dimethyl-2-(2,2,2-trifluoroacetamido)pentanoic acid
aa326	Tfa-(Me)Nva-OH		(S)-2-methyl-2-(2,2,2-trifluoroacetamido)pentanoic acid
aa327	Tfa-(Me)Ile-OH		(2S,3S)-2,3-dimethyl-2-(2,2,2-trifluoroacetamido)pentanoic acid
aa328	Tfa-(Me)Val-OH		(S)-2,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoic acid
aa329	Tfa-(Me)Gly(cPr)-OH		(S)-2-cyclopropyl-2-(2,2,2-trifluoroacetamido)propanoic acid

[0840]

Synthesis of Compound aa309



[0841]

4-(3-Phenylpropyl)piperidine (9.0 mL, 42.7 mmol) was added to a dichloromethane (47.4 mL) solution of Compound aa309-a ((R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-methylpent-4-enoic acid, Fmoc-D-(Me)Algly-OH) (5.0 g, 14.2 mmol), and the mixture was stirred at room temperature for 36 hours in a nitrogen atmosphere. Water (10 mL) and 2 N hydrochloric acid (5 mL) were added to the reaction solution to extract the product, and the aqueous layer was purified by reverse phase column chromatography (0.1% formic acid-water/0.1% formic acid-acetonitrile) to give Compound aa309-b ((R)-2-amino-2-methylpent-4-enoic acid, H-D-(Me)Algly-OH) (1.9 g, quant.), which was used in the next reaction.

LCMS (ESI) m/z = 130 (M+H)+

Retention time: 0.15 min (Analytical condition SQDFA05) (retention time of MS peak is provided)

[0842]

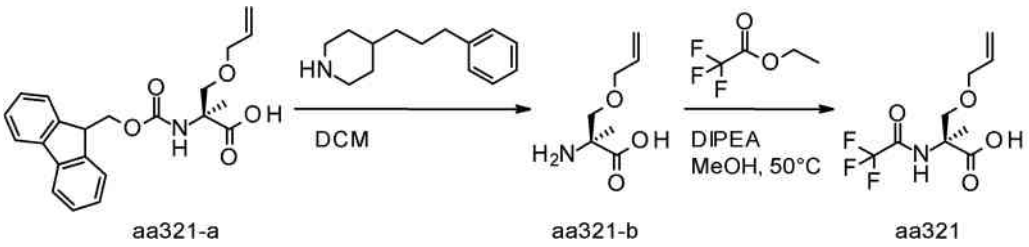
After N,N-diisopropylethylamine (7.7 mL, 44.1 mmol) and ethyl 2,2,2-trifluoroacetate (5.3 mL, 44.1 mmol) were added to a methanol (24.5 mL) solution of Compound aa309-b ((R)-2-amino-2-methylpent-4-enoic acid, H-D-(Me)Algly-OH) (1.9 g, 14.7 mmol), and the mixture was stirred at 50°C for 24 hours. The reaction solution was cooled to room temperature and then concentrated under reduced pressure, and the resulting residue was dissolved in TBME (60 mL) and then washed twice with 1 N hydrochloric acid (60 mL) and once with saturated brine (60 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure to give a crude product. The resulting crude product was purified by reverse phase column chromatography (0.1% formic acid-water/0.1% formic acid-acetonitrile) to give Compound aa309 (2.5 g, 75%).

LCMS (ESI) m/z = 224 (M-H)-

Retention time: 0.52 min (Analytical condition SQDFA05)

[0843]

Synthesis of Compound aa321



[0844]

Using Compound aa321-a ((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(allyloxy)-2-methylpropanoic acid, Fmoc-(Me)Ser(Al))-OH) (2.0 g, 5.2 mmol) as a starting material, Compound aa321-b ((S)-3-(allyloxy)-2-amino-2-methylpropanoic acid, H-

(Me)Ser(Al)-OH) (0.87 g, quant.) was obtained in the same manner as synthesis of Compound aa309-b, and was used in the next reaction.

LCMS (ESI) m/z = 160 (M+H)+

Retention time: 0.16 min (Analytical condition SQDFA05) (retention time of MS peak is provided)

[0845]

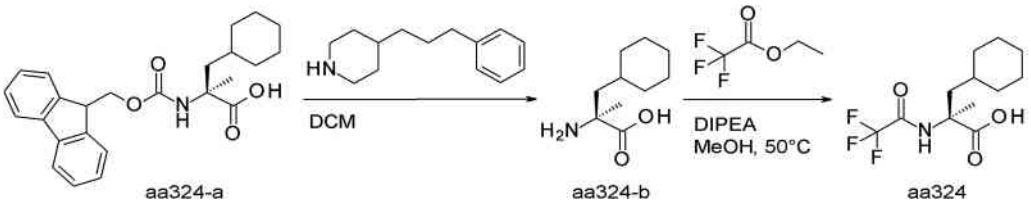
Using Compound aa321-b ((S)-3-(allyloxy)-2-amino-2-methylpropanoic acid, H-(Me)Ser(Al)-OH) (0.84 g, 5.3 mmol), Compound aa321 (1.0 g, 75%) was obtained in the same manner as synthesis of Compound aa309.

LCMS (ESI) m/z = 256 (M+H)+

Retention time: 0.55 min (Analytical condition SQDFA05)

[0846]

Synthesis of Compound aa324



aa324-a aa324-b aa324

[0847]

4-(3-Phenylpropyl)piperidine (4.7 mL, 22.1 mmol) was added to a dichloromethane (18.4 mL) solution of Compound aa324-a ((S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-cyclohexyl-2-methylpropanoic acid, Fmoc-(Me)Cha-OH) (3.0 g, 7.4 mmol), and the mixture was stirred in a nitrogen atmosphere at room temperature for 16 hours. Water (5 mL) and 2 N hydrochloric acid (5 mL) were added to the reaction solution to extract the product, and the aqueous layer was purified by reverse phase column chromatography (0.1% formic acid-water/0.1% formic acid-acetonitrile) to give Compound aa324-b ((S)-2-amino-3-cyclohexyl-2-methylpropanoic acid, H-(Me)Cha-OH) (1.1 g, 81%), which was used in the next reaction.

LCMS (ESI) m/z = 186 (M+H)+

Retention time: 0.32 min (Analytical condition SQDFA05)

[0848]

After N,N-diisopropylethylamine (3.1 mL, 18.0 mmol) and ethyl 2,2,2-trifluoroacetate (2.1 mL, 18.0 mmol) were added to a methanol (20.0 mL) solution of Compound aa324-b ((S)-2-amino-3-cyclohexyl-2-methylpropanoic acid, H-(Me)Cha-OH) (1.1 g, 6.0 mmol), and the mixture was stirred at 50°C for 2 hours. Then, N,N-diisopropylethylamine (3.1 mL, 18.0 mmol) and ethyl 2,2,2-trifluoroacetate (2.1 mL, 18.0 mmol) were added, and the mixture was stirred at 50°C for 20 hours. The reaction solution was cooled to room temperature and then concentrated under reduced pressure, and the resulting residue was dissolved in TBME (30 mL)

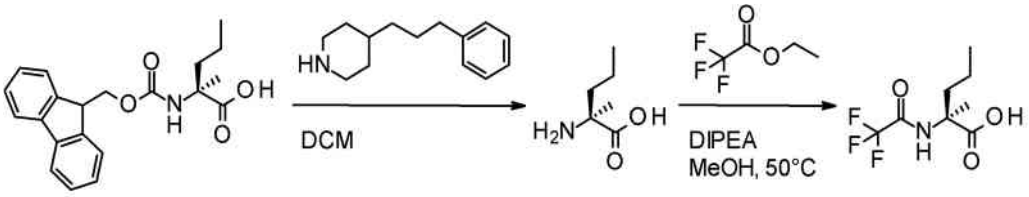
and washed twice with 1 N hydrochloric acid (30 mL) and once with saturated brine (30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure to give a crude product. The resulting crude product was purified by reverse phase column chromatography (0.1% formic acid-water/0.1% formic acid-acetonitrile) to give Compound aa324 (1.2 g, 72%).

LCMS (ESI) m/z = 280 (M-H)-

Retention time: 0.75 min (Analytical condition SQDFA05)

[0849]

Synthesis of Compound aa326



aa326-a aa326-b aa326

[0850]

Using Compound aa326-a ((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-methylpentanoic acid, Fmoc-(Me)Nva-OH) (3.0 g, 8.5 mmol) as a starting material, Compound aa326-b ((S)-2-amino-2-methylpentanoic acid, H-(Me)Nva-OH) (1.1 g, 96%) was obtained in the same manner as synthesis of Compound aa309-b, and used in the next reaction.

LCMS (ESI) m/z = 132 (M+H)+

Retention time: 0.13 min (Analytical condition SQDFA05)

[0851]

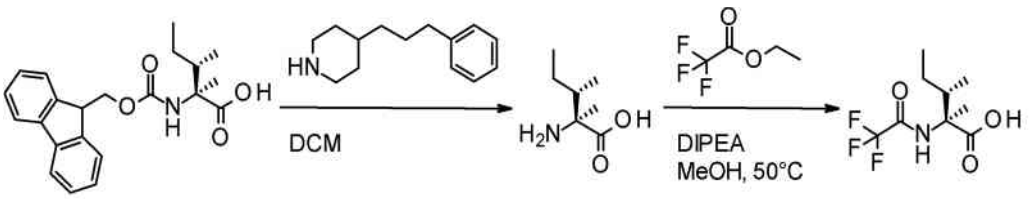
Using Compound aa326-b ((S)-2-amino-2-methylpentanoic acid, H-(Me)Nva-OH) (1.1 g, 8.2 mmol), Compound aa326 (1.2 g, 64%) was obtained in the same manner as synthesis of Compound aa309.

LCMS (ESI) m/z = 226 (M-H)-

Retention time: 0.55 min (Analytical condition SQDFA05)

[0852]

Synthesis of Compound aa327



aa327-a aa327-b aa327

[0853]

Using Compound aa327-a ((2S,3S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2,3-dimethylpentanoic acid, Fmoc-(Me)Ile-OH) (3.0 g, 8.2 mmol) as a starting material, Compound aa327-b ((2S,3S)-2-amino-2,3-dimethylpentanoic acid, H-(Me)Ile-OH) (1.1 g, 96%) was obtained in the same manner as synthesis of Compound aa309-b, and used in the next reaction.

LCMS (ESI) m/z = 146 (M+H)+

Retention time: 0.15 min (Analytical condition SQDFA05)

[0854]

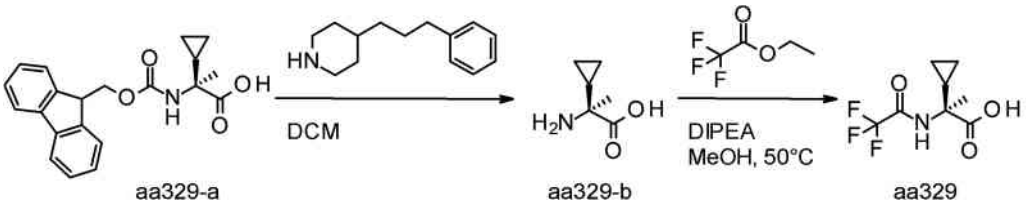
Using Compound aa327-b ((2S,3S)-2-amino-2,3-dimethylpentanoic acid, H-(Me)Ile-OH) (1.1 g, 7.9 mmol), Compound aa327 (1.4 g, 72%) was obtained in the same manner as synthesis of Compound aa309.

LCMS (ESI) m/z = 240 (M-H)-

Retention time: 0.61 min (Analytical condition SQDFA05)

[0855]

Synthesis of Compound aa329



[0856]

Compound aa329-a ((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-cyclopropylpropanoic acid, Fmoc-(Me)Gly(cPr)-OH) (3.0 g, 8.5 mmol) as a starting material, Compound aa329-b ((S)-2-amino-2-cyclopropylpropanoic acid, H-(Me)Gly(cPr)-OH) (1.1 g, 100%) was obtained in the same manner as synthesis of Compound aa309-b, and used in the next reaction.

LCMS (ESI) m/z = 130 (M+H)+

Retention time: 0.13 min (Analytical condition SQDFA05)

[0857]

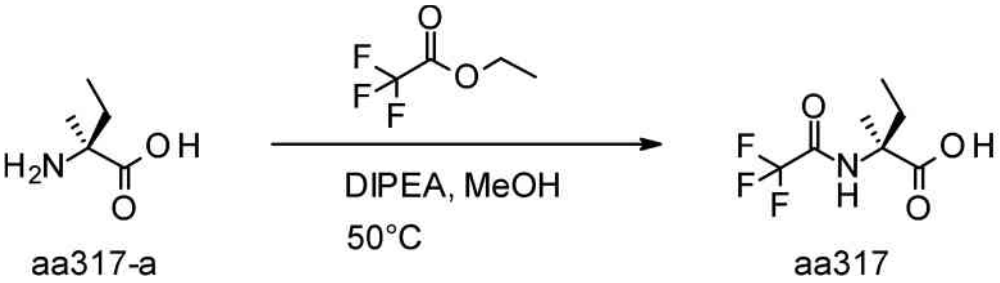
Using Compound aa329-b ((S)-2-amino-2-cyclopropylpropanoic acid, H-(Me)Gly(cPr)-OH) (1.1 g, 8.5 mmol), Compound aa329 (1.5 g, 76%) was obtained in the same manner as synthesis of Compound aa309.

LCMS (ESI) m/z = 226 (M+H)+

Retention time: 0.46 min (Analytical condition SQDFA05)

[0858]

Synthesis of Compound aa317



aa317-a aa317

[0859]

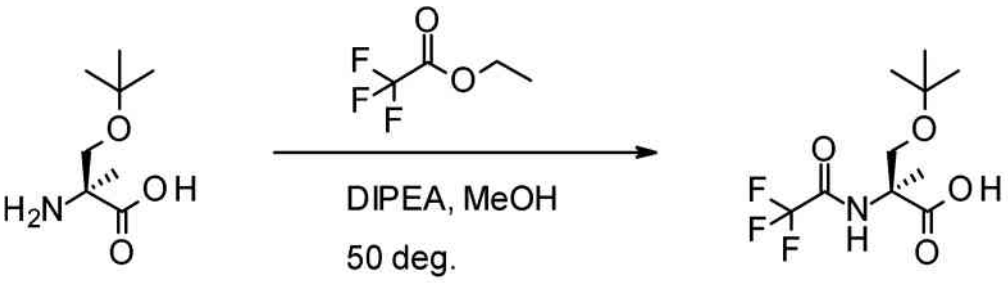
After N,N-diisopropylethylamine (82.7 g, 640 mmol) and ethyl 2,2,2-trifluoroacetate (54.6 g, 384 mmol) were added to a methanol (150 mL) solution of Compound aa317-a ((S)-2-amino-2-methylbutanoic acid, isovaline, H-(Me)Abu-OH) (15.0 g, 128 mmol), the mixture was stirred at 50°C for 16 hours. The reaction solution was cooled to room temperature and then concentrated under reduced pressure, and the resulting residue was dissolved in TBME and then washed twice with 1 N hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure to give a crude product. The resulting crude product was recrystallized from TBME/hexane (1:7) to give Compound aa317 (12 g, 44%).

LCMS (ESI) m/z = 214 (M+H)+

Retention time: 0.32 min (Analytical condition SQDFA05)

[0860]

Synthesis of Compound aa320



aa320-a aa320

[0861]

After N,N-diisopropylethylamine (5.4 mL, 30.8 mmol) and ethyl 2,2,2-trifluoroacetate (3.7 mL, 30.8 mmol) were added to a methanol (17.1 mL) solution of Compound aa320-a ((S)-2-amino-3-(tert-butoxy)-2-methylpropanoic acid, H-(Me)Ser(tBu)-OH) (1.8 g, 10.3 mmol), the mixture was stirred at 50°C for 5 hours. Then, N,N-diisopropylethylamine (2.7 mL, 15.4 mmol) and ethyl 2,2,2-trifluoroacetate (1.8 mL, 15.4 mmol) were added, and the mixture was stirred at 50°C for 16 hours. The reaction solution was cooled to room temperature and then concentrated under reduced pressure, and the resulting residue was dissolved in TBME (40 mL) and washed twice with 1 N hydrochloric acid (40 mL) and once with saturated brine (40 mL).

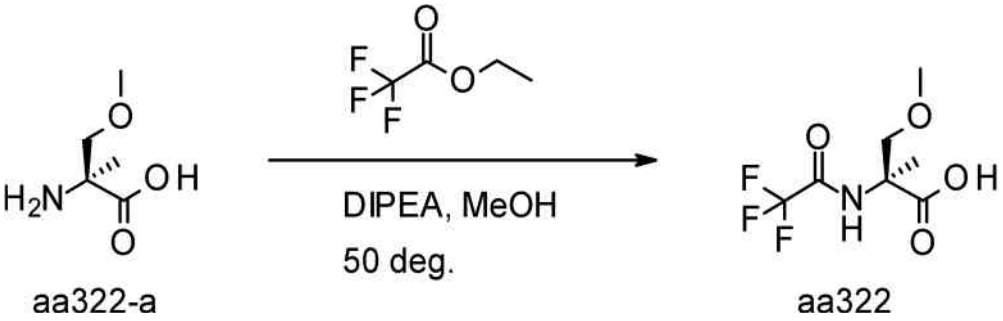
The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure to give a crude product. The resulting crude product was purified by reverse phase column chromatography (0.1% formic acid-water/0.1% formic acid-acetonitrile) to give Compound aa320 (2.3 g, 82%).

LCMS (ESI) m/z = 270 (M-H)-

Retention time: 0.65 min (Analytical condition SQDFA05)

[0862]

Synthesis of Compound aa322



aa322-a aa322

[0863]

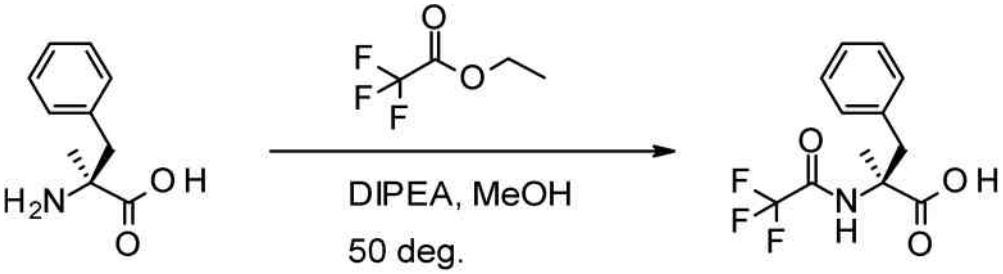
Diisopropylethylamine (5.9 mL, 33.8 mmol) and ethyl 2,2,2-trifluoroacetate (4.0 mL, 33.8 mmol) were added to a methanol (18.8 mL) solution of Compound aa322-a ((S)-2-amino-3-methoxy-2-methylpropanoic acid, H-(Me)Ser(Me)-OH) (1.5 g, 11.3 mmol), and the mixture was stirred at 50°C for 21 hours. The reaction solution was cooled to room temperature and then concentrated under reduced pressure, and the resulting residue was dissolved in TBME (45 mL) and then washed twice with 1 N hydrochloric acid (45 mL) and once with saturated brine (45 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure to give a crude product. The resulting crude product was purified by reverse phase column chromatography (0.1% formic acid-water/0.1% formic acid-acetonitrile) to give Compound aa322 (2.1 g, 80%).

LCMS (ESI) m/z = 230 (M+H)+

Retention time: 0.41 min (Analytical condition SQDFA05)

[0864]

Synthesis of Compound aa323



aa323-a aa323

[0865]

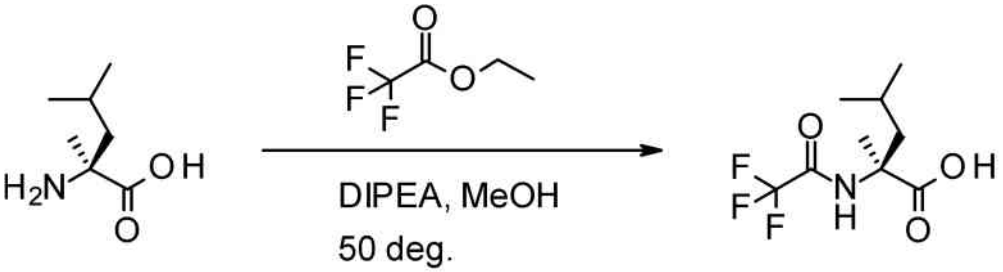
Using Compound aa323-a ((2S)-2-amino-2-methyl-3-phenylpropanoic acid, H-(Me)Phe-OH) (10.0 g, 55.8 mmol) as a starting material, Compound aa323 (8 g, 52%) was obtained in the same manner as synthesis of Compound aa317.

LCMS (ESI) m/z = 276 (M+H)+

Retention time: 0.68 min (Analytical condition SQDFA05)

[0866]

Synthesis of Compound aa325



aa325-a aa325

[0867]

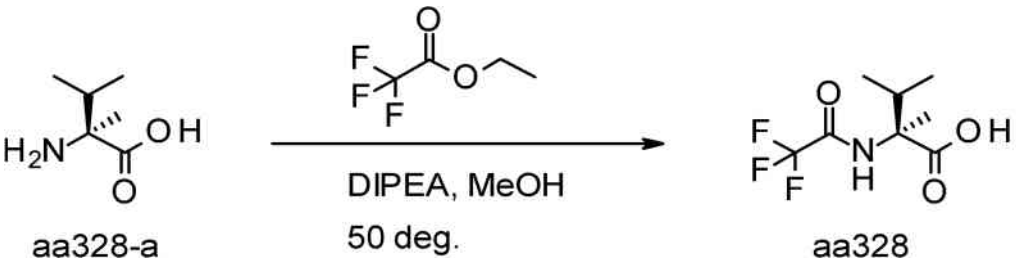
Using Compound aa325-a (2-methylleucine, (S)-2-amino-2,4-dimethylpentanoic acid, H-(Me)Leu-OH) (15.0 g, 103 mmol) as a starting material, Compound aa325 (10 g, 40%) was obtained in the same manner as synthesis of Compound aa317.

LCMS (ESI) m/z = 242 (M+H)+

Retention time: 0.66 min (Analytical condition SQDFA05)

[0868]

Synthesis of Compound aa328



aa328-a aa328

[0869]

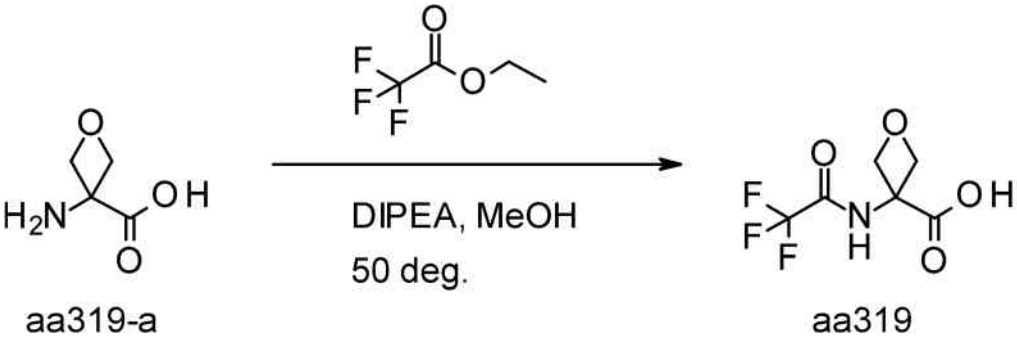
Using Compound aa328-a ((S)-2-amino-2,3-dimethylbutanoic acid, H-(Me)Val-OH) (2.0 g, 15.3 mmol) as a starting material, Compound aa328 (1.2 g, 34%) was obtained in the same manner as synthesis of Compound aa320.

LCMS (ESI) m/z = 226 (M-H)-

Retention time: 0.54 min (Analytical condition SQDFA05)

[0870]

Synthesis of Compound aa319



aa319-a aa319

[0871]

Using Compound aa319-a (3-aminooxetane-3-carboxylic acid, H-AoxeC-OH) (10.0 g, 85.4 mmol) as a starting material, Compound aa319 (9.8 g, 54%) was obtained in the same manner as synthesis of Compound aa317.

LCMS (ESI) m/z = 214 (M+H)+

Retention time: 0.50 min (Analytical condition SQDFA05)

[0872]

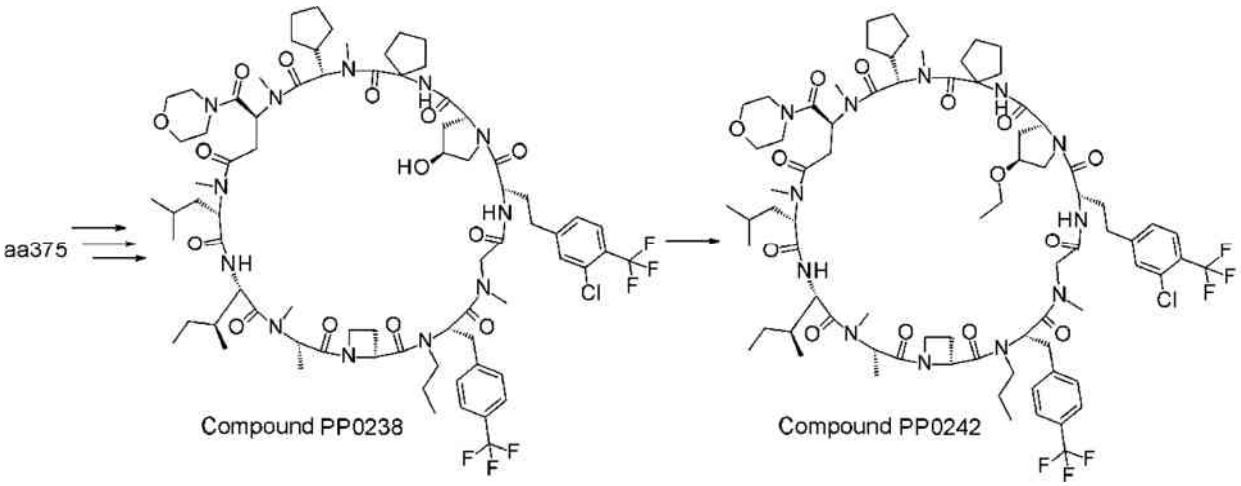
1-6. Cyclic peptide synthesis by peptide modification

1-6-1. Peptide modification by alkylation of OH

[0873]

Synthesis of Compound PP0242

Compound PP0242 was synthesized according to the following scheme.



[0874]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0238 (120.3 mg, 0.077mmol).

LCMS (ESI) m/z = 1562 (M+H)+

Retention time: 0.99 min (Analytical condition SQDFA05)

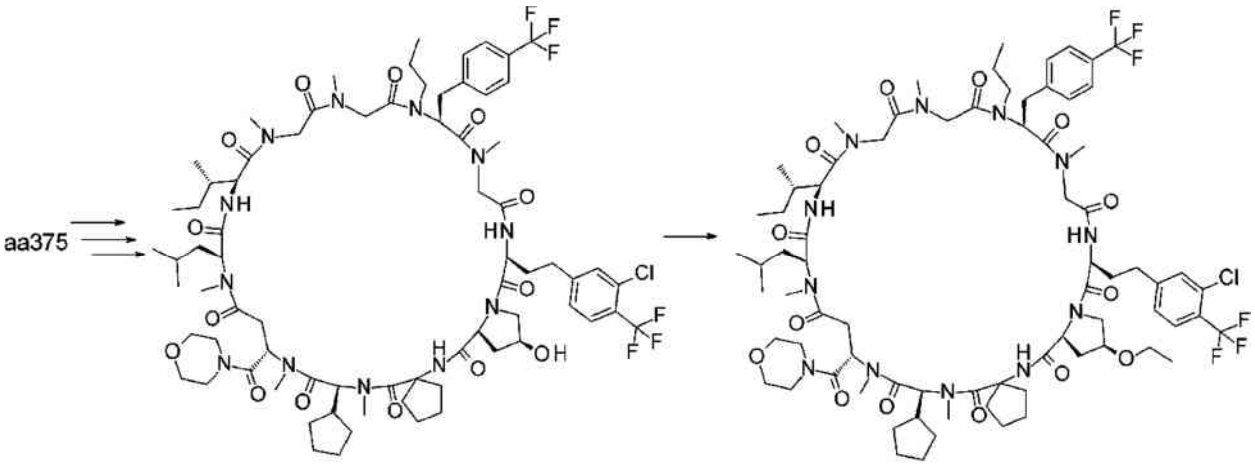
[0875]

Iodoethane (2.6 μL, 32.0 μmol), tetrabutylammonium bromide (3.1 mg, 9.6 μmol), and a 5 N aqueous sodium hydroxide solution (12.8 μL, 64.0 μmol) were added to a dichloromethane (80 μL) solution of Compound PP0238 (5.0 mg, 3.20 μmol), and the mixture was stirred at room temperature for 7 days in a nitrogen atmosphere. The resulting reaction mixture was purified by reverse phase column chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound PP0242 (2.3 mg, 45%). LC/MS data is provided in Table 36.

[0876]

Synthesis of Compound PP0243

Compound PP0243 was synthesized according to the following scheme.



[0877]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0240 (119.2 mg, 0.078 mmol).

LCMS (ESI) m/z = 1536 (M+H)+

Retention time: 0.97 min (Analytical condition SQDFA05)

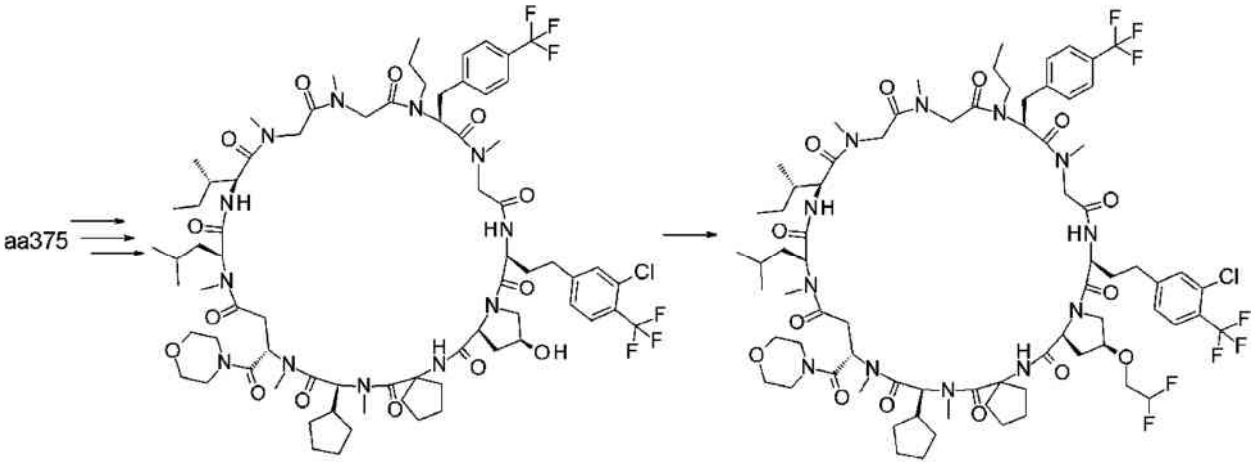
[0878]

Iodoethane (2.6 μL, 32.0 μmol), tetrabutylammonium bromide (3.1 mg, 9.6 μmol), and a 5 N aqueous sodium hydroxide solution (12.8 μL, 64.0 μmol) were added to a dichloromethane (80 μL) solution of Compound PP0240 (4.9 mg, 3.20 μmol), and the mixture was stirred at room temperature for 7 days in a nitrogen atmosphere. The resulting reaction mixture was purified by reverse phase column chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound PP0243 (2.6 mg, 52%). LC/MS data is provided in Table 36.

[0879]

Synthesis of Compound PP0245

Compound PP0245 was synthesized according to the following scheme.



Compound PP0240 Compound PP0245

[0880]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0240 (119.2 mg, 0.078 mmol).

LCMS (ESI) m/z = 1536 (M+H)+

Retention time: 0.97 min (Analytical condition SQDFA05)

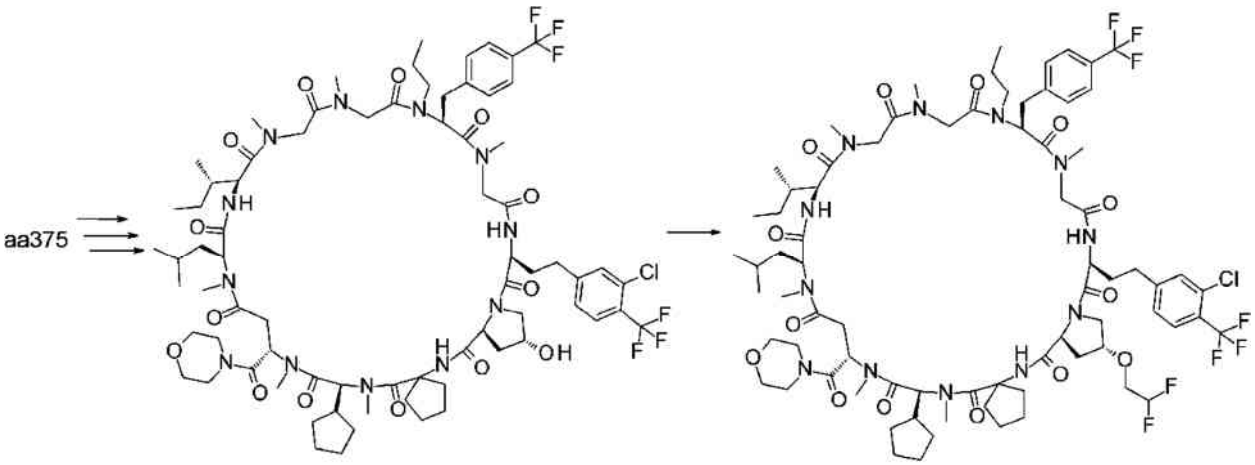
[0881]

2,2-Difluoroethyl trifluoromethanesulfonate (4.2 μL, 32.0 μmol), tetrabutylammonium bromide (3.1 mg, 9.6 μmol), and a 5 N aqueous sodium hydroxide solution (12.8 μL, 64.0 μmol) were added to a dichloromethane (80 μL) solution of Compound PP0240 (4.9 mg, 3.20 μmol), and the mixture was stirred at room temperature for 48 hours in a nitrogen atmosphere. The resulting reaction mixture was purified by reverse phase column chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound PP0245 (4.2 mg, 82%). LC/MS data is provided in Table 36.

[0882]

Synthesis of Compound PP0246

Compound PP0246 was synthesized according to the following scheme.



[0883]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0241 (109.6 mg, 0.071 mmol).

LCMS (ESI) m/z = 1536 (M+H)+

Retention time: 0.95 min (Analytical condition SQDFA05)

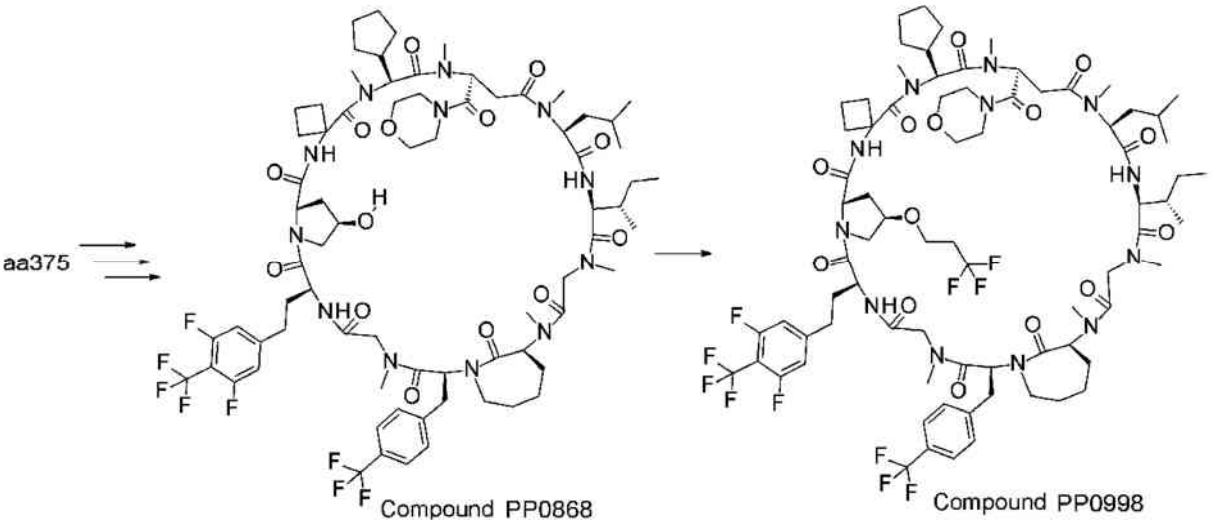
[0884]

2,2-Difluoroethyl trifluoromethanesulfonate (4.2 μL, 32.0 μmol), tetrabutylammonium bromide (3.1 mg, 9.6 μmol), and a 5 N aqueous sodium hydroxide solution (12.8 μL, 64.0 μmol) were added to a dichloromethane (80 μL) solution of Compound PP0241 (4.9 mg, 3.20 μmol), and the mixture was stirred at room temperature for 48 hours in a nitrogen atmosphere. The resulting reaction mixture was purified by reverse phase column chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound PP0246 (4.4 mg, 86%). LC/MS data is provided in Table 36.

[0885]

Synthesis of Compound PP0998

Compound PP0998 was synthesized according to the following scheme.



[0886]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0868 (76.8 mg, 0.0500 mmol).

LCMS (ESI) m/z = 1536 (M+H)+

Retention time: 0.93 min (Analytical condition SQDFA50 long)

[0887]

3,3,3-Trifluoropropyl trifluoromethanesulfonate (5.0 μL, 33.0 μmol), tetrabutylammonium bromide (3.2 mg, 9.77 μmol), and a 5 N aqueous sodium hydroxide solution (13.0 μL, 65.0 μmol) were added to a dichloromethane (65.1 μL) solution of Compound PP0868 (5.0 mg, 3.26 μmol), and the mixture was stirred at room temperature for 9 days in a nitrogen atmosphere. Dichloromethane (300 μL) and water (300 μL) were added to the resulting reaction mixture, the separated organic layer was concentrated under reduced pressure, and the resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give Compound PP0998 (0.31 mg, 6%). LC/MS data is provided in Table 36.

[0888]

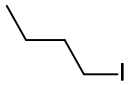
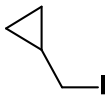
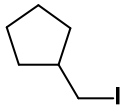
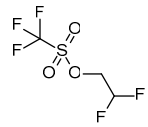
Synthesis of Compounds PP0999 to PP1003 and PP1013 to PP1015

Using Compound PP0868 as a raw material and the alkylating agents shown in Table 11, the following Compounds PP0999 to PP1003 and PP1013 to PP1015 were obtained in the same manner as synthesis of PP0998. LC/MS data is provided in Table 36.

[0889]

[Table 11]

Peptide	Alkylating agent	Raw material (mg)	Yield (mg)	Yield (%)

PP0999		5.0	0.94	18
PP1000		5.0	1.56	30
PP1001		5.0	0.16	3
PP1002		5.0	4.07	78
PP1003	Me—I	5.0	3.32	66
PP1013	-	-	1.27	24
PP1014	-	-	0.74	14
PP1015	-	-	0.20	4

* PP1013 was obtained as a by-product of synthesis of PP0999.

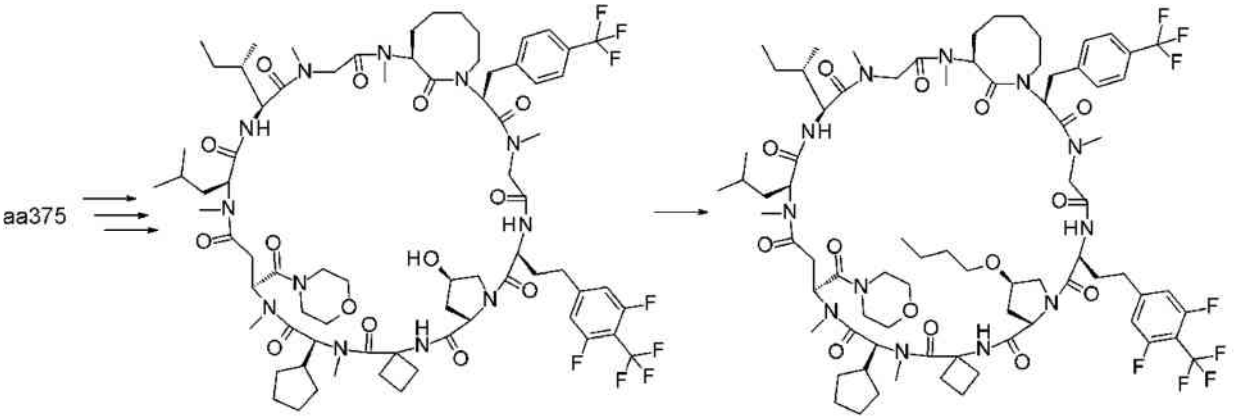
* PP1014 was obtained as a by-product of synthesis of PP1000.

* PP1015 was obtained as a by-product of synthesis of PP1001.

[0890]

Synthesis of Compound PP1004

Compound PP1004 was synthesized according to the following scheme.



[0891]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0871 (57.5 mg, 0.0371 mmol).

LCMS (ESI) m/z = 1550 (M+H)+

Retention time: 1.52 min (Analytical condition SQDFA50 long)

[0892]

1-Iodobutane (3.7 μL, 32.0 μmol), tetrabutylammonium bromide (3.1 mg, 9.68 μmol), and a 5 N aqueous sodium hydroxide solution (12.9 μL, 65.0 μmol) were added to a dichloromethane (64.5 μL) solution of Compound PP0871 (5.0 mg, 3.23 μmol), and the mixture was stirred at room temperature for 7 days in a nitrogen atmosphere. Dichloromethane (300 μL) and water (300 μL) were added to the resulting reaction mixture, the separated organic layer was concentrated under reduced pressure, and the resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give Compound PP1004 (0.76 mg, 15%). LC/MS data is provided in Table 36.

[0893]

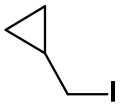
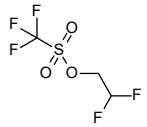
Synthesis of Compounds PP1005 to PP1006 and PP1016

Using Compound PP0871 as a raw material and the alkylating agents shown in Table 12, the following Compounds PP1005 to PP1006 and PP1016 were obtained in the same manner as synthesis of PP1004. LC/MS data is provided in Table 36.

[0894]

[Table 12]

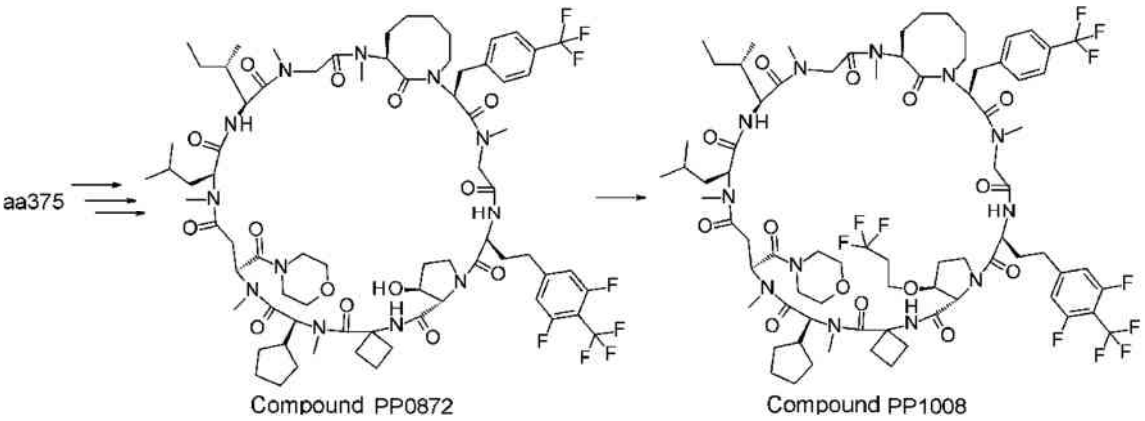
Peptide	Alkylating agent	Raw material (mg)	Yield (mg)	Yield (%)

PP1005		5.0	0.31	6
PP1006		5.0	3.34	64
PP1016	Me—I	5.0	1.14	22

[0895]

Synthesis of Compound PP1008

Compound PP1008 was synthesized according to the following scheme.



[0896]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0872 (71.7 mg, 0.0463 mmol).

LCMS (ESI) m/z = 1550 (M+H)+

Retention time: 1.64 min (Analytical condition SQDFA50 long)

[0897]

3,3,3-Trifluoropropyl trifluoromethanesulfonate (5.0 μL, 32.0 μmol), tetrabutylammonium bromide (3.1 mg, 9.68 μmol), and a 5 N aqueous sodium hydroxide solution (12.9 μL, 65.0 μmol) were added to a dichloromethane (64.5 μL) solution of Compound PP0872 (5.0 mg, 3.23 μmol), and the mixture was stirred at room temperature for 5 days in a nitrogen atmosphere. Dichloromethane (300 μL) and water (300 μL) were added to the resulting reaction mixture, the separated organic layer was concentrated under reduced pressure, and the resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give Compound PP1008 (1.76 mg, 33%). LC/MS data is provided in Table 36.

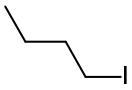
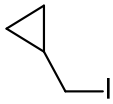
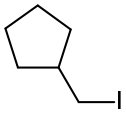
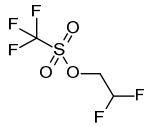
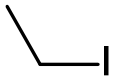
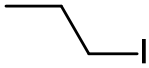
[0898]

Synthesis of Compounds PP1009 to PP1012 and PP1067 to PP1069

Using Compound PP0872 as a raw material and the alkylating agents shown in Table 13, the following Compounds PP1009 to PP1012 and PP1067 to PP1069 were obtained in the same manner as synthesis of PP1008. LC/MS data is provided in Table 36.

[0899]

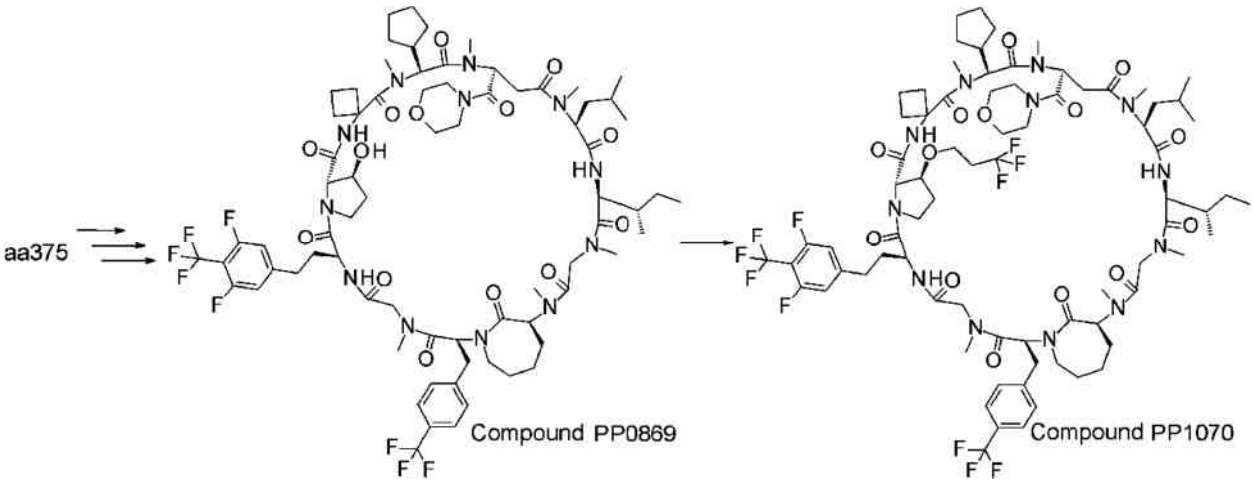
[Table 13]

Peptide	Alkylating agent	Raw material (mg)	Yield (mg)	Yield (%)
PP1009		5.0	1.52	29
PP1010		5.0	1.64	32
PP1011		5.0	0.42	8
PP1012		5.0	1.79	34
PP1067	Me—I	5.0	3.90	77
PP1068		5.0	1.66	33
PP1069		5.0	2.12	41

[0900]

Synthesis of Compound PP1070

Compound PP1070 was synthesized according to the following scheme.



[0901]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0869 (78.0 mg, 0.0508 mmol).

LCMS (ESI) m/z = 1536 (M+H)+

Retention time: 1.01 min (Analytical condition SQDFA50 long)

[0902]

3,3,3-Trifluoropropyl trifluoromethanesulfonate (5.0 μL, 33.0 μmol), tetrabutylammonium bromide (3.2 mg, 9.77 μmol), and a 5 N aqueous sodium hydroxide solution (13.0 μL, 65.0 μmol) were added to a dichloromethane (65.1 μL) solution of Compound PP0869 (5.0 mg, 3.26 μmol), and the mixture was stirred at room temperature for 5 days in a nitrogen atmosphere. Dichloromethane (300 μL) and water (300 μL) were added to the resulting reaction mixture, the separated organic layer was concentrated under reduced pressure, and the resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give Compound PP1070 (0.63 mg, 12%). LC/MS data is provided in Table 36.

[0903]

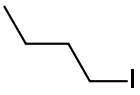
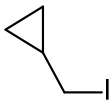
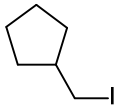
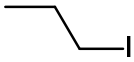
Synthesis of Compounds PP1071 to PP1073 and PP1075 to PP1077

Using Compound PP0869 as a raw material and the alkylating agents shown in Table 14, the following Compounds PP1071 to PP1077 were obtained in the same manner as synthesis of PP1070. LC/MS data is provided in Table 36.

[0904]

[Table 14]

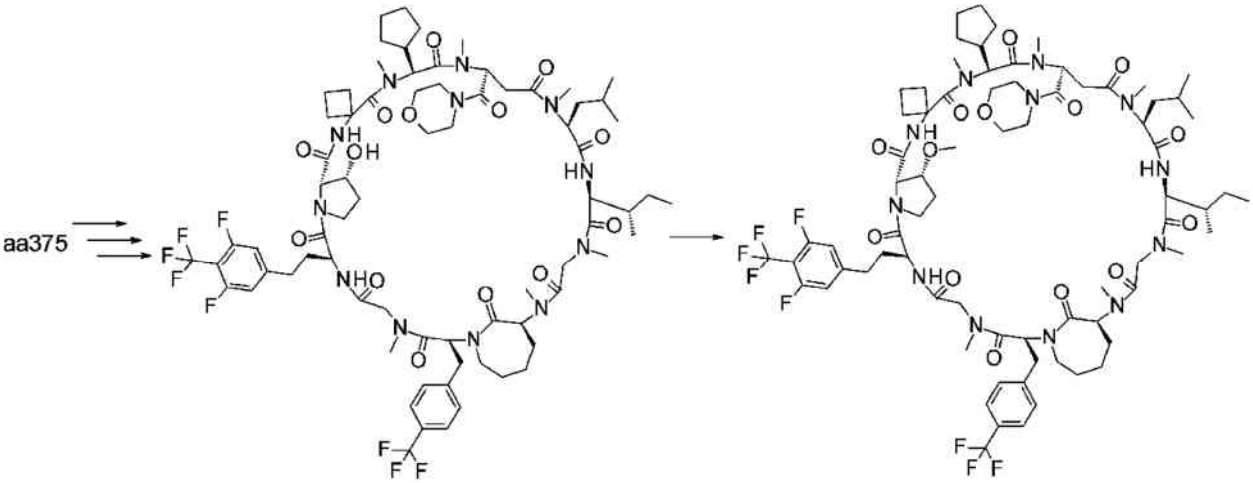
Peptide	Alkylating agent	Raw material (mg)	Yield (mg)	Yield (%)

PP1071		5.0	2.45	47
PP1072		5.0	2.37	46
PP1073		5.0	0.47	9
PP1075	Me—I	5.0	1.70	34
PP1076		5.0	3.33	65
PP1077		5.0	2.28	44

[0905]

Synthesis of Compound PP1078

Compound PP1078 was synthesized according to the following scheme.



[0906]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0870 (53.6 mg, 0.0349 mmol).

LCMS (ESI) m/z = 1536 (M+H)+

Retention time: 0.94 min (Analytical condition SQDFA50 long)

[0907]

Iodomethane (2.0 μL, 33.0 μmol), tetrabutylammonium bromide (3.2 mg, 9.77 μmol), and a 5 N aqueous sodium hydroxide solution (13.0 μL, 65.0 μmol) were added to a dichloromethane (65.1 μL) solution of Compound PP0870 (5.0 mg, 3.26 μmol), and the mixture was stirred at room temperature for 9 hours in a nitrogen atmosphere. Dichloromethane (300 μL) and water (300 μL) were added to the resulting reaction mixture, the separated organic layer was concentrated under reduced pressure, and the resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give Compound PP1078 (0.37 mg, 7%). LC/MS data is provided in Table 36.

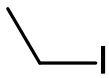
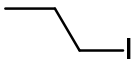
[0908]

Synthesis of Compounds PP1079, PP1080, and PP1084

Using Compound PP0870 as a raw material and the alkylating agents shown in Table 15, the following Compounds PP1079, PP1080, and PP1084 were obtained in the same manner as synthesis of PP1078. LC/MS data is provided in Table 36.

[0909]

[Table 15]

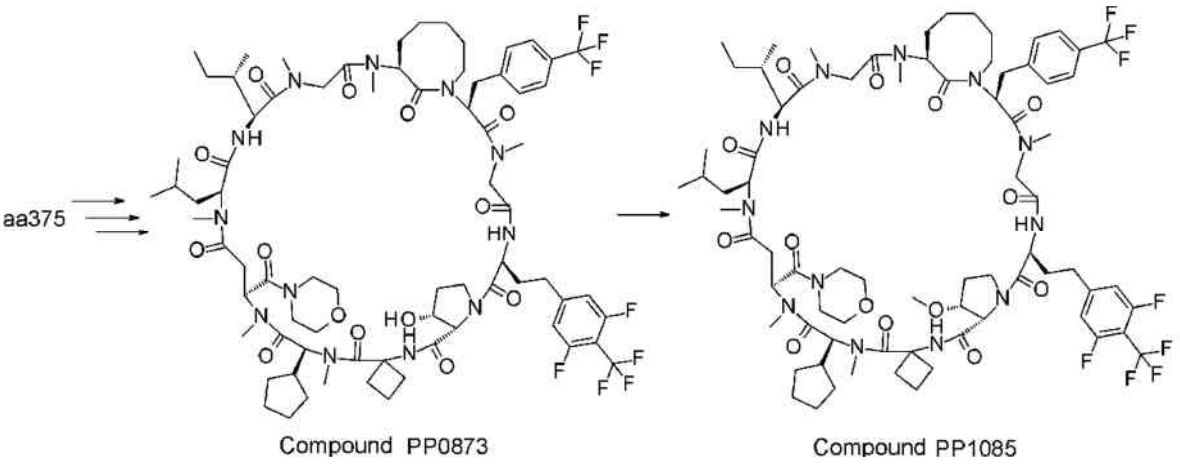
Peptide	Alkylating agent	Raw material (mg)	Yield (mg)	Yield (%)
PP1079		5.0	2.35	46
PP1080		5.0	2.17	42
PP1084	-	5.0	0.92	17

* PP1084 was obtained as a by-product of synthesis of PP1078.

[0910]

Synthesis of Compound PP1085

Compound PP1085 was synthesized according to the following scheme.



[0911]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0873 (37.3 mg, 0.0241 mmol).

LCMS (ESI) m/z = 1550 (M+H)+

Retention time: 1.50 min (Analytical condition SQDFA50 long)

[0912]

Iodomethane (2.0 μL, 32.0 μmol), tetrabutylammonium bromide (3.1 mg, 9.68 μmol), and a 5 N aqueous sodium hydroxide solution (12.9 μL, 65.0 μmol) were added to a dichloromethane (64.5 μL) solution of Compound PP0873 (5.0 mg, 3.23 μmol), and the mixture was stirred at room temperature for 9 hours in a nitrogen atmosphere. Dichloromethane (300 μL) and water (300 μL) were added to the resulting reaction mixture, the separated organic layer was concentrated under reduced pressure, and the resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give Compound PP1085 (1.0 mg, 19%). LC/MS data is provided in Table 36.

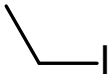
[0913]

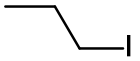
Synthesis of Compounds PP1082 and PP1083

Using Compound PP0873 as a raw material and the alkylating agents shown in Table 17, the following Compounds PP1082 and PP1083 were obtained in the same manner as synthesis of PP1081. LC/MS data is provided in Table 36.

[0914]

[Table 17]

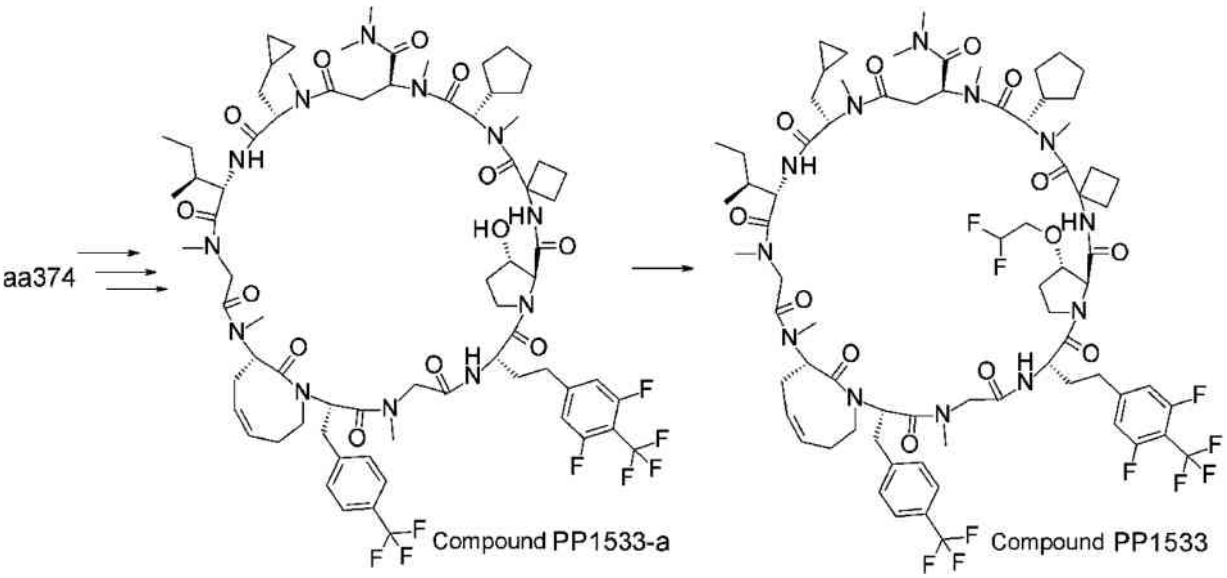
Peptide	Alkylating agent	Raw material (mg)	Yield (mg)	Yield (%)
PP1082		5.0	1.25	25

PP1083		5.0	0.93	18

[0915]

Synthesis of Compound PP1533

Compound PP1533 was synthesized according to the following scheme.



Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP1533-a (20.0 mg, 0.013 mmol).

LCMS (ESI) m/z = 1504 (M+H)+

Retention time: 0.91 min (Analytical condition SQDFA05)

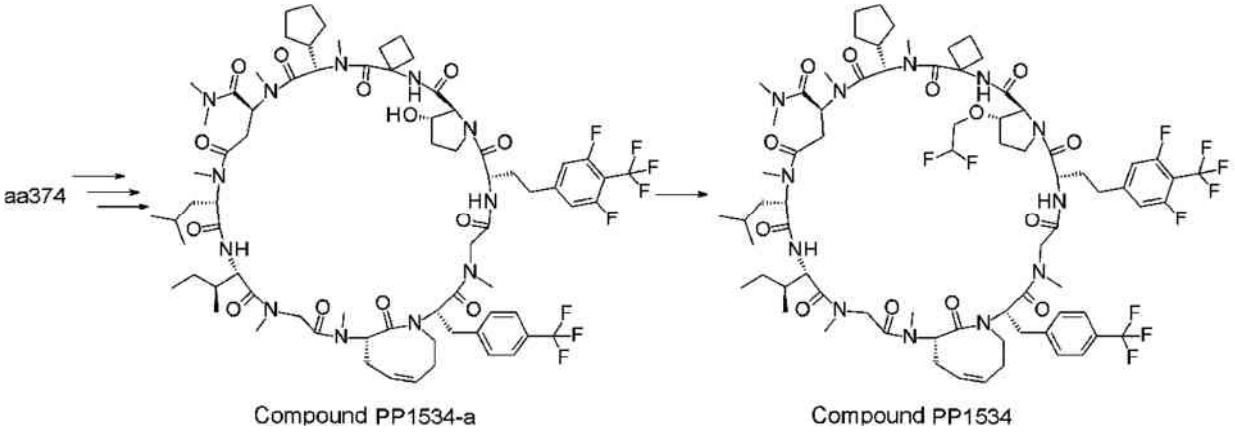
[0916]

2,2-Difluoroethyl trifluoromethanesulfonic acid (18.2 μL, 0.14 mmol), tetrabutylammonium bromide (13.3 mg, 0.041 mol), and a 5 N aqueous sodium hydroxide solution (55.1 μL, 0.28 mmol) were added to a dichloromethane (275 μL) solution of Compound PP1533-a (20.7 mg, 0.014 mmol), and the mixture was stirred at room temperature for 3 days in a nitrogen atmosphere. Dichloromethane (300 μL) and water (300 μL) were added to the resulting reaction mixture, the separated organic layer was concentrated under reduced pressure, and the resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give Compound PP1533 (11.5 mg, 54%). LC/MS data is provided in Table 36.

[0917]

Synthesis of Compound PP1534

Compound PP1534 was synthesized according to the following scheme.



[0918]

Using Compound aa374-resin as a raw material, PP1534-a (22.6mg, 0.015 mmol) was obtained in the same manner as synthesis of PP1533-a.

LCMS (ESI) m/z = 1506 (M+H)+

Retention time: 0.93 min (Analytical condition SQDFA05)

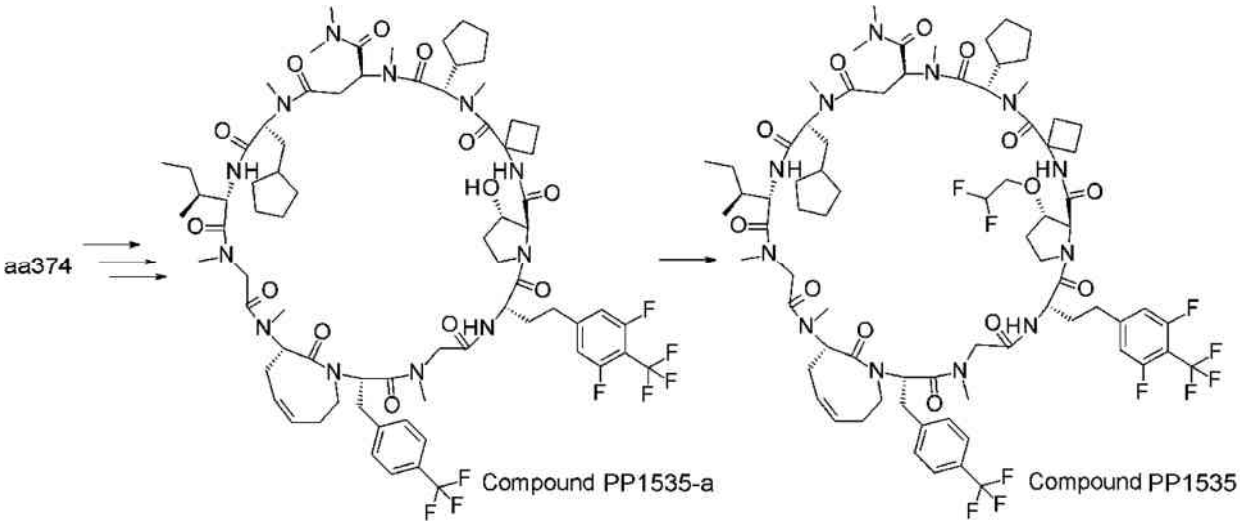
[0919]

Using Compound PP1534-a (23.4 mg, 0.016 mmol) as a raw material, PP1534 (11.5 mg, 53%) was obtained in the same manner as synthesis of PP1533. LC/MS data is provided in Table 36.

[0920]

Synthesis of Compound PP1535

Compound PP1535 was synthesized according to the following scheme.



[0921]

Using Compound aa374-resin as a raw material, PP1535-a (19.5 mg, 0.013 mmol) was obtained in the same manner as synthesis of PP1533-a.

LCMS (ESI) m/z = 1532 (M+H)+

Retention time: 0.96 min (Analytical condition SQDFA05)

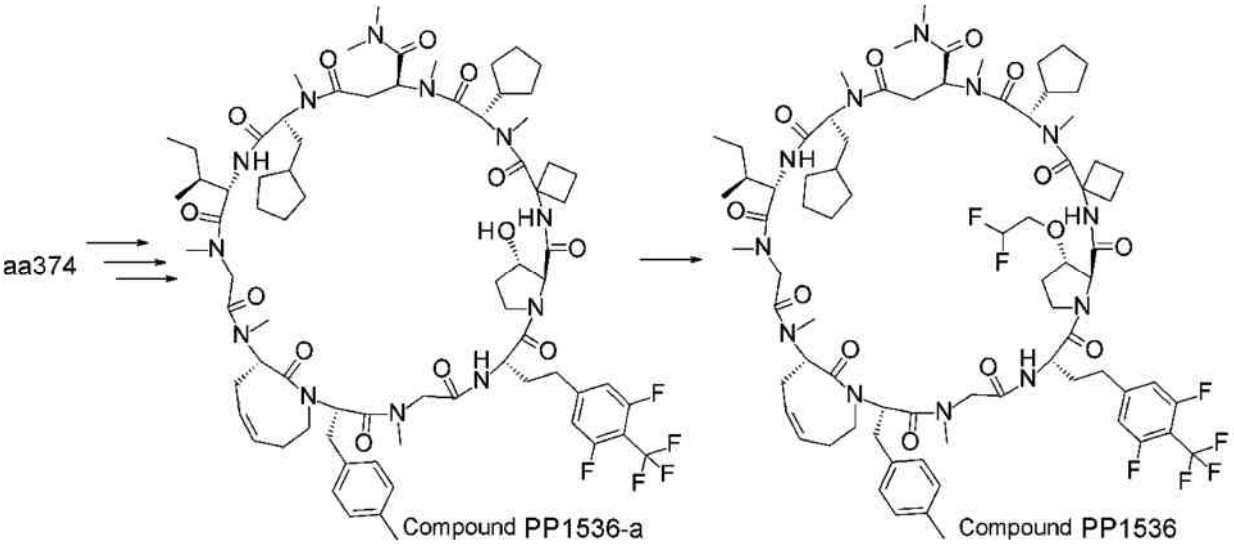
[0922]

Using Compound PP1535-a (20.3 mg, 0.013 mmol) as a raw material, PP1535 (9.4 mg, 42%) was obtained in the same manner as synthesis of PP1533. LC/MS data is provided in Table 36.

[0923]

Synthesis of Compound PP1536

Compound PP1536 was synthesized according to the following scheme.



[0924]

Using Compound aa374-resin as a raw material, PP1536-a (18.0 mg, 0.012 mmol) was obtained in the same manner as synthesis of PP1533-a.

LCMS (ESI) m/z = 1478 (M+H)+

Retention time: 0.94 min (Analytical condition SQDFA05)

[0925]

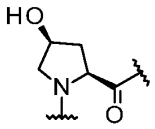
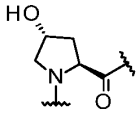
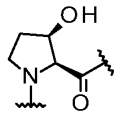
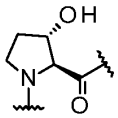
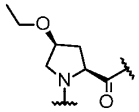
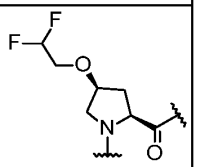
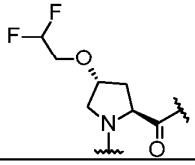
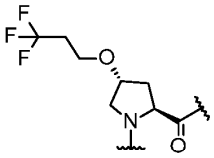
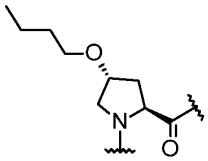
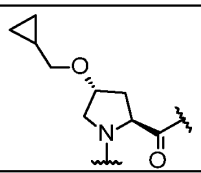
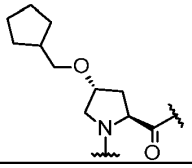
Using Compound PP1536-a (18.4 mg, 0.012 mmol) as a raw material, PP1536 (8.2 mg, 39%) was obtained in the same manner as synthesis of PP1533. LC/MS data is provided in Table 36.

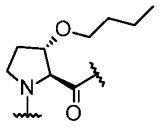
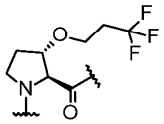
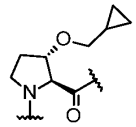
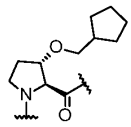
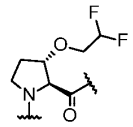
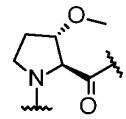
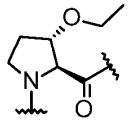
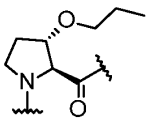
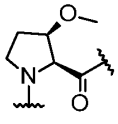
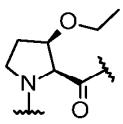
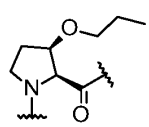
[0926]

In a cyclic compound and an oligopeptide compound synthesized by peptide modification by the alkylation of OH, abbreviations and structures of amino acids contained as partial structures are provided below.

[0927]

[Table 17-1]

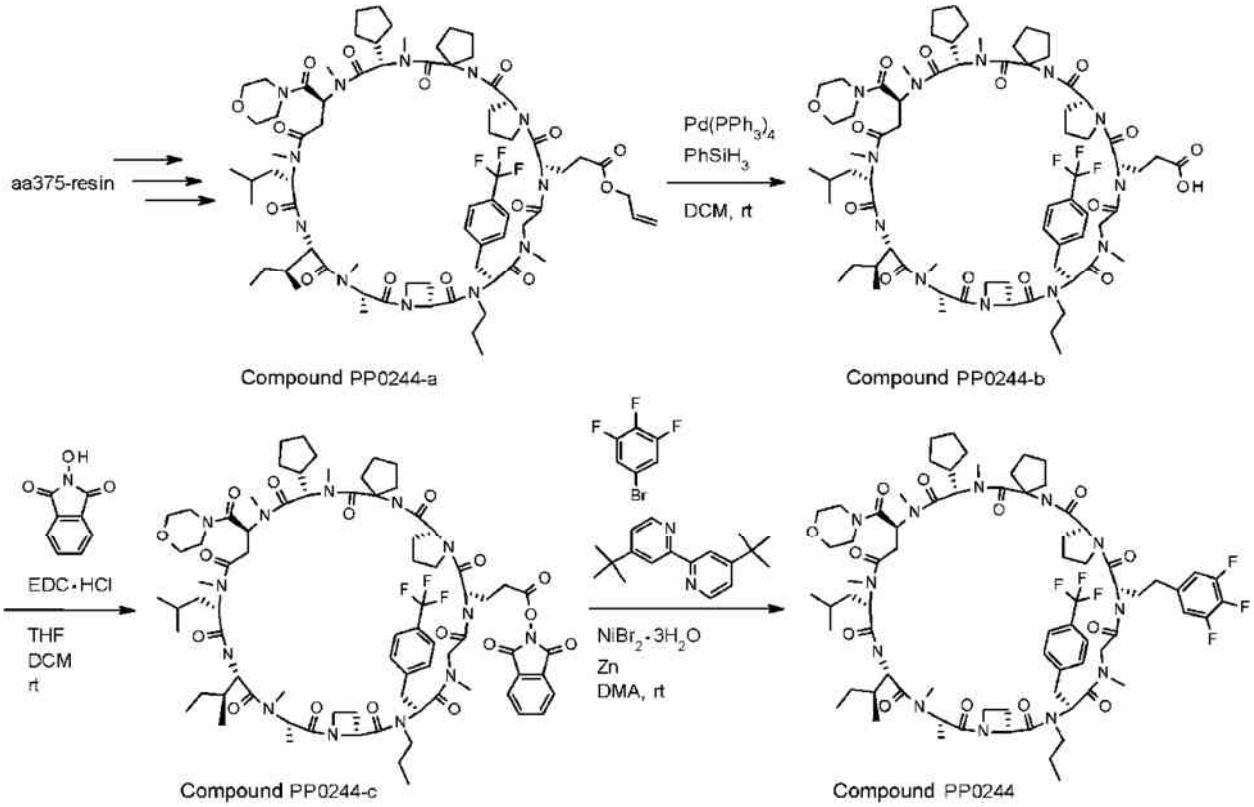
Compound No.	Abbreviation	Amino acid Structural Formula
bb016	cisHyp	
bb017	Hyp	
bb018	cisHyp(3)	
bb019	Hyp(3)	
bb020	cisHyp(Et)	
bb021	cisHyp(Et(2-F2))	
bb022	Hyp(Et(2-F2))	
bb023	Hyp(Tfp)	
bb024	Hyp(nBu)	
bb025	Hyp(Me-cPr)	
bb026	Hyp(Me-cPent)	

Compound No.	Abbreviation	Amino acid Structural Formula
bb027	Hyp(3)(nBu)	
bb028	Hyp(3)(Tfp)	
bb029	Hyp(3)(Me-cPr)	
bb030	Hyp(3)(Me-cPent)	
bb031	Hyp(3)(Et(2-F2))	
bb032	Hyp(3)(Me)	
bb033	Hyp(3)(Et)	
bb034	Hyp(3)(nPr)	
bb035	cisHyp(3)(Me)	
bb036	cisHyp(3)(Et)	
bb037	cisHyp(3)(nPr)	

[0928]

1-6-2. Peptide modification by reductive coupling reaction

Synthesis of Compound PP0244



[0929]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0244-a (456.0 mg, 0.314 mmol).

LCMS (ESI) m/z = 1452 (M+H)+

Retention time: 0.90 min (Analytical condition SQDFA05)

[0930]

Compound PP0244-a (456.0 mg, 0.314 mmol) and tetrakis(triphenylphosphine)palladium(0) (10.0 mg, 8.65 μmol) were dissolved in dichloromethane (3.0 mL), and phenylsilane (0.040 mL, 0.325 mmol) was added dropwise in a nitrogen atmosphere. The reaction solution was stirred at room temperature for 2 hours, and then purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound PP0244-b (80. 5 mg, 18%).

LCMS (ESI) m/z = 1412 (M+H)+

Retention time: 0.78 min (Analytical condition SQDFA05)

[0931]

Compound PP0244-b (5.0 mg, 3.54 μmol) was placed in a reaction vessel, then a tetrahydrofuran (20 μL) solution of N-hydroxyphthalimide (0.867 mg, 5.31 μmol) and a dichloromethane (20 μL) solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.55 mg, 3.54 μmol) were added, and the mixture was stirred overnight at room temperature. The solvent was distilled off under reduced pressure to give Compound PP0244-c as a crude product (5.51 mg, 100%).

LCMS (ESI) m/z = 1557 (M+H)+

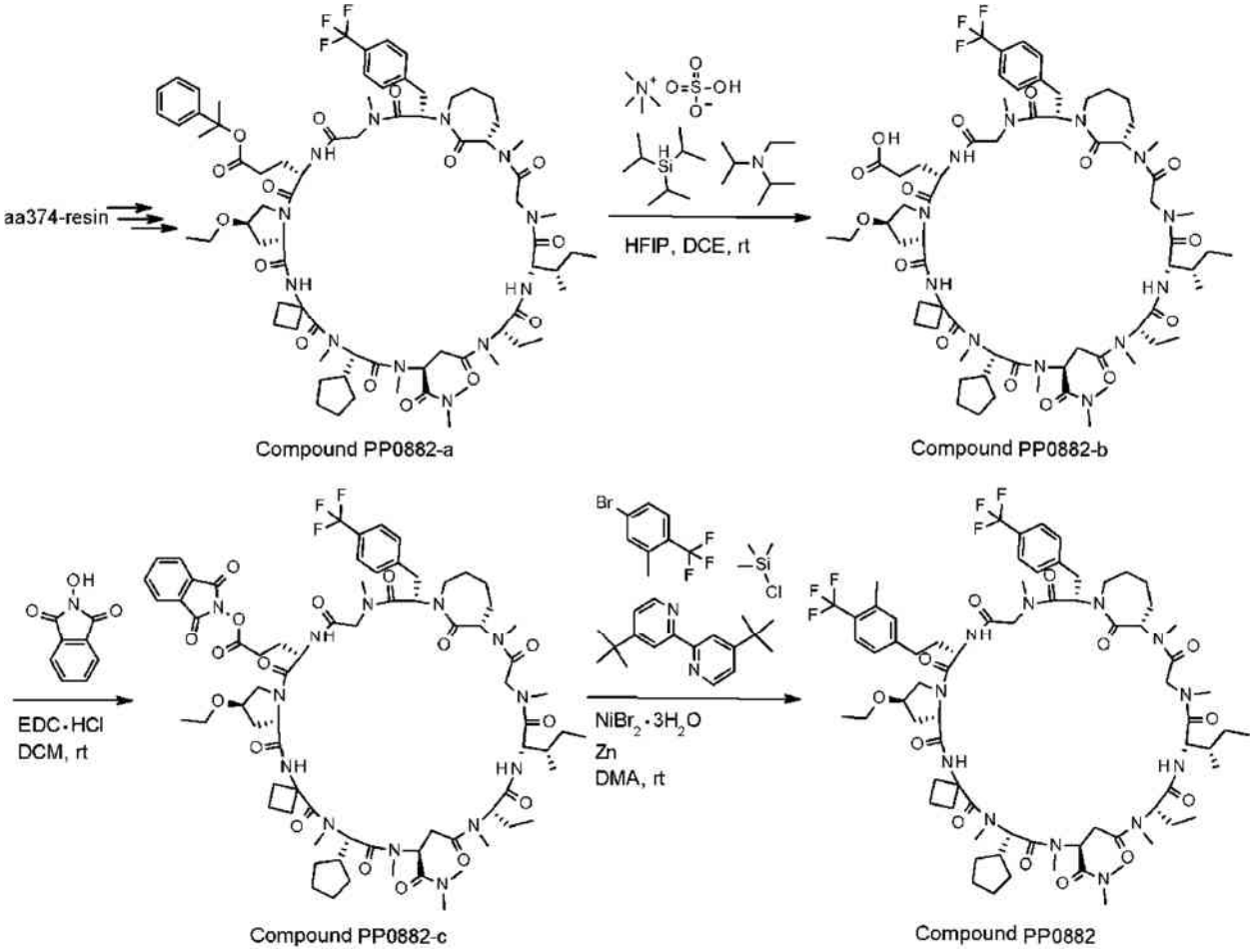
Retention time: 0.91 min (Analytical condition SQDFA05)

[0932]

In a nitrogen atmosphere, nickel(II) bromide trihydrate (0.97 mg, 3.54 μmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (0.95 mg, 3.54 μmol) were dissolved in N,N.-dimethylacetamide (91 μL), and this solution was added to an N,N-dimethylacetamide (80 μL) solution of Compound PP0244-c (5.51 mg, 3.54 μmol), zinc (3.47 mg, 53.1 μmol), and 5-bromo-1,2,3-trifluorobenzene (4.2 μL, 35.4 μmol). After being stirred at room temperature for 19 hours, the mixture was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound PP0244 (3.3 mg, 62%). LC/MS data is provided in Table 36.

[0933]

Synthesis of Compound PP0882



[0934]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0882-a (160.3 mg, 0.1086 mmol).

LCMS (ESI) m/z = 1476 (M+H)+

Retention time: 0.93 min (Analytical condition SQDFA05)

[0935]

1,1,1,3,3,3-Hexafluoro-2-propanol (11.66 mL), triisopropylsilane (0.24 mL), 1,2-dichloroethane (0.1 mL), and tetramethylammonium hydrogen sulfate (10.29 mg) were mixed, and the solution thereof (1.0 mL) was added to a reaction vessel containing Compound PP0882-a (5.0 mg, 3.39 μmol). After the mixture was stirred at room temperature for 1 hour, N,N-diisopropylethylamine (17.5 μL) was added. This was combined with a separately synthesized lot and purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound PP0882-b (123 mg).

LCMS (ESI) m/z = 1358 (M+H)+

Retention time: 0.74 min (Analytical condition SQDFA05)

[0936]

Compound PP0882-b (10.0 mg, 7.37 μmol), N-hydroxyphthalimide (1.20 mg, 7.37 μmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.12 mg, 0.011 mmol), and dichloromethane (73.7 μL) were placed in a reaction vessel, and the mixture was stirred at room temperature for 90 minutes. The reaction solution was diluted with dichloromethane (140 μL), and washed twice with water (200 μL). The organic layer was concentrated and dried under reduced pressure to give Compound PP0882-c as a crude product (11.1 mg, 100%).

LCMS (ESI) m/z = 1503 (M+H)+

Retention time: 0.87 min (Analytical condition SQDFA05)

[0937]

Nickel(II) bromide trihydrate (4.02 mg, 14.74 μmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (3.96 mg, 14.74 μmol) were dissolved in N,N-dimethylacetamide (37 μL), and the mixture was stirred at room temperature for 30 minutes in a nitrogen atmosphere. After this solution was added to an N,N-dimethylacetamide (55 μL) solution of Compound PP0882-c (11.1 mg, 7.37 μmol), zinc (7.23 mg, 111.0 μmol), and 4-bromo-2-methyl-1-(trifluoromethyl)benzene (11.1 μL, 73.7 μmol), chlorotrimethylsilane (0.94 μL, 7.37 μmol) was added, and the mixture was stirred at room temperature for 14 hours. The reaction mixture was diluted with dimethyl sulfoxide (0.8 mL), filtered, and then purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give Compound PP0882 (4.8 mg, 44%). LC/MS data is provided in Table 36.

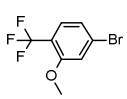
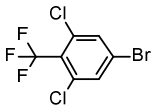
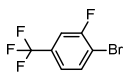
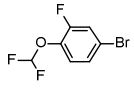
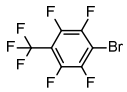
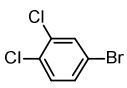
[0938]

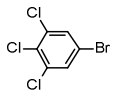
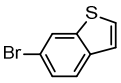
Synthesis of Compounds PP0884 to PP0888 and PP0985 to PP0988

Using Compound PP0882-c (12.17 mg, 8.1 μmol) as a raw material, PP0884 to PP0888 and PP0985 to PP0988 were obtained in the same manner as synthesis of Compound PP0882 using the bromides (10 eq) shown in Table 18. LC/MS data is provided in Table 36.

[0939]

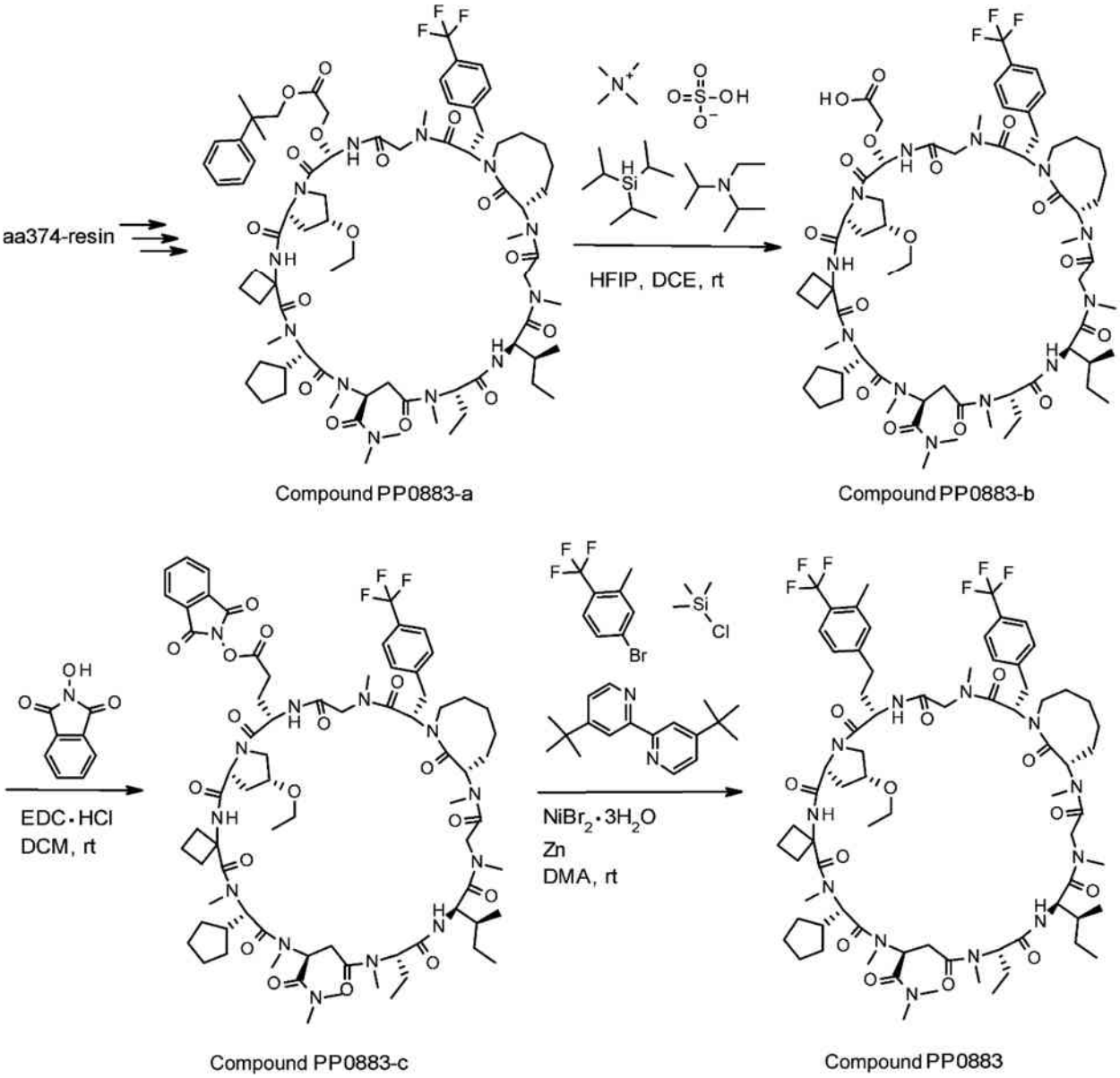
[Table 18]

Intended product	Bromide	Yield (mg)	Yield (%)	Intended product	Bromide	Yield (mg)	Yield (%)
PP0884		6.19	51	PP0985		4.18	34
PP0885		3.94	33	PP0986		3.78	32
PP0886		0.45	4	PP0987		0.44	4

PP0887		2.72	23	PP0988		4.01	33
PP0888		3.96	34				

[0940]

Synthesis of Compound PP0833



[0941]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0883-a (162.4 mg, 0.108 mmol).

LCMS (ESI) m/z = 1490 (M+H)+

Retention time: 1.03 min (Analytical condition SQDFA05)

[0942]

1,1,1,3,3,3-Hexafluoro-2-propanol (11.66 mL), triisopropylsilane (0.24 mL), 1,2-dichloroethane (0.1 mL), and tetramethylammonium hydrogen sulfate (10.29 mg) were mixed, and the solution thereof (1.0 mL) was added to a reaction vessel containing Compound PP0883-a (5.0 mg, 3.36 μmol). After the mixture was stirred at room temperature for 1 hour, N,N-diisopropylethylamine (17.5 μL) was added. This was combined with a separately synthesized lot and purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound PP0883-b (91 mg).

LCMS (ESI) m/z = 1372 (M+H)+

Retention time: 0.82 min (Analytical condition SQDFA05)

[0943]

Compound PP0883-b (10.0 mg, 7.29 μmol), N-hydroxyphthalimide (1.189 mg, 7.29 μmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.10 mg, 10.94 μmol), and dichloromethane (72.9 μL) were placed in a reaction vessel, and the mixture was stirred at room temperature for 90 minutes. The reaction solution was diluted with dichloromethane (140 μL), and washed twice with water (200 μL). The organic layer was concentrated and dried under reduced pressure to give Compound PP0883-c as a crude product (11.1 mg, 100%).

LCMS (ESI) m/z = 1517 (M+H)+

Retention time: 0.95 min (Analytical condition SQDFA05)

[0944]

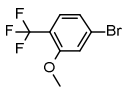
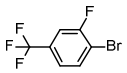
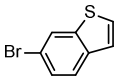
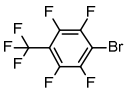
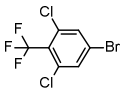
Nickel(II) bromide trihydrate (3.97 mg, 14.58 μmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (3.91 mg, 14.58 μmol) were dissolved in N,N-dimethylacetamide (37 μL), and the mixture was stirred at room temperature for 30 minutes in a nitrogen atmosphere. After this solution was added to an N,N-dimethylacetamide (55 μL) solution of Compound PP0883-c (11.1 mg, 7.29 μmol), zinc (7.15 mg, 109.0 μmol), and 4-bromo-2-methyl-1-(trifluoromethyl)benzene (11.0 μL, 72.9 μmol), chlorotrimethylsilane (0.93 μL, 7.29 μmol) was added, and the mixture was stirred at room temperature for 14 hours. The reaction mixture was diluted with dimethyl sulfoxide (0.8 mL), filtered, and then purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give Compound PP0883 (3.7 mg, 34%). LC/MS data is provided in Table 36.

[0945]

Synthesis of Compounds PP0889 to PP0893 and PP0989

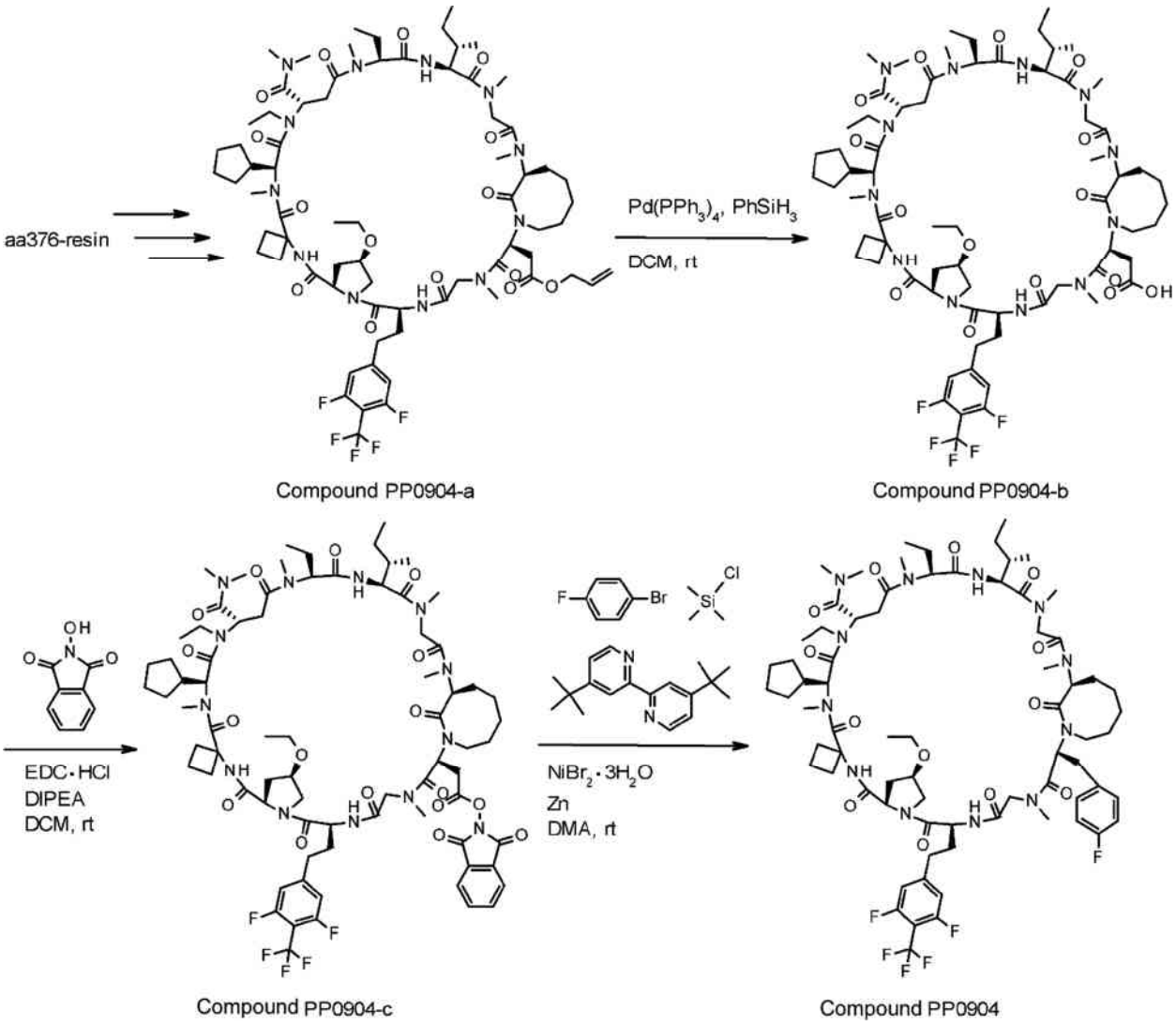
Using Compound PP0883-c (12.59 mg, 8.3 μmol) as a raw material, PP0889 to PP0893 and PP0989 were obtained in the same manner as synthesis of Compound PP0883 using the bromides (10 eq) shown in Table 19. LC/MS data is provided in Table 36.

[Table 19]

Intended product	Bromide	Yield (mg)	Yield(%)	Intended product	Bromide	Yield (mg)	Yield(%)
PP0889		1.85	15	PP0892		0.27	2
PP0890		2.03	16	PP0893		0.74	6
PP0891		0.26	2	PP0989		2.2	17

[0946]

Synthesis of Compound PP0904



[0947]

Using Compound aa376-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0904-a.

LCMS (ESI) m/z = 1462 (M+H)+

Retention time: 0.78 min (Analytical condition SQDAA50)

[0948]

The resulting Compound PP0904-a was dissolved in dichloromethane (1.0 mL), tetrakis(triphenylphosphine)palladium(0) (31.0 mg, 26.6 μmol) and phenylsilane (58.0 mg, 0.533 mmol) were added, and the mixture was stirred at room temperature for 30 minutes. After the solvent was distilled off under reduced pressure, the resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give Compound PP0904-b (22.0 mg, 0.015 mmol, 11%).

LCMS (ESI) m/z = 1422 (M+H)+

Retention time: 0.66 min (Analytical condition SQDAA50)

[0949]

Dichloromethane (155 μL) was added to a reaction vessel containing Compound PP0904-b (22.0 mg, 0.015 mmol) and N-hydroxyphthalimide (2.5 mg, 0.015 mmol). After the mixture was stirred at room temperature for 1 hour, N,N-diisopropylethylamine (4.1 μL, 0.023 mmol) was added, and the mixture was stirred at room temperature for 1 hour. Then, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.5 mg, 0.023 mmol) was added, and the mixture was stirred at room temperature for 1 hour. After dilution with dichloromethane, the organic layer was washed with a saturated aqueous ammonium chloride solution and then washed with water. After drying over anhydrous sodium sulfate and filtration, the solvent was distilled off under reduced pressure to give Compound PP0904-c (20.8 mg, 86%).

LCMS (ESI) m/z = 1567 (M+H)+

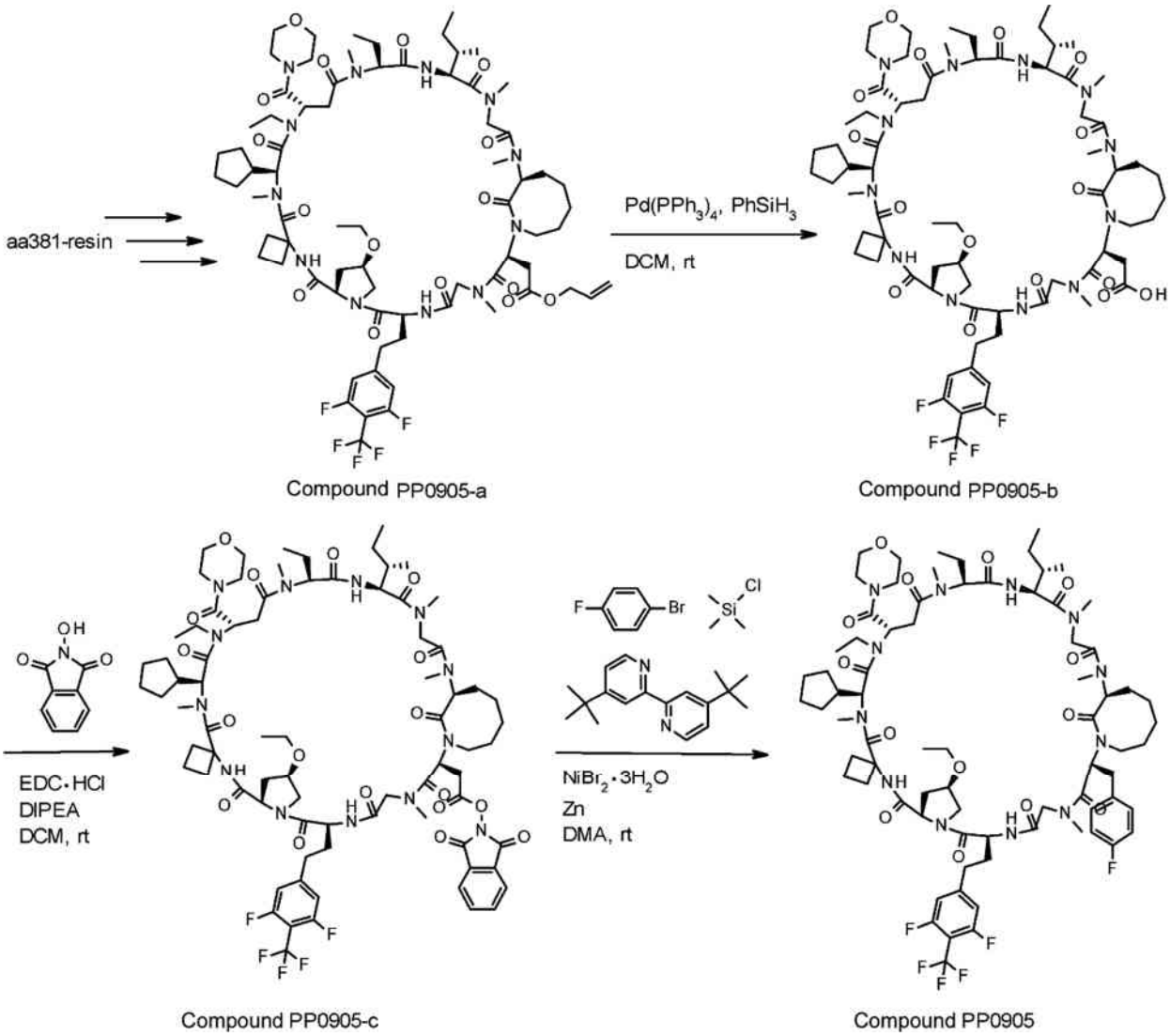
Retention time: 0.88 min (Analytical condition SQDFA40)

[0950]

Nickel(II) bromide trihydrate (1.74 mg, 6.39 μmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (1.71 mg, 6.39 μmol) were dissolved in N,N-dimethylacetamide (75 μL), and this solution was added to an N,N-dimethylacetamide (80 μL) solution of Compound PP0904-c (10.0 mg, 6.38 μmol), zinc (6.3 mg, 0.096 mmol), and 4-bromofluorobenzene (7.0 μL, 0.064 mmol). After the mixture was stirred at room temperature for 15 hours, chlorotrimethylsilane (0.82 μL, 6.39 μmol) was added, and the mixture was stirred for 3 hours. The reaction mixture was diluted with dimethyl sulfoxide, filtered, and then purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give Compound PP0904 (0.43 mg, 0.292 μmol). LC/MS data is provided in Table 36.

[0951]

Synthesis of Compound PP0905



[0952]

Using Compound aa381-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0905-a. Using this as a starting material, PP0905-b (27.0 mg, 0.018 mmol, 8%) was obtained in the same manner as synthesis of Compound PP0904-b.

LCMS (ESI) m/z = 1464 (M+H)+

Retention time: 0.66 min (Analytical condition SQDAA50)

[0953]

Using PP0905-b as a starting material, PP0905-c (26.0 mg, 88%) was obtained in the same manner as synthesis of Compound PP0904-c.

LCMS (ESI) m/z = 1609 (M+H)+

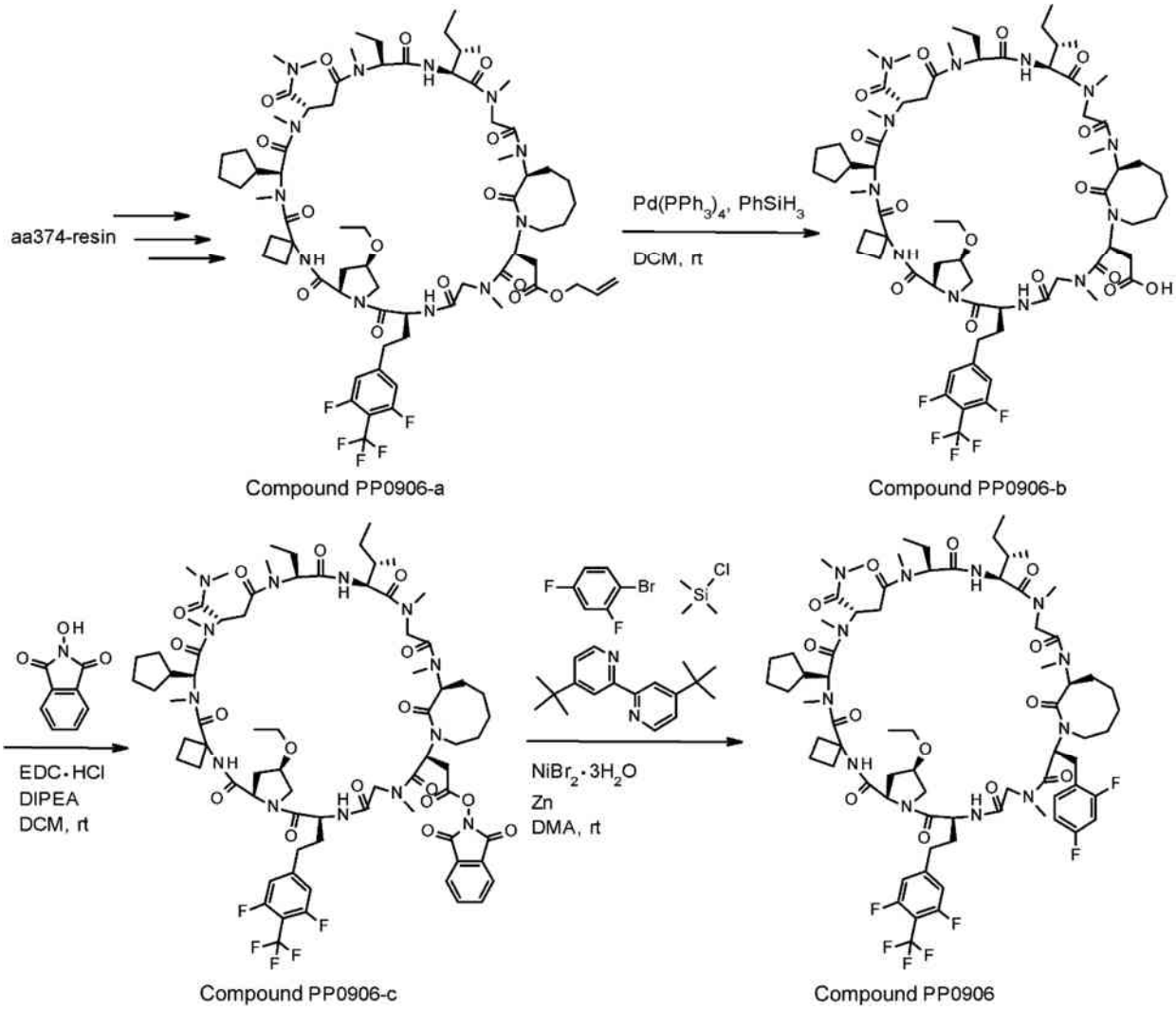
Retention time: 0.88 min (Analytical condition SQDFA40)

[0954]

Using PP0905-c as a starting material, PP0905 (1.57 mg, 1.037 μmol) was obtained in the same manner as synthesis of Compound PP0904. LC/MS data is provided in Table 36.

[0955]

Synthesis of Compound PP0906



[0956]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0906-a. Using this as a starting material, PP0906-b (138.0 mg, 18%) was obtained in the same manner as synthesis of Compound PP0904-b.

LCMS (ESI) m/z = 1408 (M+H)+

Retention time: 0.62 min (Analytical condition SQDAA50)

[0957]

Using PP0906-b as a starting material, PP0906-c (130.3 mg, 100%) was obtained in the same manner as synthesis of Compound PP0904-c.

LCMS (ESI) m/z = 1553 (M+H)+

Retention time: 0.76 min (Analytical condition SQDAA50)

[0958]

Using PP0906-c as a starting material, PP0906 (0.66 mg, 0.447 μmol) was obtained in the same manner as synthesis of Compound PP0904 using 1-bromo-2,4-difluorobenzene in place of 4-bromofluorobenzene. LC/MS data is provided in Table 36.

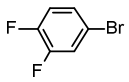
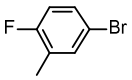
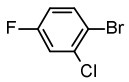
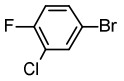
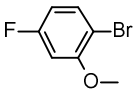
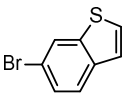
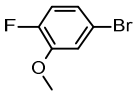
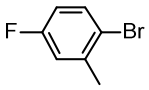
[0959]

Synthesis of Compounds PP0907 to PP0915

Using Compound PP0906-c (10 mg, 6.38 μmol) as a raw material, PP0907 to PP0915 were obtained in the same manner as synthesis of Compound PP0906 using the bromides (10 eq) shown in Table 20. LC/MS data is provided in Table 36.

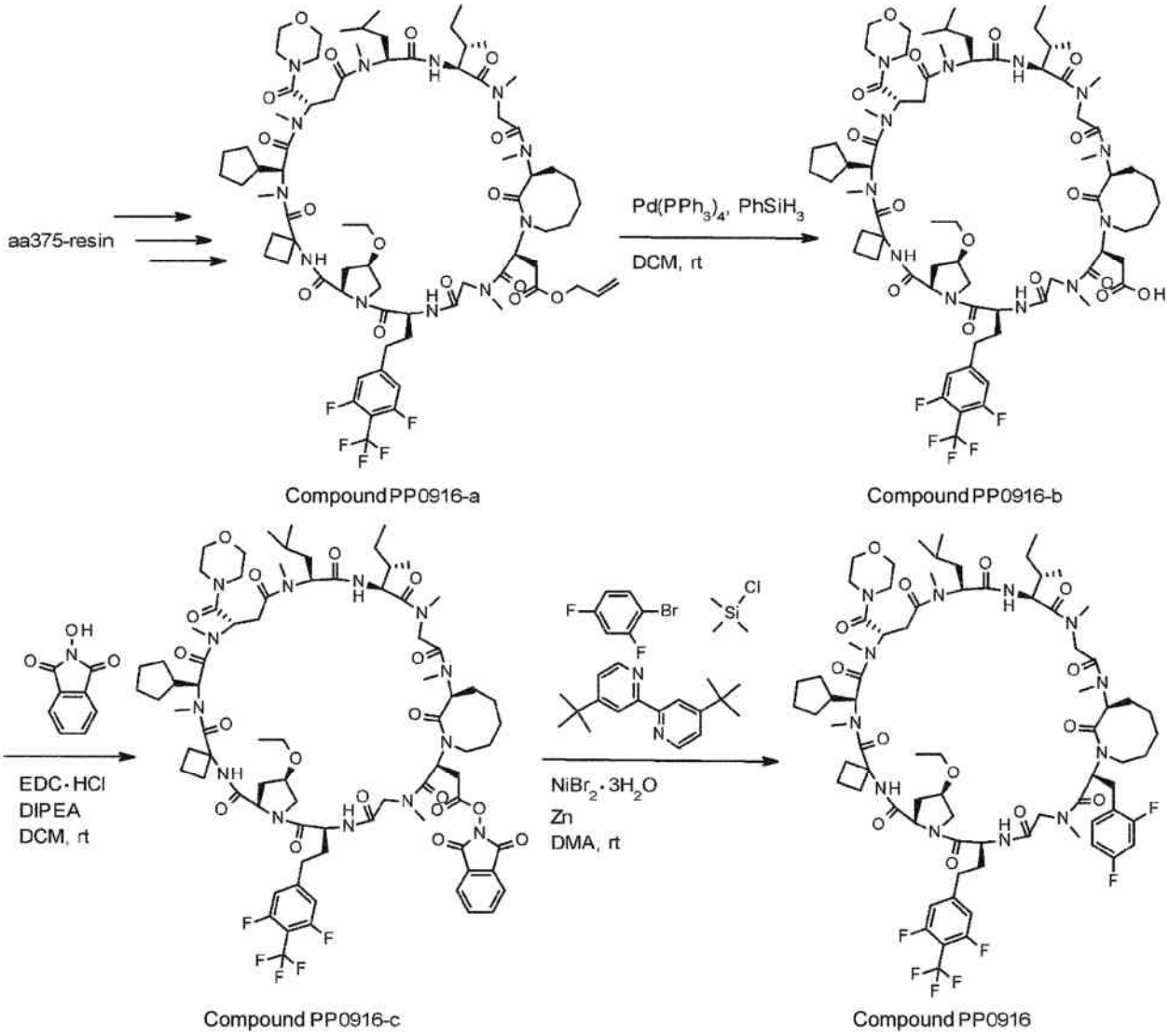
[0960]

[Table 20]

Intended product	Bromide	Yield (mg)	Yield (%)	Intended product	Bromide	Yield (mg)	Yield (%)
PP0907		0.7	7	PP0912		2.03	22
PP0908		0.61	6	PP0913		0.78	9
PP0909		1.23	13	PP0914		1.82	19
PP0910		1.72	18	PP0915		1.72	18
PP0911		0.72	8				

[0961]

<u>Synthesis of Compound PP0916</u>



[0962]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0916-a. Using this as a starting material, PP0916-b (109.0 mg, 14%) was obtained in the same manner as synthesis of Compound PP0904-b.

LCMS (ESI) m/z = 1478 (M+H)+

Retention time: 0.60 min (Analytical condition SQDAA50)

[0963]

Using PP0916-b as a starting material, PP0916-c (95.3 mg, 92%) was obtained in the same manner as synthesis of Compound PP0904-c.

LCMS (ESI) m/z = 1623 (M+H)+

Retention time: 0.78 min (Analytical condition SQDAA50)

[0964]

Using PP0916-c as a starting material, PP0916 (0.77 mg, 0.498 μmol) was obtained in the same manner as synthesis of Compound PP0904 using 1-bromo-2,4-difluorobenzene in place of 4-bromofluorobenzene. LC/MS data is provided in Table 36.

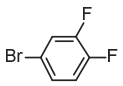
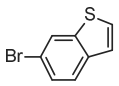
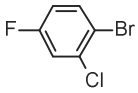
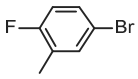
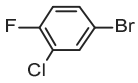
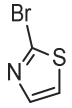
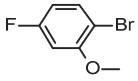
[0965]

Synthesis of Compounds PP0917 to PP0924

Using Compound PP0916-c (10 mg, 6.17 μmol) as a raw material, PP0917 to PP0924 were obtained in the same manner as synthesis of Compound PP0916 using the bromides (10 eq) shown in Table 21. LC/MS data is provided in Table 36.

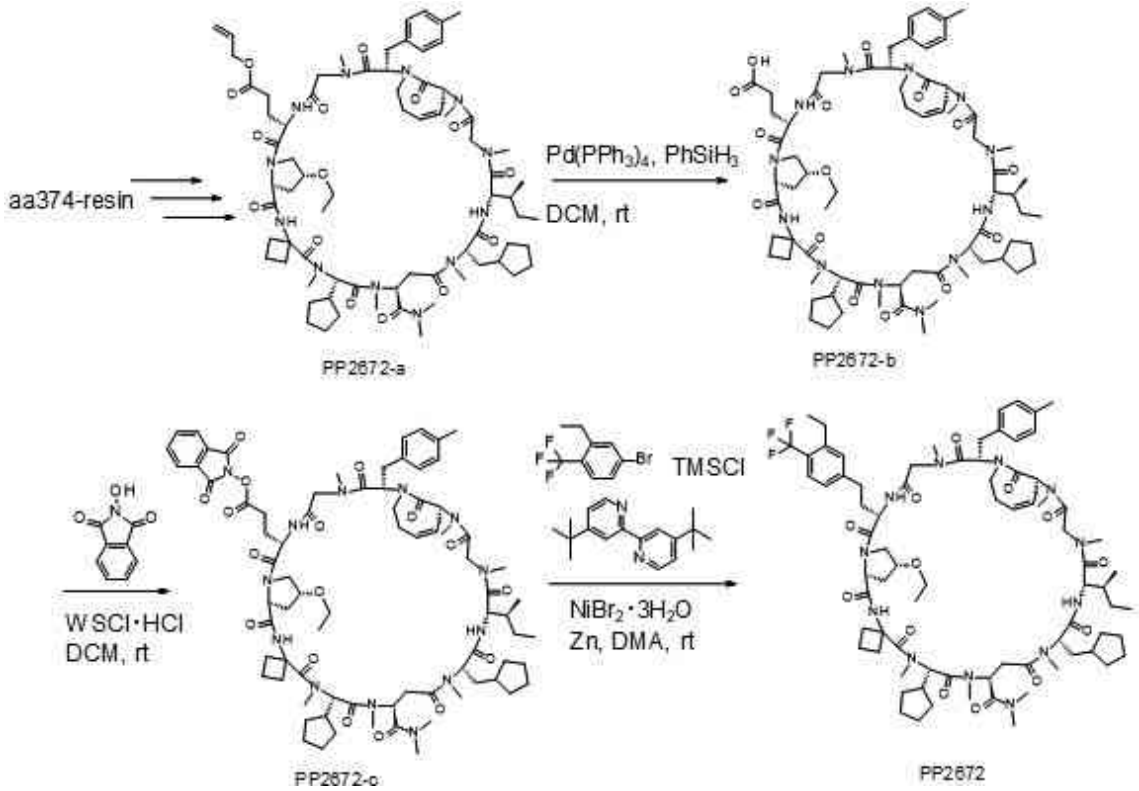
[0966]

[Table 21]

Intended product	Bromide	Yield (mg)	Yield (%)	Intended product	Bromide	Yield (mg)	Yield (%)
PP0917		0.38	4	PP0921		0.81	8
PP0918		0.29	3	PP0922		1.02	10
PP0919		1.02	10	PP0923		0.49	5
PP0920		1.23	12	PP0924		0.98	10

[0967]

Synthesis of Compound PP2672



[0968]

Using Compound aa374-resin as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give Compound PP2672-a. Using this as a starting material, PP2672-b (289 mg, 16%) was obtained in the same manner as the synthesis of Compound PP0904-b.

LCMS (ESI) m/z = 1370 (M+H)+

Retention time: 0.79 min (Analytical condition SQDFA05)

[0969]

Using PP2672-b as a starting material, PP2672-c (329 mg, quant.) was obtained in the same manner as the synthesis of Compound PP0904-c.

LCMS (ESI) m/z = 1515 (M+H)+

Retention time: 0.92 min (Analytical condition SQDFA05)

[0970]

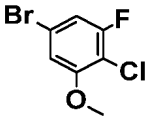
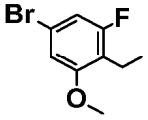
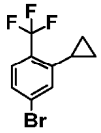
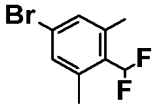
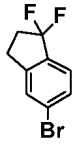
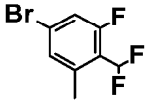
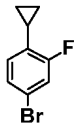
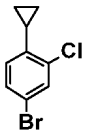
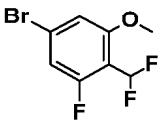
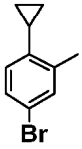
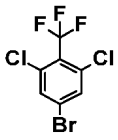
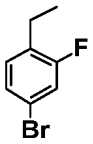
Using PP2672-c as a starting material, PP2672 (6.2 mg, 41%) was obtained in the same manner as the synthesis of Compound PP0904 except that 4-bromo-2-ethyl-1-(trifluoromethyl)benzene was used in place of 4-bromofluorobenzene. LC/MS data are provided in Table 36.

[0971]

Synthesis of Compounds PP2673 to PP2686

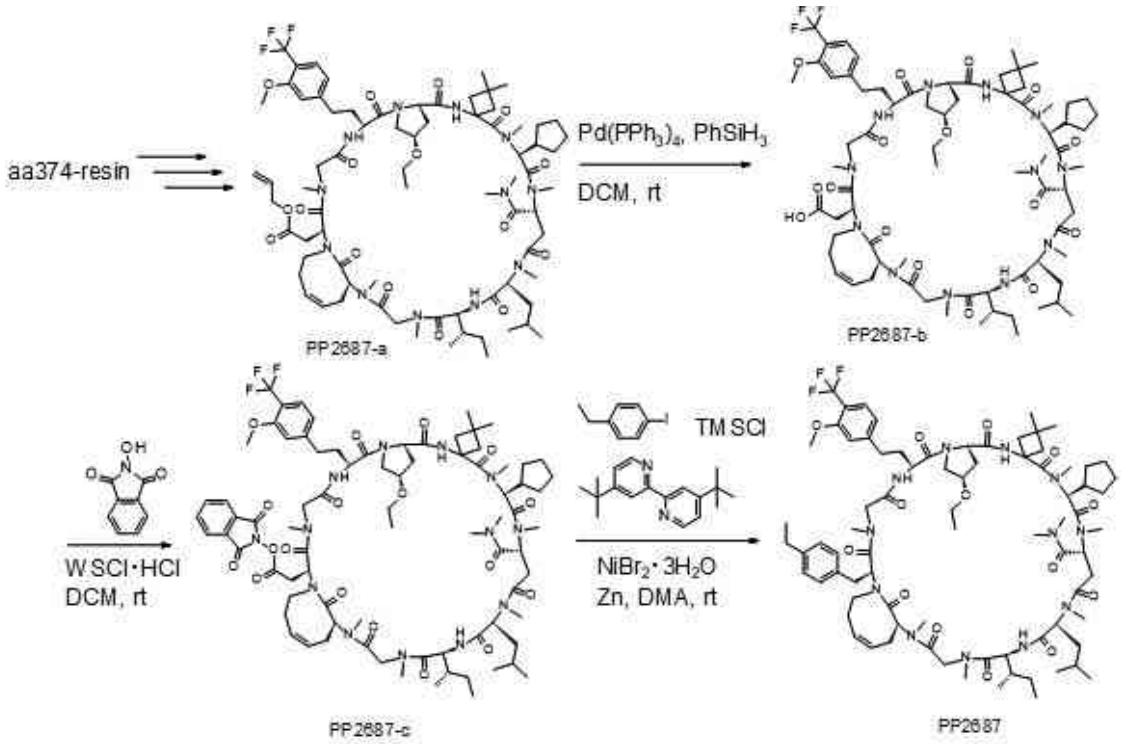
Using Compound PP2672-c as a raw material, PP2673 to PP2686 were obtained in the same manner as the synthesis of Compound PP2672 using the bromides (10 eq) shown in Table 21-1. LC/MS data are provided in Table 36.

[Table 21-1]

Intended product	Bromide	Yield (mg)	Yield (%)	Intended product	Bromide	Yield (mg)	Yield (%)
PP2673		3.3	19	PP2680		1.1	9.2
PP2674		5.4	31	PP2681		2.5	31
PP2675		6.4	36	PP2682		1.3	17
PP2676		7.6	43	PP2683		2.4	21
PP2677		7.2	40	PP2684		2.3	20
PP2678		7.3	41	PP2685		1.2	11
PP2679		2.8	28	PP2686		1.2	10

[0972]

Synthesis of Compound PP2687



[0973]

Using Compound aa374-resin as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give Compound PP2687-a. Using this as a starting material, PP2687-b (97 mg, 16%) was obtained in the same manner as the synthesis of Compound PP0904-b.

LCMS (ESI) m/z = 1456 (M+H)+

Retention time: 0.91 min (Analytical condition SQDFA05)

[0974]

Using PP2687-b as a starting material, PP2687-c (99 mg, 76%) was obtained in the same manner as the synthesis of Compound PP0904-c.

LCMS (ESI) m/z = 1601 (M+H)+

Retention time: 1.00 min (Analytical condition SQDFA05)

[0975]

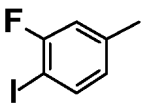
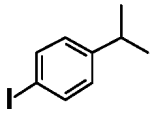
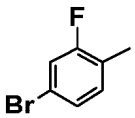
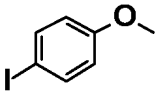
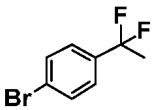
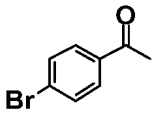
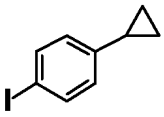
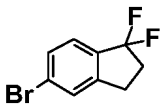
Using PP2687-c as a starting material, PP2687 (2.3 mg, 3.3%) was obtained in the same manner as the synthesis of Compound PP0904 except that 1-ethyl-4-iodobenzene was used in place of 4-bromofluorobenzene. LC/MS data are provided in Table 36.

[0976]

Synthesis of Compounds PP2688 to PP2695

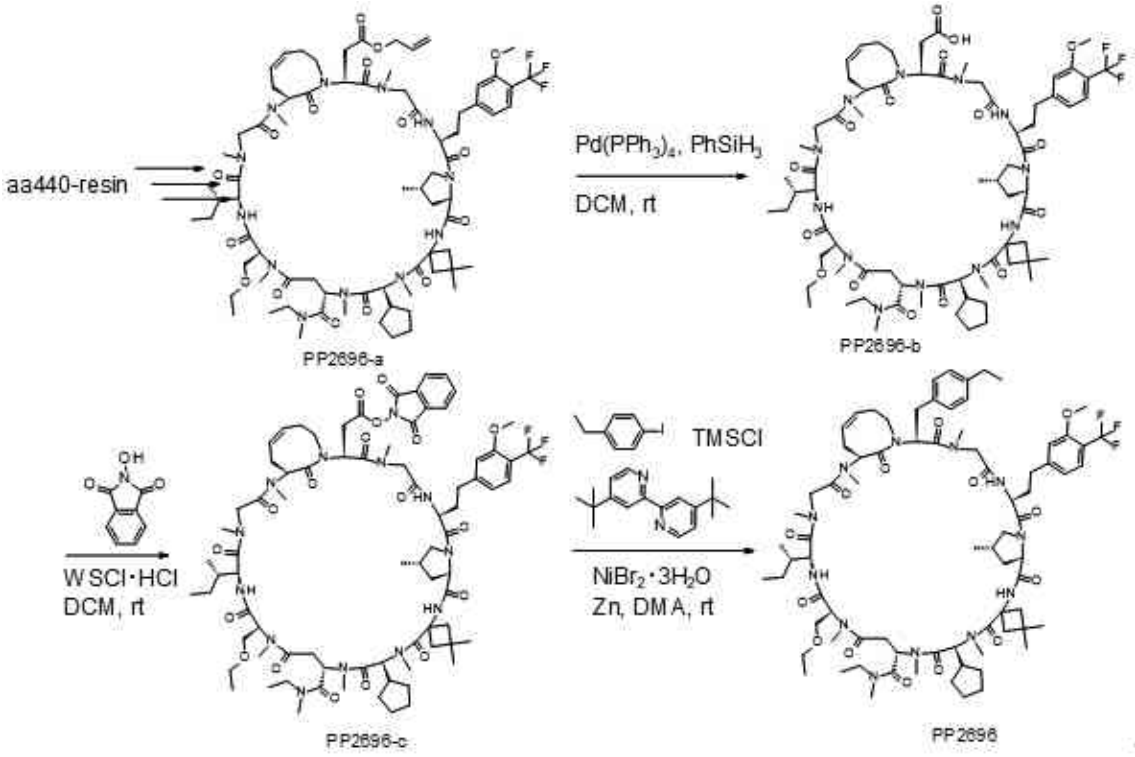
Using Compound PP2687-c as a raw material, PP2688 to PP2695 were obtained in the same manner as the synthesis of Compound PP2687 using the halides (10 eq) shown in Table 21-2. LC/MS data are provided in Table 36.

[Table 21-2]

Intended product	Bromide	Yield (mg)	Yield (%)	Intended product	Bromide	Yield (mg)	Yield (%)
PP2688		2.7	3.8	PP2692		2.2	3.1
PP2689		2.7	3.8	PP2693		2.4	3.4
PP2690		2.8	3.9	PP2694		2.4	3.4
PP2691		2.6	3.7	PP2695		0.2	0.3

[0977]

Synthesis of Compound PP2696



[0978]

Using Compound aa440-resin as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give Compound PP2696-a. Using this as a starting material, PP2696-b (117 mg, 27%) was obtained in the same manner as the synthesis of Compound PP0904-b.

LCMS (ESI) m/z = 1442 (M+H)+

Retention time: 0.92 min (Analytical condition SQDFA05)

[0979]

Using PP2696-b as a starting material, PP2696-c (115 mg, 89%) was obtained in the same manner as the synthesis of Compound PP0904-c.

LCMS (ESI) m/z = 1586 (M-H)-

Retention time: 1.02 min (Analytical condition SQDFA05)

[0980]

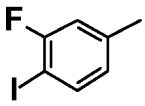
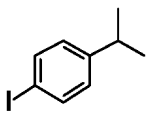
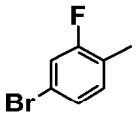
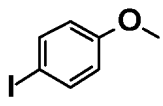
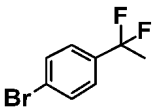
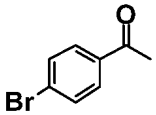
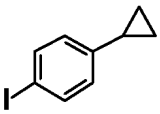
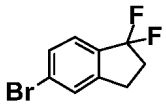
Using PP2696-c as a starting material, PP2696 (3.7 mg, 7.4%) was obtained in the same manner as the synthesis of Compound PP0904 except that 1-ethyl-4-iodobenzene was used in place of 4-bromofluorobenzene. LC/MS data are provided in Table 36.

[0981]

Synthesis of Compounds PP2697 to PP2704

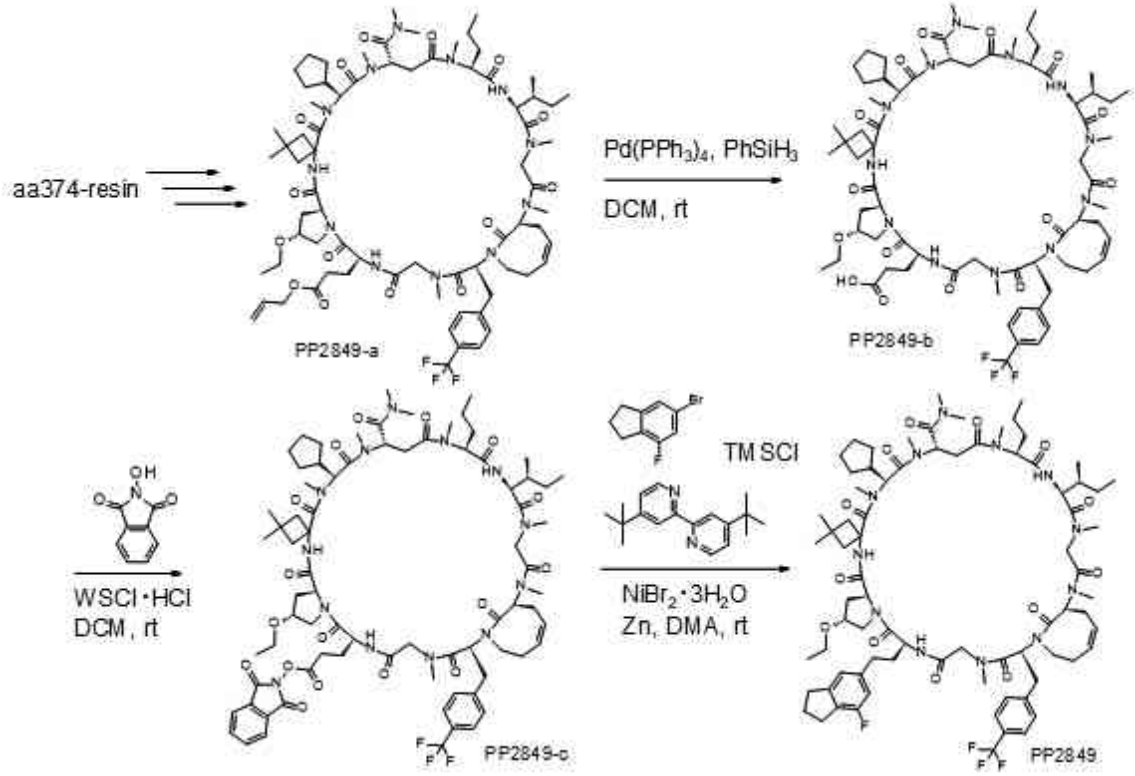
Using Compound PP2696-c as a raw material, PP2697 to PP2704 were obtained in the same manner as the synthesis of Compound PP2696 using the halides (10 eq) shown in Table 21-3. LC/MS data are provided in Table 36.

[Table 21-3]

Intended product	Bromide	Yield (mg)	Yield (%)	Intended product	Bromide	Yield (mg)	Yield (%)
PP2697		3.8	7.6	PP2701		3.5	7.0
PP2698		4.1	8.2	PP2702		3.9	7.8
PP2699		4.1	8.0	PP2703		3.7	7.3
PP2700		3.8	7.5	PP2704		0.2	0.4

[0982]

Synthesis of Compound PP2849



[0983]

Using Compound aa374-resin as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give Compound PP2849-a. Using this as a starting material, PP2849-b (345 mg, 22%) was obtained in the same manner as the synthesis of Compound PP0904-b.

LCMS (ESI) m/z = 1412 (M+H)+

Retention time: 0.80 min (Analytical condition SQDFA05)

[0984]

Using PP2849-b as a starting material, PP2849-c (395 mg, quant.%) was obtained in the same manner as the synthesis of Compound PP0904-c.

LCMS (ESI) m/z = 1557 (M+H)+

Retention time: 0.52 min (Analytical condition SQDFA50)

[0985]

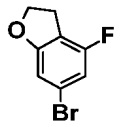
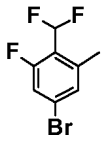
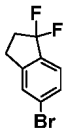
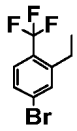
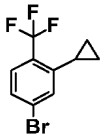
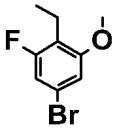
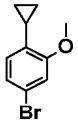
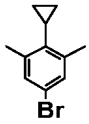
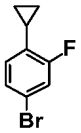
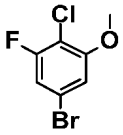
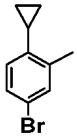
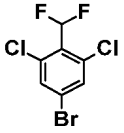
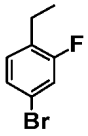
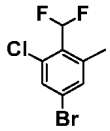
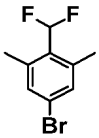
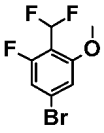
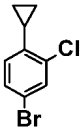
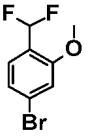
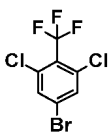
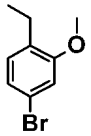
Using PP2849-c as a starting material, PP2849 (4.5 mg, 39%) was obtained in the same manner as the synthesis of Compound PP0904 except that 6-bromo-4-fluoro-2,3-dihydro-1H-indene was used in place of 4-bromofluorobenzene. LC/MS data are provided in Table 36.

[0986]

Synthesis of Compounds PP2850 to PP2869

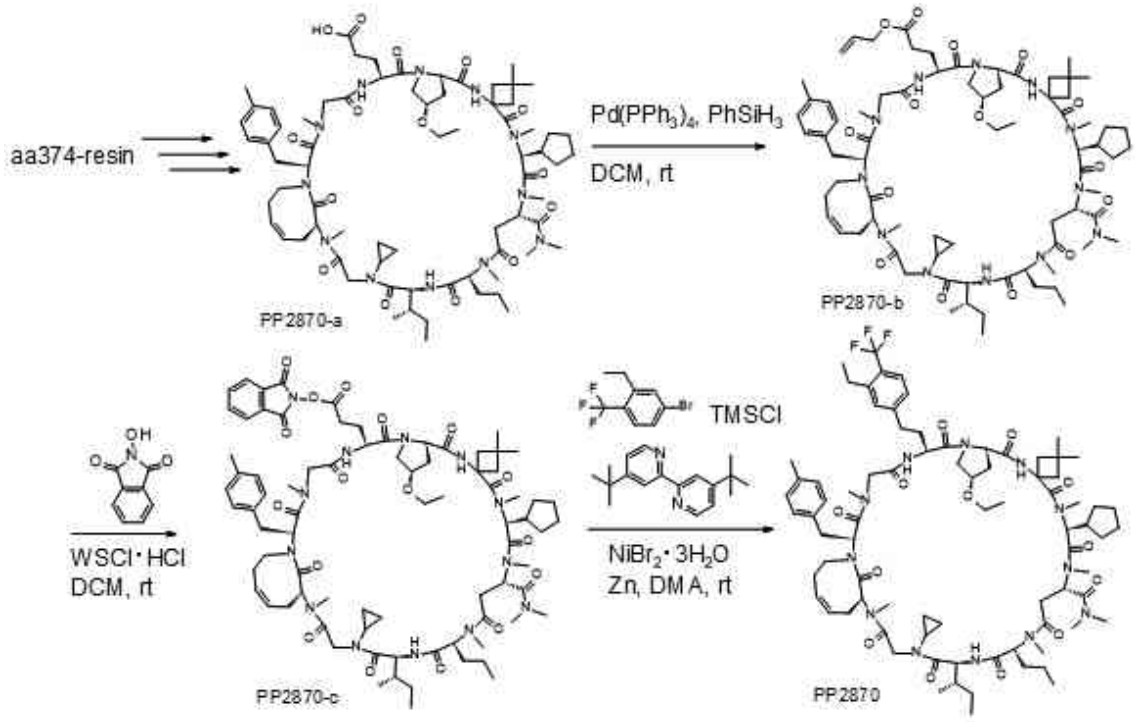
Using Compound PP2849-c as a raw material, PP2850 to PP2869 were obtained in the same manner as the synthesis of Compound PP2849 using the bromides (10 eq) shown in Table 21-4. LC/MS data are provided in Table 36.

[Table 21-4]

Intended product	Bromide	Yield (mg)	Yield (%)	Intended product	Bromide	Yield (mg)	Yield (%)
PP2850		3.5	30	PP2860		7.5	64
PP2851		5.1	44	PP2861		6.9	58
PP2852		5.1	43	PP2862		5.8	50
PP2853		5.6	48	PP2863		3.4	29
PP2854		7.0	61	PP2864		1.3	11
PP2855		3.4	29	PP2865		7.8	65
PP2856		5.0	44	PP2866		7.6	64
PP2857		5.1	44	PP2867		7.2	60
PP2858		4.6	40	PP2868		0.4	3.2
PP2859		4.3	35	PP2869		4.1	35

[0987]

Synthesis of Compound PP2870



[0988]

Using Compound aa374-resin as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give Compound PP2870-a. Using this as a starting material, PP2870-b (289 mg, 16%) was obtained in the same manner as the synthesis of Compound PP0904-b.

LCMS (ESI) m/z = 1370 (M+H)+

Retention time: 0.79 min (Analytical condition SQDFA05)

[0989]

Using PP2870-b as a starting material, PP2870-c (329 mg, quant.%) was obtained in the same manner as the synthesis of Compound PP0904-c.

LCMS (ESI) m/z = 1515 (M+H)+

Retention time: 0.92 min (Analytical condition SQDFA05)

[0990]

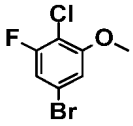
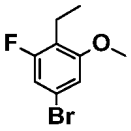
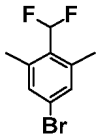
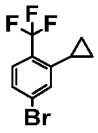
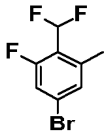
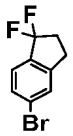
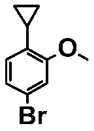
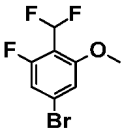
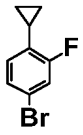
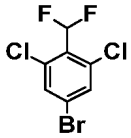
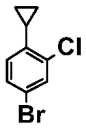
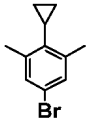
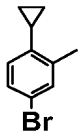
Using PP2870-c as a starting material, PP2870 (6.2 mg, 41%) was obtained in the same manner as the synthesis of Compound PP0904 except that 4-bromo-2-ethyl-1-(trifluoromethyl)benzene was used in place of 4-bromofluorobenzene. LC/MS data are provided in Table 36.

[0991]

Synthesis of Compounds PP2871 to PP2886

Using Compound PP2870-c as a raw material, PP2871 to PP2886 were obtained in the same manner as the synthesis of Compound PP2870 using the bromides (10 eq) shown in Table 21-5. LC/MS data are provided in Table 36.

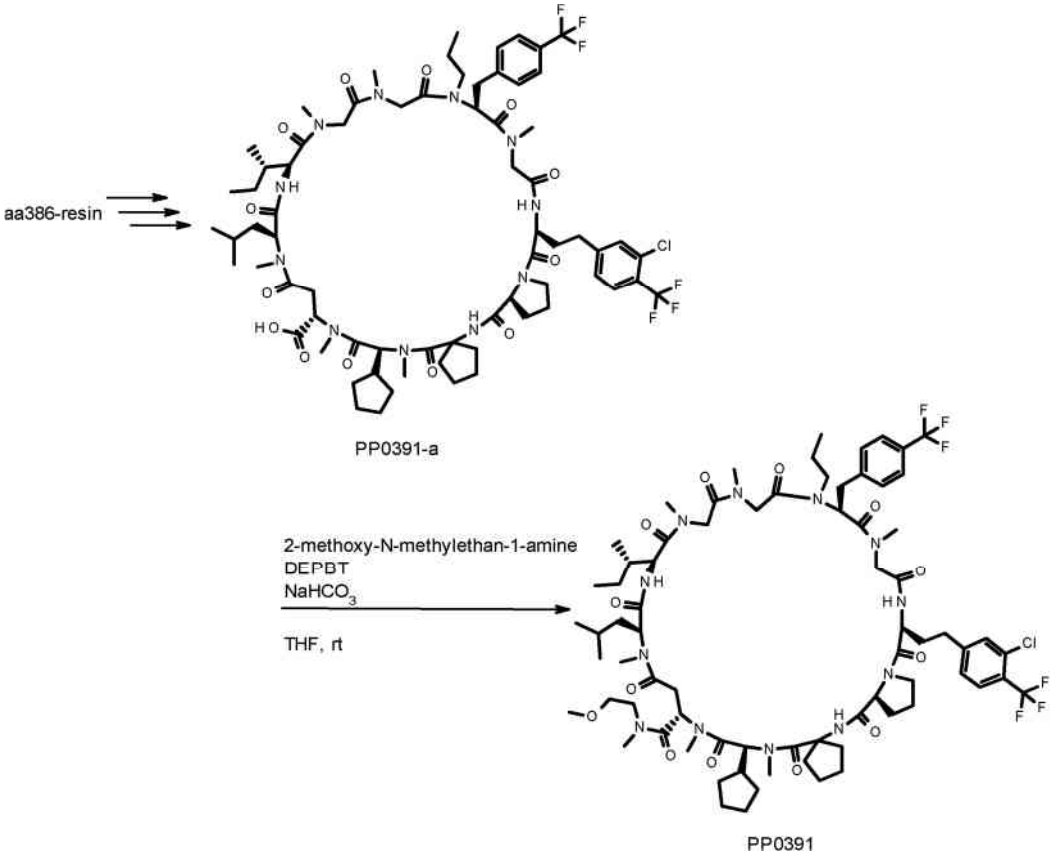
[Table 21-5]

Intended product	Bromide	Yield (mg)	Yield (%)	Intended product	Bromide	Yield (mg)	Yield (%)
PP2871		7.5	51	PP2879		6.7	46
PP2872		6.8	47	PP2880		6.3	44
PP2873		7.4	51	PP2881		6.9	46
PP2874		7.4	50	PP2882		7.8	53
PP2875		8.6	58	PP2883		8.5	59
PP2876		7.7	52	PP2884		9.3	64
PP2877		6.3	42	PP2885		8.5	58
PP2878		6.4	44	PP2886		7.6	52

[0992]

1-6-3. Peptide modification by amidation of carboxylic acid

Synthesis of Compound PP0391



[0993]

Using Compound aa386-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0391-a (5.6 mg, 0.00386 mmol).

LCMS (ESI) m/z = 1451 (M+H)+

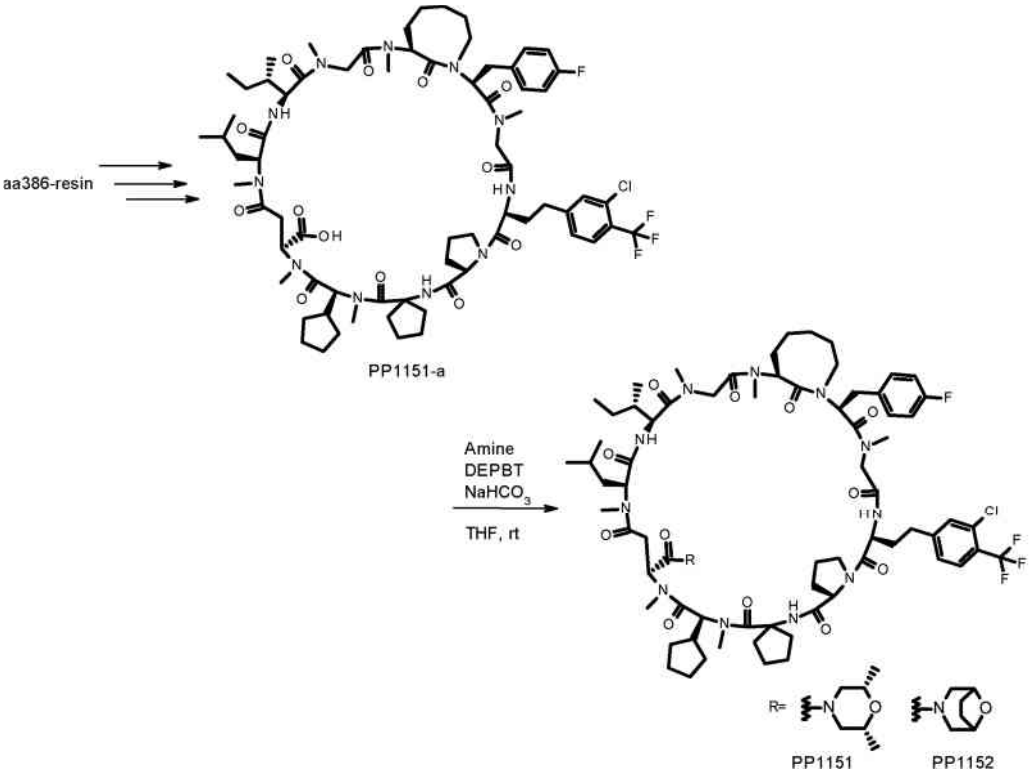
Retention time: 0.66 min (Analytical condition SQDFA50)

[0994]

2-Methoxy-N-methylethan-1-amine (0.002 mL, 0.019 mmol) was added to a THF (0.039 mL) solution of Compound PP0391-a (5.6 mg, 0.00386 mmol), sodium bicarbonate (1.62 mg, 0.019 mmol), and DEPBT (5.77 mg, 0.019 mmol), the mixture was stirred at room temperature for 1 hour, and then the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give PP0391 (5.08 mg, 86%). LC/MS data is provided in Table 36.

[0995]

Synthesis of Compounds PP1151 and PP1152

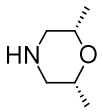
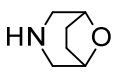


[0996]

Using Compound aa386-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP1151-a. Using the resulting Compound PP1151-a (5.0 mg), the intended compounds were obtained in the same manner as synthesis of Compound PP0391 using the amines shown in Table 22 in place of 2-methoxy-N-methylethan-1-amine. LC/MS data is provided in Table 36.

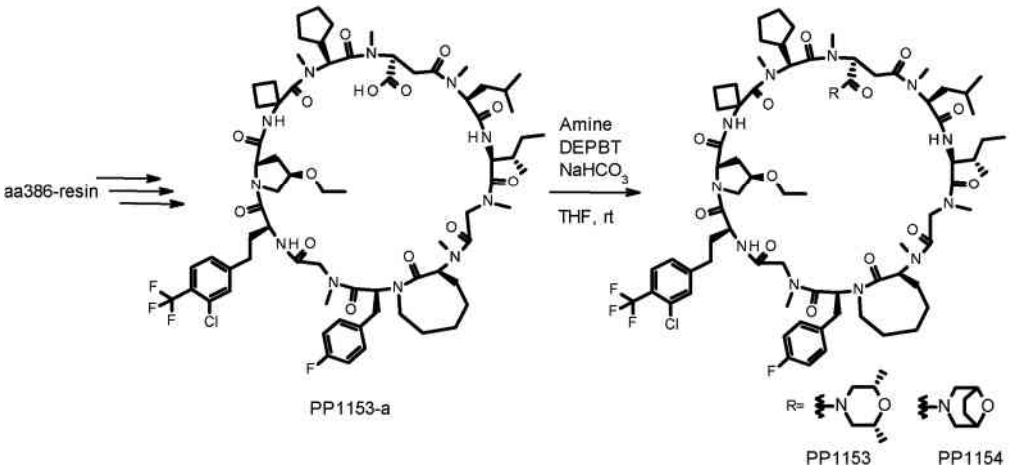
[0997]

[Table 22]

Intended product	Amine	Yield	Yield
PP1151		3.2mg	60%
PP1152		2.8mg	53%

[0998]

Synthesis of Compounds PP1153 and PP1154

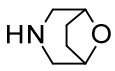


[0999]

Using Compound aa386-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP1153-a. Using the resulting Compound PP1153-a (5.1 mg), the intended compounds were obtained in the same manner as synthesis of Compound PP0391 using the amines shown in Table 23 in place of 2-methoxy-N-methylethan-1-amine. LC/MS data is provided in Table 36.

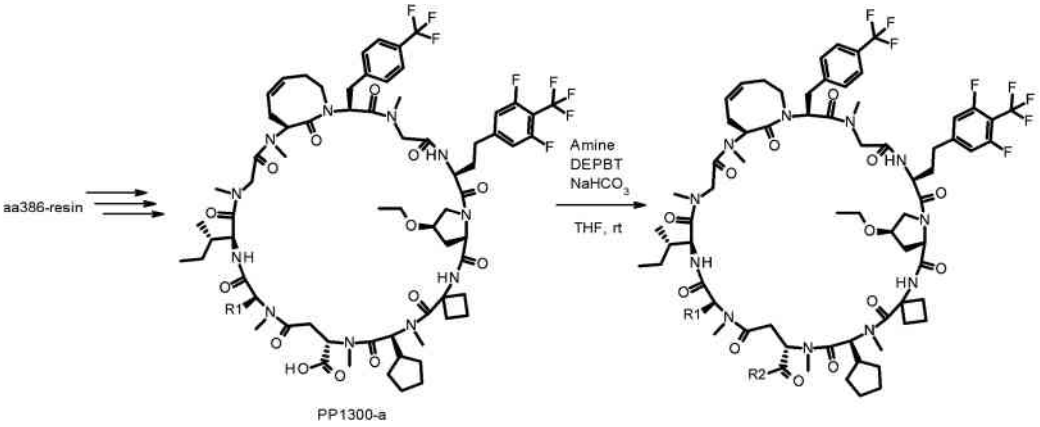
[1000]

[Table 23]

Intended product	Amine	Yield	Yield
PP1153		2.4mg	44%
PP1154		2.5mg	46%

[1001]

Synthesis of Compounds PP1300, PP1301, PP1302, PP1303, PP1304, PP1305, PP1306, PP1307, PP1308, PP1309, PP1310, PP1311, PP1312, PP1313, PP1314, PP1315, PP1316, PP1317, PP1318, PP1319, PP1320, PP1331, PP1387, PP1388, and PP1389

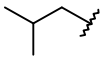
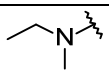
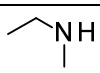
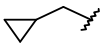
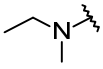
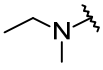
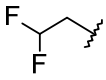
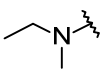
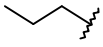
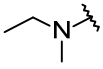
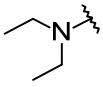
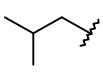
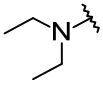
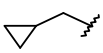
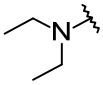
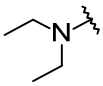


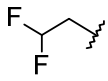
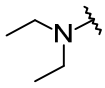
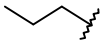
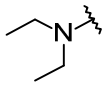
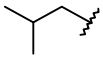
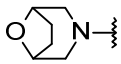
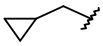
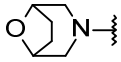
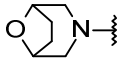
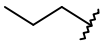
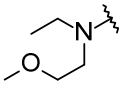
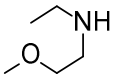
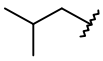
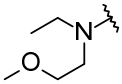
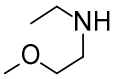
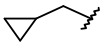
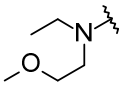
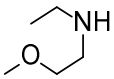
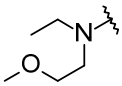
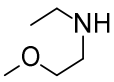
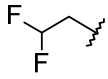
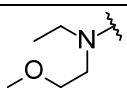
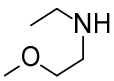
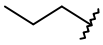
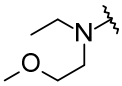
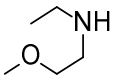
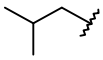
[1002]

Using Compound aa386-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP1300-a. Using the resulting Compound PP1300-a (0.00574 mmol each), the intended compounds were obtained in the same manner as synthesis of Compound PP0391 using the amines shown in Table 24 in place of 2-methoxy-N-methylethan-1-amine. LC/MS data is provided in Table 36.

[1003]

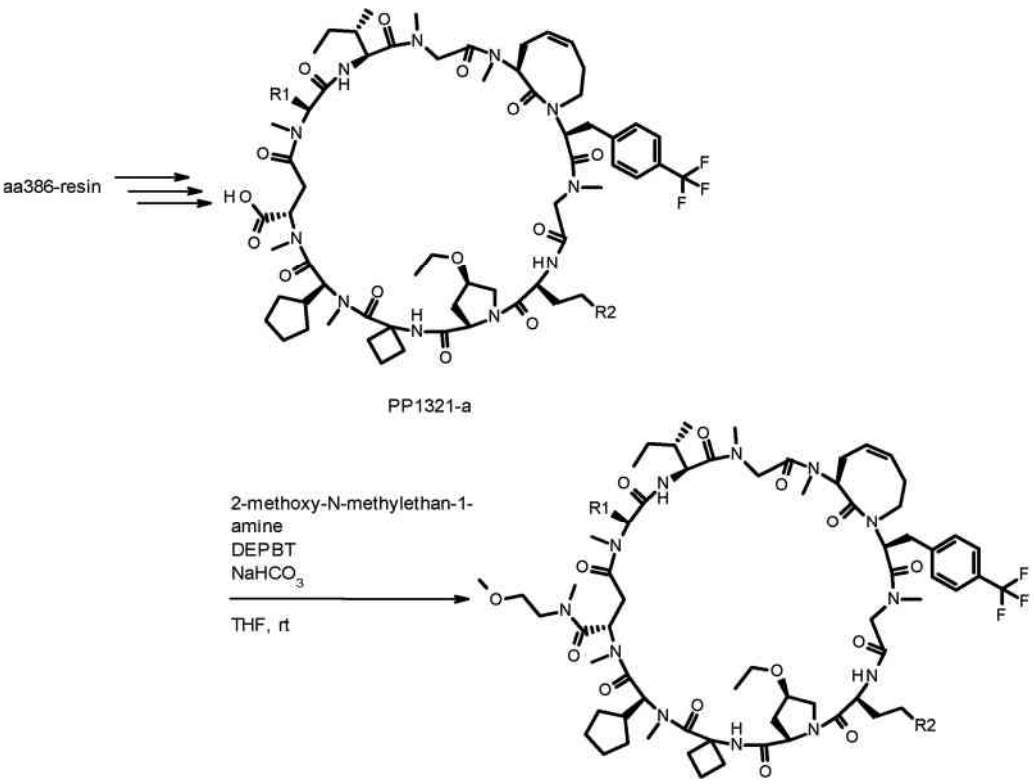
[Table 24]

Intended product	R1	R2	Amine	Yield	Yield
PP1300				3.3mg	37%
PP1301				3.1mg	35%
PP1302				3.5mg	41%
PP1303				2.0mg	23%
PP1304				3.1mg	35%
PP1305				2.8mg	31%
PP1306				2.8mg	32%
PP1307				2.0mg	22%
PP1308				3.4mg	39%

PP1309				2.4mg	27%
PP1310				2.8mg	32%
PP1311				2.6mg	28%
PP1312				2.9mg	32%
PP1313				4.3mg	48%
PP1314				4.3mg	48%
PP1315				3.3mg	36%
PP1316				3.5mg	39%
PP1317				3.0mg	33%
PP1318				3.1mg	34%
PP1319				3.8mg	43%
PP1320				2.0mg	22%
PP1331				3.4mg	38%
PP1387				2.8mg	31%
PP1388				2.0mg	22%
PP1389				2.7mg	30%

[1004]

Synthesis of Compounds PP1321, PP1322, PP1323, PP1324, PP1325, PP1326, PP1327, PP1328, and PP1329

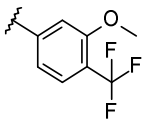
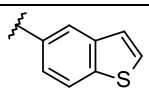
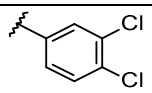
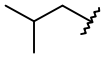
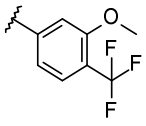


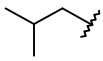
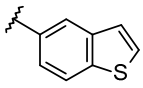
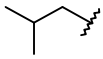
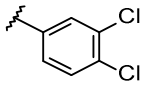
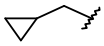
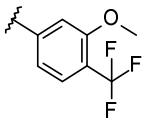
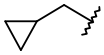
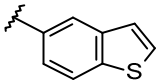
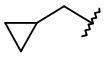
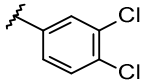
[1005]

Using Compound aa386-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP1321-a. Using the resulting Compound PP1321-a (0.00574 mmol each), the intended compounds were obtained in the same manner as synthesis of Compound PP0391. The intended products and yields are provided in Table 25. LC/MS data is provided in Table 36.

[1006]

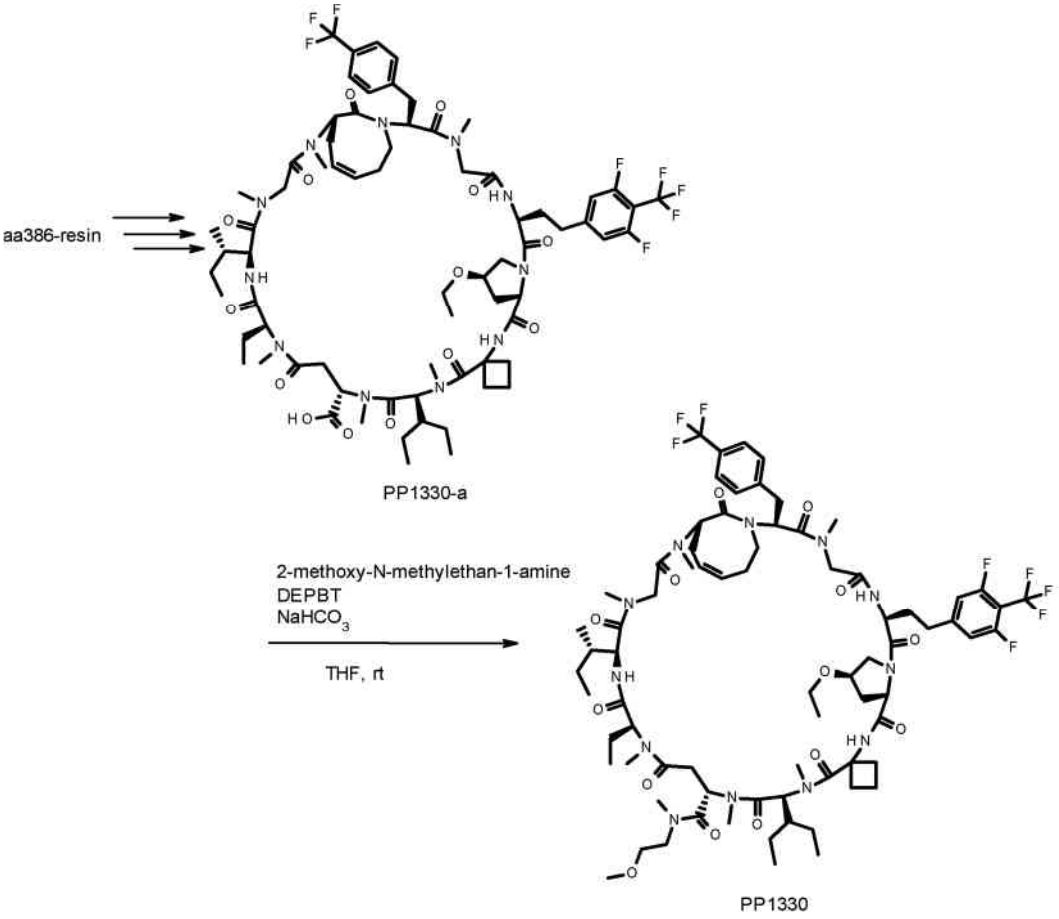
[Table 25]

Intended product	R1	R2	Yield	Yield
PP1321			4.2mg	47%
PP1322			3.6mg	42%
PP1323			3.2mg	37%
PP1324			3.0mg	33%

PP1325			2.6mg	29%
PP1326			3.8mg	43%
PP1327			3.3mg	37%
PP1328			2.8mg	32%
PP1329			2.4mg	27%

[1007]

Synthesis of Compound PP1330



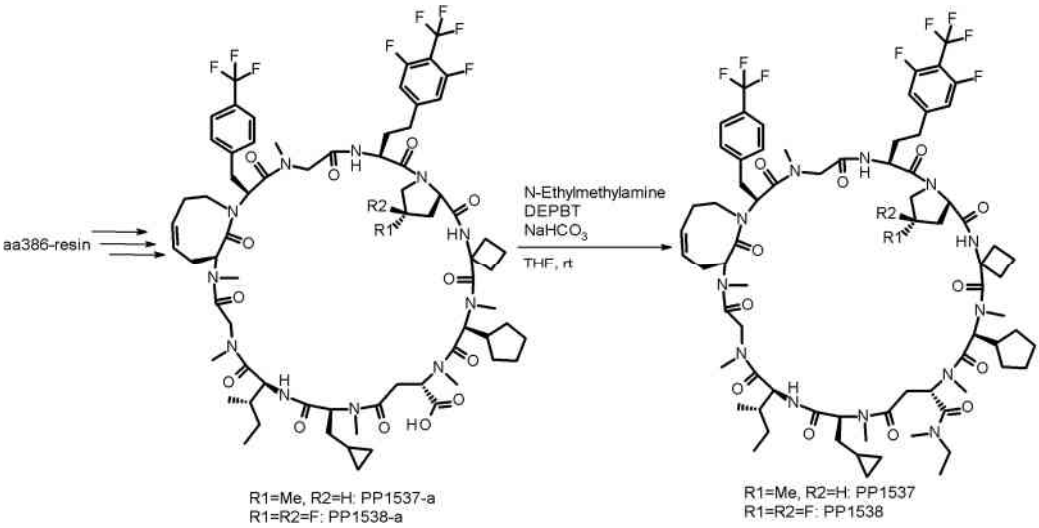
[1008]

Using Compound aa386-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP1330-

a. Using the resulting Compound PP1330-a (0.00574 mmol), the intended compound (1.3 mg, 14%) was obtained in the same manner as synthesis of Compound PP0391. LC/MS data is provided in Table 36.

[1009]

Synthesis of Compounds PP1537 and PP1538

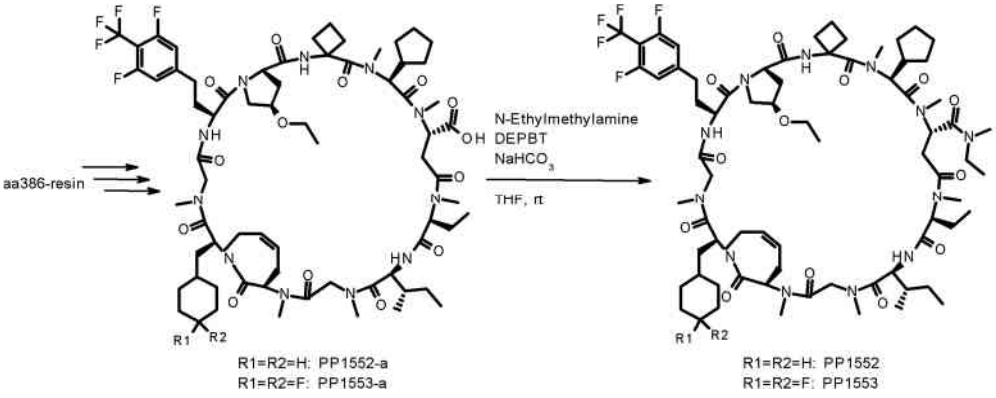


[1010]

Using Compound aa386-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compounds PP1537-a and PP1538-a. Using the resulting Compounds PP1537-a and PP1538-a (8.8 mg each), Compounds PP1537 (3.2 mg, 35%) and PP1538 (3.9 mg, 42%) were obtained in the same manner as synthesis of Compound PP0391 using N-ethylmethylamine in place of 2-methoxy-N-methylethan-1-amine. LC/MS data is provided in Table 36.

[1011]

Synthesis of Compounds PP1552 and PP1553



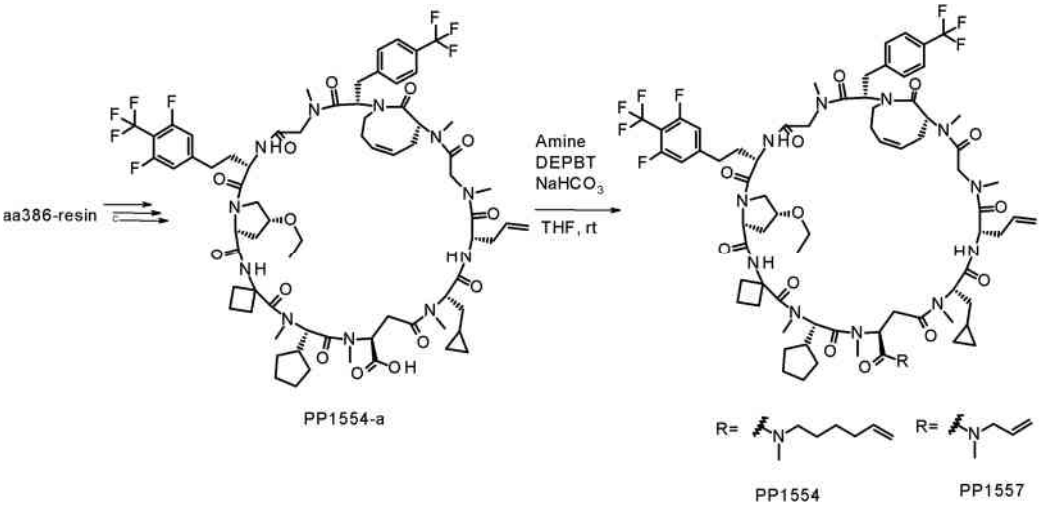
[1012]

Using Compound aa386-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compounds PP1552-

a and PP1553-a. Using the resulting Compounds PP1552-a (3.8 mg) and PP1553-a (4.5 mg), Compounds PP1552 (1.7 mg, 44%) and PP1553 (1.9 mg, 41%) were obtained in the same manner as synthesis of Compound PP0391 using N-ethylmethylamine in place of 2-methoxy-N-methylethan-1-amine. LC/MS data is provided in Table 36.

[1013]

Synthesis of Compounds PP1554 and PP1557



[1014]

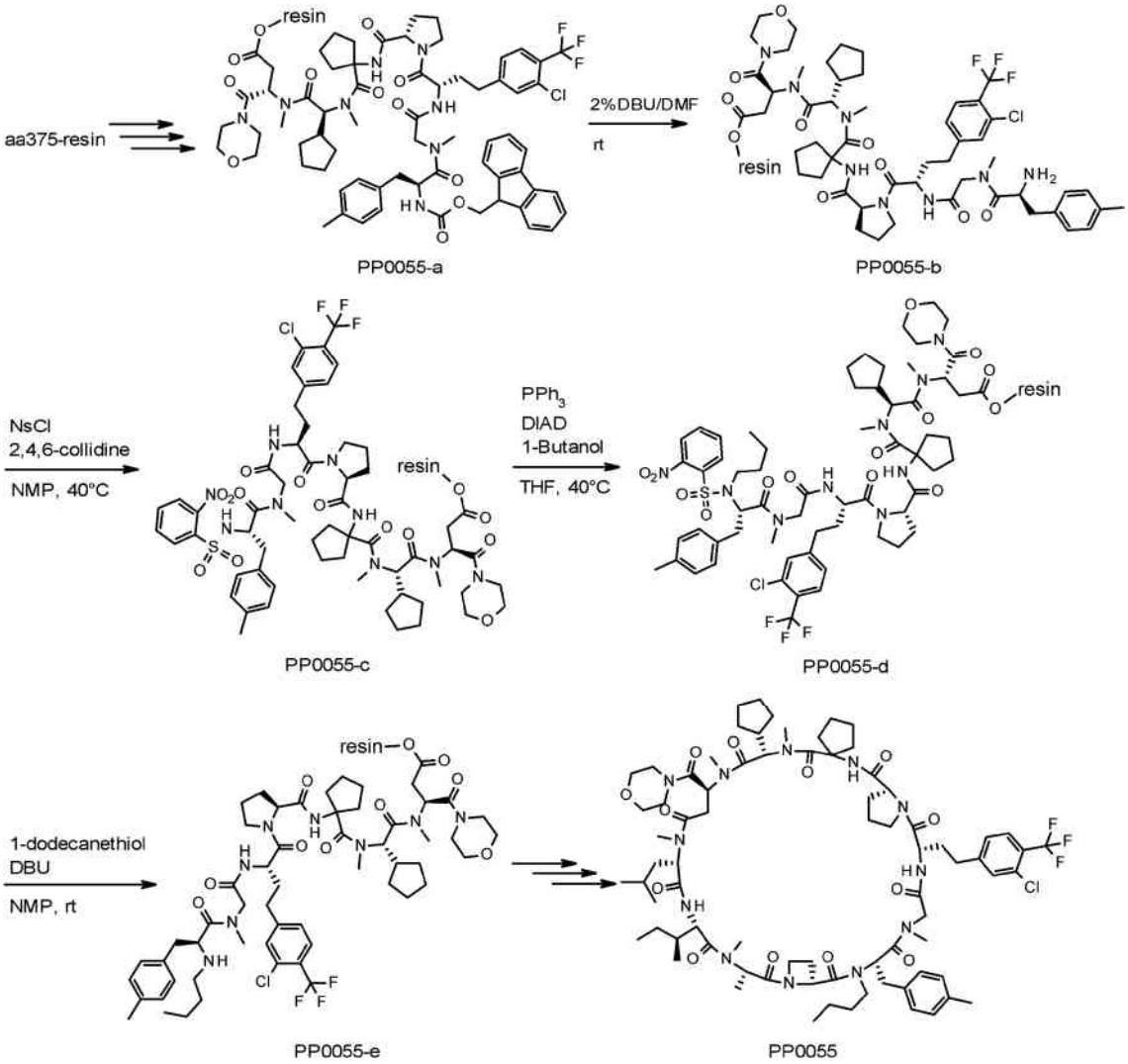
Using Compound aa386-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP1554-a. Using the resulting Compound PP1554-a (12.6 mg each), Compounds PP1554 (5.9 mg, 44%) and PP1557 (6.7 mg, 51%) were obtained in the same manner as synthesis of Compound PP0391 using N-methylhex-5-ene-1-amine or N-methylprop-2-ene-1-amine in place of 2-methoxy-N-methylethan-1-amine. LC/MS data is provided in Table 36.

[1015]

1-6-4. Peptide synthesis via N-alkylation by Mitsunobu reaction on resin

Synthesis of Compound PP0055

PP0055 was synthesized according to the following scheme.



[1016]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported Compound PP0055-a. Cleaving from the resin was performed with TFE/DCM (1/1) using a small amount of resin-supported Compound PP0055-a, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 1282 (M+H)+

Retention time: 1.02 min (Analytical condition SQDFA05)

[1017]

Compound PP0055-a-resin (100 mg, 0.384 mmol/g, 0.0384 mmol) and DCM (1 mL) were added to a filter-equipped reaction vessel to swell the resin. After DCM was removed, the resin was washed 4 times with DMF (1 mL). A DMF solution (2% v/v, 0.600 mL) of DBU was added, the mixture was shaken for 15 minutes at room temperature, and then the reaction solution was removed. The resin was washed 6 times with NMP (1 mL) to give resin-supported

Compound PP0055-b. Cleaving from the resin was performed with TFE/DCM (1/1) using a small amount of resin-supported Compound PP0055-b, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 1060 (M+H)+

Retention time: 0.62 min (Analytical condition SQDFA05)

[1018]

An NMP solution (1 mL) of nosyl chloride (34 mg, 0.154 mmol) and 2,4,6-cholidine (0.051 mL, 0.384 mmol) were added thereto, and the mixture was shaken at 40°C for 1 hour. Then, the reaction solution was removed, and the resin was washed 4 times with NMP (1 mL) and washed 4 times with DCM (1 mL) to give resin-supported Compound PP0055-c. Cleaving from the resin was performed with TFE/DCM (1/1) using a small amount of resin-supported Compound PP0055-c, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 1245 (M+H)+

Retention time: 0.89 min (Analytical condition SQDFA05)

[1019]

DCM (1 mL) was added thereto for swelling. After DCM was removed, the resin was washed twice with DCM (1 mL) and then 4 times with THF (1 mL). A THF solution (1 mL) obtained by dissolving triphenylphosphine (50 mg, 0.192 mmol), DIAD (0.038 mL, 0.192 mmol), and 1-butanol (0.035 mL, 0.384 mmol) was added, the mixture was shaken at 40°C for 30 minutes, and then the reaction solution was removed. The resin was washed 4 times with THF (1 mL) and washed 4 times with DCM (1 mL) to give resin-supported Compound PP0055-d. Cleaving from the resin was performed with TFE/DCM (1/1) using a small amount of resin-supported Compound PP0055-d, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 1301 (M+H)+

Retention time: 1.01 min (Analytical condition SQDFA05)

[1020]

DCM (1 mL) was added thereto for swelling. After DCM was removed, the resin was washed 4 times with NMP (1 mL). An NMP solution (0.200 mL) of DBU (0.020 mL, 0.134 mmol) and an NMP solution (0.250 mL) of 1-dodecanethiol (0.063 mL, 0.262 mmol) were added, and the mixture was shaken at room temperature for 1 hour. Then, the reaction solution was removed, and the resin was washed 4 times with NMP (1 mL). An NMP solution (0.200 mL) of DBU (0.020 mL, 0.134 mmol) and an NMP solution (0.250 mL) of 1-dodecanethiol (0.063 mL, 0.262 mmol) were added, and the mixture was shaken at room temperature for 13 hours. Then, the reaction solution was removed, and the resin was washed 4 times with NMP (1 mL). An NMP solution (0.200 mL) of DBU (0.020 mL, 0.134 mmol) and an NMP solution (0.250 mL) of 1-dodecanethiol (0.063 mL, 0.262 mmol) were added, and the mixture was shaken at room temperature for 1 hour. Then, the reaction solution was removed, and the resin was

washed 4 times with NMP (1 mL) and washed 4 times with DCM (1 mL) to give resin-supported Compound PP0055-e. Cleaving from the resin was performed with TFE/DCM (1/1) using a small amount of resin-supported Compound PP0055-e, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 1116 (M+H)+

Retention time: 0.66 min (Analytical condition SQDFA05)

[1021]

Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give Compound PP0055. LC/MS data is provided in Table 36.

[1022]

Synthesis of Compound PP0052, Compound PP0056, Compound PP0057, Compound PP0059, Compound PP0062, Compound PP0063, Compound PP0064, Compound PP0065, Compound PP0083, Compound PP0084, Compound PP0085, Compound PP0086, Compound PP0087, Compound PP0088, Compound PP0089, Compound PP0090, Compound PP0091, Compound PP0092, Compound PP0093, Compound PP0094, Compound PP0095, Compound PP0096, Compound PP0097, Compound PP0098, Compound PP0099, Compound PP0100, Compound PP0101, Compound PP0102, Compound PP0103, Compound PP0104, Compound PP0105, Compound PP0134, Compound PP0135, Compound PP0139, and Compound PP0140

Using resin-supported Compound PP0055-c, the reaction was carried out in the same manner as synthesis of Compound PP0055-d using the alcohols shown in Table 26 in place of 1-butanol. Moreover, the Ns group was deprotected in the same manner as synthesis of Compound PP0055-e, and subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were carried out according to the basic route to give the intended compounds. LC/MS data is provided in Table 36.

[1023]

[Table 26]

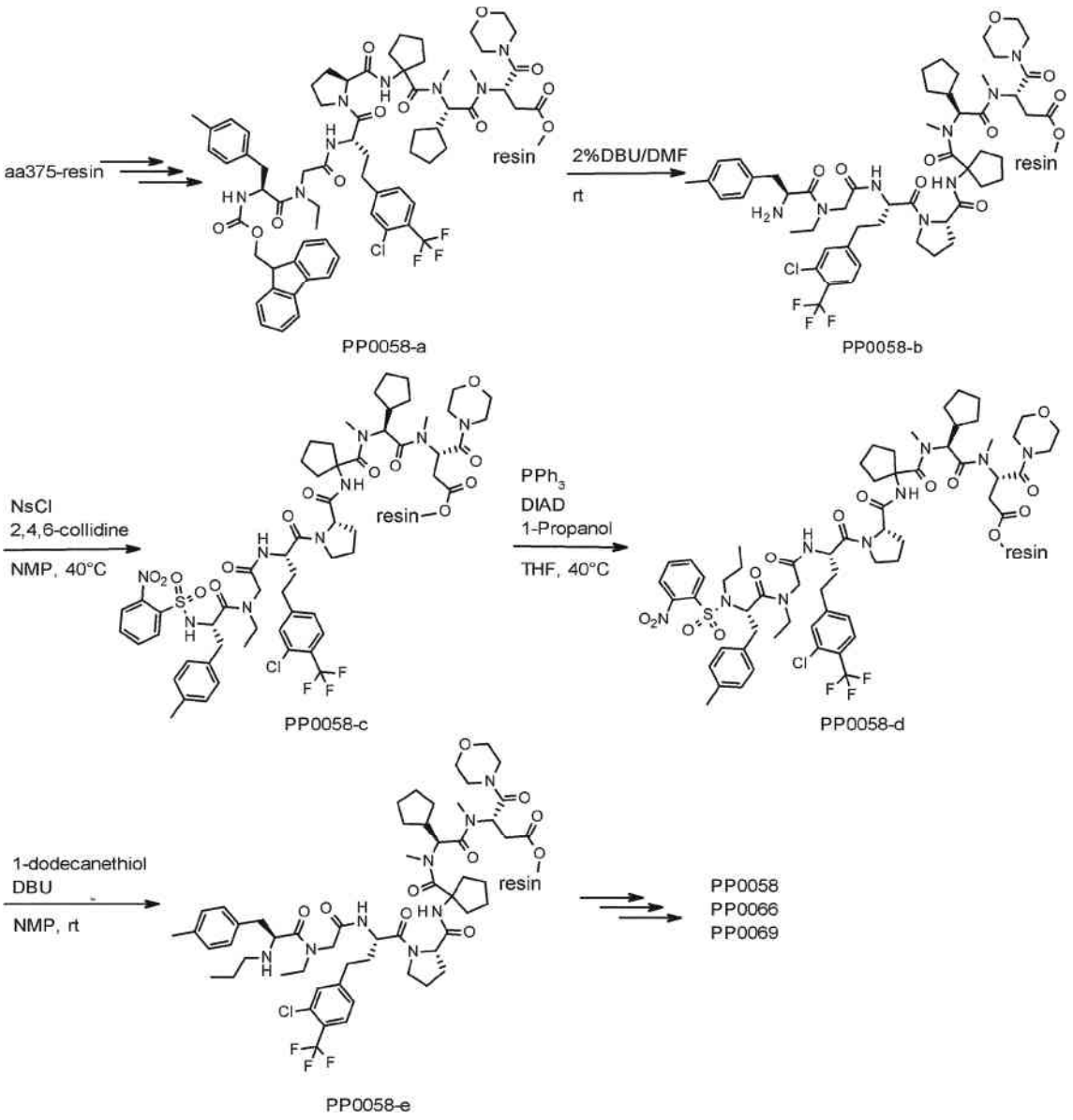
Intended product	Alcohol
Compound PP0052	1-Propanol
Compound PP0056	Isobutanol
Compound PP0057	Cyclopropylmethanol
Compound PP0059	1-Propanol
Compound PP0062	1-Butanol
Compound PP0063	Isobutanol
Compound PP0064	Cyclopropylmethanol
Compound PP0065	1-Propanol
Compound PP0083	Cyclobutylmethanol

Compound PP0084	Cyclopentylmethanol
Compound PP0085	Cyclohexylmethanol
Compound PP0086	3-Methylbutan-1-ol
Compound PP0087	4-Methylpentan-1-ol
Compound PP0088	2-Propen-1-ol
Compound PP0089	3-Buten-1-ol
Compound PP0090	2-Propyn-1-ol
Compound PP0091	3,3,3-Trifluoro-1-propanol
Compound PP0092	2-Methoxyethanol
Compound PP0093	3-Methoxy-1-propanol
Compound PP0094	2-Propanol
Compound PP0095	Cyclobutylmethanol
Compound PP0096	Cyclopentylmethanol
Compound PP0097	Cyclohexylmethanol
Compound PP0098	3-Methylbutan-1-ol
Compound PP0099	4-Methylpentan-1-ol
Compound PP0100	2-Propen-1-ol
Compound PP0101	3-Buten-1-ol
Compound PP0102	2-Propyn-1-ol
Compound PP0103	3,3,3-Trifluoro-1-propanol
Compound PP0104	2-Methoxyethanol
Compound PP0105	3-Methoxy-1-propanol
Compound PP0134	1-Propanol
Compound PP0135	1-Propanol
Compound PP0139	2-Propen-1-ol
Compound PP0140	3-Buten-1-ol

[1024]

Synthesis of Compound PP0058, Compound PP0066, and Compound PP0069

Compound PP0058, Compound PP0066, and Compound PP0069 were synthesized according to the following scheme.



[1025]

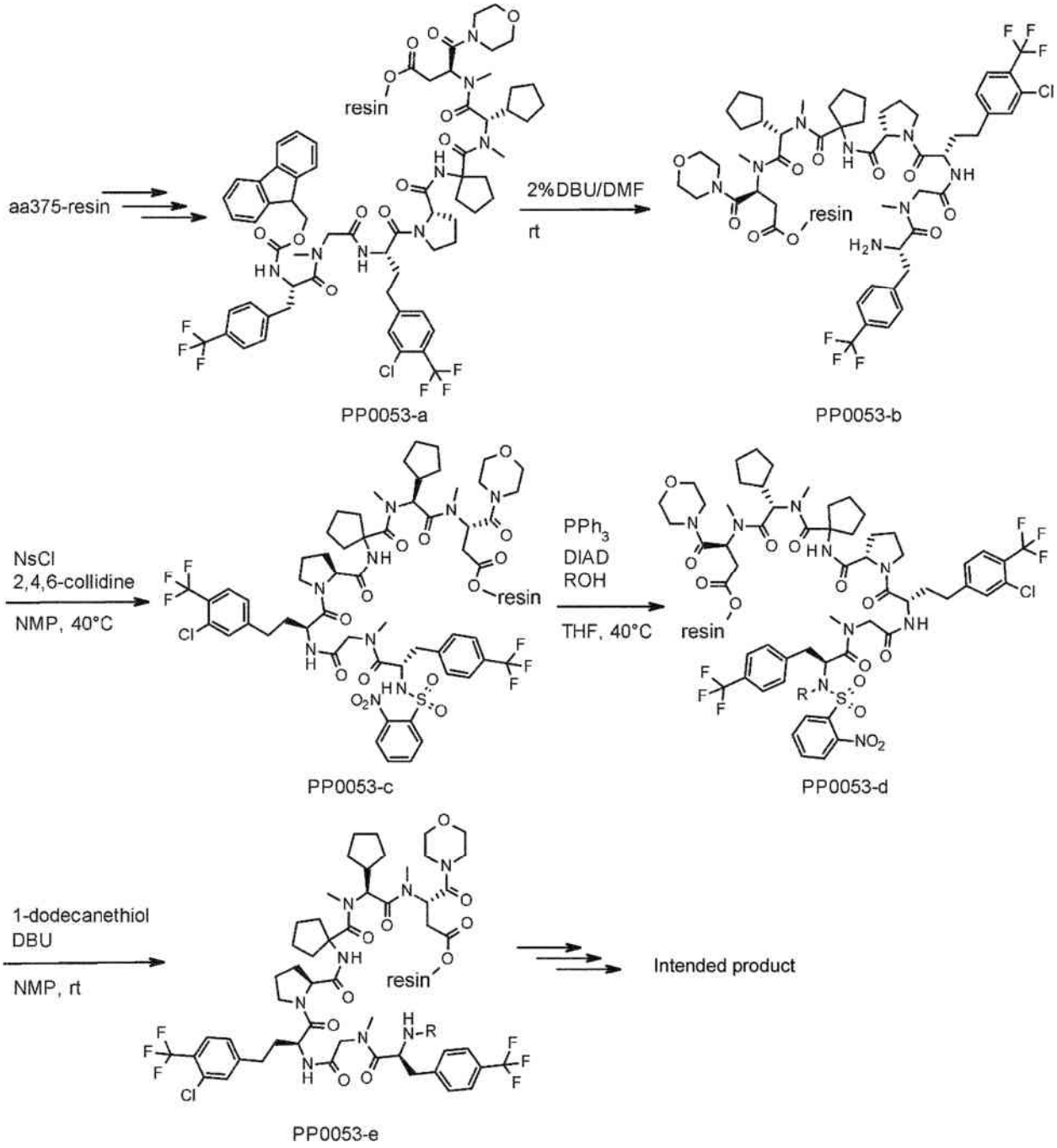
Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported Compound PP0058-a. After resin-supported Compound PP0058-b was obtained in the same manner as synthesis of Compound PP0055-b, resin-supported Compound PP0058-c was obtained in the same manner as synthesis of Compound PP0055-c. After resin-supported Compound PP0058-d was obtained in the same manner as synthesis of Compound PP0055-d using 1-propanol in place of 1-butanol, resin-supported Compound PP0058-e was obtained in the same manner as synthesis of Compound PP0055-e. Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give the intended compounds. LC/MS data is provided in Table 36.

[1026]

Synthesis of Compound PP0053, Compound PP0060, Compound PP0106, Compound PP0107, Compound PP0108, Compound PP0109, Compound PP0110, Compound PP0112, Compound PP0113, Compound PP0114, Compound PP0115, Compound PP0116, Compound PP0117, Compound PP0118, Compound PP0119, Compound PP0120, Compound PP0121, Compound PP0122, Compound PP0123, Compound PP0124, Compound PP0126, Compound PP0127, Compound PP0128, Compound PP0129, Compound PP0130, Compound PP0131, Compound PP0132, and Compound PP0133

Compound PP0053, Compound PP0060, Compound PP0106, Compound PP0107, Compound PP0108, Compound PP0109, Compound PP0110, Compound PP0112, Compound PP0113, Compound PP0114, Compound PP0115, Compound PP0116, Compound PP0117, Compound PP0118, Compound PP0119, Compound PP0120, Compound PP0121, Compound PP0122, Compound PP0123, Compound PP0124, Compound PP0126, Compound PP0127, Compound PP0128, Compound PP0129, Compound PP0130, Compound PP0131, Compound PP0132, and Compound PP0133 were synthesized according to the following scheme.

[1027]



[1028]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported Compound PP0053-a. After resin-supported Compound PP0053-b was obtained in the same manner as synthesis of Compound PP0055-b, resin-supported Compound PP0053-c was obtained in the same manner as synthesis of Compound PP0055-c. After resin-supported Compound PP0053-d was obtained in the same manner as synthesis of Compound PP0055-d using the alcohols shown in Table 27 in place of 1-butanol, resin-supported Compound PP0053-

e was obtained in the same manner as synthesis of Compound PP0055-e. Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give the intended compounds. LC/MS data is provided in Table 36.

[1029]

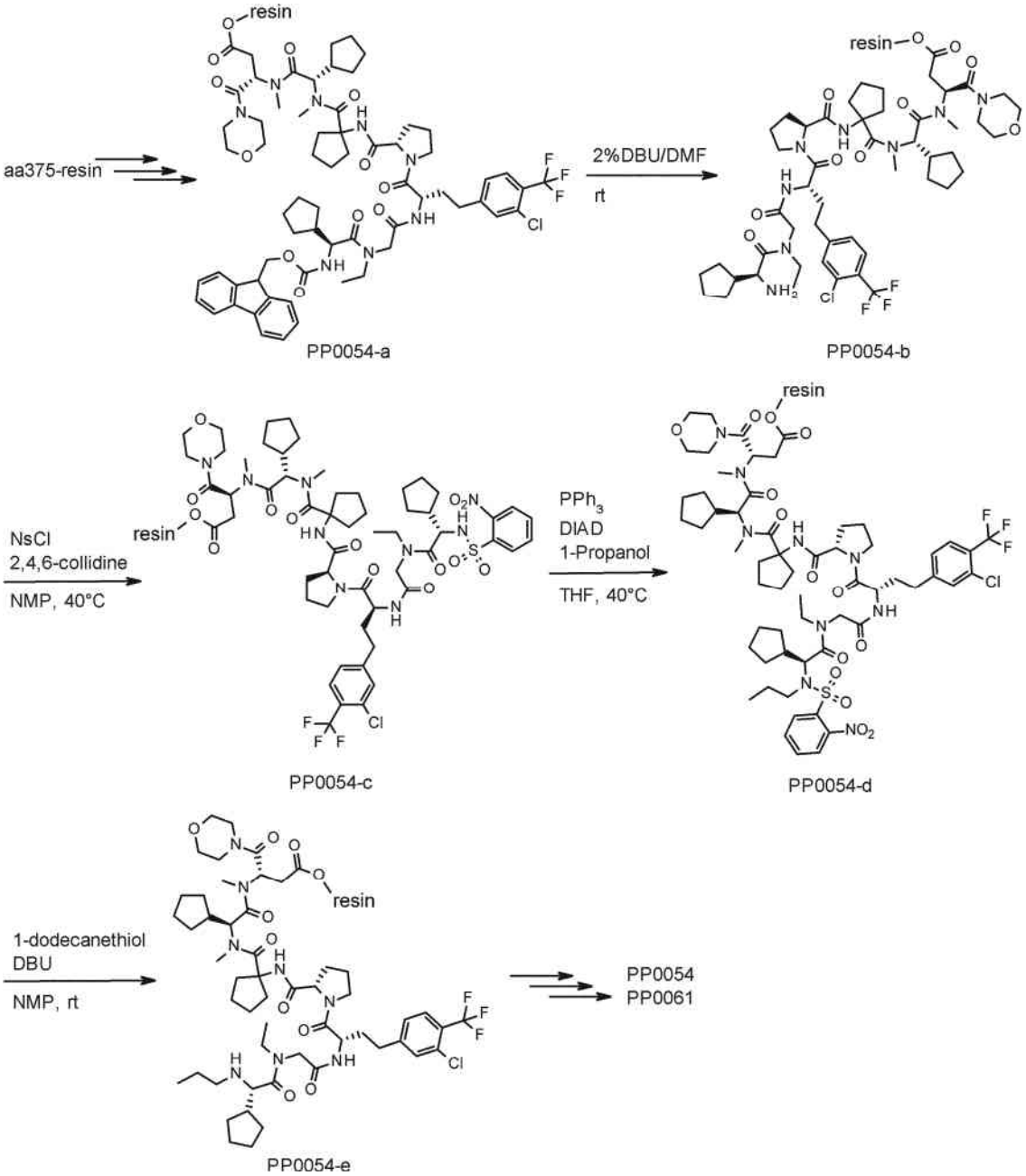
[Table 27]

Intended product	Alcohol
Compound PP0053	1-Propanol
Compound PP0060	1-Propanol
Compound PP0106	1-Butanol
Compound PP0107	Isobutanol
Compound PP0108	Cyclopropylmethanol
Compound PP0109	Cyclobutylmethanol
Compound PP0110	Cyclopentylmethanol
Compound PP0112	3-Methylbutan-1-ol
Compound PP0113	4-Methylpentan-1-ol
Compound PP0114	2-Propen-1-ol
Compound PP0115	3-Buten-1-ol
Compound PP0116	2-Propyn-1-ol
Compound PP0117	3,3,3-Trifluoro-1-propanol
Compound PP0118	2-Methoxyethanol
Compound PP0119	3-Methoxy-1-propanol
Compound PP0120	1-Butanol
Compound PP0121	Isobutanol
Compound PP0122	Cyclopropylmethanol
Compound PP0123	Cyclobutylmethanol
Compound PP0124	Cyclopentylmethanol
Compound PP0126	3-Methylbutan-1-ol
Compound PP0127	4-Methylpentan-1-ol
Compound PP0128	2-Propen-1-ol
Compound PP0129	3-Buten-1-ol
Compound PP0130	2-Propyn-1-ol
Compound PP0131	3,3,3-Trifluoro-1-propanol
Compound PP0132	2-Methoxyethanol
Compound PP0133	3-Methoxy-1-propanol

[1030]

Synthesis of Compound PP0054 and Compound PP0061

Compound PP0054 and Compound PP0061 were synthesized according to the following scheme.



[1031]

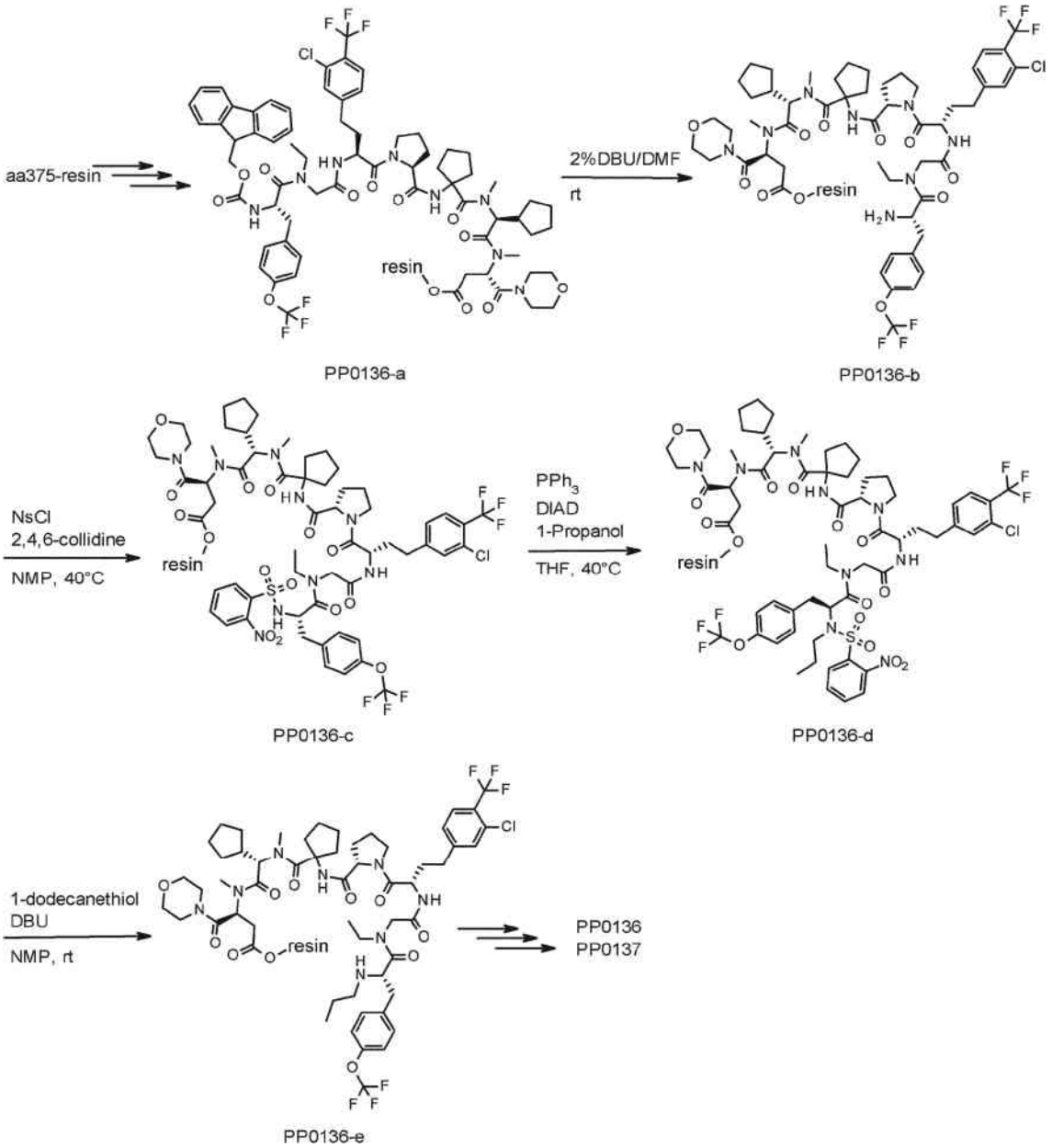
Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported Compound PP0054-a. After resin-supported Compound PP0054-b was obtained in the same manner as synthesis of Compound PP0055-b, resin-supported Compound PP0054-c was obtained in the same manner as synthesis of Compound PP0055-c. After resin-supported Compound PP0054-d was obtained in the same manner as synthesis of Compound PP0055-d

using 1-propanol in place of 1-butanol, resin-supported Compound PP0054-e was obtained in the same manner as synthesis of Compound PP0055-e. Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give the intended compounds. LC/MS data is provided in Table 36.

[1032]

Synthesis of Compound PP0136 and Compound PP0137

Compound PP0136 and Compound PP0137 were synthesized according to the following scheme.



[1033]

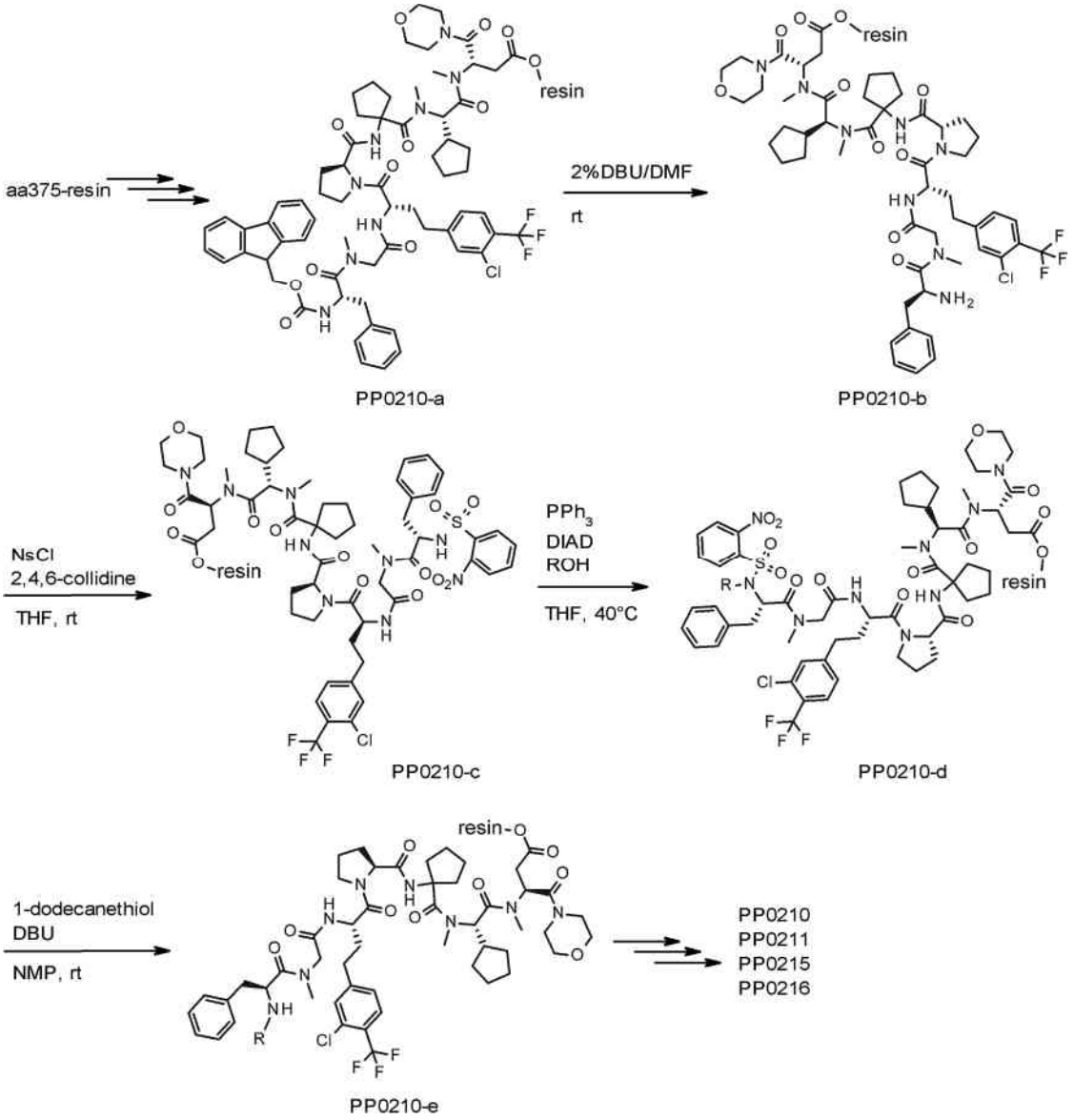
Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported

Compound PP0136-a. After resin-supported Compound PP0136-b was obtained in the same manner as synthesis of Compound PP0055-b, resin-supported Compound PP0136-c was obtained in the same manner as synthesis of Compound PP0055-c. After resin-supported Compound PP0136-d was obtained in the same manner as synthesis of Compound PP0055-d using 1-propanol in place of 1-butanol, resin-supported Compound PP0136-e was obtained in the same manner as synthesis of Compound PP0055-e. Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give the intended compounds. LC/MS data is provided in Table 36.

[1034]

Synthesis of Compound PP0210, Compound PP0211, Compound PP0215, and Compound PP0216

Compound PP0210, Compound PP0211, Compound PP0215, and Compound PP0216 were synthesized according to the following scheme.



[1035]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported Compound PP0210-a. After resin-supported Compound PP0210-b was obtained in the same manner as synthesis of Compound PP0055-b, resin-supported Compound PP0210-c was obtained in the same manner as synthesis of Compound PP0055-c using THF in place of NMP as a reaction solvent. After resin-supported Compound PP0210-d was obtained in the same manner as synthesis of Compound PP0055-d using the alcohols shown in Table 28 in place of 1-butanol, resin-supported Compound PP0210-e was obtained in the same manner as synthesis of Compound PP0055-e. Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give the intended compounds. LC/MS data is provided in Table 36.

[1036]

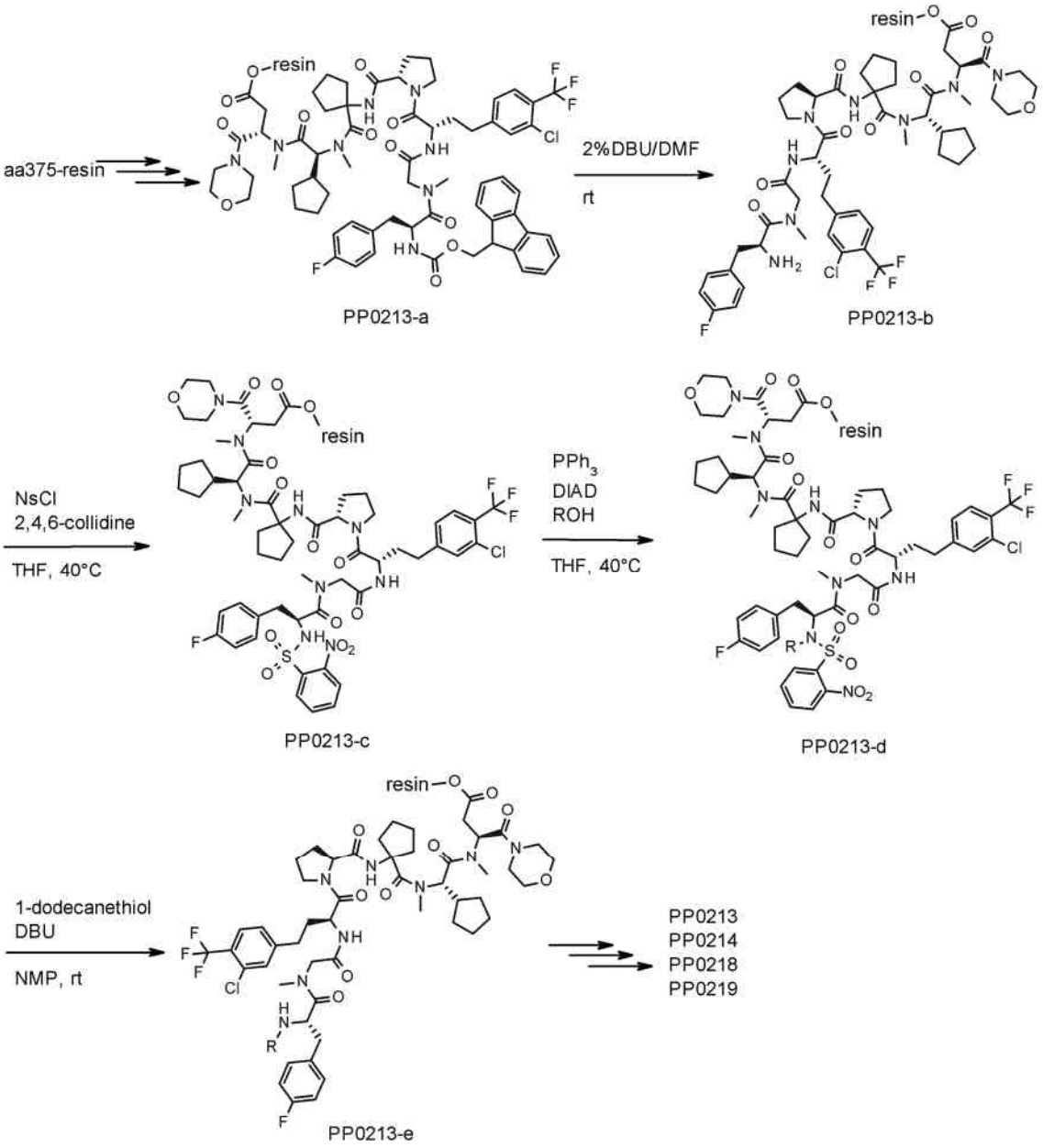
[Table 28]

Intended product	Alcohol
Compound PP0210	Ethanol
Compound PP0211	1-Propanol
Compound PP0215	Ethanol
Compound PP0216	1-Propanol

[1037]

Synthesis of Compound PP0213, Compound PP0214, Compound PP0218, and Compound PP0219

Compound PP0213, Compound PP0214, Compound PP0218, and Compound PP0219 were synthesized according to the following scheme.



[1038]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported Compound PP0213-a. After resin-supported Compound PP0213-b was obtained in the same manner as synthesis of Compound PP0055-b, resin-supported Compound PP0213-c was obtained in the same manner as synthesis of Compound PP0055-c using THF in place of NMP as a reaction solvent. After resin-supported Compound PP0213-d was obtained in the same manner as synthesis of Compound PP0055-d using the alcohols shown in Table 29 in place of 1-butanol, resin-supported Compound PP0213-e was obtained in the same manner as synthesis of Compound PP0055-e. Subsequent steps of peptide elongation, cleaving from resin, cyclization,

and purification were performed according to the basic route to give the intended compounds. LC/MS data is provided in Table 36.

[1039]

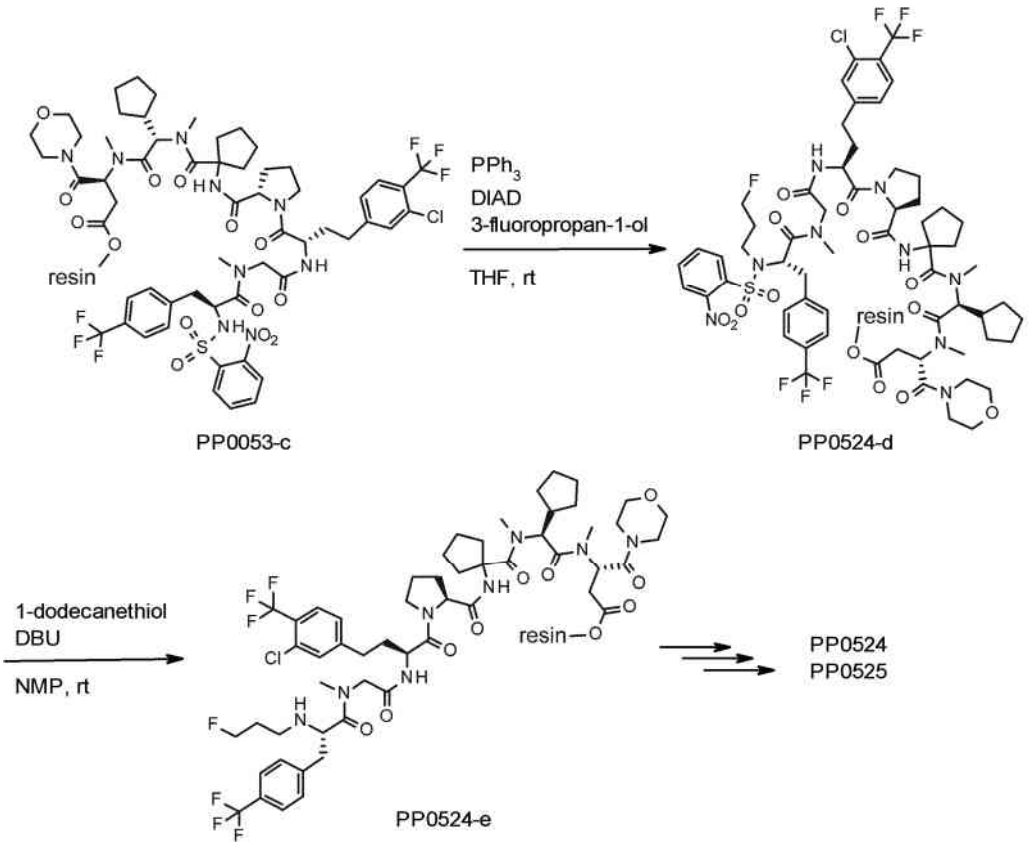
[Table 29]

Intended product	Alcohol
Compound PP0213	Ethanol
Compound PP0214	1-Propanol
Compound PP0218	Ethanol
Compound PP0219	1-Propanol

[1040]

Synthesis of Compound PP0524 and Compound PP0525

Compound PP0524 and Compound PP0525 were synthesized according to the following scheme.



[1041]

DCM (1.5 mL) was added to swell resin-supported PP0053-c (210 mg). After DCM was removed, the resin was washed 4 times with THF. Triphenylphosphine (173 mg, 0.661 mmol) was dissolved in THF (0.600 mL), a mixed solution of DIAD (0.128 mL, 0.661 mmol) and THF (0.572 mL) was added thereto, and the mixture was stirred for 15 minutes. 3-

Fluoropropan-1-ol (0.099 mL, 1.32 mmol) was added thereto, and the mixture was left to stand still for 5 minutes. This solution was added to the resin, the mixture was shaken at room temperature for 1 hour, and then the reaction solution was removed. The resin was washed 4 times with THF (1.5 mL) and washed 4 times with DCM (1.5 mL) to give resin-supported Compound PP0524-d. Cleaving from the resin was performed with TFE/DCM (1/1) using a small amount of resin-supported Compound PP0524-d, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 1359 (M+H)+

Retention time: 0.98 min (Analytical condition SQDFA05)

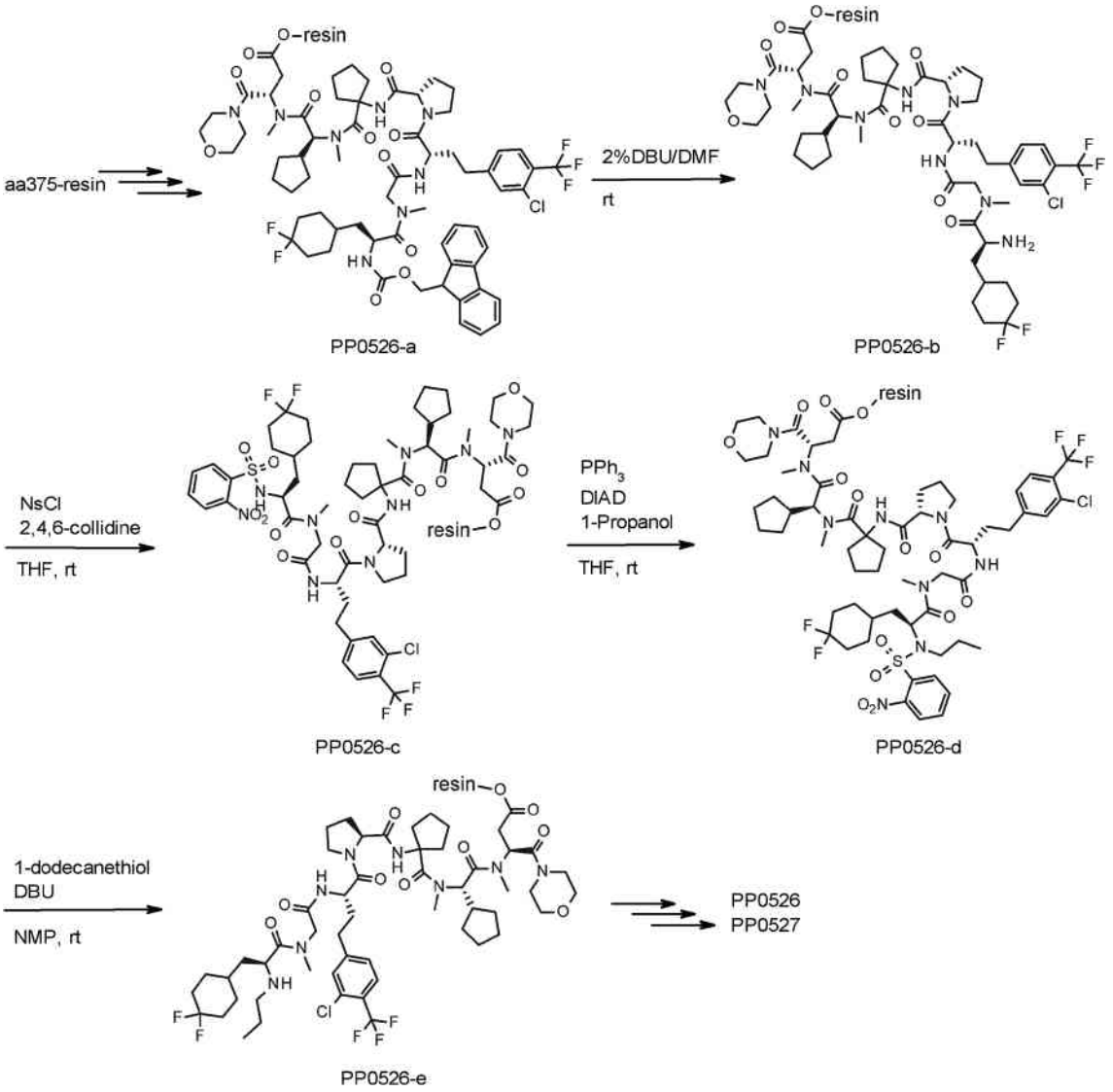
[1042]

Using this, resin-supported Compound PP0524-e was obtained in the same manner as synthesis of Compound PP0055-e. Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give the intended compounds. LC/MS data is provided in Table 36.

[1043]

Synthesis of Compound PP0526 and Compound PP0527

Compound PP0526 and Compound PP0527 were synthesized according to the following scheme.



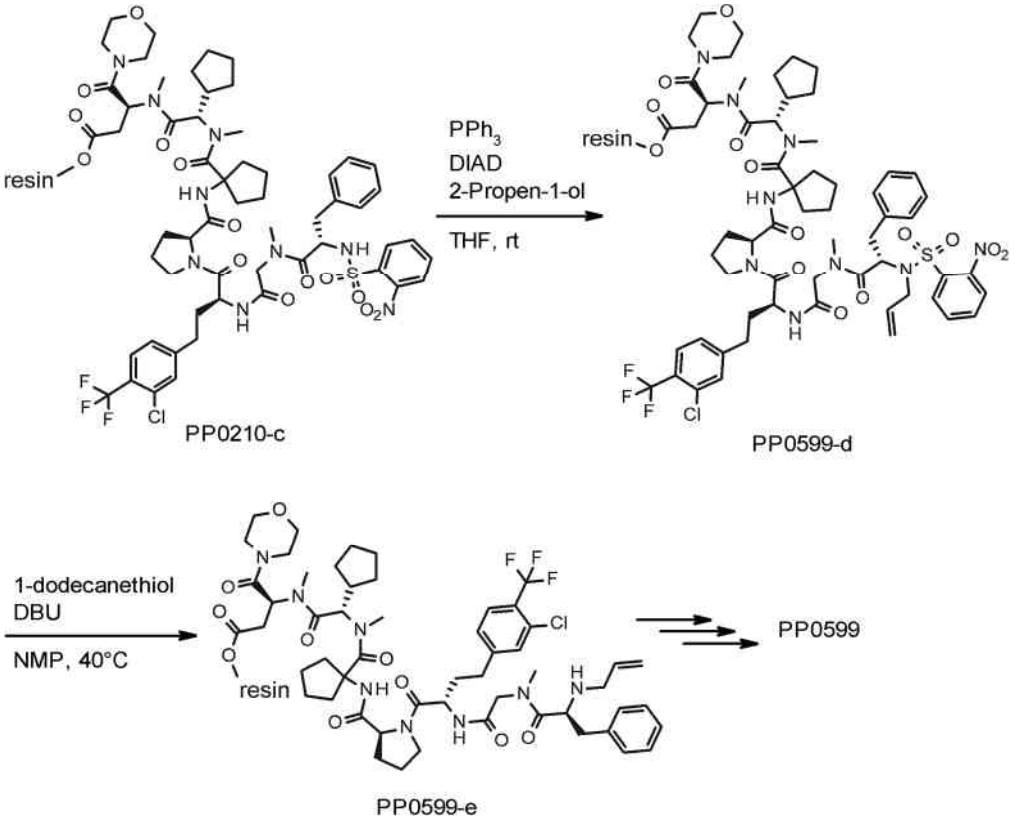
[1044]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported Compound PP0526-a. After resin-supported Compound PP0526-b was obtained in the same manner as synthesis of Compound PP0055-b, resin-supported Compound PP0526-c was obtained in the same manner as synthesis of Compound PP0055-c using THF in place of NMP as a reaction solvent. After resin-supported Compound PP0526-d was obtained in the same manner as synthesis of Compound PP0524-d allowing 1-propanol to react in place of 3-fluoropropan-1-ol, resin-supported Compound PP0526-e was obtained in the same manner as synthesis of Compound PP0055-e. Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give the intended compounds. LC/MS data is provided in Table 36.

[1045]

Synthesis of Compound PP0599

Compound PP0599 was synthesized according to the following scheme.



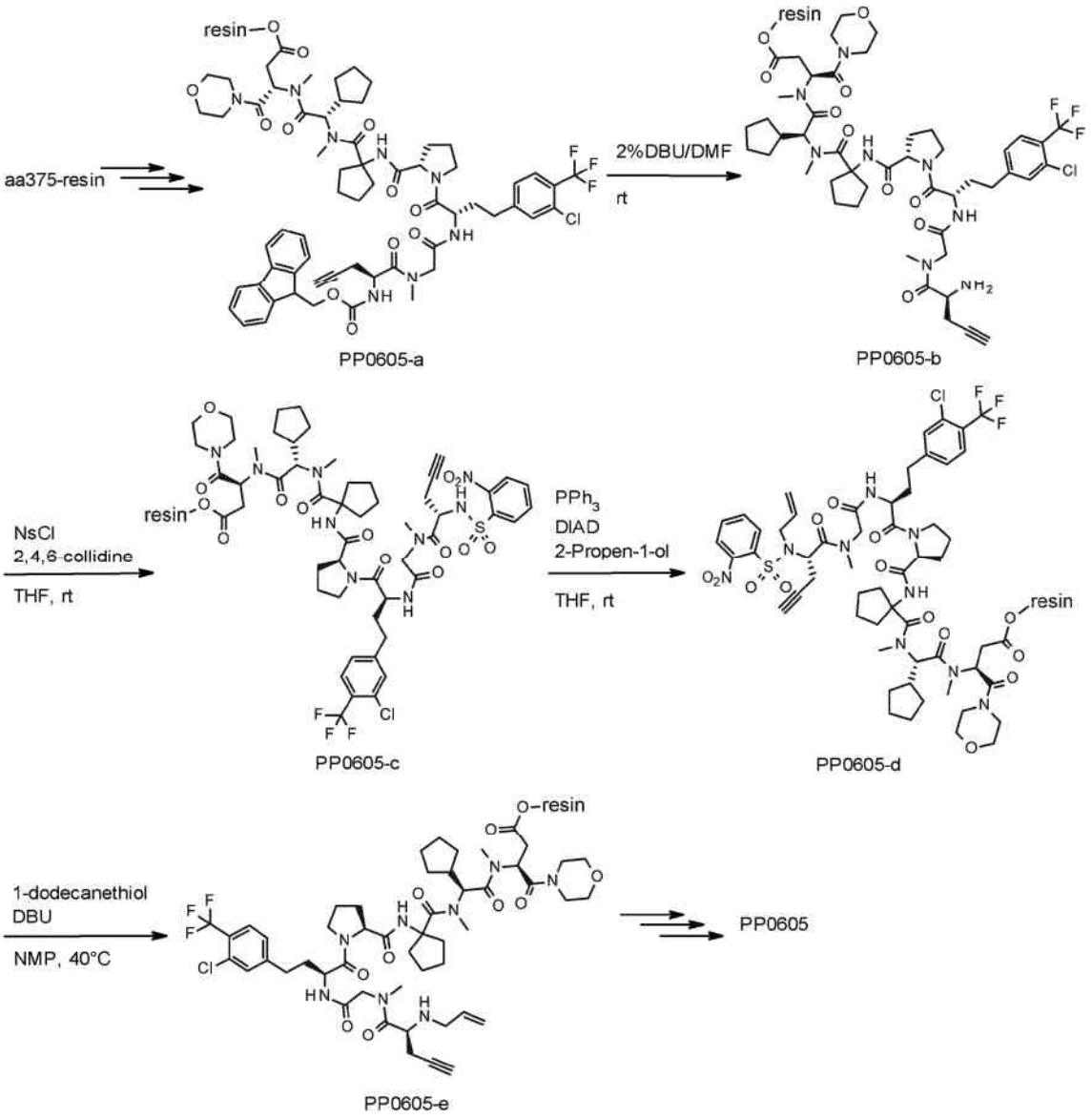
[1046]

Using resin-supported PP0210-c, resin-supported Compound PP0599-d was obtained in the same manner as synthesis of Compound PP0524-d using 2-propen-1-ol in place of 3-fluoropropan-1-ol, and then resin-supported Compound PP0599-e was obtained in the same manner as synthesis of Compound PP0055-e. Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give the intended compound. LC/MS data is provided in Table 36.

[1047]

Synthesis of Compound PP0605

Compound PP0605 was synthesized according to the following scheme.



[1048]

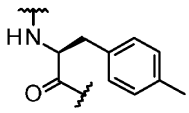
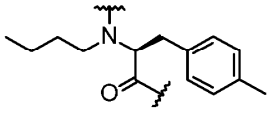
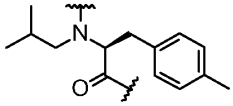
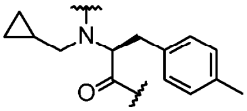
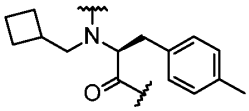
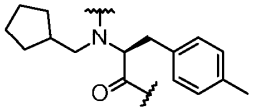
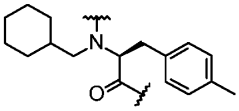
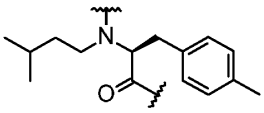
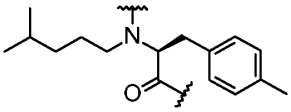
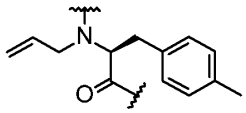
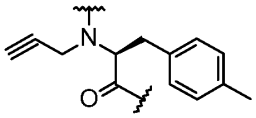
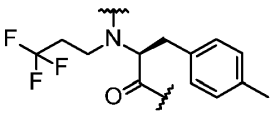
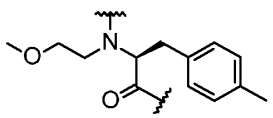
Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported Compound PP0605-a. After resin-supported Compound PP0605-b was obtained in the same manner as synthesis of Compound PP0055-b, resin-supported Compound PP0605-c was obtained in the same manner as synthesis of Compound PP0055-c using THF in place of NMP as a reaction solvent. After resin-supported Compound PP0605-d was obtained in the same manner as synthesis of Compound PP0524-d using 2-propen-1-ol in place of 3-fluoropropan-1-ol, resin-supported Compound PP0605-e was obtained in the same manner as synthesis of Compound PP0055-e. Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give the intended compound. LC/MS data is provided in Table 36.

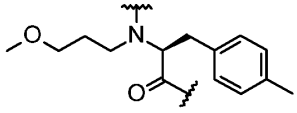
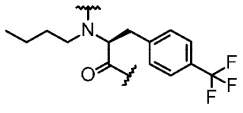
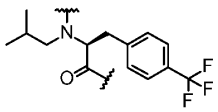
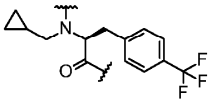
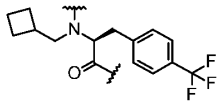
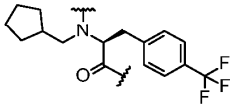
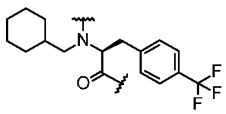
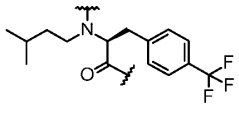
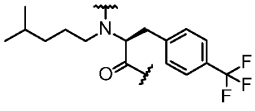
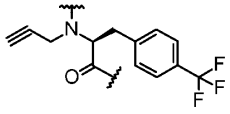
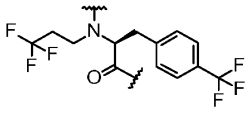
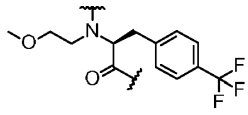
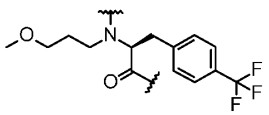
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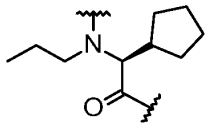
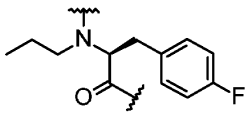
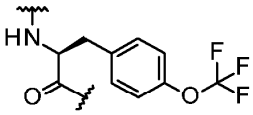
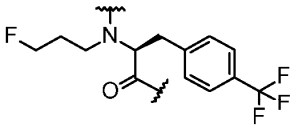
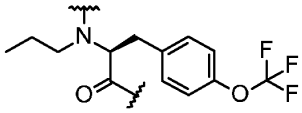
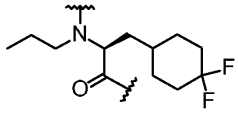
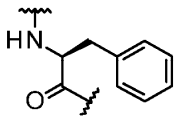
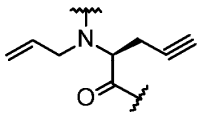
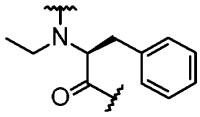
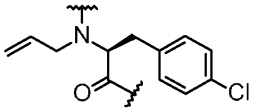
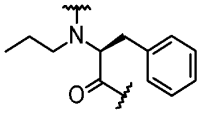
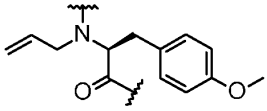
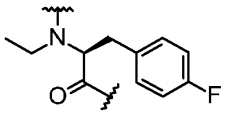
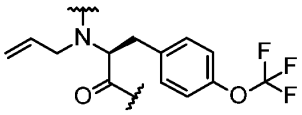
Abbreviations and structures of amino acids contained as partial structures in a cyclic compound and an oligopeptide compound synthesized via N-alkylation by a Mitsunobu reaction on a resin are provided below.

[1050]

[Table 29-1]

Compound No.	Abbreviation	Amino acid Structural Formula
bb038	Phe(4-Me)	
bb039	nBuPhe(4-Me)	
bb040	iBuPhe(4-Me)	
bb041	cPrMePhe(4-Me)	
bb042	cBuMePhe(4-Me)	
bb043	cPentMePhe(4-Me)	
bb044	cHexMePhe(4-Me)	
bb045	iPenPhe(4-Me)	
bb046	neoHexPhe(4-Me)	
bb047	AllylPhe(4-Me)	
bb048	PraPhe(4-Me)	
bb049	TfpPhe(4-Me)	
bb050	MeOEtPhe(4-Me)	

Compound No.	Abbreviation	Amino acid Structural Formula
bb051	MeOnPrPhe(4-Me)	
bb052	nBuPhe(4-CF3)	
bb053	iBuPhe(4-CF3)	
bb054	cPrMePhe(4-CF3)	
bb055	cBuMePhe(4-CF3)	
bb056	cPentMePhe(4-CF3)	
bb057	cHexMePhe(4-CF3)	
bb058	iPenPhe(4-CF3)	
bb059	neoHexPhe(4-CF3)	
bb060	PraPhe(4-CF3)	
bb061	TfpPhe(4-CF3)	
bb062	MeOEtPhe(4-CF3)	
bb063	MeOnPrPhe(4-CF3)	

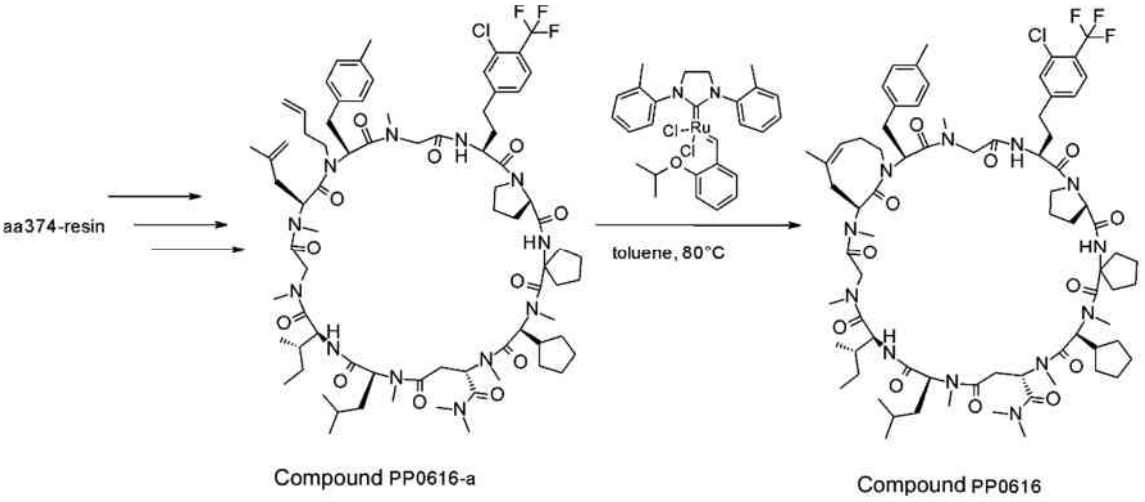
bb064	nPrGly(cPent)		bb071	nPrPhe(4-F)	
bb065	Phe(4-OCF3)		bb072	MfpPhe(4-CF3)	
bb066	nPrPhe(4-OCF3)		bb073	nPrCha(4-F2)	
bb067	Phe		bb074	AllylPRA	
bb068	EtPhe		bb075	AllylPhe(4-Cl)	
bb069	nPrPhe		bb076	AllylPhe(4-OMe)	
bb070	EtPhe(4-F)		bb077	AllylPhe(4-OCF3)	

[1051]

1-6-5. Peptide modification by olefin metathesis reaction

Synthesis of Compound PP0616

Compound PP0616 was synthesized according to the following scheme.



[1052]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0616-a (6.5 mg, 4.36 μmol).

LCMS (ESI) m/z = 1491 (M+H)+

Retention time: 0.82 min (Analytical condition SQDFA50)

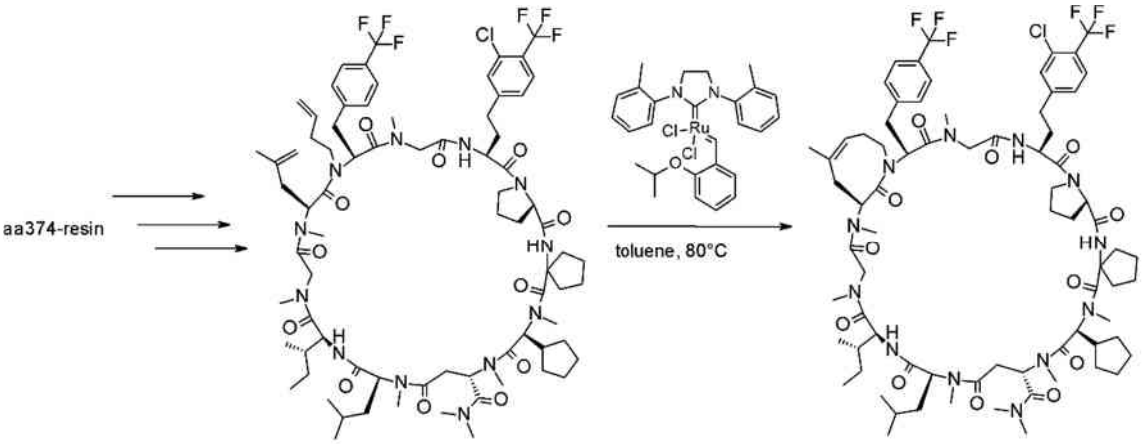
[1053]

Compound PP0616-a (6.5 mg, 4.36 μmol) and a Stewart-Grubbs catalyst (2.5 mg, 4.36 μmol) were dissolved in toluene (1 mL), and the mixture was stirred at 80°C for 24.5 hours in a nitrogen atmosphere. After cooling to room temperature, the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give PP0616 (3.3 mg, 52%). LC/MS data is provided in Table 36.

[1054]

Synthesis of Compound PP0617

Compound PP0617 was synthesized according to the following scheme.



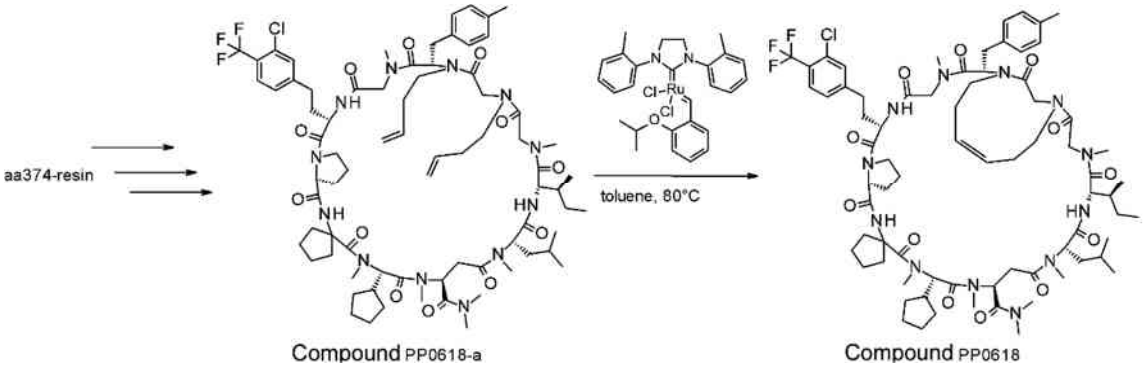
[1055]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0617-a (8.4 mg, 5.44 μmol). Using the resulting PP0617-a, PP0617 (1.7 mg, 22%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1056]

Synthesis of Compound PP0618

Compound PP0618 was synthesized according to the following scheme.



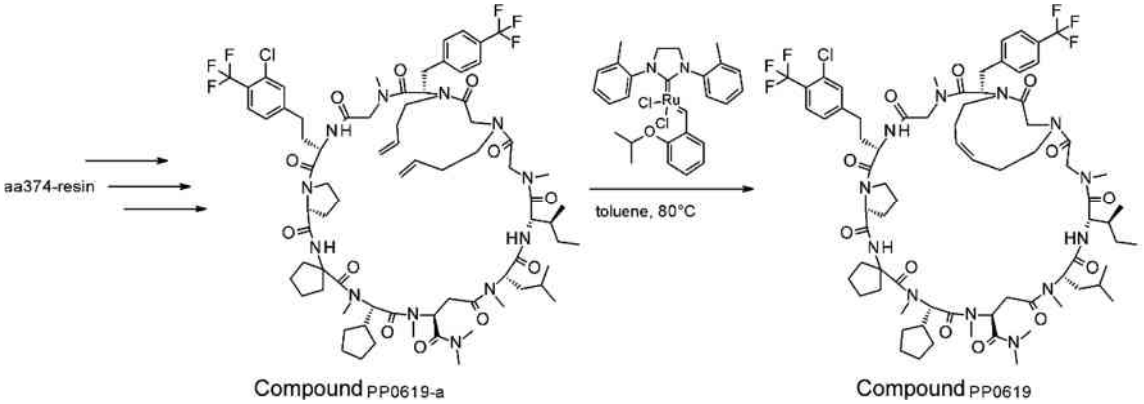
[1057]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0618-a (23.9 mg, 16.6 μmol). Using the resulting PP0618-a, PP0618 (2.4 mg, 11%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1058]

Synthesis of Compound PP0619

Compound PP0619 was synthesized according to the following scheme.



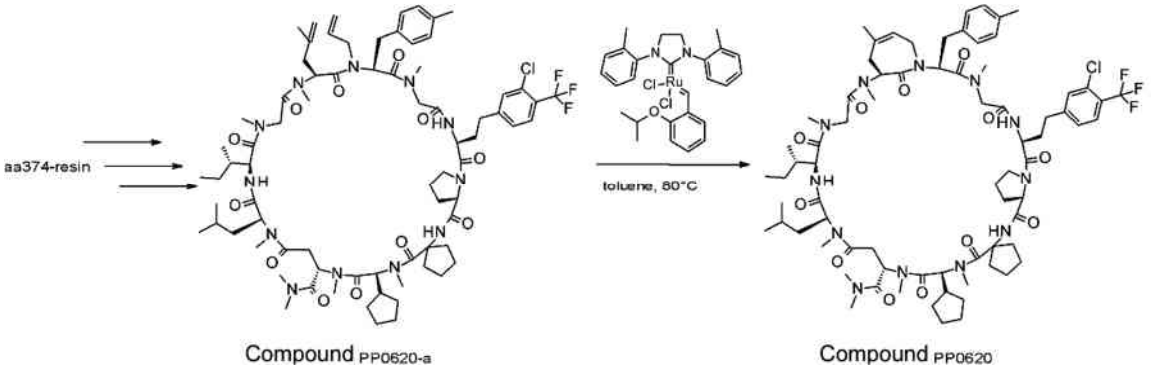
[1059]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0619-a (17.6 mg, 11.4 μmol). Using the resulting PP0619-a, PP0619 (0.57 mg, 3%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1060]

Synthesis of Compound PP0620

Compound PP0620 was synthesized according to the following scheme.



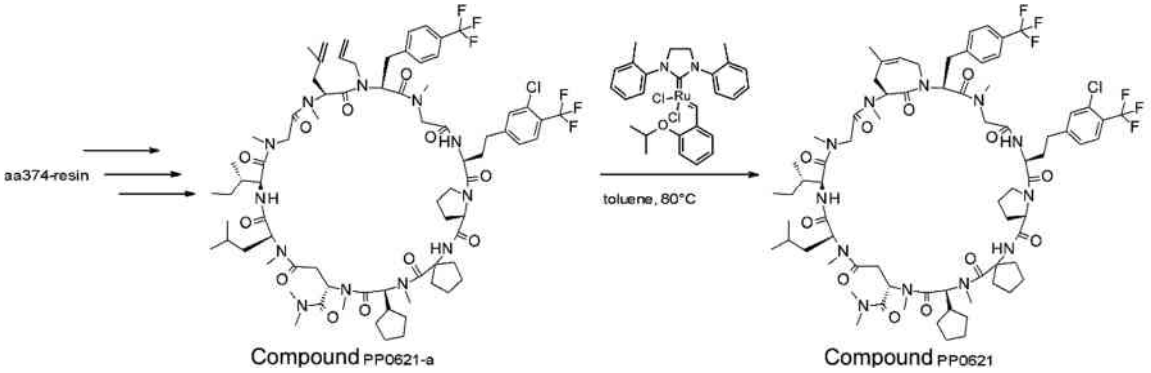
[1061]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0620-a (13.7 mg, 9.3 μmol). Using the resulting PP0620-a, PP0620 (6.7 mg, 53%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1062]

Synthesis of Compound PP0621

Compound PP0621 was synthesized according to the following scheme.



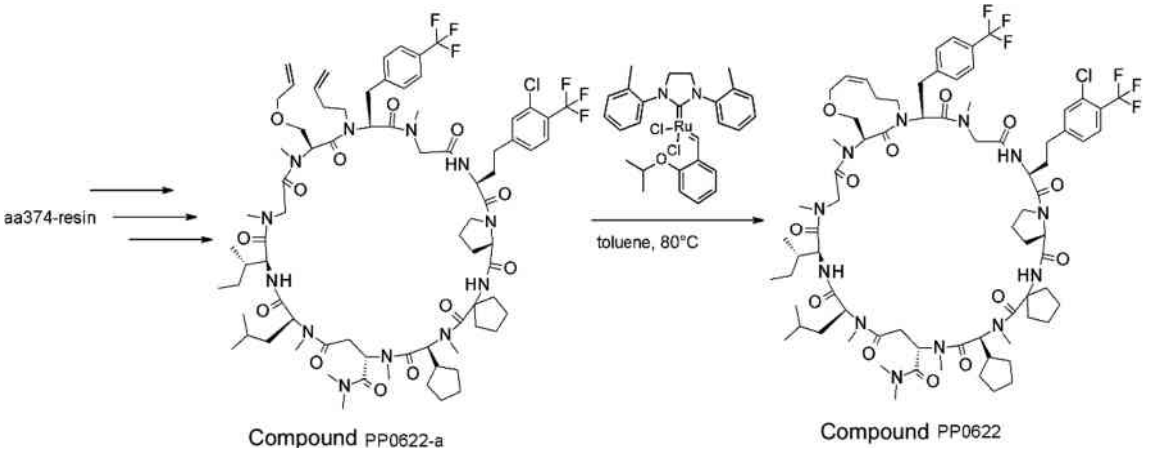
[1063]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0621-a (8.3 mg, 5.4 μmol). Using the resulting PP0621-a, PP0621 (3.9 mg, 44%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1064]

Synthesis of Compound PP0622

Compound PP0622 was synthesized according to the following scheme.



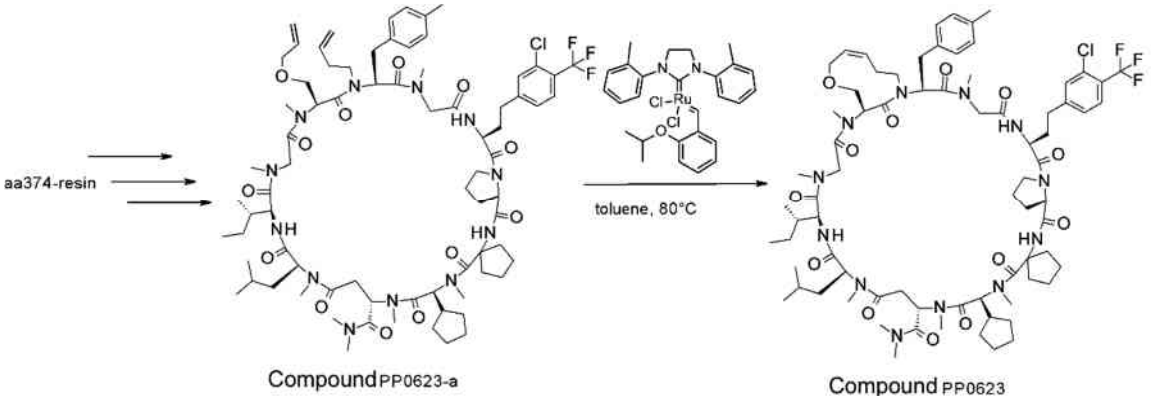
[1065]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0622-a (7.6 mg, 4.9 μmol). Using the resulting PP0622-a, PP0622 (0.25 mg, 4%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1066]

Synthesis of Compound PP0623

Compound PP0623 was synthesized according to the following scheme.



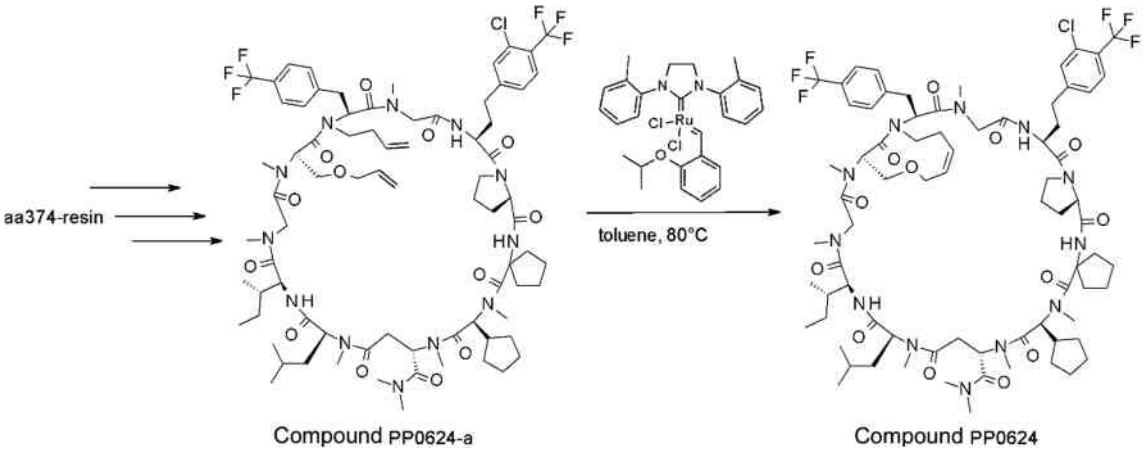
[1067]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0623-a (10.7 mg, 7.1 μmol). Using the resulting PP0623-a, PP0623 (0.4 mg, 4%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1068]

Synthesis of Compound PP0624

Compound PP0624 was synthesized according to the following scheme.



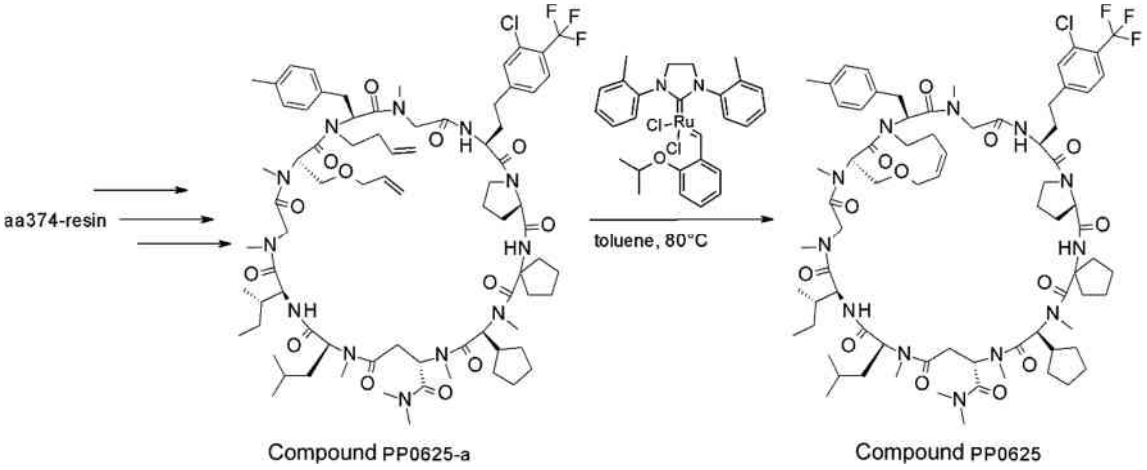
[1069]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0624-a (9.7 mg, 6.2 μmol). Using the resulting PP0624-a, PP0624 (0.3 mg, 3%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1070]

Synthesis of Compound PP0625

Compound PP0625 was synthesized according to the following scheme.



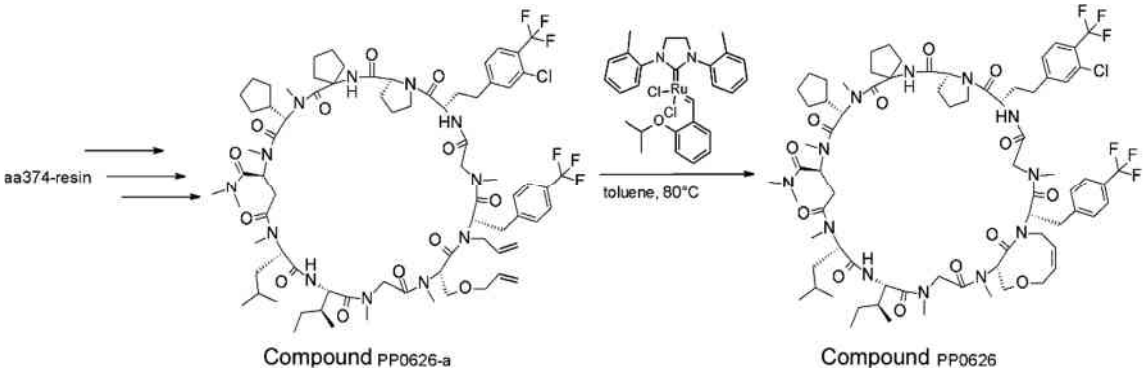
[1071]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0625-a (12.3 mg, 8.2 μmol). Using the resulting PP0625-a, PP0625 (0.3 mg, 3%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1072]

Synthesis of Compound PP0626

Compound PP0626 was synthesized according to the following scheme.



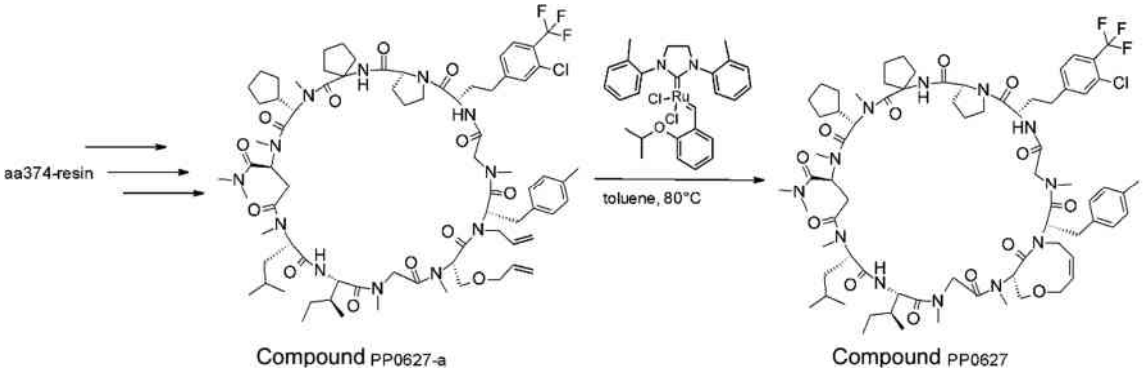
[1073]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0626-a (4.7 mg, 3.0 μmol). Using the resulting PP0626-a, PP0626 (1.6 mg, 40%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1074]

Synthesis of Compound PP0627

Compound PP0627 was synthesized according to the following scheme.



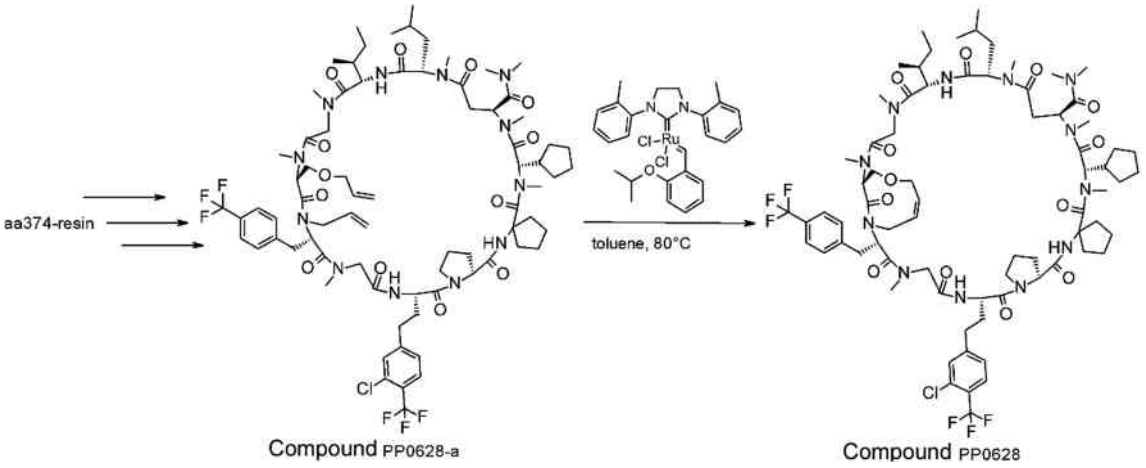
[1075]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0627-a (6.6 mg, 4.4 μmol). Using the resulting PP0627-a, PP0627 (1.2 mg, 20%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1076]

Synthesis of Compound PP0628

Compound PP0628 was synthesized according to the following scheme.



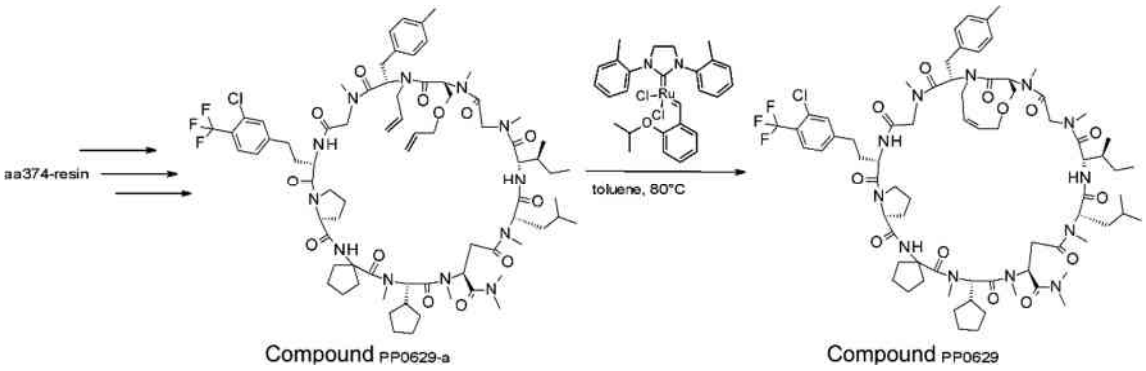
[1077]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0628-a (16.6 mg, 10.7 μmol). Using the resulting PP0628-a, PP0628 (0.5 mg, 3%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1078]

Synthesis of Compound PP0629

Compound PP0629 was synthesized according to the following scheme.



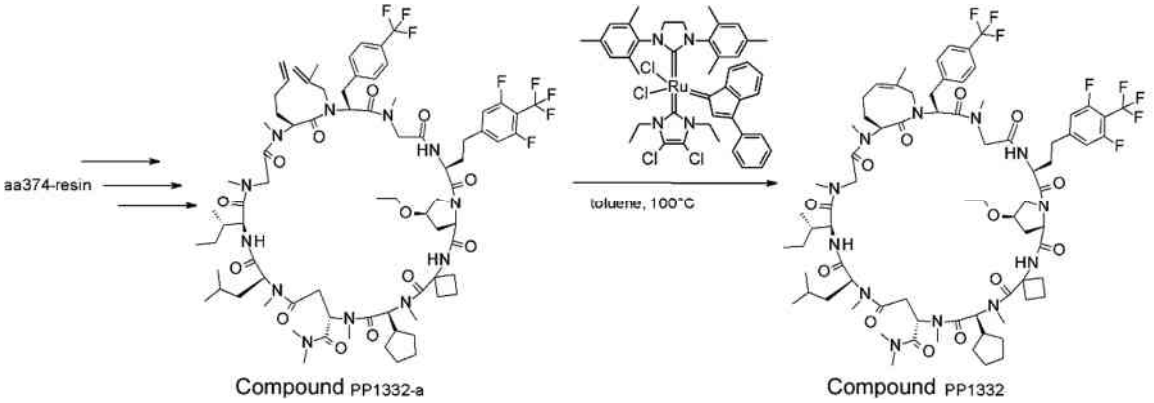
[1079]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0629-a (12.3 mg, 8.2 μmol). Using the resulting PP0629-a, PP0629 (0.7 mg, 6%) was obtained in the same manner as synthesis of Compound PP0616. LC/MS data is provided in Table 36.

[1080]

Synthesis of Compound PP1332

Compound PP1332 was synthesized according to the following scheme.



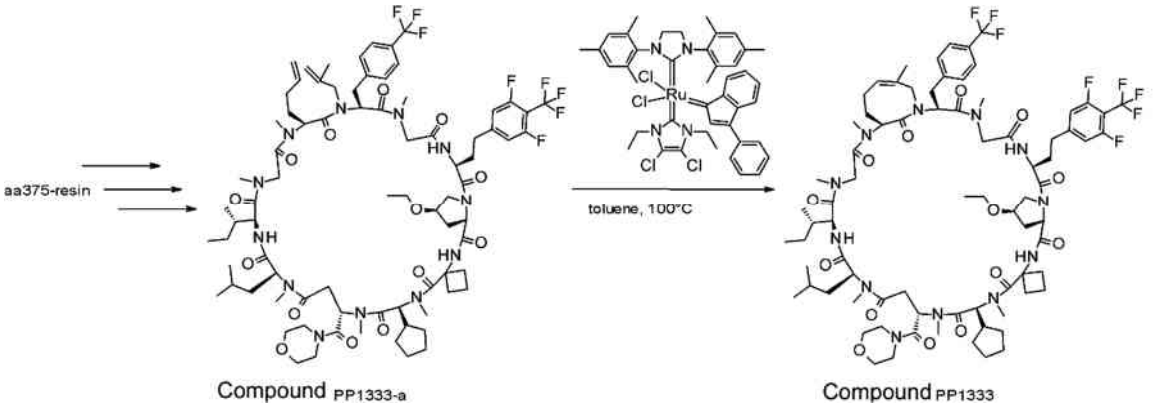
[1081]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP1332-a (40.9 mg, 25.6 μmol). The resulting Compound PP1332-a (40 mg) and 1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)(3-phenyl-1H-inden-1-ylidene)(4,5-dichloro-1,3-diethyl-1,3-dihydro-2H-imidazol-2-ylidene)ruthenium(II) chloride (22 mg, 0.025 mmol) were dissolved in toluene (3 mL), and the mixture was stirred at 100°C for 13.5 hours in a nitrogen atmosphere. After cooling to room temperature, the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give PP1332 (11.5 mg, 17%). LC/MS data is provided in Table 36.

[1082]

Synthesis of Compound PP1333

Compound PP1333 was synthesized according to the following scheme.



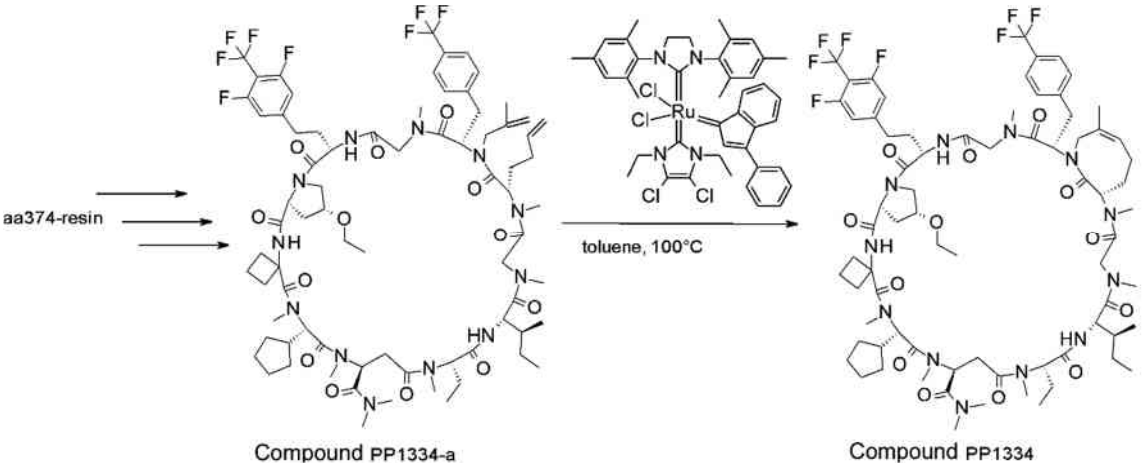
[1083]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP1333-a (55.1 mg, 34.1 μmol). Using the resulting PP1333-a, PP1333 (8.2 mg, 15%) was obtained in the same manner as synthesis of Compound PP1332. LC/MS data is provided in Table 36.

[1084]

Synthesis of Compound PP1334

Compound PP1334 was synthesized according to the following scheme.



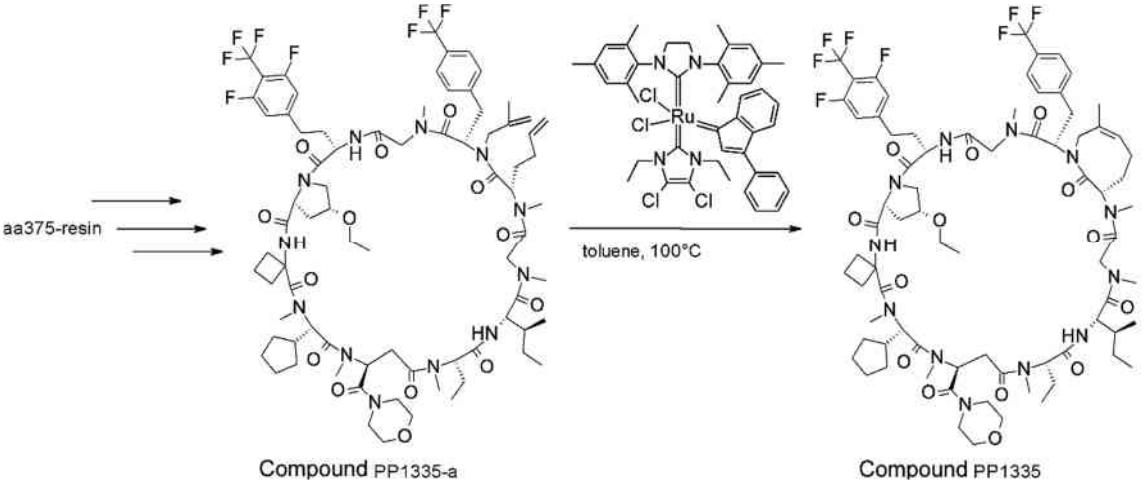
[1085]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP1334-a (76.1 mg, 49.1 μmol). Using the resulting PP1334-a, PP1334 (2.8 mg, 4%) was obtained in the same manner as synthesis of Compound PP1332. LC/MS data is provided in Table 36.

[1086]

Synthesis of Compound PP1335

Compound PP1335 was synthesized according to the following scheme.



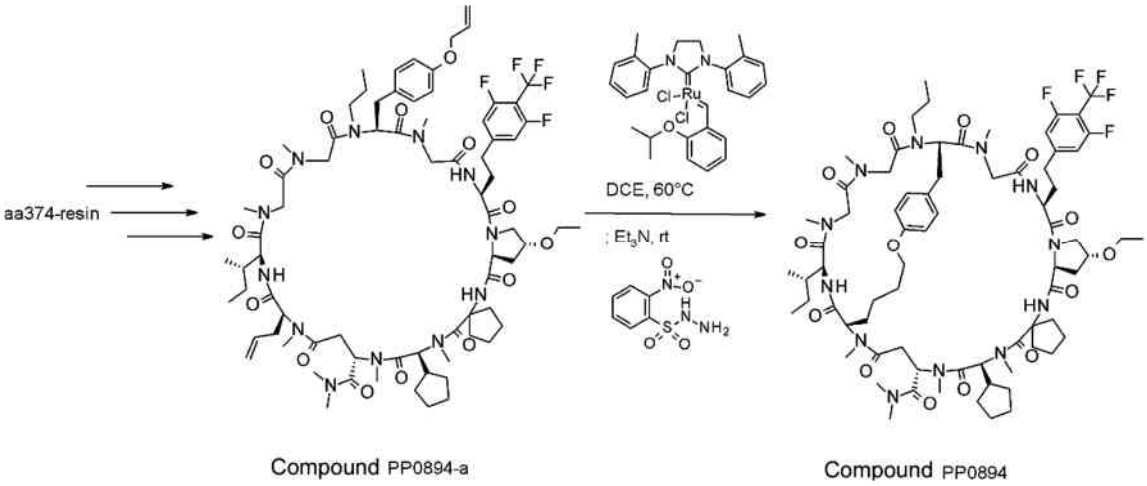
[1087]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP1335-a (71.8 mg, 45.5 μmol). Using the resulting PP1335-a, PP1335 (2.5 mg, 4%) was obtained in the same manner as synthesis of Compound PP1332. LC/MS data is provided in Table 36.

[1088]

Synthesis of Compound PP0894

Compound PP0894 was synthesized according to the following scheme.



[1089]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0894-a (26.5 mg, 18 μmol).

LCMS (ESI) m/z = 1496 (M+H)+

Retention time: 0.78 min (Analytical condition SQDAA50)

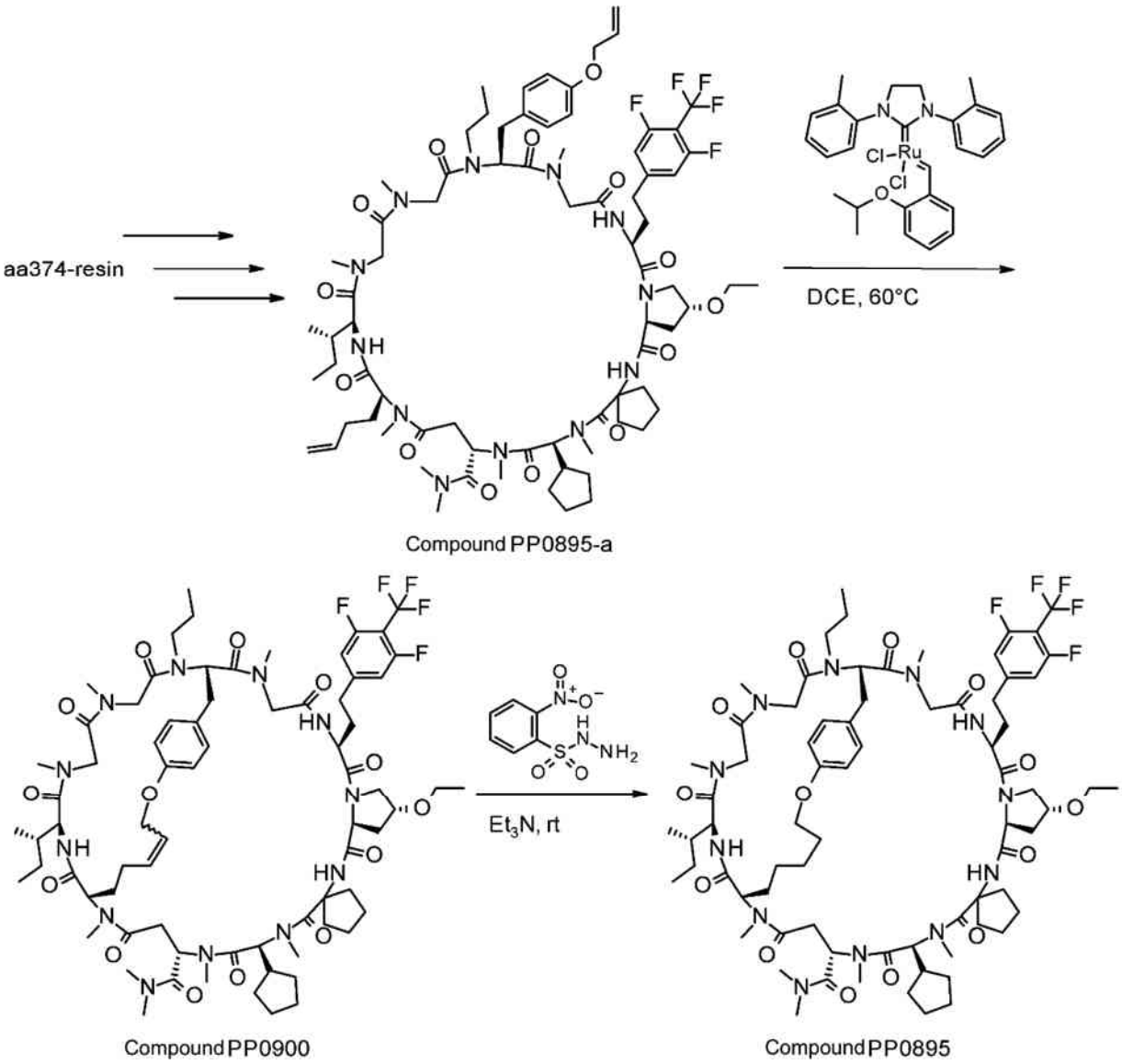
[1090]

Compound PP0894-a (26.5 mg, 18 μmol) and a Stewart-Grubbs catalyst (5.0 mg, 8.76 μmol) were dissolved in 1,2-dichloroethane (0.58 mL), and the mixture was stirred at 60°C for 20 hours in a nitrogen atmosphere. After cooling to room temperature, triethylamine (98 μL, 0.701 mmol) and 2-nitrobenzenesulfonohydrazide (152 mg, 0.701 mmol) were added, and the mixture was stirred at room temperature for 5 days. Then, the reaction solution was concentrated under reduced pressure. The resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give PP0894 (4.5 mg, 17%). LC/MS data is provided in Table 36.

[1091]

Synthesis of Compound PP0895 and Compound PP0900

Compounds PP0895 and PP0900 were synthesized according to the following scheme.



[1092]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0895-a. The resulting Compound PP0895-a (26.5 mg, 18 μmol) and a Stewart-Grubbs catalyst (5.0 mg, 8.76 μmol) were dissolved in 1,2-dichloroethane (0.58 mL), and the mixture was stirred at 60°C for 20 hours in a nitrogen atmosphere. One-third of the reaction solution was recovered and concentrated under reduced pressure, and the resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give PP0900 (2.1 mg, 8.1%). LC/MS data is provided in Table 36.

[1093]

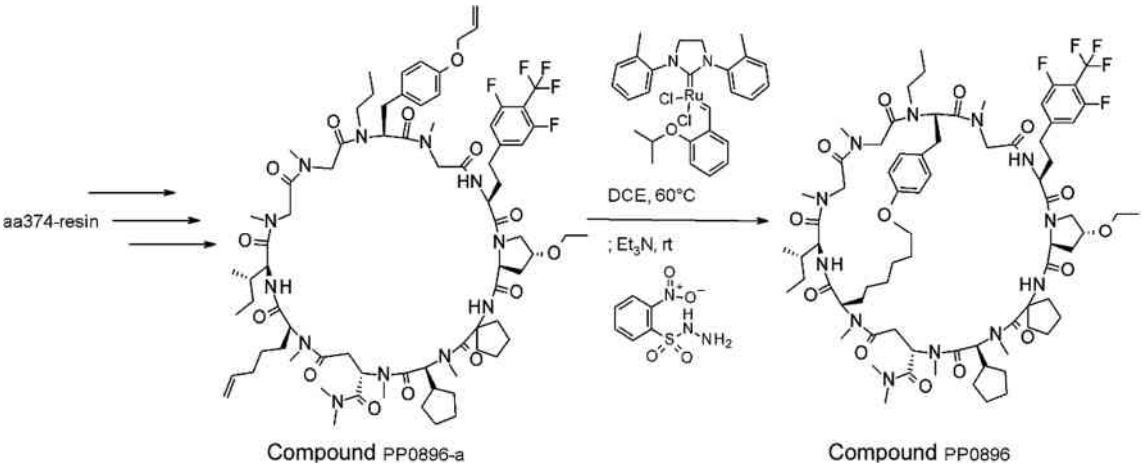
After the remaining reaction solution was cooled to room temperature, triethylamine (98 μL, 0.701 mmol) and 2-nitrobenzenesulfonohydrazide (152 mg, 0.701 mmol) were added,

and the mixture was stirred at room temperature for 5 days. Then, the reaction solution was concentrated under reduced pressure. The resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give PP0895 (4.4 mg, 17%). LC/MS data is provided in Table 36.

[1094]

Synthesis of Compound PP0896

Compound PP0896 was synthesized according to the following scheme.



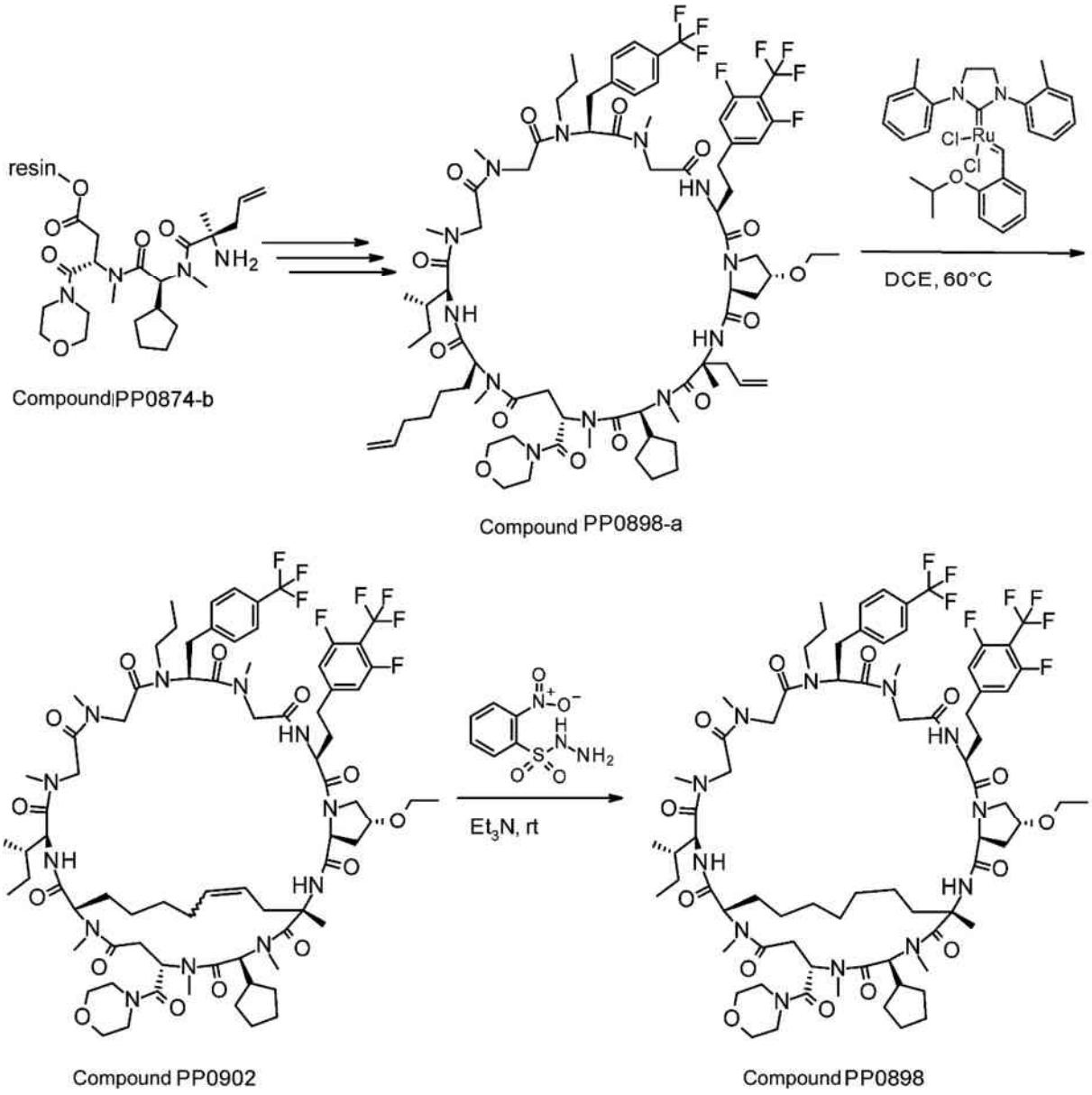
[1095]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0896-a. Using the resulting PP0896-a, PP0896 (4.5 mg, 17%) was obtained in the same manner as synthesis of Compound PP0894. LC/MS data is provided in Table 36.

[1096]

Synthesis of Compound PP0898 and Compound PP0902

Compounds PP0898 and PP0902 were synthesized according to the following scheme.



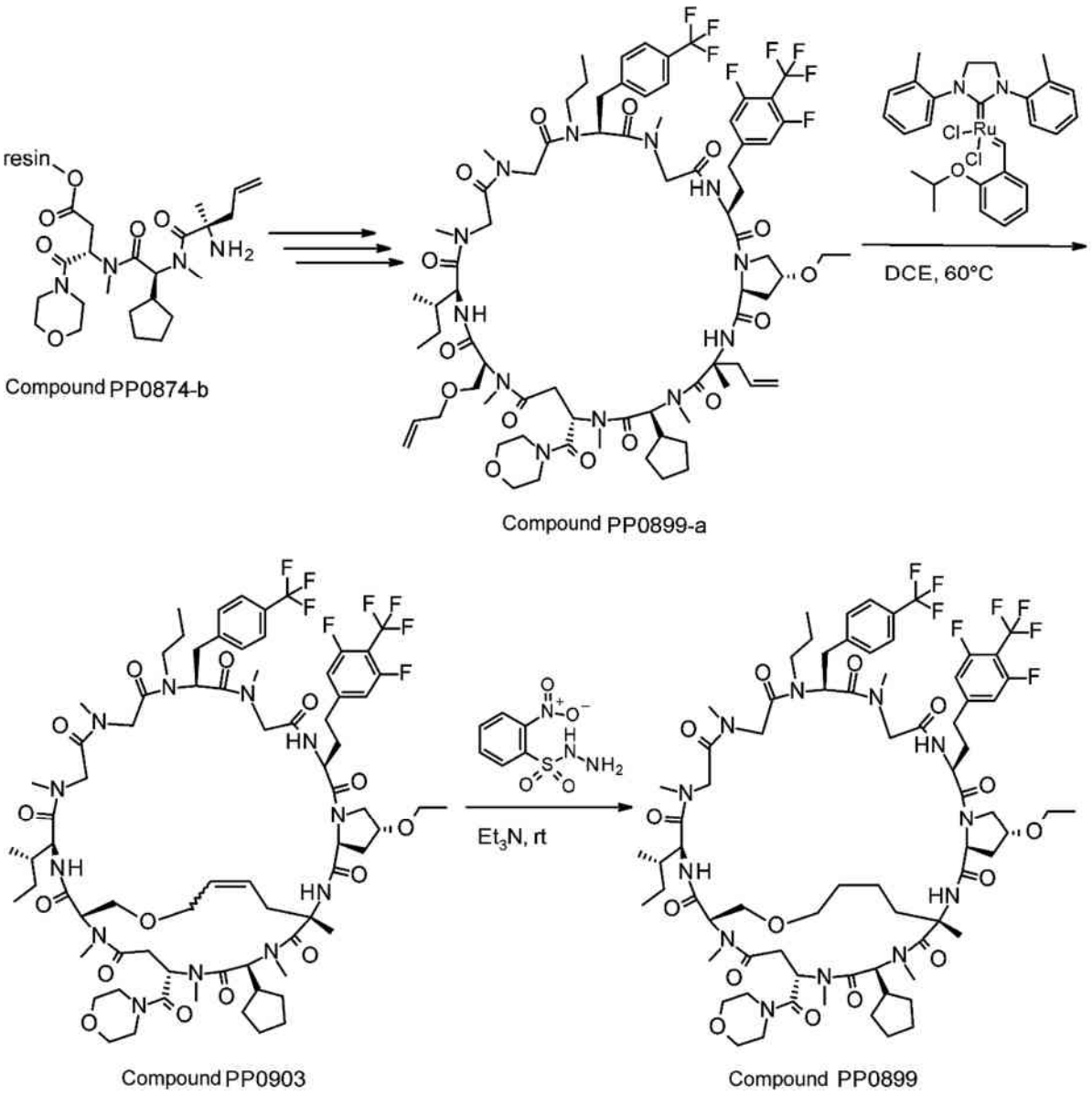
[1097]

Using, as a raw material, resin-supported PP0874-b that was a synthesis intermediate of Compound PP0874 synthesized using Compound aa375-resin, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0898-a. Using the resulting PP0898-a, PP0902 (1.1 mg, 4.2%) was obtained in the same manner as synthesis of Compound PP0900. Using Compound PP0902, PP0898 (2.0 mg, 7.7%) was obtained in the same manner as synthesis of Compound PP0895. LC/MS data is provided in Table 36.

[1098]

Synthesis of Compound PP0899 and Compound PP0903

Compounds PP0899 and PP0903 were synthesized according to the following scheme.



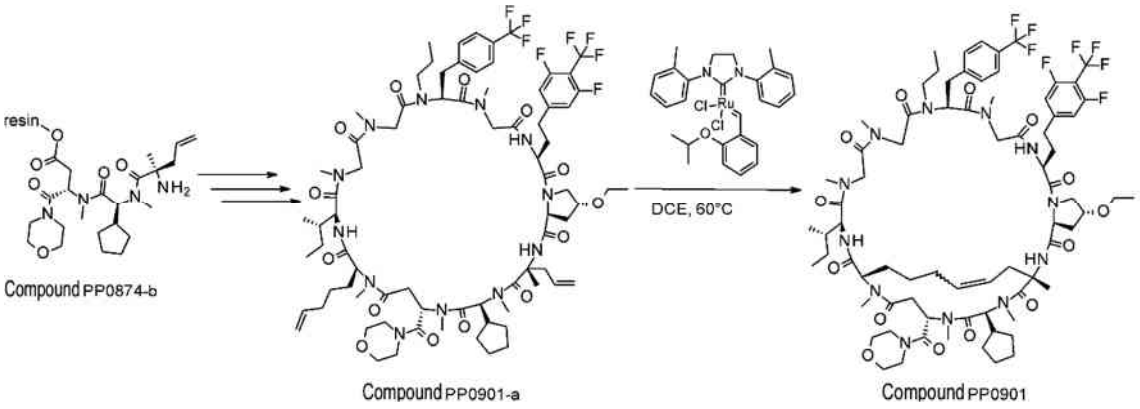
[1099]

Using, as a raw material, resin-supported PP0874-b that was a synthesis intermediate of Compound PP0874 synthesized using Compound aa375-resin, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0899-a. Using the resulting PP0899-a, PP0903 (1.1 mg, 4%) was obtained in the same manner as synthesis of Compound PP0900. Using Compound PP0903, PP0899 (3.1 mg, 12%) was obtained in the same manner as synthesis of Compound PP0895. LC/MS data is provided in Table 36.

[1100]

Synthesis of Compound PP0901

Compound PP0901 was synthesized according to the following scheme.



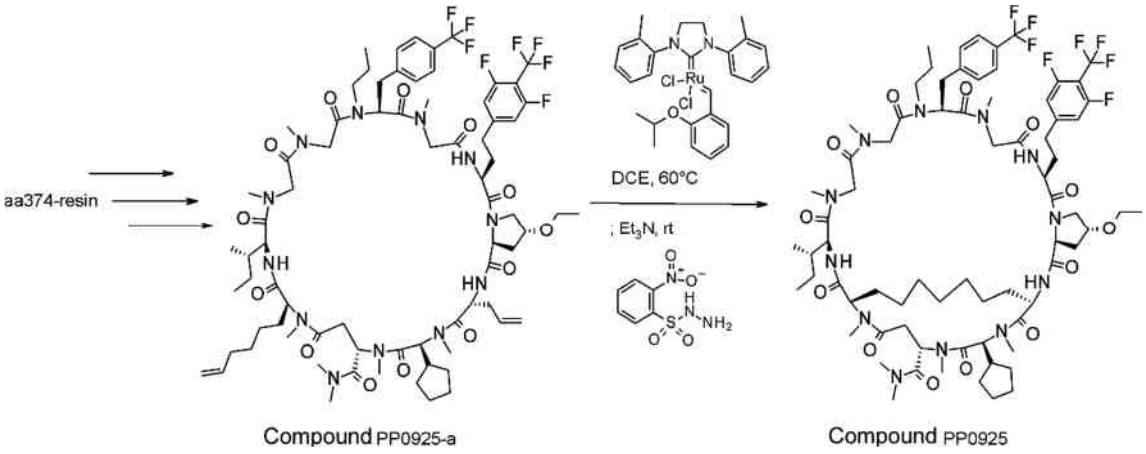
[1101]

Using, as a raw material, resin-supported synthesis intermediate PP0874-b of Compound PP0874 synthesized using Compound aa375-resin, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0901-a. The resulting Compound PP0901-a (26.5 mg, 18 μmol) and a Stewart-Grubbs catalyst (5.0 mg, 8.76 μmol) were dissolved in 1,2-dichloroethane (0.58 mL), and the mixture was stirred at 60°C for 20 hours in a nitrogen atmosphere. After being cooled to room temperature, the reaction solution was concentrated under reduced pressure. The resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give PP0901 (0.8 mg, 3%). LC/MS data is provided in Table 36.

[1102]

Synthesis of Compound PP0925

Compound PP0925 was synthesized according to the following scheme.



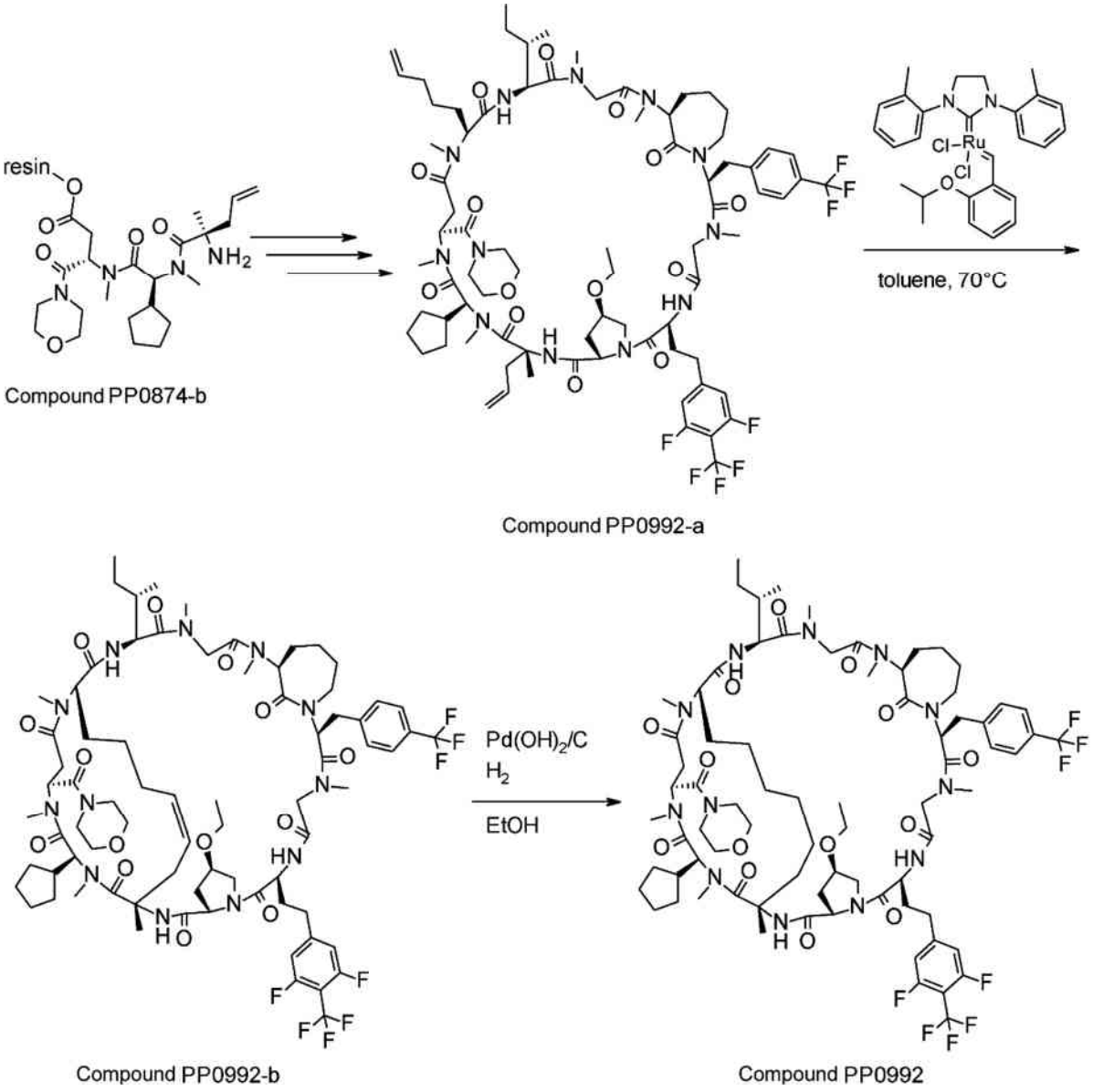
[1103]

Using Compound aa374-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0925-a. Using the resulting PP0925-a, PP0925 (1.1 mg, 4%) was obtained in the same manner as synthesis of Compound PP0894. LC/MS data is provided in Table 36.

[1104]

Synthesis of Compound PP0992

Compound PP0992 was synthesized according to the following scheme.



[1105]

Using, as a raw material, resin-supported synthesis intermediate PP0874-b of Compound PP0874 synthesized using Compound aa375-resin, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0992-a (10.07 mg, 6.33 μmol).

LCMS (ESI) m/z = 1590 (M+H)+

Retention time: 1.85 min (Analytical condition SQDFA50 long)

[1106]

Compound PP0992-a (9.09 mg, 5.72 μmol) and a Stewart-Grubbs catalyst (1.8 mg, 3.1 μmol) were dissolved in toluene (0.41 mL), and the mixture was stirred at 70°C for 5 hours in a

nitrogen atmosphere. After cooling to room temperature, the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give PP0992-b (3.5 mg, 36%).

LCMS (ESI) m/z = 1562 (M+H)+

Retention time: 0.95 min (Analytical condition SQDFA05)

[1107]

Compound PP0992-b (3.5 mg, 2.24 μmol) was dissolved in ethanol (1.5 mL), palladium hydroxide on carbon (20 wt%, 10 mg, 0.028 mmol) was added, and the mixture was stirred at room temperature for 2 hours in a hydrogen atmosphere. Subsequently, the reaction solution was filtered through Celite, Celite was washed with ethanol, and then the filtrate was concentrated under reduced pressure. The resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give PP0992 (1.3 mg, 26%).

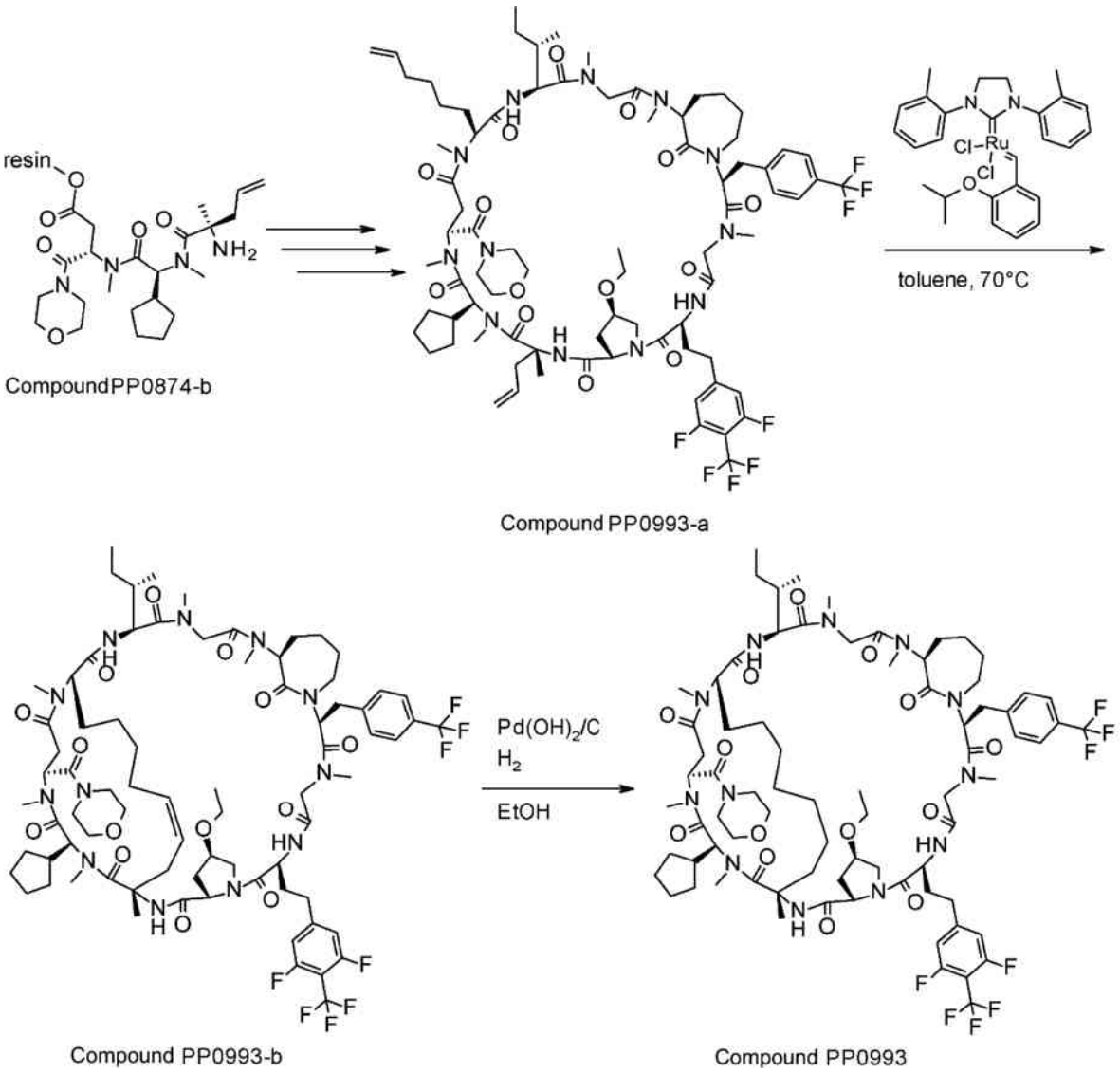
LCMS (ESI) m/z = 1564 (M+H)+

Retention time: 1.22 min (Analytical condition SQDFA50 long)

[1108]

Synthesis of Compound PP0993

Compound PP0993 was synthesized according to the following scheme.



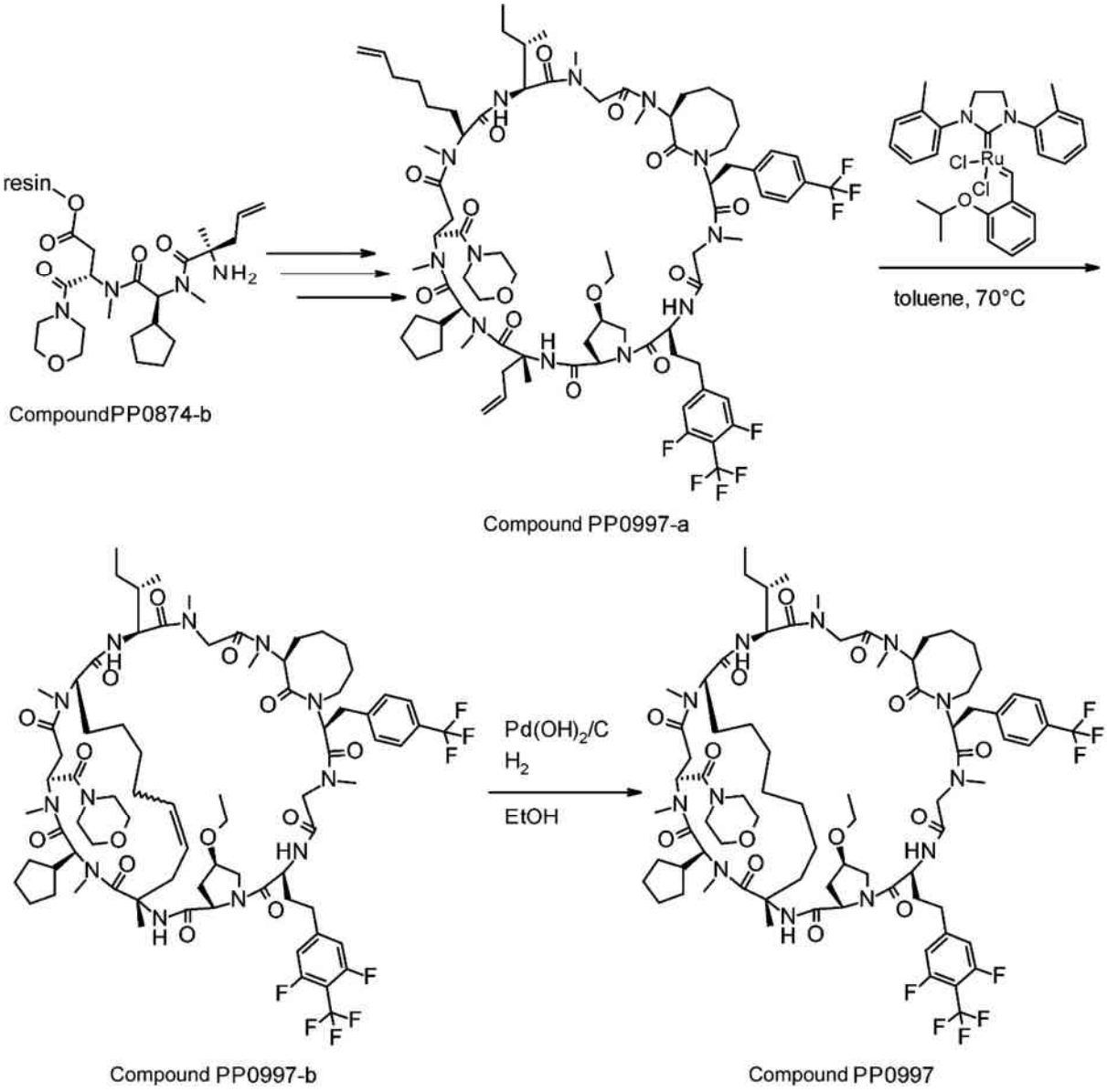
[1109]

Using, as a raw material, resin-supported synthesis intermediate PP0874-b of Compound PP0874 synthesized using Compound aa375-resin, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0993-a (10.6 mg). Using the resulting PP0993-a, PP0993-b was obtained in the same manner as synthesis of Compound PP0992-b, and then PP0993 (1.79 mg, 18%, 2 steps) was obtained in the same manner as synthesis of Compound PP0992. LC/MS data is provided in Table 36.

[1110]

Synthesis of Compound PP0997

Compound PP0997 was synthesized according to the following scheme.



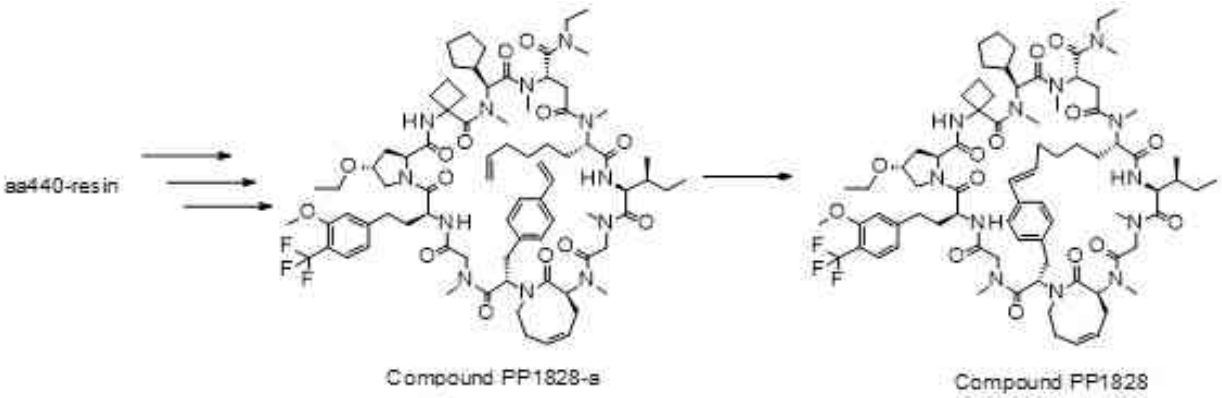
[1111]

Using, as a raw material, resin-supported synthesis intermediate PP0874-b of Compound PP0874 synthesized using Compound aa375-resin, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give Compound PP0997-a (9.5 mg). Using the resulting PP0997-a, PP0997-b was obtained in the same manner as synthesis of Compound PP0992-b. A half of this was reacted in the same manner as Compound PP0992, the other half was reacted using 10% palladium on carbon in place of palladium hydroxide, and the resulting compounds were combined to give PP0997 (1.56 mg, 31%, 2 steps). LC/MS data is provided in Table 36.

[1112]

Synthesis of Compound PP1828

Synthesis of PP1828 was carried out according to the following scheme.



[1113]

Using Compound aa440-resin (Fmoc-MeGly(cPent)-MeAsp(O-Trt(2-Cl)resin)-MeNEt) as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give Compound PP1828-a. Compound PP1828-a (10.9 mg, 7.28 μmol), 1,4-benzoquinone (3.6 mg, 33 μmol), and a Stewart-Grubbs catalyst (3.2 mg, 5.6 μmol) were dissolved in 1,4-dioxane (2.0 mL), and the mixture was stirred at 80°C for 1.5 hours in a nitrogen atmosphere. After being cooled to room temperature, the reaction solution was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give PP1828 (3.08 mg, 5.9%).

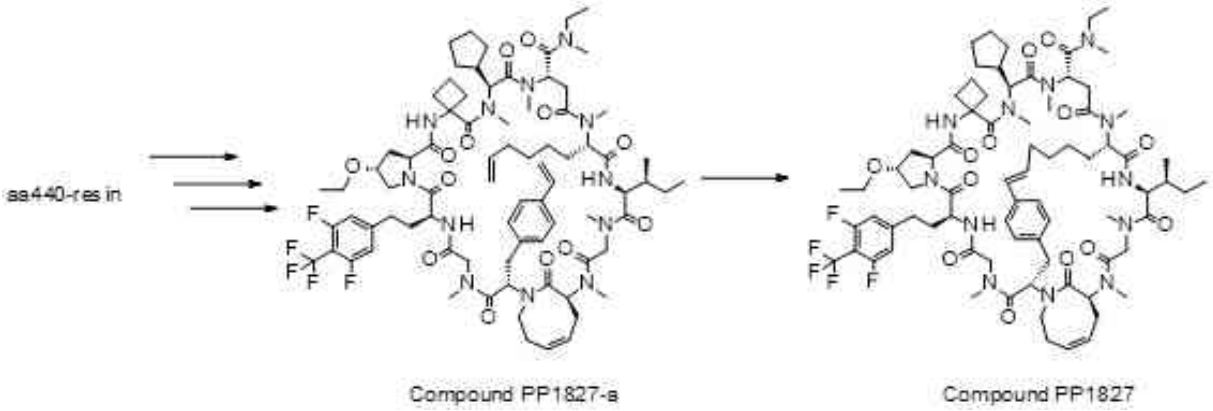
LCMS (ESI) m/z = 1498 (M+H)+

Retention time: 3.09 min (Analytical condition SQDFA05 long)

[1114]

Synthesis of Compound PP1827

Synthesis of PP1827 was carried out according to the following scheme.



[1115]

Using Compound aa440-resin (Fmoc-MeGly(cPent)-MeAsp(O-Trt(2-Cl)resin)-MeNEt) as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give Compound PP1827-a. The resulting

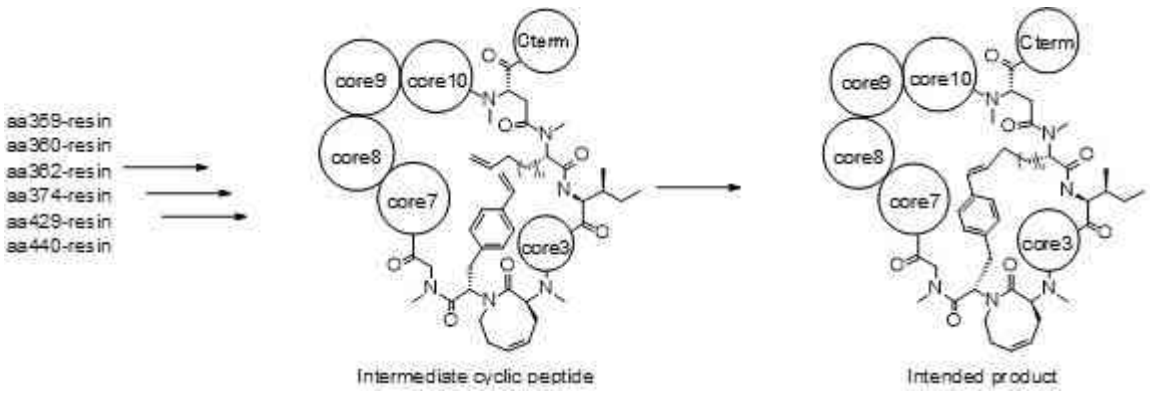
compound was divided into 3 containers, and subjected to the following experiments. Compound PP1827-a (2.6 mg, 1.7 μmol), 1,4-benzoquinone (1.1 mg, 10.2 μmol), and a Stewart-Grubbs catalyst (1.0 mg, 1.7 μmol) were dissolved in 1,4-dioxane (0.66 mL), and the mixture was stirred at 80°C for 2 hours in a nitrogen atmosphere and cooled to room temperature. Similarly, the entirety of a reaction solution obtained by stirring Compound PP1827-a (2.7 mg), the Stewart-Grubbs catalyst (1.0 mg, 1.7 μmol), and 1,4-dioxane (0.66 mL) which are other than 1,4-benzoquinone at 80°C for 2 hours and the entirety of a reaction solution obtained by stirring PP1827-a (1.6 mg), a Hoveyda-Grubbs first-generation catalyst (1.0 mg, 1.7 μmol), and 1,4-dioxane (0.66 mL) at 80°C for 2 hours were mixed, and concentrated under reduced pressure. The resulting crude product was purified by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution) to give PP1827 (2.1 mg, 3.9%).

LCMS (ESI) m/z = 1504 (M+H)+

Retention time: 3.17 min (Analytical condition SQDFA05 long)

[1116]

Using any of Compounds aa359-resin, aa360-resin, aa362-resin, aa374-resin, aa429-resin, and aa440-resin as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give a cyclic peptide as an intermediate. Using the resulting intermediate peptide, compounds shown in Table 29-2 were produced in the same manner as the synthesis of Compound PP1828 by reacting the side chain moiety of any of MeAlgly, MeAhxe(2), MeAhpe(2), MeAocte(2), and MeAnone(2) with the styrene moiety of ButenylPhe(4-CH=CH_2). Purification was carried out by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution or 0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water). The yield (amount/percentage) is provided in Table 29-3. LC/MS data are provided in Table 36.



[Table 29-2]

ID	core 1	core 2	core 3	core 4	core 5	core 6	core 7	core 8	core 9	core 10	core 11	Cterm
PP1829	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP1830	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP1831	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP1832	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP1833	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	MeNEt
PP1834	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	MeNEt
PP1835	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP1827	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	MeNEt
PP1828	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	MeNEt
PP2573	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pip
PP2574	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP2575	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP2576	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	pyrro
PP2577	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP2578	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pip
PP2579	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP2580	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP2581	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	pyrro
PP2583	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP2585	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP2586	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP2588	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP2589	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP2590	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	pip
PP2591	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	pyrro
PP2592	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP2593	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP2594	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(iPr)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP2595	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(iPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP2596	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(iPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP2597	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pip
PP2598	MeAhxe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP2600	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Pro	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP2601	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Pro	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP2602	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Pro	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP2603	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Pro	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP2604	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Pro	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	pyrro
PP2605	MeAocte(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal	MeNva(3-Et)	MeAsp2	NMe2
PP2952	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	pip
PP2953	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	pip
PP2954	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	pip
PP2955	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP2956	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal	MeNva(3-Et)	MeAsp2	pip
PP2957	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal	MeNva(3-Et)	MeAsp2	pyrro
PP2958	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	pip
PP2959	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP3039	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal	MeNva(3-Et)	MeAsp2	pip
PP3040	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal	MeNva(3-Et)	MeAsp2	pyrro
PP3041	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP3042	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	pip
PP3043	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	pyrro
PP3044	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP3045	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP3046	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal	MeNva(3-Et)	MeAsp2	pip
PP3047	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal	MeNva(3-Et)	MeAsp2	pyrro
PP3048	MeAnone(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP3049	MeAnone(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	pyrro
PP3050	MeAnone(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP3051	MeAnone(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal	MeNva(3-Et)	MeAsp2	pip
PP3052	MeAnone(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal	MeNva(3-Et)	MeAsp2	pyrro
PP3053	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(cBu)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP3054	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(cPent)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP3055	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Pro	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	pip
PP3056	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3057	MeAnone(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3058	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(cBu)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3059	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	MecVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3060	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	MecVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3061	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	MecVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3062	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	MecVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2

[Table 29-3]

ID	yield (mg)	yield (%)
PP1829	2.52	4.7
PP1830	2.28	4.3
PP1831	3.09	4.4
PP1832	3.98	5.7
PP1833	3.35	6.4
PP1834	3.23	6.2
PP1835	3.14	5.9
PP1827	2.05	3.9
PP1828	3.08	5.9
PP2573	3.02	22.8
PP2574	3.58	21.1
PP2575	2.56	15.7
PP2576	2.59	16.4
PP2577	4.75	22.3
PP2578	2.28	24.3
PP2579	2.53	27.1
PP2580	2.52	21.9
PP2581	2.73	19.3
PP2583	4.13	23.8
PP2585	4.08	25.8
PP2586	4.11	28.6
PP2588	4.19	27.0
PP2589	4.29	29.0
PP2590	4.31	27.2
PP2591	5.01	27.5
PP2592	4.22	19.0
PP2593	3.09	20.0
PP2594	2.54	19.9
PP2595	4.04	21.0
PP2596	3.5	22.6
PP2597	3.97	29.8
PP2598	0.34	1.4
PP2600	2.37	15.6
PP2601	4.56	18.8
PP2602	3.8	19.6
PP2603	2.53	17.9
PP2604	3.15	16.3
PP2605	4.19	22.2
PP2952	6.42	31.1
PP2953	3.93	21.0
PP2954	9.73	43.1
PP2955	6.03	34.1
PP2956	7.18	40.6
PP2957	7.05	31.2
PP2958	8.50	45.6
PP2959	5.12	34.8
PP3039	3.32	21.3
PP3040	7.15	37.1
PP3041	4.79	16.4
PP3042	2.94	13.6
PP3043	3.39	14.2
PP3044	4.32	21.3
PP3045	4.16	24.4
PP3046	5.42	33.0
PP3047	6.08	27.7
PP3048	2.17	10.6
PP3049	5.46	19.9
PP3050	2.02	12.3
PP3051	3.63	20.9
PP3052	3.14	14.6
PP3053	8.21	27.7
PP3054	8.66	26.6
PP3055	3.91	20.4
PP3056	4.48	15.6
PP3057	4.44	14.7
PP3058	8.67	27.3
PP3059	5.34	41.3
PP3060	4.82	44.4
PP3061	6.7	48.5
PP3062	9.35	36.8

[1117]

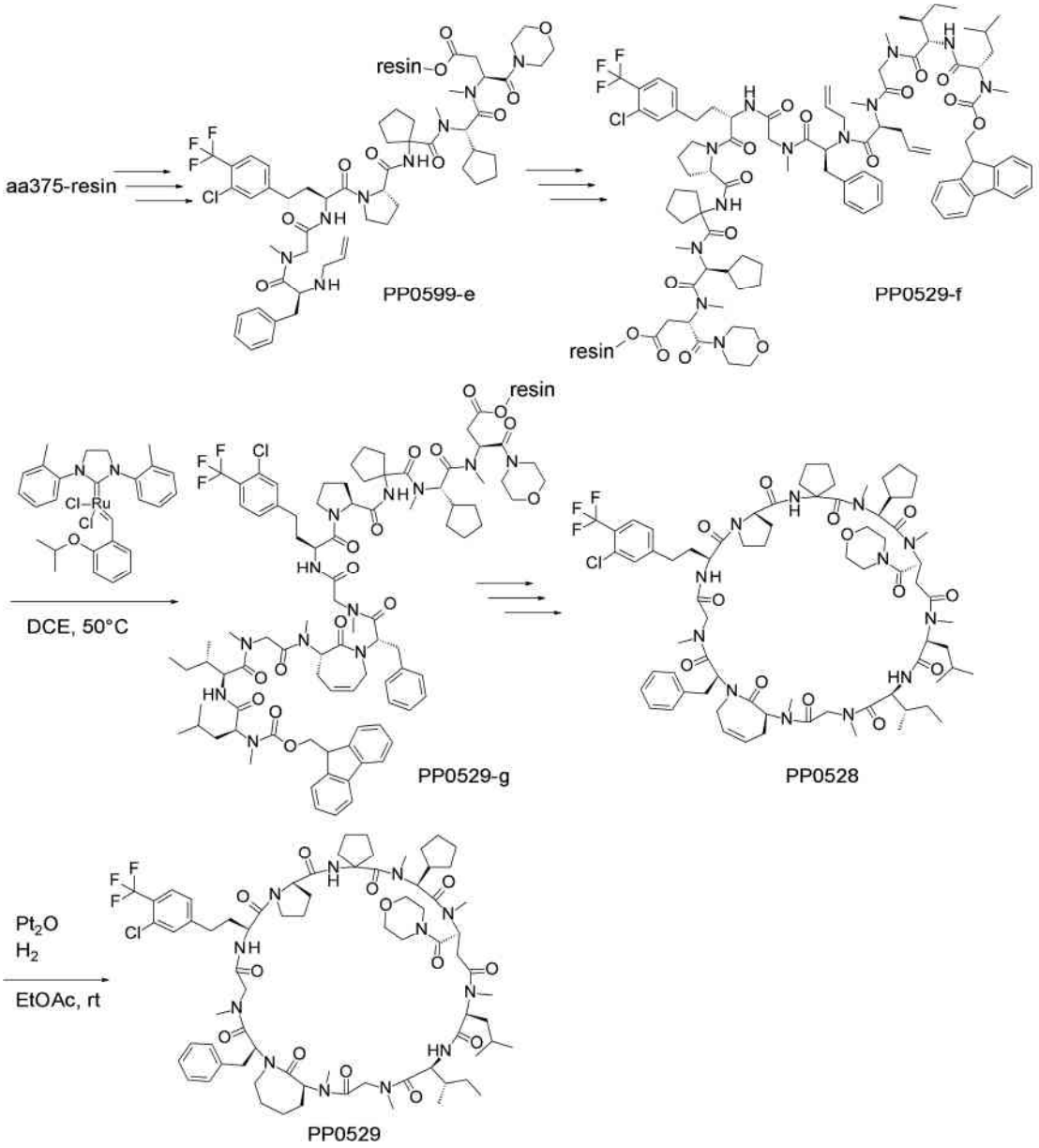
Concerning the double bonds contained in the crosslinked ring of R_1 to R_5 in PP1827, PP2583, PP2952, PP2954, PP2957, PP2958, PP3040, PP3046, PP3047, PP3049, PP3053, PP3054, PP3056, PP3057, PP3058, PP3059, PP3060, PP3061, and PP3062, the coupling constant between the protons bonded to the respective carbon atoms on the double bonds was observed at 15.0 to 16.4 Hz, and thus the double bonds were all identified as having an E structure. Further, concerning PP1828, PP1829, PP1830, PP1831, PP1832, PP1833, PP1834, PP1835, PP2573, PP2574, PP2575, PP2576, PP2577, PP2578, PP2579, PP2580, PP2581, PP2586, PP2588, PP2589, PP2590, PP2591, PP2592, PP2593, PP2594, PP2595, PP2596, PP2597, PP2598, PP2600, PP2601, PP2602, PP2603, PP2604, PP2605, PP2953, PP2955, PP2956, PP2959, PP3039, PP3044, PP3045, PP3048, PP3050, PP3051, PP3052, and PP3055, which have a similar ring structure, the double bonds are inferred as having an E structure.

[1118]

1-6-6. Peptide synthesis via N-alkylation by Mitsunobu reaction on resin and olefin metathesis reaction on resin

Synthesis of Compounds PP0528 and PP0529

Compounds PP0528 and PP0529 were synthesized according to the following scheme.



[1119]

Using, as a raw material, synthesis intermediate PP0599-e of Compound PP0599 synthesized using Compound aa375-resin, peptide elongation was performed according to the basic route to give resin-supported PP0529-f.

[1120]

Compound PP0529-f-resin (100 mg, 0.45 mmol/g, 0.045 mmol) and DCM were added to a filter-equipped reaction vessel to swell the resin, DCM was removed, and then the resin was washed 4 times with DCE. A DCE (1.5 mL) solution of a Stewart-Grubbs catalyst (5.13 mg, 0.009 mmol) was added thereto, and the mixture was shaken at 50°C for 21 hours. Then, the reaction solution was removed, and the resin was washed 4 times with DCE and then washed 4 times with DCM to give resin-supported Compound PP0529-g. Cleaving from the resin was

performed with TFE/DCM (1/1) using a small amount of resin-supported Compound PP0529-g, and the structure was verified by LC/MS.

LCMS (ESI) m/z = 1702 (M+H)+

Retention time: 3.74 min (Analytical condition SQDFA50_2)

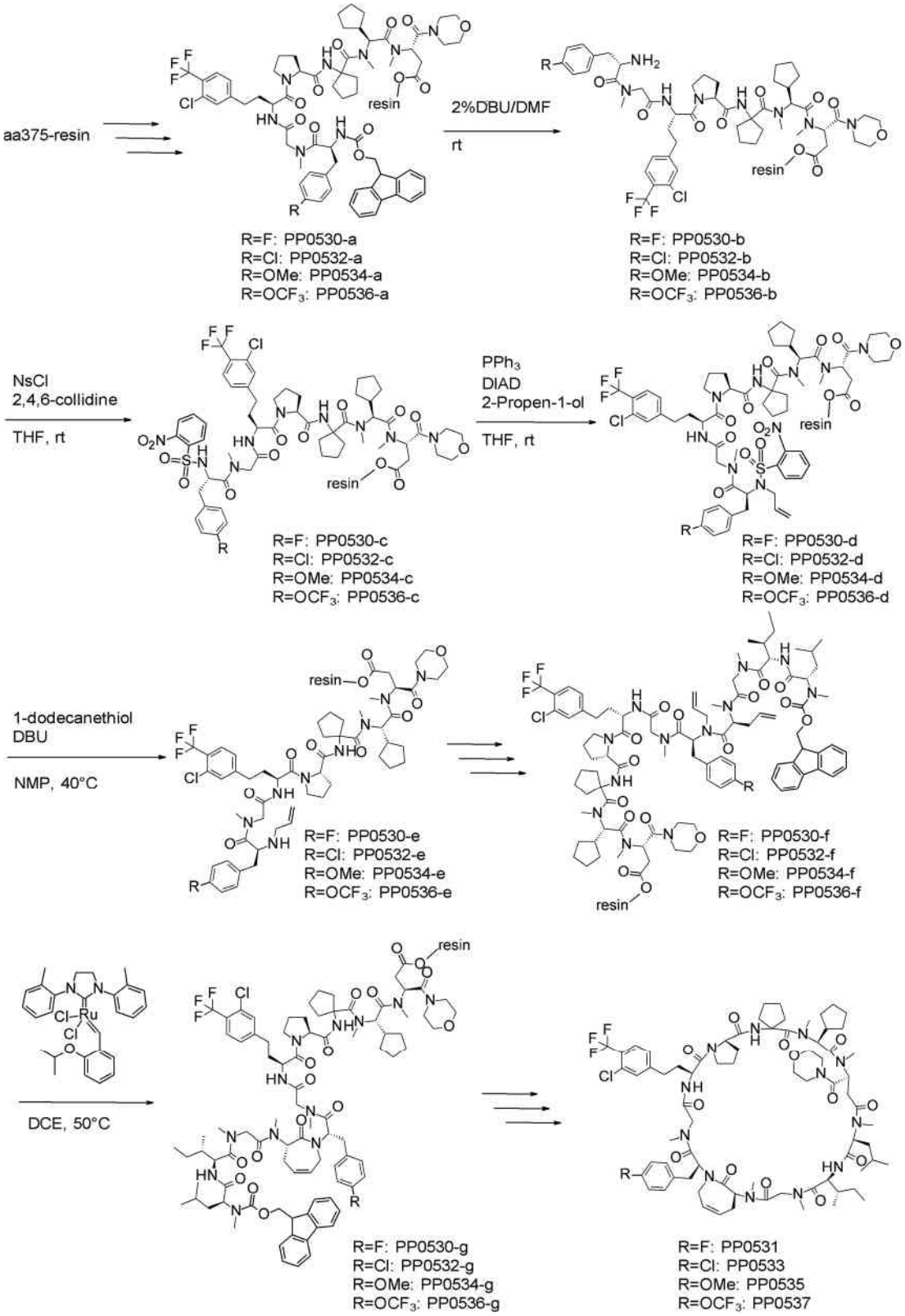
[1121]

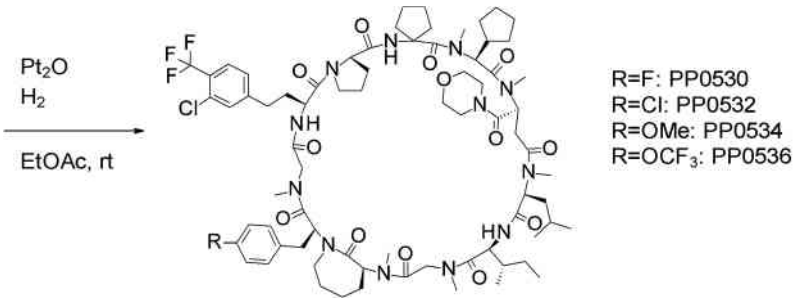
Subsequent steps of cleaving from resin, cyclization, and purification were performed according to the basic route to give Compound PP0528 (6.9 mg). LC/MS data is provided in Table 36. Moreover, a separately synthesized Compound PP0528 (132 mg, 0.09 mmol) at a crude product stage was dissolved in ethyl acetate (1 mL), platinum(IV) oxide (10.2 mg, 0.045 mmol) was added, and the mixture was stirred at room temperature for 15 hours in a hydrogen atmosphere. Platinum(IV) oxide (5.1 mg, 0.0225 mmol) was added, the mixture was stirred at room temperature in a hydrogen atmosphere for 5 more hours, then platinum(IV) oxide was filtered off, and the solvent was distilled off under reduced pressure. This was purified by reverse phase chromatography (methanol/10 mM aqueous ammonium acetate solution) to give PP0529 (9.8 mg). LC/MS data is provided in Table 36.

[1122]

Synthesis of Compounds PP0530 to PP0537

Compounds PP0530 to PP0537 were synthesized according to the following scheme.


aa375-resin
2%DBU/DMF
rt
resin
R=F: PP0530-a
R=Cl: PP0532-a
R=OMe: PP0534-a
R=OCF3: PP0536-a
R=F: PP0530-b
R=Cl: PP0532-b
R=OMe: PP0534-b
R=OCF3: PP0536-b
NsCl
2,4,6-collidine
THF, rt
PPh3
DIAD
2-Propen-1-ol
THF, rt
R=F: PP0530-c
R=Cl: PP0532-c
R=OMe: PP0534-c
R=OCF3: PP0536-c
R=F: PP0530-d
R=Cl: PP0532-d
R=OMe: PP0534-d
R=OCF3: PP0536-d
1-dodecanethiol
DBU
NMP, 40°C
R=F: PP0530-e
R=Cl: PP0532-e
R=OMe: PP0534-e
R=OCF3: PP0536-e
R=F: PP0530-f
R=Cl: PP0532-f
R=OMe: PP0534-f
R=OCF3: PP0536-f
DCE, 50°C
R=F: PP0530-g
R=Cl: PP0532-g
R=OMe: PP0534-g
R=OCF3: PP0536-g
R=F: PP0531
R=Cl: PP0533
R=OMe: PP0535
R=OCF3: PP0537



[1123]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported Compound PP0530-a, Compound PP0532-a, Compound PP0534-a, and Compound PP0536-a.

[1124]

After resin-supported Compound PP0530-b, Compound PP0532-b, Compound PP0534-b, and Compound PP0536-b were obtained in the same manner as synthesis of Compound PP0055-b, resin-supported Compound PP0530-c, Compound PP0532-c, Compound PP0534-c, and Compound PP0536-c were obtained in the same manner as synthesis of Compound PP0055-c using THF in place of NMP as a reaction solvent. After resin-supported Compound PP0530-d, Compound PP0532-d, Compound PP0534-d, and Compound PP0536-d were obtained in the same manner as Compound PP0524-d by reacting 2-propen-1-ol in place of 3-fluoropropan-1-ol, resin-supported Compound PP0530-e, Compound PP0532-e, Compound PP0534-e, and Compound PP0536-e were obtained in the same manner as synthesis of Compound PP0055-e. Subsequent peptide elongation was performed according to the basic route to give resin-supported Compound PP0530-f, Compound PP0532-f, Compound PP0534-f, and Compound PP0536-f. In the same manner as Compound PP0529-g, resin-supported Compound PP0530-g, Compound PP0532-g, Compound PP0534-g, and Compound PP0536-g were obtained.

[1125]

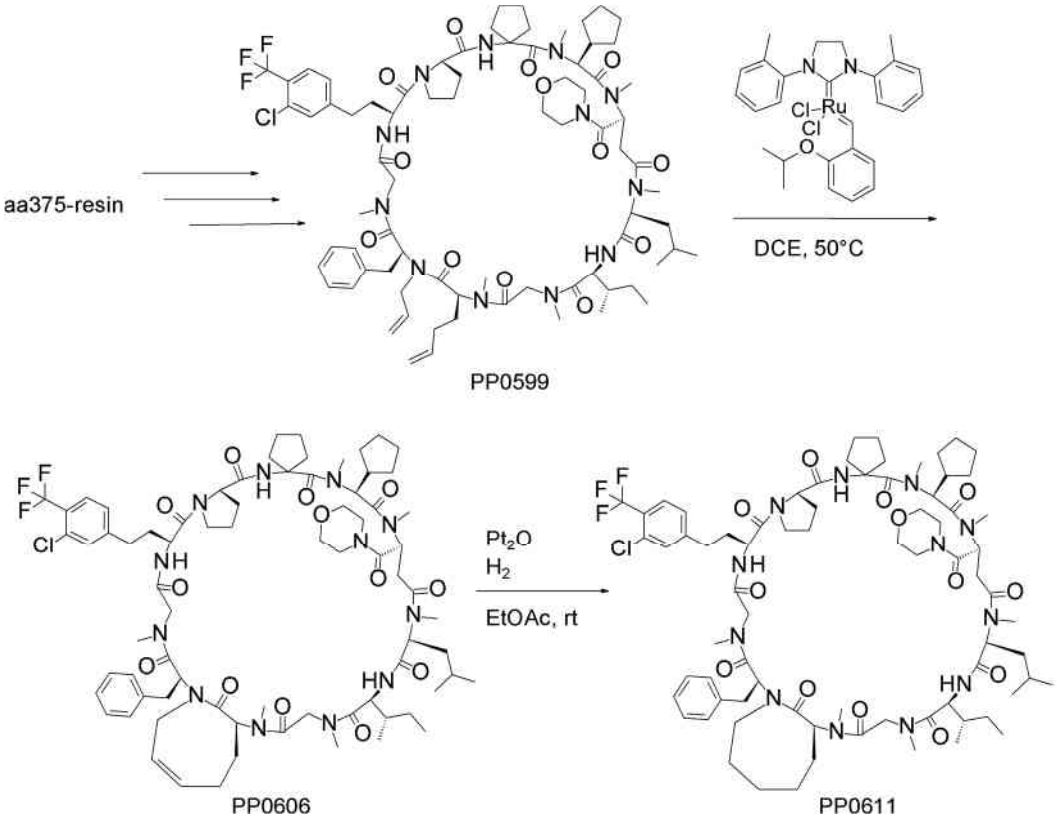
Subsequent steps of cleaving from resin, cyclization, and purification were performed according to the basic route to give Compound PP0531, Compound PP0533, Compound PP0535, and Compound PP0537. LC/MS data is provided in Table 36. Moreover, using separately synthesized Compound PP0531, Compound PP0533, Compound PP0535, and Compound PP0537 that were at a crude product stage, Compound PP0530, Compound PP0532, Compound PP0534, and Compound PP0536 were obtained in the same manner as Compound PP0529. LC/MS data is provided in Table 36.

[1126]

<u>1-6-7. Peptide synthesis via N-alkylation by Mitsunobu reaction on resin and olefin metathesis reaction</u>

Synthesis of Compounds PP0606 and PP0611

Compounds PP0606 and PP0611 were synthesized according to the following scheme.



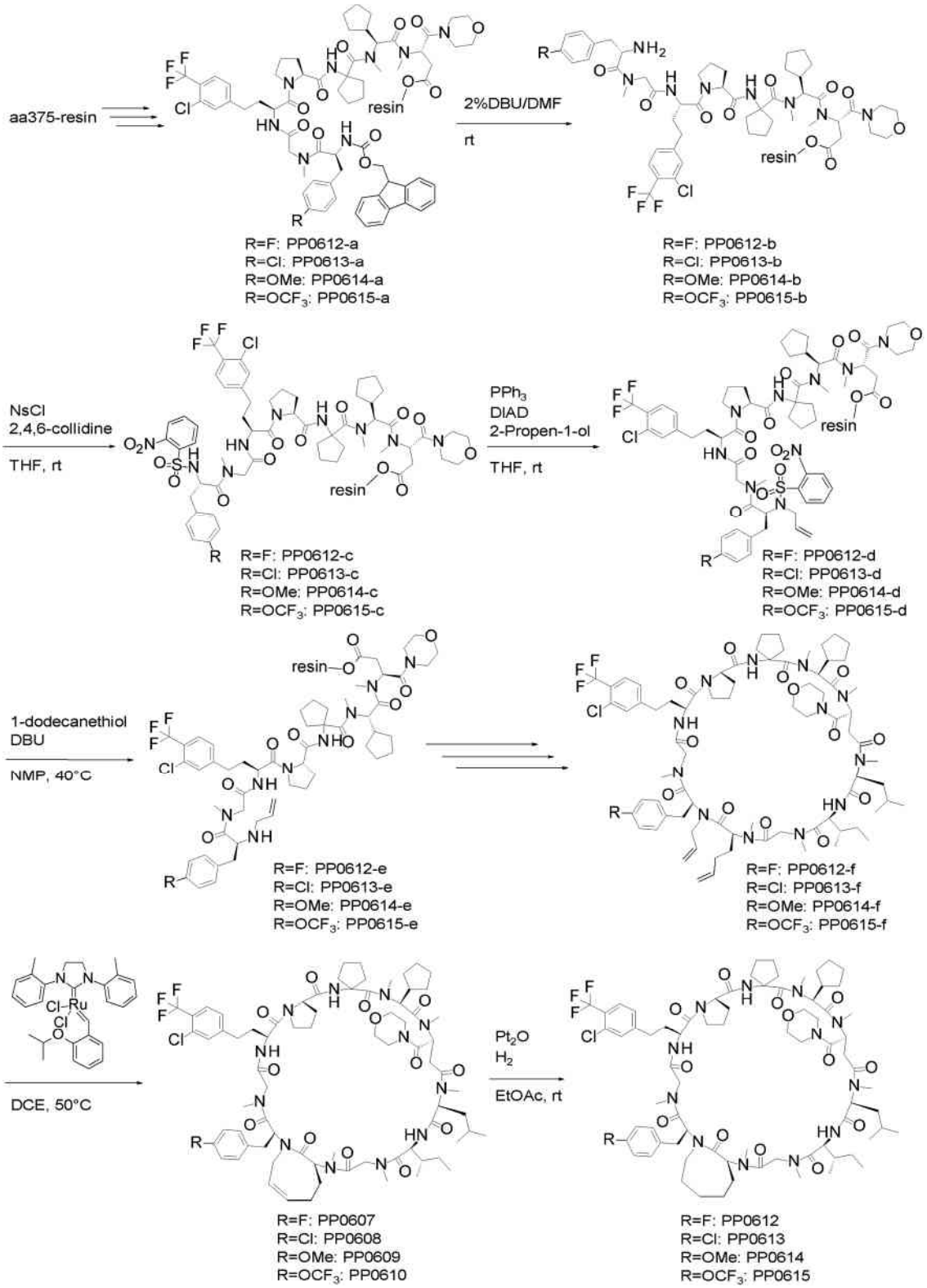
[1127]

PP0599 (25 mg, 0.017 mmol) obtained using Compound aa375-resin as a raw material and a Stewart-Grubbs catalyst (2.4 mg, 0.0042 mmol) were dissolved in DCE (1.5 mL), and after a degassing operation, the mixture was stirred at 50°C for 16 hours in a nitrogen atmosphere. A Stewart-Grubbs catalyst (2.4 mg, 0.0042 mmol) was added, and after a degassing operation, the mixture was stirred for 20 more hours at 50°C in a nitrogen atmosphere, and then the solvent was distilled off under reduced pressure. This was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound PP0606 (4.1 mg, 17%). LC/MS data is provided in Table 36. Compound PP0606 (3.6 mg, 0.0024 mmol) was dissolved in ethyl acetate (1 mL), platinum(IV) oxide (0.28 mg, 0.0012 mmol) was added, and the mixture was stirred at room temperature for 5 hours in a hydrogen atmosphere. Platinum(IV) oxide was filtered off, and the solvent was distilled off under reduced pressure. The resulting crude product was purified by reverse phase chromatography (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give Compound PP0611 (1.9 mg, 53%). LC/MS data is provided in Table 36.

[1128]

Synthesis of Compounds PP0607 to 0610 and PP0612 to 0615

Compounds PP0607 to 0610 and PP0612 to 0615 were synthesized according to the following scheme.



[1129]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported Compound PP0612-a, Compound PP0613-a, Compound PP0614-a, and Compound PP0615-a.

[1130]

After resin-supported Compound PP0612-b, Compound PP0613-b, Compound PP0614-b, and Compound PP0615-b were obtained in the same manner as synthesis of Compound PP0055-b, resin-supported Compound PP0612-c, Compound PP0613-c, Compound PP0614-c, and Compound PP0615-c were obtained in the same manner as synthesis of Compound PP0055-c using THF in place of NMP as a reaction solvent. After resin-supported Compound PP0612-d, Compound PP0613-d, Compound PP0614-d, and Compound PP0615-d were obtained in the same manner as synthesis of Compound PP0524-d by reacting 2-propen-1-ol in place of 3-fluoropropan-1-ol, resin-supported Compound PP0612-e, Compound PP0613-e, Compound PP0614-e, and Compound PP0615-e were obtained in the same manner as synthesis of Compound PP0055-e.

Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give Compound PP0612-f, Compound PP0613-f, Compound PP0614-f, and Compound PP0615-f. Compound PP0607, Compound PP0608, Compound PP0609, and Compound PP0610 were obtained in the same manner as synthesis of Compound PP0606. Yields in amount and yields in percent are provided in Table 30. LC/MS data is provided in Table 36.

[1131]

[Table 30]

Raw material	Intended product	R	Yield	Yield
Compound 0612-f	Compound 0607	F	6.9 mg	28%
Compound 0613-f	Compound 0608	Cl	7.2 mg	29%
Compound 0614-f	Compound 0609	OMe	6.9 mg	28%
Compound 0615-f	Compound 0610	OCF_3	5.3 mg	20%

[1132]

Moreover, Compound PP0612, Compound PP0613, Compound PP0614, and Compound PP0615 were obtained in the same manner as synthesis of Compound PP0611. Yields in amount and yields in percent are provided in Table 31. LC/MS data is provided in Table 36.

[1133]

[Table 31]

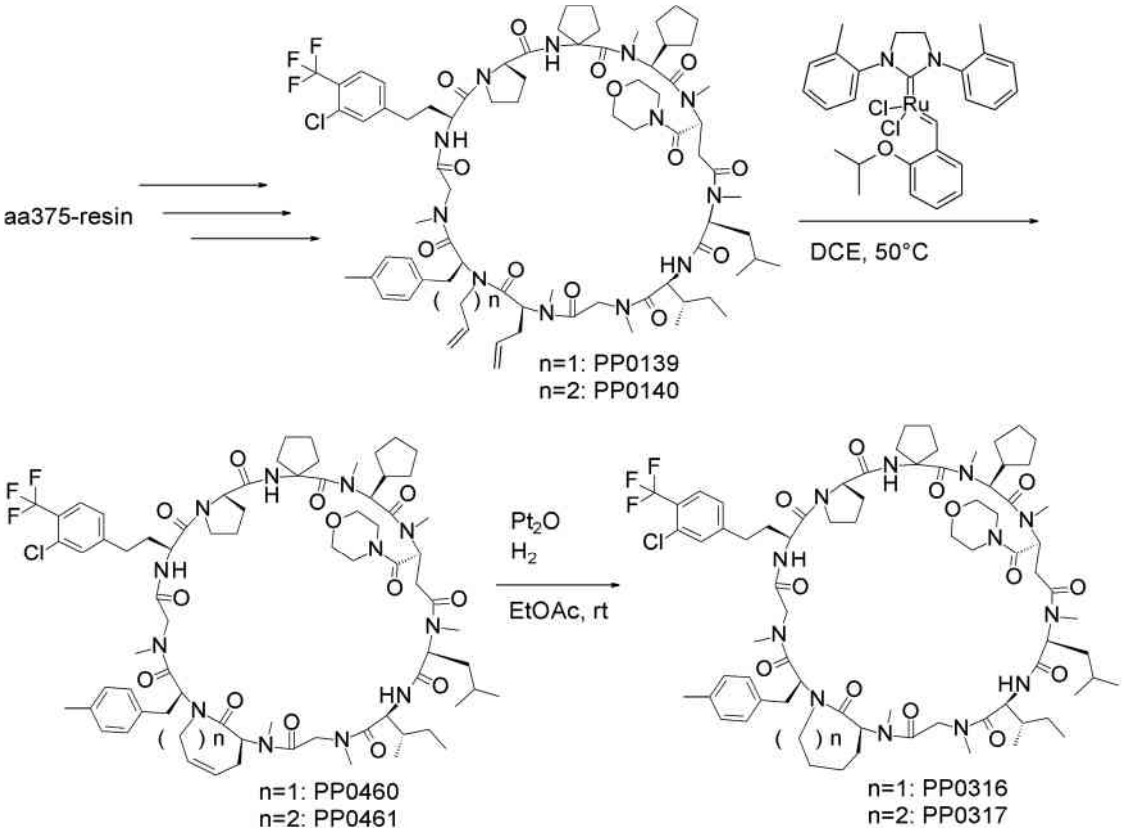
Raw material	Intended product	R	Yield	Yield

Compound 0607	Compound 0612	F	6.4 mg	100%
Compound 0608	Compound 0613	Cl	6.6 mg	98%
Compound 0609	Compound 0614	OMe	5.8 mg	91%
Compound 0610	Compound 0615	OCF_3	2.6 mg	54%

[1134]

Synthesis of Compound PP0316, Compound PP0317, Compound PP0460, and Compound PP0461

Compound PP0316, Compound PP0317, Compound PP0460, and Compound PP0461 were synthesized according to the following scheme.



[1135]

Using PP0139 and PP140 obtained from Compound aa375-resin as a raw material, Compound PP0460 and Compound PP0461 were obtained in the same manner as synthesis of Compound PP0606. Yields in amount and yields in percent are provided in Table 32. LC/MS data is provided in Table 36.

[1136]

[Table 32]

Raw material	Intended product	n	Yield	Yield
Compound 0139	Compound 0460	1	80 mg	58%

Compound 0140	Compound 0461	2	32 mg	24%

Moreover, Compound PP0316 and Compound PP0317 were obtained in the same manner as synthesis of Compound PP0611. Yields in amount and yields in percent are provided in Table 33. LC/MS data is provided in Table 36.

[1137]

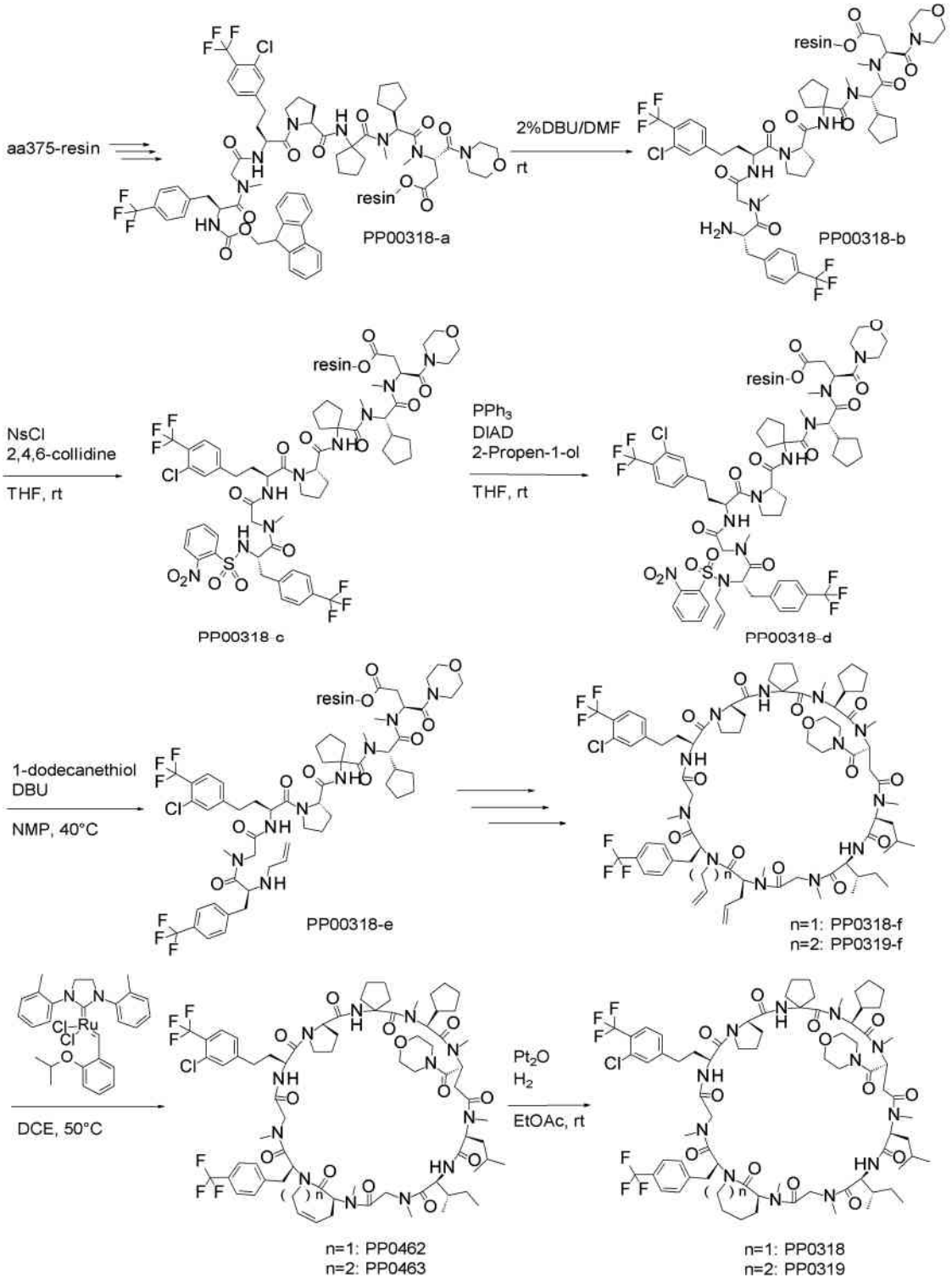
[Table 33]

Raw material	Intended product	n	Yield	Yield
Compound 0460	Compound 0316	1	60 mg	80%
Compound 0461	Compound 0317	2	18 mg	64%

[1138]

Synthesis of Compound PP0318, Compound PP0319, Compound PP0462, and Compound PP0463

Compound PP0318, Compound PP0319, Compound PP0462, and Compound PP0463 were synthesized according to the following scheme.



[1139]

Using Compound aa375-resin as a raw material, peptide synthesis by the basic peptide synthesis method described in the present Examples was performed to give resin-supported Compound PP0318-a.

[1140]

After resin-supported Compound PP0318-b was obtained in the same manner as synthesis of Compound PP0055-b, resin-supported Compound PP0318-c was obtained in the same manner as synthesis of Compound PP0055-c using THF in place of NMP as a reaction solvent. After resin-supported Compound PP0318-d was obtained in the same manner as synthesis of Compound PP0524-d by reacting 2-propen-1-ol in place of 3-fluoropropan-1-ol, resin-supported Compound PP0318-e was obtained in the same manner as synthesis of Compound PP0055-e.

[1141]

Subsequent steps of peptide elongation, cleaving from resin, cyclization, and purification were performed according to the basic route to give Compound PP0318-f and Compound PP0319-f. Compound PP0462 and Compound PP0463 were obtained in the same manner as synthesis of Compound PP0606. Yields in amount and yields in percent are provided in Table 34. LC/MS data is provided in Table 36.

[1142]

[Table 34]

Raw material	Intended product	n	Yield	Yield
Compound 0318-f	Compound 0462	1	59 mg	76%
Compound 0319-f	Compound 0463	2	18 mg	23%

[1143]

Moreover, Compound PP0318 and Compound PP0319 were obtained in the same manner as synthesis of Compound PP0611. Yields in amount and yields in percent are provided in Table 35. LC/MS data is provided in Table 36.

[1144]

[Table 35]

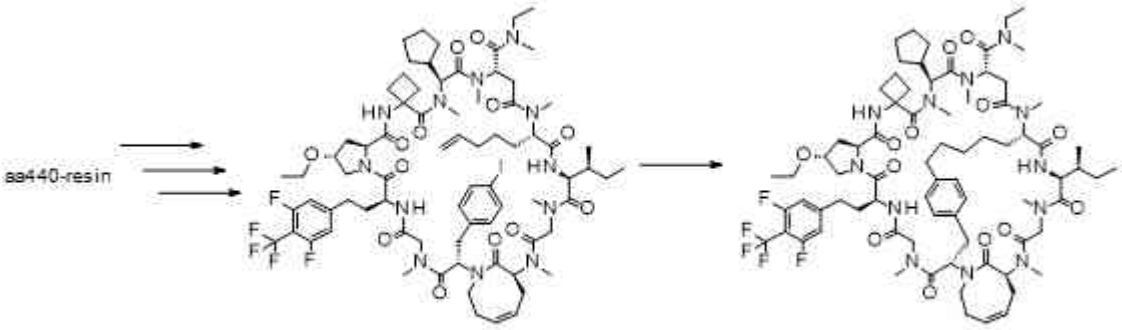
Raw material	Intended product	n	Yield	Yield
Compound 0462	Compound 0318	1	46 mg	81%
Compound 0463	Compound 0319	2	10 mg	65%

[1145]

1-6-8. Peptide modification by hydroboration reaction and Suzuki coupling

[1146]

Synthesis of Compound PP2117



Compound PP2117-a　　Compound PP2117

Using Compound aa440-resin (Fmoc-MeGly(cPent)-MeAsp(O-Trt(2-Cl)resin)-MeNEt) as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give Compound PP2117-a. A THF solution of 9-BBN (0.5 M, 240 μL, 120 μmol) was added to Compound PP2117-a (12.4 mg, 7.67 μmol), and the mixture was stirred for 1.5 hours in a nitrogen atmosphere. The resulting reaction solution was diluted with THF (500 μL), then water (4 μL, 222 μmol), cataCXium A Pd G4 (CAS No. 2230788-67-5, 2.7 mg, 3.64 μmol), and 2-tert-butyl-1,1,3,3-tetramethylguanidine (131 μL, 110 μmol) were added, and the mixture was stirred at 60°C for 1 hour in a nitrogen atmosphere. After being cooled to room temperature, the reaction solution was halved, either a 2% aqueous N-acetylcysteine solution (100 μL) or a 10% aqueous dithiothreitol solution (100 μL) was added, the mixture was stirred for 1 hour, the reaction solution was purified twice by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution, then 0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water), and the fractions were combined to give PP2117 (3.2 mg, 6.1%).

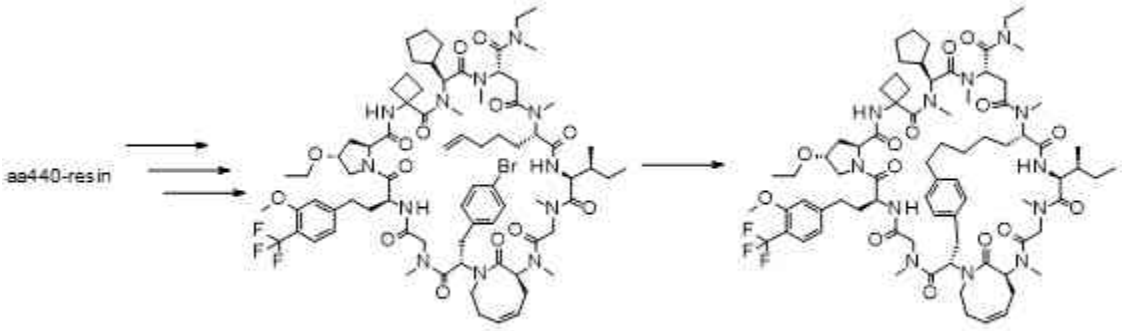
LCMS (ESI) m/z = 1492 (M+H)+

Retention time: 0.56 min (Analytical condition SQDFA50)

[1147]

Synthesis of Compound PP2118

Synthesis of PP2118 was carried out according to the following scheme.



Compound PP2118-a　　Compound PP2218

[1148]

Using Compound aa440-resin (Fmoc-MeGly(cPent)-MeAsp(O-Trt(2-Cl)resin)-MeNEt) as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give Compound PP2118-a. A THF solution of 9-BBN (0.5 M, 240 μL, 120 μmol) was added to Compound PP2118-a (12.1 mg, 7.70 μmol), and the mixture was stirred for 1.5 hours in a nitrogen atmosphere. The resulting reaction solution was diluted with THF (500 μL), then water (4 μL, 222 μmol), cataCXium Pd G4 (CAS No. 2230788-67-5, 2.7 mg, 3.64 μmol), and 2-tert-butyl-1,1,3,3-tetramethylguanidine (131 μL, 110 μmol) were added, and the mixture was stirred at 60°C for 1 hour in a nitrogen atmosphere. After being cooled to room temperature, the reaction solution was halved, either a 2% aqueous N-acetylcysteine solution (100 μL) or a 10% aqueous dithiothreitol solution (100 μL) was added, the mixture was stirred for 1 hour, the reaction solution was purified twice by reverse phase HPLC (methanol/50 mM aqueous ammonium acetate solution, then 0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water), and the fractions were combined to give PP2118 (3.2 mg, 6.1%).

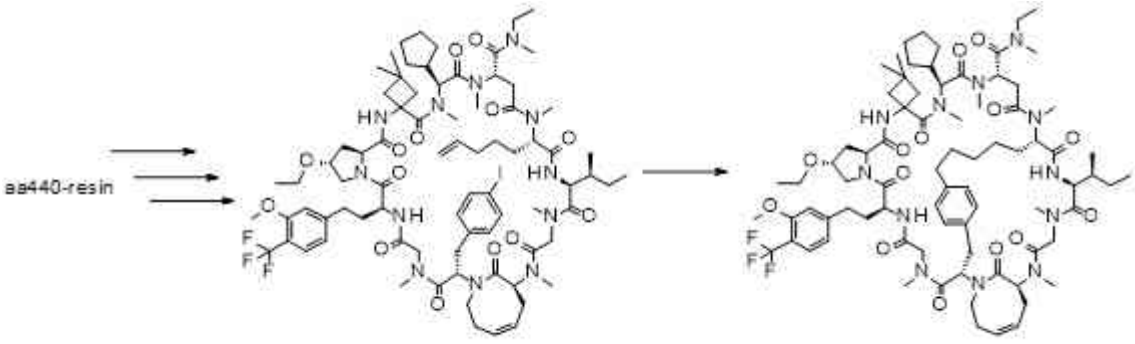
LCMS (ESI) m/z = 1486 (M+H)+

Retention time: 0.53 min (Analytical condition SQDFA50)

[1149]

Synthesis of Compound PP2259

Synthesis of PP2259 was carried out according to the following scheme.



[1150]

Using Compound aa440-resin (Fmoc-MeGly(cPent)-MeAsp(O-Trt(2-Cl)resin)-MeNEt) as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give Compound PP2259-a. The resulting compound was azeotroped twice with toluene (1 mL). A THF solution of 9-BBN (0.1 M, 137 μL, 137 μmol, 2 eq) was added to Compound PP2259-a (11.2 mg, 6.83 μmol) azeotroped with toluene, and the mixture was stirred for 1 hour in a nitrogen atmosphere. The resulting reaction solution was diluted with THF (500 μL), then water (4 μL, 222 μmol, 30 eq), [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium (2.3 mg, 3.5 μmol, 0.5 eq), and 2-tert-butyl-1,1,3,3-

tetramethylguanidine (13 μL, 110 μmol, 15 eq) were added, and the mixture was stirred at 60°C for 1 hour in a nitrogen atmosphere. After the mixture was cooled to room temperature, a 2% aqueous N-acetylcysteine solution (200 μL) was added, the mixture was stirred for 1 hour, then the reaction solution was purified by reverse phase HPLC (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give PP2259 (4.2 mg, 7.9%).

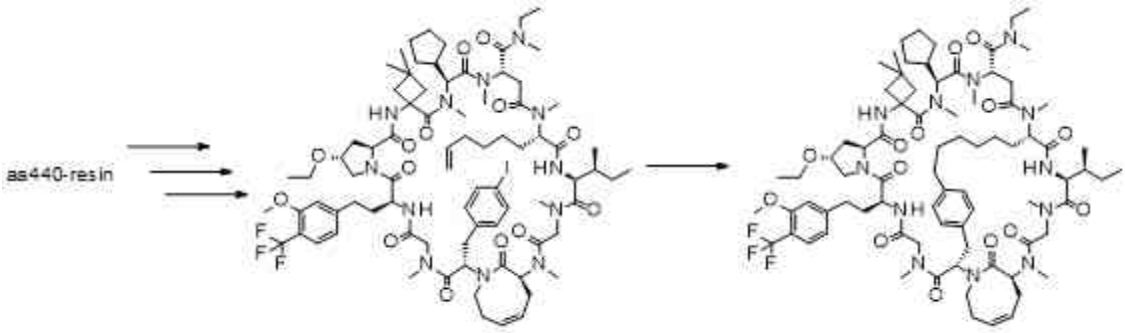
LCMS (ESI) m/z = 1514 (M+H)+

Retention time: 0.62 min (Analytical condition SQDFA50)

[1151]

Synthesis of Compound PP2260

Synthesis of PP2260 was carried out according to the following scheme.



[1152]

Using Compound aa440-resin (Fmoc-MeGly(cPent)-MeAsp(O-Trt(2-Cl)resin)-MeNEt) as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give Compound PP2260-a. The resulting compound was azeotroped twice with toluene (1 mL). A THF solution of 9-BBN (0.1 M, 143 μL, 143 μmol, 2 eq) was added to Compound PP2260-a (11.8 mg, 7.14 μmol) azeotroped with toluene, and the mixture was stirred for 1 hour in a nitrogen atmosphere. The resulting reaction solution was diluted with THF (500 μL), then water (4 μL, 222 μmol, 30 eq), cataCXium Pd G4 (CAS No. 2230788-67-5, 2.7 mg, 3.6 μmol, 0.5 eq), and 2-tert-butyl-1,1,3,3-tetramethylguanidine (13 μL, 110 μmol, 15 eq) were added, and the mixture was stirred at 60°C for 1 hour in a nitrogen atmosphere. After the mixture was cooled to room temperature, a 10% aqueous dithiothreitol solution (200 μL) was added, the mixture was stirred for 1 hour, the reaction solution was purified by reverse phase HPLC (0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water) to give PP2260 (4.1 mg, 7.6%).

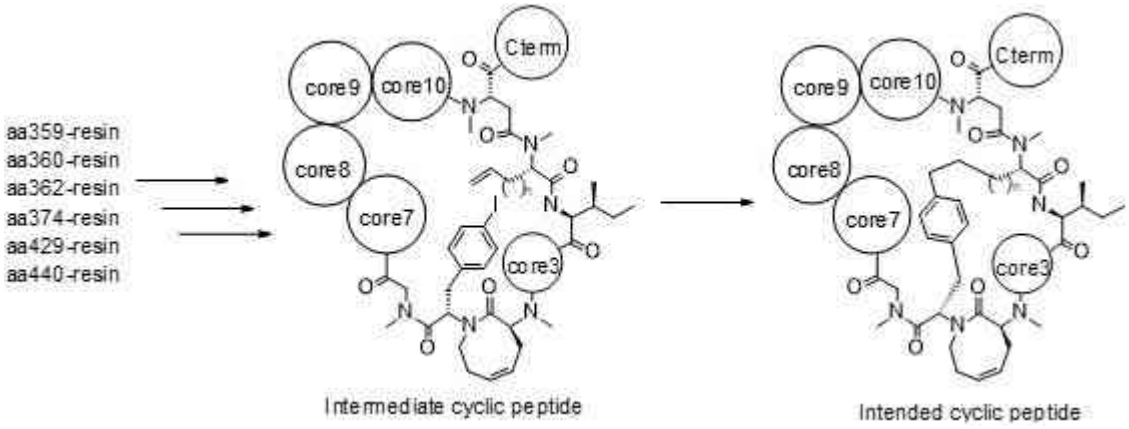
LCMS (ESI) m/z = 1528 (M+H)+

Retention time: 0.67 min (Analytical condition SQDFA50)

[1153]

Using any of Compounds aa359-resin, aa360-resin, aa362-resin, aa374-resin, aa429-resin, and aa440-resin as a raw material, peptide synthesis was carried out by the basic peptide synthesis method described in the present Examples to give a cyclic peptide as an intermediate. Using the resulting intermediate peptide, compounds shown in Table 35-1 were produced in the same manner as the synthesis of Compound PP2259 by reacting the side chain moiety of any of MeAlgly, MeAhxe(2), MeAhpe(2), MeAocte(2), and MeAnone(2) with the iodide moiety of ButenylPhe(4-I). Purification was carried out by reverse phase HPLC purification (methanol/50 mM aqueous ammonium acetate solution or 0.1% formic acid-containing acetonitrile/0.1% formic acid-containing distilled water, or both if necessary). The intended product and the yield (amount/percentage) are provided in Table 35-2. LC/MS data are provided in Table 36.

[1154]



[Table 35-1]

ID	1	2	3	4	5	6	7	8	9	10	11	Cterm
PP2117	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	MeNEt
PP2118	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	MeNEt
PP2259	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP2260	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP2261	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	NMe2
PP2262	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	NMe2
PP2263	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	MeNEt
PP2264	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	NMe2
PP2265	MeAnone(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-35-F2)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	MeNEt
PP2266	MeAnone(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP2267	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3032	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP3033	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal	MeGly(cPent)	MeAsp2	pip
PP3034	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP3035	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP3036	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pip
PP3037	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP3038	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(nPr)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP3063	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(nPr)	cVal(3-Me2)	MeNva(3-Et)	MeAsp2	NMe2
PP3064	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(nPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pip
PP3065	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(nPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro
PP3066	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3067	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(iPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3068	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(cBu)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3069	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Pro(4-cPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3070	MeAocte(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3071	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3072	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(iPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3073	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(cBu)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3074	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Pro(4-cPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3075	MeAhpe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3076	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3077	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(nPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3078	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(iPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3079	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(cBu)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3080	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(cPent)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3081	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Pro(4-cPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3082	MeAhxe(2)	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(nPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3083	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(nPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3084	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(iPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3085	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(cBu)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3086	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(cPent)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3087	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Pro(4-cPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3088	MeAlgly	Ile	cPrGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(nPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3089	MeAlgly	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(nPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	MeNEt
PP3090	MeAocte(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	MecVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3091	MeAhpe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	MecVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3092	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(34-Cl2)	Hyp(nPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	NMe2
PP3093	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(Et)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pip
PP3094	MeAhxe(2)	Ile	MeGly	MeAlgly	ButenylPhe(4-CH-CH2)	MeGly	Hph(4-CF3-3-OMe)	Hyp(nPr)	cVal(3-Me2)	MeGly(cPent)	MeAsp2	pyrro

[Table 35-2]

ID	yield (mg)	yield (%)
PP2117	3.2	6.1
PP2118	3.2	6.1
PP2259	4.2	7.9
PP2260	4.1	7.6
PP2261	2.5	3.7
PP2262	2.9	4.3
PP2263	2.1	4.0
PP2264	2.7	4.0
PP2265	2.4	4.5
PP2266	3.5	6.5
PP2267	2.8	4.1
PP3032	2.15	11.4
PP3033	2.33	10.0
PP3034	3.70	15.4
PP3035	1.38	7.6
PP3036	2.12	9.3
PP3037	1.96	9.8
PP3038	2.38	12.9
PP3063	1.19	0.9
PP3064	1.87	1.2
PP3065	1.71	1.2
PP3066	2.81	2.6
PP3067	1.4	1.3
PP3068	0.89	0.8
PP3069	0.88	0.8
PP3070	3.74	3.4
PP3071	2.85	2.7
PP3072	5.48	5.1
PP3073	2.4	2.2
PP3074	2.76	2.6
PP3075	2.26	2.1
PP3076	1.99	1.9
PP3077	4.53	4.3
PP3078	2.22	2.2
PP3079	2.58	2.5
PP3080	2.02	1.9
PP3081	3.42	3.5
PP3082	2.56	2.4
PP3083	1.7	1.7
PP3084	1.6	1.6
PP3085	1.2	1.2
PP3086	1.98	1.9
PP3087	0.9	0.9
PP3088	1.55	1.5
PP3089	1.48	1.5
PP3090	2.18	1.6
PP3091	1.53	1.1
PP3092	1.51	1.5
PP3093	0.9	0.6
PP3094	0.4	0.3

[1155]

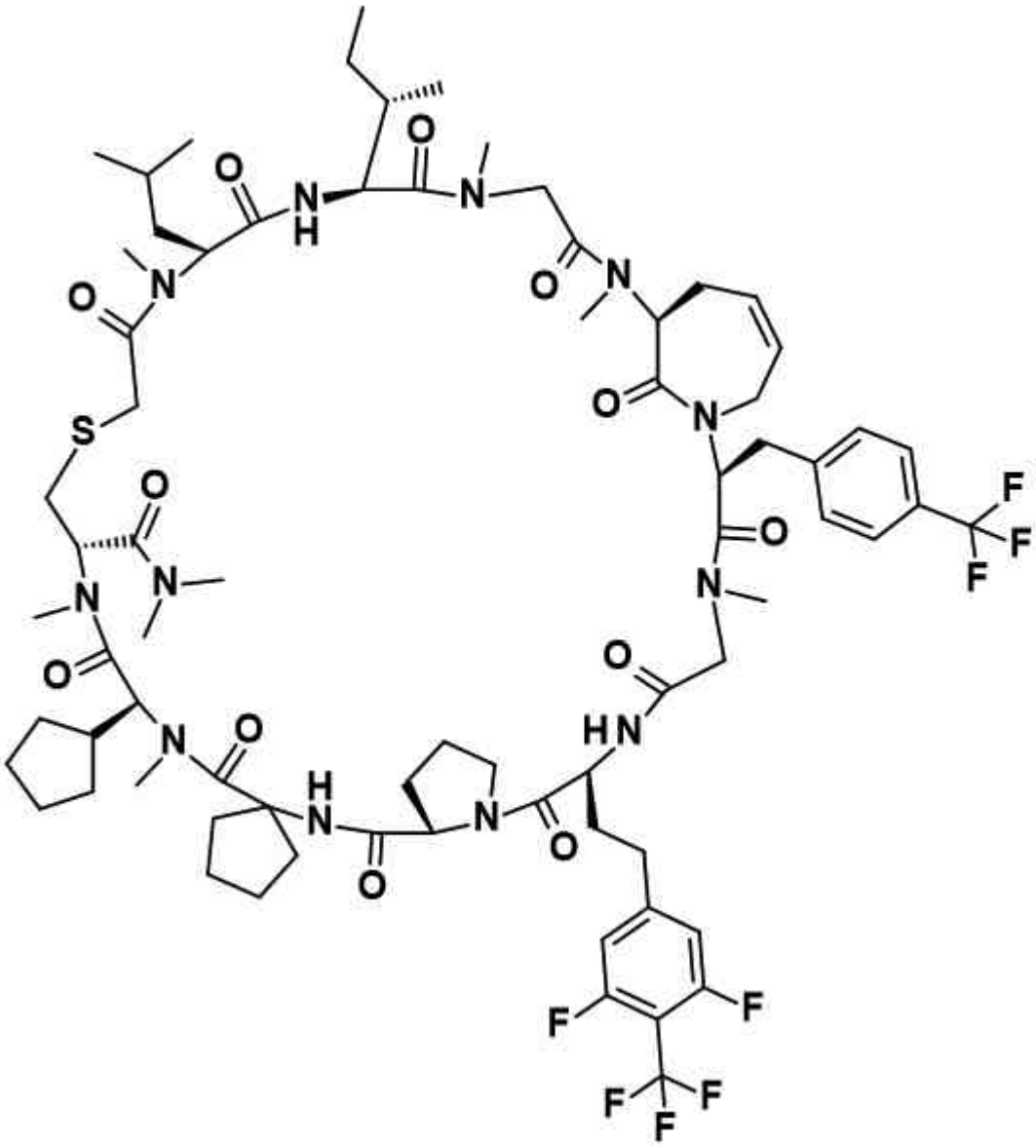
1-6-9. Synthesis of cyclic peptide having thioether group in main chain structure

Synthesis of Compound PP3108 and Compound PP3109

In the synthesis of Compound PP3108 and Compound PP3109, Compound aa439-resin (0.336 mmol/g, 100 mg) was used as a raw material, and Fmoc-MeGly(cPent)-OH, Fmoc-cLeu-OH, Fmoc-Pro-OH, Fmoc-Hph(4-CF3-35-F2)-OH, Fmoc-MeGly-OH, tp005, tp006, Fmoc-Ile-OH, and Fmoc-MeLeu-OH were used. A peptide elongation reaction by the basic Fmoc method described in the present Examples, cleaving of an elongated peptide from resin, cyclization of the cleaved peptide (using (1-cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) as a cyclization reagent), and purification of a cyclic peptide were carried out to give the intended Compound PP3108 (4.9 mg, 9.8%) and Compound PP3109 (5.6 mg, 11%).

[1156]

Compound PP3108



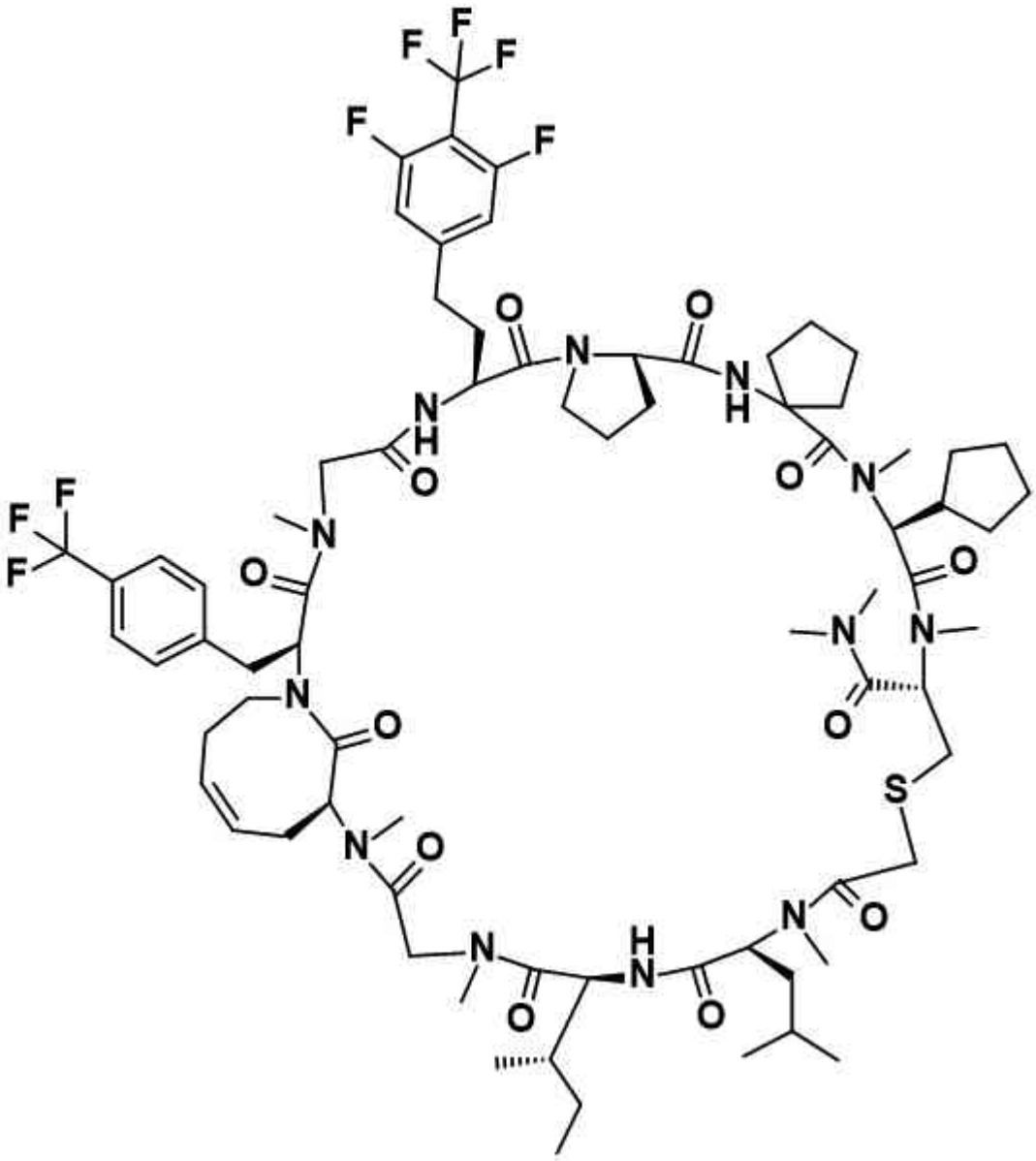
[1157]

LCMS (ESI) m/z = 1534.2 (M-H)-

Retention time: 5.989 min (Analytical condition SSC-FA-02)

[1158]

Compound PP3109



[1159]

LCMS (ESI) m/z = 1548.0 (M-H)-

Retention time: 6.083 min (Analytical condition SSC-FA-02)

[1160]

In the measurement conditions in Table 36, FA denotes SSC-FA-02/03, and AA denotes SSC-AA-02/03.

[1161]

[Table 36]

Compound No.	Analytical condition	Retention time (min)	MS Found (m/z)	MS polarity
PP0001	FA	5.285	1462.1	(M-H)-
PP0002	FA	5.776	1530.1	(M-H)-
PP0003	FA	5.504	1441.6	(M+H)+
PP0004	FA	5.528	1476.2	(M-H)-
PP0006	AA	7.936	1489.9	(M-H)-
PP0007	FA	5.081	1435.6	(M+H)+
PP0011	FA	5.204	1449.6	(M+H)+
PP0013	FA	5.120	1491.9	(M-H)-
PP0014	AA	7.951	1521.7	(M+H)+
PP0015	FA	5.405	1451.7	(M+H)+
PP0016	FA	5.643	1465.7	(M+H)+
PP0018	FA	5.321	1437.6	(M+H)+
PP0019	FA	5.552	1451.6	(M+H)+
PP0020	AA	7.809	1464.1	(M-H)-
PP0021	FA	6.133	1478.0	(M-H)-
PP0022	FA	5.495	1450.1	(M-H)-
PP0023	FA	5.713	1505.5	(M+H)+
PP0024	FA	5.419	1413.6	(M-H)-
PP0025	FA	5.555	1450.0	(M-H)-
PP0027	FA	5.724	1464.1	(M-H)-
PP0028	FA	5.736	1464.1	(M-H)-
PP0029	AA	7.771	1464.1	(M-H)-
PP0030	FA	5.965	1477.8	(M-H)-
PP0031	FA	4.945	1407.6	(M-H)-
PP0032	FA	5.312	1477.5	(M+H)+
PP0037	FA	5.348	1467.6	(M+H)+
PP0039	FA	5.147	1423.6	(M+H)+
PP0041	FA	4.941	1484.8	(M+NH4)+
PP0042	FA	5.616	1493.8	(M-H)-
PP0043	FA	5.561	1438.0	(M-H)-
PP0044	FA	5.277	1425.6	(M+H)+
PP0045	FA	5.445	1438.1	(M-H)-
PP0047	FA	6.448	1437.8	(M-H)-
PP0048	FA	6.757	1452.1	(M-H)-
PP0049	FA	6.228	1413.7	(M+H)+
PP0050	FA	6.381	1444.8	(M+NH4)+
PP0051	FA	5.737	1475.8	(M-H)-
PP0052	FA	5.991	1491.9	(M+H)+

Compound No.	Analytical condition	Retention time (min)	MS Found (m/z)	MS polarity
PP0053	FA	6.075	1545.8	(M+H)+
PP0054	FA	6.159	1454.1	(M-H)-
PP0055	FA	6.308	1505.7	(M+H)+
PP0056	FA	6.341	1504.2	(M-H)-
PP0057	FA	6.084	1502.1	(M-H)-
PP0058	FA	6.216	1504.2	(M-H)-
PP0059	FA	5.764	1464.1	(M-H)-
PP0060	FA	5.987	1518.0	(M-H)-
PP0061	FA	5.720	1429.6	(M+H)+
PP0062	AA	7.943	1478.0	(M-H)-
PP0063	FA	5.964	1478.0	(M-H)-
PP0064	AA	7.836	1499.7	(M+Na)+
PP0065	FA	6.012	1477.8	(M-H)-
PP0066	AA	7.939	1479.7	(M+H)+
PP0067	FA	6.075	1576.2	(M-H)-
PP0068	AA	7.907	1550.1	(M-H)-
PP0069	FA	6.248	1492.0	(M-H)-
PP0070	FA	6.247	1515.8	(M-H)-
PP0071	AA	7.843	1494.5	(M+NH4)+
PP0076	FA	5.551	1489.9	(M-H)-
PP0077	AA	8.029	1569.8	(M-H)-
PP0078	FA	5.900	1548.7	(M+NH4)+
PP0083	AA	8.248	1516.2	(M-H)-
PP0084	FA	6.924	1529.8	(M-H)-
PP0085	FA	7.169	1544.2	(M-H)-
PP0086	FA	6.733	1518.0	(M-H)-
PP0087	FA	6.975	1532.3	(M-H)-
PP0088	FA	5.955	1489.7	(M+H)+
PP0089	FA	6.247	1502.1	(M-H)-
PP0090	FA	5.647	1487.7	(M+H)+
PP0091	FA	6.411	1544.1	(M-H)-
PP0092	FA	5.812	1506.1	(M-H)-
PP0093	FA	5.817	1520.2	(M-H)-
PP0094	AA	7.721	1488.0	(M+Na)+
PP0095	FA	6.296	1491.6	(M+H)+
PP0096	FA	6.504	1504.2	(M-H)-
PP0097	FA	6.749	1518.2	(M-H)-
PP0098	FA	6.475	1492.2	(M-H)-

PP0099	FA	6.683	1506.0	(M-H)-
PP0100	FA	5.744	1463.7	(M+H)+
PP0101	FA	6.005	1476.0	(M-H)-
PP0102	FA	5.665	1459.7	(M-H)-
PP0103	FA	6.069	1518.1	(M-H)-
PP0104	FA	5.677	1480.2	(M-H)-
PP0105	FA	5.668	1495.7	(M+H)+
PP0106	FA	6.533	1558.1	(M-H)-
PP0107	FA	6.641	1559.6	(M+H)+
PP0108	FA	6.367	1556.1	(M-H)-
PP0109	FA	6.769	1570.2	(M-H)-
PP0110	FA	7.056	1583.7	(M-H)-
PP0112	FA	6.804	1572.2	(M-H)-
PP0113	FA	7.039	1586.1	(M-H)-
PP0114	AA	7.827	1544.1	(M+H)+
PP0115	FA	6.373	1558.1	(M+H)+
PP0116	FA	5.773	1540.2	(M-H)-
PP0117	FA	6.544	1597.7	(M-H)-
PP0118	FA	5.996	1562.1	(M+H)+
PP0119	AA	7.784	1575.8	(M+H)+
PP0120	FA	6.407	1531.8	(M-H)-
PP0121	FA	6.313	1532.1	(M-H)-
PP0122	FA	6.216	1532.1	(M+H)+
PP0123	FA	6.496	1546.1	(M+H)+
PP0124	FA	6.692	1558.2	(M-H)-
PP0126	FA	6.635	1547.7	(M+H)+
PP0127	FA	6.827	1560.1	(M-H)-
PP0128	FA	5.949	1534.7	(M+NH4)+
PP0129	FA	6.199	1529.9	(M-H)-
PP0130	FA	5.883	1513.9	(M-H)-
PP0131	FA	6.232	1573.6	(M+H)+
PP0132	FA	5.921	1533.9	(M-H)-
PP0133	FA	5.917	1547.7	(M-H)-
PP0134	FA	5.900	1505.9	(M-H)-
PP0135	FA	5.693	1481.7	(M+H)+
PP0136	AA	8.043	1560.2	(M-H)-
PP0137	FA	6.304	1534.2	(M-H)-
PP0138	FA	6.353	1504.2	(M-H)-
PP0139	FA	6.477	1502.2	(M-H)-
PP0140	FA	6.779	1516.2	(M-H)-
PP0141	FA	6.465	1557.8	(M-H)-
PP0144	FA	6.033	1505.9	(M-H)-
PP0145	FA	6.329	1532.1	(M-H)-

PP0146	FA	6.016	1505.6	(M+H)+
PP0148	FA	6.403	1532.2	(M-H)-
PP0149	FA	6.144	1545.7	(M+H)+
PP0150	FA	6.085	1477.7	(M-H)-
PP0151	AA	8.072	1581.6	(M+Na)+
PP0152	FA	6.677	1558.0	(M-H)-
PP0153	FA	6.077	1542.0	(M+Na)+
PP0154	AA	7.933	1530.1	(M-H)-
PP0155	FA	5.944	1506.1	(M+H)+
PP0156	FA	5.841	1532.1	(M+H)+
PP0158	FA	6.103	1530.1	(M-H)-
PP0162	FA	6.537	1558.0	(M-H)-
PP0165	FA	6.257	1544.0	(M-H)-
PP0166	FA	6.159	1555.7	(M-H)-
PP0168	FA	6.028	1542.0	(M-H)-
PP0169	FA	6.089	1475.9	(M-H)-
PP0170	FA	6.245	1520.8	(M+NH4)+
PP0171	FA	6.748	1534.7	(M+NH4)+
PP0172	FA	6.028	1488.1	(M-H)-
PP0173	AA	7.937	1543.7	(M-H)-
PP0174	FA	5.992	1522.8	(M+NH4)+
PP0175	FA	5.095	1574.7	(M+H)+
PP0176	FA	7.011	1531.7	(M+H)+
PP0177	FA	6.711	1530.0	(M-H)-
PP0178	FA	6.243	1502.0	(M-H)-
PP0179	FA	6.432	1527.9	(M-H)-
PP0180	FA	6.949	1542.0	(M-H)-
PP0181	FA	6.175	1513.7	(M-H)-
PP0182	FA	6.381	1570.2	(M-H)-
PP0183	FA	6.085	1530.1	(M-H)-
PP0184	AA	7.676	1599.0	(M-H)-
PP0185	AA	8.483	1557.7	(M+H)+
PP0186	FA	6.943	1556.0	(M-H)-
PP0187	FA	5.819	1543.7	(M-H)-
PP0188	FA	5.935	1515.9	(M-H)-
PP0189	FA	5.872	1503.9	(M-H)-
PP0190	FA	5.705	1491.6	(M+H)+
PP0191	FA	5.912	1570.1	(M-H)-
PP0192	FA	6.140	1543.9	(M+H)+
PP0193	FA	5.992	1529.9	(M-H)-
PP0194	FA	5.827	1516.1	(M-H)-
PP0195	FA	6.177	1553.7	(M-H)-
PP0196	FA	6.276	1581.6	(M+H)+

PP0197	AA	7.636	1527.8	(M+Na)+
PP0198	FA	6.024	1529.9	(M-H)-
PP0199	FA	5.963	1581.8	(M+H)+
PP0200	FA	6.084	1551.9	(M-H)-
PP0201	FA	6.023	1542.1	(M+H)+
PP0202	FA	5.849	1527.6	(M+H)+
PP0203	FA	6.061	1606.1	(M-H)-
PP0204	FA	6.271	1578.1	(M-H)-
PP0205	FA	6.149	1567.6	(M+H)+
PP0206	FA	5.999	1553.6	(M+H)+
PP0207	FA	6.007	1541.9	(M+H)+
PP0208	FA	6.131	1566.0	(M-H)-
PP0209	FA	7.039	1620.2	(M-H)-
PP0210	FA	5.409	1435.6	(M-H)-
PP0211	FA	5.681	1451.6	(M+H)+
PP0212	FA	5.231	1439.9	(M-H)-
PP0213	FA	5.441	1454.0	(M-H)-
PP0214	FA	5.708	1467.9	(M-H)-
PP0215	FA	5.587	1463.6	(M+H)+
PP0216	FA	5.899	1477.6	(M+H)+
PP0217	FA	5.273	1466.1	(M-H)-
PP0218	FA	5.584	1480.2	(M-H)-
PP0219	FA	5.880	1493.7	(M-H)-
PP0220	FA	5.635	1503.6	(M+H)+
PP0221	FA	5.637	1504.2	(M-H)-
PP0222	FA	6.216	1545.7	(M+H)+
PP0223	FA	5.836	1497.6	(M+H)+
PP0224	FA	5.973	1515.7	(M-H)-
PP0225	FA	5.960	1518.0	(M-H)-
PP0226	FA	6.484	1559.8	(M+H)+
PP0227	AA	7.968	1534.0	(M+Na)+
PP0228	FA	6.308	1589.9	(M+H)+
PP0229	FA	5.677	1491.6	(M+H)+
PP0230	FA	5.788	1493.6	(M+H)+
PP0231	FA	6.372	1531.7	(M-H)-
PP0232	FA	6.023	1484.0	(M-H)-
PP0233	FA	6.161	1564.1	(M+H)+
PP0234	FA	5.388	1477.6	(M+H)+
PP0235	FA	5.511	1479.8	(M+H)+
PP0236	FA	6.101	1517.7	(M-H)-
PP0237	AA	7.677	1493.7	(M+Na)+
PP0238	FA	5.729	1560.2	(M-H)-
PP0239	FA	5.512	1562.1	(M+H)+

PP0240	FA	5.587	1533.7	(M-H)-
PP0241	FA	5.384	1534.1	(M-H)-
PP0242	FA	6.333	1588.2	(M-H)-
PP0243	AA	8.097	1563.7	(M+H)+
PP0244	AA	7.768	1496.2	(M-H)-
PP0245	FA	6.284	1599.7	(M+H)+
PP0246	FA	5.897	1598.2	(M-H)-
PP0247	AA	7.775	1517.6	(M+H)+
PP0248	FA	5.639	1489.9	(M-H)-
PP0249	FA	5.896	1545.6	(M+H)+
PP0250	FA	5.859	1517.6	(M+H)+
PP0251	FA	5.996	1529.7	(M-H)-
PP0252	FA	6.333	1544.2	(M-H)-
PP0253	FA	6.479	1547.9	(M+H)+
PP0254	FA	6.025	1543.0	(M-H)-
PP0256	FA	6.420	1559.7	(M+H)+
PP0257	FA	6.197	1544.1	(M-H)-
PP0258	FA	6.204	1545.6	(M+H)+
PP0259	AA	7.921	1545.9	(M+H)+
PP0260	FA	5.899	1505.6	(M+H)+
PP0261	AA	8.028	1546.1	(M+H)+
PP0262	FA	5.775	1547.7	(M-H)-
PP0263	FA	6.343	1532.1	(M-H)-
PP0264	FA	6.232	1569.6	(M+H)+
PP0265	FA	5.860	1533.7	(M-H)-
PP0266	FA	5.788	1510.6	(M+NH4)+
PP0267	FA	6.143	1522.1	(M+H)+
PP0268	FA	5.909	1542.0	(M-H)-
PP0269	FA	5.763	1516.1	(M-H)-
PP0270	FA	5.991	1571.6	(M+H)+
PP0271	FA	5.983	1543.6	(M+H)+
PP0272	FA	6.127	1556.2	(M-H)-
PP0273	FA	6.020	1556.0	(M-H)-
PP0274	FA	6.303	1558.2	(M-H)-
PP0275	FA	5.851	1556.6	(M+H)+
PP0276	FA	6.281	1541.9	(M-H)-
PP0277	FA	6.431	1570.0	(M-H)-
PP0278	FA	6.189	1555.9	(M-H)-
PP0279	FA	6.105	1557.7	(M+H)+
PP0281	FA	6.055	1529.7	(M-H)-
PP0282	FA	6.295	1570.0	(M-H)-
PP0283	FA	5.912	1574.0	(M-H)-
PP0284	FA	6.445	1559.6	(M+H)+

PP0285	FA	6.371	1617.4	(M+Na)+
PP0286	FA	6.084	1561.6	(M+H)+
PP0287	FA	6.023	1518.0	(M-H)-
PP0288	FA	6.363	1546.0	(M-H)-
PP0289	FA	6.003	1529.9	(M-H)-
PP0290	FA	5.833	1522.7	(M+NH4)+
PP0291	FA	6.085	1557.9	(M-H)-
PP0292	FA	6.072	1529.7	(M-H)-
PP0293	FA	6.247	1543.7	(M-H)-
PP0294	FA	6.168	1518.1	(M-H)-
PP0295	FA	6.548	1558.2	(M-H)-
PP0296	FA	6.023	1562.2	(M-H)-
PP0297	FA	6.588	1545.8	(M-H)-
PP0298	FA	6.540	1582.0	(M-H)-
PP0299	FA	6.165	1548.0	(M-H)-
PP0300	FA	6.057	1506.1	(M-H)-
PP0301	FA	6.372	1536.1	(M+H)+
PP0302	FA	5.845	1529.6	(M+H)+
PP0303	FA	5.631	1501.9	(M-H)-
PP0304	FA	5.873	1557.6	(M+H)+
PP0305	FA	5.871	1528.1	(M-H)-
PP0306	FA	6.072	1541.7	(M-H)-
PP0307	FA	5.880	1515.7	(M-H)-
PP0308	FA	6.325	1557.6	(M+H)+
PP0309	FA	5.909	1561.6	(M+H)+
PP0310	FA	6.143	1573.8	(M-H)-
PP0311	FA	6.369	1544.1	(M-H)-
PP0312	FA	6.325	1582.1	(M+H)+
PP0313	FA	5.927	1545.7	(M-H)-
PP0314	FA	5.848	1504.1	(M-H)-
PP0315	FA	6.211	1533.6	(M+H)+
PP0316	FA	5.553	1477.7	(M+H)+
PP0317	FA	6.133	1491.7	(M+H)+
PP0318	FA	5.684	1530.2	(M-H)-
PP0319	FA	6.311	1544.0	(M-H)-
PP0320	FA	5.767	1491.6	(M+H)+
PP0321	FA	6.108	1539.7	(M-H)-
PP0322	FA	5.963	1527.6	(M+H)+
PP0323	FA	5.955	1547.7	(M-H)-
PP0324	FA	5.823	1533.7	(M-H)-
PP0325	FA	5.807	1491.6	(M+H)+
PP0326	FA	5.679	1477.6	(M+H)+
PP0327	AA	7.799	1525.9	(M-H)-

PP0328	FA	5.872	1513.6	(M+H)+
PP0329	FA	5.845	1534.2	(M-H)-
PP0330	FA	5.759	1521.6	(M+H)+
PP0331	FA	6.181	1519.6	(M+H)+
PP0332	FA	6.035	1504.1	(M-H)-
PP0333	AA	7.952	1555.6	(M+H)+
PP0334	FA	6.233	1541.6	(M+H)+
PP0335	FA	6.189	1563.7	(M+H)+
PP0336	FA	6.084	1547.9	(M-H)-
PP0337	FA	5.947	1517.6	(M+H)+
PP0338	FA	5.788	1503.6	(M+H)+
PP0339	FA	6.181	1553.6	(M+H)+
PP0340	FA	6.023	1539.6	(M+H)+
PP0341	FA	6.036	1559.9	(M-H)-
PP0342	FA	5.881	1545.9	(M-H)-
PP0343	FA	5.985	1529.9	(M-H)-
PP0344	FA	5.895	1515.7	(M-H)-
PP0345	FA	6.120	1565.6	(M-H)-
PP0346	FA	6.015	1552.0	(M-H)-
PP0347	FA	6.121	1575.9	(M+H)+
PP0348	FA	6.027	1560.0	(M-H)-
PP0349	FA	5.729	1515.7	(M-H)-
PP0350	FA	5.572	1501.7	(M-H)-
PP0351	FA	5.844	1553.6	(M+H)+
PP0352	FA	5.717	1539.6	(M+H)+
PP0353	FA	5.808	1561.7	(M+H)+
PP0354	AA	7.747	1546.0	(M-H)-
PP0355	FA	5.937	1462.1	(M-H)-
PP0356	FA	5.800	1449.6	(M+H)+
PP0357	FA	6.123	1499.6	(M+H)+
PP0358	AA	7.689	1485.6	(M+H)+
PP0359	FA	6.004	1506.1	(M-H)-
PP0360	FA	5.879	1493.6	(M+H)+
PP0361	FA	5.819	1449.6	(M+H)+
PP0362	FA	5.713	1433.6	(M-H)-
PP0363	FA	6.000	1485.6	(M+H)+
PP0364	FA	5.904	1469.5	(M-H)-
PP0365	FA	5.869	1491.7	(M-H)-
PP0366	FA	5.791	1477.7	(M-H)-
PP0367	FA	6.216	1477.6	(M+H)+
PP0368	FA	6.093	1463.6	(M+H)+
PP0369	FA	6.405	1513.6	(M+H)+
PP0370	FA	6.281	1497.9	(M-H)-

PP0371	FA	6.247	1521.7	(M+H)+
PP0372	FA	6.155	1505.7	(M-H)-
PP0373	FA	6.012	1475.6	(M+H)+
PP0374	FA	5.865	1461.6	(M+H)+
PP0375	FA	6.232	1509.9	(M-H)-
PP0376	FA	6.075	1497.5	(M+H)+
PP0377	FA	6.127	1517.7	(M-H)-
PP0378	FA	5.972	1505.6	(M+H)+
PP0379	FA	6.072	1489.6	(M+H)+
PP0380	FA	5.999	1475.6	(M+H)+
PP0381	FA	6.213	1523.9	(M-H)-
PP0382	FA	6.112	1511.6	(M+H)+
PP0383	FA	6.219	1532.0	(M-H)-
PP0384	FA	6.128	1518.2	(M-H)-
PP0385	FA	5.785	1475.6	(M+H)+
PP0386	FA	5.652	1461.6	(M+H)+
PP0387	FA	5.897	1511.5	(M+H)+
PP0388	FA	5.796	1497.5	(M+H)+
PP0389	FA	5.887	1518.1	(M-H)-
PP0390	FA	5.784	1505.8	(M+H)+
PP0391	FA	6.095	1519.8	(M-H)-
PP0392	FA	5.848	1549.6	(M+H)+
PP0393	FA	5.679	1491.6	(M+H)+
PP0394	FA	5.975	1539.7	(M-H)-
PP0395	FA	5.813	1527.6	(M+H)+
PP0396	FA	5.923	1550.1	(M+H)+
PP0397	FA	5.773	1534.0	(M-H)-
PP0398	FA	6.064	1536.9	(M+NH4)+
PP0399	FA	6.321	1568.0	(M-H)-
PP0400	FA	6.177	1554.2	(M-H)-
PP0401	FA	6.113	1562.2	(M-H)-
PP0402	FA	5.827	1516.0	(M-H)-
PP0403	FA	6.164	1565.7	(M-H)-
PP0404	FA	6.005	1553.7	(M+H)+
PP0405	FA	5.977	1561.9	(M+H)+
PP0406	FA	6.013	1574.2	(M-H)-
PP0407	FA	5.537	1534.7	(M+NH4)+
PP0408	FA	5.857	1565.7	(M-H)-
PP0409	FA	5.667	1551.7	(M-H)-
PP0410	FA	5.876	1575.7	(M+H)+
PP0411	FA	5.677	1560.2	(M-H)-
PP0412	FA	5.824	1462.1	(M-H)-
PP0413	FA	6.116	1511.9	(M-H)-

PP0414	FA	5.952	1497.9	(M-H)-
PP0415	FA	6.063	1520.2	(M-H)-
PP0416	FA	5.915	1505.9	(M-H)-
PP0417	FA	5.884	1461.6	(M-H)-
PP0418	FA	5.733	1449.6	(M+H)+
PP0419	FA	6.029	1497.6	(M-H)-
PP0420	FA	5.875	1483.6	(M-H)-
PP0421	FA	5.967	1505.9	(M-H)-
PP0422	FA	5.833	1492.0	(M-H)-
PP0423	FA	6.260	1508.6	(M+NH4)+
PP0424	FA	6.132	1476.1	(M-H)-
PP0425	FA	6.372	1526.0	(M-H)-
PP0426	FA	6.255	1512.0	(M-H)-
PP0427	FA	6.320	1535.6	(M+H)+
PP0428	AA	7.909	1519.7	(M-H)-
PP0429	FA	6.067	1487.9	(M-H)-
PP0430	FA	5.929	1473.9	(M-H)-
PP0431	FA	6.240	1524.1	(M-H)-
PP0432	FA	6.104	1510.0	(M-H)-
PP0433	FA	6.215	1532.0	(M-H)-
PP0434	FA	6.076	1537.2	(M+NH4)+
PP0435	FA	6.024	1487.9	(M-H)-
PP0436	FA	6.268	1537.9	(M-H)-
PP0437	FA	6.144	1523.9	(M-H)-
PP0438	FA	6.263	1546.2	(M-H)-
PP0439	FA	6.137	1534.2	(M+H)+
PP0440	FA	5.816	1488.0	(M-H)-
PP0441	FA	5.639	1473.9	(M-H)-
PP0442	AA	7.711	1524.1	(M-H)-
PP0443	FA	5.765	1509.6	(M-H)-
PP0444	FA	5.948	1532.0	(M-H)-
PP0445	AA	7.707	1519.6	(M+H)+
PP0446	FA	6.288	1547.7	(M+H)+
PP0447	FA	6.169	1534.1	(M+H)+
PP0448	AA	8.045	1531.7	(M-H)-
PP0449	FA	6.089	1517.7	(M-H)-
PP0450	FA	6.512	1561.7	(M+H)+
PP0451	FA	6.408	1547.7	(M+H)+
PP0452	FA	6.423	1558.2	(M-H)-
PP0453	FA	6.251	1543.7	(M-H)-
PP0454	FA	6.301	1573.6	(M+H)+
PP0455	FA	6.227	1558.0	(M-H)-
PP0456	FA	6.077	1558.1	(M-H)-

PP0457	FA	6.007	1543.7	(M-H)-
PP0460	FA	5.595	1473.7	(M-H)-
PP0461	FA	5.591	1489.6	(M+H)+
PP0462	FA	5.761	1529.6	(M+H)+
PP0463	FA	5.769	1543.7	(M+H)+
PP0464	AA	7.979	1568.2	(M-H)-
PP0465	FA	6.677	1540.2	(M-H)-
PP0466	FA	6.488	1526.2	(M-H)-
PP0467	AA	8.103	1577.9	(M+H)+
PP0468	FA	6.623	1549.7	(M+H)+
PP0469	FA	6.449	1536.3	(M+H)+
PP0470	FA	5.811	1448.1	(M-H)-
PP0471	FA	5.992	1525.6	(M-H)-
PP0472	FA	6.269	1498.0	(M-H)-
PP0473	FA	6.093	1484.1	(M-H)-
PP0474	FA	5.993	1535.6	(M+H)+
PP0475	FA	6.201	1506.2	(M-H)-
PP0476	FA	6.076	1492.2	(M-H)-
PP0477	FA	6.547	1561.7	(M+H)+
PP0478	AA	8.063	1533.6	(M+H)+
PP0479	FA	6.223	1532.2	(M-H)-
PP0480	FA	6.377	1533.9	(M+H)+
PP0481	FA	6.199	1545.7	(M-H)-
PP0483	FA	6.439	1561.7	(M+H)+
PP0484	FA	6.183	1559.7	(M+H)+
PP0485	FA	6.228	1571.8	(M-H)-
PP0487	FA	5.892	1504.2	(M-H)-
PP0488	FA	6.040	1518.2	(M-H)-
PP0490	AA	8.129	1546.2	(M-H)-
PP0491	FA	6.712	1582.3	(M-H)-
PP0492	FA	6.520	1589.8	(M-H)-
PP0493	FA	6.228	1561.6	(M+H)+
PP0494	FA	6.028	1563.7	(M+H)+
PP0495	FA	6.496	1576.3	(M-H)-
PP0496	FA	6.079	1518.2	(M-H)-
PP0497	AA	7.961	1531.7	(M-H)-
PP0498	FA	6.605	1561.7	(M+H)+
PP0499	FA	6.375	1568.2	(M-H)-
PP0500	AA	8.120	1533.8	(M-H)-
PP0501	FA	5.909	1552.7	(M+NH4)+
PP0502	AA	7.992	1562.2	(M-H)-
PP0503	FA	6.119	1521.7	(M+H)+
PP0504	FA	6.072	1532.2	(M-H)-

PP0505	FA	6.565	1559.8	(M-H)-
PP0506	FA	6.084	1560.2	(M-H)-
PP0507	AA	8.101	1504.2	(M-H)-
PP0508	AA	8.101	1516.2	(M-H)-
PP0509	AA	8.252	1530.2	(M-H)-
PP0510	FA	7.147	1543.8	(M-H)-
PP0511	FA	6.587	1573.7	(M+H)+
PP0512	FA	6.255	1489.7	(M-H)-
PP0513	FA	6.556	1561.7	(M+H)+
PP0514	AA	8.157	1518.2	(M-H)-
PP0515	FA	6.679	1549.7	(M+H)+
PP0516	FA	6.165	1532.2	(M-H)-
PP0520	FA	6.217	1572.2	(M-H)-
PP0521	AA	8.087	1544.2	(M-H)-
PP0522	FA	6.173	1544.2	(M-H)-
PP0523	FA	6.575	1561.7	(M+H)+
PP0524	FA	5.801	1536.0	(M-H)-
PP0525	FA	5.887	1563.7	(M+H)+
PP0526	FA	5.900	1493.9	(M+H)+
PP0527	FA	5.988	1517.8	(M-H)-
PP0528	FA	5.440	1460.1	(M-H)-
PP0529	FA	5.444	1462.0	(M-H)-
PP0530	FA	5.424	1479.7	(M-H)-
PP0531	FA	5.407	1479.6	(M+H)+
PP0532	FA	5.639	1497.6	(M+H)+
PP0533	FA	5.695	1493.8	(M-H)-
PP0534	FA	5.400	1493.7	(M+H)+
PP0535	FA	5.329	1490.1	(M-H)-
PP0536	FA	6.032	1547.6	(M+H)+
PP0537	FA	6.037	1544.0	(M-H)-
PP0538	FA	6.023	1546.2	(M-H)-
PP0539	FA	5.872	1546.2	(M-H)-
PP0540	FA	6.047	1518.2	(M-H)-
PP0541	FA	5.669	1518.2	(M-H)-
PP0542	FA	5.748	1518.1	(M-H)-
PP0543	FA	5.829	1532.2	(M-H)-
PP0544	FA	6.107	1546.2	(M-H)-
PP0545	AA	7.820	1546.2	(M-H)-
PP0546	FA	5.759	1563.2	(M+NH4)+
PP0547	AA	7.824	1557.8	(M-H)-
PP0548	FA	6.387	1572.3	(M-H)-
PP0549	FA	5.207	1490.2	(M-H)-
PP0550	FA	5.363	1504.1	(M-H)-

PP0551	AA	7.964	1561.7	(M+H)+
PP0552	FA	5.711	1532.2	(M-H)-
PP0553	FA	5.872	1568.2	(M-H)-
PP0554	AA	7.859	1575.8	(M-H)-
PP0555	FA	5.569	1546.2	(M-H)-
PP0556	FA	5.329	1549.6	(M+H)+
PP0557	FA	5.835	1562.2	(M-H)-
PP0558	FA	5.372	1566.7	(M+NH4)+
PP0559	FA	5.304	1504.2	(M-H)-
PP0560	FA	5.473	1518.2	(M-H)-
PP0561	AA	7.955	1546.2	(M-H)-
PP0562	FA	5.728	1554.2	(M-H)-
PP0563	FA	5.175	1520.2	(M-H)-
PP0564	FA	5.371	1549.6	(M+H)+
PP0565	FA	5.459	1506.2	(M-H)-
PP0566	FA	5.483	1517.7	(M-H)-
PP0567	FA	5.981	1545.7	(M-H)-
PP0568	FA	5.647	1546.2	(M-H)-
PP0569	FA	5.791	1490.1	(M-H)-
PP0570	FA	5.705	1502.2	(M-H)-
PP0571	FA	5.968	1517.7	(M+H)+
PP0572	FA	6.503	1530.2	(M-H)-
PP0573	AA	7.929	1558.2	(M-H)-
PP0574	FA	5.569	1476.2	(M-H)-
PP0575	FA	5.659	1554.2	(M-H)-
PP0576	FA	5.968	1526.2	(M-H)-
PP0577	FA	5.755	1512.1	(M-H)-
PP0578	FA	5.640	1562.3	(M-H)-
PP0579	FA	5.931	1534.2	(M-H)-
PP0580	FA	5.724	1520.2	(M-H)-
PP0581	FA	5.087	1434.1	(M-H)-
PP0582	FA	5.196	1512.1	(M-H)-
PP0583	FA	5.503	1484.1	(M-H)-
PP0584	FA	5.305	1469.6	(M-H)-
PP0585	FA	5.171	1519.7	(M-H)-
PP0586	FA	5.437	1492.1	(M-H)-
PP0587	FA	5.249	1478.1	(M-H)-
PP0588	FA	5.940	1547.7	(M+H)+
PP0589	AA	7.872	1533.7	(M-H)-
PP0590	AA	7.776	1518.2	(M-H)-
PP0591	FA	5.945	1532.2	(M-H)-
PP0594	FA	5.489	1558.2	(M-H)-
PP0595	FA	5.647	1548.6	(M+NH4)+

PP0596	FA	5.632	1530.2	(M-H)-
PP0597	FA	5.939	1546.2	(M-H)-
PP0598	FA	5.708	1520.2	(M-H)-
PP0599	FA	6.553	1502.0	(M-H)-
PP0605	FA	5.912	1450.1	(M-H)-
PP0606	AA	7.968	1473.7	(M-H)-
PP0607	FA	5.943	1492.0	(M-H)-
PP0608	FA	6.260	1507.7	(M-H)-
PP0609	FA	5.848	1504.1	(M-H)-
PP0610	FA	6.572	1559.8	(M+H)+
PP0611	FA	6.048	1476.0	(M-H)-
PP0612	FA	6.055	1494.0	(M-H)-
PP0613	FA	6.373	1511.6	(M+H)+
PP0614	FA	5.959	1506.2	(M-H)-
PP0615	FA	6.671	1562.1	(M+H)+
PP0616	AA	8.116	1459.9	(M-H)-
PP0617	AA	8.148	1513.7	(M-H)-
PP0618	AA	7.713	1446.0	(M-H)-
PP0619	FA	5.937	1501.7	(M+H)+
PP0620	FA	6.131	1446.1	(M-H)-
PP0621	FA	6.251	1501.6	(M+H)+
PP0622	FA	6.568	1531.6	(M+H)+
PP0626	AA	7.993	1516.1	(M-H)-
PP0627	FA	6.203	1462.0	(M-H)-
PP0628	FA	6.401	1515.9	(M-H)-
PP0629	AA	7.929	1461.9	(M-H)-
PP0630	AA	8.139	1545.9	(M+H)+
PP0631	FA	6.224	1527.5	(M+Na)+
PP0632	FA	6.328	1575.7	(M+H)+
PP0633	FA	6.609	1521.6	(M+H)+
PP0634	AA	8.296	1535.7	(M+H)+
PP0635	AA	8.659	1573.9	(M-H)-
PP0636	AA	8.760	1588.3	(M-H)-
PP0637	FA	7.508	1597.7	(M+H)+
PP0638	AA	8.284	1592.3	(M+H)+
PP0639	AA	8.431	1604.3	(M-H)-
PP0640	FA	7.527	1644.3	(M-H)-
PP0641	AA	8.893	1682.3	(M+Na)+
PP0642	FA	7.443	1667.7	(M+H)+
PP0643	AA	7.596	1507.9	(M+H)+
PP0644	FA	6.017	1520.2	(M-H)-
PP0645	AA	8.245	1560.2	(M-H)-
PP0646	FA	7.035	1592.9	(M+NH4)+

PP0647	AA	8.219	1583.9	(M+H)+
PP0648	AA	7.820	1575.9	(M-H)-
PP0649	AA	8.016	1591.9	(M+H)+
PP0650	FA	6.928	1632.3	(M+H)+
PP0651	FA	7.180	1646.0	(M+H)+
PP0652	AA	8.435	1671.3	(M+NH4)+
PP0653	AA	8.127	1582.7	(M+H)+
PP0654	FA	6.003	1447.7	(M-H)-
PP0655	FA	6.387	1477.7	(M+H)+
PP0656	FA	4.625	1566.9	(M-H)-
PP0657	FA	5.311	1435.7	(M+H)+
PP0658	AA	7.512	1461.7	(M-H)-
PP0659	FA	4.784	1581.2	(M-H)-
PP0660	FA	5.501	1447.7	(M-H)-
PP0661	FA	5.920	1476.2	(M-H)-
PP0662	FA	6.243	1562.2	(M-H)-
PP0663	FA	6.387	1507.7	(M+H)+
PP0664	FA	6.475	1521.6	(M+H)+
PP0665	AA	8.059	1519.7	(M+H)+
PP0666	FA	6.351	1517.6	(M+H)+
PP0667	AA	8.061	1532.2	(M-H)-
PP0668	FA	6.653	1548.2	(M+H)+
PP0669	FA	6.699	1549.9	(M+H)+
PP0670	FA	6.783	1560.2	(M-H)-
PP0671	FA	6.963	1574.3	(M-H)-
PP0672	FA	6.635	1568.2	(M-H)-
PP0673	FA	4.837	1571.2	(M+H)+
PP0674	FA	6.227	1523.6	(M+H)+
PP0675	FA	6.201	1536.1	(M-H)-
PP0678	FA	6.327	1548.0	(M-H)-
PP0679	FA	6.401	1561.9	(M-H)-
PP0680	AA	8.087	1562.2	(M+H)+
PP0681	FA	6.251	1558.2	(M-H)-
PP0682	FA	6.377	1592.9	(M+NH4)+
PP0683	FA	6.559	1589.7	(M+H)+
PP0684	FA	6.600	1591.7	(M+H)+
PP0685	FA	6.700	1604.2	(M+H)+
PP0686	FA	6.872	1616.3	(M-H)-
PP0687	FA	6.531	1611.7	(M+H)+
PP0688	FA	4.775	1612.7	(M+H)+
PP0689	FA	6.136	1564.2	(M-H)-
PP0690	FA	6.104	1578.2	(M-H)-
PP0693	AA	7.461	1493.7	(M+H)+

PP0694	FA	5.691	1506.2	(M-H)-
PP0695	AA	7.520	1506.2	(M+H)+
PP0696	AA	7.404	1501.8	(M-H)-
PP0697	FA	5.644	1517.8	(M-H)-
PP0698	FA	5.889	1533.6	(M+H)+
PP0699	FA	6.079	1535.7	(M+H)+
PP0700	FA	6.083	1547.9	(M+H)+
PP0701	FA	6.292	1562.2	(M+H)+
PP0702	FA	5.835	1554.2	(M-H)-
PP0703	FA	3.977	1555.2	(M-H)-
PP0704	FA	5.360	1508.2	(M-H)-
PP0705	FA	5.359	1523.6	(M+H)+
PP0706	AA	7.369	1493.6	(M+H)+
PP0708	FA	5.425	1535.6	(M+H)+
PP0709	FA	5.571	1549.7	(M+H)+
PP0710	FA	5.543	1548.2	(M+H)+
PP0711	FA	5.401	1544.1	(M-H)-
PP0712	FA	5.567	1560.2	(M-H)-
PP0713	FA	5.812	1575.7	(M+H)+
PP0714	FA	6.004	1577.8	(M+H)+
PP0715	FA	6.035	1590.0	(M+H)+
PP0716	FA	6.248	1603.8	(M+H)+
PP0717	FA	5.776	1597.7	(M+H)+
PP0718	AA	7.244	1597.2	(M-H)-
PP0719	FA	5.303	1549.8	(M-H)-
PP0720	FA	5.309	1565.7	(M+H)+
PP0721	FA	5.220	1535.7	(M+H)+
PP0722	AA	7.623	1552.8	(M+NH4)+
PP0723	AA	8.175	1521.8	(M+H)+
PP0724	FA	6.259	1522.7	(M+NH4)+
PP0725	FA	6.580	1557.7	(M+H)+
PP0726	AA	8.377	1604.3	(M-H)-
PP0727	FA	6.560	1590.2	(M+H)+
PP0728	FA	6.849	1641.6	(M+H)+
PP0729	FA	6.168	1492.2	(M-H)-
PP0730	FA	5.391	1479.5	(M+H)+
PP0731	FA	5.317	1581.2	(M-H)-
PP0732	AA	7.544	1568.8	(M+H)+
PP0733	FA	4.717	1582.7	(M+H)+
PP0734	FA	6.195	1479.7	(M+H)+
PP0735	FA	6.653	1481.7	(M+H)+
PP0736	FA	6.919	1493.8	(M-H)-
PP0737	AA	7.889	1480.2	(M-H)-

PP0738	FA	6.653	1495.7	(M+H)+
PP0739	FA	7.215	1535.7	(M+H)+
PP0740	AA	8.051	1552.2	(M+Na)+
PP0741	FA	5.955	1481.7	(M-H)-
PP0742	FA	6.300	1509.7	(M+H)+
PP0743	FA	6.732	1525.7	(M+H)+
PP0744	FA	5.749	1466.2	(M-H)-
PP0745	FA	6.235	1500.1	(M-H)-
PP0746	FA	6.107	1492.1	(M-H)-
PP0747	FA	6.400	1492.2	(M-H)-
PP0748	FA	6.081	1512.2	(M-H)-
PP0749	FA	6.653	1544.2	(M-H)-
PP0750	FA	6.459	1543.9	(M+H)+
PP0751	FA	6.447	1550.2	(M-H)-
PP0752	FA	6.635	1587.1	(M+NH4)+
PP0753	FA	6.112	1520.2	(M-H)-
PP0754	FA	6.075	1509.8	(M+H)+
PP0755	FA	6.152	1522.2	(M+H)+
PP0756	FA	6.615	1540.7	(M+NH4)+
PP0757	AA	8.203	1536.2	(M-H)-
PP0758	FA	6.361	1523.7	(M+H)+
PP0759	FA	6.611	1555.3	(M+NH4)+
PP0760	AA	8.443	1576.2	(M-H)-
PP0761	FA	6.501	1571.7	(M+H)+
PP0762	FA	5.869	1543.2	(M+NH4)+
PP0763	FA	6.224	1551.7	(M+H)+
PP0764	FA	6.683	1584.9	(M+NH4)+
PP0765	FA	5.636	1507.7	(M-H)-
PP0766	FA	6.139	1542.1	(M-H)-
PP0767	AA	7.645	1533.8	(M-H)-
PP0768	FA	6.324	1535.7	(M+H)+
PP0769	AA	7.692	1555.6	(M+H)+
PP0770	FA	6.197	1533.6	(M+H)+
PP0771	AA	7.875	1521.7	(M+H)+
PP0772	FA	6.147	1532.2	(M-H)-
PP0773	FA	6.605	1535.8	(M+H)+
PP0774	AA	8.264	1548.0	(M-H)-
PP0775	AA	8.021	1535.8	(M+H)+
PP0776	AA	8.173	1547.8	(M-H)-
PP0778	AA	8.213	1582.2	(M-H)-
PP0779	AA	7.795	1537.7	(M+H)+
PP0780	FA	6.335	1563.7	(M+H)+
PP0781	FA	6.735	1580.3	(M+H)+

PP0782	FA	5.808	1519.8	(M-H)-
PP0783	FA	6.280	1555.6	(M+H)+
PP0784	FA	6.172	1547.6	(M+H)+
PP0785	FA	6.397	1547.8	(M+H)+
PP0786	AA	7.799	1589.9	(M+Na)+
PP0787	FA	5.911	1567.6	(M+H)+
PP0788	AA	7.784	1501.6	(M+Na)+
PP0789	FA	5.840	1533.8	(M+H)+
PP0790	FA	5.888	1520.2	(M-H)-
PP0791	FA	5.892	1533.7	(M+H)+
PP0792	FA	6.351	1535.8	(M+H)+
PP0793	FA	6.659	1548.2	(M-H)-
PP0794	AA	7.957	1533.9	(M-H)-
PP0795	FA	6.427	1549.7	(M+H)+
PP0796	FA	6.999	1589.7	(M+H)+
PP0797	FA	6.392	1583.7	(M+H)+
PP0798	FA	5.785	1537.8	(M+H)+
PP0799	AA	8.004	1563.8	(M+H)+
PP0800	FA	6.584	1579.8	(M+H)+
PP0801	AA	7.373	1521.6	(M+H)+
PP0802	FA	5.895	1555.6	(M+H)+
PP0803	FA	5.839	1546.2	(M-H)-
PP0804	FA	6.088	1547.8	(M+H)+
PP0805	FA	6.051	1465.8	(M-H)-
PP0806	AA	7.783	1561.9	(M-H)-
PP0807	FA	5.681	1597.7	(M+H)+
PP0808	FA	5.832	1532.2	(M-H)-
PP0809	FA	5.907	1587.7	(M+H)+
PP0810	FA	5.607	1530.2	(M-H)-
PP0811	AA	7.841	1565.9	(M+H)+
PP0812	FA	5.688	1550.0	(M-H)-
PP0813	FA	5.551	1557.7	(M-H)-
PP0814	AA	7.716	1551.7	(M+H)+
PP0815	FA	6.467	1576.2	(M-H)-
PP0816	FA	6.365	1610.0	(M-H)-
PP0817	FA	6.440	1547.8	(M+H)+
PP0818	FA	6.677	1601.8	(M+H)+
PP0819	FA	6.377	1543.8	(M-H)-
PP0820	AA	8.303	1579.7	(M+H)+
PP0821	AA	8.156	1563.9	(M-H)-
PP0822	FA	6.043	1573.6	(M+H)+
PP0823	FA	6.313	1564.2	(M-H)-
PP0824	FA	5.619	1505.7	(M+H)+

PP0825	FA	5.912	1574.2	(M+H)+
PP0826	FA	6.151	1575.7	(M+H)+
PP0827	FA	6.003	1505.6	(M+H)+
PP0828	AA	8.135	1609.9	(M-H)-
PP0829	FA	6.285	1575.7	(M+H)+
PP0830	AA	8.035	1504.2	(M-H)-
PP0831	FA	6.447	1611.6	(M+H)+
PP0832	FA	5.865	1560.2	(M-H)-
PP0833	FA	5.912	1539.2	(M+NH4)+
PP0834	FA	6.159	1556.1	(M-H)-
PP0835	FA	5.616	1536.1	(M-H)-
PP0836	FA	5.961	1550.2	(M-H)-
PP0837	FA	5.941	1550.2	(M-H)-
PP0838	FA	6.355	1577.8	(M-H)-
PP0839	FA	6.600	1592.2	(M-H)-
PP0840	AA	7.792	1529.9	(M+Na)+
PP0841	AA	8.069	1579.7	(M+H)+
PP0842	FA	6.173	1576.2	(M-H)-
PP0843	FA	6.319	1600.2	(M-H)-
PP0844	AA	8.259	1592.2	(M-H)-
PP0845	FA	6.047	1536.2	(M+H)+
PP0846	FA	6.313	1570.1	(M-H)-
PP0847	FA	5.747	1551.8	(M+H)+
PP0848	AA	7.863	1546.2	(M-H)-
PP0849	FA	6.176	1562.2	(M-H)-
PP0850	AA	7.787	1473.9	(M-H)-
PP0851	FA	6.221	1596.7	(M+NH4)+
PP0852	FA	6.313	1591.7	(M+H)+
PP0853	FA	6.447	1633.6	(M+H)+
PP0854	FA	6.255	1585.9	(M+H)+
PP0855	AA	7.997	1618.6	(M+H)+
PP0856	FA	6.527	1629.8	(M+H)+
PP0857	AA	8.320	1643.9	(M-H)-
PP0858	FA	6.072	1549.7	(M-H)-
PP0859	FA	6.156	1508.1	(M-H)-
PP0860	FA	5.947	1524.7	(M+NH4)+
PP0861	FA	6.225	1543.7	(M+H)+
PP0862	FA	6.185	1583.1	(M+NH4)+
PP0863	FA	5.887	1577.6	(M+H)+
PP0864	FA	6.013	1535.8	(M+H)+
PP0865	FA	5.637	1532.1	(M-H)-
PP0866	FA	5.788	1569.7	(M+H)+
PP0867	FA	6.007	1608.8	(M+NH4)+

PP0868	FA	5.119	1535.7	(M+H)+
PP0869	FA	5.223	1535.7	(M+H)+
PP0870	FA	5.128	1535.8	(M+H)+
PP0871	FA	5.860	1566.7	(M+NH4)+
PP0872	FA	6.025	1548.2	(M-H)-
PP0873	FA	5.873	1549.7	(M+H)+
PP0874	FA	5.993	1561.7	(M+H)+
PP0875	FA	6.084	1575.7	(M+H)+
PP0876	FA	6.256	1589.7	(M+H)+
PP0877	FA	6.465	1603.7	(M+H)+
PP0878	FA	6.713	1574.2	(M-H)-
PP0879	FA	6.731	1606.7	(M+NH4)+
PP0880	AA	8.416	1604.3	(M+H)+
PP0881	FA	7.051	1617.8	(M+H)+
PP0882	FA	5.689	1470.2	(M-H)-
PP0883	FA	6.501	1484.2	(M-H)-
PP0884	FA	5.379	1485.8	(M-H)-
PP0885	FA	5.504	1474.1	(M-H)-
PP0886	FA	5.732	1528.1	(M-H)-
PP0887	FA	5.264	1445.6	(M+H)+
PP0888	AA	7.311	1444.2	(M-H)-
PP0889	FA	6.176	1499.9	(M-H)-
PP0890	FA	6.303	1506.8	(M+NH4)+
PP0891	FA	6.512	1544.1	(M+H)+
PP0892	FA	6.071	1476.8	(M+NH4)+
PP0893	AA	7.871	1457.8	(M-H)-
PP0894	FA	5.287	1468.2	(M-H)-
PP0895	FA	5.477	1481.9	(M-H)-
PP0896	FA	5.767	1496.2	(M-H)-
PP0898	AA	7.876	1565.7	(M+H)+
PP0899	FA	5.665	1553.7	(M+H)+
PP0900	AA	7.244	1480.2	(M-H)-
PP0901	AA	7.671	1547.8	(M-H)-
PP0902	FA	6.028	1563.7	(M+H)+
PP0903	AA	7.604	1549.8	(M-H)-
PP0904	AA	7.955	1470.2	(M-H)-
PP0905	FA	6.173	1513.9	(M+H)+
PP0906	FA	6.232	1474.2	(M-H)-
PP0907	FA	6.139	1473.7	(M-H)-
PP0908	FA	6.420	1489.7	(M-H)-
PP0909	FA	6.411	1491.6	(M+H)+
PP0910	FA	6.383	1494.1	(M-H)-
PP0911	FA	6.157	1470.2	(M-H)-

PP0912	AA	8.052	1471.7	(M+H)+
PP0913	FA	5.441	1446.7	(M+H)+
PP0914	AA	7.984	1485.9	(M-H)-
PP0915	FA	5.989	1487.9	(M+H)+
PP0916	FA	6.309	1545.7	(M+H)+
PP0917	FA	6.216	1543.8	(M-H)-
PP0918	FA	6.515	1560.1	(M-H)-
PP0919	FA	6.487	1560.2	(M-H)-
PP0920	FA	6.473	1565.7	(M+H)+
PP0921	FA	6.487	1563.8	(M-H)-
PP0922	AA	8.229	1540.3	(M-H)-
PP0923	AA	7.612	1515.2	(M-H)-
PP0924	FA	6.428	1557.7	(M+H)+
PP0925	AA	7.756	1509.9	(M+H)+
PP0926	FA	6.457	1629.7	(M+H)+
PP0927	FA	6.529	1646.8	(M+NH4)+
PP0928	AA	8.200	1647.7	(M+H)+
PP0929	FA	6.521	1645.7	(M+H)+
PP0930	FA	6.739	1646.2	(M+H)+
PP0931	FA	6.520	1626.0	(M+H)+
PP0932	FA	6.656	1642.7	(M+NH4)+
PP0933	FA	6.693	1625.7	(M+H)+
PP0934	FA	6.569	1604.7	(M+NH4)+
PP0935	FA	6.603	1586.2	(M-H)-
PP0936	FA	6.624	1586.2	(M-H)-
PP0937	AA	8.172	1623.0	(M+NH4)+
PP0938	FA	6.639	1602.2	(M-H)-
PP0939	FA	6.769	1604.1	(M+H)+
PP0940	FA	6.829	1603.7	(M+H)+
PP0941	FA	6.637	1582.2	(M-H)-
PP0942	FA	6.760	1584.2	(M+H)+
PP0943	AA	8.311	1584.3	(M+H)+
PP0944	FA	6.528	1563.7	(M+H)+
PP0945	FA	6.029	1564.2	(M-H)-
PP0946	FA	6.293	1579.7	(M+H)+
PP0947	FA	6.225	1594.3	(M+H)+
PP0948	FA	6.453	1630.7	(M+NH4)+
PP0949	FA	6.676	1662.7	(M+NH4)+
PP0950	AA	8.312	1626.0	(M+H)+
PP0951	AA	8.281	1644.0	(M+H)+
PP0952	FA	6.803	1676.7	(M+NH4)+
PP0953	FA	6.944	1638.3	(M-H)-
PP0954	FA	6.603	1581.9	(M-H)-

PP0955	FA	5.980	1564.2	(M+H)+
PP0956	FA	6.696	1604.0	(M+H)+
PP0958	FA	6.545	1578.3	(M-H)-
PP0959	FA	5.652	1467.7	(M+H)+
PP0960	FA	5.573	1483.6	(M+H)+
PP0961	AA	7.997	1530.1	(M+H)+
PP0962	FA	6.109	1546.2	(M-H)-
PP0963	FA	6.305	1563.6	(M+H)+
PP0964	FA	5.927	1497.7	(M+H)+
PP0965	FA	6.171	1537.9	(M-H)-
PP0966	FA	6.251	1531.7	(M+H)+
PP0967	FA	5.807	1481.6	(M+H)+
PP0968	FA	5.993	1523.9	(M-H)-
PP0969	FA	6.053	1516.2	(M-H)-
PP0970	FA	6.203	1508.1	(M-H)-
PP0971	FA	6.093	1452.2	(M-H)-
PP0972	FA	6.095	1482.2	(M-H)-
PP0973	FA	6.173	1474.2	(M-H)-
PP0975	FA	7.624	1533.9	(M-H)-
PP0976	FA	7.545	1564.3	(M-H)-
PP0977	FA	7.576	1556.1	(M-H)-
PP0978	FA	5.631	1502.1	(M-H)-
PP0979	AA	7.675	1578.9	(M+NH4)+
PP0980	FA	5.704	1518.2	(M-H)-
PP0981	FA	6.955	1629.8	(M+H)+
PP0982	FA	7.051	1586.3	(M-H)-
PP0983	FA	5.533	1489.7	(M-H)-
PP0984	AA	7.593	1516.1	(M-H)-
PP0985	AA	7.892	1524.0	(M-H)-
PP0986	AA	6.993	1471.7	(M-H)-
PP0987	FA	5.475	1455.7	(M-H)-
PP0988	AA	7.971	1489.7	(M-H)-
PP0989	FA	6.839	1539.6	(M+H)+
PP0992	FA	5.424	1563.9	(M+H)+
PP0993	FA	5.696	1577.7	(M+H)+
PP0997	FA	6.353	1591.7	(M+H)+
PP0998	FA	6.000	1629.7	(M-H)-
PP0999	FA	6.283	1590.3	(M-H)-
PP1000	AA	7.893	1590.2	(M+H)+
PP1001	FA	6.631	1617.8	(M+H)+
PP1002	FA	5.665	1597.9	(M-H)-
PP1003	AA	7.601	1548.2	(M-H)-
PP1004	FA	6.909	1604.3	(M-H)-

PP1005	AA	8.339	1626.3	(M+Na)+
PP1006	FA	6.405	1630.7	(M+NH4)+
PP1008	AA	8.244	1645.7	(M+H)+
PP1009	FA	6.955	1604.3	(M-H)-
PP1010	FA	6.699	1621.0	(M+NH4)+
PP1011	FA	7.265	1631.8	(M+H)+
PP1012	FA	6.489	1631.0	(M+NH4)+
PP1013	FA	6.729	1608.8	(M+NH4)+
PP1014	AA	8.123	1611.9	(M+Na)+
PP1015	FA	7.051	1617.8	(M+H)+
PP1016	FA	6.219	1561.8	(M-H)-
PP1017	FA	6.248	1547.8	(M-H)-
PP1018	FA	6.057	1535.7	(M+H)+
PP1019	AA	7.920	1546.2	(M-H)-
PP1020	FA	5.771	1507.7	(M+H)+
PP1021	FA	5.808	1518.2	(M-H)-
PP1022	FA	5.924	1520.2	(M-H)-
PP1024	AA	8.096	1590.3	(M-H)-
PP1025	FA	5.959	1576.2	(M-H)-
PP1026	FA	6.064	1606.7	(M+NH4)+
PP1027	FA	5.675	1547.7	(M-H)-
PP1028	FA	5.691	1561.7	(M+H)+
PP1029	AA	7.875	1561.8	(M-H)-
PP1030	FA	6.152	1608.7	(M+NH4)+
PP1031	FA	6.360	1546.2	(M-H)-
PP1032	AA	8.017	1555.8	(M+Na)+
PP1033	FA	6.181	1545.6	(M+H)+
PP1034	FA	5.912	1505.8	(M+H)+
PP1035	FA	5.881	1517.6	(M+H)+
PP1036	FA	6.043	1520.2	(M+H)+
PP1037	FA	6.359	1547.6	(M+H)+
PP1038	FA	6.264	1588.3	(M-H)-
PP1039	FA	6.065	1592.7	(M+NH4)+
PP1040	FA	6.065	1586.2	(M-H)-
PP1041	AA	7.861	1546.2	(M-H)-
PP1042	FA	5.777	1557.9	(M-H)-
PP1043	FA	5.941	1560.2	(M-H)-
PP1044	FA	6.265	1589.7	(M+H)+
PP1045	FA	6.608	1561.7	(M+H)+
PP1046	FA	6.440	1547.7	(M+H)+
PP1047	FA	6.531	1559.9	(M+H)+
PP1048	FA	6.189	1519.9	(M+H)+
PP1049	FA	6.319	1531.9	(M+H)+

PP1050	FA	6.288	1532.2	(M-H)-
PP1051	FA	6.620	1560.2	(M-H)-
PP1052	FA	5.807	1518.2	(M-H)-
PP1053	FA	6.072	1532.2	(M-H)-
PP1054	FA	5.976	1518.2	(M-H)-
PP1056	AA	7.648	1530.2	(M-H)-
PP1057	FA	5.992	1575.7	(M+H)+
PP1058	FA	6.261	1545.9	(M+H)+
PP1059	FA	5.929	1545.8	(M-H)-
PP1060	FA	6.044	1563.6	(M+H)+
PP1063	FA	5.780	1544.2	(M-H)-
PP1064	AA	7.671	1517.8	(M+H)+
PP1065	FA	5.823	1504.2	(M-H)-
PP1067	FA	6.312	1563.6	(M+H)+
PP1068	FA	6.479	1577.7	(M+H)+
PP1069	FA	6.716	1591.8	(M+H)+
PP1070	FA	5.967	1631.9	(M+H)+
PP1071	FA	6.284	1590.3	(M-H)-
PP1072	AA	7.909	1589.8	(M+H)+
PP1073	FA	6.641	1618.3	(M+H)+
PP1075	FA	5.537	1549.6	(M+H)+
PP1076	FA	5.732	1563.7	(M+H)+
PP1077	FA	6.011	1576.2	(M-H)-
PP1078	AA	7.361	1548.2	(M-H)-
PP1079	AA	7.759	1562.2	(M-H)-
PP1080	FA	6.051	1577.8	(M+H)+
PP1082	FA	6.401	1577.7	(M+H)+
PP1083	FA	6.653	1609.3	(M+NH4)+
PP1084	FA	5.477	1549.8	(M+H)+
PP1085	FA	6.173	1563.7	(M+H)+
PP1086	FA	5.815	1519.7	(M+H)+
PP1087	FA	5.608	1491.7	(M-H)-
PP1088	FA	5.253	1478.1	(M-H)-
PP1089	AA	7.491	1492.2	(M-H)-
PP1090	FA	5.711	1531.8	(M+H)+
PP1091	FA	5.492	1516.2	(M-H)-
PP1092	AA	7.515	1546.2	(M-H)-
PP1093	FA	5.676	1573.7	(M+H)+
PP1094	FA	5.495	1489.7	(M-H)-
PP1095	FA	6.157	1448.7	(M+H)+
PP1096	FA	6.688	1490.8	(M+H)+
PP1097	FA	6.003	1459.2	(M-H)-
PP1098	FA	5.993	1432.7	(M-H)-

PP1099	FA	6.355	1432.7	(M+H)+
PP1100	FA	6.528	1475.1	(M-H)-
PP1101	FA	6.099	1416.7	(M-H)-
PP1102	FA	6.528	1445.2	(M-H)-
PP1103	FA	5.424	1481.7	(M-H)-
PP1104	FA	5.535	1505.7	(M+H)+
PP1105	FA	6.016	1547.7	(M+H)+
PP1106	AA	7.469	1474.1	(M-H)-
PP1107	FA	5.843	1533.7	(M+H)+
PP1108	AA	7.376	1489.7	(M-H)-
PP1109	FA	5.671	1519.6	(M+H)+
PP1110	AA	7.577	1517.9	(M-H)-
PP1111	AA	7.600	1529.8	(M-H)-
PP1112	FA	6.104	1577.0	(M+NH4)+
PP1113	FA	5.385	1521.6	(M+H)+
PP1114	FA	5.647	1516.2	(M-H)-
PP1115	FA	5.529	1515.7	(M+H)+
PP1116	AA	7.688	1565.9	(M-H)-
PP1117	FA	6.079	1547.7	(M+H)+
PP1118	FA	5.919	1562.7	(M+NH4)+
PP1119	FA	5.551	1536.2	(M-H)-
PP1120	AA	7.349	1539.7	(M-H)-
PP1121	FA	5.601	1554.2	(M-H)-
PP1122	FA	5.167	1577.0	(M+H)+
PP1123	AA	7.657	1571.8	(M-H)-
PP1124	AA	7.379	1558.2	(M-H)-
PP1125	FA	6.317	1573.8	(M+H)+
PP1126	AA	7.655	1584.2	(M-H)-
PP1127	AA	7.815	1600.2	(M-H)-
PP1128	FA	5.533	1489.7	(M-H)-
PP1129	FA	5.568	1497.6	(M+H)+
PP1130	FA	5.319	1489.7	(M-H)-
PP1131	FA	5.267	1478.1	(M-H)-
PP1132	FA	5.405	1479.6	(M+H)+
PP1133	AA	7.509	1527.7	(M-H)-
PP1134	FA	5.625	1475.7	(M+H)+
PP1135	FA	5.355	1461.8	(M+H)+
PP1136	FA	5.765	1474.2	(M-H)-
PP1137	FA	5.643	1492.1	(M-H)-
PP1138	AA	7.303	1476.2	(M-H)-
PP1139	FA	5.311	1445.8	(M-H)-
PP1140	FA	5.249	1433.6	(M-H)-
PP1141	FA	5.629	1462.2	(M-H)-

PP1142	FA	5.868	1476.1	(M-H)-
PP1143	FA	5.436	1447.6	(M-H)-
PP1144	AA	7.804	1505.9	(M-H)-
PP1145	AA	7.487	1478.1	(M-H)-
PP1146	AA	7.409	1447.7	(M-H)-
PP1147	FA	6.083	1507.6	(M+H)+
PP1148	FA	6.739	1534.2	(M-H)-
PP1149	FA	6.693	1530.3	(M-H)-
PP1150	AA	7.776	1489.7	(M-H)-
PP1151	FA	6.608	1523.7	(M+H)+
PP1152	FA	6.169	1521.6	(M+H)+
PP1153	AA	8.340	1552.3	(M-H)-
PP1154	FA	6.147	1550.1	(M-H)-
PP1155	FA	5.957	1544.7	(M+H)+
PP1156	AA	7.688	1544.7	(M+H)+
PP1157	FA	5.939	1544.7	(M+H)+
PP1158	FA	6.536	1587.6	(M+H)+
PP1159	FA	5.964	1577.7	(M+H)+
PP1160	FA	6.277	1591.7	(M+H)+
PP1161	AA	8.323	1592.3	(M+H)+
PP1162	FA	6.900	1623.3	(M+NH4)+
PP1163	AA	8.179	1616.2	(M-H)-
PP1164	FA	6.441	1617.7	(M+H)+
PP1165	AA	8.039	1637.3	(M+H)+
PP1166	FA	6.287	1637.3	(M+H)+
PP1167	AA	7.977	1637.2	(M+H)+
PP1168	FA	6.872	1680.1	(M+H)+
PP1169	FA	6.585	1575.6	(M+H)+
PP1170	FA	6.533	1574.2	(M-H)-
PP1171	FA	6.425	1594.8	(M+H)+
PP1172	FA	6.393	1594.7	(M+H)+
PP1173	FA	6.416	1594.7	(M+H)+
PP1174	FA	6.972	1637.7	(M+H)+
PP1175	FA	5.511	1483.7	(M-H)-
PP1176	FA	5.735	1498.2	(M-H)-
PP1177	AA	7.697	1535.8	(M+H)+
PP1178	FA	5.811	1525.7	(M+H)+
PP1179	FA	5.547	1514.2	(M-H)-
PP1180	AA	7.696	1528.2	(M-H)-
PP1181	FA	5.991	1560.2	(M-H)-
PP1182	FA	4.067	1563.3	(M+H)+
PP1183	FA	6.015	1565.9	(M-H)-
PP1184	AA	7.915	1565.8	(M-H)-

PP1185	FA	5.825	1603.8	(M+NH4)+
PP1186	AA	7.707	1587.2	(M+H)+
PP1187	FA	5.829	1586.8	(M+H)+
PP1188	FA	6.431	1629.7	(M+H)+
PP1189	AA	7.653	1441.7	(M-H)-
PP1190	AA	7.765	1479.7	(M+Na)+
PP1191	AA	7.675	1491.7	(M-H)-
PP1192	AA	7.845	1482.2	(M-H)-
PP1193	FA	5.637	1472.2	(M-H)-
PP1194	FA	5.600	1486.2	(M-H)-
PP1195	AA	7.931	1518.2	(M-H)-
PP1196	FA	4.143	1518.8	(M-H)-
PP1197	FA	6.119	1524.2	(M-H)-
PP1198	FA	6.065	1523.8	(M-H)-
PP1199	FA	5.584	1493.7	(M+H)+
PP1200	FA	5.756	1524.8	(M+NH4)+
PP1201	AA	7.749	1535.7	(M+H)+
PP1202	FA	6.536	1563.9	(M+H)+
PP1203	FA	5.868	1532.2	(M-H)-
PP1204	FA	6.251	1561.7	(M+H)+
PP1205	AA	7.549	1522.2	(M-H)-
PP1206	FA	5.335	1487.7	(M+H)+
PP1207	AA	7.448	1499.8	(M-H)-
PP1208	FA	5.652	1515.8	(M+H)+
PP1209	AA	7.608	1528.3	(M-H)-
PP1210	FA	6.345	1558.3	(M+H)+
PP1211	FA	5.637	1544.8	(M+NH4)+
PP1212	FA	6.049	1555.7	(M+H)+
PP1213	FA	5.344	1516.2	(M-H)-
PP1214	FA	5.631	1457.6	(M+H)+
PP1215	FA	5.824	1471.6	(M+H)+
PP1216	AA	7.828	1486.1	(M+H)+
PP1217	FA	6.039	1497.8	(M-H)-
PP1218	FA	6.607	1527.7	(M+H)+
PP1219	AA	7.847	1496.0	(M-H)-
PP1220	AA	8.073	1524.2	(M-H)-
PP1221	FA	5.649	1486.0	(M-H)-
PP1222	FA	5.239	1445.7	(M+H)+
PP1223	AA	7.503	1457.9	(M-H)-
PP1224	FA	5.563	1472.2	(M-H)-
PP1225	FA	5.691	1488.0	(M+H)+
PP1226	AA	8.040	1514.3	(M-H)-
PP1227	AA	7.605	1484.2	(M-H)-

PP1228	AA	7.867	1512.3	(M-H)-
PP1229	AA	7.435	1474.2	(M-H)-
PP1230	FA	5.683	1473.7	(M+H)+
PP1231	FA	5.797	1487.7	(M+H)+
PP1232	AA	7.791	1500.2	(M-H)-
PP1233	FA	5.783	1498.2	(M-H)-
PP1234	AA	7.499	1505.8	(M+H)+
PP1235	AA	7.947	1559.7	(M+H)+
PP1242	FA	6.381	1561.7	(M+H)+
PP1243	FA	5.303	1498.2	(M-H)-
PP1244	FA	5.468	1512.2	(M-H)-
PP1245	FA	5.629	1545.0	(M+NH4)+
PP1246	AA	7.908	1555.8	(M+H)+
PP1247	FA	5.460	1525.7	(M+H)+
PP1248	FA	5.913	1570.7	(M+NH4)+
PP1249	FA	5.547	1468.0	(M-H)-
PP1250	AA	7.691	1482.1	(M-H)-
PP1251	FA	5.847	1497.7	(M+H)+
PP1252	FA	6.417	1524.1	(M-H)-
PP1253	AA	7.715	1496.0	(M+H)+
PP1254	FA	6.123	1523.6	(M+H)+
PP1255	AA	7.335	1456.2	(M-H)-
PP1256	FA	5.347	1471.7	(M+H)+
PP1257	AA	7.549	1484.2	(M-H)-
PP1258	FA	5.872	1519.8	(M-H)-
PP1259	FA	6.092	1513.7	(M+H)+
PP1260	FA	5.344	1482.2	(M-H)-
PP1261	FA	5.805	1511.8	(M+H)+
PP1262	FA	5.427	1471.7	(M+H)+
PP1263	FA	5.732	1497.9	(M-H)-
PP1264	FA	6.008	1524.2	(M-H)-
PP1265	AA	7.596	1481.9	(M-H)-
PP1266	FA	5.564	1533.7	(M-H)-
PP1267	FA	5.824	1589.7	(M+H)+
PP1268	FA	5.659	1547.7	(M+H)+
PP1269	FA	5.432	1502.2	(M-H)-
PP1270	FA	5.327	1490.2	(M-H)-
PP1271	FA	5.203	1445.7	(M-H)-
PP1272	AA	7.575	1487.8	(M-H)-
PP1273	FA	5.551	1475.7	(M+H)+
PP1274	AA	7.539	1540.2	(M-H)-
PP1275	FA	6.077	1532.2	(M-H)-
PP1276	FA	5.689	1519.9	(M+H)+

PP1277	FA	5.968	1532.2	(M-H)-
PP1278	FA	5.320	1505.8	(M-H)-
PP1279	FA	5.421	1534.2	(M-H)-
PP1280	FA	5.469	1492.2	(M-H)-
PP1281	FA	5.535	1546.1	(M+H)+
PP1282	FA	5.740	1575.7	(M+H)+
PP1283	FA	5.593	1573.7	(M+H)+
PP1284	AA	7.412	1532.2	(M-H)-
PP1285	FA	5.439	1583.6	(M+H)+
PP1286	FA	5.663	1549.7	(M+H)+
PP1287	FA	5.864	1575.8	(M-H)-
PP1288	AA	7.624	1560.2	(M-H)-
PP1289	FA	6.219	1545.7	(M+H)+
PP1290	FA	6.519	1574.0	(M+H)+
PP1291	FA	6.359	1571.7	(M+H)+
PP1292	FA	6.045	1530.2	(M-H)-
PP1293	FA	6.211	1580.2	(M-H)-
PP1294	FA	6.377	1558.2	(M-H)-
PP1295	FA	6.000	1559.7	(M+H)+
PP1296	FA	5.868	1557.7	(M+H)+
PP1297	AA	7.569	1516.2	(M-H)-
PP1298	FA	5.740	1565.8	(M-H)-
PP1299	FA	5.865	1562.8	(M+NH4)+
PP1300	FA	6.151	1547.7	(M+H)+
PP1301	FA	5.992	1544.2	(M-H)-
PP1302	FA	5.676	1504.1	(M-H)-
PP1303	FA	5.844	1554.2	(M-H)-
PP1304	FA	5.995	1532.2	(M-H)-
PP1305	FA	6.144	1532.2	(M-H)-
PP1306	FA	6.459	1561.7	(M+H)+
PP1307	FA	6.293	1559.9	(M+H)+
PP1308	FA	5.967	1519.7	(M+H)+
PP1309	FA	6.141	1569.6	(M+H)+
PP1310	FA	6.301	1546.2	(M-H)-
PP1311	FA	5.915	1602.3	(M+H)+
PP1312	FA	5.753	1617.0	(M+NH4)+
PP1313	FA	5.436	1558.2	(M-H)-
PP1314	FA	5.607	1590.8	(M+NH4)+
PP1315	AA	7.737	1585.9	(M-H)-
PP1316	FA	5.688	1549.7	(M+H)+
PP1317	FA	5.995	1577.7	(M+H)+
PP1318	FA	5.843	1574.2	(M-H)-
PP1319	AA	7.475	1533.9	(M-H)-

PP1320	FA	5.704	1584.2	(M-H)-
PP1321	FA	5.451	1543.7	(M+H)+
PP1322	FA	5.337	1499.8	(M-H)-
PP1323	FA	5.713	1513.6	(M+H)+
PP1324	FA	5.793	1570.3	(M-H)-
PP1325	FA	5.675	1528.2	(M-H)-
PP1326	AA	7.889	1542.1	(M+H)+
PP1327	FA	5.620	1568.3	(M-H)-
PP1328	FA	5.512	1527.7	(M+H)+
PP1329	FA	5.864	1556.7	(M+NH4)+
PP1330	FA	5.904	1551.7	(M+H)+
PP1331	FA	5.848	1563.7	(M+H)+
PP1333	FA	6.700	1589.8	(M+H)+
PP1334	FA	6.580	1519.7	(M+H)+
PP1335	AA	8.217	1560.2	(M-H)-
PP1336	FA	5.760	1474.1	(M-H)-
PP1337	FA	5.693	1516.2	(M-H)-
PP1338	FA	5.500	1502.1	(M-H)-
PP1339	FA	6.060	1542.2	(M-H)-
PP1340	FA	5.845	1483.8	(M-H)-
PP1341	AA	7.875	1540.2	(M-H)-
PP1342	FA	6.224	1513.9	(M-H)-
PP1343	FA	5.909	1542.2	(M-H)-
PP1344	FA	5.701	1528.2	(M-H)-
PP1345	FA	6.132	1554.2	(M-H)-
PP1346	FA	5.961	1500.2	(M-H)-
PP1347	FA	6.155	1533.8	(M-H)-
PP1348	FA	6.073	1595.0	(M+NH4)+
PP1349	FA	6.011	1490.2	(M-H)-
PP1350	FA	5.919	1533.7	(M+H)+
PP1351	FA	5.971	1575.7	(M+H)+
PP1352	FA	6.032	1535.7	(M+H)+
PP1353	FA	5.951	1594.8	(M+NH4)+
PP1354	FA	5.827	1561.9	(M-H)-
PP1355	FA	6.349	1603.8	(M+H)+
PP1356	FA	6.199	1561.8	(M+H)+
PP1357	AA	7.967	1574.2	(M+H)+
PP1358	FA	6.139	1532.1	(M-H)-
PP1359	FA	6.060	1592.7	(M+NH4)+
PP1360	FA	5.929	1560.1	(M-H)-
PP1361	FA	6.429	1601.7	(M+H)+
PP1362	FA	6.301	1558.1	(M-H)-
PP1363	FA	5.805	1532.2	(M+H)+

PP1364	FA	5.861	1490.2	(M-H)-
PP1365	FA	5.781	1531.8	(M-H)-
PP1366	FA	5.615	1519.6	(M+H)+
PP1367	AA	8.011	1557.9	(M-H)-
PP1368	AA	7.852	1515.9	(M-H)-
PP1369	FA	5.765	1560.2	(M-H)-
PP1370	FA	5.812	1519.9	(M-H)-
PP1371	FA	5.745	1563.7	(M+H)+
PP1372	FA	5.612	1547.9	(M-H)-
PP1373	FA	6.120	1589.7	(M+H)+
PP1374	FA	5.983	1564.7	(M+NH4)+
PP1375	FA	5.852	1557.8	(M-H)-
PP1376	FA	5.928	1517.8	(M-H)-
PP1377	AA	7.845	1561.8	(M+H)+
PP1378	AA	7.735	1564.9	(M+NH4)+
PP1379	FA	6.200	1587.7	(M+H)+
PP1380	FA	6.089	1544.2	(M-H)-
PP1381	FA	5.613	1517.7	(M+H)+
PP1382	FA	5.653	1476.1	(M-H)-
PP1383	FA	5.583	1520.2	(M+H)+
PP1384	FA	5.400	1504.2	(M-H)-
PP1385	FA	5.967	1545.7	(M+H)+
PP1386	FA	6.115	1535.1	(M+NH4)+
PP1387	FA	6.464	1561.9	(M+H)+
PP1388	FA	6.303	1559.6	(M+H)+
PP1389	FA	6.311	1547.7	(M+H)+
PP1390	FA	5.417	1461.7	(M+H)+
PP1391	FA	5.585	1487.7	(M+H)+
PP1392	FA	5.889	1532.2	(M-H)-
PP1393	AA	7.932	1600.0	(M-H)-
PP1394	AA	7.883	1546.3	(M-H)-
PP1395	AA	7.717	1548.2	(M-H)-
PP1396	AA	7.880	1559.7	(M+H)+
PP1397	FA	6.065	1545.9	(M-H)-
PP1398	AA	8.033	1577.8	(M+H)+
PP1399	FA	6.152	1587.8	(M-H)-
PP1400	FA	6.135	1522.3	(M-H)-
PP1401	FA	6.012	1535.8	(M+H)+
PP1402	FA	6.027	1539.7	(M+H)+
PP1403	FA	6.073	1526.2	(M+H)+
PP1404	FA	6.577	1480.7	(M-H)-
PP1405	FA	6.612	1468.6	(M+H)+
PP1406	AA	7.607	1516.2	(M-H)-

PP1407	FA	5.520	1477.7	(M+H)+
PP1408	AA	7.584	1536.7	(M+NH4)+
PP1409	FA	5.711	1502.2	(M-H)-
PP1410	FA	6.169	1418.9	(M-H)-
PP1411	FA	5.968	1506.3	(M+H)+
PP1412	AA	7.989	1530.3	(M-H)-
PP1413	AA	8.175	1448.7	(M+H)+
PP1414	AA	7.632	1477.9	(M-H)-
PP1415	AA	7.667	1522.2	(M+H)+
PP1416	FA	5.856	1504.3	(M-H)-
PP1417	FA	6.381	1420.8	(M-H)-
PP1418	FA	6.243	1614.3	(M-H)-
PP1419	FA	6.464	1598.3	(M-H)-
PP1420	FA	6.109	1561.8	(M+H)+
PP1421	FA	6.329	1544.3	(M-H)-
PP1422	FA	5.837	1585.9	(M-H)-
PP1423	FA	6.085	1588.7	(M+NH4)+
PP1424	AA	7.751	1551.3	(M+NH4)+
PP1425	FA	5.940	1517.7	(M+H)+
PP1426	FA	4.965	1432.2	(M-H)-
PP1427	FA	5.144	1434.2	(M-H)-
PP1428	AA	8.004	1469.9	(M-H)-
PP1429	FA	5.699	1506.3	(M-H)-
PP1430	FA	6.507	1500.0	(M+H)+
PP1431	FA	6.131	1535.9	(M+H)+
PP1432	FA	6.237	1472.3	(M-H)-
PP1433	FA	5.861	1508.3	(M-H)-
PP1434	AA	7.965	1457.8	(M+H)+
PP1435	FA	6.085	1471.8	(M+H)+
PP1436	FA	5.544	1493.7	(M+H)+
PP1437	FA	5.663	1506.3	(M-H)-
PP1438	FA	6.015	1487.8	(M+H)+
PP1439	FA	6.131	1500.3	(M-H)-
PP1440	FA	5.564	1522.0	(M-H)-
PP1441	FA	5.676	1535.9	(M-H)-
PP1442	FA	5.488	1505.7	(M+H)+
PP1443	FA	5.885	1467.8	(M-H)-
PP1444	AA	7.355	1491.8	(M+H)+
PP1445	AA	7.763	1455.8	(M+H)+
PP1446	AA	7.881	1469.7	(M+H)+
PP1447	FA	5.481	1505.8	(M+H)+
PP1448	FA	5.311	1470.1	(M-H)-
PP1449	FA	5.375	1510.2	(M-H)-

PP1450	FA	5.488	1491.7	(M-H)-
PP1451	FA	5.473	1501.7	(M-H)-
PP1452	AA	7.363	1478.2	(M-H)-
PP1453	FA	5.677	1506.3	(M-H)-
PP1454	FA	5.431	1491.8	(M+H)+
PP1455	FA	5.756	1518.3	(M-H)-
PP1456	FA	5.275	1479.9	(M+H)+
PP1457	AA	7.371	1447.7	(M-H)-
PP1458	FA	5.947	1533.8	(M+H)+
PP1459	FA	5.857	1521.7	(M+H)+
PP1460	FA	5.896	1521.7	(M+H)+
PP1461	FA	5.057	1433.7	(M-H)-
PP1462	FA	5.712	1435.7	(M+H)+
PP1463	AA	7.776	1475.7	(M+H)+
PP1464	FA	5.871	1455.9	(M-H)-
PP1465	FA	5.880	1465.8	(M-H)-
PP1466	FA	5.697	1441.8	(M-H)-
PP1467	FA	6.031	1471.7	(M+H)+
PP1468	AA	7.808	1454.2	(M-H)-
PP1469	FA	6.119	1482.3	(M-H)-
PP1470	FA	5.681	1442.2	(M-H)-
PP1471	FA	5.720	1411.8	(M-H)-
PP1472	FA	6.307	1497.8	(M+H)+
PP1473	AA	8.117	1483.9	(M-H)-
PP1474	FA	6.255	1485.8	(M+H)+
PP1475	FA	5.435	1397.8	(M-H)-
PP1476	FA	5.559	1457.8	(M-H)-
PP1477	FA	5.440	1460.2	(M-H)-
PP1478	FA	5.333	1444.2	(M-H)-
PP1479	FA	5.215	1445.7	(M-H)-
PP1480	AA	7.805	1460.0	(M-H)-
PP1481	FA	5.632	1462.2	(M-H)-
PP1482	FA	5.499	1447.7	(M+H)+
PP1483	FA	5.383	1448.2	(M-H)-
PP1484	FA	5.401	1443.7	(M+H)+
PP1485	FA	5.524	1439.5	(M-H)-
PP1486	AA	7.860	1470.2	(M-H)-
PP1487	FA	5.971	1467.8	(M-H)-
PP1488	FA	5.497	1483.7	(M+H)+
PP1489	FA	6.191	1436.9	(M-H)-
PP1490	FA	5.980	1424.7	(M+H)+
PP1491	AA	8.220	1465.2	(M-H)-
PP1492	AA	8.020	1452.7	(M+H)+

PP1493	FA	6.399	1440.7	(M+H)+
PP1494	FA	6.183	1425.1	(M-H)-
PP1495	AA	7.635	1535.9	(M-H)-
PP1496	AA	7.413	1522.2	(M-H)-
PP1497	FA	5.436	1505.6	(M+H)+
PP1498	FA	5.876	1555.6	(M+H)+
PP1499	FA	5.815	1500.2	(M-H)-
PP1500	FA	5.736	1522.1	(M-H)-
PP1501	FA	5.937	1532.2	(M-H)-
PP1502	AA	7.665	1531.8	(M-H)-
PP1503	FA	5.743	1544.2	(M-H)-
PP1504	AA	7.969	1582.2	(M-H)-
PP1505	FA	6.292	1582.2	(M-H)-
PP1506	FA	6.220	1595.7	(M+H)+
PP1507	AA	7.760	1531.8	(M-H)-
PP1508	FA	5.968	1533.6	(M+H)+
PP1509	FA	5.904	1544.2	(M-H)-
PP1510	FA	5.981	1525.9	(M-H)-
PP1511	AA	7.813	1515.7	(M+H)+
PP1512	FA	5.919	1549.6	(M+H)+
PP1513	FA	5.925	1535.8	(M-H)-
PP1514	FA	5.755	1497.7	(M+H)+
PP1515	AA	7.488	1481.8	(M-H)-
PP1516	AA	7.971	1524.3	(M-H)-
PP1517	AA	7.741	1511.7	(M+H)+
PP1518	FA	5.907	1498.2	(M-H)-
PP1519	AA	7.551	1485.7	(M+H)+
PP1520	FA	6.412	1438.8	(M-H)-
PP1521	FA	6.200	1424.7	(M-H)-
PP1522	FA	6.879	1466.8	(M-H)-
PP1523	AA	8.104	1454.7	(M+H)+
PP1524	FA	6.605	1440.9	(M-H)-
PP1525	AA	7.932	1428.7	(M+H)+
PP1526	FA	5.655	1538.2	(M-H)-
PP1527	FA	5.416	1524.2	(M-H)-
PP1528	AA	7.601	1493.8	(M-H)-
PP1529	FA	5.335	1499.2	(M+NH4)+
PP1530	FA	6.001	1541.0	(M+NH4)+
PP1531	FA	5.759	1507.9	(M-H)-
PP1532	FA	5.747	1497.7	(M+H)+
PP1533	AA	7.528	1565.9	(M-H)-
PP1534	FA	5.857	1569.7	(M+H)+
PP1535	FA	6.119	1595.7	(M+H)+

PP1536	FA	5.976	1541.7	(M+H)+
PP1537	FA	6.085	1514.2	(M-H)-
PP1538	FA	6.028	1537.6	(M+H)+
PP1552	AA	7.925	1456.2	(M-H)-

PP1553	FA	5.576	1492.2	(M-H)-
PP1554	AA	8.196	1583.7	(M+H)+
PP1557	AA	7.747	1539.9	(M-H)-

PP1558	AA	7.908	1565.3	$(M+NH_4)+$		PP1608	FA	6.600	1498.6	(M+H)+
PP1559	AA	7.691	1526.2	(M-H)-		PP1609	AA	7.920	1496.6	(M+H)+
PP1560	FA	5.992	1540.2	(M-H)-		PP1610	AA	8.288	1516.7	(M+H)+
PP1561	FA	6.204	1572.9	$(M+NH_4)+$		PP1611	AA	8.208	1514.6	(M+H)+
PP1562	FA	6.160	1573.0	$(M+NH_4)+$		PP1612	AA	7.989	1488.7	(M+H)+
PP1563	FA	5.988	1552.4	(M-H)-		PP1613	AA	7.927	1486.7	(M+H)+
PP1564	FA	6.257	1585.3	$(M+NH_4)+$		PP1614	AA	8.115	1524.6	(M+H)+
PP1565	FA	6.461	1582.3	(M+H)+		PP1615	AA	8.041	1522.7	(M+H)+
PP1566	AA	7.821	1552.7	$(M+NH_4)+$		PP1616	AA	7.749	1480.7	(M+H)+
PP1568	AA	7.964	1582.2	(M+Na)+		PP1617	AA	7.637	1454.7	(M+H)+
PP1569	AA	7.920	1564.2	(M+H)+		PP1620	AA	8.259	1426.7	(M+H)+
PP1570	FA	6.217	1546.3	(M-H)-		PP1622	AA	8.452	1492.7	(M+H)+
PP1571	FA	6.527	1560.0	(M-H)-		PP1623	AA	8.305	1490.7	(M+H)+
PP1572	FA	6.585	1591.7	(M+H)+		PP1624	AA	8.091	1464.6	(M+H)+
PP1573	FA	6.211	1566.3	(M-H)-		PP1625	AA	7.991	1462.6	(M+H)+
PP1574	FA	6.333	1561.9	(M+H)+		PP1626	FA	6.973	1500.6	(M+H)+
PP1575	FA	6.881	1606.3	(M+H)+		PP1627	AA	8.080	1498.7	(M+H)+
PP1576	AA	8.111	1561.8	(M+H)+		PP1628	AA	8.536	1518.7	(M+H)+
PP1577	AA	8.172	1537.8	(M+H)+		PP1629	FA	7.181	1516.7	(M+H)+
PP1578	AA	8.343	1552.3	(M+H)+		PP1630	AA	8.204	1491.2	(M+H)+
PP1579	AA	8.029	1546.2	(M-H)-		PP1631	AA	8.123	1488.7	(M+H)+
PP1580	FA	6.640	1579.2	$(M+NH_4)+$		PP1632	AA	8.295	1526.7	(M+H)+
PP1582	AA	8.784	1559.2	(M-H)-		PP1633	AA	8.229	1523.2	(M-H)-
PP1583	FA	7.421	1533.0	(M-H)-		PP1634	FA	7.851	1545.2	(M+H)+
PP1584	AA	8.520	1531.2	(M-H)-		PP1635	AA	8.684	1542.7	(M+H)+
PP1586	AA	8.591	1568.7	(M+H)+		PP1636	AA	8.468	1516.7	(M+H)+
PP1587	AA	8.632	1506.7	(M+H)+		PP1637	AA	8.403	1514.7	(M+H)+
PP1588	AA	8.492	1522.2	$(M+NH_4)+$		PP1639	AA	8.500	1549.2	(M-H)-
PP1589	AA	8.289	1478.7	(M+H)+		PP1640	FA	5.499	1606.8	$(M+NH_4)+$
PP1590	AA	8.180	1476.7	(M+H)+		PP1641	FA	5.891	1517.7	(M-H)-
PP1591	AA	8.352	1514.7	(M+H)+		PP1643	AA	7.899	1583.7	(M+H)+
PP1592	AA	8.265	1512.6	(M+H)+		PP1644	FA	6.128	1585.7	(M-H)-
PP1593	AA	8.721	1532.7	(M+H)+		PP1645	FA	6.215	1546.4	(M-H)-
PP1594	AA	8.617	1531.2	(M+H)+		PP1646	FA	6.489	1561.8	(M+H)+
PP1595	AA	8.395	1504.7	(M+H)+		PP1648	FA	6.481	1574.2	(M+H)+
PP1596	AA	8.313	1502.7	(M+H)+		PP1649	FA	6.412	1578.9	$(M+NH_4)+$
PP1598	AA	8.400	1538.7	(M+H)+		PP1650	FA	6.355	1560.0	(M-H)-
PP1599	AA	8.156	1496.7	(M+H)+		PP1651	FA	6.459	1572.3	(M-H)-
PP1600	AA	8.020	1470.7	(M+H)+		PP1653	AA	7.856	1540.3	(M-H)-
PP1601	AA	8.405	1414.7	(M+H)+		PP1654	FA	6.403	1572.9	$(M+NH_4)+$
PP1603	AA	8.695	1442.7	(M+H)+		PP1655	FA	6.093	1578.3	(M+H)+
PP1605	AA	8.229	1490.7	(M+H)+		PP1656	FA	6.216	1588.8	$(M+NH_4)+$
PP1606	AA	8.119	1489.1	(M+H)+		PP1657	AA	7.909	1571.8	(M+H)+
PP1607	AA	7.893	1462.7	(M+H)+		PP1658	FA	6.184	1539.7	(M+H)+

PP1660	AA	8.020	1547.2	$(M+NH_4)+$		PP1714	AA	7.972	1554.2	(M+H)+
PP1661	FA	6.581	1530.3	(M-H)-		PP1715	FA	6.363	1553.8	(M+H)+
PP1662	FA	6.501	1530.2	(M-H)-		PP1716	AA	8.016	1566.2	(M+H)+
PP1663	FA	6.189	1521.6	(M+H)+		PP1717	AA	7.724	1541.7	(M+H)+
PP1665	FA	6.529	1560.2	(M-H)-		PP1718	AA	7.992	1569.7	(M+H)+
PP1666	FA	5.971	1519.6	(M+H)+		PP1721	AA	7.981	1554.2	(M+H)+
PP1667	FA	6.224	1558.2	(M-H)-		PP1722	FA	5.993	1543.8	(M+H)+
PP1668	AA	8.079	1575.9	(M-H)-		PP1727	FA	6.205	1516.2	(M-H)-
PP1670	FA	6.651	1561.9	(M+H)+		PP1728	FA	6.307	1529.7	(M+H)+
PP1671	FA	6.157	1563.7	(M+H)+		PP1729	FA	6.356	1533.7	(M+H)+
PP1672	AA	8.133	1578.2	(M+H)+		PP1731	FA	6.260	1555.8	(M+H)+
PP1673	FA	6.879	1606.3	(M+H)+		PP1732	AA	7.944	1569.8	(M+H)+
PP1674	FA	5.632	1512.4	(M-H)-		PP1733	FA	6.392	1606.2	(M+H)+
PP1675	FA	5.928	1581.7	(M+H)+		PP1734	FA	6.473	1624.2	(M+H)+
PP1676	FA	6.260	1573.3	$(M+NH_4)+$		PP1735	FA	6.259	1567.7	(M-H)-
PP1677	FA	5.779	1554.8	$(M+NH_4)+$		PP1736	FA	6.561	1583.7	(M+H)+
PP1678	AA	7.967	1585.3	$(M+NH_4)+$		PP1737	FA	6.391	1580.2	(M+H)+
PP1679	FA	5.915	1558.3	(M+H)+		PP1738	FA	6.256	1581.7	(M+H)+
PP1682	AA	7.832	1558.2	(M+H)+		PP1739	FA	6.551	1595.7	(M+H)+
PP1683	FA	6.364	1517.8	(M+H)+		PP1740	FA	6.164	1569.7	(M+H)+
PP1684	AA	8.164	1542.1	(M-H)-		PP1741	FA	6.064	1570.3	(M+H)+
PP1687	FA	6.327	1571.7	(M+H)+		PP1742	FA	6.128	1598.7	$(M+NH_4)+$
PP1688	AA	7.523	1562.1	(M+H)+		PP1743	FA	6.196	1603.2	$(M+NH_4)+$
PP1689	AA	7.737	1521.7	(M+H)+		PP1744	AA	8.092	1614.3	(M+H)+
PP1691	AA	7.749	1531.7	(M+H)+		PP1746	AA	7.887	1549.1	$(M+NH_4)+$
PP1692	AA	7.945	1545.7	(M+H)+		PP1747	AA	7.759	1566.2	(M-H)-
PP1693	AA	7.861	1534.0	(M-H)-		PP1748	FA	6.205	1544.3	(M-H)-
PP1694	FA	6.349	1549.7	(M+H)+		PP1749	FA	6.196	1558.1	(M+H)+
PP1696	AA	7.957	1551.7	(M+H)+		PP1750	FA	6.392	1558.2	(M-H)-
PP1697	AA	8.031	1587.9	(M+Na)+		PP1751	AA	8.076	1560.1	(M+H)+
PP1698	AA	8.215	1578.3	(M-H)-		PP1752	FA	6.437	1572.1	(M+H)+
PP1699	AA	7.909	1532.0	(M-H)-		PP1753	AA	7.813	1569.3	(M+Na)+
PP1700	AA	7.791	1570.2	(M+H)+		PP1754	FA	6.291	1576.1	(M+H)+
PP1701	AA	7.597	1572.2	(M-H)-		PP1757	AA	8.087	1564.1	(M+H)+
PP1702	AA	7.816	1588.2	(M+H)+		PP1758	FA	6.044	1511.9	(M-H)-
PP1703	FA	6.120	1542.2	(M-H)-		PP1759	FA	6.033	1526.1	(M+H)+
PP1704	AA	8.124	1560.3	(M-H)-		PP1760	FA	6.241	1527.7	(M+H)+
PP1705	FA	6.528	1573.8	(M+H)+		PP1761	FA	6.177	1526.2	(M-H)-
PP1706	AA	7.849	1567.2	$(M+NH_4)+$		PP1762	AA	8.099	1540.2	(M+H)+
PP1707	FA	5.896	1510.3	(M-H)-		PP1763	AA	8.125	1544.2	(M+H)+
PP1709	AA	7.623	1560.2	(M-H)-		PP1764	AA	8.045	1561.2	$(M+NH_4)+$
PP1710	FA	6.144	1578.3	(M-H)-		PP1765	AA	7.795	1548.3	(M+H)+
PP1711	FA	6.217	1540.2	(M+H)+		PP1767	FA	6.097	1548.1	(M+H)+
PP1713	FA	6.231	1551.8	(M+H)+		PP1768	FA	6.196	1546.3	(M-H)-

PP1769	FA	6.077	1546.4	(M-H)-		PP1818	AA	7.941	1458.2	(M+H)+
PP1771	FA	6.479	1561.7	(M+H)+		PP1819	FA	6.377	1473.4	(M+H)+
PP1772	FA	6.388	1561.9	(M+H)+		PP1820	FA	6.493	1432.2	(M+H)+
PP1773	AA	8.093	1560.3	(M-H)-		PP1821	FA	5.871	1461.6	(M-H)-
PP1776	FA	5.999	1490.2	(M-H)-		PP1822	FA	5.683	1417.7	(M-H)-
PP1777	AA	7.727	1490.3	(M-H)-		PP1823	FA	6.043	1475.7	(M-H)-
PP1779	FA	5.569	1520.1	(M+H)+		PP1825	FA	6.259	1561.3	(M+H)+
PP1780	FA	5.317	1474.2	(M-H)-		PP1826	FA	6.137	1545.9	(M-H)-
PP1781	AA	7.419	1464.2	(M-H)-		PP1827	FA	5.697	1503.8	(M+H)+
PP1782	FA	5.153	1420.3	(M-H)-		PP1828	FA	5.503	1497.8	(M+H)+
PP1783	FA	5.467	1477.7	(M+H)+		PP1829	FA	6.296	1531.8	(M+H)+
PP1784	FA	5.213	1432.3	(M-H)-		PP1830	FA	6.123	1542.5	$(M+NH_4)+$
PP1785	FA	5.668	1490.3	(M-H)-		PP1831	FA	6.029	1517.8	(M+H)+
PP1786	FA	5.432	1447.7	(M+H)+		PP1832	FA	5.848	1529.0	$(M+NH_4)+$
PP1788	AA	7.464	1446.3	(M-H)-		PP1833	FA	5.473	1506.4	$(M+NH_4)+$
PP1789	FA	5.693	1461.9	(M+H)+		PP1834	FA	5.283	1501.3	$(M+NH_4)+$
PP1790	AA	7.716	1492.0	(M-H)-		PP1835	FA	6.069	1516.0	(M-H)-
PP1791	AA	7.531	1450.1	(M+H)+		PP1836	AA	7.579	1444.2	(M+H)+
PP1792	AA	7.692	1462.4	(M-H)-		PP1837	FA	6.201	1498.1	(M+H)+
PP1793	AA	7.583	1478.4	(M-H)-		PP1838	FA	5.519	1442.4	(M-H)-
PP1794	FA	5.392	1434.3	(M-H)-		PP1839	AA	7.921	1470.3	(M-H)-
PP1795	FA	5.648	1489.7	(M-H)-		PP1840	FA	5.577	1444.3	(M+H)+
PP1796	AA	7.409	1465.2	$(M+NH_4)+$		PP1841	FA	6.097	1471.7	(M+H)+
PP1797	FA	5.919	1518.2	(M+H)+		PP1842	FA	5.516	1442.4	(M-H)-
PP1798	FA	5.683	1471.9	(M-H)-		PP1844	FA	5.939	1446.2	(M-H)-
PP1799	FA	5.660	1449.7	(M+H)+		PP1846	FA	5.844	1447.6	(M+H)+
PP1800	AA	7.576	1460.3	(M-H)-		PP1848	AA	7.795	1447.6	(M+H)+
PP1801	FA	5.945	1486.3	(M-H)-		PP1849	FA	6.016	1471.7	(M+H)+
PP1802	FA	5.719	1461.8	(M+H)+		PP1850	FA	5.839	1447.6	(M+H)+
PP1803	AA	7.785	1474.4	(M-H)-		PP1851	AA	7.664	1501.7	(M+H)+
PP1804	FA	5.693	1531.9	(M-H)-		PP1852	FA	5.765	1447.6	(M+H)+
PP1805	FA	5.436	1488.2	(M-H)-		PP1853	FA	5.360	1428.4	(M-H)-
PP1806	AA	7.547	1478.3	(M-H)-		PP1854	AA	7.684	1469.4	(M+Na)+
PP1807	FA	5.288	1435.7	(M+H)+		PP1855	AA	7.369	1429.7	(M+H)+
PP1808	FA	5.581	1490.1	(M-H)-		PP1856	FA	5.852	1447.8	(M-H)-
PP1809	AA	7.423	1465.2	$(M+NH_4)+$		PP1857	FA	5.292	1447.3	$(M+NH_4)+$
PP1810	FA	5.740	1505.9	(M+H)+		PP1859	FA	5.227	1430.2	(M+H)+
PP1811	FA	5.504	1460.2	(M-H)-		PP1860	FA	5.799	1449.7	(M+H)+
PP1812	AA	7.540	1448.2	(M-H)-		PP1861	FA	5.284	1440.4	(M-H)-
PP1813	FA	5.588	1460.2	(M-H)-		PP1862	AA	7.695	1450.3	(M+H)+
PP1814	AA	7.717	1474.2	(M-H)-		PP1863	FA	5.225	1440.4	(M-H)-
PP1815	FA	6.153	1517.6	(M-H)-		PP1864	AA	7.623	1467.3	$(M+NH_4)+$
PP1816	AA	7.645	1429.6	(M-H)-		PP1865	FA	5.469	1442.3	(M-H)-
PP1817	FA	6.024	1447.6	(M+H)+		PP1866	FA	5.619	1448.4	(M-H)-

PP1867	FA	5.412	1442.4	(M-H)-		PP1911	FA	6.275	1497.9	(M+H)+
PP1868	FA	5.879	1475.3	$(M+NH_4)+$		PP1913	AA	7.848	1565.2	$(M+NH_4)+$
PP1869	AA	7.411	1458.3	(M-H)-		PP1914	FA	5.860	1493.6	(M+H)+
PP1870	FA	5.792	1456.4	(M-H)-		PP1915	AA	8.093	1560.4	(M+H)+
PP1871	FA	5.211	1458.4	(M-H)-		PP1916	FA	5.925	1492.2	(M-H)-
PP1872	FA	5.808	1486.4	(M-H)-		PP1917	FA	6.399	1590.4	(M-H)-
PP1873	AA	7.563	1474.3	(M+H)+		PP1918	FA	6.004	1506.2	(M-H)-
PP1874	FA	6.220	1460.2	(M-H)-		PP1919	AA	8.085	1590.0	(M-H)-
PP1875	FA	5.693	1478.4	(M-H)-		PP1920	FA	6.113	1536.2	(M-H)-
PP1876	FA	6.124	1460.3	(M-H)-		PP1921	AA	8.113	1590.4	(M-H)-
PP1877	FA	5.609	1480.3	(M+H)+		PP1922	AA	7.480	1506.2	(M-H)-
PP1878	FA	5.859	1495.1	$(M+NH_4)+$		PP1923	FA	6.164	1616.4	(M-H)-
PP1879	FA	5.501	1484.3	(M-H)-		PP1925	FA	6.241	1560.4	(M+H)+
PP1880	FA	6.141	1491.7	(M+H)+		PP1926	FA	6.055	1506.3	(M-H)-
PP1881	AA	7.921	1524.4	(M+Na)+		PP1927	AA	8.071	1570.3	(M+Na)+
PP1882	FA	6.128	1462.4	(M-H)-		PP1928	FA	6.119	1537.2	$(M+NH_4)+$
PP1883	FA	6.449	1506.2	(M+H)+		PP1929	AA	8.004	1542.4	(M-H)-
PP1884	AA	7.880	1462.3	(M-H)-		PP1930	FA	6.532	1503.6	(M+H)+
PP1885	FA	6.072	1470.5	(M-H)-		PP1931	FA	6.131	1542.4	(M-H)-
PP1886	FA	6.052	1492.4	(M-H)-		PP1932	FA	6.161	1509.9	(M-H)-
PP1887	FA	5.995	1502.4	(M+H)+		PP1934	FA	6.071	1509.1	$(M+NH_4)+$
PP1888	FA	5.823	1457.7	(M+H)+		PP1935	FA	6.017	1491.6	(M+H)+
PP1889	FA	6.092	1471.7	(M+H)+		PP1936	FA	6.197	1521.6	(M+H)+
PP1890	FA	5.737	1456.4	(M-H)-		PP1937	FA	6.011	1535.9	(M+H)+
PP1891	AA	7.837	1470.3	(M-H)-		PP1938	FA	6.128	1562.3	(M-H)-
PP1892	AA	7.688	1486.0	(M-H)-		PP1941	FA	6.237	1533.8	(M-H)-
PP1893	FA	6.419	1474.3	(M-H)-		PP1942	FA	6.345	1546.3	(M-H)-
PP1894	AA	8.072	1476.1	(M+H)+		PP1943	FA	6.035	1558.3	(M-H)-
PP1895	FA	5.815	1476.3	(M-H)-		PP1944	AA	7.965	1560.4	(M+H)+
PP1896	FA	6.023	1490.3	(M-H)-		PP1945	FA	6.639	1572.3	(M-H)-
PP1897	FA	5.575	1454.3	(M-H)-		PP1946	FA	6.001	1518.2	(M-H)-
PP1898	FA	5.821	1468.4	(M-H)-		PP1947	FA	6.237	1518.2	(M-H)-
PP1899	FA	6.092	1482.4	(M-H)-		PP1948	FA	6.028	1520.1	(M+H)+
PP1900	FA	5.520	1456.4	(M+H)+		PP1949	FA	6.159	1519.6	(M+H)+
PP1901	AA	7.687	1470.2	(M+H)+		PP1950	FA	6.037	1517.8	(M-H)-
PP1902	AA	7.857	1482.3	(M-H)-		PP1952	FA	6.071	1520.1	(M+H)+
PP1903	AA	7.709	1500.4	(M+H)+		PP1953	FA	5.936	1518.2	(M-H)-
PP1904	FA	5.759	1456.4	(M-H)-		PP1954	FA	6.140	1518.2	(M-H)-
PP1905	FA	6.000	1488.8	$(M+NH_4)+$		PP1955	FA	5.913	1532.1	(M+H)+
PP1906	FA	6.280	1484.4	(M-H)-		PP1956	FA	6.005	1476.2	(M-H)-
PP1907	FA	5.696	1456.3	(M-H)-		PP1957	FA	6.160	1502.2	(M-H)-
PP1908	AA	7.796	1489.4	$(M+NH_4)+$		PP1958	FA	6.016	1506.2	(M-H)-
PP1909	FA	6.209	1503.2	$(M+NH_4)+$		PP1959	FA	6.028	1520.1	(M+H)+
PP1910	AA	7.641	1505.4	$(M+NH_4)+$		PP1960	FA	6.096	1464.2	(M-H)-

PP1961	FA	6.301	1490.2	(M-H)-		PP2010	AA	7.924	1590.0	(M-H)-
PP1963	FA	5.980	1536.1	(M+H)+		PP2011	FA	6.169	1521.9	(M-H)-
PP1964	FA	6.183	1548.3	(M-H)-		PP2012	FA	6.400	1584.2	(M-H)-
PP1965	FA	6.484	1562.2	(M-H)-		PP2013	FA	5.919	1561.4	(M-H)-
PP1967	FA	6.059	1518.2	(M-H)-		PP2014	FA	6.096	1570.0	(M-H)-
PP1968	FA	6.108	1517.9	(M-H)-		PP2015	FA	5.911	1555.4	(M-H)-
PP1969	FA	6.115	1517.9	(M-H)-		PP2016	FA	5.856	1555.4	(M-H)-
PP1970	FA	6.055	1518.2	(M-H)-		PP2017	FA	6.175	1569.8	(M-H)-
PP1971	FA	6.037	1518.3	(M-H)-		PP2018	FA	5.735	1555.7	(M-H)-
PP1972	FA	6.279	1545.4	(M-H)-		PP2019	FA	5.725	1525.9	(M-H)-
PP1973	FA	6.353	1584.0	(M-H)-		PP2020	AA	7.812	1540.0	(M-H)-
PP1974	FA	6.568	1559.9	(M-H)-		PP2021	FA	5.557	1524.1	(M-H)-
PP1975	FA	6.212	1586.3	(M+H)+		PP2022	FA	5.809	1537.9	(M-H)-
PP1976	FA	6.583	1529.8	(M-H)-		PP2023	FA	6.128	1552.1	(M-H)-
PP1977	FA	6.235	1553.9	(M-H)-		PP2024	FA	6.025	1531.8	(M-H)-
PP1979	FA	5.961	1540.1	(M-H)-		PP2025	FA	6.019	1525.9	(M-H)-
PP1980	FA	6.395	1527.5	(M-H)-		PP2026	FA	5.721	1511.8	(M-H)-
PP1981	FA	6.057	1552.1	(M-H)-		PP2027	FA	5.983	1526.1	(M-H)-
PP1983	FA	6.357	1565.7	(M-H)-		PP2028	FA	6.287	1539.7	(M-H)-
PP1984	FA	6.657	1541.3	(M-H)-		PP2029	FA	5.825	1525.8	(M-H)-
PP1985	FA	6.323	1565.9	(M-H)-		PP2030	AA	8.088	1596.1	(M-H)-
PP1987	FA	6.055	1551.9	(M-H)-		PP2031	FA	6.628	1589.9	(M-H)-
PP1988	FA	6.156	1562.1	(M-H)-		PP2032	FA	6.325	1575.8	(M-H)-
PP1989	FA	6.504	1559.9	(M-H)-		PP2033	FA	6.448	1590.4	(M-H)-
PP1990	FA	5.951	1532.0	(M-H)-		PP2034	AA	8.095	1560.1	(M-H)-
PP1991	FA	6.535	1554.1	(M-H)-		PP2036	FA	6.291	1557.8	(M-H)-
PP1992	FA	6.265	1545.9	(M-H)-		PP2037	FA	6.587	1572.1	(M-H)-
PP1993	FA	6.243	1539.9	(M-H)-		PP2038	FA	6.544	1574.0	(M+H)+
PP1994	FA	6.103	1544.0	(M-H)-		PP2040	FA	6.715	1566.0	(M-H)-
PP1995	FA	6.503	1553.7	(M-H)-		PP2041	AA	8.279	1560.1	(M-H)-
PP1996	FA	6.043	1544.3	(M-H)-		PP2042	FA	6.479	1546.0	(M-H)-
PP1997	FA	6.241	1539.7	(M-H)-		PP2043	FA	6.725	1559.8	(M-H)-
PP1998	FA	6.347	1557.8	(M-H)-		PP2044	FA	6.200	1506.3	(M-H)-
PP1999	FA	6.043	1539.4	(M-H)-		PP2045	FA	6.480	1558.3	(M-H)-
PP2000	FA	6.235	1537.8	(M-H)-		PP2046	AA	7.969	1556.3	(M-H)-
PP2001	FA	6.331	1553.5	(M-H)-		PP2047	FA	5.607	1464.3	(M-H)-
PP2002	FA	6.263	1531.6	(M-H)-		PP2048	FA	5.901	1516.2	(M-H)-
PP2003	FA	6.345	1523.9	(M-H)-		PP2049	FA	5.717	1515.6	(M+H)+
PP2004	FA	5.963	1518.0	(M-H)-		PP2050	AA	8.169	1551.0	$(M+NH_4)+$
PP2005	FA	6.083	1509.4	(M-H)-		PP2051	AA	7.737	1550.3	(M-H)-
PP2006	AA	7.963	1532.0	(M-H)-		PP2052	FA	6.320	1530.3	(M-H)-
PP2007	FA	6.160	1521.9	(M-H)-		PP2053	AA	7.919	1566.4	(M+H)+
PP2008	FA	6.516	1546.1	(M-H)-		PP2054	FA	6.223	1533.3	$(M+NH_4)+$
PP2009	FA	6.432	1535.4	(M-H)-		PP2055	FA	6.137	1539.2	$(M+NH_4)+$

PP2056	AA	7.997	1526.4	(M-H)-		PP2109	FA	6.515	1532.3	(M-H)-
PP2057	FA	6.435	1552.7	$(M+NH_4)+$		PP2117	FA	5.437	1492.0	(M+H)+
PP2058	AA	8.039	1526.4	(M-H)-		PP2118	FA	5.233	1484.0	(M-H)-
PP2059	FA	5.801	1536.4	(M-H)-		PP2119	FA	6.471	1560.0	(M-H)-
PP2060	FA	6.108	1524.3	(M-H)-		PP2120	FA	6.548	1484.1	(M-H)-
PP2061	FA	5.639	1492.3	(M-H)-		PP2121	FA	6.183	1550.0	(M-H)-
PP2062	FA	6.319	1533.9	(M-H)-		PP2122	AA	8.148	1457.8	(M-H)-
PP2063	AA	7.685	1506.3	(M-H)-		PP2123	FA	6.328	1576.0	(M-H)-
PP2064	AA	7.968	1494.4	(M-H)-		PP2124	FA	6.539	1558.0	(M-H)-
PP2065	FA	5.737	1496.2	(M-H)-		PP2125	FA	6.475	1548.2	(M-H)-
PP2066	FA	6.035	1530.3	(M+H)+		PP2126	FA	6.260	1548.0	(M-H)-
PP2067	FA	6.044	1510.4	(M-H)-		PP2127	FA	6.515	1562.2	(M-H)-
PP2068	FA	5.948	1489.7	(M+H)+		PP2128	FA	6.421	1573.8	(M-H)-
PP2069	FA	5.559	1495.6	(M+H)+		PP2130	FA	6.559	1546.0	(M-H)-
PP2070	FA	5.851	1508.4	(M-H)-		PP2131	FA	6.344	1546.2	(M-H)-
PP2071	FA	5.831	1508.4	(M-H)-		PP2132	FA	6.617	1560.1	(M-H)-
PP2072	FA	6.136	1522.3	(M-H)-		PP2133	FA	6.643	1575.6	(M+H)+
PP2073	FA	6.179	1558.2	(M+H)+		PP2135	FA	6.527	1548.2	(M-H)-
PP2074	FA	6.485	1572.4	(M+H)+		PP2137	FA	6.264	1506.0	(M-H)-
PP2075	FA	6.400	1527.7	(M+H)+		PP2138	FA	6.737	1572.1	(M-H)-
PP2076	FA	6.689	1540.3	(M-H)-		PP2139	FA	6.128	1522.1	(M-H)-
PP2077	AA	7.863	1530.6	$(M+NH_4)+$		PP2140	FA	6.619	1546.1	(M-H)-
PP2078	FA	5.973	1521.1	$(M+NH_4)+$		PP2141	AA	8.064	1508.1	(M-H)-
PP2079	FA	6.275	1516.2	(M-H)-		PP2142	FA	6.356	1506.4	(M+H)+
PP2080	AA	7.699	1500.3	(M-H)-		PP2143	FA	5.965	1467.6	(M+H)+
PP2081	FA	6.093	1515.6	(M+H)+		PP2144	FA	6.235	1520.1	(M-H)-
PP2082	FA	6.048	1514.2	(M-H)-		PP2145	FA	6.123	1492.1	(M-H)-
PP2083	AA	8.031	1528.2	(M-H)-		PP2146	FA	6.371	1492.3	(M-H)-
PP2087	AA	7.925	1557.6	(M+H)+		PP2147	FA	6.179	1480.1	(M-H)-
PP2091	FA	6.004	1569.2	$(M+NH_4)+$		PP2148	FA	6.455	1506.0	(M-H)-
PP2093	FA	6.337	1520.2	(M+H)+		PP2149	FA	6.333	1507.5	(M+H)+
PP2094	FA	6.387	1518.4	(M-H)-		PP2150	FA	6.052	1465.5	(M+H)+
PP2095	FA	6.199	1516.3	(M-H)-		PP2151	FA	6.477	1520.1	(M-H)-
PP2096	AA	7.893	1502.4	(M+H)+		PP2152	FA	6.217	1492.3	(M+H)+
PP2097	FA	6.113	1531.3	$(M+NH_4)+$		PP2153	FA	6.348	1494.3	(M-H)-
PP2098	FA	6.149	1512.3	(M-H)-		PP2154	FA	6.268	1478.0	(M-H)-
PP2099	FA	5.964	1510.3	(M-H)-		PP2155	FA	6.196	1554.2	(M-H)-
PP2101	FA	6.448	1574.4	(M+H)+		PP2156	FA	6.569	1518.1	(M-H)-
PP2102	FA	6.528	1572.4	(M-H)-		PP2157	FA	5.897	1544.2	(M-H)-
PP2103	FA	6.379	1570.3	(M-H)-		PP2158	FA	6.436	1491.6	(M-H)-
PP2105	FA	6.224	1568.2	(M+H)+		PP2159	FA	6.051	1570.1	(M-H)-
PP2106	FA	6.301	1566.4	(M-H)-		PP2160	FA	6.208	1542.0	(M-H)-
PP2107	FA	6.129	1566.3	(M+H)+		PP2161	FA	6.305	1556.3	(M-H)-
PP2108	AA	8.140	1522.4	(M+H)+		PP2163	FA	6.059	1542.0	(M+H)+

PP2164	FA	6.420	1568.1	(M-H)-		PP2218	FA	6.152	1493.5	(M+H)+
PP2165	FA	6.240	1541.6	(M-H)-		PP2219	FA	6.275	1492.0	(M-H)-
PP2166	FA	6.016	1500.1	(M-H)-		PP2220	FA	5.949	1462.2	(M-H)-
PP2167	FA	5.856	1516.1	(M-H)-		PP2221	FA	6.096	1489.8	(M-H)-
PP2168	FA	6.141	1502.3	(M-H)-		PP2222	FA	6.188	1480.0	(M+H)+
PP2169	FA	5.837	1486.3	(M-H)-		PP2223	FA	6.203	1476.2	(M-H)-
PP2170	FA	5.887	1473.6	(M-H)-		PP2224	FA	6.073	1496.6	$(M+NH_4)+$
PP2171	FA	6.041	1500.2	(M-H)-		PP2225	FA	5.904	1478.0	(M-H)-
PP2172	FA	6.257	1514.2	(M-H)-		PP2226	AA	7.797	1503.9	(M-H)-
PP2173	FA	6.057	1488.3	(M-H)-		PP2227	FA	6.089	1462.0	(M-H)-
PP2174	AA	8.243	1539.9	(M-H)-		PP2229	FA	6.440	1506.2	(M-H)-
PP2175	FA	6.547	1513.9	(M+H)+		PP2230	AA	8.119	1491.6	(M-H)-
PP2176	FA	6.596	1525.8	(M-H)-		PP2231	FA	6.232	1475.7	(M-H)-
PP2178	FA	6.428	1511.4	(M+H)+		PP2232	FA	6.200	1492.0	(M-H)-
PP2179	FA	6.492	1498.1	(M-H)-		PP2233	FA	5.851	1448.0	(M-H)-
PP2180	FA	6.719	1538.1	(M-H)-		PP2234	FA	6.285	1490.0	(M-H)-
PP2181	AA	8.216	1512.1	(M-H)-		PP2235	FA	6.537	1504.0	(M-H)-
PP2182	FA	6.329	1469.8	(M-H)-		PP2237	FA	5.869	1445.6	(M-H)-
PP2183	FA	6.216	1487.5	(M+H)+		PP2238	FA	6.157	1460.0	(M-H)-
PP2184	FA	6.344	1459.5	(M+H)+		PP2242	FA	5.483	1458.2	(M-H)-
PP2185	FA	6.421	1471.9	(M-H)-		PP2257	FA	6.225	1490.0	(M-H)-
PP2186	FA	6.023	1429.8	(M-H)-		PP2259	FA	5.783	1511.9	(M-H)-
PP2187	FA	6.201	1455.9	(M-H)-		PP2260	AA	7.825	1526.2	(M-H)-
PP2188	FA	6.257	1443.8	(M-H)-		PP2261	AA	7.179	1476.2	(M-H)-
PP2189	FA	5.912	1461.5	(M-H)-		PP2262	FA	4.957	1470.2	(M-H)-
PP2190	FA	6.111	1489.7	(M-H)-		PP2263	FA	5.505	1497.5	(M-H)-
PP2191	FA	6.179	1476.1	(M-H)-		PP2264	FA	5.225	1483.8	(M-H)-
PP2192	FA	6.049	1516.2	(M-H)-		PP2268	FA	6.137	1515.9	(M-H)-
PP2193	AA	8.176	1490.3	(M-H)-		PP2269	FA	5.912	1512.3	(M-H)-
PP2195	FA	5.952	1490.0	(M-H)-		PP2270	FA	6.419	1513.8	(M-H)-
PP2196	FA	6.337	1504.0	(M-H)-		PP2271	FA	6.111	1521.0	$(M+NH_4)+$
PP2197	FA	5.652	1486.1	(M-H)-		PP2272	FA	6.377	1515.6	(M-H)-
PP2198	FA	6.151	1502.1	(M-H)-		PP2273	FA	6.372	1516.0	(M-H)-
PP2199	SQD	1.050	1493.9	(M+H)+		PP2275	AA	8.187	1543.8	(M-H)-
PP2200	FA	6.428	1492.1	(M-H)-		PP2312	FA	5.669	1525.8	(M-H)-
PP2202	FA	6.291	1491.8	(M-H)-		PP2313	FA	6.263	1554.1	(M-H)-
PP2203	FA	6.717	1520.3	(M-H)-		PP2314	FA	5.736	1556.2	(M-H)-
PP2207	FA	6.516	1505.8	(M-H)-		PP2315	FA	6.072	1570.3	(M-H)-
PP2208	FA	6.365	1476.0	(M-H)-		PP2316	FA	6.085	1552.1	(M-H)-
PP2209	FA	6.325	1504.1	(M-H)-		PP2317	FA	6.079	1554.1	(M-H)-
PP2210	FA	6.120	1459.7	(M-H)-		PP2318	FA	6.163	1582.1	(M-H)-
PP2212	FA	6.379	1474.0	(M-H)-		PP2319	FA	5.867	1569.7	(M-H)-
PP2214	FA	6.671	1488.1	(M-H)-		PP2320	FA	5.915	1551.5	(M-H)-
PP2216	AA	7.876	1462.2	(M-H)-		PP2322	FA	5.975	1582.2	(M-H)-

PP2323	FA	5.815	1504.3	(M-H)-		PP2370	FA	5.848	1435.6	(M+H)+
PP2325	FA	6.177	1500.1	(M-H)-		PP2371	FA	5.727	1449.9	(M-H)-
PP2326	FA	5.604	1502.1	(M-H)-		PP2372	FA	6.309	1461.6	(M+H)+
PP2327	FA	6.269	1530.2	(M-H)-		PP2373	FA	6.181	1476.3	(M-H)-
PP2328	FA	5.995	1498.1	(M-H)-		PP2374	FA	6.204	1460.2	(M-H)-
PP2329	AA	7.744	1500.1	(M-H)-		PP2375	FA	6.143	1476.1	(M-H)-
PP2330	FA	6.083	1527.7	(M-H)-		PP2376	FA	5.533	1471.4	(M+H)+
PP2331	FA	6.067	1529.9	(M-H)-		PP2377	FA	5.659	1500.1	(M-H)-
PP2332	FA	5.804	1498.2	(M-H)-		PP2378	FA	5.952	1495.6	(M-H)-
PP2333	FA	6.072	1465.7	(M-H)-		PP2379	FA	6.071	1526.1	(M-H)-
PP2334	FA	5.879	1530.3	(M+H)+		PP2380	FA	5.785	1496.2	(M-H)-
PP2335	FA	5.727	1468.1	(M-H)-		PP2381	FA	5.957	1526.3	(M-H)-
PP2336	FA	5.760	1463.7	(M-H)-		PP2382	FA	5.837	1527.6	(M-H)-
PP2337	FA	6.515	1492.3	(M-H)-		PP2383	FA	5.655	1543.6	(M-H)-
PP2338	FA	5.619	1480.3	(M-H)-		PP2385	FA	5.567	1458.2	(M-H)-
PP2339	FA	6.144	1494.3	(M-H)-		PP2386	FA	6.048	1498.1	(M-H)-
PP2340	FA	6.223	1490.3	(M-H)-		PP2387	FA	5.480	1459.5	(M+H)+
PP2341	FA	6.401	1492.3	(M-H)-		PP2388	AA	7.869	1512.3	(M-H)-
PP2342	FA	6.079	1506.3	(M-H)-		PP2389	FA	5.765	1491.6	(M-H)-
PP2344	FA	6.100	1490.1	(M-H)-		PP2390	FA	5.676	1514.3	(M-H)-
PP2345	FA	5.720	1502.1	(M-H)-		PP2391	FA	5.680	1494.0	(M-H)-
PP2347	FA	5.556	1518.1	(M-H)-		PP2392	FA	5.712	1502.2	(M-H)-
PP2348	AA	7.396	1500.2	(M-H)-		PP2393	FA	5.713	1472.0	(M-H)-
PP2349	FA	6.140	1528.3	(M-H)-		PP2394	FA	6.085	1476.1	(M-H)-
PP2350	FA	5.516	1530.3	(M-H)-		PP2395	FA	5.945	1505.7	(M-H)-
PP2351	FA	5.944	1544.1	(M-H)-		PP2396	FA	5.956	1508.2	(M-H)-
PP2352	FA	5.843	1526.3	(M-H)-		PP2397	FA	5.856	1508.1	(M-H)-
PP2353	FA	5.949	1528.3	(M-H)-		PP2398	FA	6.004	1516.3	(M-H)-
PP2354	FA	5.933	1556.1	(M-H)-		PP2399	FA	6.469	1489.9	(M-H)-
PP2355	FA	5.833	1544.3	(M-H)-		PP2400	FA	6.347	1520.1	(M-H)-
PP2356	FA	5.648	1526.3	(M-H)-		PP2401	FA	6.233	1519.9	(M-H)-
PP2357	FA	5.793	1556.3	(M-H)-		PP2402	AA	8.067	1520.1	(M-H)-
PP2358	FA	5.732	1496.2	(M-H)-		PP2403	FA	6.264	1522.0	(M-H)-
PP2359	FA	5.541	1511.6	(M-H)-		PP2404	FA	6.144	1522.3	(M-H)-
PP2360	FA	6.183	1522.1	(M-H)-		PP2405	FA	6.316	1500.1	(M-H)-
PP2361	FA	5.952	1538.0	(M-H)-		PP2406	FA	6.209	1530.3	(M-H)-
PP2362	FA	5.984	1521.6	(M-H)-		PP2407	FA	6.561	1506.3	(M-H)-
PP2363	FA	5.741	1538.0	(M-H)-		PP2408	FA	6.448	1536.3	(M-H)-
PP2364	FA	5.613	1442.4	(M-H)-		PP2409	FA	6.293	1496.1	(M-H)-
PP2365	FA	5.701	1472.2	(M-H)-		PP2410	FA	6.555	1510.1	(M-H)-
PP2366	FA	6.071	1467.6	(M-H)-		PP2411	FA	6.768	1516.3	(M-H)-
PP2367	FA	6.167	1498.1	(M-H)-		PP2412	FA	5.867	1486.3	(M-H)-
PP2368	FA	5.865	1467.6	(M-H)-		PP2413	AA	7.915	1500.3	(M-H)-
PP2369	FA	5.947	1498.1	(M-H)-		PP2414	FA	6.355	1506.3	(M-H)-

PP2415	FA	6.167	1500.0	(M-H)-		PP2464	FA	6.079	1546.1	(M-H)-
PP2416	FA	6.440	1514.1	(M-H)-		PP2465	FA	6.641	1504.3	(M-H)-
PP2417	FA	6.657	1520.3	(M-H)-		PP2466	FA	6.329	1452.1	(M-H)-
PP2418	FA	6.000	1512.0	(M-H)-		PP2467	FA	6.623	1504.0	(M-H)-
PP2419	FA	6.255	1526.4	(M-H)-		PP2468	FA	6.528	1486.1	(M-H)-
PP2422	FA	6.067	1508.3	(M-H)-		PP2469	FA	6.496	1534.1	(M-H)-
PP2423	FA	6.105	1516.1	(M-H)-		PP2470	FA	6.261	1496.3	(M-H)-
PP2424	FA	6.343	1522.2	(M-H)-		PP2471	FA	6.527	1506.0	(M-H)-
PP2425	FA	6.133	1516.1	(M-H)-		PP2472	FA	6.329	1553.5	(M+H)+
PP2426	FA	6.381	1521.7	(M-H)-		PP2475	FA	6.420	1506.1	(M-H)-
PP2427	FA	6.175	1512.2	(M-H)-		PP2477	FA	6.051	1516.1	(M-H)-
PP2428	FA	6.288	1548.1	(M-H)-		PP2479	FA	6.560	1502.2	(M-H)-
PP2429	FA	6.461	1526.3	(M-H)-		PP2480	FA	6.015	1528.1	(M-H)-
PP2430	FA	6.649	1532.1	(M-H)-		PP2481	FA	6.349	1522.3	(M-H)-
PP2431	FA	6.228	1542.3	(M-H)-		PP2482	FA	6.031	1516.1	(M-H)-
PP2432	FA	6.343	1578.1	(M-H)-		PP2483	FA	6.284	1516.1	(M-H)-
PP2433	FA	5.944	1528.3	(M-H)-		PP2484	FA	6.419	1550.3	(M-H)-
PP2436	FA	6.401	1578.1	(M-H)-		PP2485	FA	6.277	1534.3	(M-H)-
PP2437	FA	6.081	1478.2	(M-H)-		PP2488	FA	6.636	1499.9	(M-H)-
PP2438	FA	5.696	1518.3	(M-H)-		PP2489	FA	6.291	1522.3	(M-H)-
PP2439	FA	5.992	1478.0	(M-H)-		PP2490	FA	6.557	1522.2	(M-H)-
PP2440	FA	5.971	1524.0	(M-H)-		PP2492	FA	6.443	1520.1	(M-H)-
PP2441	FA	6.119	1486.3	(M-H)-		PP2494	FA	6.144	1498.0	(M-H)-
PP2442	FA	5.893	1488.0	(M-H)-		PP2495	FA	6.365	1532.1	(M-H)-
PP2443	AA	7.855	1486.1	(M-H)-		PP2496	FA	6.445	1492.2	(M-H)-
PP2444	FA	6.069	1522.0	(M-H)-		PP2497	FA	6.173	1486.2	(M-H)-
PP2445	FA	5.901	1516.1	(M-H)-		PP2498	FA	6.389	1520.0	(M-H)-
PP2446	FA	5.843	1532.3	(M-H)-		PP2499	FA	6.653	1538.7	$(M+NH_4)+$
PP2447	FA	6.027	1486.3	(M-H)-		PP2500	FA	6.413	1504.2	(M-H)-
PP2448	FA	6.199	1494.0	(M-H)-		PP2501	FA	6.792	1516.0	(M-H)-
PP2449	FA	5.901	1516.1	(M-H)-		PP2502	FA	5.905	1461.5	(M-H)-
PP2450	FA	6.088	1537.7	(M-H)-		PP2504	FA	5.835	1472.0	(M-H)-
PP2451	FA	6.357	1490.0	(M-H)-		PP2505	FA	5.751	1472.3	(M-H)-
PP2452	FA	6.120	1482.3	(M-H)-		PP2506	FA	6.181	1476.0	(M-H)-
PP2453	FA	6.344	1490.0	(M-H)-		PP2507	FA	6.049	1505.8	(M-H)-
PP2454	AA	7.987	1515.6	(M+Na)+		PP2508	FA	6.423	1518.1	(M-H)-
PP2455	FA	6.375	1492.2	(M-H)-		PP2509	FA	6.675	1501.4	(M+H)+
PP2456	FA	6.444	1488.2	(M-H)-		PP2510	FA	6.232	1512.3	(M-H)-
PP2457	FA	6.268	1492.2	(M-H)-		PP2511	FA	6.667	1525.7	(M-H)-
PP2458	FA	6.033	1521.1	$(M+NH_4)+$		PP2512	FA	6.260	1535.2	$(M+NH_4)+$
PP2460	FA	6.188	1537.6	(M+H)+		PP2513	FA	6.736	1490.1	(M-H)-
PP2461	FA	6.292	1500.1	(M-H)-		PP2514	FA	6.031	1510.1	(M-H)-
PP2462	FA	6.317	1508.0	(M-H)-		PP2515	FA	7.073	1528.3	(M-H)-
PP2463	FA	6.180	1530.3	(M-H)-		PP2516	FA	6.308	1506.0	(M-H)-

PP2517	AA	8.683	1493.5	(M+H)+		PP2563	FA	6.537	1477.4	(M+H)+
PP2518	FA	6.089	1500.3	(M-H)-		PP2564	FA	6.908	1514.1	(M-H)-
PP2519	FA	6.536	1560.1	(M-H)-		PP2565	AA	8.583	1477.9	(M-H)-
PP2520	FA	6.271	1536.0	(M-H)-		PP2566	FA	6.360	1545.7	(M-H)-
PP2521	FA	6.595	1523.8	(M-H)-		PP2567	FA	6.395	1528.9	$(M+NH_4)+$
PP2522	FA	6.052	1530.3	(M-H)-		PP2568	FA	6.393	1550.3	(M-H)-
PP2523	FA	6.567	1564.3	(M-H)-		PP2569	FA	6.500	1515.4	(M+H)+
PP2524	FA	6.511	1516.0	(M-H)-		PP2570	FA	6.608	1531.9	(M-H)-
PP2525	AA	8.288	1527.9	(M-H)-		PP2571	FA	6.656	1497.4	(M+H)+
PP2526	FA	6.335	1514.1	(M-H)-		PP2572	FA	6.575	1536.3	(M-H)-
PP2527	FA	6.607	1556.1	(M-H)-		PP2573	FA	6.411	1560.5	$(M+NH_4)+$
PP2528	FA	6.383	1504.0	(M-H)-		PP2574	FA	5.873	1528.2	(M-H)-
PP2529	FA	6.775	1569.6	(M-H)-		PP2575	FA	5.852	1504.0	(M-H)-
PP2530	FA	6.353	1535.6	(M+H)+		PP2576	FA	5.976	1530.3	(M-H)-
PP2531	AA	7.967	1494.2	(M-H)-		PP2577	FA	6.103	1481.4	(M+H)+
PP2532	FA	5.975	1490.0	(M-H)-		PP2578	FA	6.511	1507.4	(M+H)+
PP2533	AA	8.221	1551.4	(M+Na)+		PP2579	AA	7.833	1510.8	$(M+NH_4)+$
PP2534	FA	5.771	1483.6	(M-H)-		PP2580	FA	5.911	1486.5	$(M+NH_4)+$
PP2535	FA	6.479	1507.9	(M-H)-		PP2581	FA	6.063	1493.8	(M-H)-
PP2536	FA	5.785	1488.2	(M-H)-		PP2583	FA	6.408	1554.0	(M-H)-
PP2537	FA	6.576	1473.5	(M+H)+		PP2586	FA	5.509	1490.2	(M-H)-
PP2539	FA	5.839	1478.0	(M-H)-		PP2588	FA	5.575	1496.5	$(M+NH_4)+$
PP2540	FA	5.611	1472.2	(M-H)-		PP2589	FA	5.575	1455.5	(M+H)+
PP2541	FA	5.761	1508.0	(M-H)-		PP2590	FA	6.331	1512.6	$(M+NH_4)+$
PP2542	FA	5.539	1504.0	(M+H)+		PP2591	AA	7.741	1498.9	$(M+NH_4)+$
PP2543	FA	6.053	1488.2	(M-H)-		PP2592	FA	6.320	1512.4	$(M+NH_4)+$
PP2545	FA	5.907	1476.0	(M-H)-		PP2593	FA	6.159	1507.9	(M+H)+
PP2546	FA	5.848	1505.9	(M-H)-		PP2594	FA	6.072	1537.2	$(M+NH_4)+$
PP2547	FA	5.577	1522.4	(M+H)+		PP2595	FA	6.320	1512.9	$(M+NH_4)+$
PP2548	FA	5.375	1515.5	(M+H)+		PP2596	AA	7.975	1505.9	(M-H)-
PP2549	FA	5.660	1517.8	(M-H)-		PP2597	FA	6.147	1493.5	(M+H)+
PP2550	FA	5.645	1520.3	(M-H)-		PP2598	FA	6.247	1492.2	(M-H)-
PP2551	FA	5.425	1514.1	(M-H)-		PP2600	FA	5.611	1460.0	(M-H)-
PP2552	FA	5.731	1520.0	(M+H)+		PP2601	FA	5.824	1436.1	(M-H)-
PP2553	FA	6.060	1550.0	(M+H)+		PP2602	FA	5.676	1447.5	(M-H)-
PP2554	FA	5.857	1542.3	(M-H)-		PP2603	FA	5.659	1425.4	(M+H)+
PP2555	AA	8.049	1545.9	(M-H)-		PP2604	FA	5.825	1449.8	(M-H)-
PP2556	FA	6.125	1548.0	(M-H)-		PP2605	FA	6.024	1481.4	(M+H)+
PP2557	FA	5.904	1542.4	(M-H)-		PP2606	FA	6.780	1590.0	(M-H)-
PP2558	FA	6.207	1546.1	(M-H)-		PP2608	FA	6.968	1604.3	(M-H)-
PP2559	FA	6.451	1483.5	(M+H)+		PP2610	FA	6.911	1555.4	(M+H)+
PP2560	FA	6.704	1521.7	(M+H)+		PP2612	FA	7.109	1569.5	(M+H)+
PP2561	FA	6.779	1503.3	$(M+NH_4)+$		PP2614	FA	6.735	1544.2	(M-H)-
PP2562	AA	8.208	1512.2	(M-H)-		PP2615	FA	6.716	1576.3	(M-H)-

PP2616	AA	8.399	1507.9	(M-H)-		PP2671	FA	6.792	1567.6	(M+H)+
PP2618	FA	6.788	1538.1	(M-H)-		PP2672	FA	6.280	1496.3	(M-H)-
PP2619	FA	6.907	1562.3	(M-H)-		PP2673	FA	5.659	1482.4	(M-H)-
PP2622	FA	6.337	1576.0	(M+H)+		PP2674	FA	6.103	1476.1	(M-H)-
PP2624	FA	6.415	1539.3	(M+H)+		PP2675	FA	5.731	1478.1	(M-H)-
PP2626	FA	6.607	1560.0	(M-H)-		PP2676	FA	5.663	1482.2	(M-H)-
PP2627	FA	6.901	1589.9	(M-H)-		PP2677	FA	5.977	1497.8	(M-H)-
PP2628	FA	6.701	1525.4	(M+H)+		PP2678	FA	5.521	1498.1	(M-H)-
PP2630	FA	7.033	1552.1	(M-H)-		PP2679	FA	6.307	1537.7	(M+H)+
PP2631	FA	6.556	1584.3	(M-H)-		PP2681	FA	6.192	1509.7	(M+H)+
PP2633	FA	6.759	1598.3	(M-H)-		PP2683	FA	5.773	1459.7	(M+H)+
PP2634	AA	8.184	1588.4	(M-H)-		PP2684	FA	6.069	1476.2	(M+H)+
PP2635	FA	6.367	1539.9	(M-H)-		PP2685	FA	6.003	1454.4	(M-H)-
PP2637	FA	6.407	1539.0	$(M+NH_4)+$		PP2686	FA	5.817	1447.7	(M+H)+
PP2638	AA	8.244	1483.5	(M-H)-		PP2687	FA	6.243	1514.3	(M-H)-
PP2639	FA	6.561	1554.1	(M-H)-		PP2688	FA	6.092	1518.2	(M-H)-
PP2640	FA	6.580	1535.4	(M+H)+		PP2689	FA	6.059	1518.2	(M-H)-
PP2641	AA	8.371	1521.8	(M+Na)+		PP2690	FA	6.076	1550.3	(M-H)-
PP2642	AA	8.316	1539.8	(M-H)-		PP2691	FA	6.247	1526.1	(M-H)-
PP2643	FA	6.620	1521.3	(M+H)+		PP2692	FA	6.492	1528.4	(M-H)-
PP2644	AA	8.369	1483.8	(M-H)-		PP2693	FA	5.804	1518.2	(M+H)+
PP2645	AA	8.343	1566.0	(M-H)-		PP2694	FA	5.616	1528.4	(M-H)-
PP2646	AA	8.264	1546.0	(M-H)-		PP2695	FA	6.063	1581.3	$(M+NH_4)+$
PP2648	FA	6.859	1555.4	(M+H)+		PP2696	FA	6.275	1500.3	(M-H)-
PP2649	FA	6.539	1537.5	(M+H)+		PP2697	FA	6.117	1504.2	(M-H)-
PP2650	FA	6.669	1501.7	(M+H)+		PP2698	FA	6.124	1503.7	(M-H)-
PP2651	FA	6.955	1581.8	(M+H)+		PP2699	FA	6.099	1535.6	(M-H)-
PP2652	FA	6.641	1561.9	(M-H)-		PP2700	FA	6.255	1512.3	(M-H)-
PP2654	FA	6.395	1576.3	(M-H)-		PP2701	AA	8.196	1514.3	(M-H)-
PP2655	FA	6.532	1588.3	(M-H)-		PP2702	FA	5.807	1502.1	(M-H)-
PP2656	FA	6.759	1602.3	(M-H)-		PP2703	FA	5.624	1532.5	$(M+NH_4)+$
PP2657	FA	6.544	1588.2	(M-H)-		PP2704	FA	6.109	1548.4	(M-H)-
PP2659	FA	5.972	1508.2	(M-H)-		PP2706	FA	6.205	1494.3	(M-H)-
PP2660	FA	6.180	1523.6	(M+H)+		PP2708	FA	6.340	1524.1	(M-H)-
PP2661	FA	6.263	1526.2	(M-H)-		PP2710	FA	5.971	1488.1	(M-H)-
PP2662	AA	8.237	1540.0	(M-H)-		PP2712	FA	6.123	1518.1	(M-H)-
PP2663	FA	6.691	1602.3	(M-H)-		PP2714	FA	6.240	1460.3	(M+H)+
PP2664	FA	6.813	1614.3	(M-H)-		PP2716	FA	6.389	1487.7	(M-H)-
PP2665	FA	7.031	1628.3	(M-H)-		PP2718	FA	6.499	1520.1	(M-H)-
PP2666	FA	6.851	1614.3	(M-H)-		PP2720	FA	6.384	1535.7	(M-H)-
PP2667	FA	7.024	1628.4	(M-H)-		PP2722	FA	6.277	1514.1	(M-H)-
PP2668	FA	6.327	1534.2	(M-H)-		PP2724	FA	6.161	1530.3	(M-H)-
PP2669	FA	6.523	1548.2	(M-H)-		PP2726	FA	6.551	1485.5	(M+H)+
PP2670	FA	6.591	1553.4	(M+H)+		PP2728	FA	6.440	1500.2	(M-H)-

PP2730	FA	6.377	1548.2	(M-H)-		PP2787	FA	6.389	1492.1	(M-H)-
PP2732	AA	8.056	1564.3	(M-H)-		PP2788	FA	5.749	1505.7	(M-H)-
PP2734	FA	6.159	1542.2	(M-H)-		PP2789	FA	6.021	1508.1	(M-H)-
PP2736	FA	6.053	1558.3	(M-H)-		PP2790	AA	7.643	1452.1	(M-H)-
PP2738	AA	8.199	1512.0	(M-H)-		PP2791	FA	5.812	1453.7	(M-H)-
PP2740	FA	6.332	1527.5	(M-H)-		PP2796	AA	7.867	1491.6	(M-H)-
PP2742	FA	6.635	1574.3	(M-H)-		PP2797	FA	5.783	1477.6	(M-H)-
PP2744	FA	6.369	1576.2	(M-H)-		PP2798	FA	5.709	1478.2	(M-H)-
PP2746	FA	6.421	1568.1	(M-H)-		PP2799	FA	5.761	1441.8	(M-H)-
PP2748	FA	6.137	1569.6	(M-H)-		PP2800	FA	6.216	1505.6	(M-H)-
PP2749	FA	6.697	1539.4	(M+H)+		PP2801	FA	6.115	1504.2	(M-H)-
PP2750	AA	8.179	1540.1	(M-H)-		PP2802	FA	6.007	1492.3	(M-H)-
PP2751	FA	6.053	1491.6	(M-H)-		PP2803	FA	5.932	1498.2	(M-H)-
PP2752	FA	6.201	1521.6	(M-H)-		PP2804	FA	5.713	1478.0	(M-H)-
PP2753	FA	5.839	1486.1	(M-H)-		PP2805	AA	8.045	1467.5	(M-H)-
PP2754	FA	5.980	1516.3	(M-H)-		PP2806	AA	8.213	1574.1	(M-H)-
PP2755	FA	6.071	1456.1	(M-H)-		PP2807	FA	5.979	1532.0	(M-H)-
PP2756	FA	6.223	1486.1	(M-H)-		PP2808	FA	6.503	1520.3	(M-H)-
PP2757	FA	6.379	1518.2	(M-H)-		PP2809	FA	5.776	1525.8	(M-H)-
PP2760	FA	6.049	1527.6	(M-H)-		PP2810	FA	6.349	1473.8	(M-H)-
PP2761	AA	8.205	1481.8	(M-H)-		PP2811	AA	7.927	1496.0	(M-H)-
PP2762	AA	8.177	1498.0	(M-H)-		PP2812	FA	6.707	1489.4	(M+H)+
PP2763	FA	6.123	1562.0	(M-H)-		PP2813	FA	6.268	1558.1	(M-H)-
PP2764	FA	6.024	1542.0	(M+H)+		PP2814	FA	6.611	1489.5	(M+H)+
PP2765	FA	5.907	1556.3	(M-H)-		PP2815	AA	7.840	1551.7	(M-H)-
PP2766	FA	6.264	1528.5	$(M+NH_4)+$		PP2816	FA	6.765	1502.3	(M+H)+
PP2767	FA	6.167	1525.5	(M-H)-		PP2817	FA	6.267	1540.8	$(M+NH_4)+$
PP2768	FA	6.520	1572.3	(M-H)-		PP2818	FA	7.097	1532.7	$(M+NH_4)+$
PP2769	FA	6.240	1574.0	(M-H)-		PP2819	AA	8.221	1535.9	(M-H)-
PP2770	FA	6.315	1566.3	(M-H)-		PP2820	FA	6.523	1457.5	(M+H)+
PP2771	FA	6.020	1568.3	(M-H)-		PP2821	AA	8.080	1561.6	(M+Na)+
PP2772	FA	6.023	1469.7	(M-H)-		PP2822	FA	6.369	1528.9	$(M+NH_4)+$
PP2773	FA	6.115	1542.1	(M-H)-		PP2823	FA	6.396	1544.1	(M-H)-
PP2776	FA	6.231	1546.2	(M-H)-		PP2824	FA	6.221	1521.6	(M-H)-
PP2777	FA	6.813	1506.1	(M-H)-		PP2825	FA	5.976	1552.3	(M-H)-
PP2778	FA	6.300	1450.0	(M-H)-		PP2826	FA	6.267	1556.1	(M-H)-
PP2779	FA	6.611	1452.1	(M-H)-		PP2827	FA	6.435	1520.1	(M-H)-
PP2780	FA	5.708	1527.6	(M-H)-		PP2828	FA	6.191	1550.3	(M-H)-
PP2781	FA	5.960	1530.0	(M-H)-		PP2829	FA	6.472	1553.9	(M-H)-
PP2782	FA	5.519	1474.3	(M-H)-		PP2830	AA	8.208	1540.1	(M-H)-
PP2783	FA	5.760	1476.2	(M-H)-		PP2831	FA	6.457	1574.0	(M-H)-
PP2784	FA	6.280	1544.2	(M-H)-		PP2832	FA	6.145	1551.8	(M+H)+
PP2785	FA	6.588	1546.0	(M-H)-		PP2833	FA	6.180	1585.8	(M+H)+
PP2786	FA	6.111	1489.7	(M-H)-		PP2834	FA	6.311	1541.5	(M+H)+

PP2835	FA	6.177	1527.4	(M+H)+		PP2881	FA	6.707	1522.1	(M-H)-
PP2836	FA	6.205	1559.8	(M-H)-		PP2883	FA	6.267	1484.1	(M-H)-
PP2837	FA	6.029	1509.6	(M-H)-		PP2884	FA	6.308	1472.1	(M-H)-
PP2838	FA	6.079	1544.0	(M-H)-		PP2885	AA	8.295	1488.1	(M-H)-
PP2839	FA	6.181	1510.1	(M-H)-		PP2886	FA	6.524	1468.1	(M-H)-
PP2840	FA	5.932	1540.0	(M-H)-		PP2888	AA	8.199	1536.1	(M+H)+
PP2841	AA	7.976	1543.9	(M-H)-		PP2889	FA	6.476	1545.3	$(M+NH_4)+$
PP2842	FA	6.152	1556.0	(M-H)-		PP2890	FA	6.416	1481.8	(M+H)+
PP2843	AA	8.048	1520.0	(M-H)-		PP2891	AA	8.177	1472.3	(M-H)-
PP2844	FA	6.335	1554.0	(M-H)-		PP2892	FA	6.859	1533.7	(M+H)+
PP2845	AA	7.976	1533.9	(M+Na)+		PP2893	FA	6.203	1542.3	$(M+NH_4)+$
PP2846	FA	5.877	1540.2	(M-H)-		PP2894	FA	6.661	1480.4	(M+H)+
PP2847	FA	6.183	1544.0	(M-H)-		PP2895	FA	6.008	1487.8	$(M+NH_4)+$
PP2848	FA	6.485	1504.0	(M-H)-		PP2896	FA	6.300	1531.3	(M-H)-
PP2849	FA	6.236	1500.2	(M-H)-		PP2897	FA	5.977	1528.4	$(M+NH_4)+$
PP2850	FA	5.533	1501.7	(M-H)-		PP2898	FA	6.095	1478.9	(M+H)+
PP2852	FA	6.504	1550.0	(M-H)-		PP2899	FA	5.781	1455.5	(M-H)-
PP2853	FA	6.061	1512.3	(M-H)-		PP2900	FA	6.797	1528.3	(M-H)-
PP2854	FA	6.109	1500.1	(M-H)-		PP2901	FA	5.625	1496.9	(M+H)+
PP2855	FA	6.333	1495.6	(M-H)-		PP2902	AA	8.317	1474.4	(M-H)-
PP2856	FA	6.161	1488.3	(M-H)-		PP2904	FA	6.497	1525.5	(M-H)-
PP2857	FA	5.945	1519.8	(M-H)-		PP2905	FA	5.593	1510.3	(M+H)+
PP2858	FA	6.411	1517.6	(M+H)+		PP2906	FA	6.292	1471.5	(M-H)-
PP2859	AA	8.267	1580.3	(M+H)+		PP2907	FA	6.101	1518.3	(M-H)-
PP2860	FA	5.881	1542.5	$(M+NH_4)+$		PP2908	FA	6.263	1512.7	(M+H)+
PP2861	FA	6.511	1540.2	(M+H)+		PP2909	FA	5.573	1478.3	(M-H)-
PP2862	FA	6.343	1518.3	(M-H)-		PP2910	AA	7.989	1457.5	(M-H)-
PP2863	FA	6.645	1510.3	(M-H)-		PP2911	FA	5.092	1450.3	(M-H)-
PP2864	FA	5.904	1523.9	(M-H)-		PP2912	FA	5.909	1515.8	$(M+NH_4)+$
PP2865	FA	6.160	1559.8	(M-H)-		PP2913	FA	6.317	1558.4	(M-H)-
PP2866	FA	6.205	1540.0	(M-H)-		PP2914	FA	5.697	1443.4	(M-H)-
PP2867	FA	5.716	1540.0	(M-H)-		PP2915	FA	5.887	1474.3	(M-H)-
PP2868	FA	5.692	1540.7	$(M+NH_4)+$		PP2916	FA	6.348	1521.6	(M+H)+
PP2869	FA	6.197	1500.3	(M-H)-		PP2917	AA	7.725	1522.3	(M-H)-
PP2870	FA	6.725	1510.3	(M-H)-		PP2918	FA	6.041	1492.3	(M-H)-
PP2871	FA	6.103	1496.1	(M-H)-		PP2920	AA	7.939	1484.1	(M-H)-
PP2872	FA	6.544	1509.2	$(M+NH_4)+$		PP2921	FA	6.265	1454.0	(M-H)-
PP2873	FA	6.159	1492.4	(M-H)-		PP2922	FA	6.144	1466.4	(M-H)-
PP2874	FA	6.095	1495.7	(M-H)-		PP2923	AA	7.680	1468.3	(M-H)-
PP2875	FA	6.425	1511.6	(M-H)-		PP2928	FA	6.740	1516.3	(M-H)-
PP2876	FA	5.951	1512.1	(M-H)-		PP2929	FA	6.316	1518.3	(M-H)-
PP2877	FA	6.377	1533.4	(M+H)+		PP2931	FA	6.245	1464.2	(M-H)-
PP2879	FA	6.431	1472.2	(M-H)-		PP2932	FA	5.867	1466.3	(M-H)-
PP2880	FA	5.748	1474.2	(M-H)-		PP2934	AA	7.883	1514.4	(M+H)+

PP2935	FA	5.977	1514.3	(M-H)-		PP2985	FA	6.333	1540.1	(M-H)-
PP2936	FA	5.960	1484.3	(M-H)-		PP2986	FA	6.467	1538.2	(M-H)-
PP2937	FA	5.852	1460.4	(M-H)-		PP2987	FA	6.447	1514.1	(M-H)-
PP2938	FA	5.505	1462.4	(M-H)-		PP2988	FA	6.025	1504.4	(M-H)-
PP2941	FA	6.033	1487.6	(M+H)+		PP2989	FA	6.259	1506.3	(M-H)-
PP2946	FA	6.283	1532.3	(M-H)-		PP2990	FA	6.219	1486.4	(M-H)-
PP2947	FA	6.099	1478.1	(M-H)-		PP2991	FA	6.116	1480.3	(M-H)-
PP2948	FA	6.524	1530.3	(M-H)-		PP2992	FA	5.808	1498.4	(M-H)-
PP2949	FA	6.351	1476.3	(M-H)-		PP2993	FA	5.924	1506.2	(M-H)-
PP2950	FA	5.992	1531.1	(M+H)+		PP2994	FA	6.016	1480.1	(M-H)-
PP2951	AA	7.791	1475.3	(M-H)-		PP2995	FA	6.005	1480.3	(M-H)-
PP2952	FA	6.541	1546.4	(M+H)+		PP2996	AA	8.119	1570.2	(M-H)-
PP2953	FA	6.660	1526.9	$(M+NH_4)+$		PP2997	FA	6.417	1476.2	(M-H)-
PP2954	AA	7.919	1540.3	(M-H)-		PP2998	FA	6.335	1516.2	(M-H)-
PP2955	FA	6.400	1549.4	$(M+NH_4)+$		PP2999	FA	6.447	1488.3	(M-H)-
PP2956	FA	6.559	1543.7	(M+H)+		PP3000	FA	5.547	1572.1	(M-H)-
PP2957	FA	6.020	1530.4	(M+H)+		PP3001	FA	6.341	1462.2	(M-H)-
PP2958	FA	6.521	1523.1	$(M+NH_4)+$		PP3002	FA	5.379	1518.1	(M-H)-
PP2959	FA	6.475	1513.2	$(M+NH_4)+$		PP3003	FA	6.047	1488.0	(M-H)-
PP2960	FA	6.047	1480.3	(M-H)-		PP3004	FA	6.167	1462.2	(M-H)-
PP2961	FA	6.456	1532.2	(M-H)-		PP3005	FA	6.041	1500.3	(M-H)-
PP2962	AA	8.156	1441.9	(M-H)-		PP3006	FA	5.853	1474.3	(M-H)-
PP2963	FA	6.228	1478.3	(M-H)-		PP3007	FA	5.753	1500.0	(M-H)-
PP2964	FA	6.672	1530.1	(M-H)-		PP3008	FA	5.793	1474.3	(M-H)-
PP2965	FA	6.563	1530.2	(M-H)-		PP3009	FA	6.189	1470.3	(M-H)-
PP2966	AA	7.964	1478.1	(M-H)-		PP3010	FA	6.220	1482.3	(M-H)-
PP2967	FA	6.339	1476.2	(M-H)-		PP3011	FA	6.059	1456.2	(M-H)-
PP2968	FA	6.335	1526.4	(M-H)-		PP3012	FA	5.869	1482.2	(M-H)-
PP2969	FA	6.480	1546.2	(M-H)-		PP3013	FA	5.959	1456.3	(M-H)-
PP2970	FA	5.832	1474.3	(M-H)-		PP3014	FA	6.759	1572.1	(M-H)-
PP2971	FA	6.519	1558.2	(M-H)-		PP3015	FA	6.685	1558.1	(M-H)-
PP2972	AA	8.081	1498.1	(M-H)-		PP3017	FA	6.524	1558.1	(M-H)-
PP2973	AA	8.073	1532.2	(M-H)-		PP3018	AA	8.265	1518.2	(M-H)-
PP2974	FA	6.131	1445.8	(M+H)+		PP3019	FA	6.489	1504.1	(M-H)-
PP2975	FA	6.192	1558.1	(M-H)-		PP3021	FA	6.353	1505.4	(M+H)+
PP2976	FA	6.215	1523.9	(M-H)-		PP3022	FA	5.872	1574.1	(M-H)-
PP2977	FA	6.259	1532.2	(M-H)-		PP3026	FA	5.624	1520.2	(M-H)-
PP2978	FA	5.941	1470.3	(M-H)-		PP3030	FA	6.300	1534.4	(M-H)-
PP2979	FA	6.697	1528.2	(M-H)-		PP3031	FA	6.657	1497.5	(M+H)+
PP2980	FA	6.337	1522.0	(M-H)-		PP3032	FA	5.919	1514.4	(M-H)-
PP2981	FA	6.735	1540.2	(M-H)-		PP3033	FA	5.880	1524.4	(M-H)-
PP2982	FA	6.055	1468.1	(M-H)-		PP3034	FA	5.919	1538.3	(M-H)-
PP2983	FA	6.647	1514.1	(M-H)-		PP3035	FA	5.607	1500.4	(M-H)-
PP2984	FA	6.287	1556.2	(M-H)-		PP3036	FA	6.156	1539.9	(M+H)+

PP3037	FA	5.600	1523.8	(M-H)-		PP3084	FA	5.783	1498.2	(M-H)-
PP3038	FA	5.808	1500.4	(M-H)-		PP3085	FA	5.949	1510.0	(M-H)-
PP3039	FA	6.689	1524.9	$(M+NH_4)+$		PP3086	FA	6.189	1524.4	(M-H)-
PP3040	FA	6.124	1493.4	(M+H)+		PP3087	FA	5.604	1466.2	(M-H)-
PP3044	FA	6.105	1518.1	(M-H)-		PP3088	FA	6.248	1524.1	(M-H)-
PP3045	AA	7.909	1482.0	(M-H)-		PP3089	AA	7.901	1469.4	(M+H)+
PP3046	FA	6.276	1495.4	(M+H)+		PP3090	FA	6.193	1526.1	(M-H)-
PP3047	FA	5.712	1480.1	(M-H)-		PP3091	FA	5.963	1512.3	(M-H)-
PP3048	FA	6.433	1532.4	(M-H)-		PP3092	FA	5.997	1469.5	(M+H)+
PP3049	AA	7.837	1491.9	(M-H)-		PP3093	FA	6.052	1524.1	(M-H)-
PP3050	FA	6.499	1497.4	(M+H)+		PP3094	FA	5.849	1524.1	(M-H)-
PP3051	FA	6.605	1507.6	(M-H)-		PP3095	FA	6.699	1592.4	(M-H)-
PP3052	FA	6.025	1493.9	(M-H)-		PP3096	FA	6.632	1540.4	(M+H)+
PP3053	FA	6.445	1517.8	(M-H)-		PP3097	FA	6.199	1580.4	(M+H)+
PP3054	FA	6.717	1533.4	(M+H)+		PP3098	FA	6.112	1524.4	(M-H)-
PP3055	FA	6.424	1465.4	(M+H)+		PP3099	FA	6.524	1594.3	(M+H)+
PP3056	FA	5.672	1452.0	(M-H)-		PP3100	FA	6.423	1538.4	(M-H)-
PP3057	FA	6.404	1493.9	(M-H)-		PP3101	FA	6.023	1578.4	(M-H)-
PP3058	FA	6.616	1524.5	$(M+NH_4)+$		PP3102	FA	5.915	1526.2	(M+H)+
PP3059	FA	6.168	1498.5	$(M+NH_4)+$		PP3103	FA	6.276	1566.4	(M-H)-
PP3060	FA	6.128	1516.2	(M-H)-		PP3104	FA	6.141	1512.4	(M-H)-
PP3061	AA	8.037	1524.9	$(M+NH_4)+$		PP3105	FA	5.753	1552.3	(M-H)-
PP3062	AA	7.981	1493.6	(M-H)-		PP3106	FA	5.616	1498.3	(M-H)-
PP3063	FA	5.748	1486.0	(M-H)-		PP3108	FA	5.989	1534.2	(M-H)-
PP3064	FA	6.260	1524.3	(M-H)-		PP3109	FA	6.083	1548.0	(M-H)-
PP3065	FA	5.752	1510.0	(M-H)-		PP3110	FA	6.917	1598.4	(M-H)-
PP3066	FA	5.829	1511.9	(M-H)-		PP3111	FA	6.932	1546.3	(M+H)+
PP3067	FA	6.045	1526.1	(M-H)-		PP3112	FA	6.408	1584.1	(M-H)-
PP3068	FA	6.267	1537.7	(M-H)-		PP3113	FA	6.312	1530.3	(M-H)-
PP3069	FA	5.955	1495.5	(M+H)+		PP3114	FA	6.748	1598.4	(M-H)-
PP3070	FA	6.140	1538.2	(M-H)-		PP3115	FA	6.651	1544.4	(M-H)-
PP3071	FA	6.035	1483.4	(M+H)+		PP3116	FA	6.232	1584.3	(M-H)-
PP3072	FA	5.720	1512.1	(M-H)-		PP3117	FA	6.125	1530.3	(M-H)-
PP3073	FA	5.929	1524.2	(M-H)-		PP3118	FA	6.501	1572.3	(M-H)-
PP3074	FA	5.615	1480.2	(M-H)-		PP3119	FA	6.367	1518.3	(M-H)-
PP3075	FA	5.944	1523.5	(M-H)-		PP3120	FA	5.971	1558.2	(M-H)-
PP3076	FA	5.733	1467.8	(M-H)-		PP3121	FA	5.831	1504.2	(M-H)-
PP3077	FA	5.711	1498.3	(M-H)-						
PP3078	FA	5.872	1512.1	(M-H)-						
PP3079	FA	6.055	1543.4	$(M+NH_4)+$						
PP3080	FA	6.057	1524.1	(M-H)-						
PP3081	FA	5.748	1480.3	(M-H)-						
PP3082	FA	6.144	1525.7	(M+H)+						
PP3083	FA	5.876	1498.3	(M-H)-						

[1162]

Example 2 Pharmacological test

Evaluation of compound binding to KRAS, NRAS, and HRAS by surface plasmon resonance (SPR)

Surface plasmon resonance was used to analyze the binding affinity of compounds for KRAS, NRAS, and HRAS. The apparatus used was Biacore 8K, 8K+, or T200 (GE Healthcare), and the running buffer used was HBS (10 mM HEPES-NaOH, 150 mM NaCl, pH 7.4) containing 1 mM DTT, 10 mM $MgCl_2$, 0.01% Tween 20, 10 μM GDP, and 4% DMSO. The dilution series of each compound solution was prepared by, first, preparing a dilution series of a compound solution having a concentration 100-fold greater than the final concentration using DMSO as a solvent, and then diluting the solution 100-fold with a dilution buffer (1 mM DTT, 10 mM $MgCl_2$, 0.01% Tween 20, 10 μM GDP, 3.03% DMSO-containing HBS).

[1163]

Biotinylated Avi-tag fusion KRAS, NRAS, and HRAS proteins were expressed in E. coli BL21 (DE3) strains, and after cells were homogenized, they were purified using Streptavidin Mutein Matrix and Superdex 75. After purification, GDP-loaded KRAS, NRAS, and HRAS proteins were immobilized on the surface of Sensor Chip CAP (Cytiva) coated with Biotin CAPture Reagent in an immobilization amount of about 100 to 300 RU. Binding of each compound was evaluated by the Single Cycle Kinetics method, and a running buffer or a compound solution was added to the RAS protein non-immobilized surface and the immobilized surface to obtain a binding response. The flow rate was set to 100 μL/min, and in the compound-adding cycle, compound solutions having different concentrations were intermittently added for 75 seconds each, starting from a low concentration. The dissociation phase was observed for 3500 seconds. In the blank cycle, a running buffer was intermittently added and not the compound solution. The Biotin CAPture Reagent and RAS proteins were immobilized for each cycle, and at the end of each cycle, the sensor chip was regenerated by the regeneration solution appended to the Biotin CAPture Kit (Cytiva). Measurement was carried out at 30°C.

[1164]

The resulting sensorgram was subjected to curve fitting based on a 1:1 binding model on Biacore Insight Evaluation Software or T200 Evaluation Software, and thereby the dissociation constant KD of each compound with respect to KRAS, NRAS, and HRAS was determined. Table 37 shows the KD value of each test compound with respect to GDP-bound KRAS wild-type protein, and the ratio of the KD value with respect to GDP-bound NRAS wild-type protein and HRAS wild-type protein to the KD value with respect to KRAS. A compound having a KD ratio of 0.1 or more and less than 3 is denoted as C, a compound having 3 or more and less than 10 is denoted as B, a compound having 10 or more and less than 20 is denoted as

A, and a compound having 20 or more is denoted as AA. Blank indicates a compound from which the KD value with respect to NRAS or HRAS was not obtained.

[1165]

Measurement of NCI-H441 cell proliferation inhibitory activity

A test compound was dispensed into a U-bottom 384-well plate as 40 nL serially diluted dimethyl sulfoxide solutions using a liquid handler Echo (LABCYTE). As for human lung cancer strain NCI-H441 (ATCC), a cell suspension was prepared so as to have 250 cells/40 μL in an RPMI-1640 medium (Sigma) supplemented with 10% fetal bovine serum (Sigma), a 2.5 g/L D-(+)-glucose solution, 10 mmol/L HEPES, and 1 mmol/L sodium pyruvate. This cell suspension was dispensed in an amount of 40 μL per well into a plate containing the test compound, and cultured at 37°C in a 5% carbon dioxide gas incubator. Four days later, 20 μL of CellTiter-Glo (registered trademark) (Promega) was added to each well and fluorescence was measured. From the growth inhibition ratio attained when the test compound was added to that of the control to which the test compound was not added, the cell proliferation inhibitory activity of the test compound was calculated in terms of a 50% proliferation inhibitory concentration (an IC_{50} value). The IC_{50} value of each test compound is shown in Table 37.

[1166]

[Table 37]

Compound No.	KRAS KD (M)	NRAS /KRAS	HRAS /KRAS	NCI-H441 IC_{50} (nM)
PP0001	1.4E-10	C	C	6.3
PP0002	1.8E-10	C	C	2.1
PP0003	2.0E-09	C	C	41.4
PP0004	2.4E-09	C	C	52.9
PP0006	1.5E-09	C	C	20.6
PP0007	7.4E-11	C	C	4.8
PP0011	3.0E-10	C	C	5.8
PP0013	7.3E-11	C	C	9.8
PP0014	9.0E-11	C	C	2.0
PP0015	2.7E-09	C	C	24.5
PP0016	1.6E-09	C	C	24.6
PP0018	7.7E-11	C	C	7.0
PP0019	3.4E-10	C	C	6.7
PP0020	7.7E-10	C	C	9.9
PP0021	6.5E-10	C	C	9.8
PP0022	1.8E-10	B	C	14.4
PP0023	1.4E-10	B	C	4.5
PP0024	5.9E-09	B	C	101.6
PP0025	2.4E-09	C	C	27.5
PP0027	8.0E-10	C	C	17.1
PP0028	2.4E-09	C	C	54.5
PP0029	7.0E-09	C	C	26.4
PP0030	7.7E-09	C	C	86.7
PP0031	1.8E-10	B	C	11.4
PP0032	3.7E-10	C	C	26.9
PP0037	7.6E-09	C	C	429.7
PP0039	1.7E-10	C	C	20.1
PP0041	1.2E-10	B	C	62.7
PP0042	1.2E-10	C	C	7.2
PP0043	8.7E-10	C	C	20.4
PP0044	3.6E-09	C	C	142.2
PP0045	2.3E-09	C	C	292.3
PP0047	1.8E-08	C	C	229.3
PP0048	6.3E-08	C	C	464.1
PP0049	6.3E-09	C	C	201.4
PP0050	2.3E-08	B	C	499.0
PP0051	9.1E-10	C	C	22.1
PP0052	1.2E-10	C	B	1.7
PP0053	1.2E-10	C	C	4.6
PP0054	4.5E-09	C	C	82.0
PP0055	2.7E-10	C	C	3.5
PP0056	2.9E-09	C	B	49.6

Compound No.	KRAS KD (M)	NRAS /KRAS	HRAS /KRAS	NCI-H441 IC_{50} (nM)
PP0057	2.1E-10	C	B	6.2
PP0058	2.0E-09	C	C	25.8
PP0059	1.5E-10	B	C	6.1
PP0060	9.9E-11	B	B	1.5
PP0061	3.8E-09	B	C	84.4
PP0062	2.1E-10	C	C	3.8
PP0063	2.9E-09	C	C	39.3
PP0064	4.2E-10	C	C	9.9
PP0065	5.4E-10	C	C	4.3
PP0066	1.4E-09	B	C	26.1
PP0067	7.2E-11	C	C	2.7
PP0068	1.4E-10	C	C	9.1
PP0069	6.9E-09	C	C	39.7
PP0070	1.6E-10	C	B	2.1
PP0071	1.5E-10			3.8
PP0076	6.4E-11	C	C	10.9
PP0077	2.0E-10	C	B	5.3
PP0078	1.9E-10	C	B	4.8
PP0083	1.1E-09			11.3
PP0084	2.7E-09	C	B	50.0
PP0085	8.4E-09	C	C	108.5
PP0086	2.6E-10	C	B	6.4
PP0087	7.5E-10	C	C	24.0
PP0088	1.2E-10			4.1
PP0089	1.7E-10	C	B	5.5
PP0090	8.3E-11			1.9
PP0091	2.3E-10	C	B	4.1
PP0092	1.5E-10	C	C	3.7
PP0093	7.6E-11	C	B	2.2
PP0094	9.4E-10	C	C	10.6
PP0095	7.9E-10	C	C	18.2
PP0096	2.8E-09	C	C	68.9
PP0097	9.3E-09	C	C	240.1
PP0098	2.3E-10			9.4
PP0099	7.0E-10			18.7
PP0100	1.9E-10	B	C	24.3
PP0101	1.6E-10	B	C	10.4
PP0102	2.0E-10	C	C	13.4
PP0103	1.5E-10	B	C	8.2
PP0104	2.5E-10	B	C	6.7
PP0105	1.4E-10	B	C	8.3
PP0106	1.9E-10	C	B	12.3

PP0107	1.7E-09	C	C	32.2
PP0108	2.0E-10	C	C	9.0
PP0109	1.3E-09	C	B	21.7
PP0110	4.0E-09	C	B	56.5
PP0112	3.6E-10	C	B	6.1
PP0113	7.5E-10	C	B	7.1
PP0114	1.6E-10	C	C	6.1
PP0115	2.1E-10	C	C	2.0
PP0116	2.7E-10	C	C	6.8
PP0117	1.9E-10	B	B	9.2
PP0118	2.1E-10	C	C	6.0
PP0119	1.0E-10	C	C	1.6
PP0120	1.9E-10	B	C	5.6
PP0121	2.1E-09	C	C	29.5
PP0122	3.2E-10	C	C	12.0
PP0123	8.3E-10	B	C	12.5
PP0124	3.5E-09	C	C	48.8
PP0126	4.3E-10	C	C	9.3
PP0127	9.2E-10	C	C	25.3
PP0128	2.5E-10	C	C	10.4
PP0129	2.0E-10	B	C	8.8
PP0130	2.5E-10	C	C	8.8
PP0131	1.4E-10	B	C	11.1
PP0132	2.0E-10	C	C	14.8
PP0133	8.0E-11	B	C	6.4
PP0134	6.6E-10	C	B	18.5
PP0135	7.5E-10	B	C	26.1
PP0136	1.3E-09			19.6
PP0137	4.7E-10			13.4
PP0138	7.7E-10	C	C	20.6
PP0139	2.3E-07	C	C	1495.7
PP0140	8.0E-07	C	B	712.5
PP0141	5.5E-10	C	B	3.5
PP0144	2.4E-10	B	C	18.3
PP0145	5.0E-10	B	B	8.8
PP0146	4.2E-10	B	B	23.9
PP0148	3.4E-09	B	B	38.0
PP0149	2.3E-08	C	B	317.4
PP0150	1.7E-09	B	C	49.1
PP0151	5.0E-10	C	C	5.3
PP0152	2.8E-09	C	B	37.9
PP0153	3.3E-10	C	C	11.6
PP0154	2.3E-10	C	B	9.9
PP0155	1.8E-10	B	C	2.8

PP0156	1.2E-10	C	B	8.1
PP0158	8.5E-10	A	B	15.4
PP0162	1.7E-08	B	C	165.8
PP0165	2.9E-09	B	B	35.0
PP0166	2.0E-09	C	B	24.9
PP0168	6.7E-10	C	B	26.6
PP0169	3.5E-11	B	B	2.3
PP0170	1.2E-10	B	B	5.2
PP0171	3.1E-10	B	C	6.9
PP0172	1.3E-10	B	C	3.8
PP0173	6.7E-10	B	C	11.6
PP0174	1.5E-10	B	B	5.2
PP0175	3.5E-10	B	B	6.6
PP0176	5.5E-10	B	C	17.7
PP0177	5.5E-10	B	C	34.4
PP0178	7.3E-11	C	B	1.5
PP0179	1.1E-10	C	B	4.5
PP0180	7.2E-10	C	C	7.5
PP0181	8.1E-11	C	B	1.5
PP0182	8.8E-10	C	B	6.2
PP0183	1.7E-10	C	B	1.6
PP0184	3.2E-10	C	B	2.1
PP0185	1.1E-09	C	B	32.2
PP0186	1.7E-09	C	B	20.5
PP0187	1.9E-10	B	C	3.0
PP0188	2.5E-10	B	C	3.9
PP0189	2.2E-10	B	C	3.0
PP0190	1.3E-10	B	B	4.1
PP0191	1.4E-10	C	B	3.9
PP0192	1.9E-10	C	B	2.6
PP0193	1.7E-10	C	C	1.4
PP0194	9.0E-11	C	B	1.9
PP0195	9.1E-11	B	C	2.7
PP0196	1.5E-10	C	C	3.7
PP0197	1.3E-10	B	C	3.6
PP0198	1.9E-10	C	B	5.7
PP0199	1.3E-10	B	C	3.5
PP0200	2.2E-10	C	C	2.5
PP0201	6.0E-11	B	C	3.4
PP0202	7.6E-11	B	C	3.9
PP0203	9.4E-11	C	C	2.8
PP0204	2.1E-10	C	C	5.4
PP0205	1.1E-10	C	C	4.6
PP0206	7.1E-11	C	B	2.2

PP0207	6.6E-11	B	C	1.9
PP0208	2.6E-10	C	C	4.6
PP0209	1.1E-07	C	C	568.8
PP0210	5.2E-10	C	C	17.1
PP0211	2.7E-10	B	C	10.8
PP0212	9.8E-11	C	C	26.6
PP0213	2.5E-10	C	C	10.3
PP0214	1.3E-10	B	C	5.4
PP0215	4.1E-10	C	C	4.8
PP0216	2.8E-10	C	B	3.0
PP0217	1.8E-10	C	C	18.1
PP0218	2.0E-10	C	C	3.9
PP0219	1.3E-10	C	B	2.2
PP0220	3.5E-10	C	C	7.7
PP0221	1.9E-10	C	C	2.9
PP0222	5.7E-10	C	C	17.1
PP0223	4.0E-10	C	C	5.0
PP0224	2.2E-10	C	B	2.0
PP0225	2.3E-10	C	C	2.4
PP0226	4.7E-10	C	B	15.3
PP0227	2.6E-10	C	B	4.1
PP0228	3.7E-11	C	B	1.8
PP0229	2.5E-10	B	B	24.7
PP0230	3.9E-10	B	C	15.5
PP0231	5.5E-10	B	C	13.1
PP0232	2.8E-10	B	B	4.7
PP0233	5.2E-11	B	C	1.6
PP0234	4.9E-10	B	C	49.9
PP0235	1.5E-10	B	C	4.5
PP0236	5.4E-10	B	C	20.3
PP0237	2.8E-10	B	C	4.0
PP0238	4.1E-11	C	C	1.3
PP0239	5.0E-11	C	B	6.2
PP0240	3.5E-11	B	C	7.9
PP0241	5.2E-11	B	C	4.9
PP0242	2.0E-10	C	C	5.0
PP0243	3.1E-10	B	C	23.2
PP0244	3.5E-09	C	B	17.4
PP0245	3.7E-10			22.9
PP0246	5.4E-11	B	C	1.8
PP0247	3.8E-10	B	C	41.3
PP0248	1.1E-09	B	B	84.0
PP0249	6.9E-10	B	C	25.5
PP0250	1.2E-10	B	C	6.7

PP0251	2.5E-10			8.4
PP0252	3.4E-10	B	B	19.4
PP0253	5.5E-10	B	B	15.1
PP0254	1.6E-10	B	C	5.6
PP0256	9.9E-10	B	C	26.6
PP0257	1.4E-09	B	B	30.8
PP0258	5.2E-10	B	C	11.3
PP0259	4.2E-10	C	B	10.2
PP0260	3.9E-10	B	C	16.8
PP0261	1.4E-10	B	C	4.6
PP0262	4.4E-11	B	B	1.9
PP0263	4.7E-10	B	C	19.2
PP0264	4.2E-10	B	C	16.4
PP0265	2.8E-10	B	C	13.3
PP0266	2.0E-10	B	C	15.2
PP0267	8.7E-10	B	B	38.2
PP0268	3.4E-10	C	B	15.4
PP0269	1.4E-09	C	B	34.7
PP0270	7.6E-10	C	B	8.5
PP0271	2.2E-10	C	B	6.5
PP0272	1.7E-10	C	B	3.7
PP0273	5.6E-10	C	B	12.2
PP0274	4.7E-10	C	B	9.1
PP0275	3.0E-10	C	C	9.3
PP0276	1.5E-07			752.2
PP0277	5.3E-10	C	C	6.7
PP0278	6.2E-10	C	B	12.4
PP0279	3.6E-10			15.0
PP0281	4.8E-10	C	C	7.8
PP0282	1.1E-10	C	C	3.9
PP0283	6.3E-11	C	C	1.9
PP0284	6.7E-10	C	B	29.0
PP0285	7.5E-10	C	B	18.9
PP0286	5.2E-10	C	B	35.0
PP0287	2.6E-10	C	C	14.5
PP0288	4.2E-10	C	B	14.3
PP0289	2.2E-09	B	B	76.4
PP0290	4.8E-09	B	C	149.0
PP0291	2.2E-09	B	B	31.0
PP0292	5.4E-10	B	C	36.3
PP0293	8.4E-10	B	C	37.6
PP0294	1.7E-09	B	C	55.4
PP0295	5.2E-10	B	C	33.2
PP0296	1.5E-10	B	C	4.3

PP0297	2.3E-09	B	C	74.3
PP0298	3.0E-09	B	C	41.1
PP0299	1.4E-09	B	B	20.2
PP0300	1.4E-09	B	C	73.9
PP0301	4.8E-09	B	C	88.2
PP0302	1.6E-09	B	C	126.2
PP0303	4.0E-09	B	B	349.2
PP0304	1.9E-09	B	B	112.4
PP0305	9.6E-10	B	C	49.6
PP0306	1.2E-09	B	B	141.5
PP0307	2.1E-09	B	B	204.8
PP0308	1.1E-09	B	B	56.0
PP0309	2.9E-10	B	B	11.7
PP0310	4.5E-10	B	C	13.8
PP0311	3.3E-09	B	B	146.6
PP0312	3.4E-09	B	B	82.4
PP0313	2.2E-09	B	C	56.6
PP0314	1.6E-09	B	C	58.1
PP0315	3.8E-09	B	B	148.0
PP0316	5.4E-11	C	B	2.8
PP0317	8.6E-10	B	B	32.2
PP0318	3.4E-11	B	B	2.3
PP0319	1.8E-09	B	B	23.5
PP0320	9.0E-10	B	B	92.3
PP0321	1.0E-09	B	B	55.7
PP0322	8.4E-10	B	C	74.2
PP0323	2.5E-10	B	B	64.0
PP0324	4.1E-10	B	B	38.5
PP0325	1.1E-09	B	B	163.2
PP0326	1.5E-09	B	B	172.5
PP0327	1.9E-09	B	B	162.5
PP0328	1.6E-09	B	B	242.6
PP0329	7.4E-10	B	C	65.8
PP0330	9.5E-10	B	C	98.2
PP0331	2.8E-09	B	B	84.7
PP0332	3.2E-09	B	B	167.1
PP0333	2.4E-09	B	C	41.6
PP0334	4.7E-09	B	C	129.7
PP0335	1.3E-09	B	C	41.7
PP0336	1.6E-09	B	B	73.2
PP0337	2.5E-09	B	B	333.4
PP0338	3.6E-09	B	B	295.9
PP0339	5.0E-09	B	B	157.9
PP0340	3.7E-09	B	B	177.3

PP0341	1.4E-09	B	B	134.9
PP0342	1.7E-09	B	B	141.0
PP0343	1.3E-09	C	B	47.6
PP0344	1.1E-09	C	B	82.9
PP0345	1.3E-09	C	B	54.9
PP0346	1.2E-09	C	B	69.5
PP0347	3.6E-10	C	B	10.9
PP0348	3.8E-10	C	B	15.1
PP0349	7.3E-10	C	B	75.9
PP0350	1.1E-09	C	B	69.8
PP0351	1.1E-09	C	B	39.0
PP0352	8.2E-10	C	B	72.4
PP0353	4.7E-10	C	B	46.7
PP0354	4.4E-10	C	B	24.7
PP0355	3.3E-10	B	B	48.2
PP0356	4.9E-10	B	B	99.4
PP0357	4.0E-10	B	B	39.8
PP0358	3.3E-10	B	C	34.8
PP0359	1.4E-10	B	B	33.1
PP0360	2.5E-10	B	C	18.0
PP0361	7.2E-10	B	C	69.0
PP0362	1.0E-09	B	B	148.6
PP0363	1.0E-09	B	C	91.4
PP0364	7.7E-10	B	B	103.0
PP0365	2.9E-10	B	B	42.6
PP0366	3.8E-10	B	B	80.2
PP0367	1.3E-09	B	B	99.1
PP0368	1.7E-09	B	B	114.8
PP0369	1.9E-09	B	C	68.9
PP0370	1.5E-09	B	C	63.2
PP0371	4.8E-10	B	C	30.9
PP0372	7.9E-10	B	B	34.2
PP0373	1.2E-09	B	B	152.0
PP0374	1.8E-09	B	B	141.9
PP0375	2.3E-09	B	B	57.1
PP0376	2.0E-09	B	B	114.2
PP0377	7.0E-10	B	C	33.4
PP0378	8.5E-10	B	B	109.6
PP0379	3.8E-10	C	B	4.4
PP0380	5.9E-10	C	B	16.4
PP0381	4.9E-10	C	B	11.1
PP0382	3.5E-10	C	B	12.1
PP0383	2.4E-10	C	B	2.6
PP0384	1.8E-10	C	B	7.0

PP0385	3.7E-10			15.2
PP0386	6.9E-10	C	B	29.6
PP0387	5.4E-10	C	B	20.0
PP0388	7.8E-10	C	B	11.6
PP0389	1.6E-10	C	B	3.0
PP0390	2.0E-10	C	B	7.6
PP0391	9.2E-11	B	B	1.1
PP0392	6.7E-11	B	C	0.9
PP0393	1.1E-10	B	B	2.7
PP0394	2.4E-10	C	C	2.6
PP0395	6.8E-11	B	C	0.8
PP0396	1.3E-10	B	C	0.9
PP0397	1.2E-10	C	C	0.7
PP0398	4.8E-10	B	C	3.6
PP0399	3.3E-10	B	C	6.3
PP0400	1.7E-10	B	B	7.8
PP0401	1.5E-10	B	B	5.1
PP0402	1.2E-09	B	C	58.1
PP0403	8.3E-10	B	B	19.4
PP0404	3.7E-10	B	C	21.7
PP0405	3.1E-10	B	C	14.3
PP0406	4.2E-11	C	B	2.5
PP0407	1.1E-10	C	B	7.6
PP0408	9.4E-11	C	B	5.7
PP0409	5.6E-11	C	C	4.4
PP0410	5.8E-11	C	B	1.4
PP0411	4.6E-11	C	C	2.8
PP0412	4.3E-11	B	C	1.8
PP0413	4.9E-11	C	C	2.0
PP0414	2.9E-11	B	C	1.9
PP0415	1.8E-11	B	B	1.9
PP0416	2.7E-11	B	C	1.1
PP0417	7.4E-11	B	C	3.9
PP0418	7.4E-11	B	C	4.6
PP0419	6.7E-11	B	C	4.2
PP0420	3.4E-11	B	C	1.2
PP0421	3.3E-11	B	C	2.0
PP0422	1.7E-11	B	B	1.6
PP0423	1.8E-10	B	C	7.1
PP0424	1.7E-10	B	C	9.5
PP0425	9.9E-11	B	C	6.5
PP0426	1.2E-10	C	C	4.8
PP0427	1.1E-10	B	C	2.2
PP0428	6.3E-11	B	C	4.6

PP0429	3.9E-10	B	C	12.4
PP0430	2.6E-10	B	B	27.9
PP0431	3.5E-10	B	C	9.9
PP0432	1.7E-10	B	B	10.7
PP0433	1.5E-10	B	B	11.0
PP0434	1.2E-10	B	C	9.7
PP0435	4.7E-11	C	C	2.6
PP0436	5.4E-11	C	C	1.0
PP0437	3.6E-11	C	B	1.2
PP0438	3.0E-11	C	C	1.0
PP0439	2.1E-11			0.7
PP0440	4.6E-11	C	B	4.4
PP0441	7.2E-11	C	C	3.4
PP0442	3.7E-11	C	C	0.8
PP0443	2.7E-11	C	C	0.9
PP0444	3.1E-11	C	C	1.4
PP0445	2.5E-11	C	C	1.7
PP0446	1.0E-10	B	C	1.6
PP0447	1.8E-10	B	C	3.9
PP0448	1.5E-10	B	C	2.0
PP0449	3.5E-10	C	C	9.2
PP0450	3.8E-10	B	C	8.4
PP0451	7.5E-10			11.2
PP0452	7.3E-10	B	B	34.1
PP0453	1.2E-09	B	C	20.3
PP0454	7.3E-11	C	C	2.9
PP0455	1.8E-10			9.9
PP0456	7.0E-11	C	C	7.0
PP0457	8.3E-11	C	B	12.1
PP0460	1.4E-10	C	C	5.4
PP0461	4.9E-10	A	A	23.2
PP0462	3.2E-10	C	C	15.1
PP0463	5.4E-10	A	A	26.3
PP0464	9.2E-10	B	B	17.6
PP0465	5.1E-10	B	B	18.0
PP0466	2.0E-10	B	B	22.6
PP0467	5.9E-10	B	B	33.8
PP0468	8.0E-10	B	B	37.2
PP0469	7.6E-10	B	B	36.1
PP0470	5.5E-10	B	B	51.9
PP0471	9.3E-10	B	B	37.7
PP0472	7.7E-10	B	B	24.4
PP0473	5.6E-10	C	C	14.8
PP0474	6.3E-10	B	B	19.9

PP0475	4.6E-10	B	B	18.7
PP0476	2.0E-10	B	B	4.9
PP0477	1.1E-08	A	A	138.6
PP0478	4.0E-07			2751.8
PP0479	2.9E-08	B	B	2435.2
PP0480	3.1E-09	A	B	47.3
PP0481	8.5E-07	B	B	>1000
PP0483	3.4E-08	B	B	524.9
PP0484	3.2E-09	A	B	165.1
PP0485	2.8E-08	A	B	1264.5
PP0487	1.7E-09	B	B	260.4
PP0488	2.8E-09	A	B	54.3
PP0490	2.4E-09	B	B	50.5
PP0491	1.1E-09	B	B	33.1
PP0492	1.2E-09	B	B	31.9
PP0493	2.0E-09	B	B	628.4
PP0494	5.1E-10	B	B	135.9
PP0495	5.1E-09	A	B	837.4
PP0496	4.8E-09	B	B	398.7
PP0497	8.5E-10	B	B	44.2
PP0498	1.8E-08	B	B	147.2
PP0499	1.1E-09	B	B	44.9
PP0500	1.8E-08	B	B	962.8
PP0501	3.2E-09	B	B	715.8
PP0502	1.2E-08	A	B	1818.1
PP0503	4.4E-09	A	B	282.9
PP0504	1.4E-08	B	B	234.9
PP0505	1.0E-08	B	B	209.6
PP0506	2.5E-08	B	B	705.0
PP0507	9.4E-10	B	B	62.1
PP0508	2.9E-09	B	B	251.6
PP0509	2.4E-09	B	B	108.6
PP0510	1.2E-08	B	B	391.2
PP0511	1.6E-08	A	B	413.5
PP0512	3.7E-10	B	B	29.4
PP0513	6.2E-09	B	B	238.3
PP0514	1.1E-08	B	B	311.3
PP0515	2.9E-08	B	B	632.8
PP0516	1.0E-08	B	B	457.0
PP0520	9.9E-10	B	B	17.1
PP0521	7.2E-08	B	B	585.5
PP0522	2.8E-09	B	B	83.0
PP0523	1.2E-08	A	B	734.1
PP0524	1.1E-10	B	C	4.8

PP0525	1.4E-10	C	B	2.1
PP0526	7.4E-11	B	C	6.6
PP0527	2.1E-10	C	C	5.7
PP0528	3.7E-10	C	C	21.8
PP0529	9.5E-11	C	B	6.5
PP0530	6.0E-11	C	B	7.0
PP0531	1.4E-10	C	B	21.2
PP0532	6.6E-11	C	B	6.9
PP0533	1.7E-10	C	C	8.9
PP0534	1.6E-10	B	B	16.7
PP0535	5.0E-10	C	B	55.4
PP0536	6.3E-10	B	B	21.8
PP0537	5.8E-09	C	C	196.7
PP0538	6.7E-10	B	B	78.0
PP0539	1.7E-10	B	B	6.3
PP0540	1.7E-08	B	B	765.9
PP0541	4.7E-10	B	B	83.3
PP0542	1.1E-10	B	B	3.4
PP0543	1.0E-09	B	B	41.5
PP0544	1.8E-08	B	B	646.9
PP0545	2.4E-10	B	B	14.0
PP0546	1.4E-10	B	B	5.9
PP0547	3.6E-10	B	B	21.5
PP0548	1.5E-08	C	B	500.8
PP0549	6.2E-11	C	B	13.0
PP0550	5.7E-11	B	B	4.9
PP0551	3.8E-08	C	B	401.4
PP0552	5.2E-11	B	B	2.8
PP0553	4.9E-11	B	B	5.6
PP0554	3.6E-11	B	B	1.6
PP0555	6.6E-11	B	B	48.5
PP0556	2.4E-11	C	B	21.0
PP0557	1.1E-10	B	B	14.8
PP0558	6.7E-11	B	B	31.4
PP0559	1.6E-10	B	B	23.1
PP0560	5.0E-11	B	B	5.2
PP0561	3.1E-10	B	B	20.9
PP0562	4.0E-11	B	B	4.4
PP0563	1.0E-10	B	B	29.0
PP0564	1.8E-10	B	B	18.4
PP0565	1.6E-10	C	B	11.5
PP0566	2.9E-10	B	B	18.4
PP0567	2.1E-10	B	B	8.3
PP0568	1.1E-09	B	B	79.5

PP0569	3.4E-11	C	B	2.8
PP0570	4.6E-11	B	B	7.5
PP0571	5.0E-11	B	B	5.4
PP0572	1.4E-10	B	B	9.0
PP0573	3.4E-10	B	B	8.7
PP0574	2.6E-11	C	B	3.1
PP0575	2.3E-11	B	B	3.2
PP0576	1.9E-11	C	B	2.4
PP0577	1.9E-11	C	C	2.4
PP0578	2.9E-11	B	B	2.2
PP0579	1.7E-11	C	B	2.4
PP0580	1.5E-11	C	C	1.8
PP0581	2.0E-11	C	B	8.0
PP0582	2.0E-11	C	B	9.6
PP0583	1.9E-11	C	C	10.3
PP0584	7.7E-12	C	C	7.0
PP0585	2.2E-11	B	B	6.2
PP0586	1.0E-11	C	B	5.3
PP0587	1.4E-11	C	C	5.1
PP0588	1.1E-10	B	B	16.7
PP0589	3.6E-10	B	B	24.8
PP0590	2.7E-10	C	B	20.9
PP0591	8.7E-08	B	B	3887.5
PP0594	7.3E-11	C	B	2.5
PP0595	1.0E-09	C	B	80.0
PP0596	1.0E-10	B	B	8.3
PP0597	3.3E-10	B	B	18.2
PP0598	2.9E-10	B	B	19.6
PP0599	1.8E-07	C	B	2800.0
PP0605	2.8E-07	C	C	888.7
PP0606	1.8E-09	C	B	266.0
PP0607	9.7E-10	C	B	119.0
PP0608	1.7E-09	C	B	252.2
PP0609	3.9E-09	B	B	468.3
PP0610	4.9E-08	B	B	689.4
PP0611	7.3E-10	B	B	88.9
PP0612	3.9E-10	B	B	43.3
PP0613	6.0E-10	B	B	42.4
PP0614	1.1E-09	B	B	110.3
PP0615	6.2E-09	B	B	216.3
PP0616	4.9E-09	B	B	73.8
PP0617	6.9E-09	B	B	159.1
PP0618	6.2E-09	C	C	79.1
PP0619	3.7E-09	C	C	70.7

PP0620	6.9E-10	C	C	38.4
PP0621	2.4E-09	C	C	83.6
PP0622	1.1E-08	B	B	330.2
PP0626	7.1E-09	C	C	158.0
PP0627	3.3E-09	C	C	98.3
PP0628	2.4E-09	C	C	46.3
PP0629	2.4E-09	B	C	45.1
PP0630	6.9E-09	C	B	388.8
PP0631	5.9E-10	C	B	41.4
PP0632	1.1E-09	C	B	56.7
PP0633	2.3E-09	B	B	116.3
PP0634	4.0E-09	B	B	273.8
PP0635	2.7E-09	B	B	85.6
PP0636	8.6E-09	A	A	728.8
PP0637	2.3E-08	B	B	951.6
PP0638	3.4E-09	B	B	340.7
PP0639	8.5E-09	B	B	630.6
PP0640	2.0E-08	B	B	>600
PP0641	2.6E-08	A	A	>1300
PP0642	1.1E-07	B	B	2650.9
PP0643	7.4E-11	C	B	6.5
PP0644	1.5E-10	C	B	20.7
PP0645	2.8E-11	B	B	12.0
PP0646	1.4E-10	C	B	17.0
PP0647	6.8E-10	C	B	45.0
PP0648	2.1E-10	B	B	20.8
PP0649	7.5E-10	C	B	30.2
PP0650	6.2E-10	C	B	45.7
PP0651	6.0E-10	B	B	136.3
PP0652	2.5E-09	B	B	208.5
PP0653	1.4E-09	B	B	165.7
PP0654	2.0E-09	B	B	690.0
PP0655	1.9E-09	B	B	124.7
PP0656	3.9E-11	C	C	26.5
PP0657	7.6E-11	B	B	32.9
PP0658	3.4E-11	C	B	10.3
PP0659	4.2E-10	B	B	184.2
PP0660	2.9E-10	B	B	131.3
PP0661	3.4E-10	C	B	56.6
PP0662	3.1E-09	B	B	1569.0
PP0663	2.8E-10	B	B	22.7
PP0664	1.9E-10	B	B	15.3
PP0665	2.4E-10	B	B	15.6
PP0666	3.3E-10	B	B	19.1

PP0667	2.7E-10	B	B	8.8
PP0668	3.8E-10	B	B	22.7
PP0669	5.2E-10	B	B	20.3
PP0670	2.8E-10	B	B	11.3
PP0671	6.7E-10	B	B	32.5
PP0672	3.0E-10	B	B	19.7
PP0673	1.2E-10	B	B	52.5
PP0674	1.6E-10	B	B	13.9
PP0675	2.2E-10	B	B	25.5
PP0678	4.7E-10	B	B	35.6
PP0679	5.8E-10	B	B	40.2
PP0680	4.3E-10	B	B	21.2
PP0681	4.4E-10	B	B	24.2
PP0682	5.4E-10	B	B	22.6
PP0683	6.1E-10	B	B	44.7
PP0684	1.1E-09	B	B	45.0
PP0685	8.0E-10	B	B	52.3
PP0686	1.0E-09	B	B	65.7
PP0687	6.4E-10	B	B	44.1
PP0688	2.1E-10	A	B	187.4
PP0689	3.0E-10	B	B	34.4
PP0690	4.6E-10	B	B	60.7
PP0693	1.6E-11	C	C	3.8
PP0694	2.5E-11	C	C	3.5
PP0695	1.5E-11	C	C	2.9
PP0696	1.2E-11	B	B	3.3
PP0697	2.1E-11	C	C	3.8
PP0698	1.5E-11	C	C	4.1
PP0699	3.6E-11	C	C	2.9
PP0700	1.3E-11	C	B	2.9
PP0701	1.7E-11	C	B	3.8
PP0702	4.4E-11	C	C	3.3
PP0703	1.3E-11	C	B	26.7
PP0704	1.1E-11	C	C	11.4
PP0705	2.7E-11	C	C	17.5
PP0706	3.6E-09	B	B	5394.0
PP0708	2.6E-11	B	B	5.5
PP0709	3.0E-11	C	B	1.0
PP0710	2.9E-11	C	B	4.9
PP0711	2.5E-11	C	B	6.5
PP0712	4.2E-11	C	C	7.1
PP0713	3.3E-11	C	B	4.2
PP0714	4.7E-11	C	B	5.1
PP0715	3.5E-11	C	B	4.5

PP0716	5.5E-11	C	B	6.3
PP0717	3.2E-11	B	B	4.8
PP0718	2.9E-11	C	B	42.3
PP0719	2.0E-11	C	B	8.5
PP0720	3.6E-11	C	B	13.7
PP0721	1.1E-08	B	B	4701.7
PP0722	2.5E-08	C	B	2599.5
PP0723	4.7E-10	B	B	10.8
PP0724	4.4E-10	B	B	127.3
PP0725	5.0E-09	B	B	193.9
PP0726	1.1E-09	B	B	32.7
PP0727	1.3E-09	B	B	85.2
PP0728	1.1E-08	B	B	252.0
PP0729	2.7E-09	B	B	216.0
PP0730	9.4E-11	C	C	29.6
PP0731	1.6E-09	B	B	109.6
PP0732	3.9E-11	C	B	39.6
PP0733	7.7E-10	B	B	220.1
PP0734	3.8E-10	B	C	28.8
PP0735	2.7E-10	B	C	40.9
PP0736	1.8E-09	B	C	129.9
PP0737	5.5E-10	B	C	38.2
PP0738	6.4E-10	B	B	99.2
PP0739	3.7E-09	B	C	296.8
PP0740	4.7E-10	B	C	51.2
PP0741	2.8E-10	B	B	51.5
PP0742	5.1E-10	B	B	73.3
PP0743	6.8E-10	B	C	76.3
PP0744	6.0E-11	B	B	57.0
PP0745	2.9E-11	B	C	3.9
PP0746	4.3E-10	B	C	35.4
PP0747	3.6E-10	B	C	45.9
PP0748	8.0E-11	B	B	10.7
PP0749	5.9E-10	B	C	19.8
PP0750	3.7E-10	B	C	11.1
PP0751	5.2E-10	B	C	25.5
PP0752	5.4E-10	B	B	25.8
PP0753	1.4E-10	B	C	8.2
PP0754	4.9E-10	B	C	40.4
PP0755	5.6E-10	B	B	83.8
PP0756	8.7E-10	B	B	69.5
PP0757	4.0E-09	B	C	480.2
PP0758	1.6E-09	B	C	153.1
PP0759	2.7E-09	B	B	184.7

PP0760	1.6E-08	B	C	309.6
PP0761	1.6E-09	B	C	58.4
PP0762	7.3E-10	B	B	30.1
PP0763	9.8E-10	B	B	83.0
PP0764	3.4E-09	B	B	215.3
PP0765	3.1E-10	B	C	123.0
PP0766	9.6E-11	B	B	8.7
PP0767	1.9E-09	B	C	157.5
PP0768	9.7E-10	B	C	36.1
PP0769	2.1E-10	B	C	43.3
PP0770	8.4E-10	B	B	62.2
PP0771	3.3E-09	B	B	203.7
PP0772	4.3E-09	B	B	434.5
PP0773	4.0E-09	B	B	170.1
PP0774	1.7E-08	B	B	478.1
PP0775	9.2E-09	B	B	416.7
PP0776	1.5E-08	B	B	591.2
PP0778	1.0E-08	B	B	545.9
PP0779	5.1E-09	B	B	364.5
PP0780	7.8E-09	B	B	527.3
PP0781	1.7E-08	B	B	651.2
PP0782	2.3E-09	B	B	425.1
PP0783	8.5E-10	B	B	122.1
PP0784	1.7E-08	B	B	446.6
PP0785	3.0E-09	B	B	324.4
PP0786	6.0E-10	B	B	44.8
PP0787	3.4E-10	C	B	38.3
PP0788	5.4E-11	B	C	7.1
PP0789	1.2E-10	C	B	12.5
PP0790	5.6E-10	C	B	28.8
PP0791	9.8E-10	C	B	86.0
PP0792	9.0E-10	C	B	111.9
PP0793	3.4E-09	C	B	689.7
PP0794	1.5E-09	C	B	122.5
PP0795	2.5E-09	C	B	355.8
PP0796	7.5E-09	C	B	437.6
PP0797	1.7E-09	C	B	80.6
PP0798	1.9E-09	C	B	61.5
PP0799	1.5E-09	C	B	36.3
PP0800	2.7E-09	C	B	186.4
PP0801	4.5E-10	C	B	28.7
PP0802	8.2E-11	C	B	6.5
PP0803	1.7E-09	C	B	52.5
PP0804	1.4E-09	C	B	40.9

PP0805	1.6E-10	B	C	10.3
PP0806	1.9E-10	B	B	16.9
PP0807	5.9E-11	B	B	16.7
PP0808	2.7E-11	B	B	16.7
PP0809	2.7E-11	B	B	8.4
PP0810	4.0E-11	B	B	12.8
PP0811	8.3E-11	B	B	9.8
PP0812	2.2E-10	B	B	17.9
PP0813	4.0E-10	C	B	90.3
PP0814	3.9E-11	B	B	19.4
PP0815	3.9E-09	B	B	344.7
PP0816	5.0E-10	A	B	92.5
PP0817	3.6E-10	A	B	111.7
PP0818	1.7E-09	B	B	43.7
PP0819	5.6E-10	A	B	75.7
PP0820	1.2E-09	A	B	60.1
PP0821	2.0E-09	A	B	250.2
PP0822	5.7E-09	B	B	1988.1
PP0823	8.2E-10	A	B	130.5
PP0824	5.5E-11	A	A	23.6
PP0825	2.3E-10	A	A	26.5
PP0826	1.3E-10	C	B	11.5
PP0827	1.1E-10	C	C	15.7
PP0828	1.7E-10	C	C	7.3
PP0829	8.1E-11	B	C	4.4
PP0830	5.8E-11	C	C	3.4
PP0831	3.2E-10	C	C	3.7
PP0832	2.1E-10	C	C	21.5
PP0833	9.0E-10	B	B	41.3
PP0834	1.9E-10	A	B	13.6
PP0835	1.4E-10	B	B	122.1
PP0836	6.3E-10	B	B	359.8
PP0837	1.9E-10	B	B	63.4
PP0838	5.3E-10	B	B	50.4
PP0839	1.1E-09	B	B	122.5
PP0840	5.0E-09	B	B	571.8
PP0841	7.3E-10	B	B	112.5
PP0842	6.0E-10	B	B	173.8
PP0843	5.2E-10	B	B	38.6
PP0844	1.2E-09	B	B	50.2
PP0845	2.2E-09	B	B	134.9
PP0846	9.9E-10	B	B	22.2
PP0847	2.8E-10	B	B	135.6
PP0848	5.7E-10	B	B	37.5

PP0849	4.6E-10	B	B	35.7
PP0850	1.2E-08	B	B	3085.5
PP0851	5.2E-10	B	B	37.9
PP0852	4.6E-10	B	B	35.3
PP0853	6.7E-10	B	B	24.3
PP0854	3.8E-10	B	B	21.7
PP0855	8.4E-10	B	B	114.2
PP0856	9.6E-10	B	B	66.7
PP0857	1.4E-09	B	B	111.2
PP0858	6.6E-10	B	B	52.5
PP0859	3.1E-10	B	B	22.4
PP0860	1.1E-09	B	B	142.8
PP0861	6.6E-10	B	B	20.7
PP0862	1.1E-09	B	B	81.1
PP0863	6.0E-10	B	B	228.5
PP0864	4.9E-10	B	B	185.2
PP0865	1.1E-09	B	B	767.1
PP0866	5.3E-10	B	B	197.4
PP0867	1.2E-09	B	B	205.9
PP0868	5.3E-11	C	B	70.8
PP0869	5.6E-11	B	B	134.3
PP0870	5.7E-11	B	B	79.7
PP0871	4.0E-10	B	B	438.1
PP0872	1.7E-09	A	A	2599.3
PP0873	8.6E-10	A	B	896.1
PP0874	1.0E-10	C	B	4.9
PP0875	9.6E-11	C	B	4.8
PP0876	4.0E-10	C	C	7.1
PP0877	2.1E-10	C	B	18.8
PP0878	3.2E-09	B	B	85.9
PP0879	8.6E-09	B	B	194.9
PP0880	4.5E-09	B	B	160.2
PP0881	5.5E-09			374.1
PP0882	2.0E-11	C	B	7.1
PP0883	3.7E-10	B	B	59.3
PP0884	2.2E-11	C	C	6.2
PP0885	9.8E-11	C	B	11.5
PP0886	8.6E-11	C	B	14.3
PP0887	9.3E-11	C	C	19.0
PP0888	1.7E-10	C	B	25.6
PP0889	1.3E-10	B	B	26.7
PP0890	1.2E-09	B	B	183.0
PP0891	6.2E-10	B	B	154.0
PP0892	3.3E-10	B	B	53.6

PP0893	1.3E-09	B	B	226.5
PP0894	8.8E-12	C	C	3.7
PP0895	7.2E-12	C	C	2.2
PP0896	1.8E-11	C	C	3.1
PP0898	8.8E-10	B	B	119.8
PP0899	9.9E-10	A	B	922.8
PP0900	1.2E-11	C	C	4.9
PP0901	3.0E-09	B	B	332.0
PP0902	6.3E-10	A	B	72.6
PP0903	3.6E-09	B	C	596.2
PP0904	8.0E-10	B	B	58.7
PP0905	7.9E-10	B	B	92.0
PP0906	2.9E-10	B	B	36.9
PP0907	1.6E-10	B	B	24.8
PP0908	1.9E-10	B	B	38.5
PP0909	4.8E-10	B	B	58.1
PP0910	6.2E-10	B	B	66.2
PP0911	6.0E-11	B	B	10.2
PP0912	3.2E-10	B	B	40.5
PP0913	1.1E-09	B	B	206.4
PP0914	4.3E-10	B	B	40.2
PP0915	1.4E-10	B	B	37.6
PP0916	3.4E-10	B	B	35.9
PP0917	1.6E-10	B	B	25.2
PP0918	4.0E-10	B	B	27.7
PP0919	8.1E-10	B	B	109.5
PP0920	2.9E-10	B	B	75.5
PP0921	2.6E-09	B	B	139.0
PP0922	5.0E-10	B	B	98.2
PP0923	1.6E-09	B	B	445.2
PP0924	8.2E-10	B	B	92.0
PP0925	1.1E-09	A	B	91.0
PP0926	2.4E-09	B	B	113.4
PP0927	1.0E-09	A	B	112.9
PP0928	1.0E-09	A	B	182.3
PP0929	2.7E-09	A	B	316.8
PP0930	1.8E-09	A	B	141.9
PP0931	1.9E-09	A	B	180.7
PP0932	2.9E-09	B	B	158.3
PP0933	1.6E-09	A	B	150.1
PP0934	7.2E-10	B	B	51.8
PP0935	4.3E-10	B	B	26.9
PP0936	4.2E-10	B	B	42.4
PP0937	1.0E-09	B	B	39.0

PP0938	1.1E-09	B	B	175.1
PP0939	9.1E-10	B	B	114.1
PP0940	2.0E-09	B	C	110.1
PP0941	1.2E-09	B	B	63.9
PP0942	9.9E-10	B	B	66.1
PP0943	1.1E-09	B	B	154.2
PP0944	3.9E-09	A	A	344.2
PP0945	3.7E-09	B	A	986.7
PP0946	2.2E-09	A	B	377.8
PP0947	3.4E-09	A	A	596.6
PP0948	3.2E-09	A	A	234.5
PP0949	6.7E-09	A	A	658.8
PP0950	6.0E-09	A	B	958.4
PP0951	6.3E-09	A	A	945.5
PP0952	8.5E-09	A	A	1080.4
PP0953	2.7E-08	A	A	1612.8
PP0954	7.5E-09	A	A	438.5
PP0955	1.9E-08	A	A	6475.4
PP0956	7.2E-09	A	A	690.3
PP0958	7.5E-09	B	B	1038.1
PP0959	3.9E-10	B	B	156.2
PP0960	3.7E-10	B	B	101.4
PP0961	6.2E-10	B	B	53.6
PP0962	6.5E-10	B	B	83.9
PP0963	7.8E-10	B	B	100.0
PP0964	5.9E-10	B	B	56.6
PP0965	5.7E-10	B	B	48.8
PP0966	2.3E-10	B	B	34.6
PP0967	3.3E-10	B	B	77.7
PP0968	3.2E-10	B	B	38.8
PP0969	1.2E-10	B	B	13.6
PP0970	2.2E-09	B	B	340.5
PP0971	3.4E-10	B	B	54.0
PP0972	1.5E-10	B	B	15.8
PP0973	8.5E-11	B	B	11.6
PP0975	8.9E-09			1567.6
PP0976	4.8E-09	B	B	1178.5
PP0977	7.7E-09	B	A	1115.5
PP0978	8.8E-11	A	B	22.7
PP0979	1.7E-09	AA	A	281.1
PP0980	8.8E-10	A	B	222.8
PP0981	1.1E-08	AA	A	797.4
PP0982	9.9E-10	AA	A	372.4
PP0983	7.8E-11	A	A	19.5

PP0984	2.8E-10	A	A	64.6
PP0985	2.2E-11	C	C	12.2
PP0986	2.7E-10	C	C	45.9
PP0987	2.4E-11	C	C	6.8
PP0988	4.6E-11	C	B	10.3
PP0989	1.3E-09	B	B	134.8
PP0992	4.6E-09	B	B	790.3
PP0993	1.4E-09	B	B	331.8
PP0997	5.6E-08	A	A	2627.1
PP0998	1.2E-10	B	B	19.7
PP0999	1.1E-10	C	B	7.6
PP1000	3.9E-11	B	B	7.5
PP1001	1.0E-10	B	B	28.1
PP1002	2.5E-11	B	B	2.1
PP1003	7.6E-11	C	B	29.1
PP1004	3.7E-09	B	B	254.6
PP1005	1.1E-09	A	A	274.7
PP1006	3.2E-10	B	B	81.9
PP1008	1.1E-09	A	B	101.6
PP1009	2.0E-09	B	B	195.0
PP1010	1.5E-09	B	B	179.1
PP1011	3.7E-09	A	B	314.2
PP1012	9.0E-10	A	B	41.6
PP1013	3.4E-09	C	C	269.3
PP1014	1.1E-09	C	C	114.4
PP1015	5.0E-09	C	C	110.0
PP1016	2.7E-10	A	B	61.2
PP1017	4.8E-11	C	B	5.0
PP1018	1.7E-11	C	B	6.8
PP1019	5.5E-11	C	B	7.4
PP1020	2.2E-11	C	B	18.0
PP1021	5.7E-11	C	B	14.0
PP1022	3.6E-11	C	B	17.5
PP1024	8.8E-11	B	B	12.7
PP1025	5.6E-11	C	B	10.7
PP1026	1.2E-10	B	B	10.4
PP1027	5.6E-11	C	B	7.2
PP1028	9.9E-11	B	B	17.3
PP1029	7.8E-11	C	B	24.3
PP1030	2.6E-10	B	B	27.9
PP1031	6.7E-10	C	C	86.2
PP1032	3.8E-10	C	C	43.9
PP1033	4.3E-10	C	C	67.2
PP1034	4.3E-10	C	C	96.8

PP1035	5.2E-10	C	C	127.6
PP1036	7.5E-10	C	C	149.8
PP1037	7.6E-10	C	C	296.0
PP1038	3.0E-09	C	C	187.8
PP1039	5.9E-10	C	C	98.4
PP1040	1.2E-09	C	C	18.7
PP1041	5.7E-10	C	C	223.4
PP1042	1.3E-09	C	C	348.8
PP1043	2.4E-09	C	C	386.8
PP1044	1.8E-09	C	C	44.1
PP1045	1.7E-09	C	C	206.7
PP1046	3.8E-10	C	C	109.4
PP1047	8.5E-10	C	C	117.2
PP1048	4.9E-10	C	C	133.8
PP1049	9.1E-10	C	C	358.6
PP1050	9.4E-10	C	C	815.0
PP1051	1.8E-09	C	C	285.7
PP1052	2.5E-10	A	A	58.7
PP1053	2.3E-10	A	A	67.8
PP1054	3.9E-09	A	B	468.9
PP1056	2.1E-10	A	A	75.0
PP1057	3.1E-10	A	B	96.9
PP1058	2.9E-09	A	B	599.1
PP1059	9.1E-10	A	B	200.7
PP1060	2.6E-09	A	A	306.8
PP1063	1.2E-09	A	A	380.1
PP1064	1.7E-08	A	A	1392.2
PP1065	4.5E-10	A	B	96.7
PP1067	2.9E-09	B	B	299.0
PP1068	1.1E-09	A	B	120.9
PP1069	2.5E-09	A	B	126.9
PP1070	7.5E-11	B	B	11.9
PP1071	1.0E-10	B	B	24.7
PP1072	6.3E-11	B	B	13.0
PP1073	3.6E-10	B	B	83.7
PP1075	6.6E-11	B	B	21.8
PP1076	6.8E-11	B	B	4.6
PP1077	8.5E-11	B	B	14.9
PP1078	4.7E-10	B	B	610.2
PP1079	2.3E-10	B	B	27.2
PP1080	2.4E-10	B	B	39.2
PP1082	3.5E-09	A	B	299.6
PP1083	3.4E-09	B	B	221.4
PP1084	9.1E-11	C	B	83.9

PP1085	9.5E-10	A	A	589.9
PP1086	1.3E-10	AA	A	22.4
PP1087	9.5E-11	A	A	40.4
PP1088	5.5E-10	A	A	195.0
PP1089	1.2E-10	AA	A	57.3
PP1090	8.6E-11	AA	A	20.9
PP1091	1.1E-10	A	B	17.9
PP1092	1.5E-10	A	A	15.8
PP1093	5.8E-10	AA	A	78.7
PP1094	8.4E-10	A	B	778.0
PP1095	1.8E-10	B	B	14.9
PP1096	2.4E-10	B	B	38.1
PP1097	1.2E-10	B	B	10.2
PP1098	6.8E-10	B	B	100.9
PP1099	5.8E-10	B	A	68.1
PP1100	1.9E-10	B	B	17.6
PP1101	4.6E-10	B	B	68.4
PP1102	9.5E-10	B	A	83.1
PP1103	3.6E-11	A	B	34.8
PP1104	5.9E-11	A	A	44.6
PP1105	7.0E-11	A	A	12.0
PP1106	8.1E-10	A	A	154.6
PP1107	3.8E-11	A	A	5.4
PP1108	3.3E-11	A	A	28.3
PP1109	1.2E-10	A	B	17.0
PP1110	5.6E-11	A	B	11.2
PP1111	4.5E-11	A	A	13.0
PP1112	6.0E-11	A	B	10.4
PP1113	3.1E-11	A	A	21.4
PP1114	5.4E-11	A	A	12.2
PP1115	5.4E-11	A	A	29.0
PP1116	6.9E-11	A	A	19.8
PP1117	7.0E-11	A	A	16.5
PP1118	5.6E-11	A	B	6.5
PP1119	3.7E-11	A	A	25.5
PP1120	4.2E-11	A	A	20.6
PP1121	4.9E-11	A	A	17.3
PP1122	4.7E-11	A	B	274.9
PP1123	7.2E-11	A	B	13.4
PP1124	5.6E-11	A	B	12.4
PP1125	7.0E-11	A	A	15.0
PP1126	8.9E-11	A	A	7.1
PP1127	1.1E-10	AA	A	11.9
PP1128	1.2E-10	AA	A	120.7

PP1129	5.6E-11	A	B	10.2
PP1130	3.5E-11	A	B	19.6
PP1131	2.5E-11	A	B	32.0
PP1132	6.6E-11	A	B	86.8
PP1133	5.0E-11	A	A	16.5
PP1134	6.0E-11	A	B	20.0
PP1135	9.4E-11	A	A	43.9
PP1136	1.4E-10	A	A	193.4
PP1137	1.1E-10	AA	A	141.7
PP1138	1.9E-10	A	A	244.5
PP1139	4.3E-10	A	A	296.8
PP1140	1.5E-10	A	A	1776.6
PP1141	3.2E-10	AA	A	423.6
PP1142	6.5E-10	A	A	321.5
PP1143	1.7E-10	A	A	75.3
PP1144	2.4E-10	AA	A	155.4
PP1145	2.1E-10	A	B	140.0
PP1146	3.2E-10	A	B	202.3
PP1147	7.1E-10	A	A	888.4
PP1148	1.2E-09	A	A	357.1
PP1149	4.3E-10	A	A	173.0
PP1150	1.7E-10	AA	A	42.7
PP1151	6.4E-10	B	B	97.1
PP1152	1.3E-09	B	B	299.8
PP1153	2.8E-10	B	B	15.5
PP1154	4.3E-10	B	B	69.6
PP1155	1.5E-10	B	B	73.1
PP1156	6.3E-11	B	B	33.7
PP1157	6.1E-11	B	B	30.3
PP1158	1.8E-10	B	B	57.5
PP1159	3.6E-11	C	B	13.0
PP1160	3.2E-11	B	B	18.4
PP1161	6.0E-10	B	B	153.4
PP1162	1.2E-09	B	B	198.5
PP1163	5.9E-10	B	B	93.3
PP1164	5.2E-10	B	B	95.9
PP1165	1.5E-09	A	B	295.3
PP1166	5.0E-10	B	B	124.5
PP1167	5.0E-10	B	B	134.1
PP1168	1.8E-09	A	A	337.7
PP1169	3.2E-10	B	B	74.0
PP1170	2.3E-10	B	B	64.7
PP1171	6.9E-10	B	B	117.5
PP1172	1.7E-10	B	B	48.3

PP1173	1.8E-10	B	B	70.8
PP1174	1.0E-09	B	B	85.2
PP1175	1.6E-10	B	B	23.5
PP1176	1.3E-10	B	B	50.0
PP1177	8.1E-11	B	B	32.5
PP1178	1.6E-10	B	B	26.3
PP1179	9.1E-11	B	B	56.9
PP1180	1.7E-10	B	B	46.9
PP1181	1.9E-10	B	B	26.3
PP1182	8.0E-11	B	B	134.5
PP1183	2.6E-10	B	B	27.8
PP1184	1.6E-10	B	B	91.9
PP1185	5.0E-10	B	B	175.0
PP1186	9.4E-11	B	B	54.4
PP1187	1.2E-10	B	B	52.3
PP1188	4.3E-10	B	B	33.5
PP1189	6.6E-11	B	B	16.1
PP1190	9.2E-11	B	B	15.5
PP1191	5.6E-11	A	B	13.0
PP1192	4.0E-11	B	A	10.5
PP1193	7.0E-11	B	B	16.3
PP1194	6.8E-11	B	B	25.3
PP1195	7.4E-11	B	B	18.3
PP1196	4.0E-11	B	B	50.8
PP1197	9.6E-11	B	B	14.8
PP1198	1.9E-10	B	B	35.2
PP1199	1.7E-10	A	A	39.1
PP1200	2.0E-10	AA	A	19.2
PP1201	1.7E-10	AA	A	9.7
PP1202	4.0E-10			24.1
PP1203	2.3E-10	A	A	20.8
PP1204	2.4E-10	AA	A	23.4
PP1205	1.6E-10	AA	A	25.4
PP1206	1.7E-10	AA	A	109.4
PP1207	2.1E-10	AA	A	29.9
PP1208	1.7E-10	AA	A	24.4
PP1209	2.2E-10	AA	A	15.9
PP1210	4.0E-10	AA	A	44.3
PP1211	2.7E-10	A	B	26.8
PP1212	2.8E-10	AA	A	35.6
PP1213	1.8E-10	AA	A	40.4
PP1214	3.4E-10	AA	A	93.4
PP1215	4.2E-10	AA	A	33.4
PP1216	3.9E-10	AA	A	19.8

PP1217	4.8E-10	AA	A	17.8
PP1218	8.8E-10	AA	A	67.9
PP1219	3.5E-10	AA	A	21.4
PP1220	5.7E-10	AA	A	22.2
PP1221	4.0E-10	AA	A	40.6
PP1222	1.2E-09	A	A	301.2
PP1223	1.2E-09	AA	A	117.3
PP1224	1.2E-09	A	A	122.4
PP1225	1.1E-09	AA	A	92.5
PP1226	2.4E-09	AA	A	105.8
PP1227	1.6E-09	A	A	127.6
PP1228	1.6E-09	AA	A	55.1
PP1229	1.3E-09	A	A	144.5
PP1230	7.7E-10	A	A	109.7
PP1231	5.6E-10	AA	A	23.1
PP1232	6.7E-10	A	A	59.7
PP1233	6.6E-10	AA	A	34.7
PP1234	3.8E-09	B	C	398.0
PP1235	6.7E-09	B	C	386.0
PP1242	7.6E-11	A	A	12.8
PP1243	5.8E-11	A	A	13.2
PP1244	6.1E-11	A	B	8.9
PP1245	6.0E-11	A	B	3.7
PP1246	8.1E-11	A	A	9.0
PP1247	4.6E-11	A	A	6.4
PP1248	6.9E-11	A	A	7.3
PP1249	1.8E-10	A	A	55.4
PP1250	1.9E-10	AA	A	18.7
PP1251	1.8E-10	AA	A	10.2
PP1252	3.0E-10	AA	A	51.2
PP1253	2.0E-10	A	A	22.2
PP1254	2.0E-10	AA	A	28.3
PP1255	3.9E-10	A	A	156.0
PP1256	3.6E-10	A	A	69.0
PP1257	3.3E-10	A	A	54.3
PP1258	1.9E-10	AA	A	21.3
PP1259	4.9E-10	A	A	62.0
PP1260	3.7E-10	A	A	60.4
PP1261	4.4E-10	A	A	76.8
PP1262	2.4E-10	A	B	56.7
PP1263	2.3E-10	A	A	18.9
PP1264	3.7E-10	A	B	15.9
PP1265	1.7E-10	A	B	14.1
PP1266	4.5E-11	A	A	12.2

PP1267	4.6E-11	A	A	10.8
PP1268	4.5E-11	A	A	12.1
PP1269	9.1E-11	A	B	29.0
PP1270	1.3E-10	A	B	53.5
PP1271	5.4E-11	AA	A	90.7
PP1272	1.1E-10	A	A	24.0
PP1273	1.2E-10	A	B	16.5
PP1274	3.2E-11	A	A	7.5
PP1275	4.7E-11	A	A	4.9
PP1276	6.6E-11	A	B	20.8
PP1277	2.5E-10	A	A	79.8
PP1278	1.4E-10	A	B	45.7
PP1279	2.7E-10	A	A	72.6
PP1280	1.5E-10	A	A	34.4
PP1281	1.4E-10	AA	A	10.2
PP1282	2.0E-10	A	A	12.3
PP1283	2.0E-10	AA	A	42.6
PP1284	1.2E-10	AA	A	54.8
PP1285	1.5E-10	AA	A	24.6
PP1286	6.5E-10	AA	A	58.8
PP1287	5.6E-10	AA	A	49.7
PP1288	1.8E-10	AA	A	22.2
PP1289	1.7E-10	AA	A	34.7
PP1290	2.4E-10	AA	A	15.4
PP1291	2.4E-10	A	A	16.7
PP1292	1.6E-10	A	A	24.6
PP1293	2.2E-10	AA	A	4.9
PP1294	2.9E-10	A	A	10.0
PP1295	1.2E-10	AA	A	6.2
PP1296	1.2E-10	AA	A	14.7
PP1297	8.7E-11	AA	A	23.1
PP1298	1.3E-10	AA	A	11.4
PP1299	1.4E-10	A	A	11.0
PP1300	8.2E-11	A	A	9.5
PP1301	8.3E-11	A	A	4.7
PP1302	5.7E-11	A	A	9.2
PP1303	6.8E-11	AA	A	4.2
PP1304	7.0E-11	A	A	8.8
PP1305	1.2E-10	AA	A	13.0
PP1306	2.0E-10	AA	A	14.7
PP1307	1.4E-10	A	A	7.0
PP1308	1.0E-10	A	A	10.9
PP1309	1.6E-10	A	A	5.3
PP1310	1.3E-10	AA	A	4.5

PP1311	3.9E-10	AA	A	40.3
PP1312	4.2E-10	AA	A	72.8
PP1313	2.7E-10	AA	A	66.3
PP1314	4.0E-10	A	A	57.2
PP1315	3.4E-10	AA	A	34.5
PP1316	7.2E-11	A	A	13.2
PP1317	9.4E-11	A	B	7.6
PP1318	9.1E-11	A	A	11.5
PP1319	6.9E-11	A	B	57.5
PP1320	5.7E-11	A	A	7.7
PP1321	8.0E-11	A	B	13.9
PP1322	5.9E-10	A	A	56.2
PP1323	2.6E-10	AA	A	41.8
PP1324	9.3E-11	A	A	4.4
PP1325	5.5E-10	A	A	42.7
PP1326	2.7E-10	AA	A	23.1
PP1327	1.1E-10	A	A	12.4
PP1328	5.6E-10	A	A	134.3
PP1329	2.4E-10	AA	A	34.5
PP1330	4.2E-10	AA	A	79.6
PP1331	8.0E-11	A	A	13.9
PP1333	5.8E-08	C	B	979.5
PP1334	1.1E-08	B	B	968.3
PP1335	1.8E-08	B	B	736.5
PP1336	7.4E-11	B	B	10.8
PP1337	1.7E-10	B	B	29.8
PP1338	1.4E-10	B	B	35.0
PP1339	6.5E-10	A	B	42.1
PP1340	8.1E-11	B	B	10.9
PP1341	8.1E-10	A	B	46.3
PP1342	9.1E-11	B	B	5.0
PP1343	2.7E-10	A	B	19.3
PP1344	1.4E-10	B	B	16.7
PP1345	7.1E-10	A	B	34.8
PP1346	8.4E-11	B	B	7.2
PP1347	1.7E-11	B	B	3.6
PP1348	7.6E-11	B	B	8.7
PP1349	9.0E-11	C	B	14.7
PP1350	1.8E-10	B	B	20.1
PP1351	1.3E-10	A	B	12.8
PP1352	2.4E-11	A	B	4.6
PP1353	1.0E-10	A	B	3.7
PP1354	5.6E-11	A	B	3.6
PP1355	1.6E-10	A	B	10.2

PP1356	4.7E-11	B	B	3.3
PP1357	1.3E-10	A	B	5.4
PP1358	3.0E-11	A	B	4.1
PP1359	6.8E-11	A	B	3.2
PP1360	5.5E-11	A	B	4.9
PP1361	1.5E-10	A	B	6.2
PP1362	3.7E-11	A	B	3.7
PP1363	3.2E-10	A	B	34.7
PP1364	5.0E-11	A	B	7.1
PP1365	1.3E-10	A	B	4.2
PP1366	1.1E-10	A	B	14.0
PP1367	3.4E-10	A	B	29.3
PP1368	6.1E-11	A	B	2.9
PP1369	2.6E-10	B	B	13.4
PP1370	5.7E-11	C	C	2.3
PP1371	7.7E-11	A	B	5.1
PP1372	7.8E-11	B	B	5.0
PP1373	3.5E-10	B	B	12.2
PP1374	3.3E-11	B	B	1.9
PP1375	2.3E-10	B	B	11.5
PP1376	3.7E-11	B	B	3.5
PP1377	8.7E-11	B	B	5.8
PP1378	8.1E-11	B	C	6.6
PP1379	2.9E-10	A	B	10.3
PP1380	4.5E-11	B	B	4.1
PP1381	7.2E-10	B	B	80.4
PP1382	6.8E-11	B	B	15.8
PP1383	1.7E-10	B	B	11.2
PP1384	1.1E-10	A	B	13.5
PP1385	8.0E-10	B	B	19.6
PP1386	8.2E-11	B	B	4.2
PP1387	9.8E-11	A	B	15.3
PP1388	7.6E-11	A	B	8.8
PP1389	6.6E-11	AA	A	2.4
PP1390	1.1E-09	A	A	305.4
PP1391	1.6E-09	A	A	271.1
PP1392	4.7E-11	A	A	1.4
PP1393	1.9E-10	A	A	18.2
PP1394	2.4E-10	AA	A	25.1
PP1395	6.3E-11	A	B	3.8
PP1396	1.4E-10	AA	A	19.4
PP1397	7.3E-11	A	A	3.7
PP1398	3.2E-11	A	A	2.3
PP1399	1.9E-10	A	A	18.8

PP1400	4.9E-11	A	B	5.1
PP1401	2.6E-10	A	A	34.4
PP1402	3.0E-10	A	A	82.0
PP1403	6.0E-10	AA	A	110.6
PP1404	4.8E-09	A	A	498.2
PP1405	8.5E-09	A	A	466.1
PP1406	7.2E-11	A	B	10.9
PP1407	7.4E-11	A	A	18.7
PP1408	2.2E-10	A	A	37.6
PP1409	2.1E-10	A	A	43.5
PP1410	3.2E-10	B	B	51.0
PP1411	8.0E-11	A	B	6.0
PP1412	1.9E-10	A	A	23.0
PP1413	4.2E-10	B	B	62.5
PP1414	7.4E-11	A	B	4.4
PP1415	2.5E-10	A	A	9.5
PP1416	1.7E-10	A	A	3.8
PP1417	2.6E-10	B	B	18.4
PP1418	2.4E-10	AA	A	29.9
PP1419	2.6E-10	AA	A	40.4
PP1420	3.5E-10	A	A	31.4
PP1421	3.0E-10	A	A	27.9
PP1422	2.2E-10	AA	A	14.1
PP1423	1.4E-10	AA	A	4.4
PP1424	2.3E-10	A	A	26.3
PP1425	2.4E-10	A	B	20.2
PP1426	1.0E-09	A	B	474.8
PP1427	9.9E-10	A	B	465.1
PP1428	8.7E-10	AA	A	38.8
PP1429	5.2E-10	AA	A	38.7
PP1430	8.5E-10	A	A	70.4
PP1431	5.7E-10	AA	A	41.2
PP1432	6.1E-10	AA	A	51.3
PP1433	4.6E-10	AA	A	44.4
PP1434	6.9E-10	A	A	111.8
PP1435	1.1E-09	A	A	178.0
PP1436	2.9E-10	AA	A	47.4
PP1437	6.1E-10	A	A	219.8
PP1438	5.5E-10	AA	A	89.4
PP1439	1.2E-09	AA	A	87.3
PP1440	3.5E-10	AA	A	69.7
PP1441	7.0E-10	A	A	87.6
PP1442	1.3E-10	A	A	48.3
PP1443	1.5E-10	AA	A	34.8

PP1444	1.9E-10	A	A	102.6
PP1445	2.7E-10	A	A	92.8
PP1446	2.0E-10	A	A	32.0
PP1447	1.2E-10	A	A	28.9
PP1448	5.9E-11	A	A	8.3
PP1449	9.8E-11	A	A	30.6
PP1450	1.4E-10	A	A	50.1
PP1451	1.4E-10	A	A	61.1
PP1452	1.3E-10	A	A	30.5
PP1453	1.2E-10	A	A	13.6
PP1454	9.6E-11	A	A	15.2
PP1455	1.1E-10	A	A	13.4
PP1456	1.2E-10	A	A	90.0
PP1457	1.5E-10	A	A	30.4
PP1458	1.5E-10	A	A	18.2
PP1459	2.0E-10	A	A	38.6
PP1460	2.3E-10	A	A	32.9
PP1461	2.7E-10	A	A	120.7
PP1462	1.2E-10	A	A	27.5
PP1463	1.3E-10	A	A	44.5
PP1464	1.5E-10	A	A	32.3
PP1465	3.6E-10	A	A	34.1
PP1466	1.4E-10	A	A	33.2
PP1467	1.2E-10	A	A	11.2
PP1468	1.2E-10	A	A	9.5
PP1469	1.8E-10	A	A	22.2
PP1470	2.2E-10	A	A	110.7
PP1471	2.5E-10	A	A	48.2
PP1472	1.4E-10	A	A	37.1
PP1473	1.9E-10	A	A	36.6
PP1474	2.3E-10	A	A	48.2
PP1475	5.5E-10	A	A	48.9
PP1476	1.0E-09	A	B	215.5
PP1477	1.4E-09	A	B	308.8
PP1478	3.4E-10	A	A	101.8
PP1479	4.9E-10	A	B	139.8
PP1480	9.2E-10	A	B	85.8
PP1481	1.2E-09	A	B	14.8
PP1482	4.5E-10	A	B	76.4
PP1483	5.1E-10	A	B	90.3
PP1484	4.5E-10	A	A	59.3
PP1485	2.8E-10	A	A	30.5
PP1486	4.6E-10	A	A	15.0
PP1487	3.4E-10	A	A	46.6

PP1488	8.1E-11	A	B	23.2
PP1489	2.6E-09	B	B	118.1
PP1490	6.0E-10	B	B	48.9
PP1491	3.7E-09	B	A	197.9
PP1492	9.4E-10	B	B	129.2
PP1493	2.3E-09	B	B	135.1
PP1494	5.8E-10	B	B	142.5
PP1495	5.5E-10	A	B	98.7
PP1496	2.6E-10	A	B	36.7
PP1497	2.2E-11	A	A	10.7
PP1498	6.9E-11	A	A	10.3
PP1499	5.4E-11	A	B	5.5
PP1500	3.9E-11	A	A	6.9
PP1501	2.4E-11	A	A	1.5
PP1502	3.8E-11	A	A	2.0
PP1503	1.1E-10	A	A	3.8
PP1504	3.2E-10	A	A	38.0
PP1505	9.2E-11	A	A	4.0
PP1506	3.4E-10	AA	A	73.4
PP1507	1.7E-10	A	A	16.2
PP1508	1.5E-10	A	A	28.1
PP1509	4.0E-10	A	A	67.9
PP1510	1.1E-10	AA	A	34.5
PP1511	9.9E-11	AA	A	13.7
PP1512	8.4E-11	AA	A	16.9
PP1513	7.1E-11	A	A	8.3
PP1514	6.5E-10	A	A	72.7
PP1515	4.2E-10	A	A	91.9
PP1516	9.8E-10	A	B	45.7
PP1517	4.3E-10	A	A	33.6
PP1518	5.8E-10	A	B	49.4
PP1519	4.1E-10	A	A	78.2
PP1520	6.6E-09	A	A	575.0
PP1521	2.6E-09	A	B	173.2
PP1522	8.8E-09	A	A	566.7
PP1523	4.1E-09			320.2
PP1524	5.7E-09	B	B	438.6
PP1525	1.7E-09	A	A	131.6
PP1526	1.3E-09	A	A	118.0
PP1527	9.5E-10	A	A	142.9
PP1528	2.0E-10	A	B	45.6
PP1529	8.1E-11	A	B	30.2
PP1530	2.1E-10	A	B	17.2
PP1531	1.2E-10	A	B	13.9

PP1532	1.9E-10	A	B	13.4
PP1533	1.3E-10	AA	A	23.8
PP1534	1.3E-10	AA	A	24.7
PP1535	1.8E-10	A	A	18.9
PP1536	2.0E-10	A	B	24.8
PP1537	6.7E-11	AA	A	7.9
PP1538	8.6E-11	A	B	7.5
PP1552	1.9E-10	A	A	15.9
PP1553	1.3E-10	A	A	12.1
PP1554	2.7E-09	A	A	120.8
PP1557	1.2E-09	A	A	86.3
PP1558	1.1E-10	A	B	3.4
PP1559	4.7E-11	A	A	1.8
PP1560	6.9E-11	A	B	1.8
PP1561	6.4E-11	A	B	2.7
PP1562	4.6E-11	A	A	1.7
PP1563	4.8E-11	A	A	2.6
PP1564	7.3E-11	A	A	3.0
PP1565	1.1E-10	A	B	6.5
PP1566	2.6E-11	A	A	2.3
PP1568	3.1E-11	A	A	2.2
PP1569	1.1E-10	A	B	2.8
PP1570	5.1E-11	AA	A	2.6
PP1571	1.5E-10	A	A	6.8
PP1572	7.8E-11	A	A	3.6
PP1573	1.2E-10	A	A	5.2
PP1574	1.5E-10	A	A	6.5
PP1575	5.5E-10	B	B	11.1
PP1576	1.4E-10	AA	A	7.6
PP1577	1.7E-10	B	B	6.7
PP1578	2.0E-10	A	A	12.6
PP1579	8.7E-11	A	B	4.1
PP1580	1.7E-10	A	A	9.7
PP1582	5.7E-10	A	A	27.4
PP1583	7.8E-10	B	B	45.7
PP1584	5.6E-10	B	B	66.4
PP1586	7.6E-10	A	A	85.5
PP1587	3.6E-09	A	A	106.4
PP1588	6.0E-10	B	B	24.2
PP1589	1.8E-09	A	A	86.6
PP1590	2.9E-10	A	B	8.0
PP1591	4.6E-09	A	A	85.4
PP1592	7.1E-10	A	B	17.2
PP1593	4.3E-09	A	A	143.9

PP1594	7.1E-10	A	A	48.8	PP1646	1.2E-10	A	A	2.8
PP1595	2.3E-09	A	A	64.6	PP1648	1.1E-10	A	A	2.1
PP1596	5.6E-10	A	B	18.1	PP1649	6.4E-11	A	B	2.2
PP1598	7.6E-10	A	A	36.6	PP1650	5.7E-11	A	A	1.2
PP1599	3.7E-10	A	A	10.2	PP1651	7.9E-11	A	B	2.3
PP1600	3.2E-10	A	B	13.8	PP1653	9.7E-11	A	A	1.6
PP1601	2.1E-09	B	A	78.6	PP1654	9.7E-11	A	A	2.5
PP1603	5.3E-09	B	B	132.0	PP1655	8.3E-11	A	A	1.6
PP1605	7.9E-10	A	A	31.6	PP1656	6.5E-11	AA	A	1.5
PP1606	3.7E-10	B	B	12.6	PP1657	6.0E-11	A	B	2.0
PP1607	5.7E-10		A	39.3	PP1658	1.2E-10	A	A	3.8
PP1608	6.7E-10	A	A	70.1	PP1660	1.1E-10	A	A	4.3
PP1609	2.0E-10	A	A	37.0	PP1661	1.9E-10	A	A	5.7
PP1610	1.4E-09	A	A	86.8	PP1662	1.4E-10	A	B	6.4
PP1611	1.3E-09	B	B	28.0	PP1663	3.8E-11	AA	A	3.6
PP1612	1.2E-09	B	B	61.9	PP1665	6.6E-11	AA	A	3.1
PP1613	1.5E-10	B	B	14.7	PP1666	7.6E-11	A	A	8.1
PP1614	1.1E-09	A	A	54.2	PP1667	8.1E-11	A	A	2.0
PP1615	4.5E-10	B	B	20.9	PP1668	1.3E-10	A	A	5.3
PP1616	2.9E-10	B	B	33.5	PP1670	1.0E-10	A	A	6.7
PP1617	2.6E-10	B	B	41.9	PP1671	7.7E-11	A	A	3.0
PP1620	6.4E-09	B	B	170.3	PP1672	8.7E-11	A	A	6.0
PP1622	1.3E-09	A	A	28.1	PP1673	1.6E-10	A	A	6.0
PP1623	1.9E-10	A	A	4.5	PP1674	3.6E-11	A	A	5.1
PP1624	1.1E-09	A	A	55.8	PP1675	7.1E-11	A	B	3.0
PP1625	2.9E-10	B	B	20.2	PP1676	1.2E-10	A	A	5.0
PP1626	3.0E-09	A	A	108.1	PP1677	4.2E-11	A	A	3.4
PP1627	2.5E-10	A	A	22.9	PP1678	1.7E-10	A	B	5.6
PP1628	2.5E-09	A	A	149.9	PP1679	6.5E-11	A	A	3.1
PP1629	3.6E-10	B	B	20.7	PP1682	8.2E-11	AA	A	2.6
PP1630	1.8E-09	A	A	144.5	PP1683	9.7E-11	A	A	2.5
PP1631	3.3E-10	A	B	17.6	PP1684	1.5E-10	A	A	7.7
PP1632	3.7E-09	A	A	115.6	PP1687	7.5E-11	A	A	2.7
PP1633	6.0E-10	A	B	15.1	PP1688	2.5E-11	A	A	1.5
PP1634	5.1E-09	A	A	144.5	PP1689	2.3E-11	A	B	1.4
PP1635	6.4E-10	B	A	36.3	PP1691	6.0E-11	A	A	3.1
PP1636	2.8E-09	A	A	95.2	PP1692	1.1E-10	AA	A	4.3
PP1637	3.2E-10	A	A	32.5	PP1693	2.7E-11	AA	A	1.1
PP1639	6.8E-10	A	A	44.8	PP1694	5.1E-11	A	A	4.1
PP1640	1.4E-10	B	B	28.3	PP1696	4.1E-11	AA	A	2.9
PP1641	9.8E-11	A	A	4.6	PP1697	4.7E-11	A	A	3.6
PP1643	5.5E-11	A	A	1.6	PP1698	7.5E-11	A	A	5.1
PP1644	3.8E-11	A	A	2.7	PP1699	9.5E-11	A	A	2.5
PP1645	4.0E-11	A	A	1.8	PP1700	1.1E-10	A	A	3.6

PP1701	8.0E-11	A	A	3.7	PP1757	3.1E-10	AA	A	7.1
PP1702	8.5E-11	A	A	4.9	PP1758	1.9E-10	AA	A	6.0
PP1703	1.3E-10	A	A	7.2	PP1759	1.5E-10	A	A	6.2
PP1704	1.4E-10	A	A	10.3	PP1760	1.7E-10	A	A	6.2
PP1705	1.4E-10	AA	A	8.0	PP1761	1.7E-10	A	A	5.2
PP1706	7.5E-11	A	A	6.7	PP1762	2.6E-10	A	A	8.4
PP1707	3.7E-11	AA	A	7.4	PP1763	2.3E-10	A	A	13.3
PP1709	5.8E-11	A	A	3.8	PP1764	1.1E-10	AA	A	11.1
PP1710	1.0E-10	A	B	4.1	PP1765	8.4E-11	A	A	16.8
PP1711	9.3E-11	A	B	5.0	PP1767	3.4E-10	A	B	17.9
PP1713	9.6E-11	A	A	7.9	PP1768	3.2E-10	A	A	4.9
PP1714	1.0E-10	A	A	4.3	PP1769	7.8E-10	A	A	12.9
PP1715	6.1E-11	AA	A	2.7	PP1771	9.7E-11	A	A	6.6
PP1716	9.9E-11	AA	A	3.8	PP1772	2.3E-10	B	B	13.4
PP1717	5.1E-11	A	A	2.4	PP1773	5.3E-10	A	A	39.9
PP1718	6.7E-11	AA	A	2.5	PP1776	5.4E-10	A	A	98.7
PP1721	3.0E-10	A	A	10.0	PP1777	3.6E-10	A	B	79.3
PP1722	6.0E-11	AA	A	1.8	PP1779	3.4E-11	A	B	5.4
PP1727	1.3E-10	A	A	4.0	PP1780	6.5E-11	A	A	8.2
PP1728	1.6E-10	A	A	18.3	PP1781	2.4E-11	A	B	2.1
PP1729	2.0E-10	AA	A	20.6	PP1782	4.4E-11	A	B	6.7
PP1731	7.0E-11	A	A	7.4	PP1783	2.8E-11	A	B	3.5
PP1732	9.9E-11	AA	A	6.4	PP1784	8.3E-11	A	B	7.8
PP1733	1.1E-10	A	A	3.8	PP1785	5.1E-11	A	A	6.9
PP1734	1.7E-10	A	A	4.4	PP1786	1.4E-10	A	B	11.4
PP1735	8.1E-11	AA	A	2.2	PP1787	7.1E-11	A	B	9.0
PP1736	1.3E-10	A	A	3.6	PP1788	6.3E-11	B	B	6.2
PP1737	1.1E-10	A	A	2.7	PP1789	1.3E-10	A	A	9.5
PP1738	7.1E-11	AA	A	5.1	PP1790	3.0E-11	A	B	1.7
PP1739	5.4E-11	AA	AA	5.5	PP1791	4.2E-11	A	A	3.7
PP1740	5.3E-11	A	A	3.6	PP1792	8.0E-11	A	B	9.6
PP1741	3.9E-11	A	B	2.3	PP1793	2.3E-11	A	B	2.4
PP1742	5.1E-11	A	A	1.6	PP1794	6.0E-11	A	B	8.7
PP1743	7.6E-11	AA	A	5.1	PP1795	3.1E-11	A	B	3.0
PP1744	1.3E-10	A	A	5.3	PP1796	5.7E-11	A	B	5.3
PP1746	5.4E-11	A	A	1.9	PP1797	1.0E-10	A	A	5.1
PP1747	5.8E-11	A	A	2.3	PP1798	1.5E-10	A	B	7.8
PP1748	6.2E-11	A	B	3.1	PP1799	6.8E-11	B	B	7.6
PP1749	3.9E-11	A	A	3.3	PP1800	5.1E-11	A	A	6.5
PP1750	6.9E-11	A	B	3.4	PP1801	2.1E-10	A	B	13.0
PP1751	4.7E-11	A	A	2.2	PP1802	8.2E-11	A	B	5.8
PP1752	8.5E-11	A	A	5.8	PP1803	1.0E-10	A	B	7.6
PP1753	3.8E-11	A	A	5.9	PP1804	5.6E-11	A	A	3.5
PP1754	6.4E-11	A	A	3.0	PP1805	7.1E-11	A	A	7.0

PP1806	6.0E-11	A	B	4.0
PP1807	6.2E-11	A	B	5.0
PP1808	8.4E-11	A	B	8.8
PP1809	1.2E-10	A	B	22.4
PP1810	1.6E-10	A	B	4.6
PP1811	2.3E-10	A	B	14.3
PP1812	5.9E-11	A	A	7.8
PP1813	1.2E-10	A	B	22.6
PP1814	2.7E-10	A	A	26.2
PP1815	3.4E-10	B	B	83.0
PP1816	1.2E-09	B	C	63.8
PP1817	4.7E-10	C	C	20.4
PP1818	9.0E-10	C	B	74.8
PP1819	1.0E-09	C	C	148.7
PP1820	6.0E-10	C	C	40.7
PP1821	6.3E-10	A	A	104.7
PP1822	1.1E-09	A	B	107.0
PP1823	1.0E-09	A	A	55.9
PP1825	1.4E-10	A	A	8.0
PP1826	3.2E-10	A	A	17.6
PP1827	2.9E-11	A	A	2.4
PP1828	3.9E-11	A	B	1.9
PP1829	3.3E-11	A	B	2.3
PP1830	5.4E-11	A	B	4.7
PP1831	2.5E-11	A	A	3.0
PP1832	4.0E-11	B	B	2.5
PP1833	4.4E-11	A	A	2.7
PP1834	6.5E-11	A	B	2.1
PP1835	5.1E-11	A	B	4.9
PP1836	1.0E-10	A	B	10.7
PP1837	2.0E-10	A	A	15.6
PP1838	1.0E-10	A	A	20.0
PP1839	3.1E-10	A	B	24.3
PP1840	1.2E-10	A	B	26.8
PP1841	3.8E-10	AA	A	24.3
PP1842	1.9E-10	A	B	26.9
PP1844	7.0E-11	A	B	12.3
PP1846	1.0E-10	A	B	9.8
PP1848	1.1E-10	A	A	22.5
PP1849	3.8E-10	A	A	37.1
PP1850	1.6E-10	A	B	49.1
PP1851	1.8E-09	A	A	165.4
PP1852	7.1E-11	A	B	6.0
PP1853				30.4

PP1854	9.6E-11	A	A	5.2
PP1855	1.9E-10	AA	A	17.7
PP1856	1.1E-10	A	A	1.4
PP1857	9.1E-11	A	B	5.0
PP1859	1.4E-10	A	A	28.8
PP1860	1.1E-10	A	A	10.3
PP1861	9.1E-11	A	B	25.7
PP1862	1.2E-10	A	A	22.2
PP1863	1.3E-10	A	A	88.8
PP1864	6.4E-11	A	B	10.2
PP1865	8.3E-11	A	B	36.0
PP1866	9.3E-11	A	B	11.1
PP1867	1.7E-10	A	B	47.8
PP1868	8.7E-11	A	B	10.7
PP1869	1.3E-10	A	A	36.4
PP1870	1.9E-10	A	A	12.4
PP1871	9.9E-11	A	A	13.1
PP1872	1.2E-10	A	A	12.4
PP1873	7.5E-11	A	B	8.5
PP1874	1.3E-10	A	A	9.9
PP1875	8.3E-11	A	B	7.7
PP1876	2.0E-10	A	A	23.0
PP1877	1.6E-10	A	A	18.4
PP1878	6.3E-11	A	A	8.8
PP1879	1.8E-10	A	B	16.9
PP1880	1.5E-10	A	B	15.6
PP1881	2.9E-10	A	A	16.7
PP1882	1.2E-10	A	B	20.2
PP1883	2.8E-10	A	A	24.0
PP1884	1.6E-10	A	A	17.3
PP1885	2.3E-10	AA	A	18.3
PP1886	1.2E-10	A	B	1.9
PP1887	3.0E-10	A	B	19.2
PP1888	7.4E-11	A	B	3.5
PP1889	2.1E-10	A	B	12.5
PP1890	1.5E-10	A	B	3.6
PP1891	2.9E-10	A	A	2.6
PP1892	7.4E-11	A	B	4.8
PP1893	1.7E-10	A	B	18.5
PP1894	2.0E-10	A	A	15.9
PP1895	1.3E-10	A	B	15.6
PP1896	6.0E-11	A	B	5.3
PP1897	1.6E-10	B	B	22.6
PP1898	1.3E-10	B	B	6.3

PP1899	1.2E-10	A	B	15.1	PP1948	4.1E-10	C	C	16.2
PP1900	1.7E-10	A	A	24.7	PP1949	9.2E-10	C	C	9.3
PP1901	9.8E-11	A	B	7.6	PP1950	1.9E-09	B	C	32.5
PP1902	2.0E-10	A	A	12.5	PP1952	1.3E-10	B	B	14.0
PP1903	6.3E-11	A	B	5.5	PP1953	4.2E-10	B	B	8.7
PP1904	1.2E-10	A	B	18.3	PP1954	7.7E-10	B	B	8.1
PP1905	7.5E-11	A	A	6.7	PP1955	8.2E-10	C	B	4.4
PP1906	1.5E-10	A	A	10.8	PP1956	2.8E-10	B	B	2.2
PP1907	1.7E-10	AA	A	23.6	PP1957	3.6E-10	C	B	8.6
PP1908	1.1E-10	A	B	10.1	PP1958	5.3E-10	B	B	57.8
PP1909	3.4E-10	A	B	15.3	PP1959	5.5E-10	C	B	14.7
PP1910	1.4E-10	A	B	9.7	PP1960	1.7E-10	B	C	6.0
PP1911	2.1E-10	A	A	11.7	PP1961	2.2E-10	C	C	8.0
PP1913	3.7E-10	A	A	44.0	PP1963	1.8E-10	B	C	9.1
PP1914				39.7	PP1964	1.9E-10	B	B	10.3
PP1915	3.1E-10	A	A	18.5	PP1965	3.0E-10	B	B	17.4
PP1916	4.9E-10	B	C	16.8	PP1967	3.6E-10	B	B	10.9
PP1917	2.9E-10	A	A	22.5	PP1968	7.6E-10	C	C	13.5
PP1918	1.9E-10	B	C	32.8	PP1969	2.1E-09	B	C	74.0
PP1919	2.3E-10	A	A	6.3	PP1970	6.2E-10	B	B	16.8
PP1920	3.1E-10	B	C	32.4	PP1971	5.0E-09	B	B	38.0
PP1921	5.5E-11	A	A	7.8	PP1972	1.5E-10	A	A	13.2
PP1922	2.3E-10	B	C	44.1	PP1973	9.9E-11	A	B	8.7
PP1923	3.4E-09	A	A	68.0	PP1974	1.8E-10	A	A	50.0
PP1925	2.3E-10	A	A	9.7	PP1975	1.1E-10	A	A	13.4
PP1926	3.6E-10	B	B	17.4	PP1976	3.7E-10	AA	A	92.0
PP1927	8.5E-10	A	A	23.5	PP1977	1.5E-10	AA	A	20.2
PP1928	2.5E-10	B	B	18.4	PP1979	8.7E-11	AA	A	12.5
PP1929	6.6E-10	A	A	41.7	PP1980	3.6E-10	A	B	30.1
PP1930	2.3E-10	B	C	7.0	PP1981	1.0E-10	A	A	20.7
PP1931	1.2E-10	A	B	9.5	PP1983	1.4E-10	AA	A	20.2
PP1932	1.5E-10	A	A	13.1	PP1984	3.0E-10	A	A	50.8
PP1934	7.2E-10	A	A	68.5	PP1985	2.3E-10		B	17.7
PP1935	4.6E-10	A	A	13.1	PP1987	5.3E-11	A	A	6.6
PP1936	4.0E-10	AA	A	12.3	PP1988	6.0E-11	A	A	11.0
PP1937	3.1E-10	A	A	6.8	PP1989	1.9E-10	A	A	11.1
PP1938	3.4E-10	AA	A	34.6	PP1990	1.4E-10	A	A	6.6
PP1941	1.7E-10	A	A	9.2	PP1991	1.5E-10	A	A	10.8
PP1942	1.5E-10	AA	A	25.7	PP1992	2.1E-10	AA	B	17.7
PP1943	1.1E-10	A	B	9.2	PP1993	1.2E-10	A	A	13.3
PP1944	1.9E-10	A	A	14.8	PP1994	1.0E-10	AA	A	22.4
PP1945	3.1E-10	AA	A	33.8	PP1995	2.1E-10	A	B	17.8
PP1946	1.6E-10	B	C	15.2	PP1996	1.2E-10	A	B	15.5
PP1947	3.7E-10	B	B	22.0	PP1997	9.8E-11	A	B	14.2

PP1998	1.7E-10	A	B	16.1	PP2044	1.4E-10	A	A	5.0
PP1999	1.3E-10	A	B	26.6	PP2045	1.7E-10	A	B	5.1
PP2000	1.8E-10	A	B	17.7	PP2046	6.3E-11	A	A	2.2
PP2001	1.1E-10	A	A	18.1	PP2047	1.3E-10	A	B	5.5
PP2002				15.7	PP2048	7.1E-11	A	B	3.6
PP2003	3.4E-10	A	B	11.3	PP2049	4.0E-11	A	B	6.1
PP2004	6.2E-11	A	A	5.1	PP2050	1.9E-10	A	A	7.5
PP2005	1.3E-10	A	A	10.7	PP2051	1.2E-10	A	A	6.9
PP2006	1.1E-10	A	A	7.8	PP2052	1.6E-10	A	A	4.1
PP2007	1.4E-10	AA	B	14.9	PP2053	1.3E-10	A	A	9.3
PP2008	1.3E-10	A	A	15.2	PP2054	4.1E-10	A	A	8.5
PP2009	1.9E-10	A	A	19.7	PP2055	1.8E-10	A	B	16.1
PP2010	1.4E-10	A	B	6.6	PP2056	3.3E-10	A	A	7.3
PP2011	1.1E-10	A	A	10.3	PP2057	2.6E-10	A	A	12.3
PP2012	9.7E-11	AA	A	11.6	PP2058	2.1E-10	A	A	3.7
PP2013	1.3E-10	A	B	7.7	PP2059	9.3E-11	A	A	4.9
PP2014	9.3E-11	A	A	6.9	PP2060	1.6E-10	A	A	7.4
PP2015	1.1E-10	A	B	5.6	PP2061	7.5E-11	AA	A	6.1
PP2016	1.1E-10	A	A	8.2	PP2062	1.9E-10	AA	A	13.7
PP2017	9.3E-11	A	A	2.5	PP2063	9.0E-11	AA	A	13.6
PP2018	1.0E-10	A	B	5.3	PP2064	2.6E-10	A	A	13.6
PP2019	1.6E-10	A	A	4.5	PP2065	2.2E-10	A	B	17.0
PP2020	1.9E-10	A	A	8.3	PP2066	2.5E-10	A	B	3.2
PP2021	1.2E-10	A	B	4.9	PP2067	2.4E-10	AA	A	17.7
PP2022	1.1E-10	A	A	2.7	PP2068	3.6E-10	A	B	11.1
PP2023	1.1E-10	A	B	10.5	PP2069	8.2E-11	AA	A	27.4
PP2024	8.2E-11	A	B	10.1	PP2070	1.1E-10	A	A	11.3
PP2025	6.1E-11	A	B	13.4	PP2071	1.0E-10	A	A	6.2
PP2026	8.9E-11	A	A	22.6	PP2072	1.2E-10	A	A	8.5
PP2027	1.1E-10	A	B	14.0	PP2073	7.8E-11	A	A	3.5
PP2028	1.1E-10	A	B	17.5	PP2074	1.1E-10	A	A	5.9
PP2029	6.9E-11	A	B	18.9	PP2075	2.2E-10	A	A	11.8
PP2030	1.2E-10	A	A	4.5	PP2076	3.9E-10	A	A	15.6
PP2031	1.4E-10	B	B	5.5	PP2077	1.2E-10	A	A	10.9
PP2032	6.1E-11	A	B	8.1	PP2078	1.7E-10	AA	A	10.3
PP2033				11.8	PP2079	2.9E-10	A	A	16.0
PP2034	1.9E-10	A	A	8.8	PP2080	9.3E-11	A	A	17.8
PP2036	8.9E-11	A	A	9.1	PP2081	1.2E-10	A	A	11.2
PP2037	1.2E-10	A	A	16.0	PP2082	1.1E-10	AA	A	7.8
PP2038	1.6E-10	A	A	5.5	PP2083	2.2E-10	A	B	10.3
PP2040	3.1E-10	A	A	10.5	PP2087	1.5E-10	A	A	4.8
PP2041	1.9E-10	A	A	7.7	PP2091	1.8E-10	A	B	4.6
PP2042	1.4E-10	A	A	5.9	PP2093	3.3E-10	A	A	7.4
PP2043	2.1E-10	A	A	28.0	PP2094	2.9E-10	A	A	5.4

PP2095	1.5E-10	A	A	5.7	PP2151	2.9E-10	A	A	23.3
PP2096	4.2E-10	A	A	10.7	PP2152	6.7E-10	AA	A	29.4
PP2097	3.0E-10	A	A	8.0	PP2153	4.9E-10	A	A	20.0
PP2098	2.0E-10	A	A	8.4	PP2154	3.6E-10	A	A	17.7
PP2099	1.4E-10	A	A	9.1	PP2155	3.7E-10	A	B	10.7
PP2101	3.2E-10	A	B	16.6	PP2156	4.1E-10	AA	A	20.6
PP2102	1.6E-10	A	A	7.0	PP2157	1.9E-10	A	A	5.9
PP2103	2.5E-10	A	A	4.3	PP2158	7.9E-10	AA	A	25.4
PP2105	1.8E-10	A	A	10.4	PP2159	3.3E-10	AA	A	19.5
PP2106	2.0E-10	A	A	6.1	PP2160	2.2E-10	A	A	5.4
PP2107	1.5E-10	A	A	7.8	PP2161	2.0E-10	AA	A	12.4
PP2108	3.4E-10	A	A	17.6	PP2163	4.1E-10	A	A	18.2
PP2109	2.9E-10	A	A	5.7	PP2164	2.9E-10	A	A	14.2
PP2117	1.7E-10	A	A	28.9	PP2165	5.1E-10	A	A	17.5
PP2118	1.5E-10	A	B	8.1	PP2166	2.9E-10	A	A	23.7
PP2119	5.0E-09	A	B	8.9	PP2167	7.1E-10	AA	A	39.1
PP2120	9.1E-10	AA	A	75.5	PP2168	3.3E-10	A	A	16.9
PP2121	1.5E-09	AA	A	11.4	PP2169	6.3E-10	AA	A	62.1
PP2122	1.4E-09	AA	A	106.8	PP2170	3.3E-10	A	A	8.5
PP2123	2.5E-10	A	A	24.3	PP2171	7.5E-10	A	A	19.6
PP2124	2.6E-10	AA	A	18.7	PP2172	5.1E-10	A	B	5.8
PP2125	2.2E-10	AA	A	4.0	PP2173	5.5E-10	A	A	19.9
PP2126	2.3E-10	A	B	13.4	PP2174	4.0E-10	AA	A	24.0
PP2127	1.8E-10	AA	A	12.5	PP2175	4.5E-10	AA	A	25.7
PP2128	4.0E-10	AA	A	14.8	PP2176	4.7E-10	AA	A	52.9
PP2130	6.2E-10	AA	A	7.5	PP2178	4.9E-10	AA	A	35.9
PP2131	4.3E-10	A	A	22.3	PP2179	1.5E-09	AA	A	13.5
PP2132	2.7E-10	AA	A	18.4	PP2180	6.6E-10	AA	A	27.8
PP2133	1.9E-10	AA	A	16.2	PP2181	1.4E-09	AA	A	40.3
PP2135	4.9E-10	AA	A	15.7	PP2182	7.2E-10	AA	A	19.5
PP2137	3.7E-10	A	A	16.8	PP2183	6.8E-10	A	A	34.7
PP2138	4.4E-10	A	A	15.7	PP2184	7.0E-10	AA	A	29.2
PP2139	3.8E-10	AA	A	38.0	PP2185	7.1E-10	AA	A	36.1
PP2140	7.0E-10	AA	A	24.7	PP2186	2.3E-09	AA	A	33.7
PP2141	1.7E-10	A	A	9.4	PP2187	6.9E-10	AA	A	31.4
PP2142	3.0E-10	AA	A	10.3	PP2188	7.1E-10	AA	A	26.7
PP2143	3.1E-10	A	A	6.6	PP2189	1.7E-10	A	A	10.5
PP2144	4.8E-10	AA	A	29.0	PP2190	9.1E-10	A	A	84.5
PP2145	3.9E-10	A	A	17.2	PP2191	2.3E-10	A	B	91.6
PP2146	3.3E-10	A	A	8.2	PP2192	3.3E-09	A	A	91.9
PP2147	3.3E-10	A	B	9.7	PP2193	4.1E-10	A	A	33.1
PP2148	3.4E-10	A	A	41.5	PP2195	9.6E-11	A	A	7.8
PP2149	5.8E-10	A	A	17.7	PP2196	2.4E-10	A	B	6.6
PP2150	3.8E-09	AA	A	58.0	PP2197	1.5E-10	A	B	4.6

PP2198	2.1E-10	A	A	13.8	PP2273	1.9E-10	AA	A	16.0
PP2199	1.6E-10	A	B	10.3	PP2275	3.6E-10	A	A	12.2
PP2200	3.0E-09	A	A	49.9	PP2312	3.0E-11	A	B	1.6
PP2202	4.9E-09	A	A	94.7	PP2313	4.9E-10	AA	A	7.4
PP2203	3.4E-10	A	A	20.5	PP2314	2.3E-11	A	A	1.8
PP2207	7.9E-10	A	A	25.8	PP2315	3.3E-10	A	A	9.0
PP2208	2.0E-10	A	A	17.8	PP2316	1.2E-10	A	A	1.6
PP2209	8.1E-10	A	A	37.0	PP2317	4.0E-10	A	A	12.5
PP2210	1.3E-10	A	B	6.2	PP2318	1.2E-10	A	A	3.3
PP2212	3.4E-10	A	B	23.5	PP2319	3.5E-10	AA	A	9.6
PP2214	3.0E-10	A	A	29.6	PP2320	1.1E-10	A	A	0.6
PP2216	2.3E-10	A	A	50.8	PP2322	1.8E-10	A	B	5.8
PP2218	2.9E-10	A	A	24.0	PP2323	1.4E-10	A	A	3.7
PP2219	1.6E-09	A	A	50.9	PP2325	4.0E-10	A	A	8.2
PP2220	1.4E-10	A	A	32.1	PP2326	3.1E-11	A	B	1.6
PP2221	1.7E-09	A	A	40.5	PP2327	5.0E-10	A	A	9.9
PP2222	1.8E-10	AA	A	6.8	PP2328	7.9E-11	A	A	2.2
PP2223	1.0E-10	A	A	5.3	PP2329	4.2E-10	A	A	6.5
PP2224	3.8E-10	A	A	15.4	PP2330	1.1E-10	A	A	5.5
PP2225	2.0E-10	A	A	41.4	PP2331	3.6E-10	AA	A	11.8
PP2226	8.2E-10	A	A	14.7	PP2332	1.0E-10	A	B	3.8
PP2227	2.7E-10	A	A	50.3	PP2333	1.9E-09	A	A	44.7
PP2229	3.8E-10	A	A	39.8	PP2334	1.3E-10	A	B	5.7
PP2230	8.2E-11	A	A	7.0	PP2335	1.4E-09	A	A	64.2
PP2231	1.8E-10	A	B	16.2	PP2336	4.1E-10	A	A	16.3
PP2232	2.2E-10	A	A	18.7	PP2337	3.2E-09	A	A	33.9
PP2233	1.8E-10	A	A	27.6	PP2338	5.1E-10	A	B	34.1
PP2234	1.9E-10	A	A	11.1	PP2339	2.6E-09	A	A	59.3
PP2235	2.8E-10	A	A	22.1	PP2340	1.1E-09	B	B	44.9
PP2237	1.4E-10	A	A	64.7	PP2341	3.6E-09	A	A	133.0
PP2238	2.0E-10	A	A	39.3	PP2342	5.5E-10	A	A	70.3
PP2242	1.8E-09	A	A	178.4	PP2344	9.5E-10	A	A	44.9
PP2257	6.3E-10	AA	A	48.6	PP2345	1.7E-09	A	A	77.2
PP2259	1.2E-10	A	B	6.5	PP2347	1.6E-09	A	A	142.9
PP2260	1.2E-10	A	A	1.9	PP2348	3.4E-10	A	A	52.7
PP2261	1.8E-10	A	A	16.6	PP2349	3.8E-09	A	A	73.2
PP2262	2.4E-10	A	B	3.8	PP2350	3.5E-10	A	A	60.3
PP2263	9.8E-10	A	A	19.5	PP2351	3.2E-09	A	A	177.4
PP2264	1.1E-10	AA	A	13.1	PP2352	7.6E-10	A	A	15.6
PP2268	1.2E-10	A	A	9.8	PP2353	4.1E-09	A	A	68.8
PP2269	3.8E-10	A	A	20.0	PP2354	7.9E-10	A	A	9.3
PP2270	2.4E-10	B	B	10.4	PP2355	3.9E-09	AA	A	103.0
PP2271	2.9E-10	A	A	60.6	PP2356	9.4E-10	A	A	14.7
PP2272	4.9E-10	AA	A	105.9	PP2357	1.2E-09	A	B	59.7

PP2358	2.0E-11	A	B	2.5	PP2403	2.2E-10	A	A	7.2
PP2359	2.0E-11	A	B	7.6	PP2404	9.0E-11	A	A	4.1
PP2360	1.6E-10	A	B	2.9	PP2405	3.1E-10	A	A	8.6
PP2361	6.4E-11	A	A	4.4	PP2406	2.9E-10	A	A	21.3
PP2362	7.6E-11	A	A	4.8	PP2407	5.0E-10	A	A	60.1
PP2363	6.2E-11	A	B	7.5	PP2408	2.3E-10	A	A	21.3
PP2364	1.6E-11	A	B	4.6	PP2409	4.8E-10	A	B	31.9
PP2365	2.0E-11	A	B	3.3	PP2410	1.1E-09	A	A	107.9
PP2366	4.8E-11	A	A	4.5	PP2411	1.0E-09	A	A	91.4
PP2367	7.5E-11	A	B	2.1	PP2412	1.5E-10	A	B	21.0
PP2368	4.5E-11	A	A	4.1	PP2413	2.5E-10	A	A	115.4
PP2369	6.2E-11	A	B	4.5	PP2414	3.3E-10	A	A	9.8
PP2370	5.4E-10	B	B	25.7	PP2415	9.3E-11	AA	A	10.3
PP2371	6.4E-10	A	B	41.9	PP2416	2.9E-10	A	B	33.1
PP2372	7.9E-10	A	B	3.3	PP2417	3.0E-10	A	A	15.9
PP2373	6.6E-10	A	A	6.5	PP2418	9.7E-10	A	B	132.1
PP2374	8.5E-10	A	A	67.2	PP2419	2.0E-09	A	A	125.1
PP2375	1.1E-09	A	B	171.7	PP2422	4.6E-10	A	A	117.4
PP2376	2.8E-10	A	A	4.8	PP2423	3.8E-10	A	A	71.9
PP2377	3.2E-10	A	A	5.7	PP2424	3.7E-10	A	A	50.9
PP2378	8.8E-10	B	A	48.3	PP2425	2.3E-10	AA	A	51.7
PP2379	7.6E-10	A	A	2.2	PP2426	3.1E-10	AA	A	48.0
PP2380	8.5E-10	A	A	2.1	PP2427	7.0E-10	AA	A	36.6
PP2381	9.3E-10	A	A	3.2	PP2428	6.2E-10	A	A	4.8
PP2382	1.2E-10	A	A	4.6	PP2429	4.5E-09	A	B	8.3
PP2383	1.2E-10	A	A	5.2	PP2430	1.4E-09	AA	A	33.2
PP2385	1.2E-10	A	B	7.8	PP2431	2.3E-09	A	A	79.5
PP2386	1.2E-09	A	B	28.1	PP2432	1.4E-09	A	A	138.1
PP2387	1.1E-10	A	A	16.5	PP2433	2.1E-09	AA	A	120.0
PP2388	3.3E-10	A	B	22.9	PP2436	1.6E-09	A	A	126.4
PP2389	7.9E-11	A	B	21.3	PP2437	1.2E-10	A	A	18.8
PP2390	2.8E-10	A	B	96.7	PP2438	6.4E-10	A	A	41.4
PP2391	4.3E-11	A	A	8.9	PP2439	1.2E-10	A	A	6.6
PP2392	1.1E-10	A	A	25.4	PP2440	4.4E-10	A	A	20.1
PP2393	1.2E-10	A	A	28.2	PP2441	2.9E-10	AA	A	22.9
PP2394	1.2E-10	A	B	8.3	PP2442	9.7E-10	A	A	79.7
PP2395	7.2E-11	A	B	6.3	PP2443	1.3E-10	A	A	9.1
PP2396	6.9E-11	A	A	4.1	PP2444	5.9E-10	A	A	32.3
PP2397	5.1E-11	A	A	4.7	PP2445	1.4E-10	A	B	11.7
PP2398	2.3E-10	A	A	11.4	PP2446	8.1E-10	A	A	124.4
PP2399	3.1E-10	AA	A	7.7	PP2447	1.1E-10	A	B	8.6
PP2400	2.0E-10	A	A	5.8	PP2448	1.4E-09	A	A	26.9
PP2401	1.2E-10	A	A	5.3	PP2449	6.1E-11	A	A	7.8
PP2402	9.2E-11	A	A	10.6	PP2450	5.5E-10	A	A	29.2

PP2451	1.7E-10	A	A	8.6	PP2505	1.3E-10	A	B	17.2
PP2452	1.5E-09	A	A	43.4	PP2506	1.3E-10	A	A	10.6
PP2453	9.0E-11	A	A	9.2	PP2507	6.1E-11	AA	A	8.9
PP2454	1.2E-09	AA	A	80.2	PP2508	3.4E-09	A	B	123.8
PP2455	3.2E-10	AA	A	23.4	PP2509	2.6E-09	AA	A	91.3
PP2456	1.1E-09	A	A	18.8	PP2510	3.9E-09	A	B	180.5
PP2457	1.7E-10	A	A	13.3	PP2511	9.5E-10	A	A	107.3
PP2458	1.3E-09	A	A	80.7	PP2512	2.0E-09	A	A	108.7
PP2460	7.1E-10	A	A	18.7	PP2513	2.6E-09	A	A	303.1
PP2461	1.5E-10	A	A	10.6	PP2514	2.4E-09	A	B	86.8
PP2462	1.6E-09	A	A	87.2	PP2515	5.1E-09	A	A	383.7
PP2463	1.1E-10	A	A	6.5	PP2516	2.9E-09	A	B	124.4
PP2464	9.8E-10	A	A	66.0	PP2517	9.3E-09		A	561.6
PP2465	5.1E-10	AA	A	39.4	PP2518	3.3E-09	A	A	81.2
PP2466	3.9E-09	A	A	170.3	PP2519	8.2E-10	A	A	27.0
PP2467	2.6E-10	A	B	21.8	PP2520	3.3E-09	A	A	209.7
PP2468	1.3E-09	AA	A	72.2	PP2521	2.8E-09	A	A	129.0
PP2469	1.9E-10	A	B	15.7	PP2522	3.2E-09	B	B	113.4
PP2470	1.8E-09	A	A	117.8	PP2523	1.7E-09	A	A	91.9
PP2471	1.6E-10	A	A	15.3	PP2524	3.6E-09	A	B	185.3
PP2472	5.8E-10	A	A	42.3	PP2525	3.8E-09	AA	A	142.4
PP2475	1.5E-09	AA	A	175.6	PP2526	4.0E-09	A	B	54.5
PP2477	1.8E-09	A	A	126.6	PP2527	6.5E-10	AA	A	31.0
PP2479	1.4E-09	AA	A	26.0	PP2528	4.6E-09	A	B	206.8
PP2480	8.4E-10	A	A	30.5	PP2529	7.7E-10	AA	A	64.0
PP2481	1.6E-09	A	A	33.6	PP2530	3.6E-09	A	B	131.3
PP2482	9.3E-10	A	A	23.8	PP2531	5.1E-10	AA	A	16.3
PP2483	1.6E-09	A	A	195.4	PP2532	4.1E-09	A	B	143.6
PP2484	1.0E-09	A	A	74.3	PP2533	4.9E-10	AA	A	20.0
PP2485	7.8E-10	A	A	55.5	PP2534	4.1E-09	A	B	195.4
PP2488	1.6E-09	A	A	170.9	PP2535	5.4E-10	AA	A	26.8
PP2489	5.5E-10	A	A	30.5	PP2536	2.4E-09	A	B	152.3
PP2490	1.7E-09	AA	A	161.9	PP2537	7.4E-10	AA	A	75.1
PP2492	2.4E-09	AA	A	76.7	PP2539	4.3E-09	A	B	330.4
PP2494	1.8E-09	A	A	39.6	PP2540	4.6E-09	A	B	562.4
PP2495	8.4E-10	A	A	17.4	PP2541	4.9E-09	A	B	373.6
PP2496	6.2E-09	A	A	97.3	PP2542	4.6E-09	B	B	393.8
PP2497	1.5E-09	A	A	84.8	PP2543	4.2E-09		B	179.1
PP2498	6.7E-10	A	A	21.9	PP2545	4.3E-09	A	A	279.0
PP2499	2.1E-09	AA	A	115.2	PP2546	4.7E-09	B	B	295.0
PP2500	1.7E-09	A	A	125.4	PP2547	4.4E-09	A	B	1063.5
PP2501	1.8E-09	AA	A	180.0	PP2548	7.8E-09	A	B	1046.6
PP2502	6.5E-11	A	A	7.9	PP2549	6.0E-09	A	B	506.3
PP2504	1.6E-10	A	B	12.9	PP2550	2.9E-10	A	B	38.5

PP2551	4.0E-10	A	B	36.4	PP2600	1.7E-10	A	A	2.9
PP2552	2.8E-10	A	B	30.5	PP2601	2.0E-10	A	A	8.9
PP2553	3.4E-09	A	B	120.7	PP2602	2.5E-10	A	A	12.8
PP2554	5.6E-09	A	B	271.4	PP2603	4.4E-10	AA	A	25.7
PP2555	4.1E-09	A	B	211.9	PP2604	4.0E-10	AA	A	20.8
PP2556	2.1E-10	A	B	9.4	PP2605	3.4E-10	AA	A	8.7
PP2557	3.0E-10	A	B	14.2	PP2606	8.1E-10	AA	AA	68.7
PP2558	3.2E-10	A	B	14.1	PP2608	1.4E-09	AA	A	53.0
PP2559	9.1E-10	A	A	103.2	PP2610	1.3E-09	AA	A	125.5
PP2560	1.0E-09	AA	A	46.3	PP2612	2.4E-09	AA	A	199.3
PP2561	1.9E-09	AA	A	96.4	PP2614	2.7E-10	A	A	12.1
PP2562	9.1E-10	B	B	46.5	PP2615	2.0E-09	A	A	88.7
PP2563	2.3E-09	A	A	107.5	PP2616	8.0E-10	A	A	66.4
PP2564	7.6E-09	A	A	222.3	PP2618	1.4E-09	A	A	69.5
PP2565	8.2E-09	A	A	206.5	PP2619	1.2E-09	AA	A	131.5
PP2566	5.7E-10	A	B	17.6	PP2622	5.3E-10	A	B	43.8
PP2567	1.9E-09	A	A	101.6	PP2624	1.3E-09	A	A	174.0
PP2568	1.2E-09	A	B	23.4	PP2626	4.1E-10	A	A	33.4
PP2569	2.8E-09	AA	A	184.9	PP2627	2.6E-09	A	A	95.2
PP2570	3.9E-10	A	A	8.9	PP2628	9.0E-10	A	A	67.9
PP2571	1.0E-09	A	A	76.1	PP2630	3.0E-09	A	B	190.3
PP2572	1.2E-09	A	A	82.7	PP2631	5.0E-10	AA	A	56.9
PP2573	1.0E-10	A	A	10.1	PP2633	6.4E-10	AA	A	29.0
PP2574	5.1E-11	A	A	4.2	PP2634	6.8E-10	A	A	45.4
PP2575	8.6E-11	A	A	4.1	PP2635	9.7E-10	AA	A	50.2
PP2576	1.4E-10	A	A	5.7	PP2637	1.0E-09	AA	A	61.4
PP2577	1.2E-10	A	A	4.1	PP2638	2.5E-09	AA	A	97.0
PP2578	2.7E-10	AA	A	17.7	PP2639	1.1E-09	AA	A	81.6
PP2579	1.7E-10	A	A	14.5	PP2640	1.4E-09	AA	A	84.1
PP2580	2.0E-10	AA	A	7.9	PP2641	2.0E-09	AA	A	98.6
PP2581	2.1E-10	AA	A	32.1	PP2642	4.4E-10	AA	A	36.6
PP2583	1.1E-10	A	A	4.1	PP2643	4.9E-10	AA	A	32.7
PP2586	1.7E-10	A	B	14.4	PP2644	8.1E-10	AA	A	75.0
PP2588	2.6E-10	A	A	13.2	PP2645	1.1E-09	AA	A	86.7
PP2589	4.5E-10	AA	A	74.1	PP2646	1.6E-09	AA	A	92.6
PP2590	1.3E-09	AA	A	27.1	PP2648	8.5E-10	A	A	68.5
PP2591	5.6E-10	AA	A	9.1	PP2649	4.0E-10	AA	A	61.0
PP2592	1.3E-10	A	A	7.9	PP2650	9.8E-10	AA	A	42.2
PP2593	1.5E-10	A	A	11.5	PP2651	1.9E-09	AA	A	147.1
PP2594	1.0E-10	A	A	6.0	PP2652	1.5E-09	AA	A	82.7
PP2595	1.7E-10	A	B	12.7	PP2654	1.2E-10	A	A	12.4
PP2596	1.6E-10	A	A	13.7	PP2655	1.0E-10	AA	A	17.0
PP2597	5.1E-10	A	A	20.1	PP2656	3.1E-10	A	B	22.5
PP2598	1.9E-09	A	A	23.0	PP2657	4.4E-10	A	A	29.2

PP2659	1.9E-10	A	A	20.6
PP2660	1.8E-10	A	A	14.3
PP2661	2.7E-10	AA	A	13.4
PP2662	2.9E-10	AA	A	13.1
PP2663	2.4E-10		A	11.2
PP2664	3.7E-10	A	B	19.8
PP2665	5.6E-10	A	A	23.4
PP2666	7.2E-10	AA	AA	28.6
PP2667	1.8E-09	A	A	30.6
PP2668	1.8E-10	A	A	10.3
PP2669	2.9E-10	A	A	18.7
PP2670	4.8E-10	AA	A	25.2
PP2671	6.7E-10	A	A	26.3
PP2672	1.9E-10	B	B	9.5
PP2673	6.9E-10	A	A	50.8
PP2674	5.0E-10	A	A	48.6
PP2675	4.5E-09	A	A	138.4
PP2676	8.7E-10	A	A	60.8
PP2677	1.3E-09	A	A	70.6
PP2678	5.5E-10	A	B	45.5
PP2679	9.9E-11	A	A	17.7
PP2681	3.7E-10	A	A	29.1
PP2683	8.7E-10	A	A	63.3
PP2684	4.3E-10	A	A	57.9
PP2685	2.1E-09	A	A	133.4
PP2686	3.3E-09	A	A	162.1
PP2687	7.7E-11	A	A	2.9
PP2688	1.3E-10	A	B	6.9
PP2689	1.8E-10	A	B	6.2
PP2690	3.9E-11	AA	A	3.0
PP2691	5.6E-11	AA	A	3.5
PP2692	1.4E-10	A	A	7.7
PP2693	1.8E-10	A	B	10.4
PP2694	1.9E-10	A	B	12.0
PP2695	5.4E-11	A	B	3.8
PP2696	1.9E-10	A	B	20.5
PP2697	4.8E-10	A	A	42.8
PP2698	3.8E-10	A	A	30.4
PP2699	1.3E-10	A	B	14.2
PP2700	2.0E-10	A	B	23.1
PP2701	2.4E-10	A	A	21.7
PP2702	1.8E-10	A	B	21.4
PP2703	2.6E-10	AA	A	80.5
PP2704	1.5E-10	B	B	10.7

PP2706	7.6E-11	A	B	2.3
PP2708	7.2E-11	A	A	5.1
PP2710	1.0E-10	B	B	5.3
PP2712	1.1E-10	A	B	6.3
PP2714	2.5E-10	A	A	13.2
PP2716	3.4E-10	A	A	13.8
PP2718	3.3E-10	A	A	7.6
PP2720	3.5E-10	A	A	7.7
PP2722	4.0E-10	B	B	13.9
PP2724	4.3E-10	A	B	20.0
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PP2728	1.1E-09	AA	A	54.3
PP2730	6.5E-11	A	A	5.8
PP2732	6.7E-11	A	A	5.3
PP2734	1.0E-10	A	B	3.1
PP2736	6.1E-11	A	A	7.5
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PP2742	2.6E-10	AA	A	14.9
PP2744	2.3E-10	A	A	10.7
PP2746	2.8E-10	A	A	10.2
PP2748	2.0E-10	A	A	7.1
PP2749	8.7E-10	AA	A	22.1
PP2750	5.4E-10	AA	A	19.0
PP2751	8.5E-10	A	A	39.3
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PP2755	5.6E-10	A	A	35.7
PP2756	6.2E-10	A	A	93.6
PP2757	4.3E-09	A	A	91.1
PP2760	4.8E-09	A	B	144.4
PP2761	2.8E-09	A	A	68.4
PP2762	2.9E-09	A	A	122.3
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PP2772	4.3E-10	B	B	28.1

PP2773	5.2E-10	B	B	8.6	PP2823	1.3E-10	A	A	7.6
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PP2782	4.9E-10	A	A	59.1	PP2830	3.7E-10	A	A	28.8
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PP2787	3.6E-10	AA	A	22.1	PP2835	1.9E-10	A	A	13.0
PP2788	4.5E-10	A	A	24.4	PP2836	6.5E-11	A	A	5.1
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PP2802	3.4E-11	AA	A	5.5	PP2846	9.1E-11	AA	A	5.1
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PP2821	1.8E-09	A	A	90.4	PP2866	7.3E-10	A	A	39.6
PP2822	2.6E-10	A	A	14.1	PP2867	2.2E-10	A	A	17.1

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PP2869	9.0E-10	A	A	37.6	PP2917	1.4E-09	AA	A	130.2
PP2870	5.8E-10	A	A	11.5	PP2918	1.8E-09	AA	A	126.2
PP2871	1.5E-09	A	A	28.4	PP2920	4.0E-09	AA	A	118.3
PP2872	2.3E-09	A	A	88.3	PP2921	6.9E-09	AA	A	160.1
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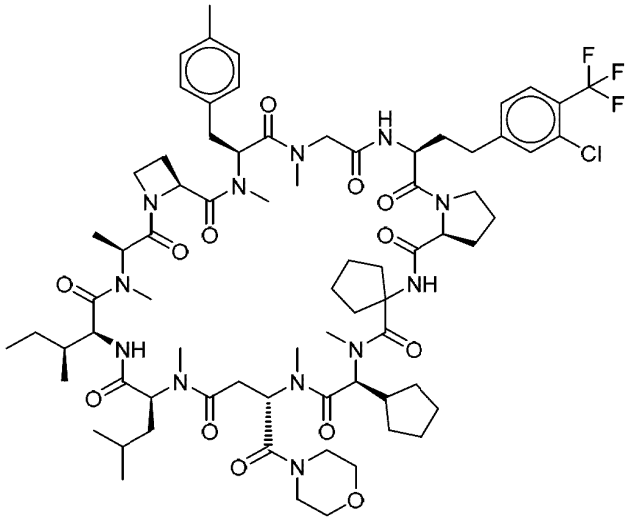
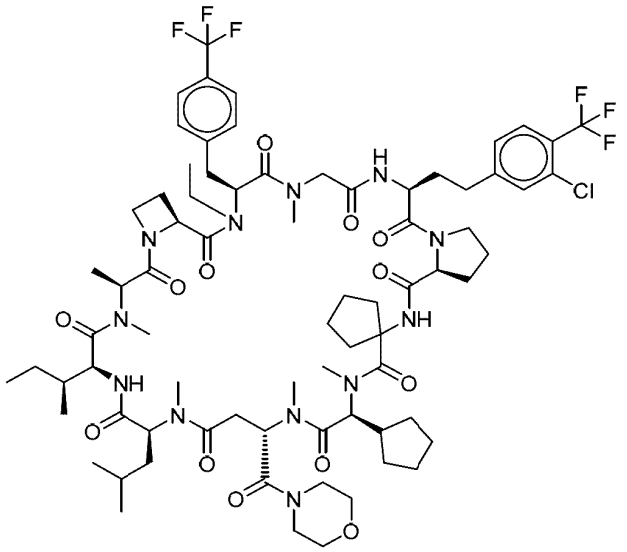
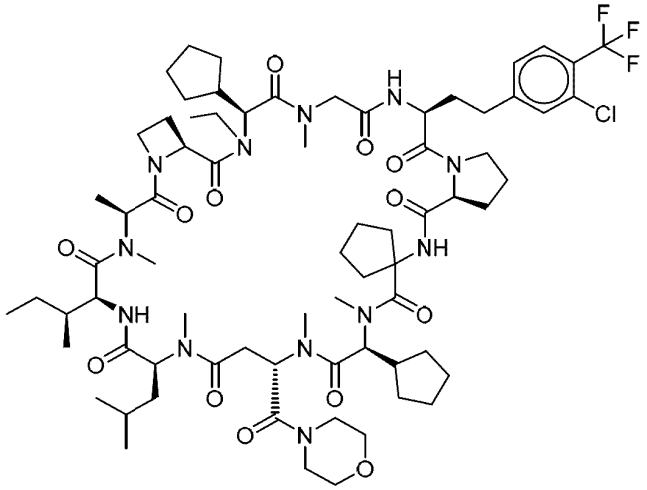
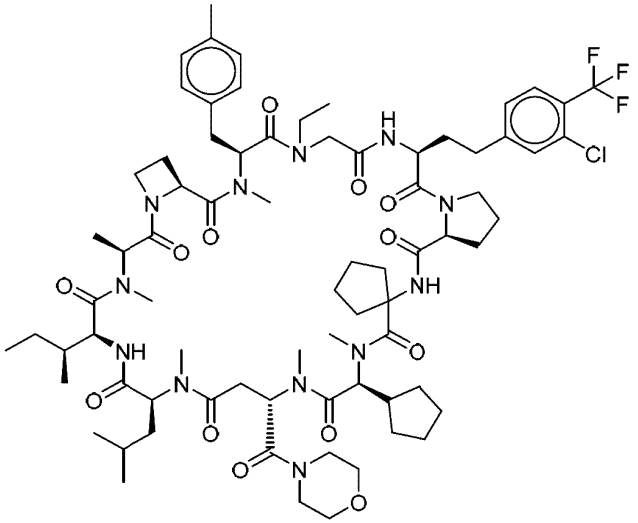
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PP2978	1.1E-10	A	A	5.9	PP3030	3.1E-10	AA	A	22.4
PP2979	2.8E-10	A	B	5.0	PP3031	1.9E-09	AA	A	94.2
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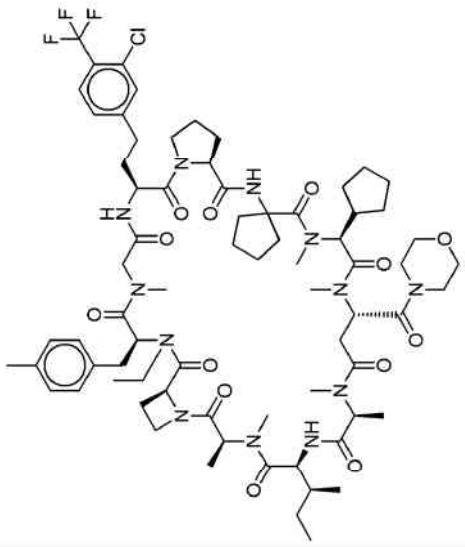
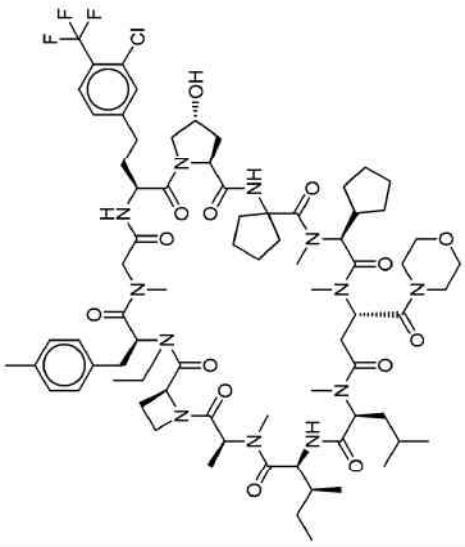
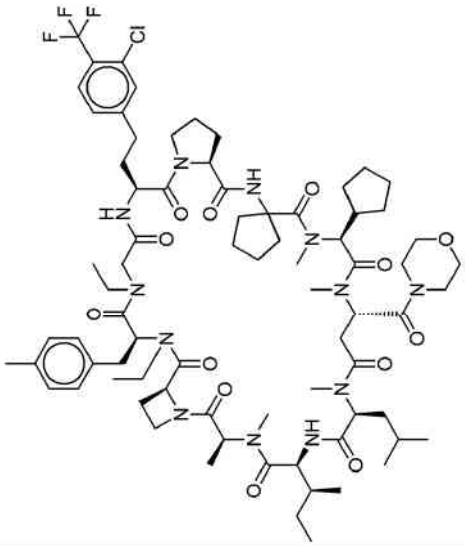
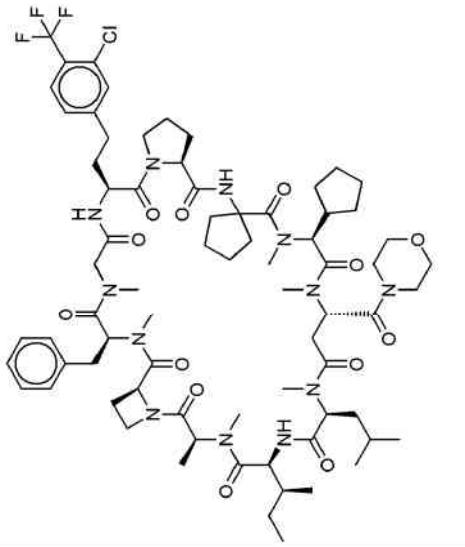
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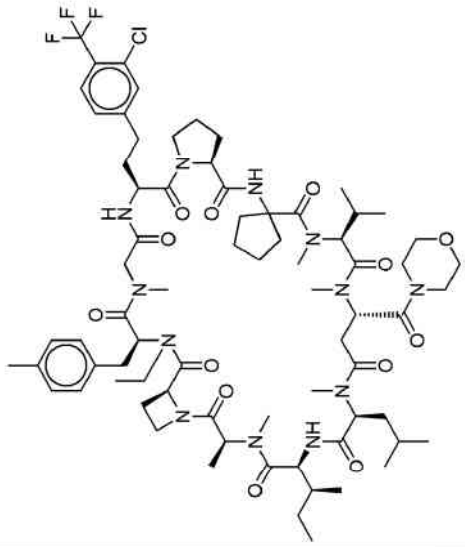
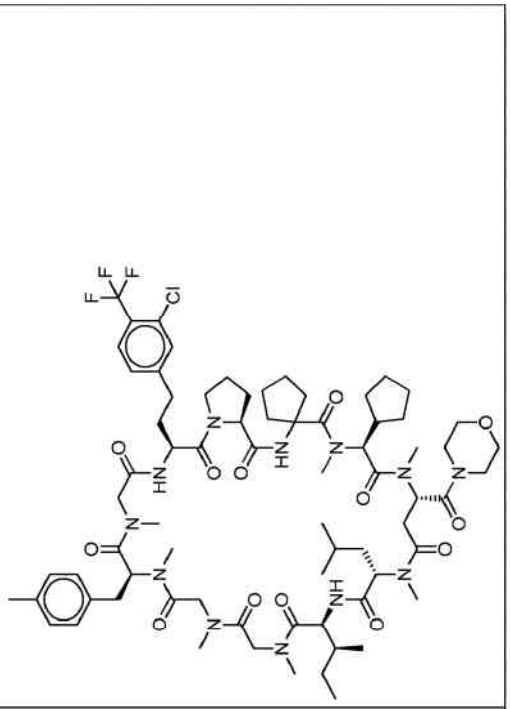
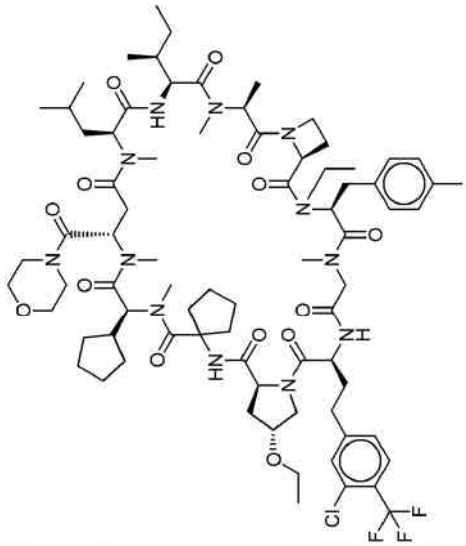
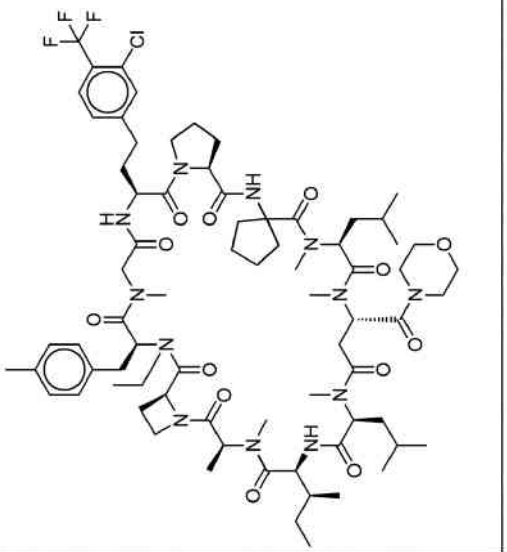
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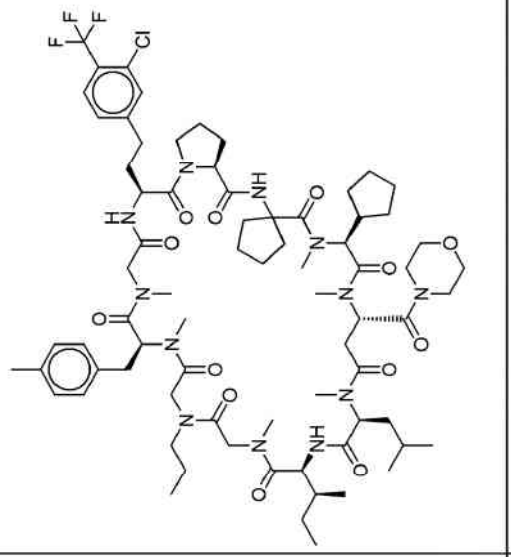
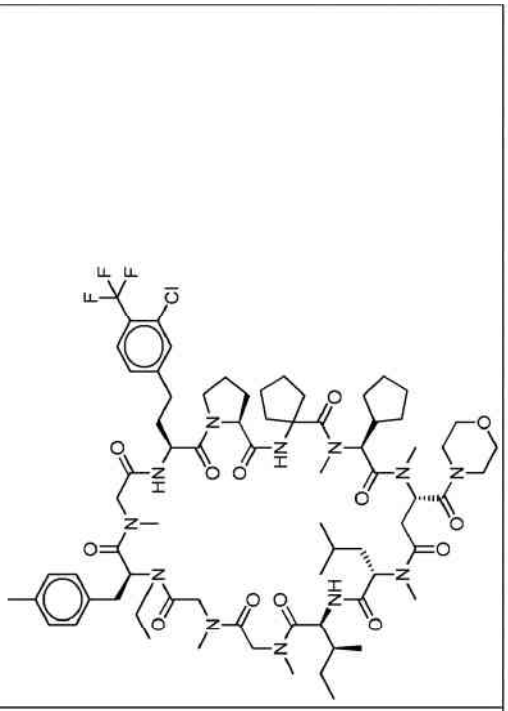
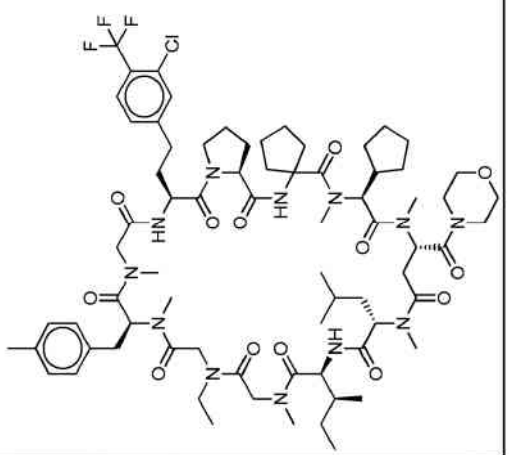
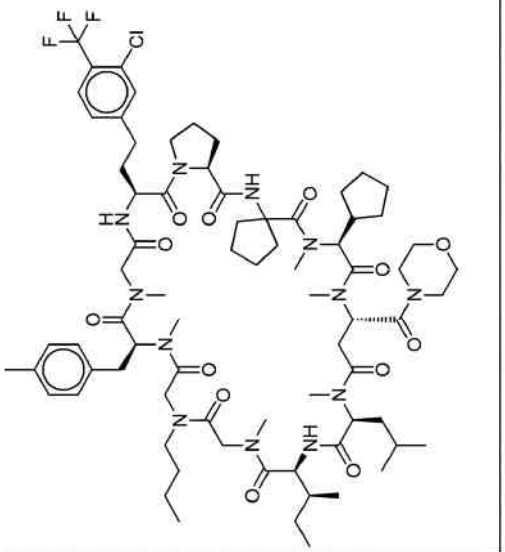
List of structures of cyclic compounds

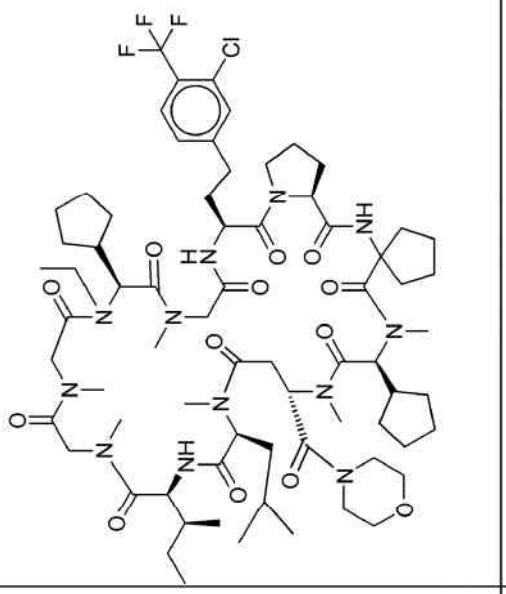
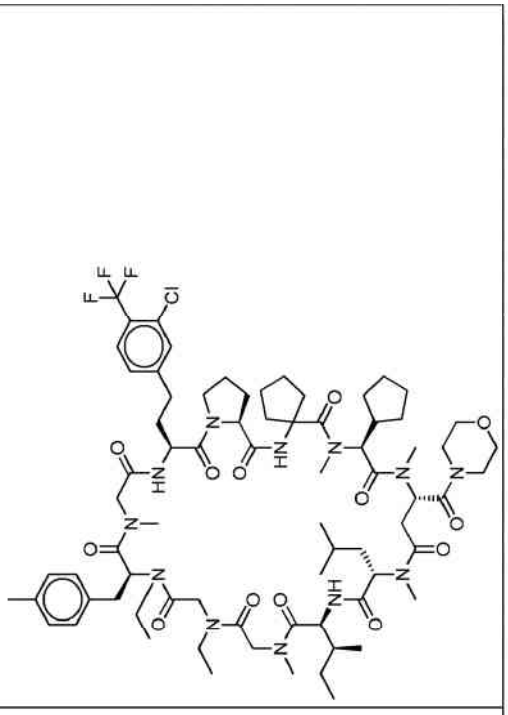
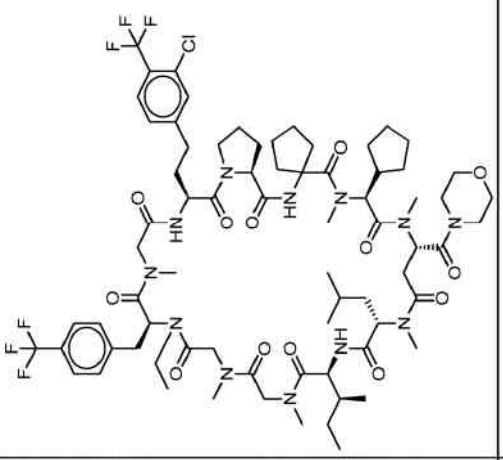
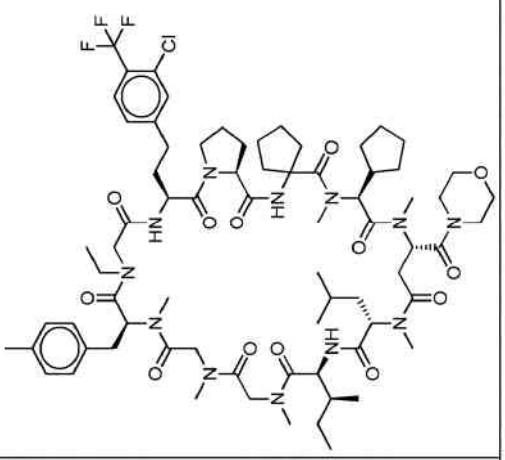
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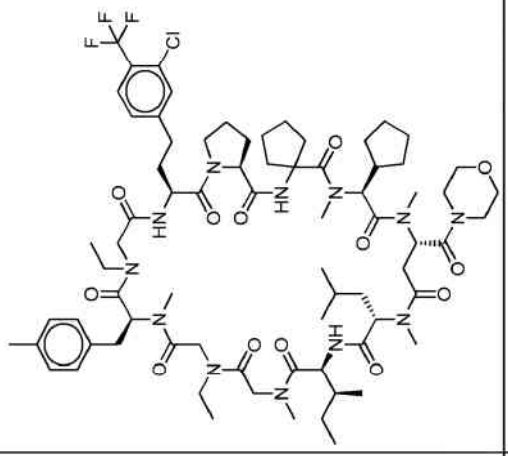
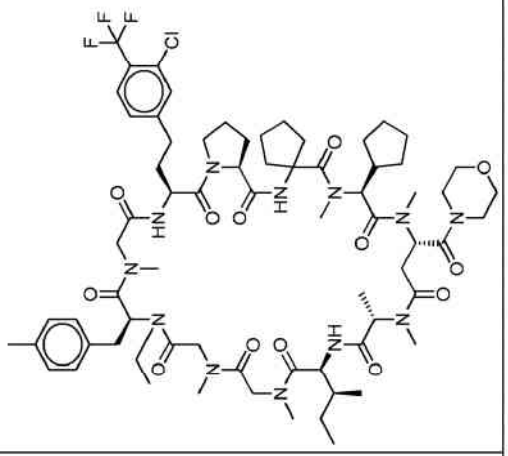
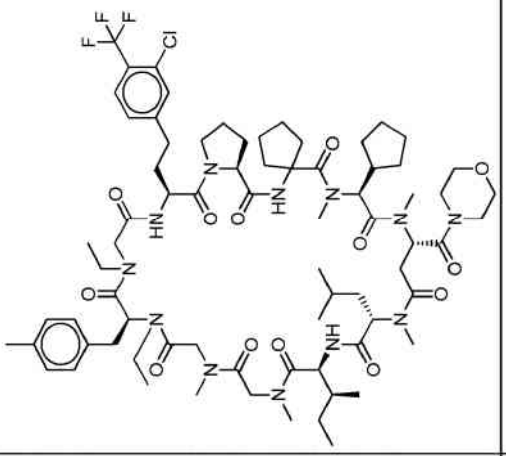
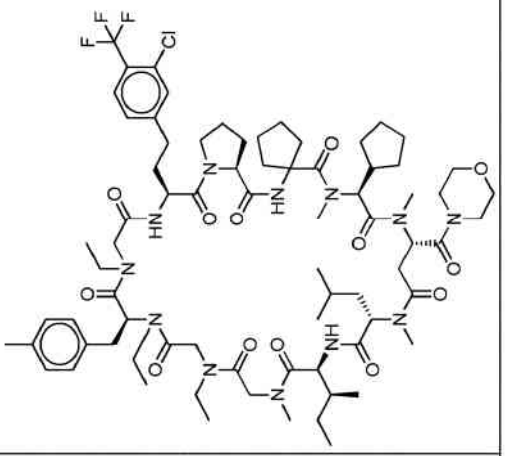
Compound No.	Structural Formula	Compound No.	Structural Formula
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PP0003		PP0004	

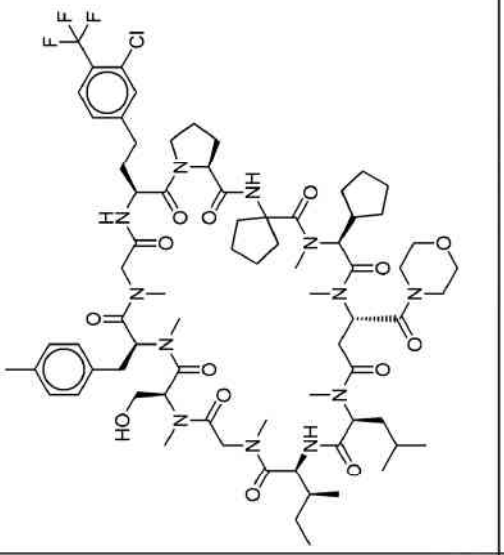
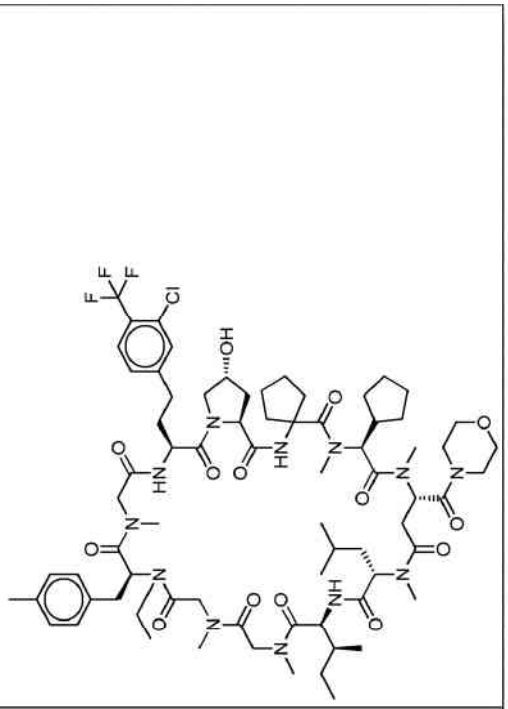
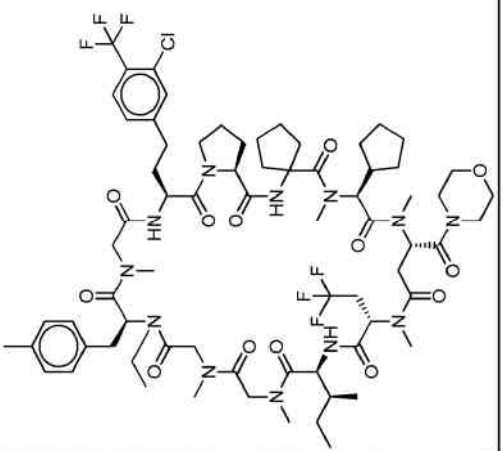
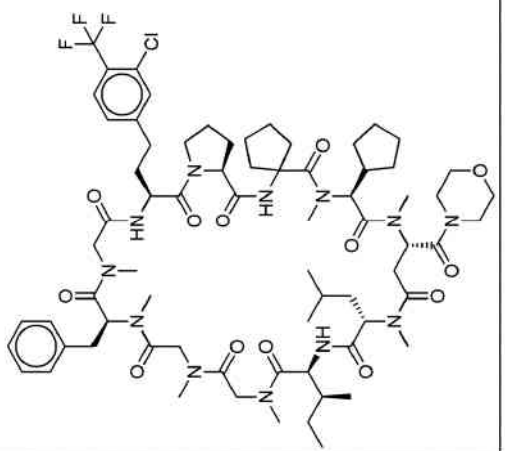
	
PP0 007	PP0 013
	
PP0 006	PP0 011

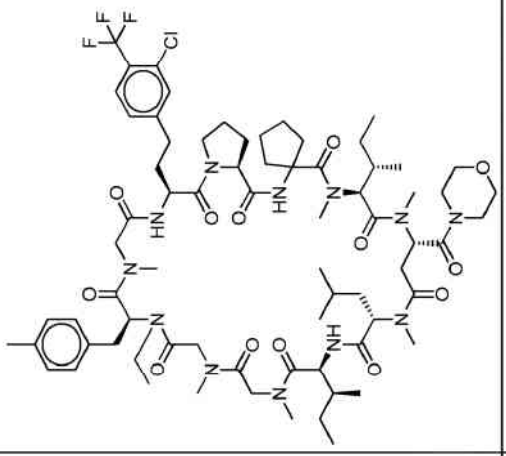
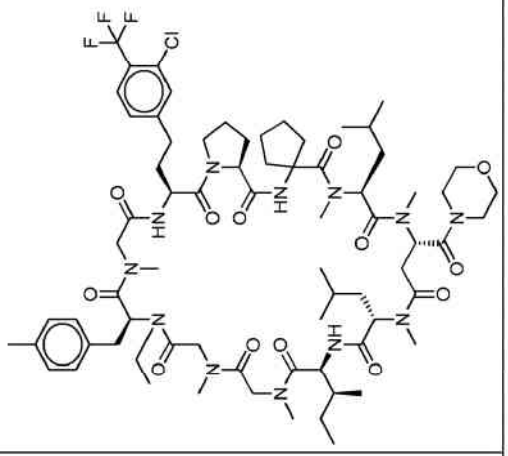
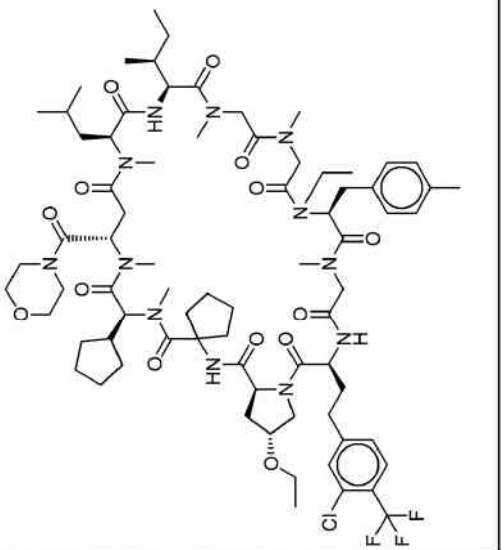
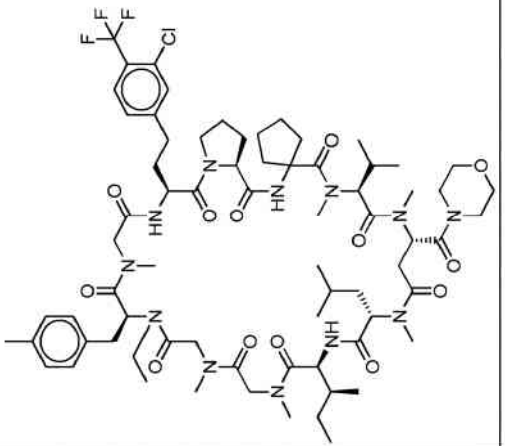
	
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PP0 014	PP0 016

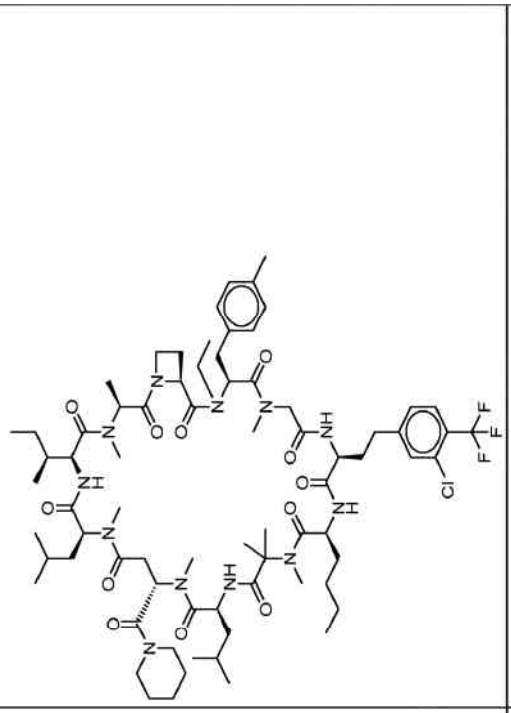
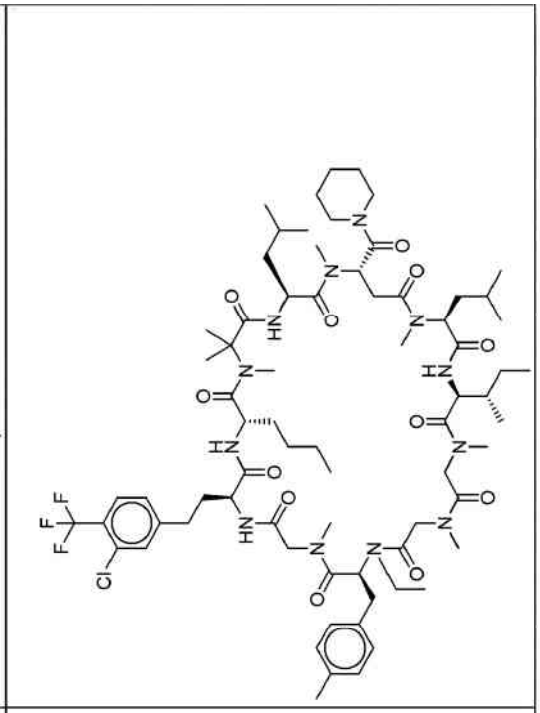
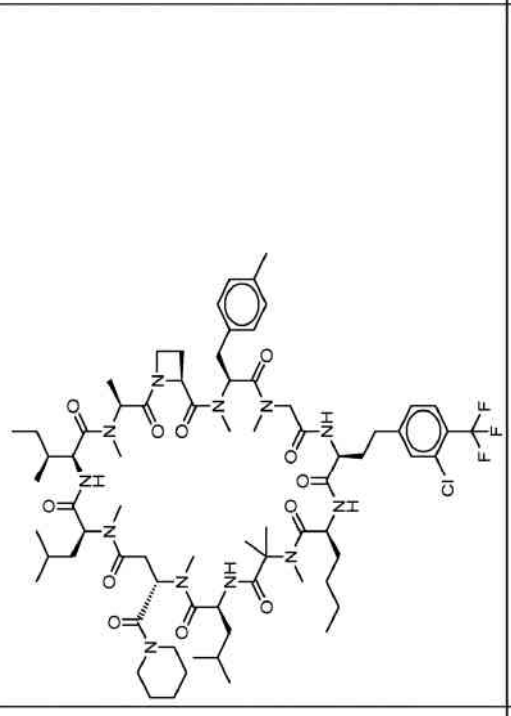
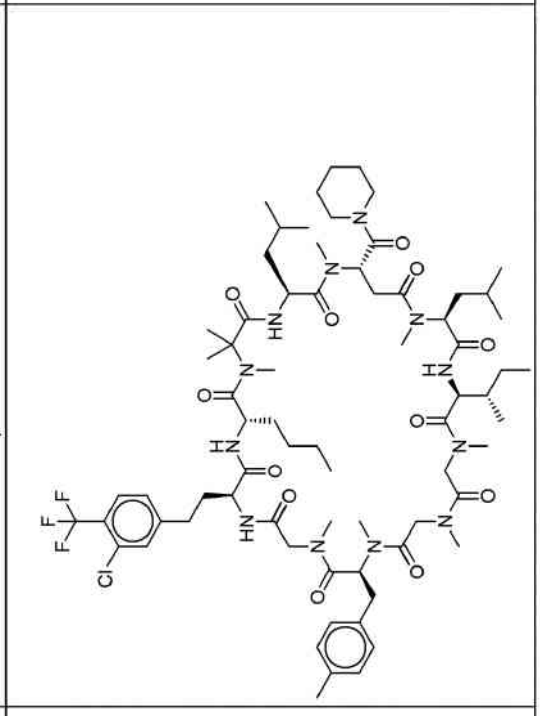
	
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PP0 019	PP0 021

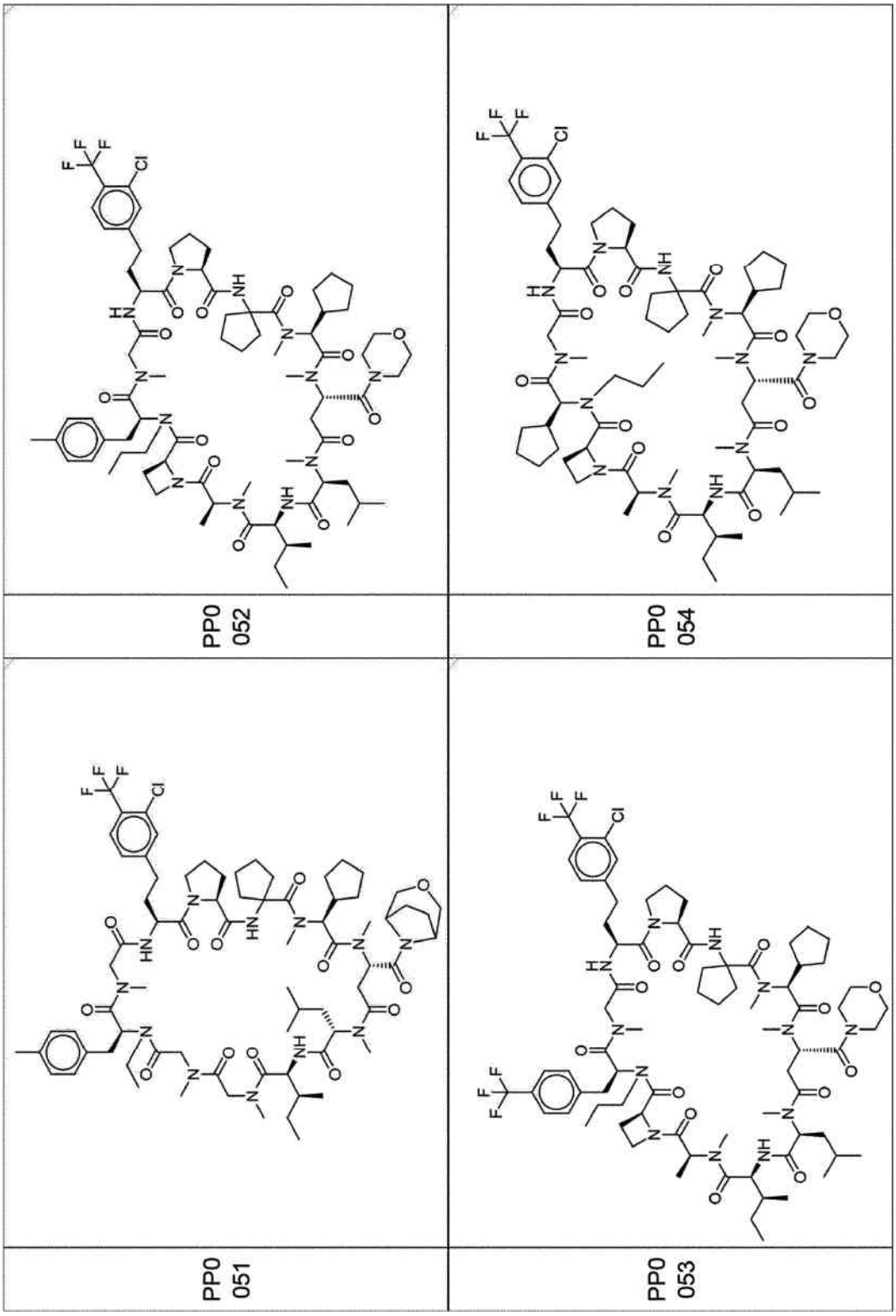
	
PP0 024	PP0 027
	
PP0 023	PP0 025

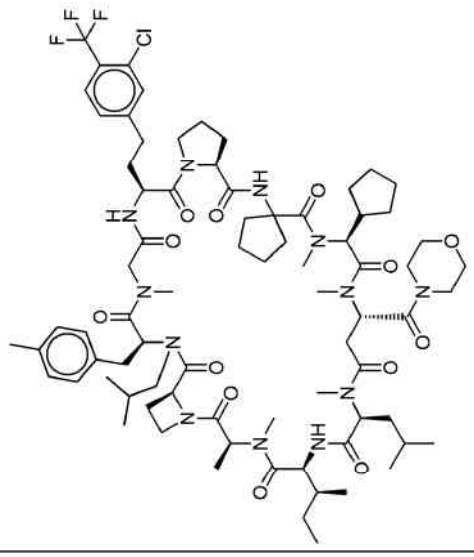
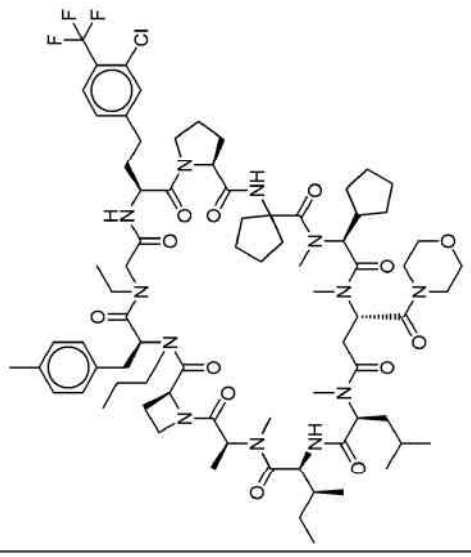
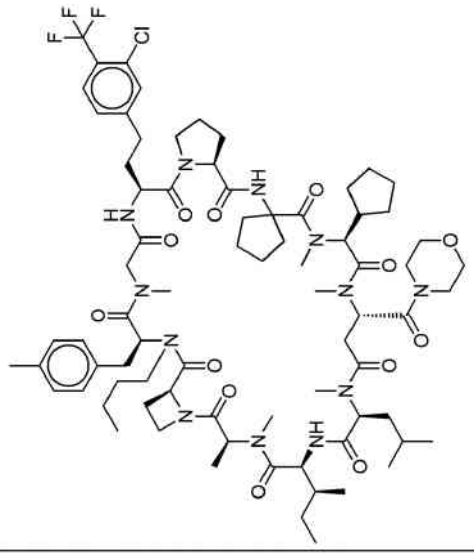
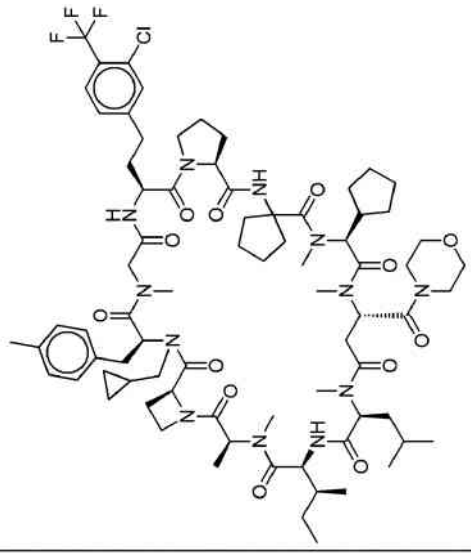
	
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PP0 028	PP0 030

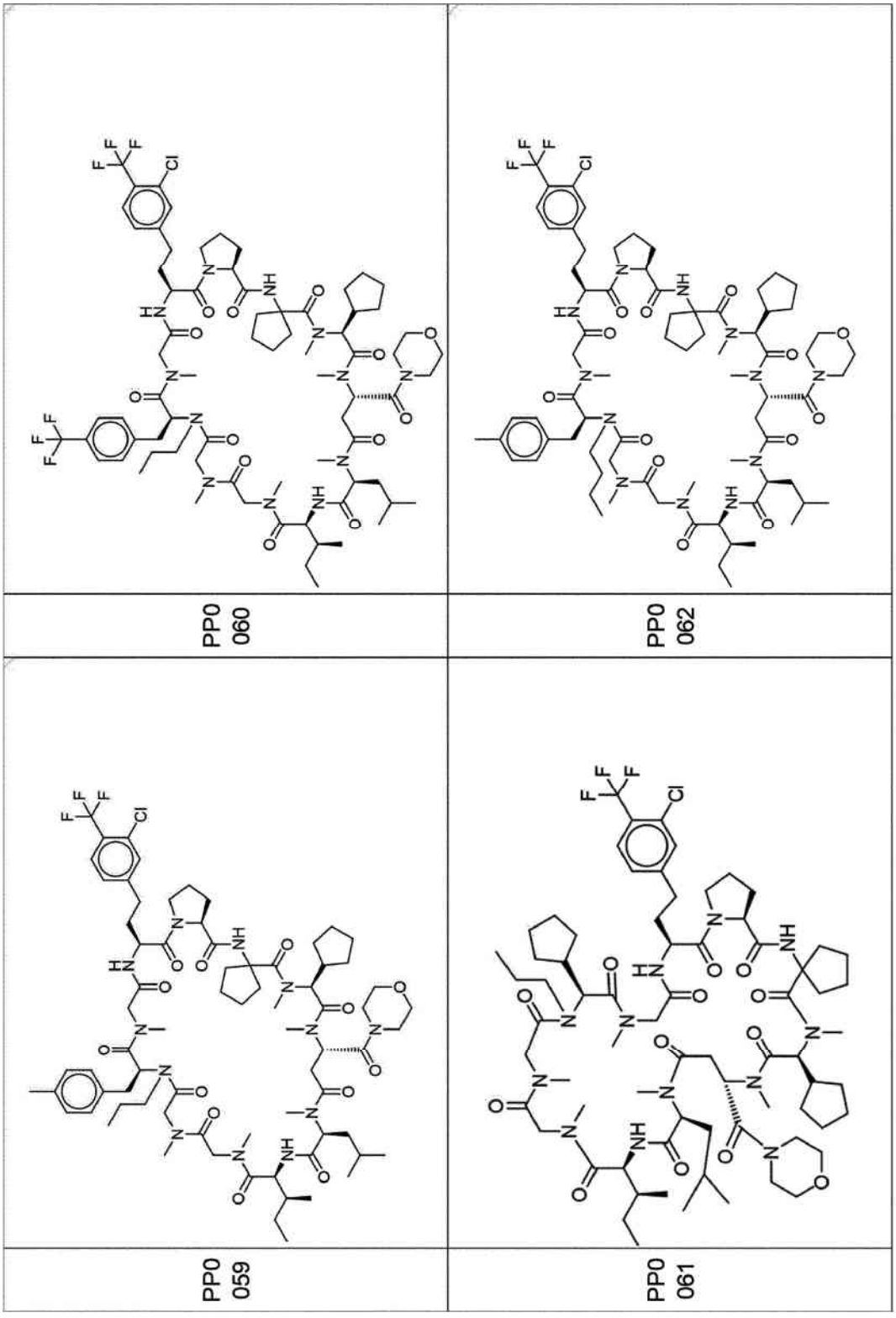
	
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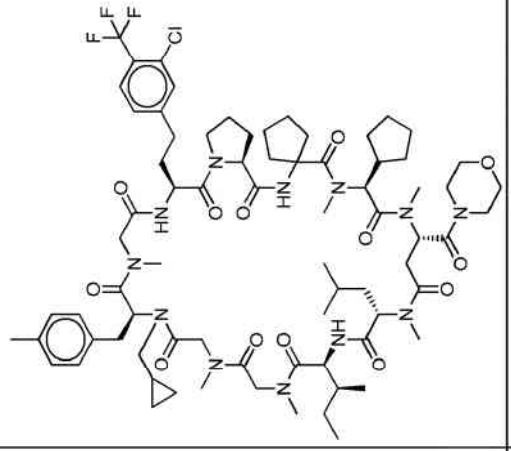
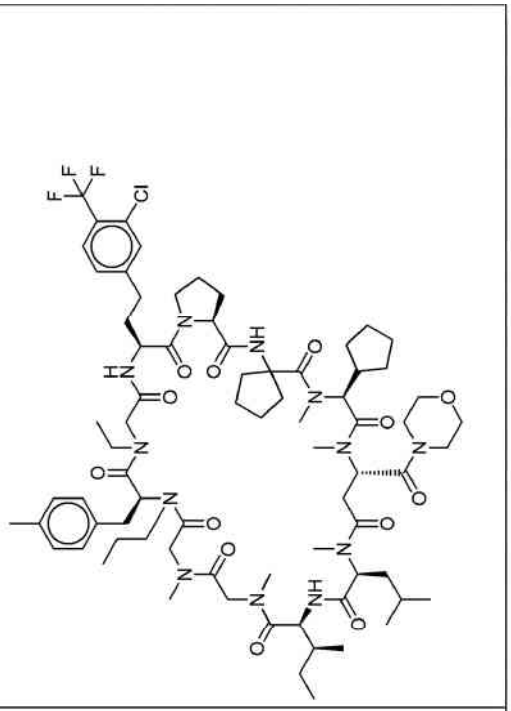
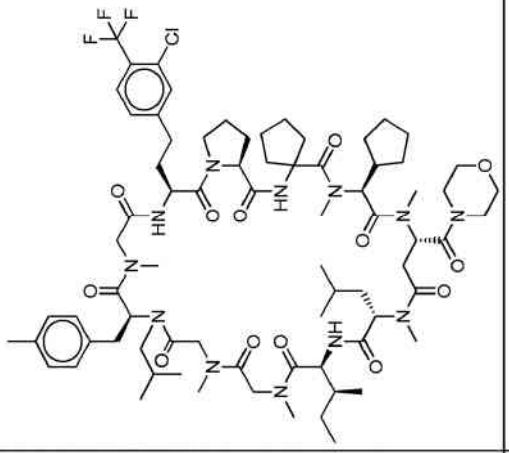
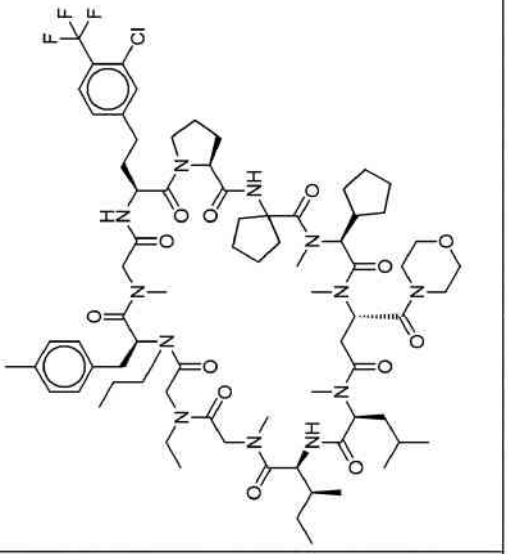
	
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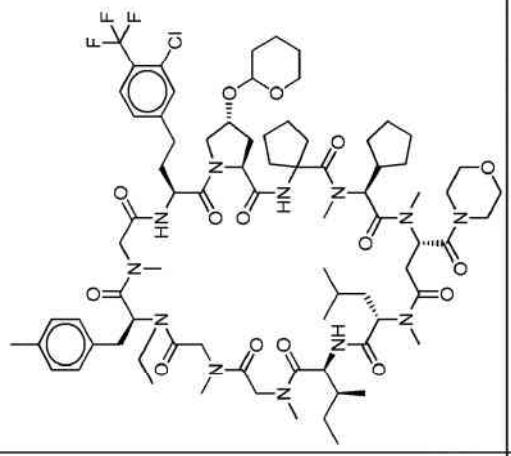
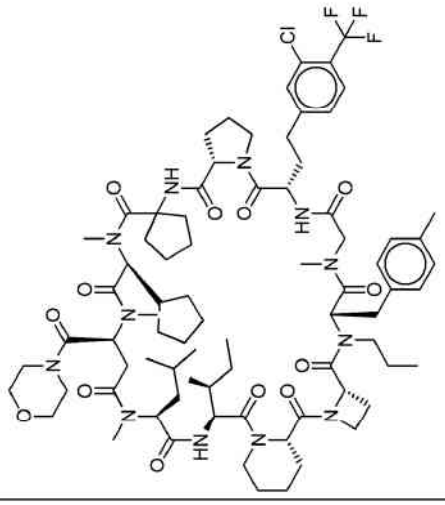
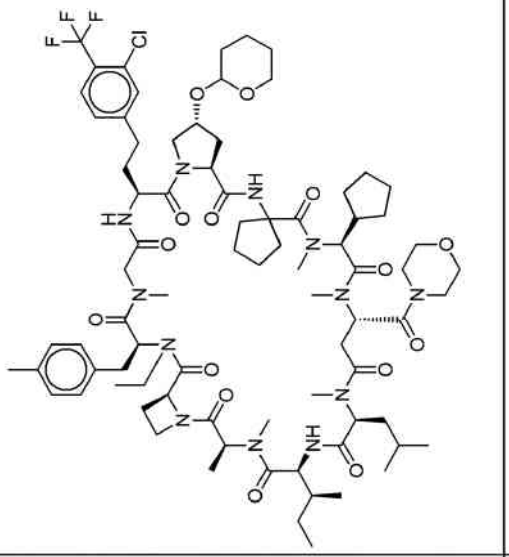
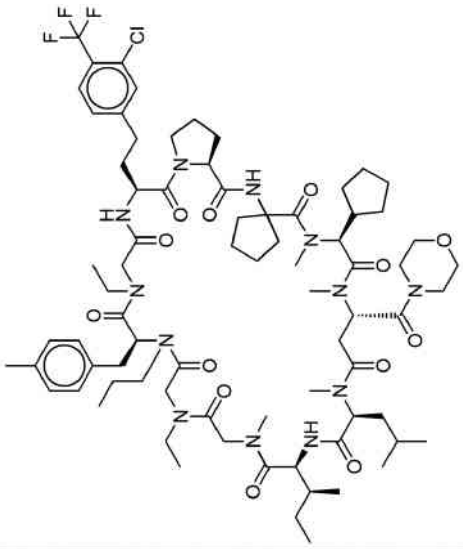
	
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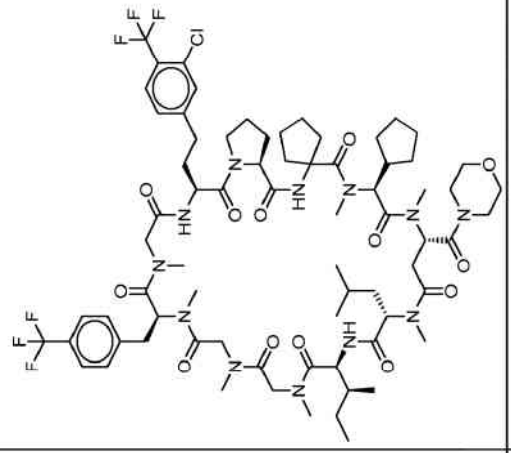
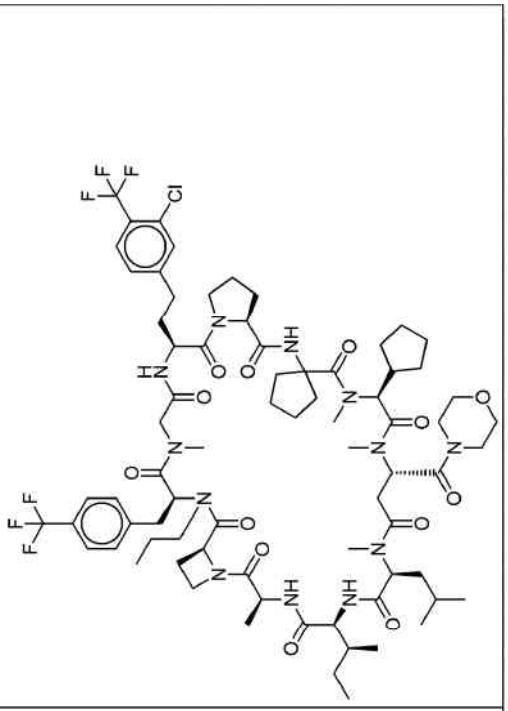
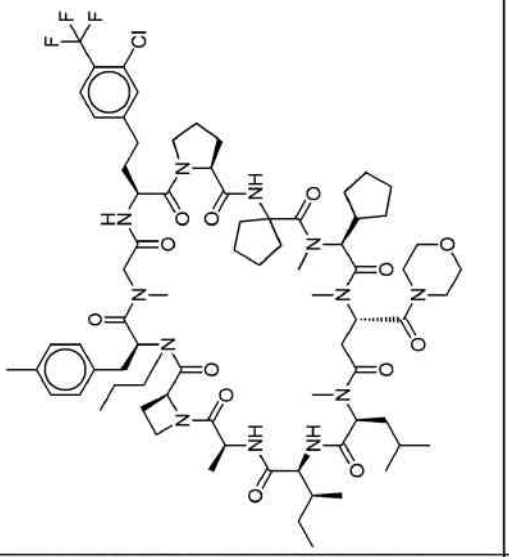
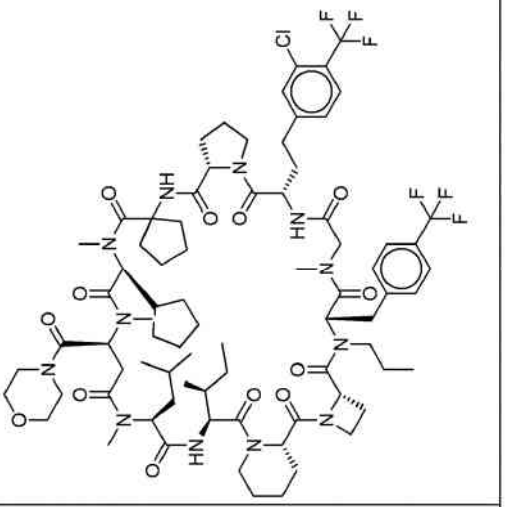

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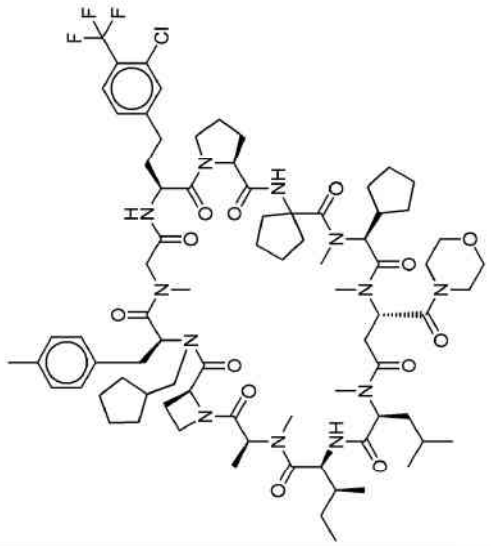
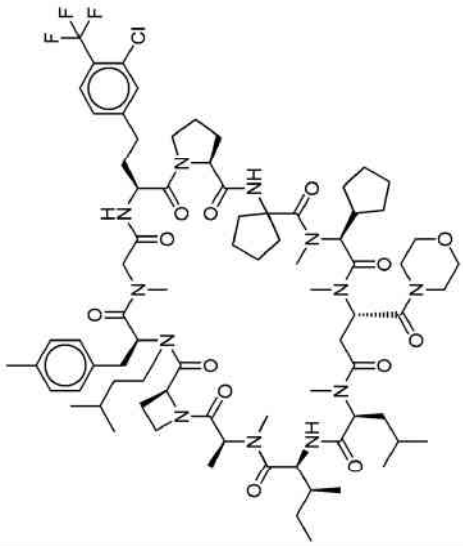
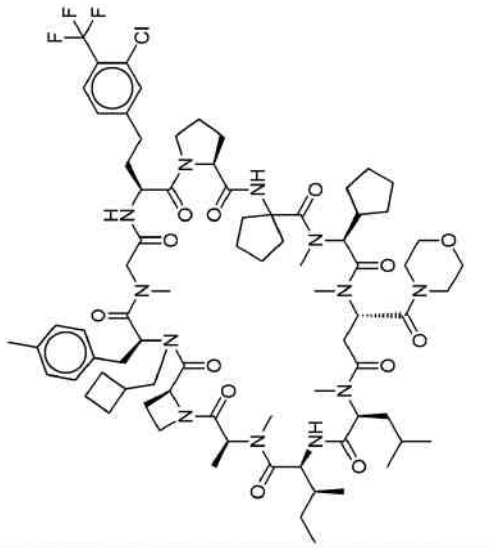
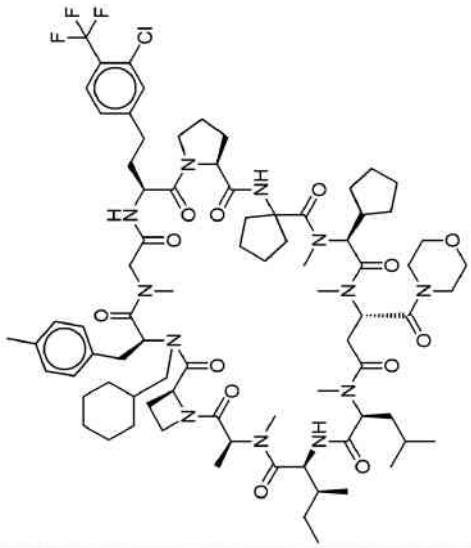
	
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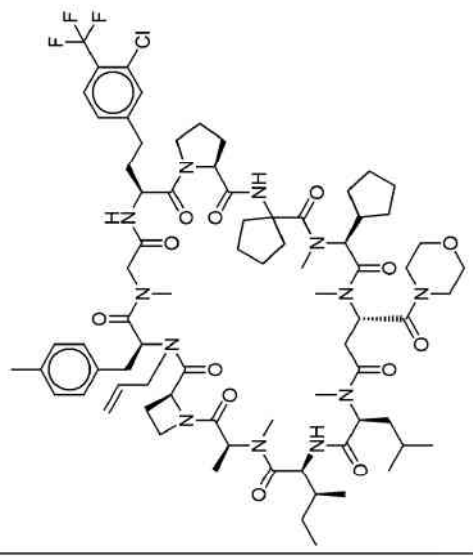
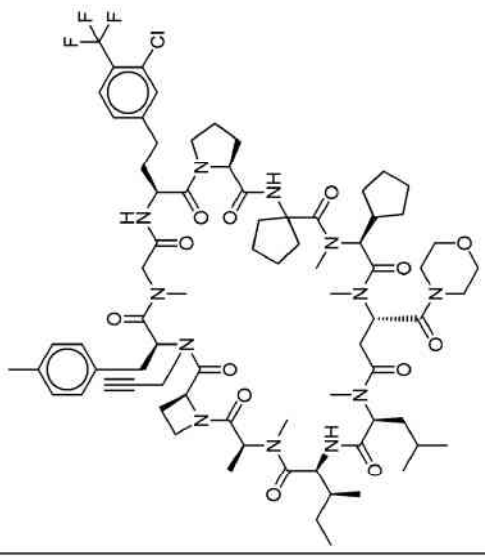
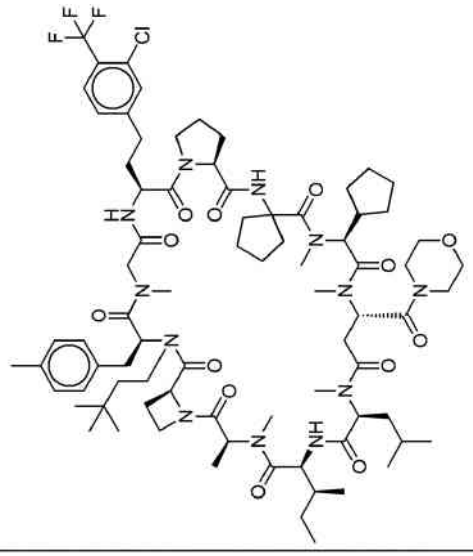
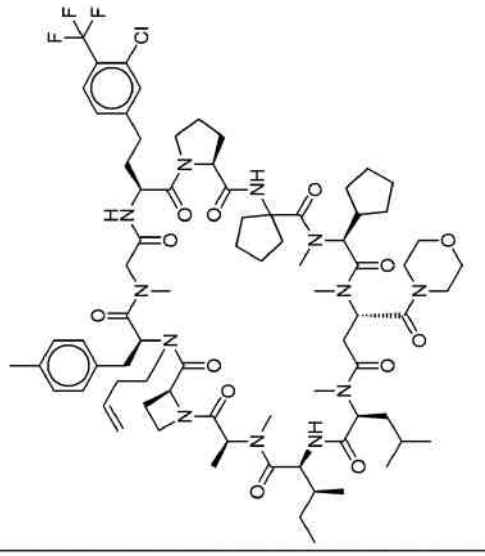

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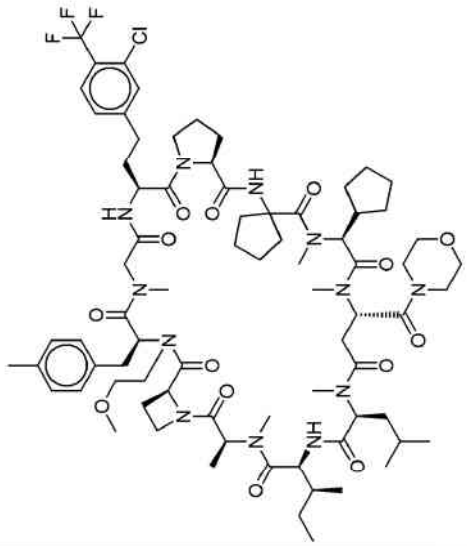
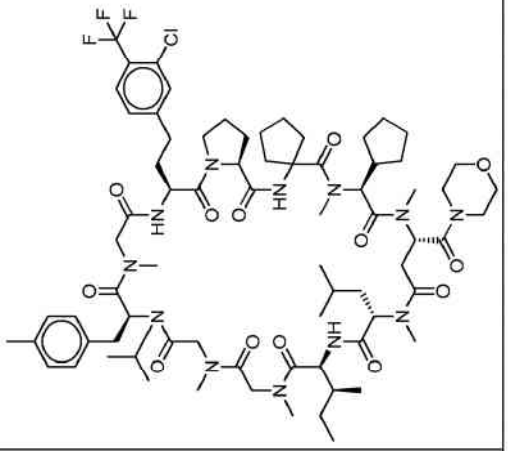
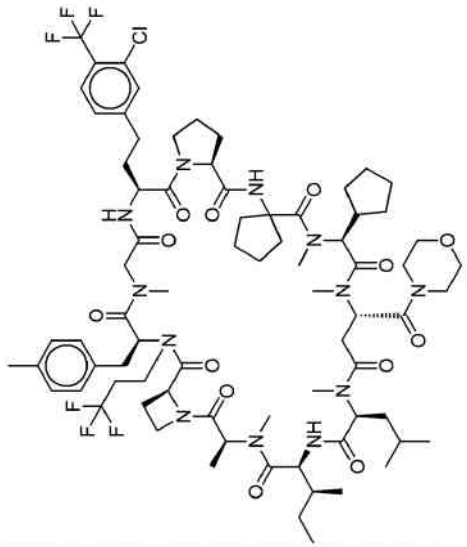
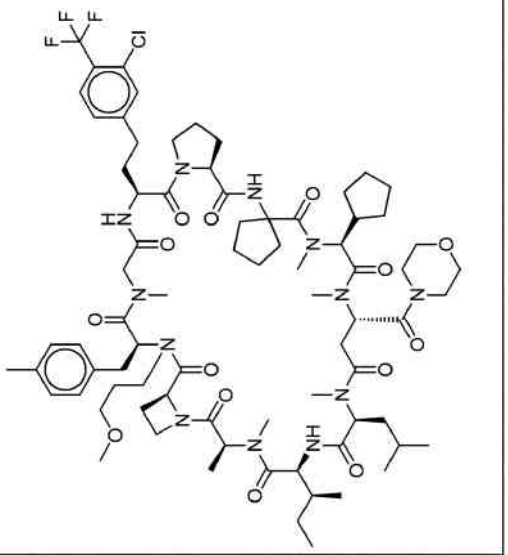
	
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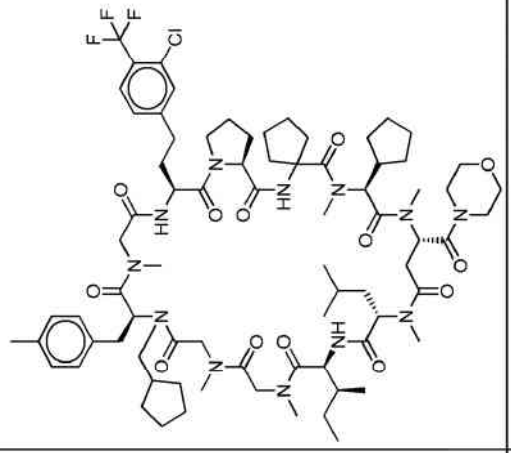
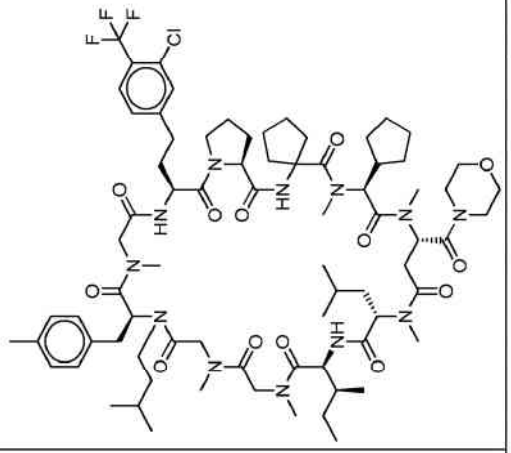
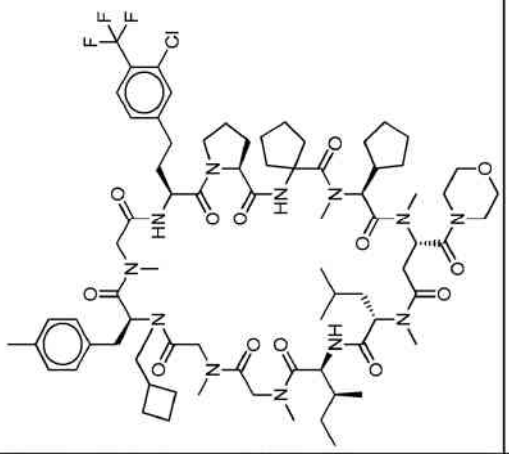
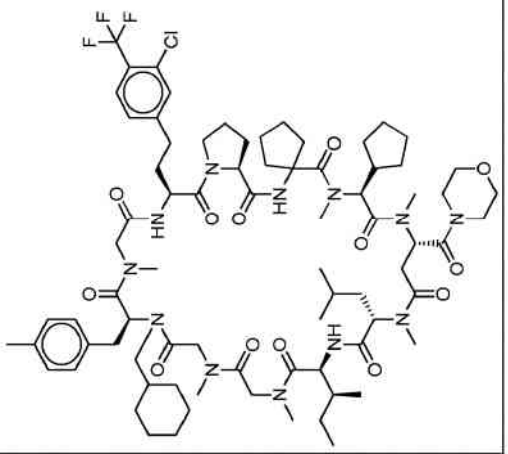
	
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PP0 067	PP0 069

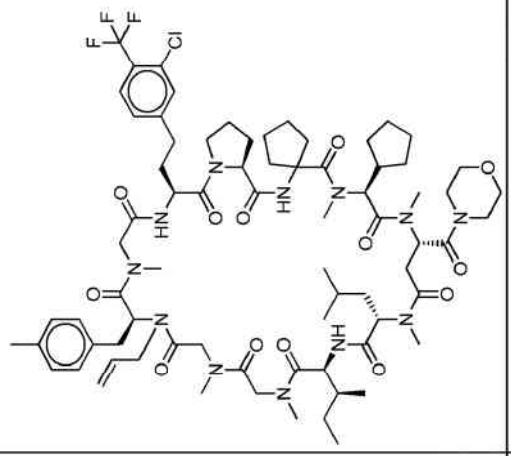
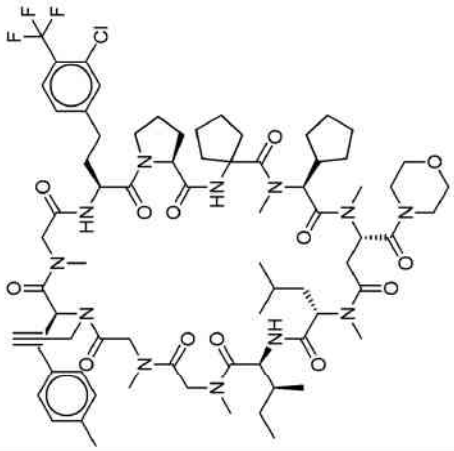
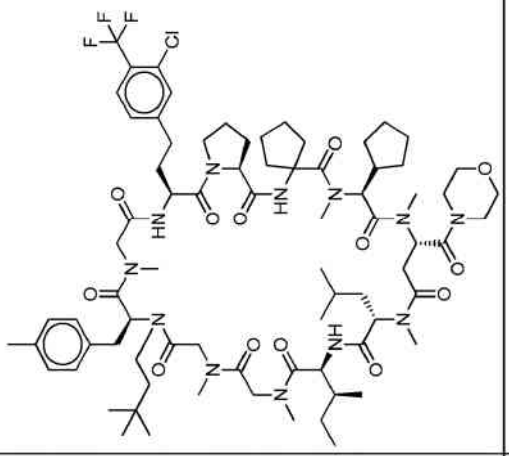
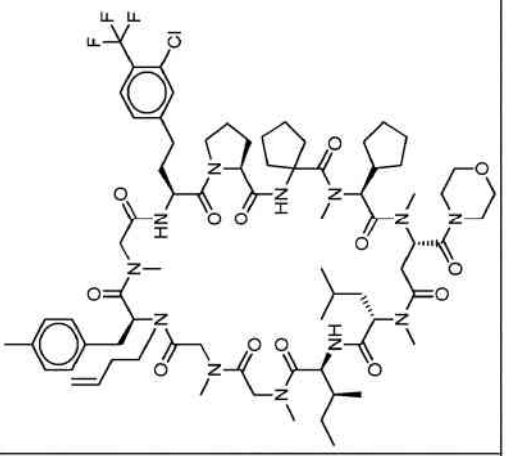
	
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PP0 071	PP0 077

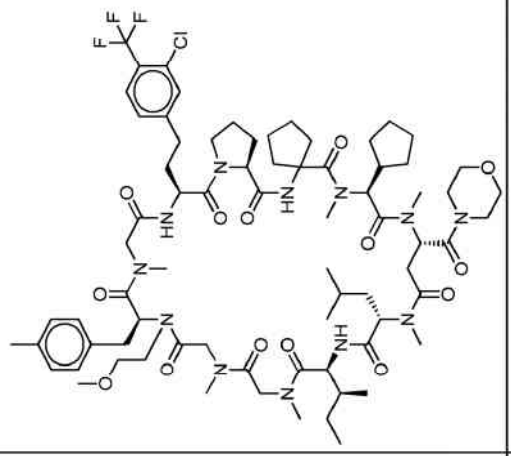
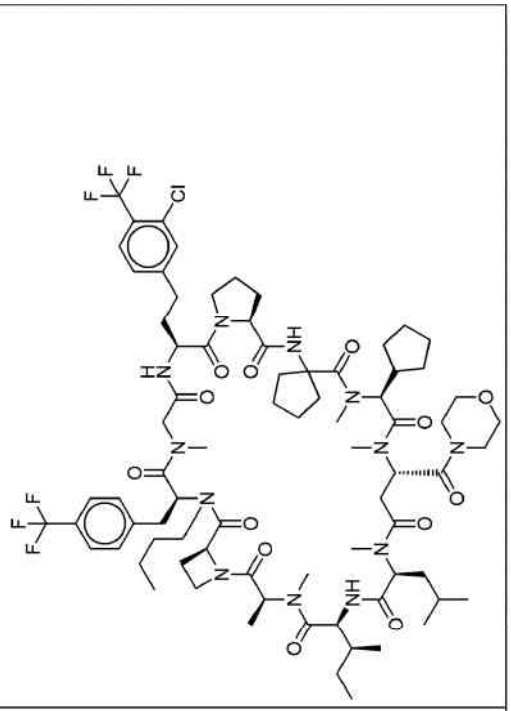
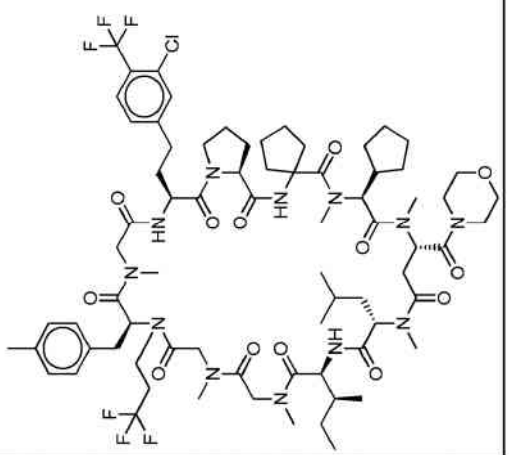
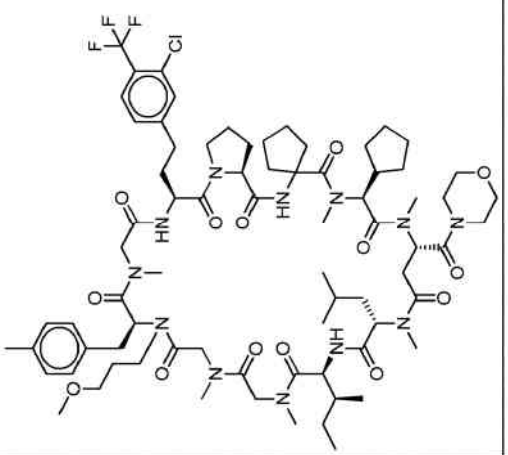
	
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PP0 083	PP0 085

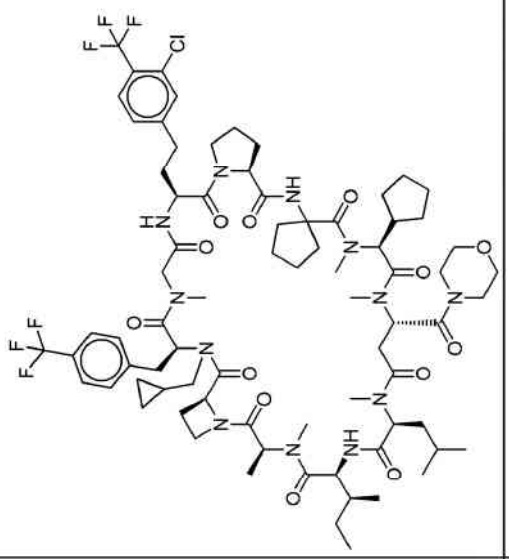
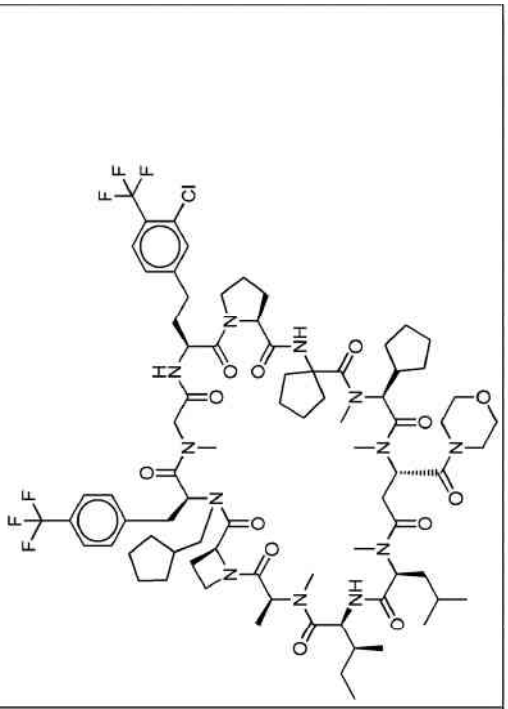
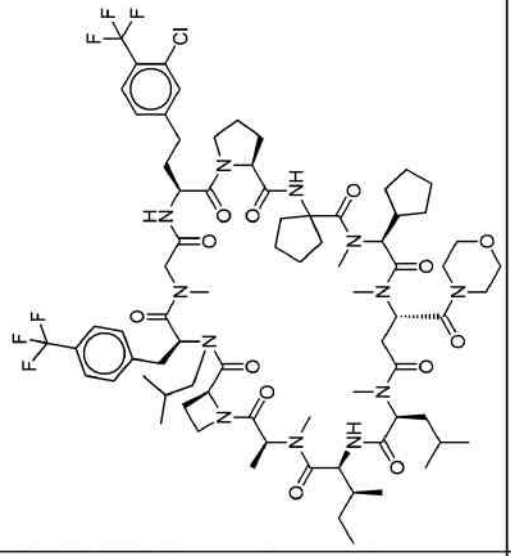
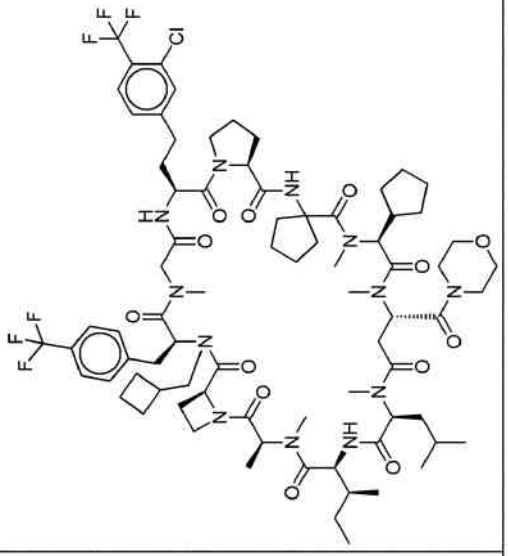
	
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PP0 087	PP0 089

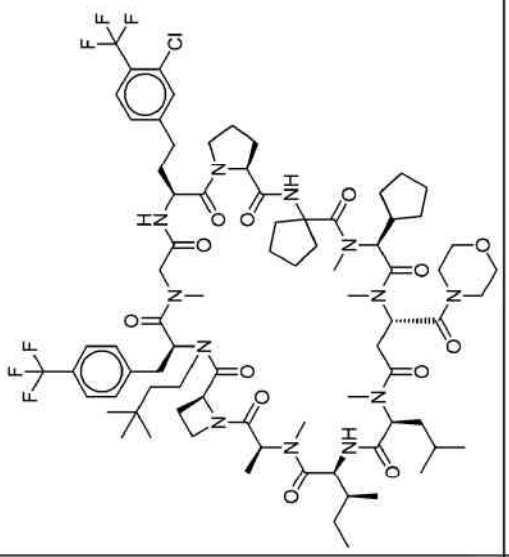
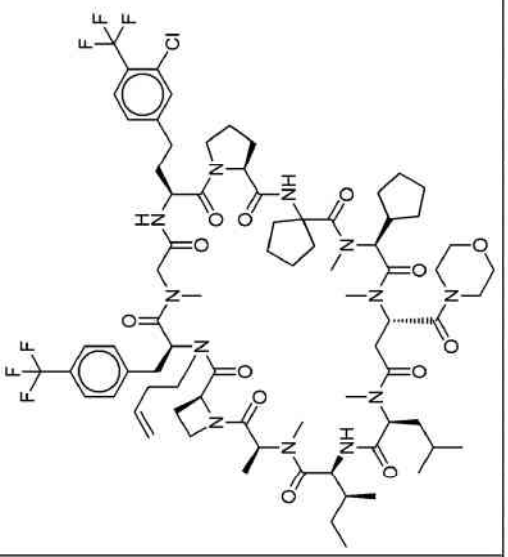
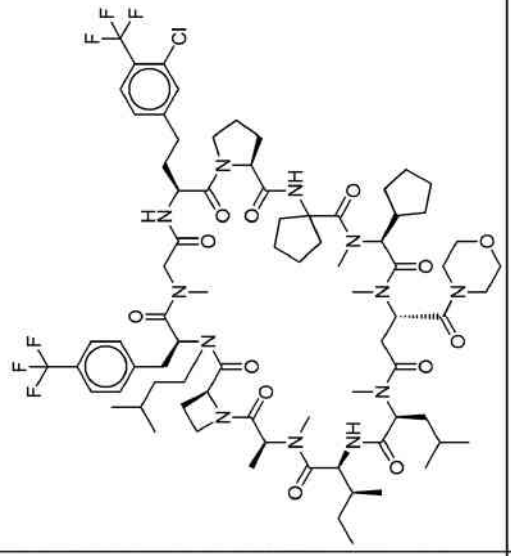
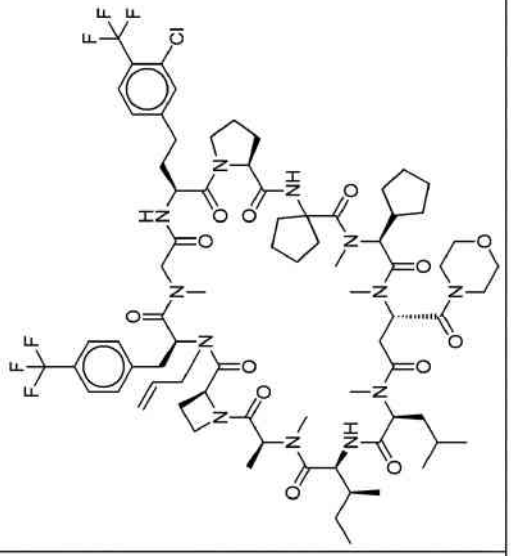
	
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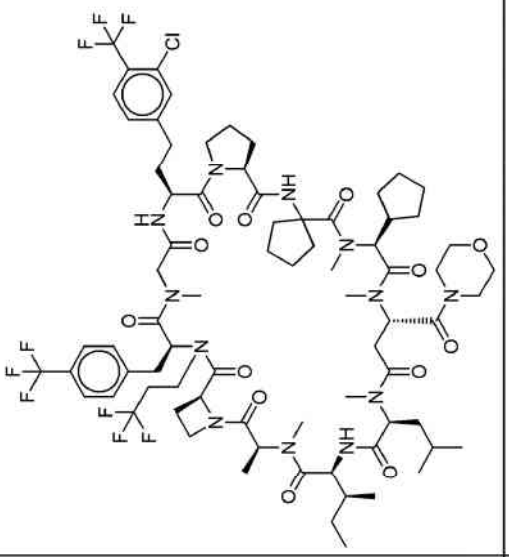
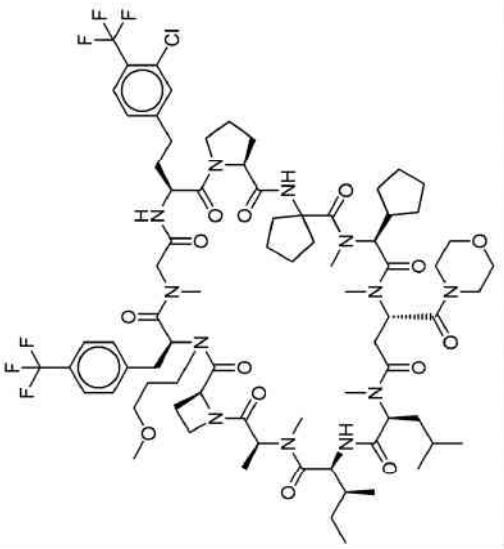
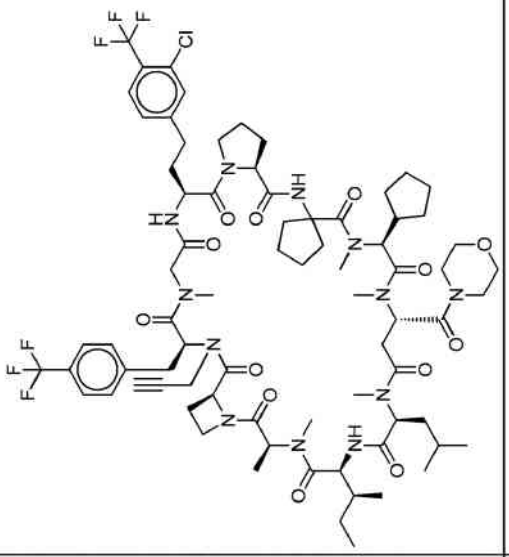
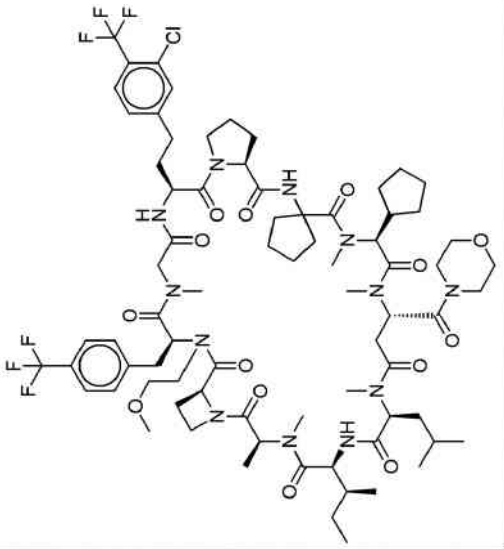
	
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PP0 095	PP0 097

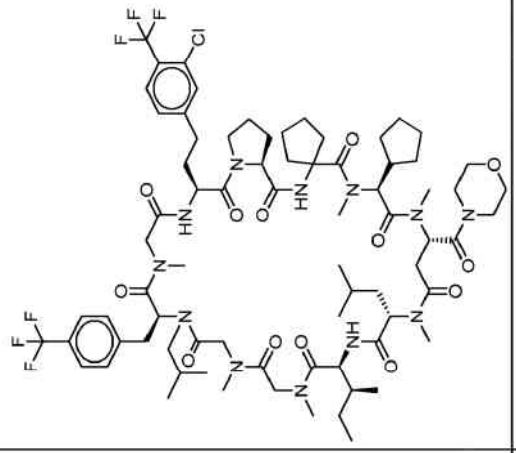
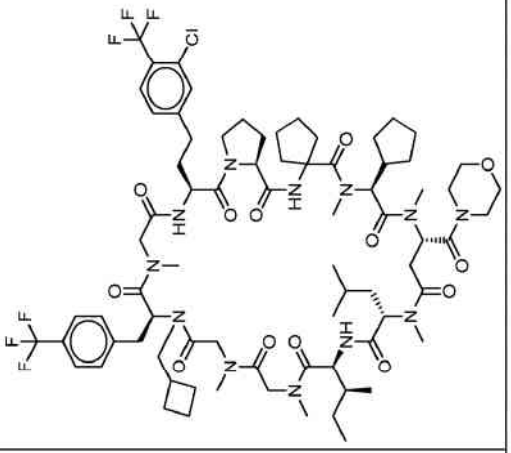
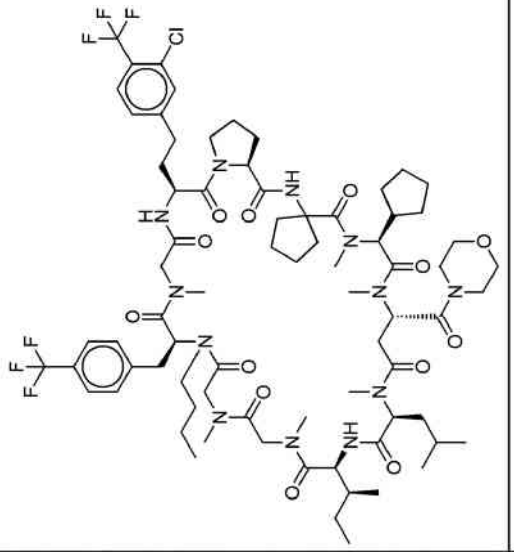
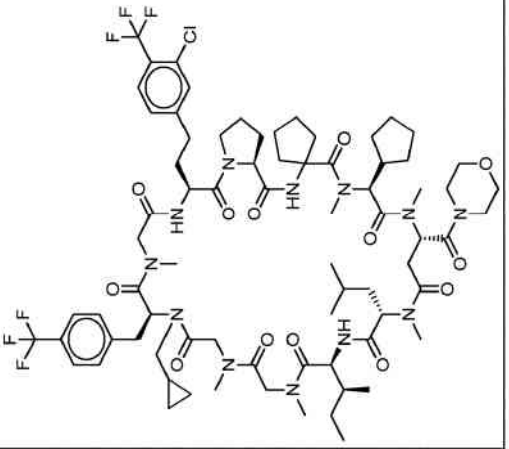
	
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PP0 099	PP0 101

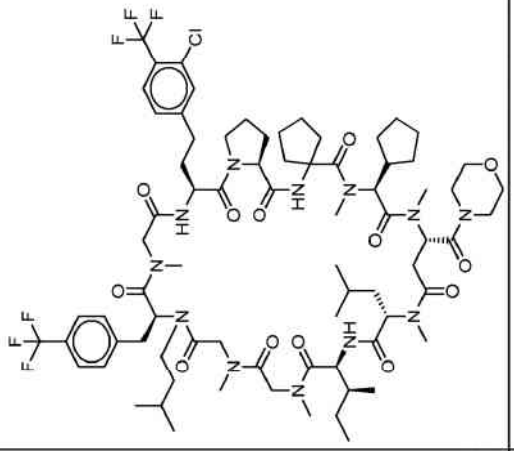
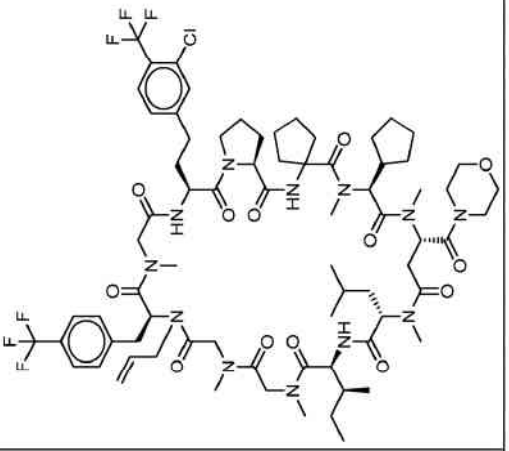
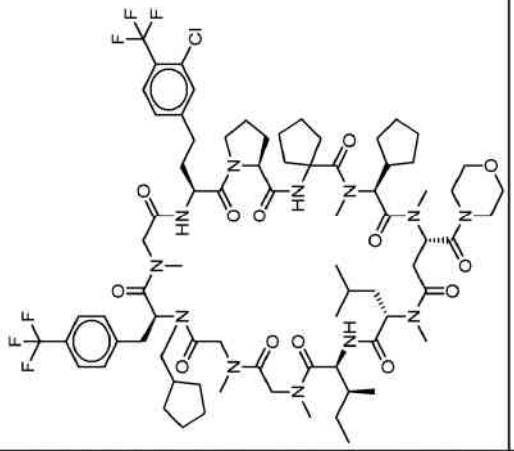
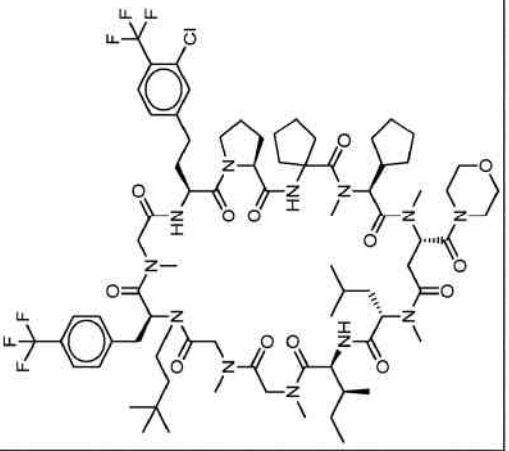
	
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PP0 103	PP0 105

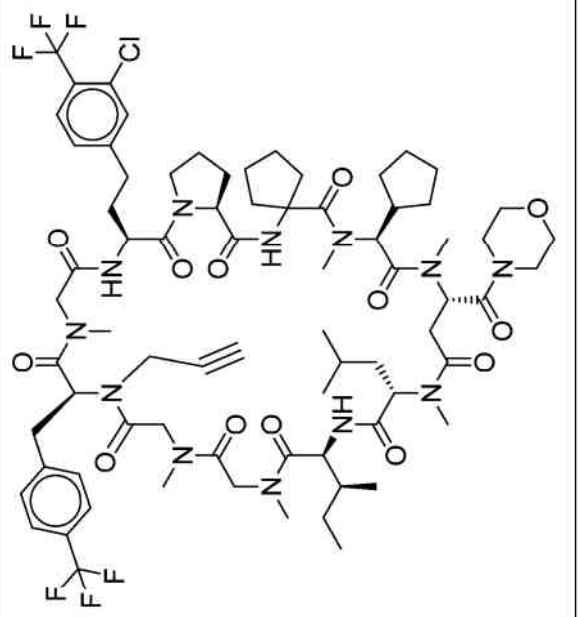
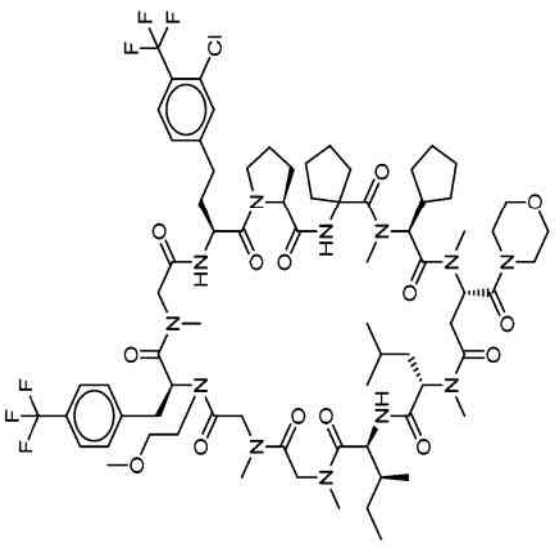
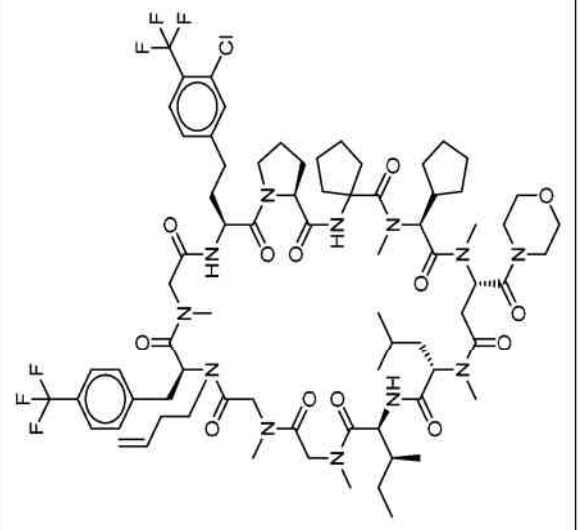
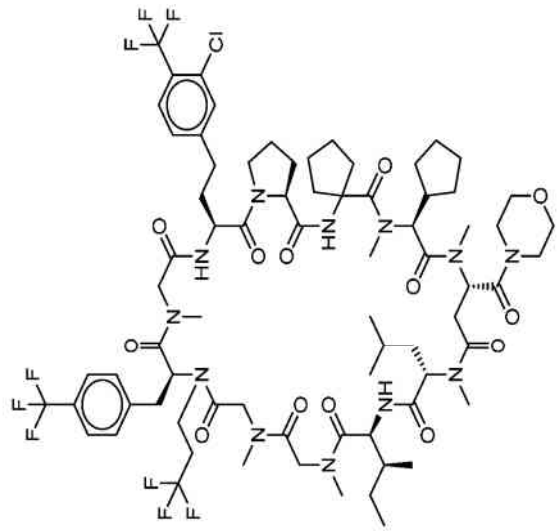
	
PP0 107	PP0 108
	
PP0 109	PP0 110

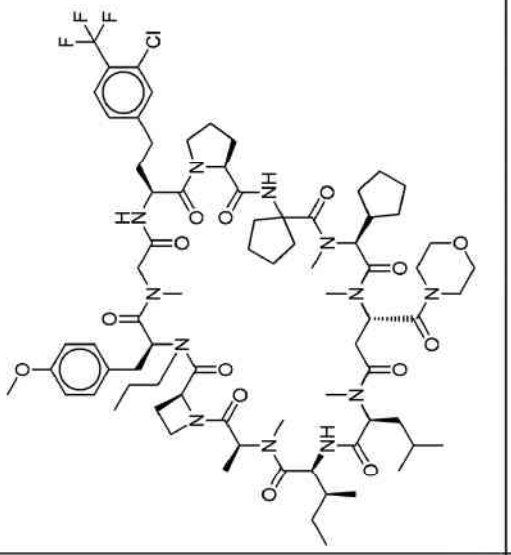
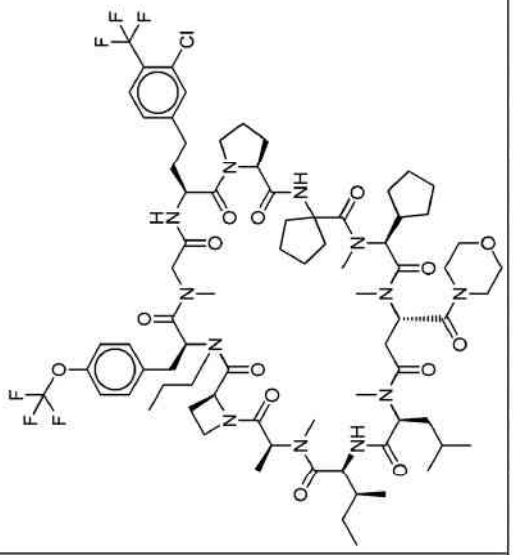
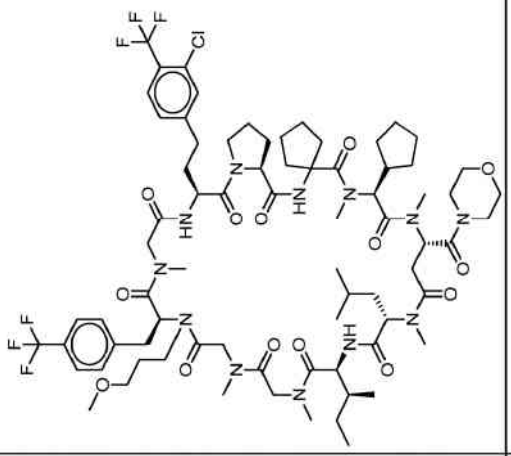
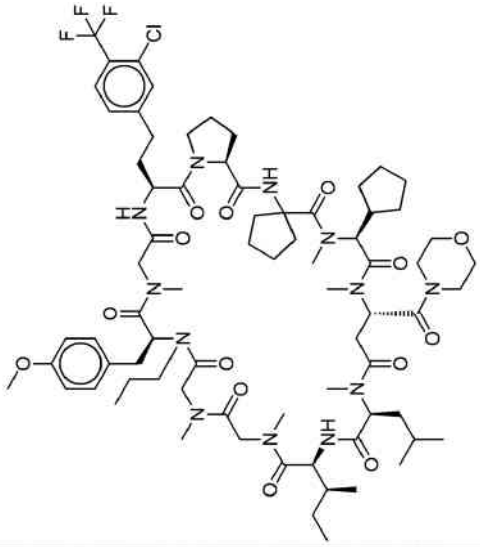
	
PP0 113	PP0 115
	
PP0 112	PP0 114

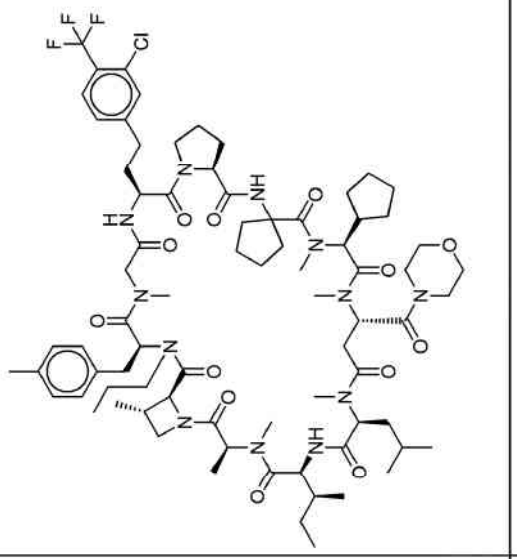
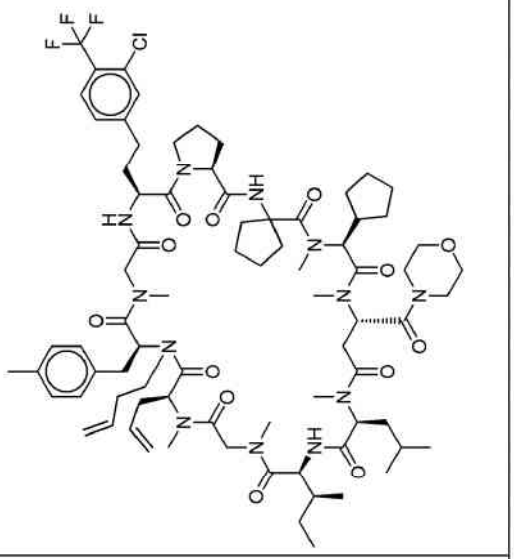
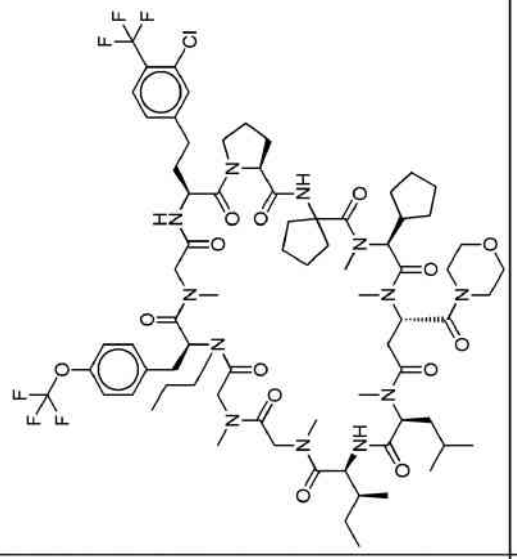
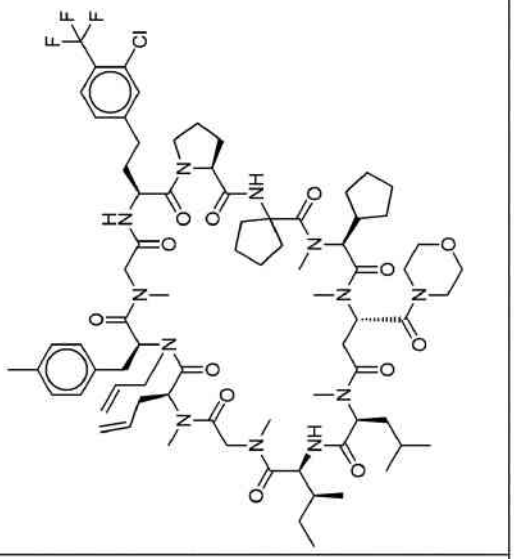
	
PP0 117	PP0 119
	
PP0 116	PP0 118

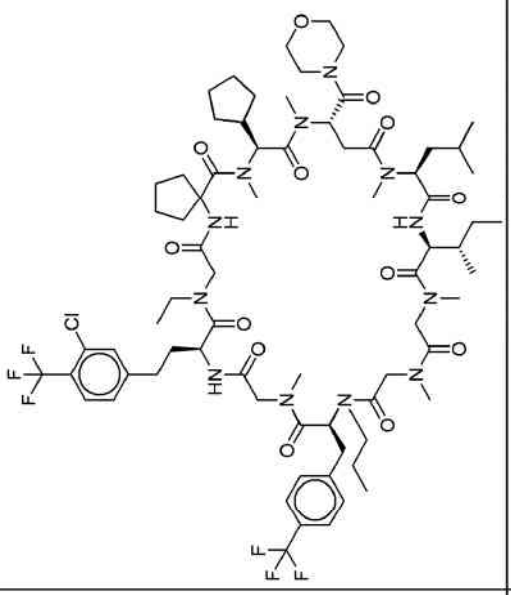
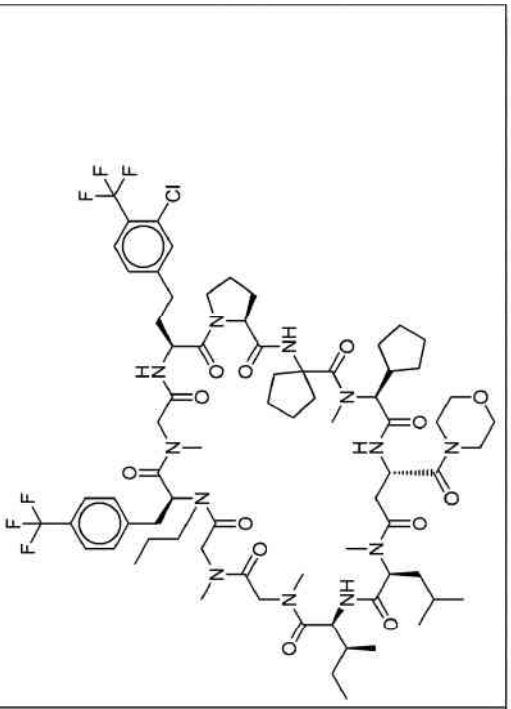
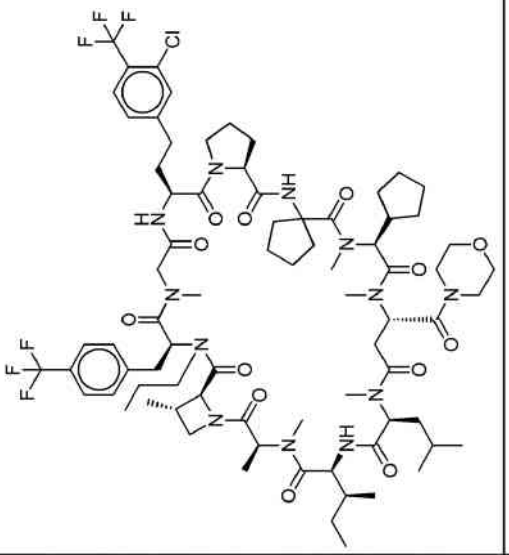
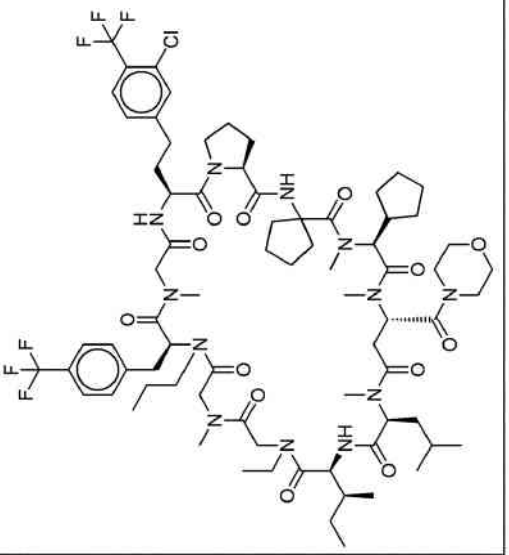
	
PP0 121	PP0 123
	
PP0 120	PP0 122

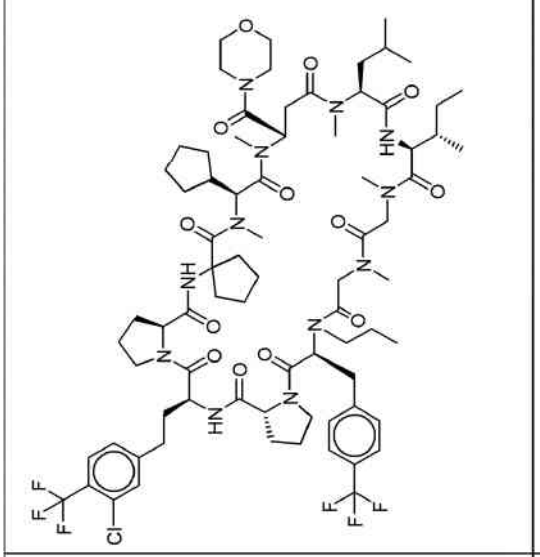
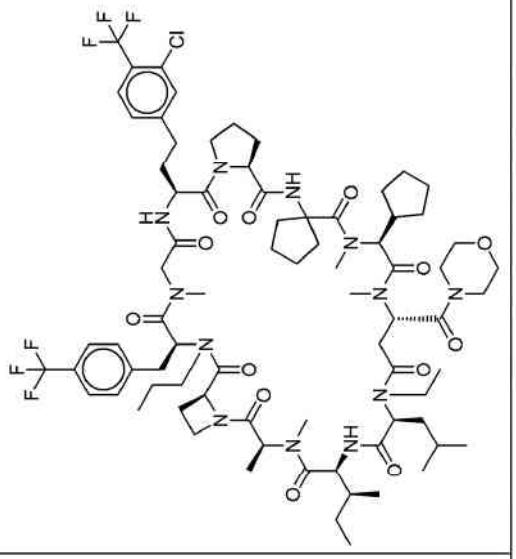
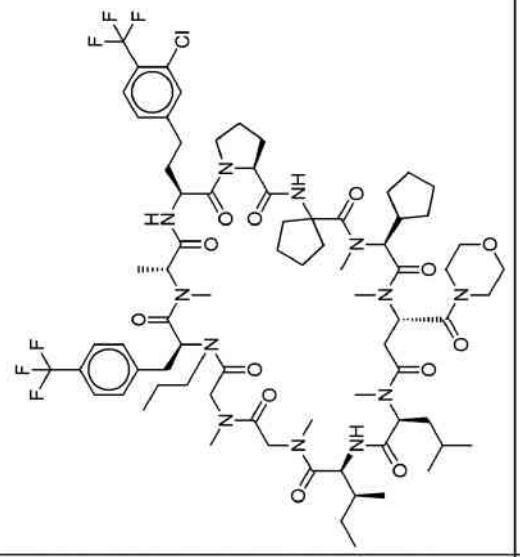
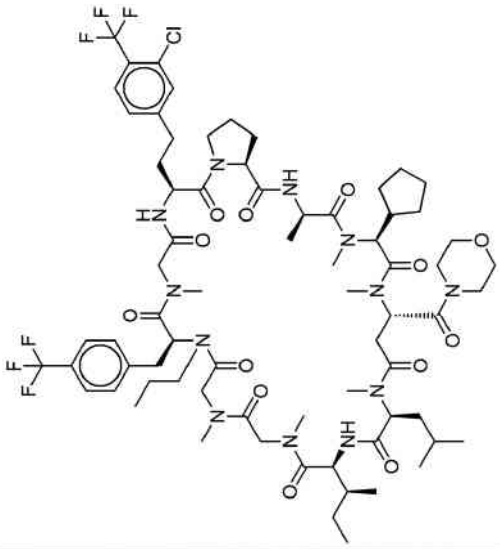
	
PP0 126	PP0 128
	
PP0 124	PP0 127

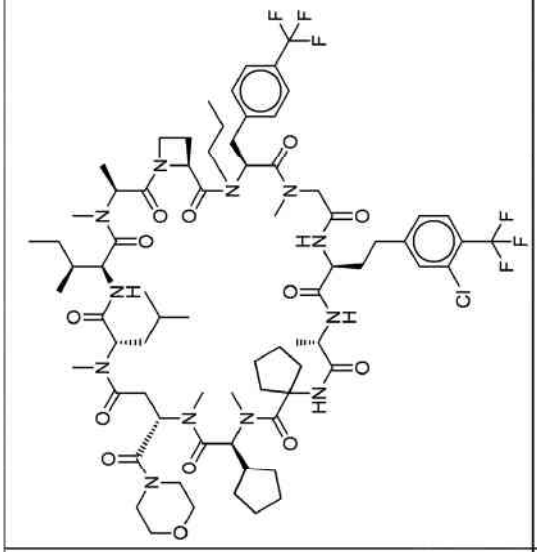
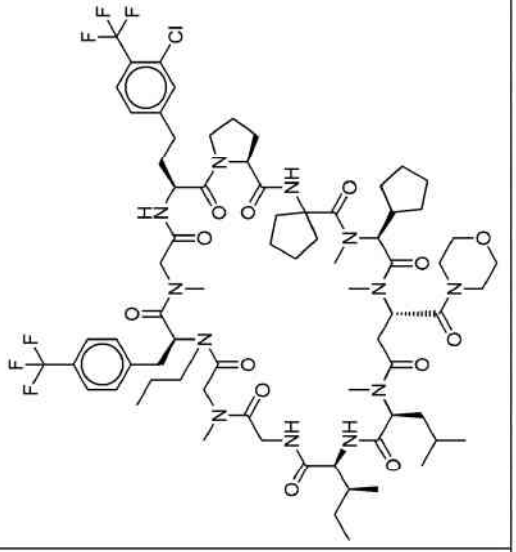
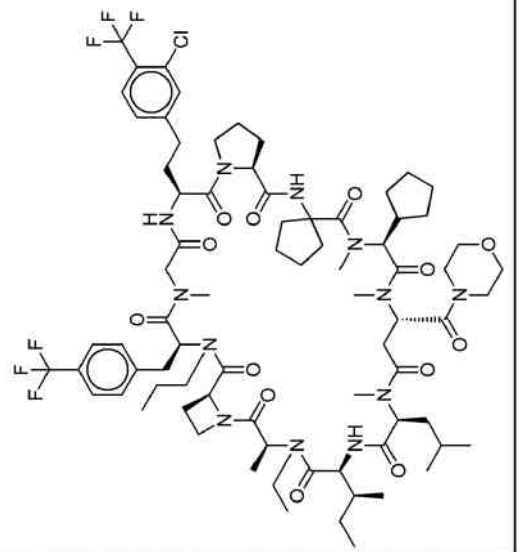
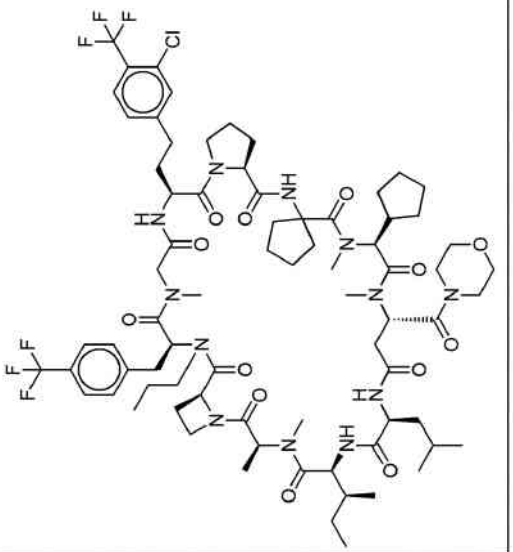
	
PP0 130	PP0 132
	
PP0 129	PP0 131

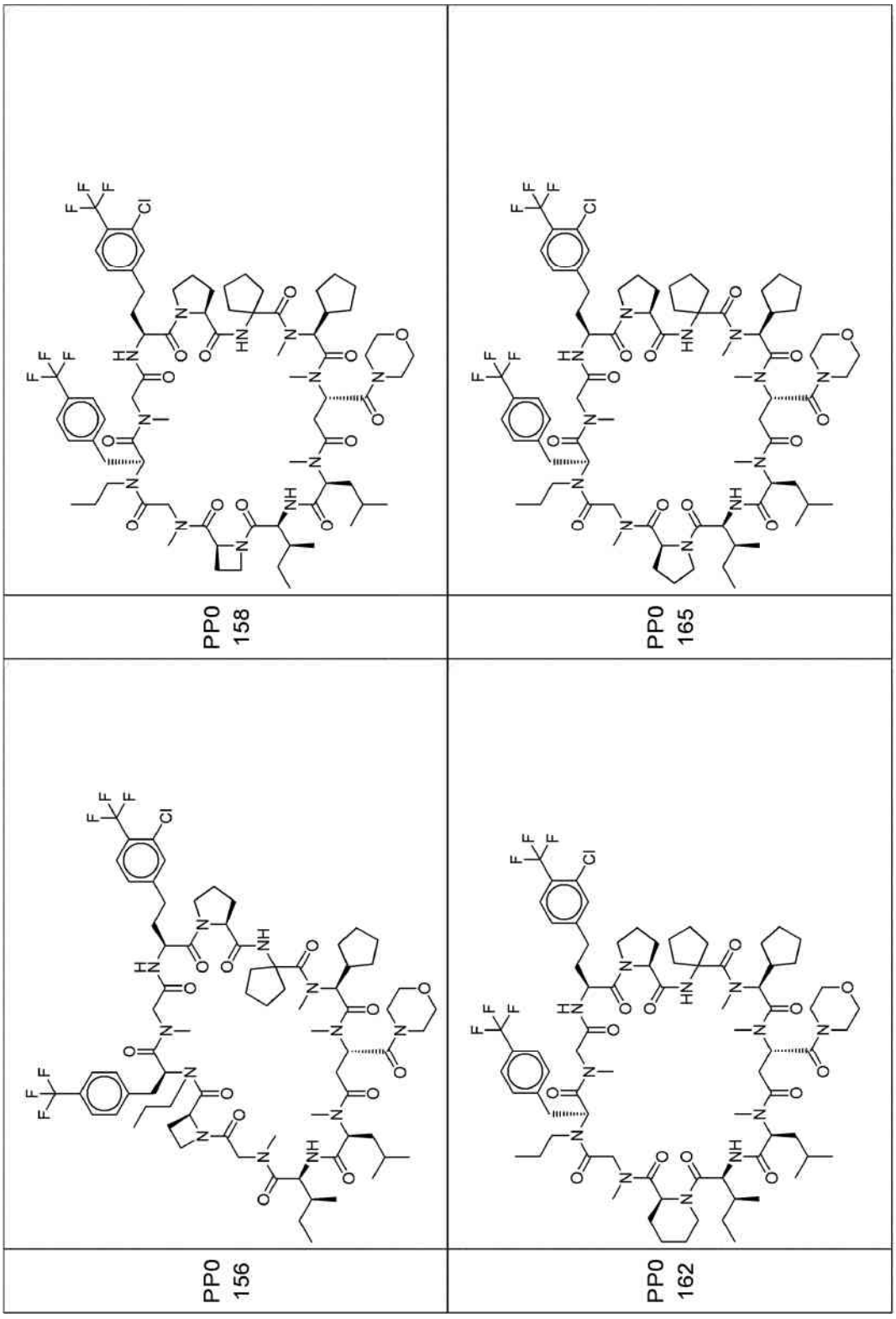
	
PP0 134	PP0 136
	
PP0 133	PP0 135

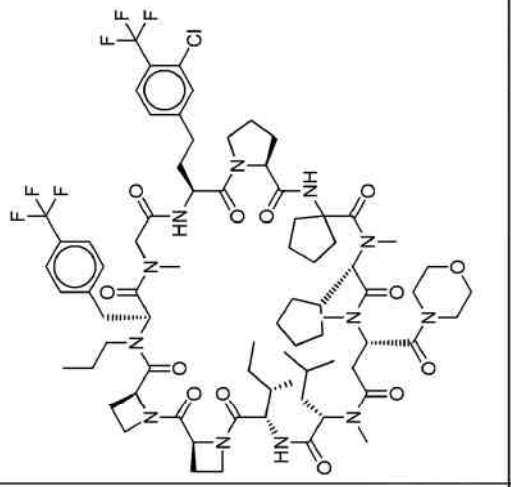
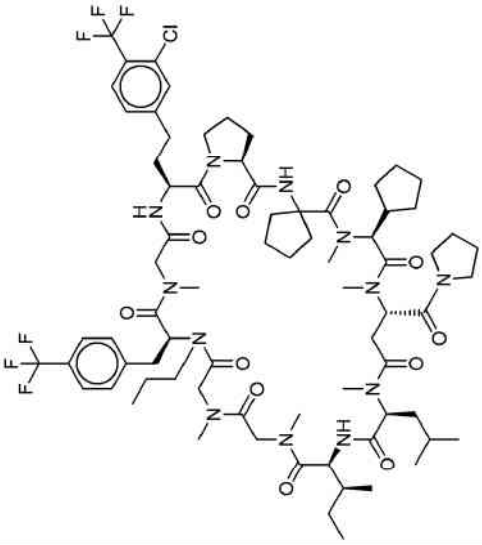
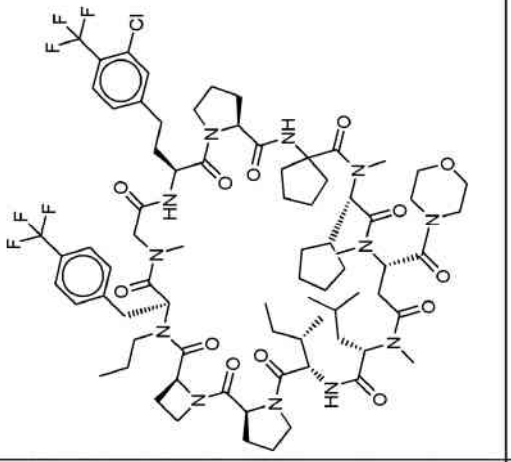
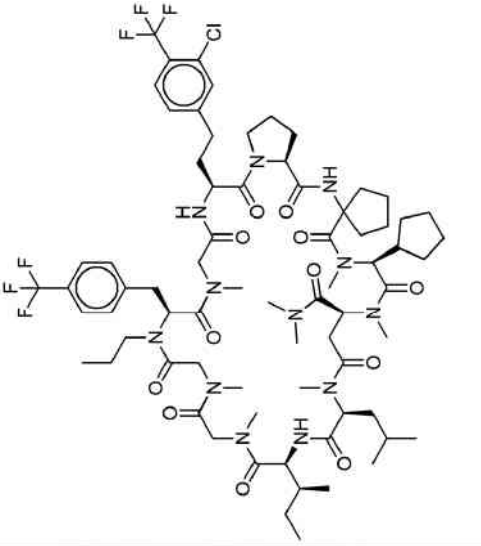
	
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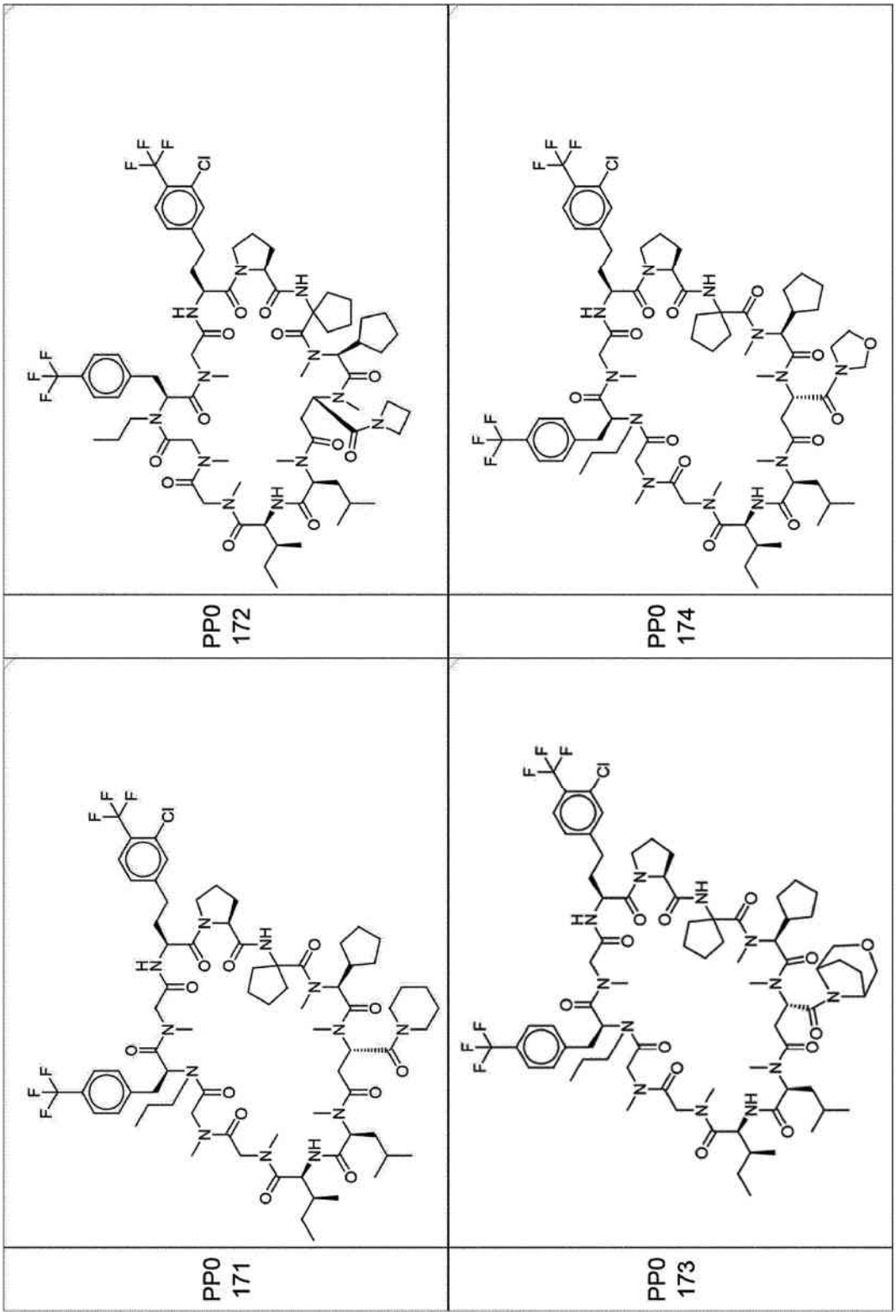
	
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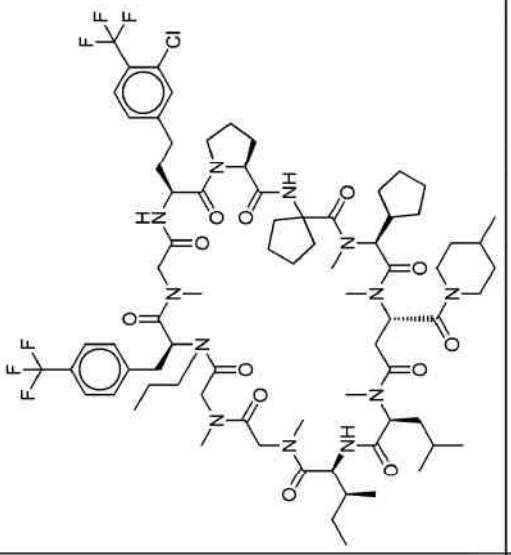
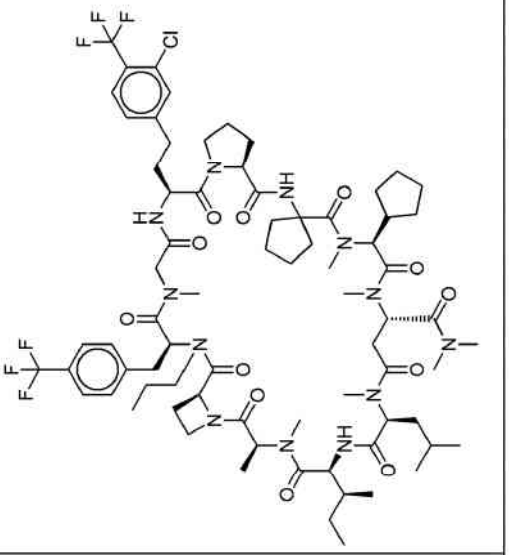
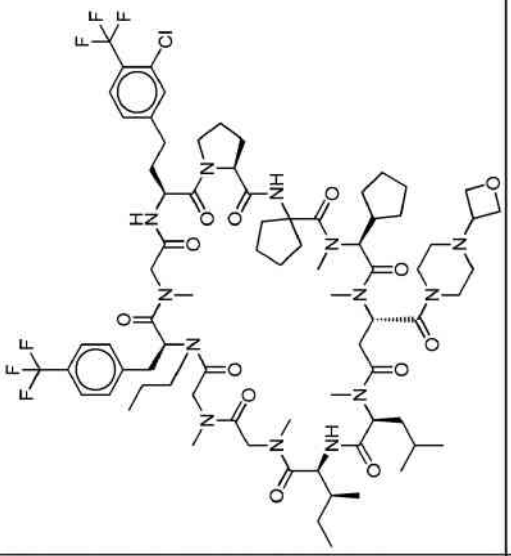
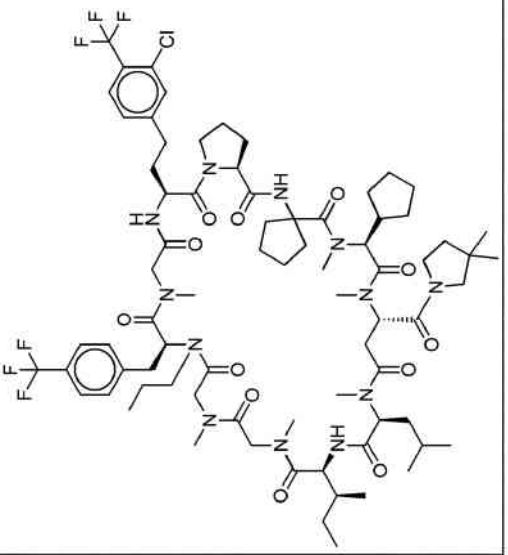
	
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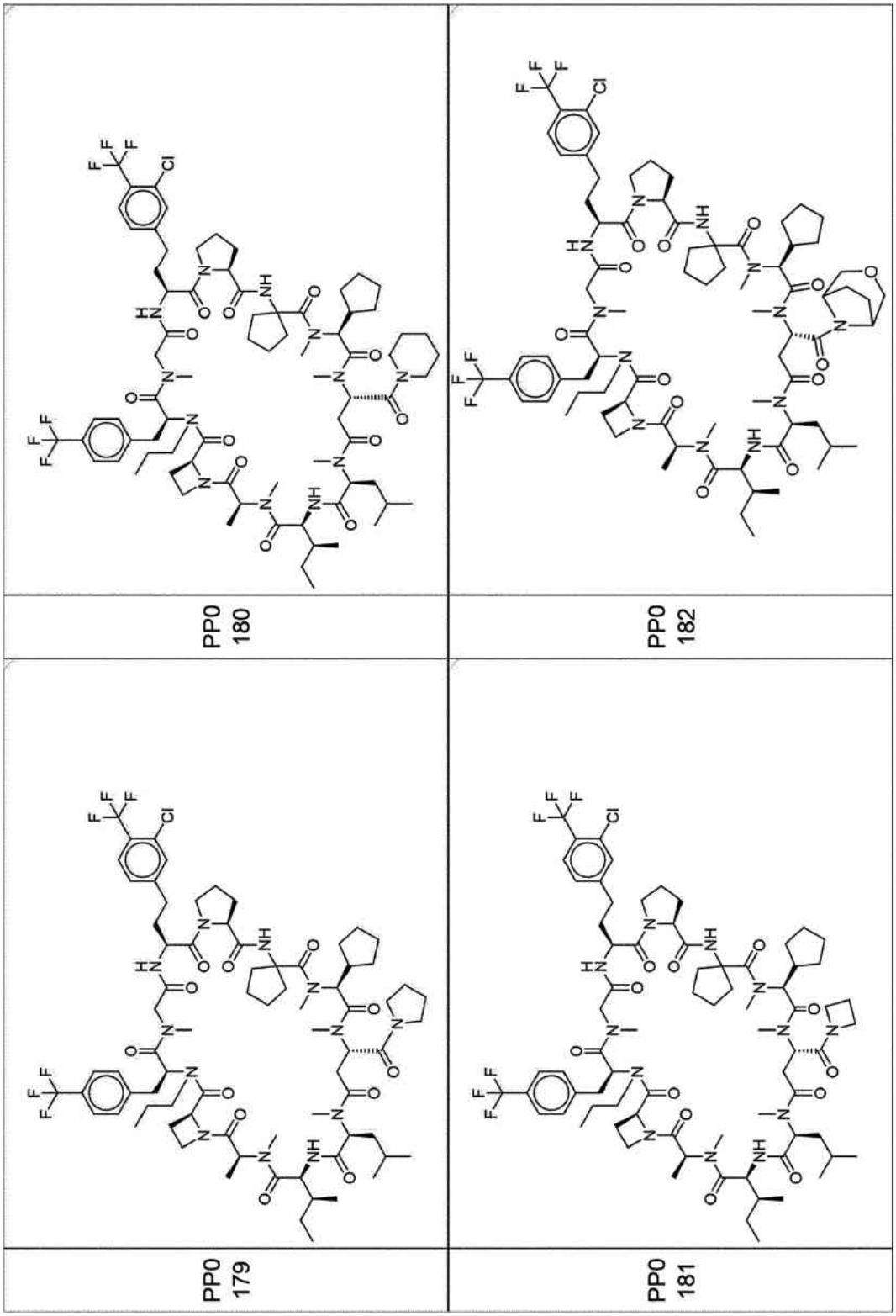
	
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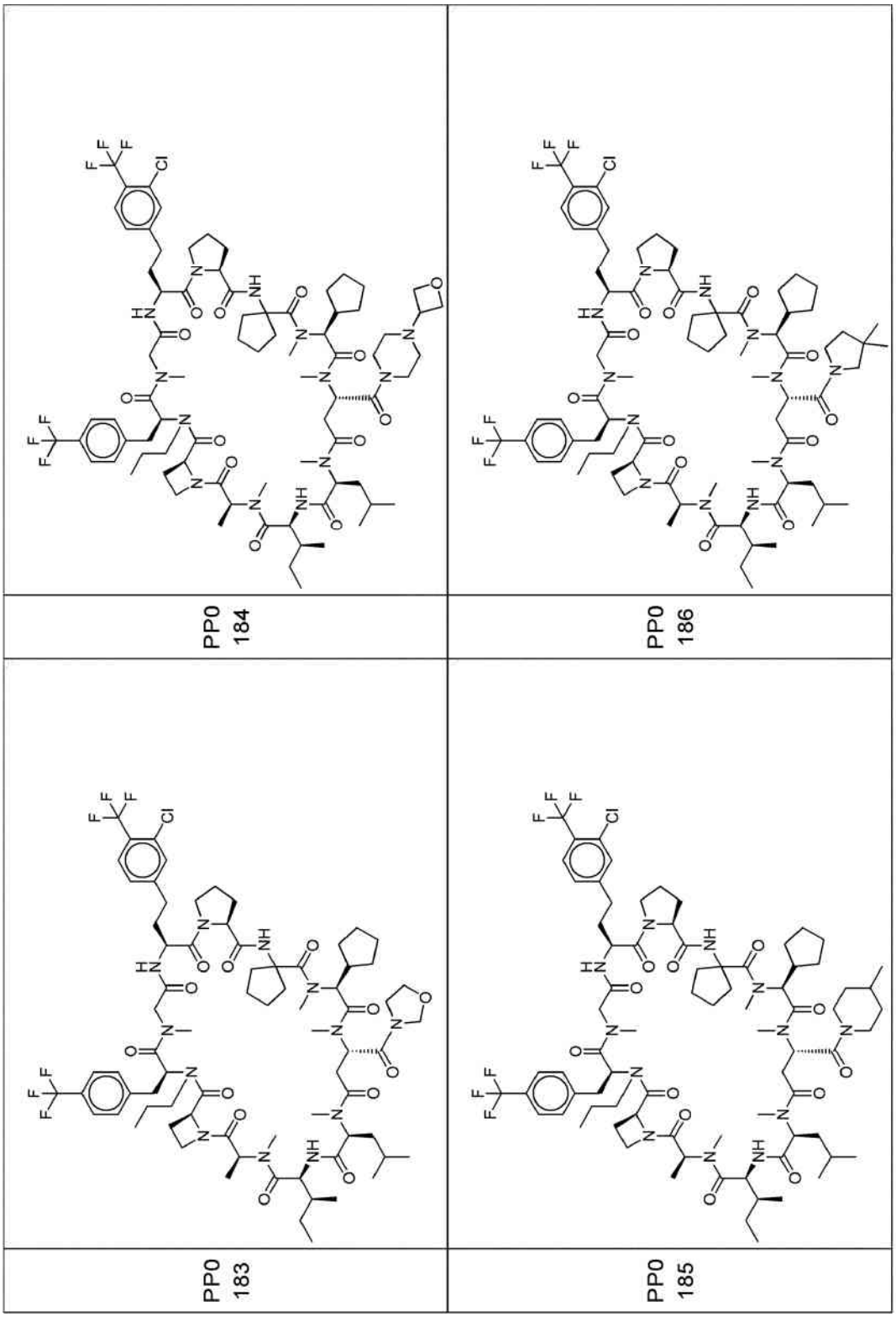

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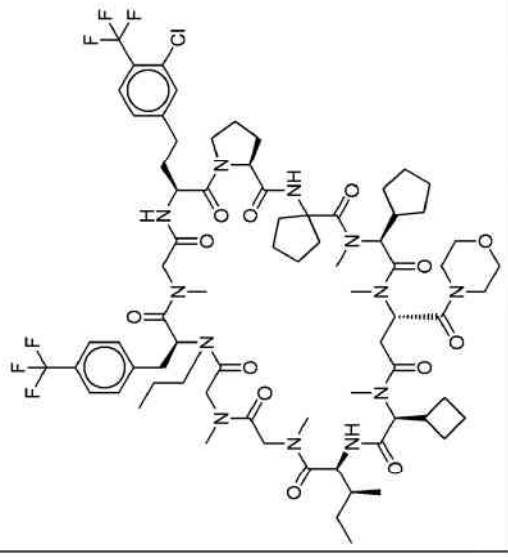
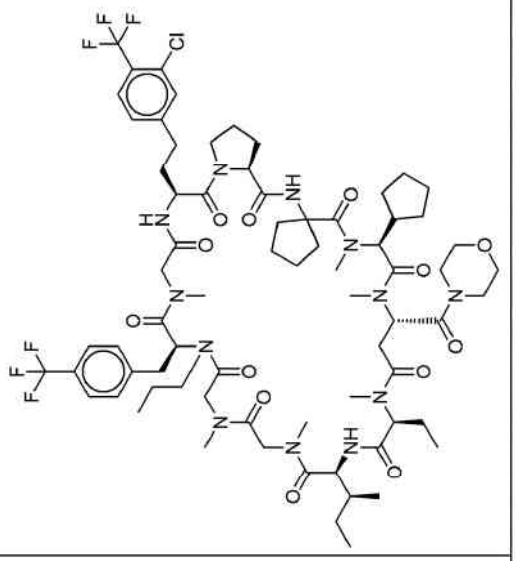
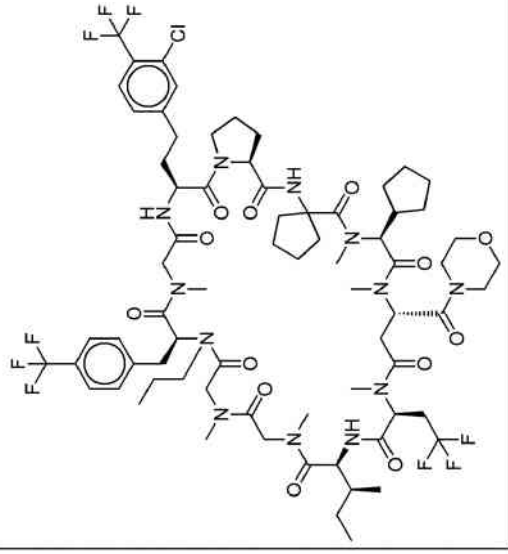
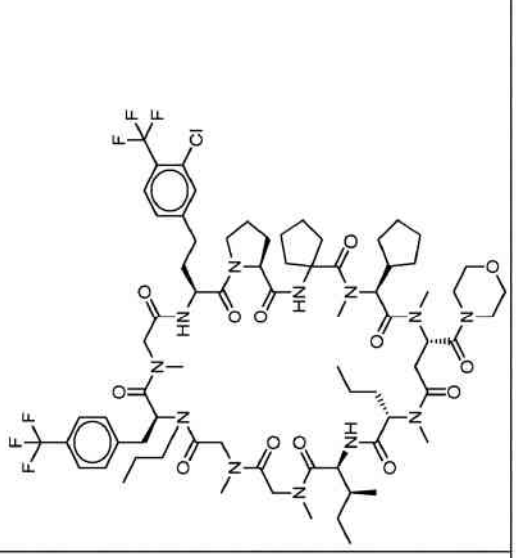
	
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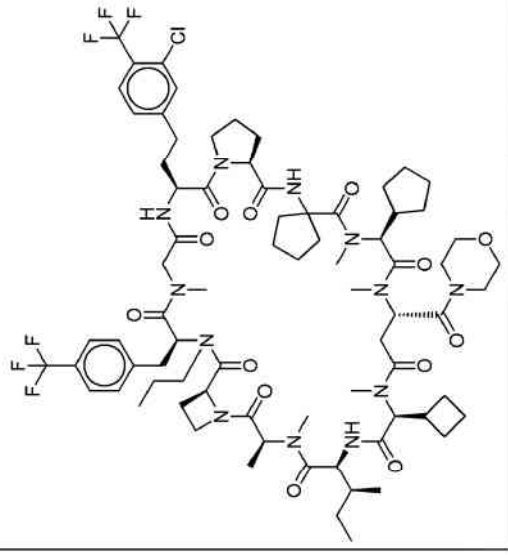
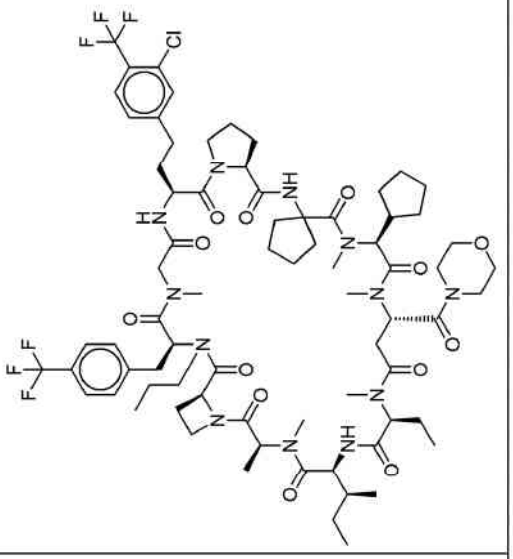
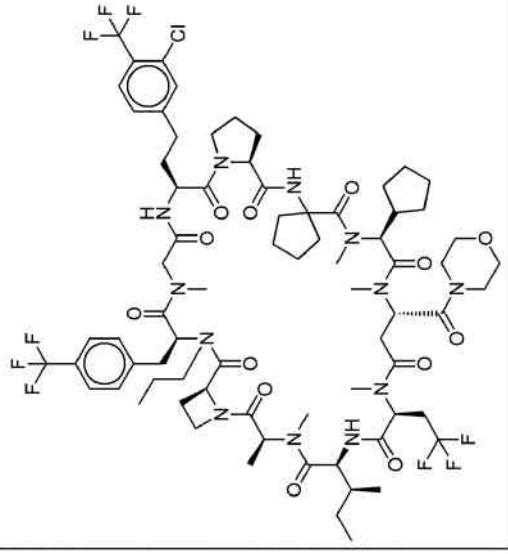
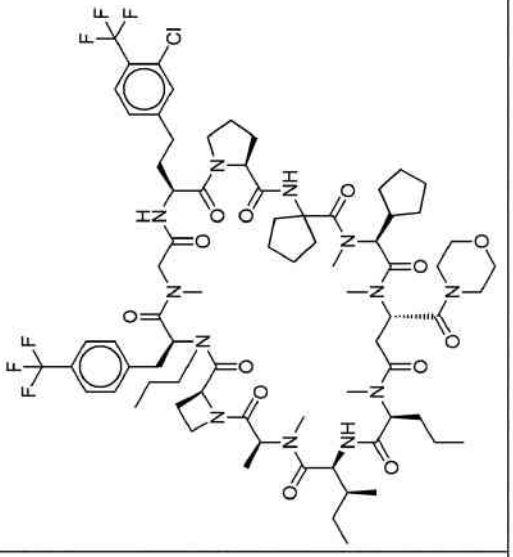

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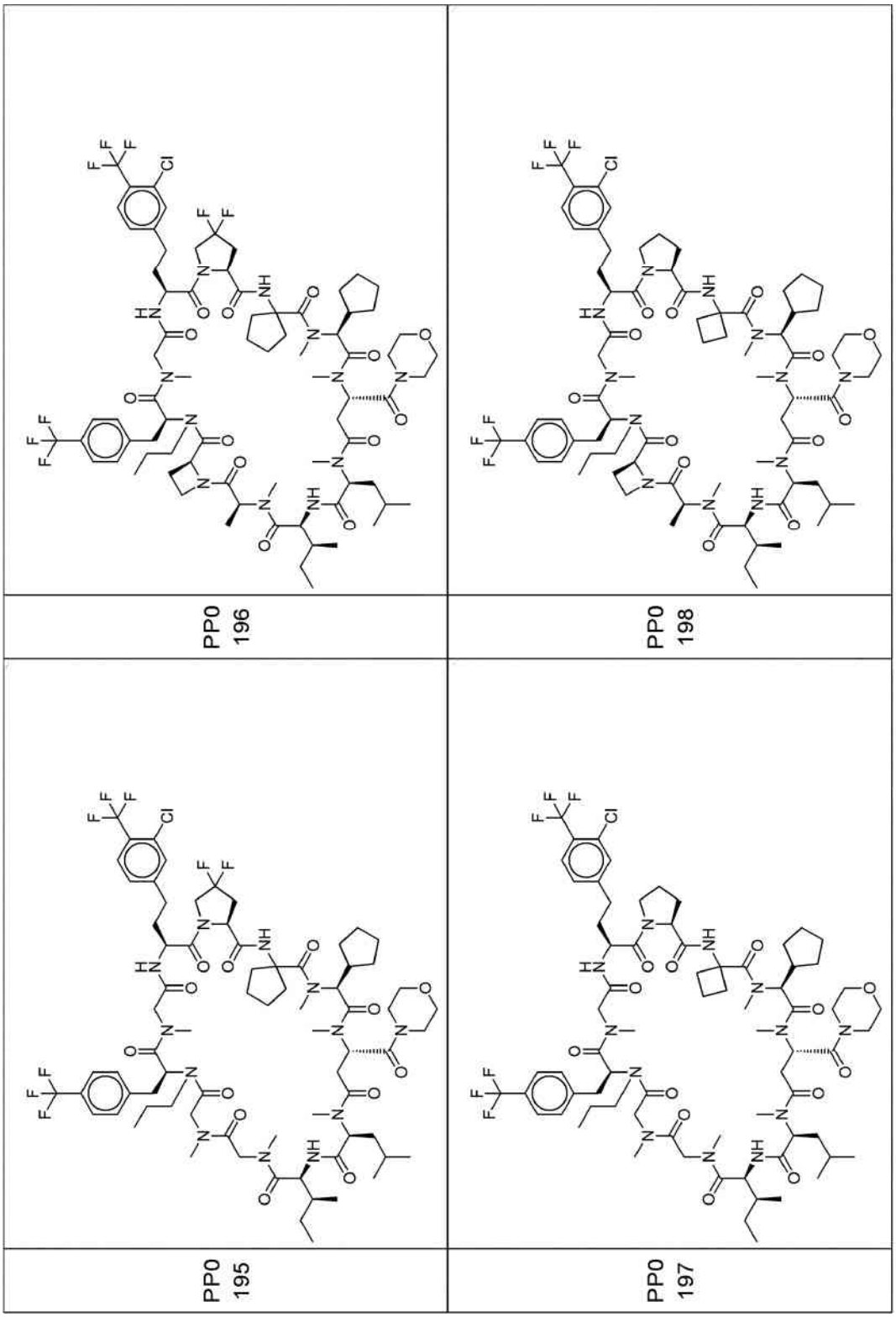
	
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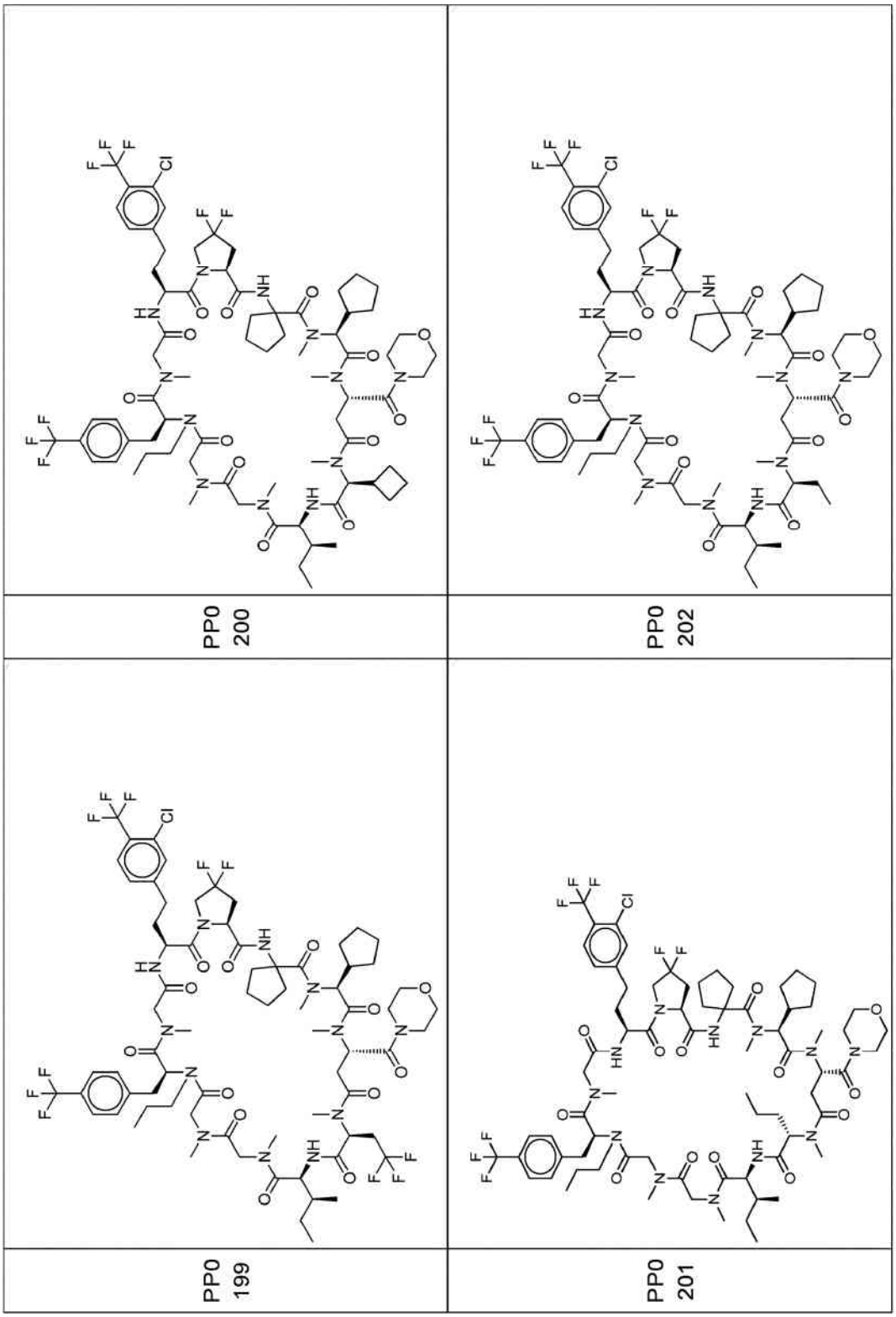

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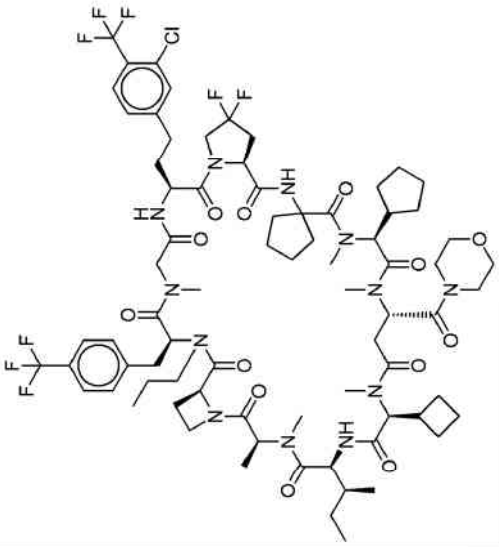
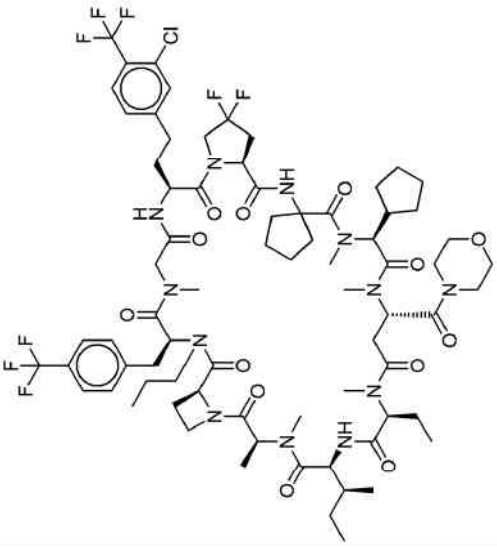
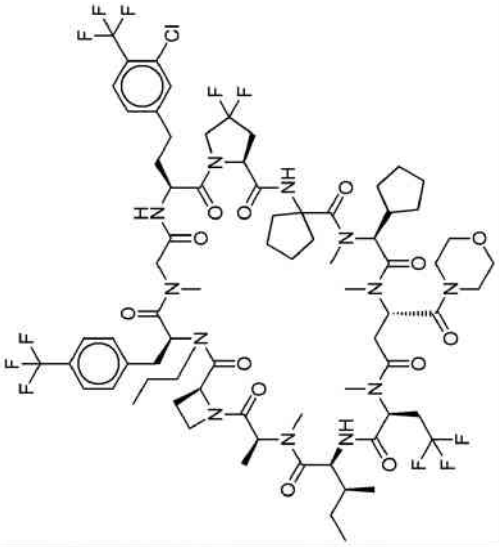
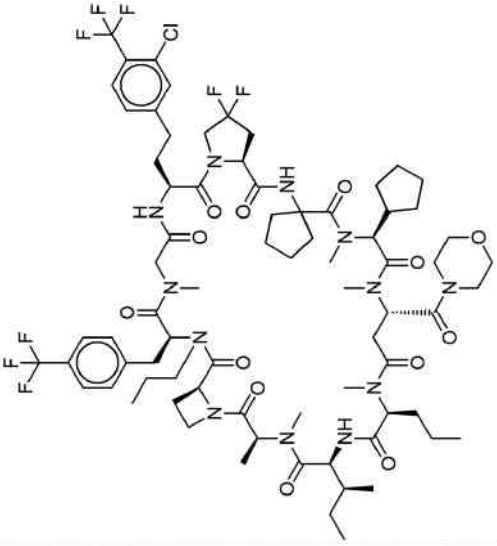

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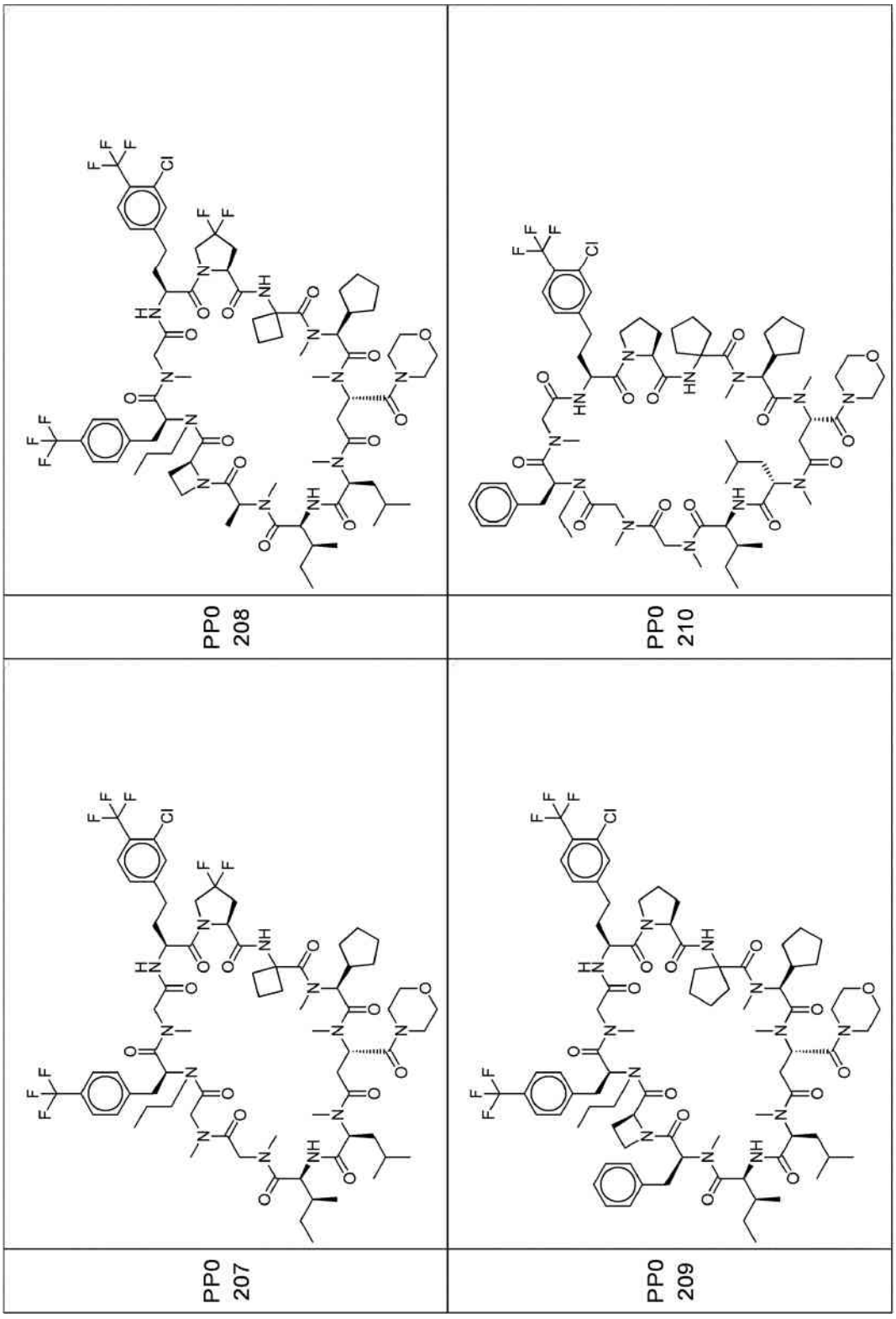
	
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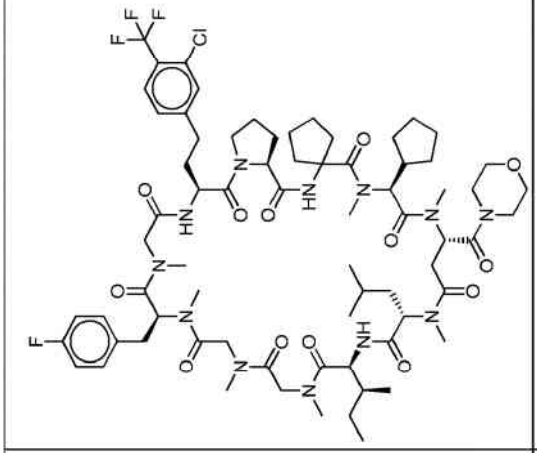
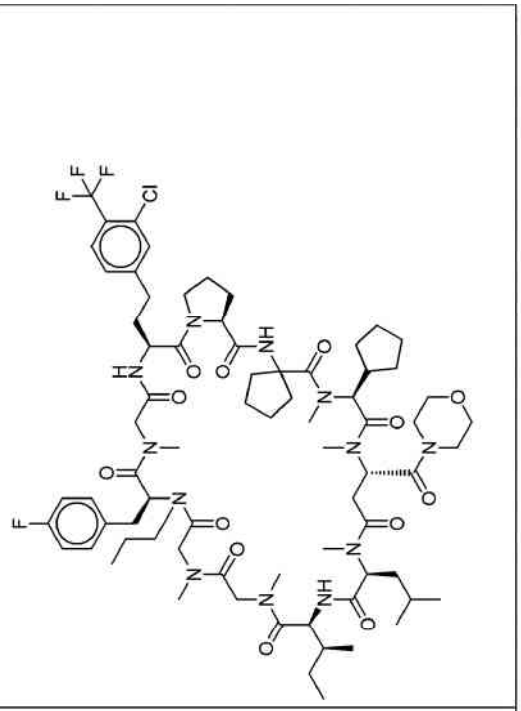
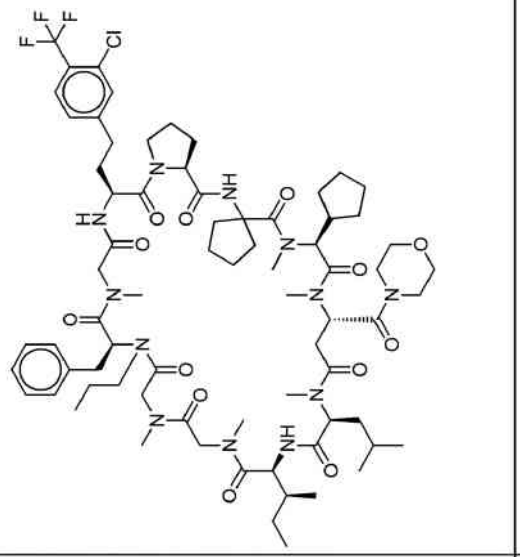
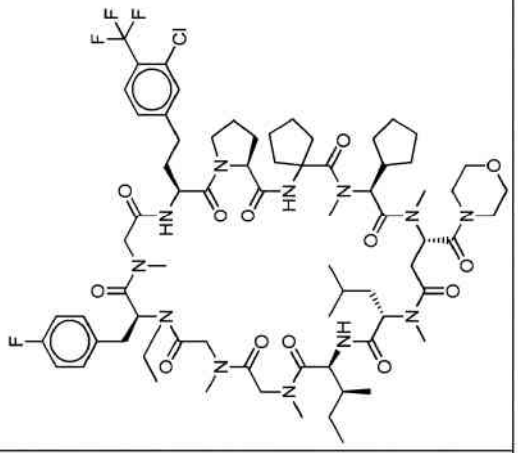
	
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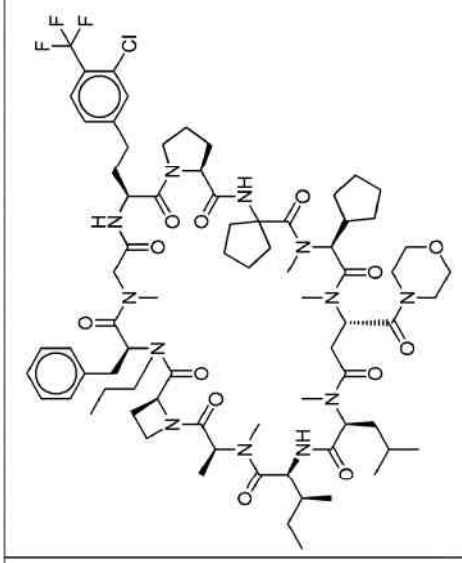
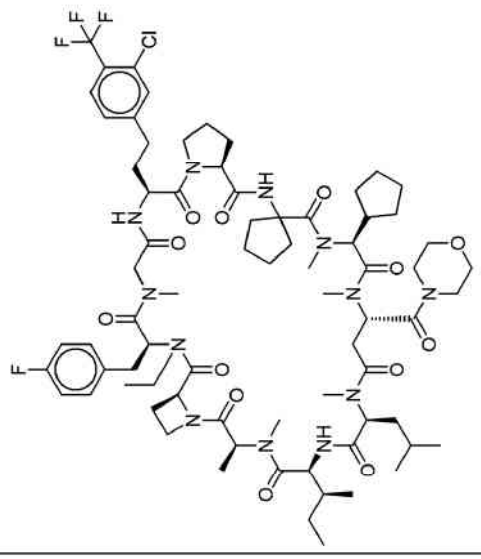
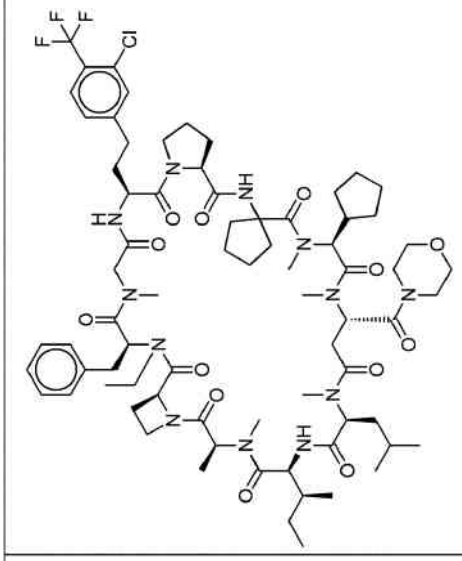
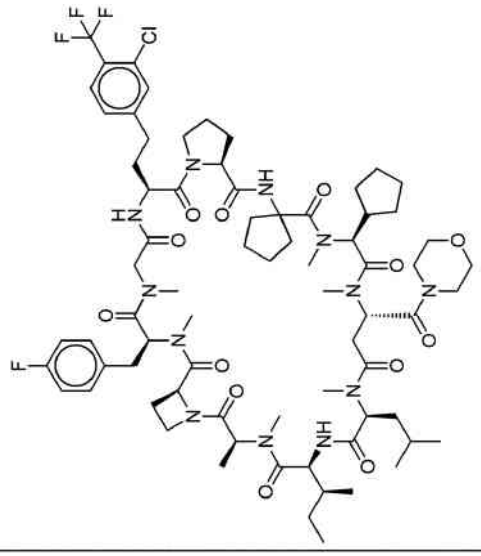

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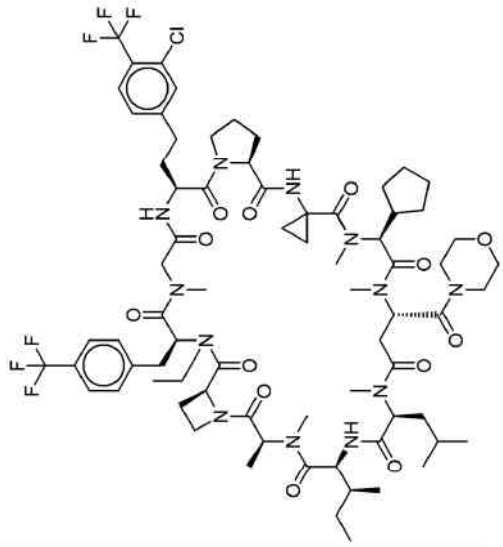
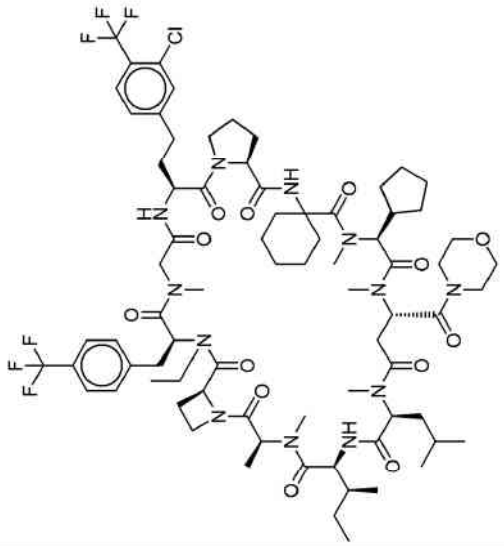
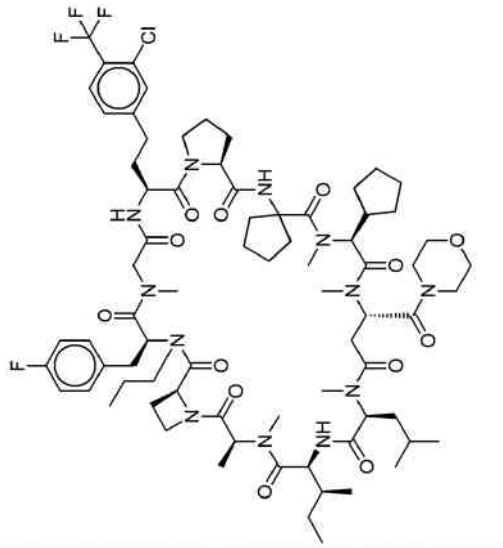
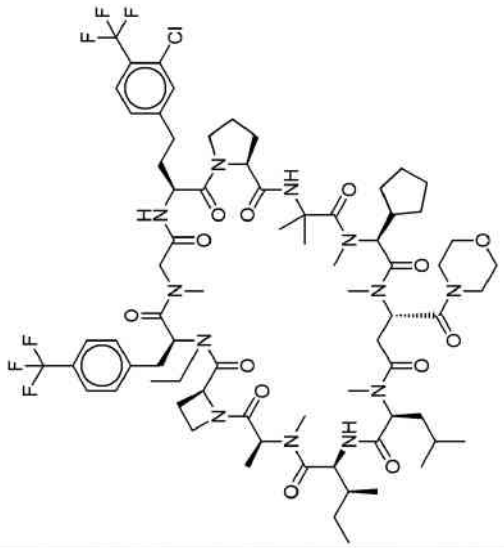

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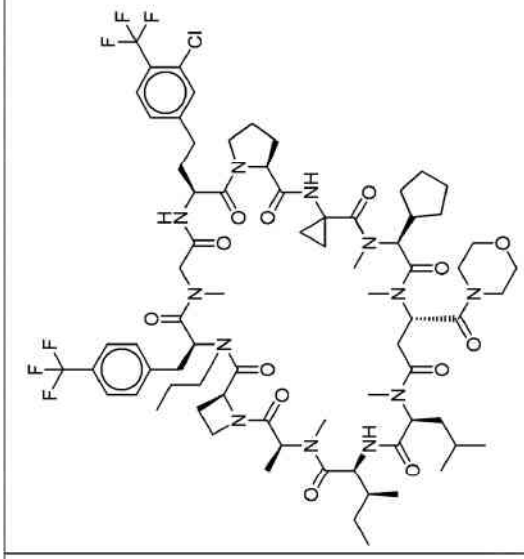
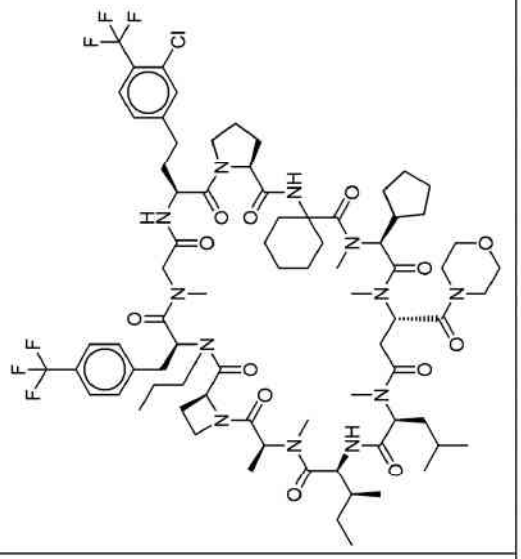
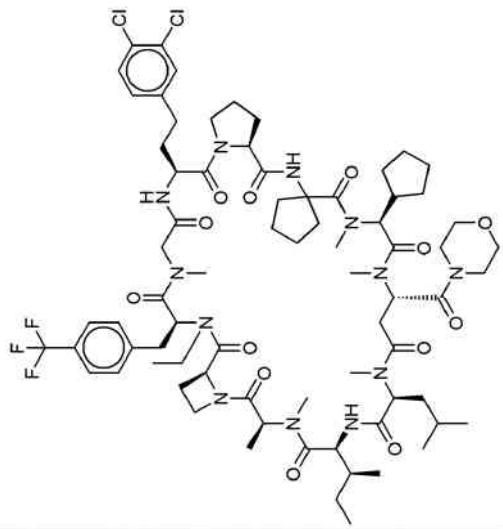
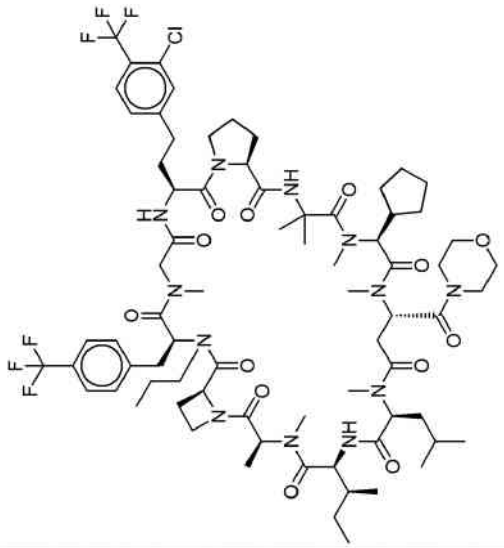
	
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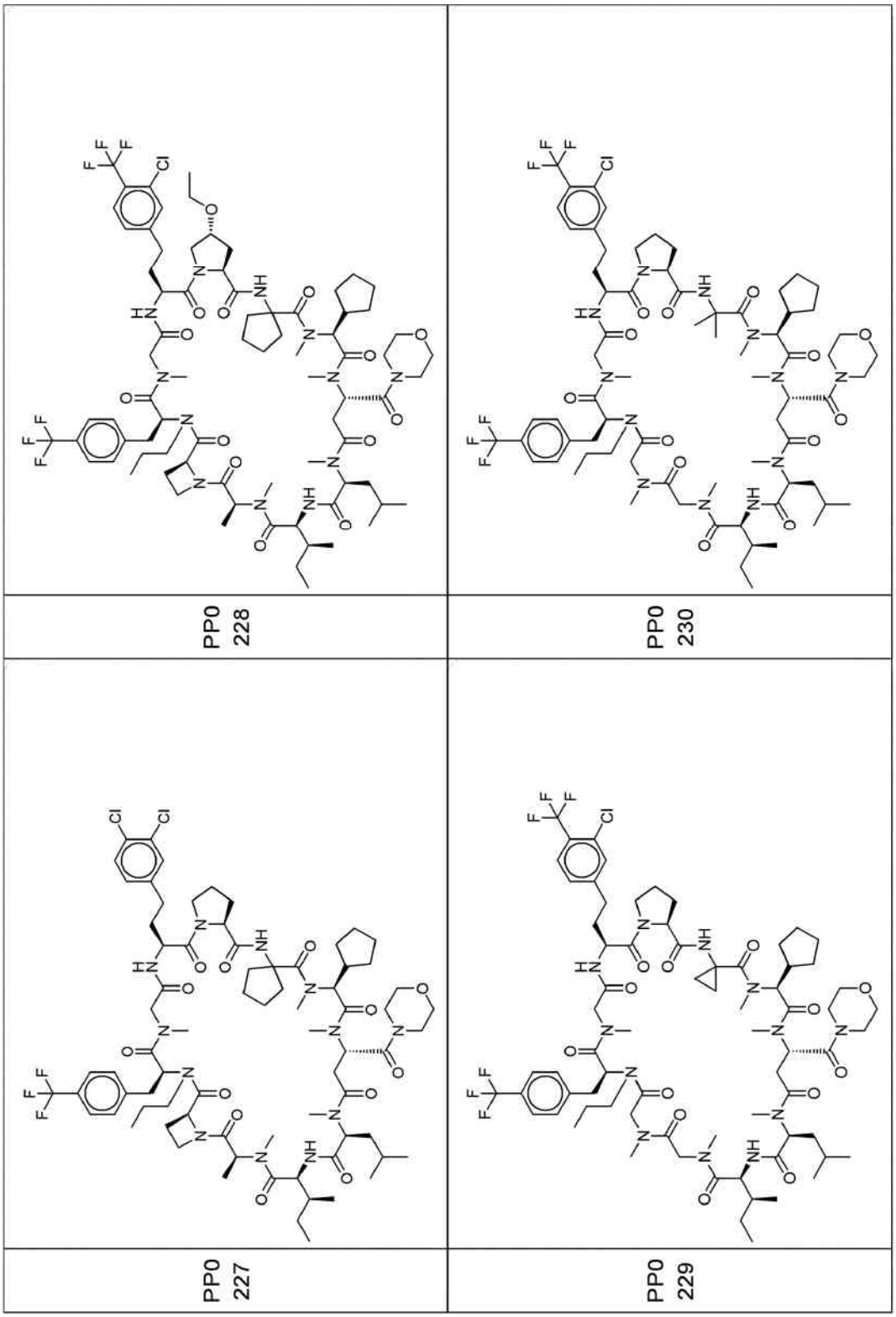

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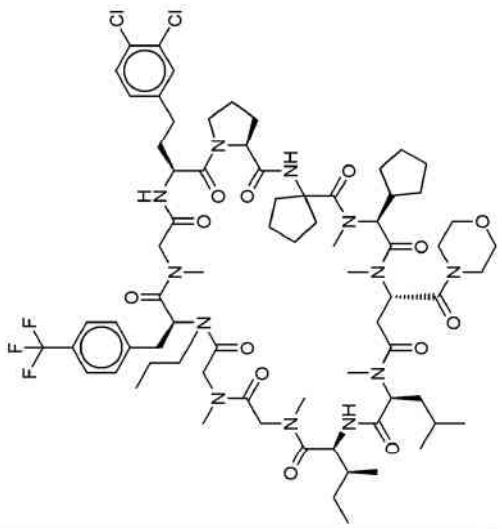
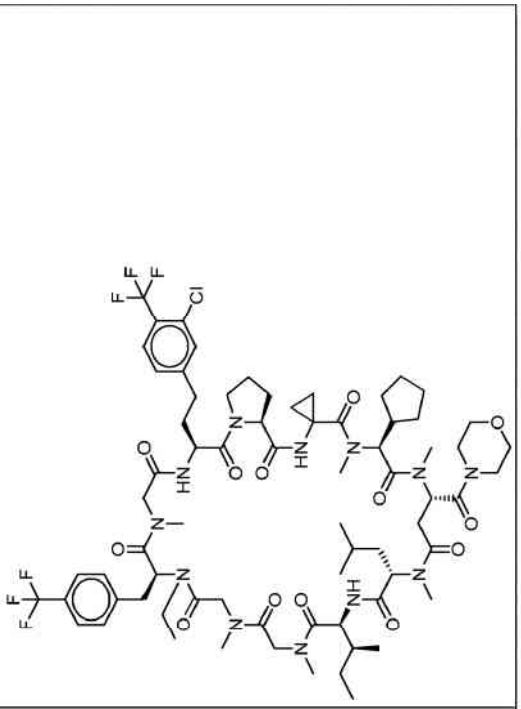
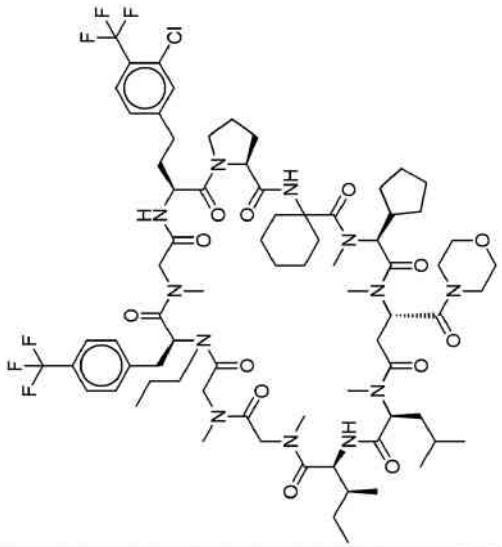
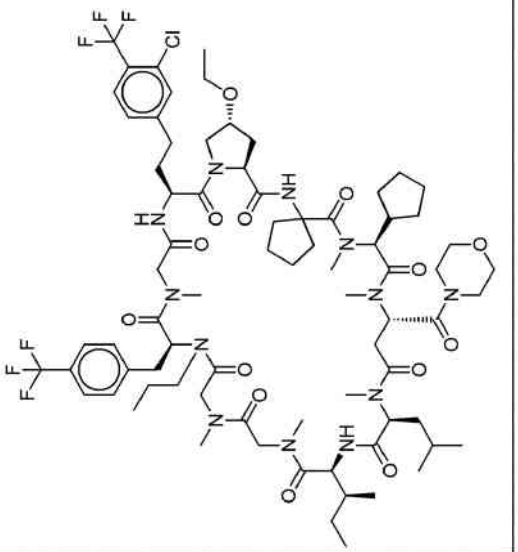
	
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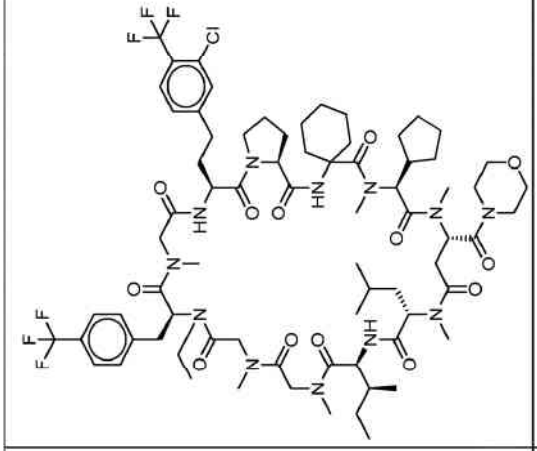
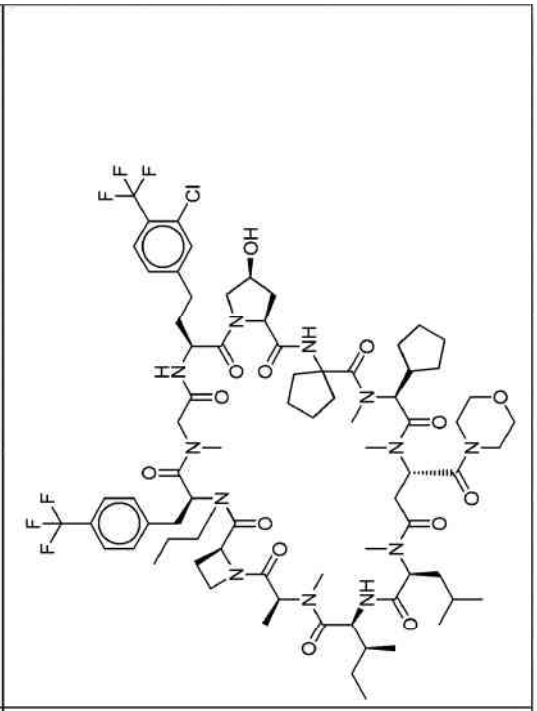
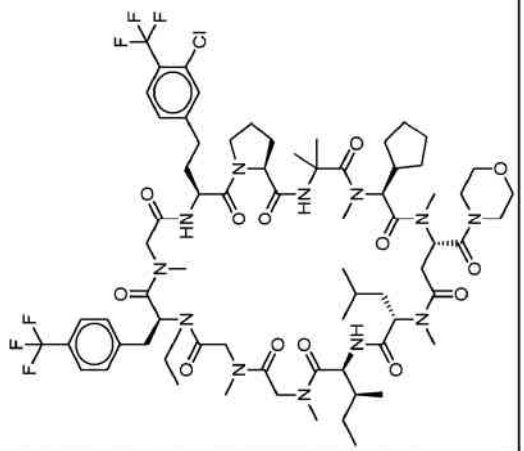
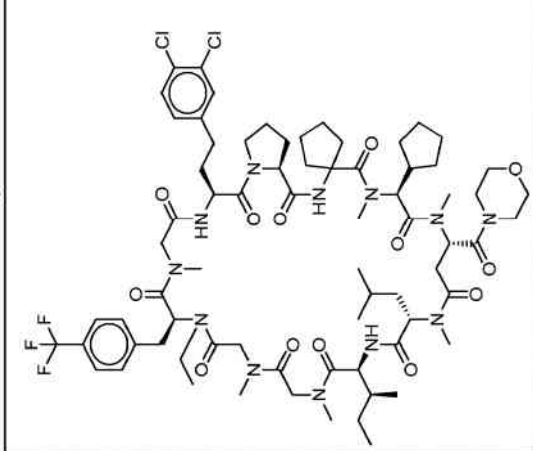
	
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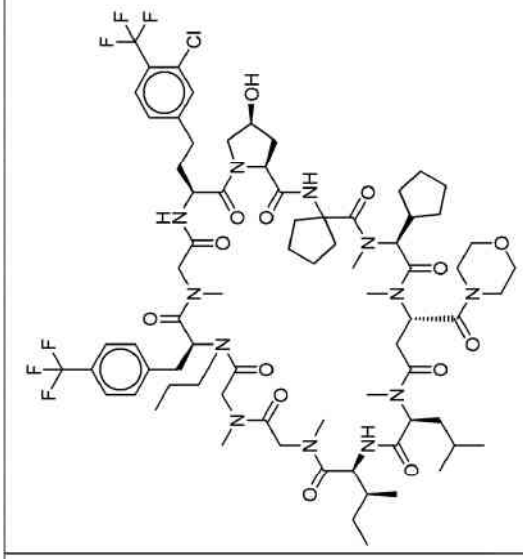
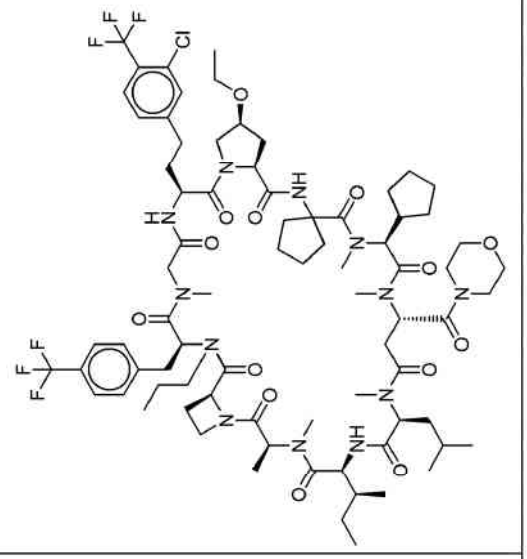
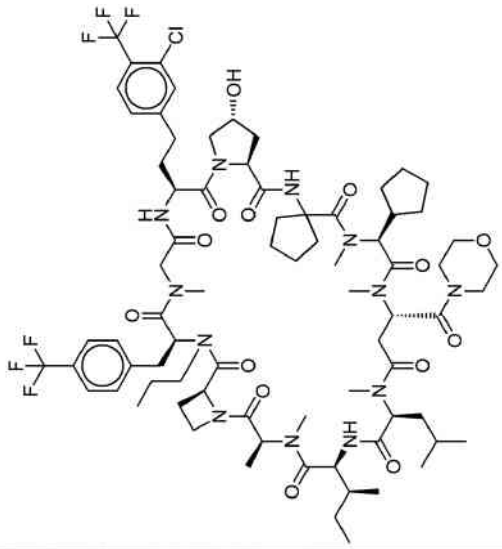
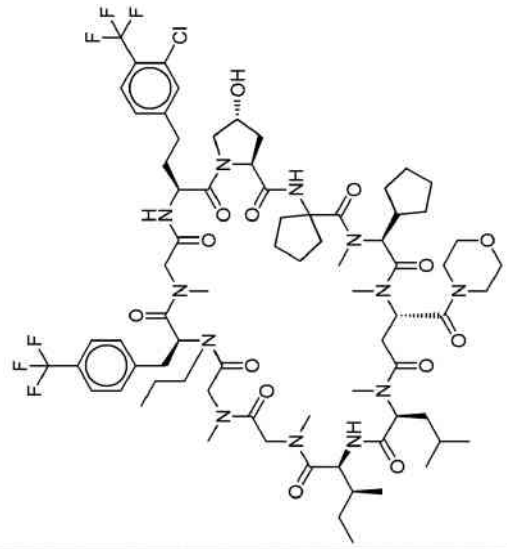
	
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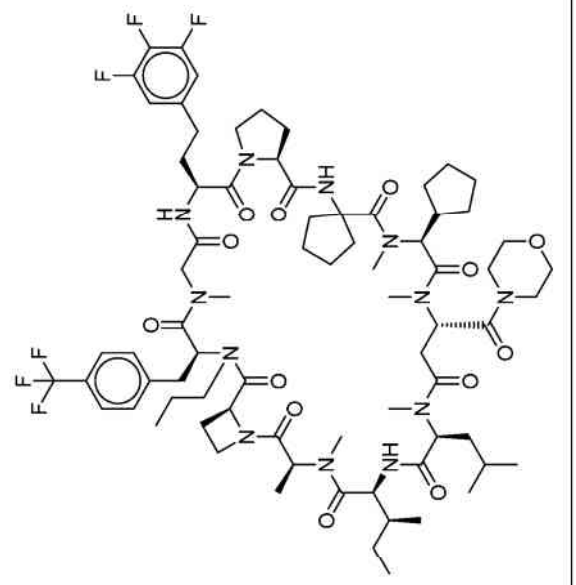
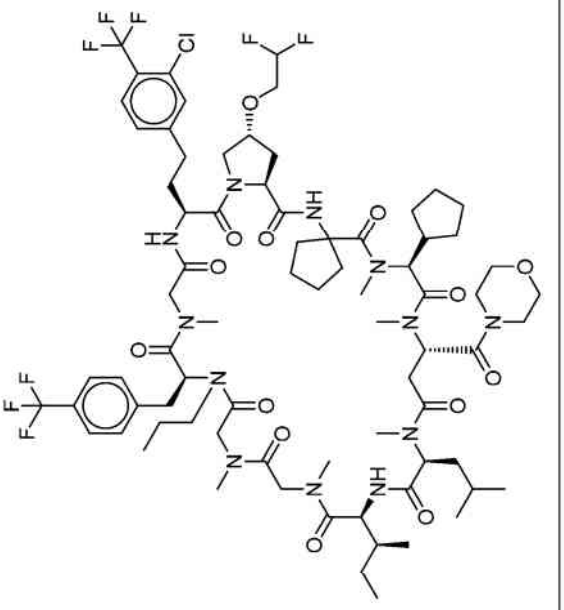
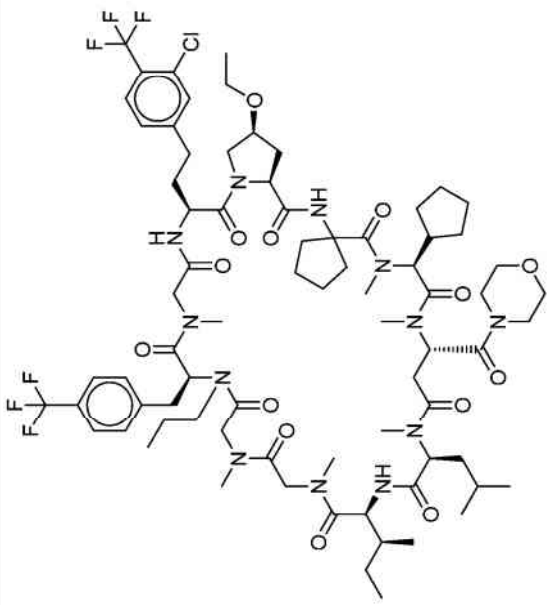
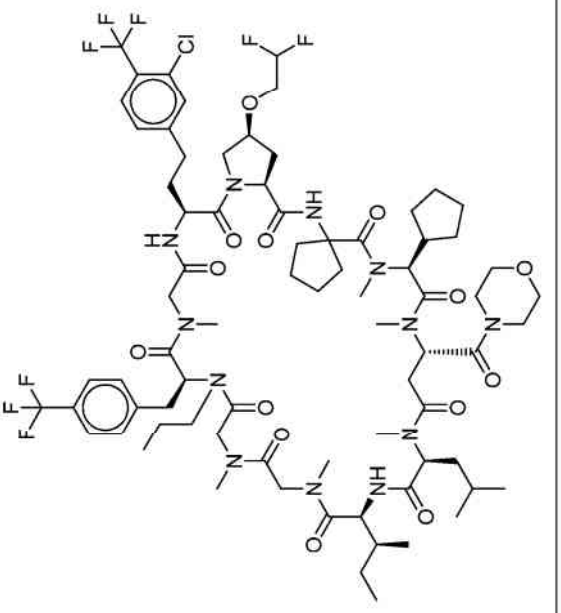
	
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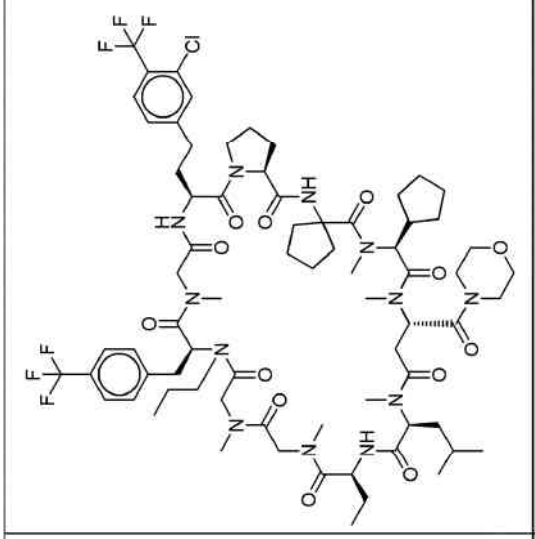
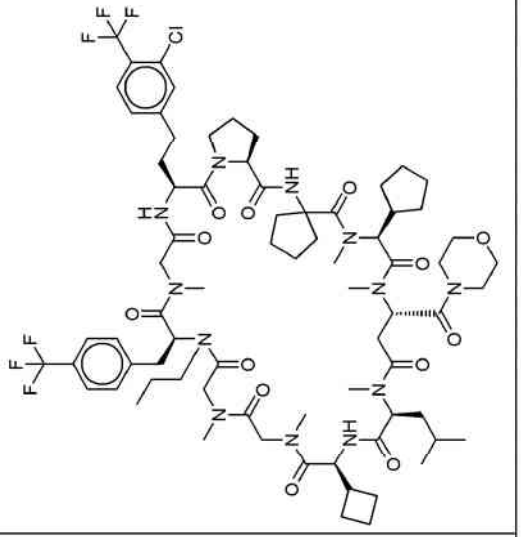
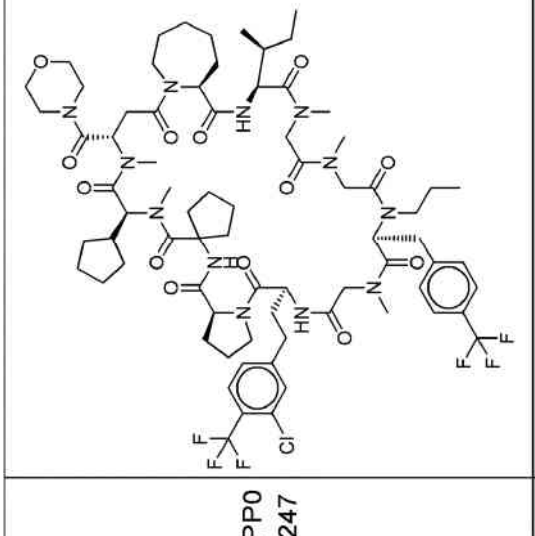
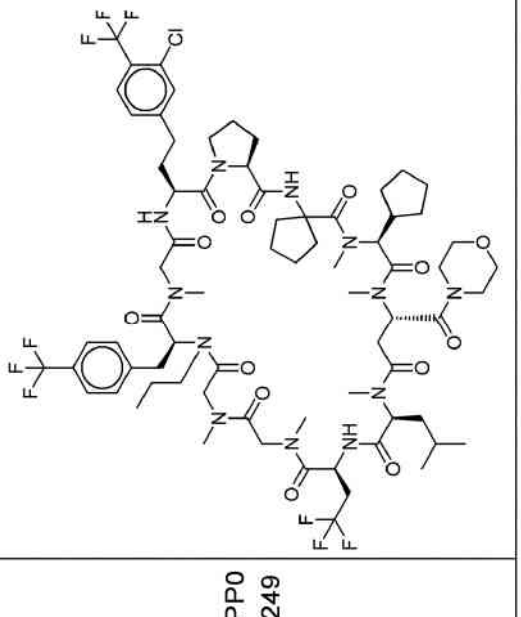

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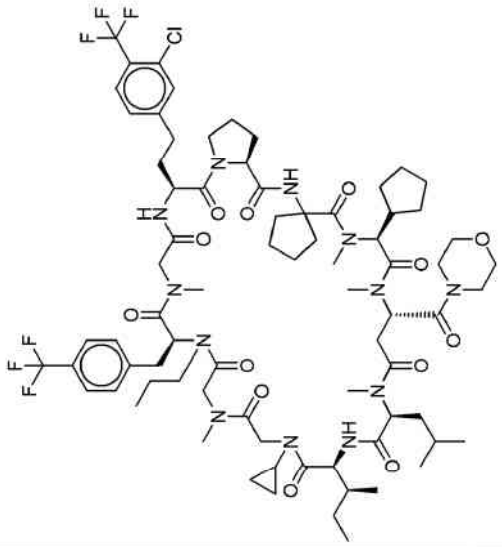
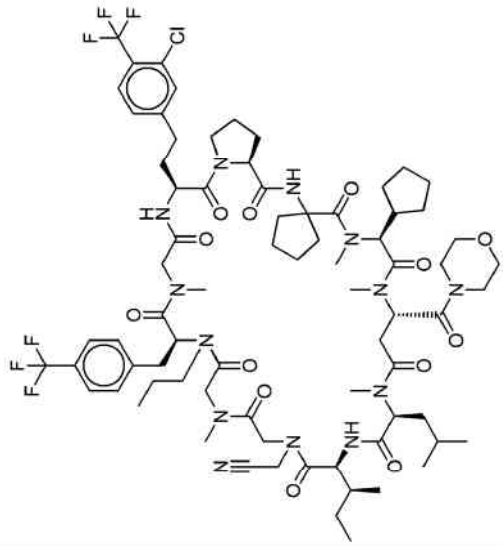
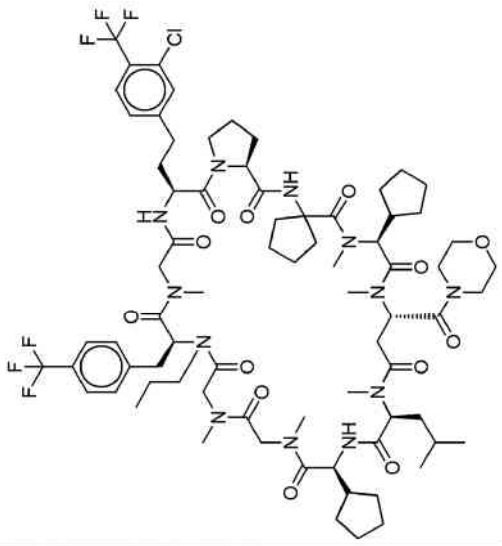
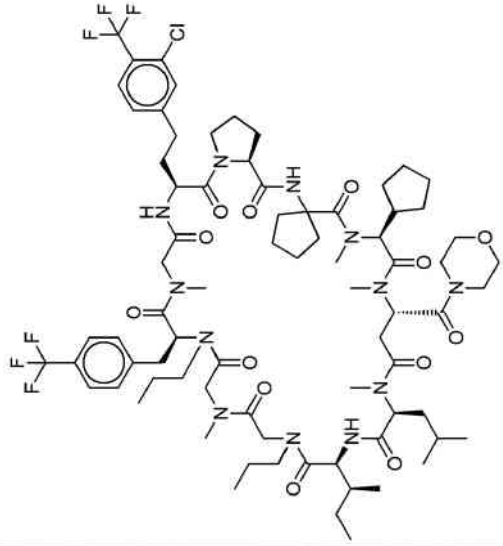
	
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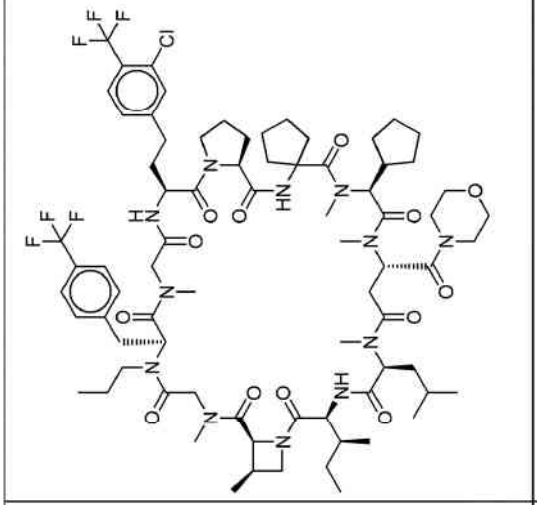
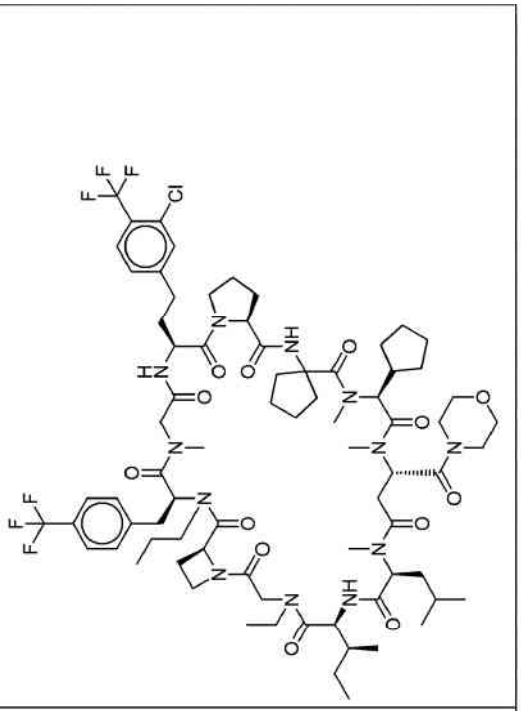
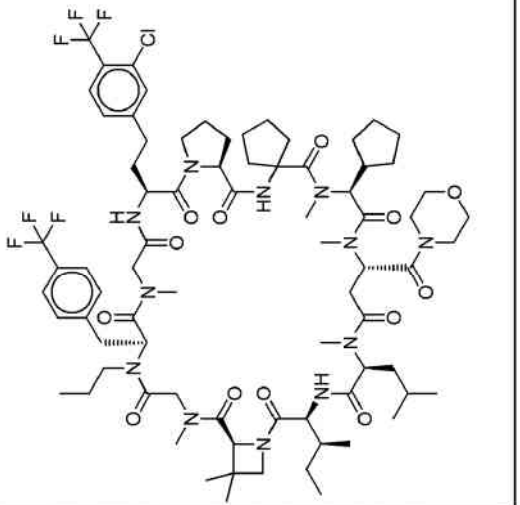
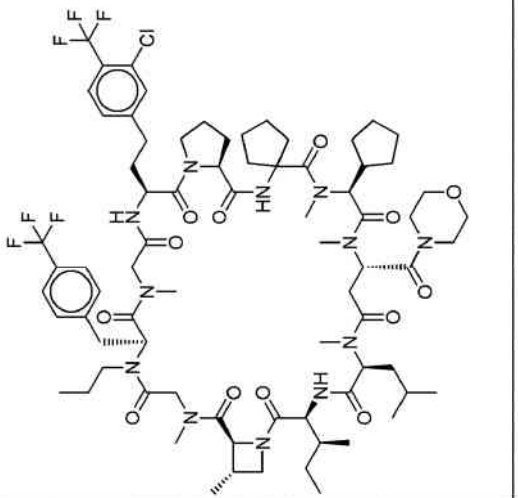
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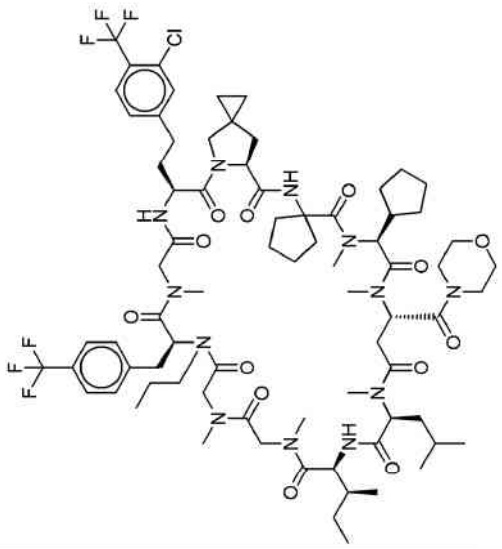
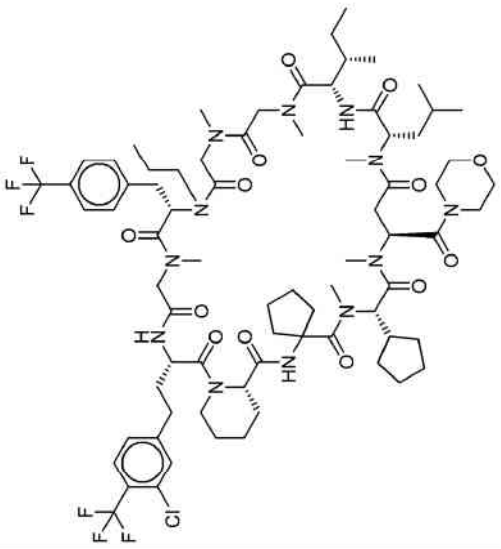
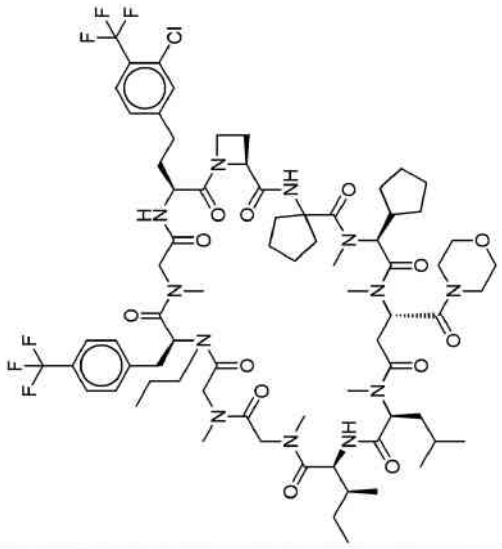
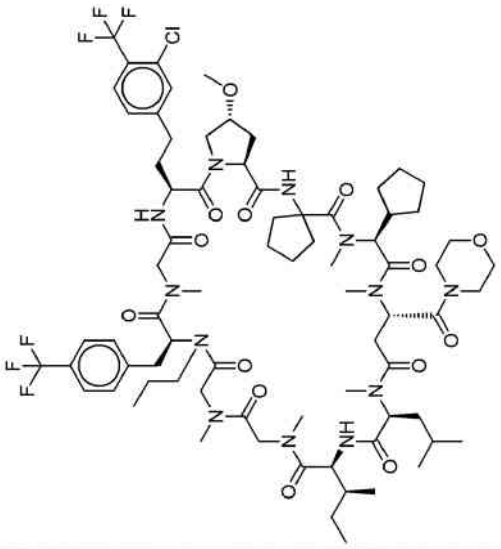
	
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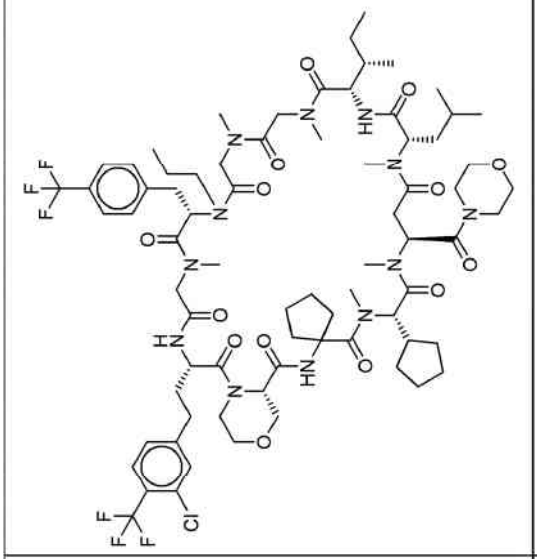
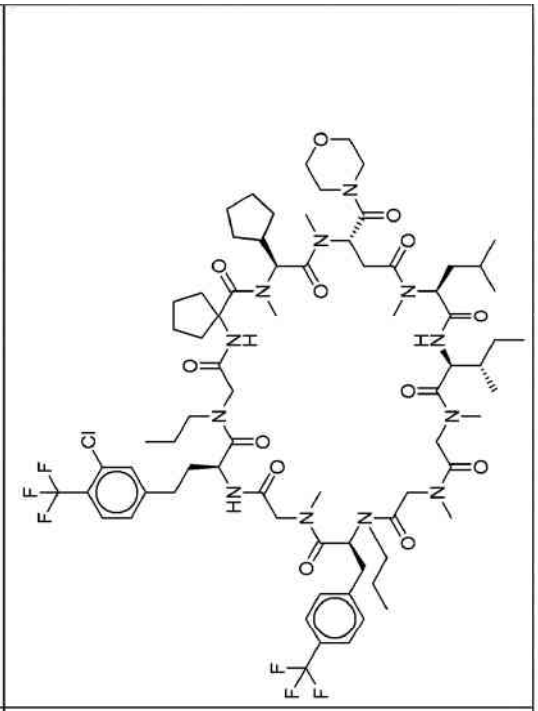
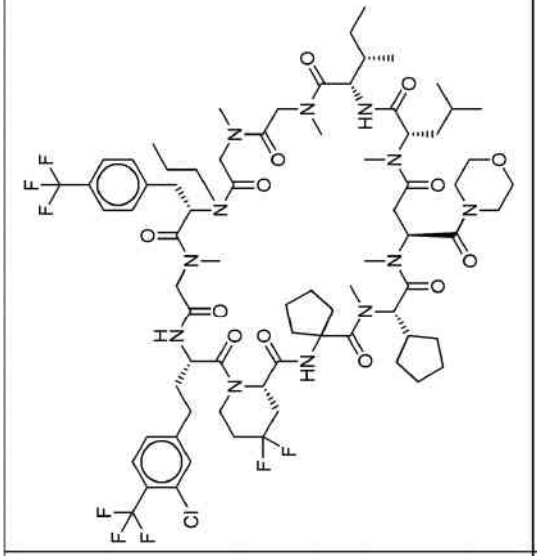
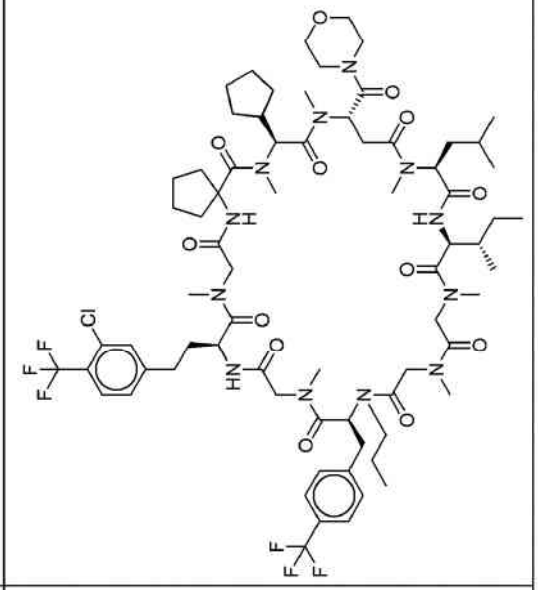
	
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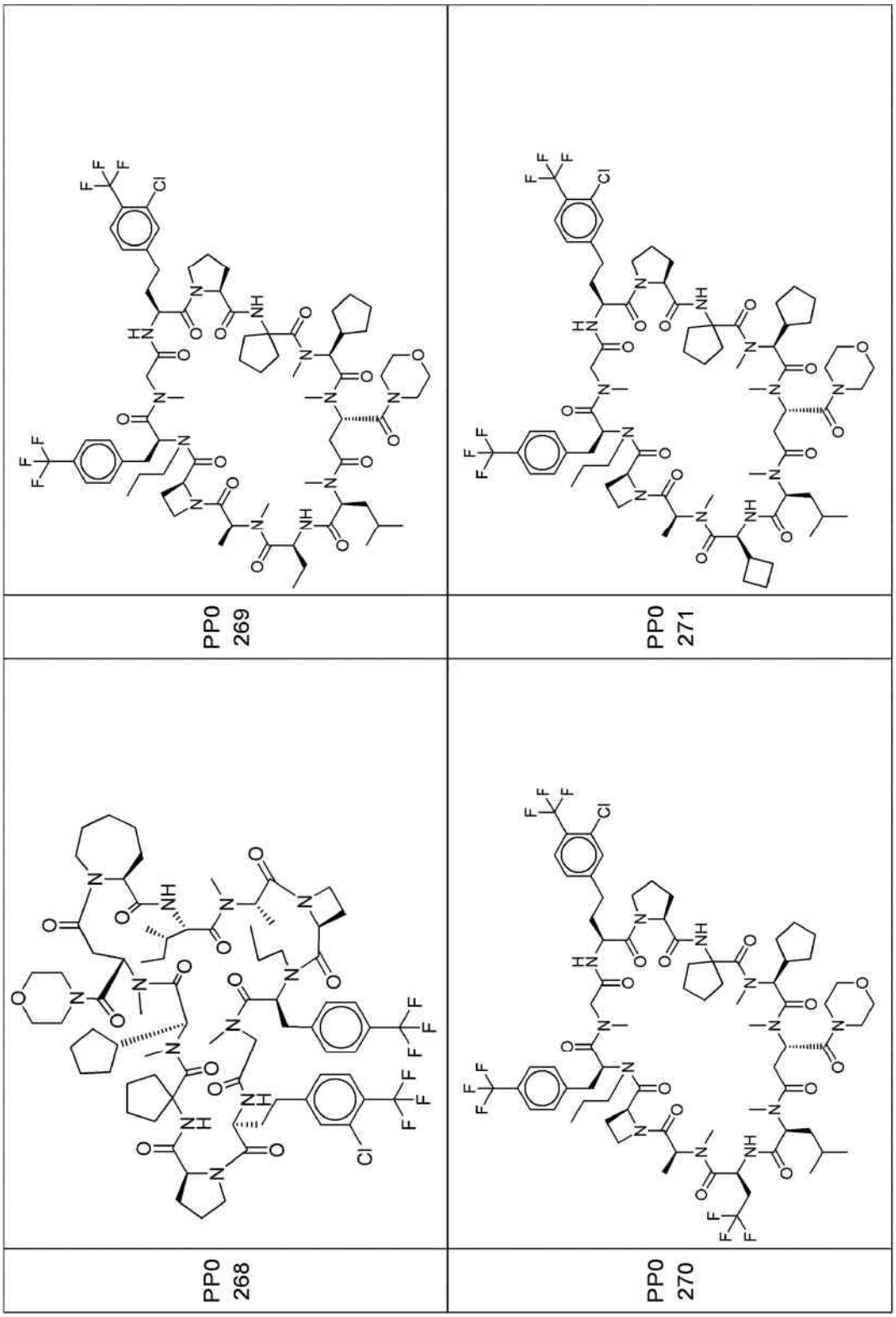
	
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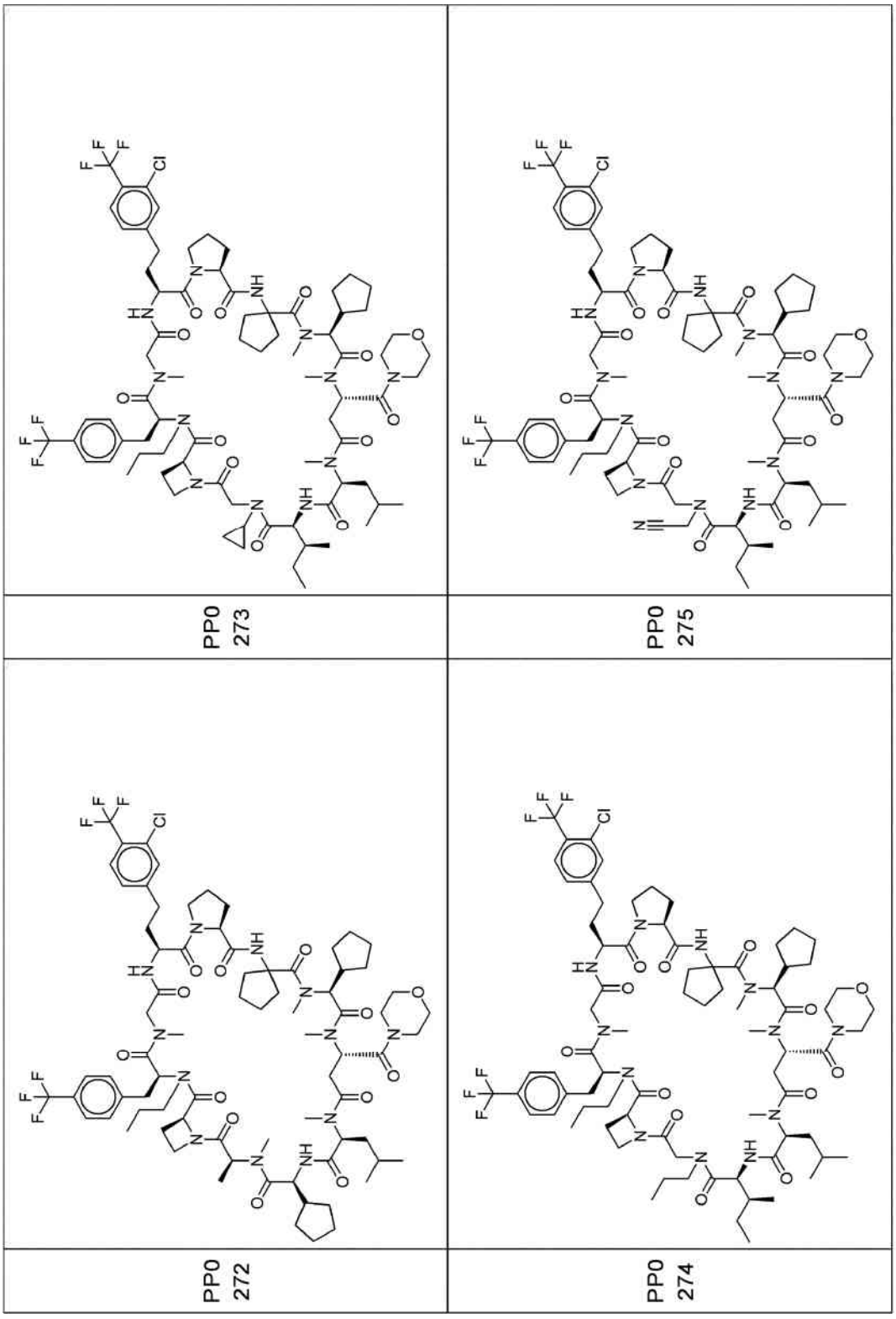
	
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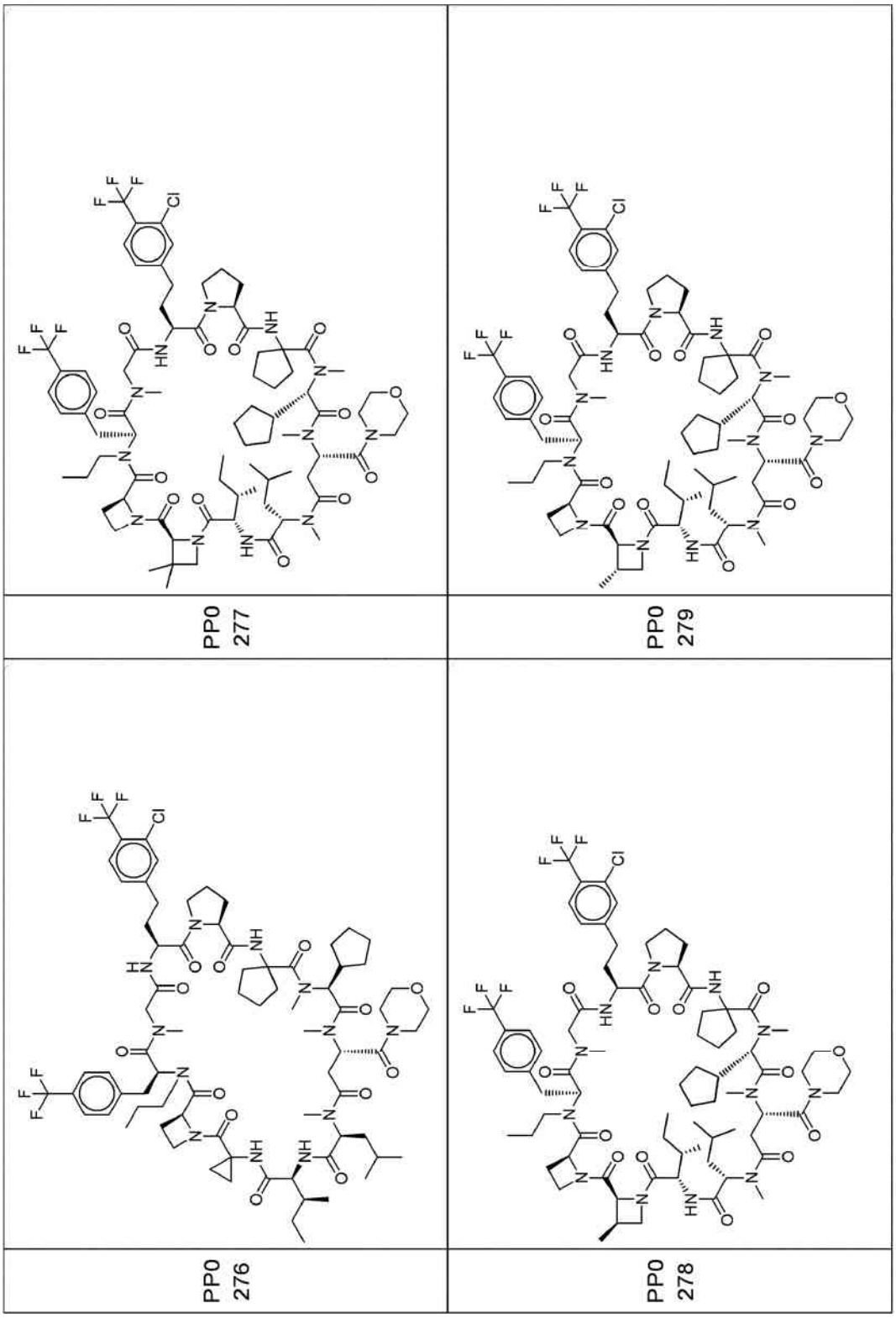
	
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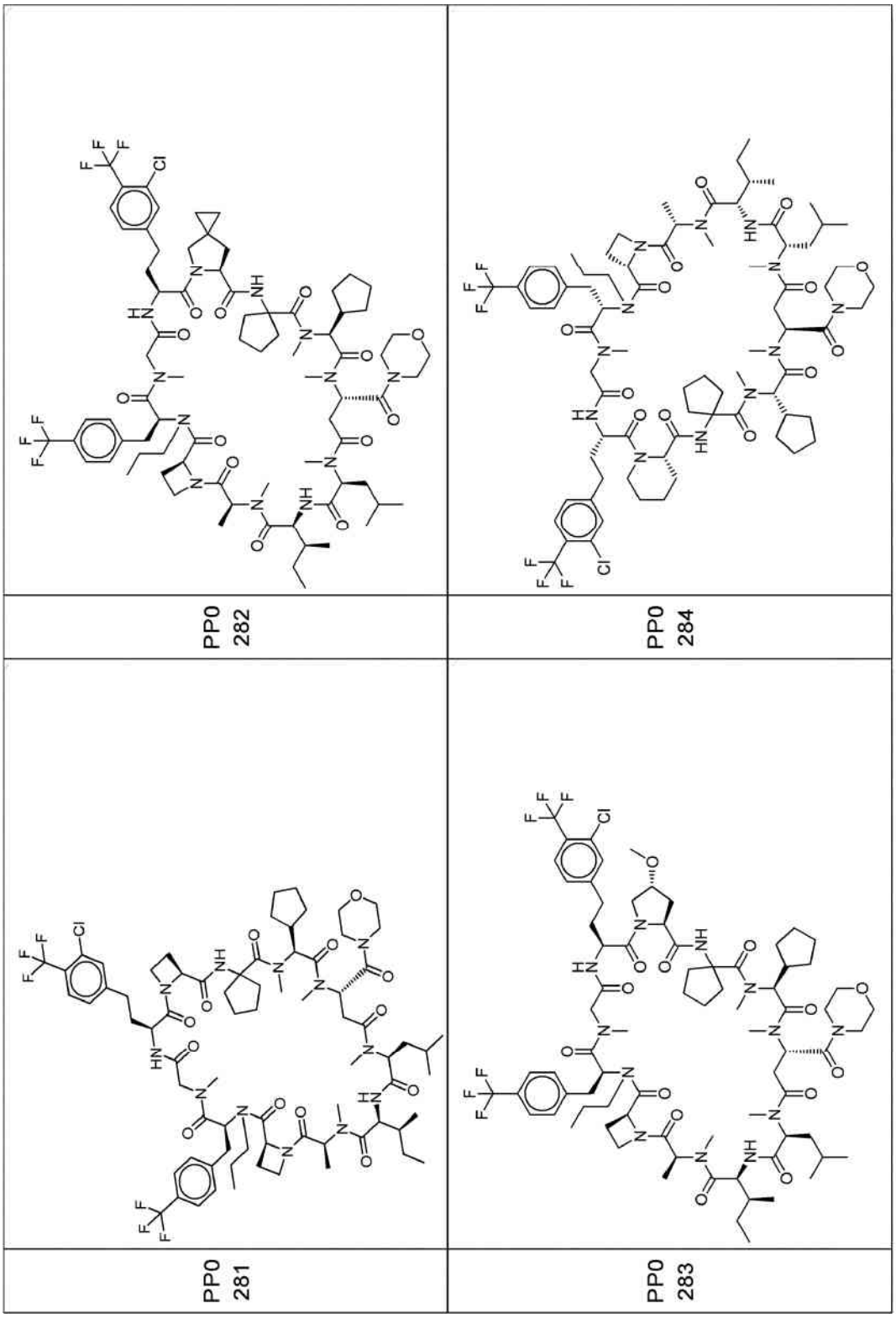
	
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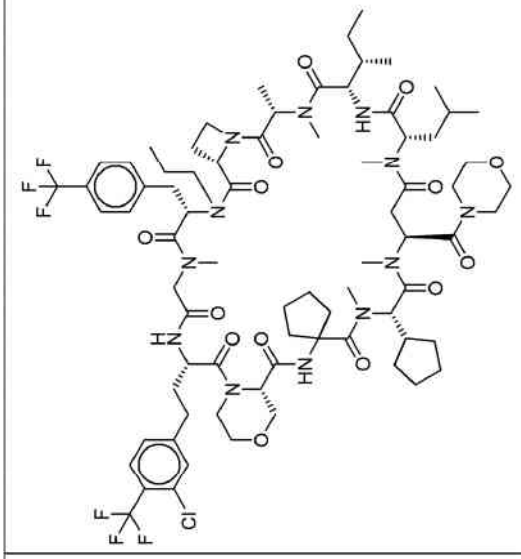
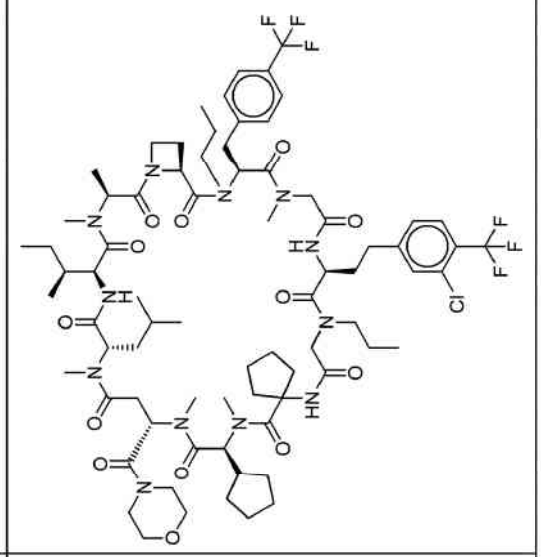
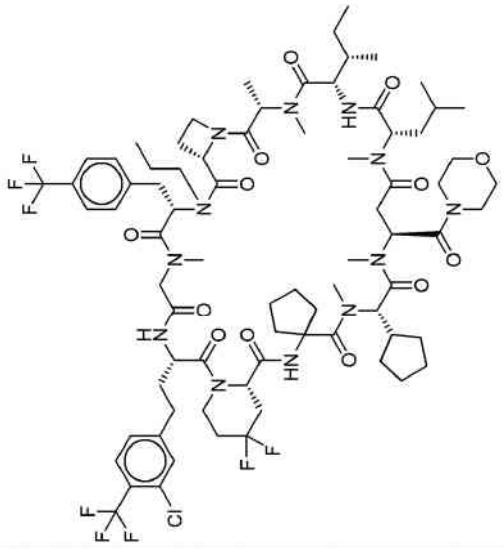
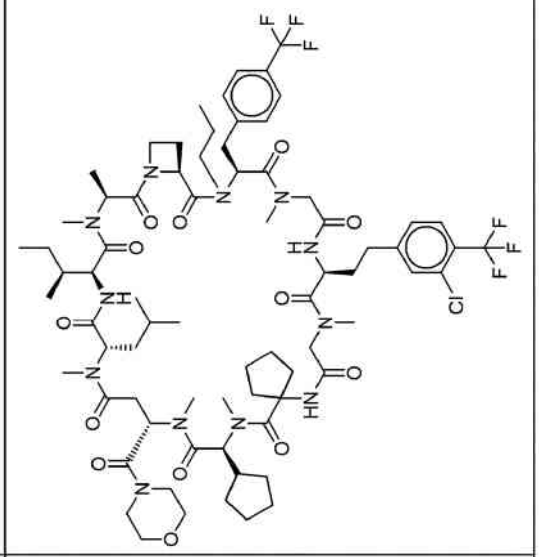
	
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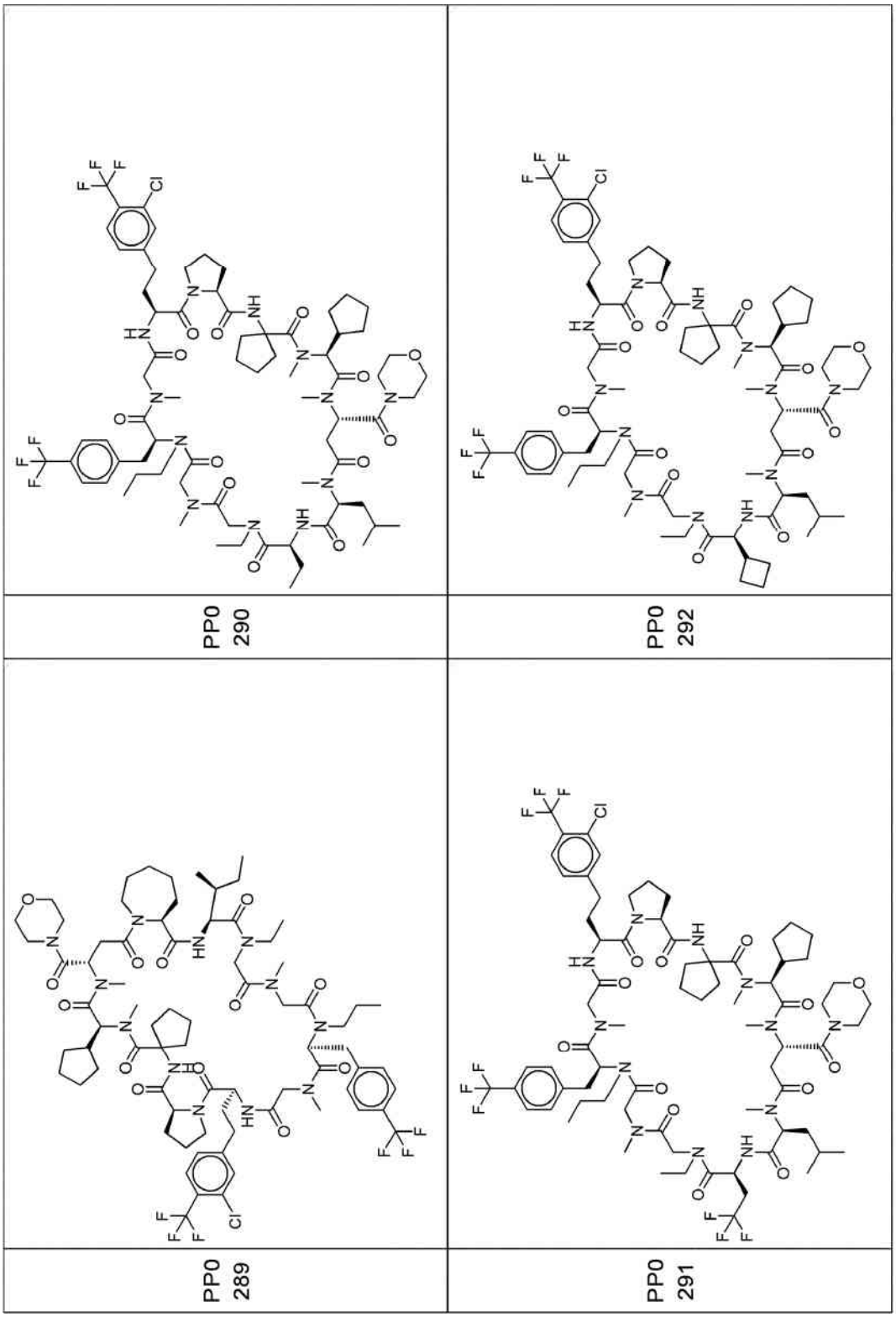

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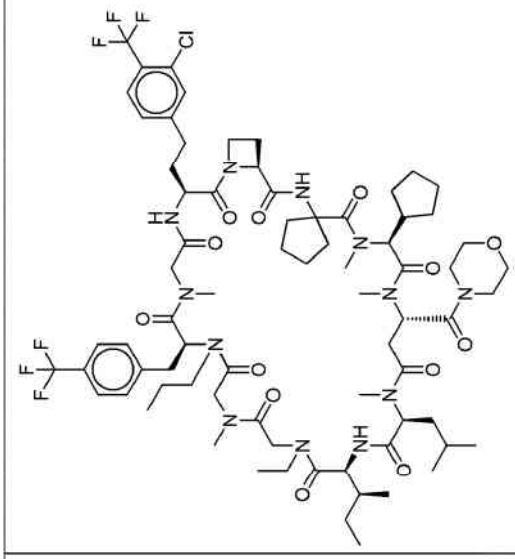
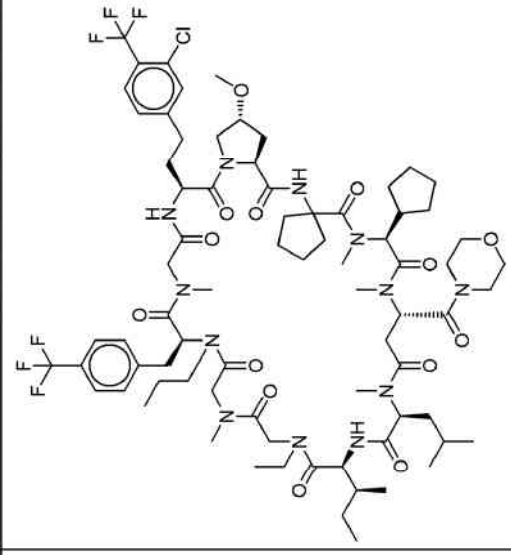

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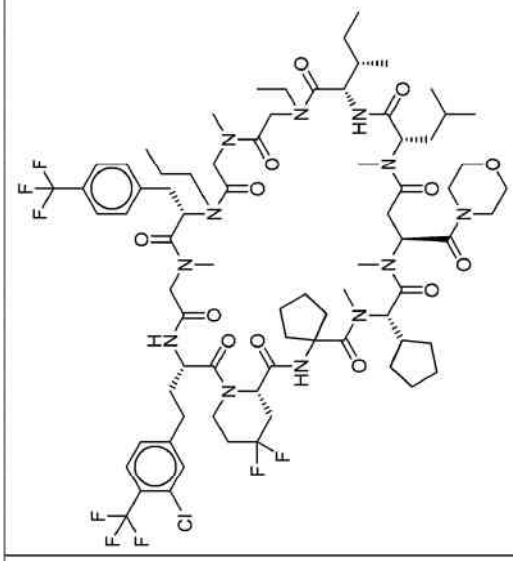
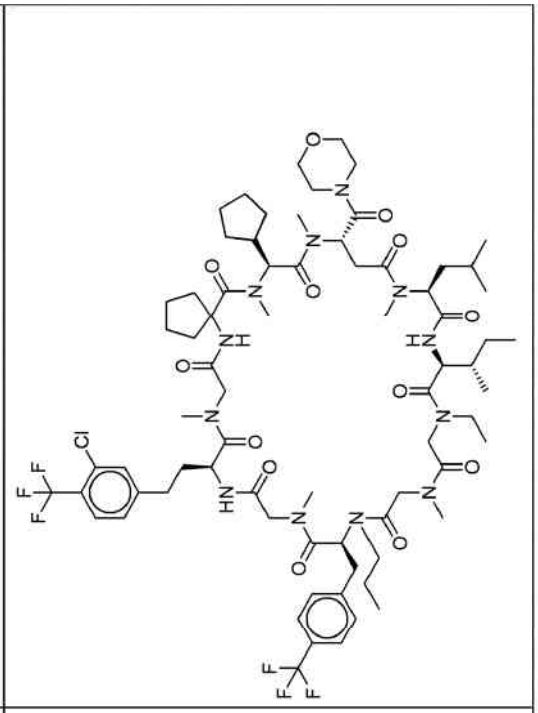
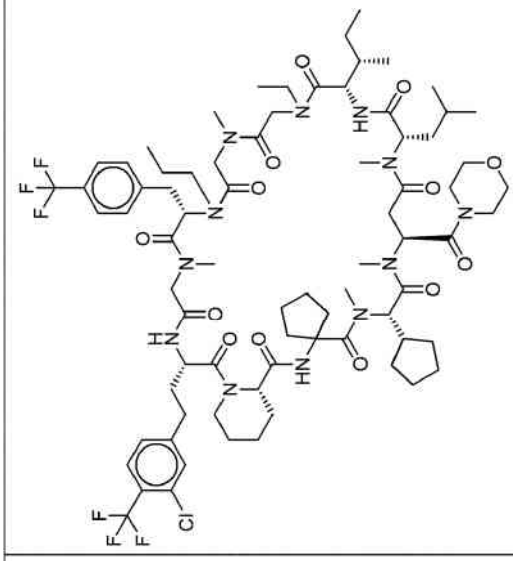
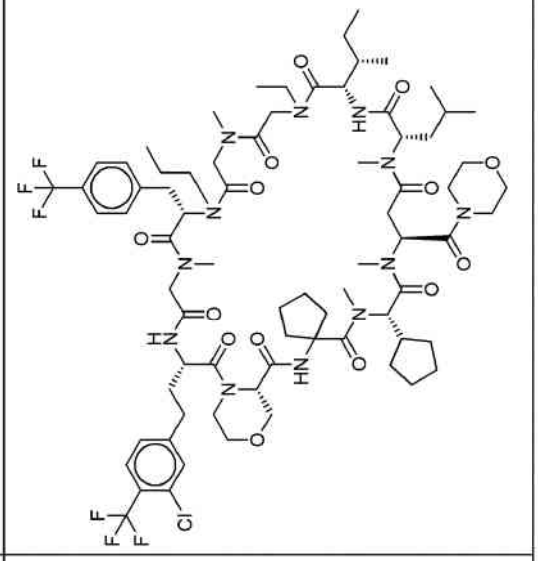

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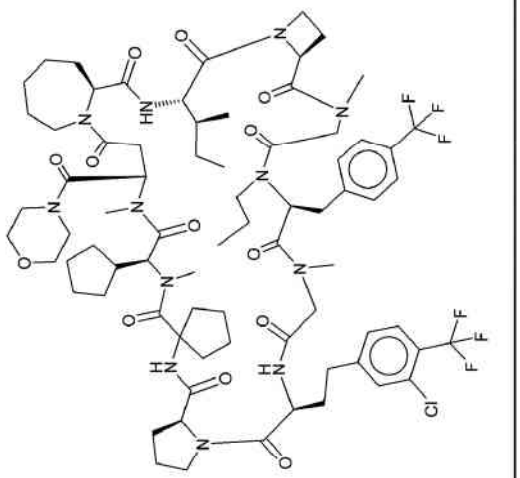
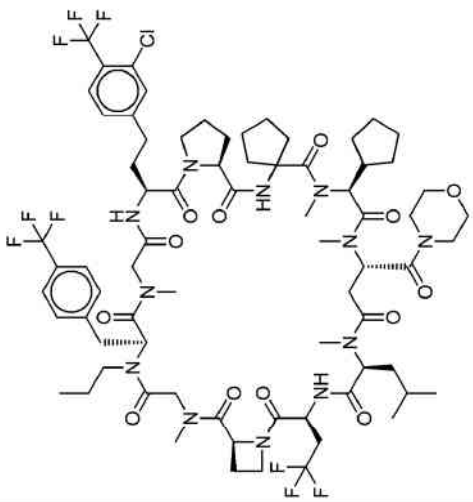
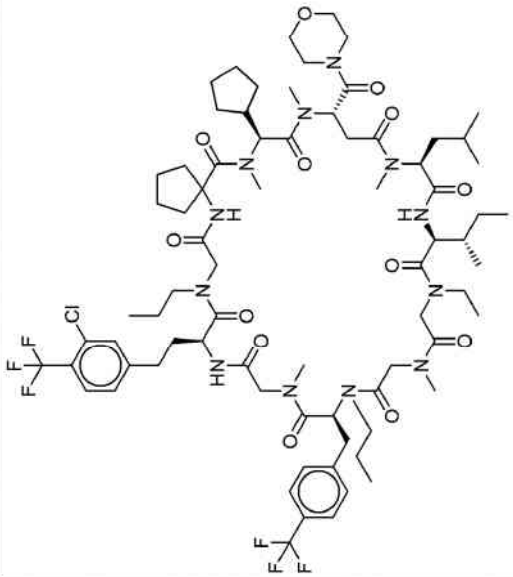
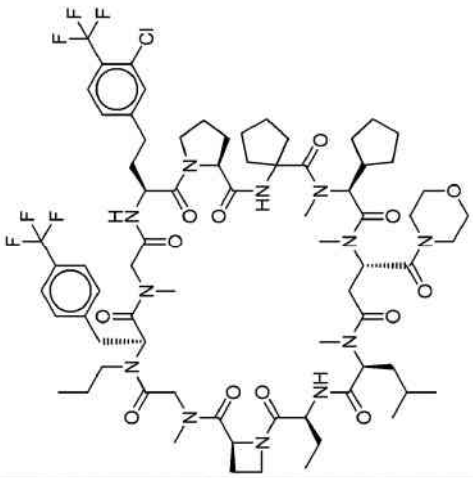

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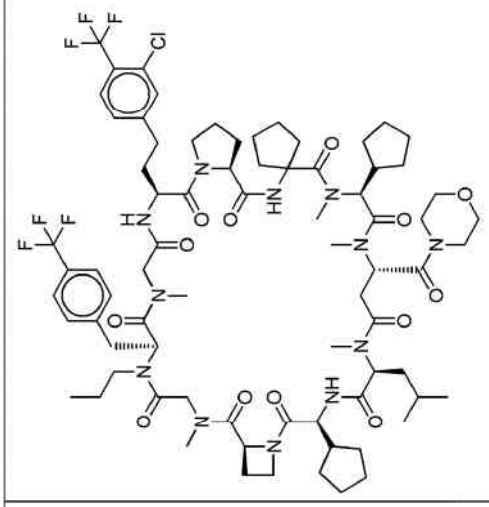
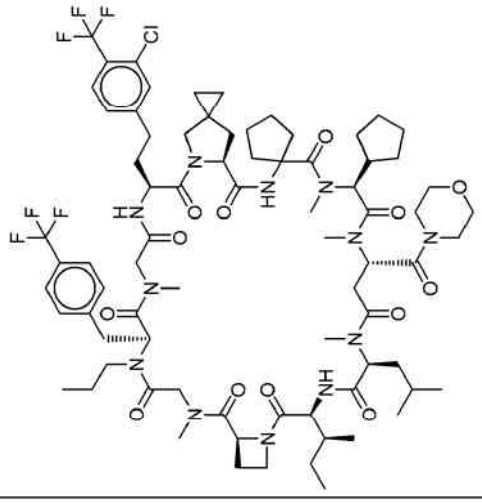
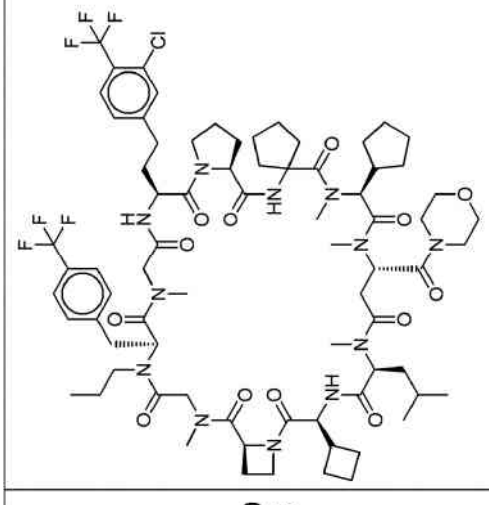
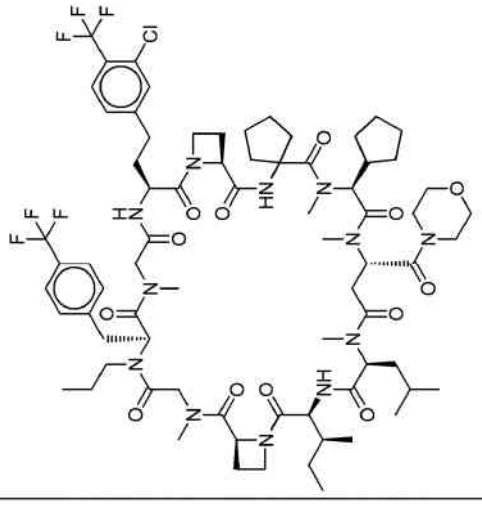
	
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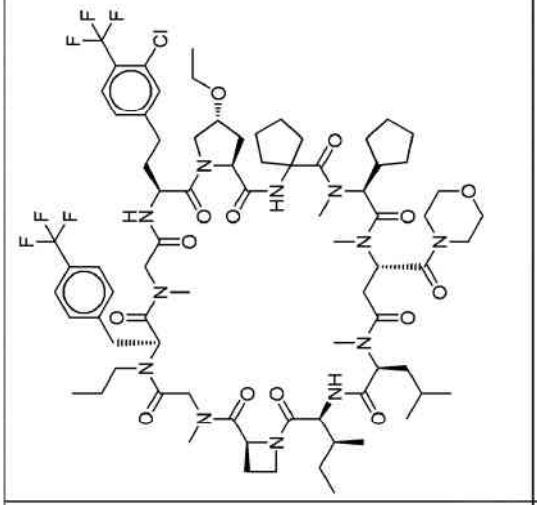
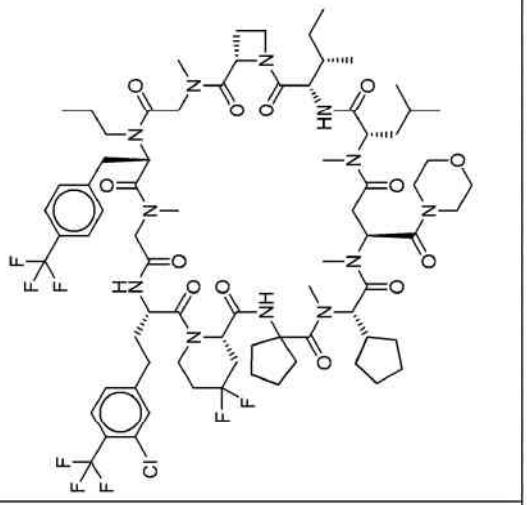
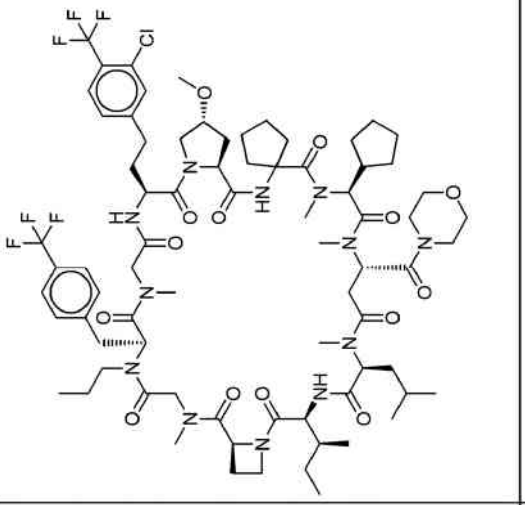
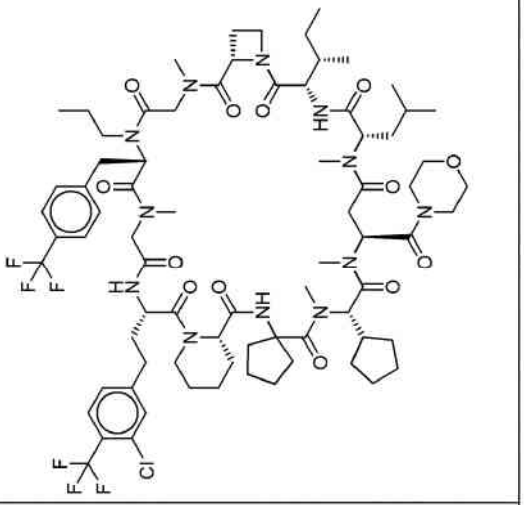

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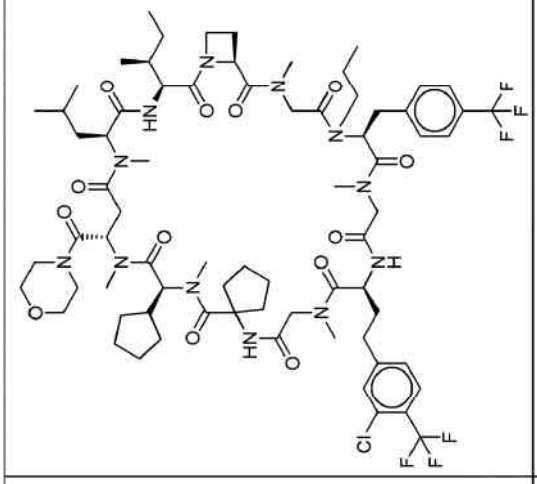
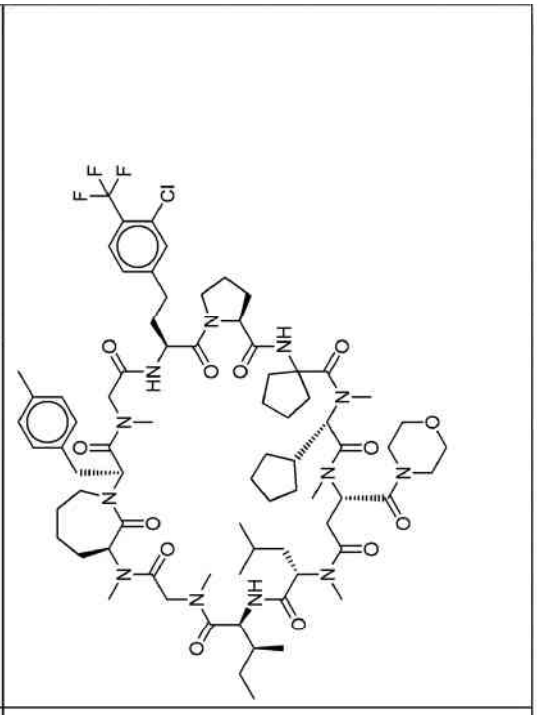
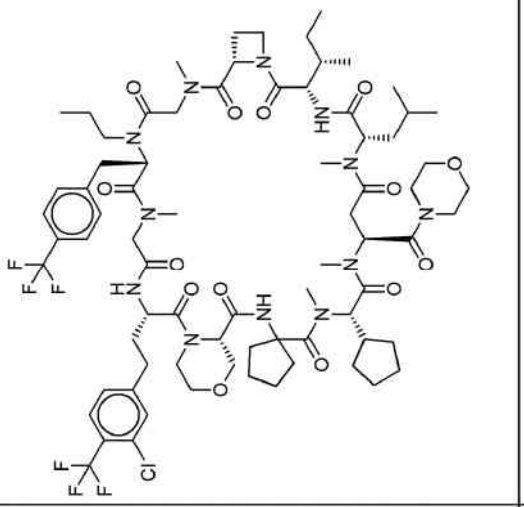
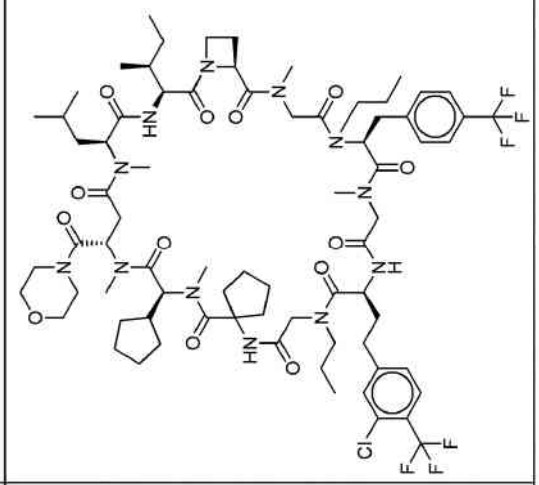
	
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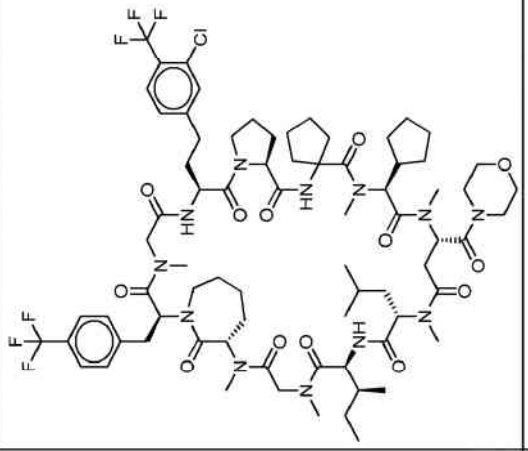
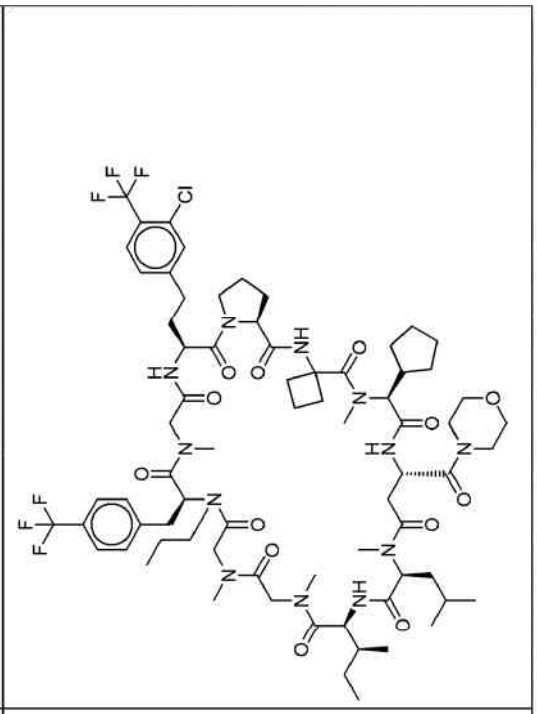
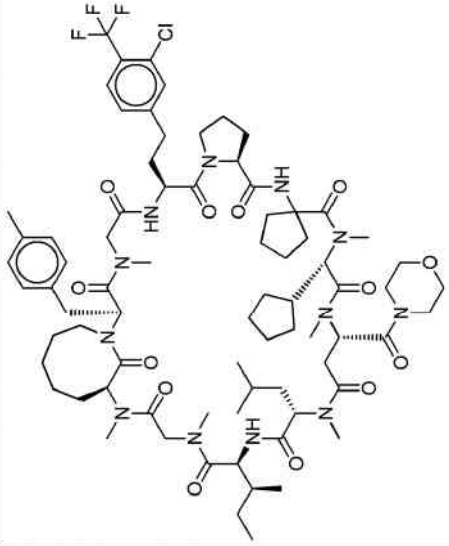
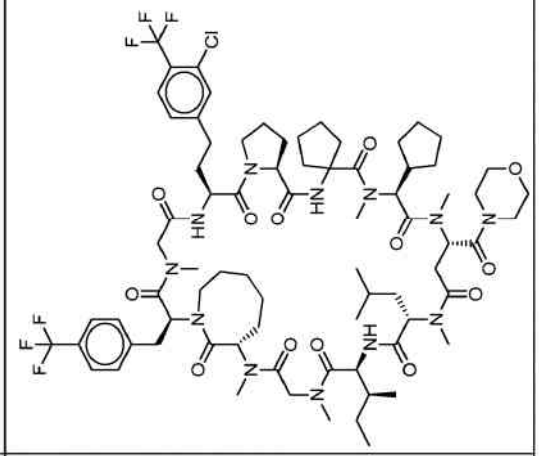
	
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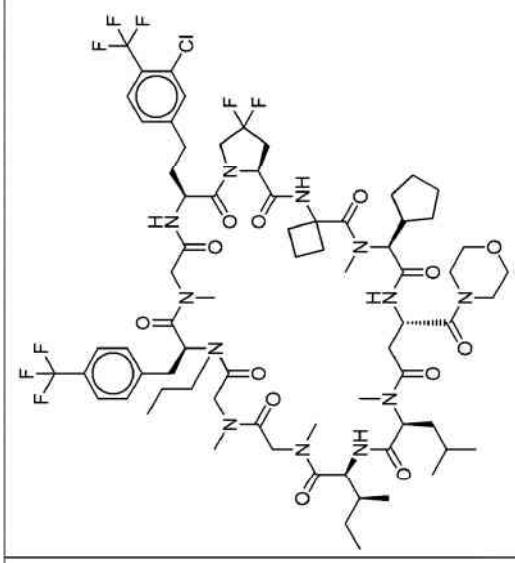
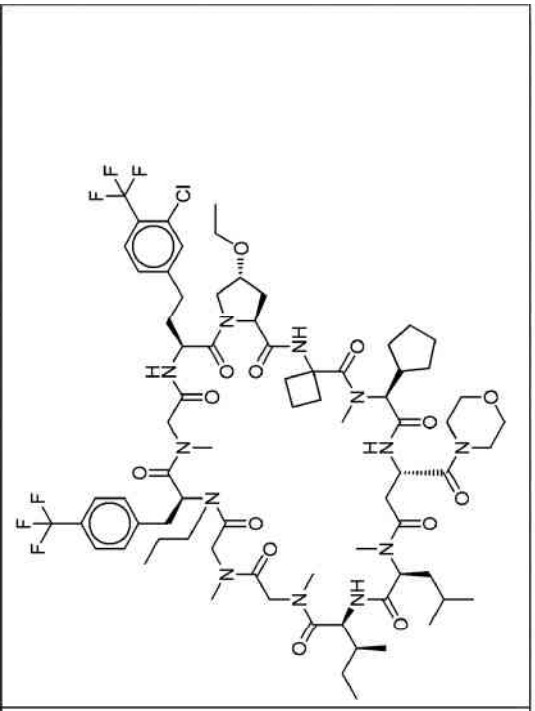
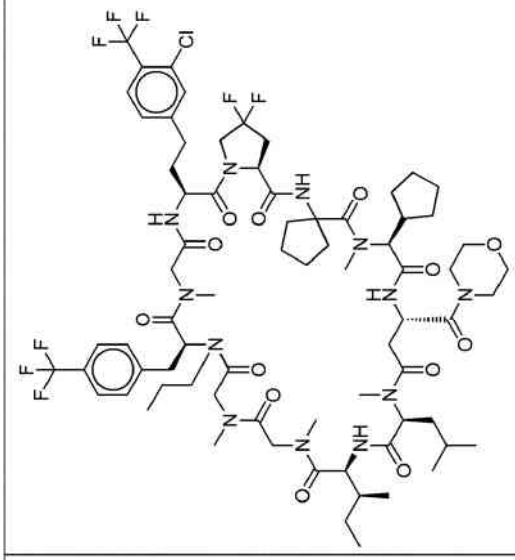
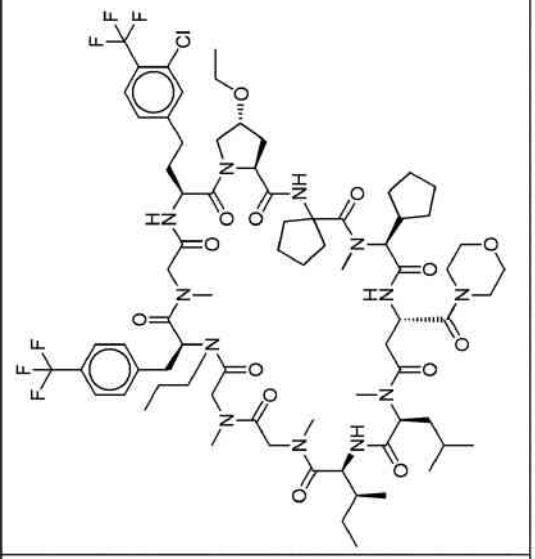
	
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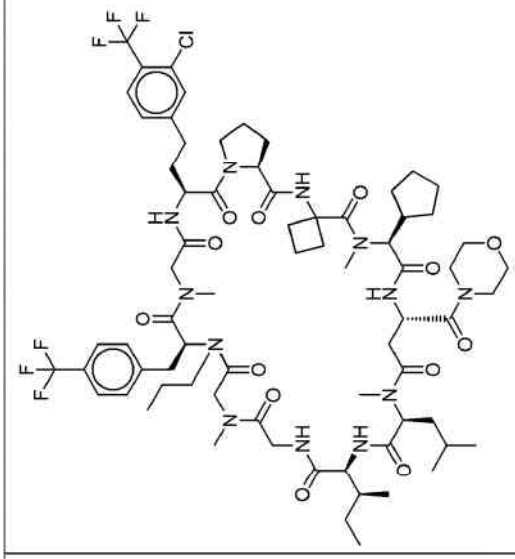
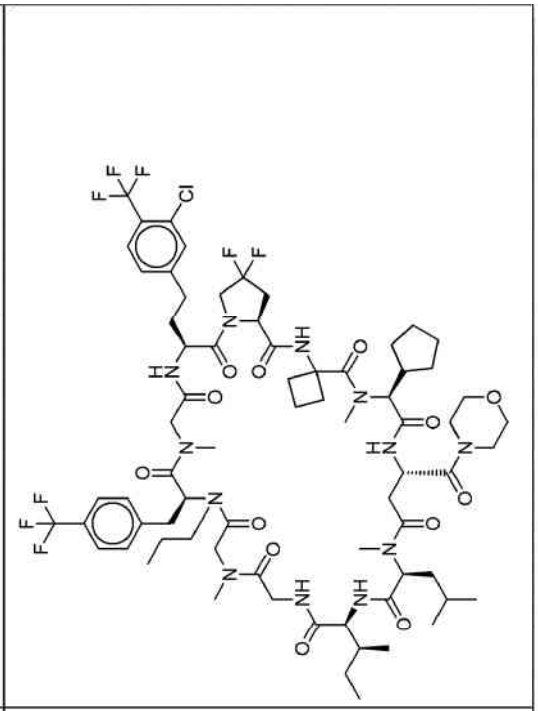
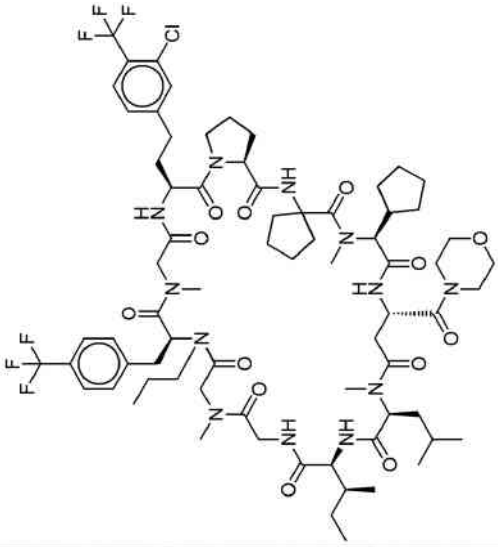
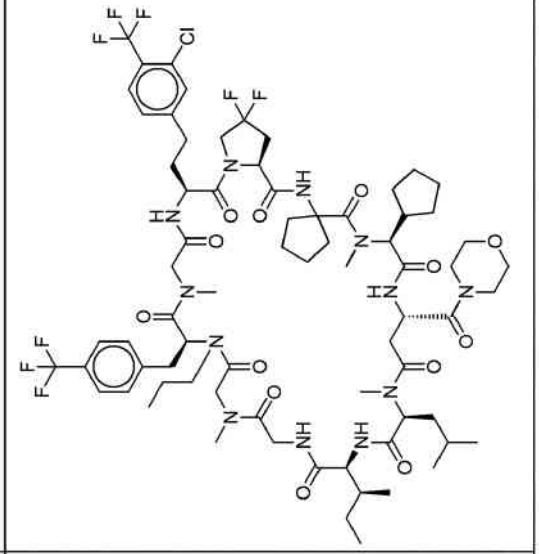
	
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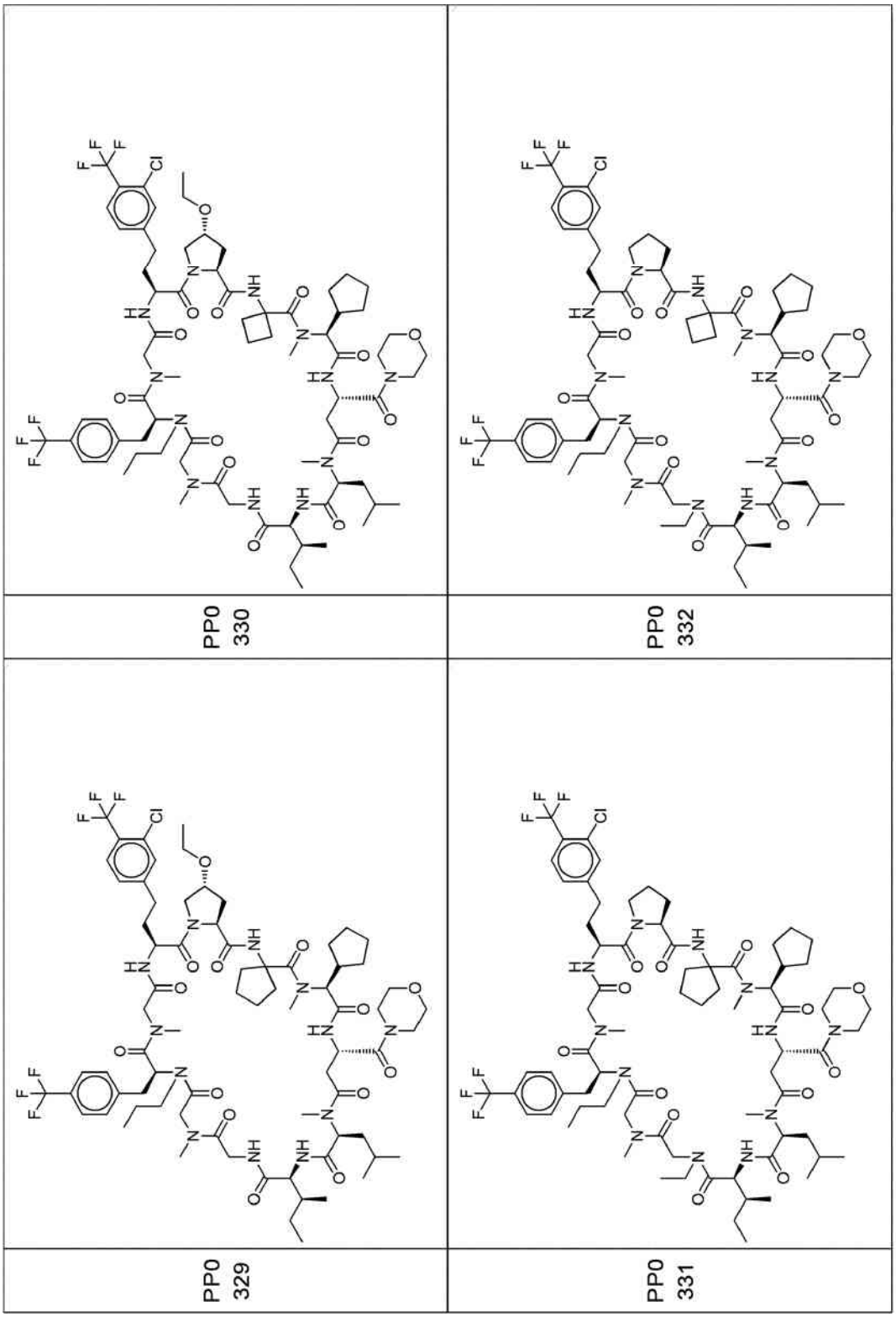
	
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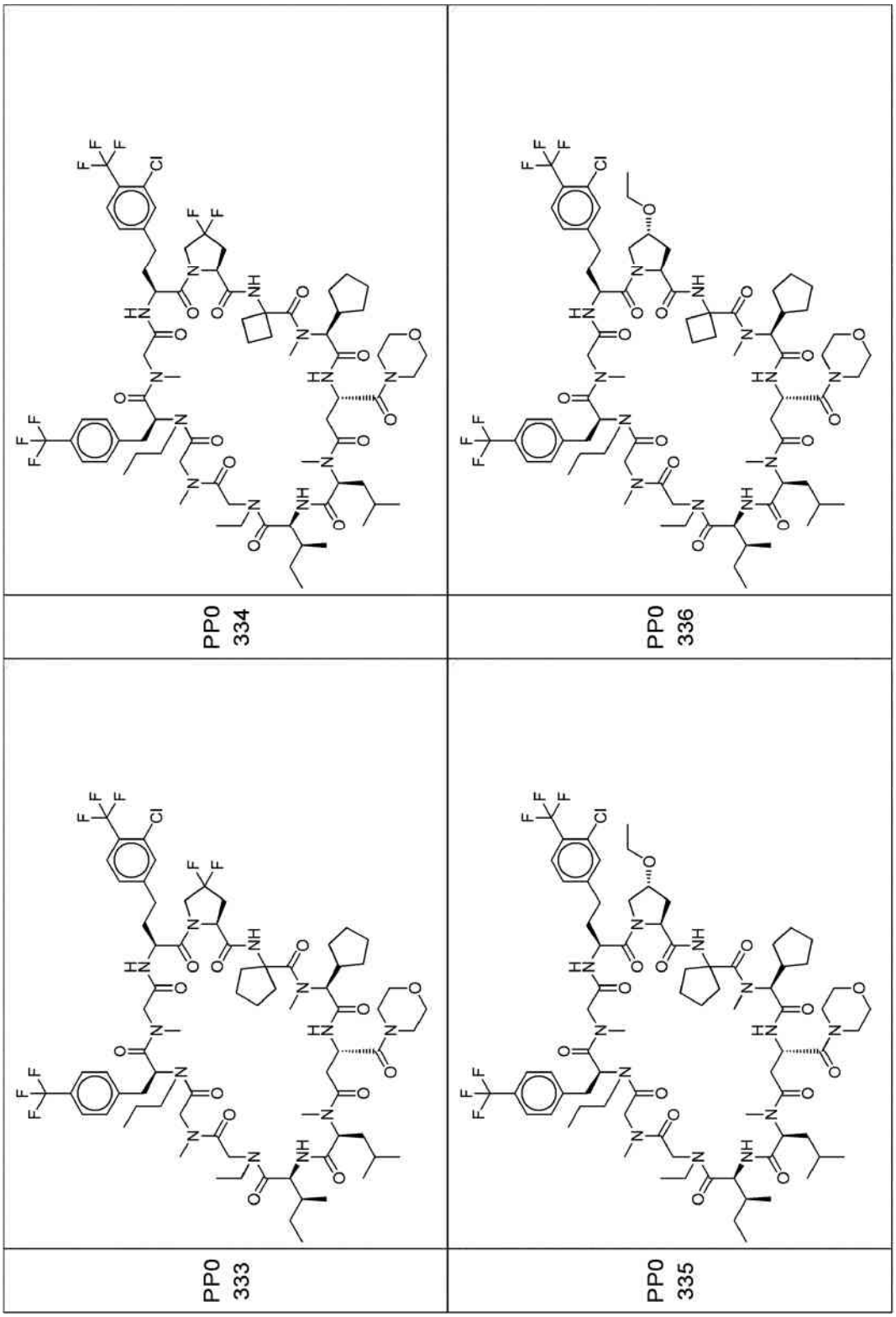
	
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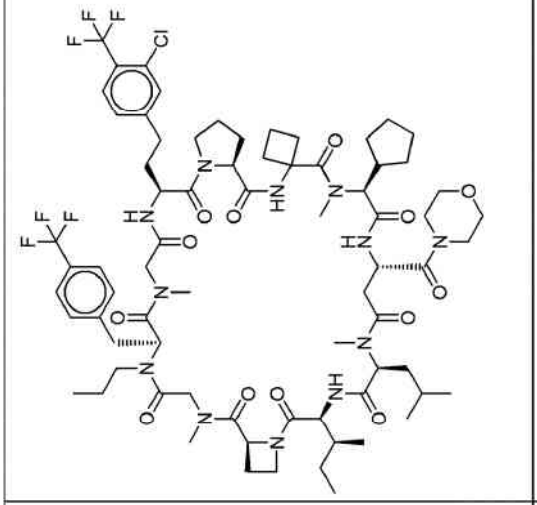
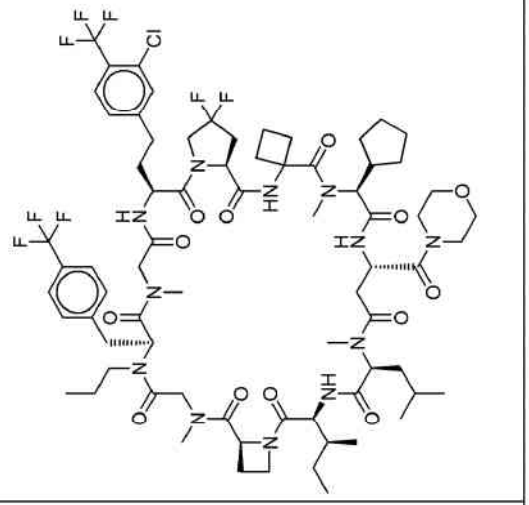
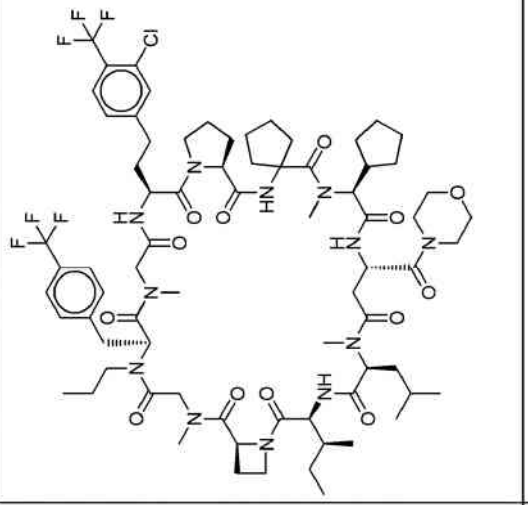
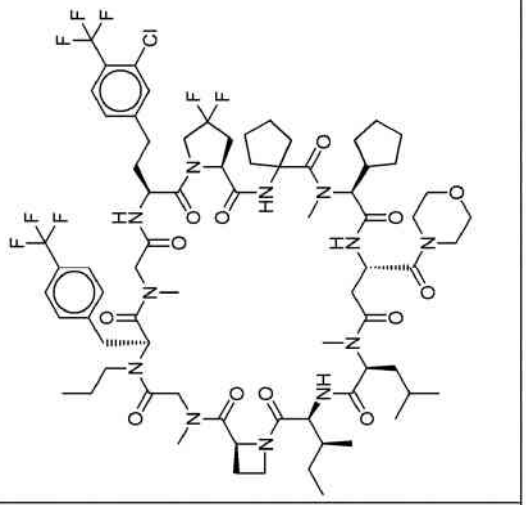
	
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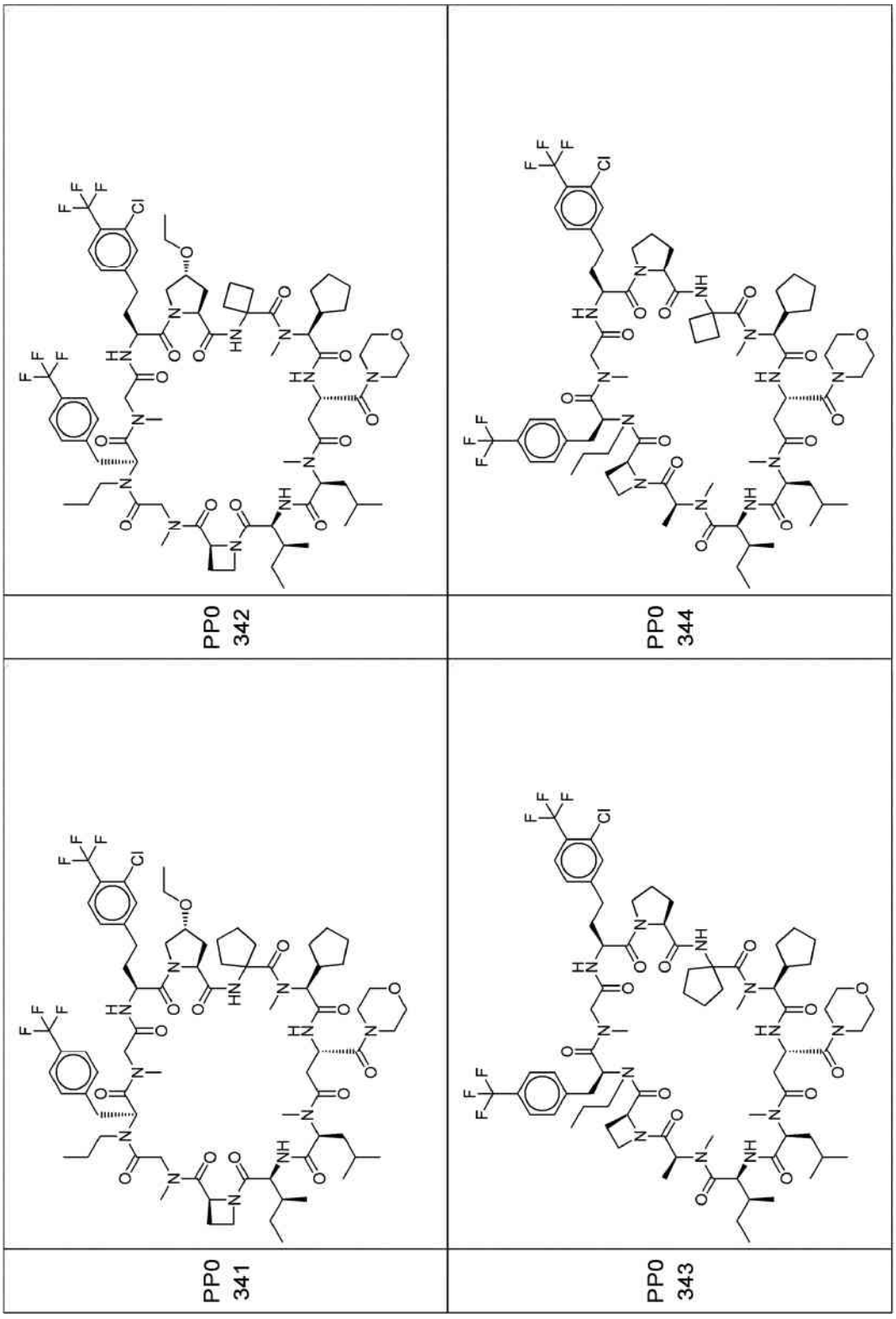
	
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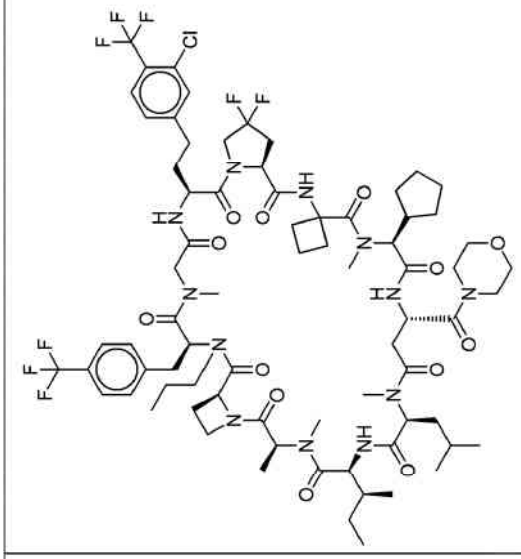
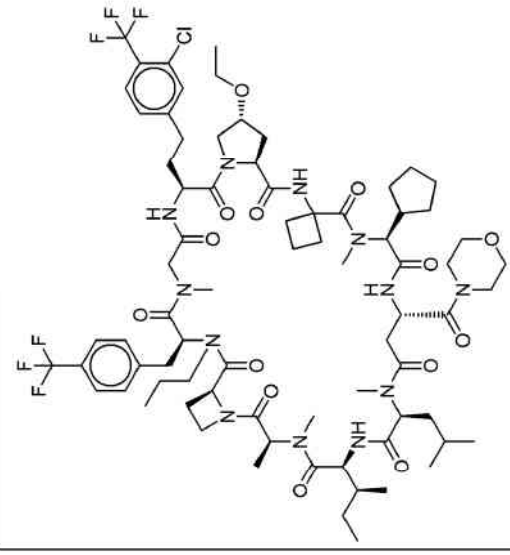
	
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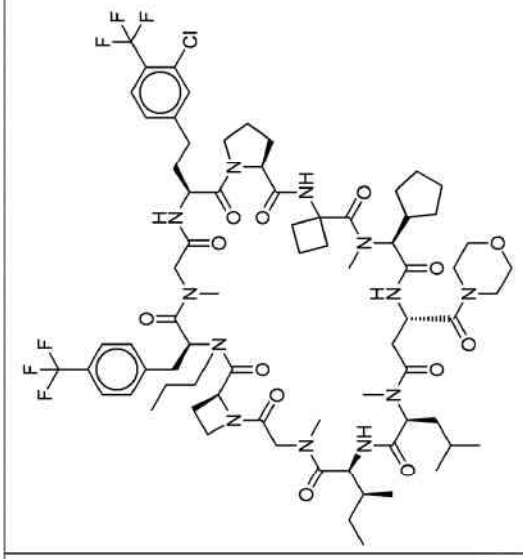
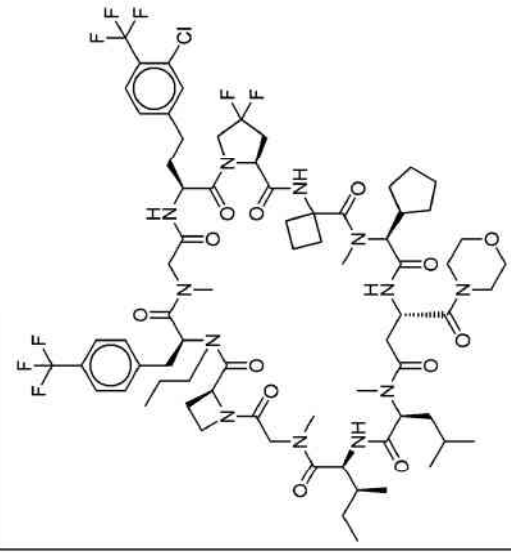
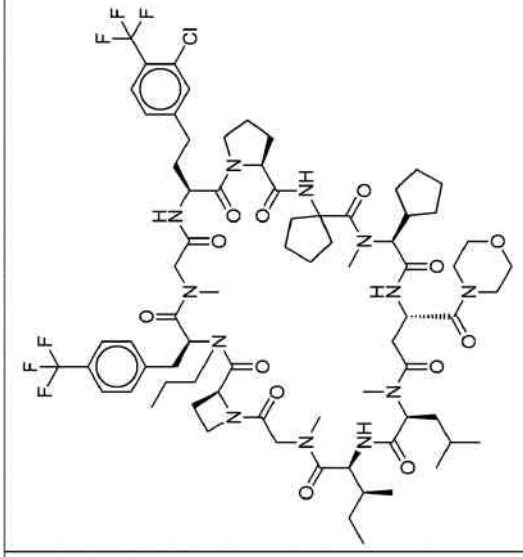
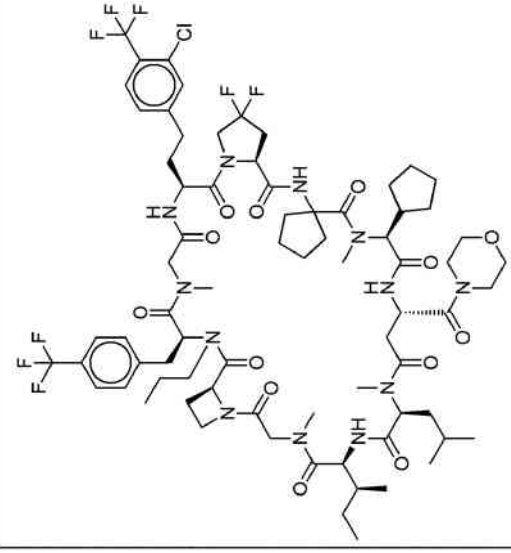

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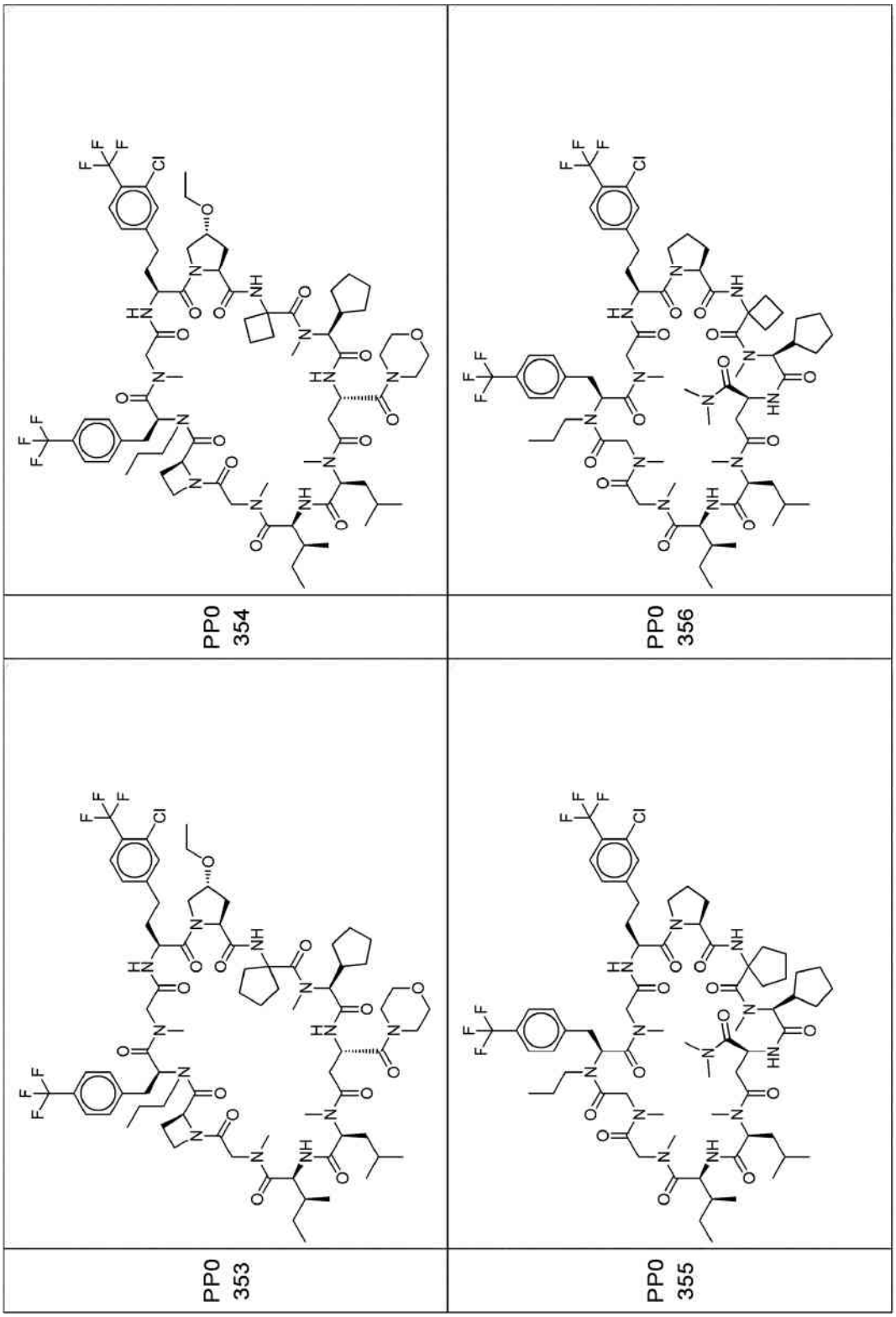

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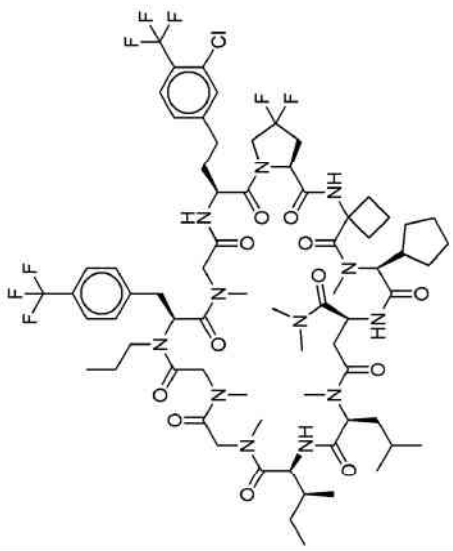
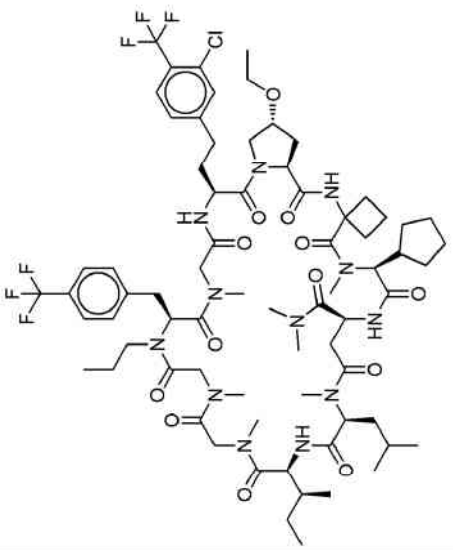
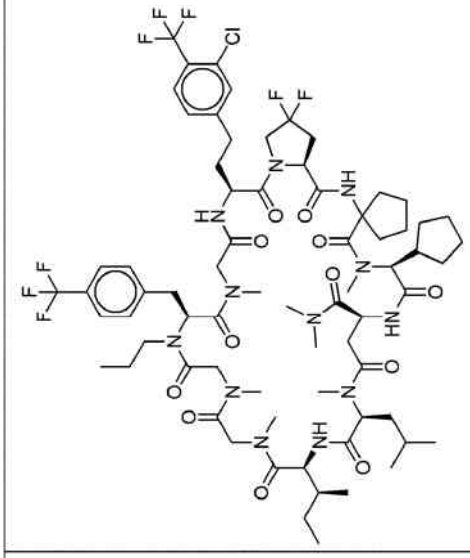
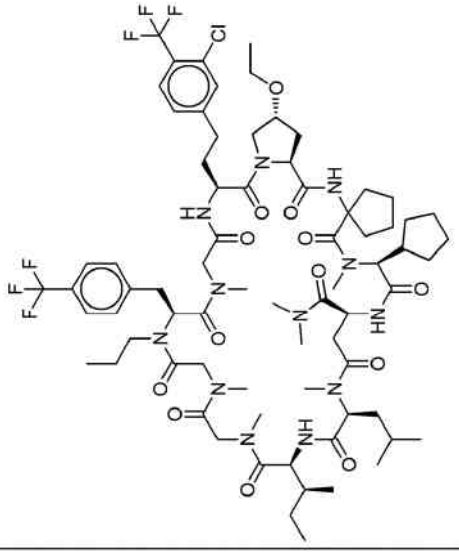
	
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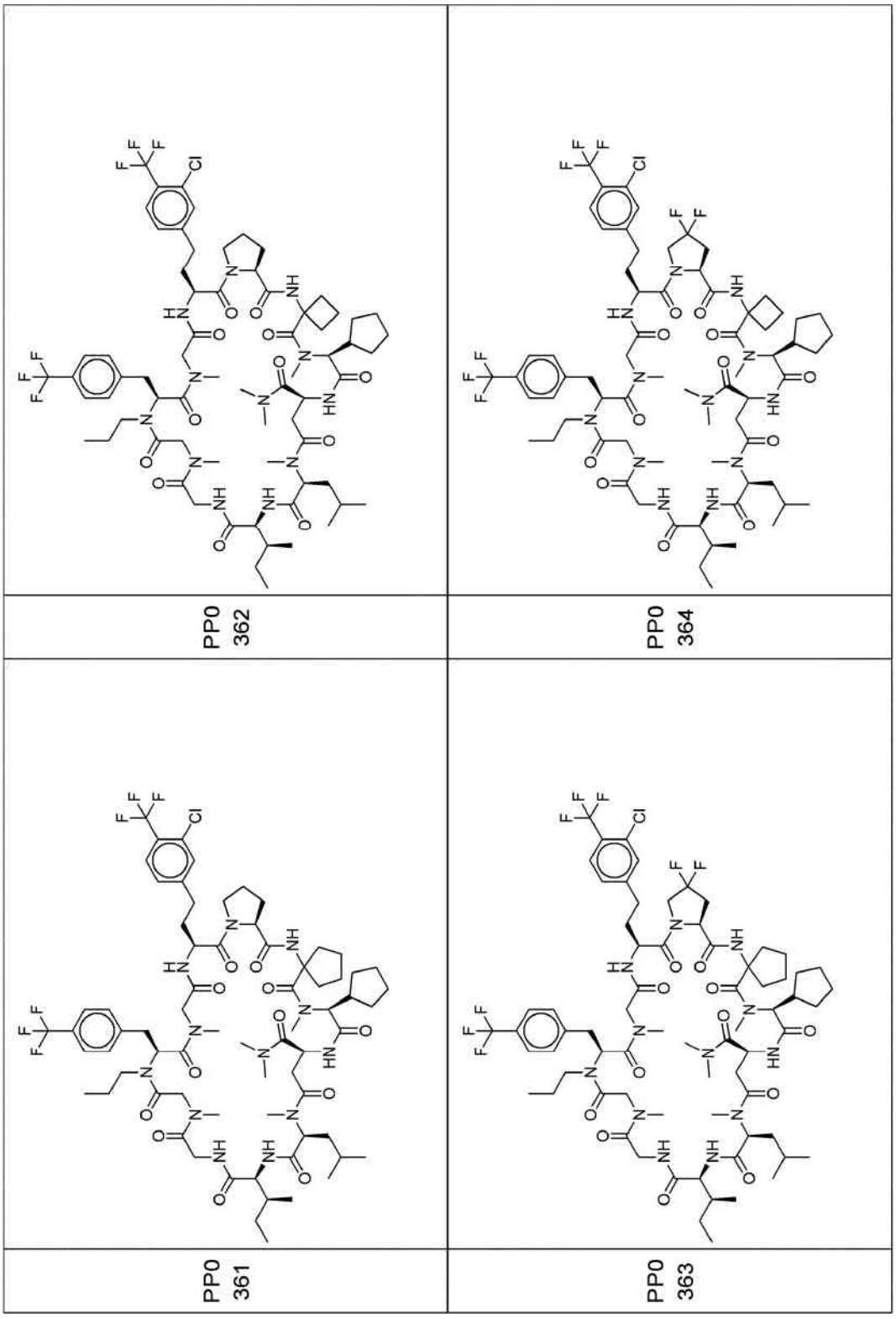

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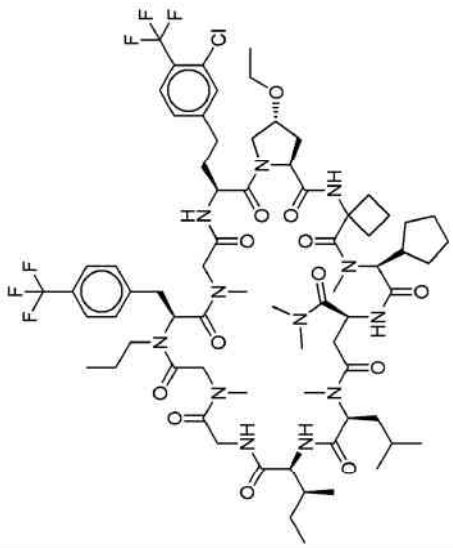
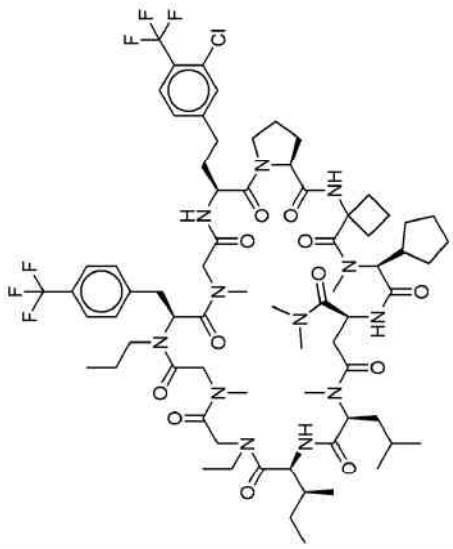
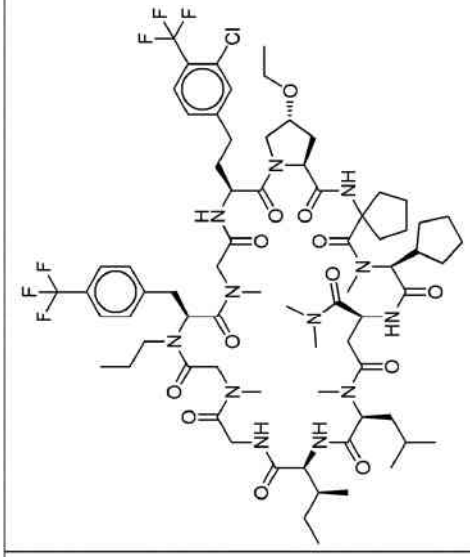
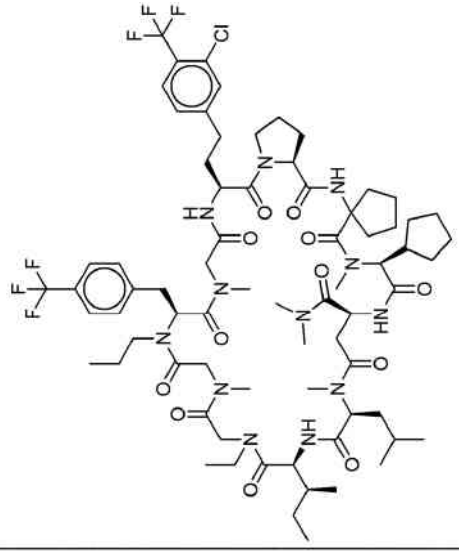
	
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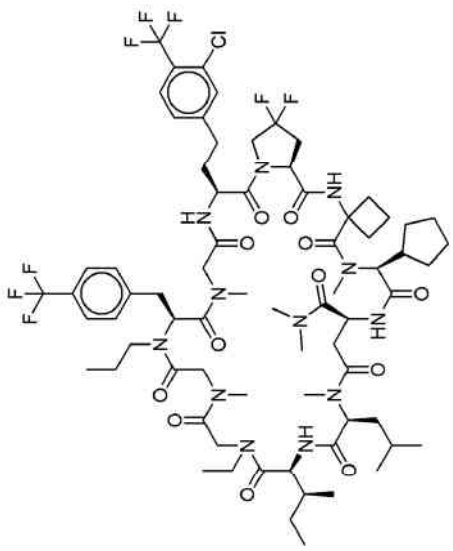
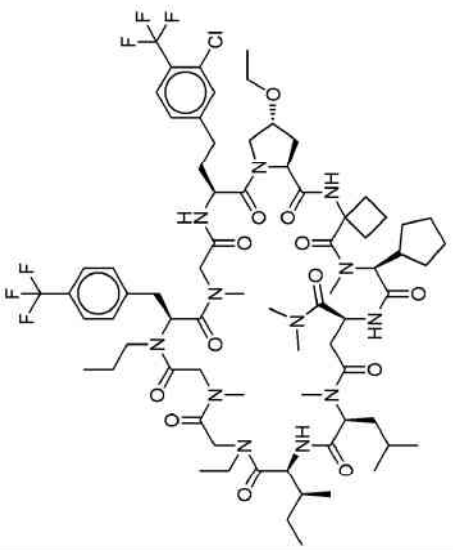
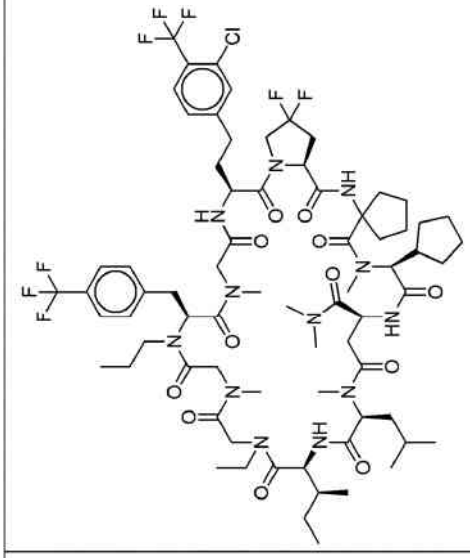
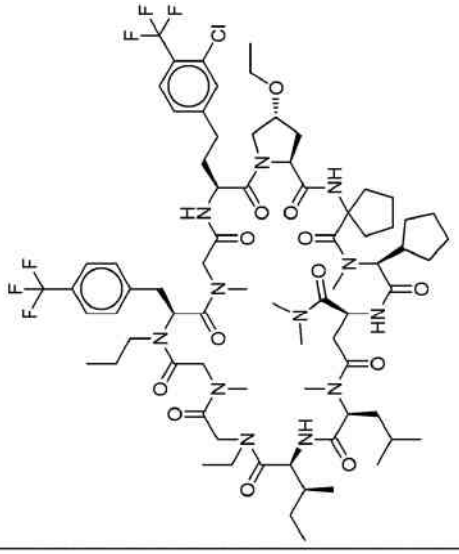
	
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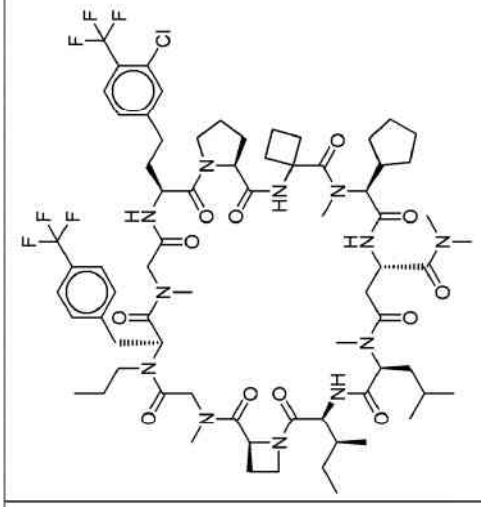
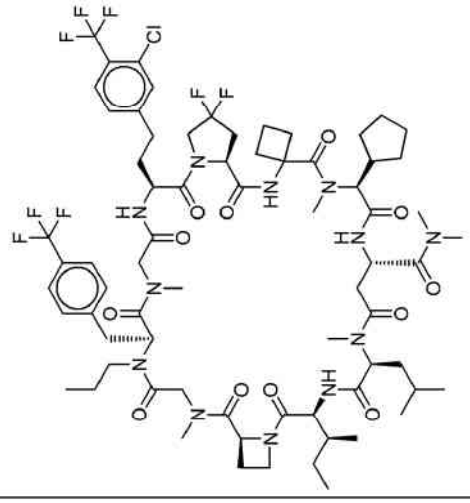
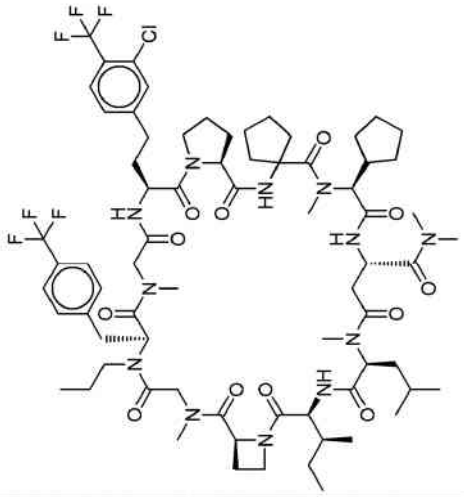
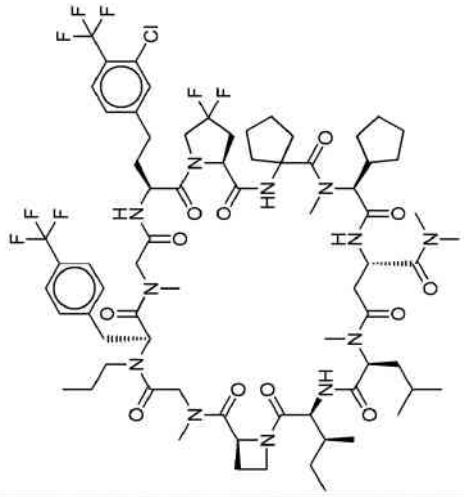

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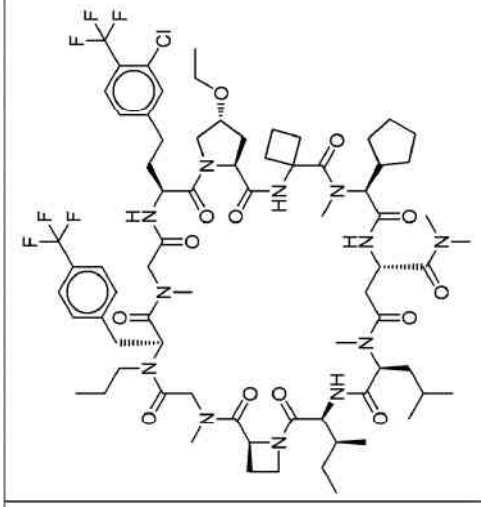
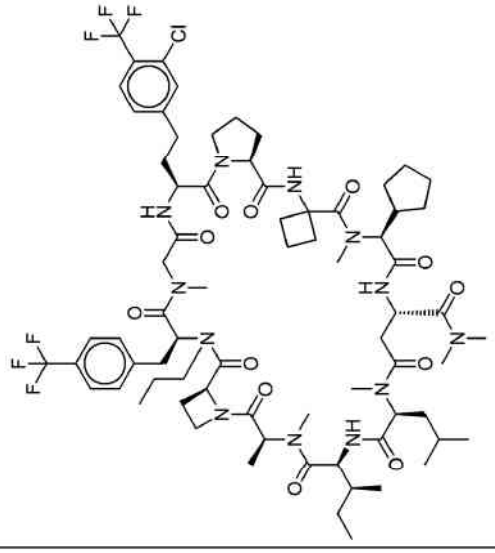
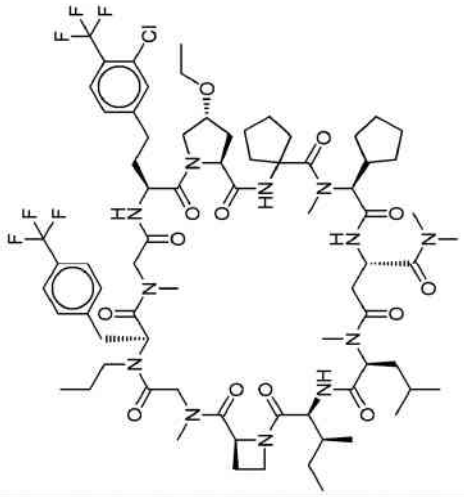
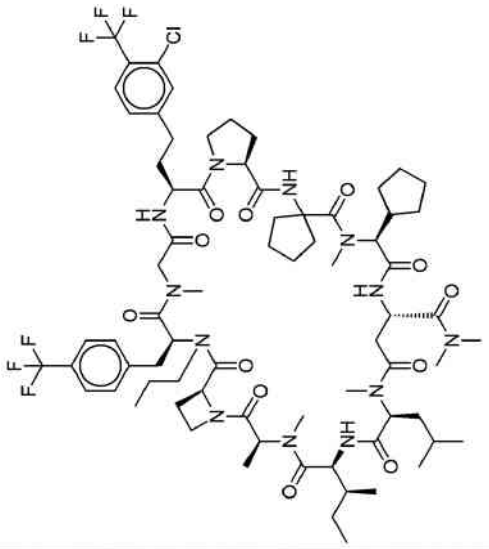
	
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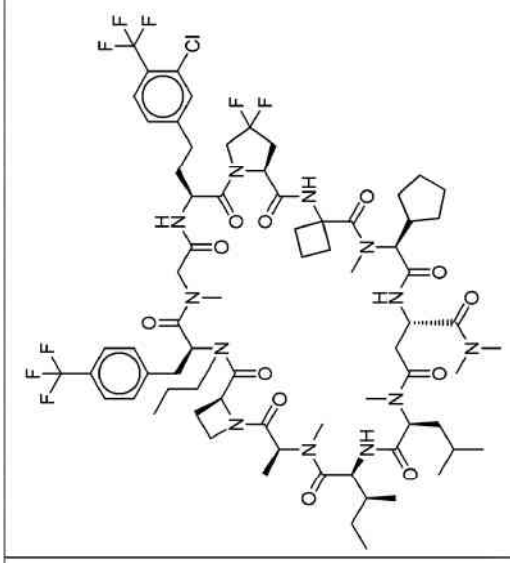
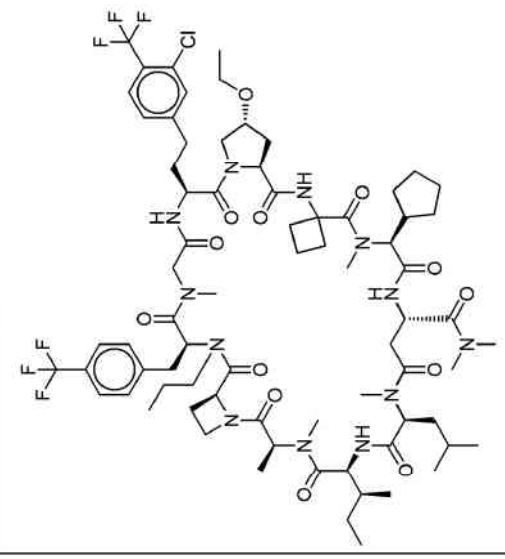
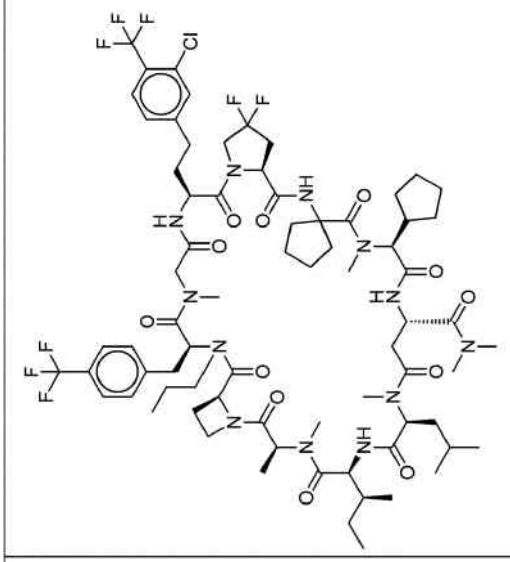
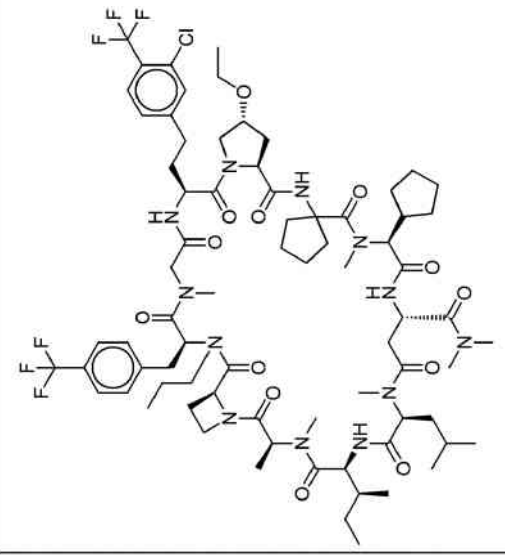

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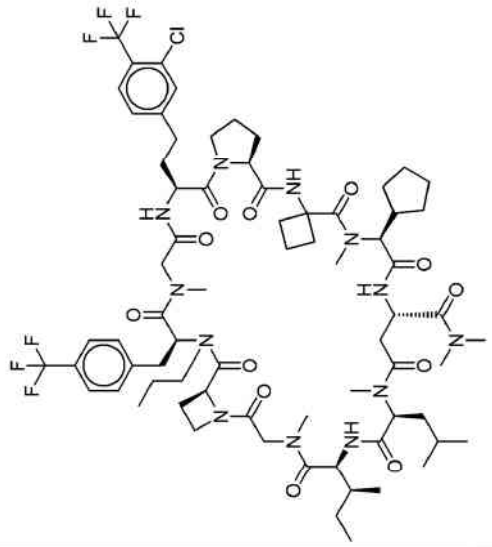
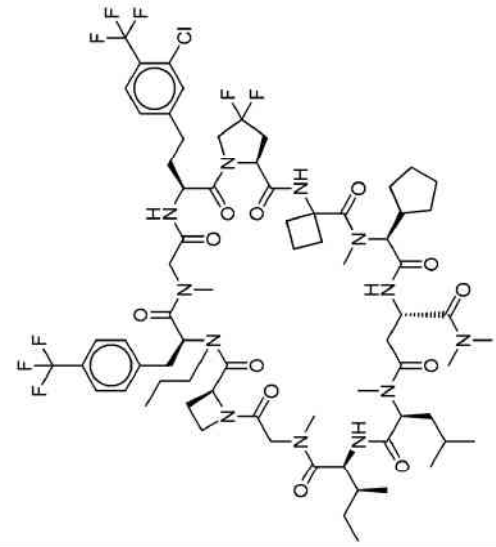
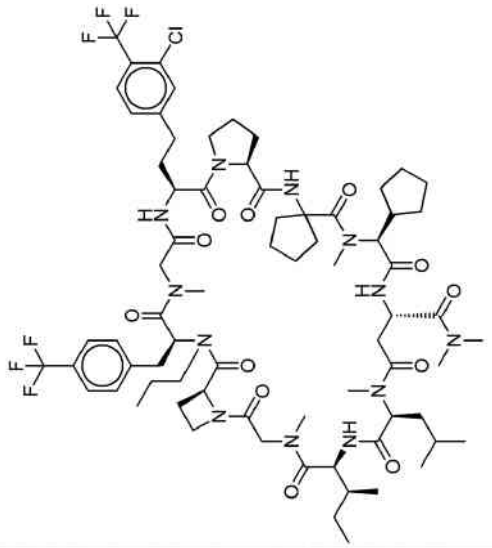
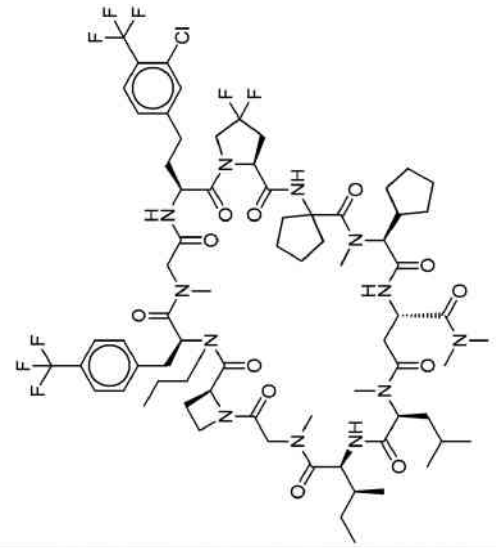
	
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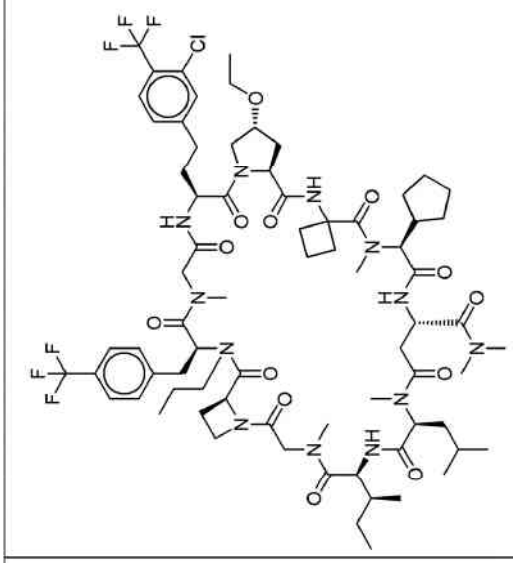
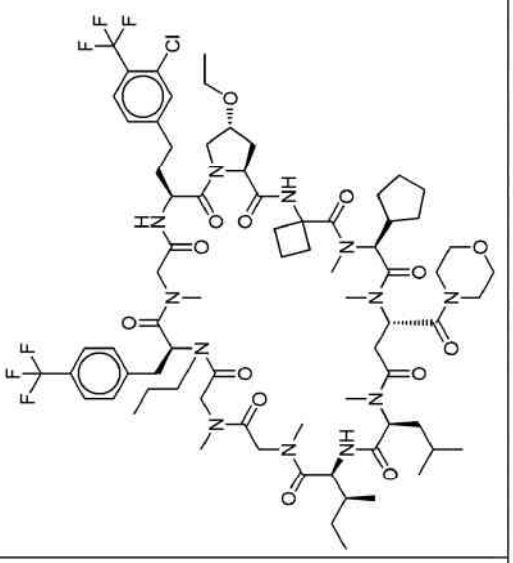
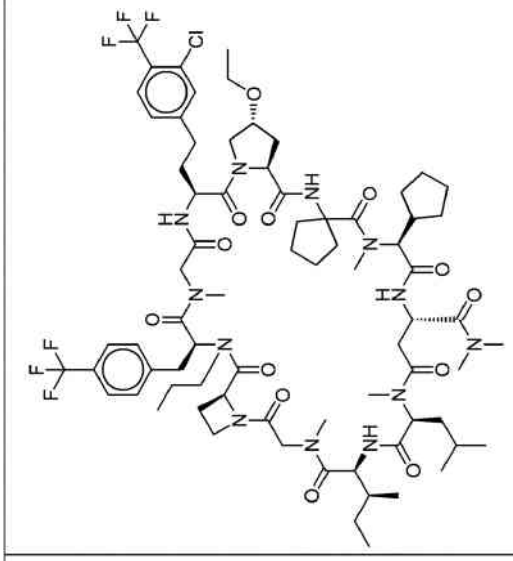
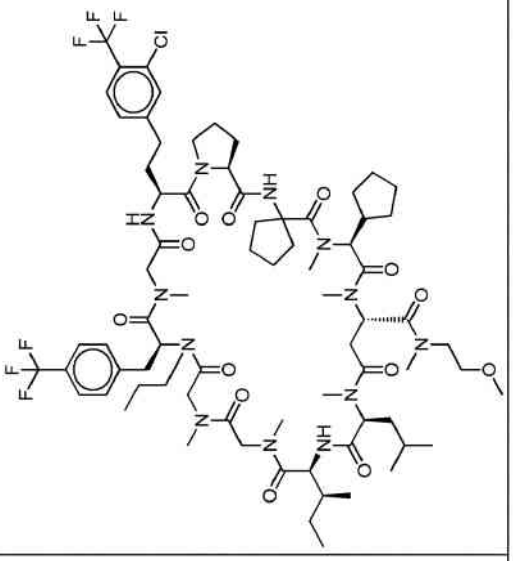
	
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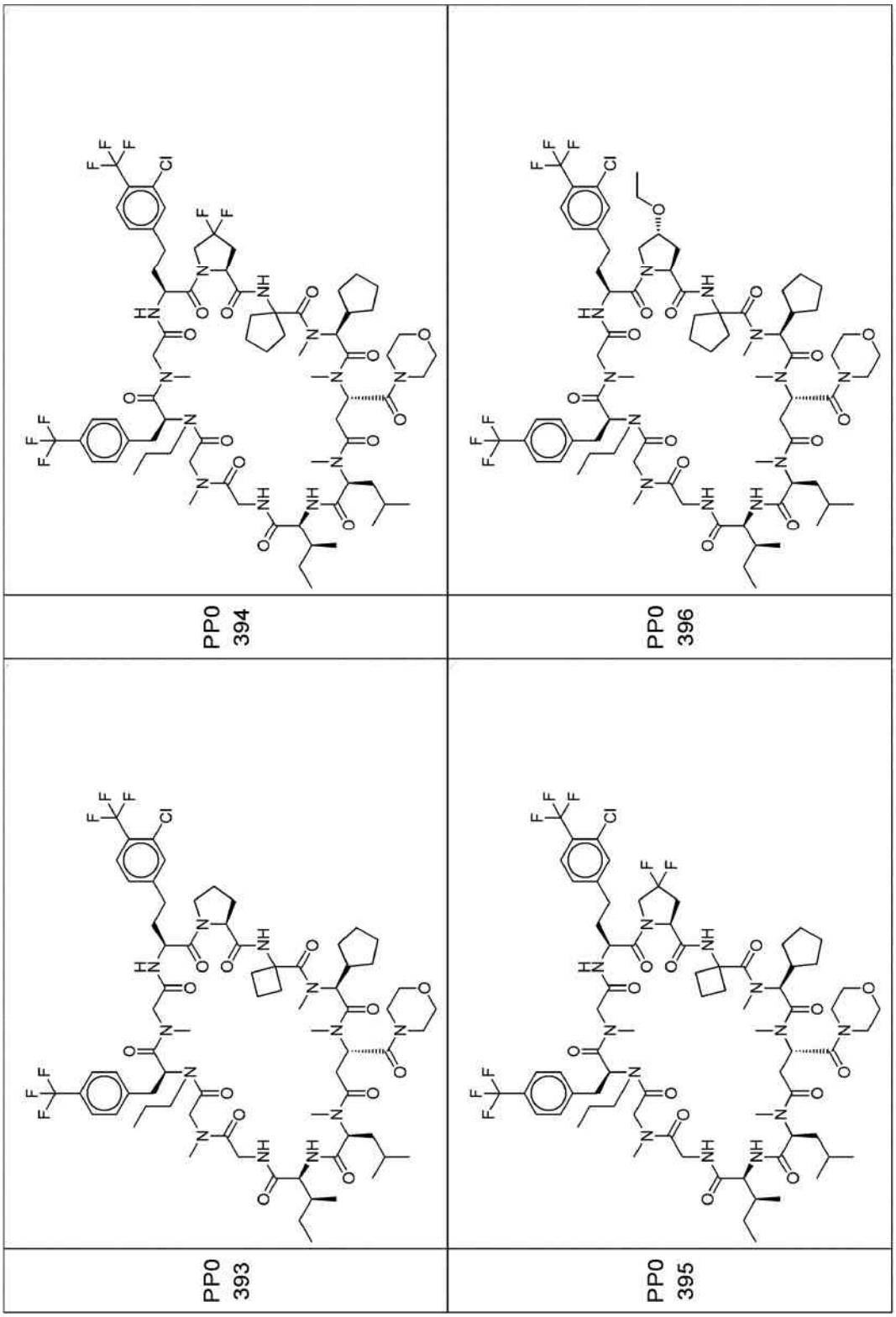
	
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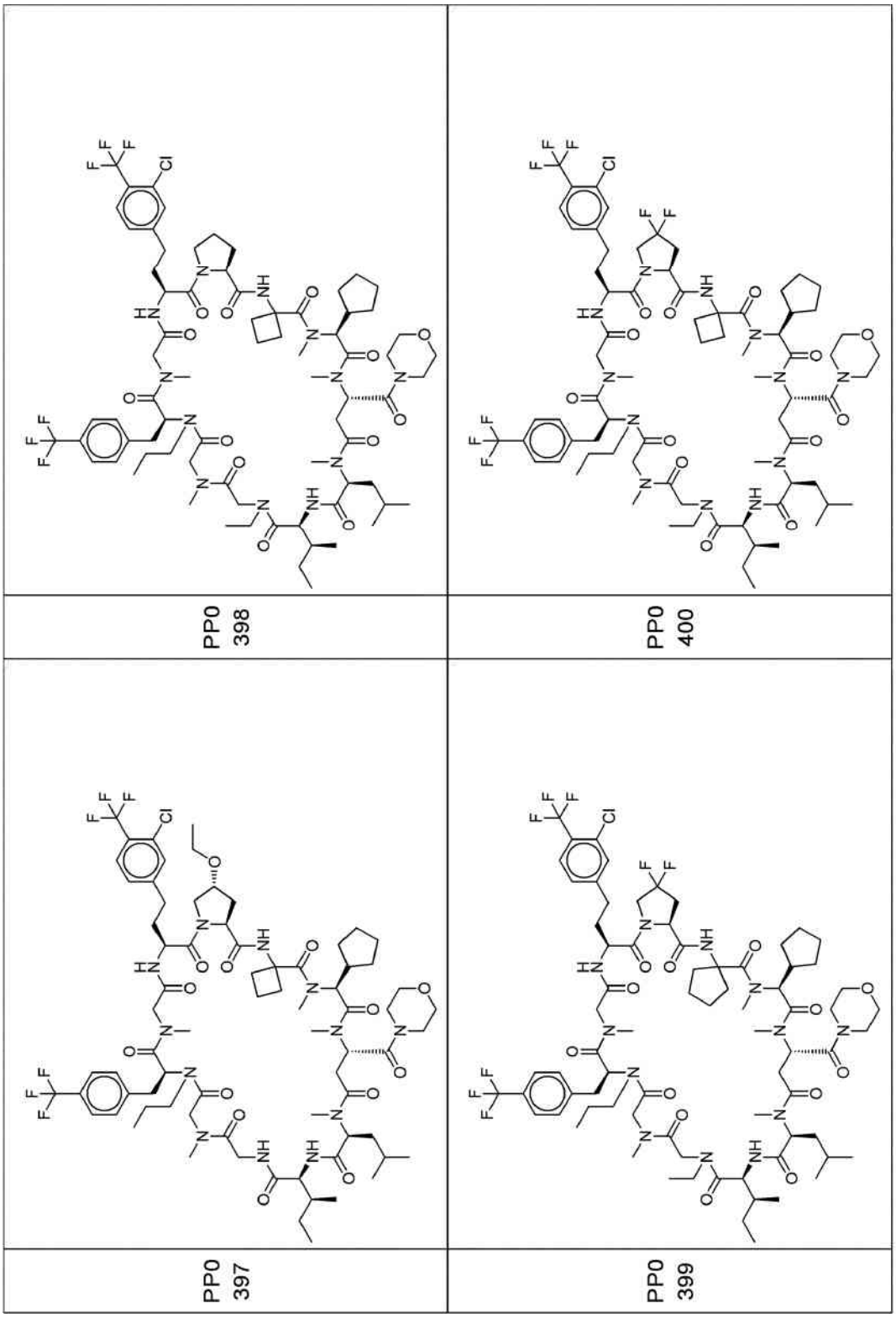
	
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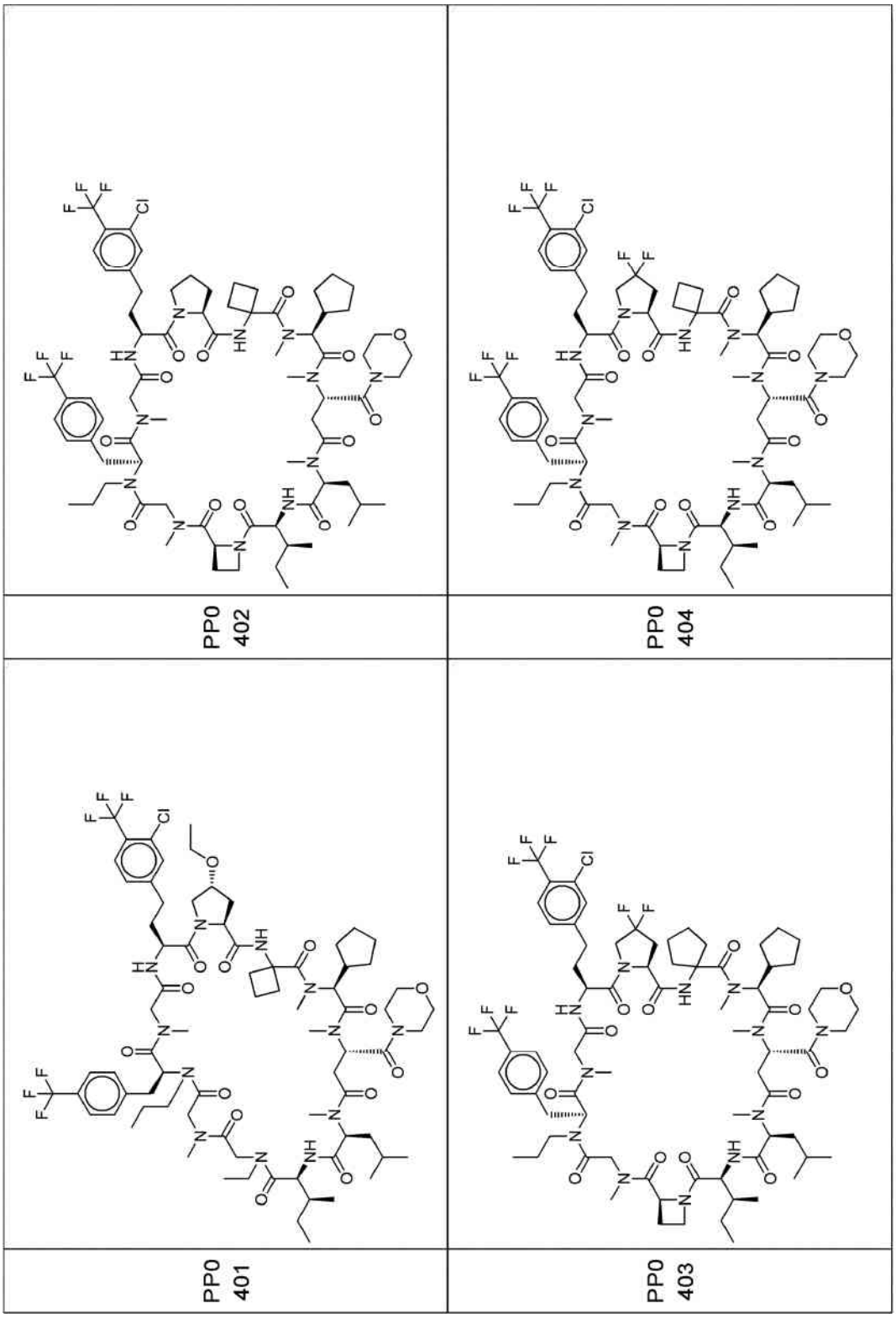
	
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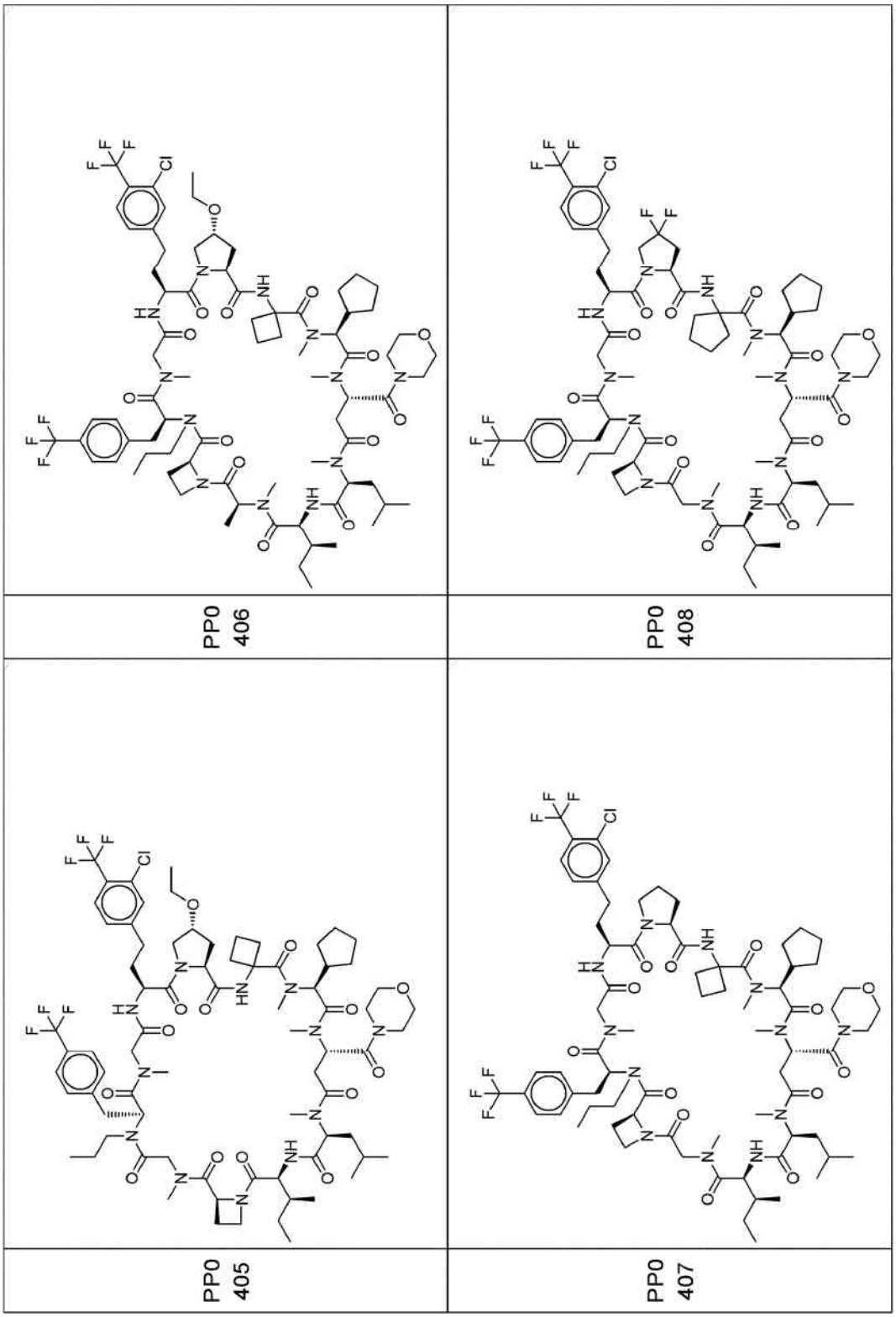
	
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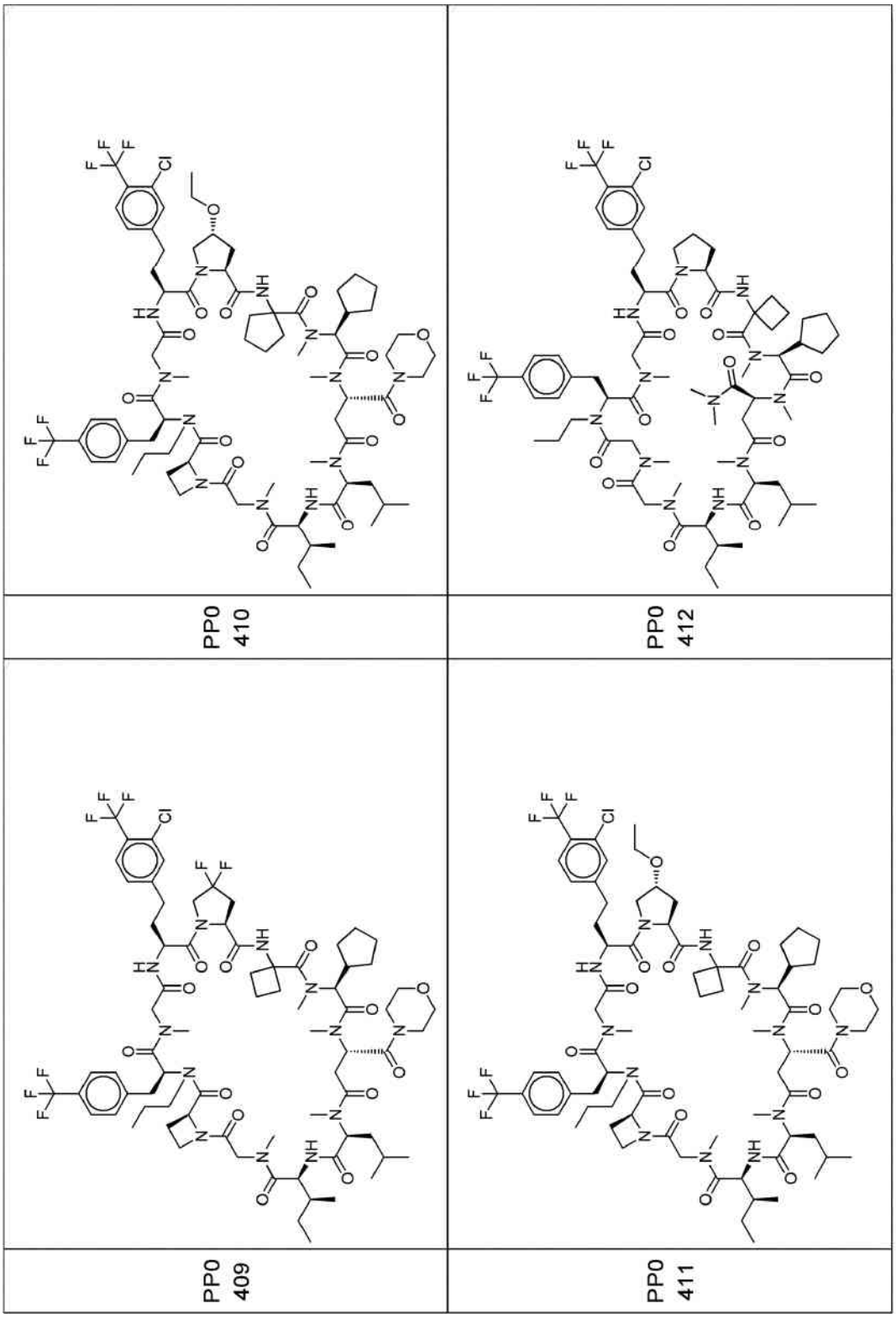
	
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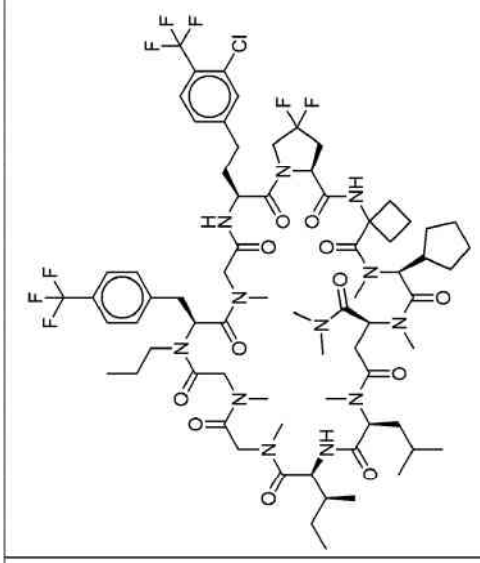
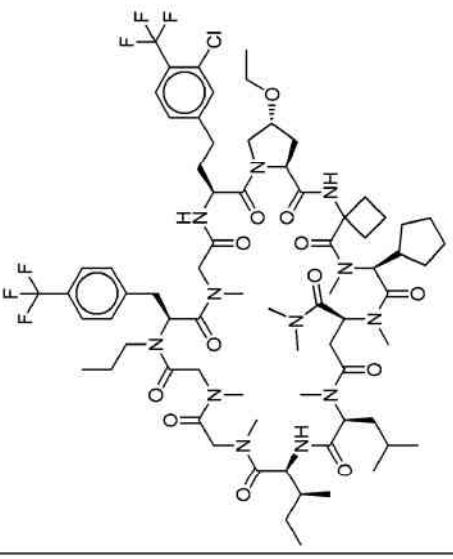
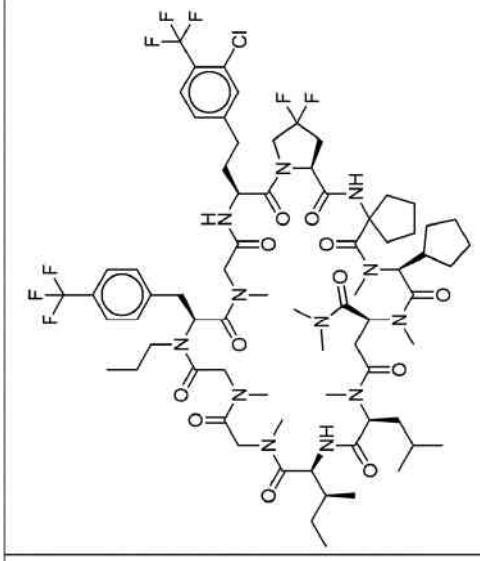
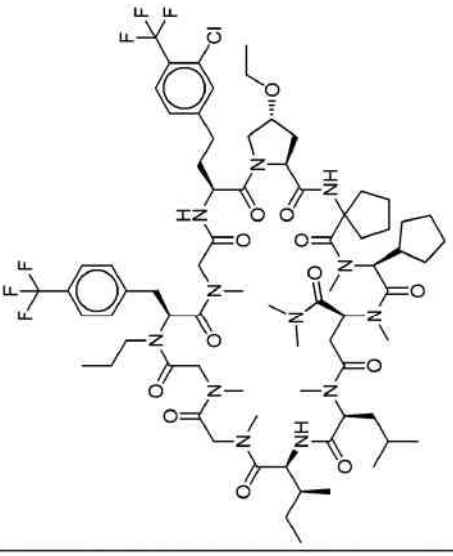

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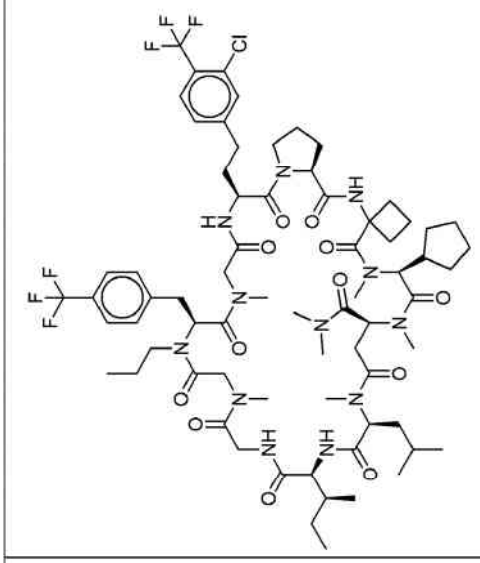
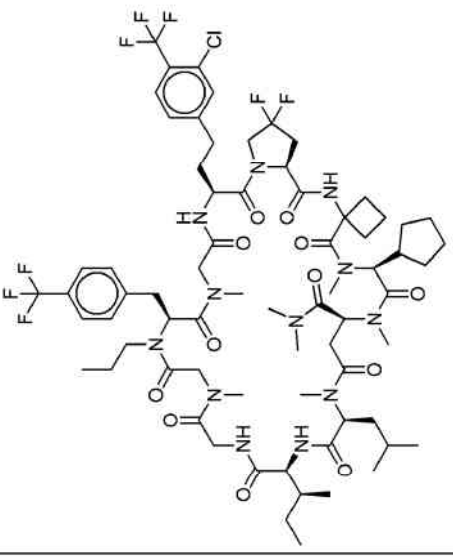
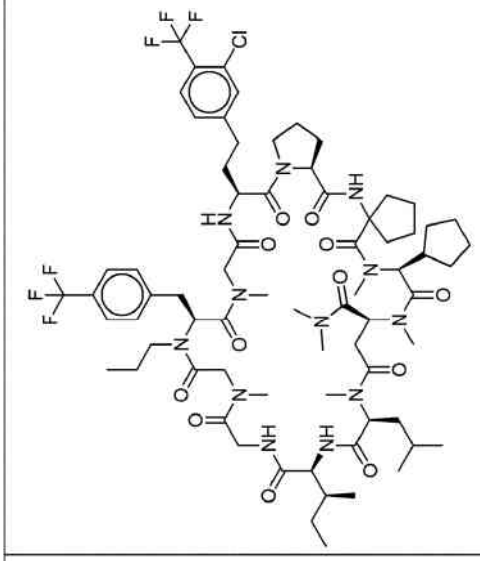
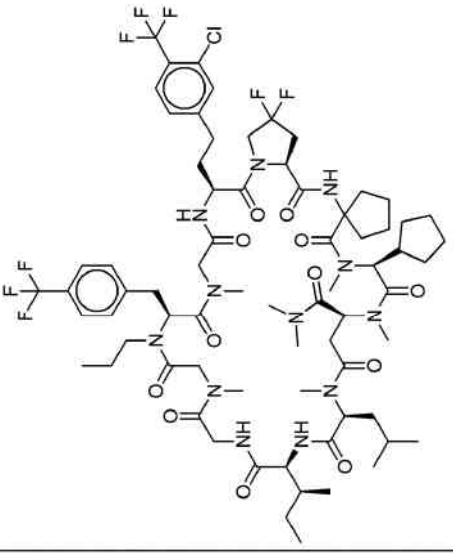

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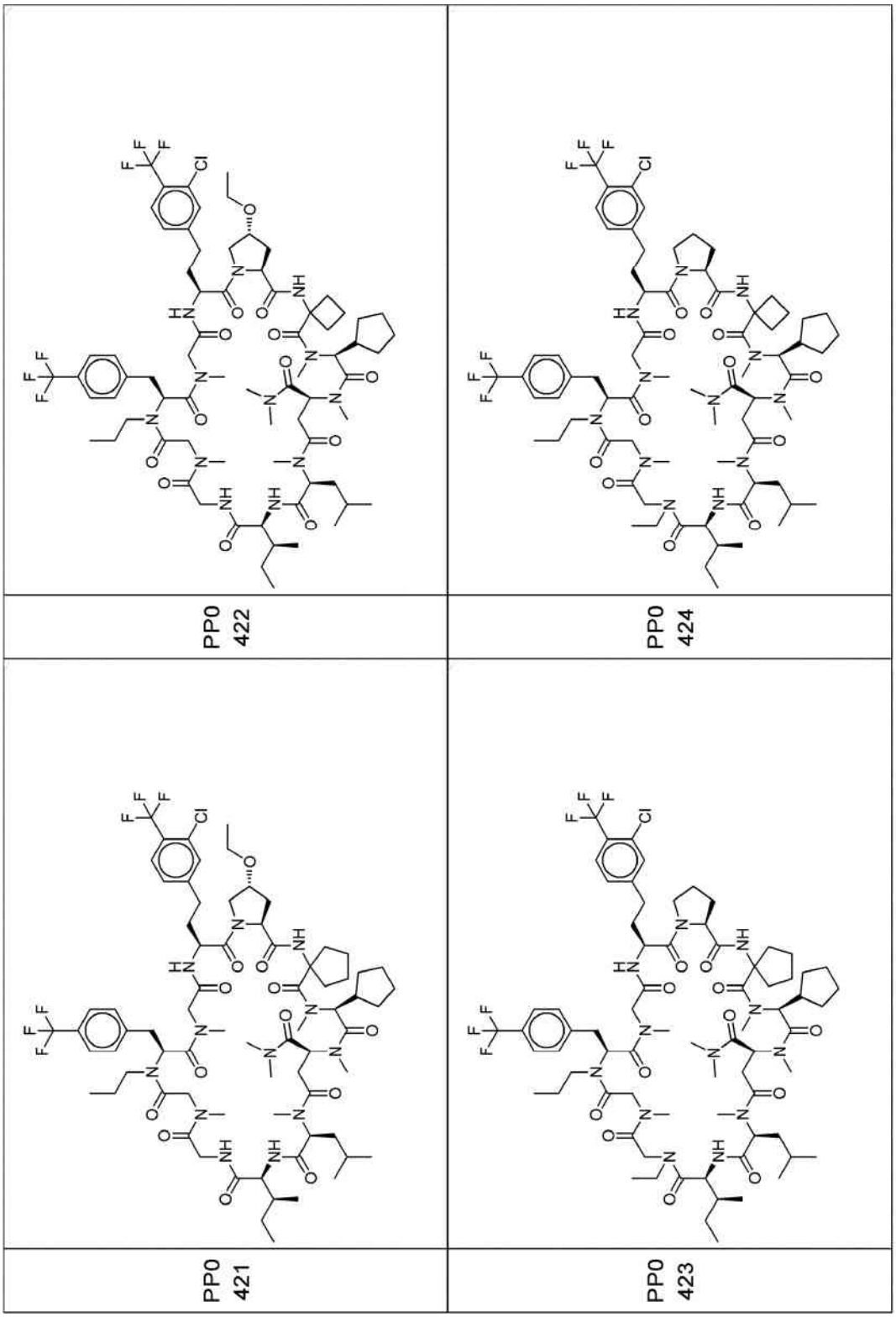

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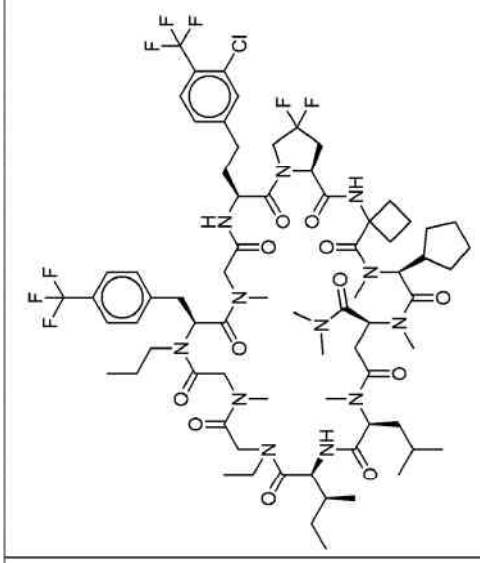
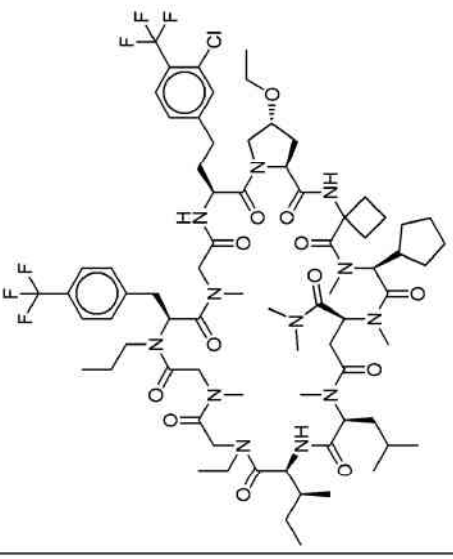
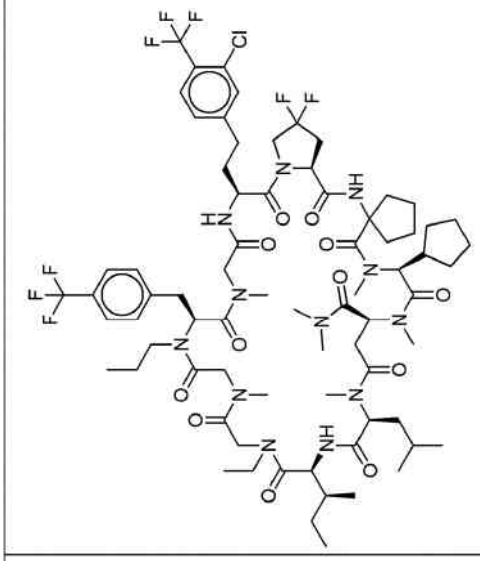
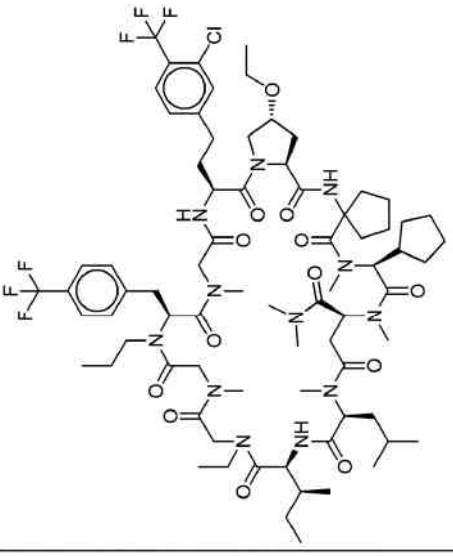

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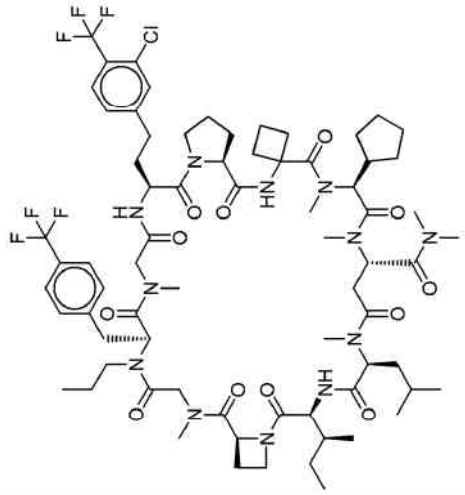
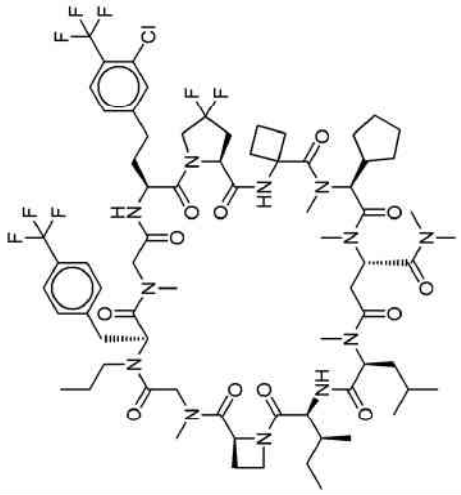
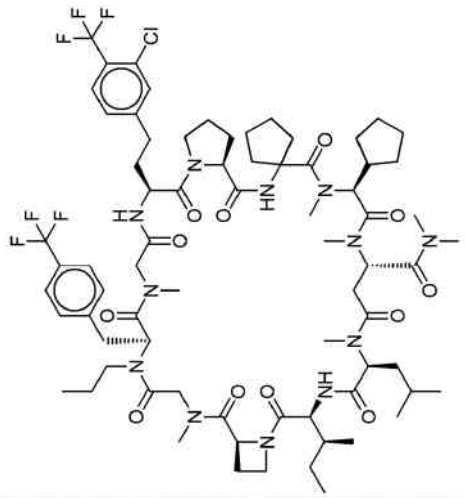
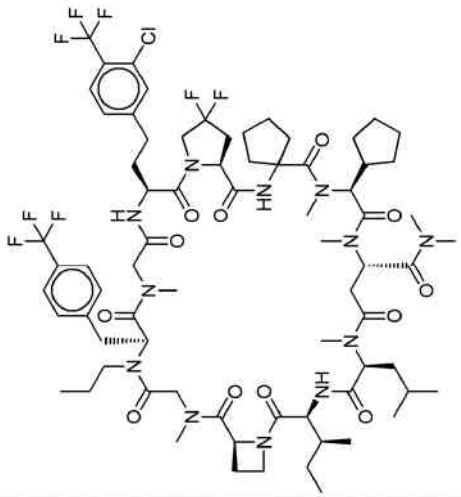

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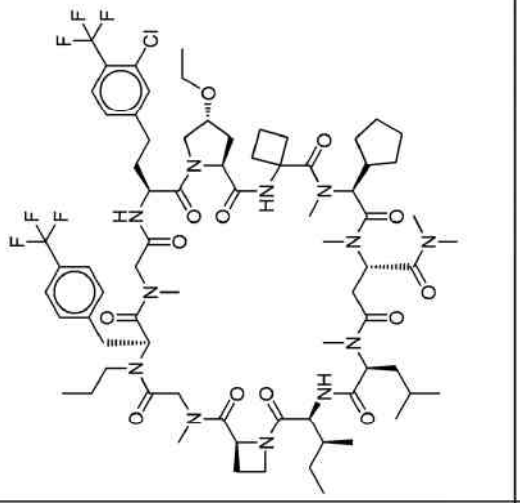
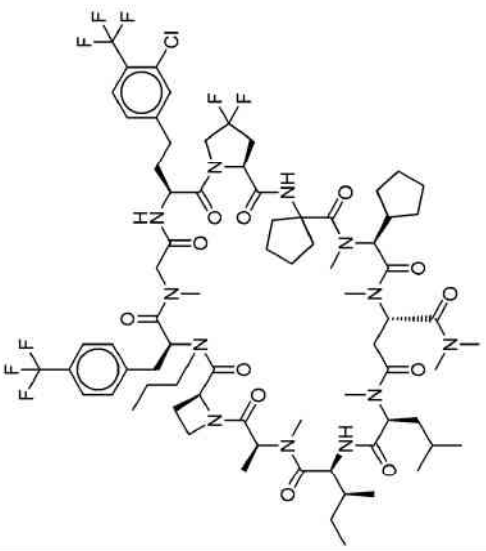
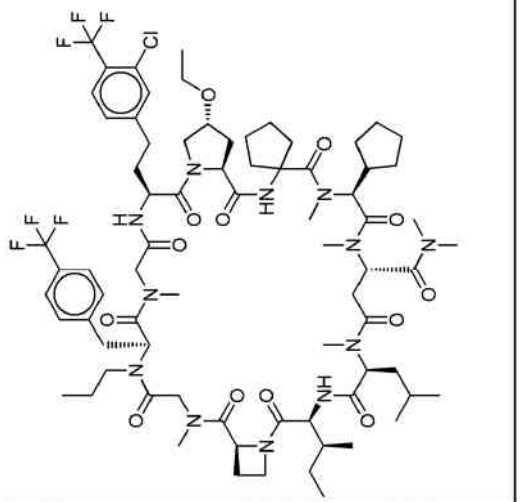
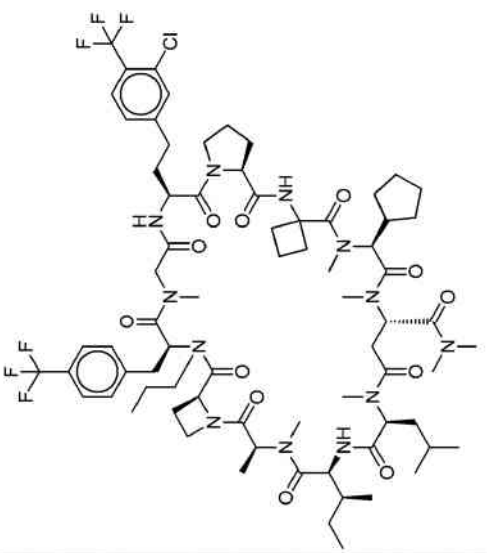
	
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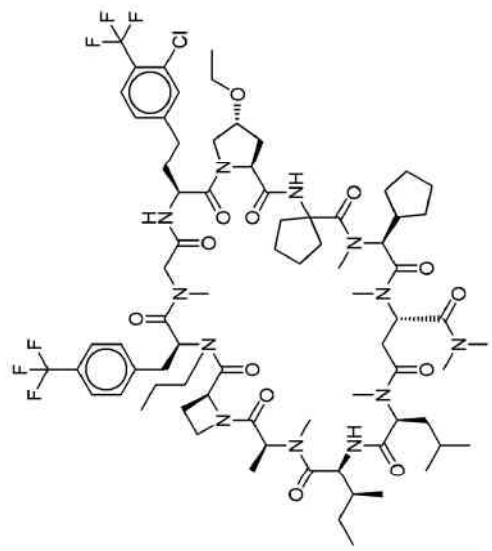
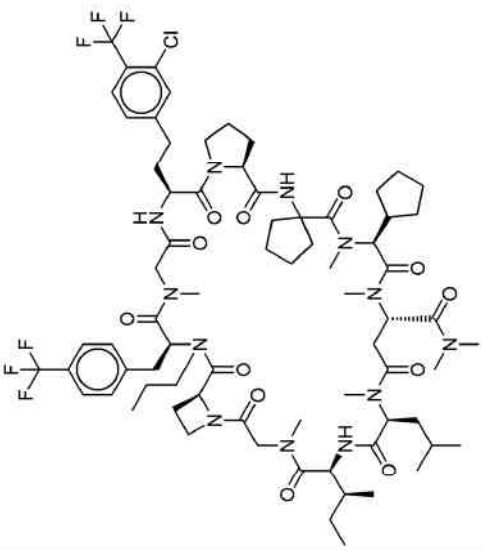
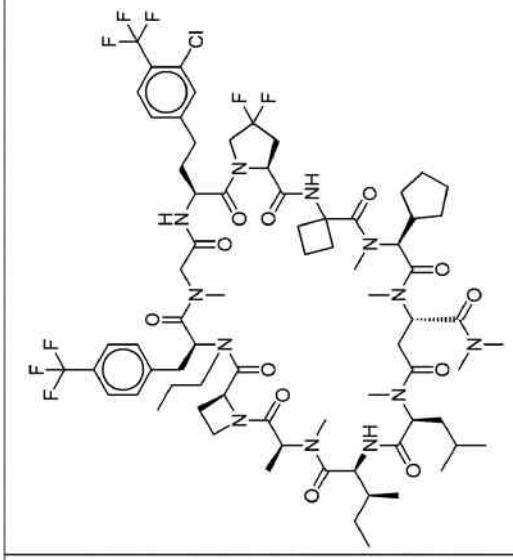
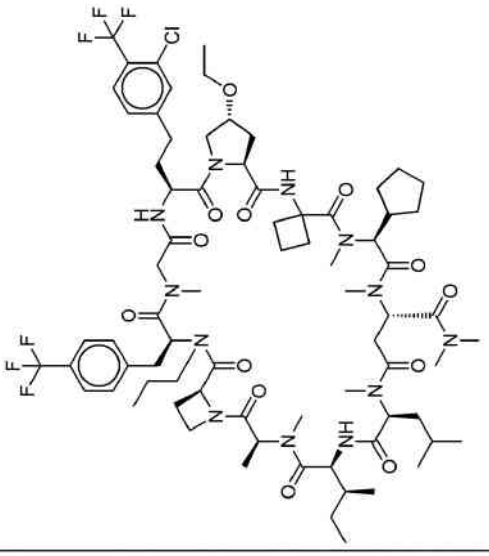
	
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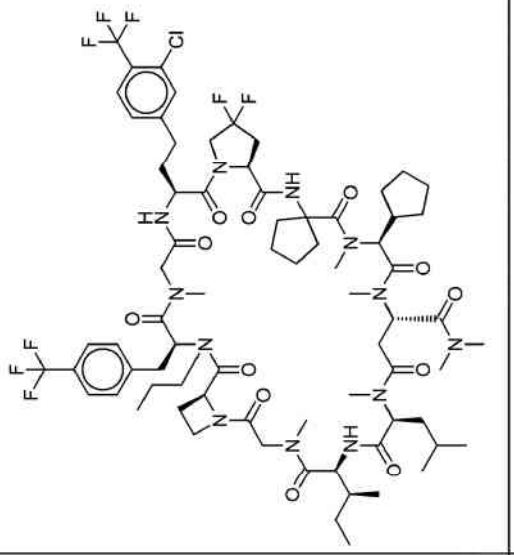
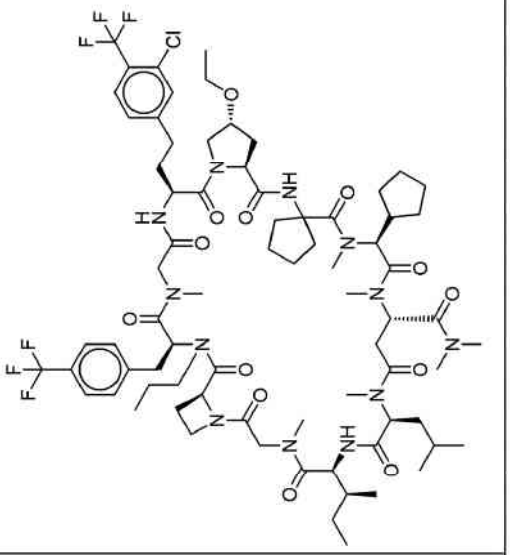
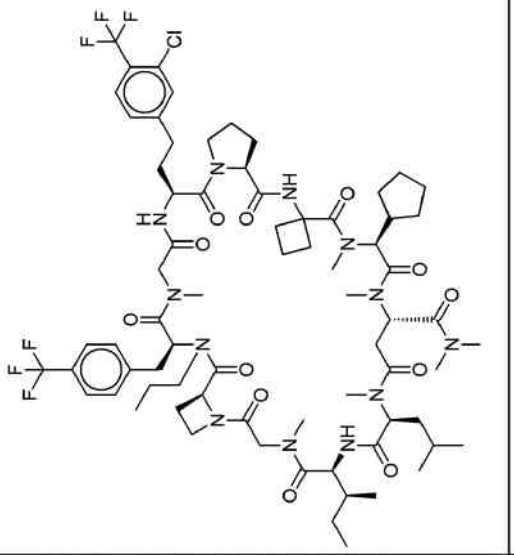
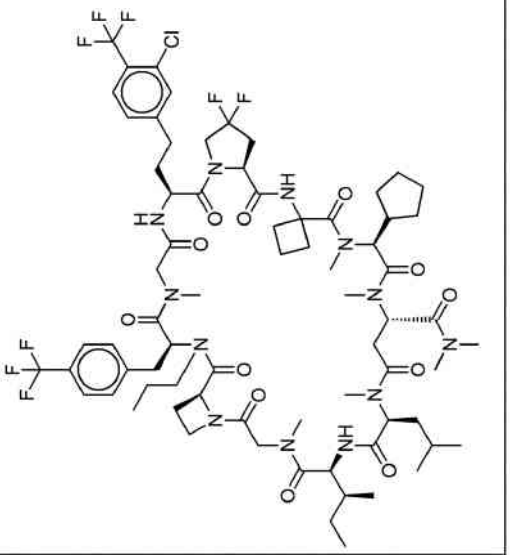

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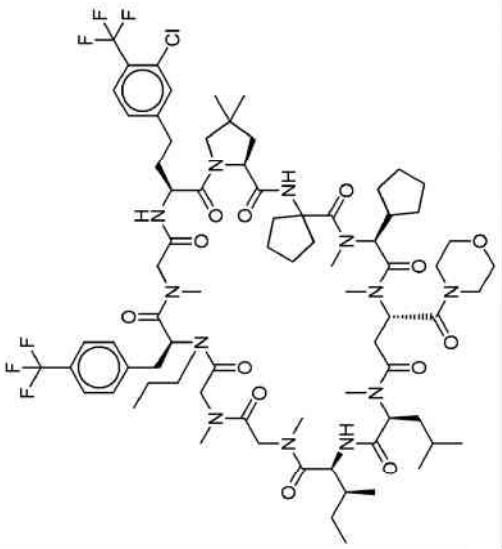
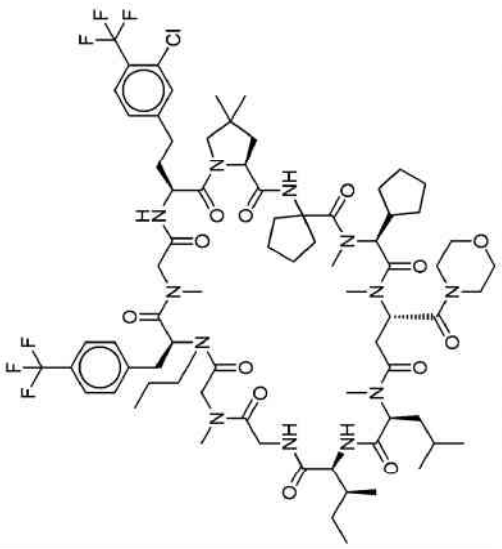
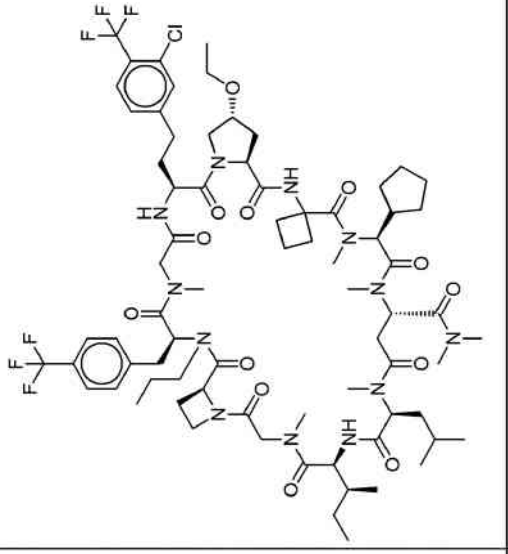
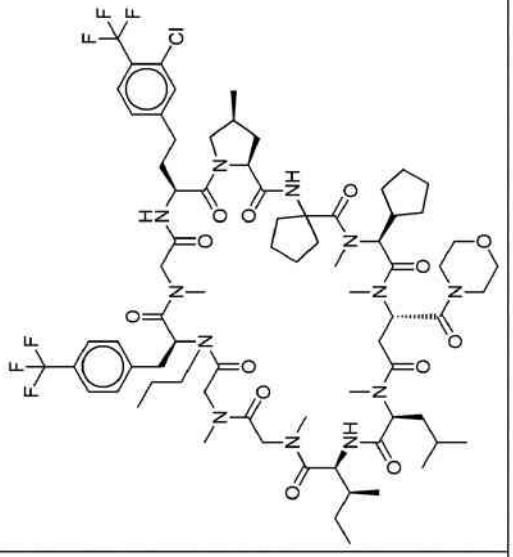
	
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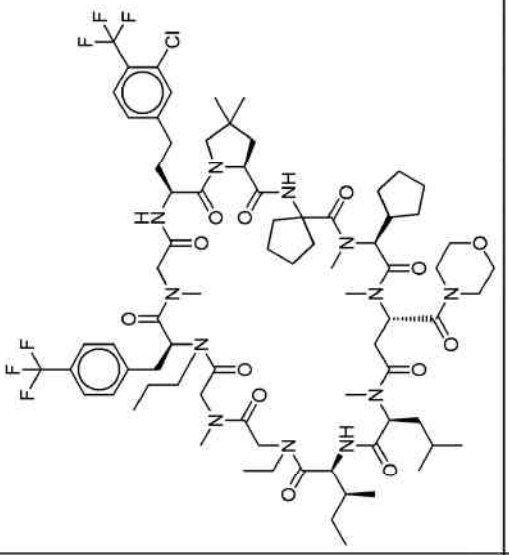
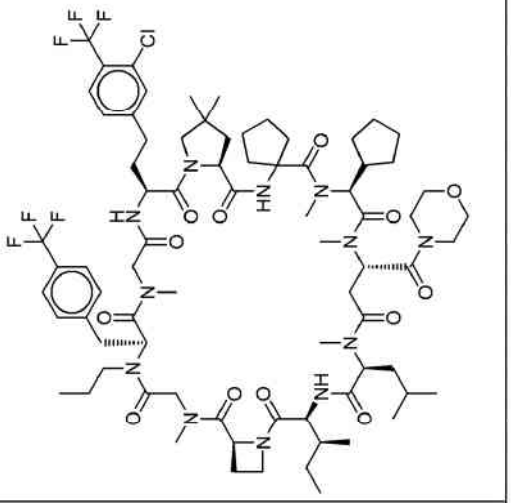
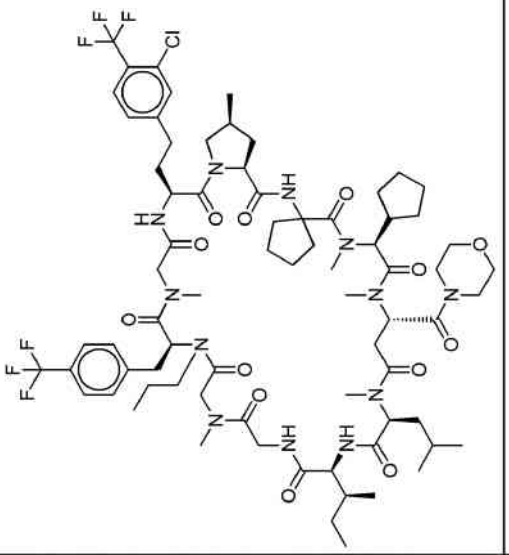
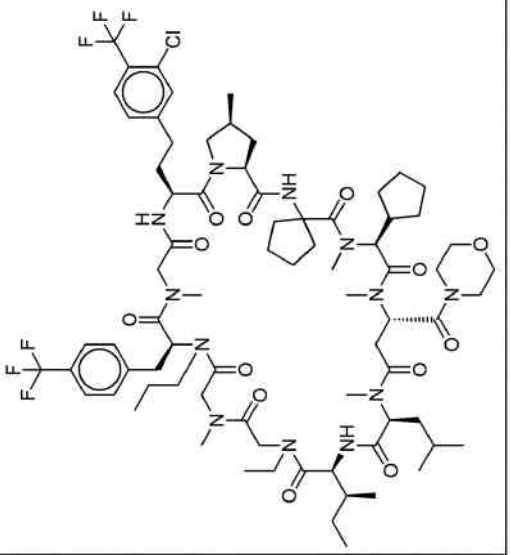
	
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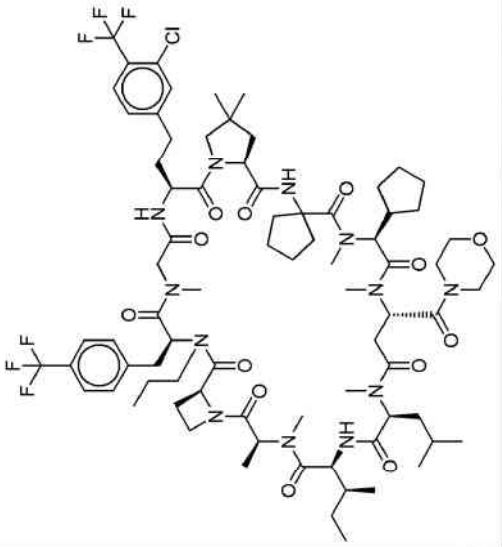
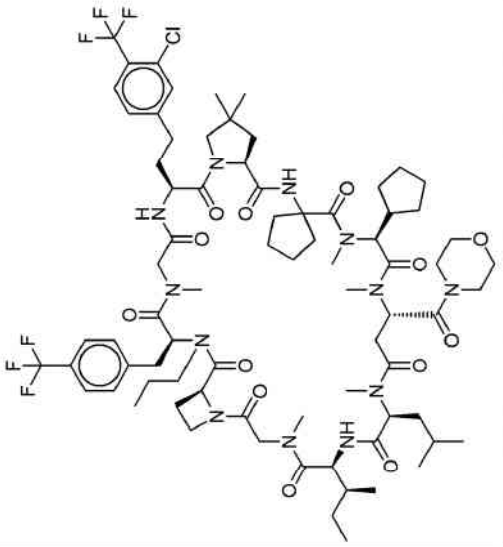
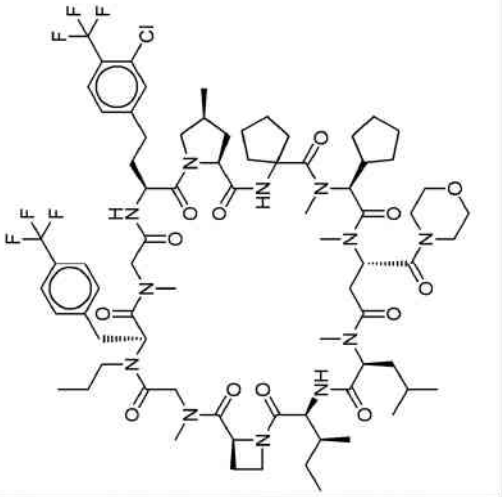
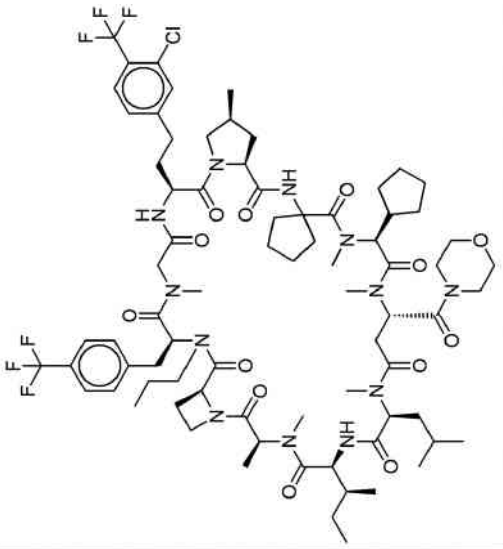
	
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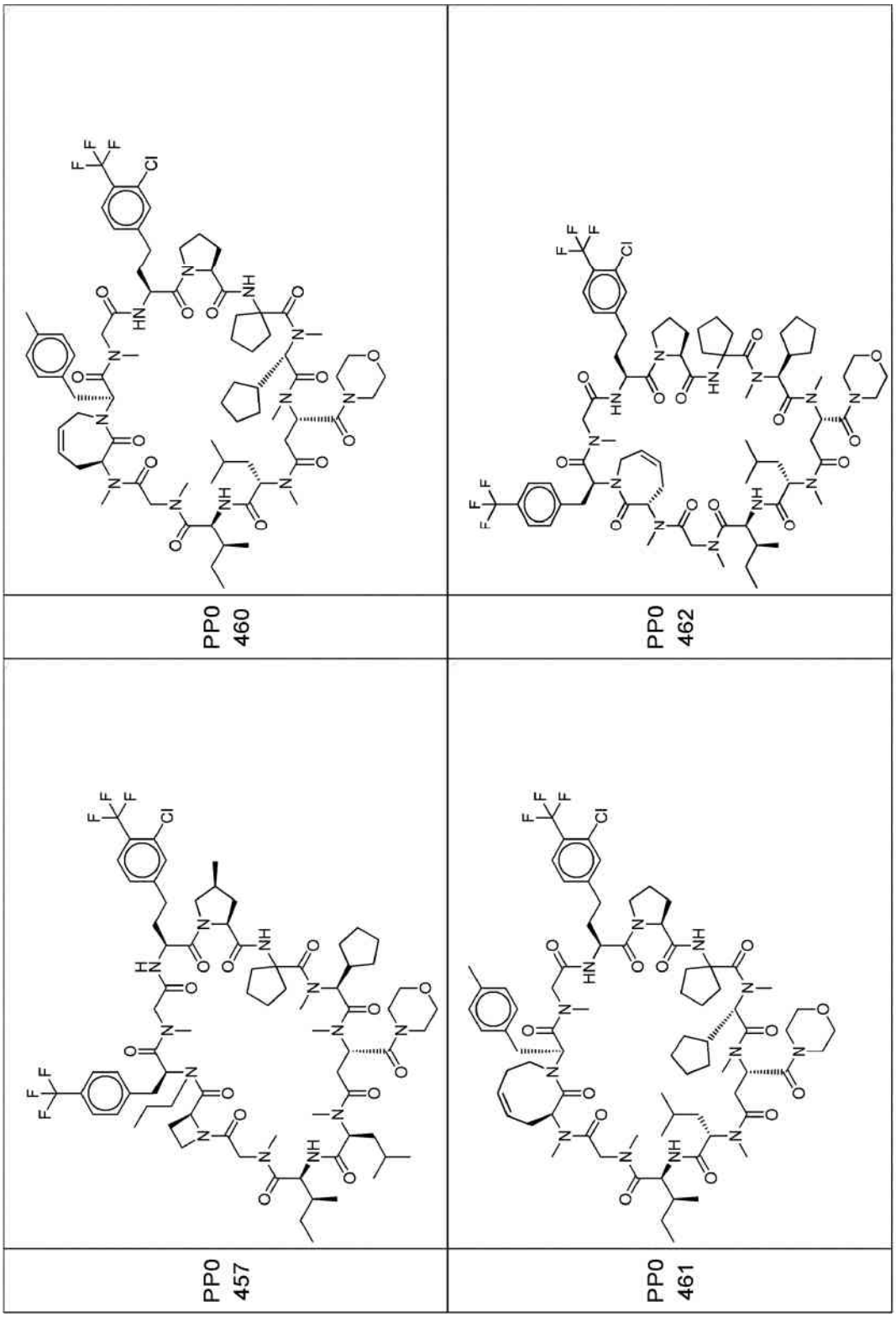
	
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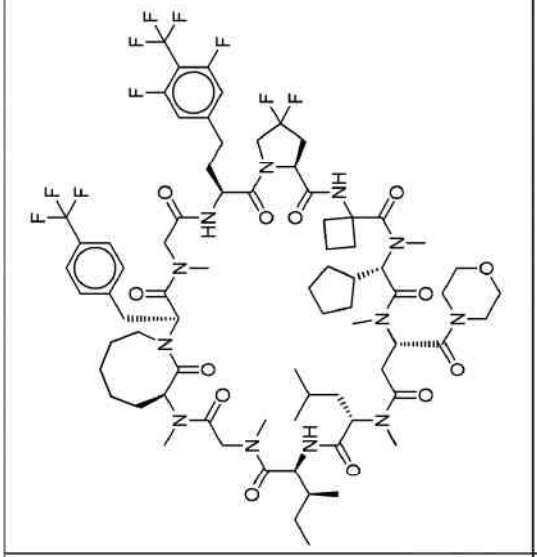
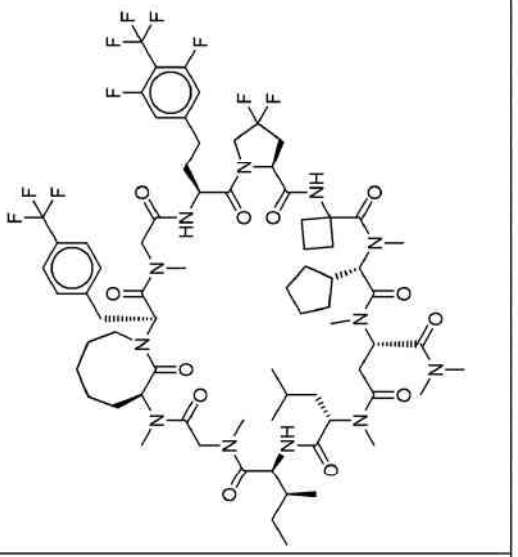
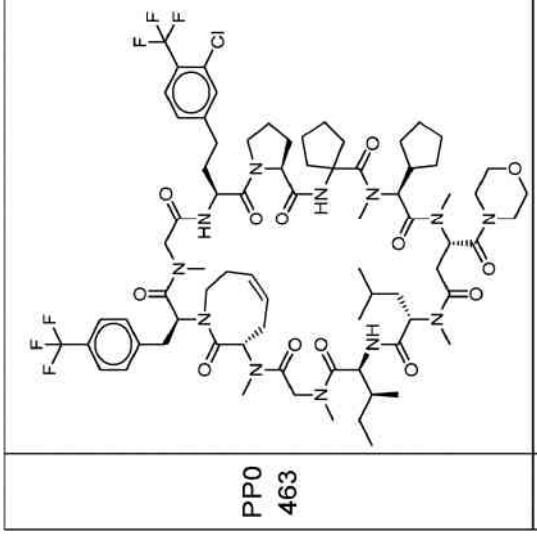
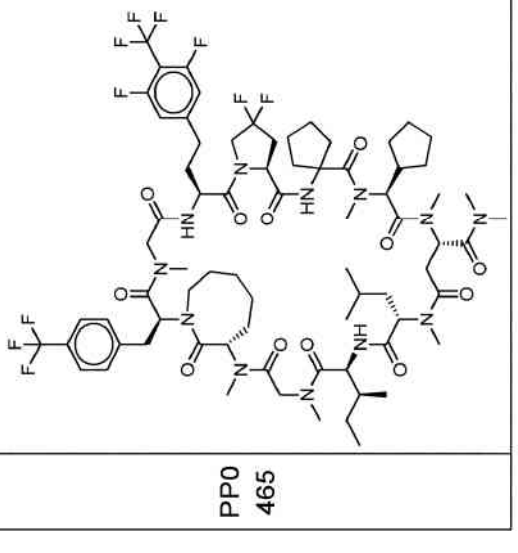
	
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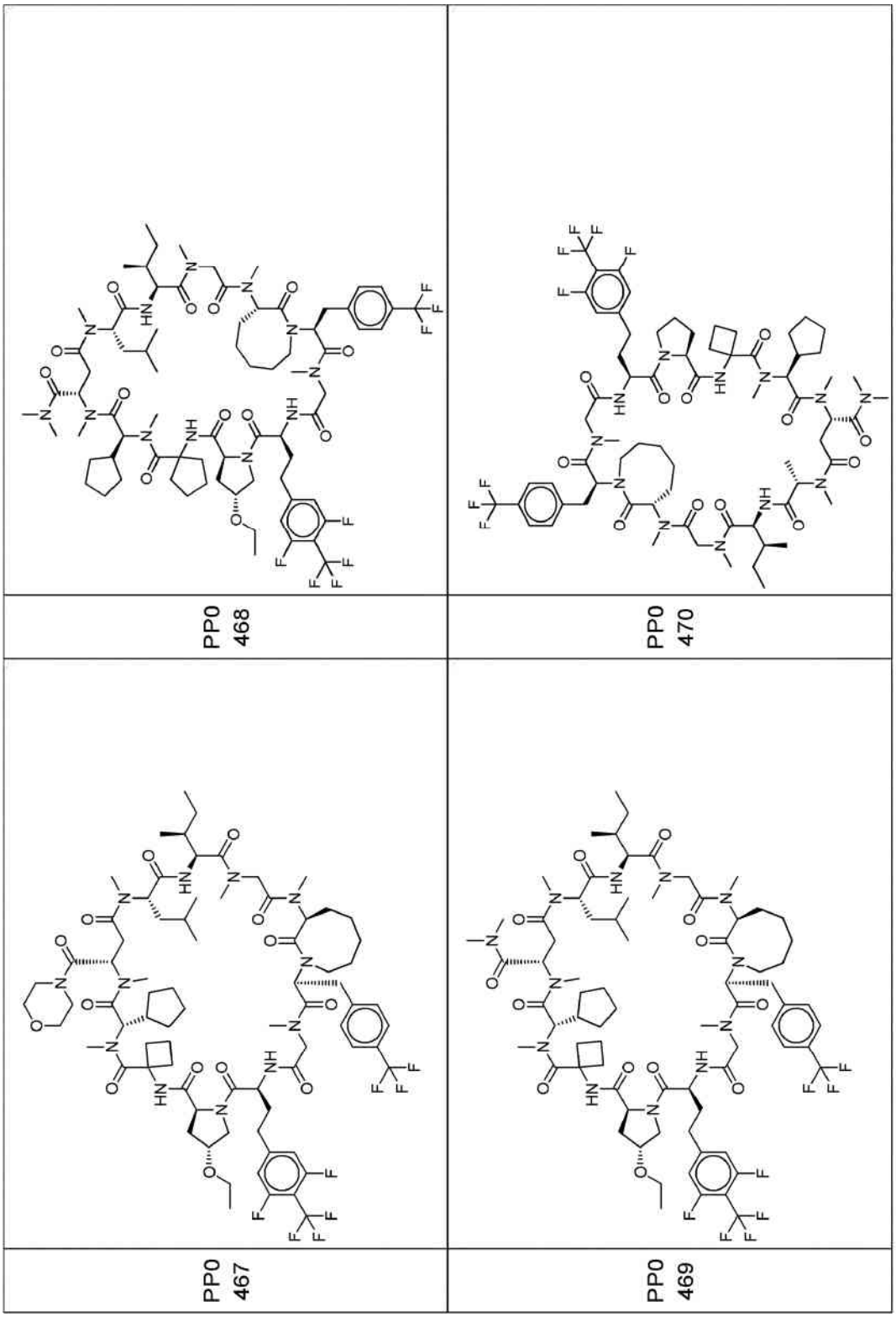
	
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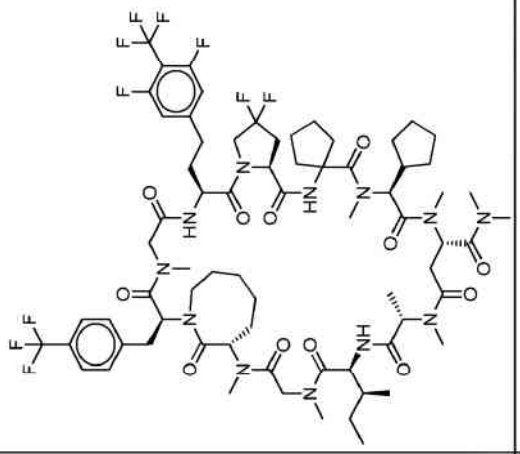
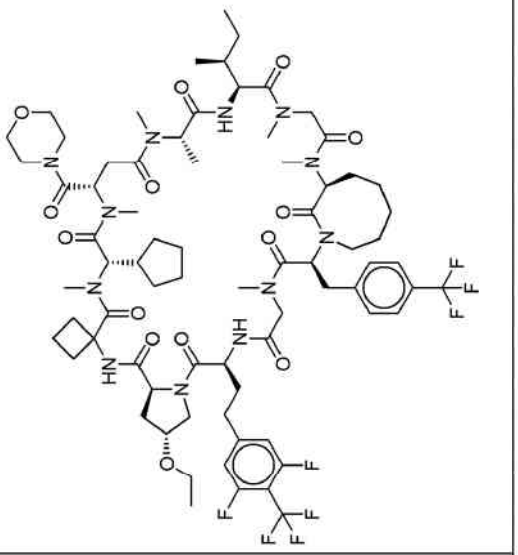
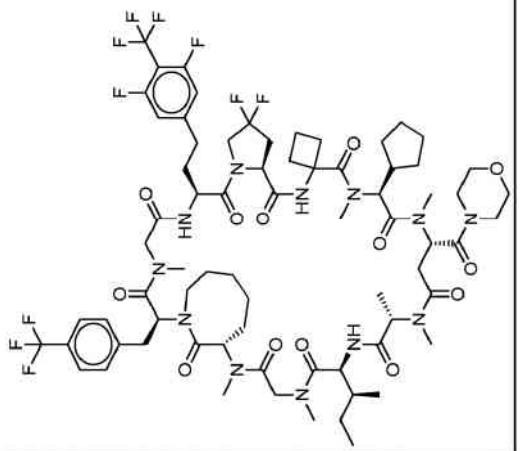
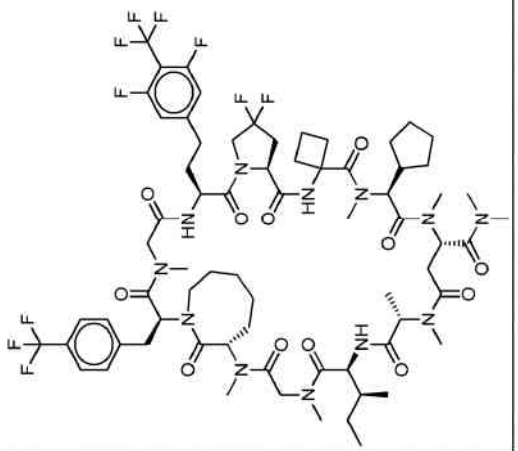
	
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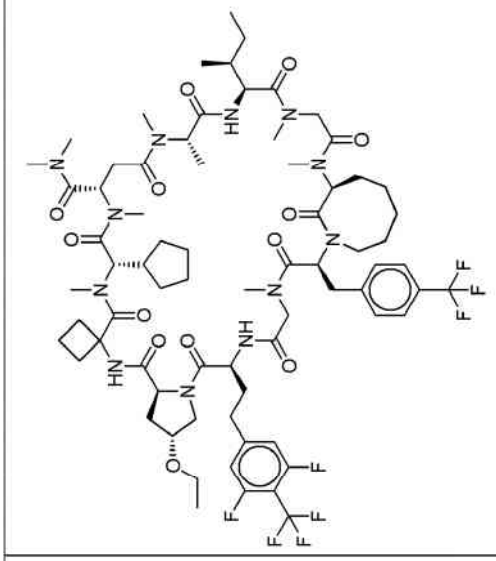
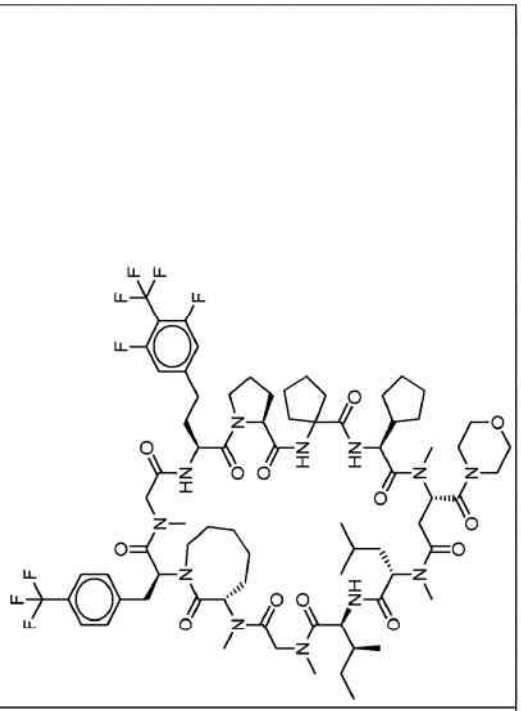
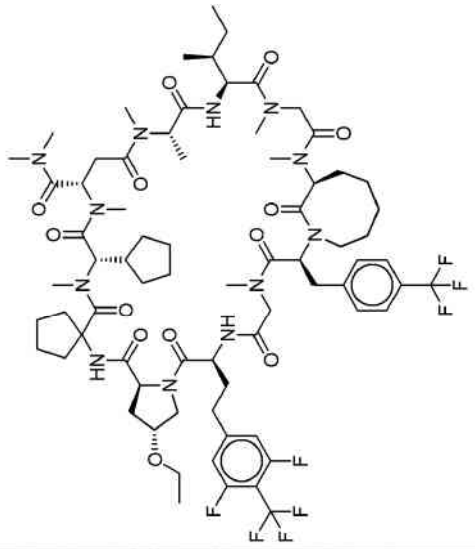
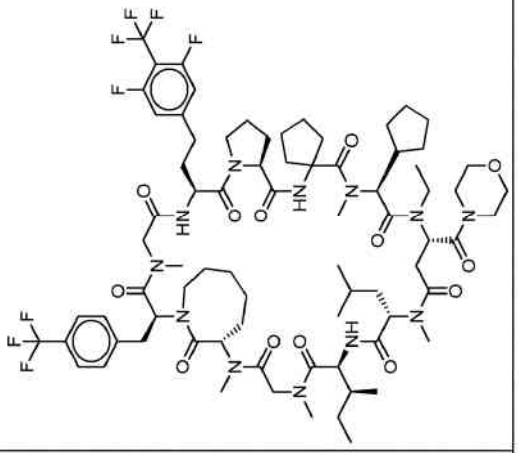
	
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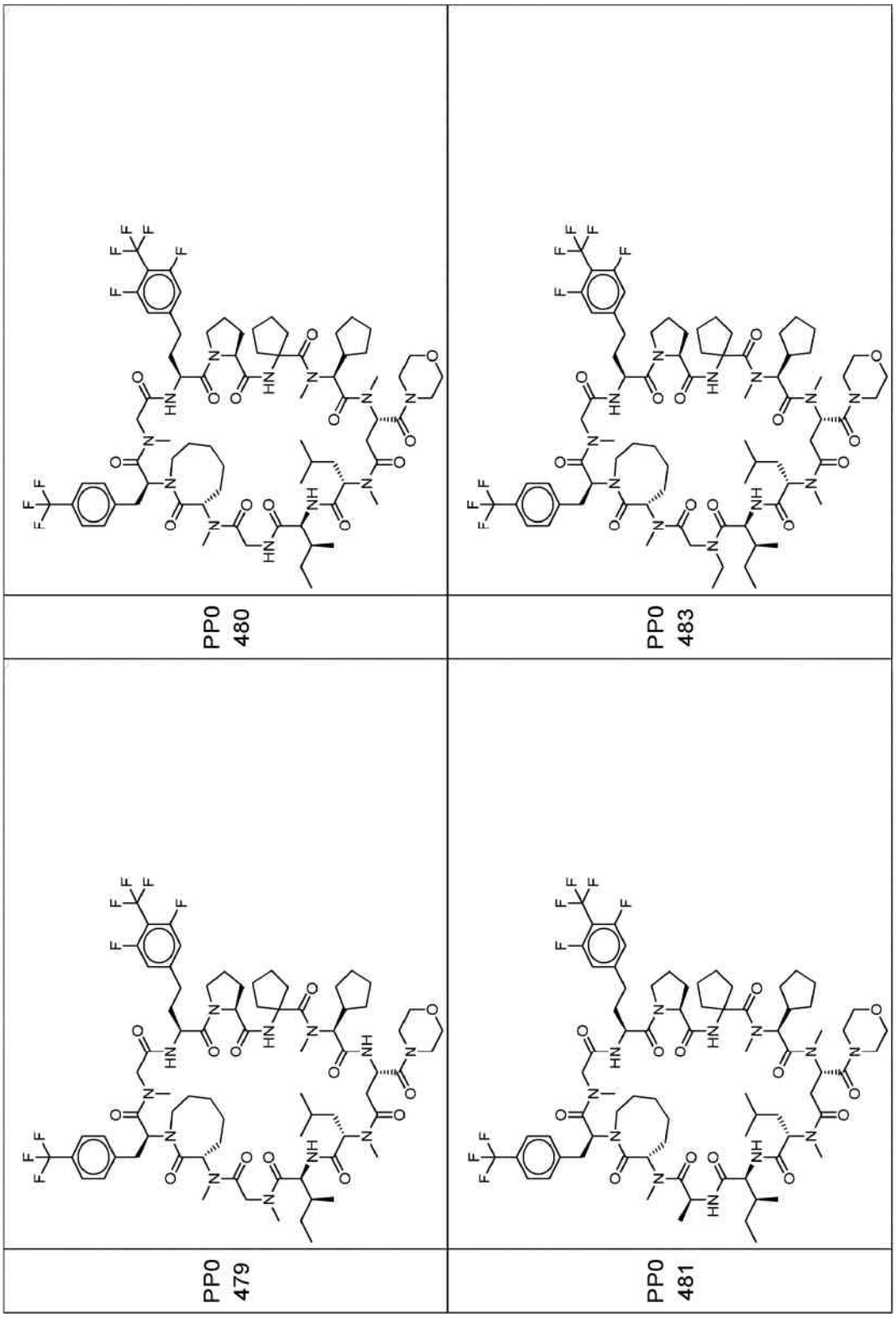

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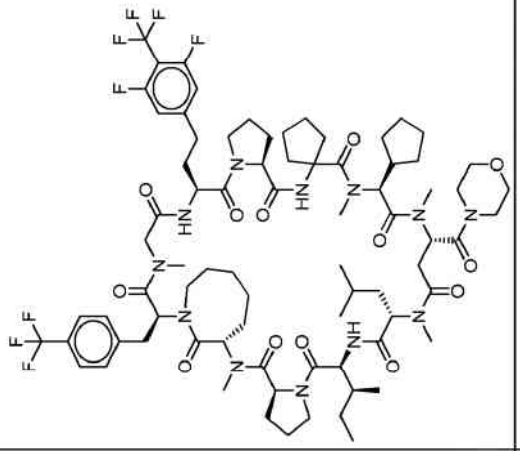
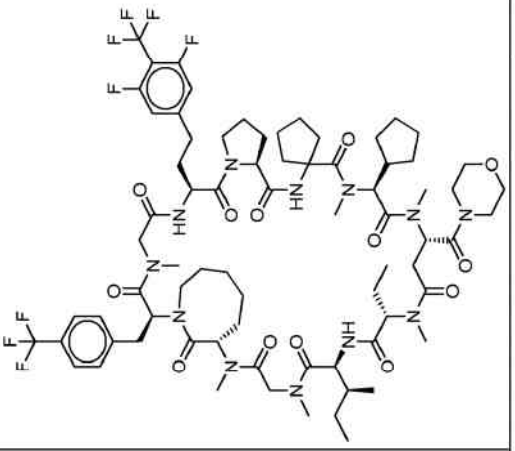
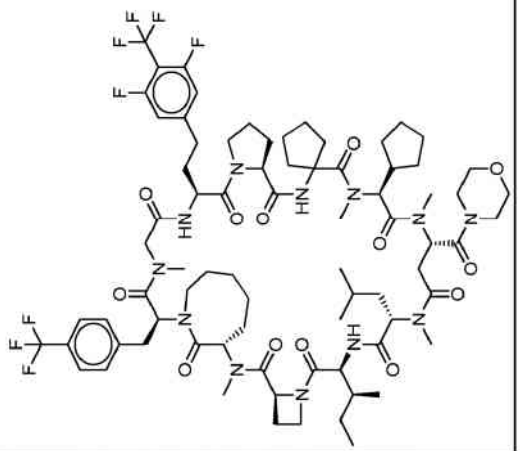
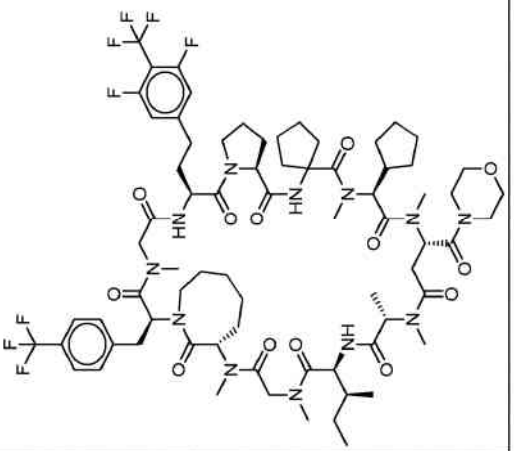
	
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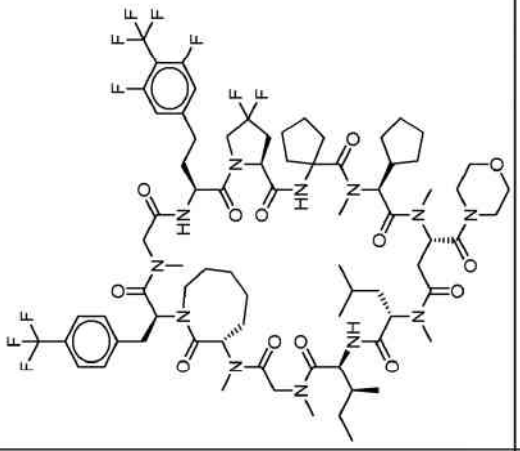
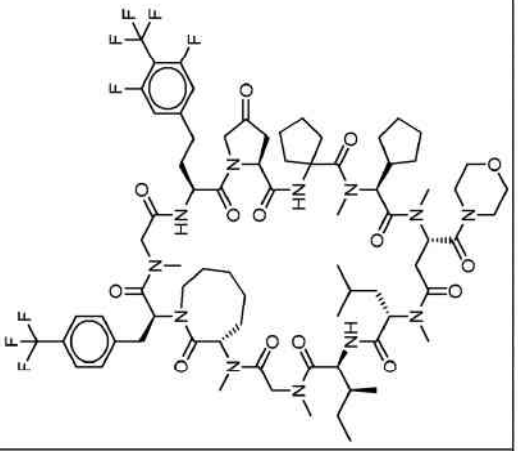
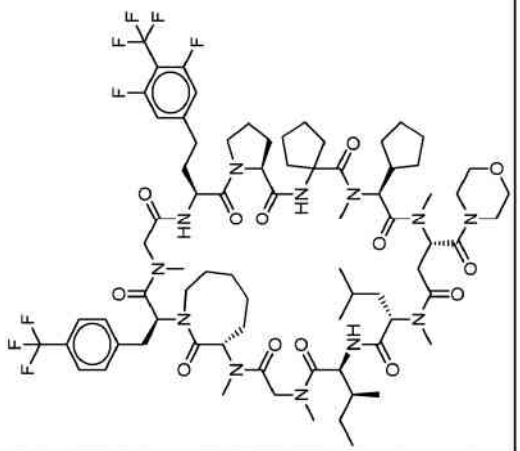
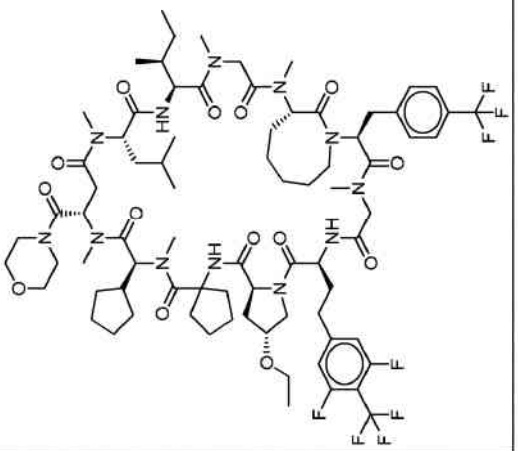

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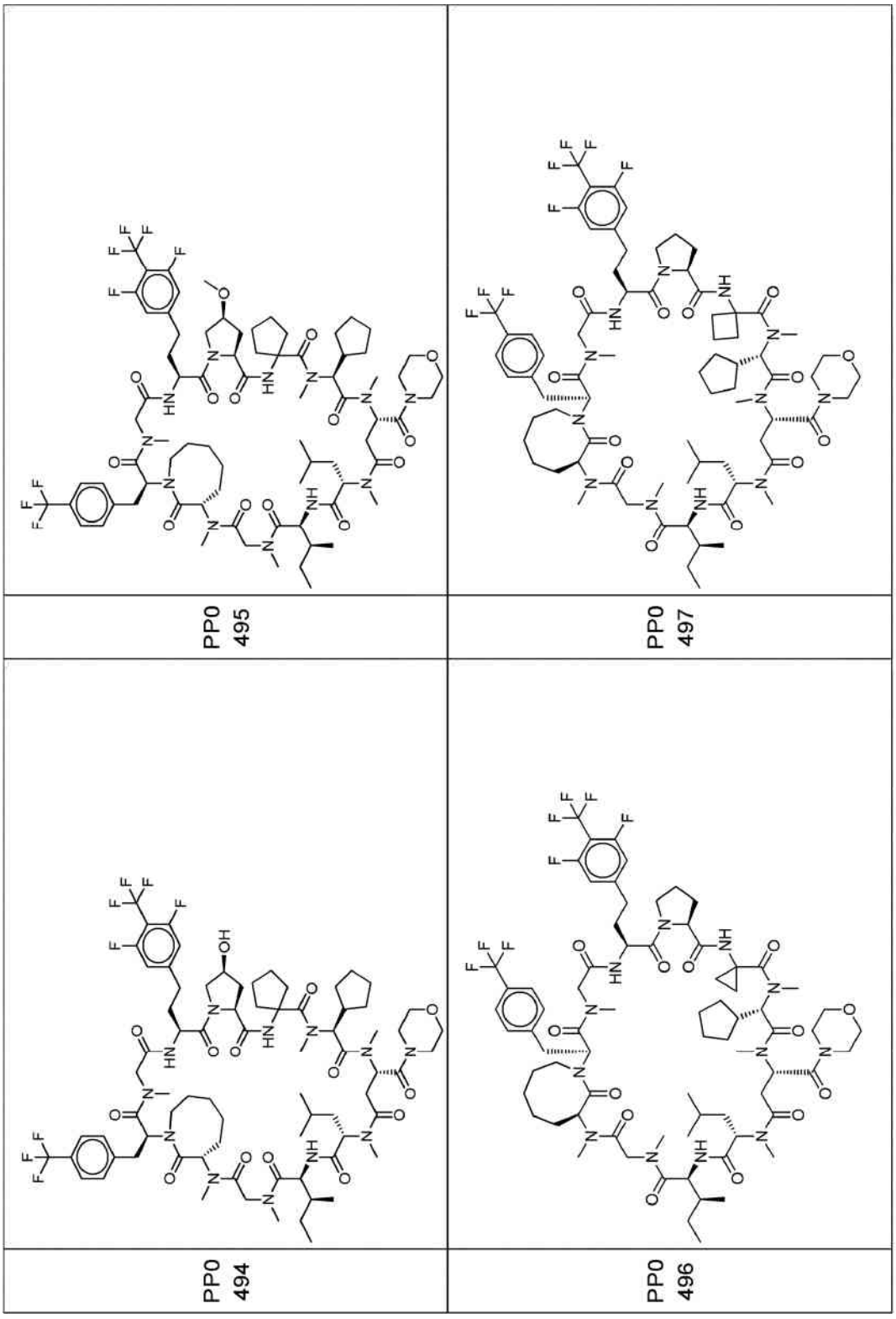
	
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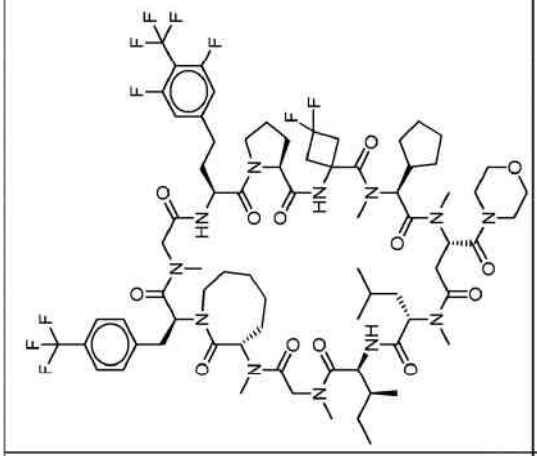
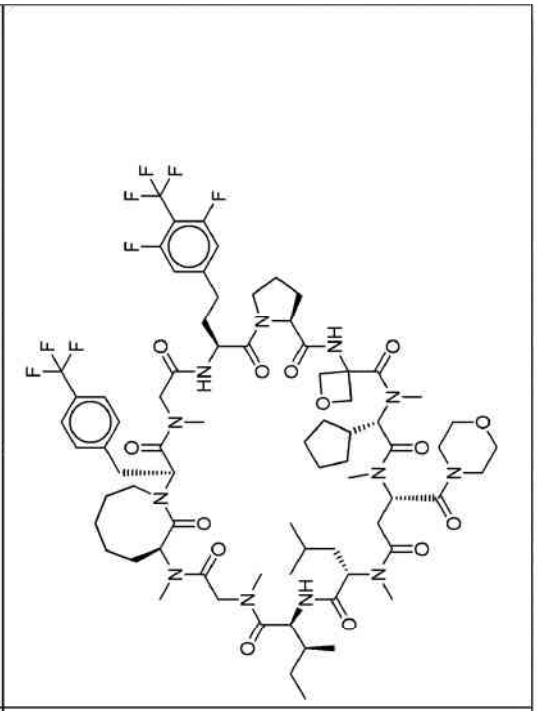
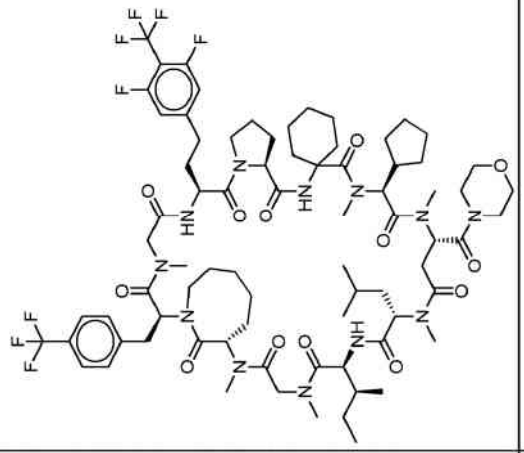
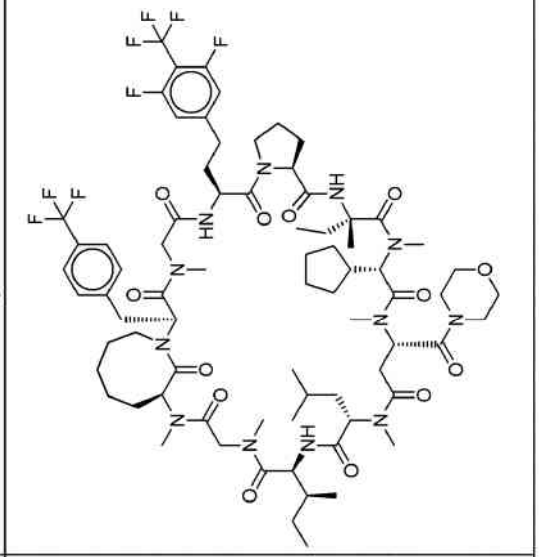
	
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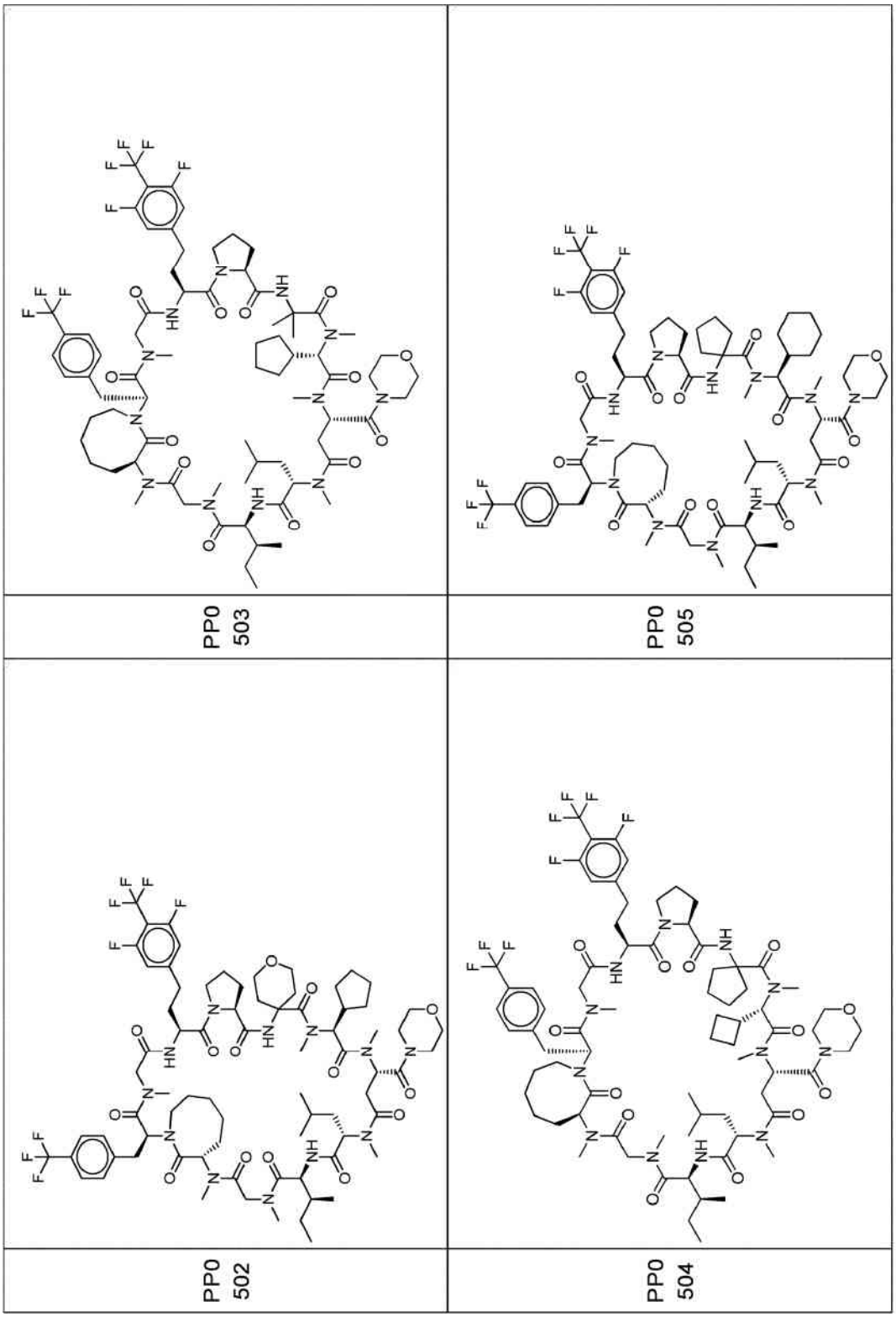

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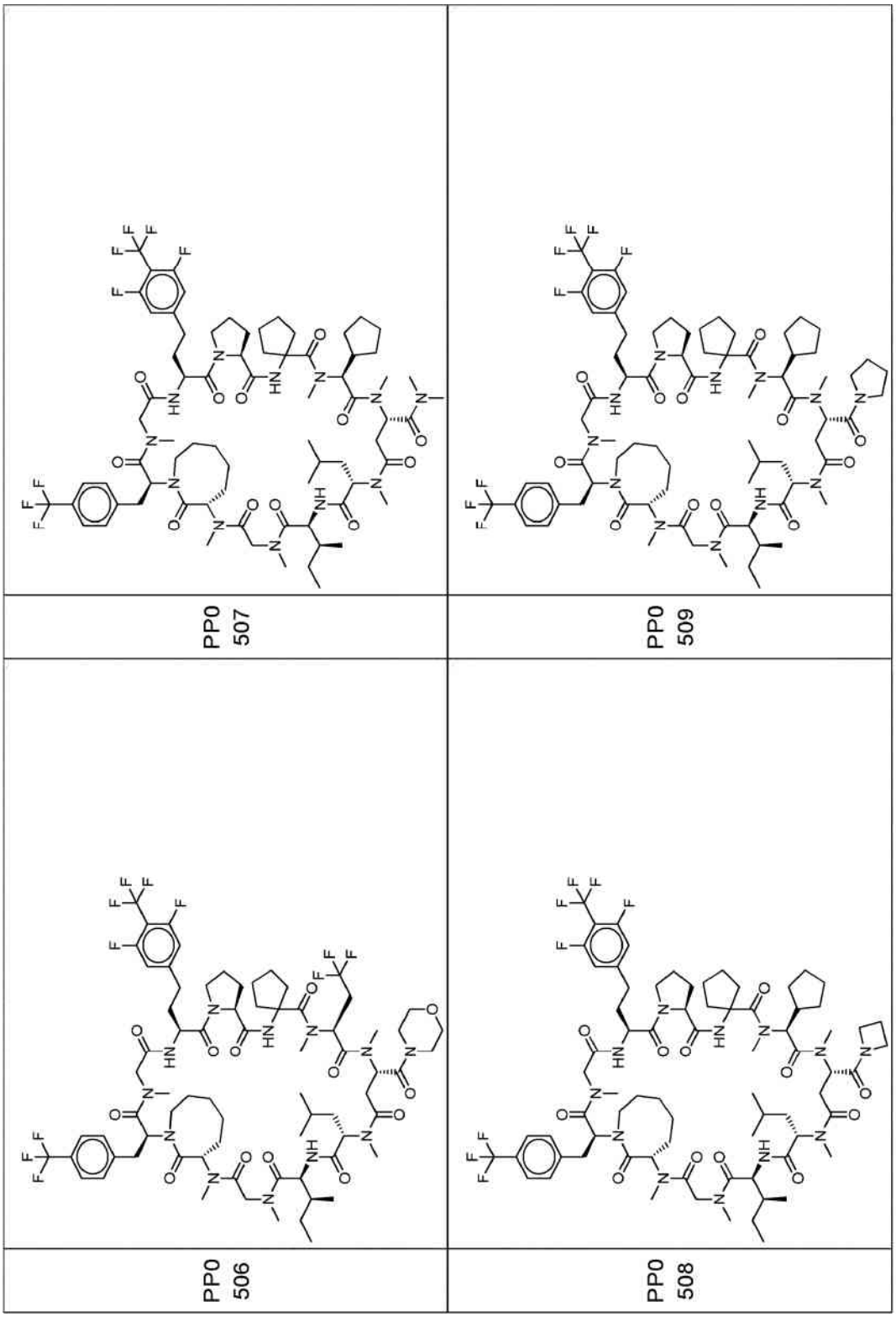
	
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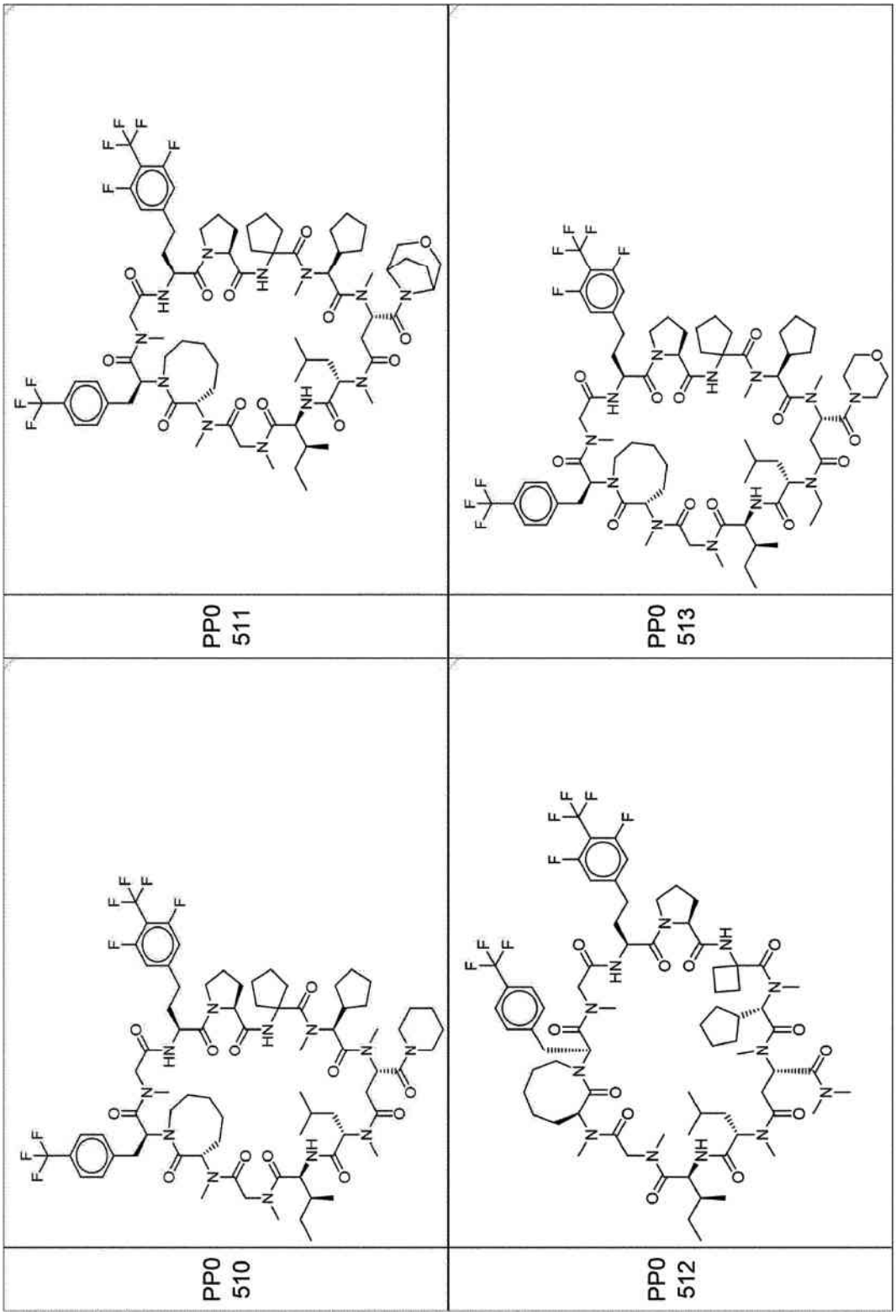
	
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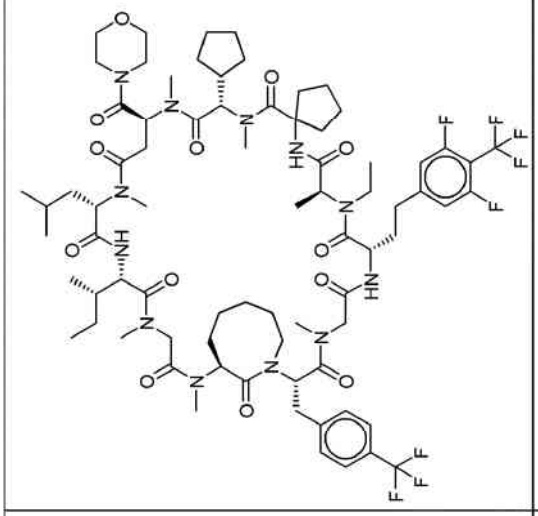
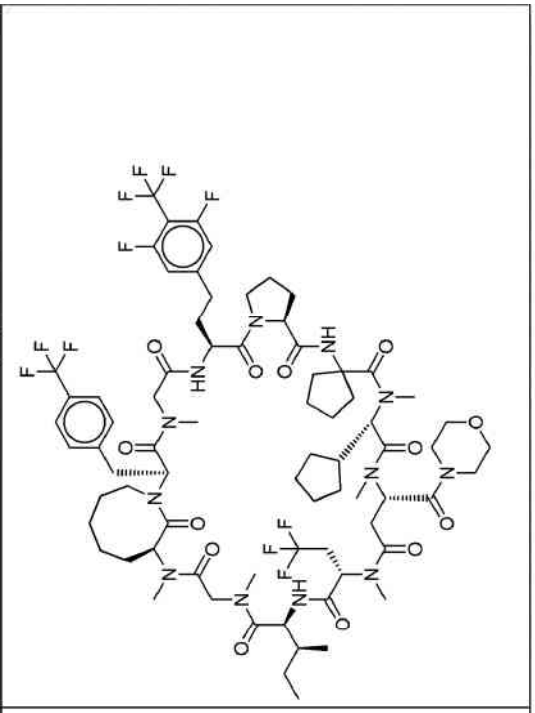
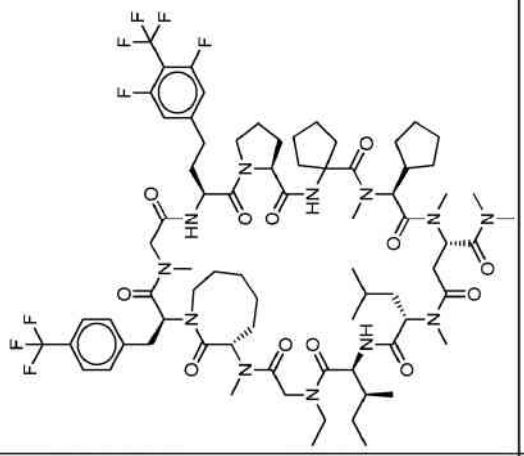
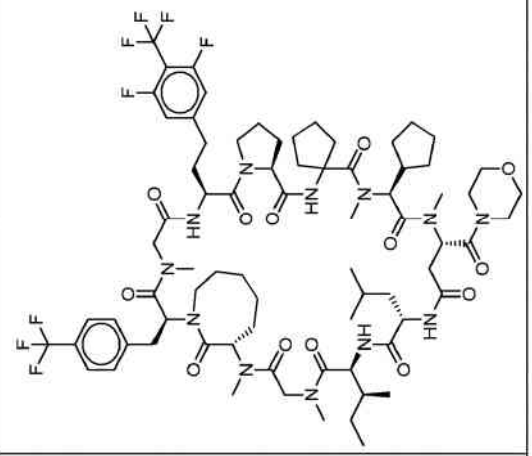

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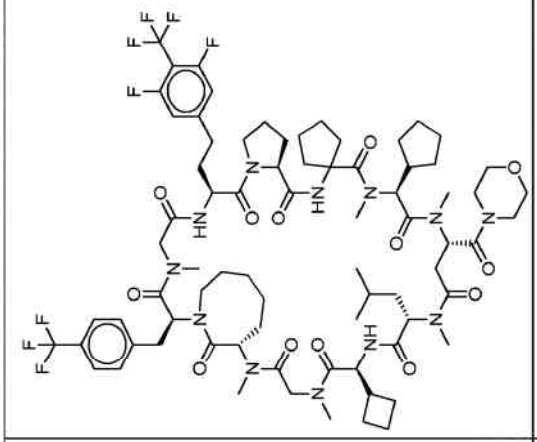
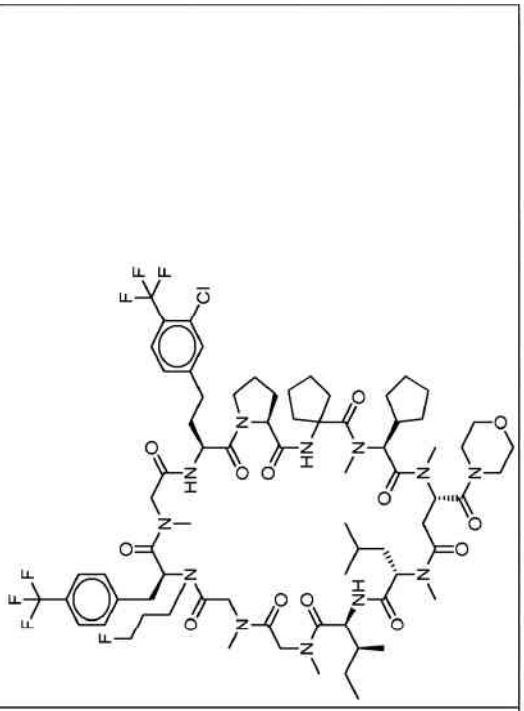
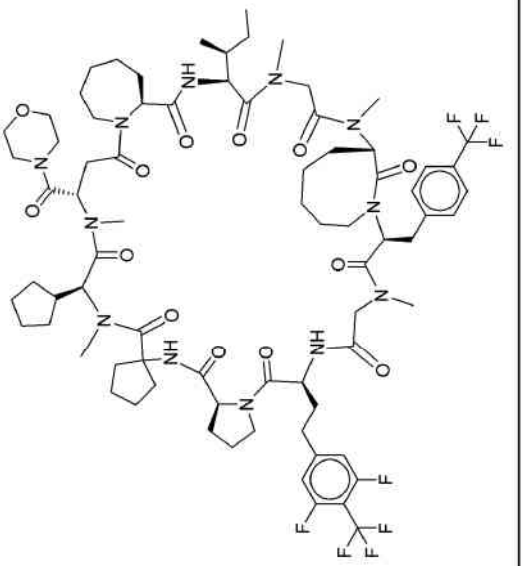
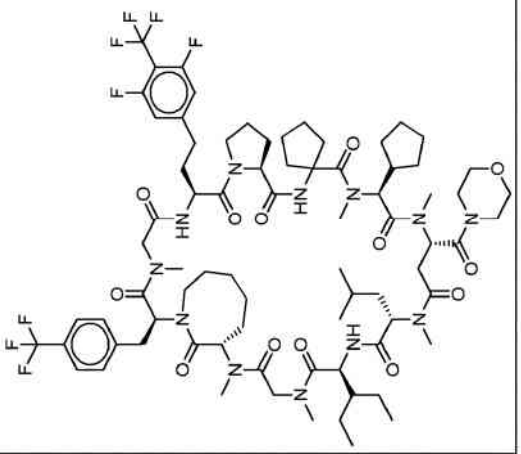
	
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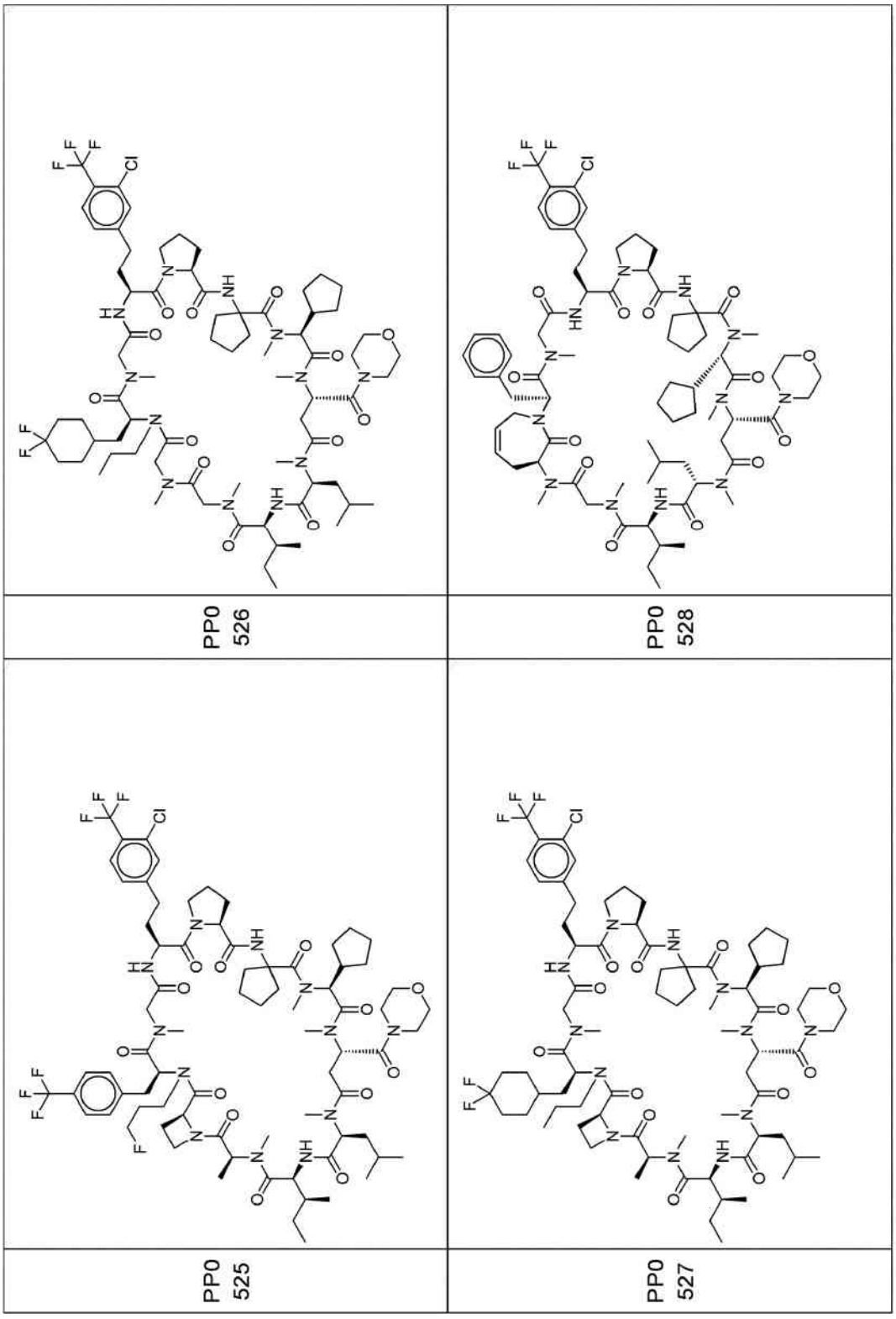

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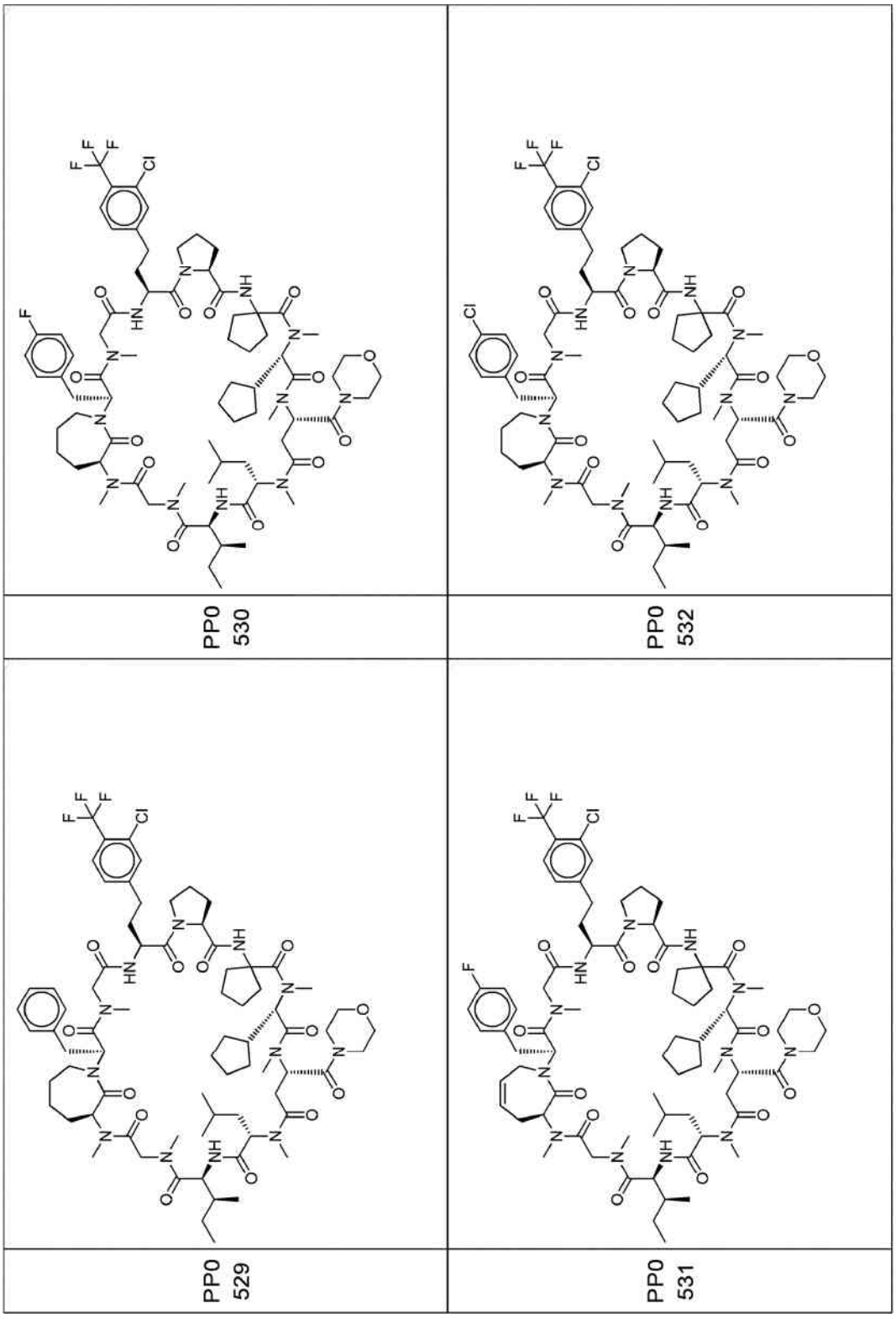

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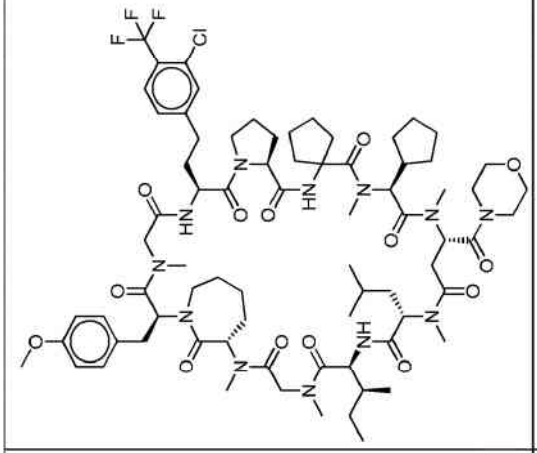
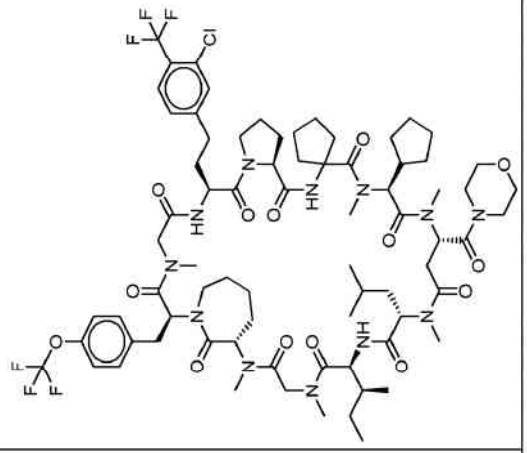
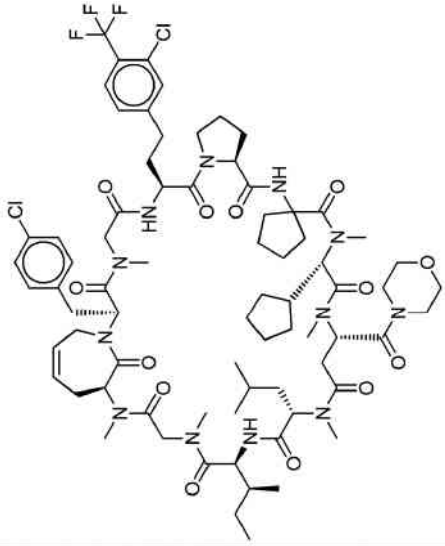
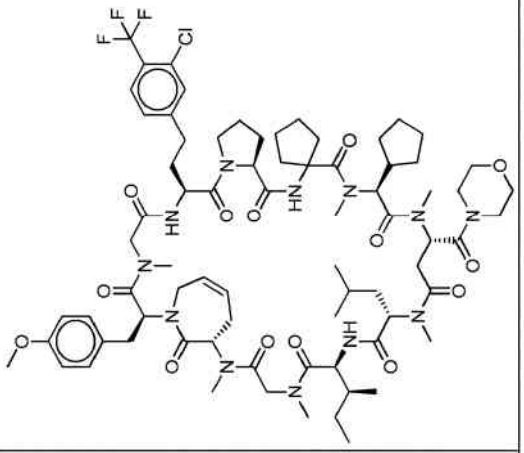

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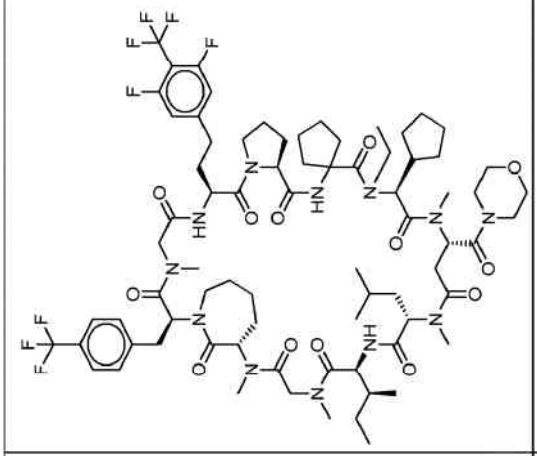
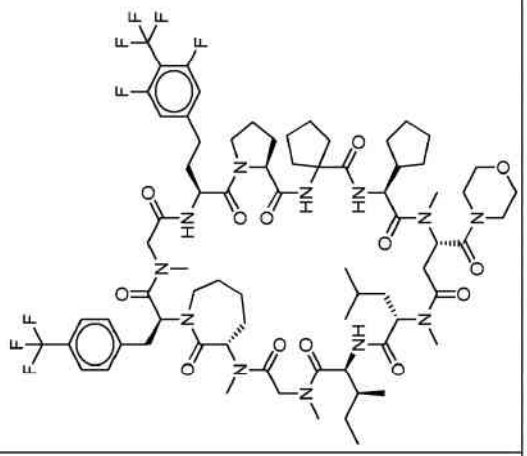
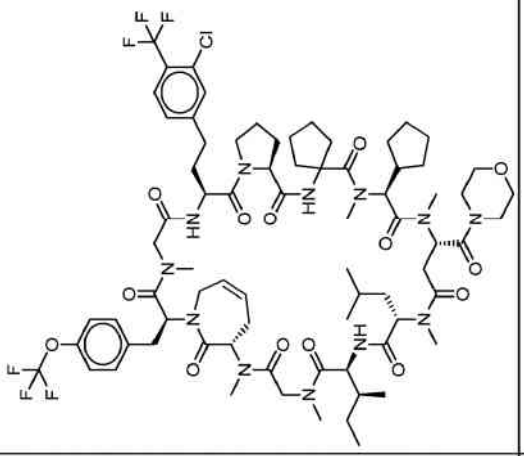
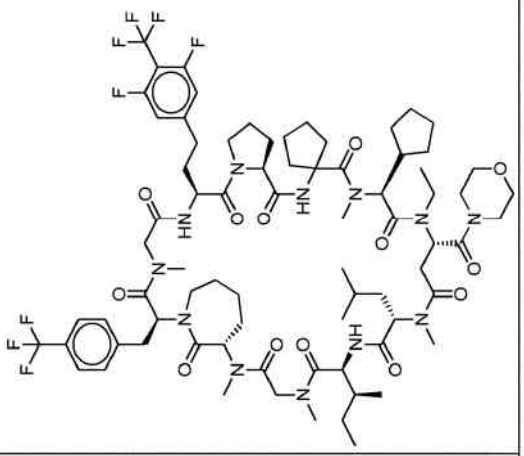
	
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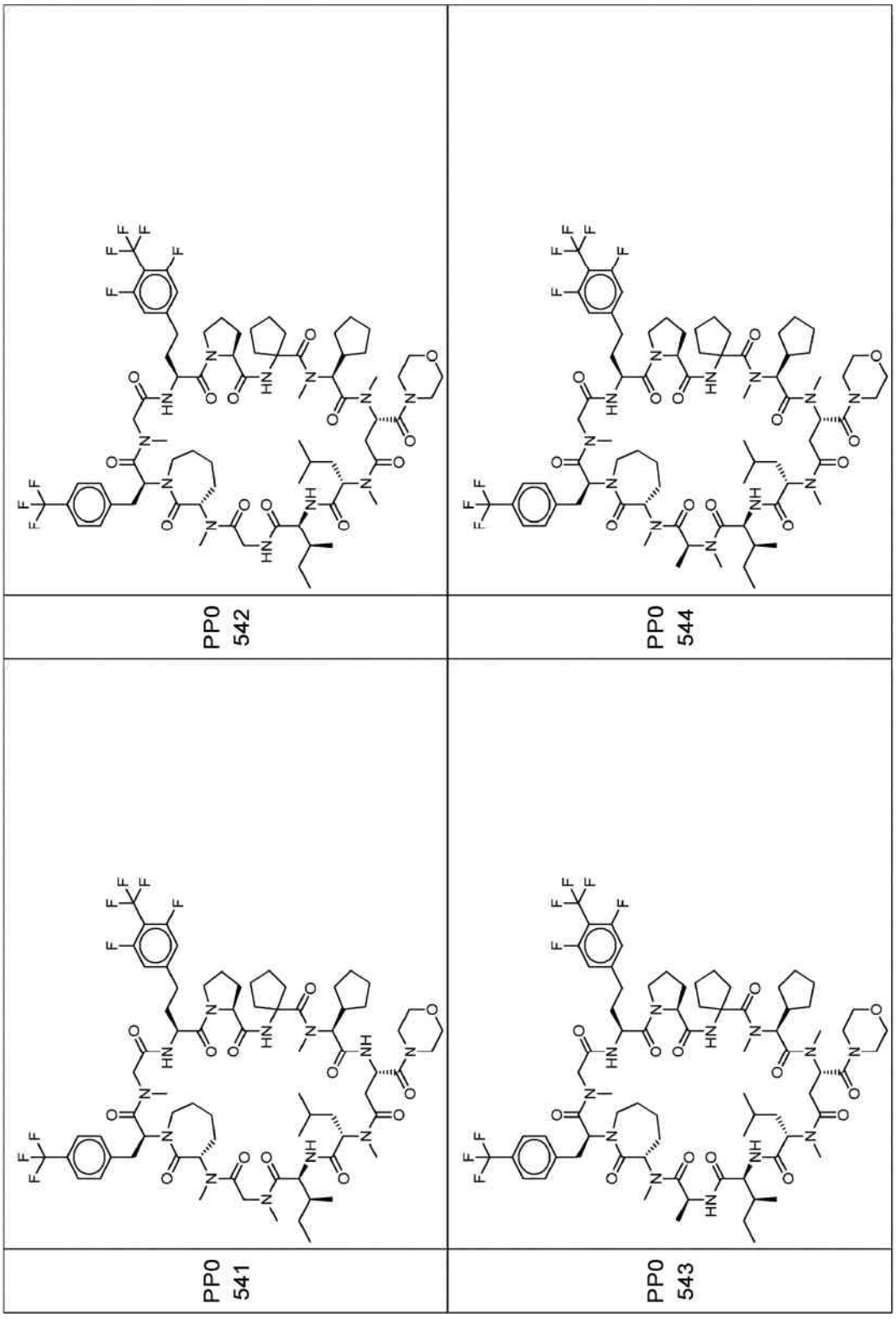
	
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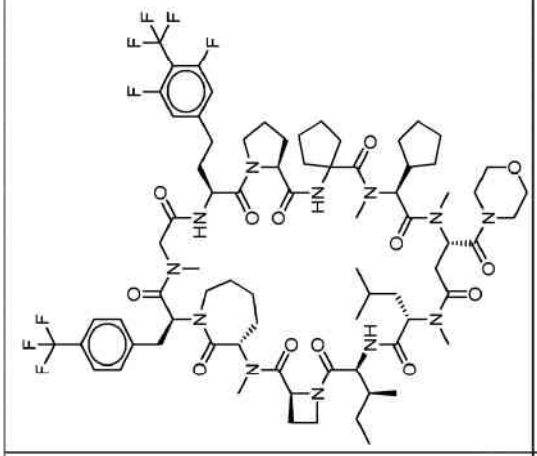
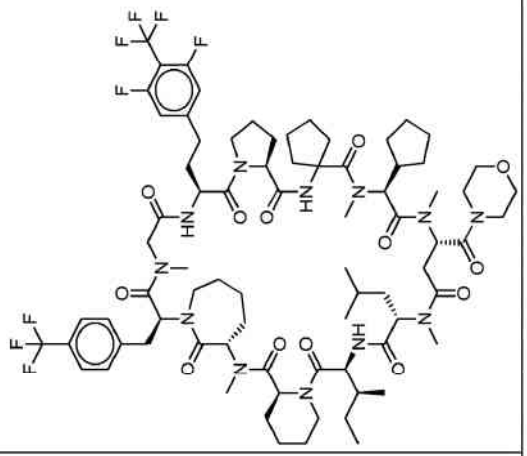
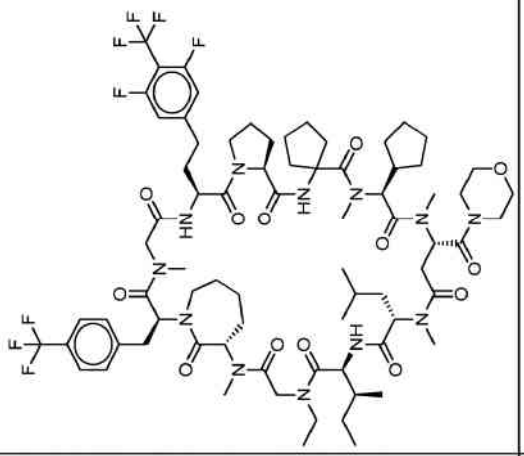
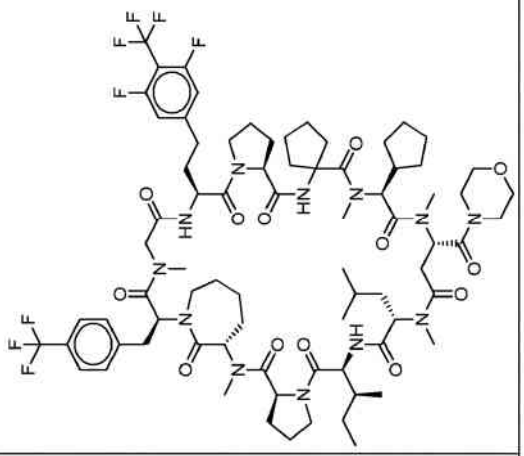

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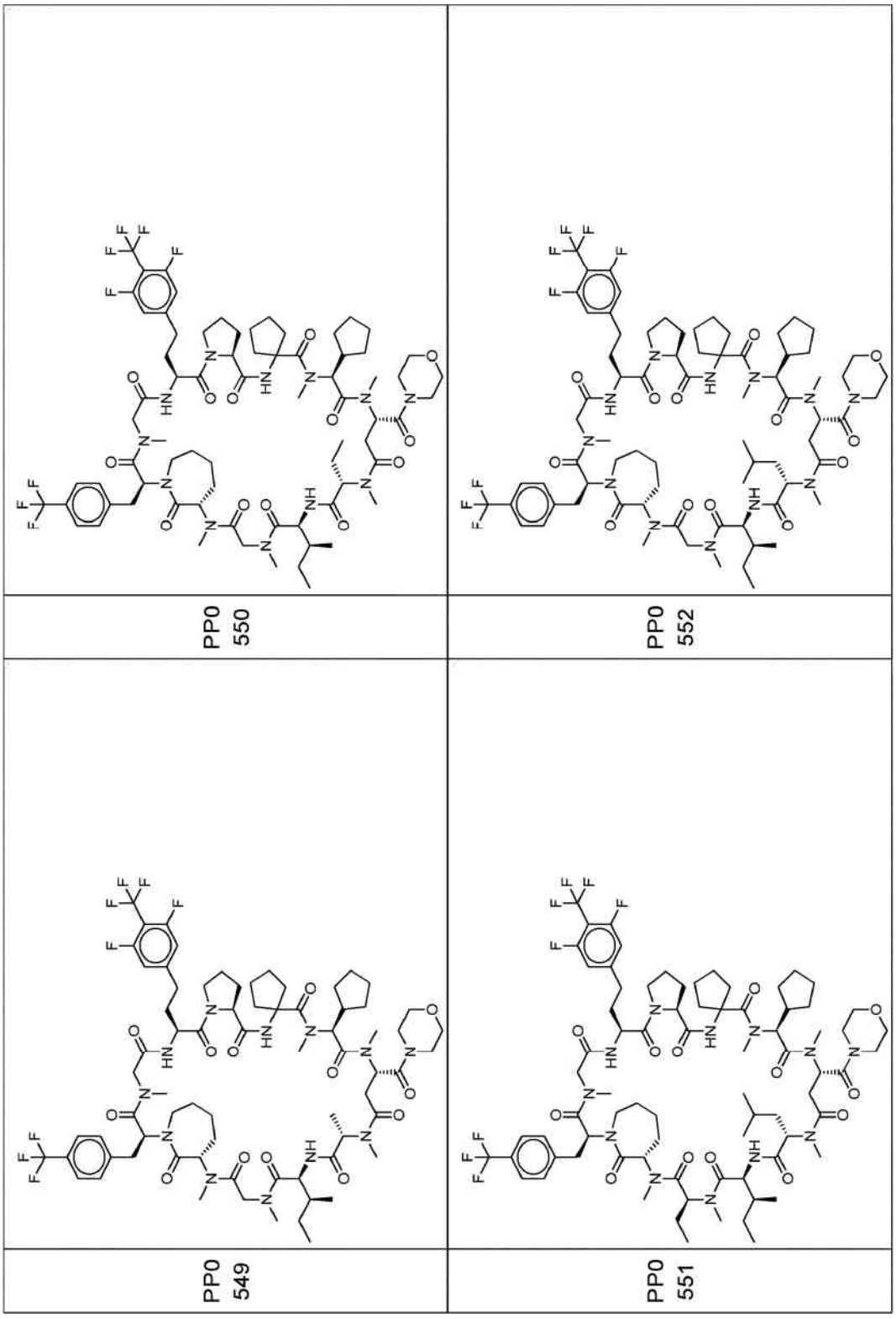

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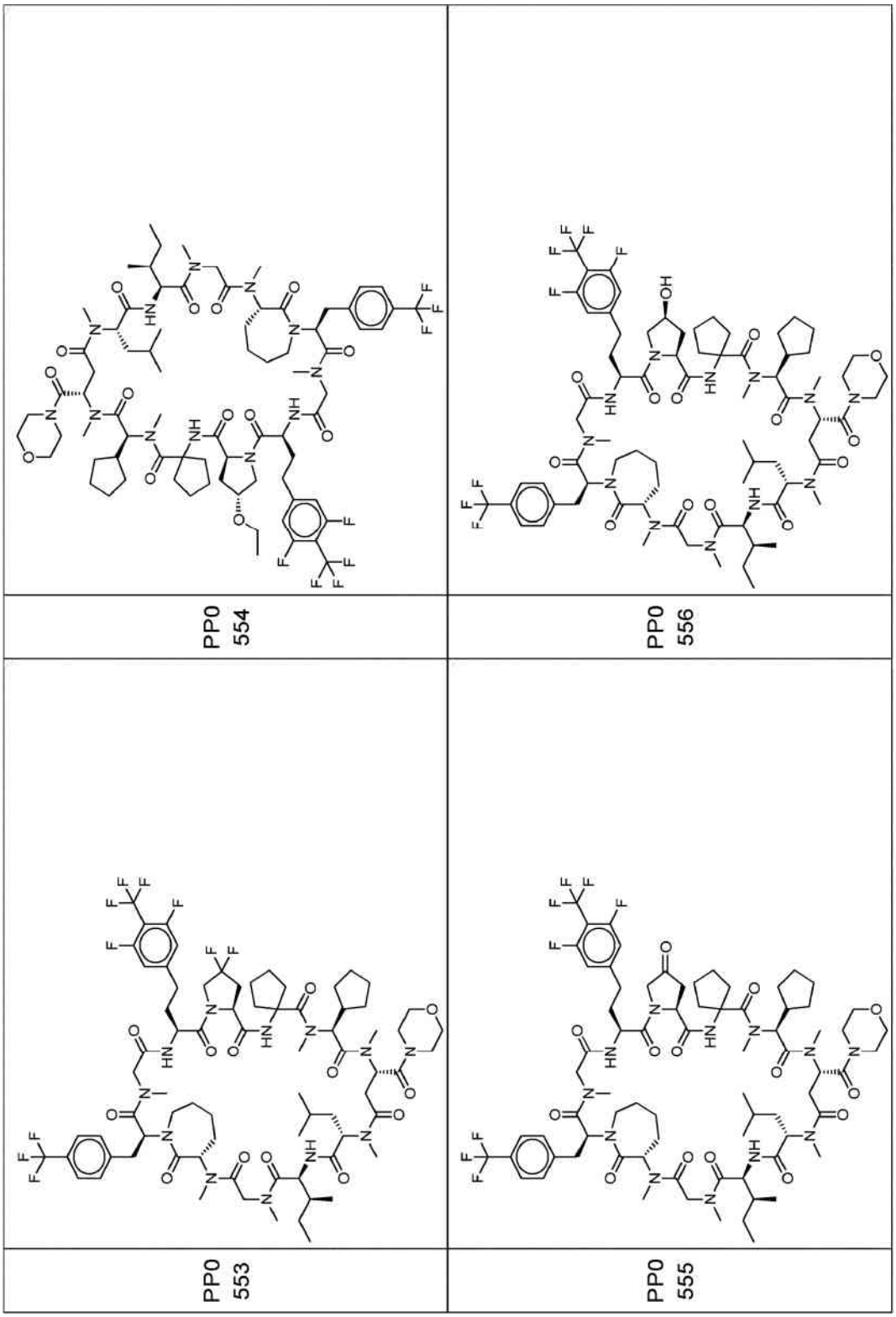
	
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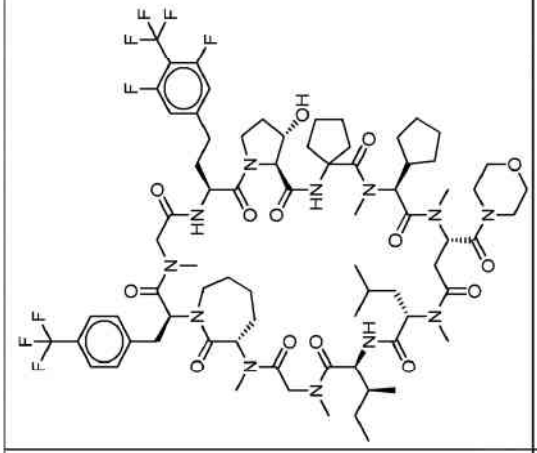
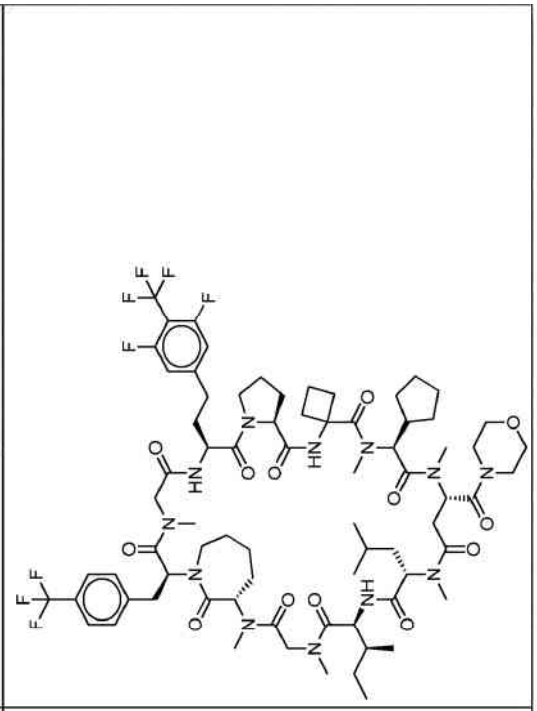
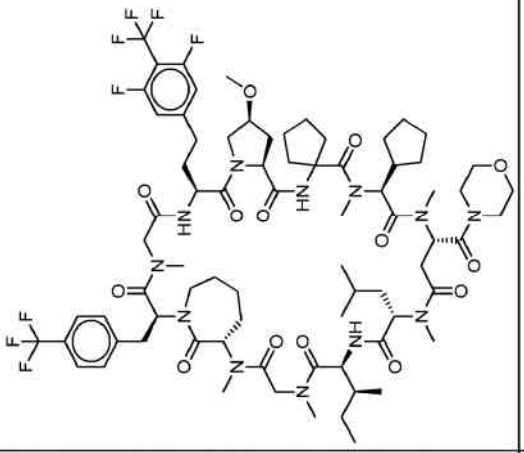
	
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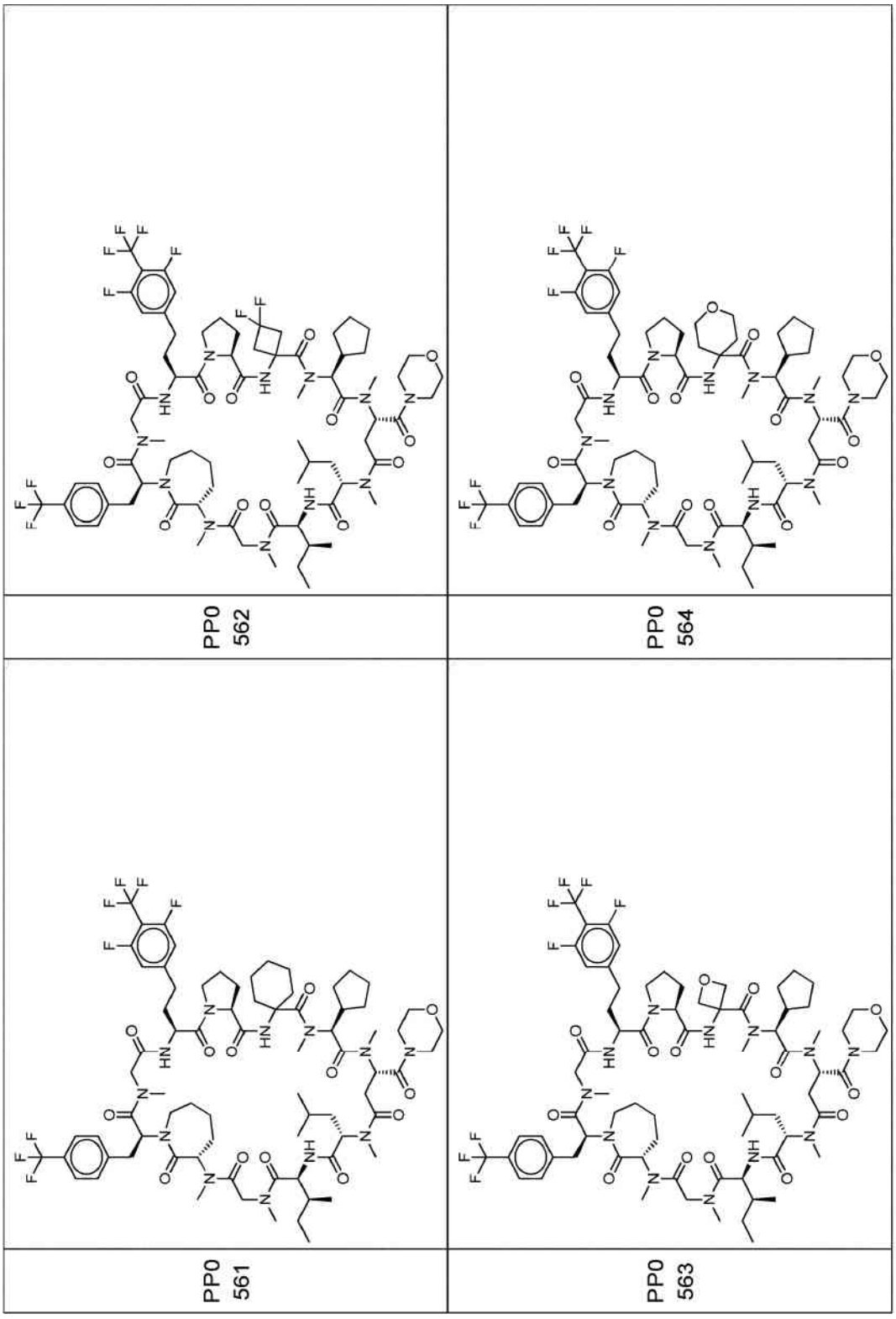

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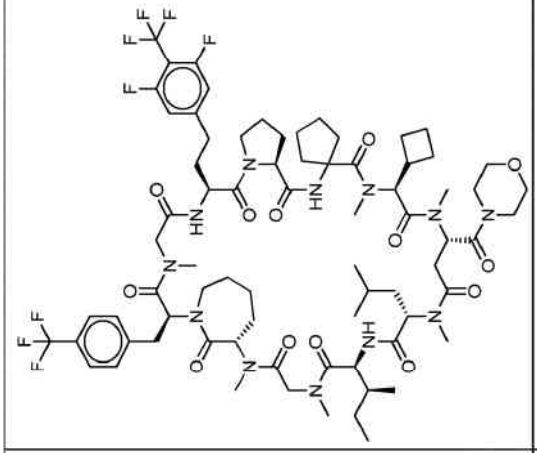
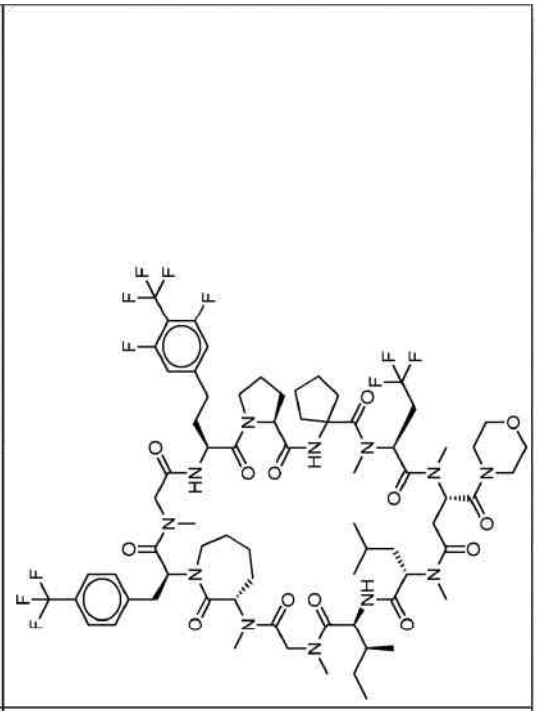
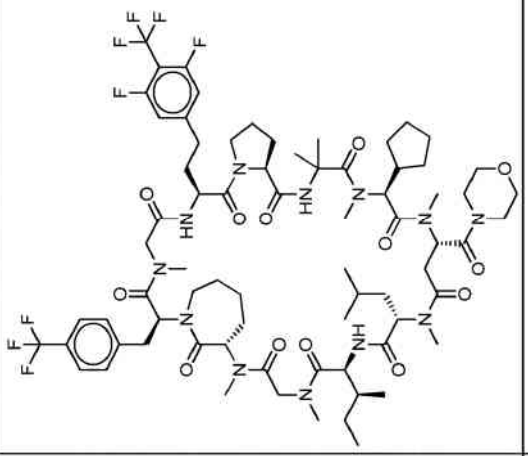
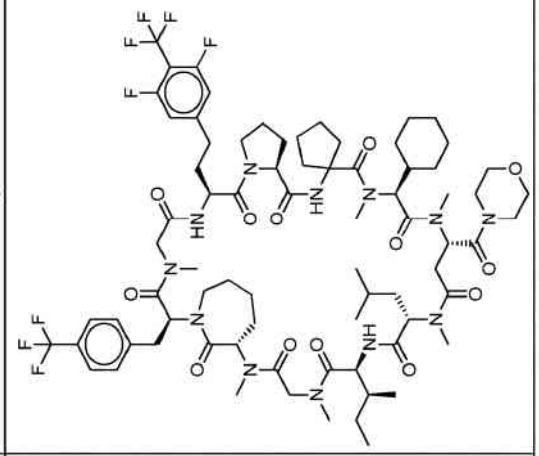
	
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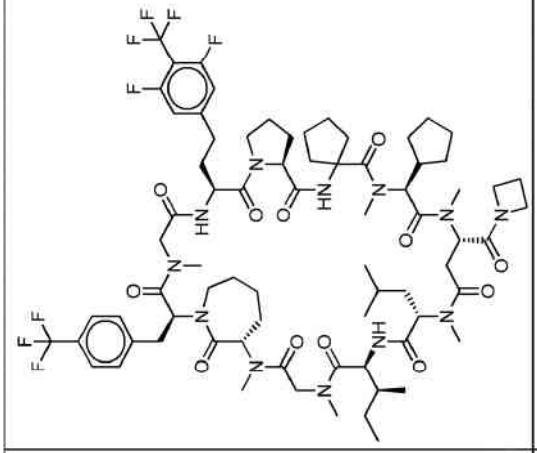
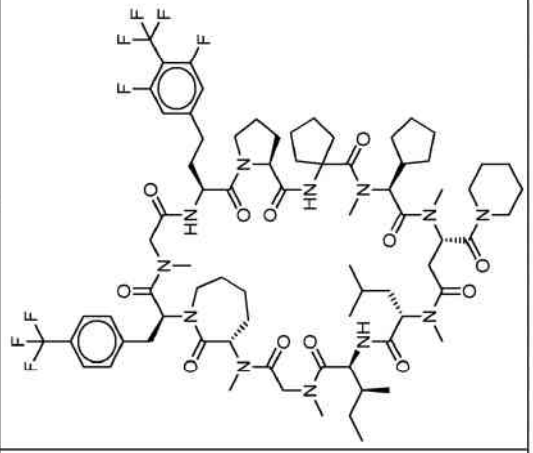
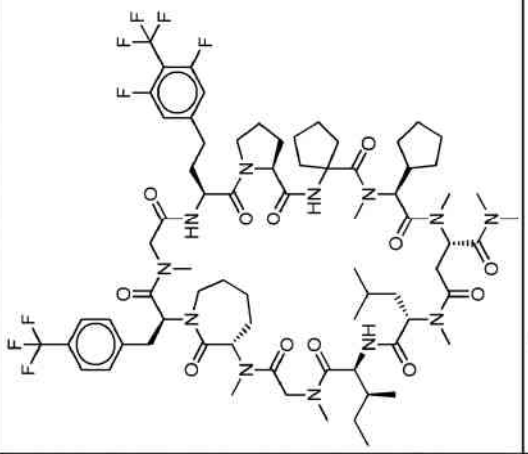
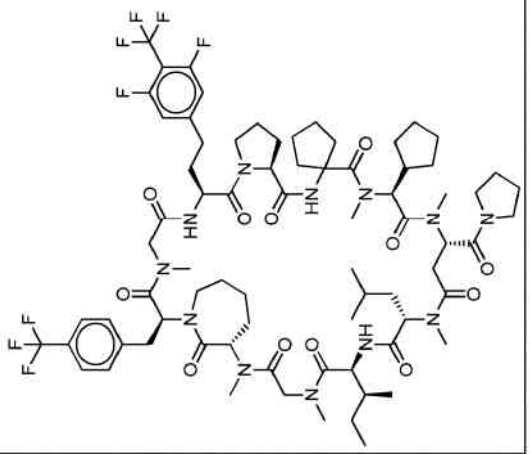

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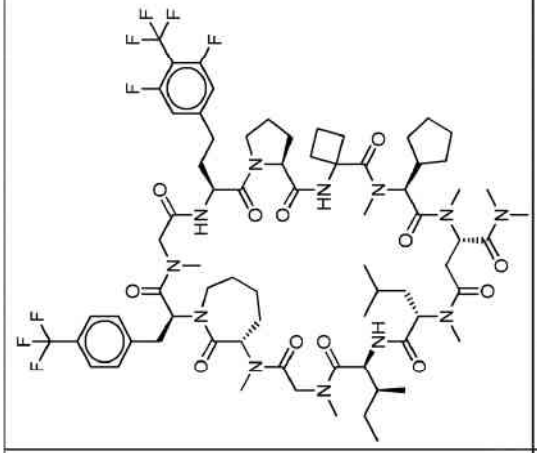
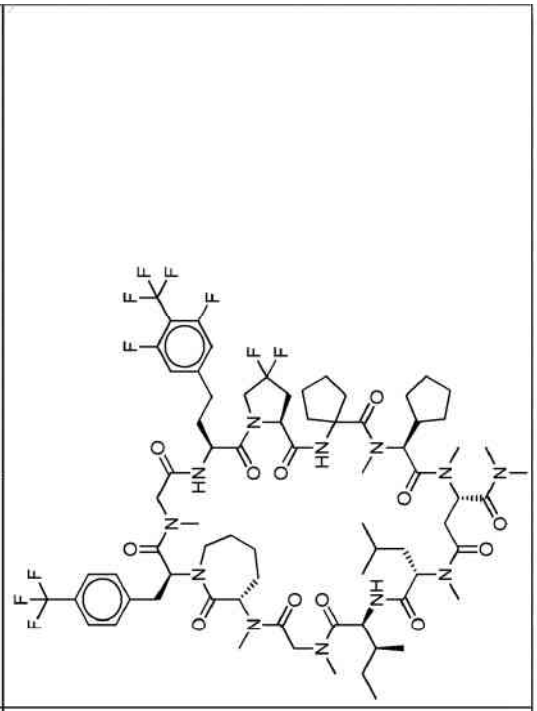
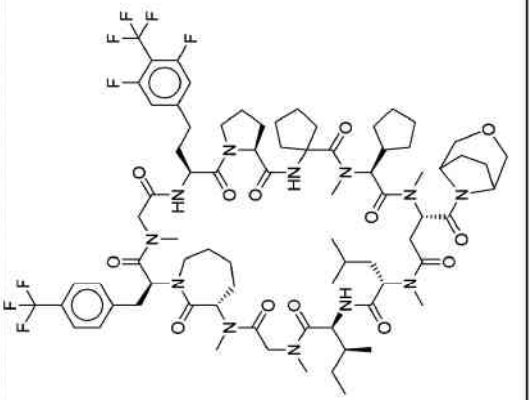

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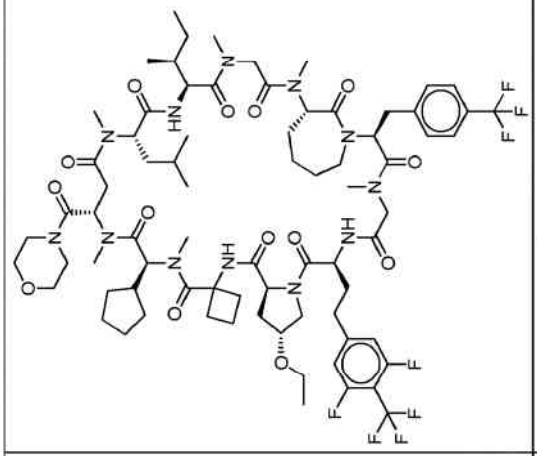
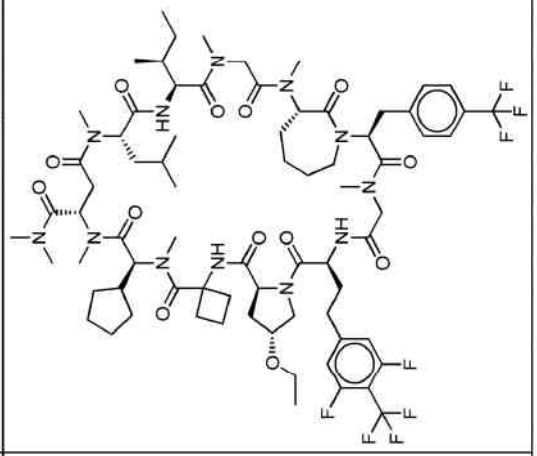
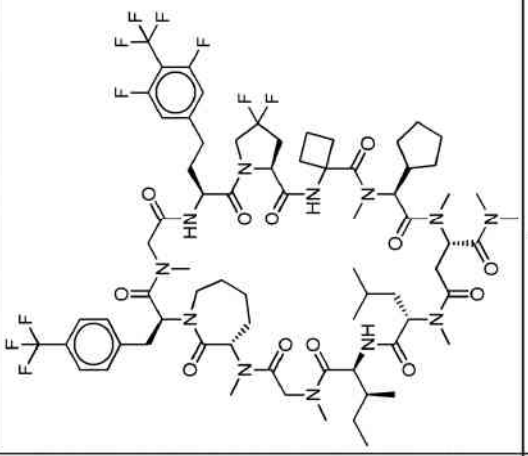
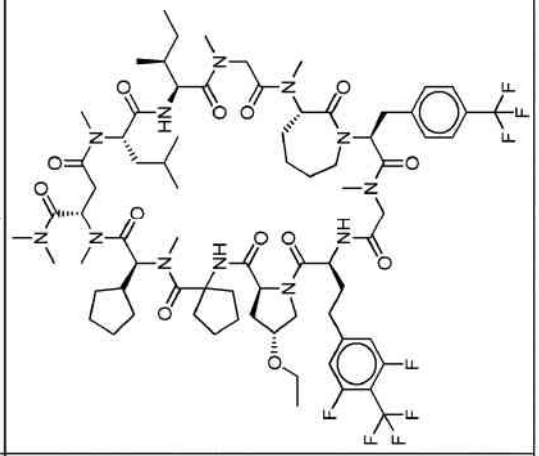
	
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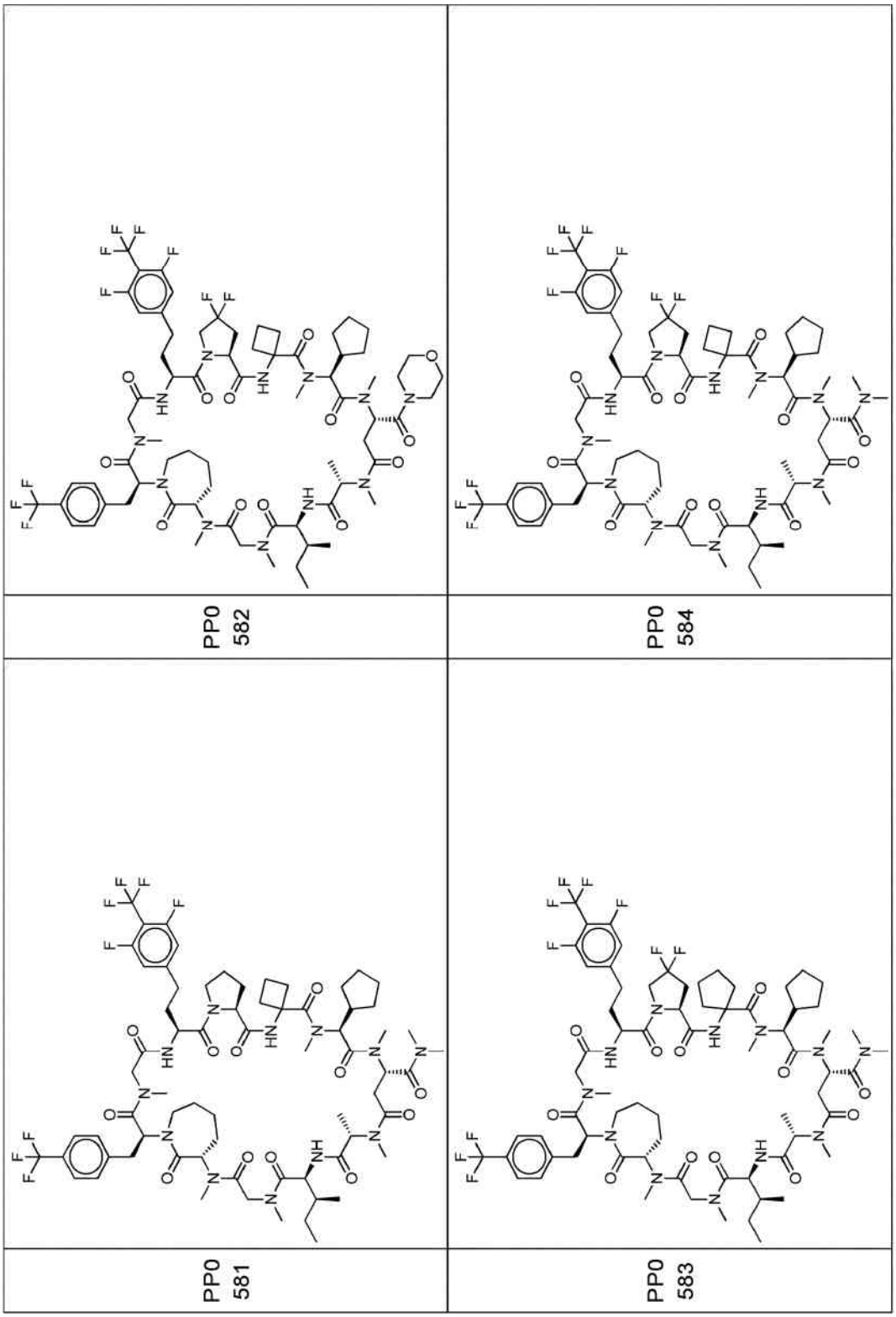

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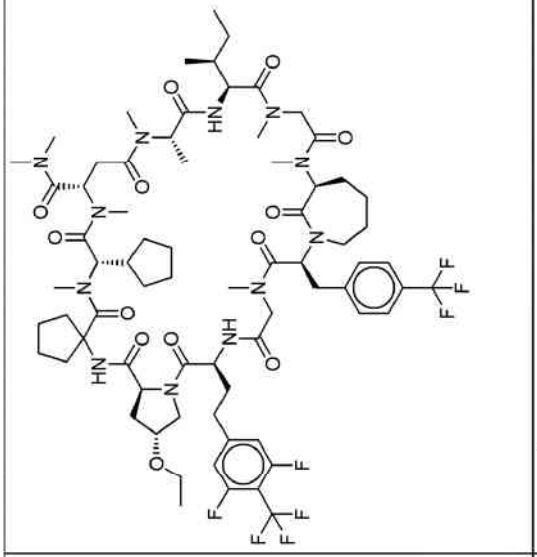
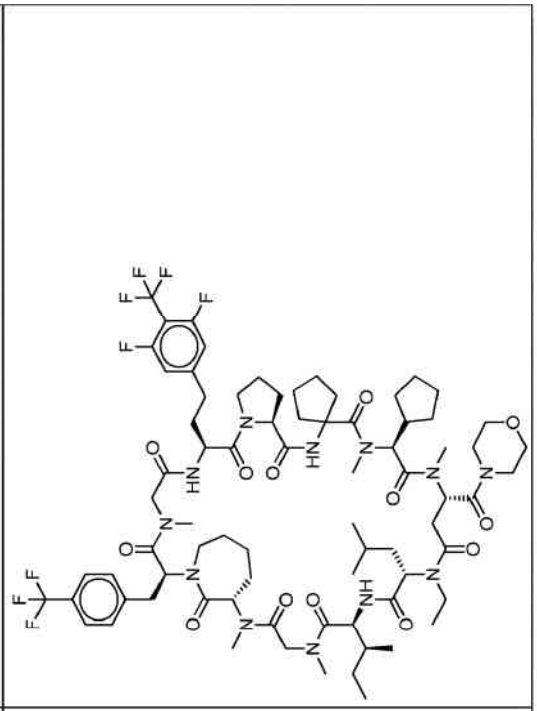
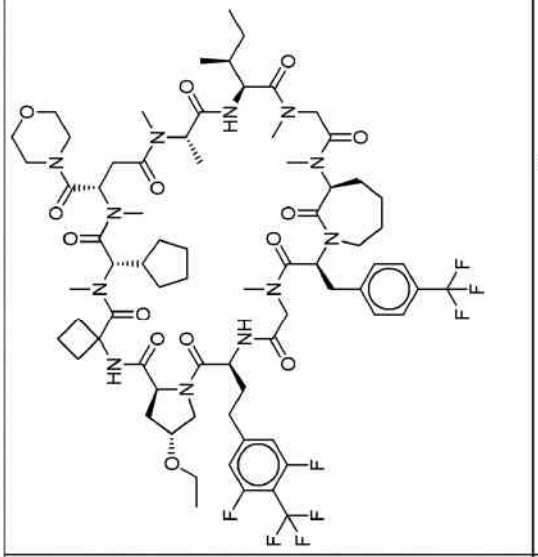
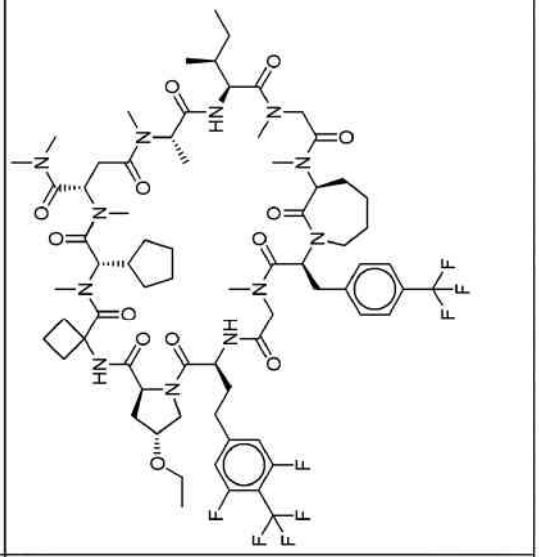
	
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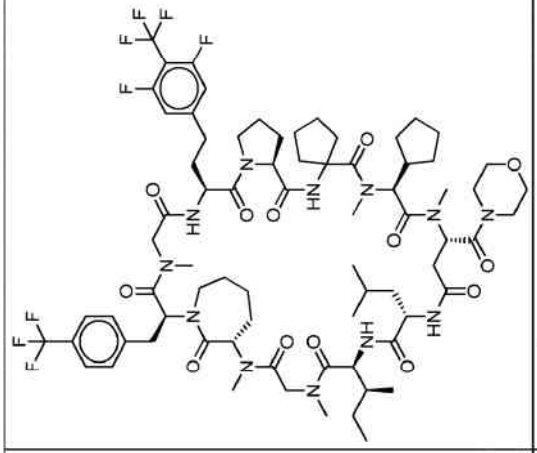
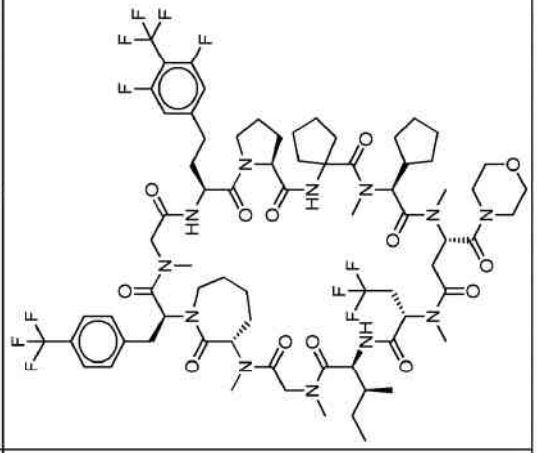
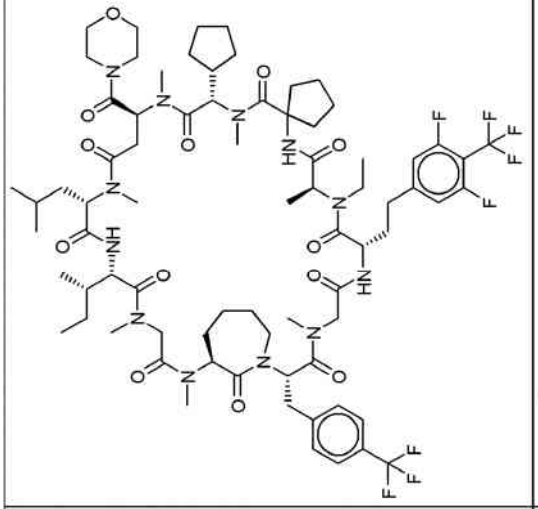
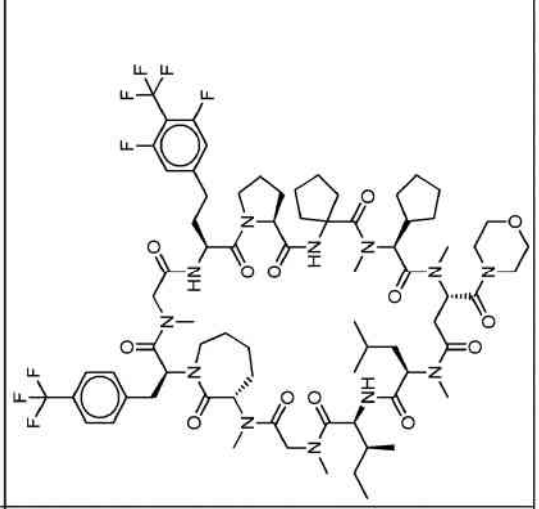
	
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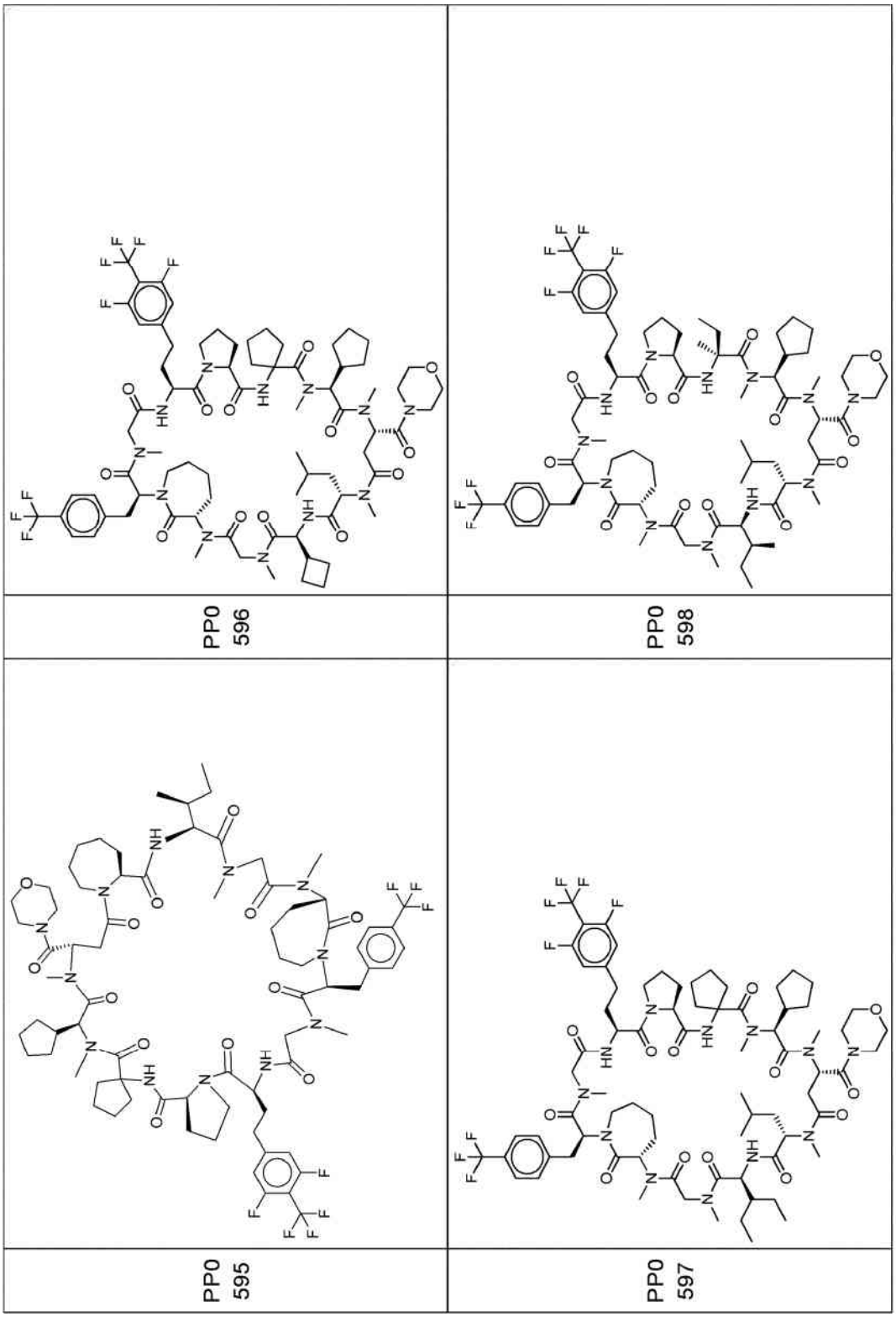
	
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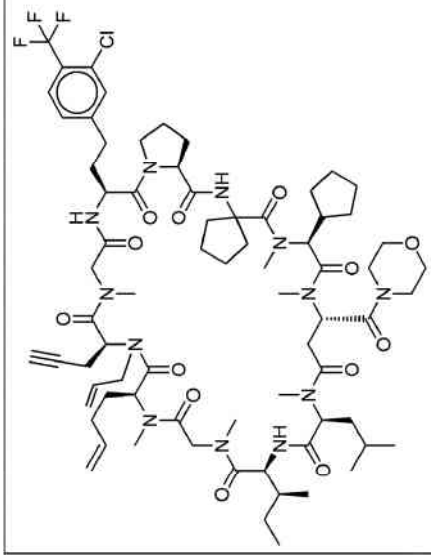
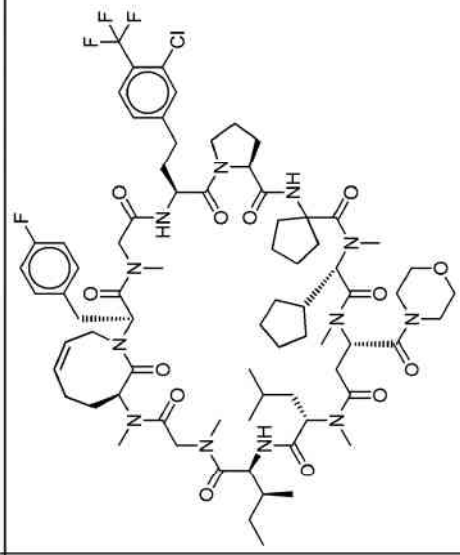
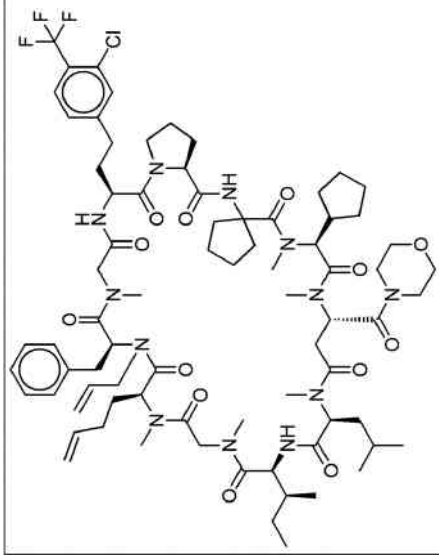
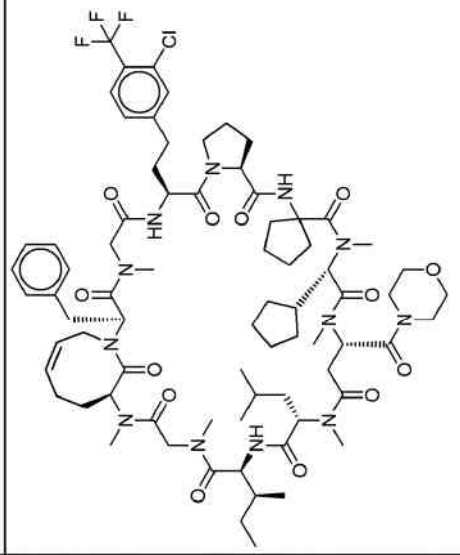
	
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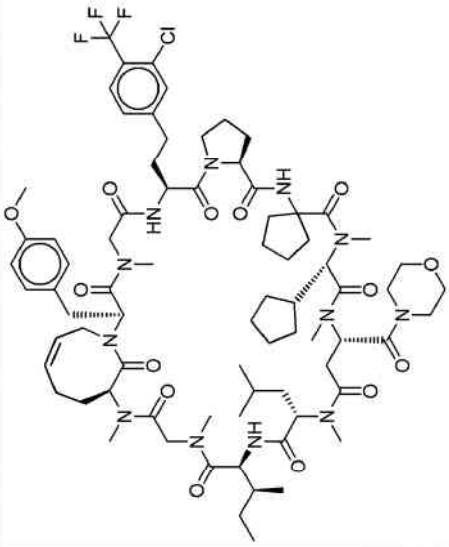
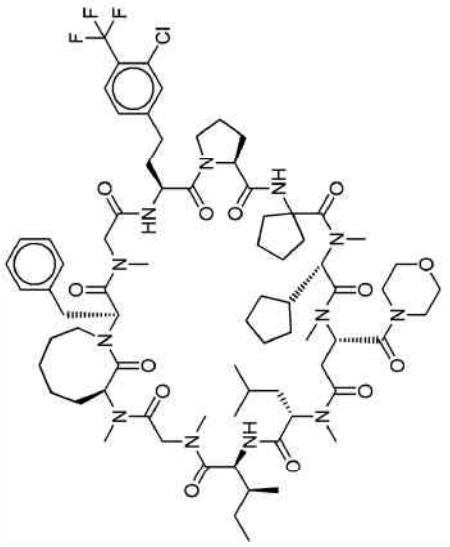
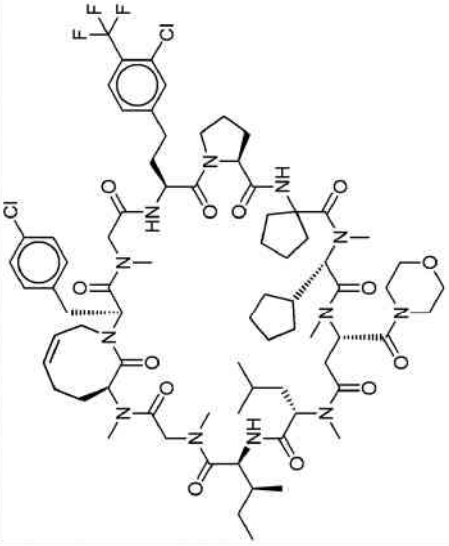
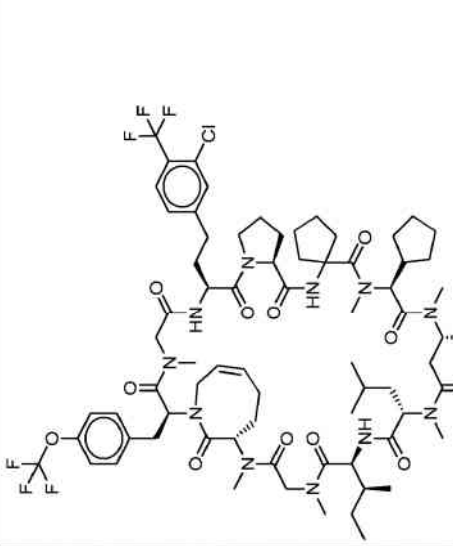

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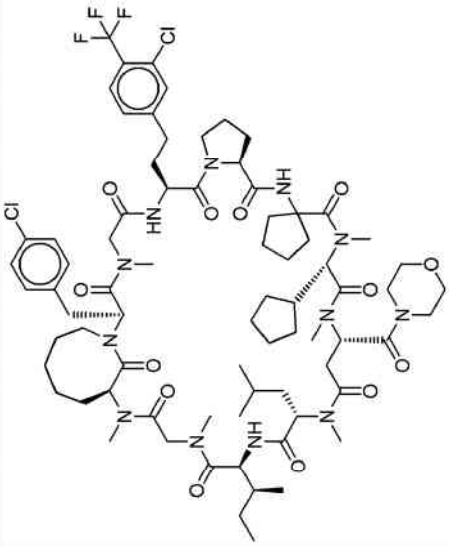
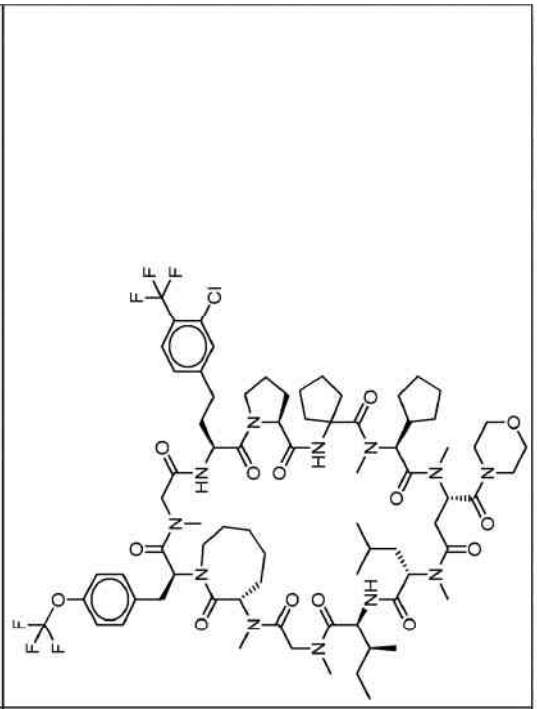
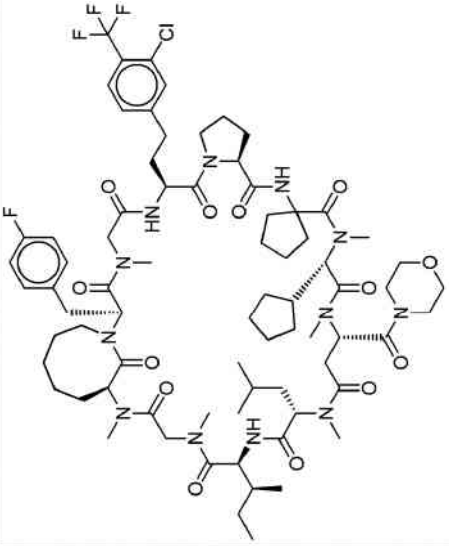
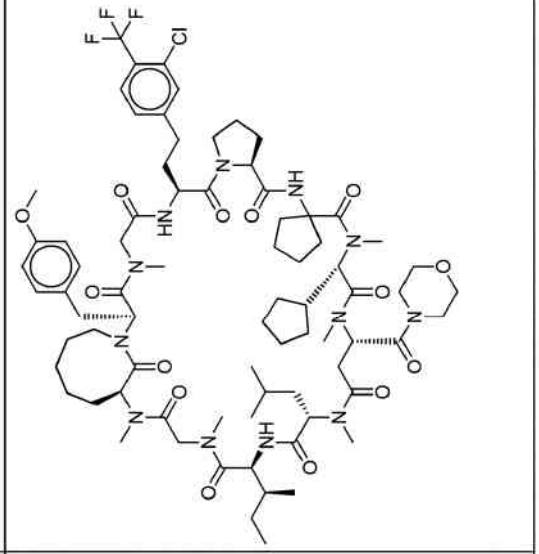
	
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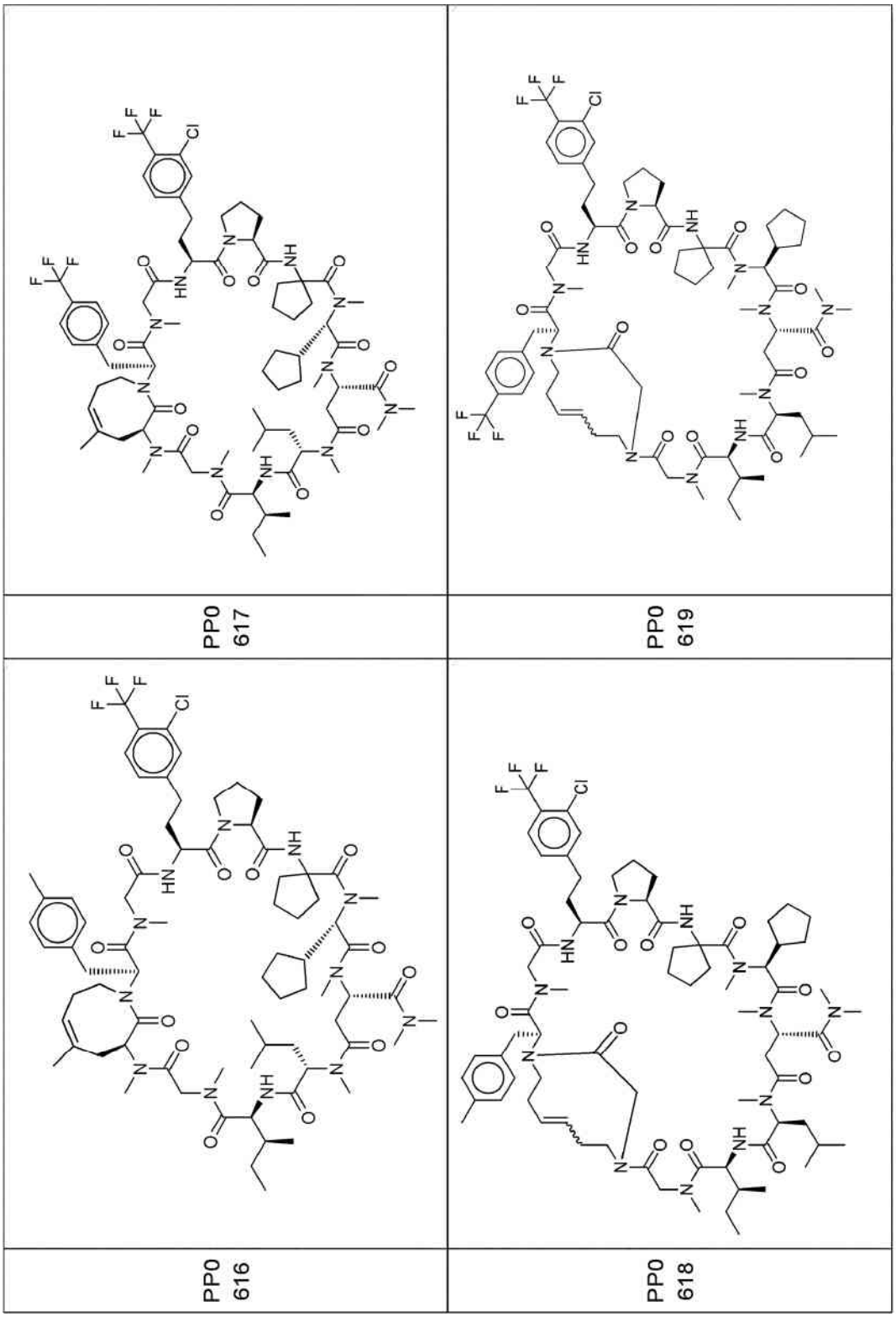
	
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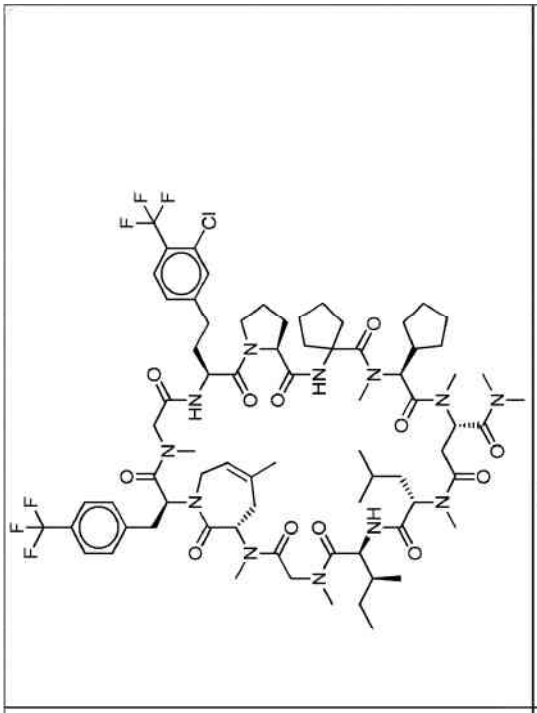
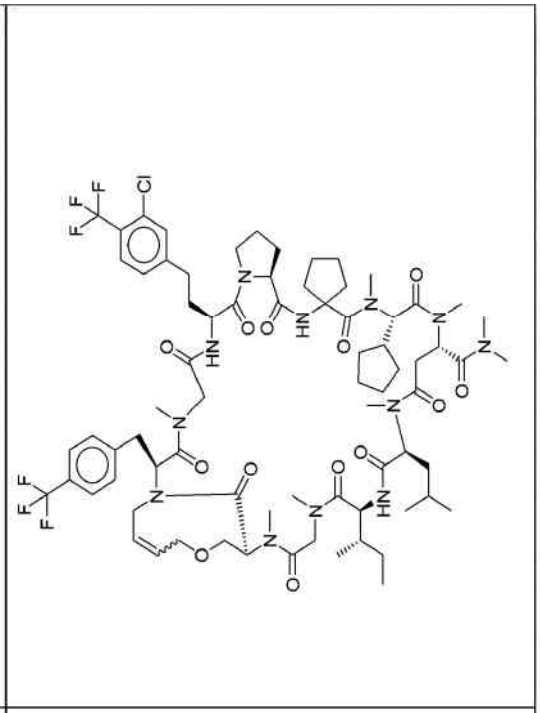
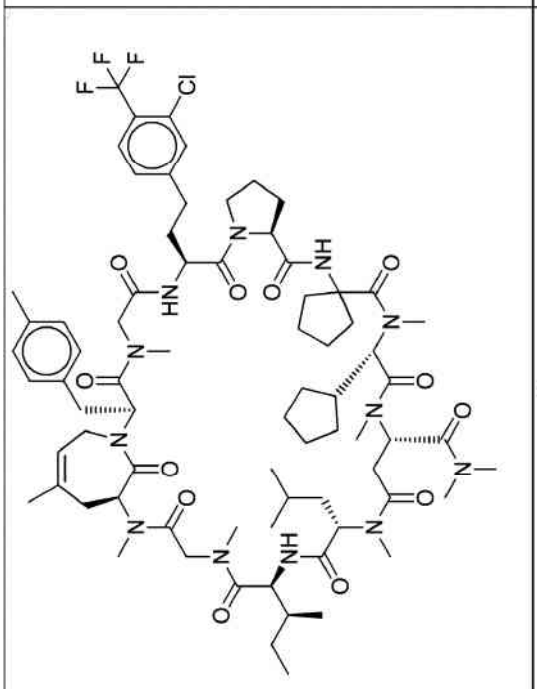
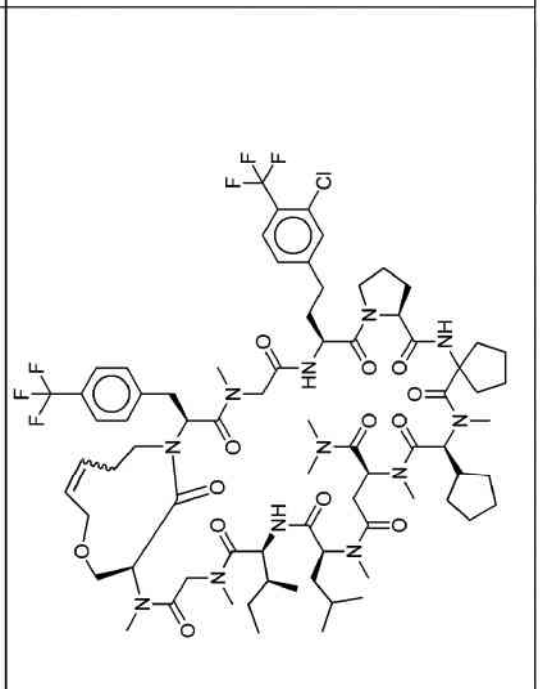

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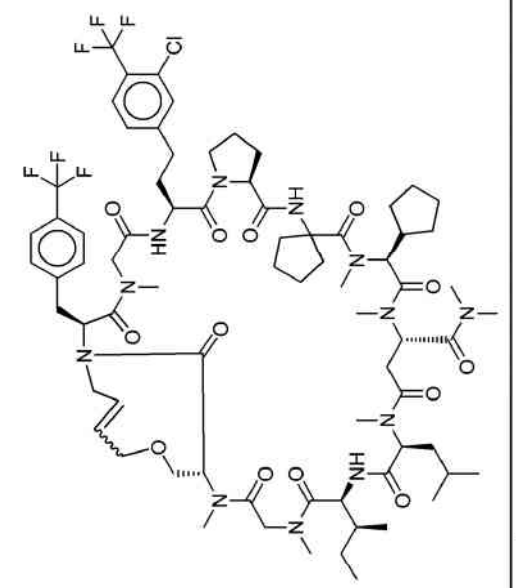
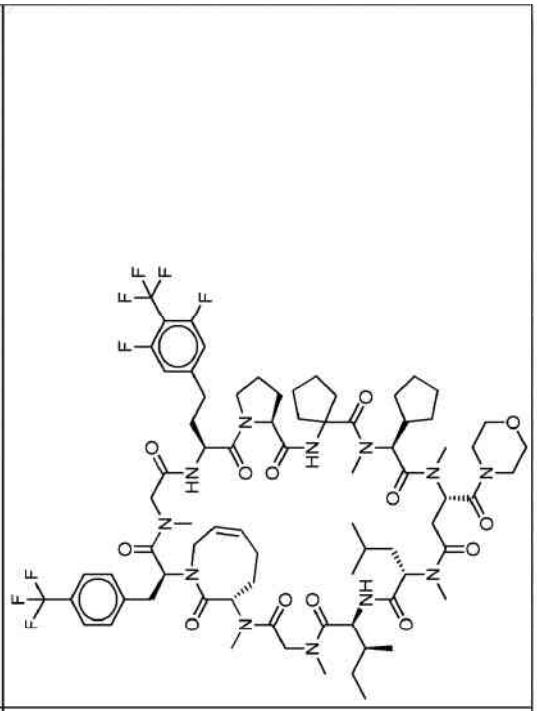
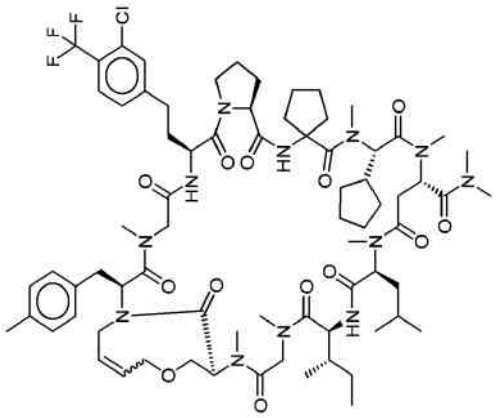
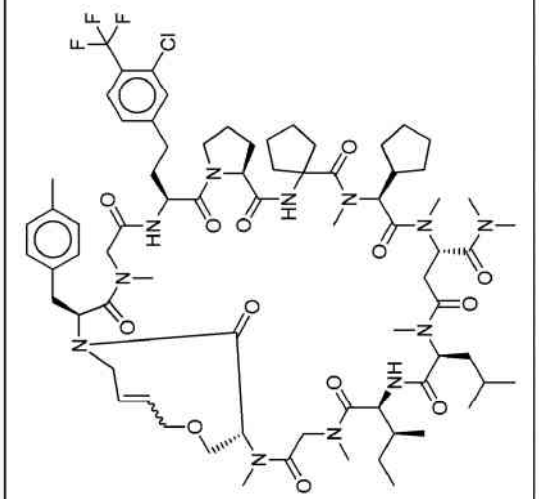
	
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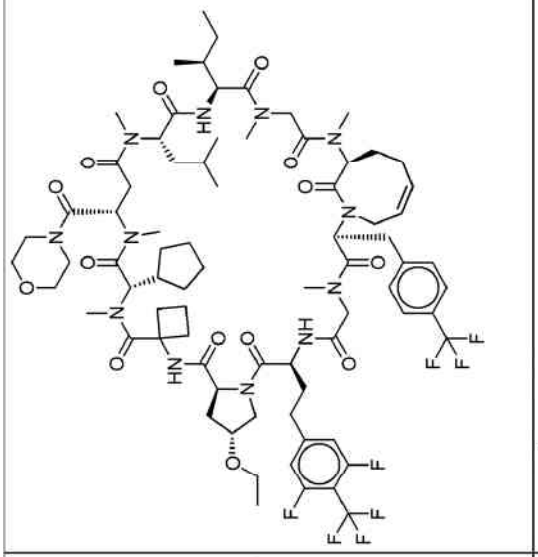
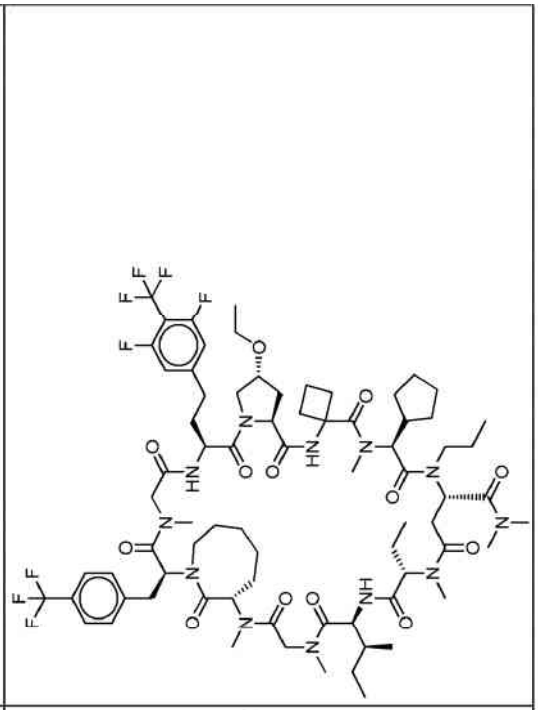
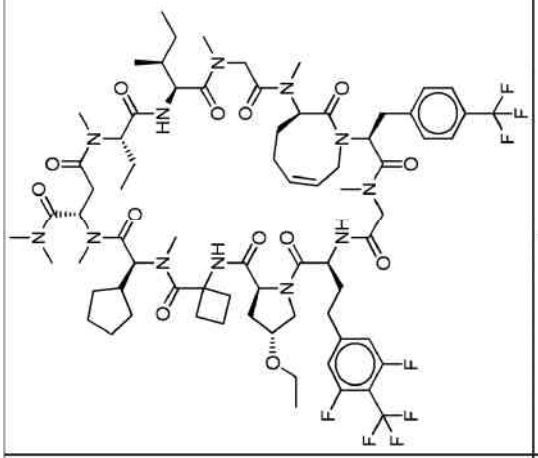
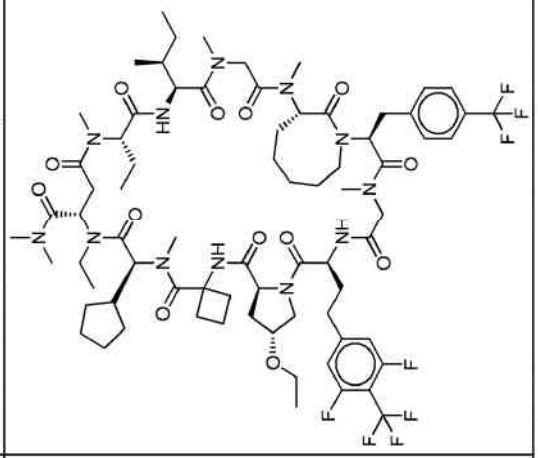
	
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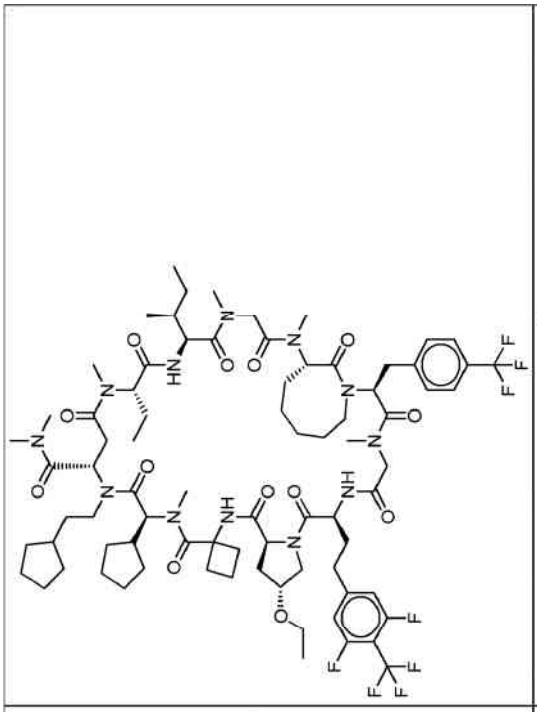
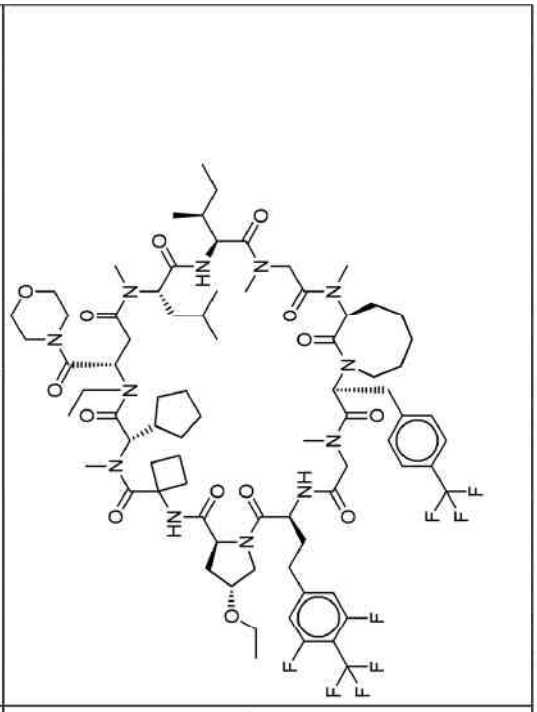
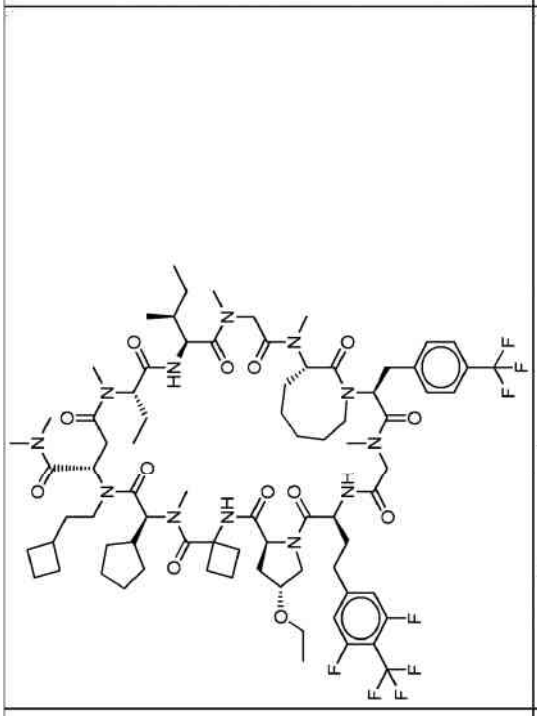
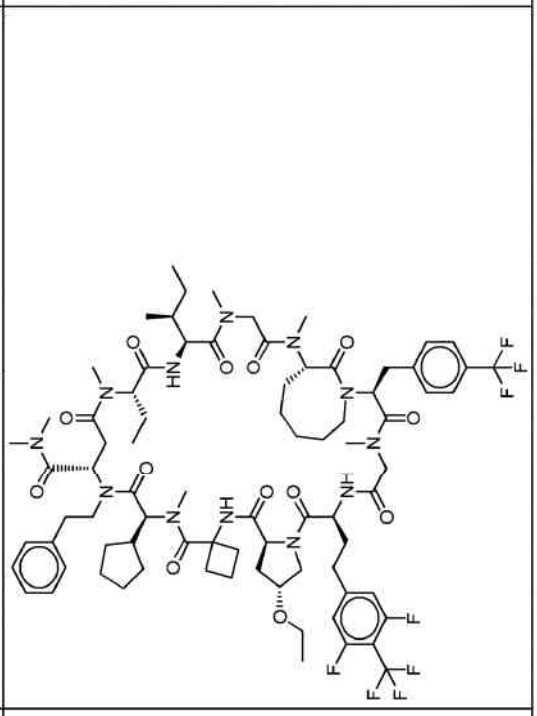
	
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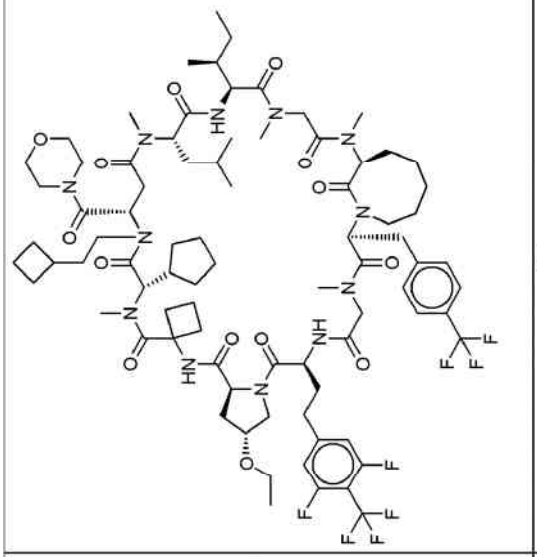
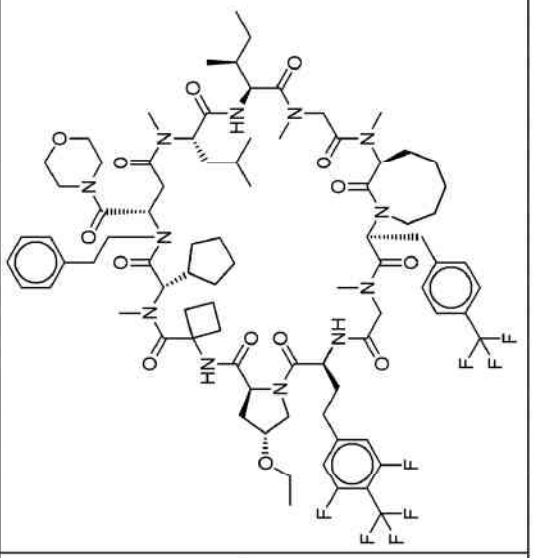
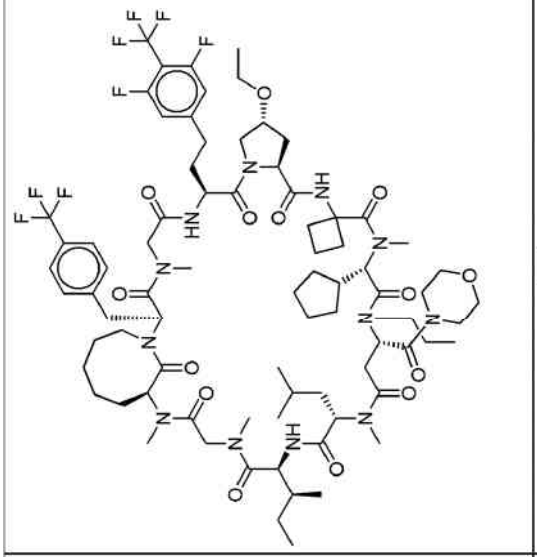
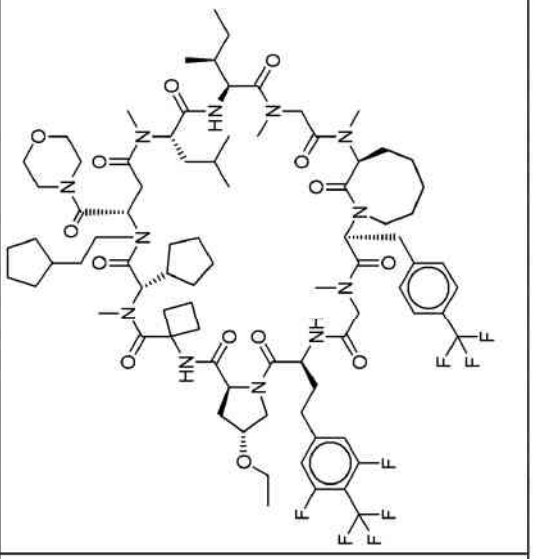

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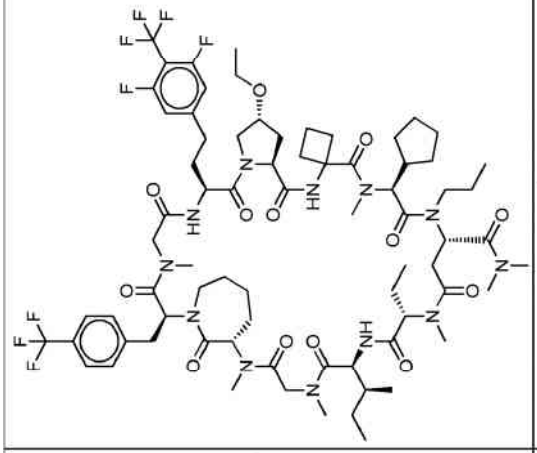
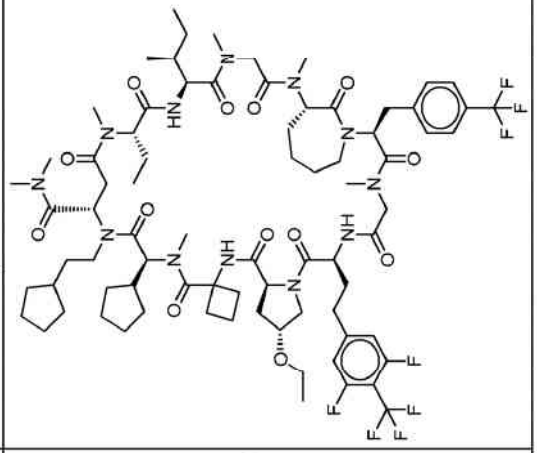
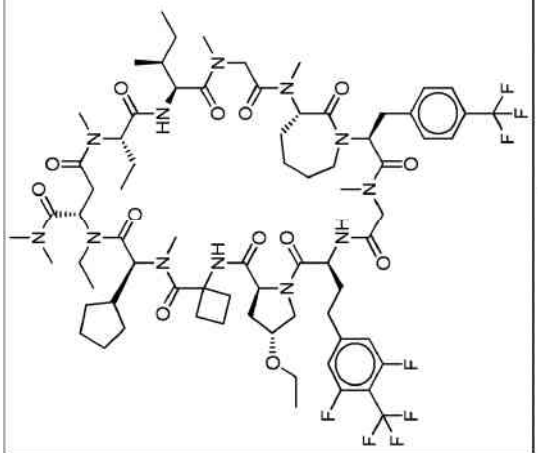
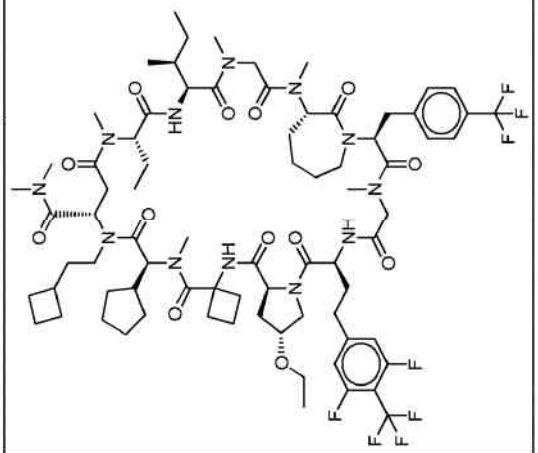
	
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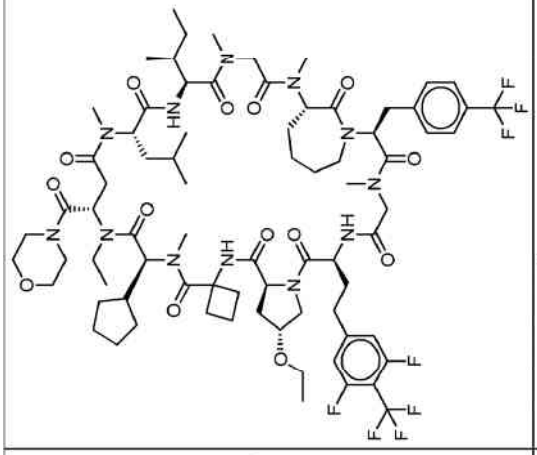
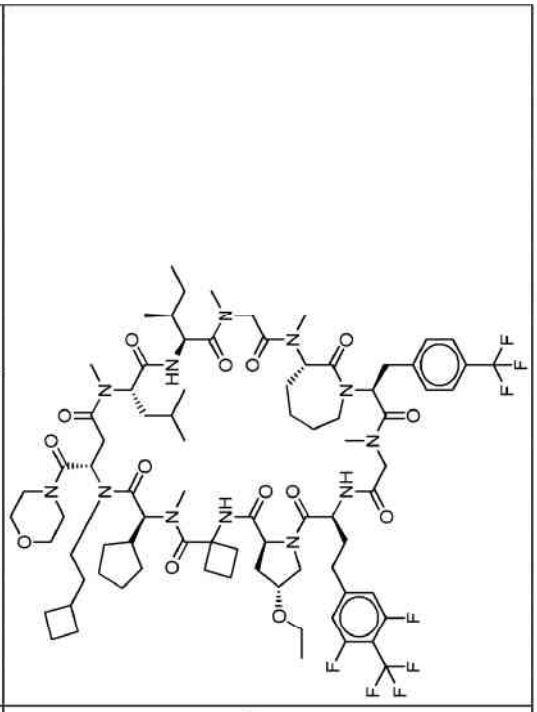
	
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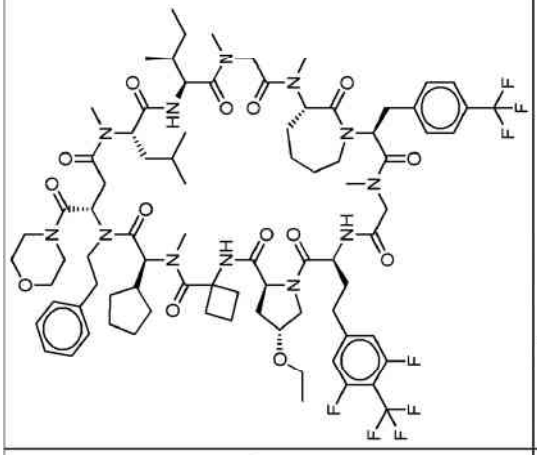
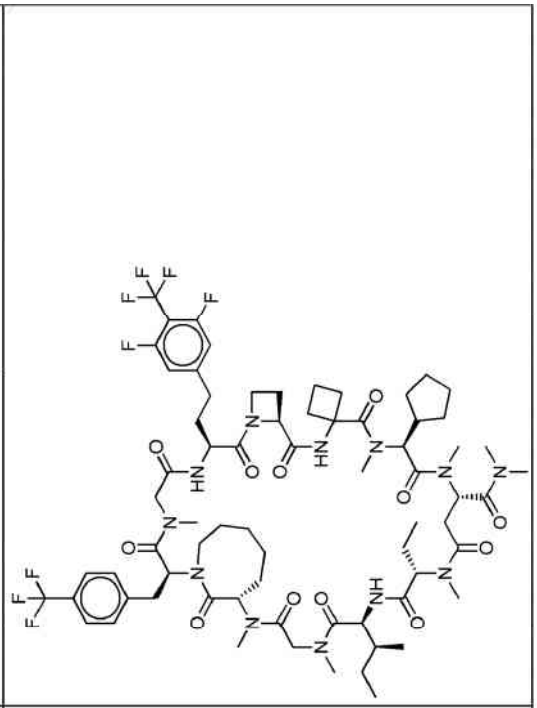
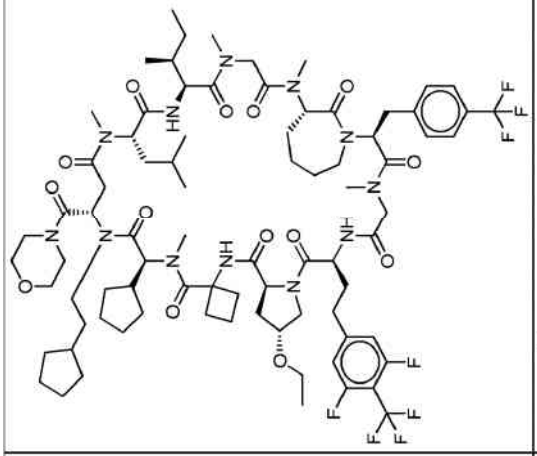
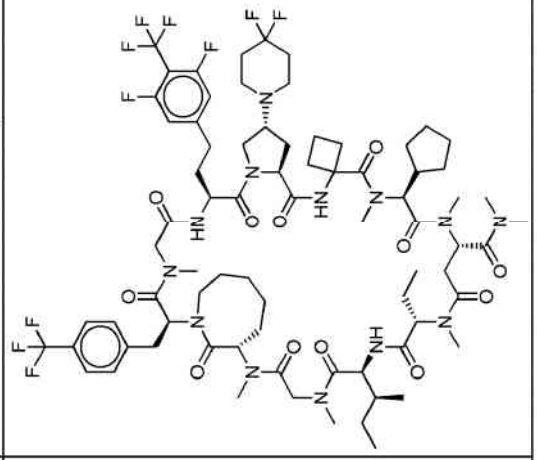
	
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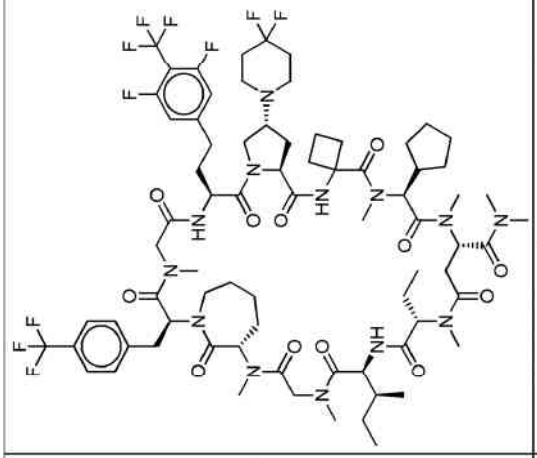
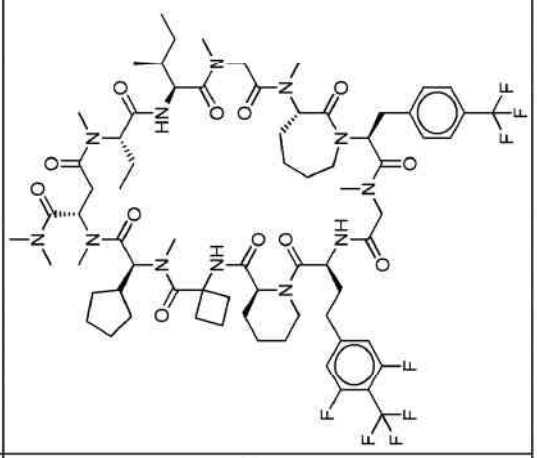
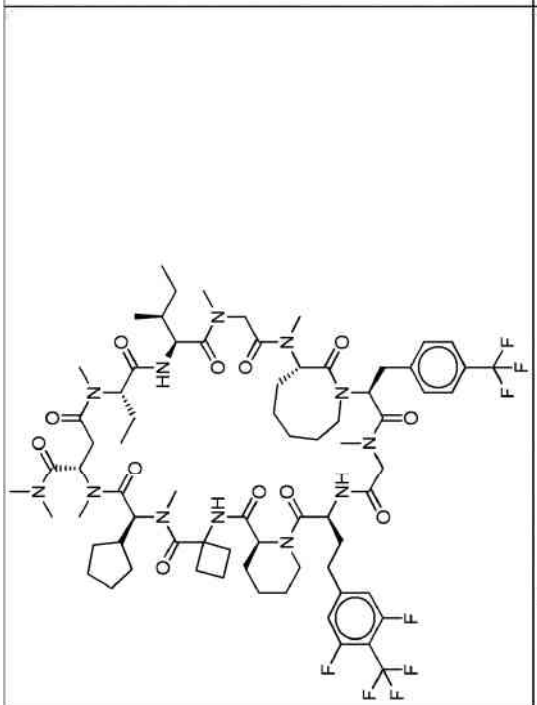
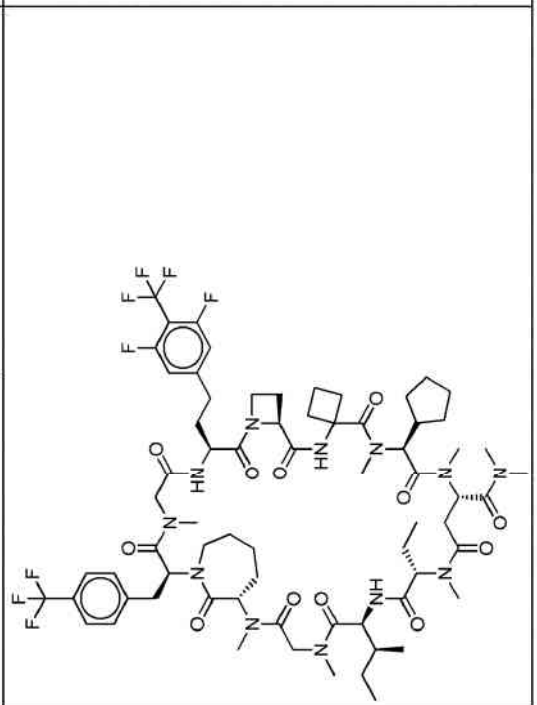
	
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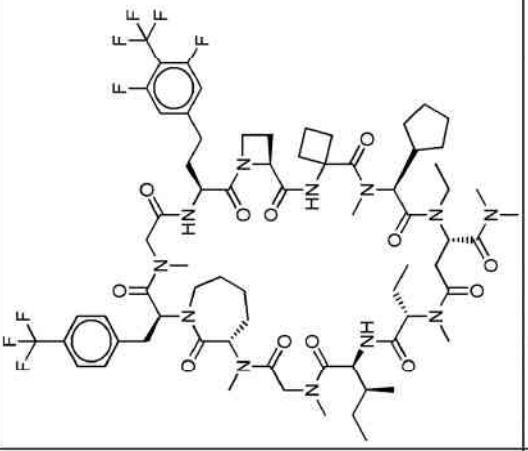
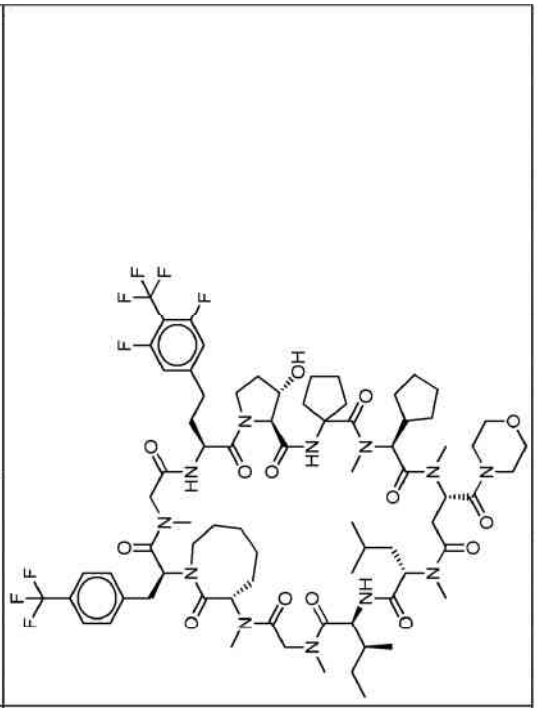
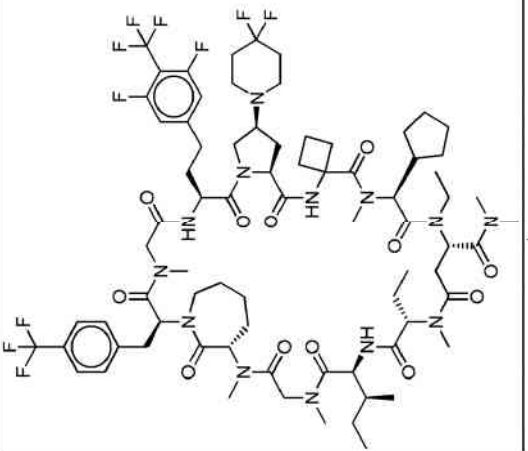
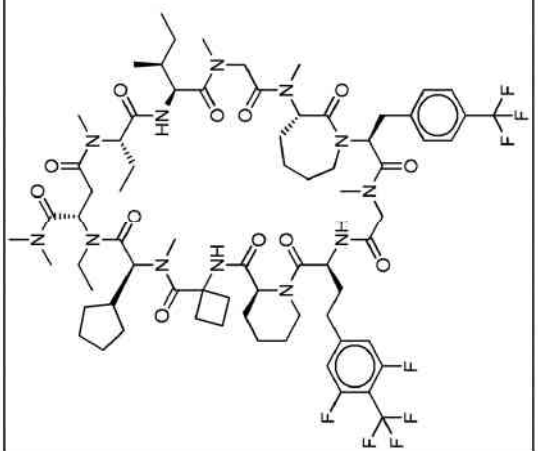
	
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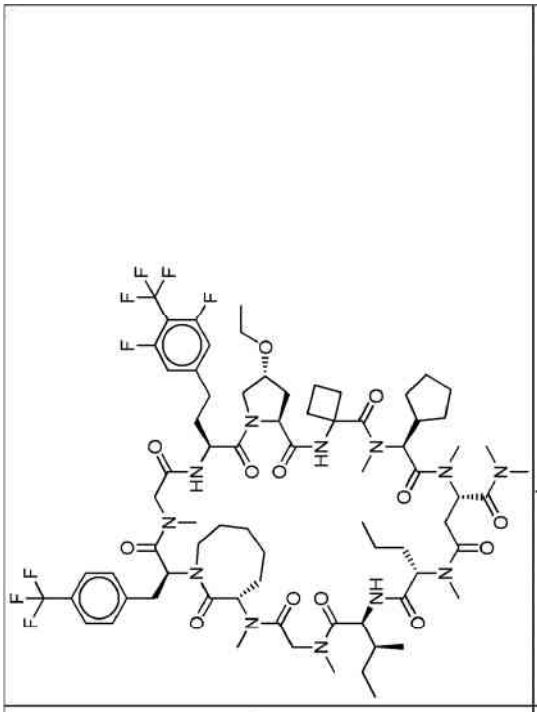
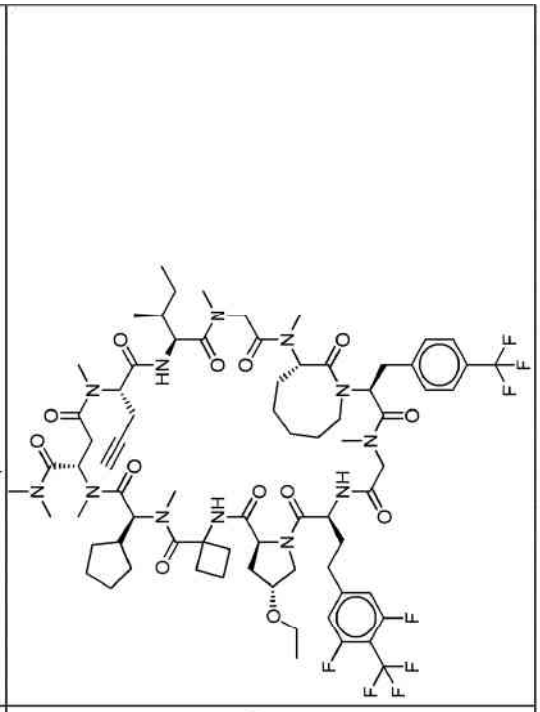
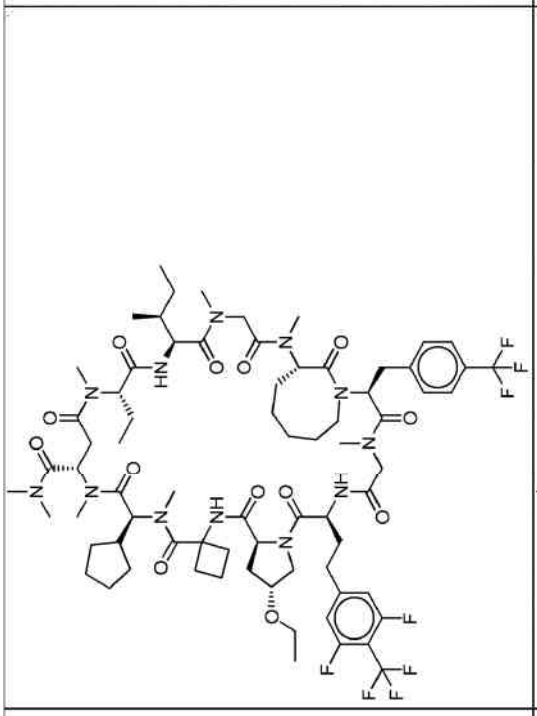
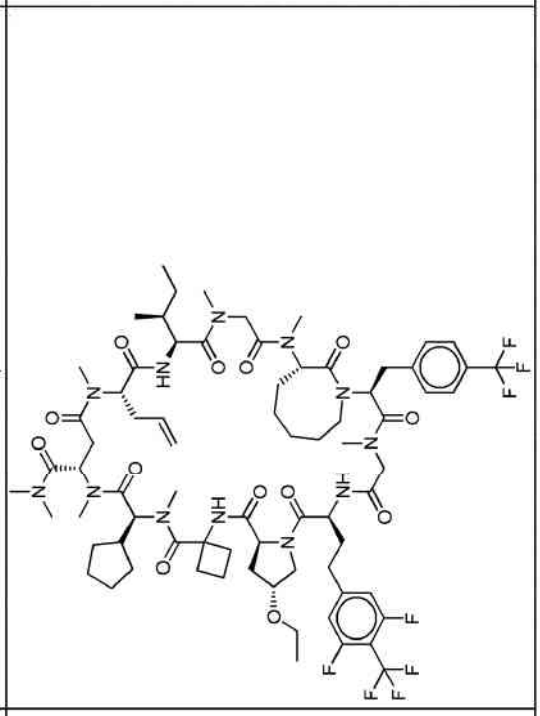
	
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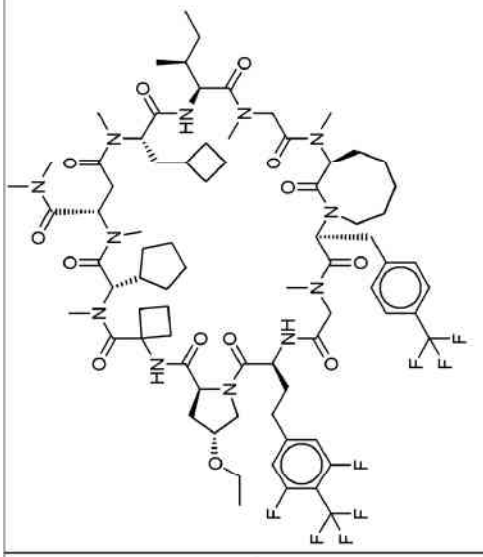
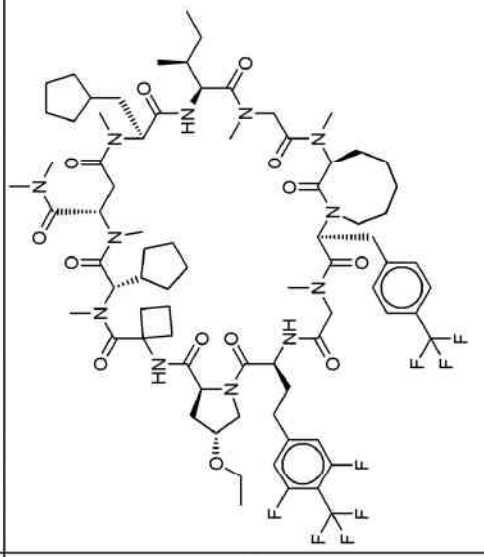
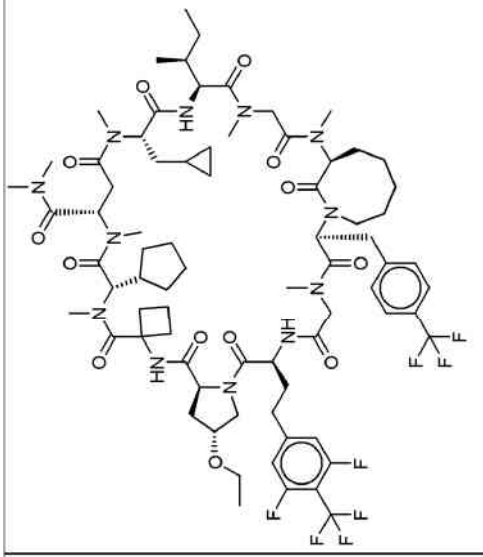
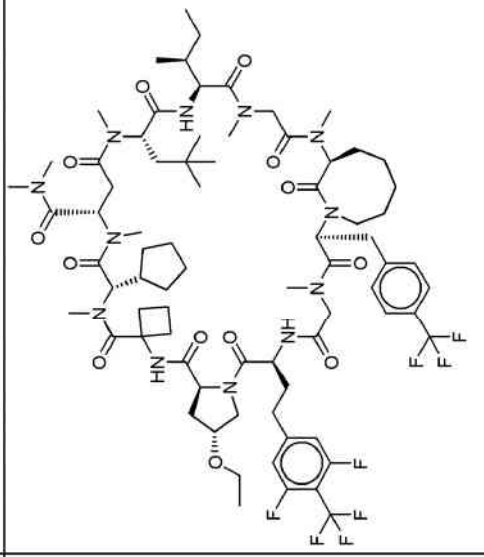
	
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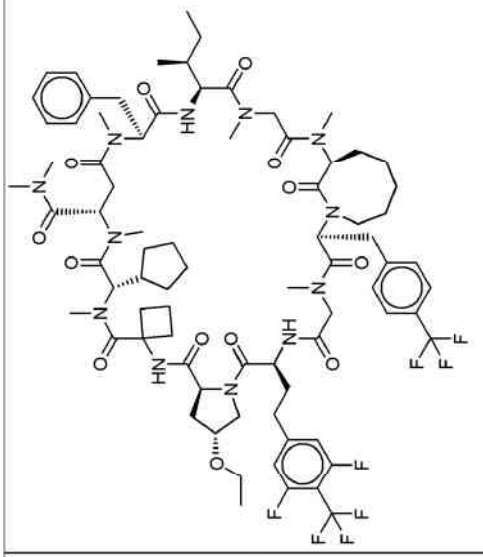
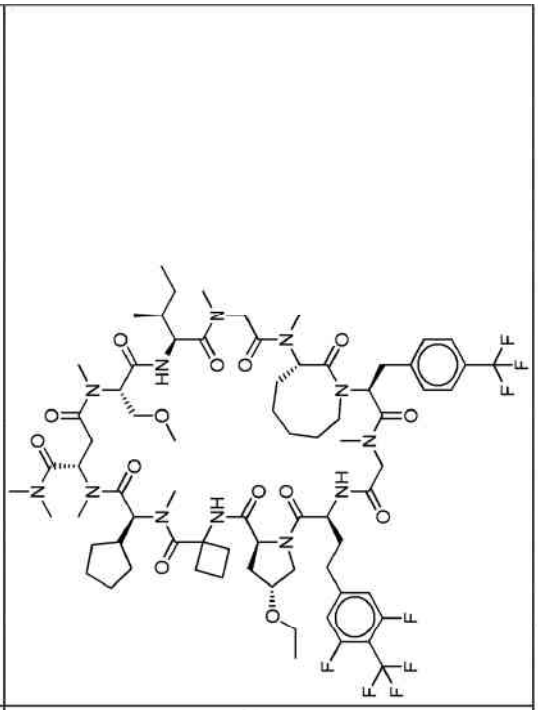
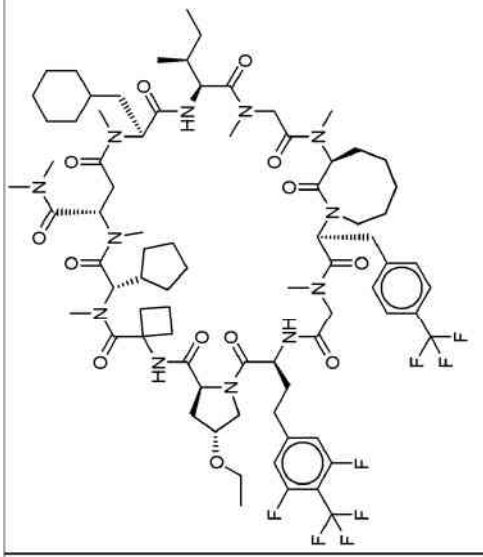
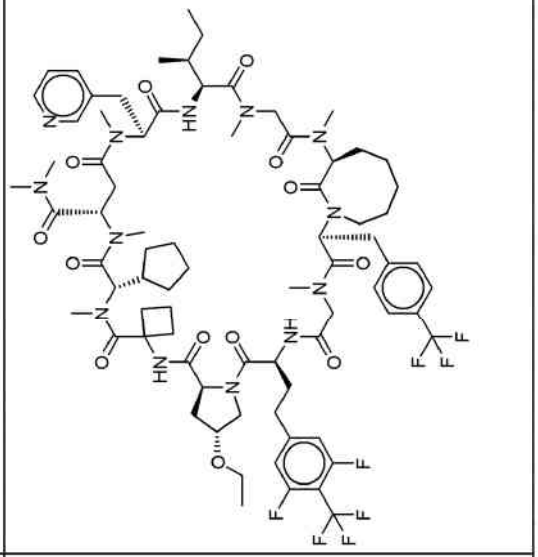
	
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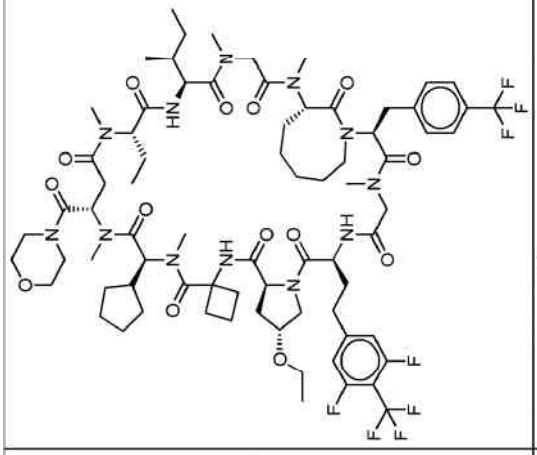
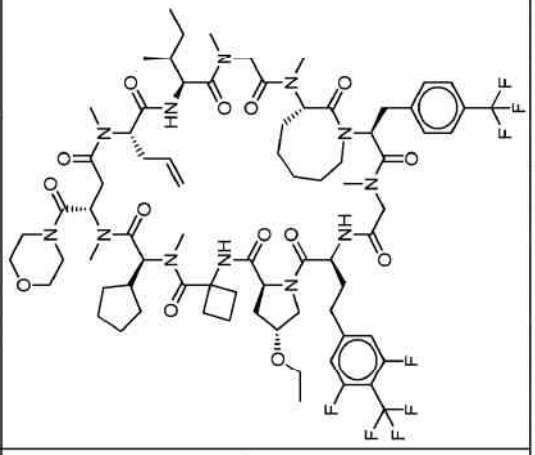
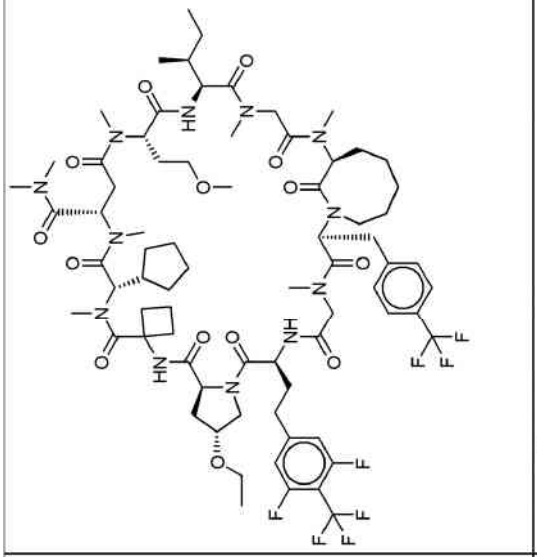
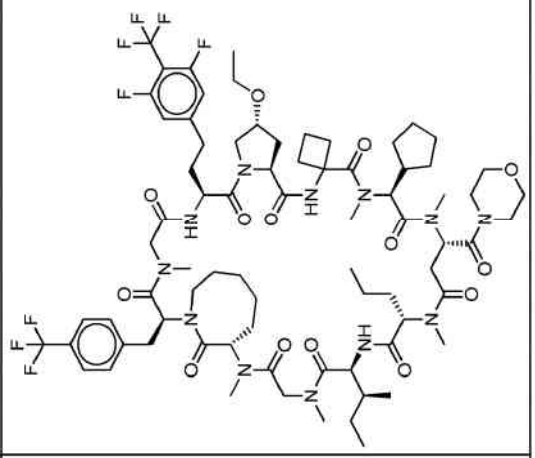
	
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PP0 655	PP0 657

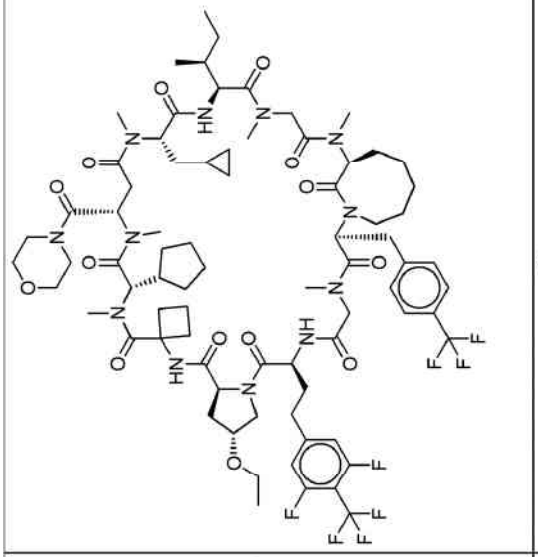
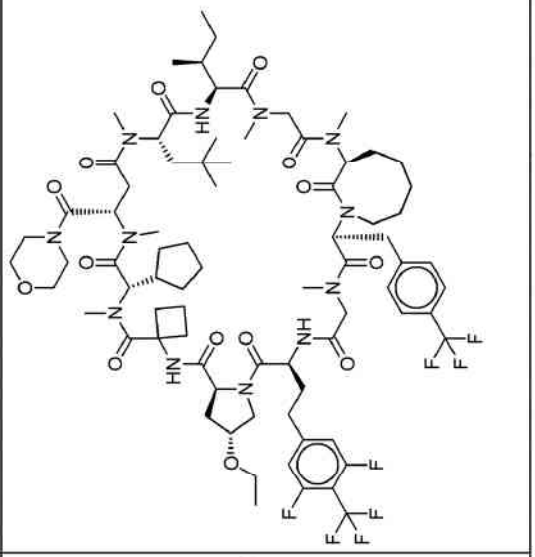
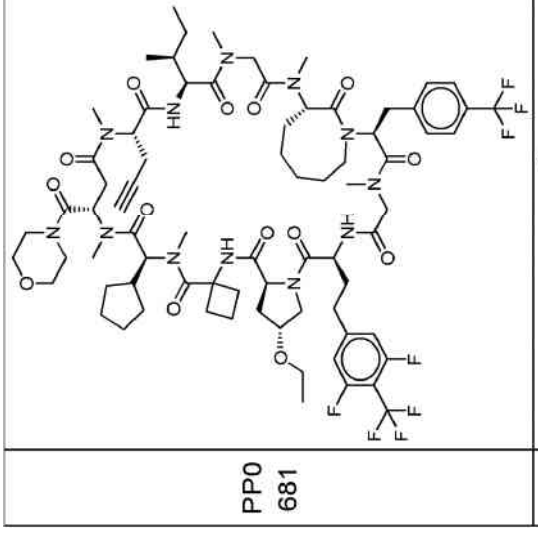
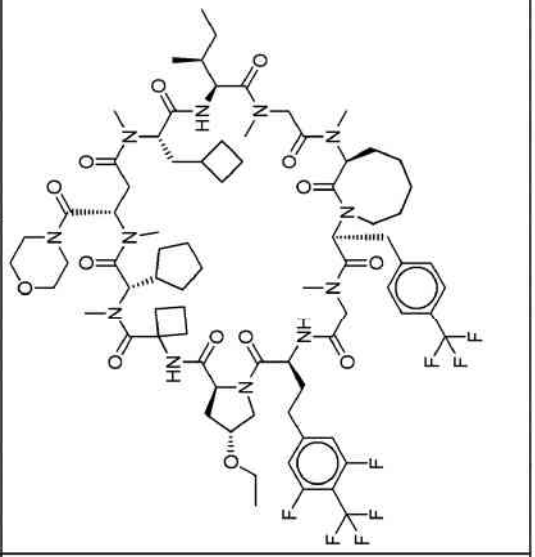
	
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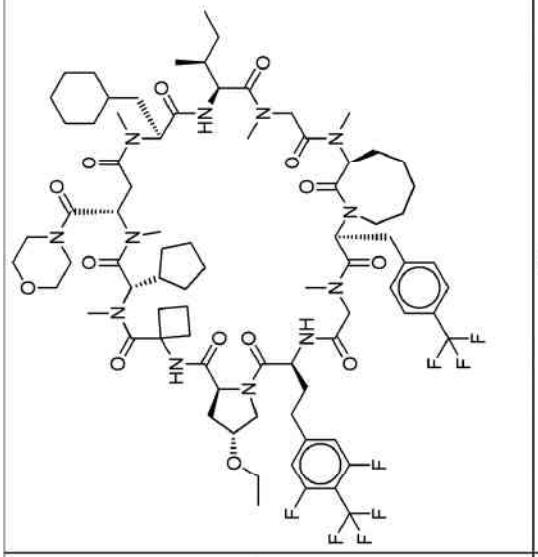
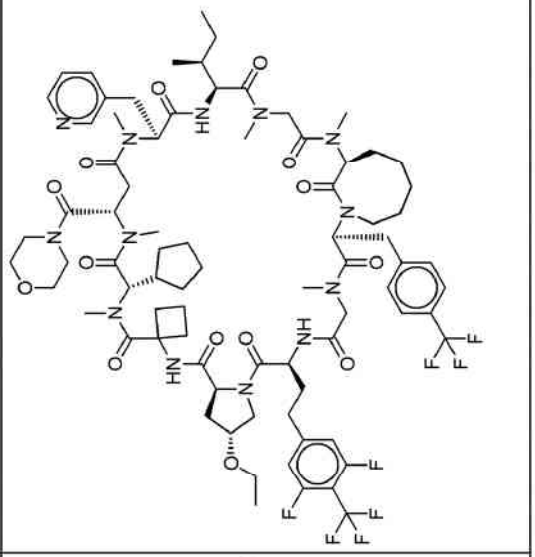
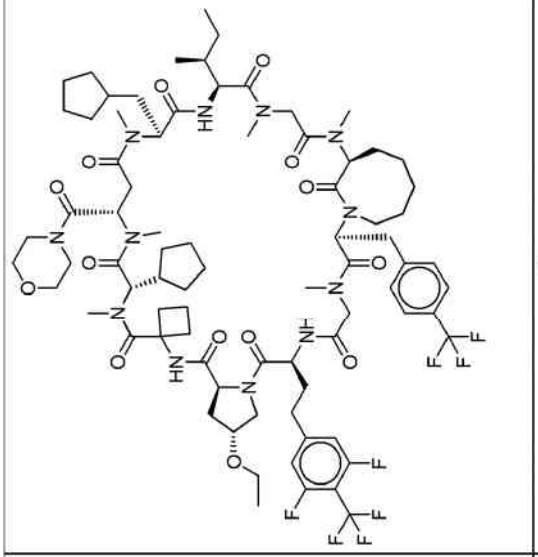
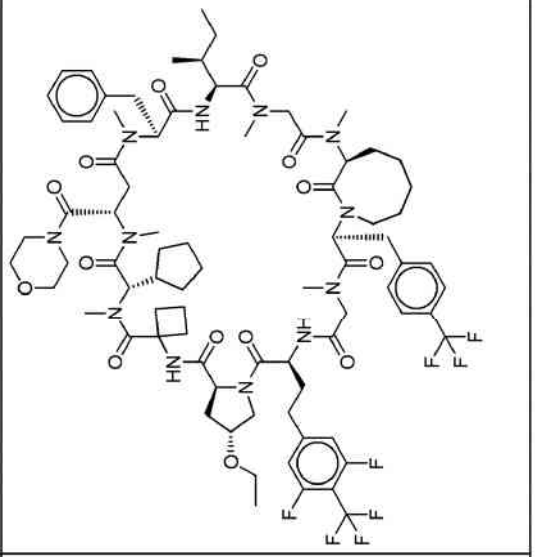
	
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PP0 663	PP0 665

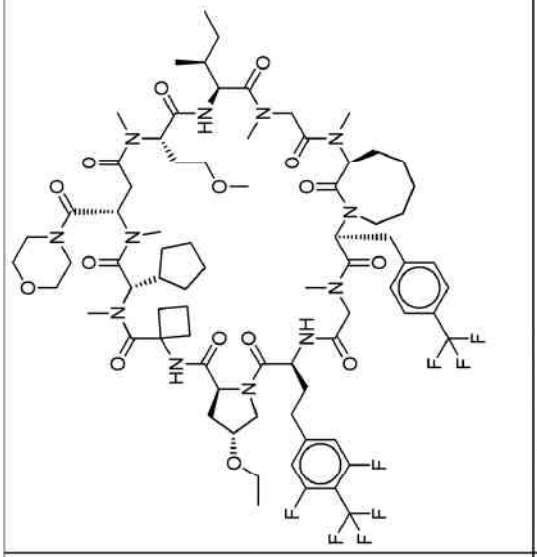
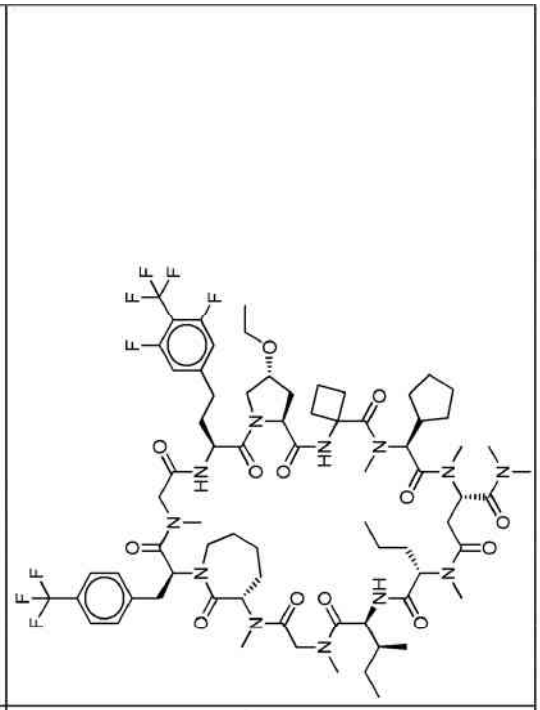
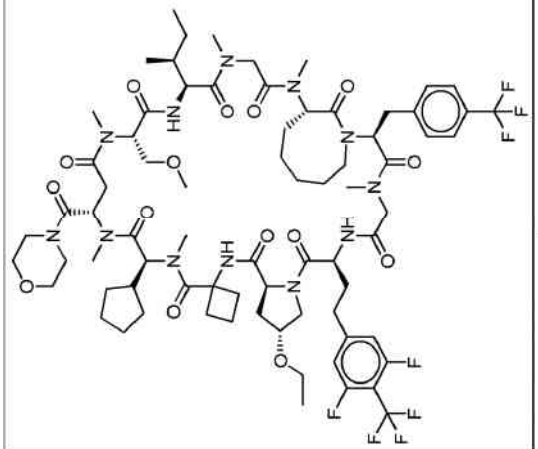
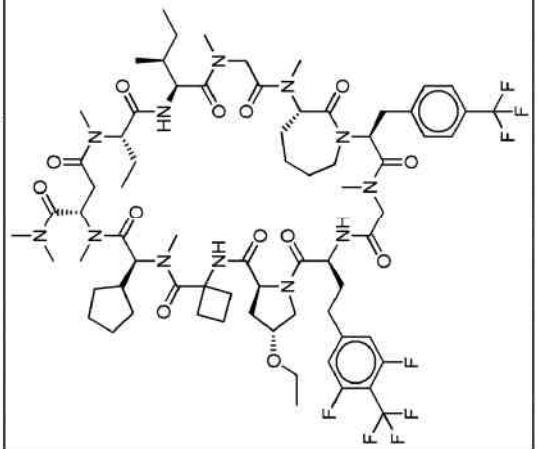
	
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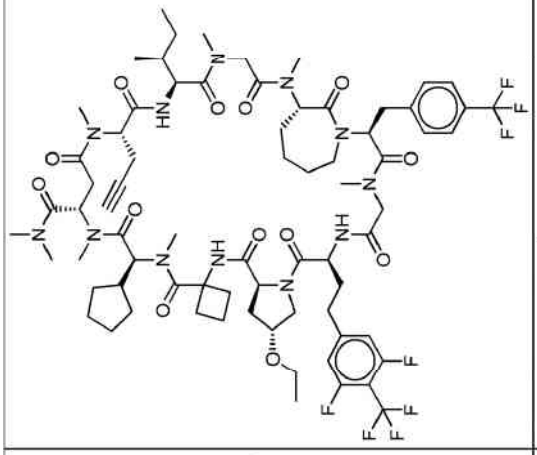
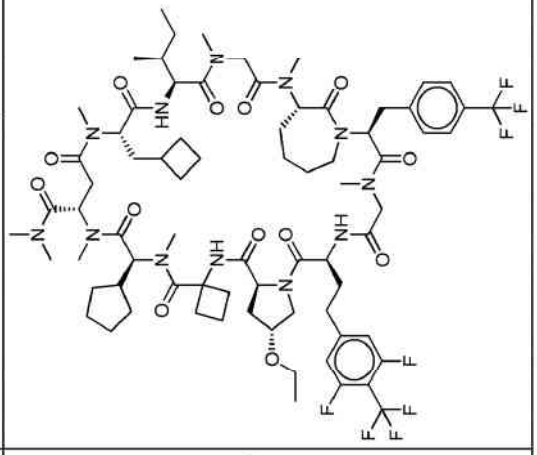
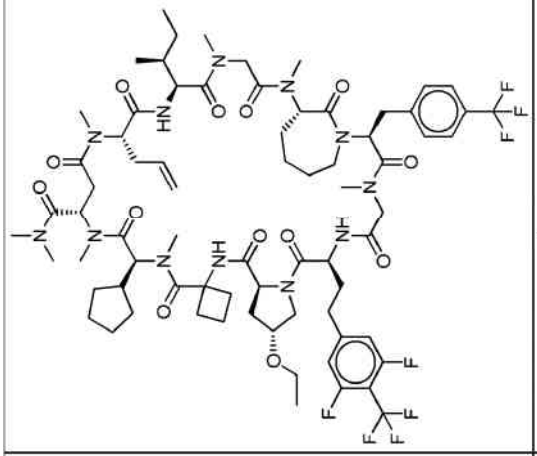
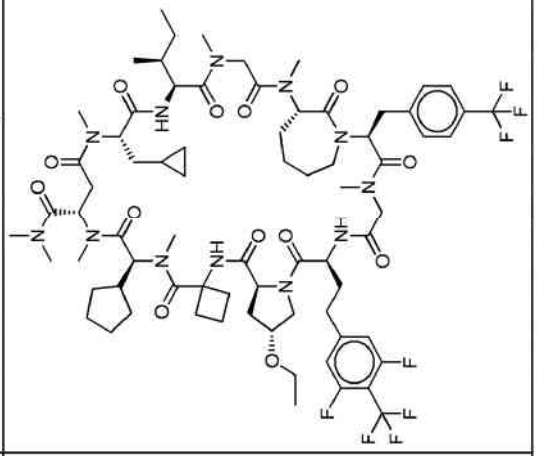
	
PP0 672	PP0 674
	
PP0 671	PP0 673

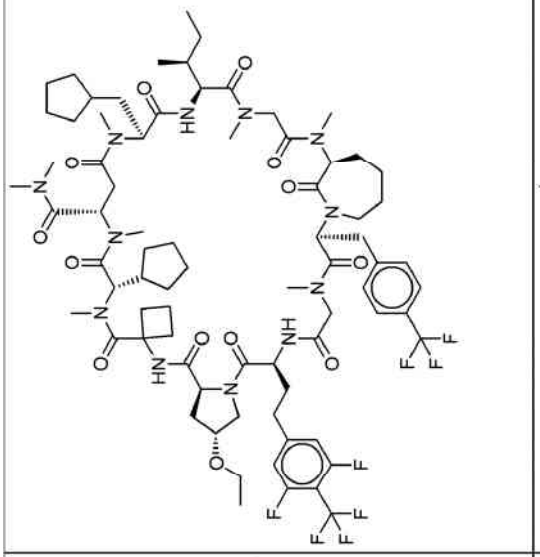
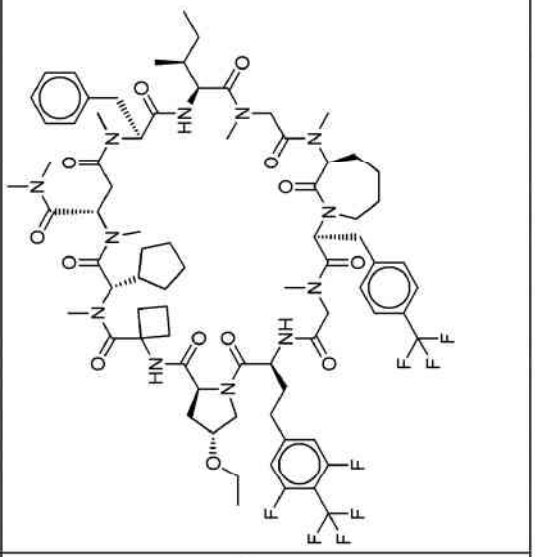
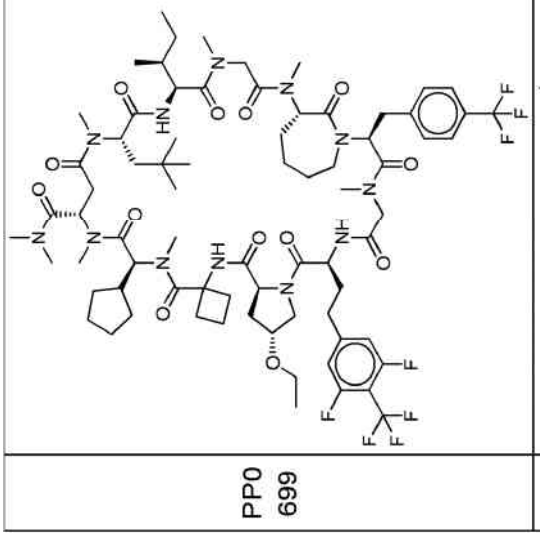
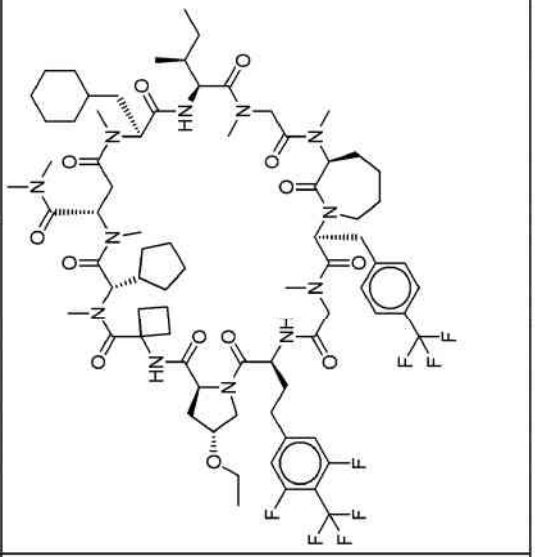
	
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PP0 675	PP0 679

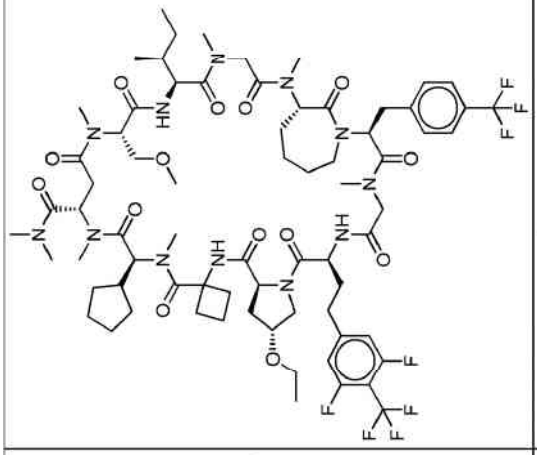
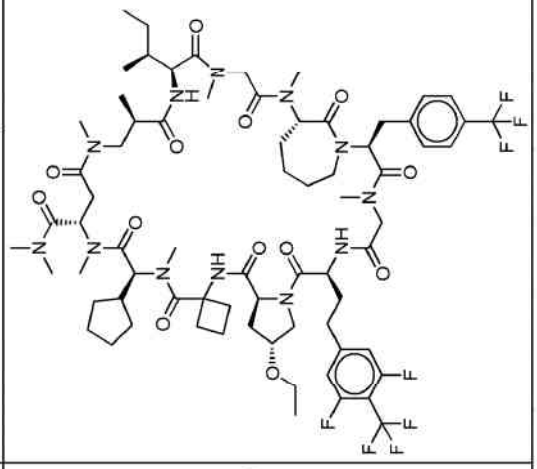
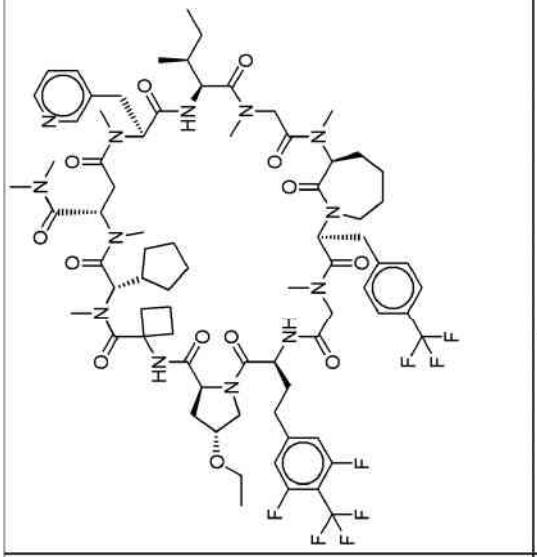
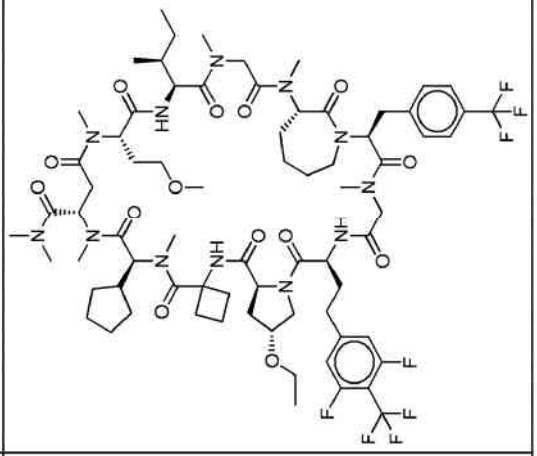
	
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PP0 681	PP0 683

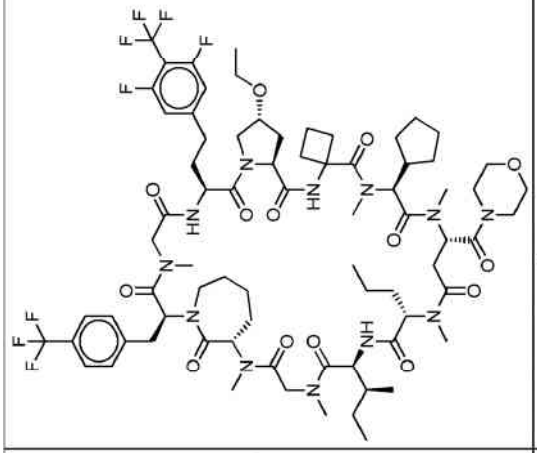
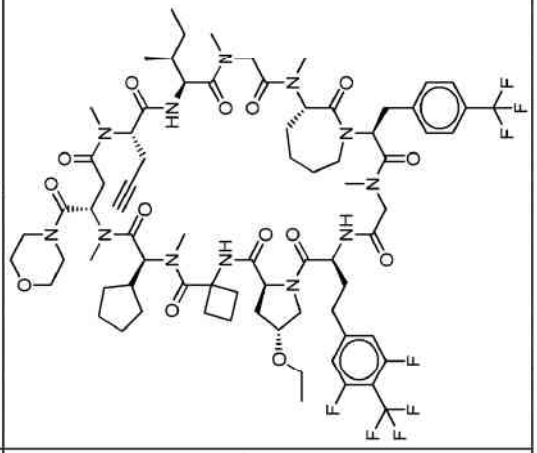
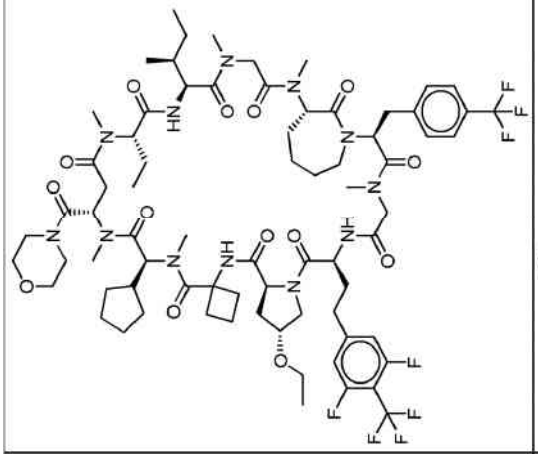
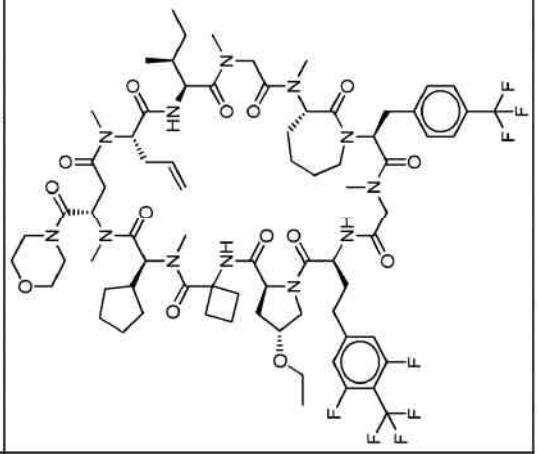
	
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PP0 685	PP0 687

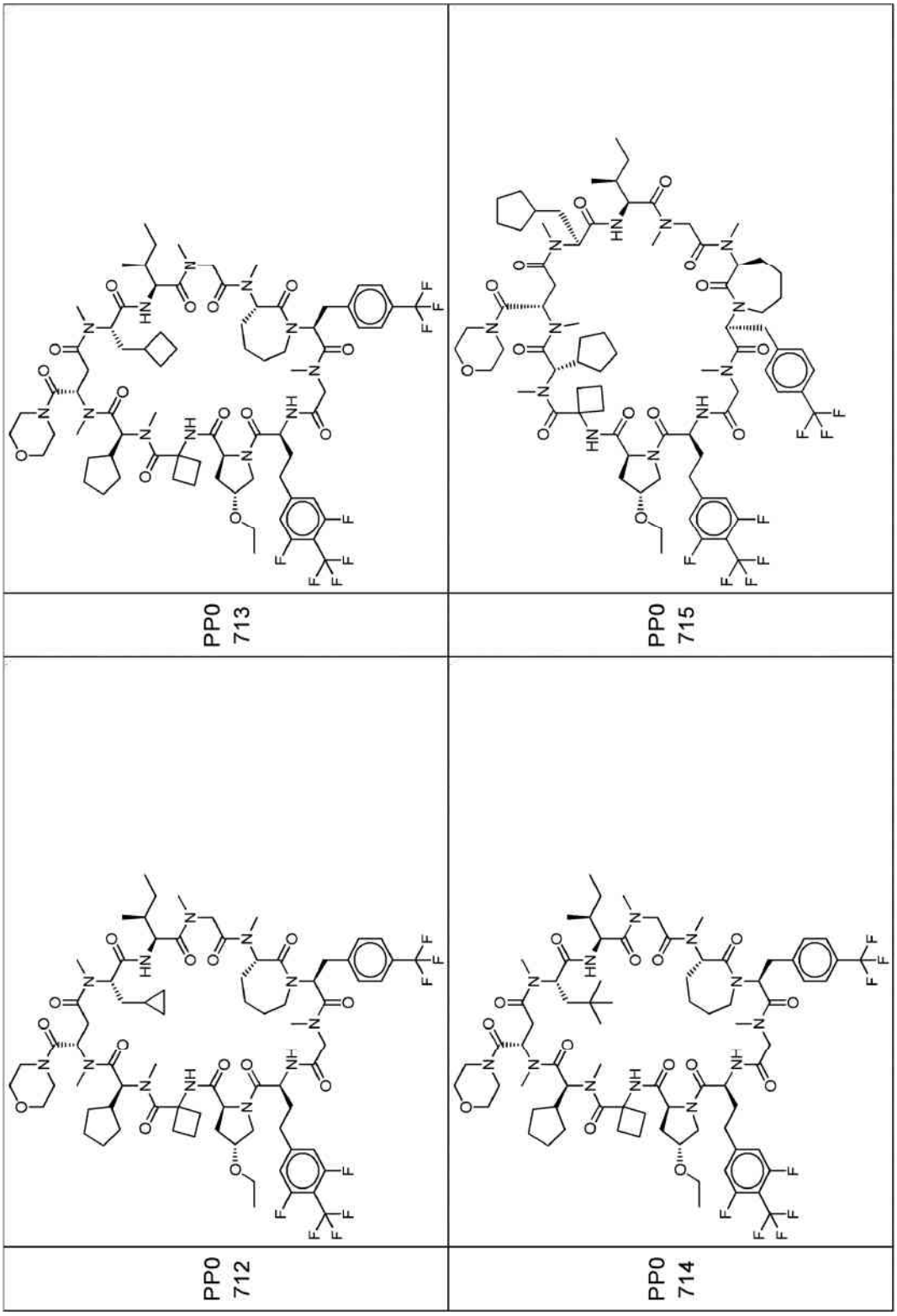
	
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PP0 689	PP0 693

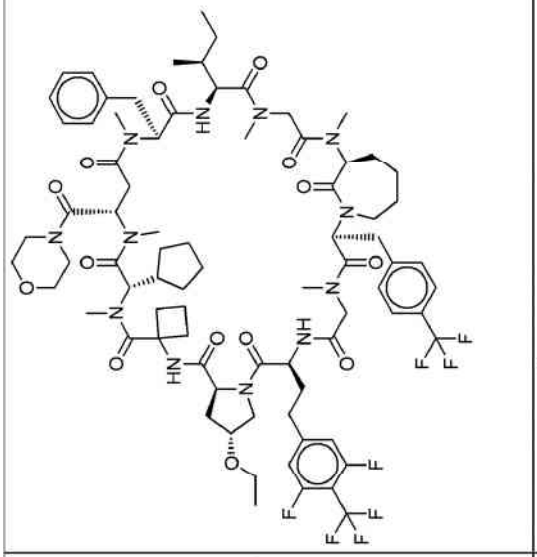
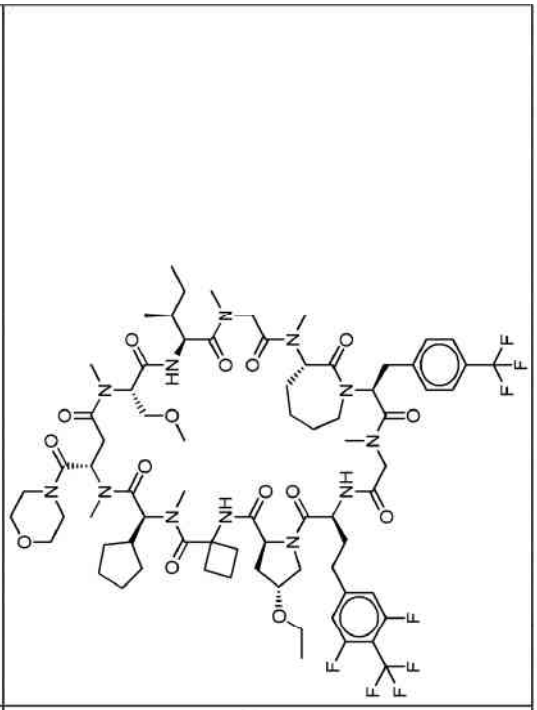
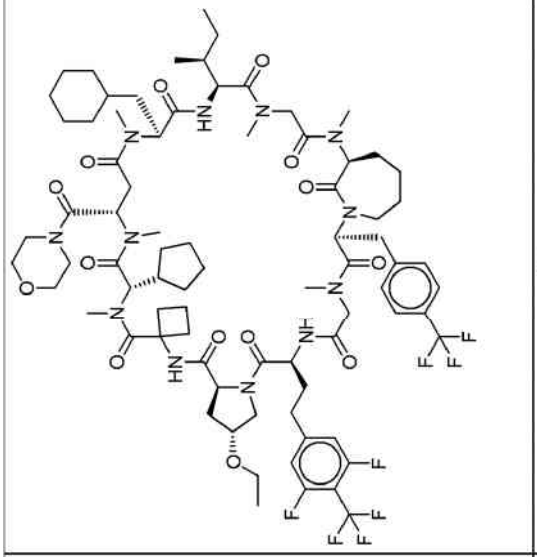
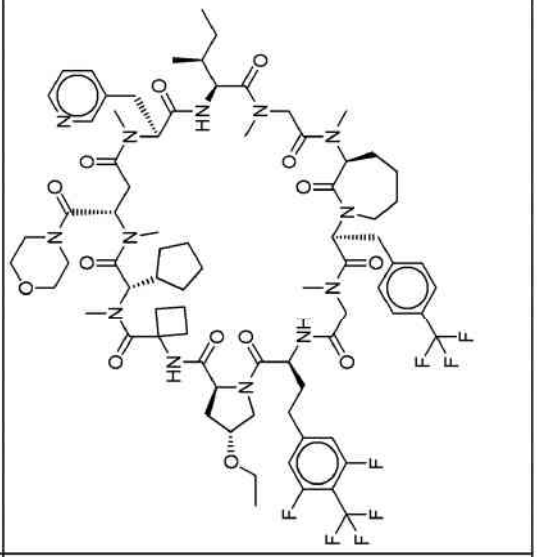
	
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PP0 695	PP0 697

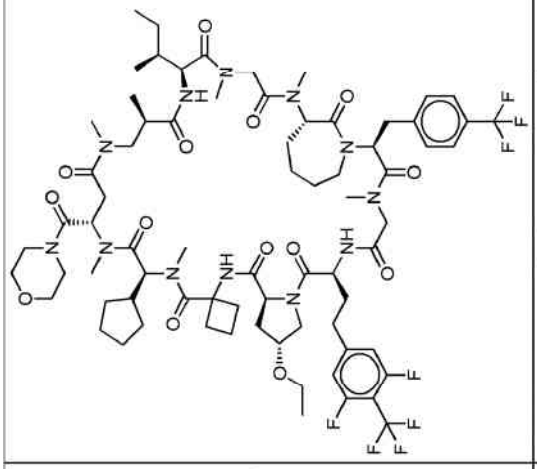
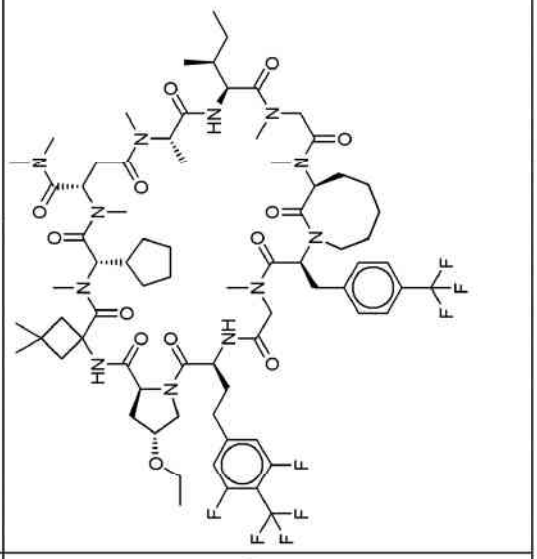
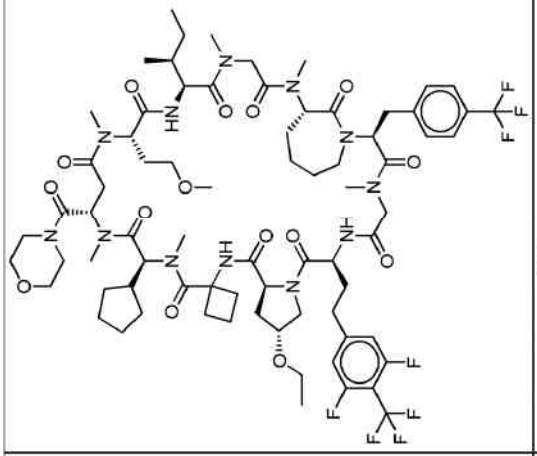
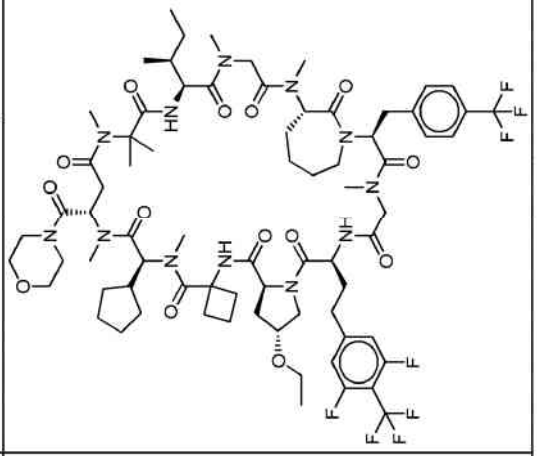
	
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PP0 699	PP0 701

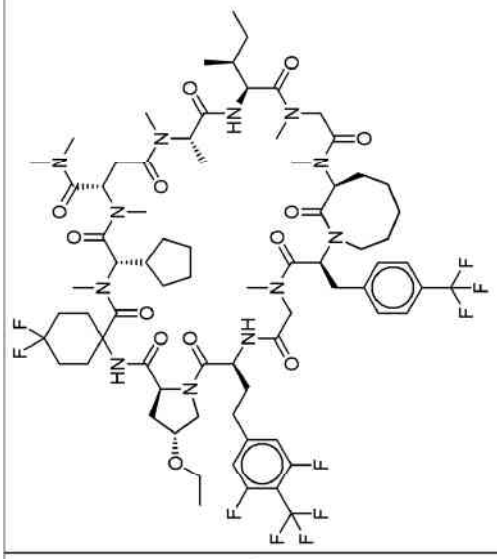
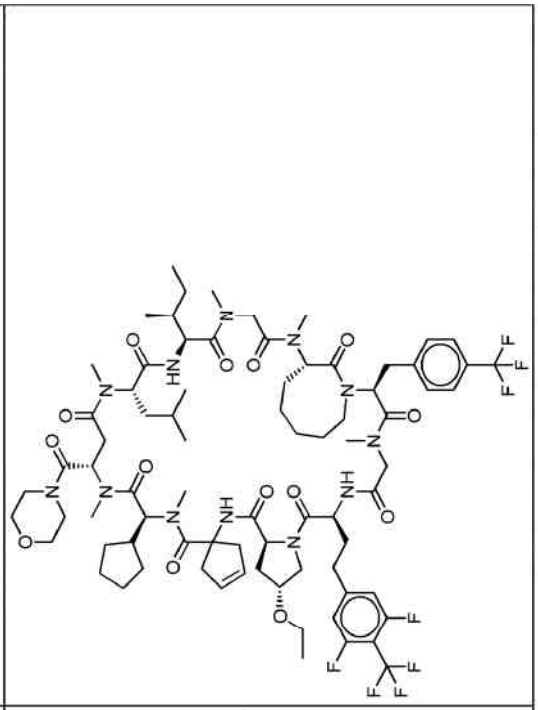
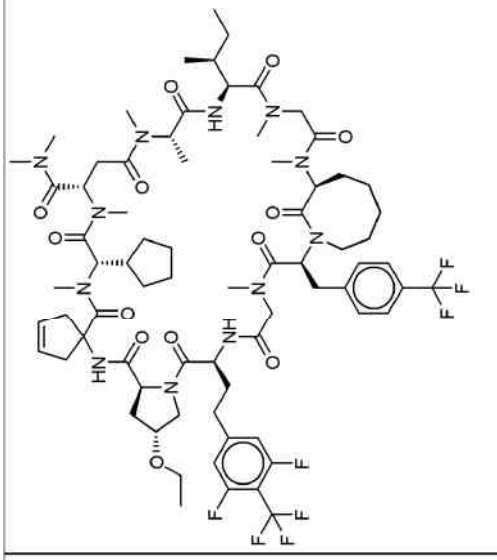
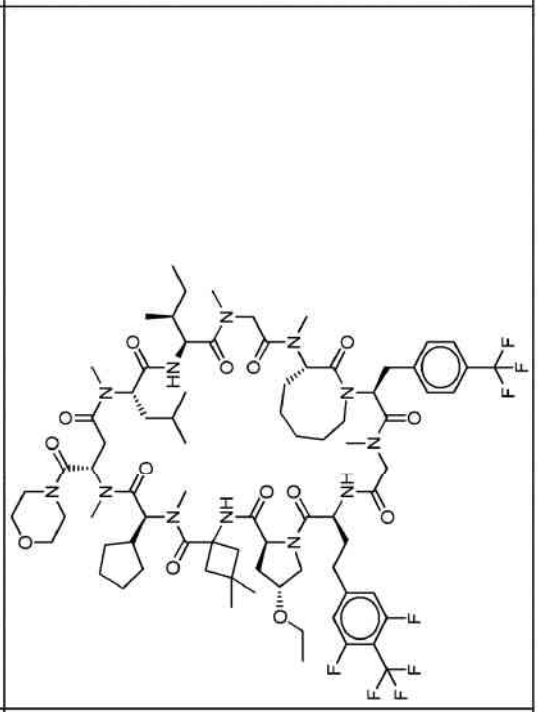
	
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PP0 703	PP0 705

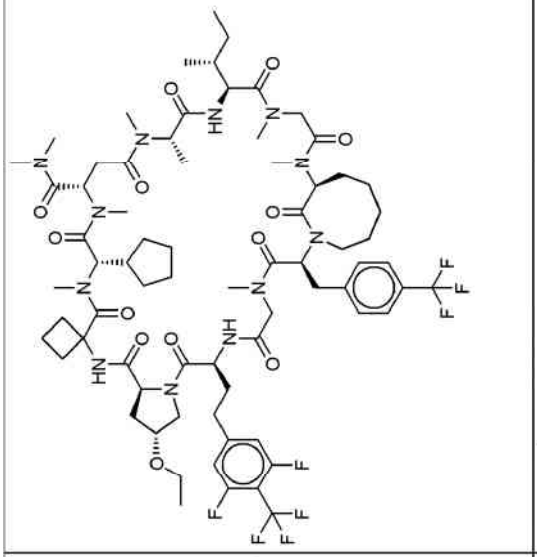
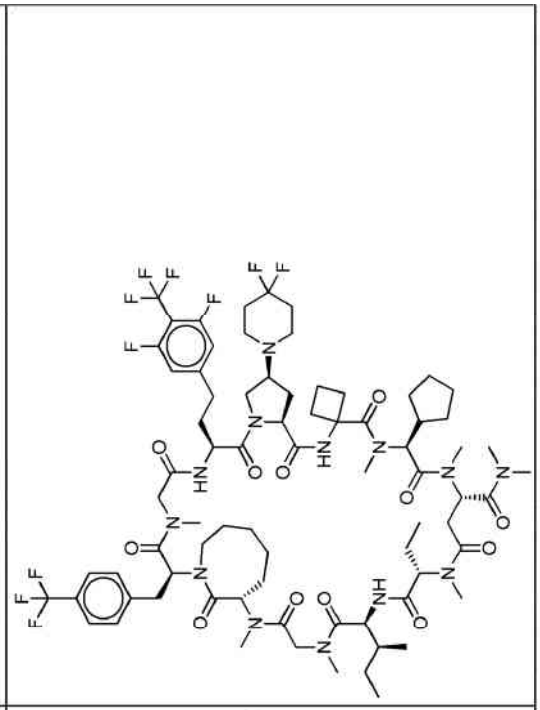
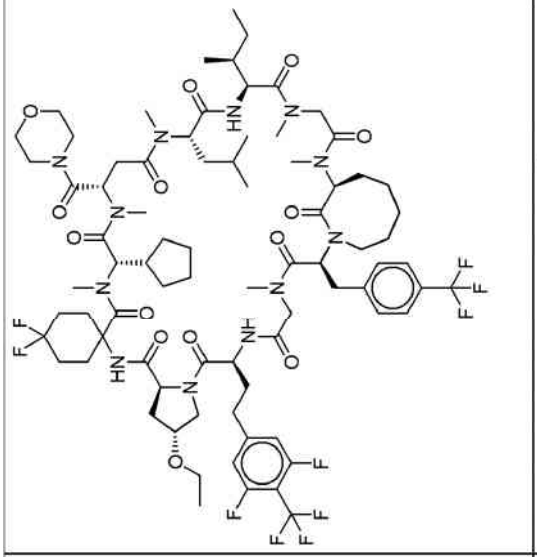
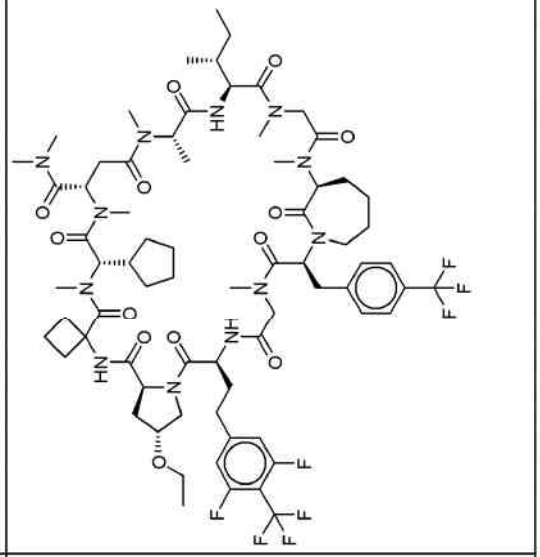
	
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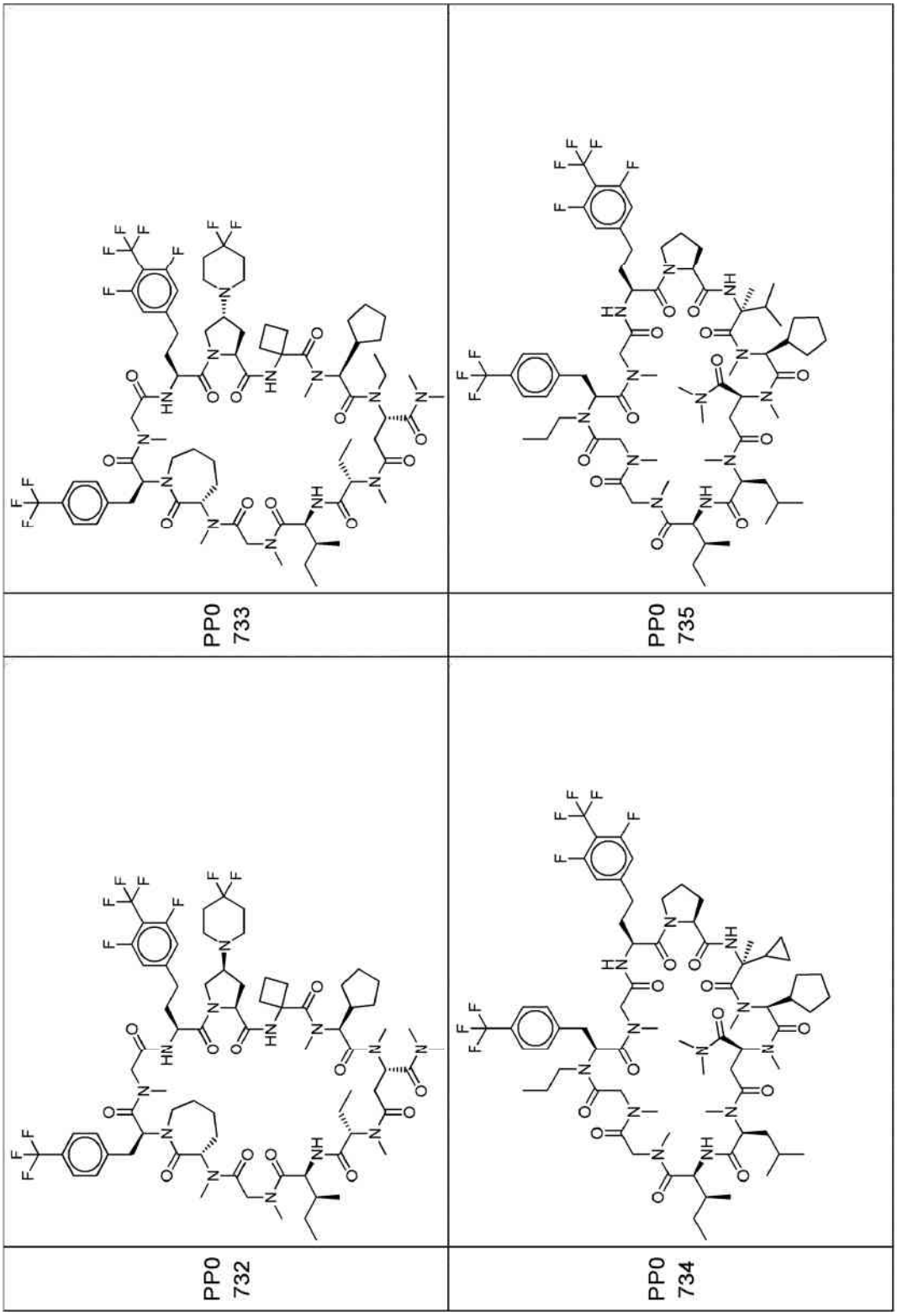

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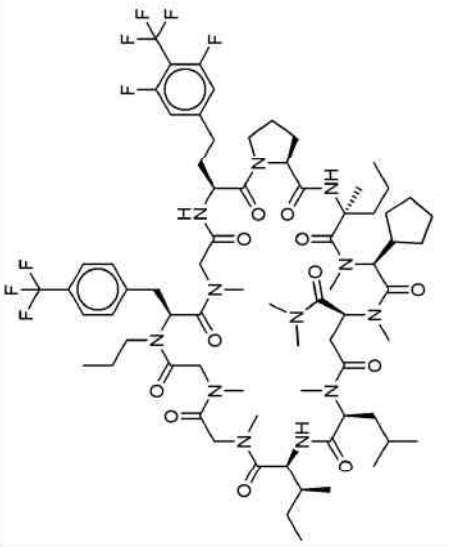
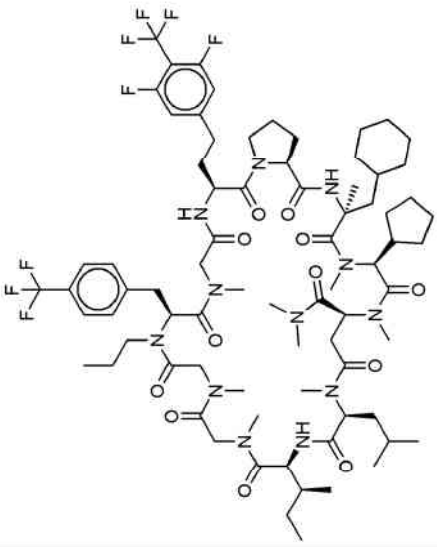
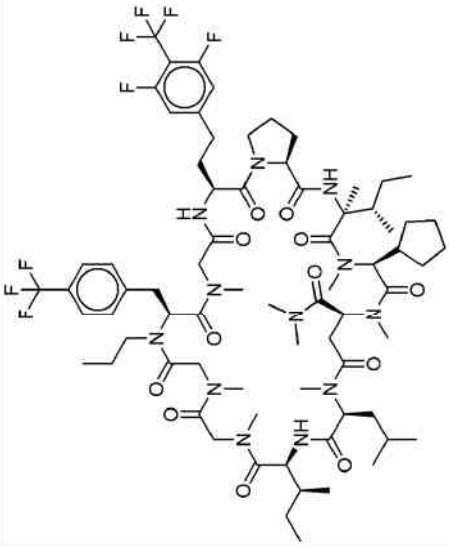
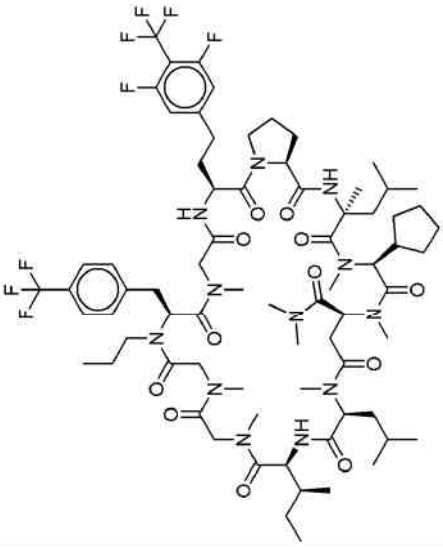
	
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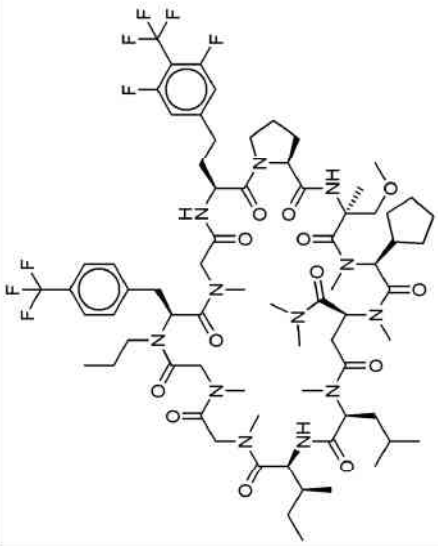
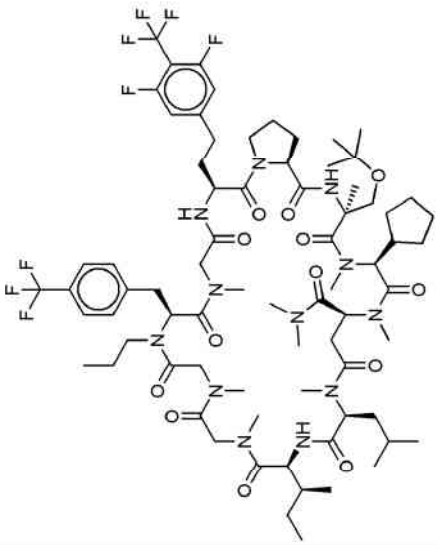
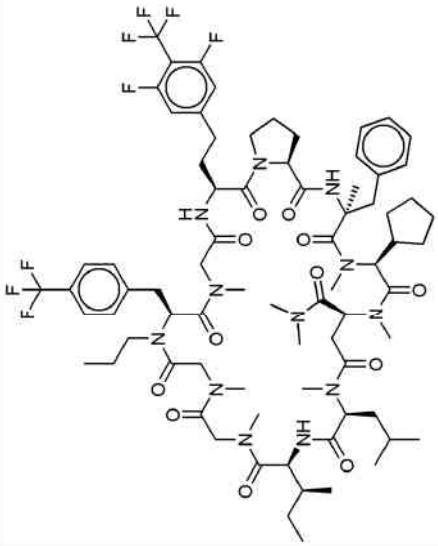
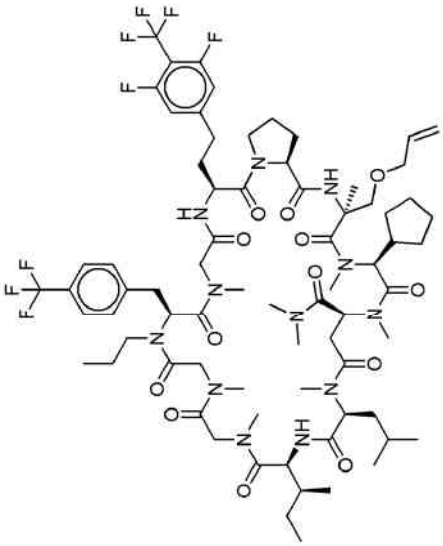
	
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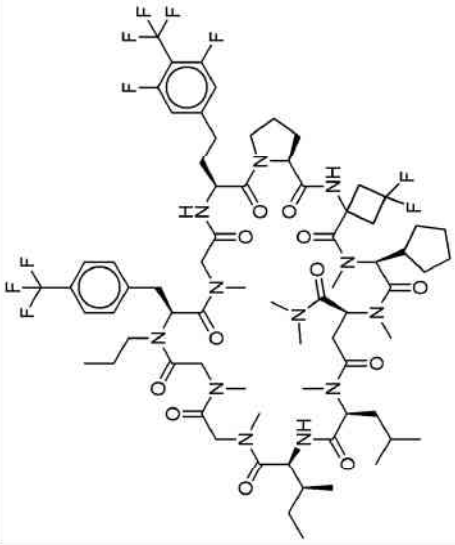
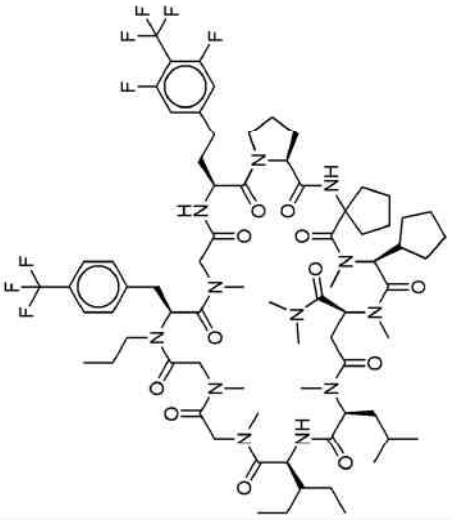
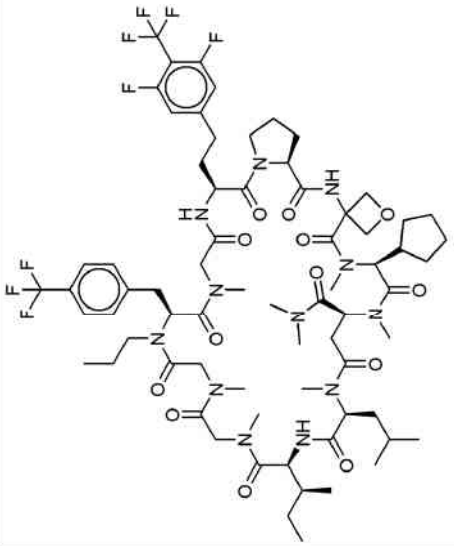
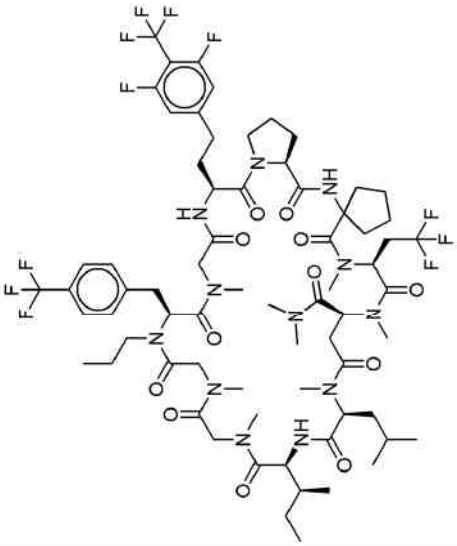
	
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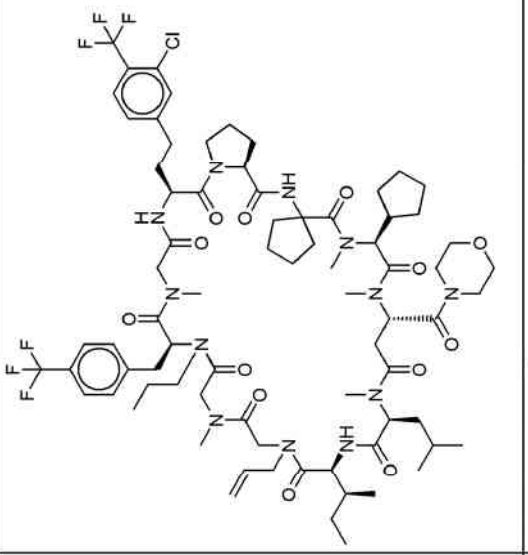
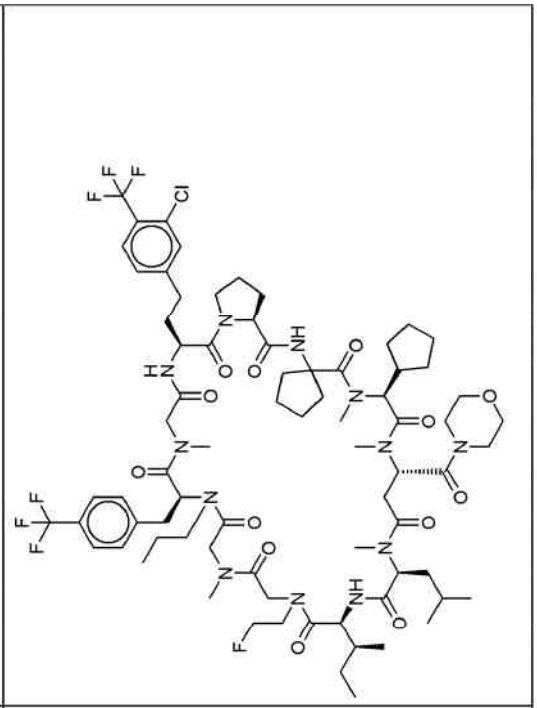
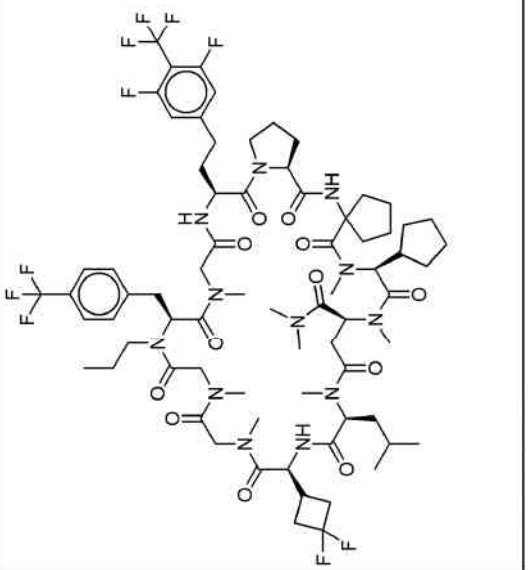
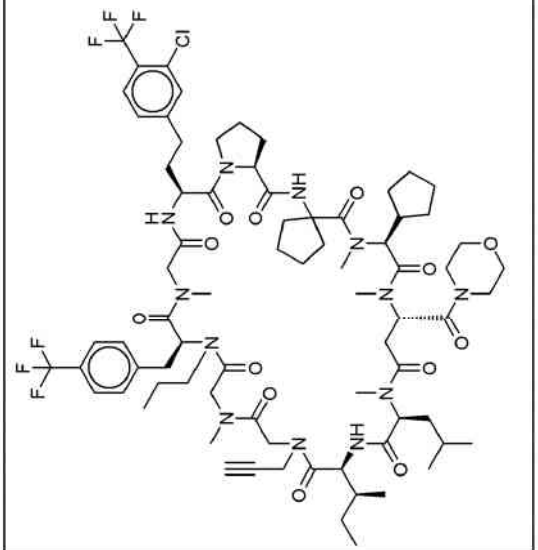
	
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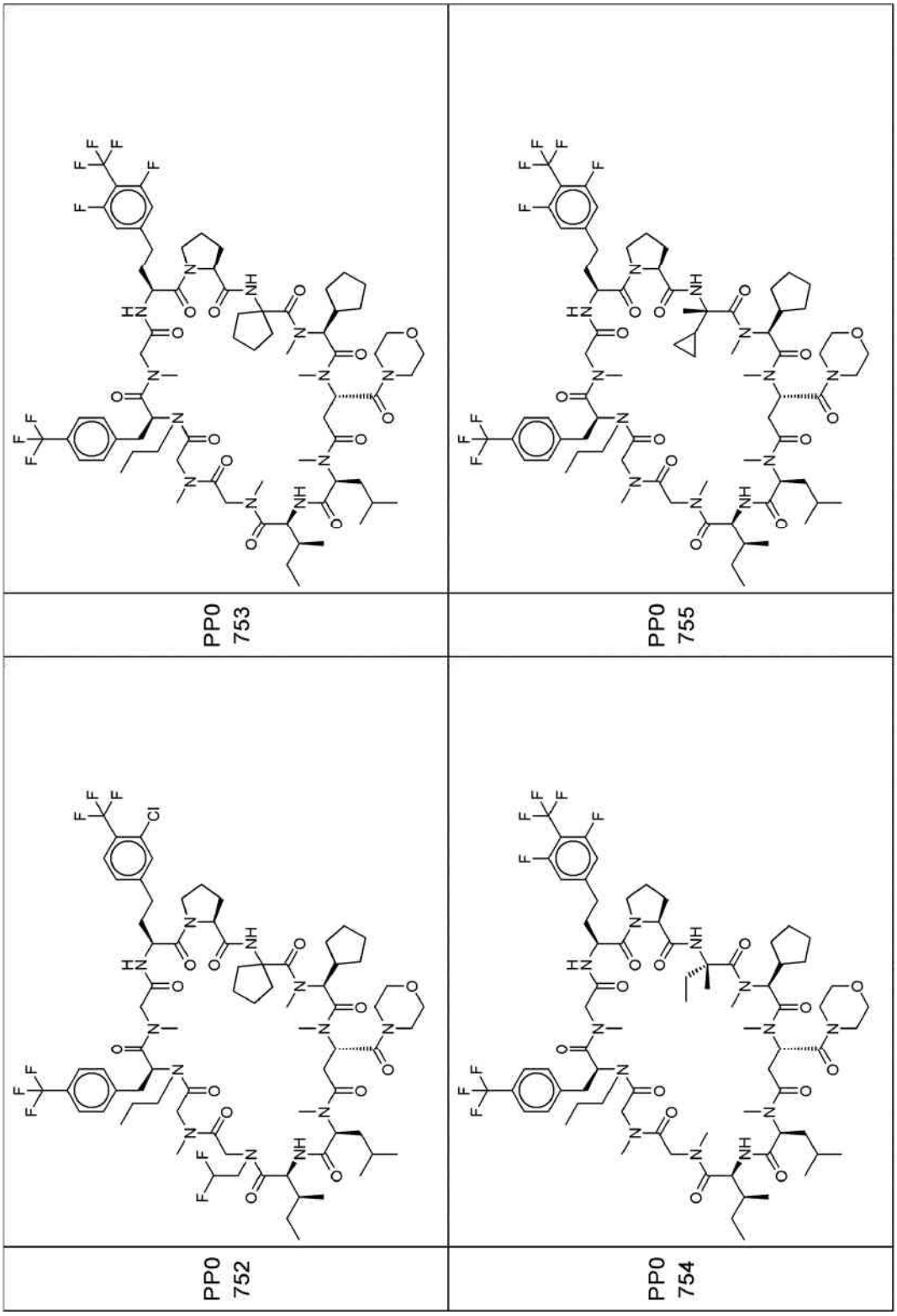

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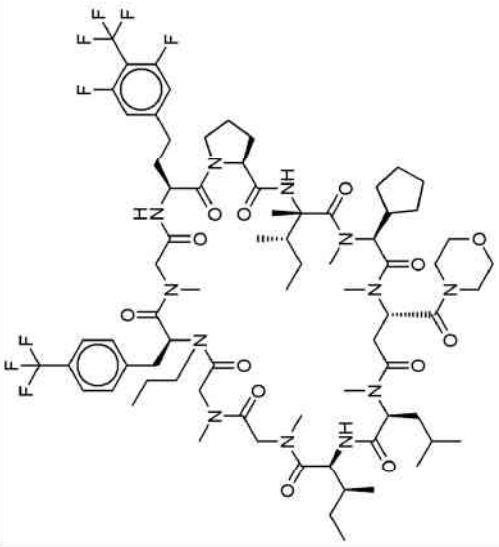
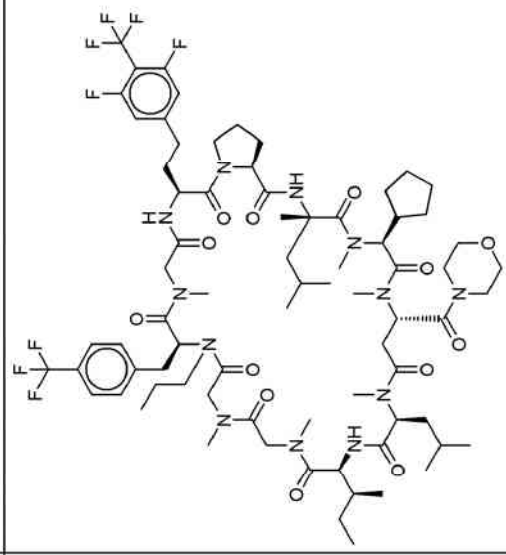
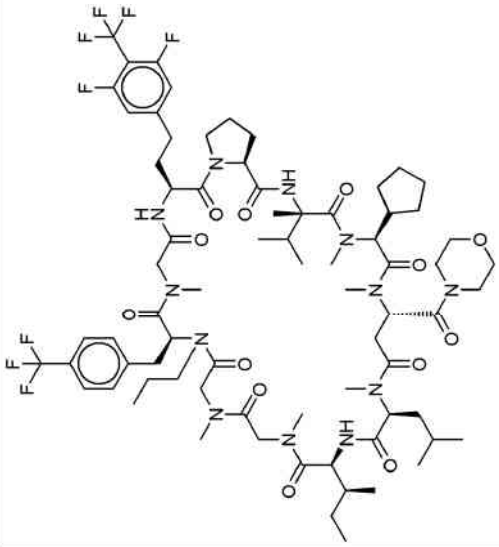
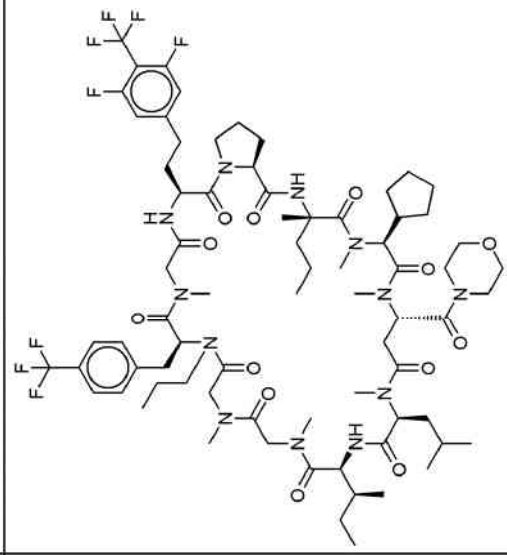
	
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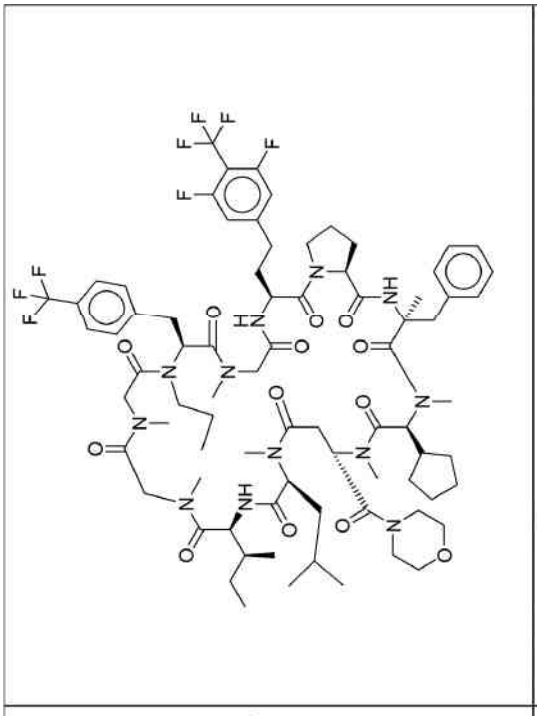
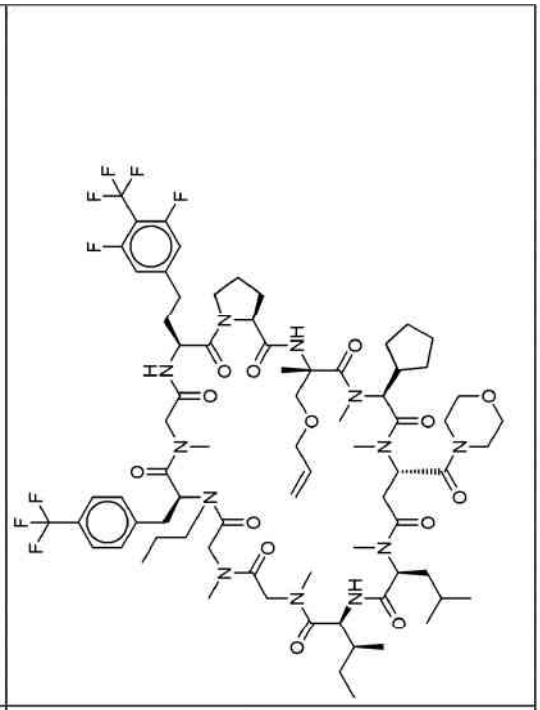
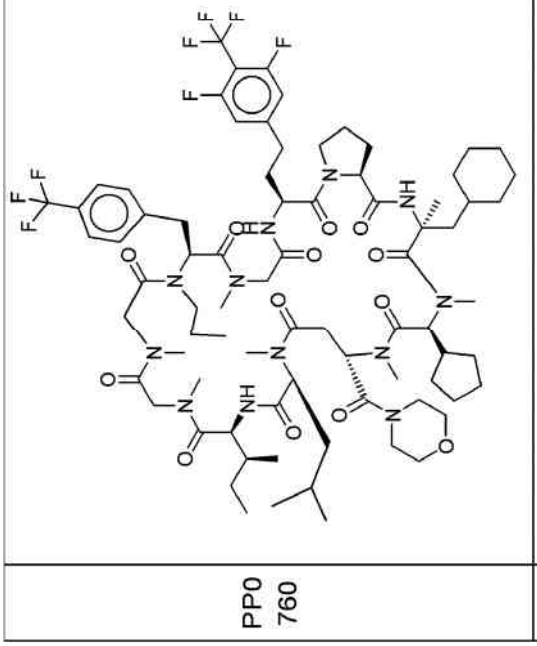
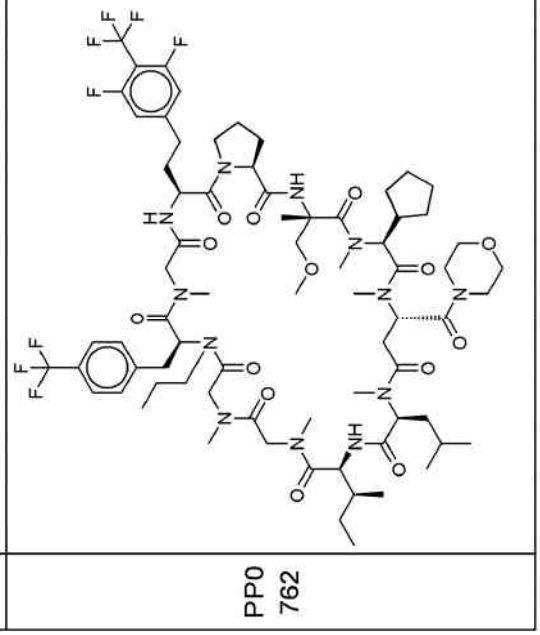
	
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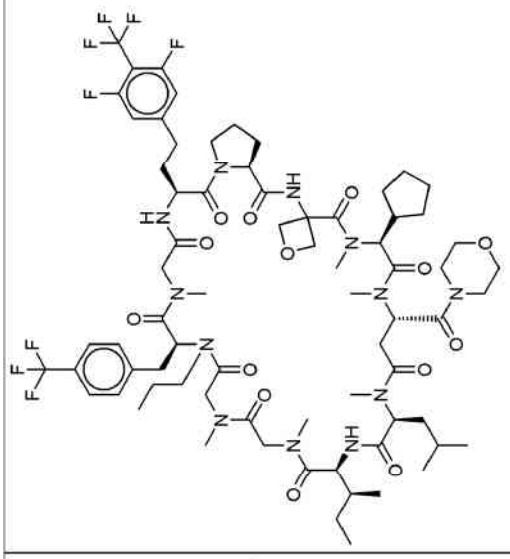
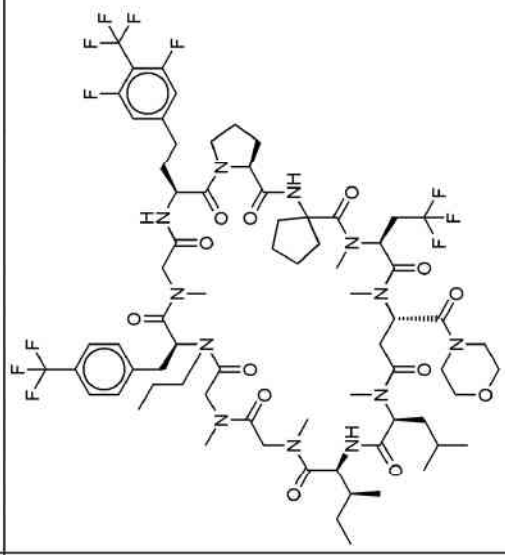
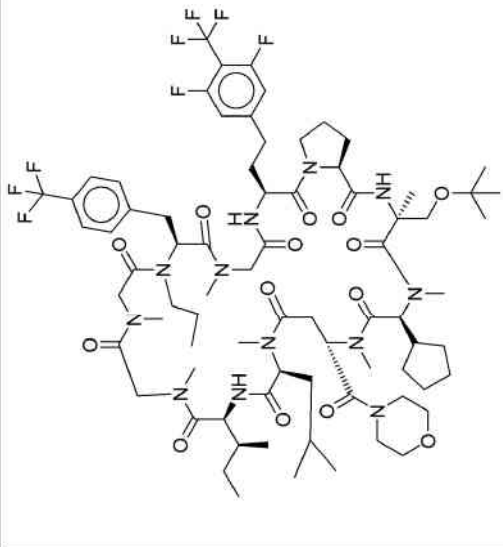
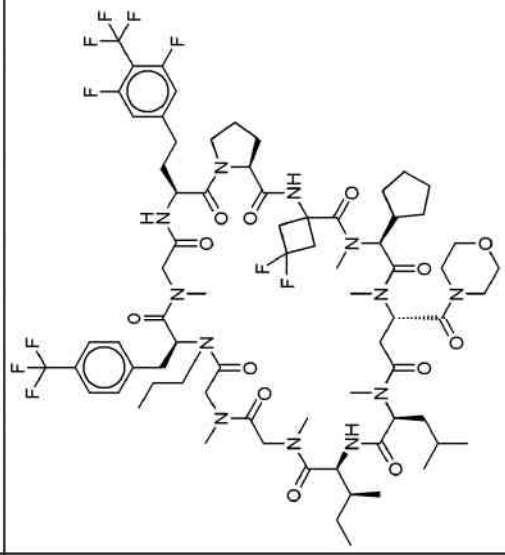
	
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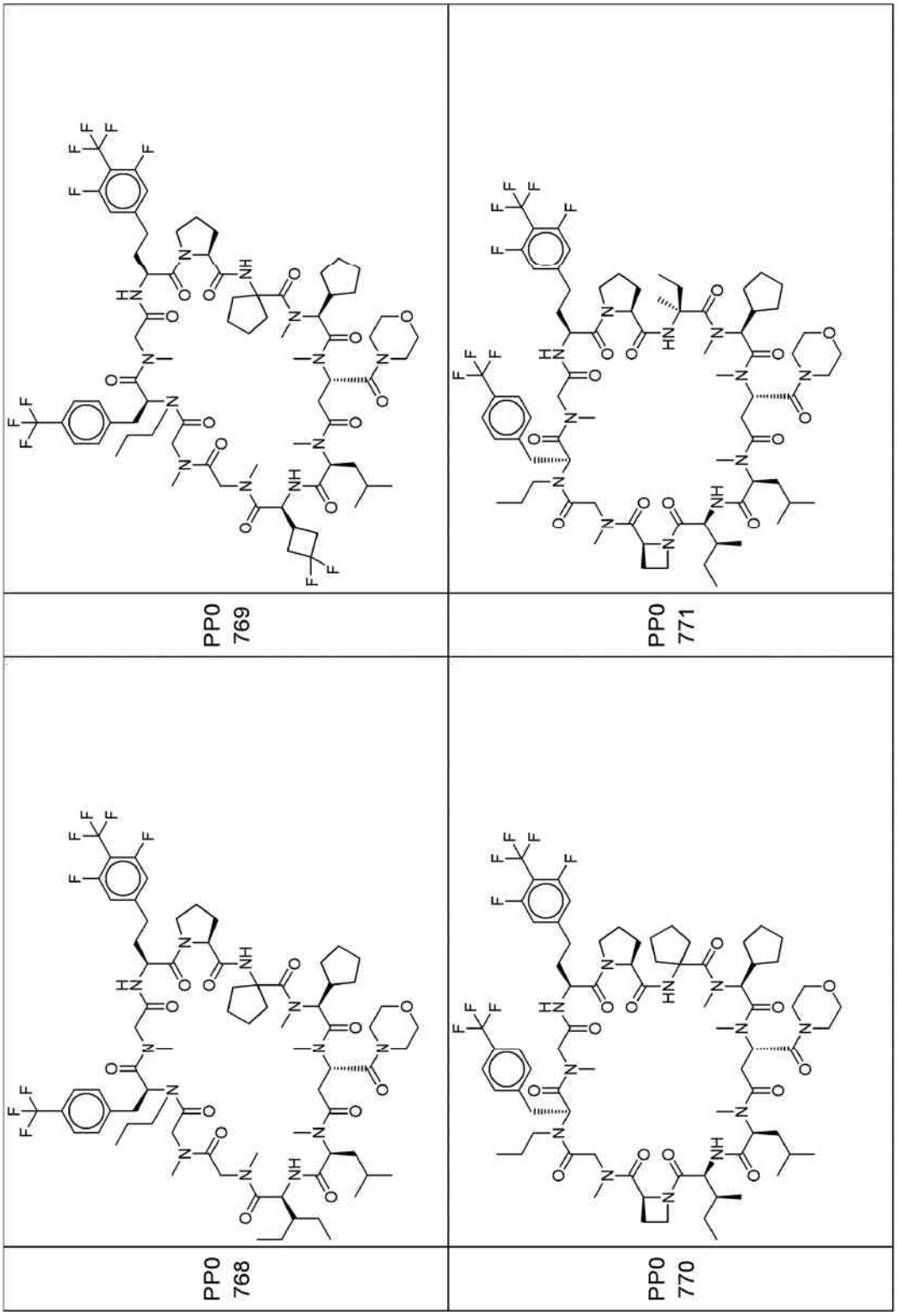
	
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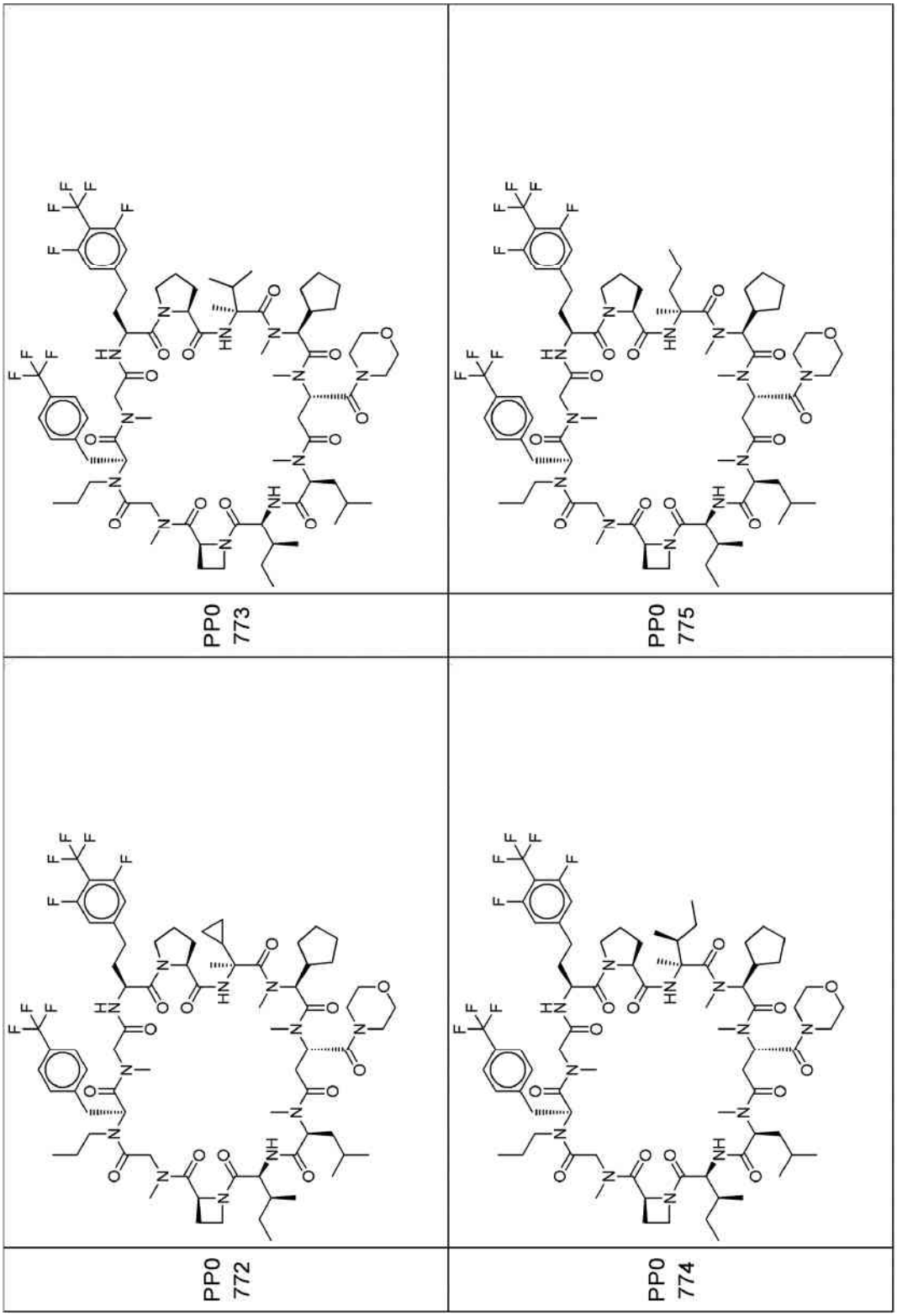

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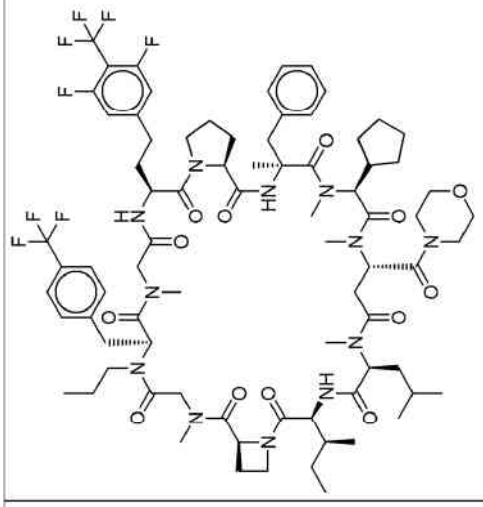
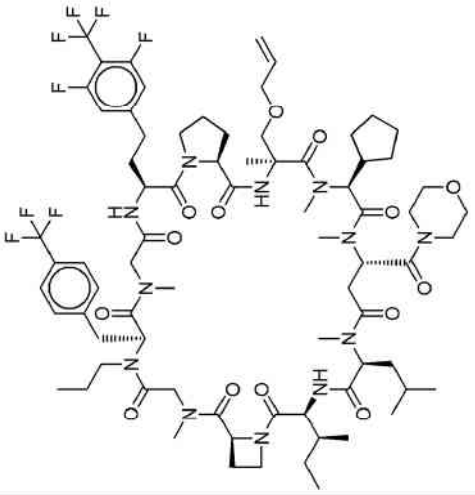
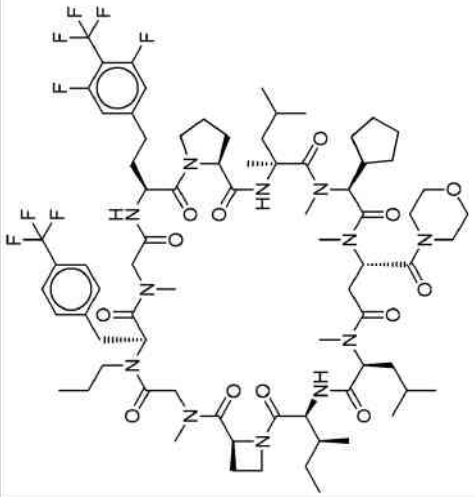
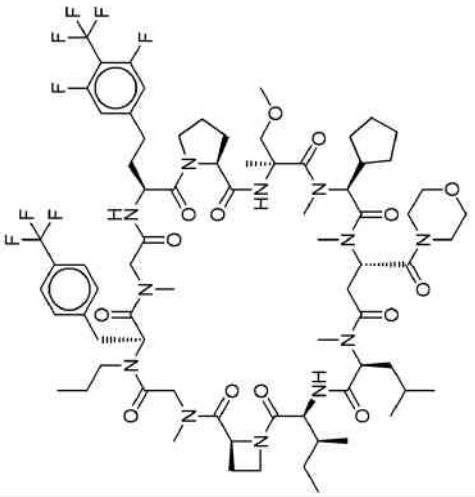
	
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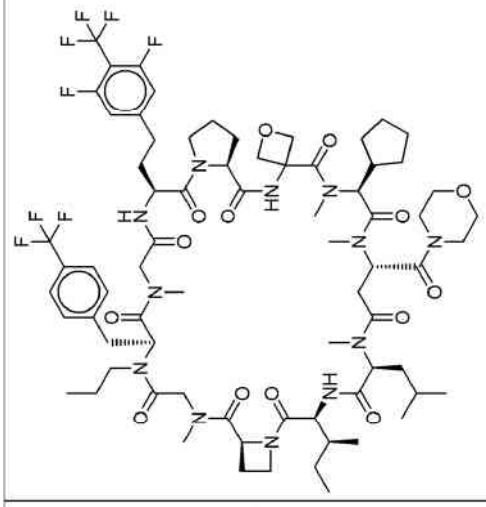
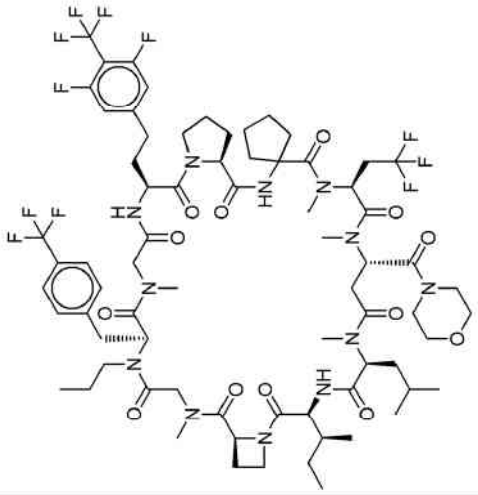
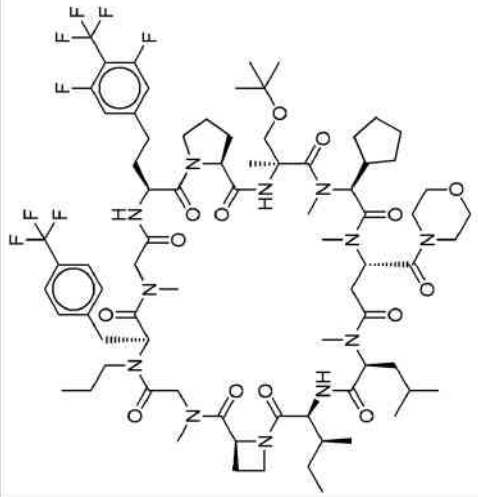
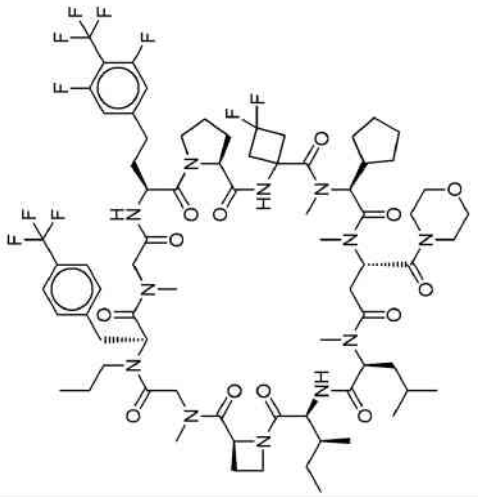
	
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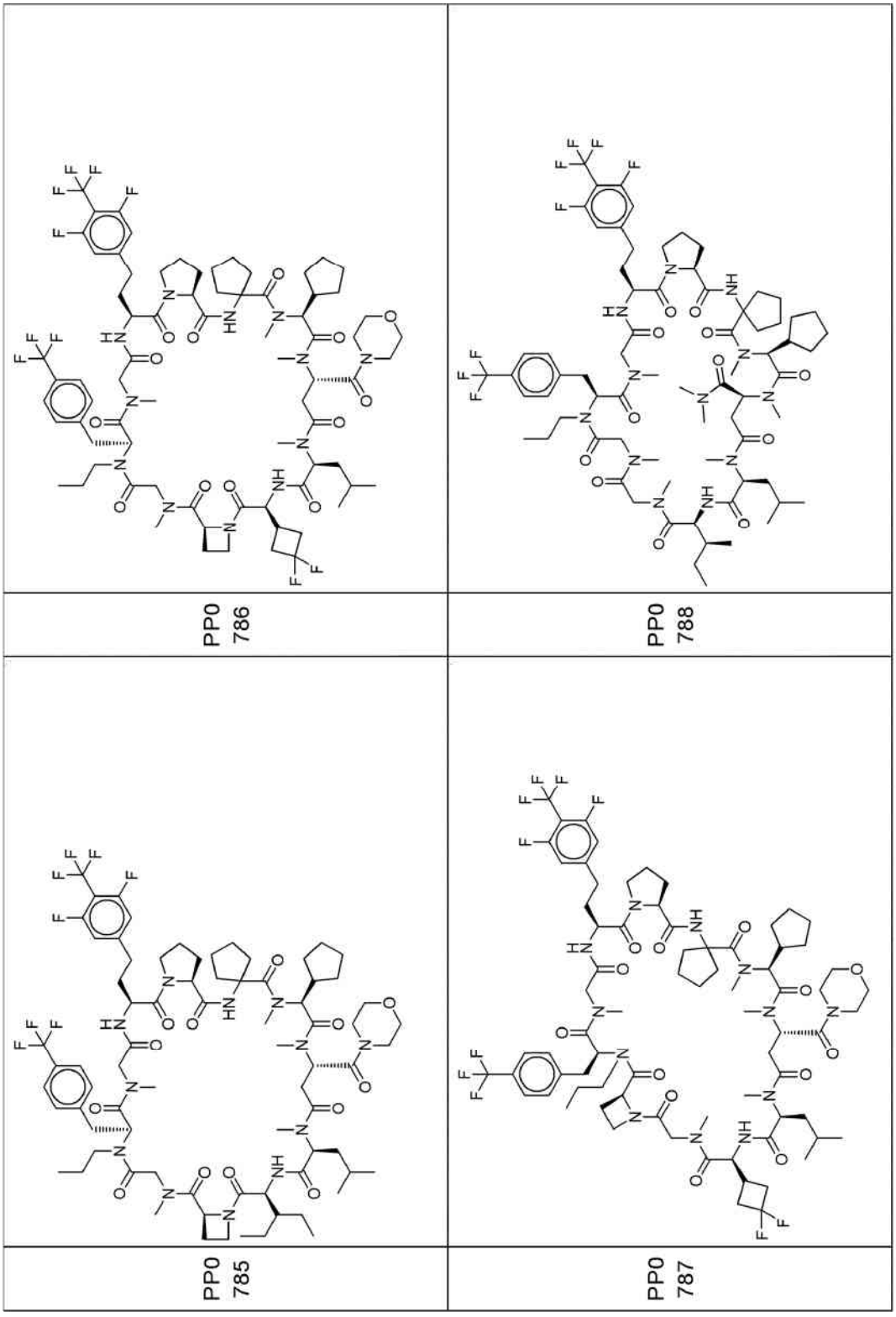
	
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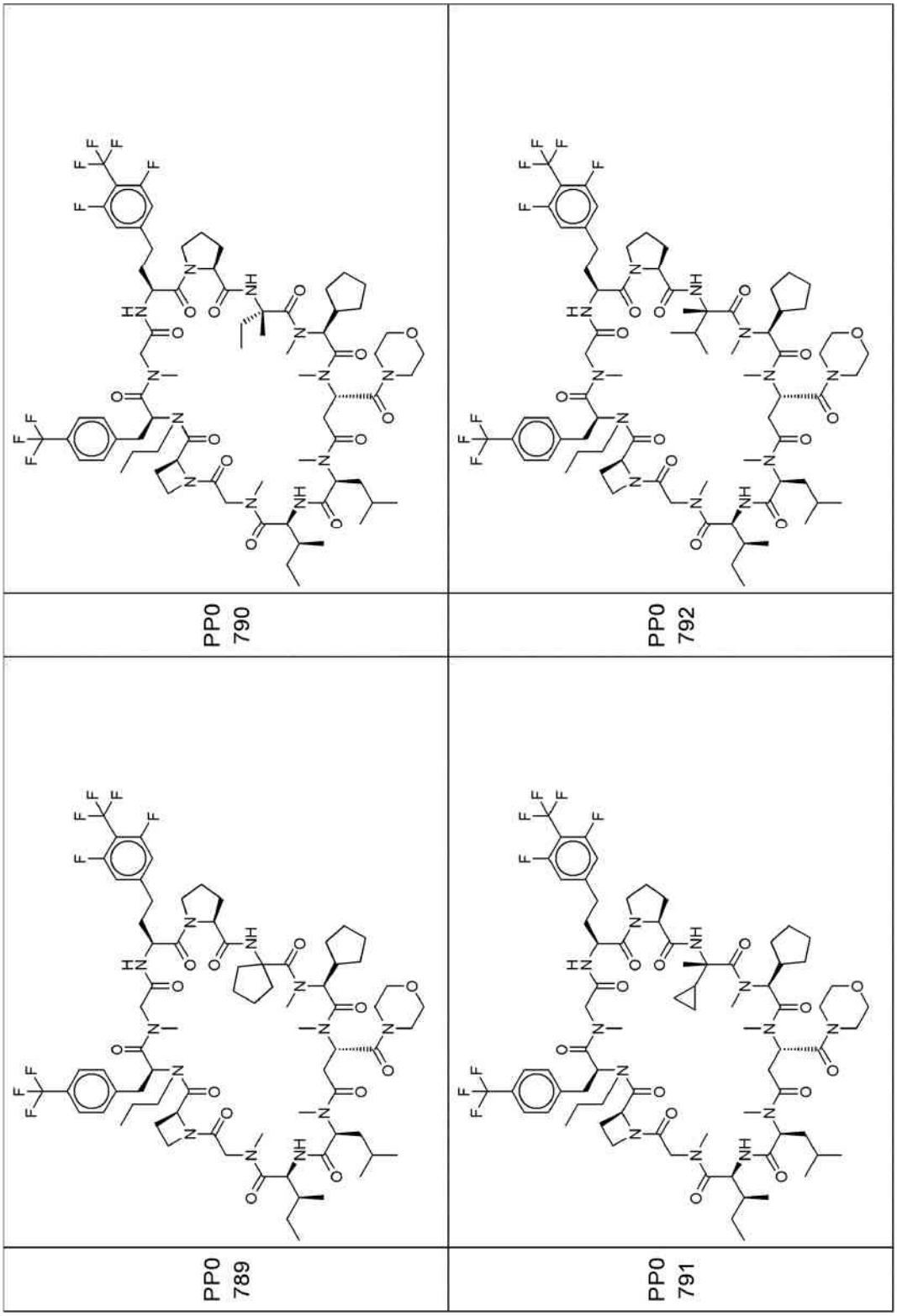

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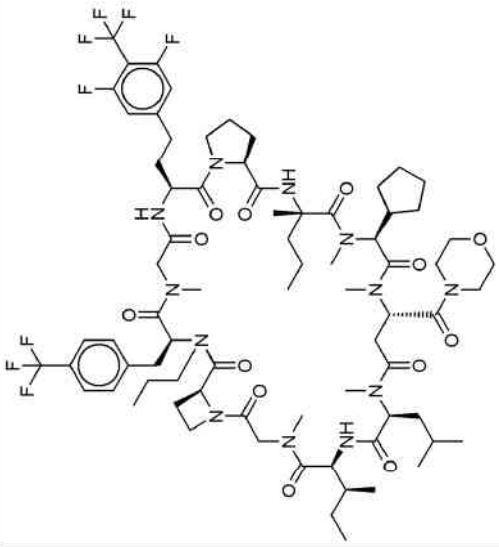
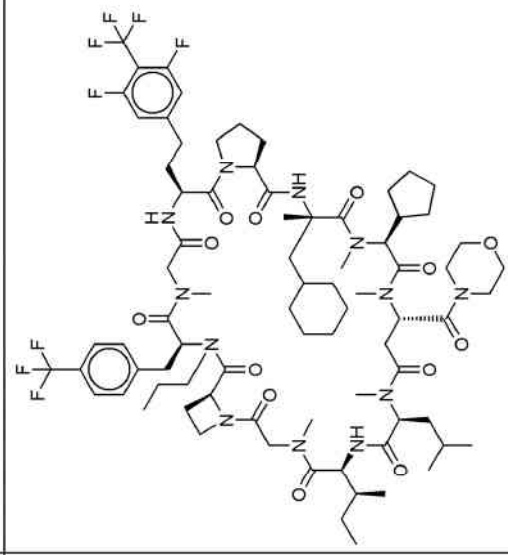
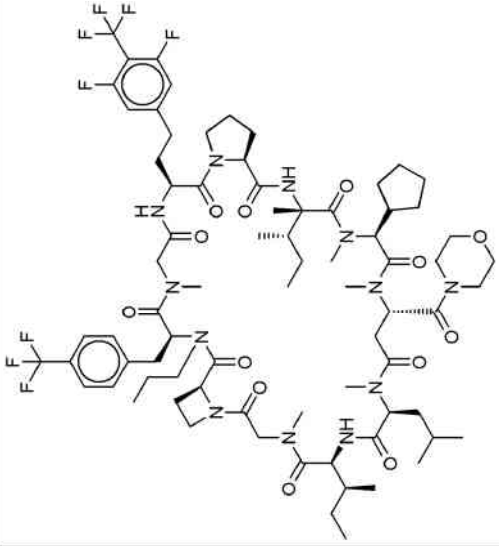
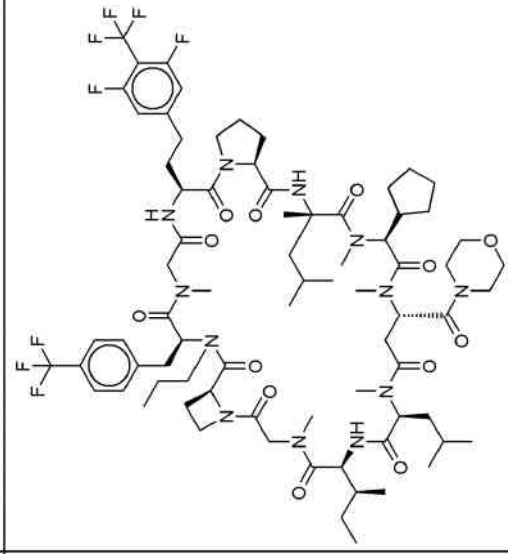

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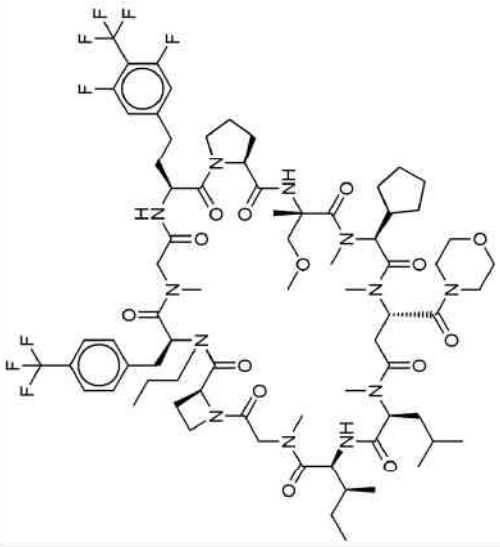
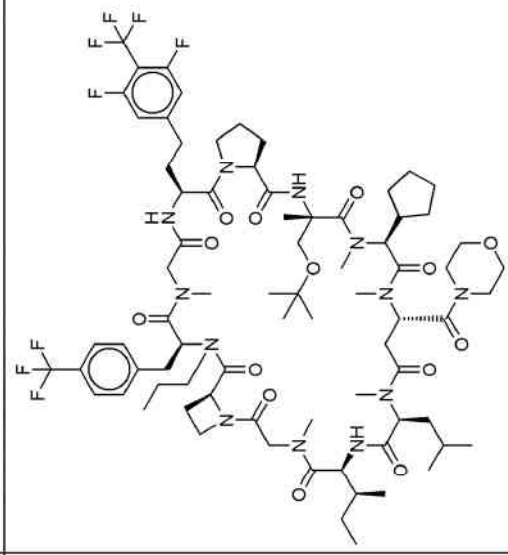
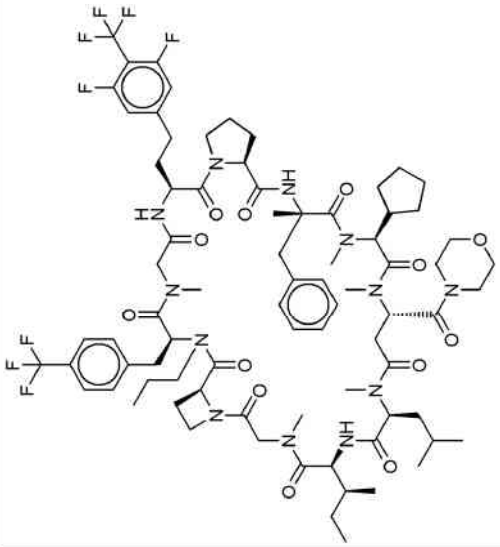
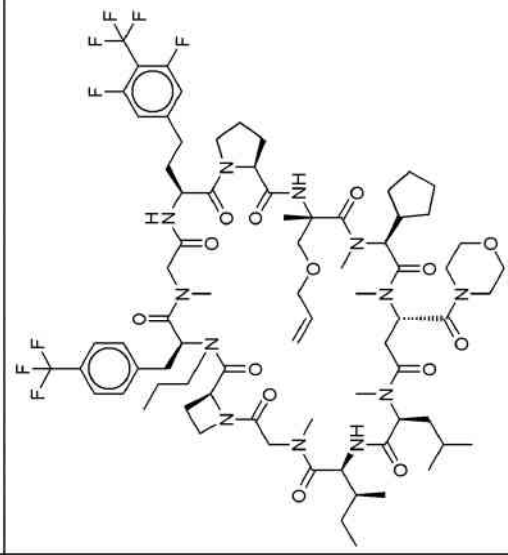
	
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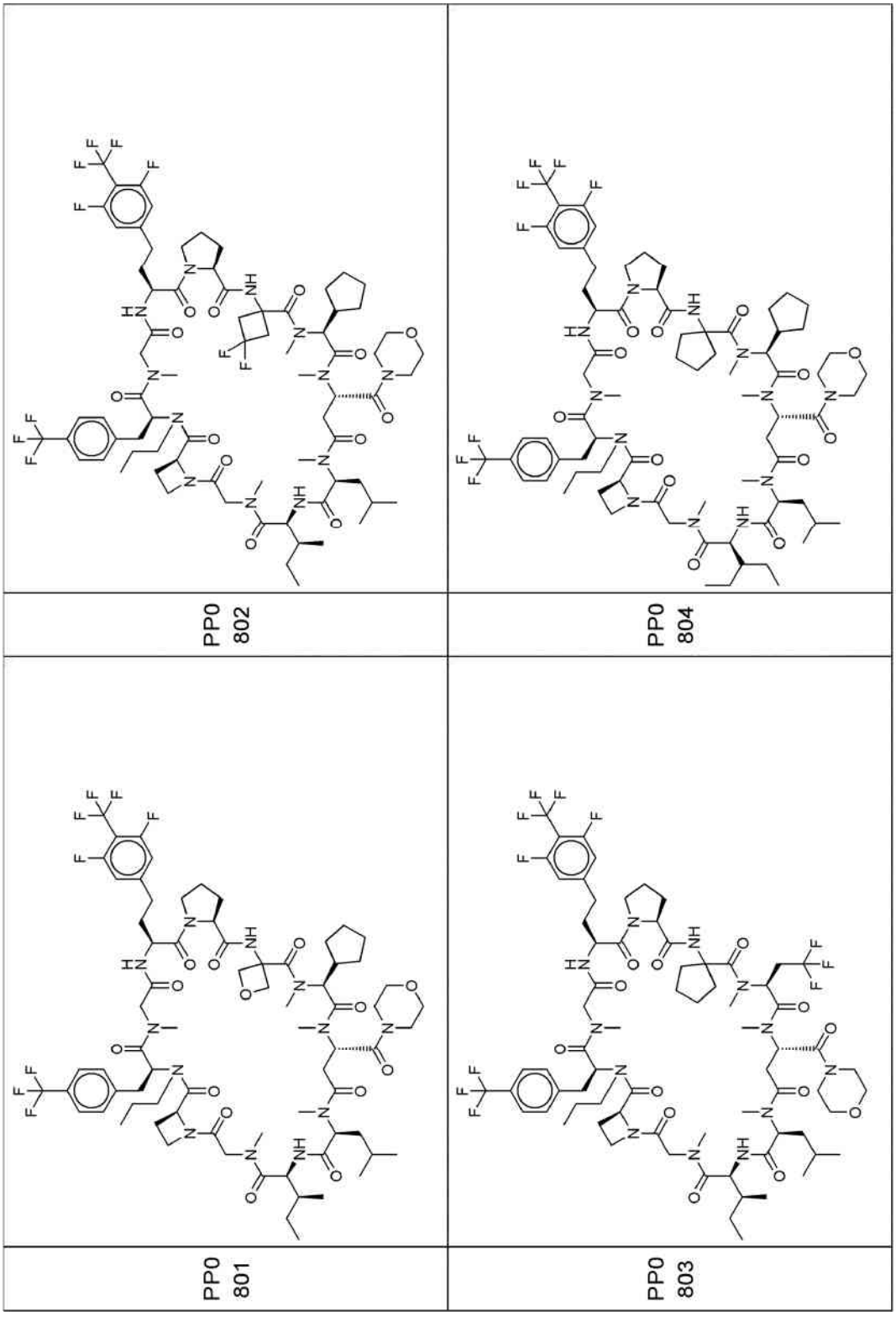
	
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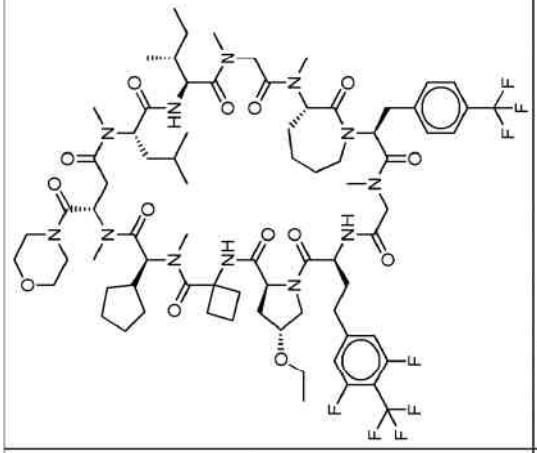
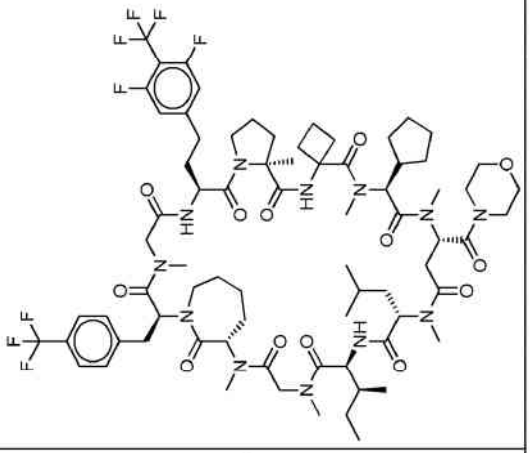
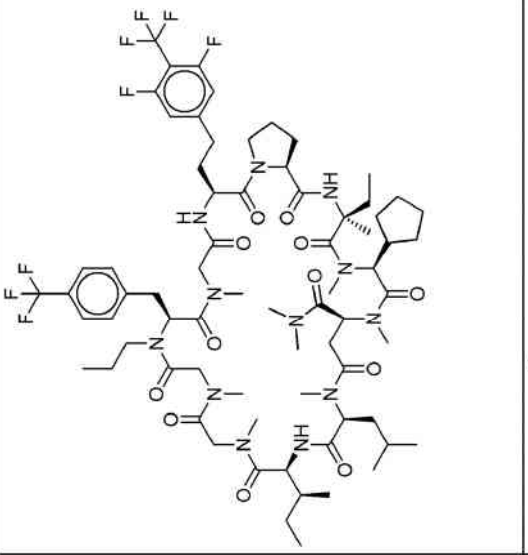
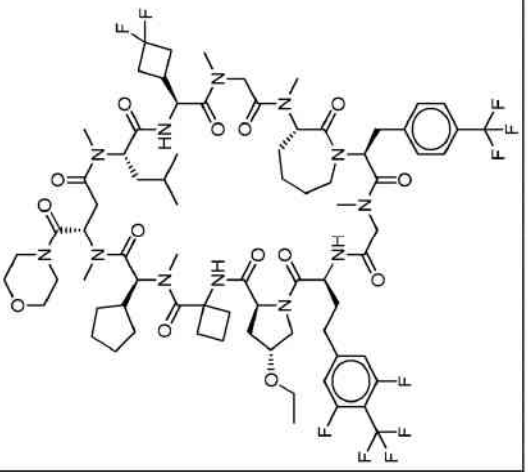

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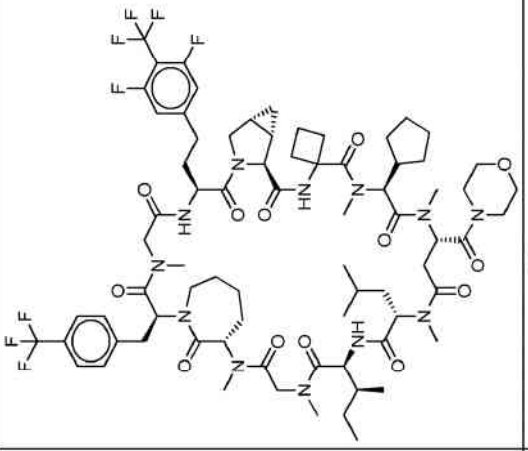
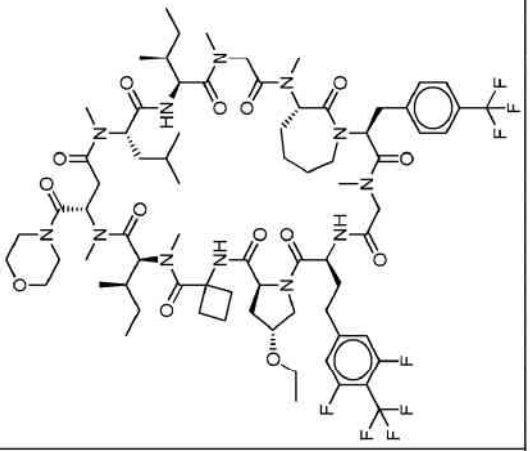
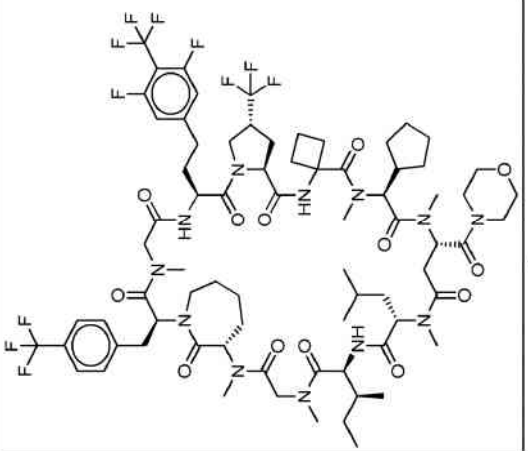
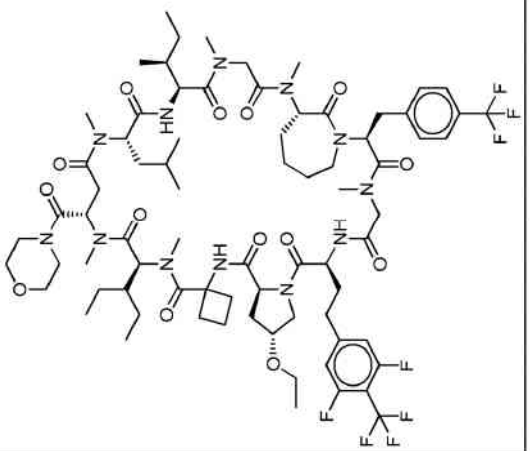

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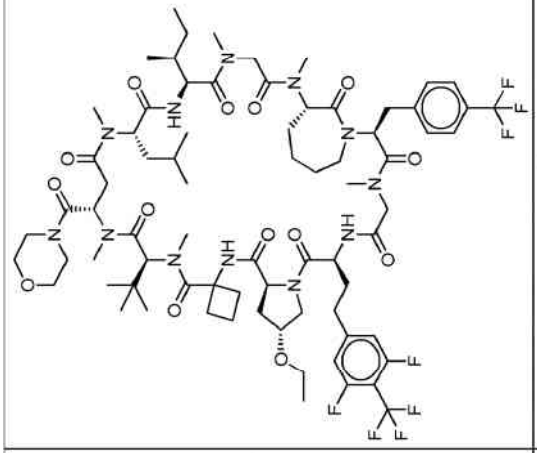
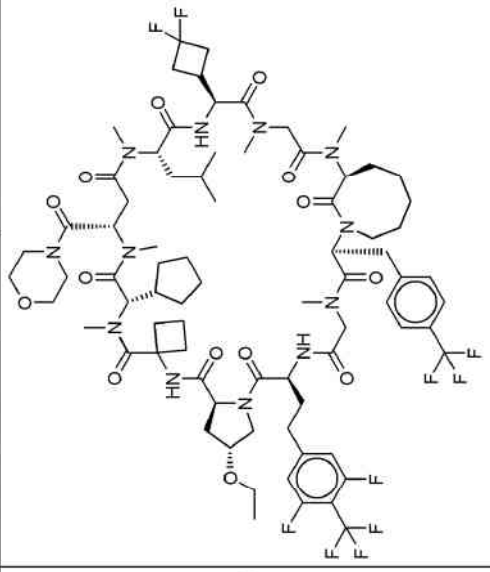
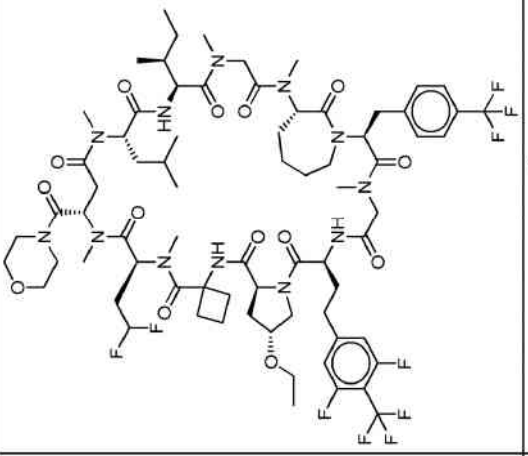
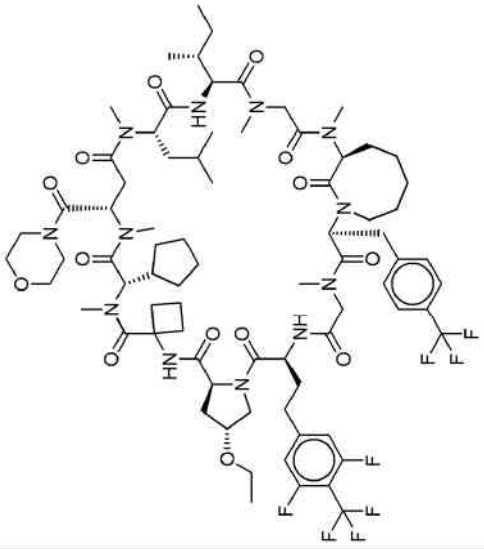
	
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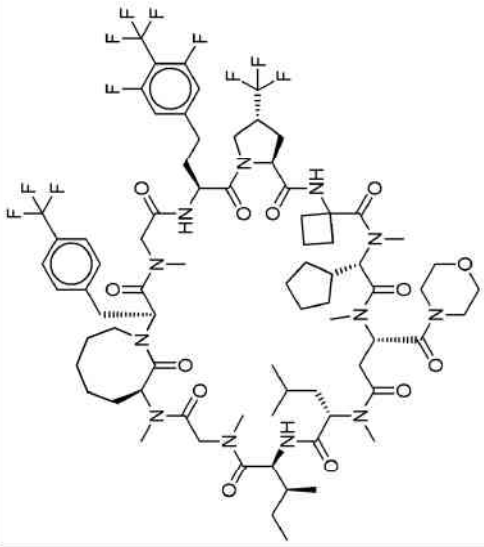
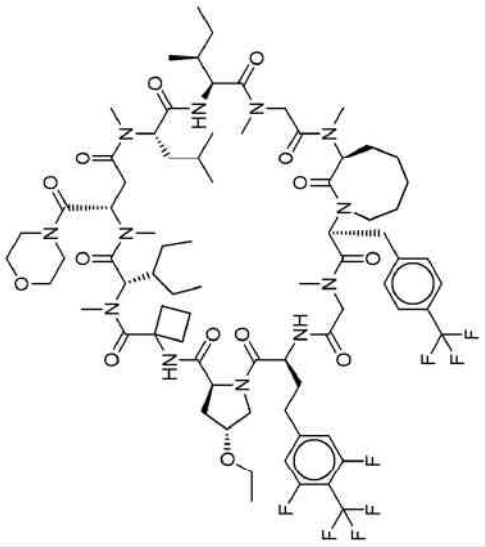
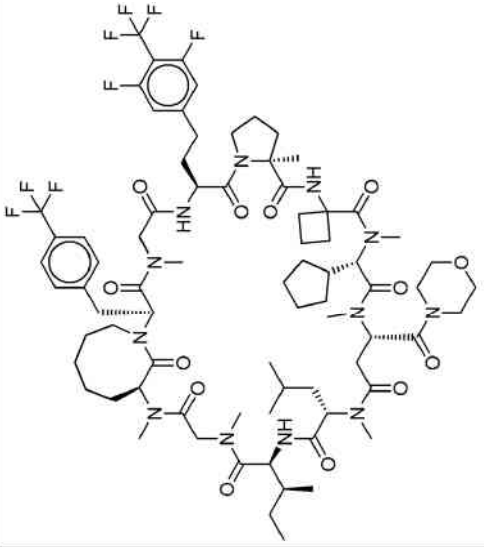
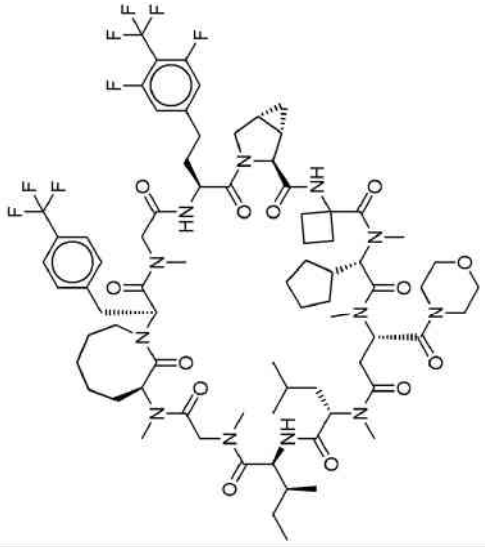
	
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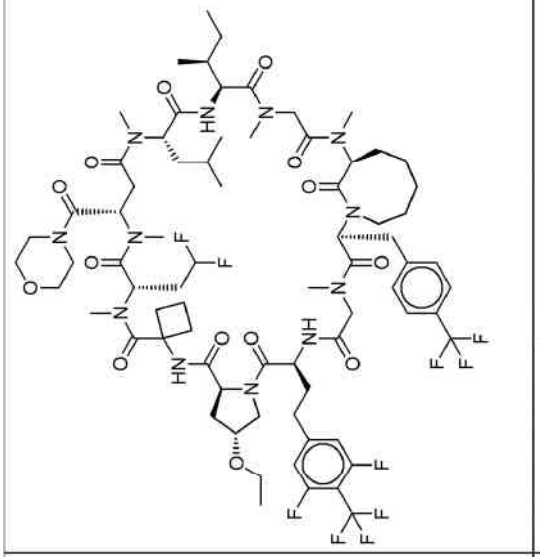
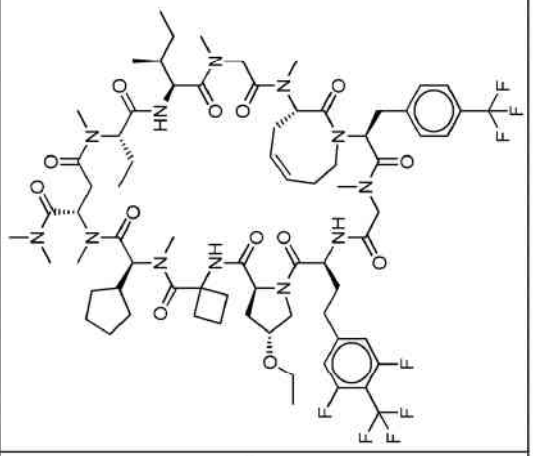
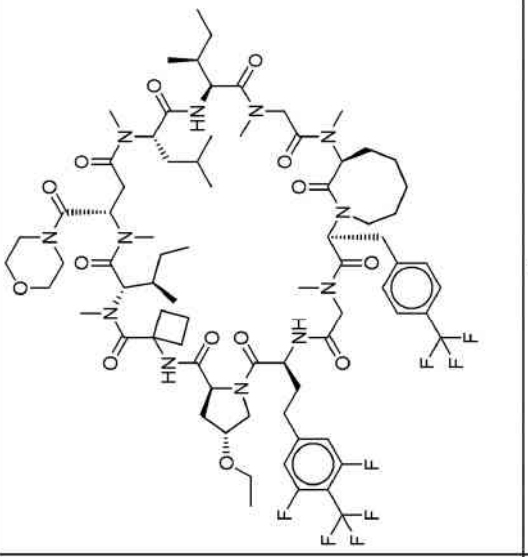
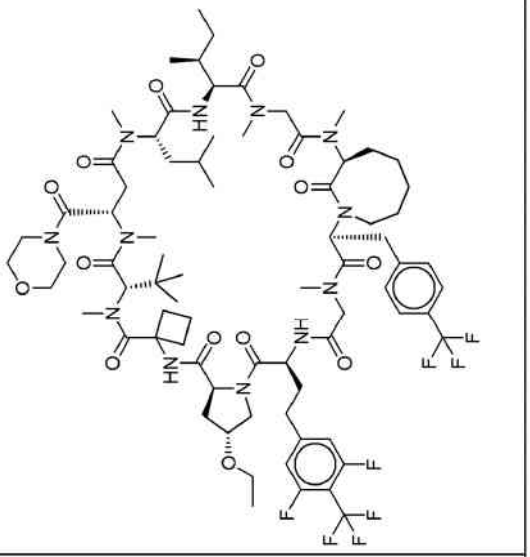

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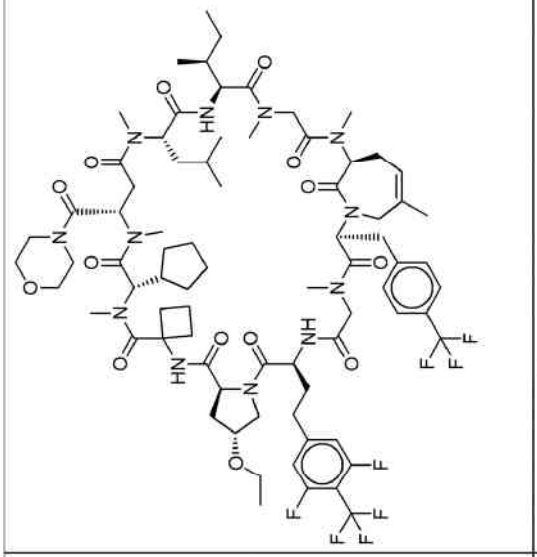
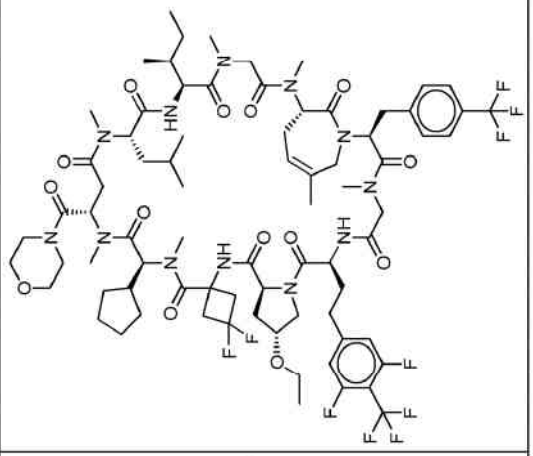
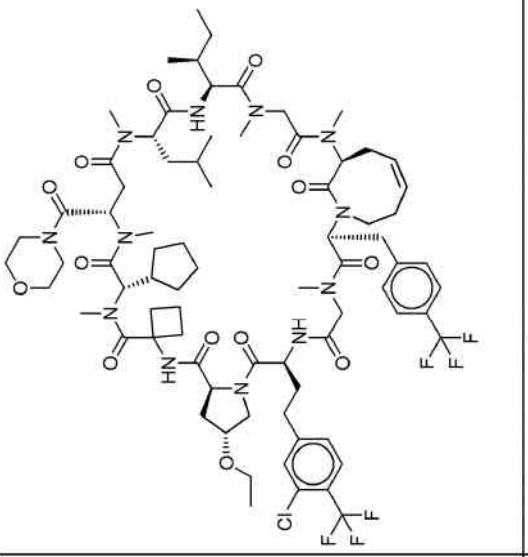
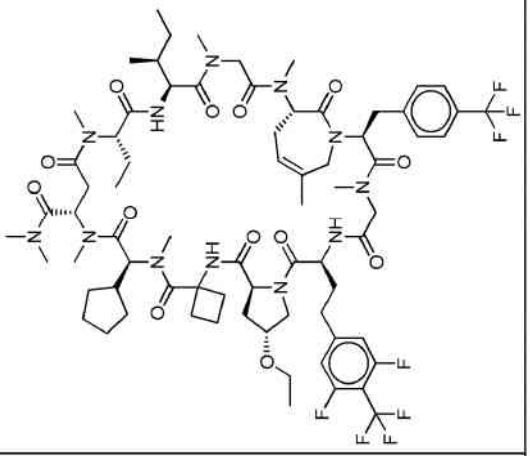
	
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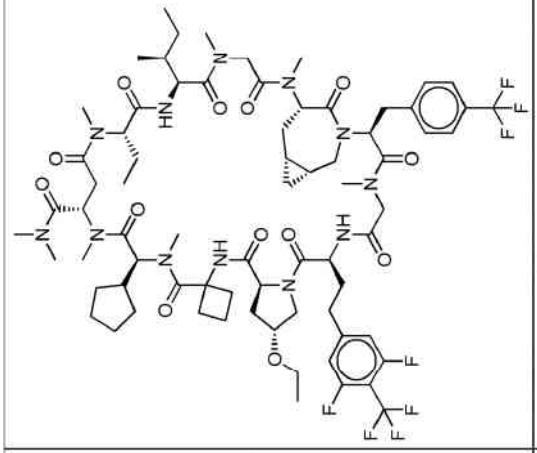
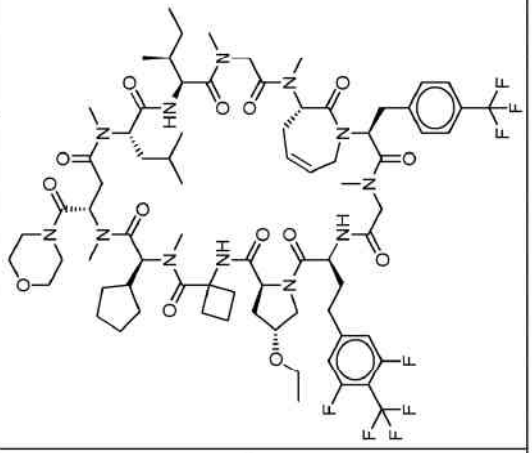
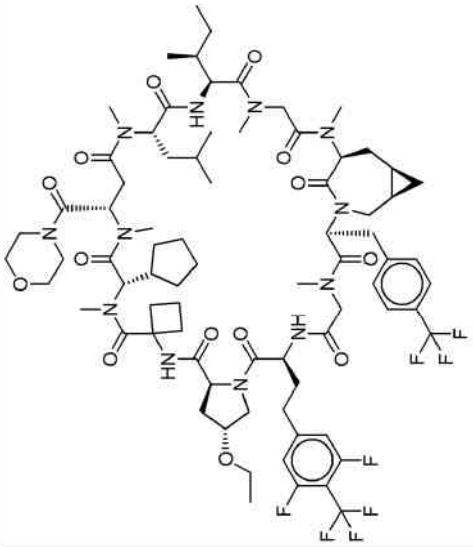
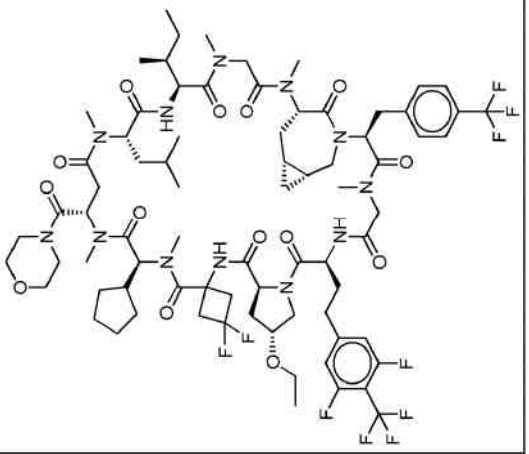
	
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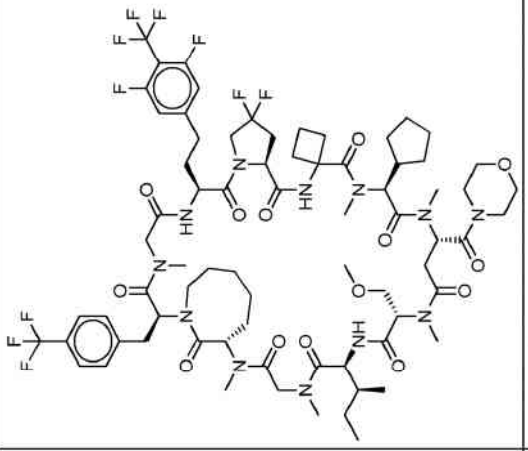
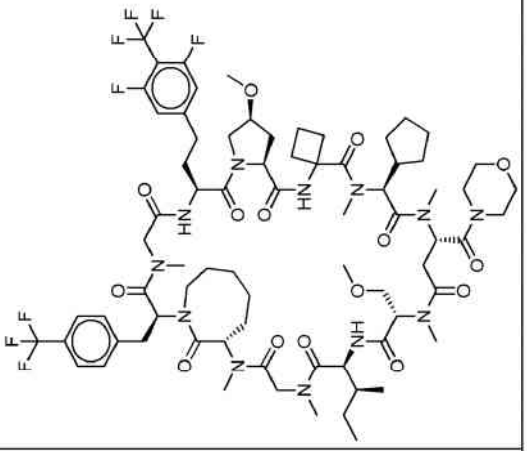
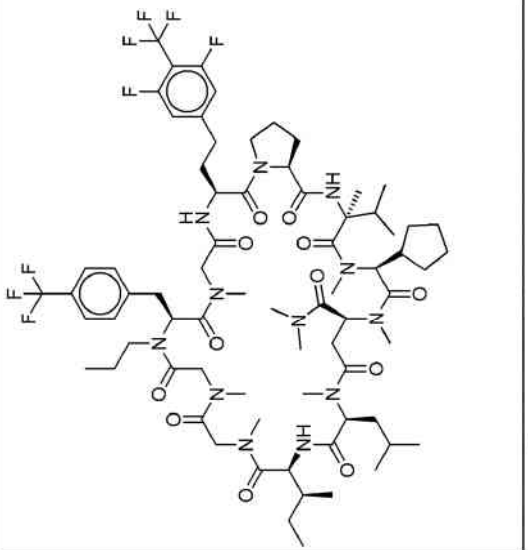
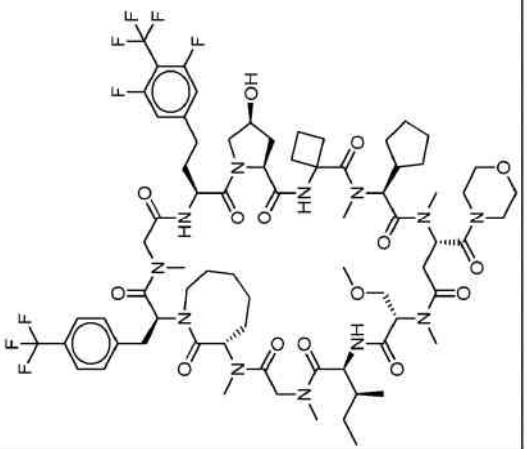
	
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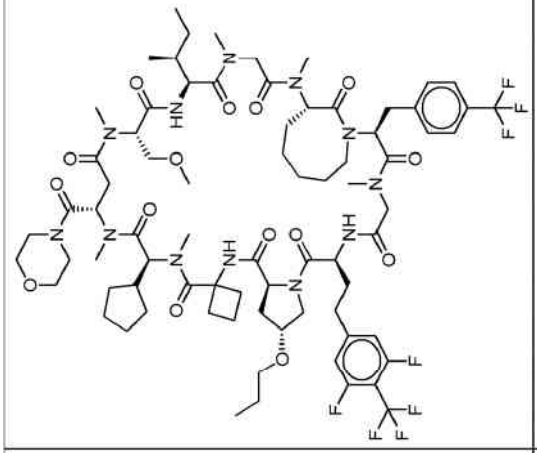
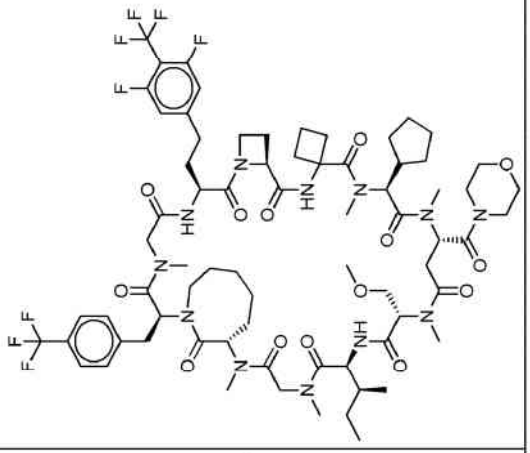
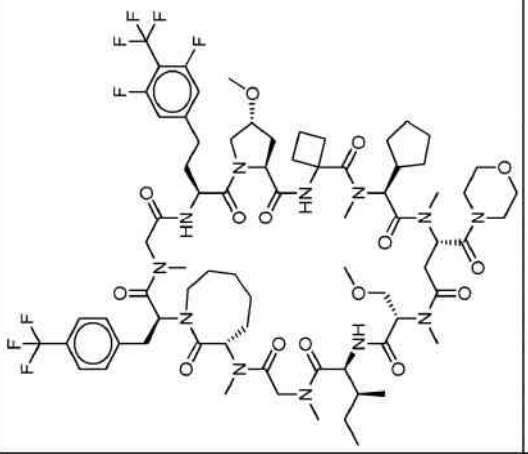
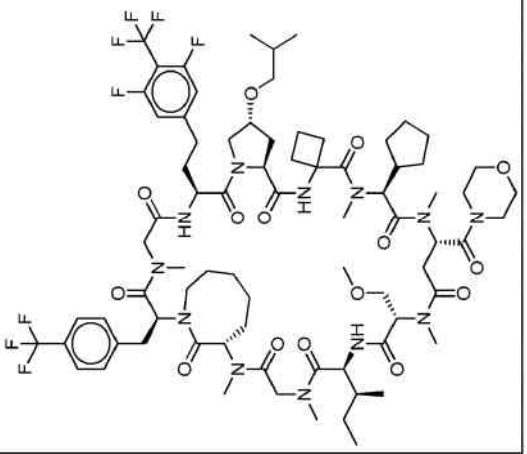
	
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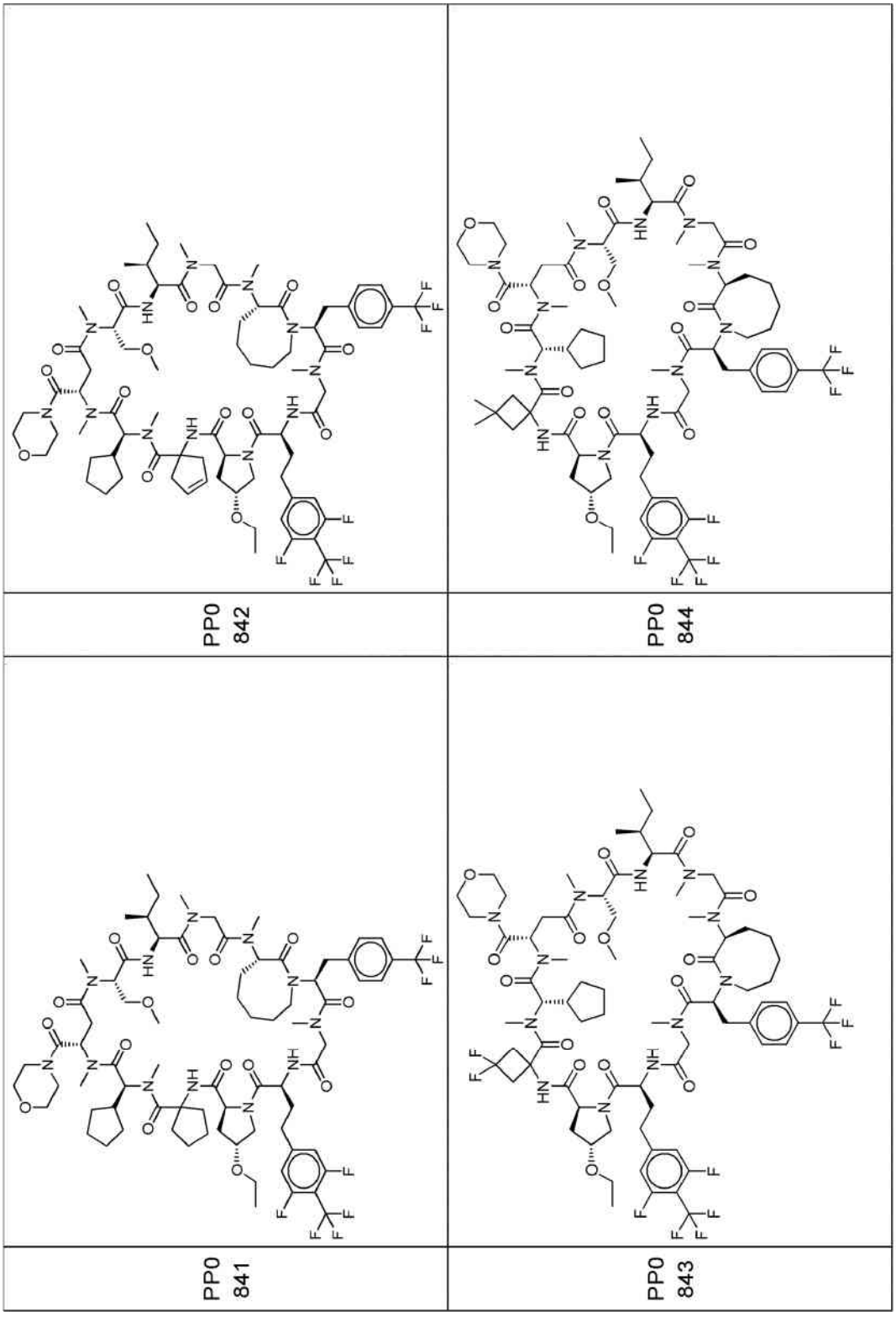
	
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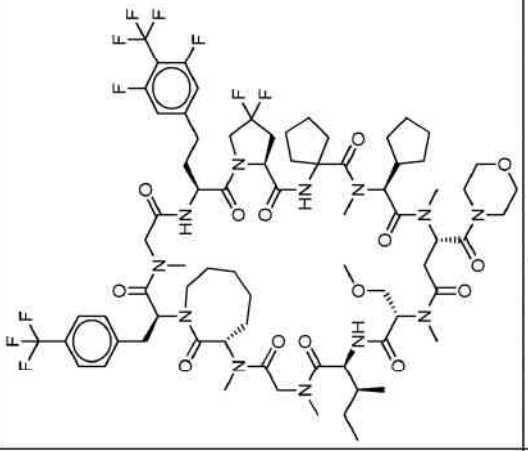
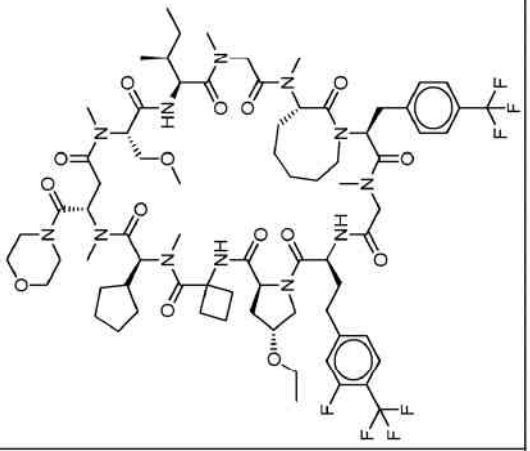
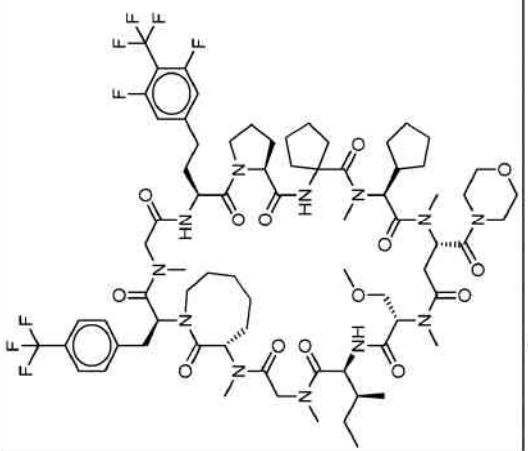
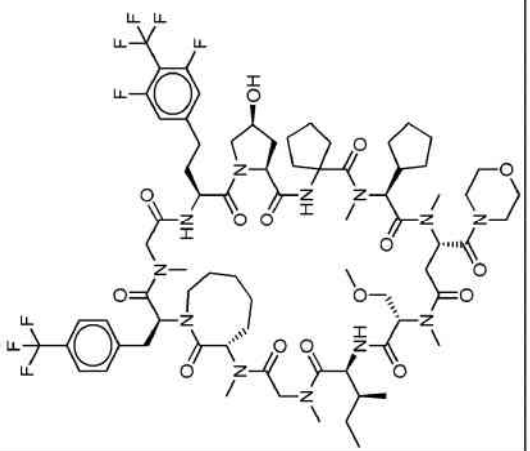
	
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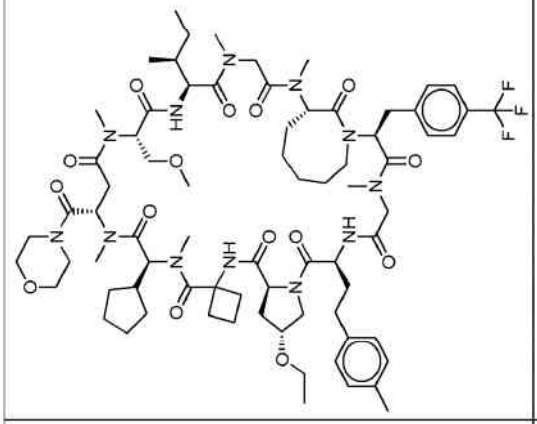
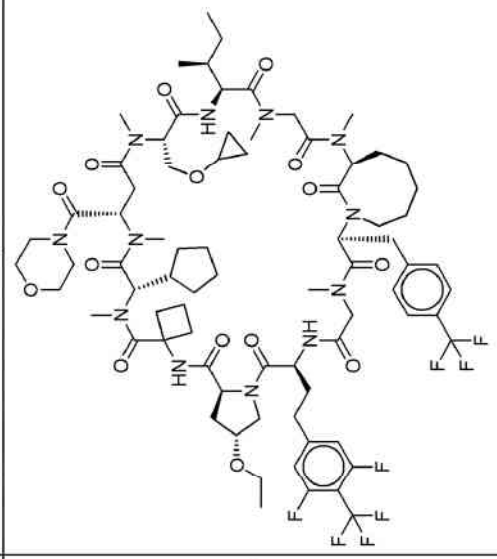
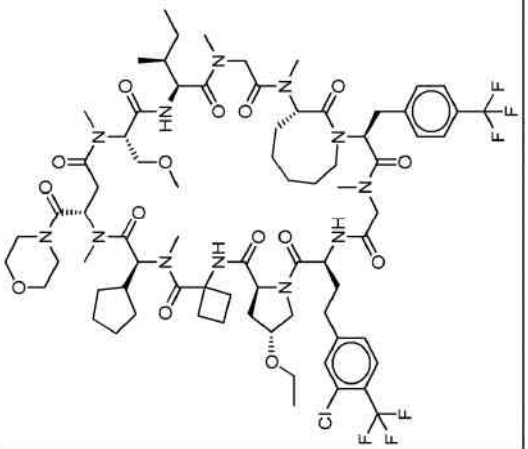
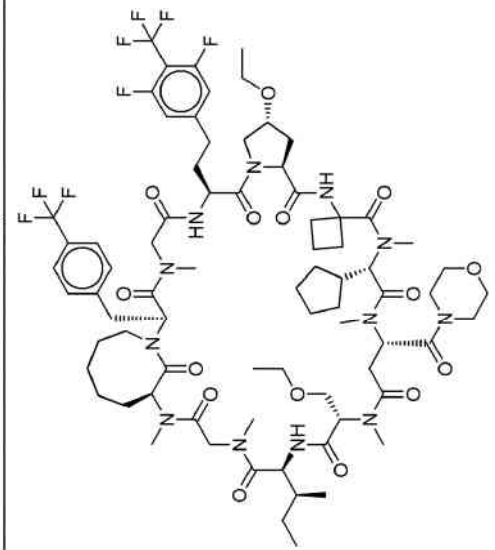
	
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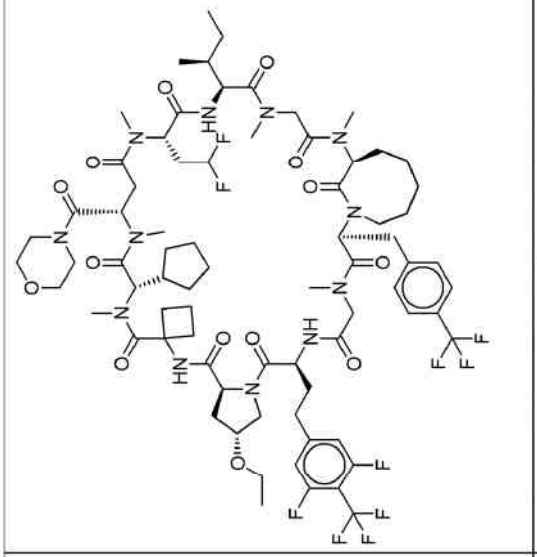
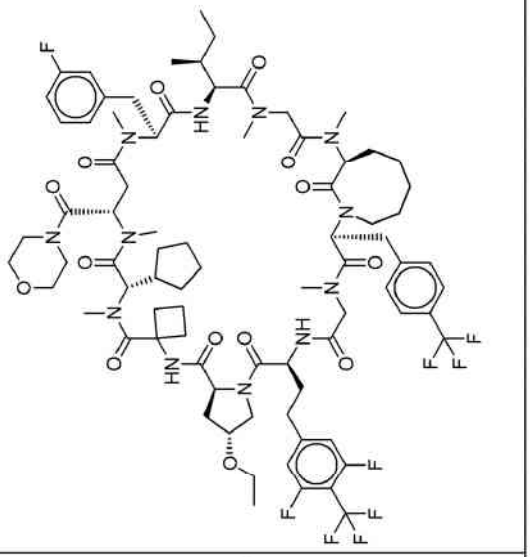
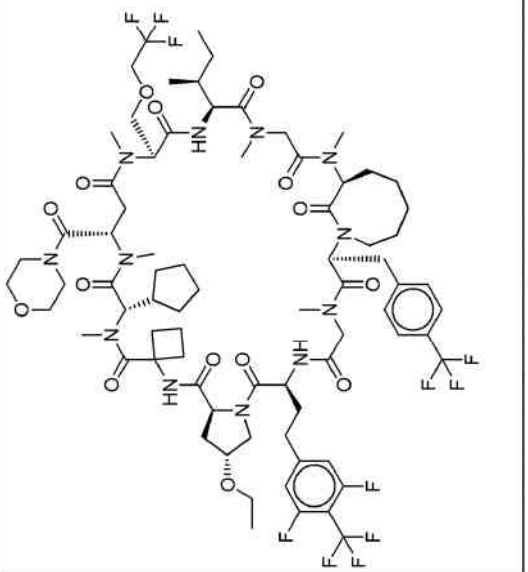
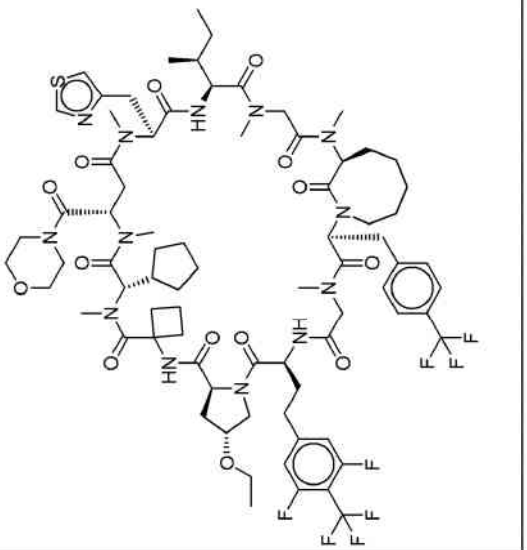
	
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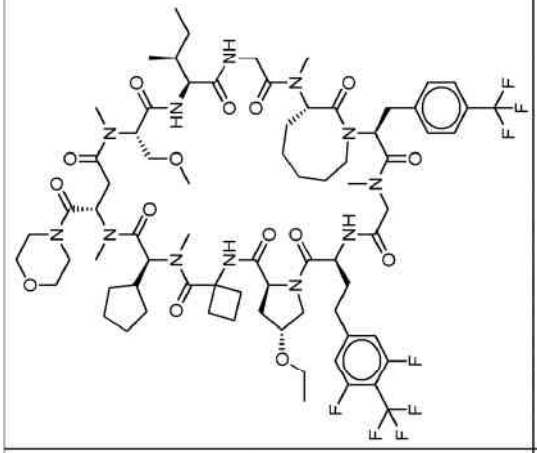
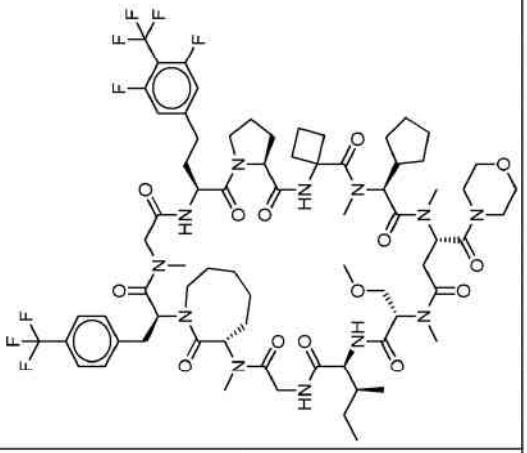
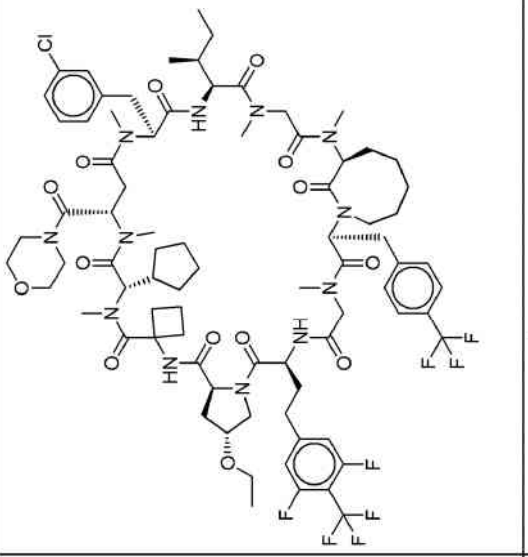
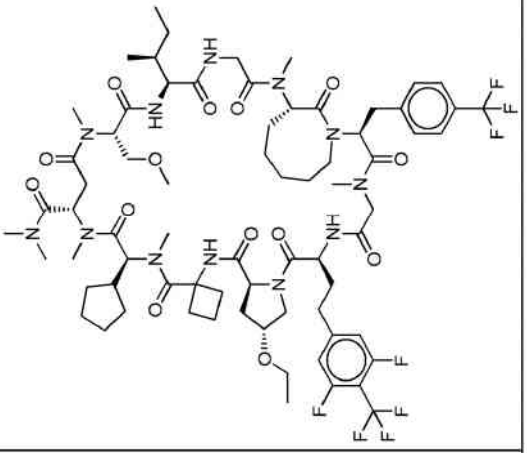
	
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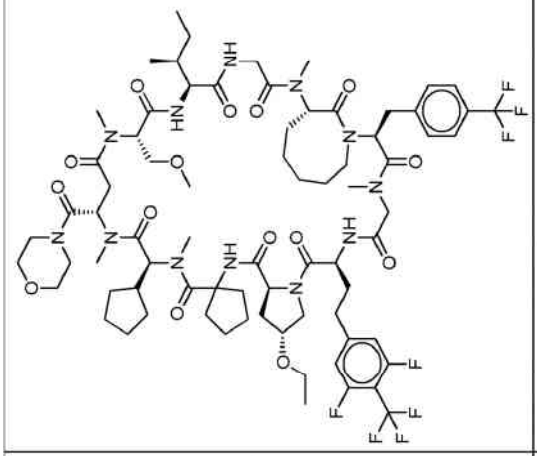
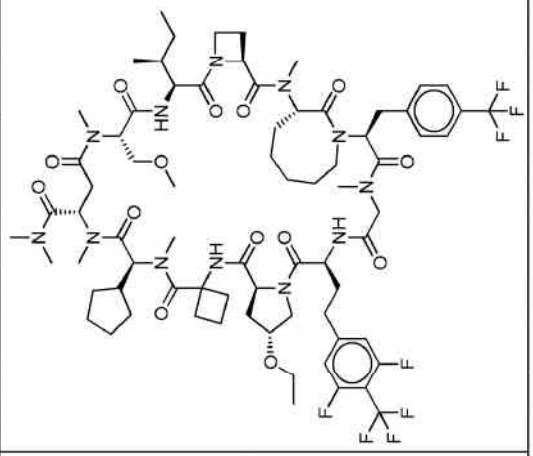
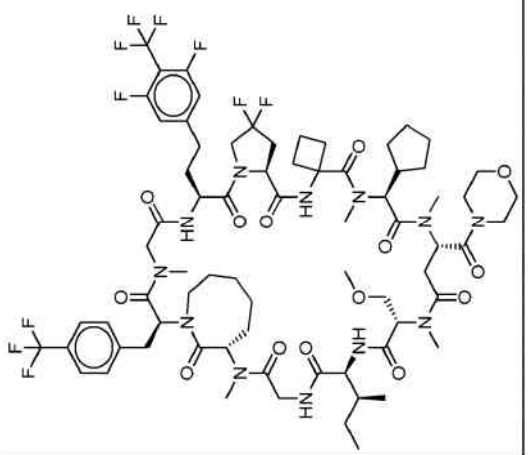
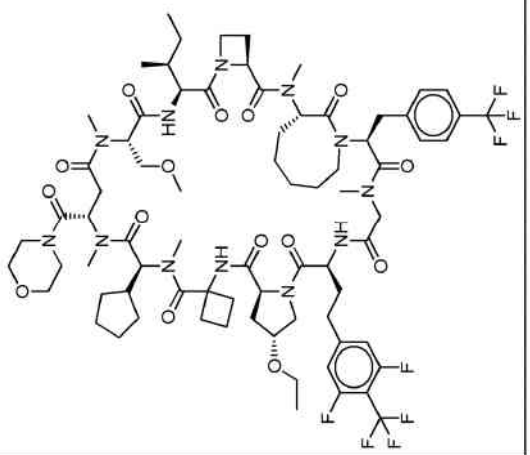

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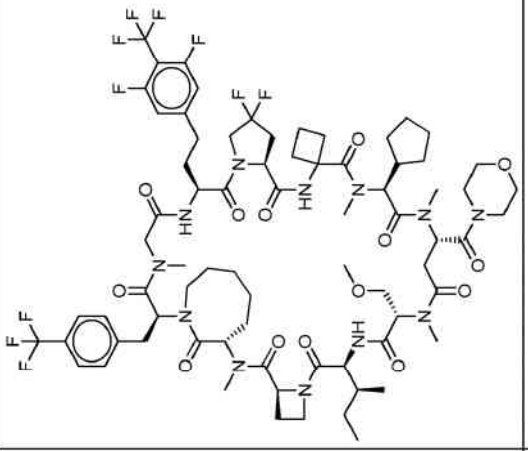
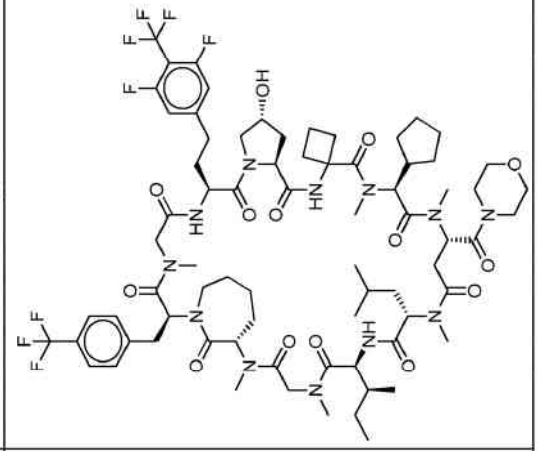
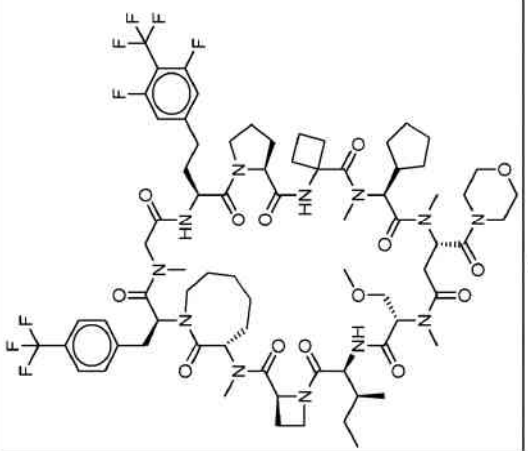
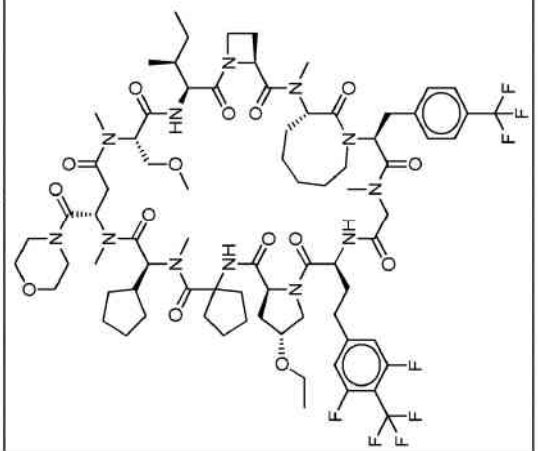
	
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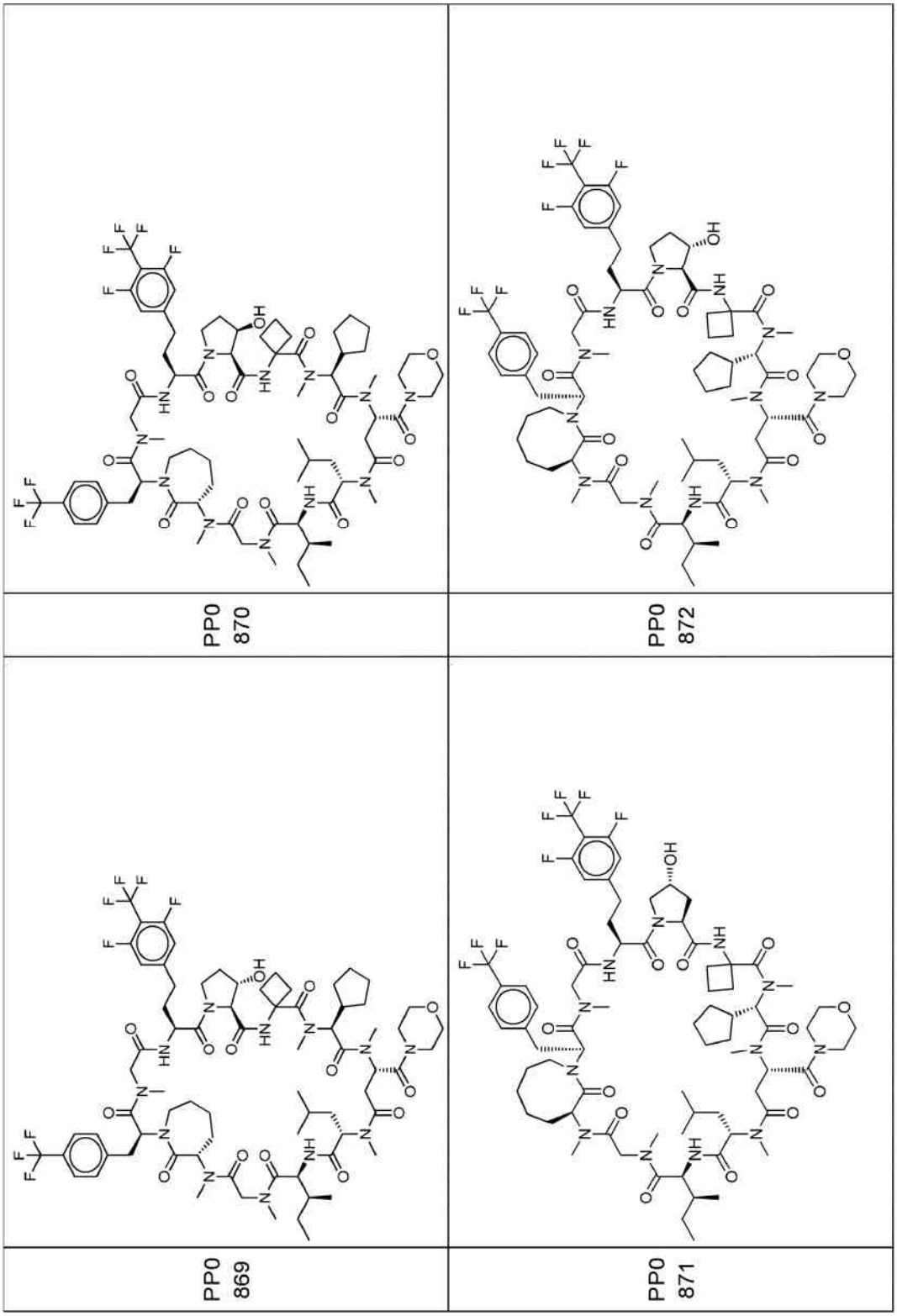
	
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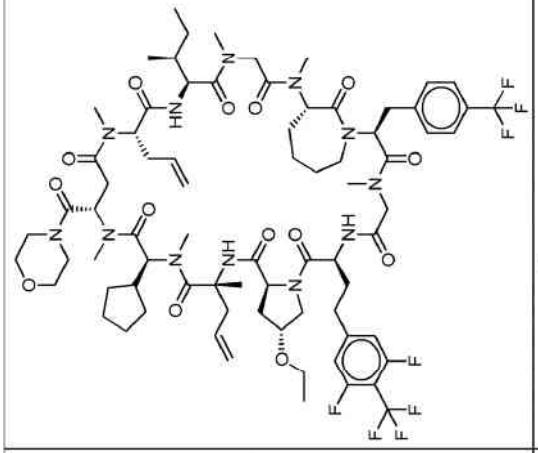
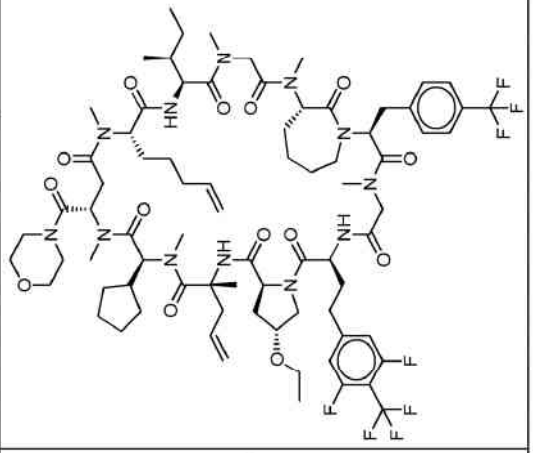
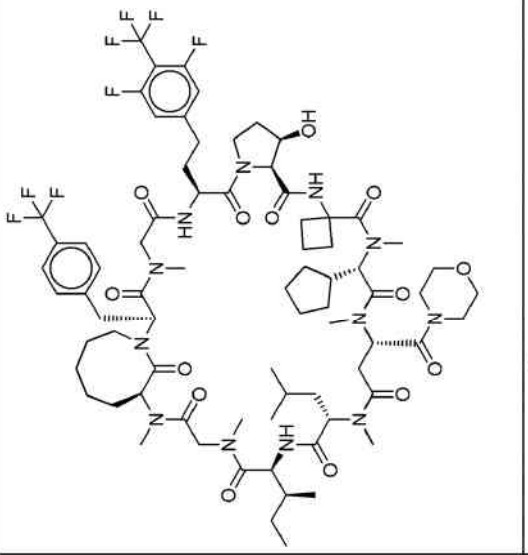
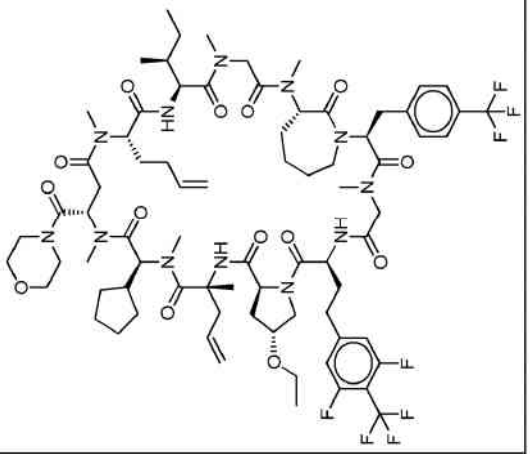
	
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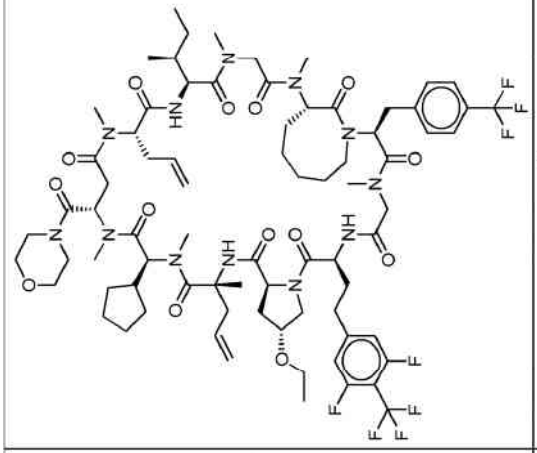
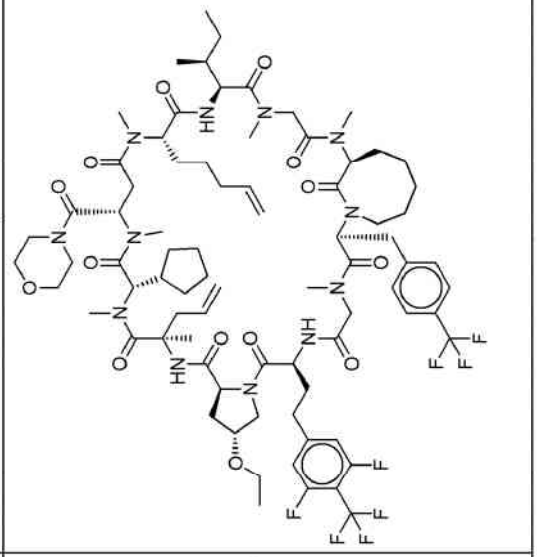
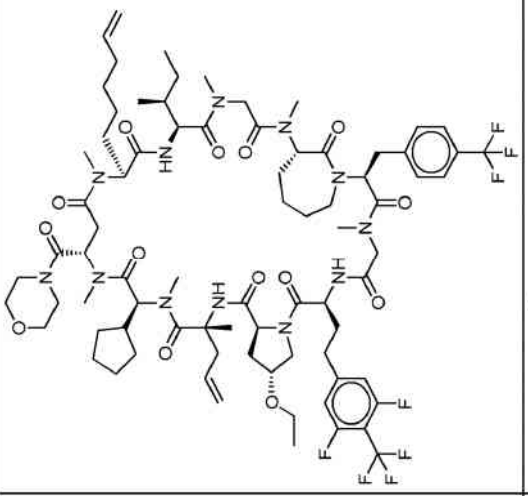
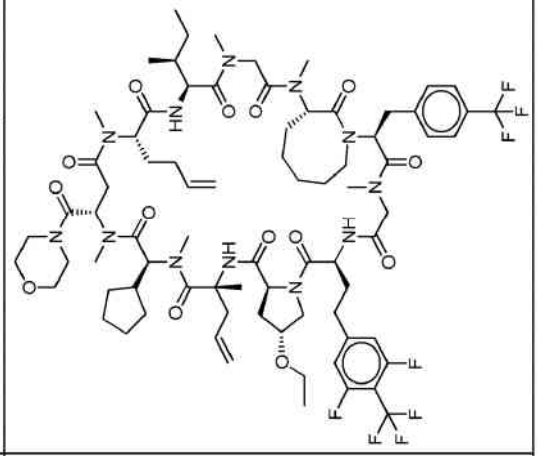
	
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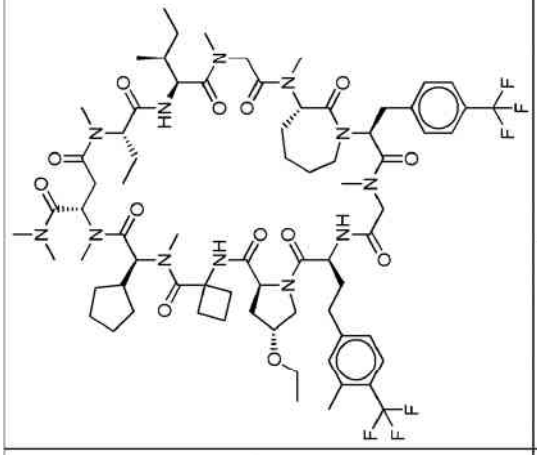
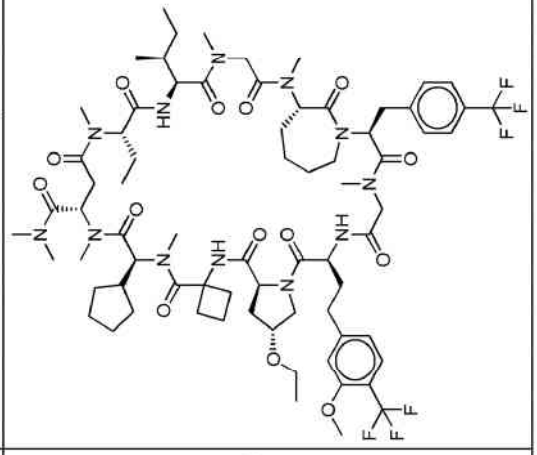
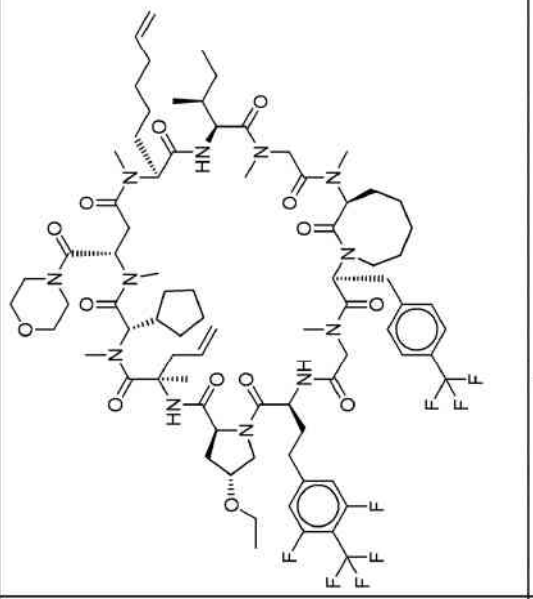
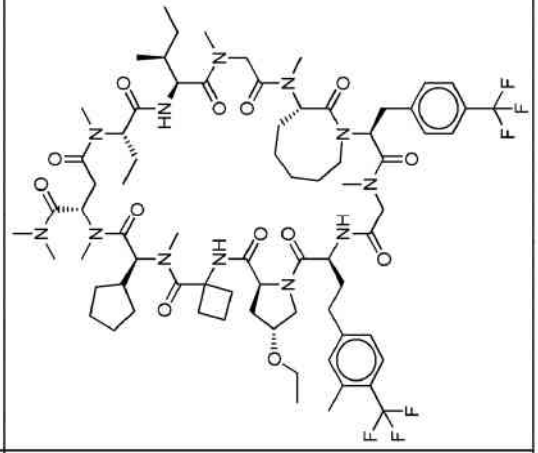
	
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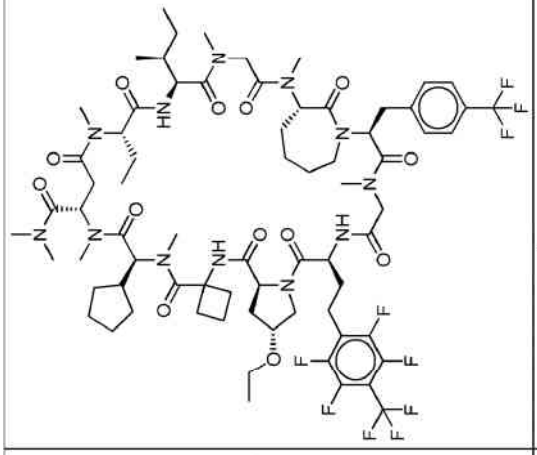
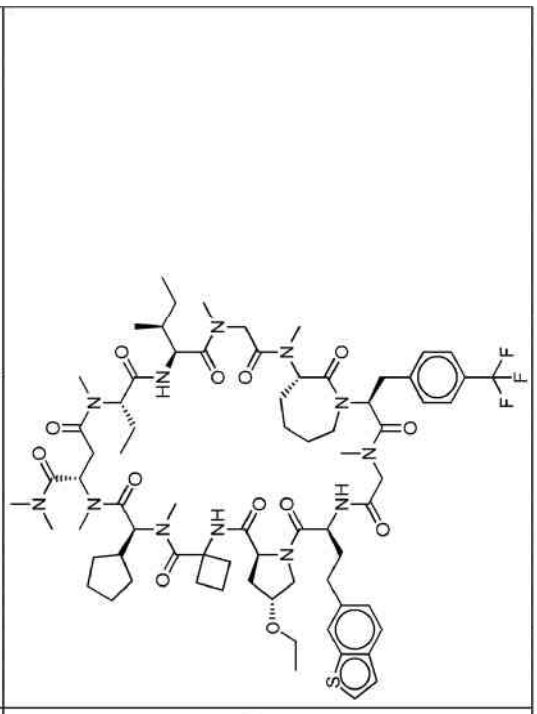
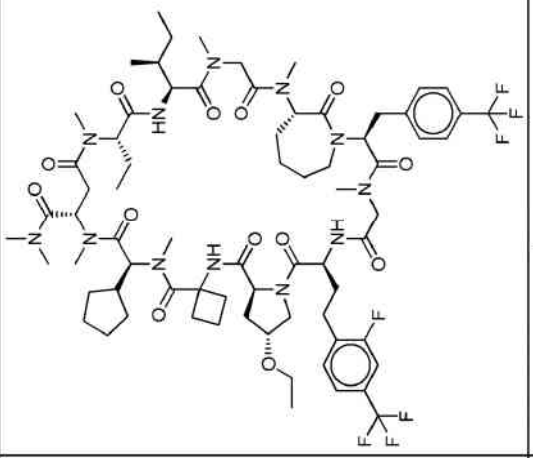
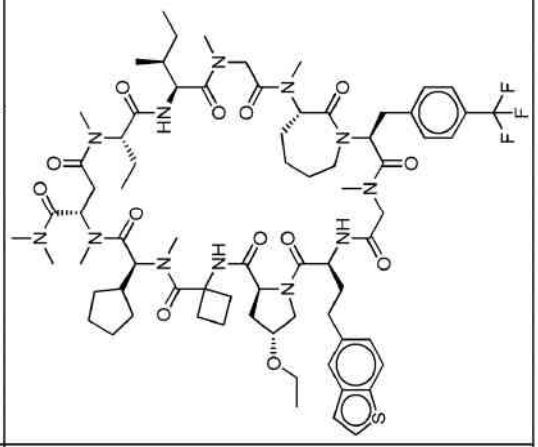
	
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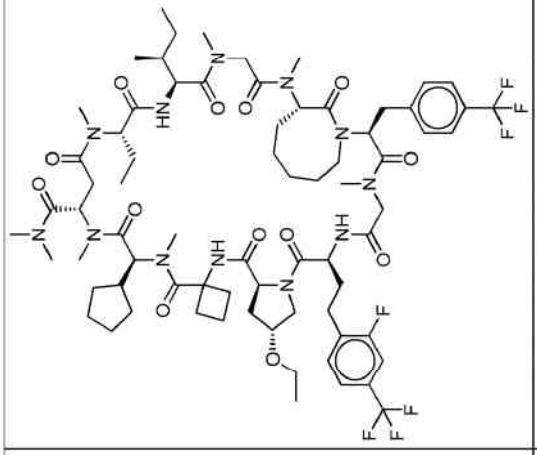
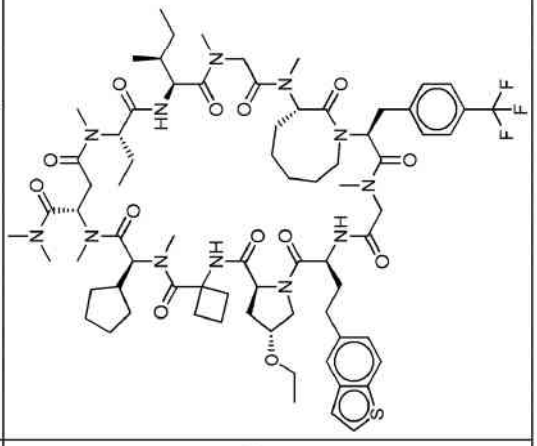
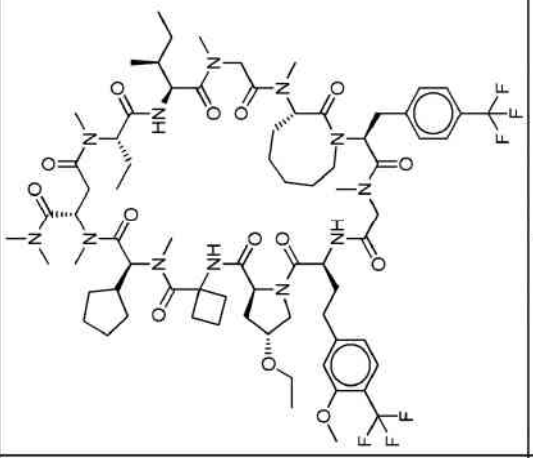
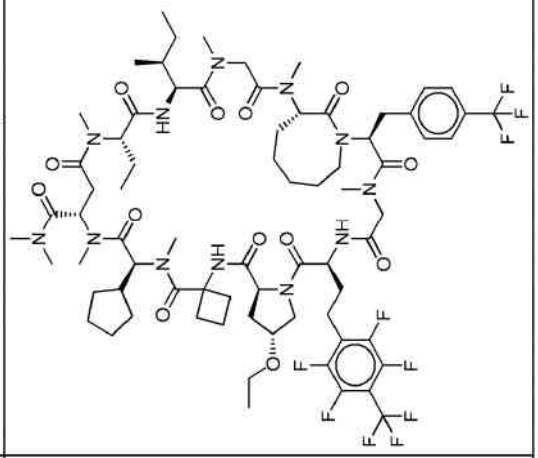

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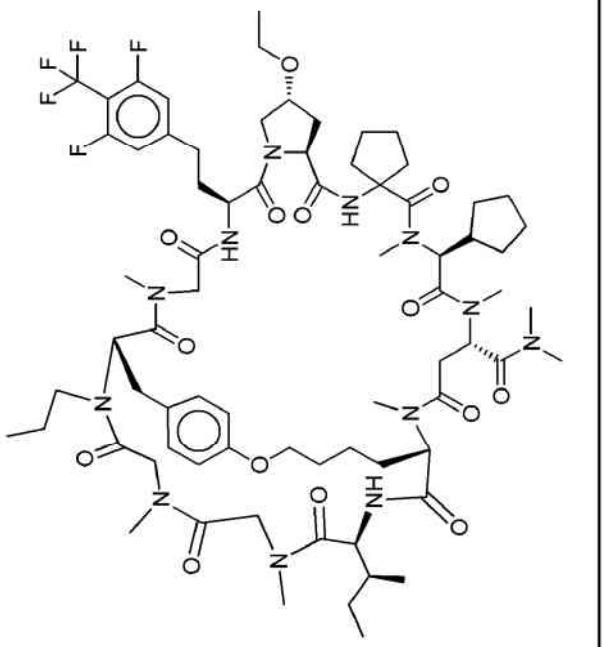
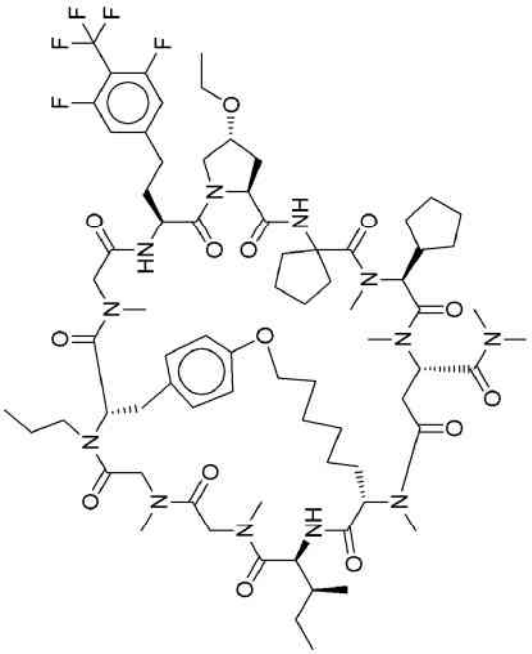
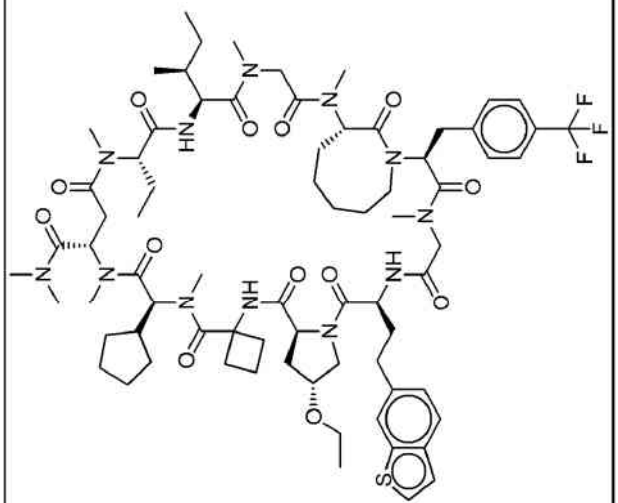
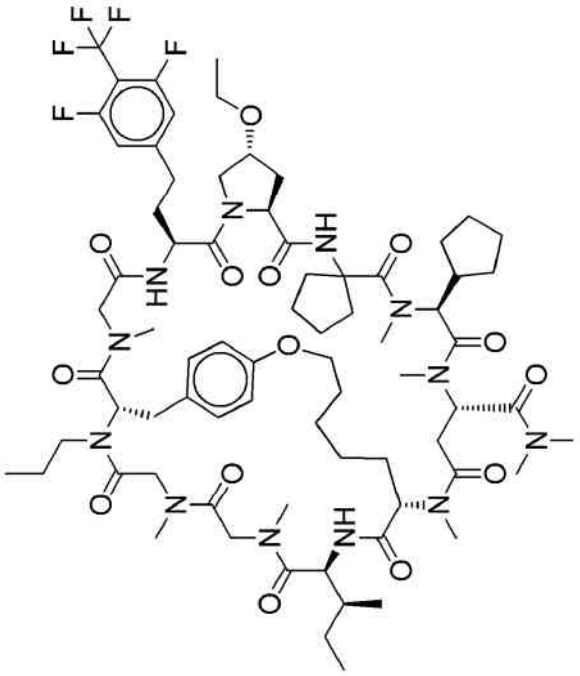
	
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PP0 873	PP0 875

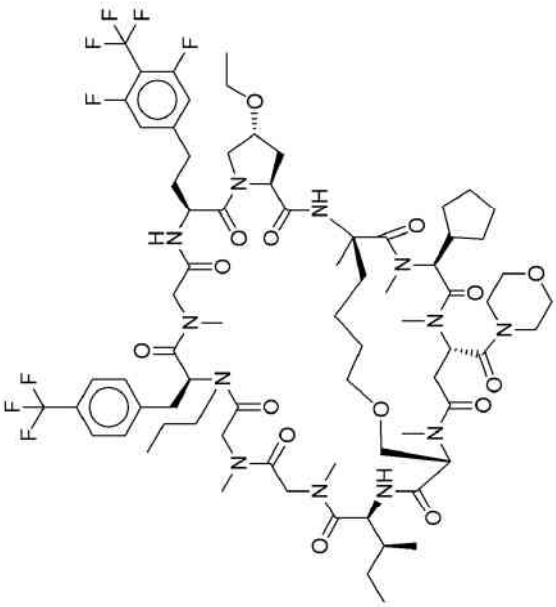
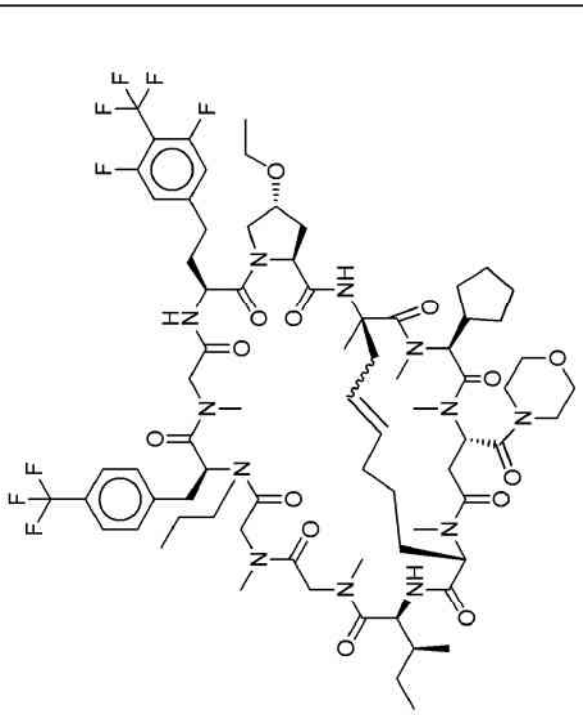
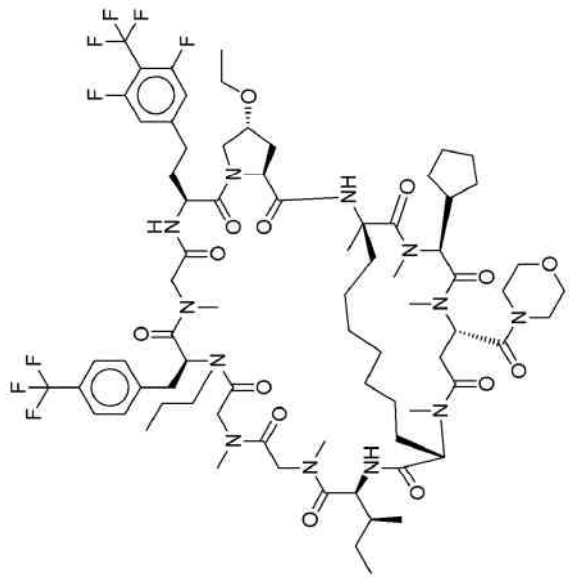
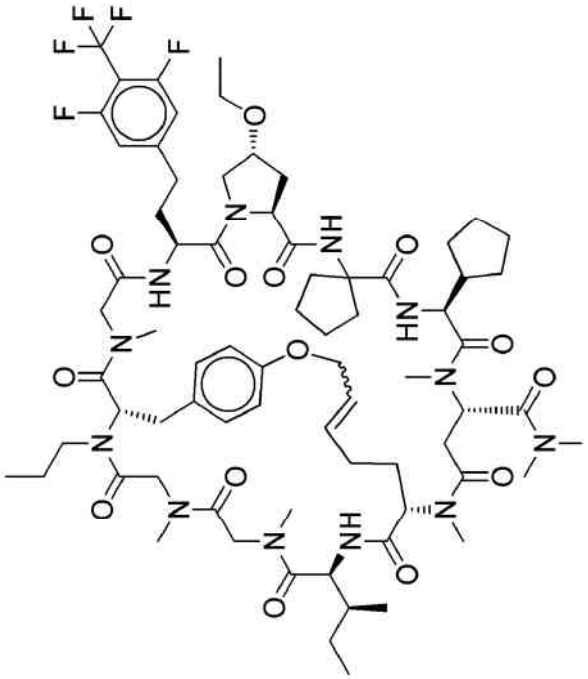
	
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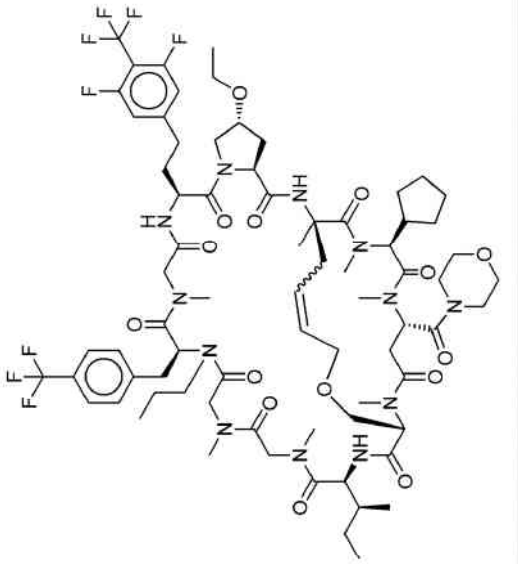
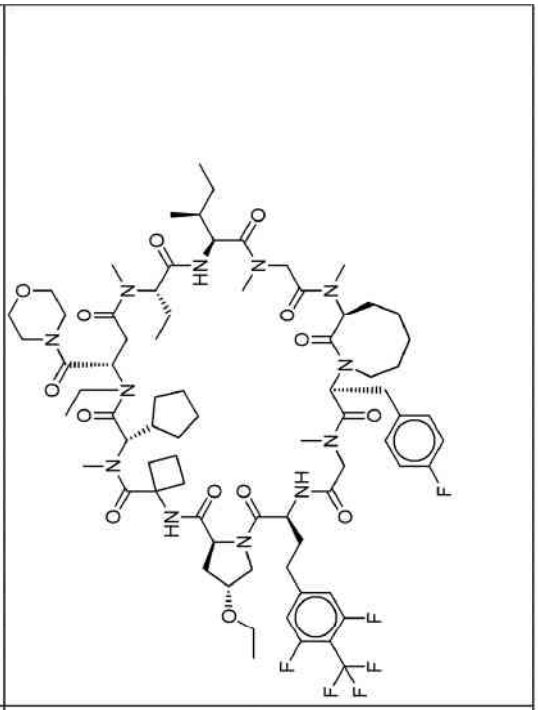
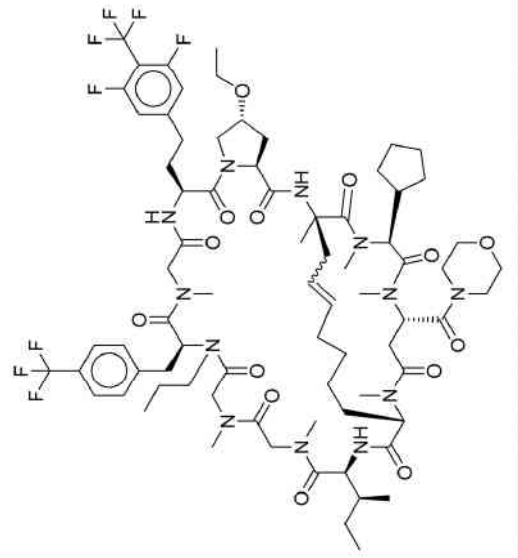
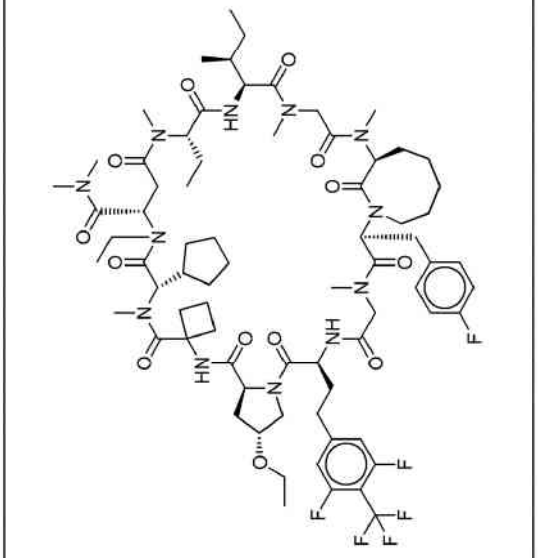
	
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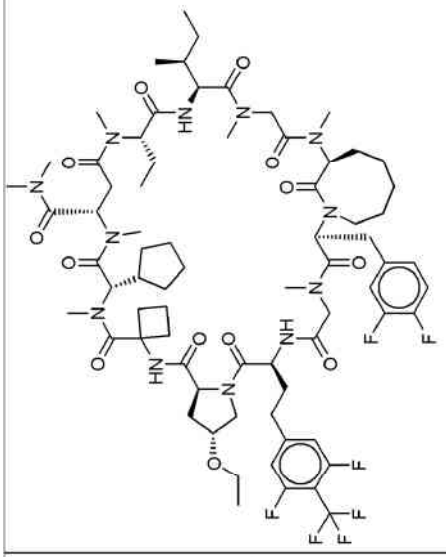
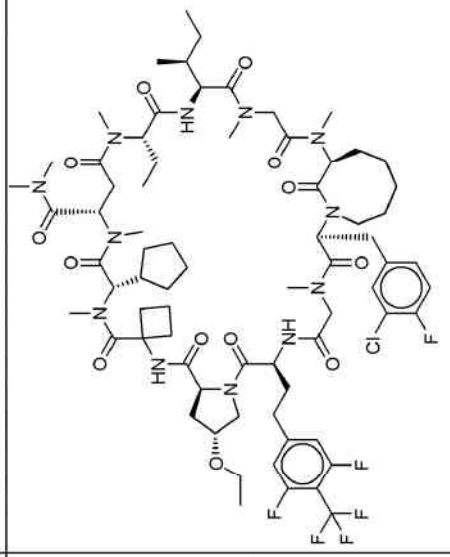
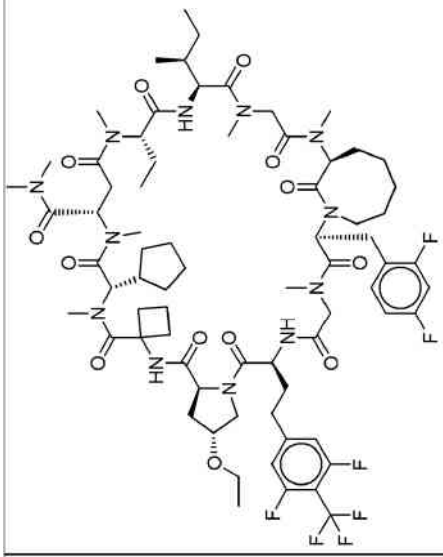
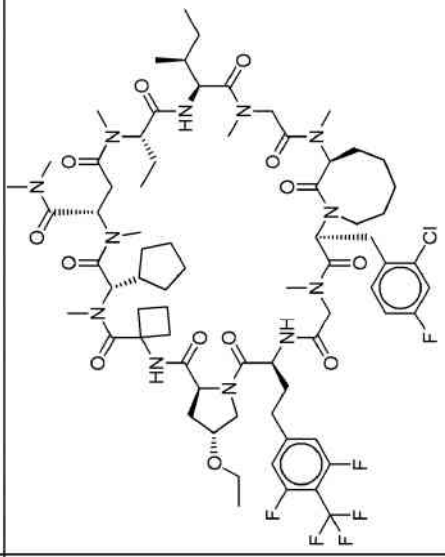
	
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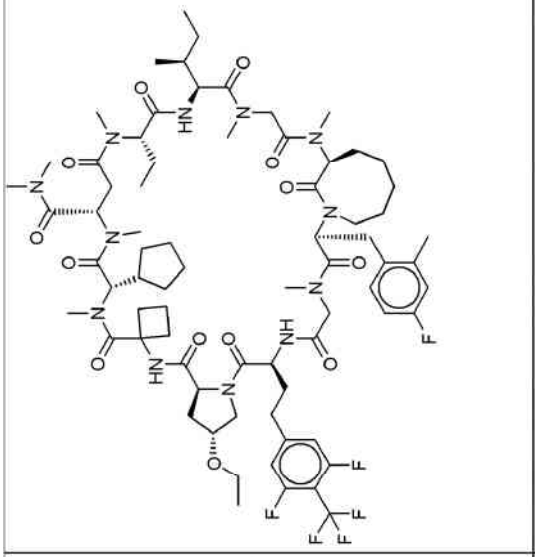
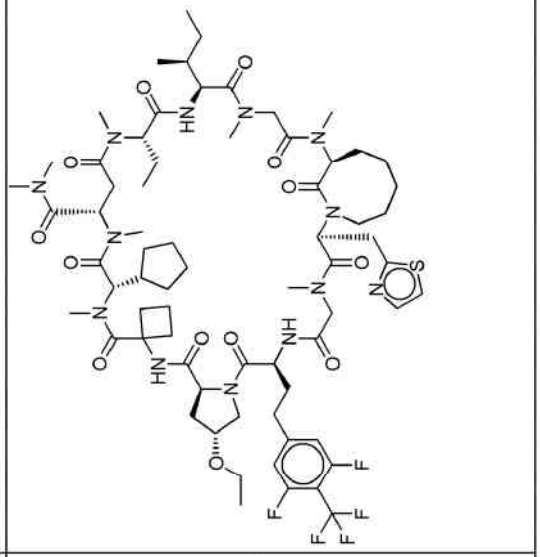
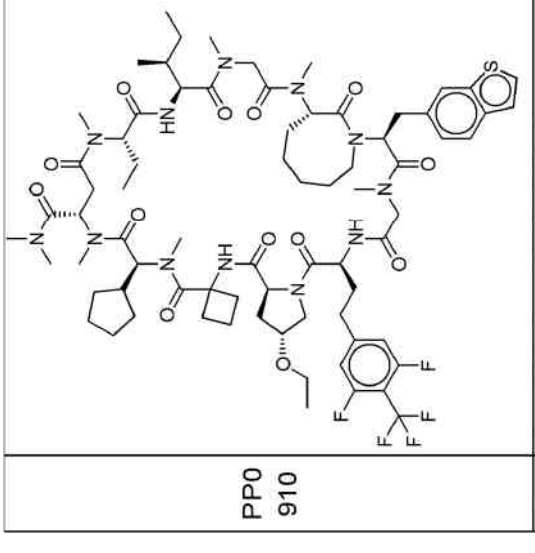
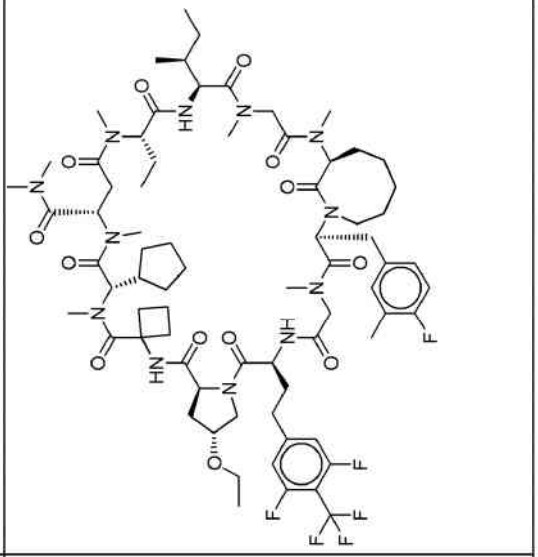
	
PP0 890	PP0 892
	
PP0 889	PP0 891

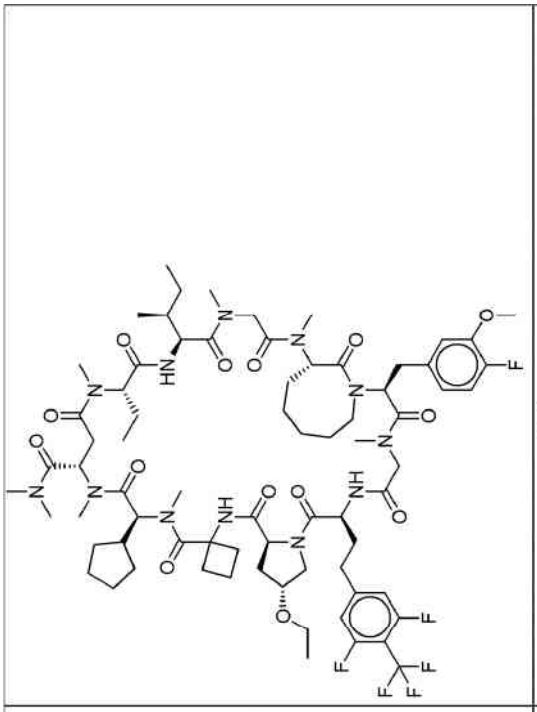
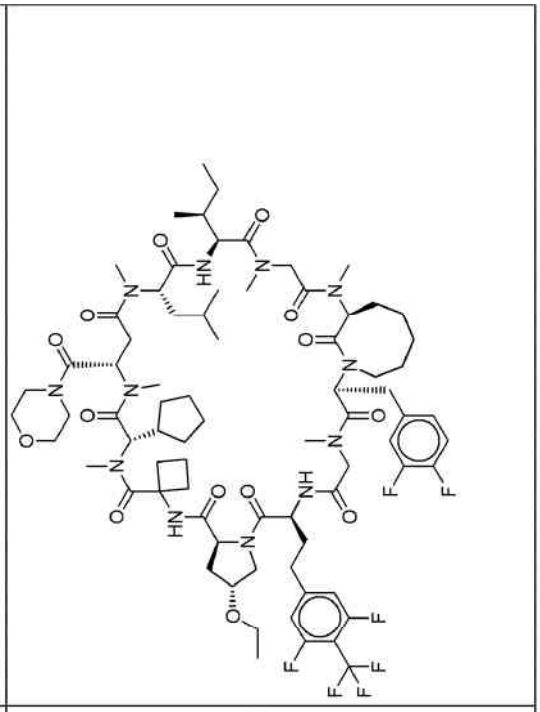
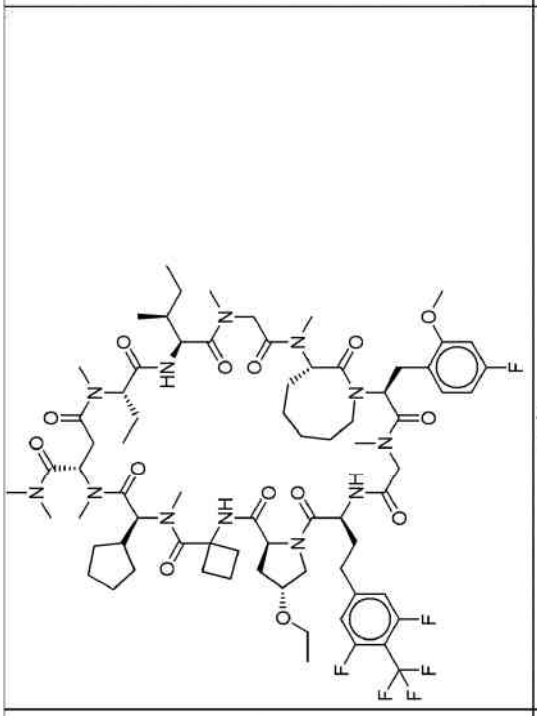
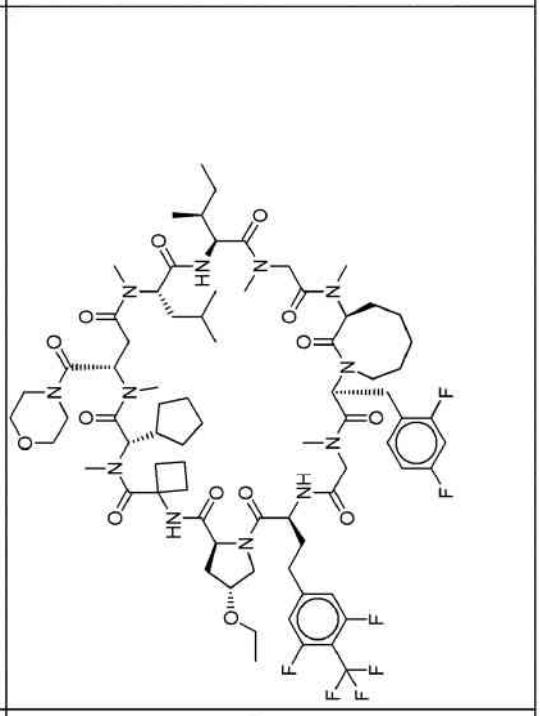
	
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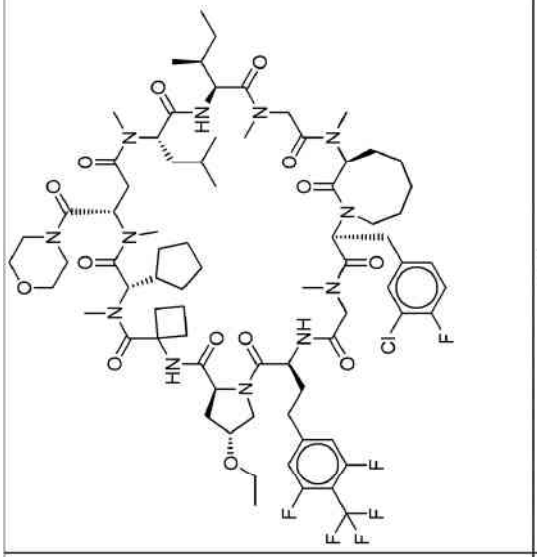
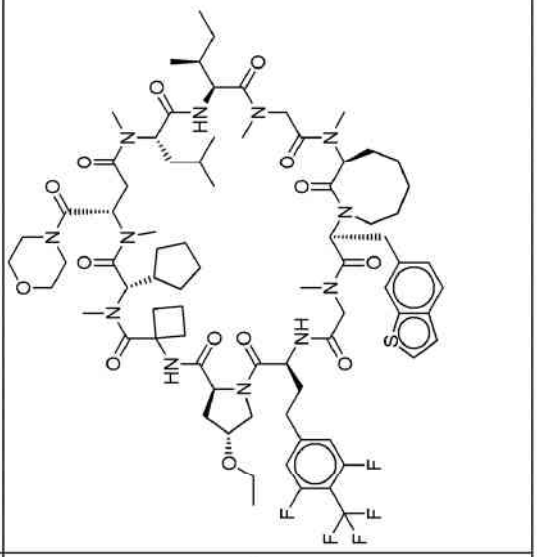
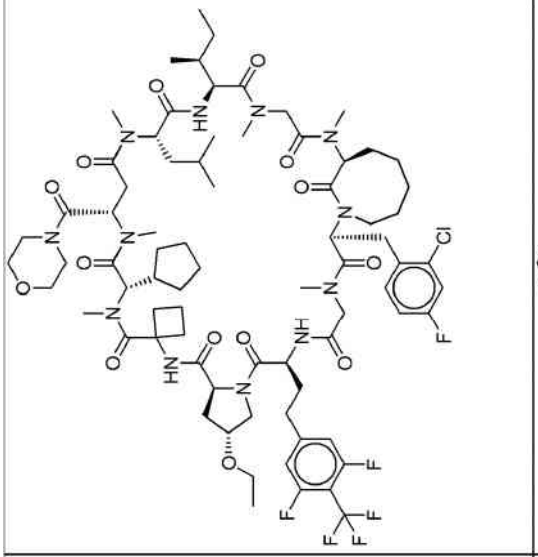
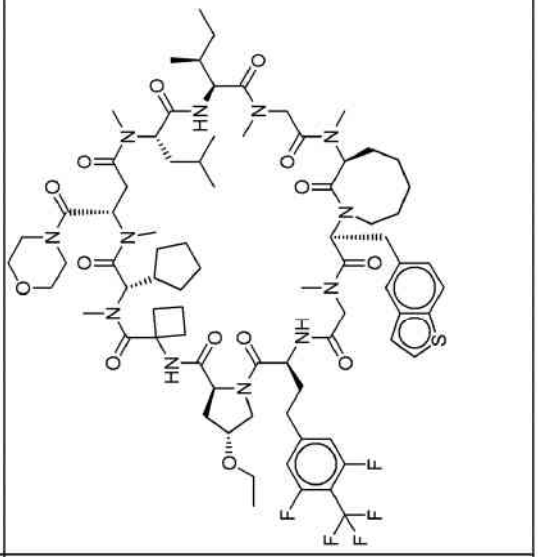
	
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PP0 898	PP0 900

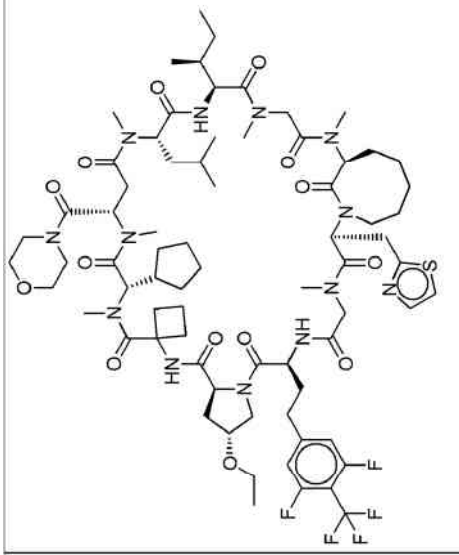
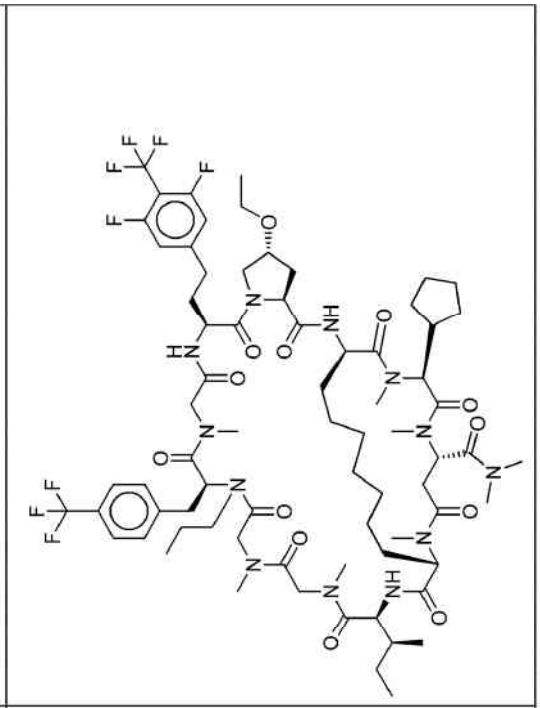
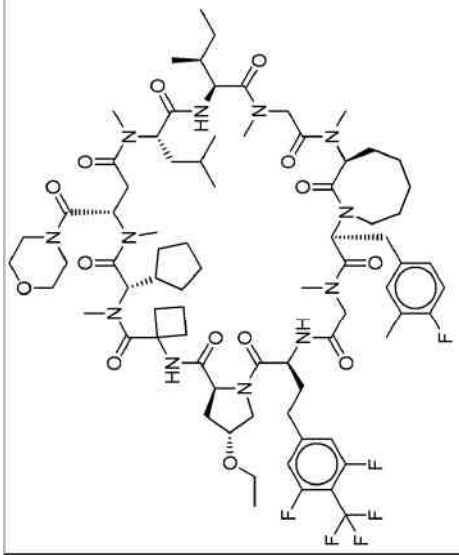
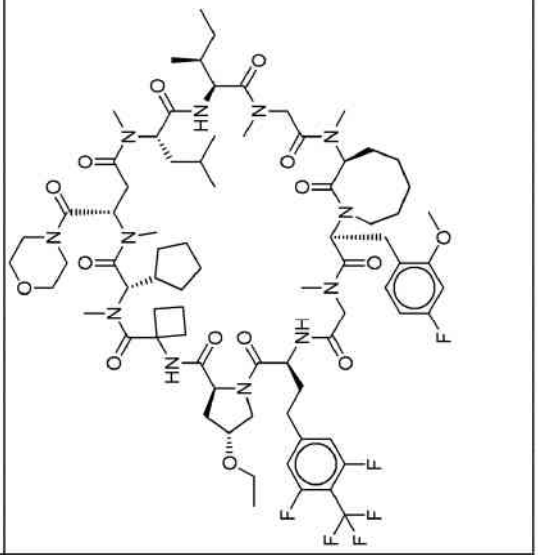
	
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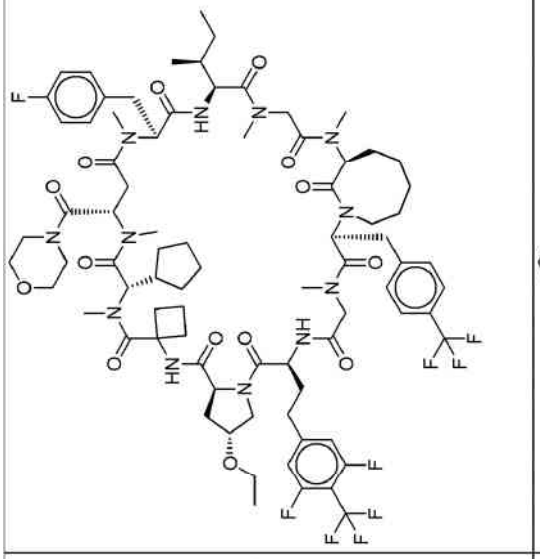
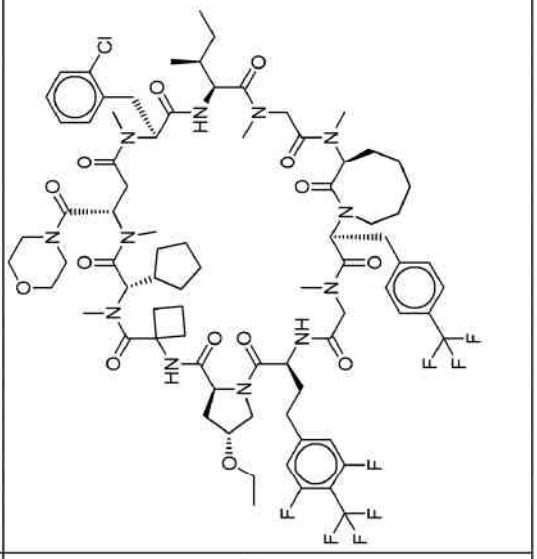
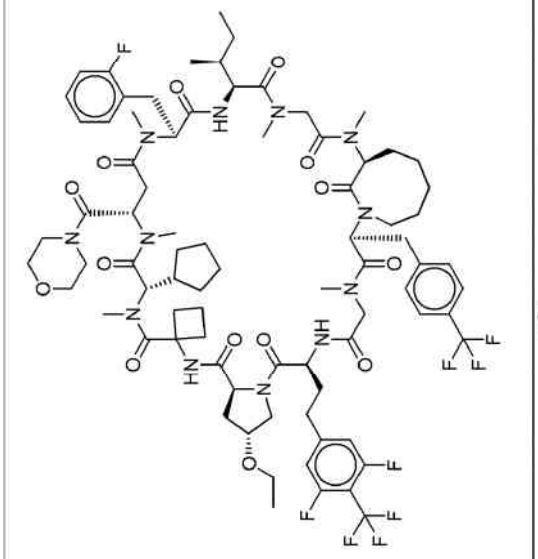
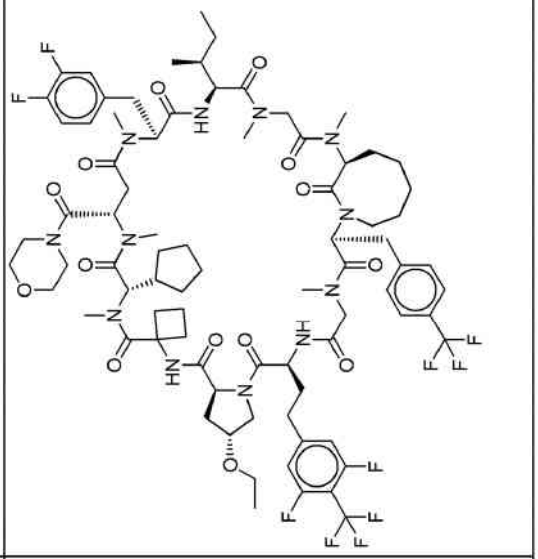
	
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PP0 906	PP0 908

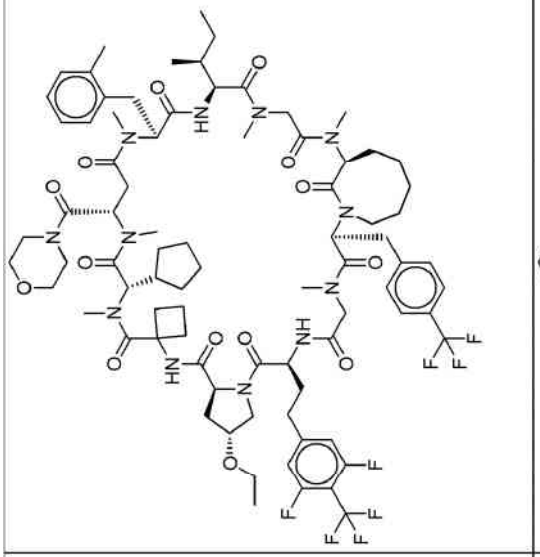
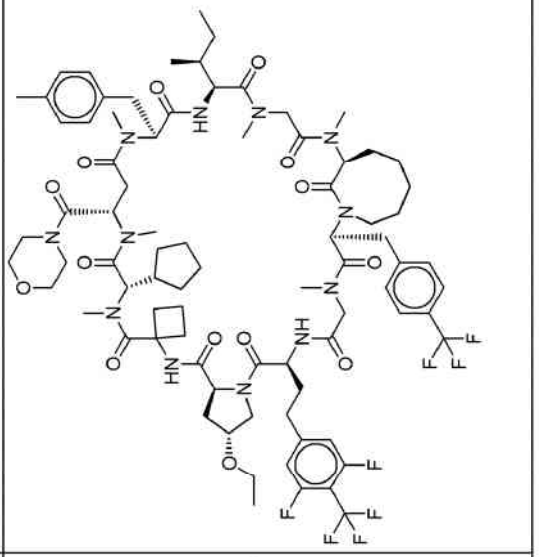
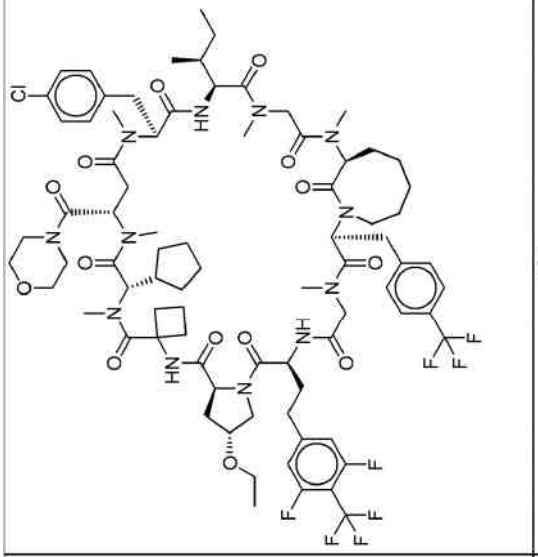
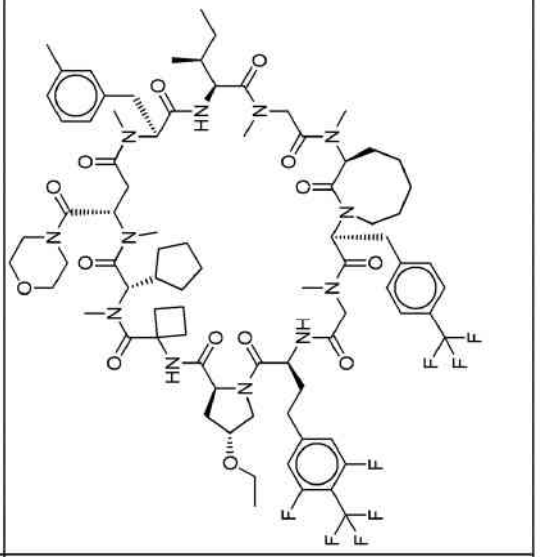
	
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PP0 910	PP0 912

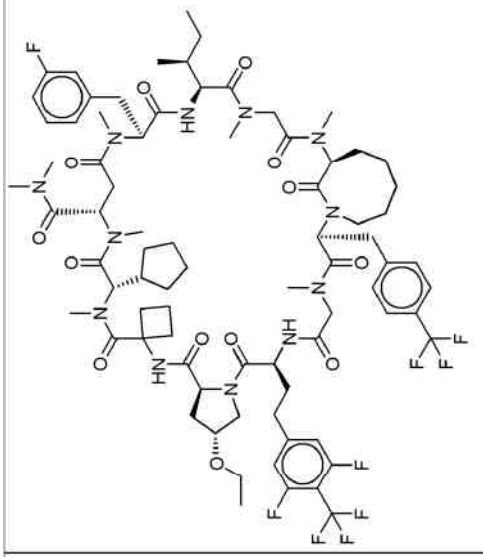
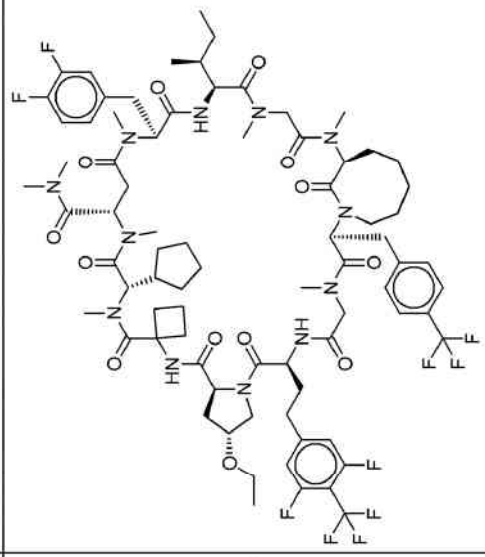
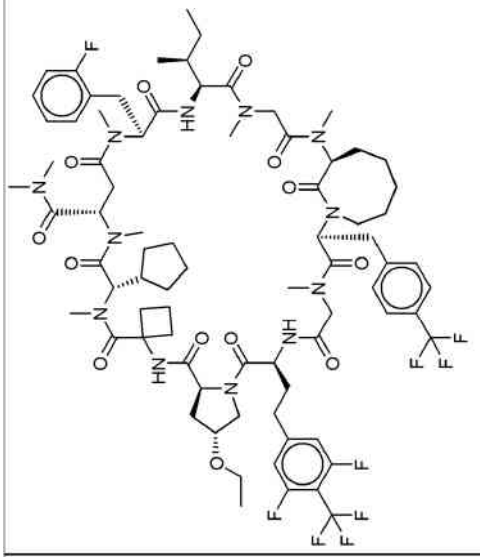
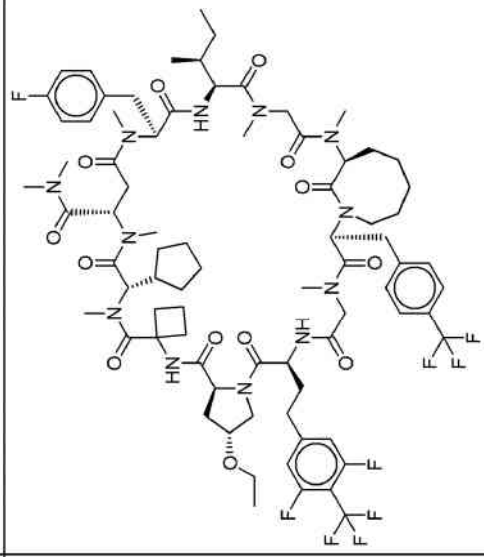
	
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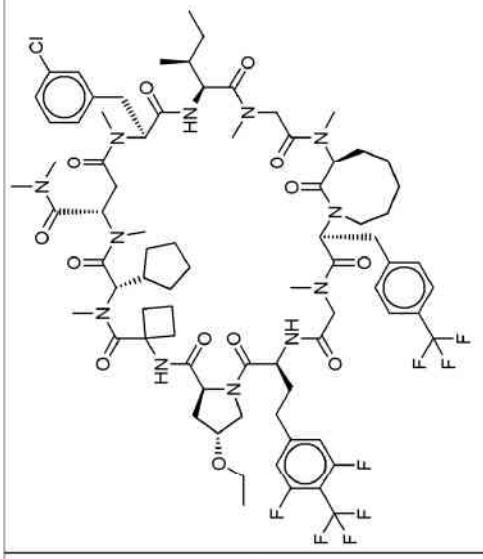
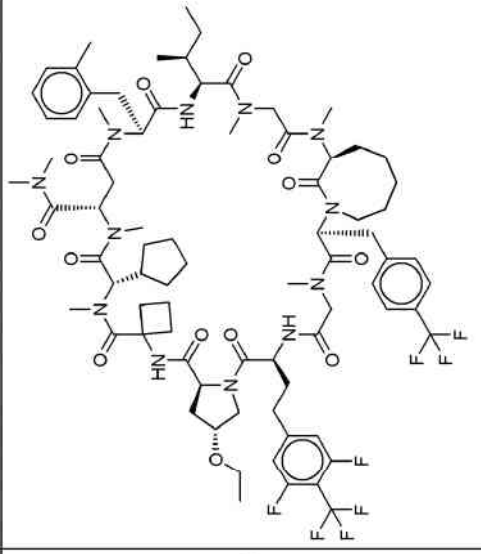
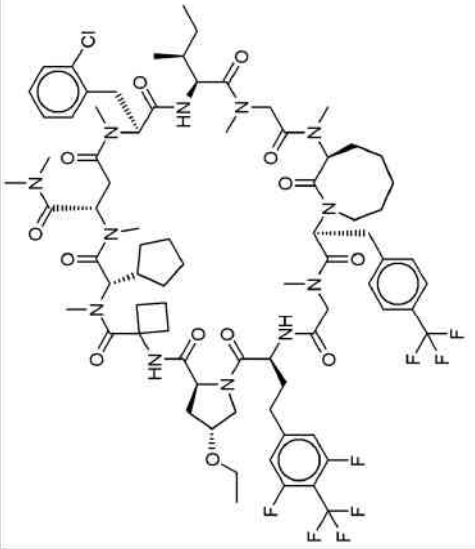
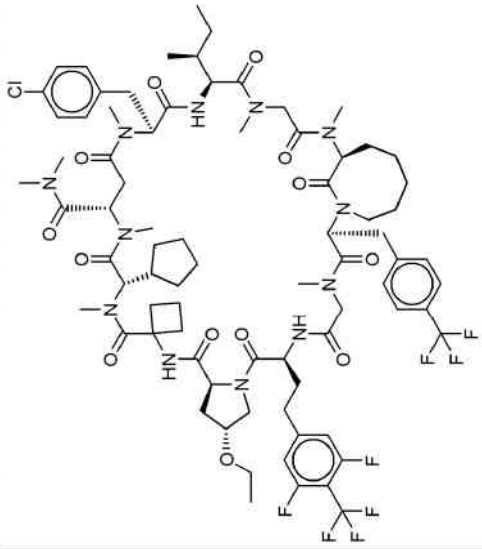
	
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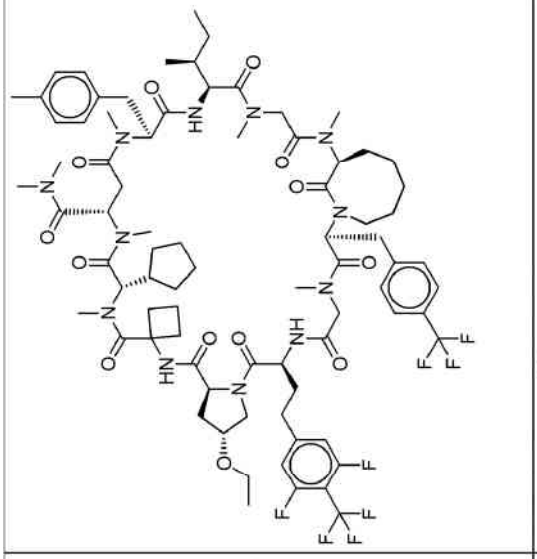
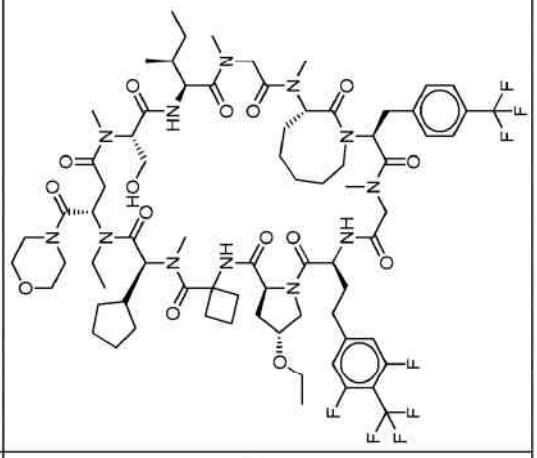
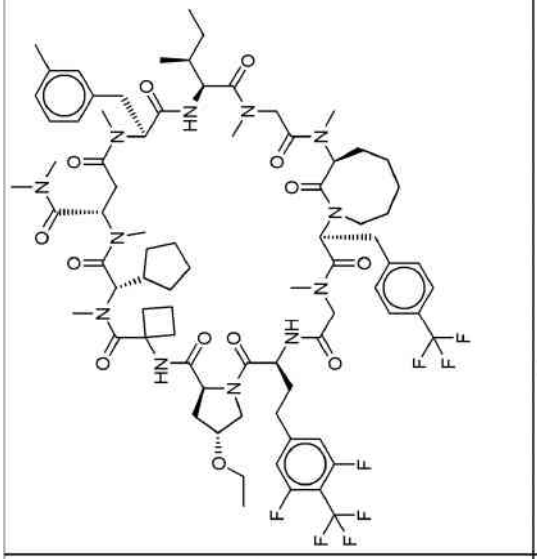
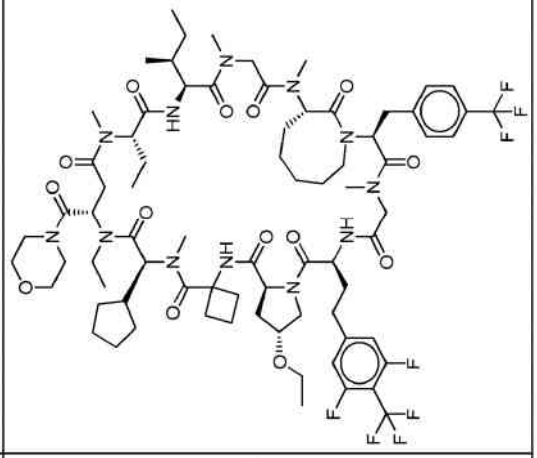
	
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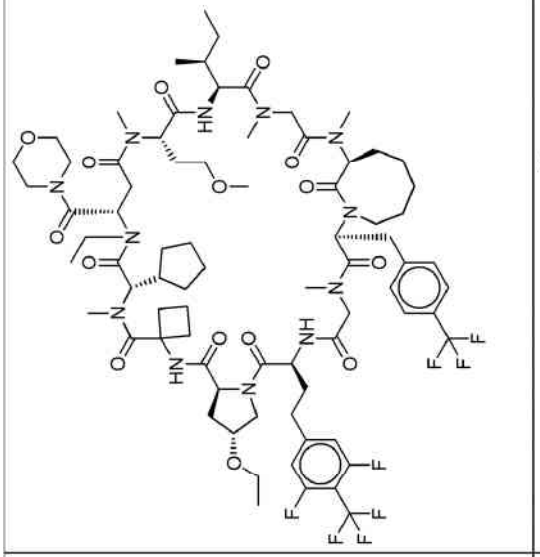
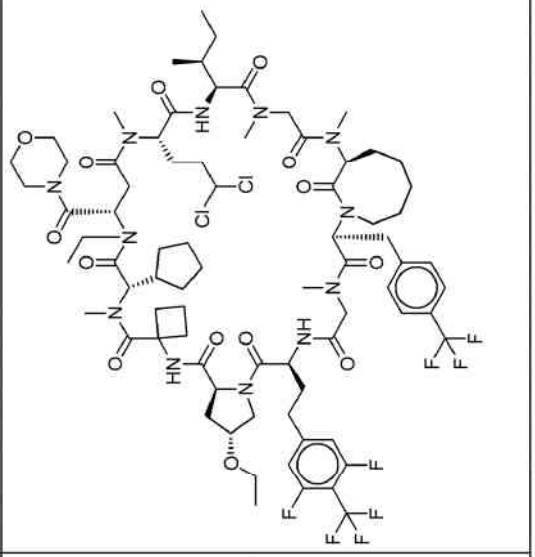
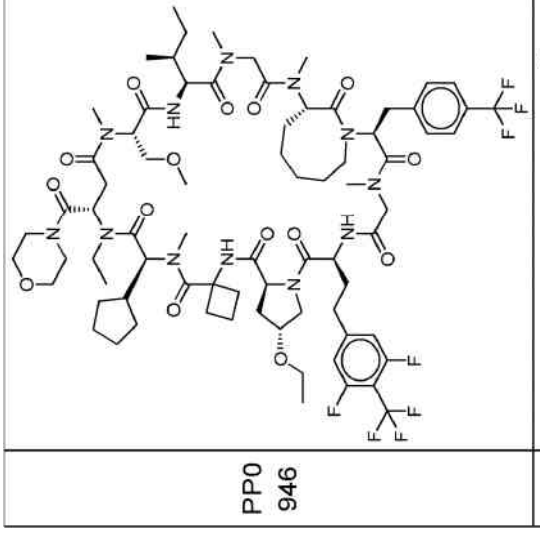
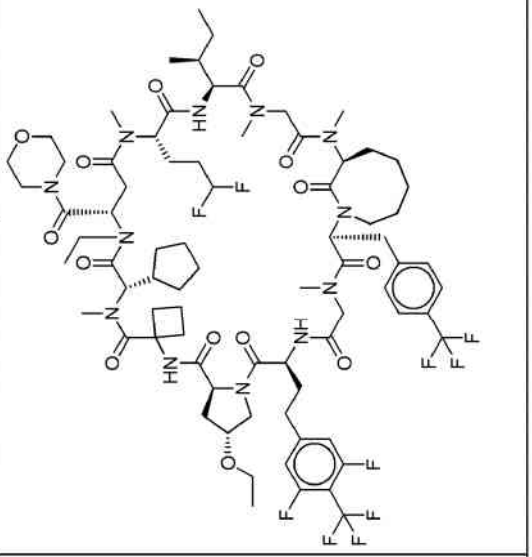
	
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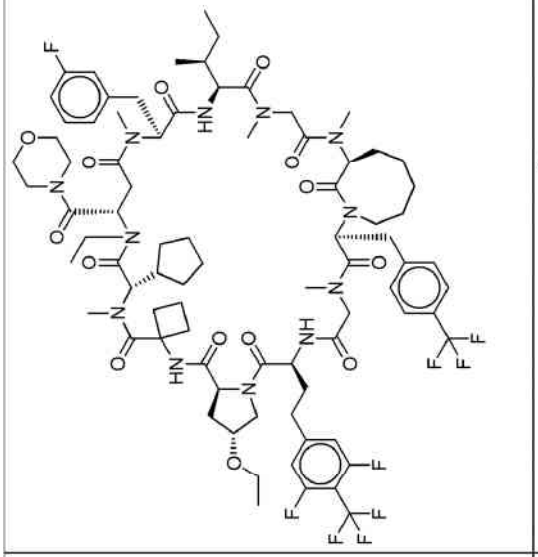
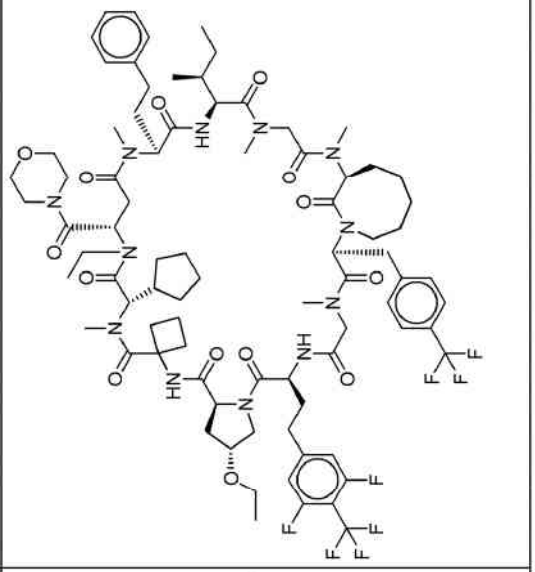
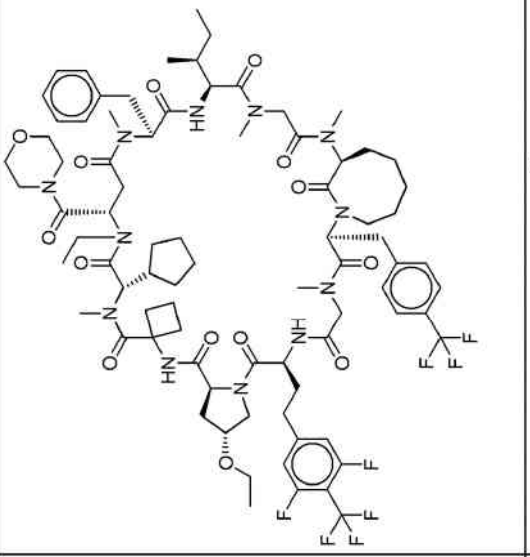
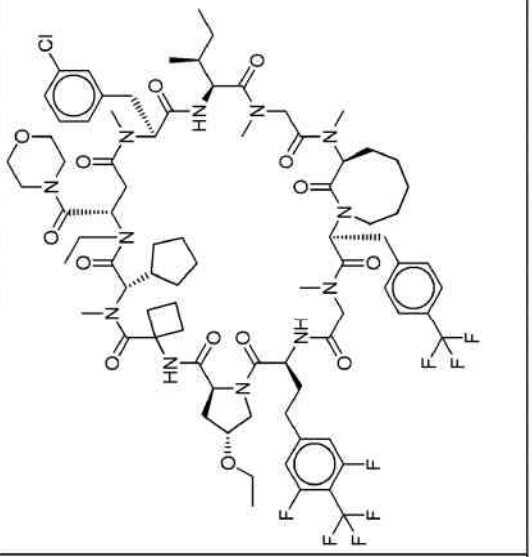
	
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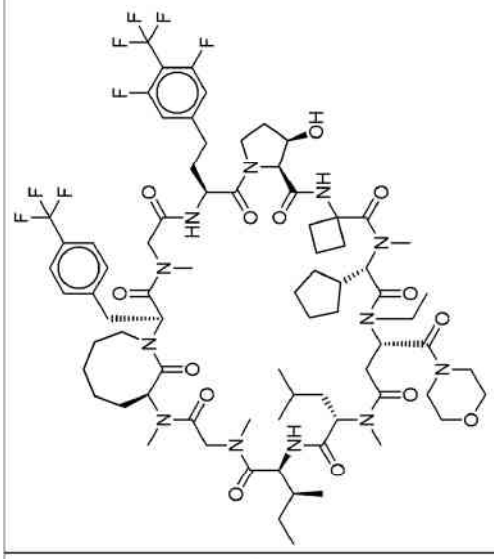
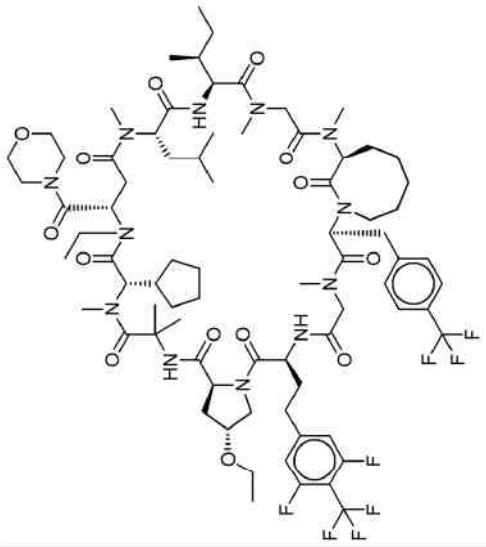
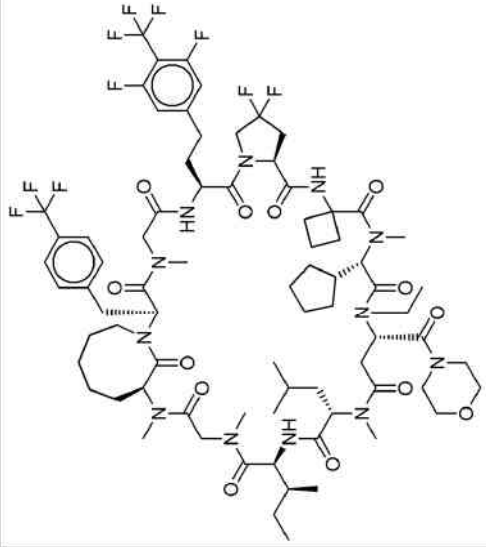
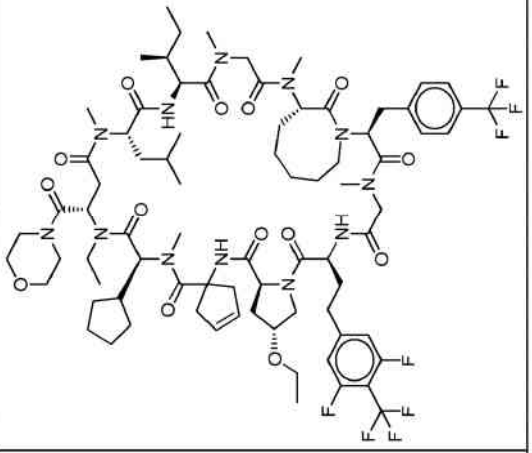
	
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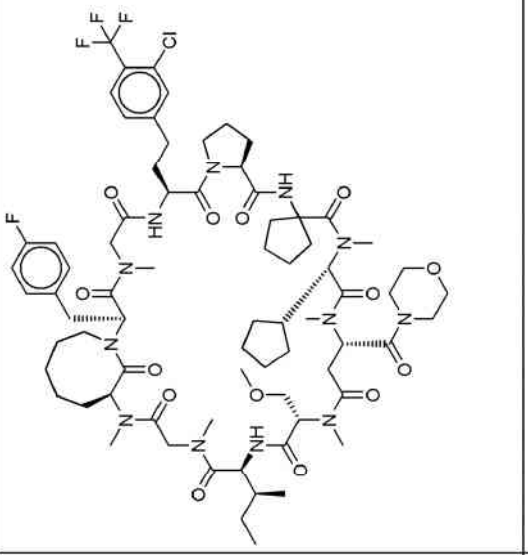
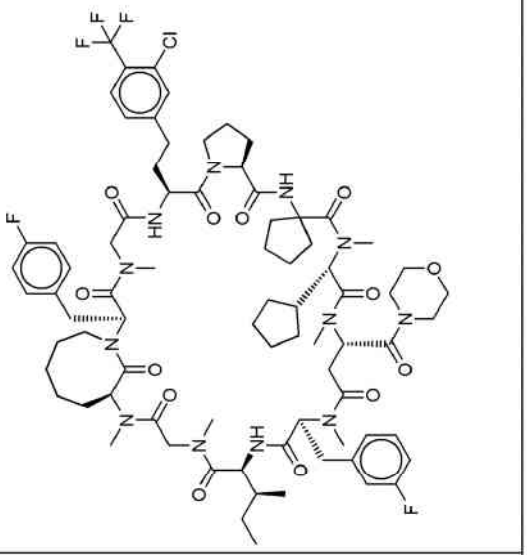
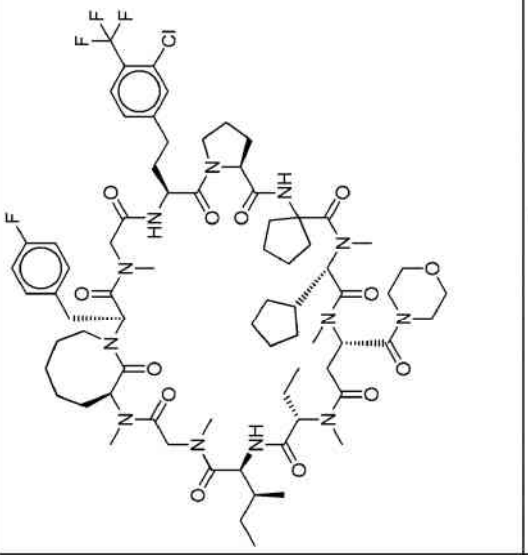
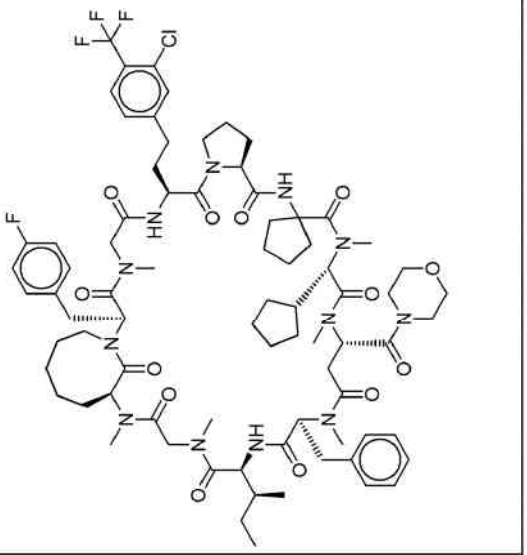
	
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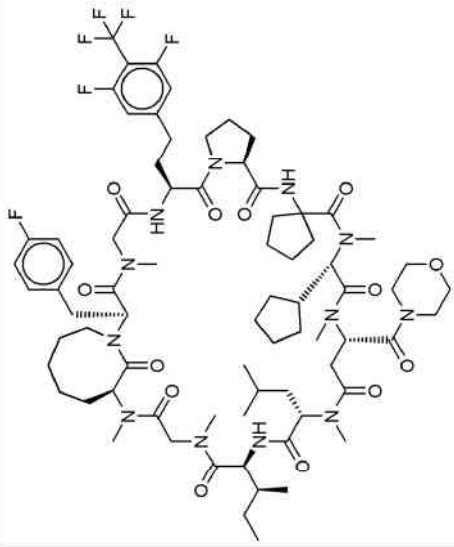
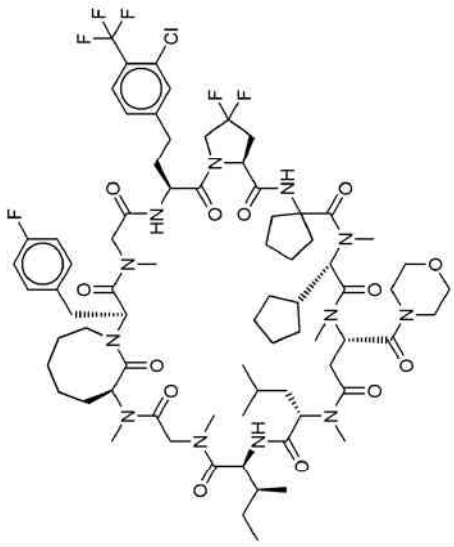
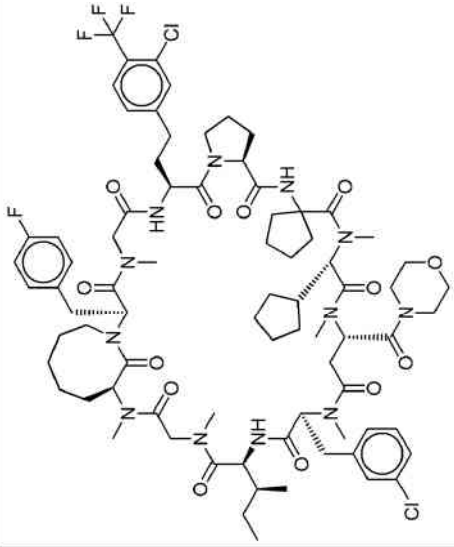
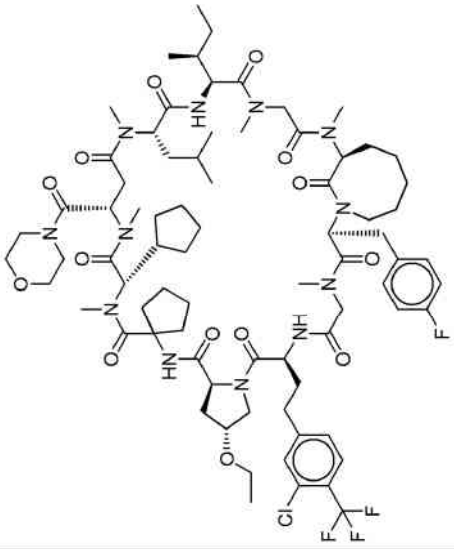
	
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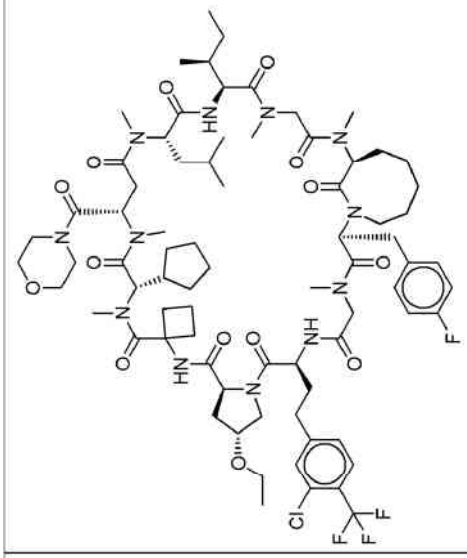
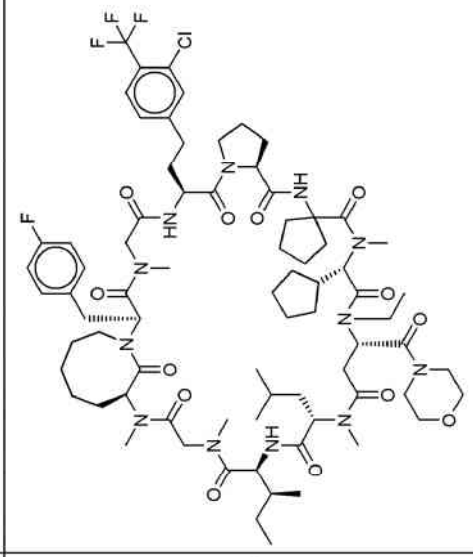
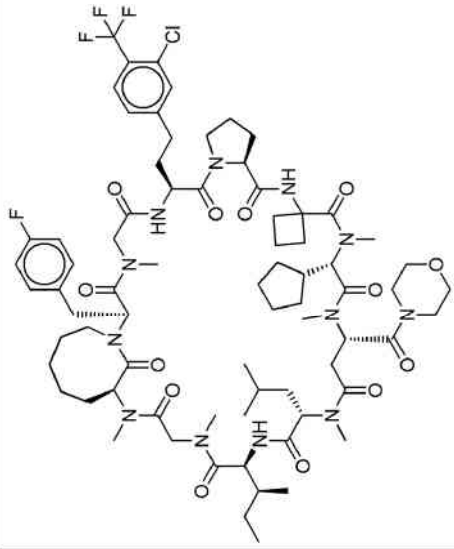
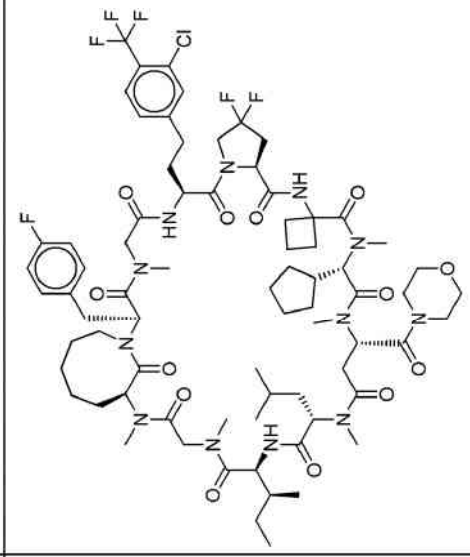
	
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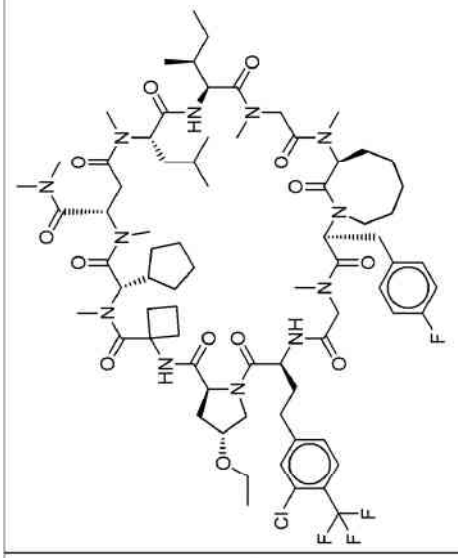
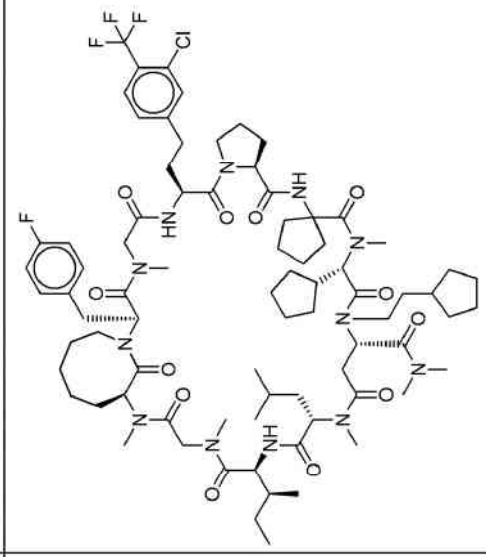
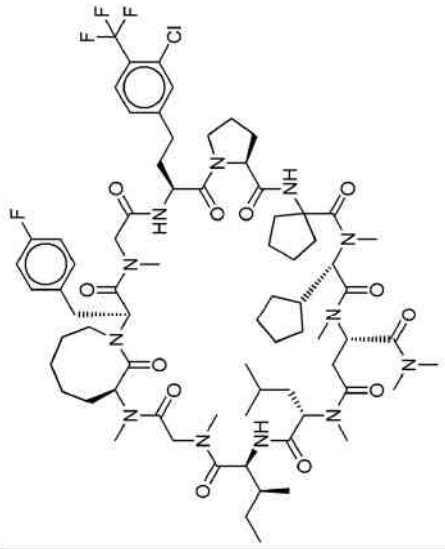
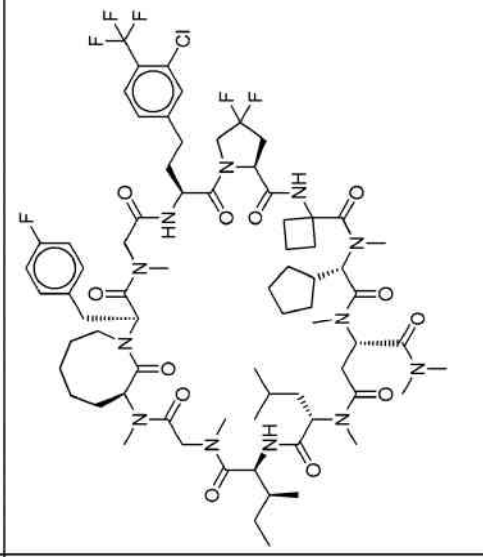
	
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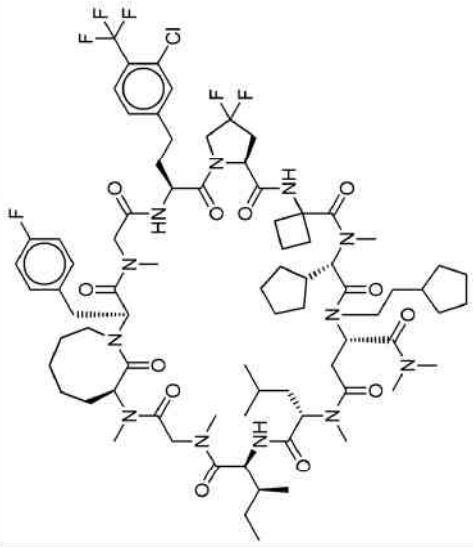
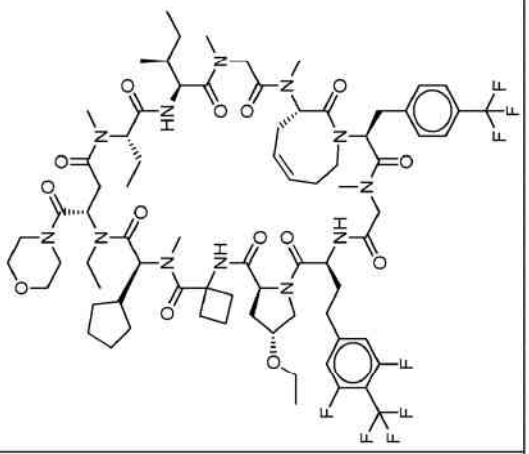
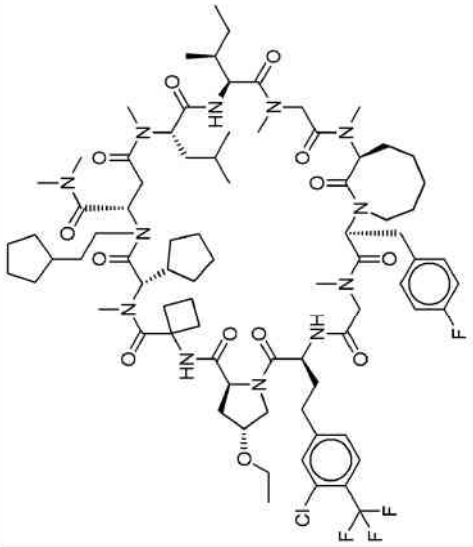
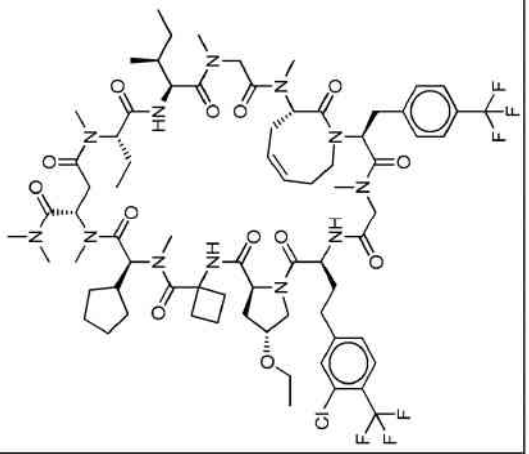
	
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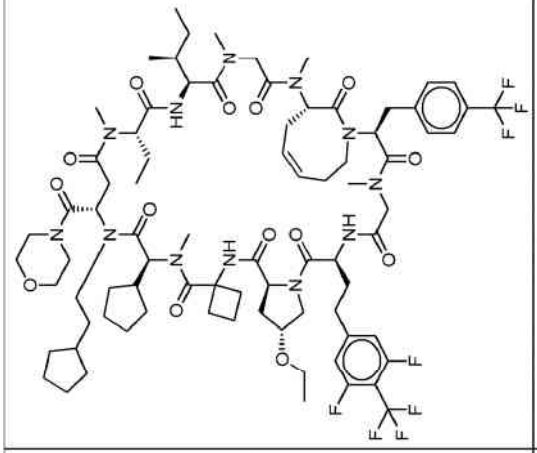
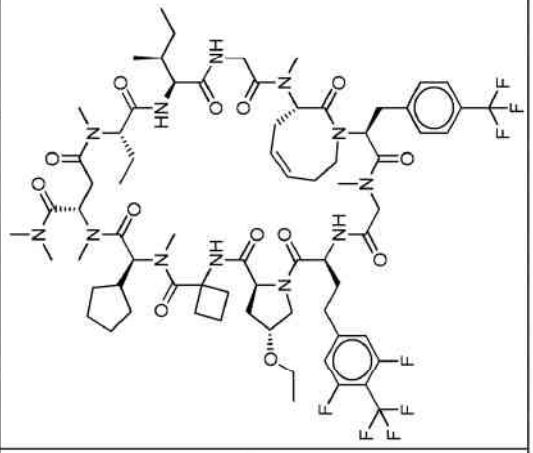
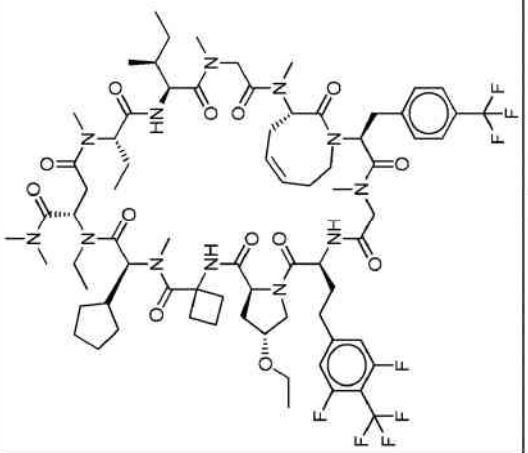
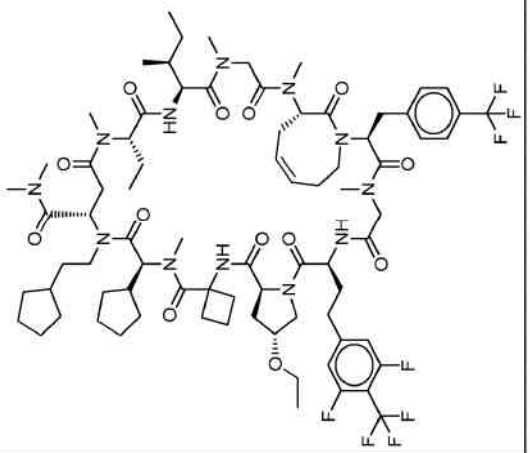
	
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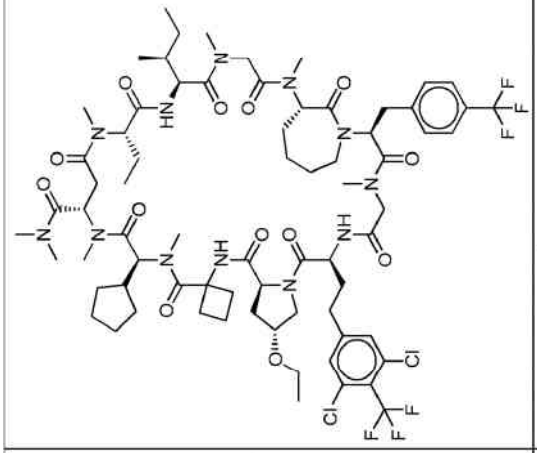
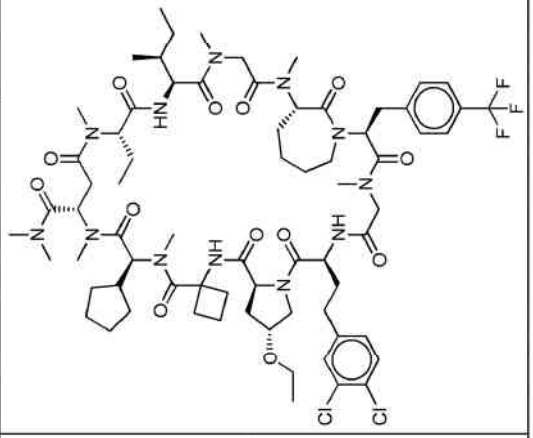
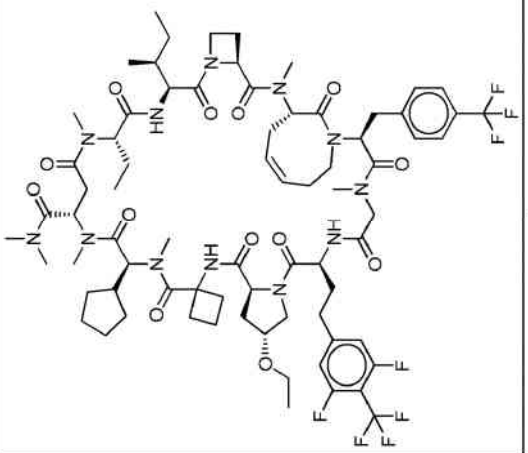
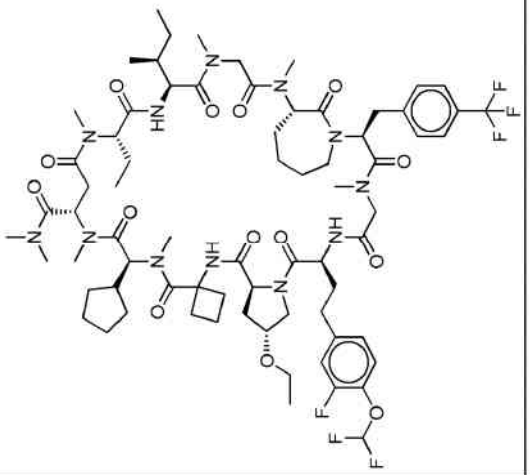
	
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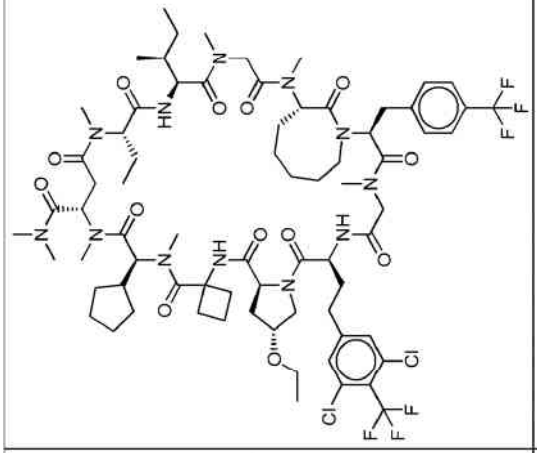
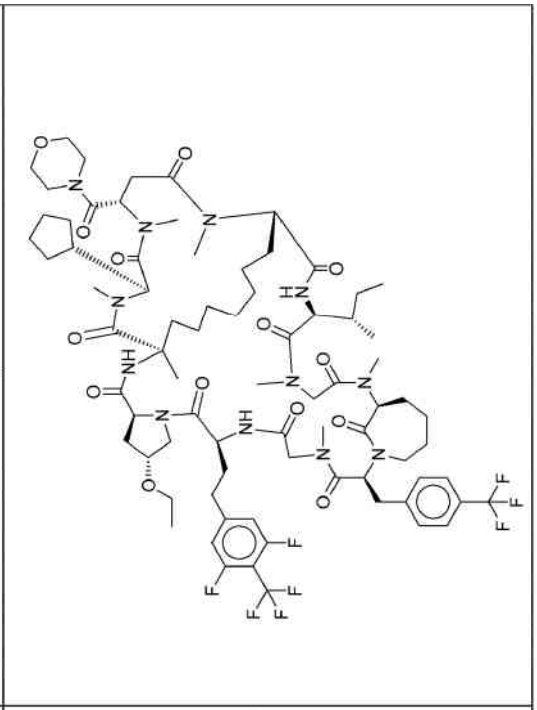
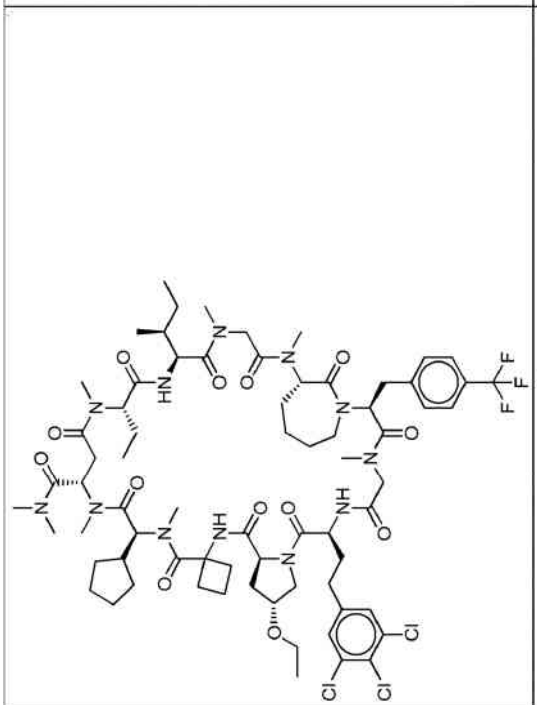
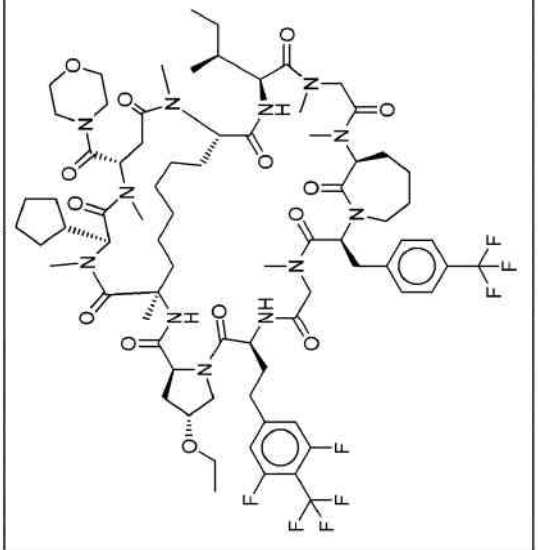
	
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PP0 967	PP0 969

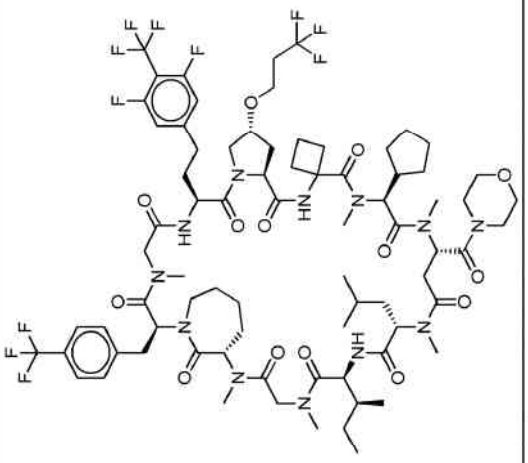
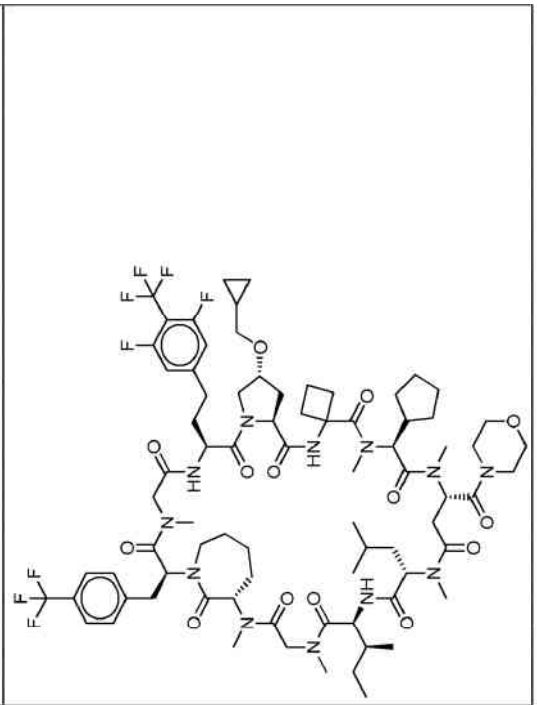
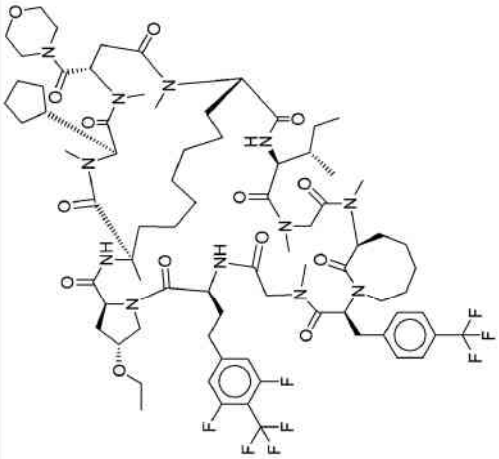
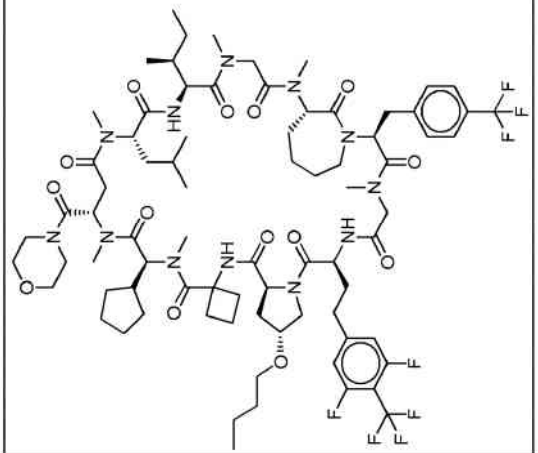
	
PP0 972	PP0 975
	
PP0 971	PP0 973

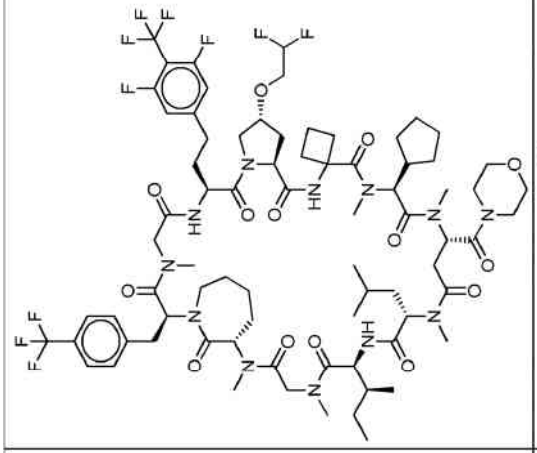
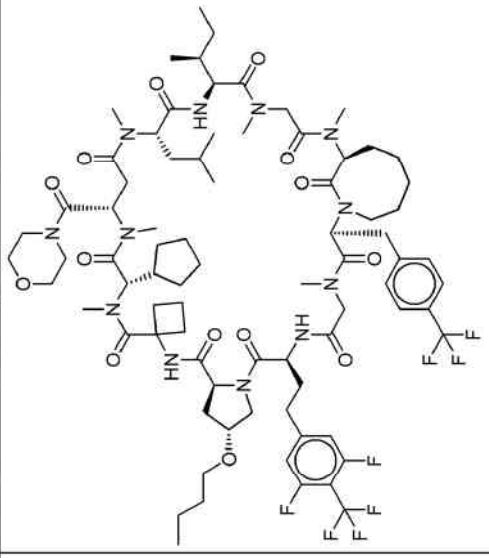
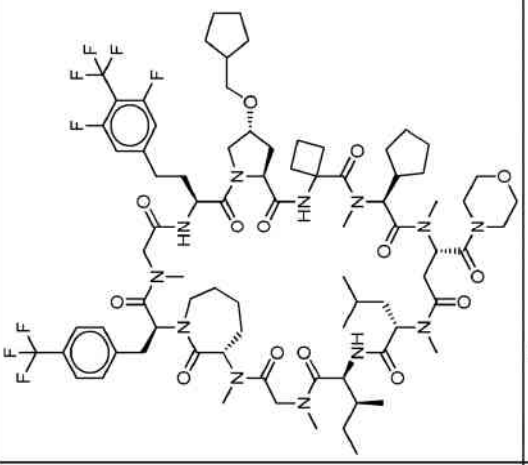
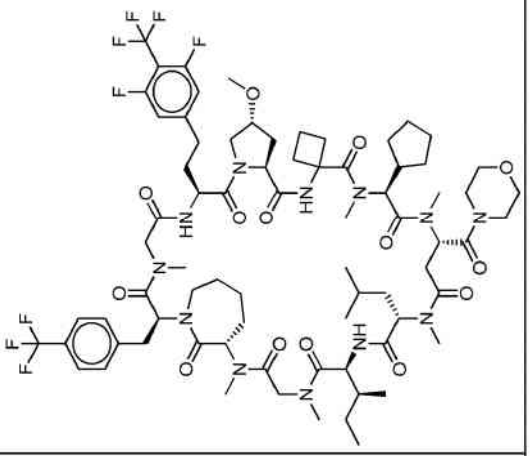
	
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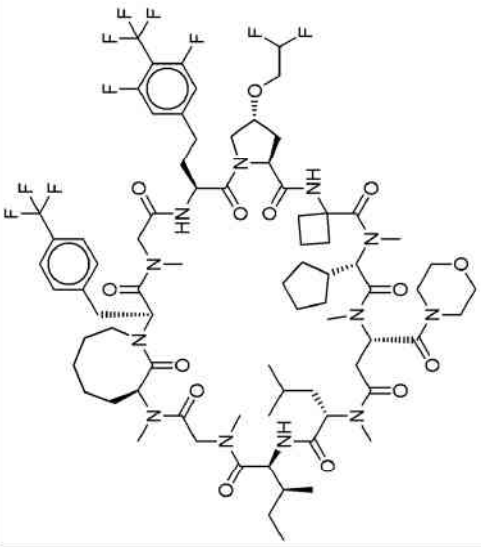
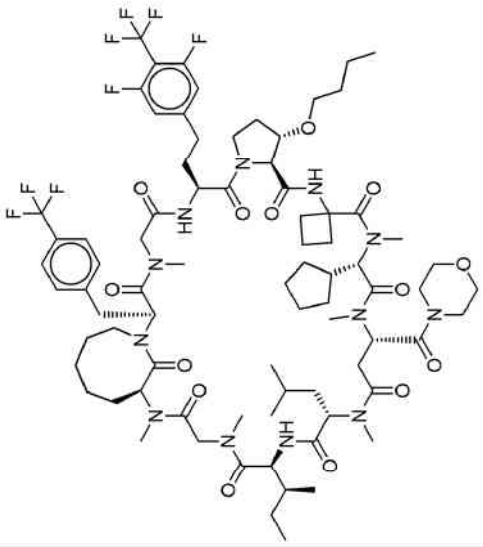
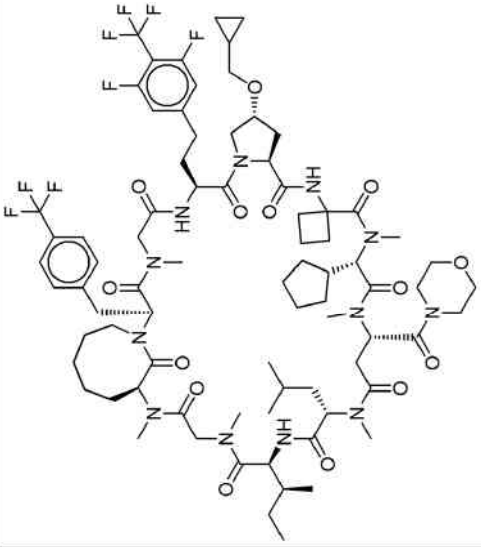
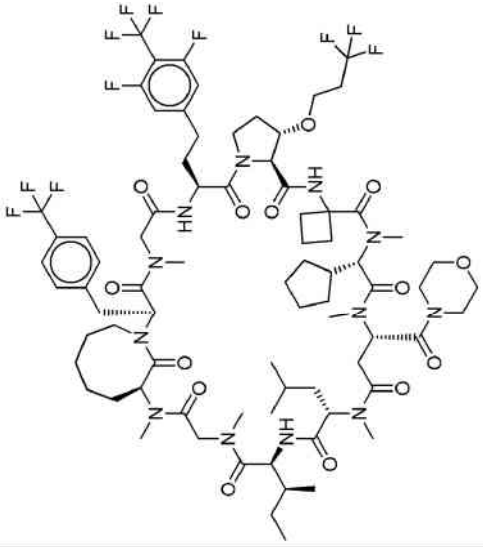
	
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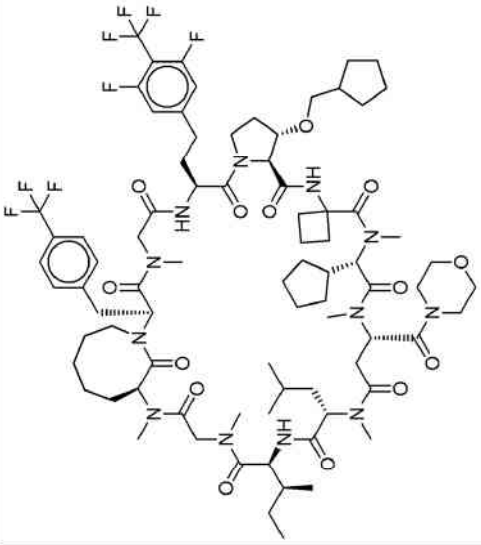
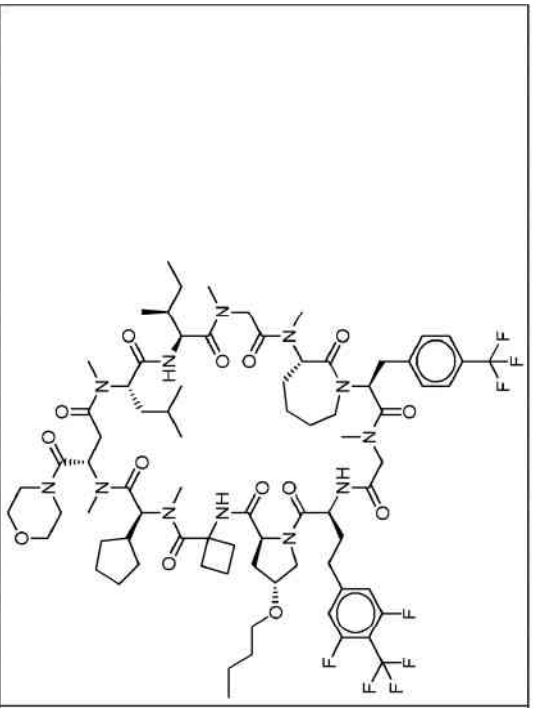
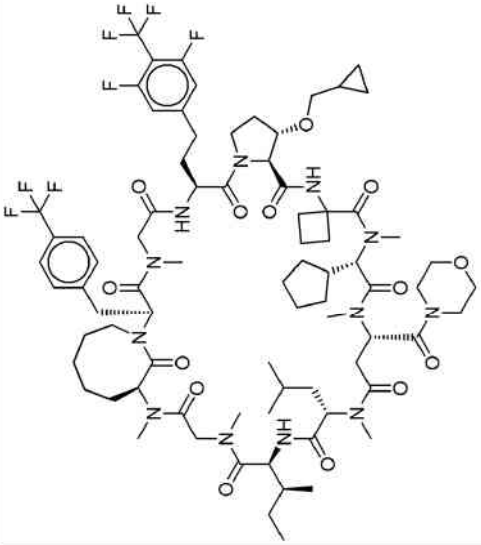
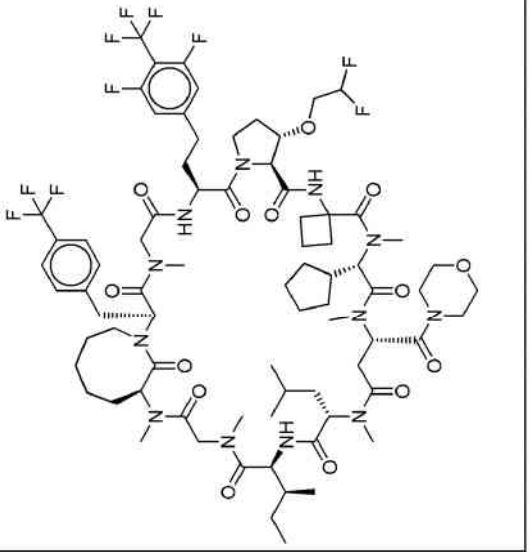
	
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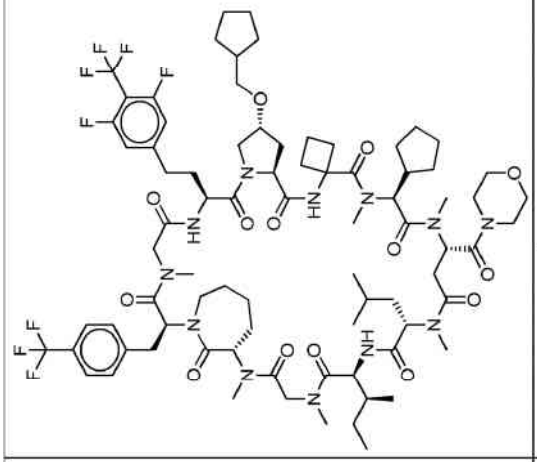
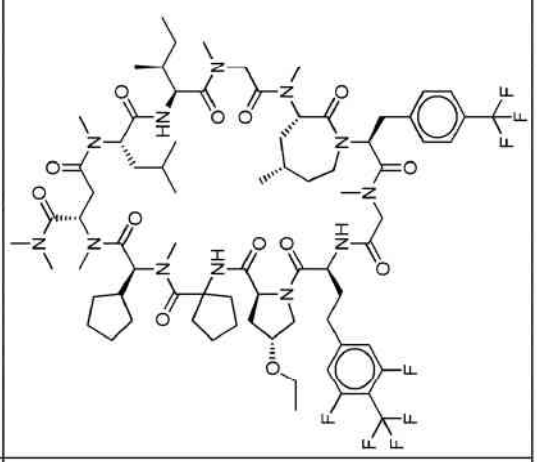
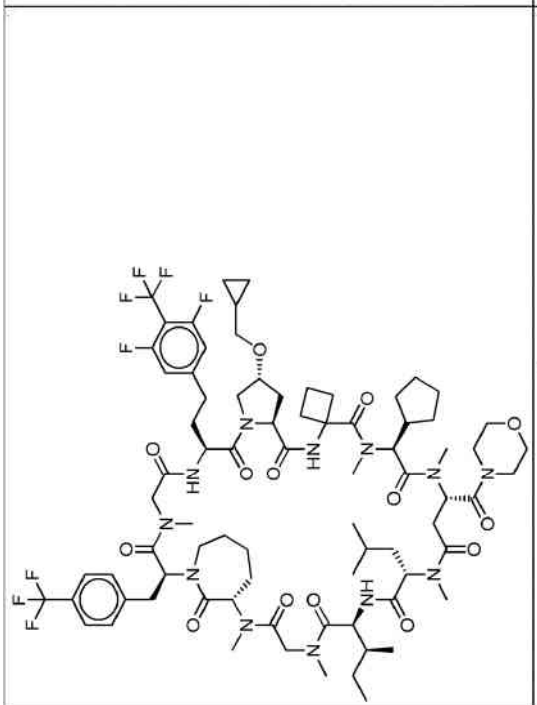
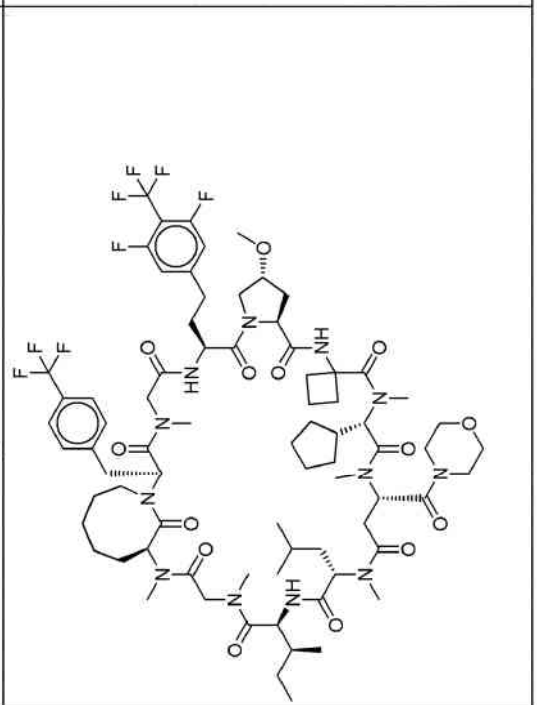
	
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PP0 988	PP0 992

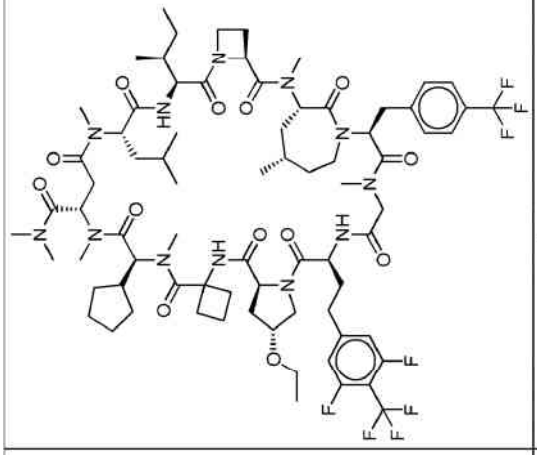
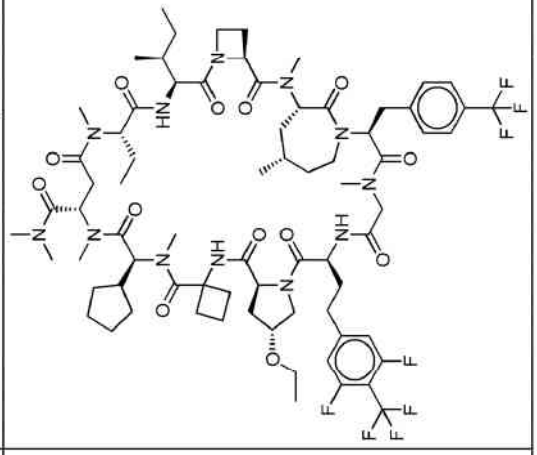
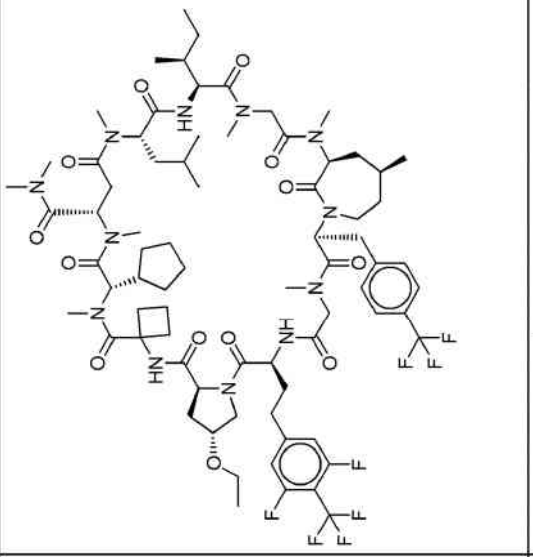
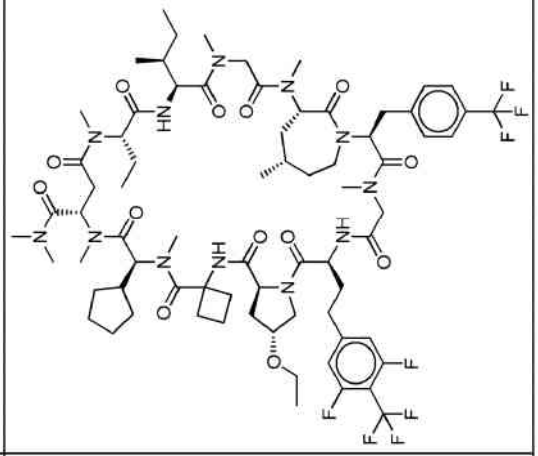
	
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PP0 997	PP0 999

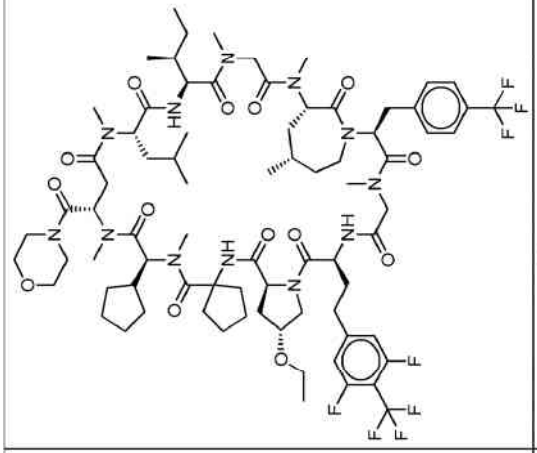
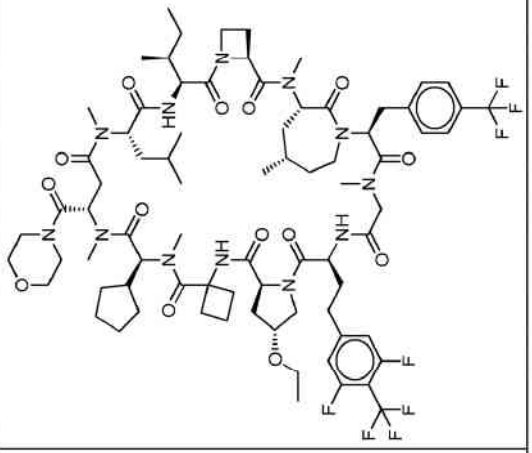
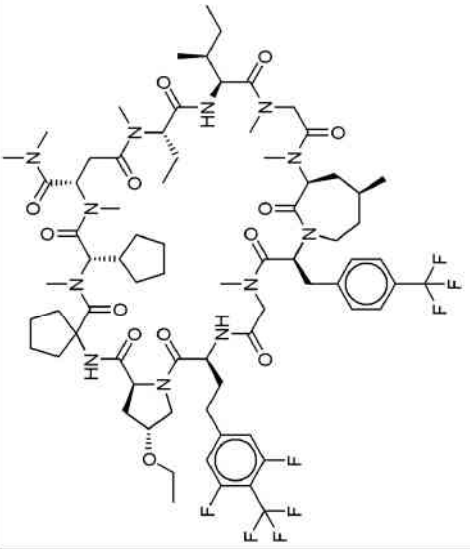
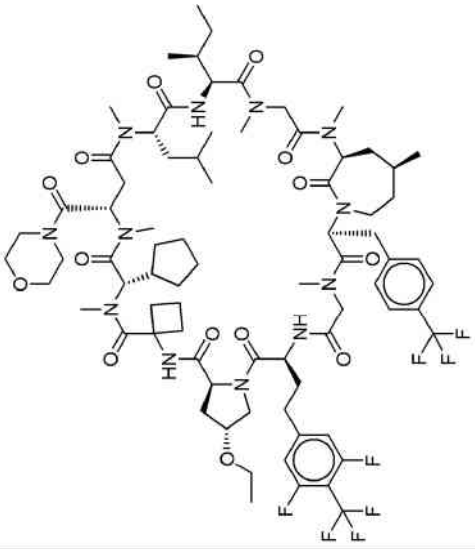
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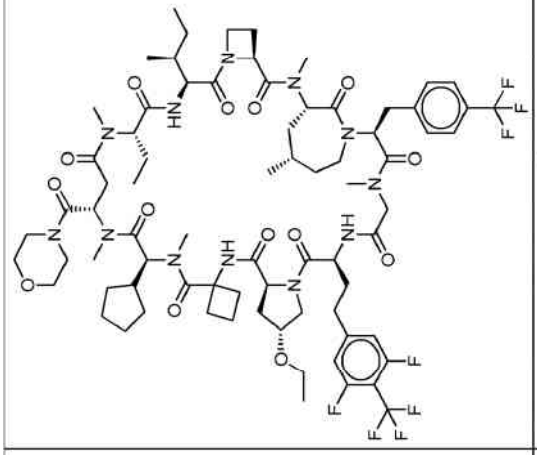
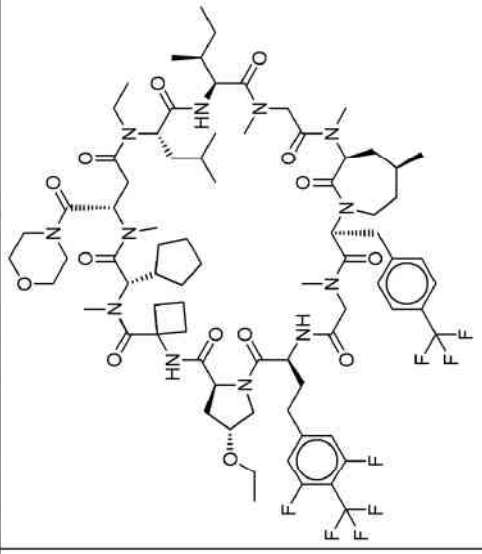
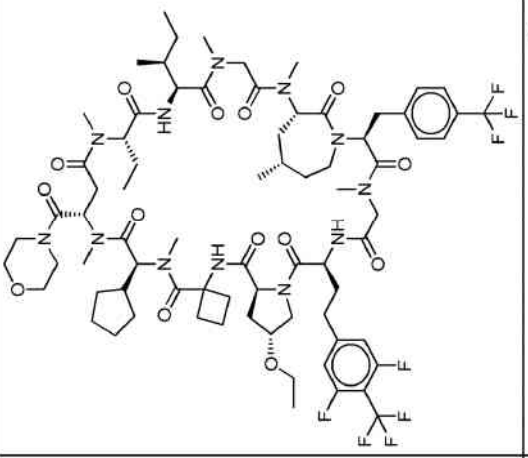
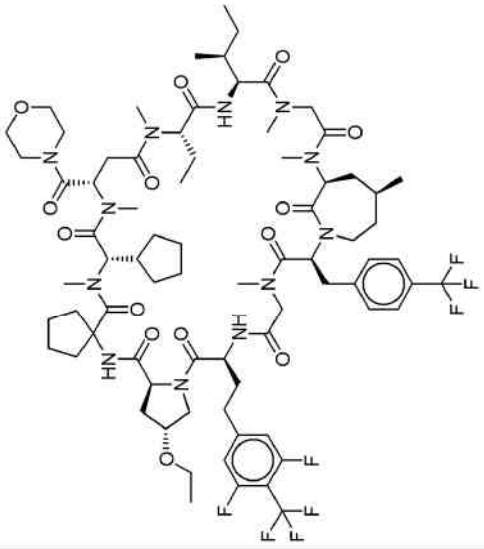
	
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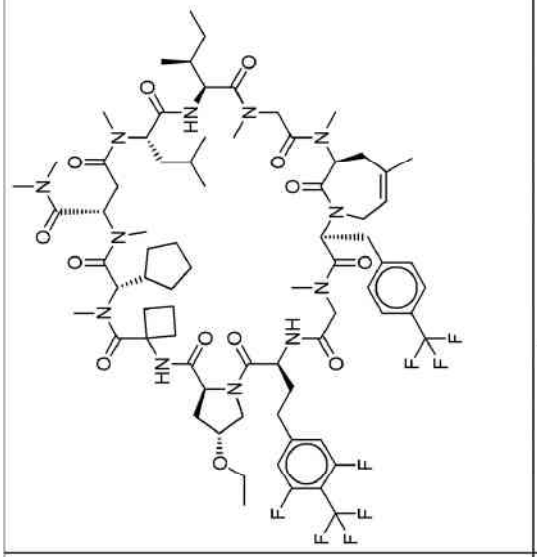
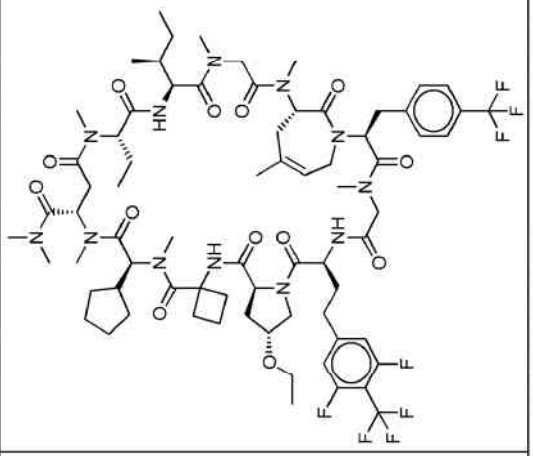
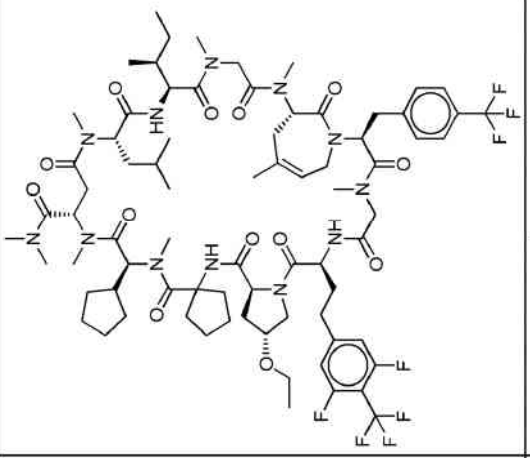
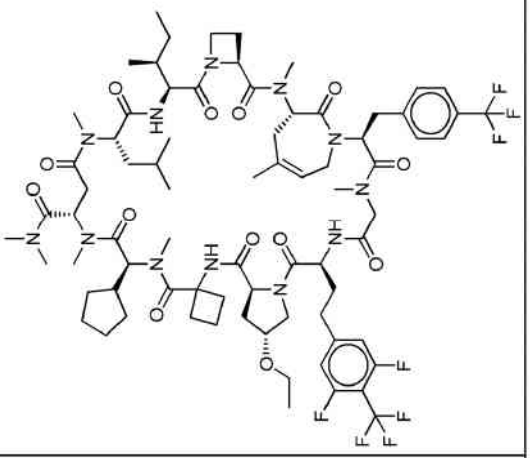
	
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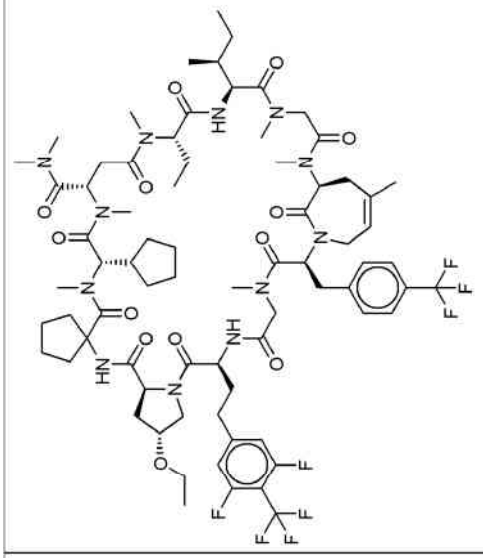
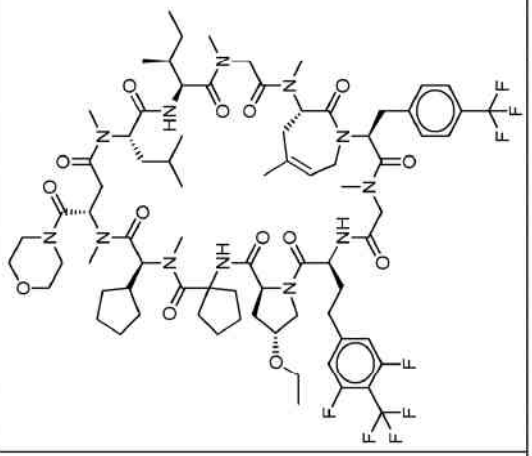
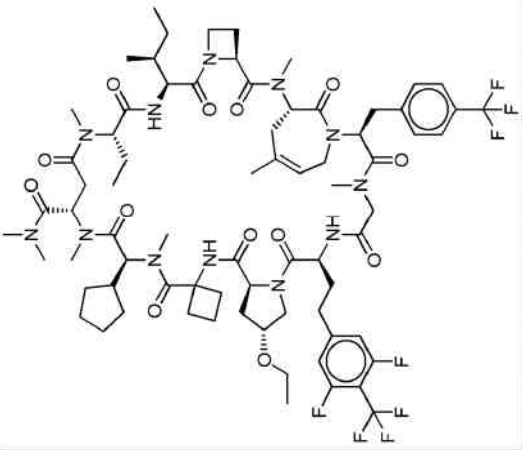
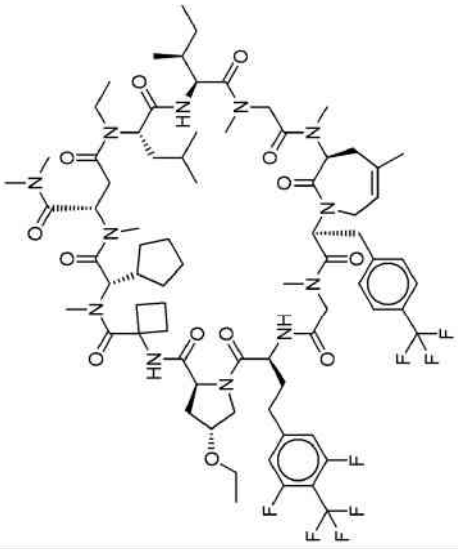
	
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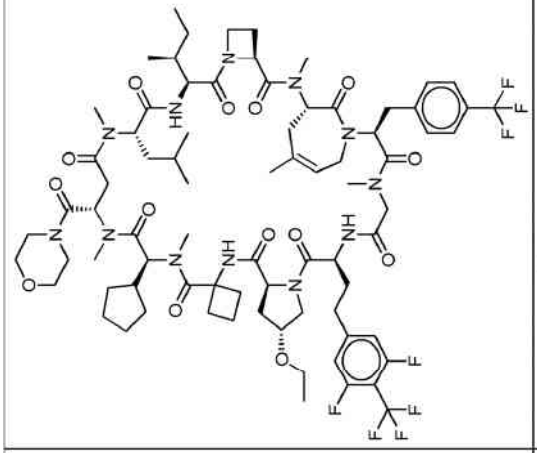
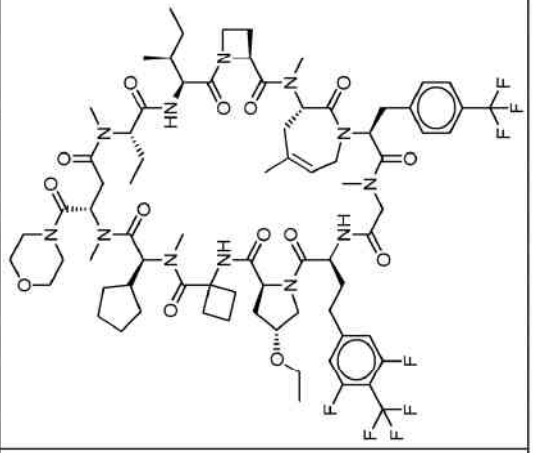
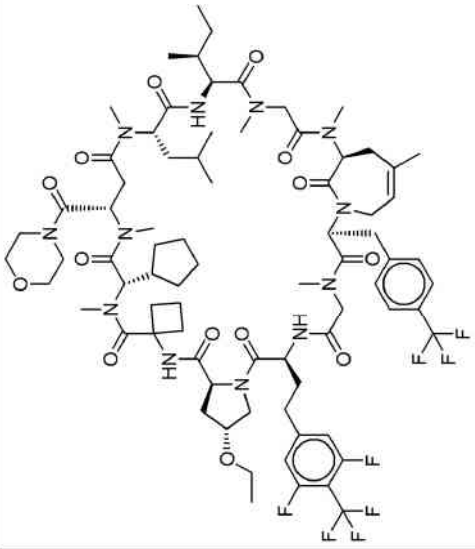
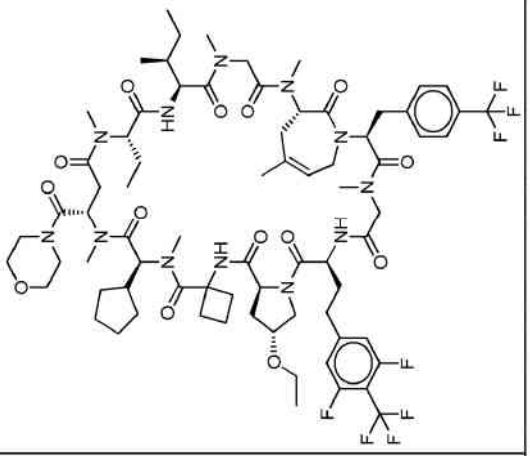
	
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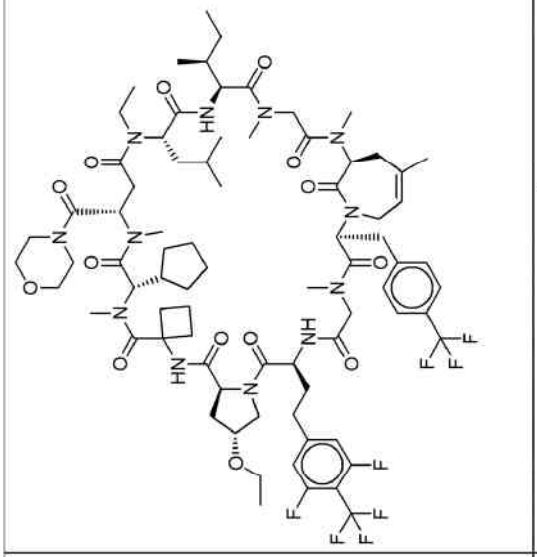
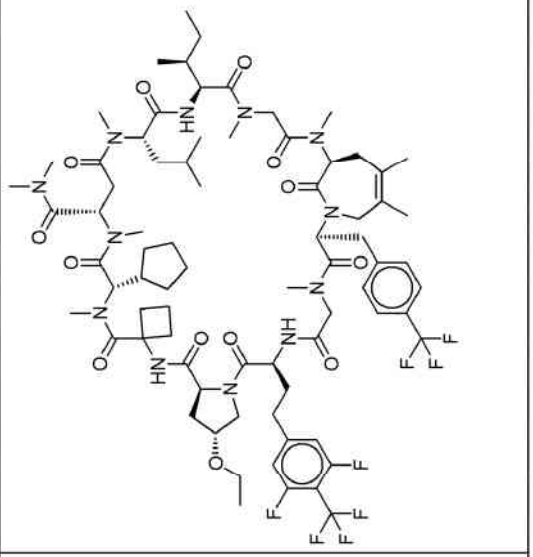
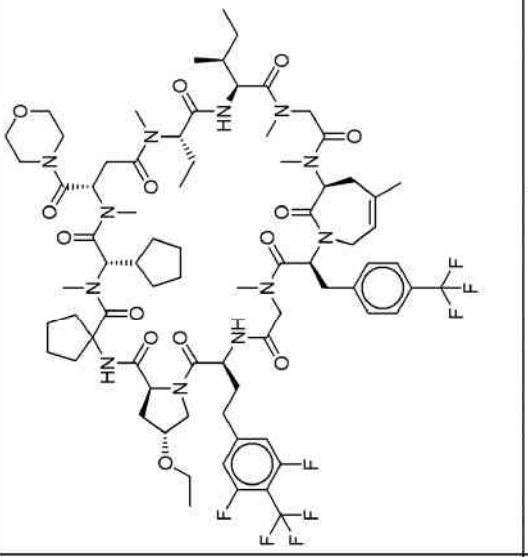
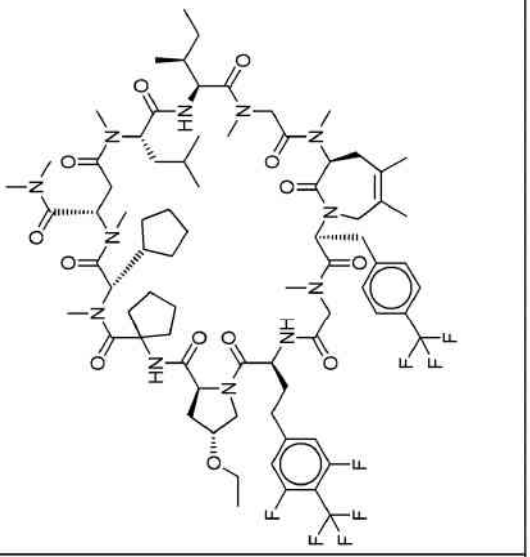
	
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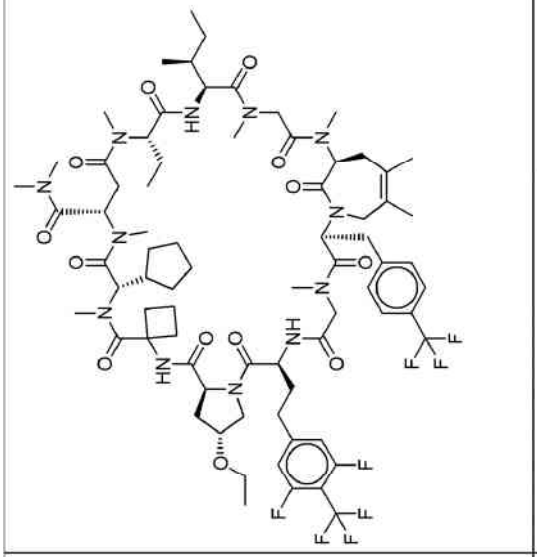
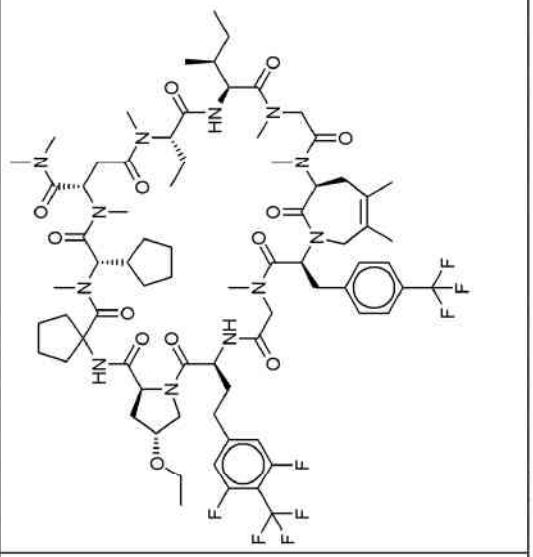
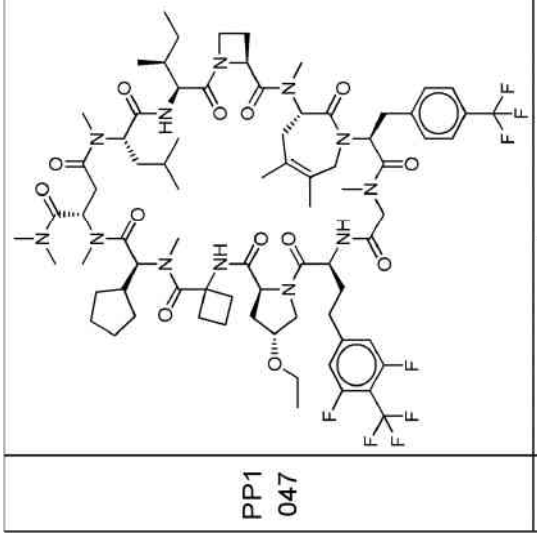
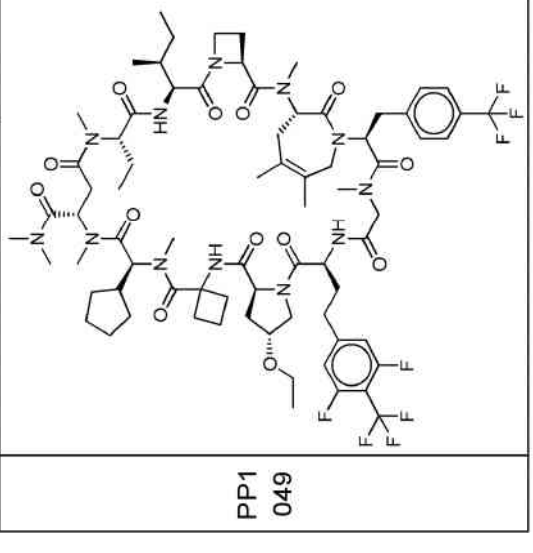
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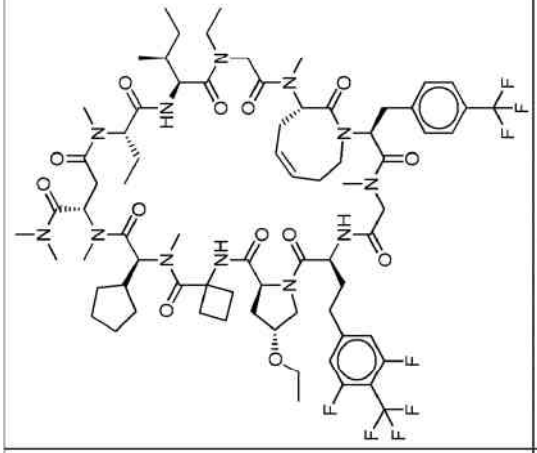
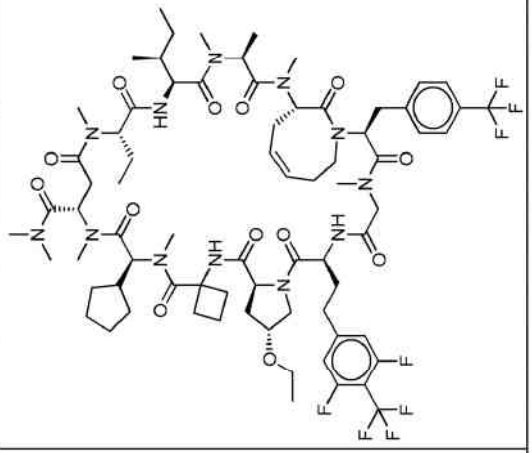
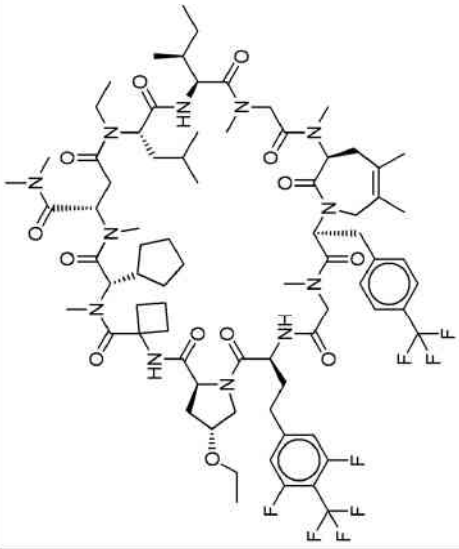
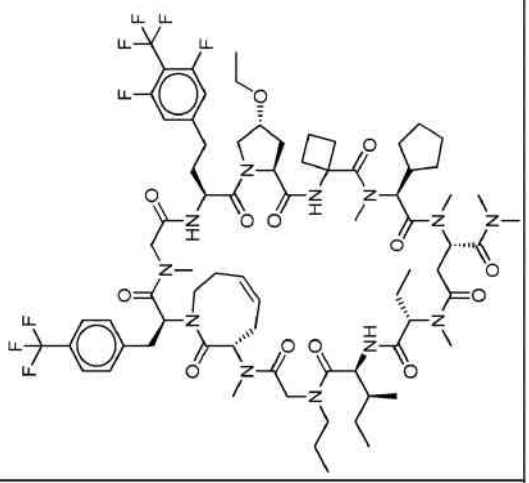
	
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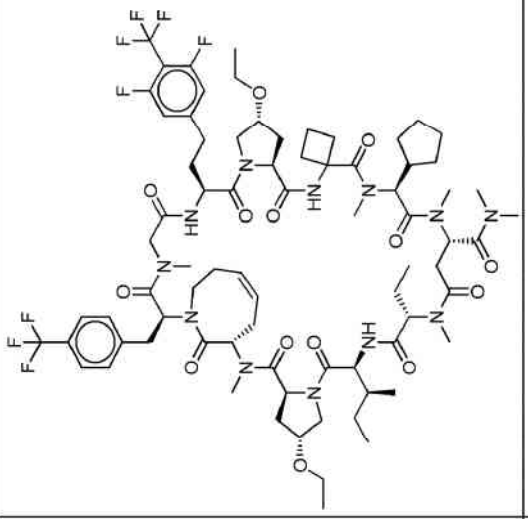
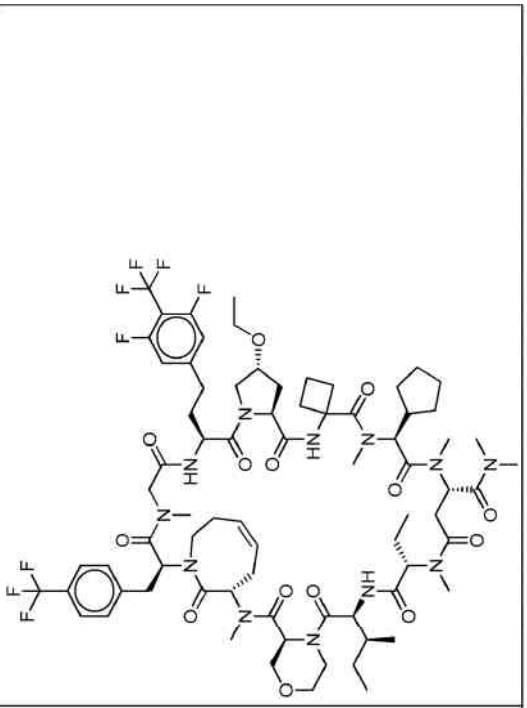
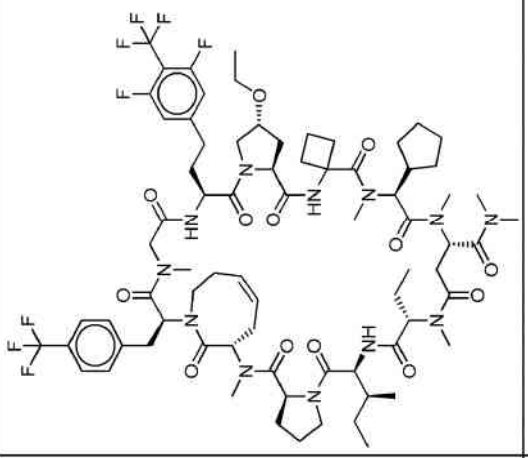
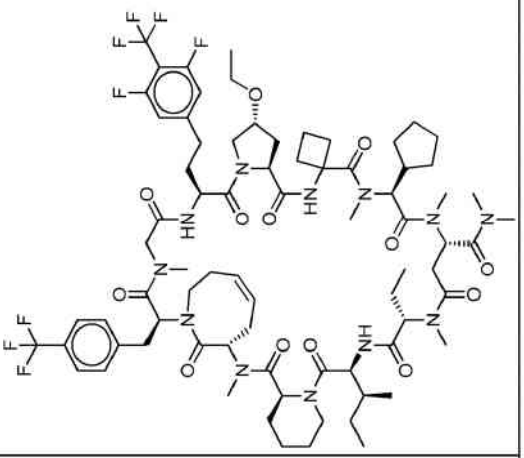
	
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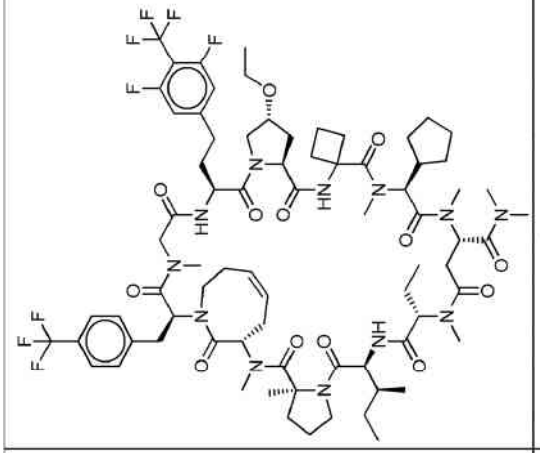
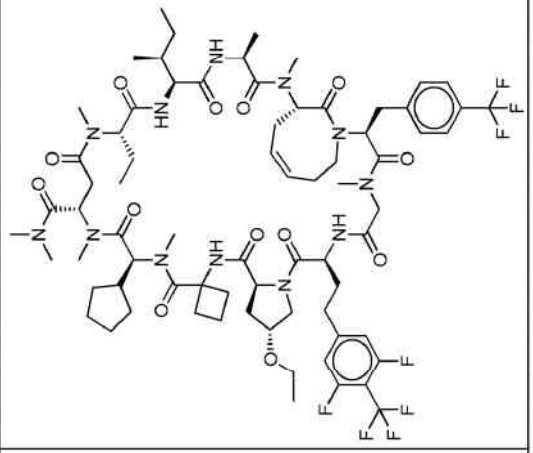
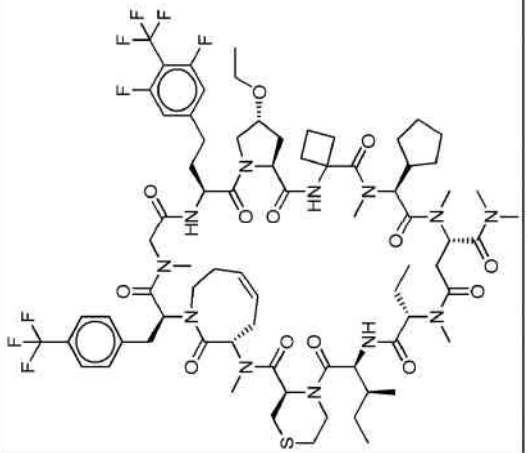
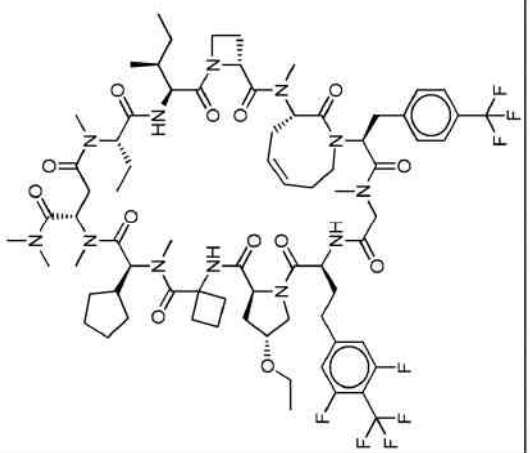
	
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PP1 039	PP1 041

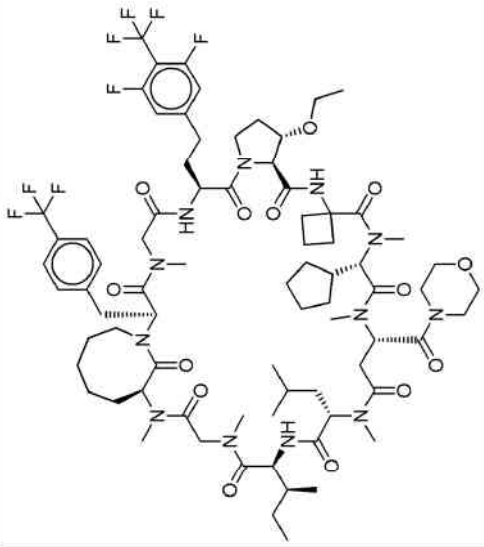
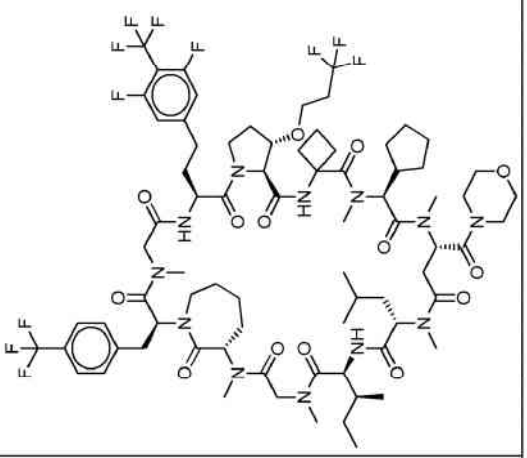
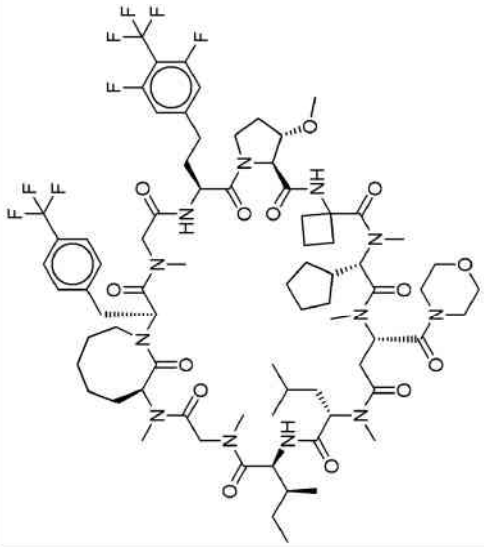
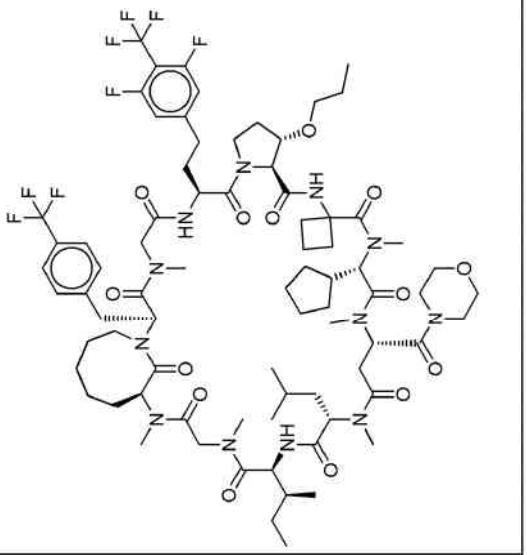
	
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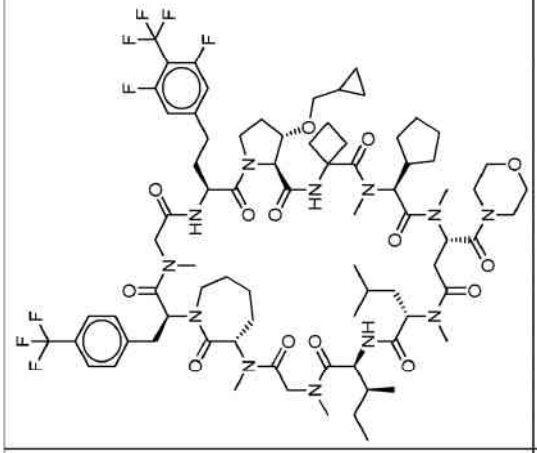
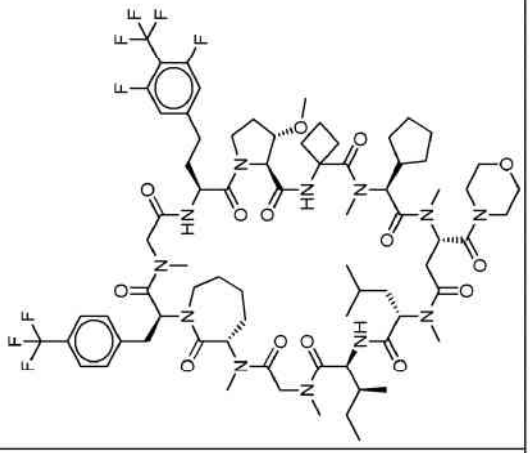
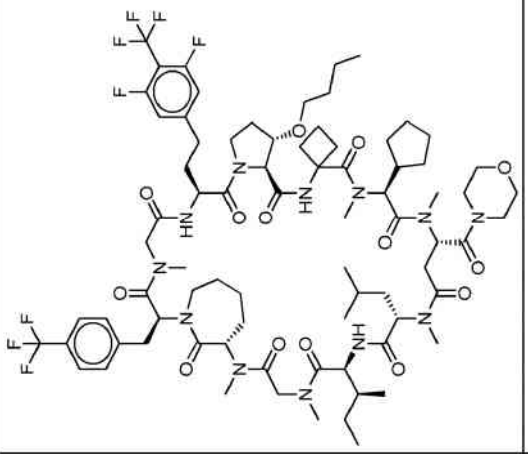
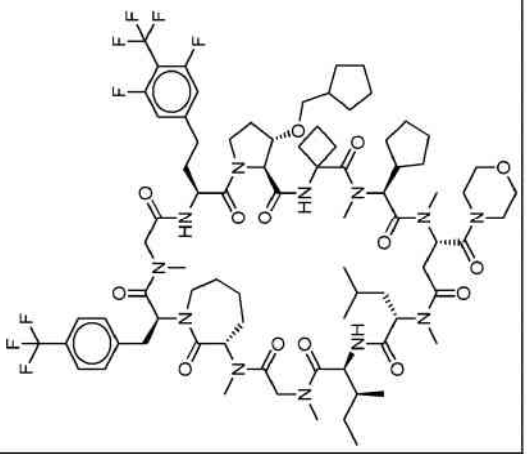
	
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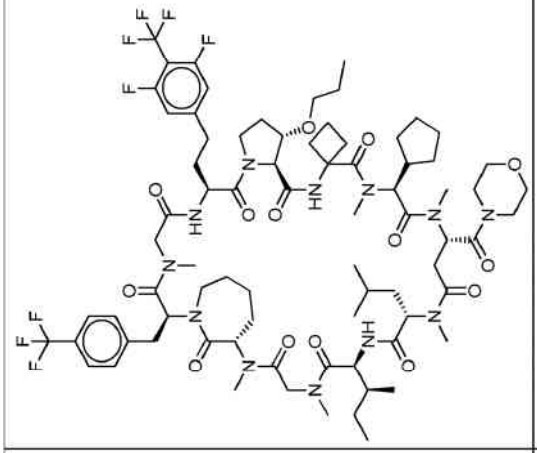
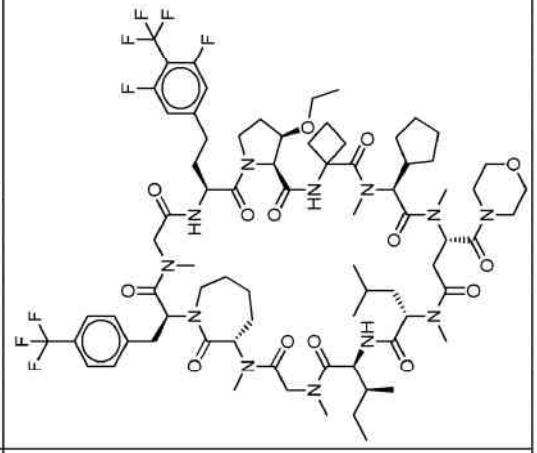
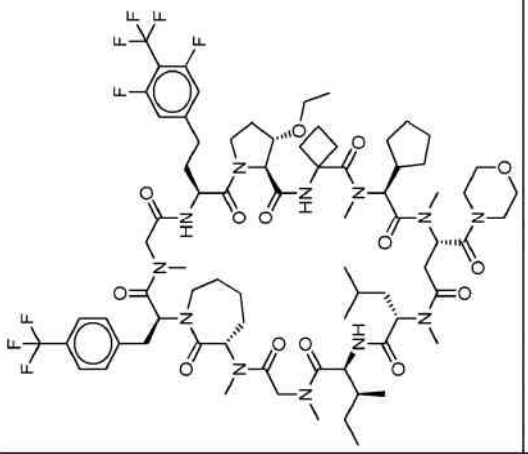
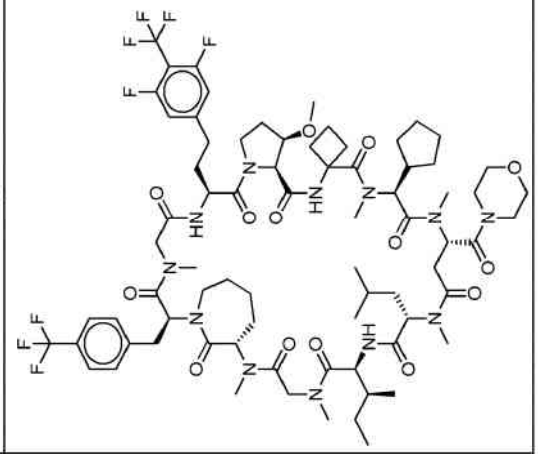
	
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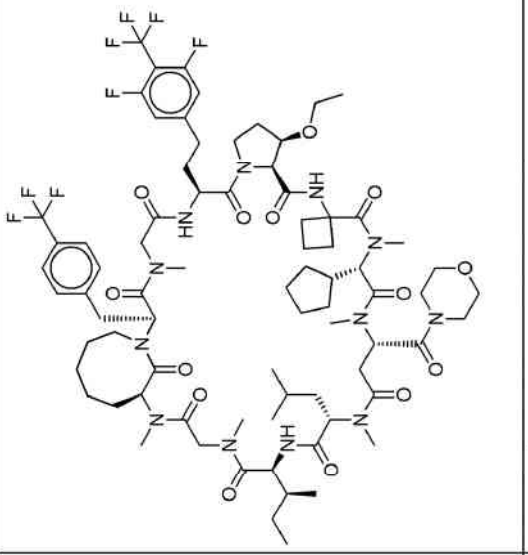
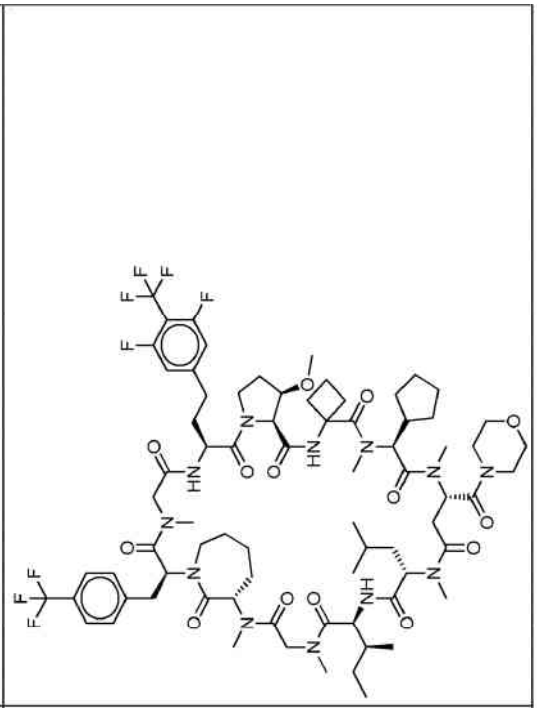
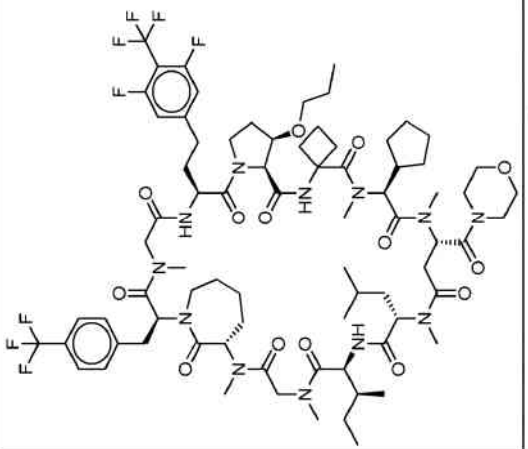
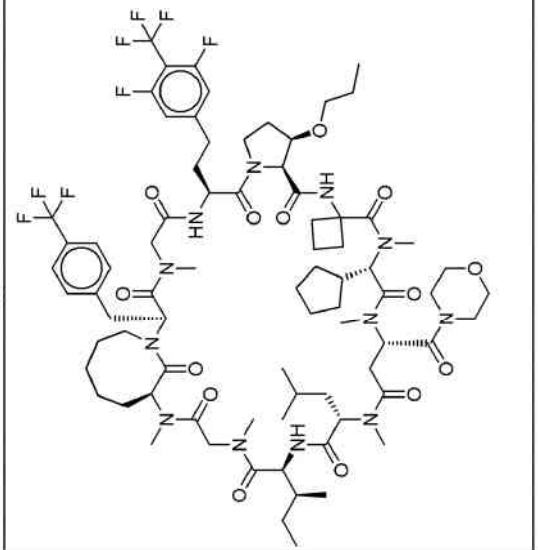
	
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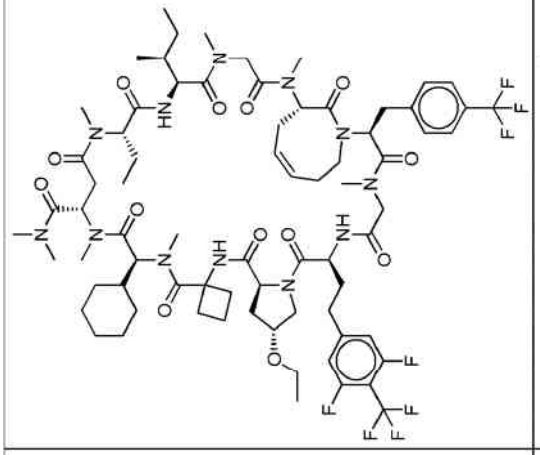
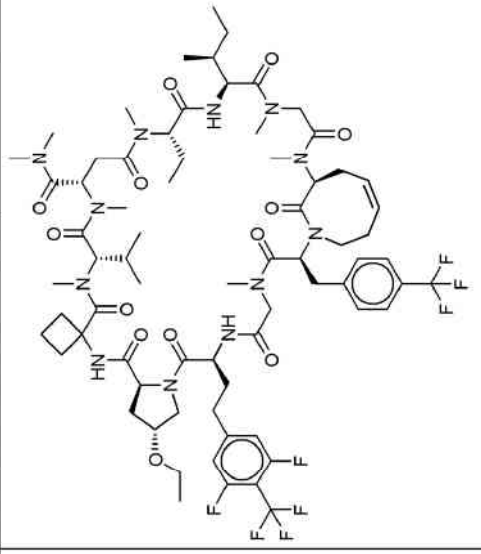
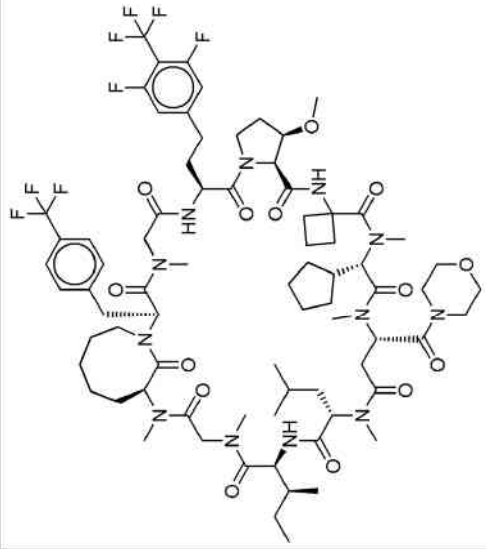
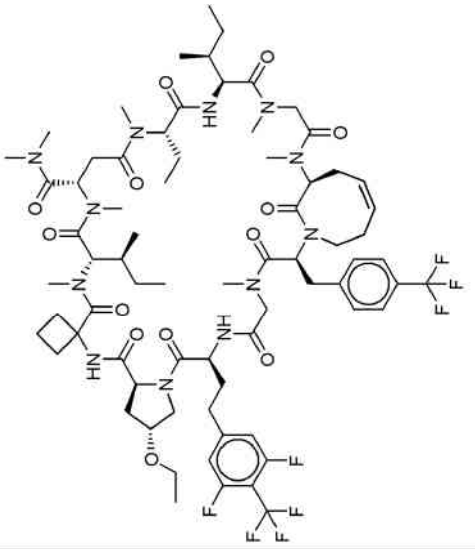
	
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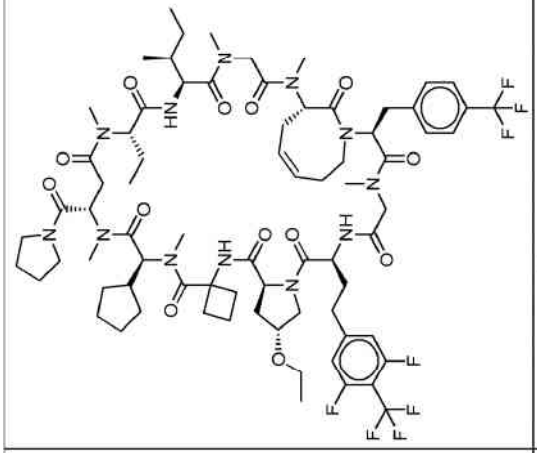
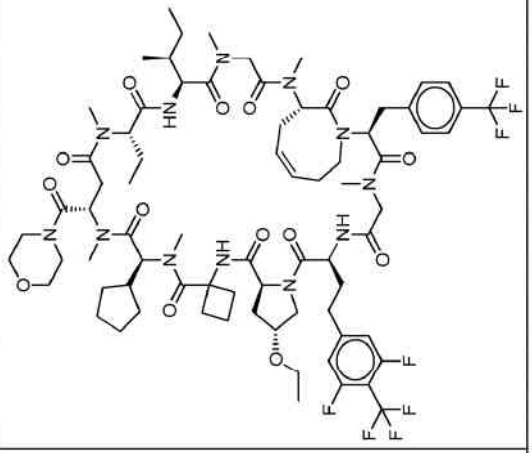
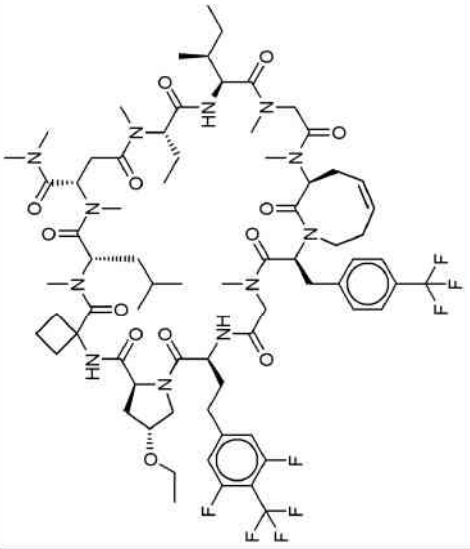
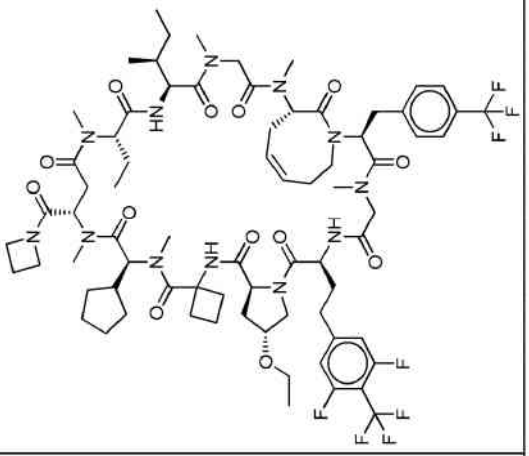
	
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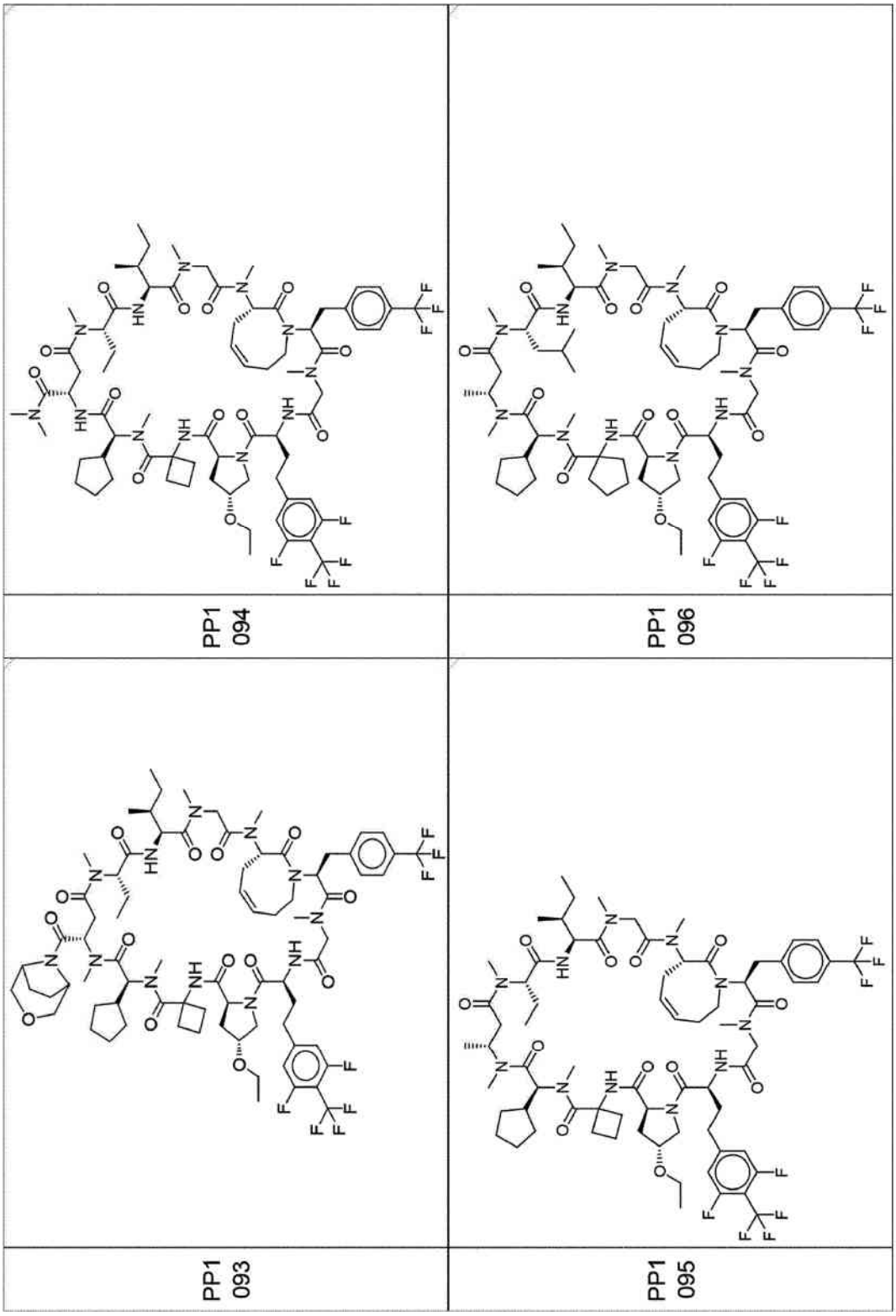
	
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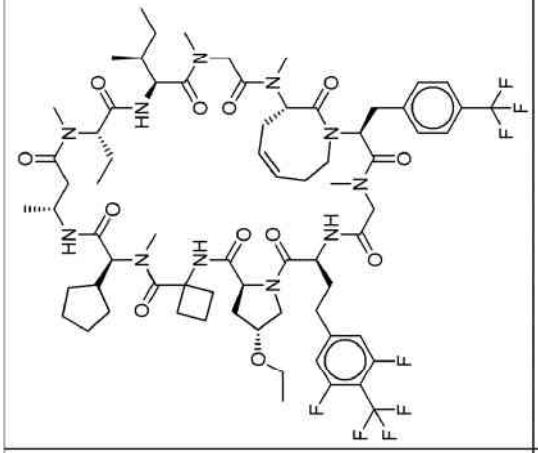
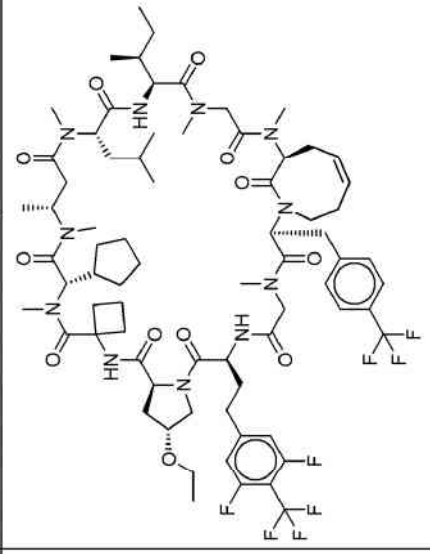
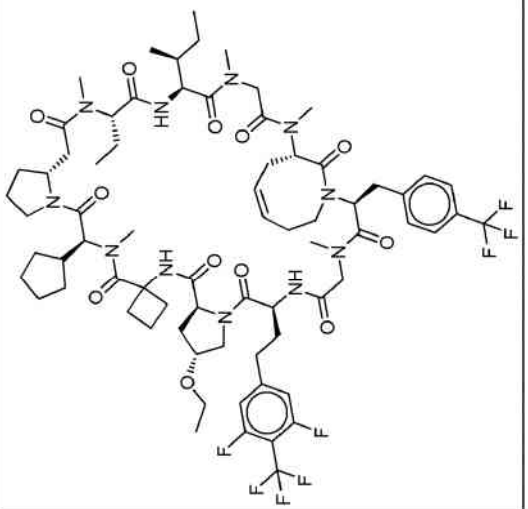
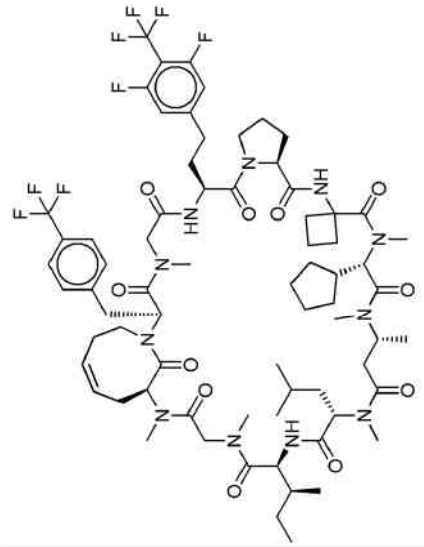
	
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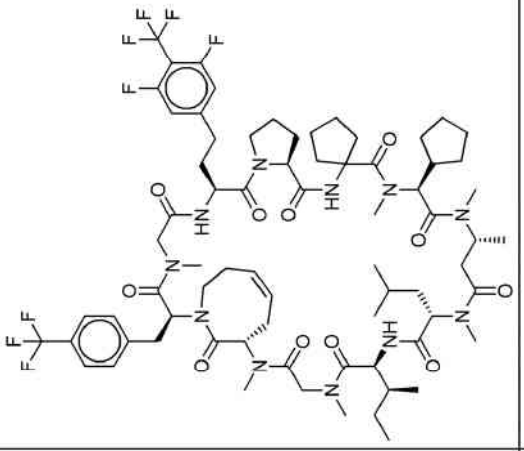
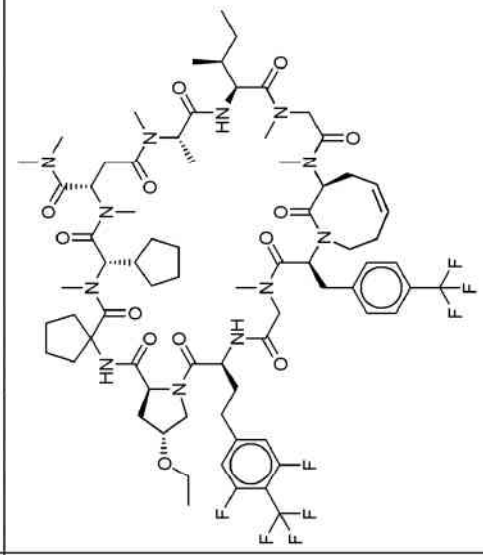
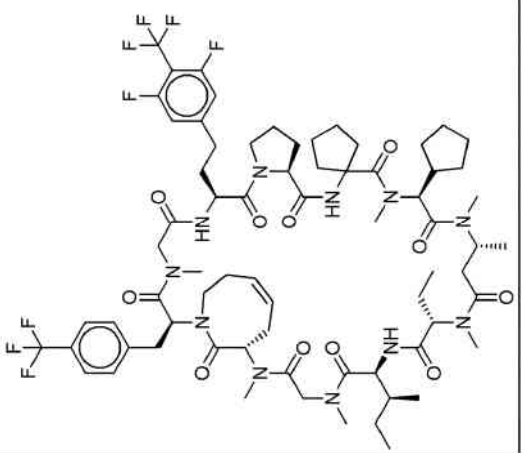
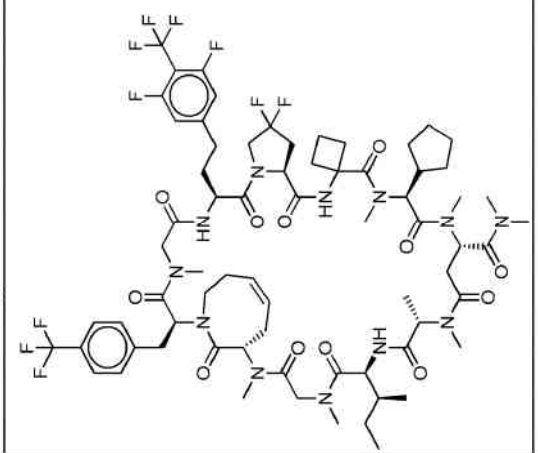
	
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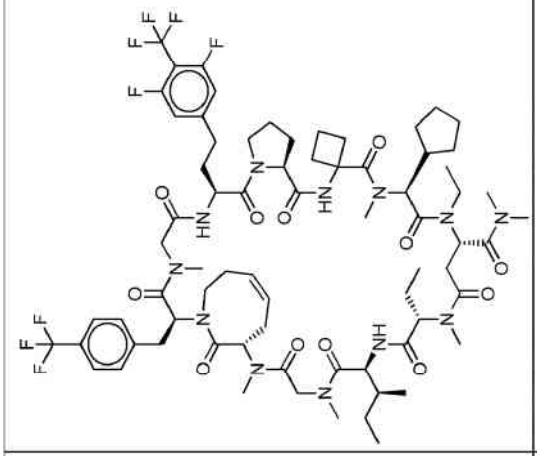
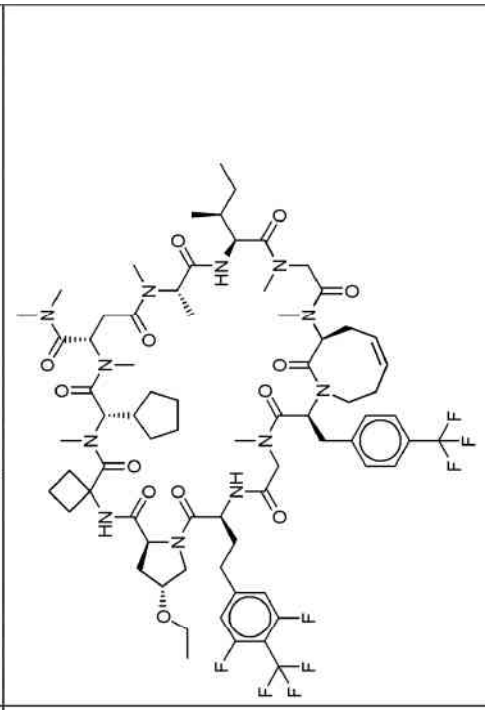
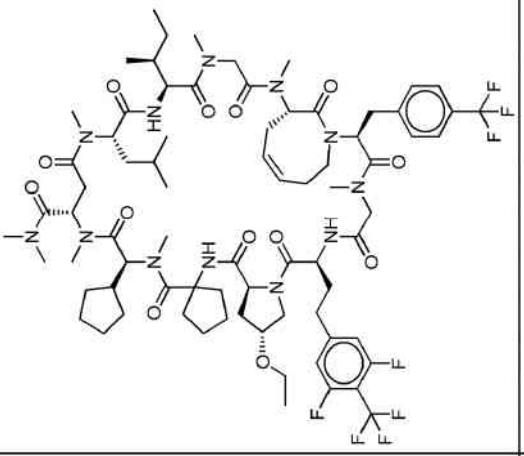
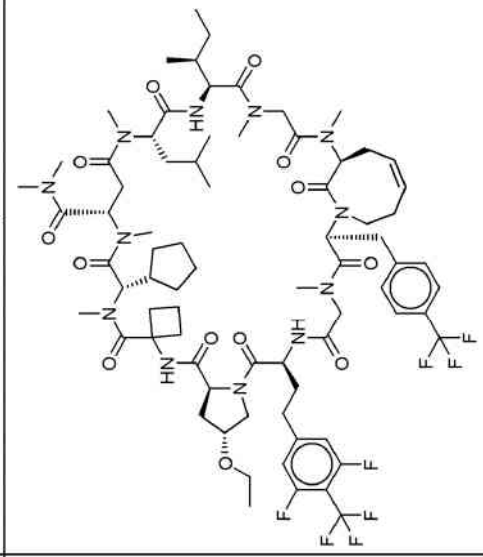
	
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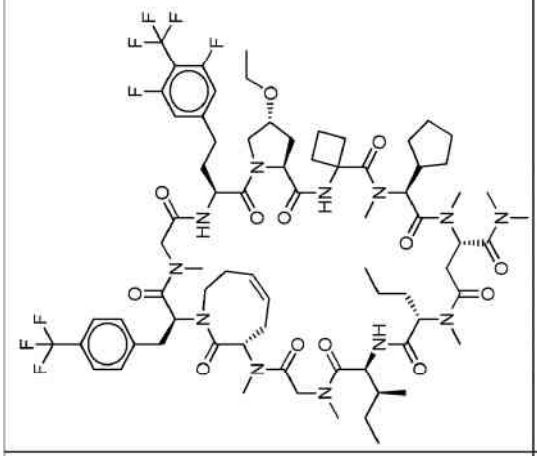
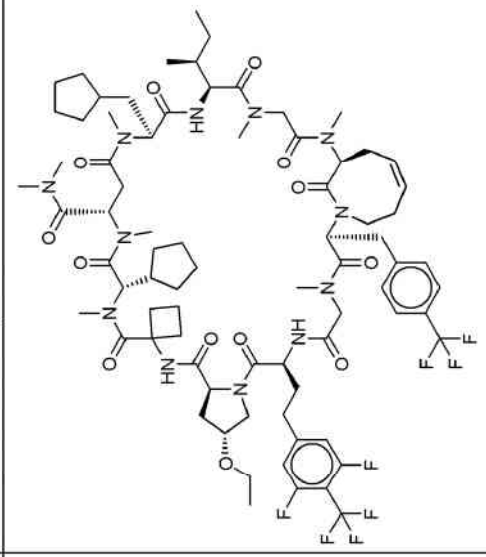
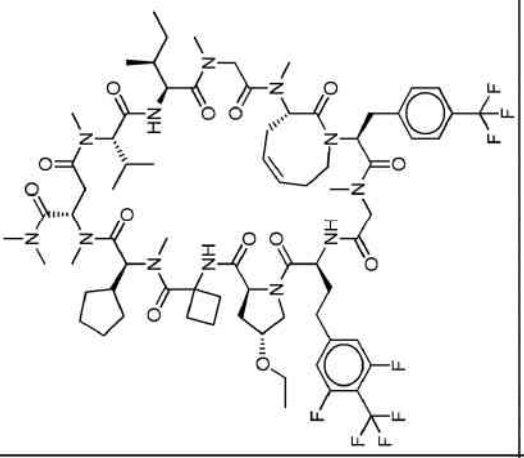
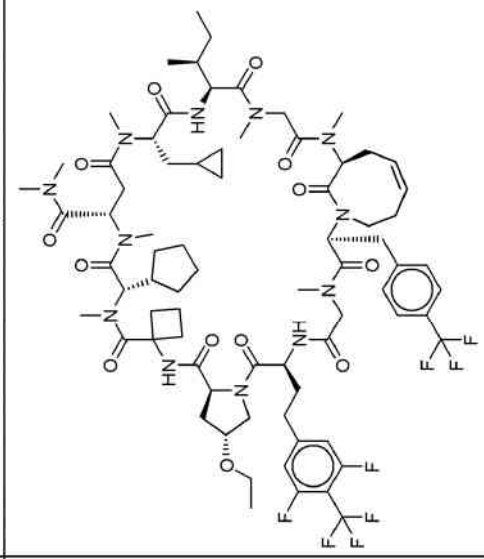
	
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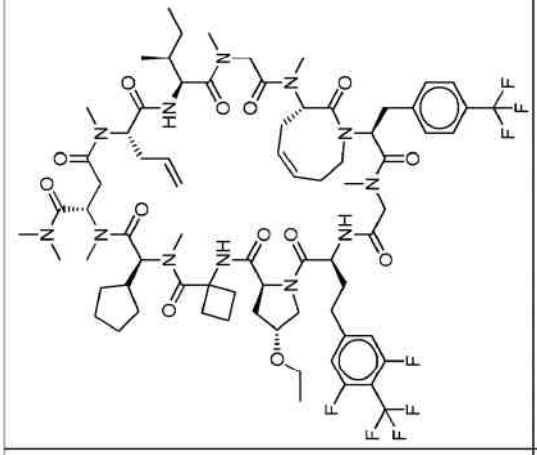
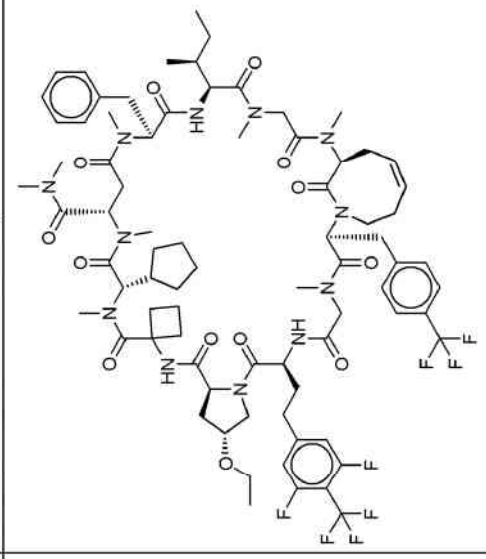
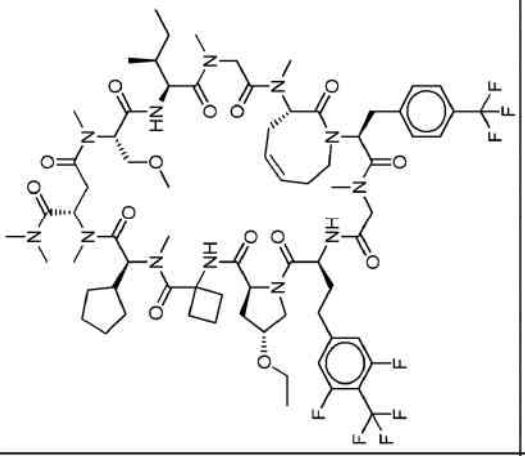
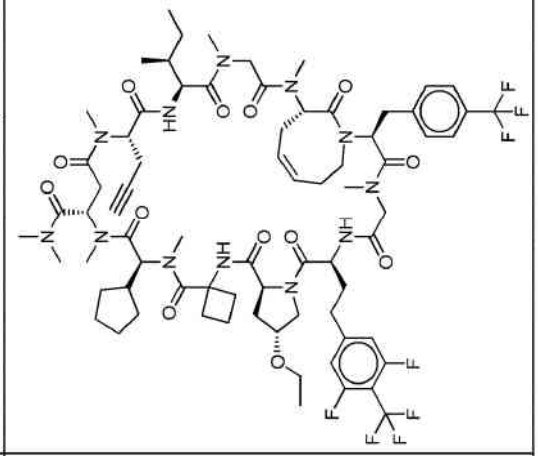

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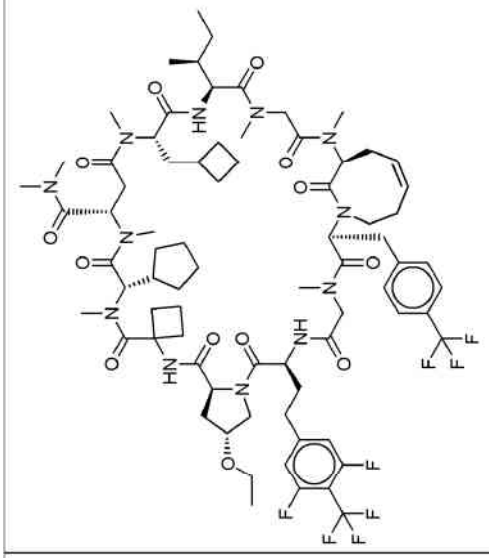
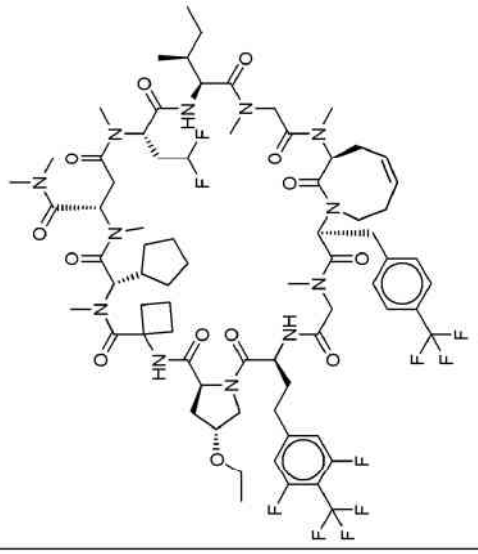
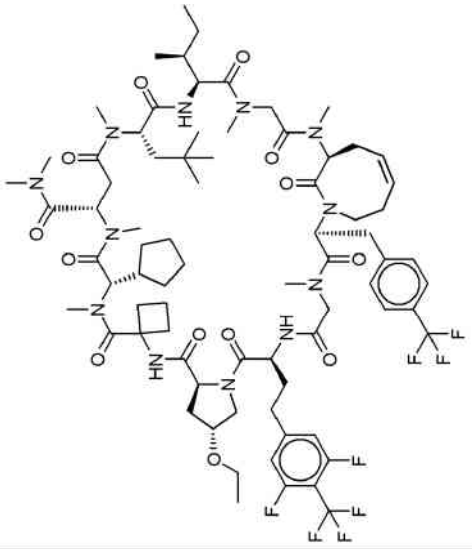
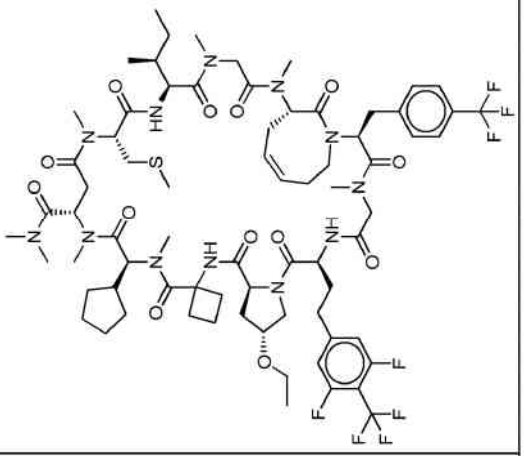
	
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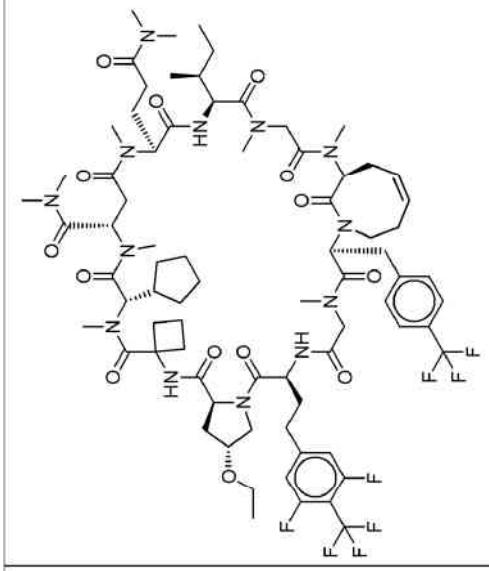
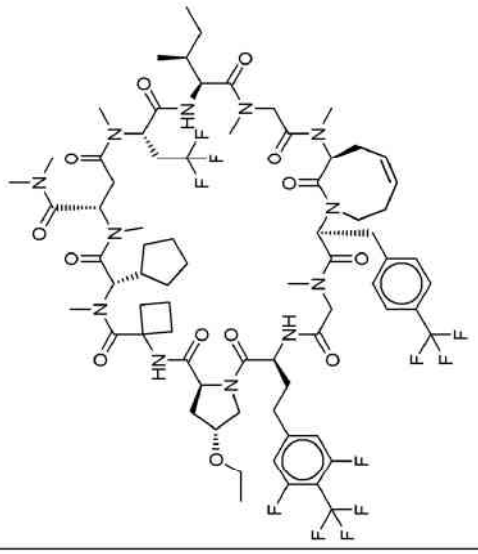
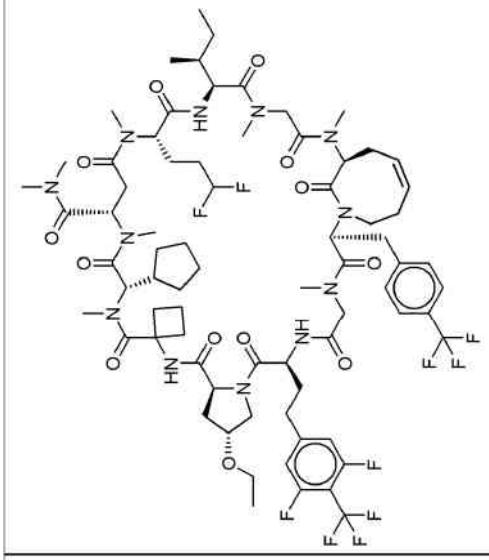
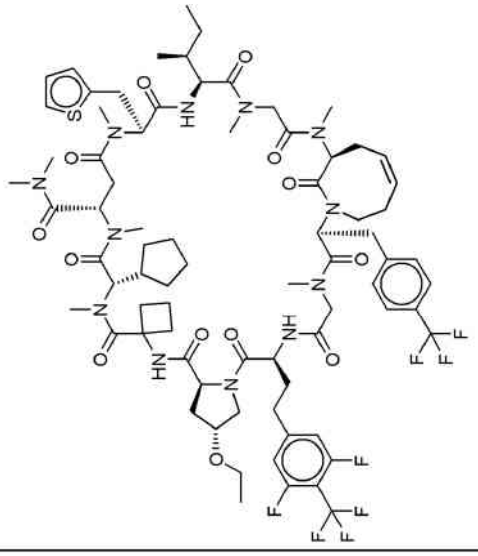
	
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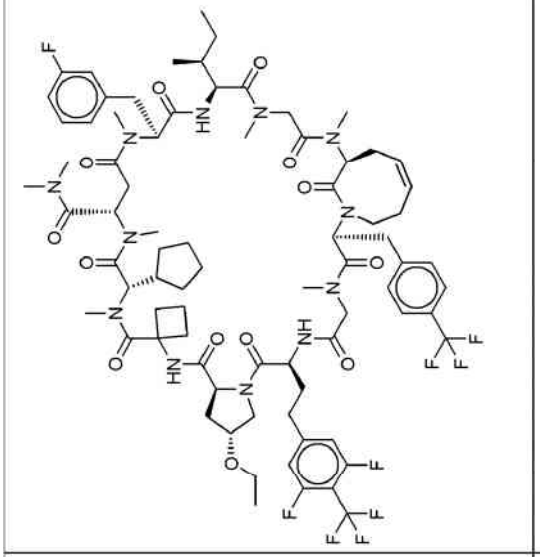
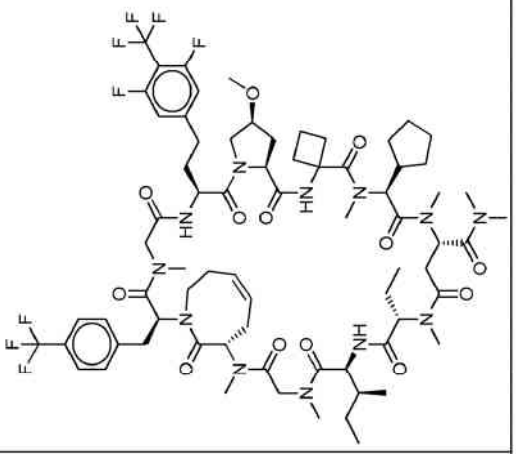
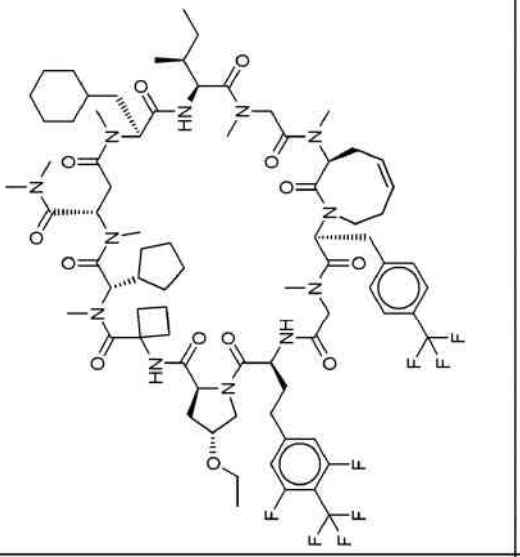
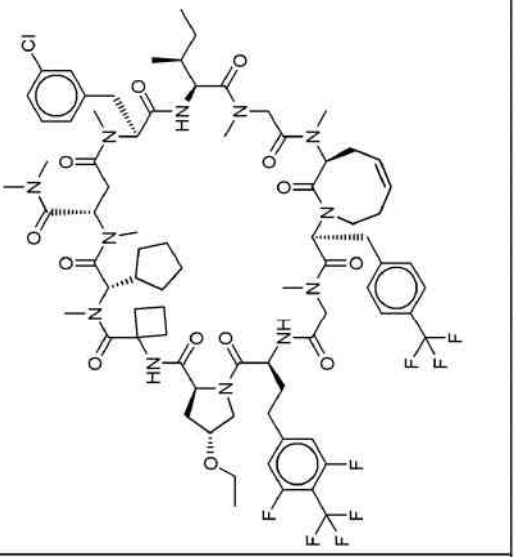
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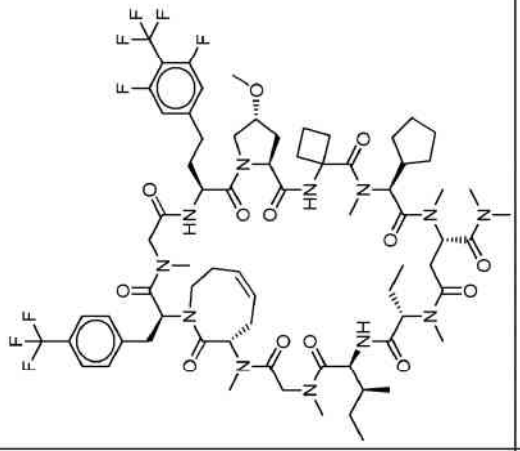
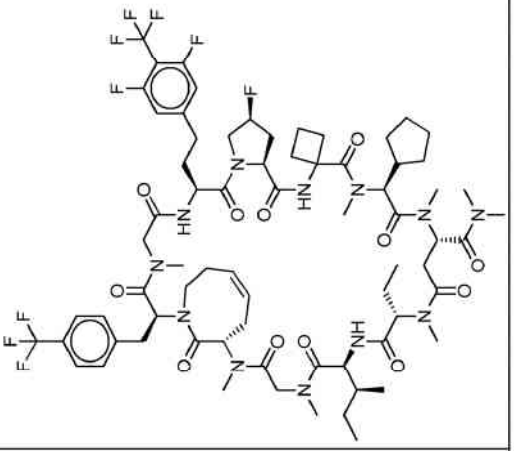
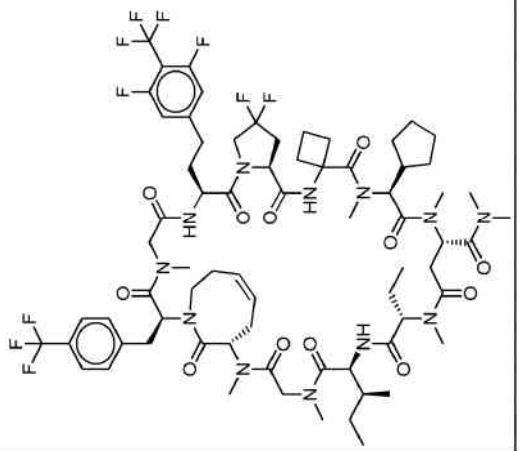
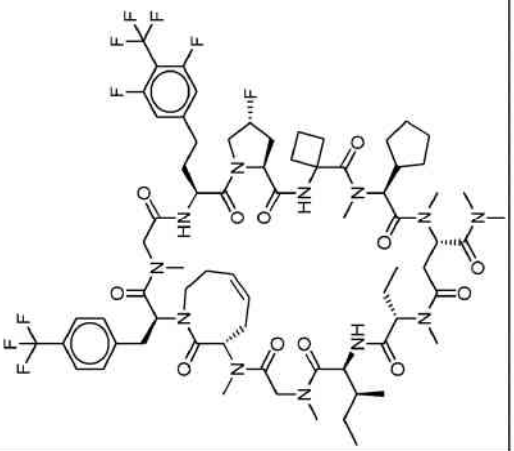
	
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PP1 109	PP1 111

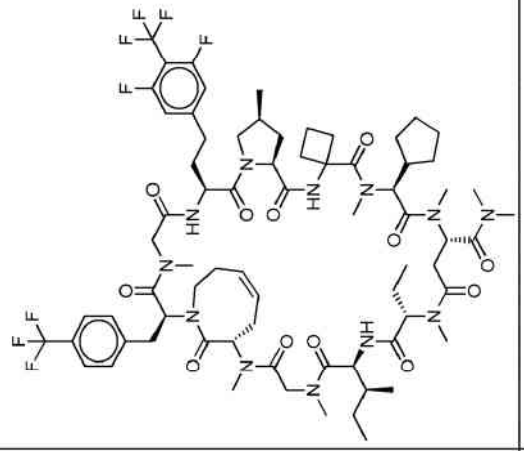
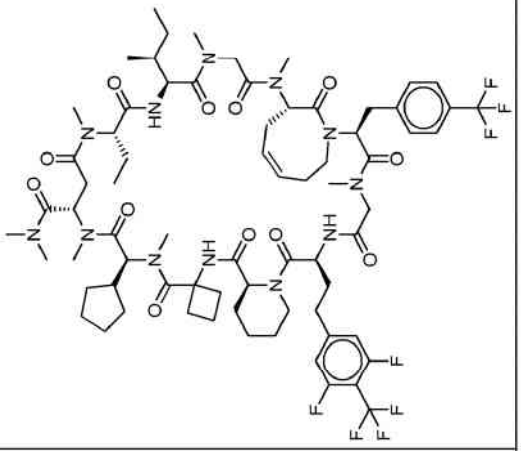
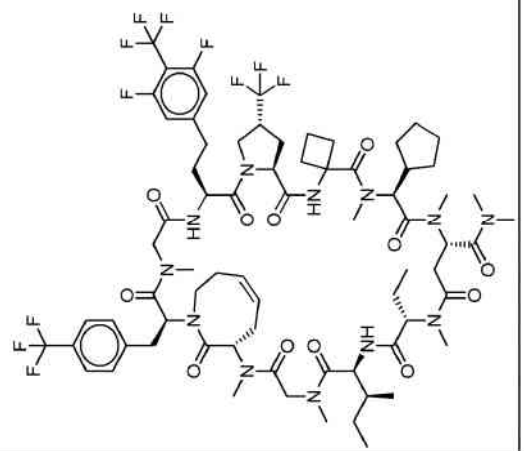
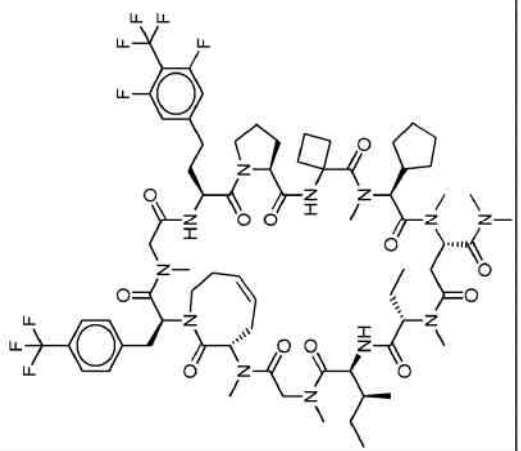
	
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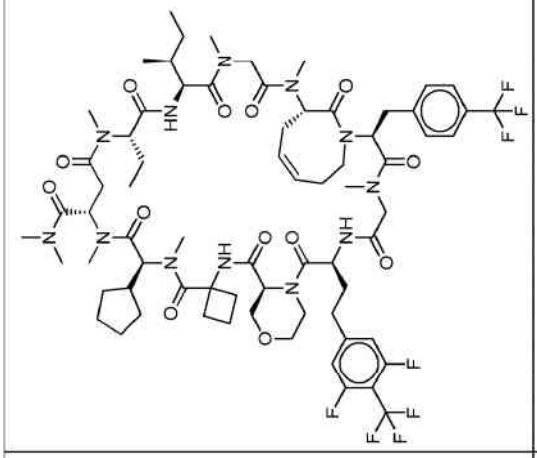
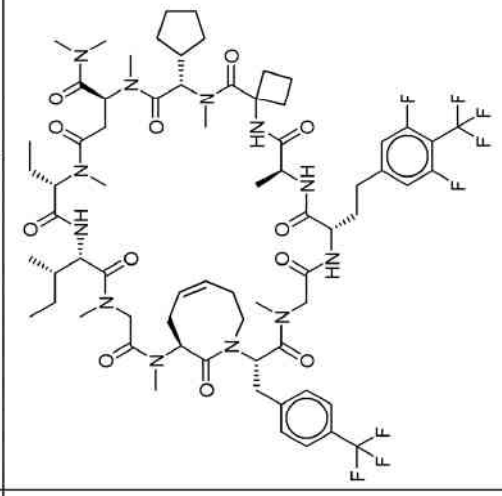
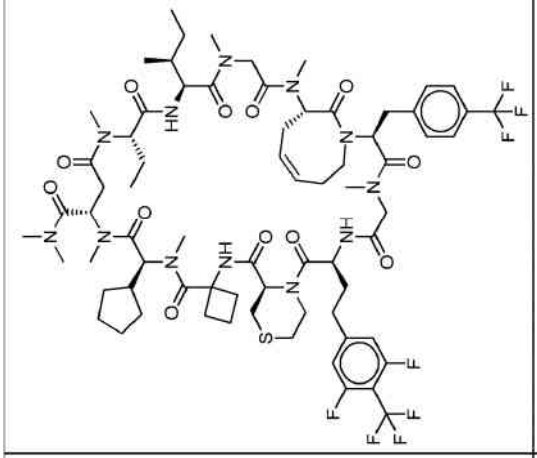
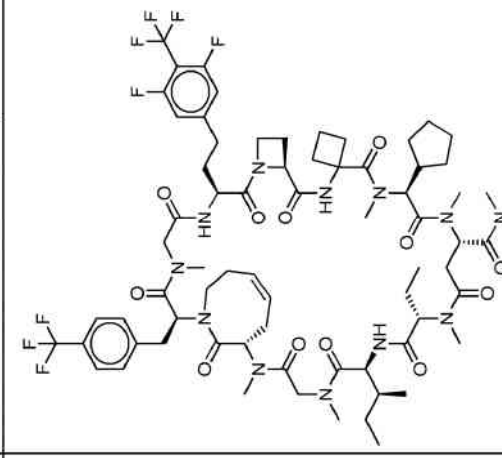
	
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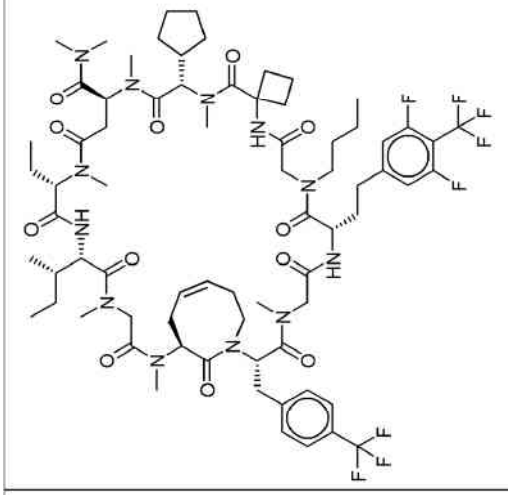
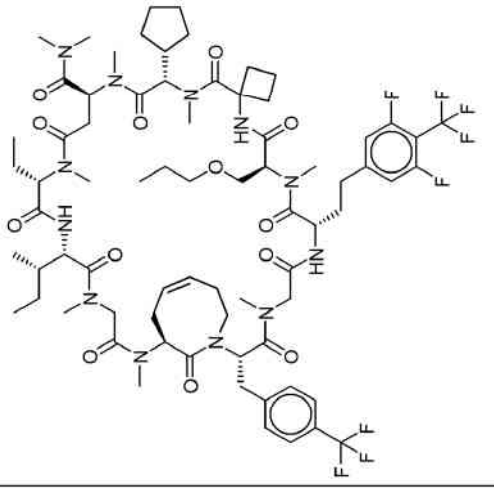
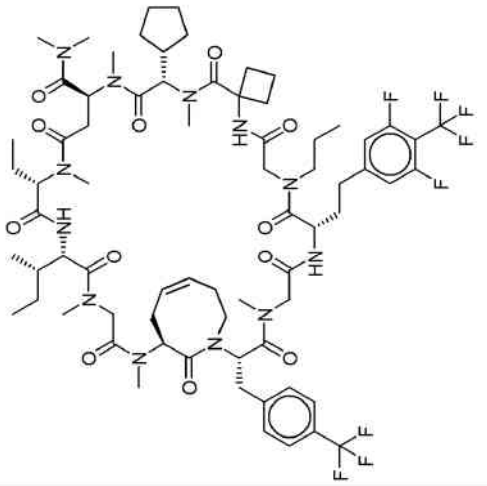
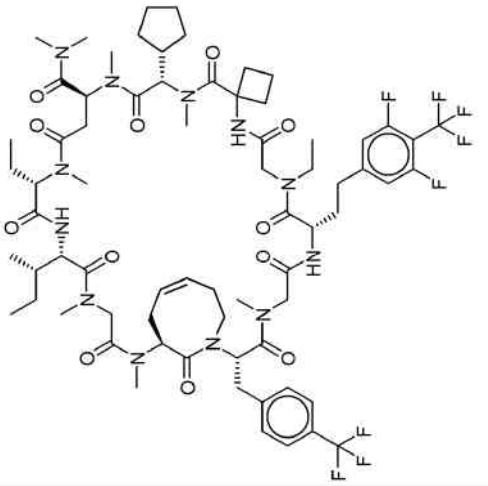
	
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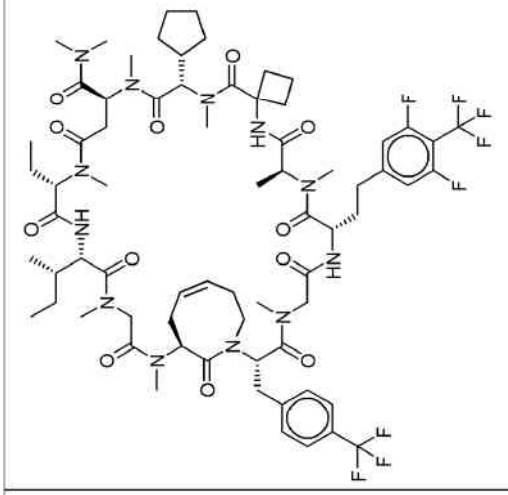
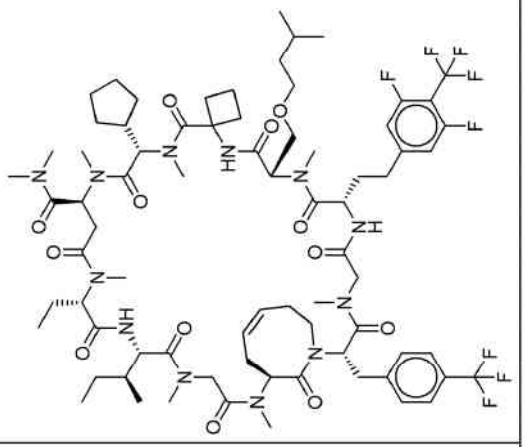
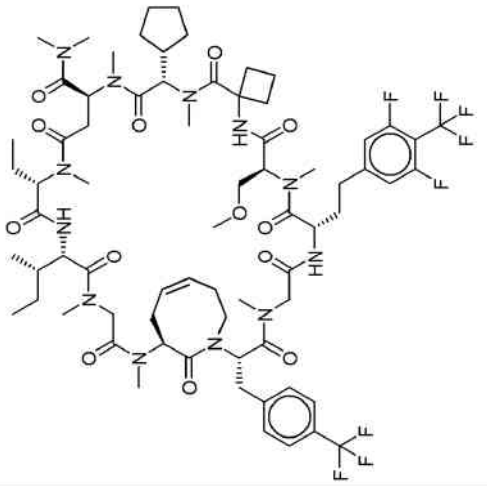
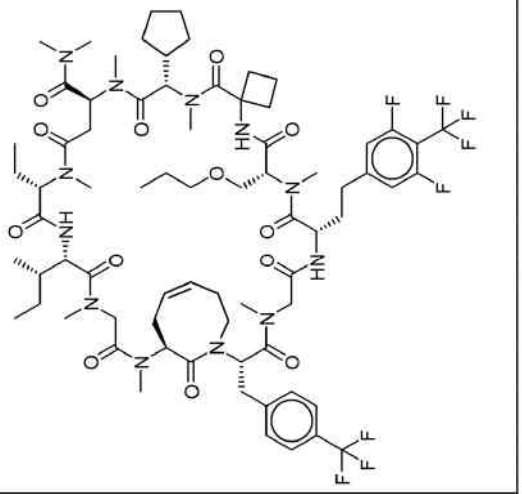
	
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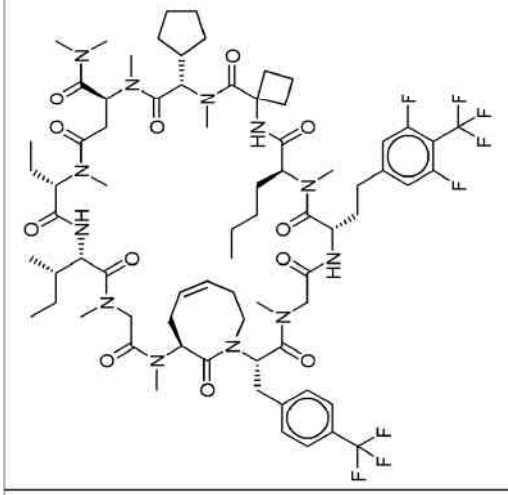
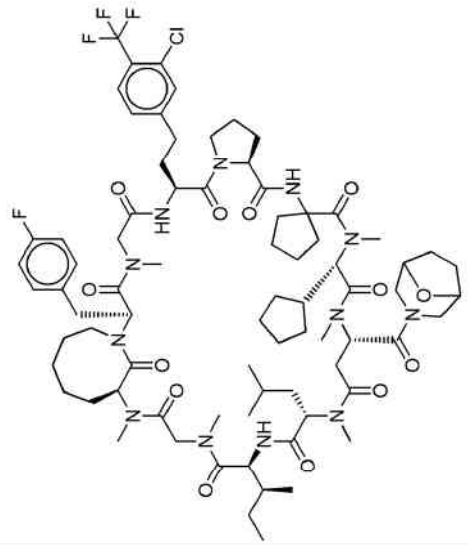
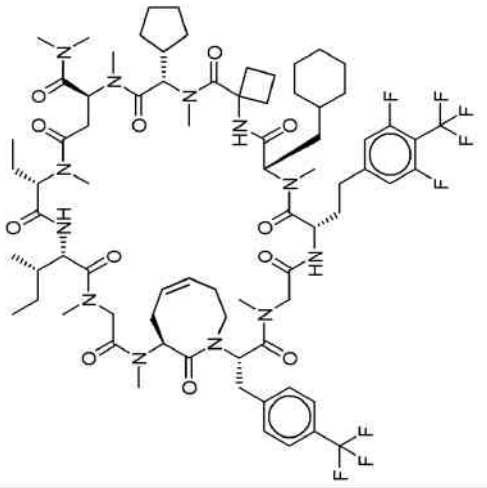
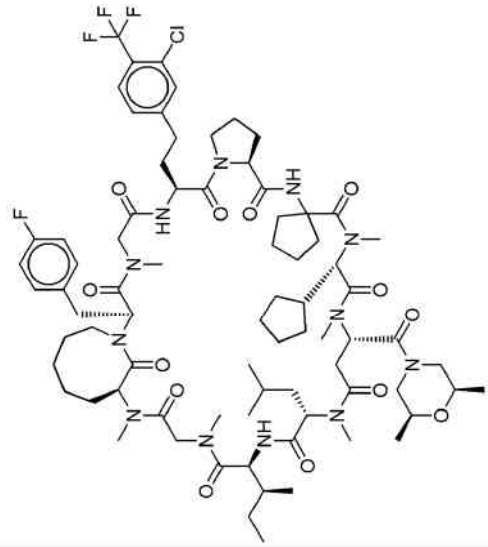
	
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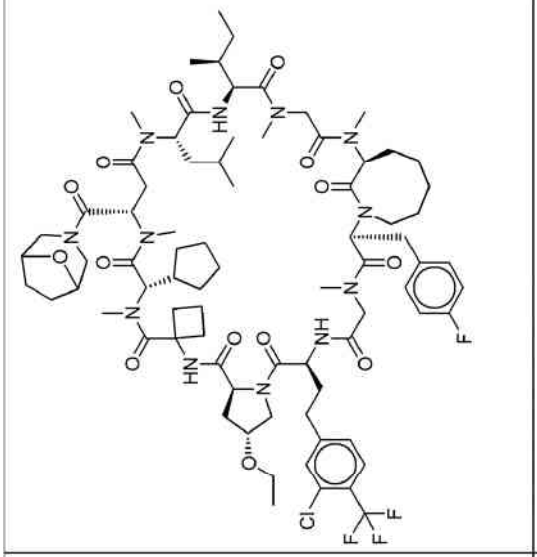
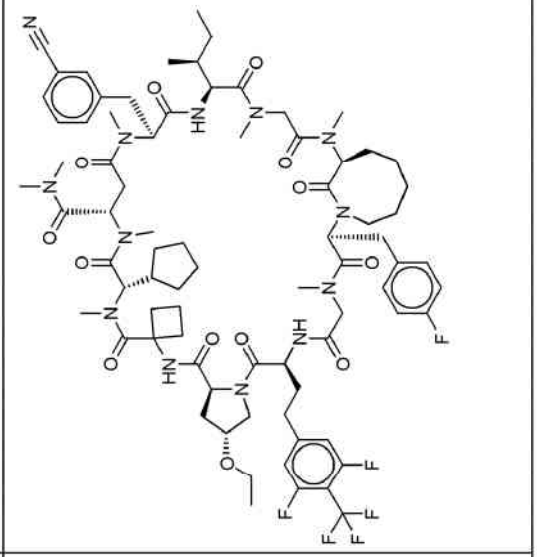
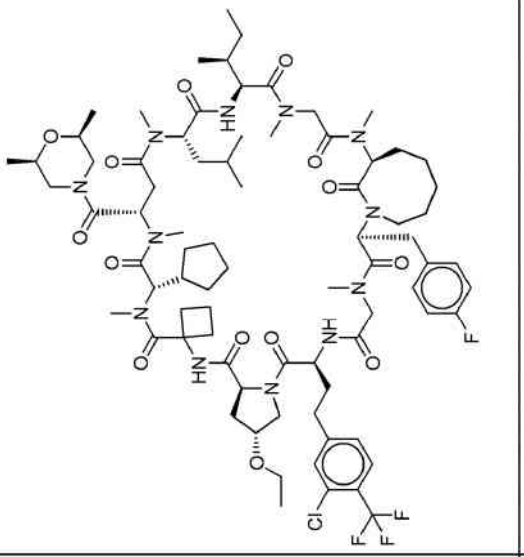
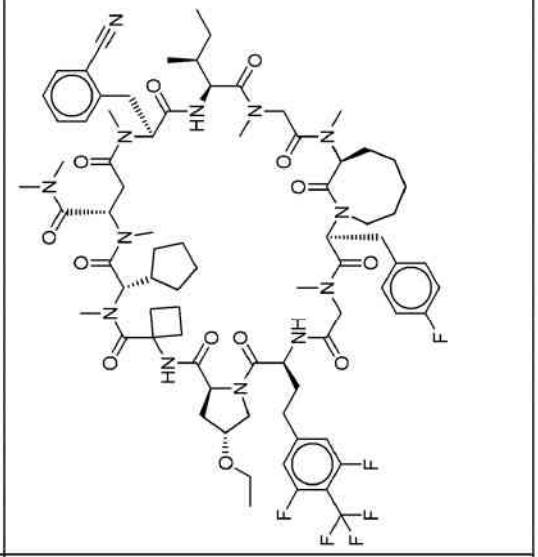
	
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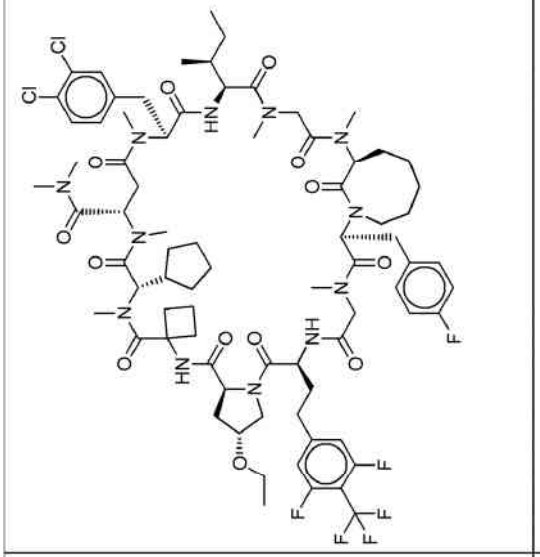
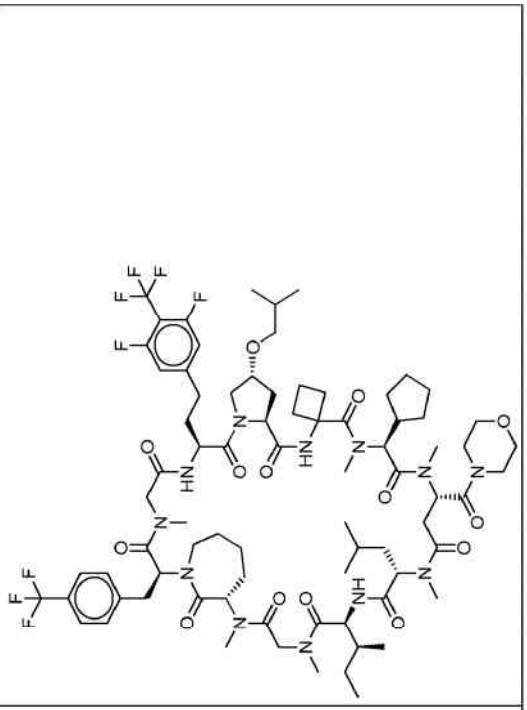
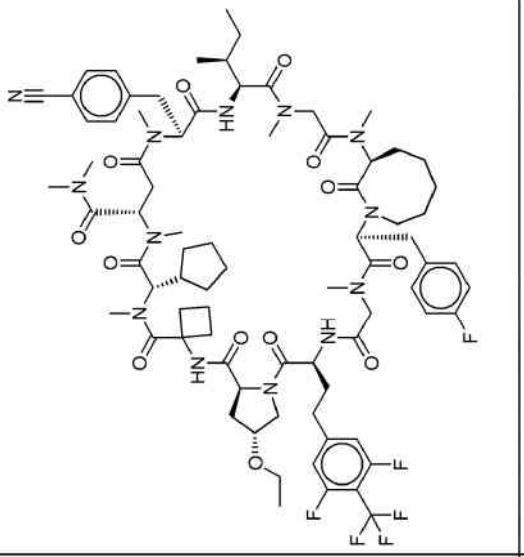
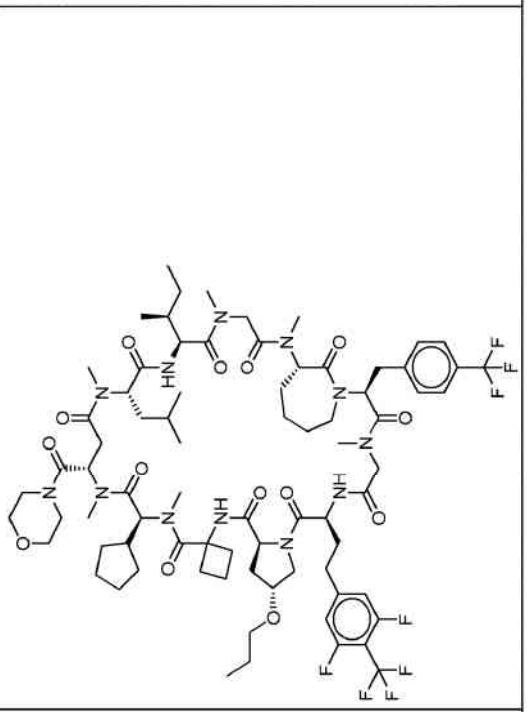
	
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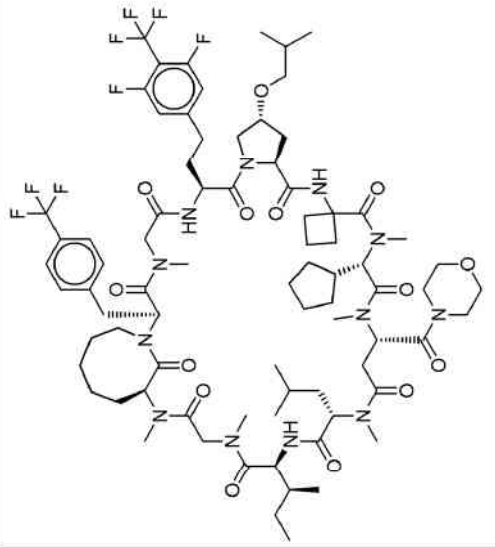
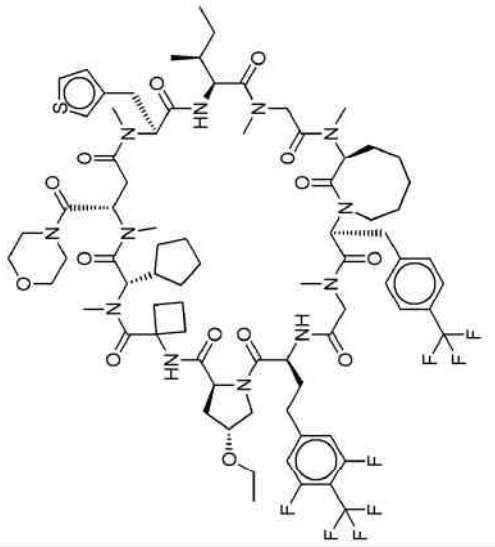
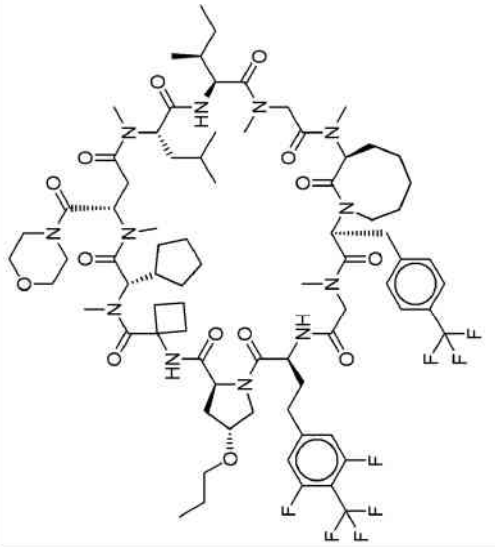
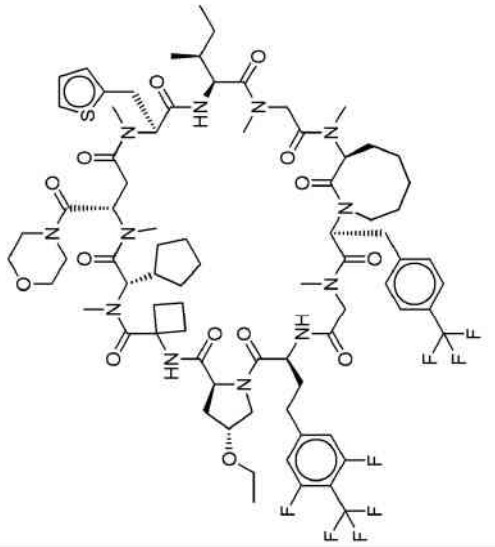
	
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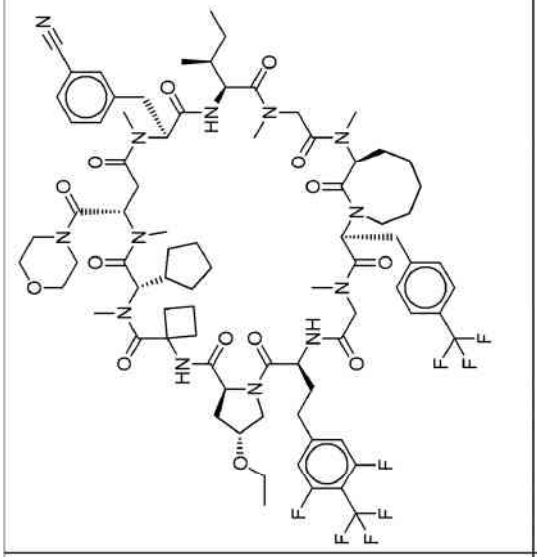
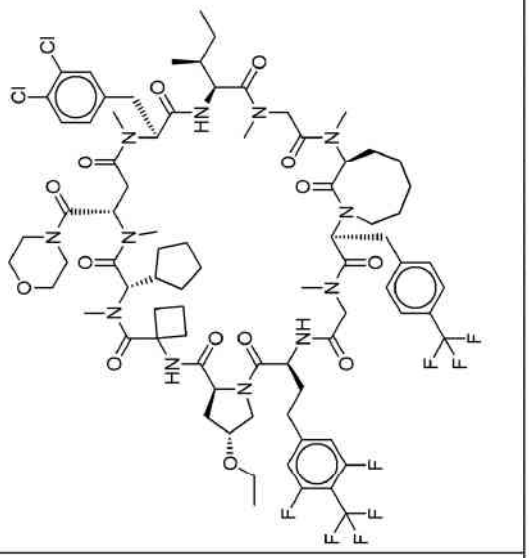
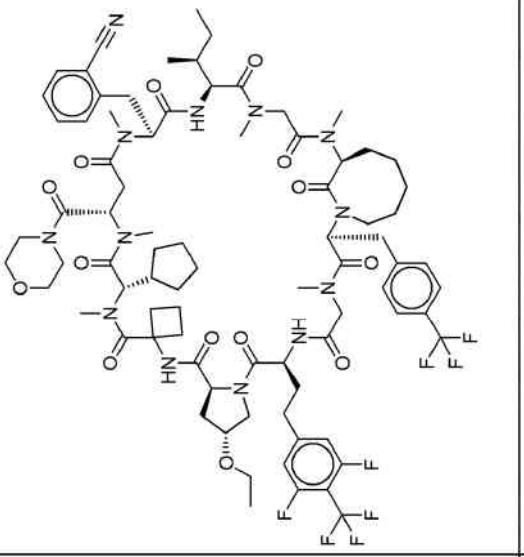
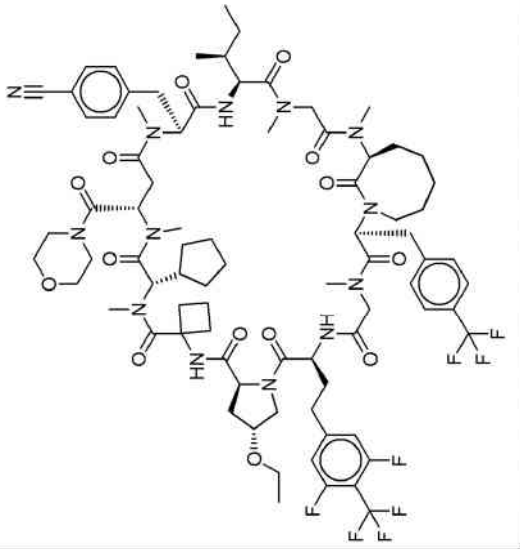
	
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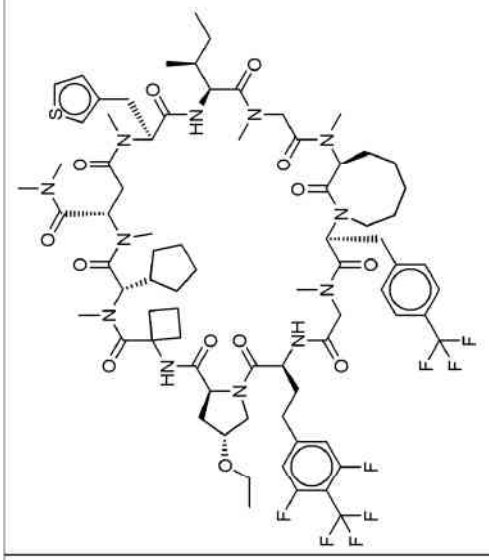
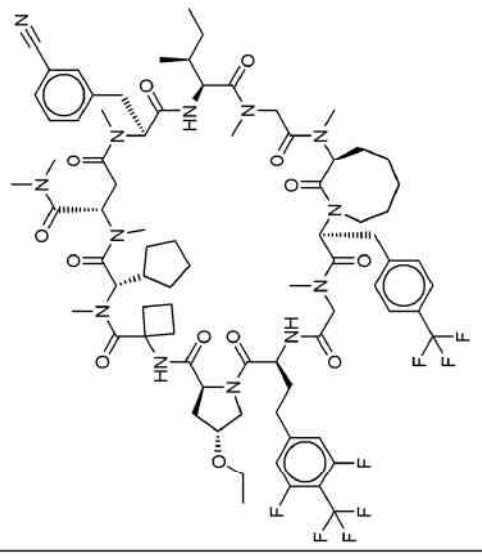
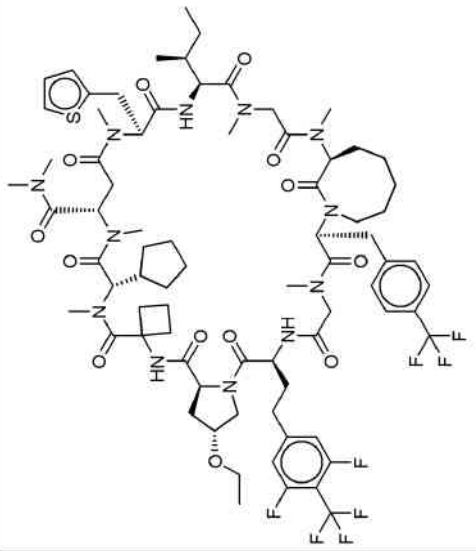
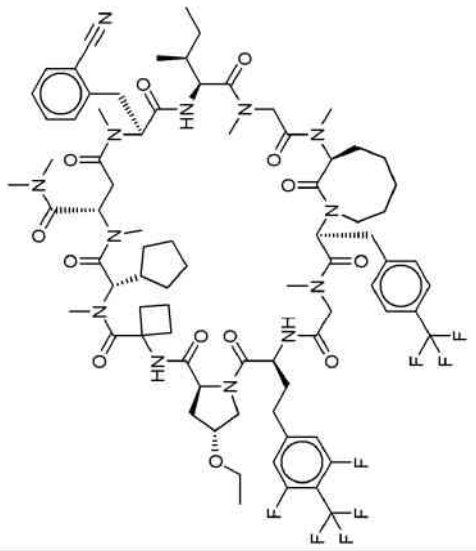
	
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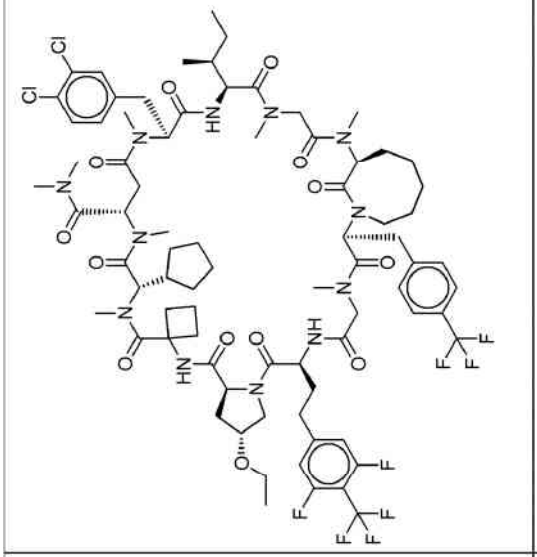
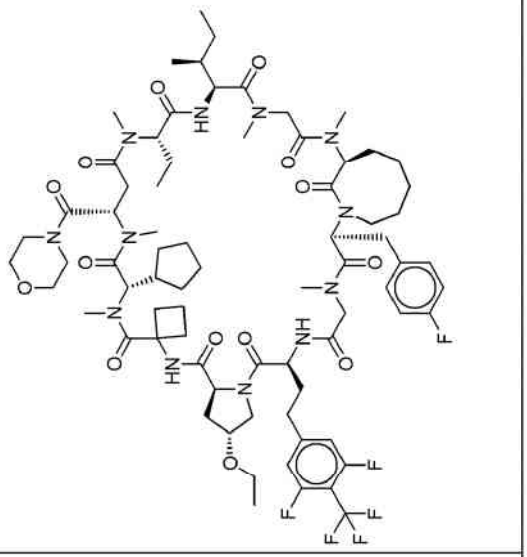
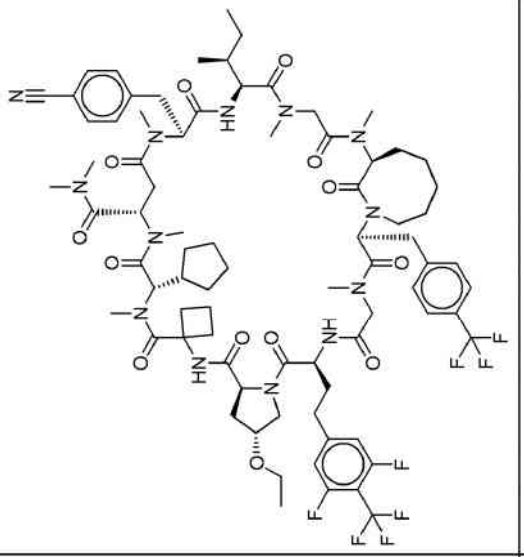
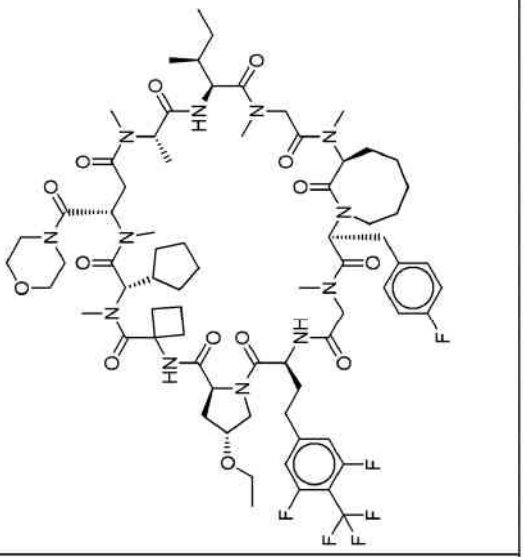
	
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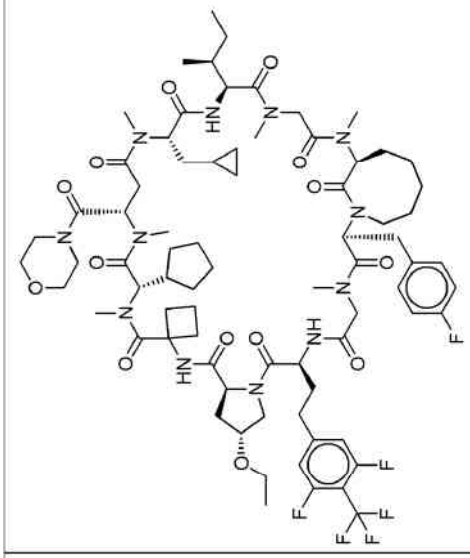
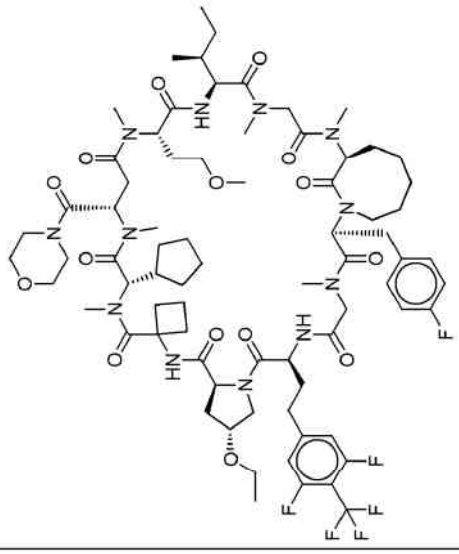
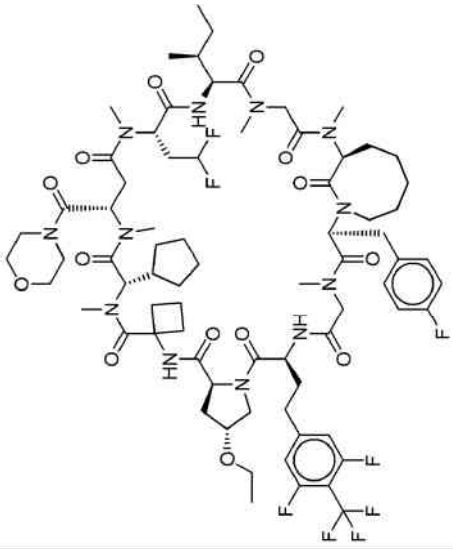
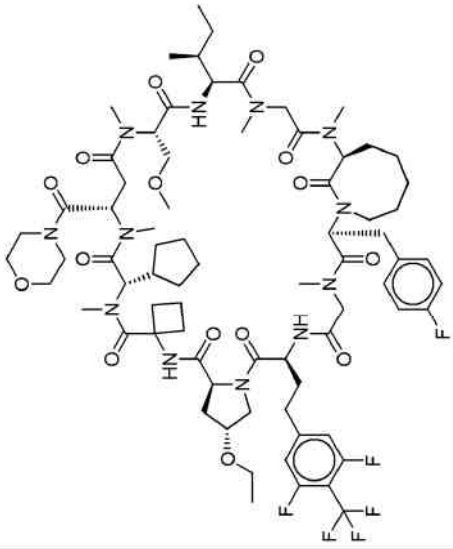
	
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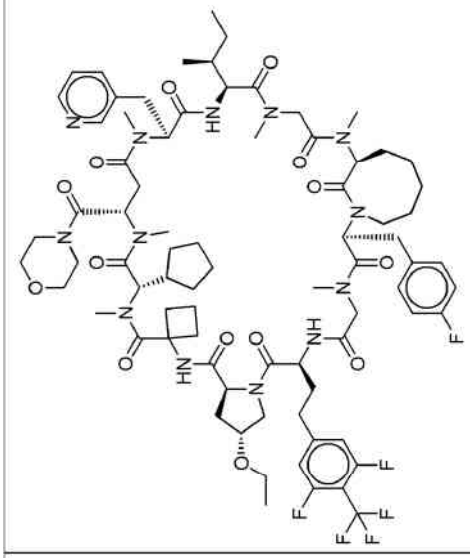
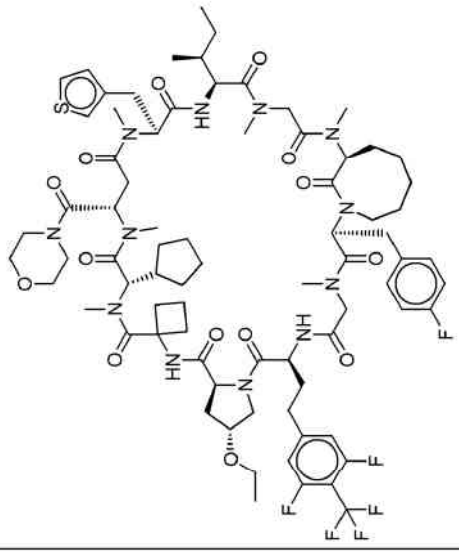
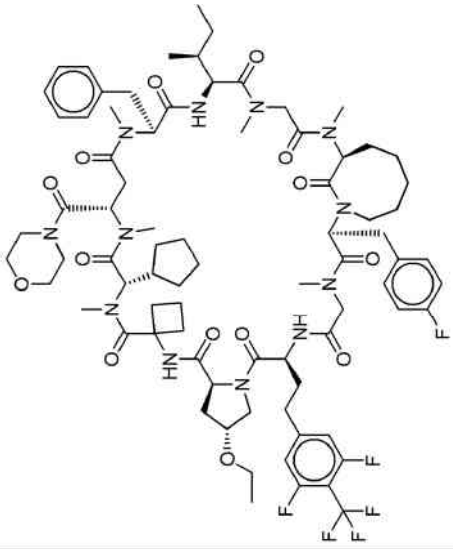
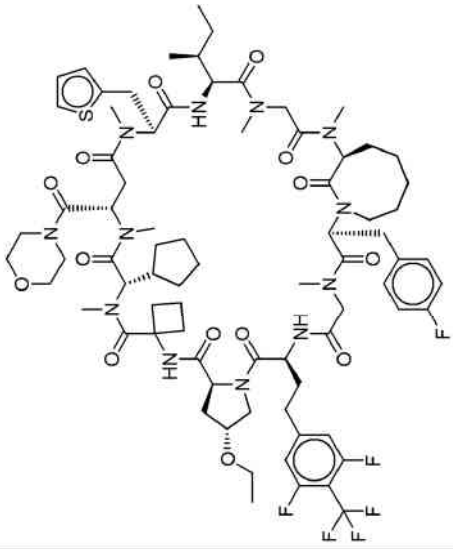
	
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PP1 161	PP1 163

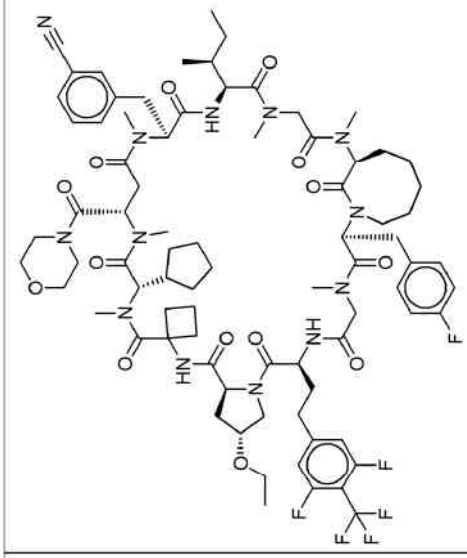
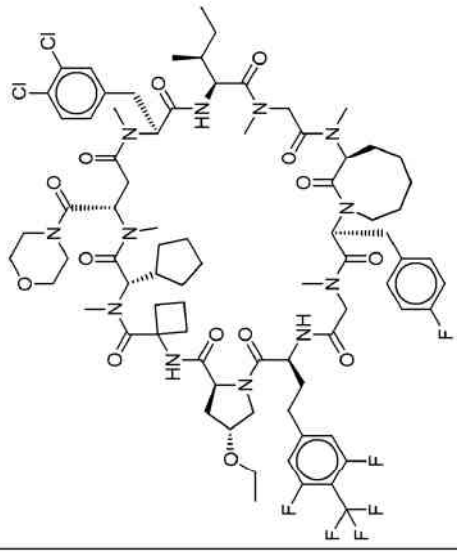
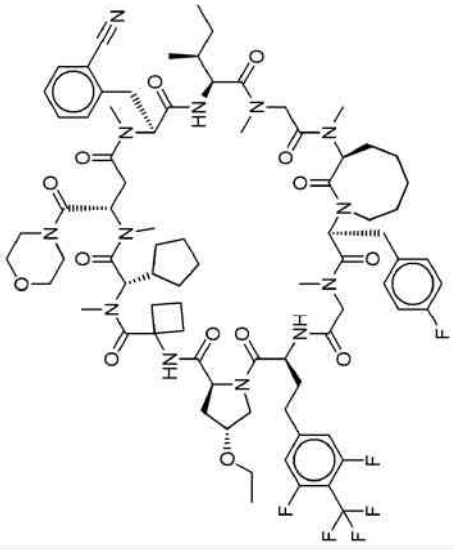
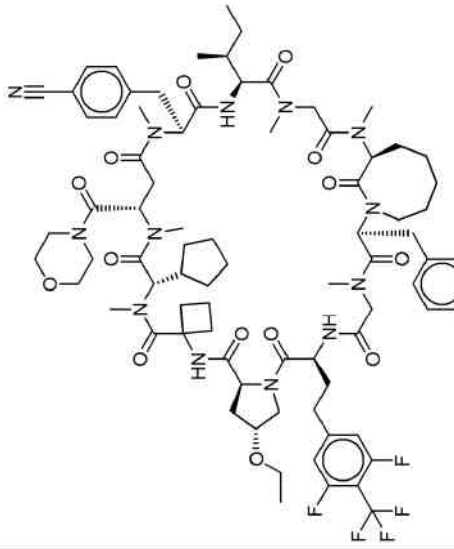
	
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PP1 165	PP1 167

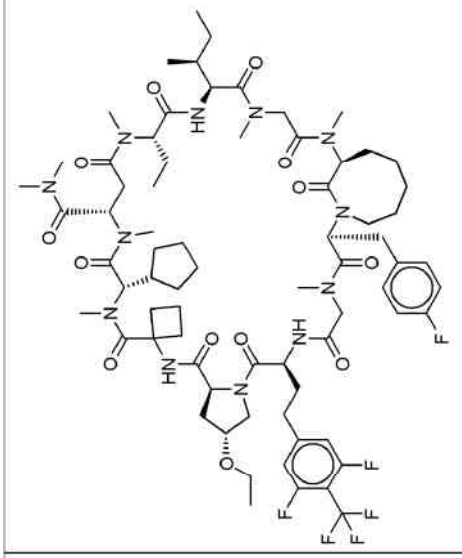
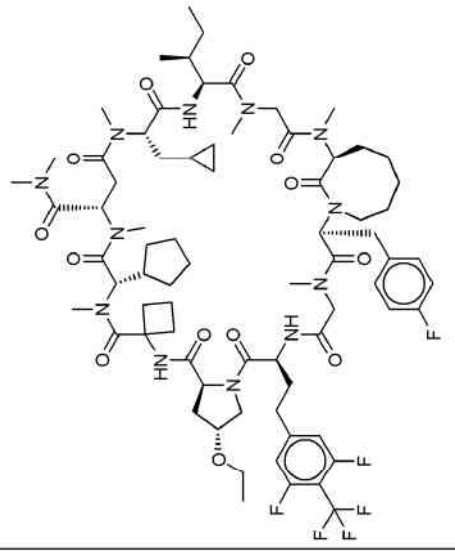
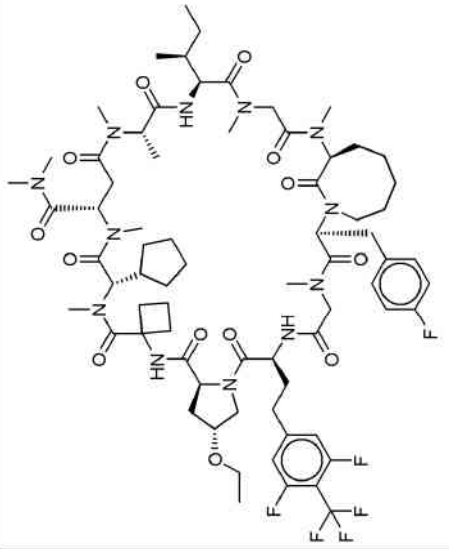
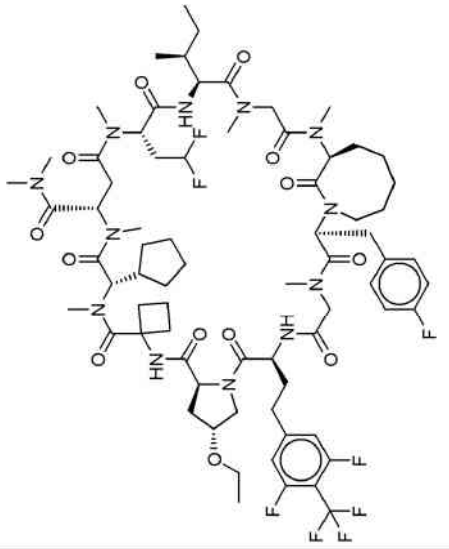
	
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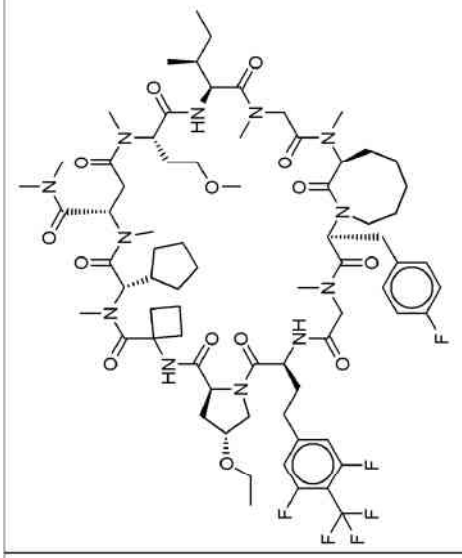
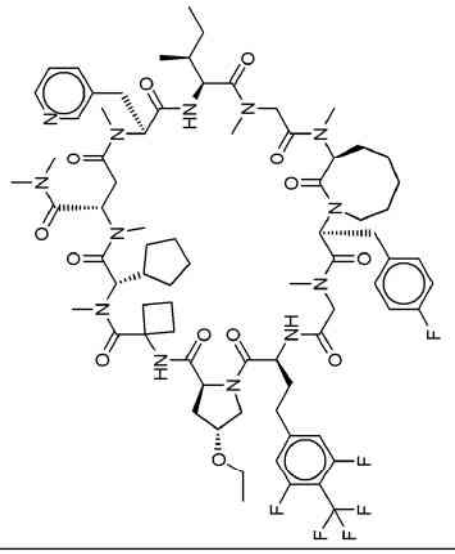
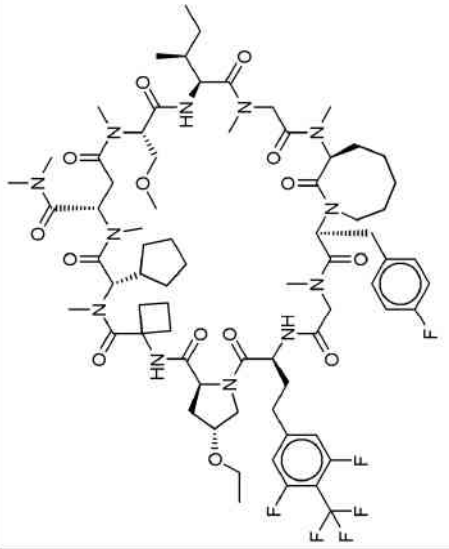
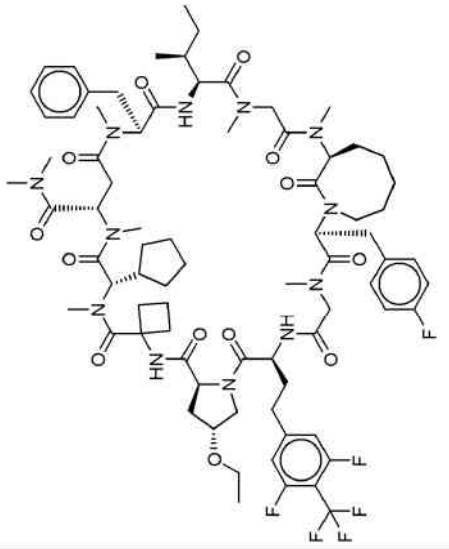
	
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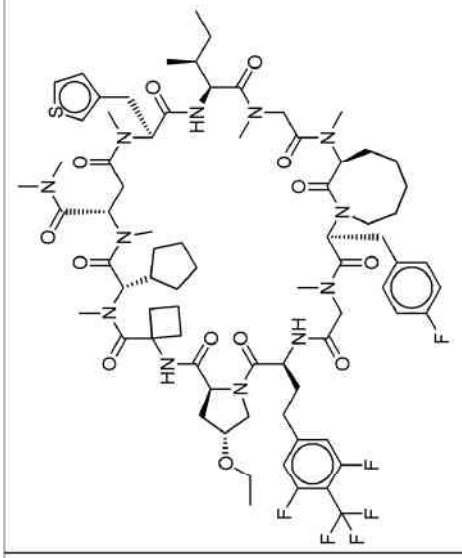
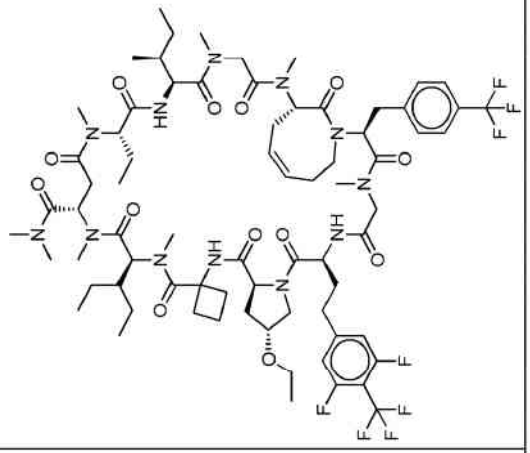
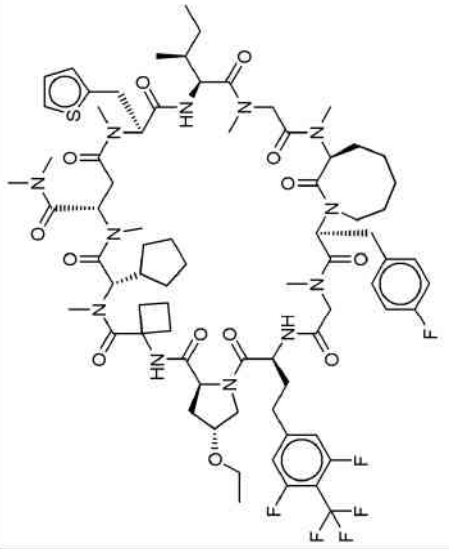
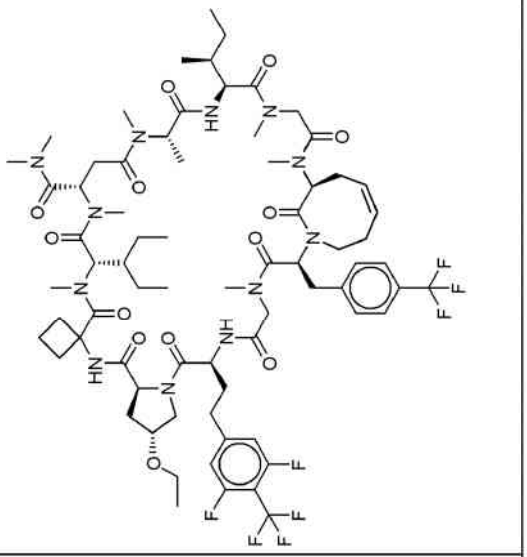
	
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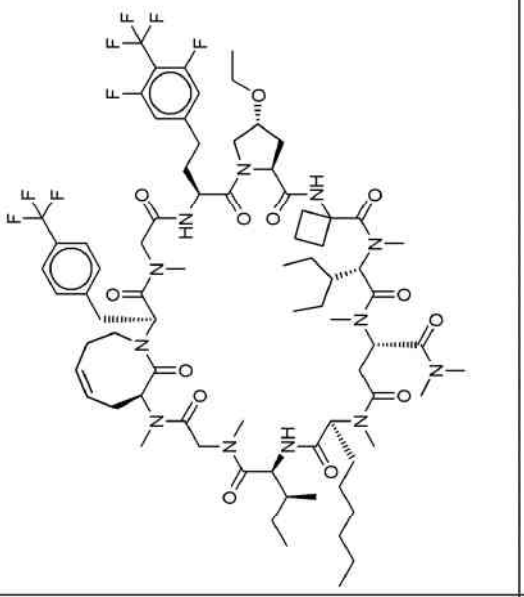
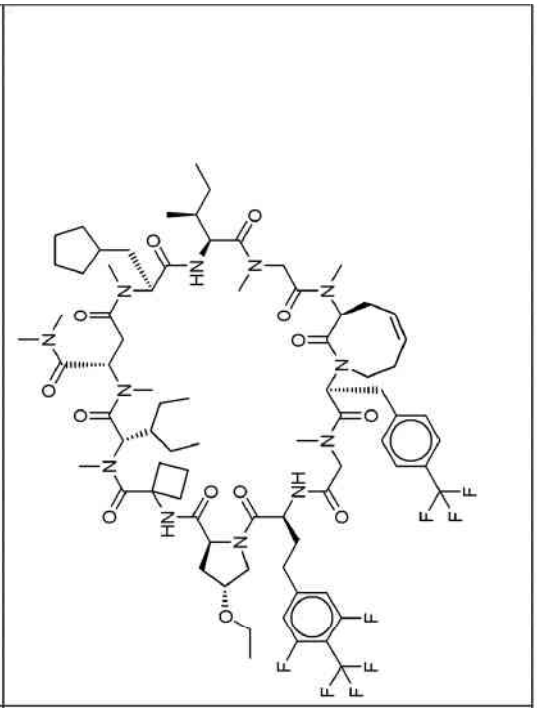
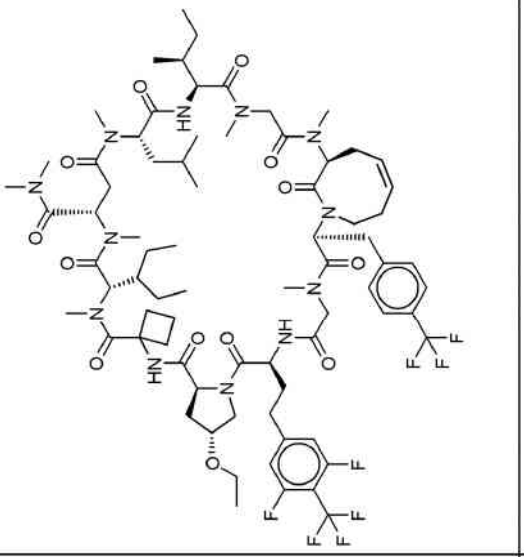
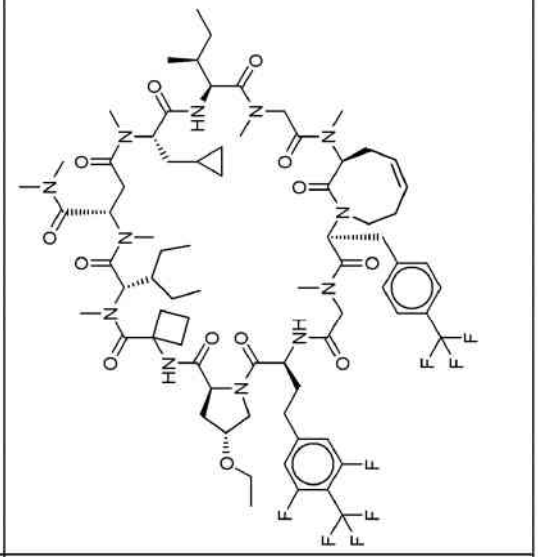
	
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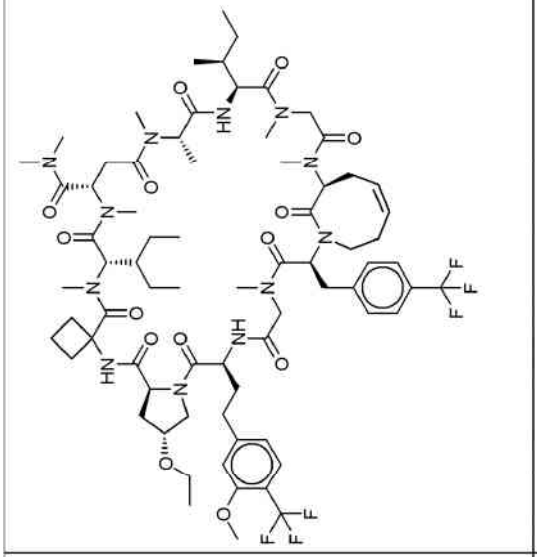
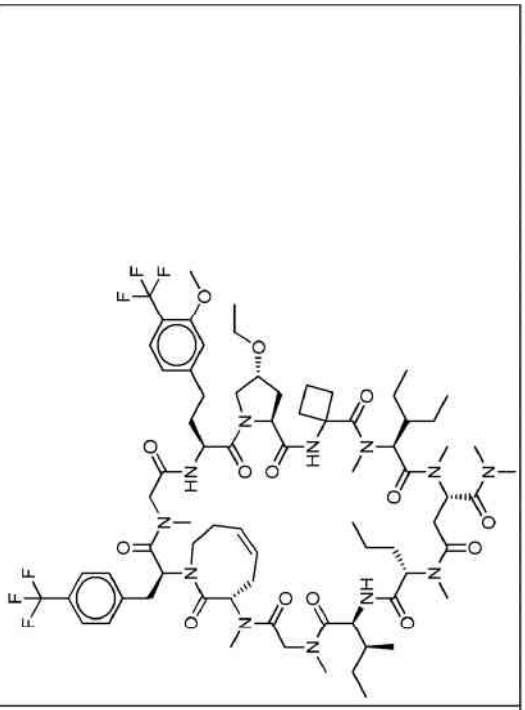
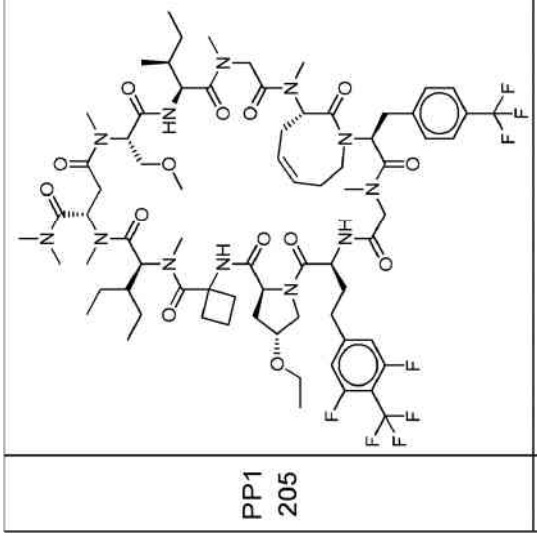
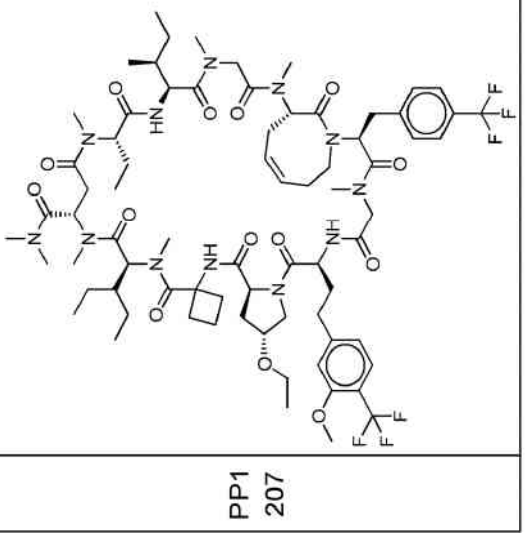
	
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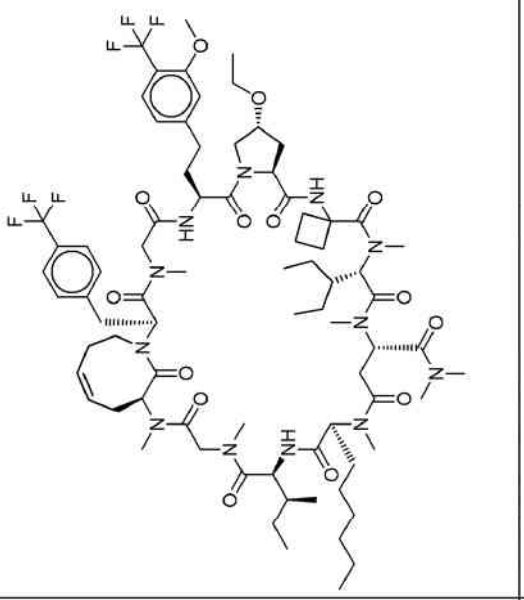
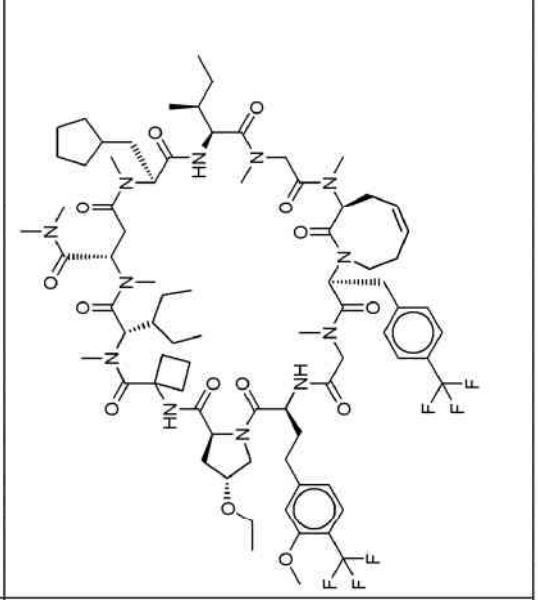
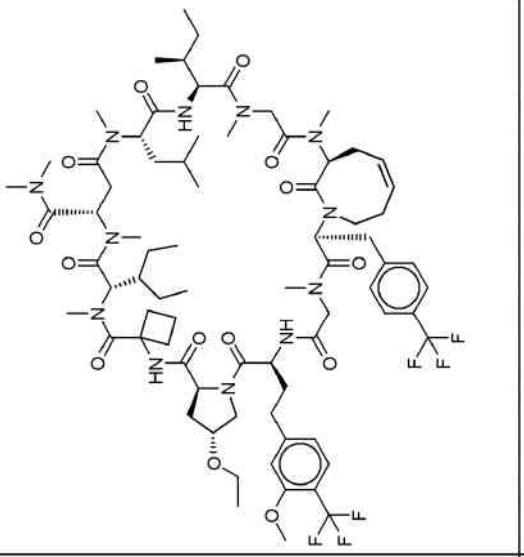
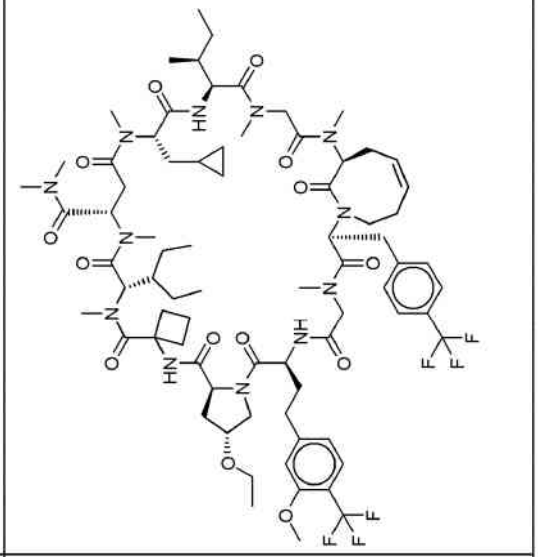
	
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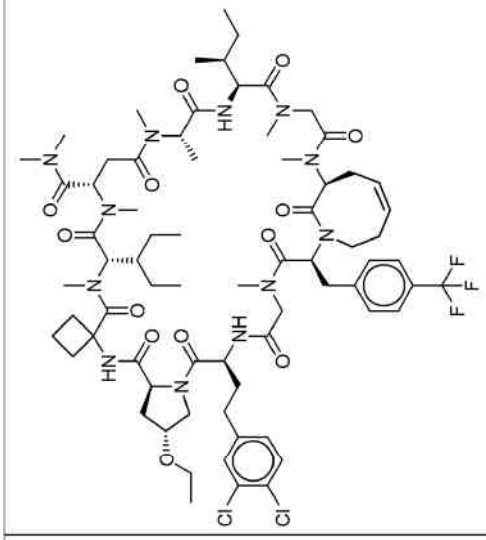
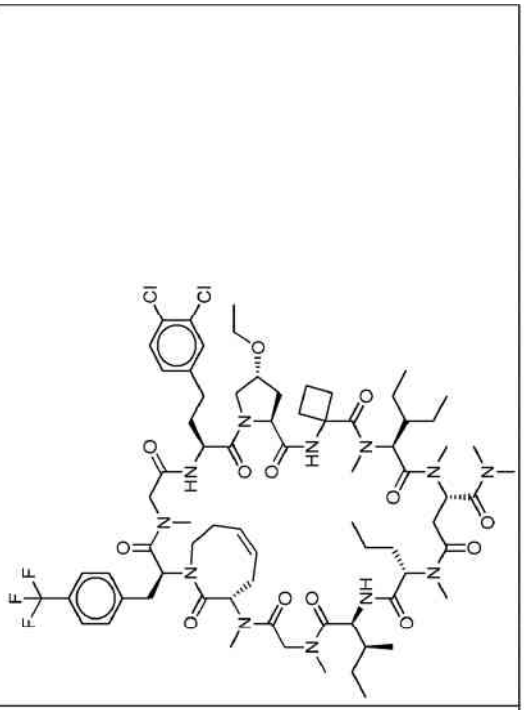
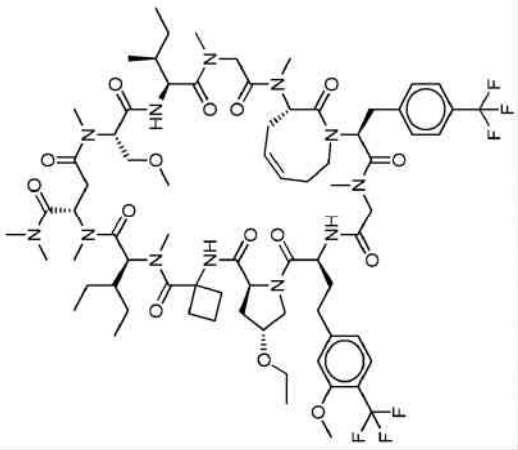
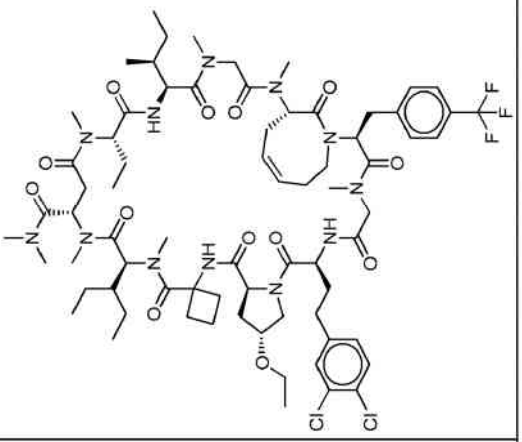
	
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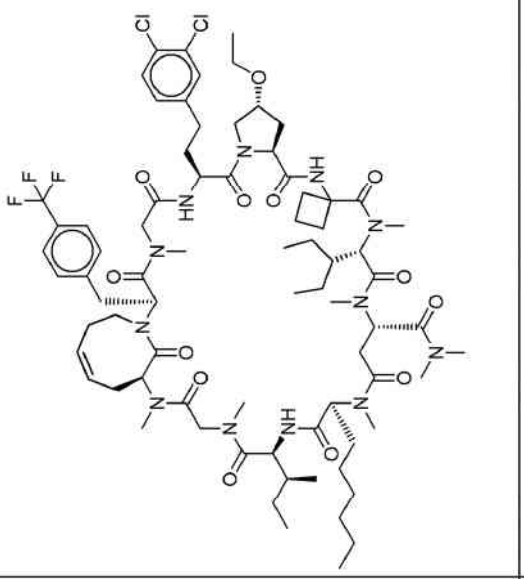
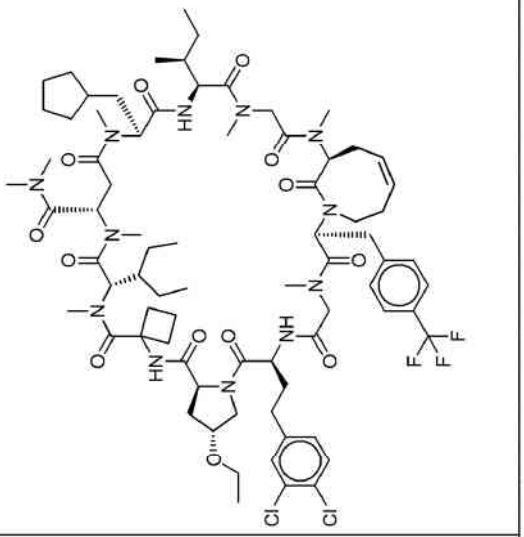
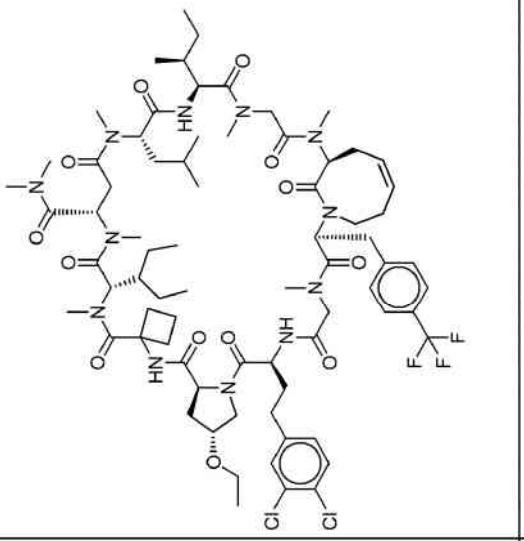
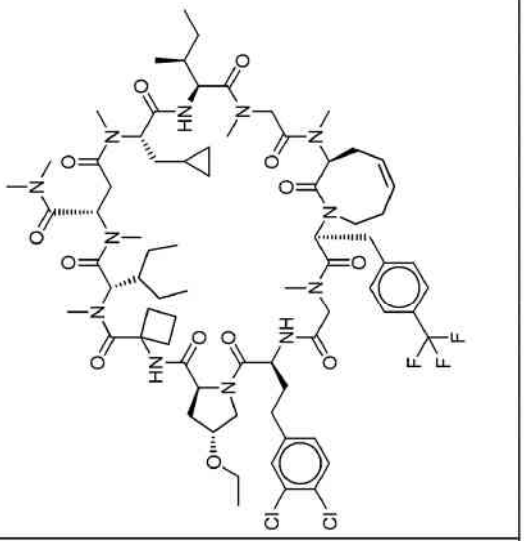
	
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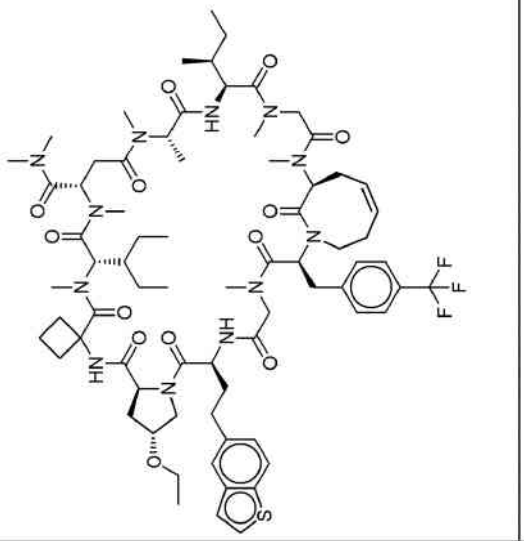
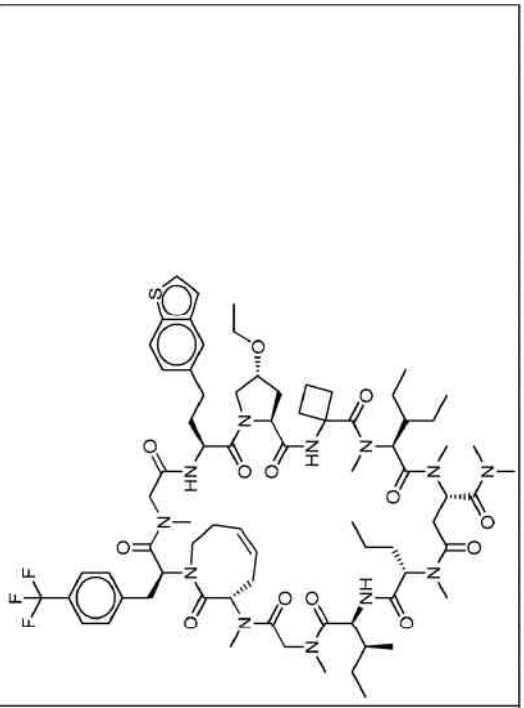
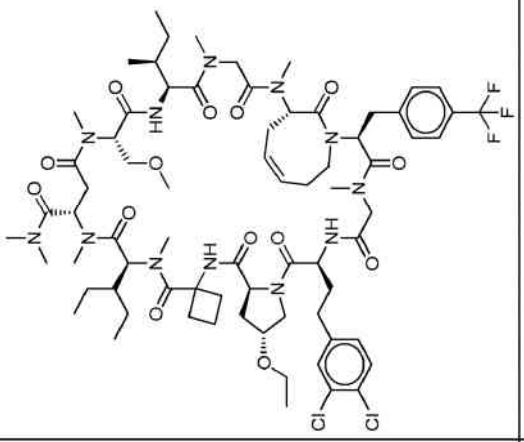
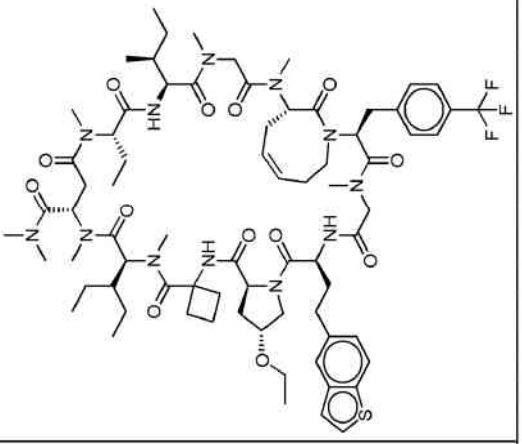
	
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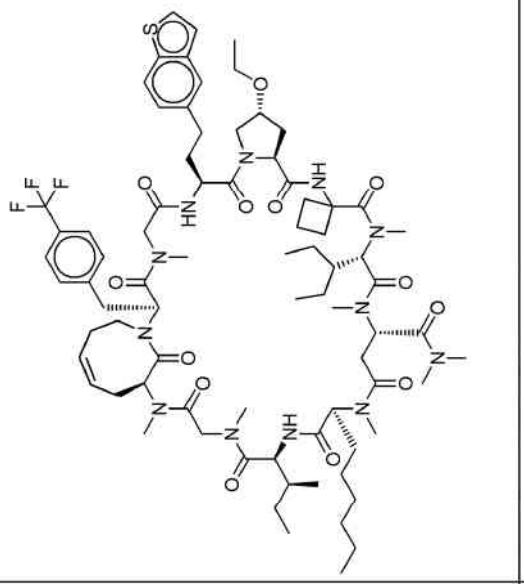
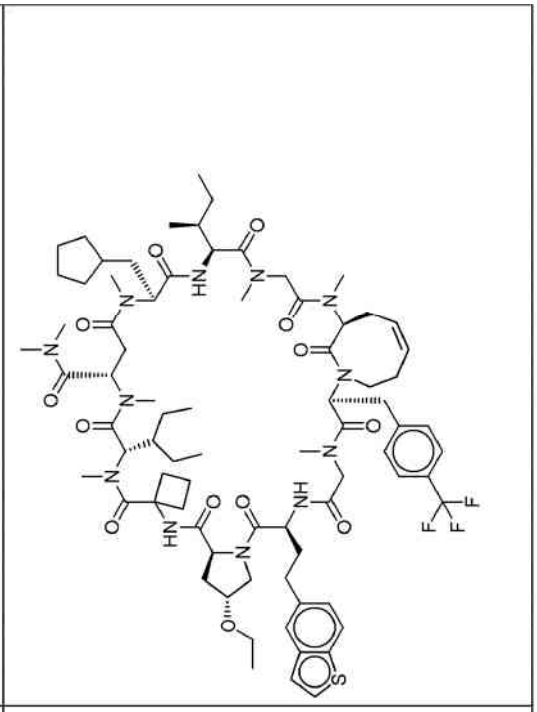
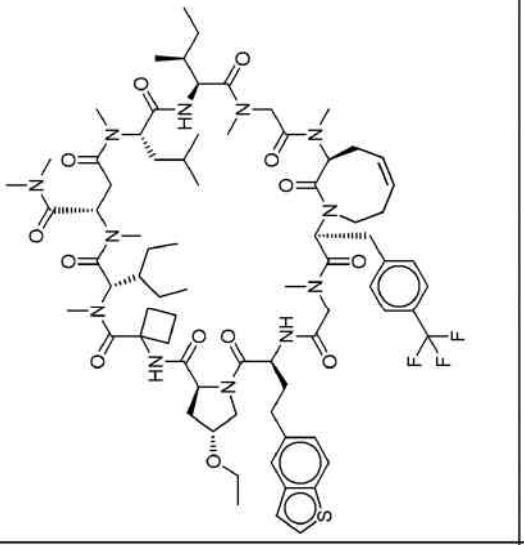
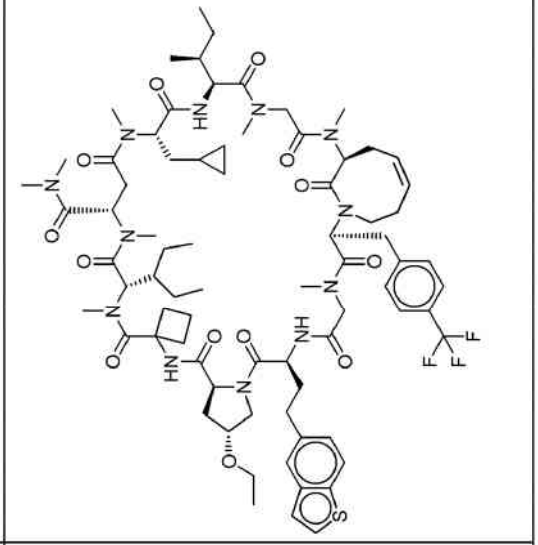
	
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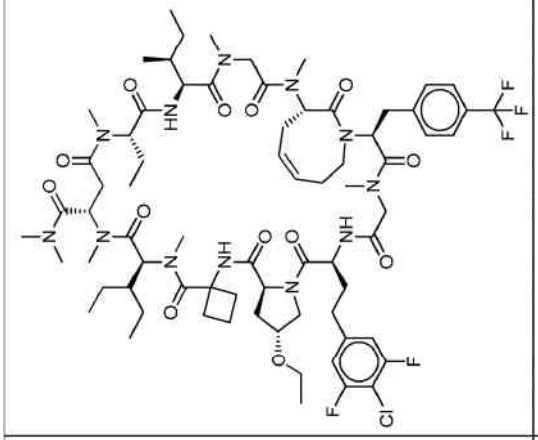
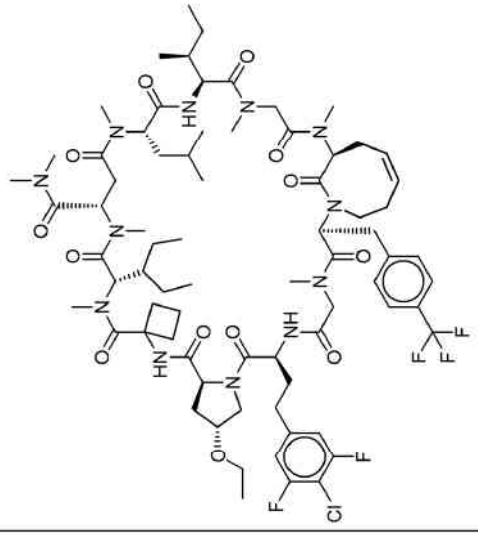
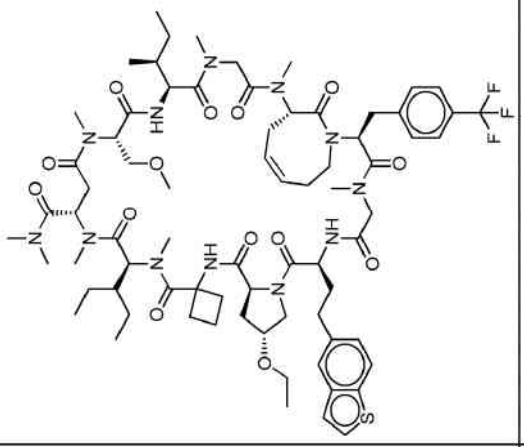
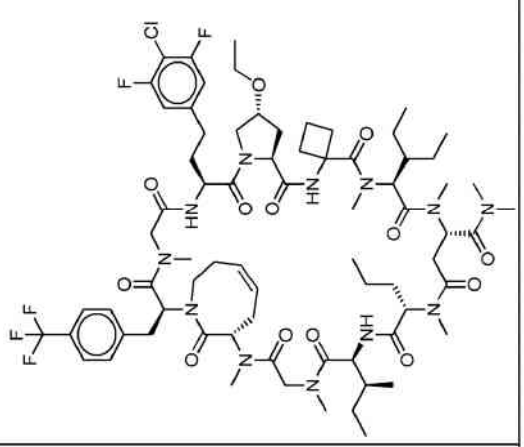
	
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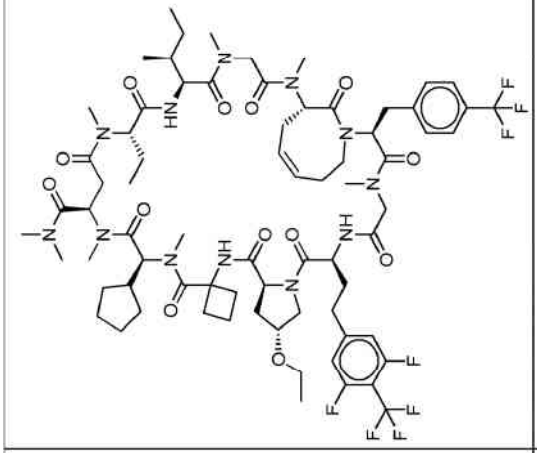
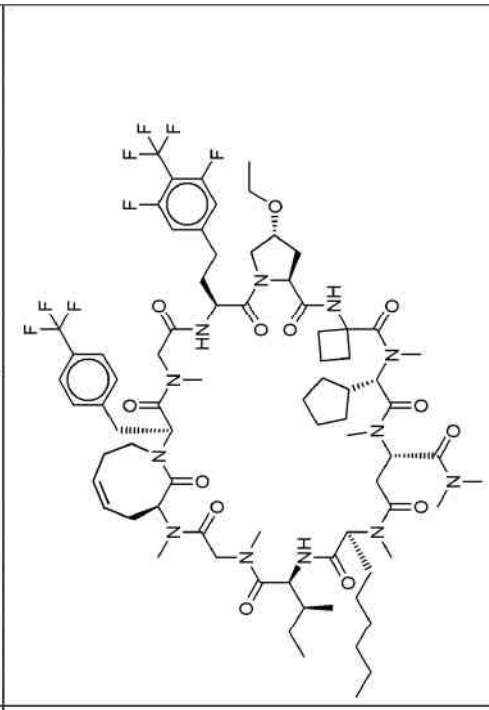
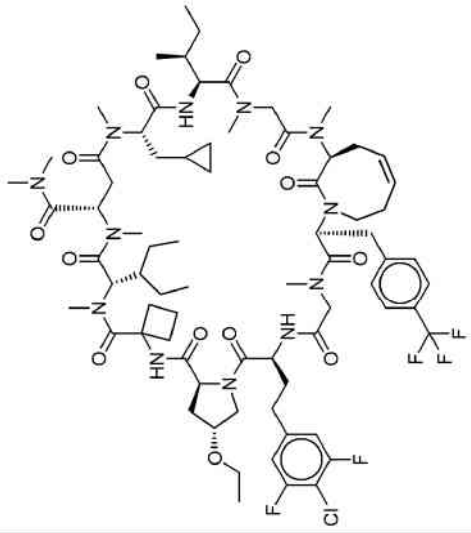
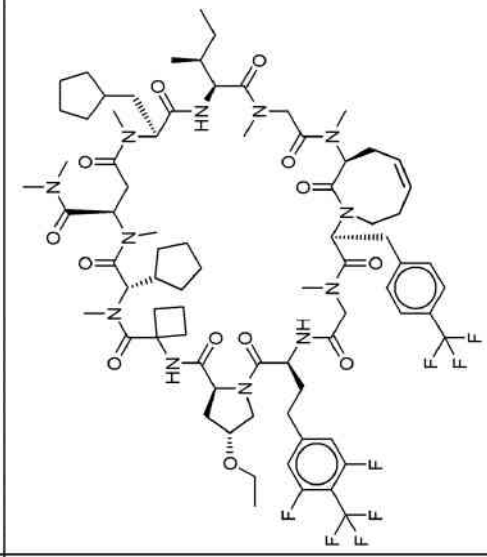
	
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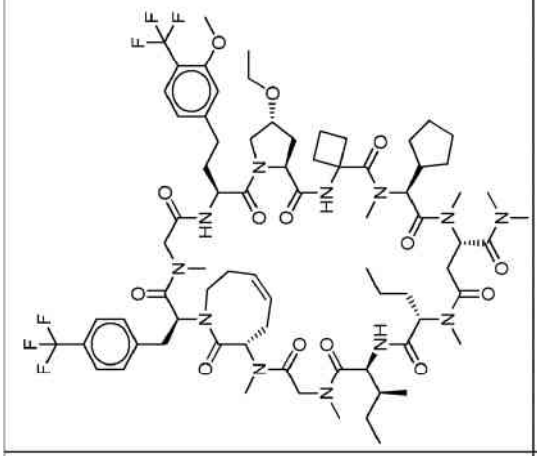
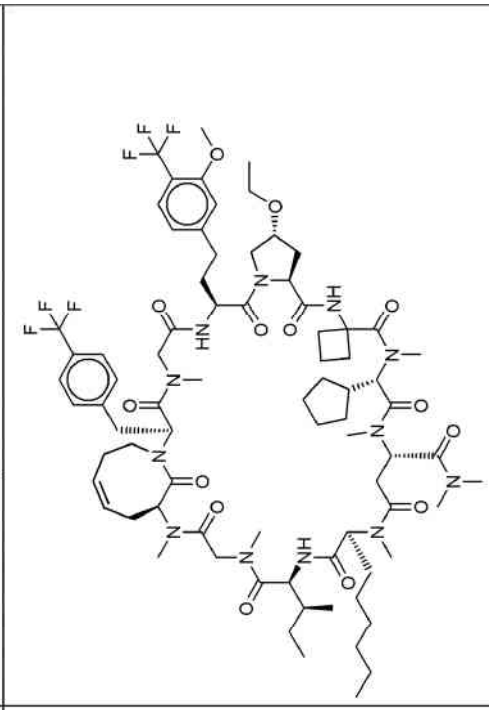
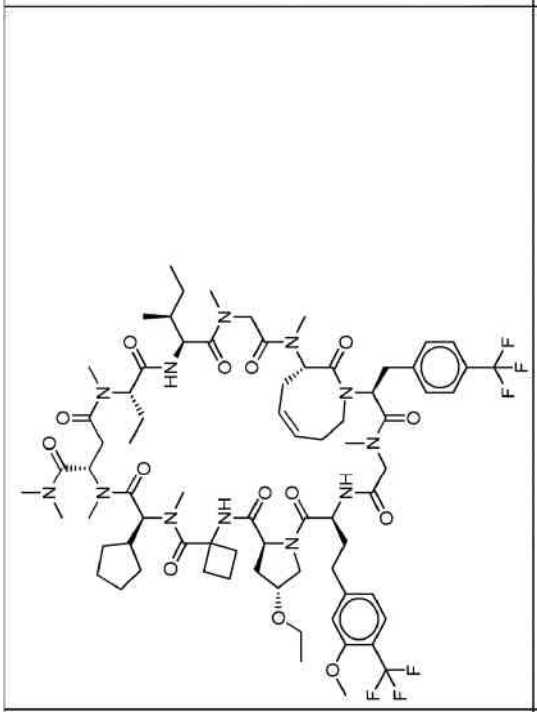
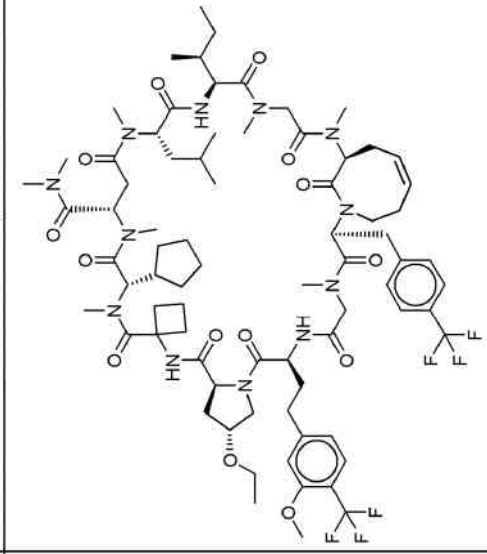
	
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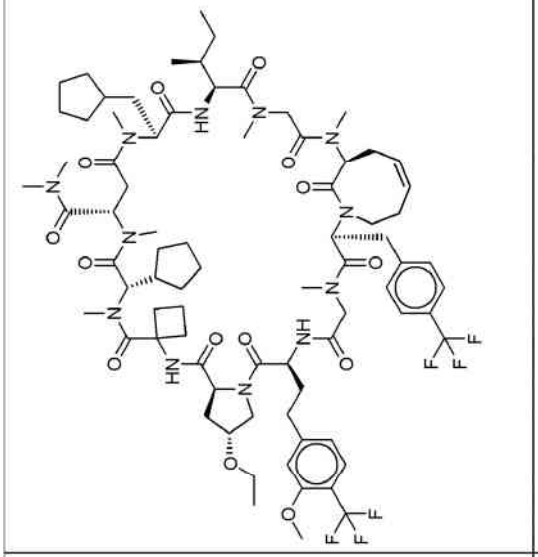
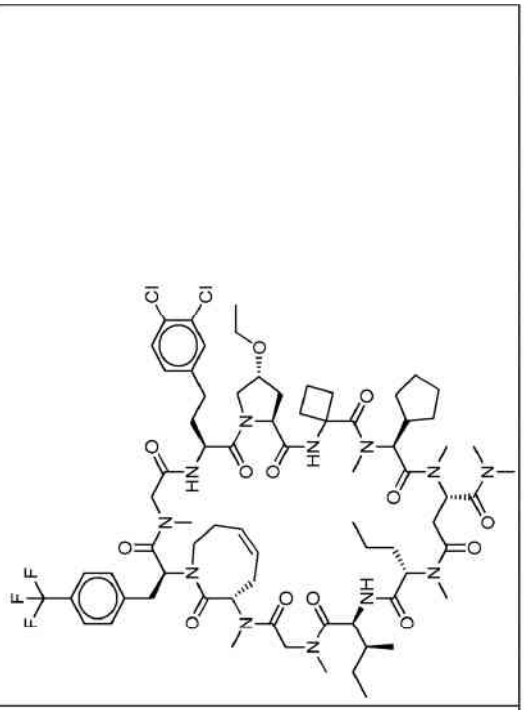
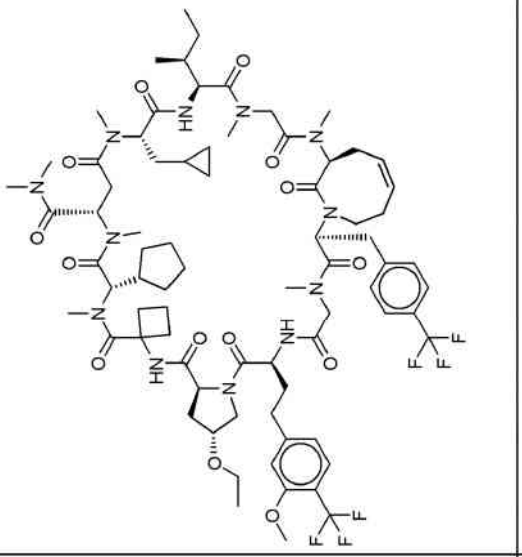
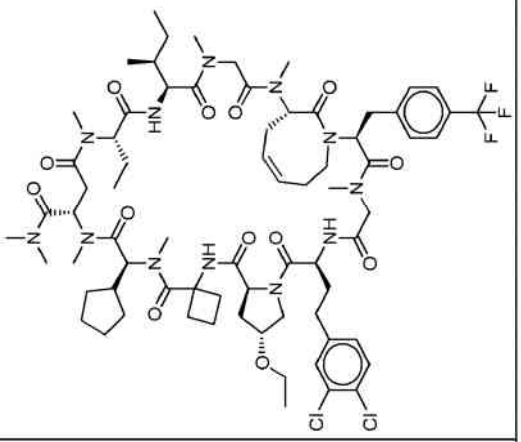
	
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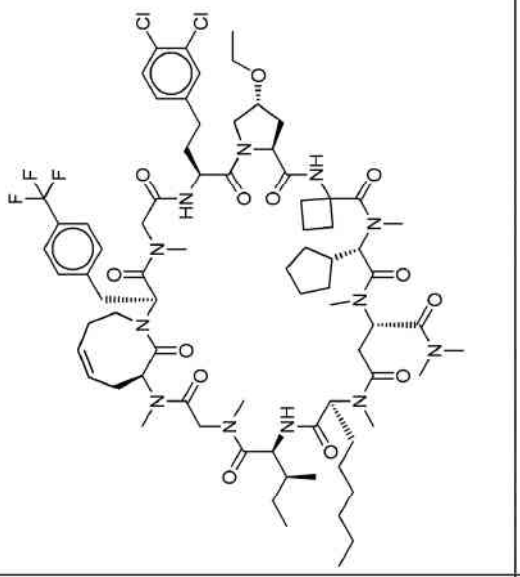
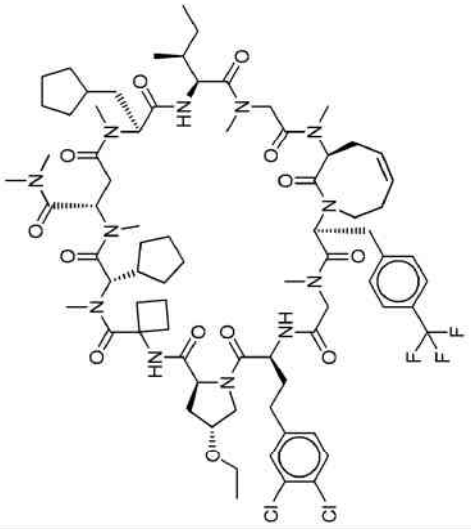
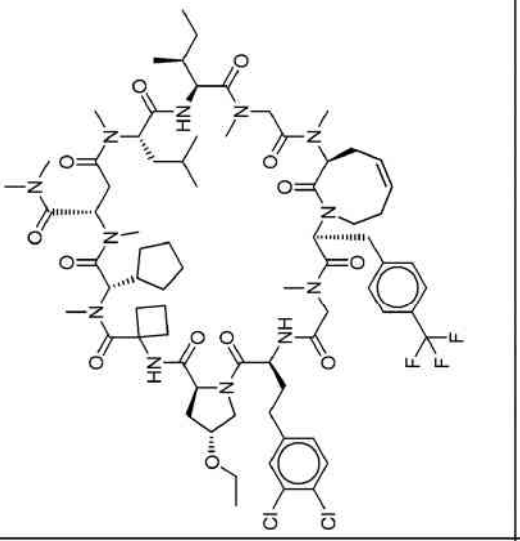
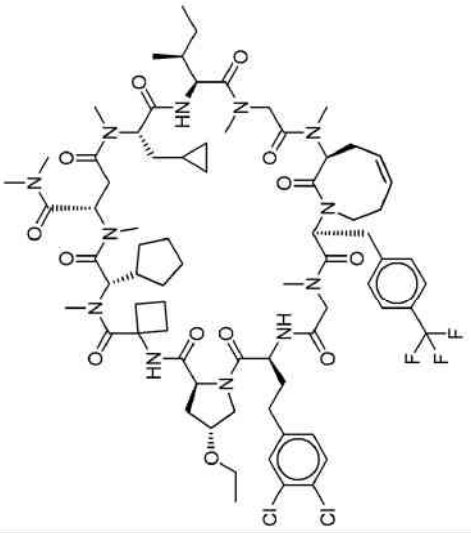
	
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PP1 225	PP1 227

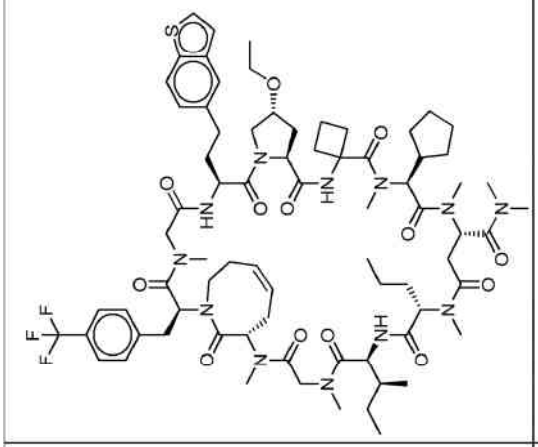
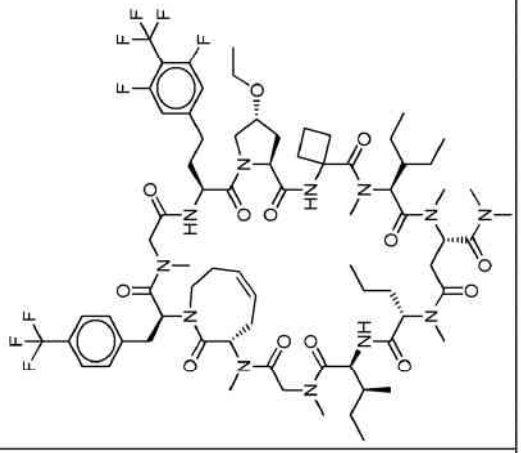
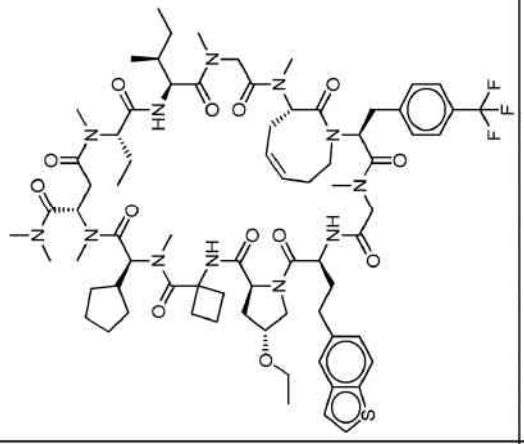
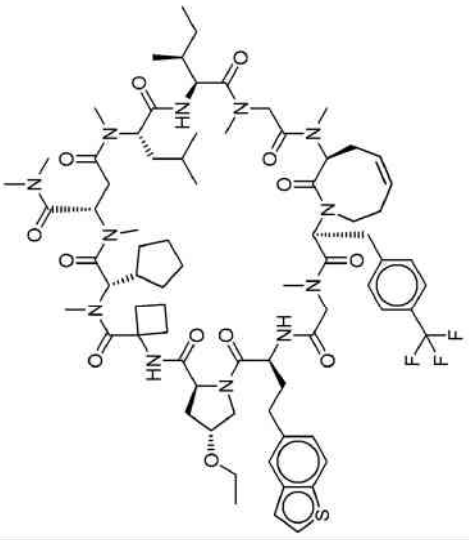
	
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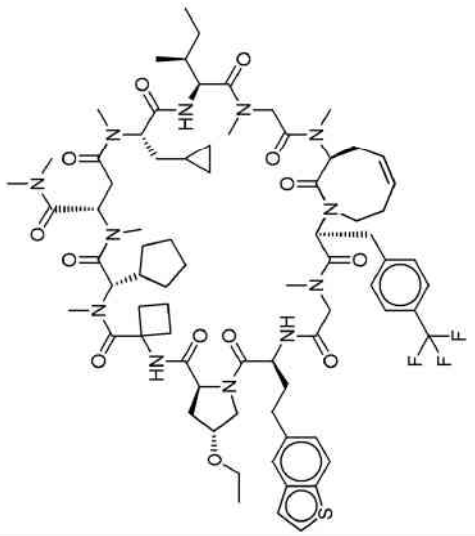
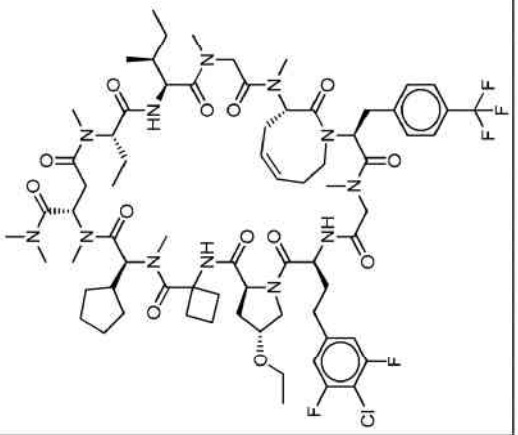
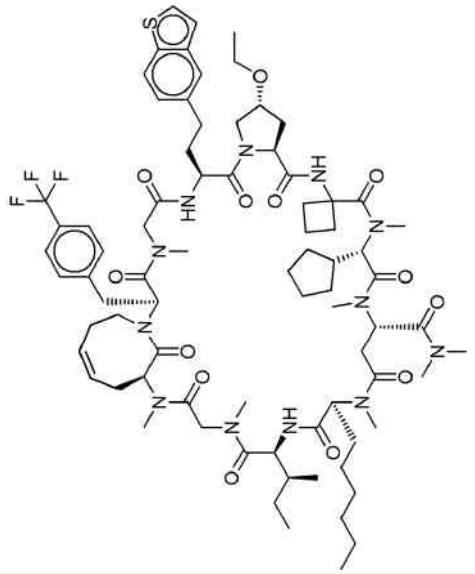
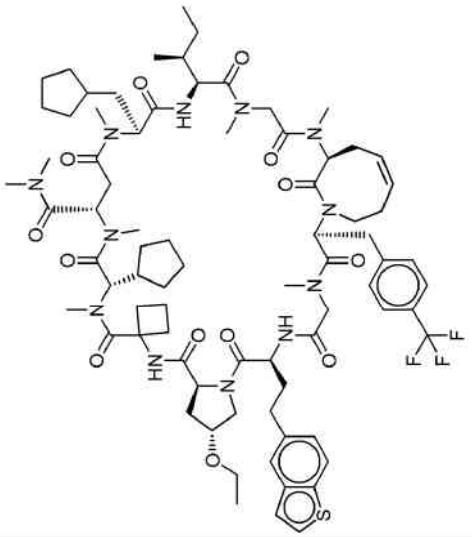
	
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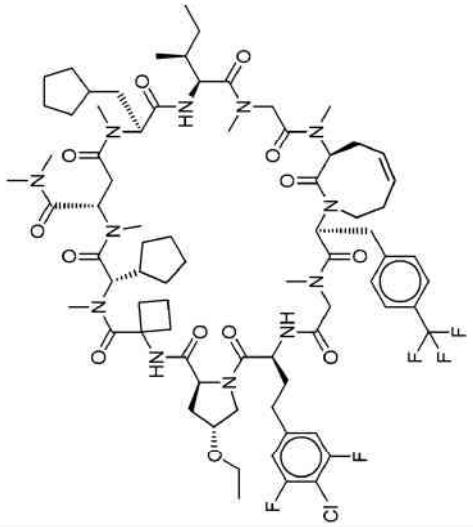
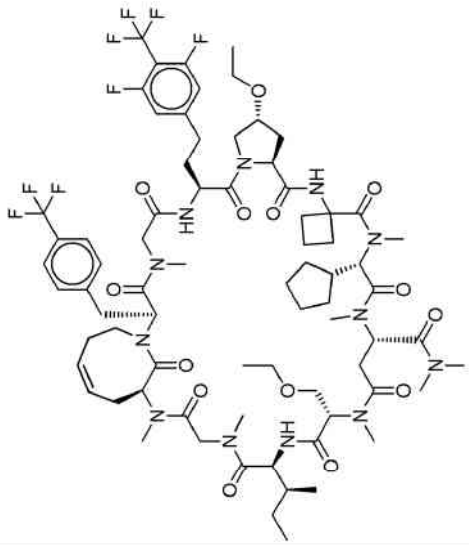
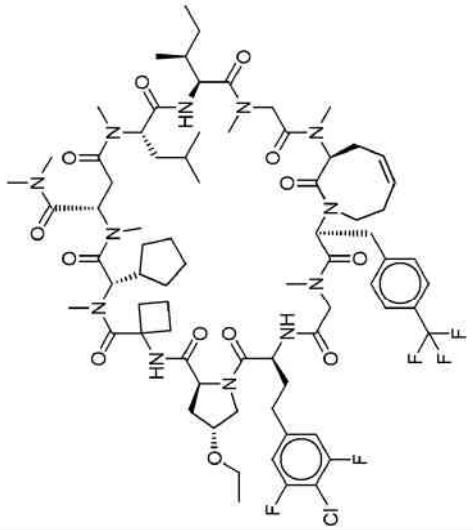
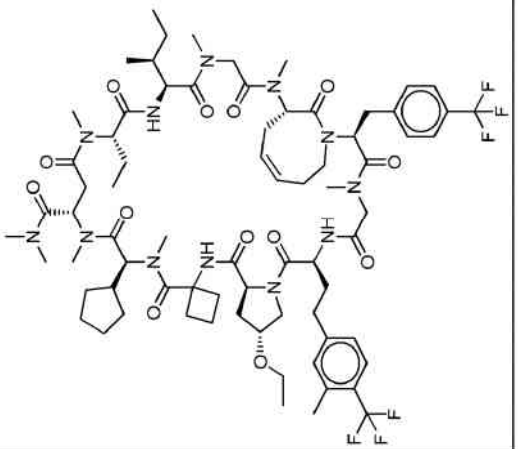
	
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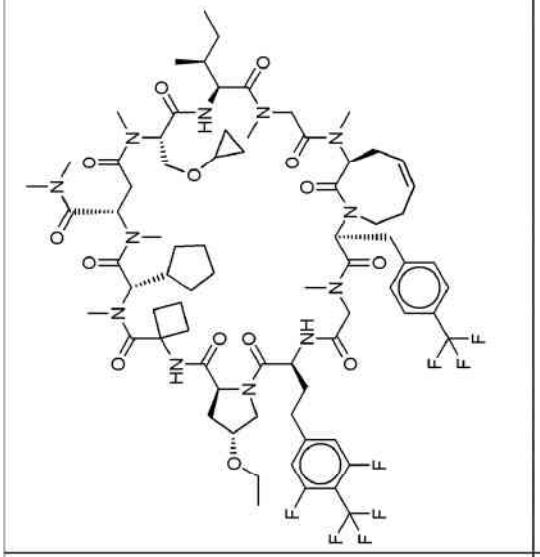
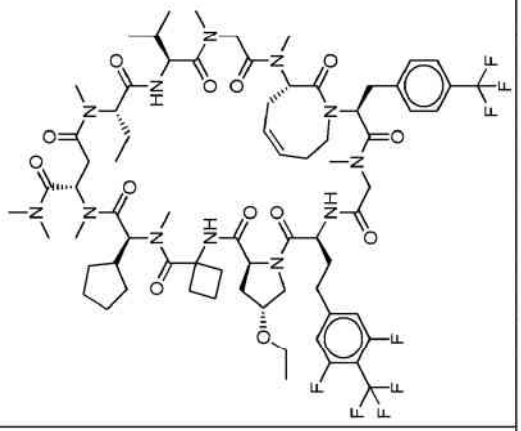
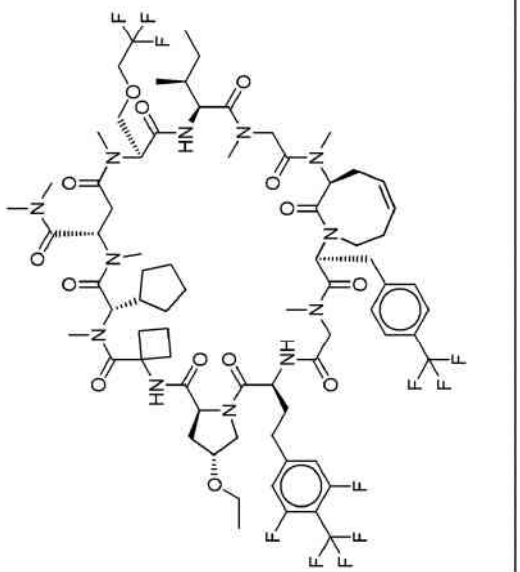
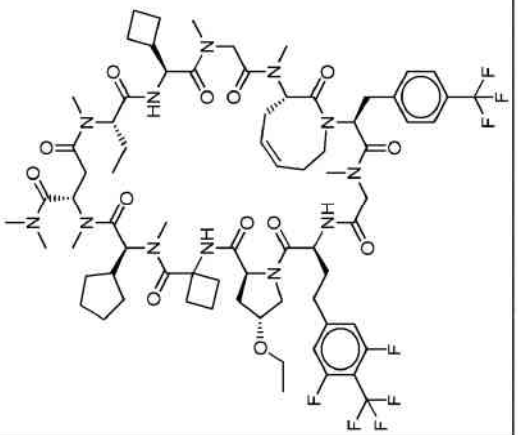
	
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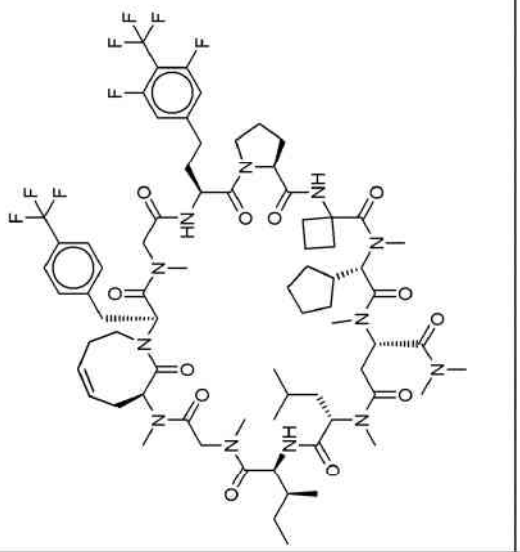
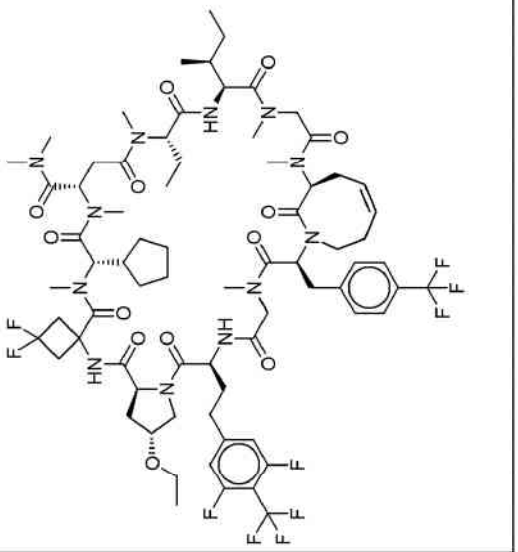
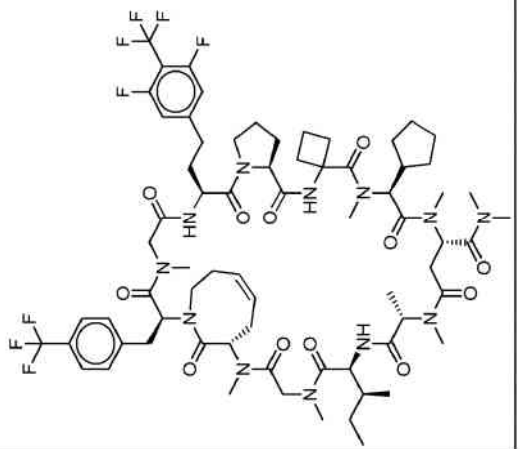
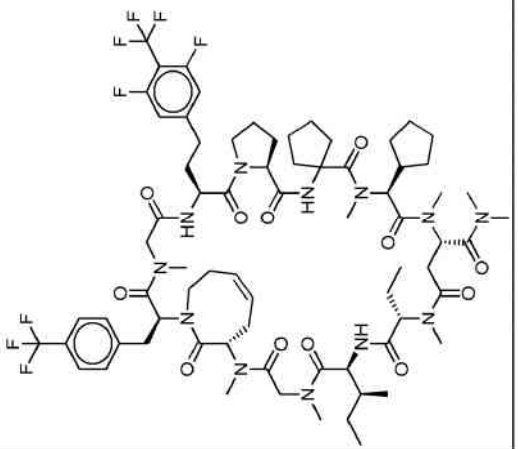
	
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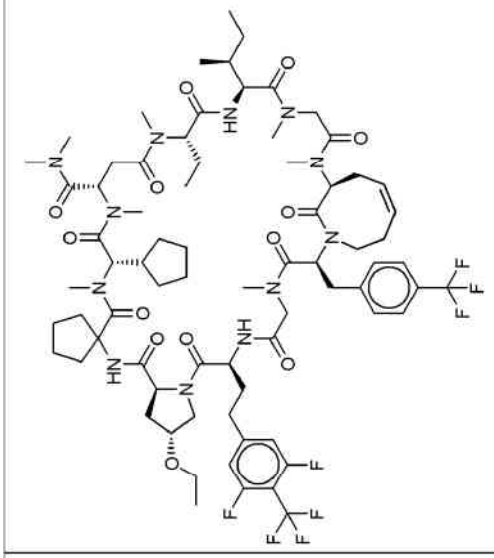
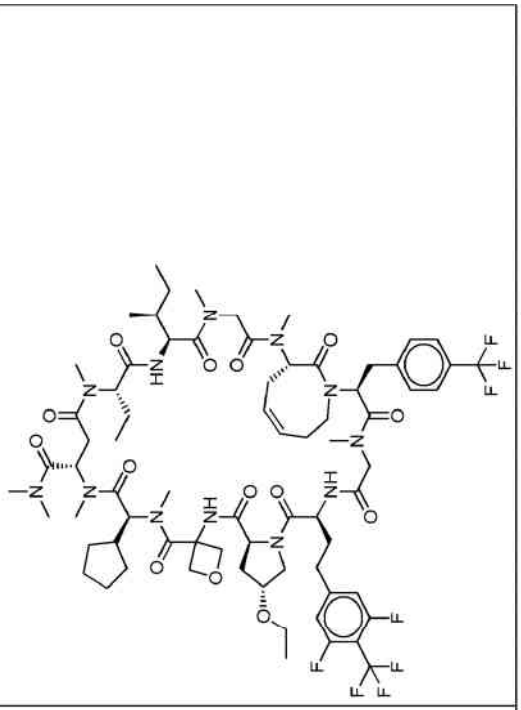
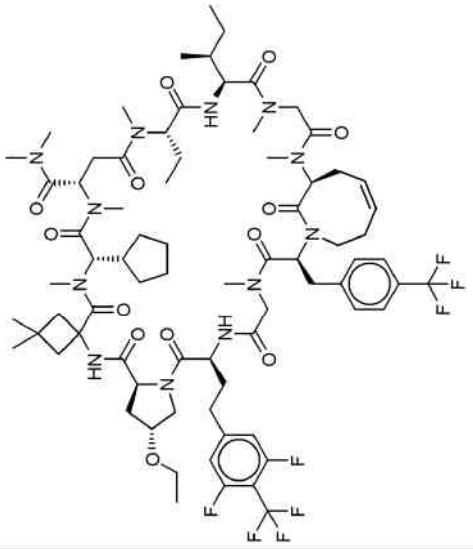
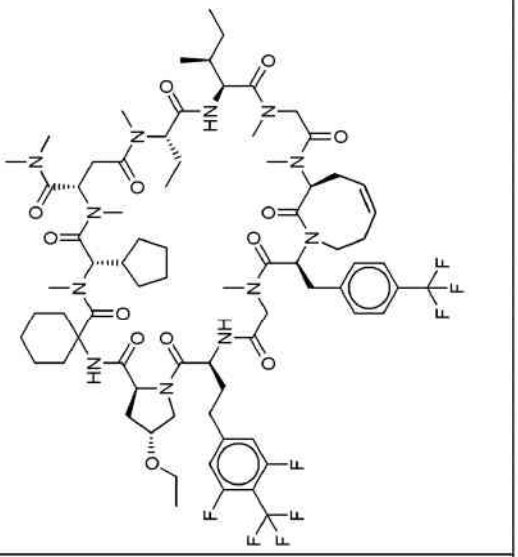
	
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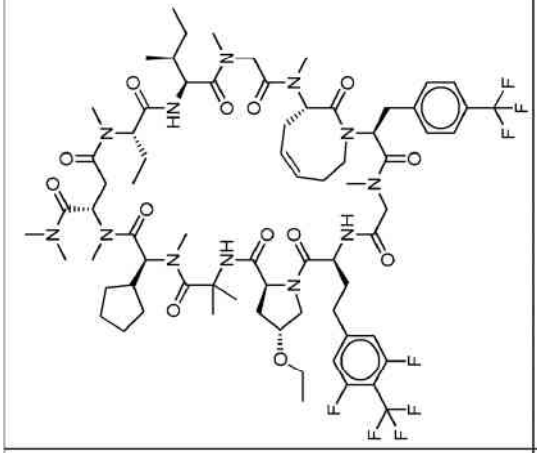
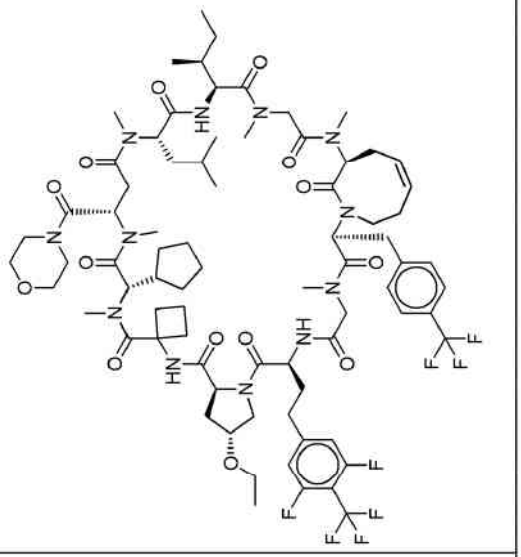
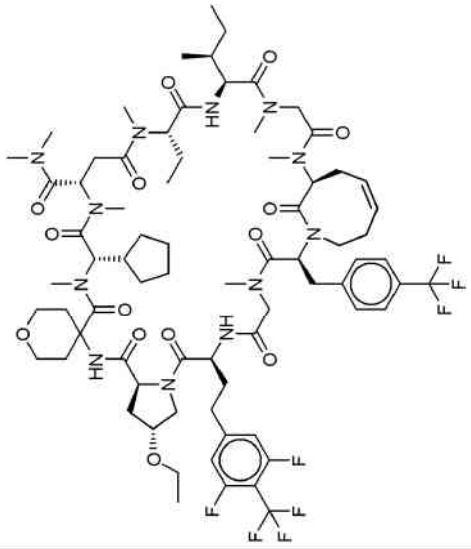
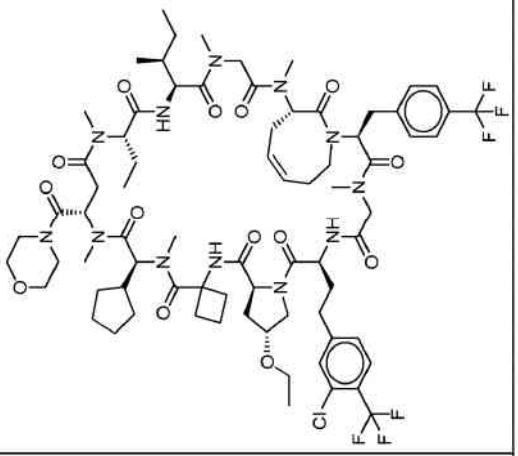
	
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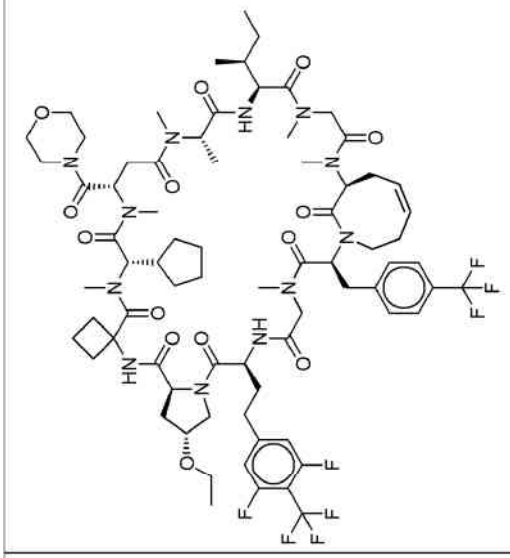
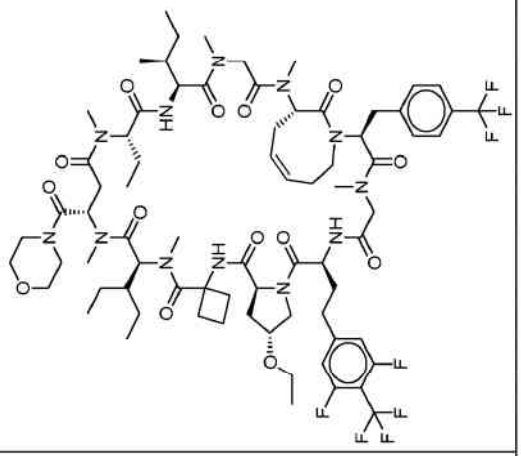
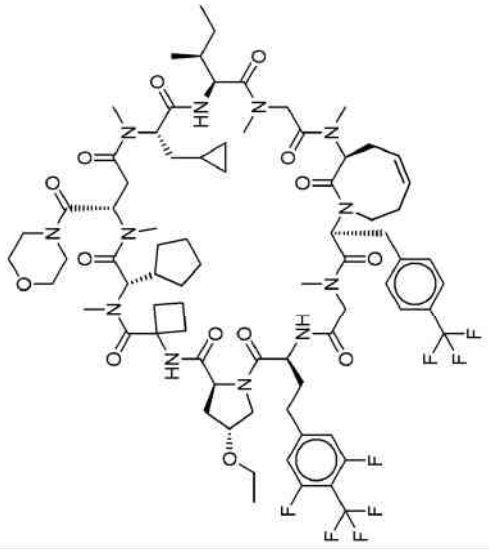
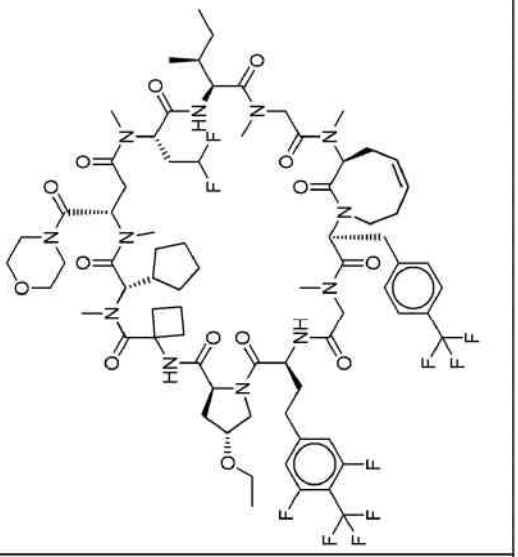
	
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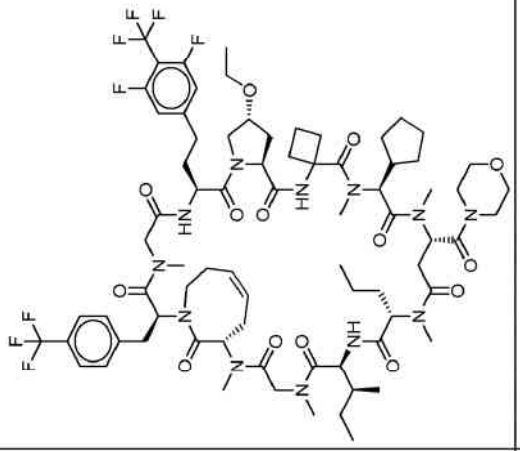
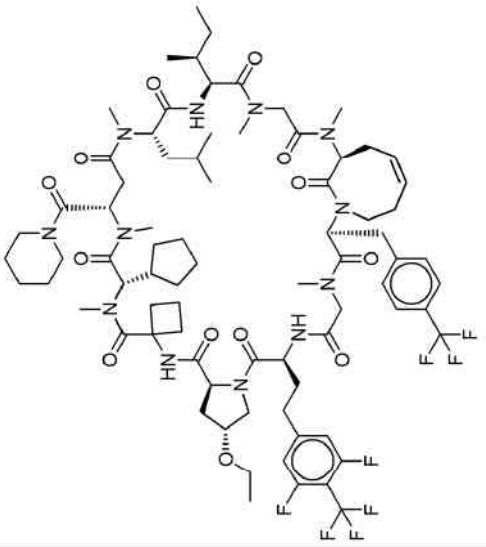
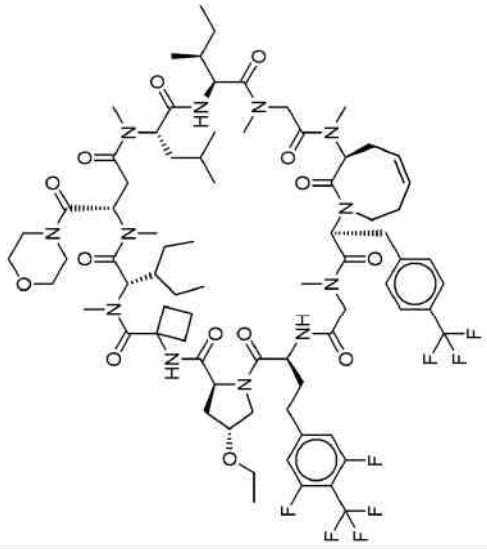
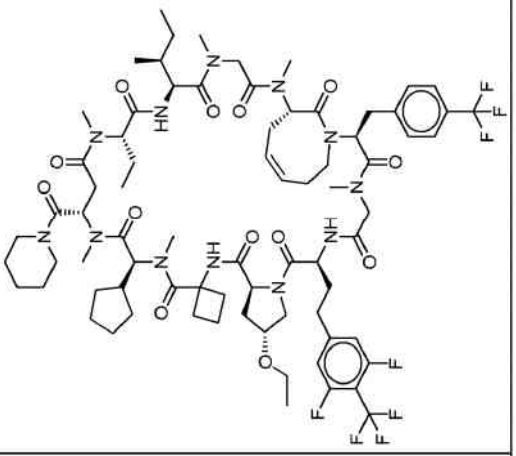
	
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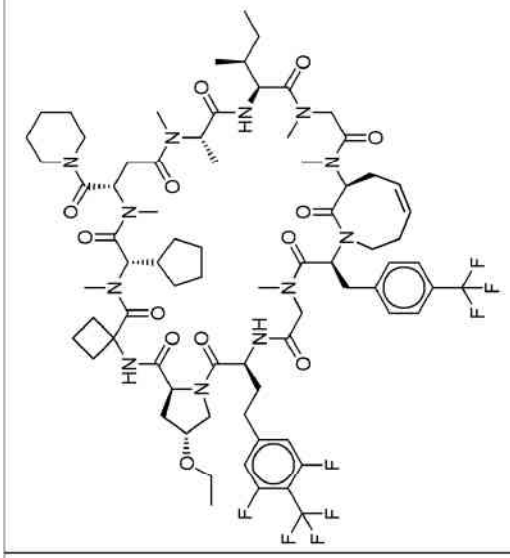
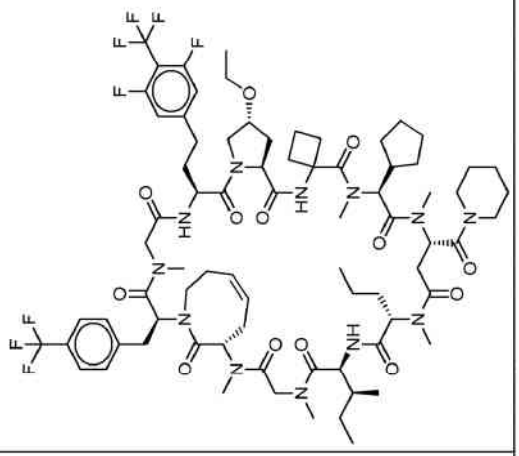
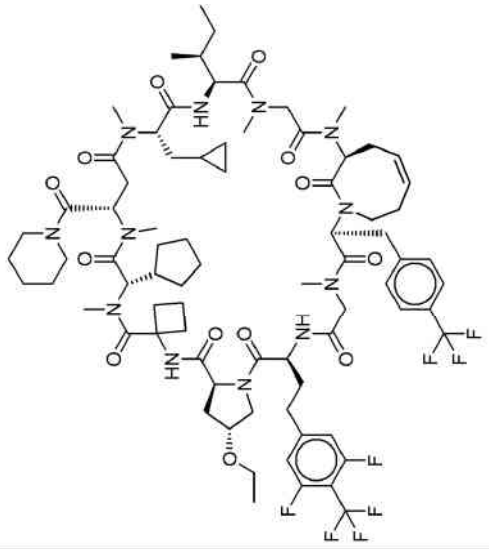
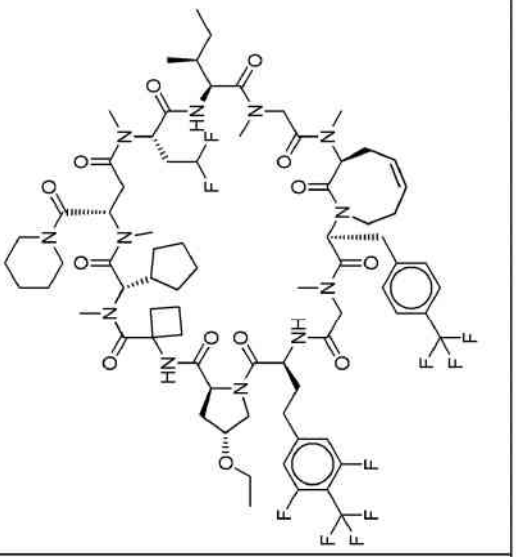
	
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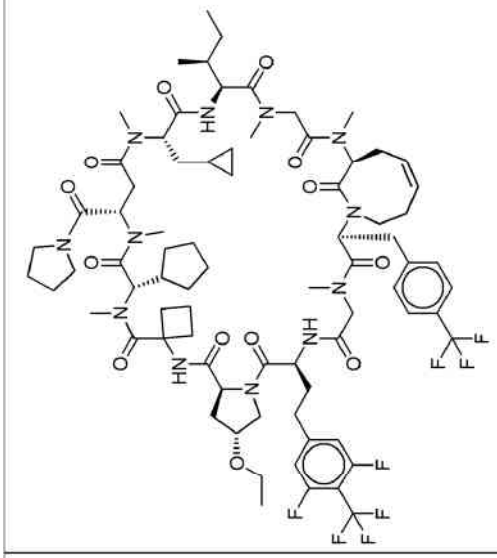
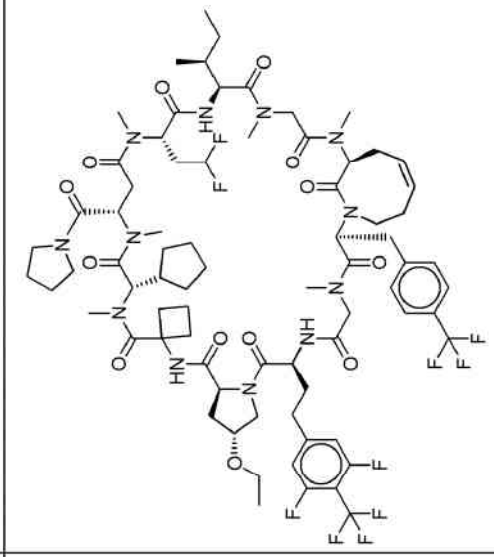
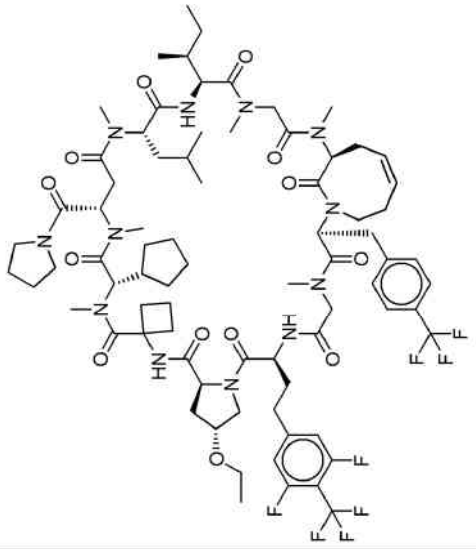
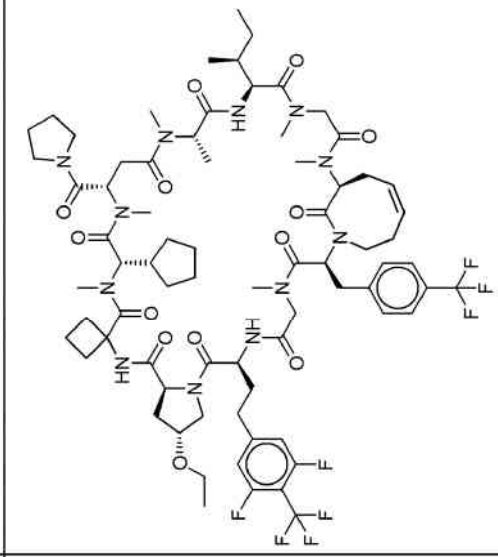
	
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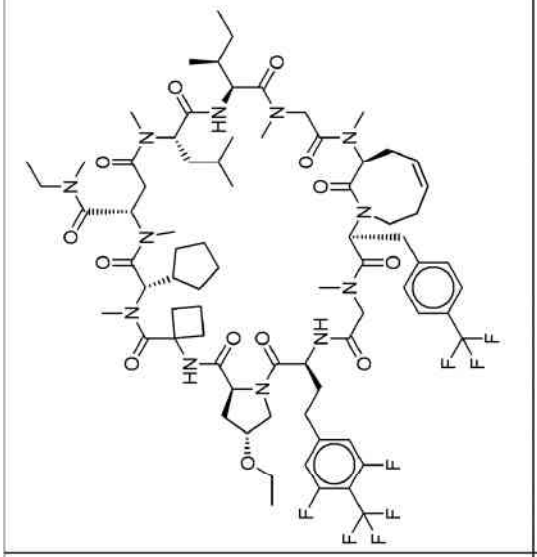
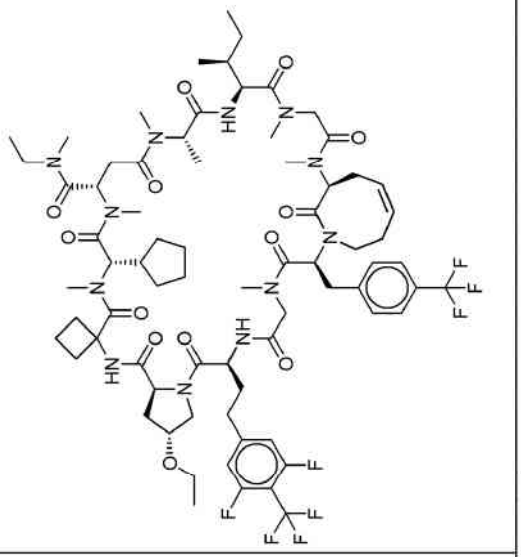
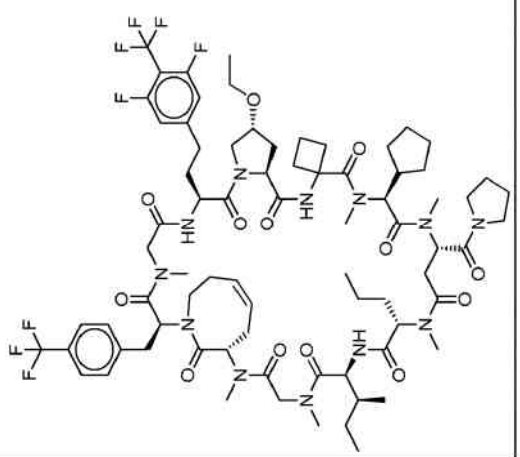
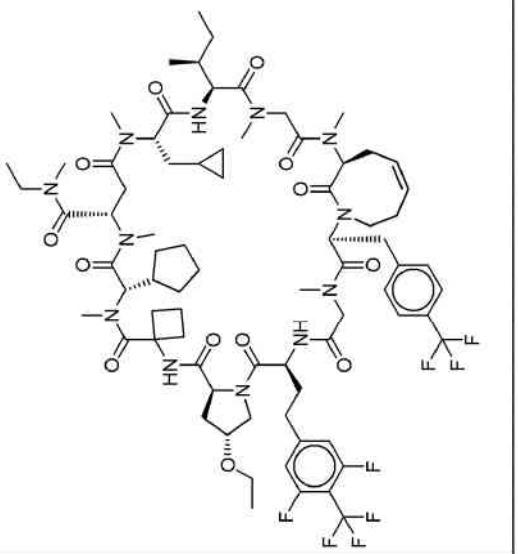
	
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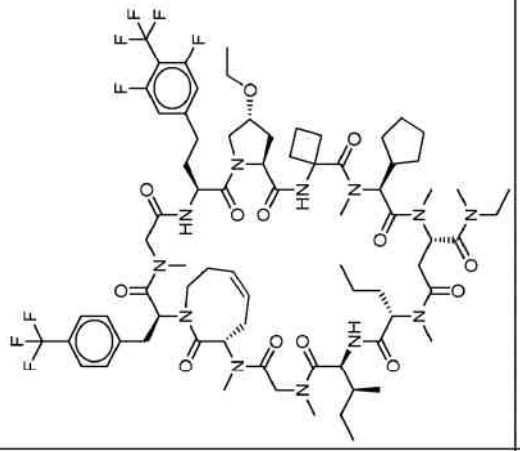
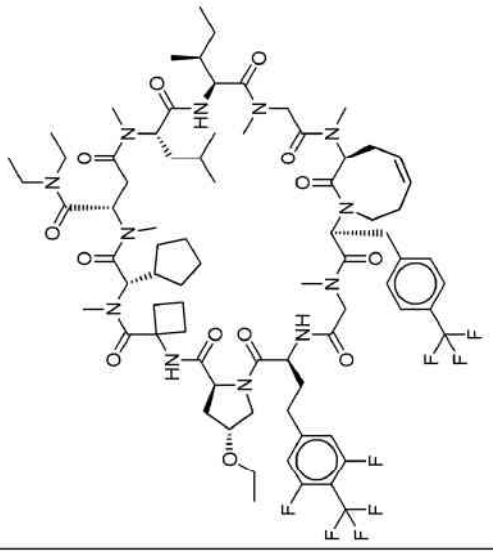
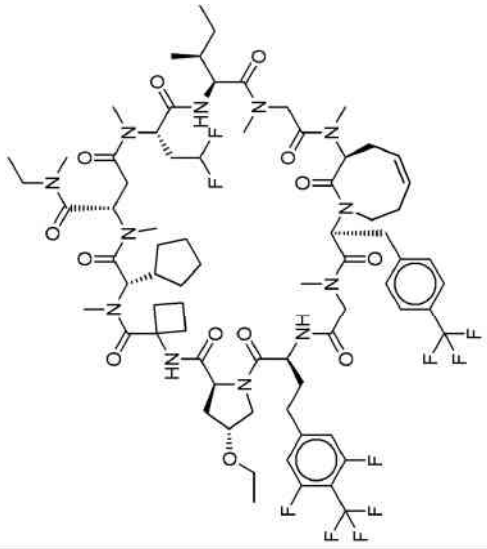
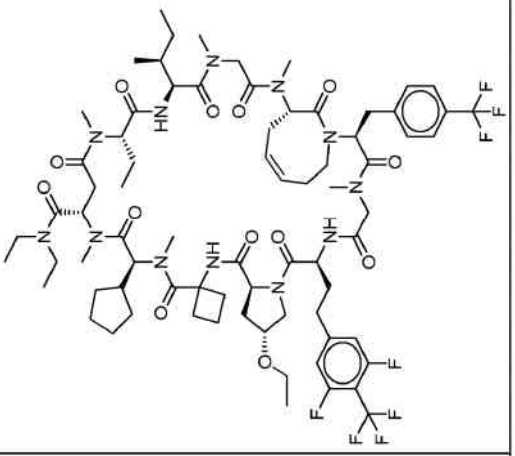
	
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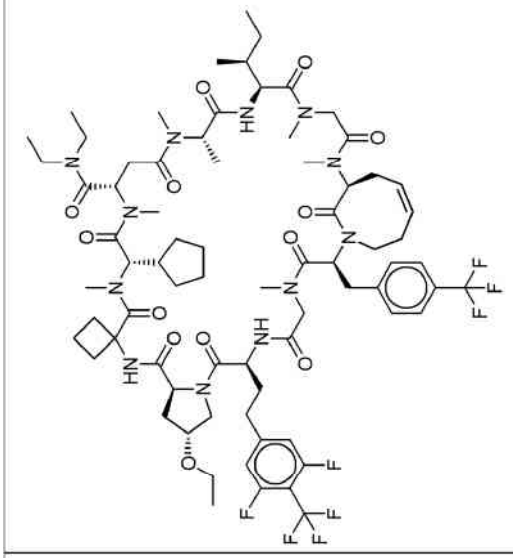
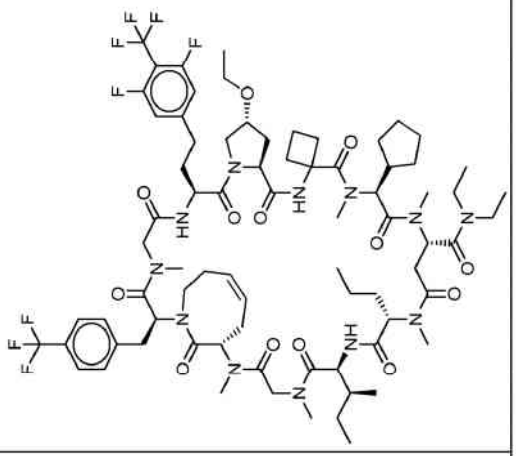
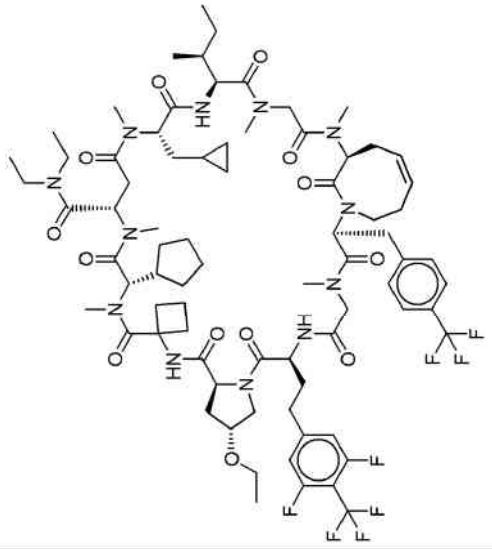
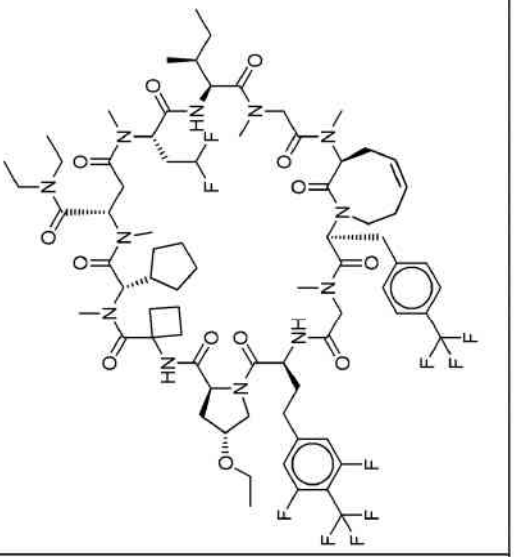
	
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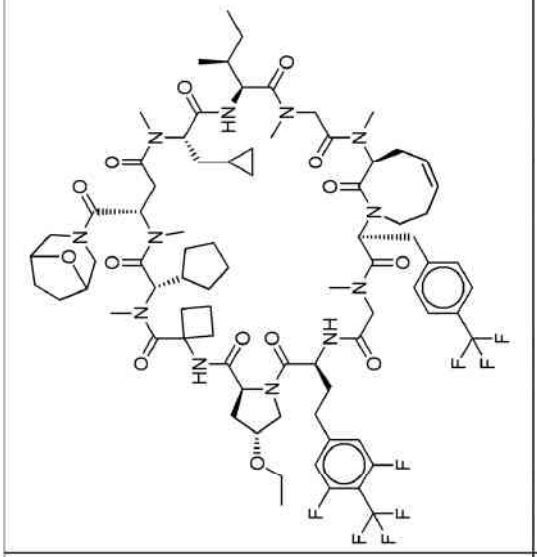
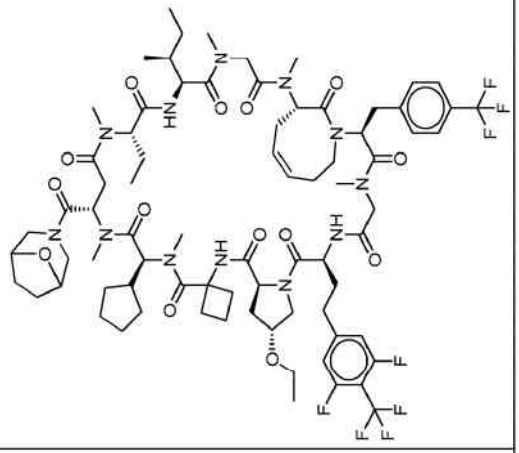
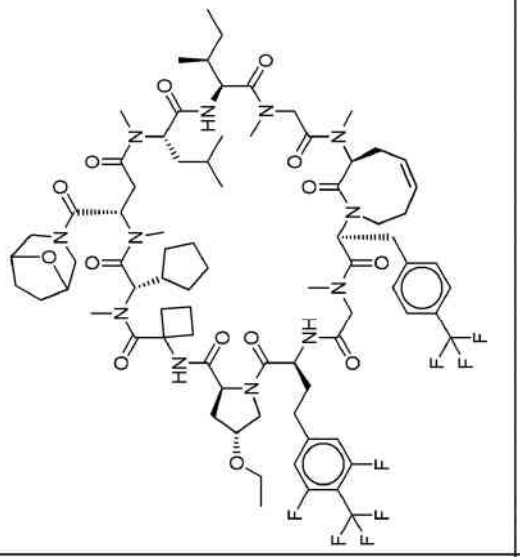
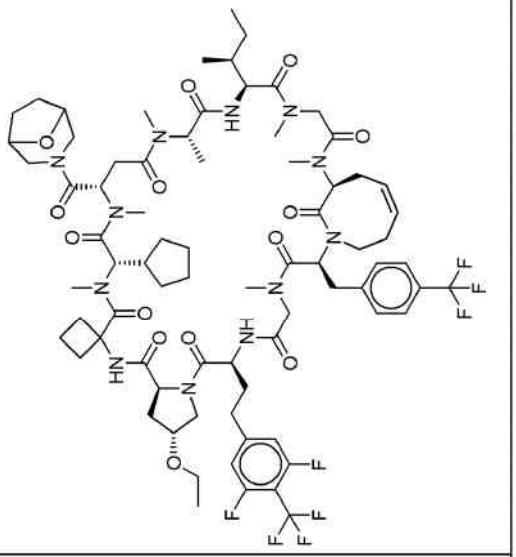
	
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PP1 291	PP1 293

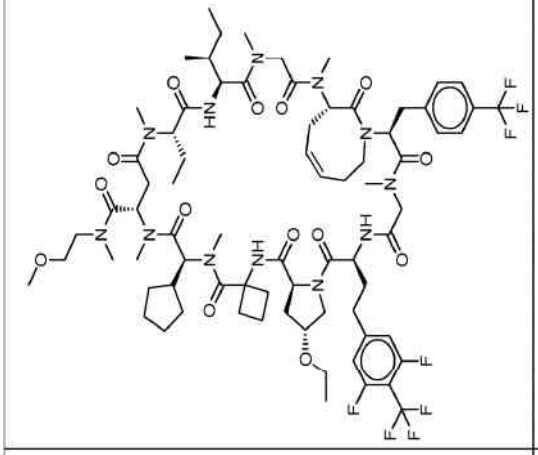
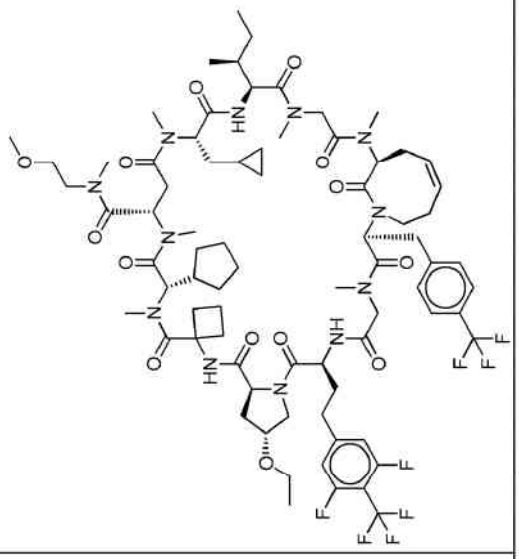
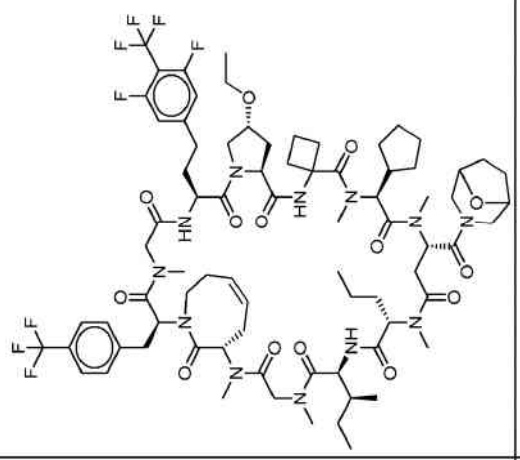
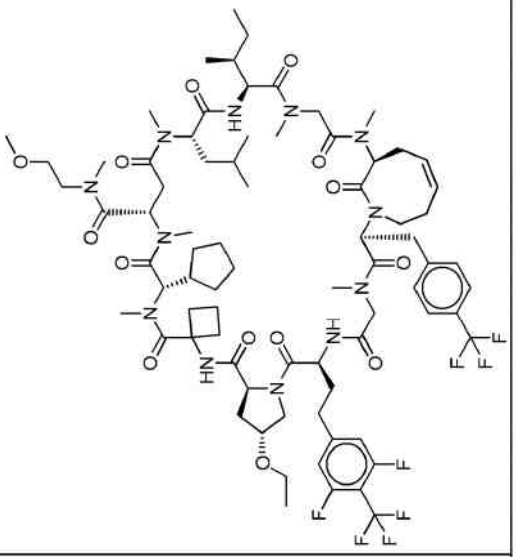
	
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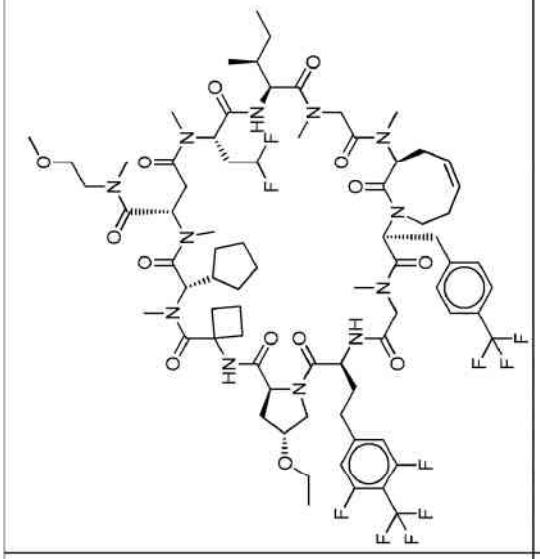
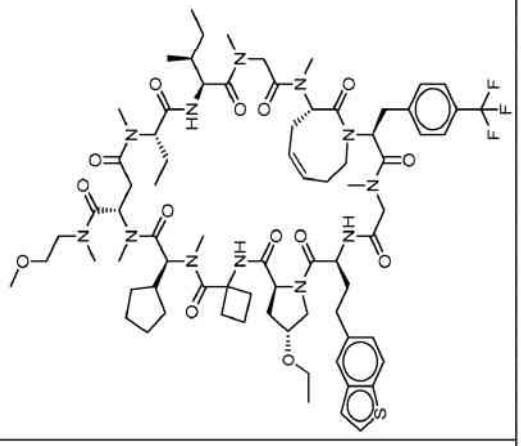
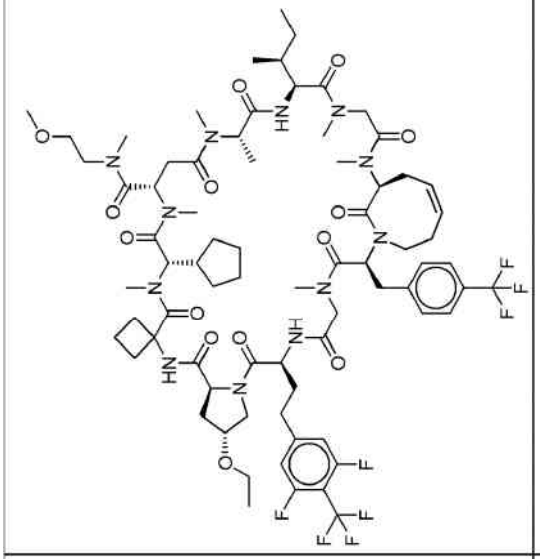
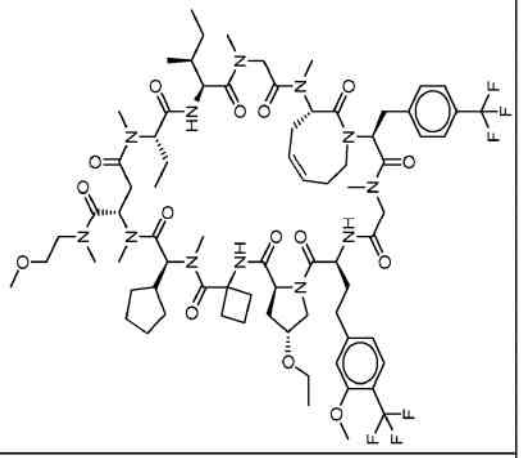
	
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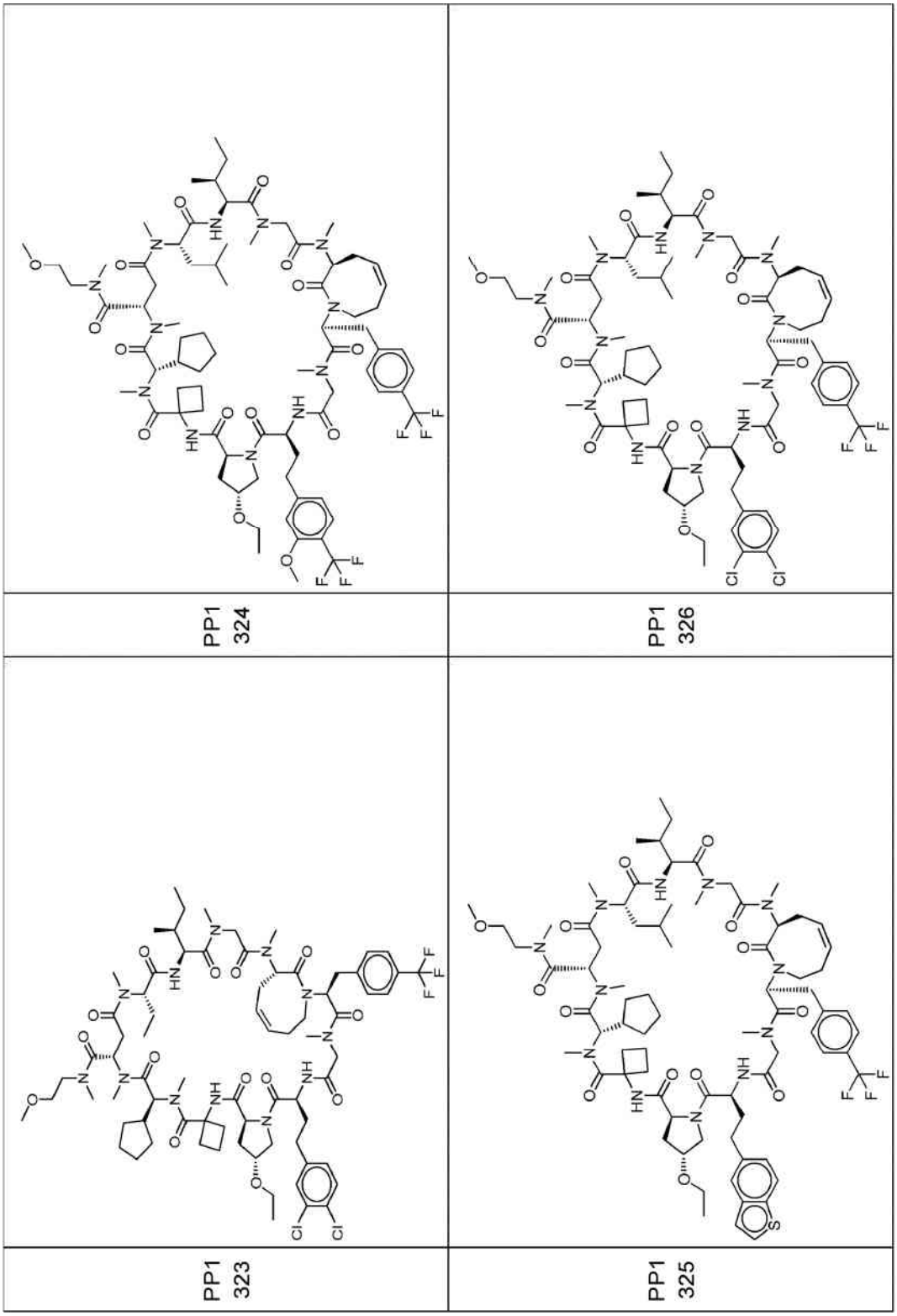
	
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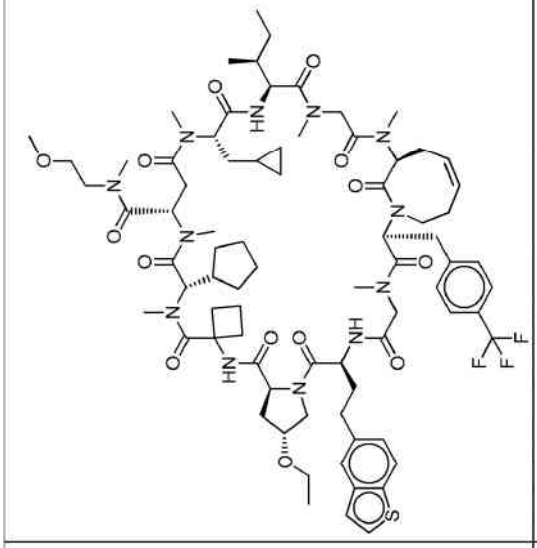
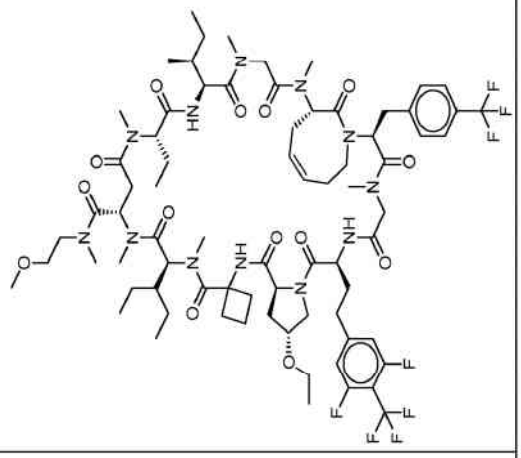
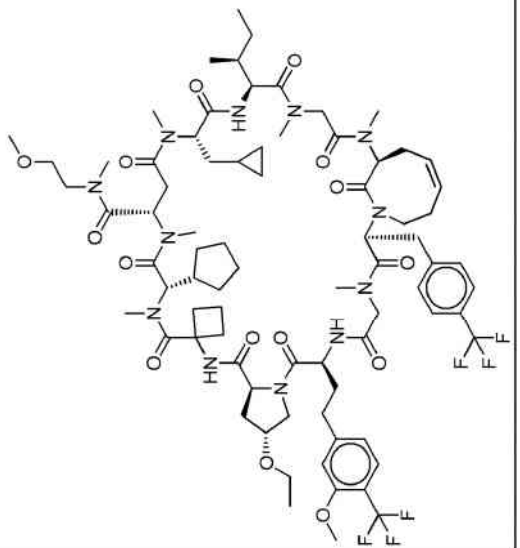
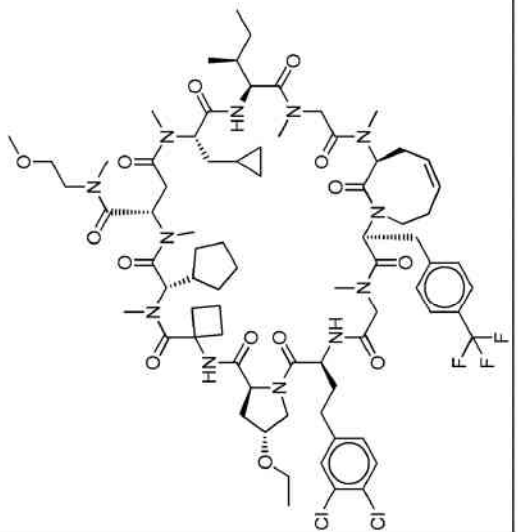
	
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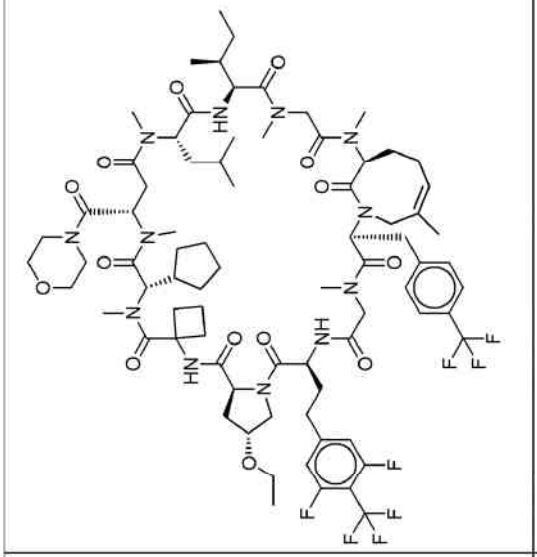
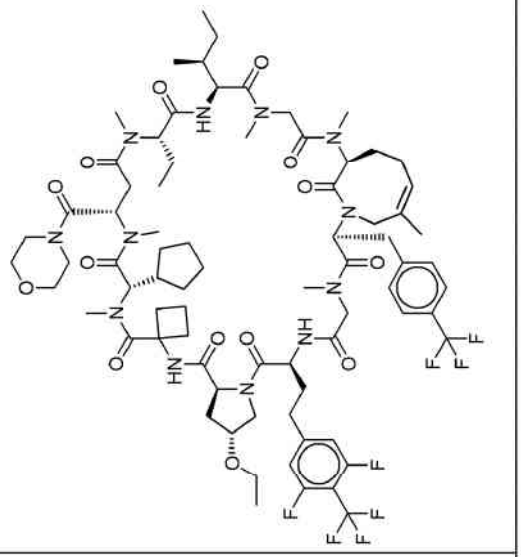
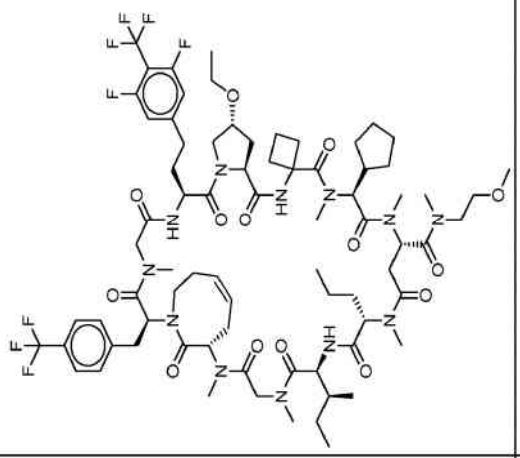
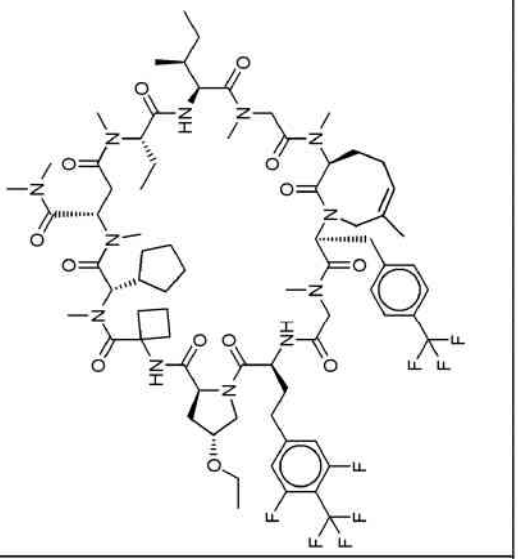
	
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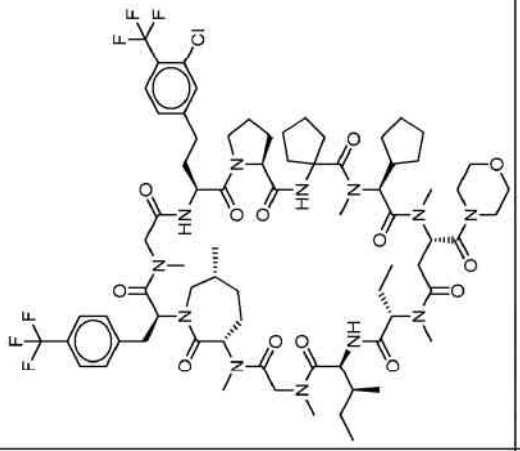
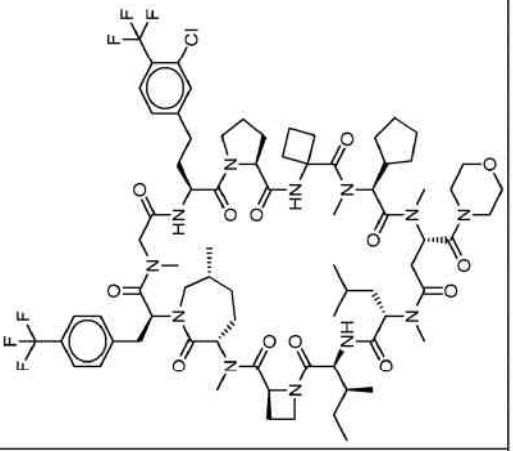
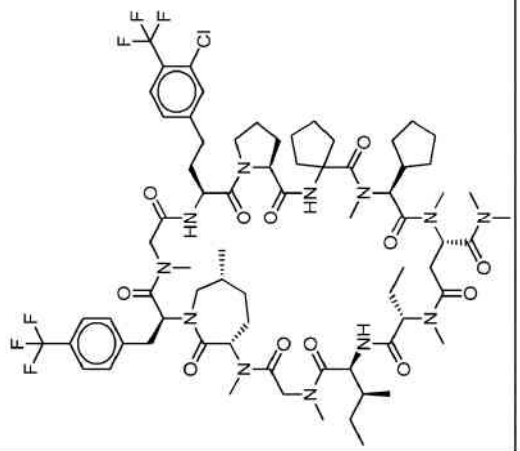
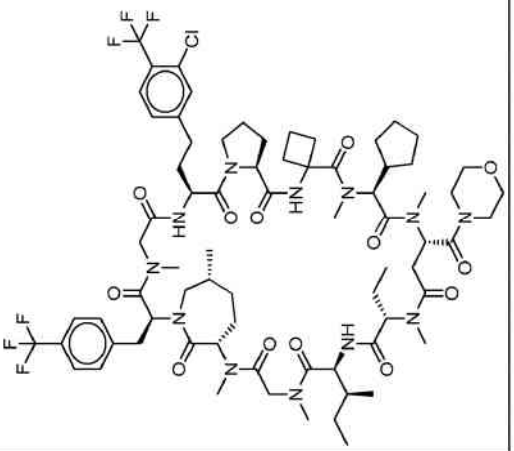
	
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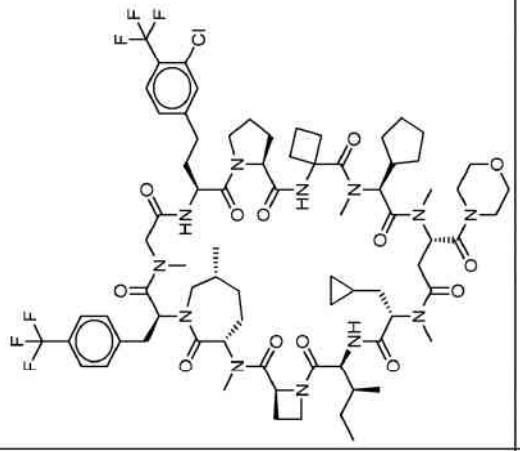
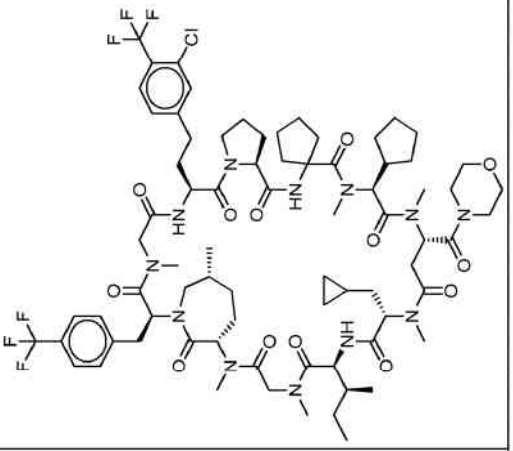
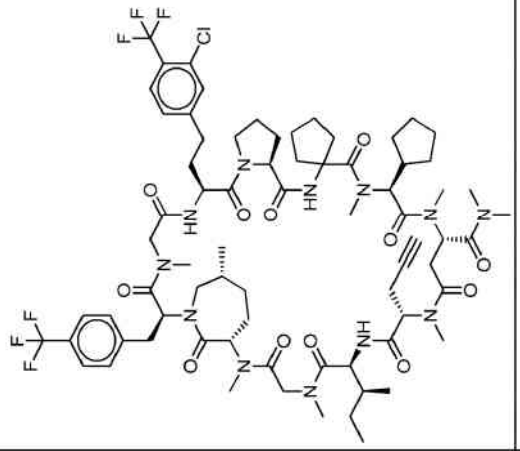
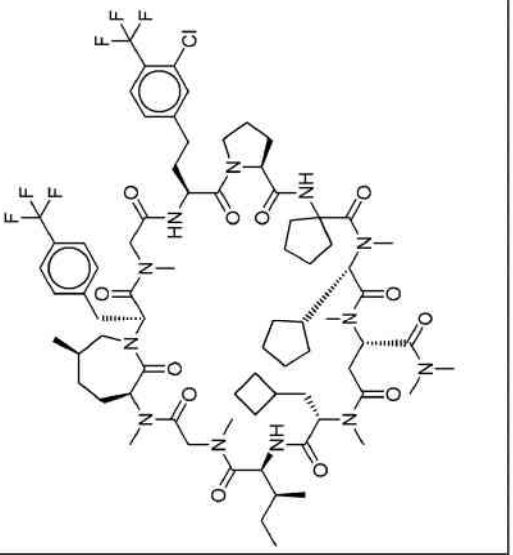
	
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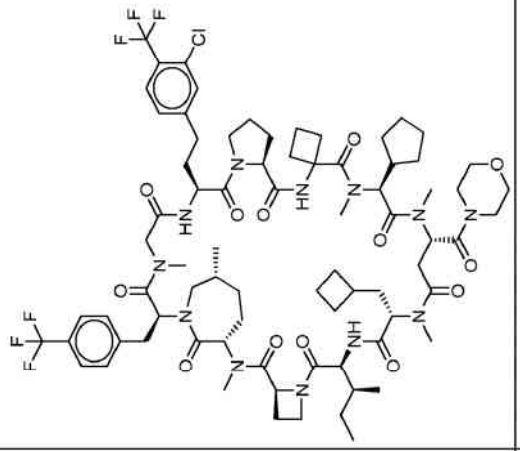
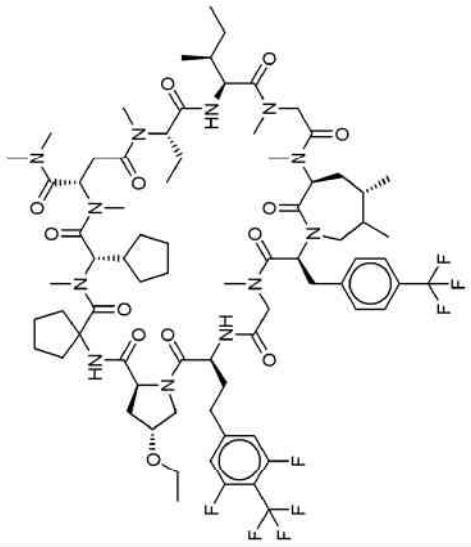
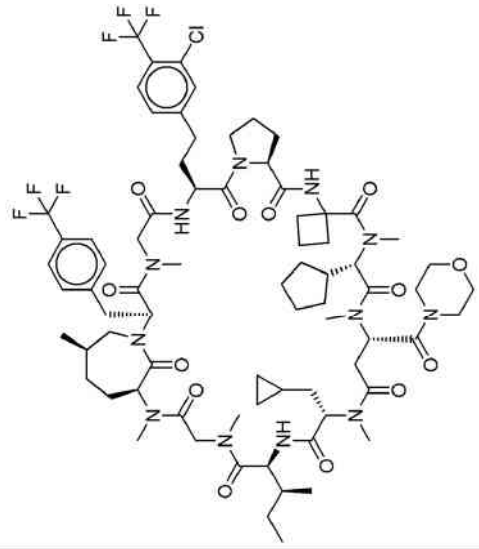
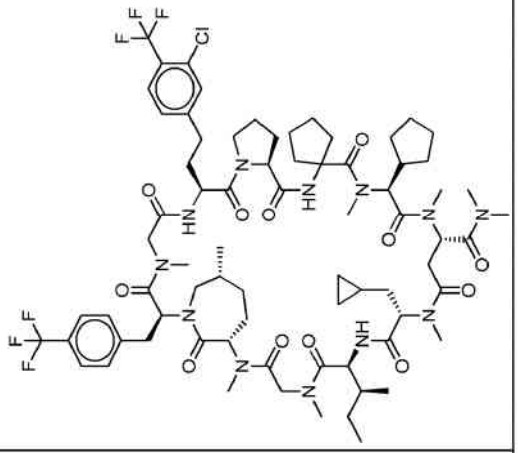

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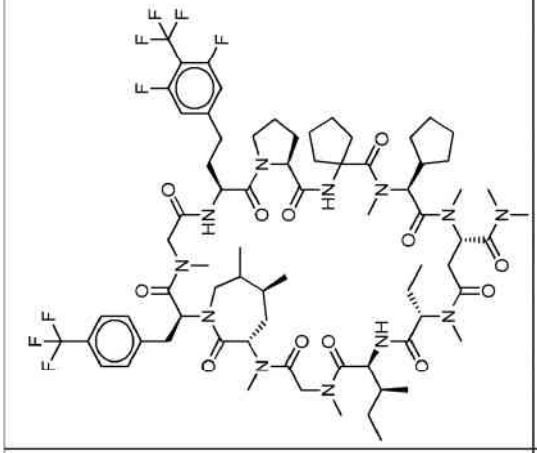
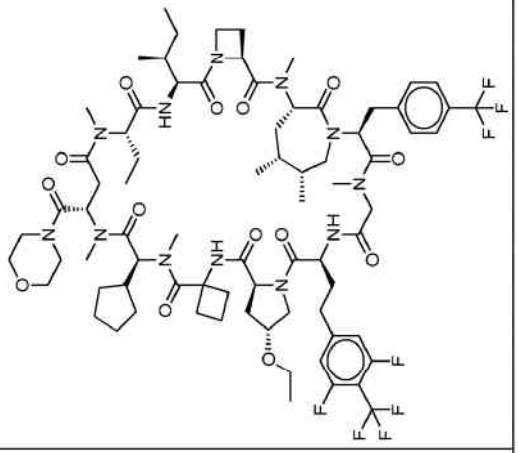
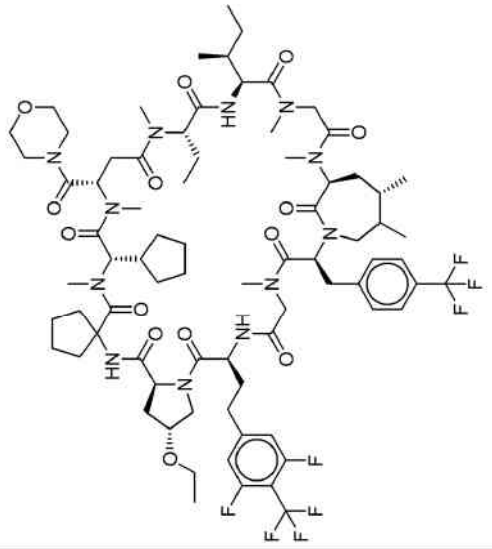
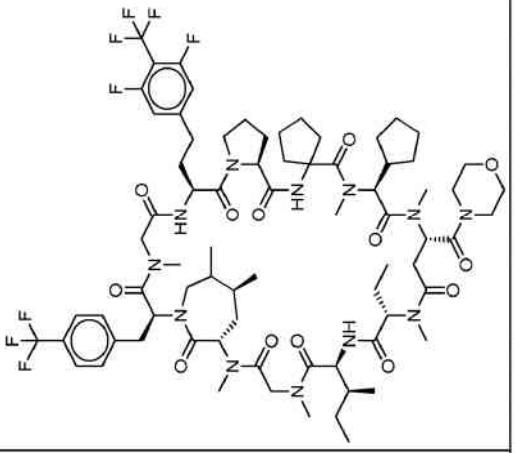
	
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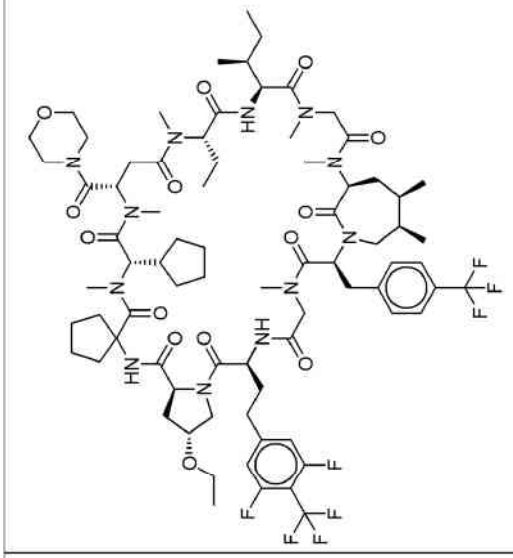
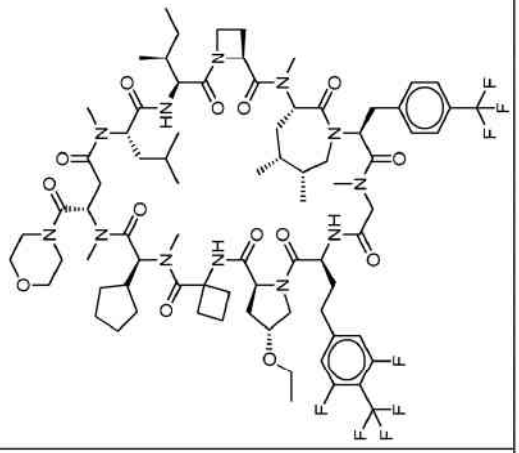
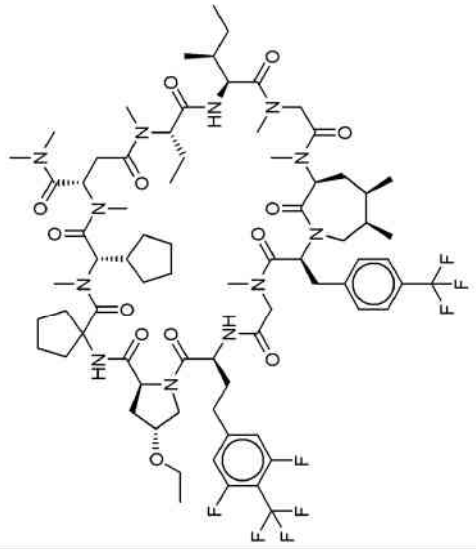
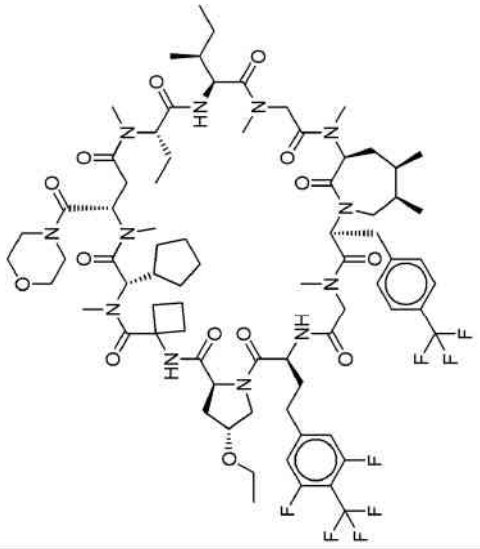
	
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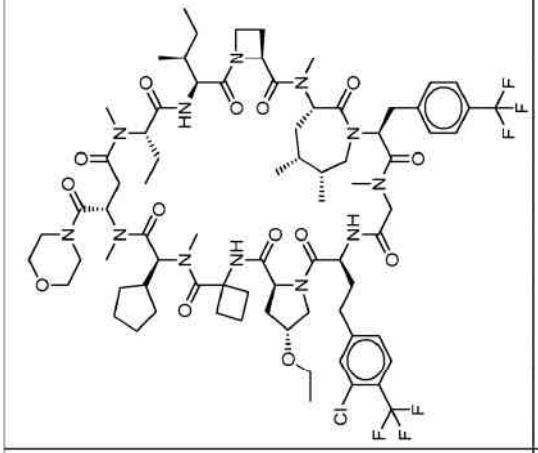
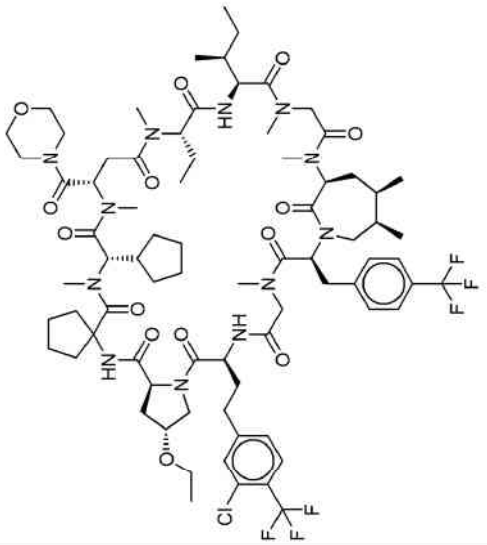
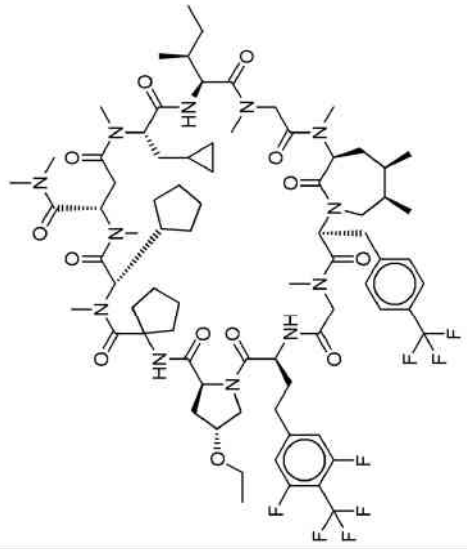
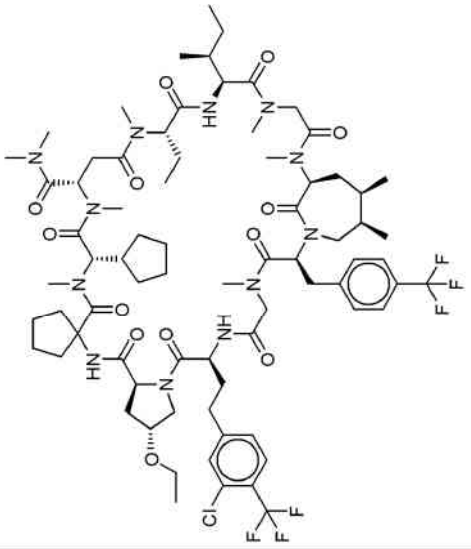
	
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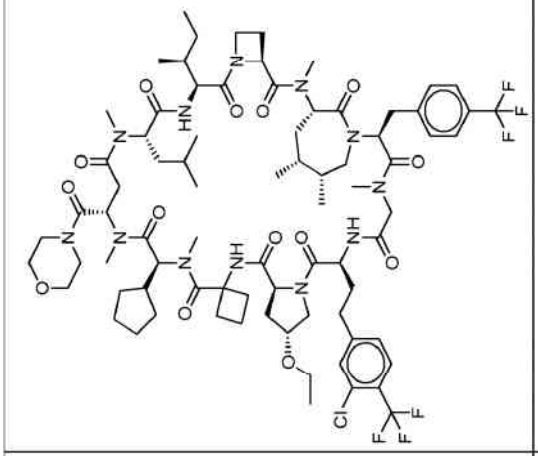
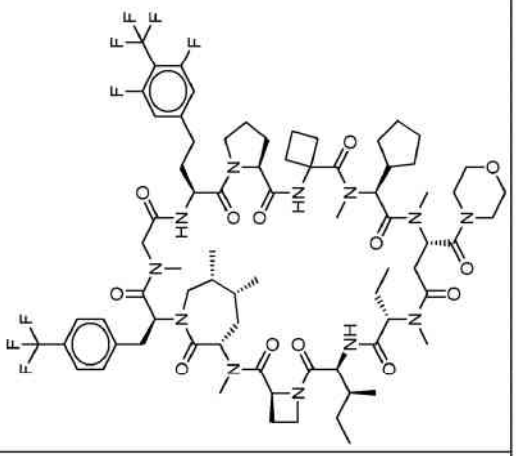
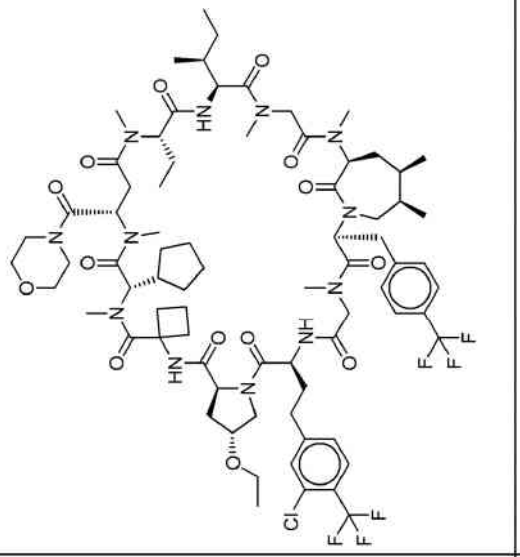
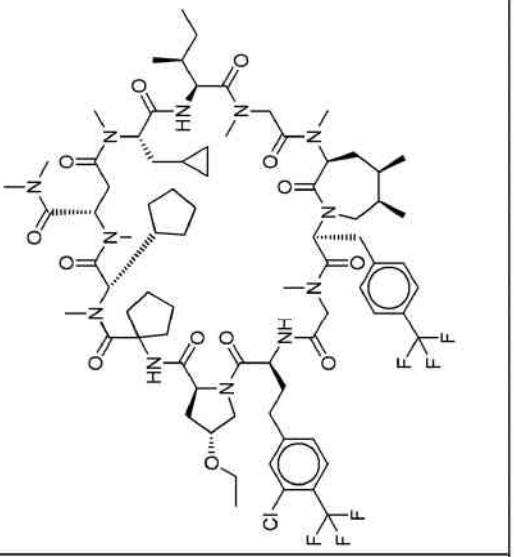
	
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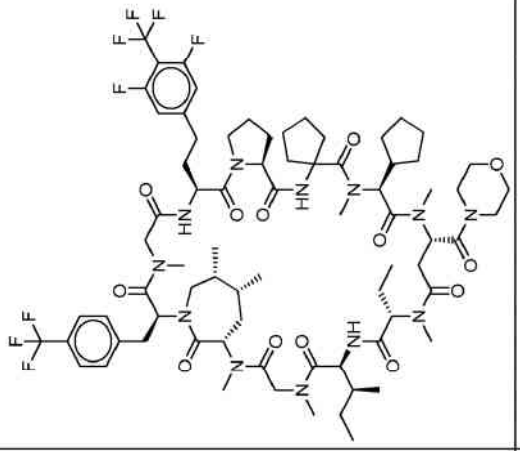
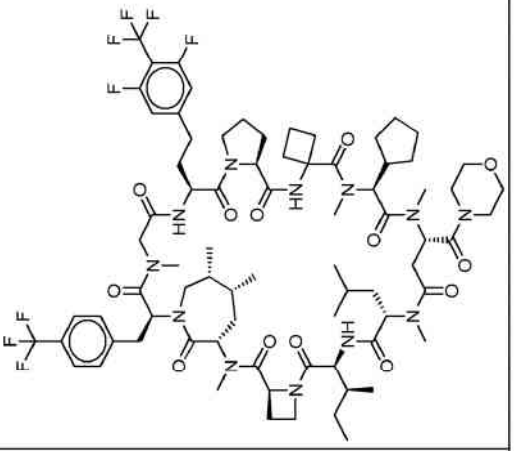
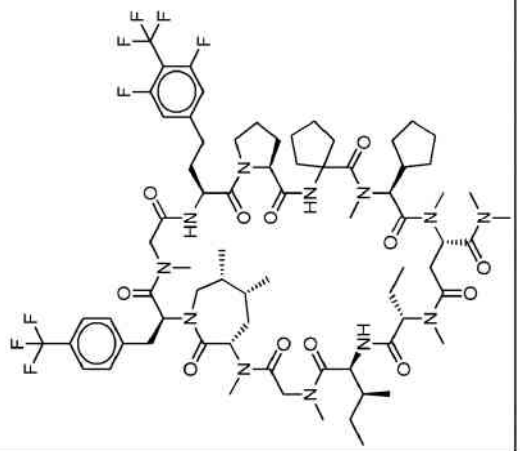
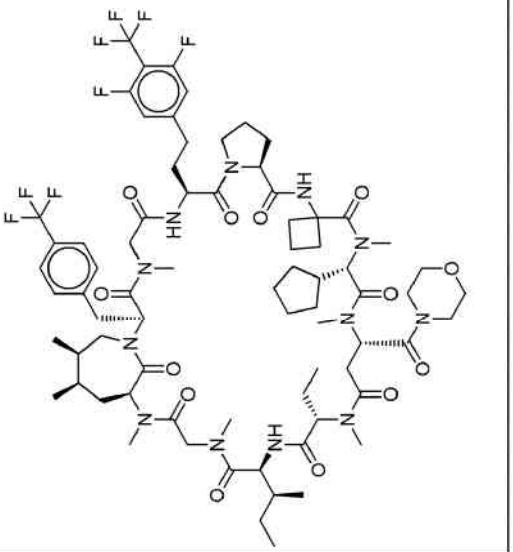
	
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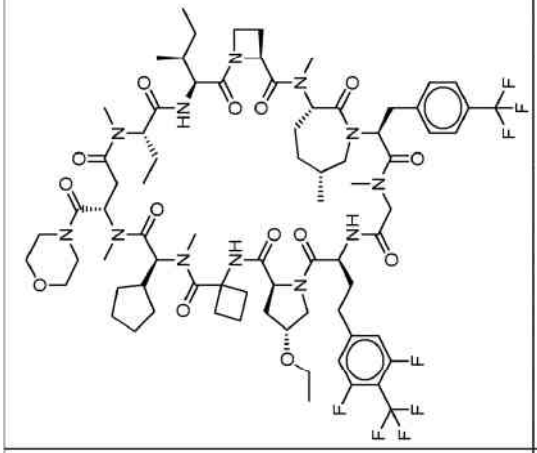
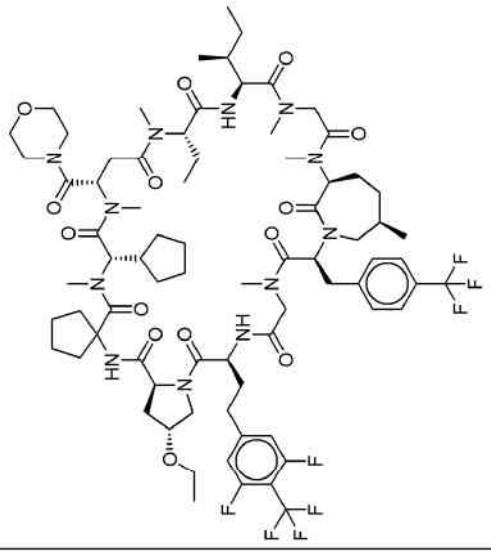
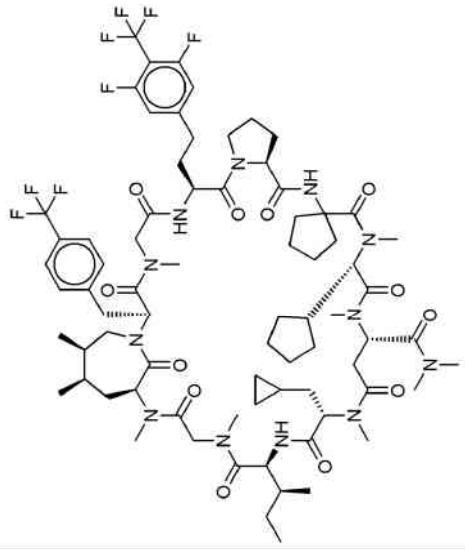
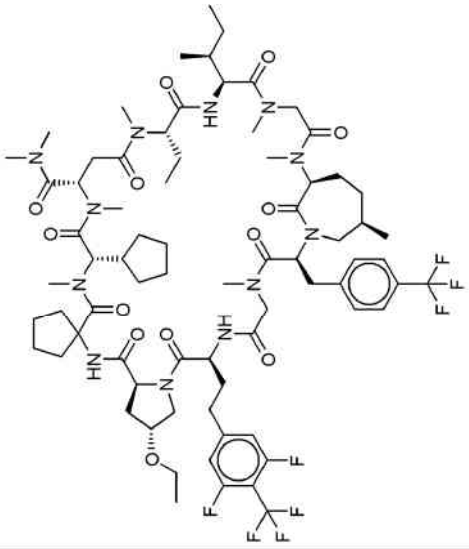
	
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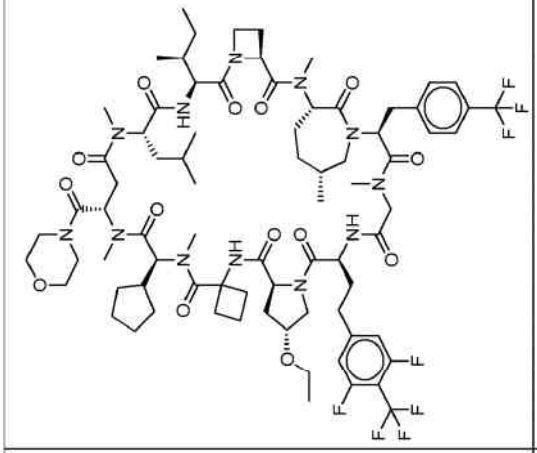
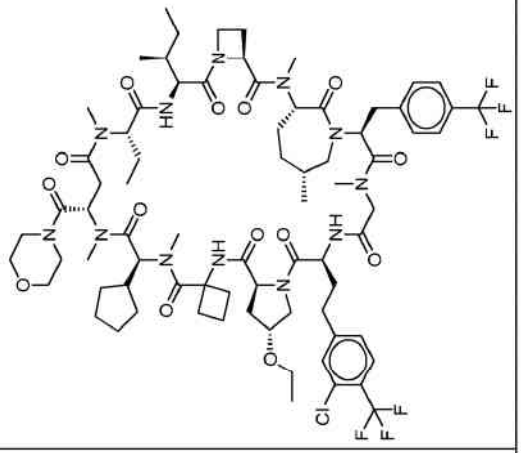
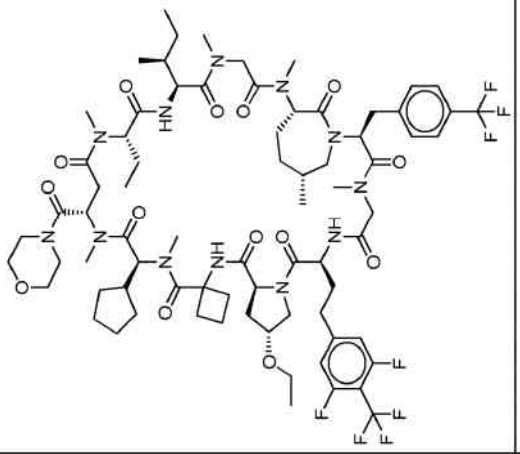
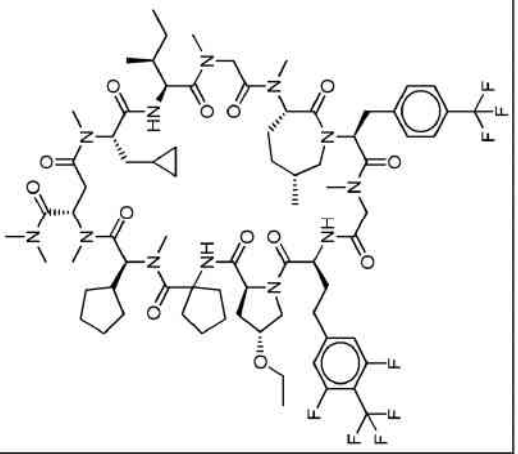
	
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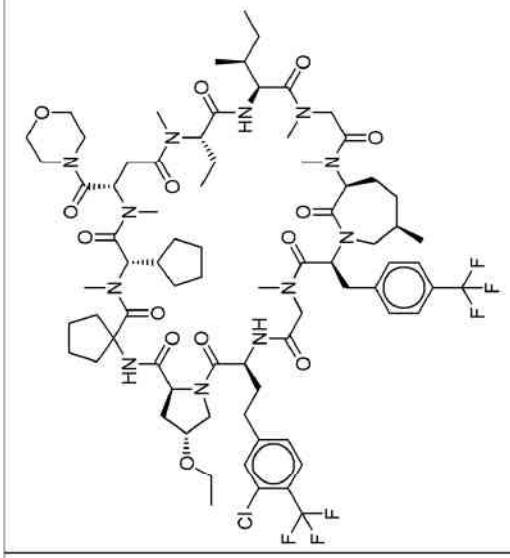
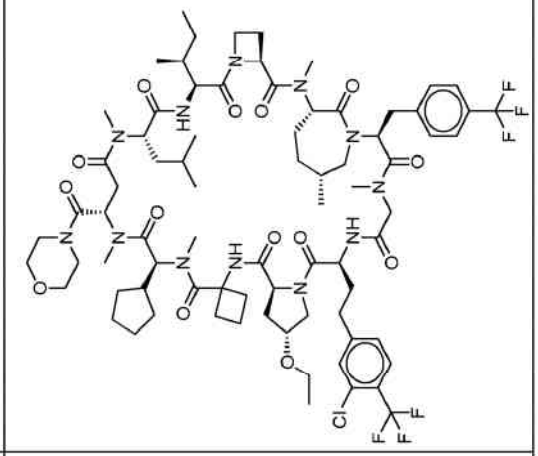
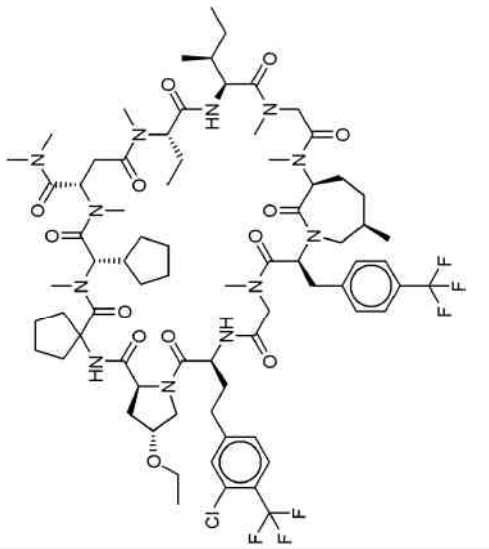
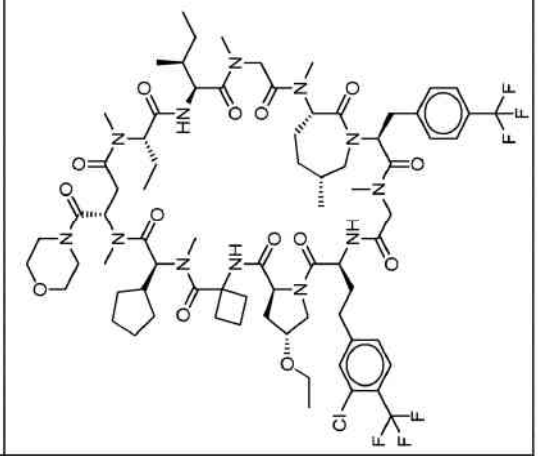
	
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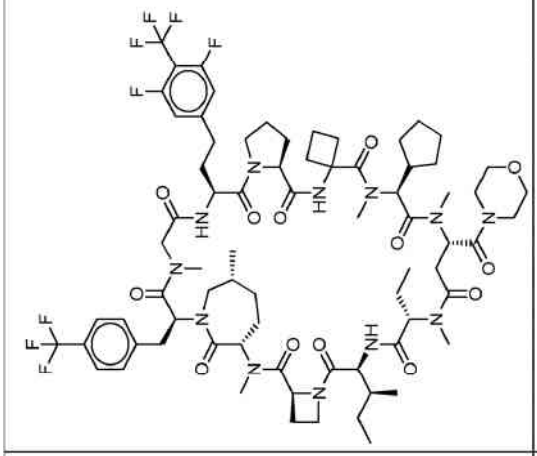
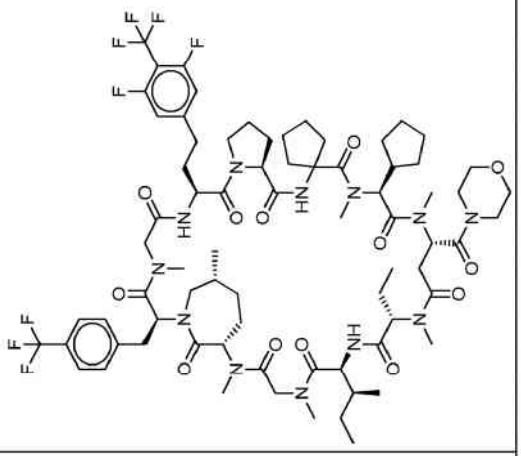
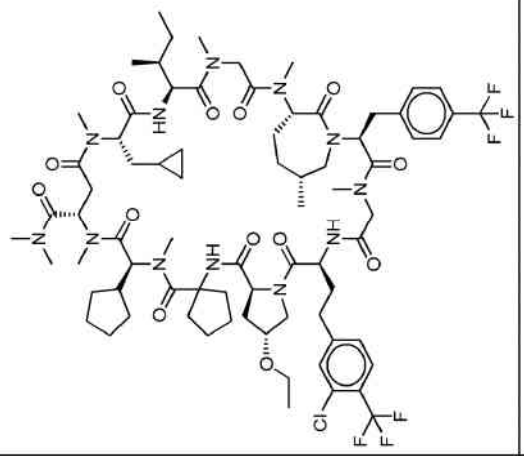
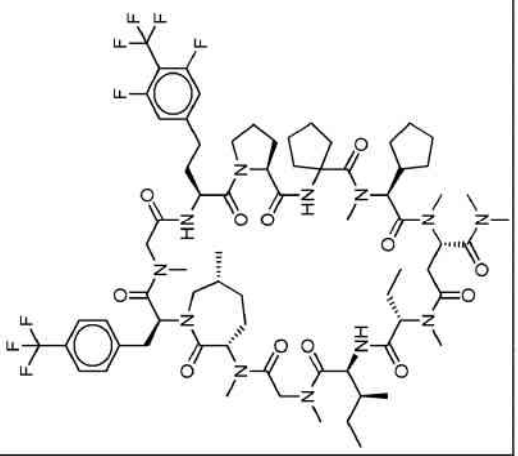
	
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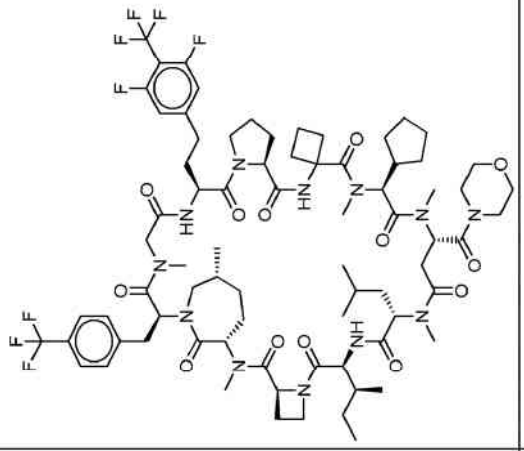
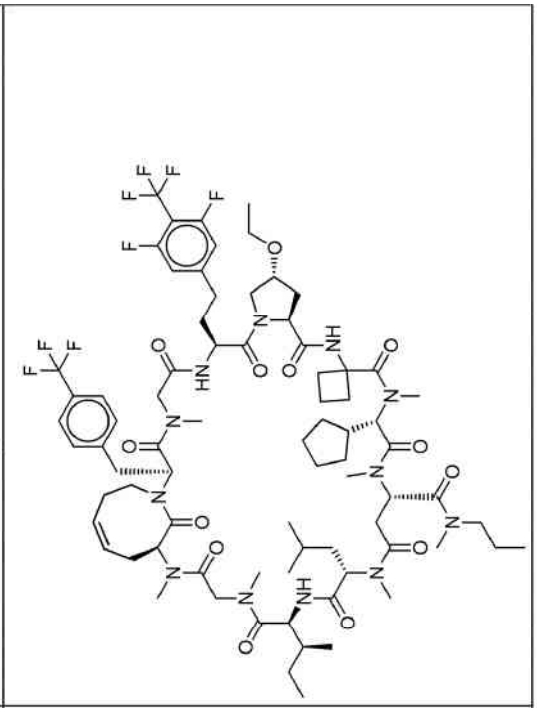
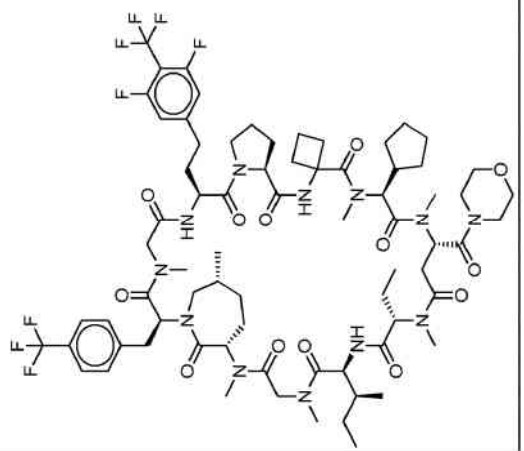
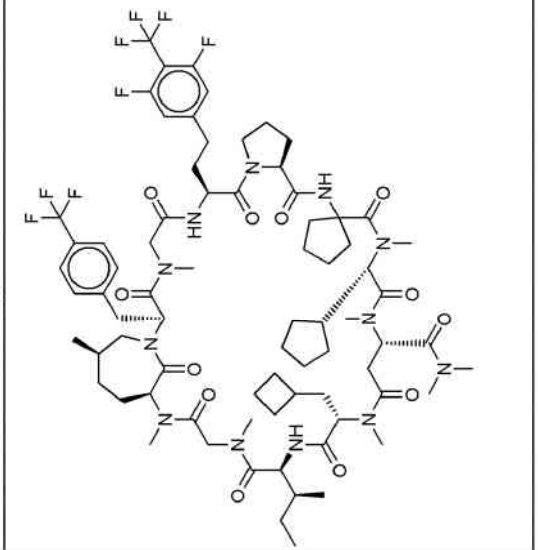
	
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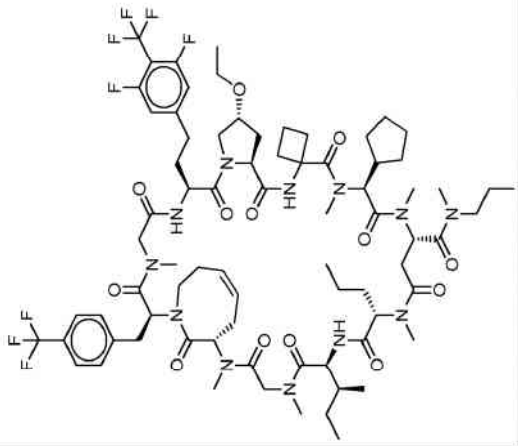
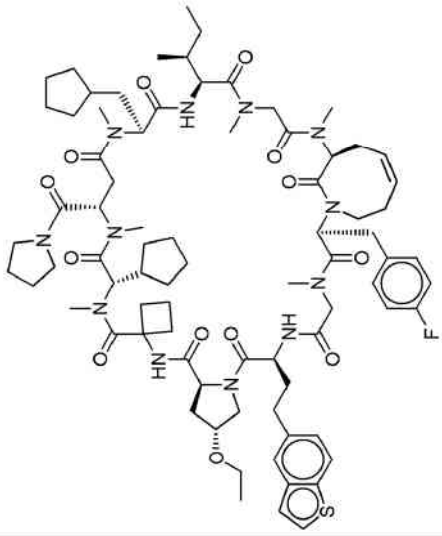
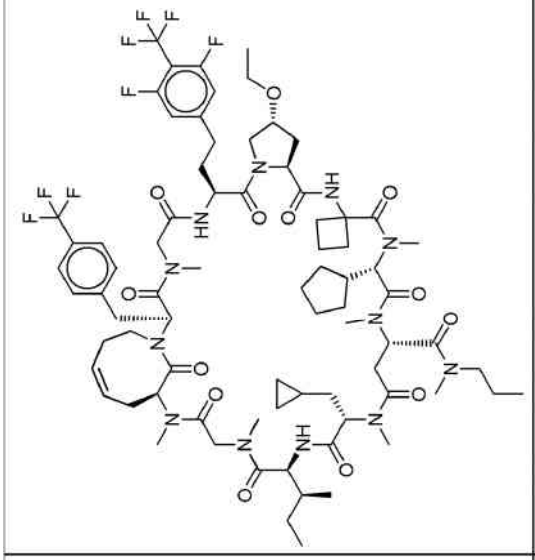
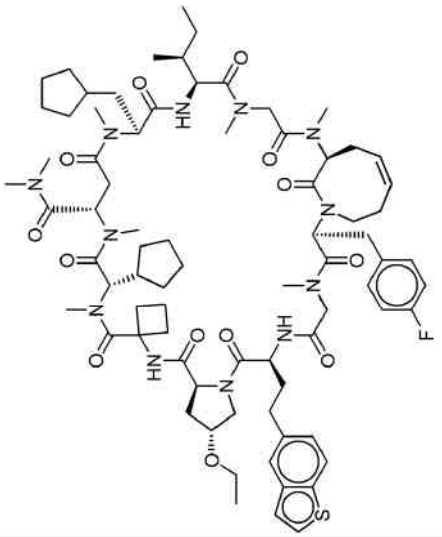
	
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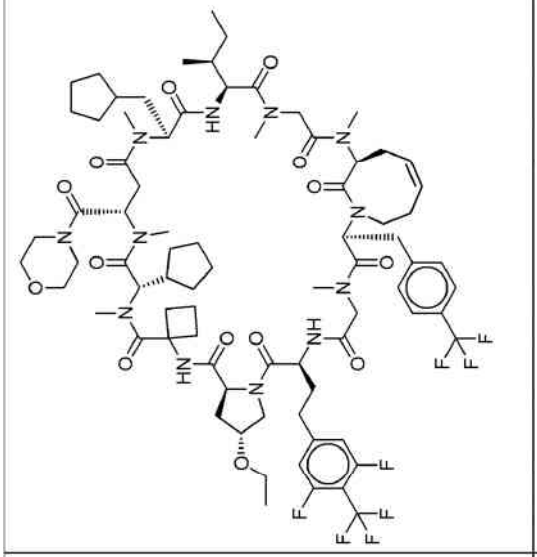
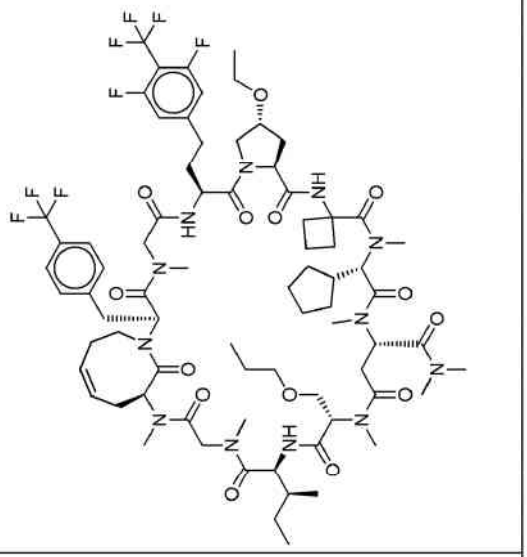
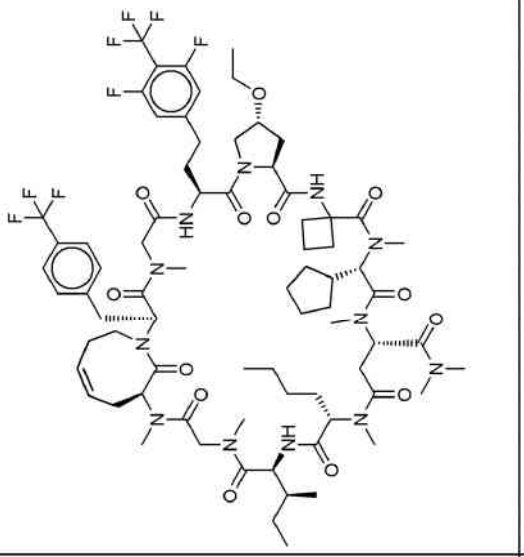
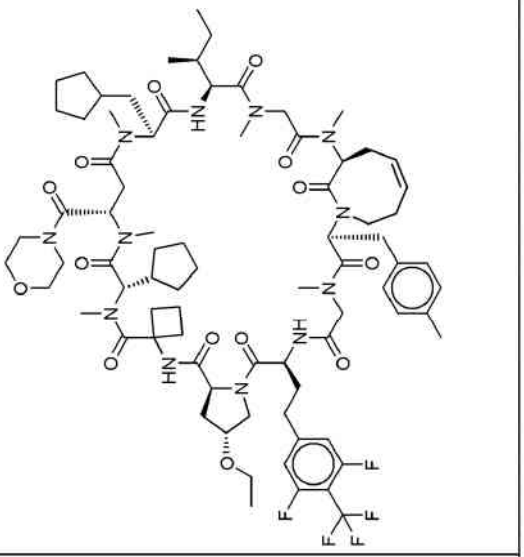
	
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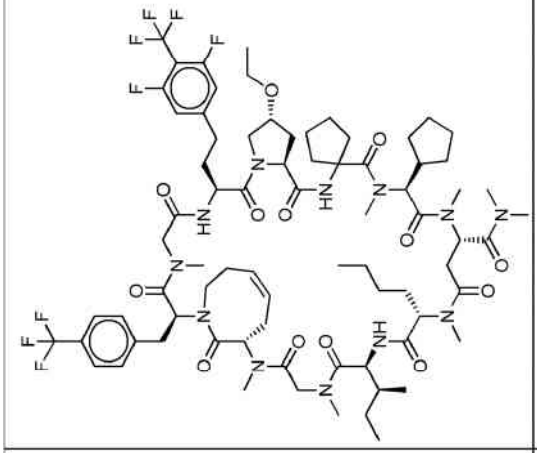
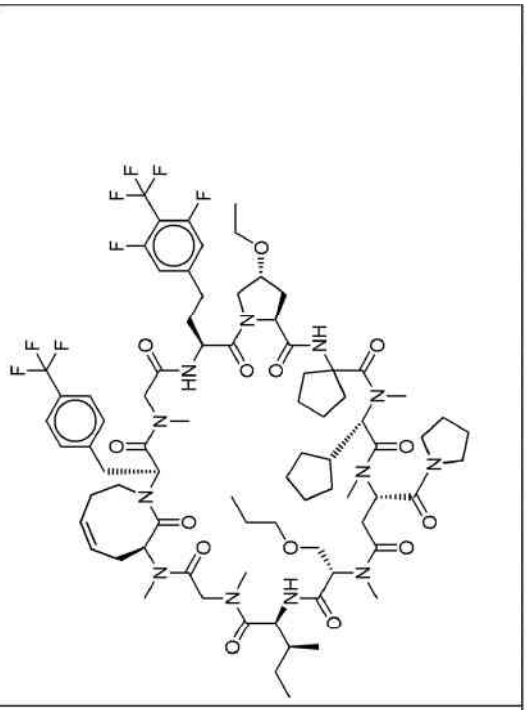
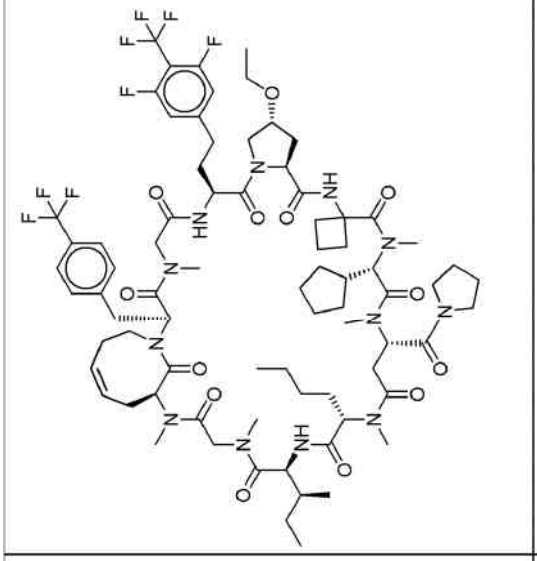
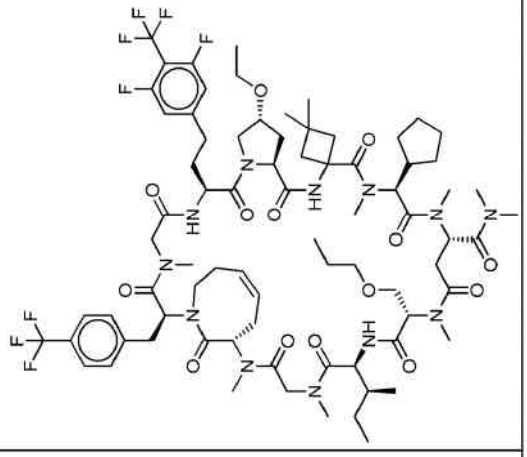
	
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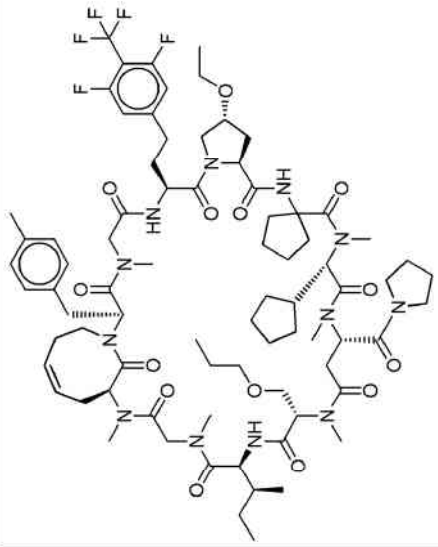
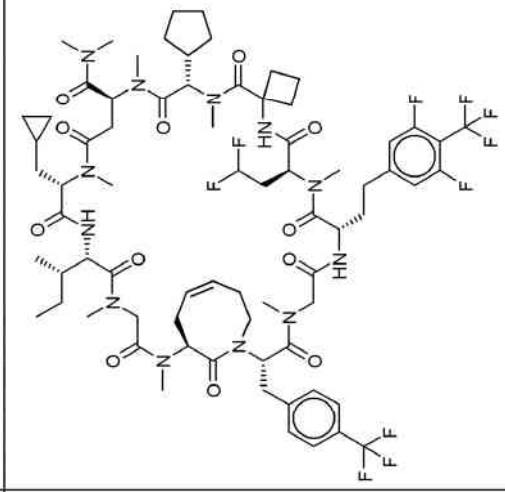
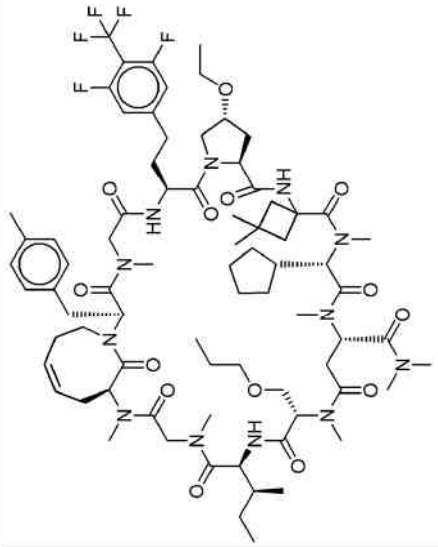
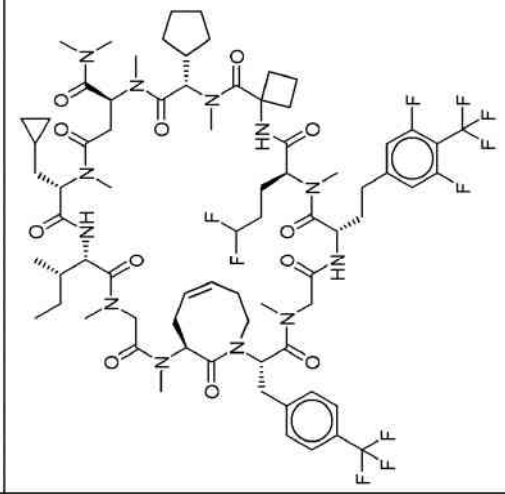
	
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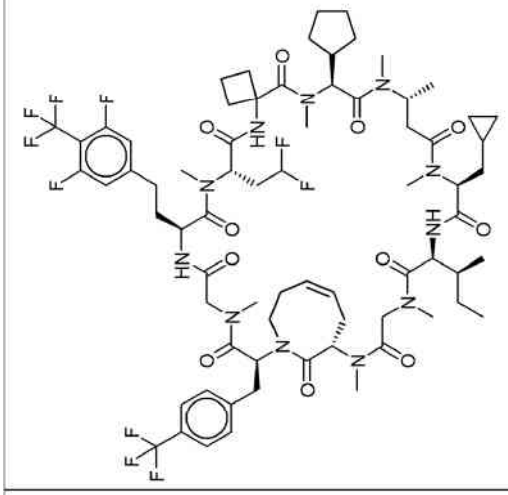
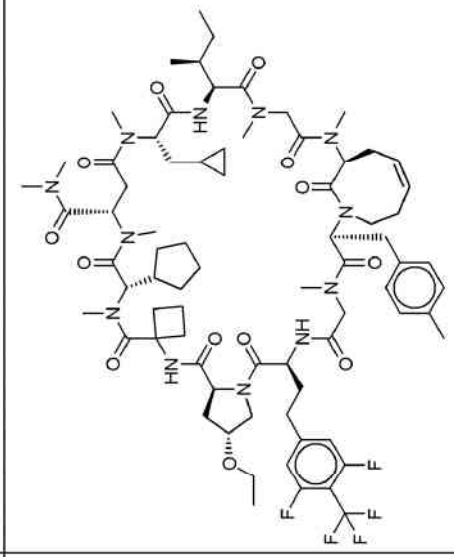
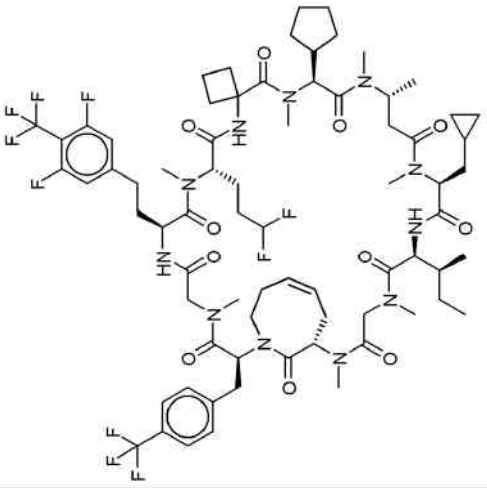
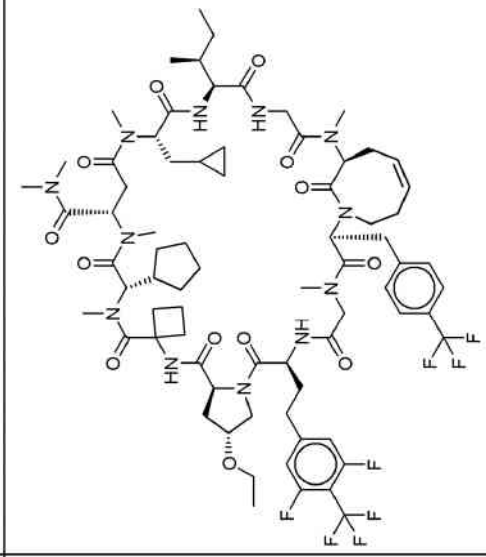
	
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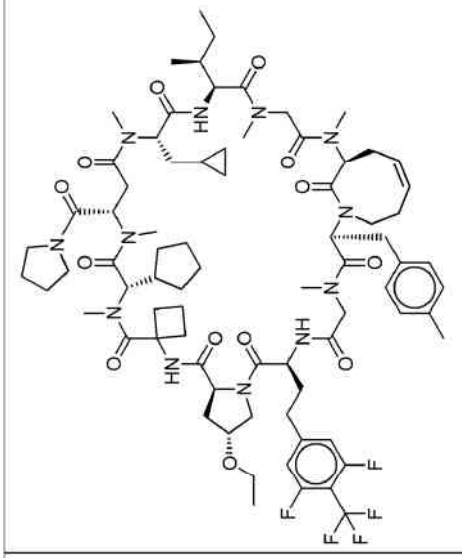
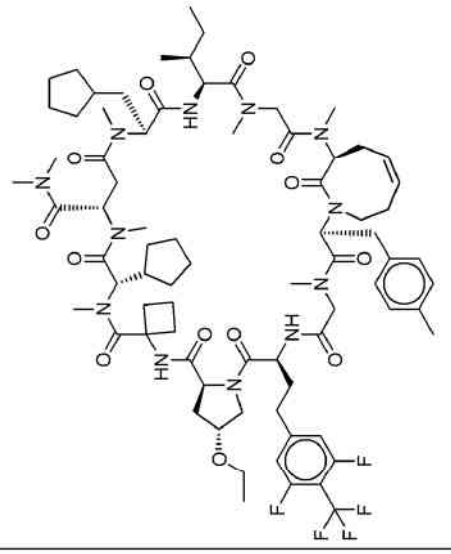
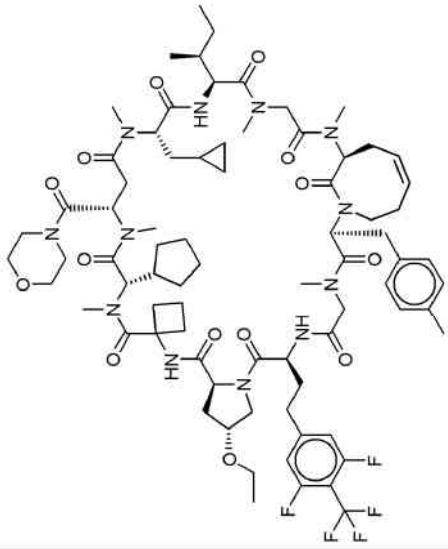
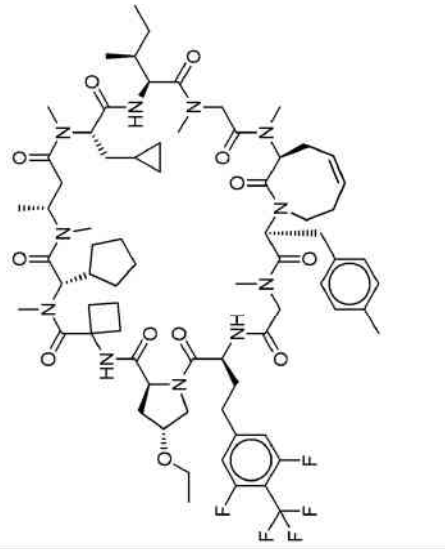
	
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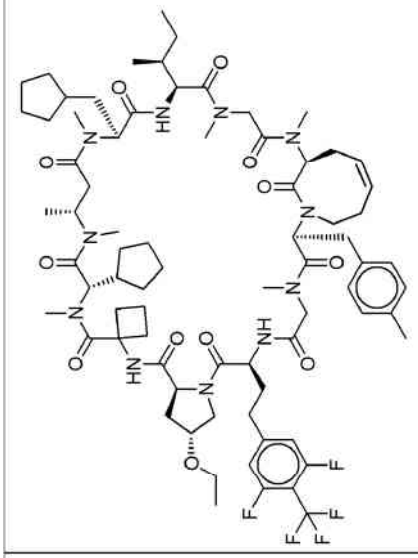
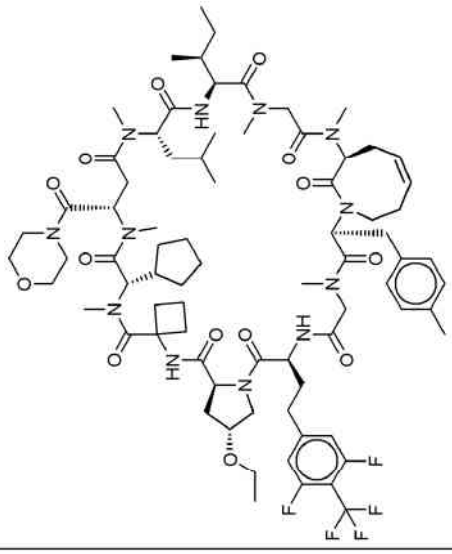
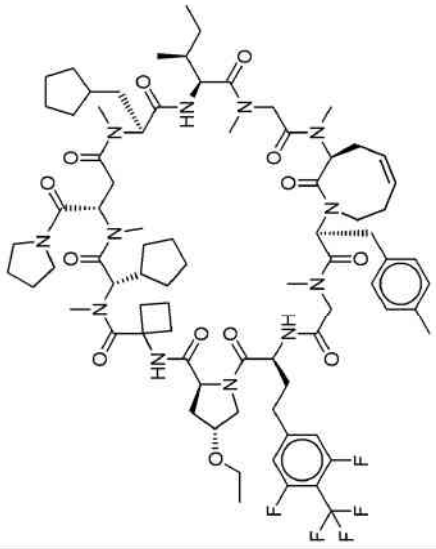
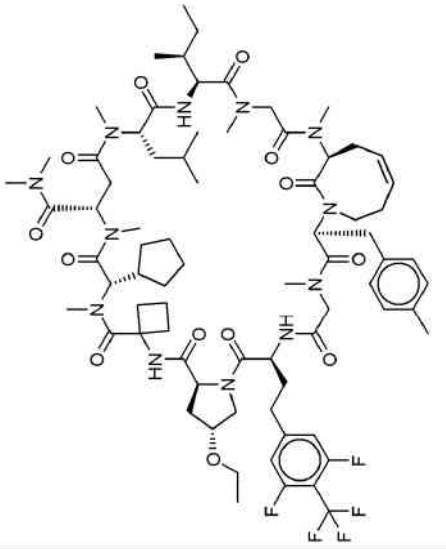
	
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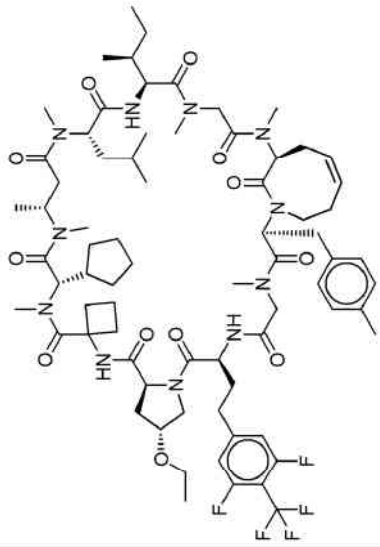
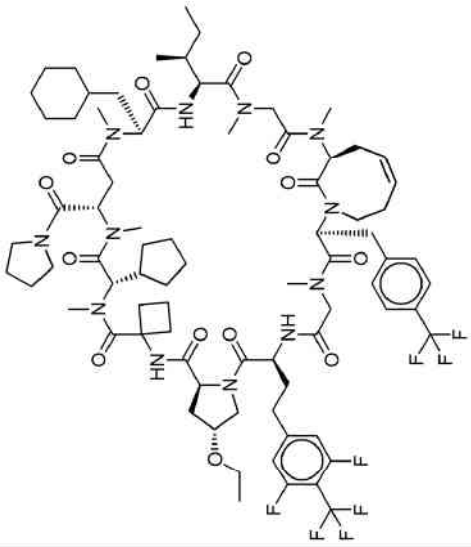
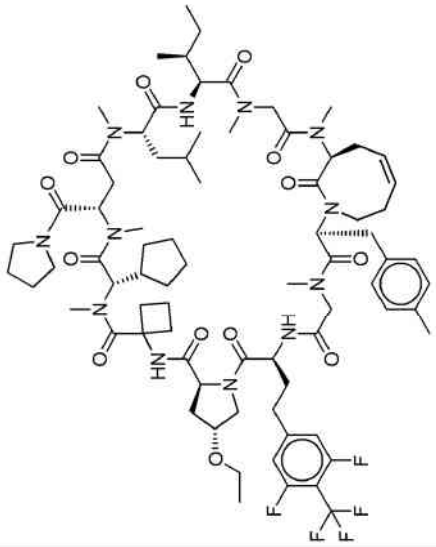
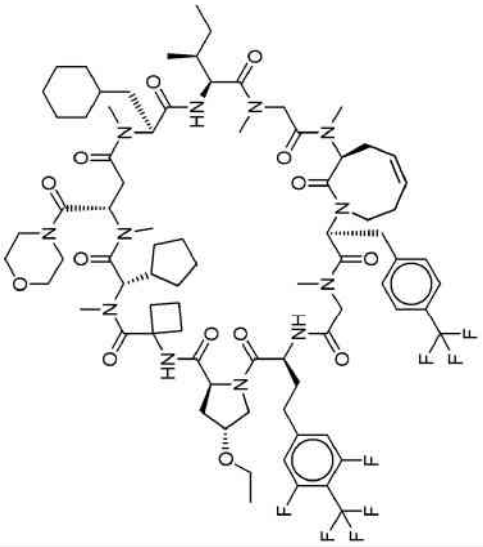
	
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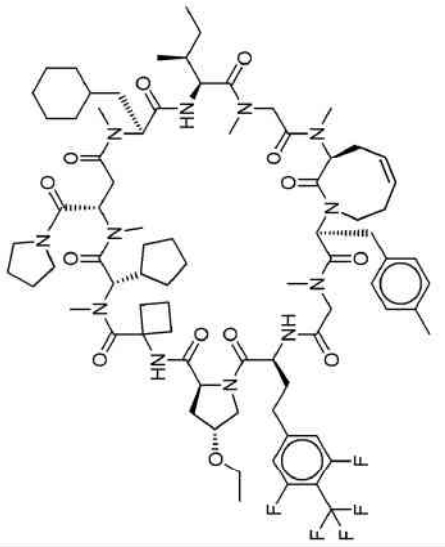
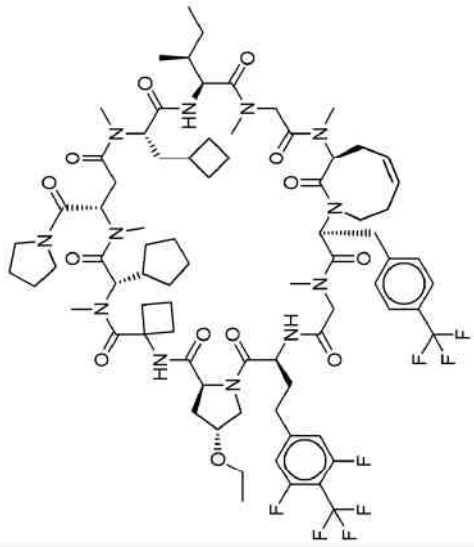
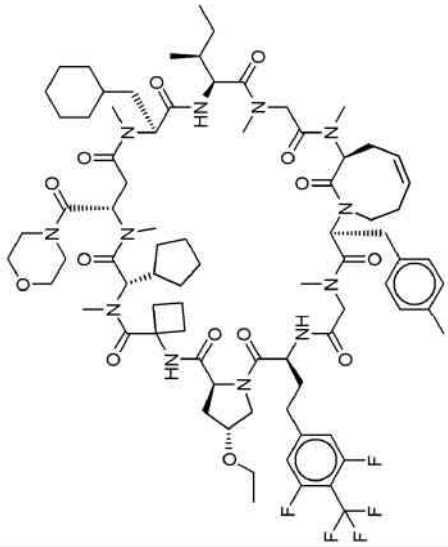
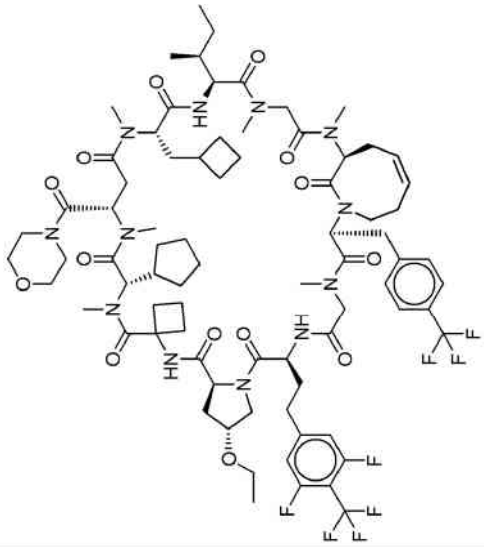
	
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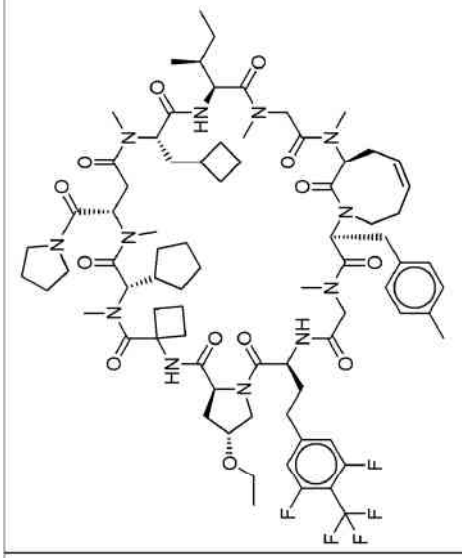
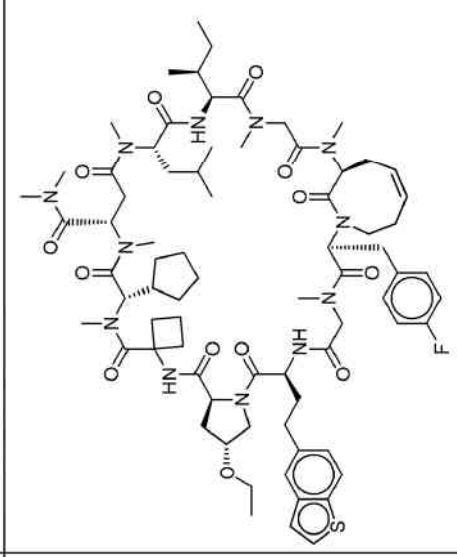
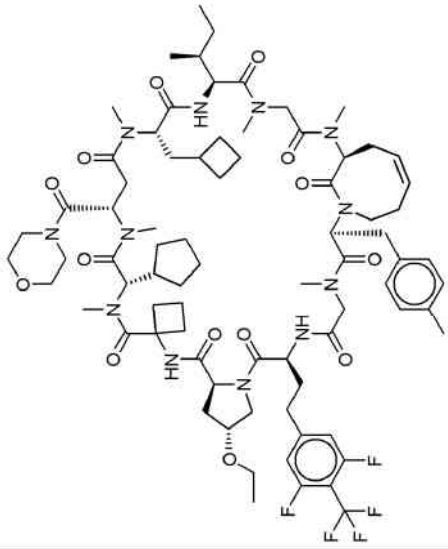
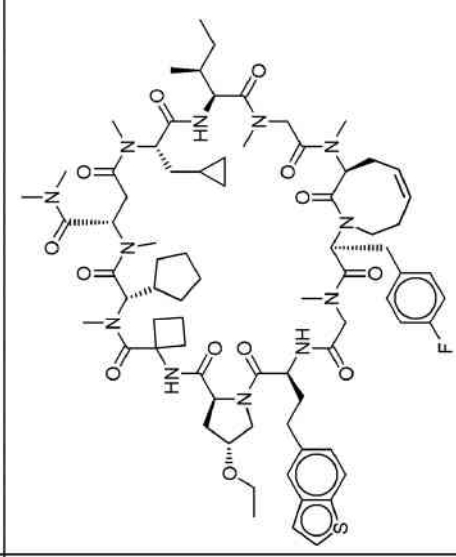
	
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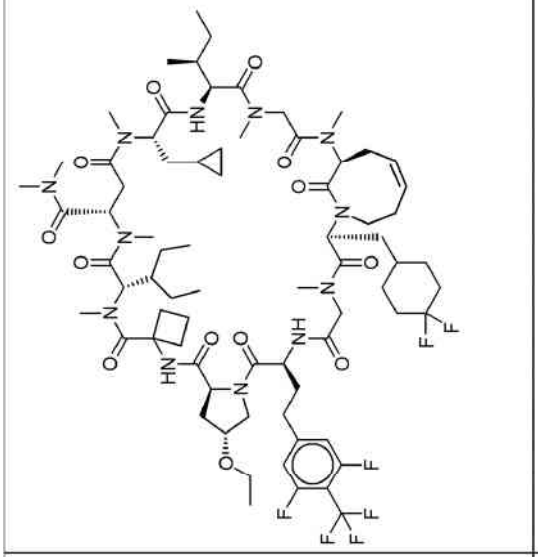
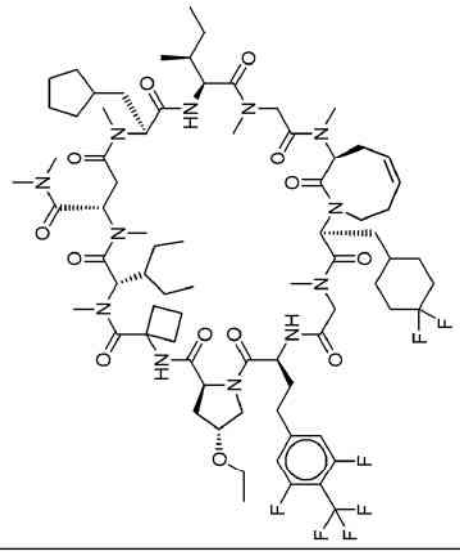
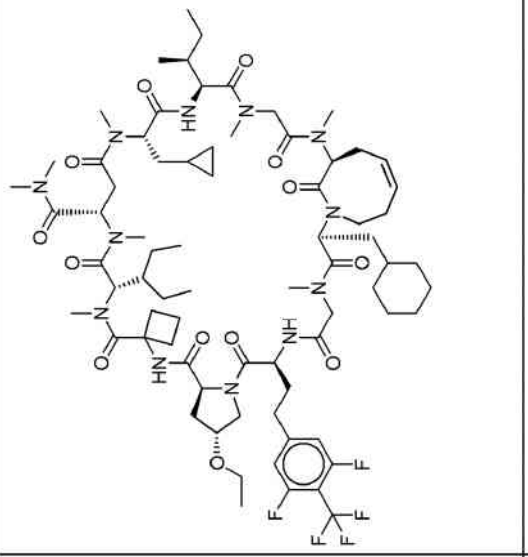
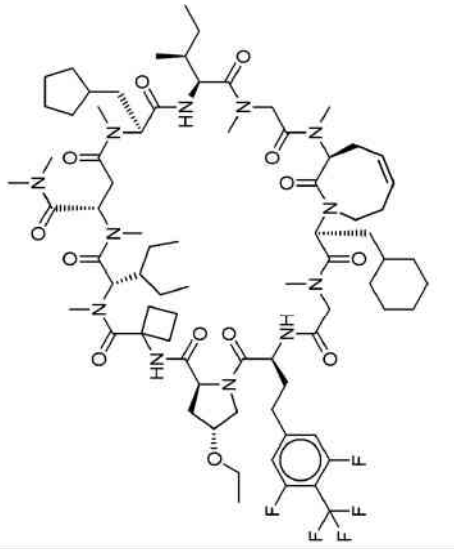
	
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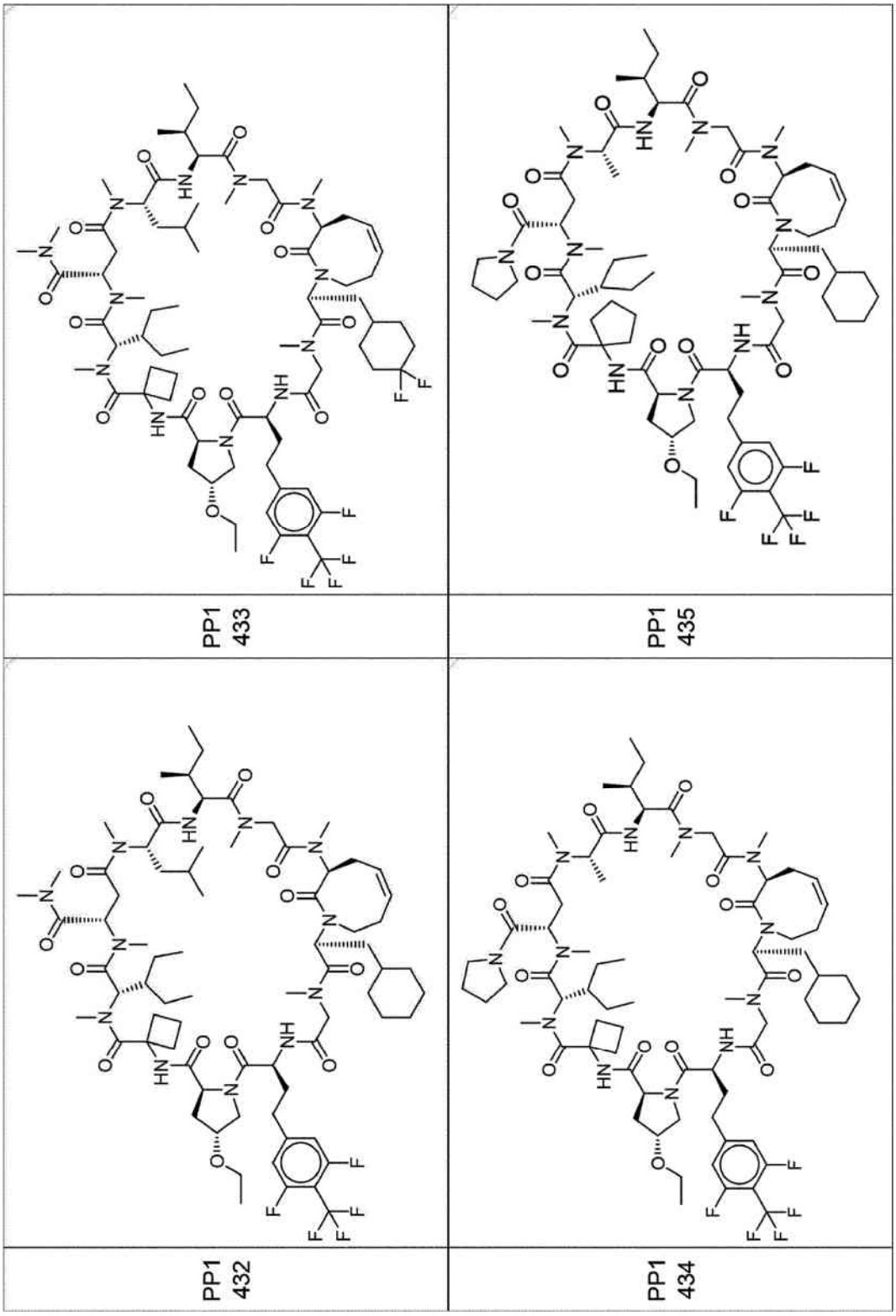
	
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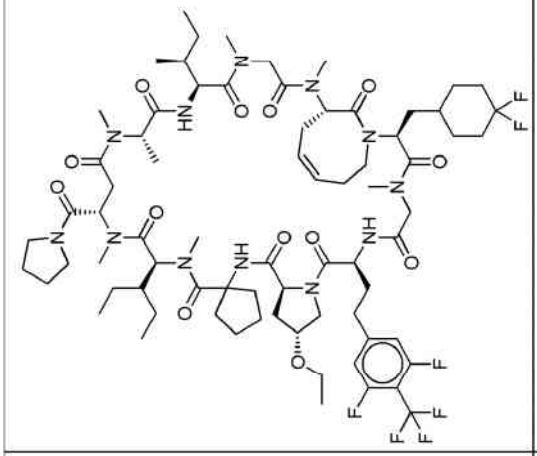
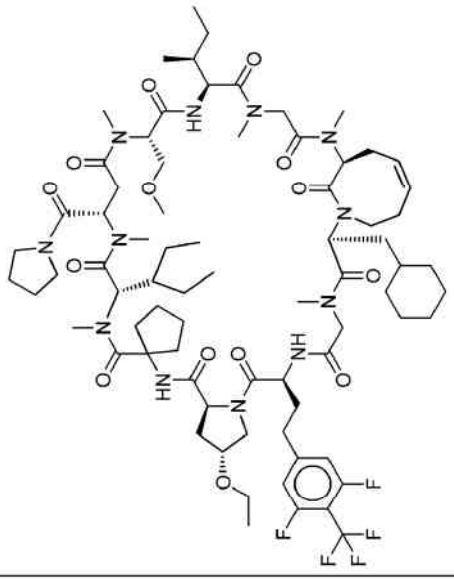
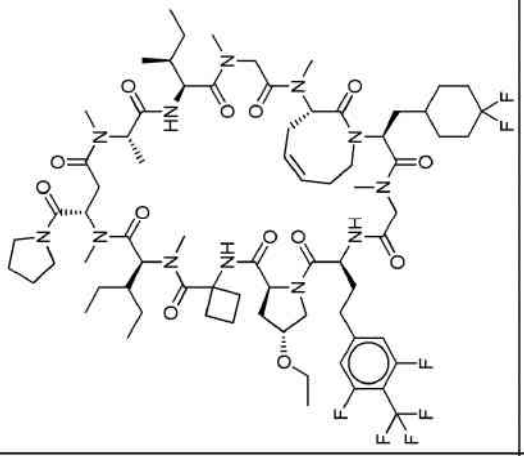
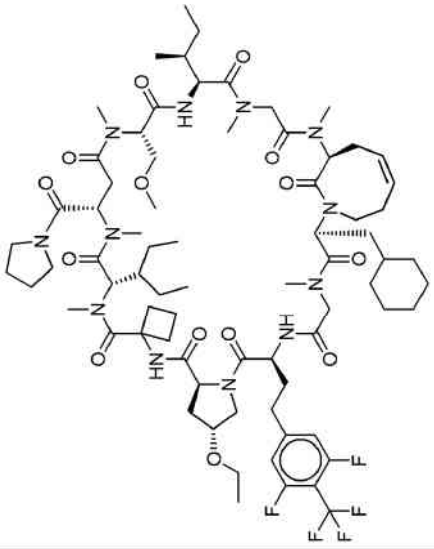
	
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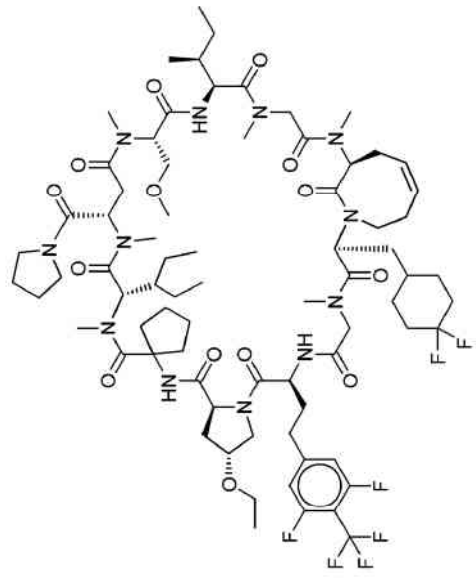
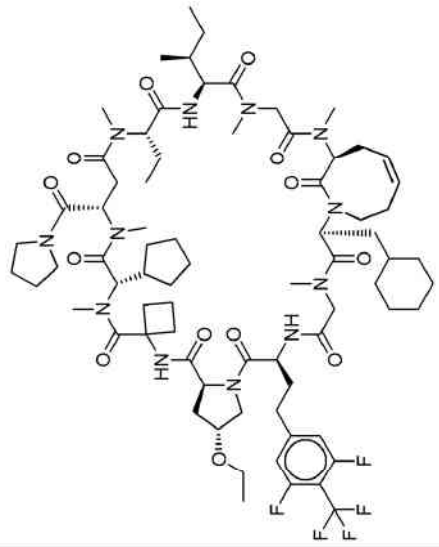
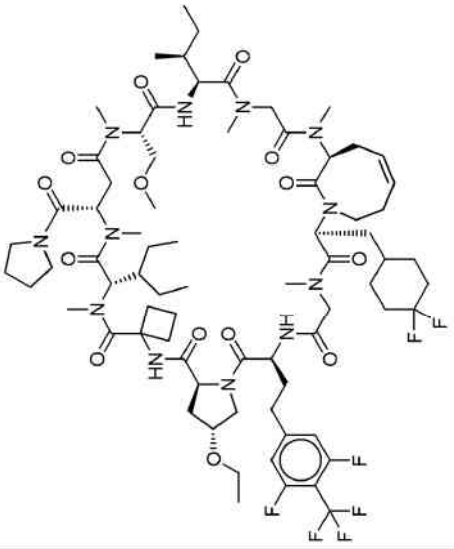
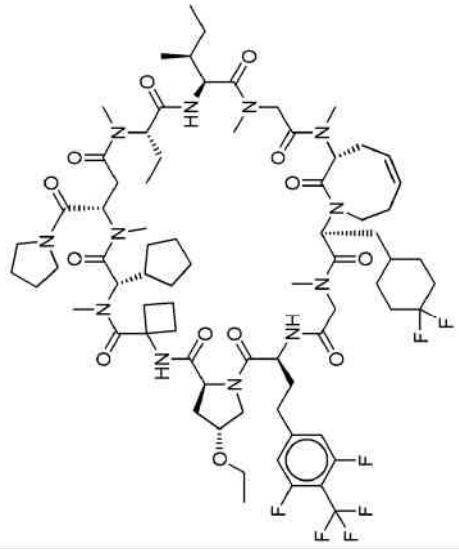
	
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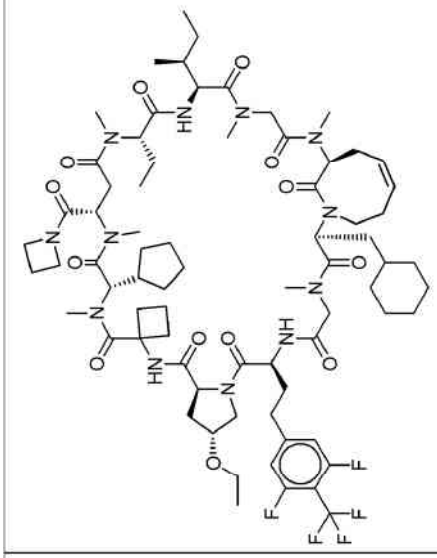
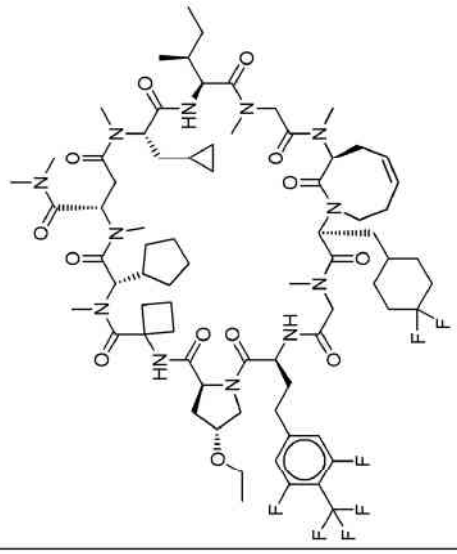
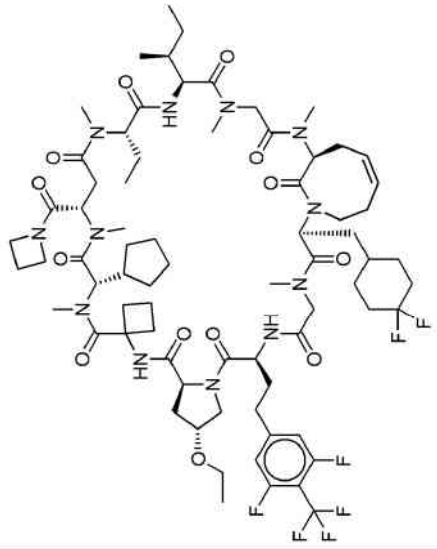
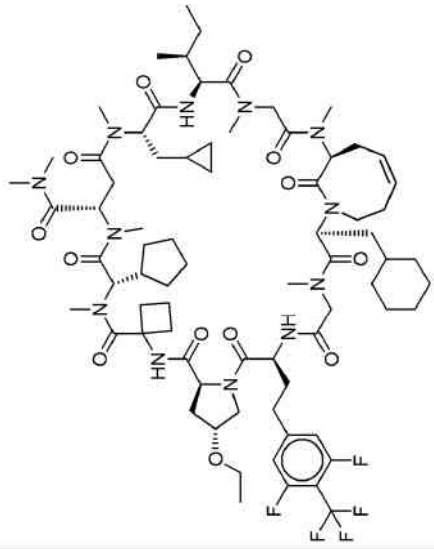
	
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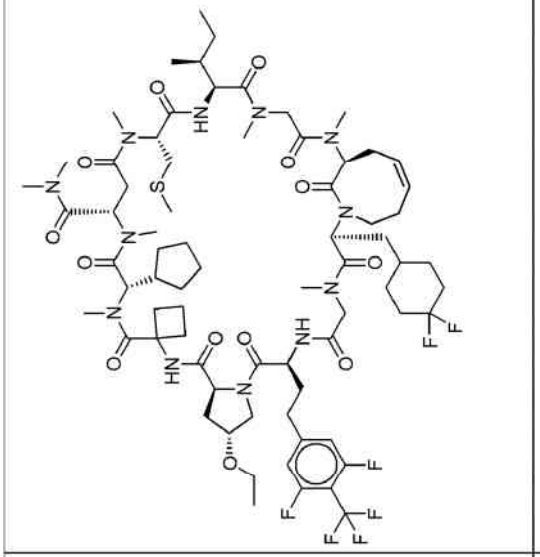
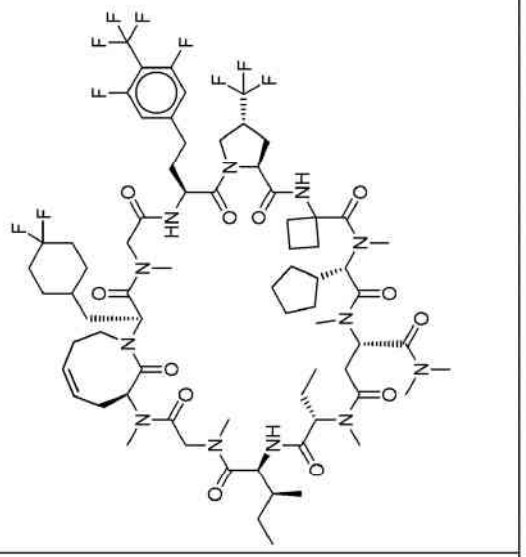
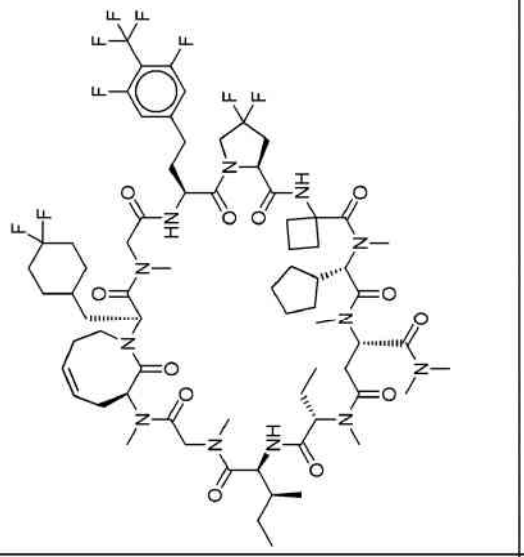
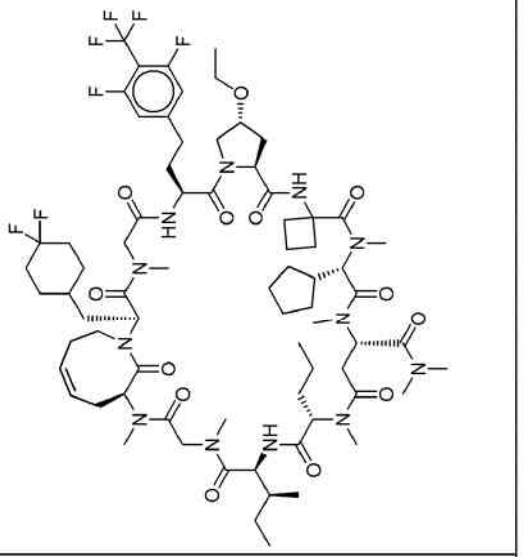
	
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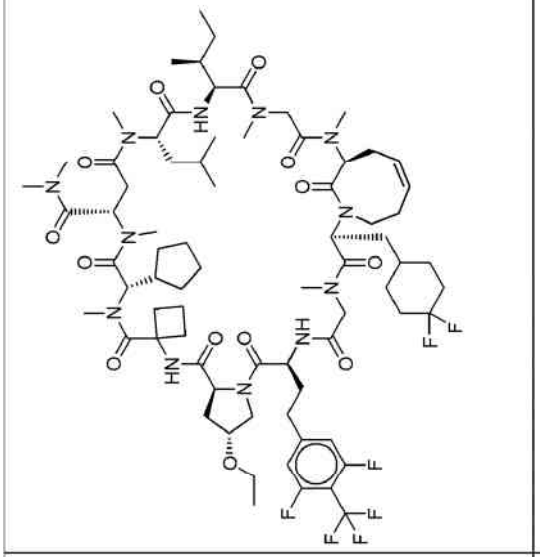
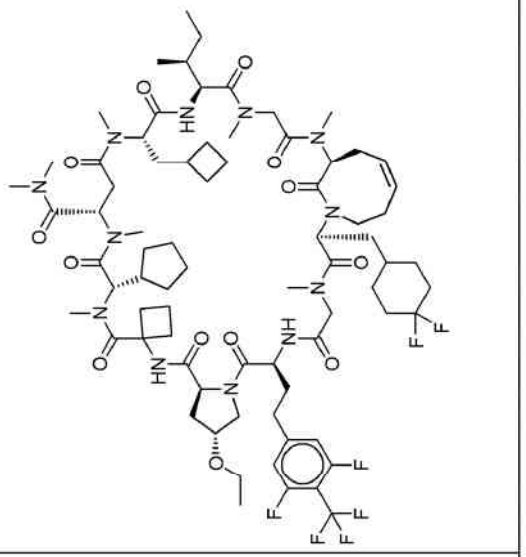
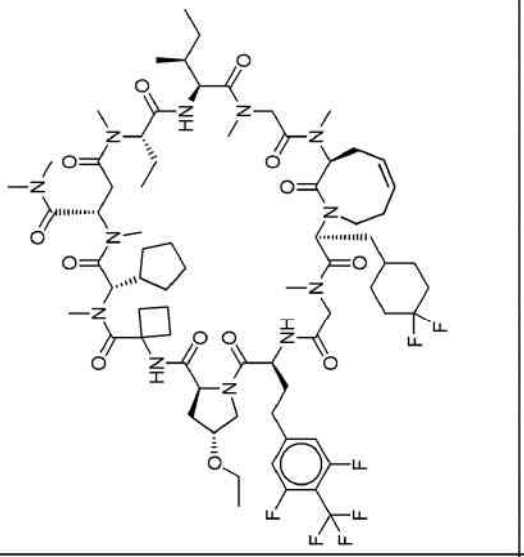
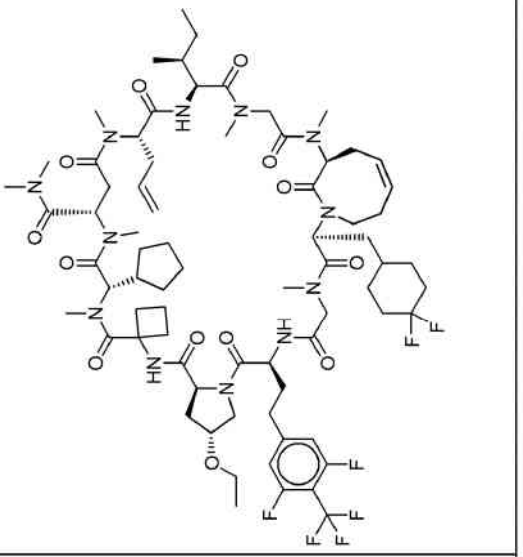

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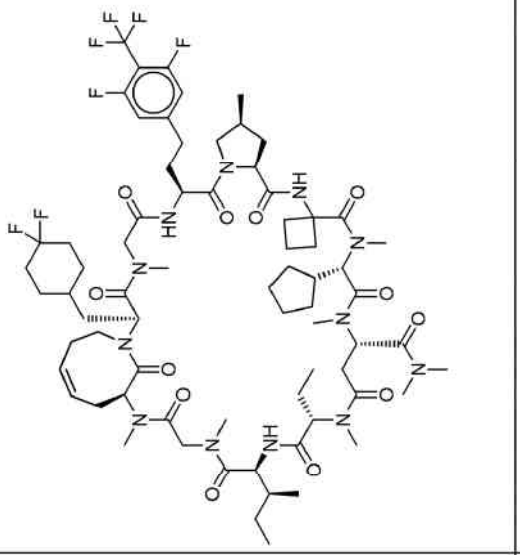
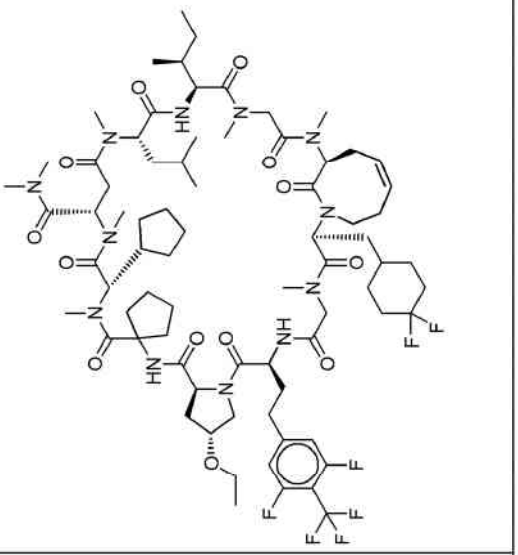
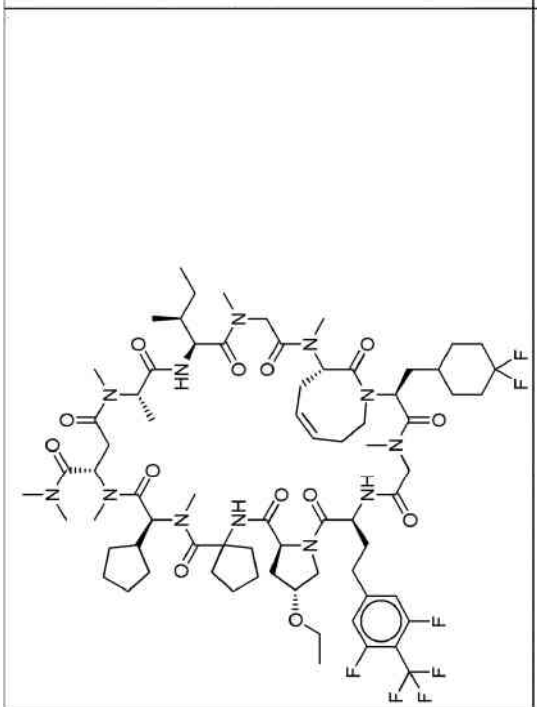
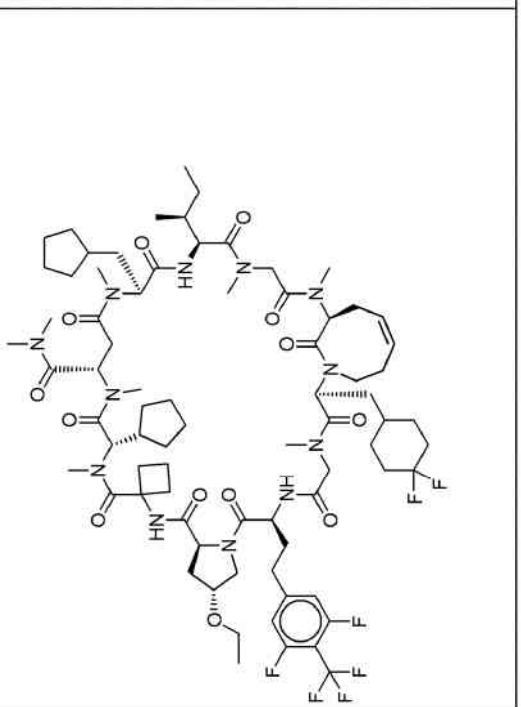
	
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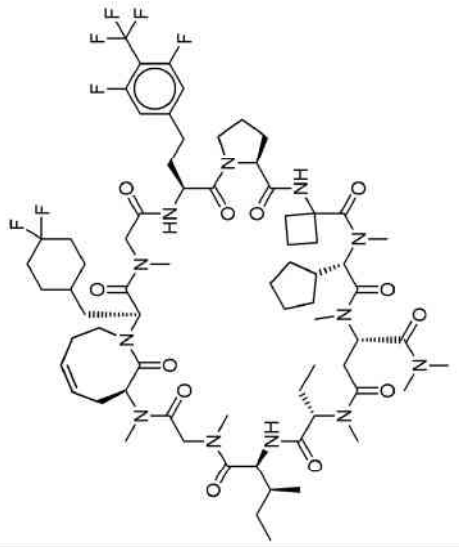
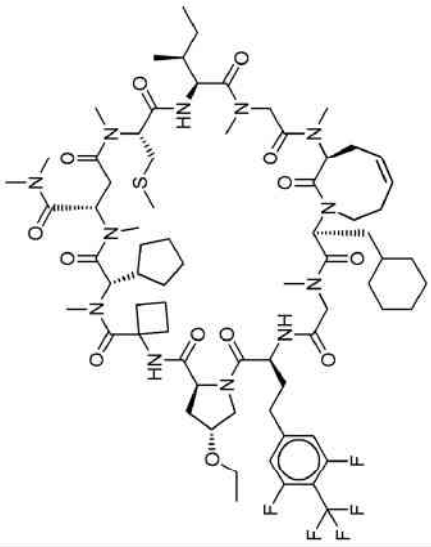
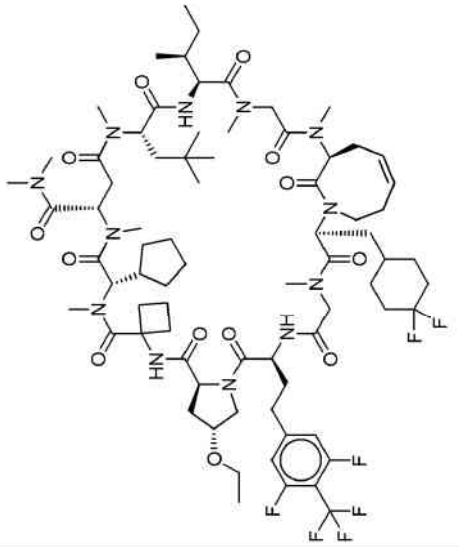
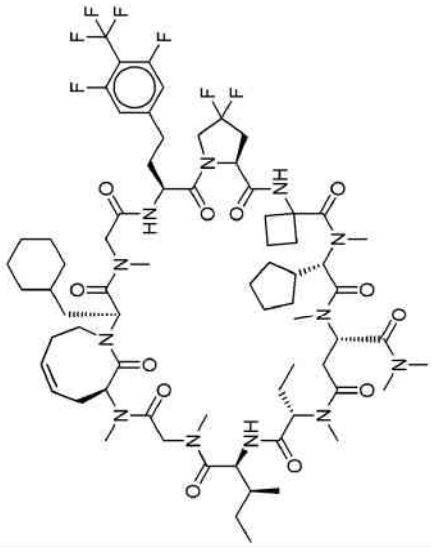
	
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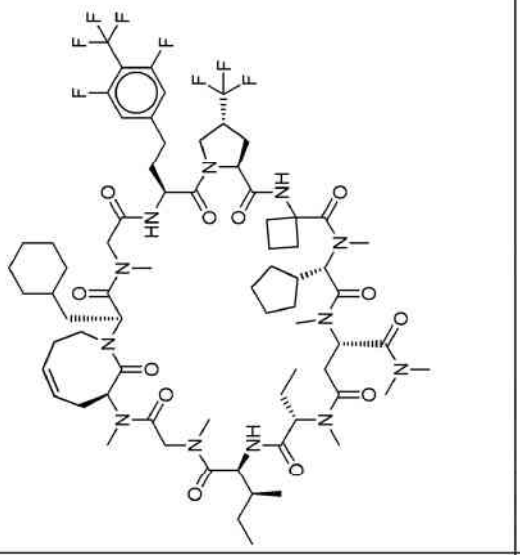
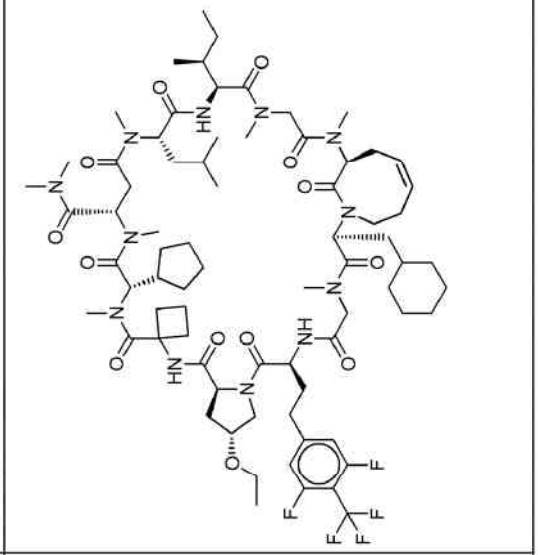
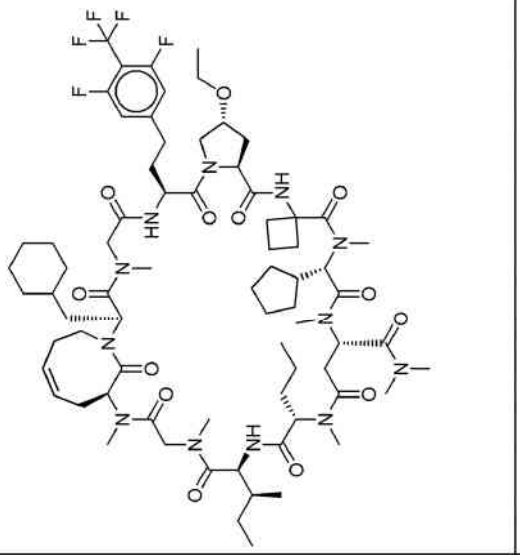
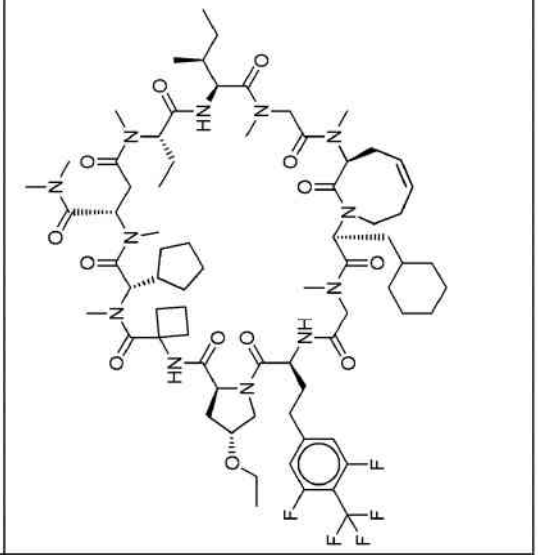
	
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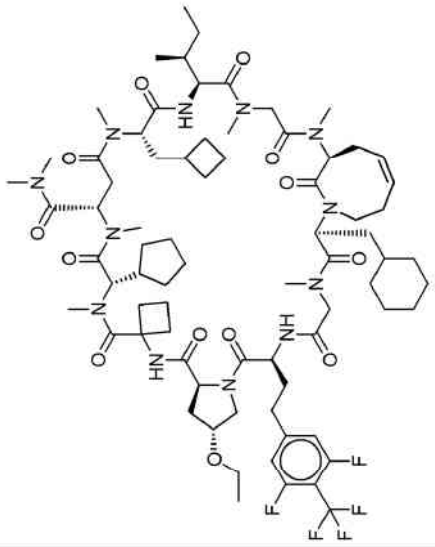
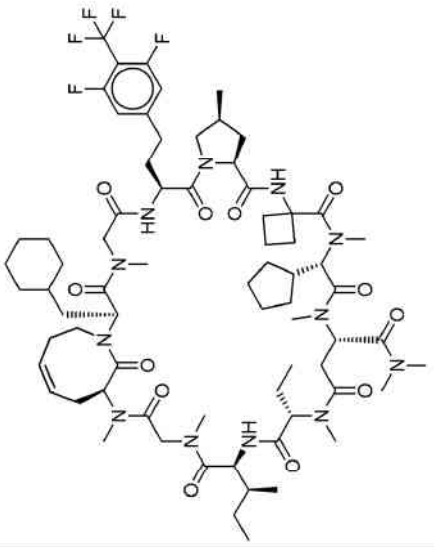
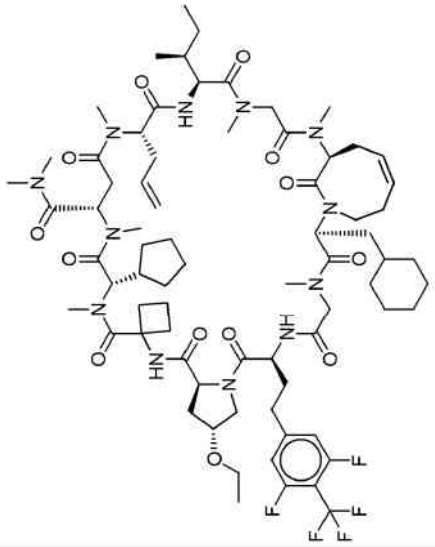
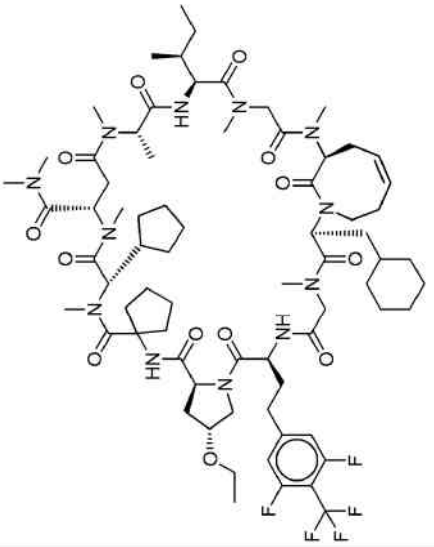
	
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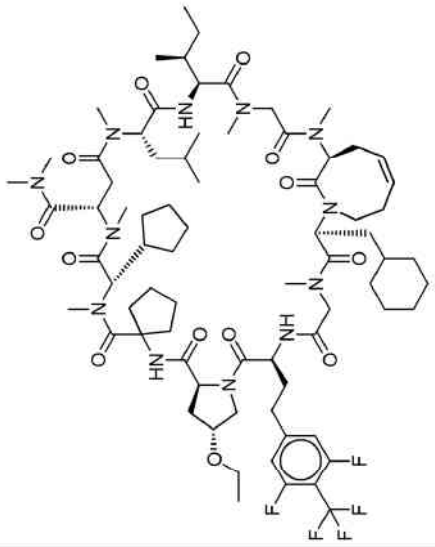
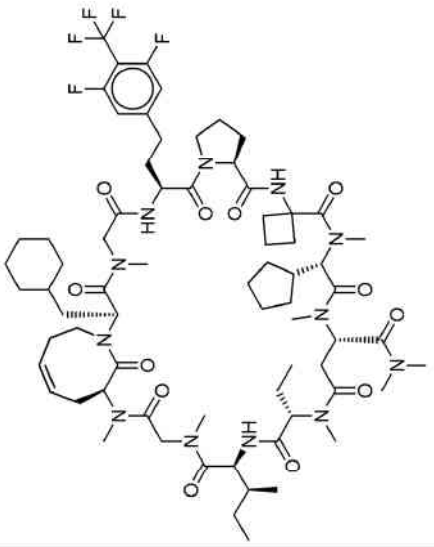
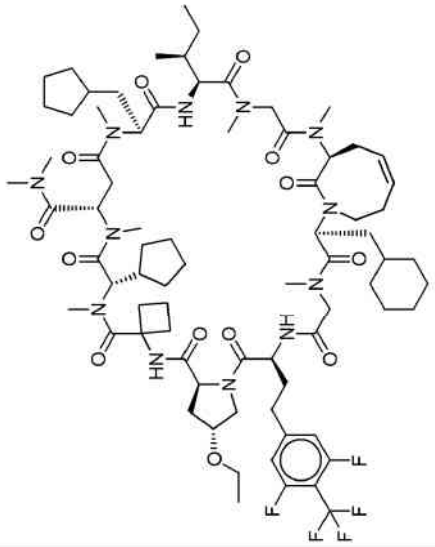
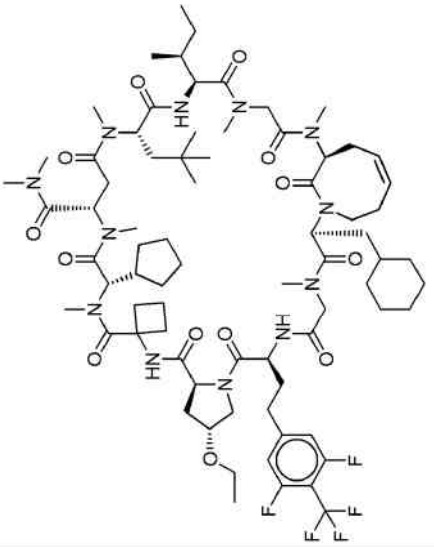
	
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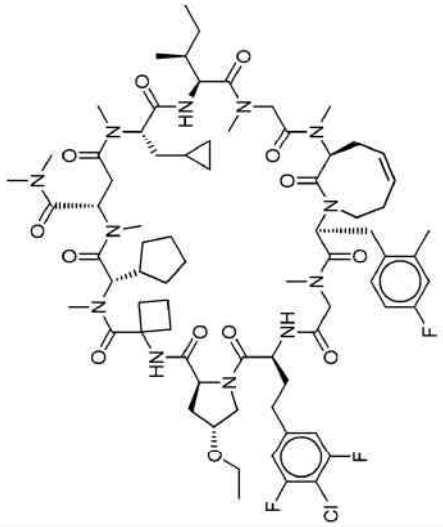
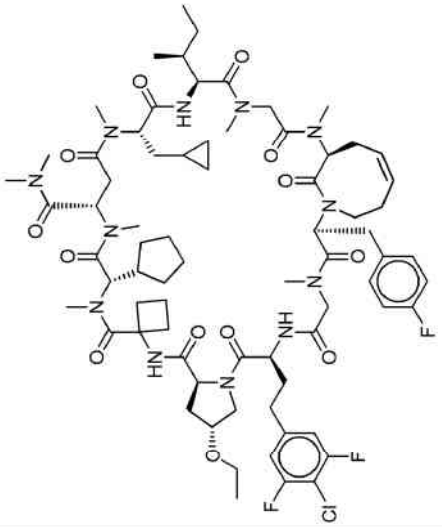
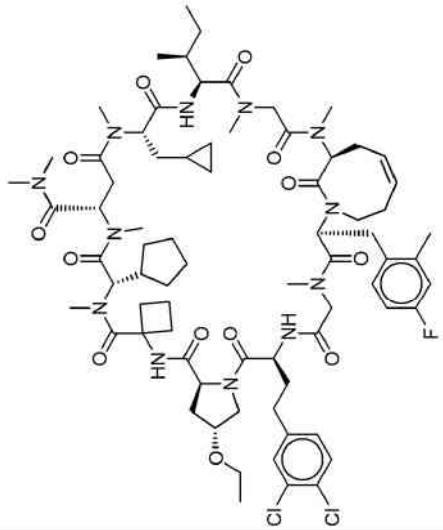
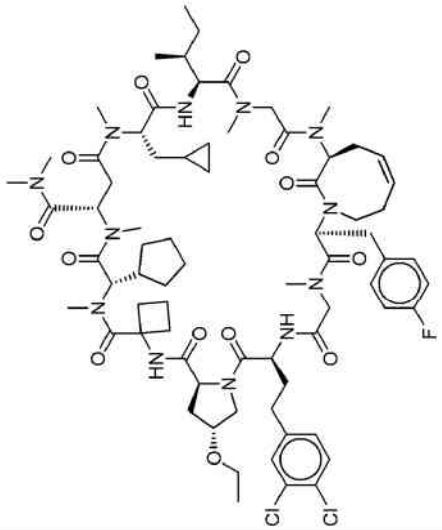
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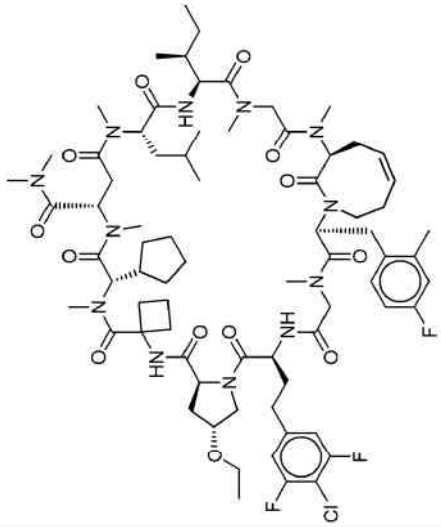
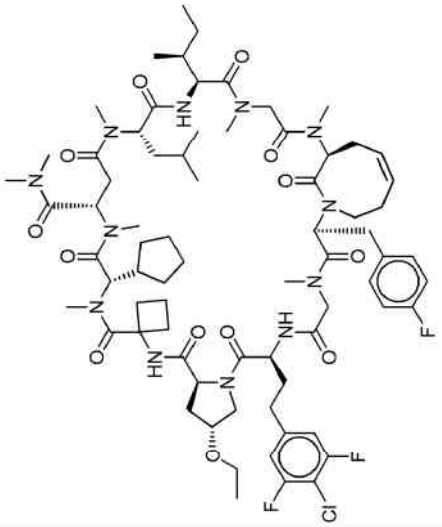
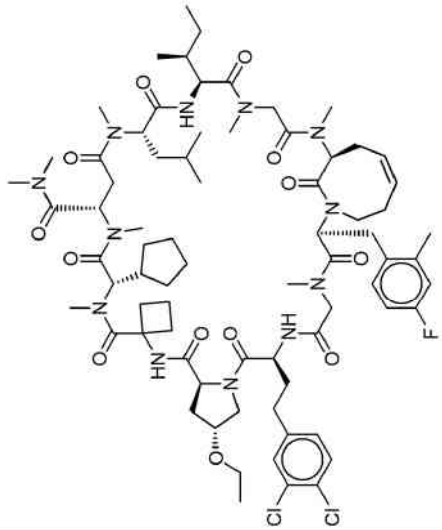
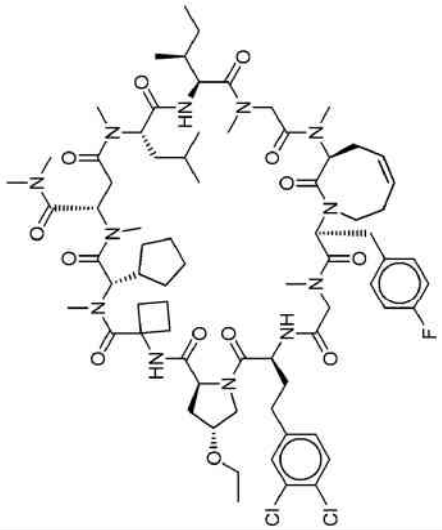
	
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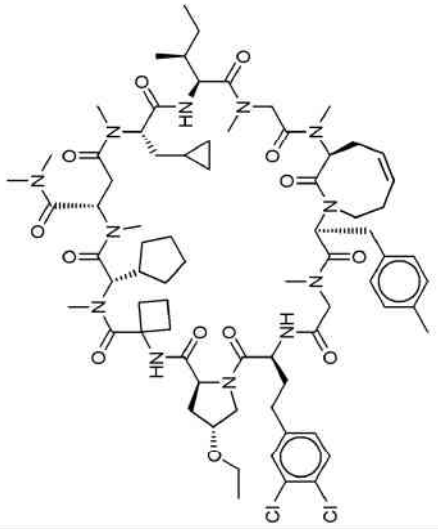
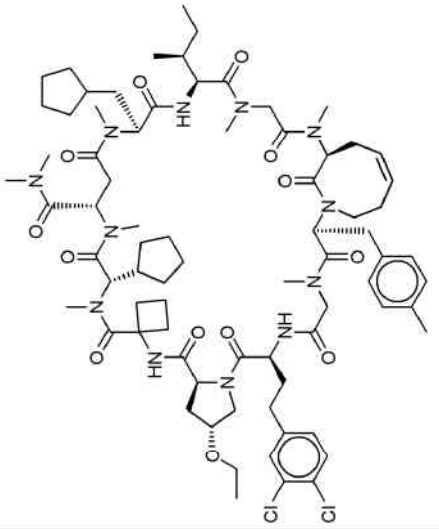
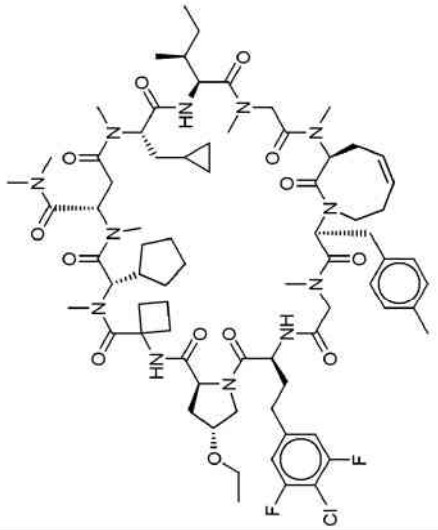
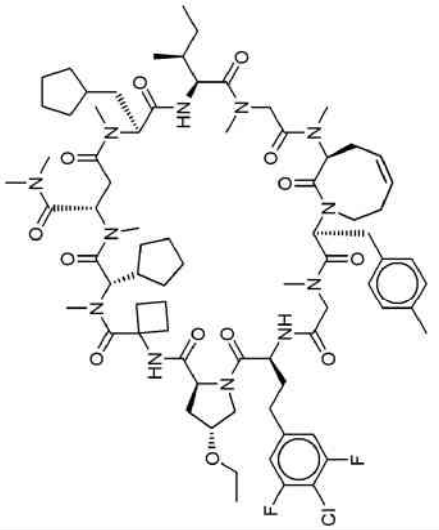
	
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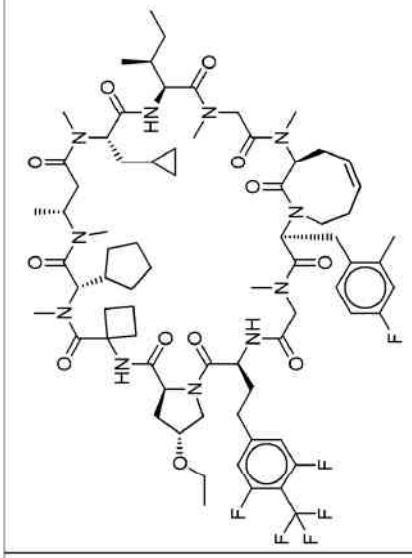
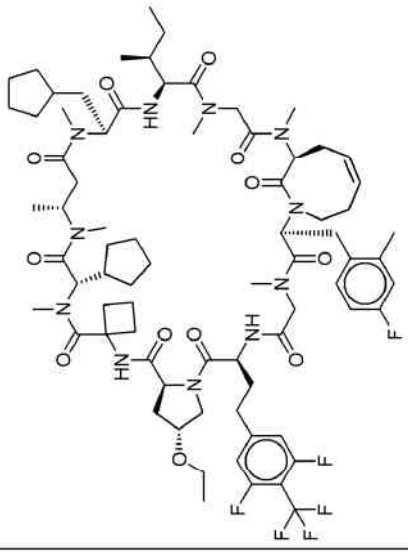
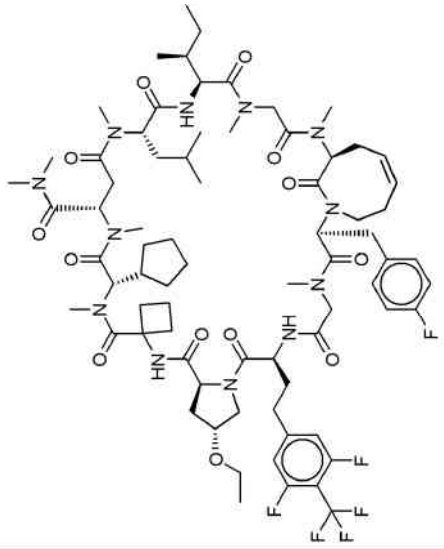
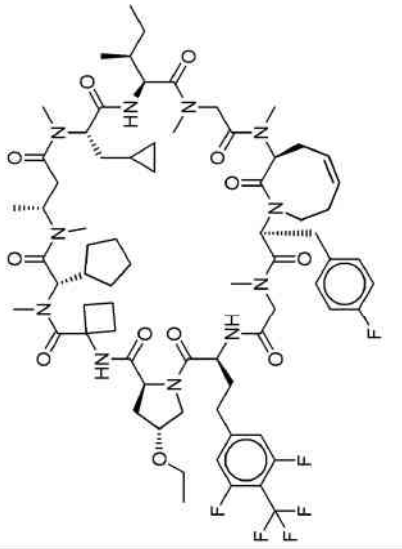
	
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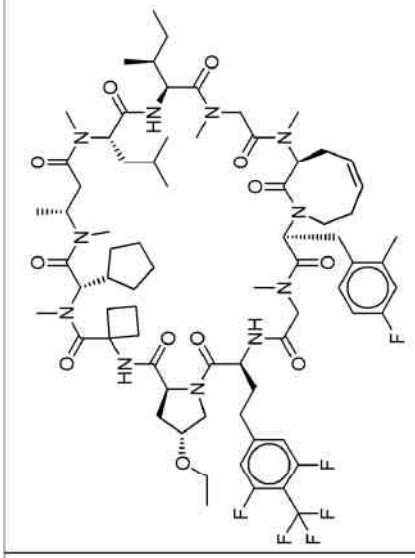
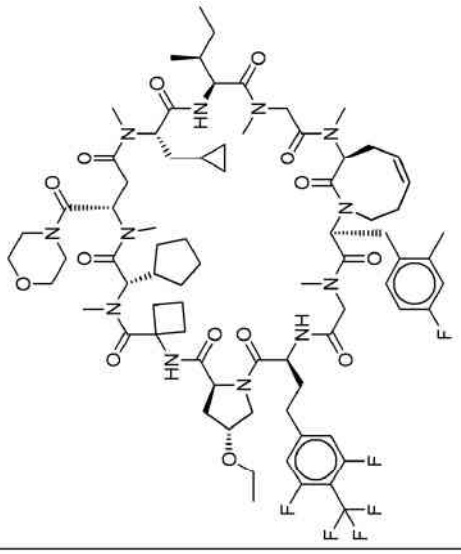
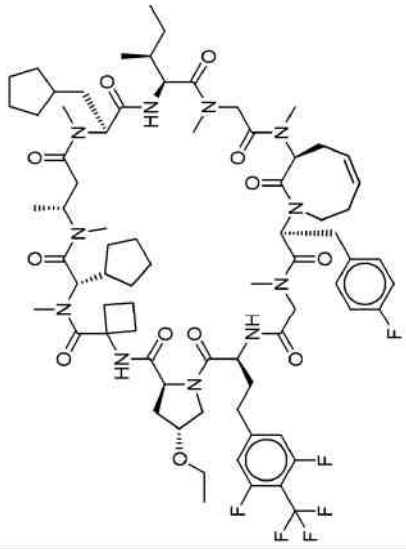
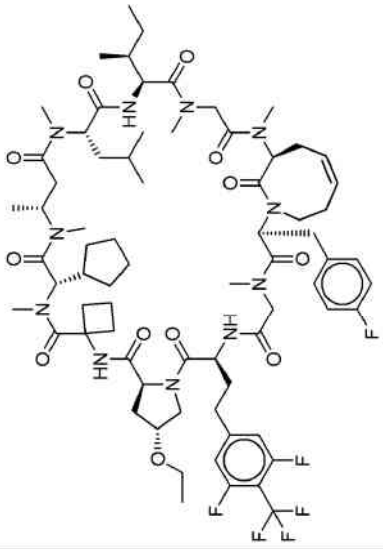
	
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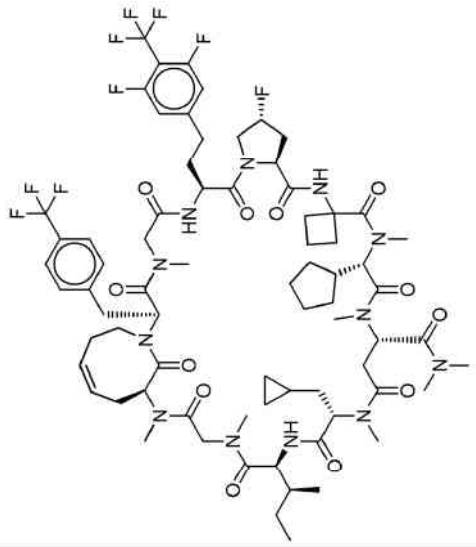
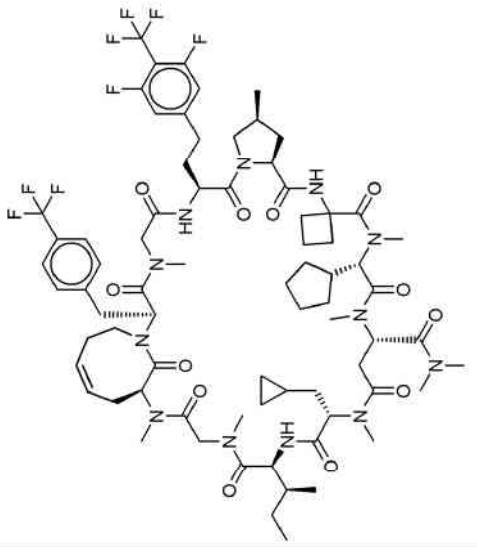
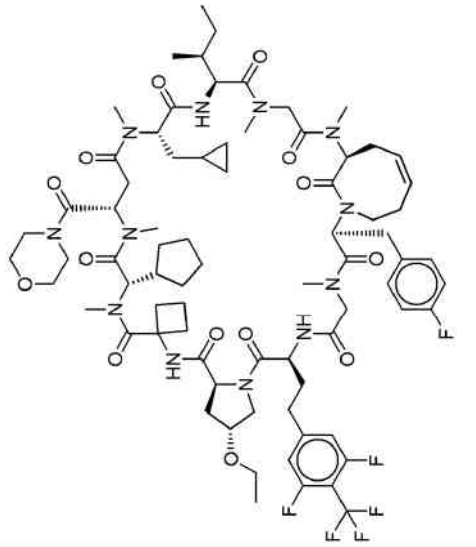
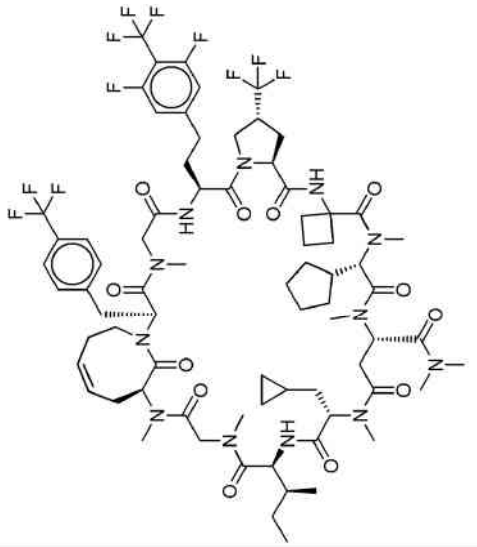
	
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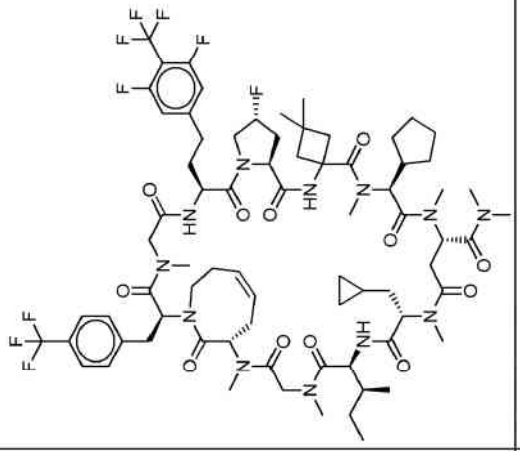
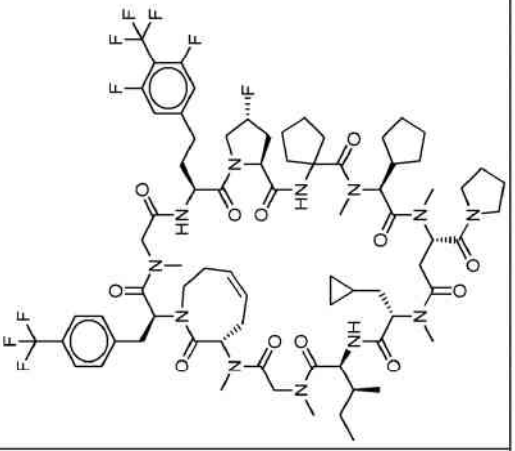
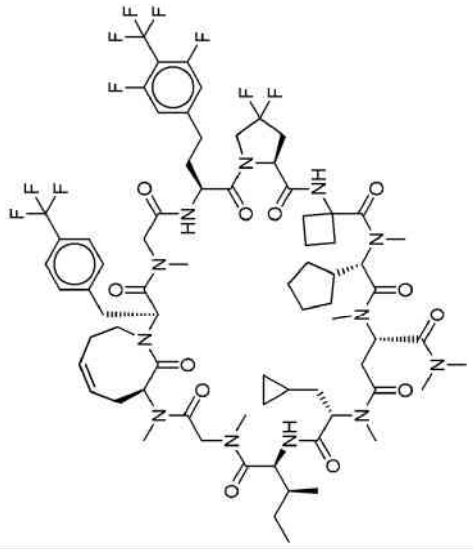
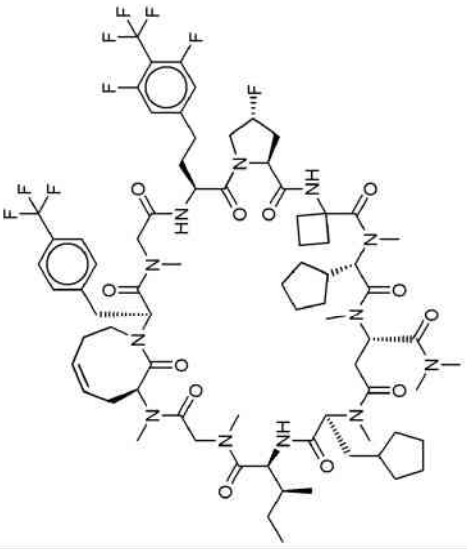
	
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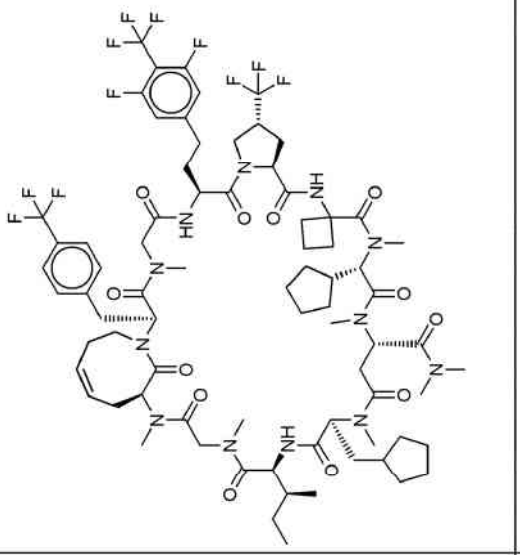
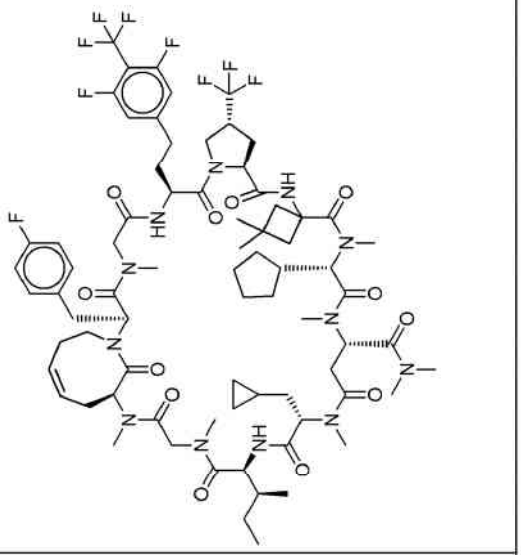
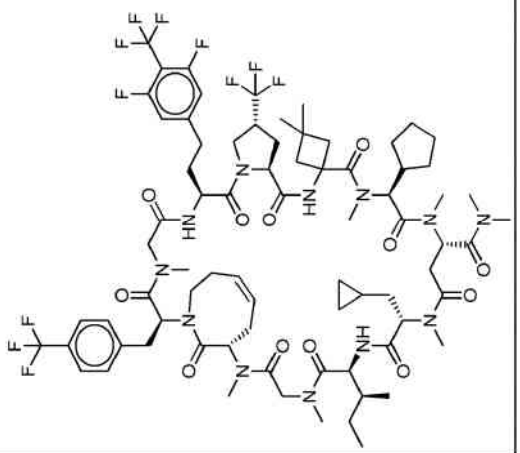
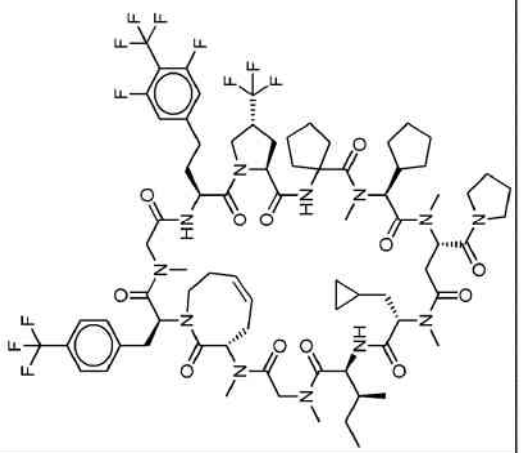
	
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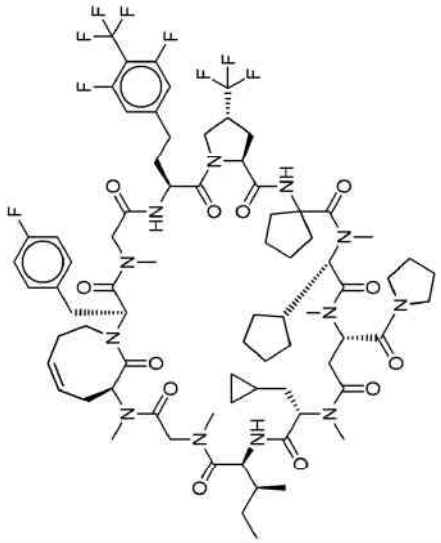
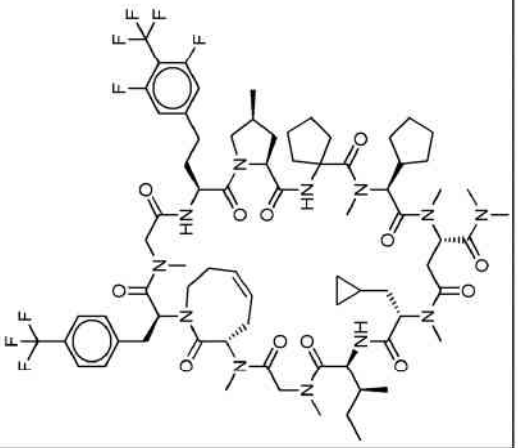
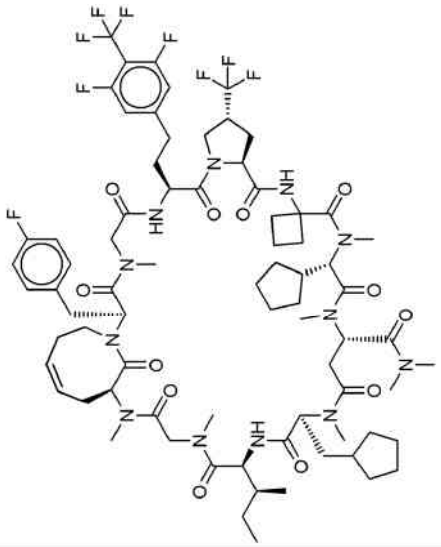
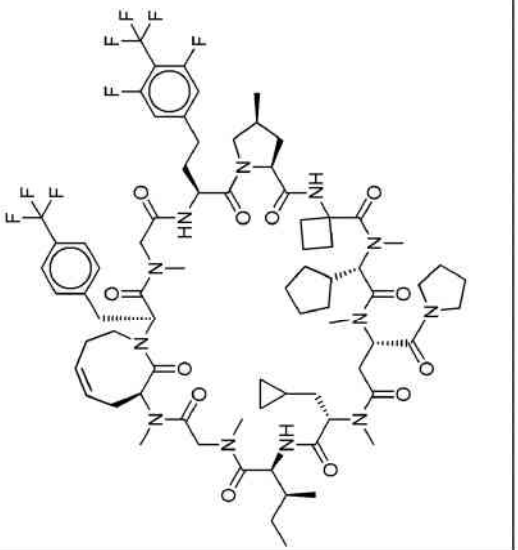
	
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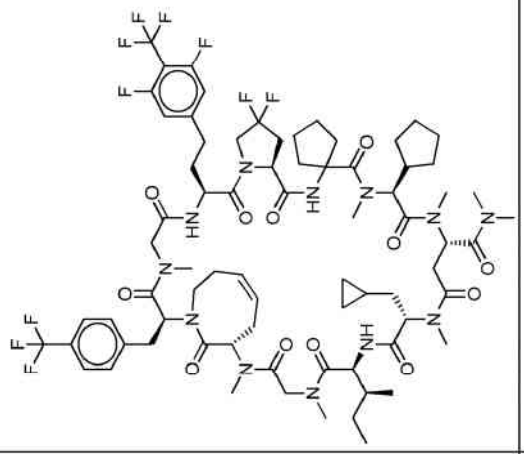
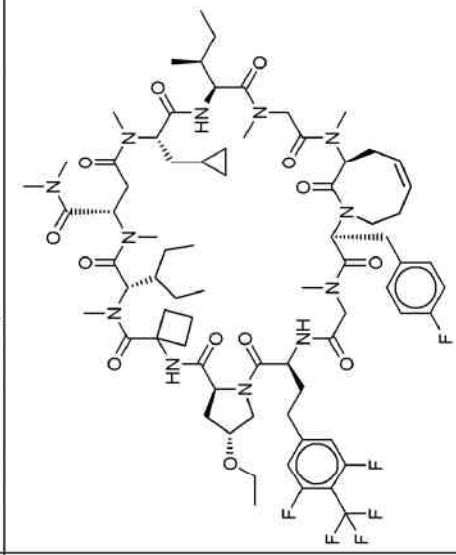
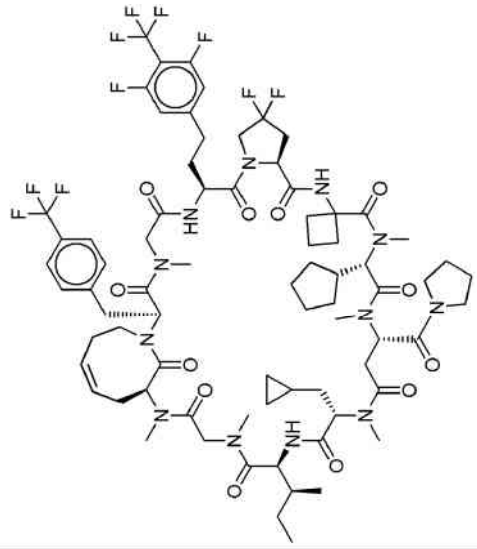
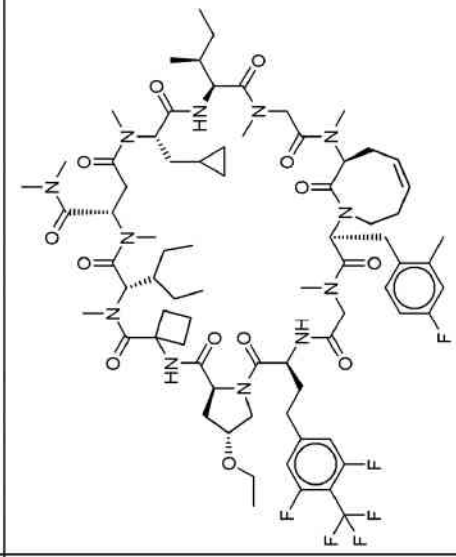
	
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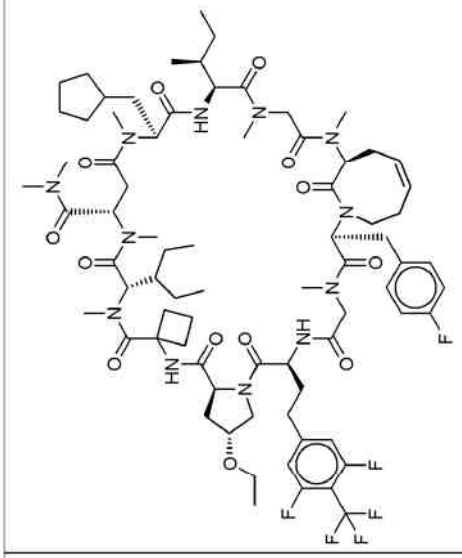
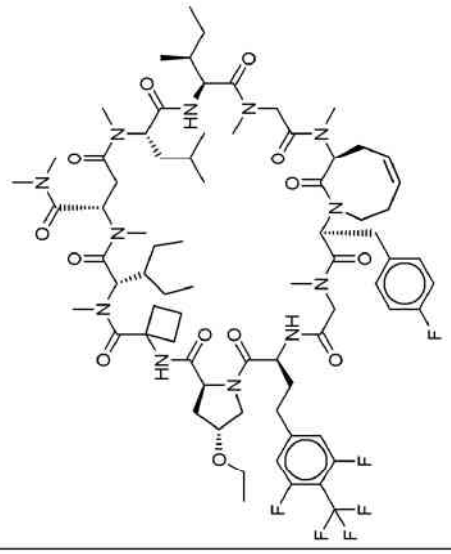
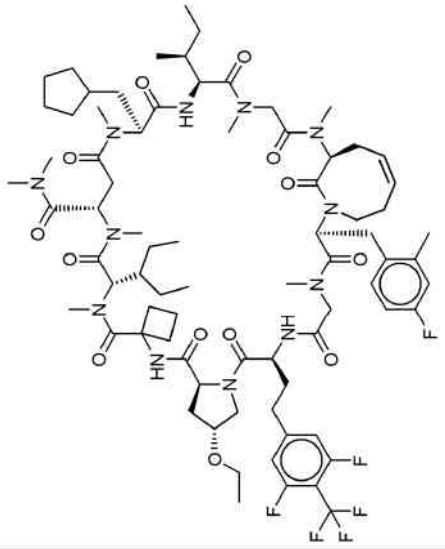
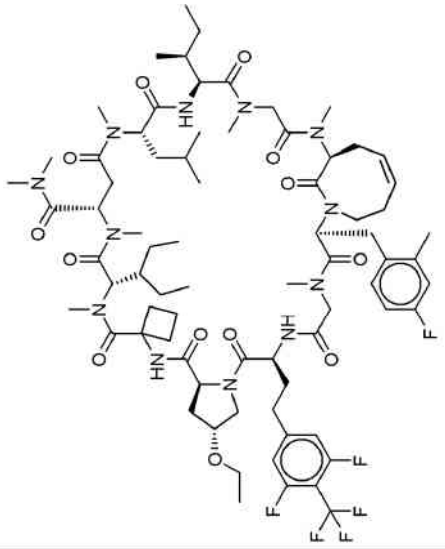
	
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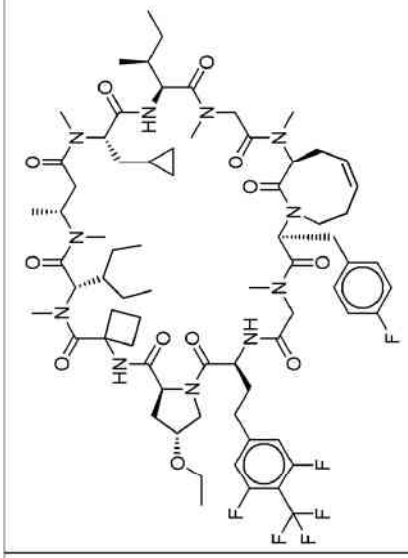
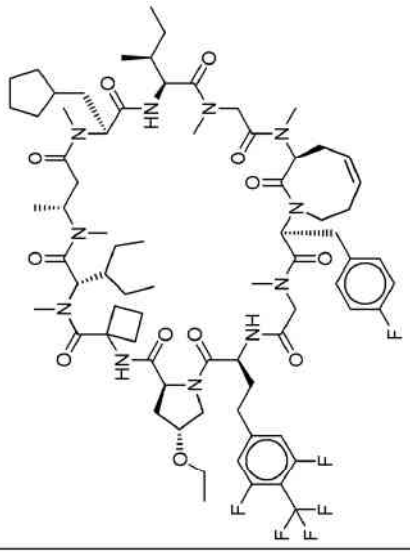
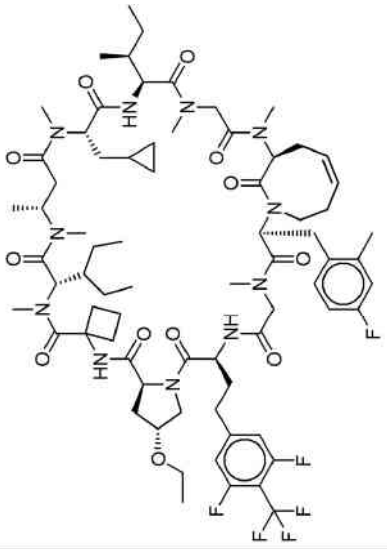
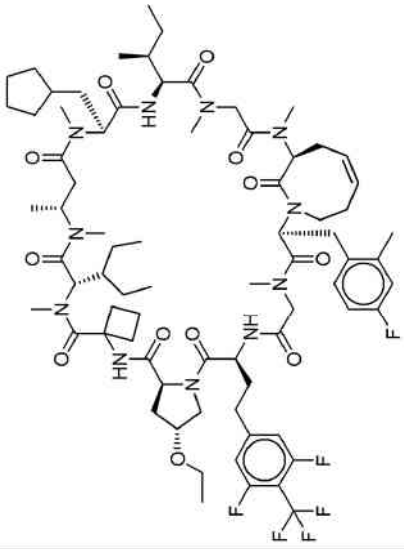
	
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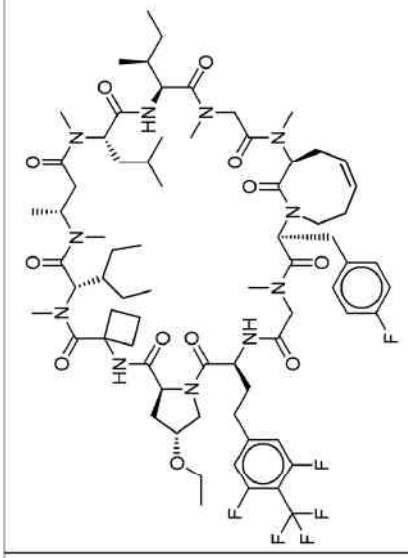
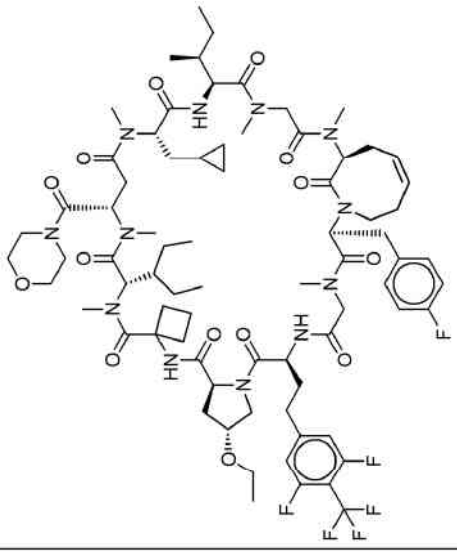
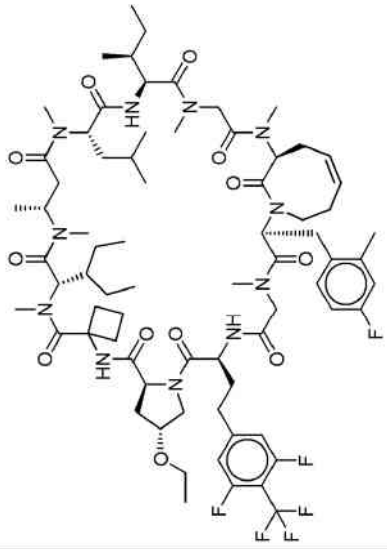
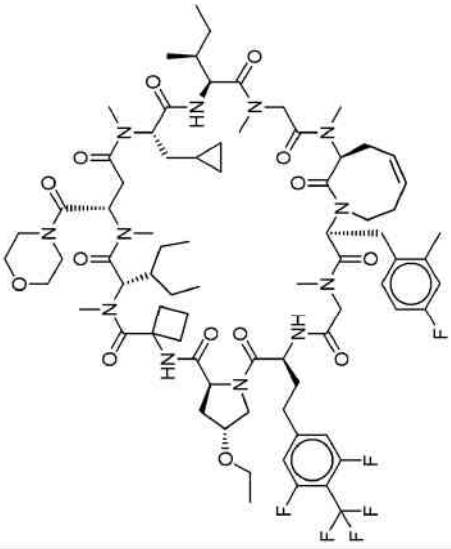
	
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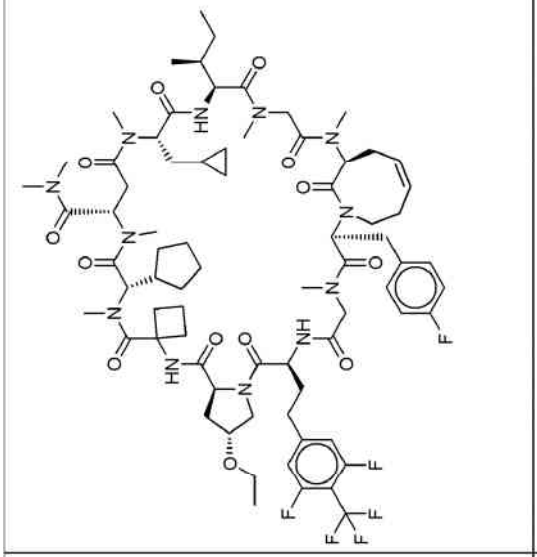
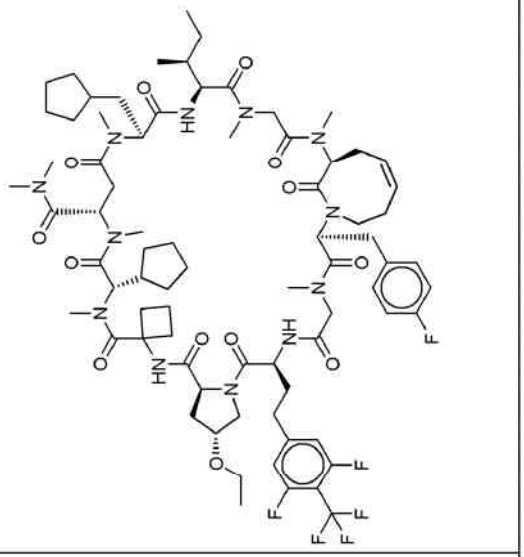
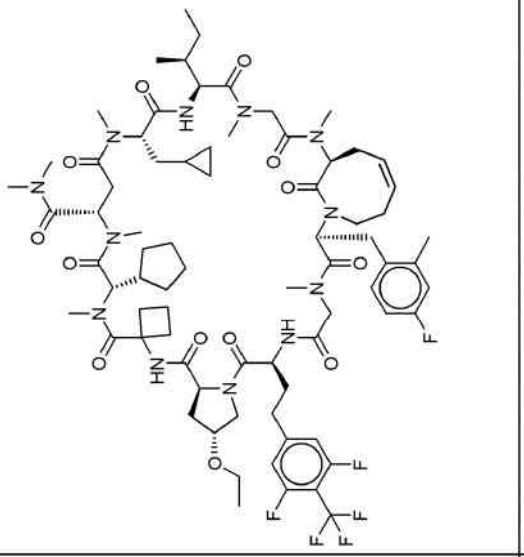
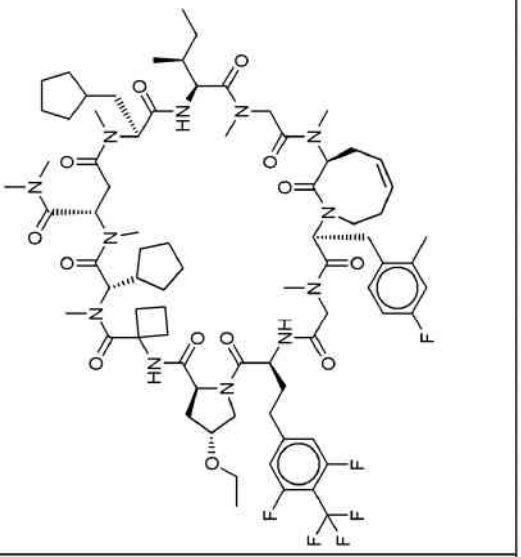
	
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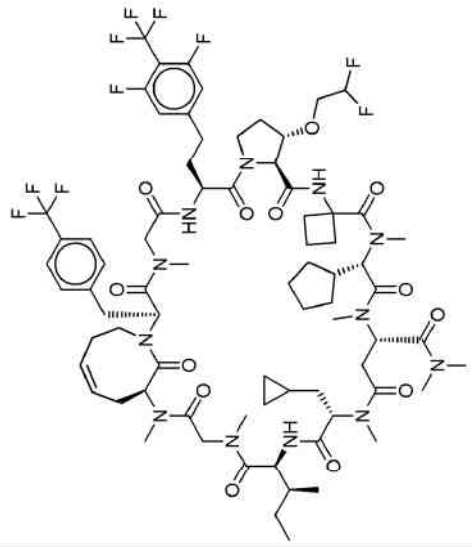
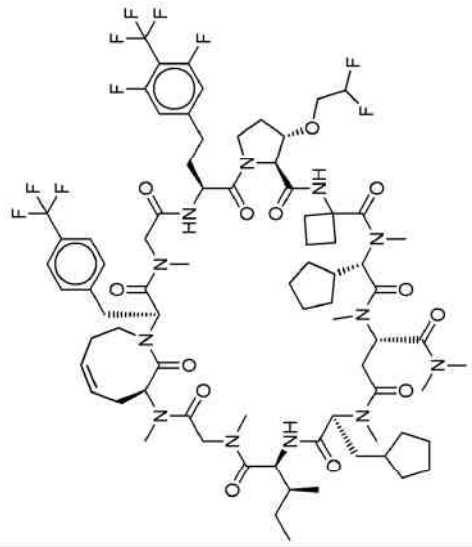
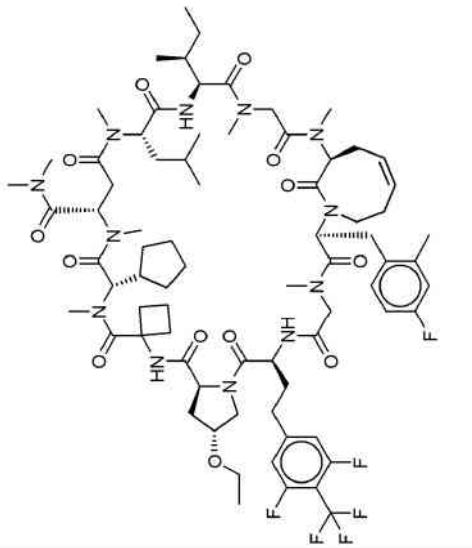
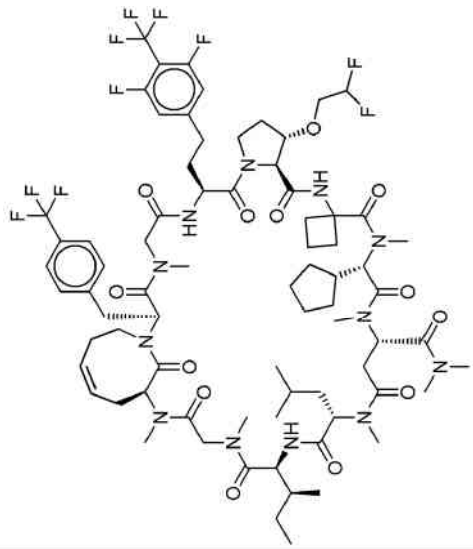
	
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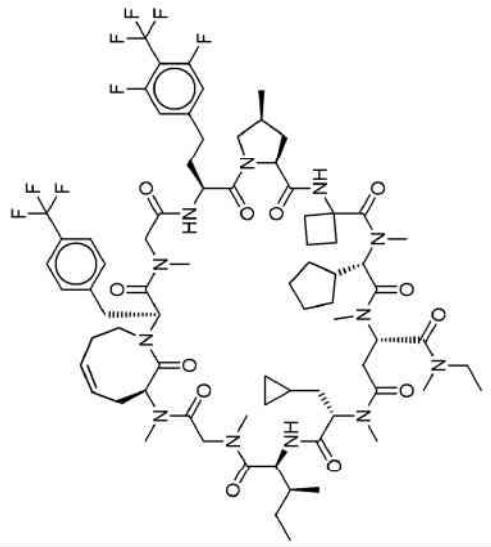
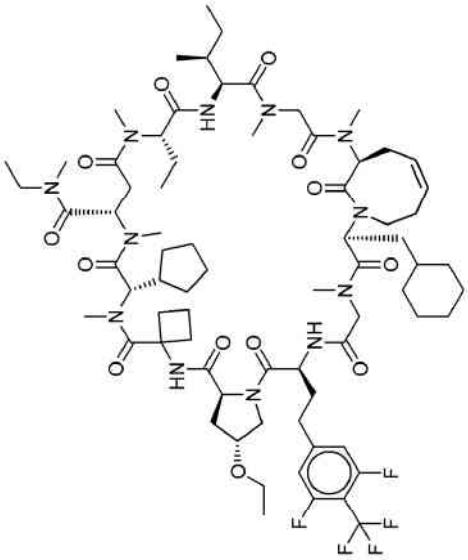
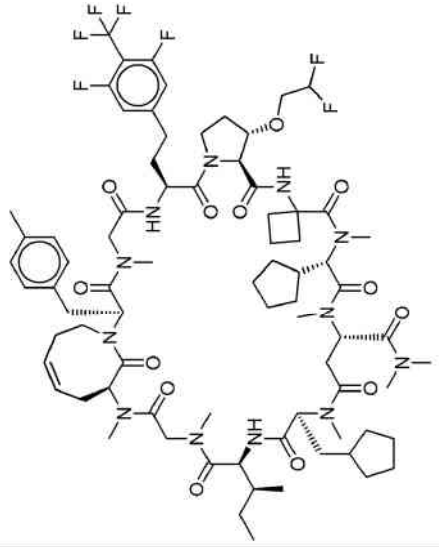
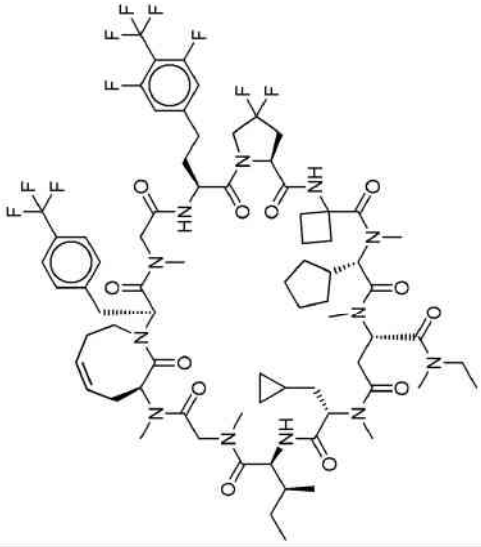
	
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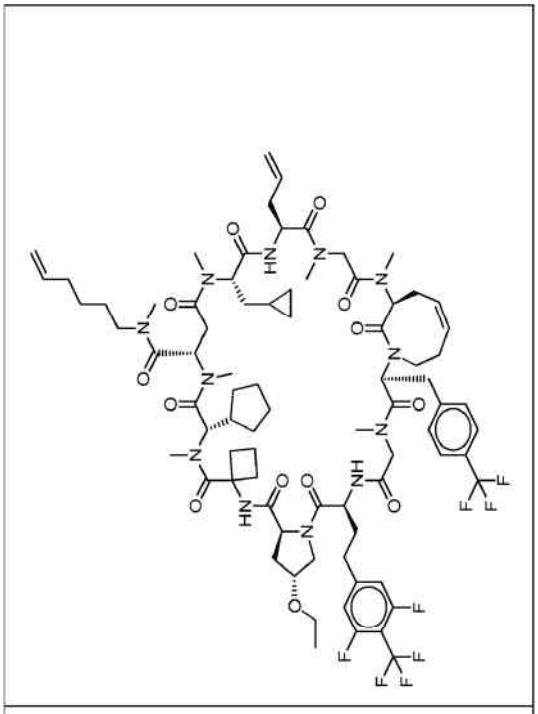
	
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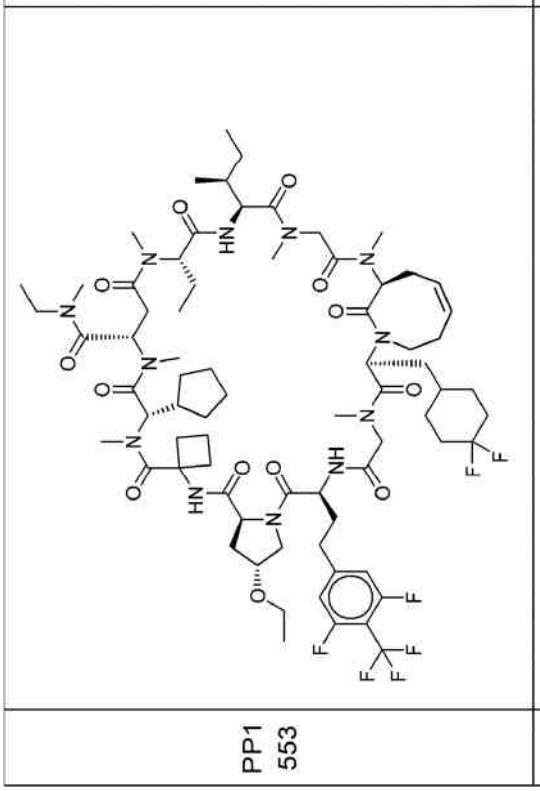
	
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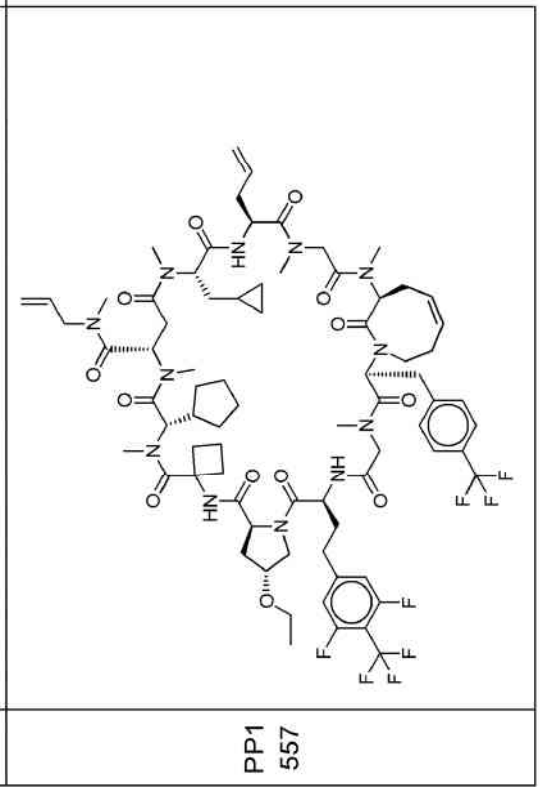
	
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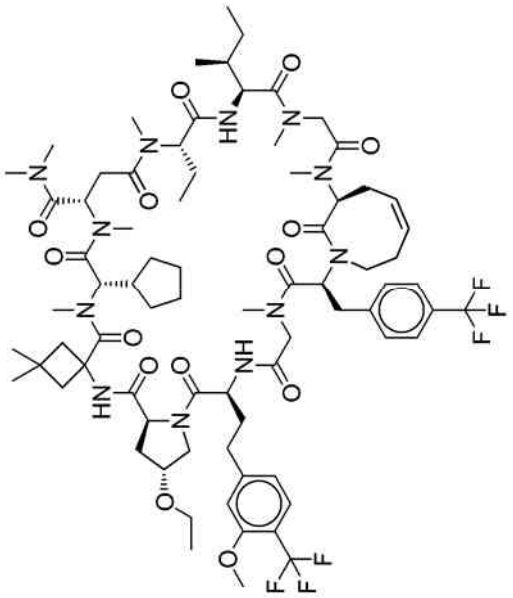
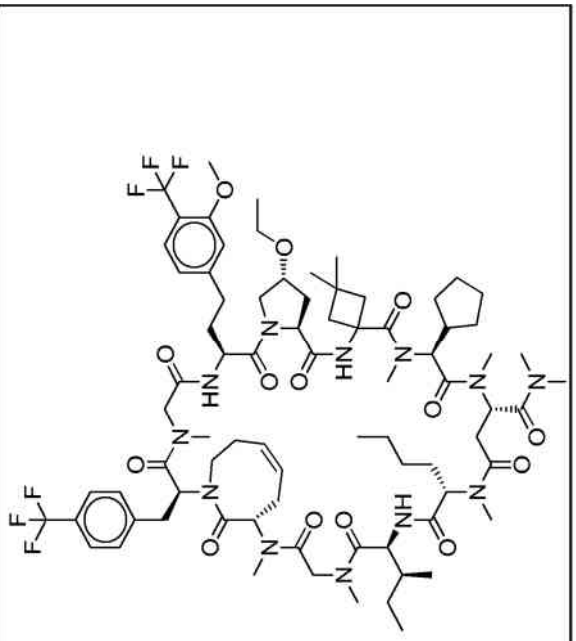
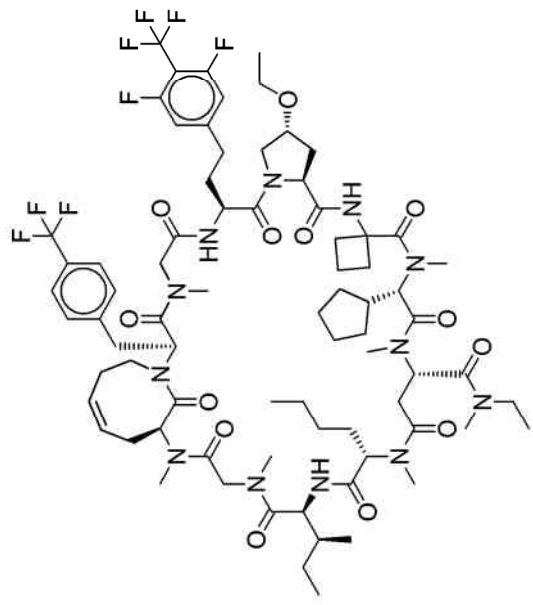
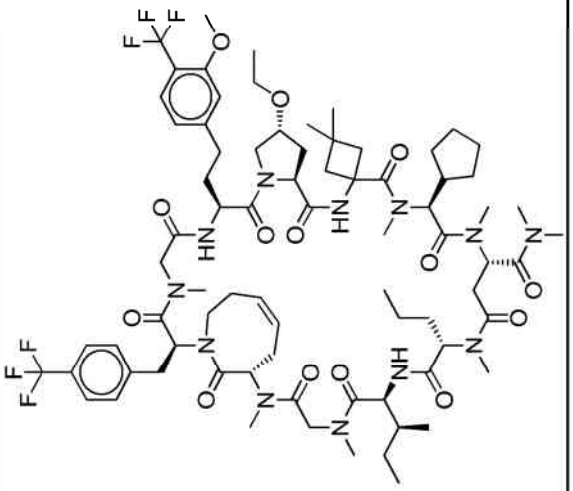
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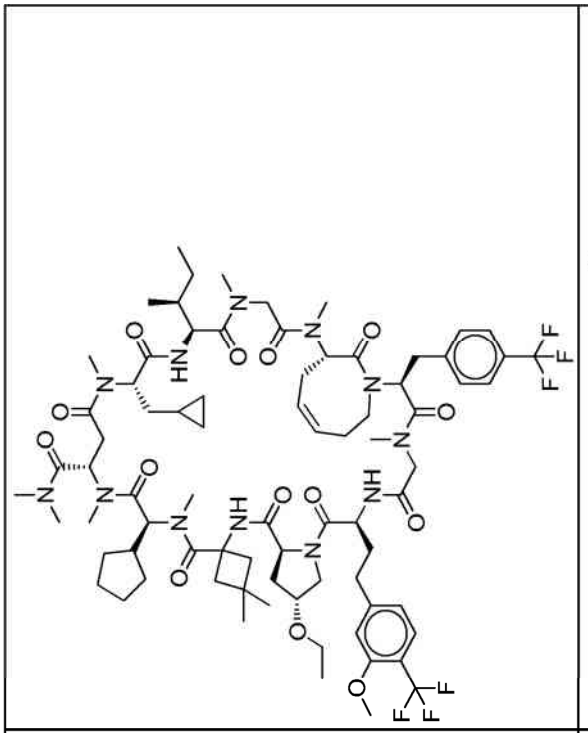
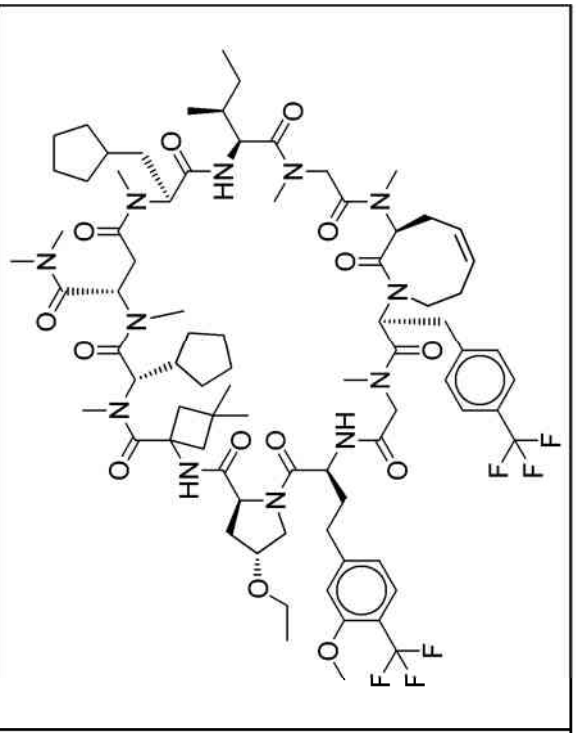
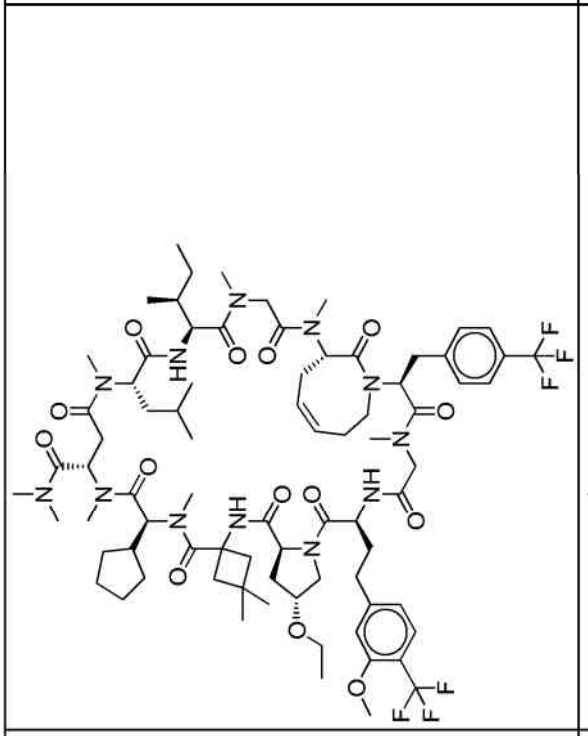
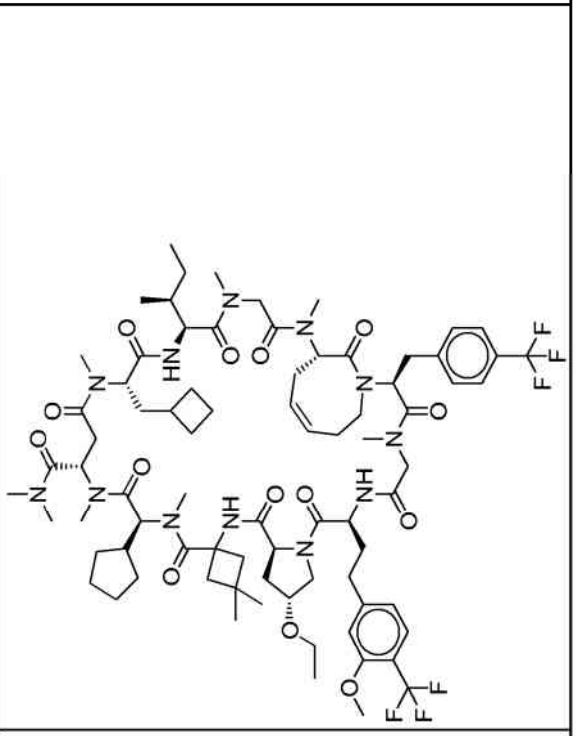


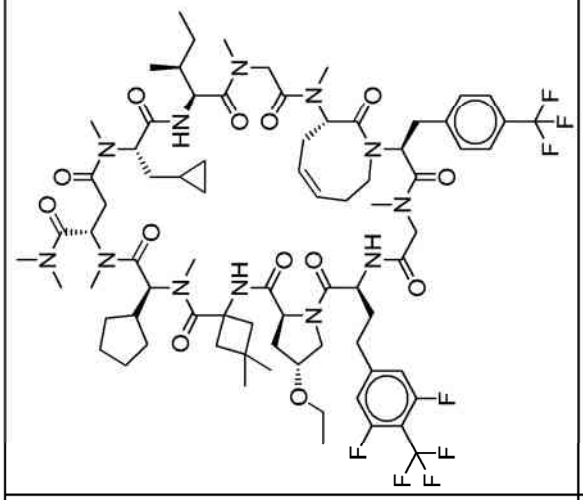
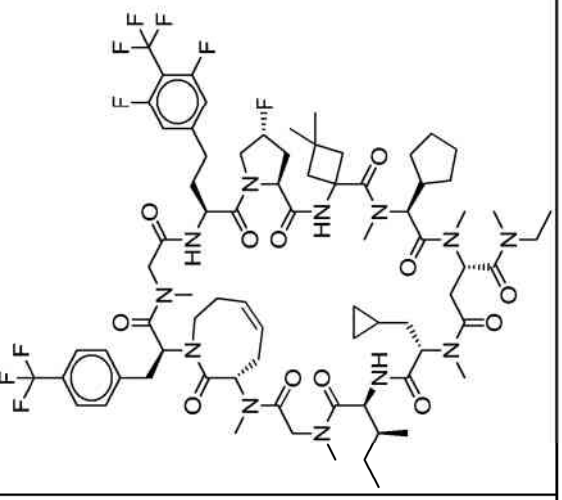
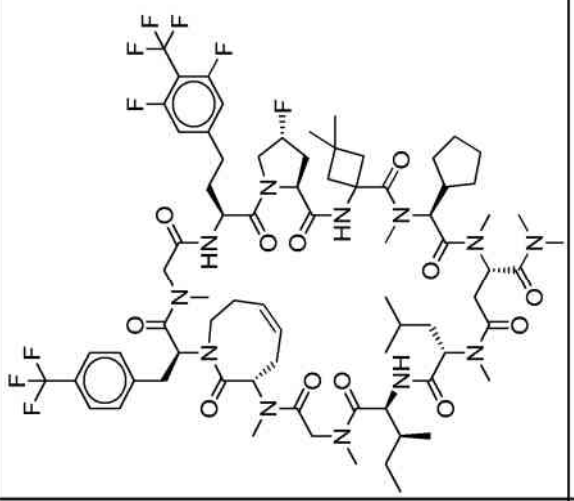
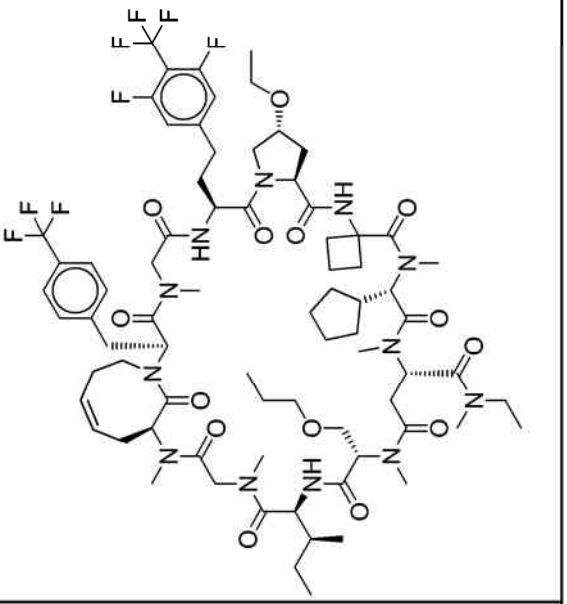
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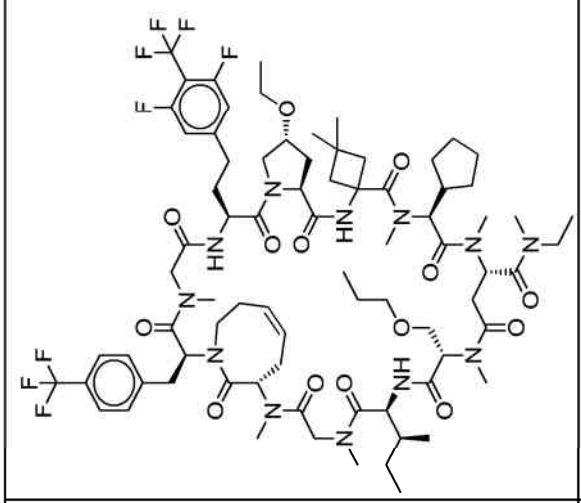
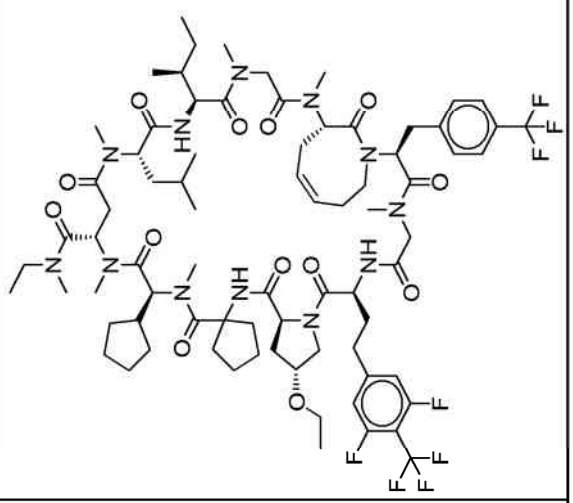
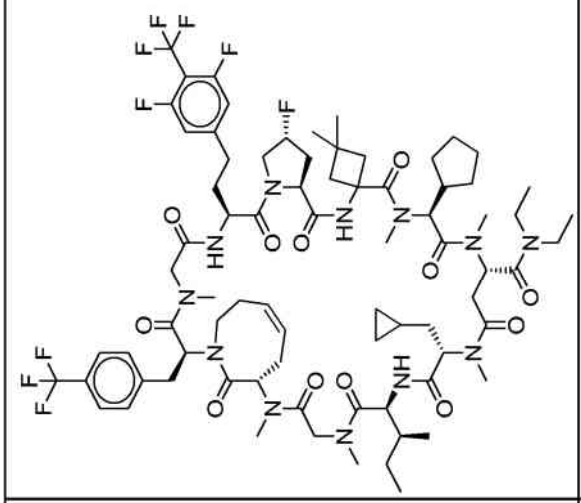
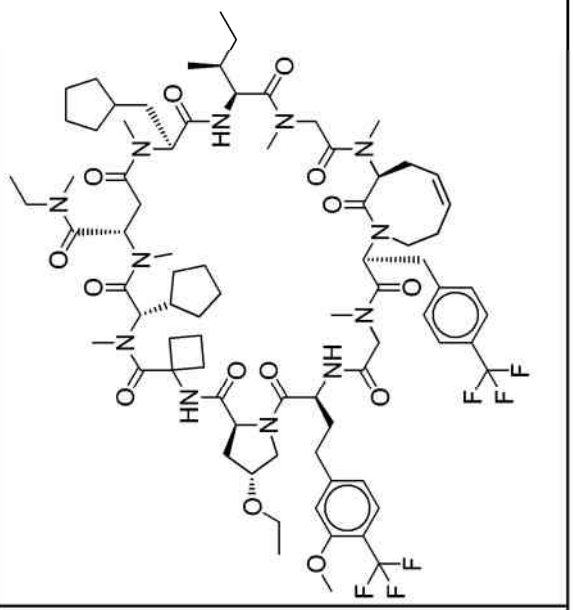


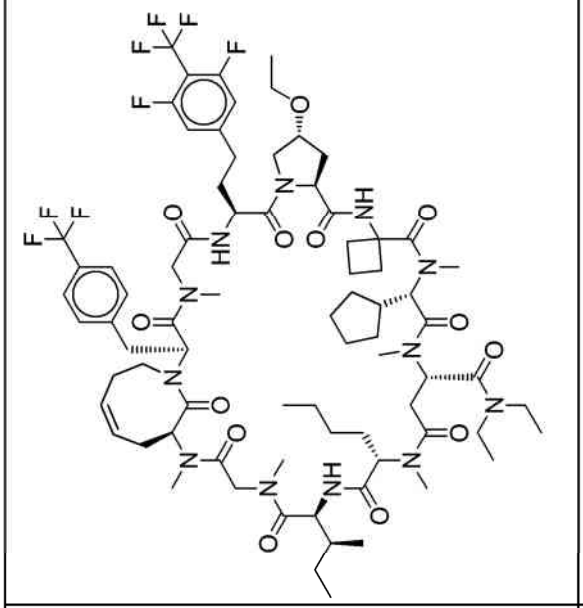
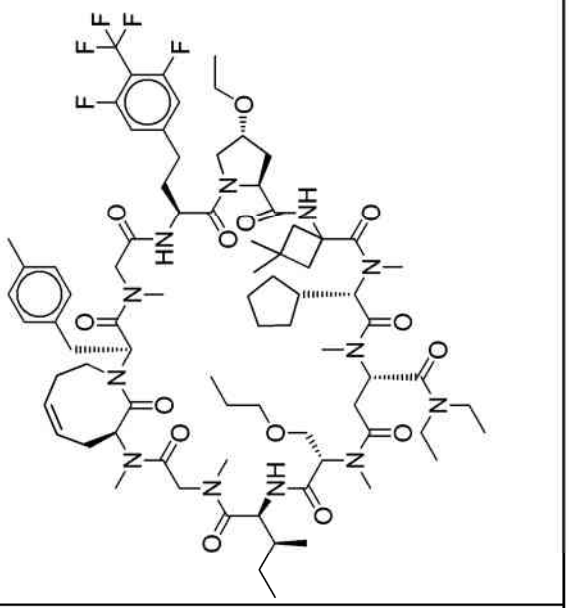
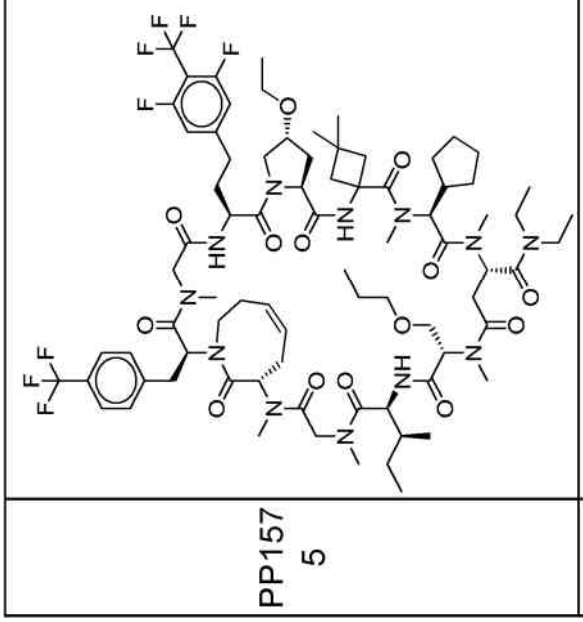
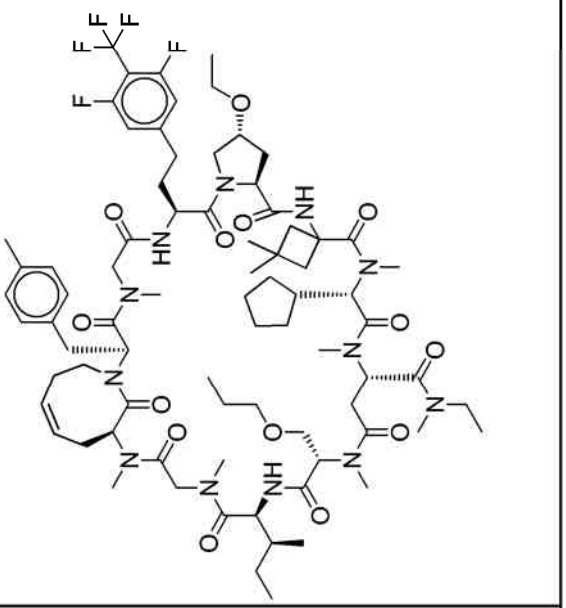
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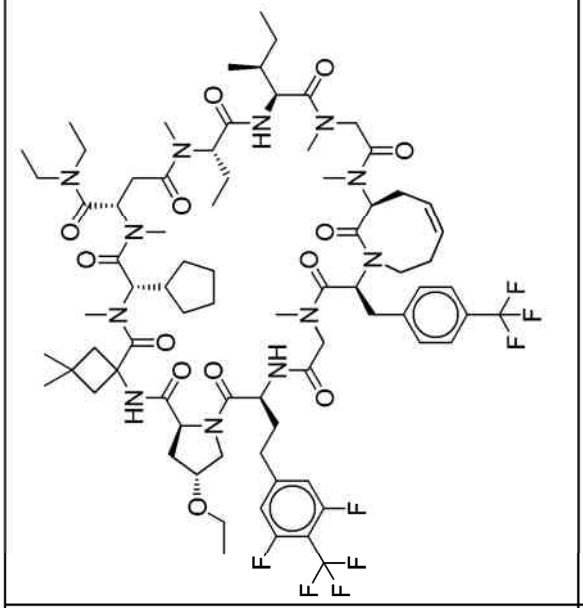
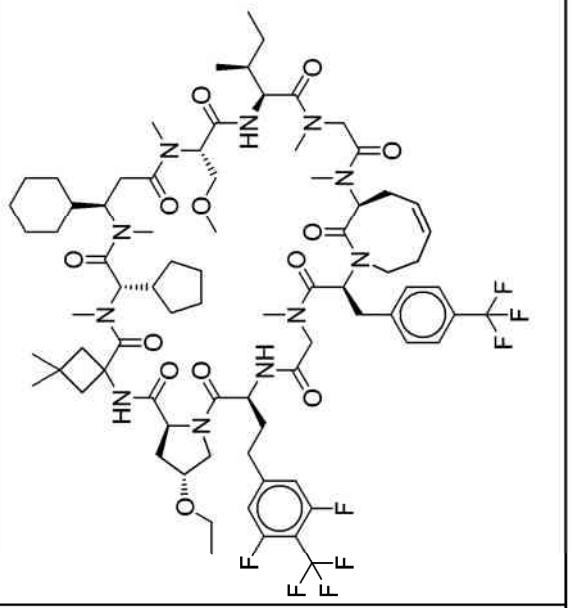
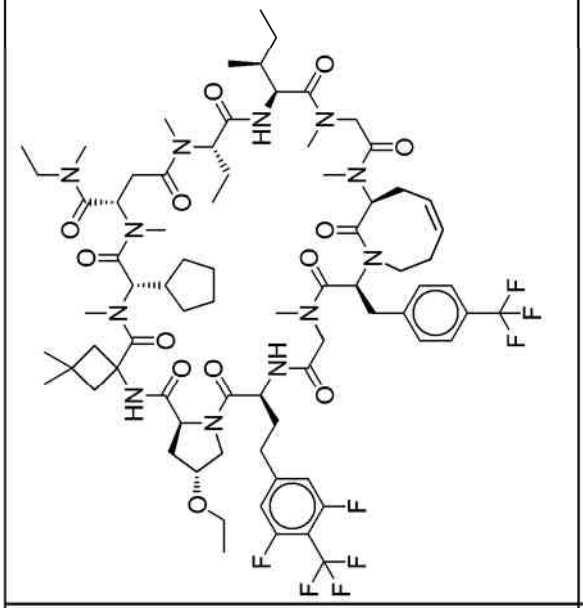
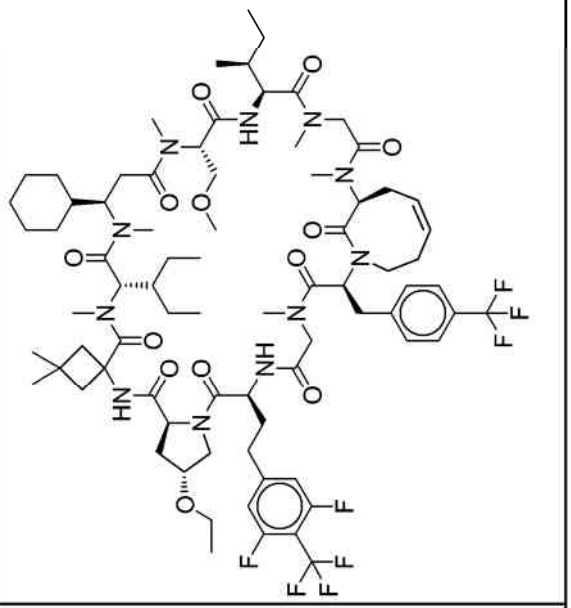
	
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PP1558	PP1560

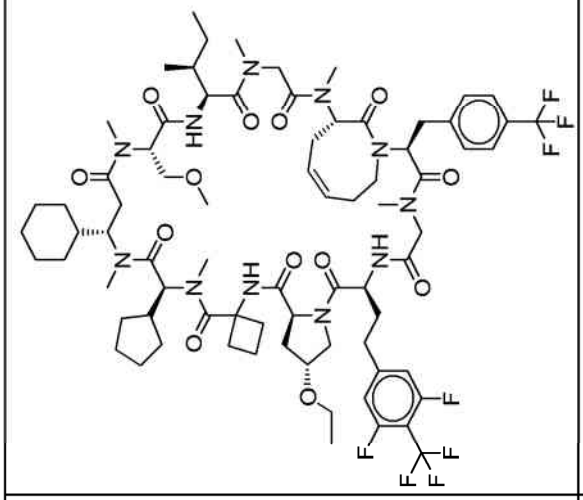
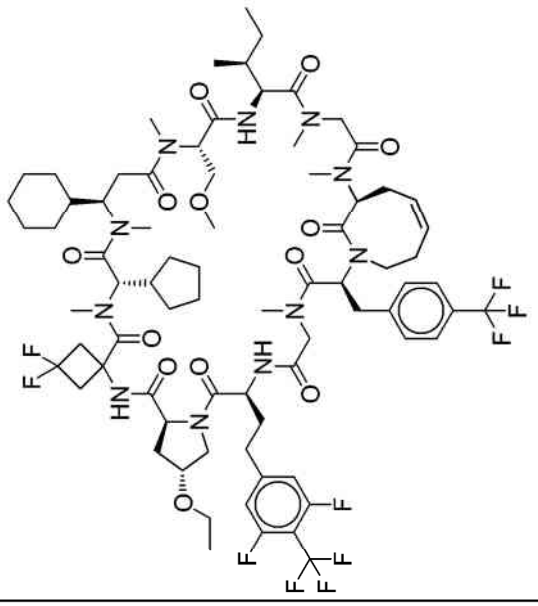
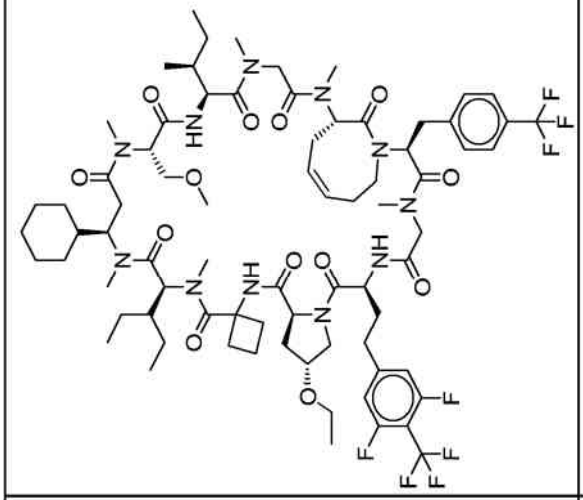
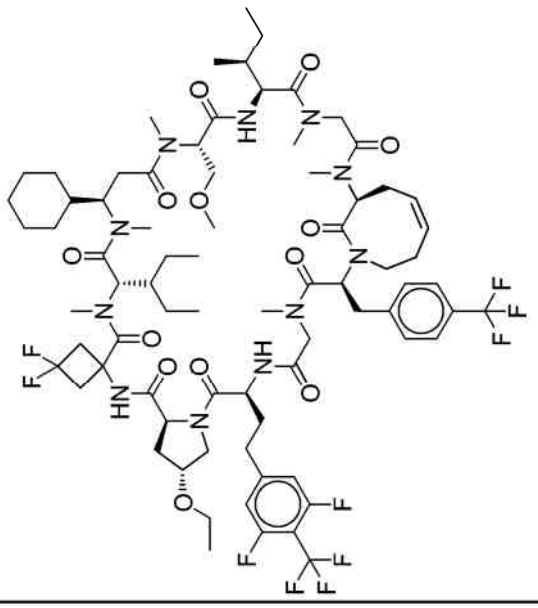
	
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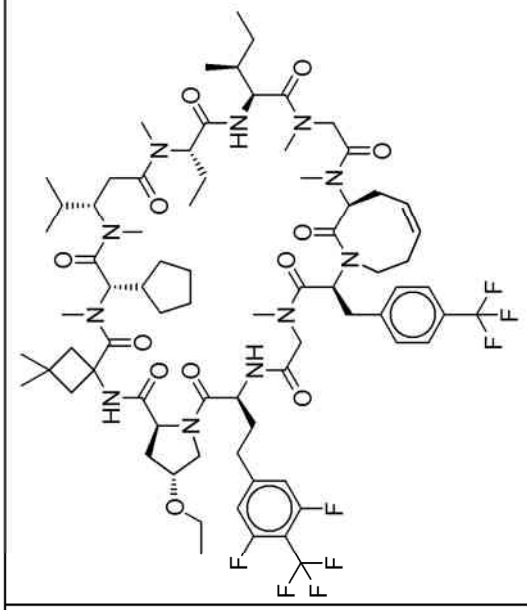
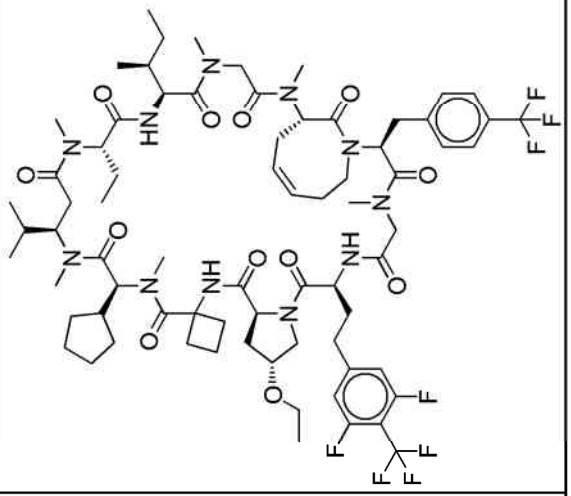
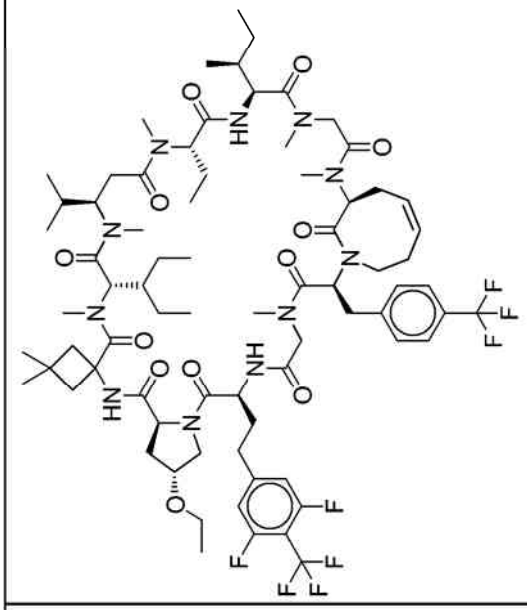
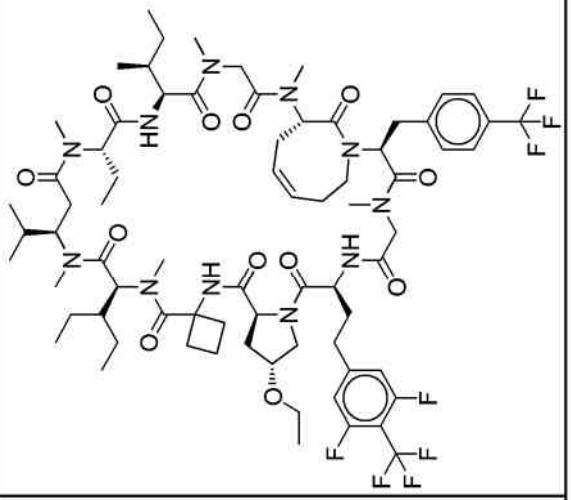
	
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PP1566	PP1569

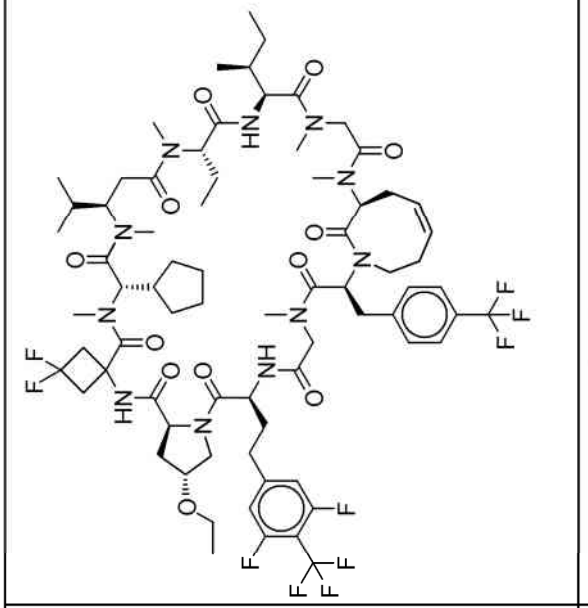
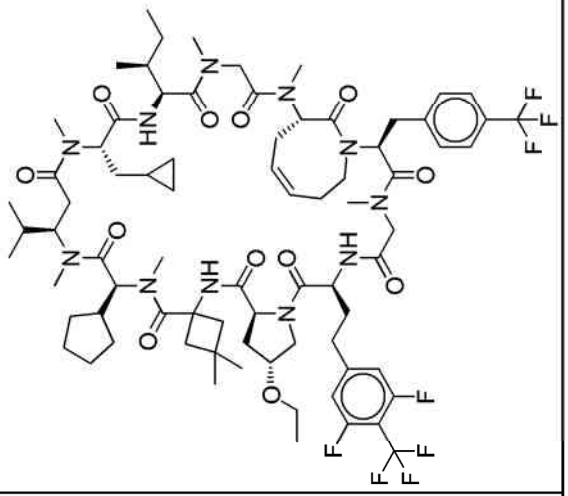
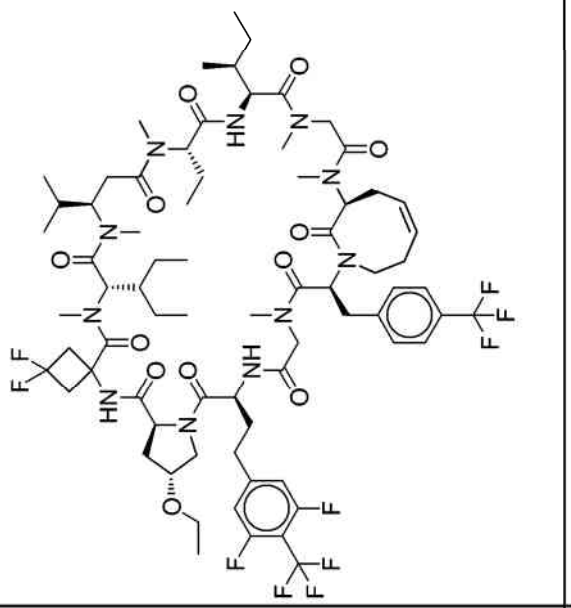
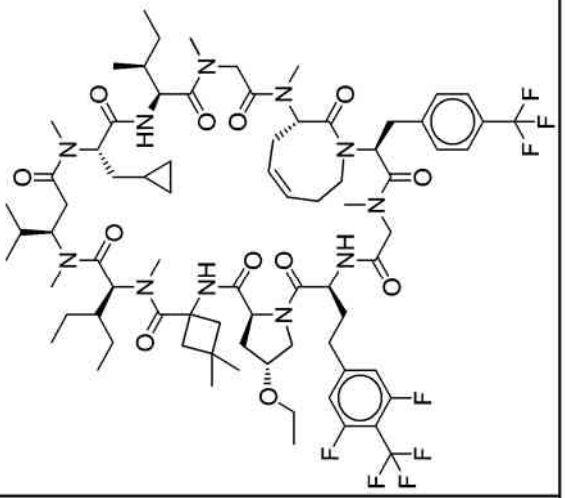
	
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PP157 1	PP157 3

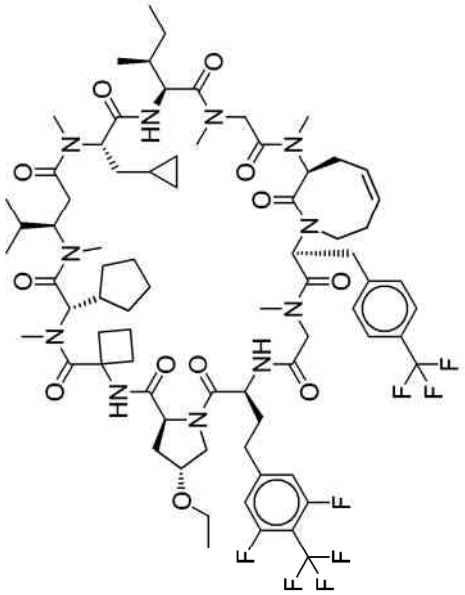
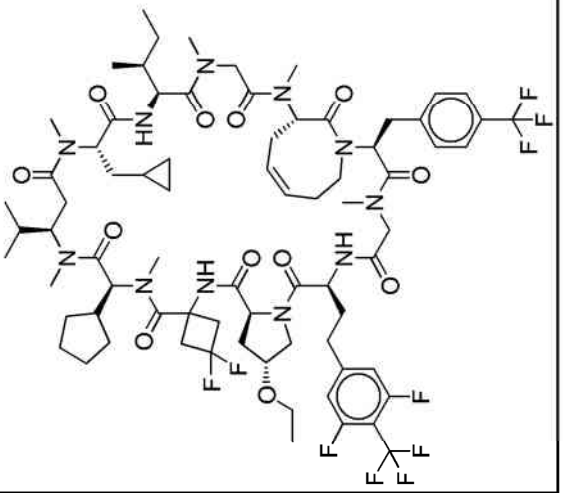
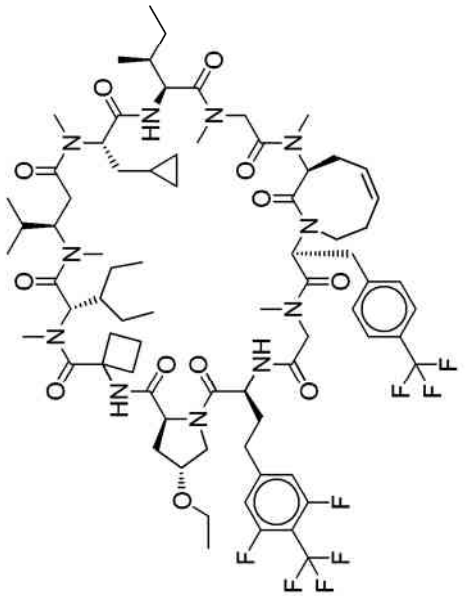
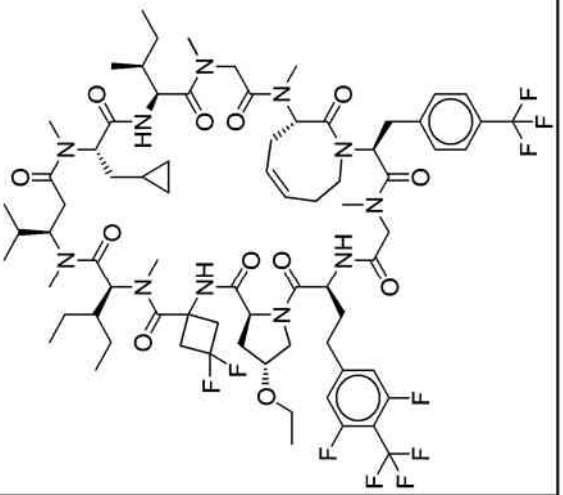
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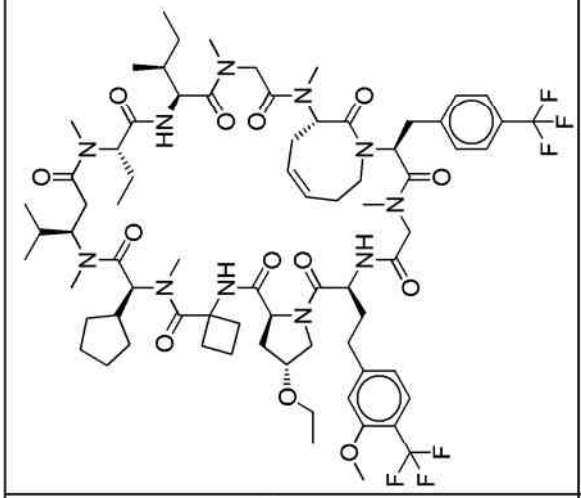
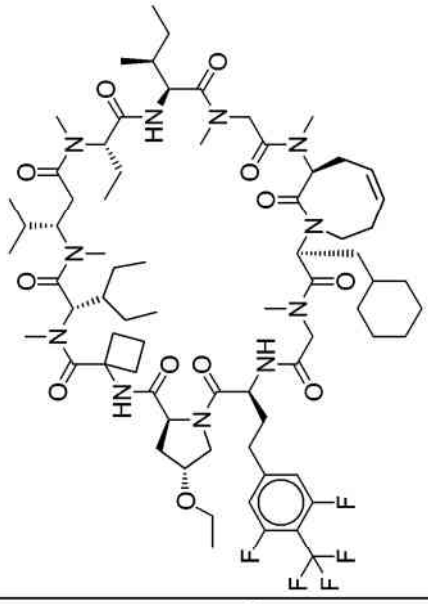
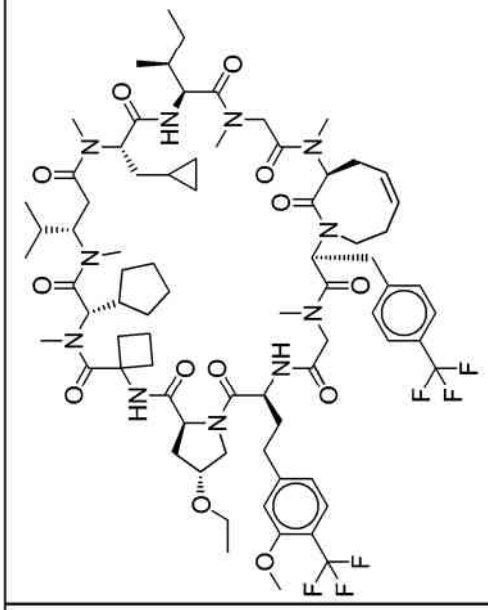
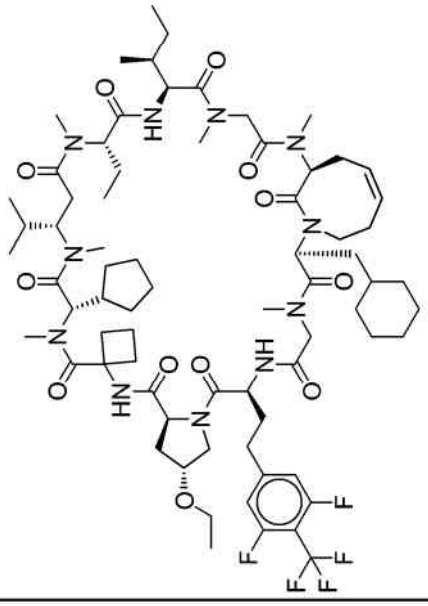
	
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PP1579	PP1581

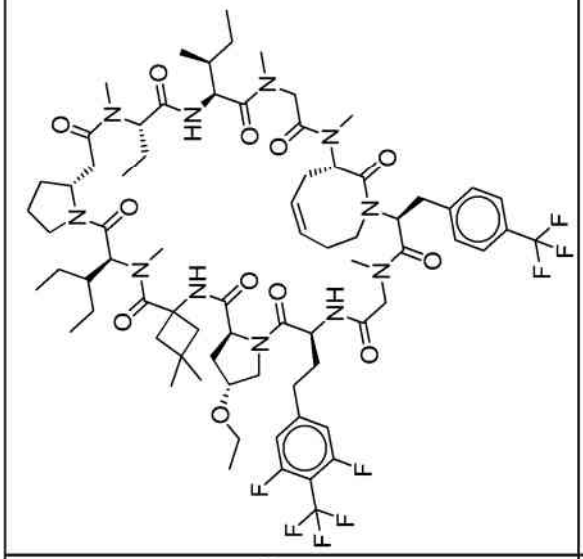
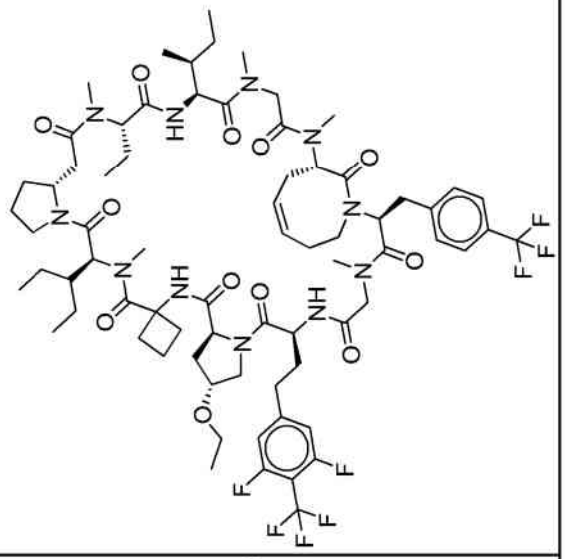
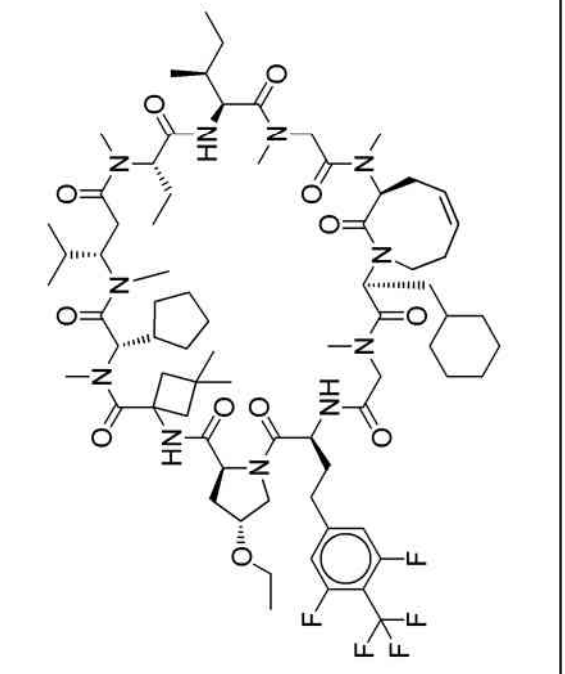
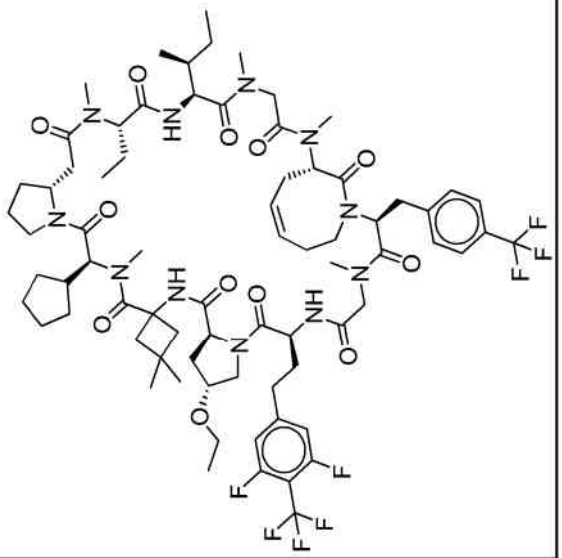
	
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PP158 3	PP158 5

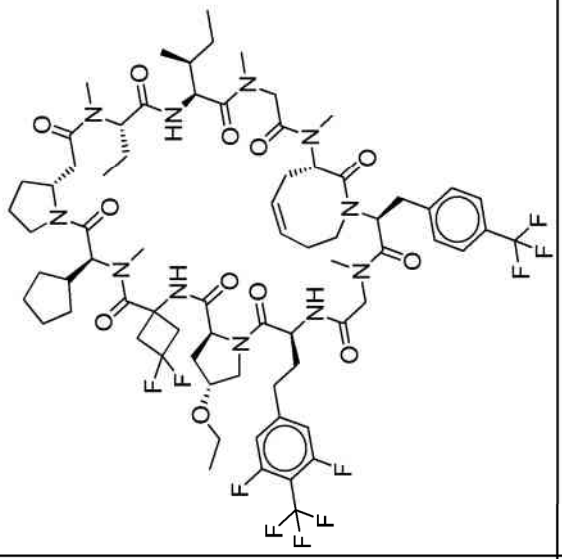
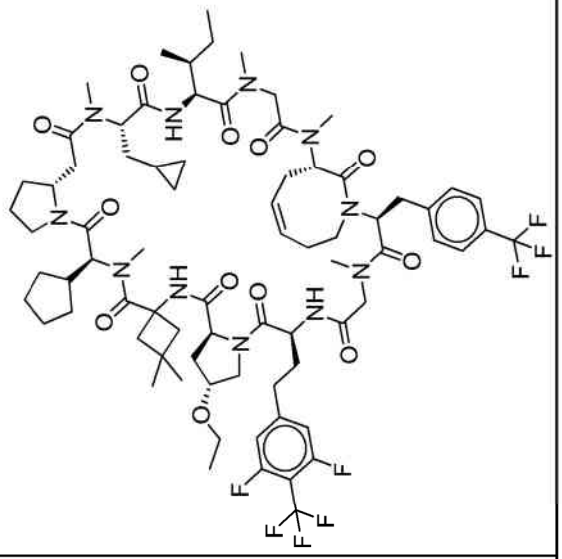
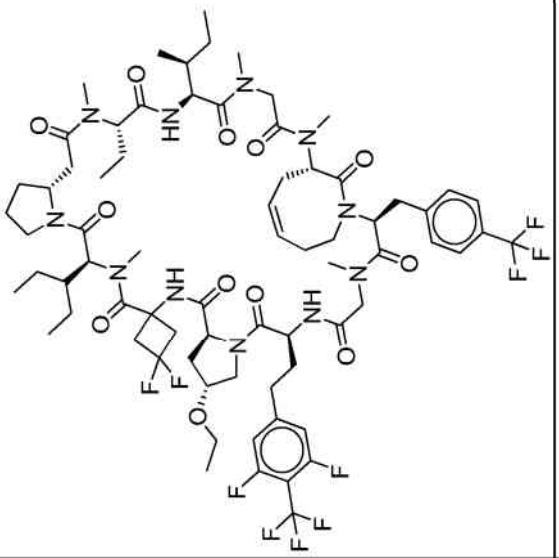
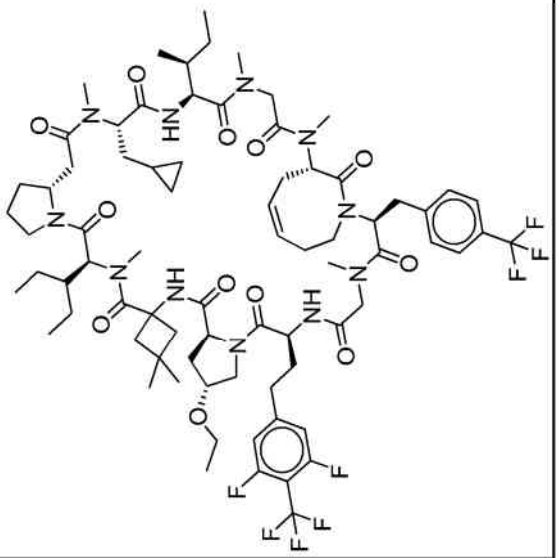
	
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PP1587	PP1589

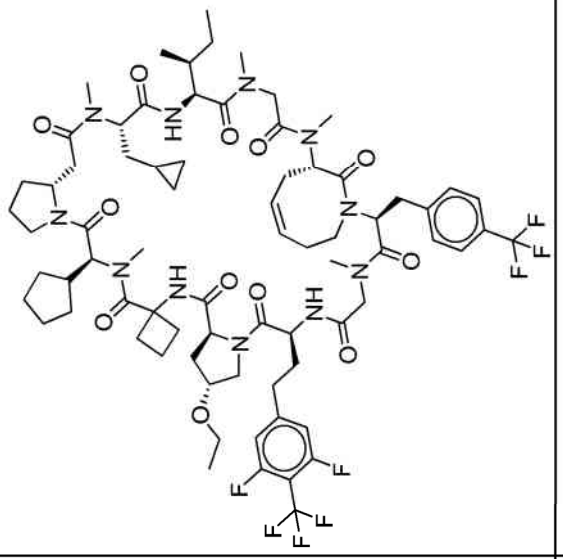
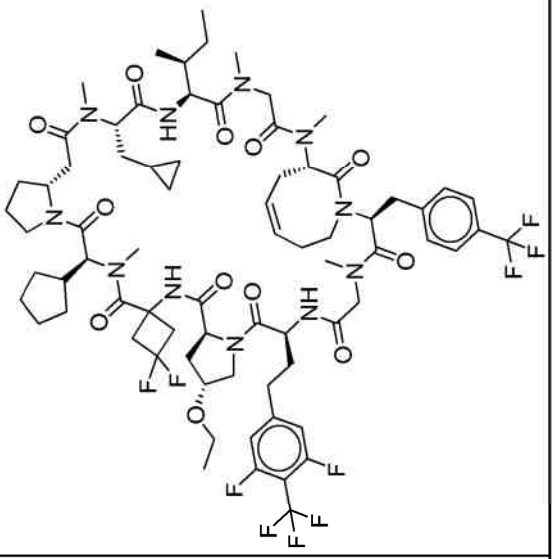
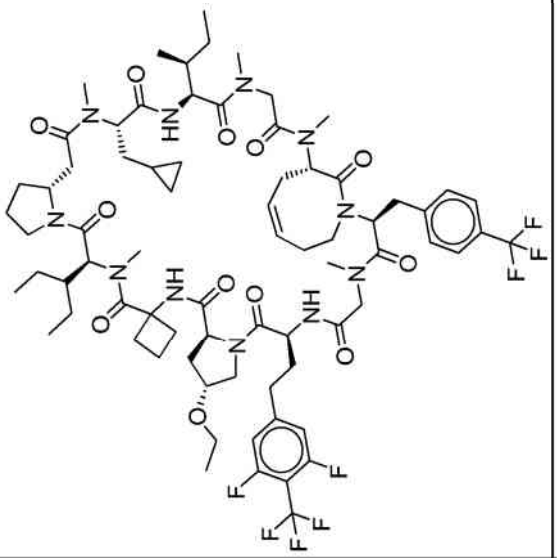
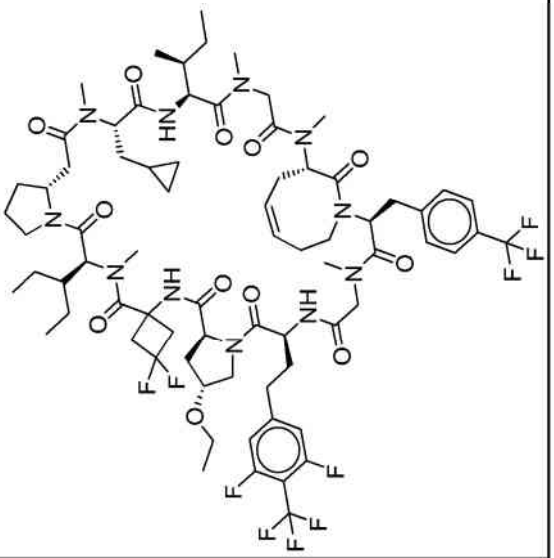
	
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PP159 1	PP159 3

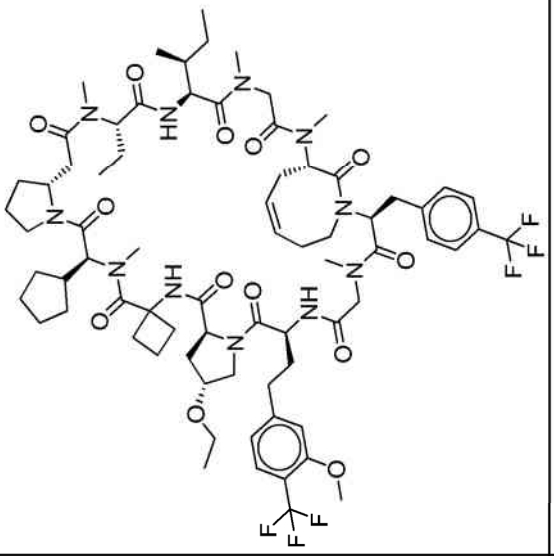
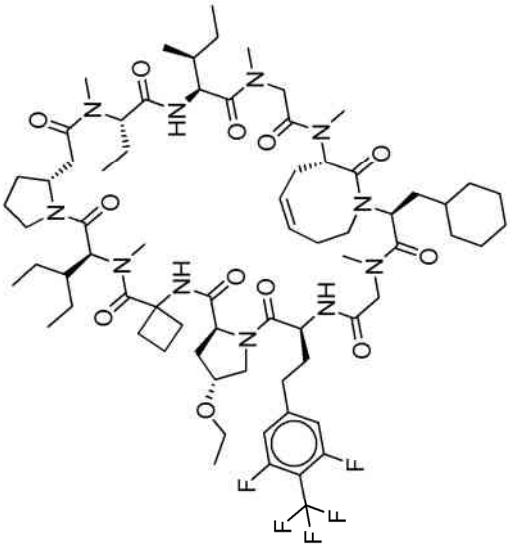
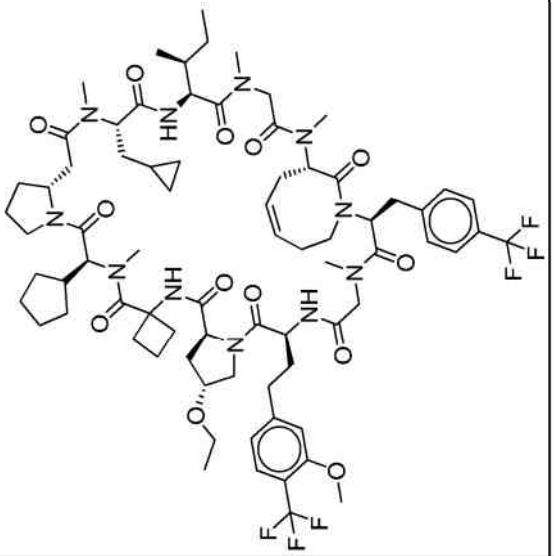
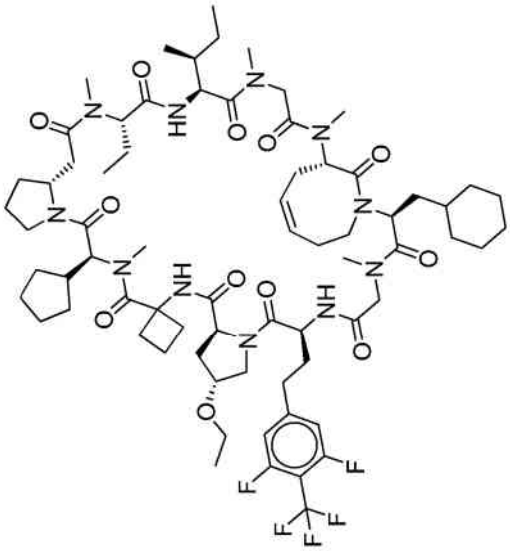
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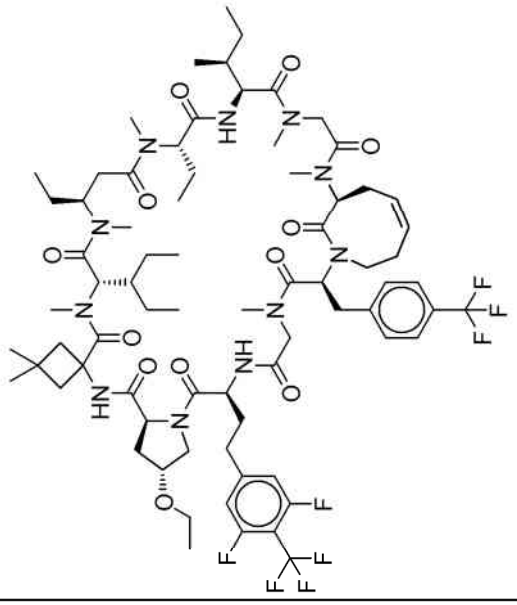
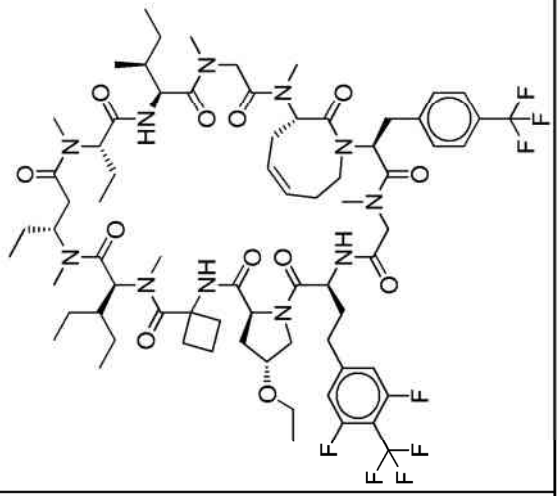
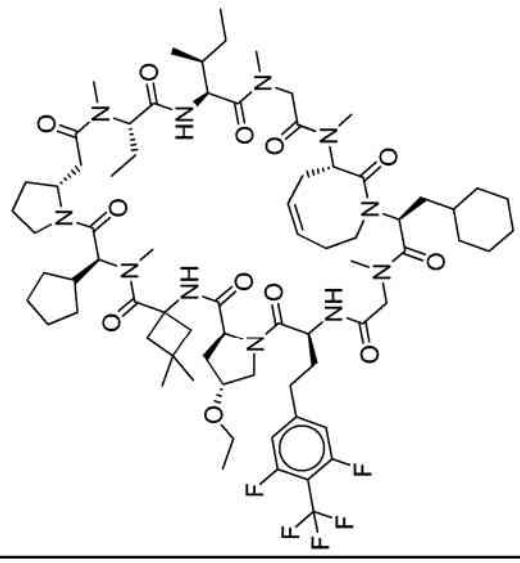
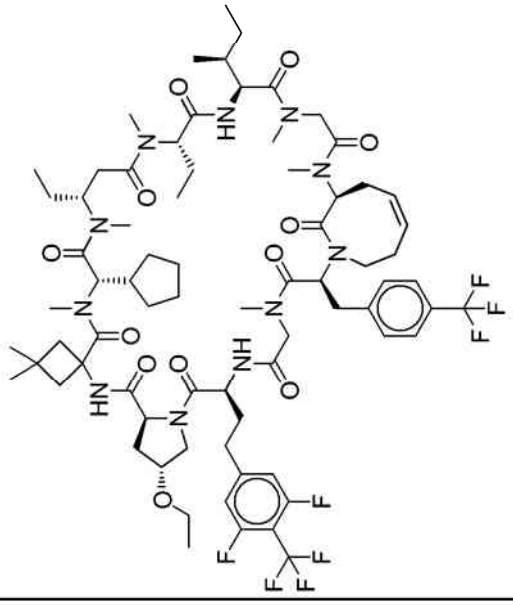
	
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PP1599	PP1601

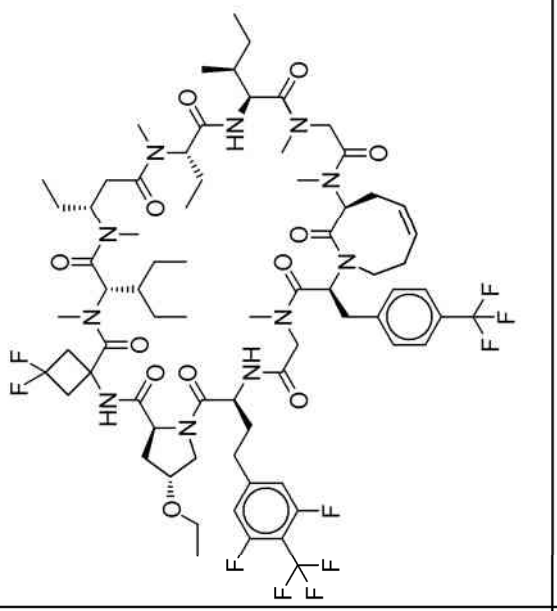
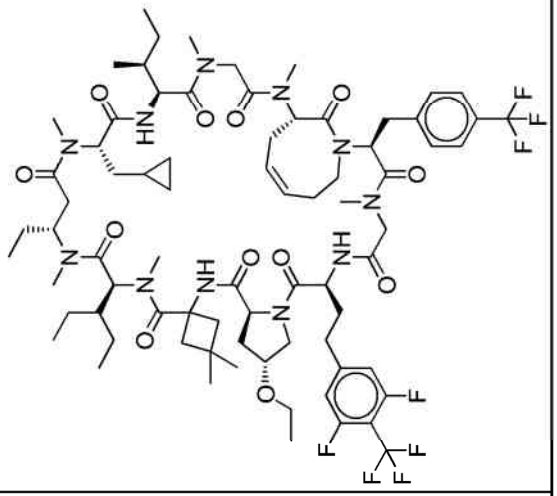
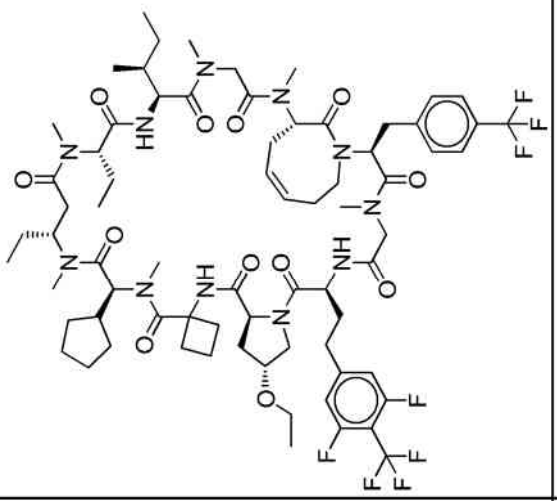
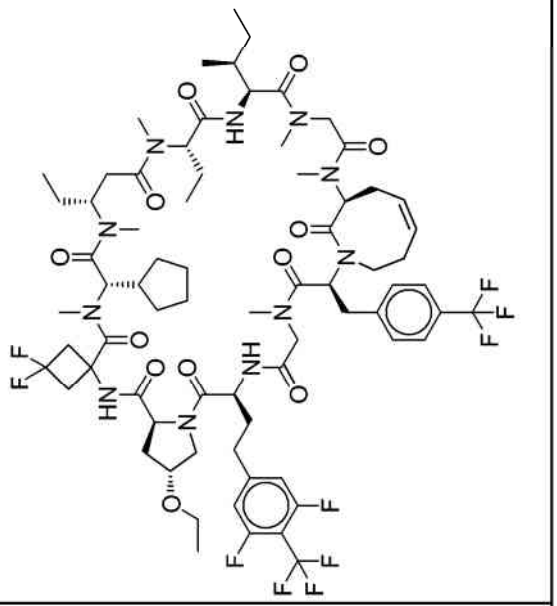
	
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PP160 3	PP160 6

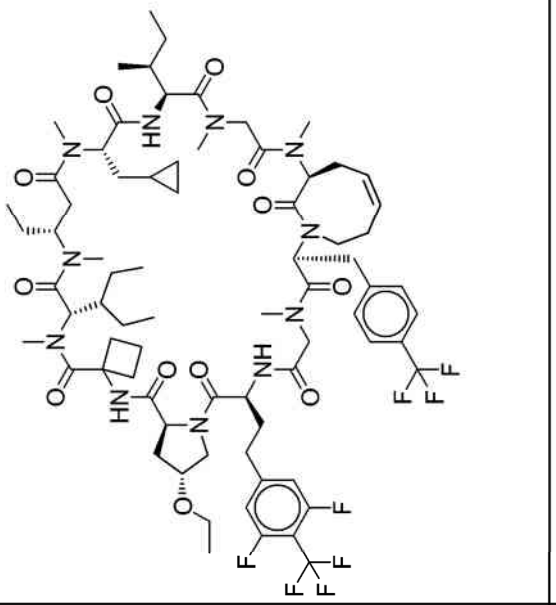
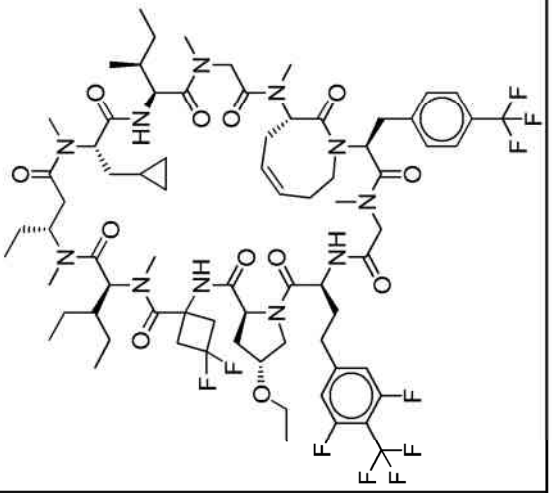
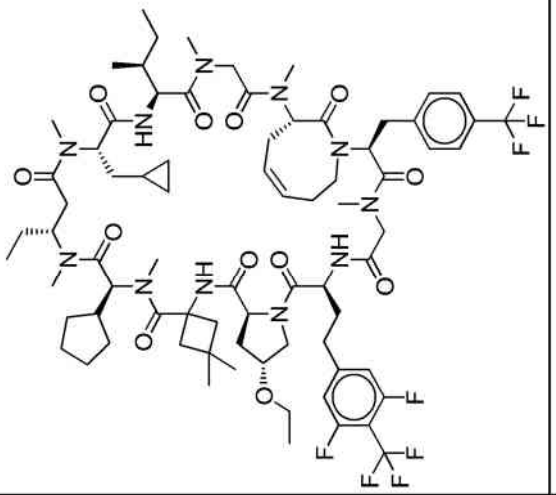
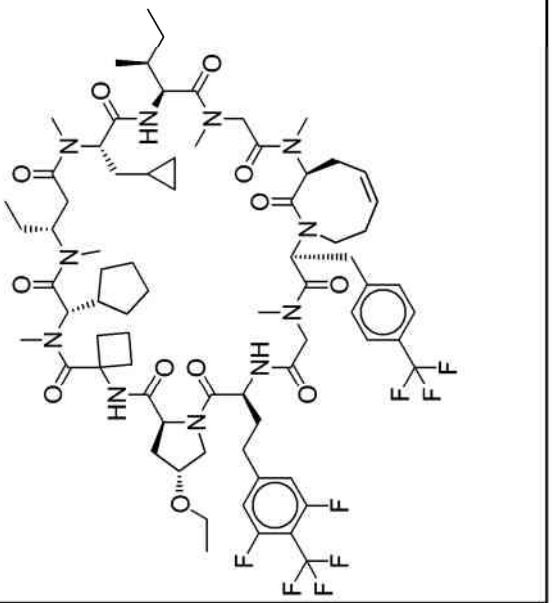
	
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PP1608	PP1610

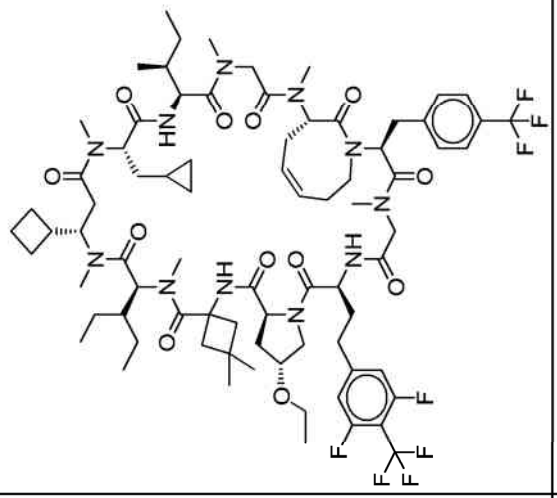
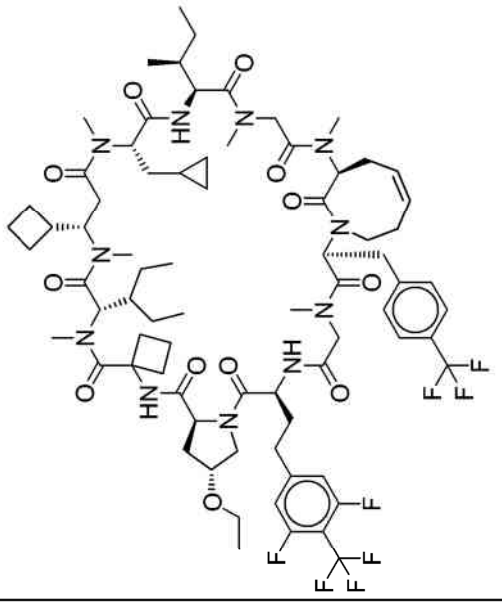
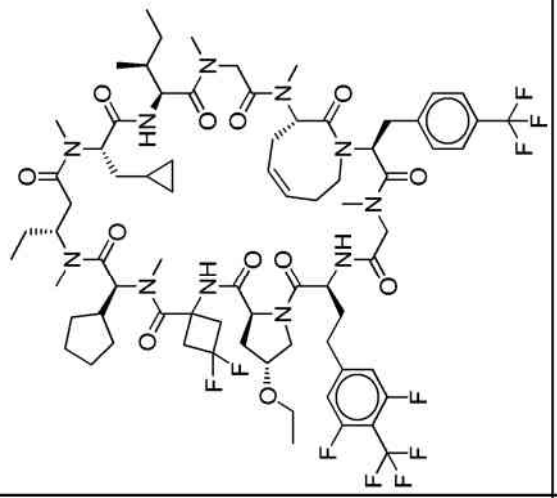
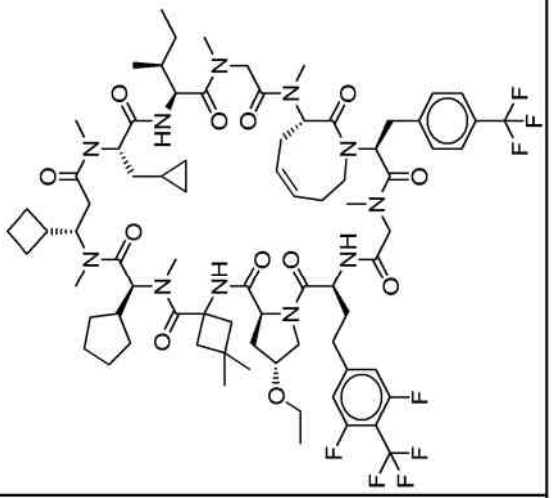
	
PP161 3	PP161 5
	
PP161 2	PP161 4

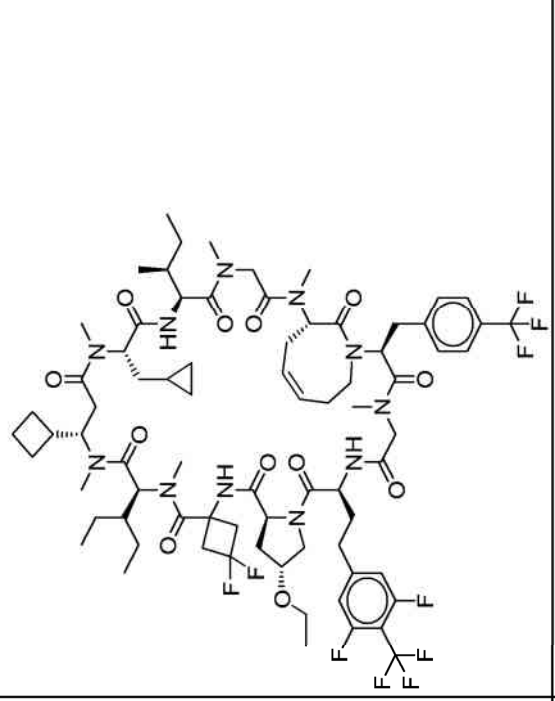
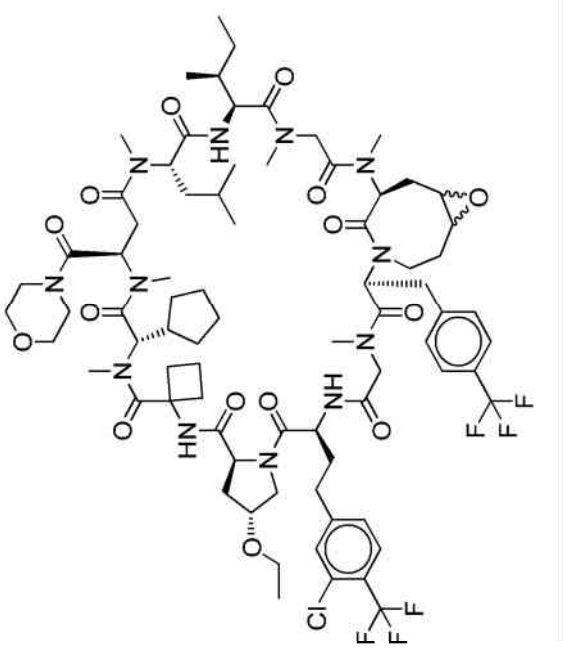
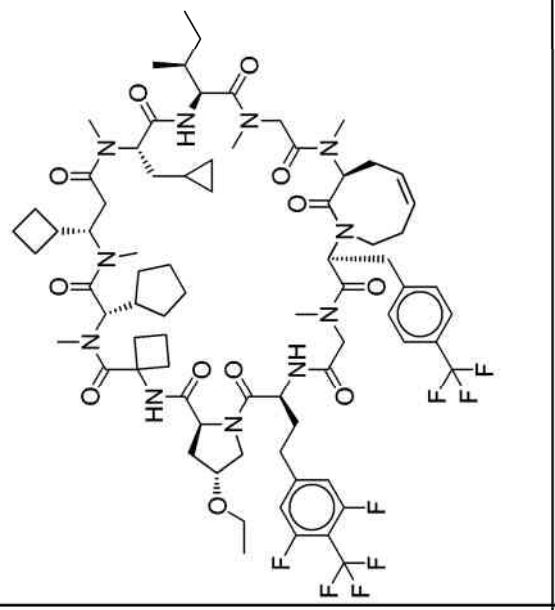
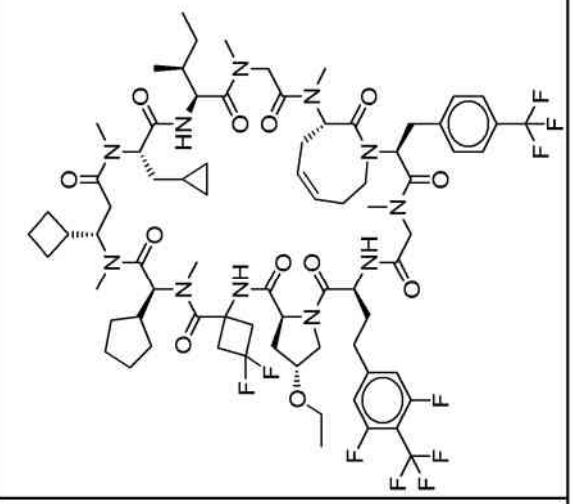
	
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PP161 6	PP161 8

	
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PP1620	PP1623

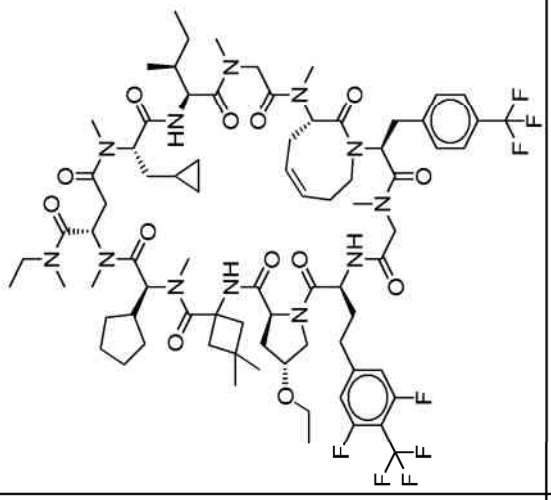
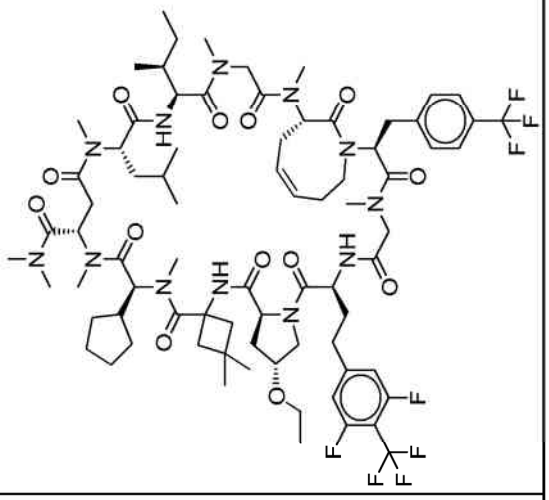
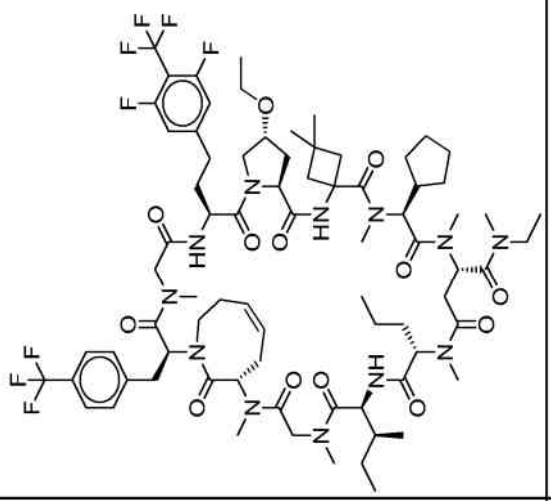
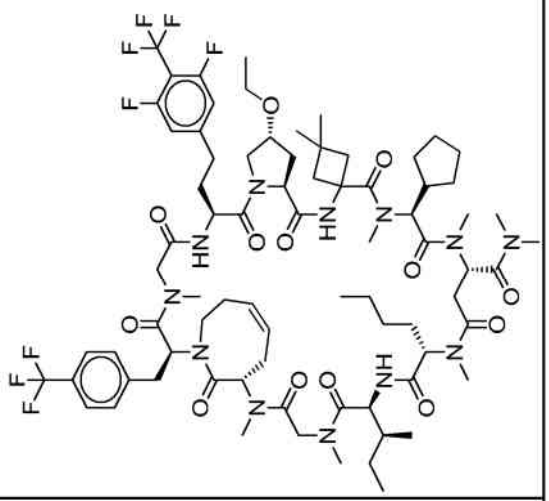
	
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PP162 5	PP162 7

	
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PP1629	PP1631

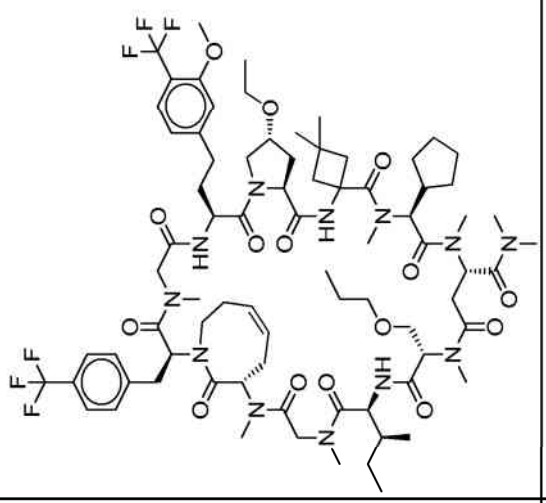
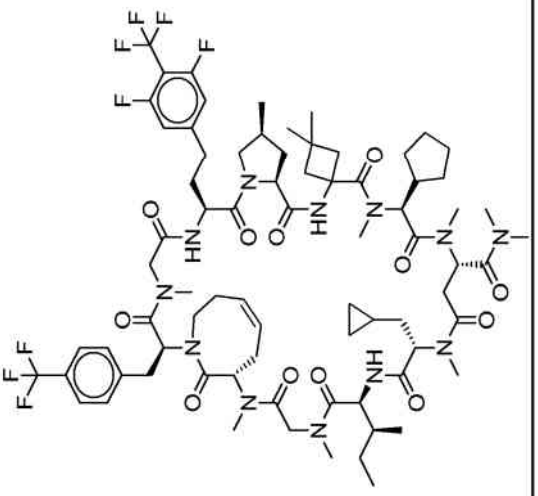
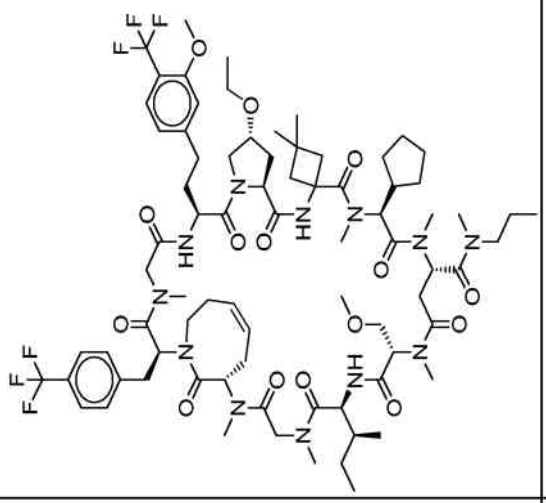
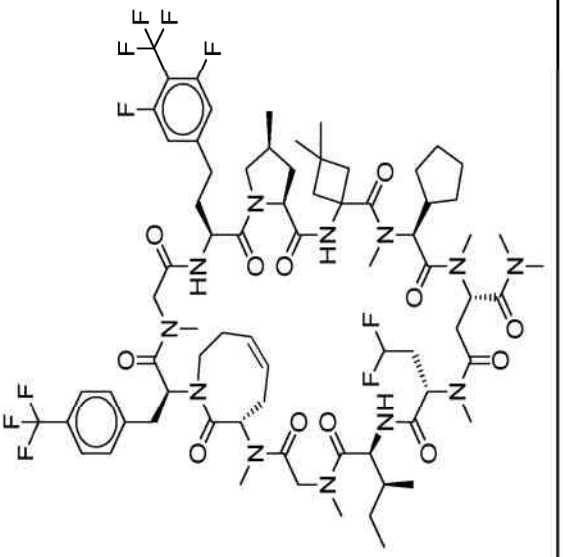
	
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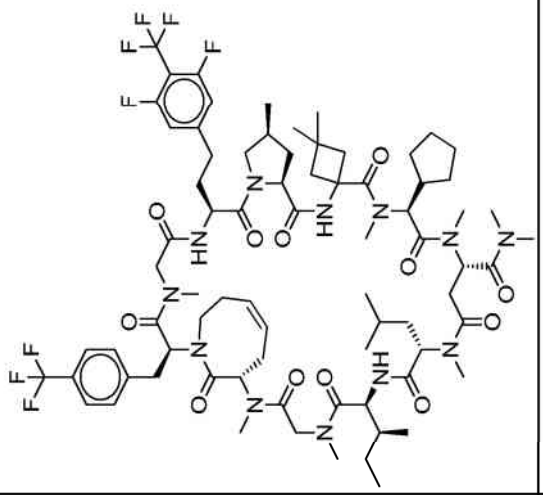
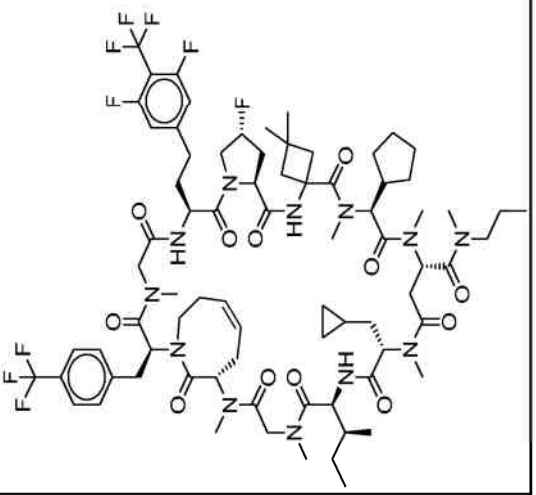
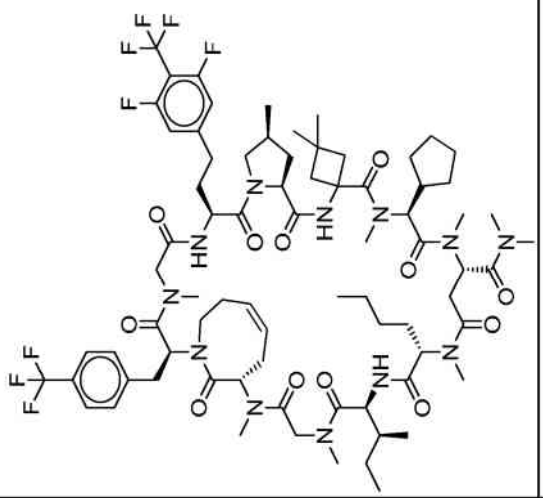
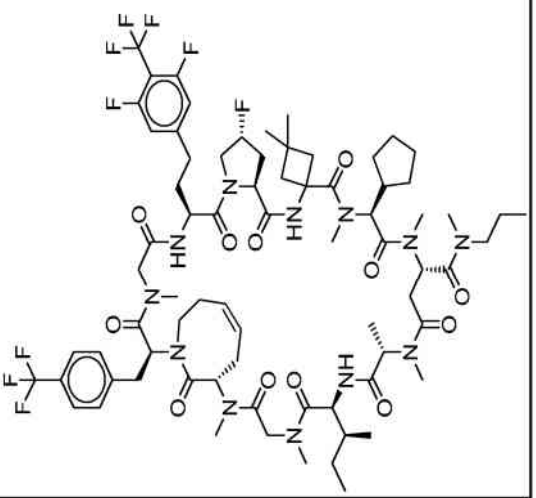
	
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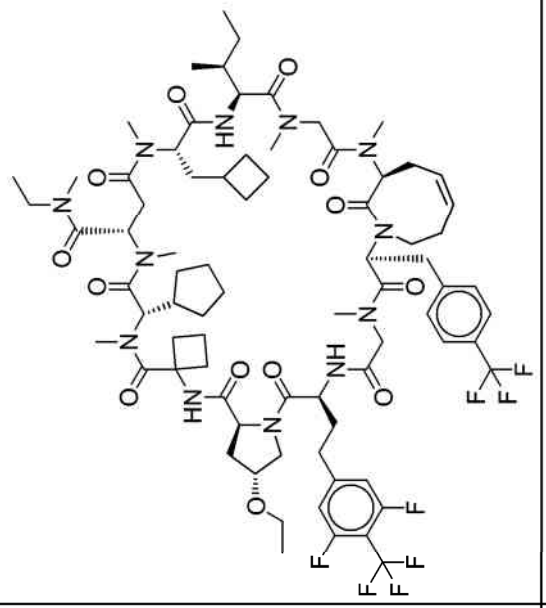
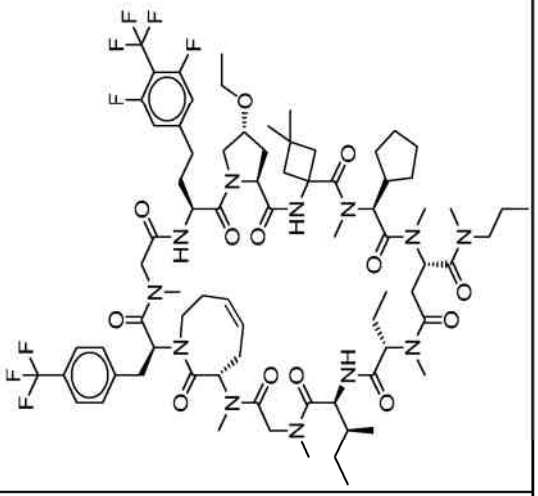
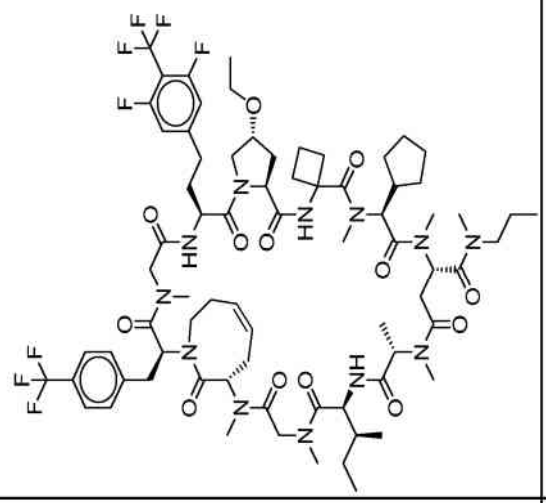
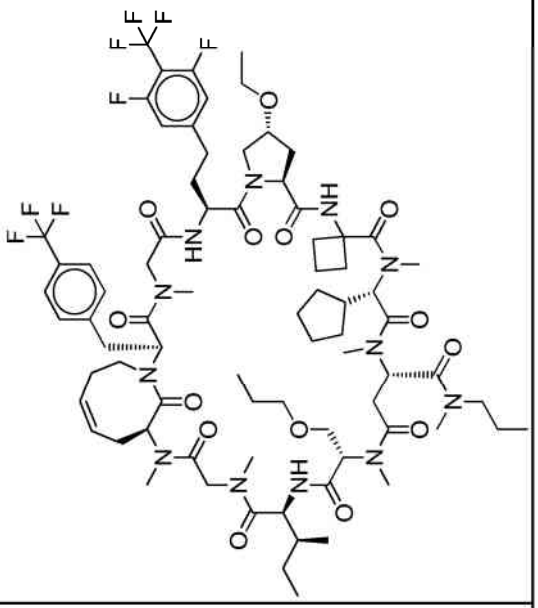
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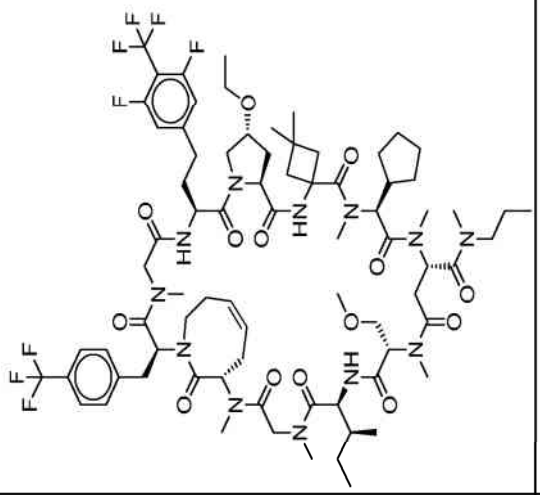
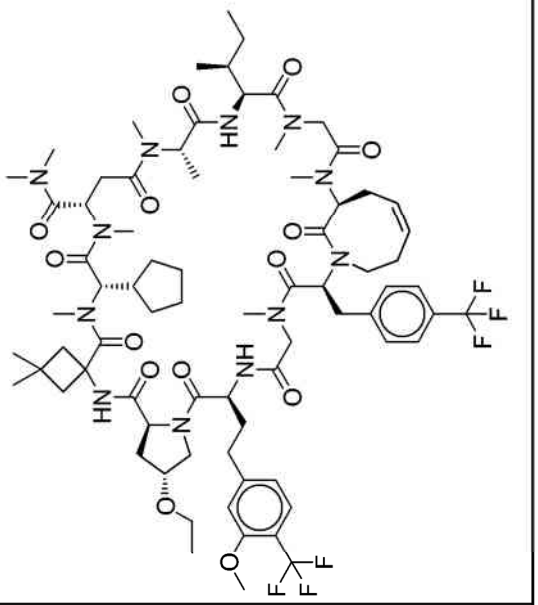
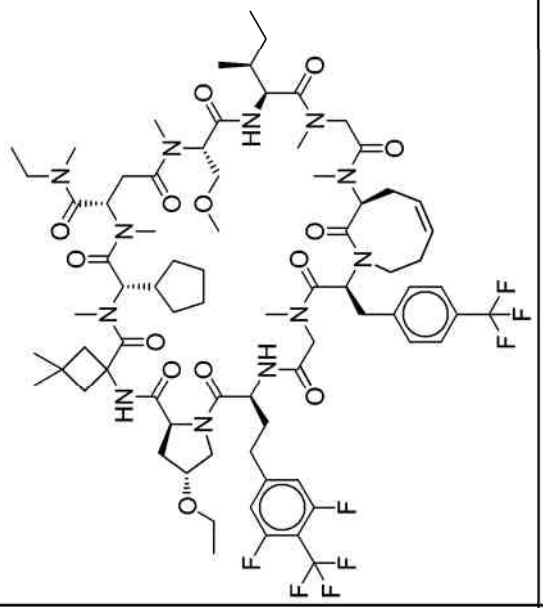
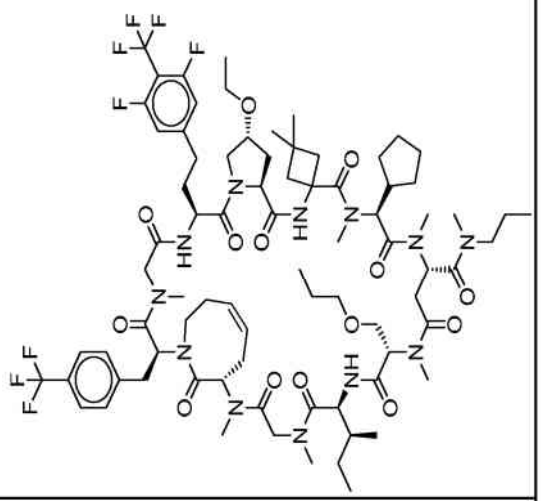
	
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PP1646	PP1649

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PP165 1	PP165 4

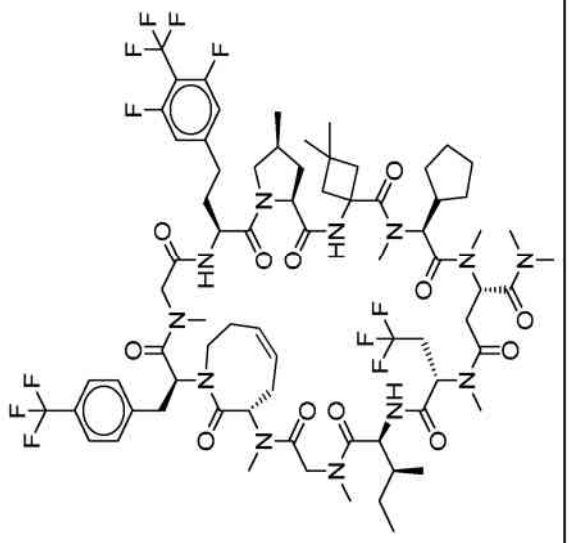
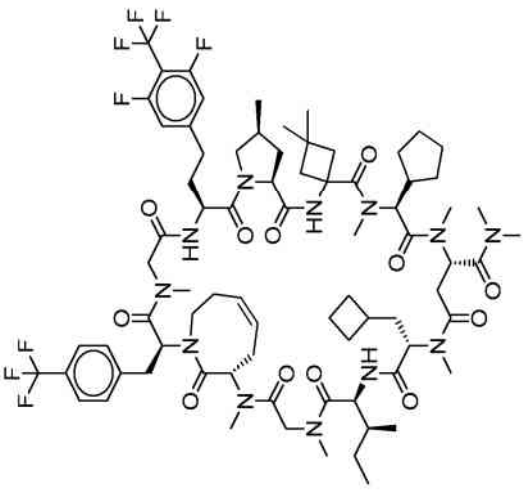
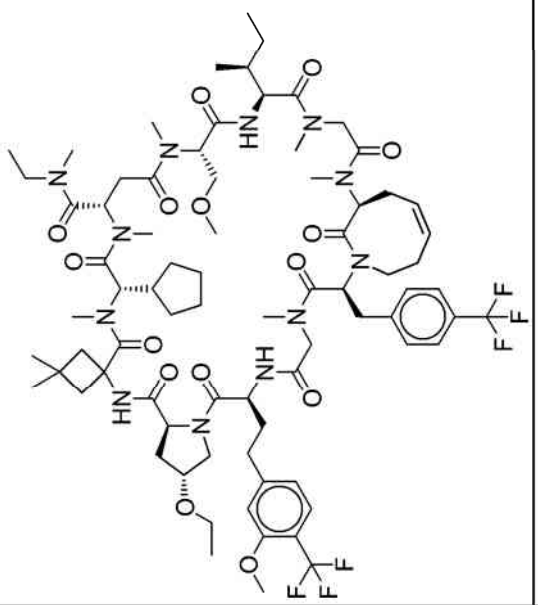
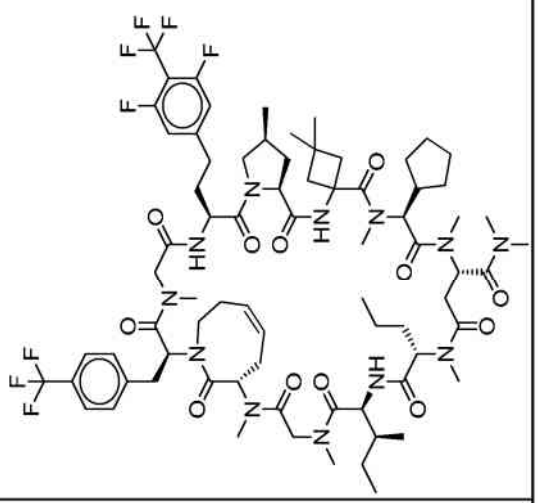
	
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PP1656	PP1658

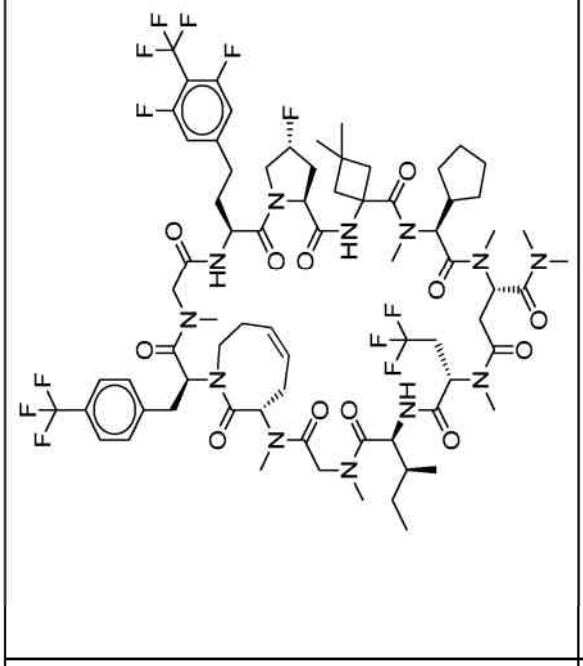
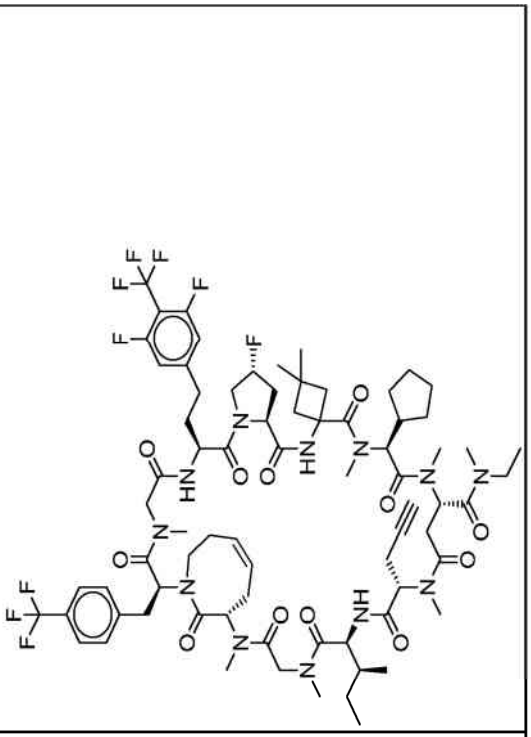
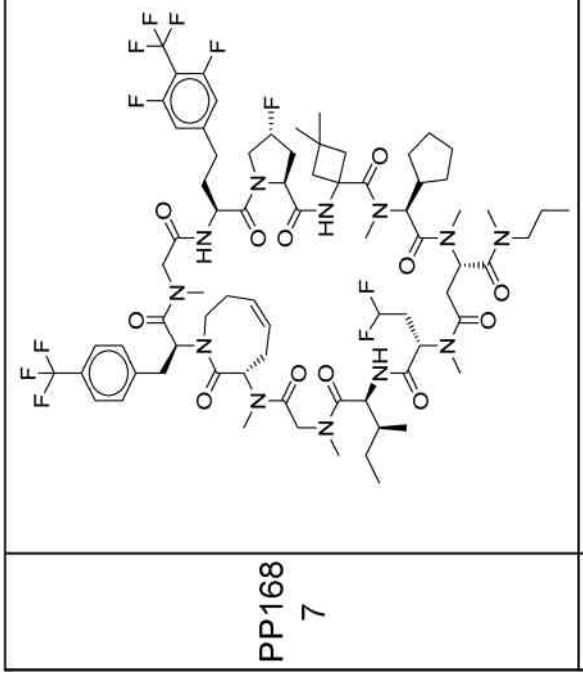
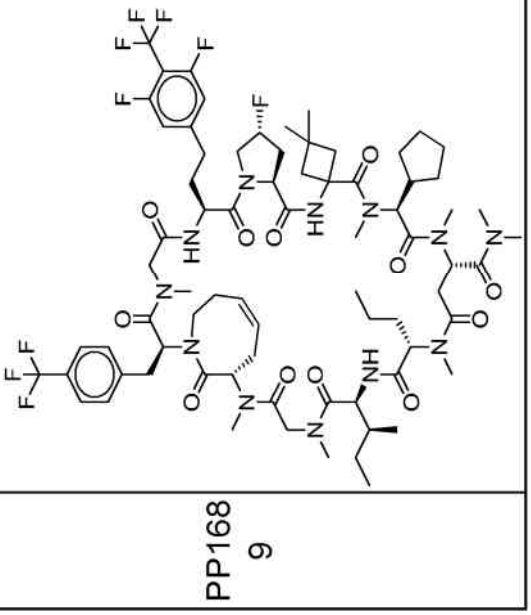
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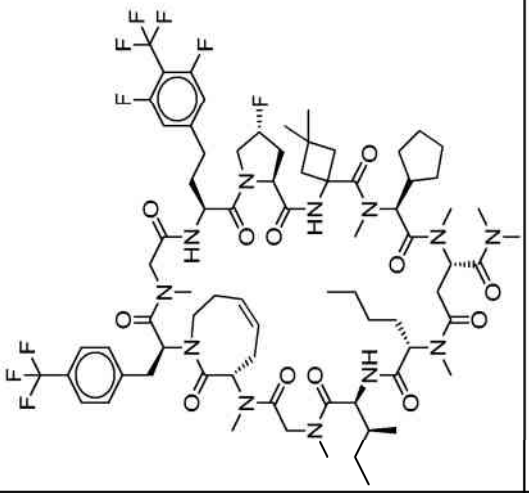
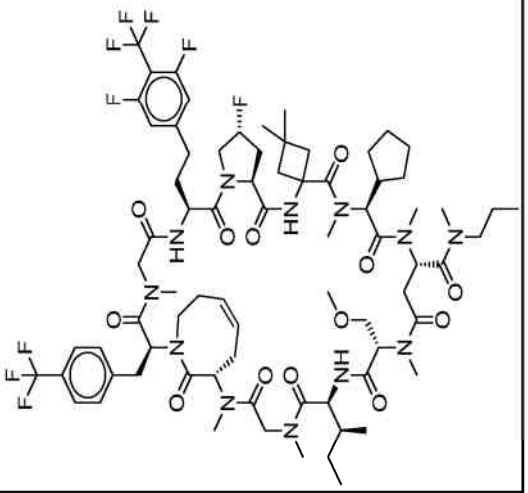
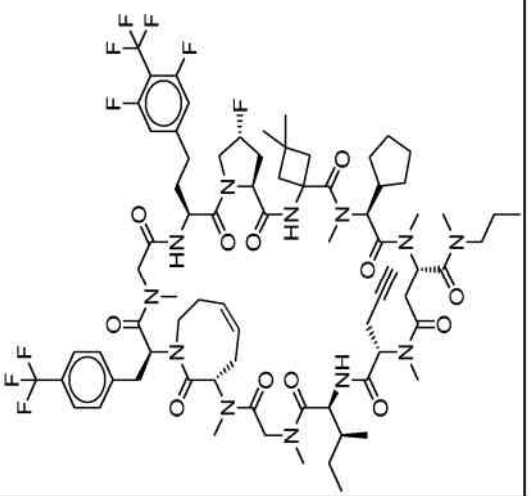
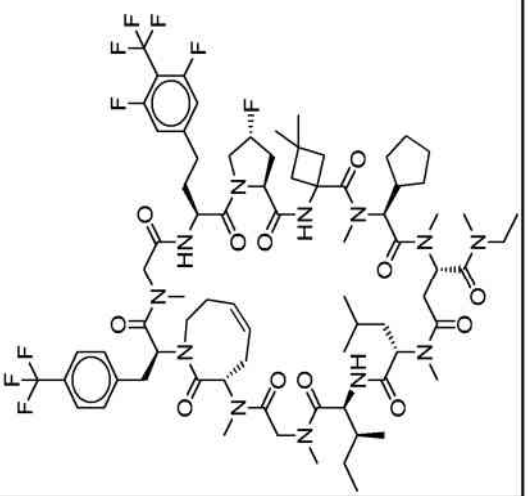
	
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PP1666	PP1668

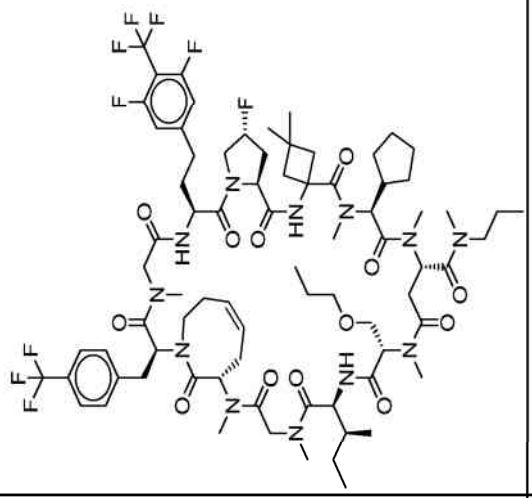
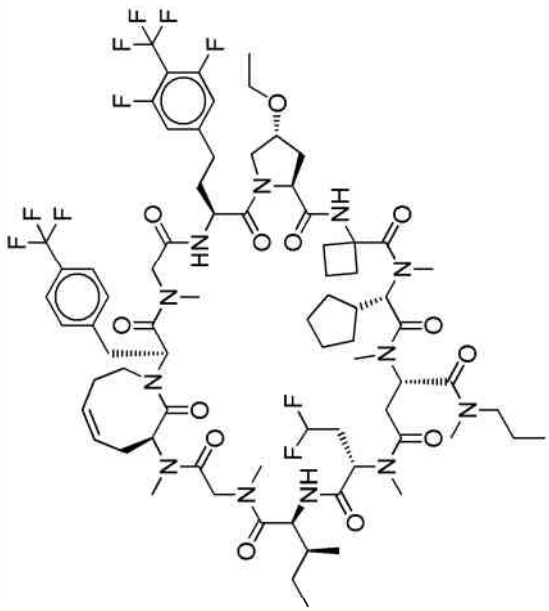
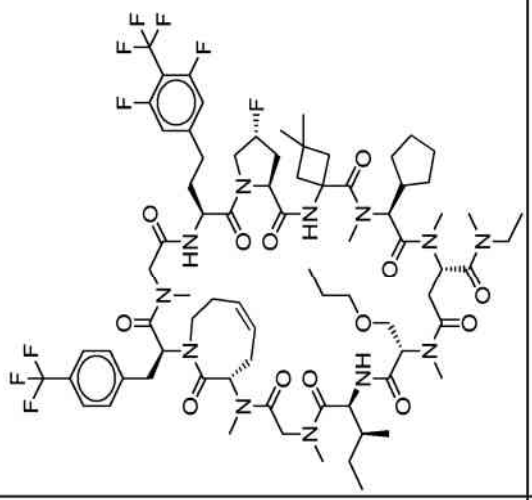
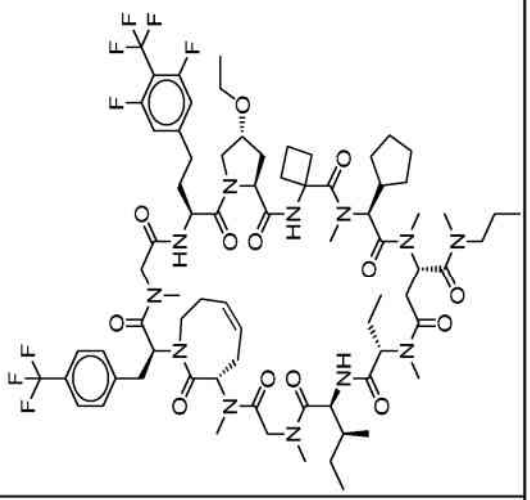
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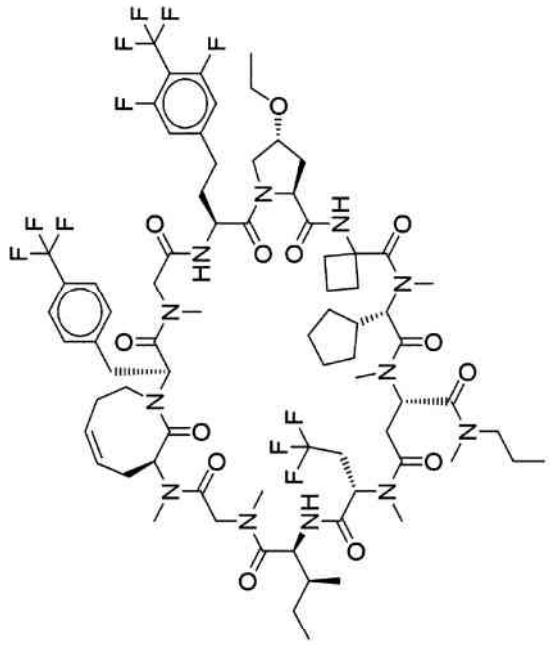
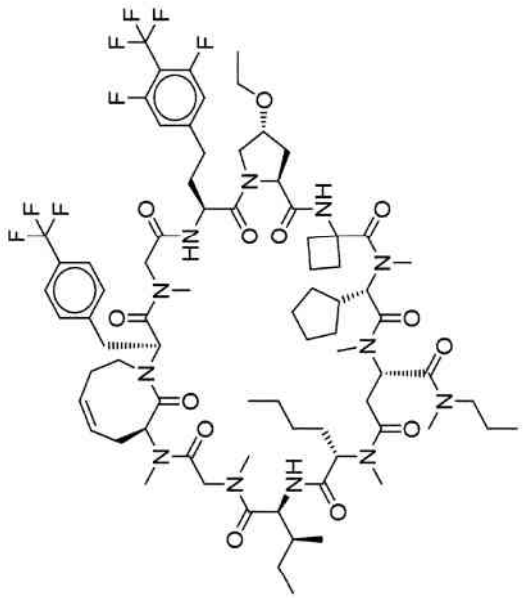
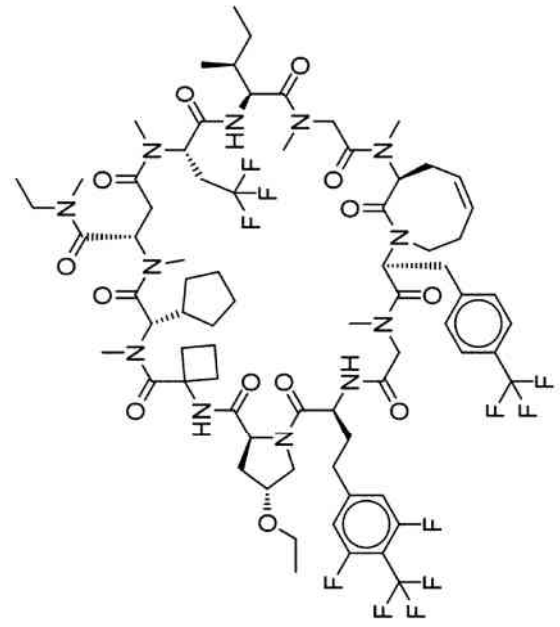
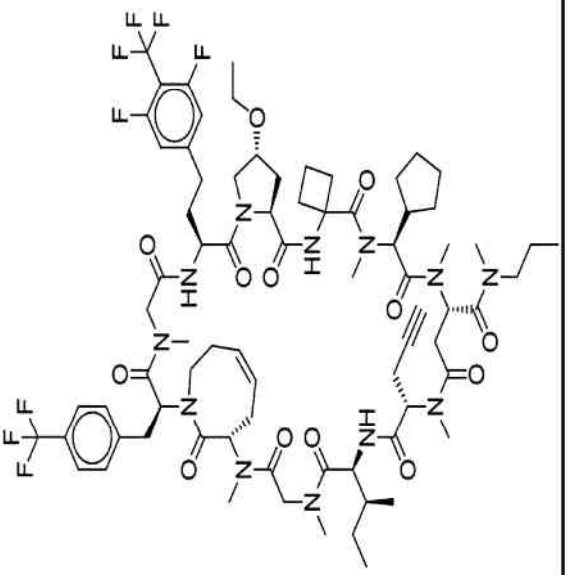
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PP167 5	PP167 7

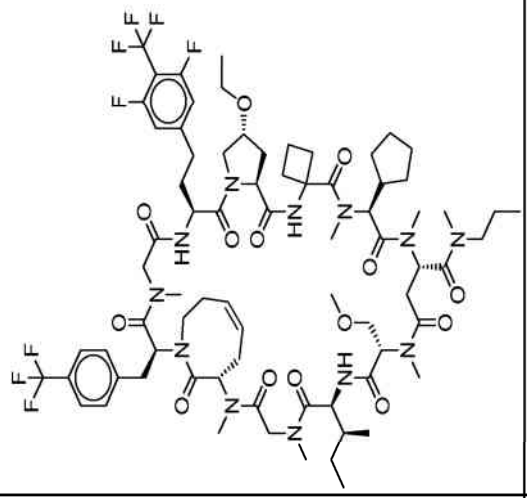
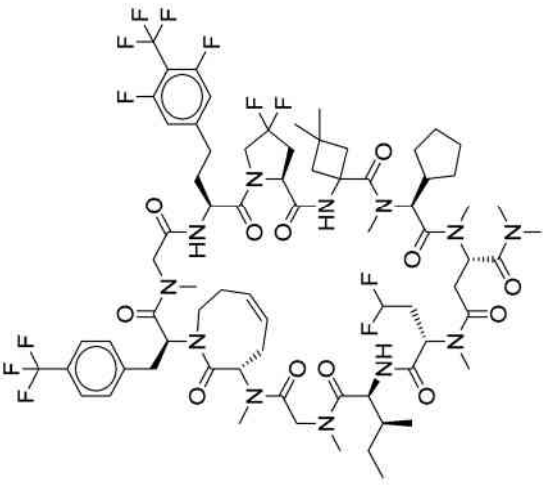
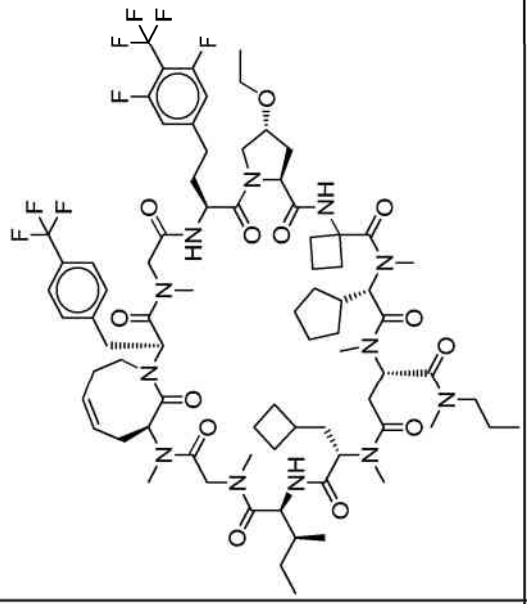
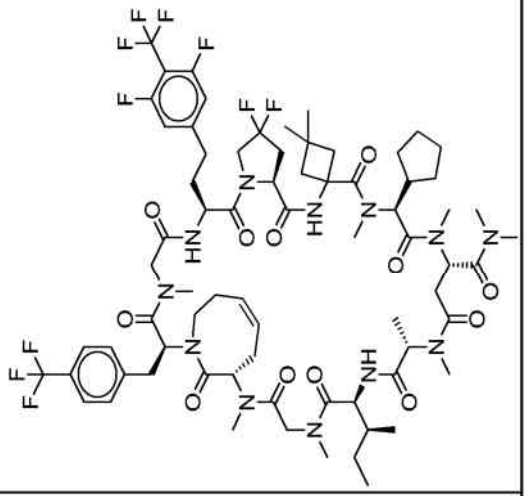
	
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PP167 9	PP168 3

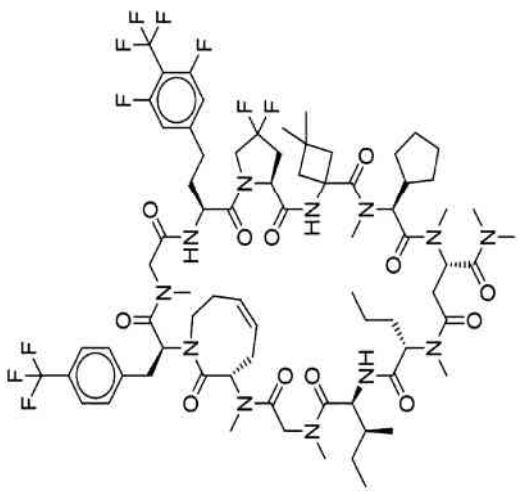
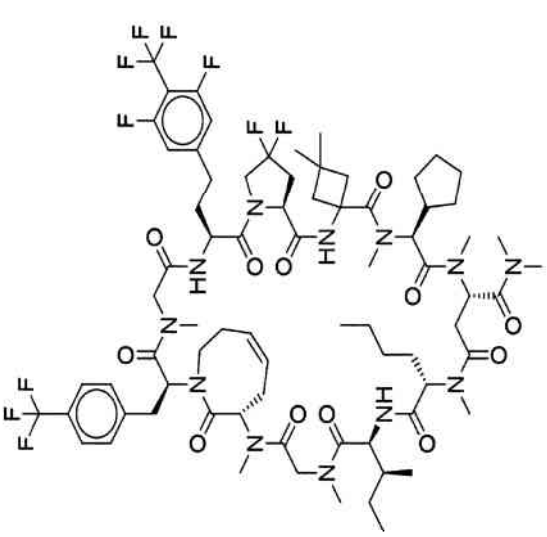
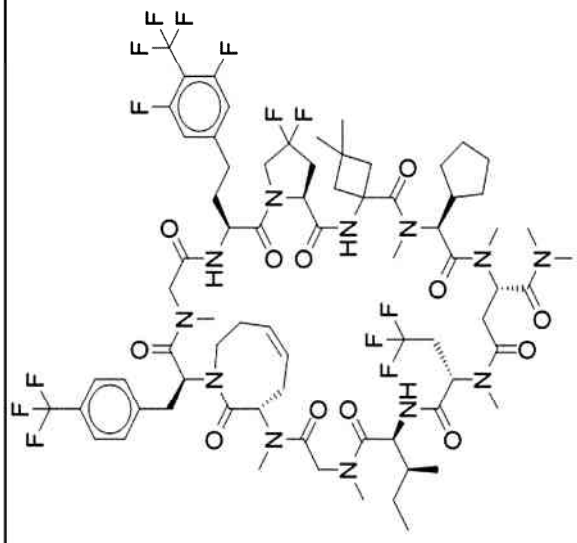
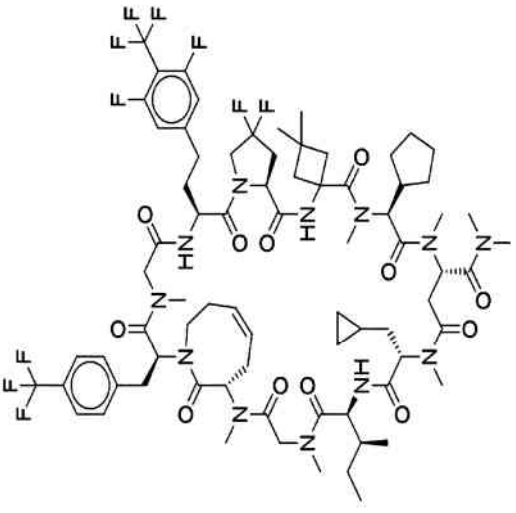
	
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PP168 7	PP168 9

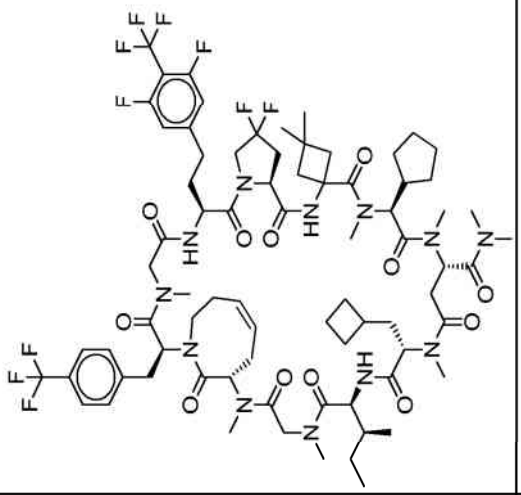
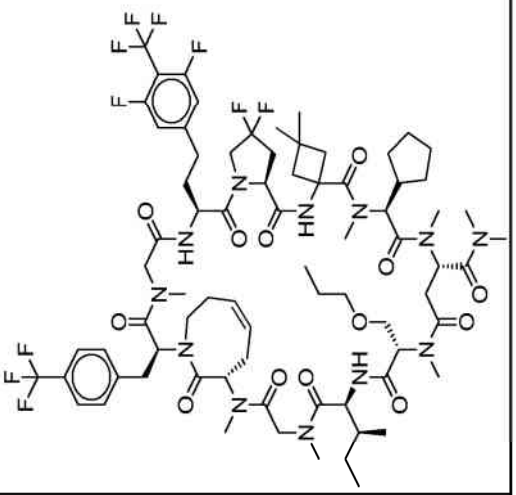
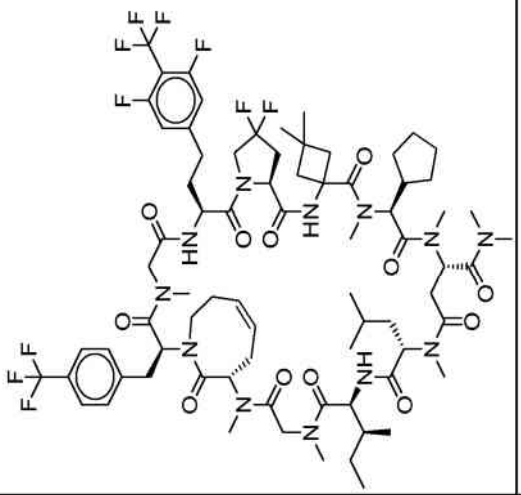
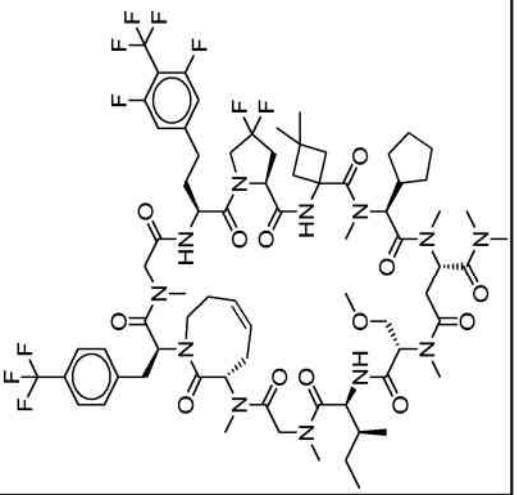
	
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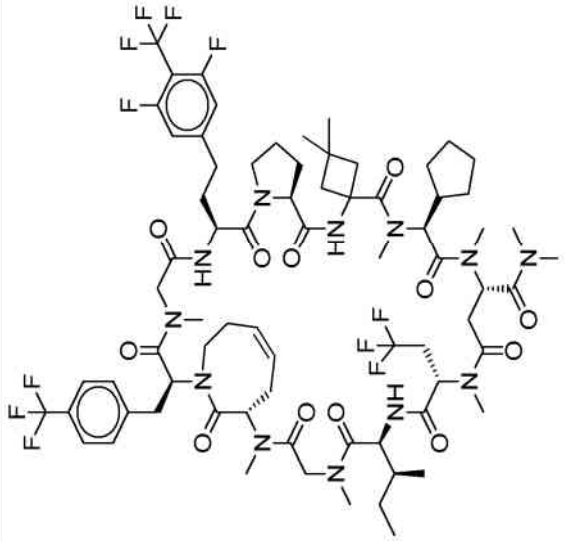
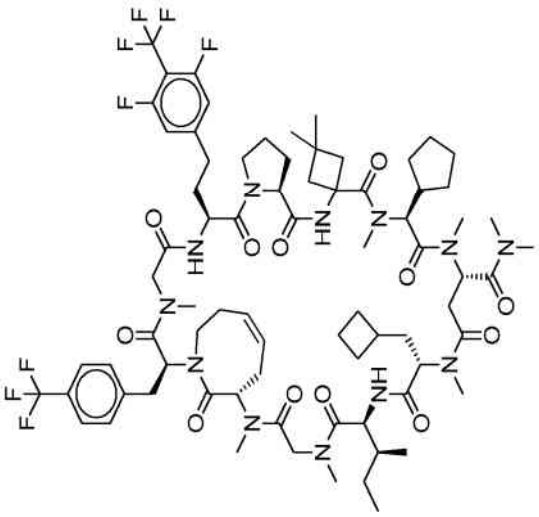
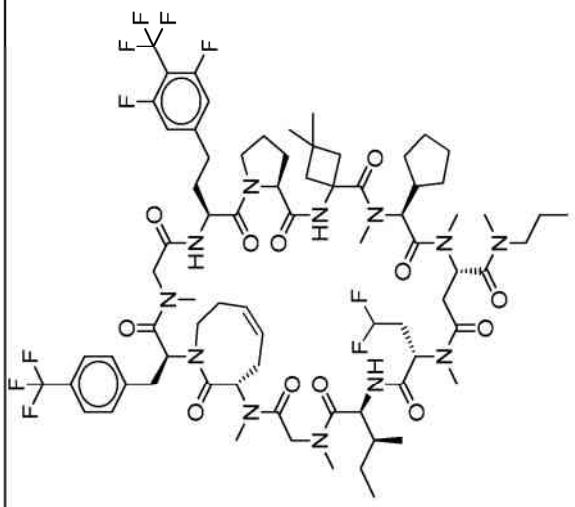
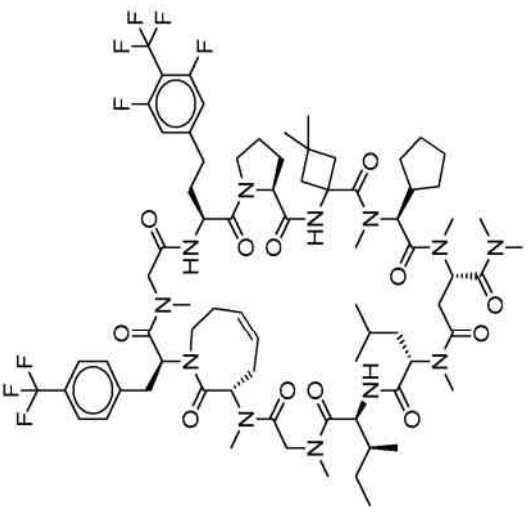
	
PP1698	PP1700
	
PP1697	PP1699

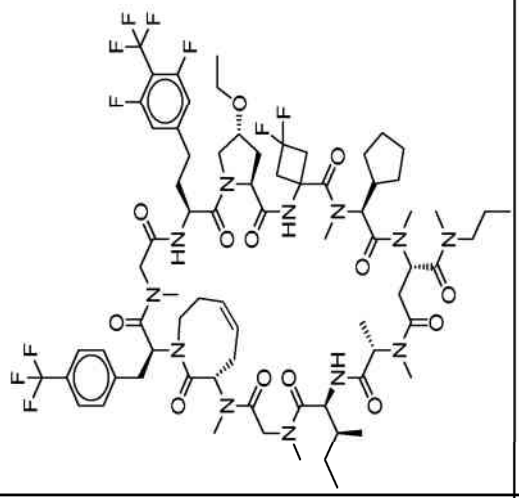
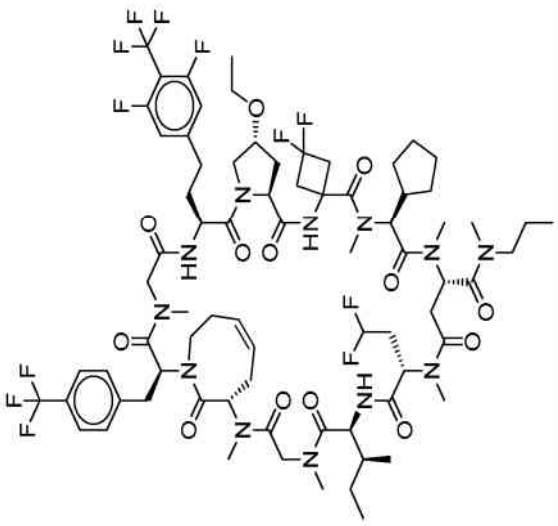
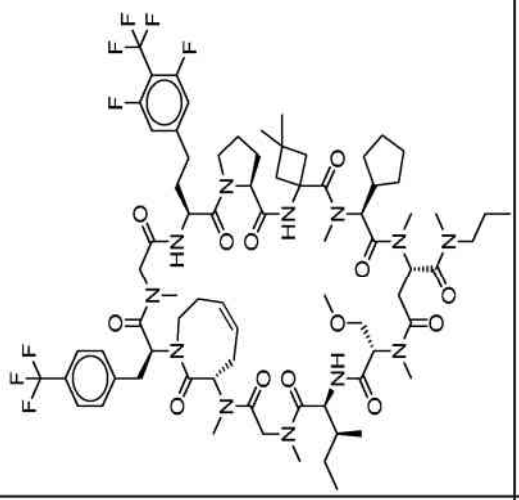
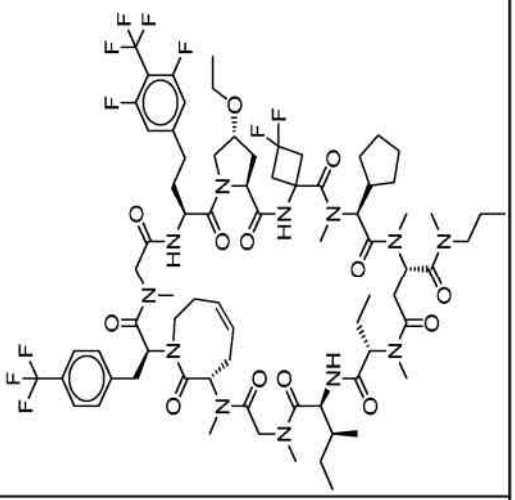
	
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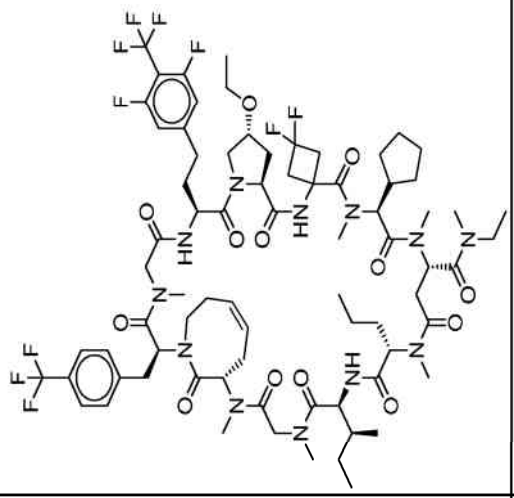
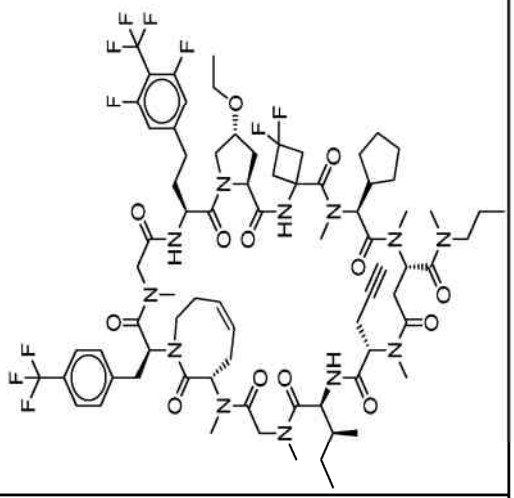
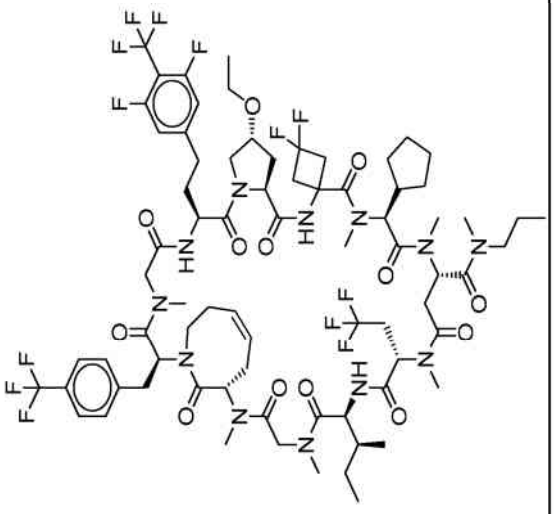
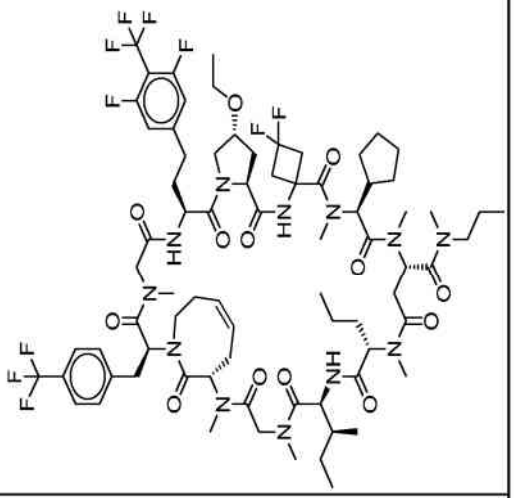
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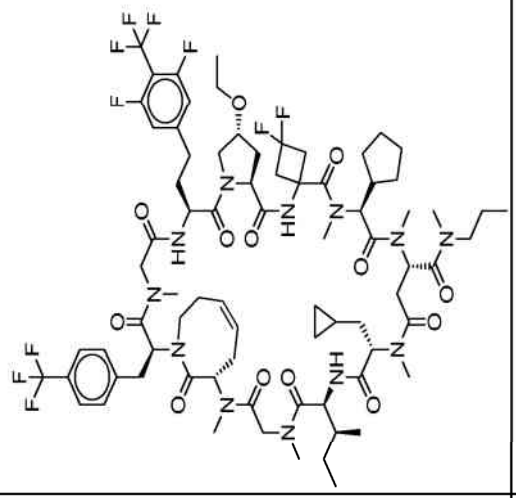
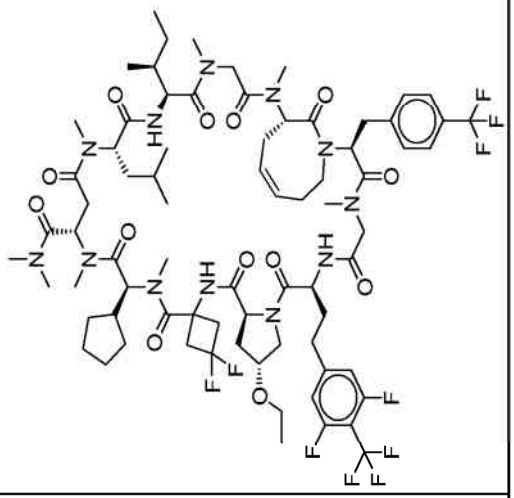
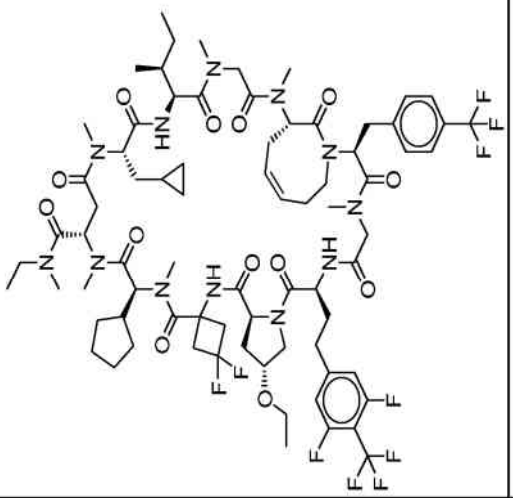
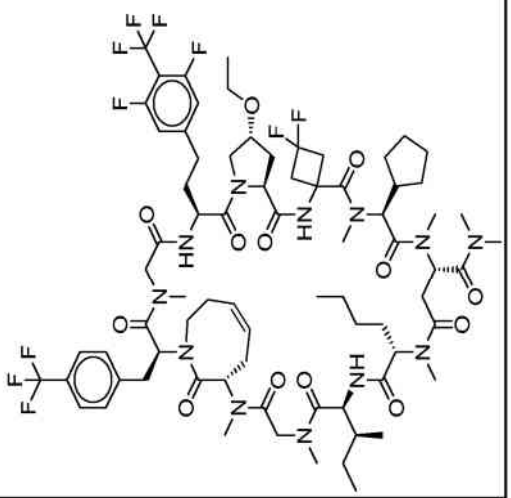
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PP172 1	PP172 7

	
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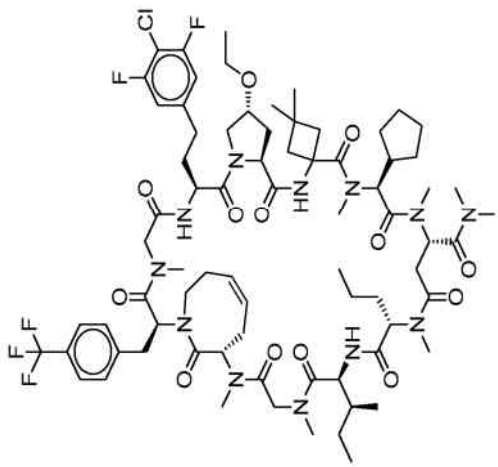
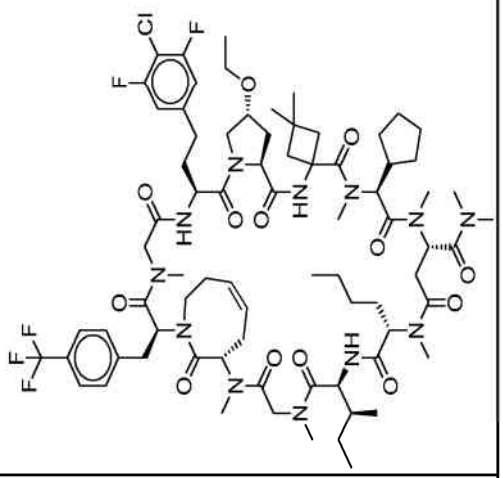
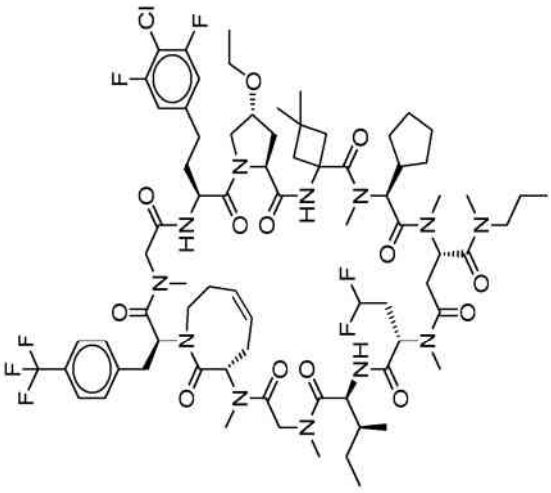
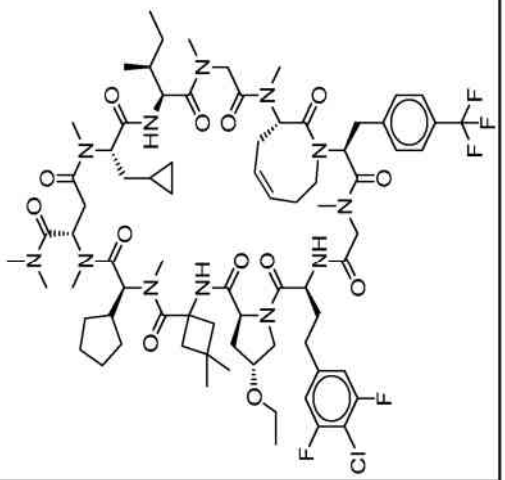
	
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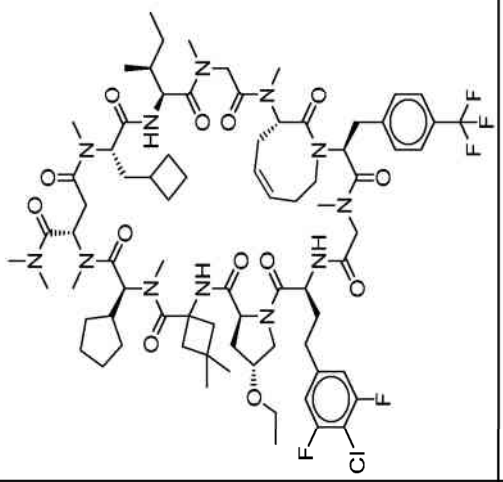
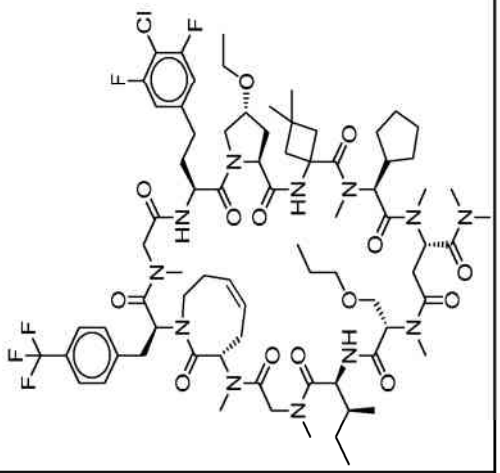
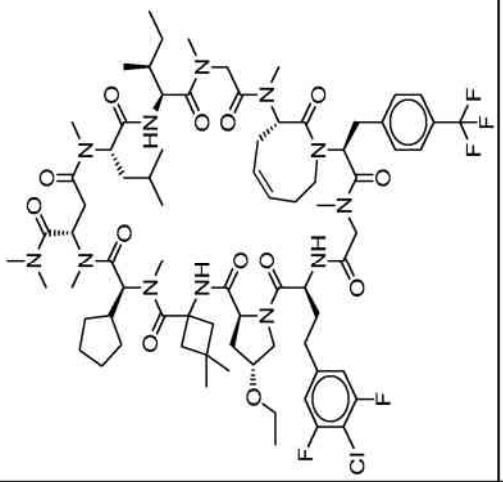
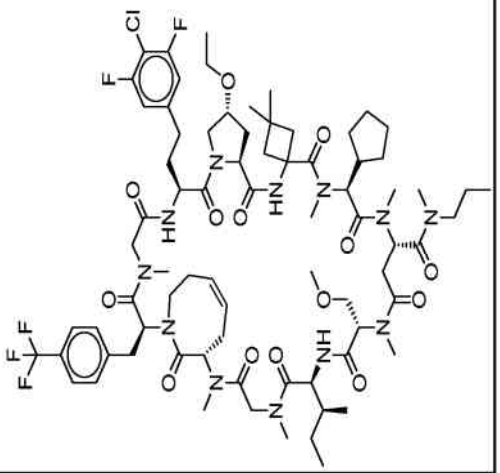
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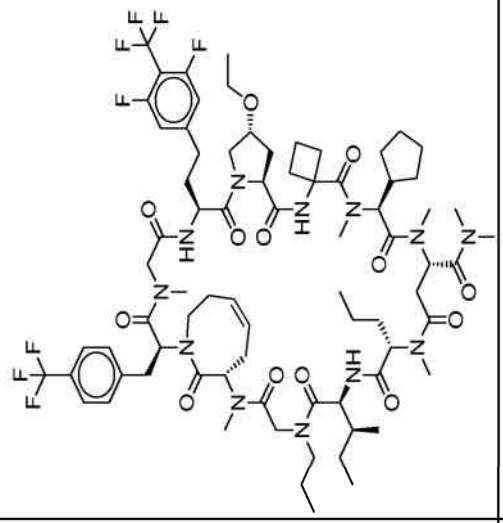
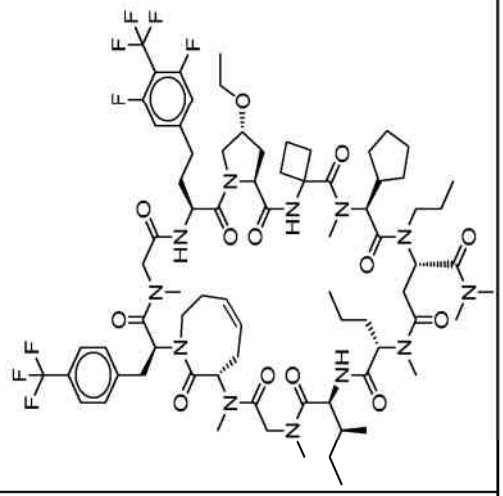
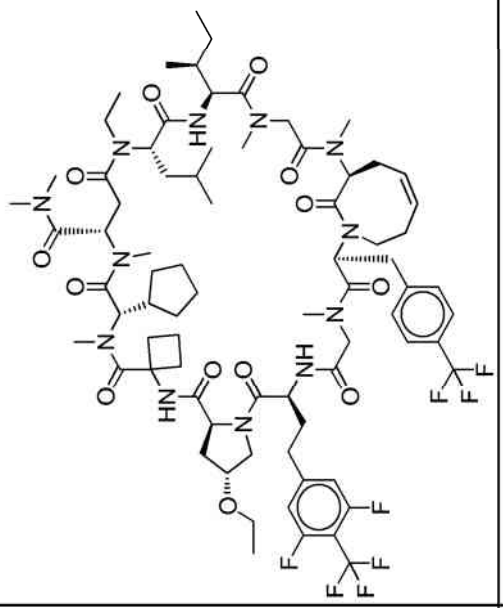
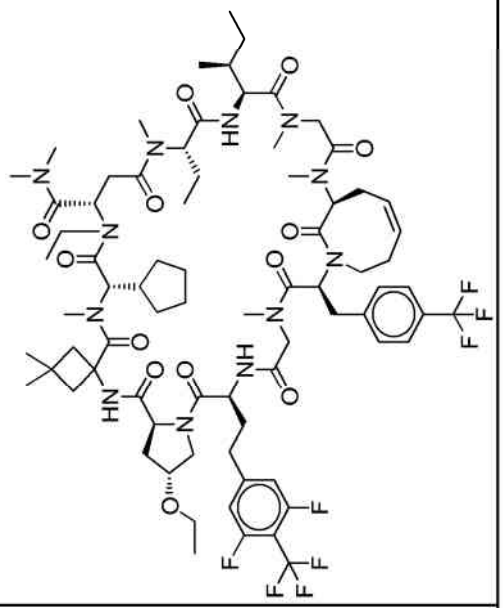
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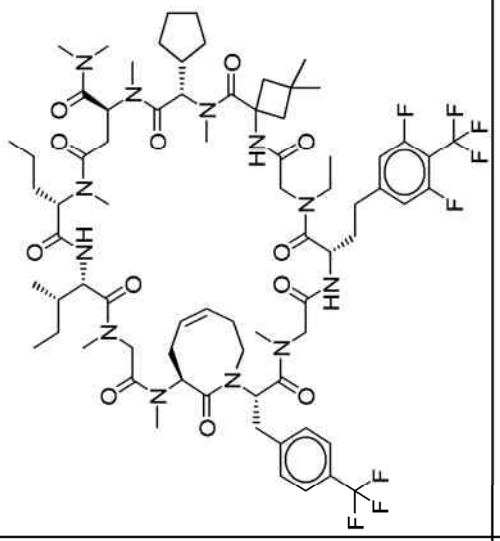
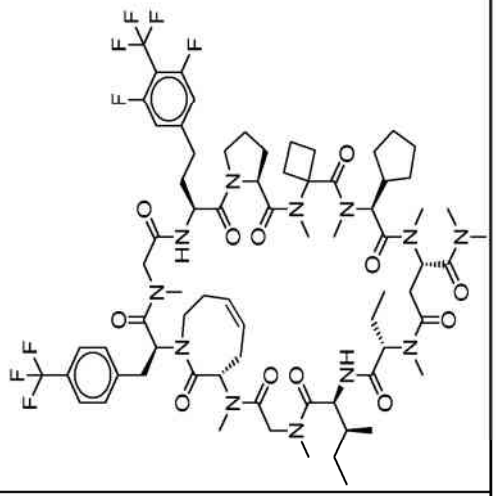
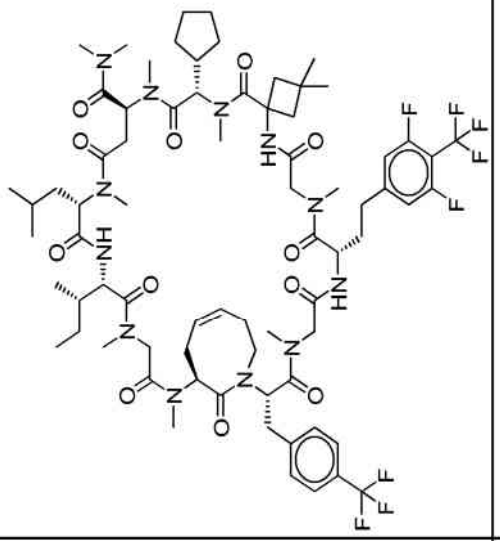
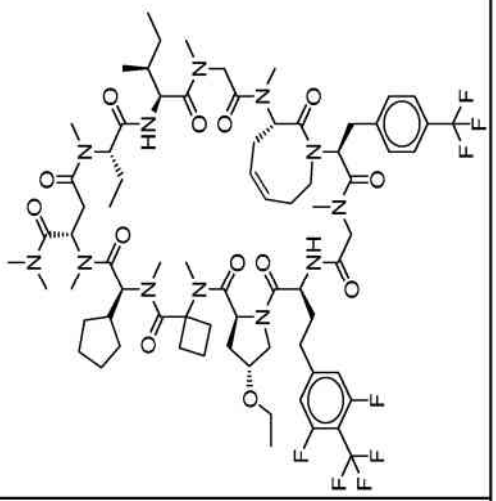
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PP175 1	PP175 3

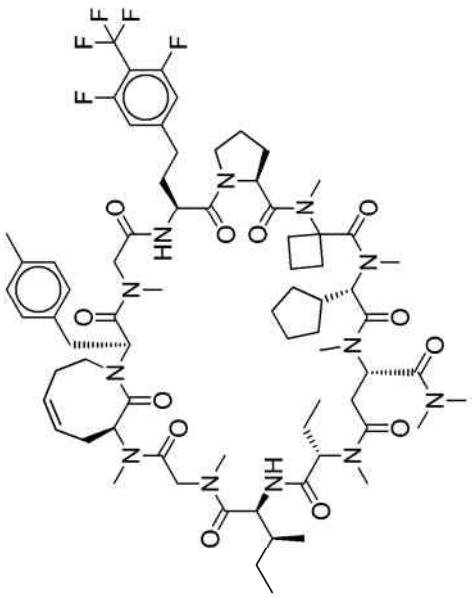
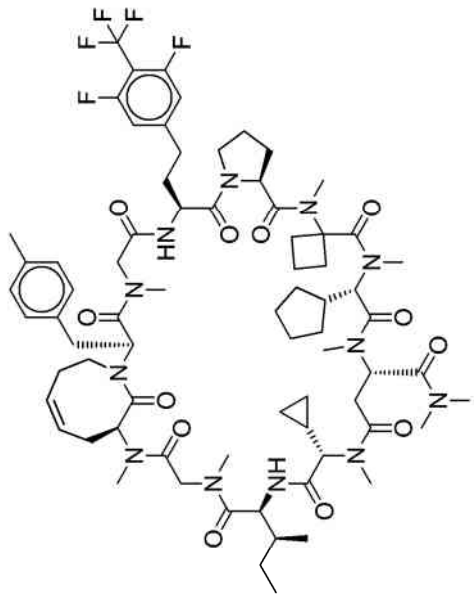
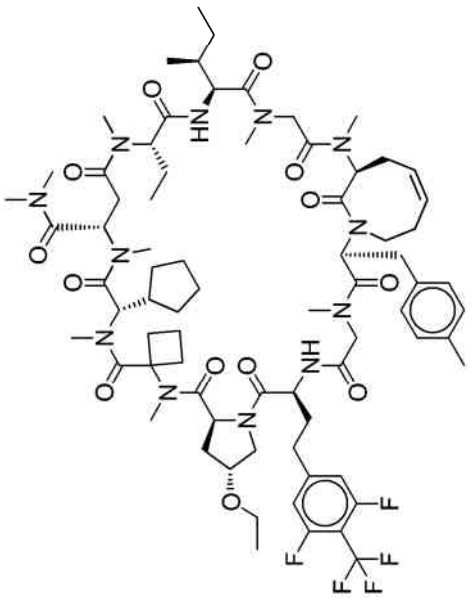
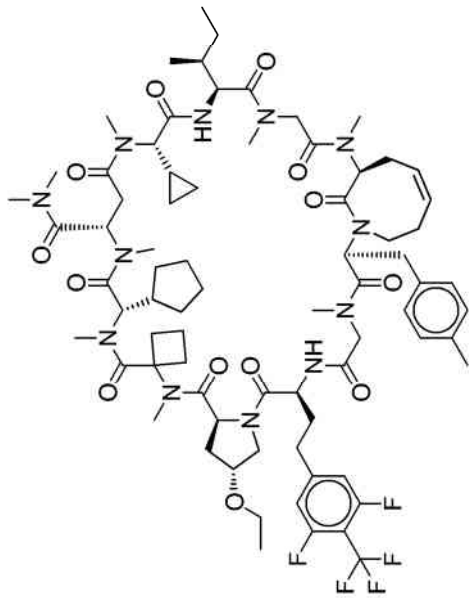
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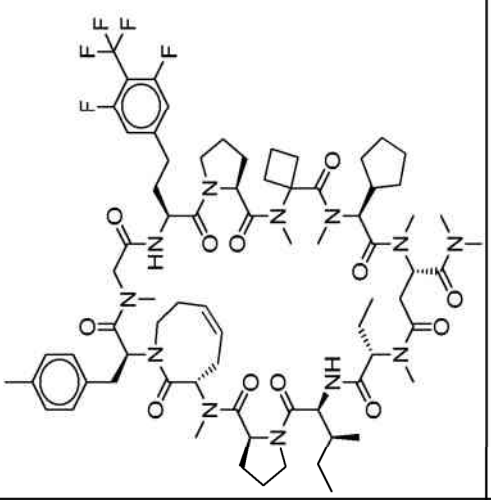
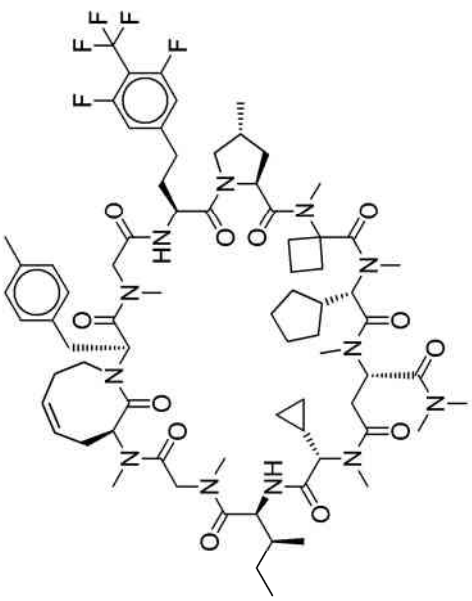
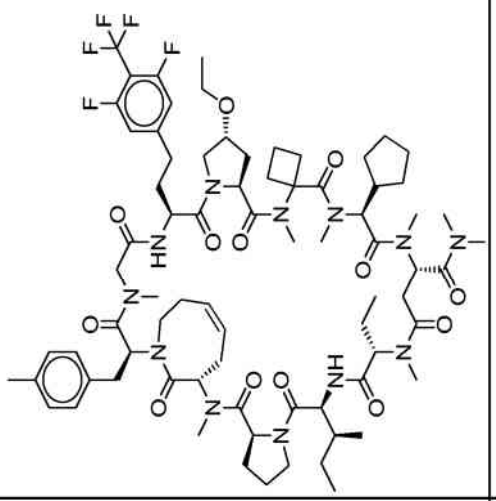
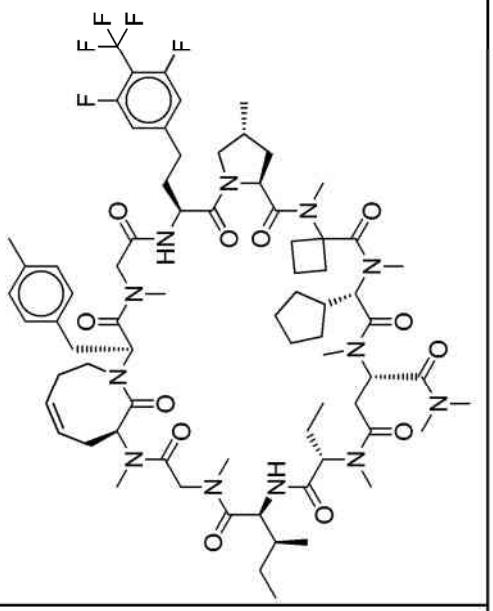
	
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PP176 1	PP176 3

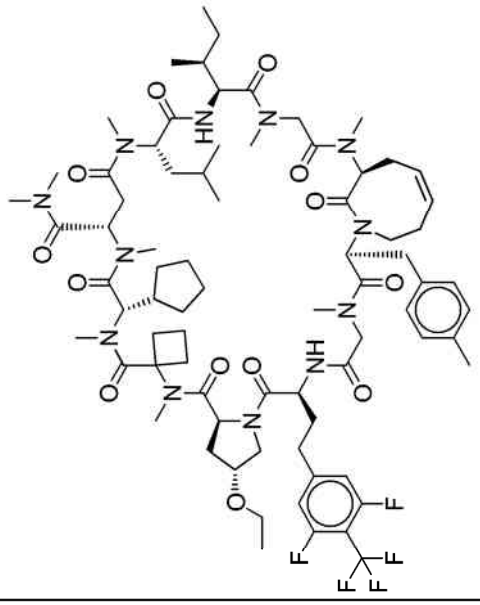
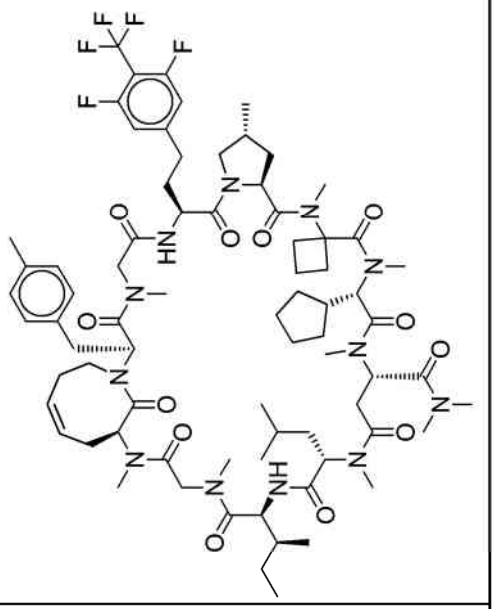
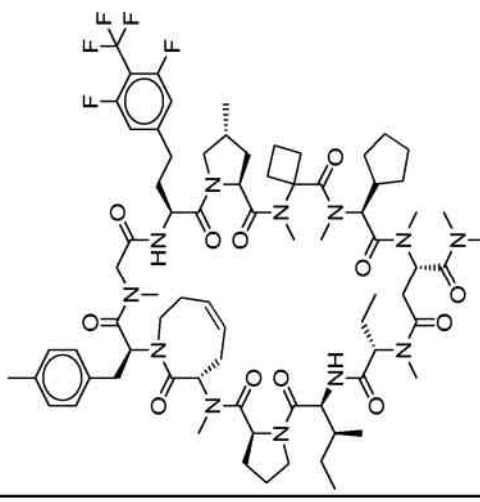
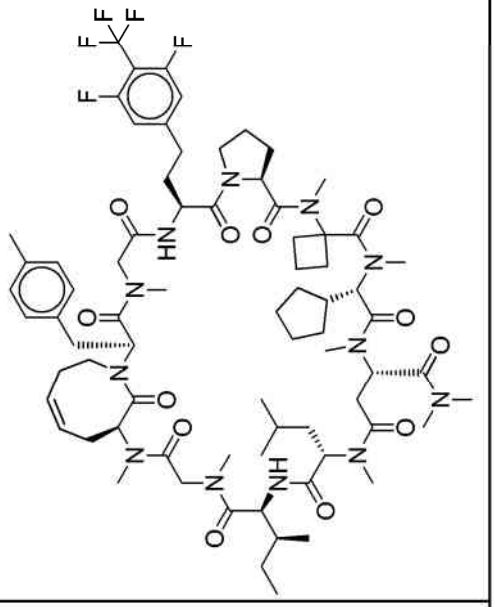
	
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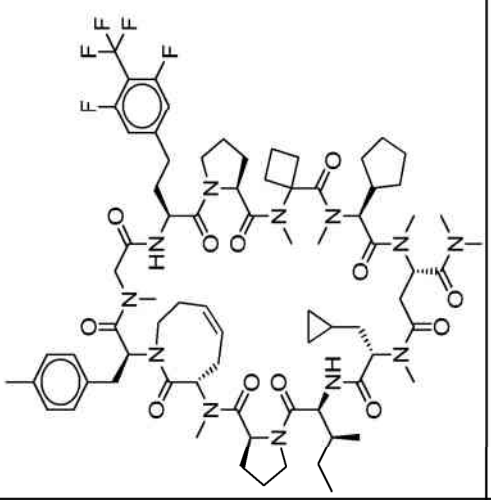
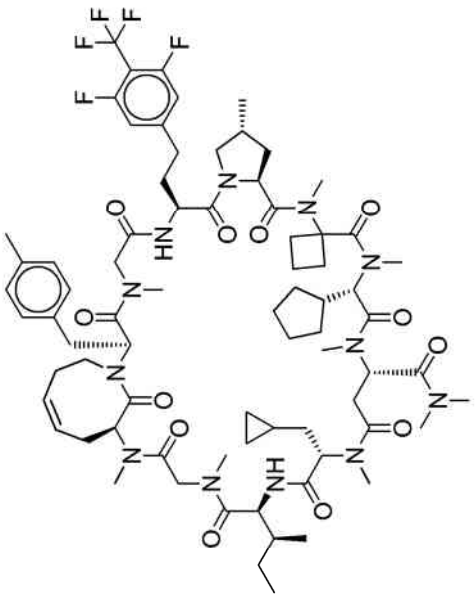
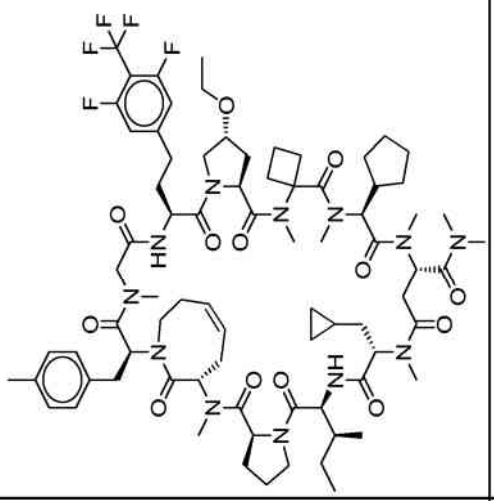
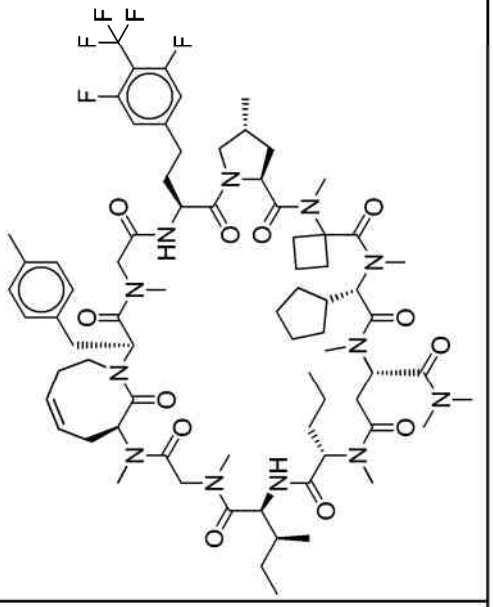
	
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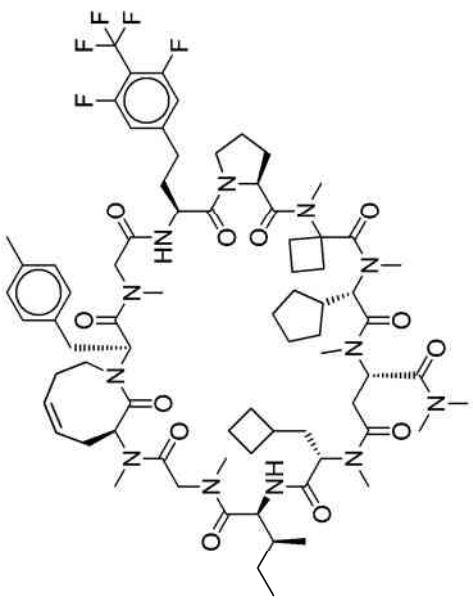
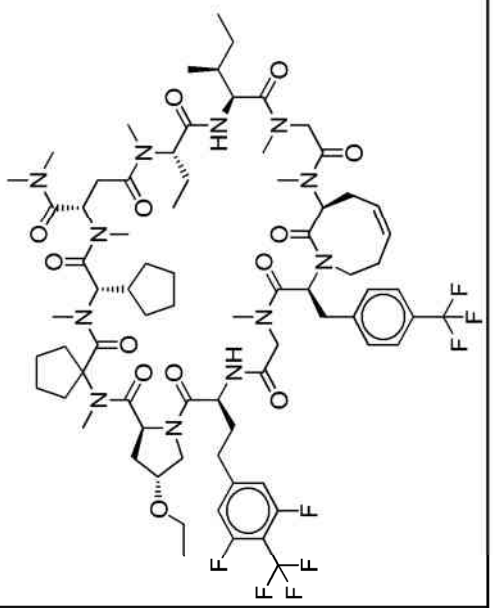
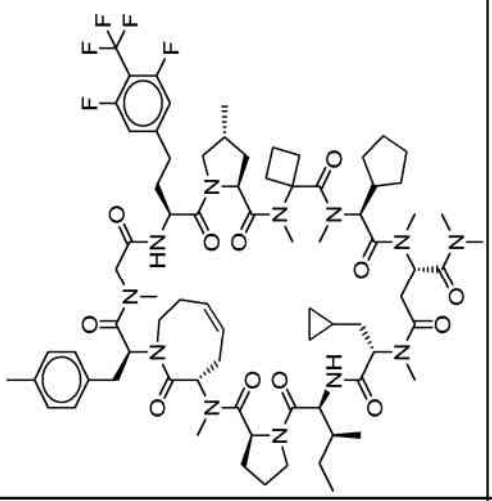
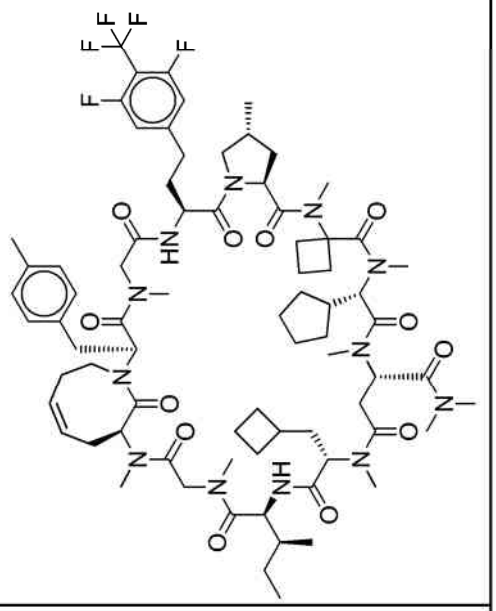
	
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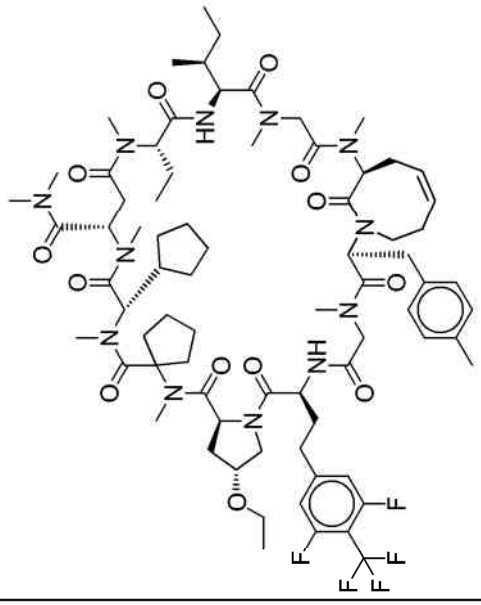
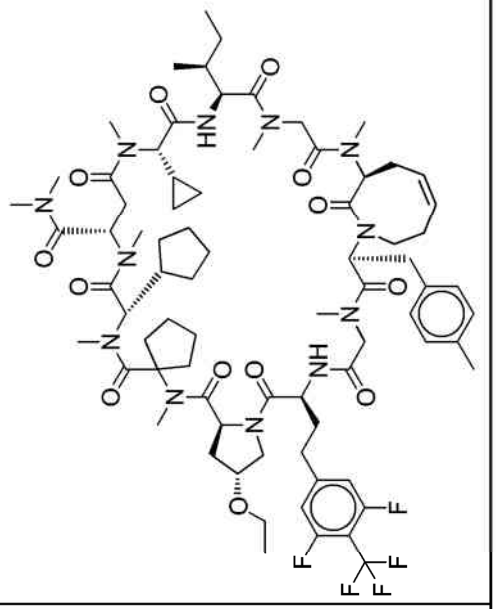
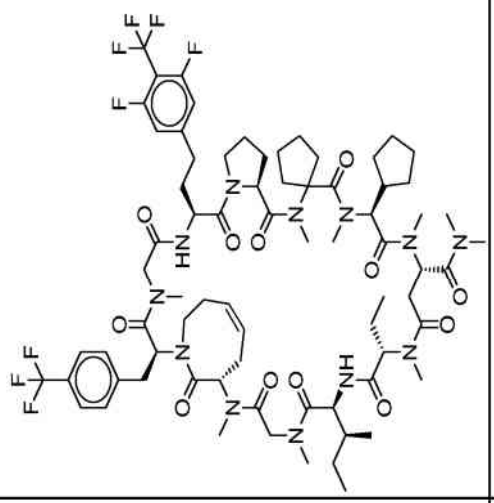
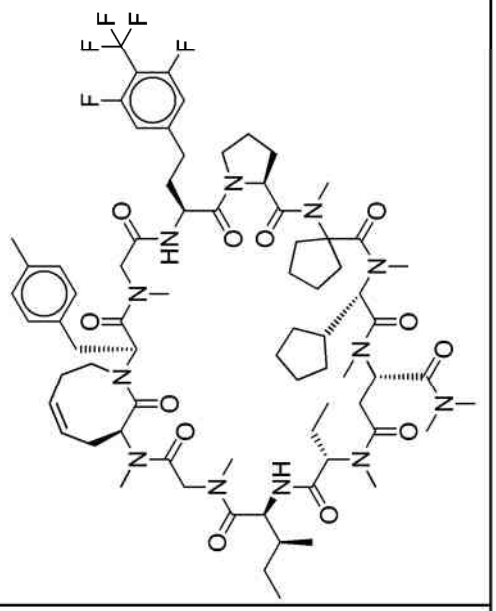
	
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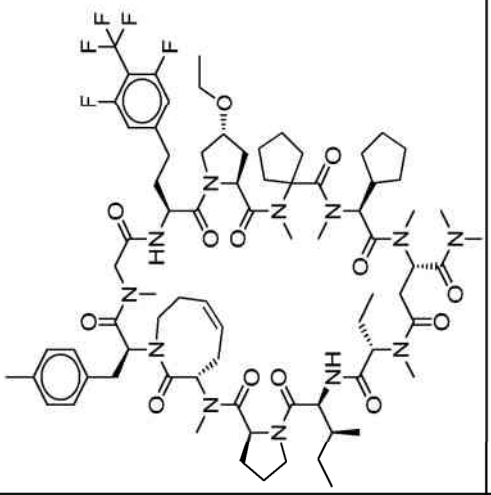
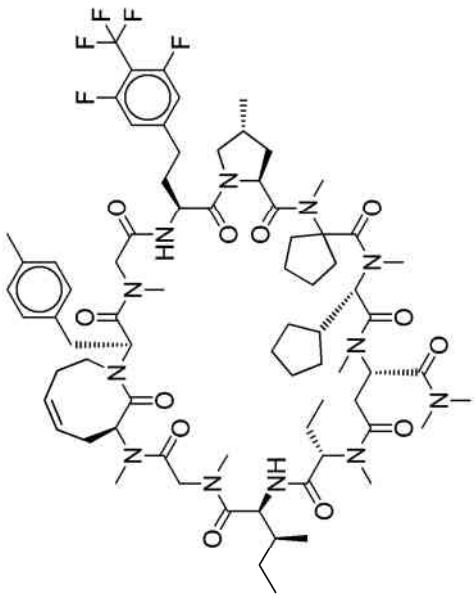
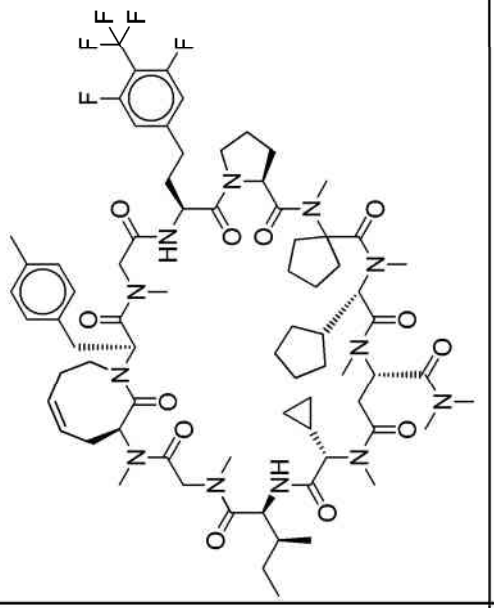
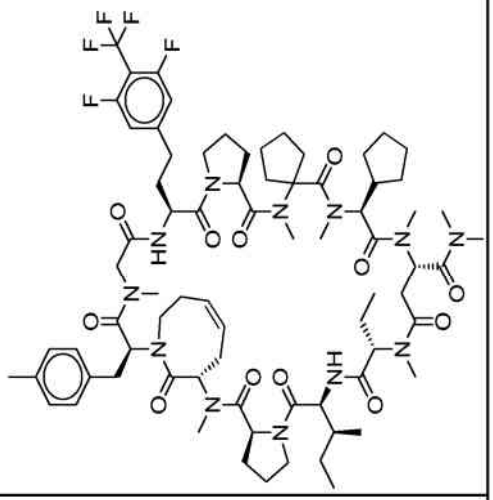
	
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PP1789	PP1791

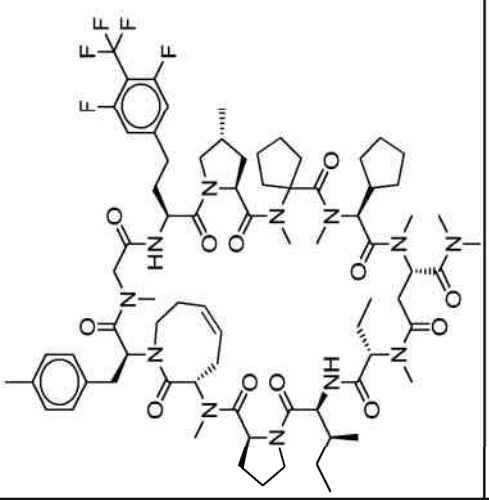
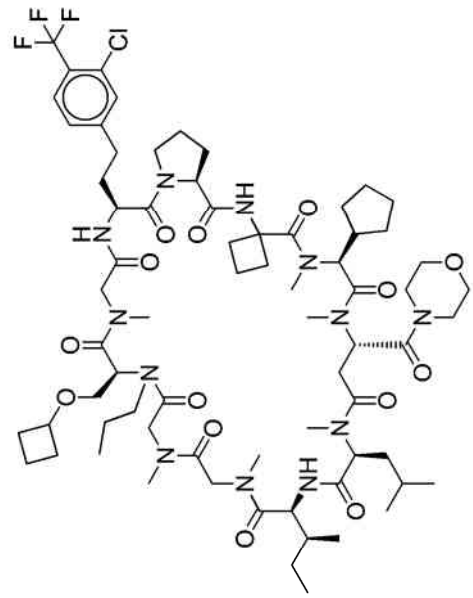
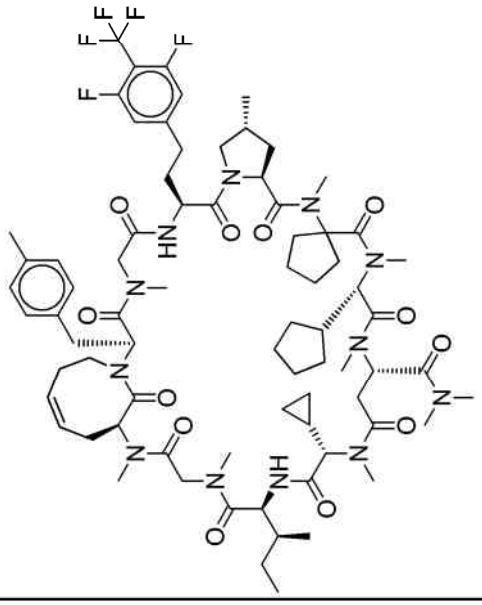
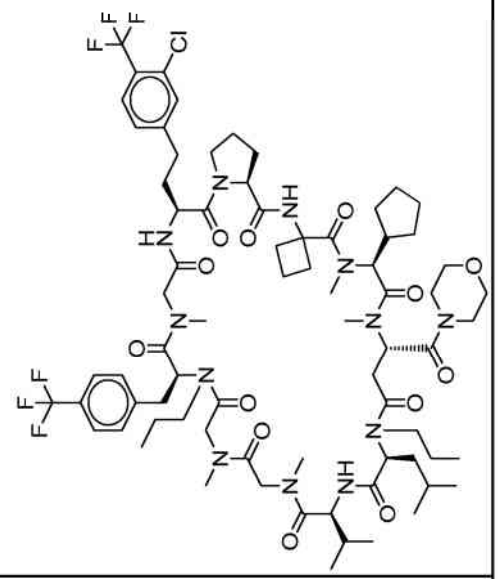
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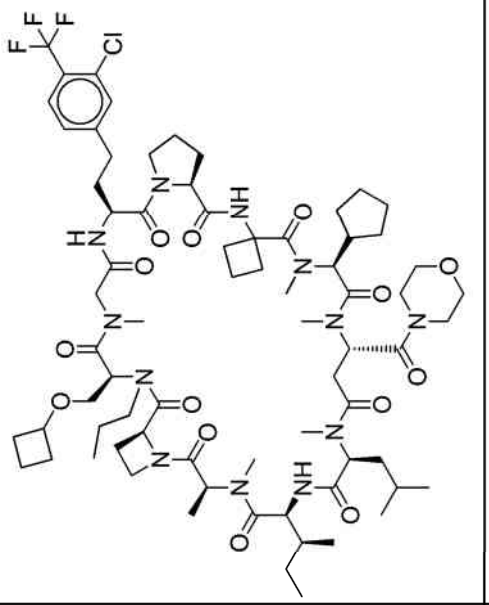
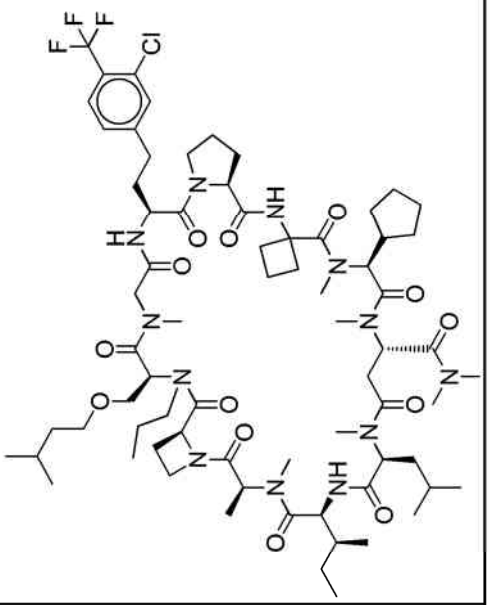
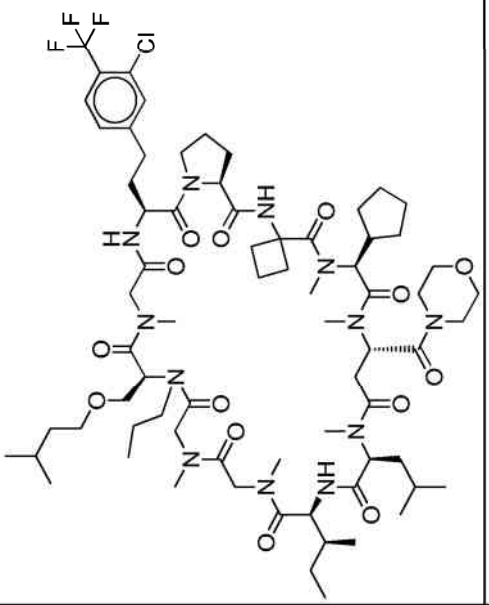
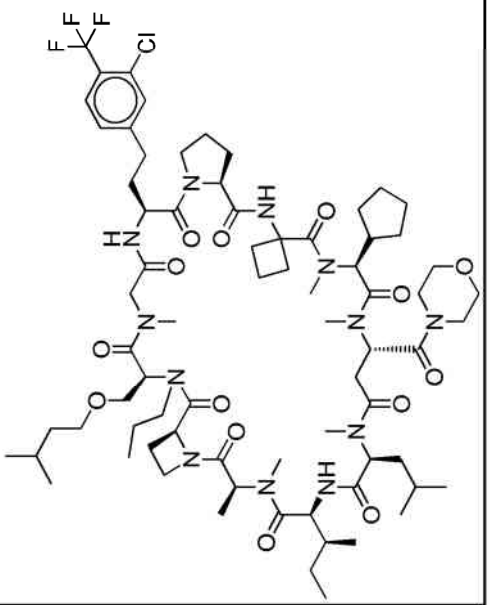
	
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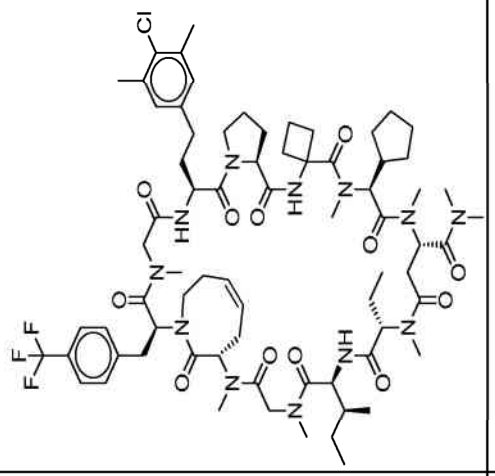
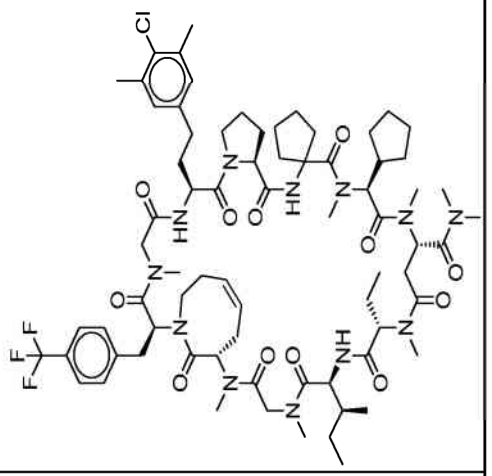
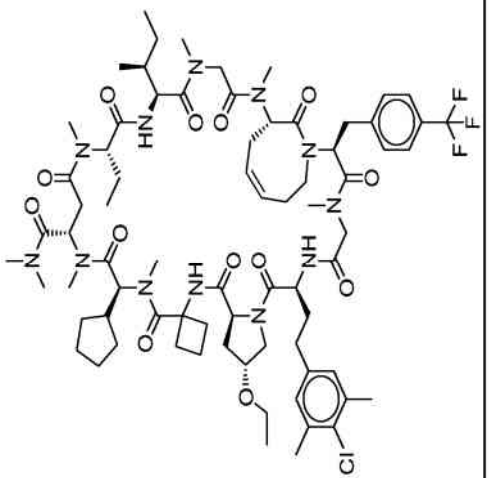
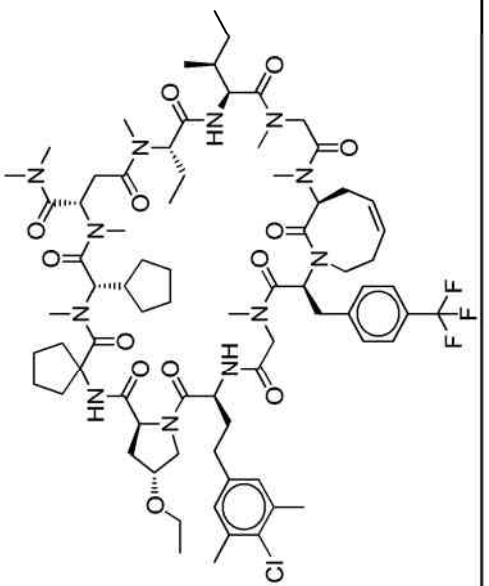
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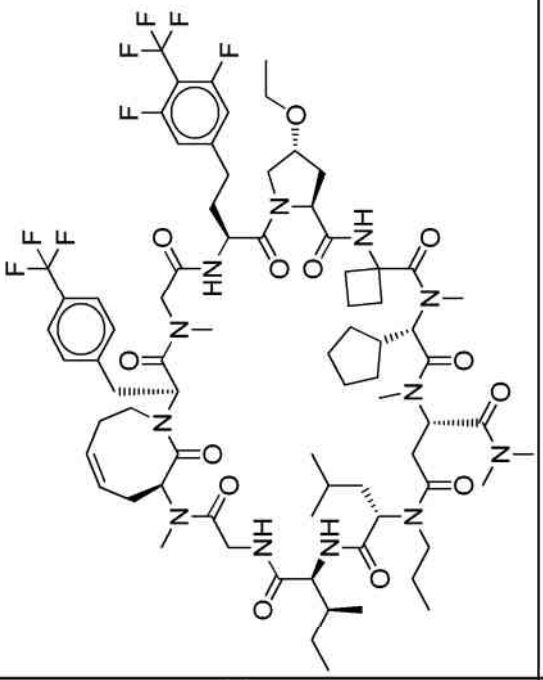
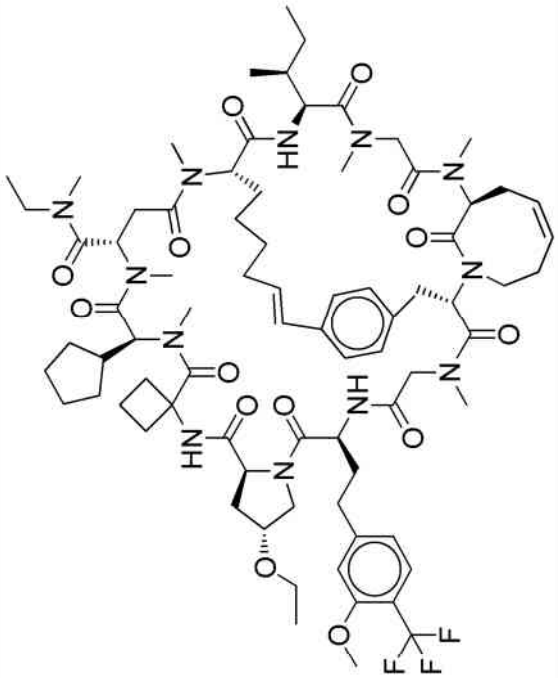
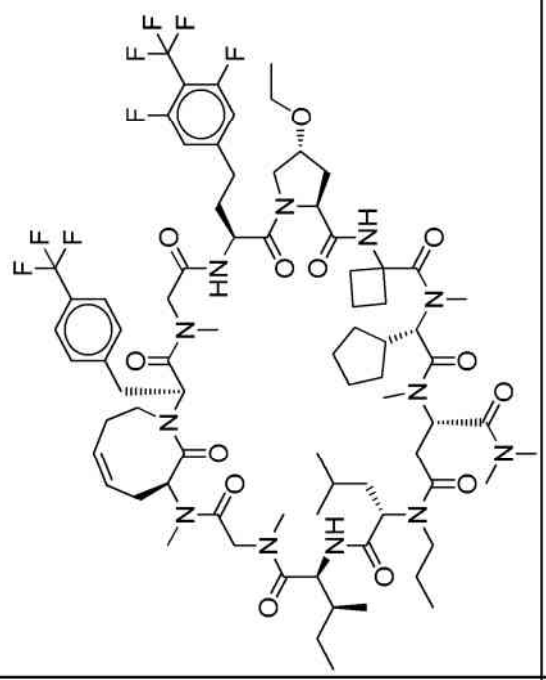
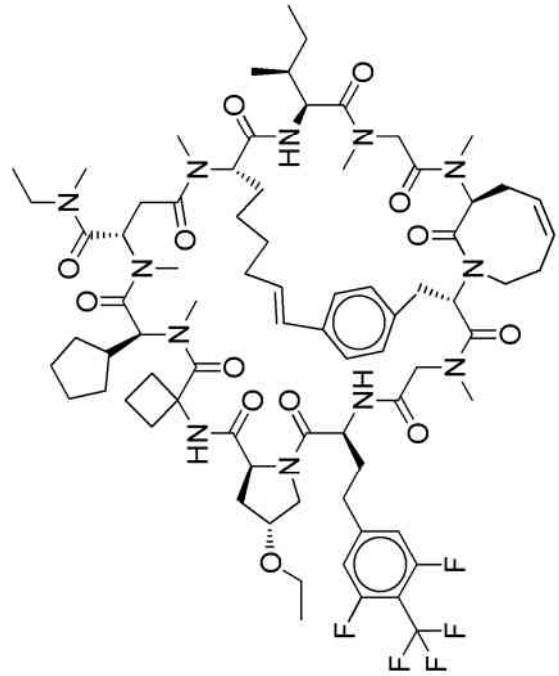
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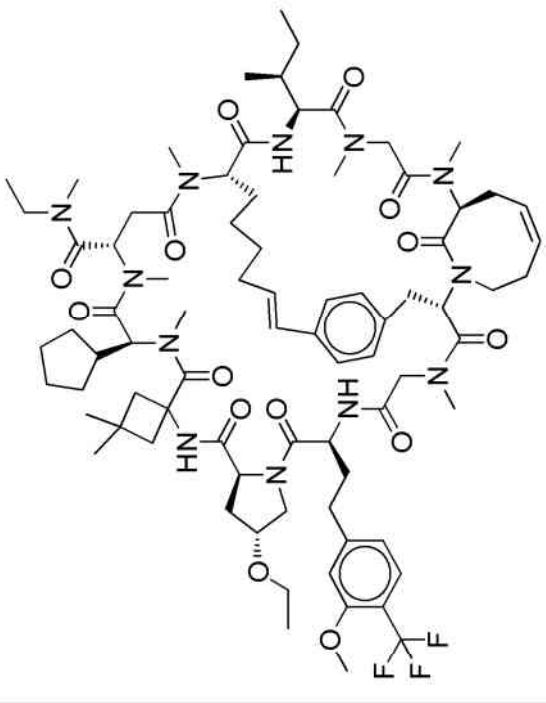
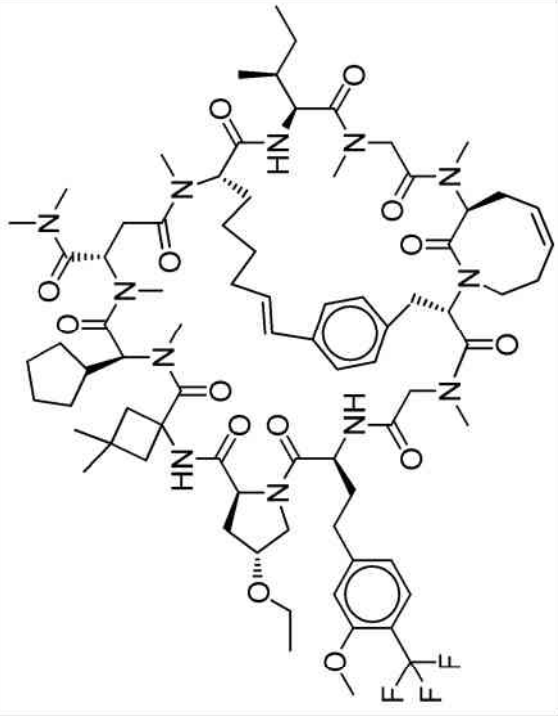
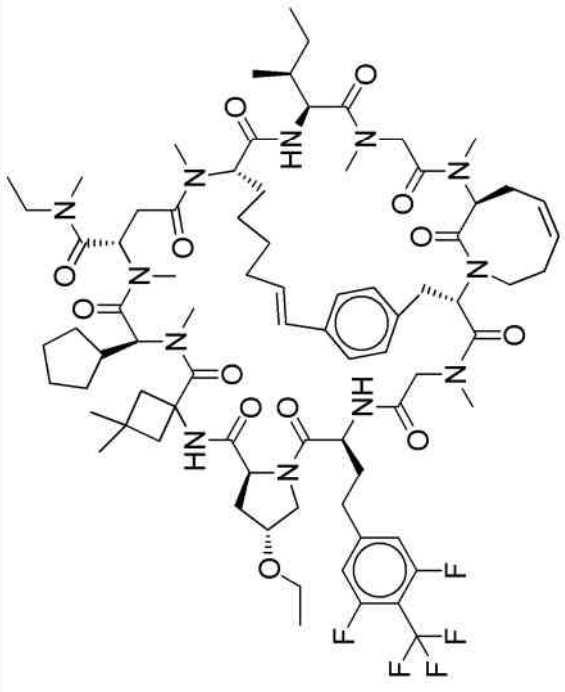
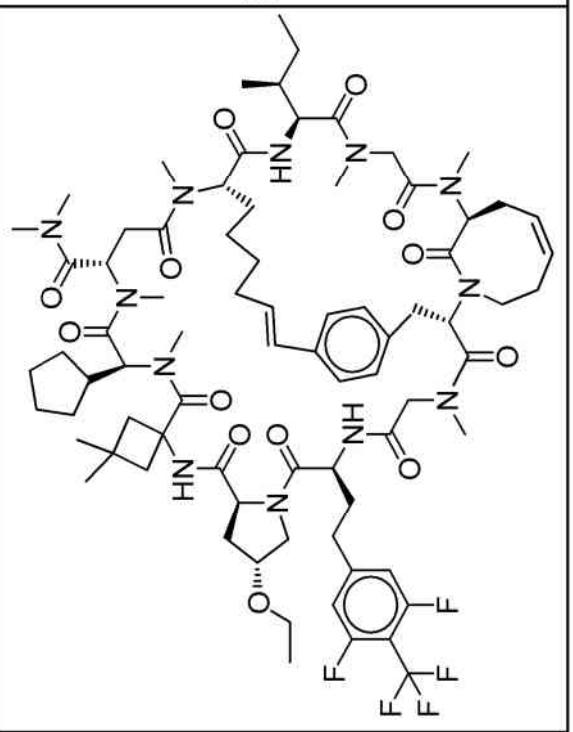
	
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PP1809	PP1811

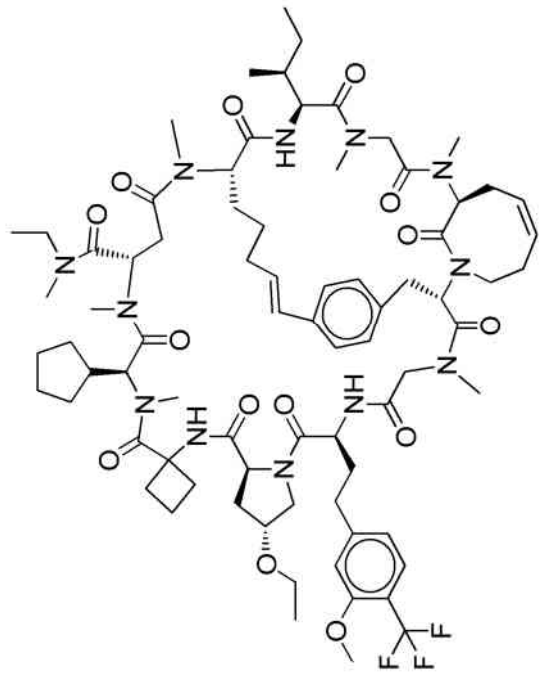
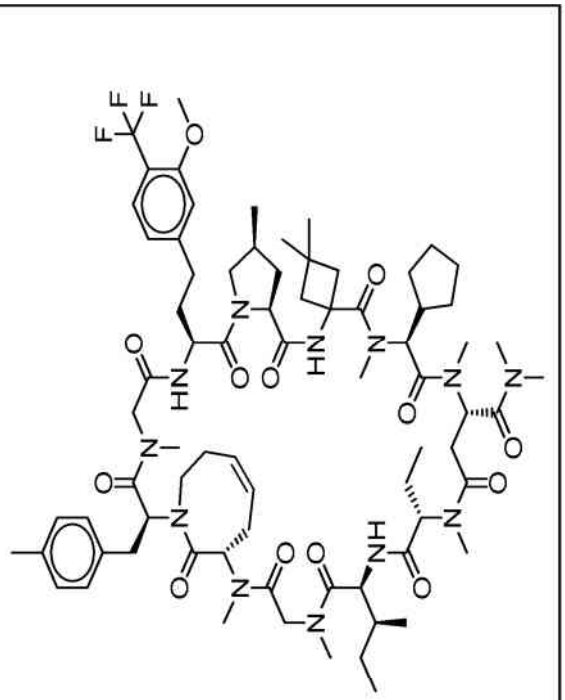
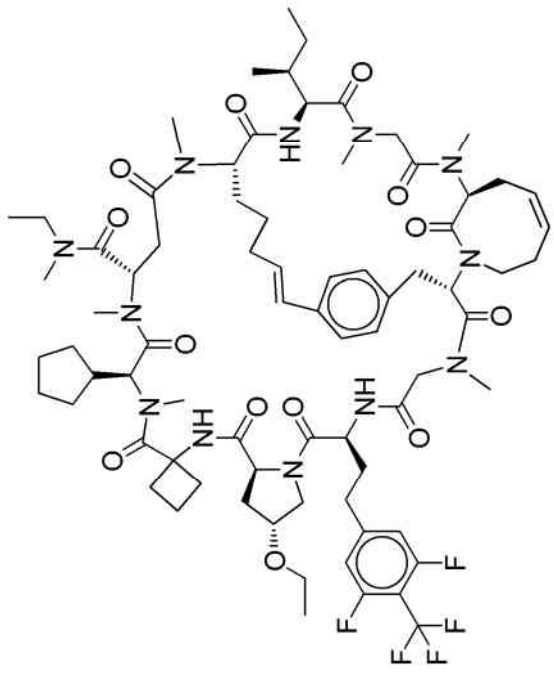
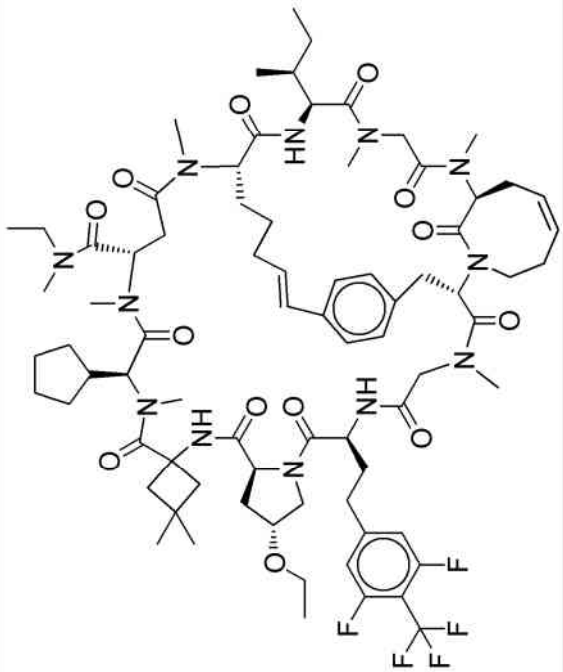
	
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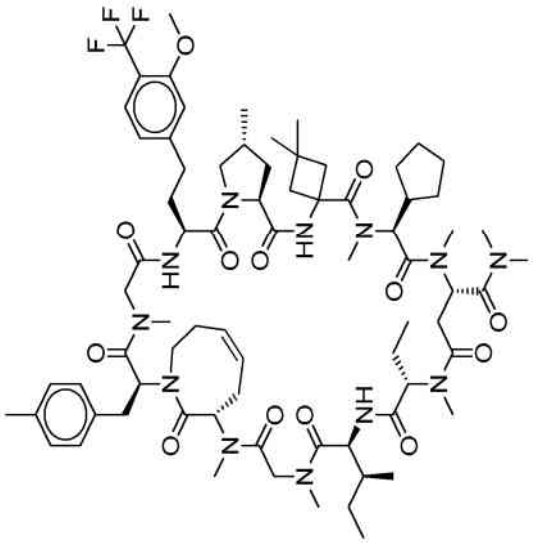
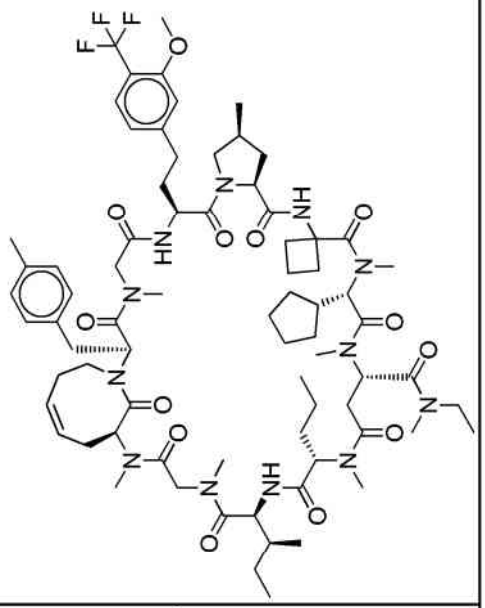
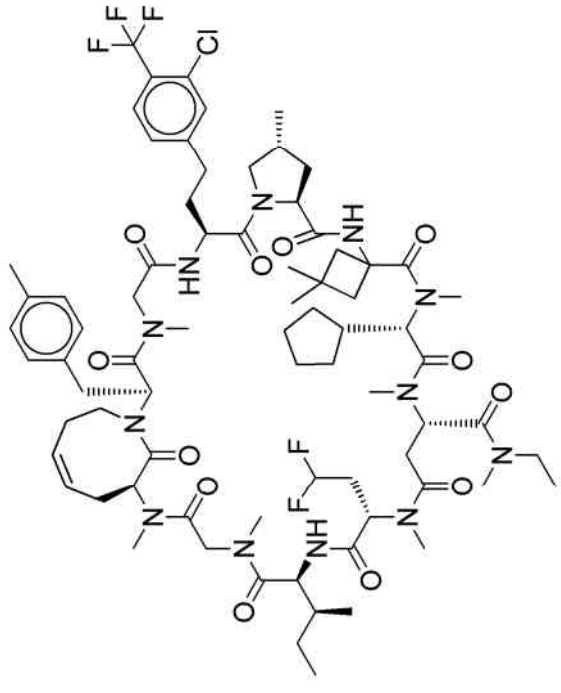
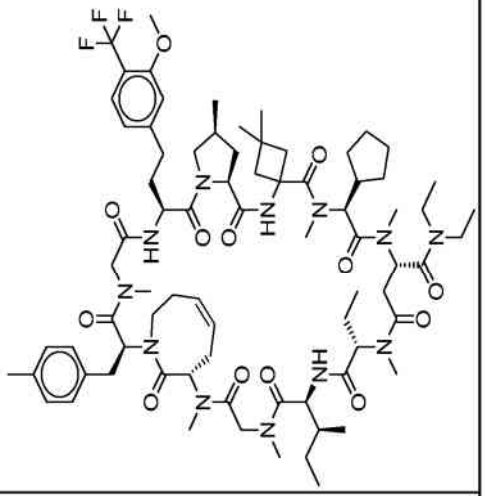
	
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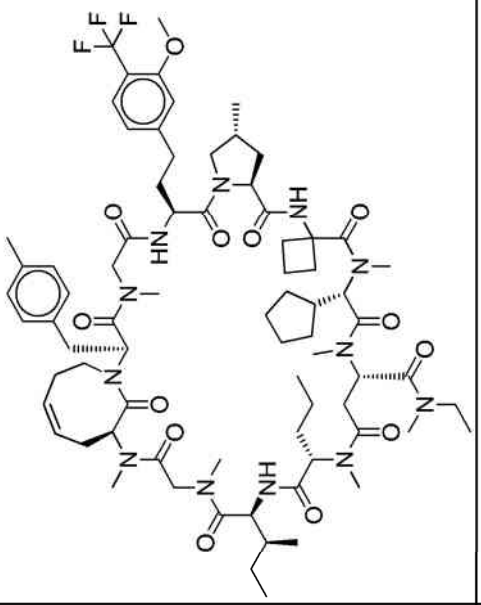
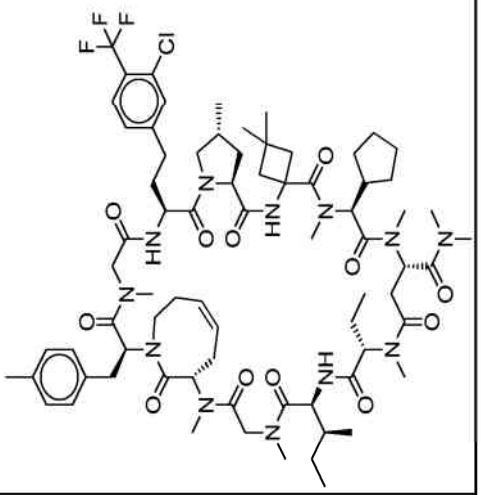
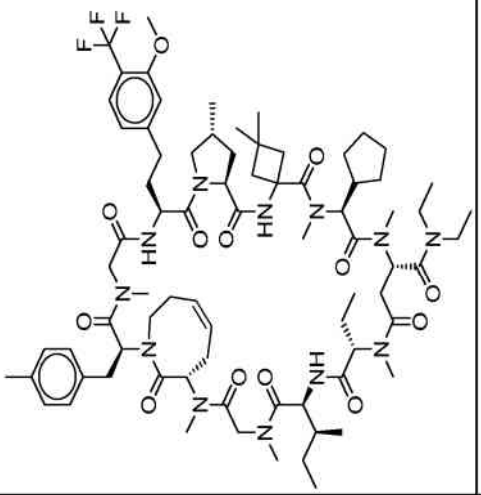
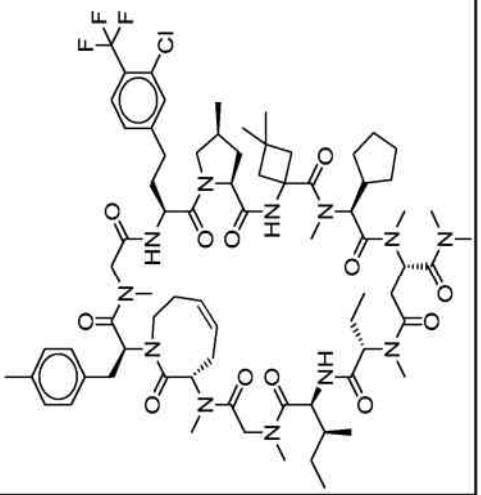
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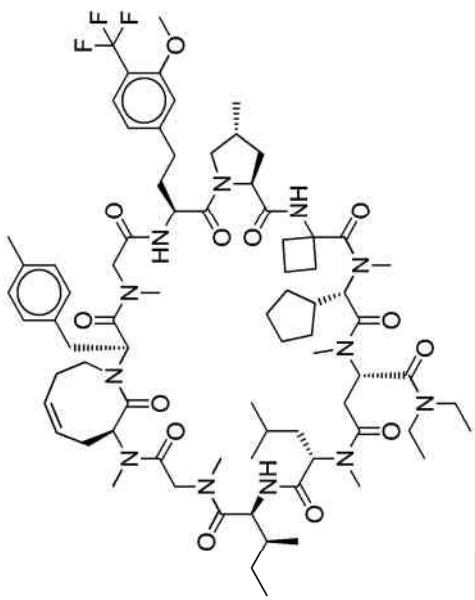
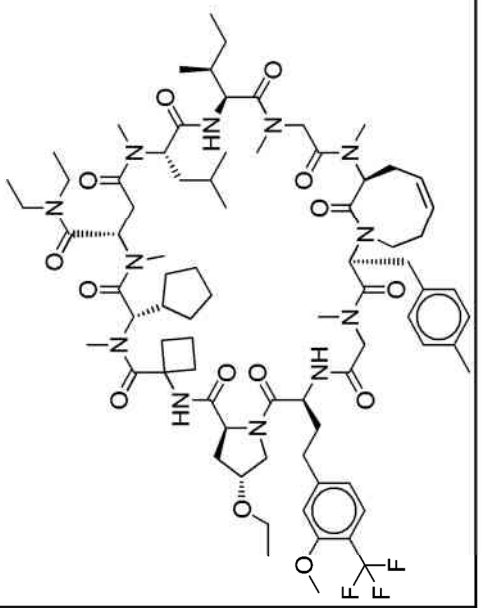
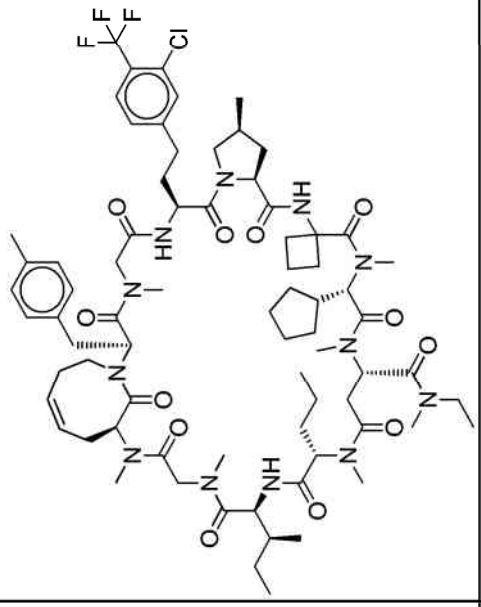
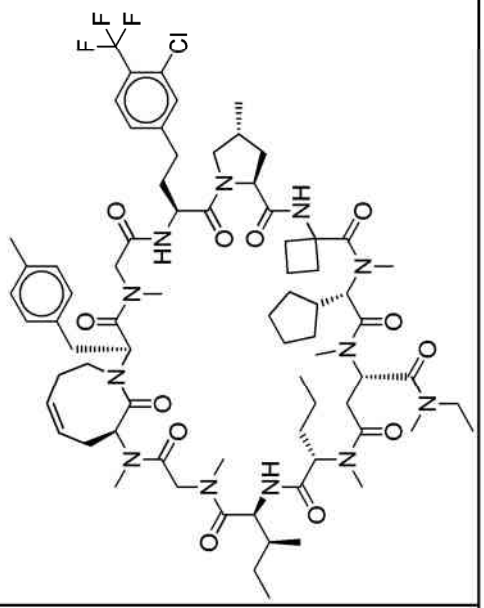
	
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PP182 5	PP182 7

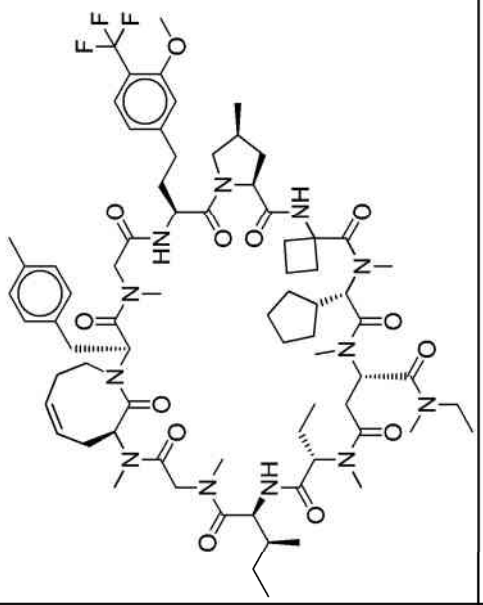
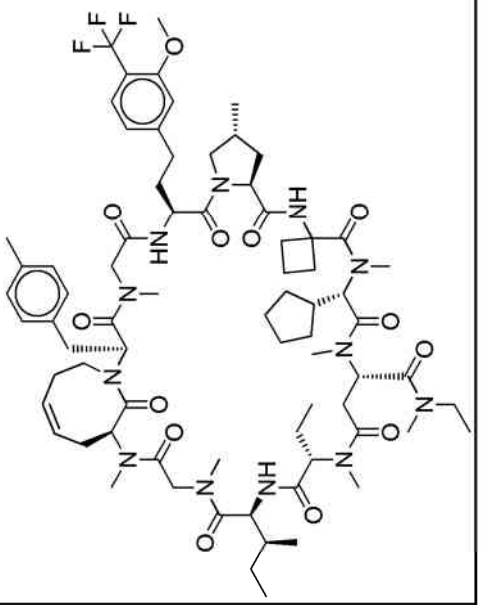
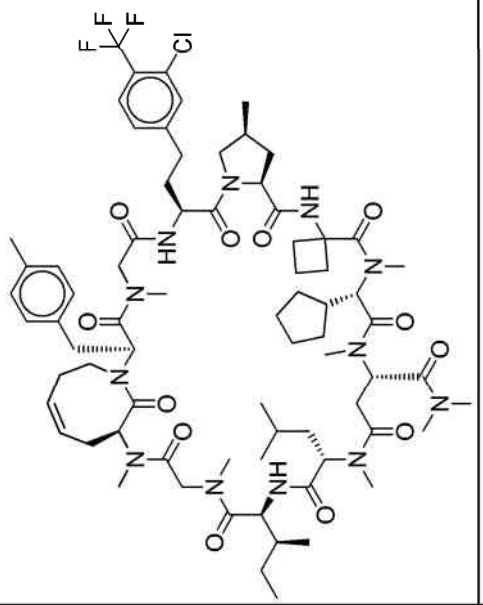
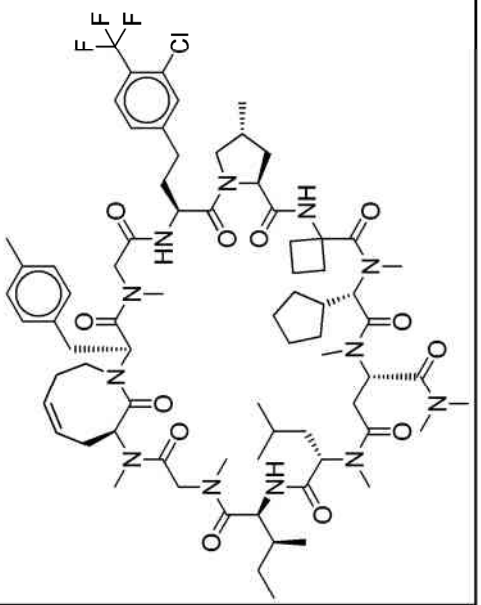
	
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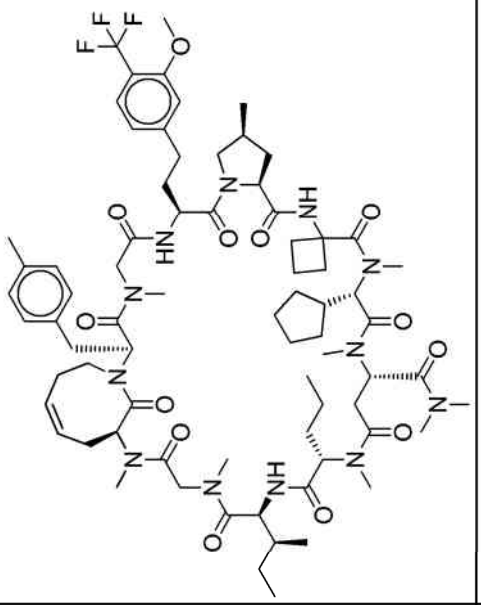
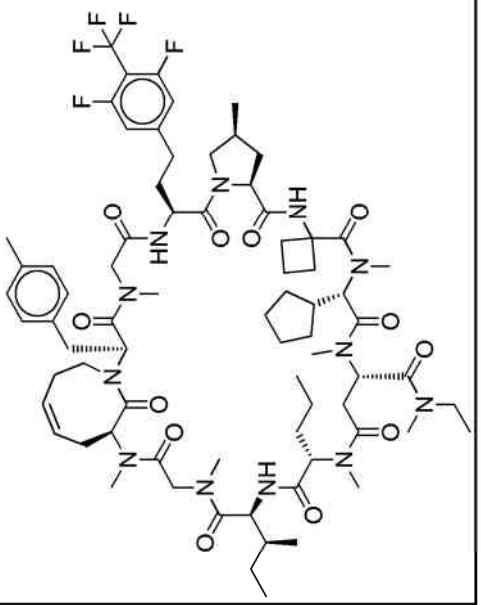
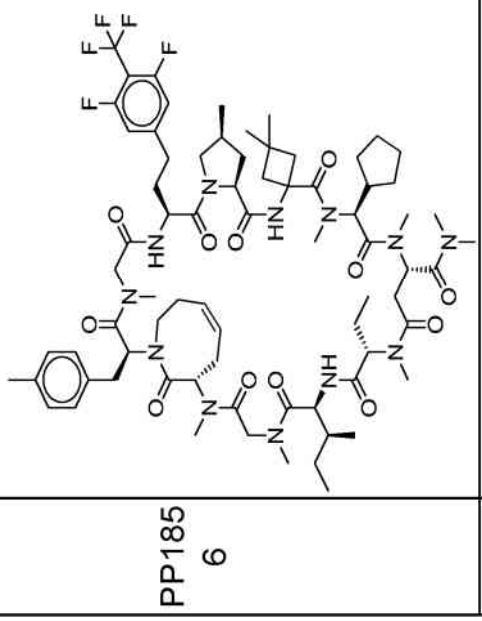
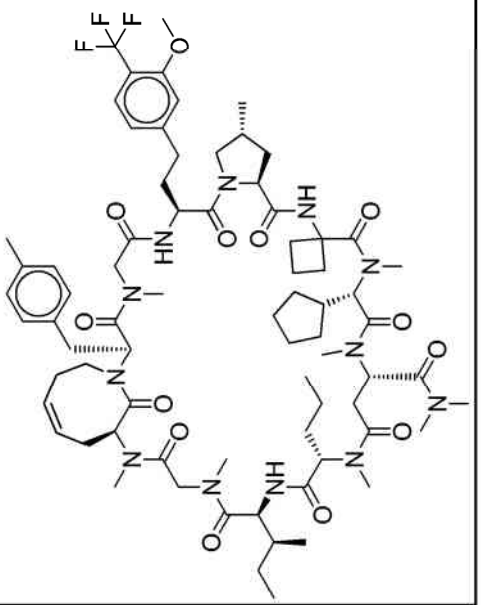
	
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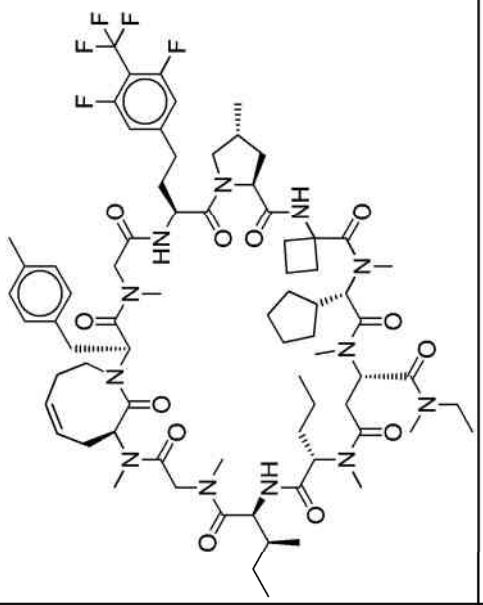
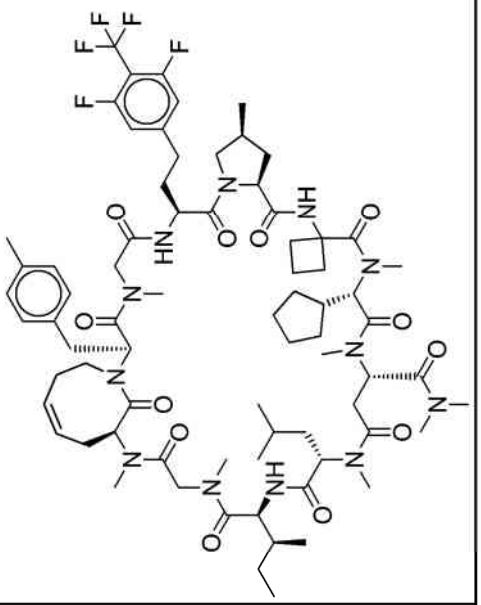
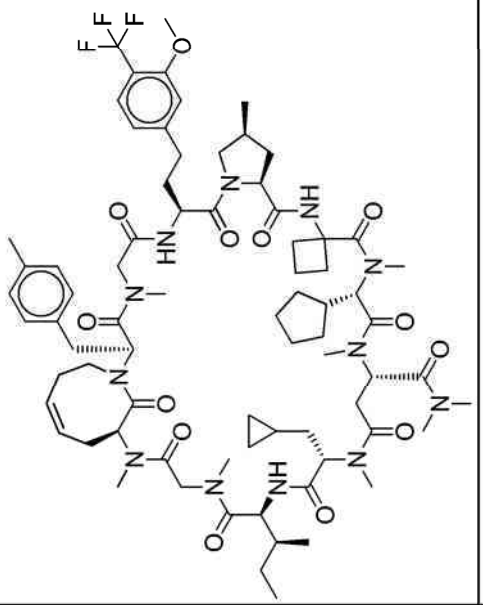
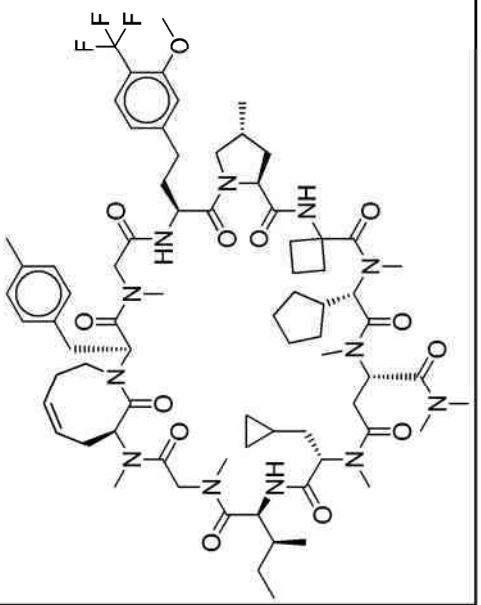
	
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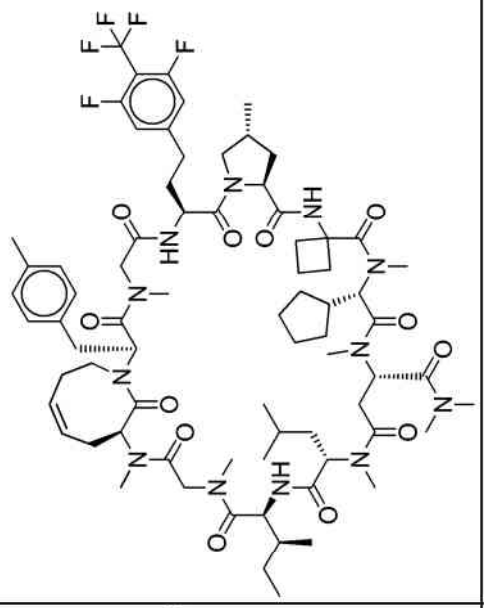
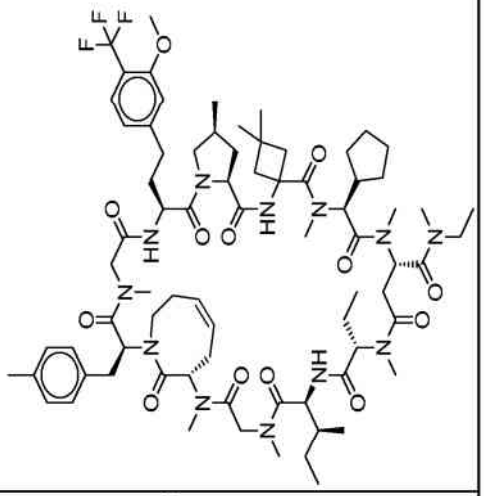
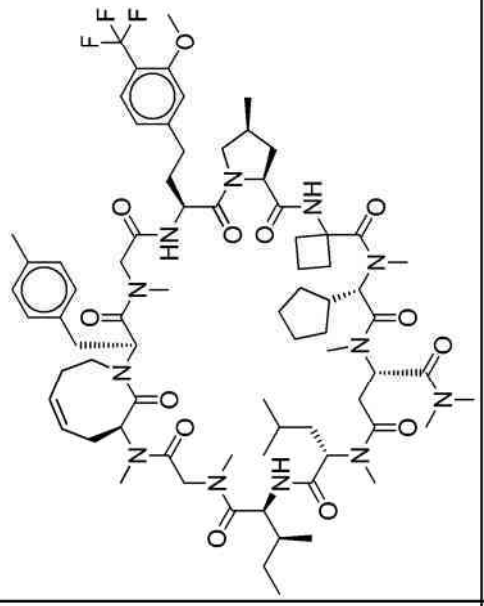
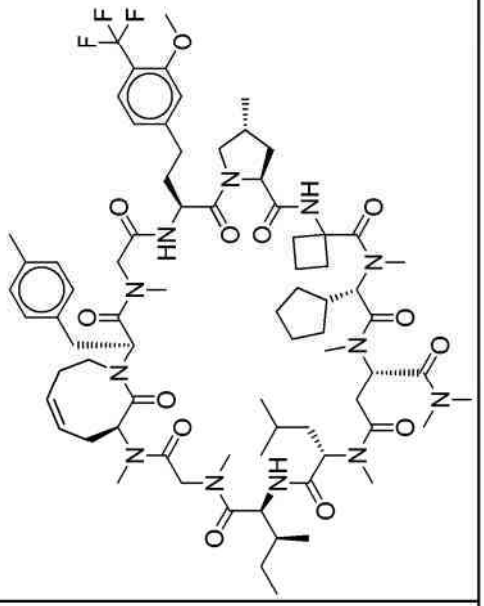
	
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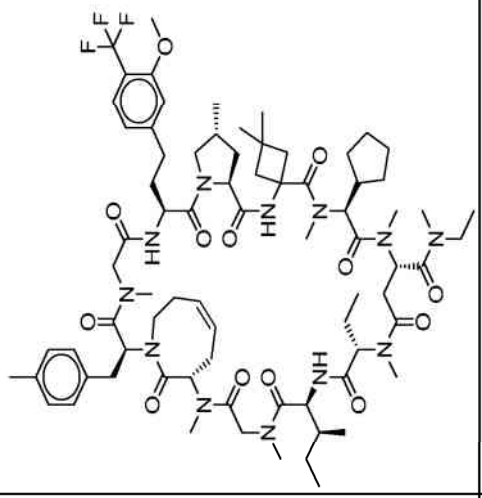
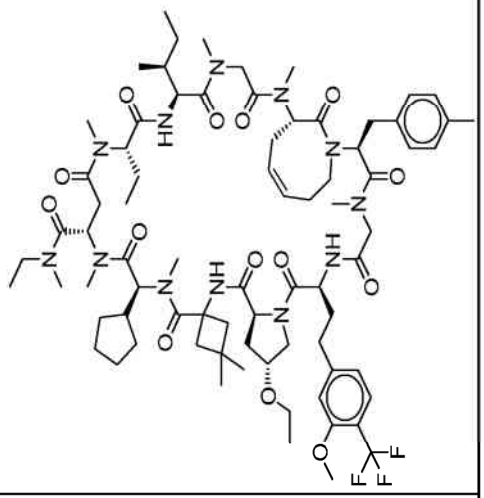
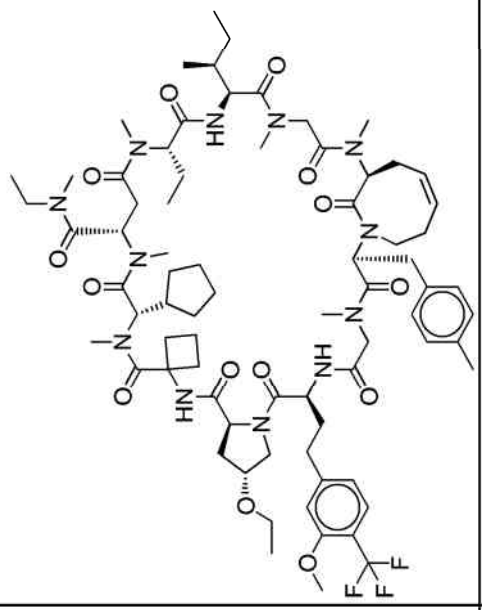
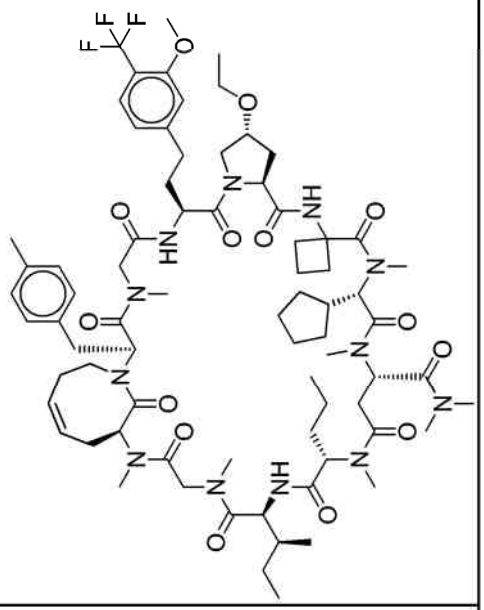
	
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PP1848	PP1850

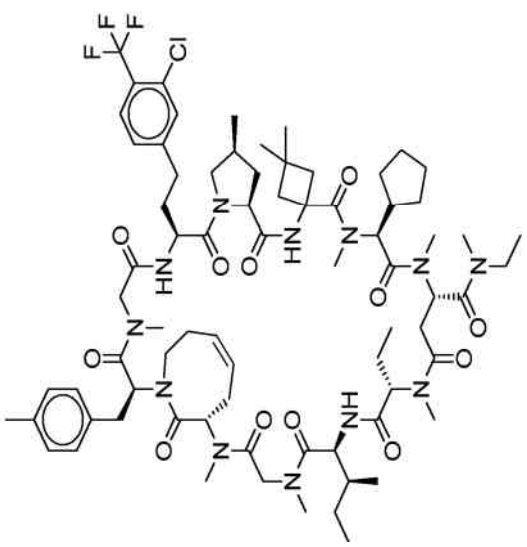
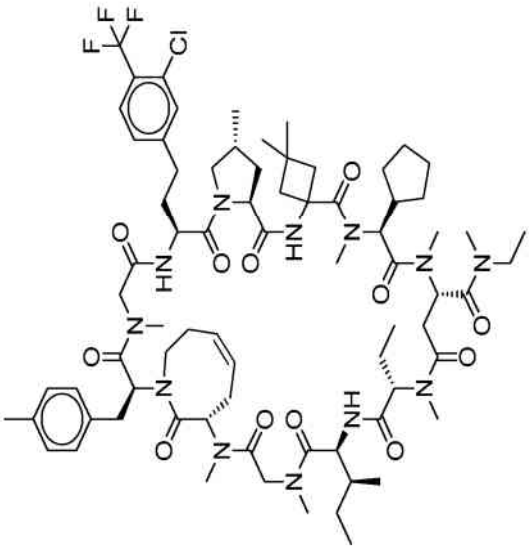
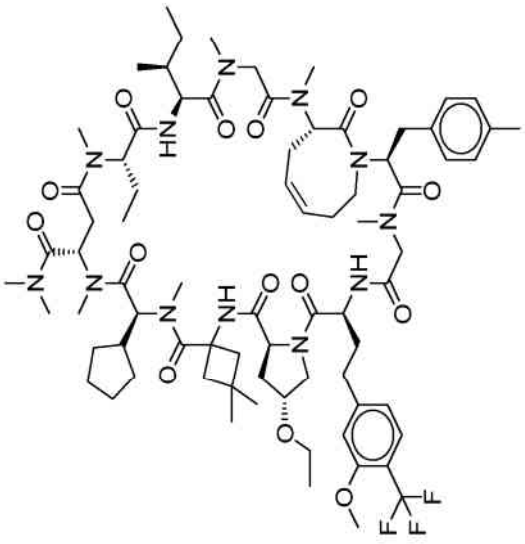
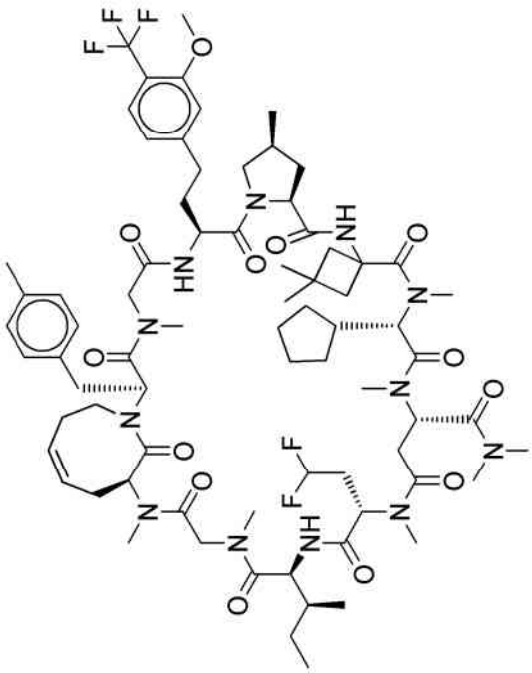
	
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PP185 2	PP185 4

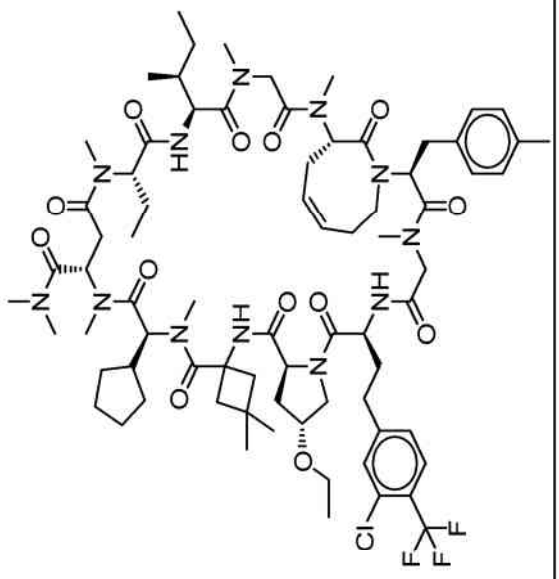
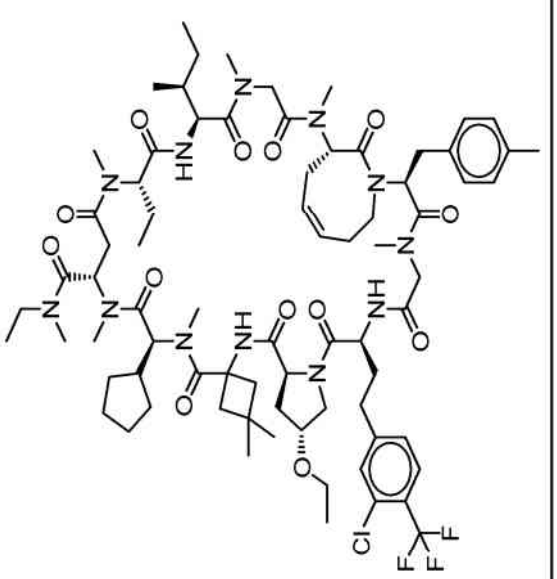
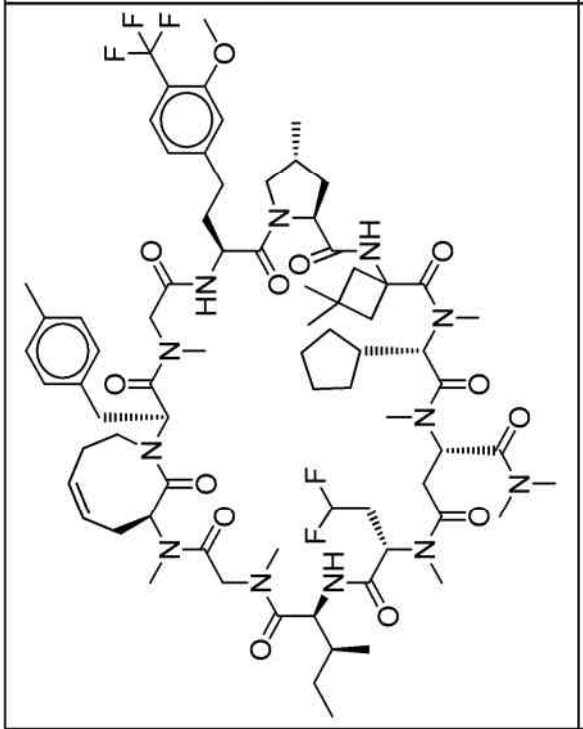
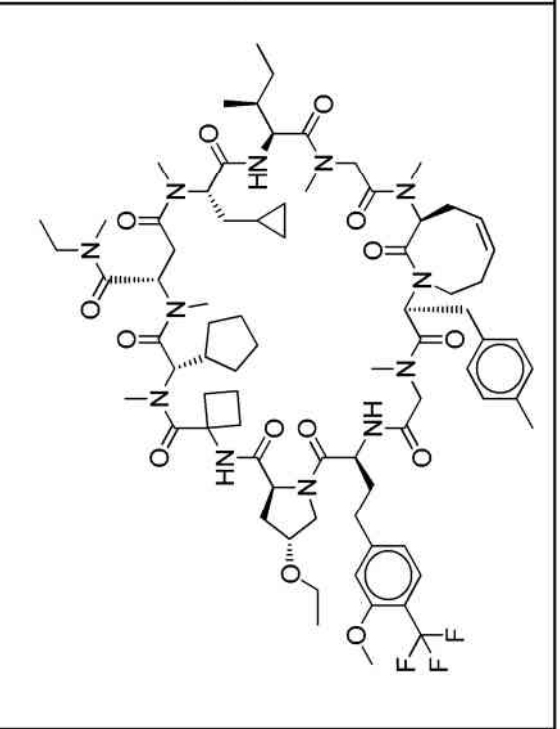
	
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PP1856	PP1859

	
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PP186 1	PP186 3

	
PP186 6	PP186 8
	
PP186 5	PP186 7

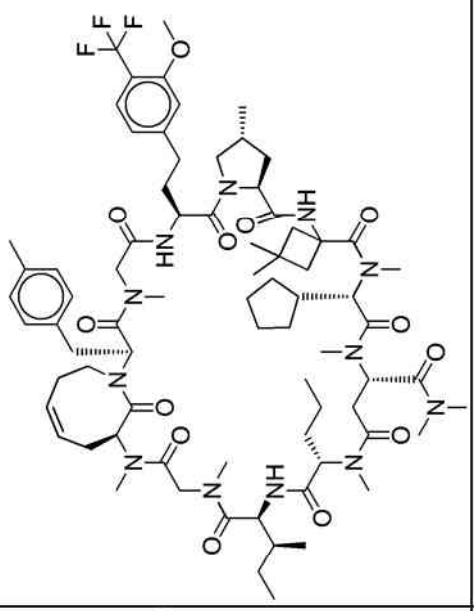
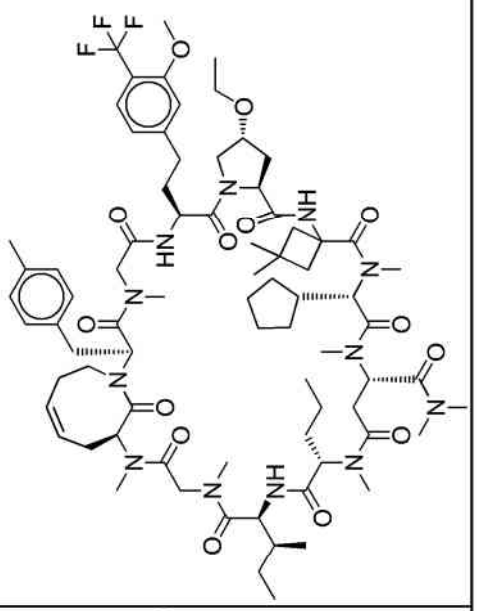
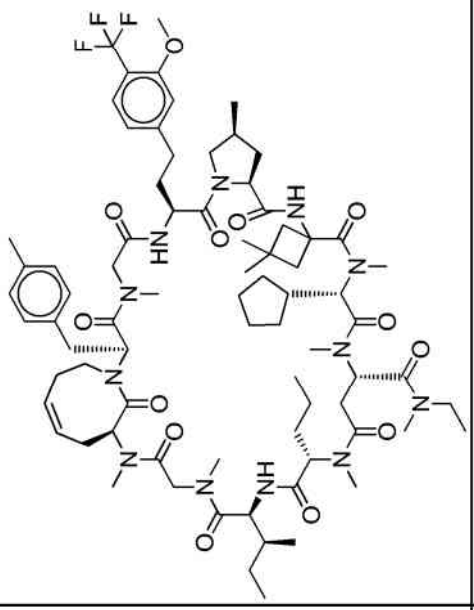
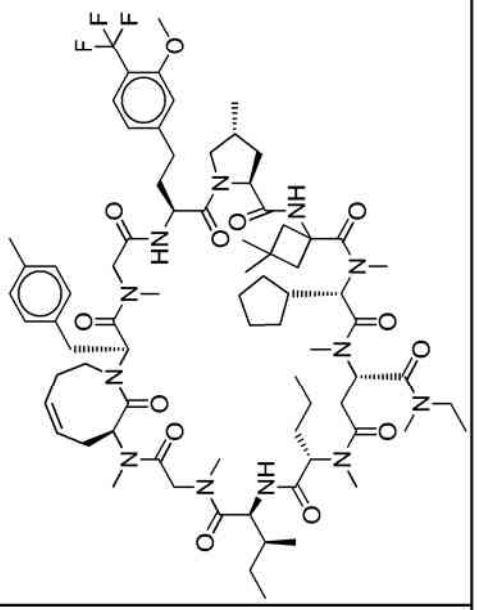
	
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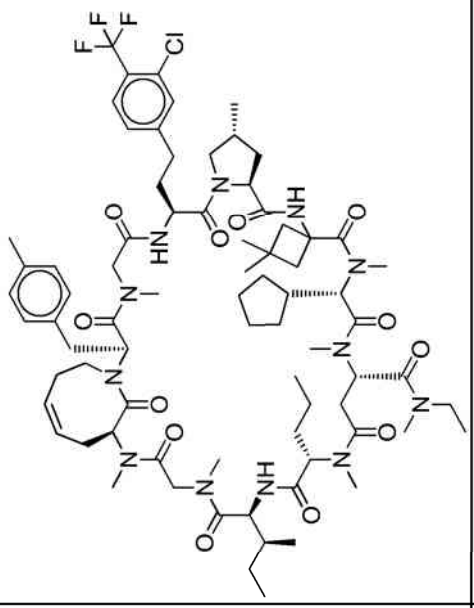
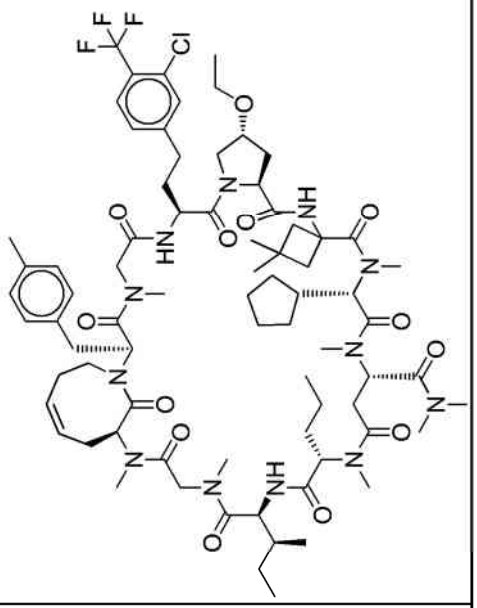
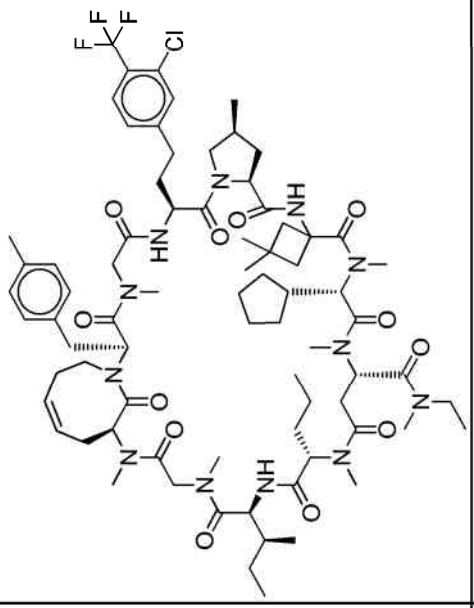
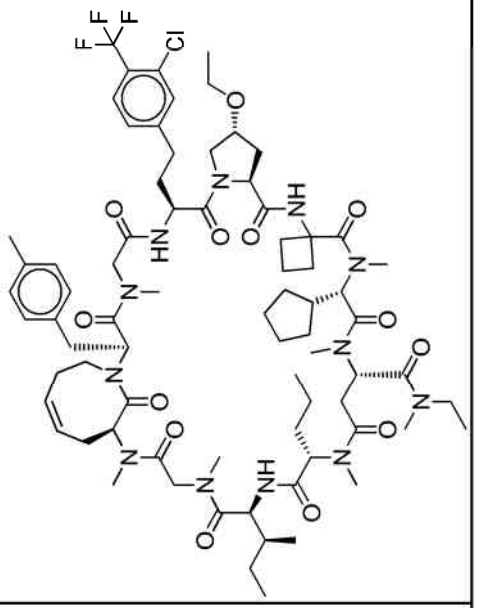
	
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PP187 3	PP187 5

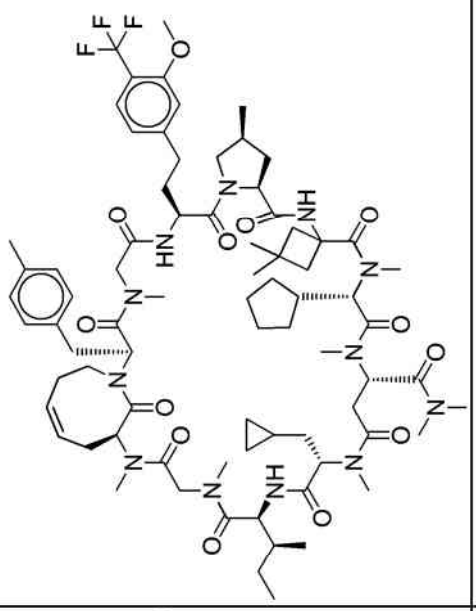
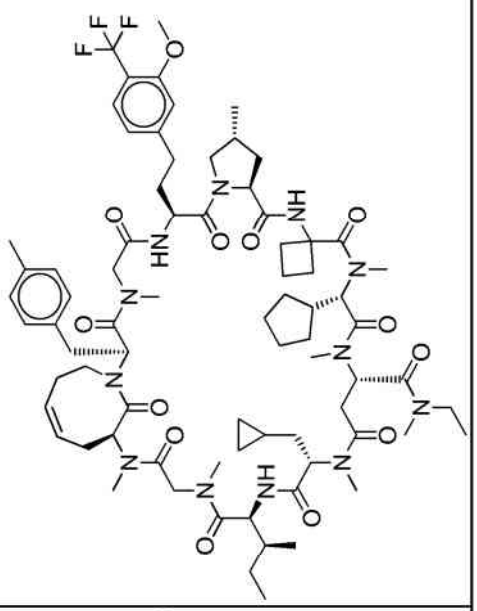
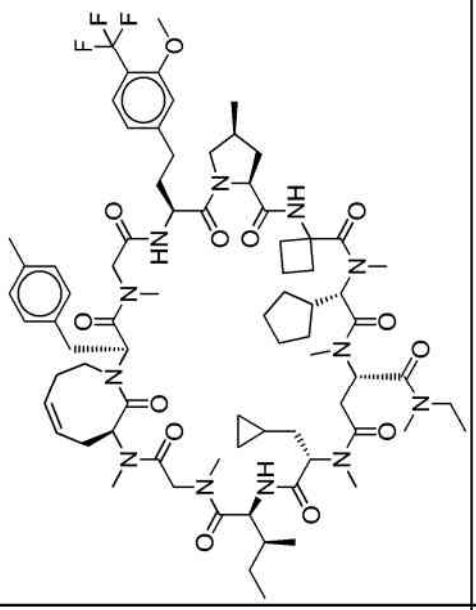
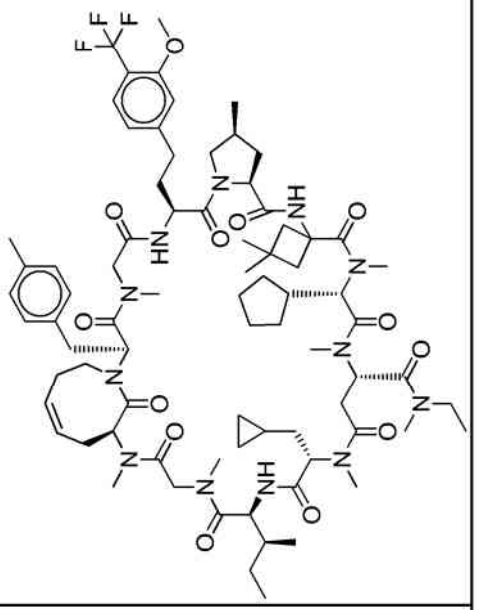
	
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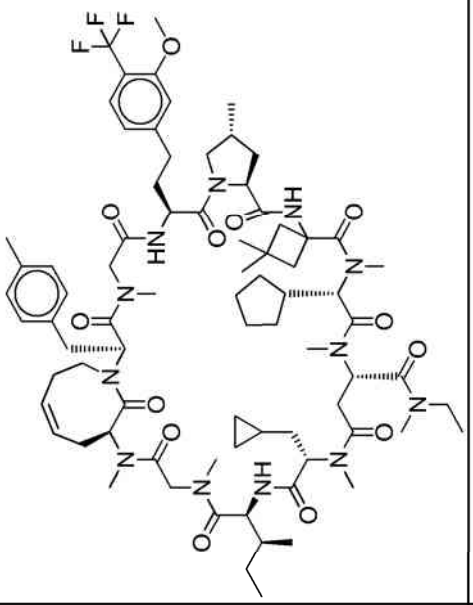
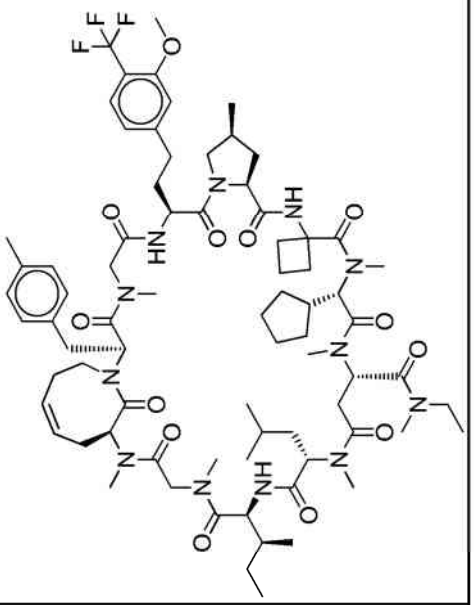
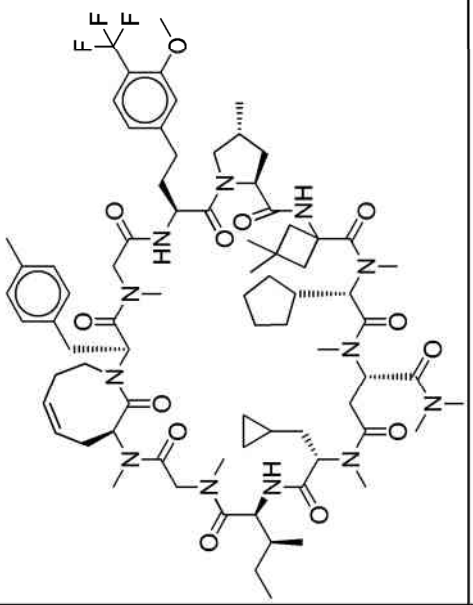
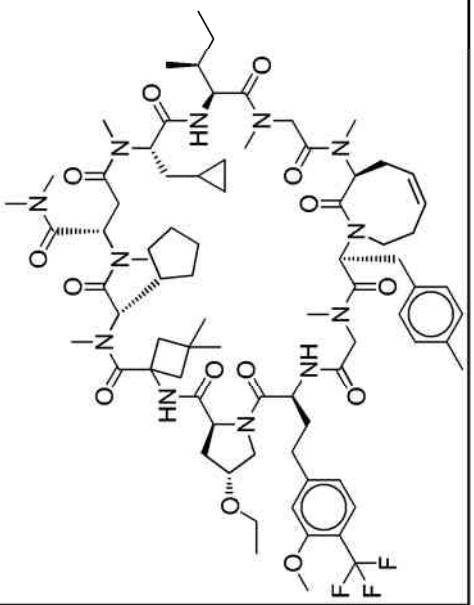
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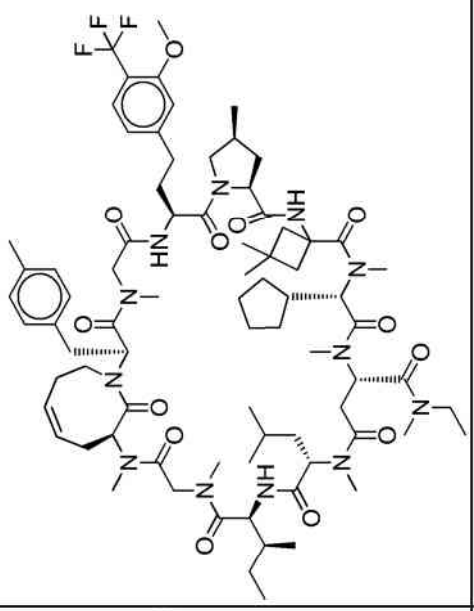
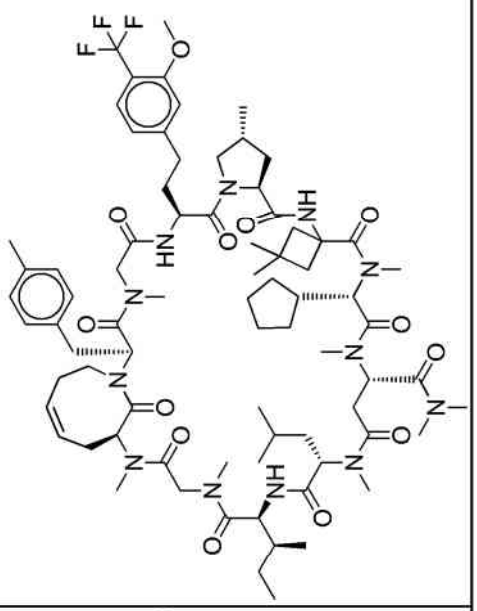
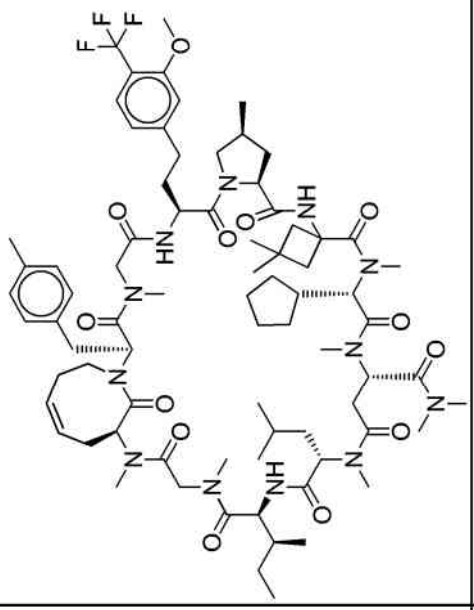
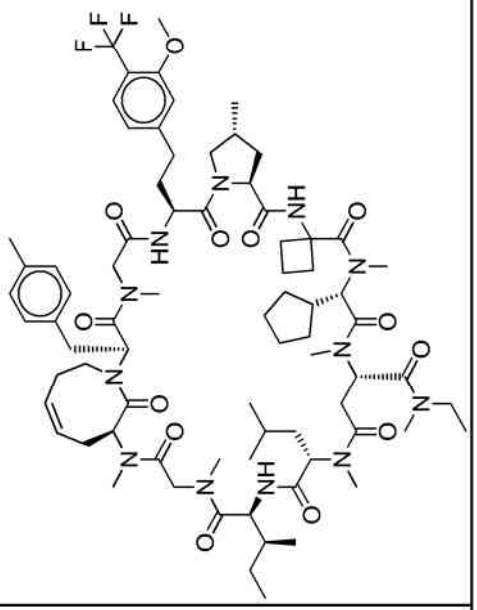
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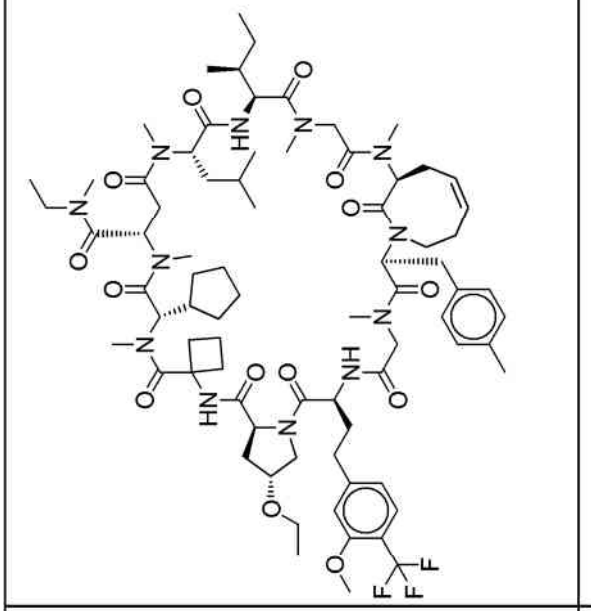
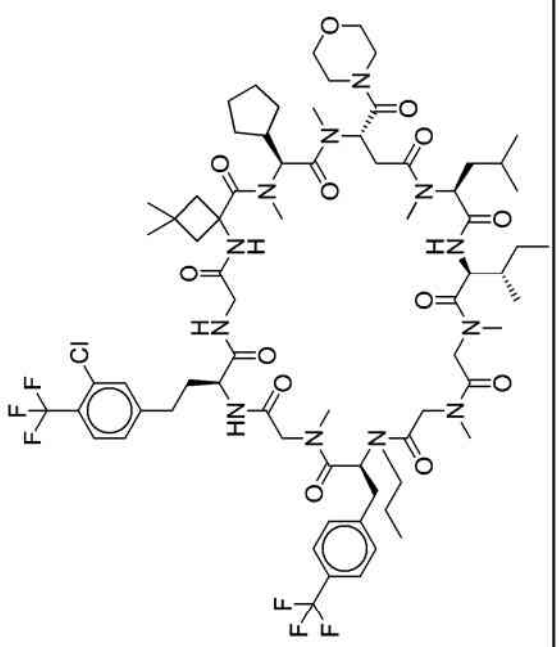
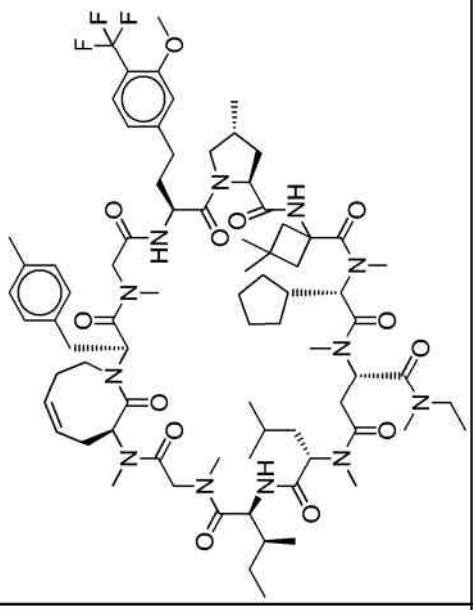
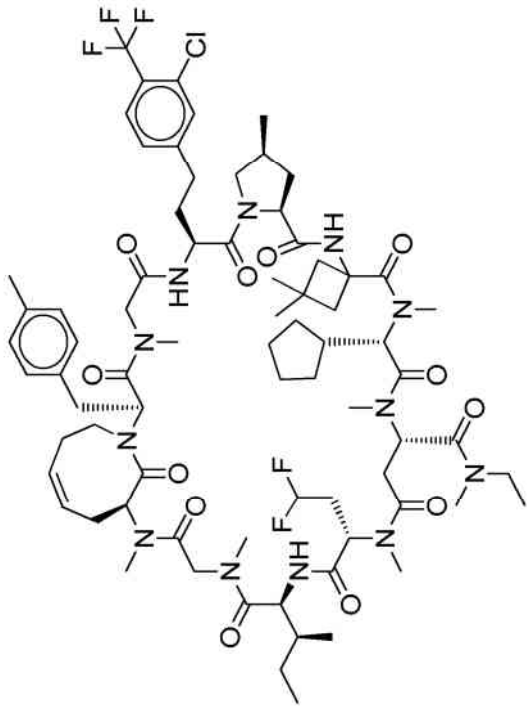
	
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PP1889	PP1891

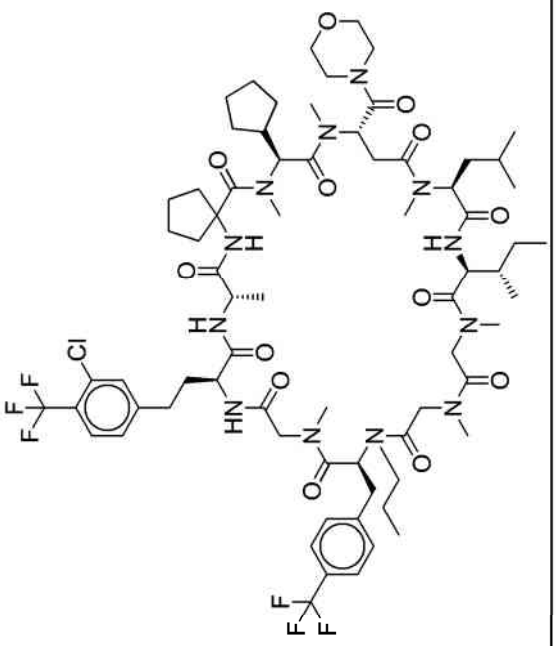
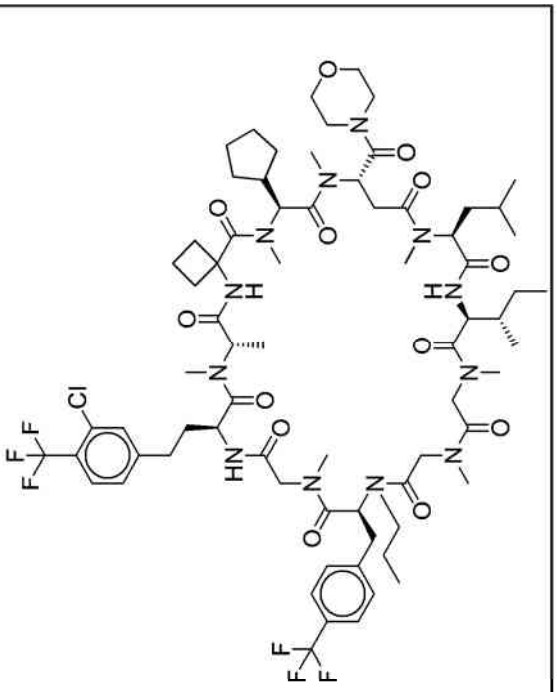
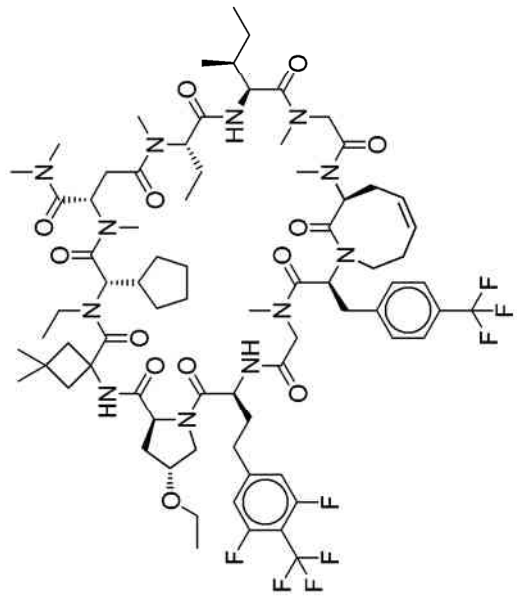
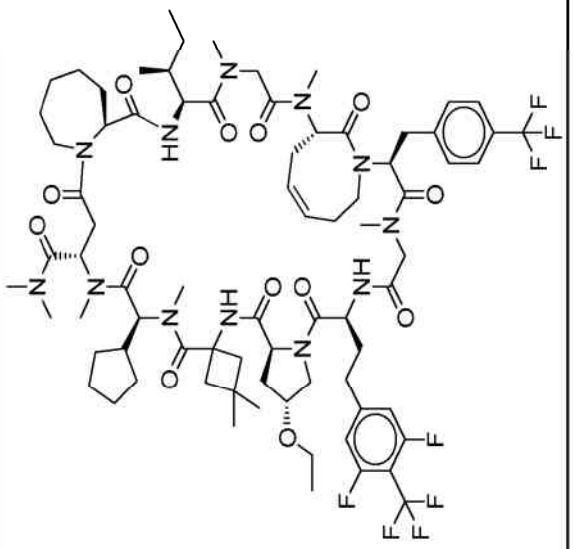
	
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PP189 3	PP189 5

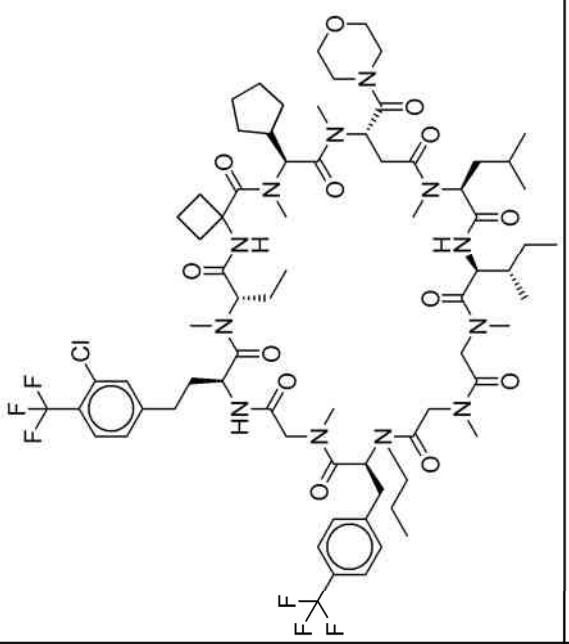
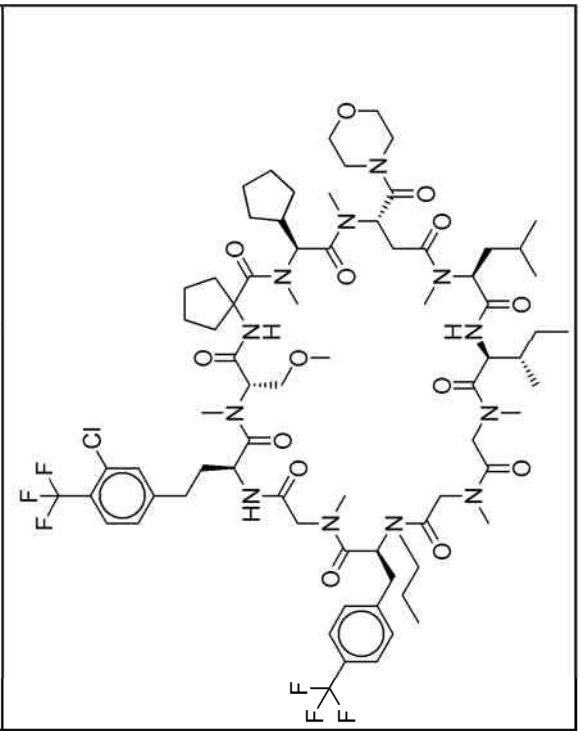
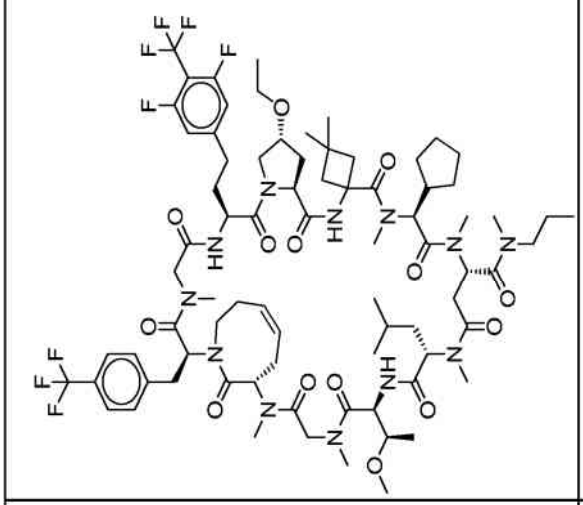
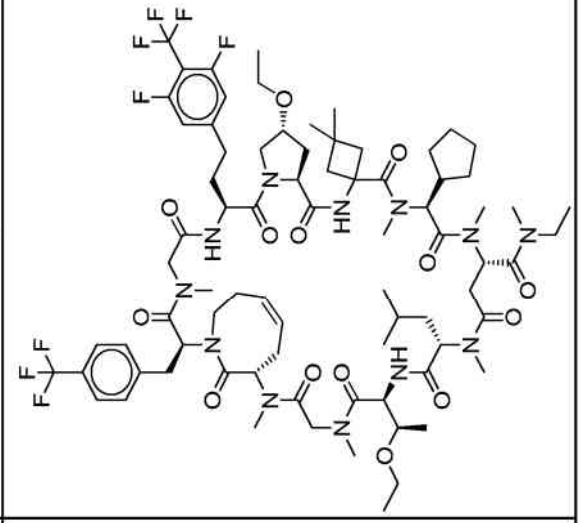
	
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PP1897	PP1899

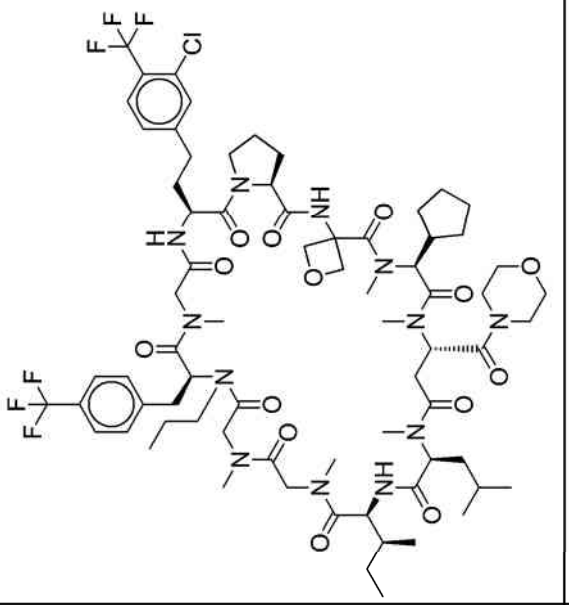
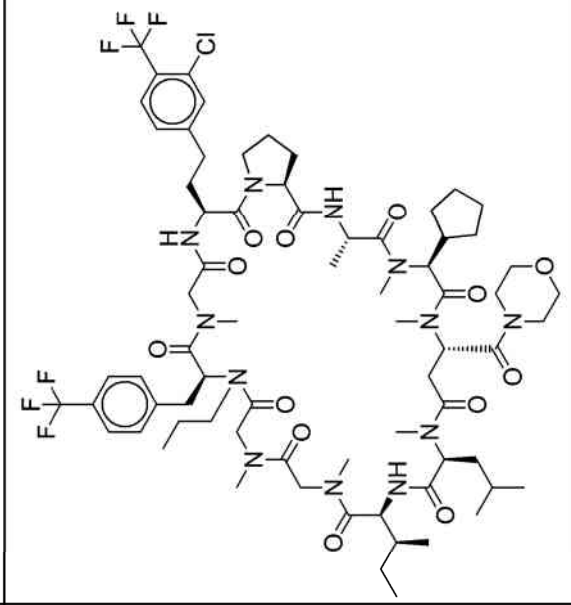
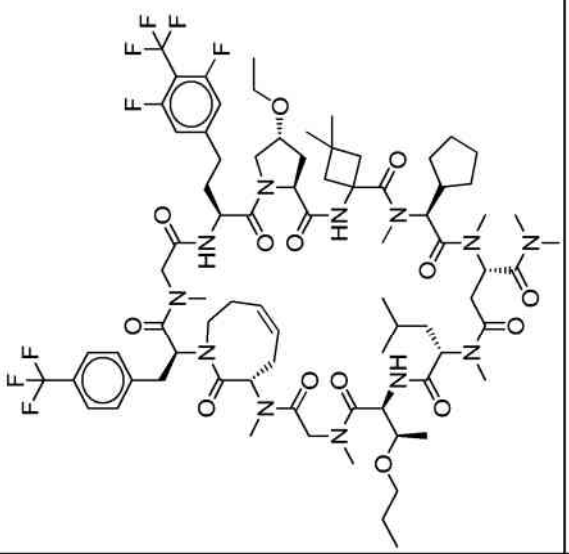
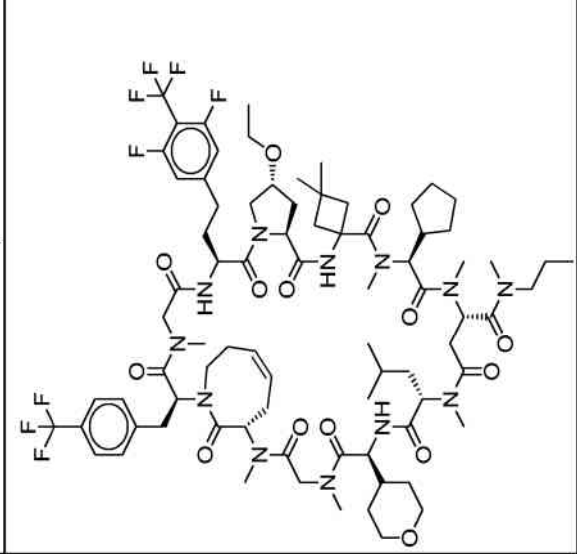
	
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PP190 1	PP190 3

	
PP190 6	PP190 8
	
PP190 5	PP190 7

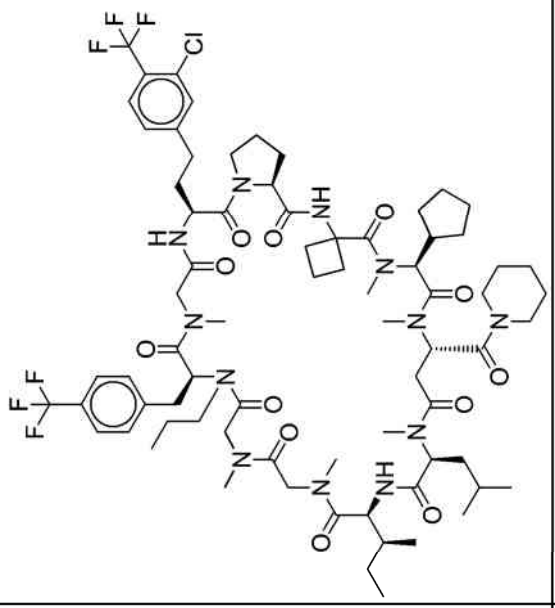
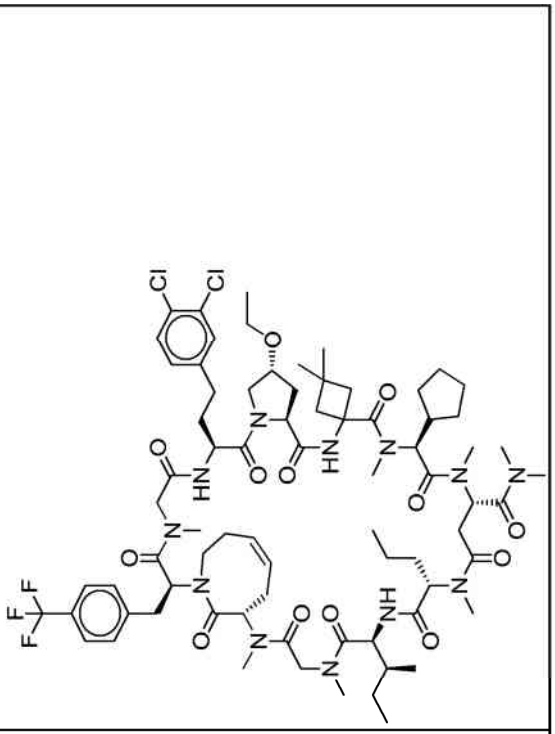
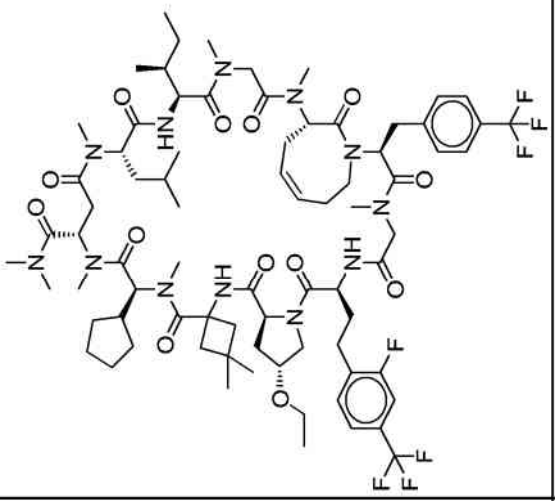
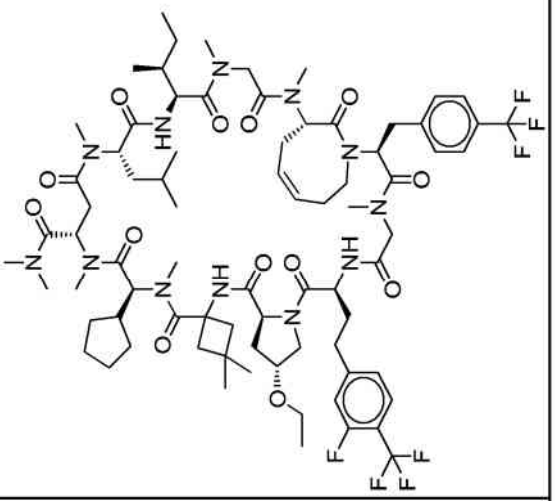
	
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PP1909	PP1911

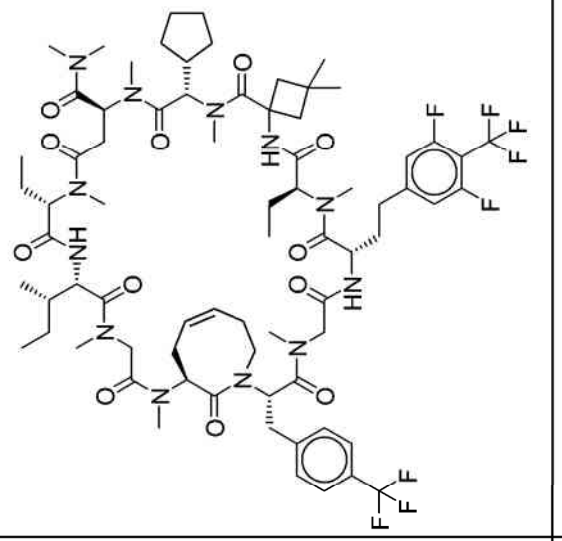
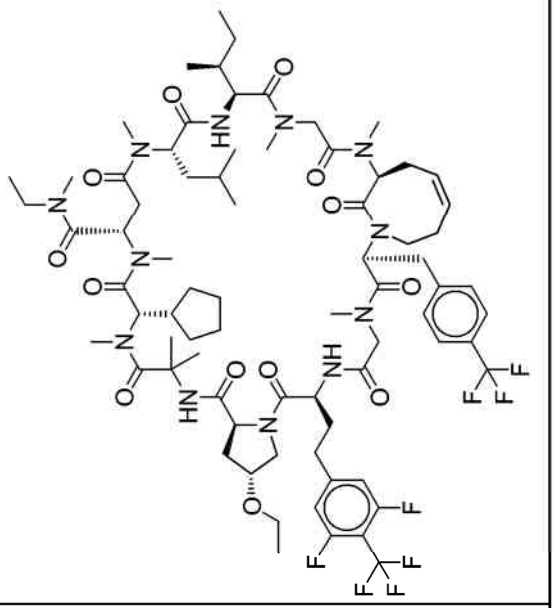
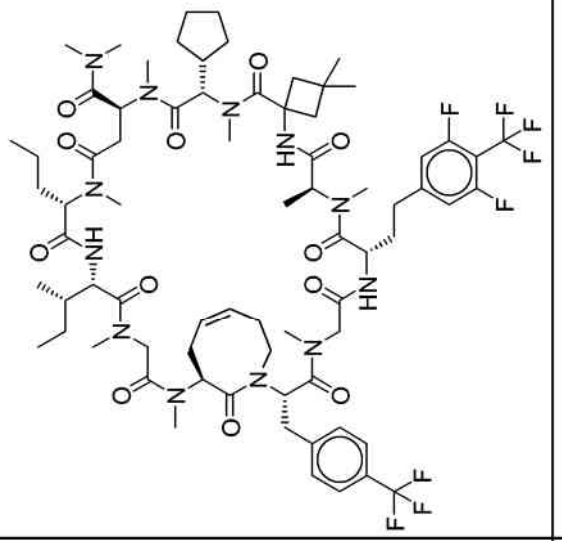
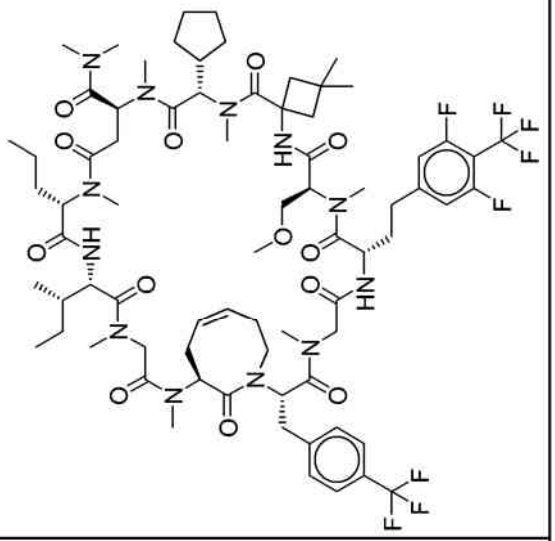
	
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PP191 3	PP191 5

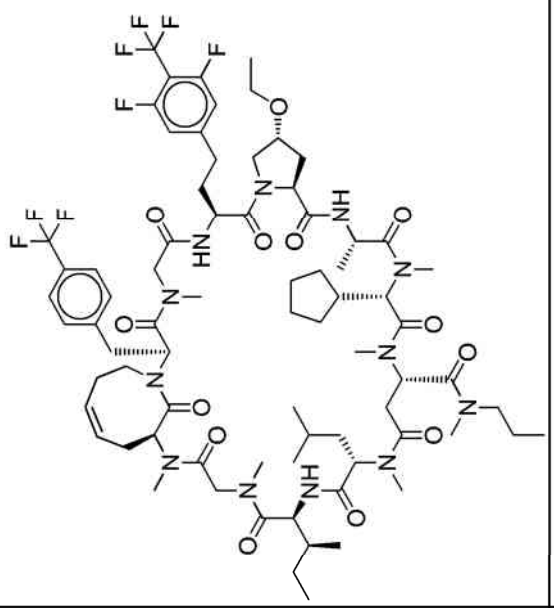
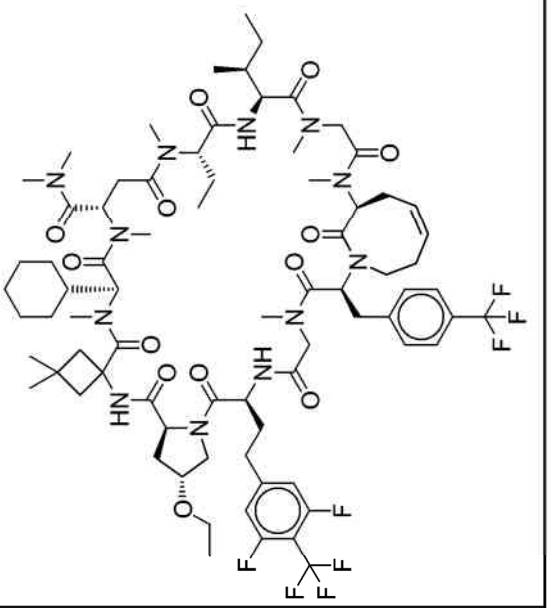
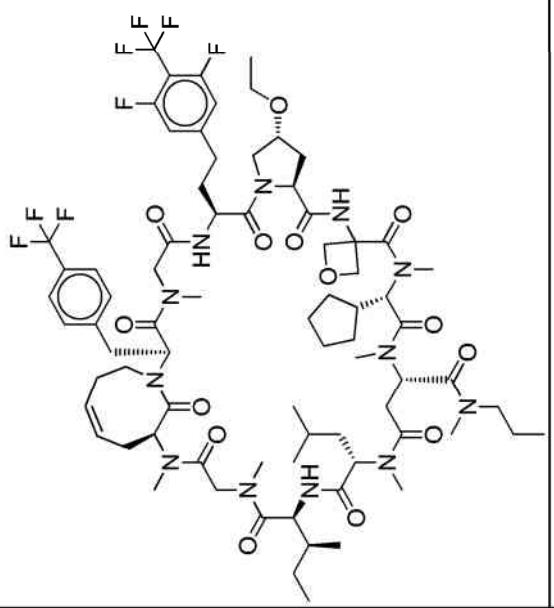
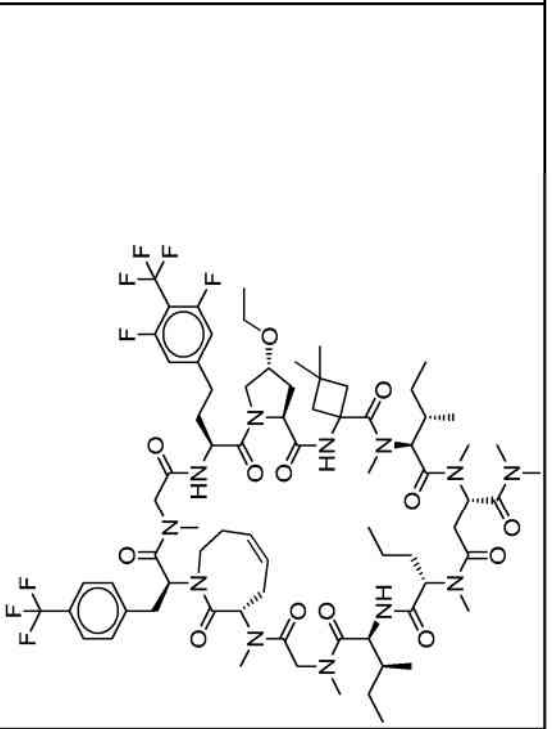
	
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PP1917	PP1919

	
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PP192 1	PP192 3

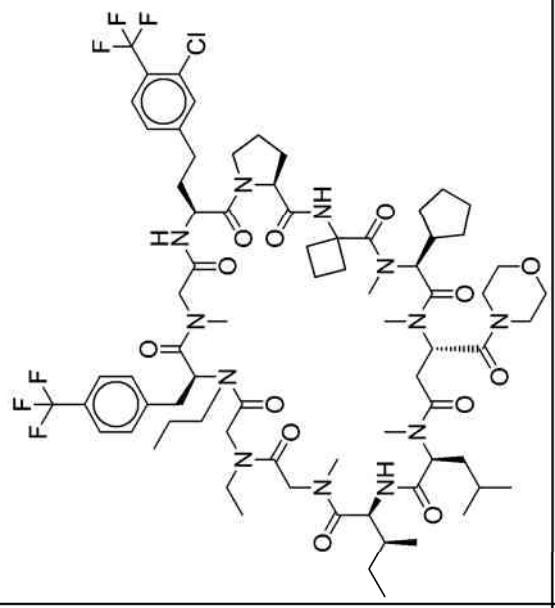
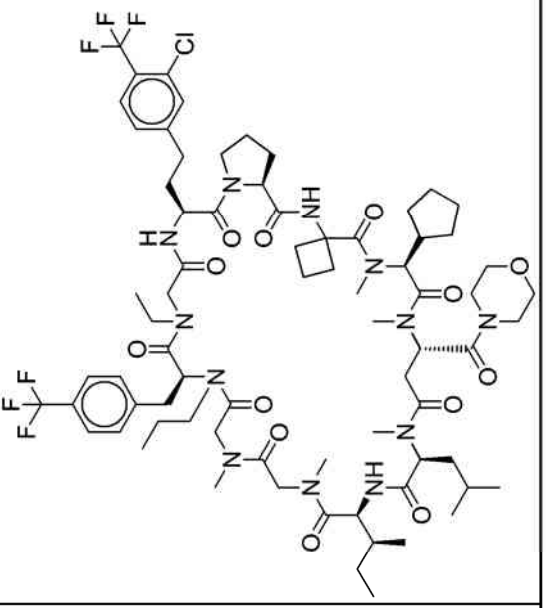
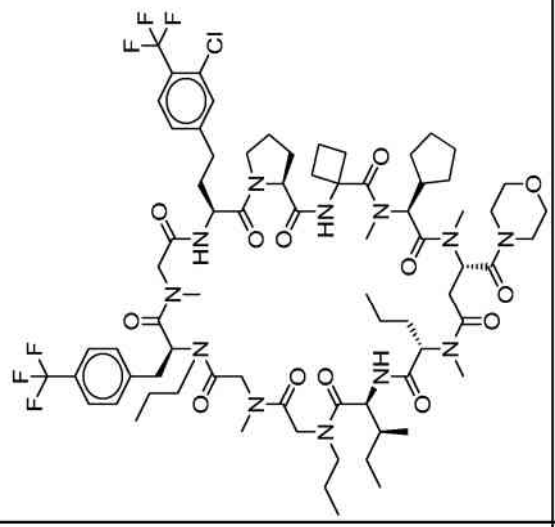
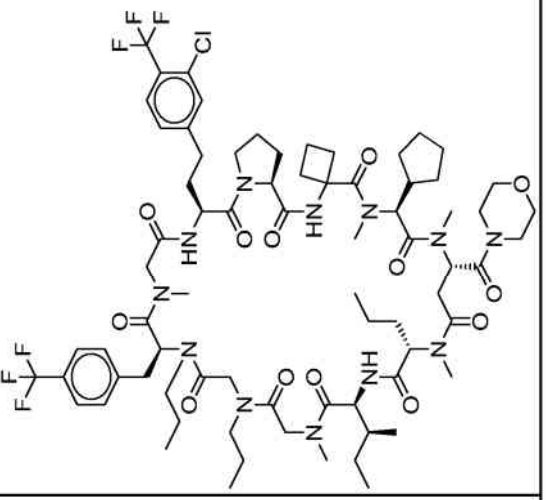
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PP192 5	PP192 7

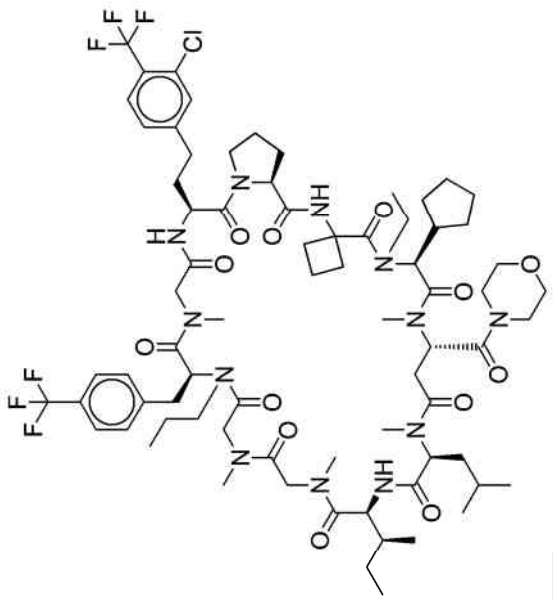
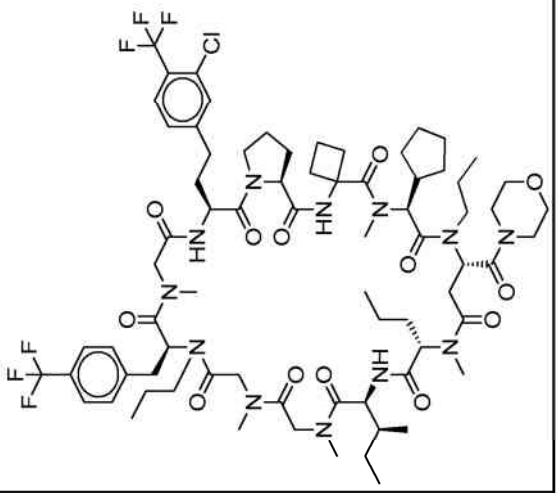
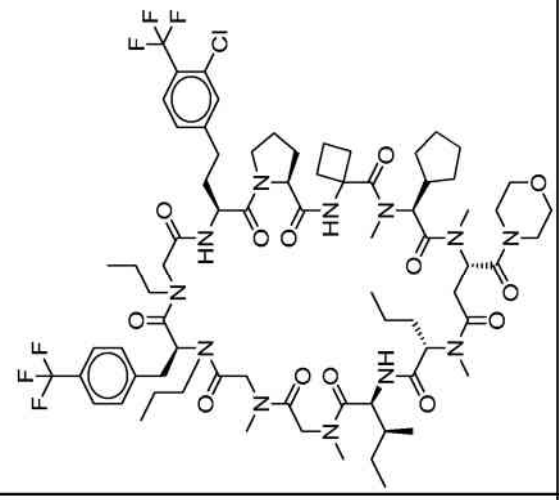
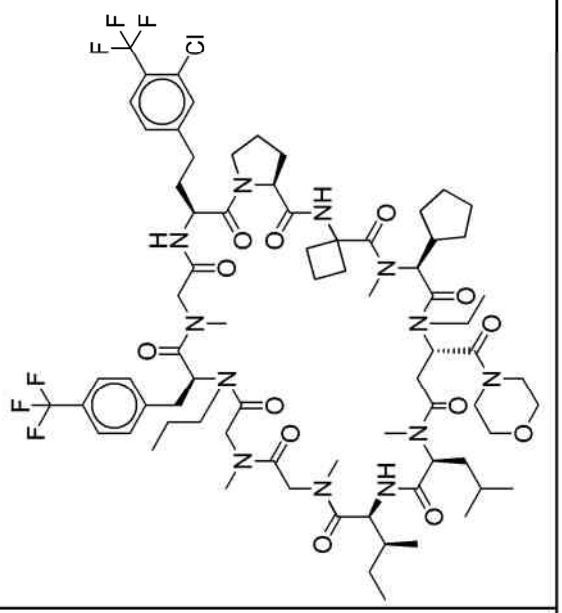
	
PP1930	PP1932
	
PP1929	PP1931

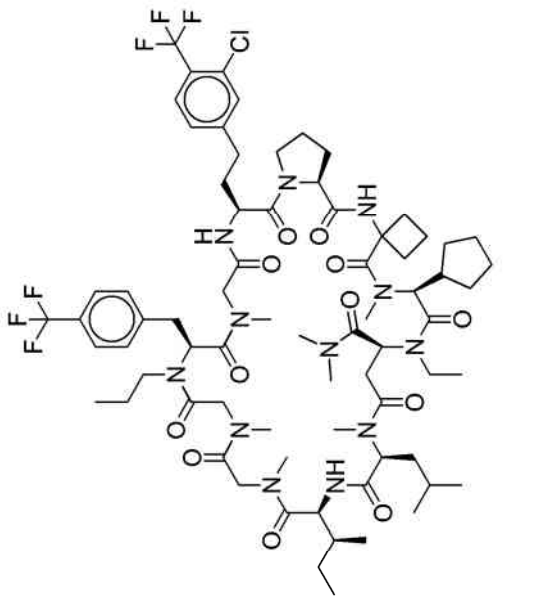
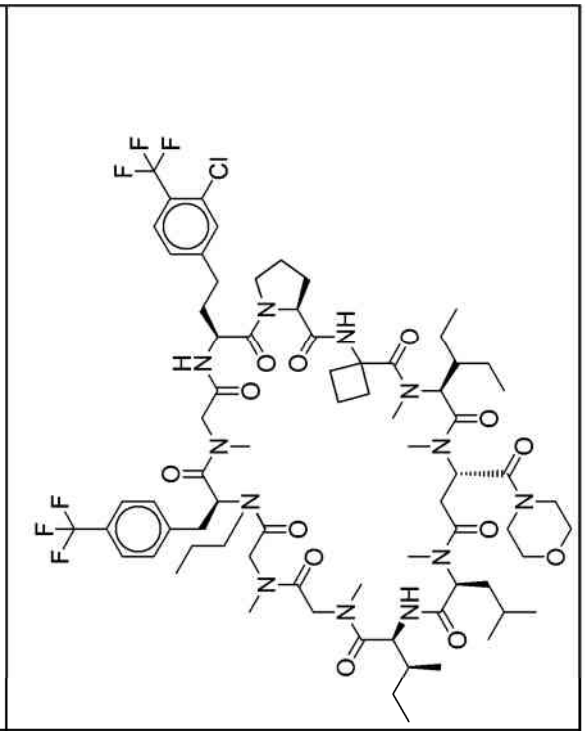
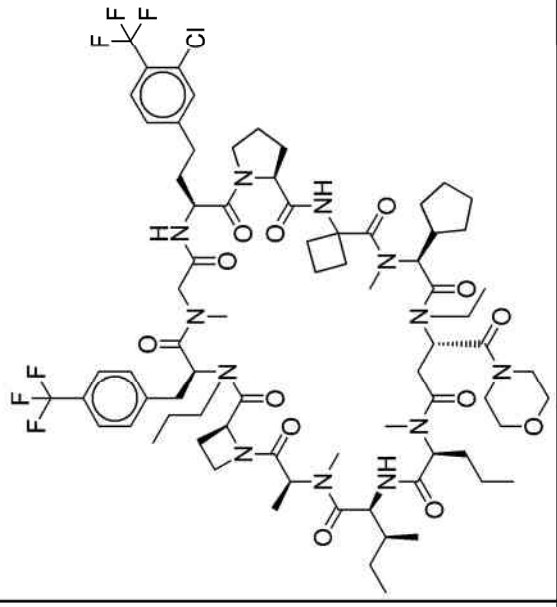
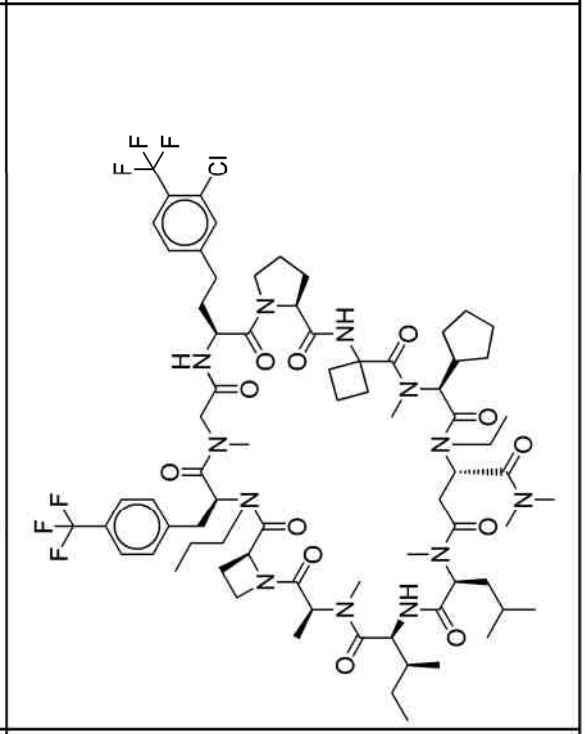
	
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PP193 4	PP193 6

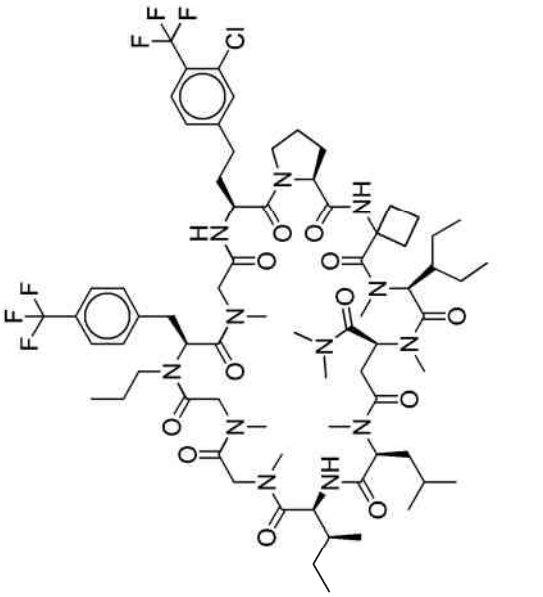
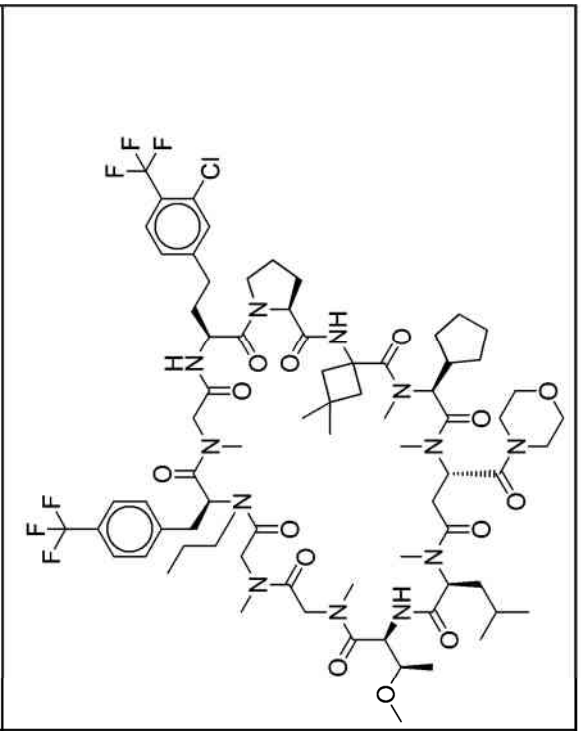
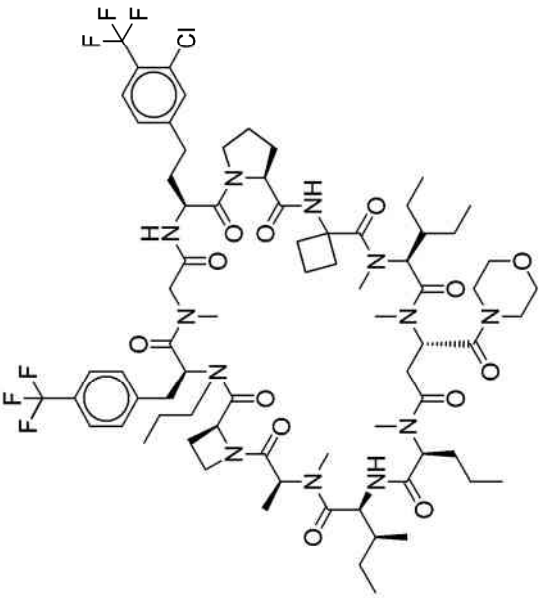
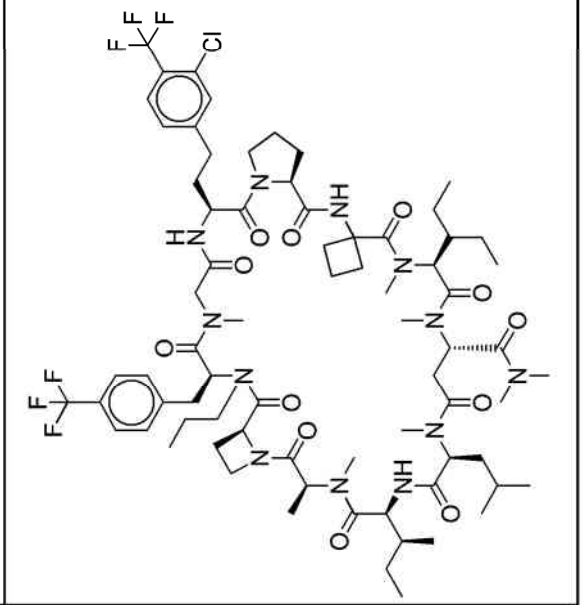
	
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PP194 3	PP194 5

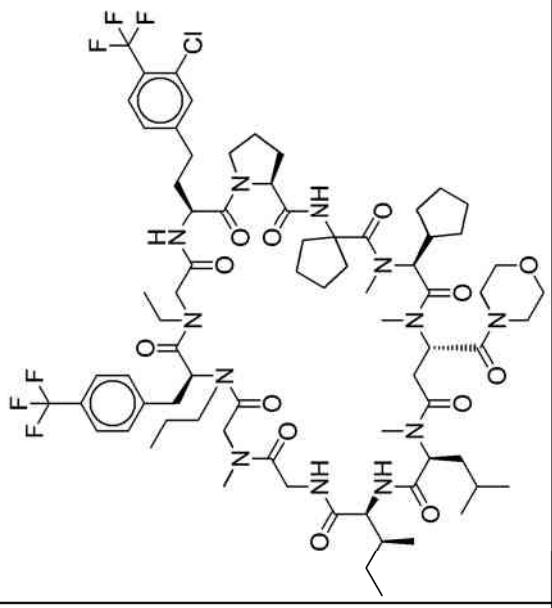
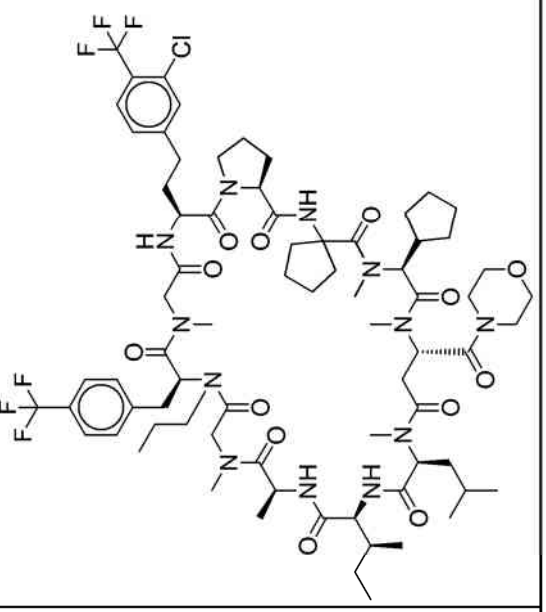
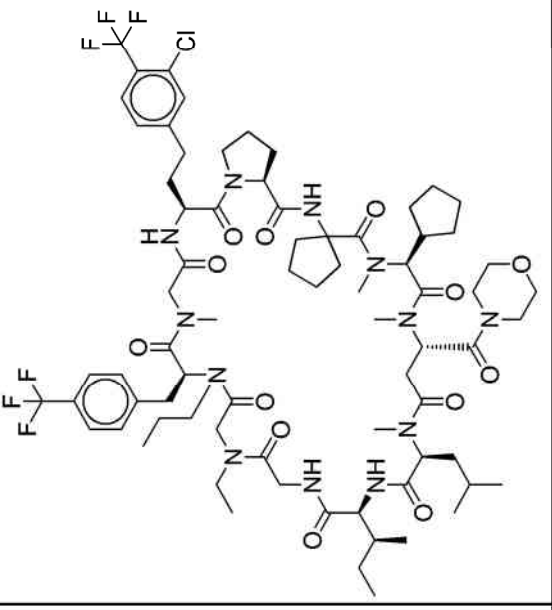
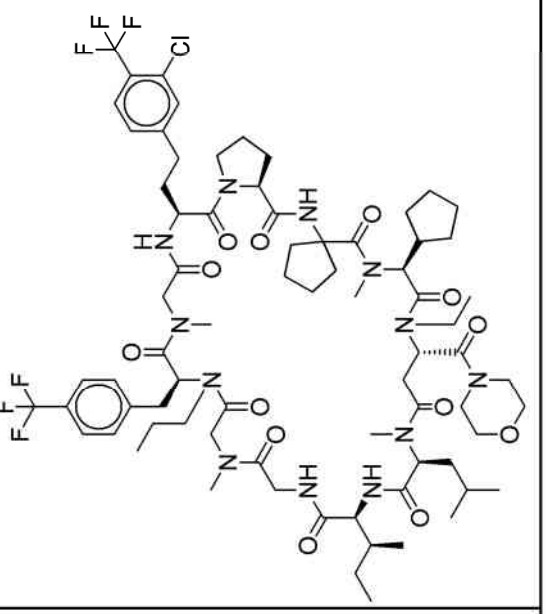
	
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PP1947	PP1949

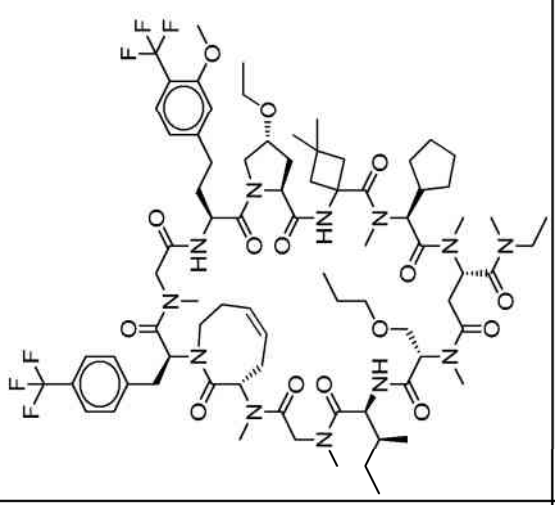
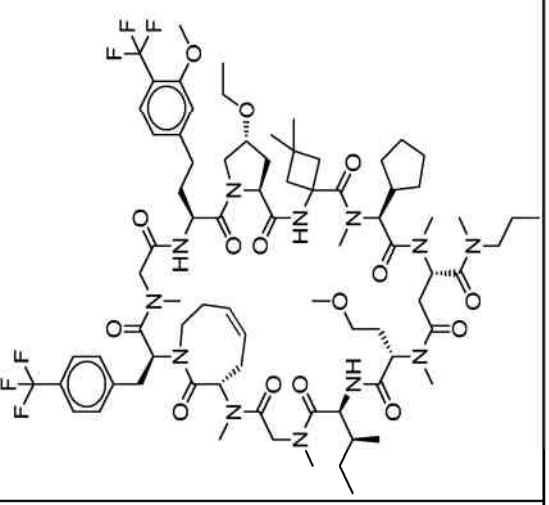
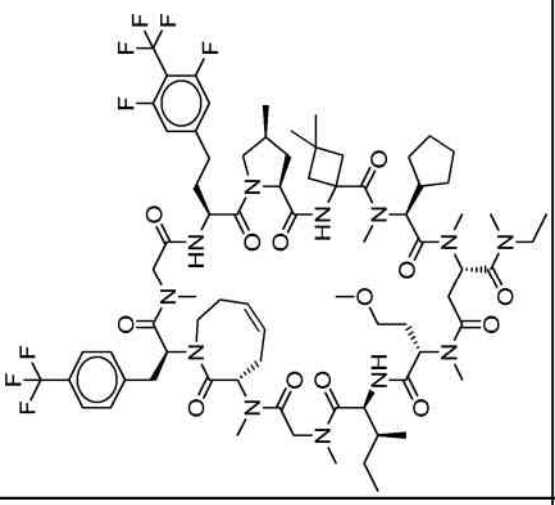
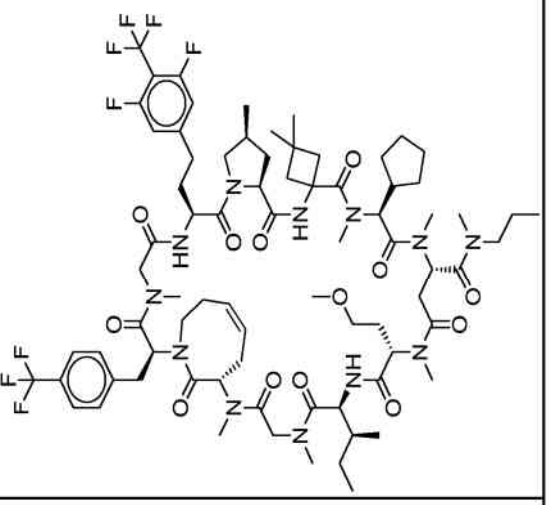
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PP195 3	

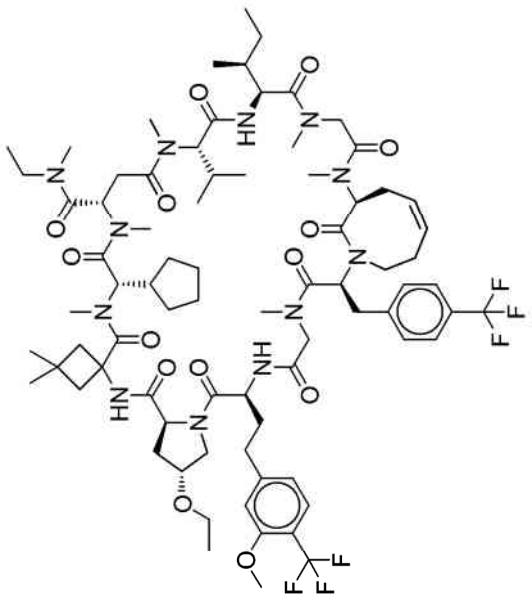
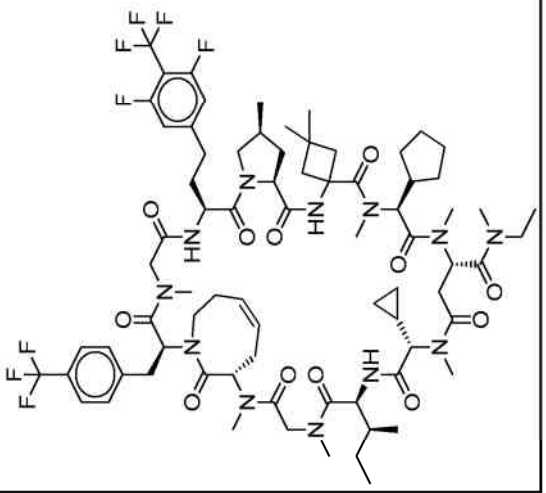
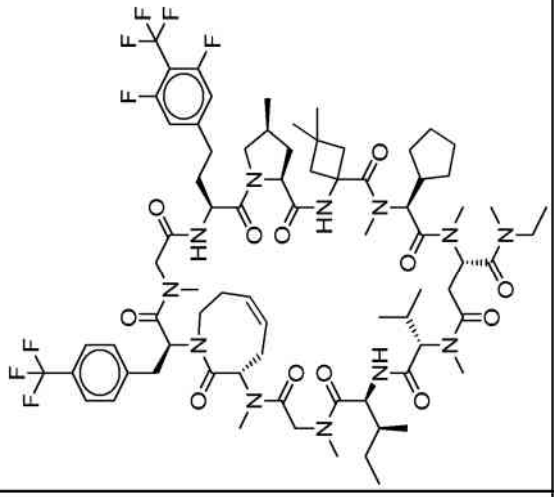
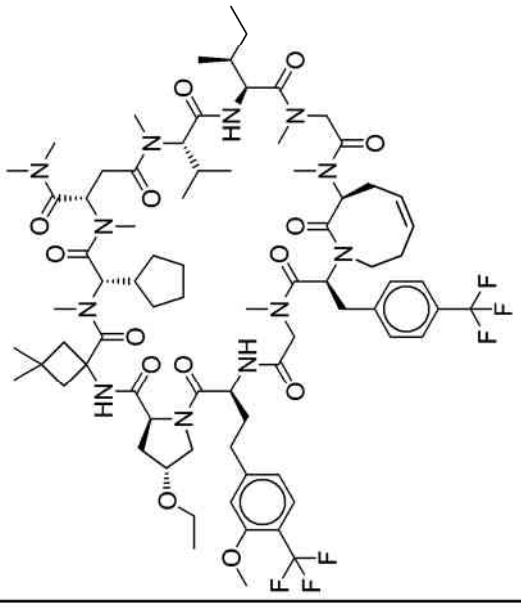
	
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PP1955	PP1957

	
PP1960	PP1963
	
PP1959	PP1961

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PP196 4	PP196 6

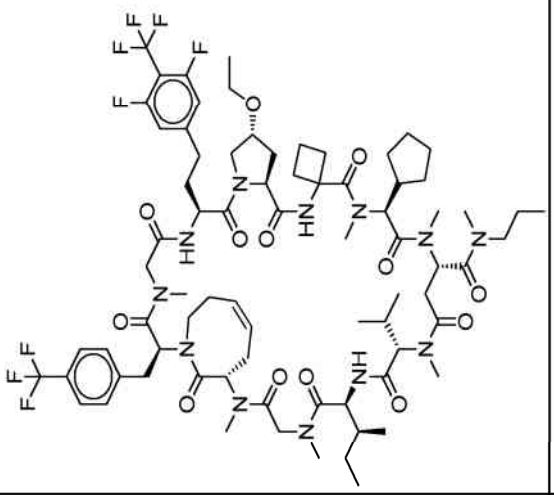
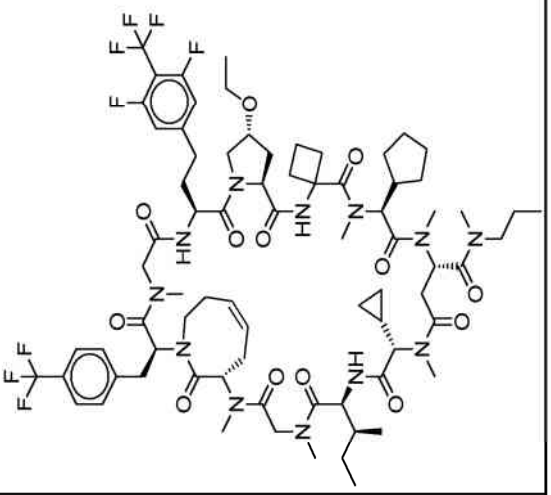
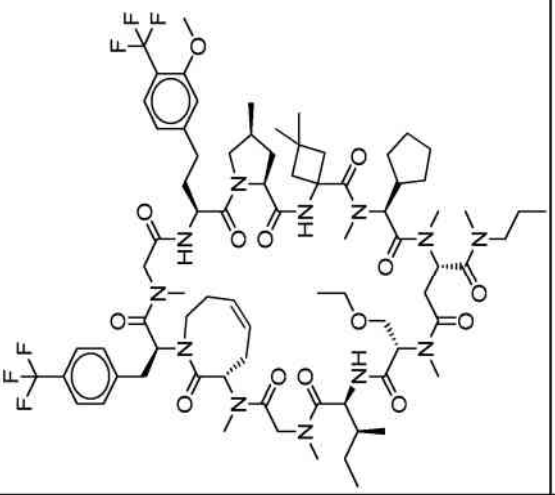
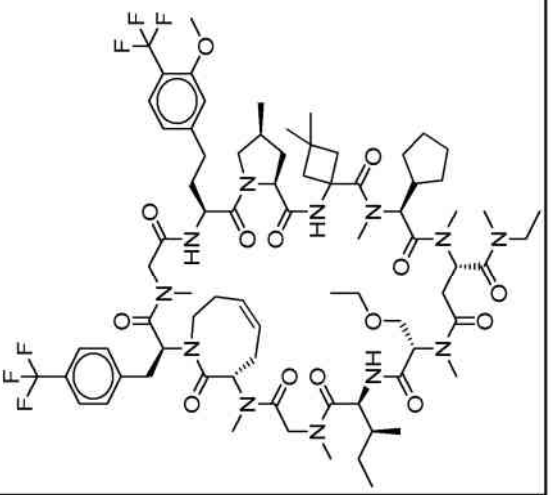
	
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PP1968	PP1970

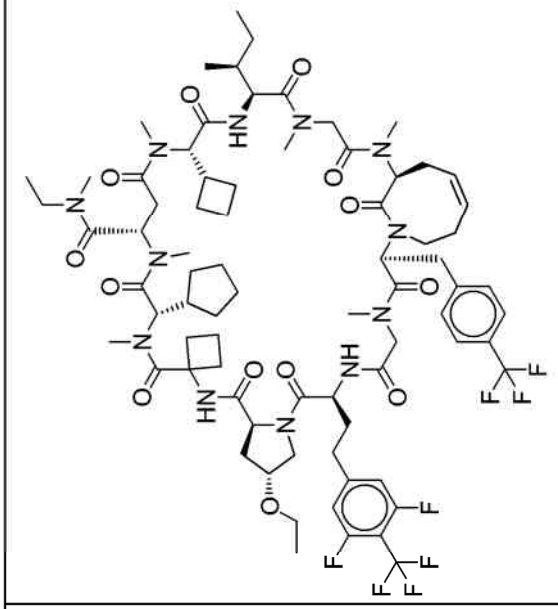
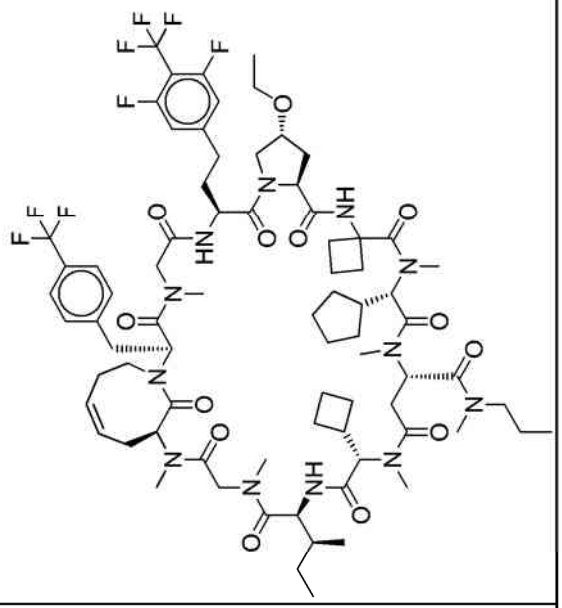
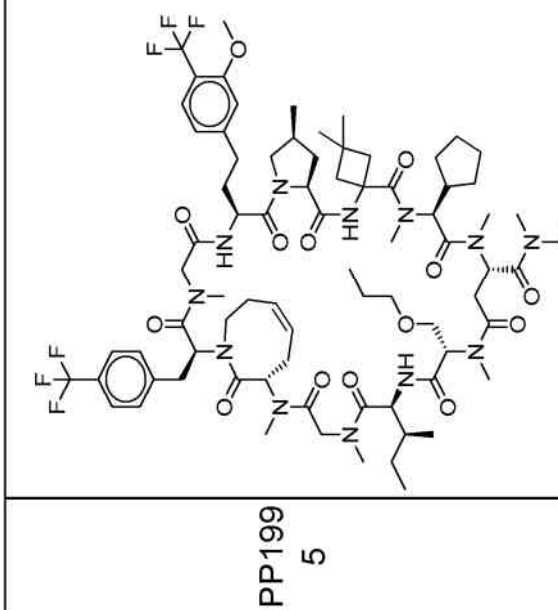
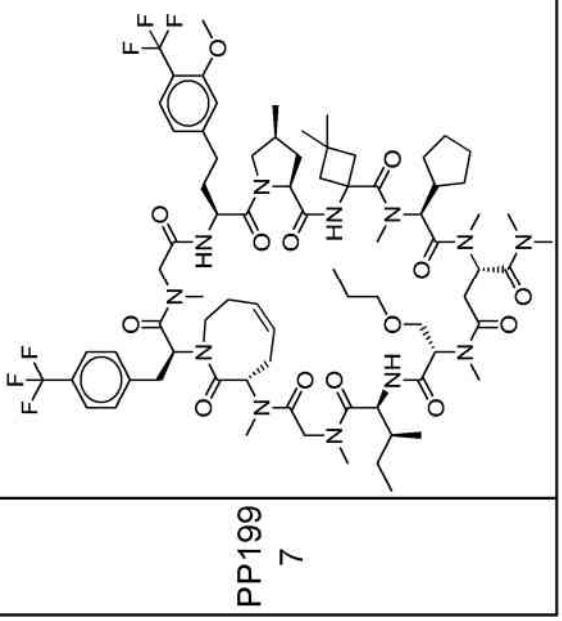
	
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PP197 2	PP197 4

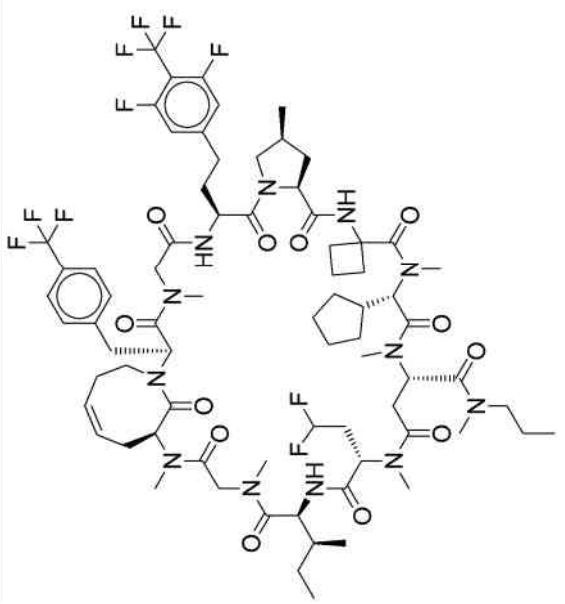
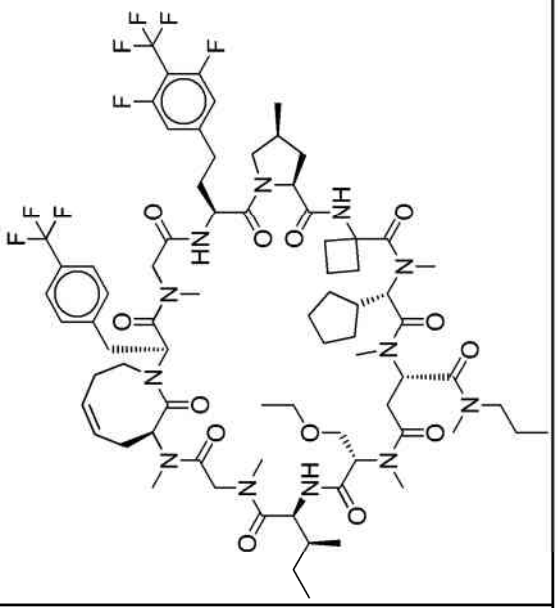
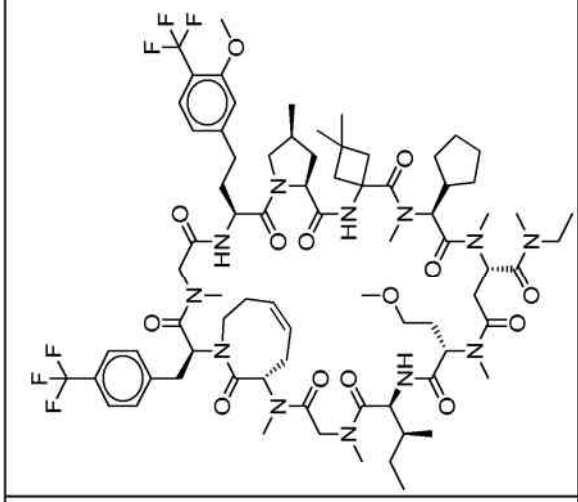
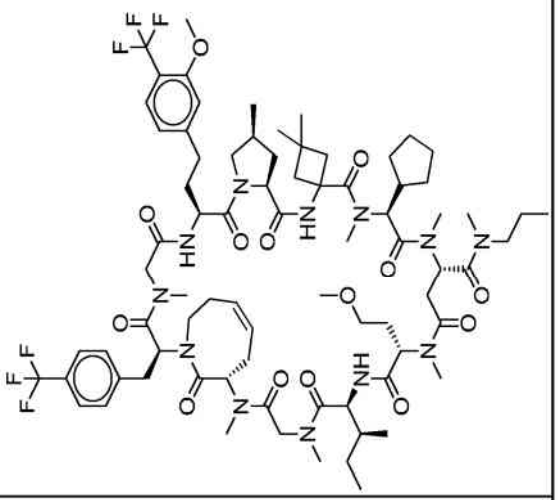
	
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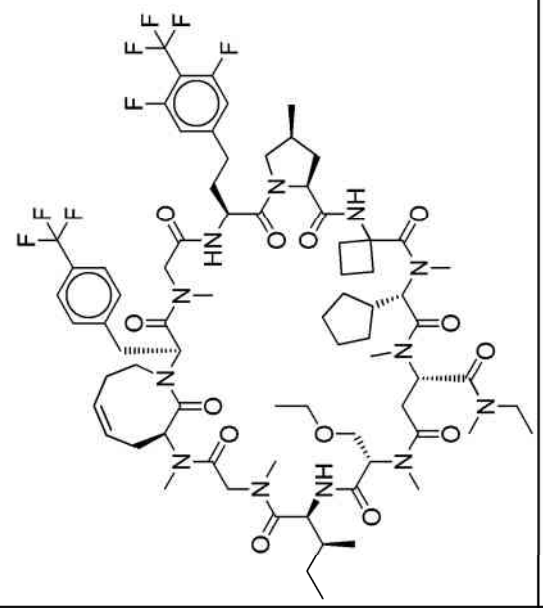
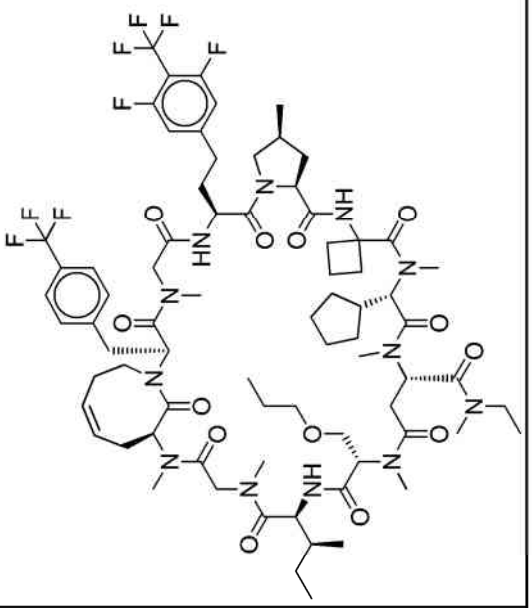
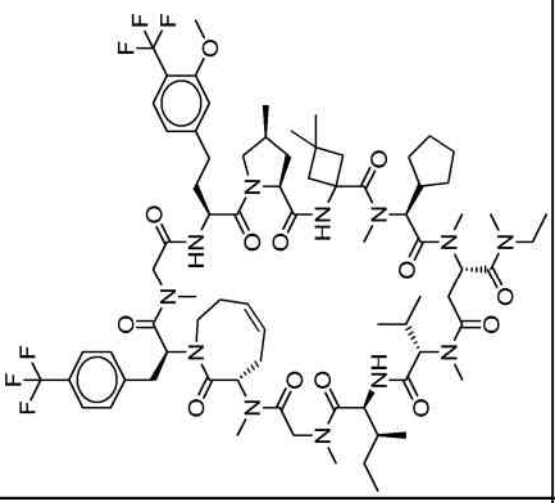
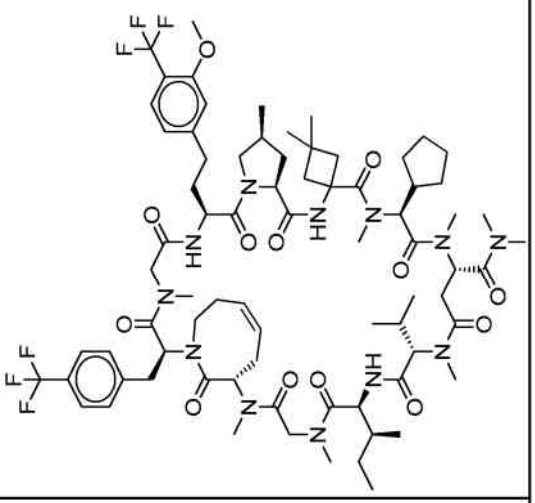
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PP198 1	PP198 4

PP1988	PP1990
PP1987	PP1989

	
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PP199 1	PP199 3

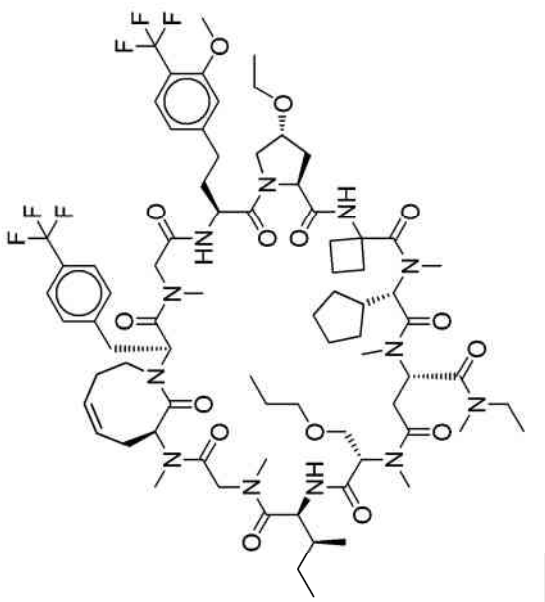
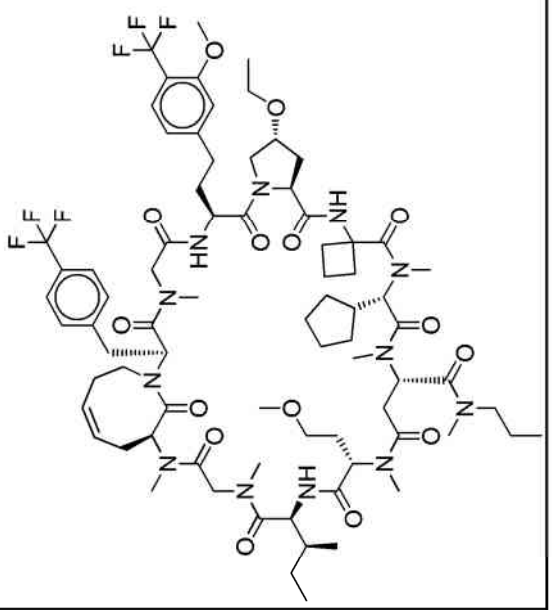
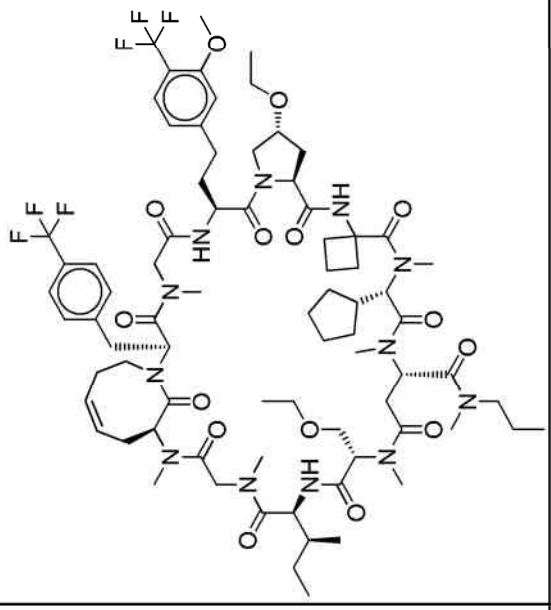
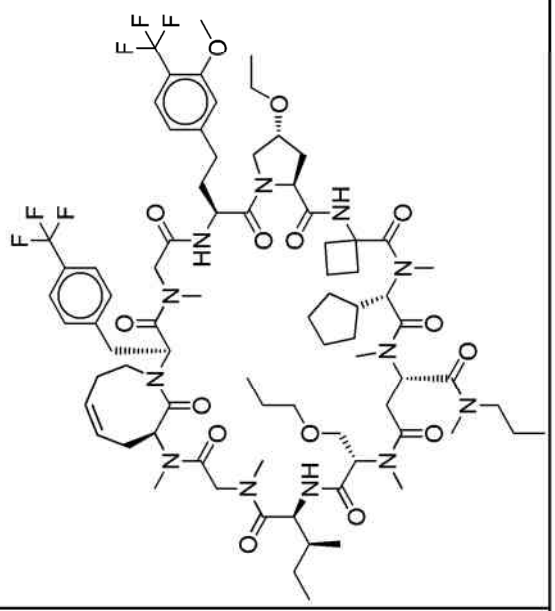
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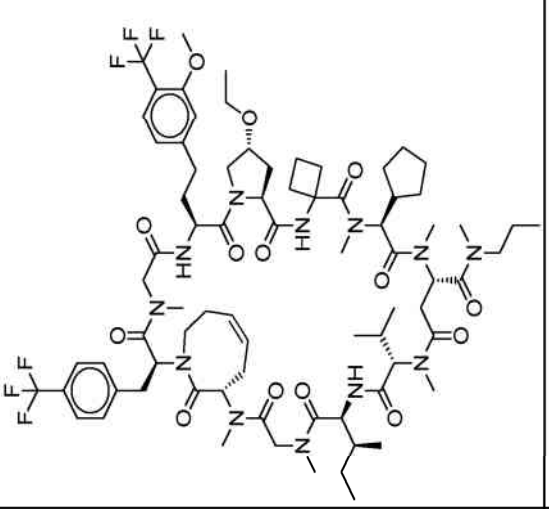
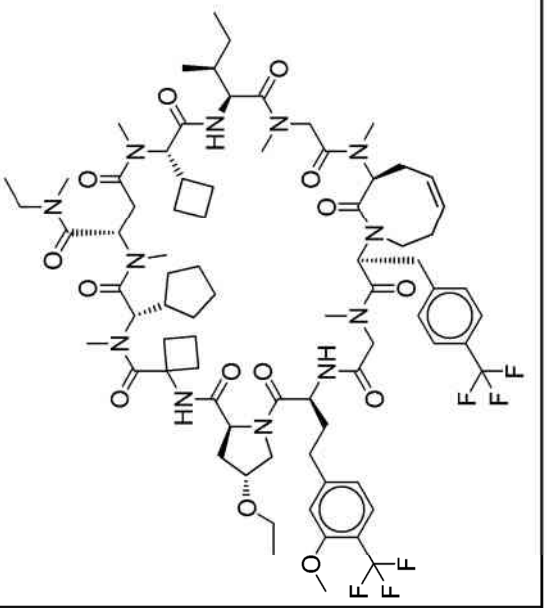
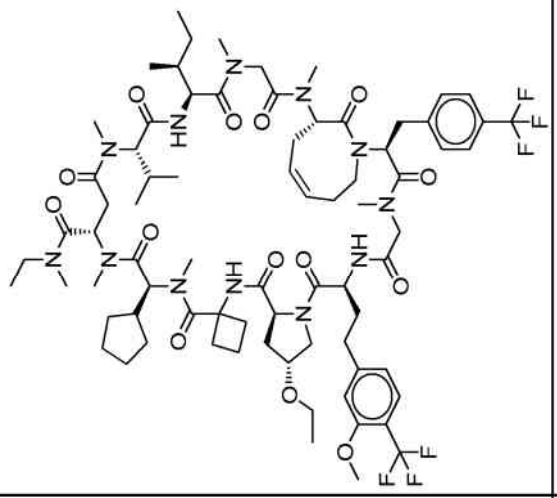
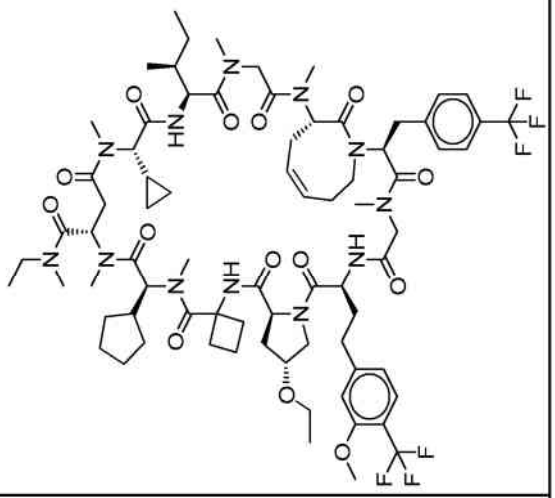
	
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PP1999	PP2001

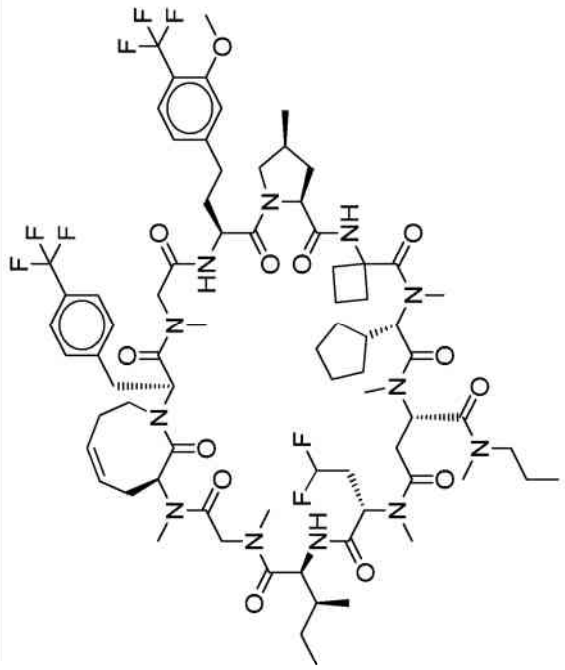
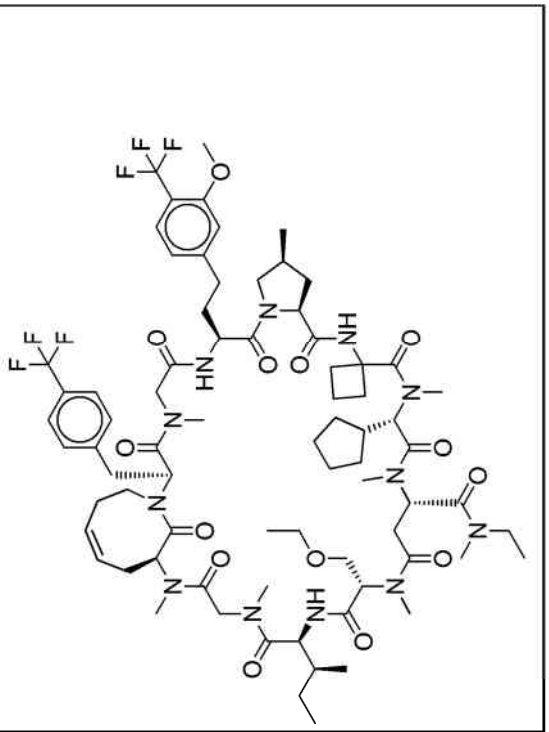
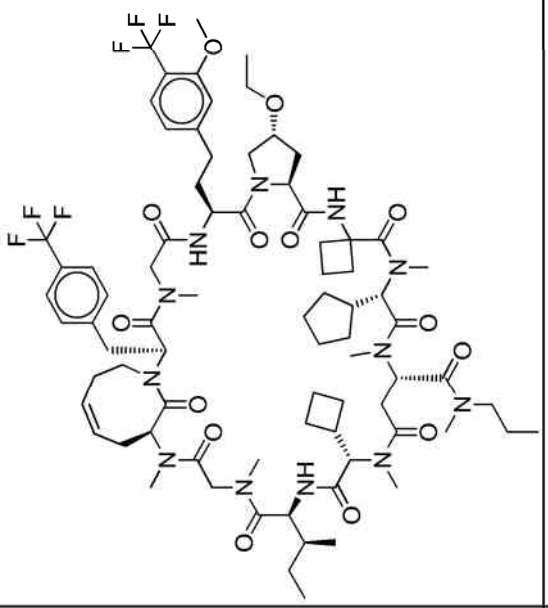
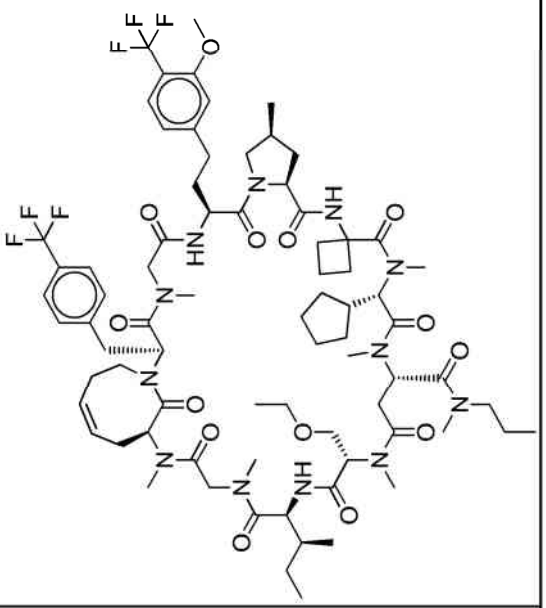
	
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PP2003	PP2005

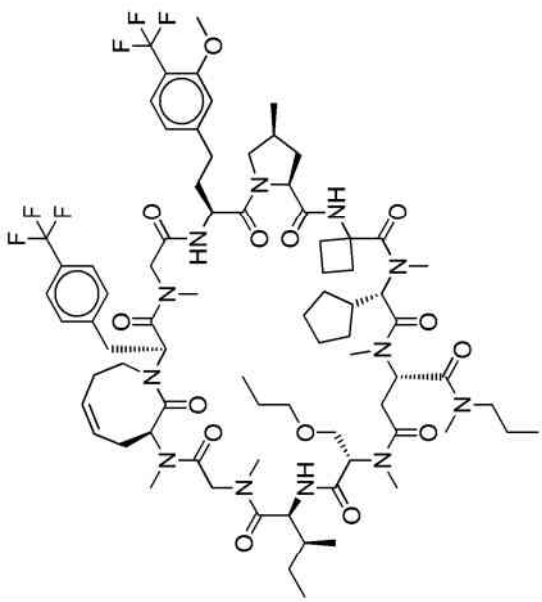
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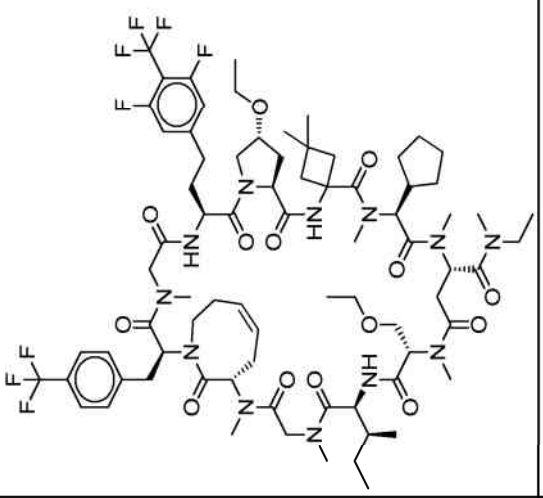
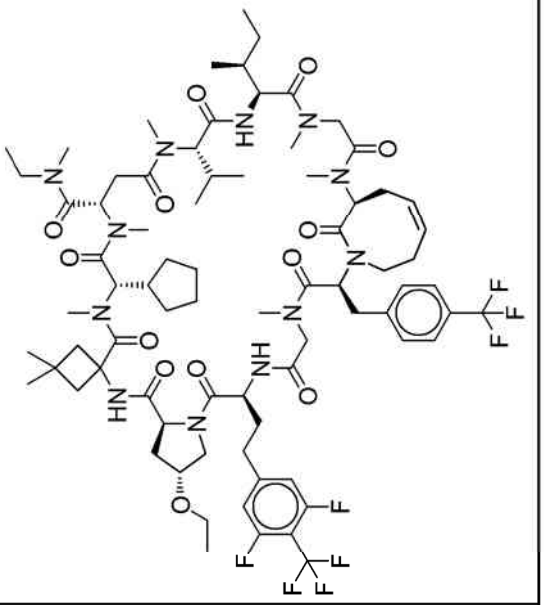
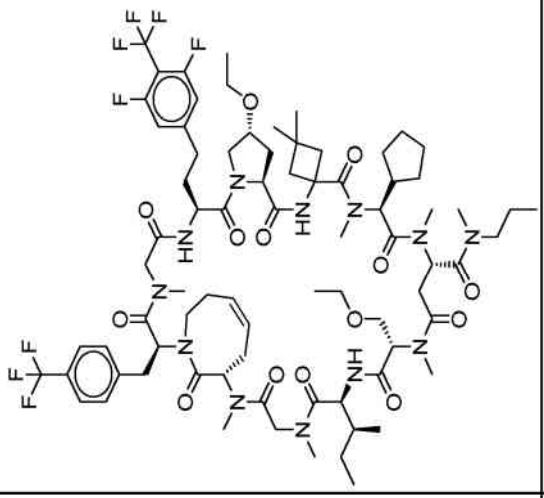
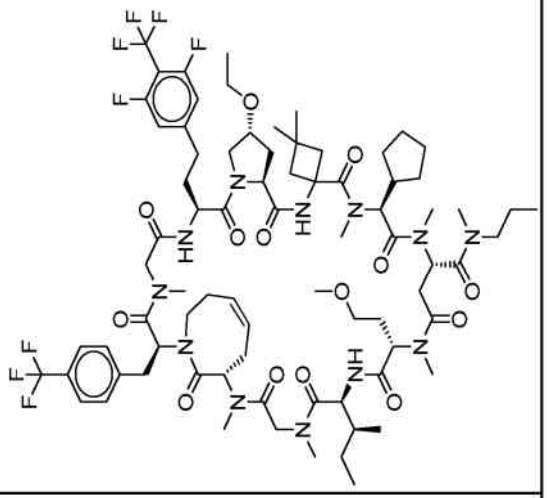
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PP201 1	PP201 3

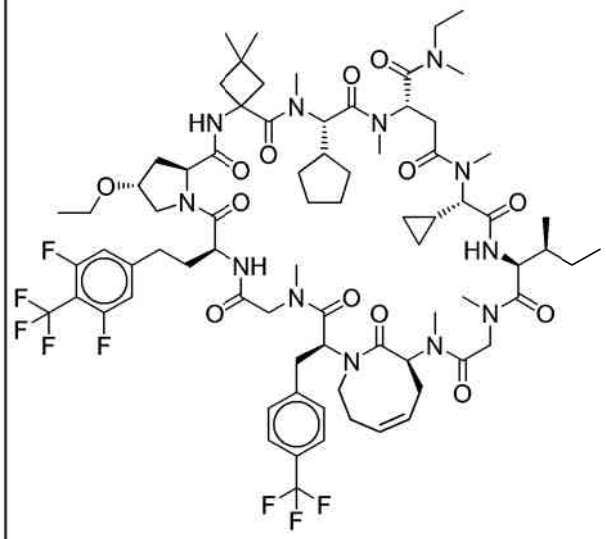
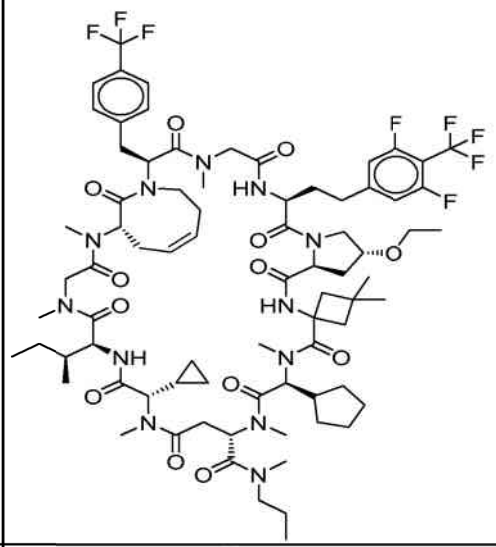
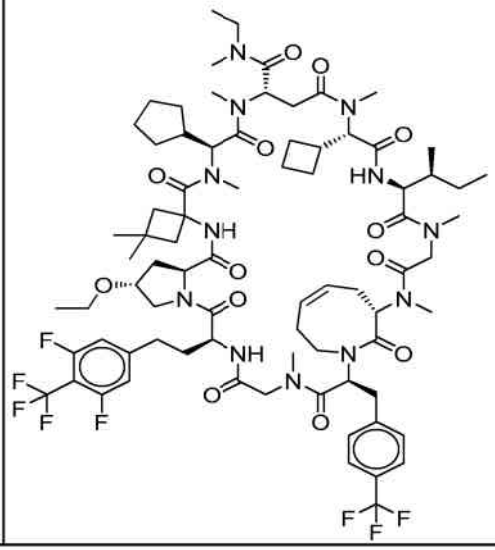
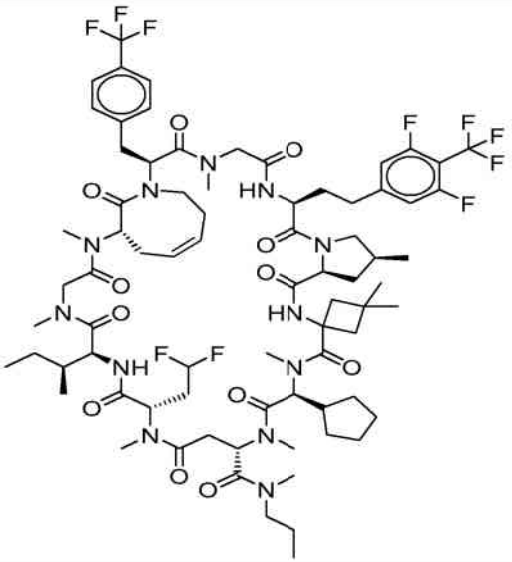
	
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PP201 5	PP201 7

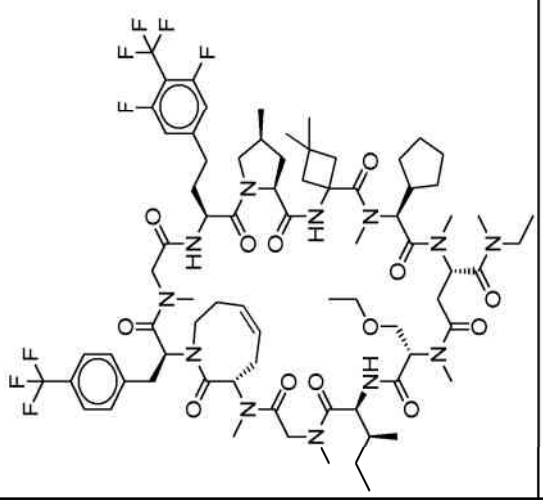
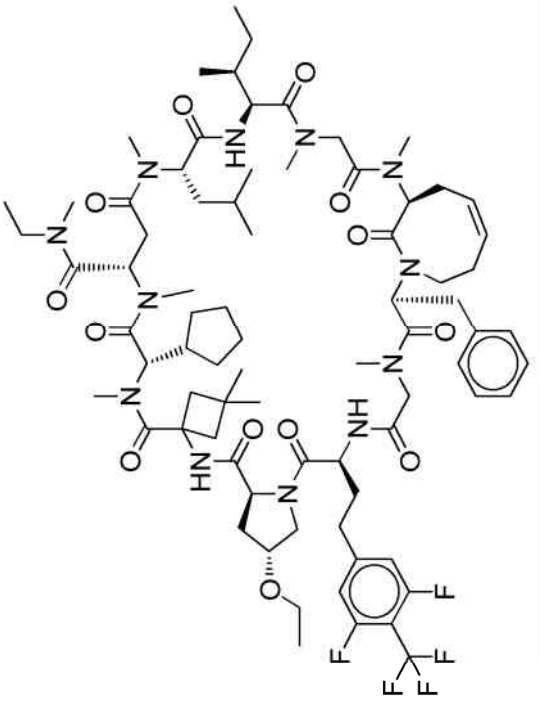
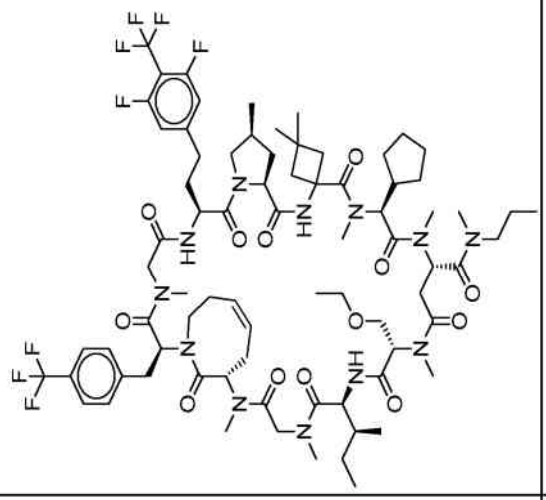
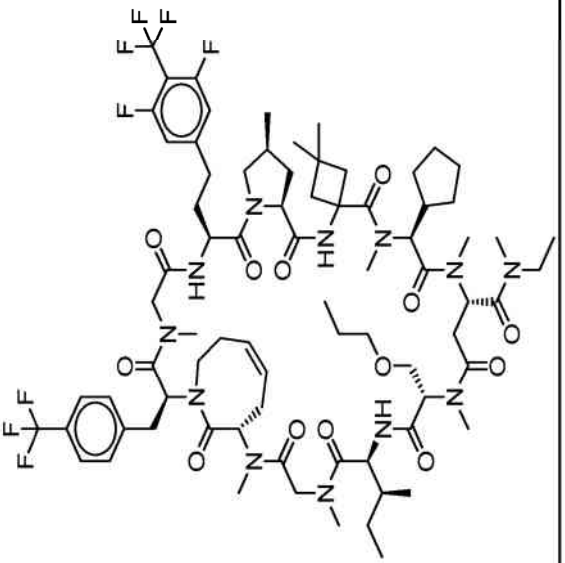
	
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PP202 3	PP202 5

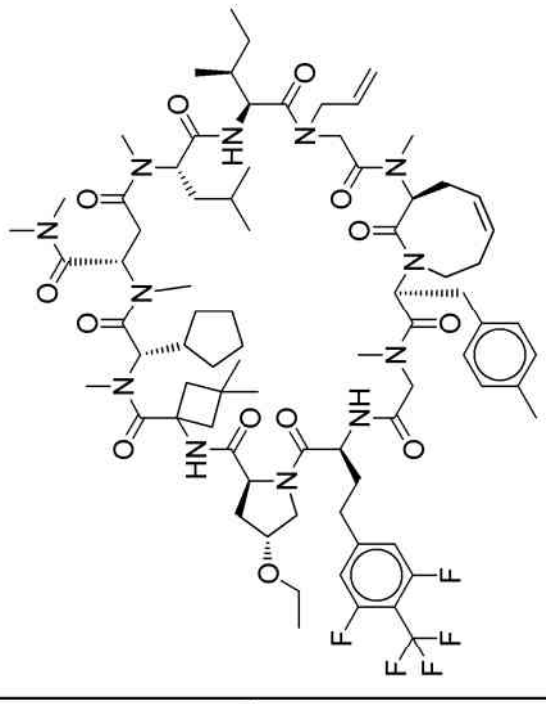
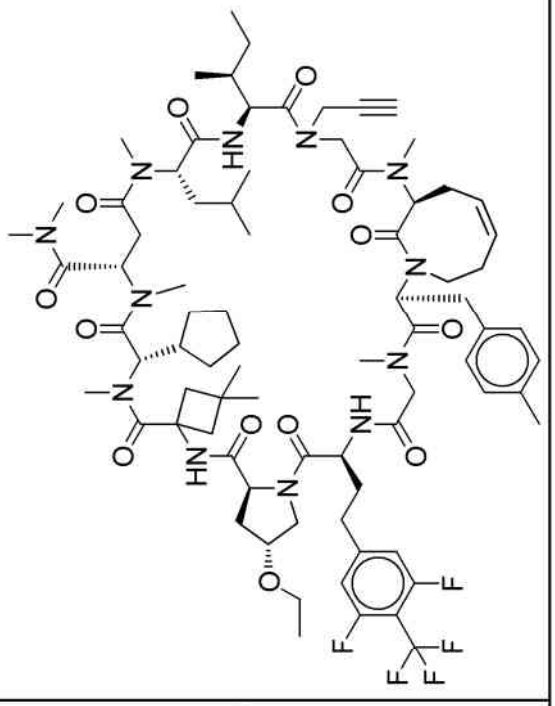
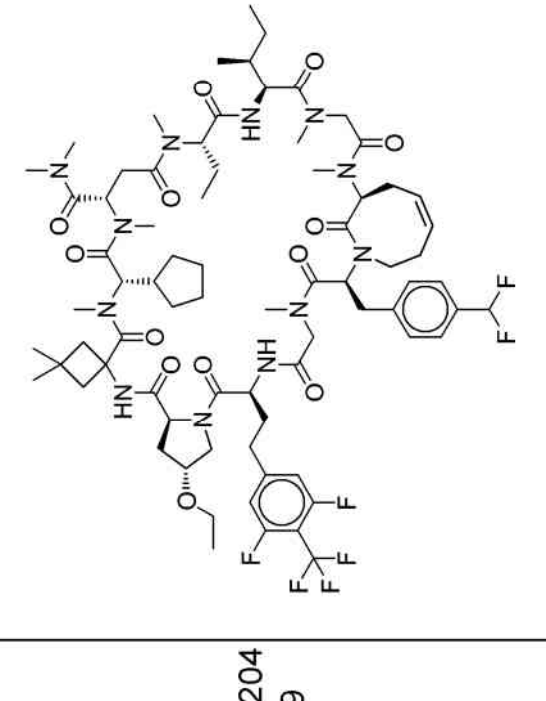
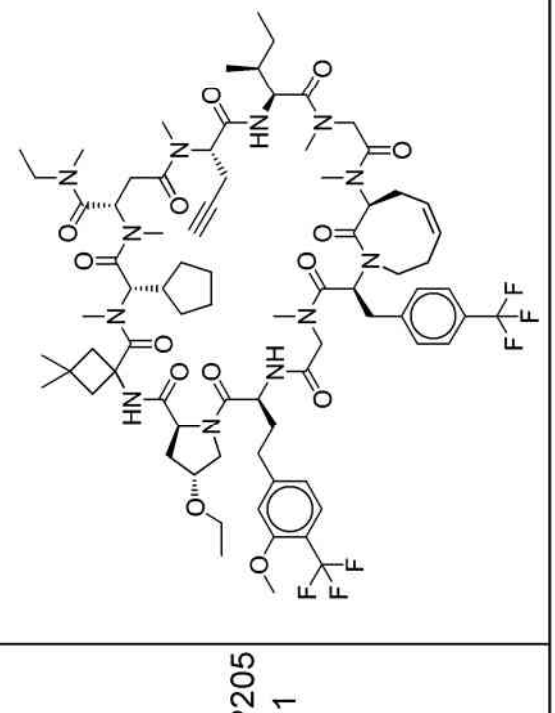
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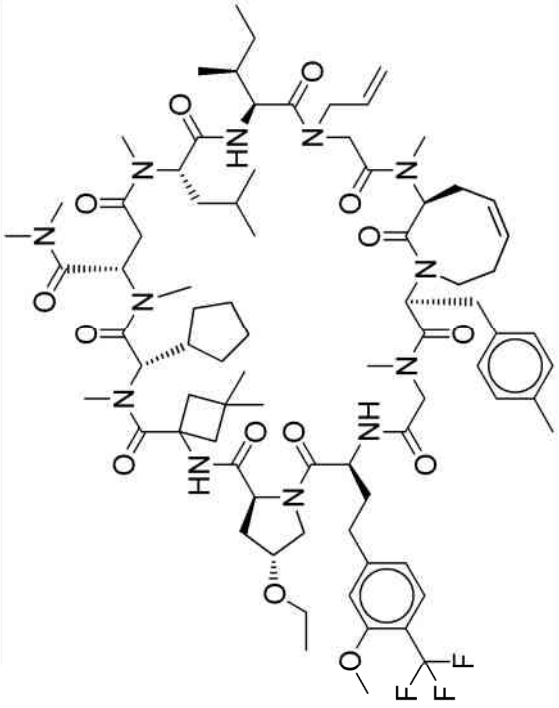
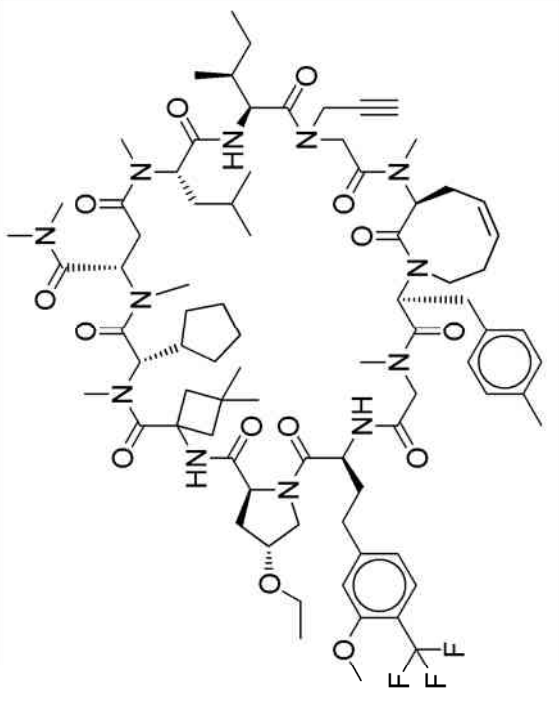
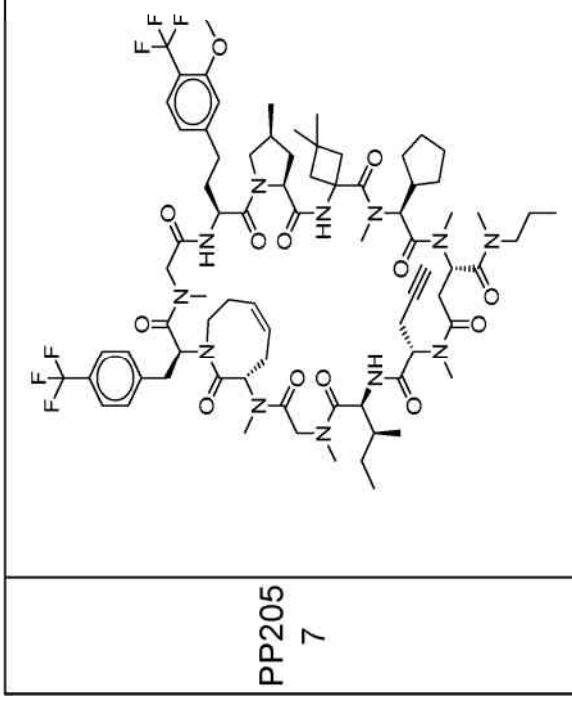
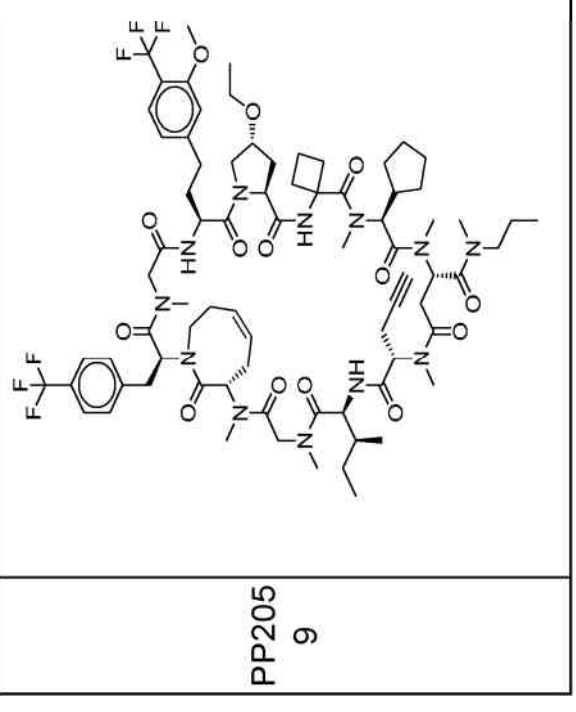
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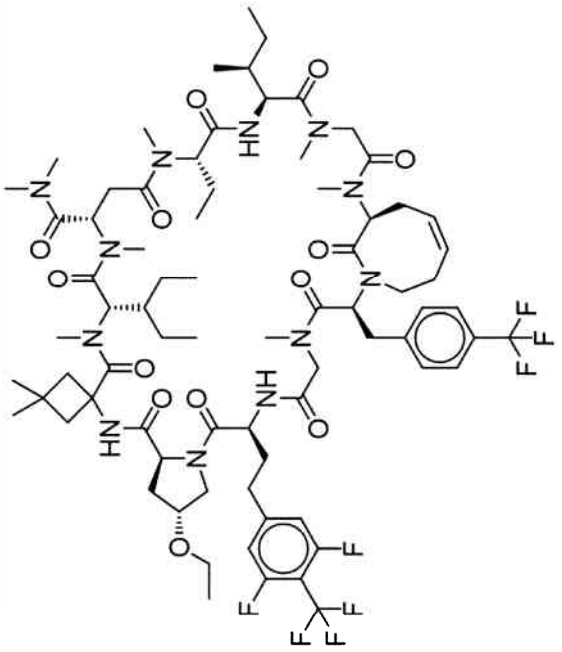
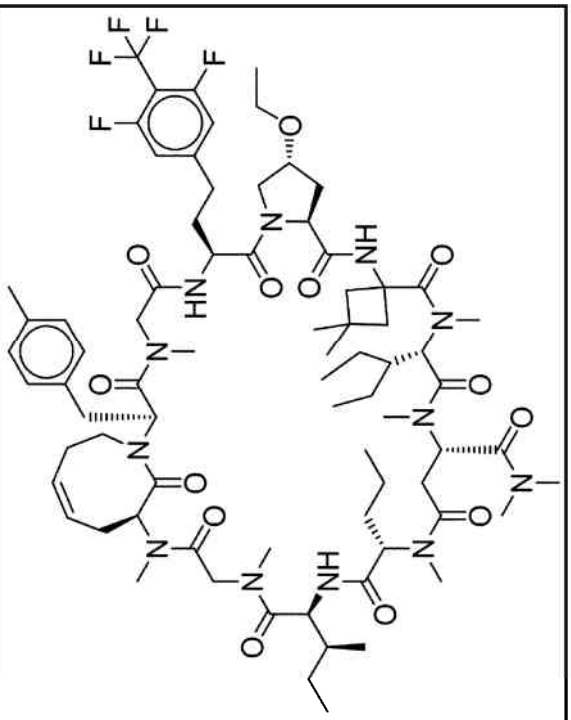
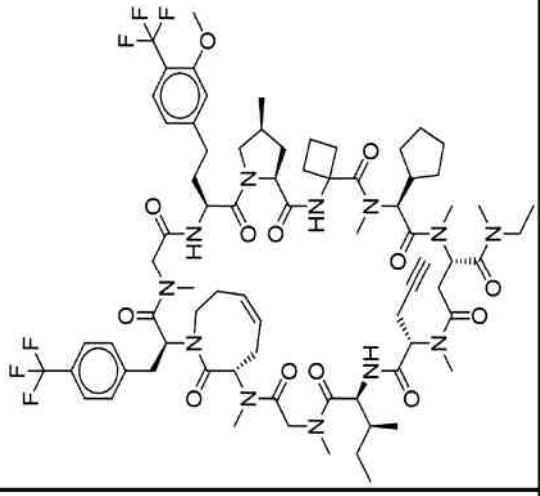
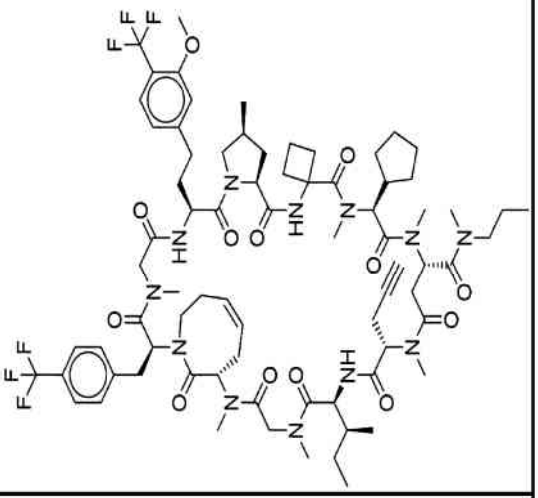
	
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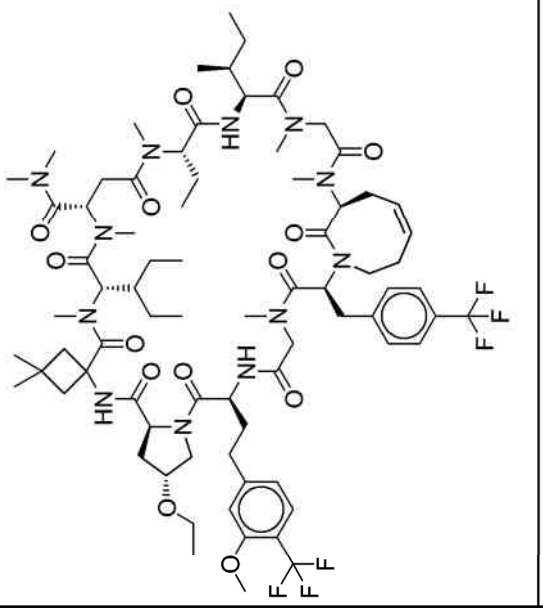
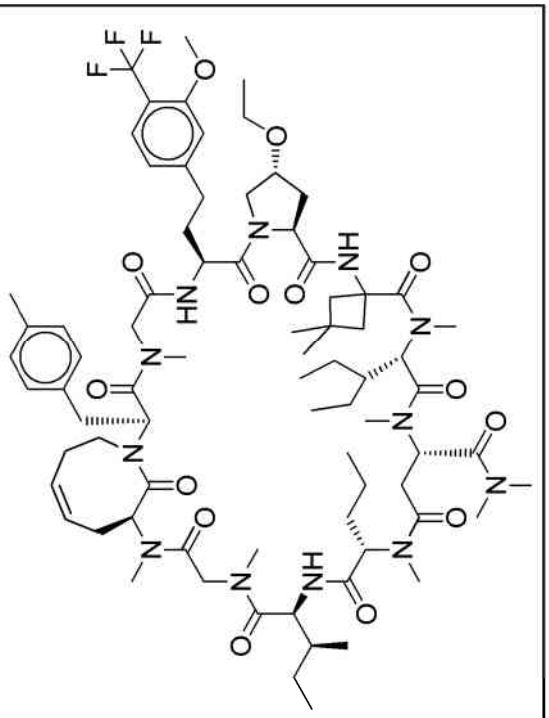
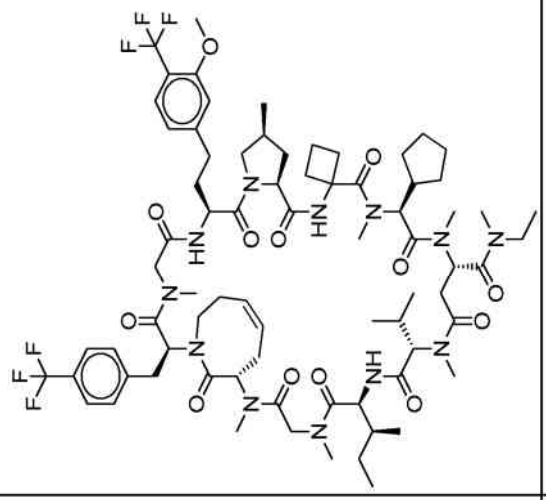
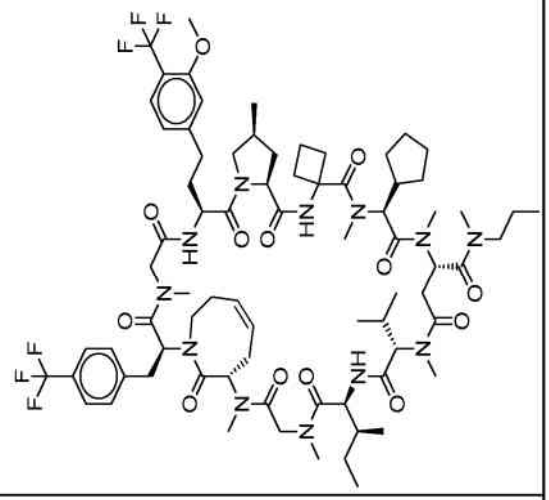
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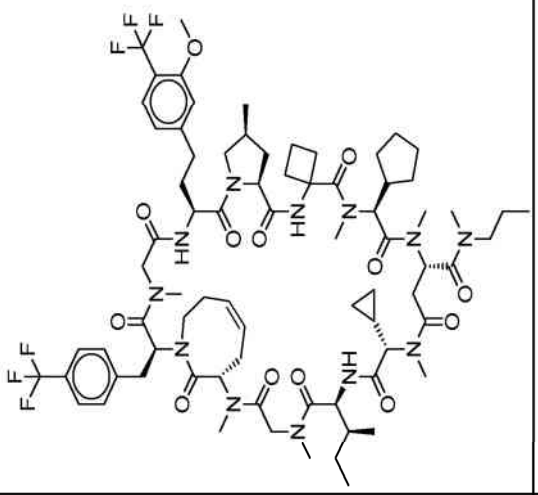
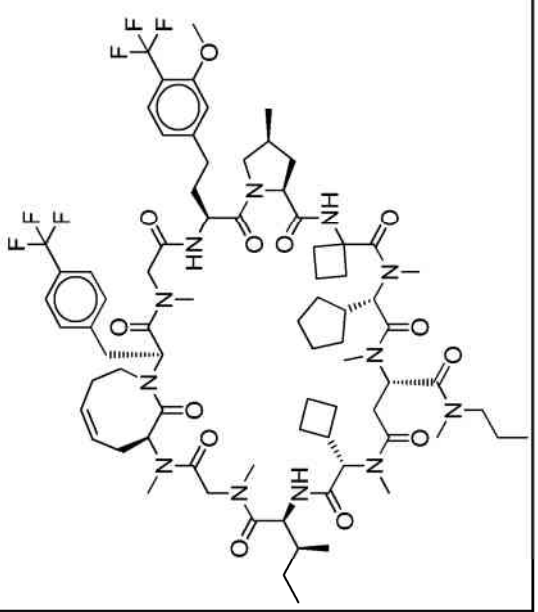
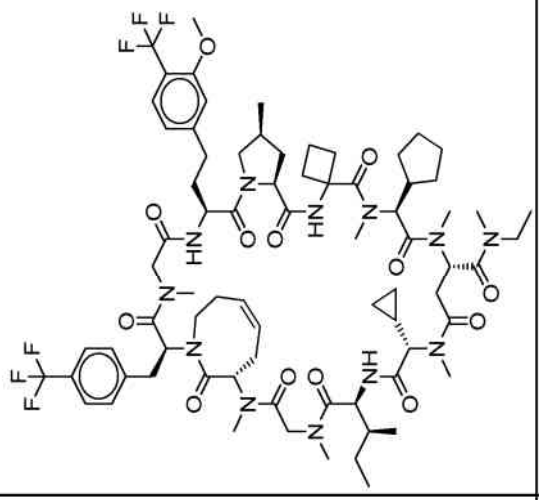
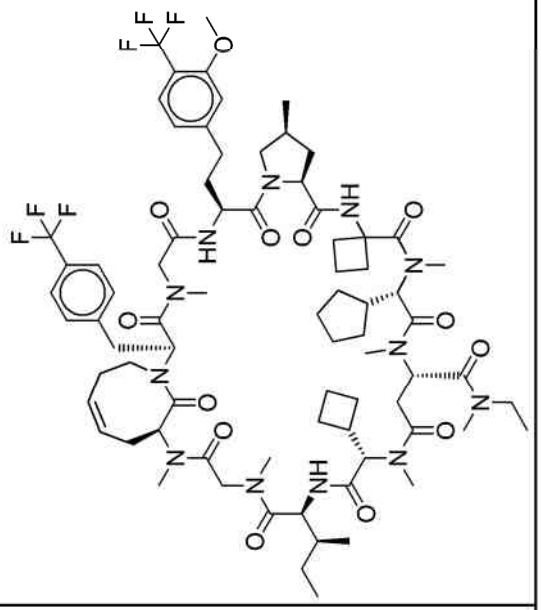
	
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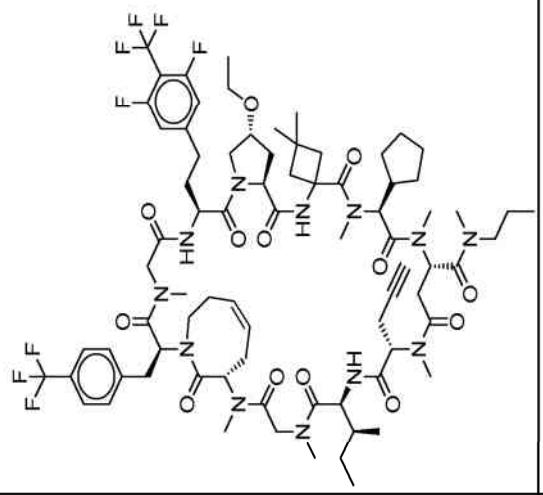
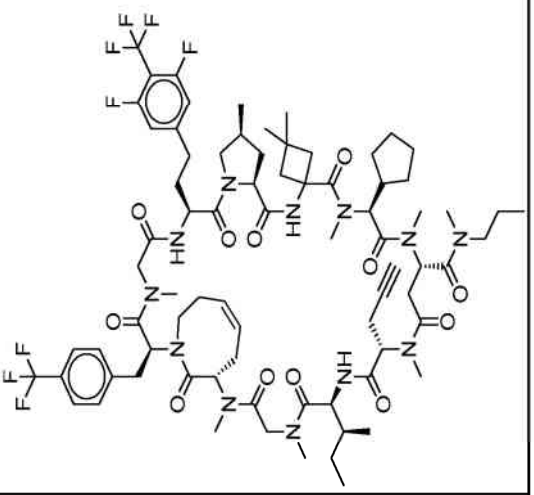
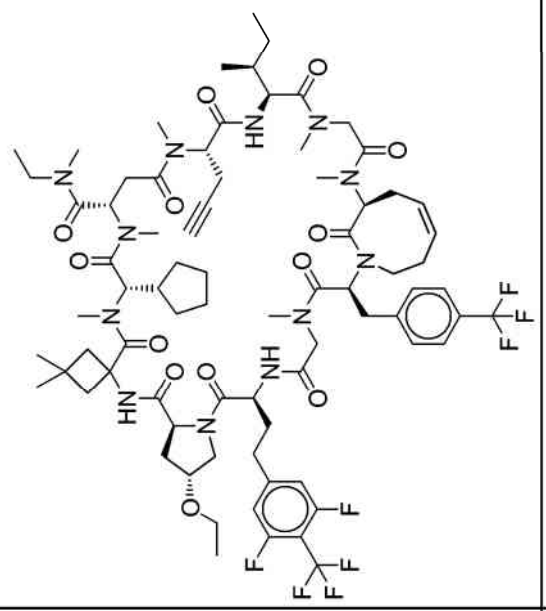
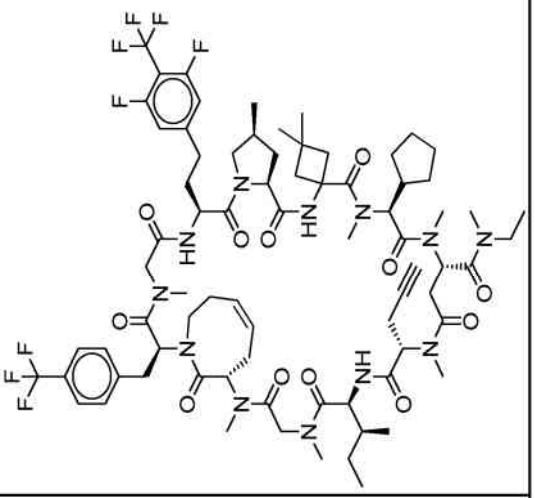
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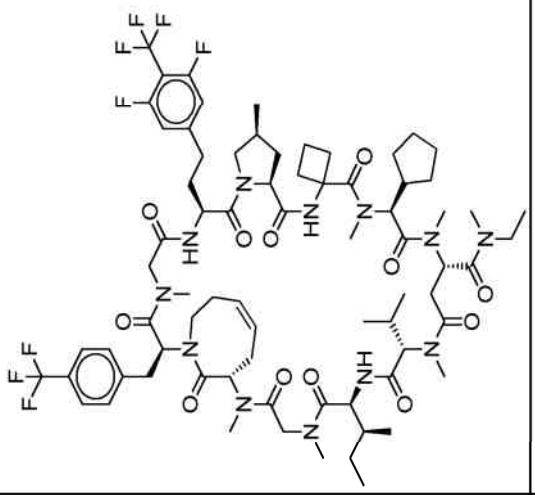
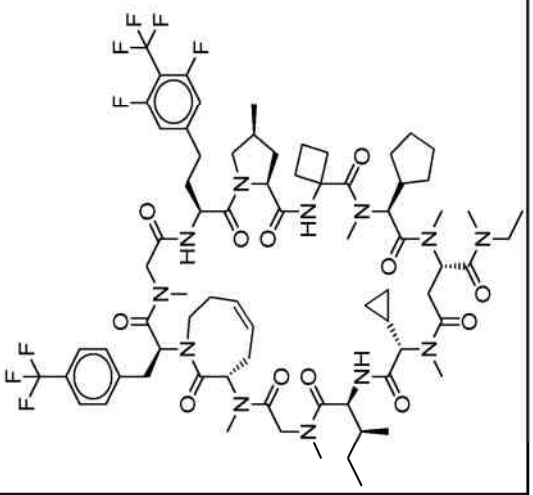
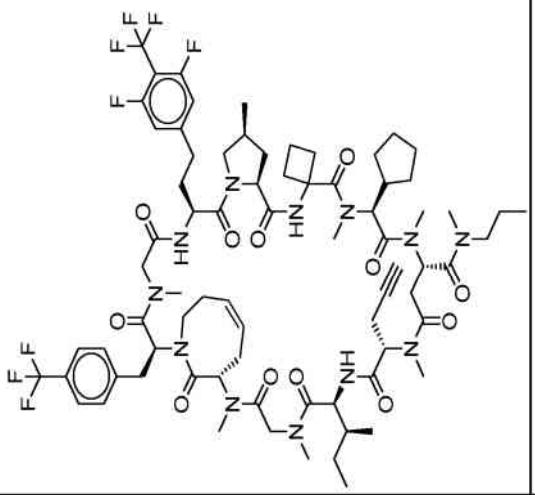
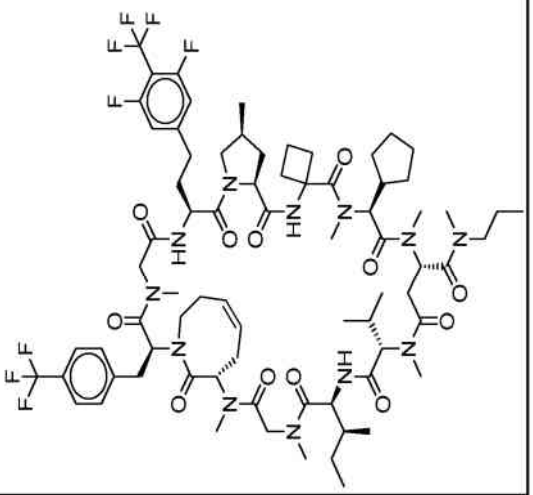
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PP2057	PP2059
	

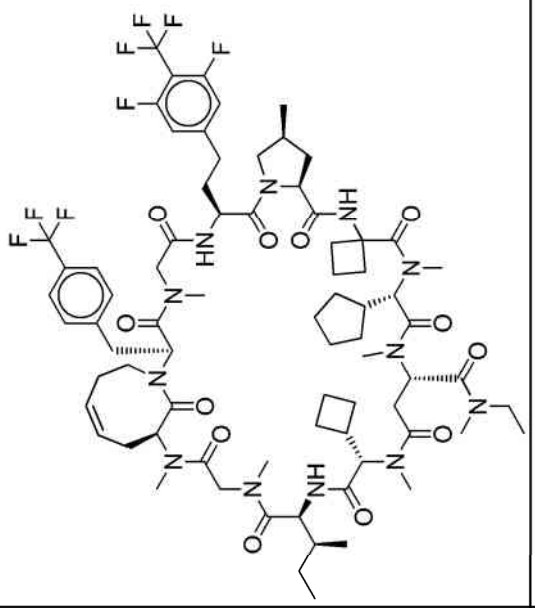
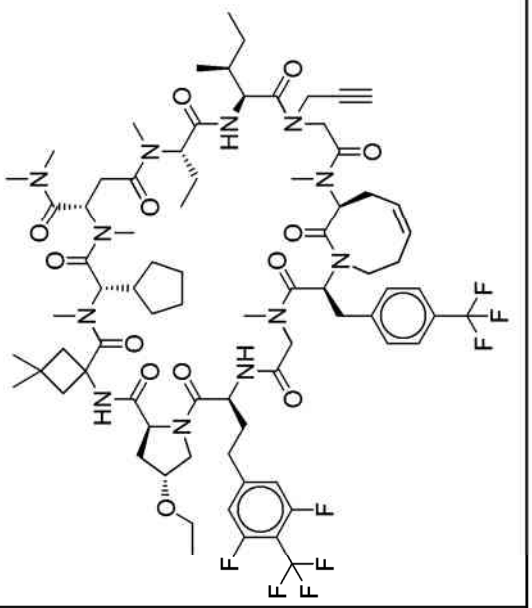
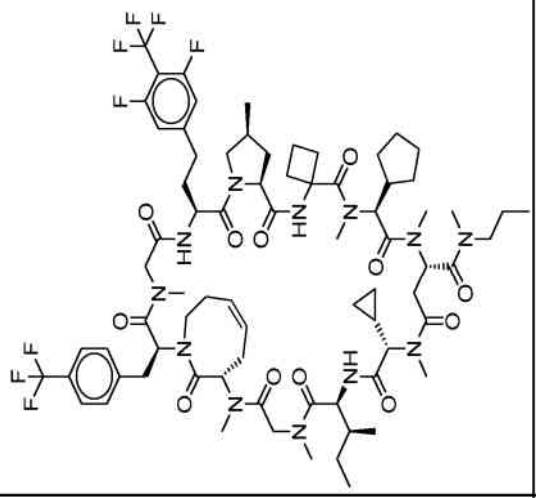
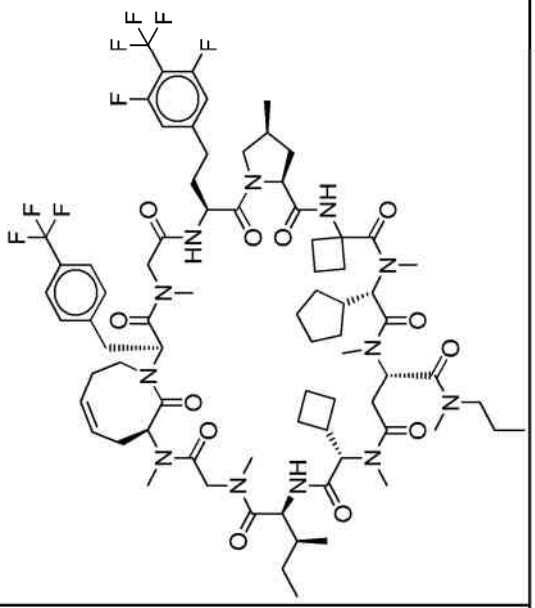
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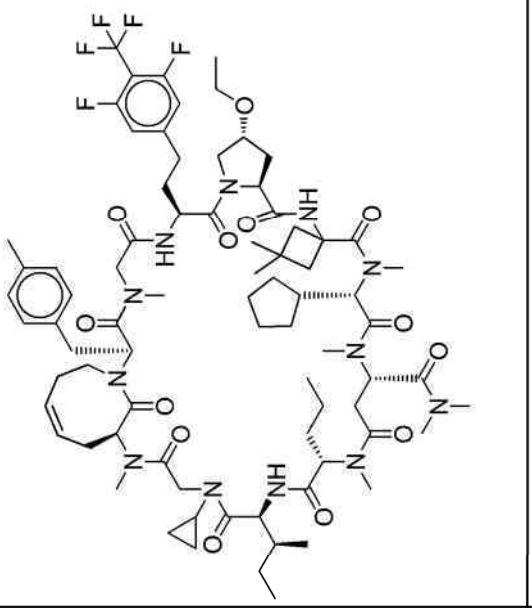
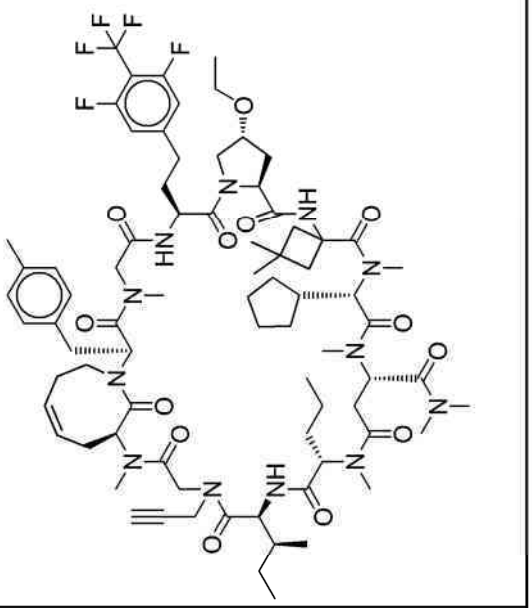
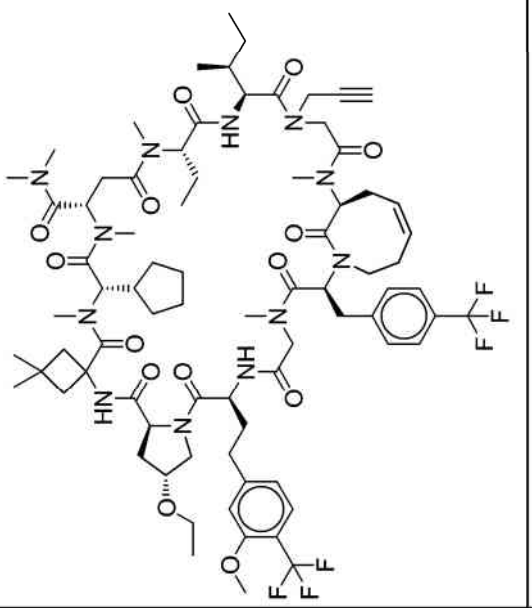
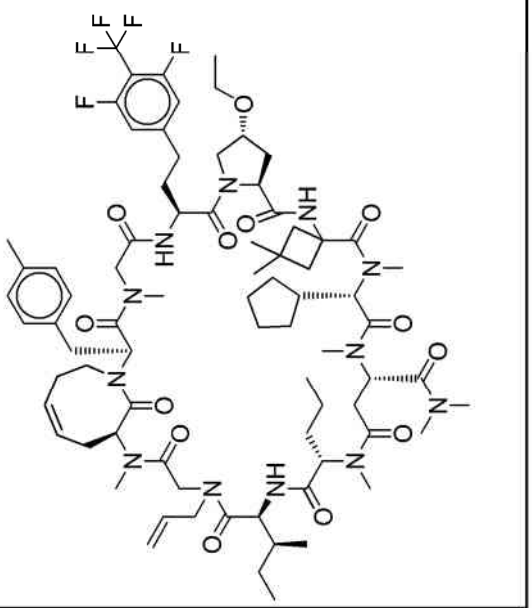
	
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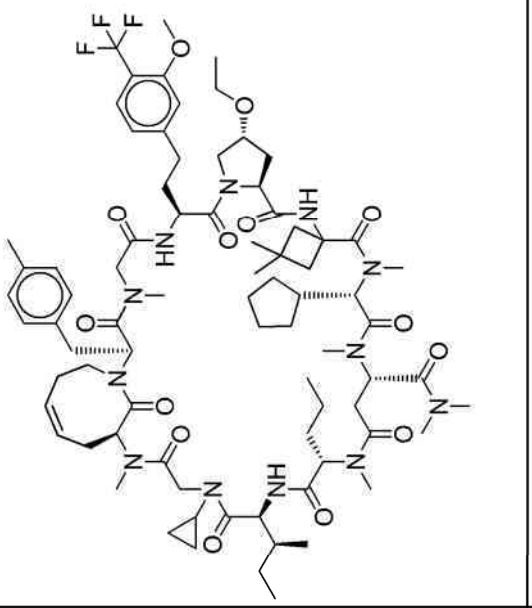
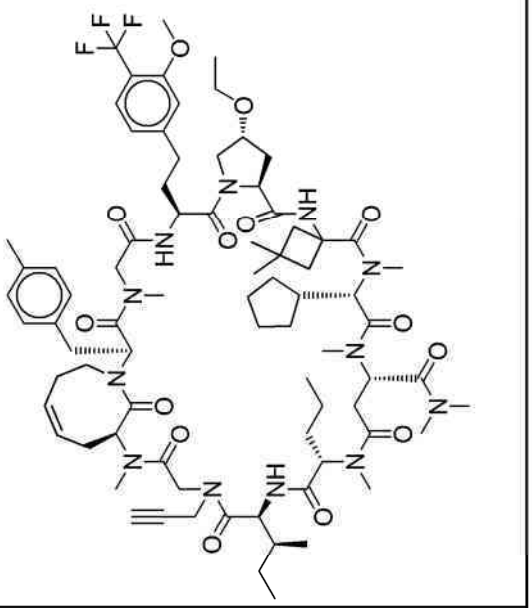
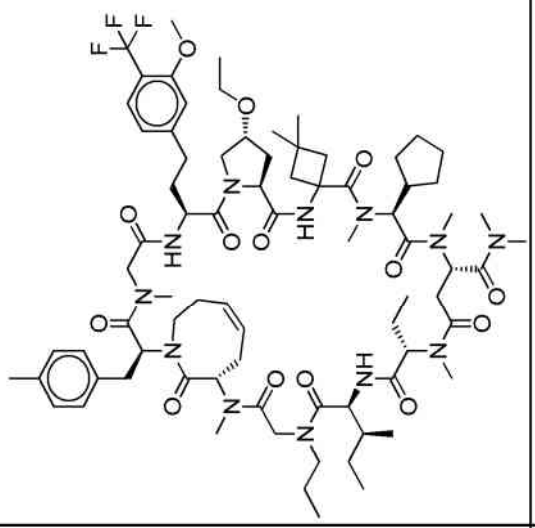
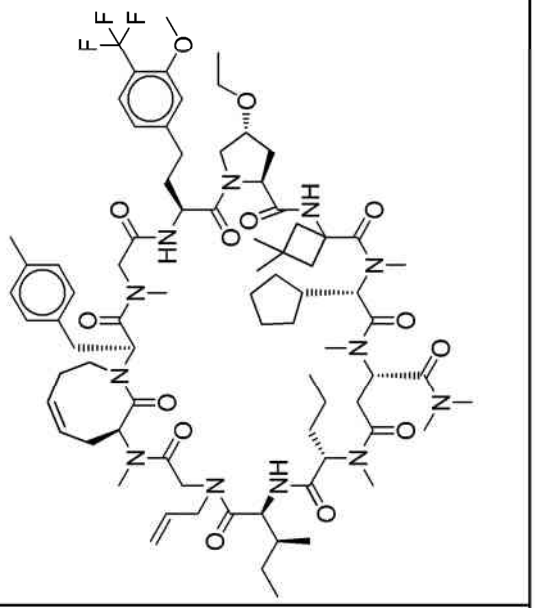
	
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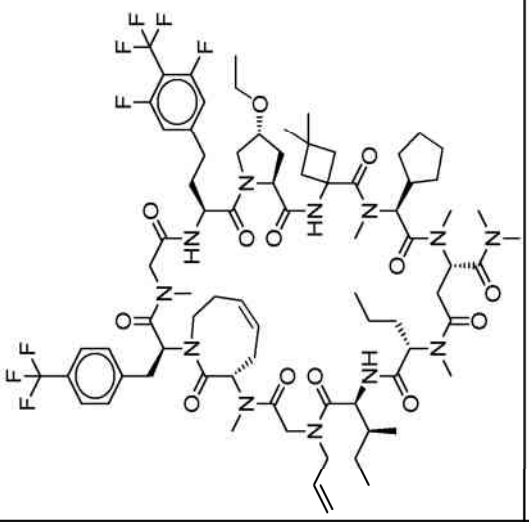
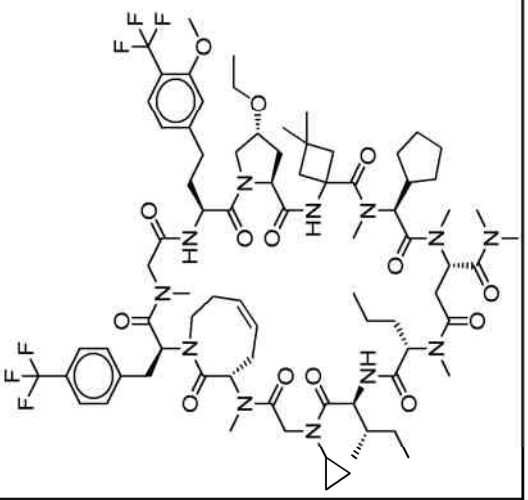
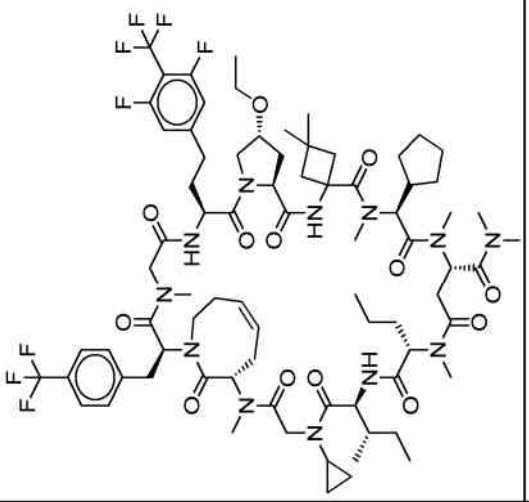
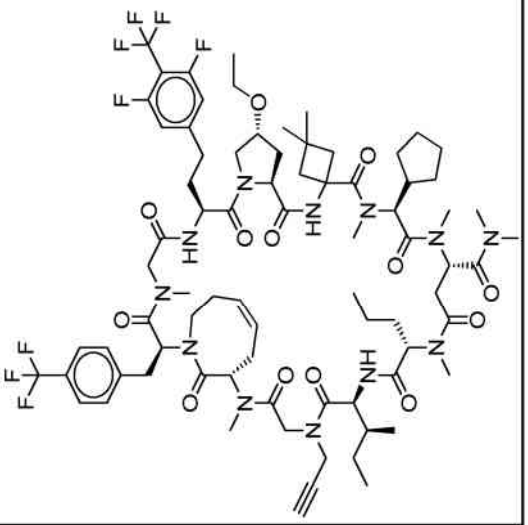
	
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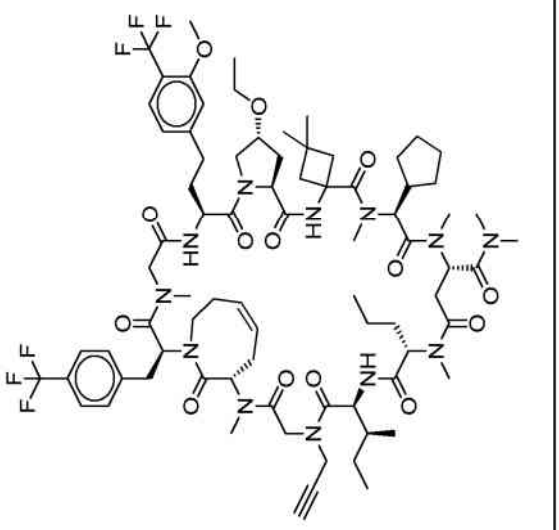
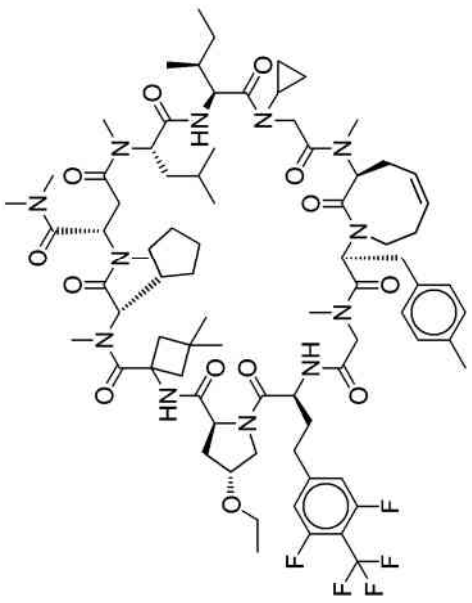
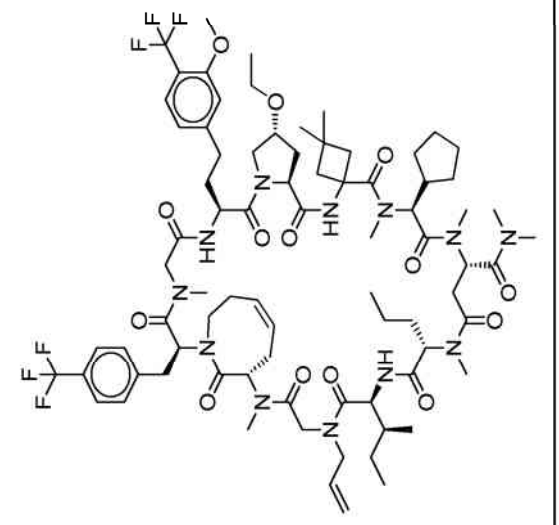
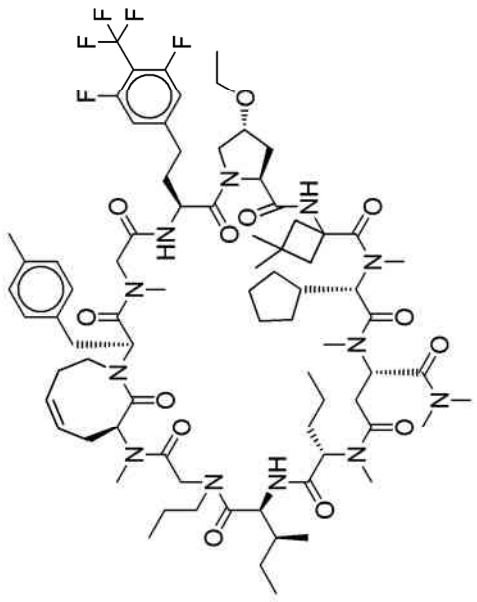
	
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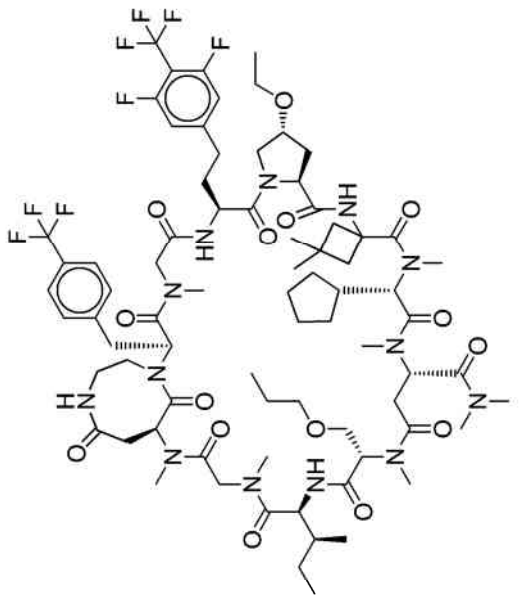
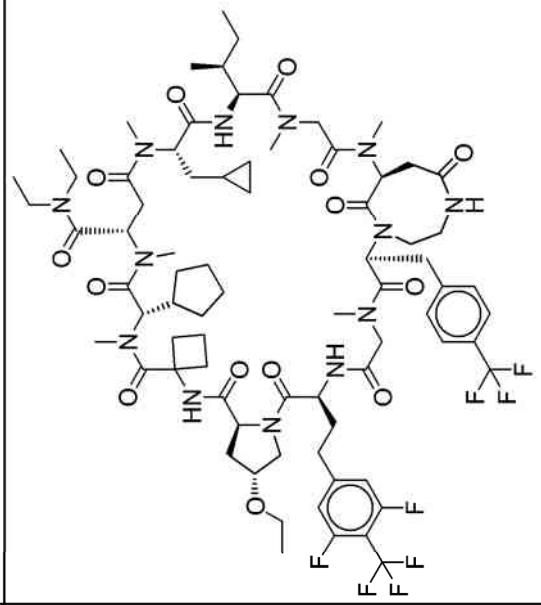
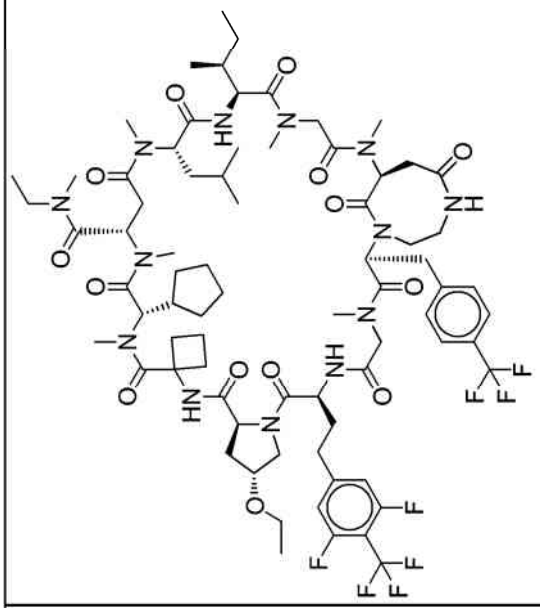
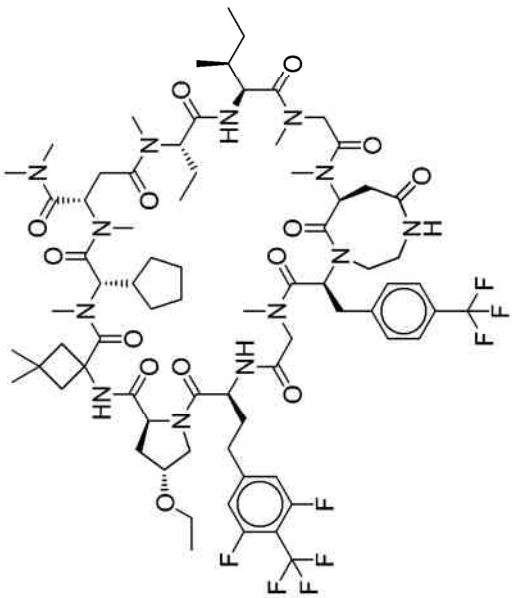
	
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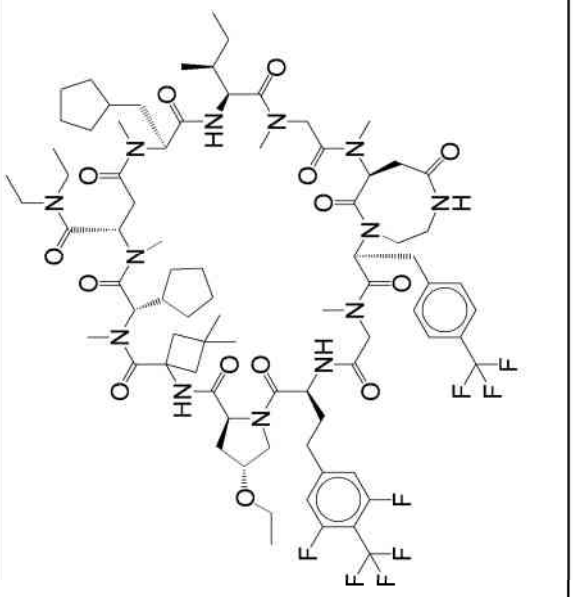
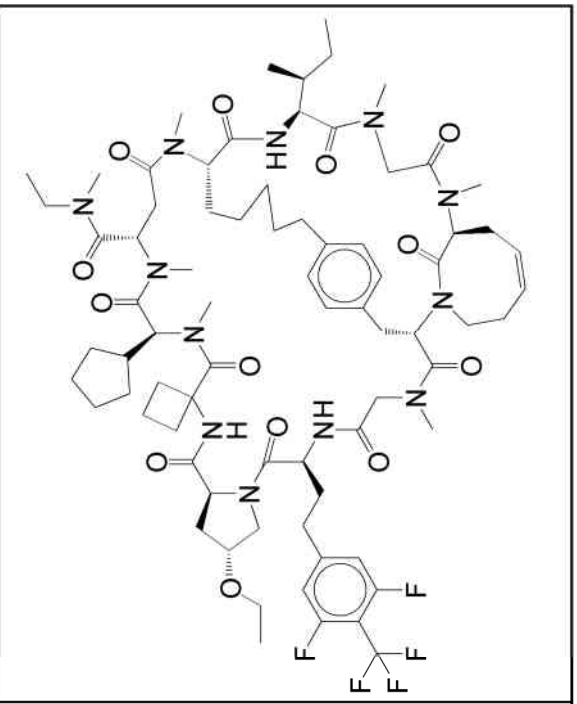
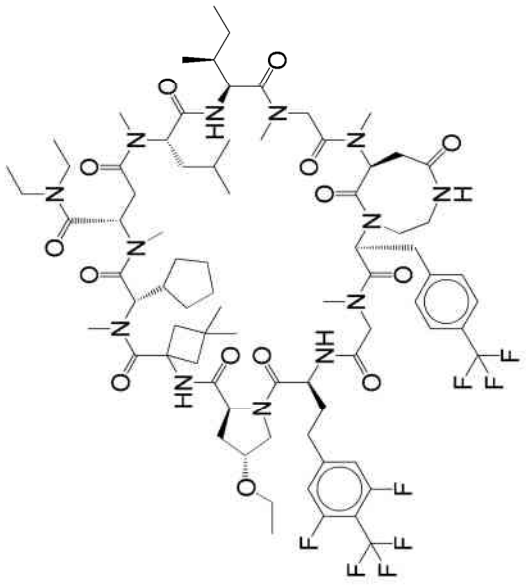
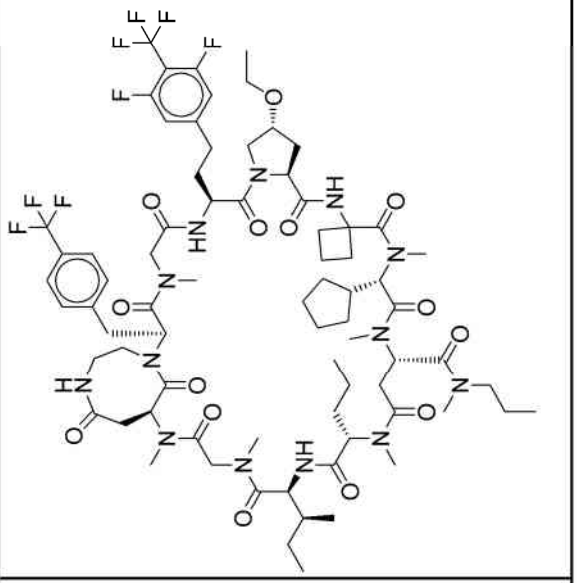
	
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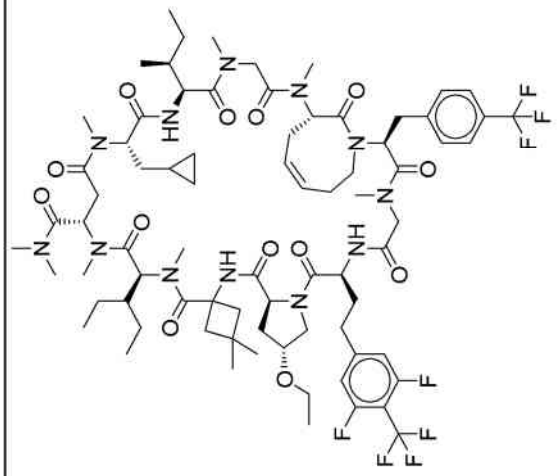
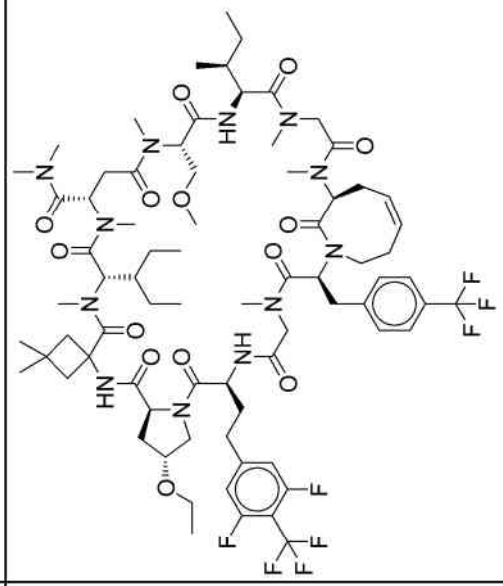
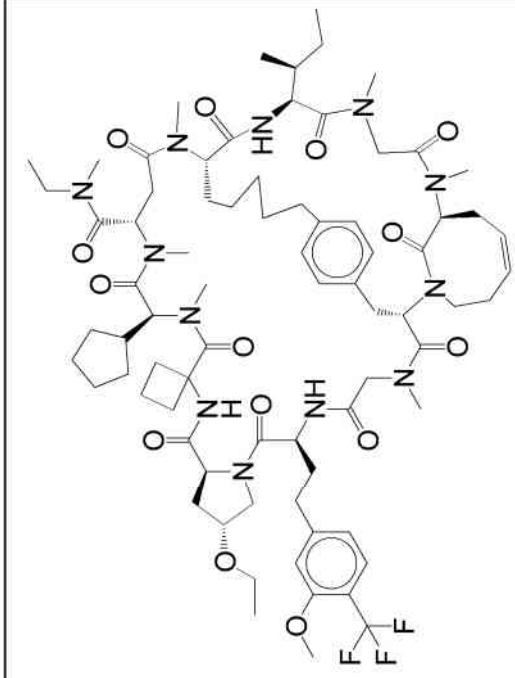
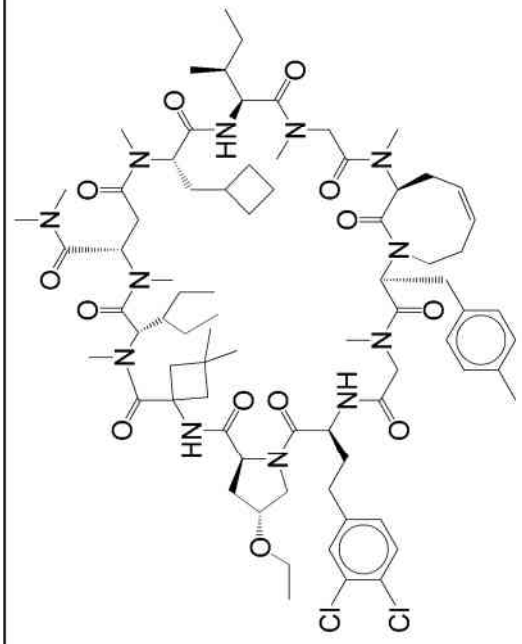
	
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PP209 6	PP209 8

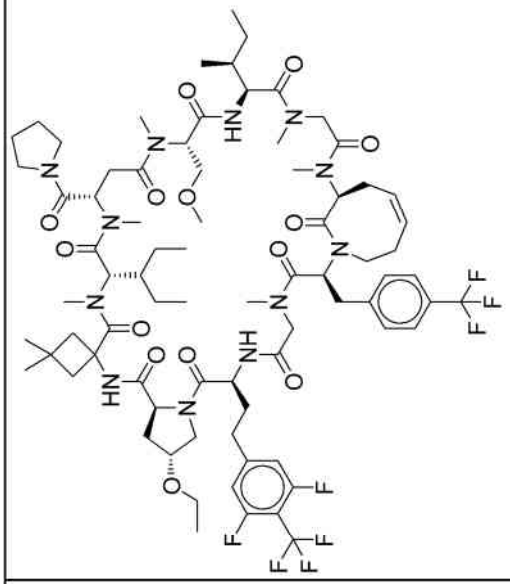
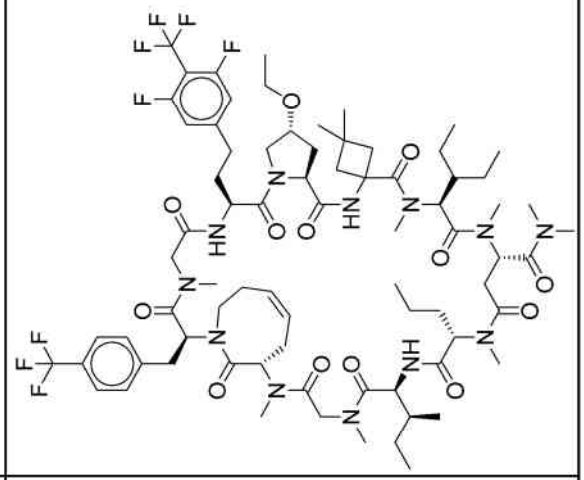
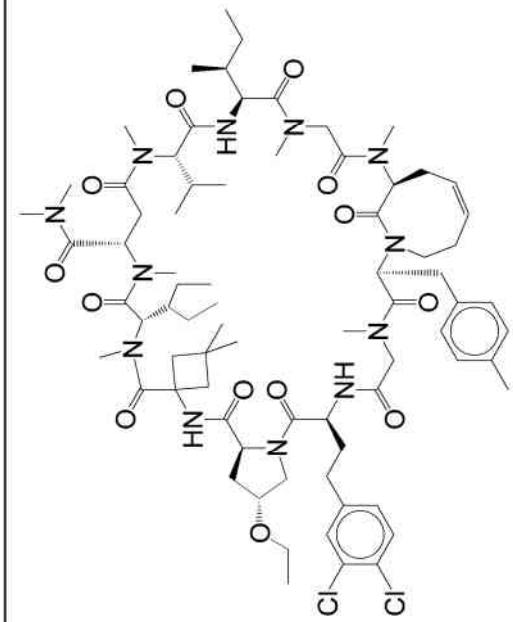
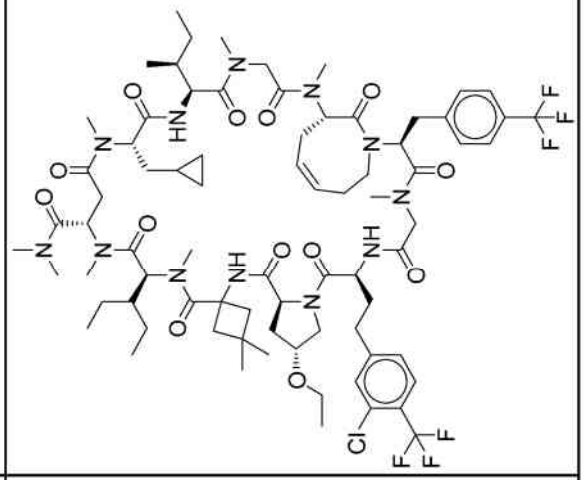
	
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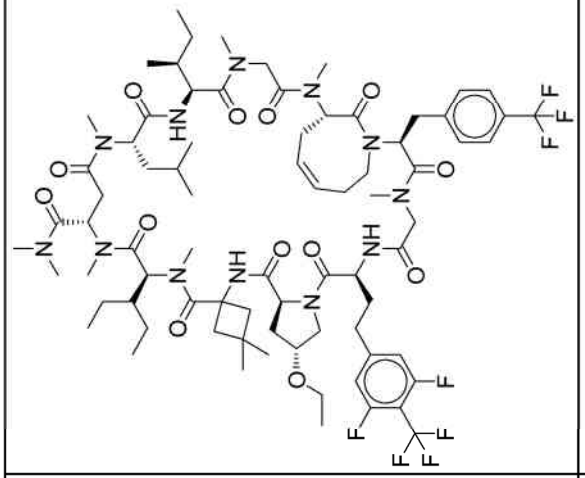
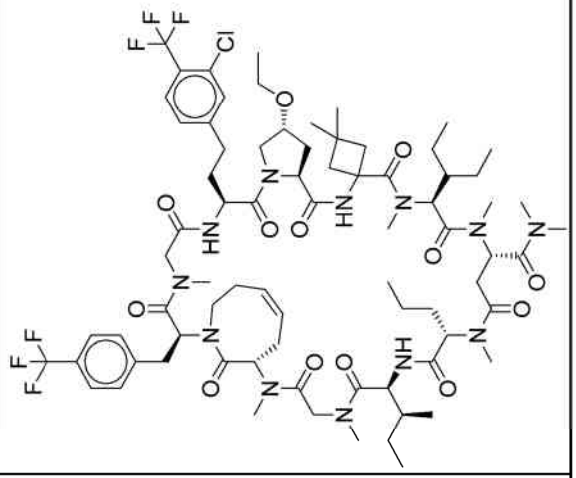
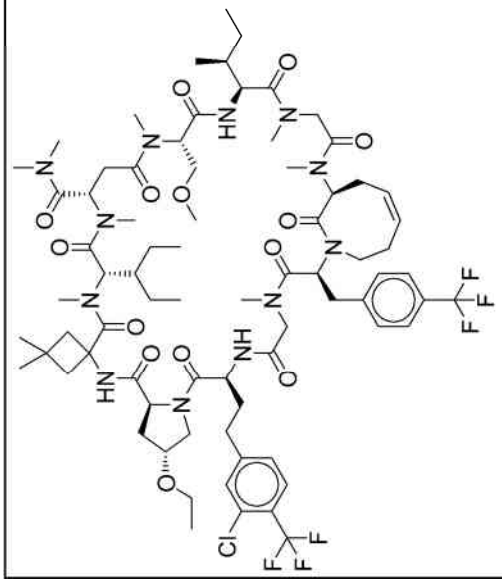
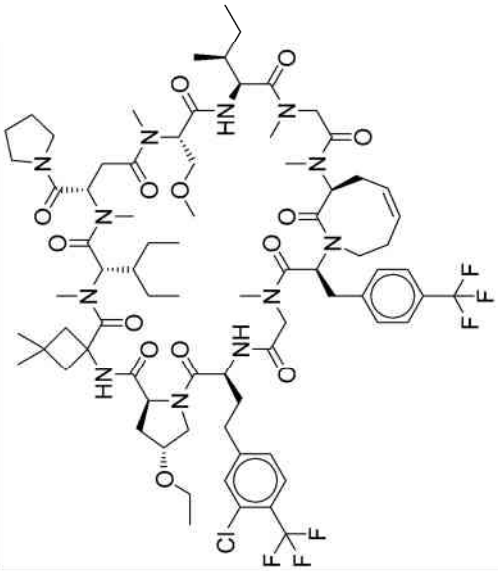
	
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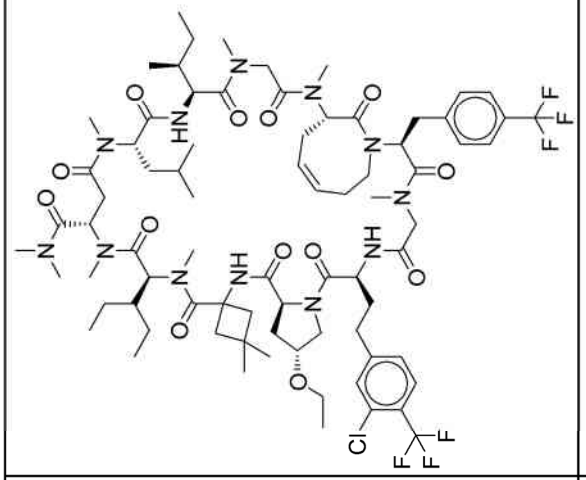
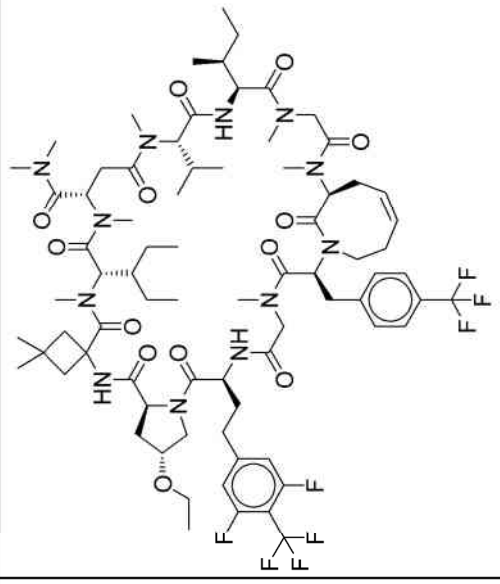
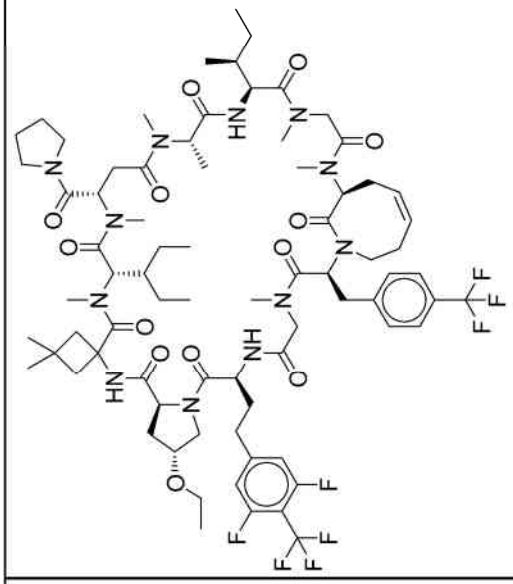
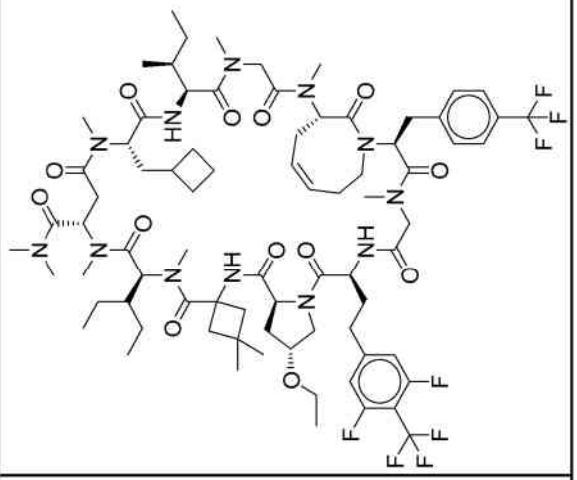
	
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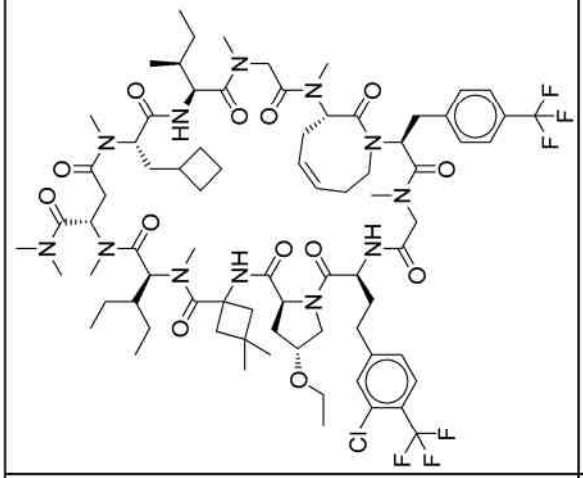
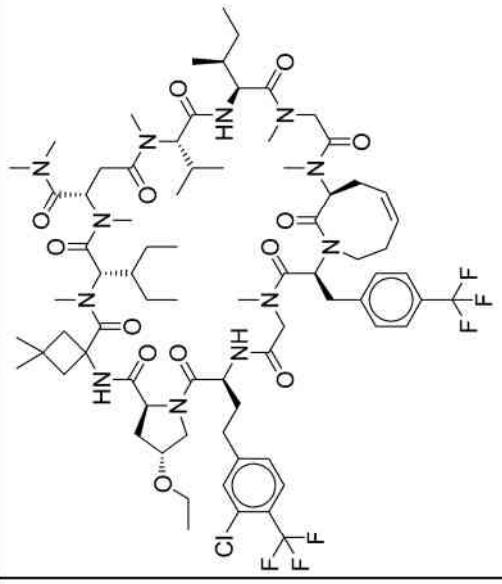
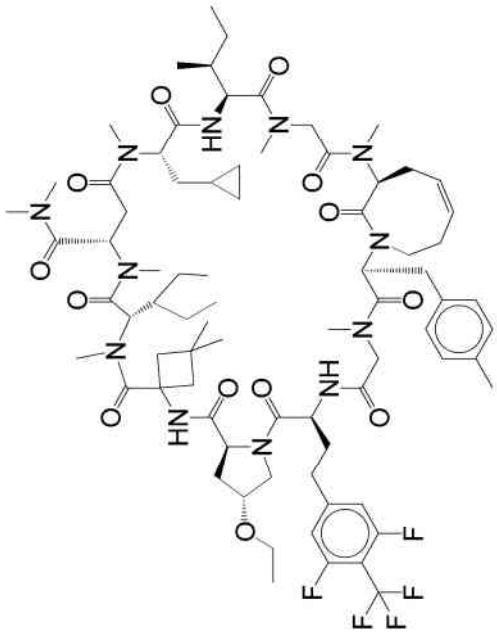
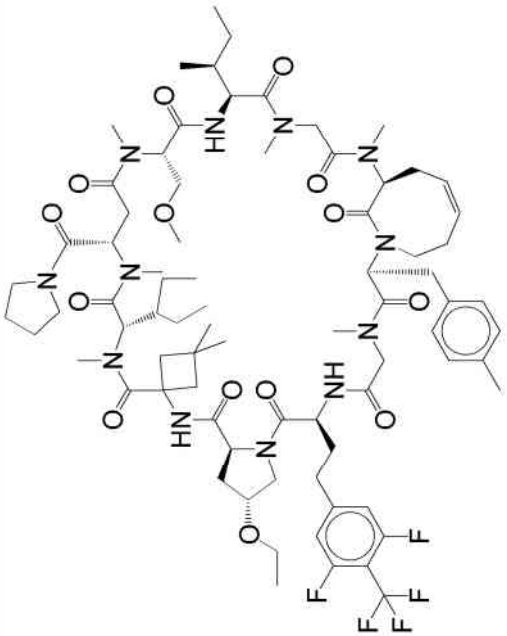
	
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PP211 4	PP211 6

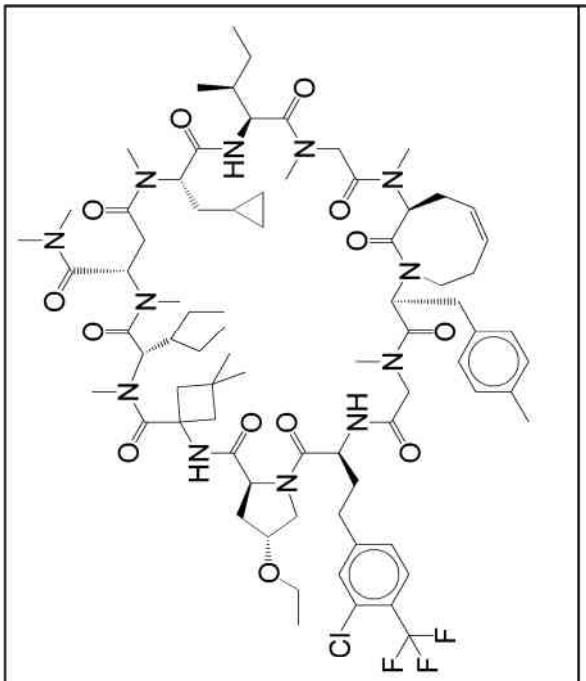
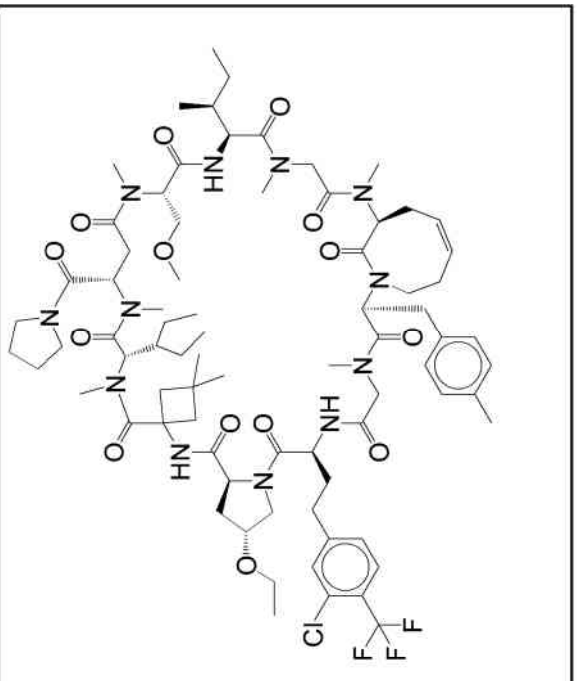
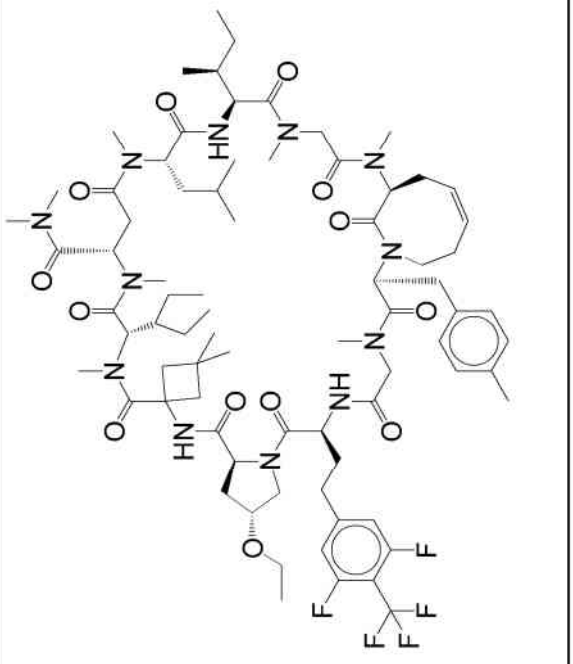
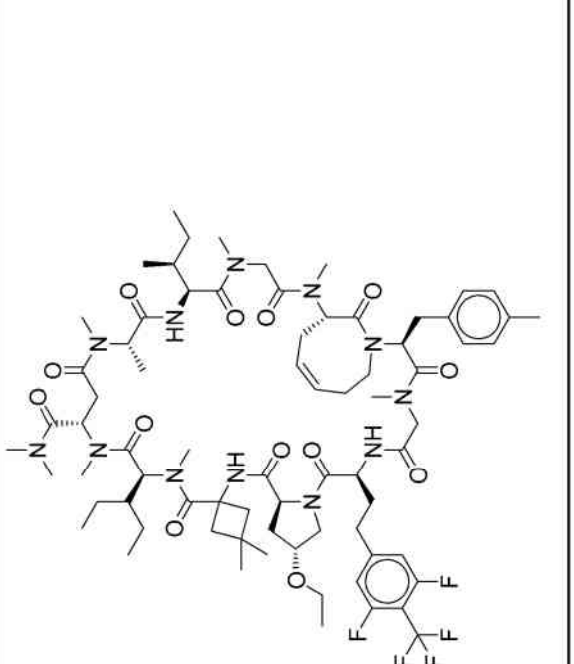
	
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PP2118	PP2120

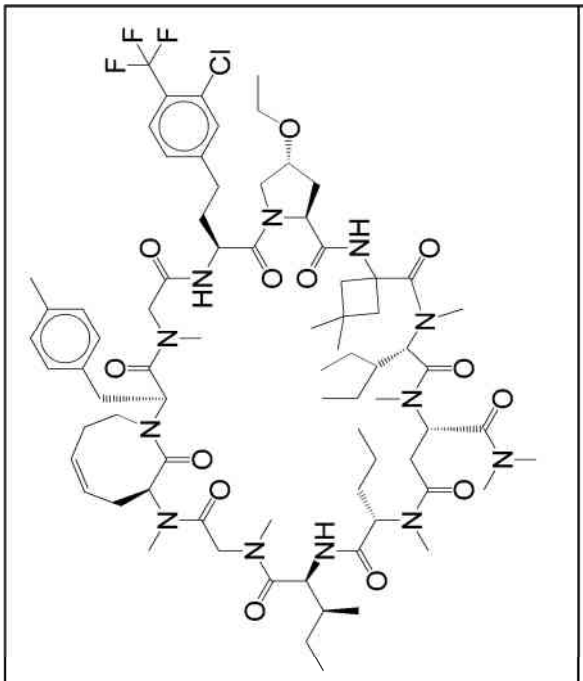
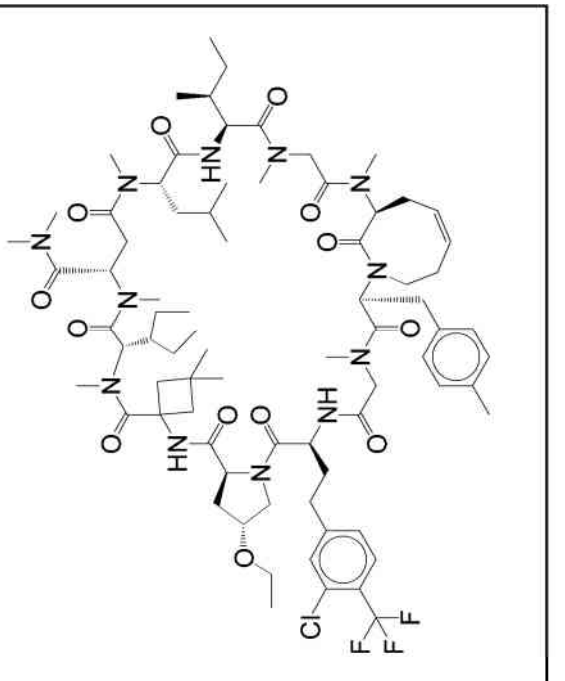
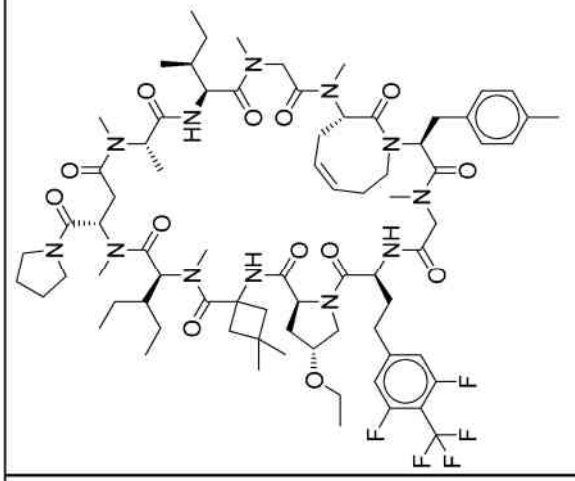
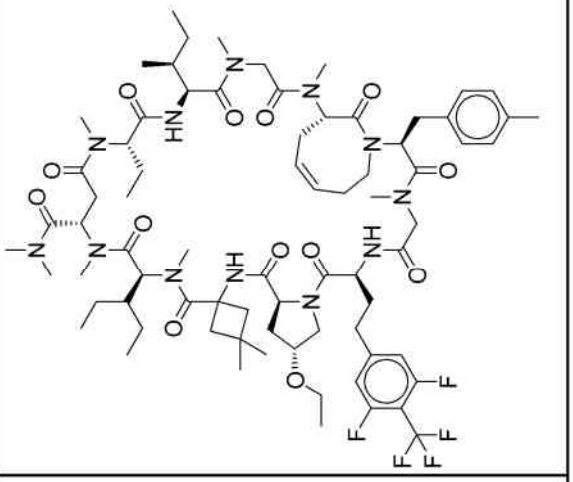
	
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PP212 2	PP212 4

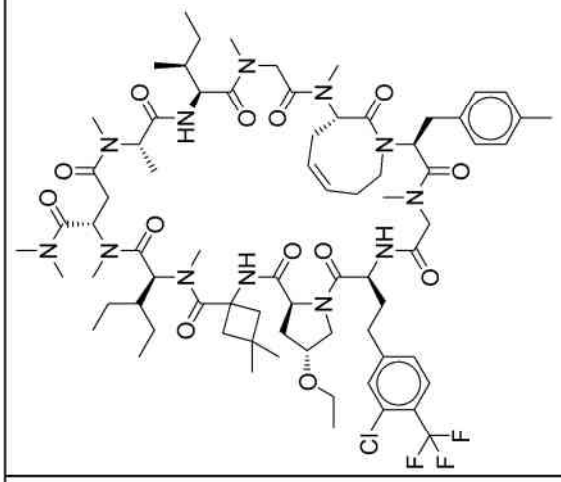
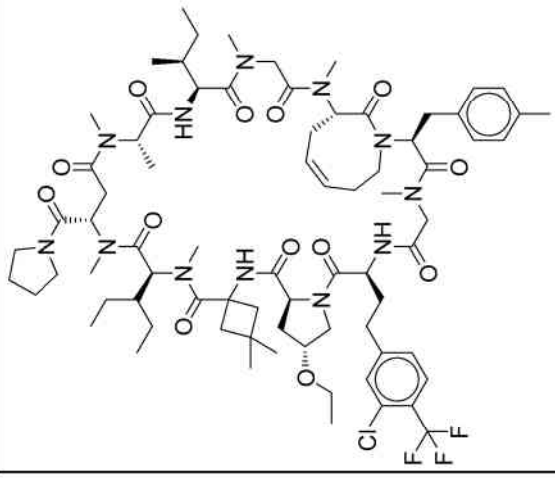
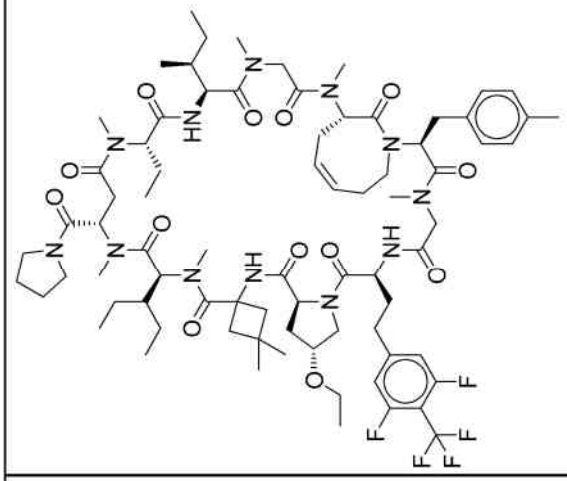
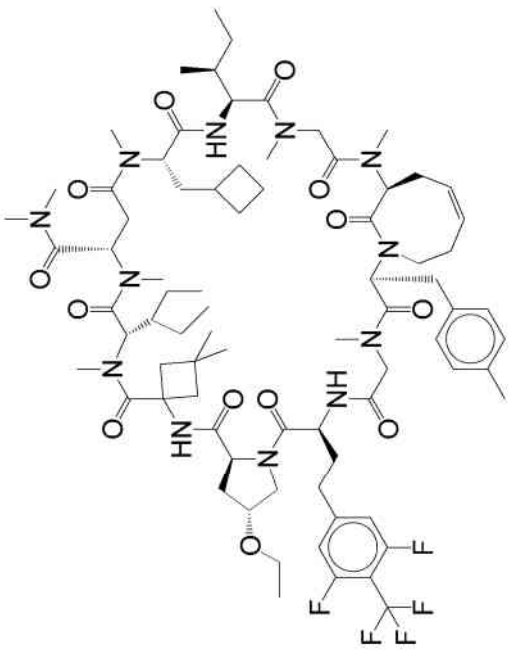
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PP2126	PP2128
	

	
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PP213 1	PP213 3

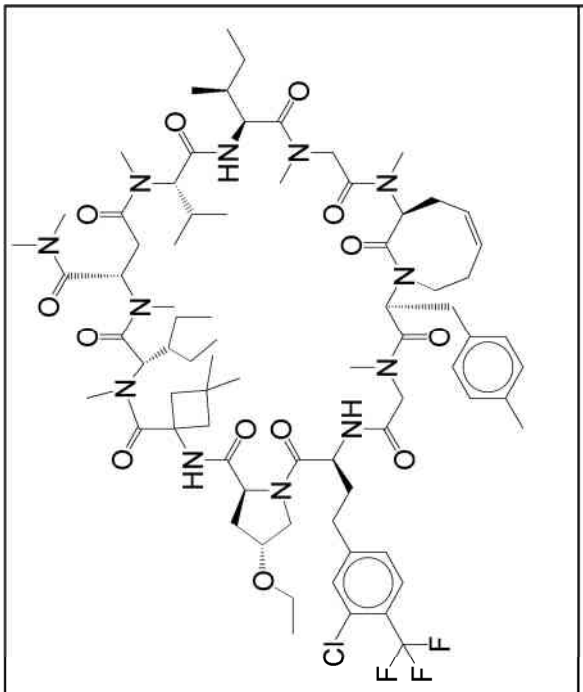
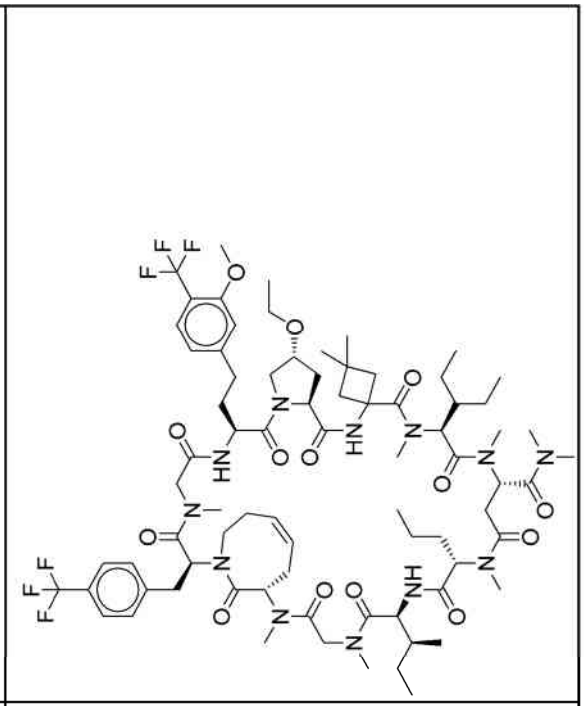
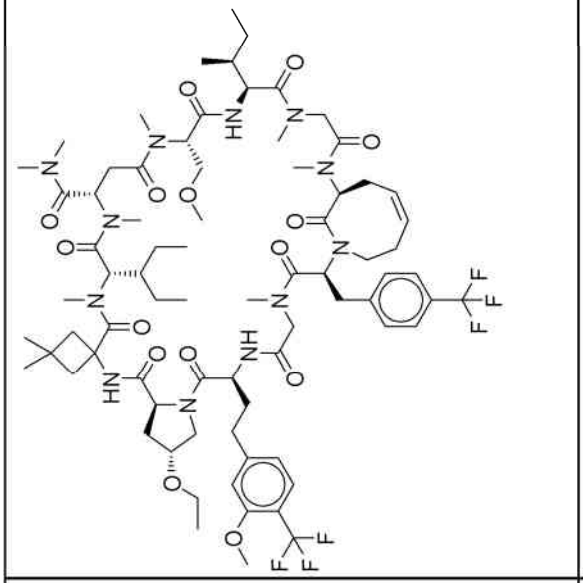
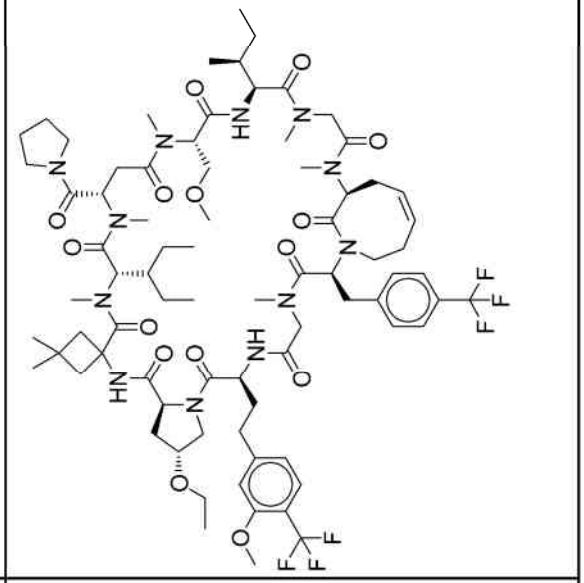
	
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PP2137	PP2139

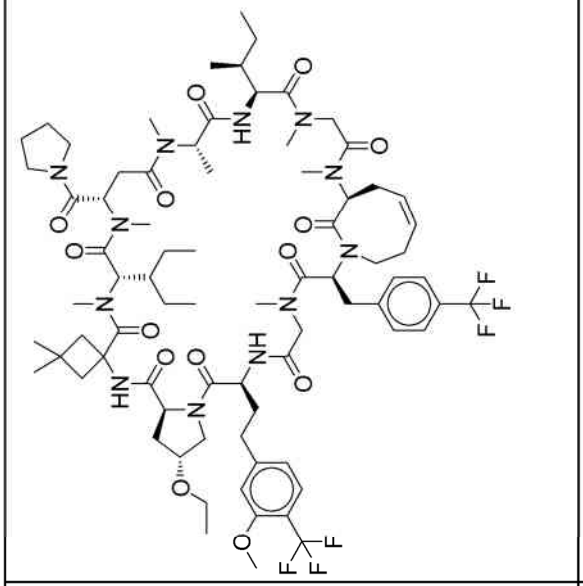
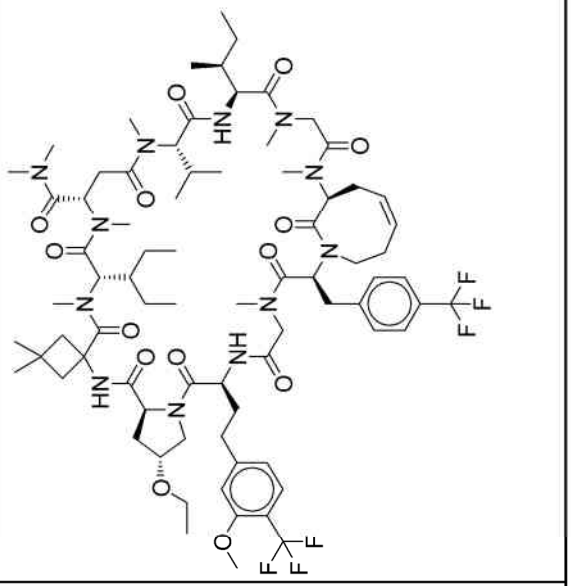
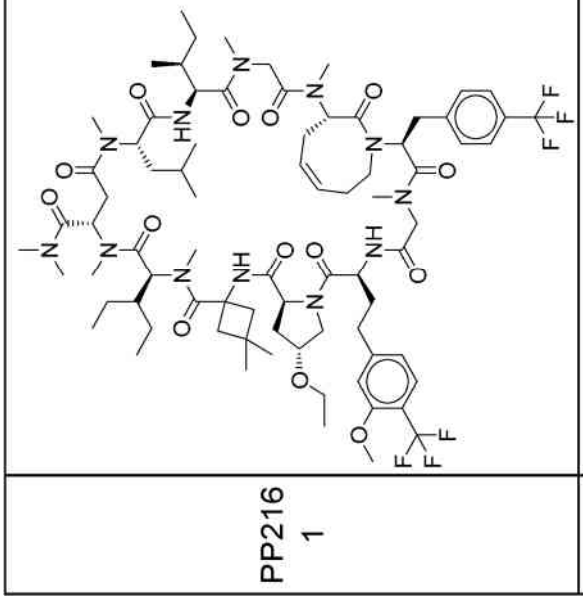
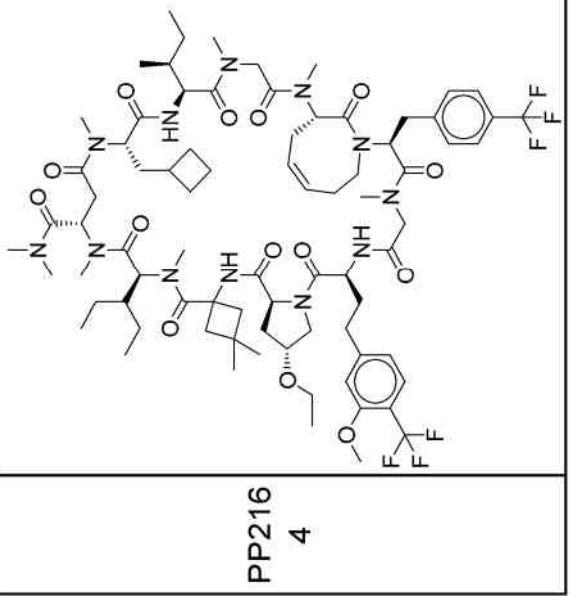
	
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PP214 1	PP214 3

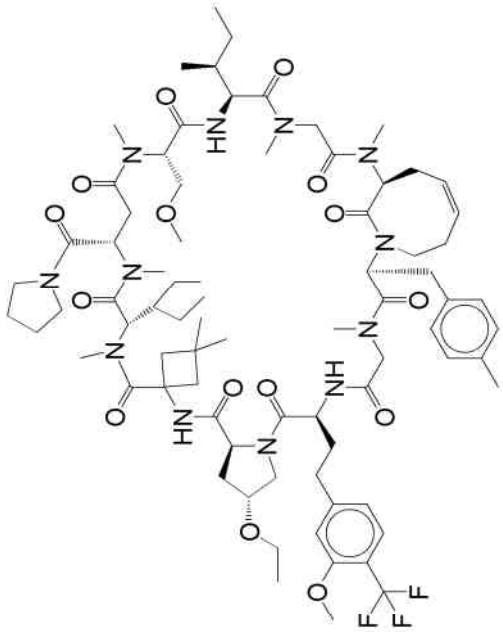
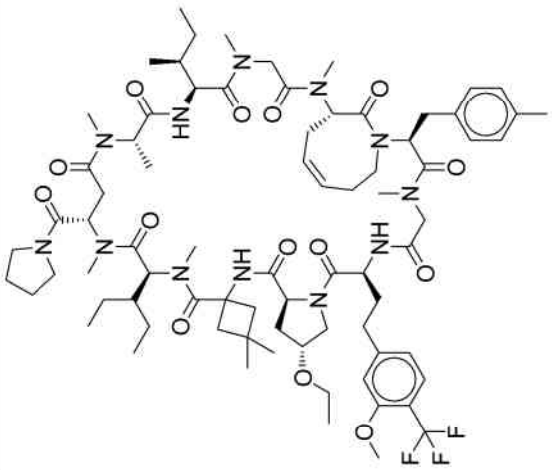
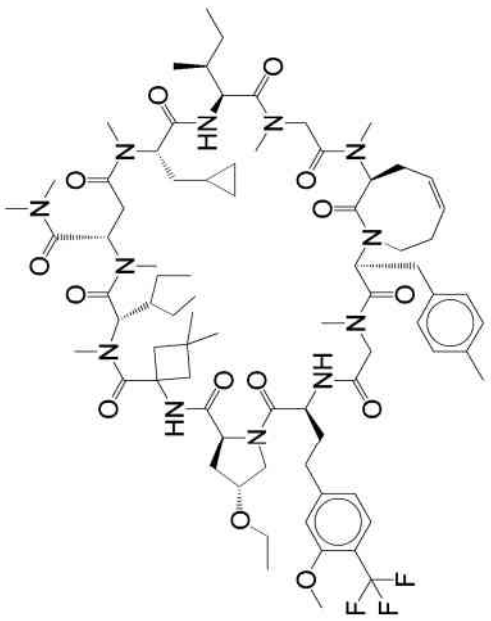
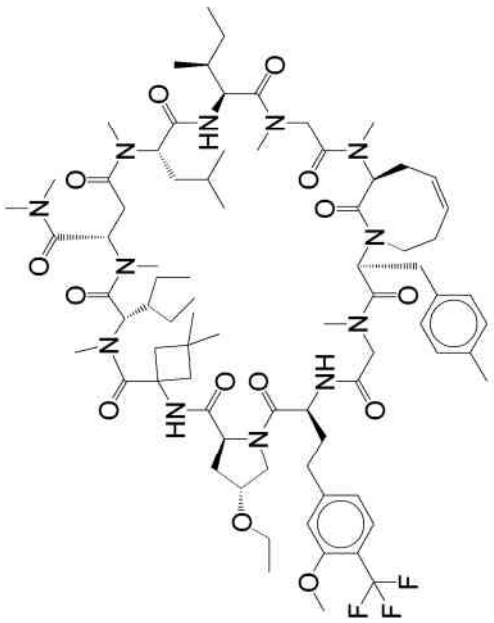
	
PP214 6	PP214 8
	
PP214 5	PP214 7

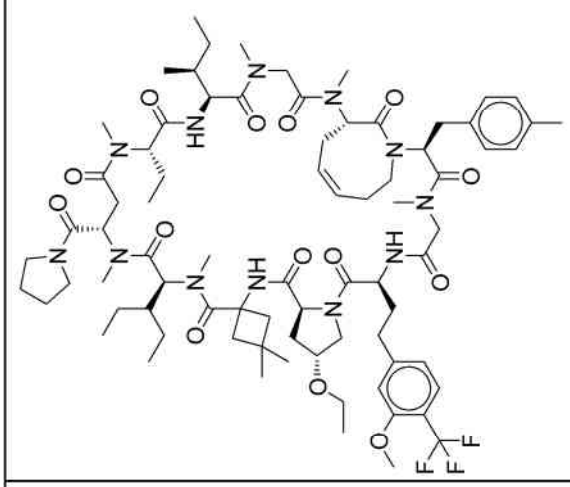
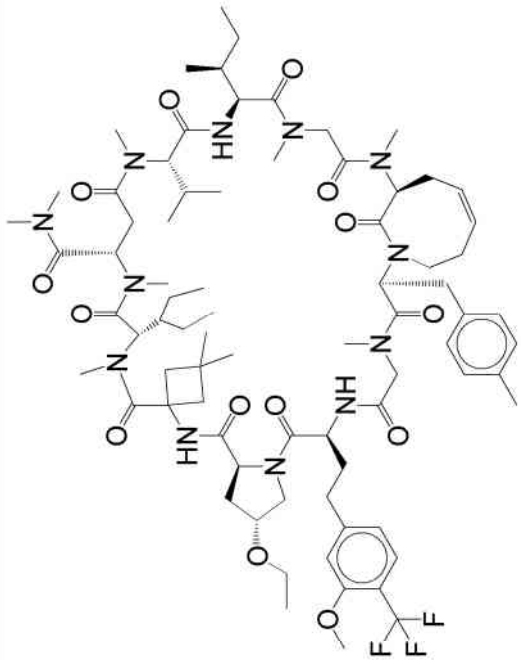
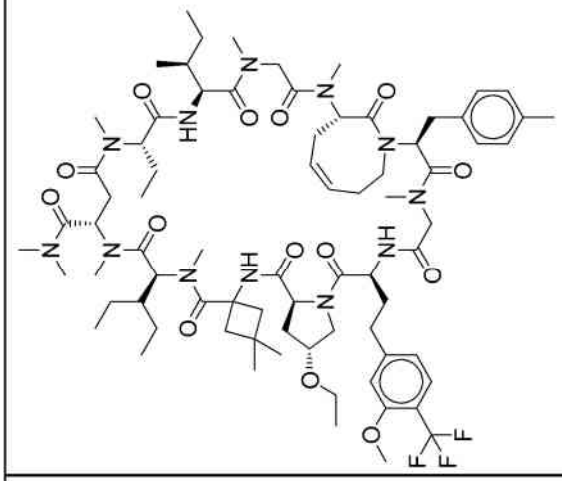
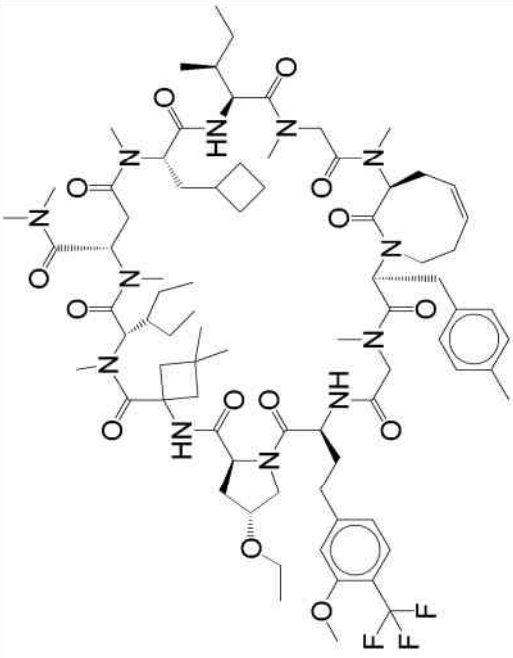
	
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PP2149	PP2151

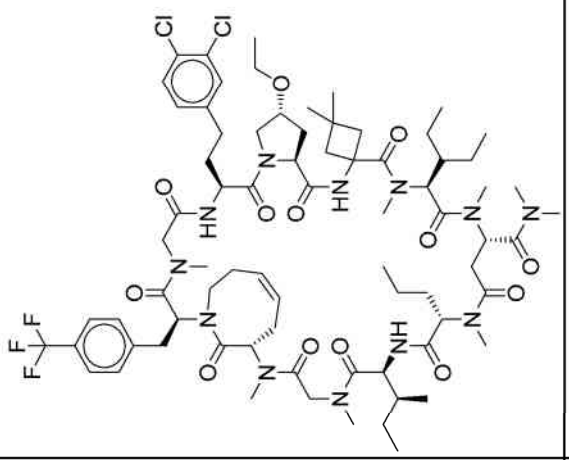
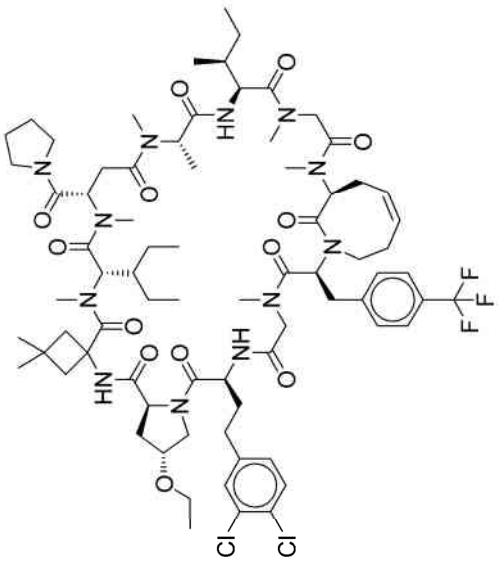
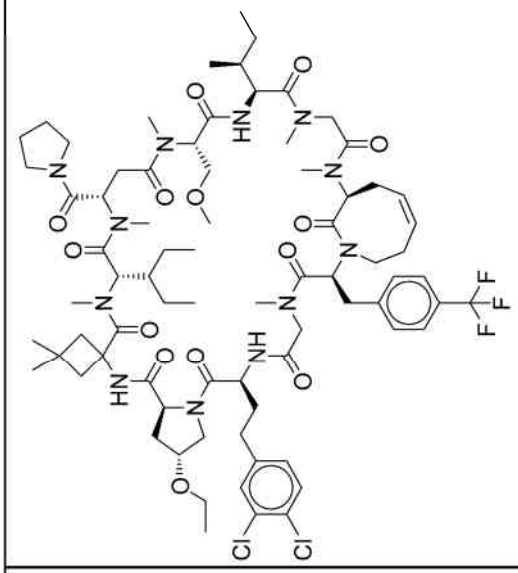
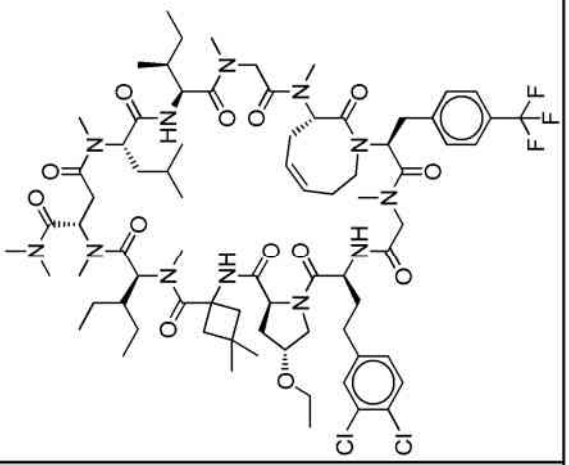
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PP215 3	PP215 5

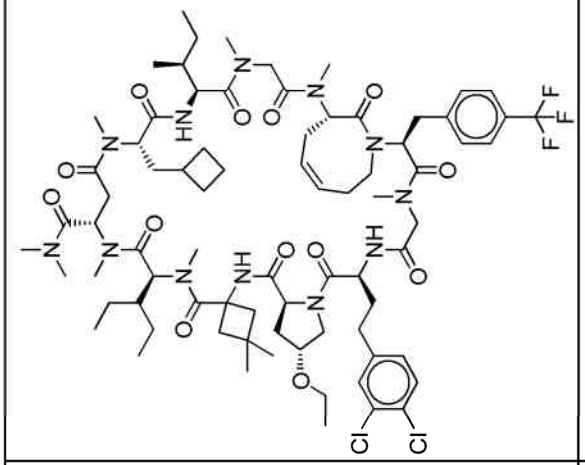
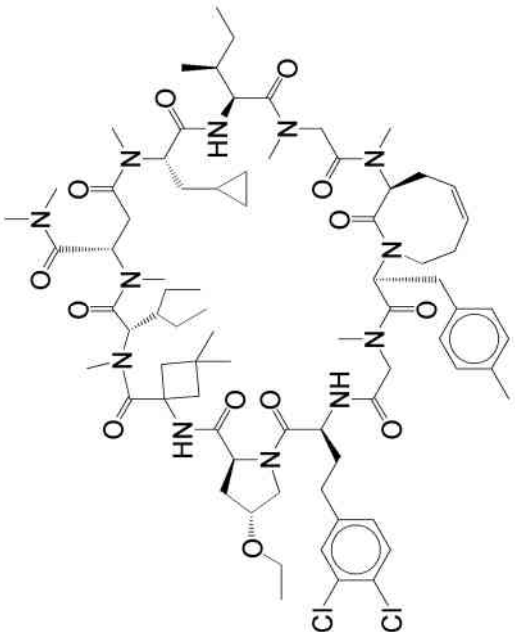
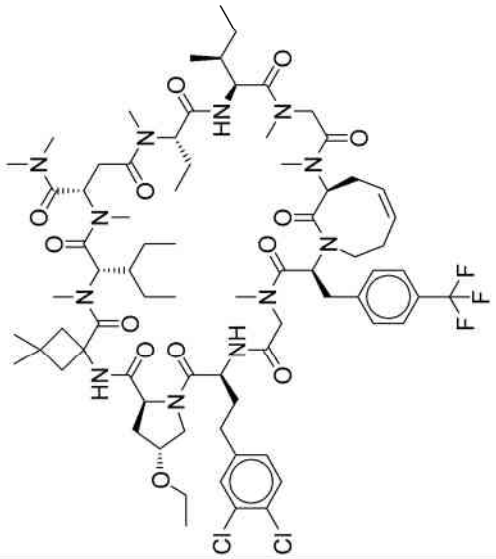
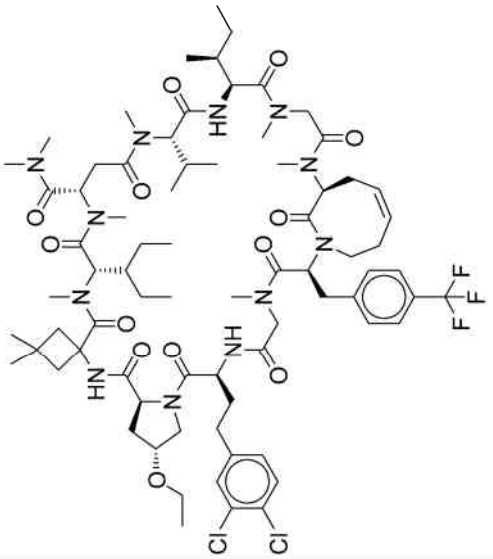
	
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PP2157	PP2159

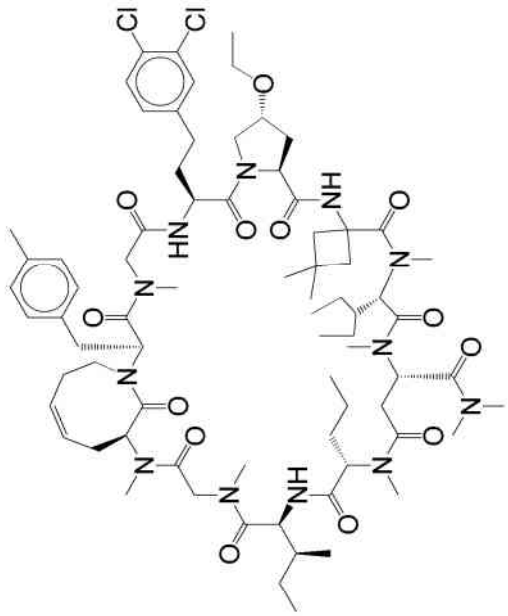
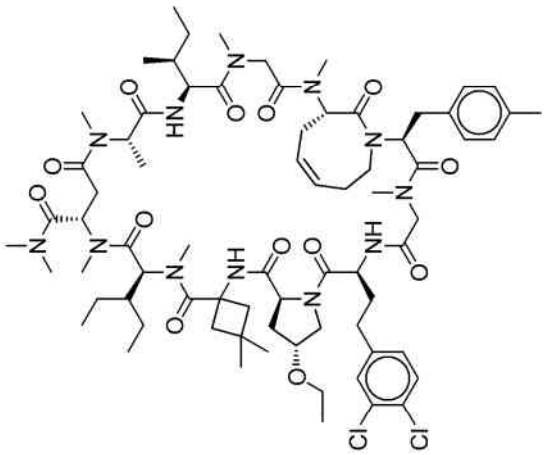
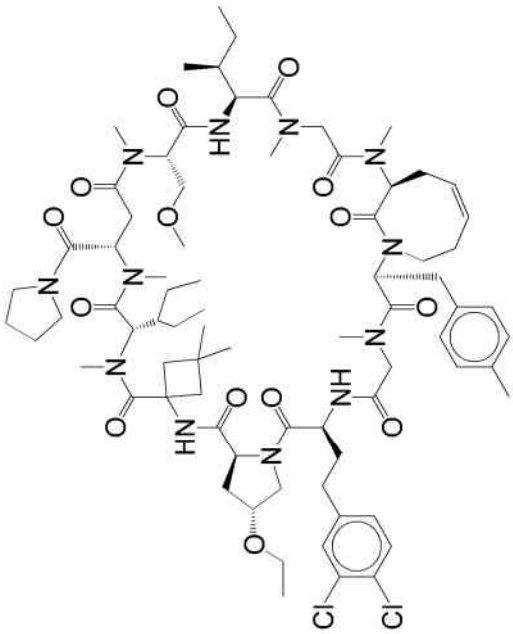
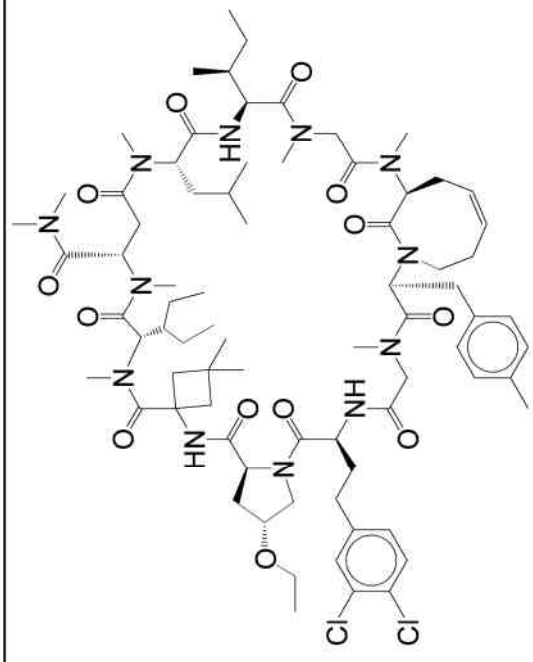
	
PP216 3	PP216 5
	
PP216 1	PP216 4

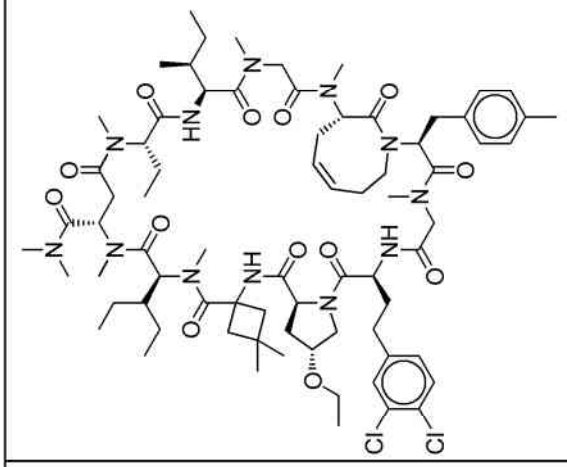
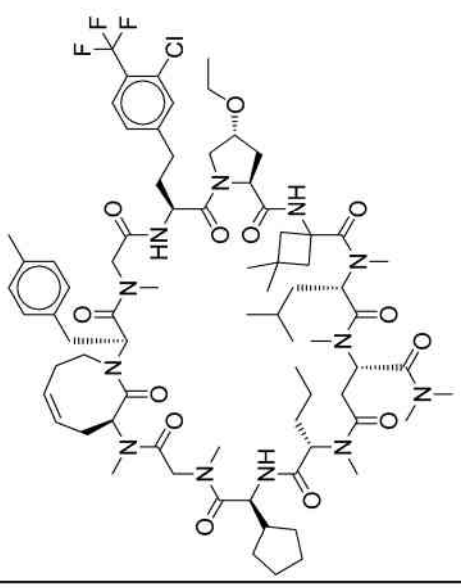
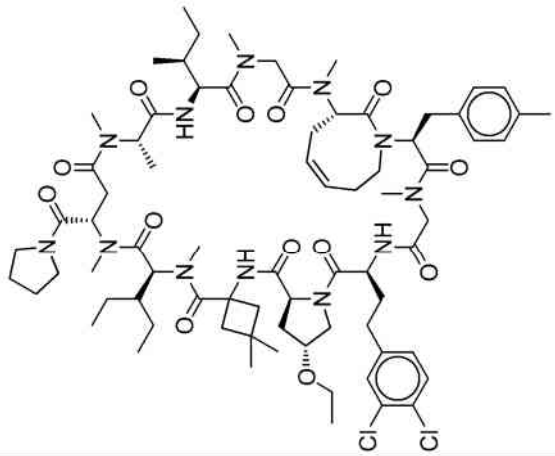
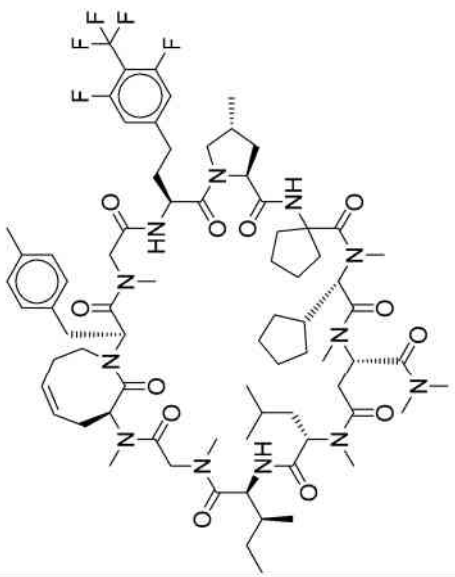
	
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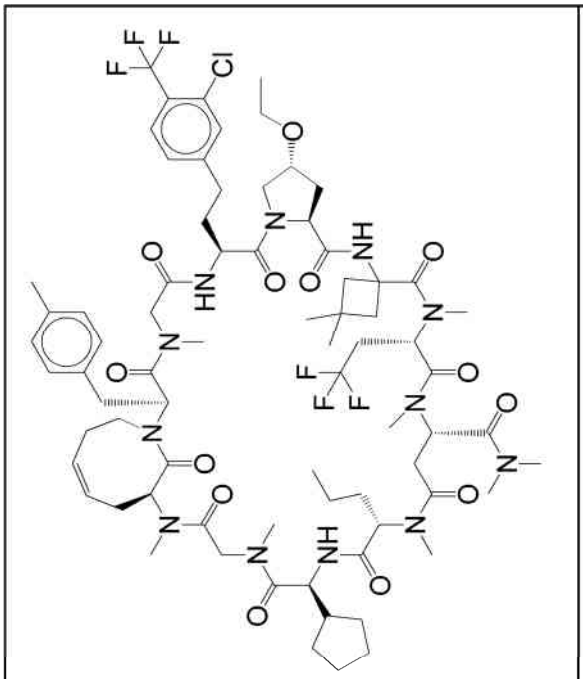
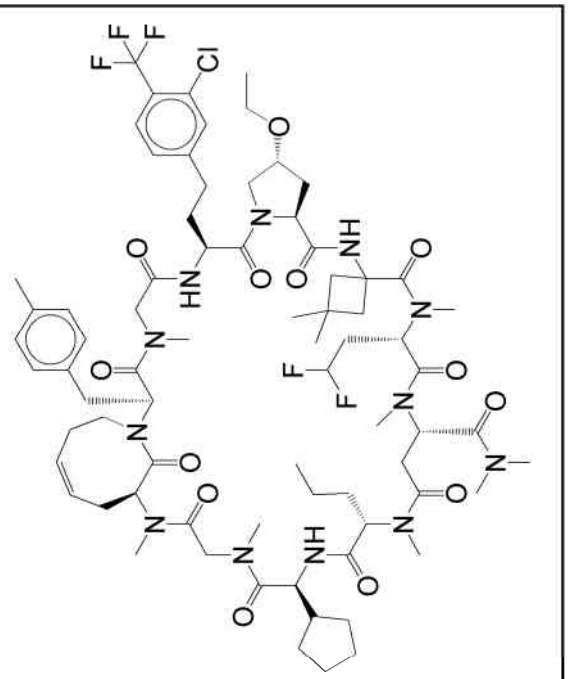
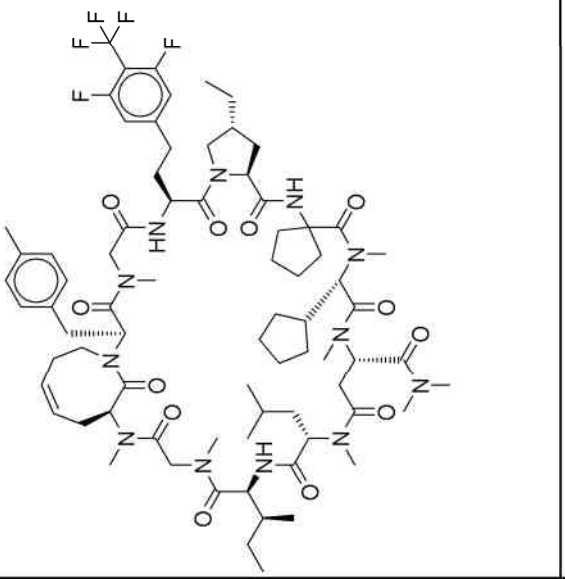
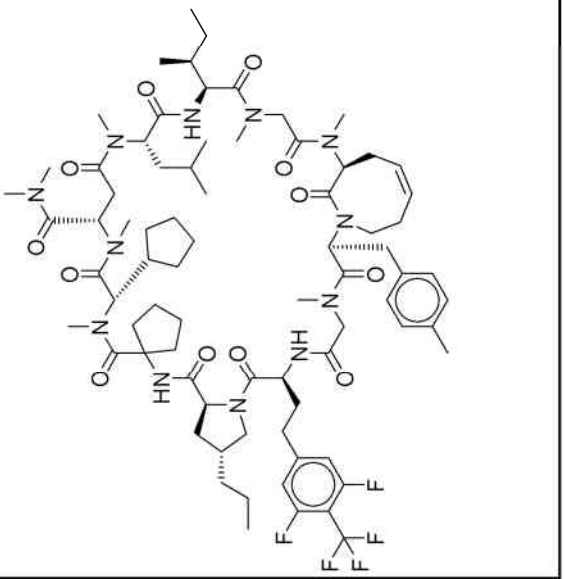
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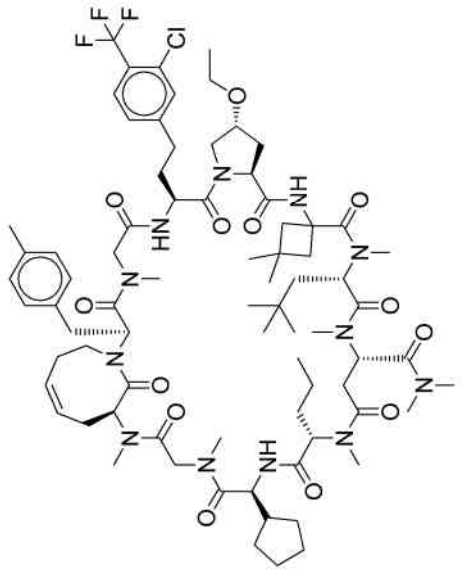
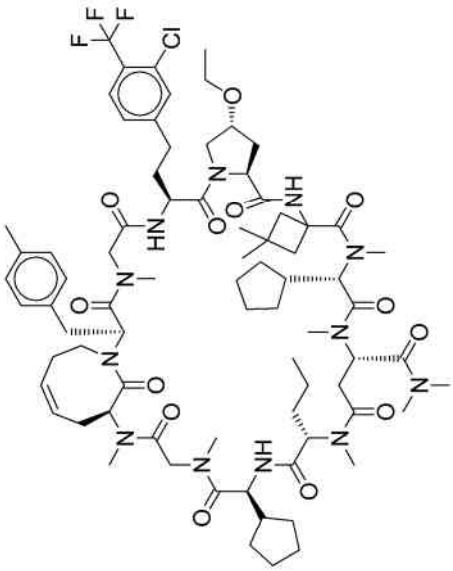
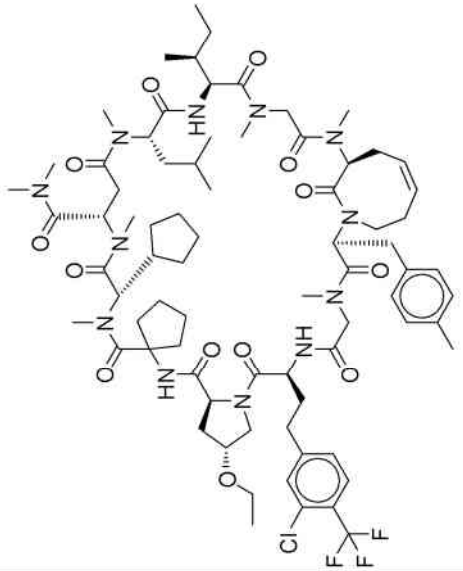
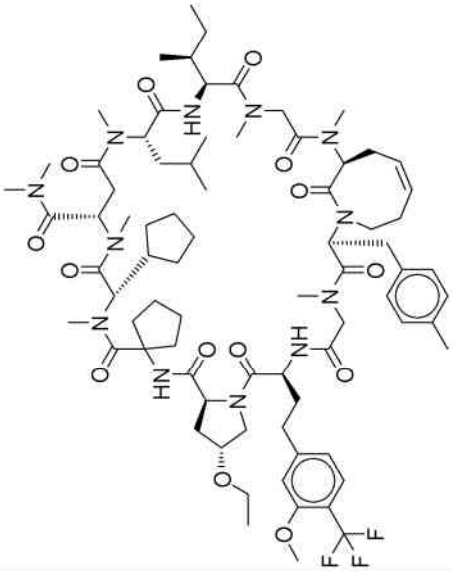
	
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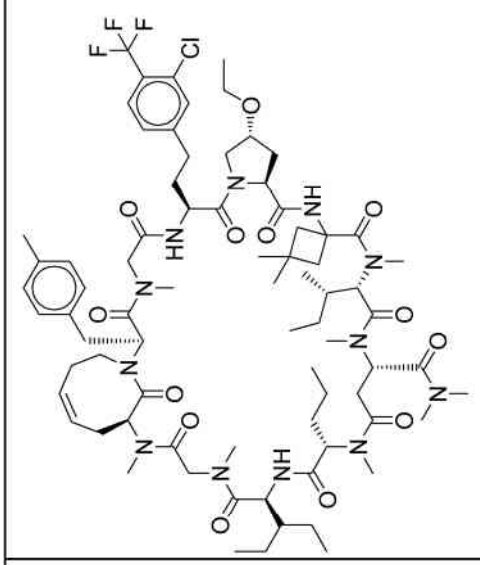
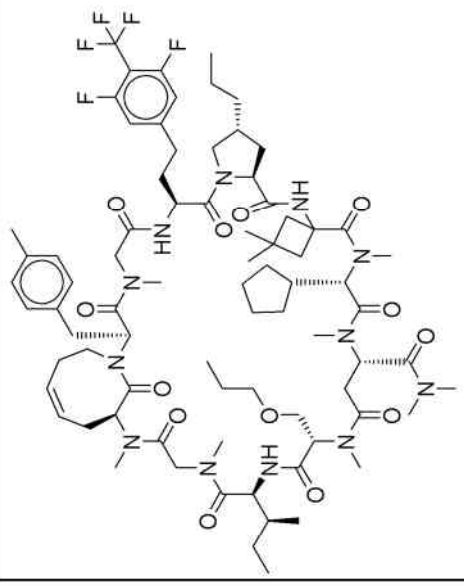
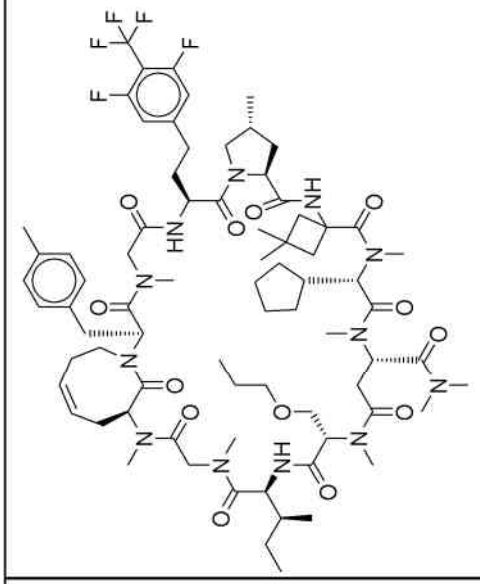
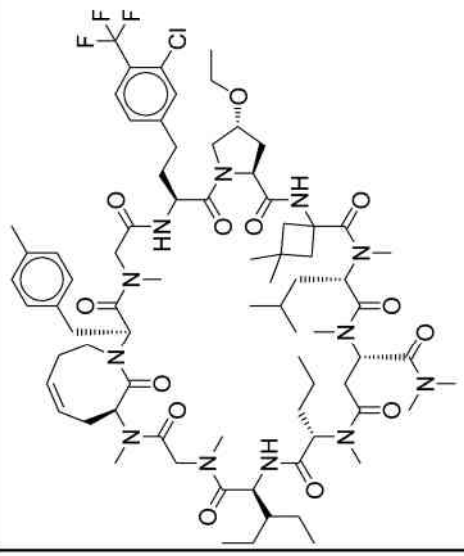
	
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PP2179	PP2181

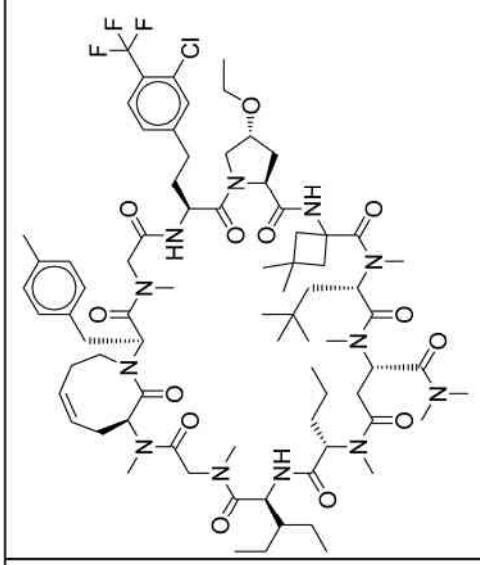
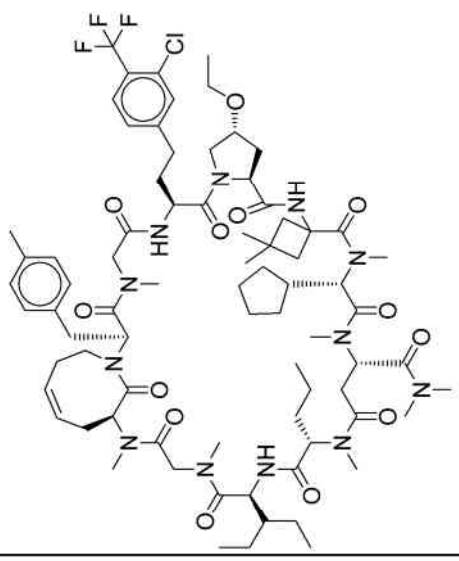
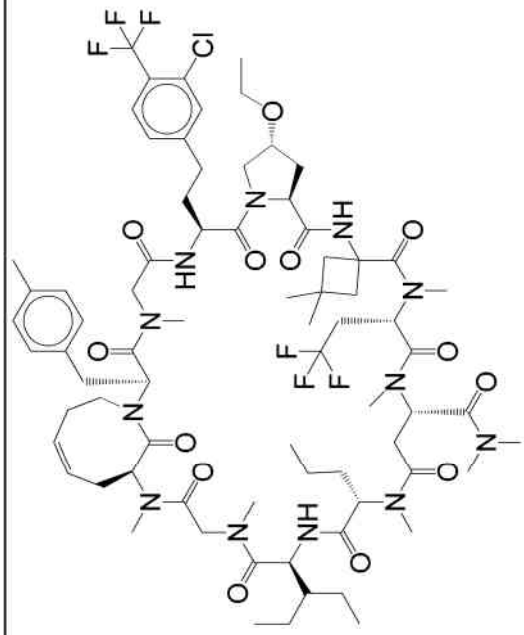
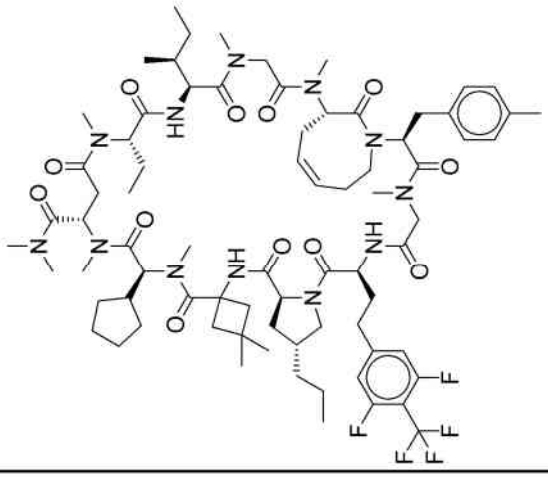
	
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PP218 3	PP218 5

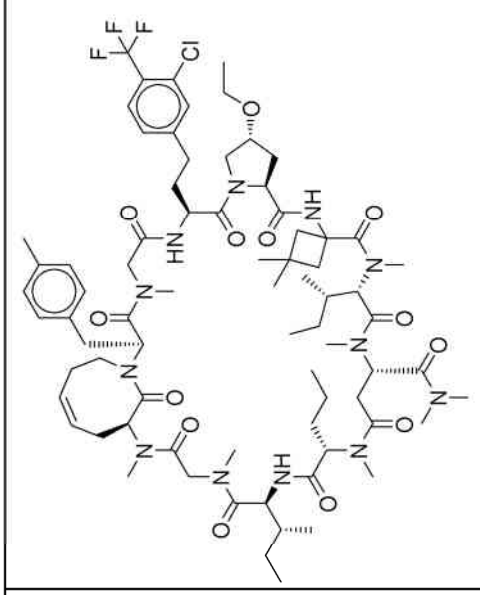
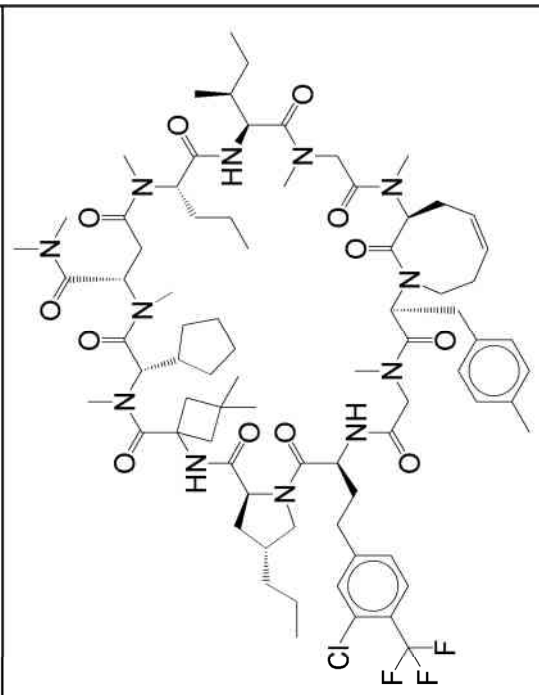
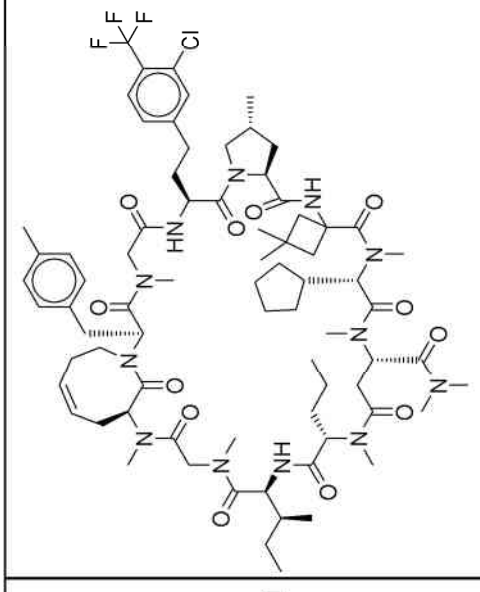
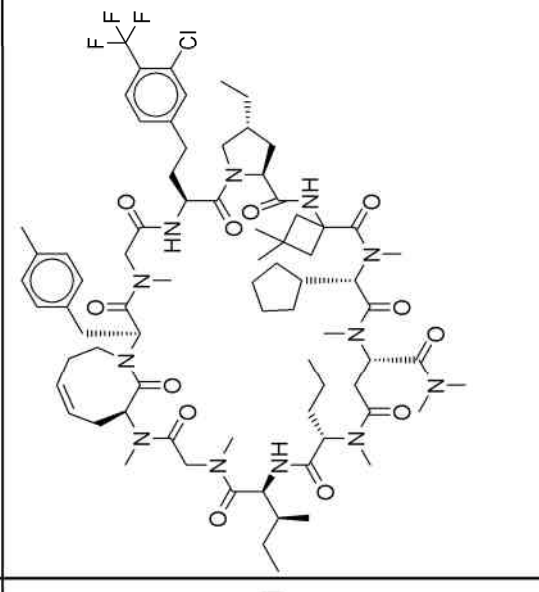
	
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PP2187	PP2189

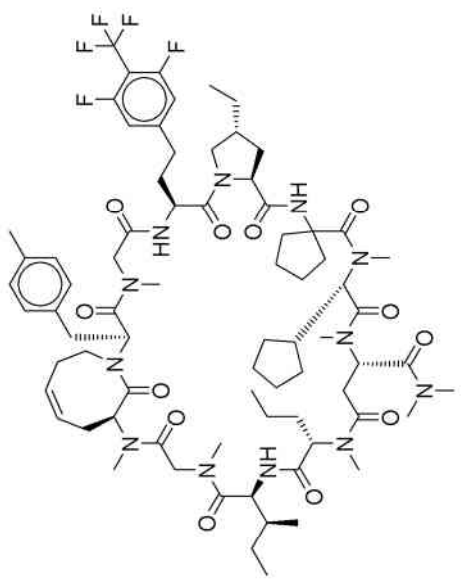
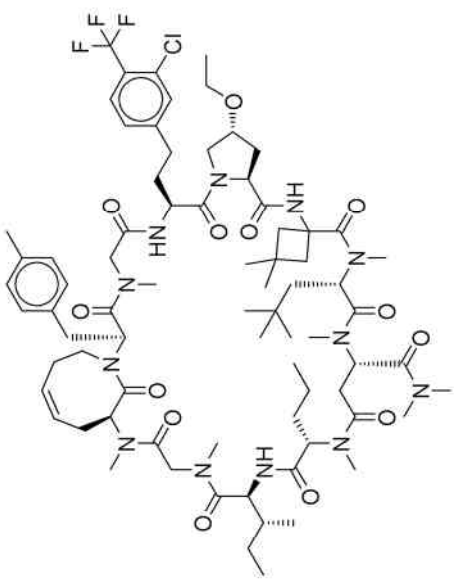
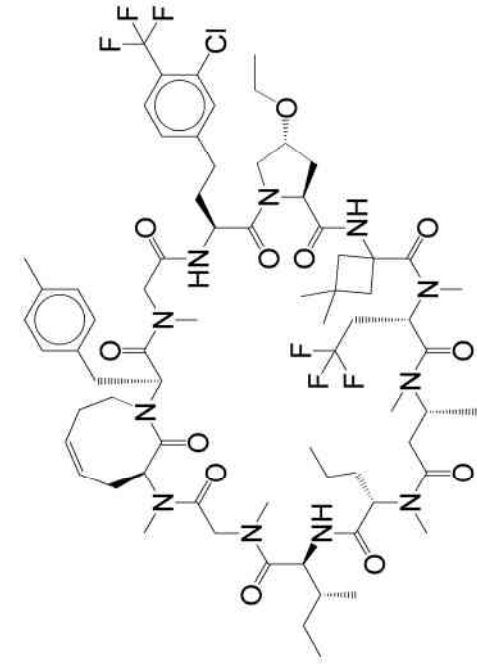
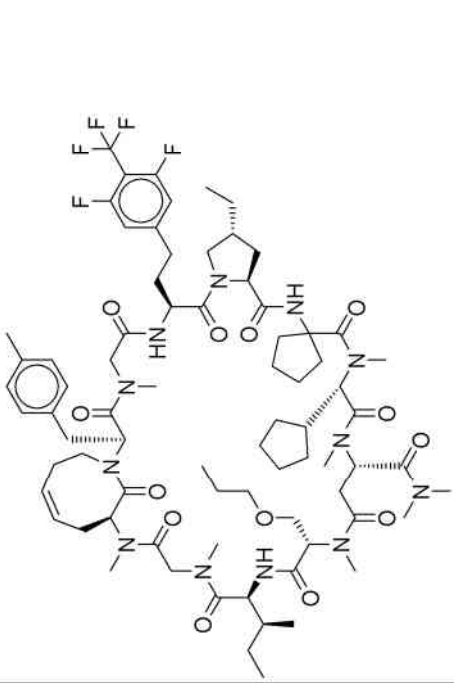
	
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PP219 1	PP219 3

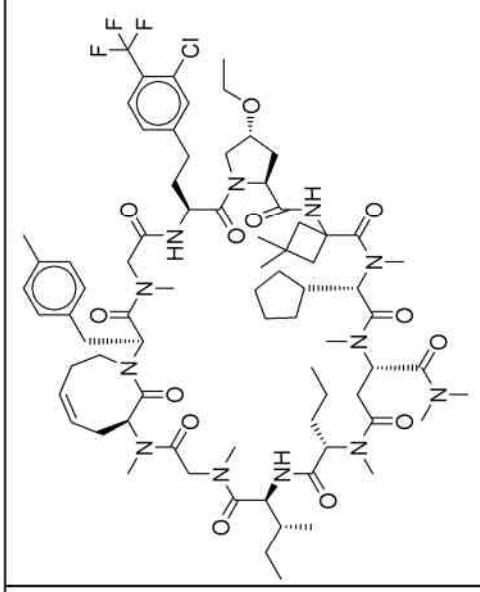
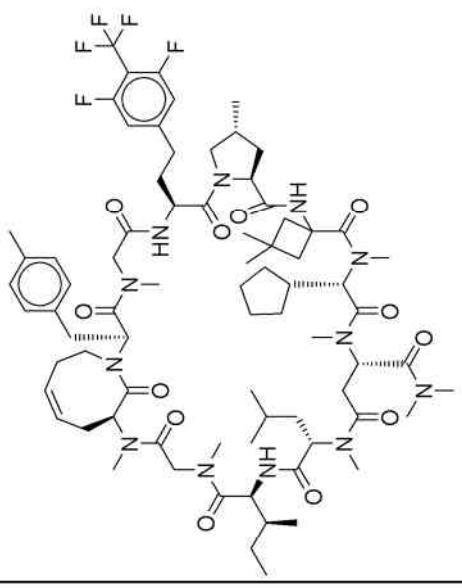
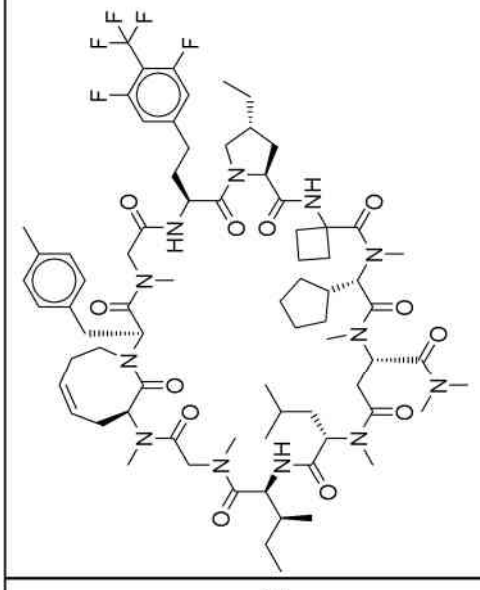
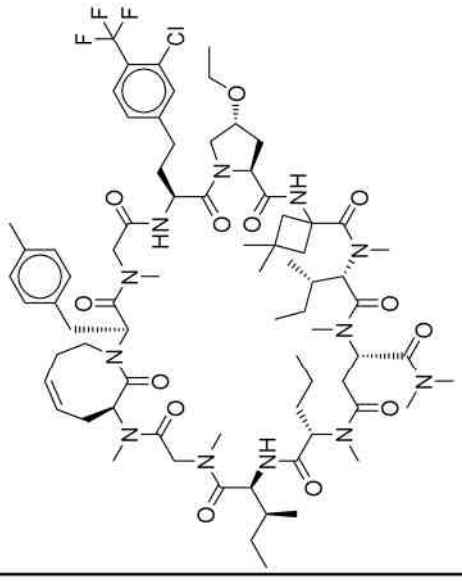
	
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PP219 5	PP219 7

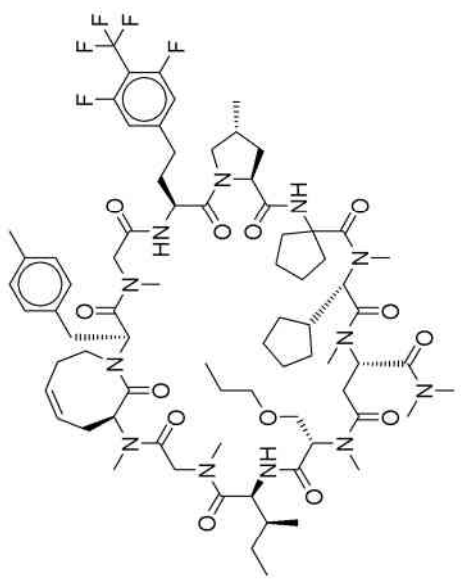
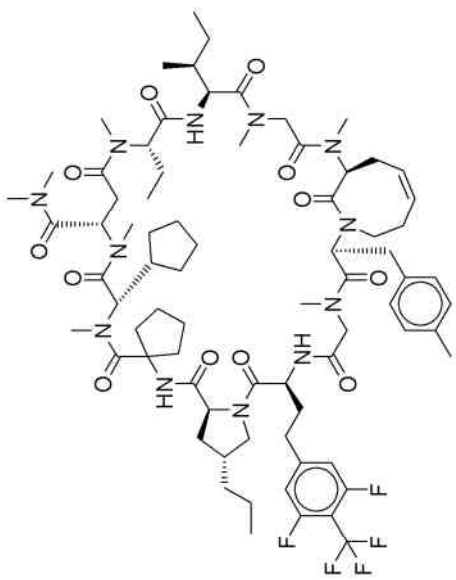
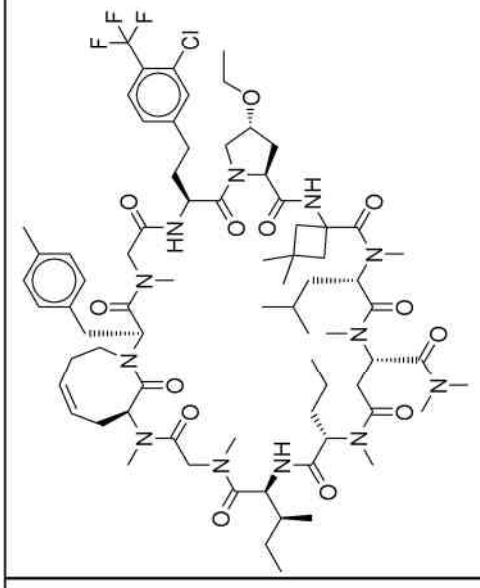
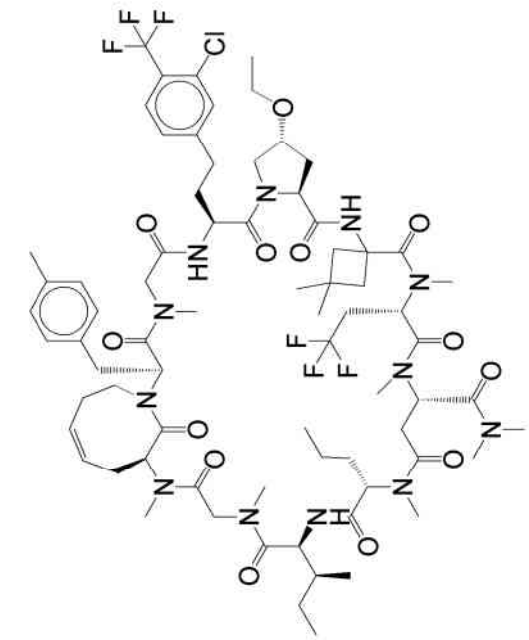
	
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PP2199	PP2202

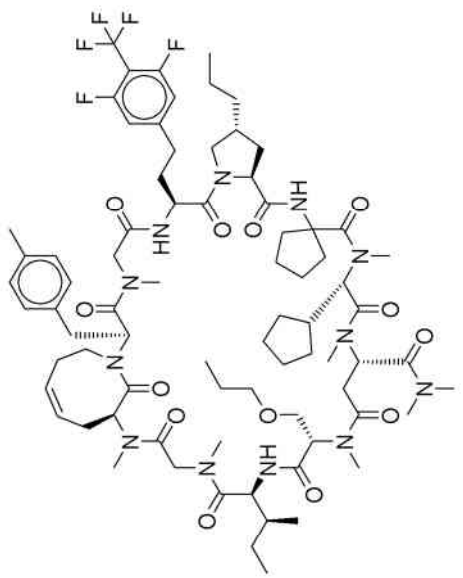
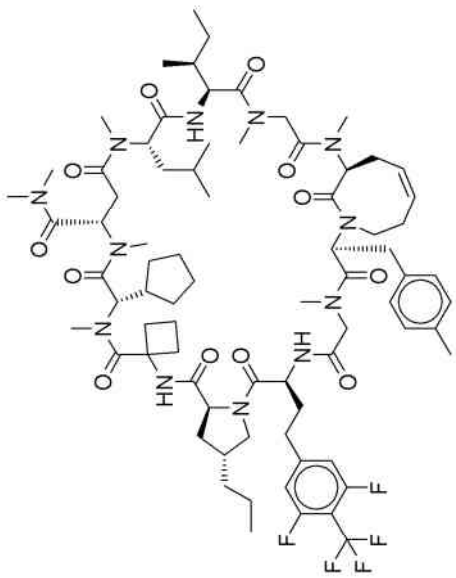
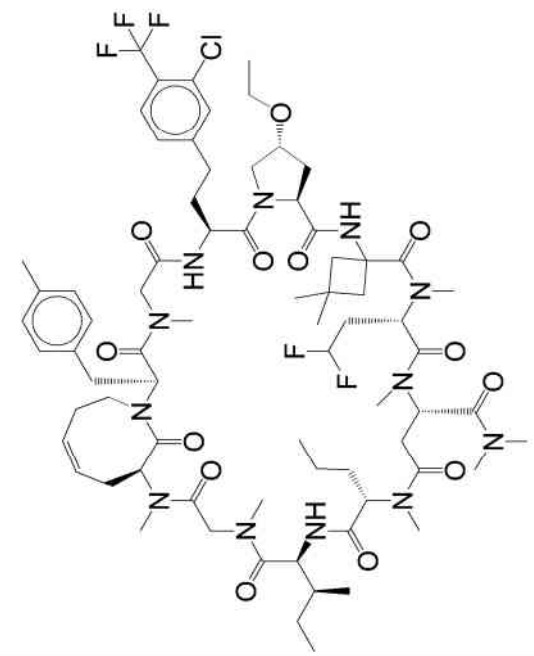
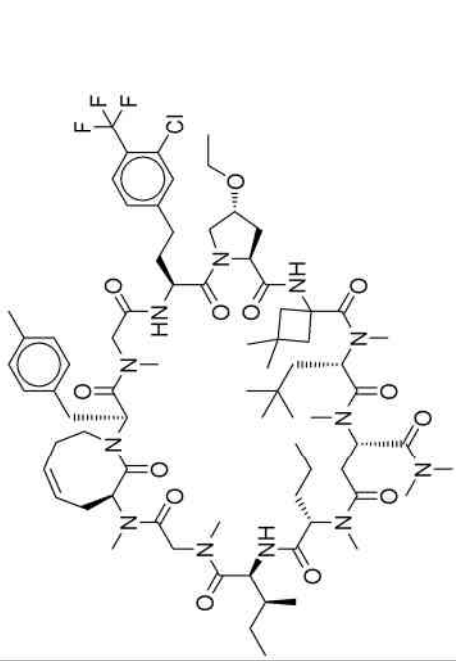
	
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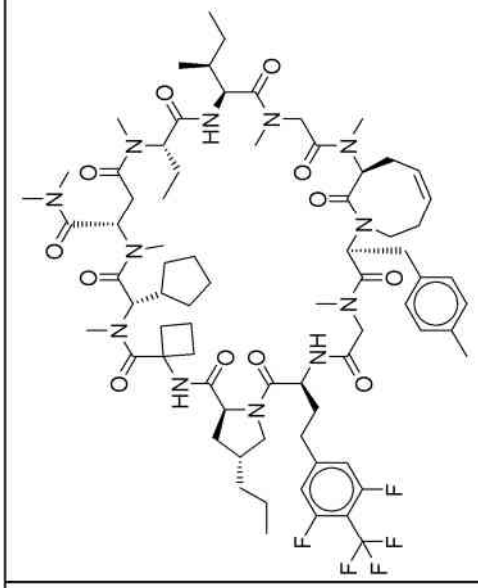
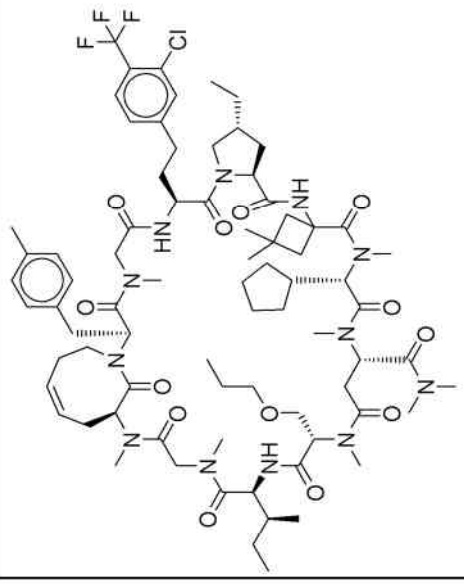
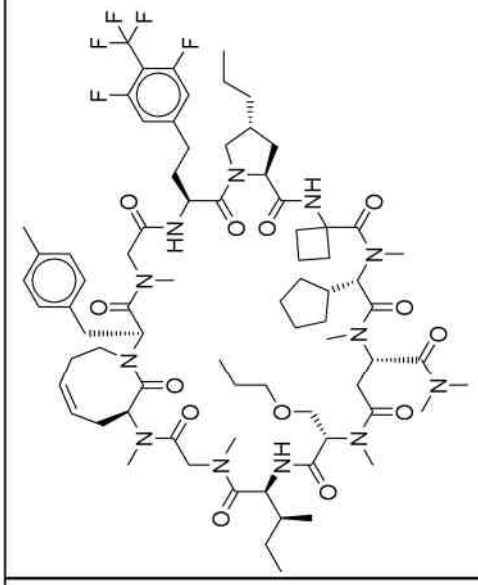
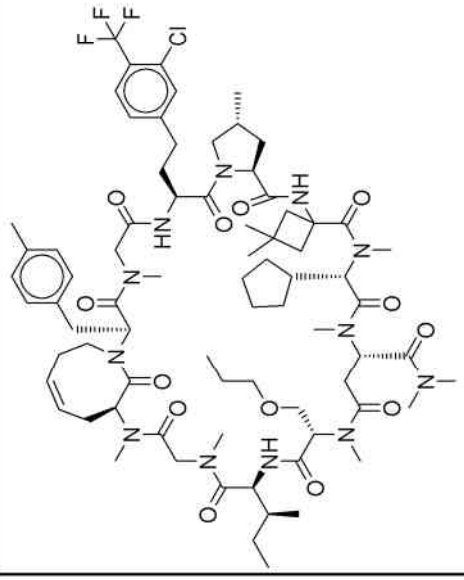
	
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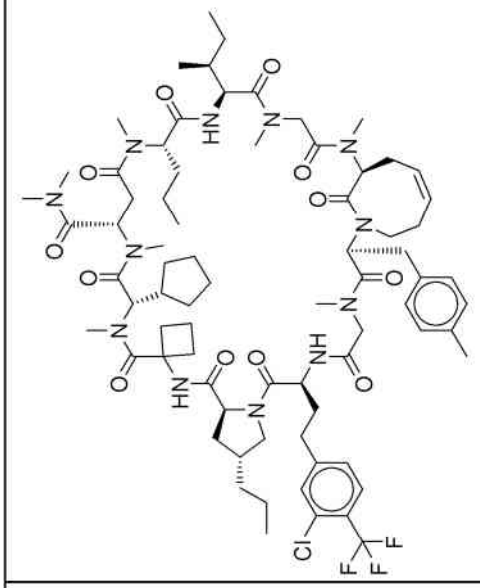
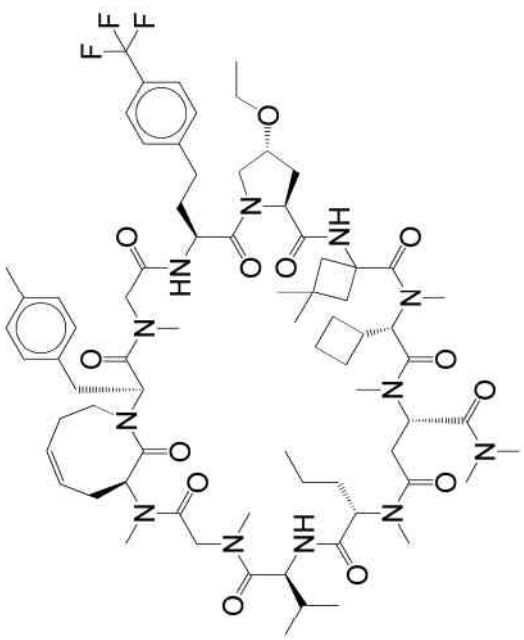
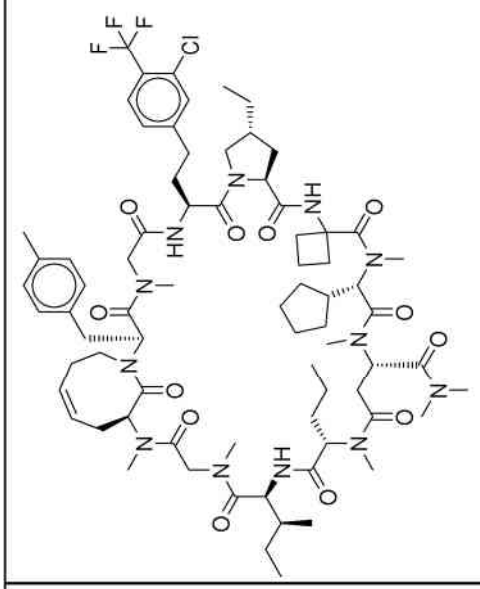
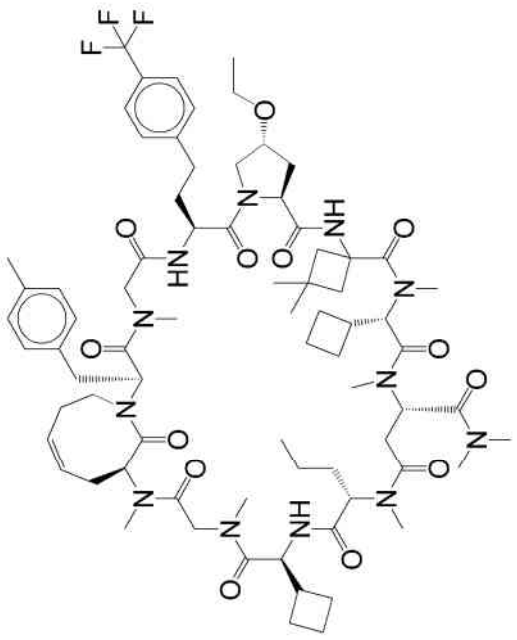
	
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PP221 5	PP221 8

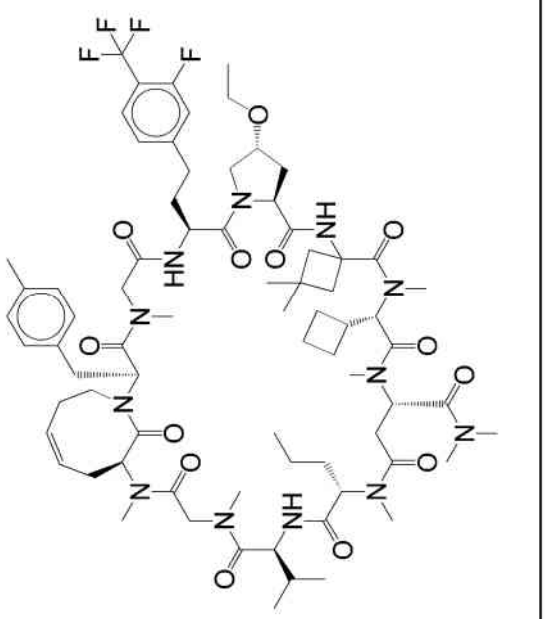
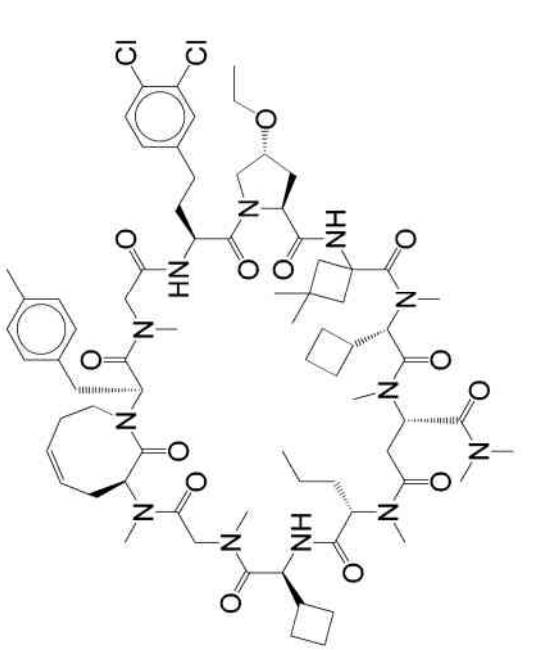
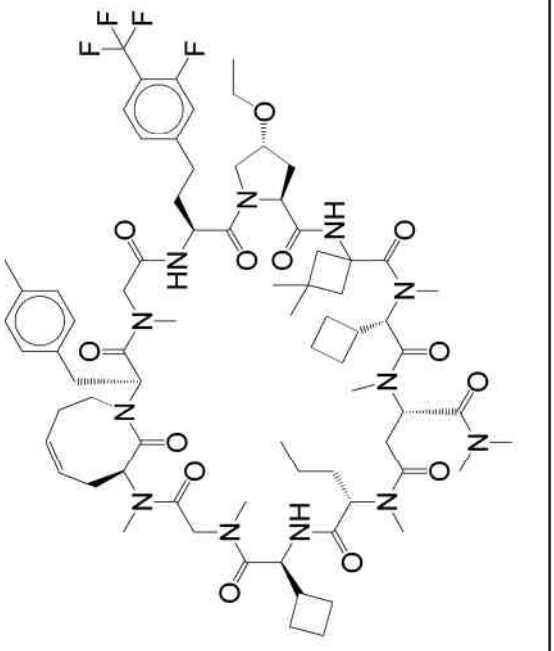
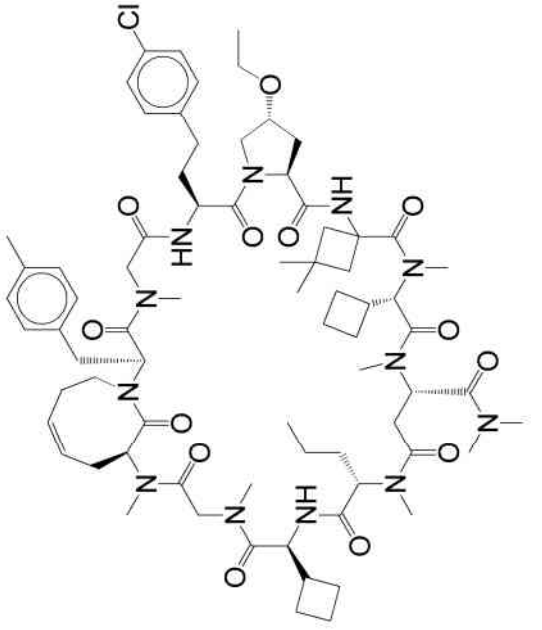
	
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PP222 0	PP222 2

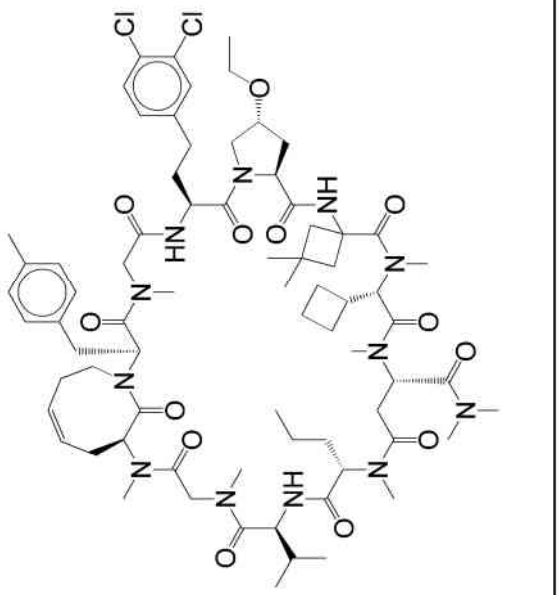
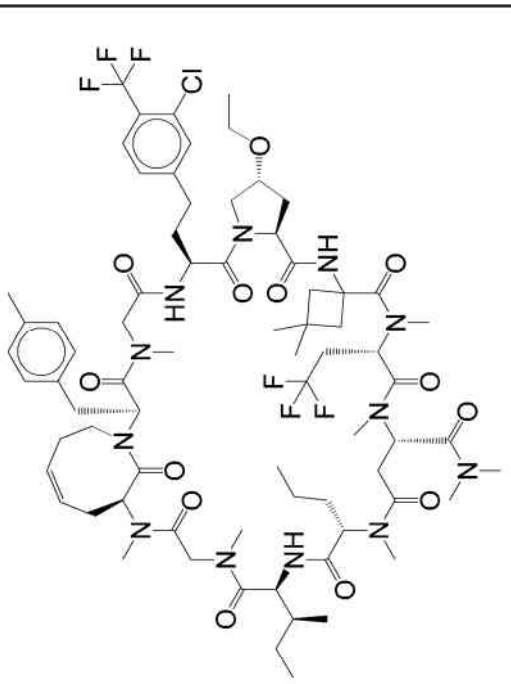
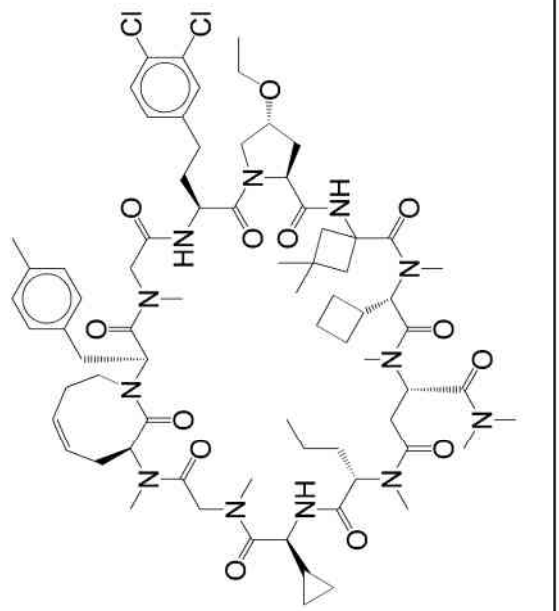
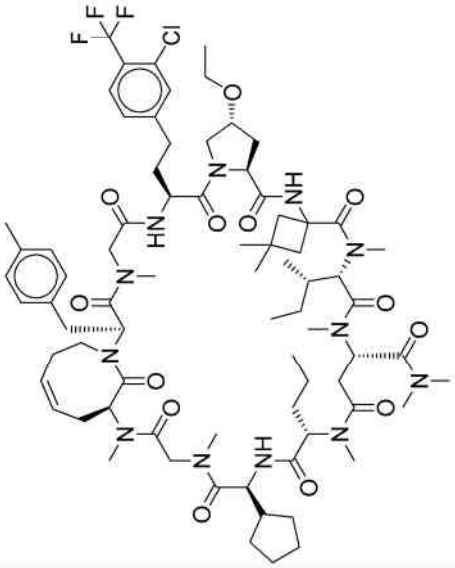
	
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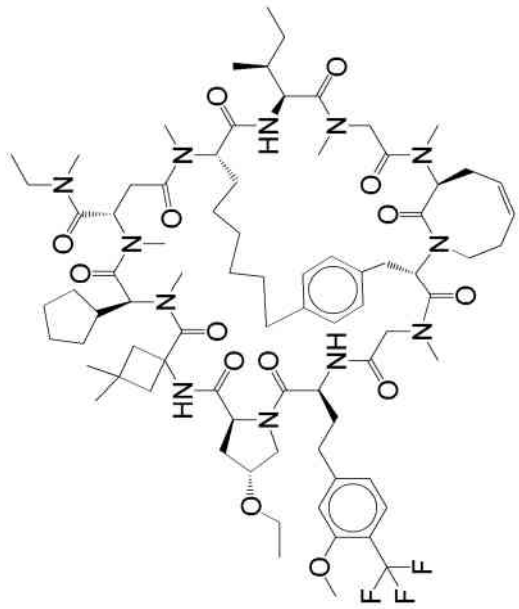
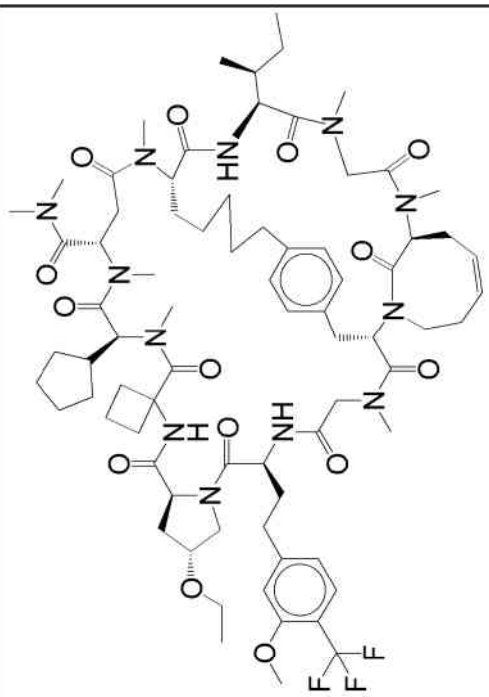
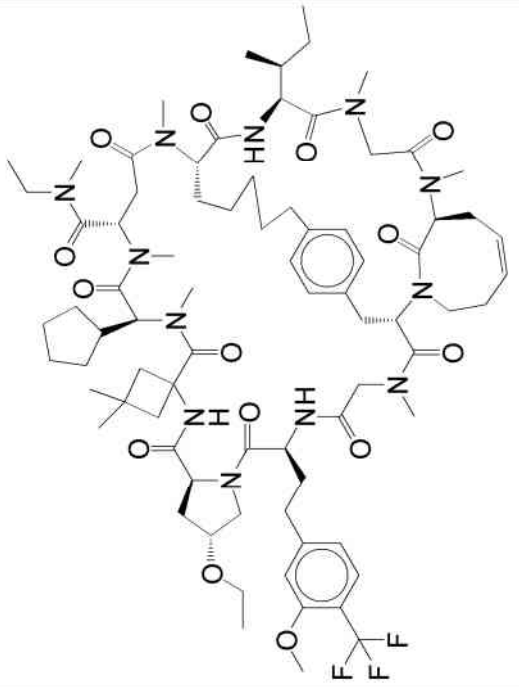
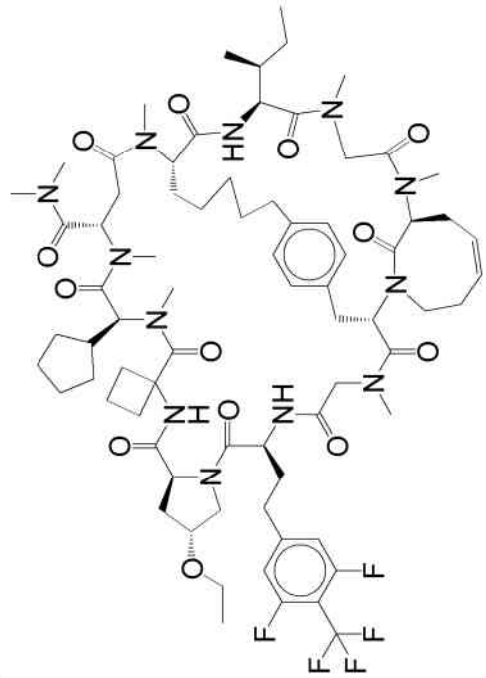
	
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PP2228	PP2230

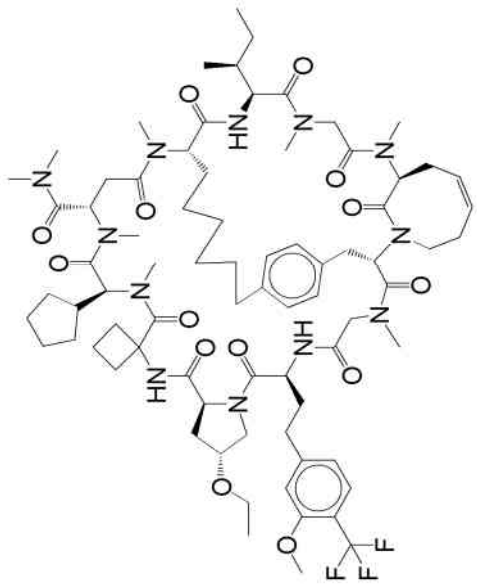
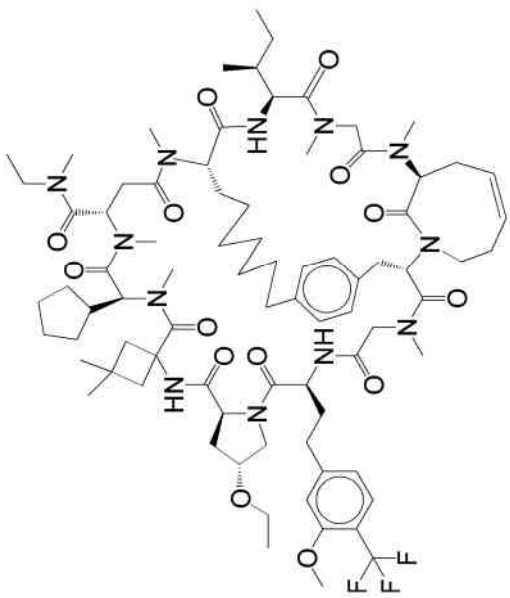
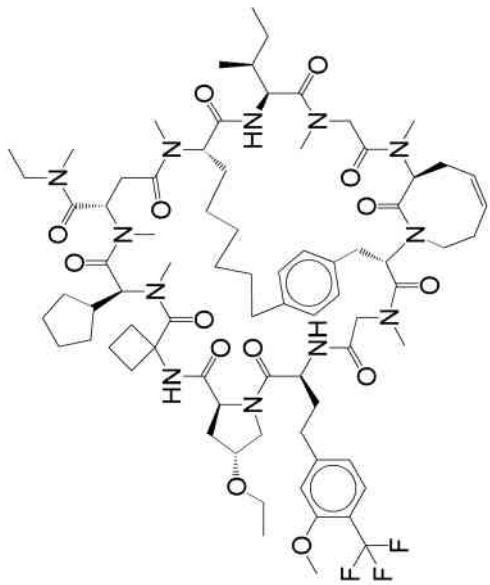
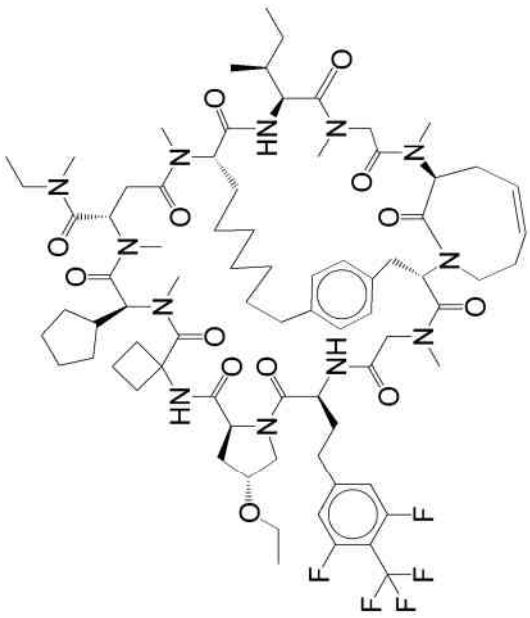
	
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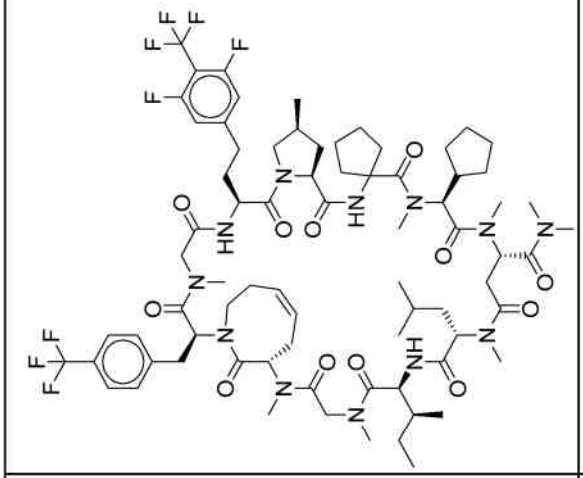
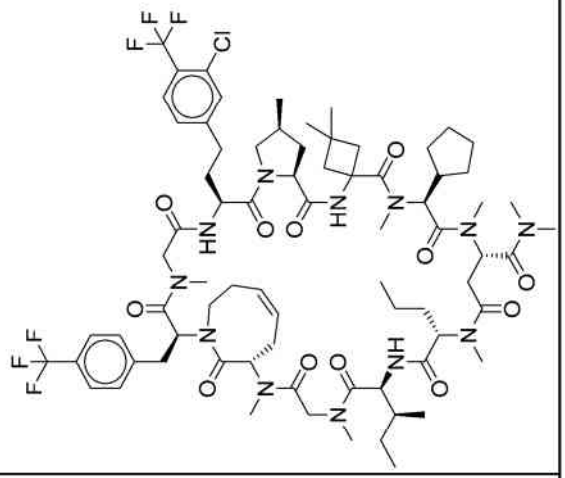
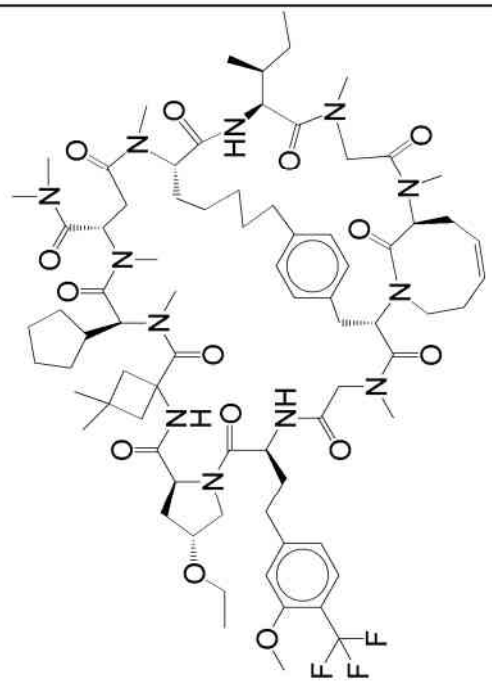
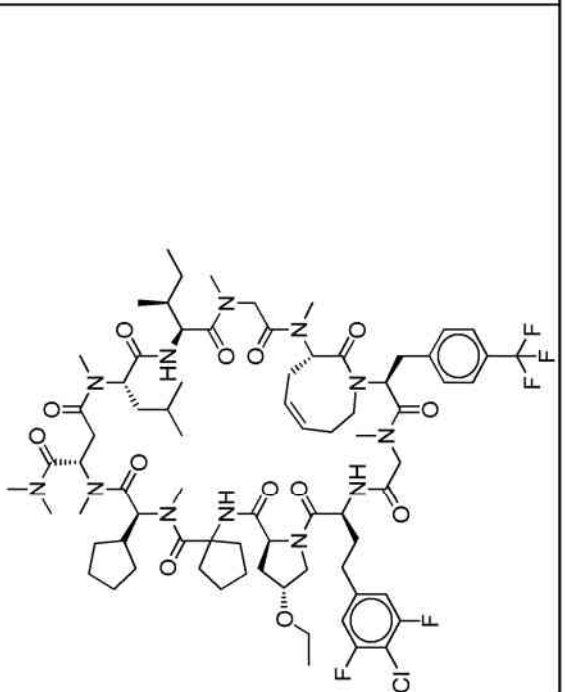
	
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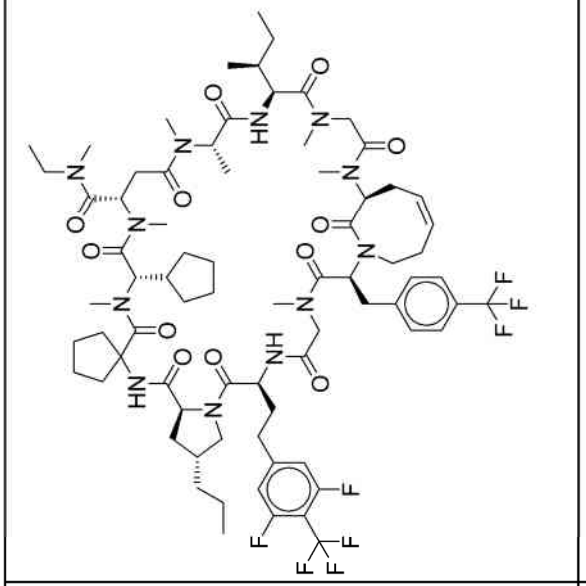
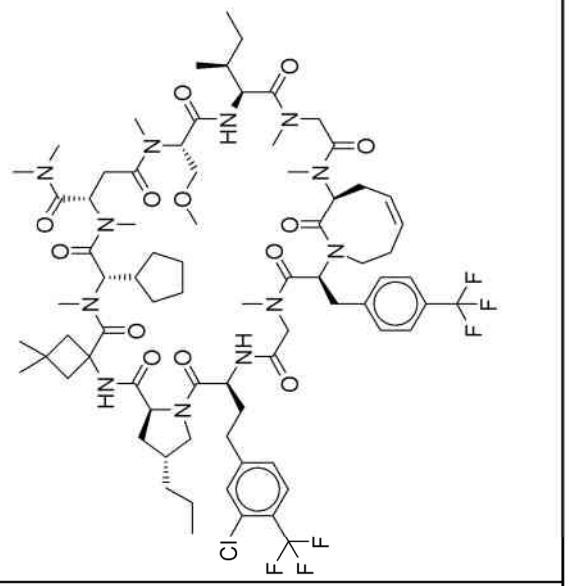
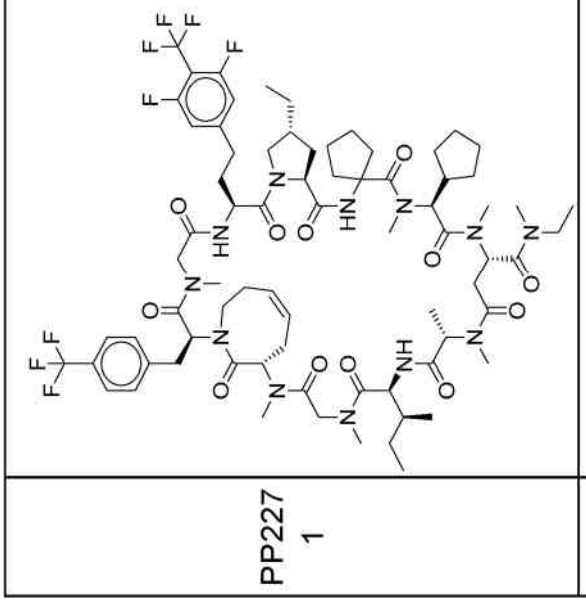
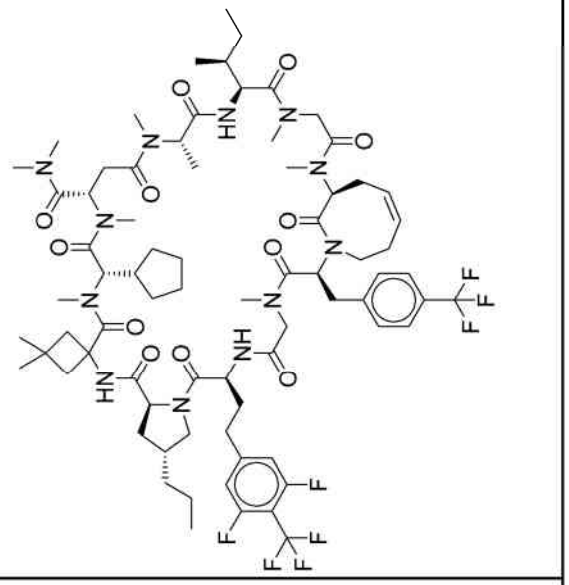
	
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PP224 2	PP224 5

	
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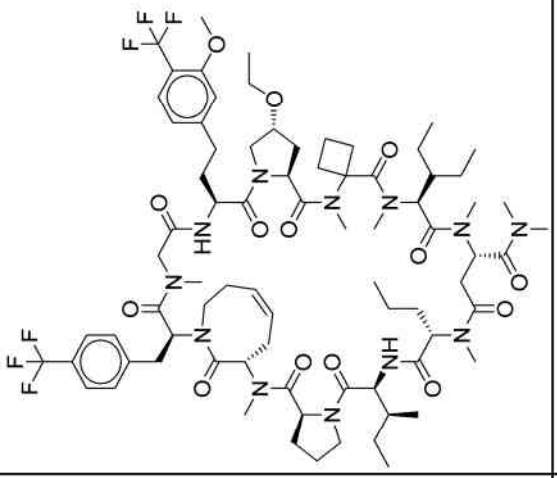
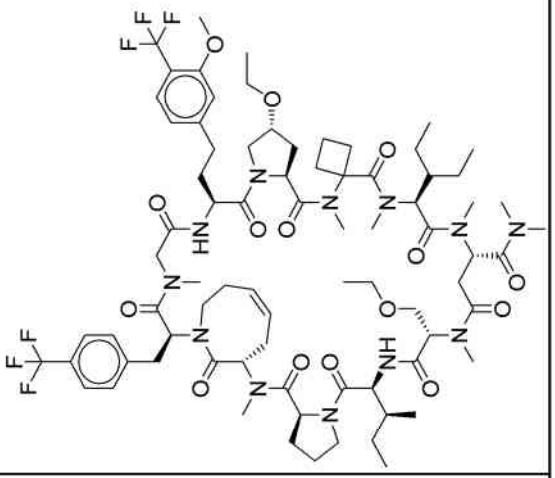
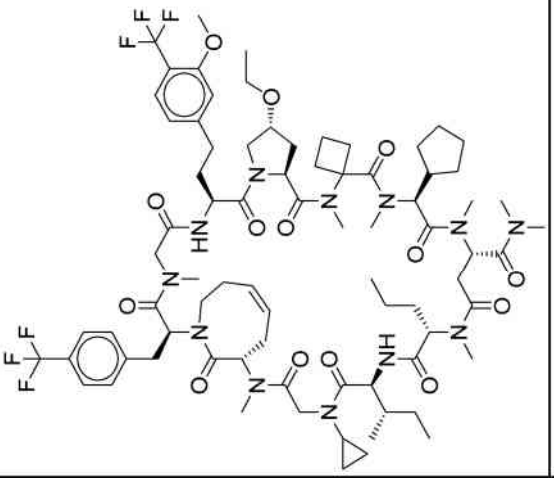
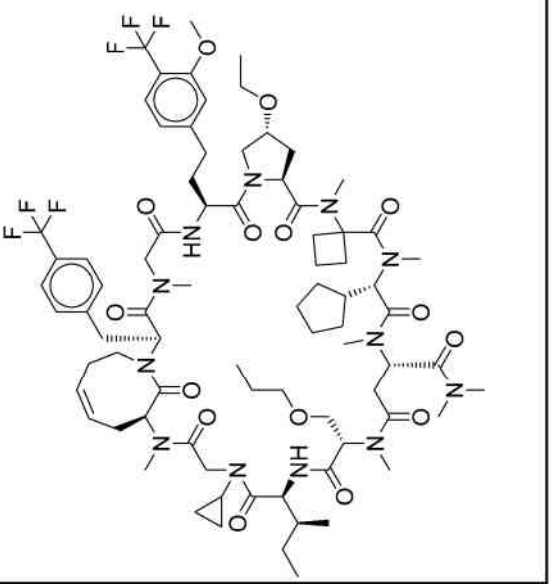
	
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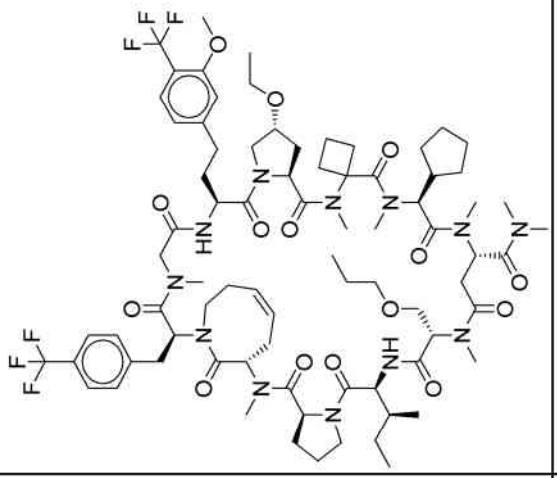
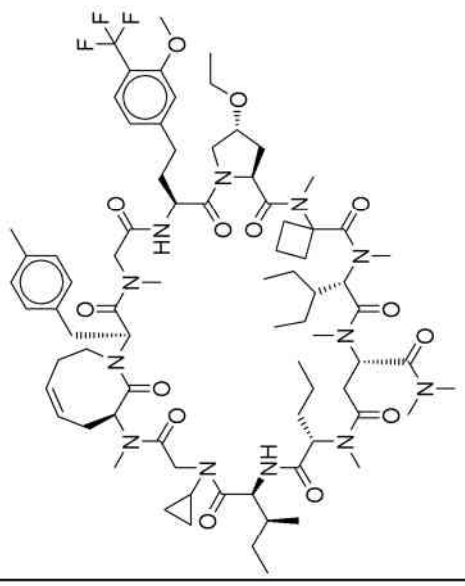
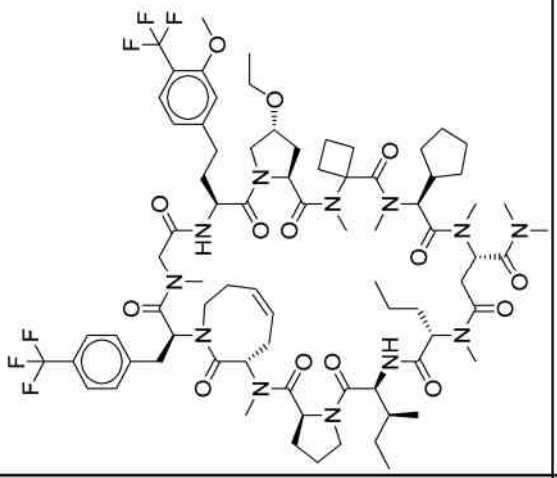
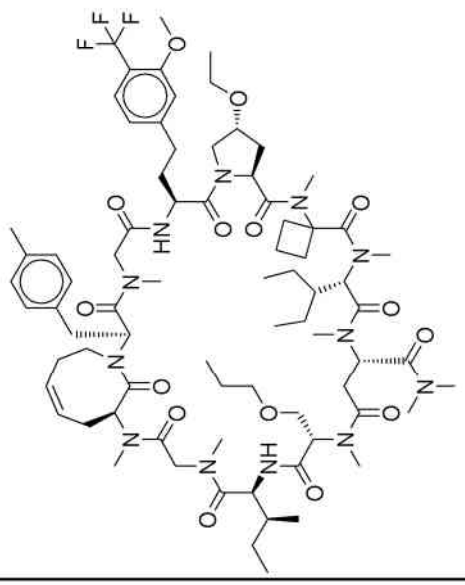
	
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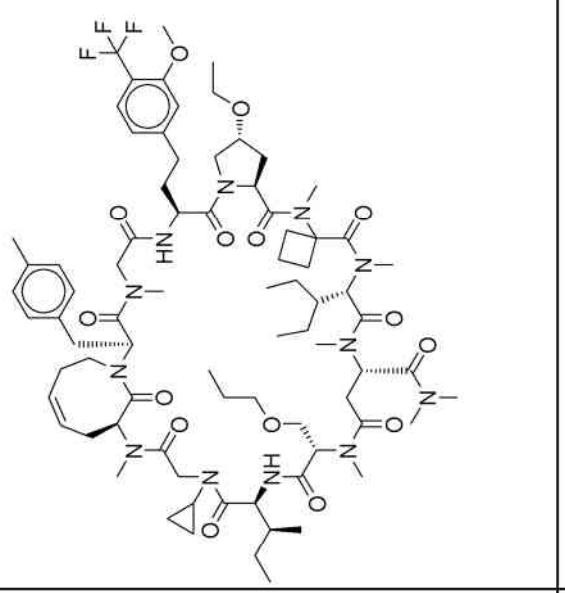
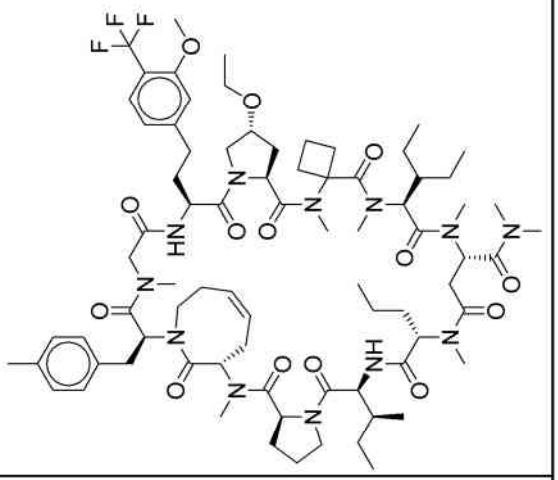
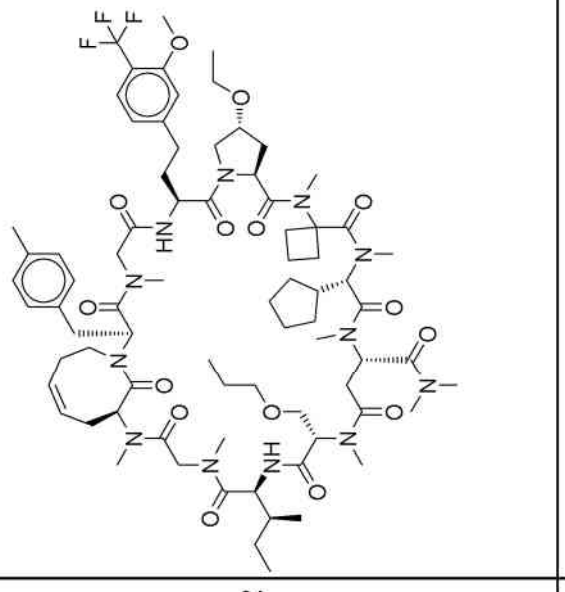
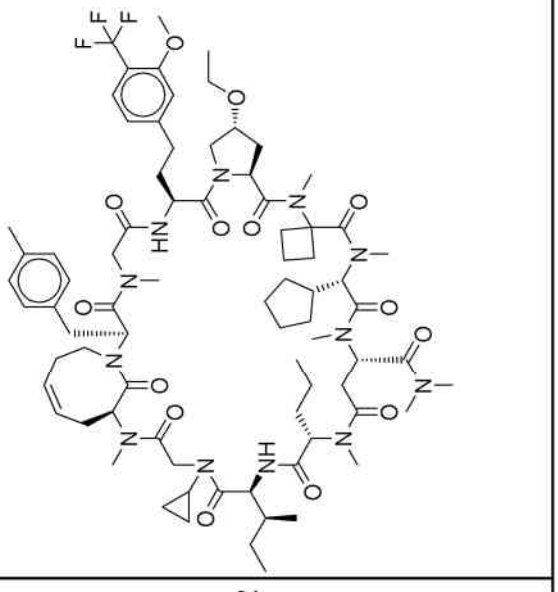
	
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PP227 1	PP227 3

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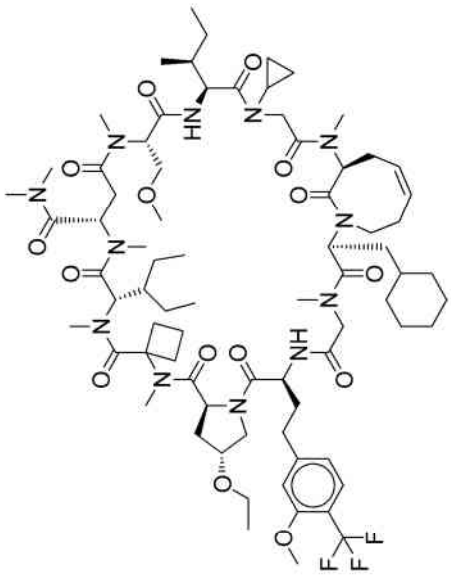
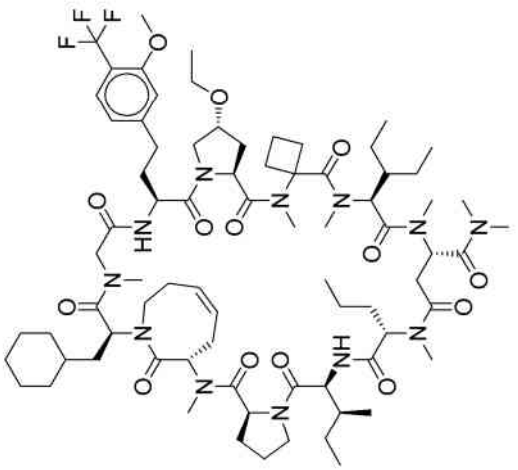
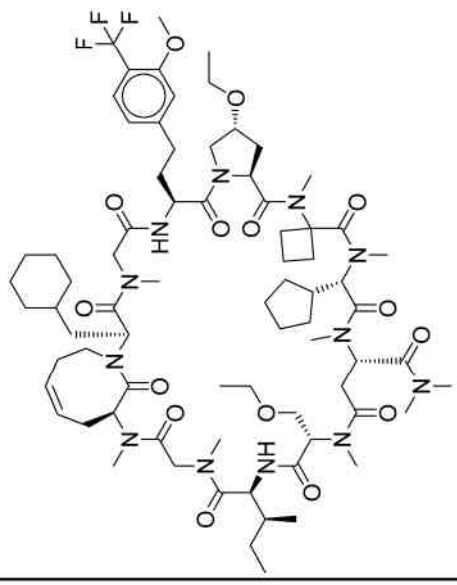
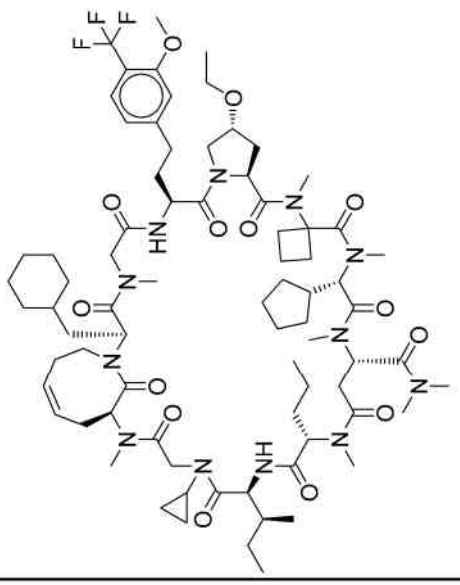
	
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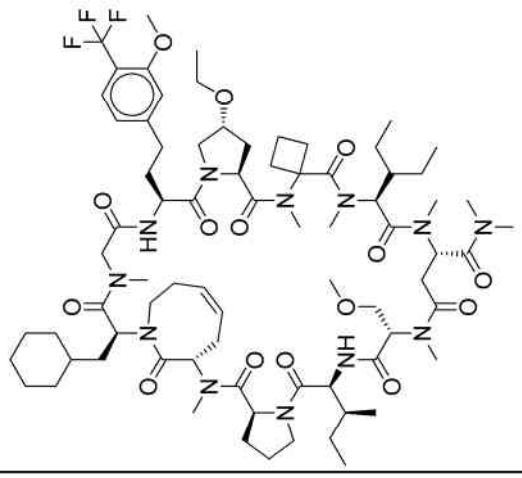
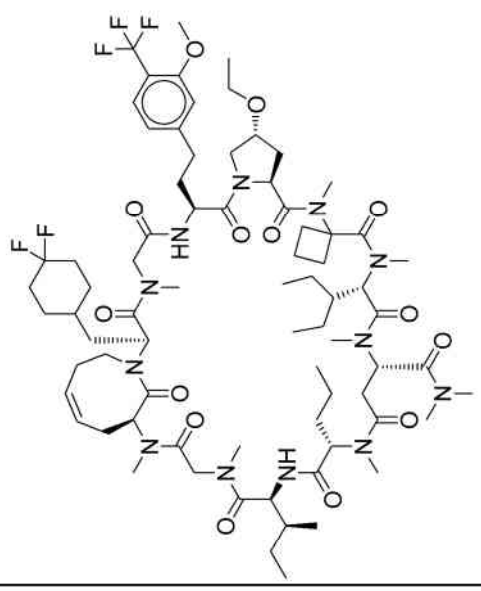
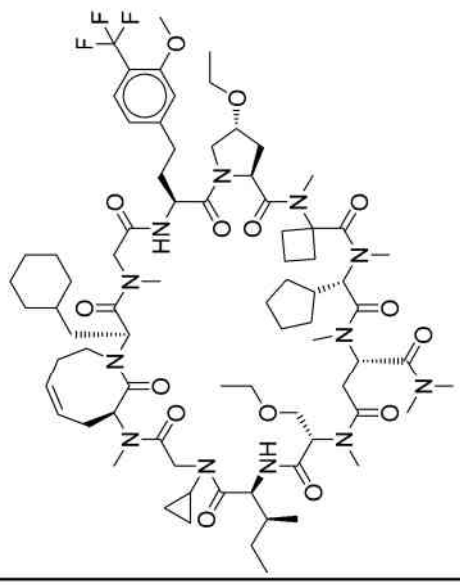
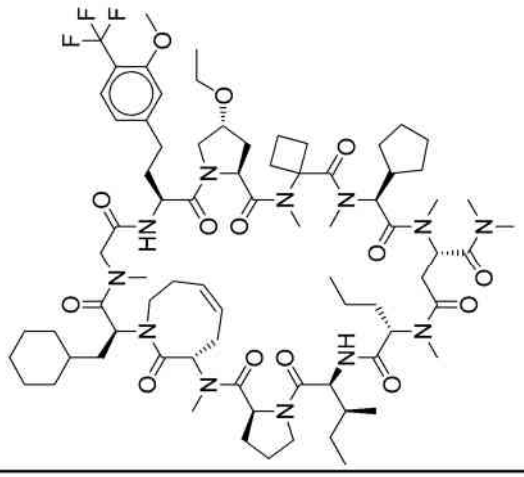
	
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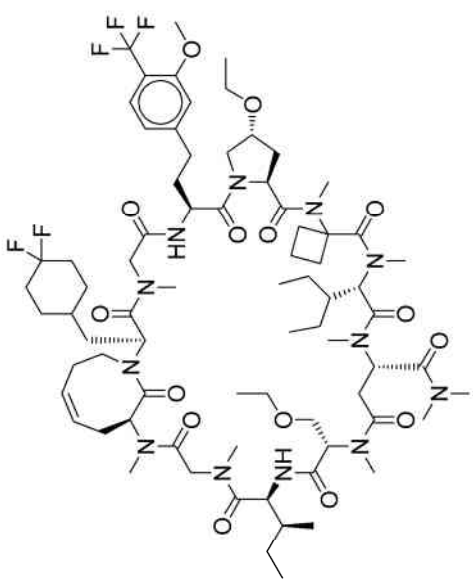
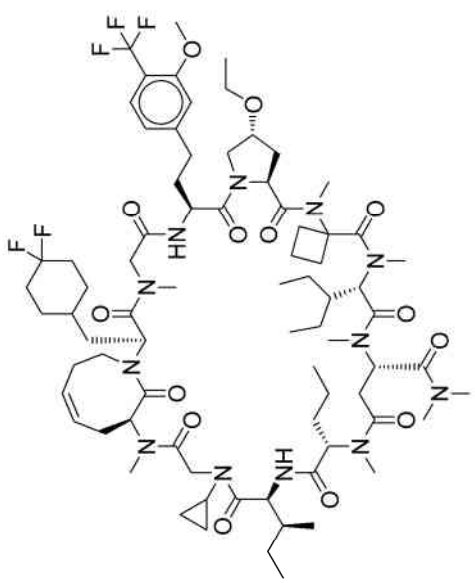
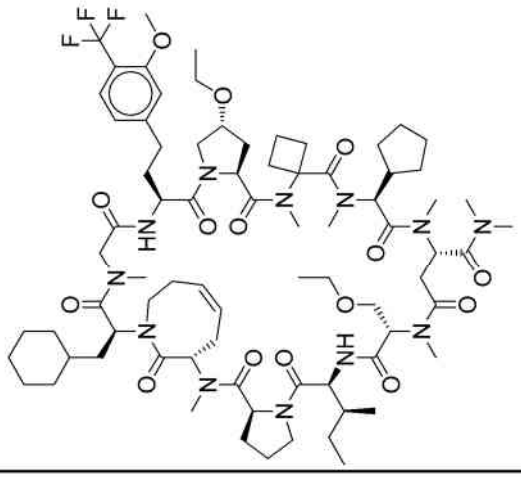
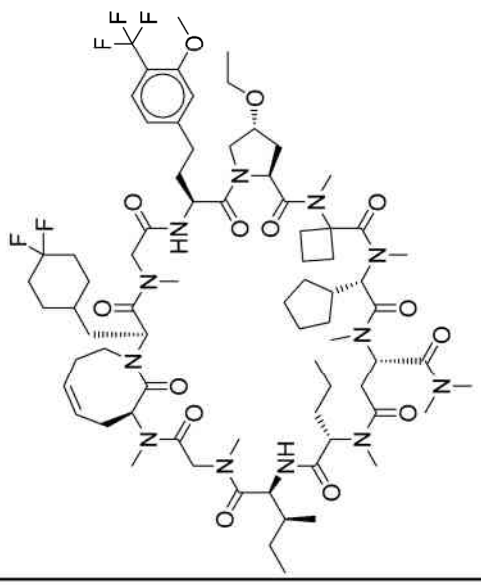
	
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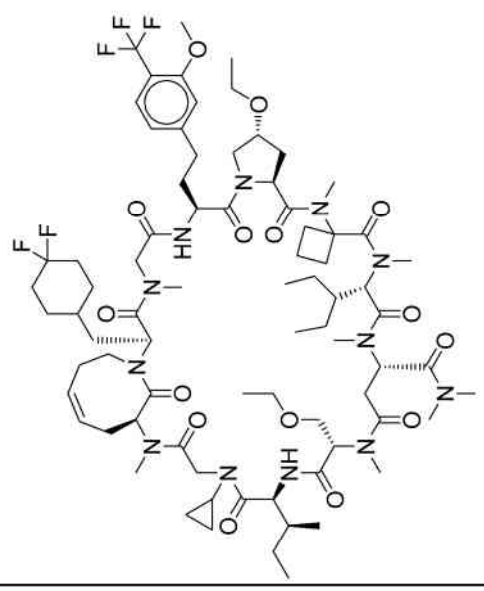
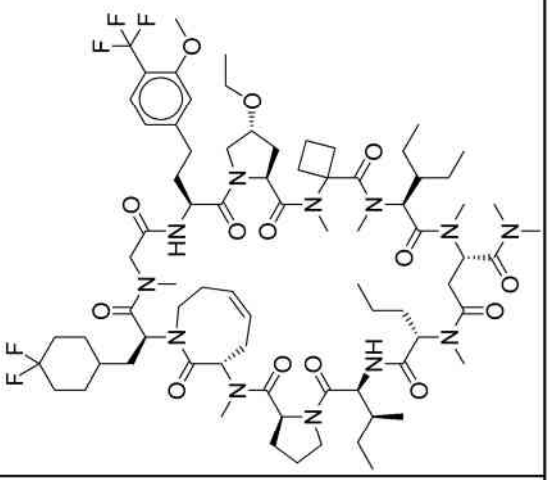
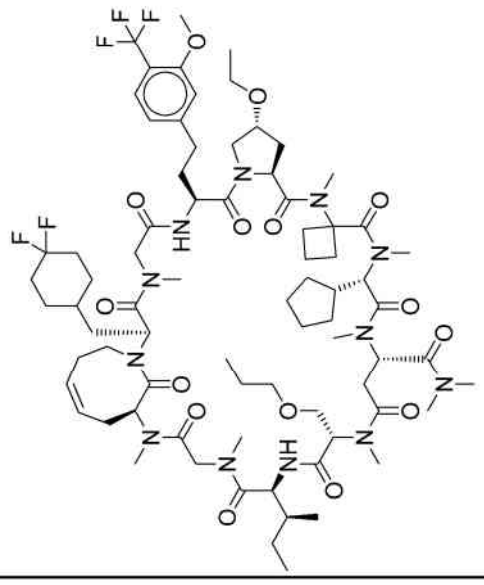
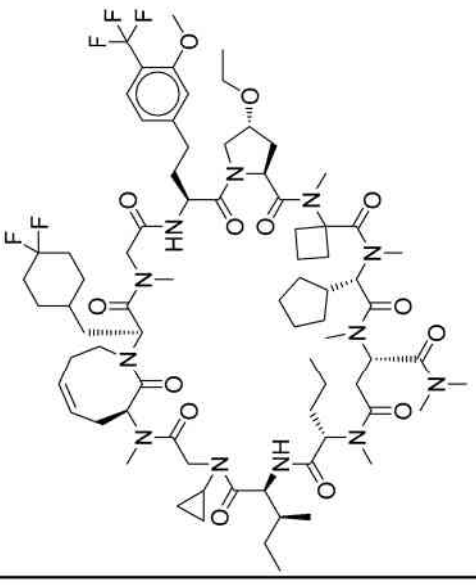
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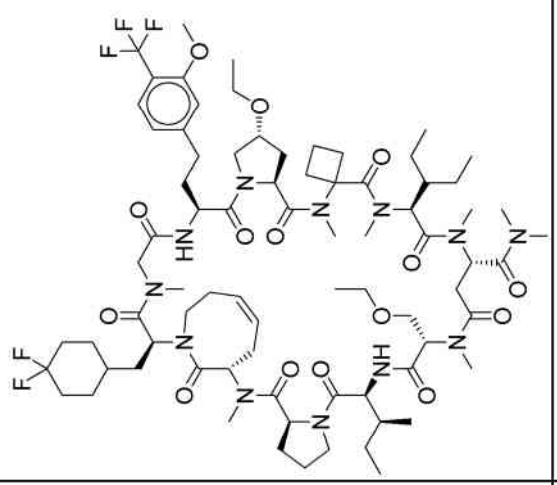
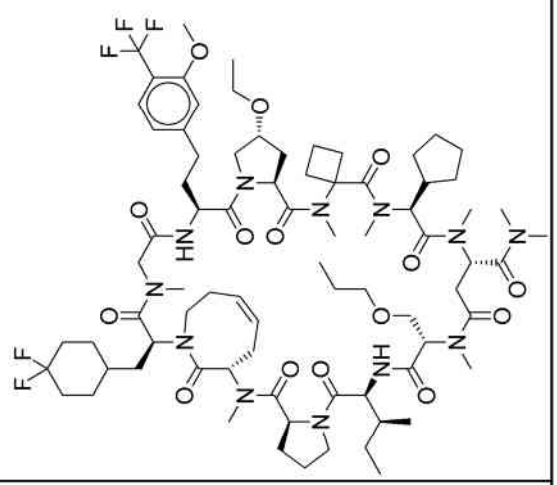
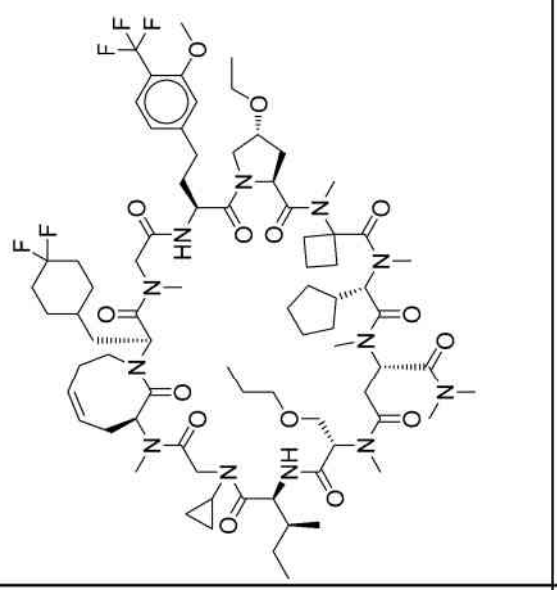
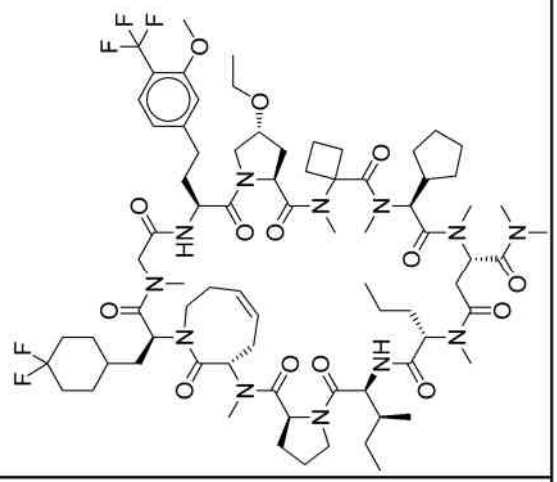
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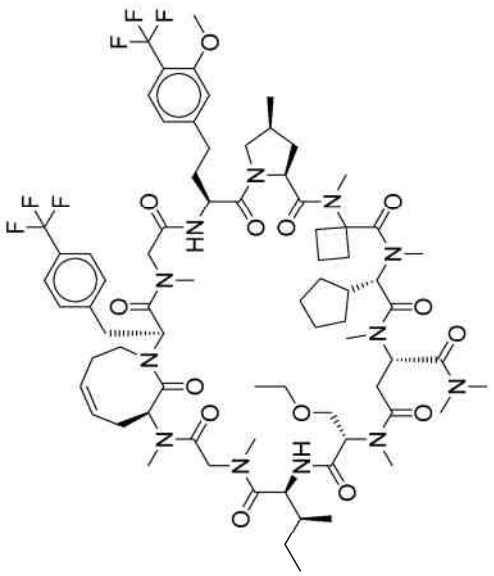
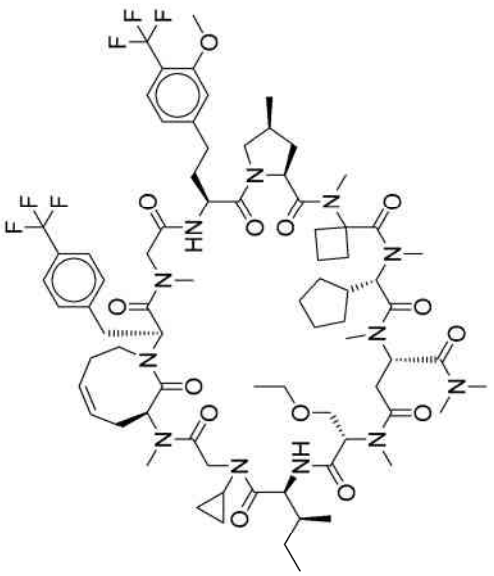
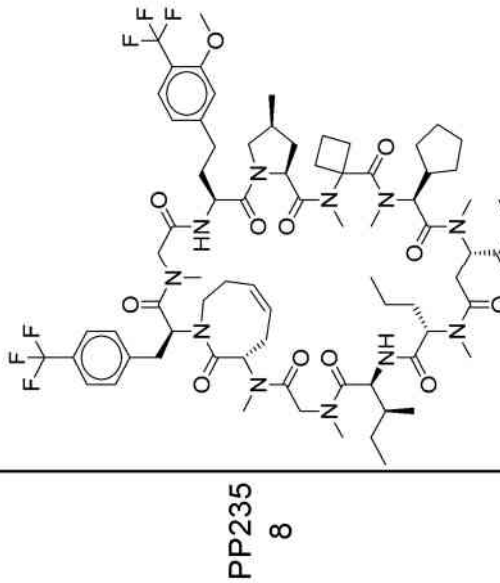
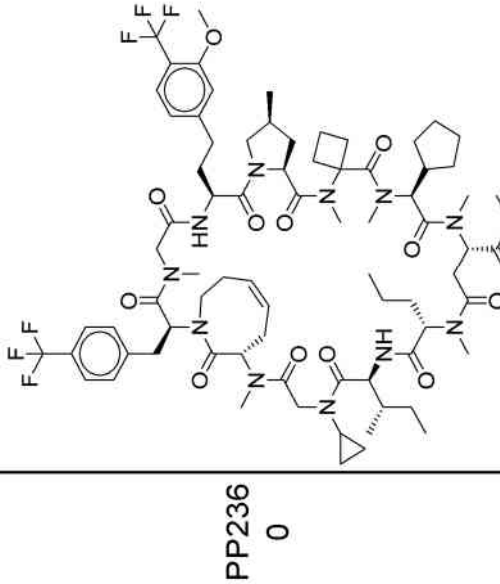
	
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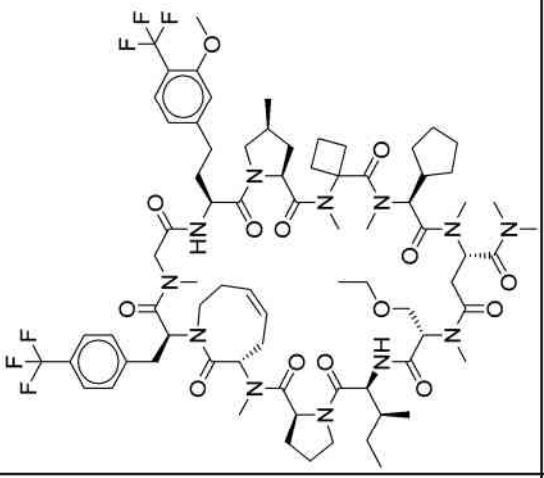
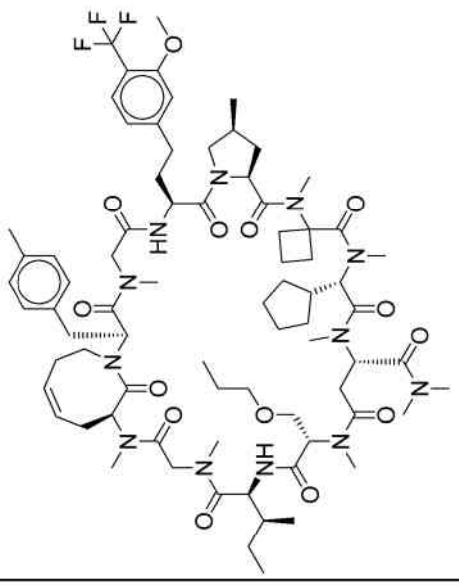
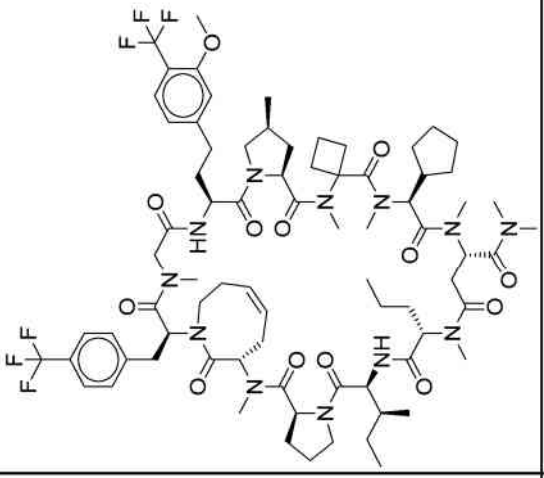
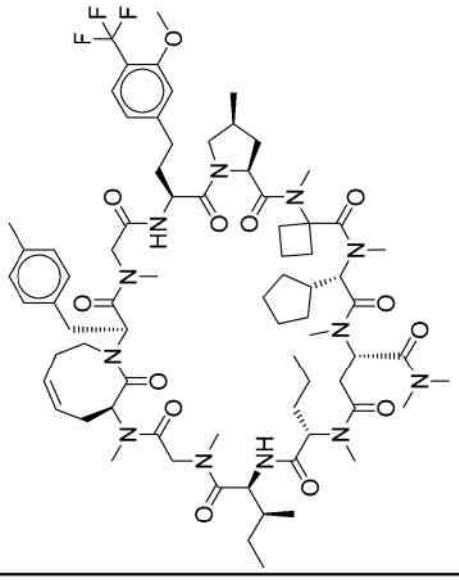
	
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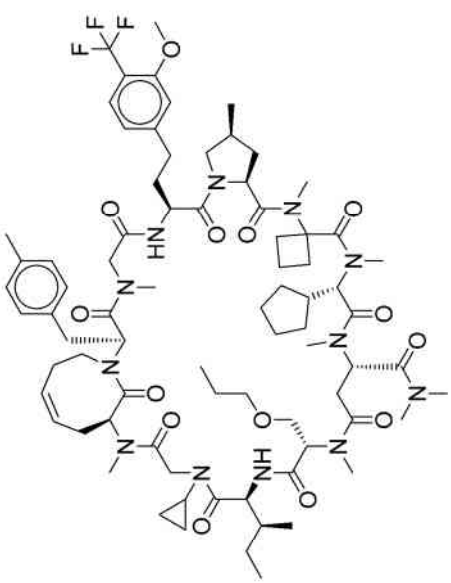
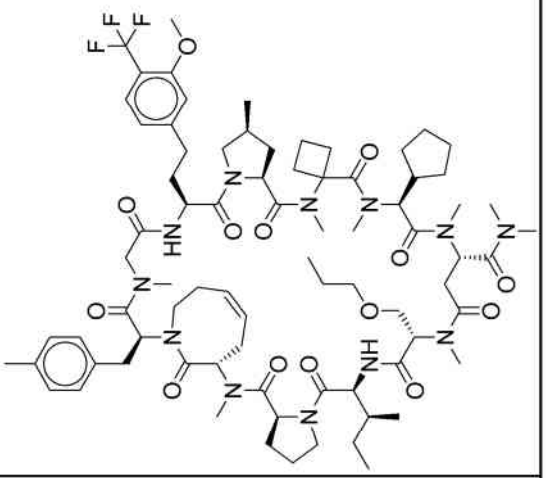
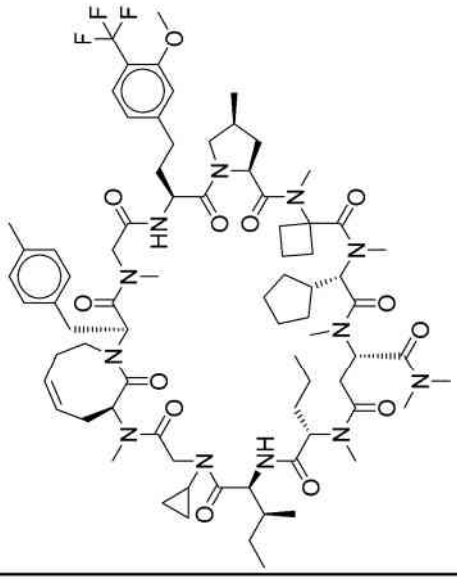
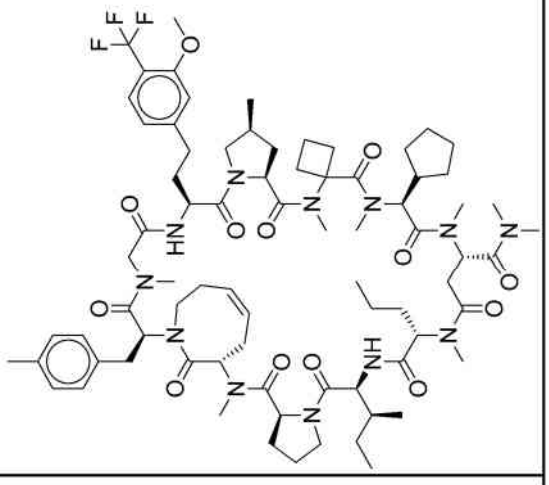
	
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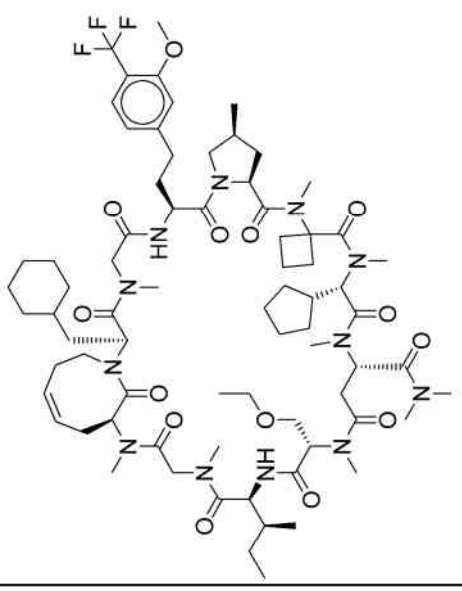
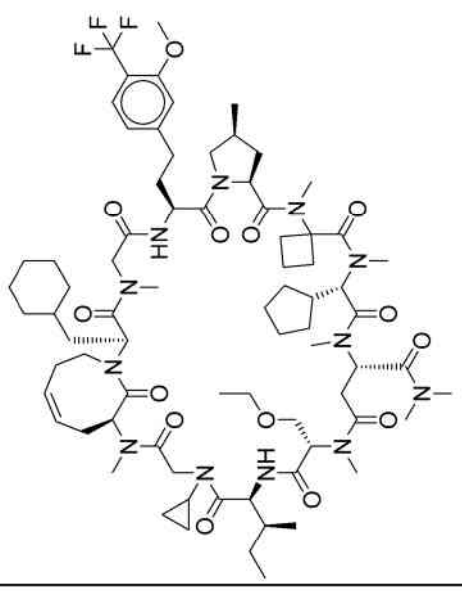
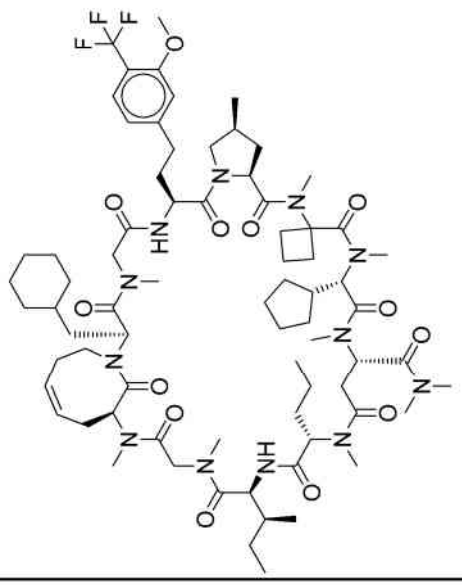
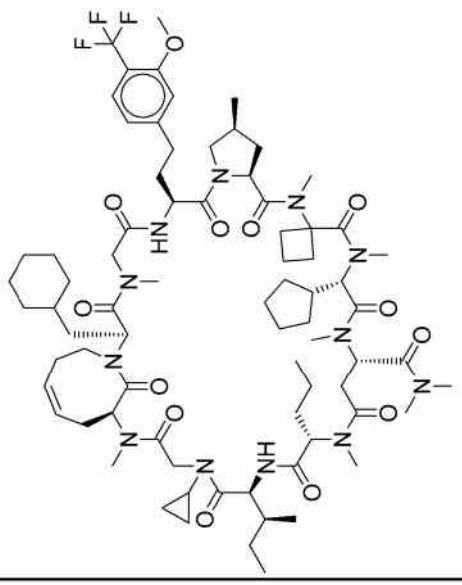
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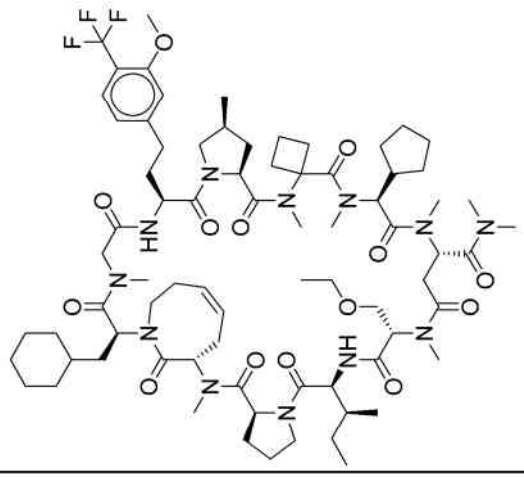
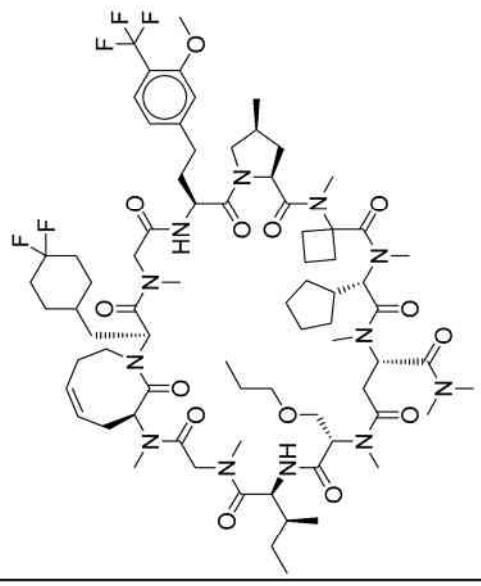
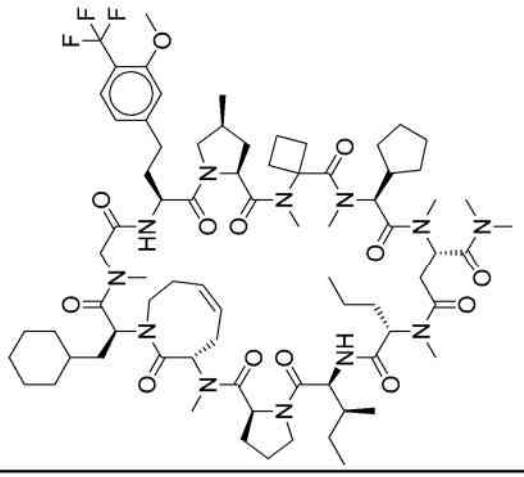
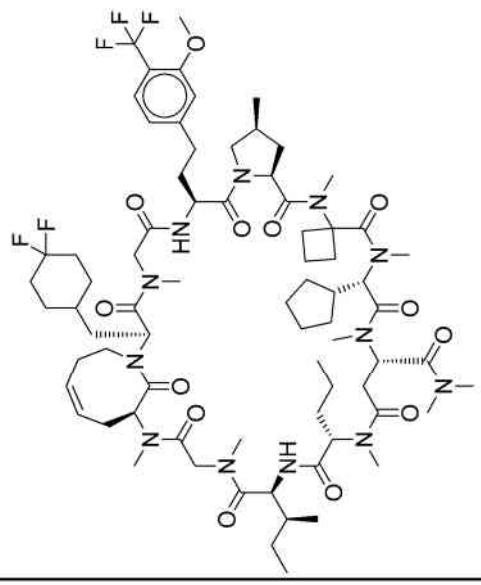
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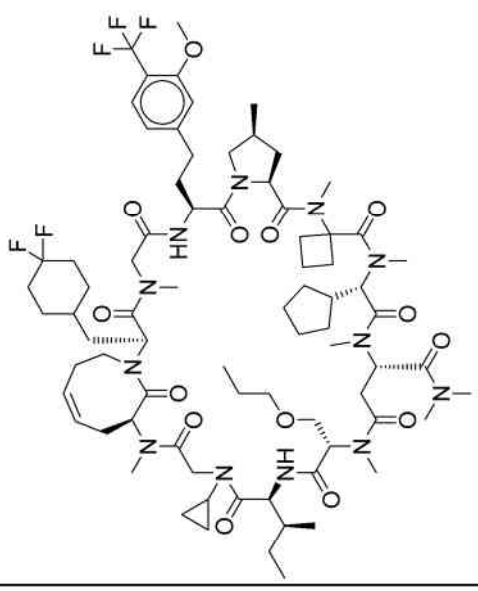
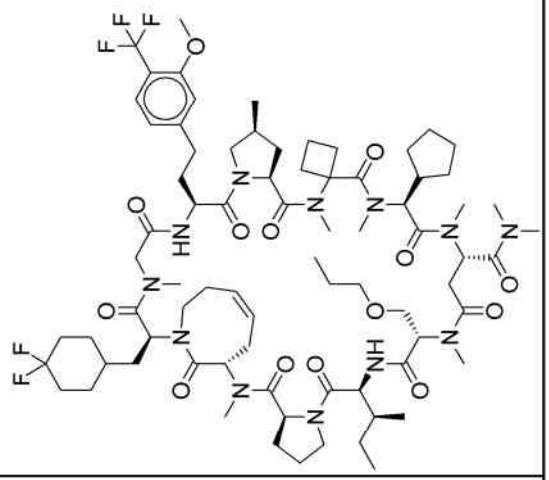
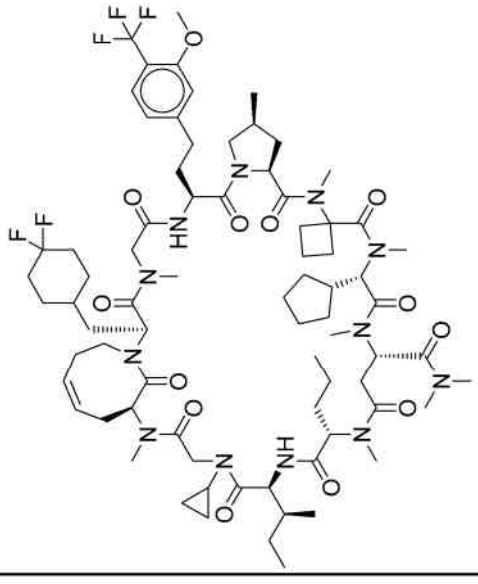
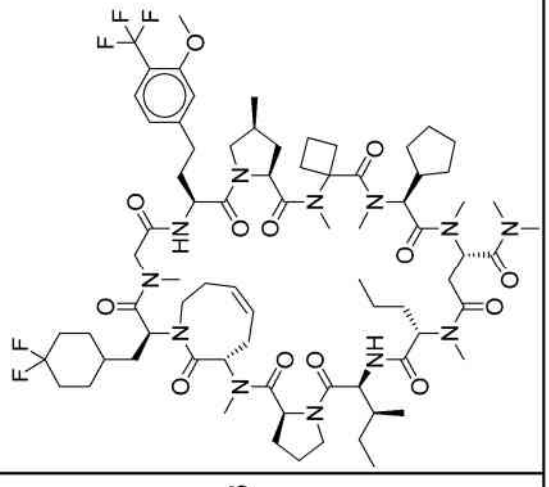
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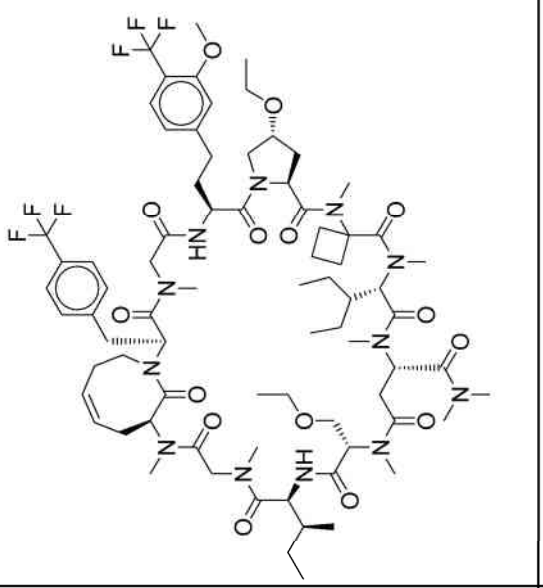
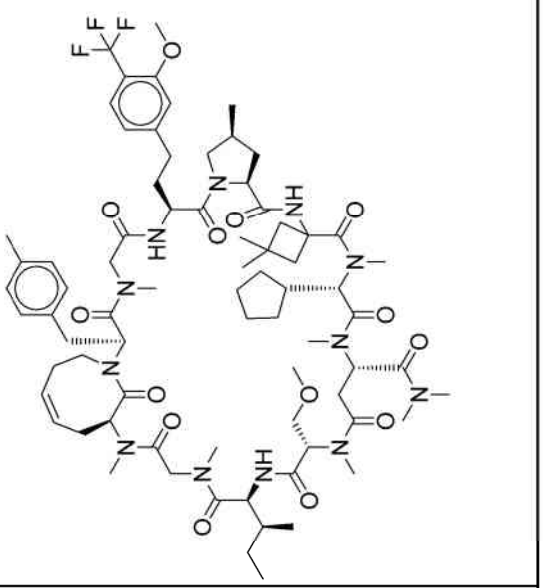
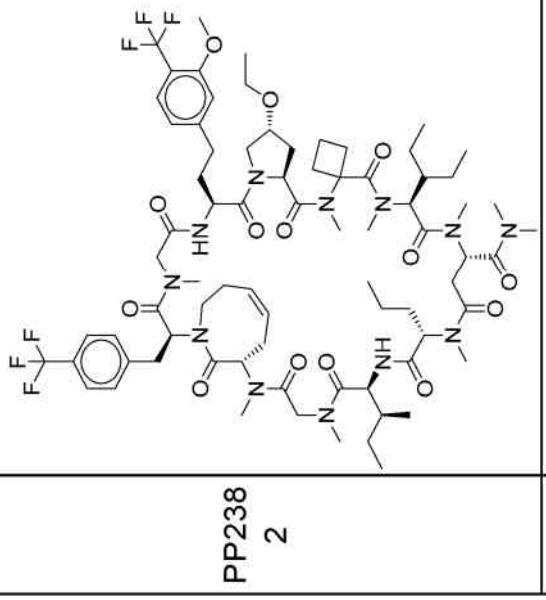
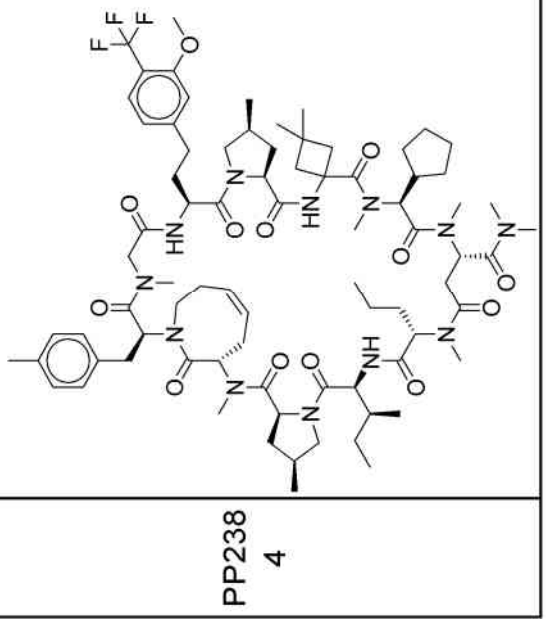
	
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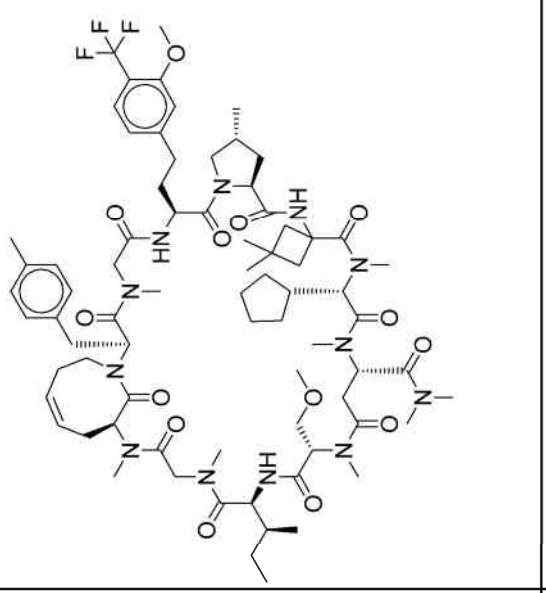
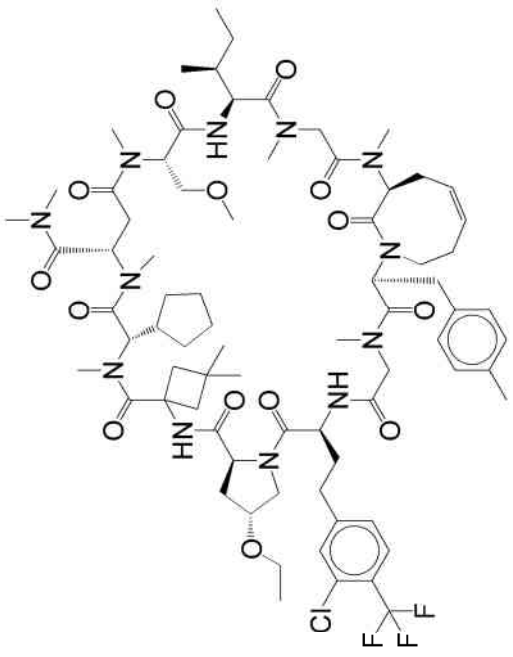
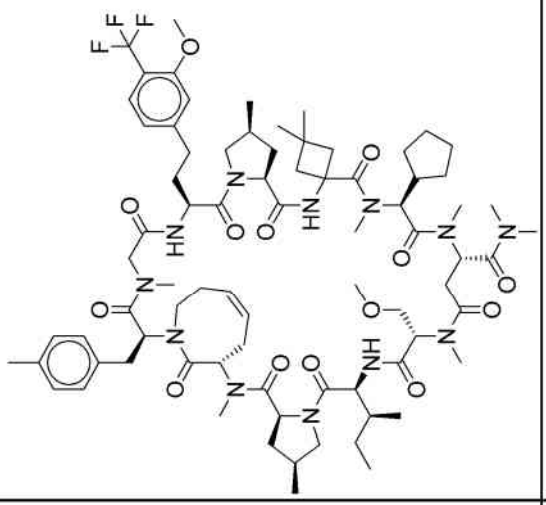
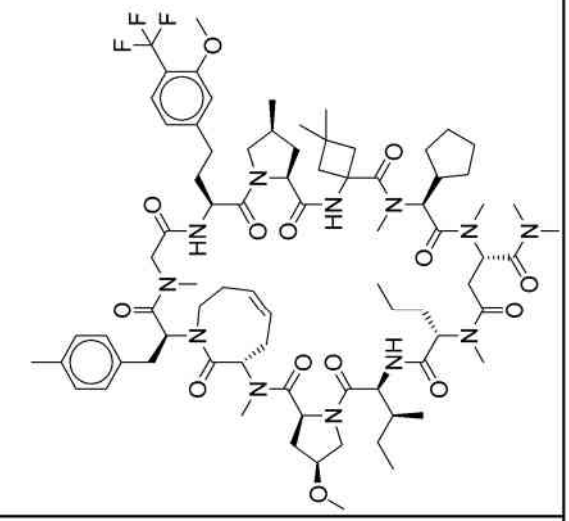
	
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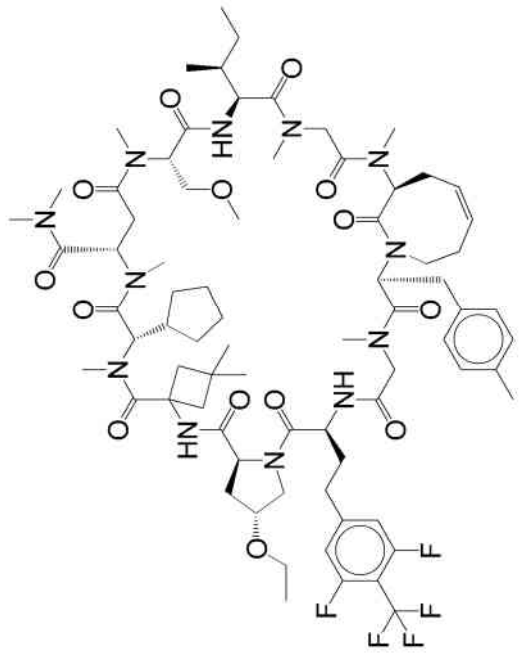
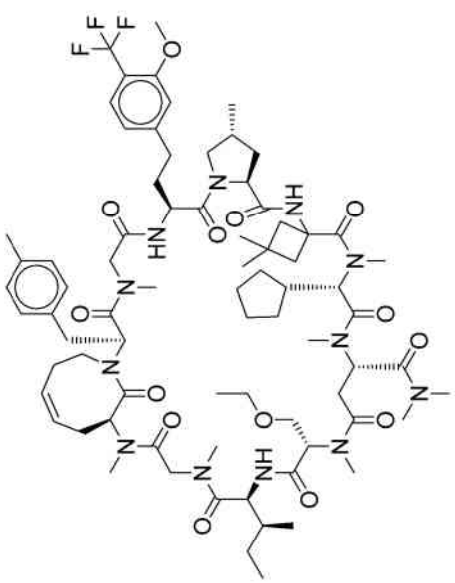
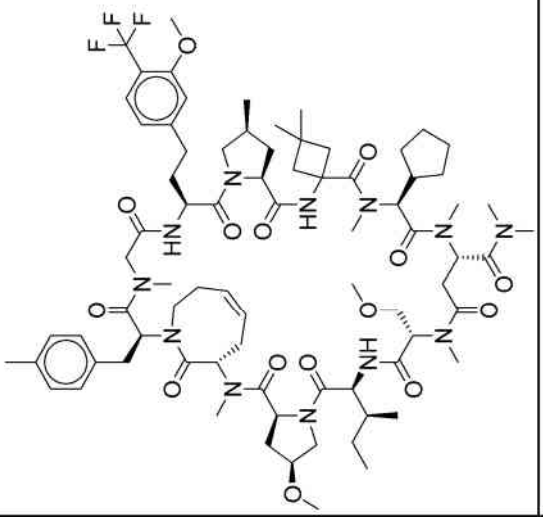
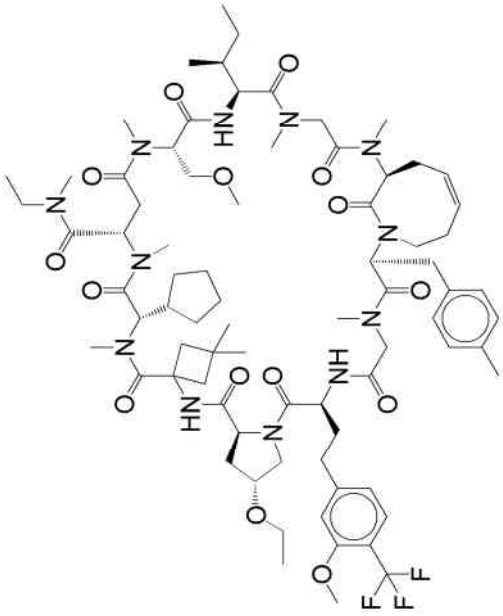
	
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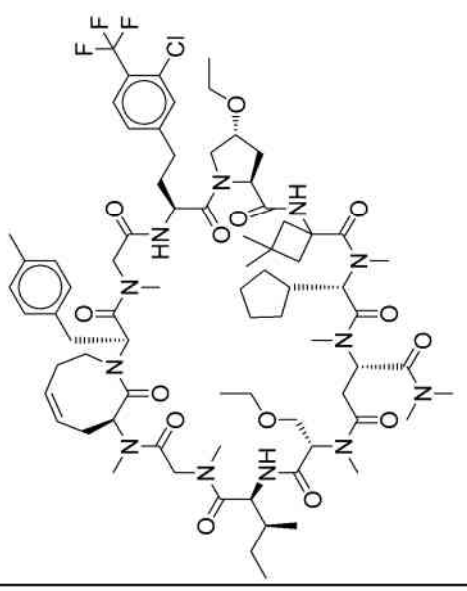
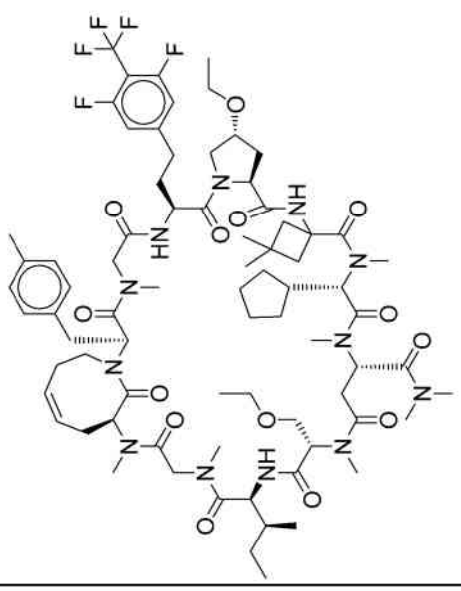
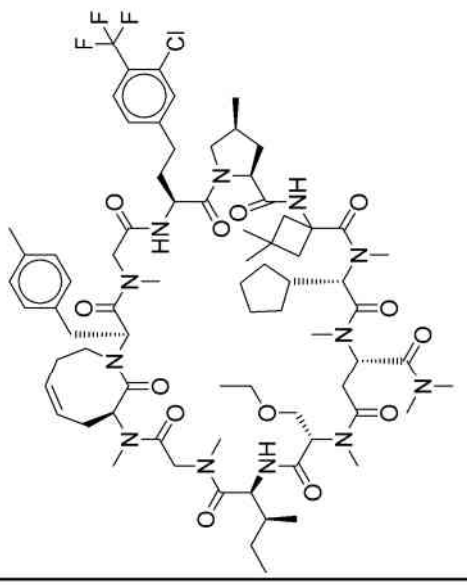
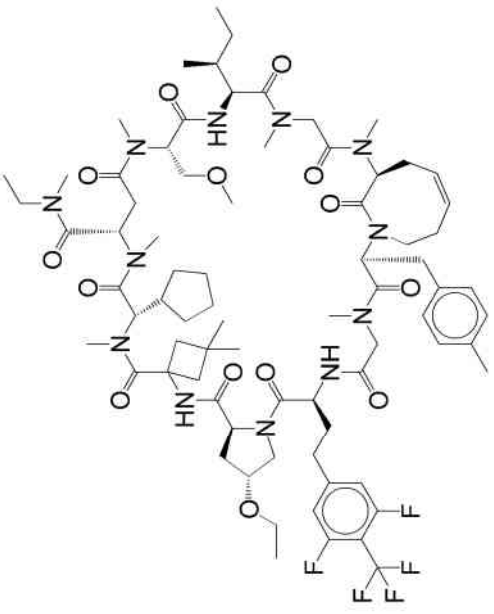
	
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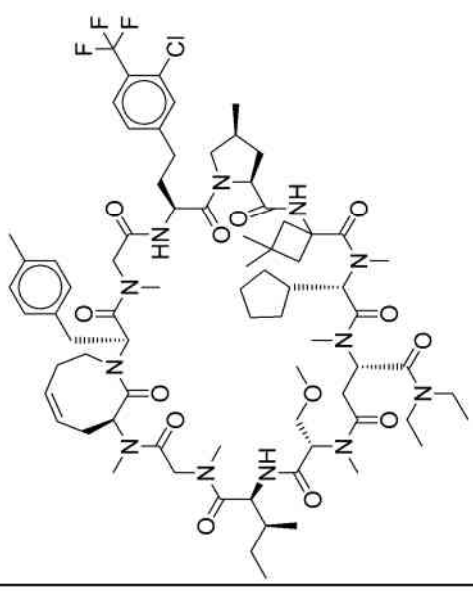
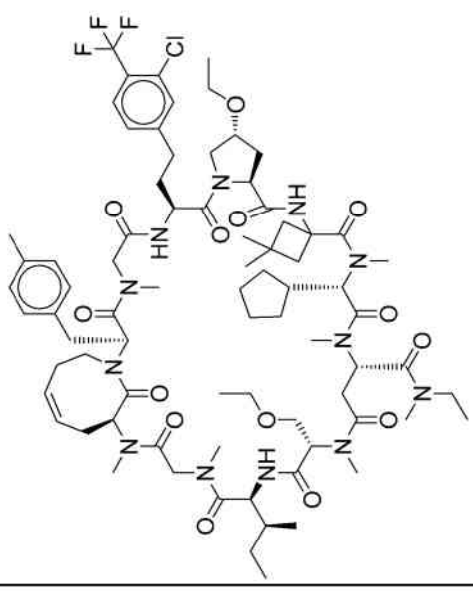
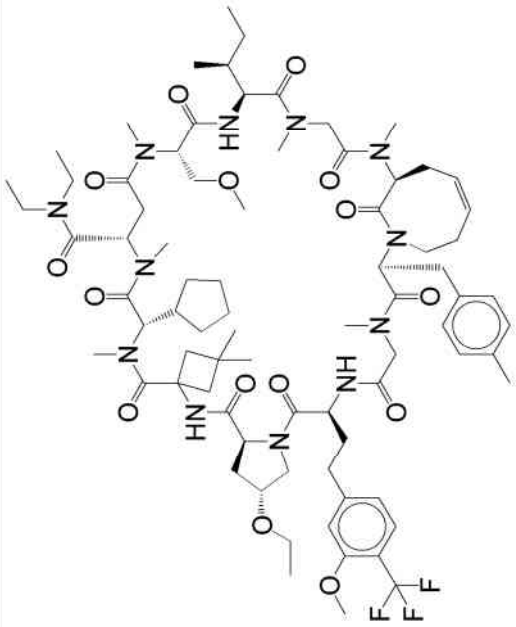
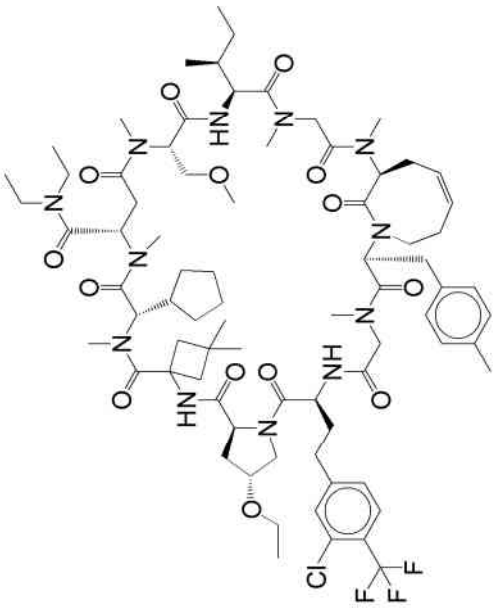
	
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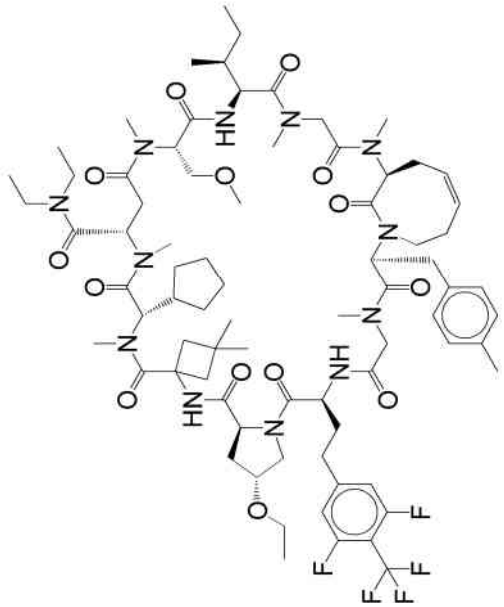
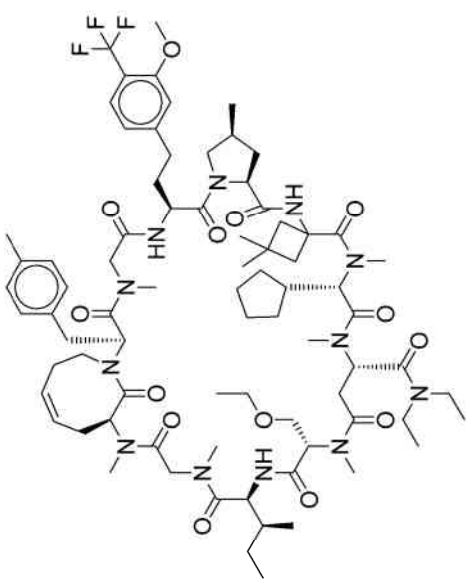
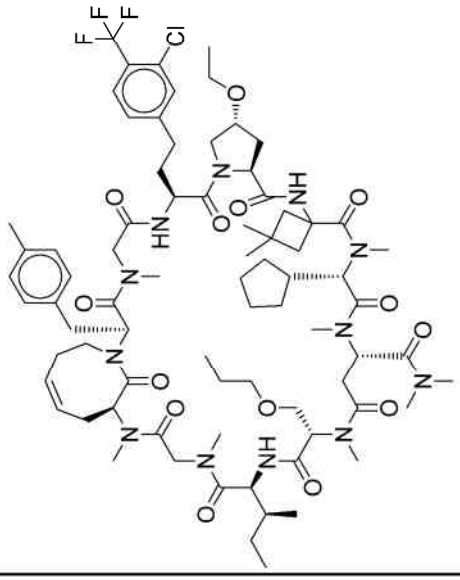
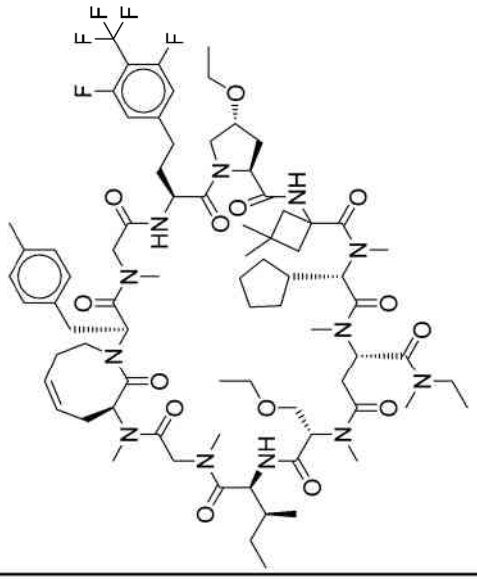
	
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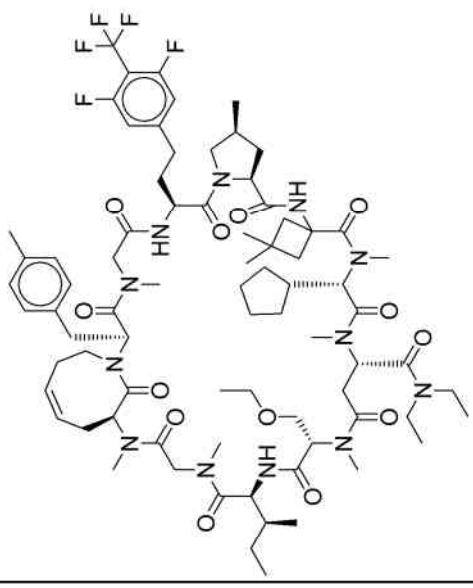
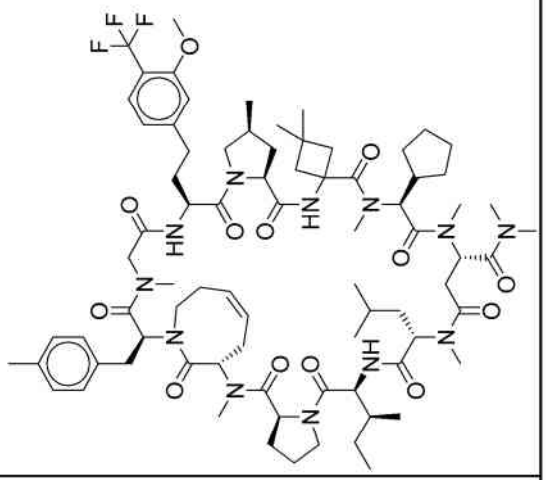
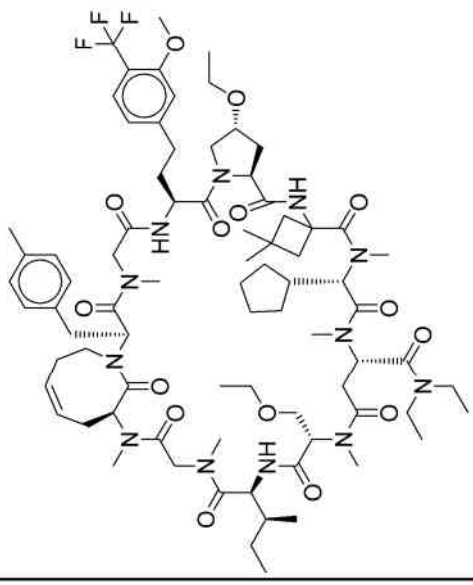
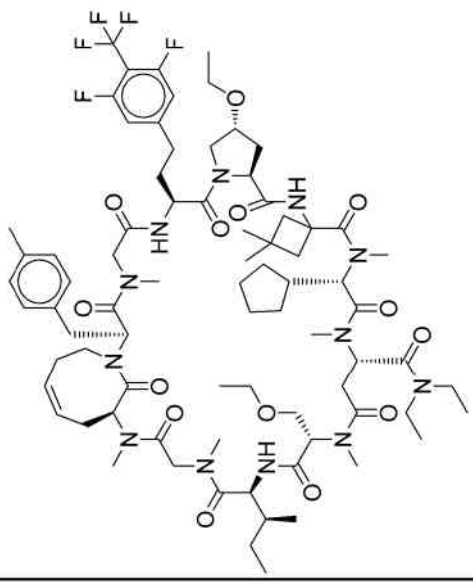
	
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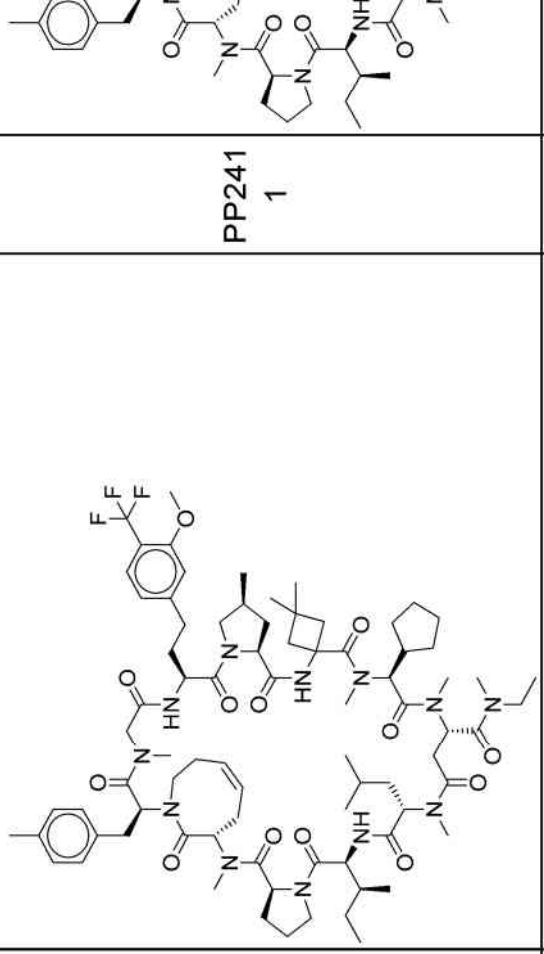
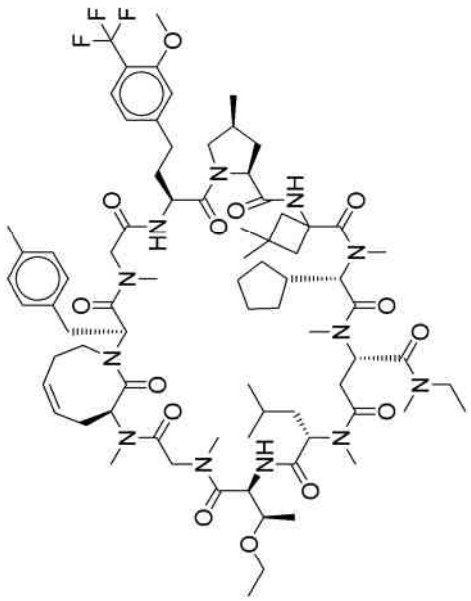
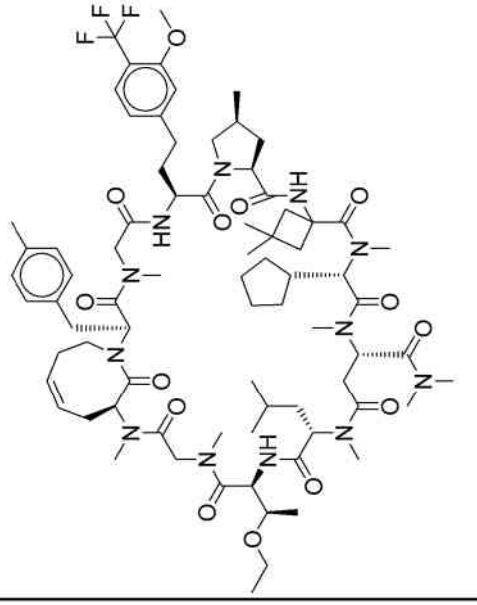
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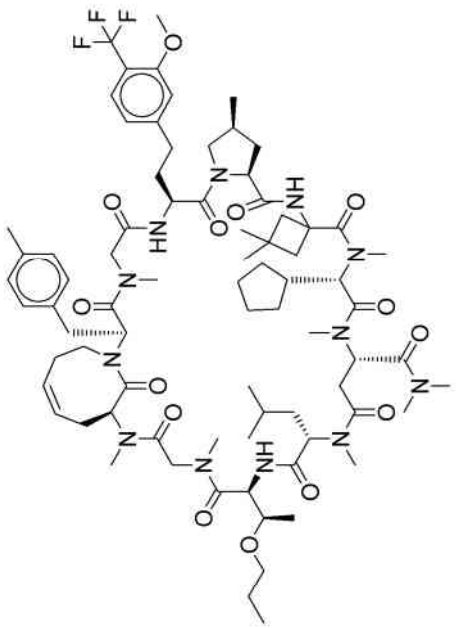
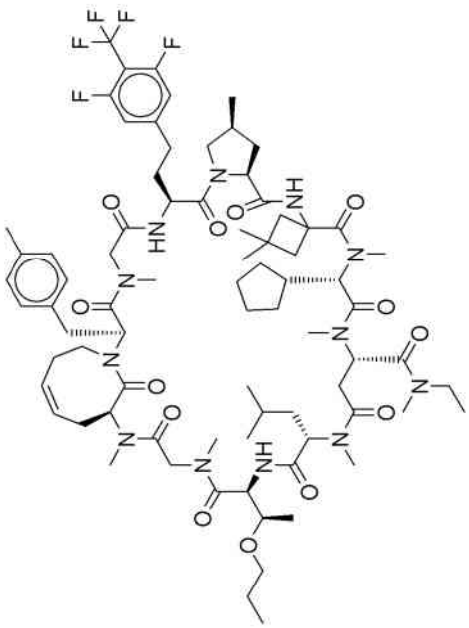
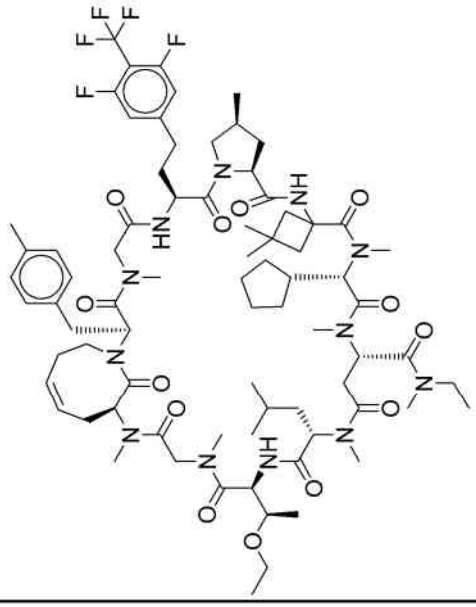
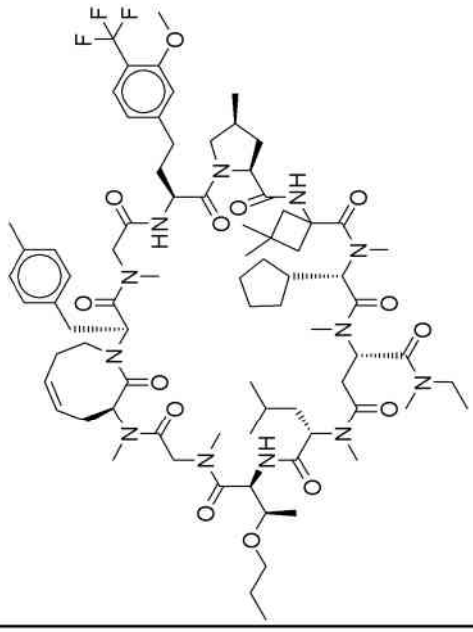
	
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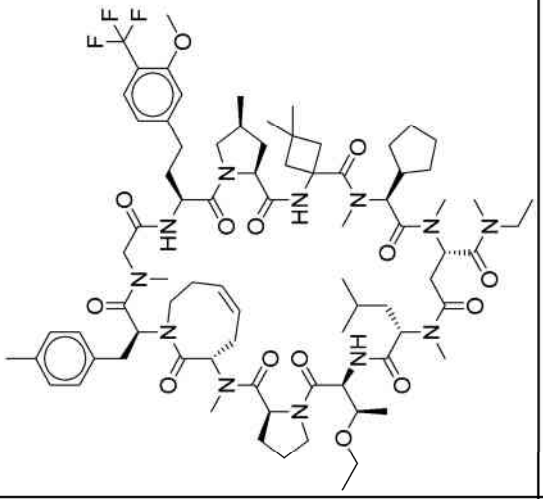
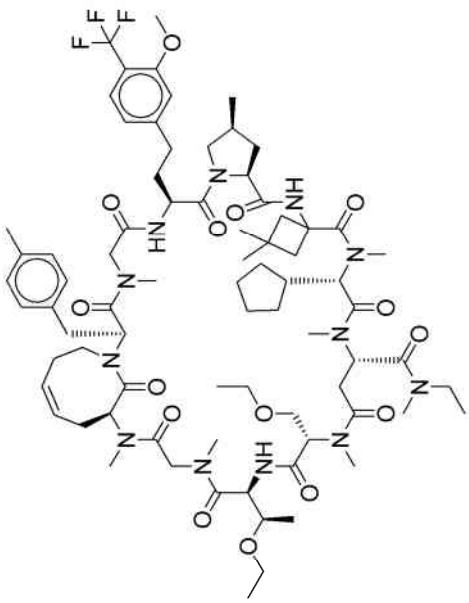
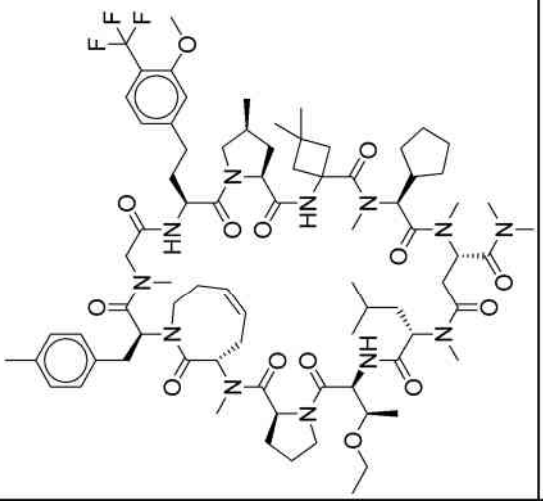
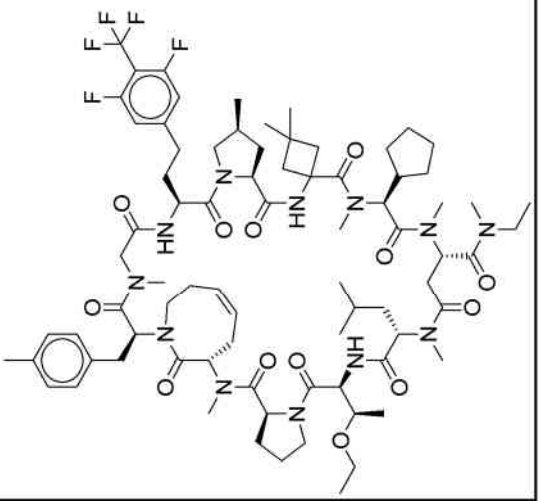
	
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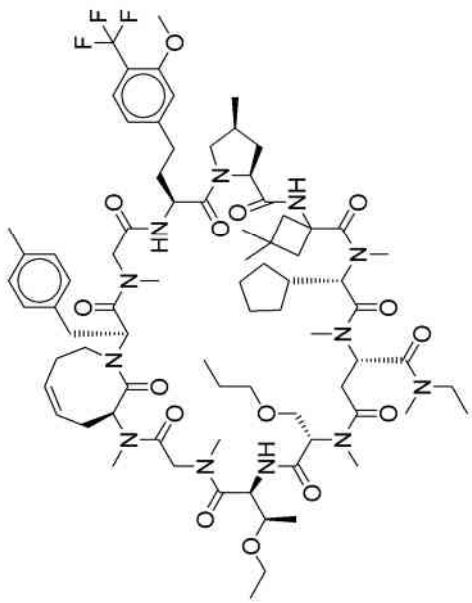
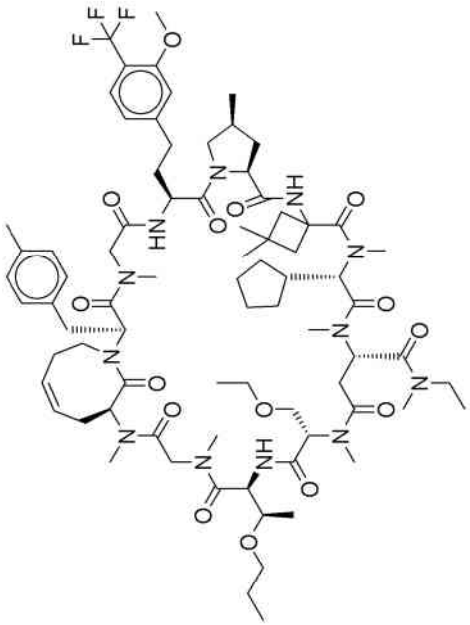
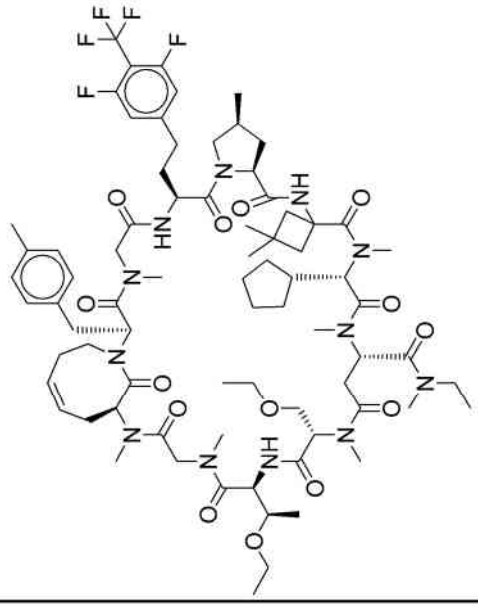
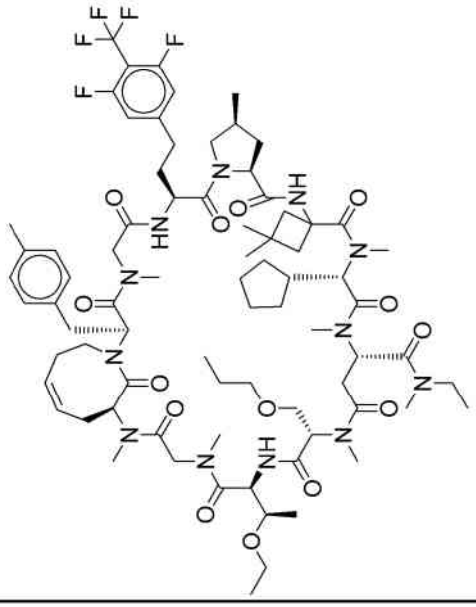
	
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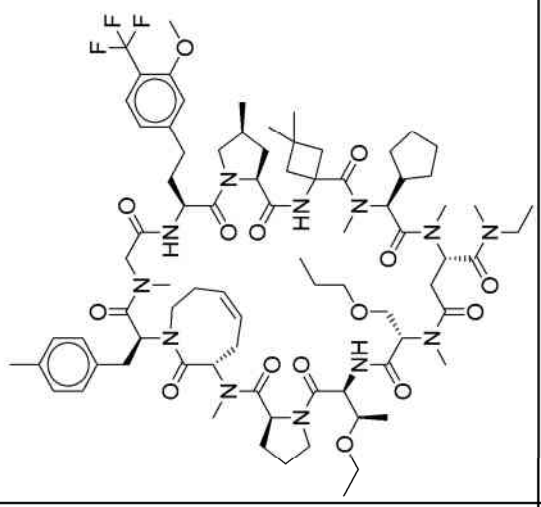
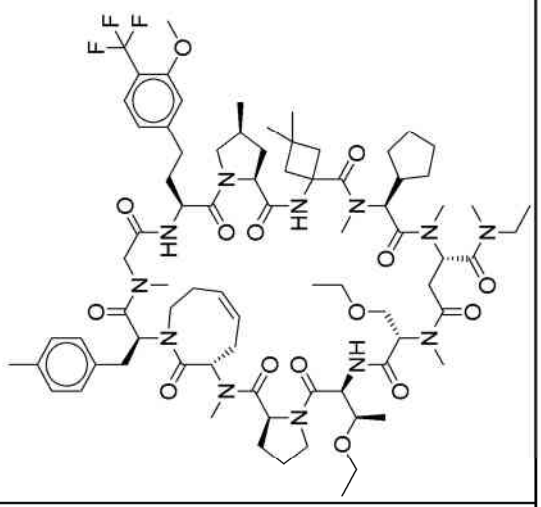
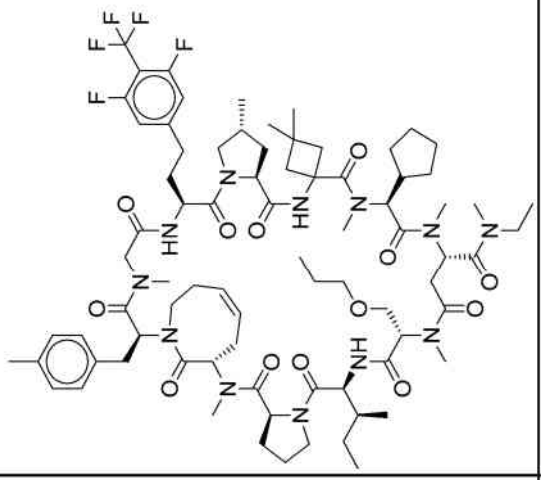
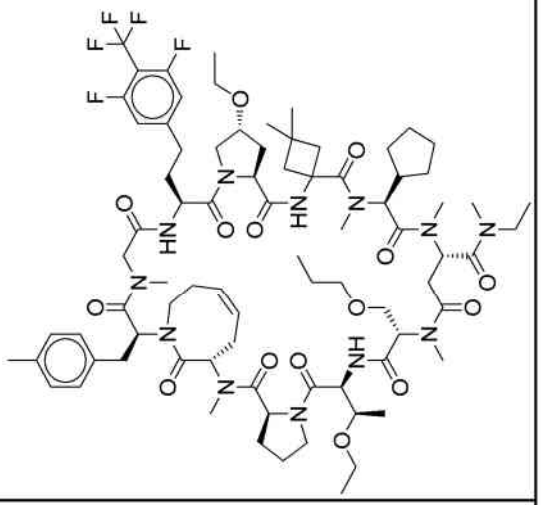
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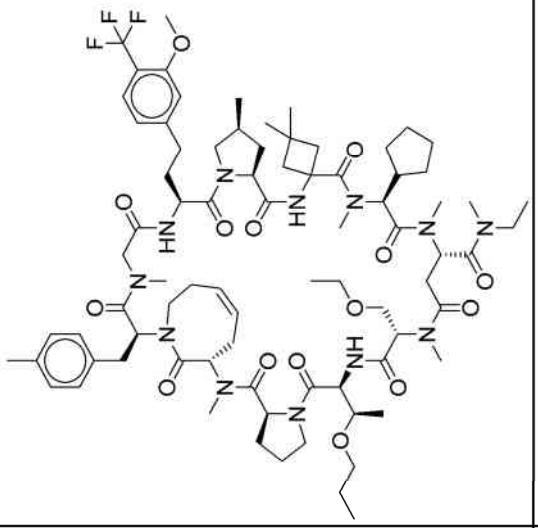
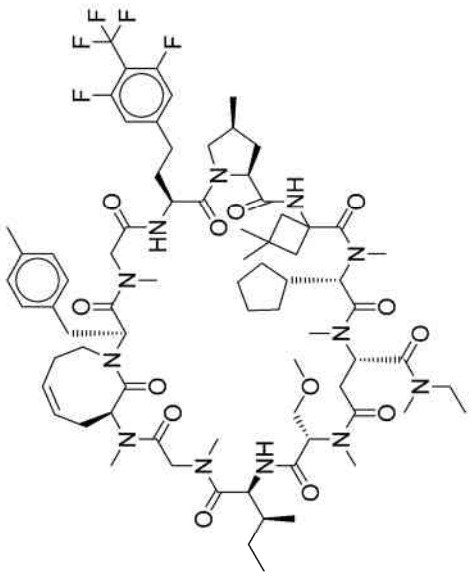
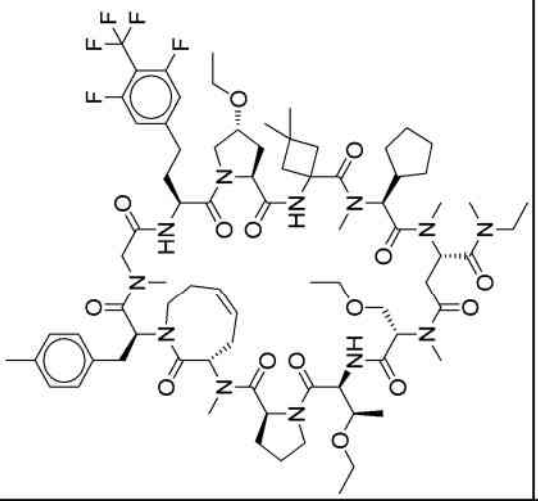
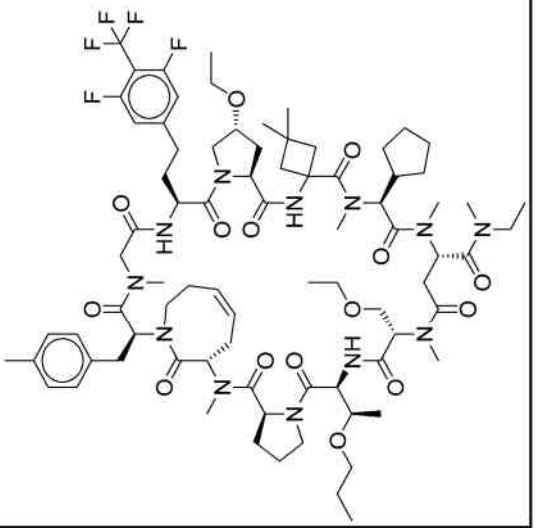
	
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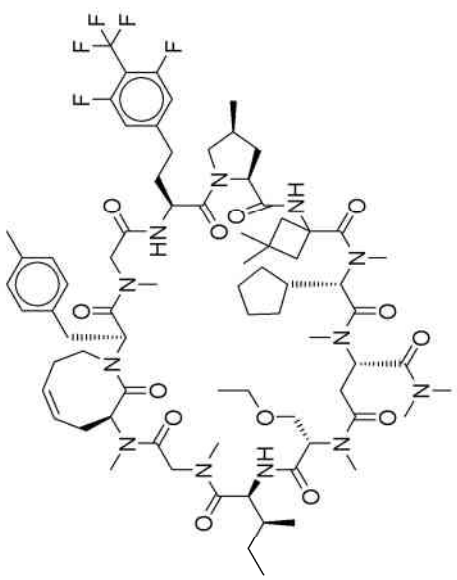
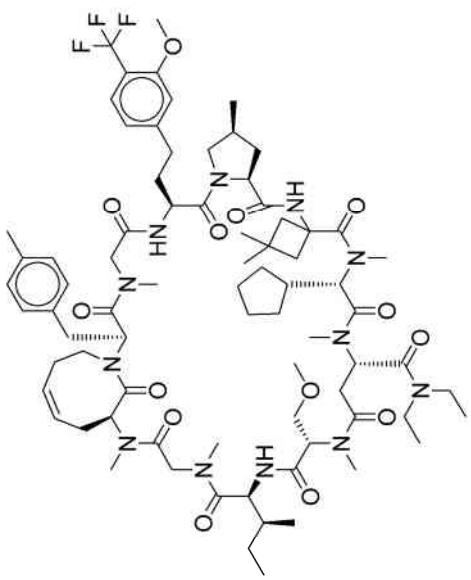
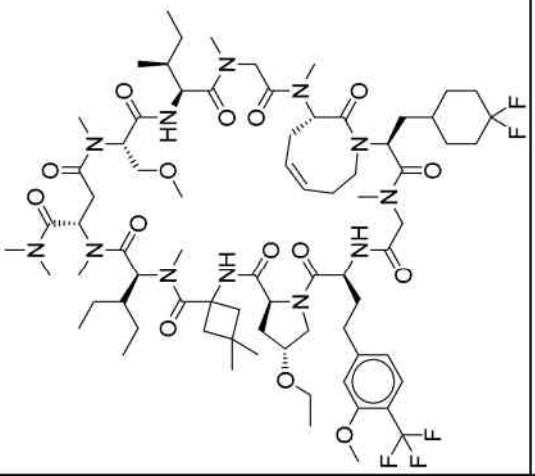
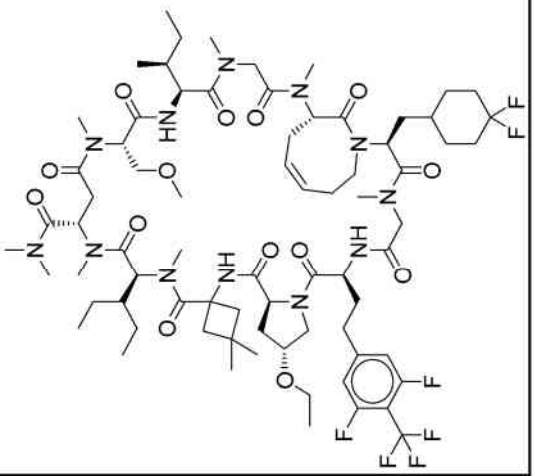
	
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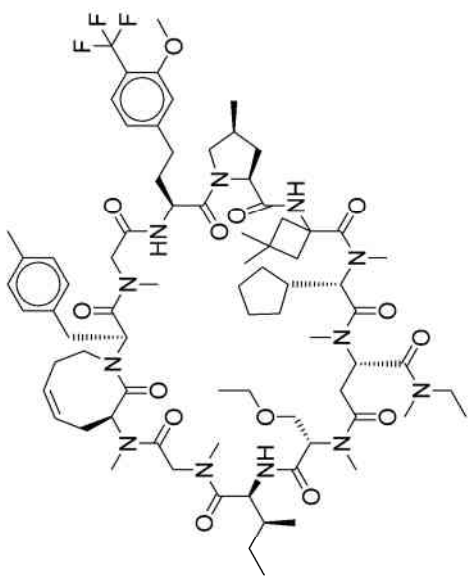
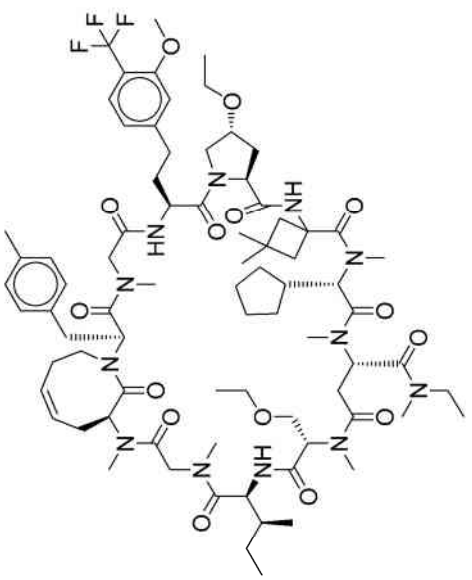
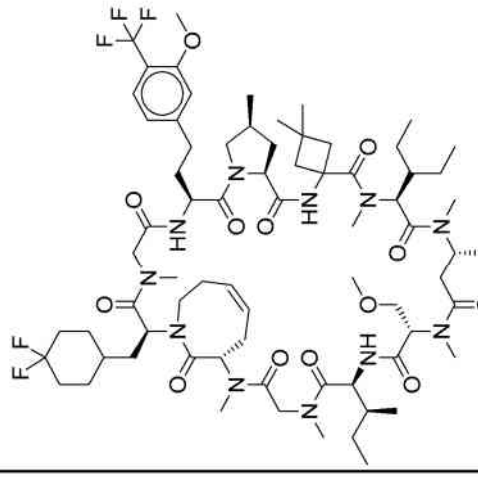
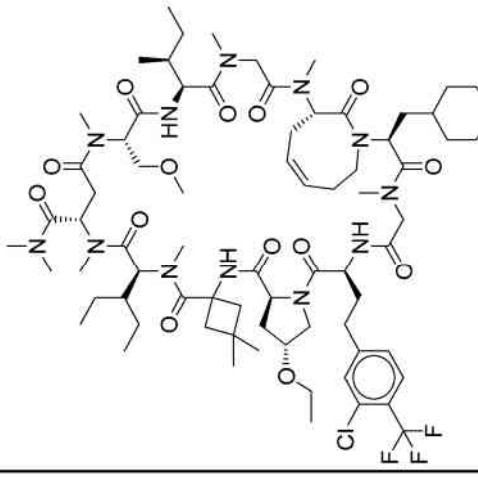
	
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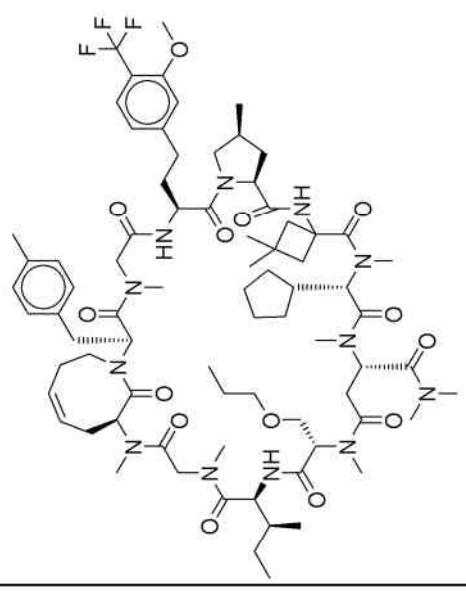
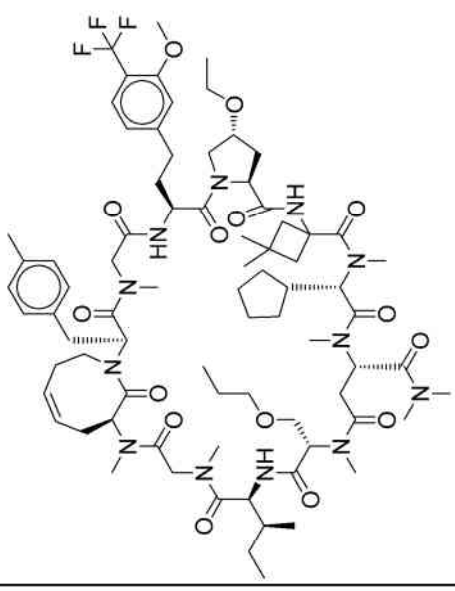
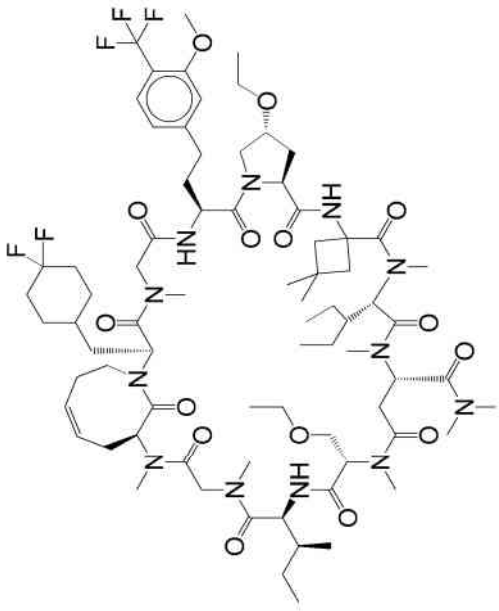
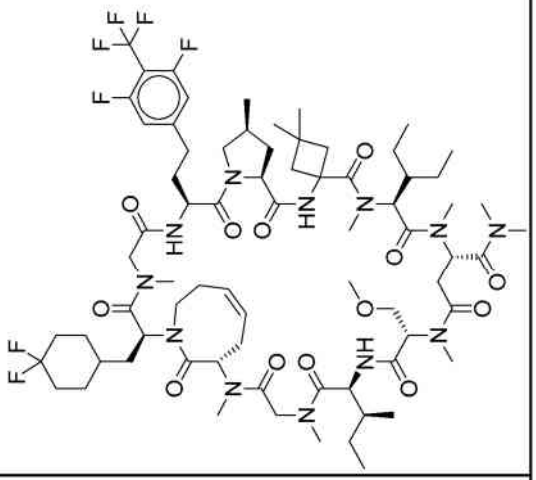
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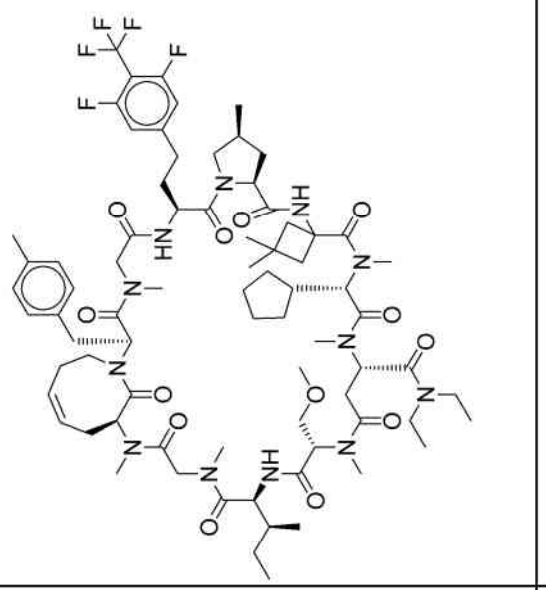
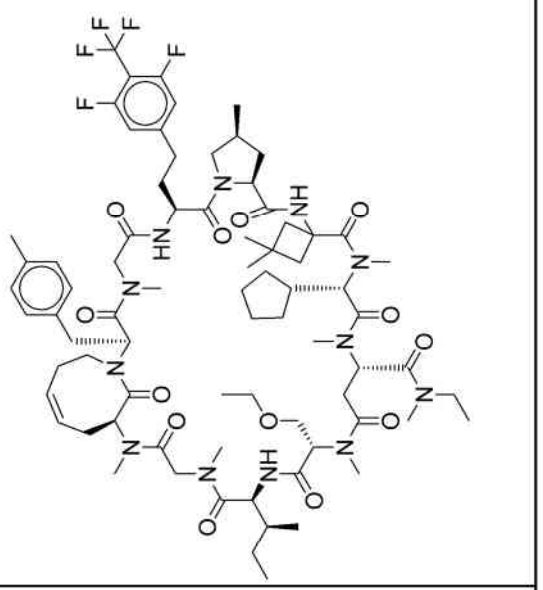
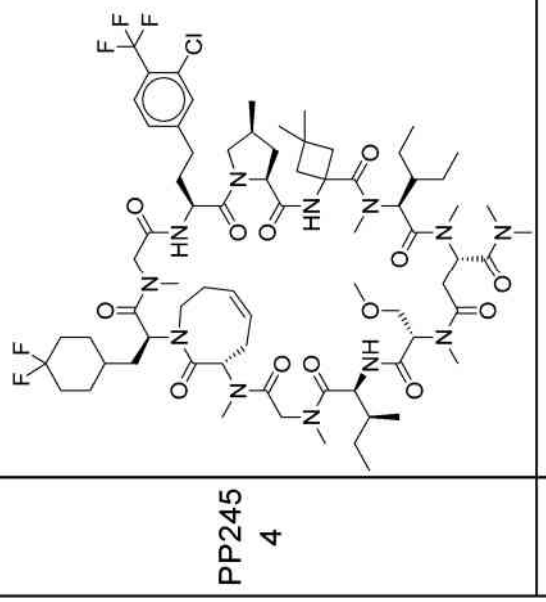
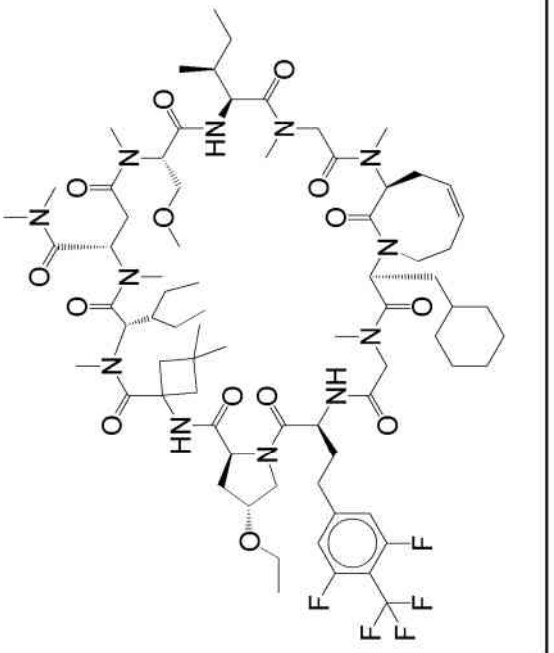
	
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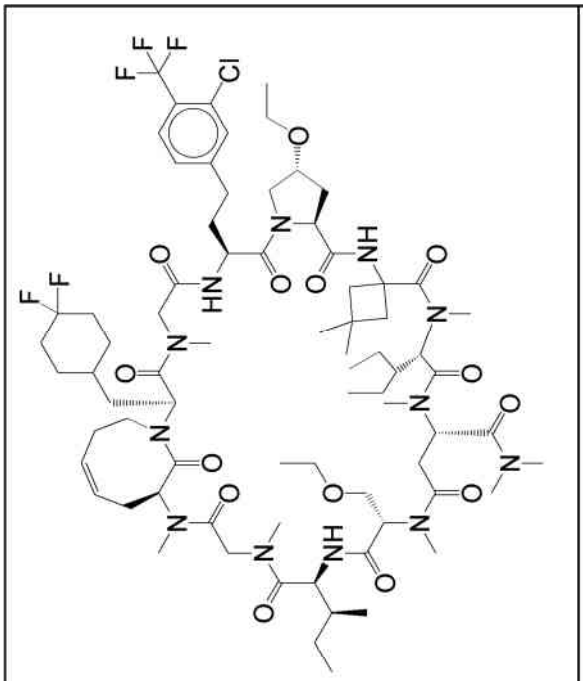
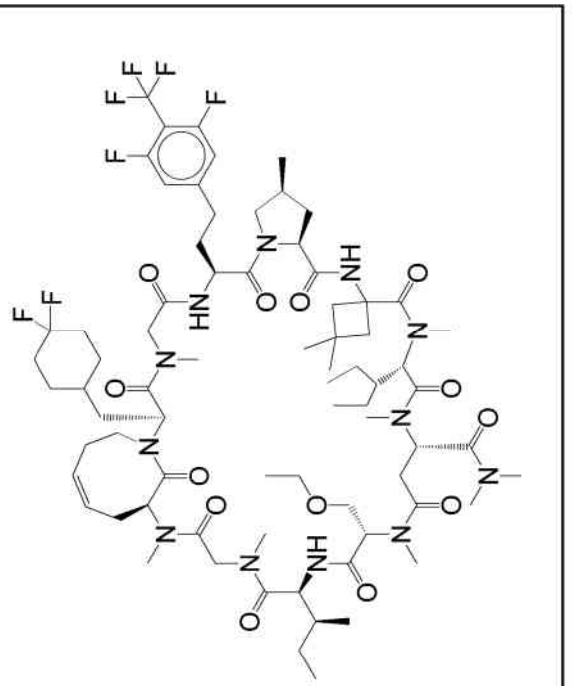
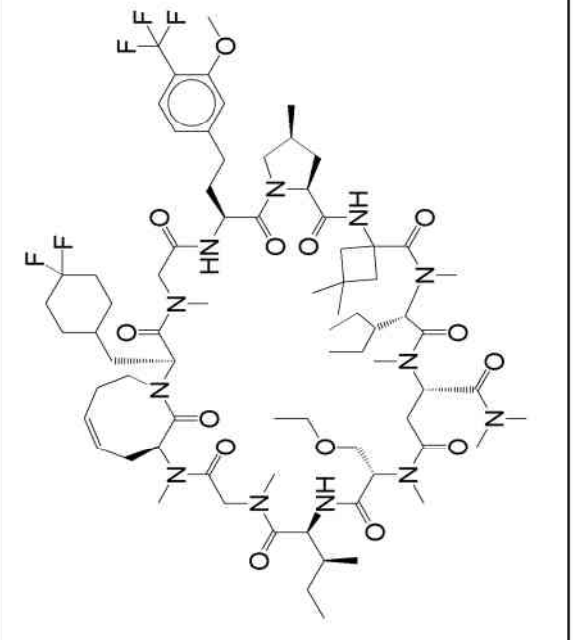
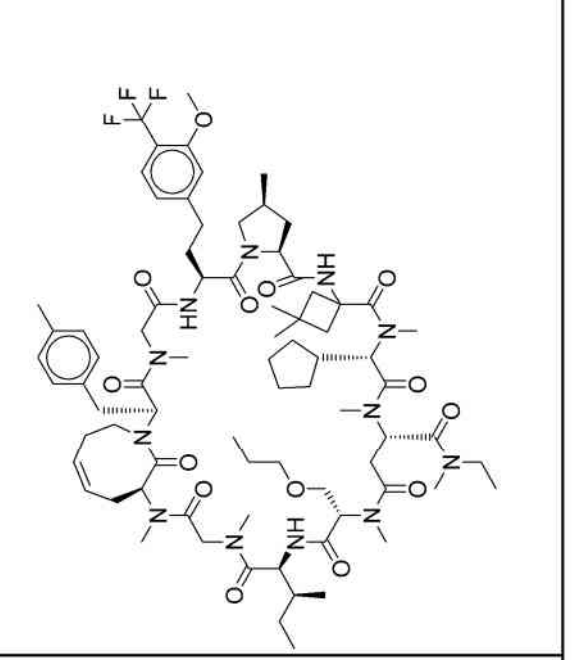
	
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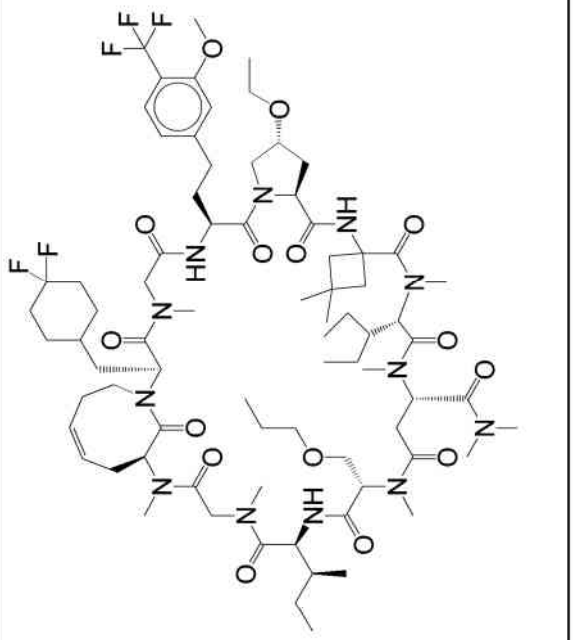
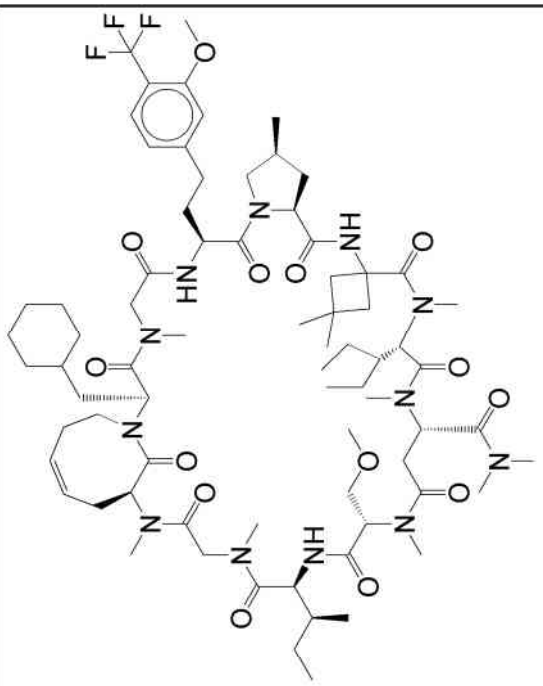
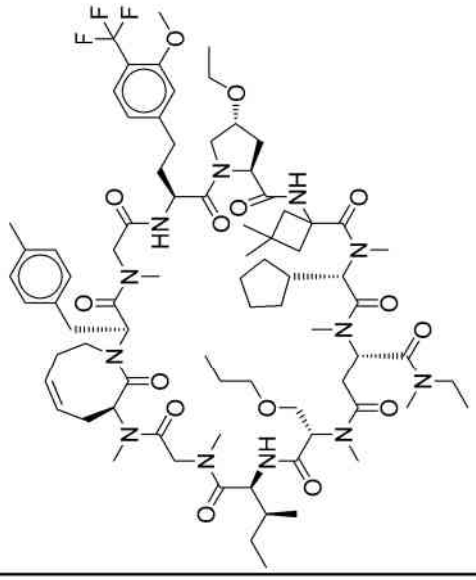
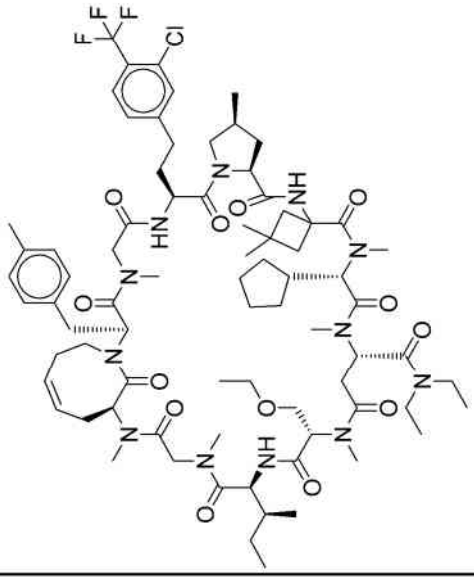
	
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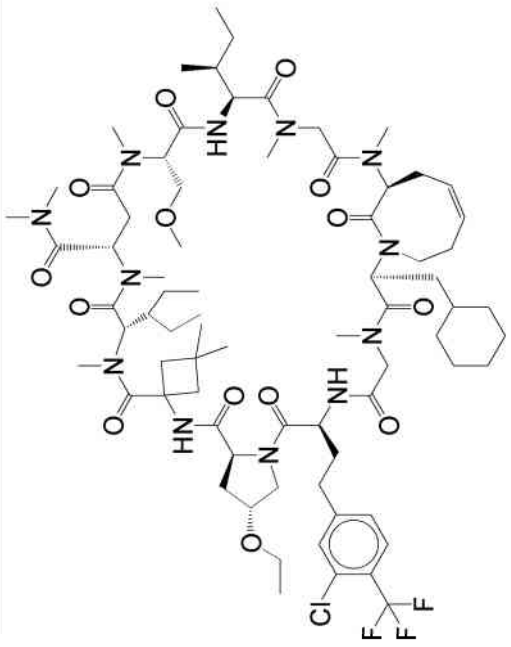
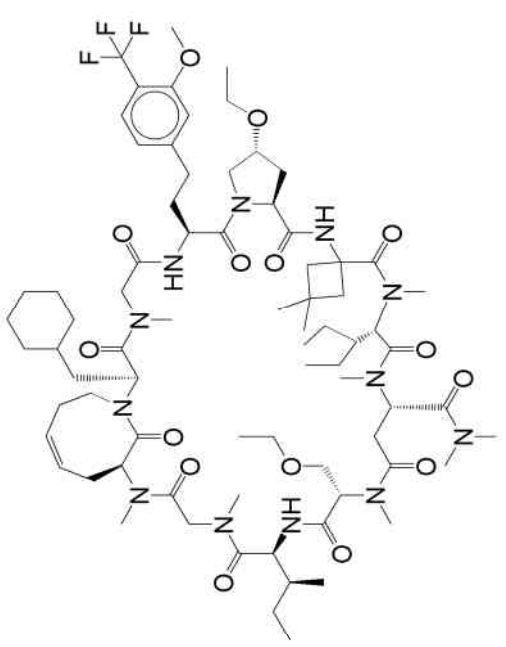
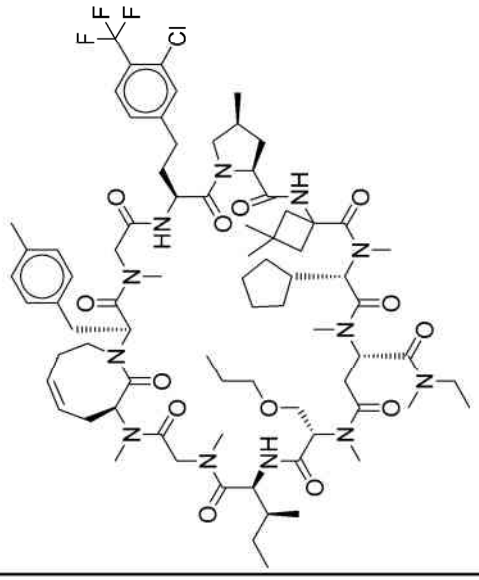
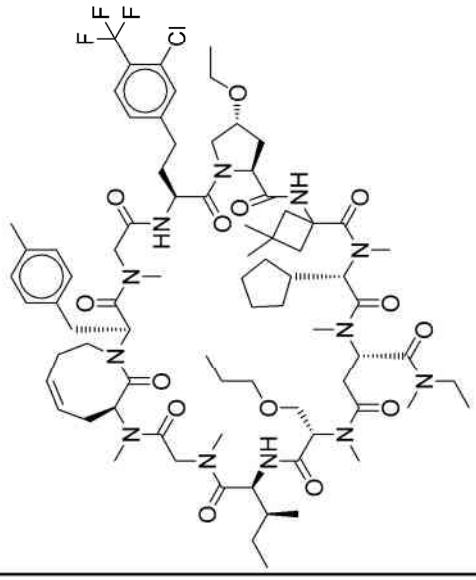
	
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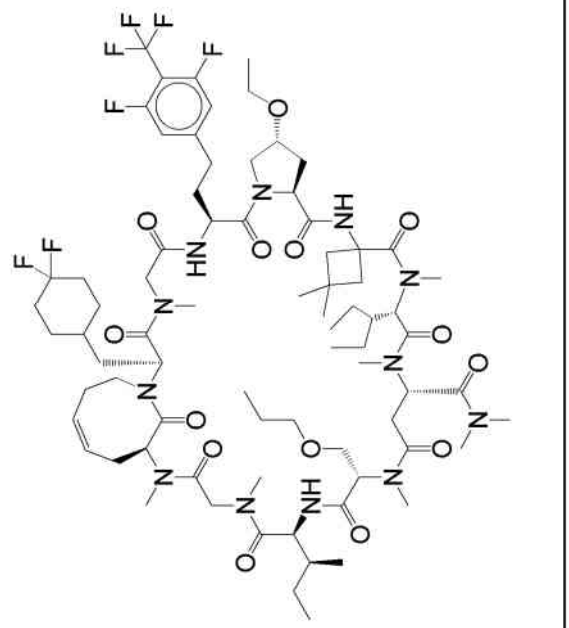
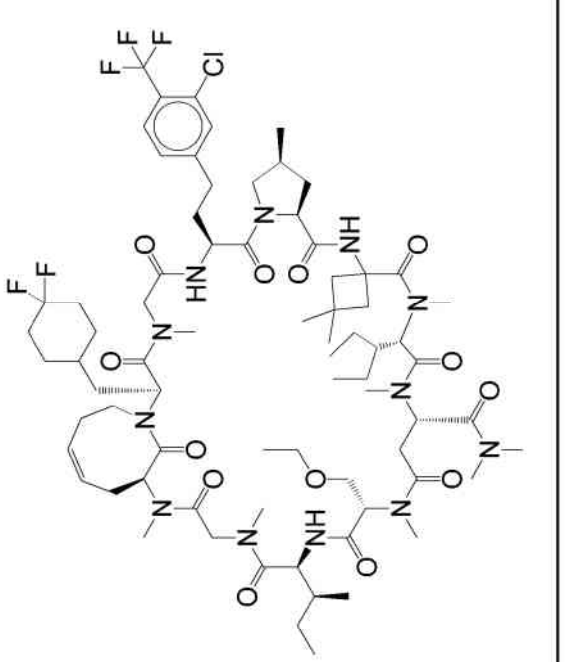
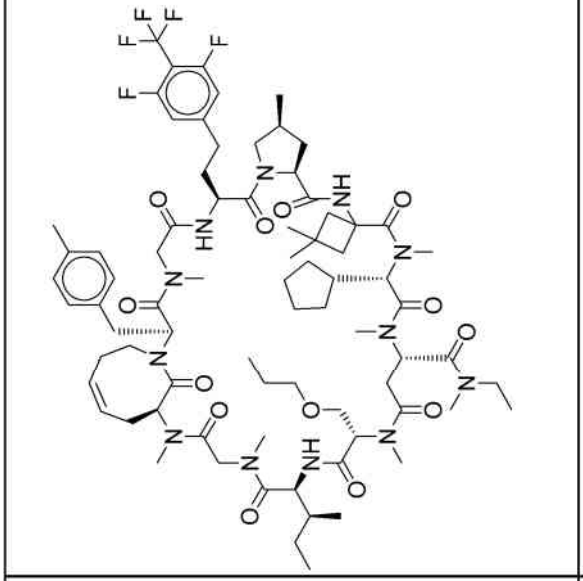
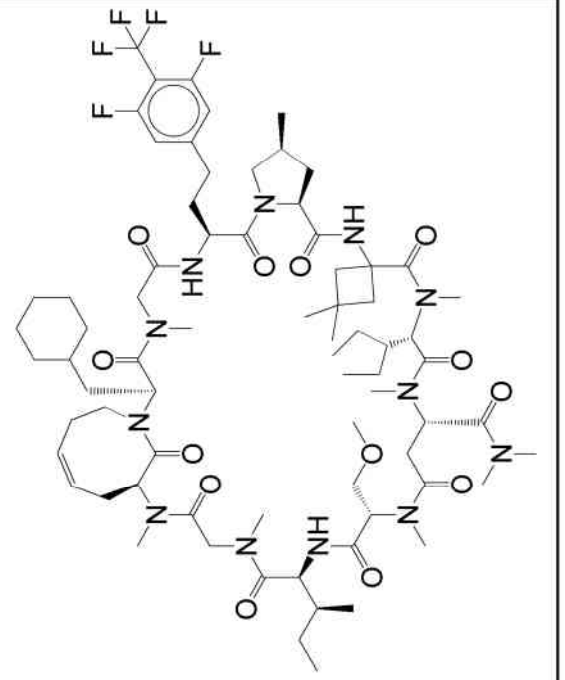
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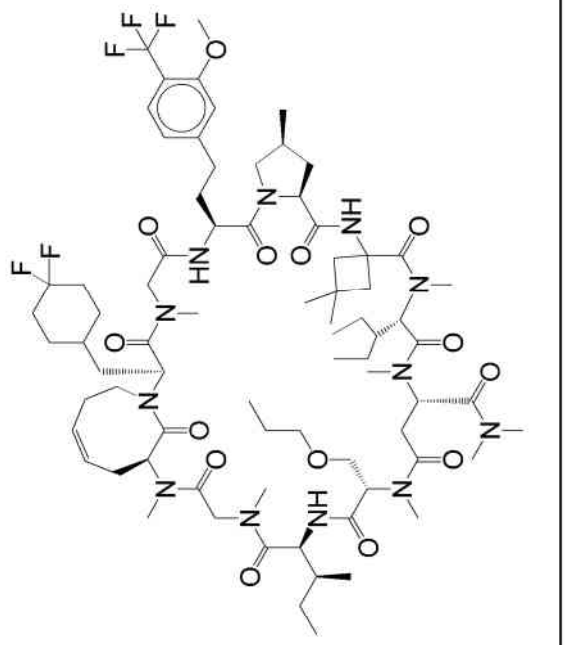
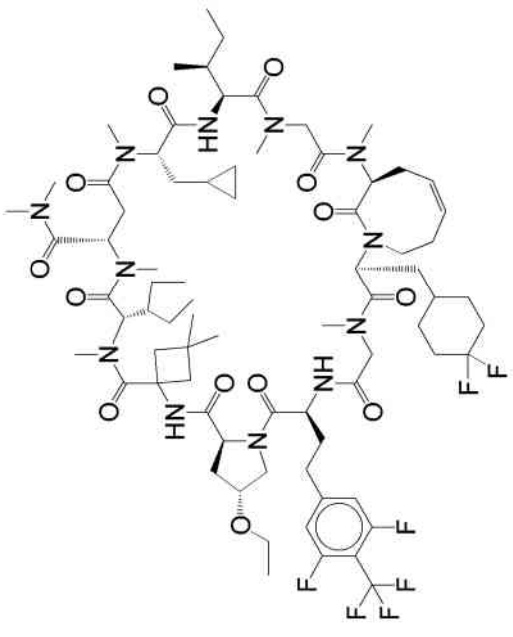
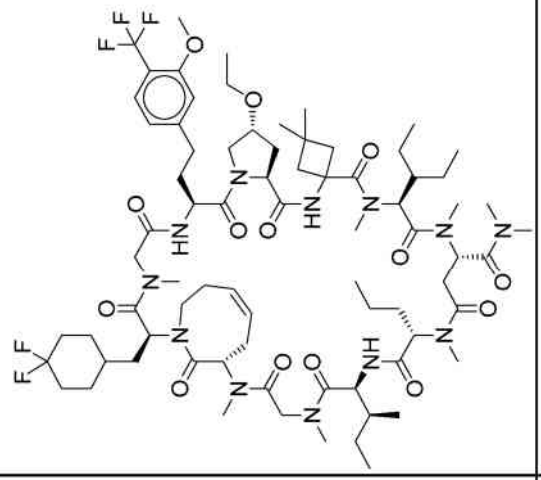
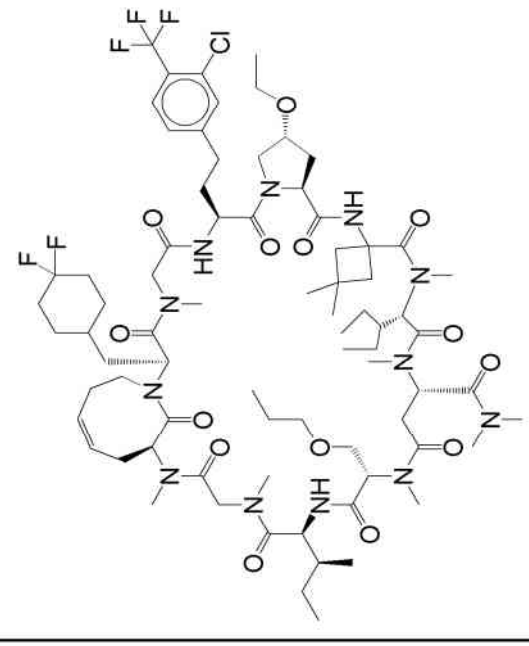
	
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PP2458	PP2461

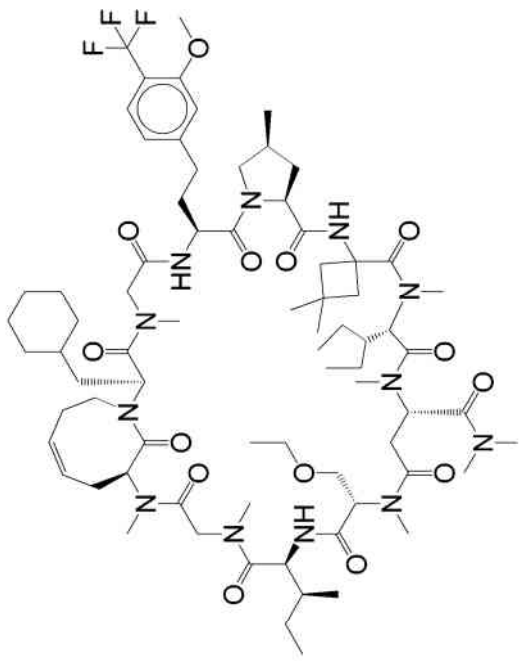
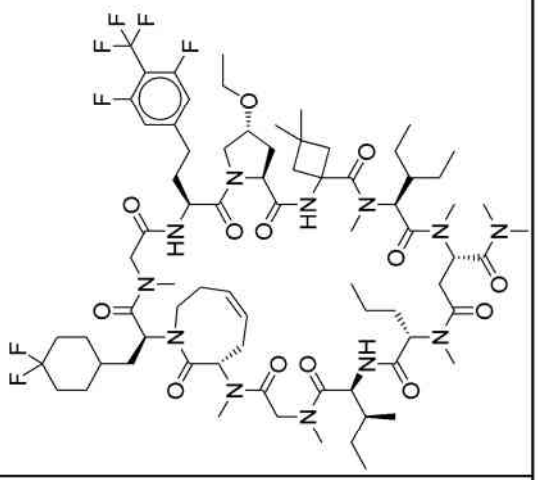
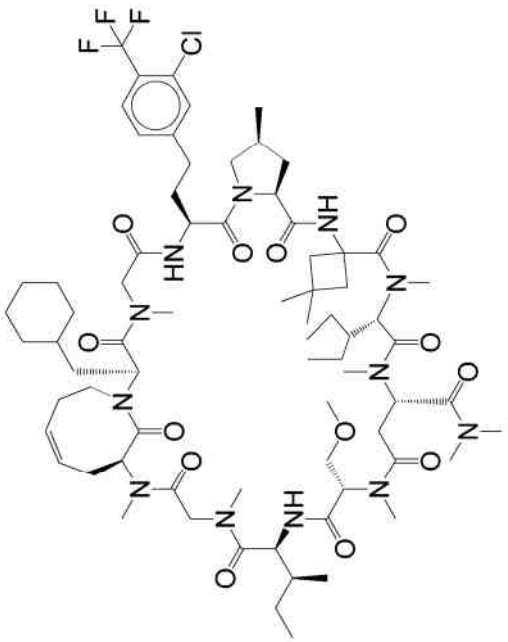
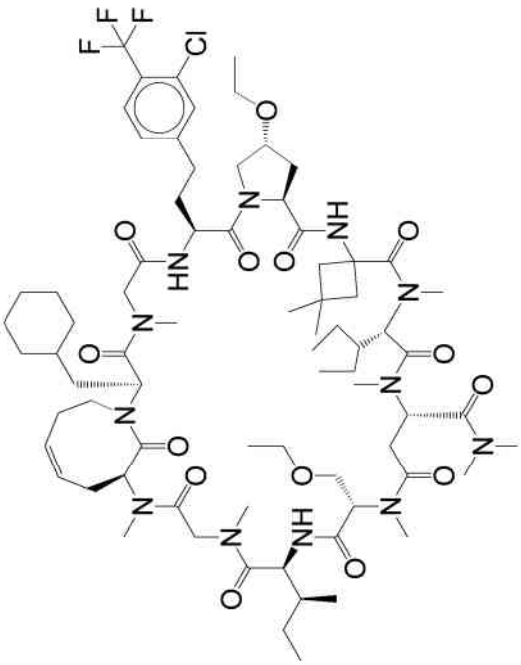
	
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PP246 3	PP246 5

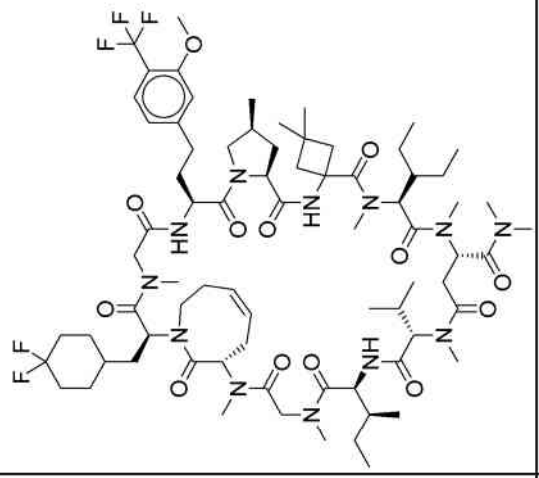
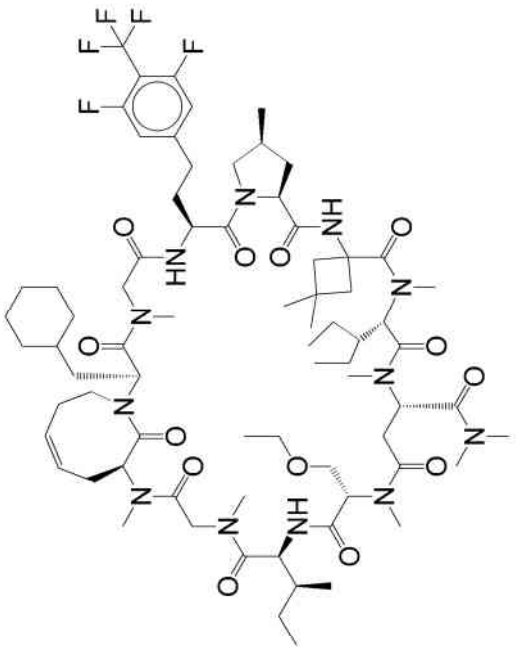
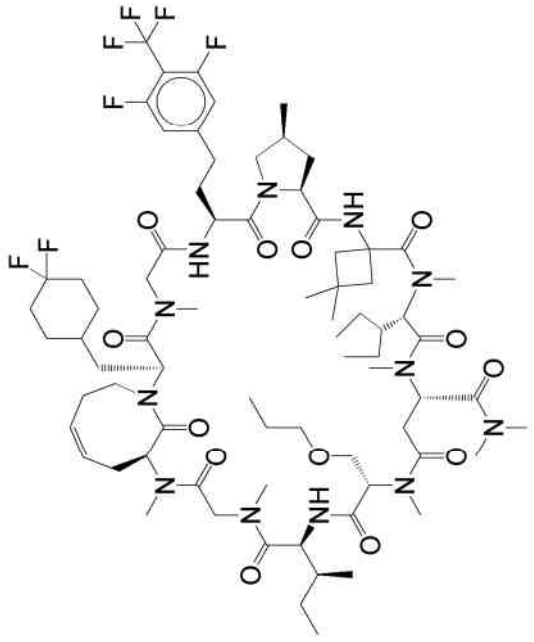
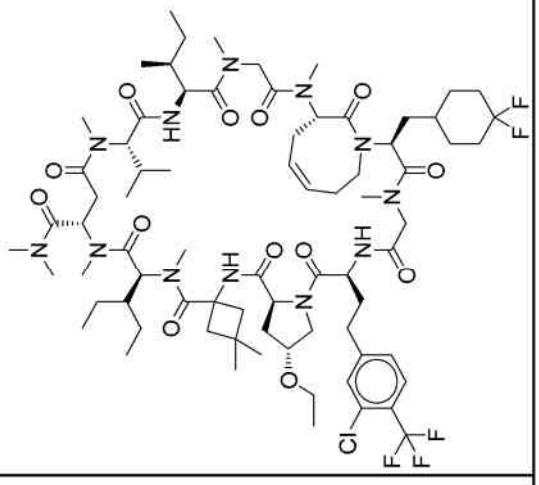
	
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PP2467	PP2469

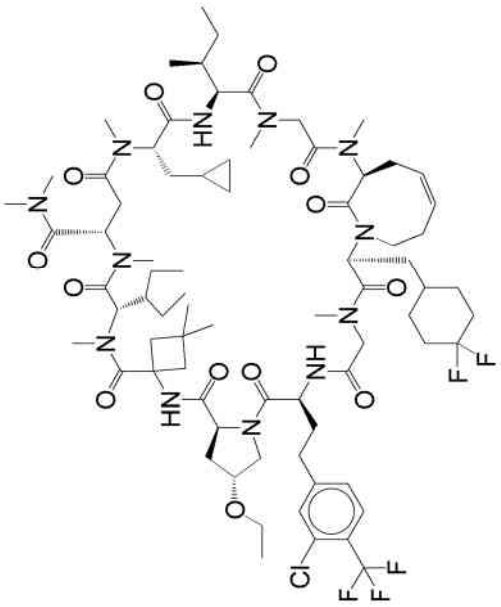
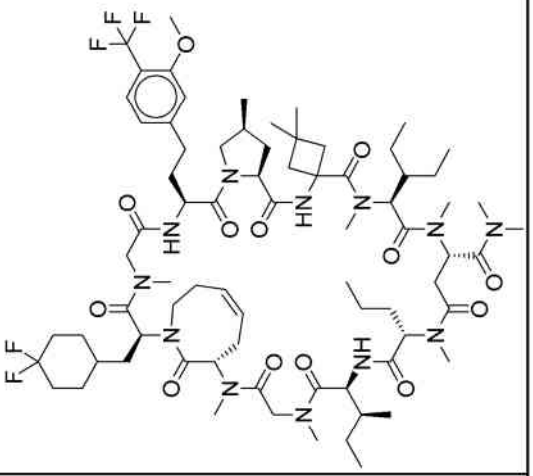
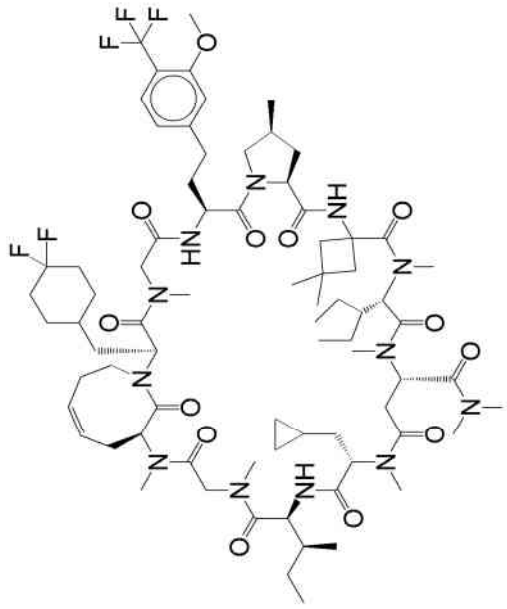
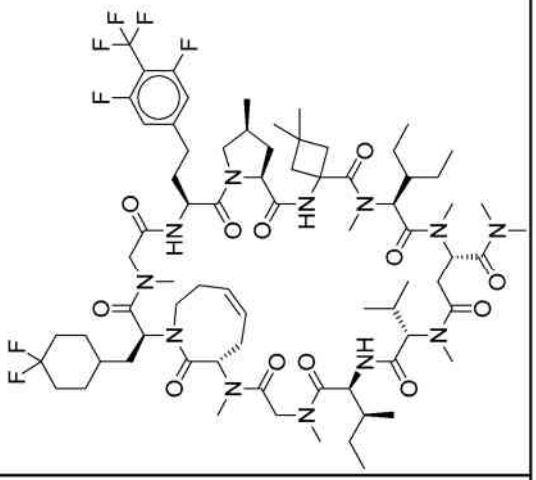
	
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PP247 1	PP247 3

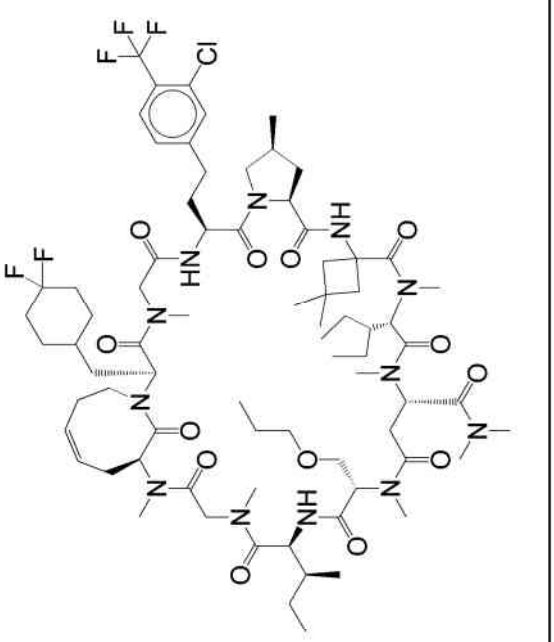
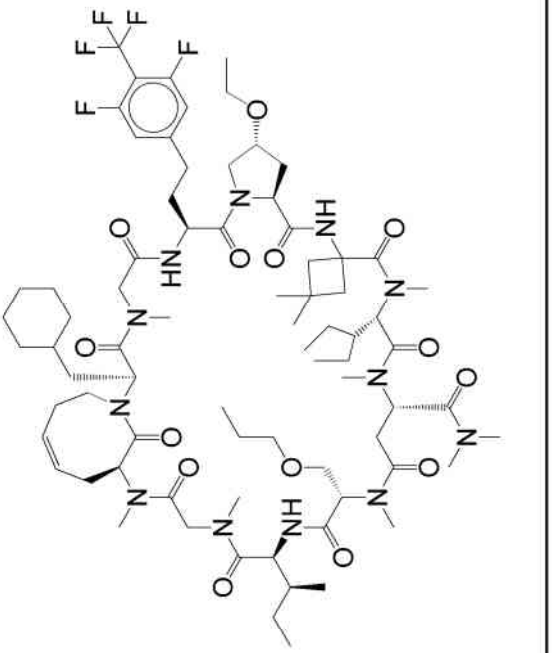
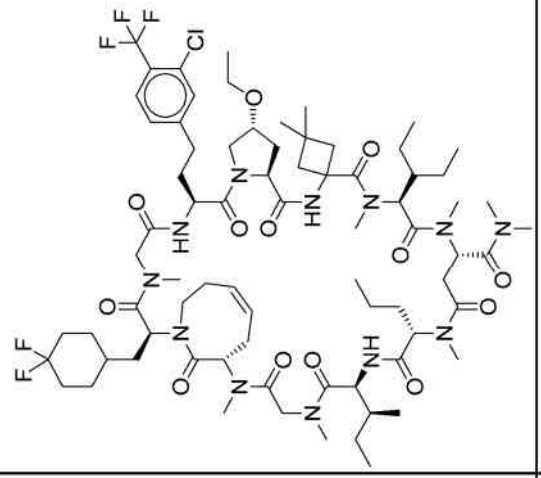
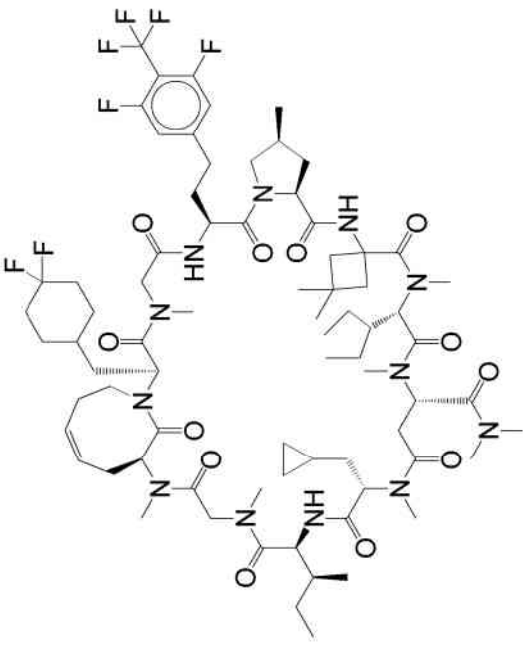
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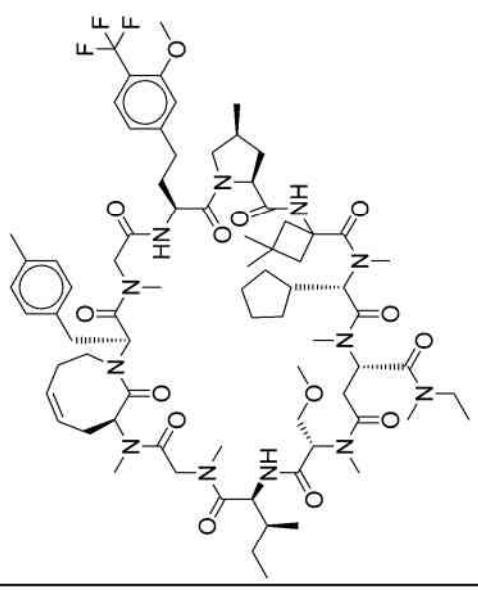
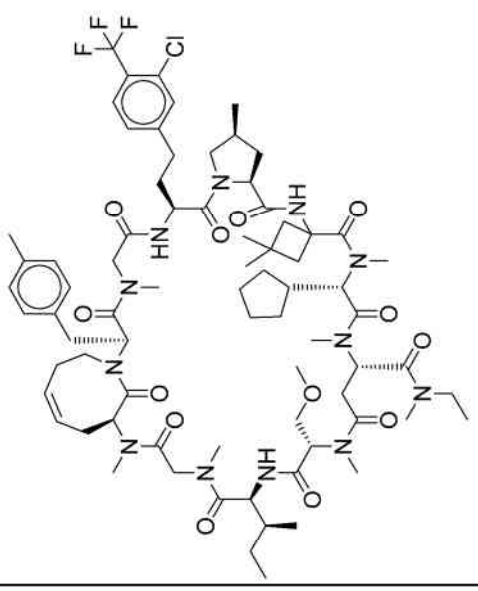
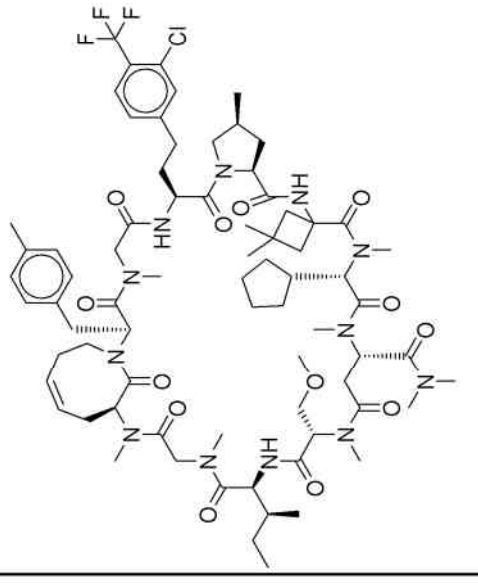
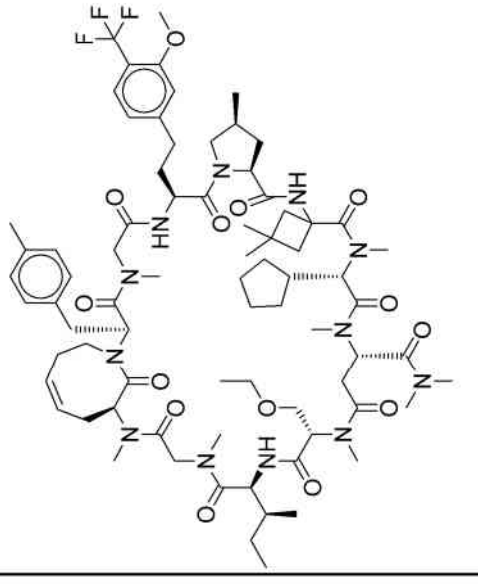
	
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PP248 2	PP248 4

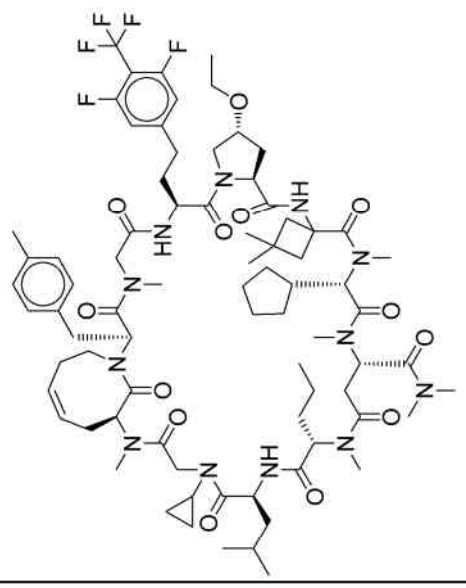
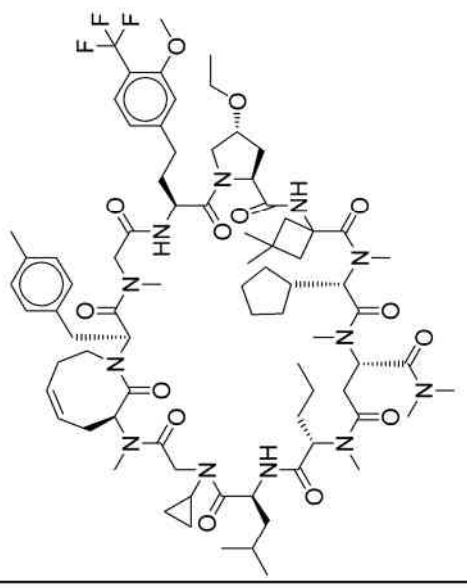
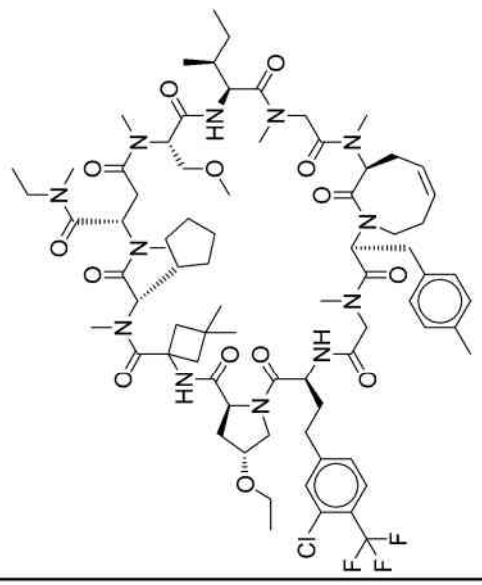
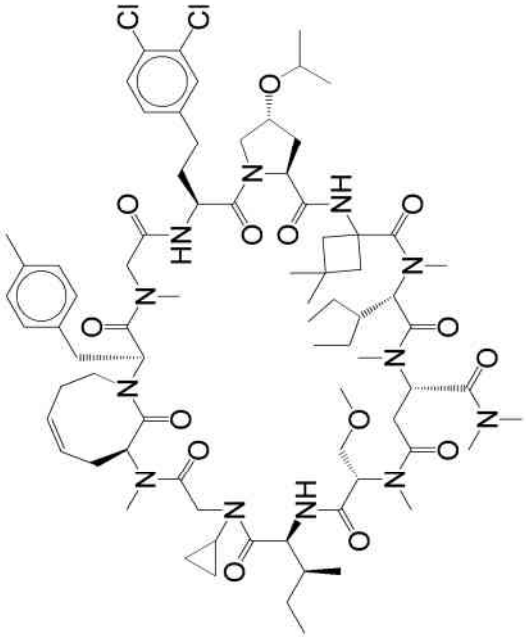
	
PP248 7	PP248 9
	
PP248 6	PP248 8

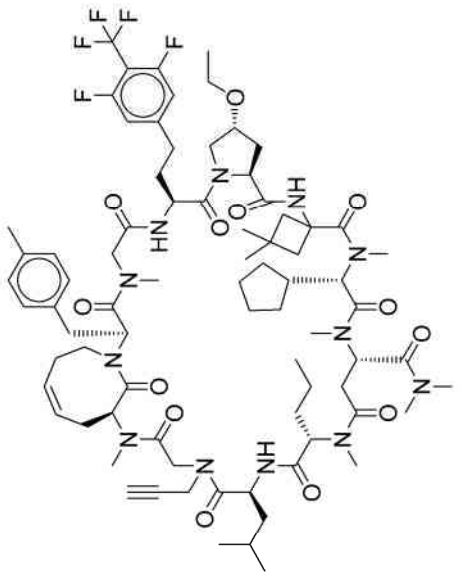
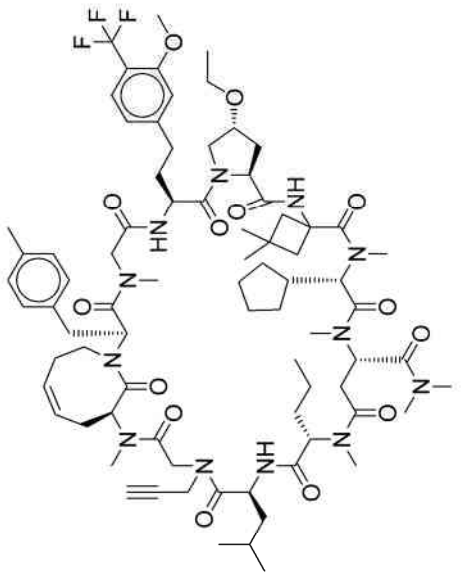
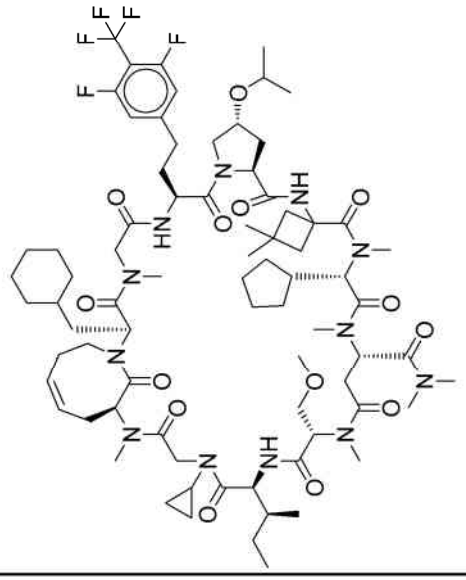
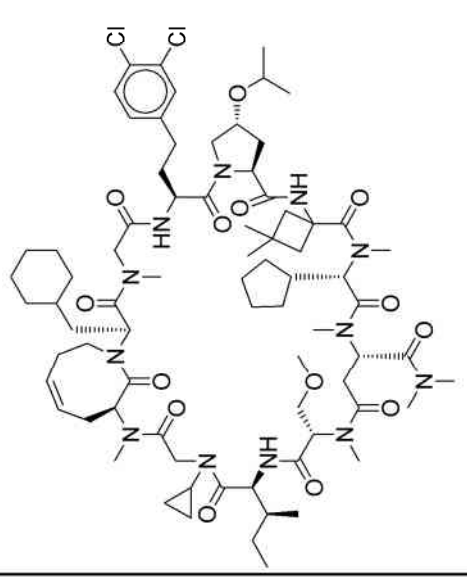
	
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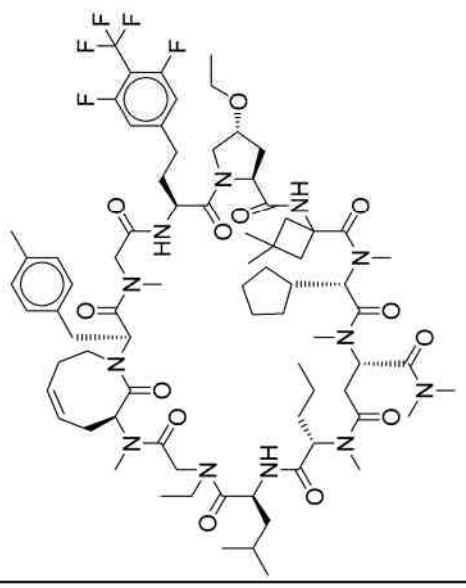
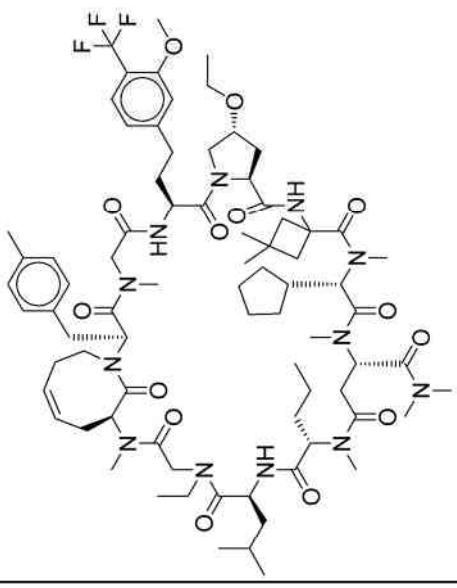
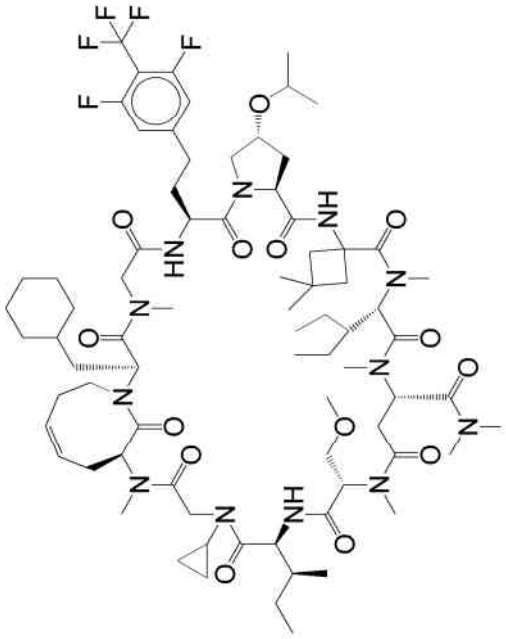
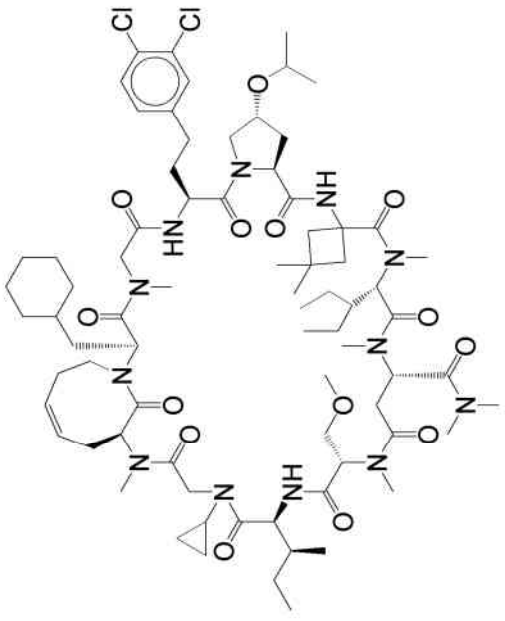
	
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PP249 4	PP249 6

	
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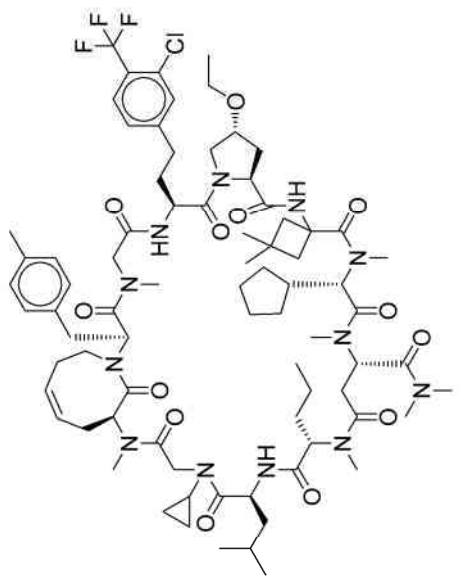
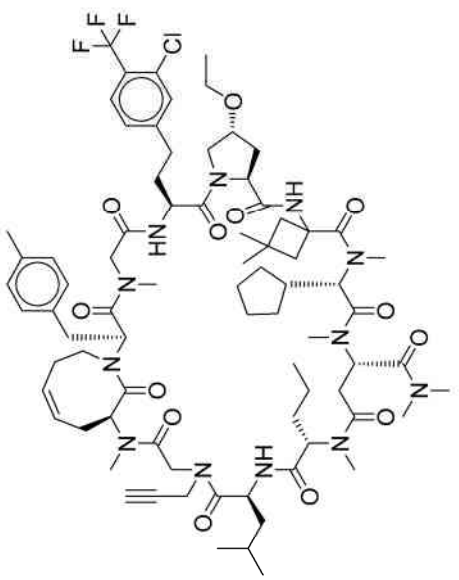
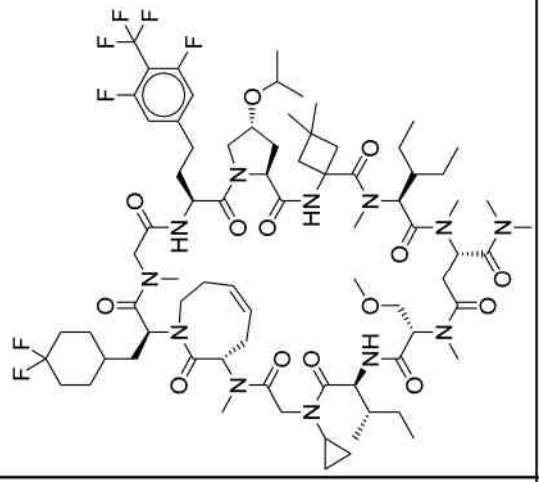
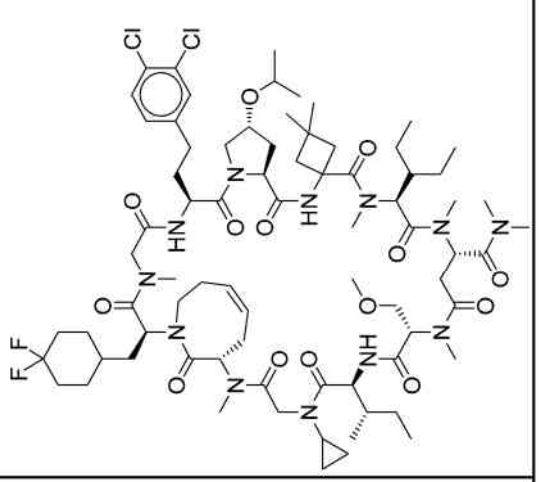
	
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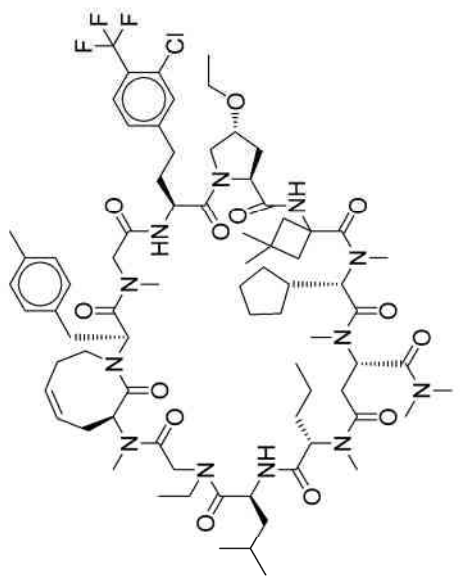
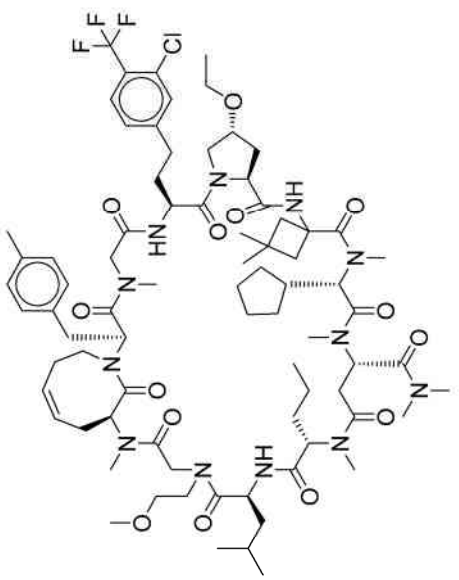
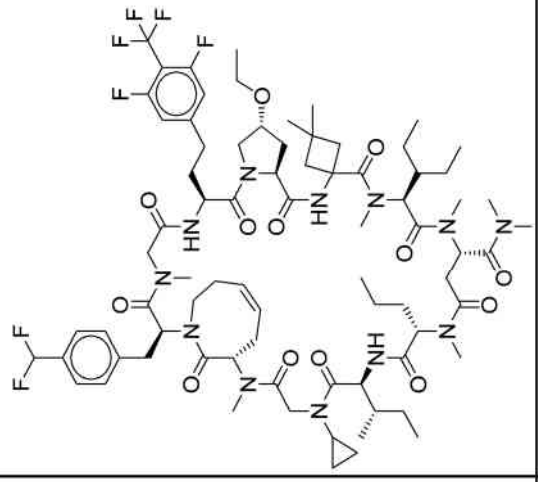
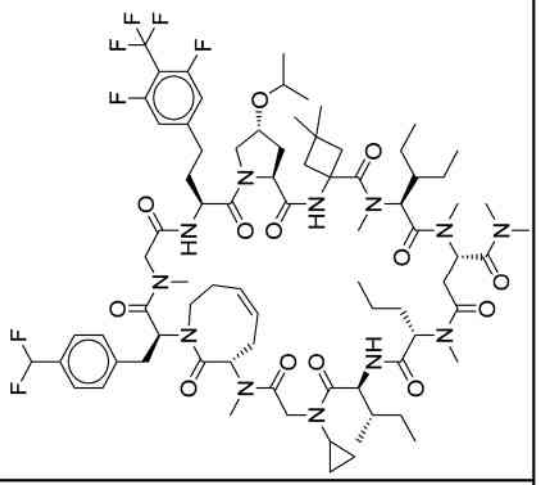
	
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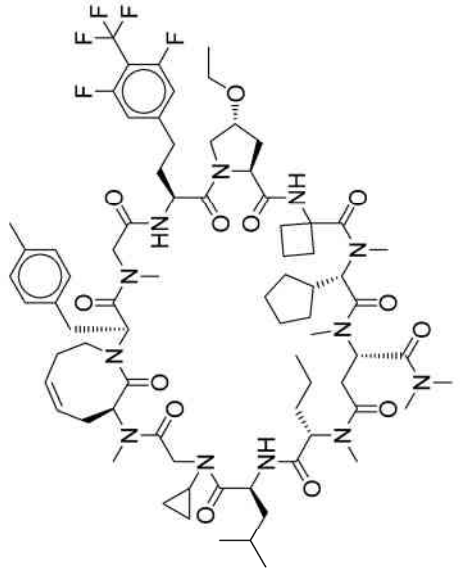
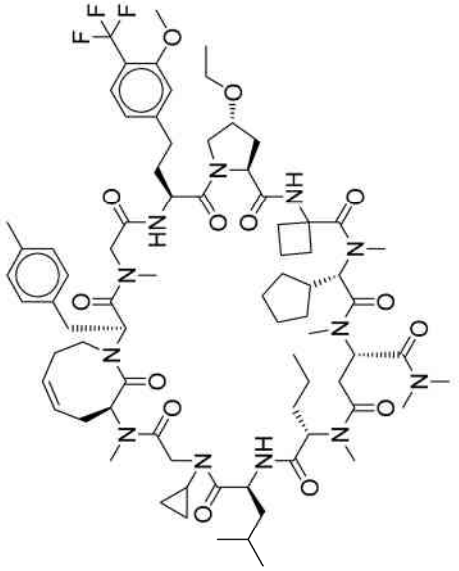
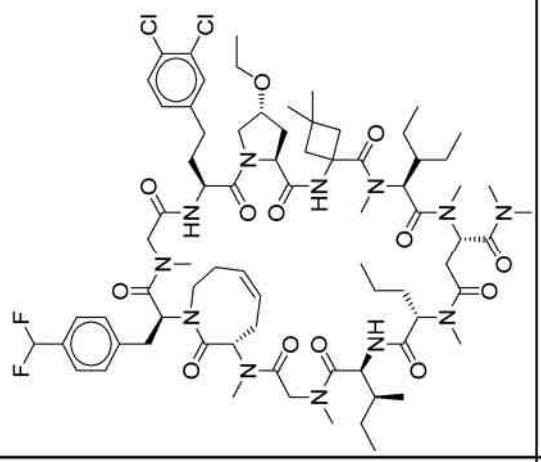
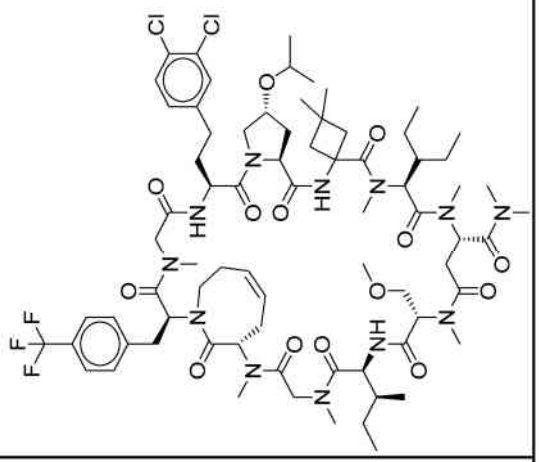
	
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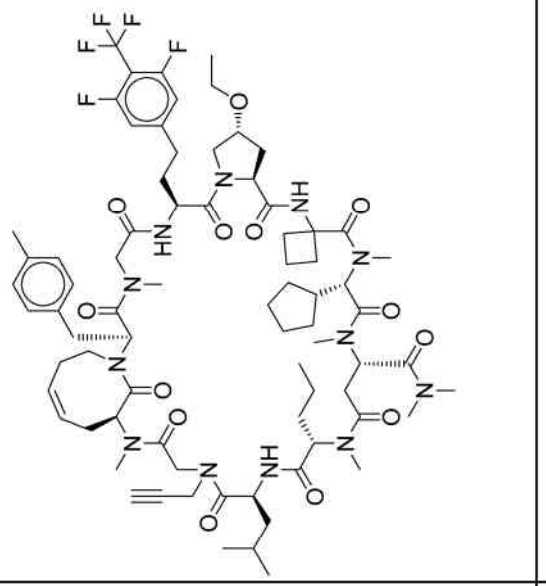
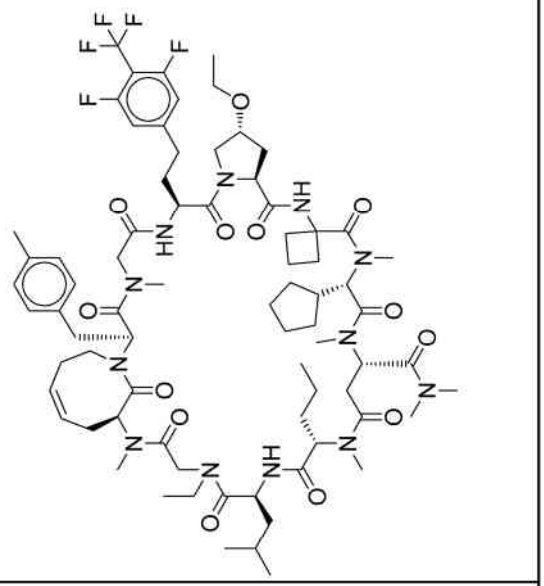
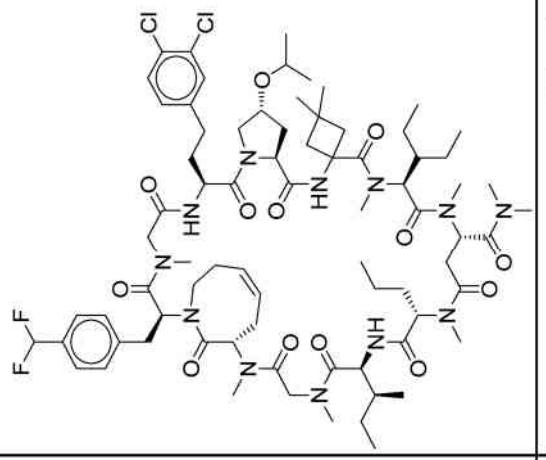
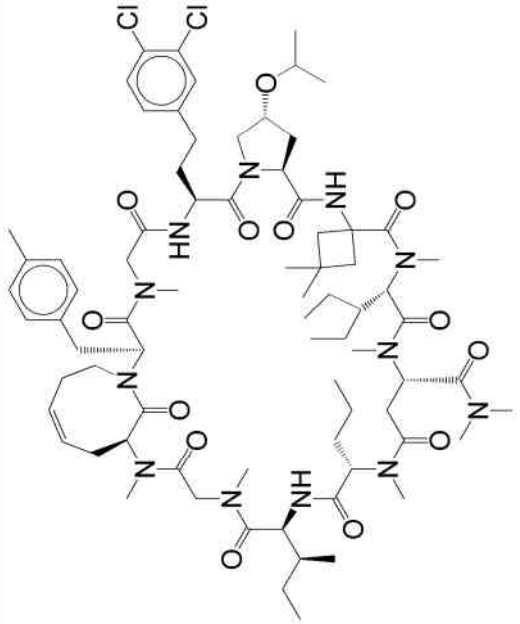
	
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PP251 5	PP251 7

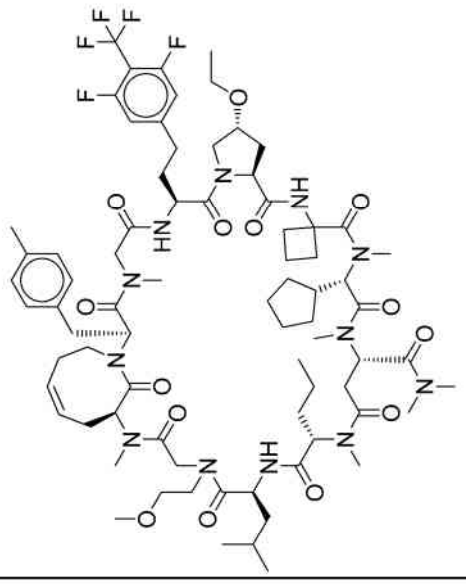
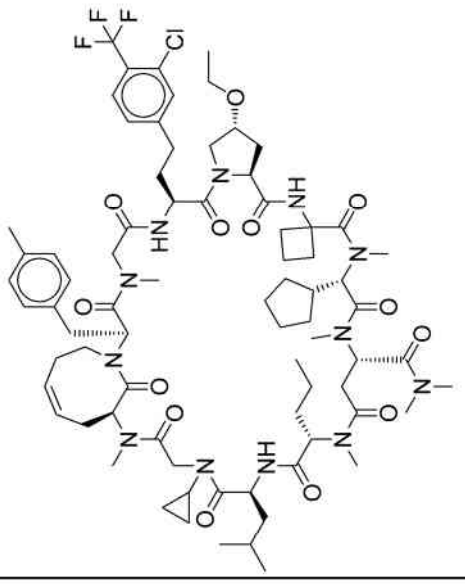
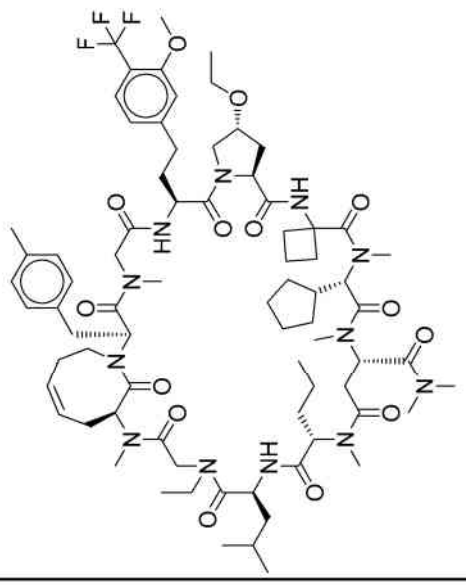
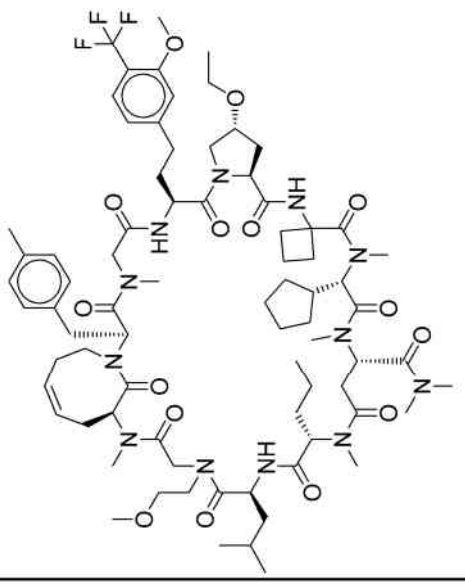
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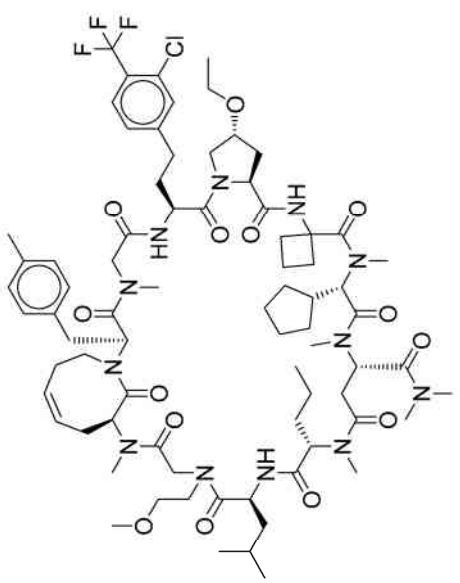
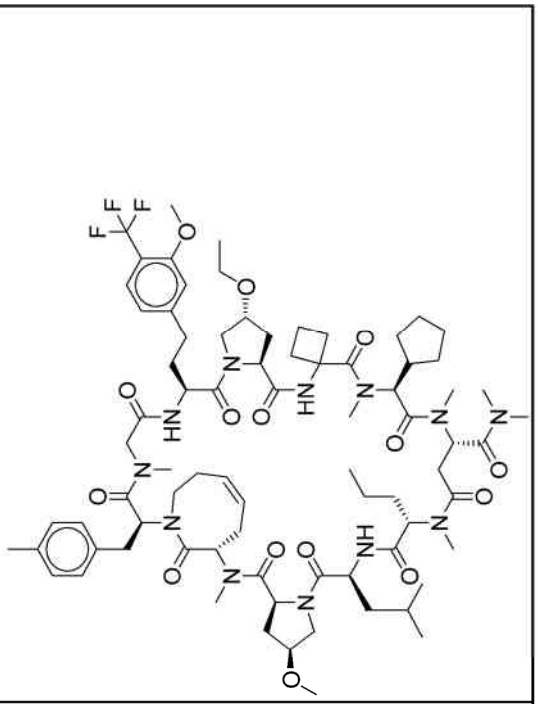
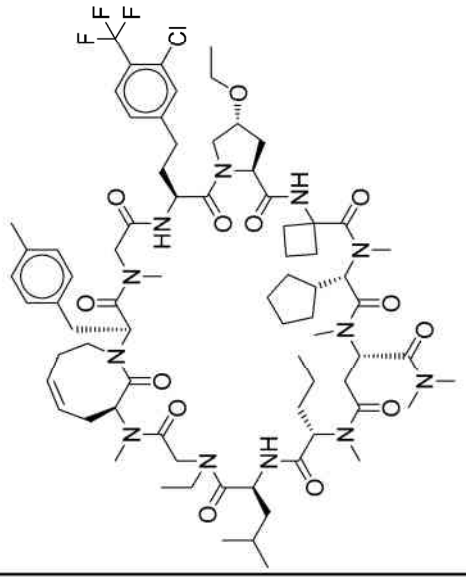
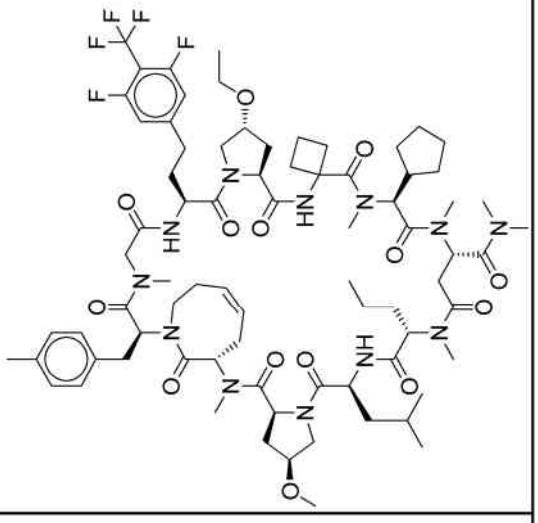
	
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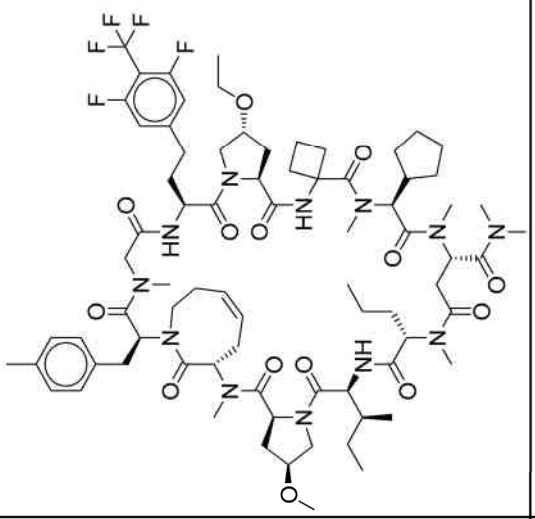
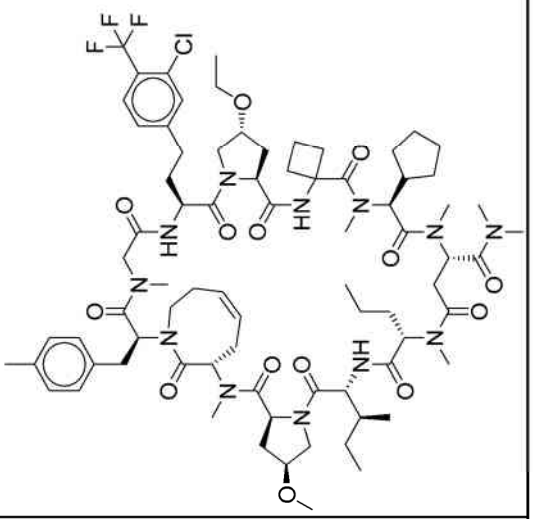
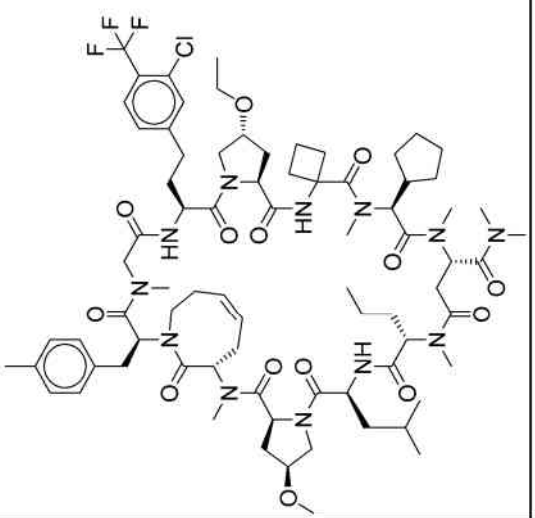
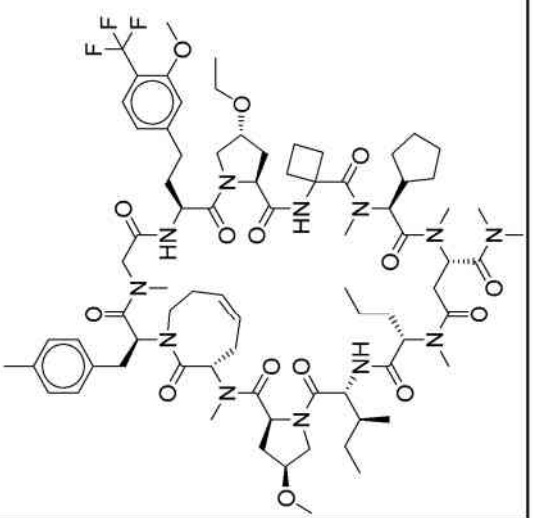
	
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PP2527	PP2529

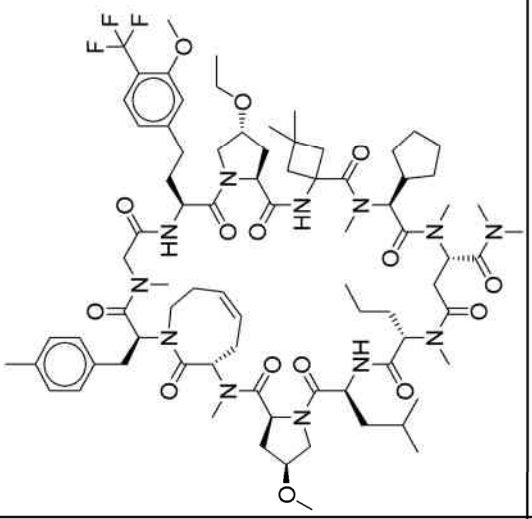
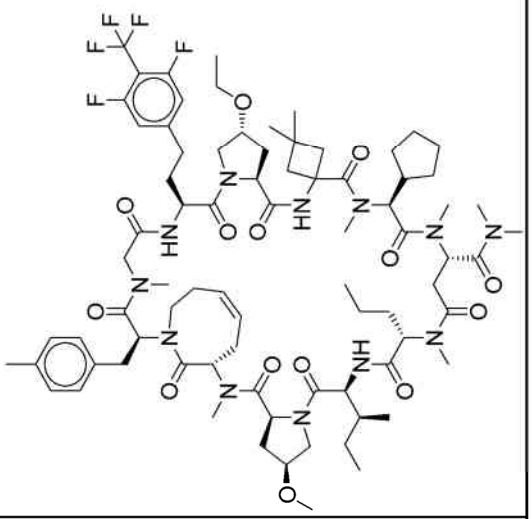
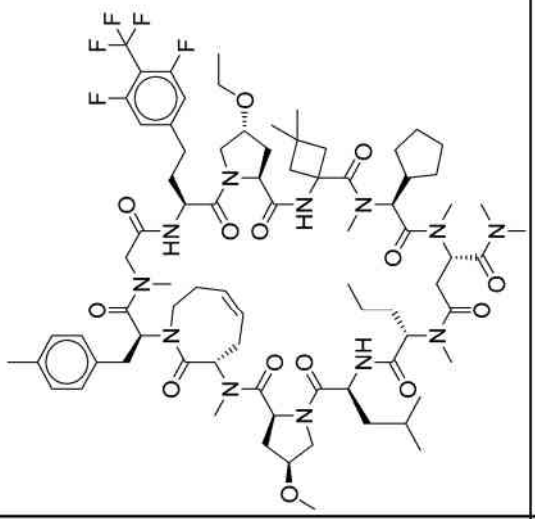
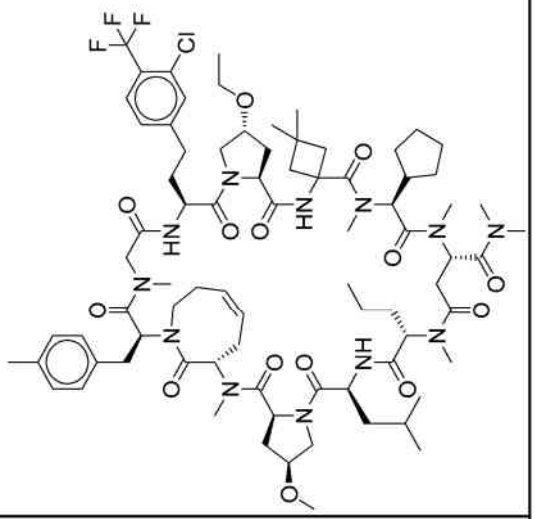
	
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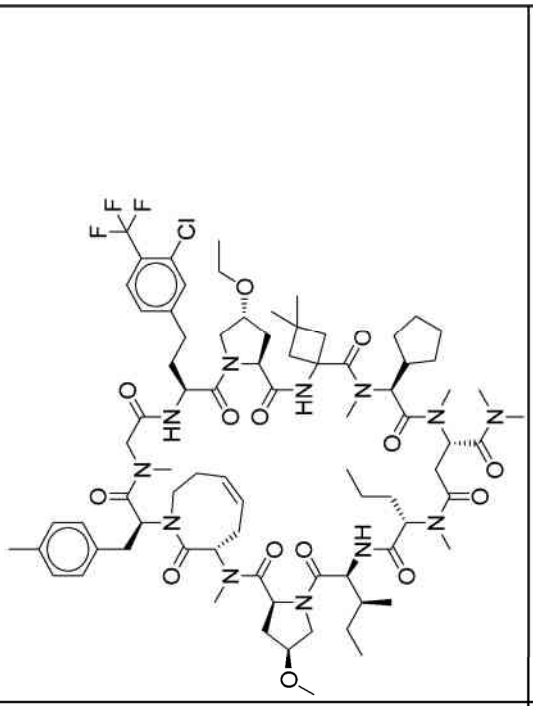
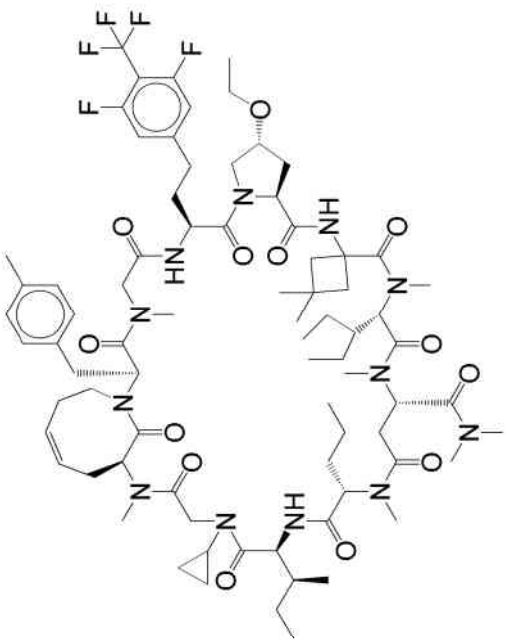
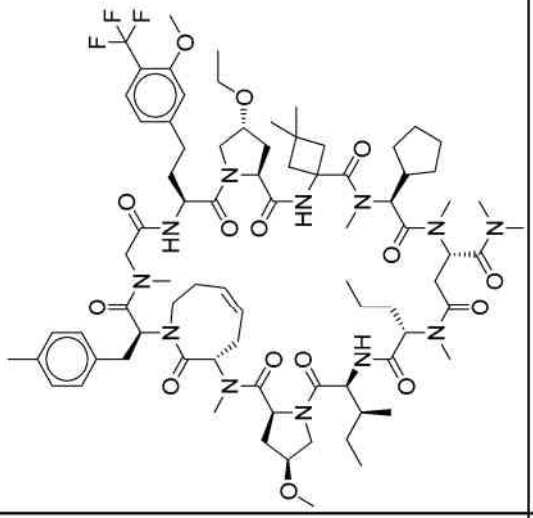
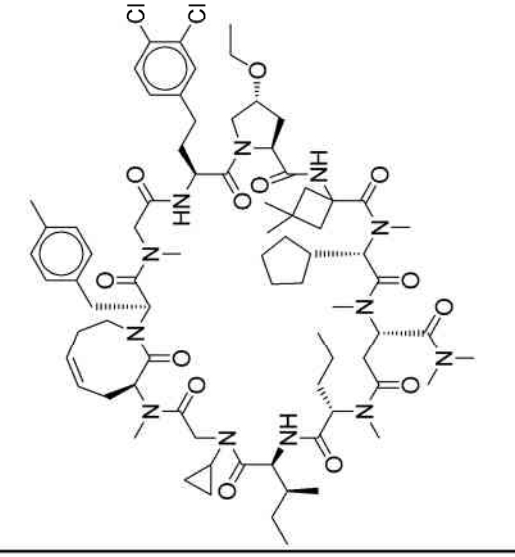
	
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PP253 5	PP253 7

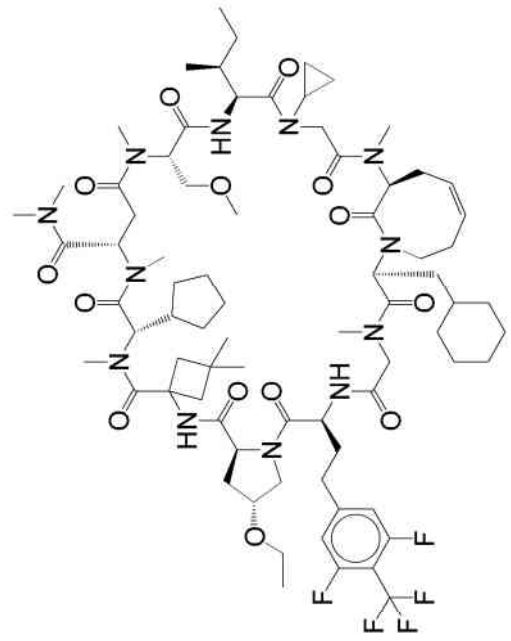
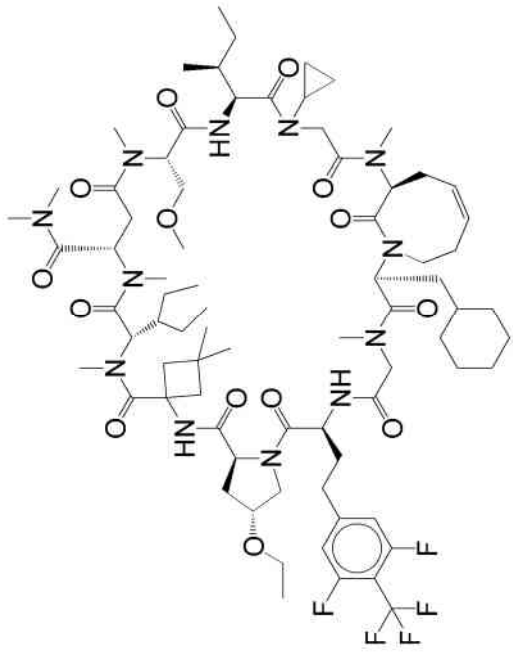
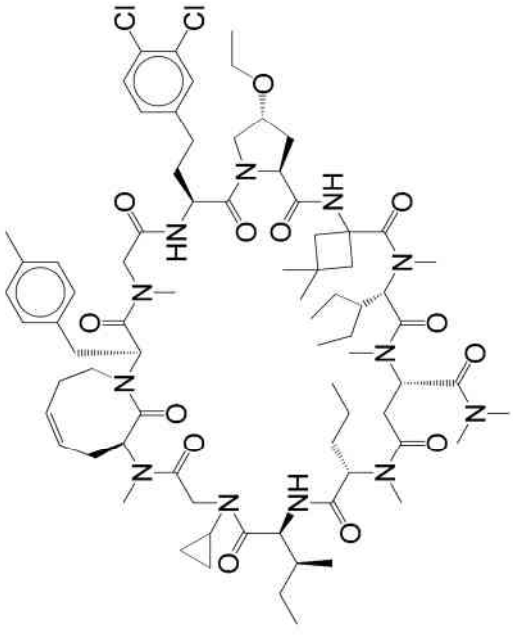
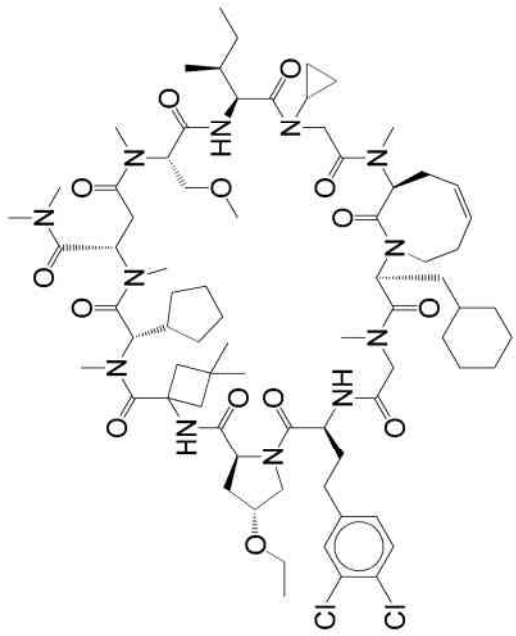
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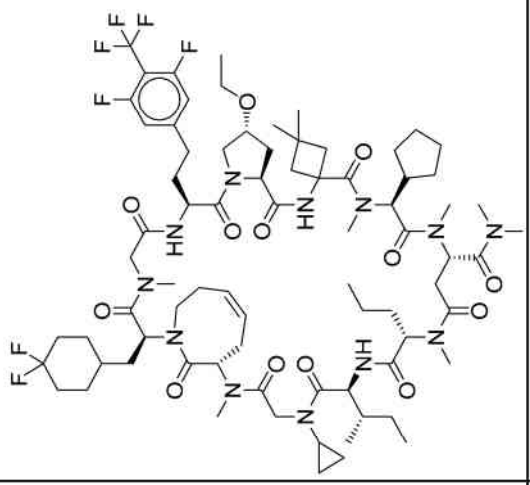
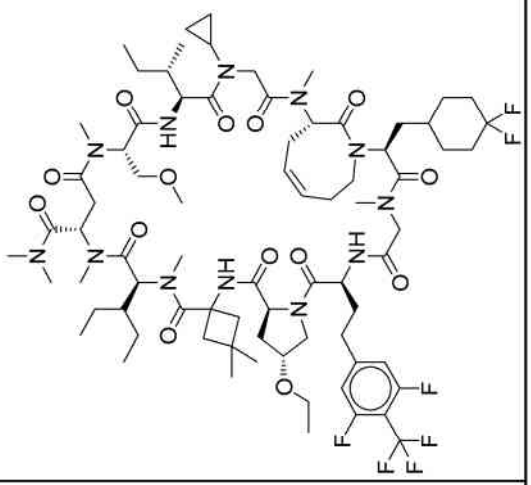
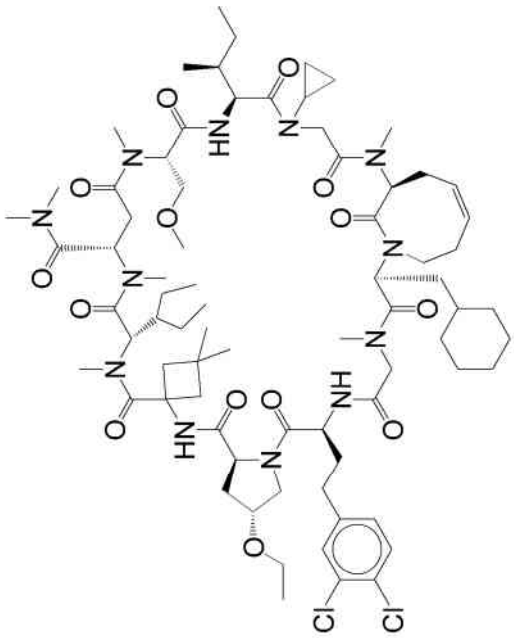
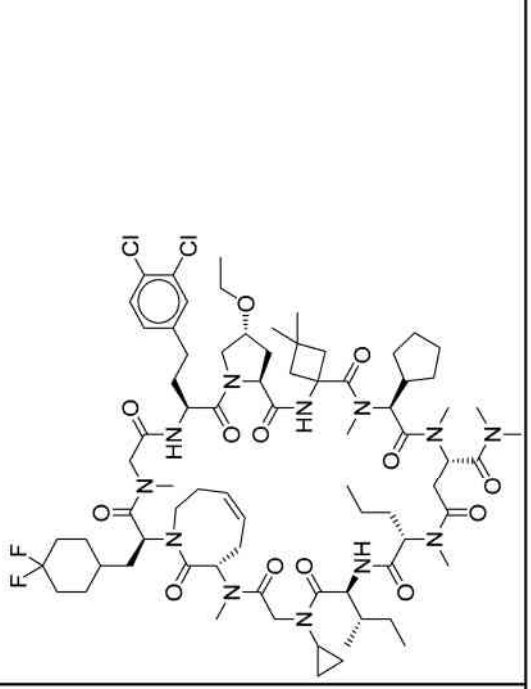
	
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PP254 5	PP254 7

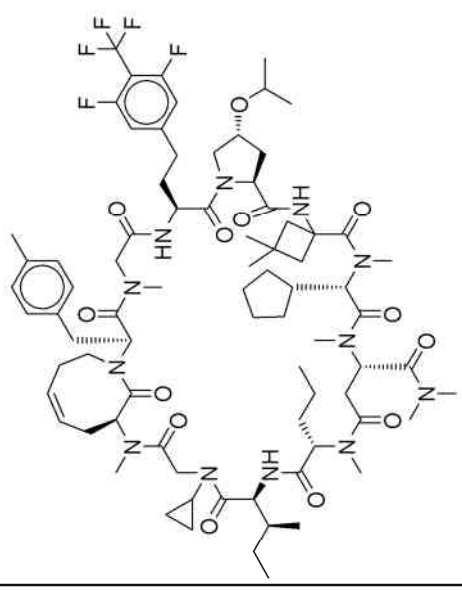
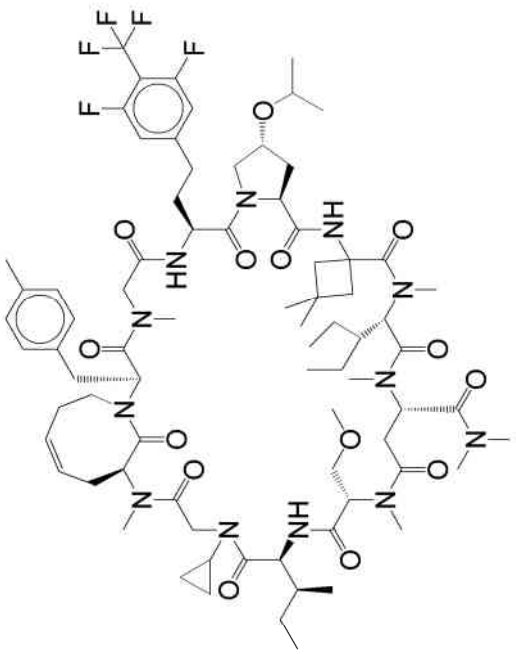
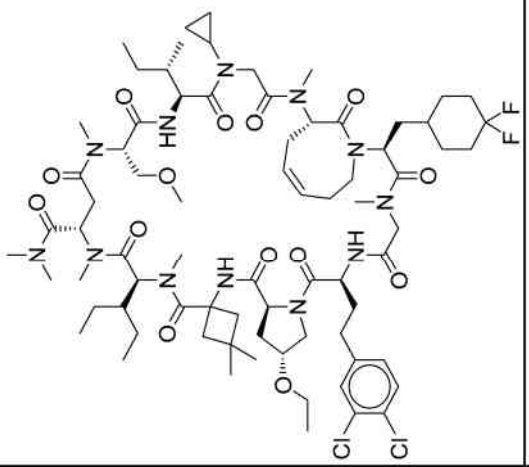
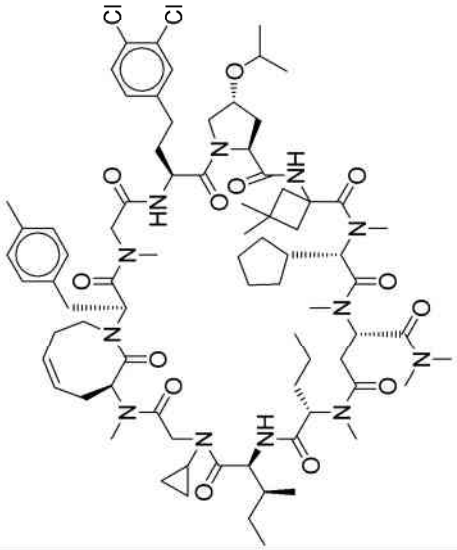
	
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PP2549	PP2551

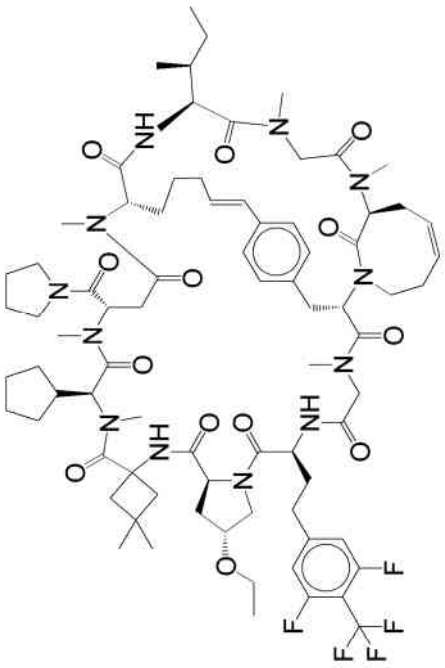
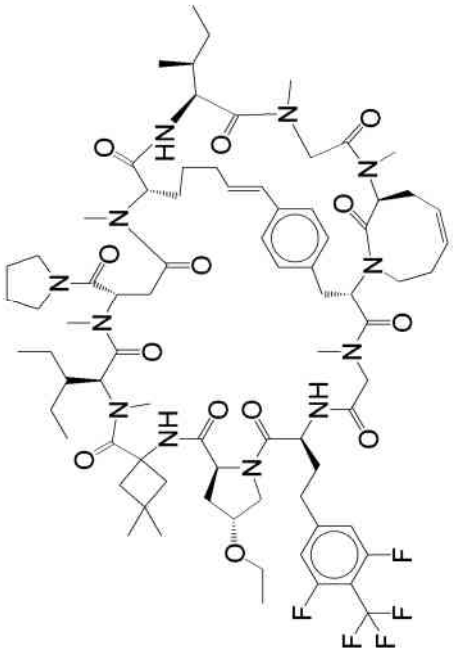
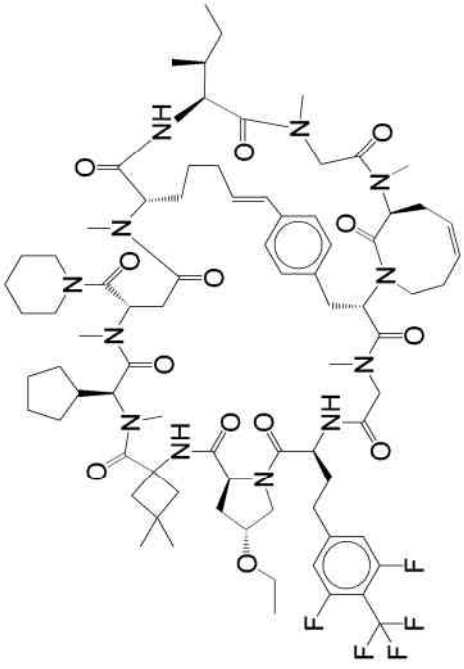
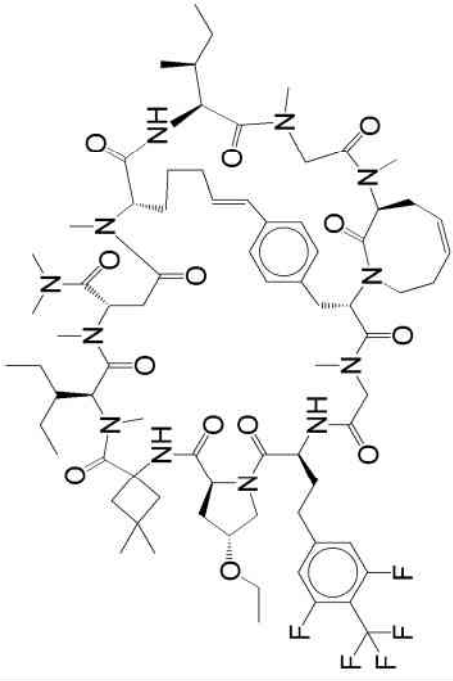
	
PP255 4	PP255 6
	
PP255 3	PP255 5

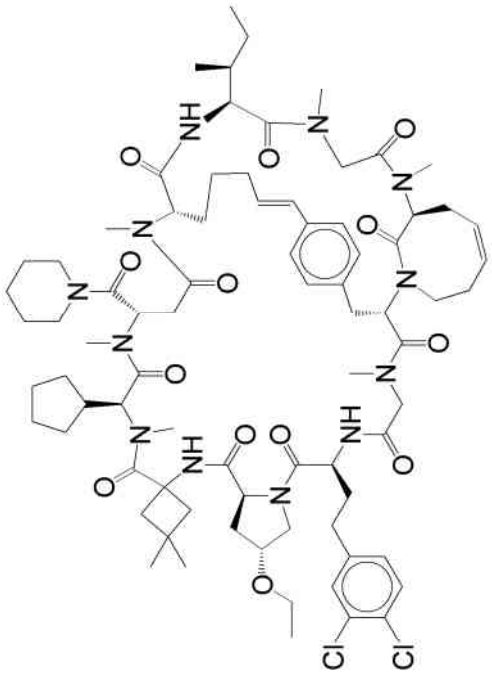
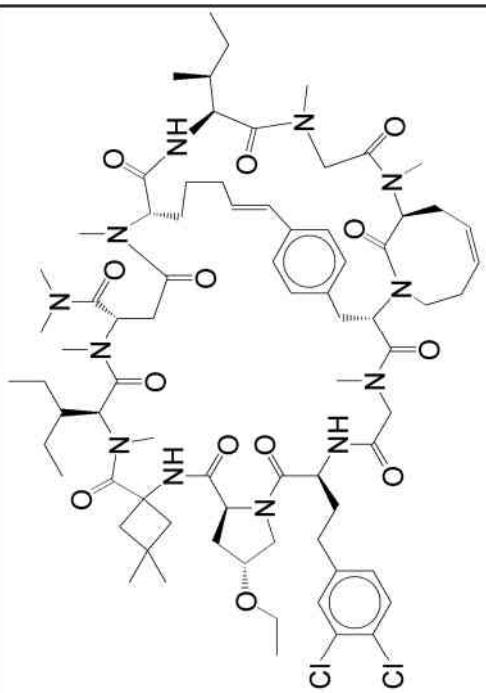
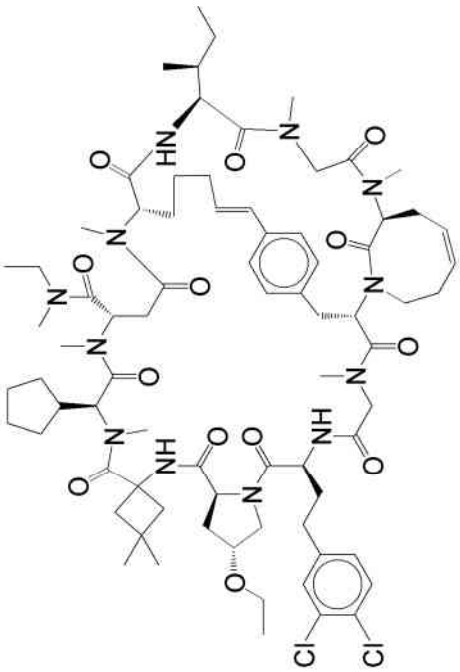
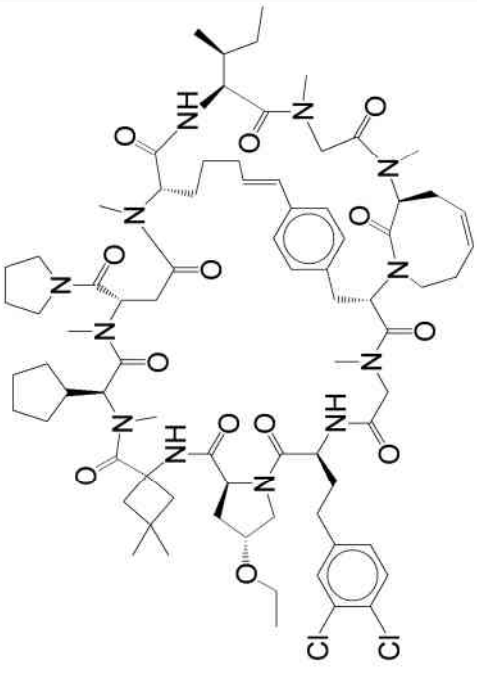
	
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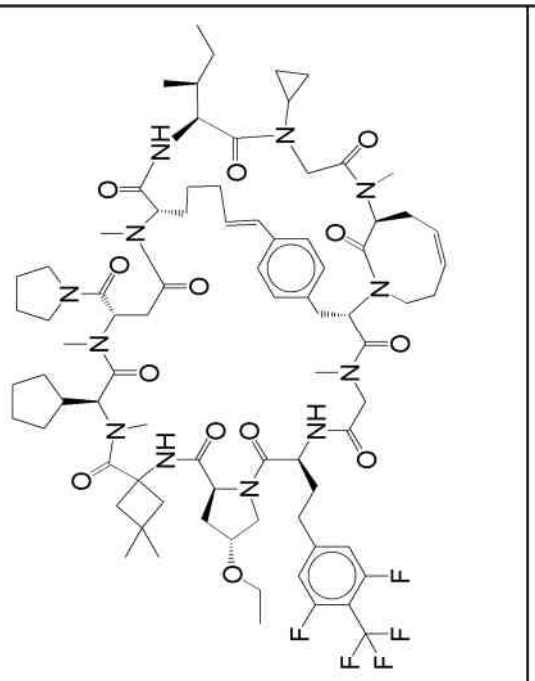
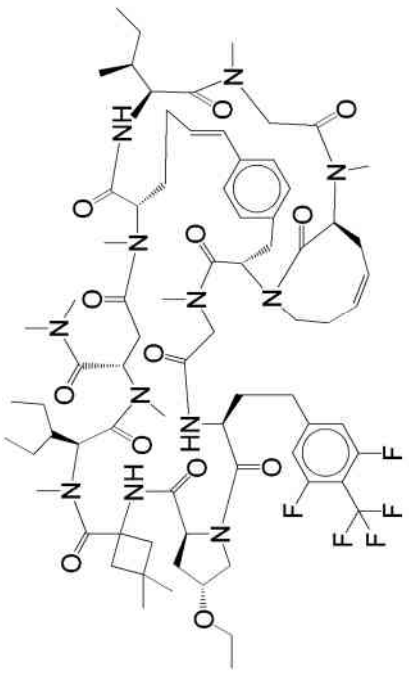
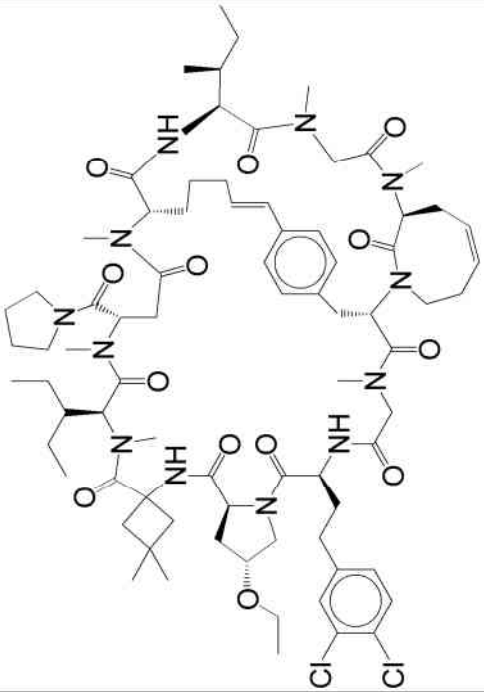
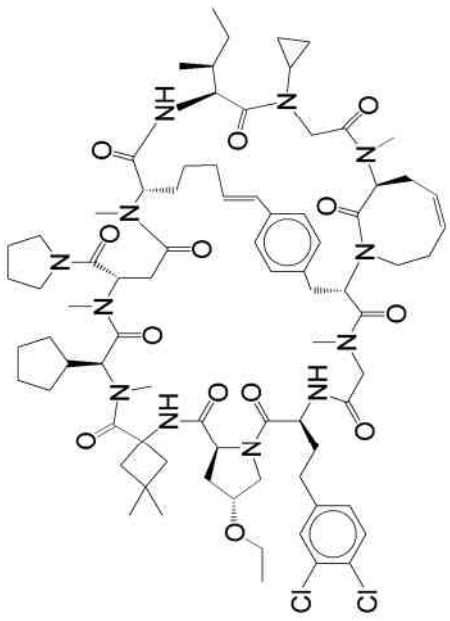
	
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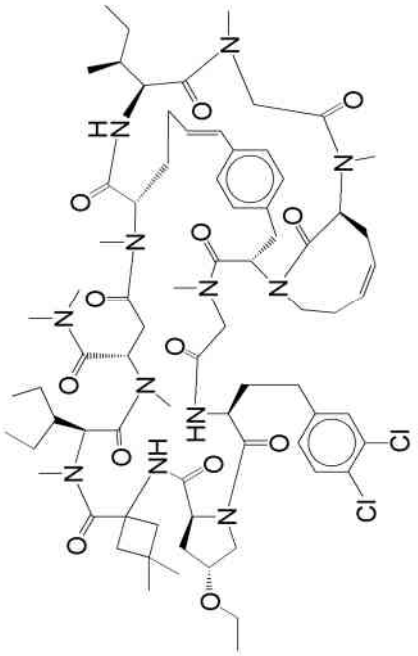
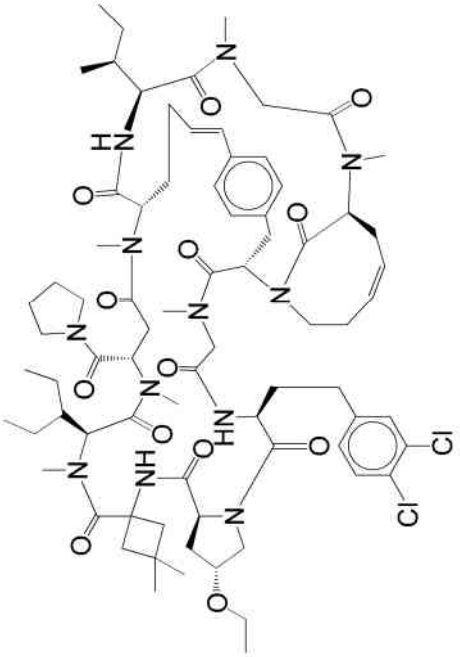
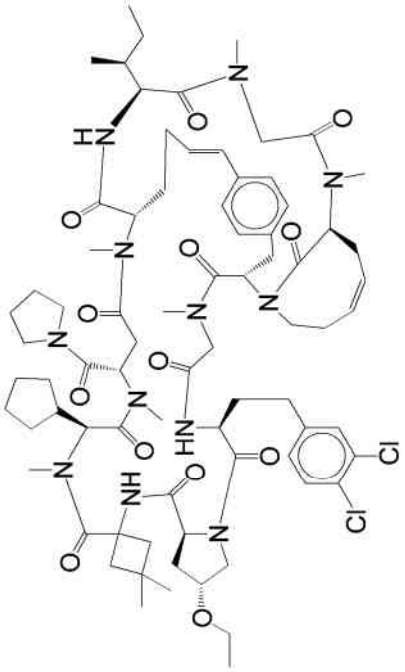
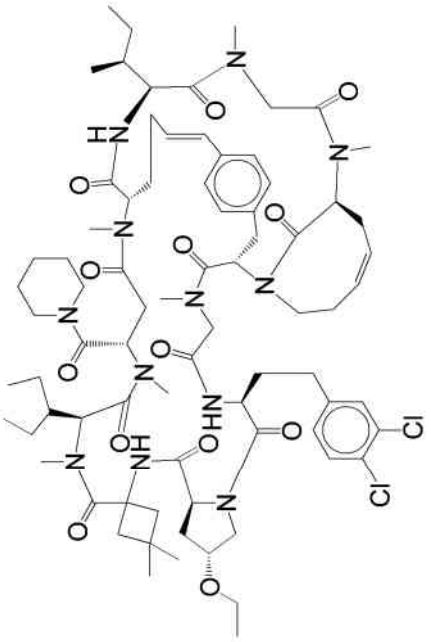
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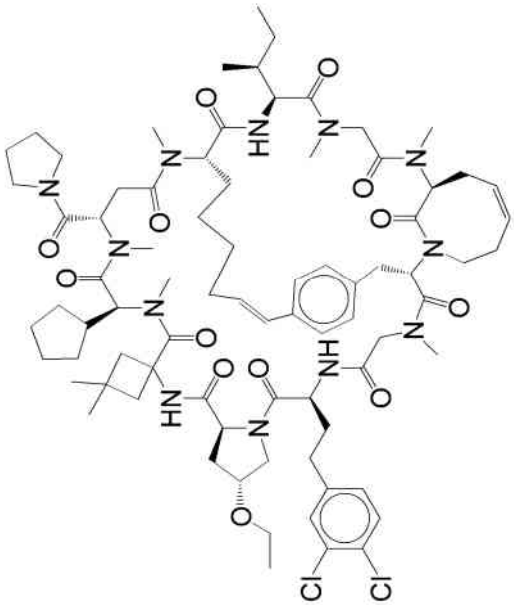
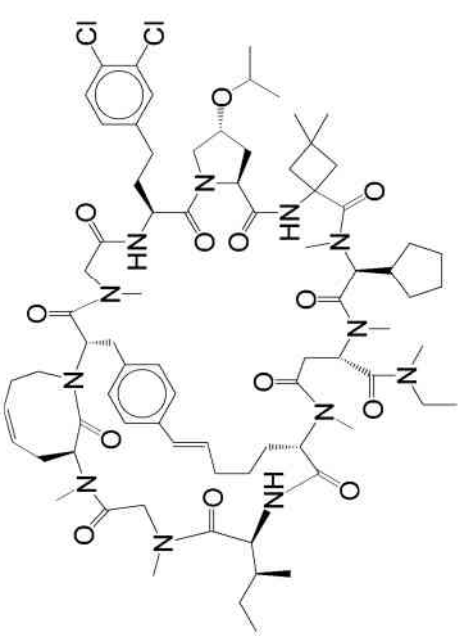
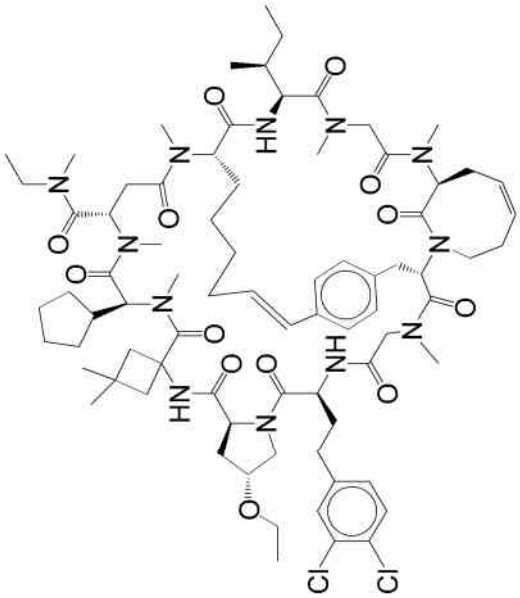
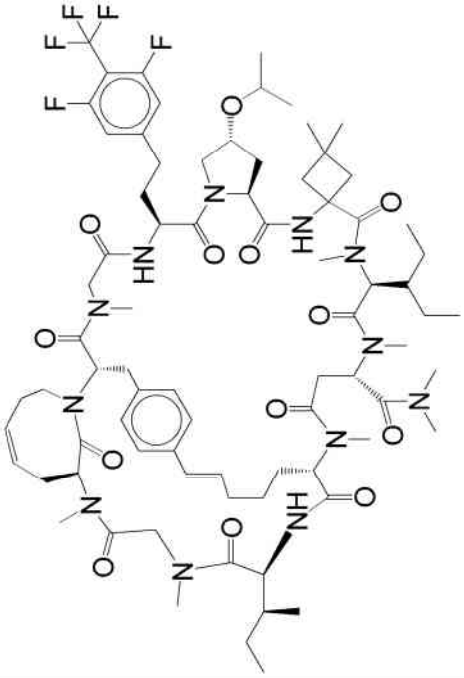
	
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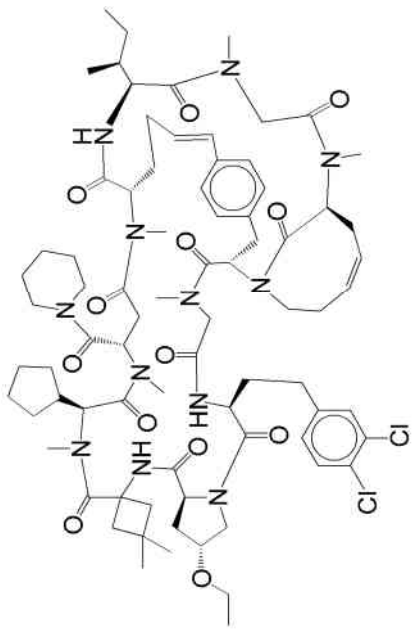
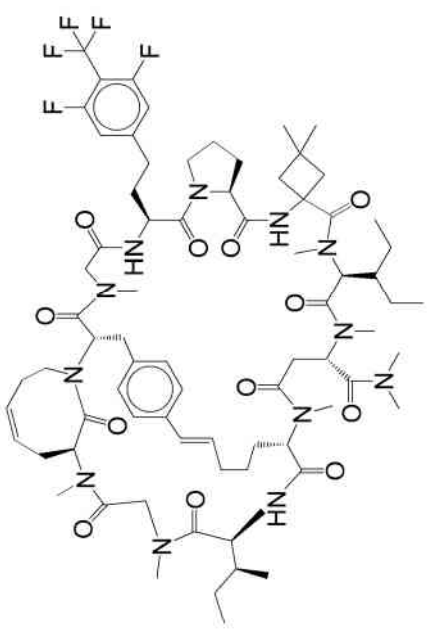
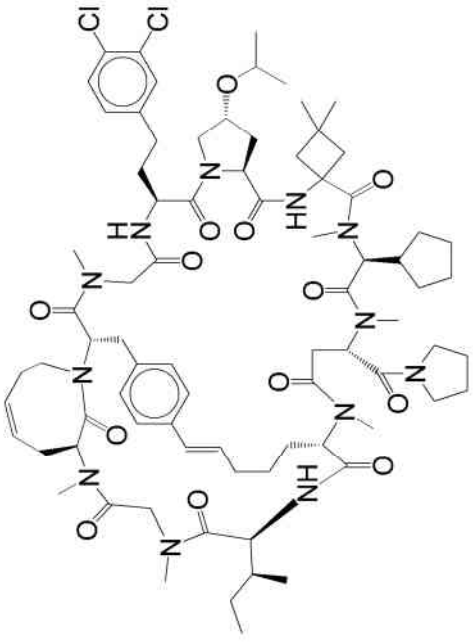
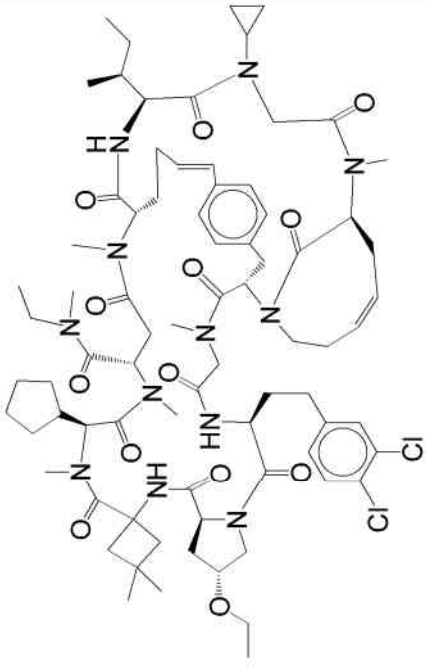
	
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PP257 3	PP257 5

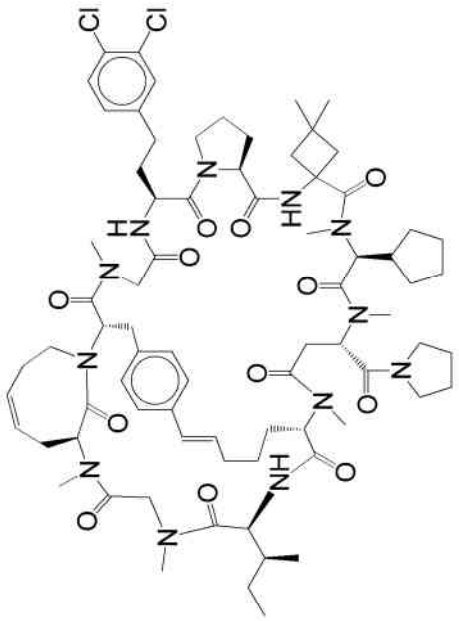
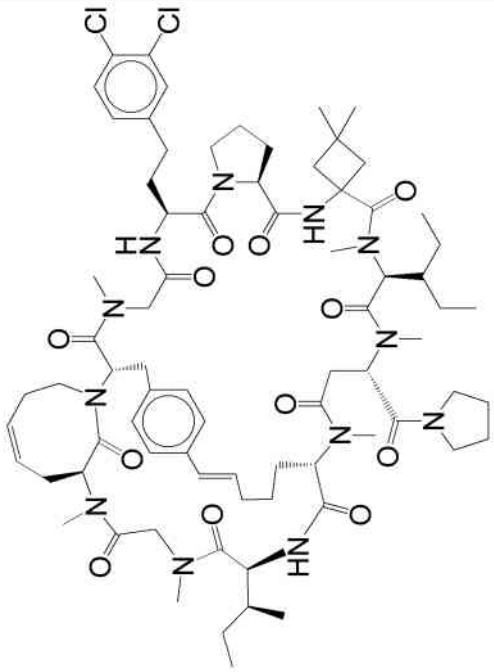
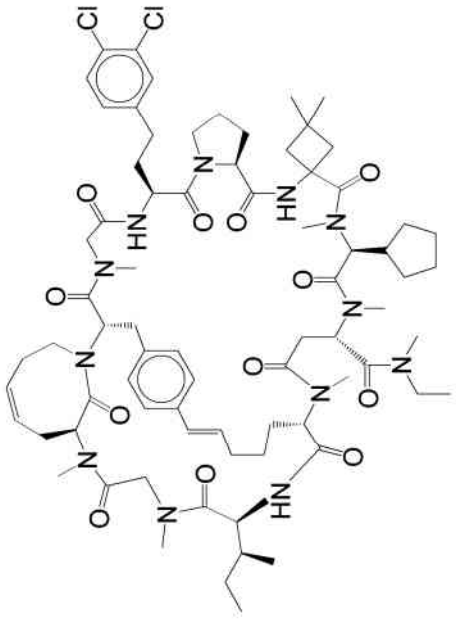
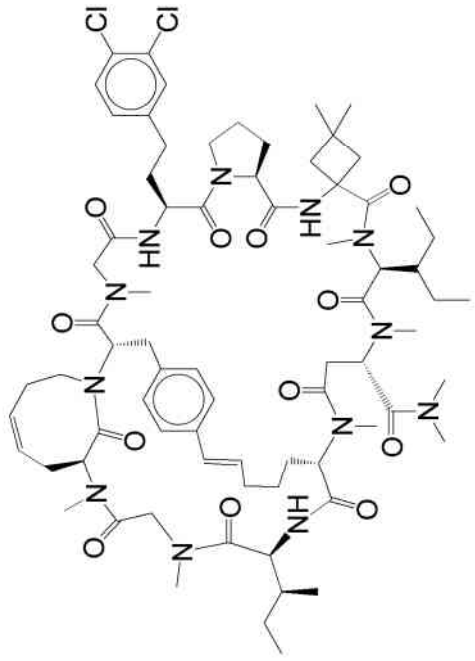
	
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PP2577	PP2579

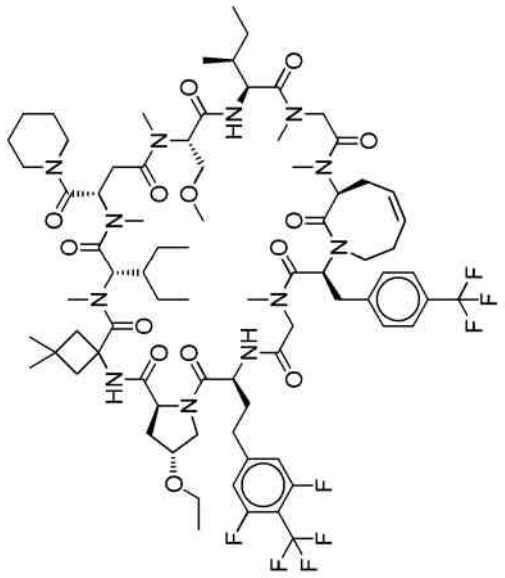
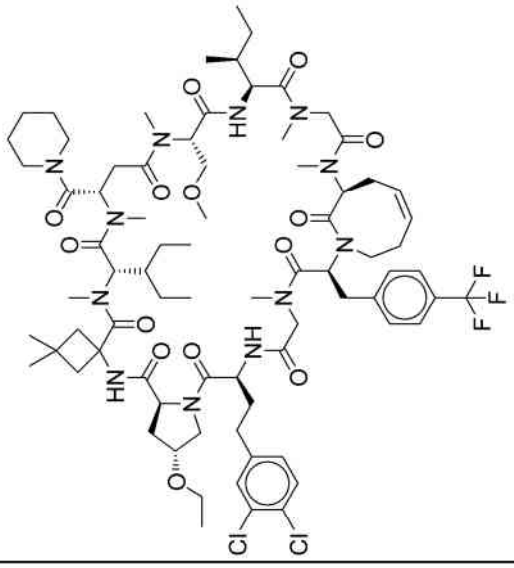
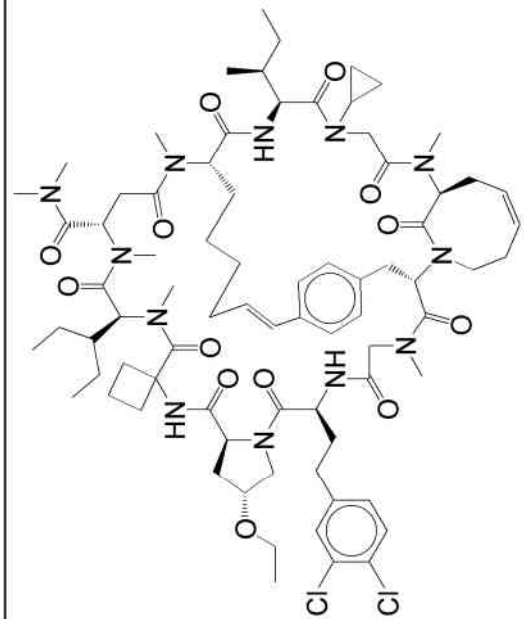
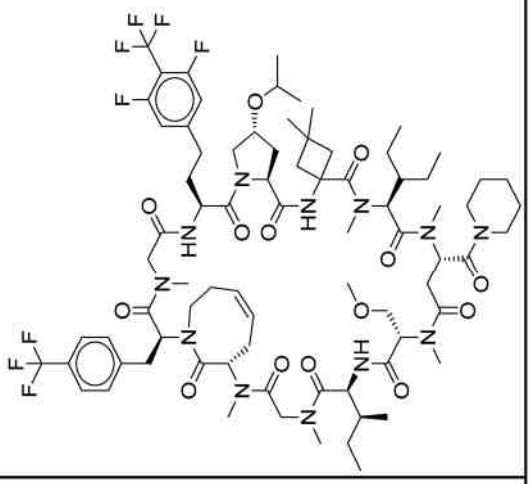
	
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PP258 1	PP258 5

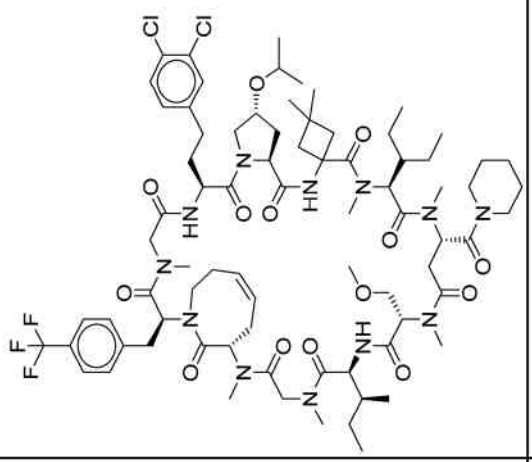
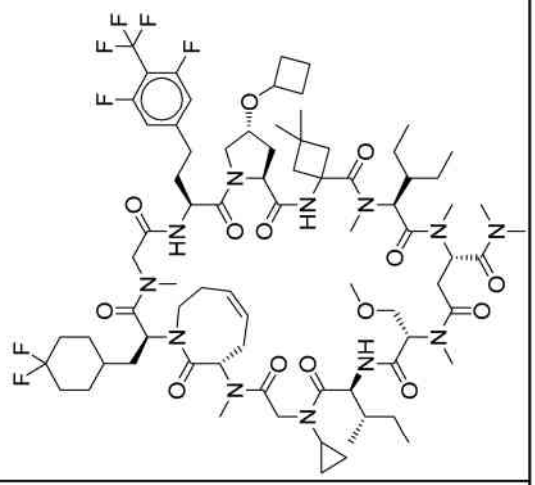
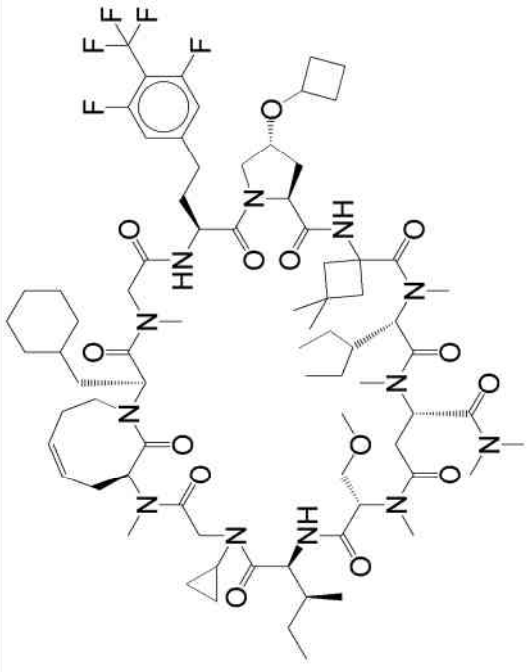
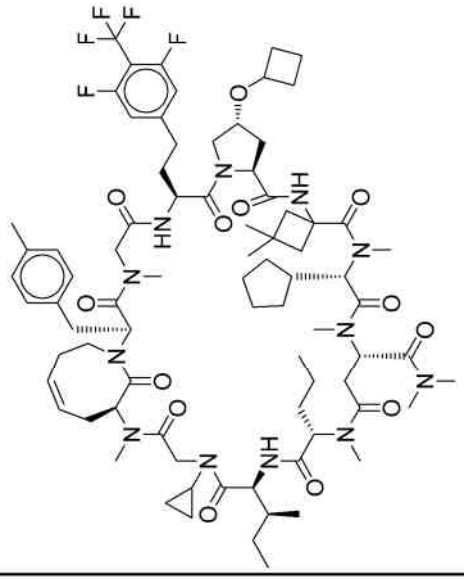
	
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PP2588	PP2590

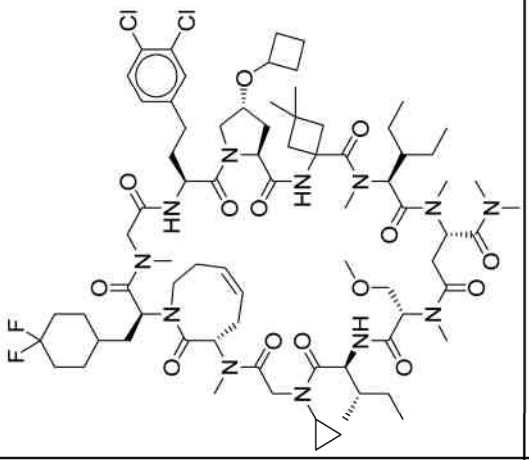
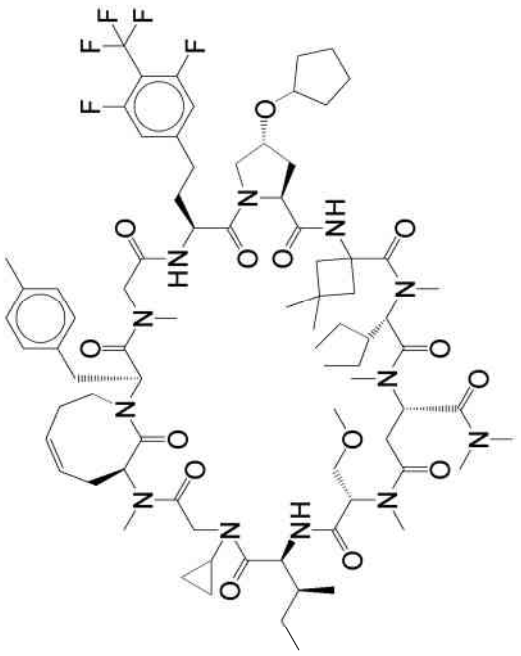
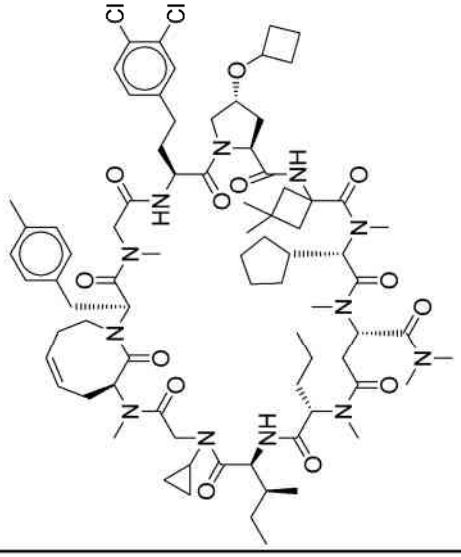
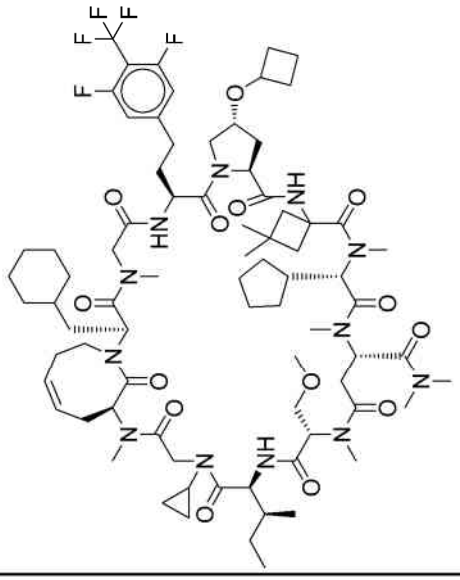
	
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PP259 2	PP259 4

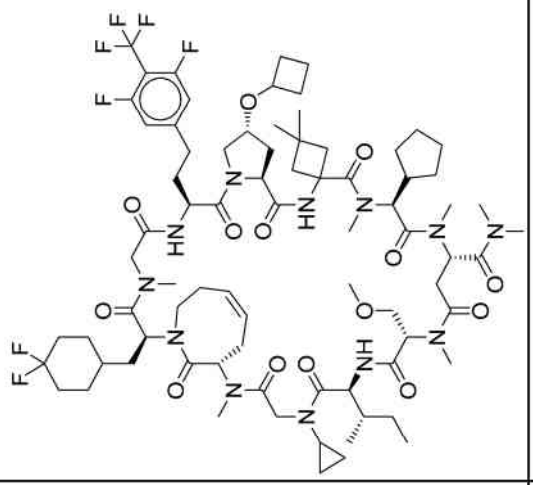
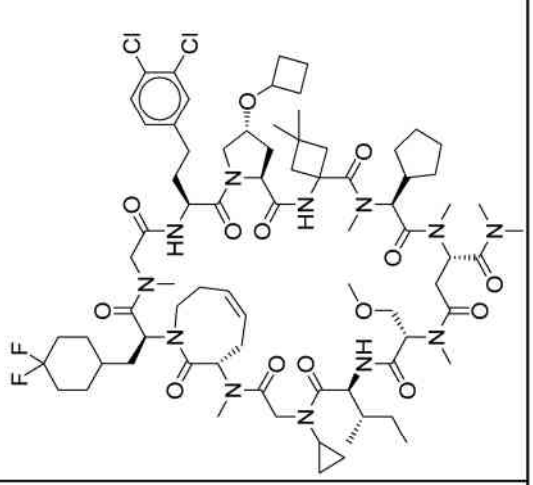
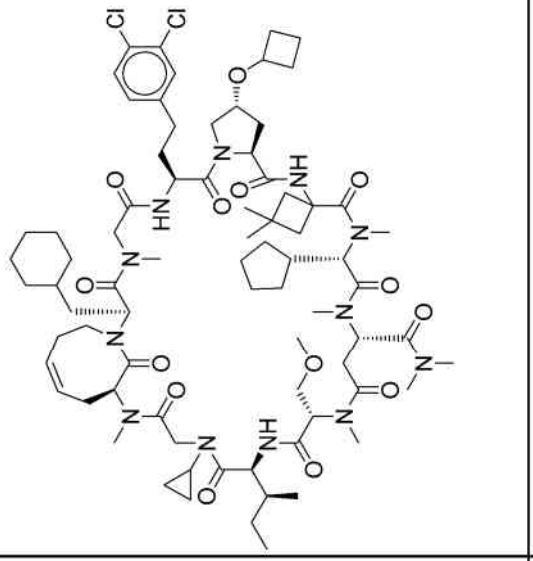
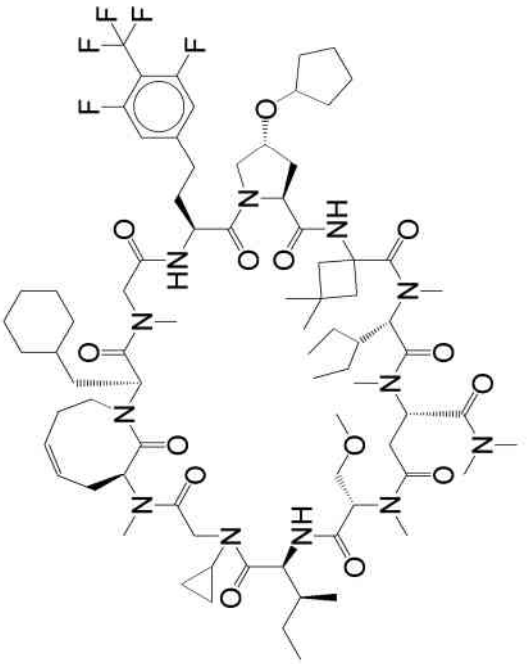
	
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PP2596	PP2598

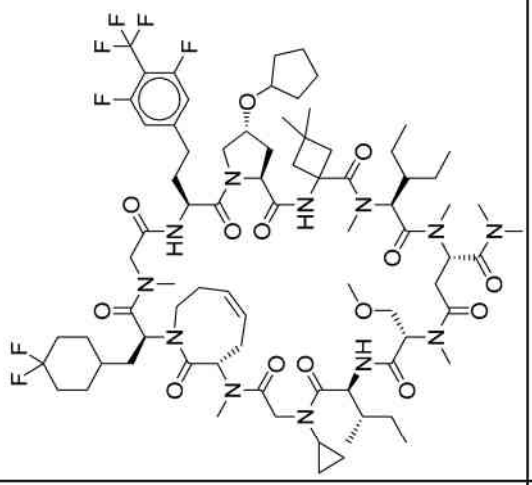
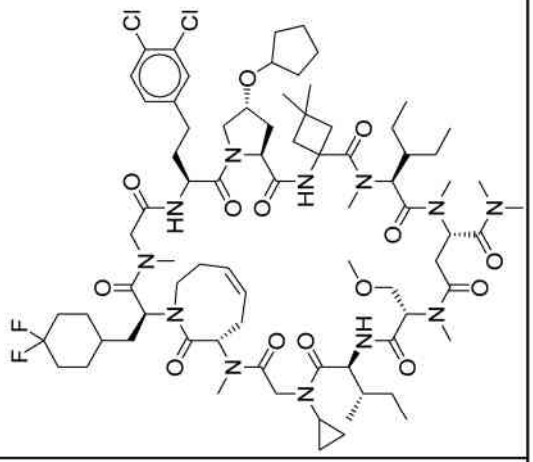
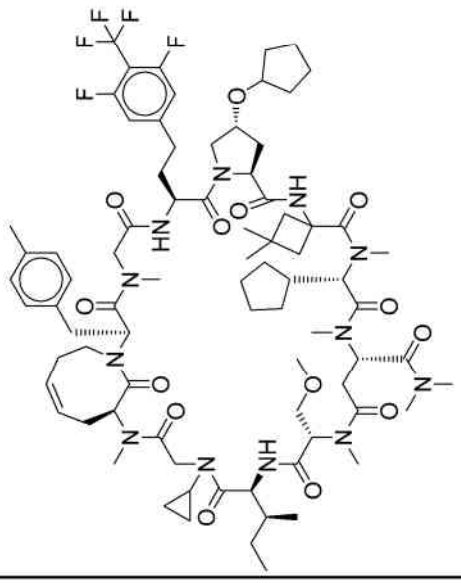
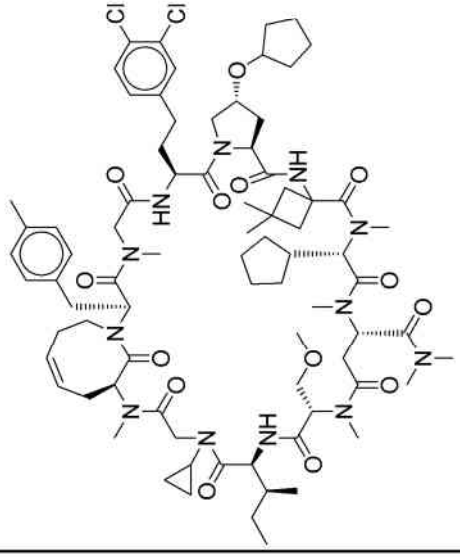
	
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PP260 1	PP260 3

	
PP2606	PP2610
	
PP2605	PP2608

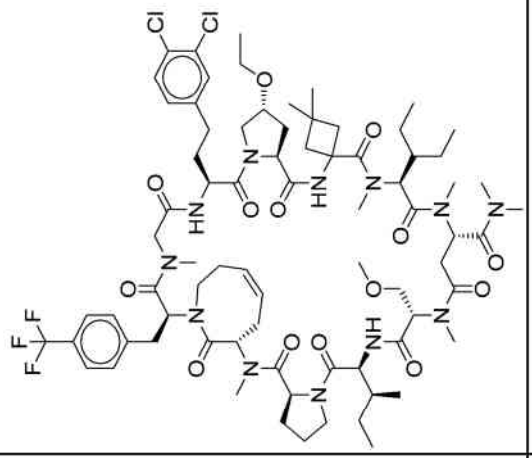
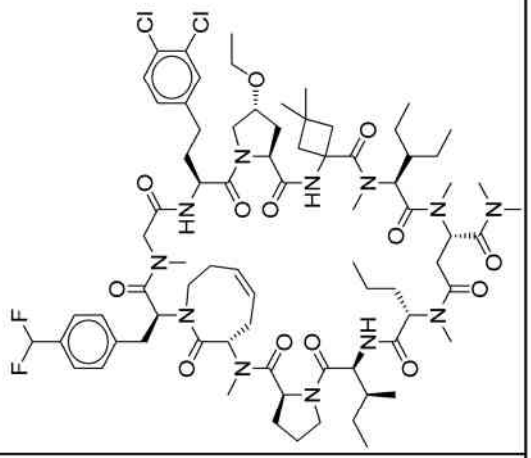
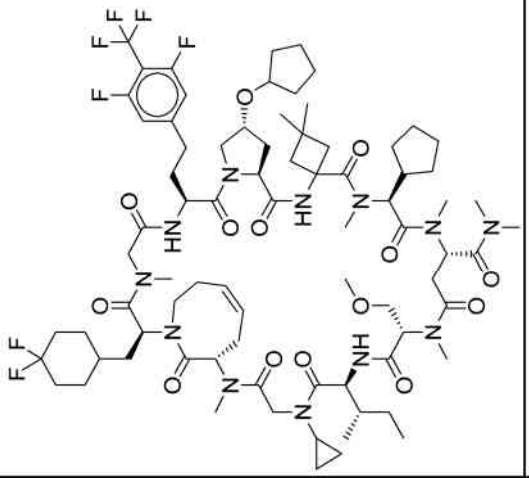
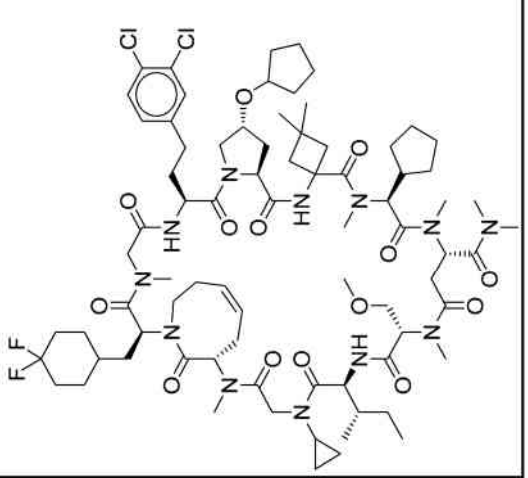
	
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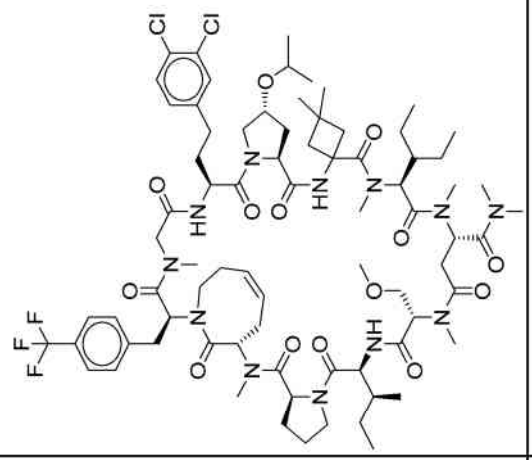
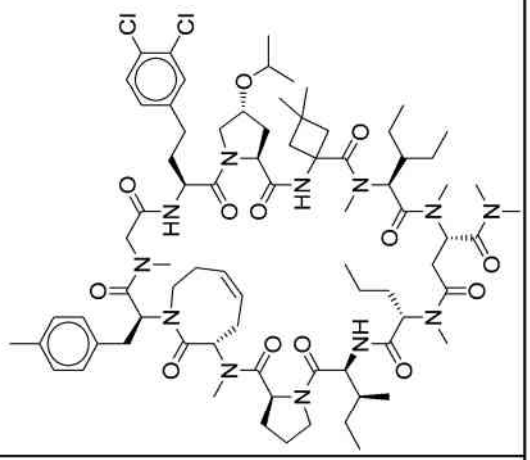
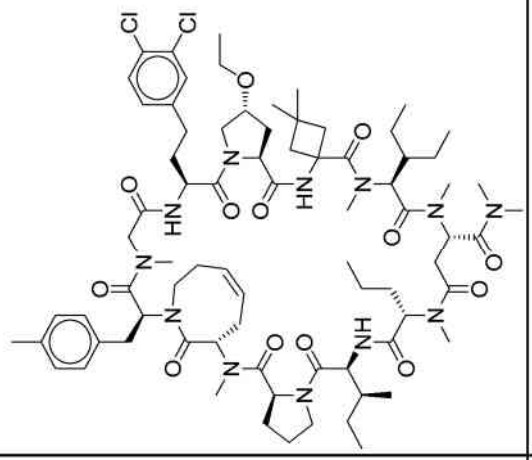
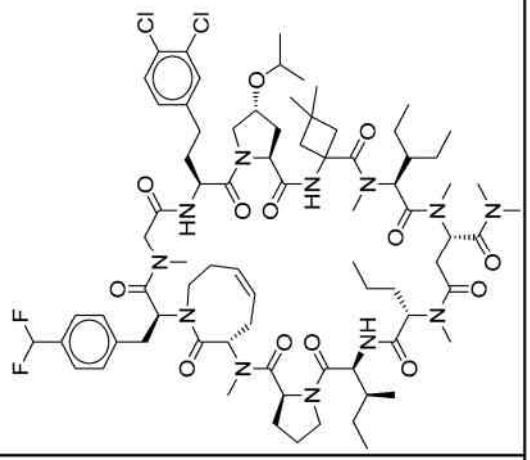
	
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PP261 6	PP261 8

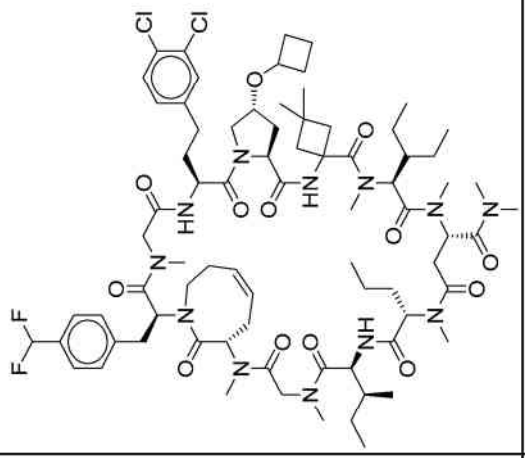
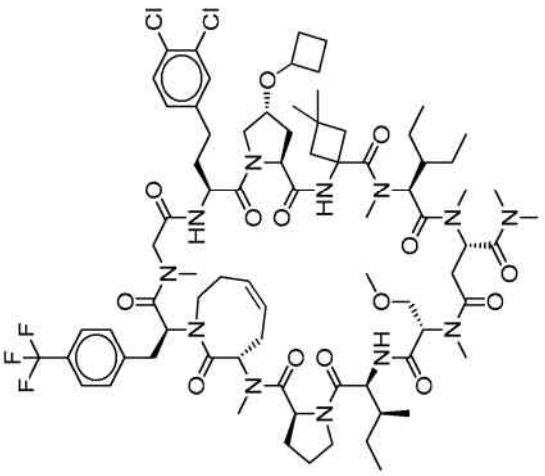
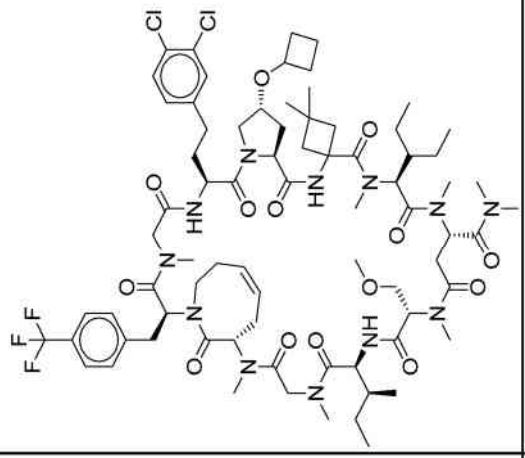
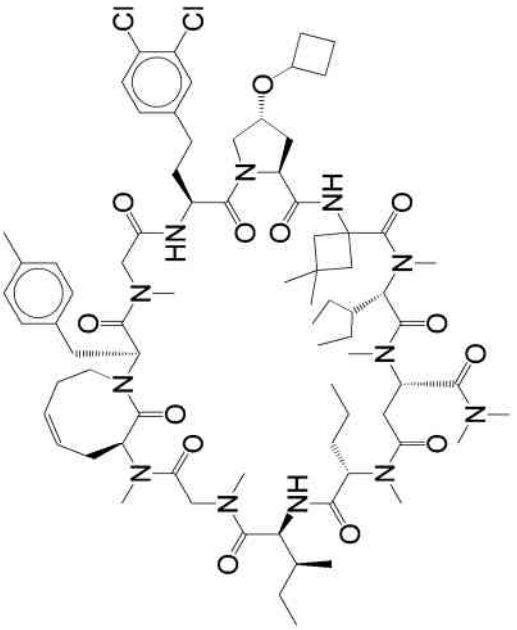
	
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PP262 0	PP262 3

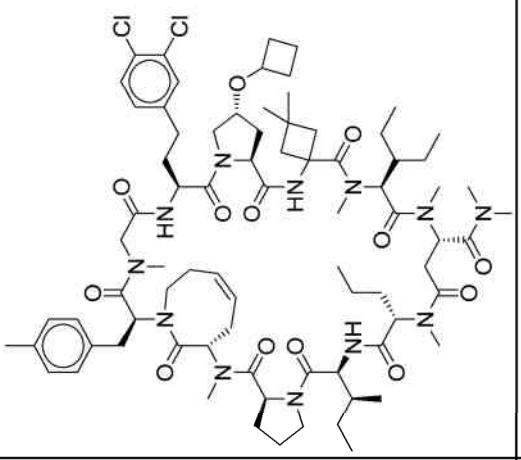
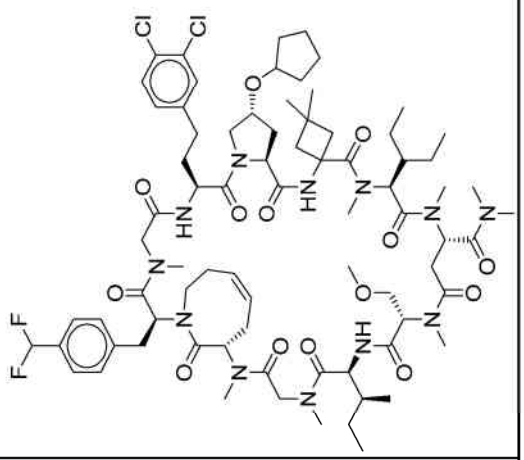
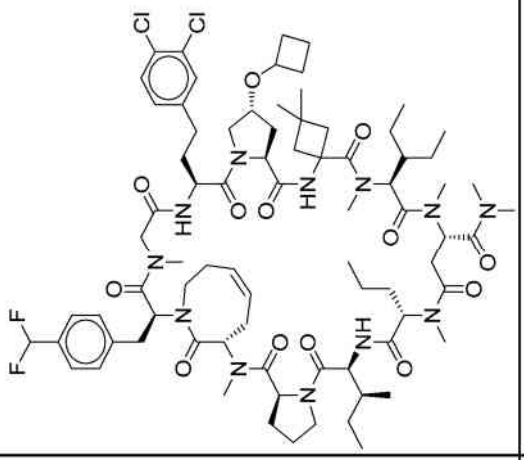
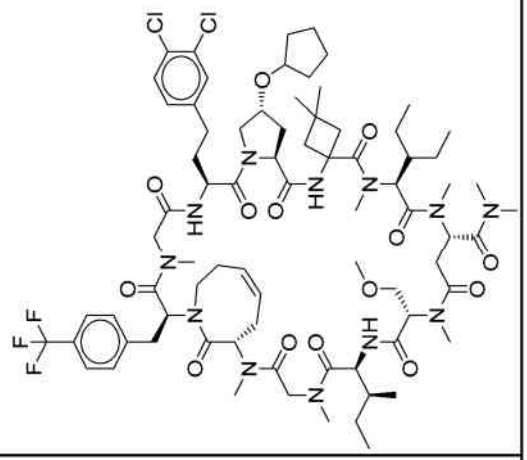
	
PP262 7	PP262 9
	
PP262 6	PP262 8

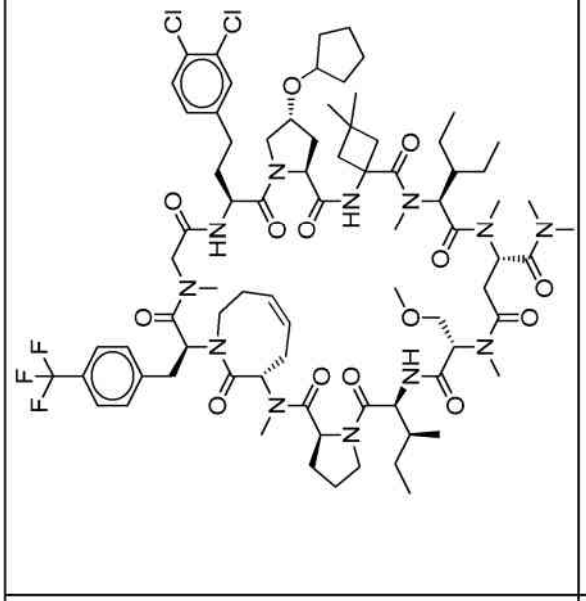
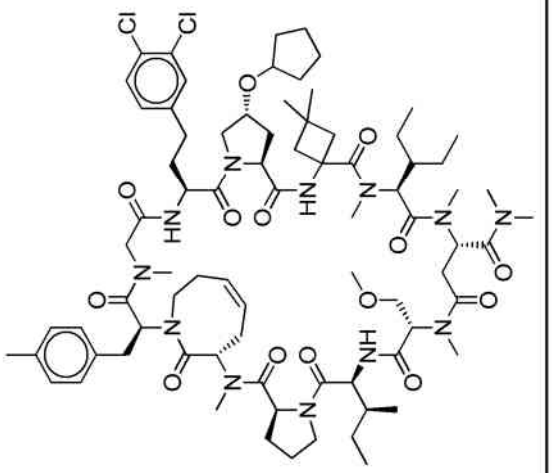
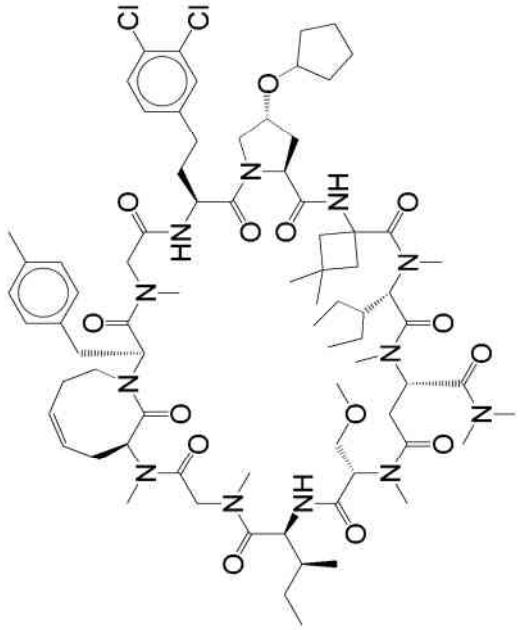
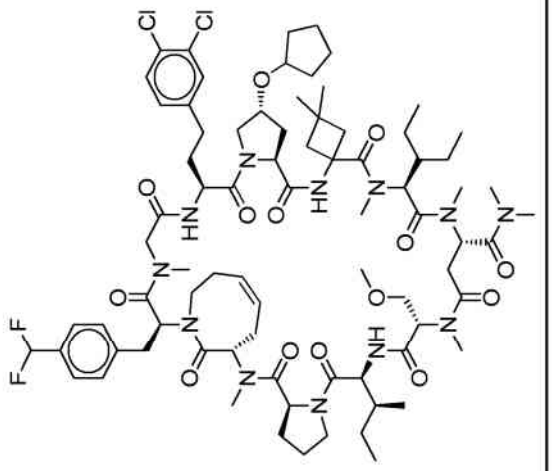
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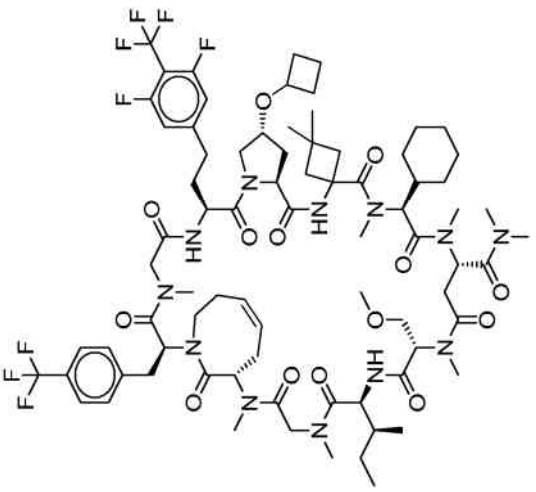
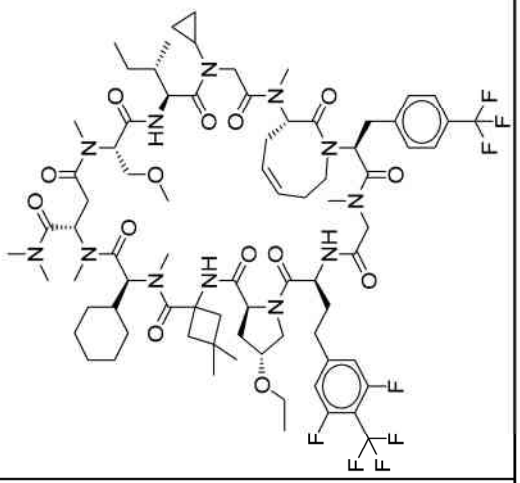
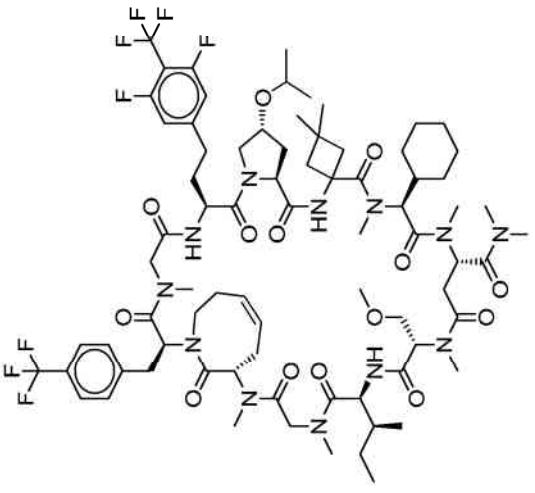
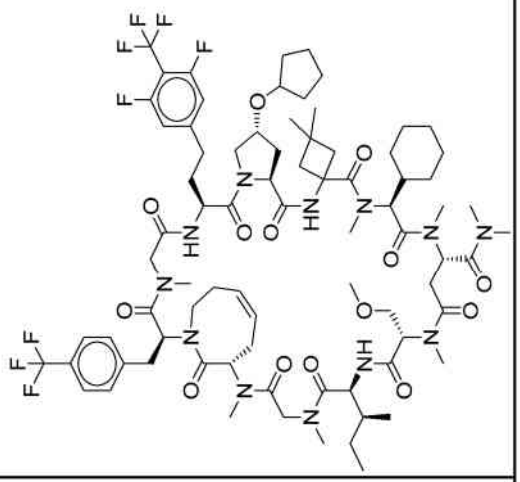
	
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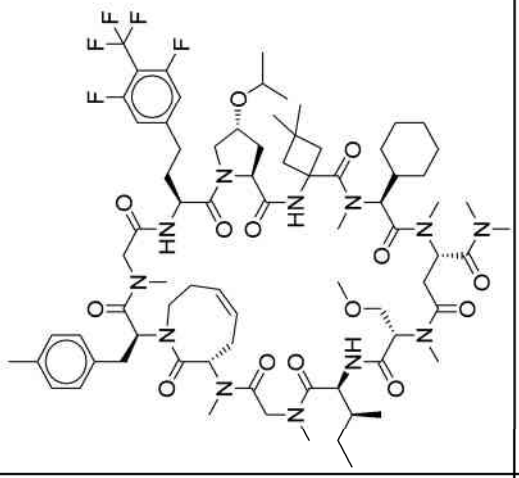
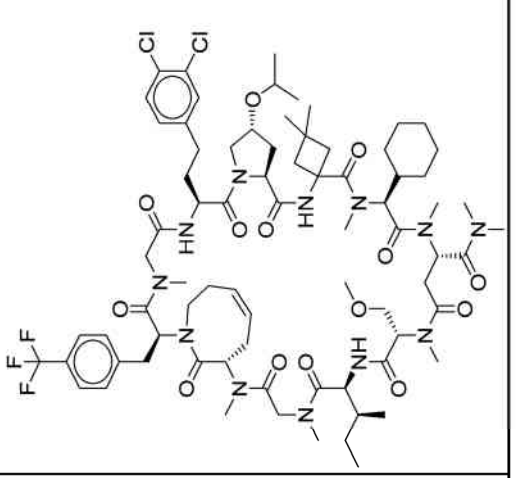
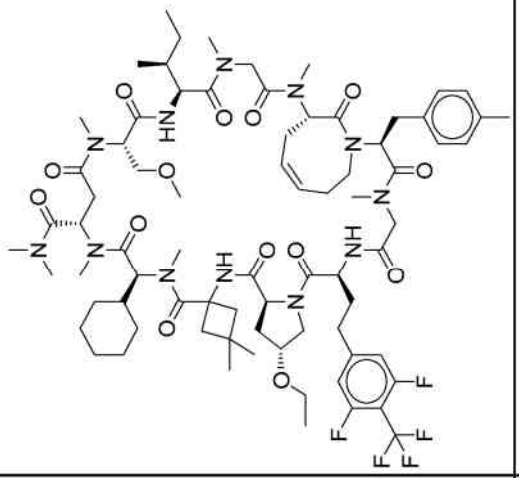
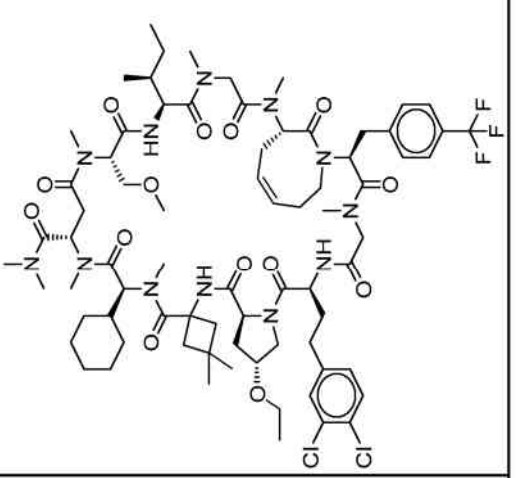
	
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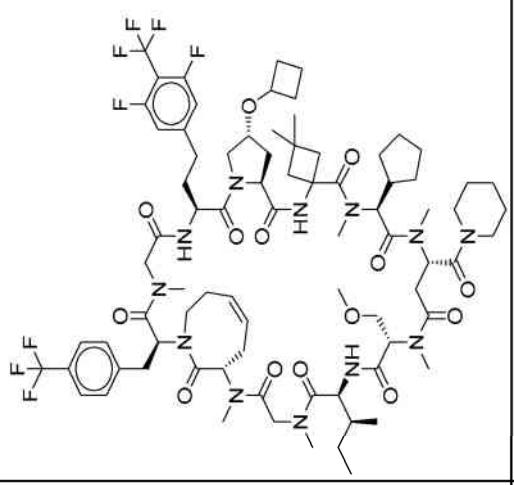
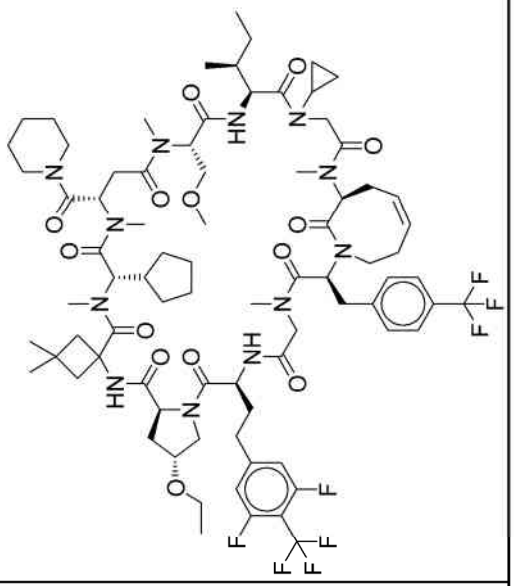
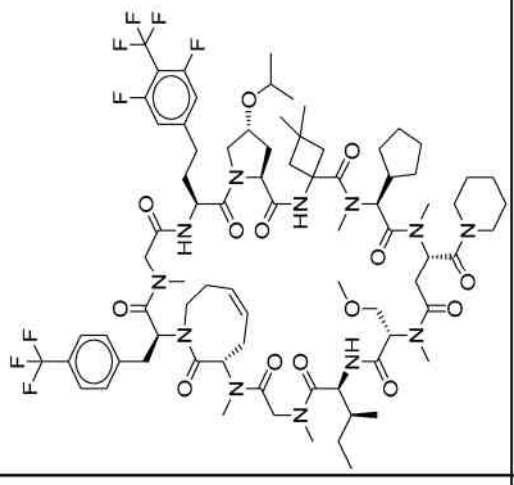
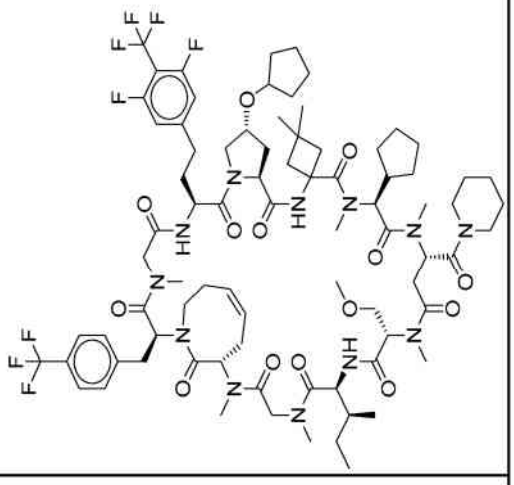
	
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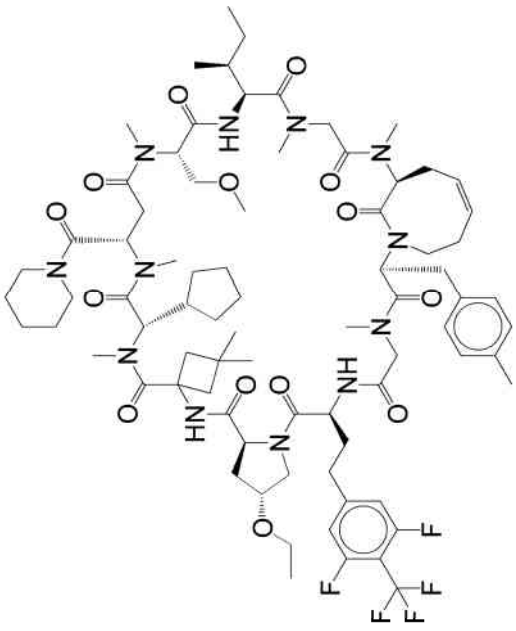
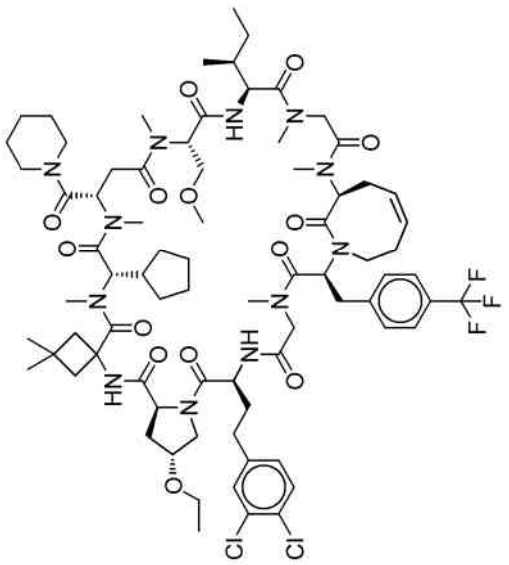
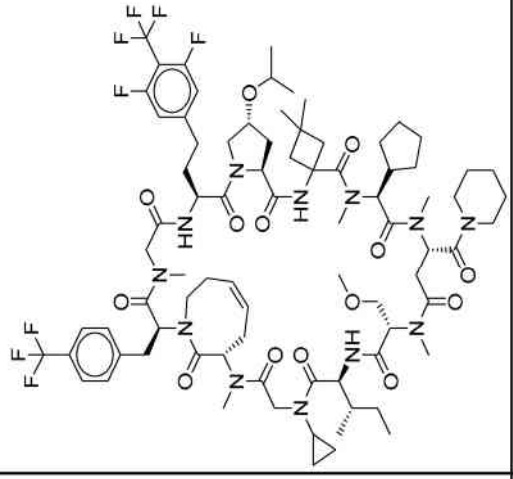
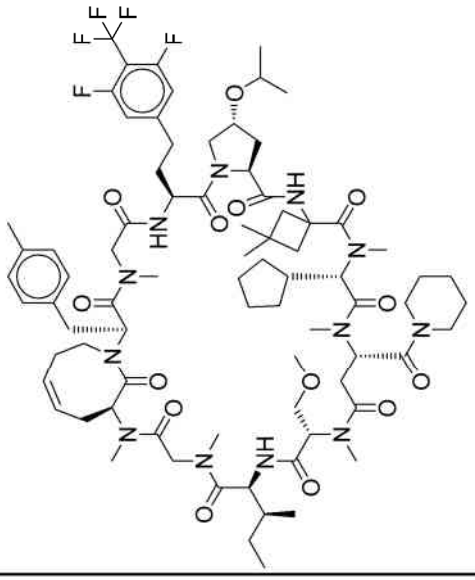
	
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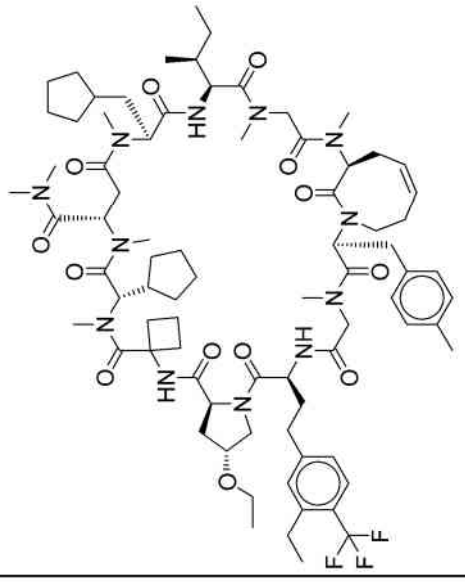
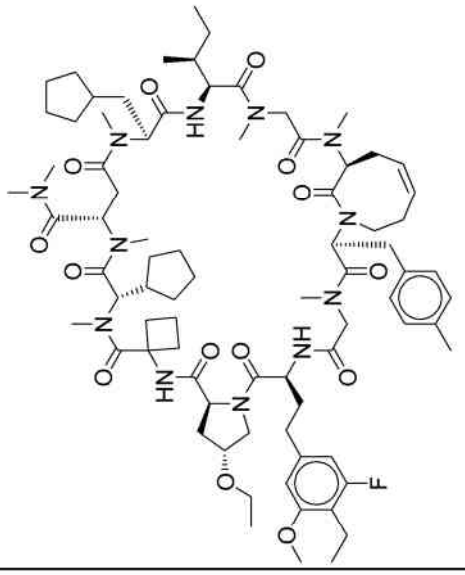
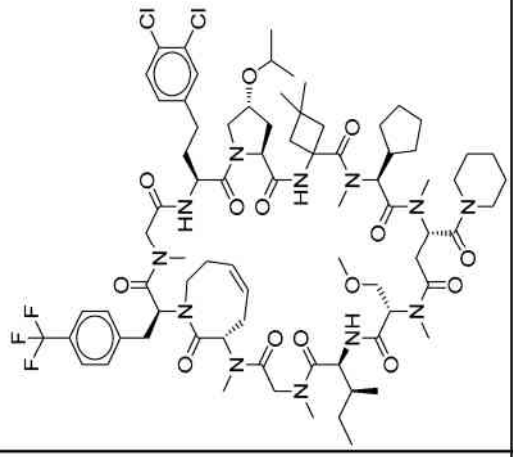
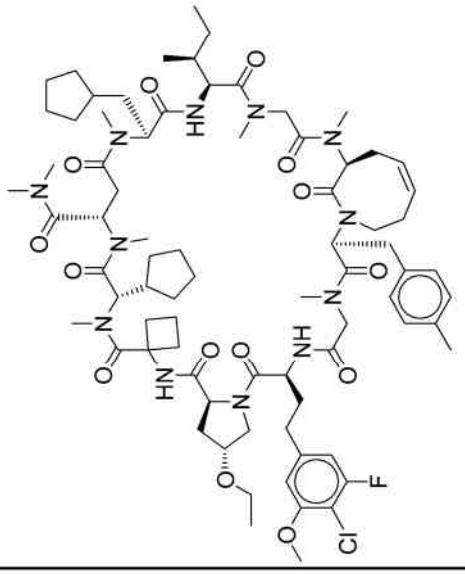
	
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PP265 0	PP265 2

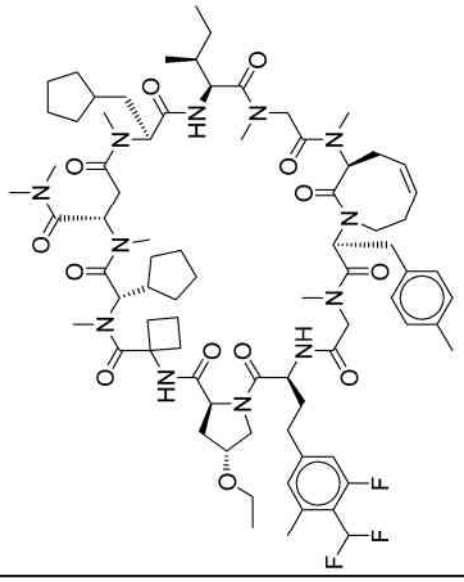
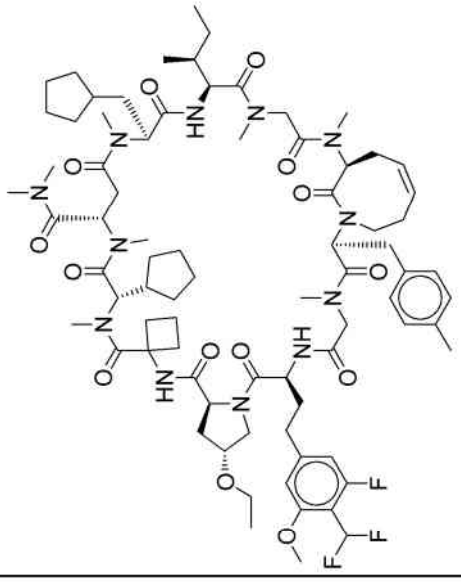
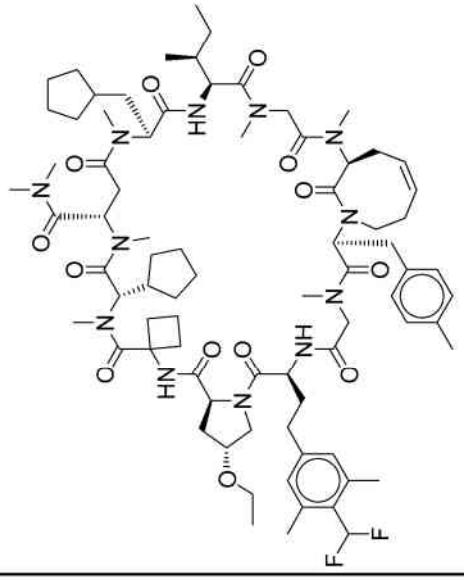
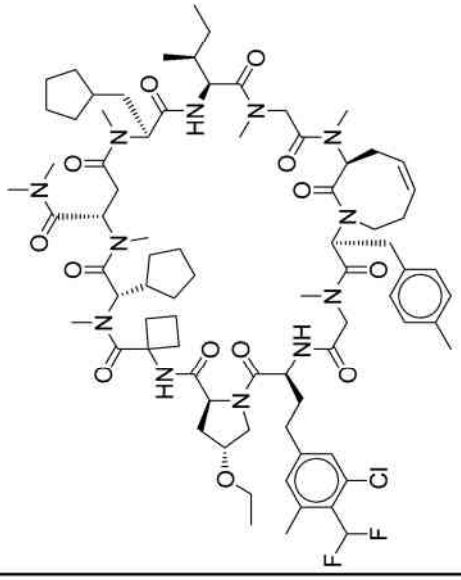
	
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PP265 4	PP265 6

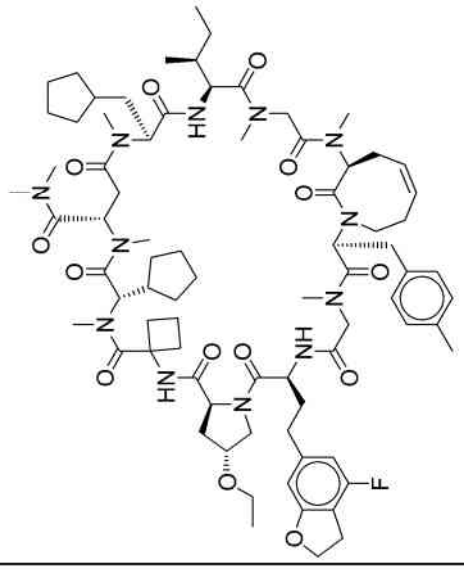
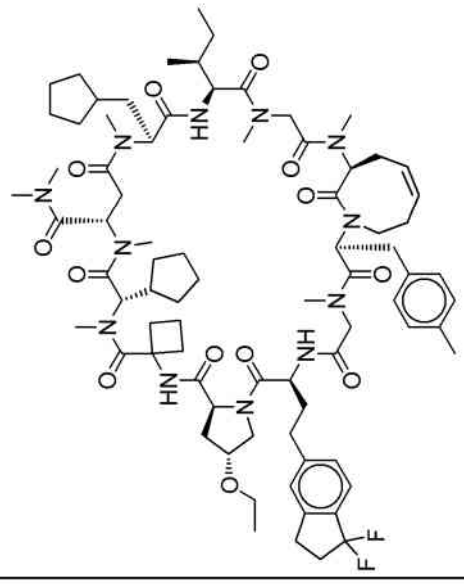
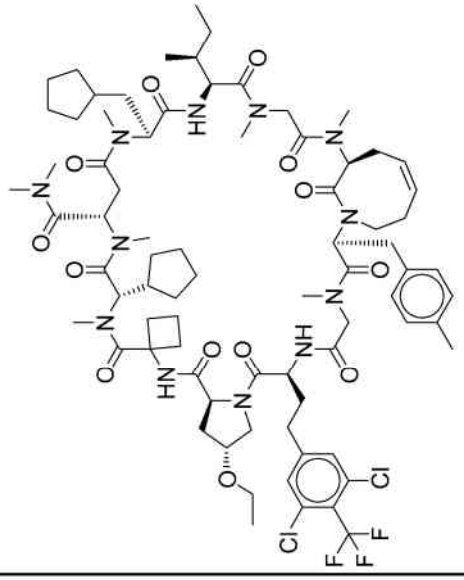
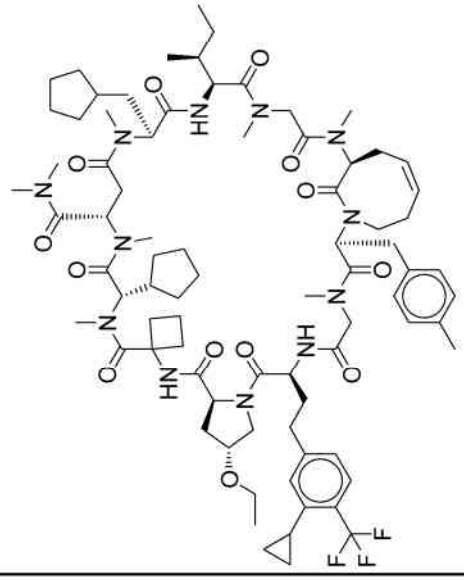
	
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PP2659	PP2661

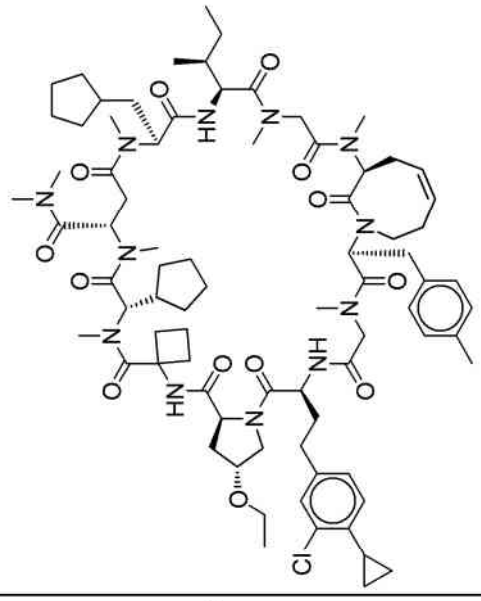
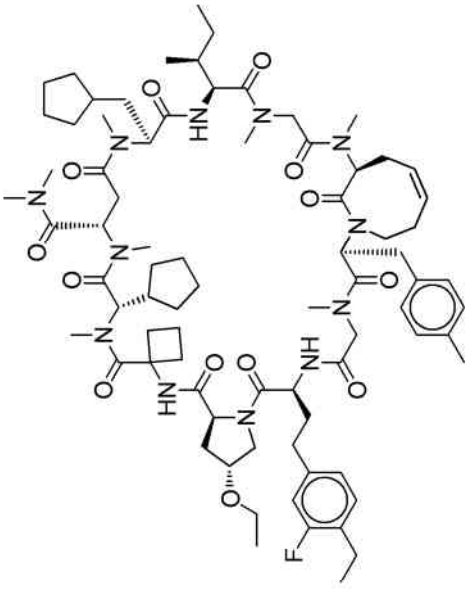
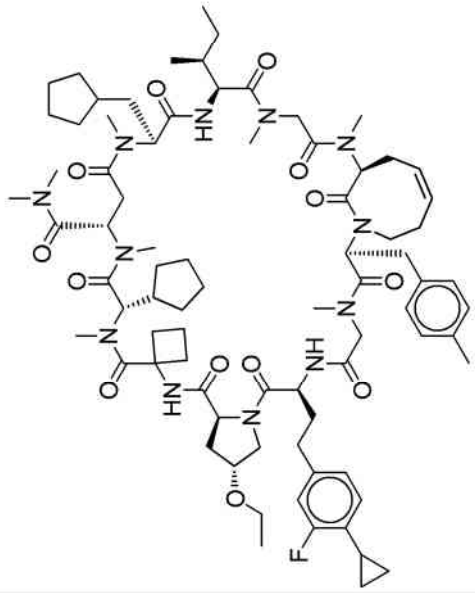
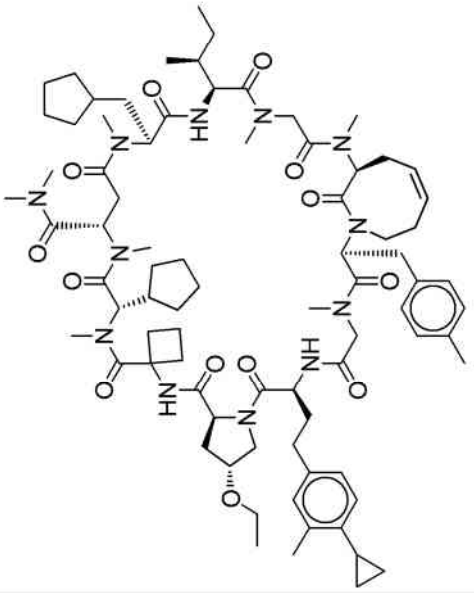
	
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PP266 3	PP266 5

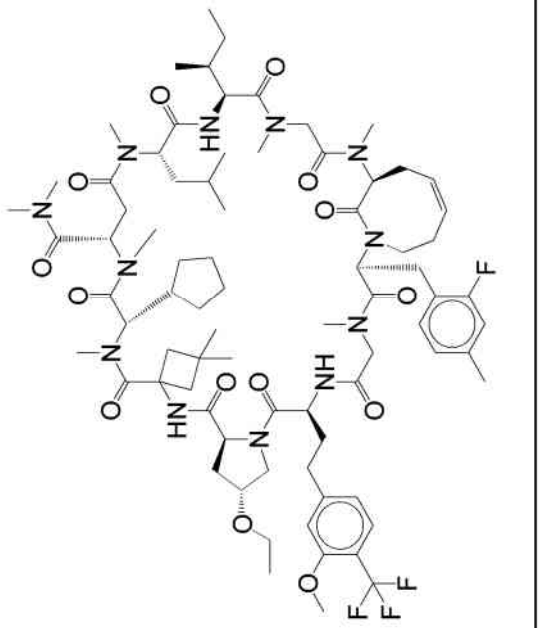
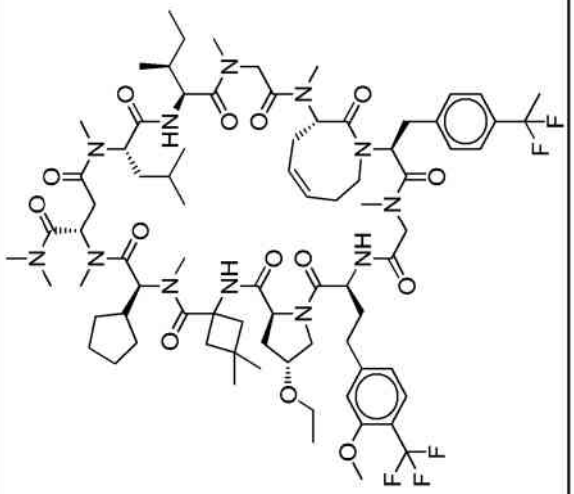
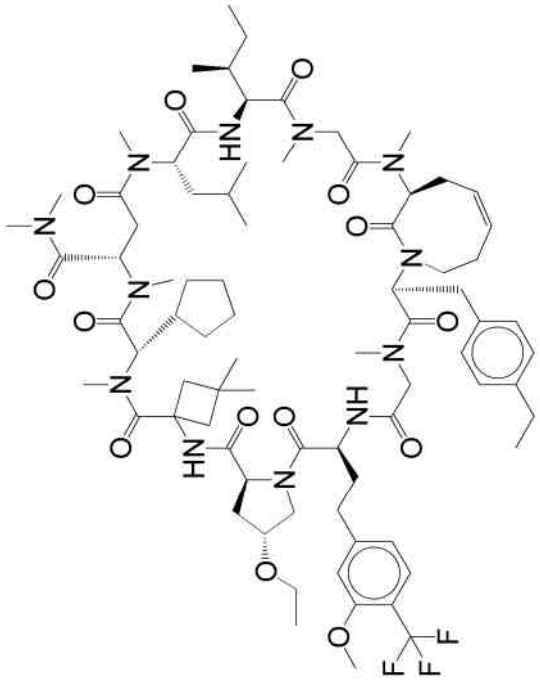
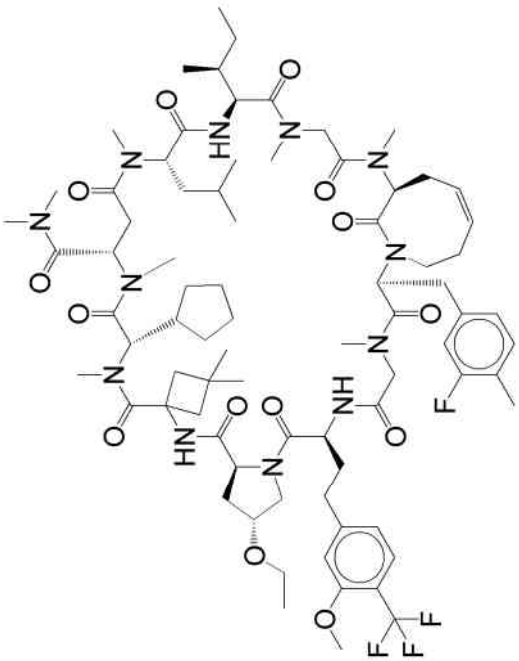
	
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PP2667	PP2669

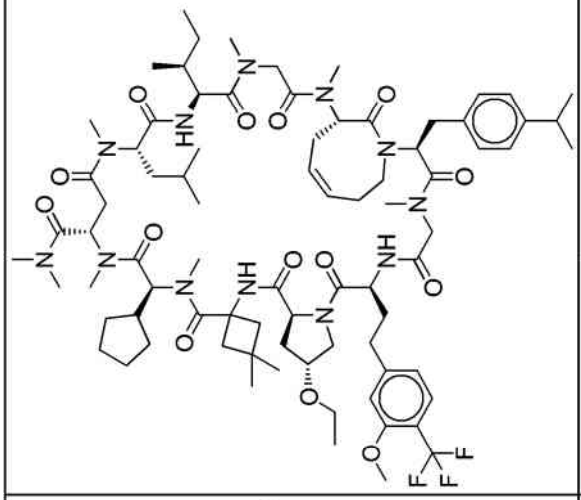
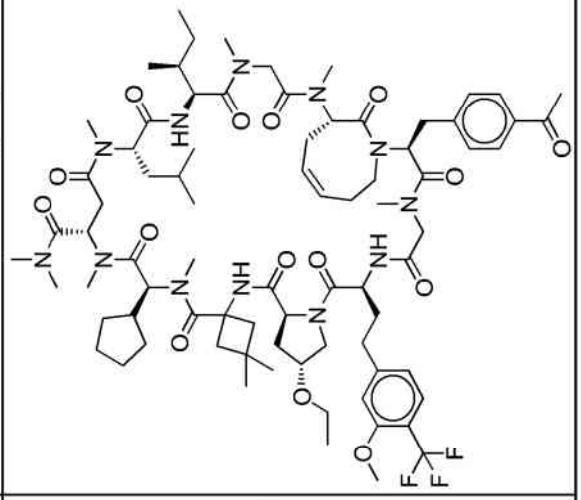
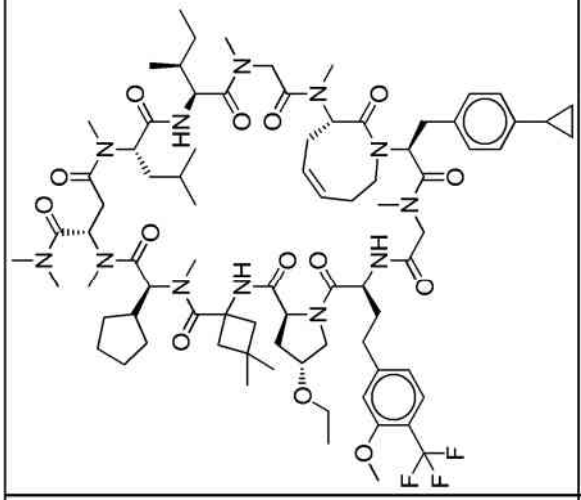
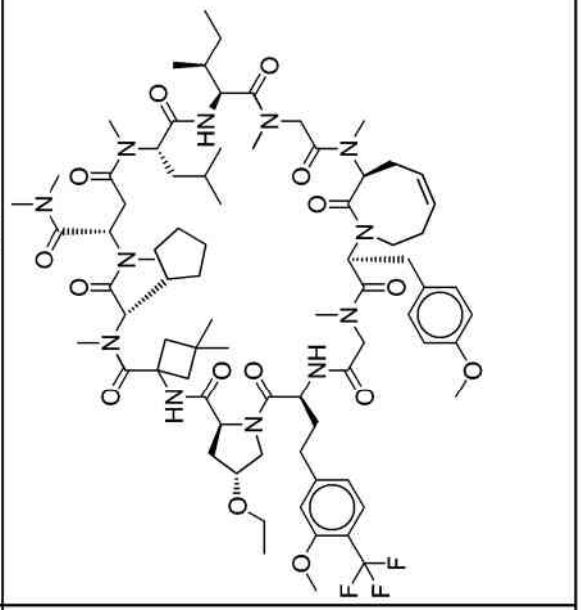
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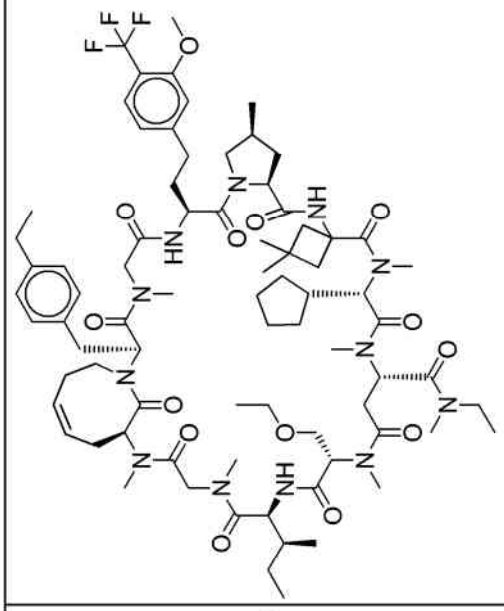
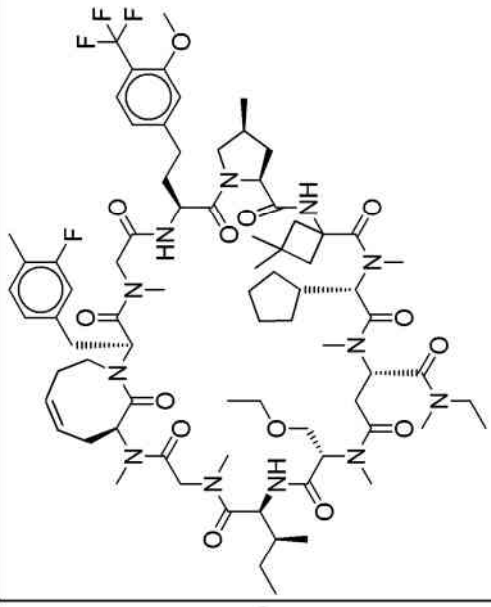
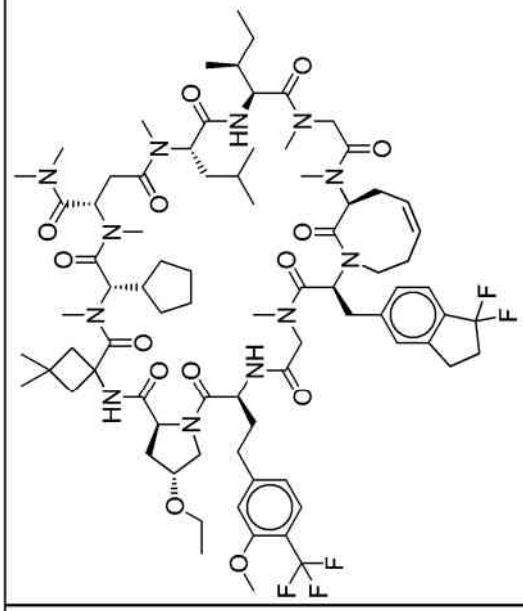
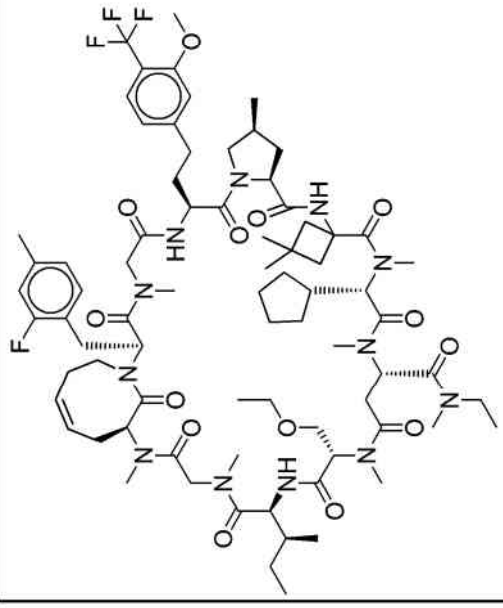
	
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PP267 5	PP267 7

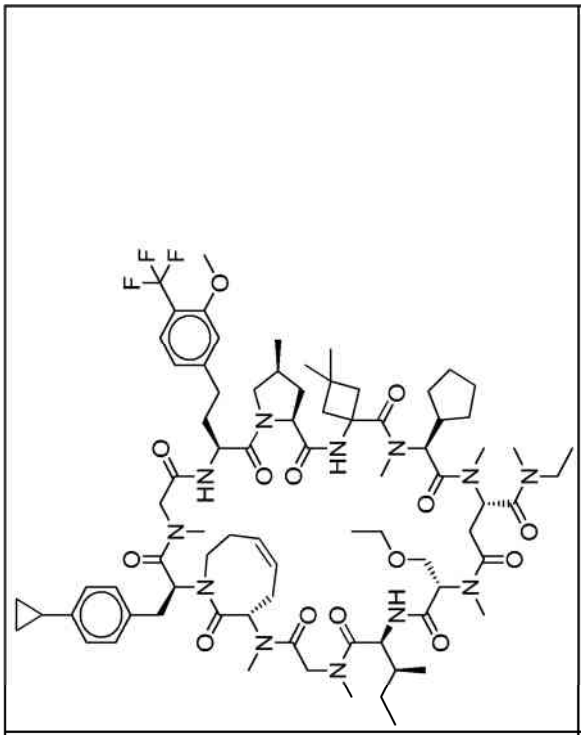
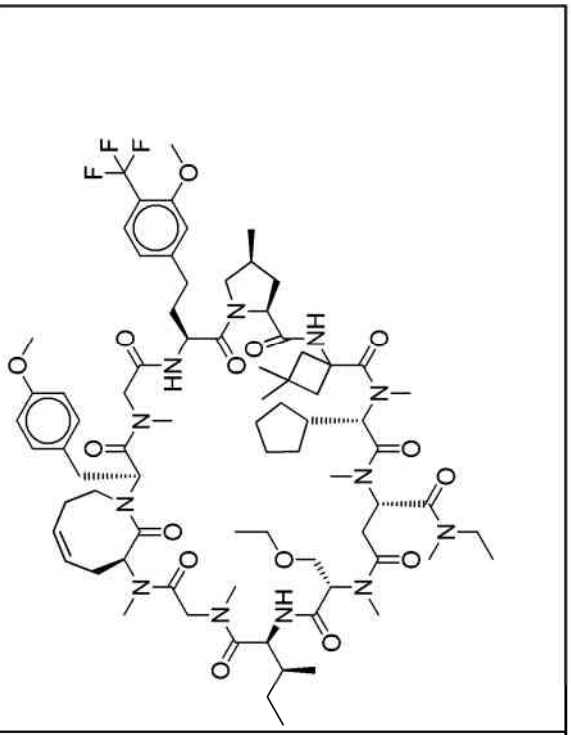
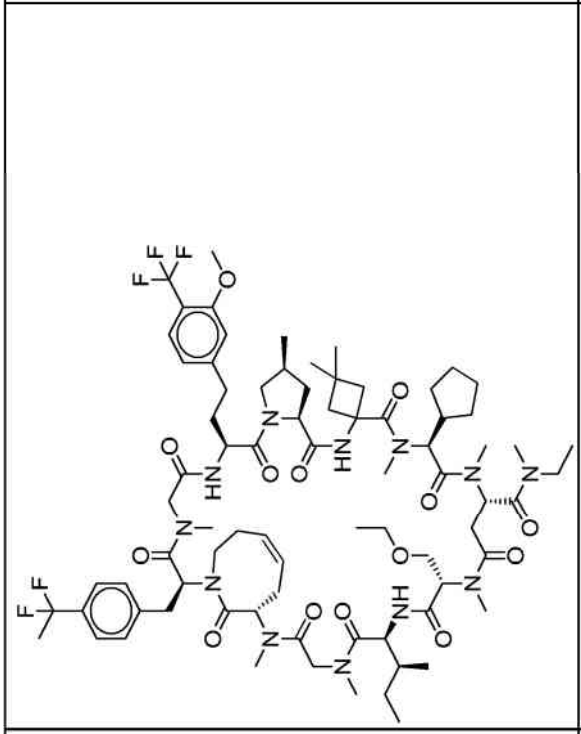
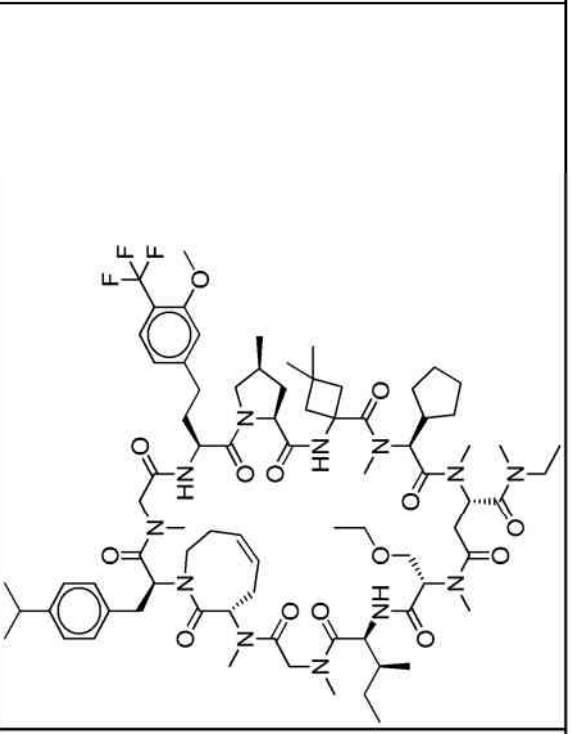
	
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PP2679	PP2681

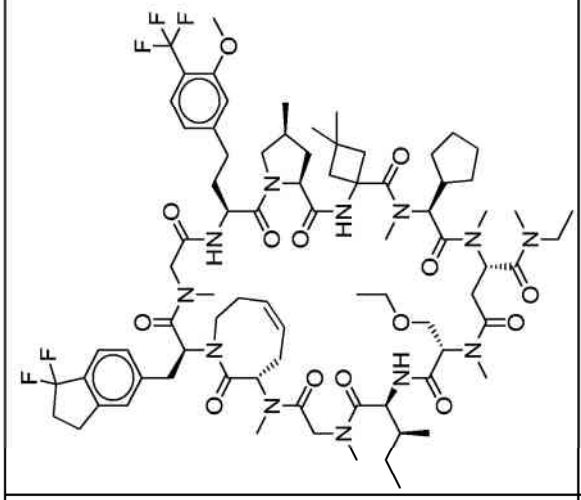
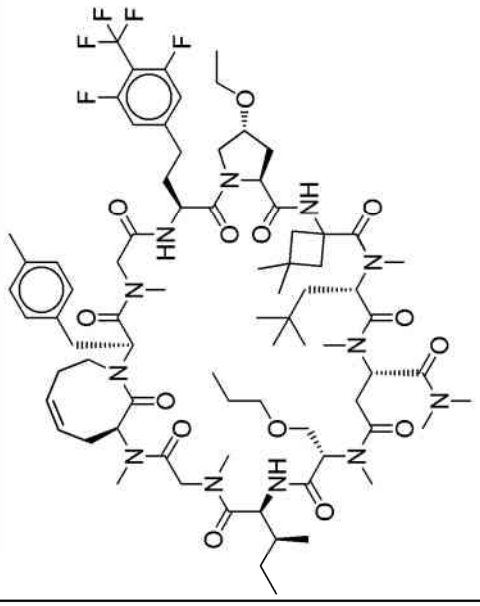
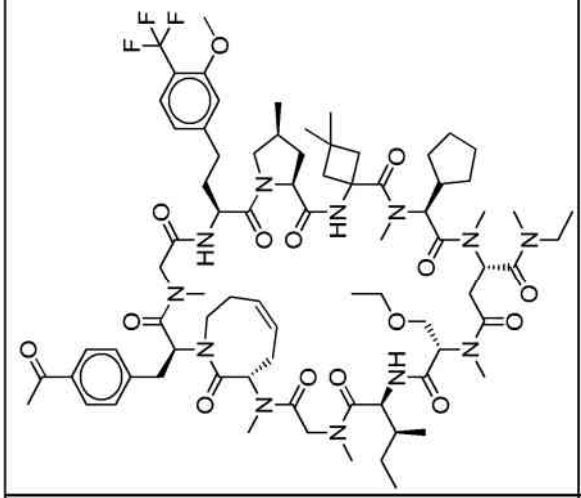
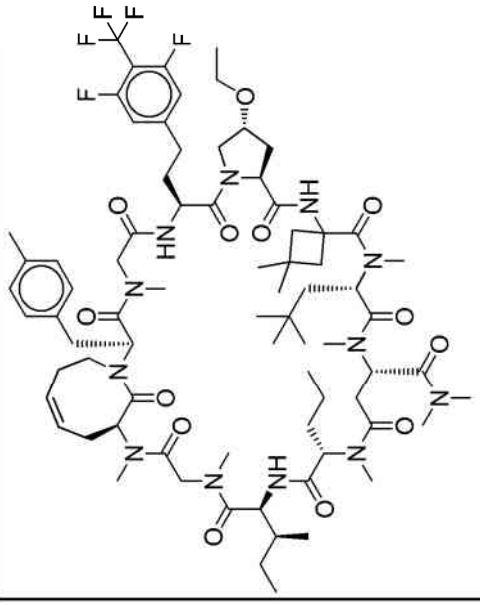
	
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PP268 3	PP268 5

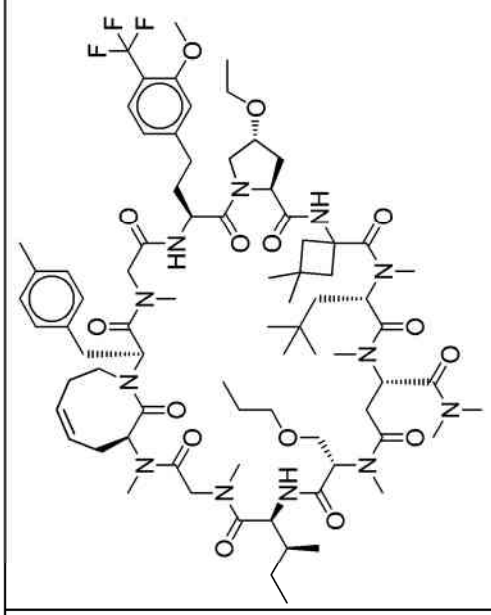
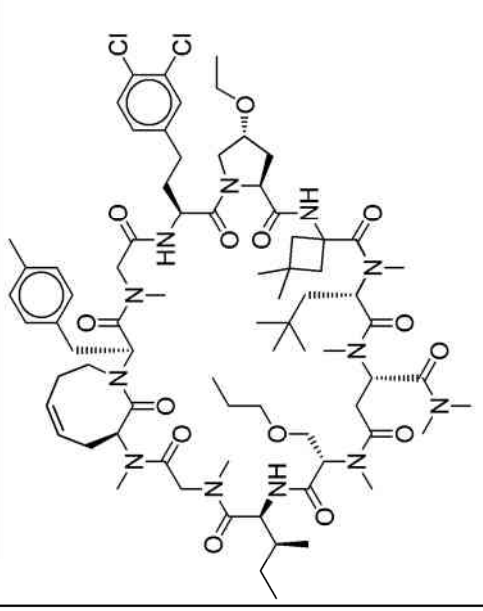
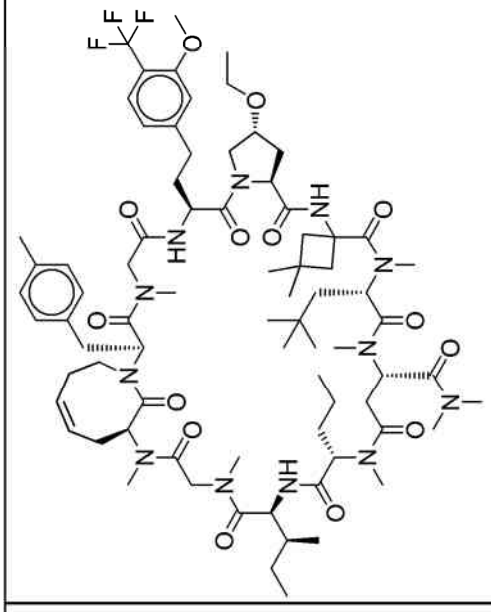
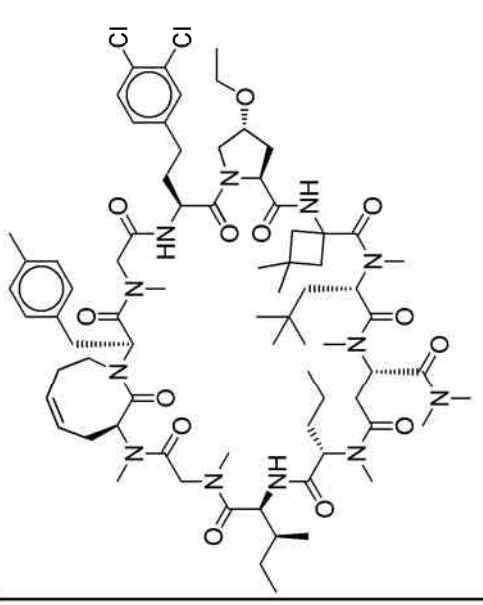
	
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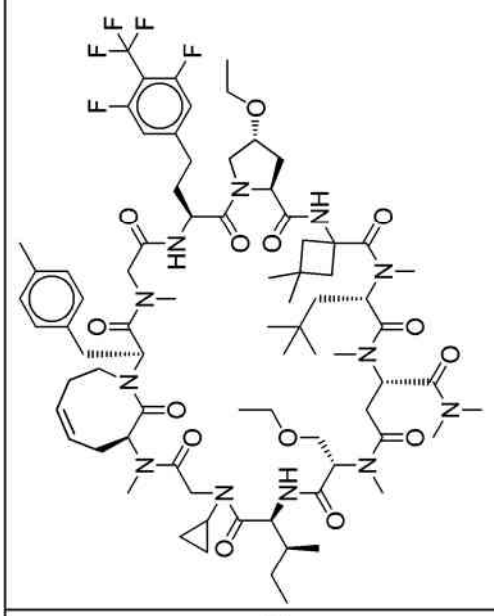
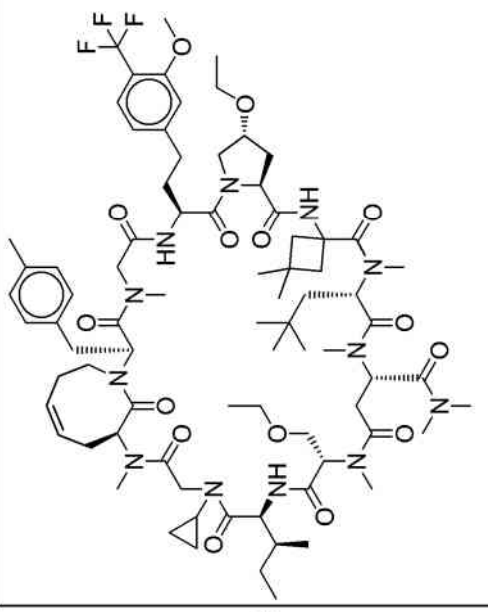
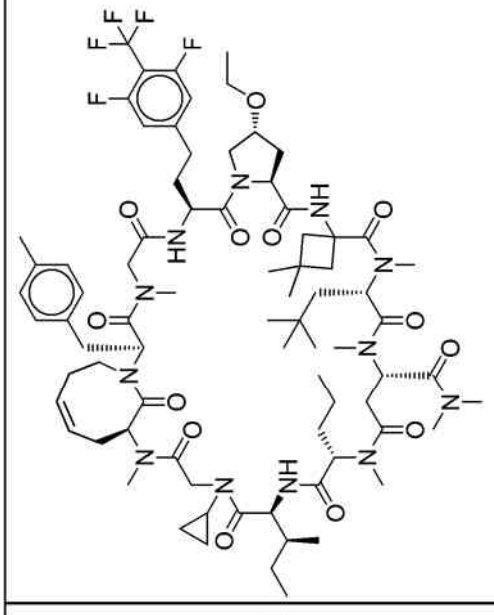
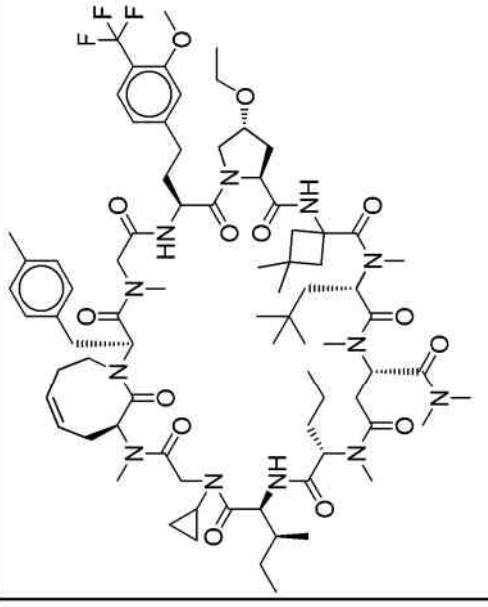
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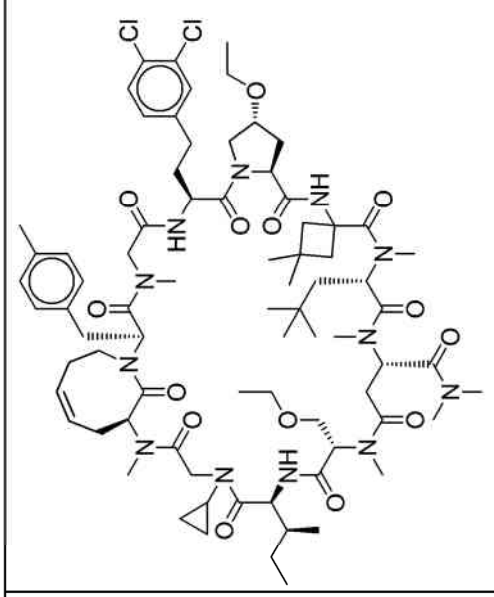
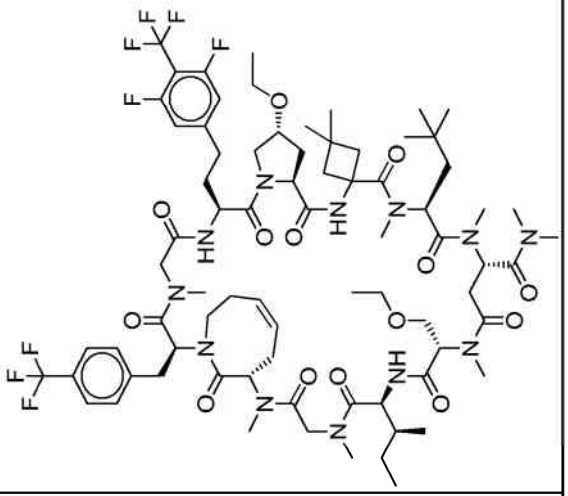
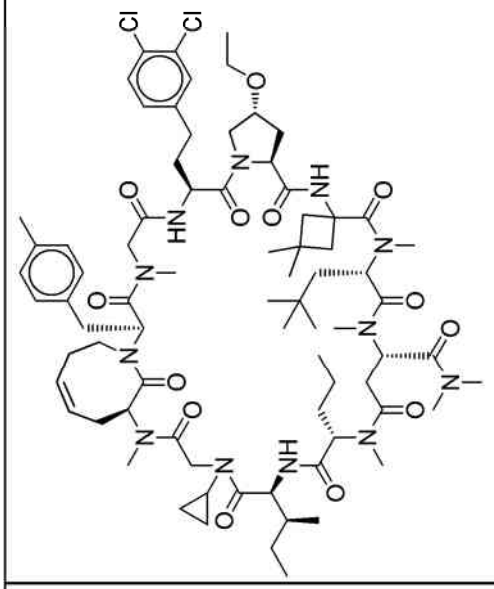
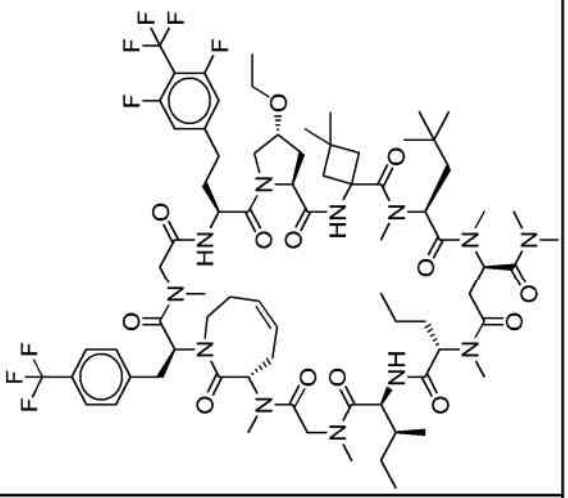
	
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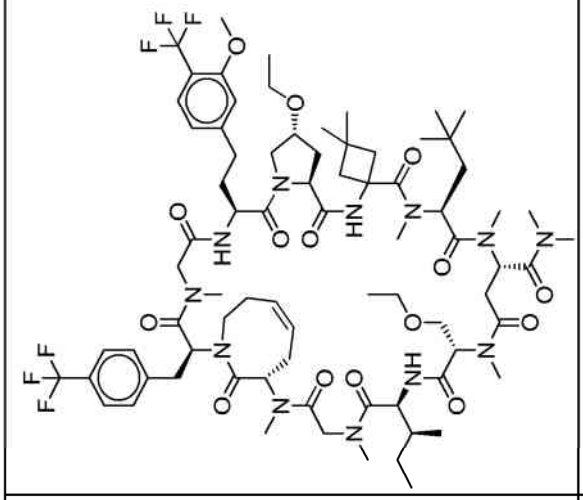
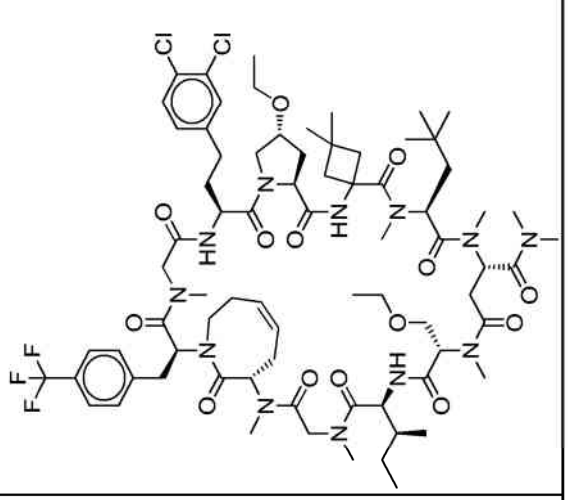
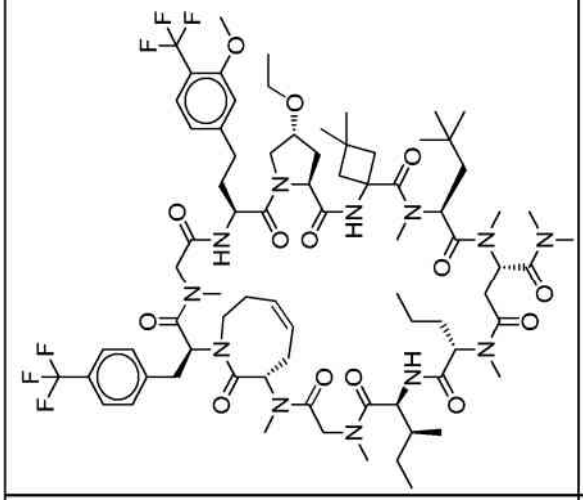
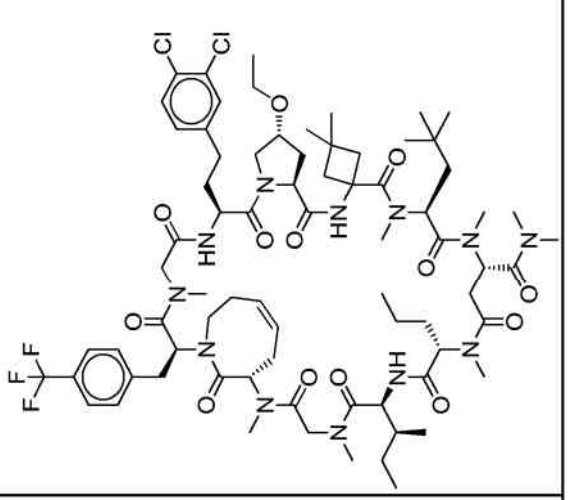
	
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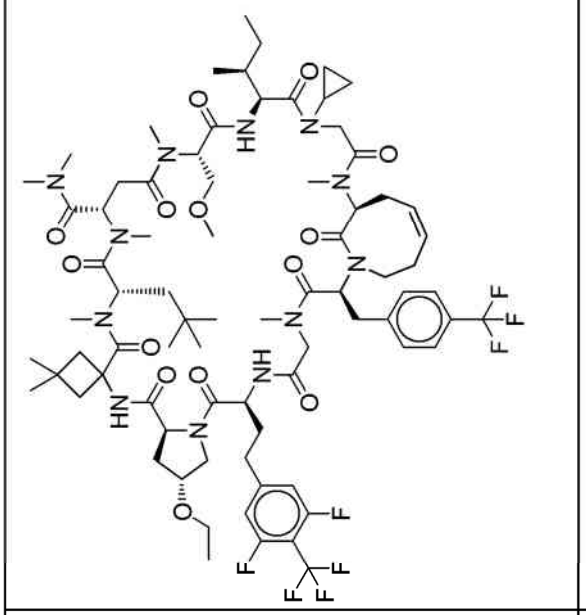
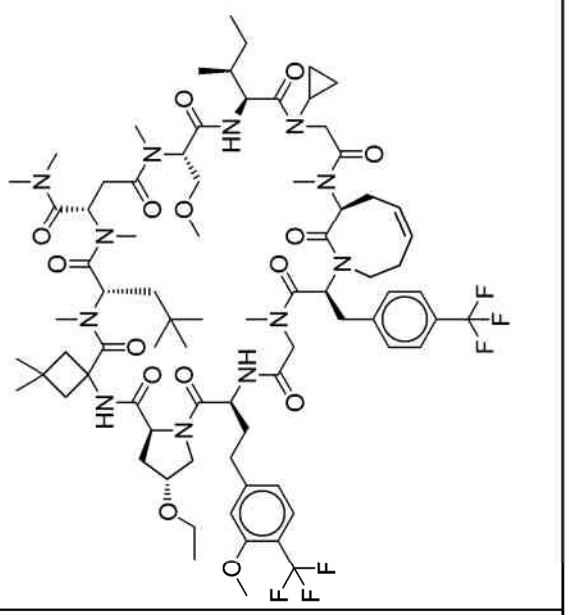
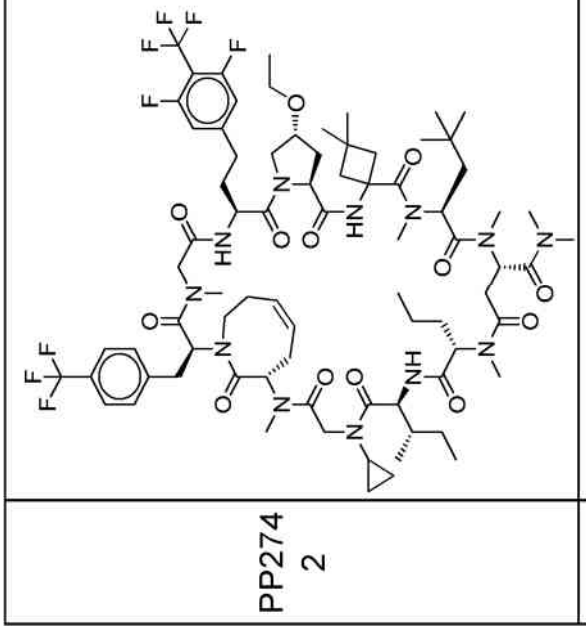
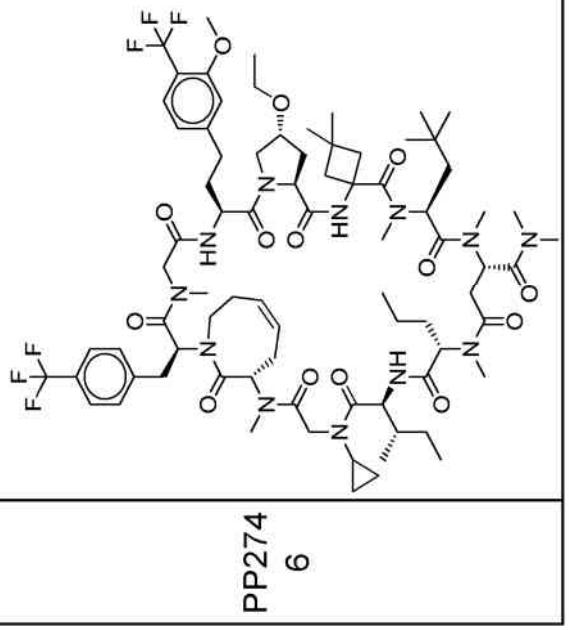
	
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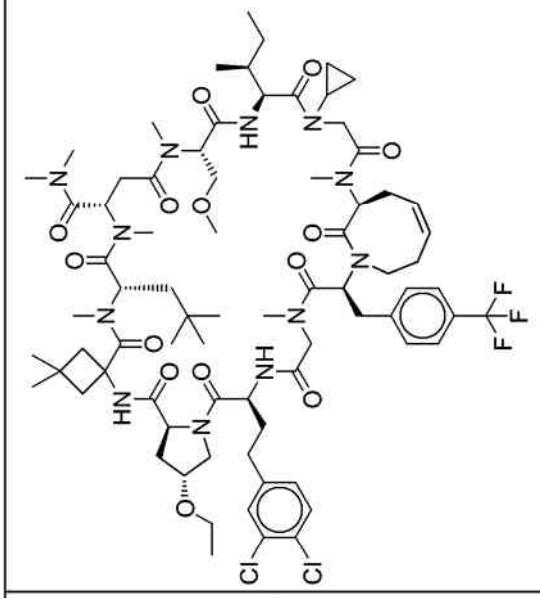
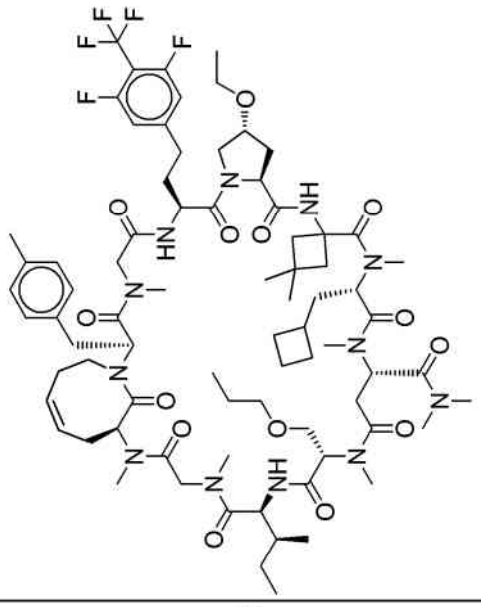
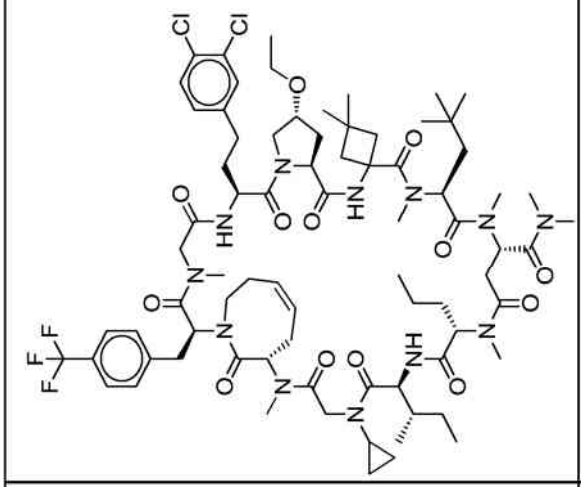
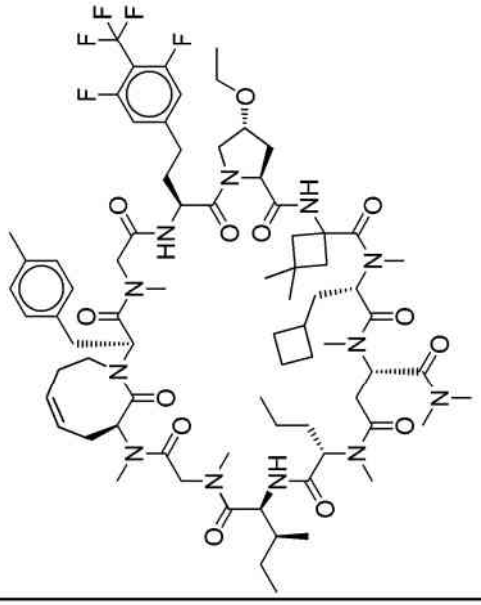
	
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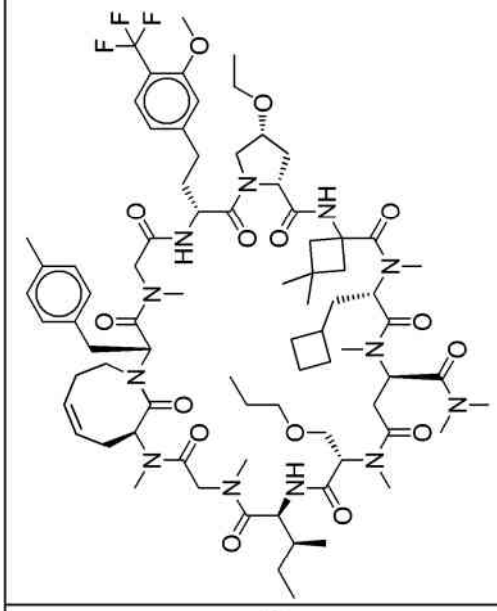
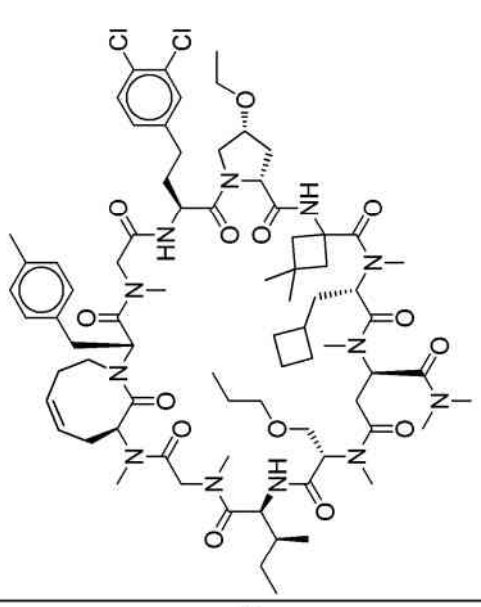
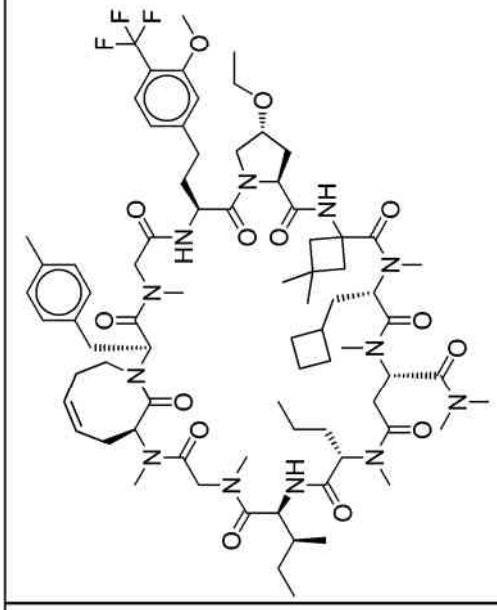
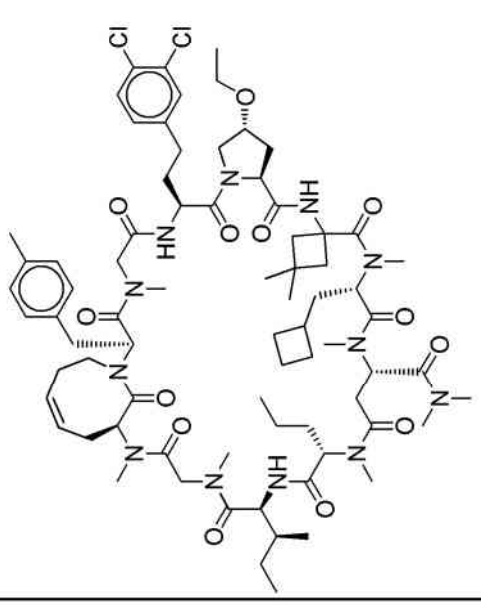
	
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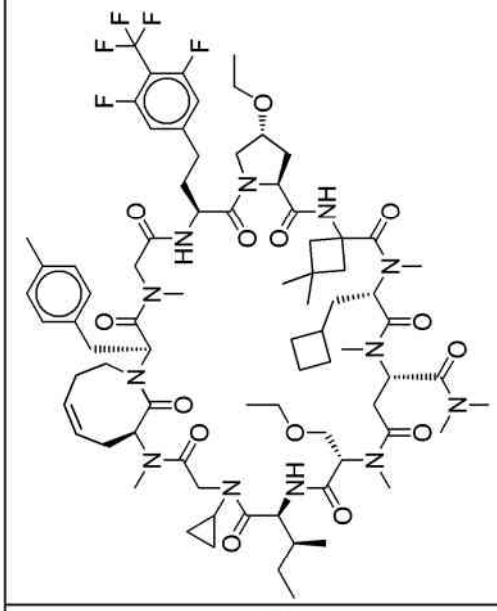
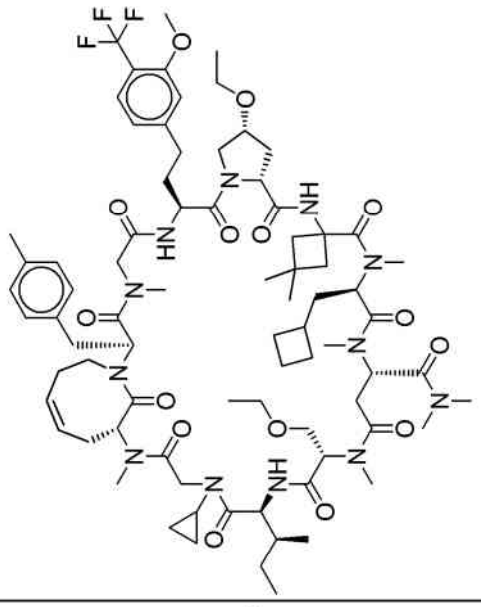
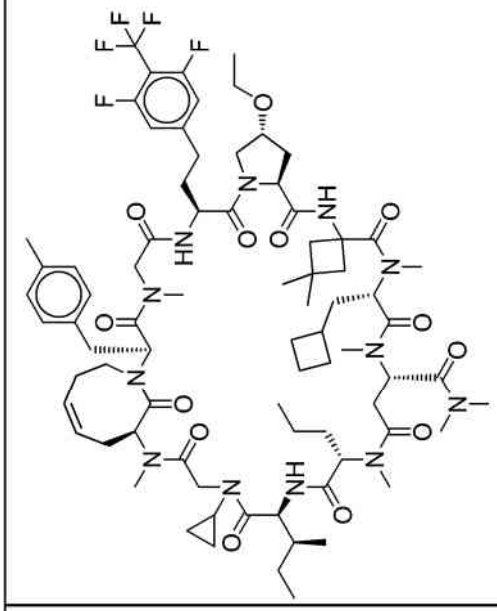
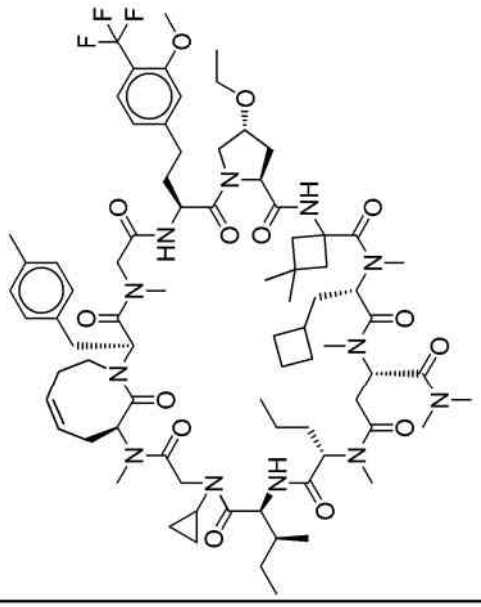
	
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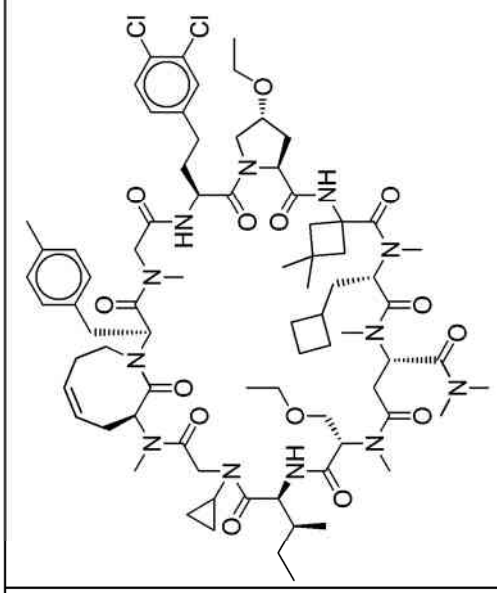
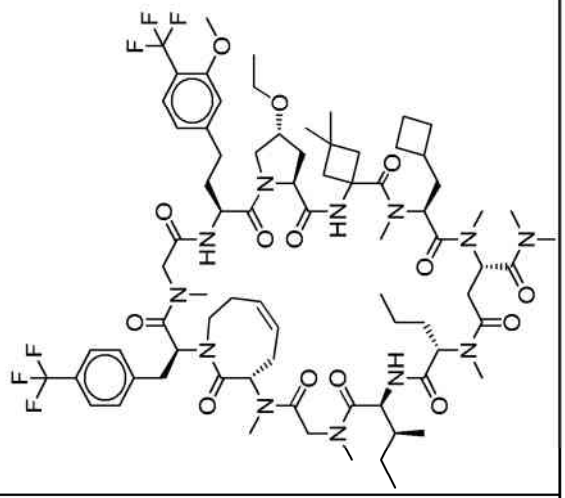
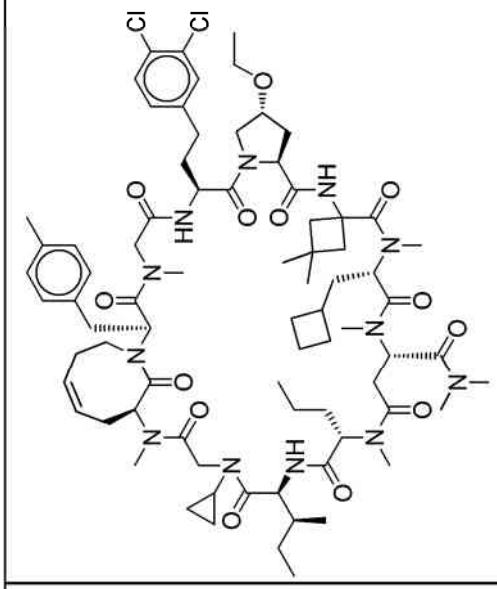
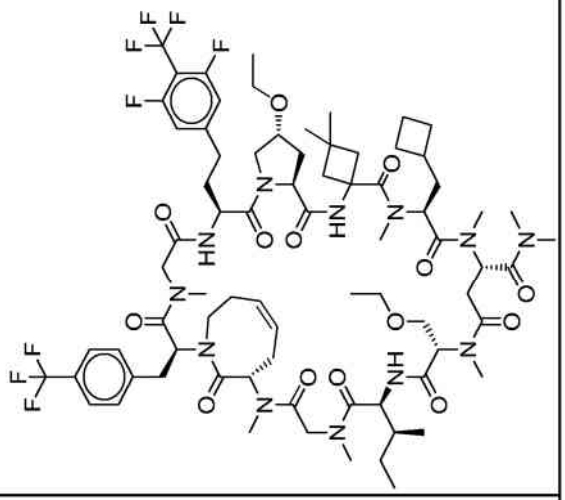
	
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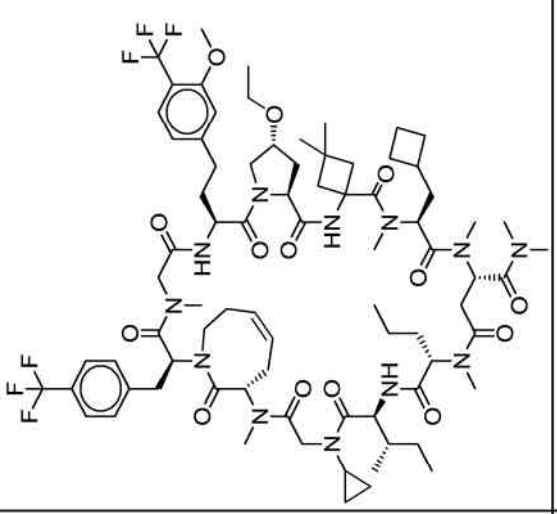
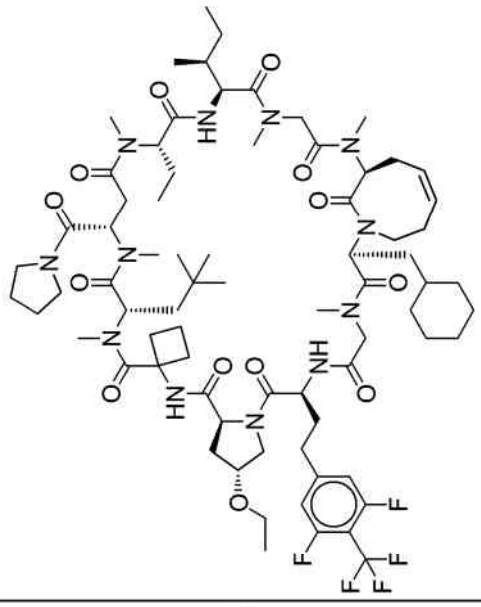
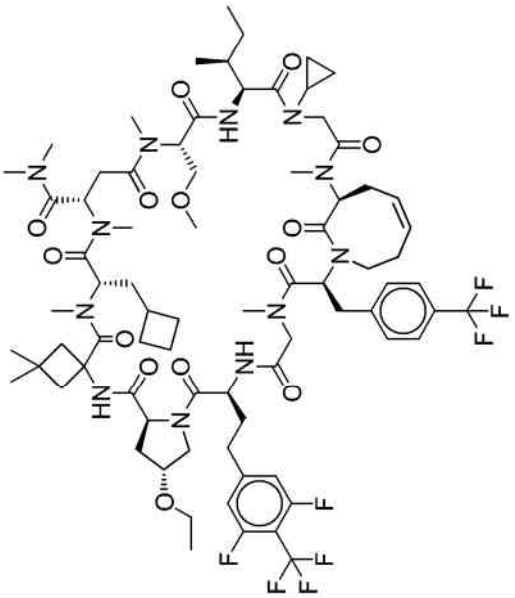
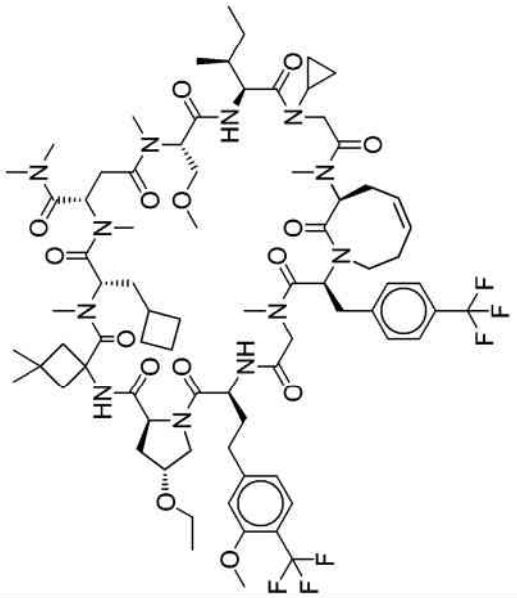
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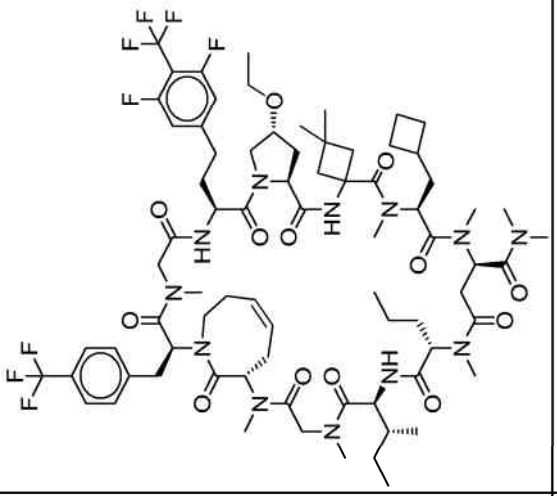
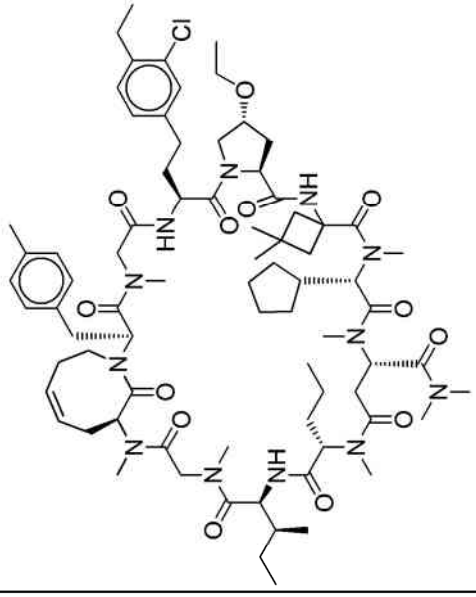
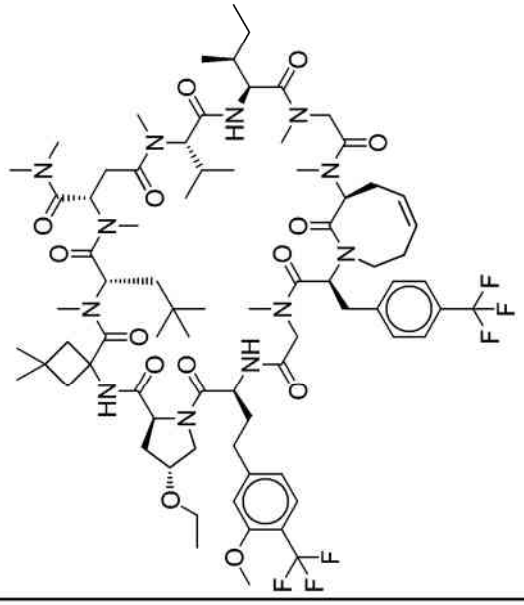
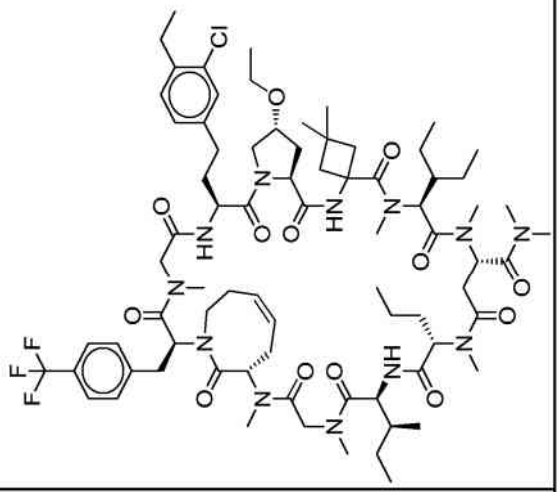
	
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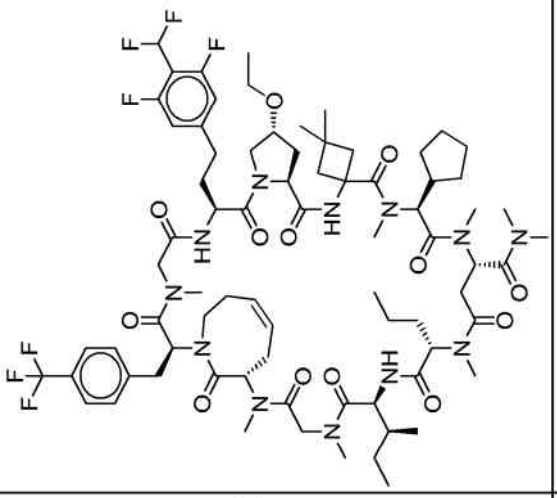
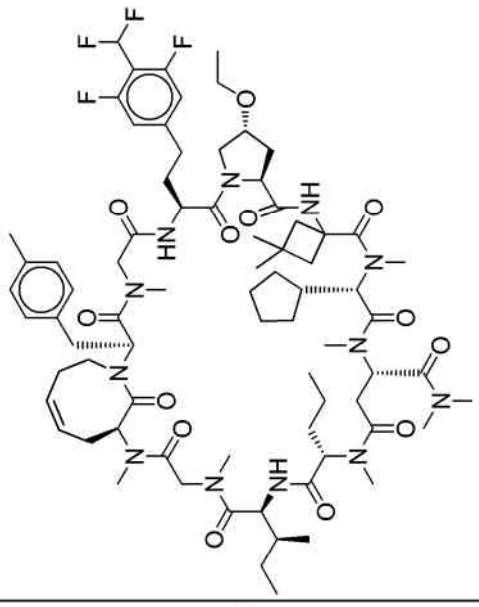
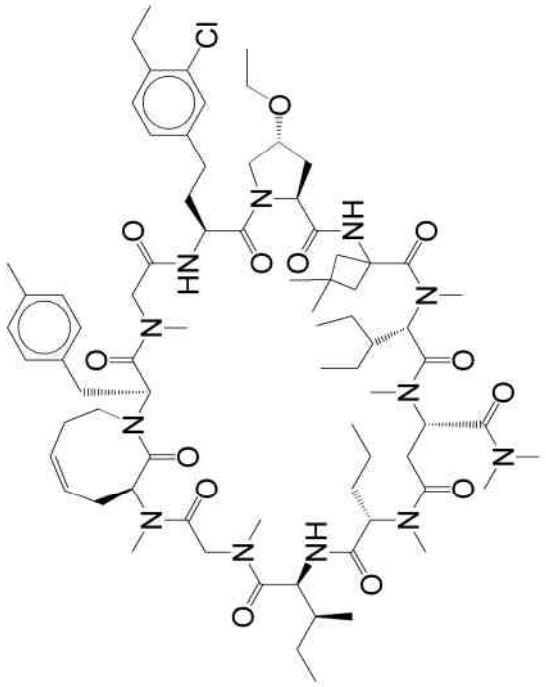
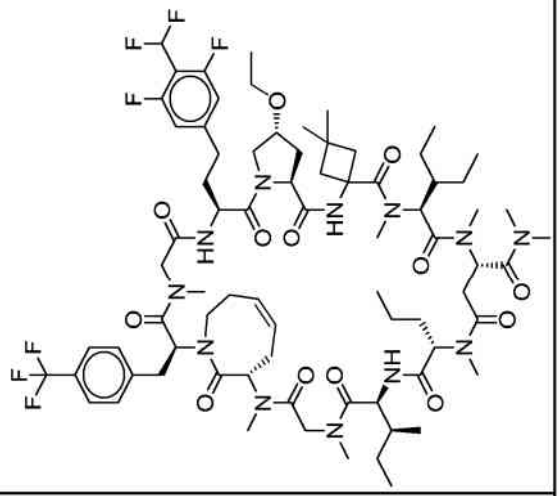
	
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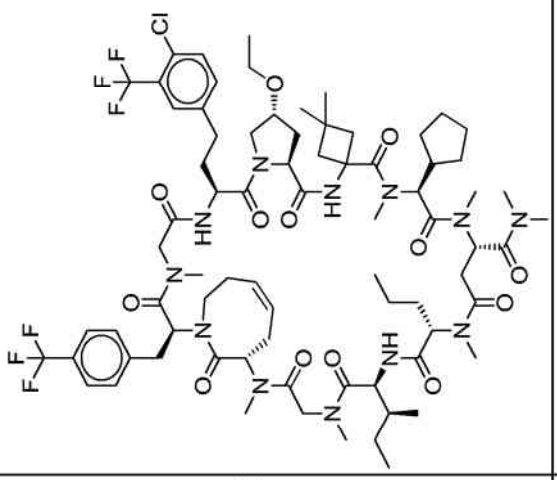
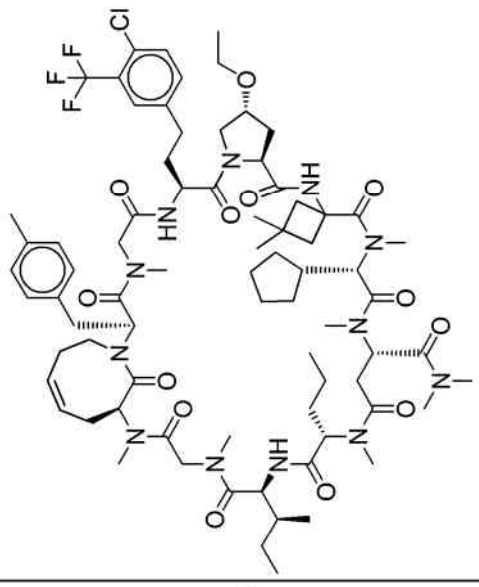
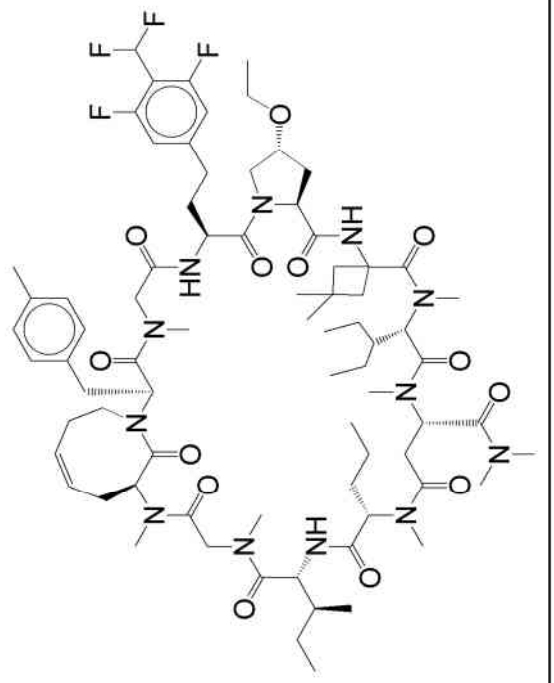
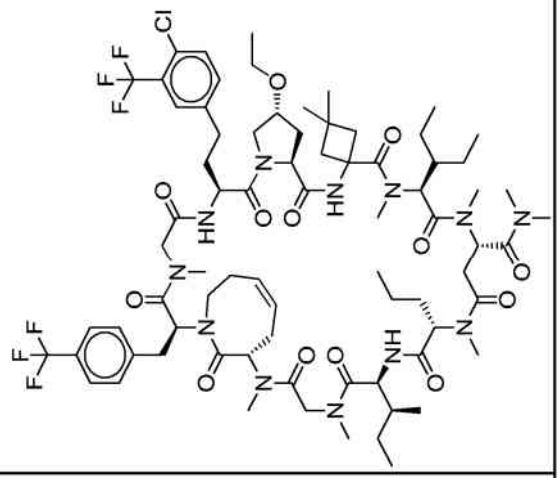
	
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PP2761	PP2763

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PP276 5	PP276 7

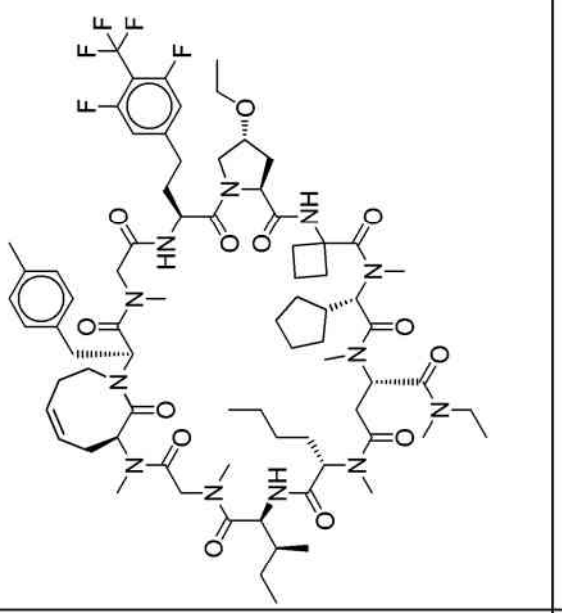
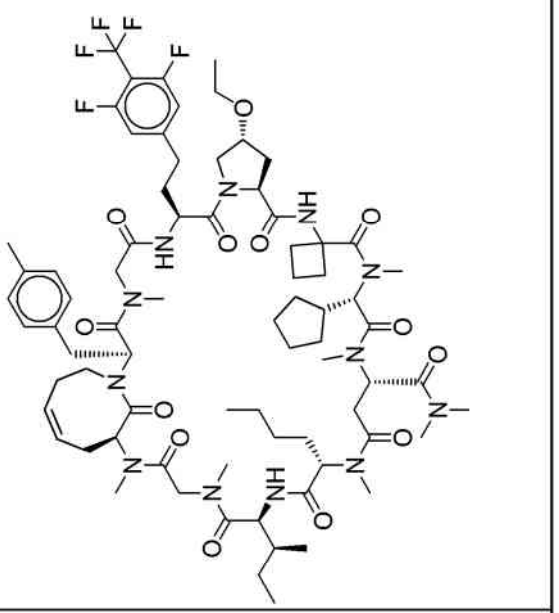
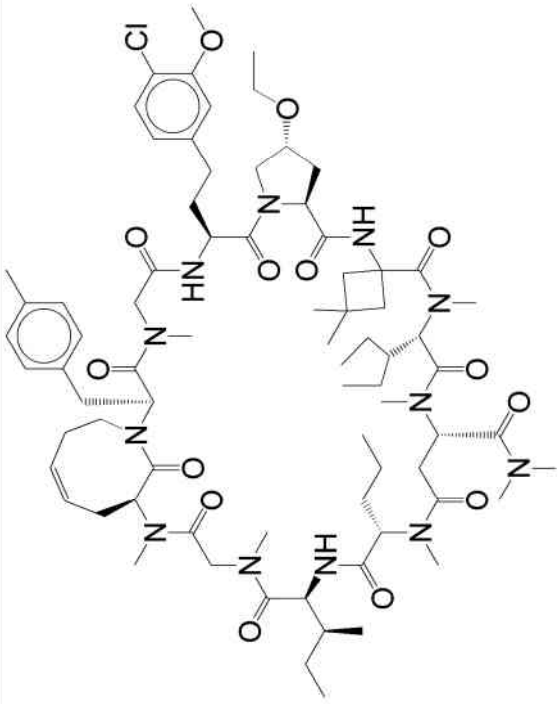
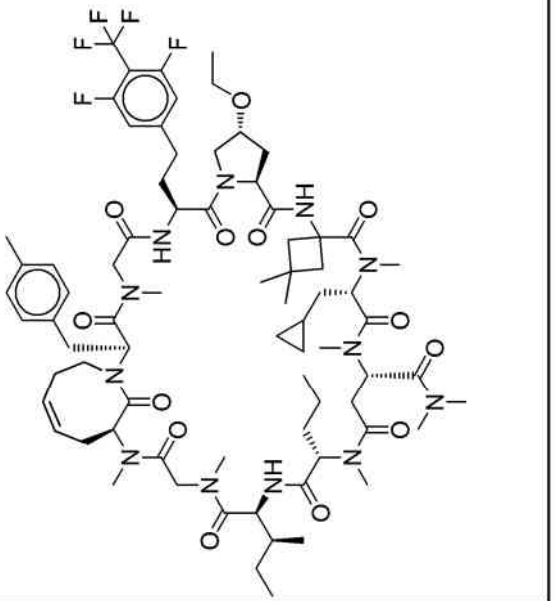
	
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PP2769	PP2771

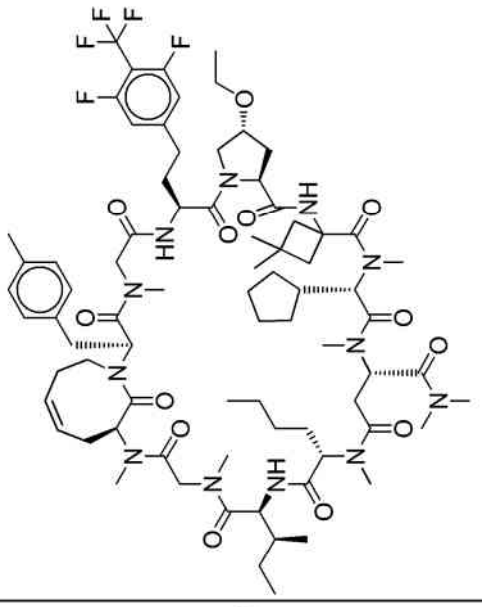
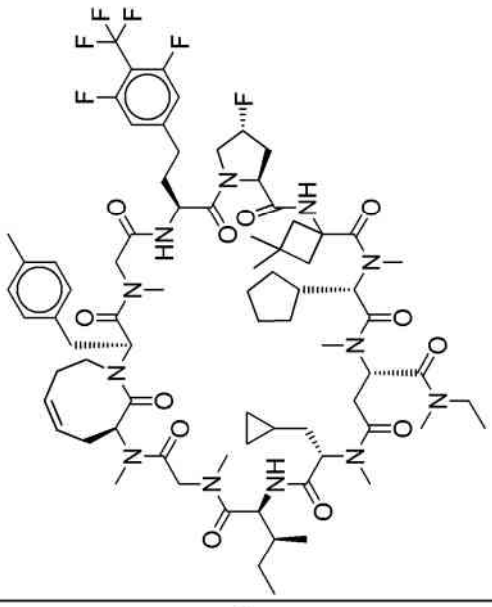
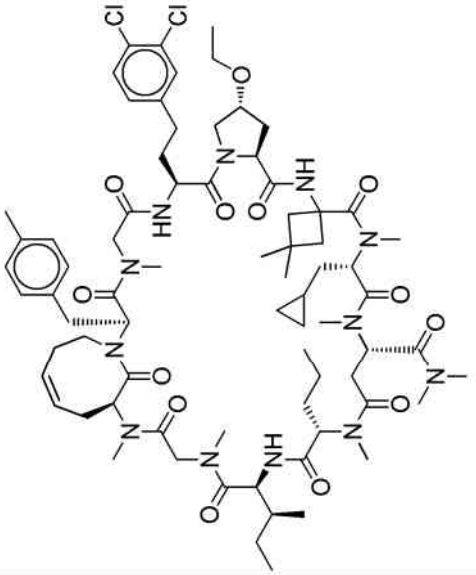
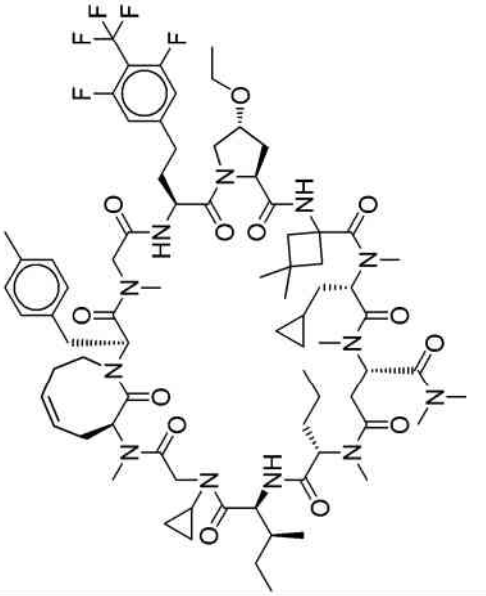
	
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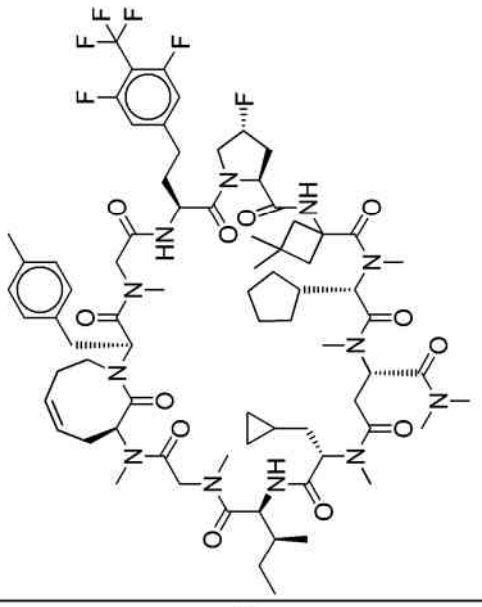
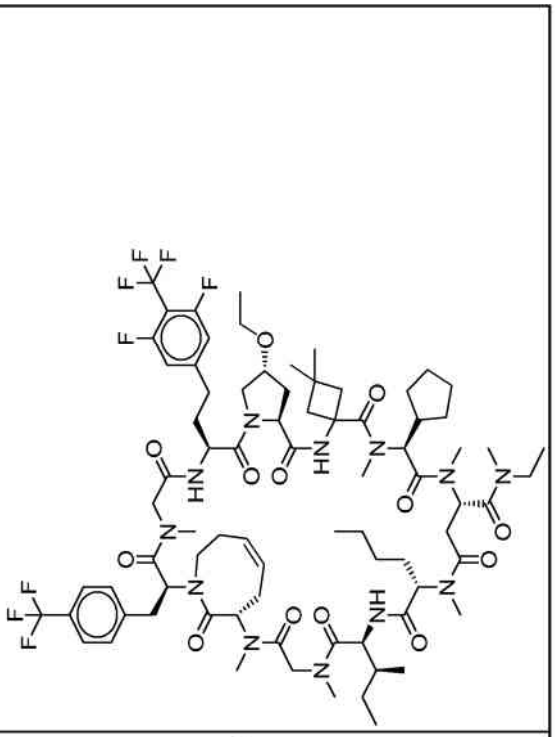
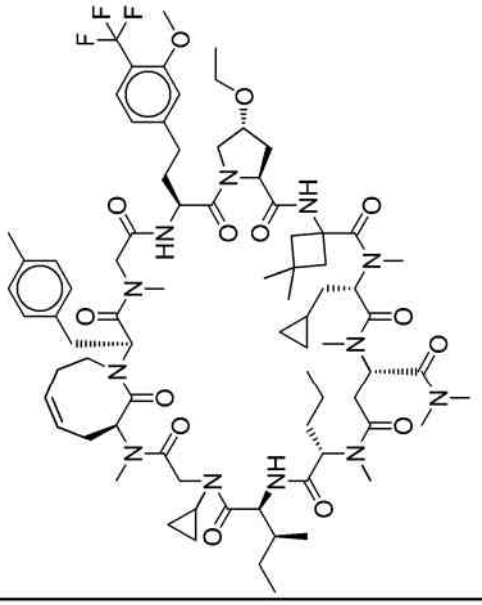
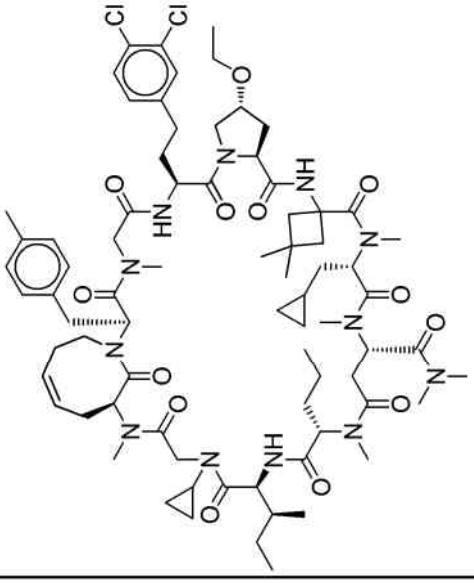
	
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PP2779	PP2781

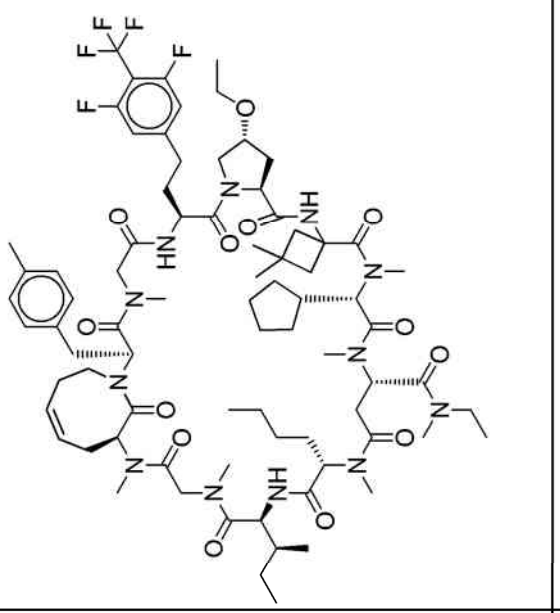
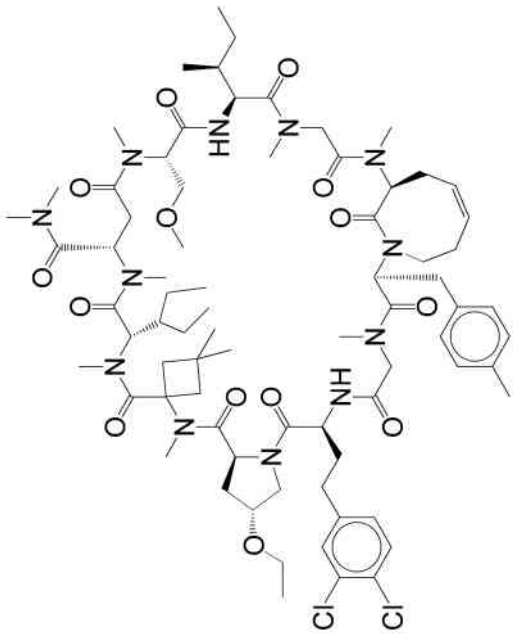
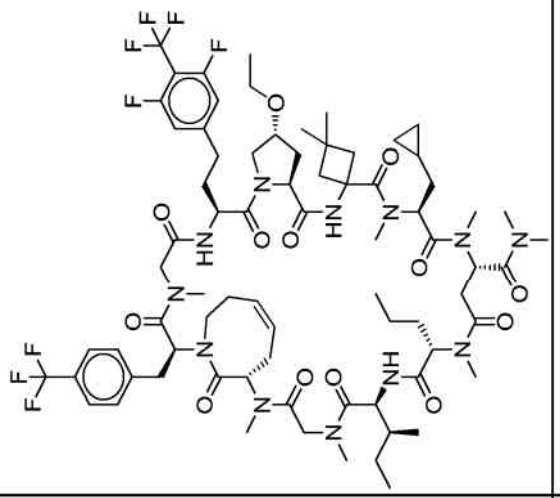
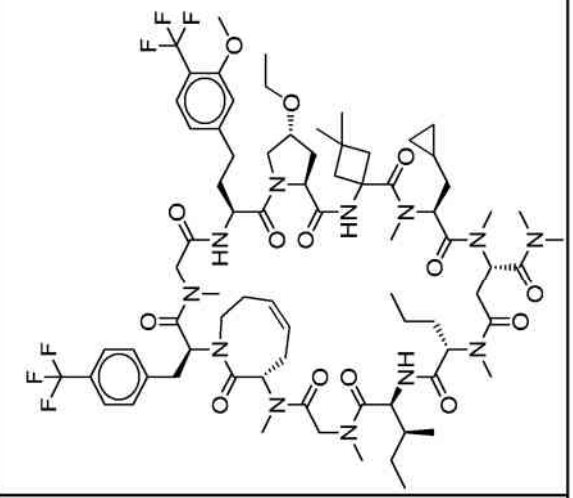
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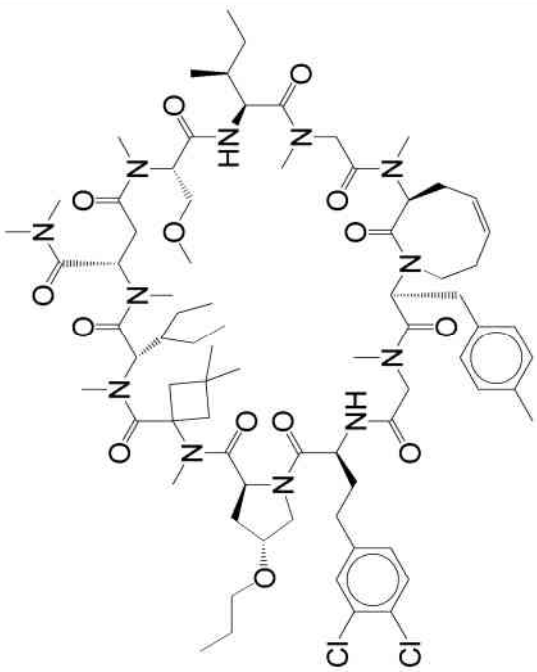
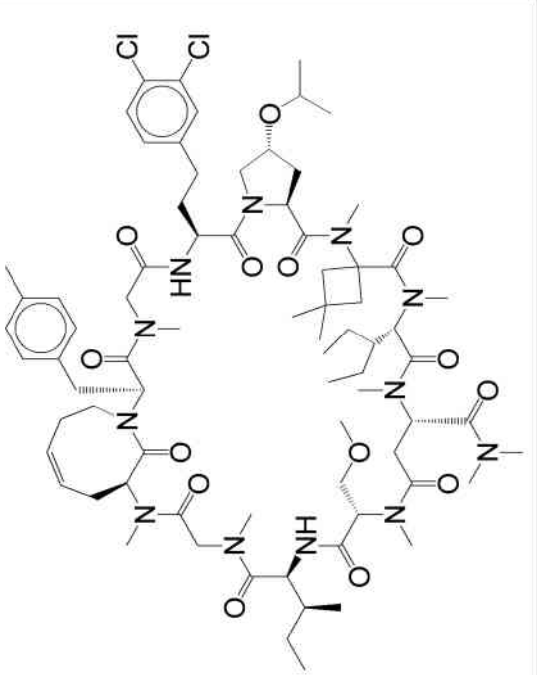
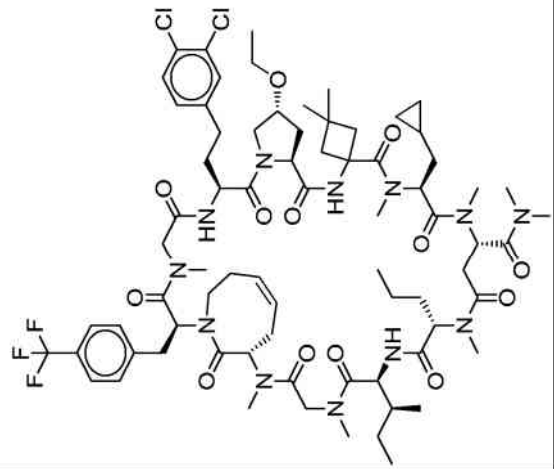
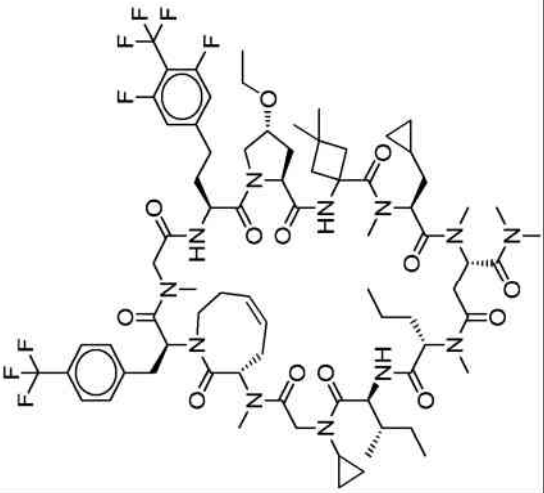
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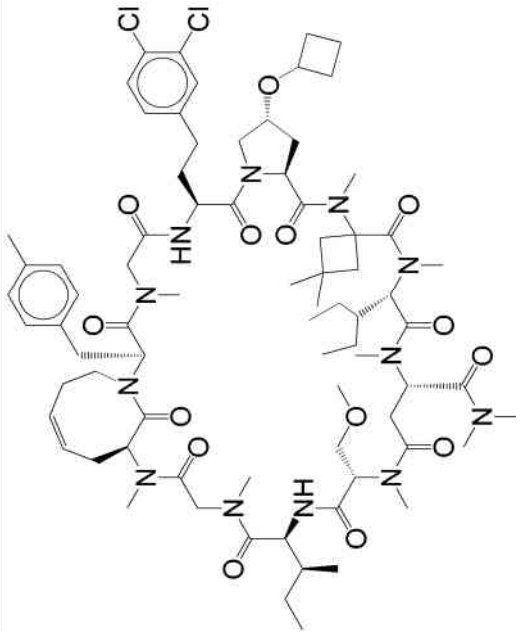
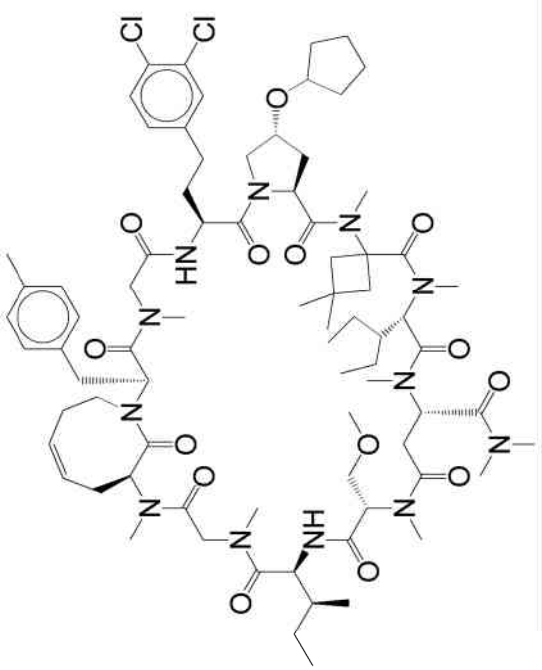
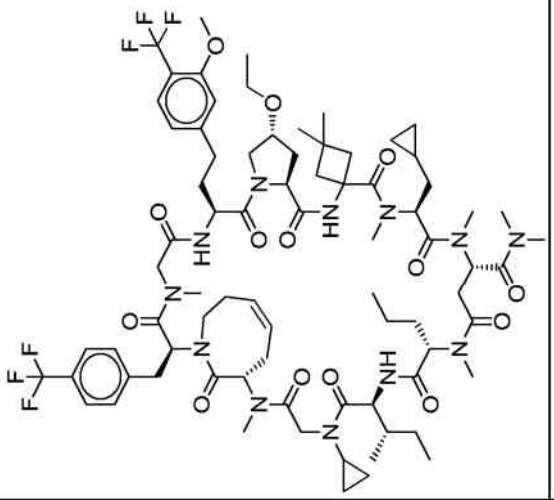
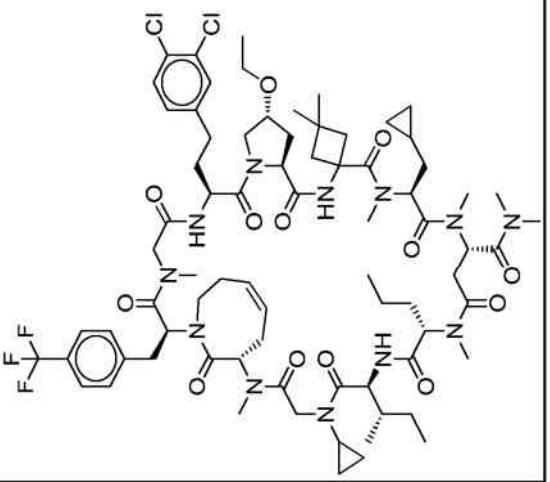
	
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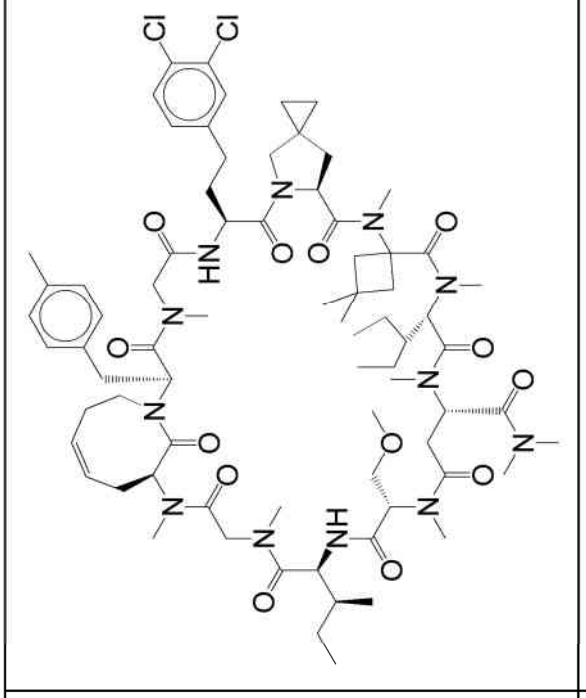
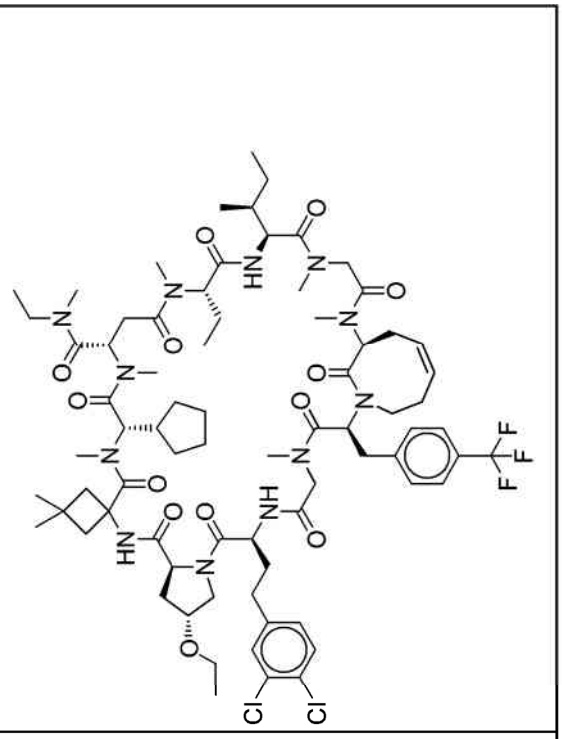
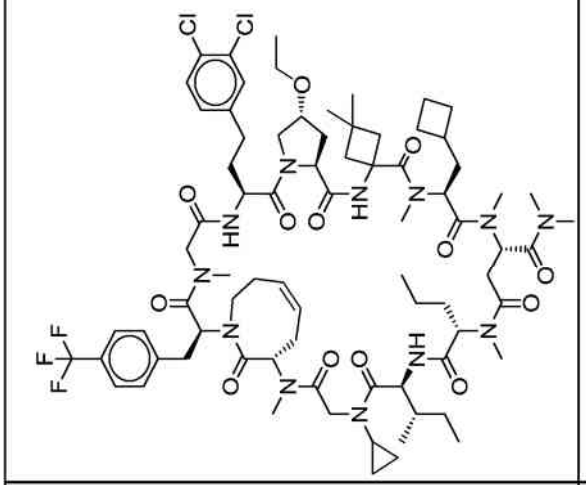
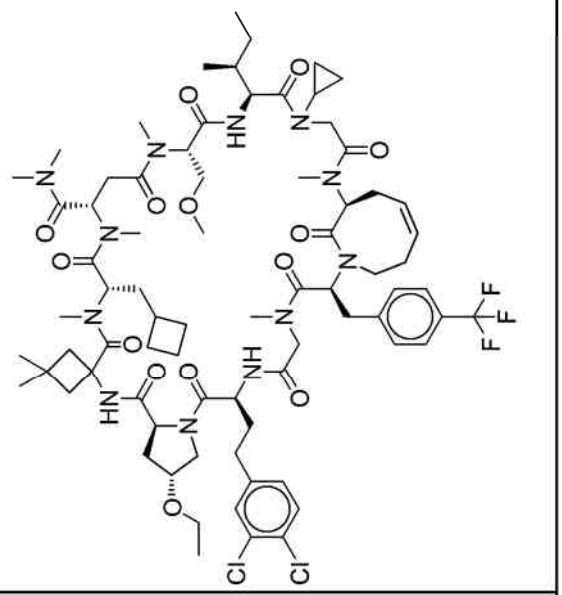
	
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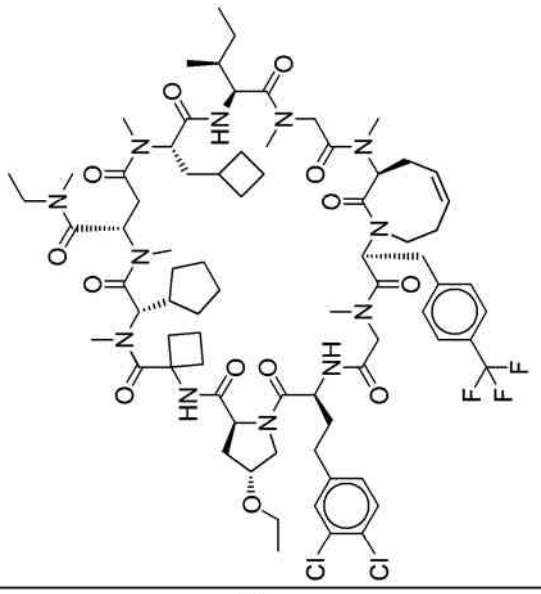
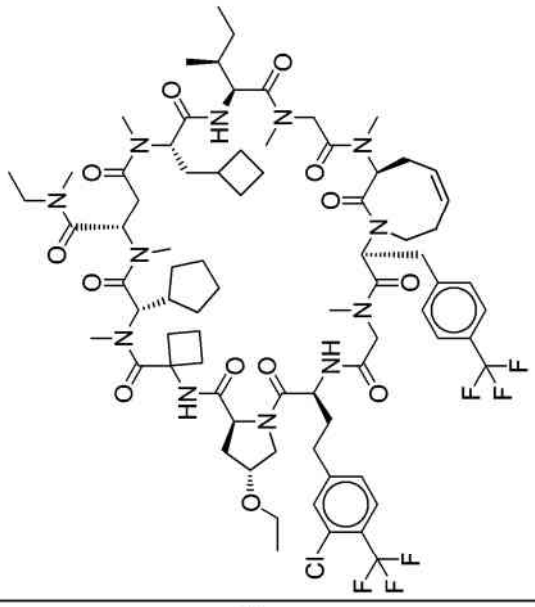
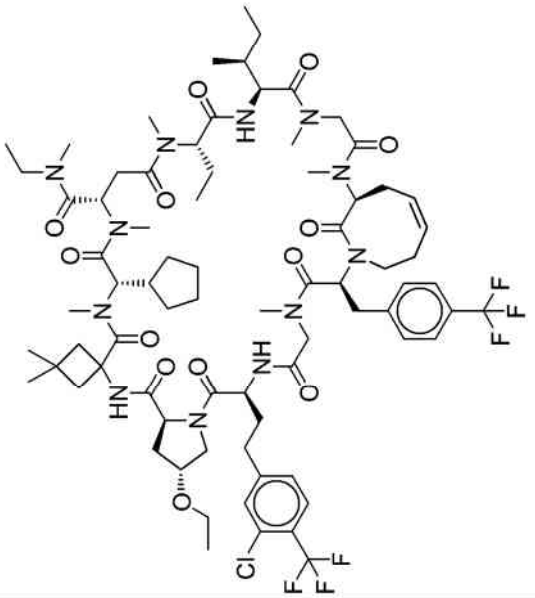
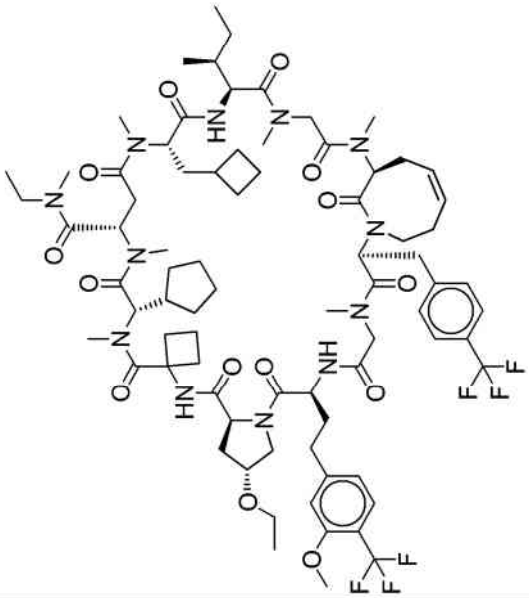
	
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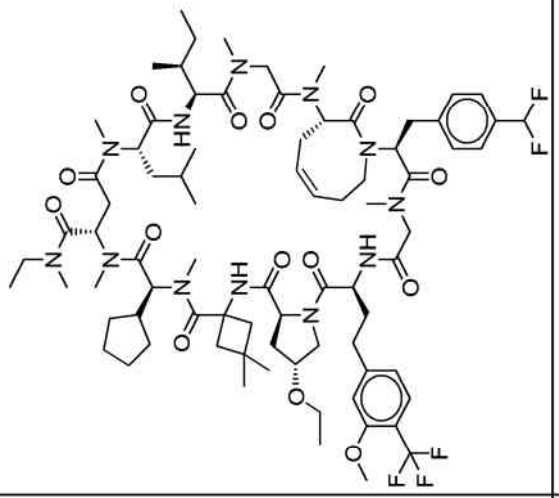
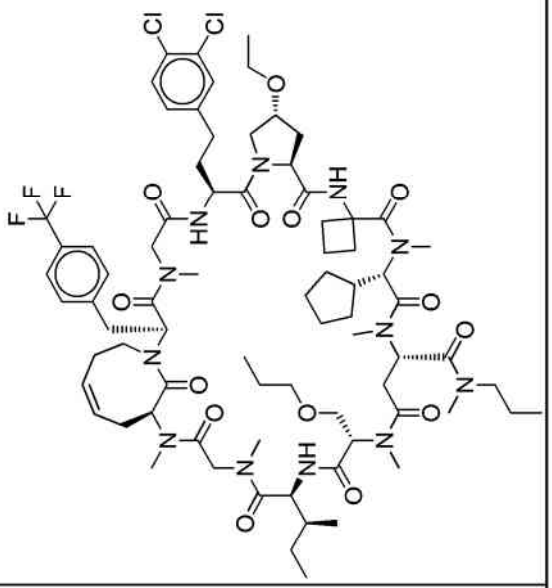
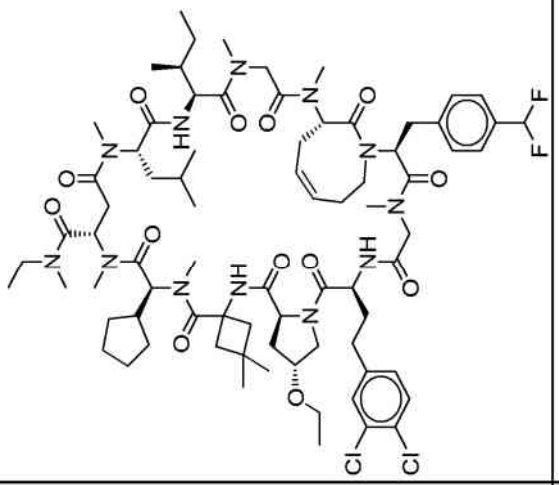
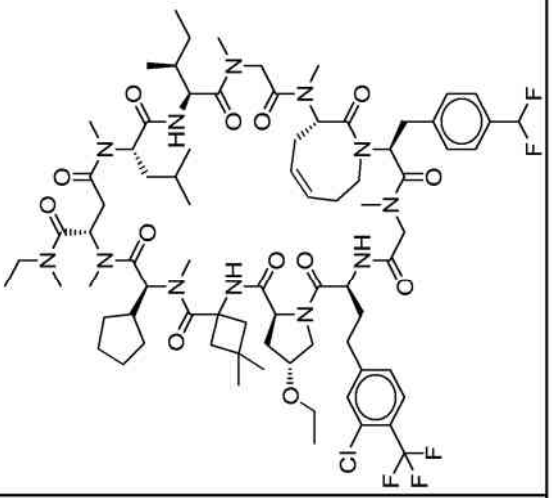
	
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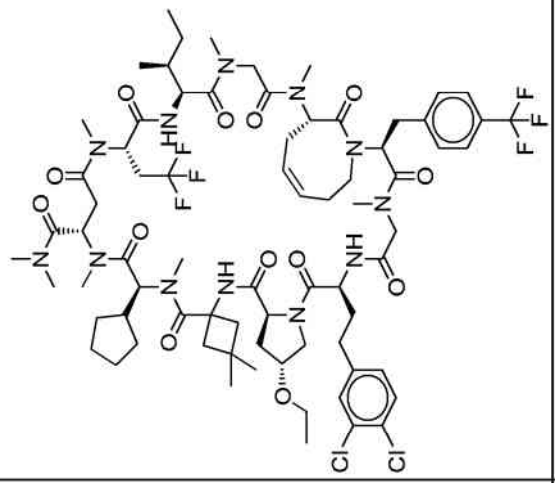
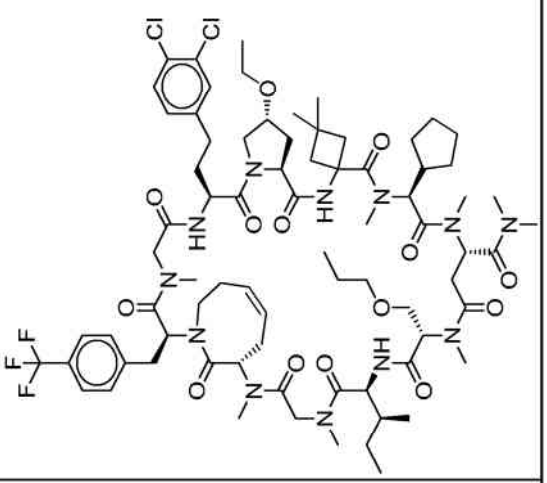
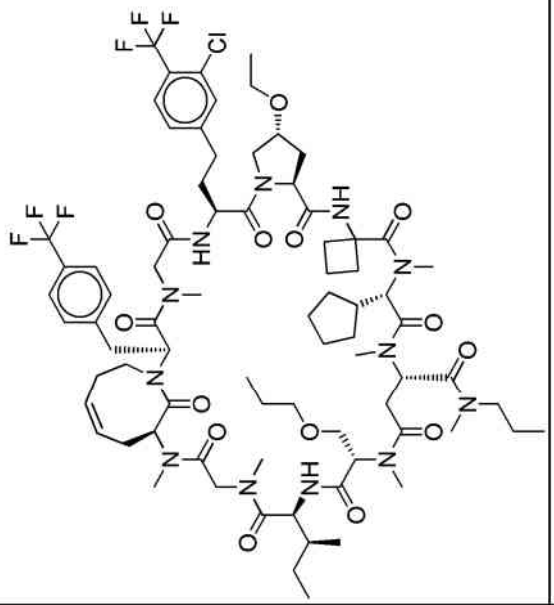
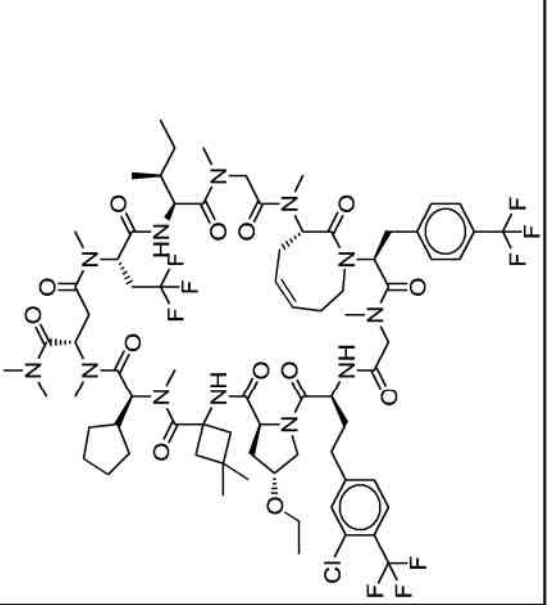
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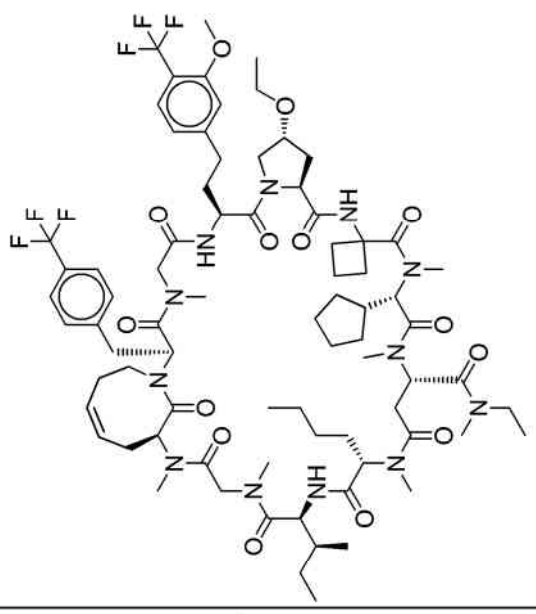
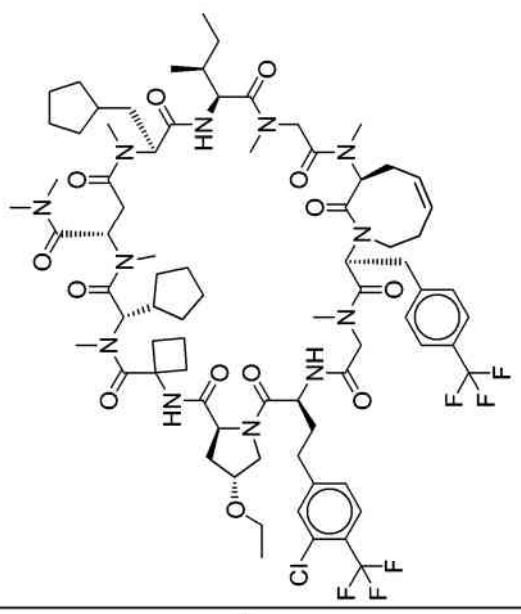
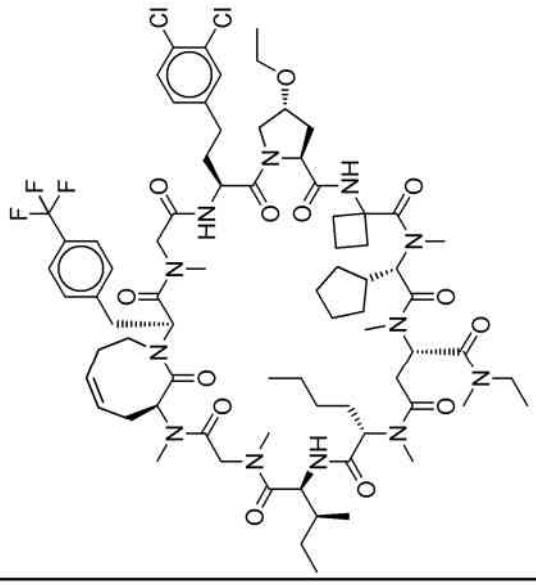
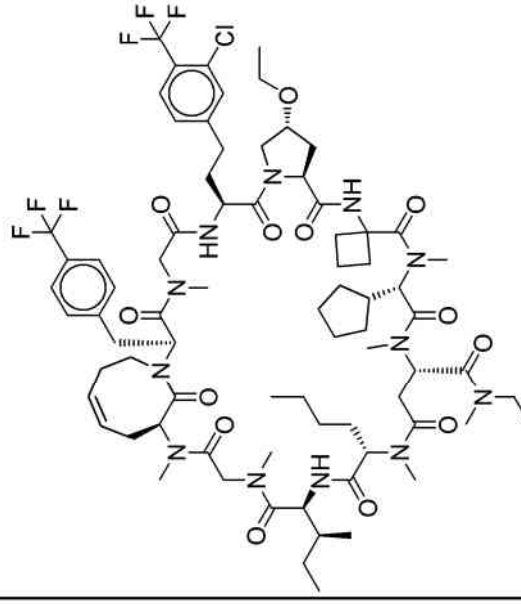
	
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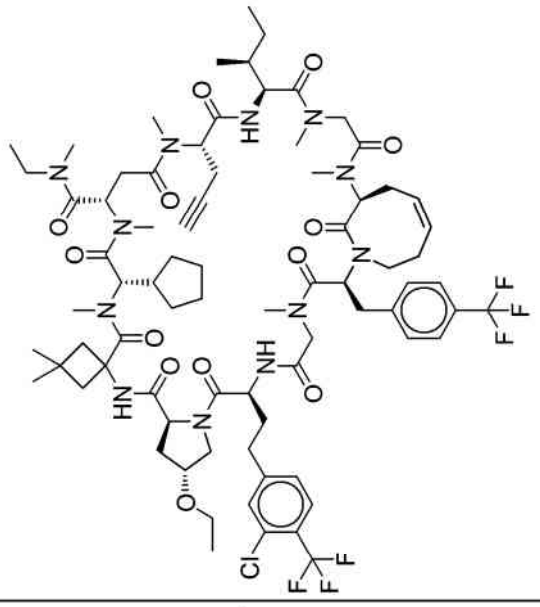
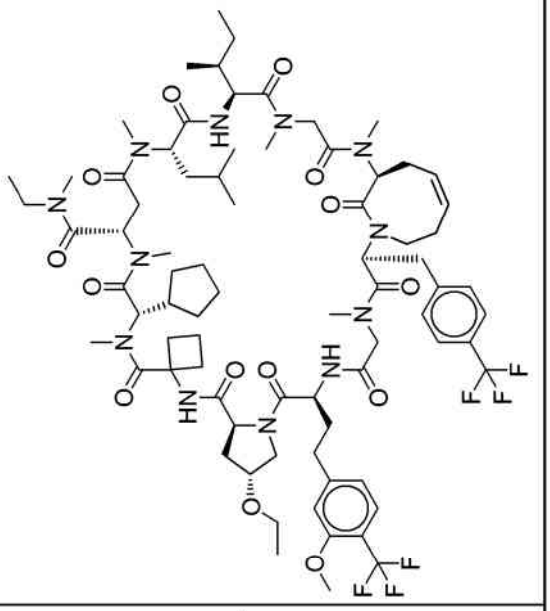
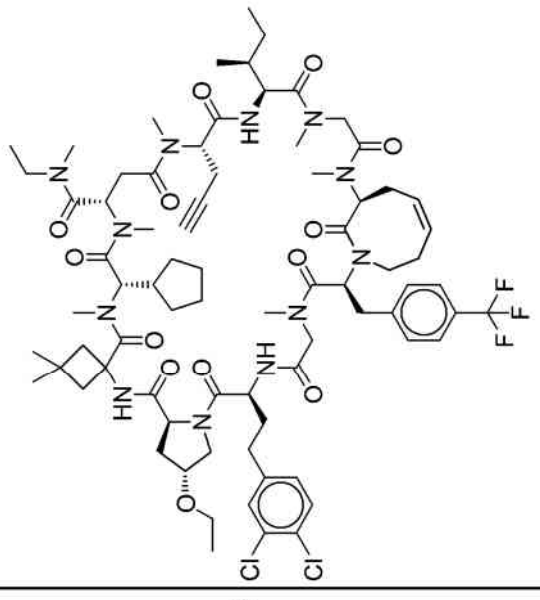
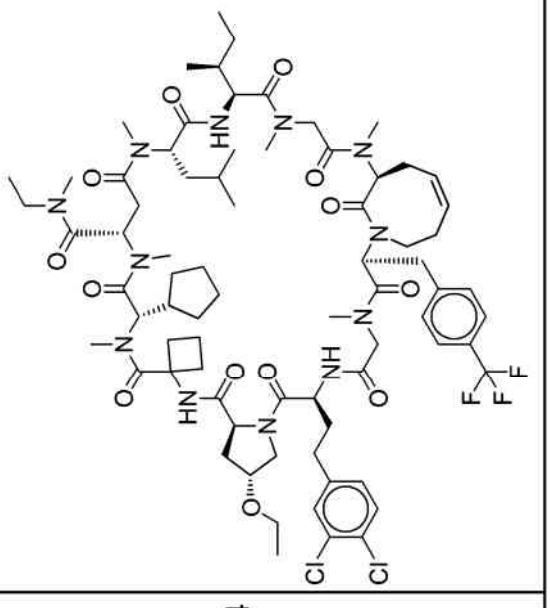
	
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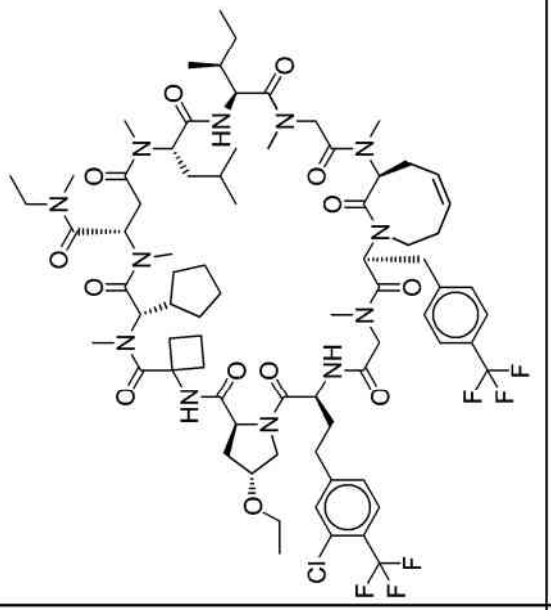
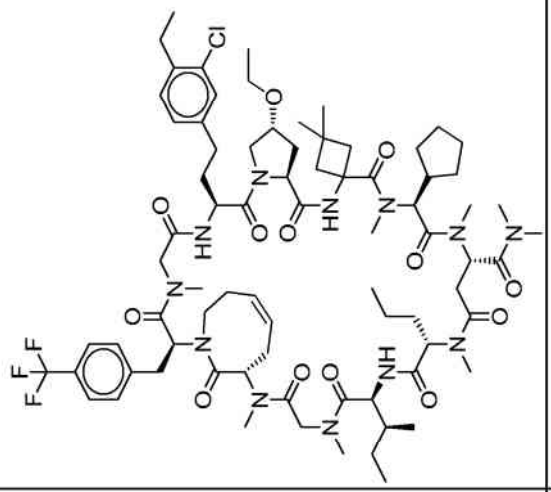
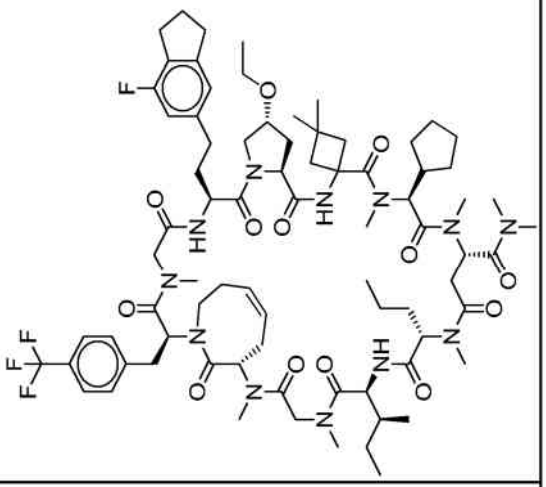
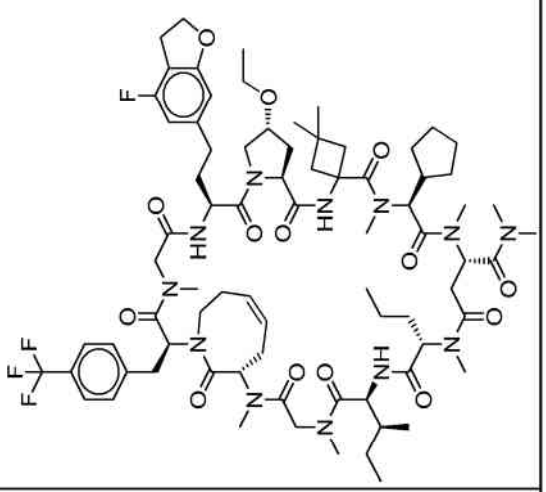
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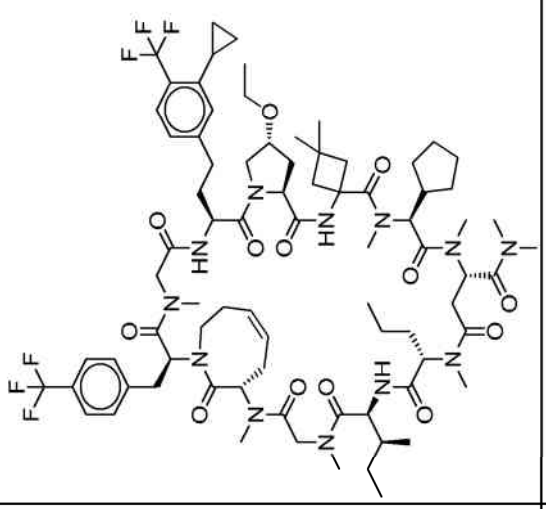
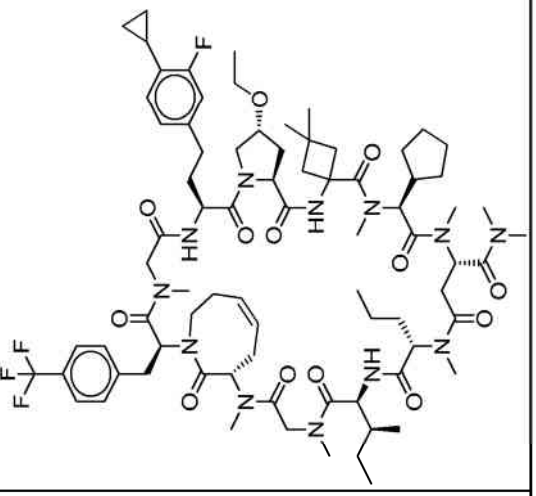
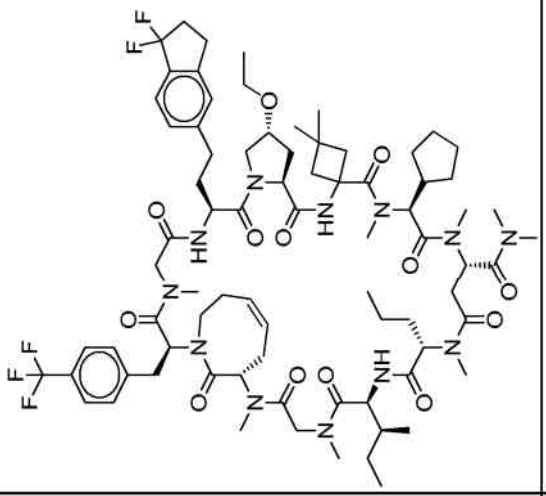
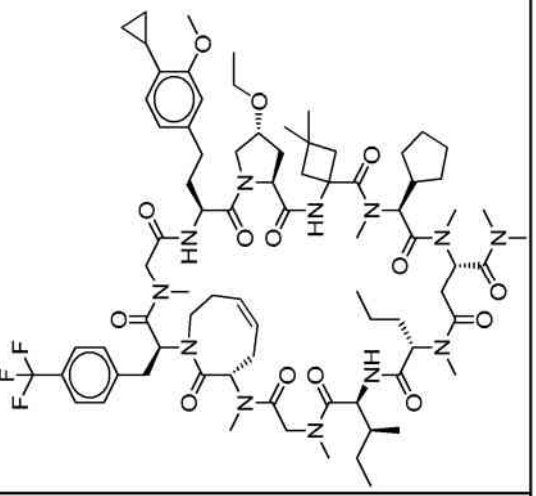
	
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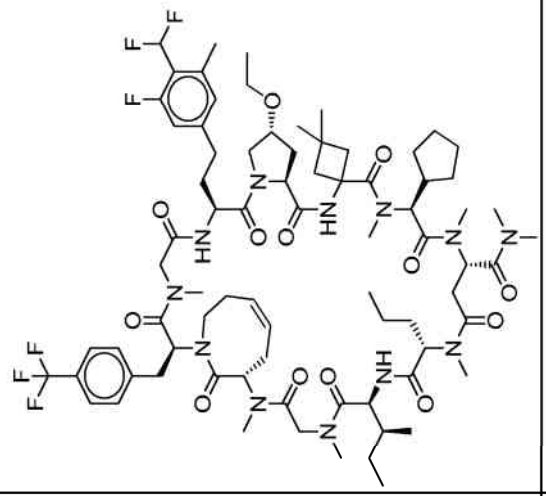
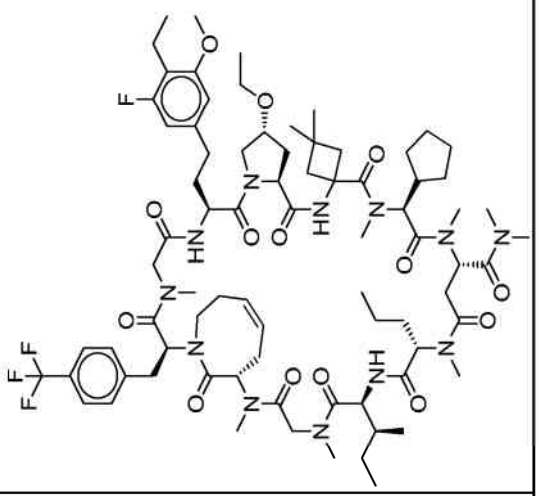
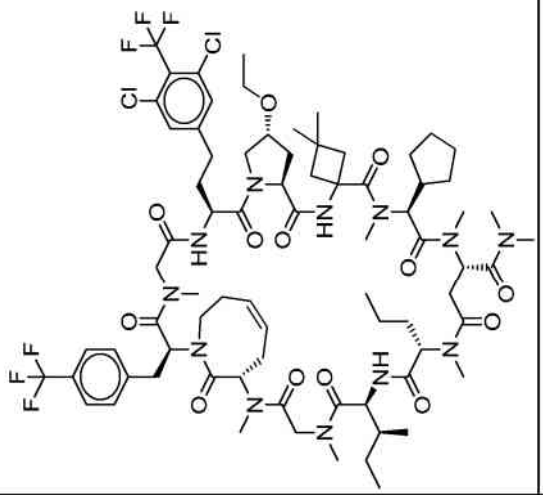
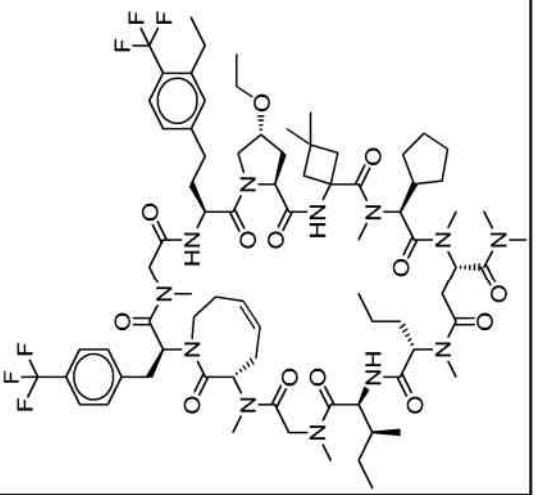
	
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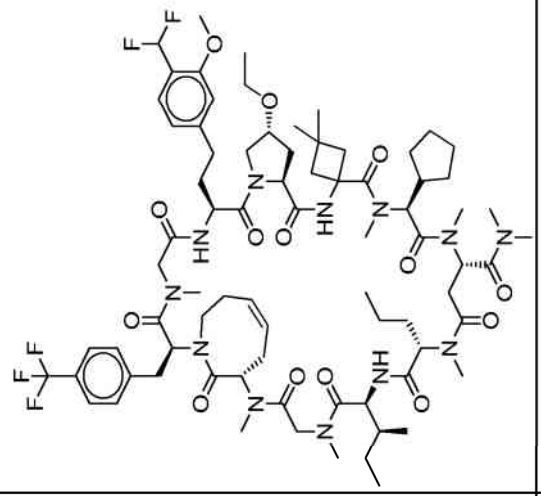
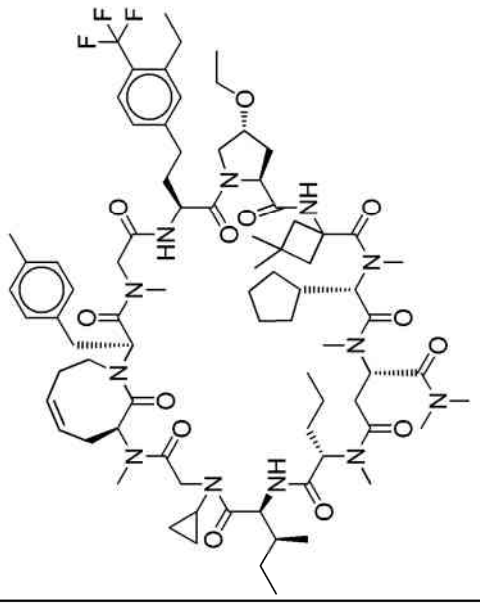
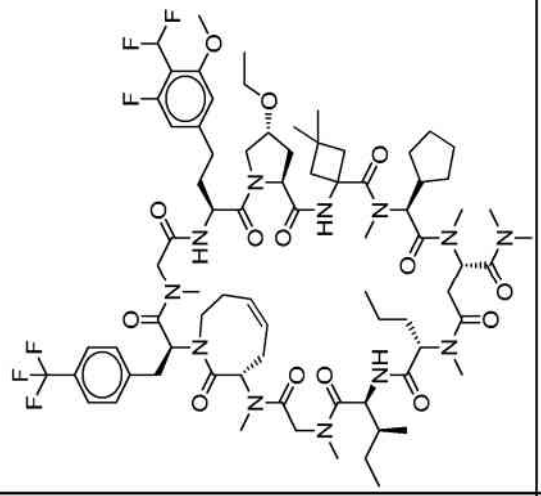
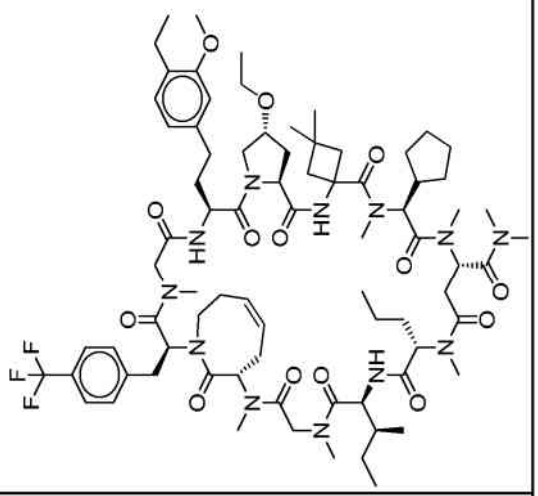
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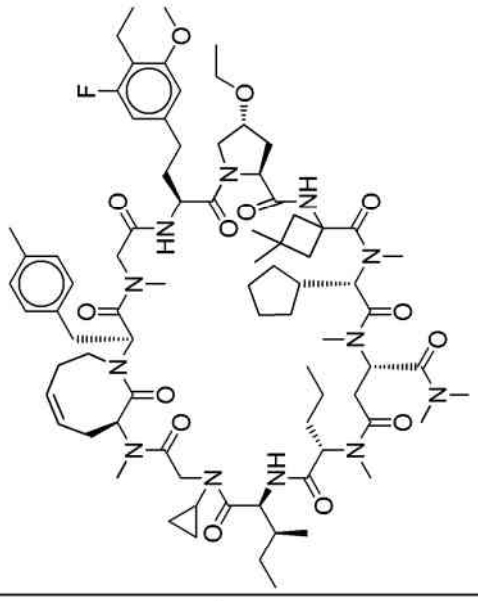
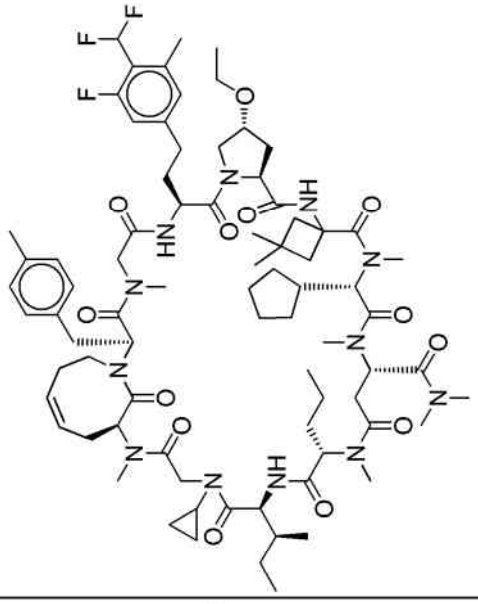
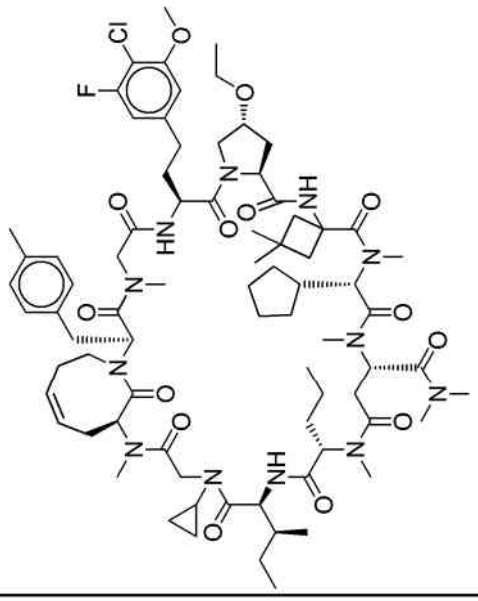
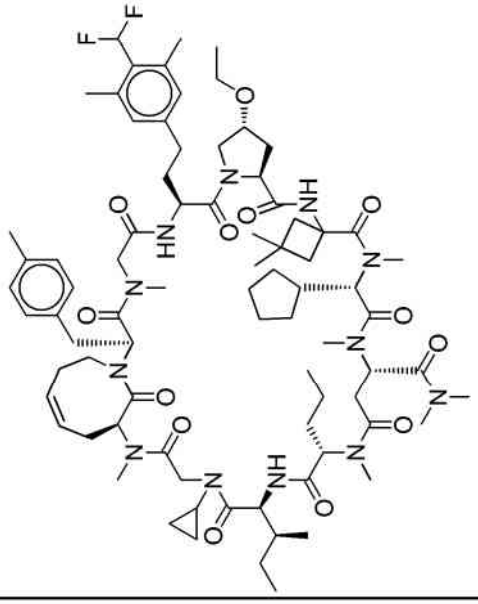
	
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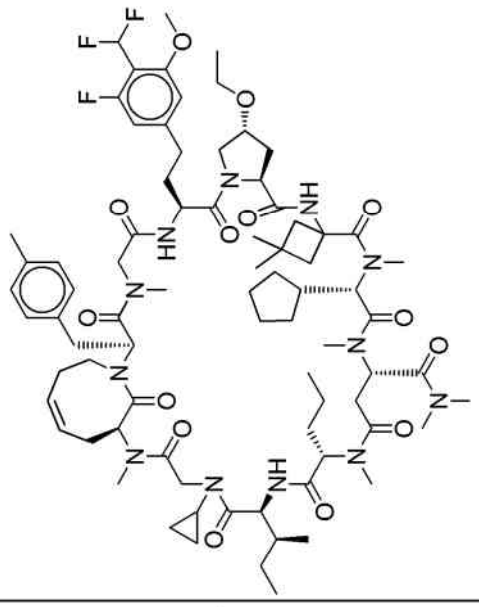
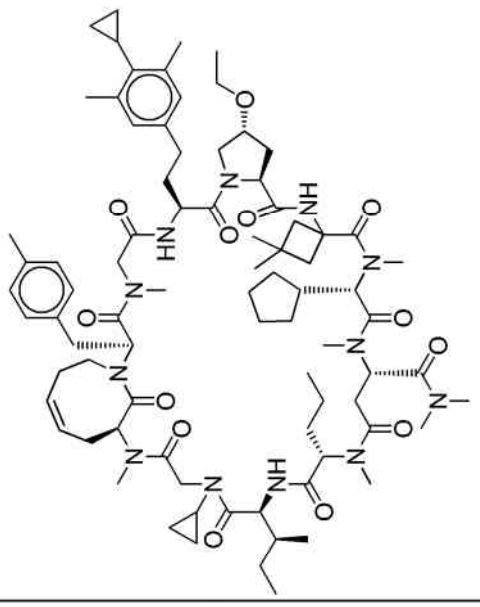
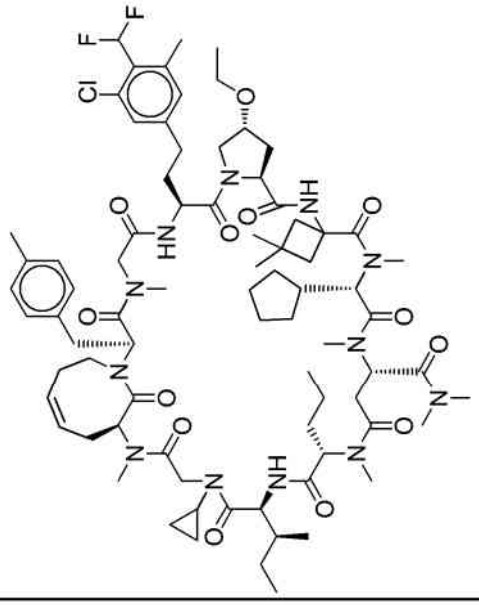
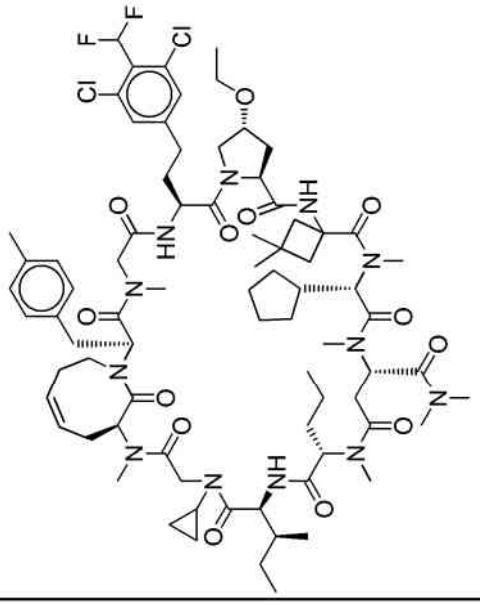
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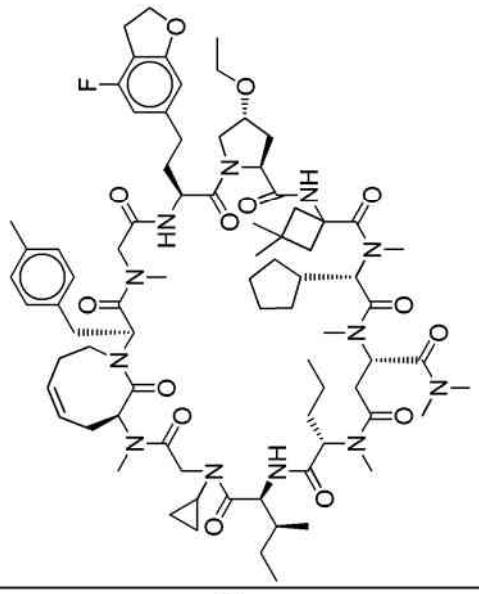
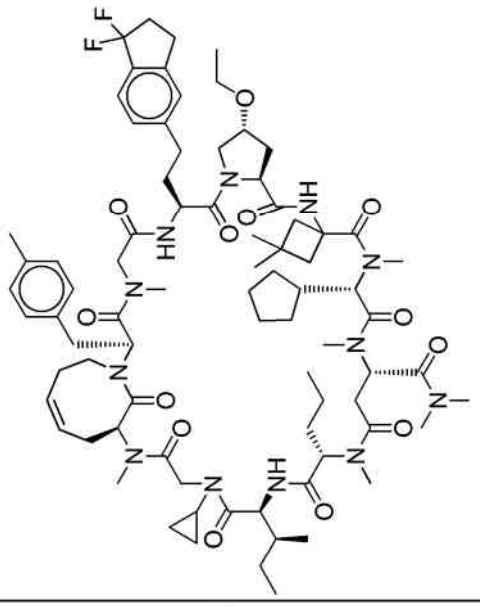
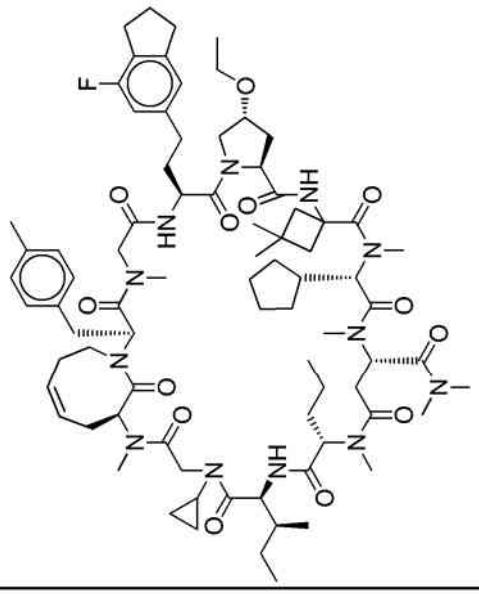
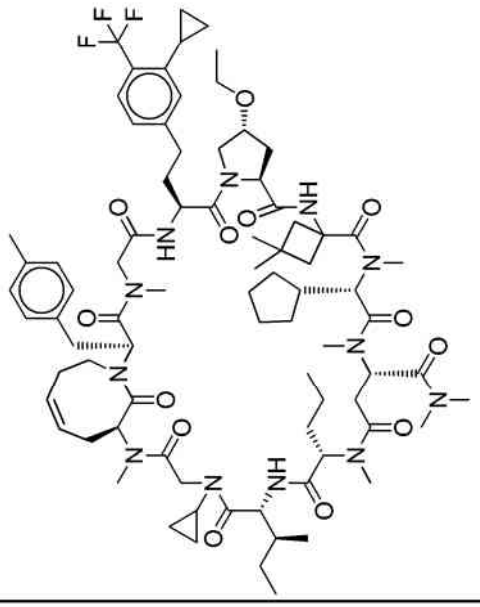
	
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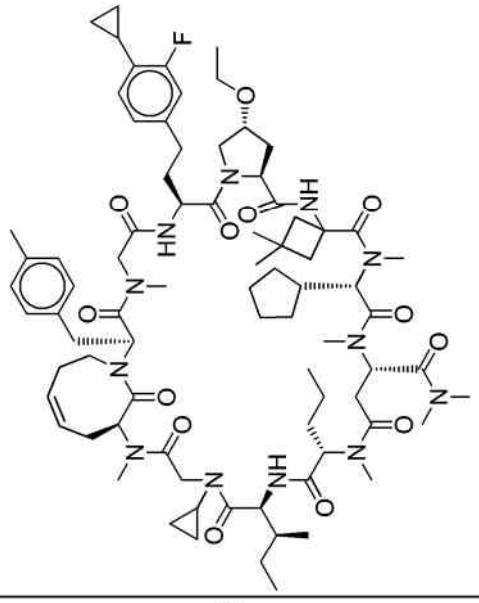
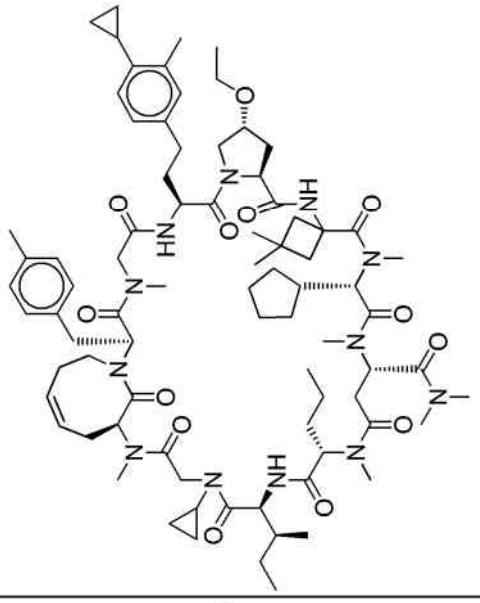
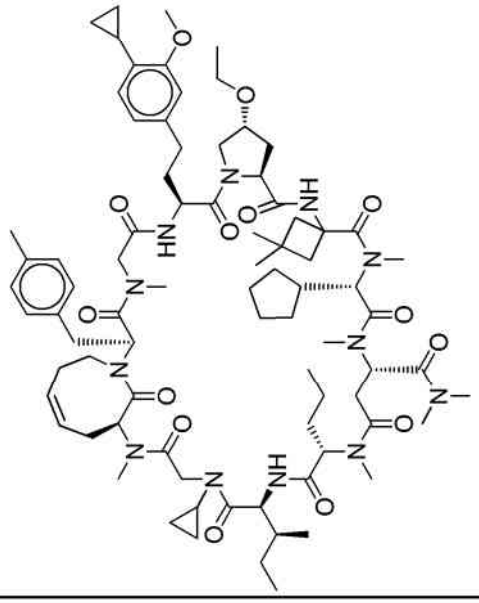
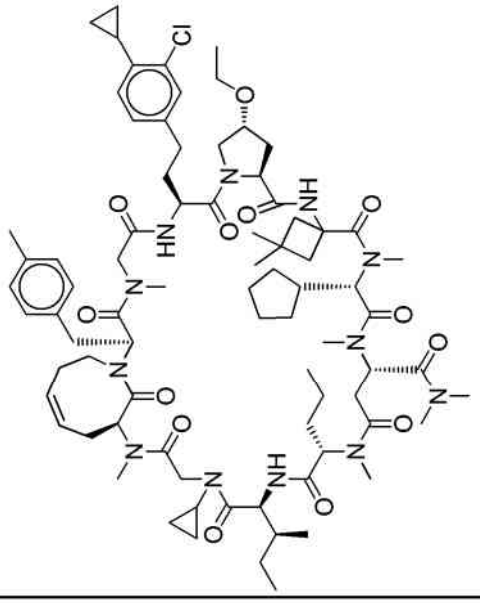
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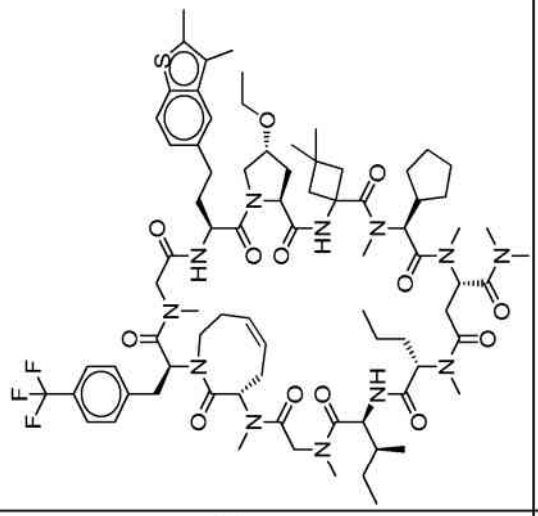
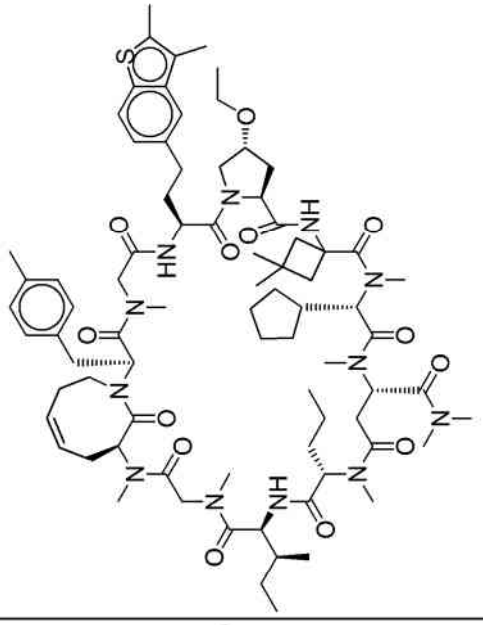
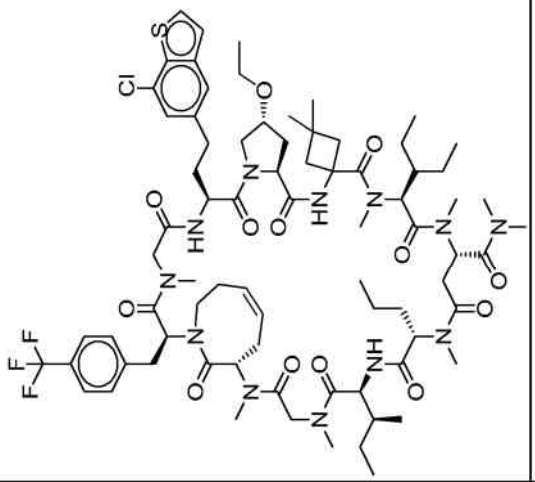
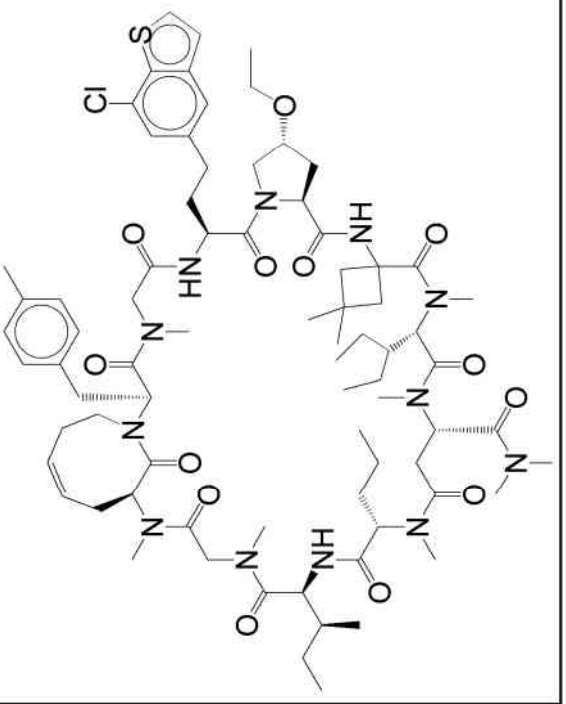
	
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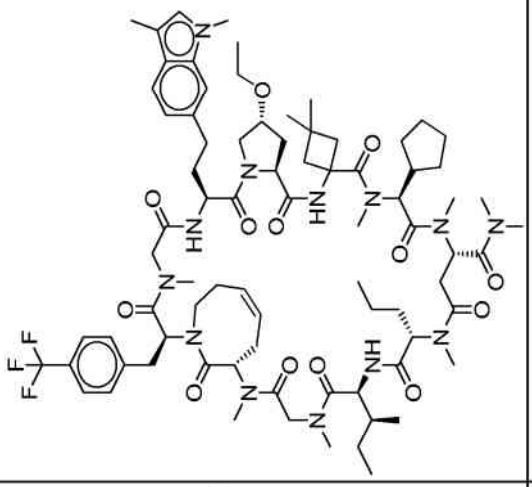
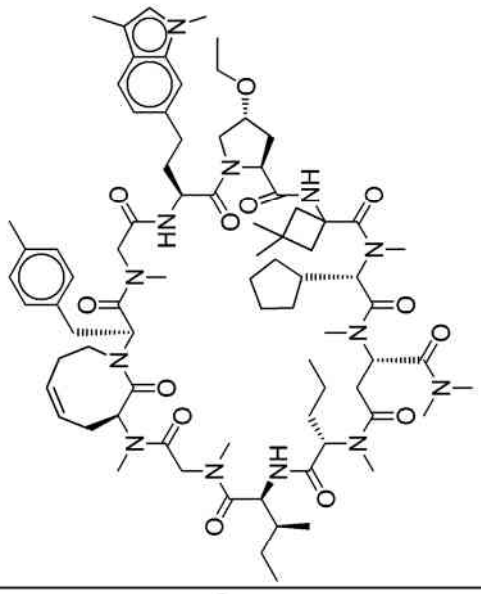
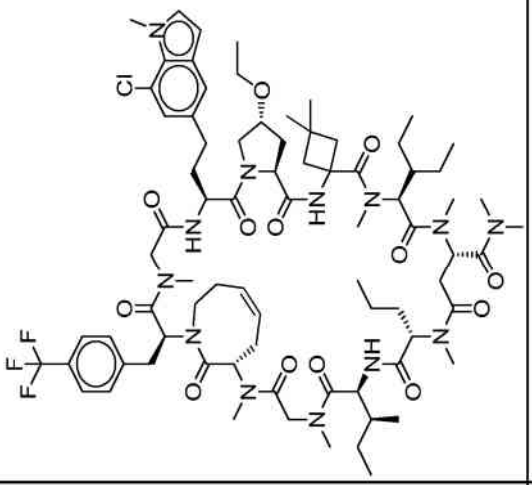
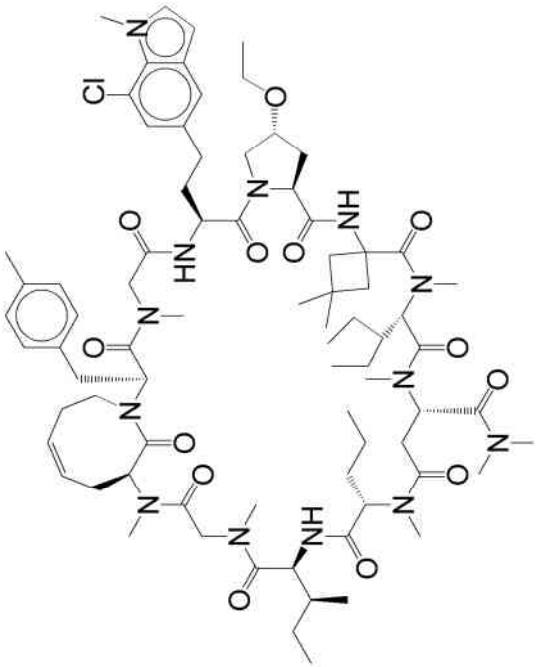
	
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PP287 5	PP287 7

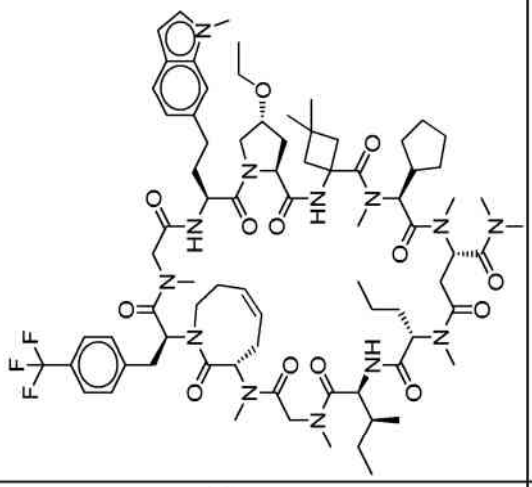
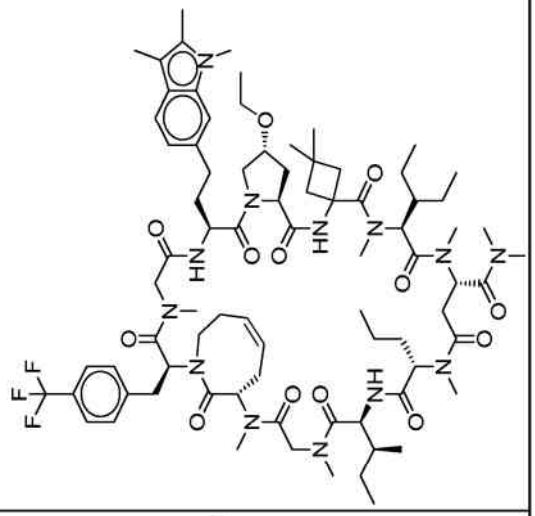
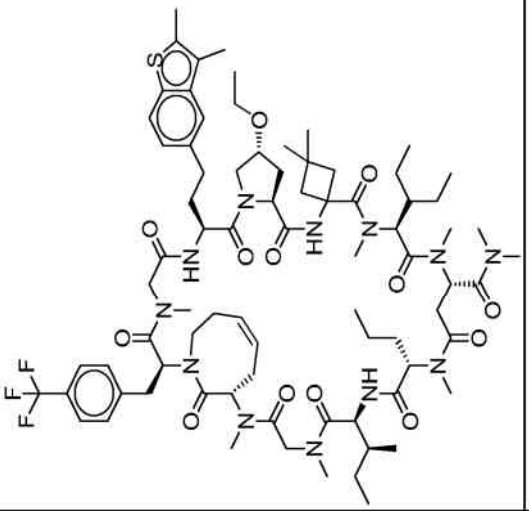
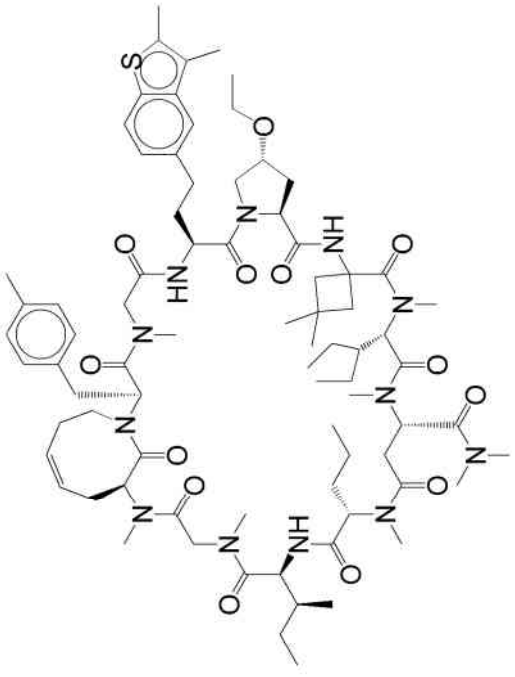
	
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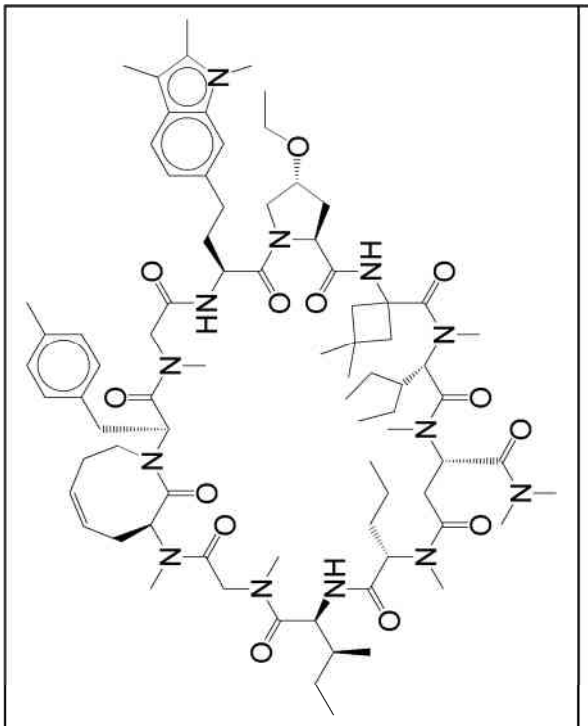
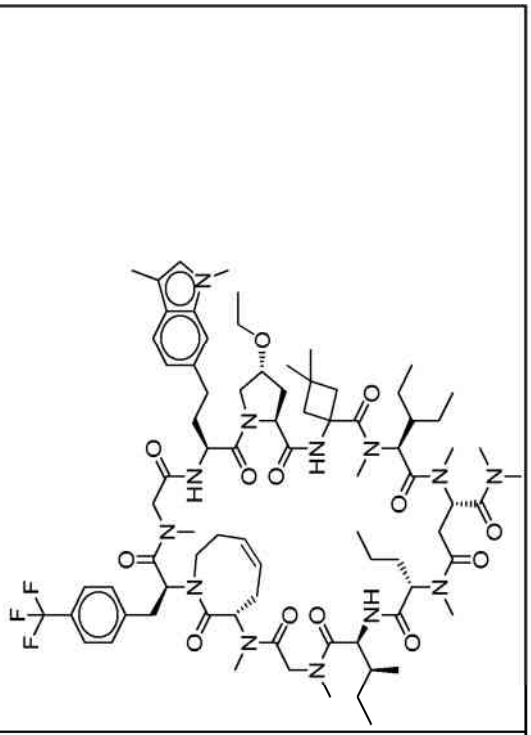
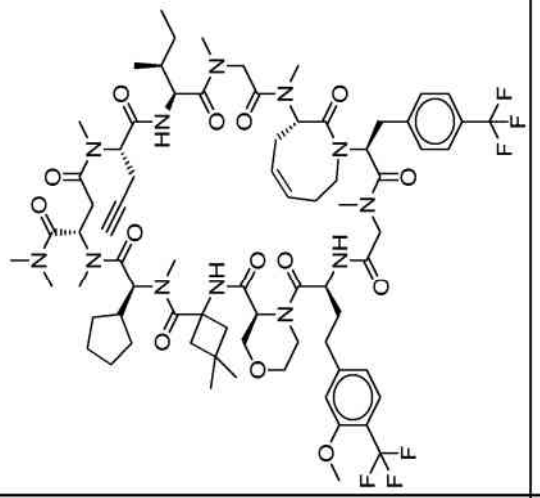
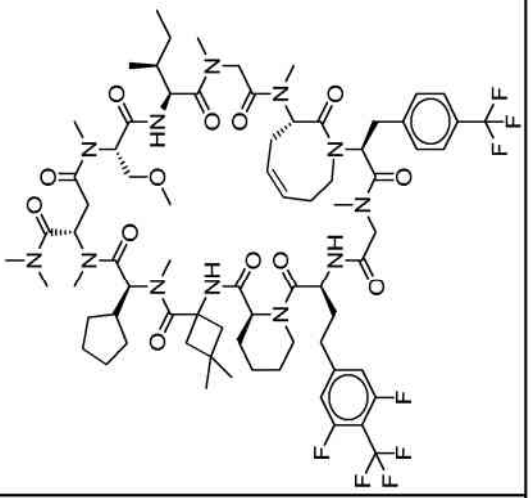
	
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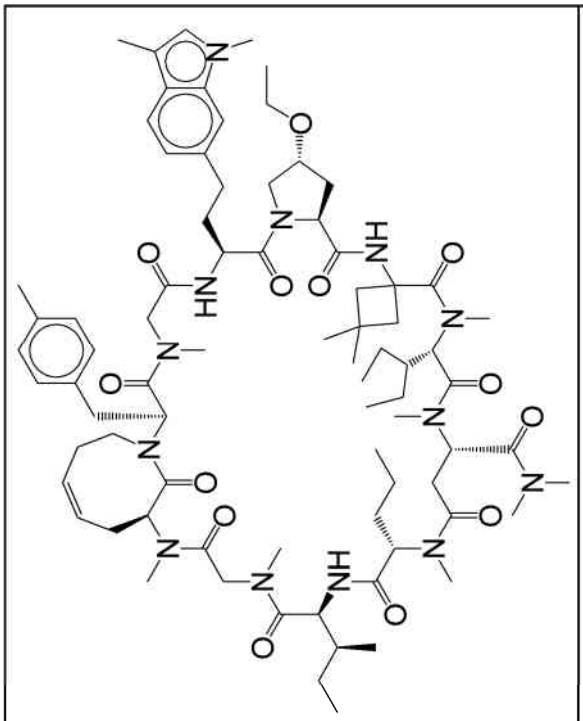
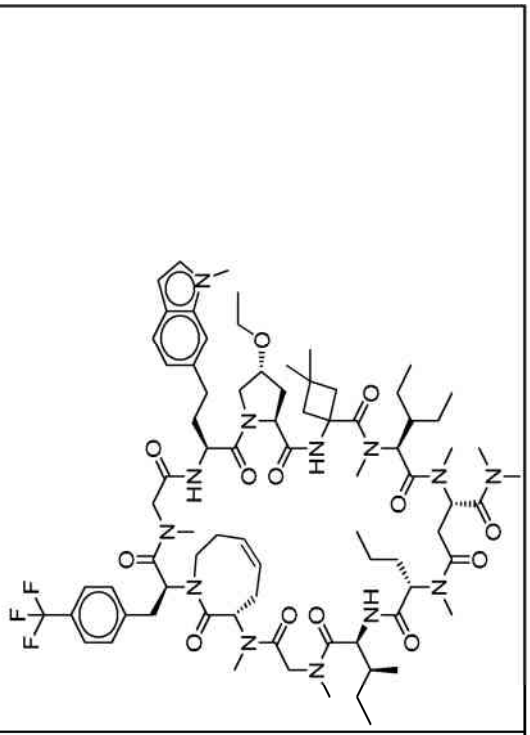
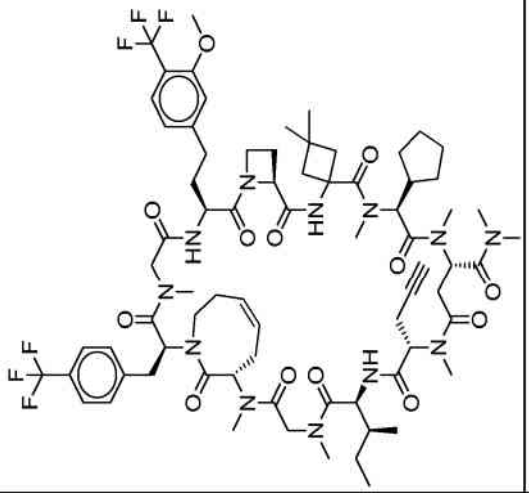
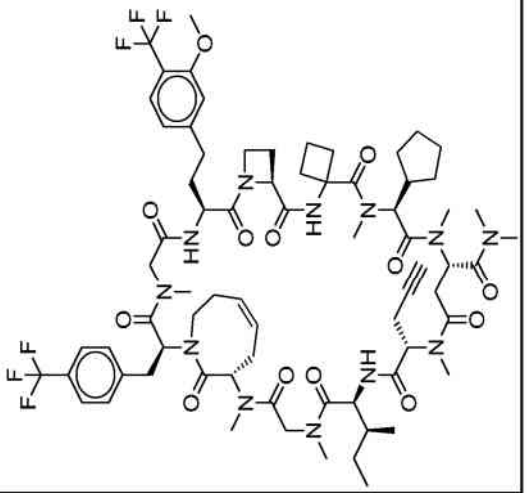
	
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PP2888	PP2890

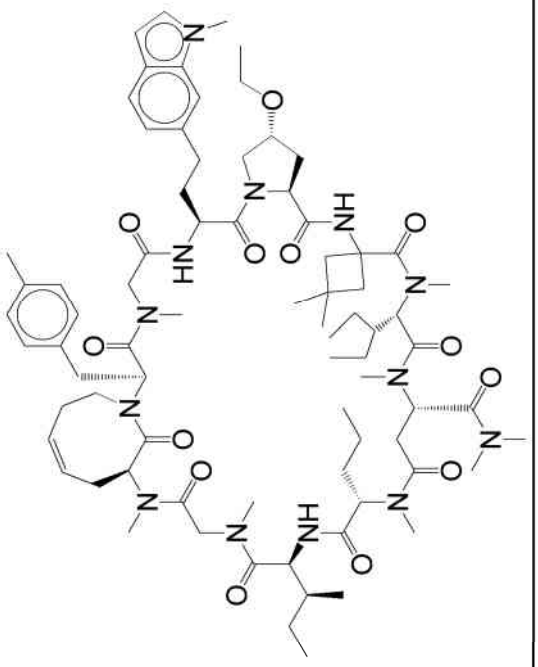
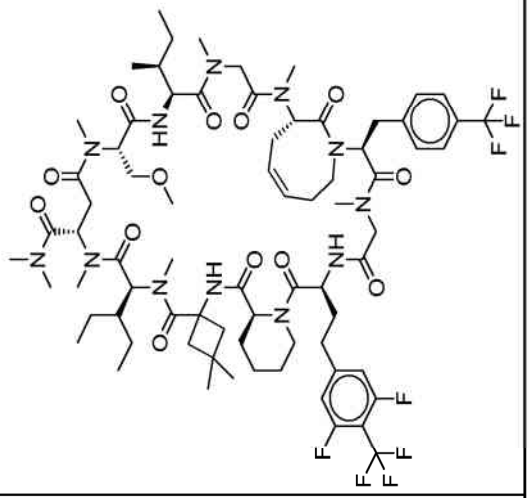
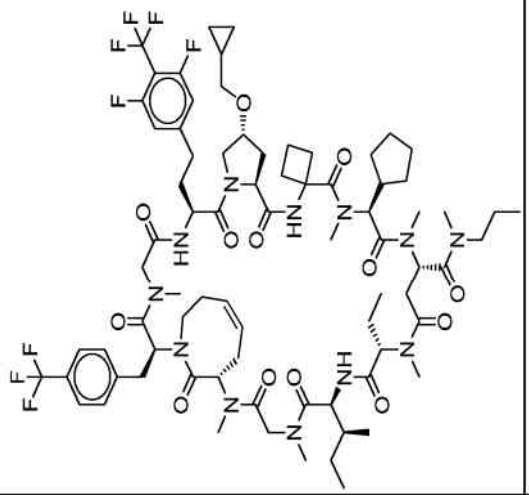
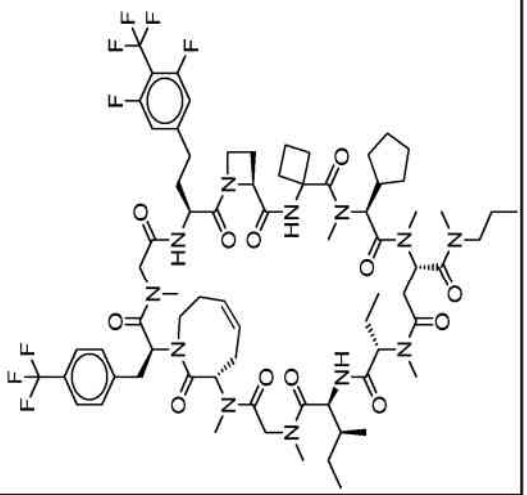
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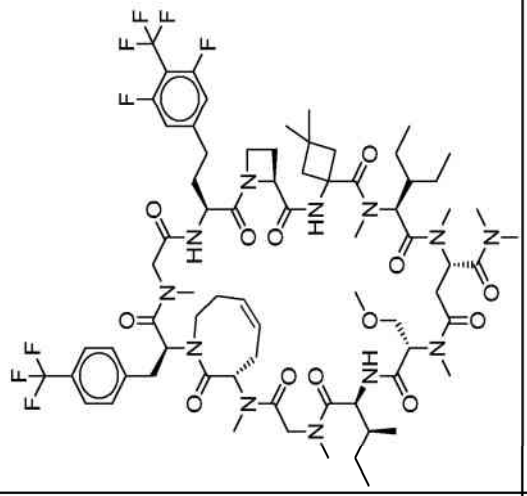
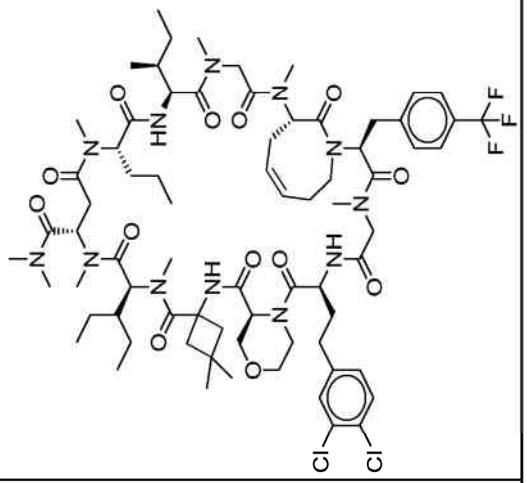
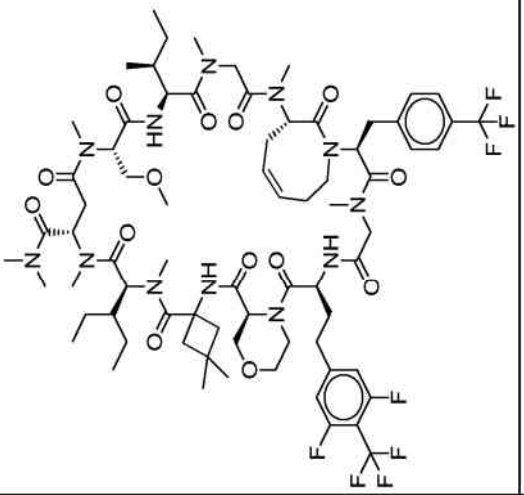
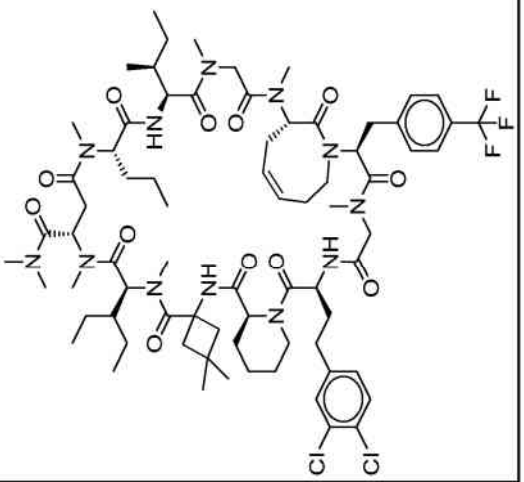
	
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PP2900	PP2902

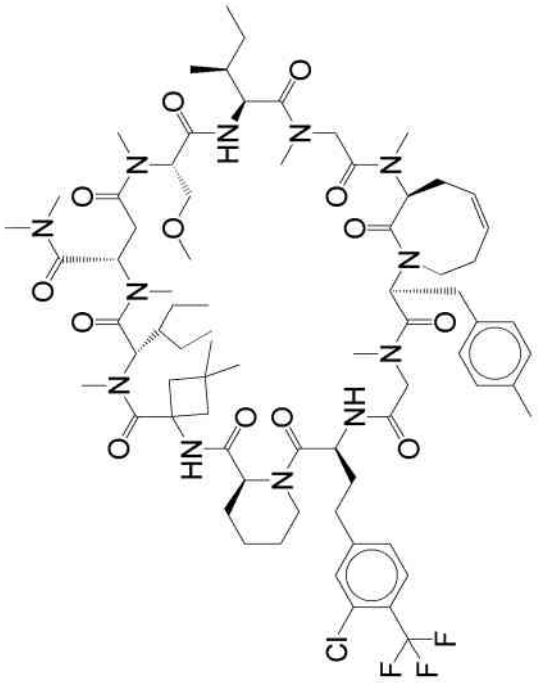
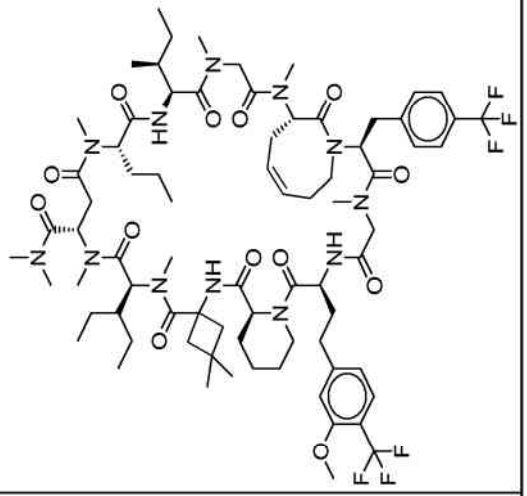
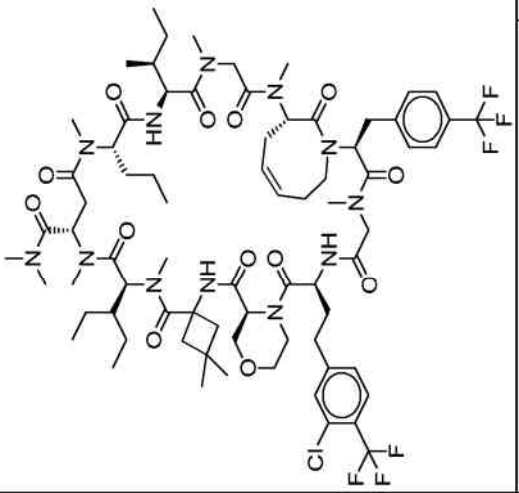
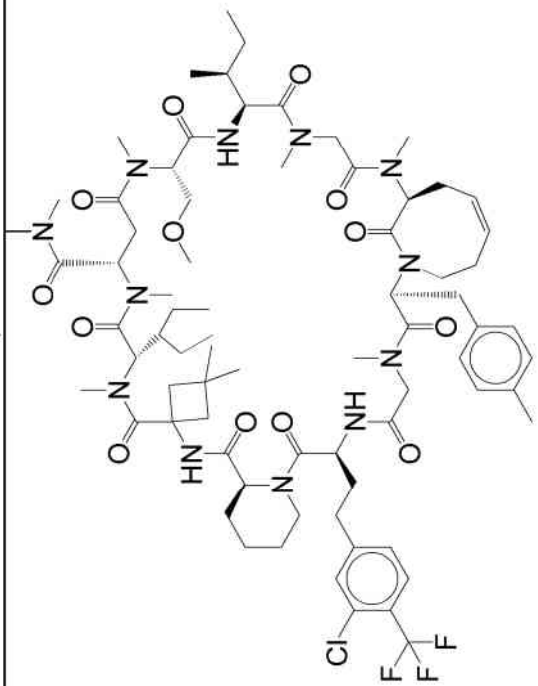
	
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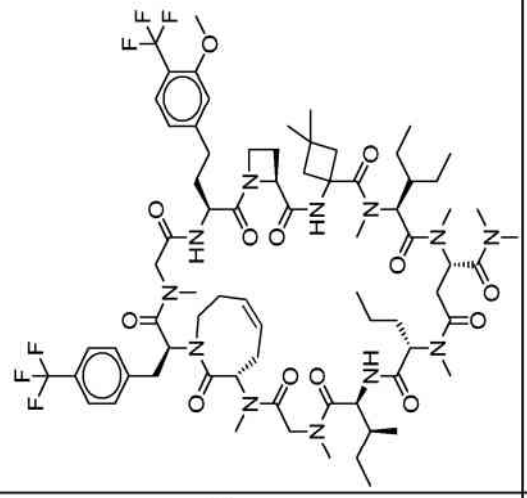
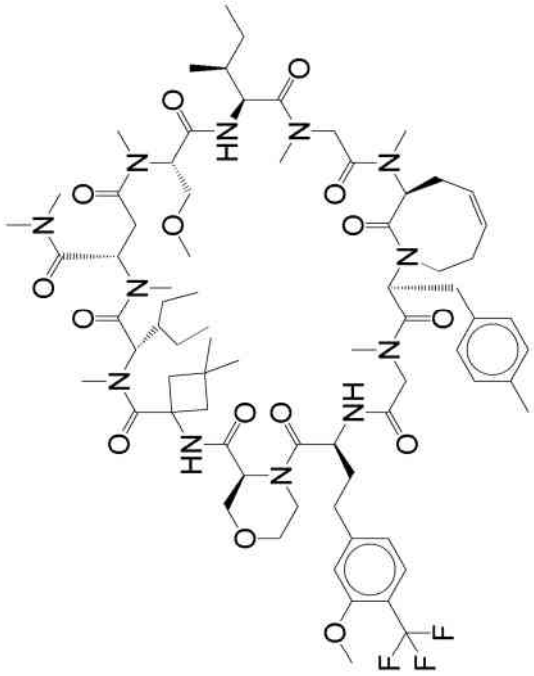
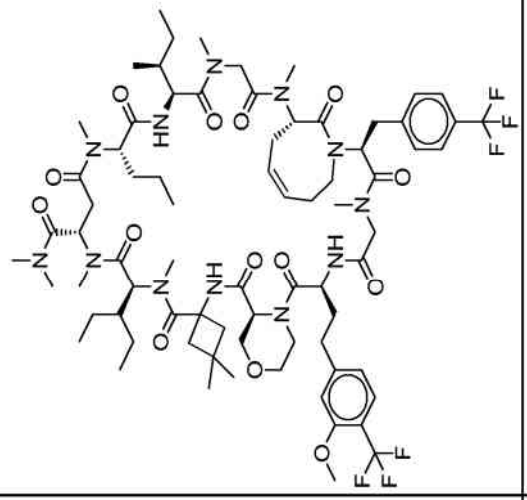
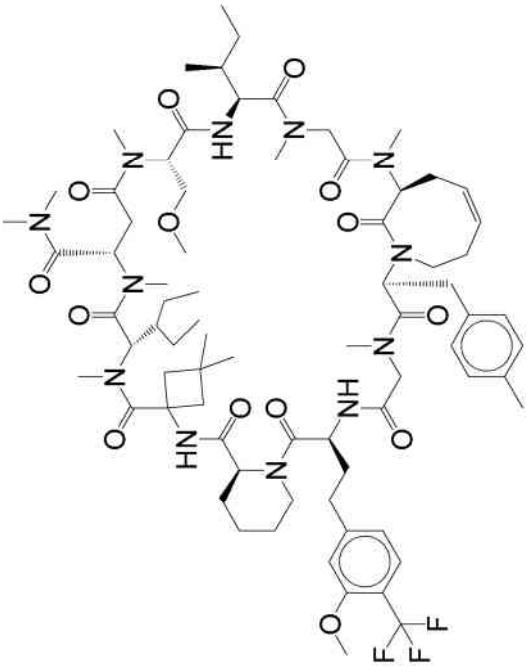
	
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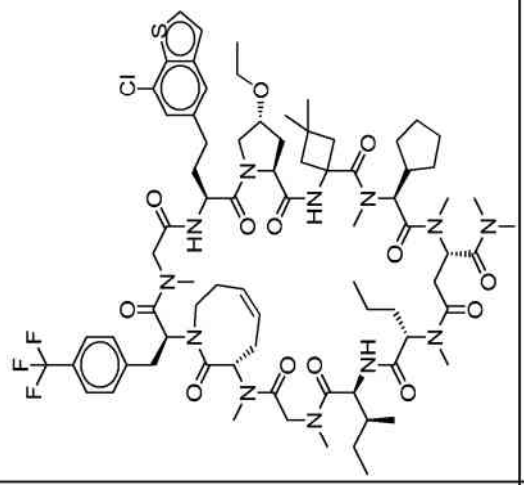
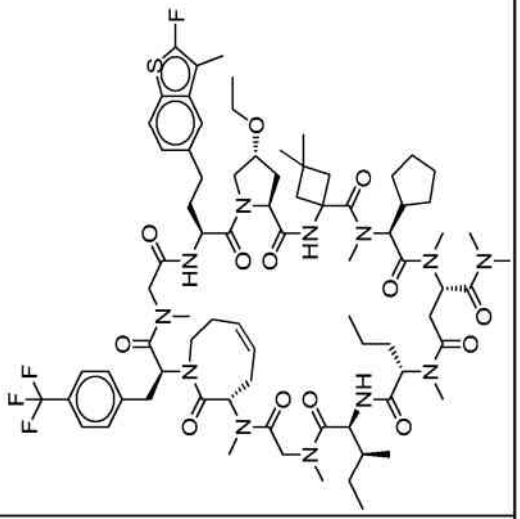
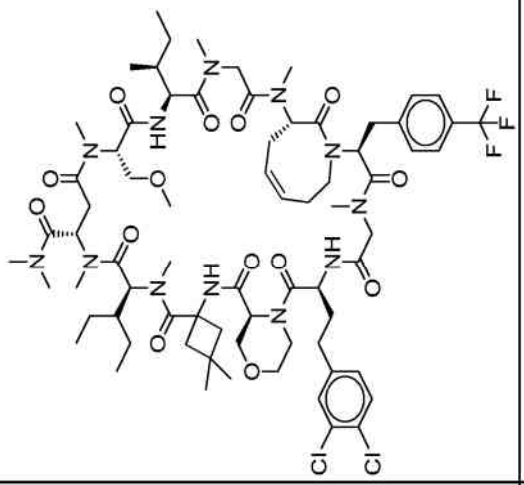
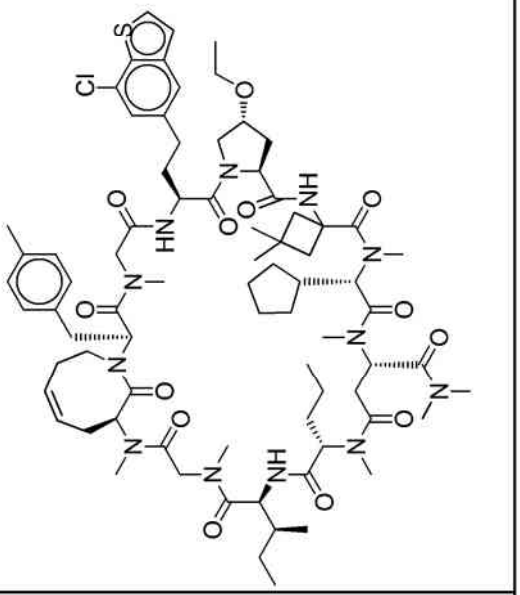
	
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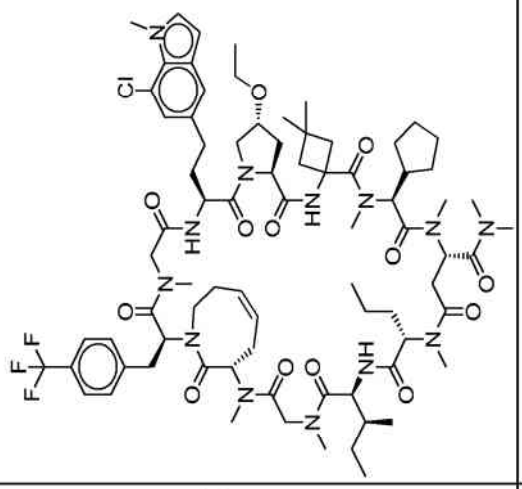
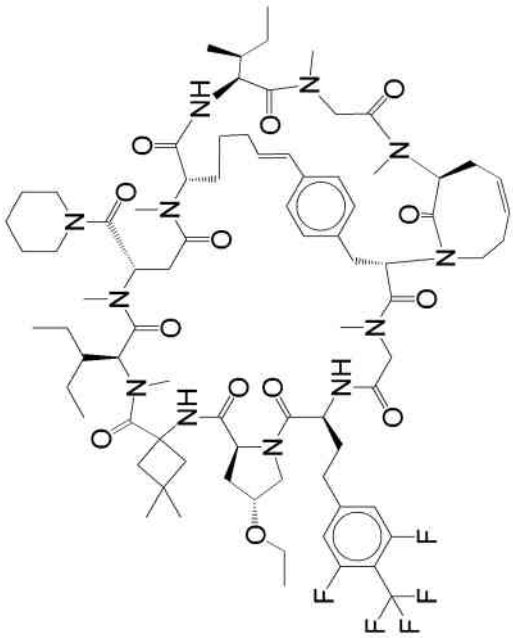
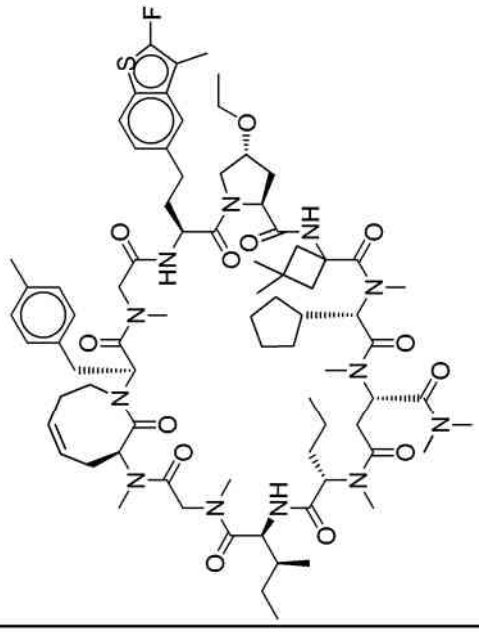
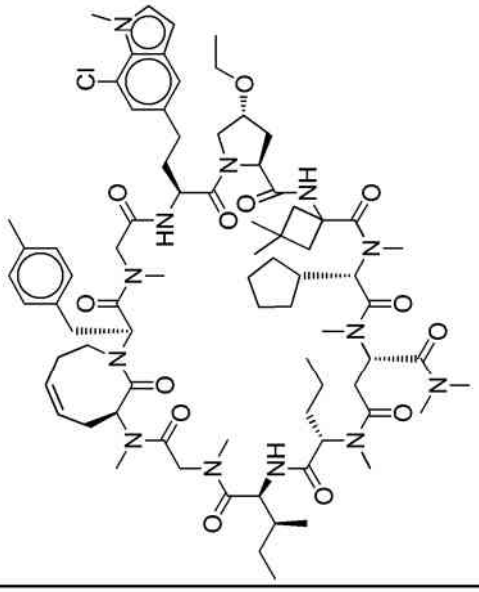
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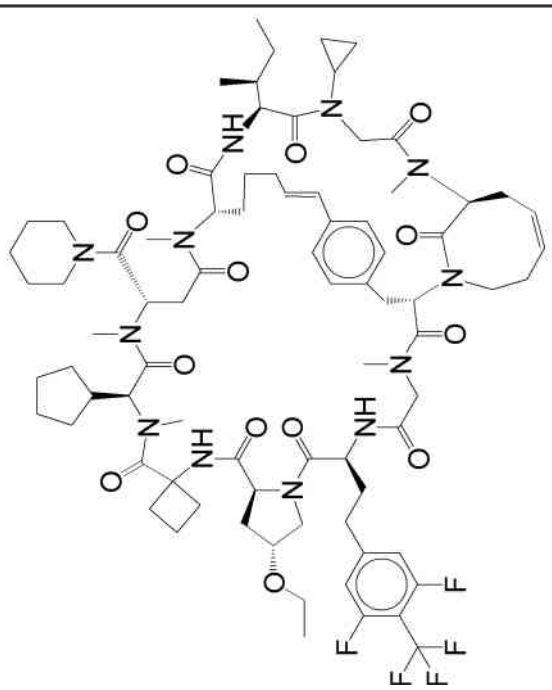
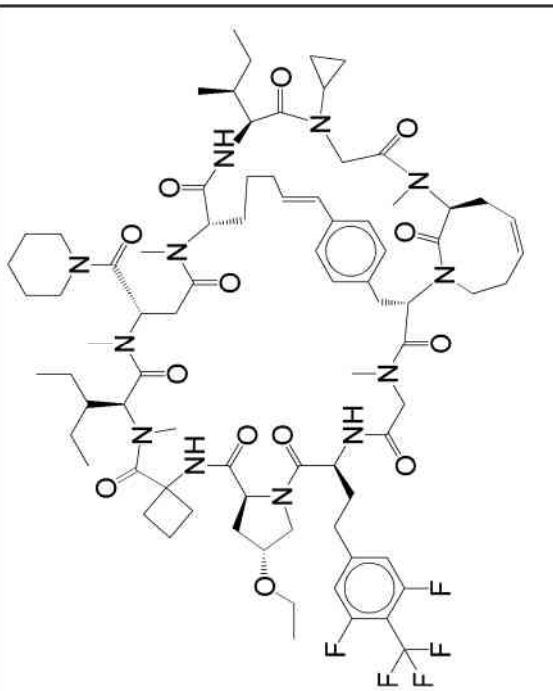
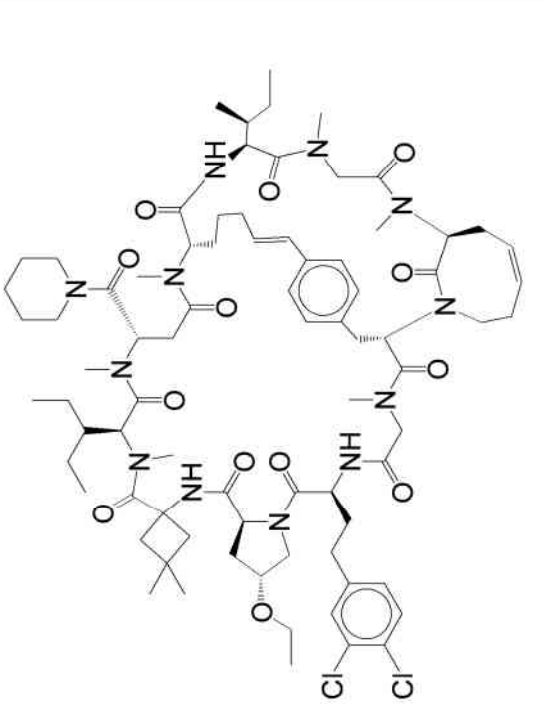
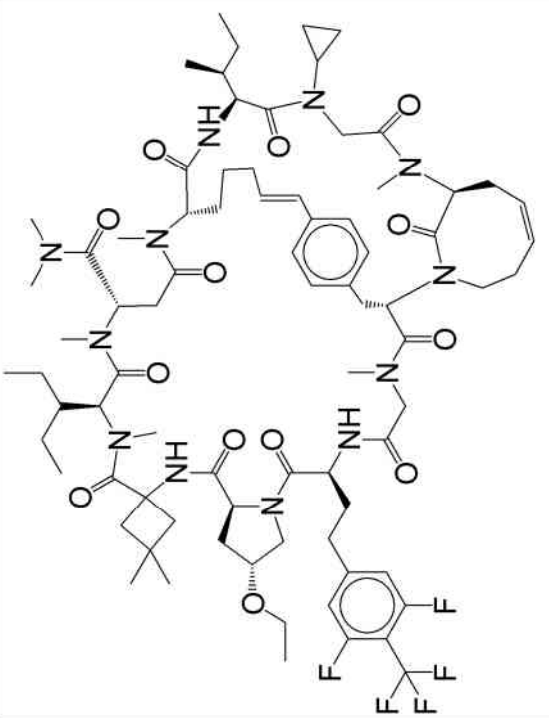
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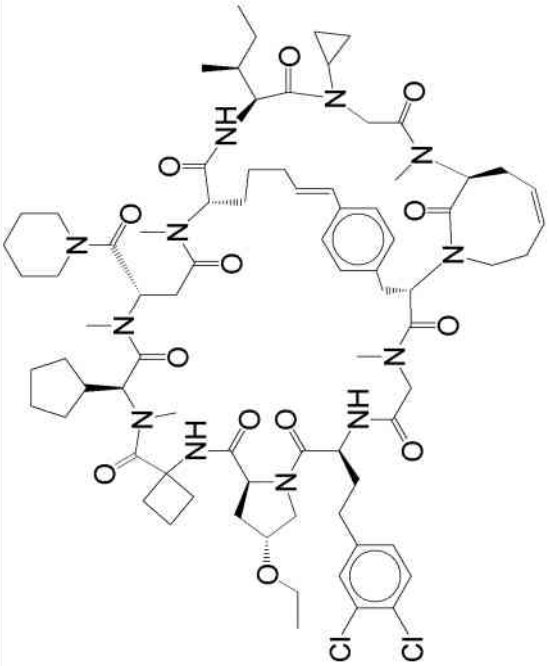
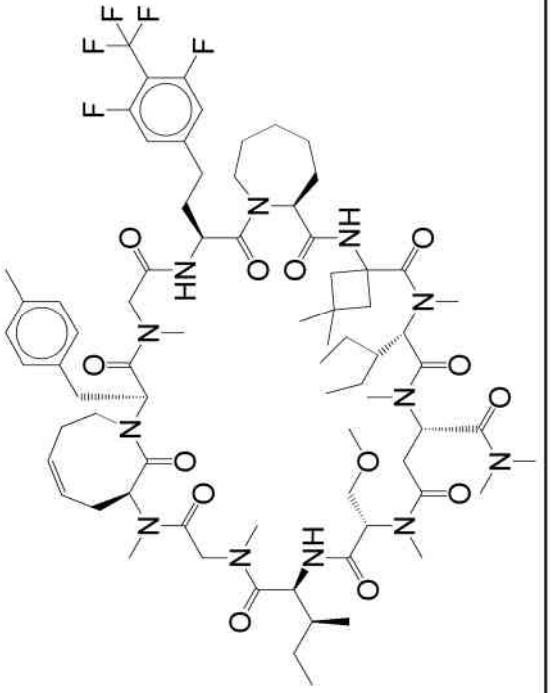
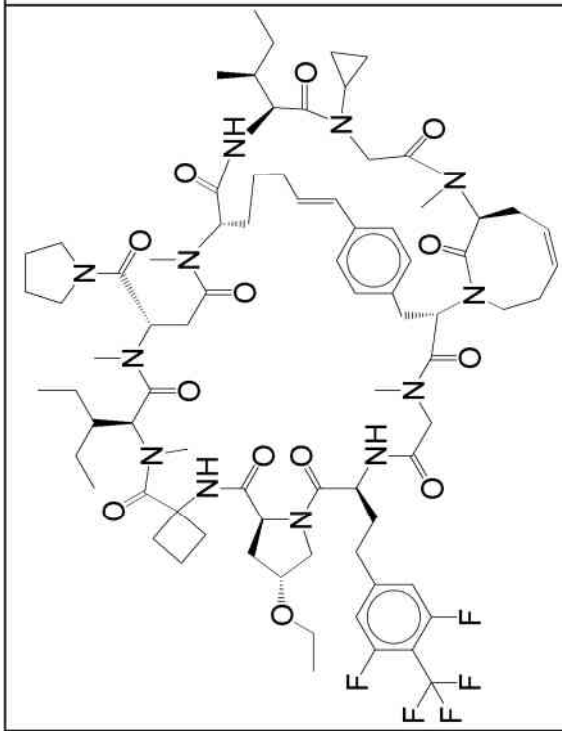
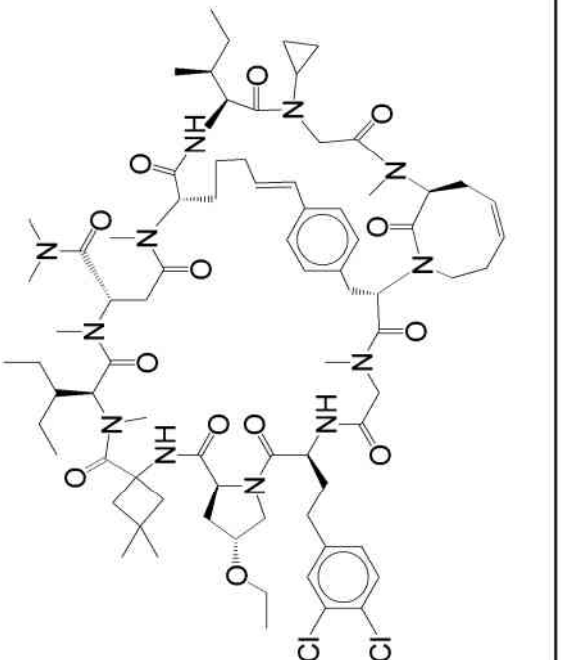
	
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PP292 9	PP293 2

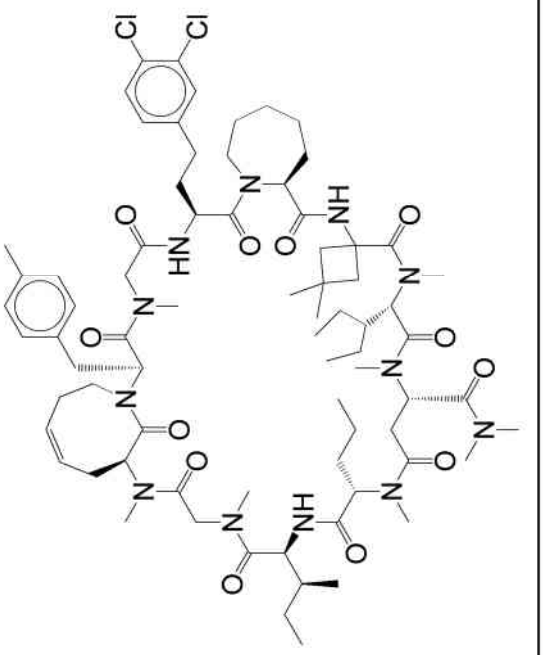
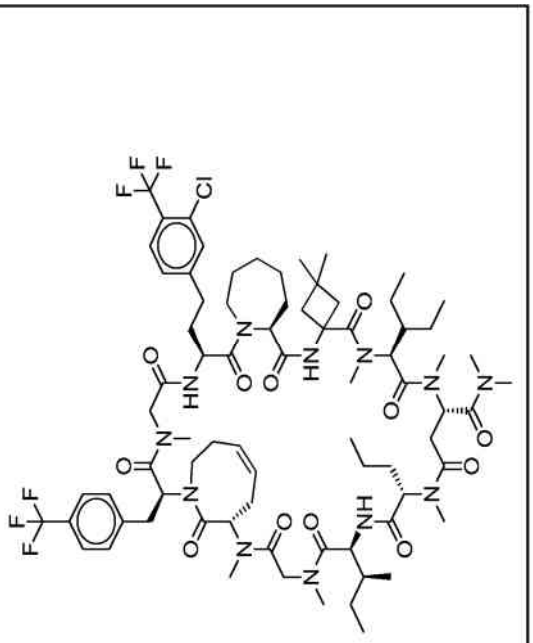
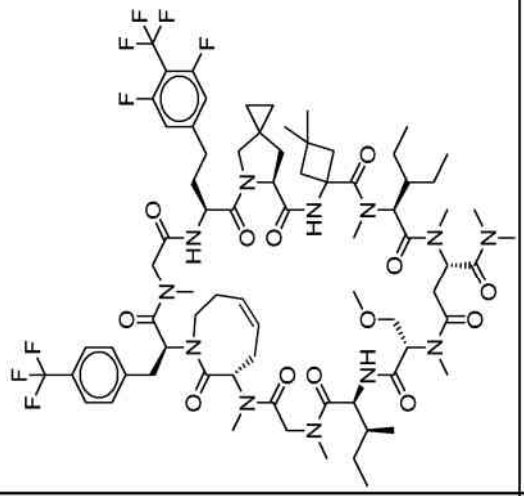
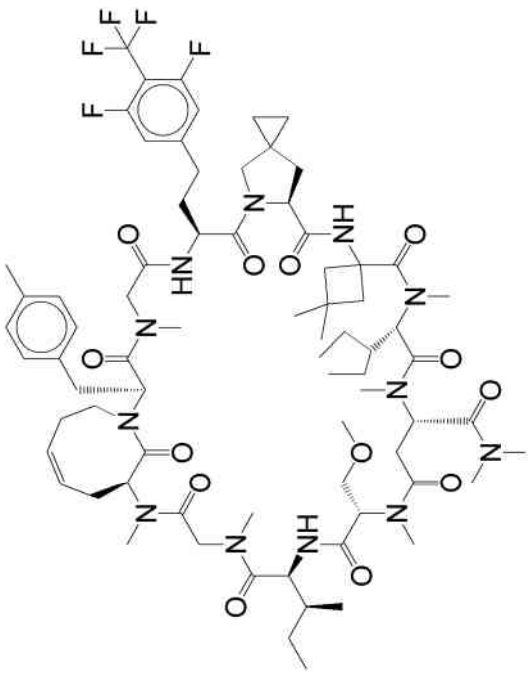
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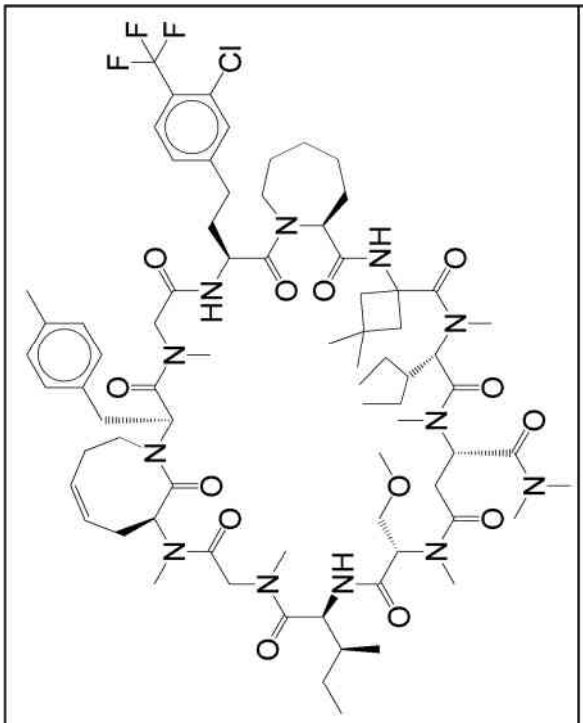
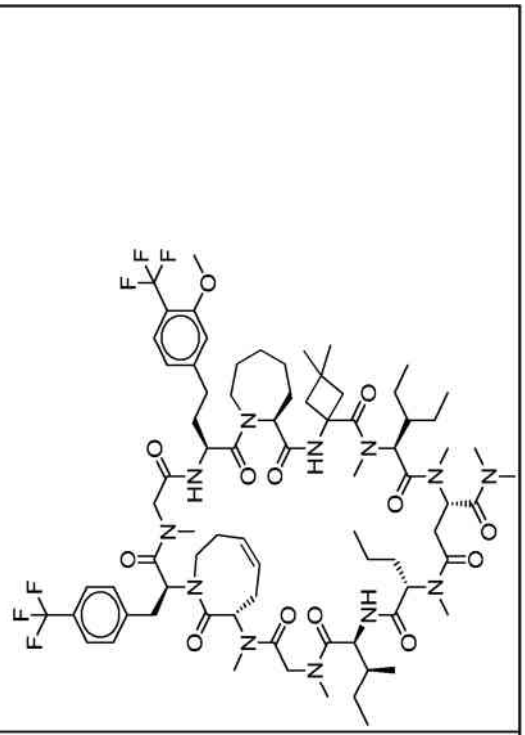
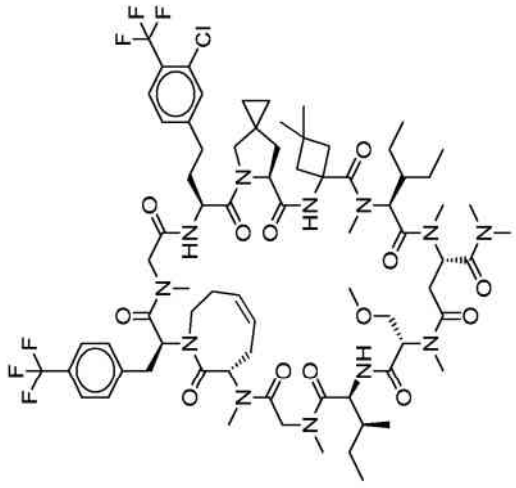
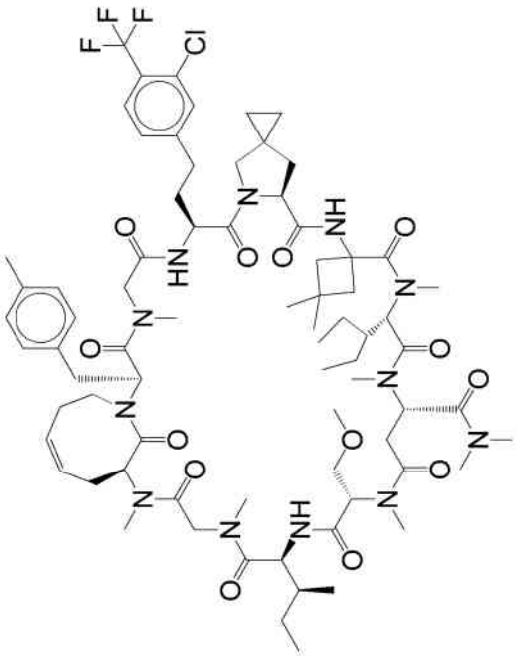
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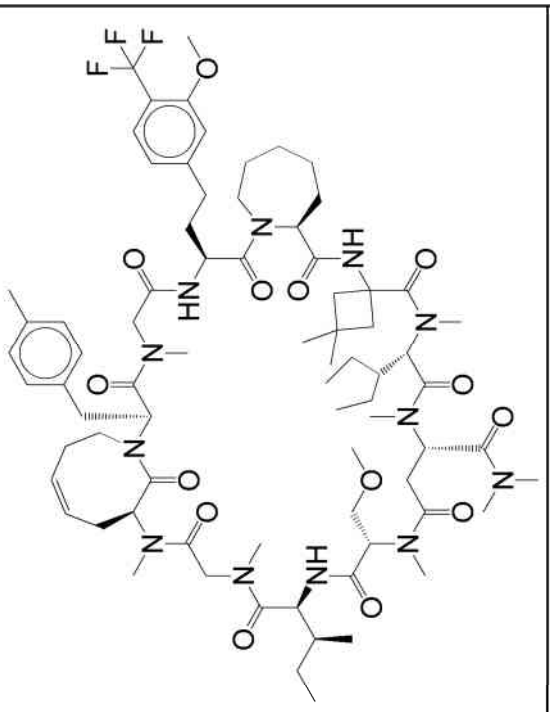
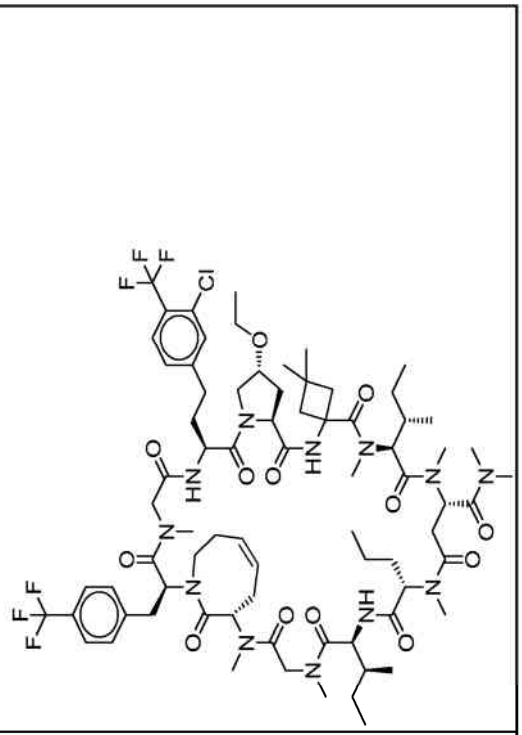
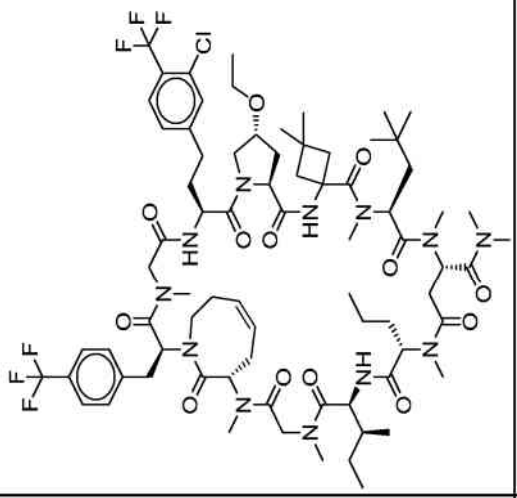
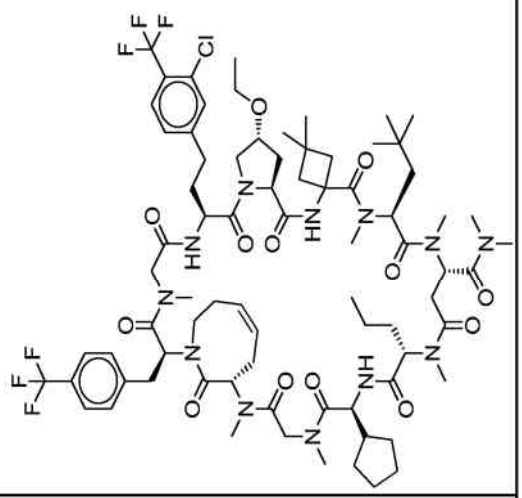
	
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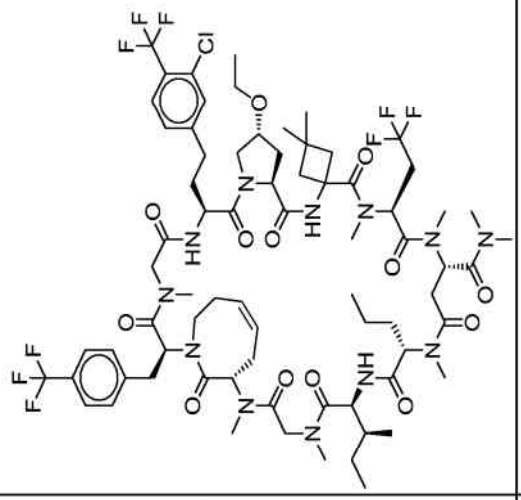
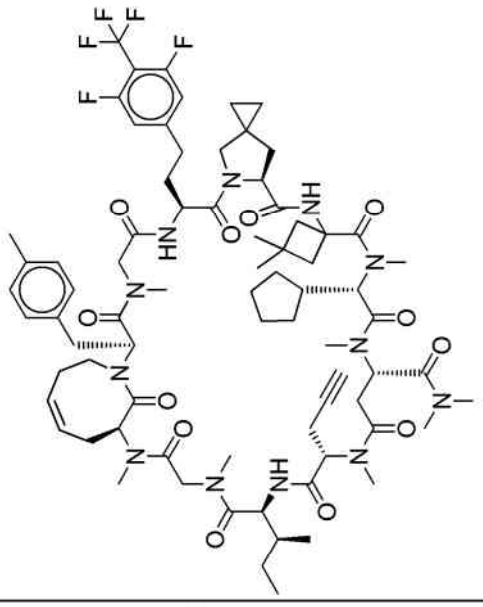
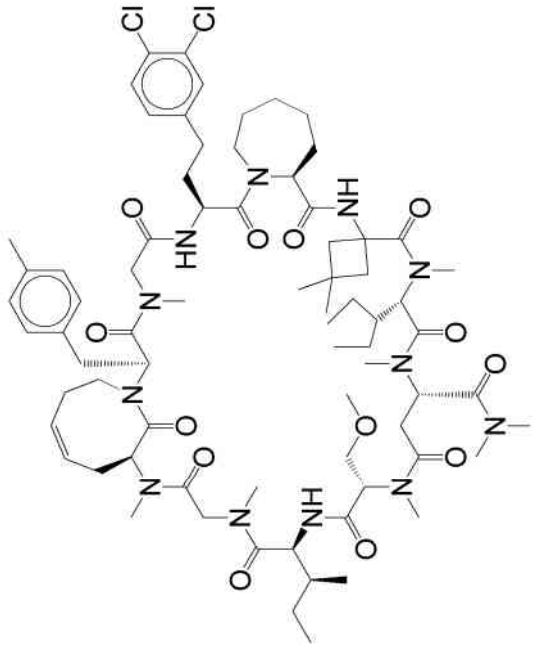
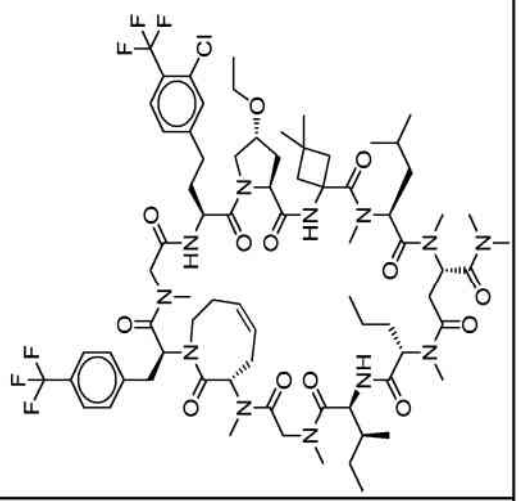
	
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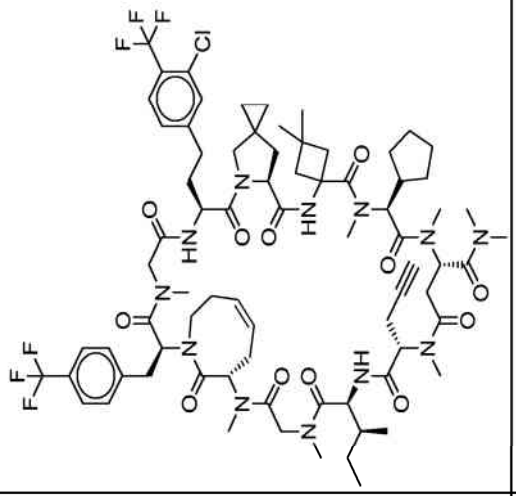
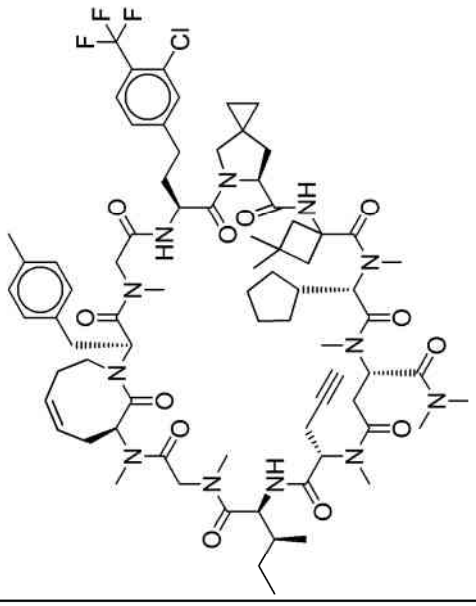
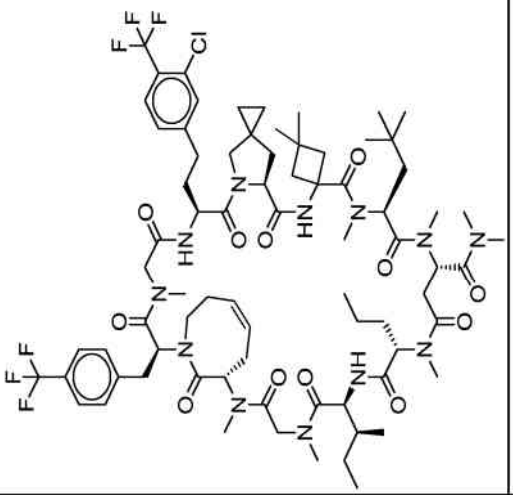
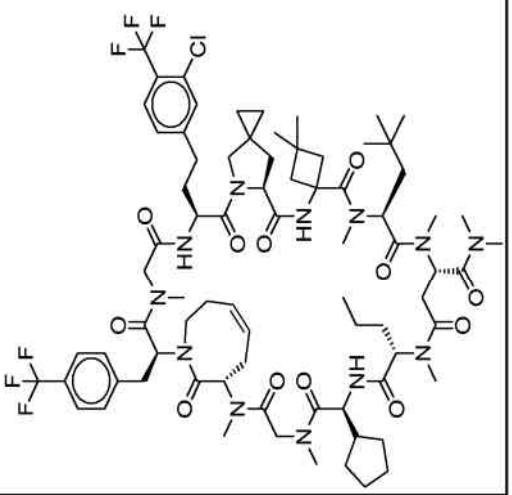
	
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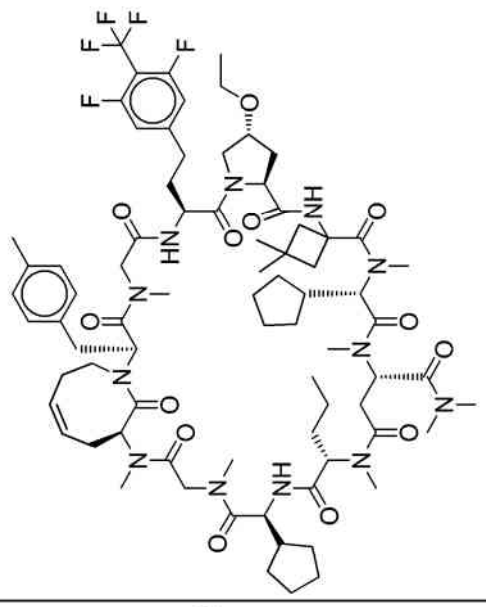
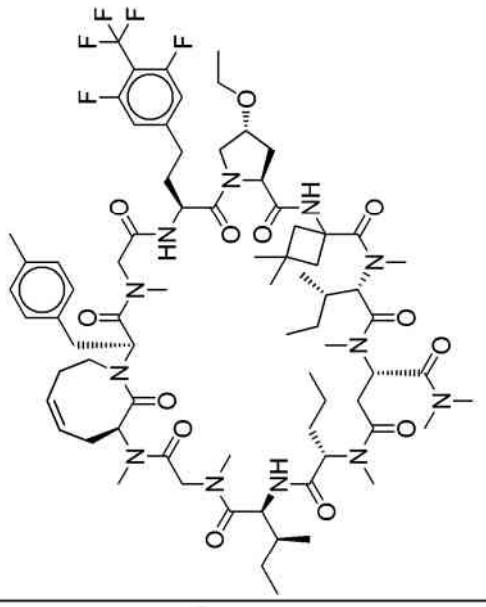
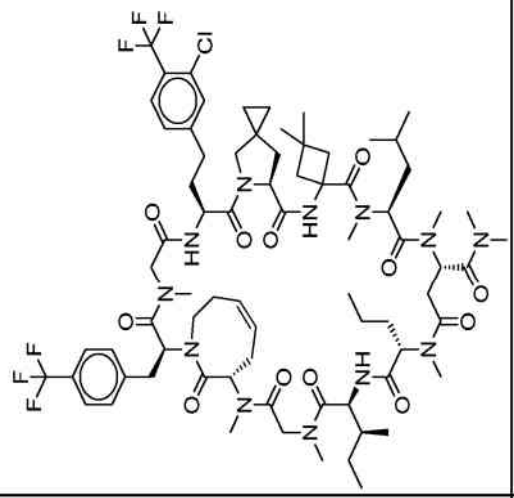
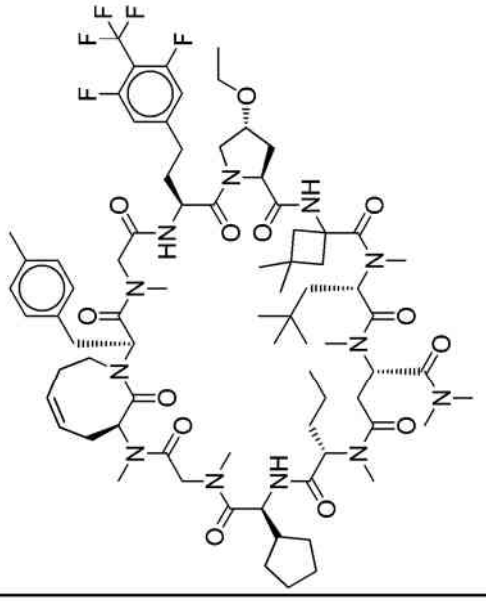
	
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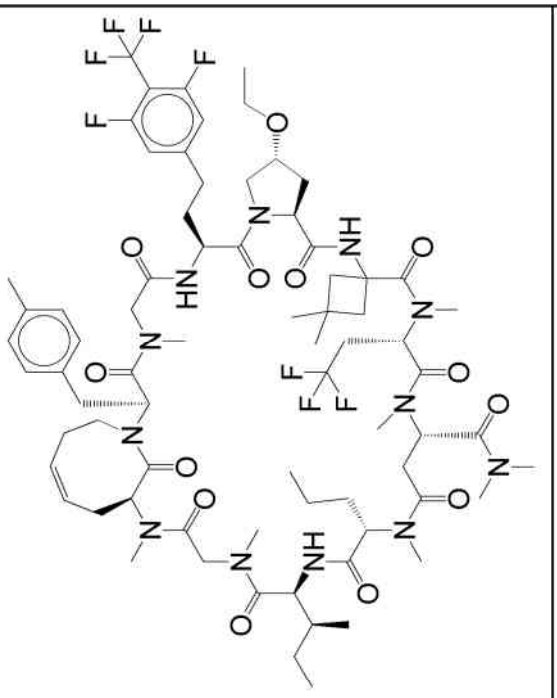
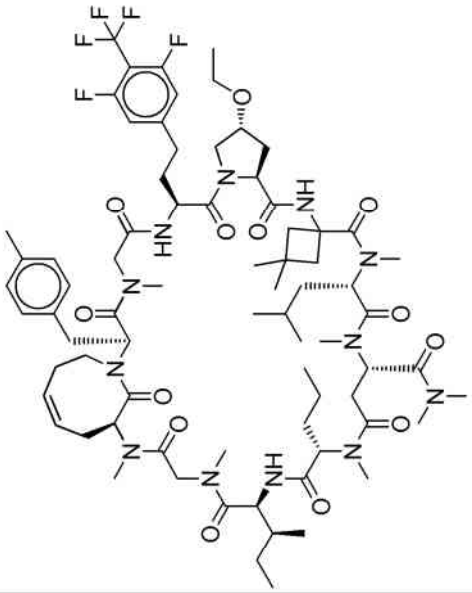
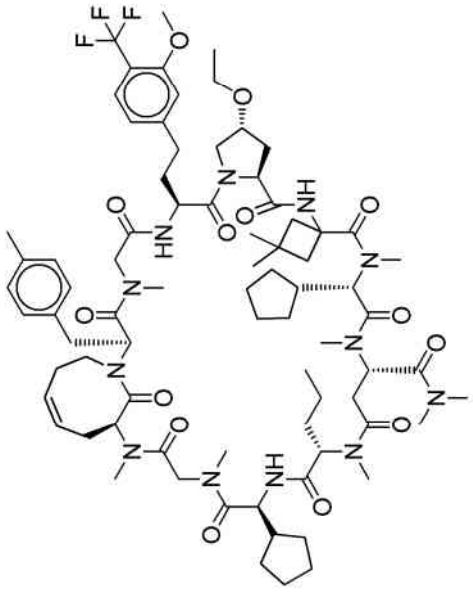
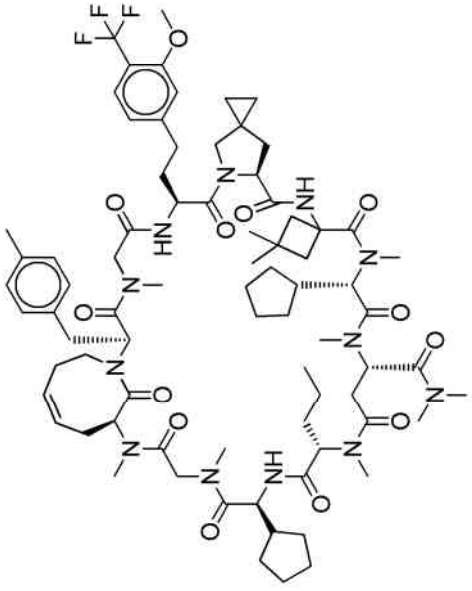
	
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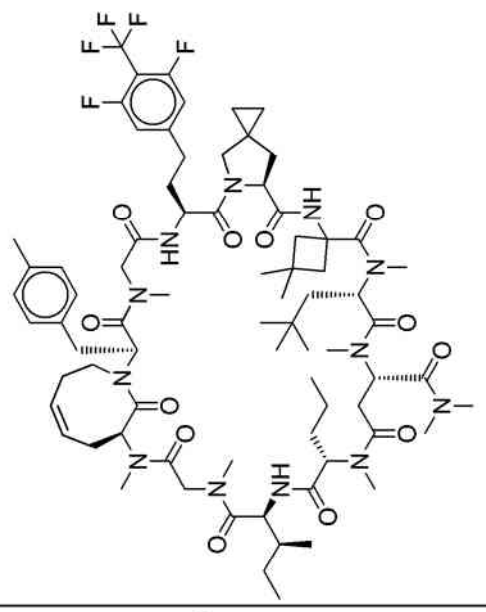
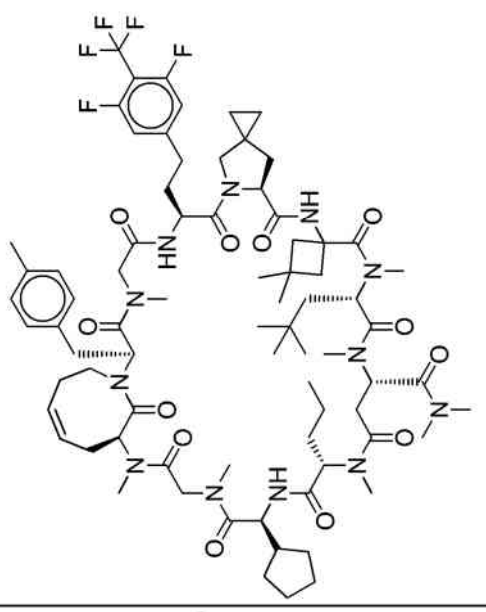
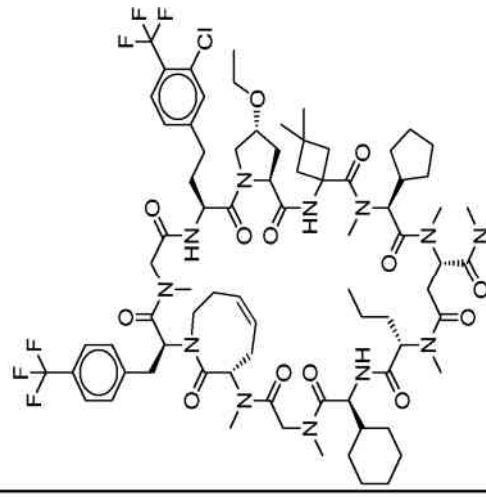
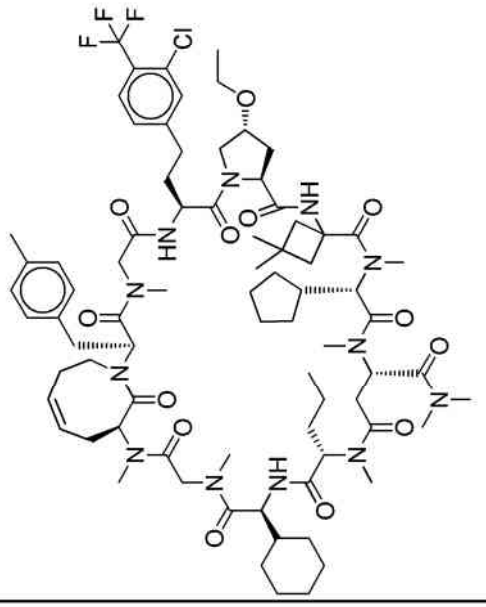
	
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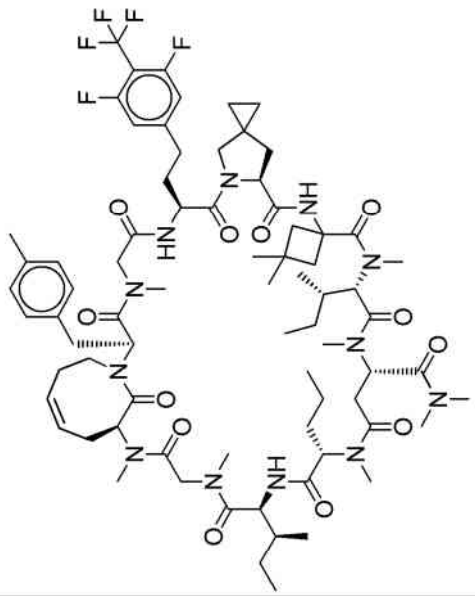
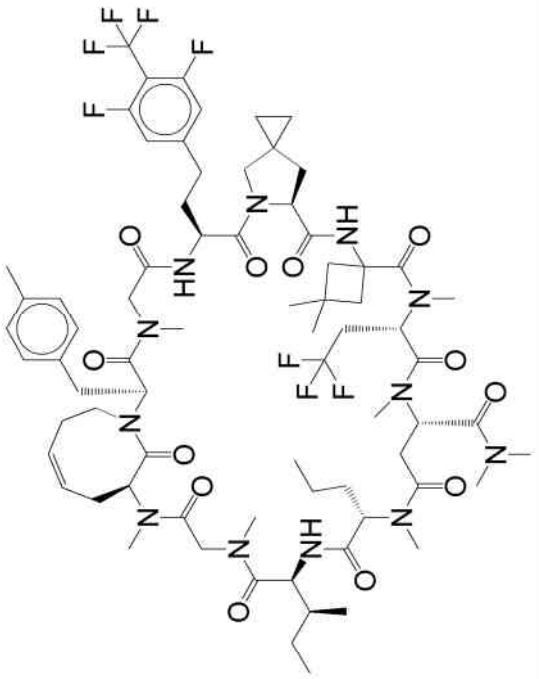
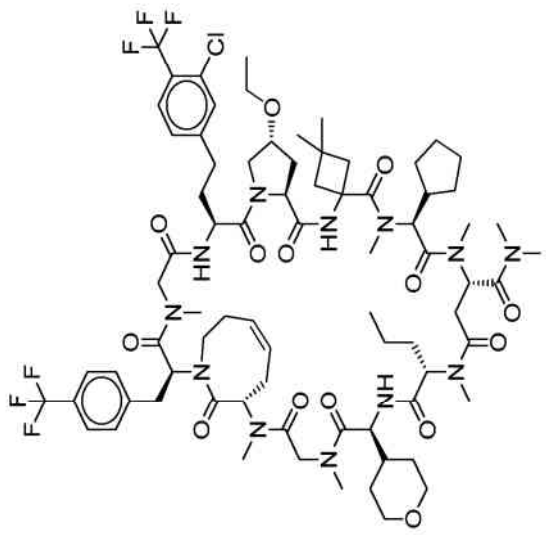
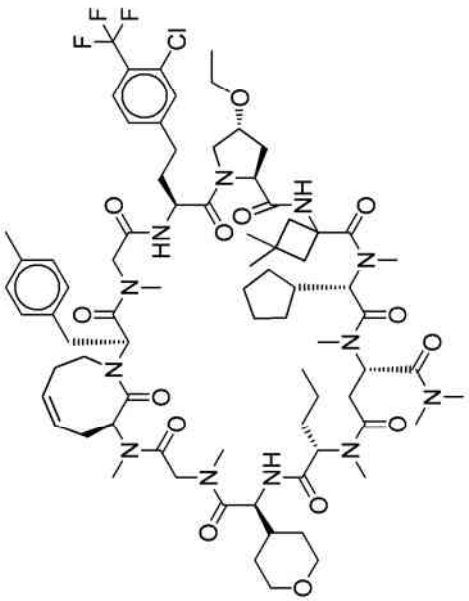
	
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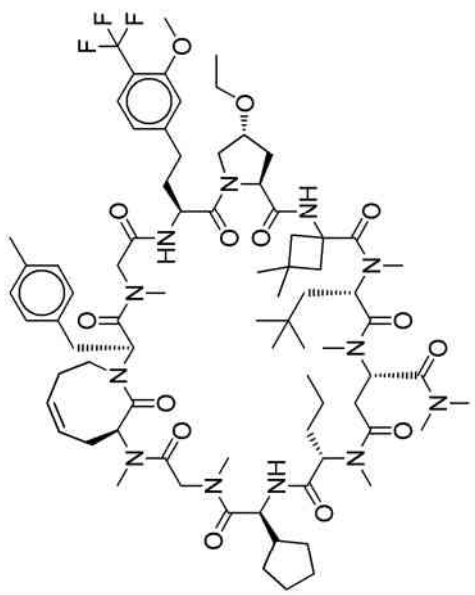
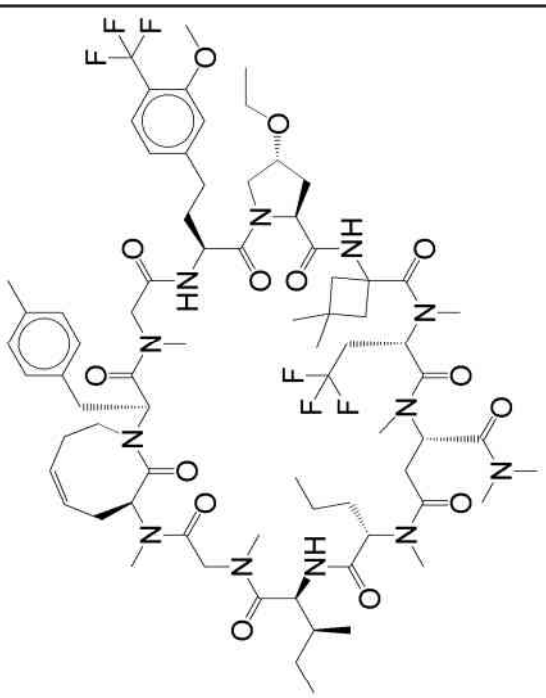
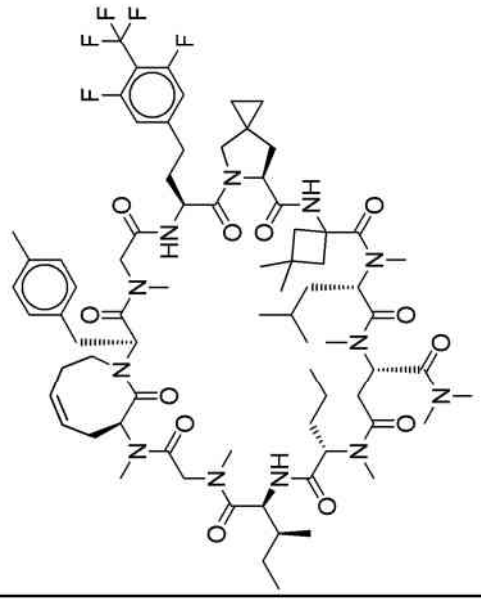
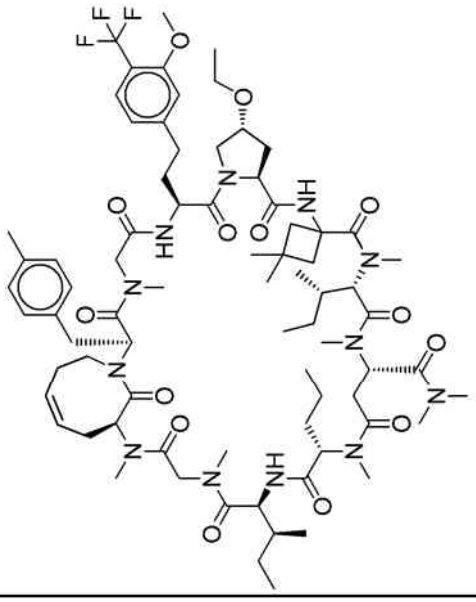
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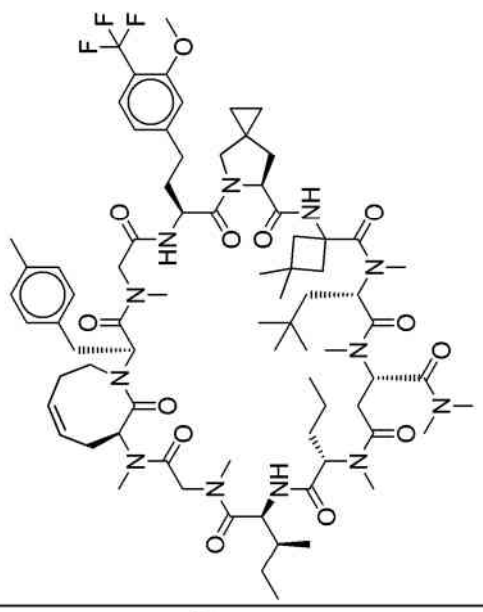
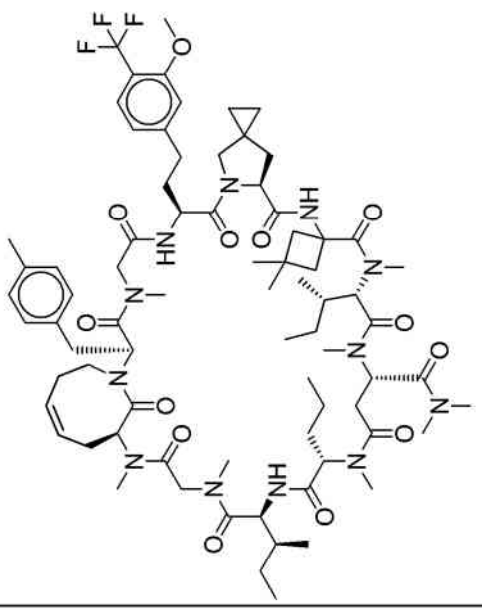
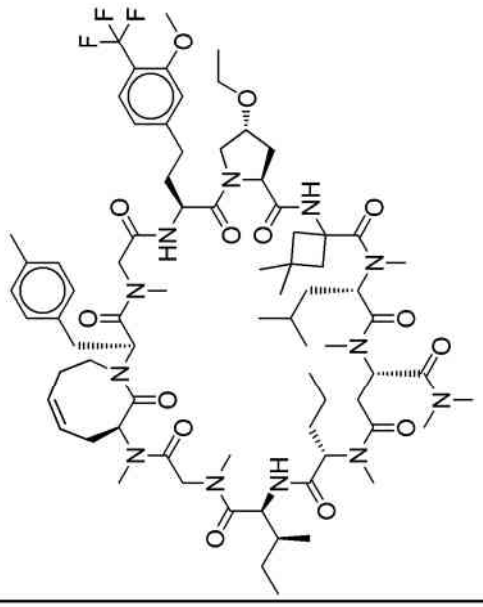
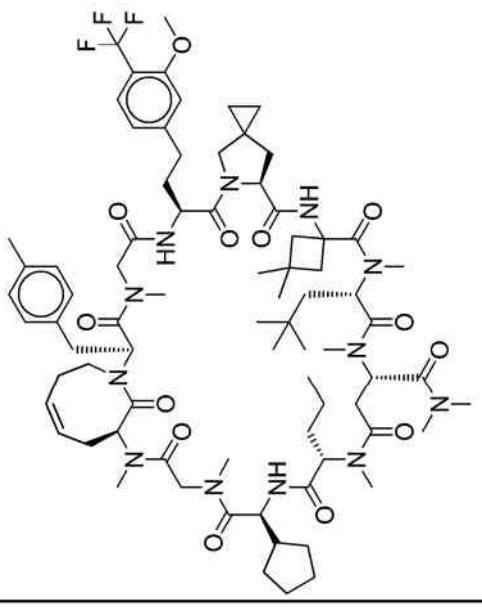
	
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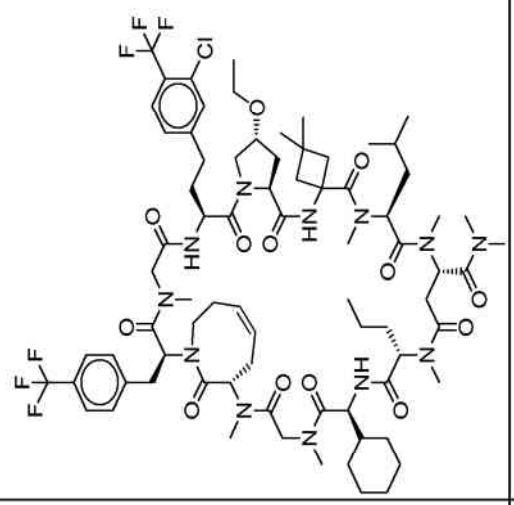
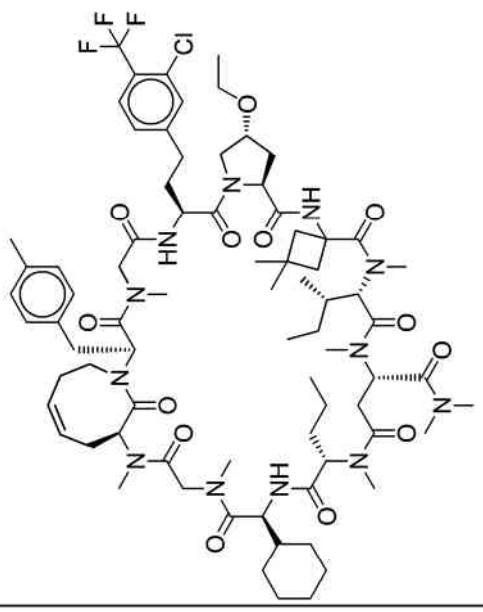
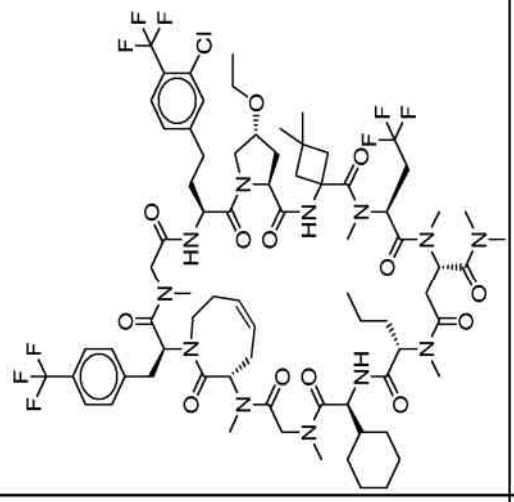
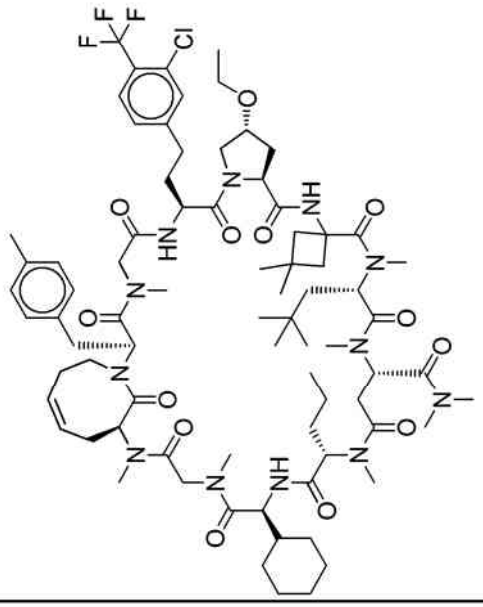
	
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PP299 6	PP299 8

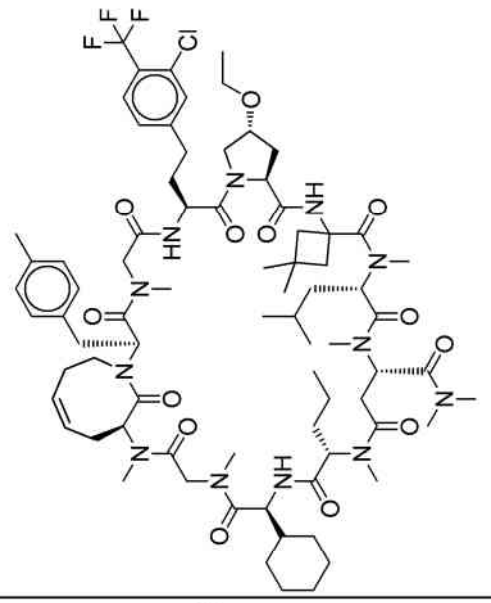
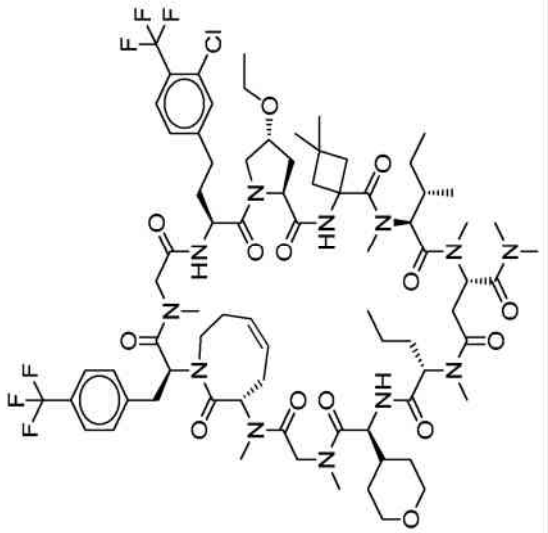
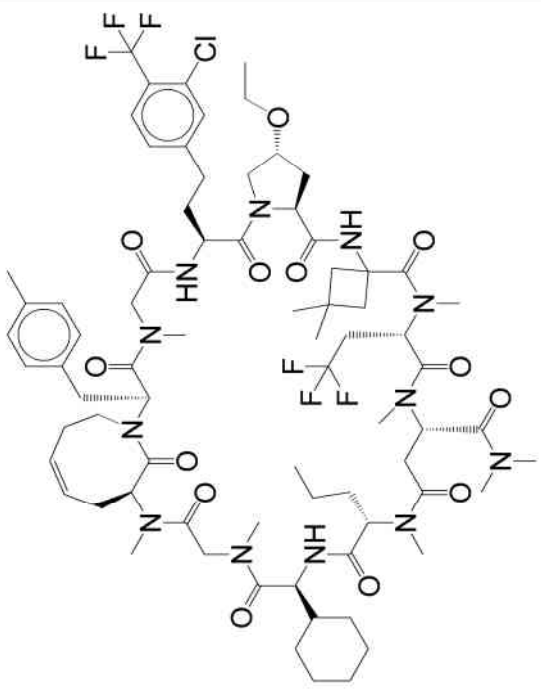
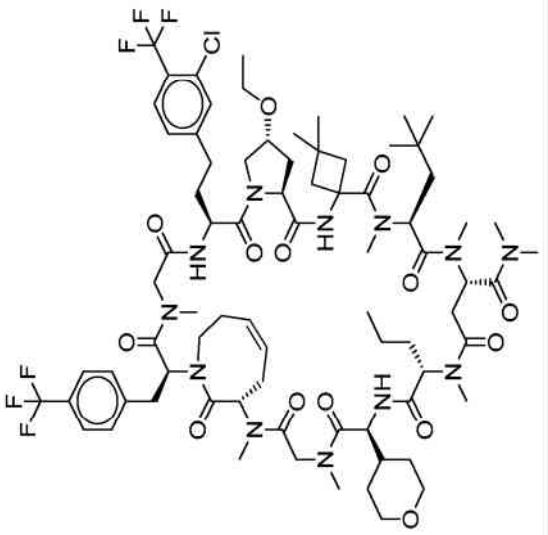
	
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PP300 6	

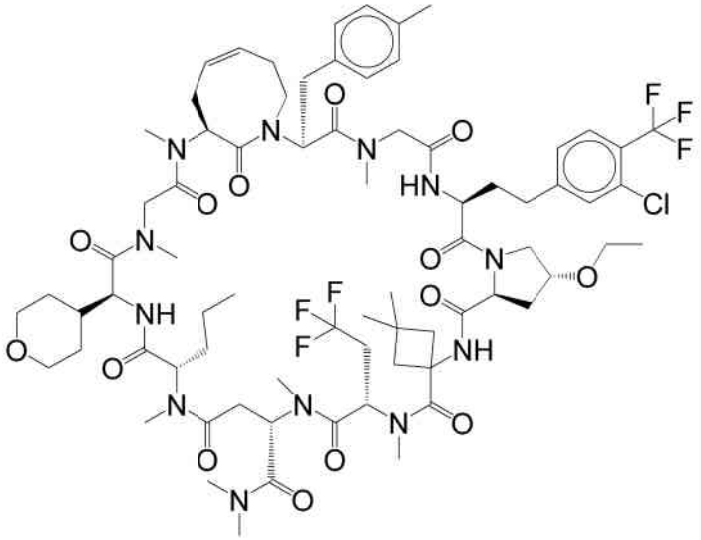
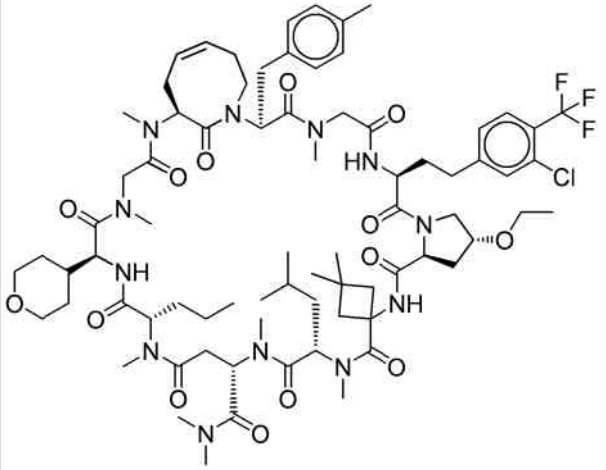
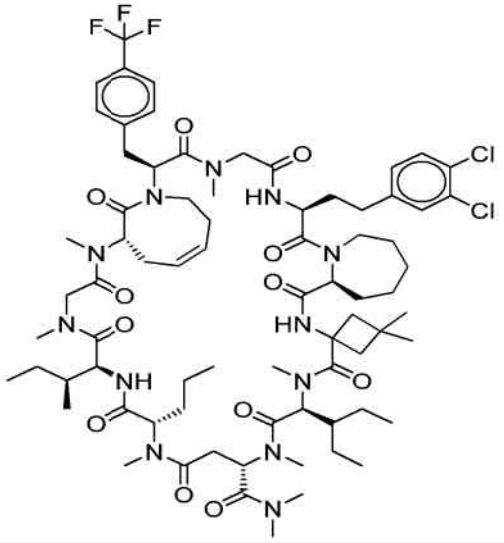
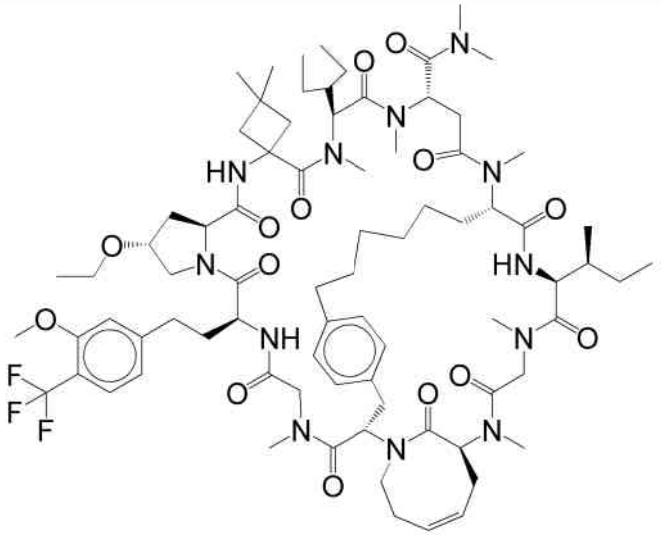
	
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PP3008	PP3010

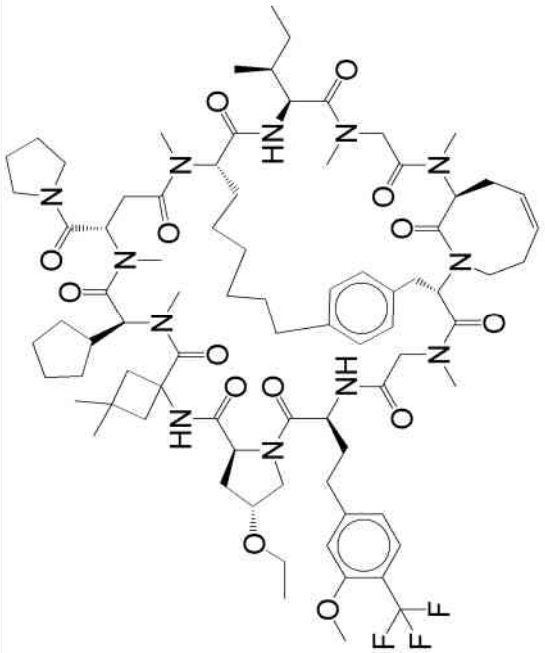
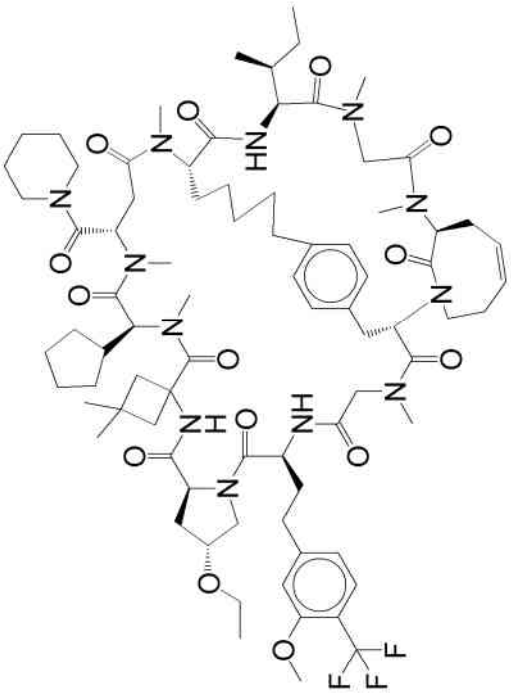
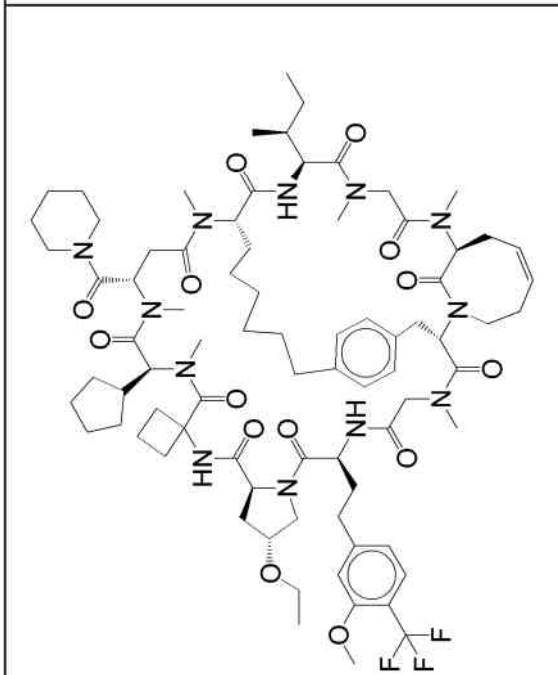
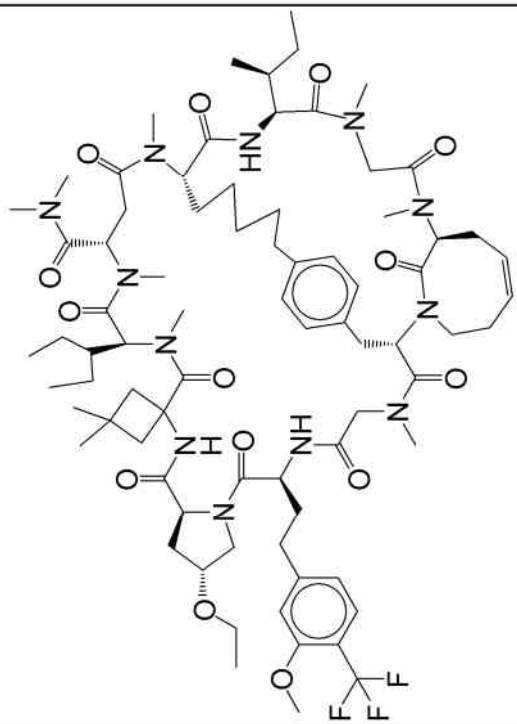
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PP301 2	PP301 4

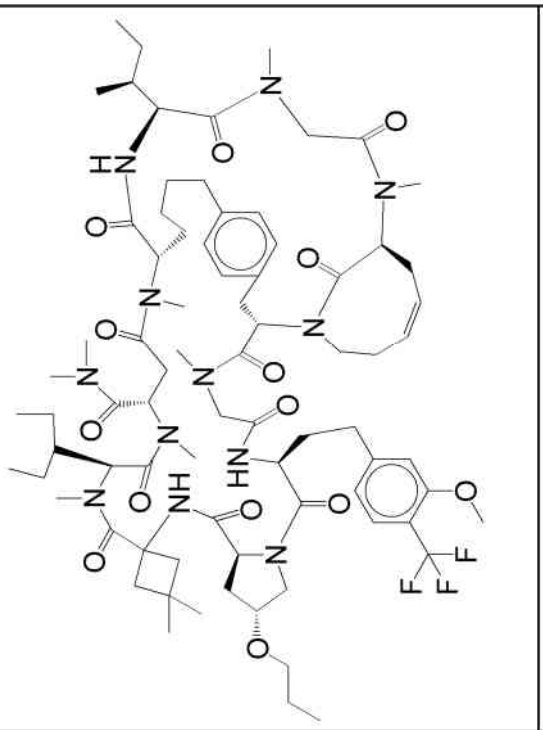
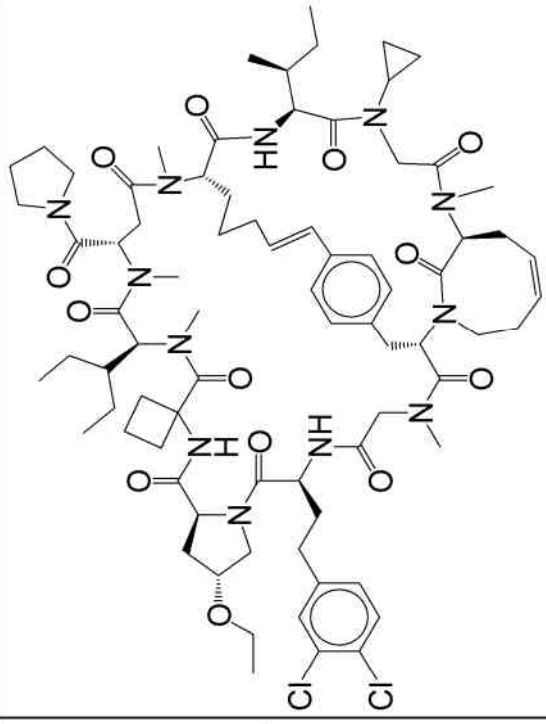
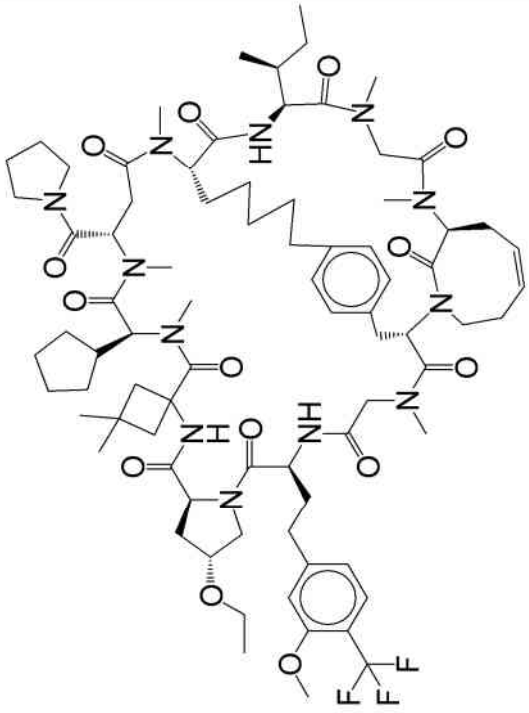
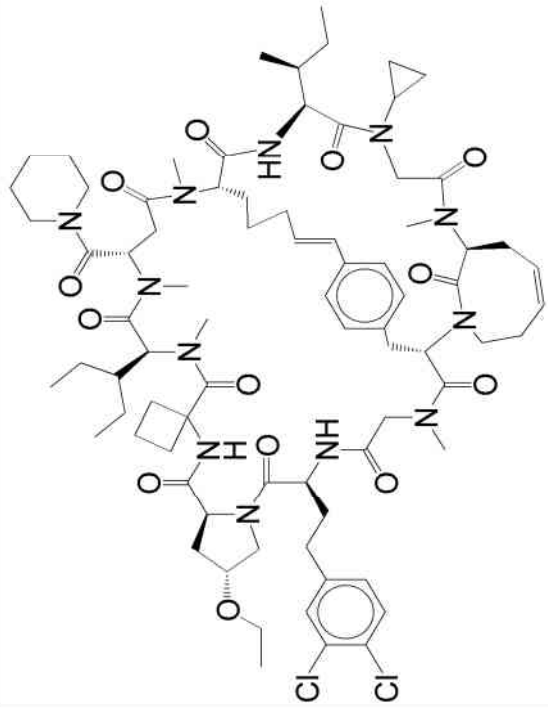
	
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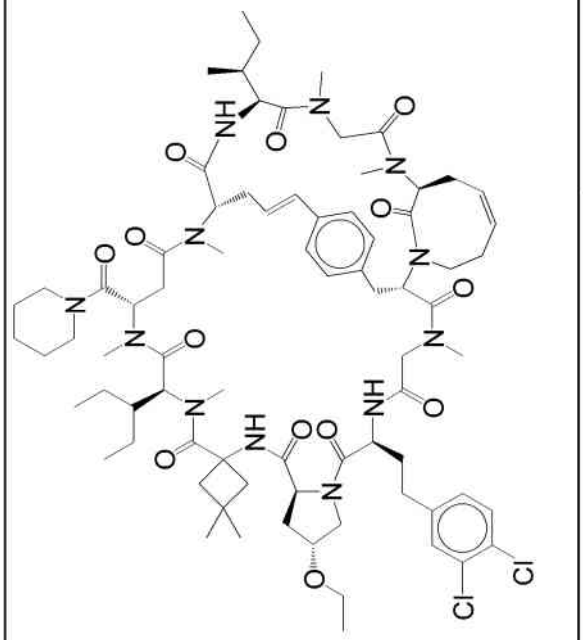
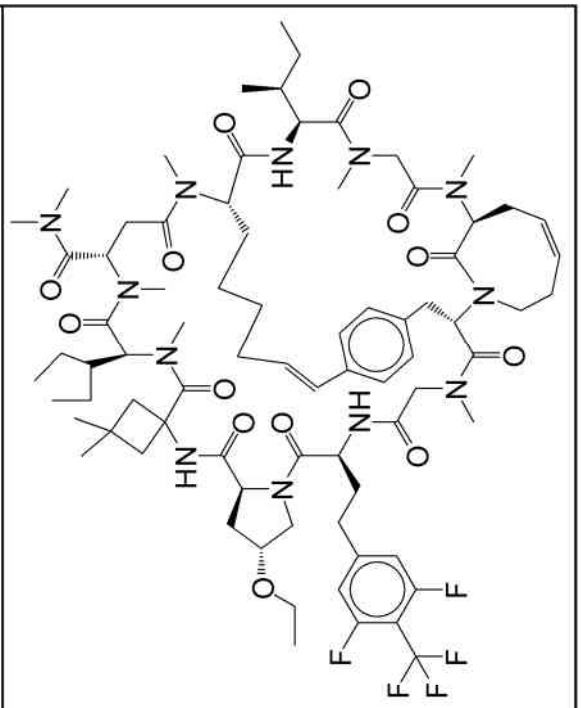
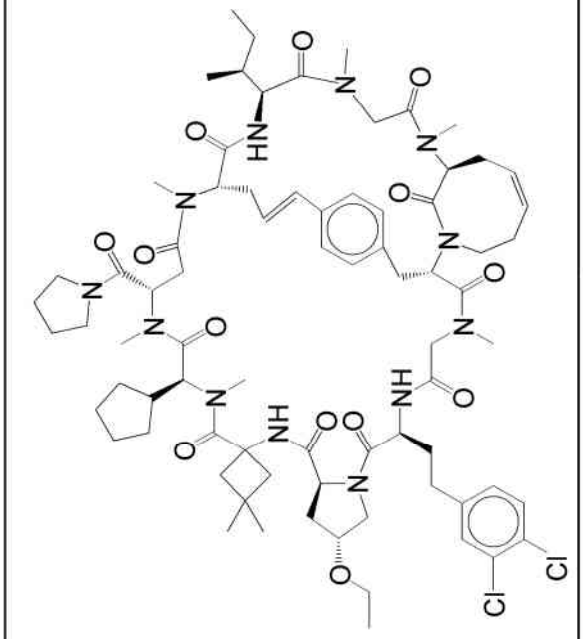
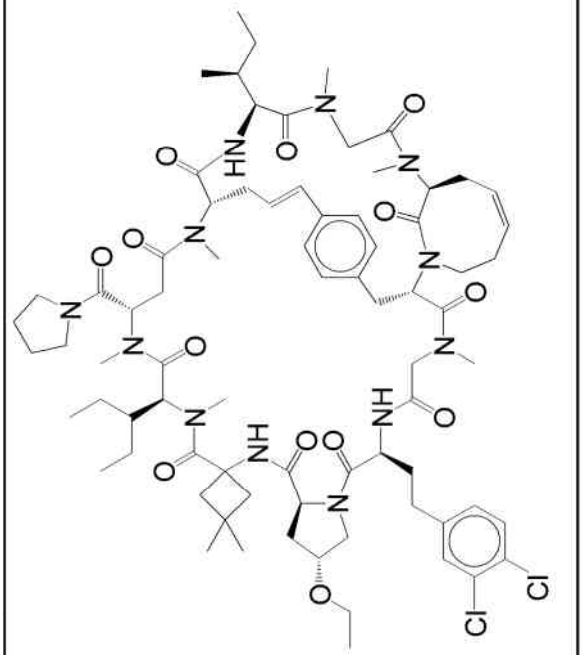
	
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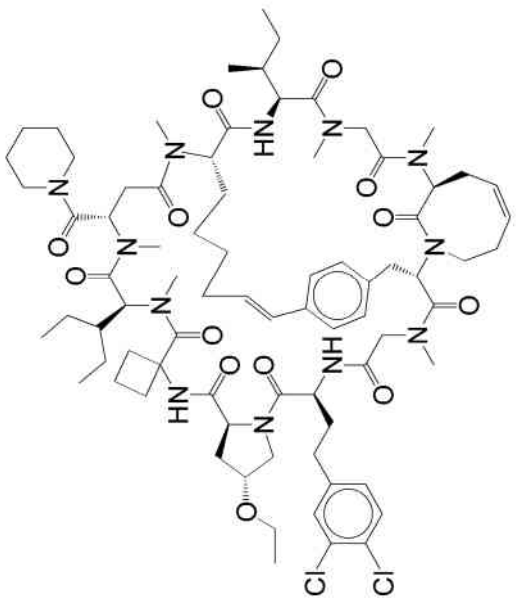
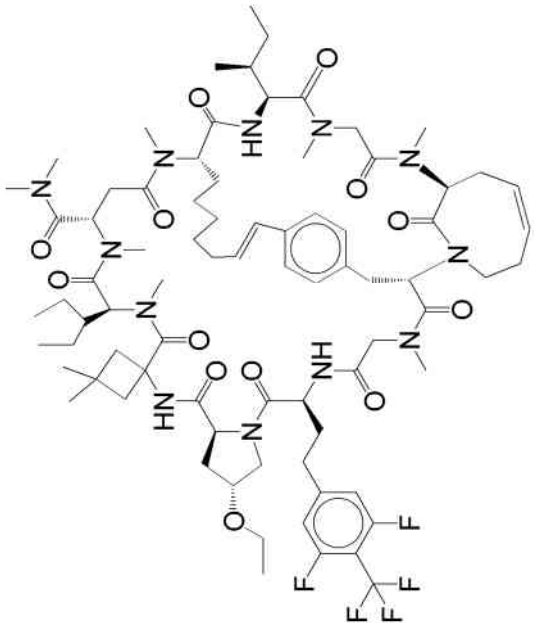
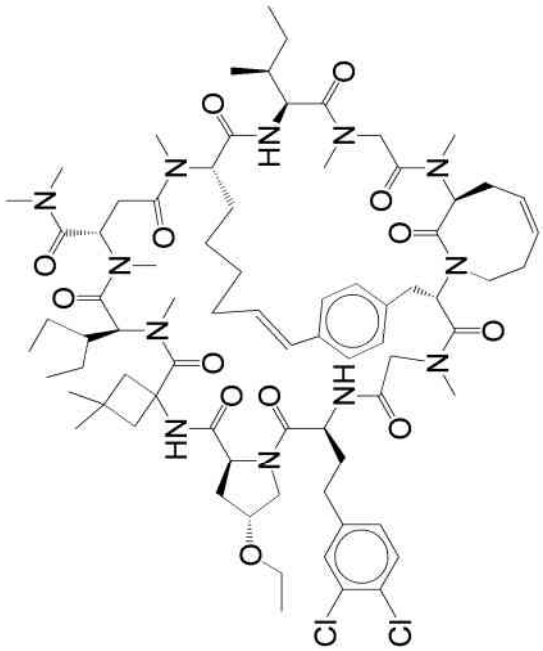
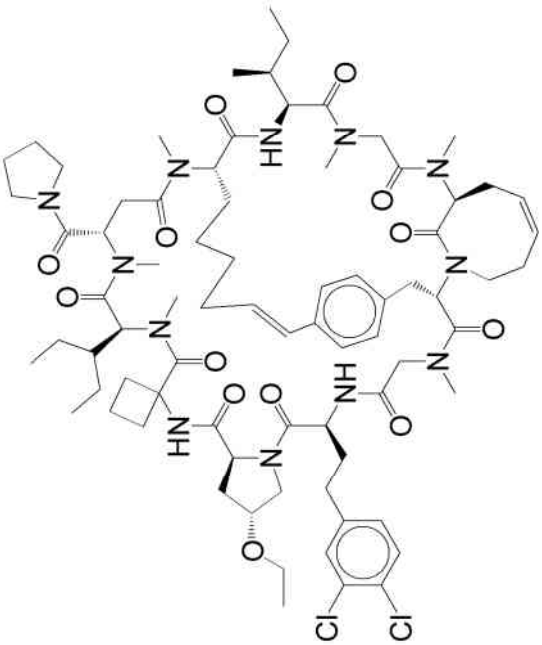
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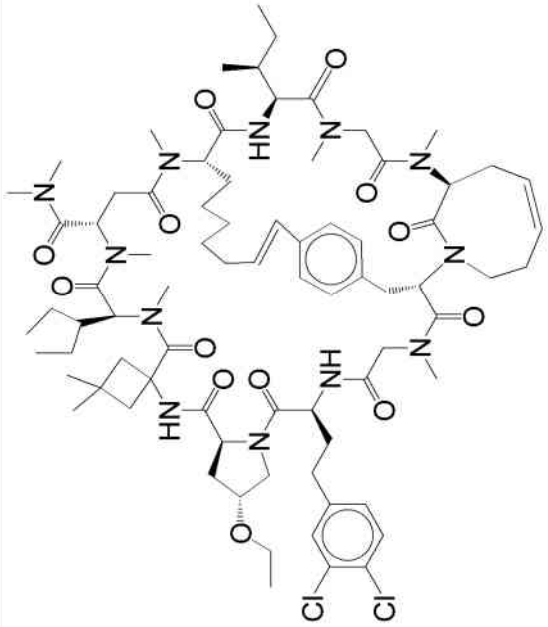
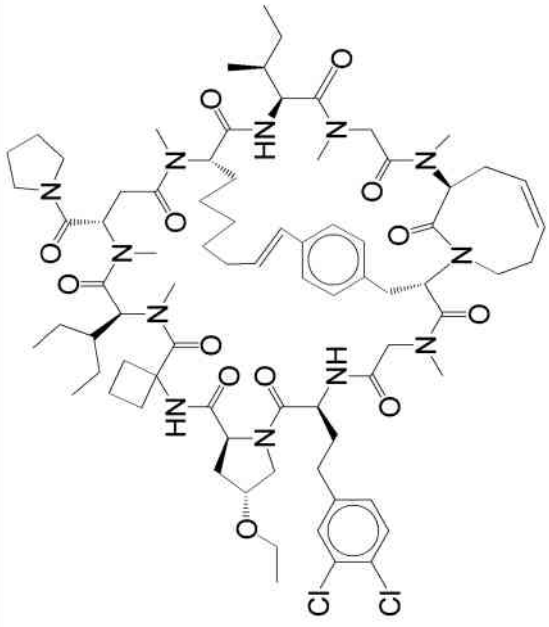
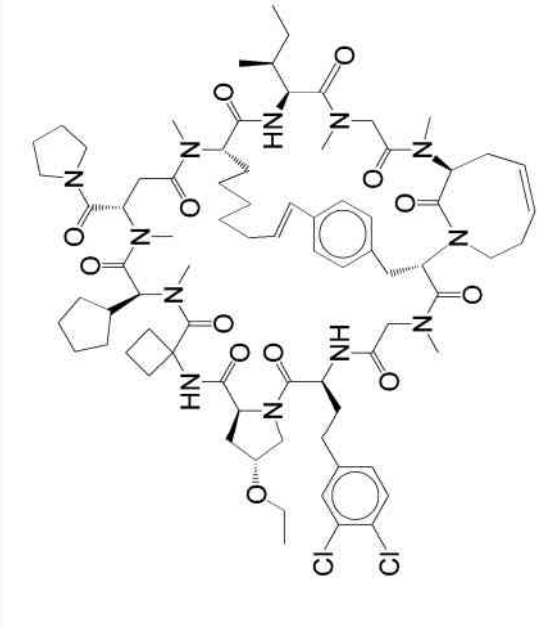
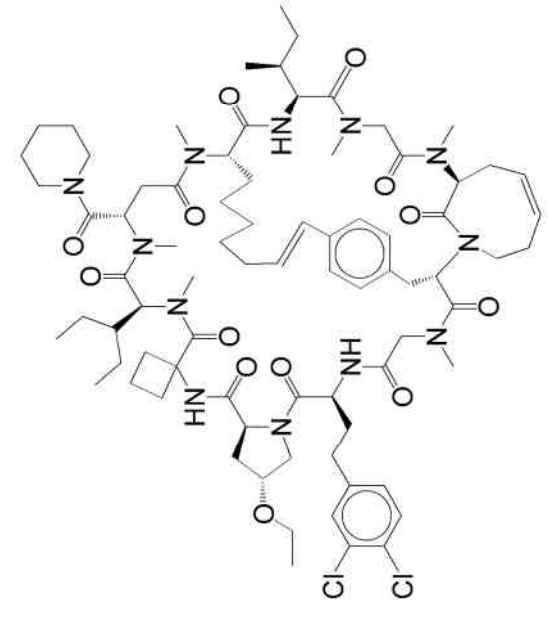
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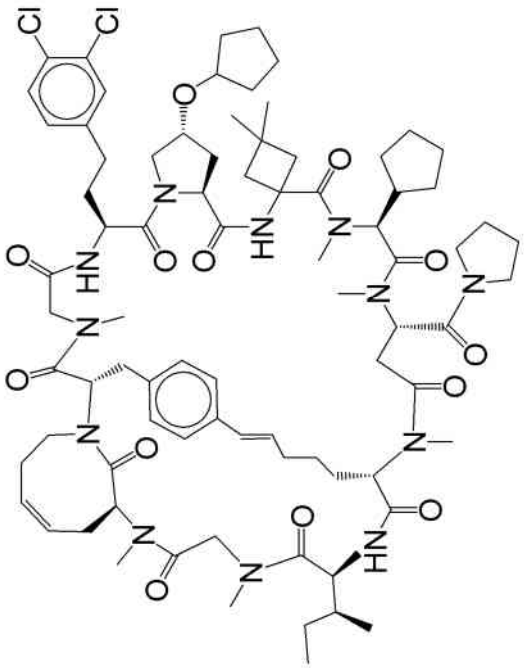
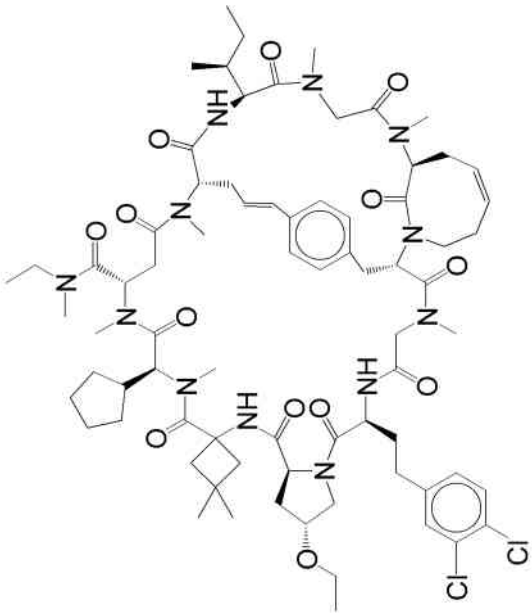
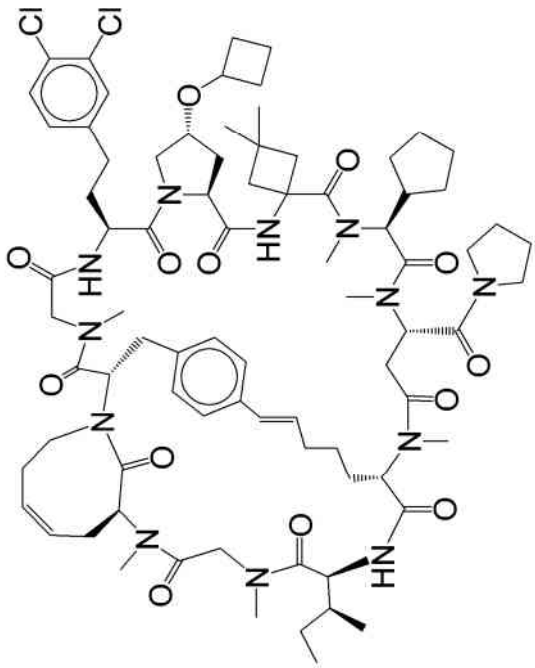
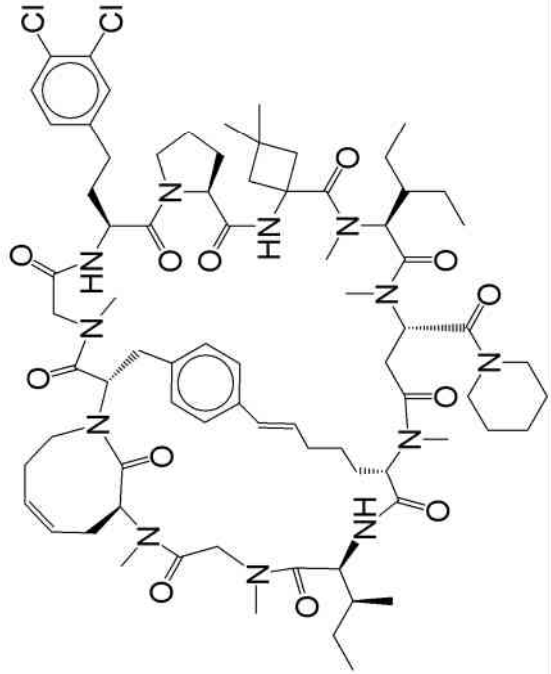
	
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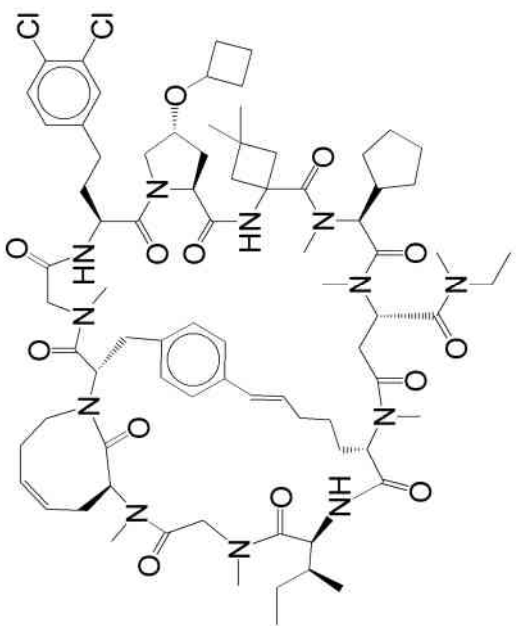
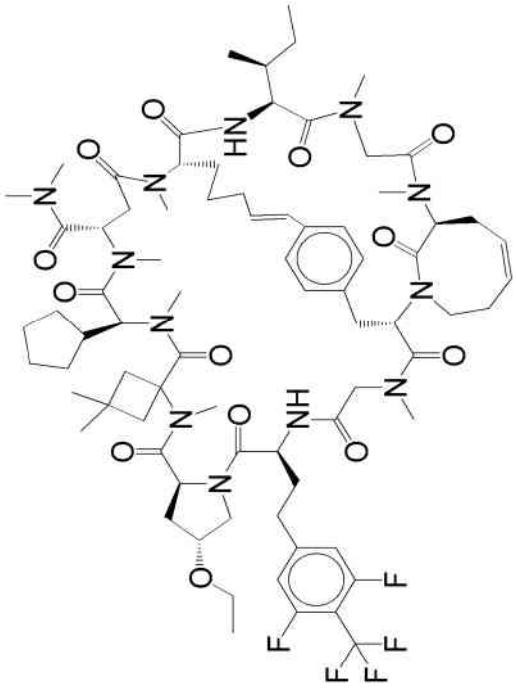
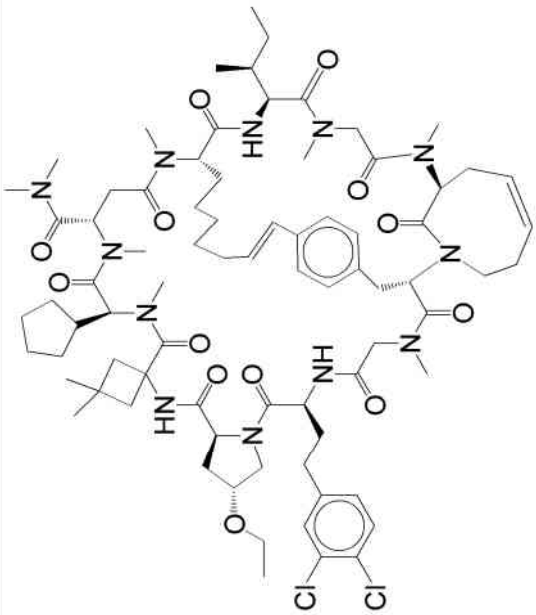
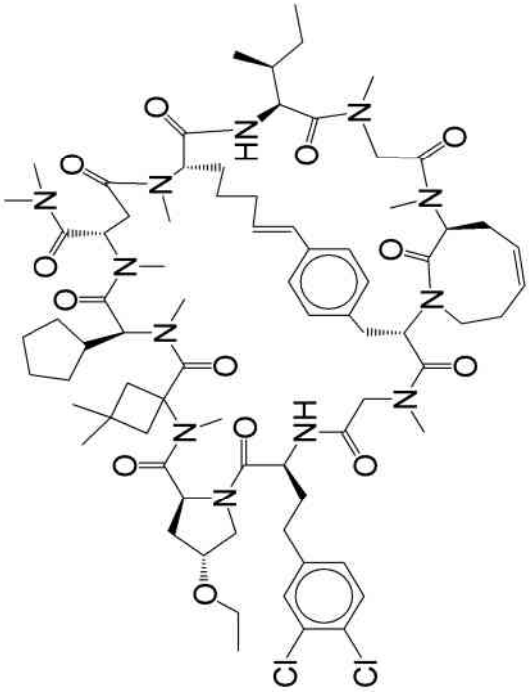
	
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PP3037	PP3039

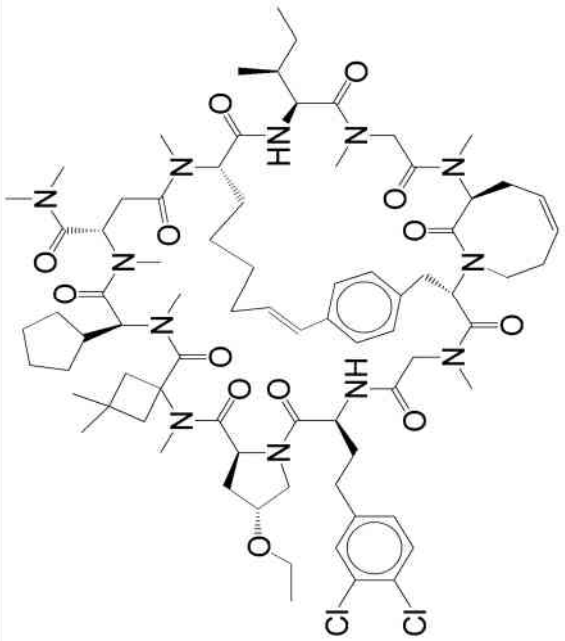
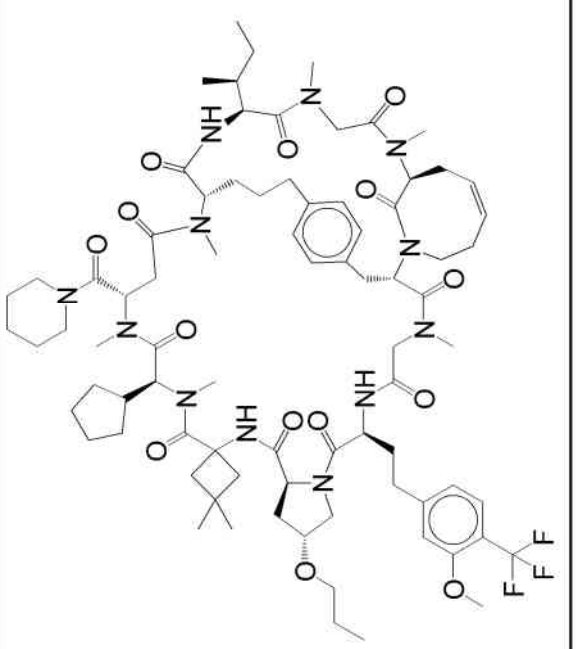
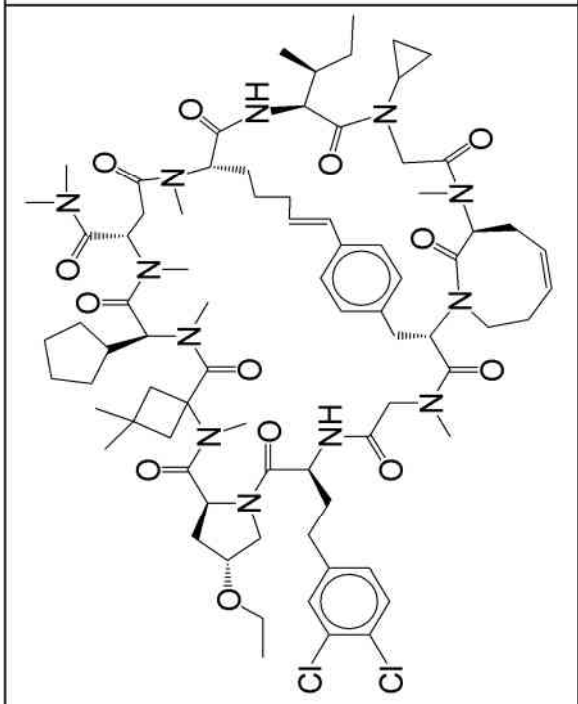
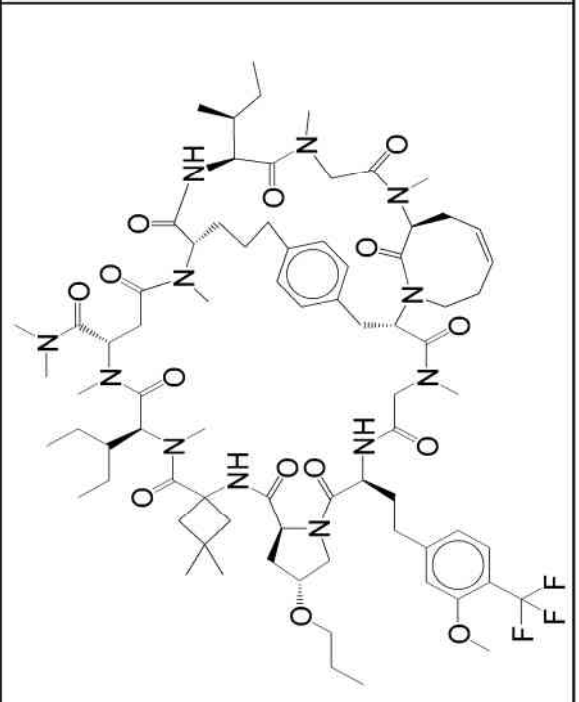
	
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PP304 1	PP304 3

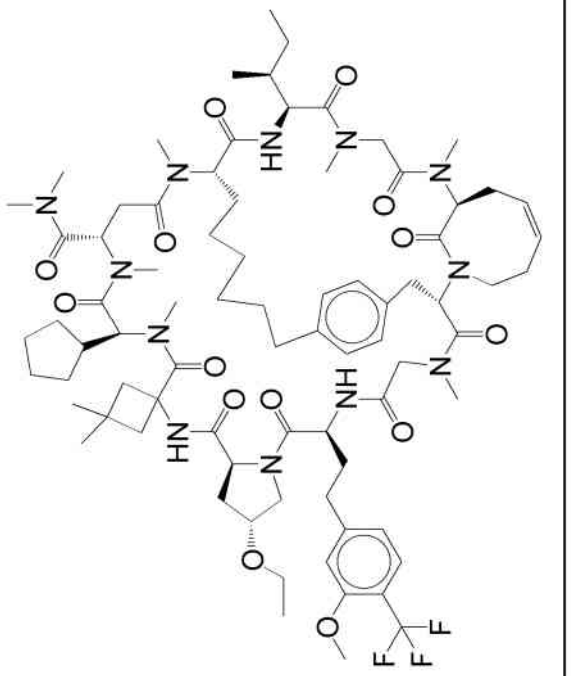
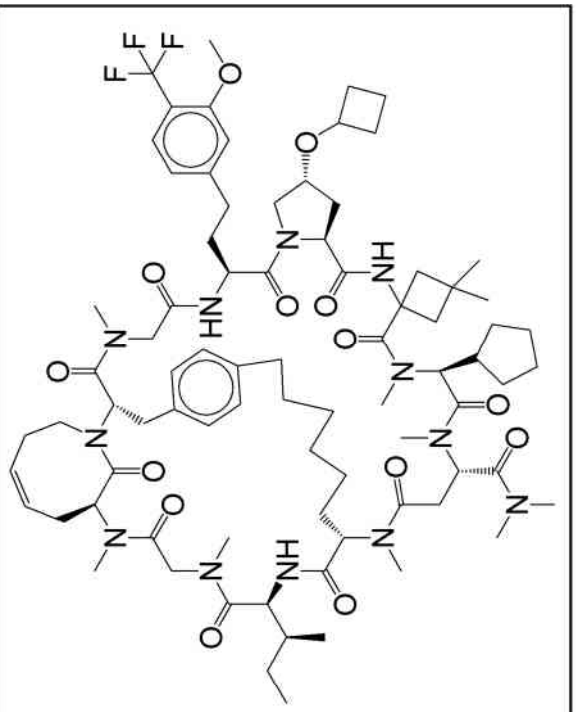
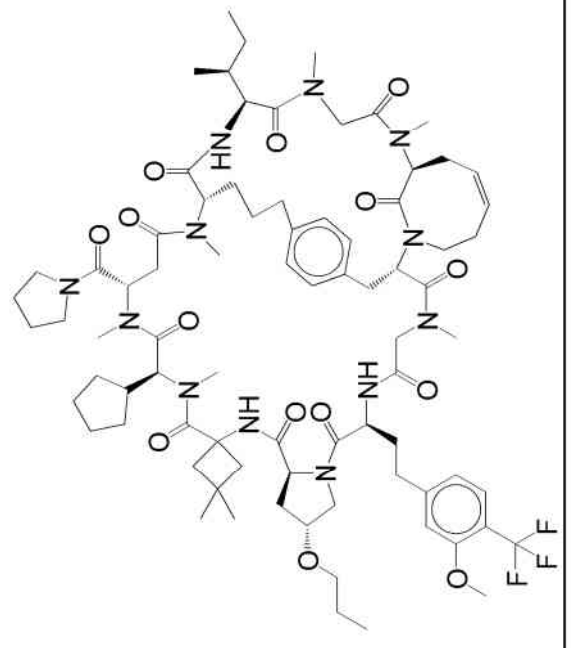
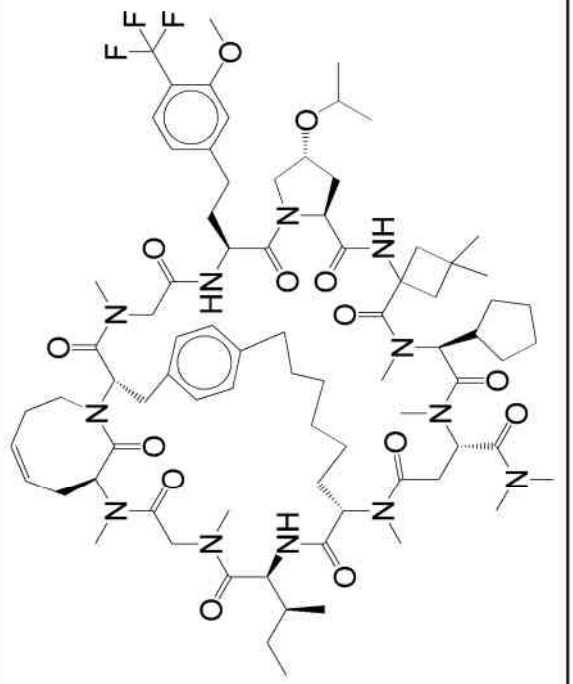
	
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PP304 5	PP304 7

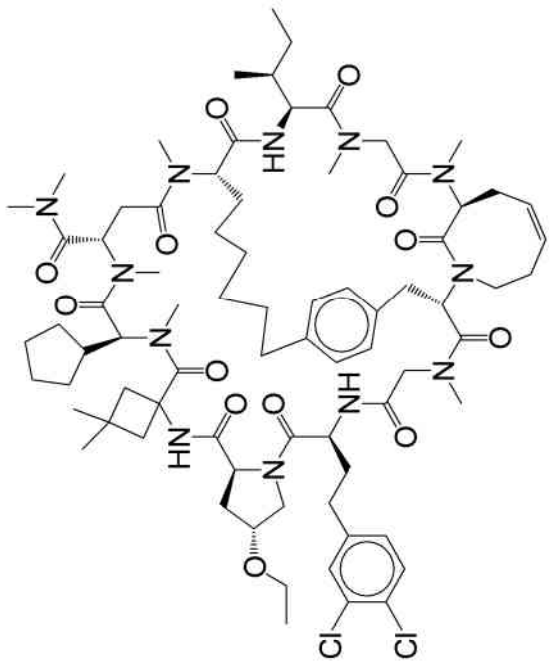
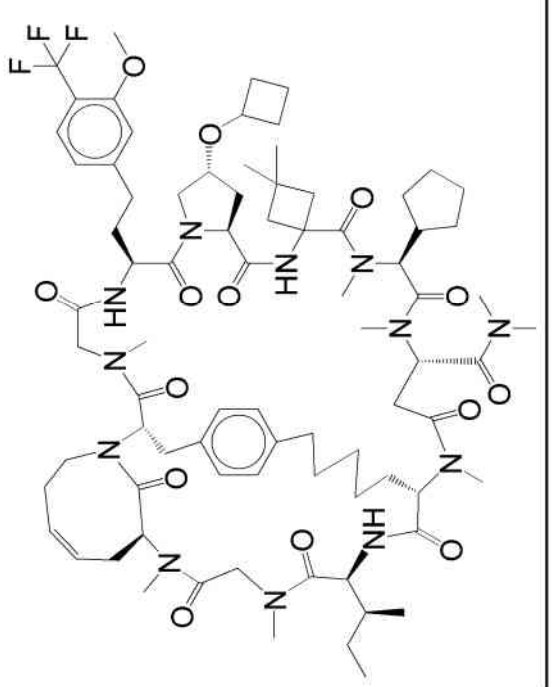
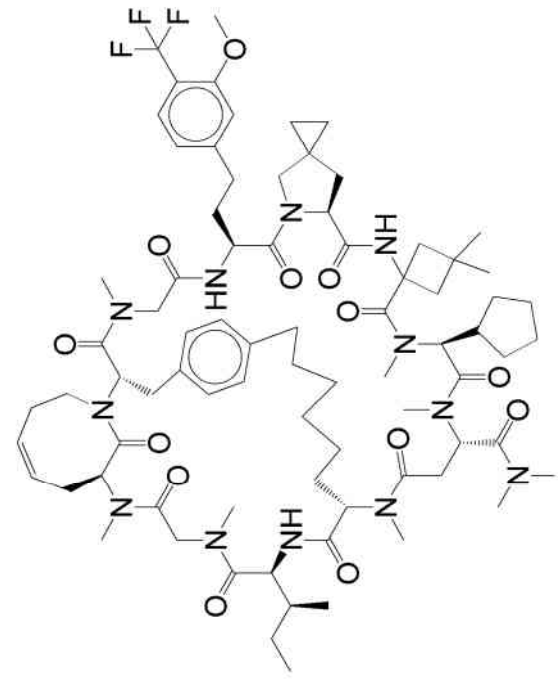
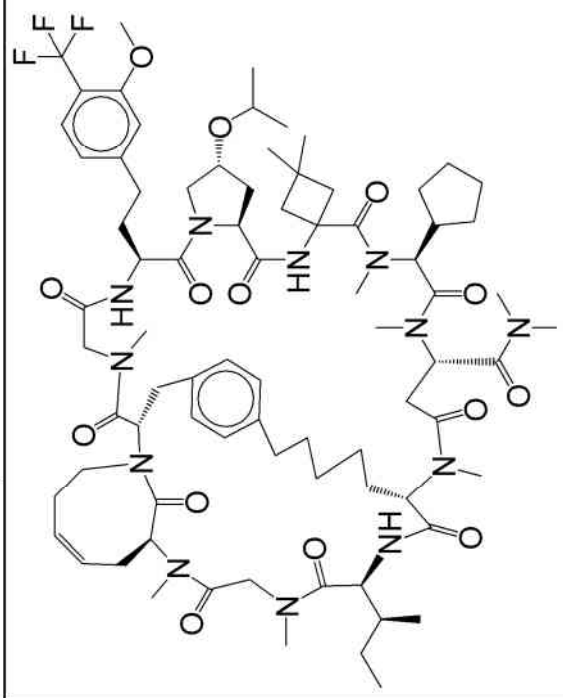
	
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PP3049	PP3051

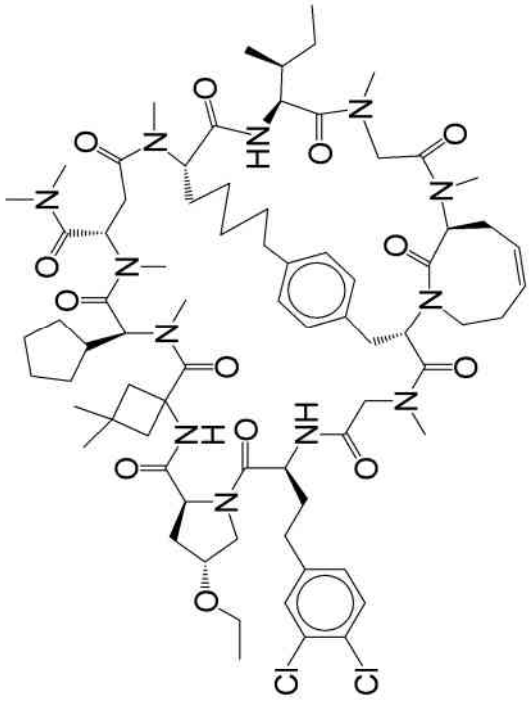
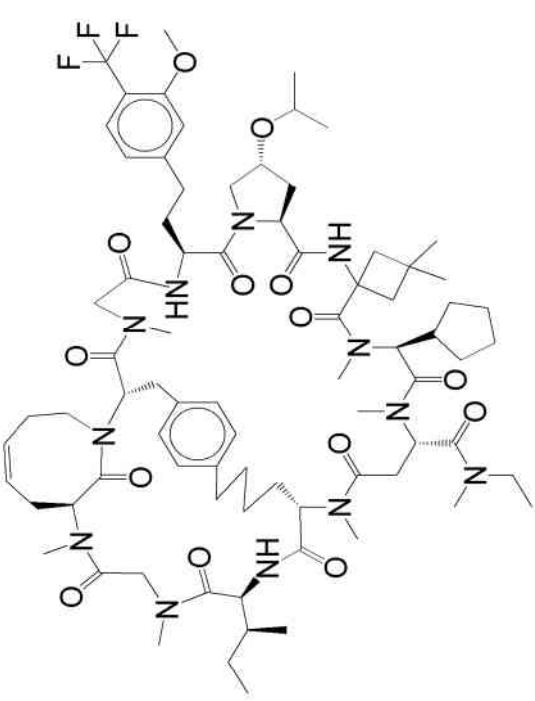
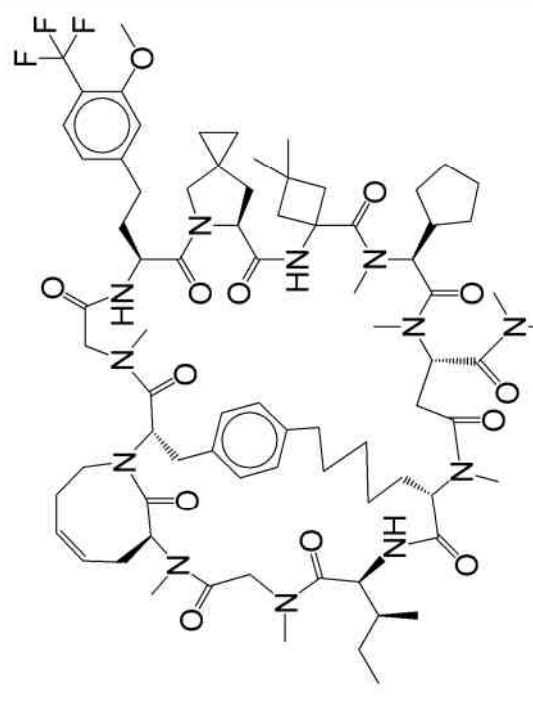
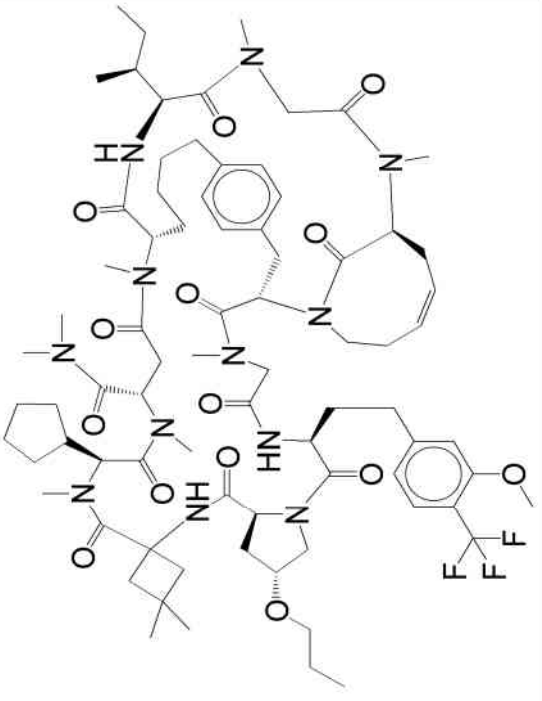
	
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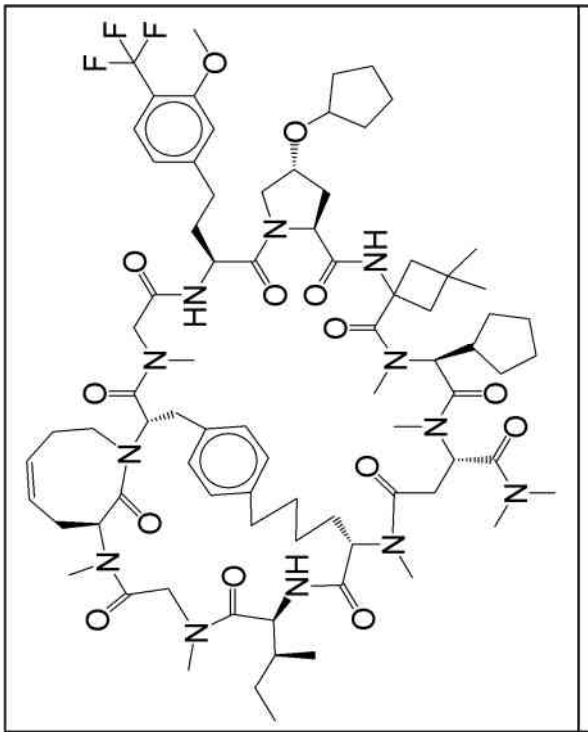
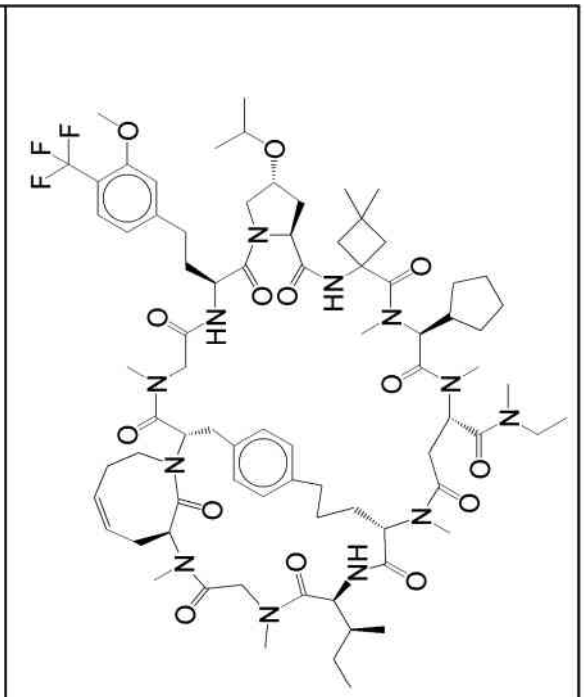
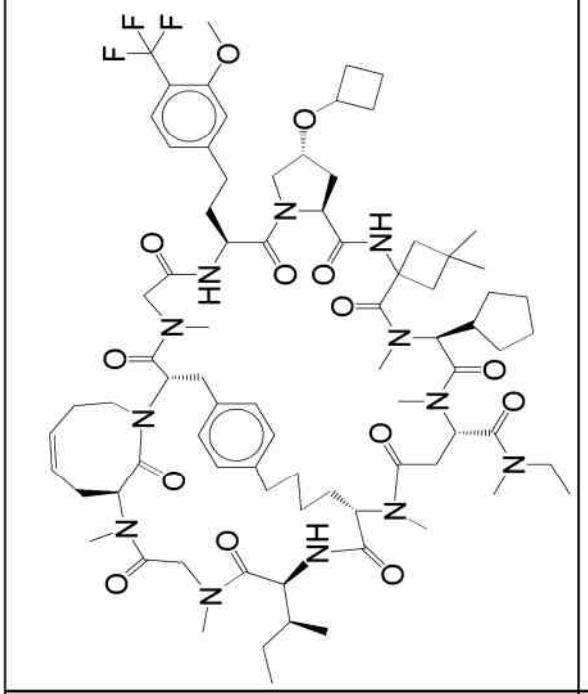
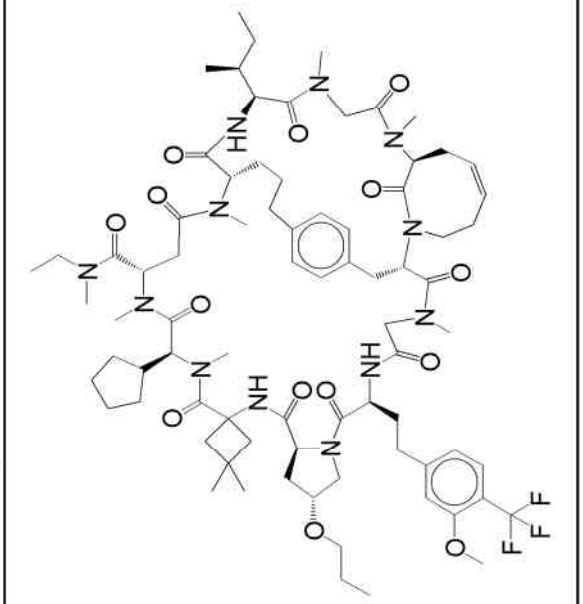
	
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PP3057	PP3059

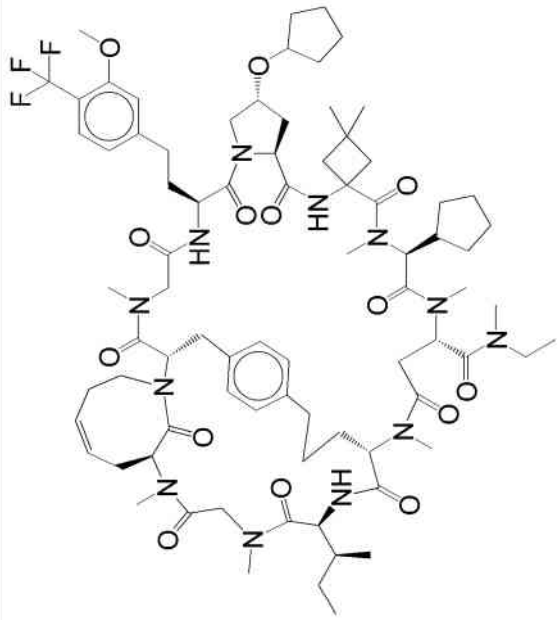
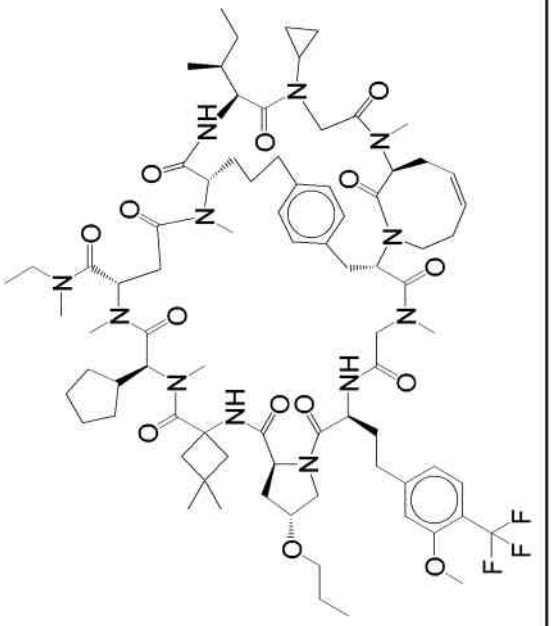
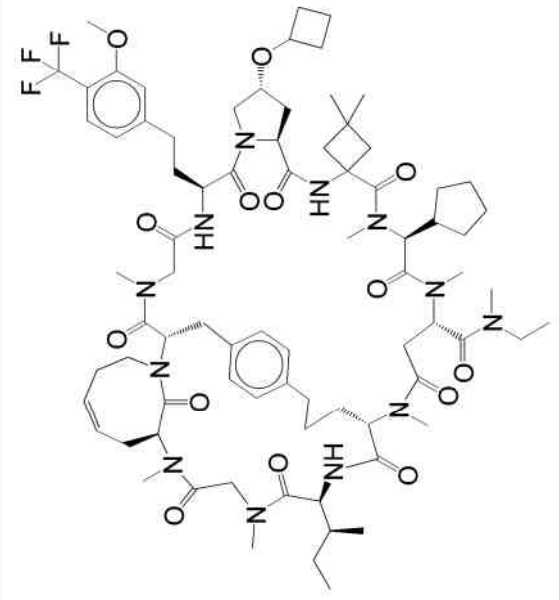
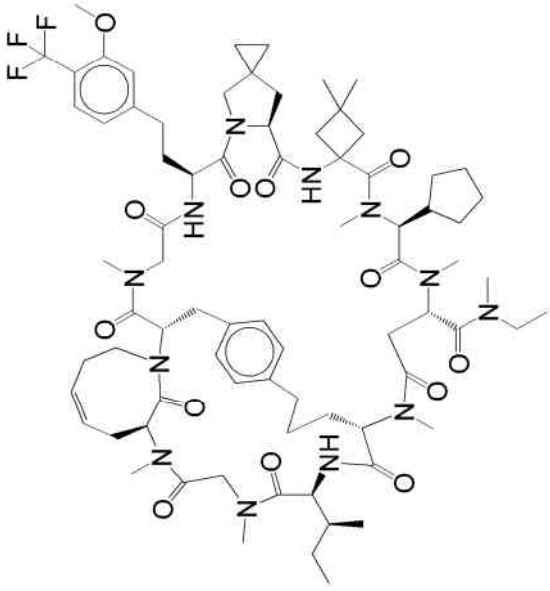
	
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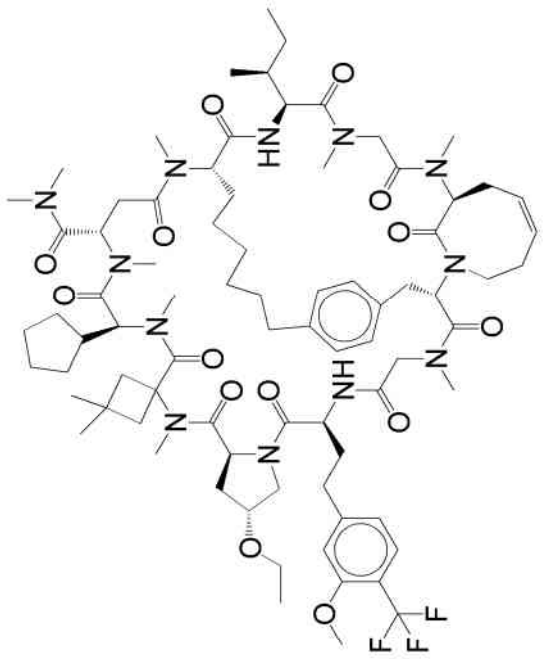
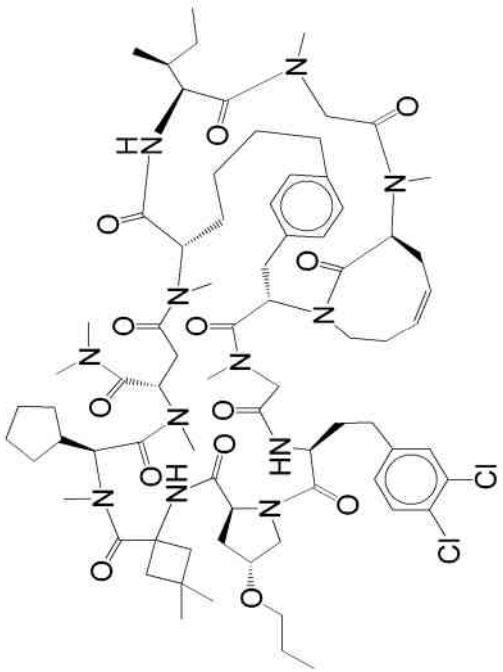
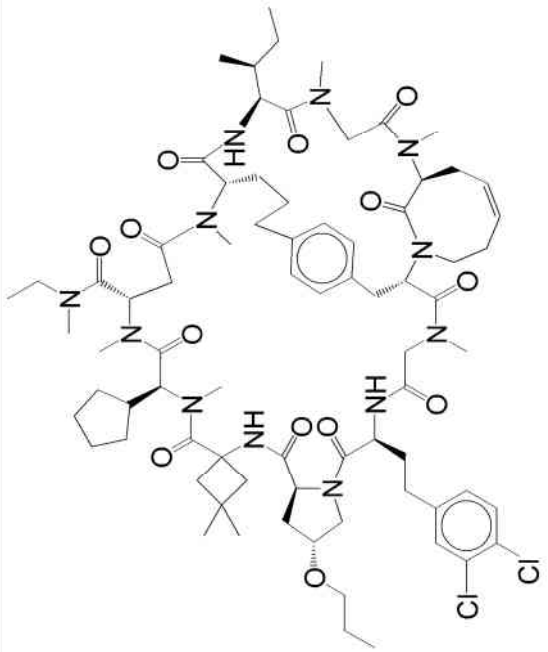
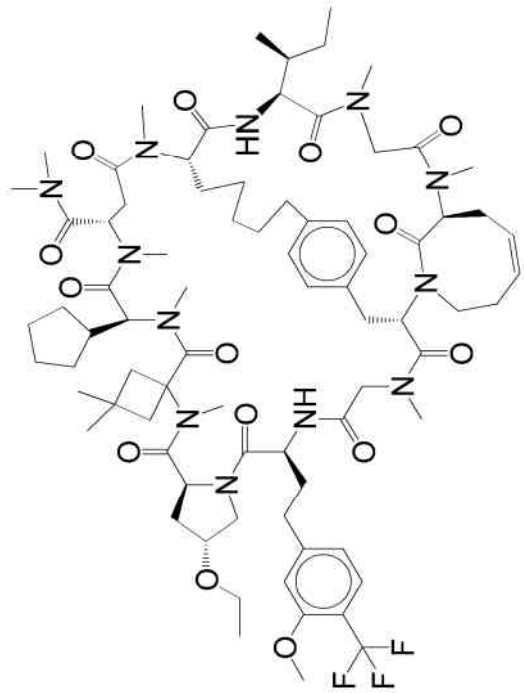
	
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PP306 5	PP306 7

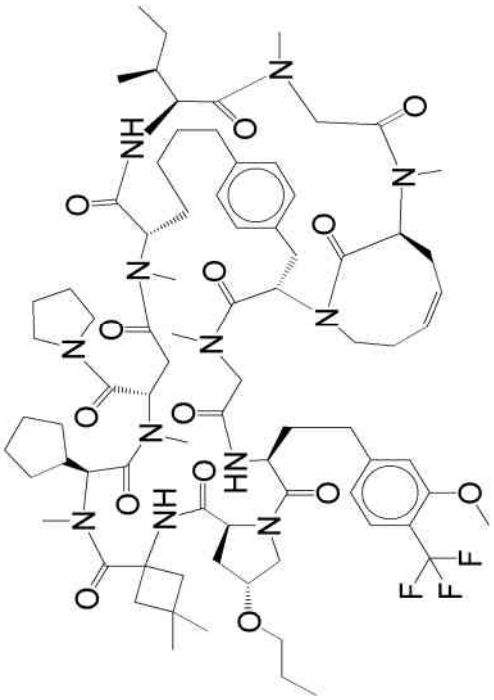
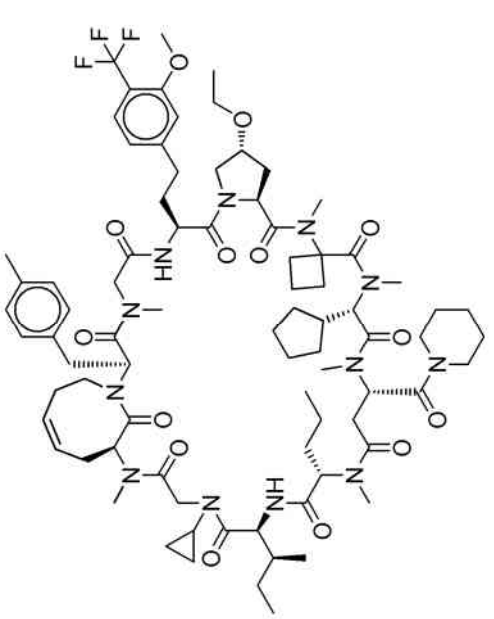
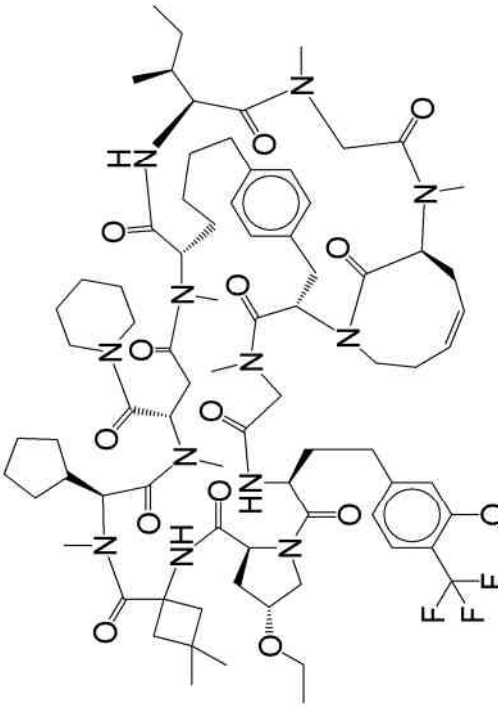
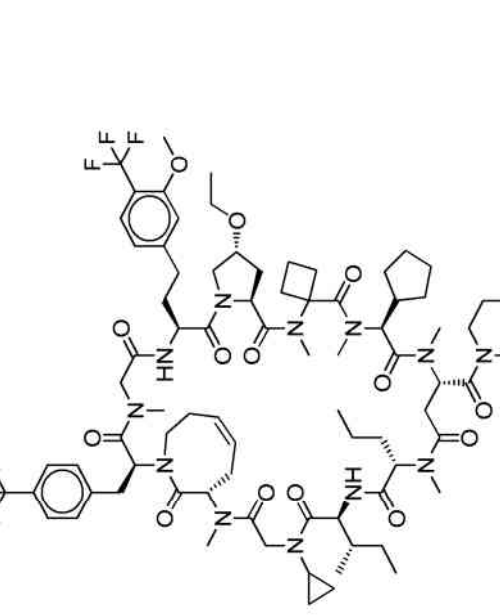
	
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PP306 9	PP307 2

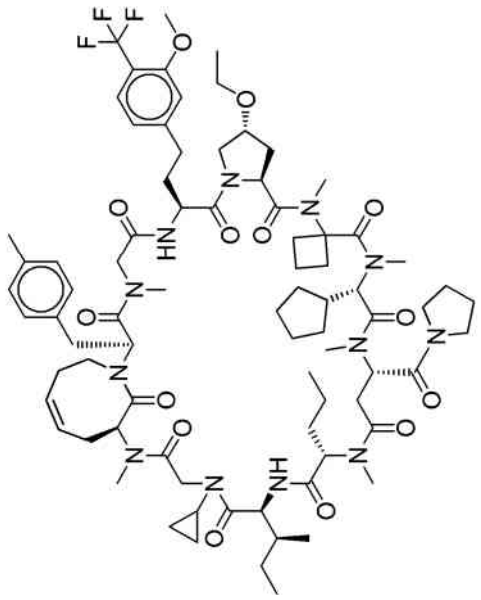
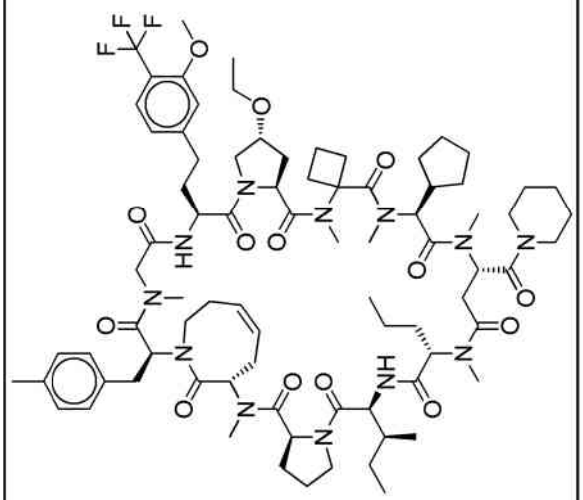
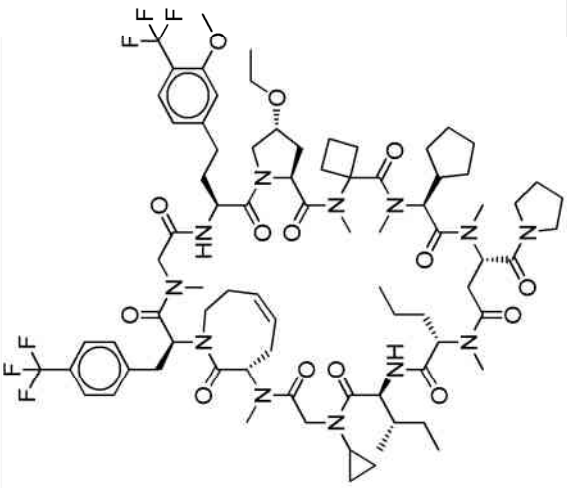
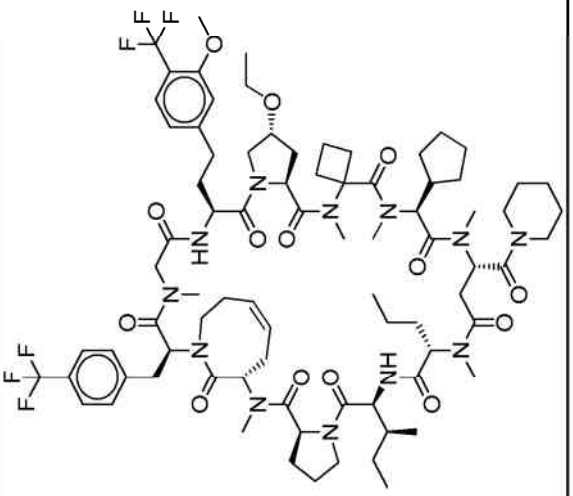
	
PP307 6	PP307 8
	
PP307 4	PP307 7

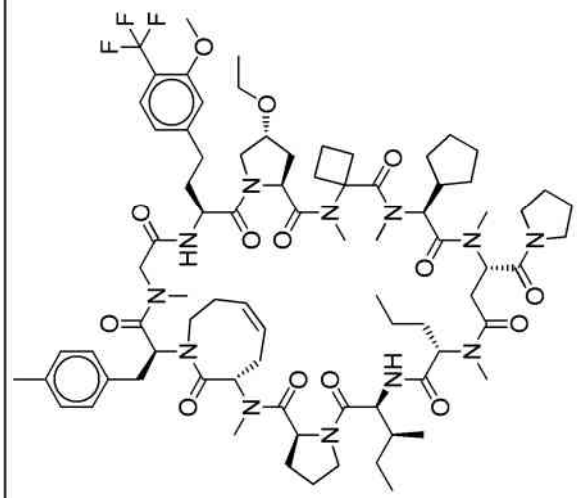
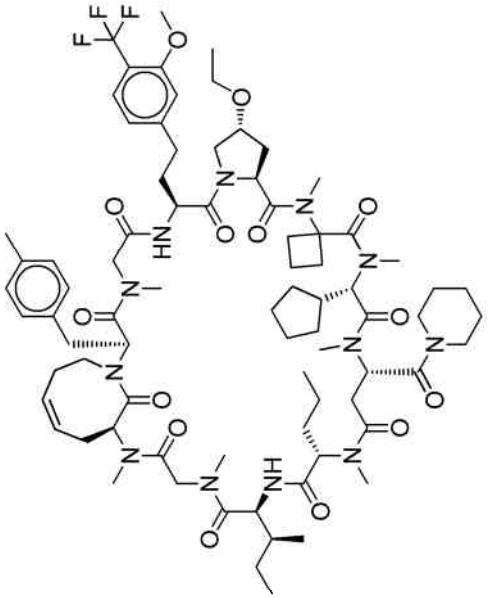
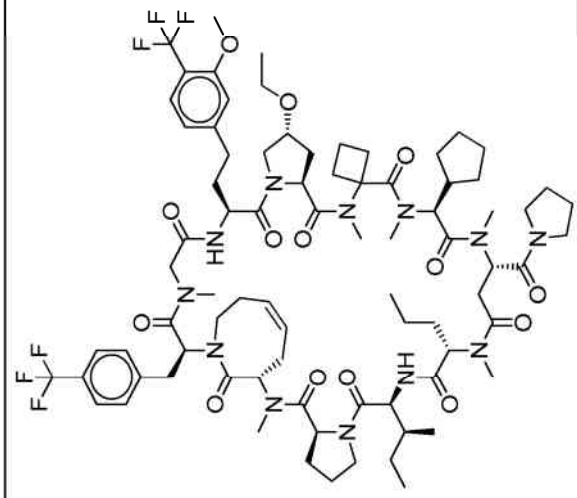
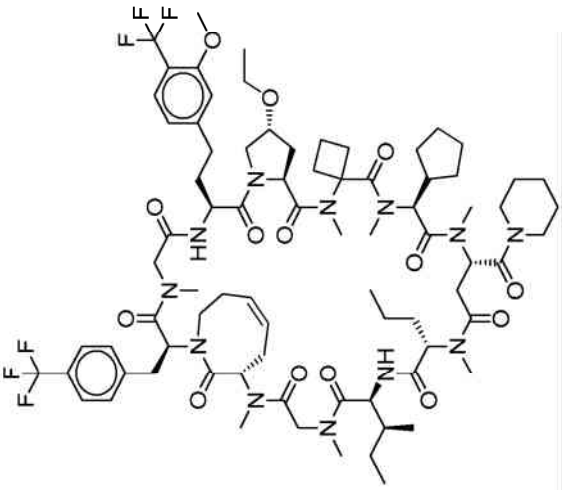
	
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PP3079	PP3083

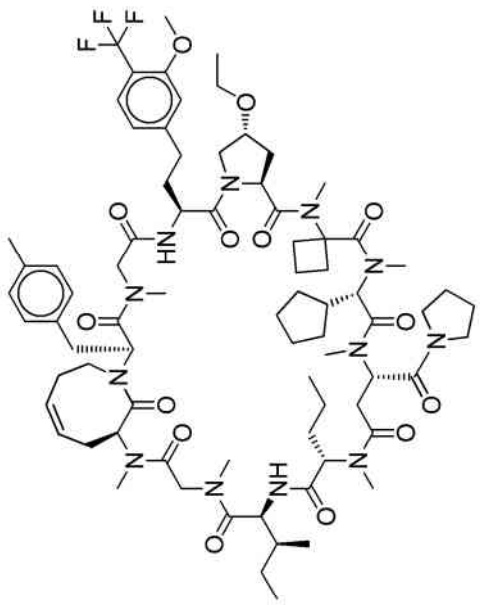
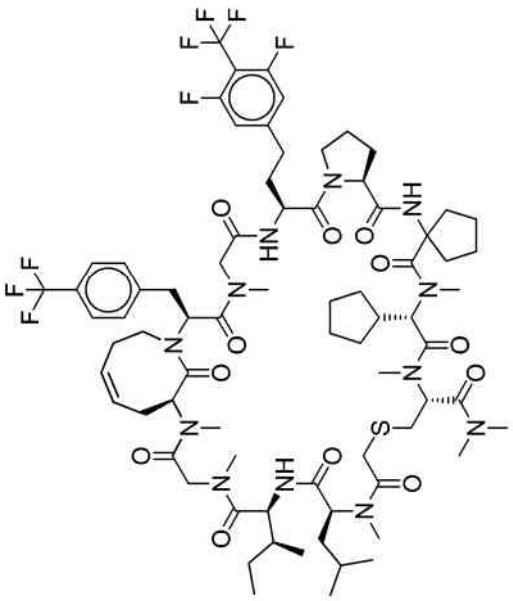
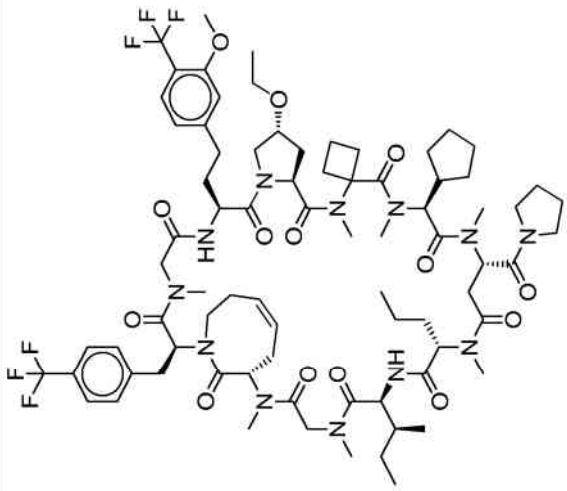
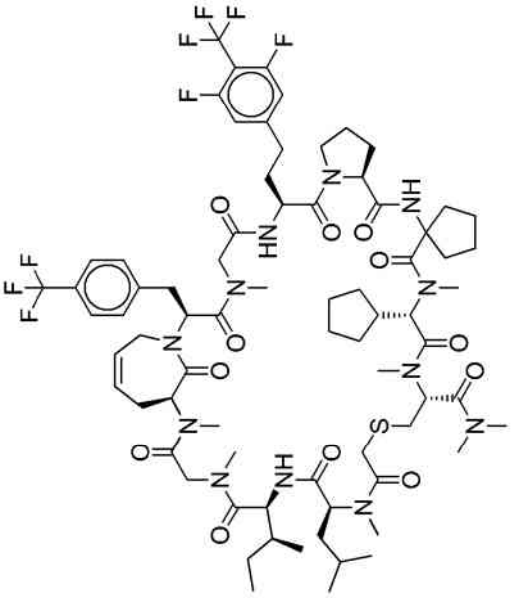
	
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PP308 5	PP308 7

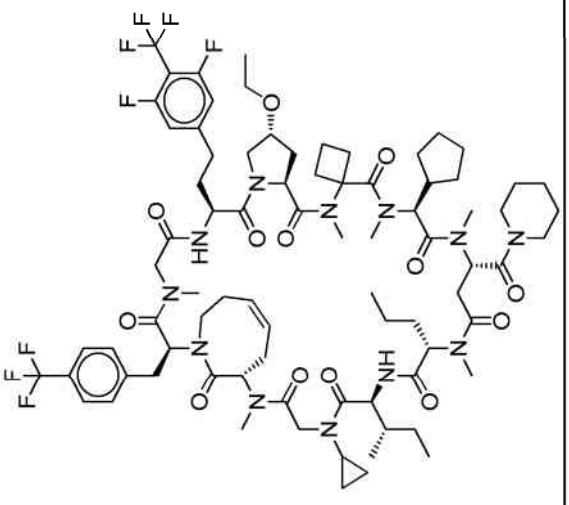
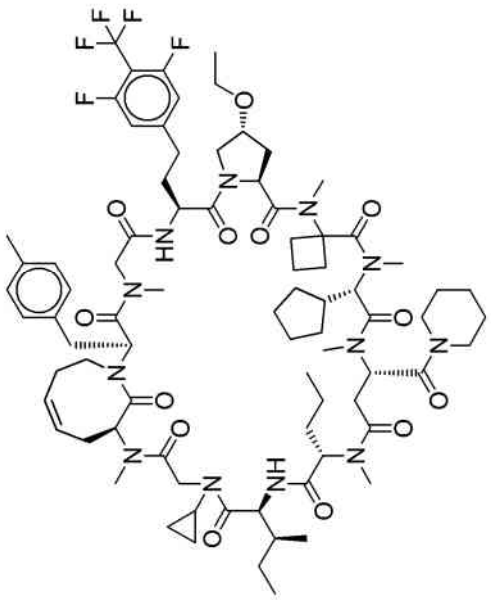
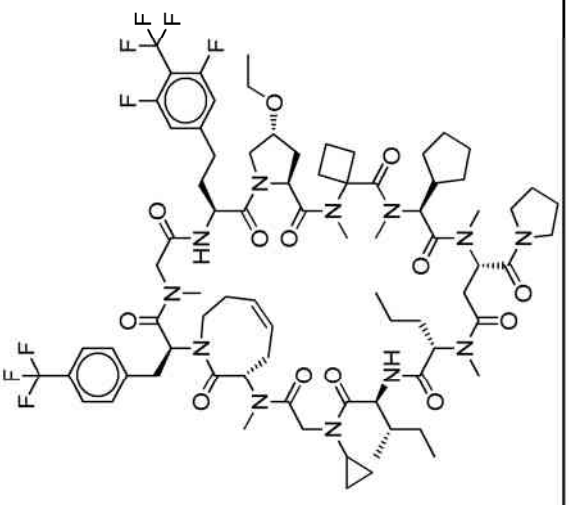
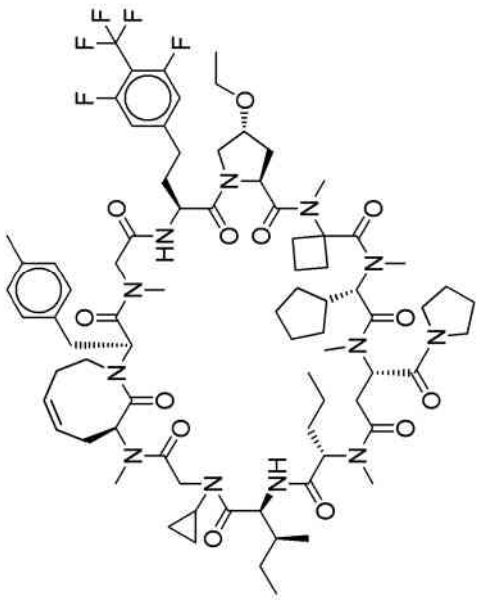
	
PP3090	PP3092
	
PP3089	PP3091

	
PP309 4	PP309 6
	
PP309 3	PP309 5

PP3098	PP3100
	
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PP3102	
PP3104	
PP3101	
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PP310 6	
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PP310 5	
PP310 8	

PP3110	
PP3111	
PP3112	
PP3113	

PP311 5	PP311 7
PP311 4	PP311 6

PP3119	PP3121
PP3118	PP3120

[Industrial Applicability]

[1168]

The present invention provides cyclic compounds that selectively inhibit KRAS.

[CLAIMS]

[Claim 1] A compound which is (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,2,14,18,21,24,36-octamethyl-10-[(1S)-1-methylpropyl]-3,9,12,15,19,22,25,31,34,37,45-undecaoxo-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-17-carboxamide.

[Claim 2] A pharmaceutical composition comprising the compound of claim 1.

[Claim 3] Use of a pharmaceutical composition in the manufacture of a medicament for selectively inhibiting KRAS in a subject, wherein the composition comprises the compound according to claim 1.

[Claim 4] Use of a pharmaceutical composition in the manufacture of a medicament for treating or preventing cancer in a subject, wherein the composition comprises an effective amount of the compound according to claim 1.

[Claim 5] The use according to claim 4, wherein the cancer is lung cancer.

[Claim 6] The use according to claim 4, wherein the subject is a human.

[Claim 7] A solvate of (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,2,14,18,21,24,36-octamethyl-10-[(1S)-1-methylpropyl]-3,9,12,15,19,22,25,31,34,37,45-undecaoxo-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-17-carboxamide.

[Claim 8] The solvate according to claim 7, which is a hydrate.

[Claim 9] A pharmaceutical composition comprising the solvate of claim 7 or 8.

[Claim 10] Use of a pharmaceutical composition in the manufacture of a medicament for selectively inhibiting KRAS in a subject, wherein the composition comprises the solvate according to claim 7 or 8.

[Claim 11] Use of a pharmaceutical composition in the manufacture of a medicament for treating or preventing cancer in a subject, wherein the composition comprises an effective amount of the solvate according to claim 7 or 8.

[Claim 12] The use according to claim 11, wherein the cancer is lung cancer.

[Claim 13] The use according to claim 11, wherein the subject is a human.

[Claim 14] A salt of (1S,4S,10S,13S,17S,20S,26S,28R,32S,38S,42Z)-20-cyclopentyl-28-ethoxy-32-[2-[3-methoxy-4-(trifluoromethyl)phenyl]ethyl]-N,N,2,14,18,21,24,36-octamethyl-10-[(1S)-1-methylpropyl]-3,9,12,15,19,22,25,31,34,37,45-undecaoxo-13-propyl-38-[[4-(trifluoromethyl)phenyl]methyl]spiro[2,8,11,14,18,21,24,30,33,36,39-undecazatetracyclo[37.5.1.$0^{4,8}$.$0^{26,30}$]pentatetracont-42-ene-23,1'-cyclobutane]-17-carboxamide, or a solvate thereof.

[Claim 15] A pharmaceutical composition comprising the salt of claim 14, or a solvate thereof.

[Claim 16] Use of a pharmaceutical composition in the manufacture of a medicament for selectively inhibiting KRAS in a subject, wherein the composition comprises the salt of claim 14, or a solvate thereof.

[Claim 17] Use of a pharmaceutical composition in the manufacture of a medicament for treating or preventing cancer in a subject, wherein the composition comprises an effective amount of the salt of claim 14, or a solvate thereof.

[Claim 18] The use according to claim 17, wherein the cancer is lung cancer.

[Claim 19] The use according to claim 17, wherein the subject is a human.