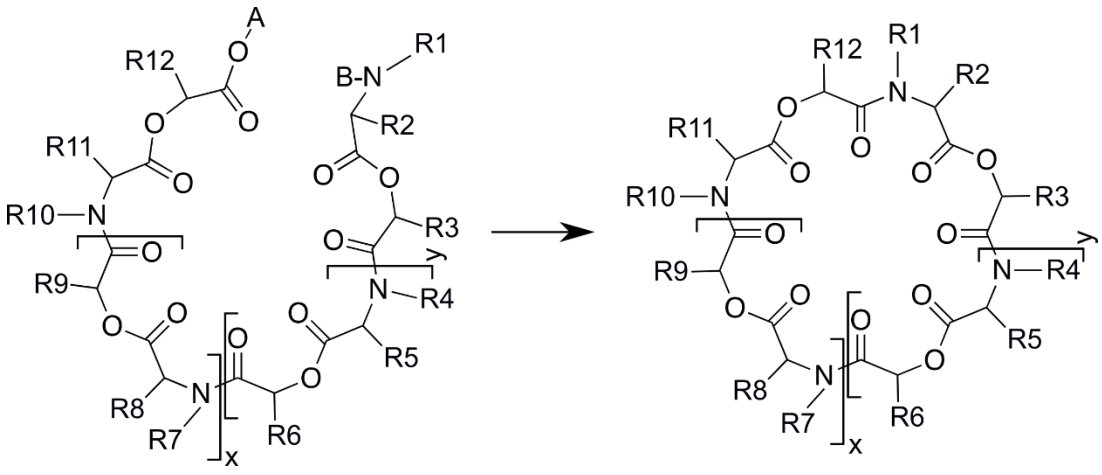
Patent claims

1. A method for the synthesis of cyclic depsipeptides according to the general formula (I) from depsipeptides according to the general formula (II):



(II) (I)

wherein B is an amine protecting group and A is a carboxylic acid protecting group,

the method comprising the steps of:

- deprotecting the amine group which is protected by the B group, thereby obtaining a deprotected amine group;
- deprotecting the carboxylic acid which is protected by the A group, thereby obtaining a deprotected carboxylic acid group;
- condensation of the deprotected amine and carboxylic acid groups by a coupling agent, thereby obtaining the cyclic depsipeptide (I)

whereby R2 and R8 each, independent of each other, represent hydrogen, straight-chain or branched C1-C8-alkyl, in particular methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, sec-pentyl, hexyl, isohexyl, sec-hexyl, heptyl, isoheptyl, sec-heptyl, tert-heptyl, octyl, isooctyl, sec-octyl, straight-chain or branched halogenated C1-C8 alkyl, in particular fluorinated sec-butyl, hydroxy-C1-C6-alkyl, in particular hydroxymethyl, 1-hydroxyethyl, C1-C4-alkanoyloxy-C1-C6-alkyl, in particular acetoxymethyl, 1-acetoxyethyl, C1-C4-alkoxy-C1-C6-alkyl, in particular methoxymethyl, 1-methoxyethyl, aryl-C1-C4-alkyloxy-C1-C6-alkyl, in particular benzyloxymethyl, 1-benzyloxyethyl, mercapto-C1-C6-alkyl, in particular mercaptomethyl, C1-C4-alkylthio-C1-C6-alkyl, in particular methylthioethyl, C1-C4-alkylsulphinyl-C1-C6-alkyl, in

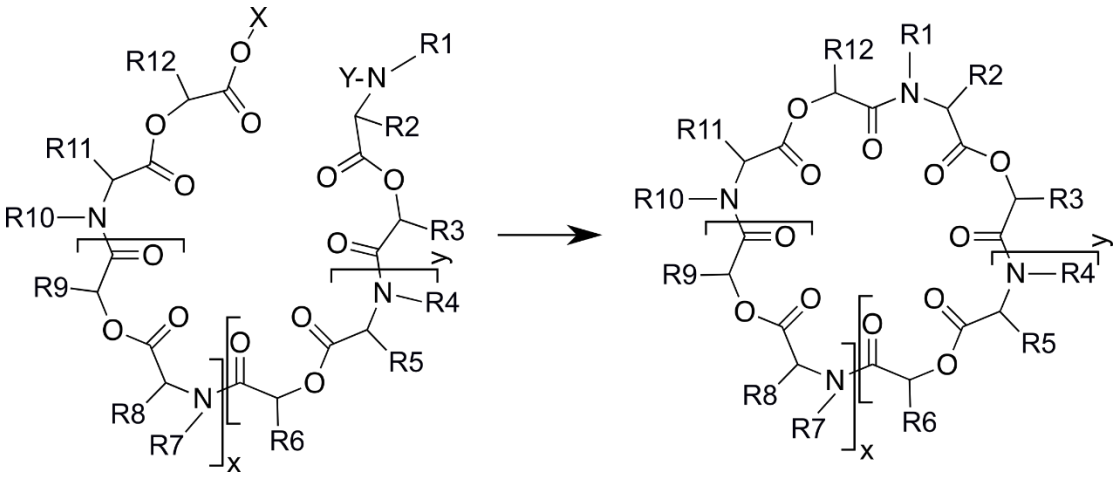
particular methylsulphinylethyl, C1-C4-alkylsulphonyl-C1-C6-alkyl, in particular methylsulphonylethyl, carboxy-C1-C6-alkyl, in particular carboxymethyl, carboxyethyl, C1-C4-alkoxycarbonyl-C1-C6-alkyl, in particular methoxycarbonylmethyl, ethoxycarbonylethyl, C1-C4-arylalkoxycarbonyl-C1-C6-alkyl, in particular benzyloxycarbonylmethyl, carbamoyl-C1-C6-alkyl, in particular carbamoylmethyl, carbamoylethyl, amino-C1-C6-alkyl, in particular aminopropyl, aminobutyl, C1-C4-alkylamino-C1-C6-alkyl, in particular methylaminopropyl, methylaminobutyl, C1-C4-dialkylamino-C1-C6-alkyl, in particular dimethylaminopropyl, dimethylaminobutyl, guanidino-C1-C6-alkyl, in particular guanidinopropyl, C1-C4-alkoxycarbonylamino-C1-C6-alkyl, in particular tert-butoxycarbonylaminopropyl, tert-butoxycarbonylaminobutyl, 9-fluorenylmethoxycarbonyl(Fmoc)amino-C1-C6-alkyl, in particular 9-fluorenylmethoxycarbonyl(Fmoc)aminopropyl, 9-fluorenylmethoxycarbonyl(Fmoc)aminobutyl, C2-C8-alkenyl, in particular vinyl, allyl, butenyl, C3-C7-cycloalkyl, in particular cyclopentyl, cyclohexyl, cycloheptyl, C3-C7-cycloalkyl-C1-C4-alkyl, in particular cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, benzyl, substituted benzyl, phenyl, phenyl-C1-C4-alkyl, in particular phenylmethyl which may optionally be substituted by radicals from the group consisting of halogen, in particular fluorine, chlorine, bromine or iodine,

wherein x is 1, y is 1, R1, R4, R7 and R10 are methyl, R6 and R12 are methyl, R5 and R11 are, independent of each other, straight-chain or branched C1-C4-alkyl or straight-chain or branched halogenated C1-C4-alkyl and R3 and R9 are, independent of each other, benzyl or substituted benzyl, and

wherein the coupling agent is T3P® (Propylphosphonic anhydride, 2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide, PPACA).

2. The method according to claim 1, wherein R3 and/or R9 are p-morpholino substituted benzyl.

3. The method according to claim 1 or 2, whereby the cyclic depsipeptides according to the general formula (I) are synthesized from depsipeptides according to the general formula (IIa):



(IIa) (I)

wherein Y is an amine protecting group and X is a carboxylic acid protecting group,

the method comprising the steps of:

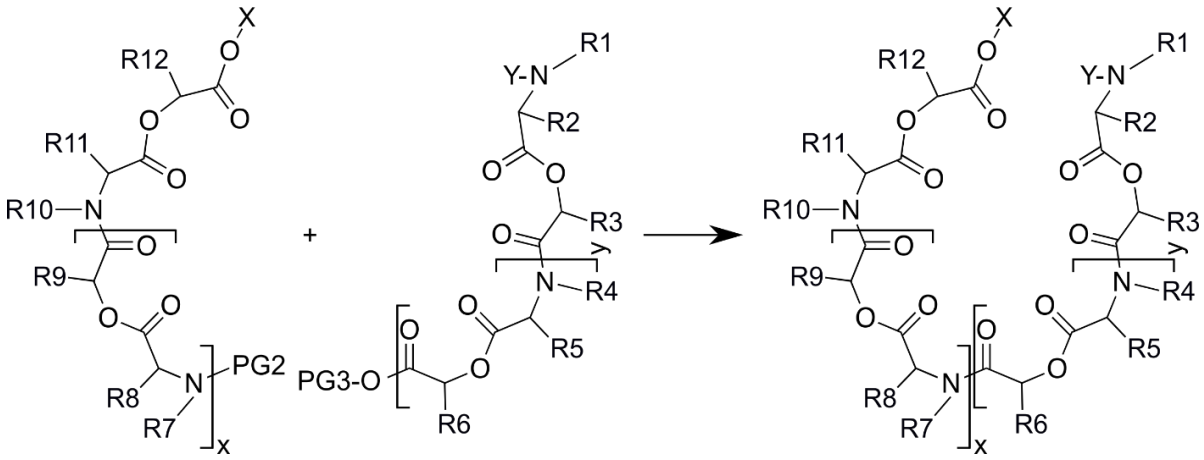
- deprotecting the amine group which is protected by the Y group in the presence of an acid, thereby obtaining a deprotected amine group;
- deprotecting the carboxylic acid which is protected by the X group via hydrogenolysis, thereby obtaining a deprotected carboxylic acid group;
- condensation of the deprotected amine and carboxylic acid groups, thereby obtaining the cyclic depsipeptide (I).

4. The method according to any of the claims 1 to 3, whereby X is an substituted or unsubstituted –CH_2-Aryl group.

5. The method according to any of the claims 1 to 4, whereby X is selected from the group consisting of benzyl (Bn), 4-methoxy-benzyl (PMB), 3,4-dimethoxybenzyl (DPMB), 4-phenyl-benzyl (PPB), 2-naphthylmethyl (Nap), and Benzyloxymethyl acetal (BOM).

6. The method according to any of the claims 1 to 5, whereby Y is t.-Butyloxycarbonyl (BOC).

7. The method according to one of claims 1 to 6, wherein the depsipeptide according to the general formula (IIa) is obtained from precursors according to the general formulas (IV) and (III):



(IV) (III) (IIa)

by:

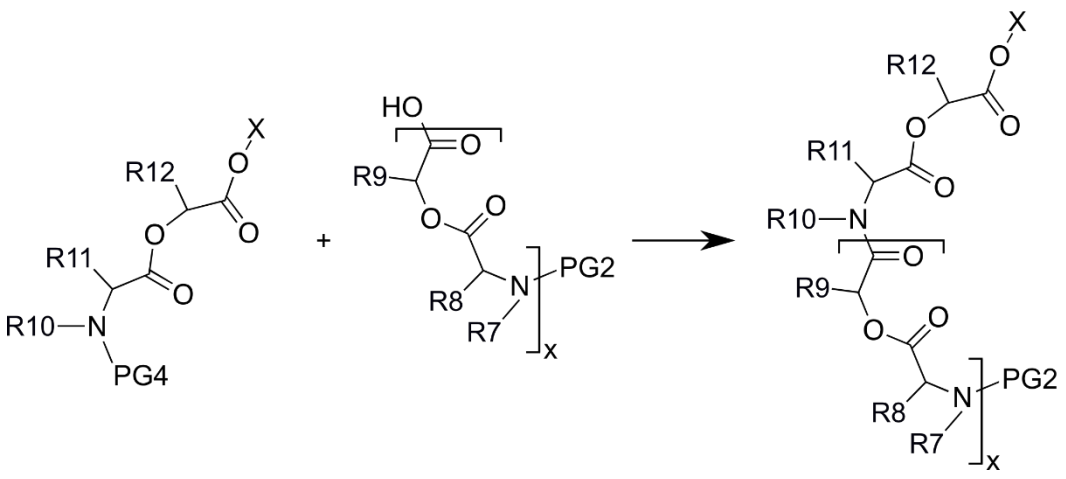
- in precursor (IV), deprotecting the amine group which is protected by the PG2 group in the presence of a base, thereby obtaining a deprotected amine group;

- in precursor (III), deprotecting the carboxylic acid which is protected by the PG3 group in the presence of an acid, thereby obtaining a deprotected carboxylic acid group;

- condensation of the deprotected amine and carboxylic acid groups, thereby obtaining the depsipeptide (II);

wherein R1 to R12, X, Y, x, and y have a meaning as defined in one of claims 1 to 3, PG2 is an amine protecting group and PG3 is a carboxylic acid protecting group.

8. The method according to any of the claims 1 to 7, wherein the precursor according to the general formula (IV) is obtained from precursors according to the general formulas (VI) and (V):



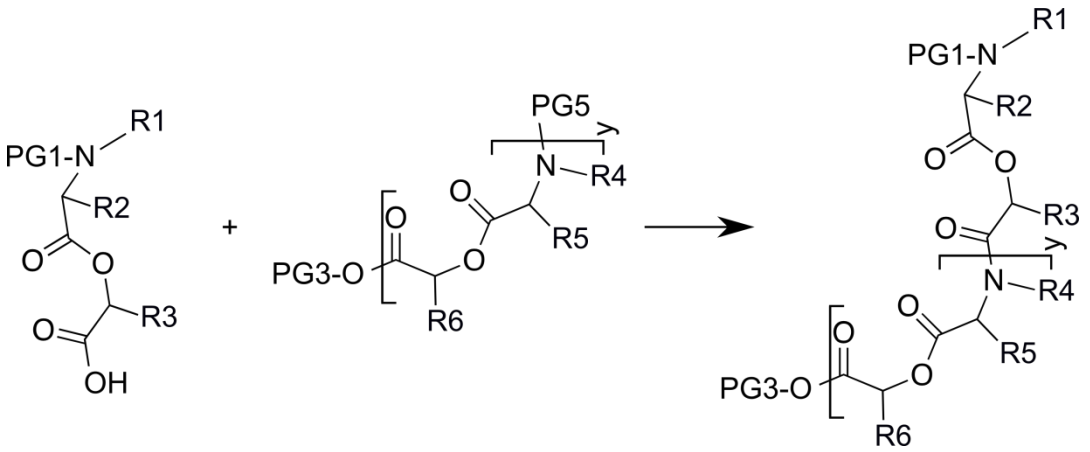
(VI) (V) (IV)

by:

- in precursor (VI), deprotecting the amine group which is protected by the PG4 group in the presence of a base, thereby obtaining a deprotected amine group;
- condensation of the deprotected amine group of precursor (VI) and carboxylic acid group of precursor (V), thereby obtaining the precursor (IV);

wherein R7 to R12, X and x have a meaning as defined above, PG2 has a meaning as defined above and PG4 is an amine protecting group.

9. The method according to any of the claims 1 to 8, wherein the precursor according to the general formula (III) is obtained from precursors according to the general formulas (VIII) and (VII):



(VIII) (VII) (III)

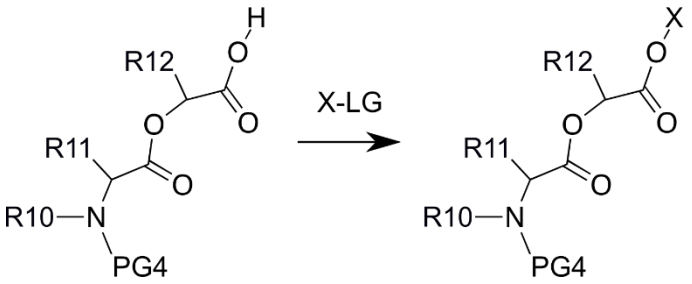
by:

- in precursor (VII), deprotecting the amine group which is protected by the PG5 group in the presence of a base, thereby obtaining a deprotected amine group;
- condensation of the deprotected amine group of precursor (VII) and carboxylic acid group of precursor (VIII), thereby obtaining the precursor (III);

wherein R1 to R6, PG1 and y have a meaning as defined in one of claims 1 to 3, PG3 has a meaning as defined in claim 3 and PG5 is an amine protecting group.

10. The method according to any of the claims 1 to 9, wherein the precursor according to the general

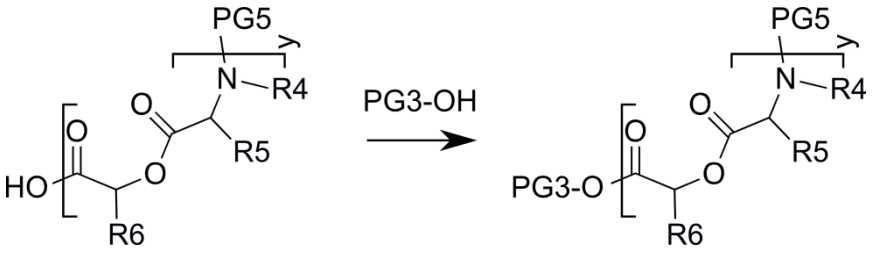
formula (VI) is obtained from the esterification of a precursor according to the general formula (IX) with X-LG:



(IX) (VI)

wherein R10 to R12 and X have a meaning as defined above and PG4 has a meaning also as defined above and LG is a leaving group.

11. The method according to any of the claims 1 to 10, wherein the precursor according to the general formula (VII) is obtained from the esterification of a precursor according to the general formula (X) with PG3-OH:



(X) (VII)

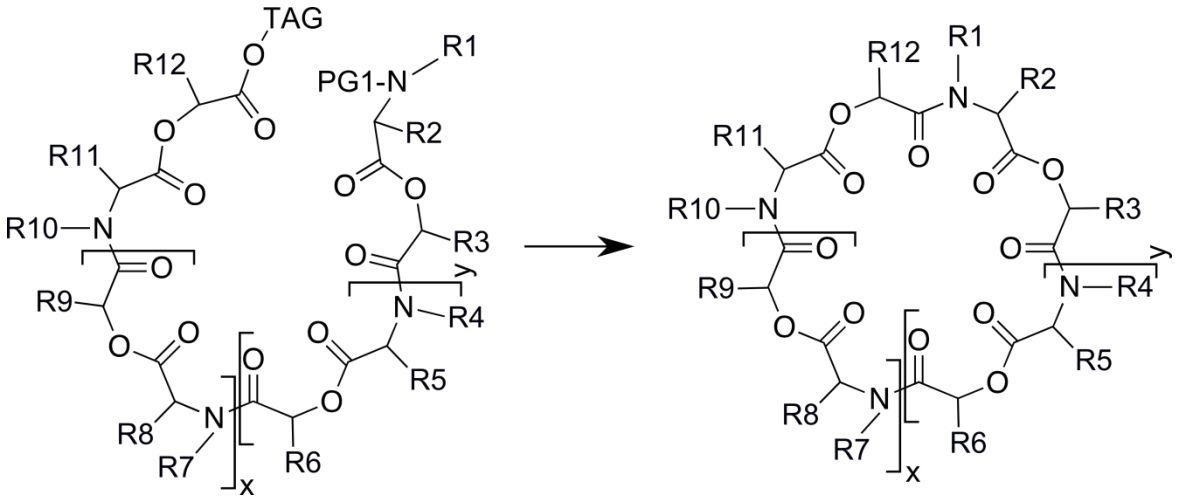
wherein R4 to R6 and y have a meaning as defined above, PG3 also has a meaning as defined above and PG5 also has a meaning as defined above

12. The method according to one of claims 1 to 11, wherein PG3 is X.

13. The method according to any of the claims 1 to 12, wherein precursors (III) and (IV) are identical.

14. The method according to any of the claims 1 to 13, wherein R3 and R9 are identical, R2 and R8 are identical, R5 and R11 are identical.

15. The method according to any of the claims 1 to 2, including the step of synthesis of cyclic depsipeptides according to the general formula (I) from depsipeptides according to the general formula (IIb):



(IIb) (I)

wherein PG1 is an amine protecting group and TAG is a carboxylic acid protecting group,

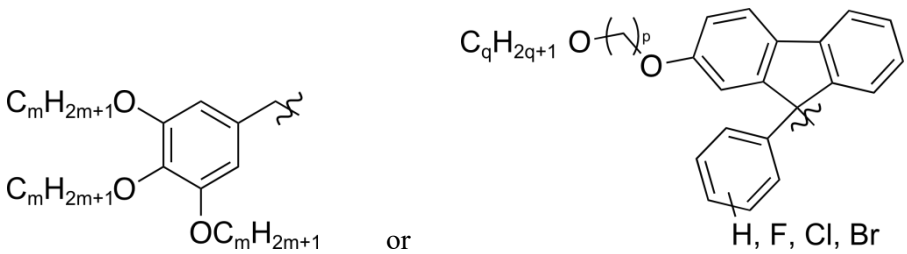
the method comprising the steps of:

- deprotecting the amine group which is protected by the PG1 group in the presence of a base, thereby obtaining a deprotected amine group;
- deprotecting the carboxylic acid which is protected by the TAG group in the presence of an acid, thereby obtaining a deprotected carboxylic acid group;
- condensation of the deprotected amine and carboxylic acid groups, thereby obtaining the cyclic depsipeptide (I);

characterized in that the TAG group comprises a moiety Aryl−O−$(CH_2)_n$− with Aryl representing an aromatic moiety and n being ≥ 13.

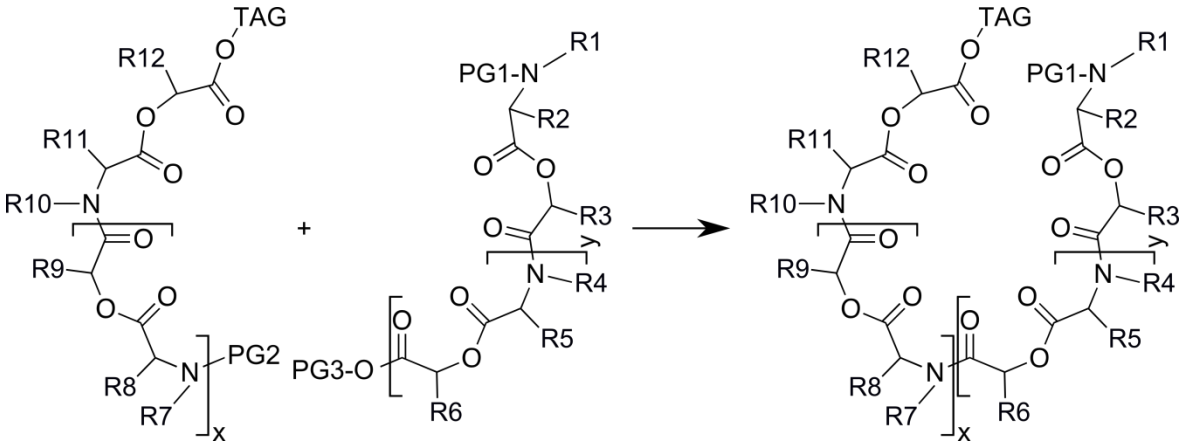
16. The method according to claim 15, wherein PG1 is 9-fluorenylmethoxycarbonyl (Fmoc), t-butyl carbamate (Boc), benzyl carbamate (Z), acetamide, trifluoroacetamide, phthalimide, benzyl (Bn), triphenylmethyl (Tr), benzylidene or p-toluenesulfonamide (Ts)

and TAG is:



wherein m is ≥ 15 to ≤ 25, p is ≥ 8 to ≤ 18 and q is ≥ 15 to ≤ 25.

17. The method according to claim 15 or 16, wherein the depsipeptide according to the general formula (IIb) is obtained from precursors according to the general formulas (IVb) and (IIIb):



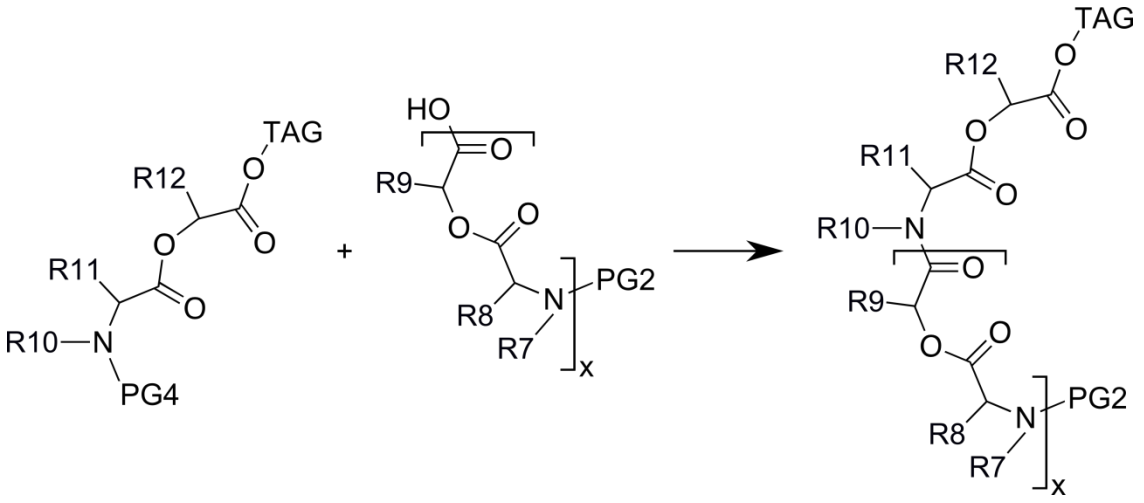
(IVb) (IIIb) (IIb)

by:

- in precursor (IVb), deprotecting the amine group which is protected by the PG2 group in the presence of a base, thereby obtaining a deprotected amine group;
- in precursor (IIIb), deprotecting the carboxylic acid which is protected by the PG3 group in the presence of an acid, thereby obtaining a deprotected carboxylic acid group;
- condensation of the deprotected amine and carboxylic acid groups, thereby obtaining the depsipeptide (IIb);

wherein R1 to R12, TAG, PG1, x, and y have a meaning as defined in one of claims 1 to 2, PG2 is an amine protecting group and PG3 is a carboxylic acid protecting group.

18. The method according to any of the claims 15 to 17, wherein the precursor according to the general formula (IVb) is obtained from precursors according to the general formulas (VIb) and (Vb):



(VIb) (Vb) (IVb)

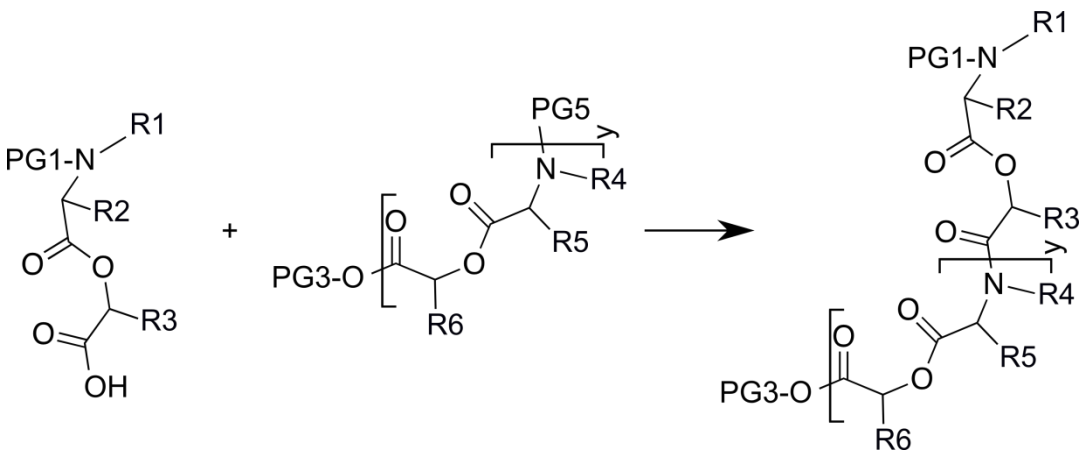
by:

- in precursor (VIb), deprotecting the amine group which is protected by the PG4 group in the presence of a base, thereby obtaining a deprotected amine group;

- condensation of the deprotected amine group of precursor (VIb) and carboxylic acid group of precursor (Vb), thereby obtaining the precursor (IVb);

wherein R7 to R12, TAG and x have a meaning as defined in one of claims 1 to 17, PG2 has a meaning as defined in claim 16 and PG4 is an amine protecting group.

19. The method according to any of the claims 15 to 18, wherein the precursor according to the general formula (IIIb) is obtained from precursors according to the general formulas (VIIIb) and (VIIb):



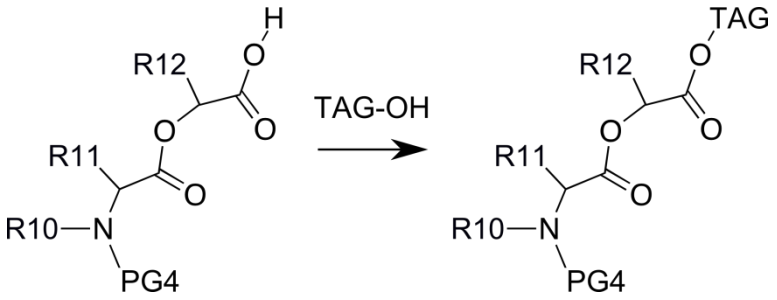
(VIIIb) (VIIb) (IIIb)

by:

- in precursor (VIIb), deprotecting the amine group which is protected by the PG5 group in the presence of a base, thereby obtaining a deprotected amine group;
- condensation of the deprotected amine group of precursor (VIIb) and carboxylic acid group of precursor (VIIIb), thereby obtaining the precursor (IIIb);

wherein R1 to R6, PG1 and y have a meaning as defined in one of claims 1 to 17, PG3 has a meaning as defined in claim 16 and PG5 is an amine protecting group.

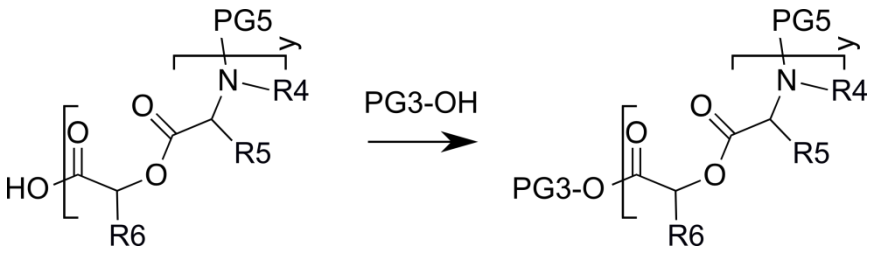
20. The method according to any of the claims 15 to 19, wherein the precursor according to the general formula (VIb) is obtained from the esterification of a precursor according to the general formula (IXb) with TAG-OH:



(IXb) (VIb)

wherein R10 to R12 and TAG have a meaning as defined in one of claims 1 to 17 and PG4 has a meaning as defined in claim 16.

21. The method according to any of the claims 15 to 20, wherein the precursor according to the general formula (VIIb) is obtained from the esterification of a precursor according to the general formula (Xb) with PG3-OH:



(Xb) (VIIb)

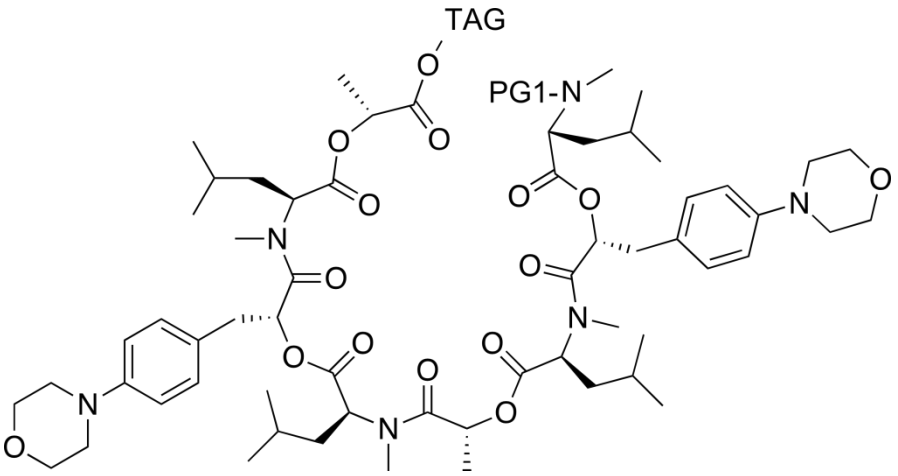
wherein R4 to R6 and y have a meaning as defined in one of claims 1 to 19, PG3 has a meaning as defined in claim 16 and PG5 has a meaning as defined in claim 18.

22. The method according to one of claims 15 to 21, wherein PG3 is TAG as defined in any of the claims 15 to 21.

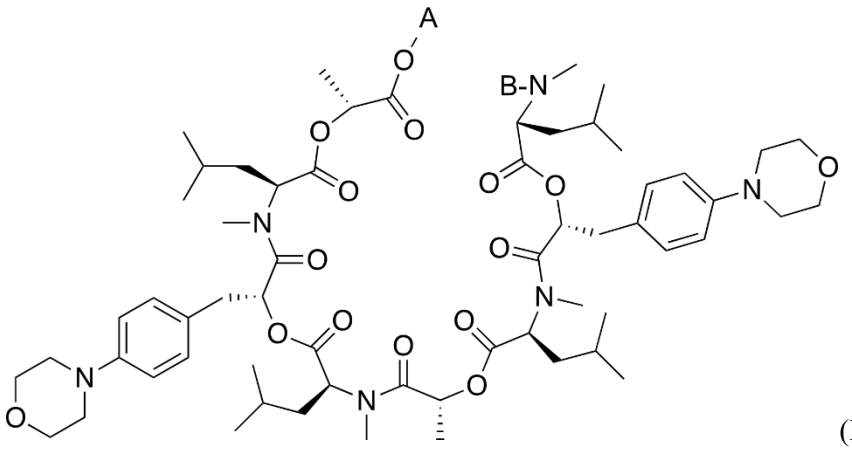
23. The method according to one of claims 15 to 22, wherein at least one reaction step of the reaction steps resulting in a TAG-bearing molecule is followed by precipitation of crude reaction product in methanol, thereby purifying the crude reaction product.

24. The method according to one of claims 15 to 22, wherein at least one step of the reaction steps in which TAG-protected carboxylic acid groups are deprotected is followed by precipitation of cleaved TAG-OH in methanol and removal of the precipitate by filtration, thereby purifying the crude reaction product.

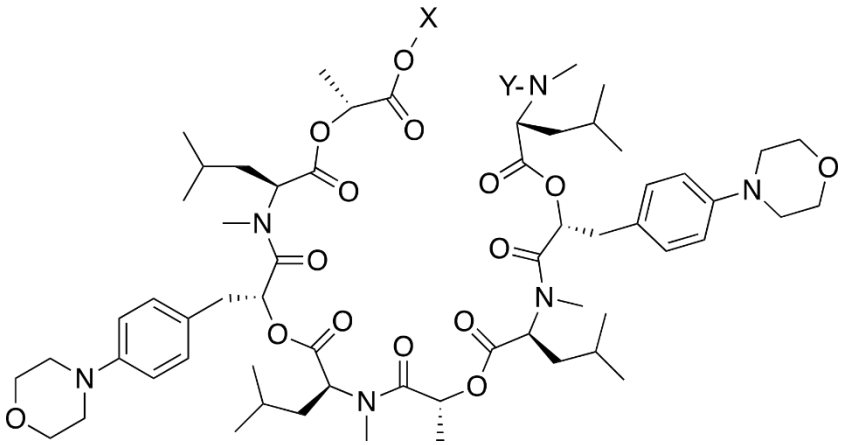
25. The method according to one of claims 1 to 24, wherein the depsipeptide (II) is selected from one of the general formulas (II-1) to (II-14b):



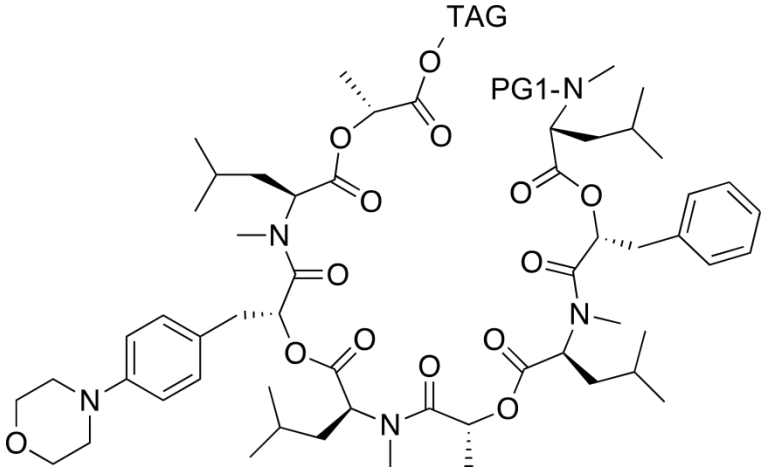
(II-1)



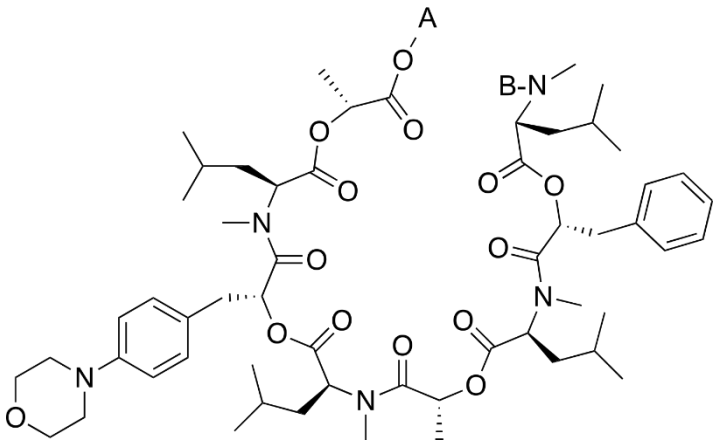
(II- 1a)



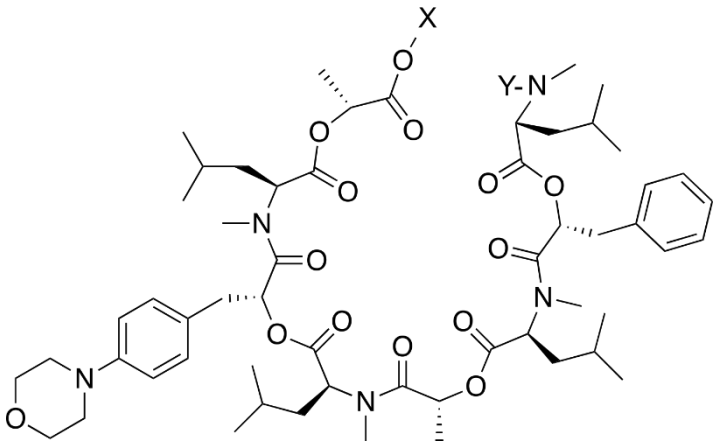
(II- 1b)



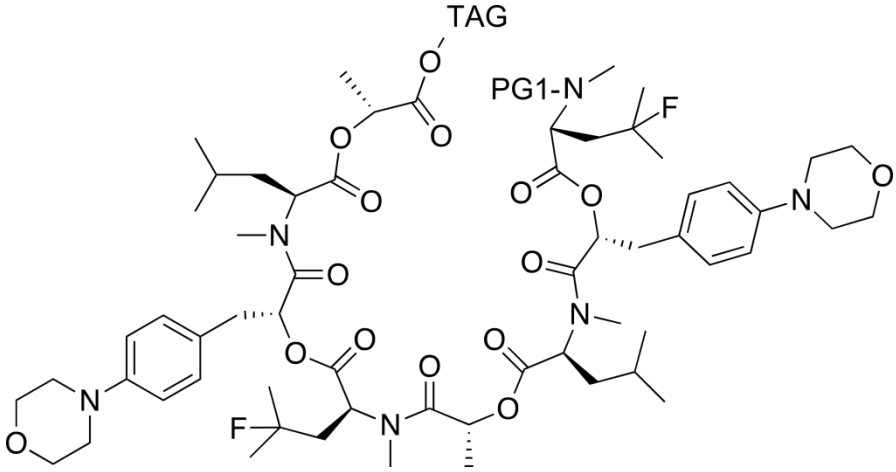
(II-2)



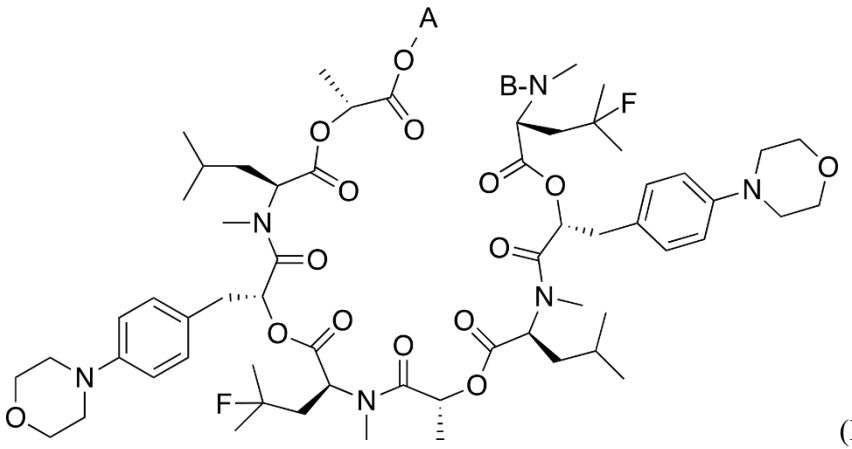
(II-2a)



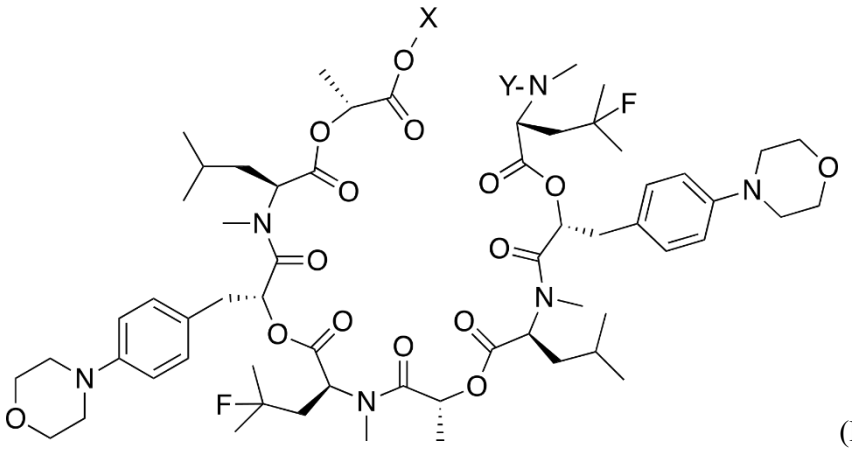
(II- 2b)



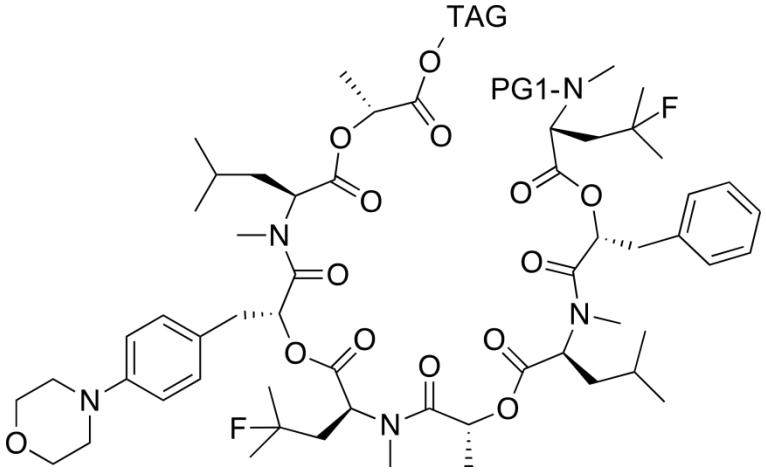
(II-3)



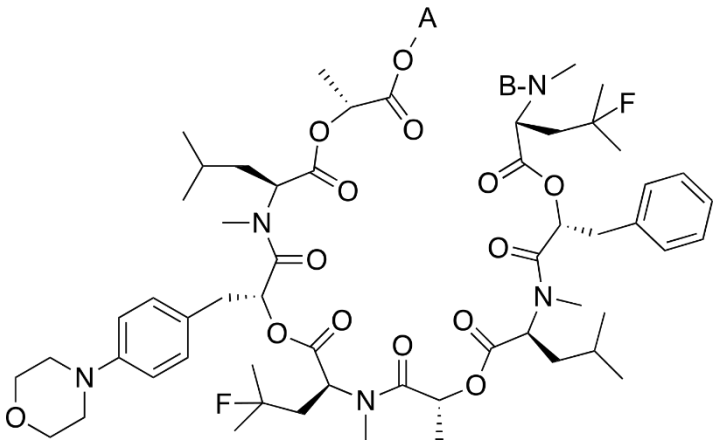
(II-3a)



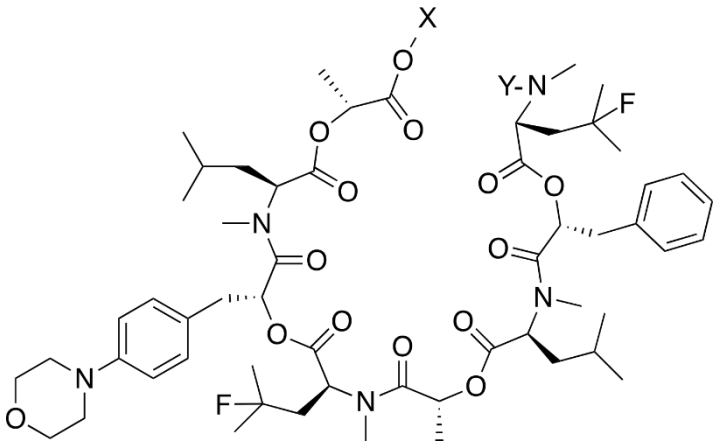
(II-3b)



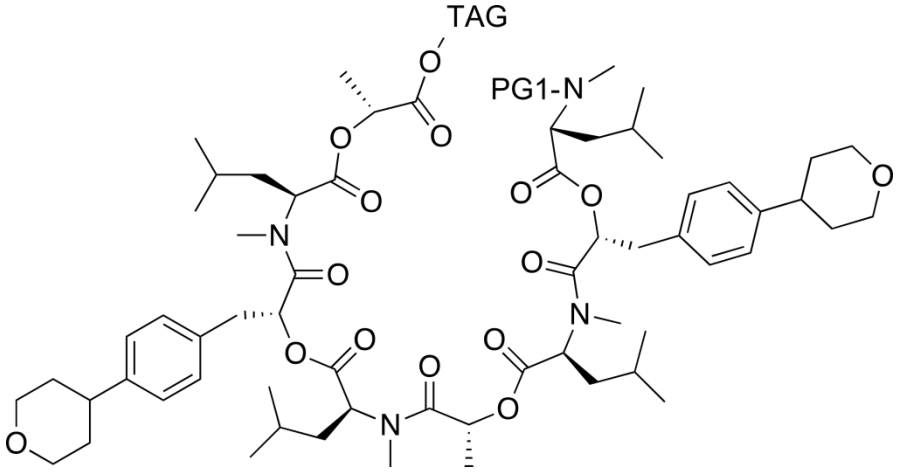
(II-4)



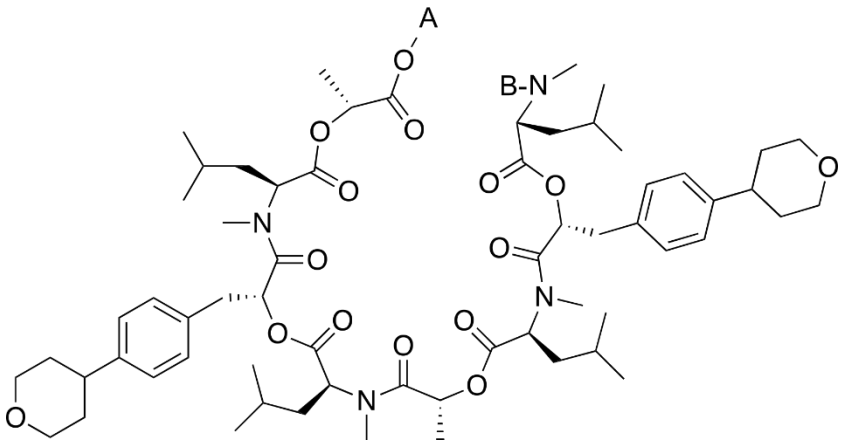
(II-4a)



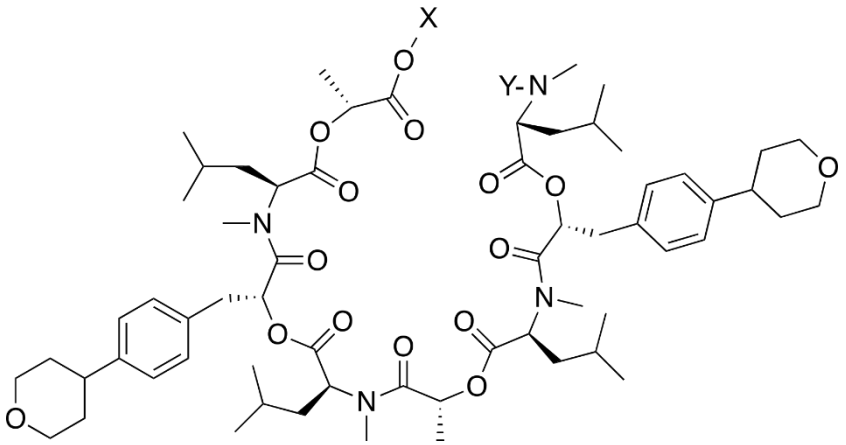
(II- 4b)



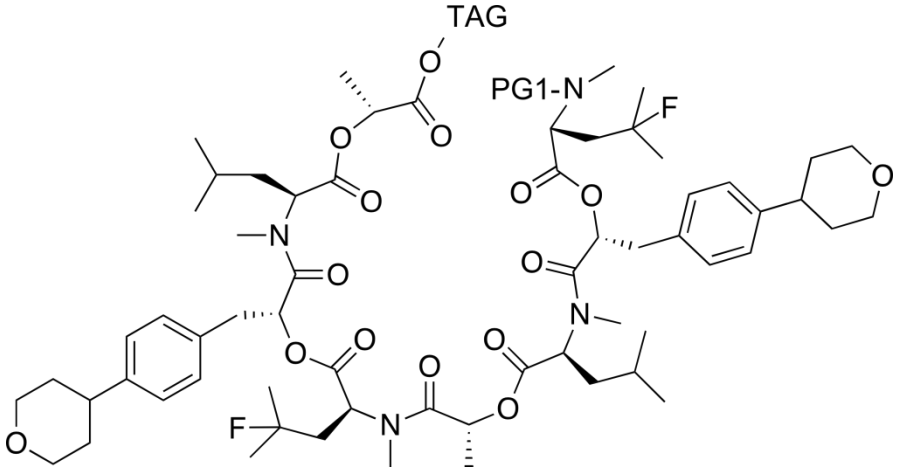
(II-5)



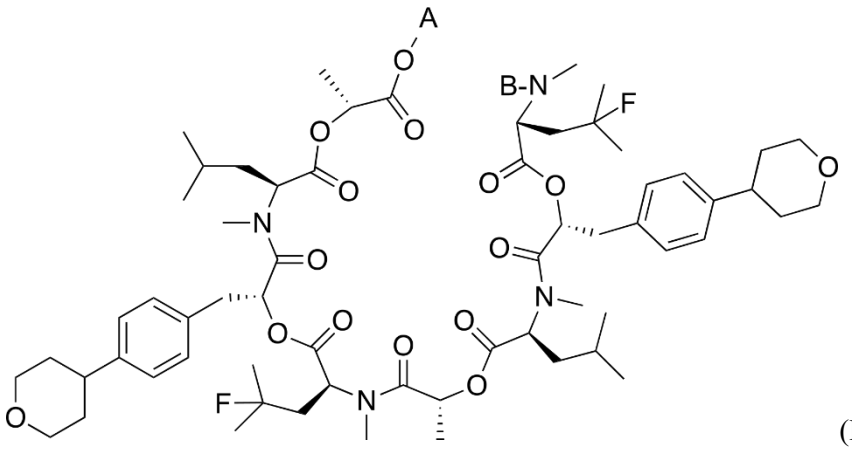
(II-5a)



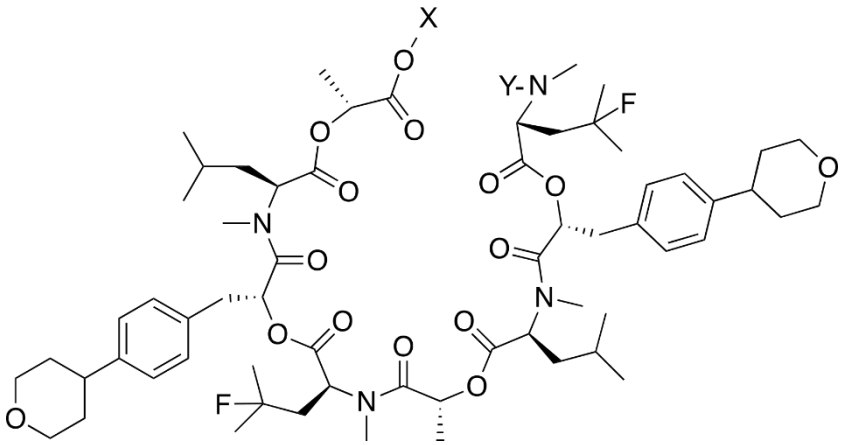
(II-5b)



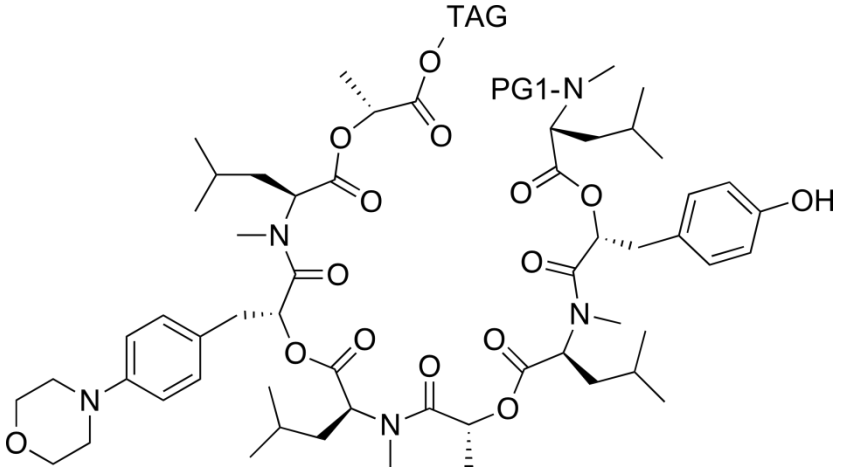
(II-6)



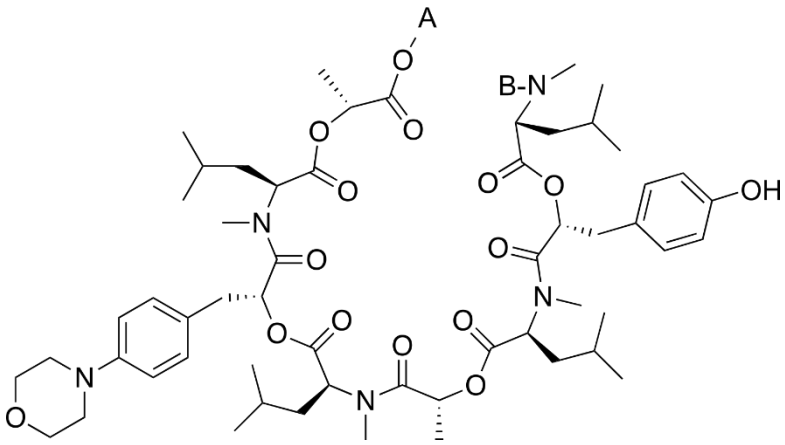
(II- 6a)



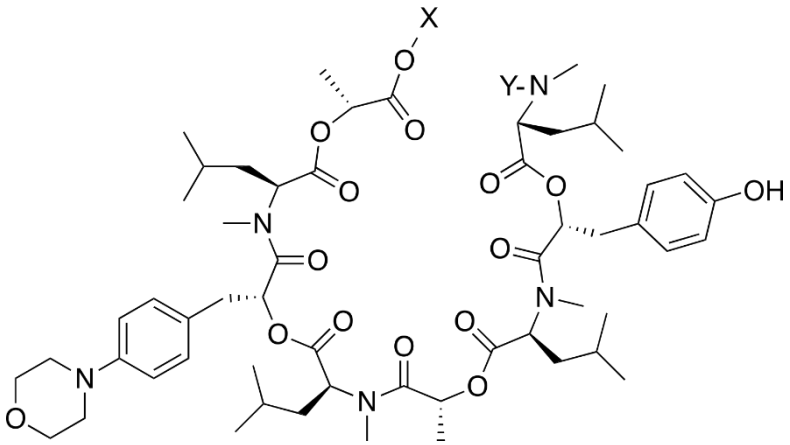
(II-6b)



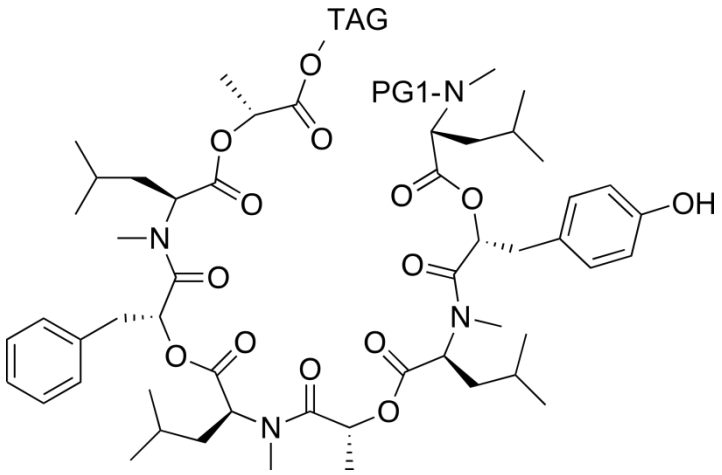
(II-7)



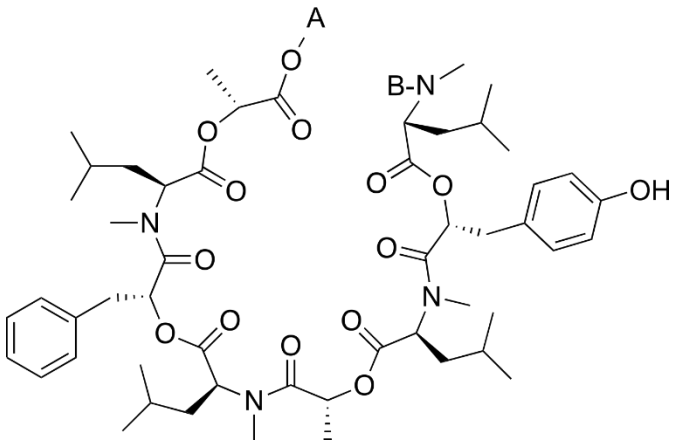
(II-7a)



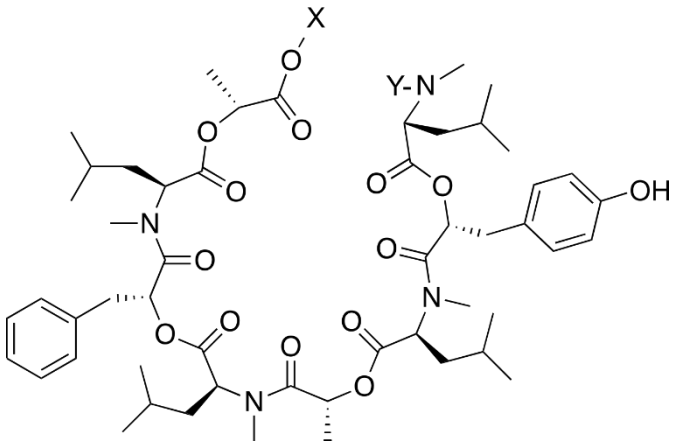
(II-7b)



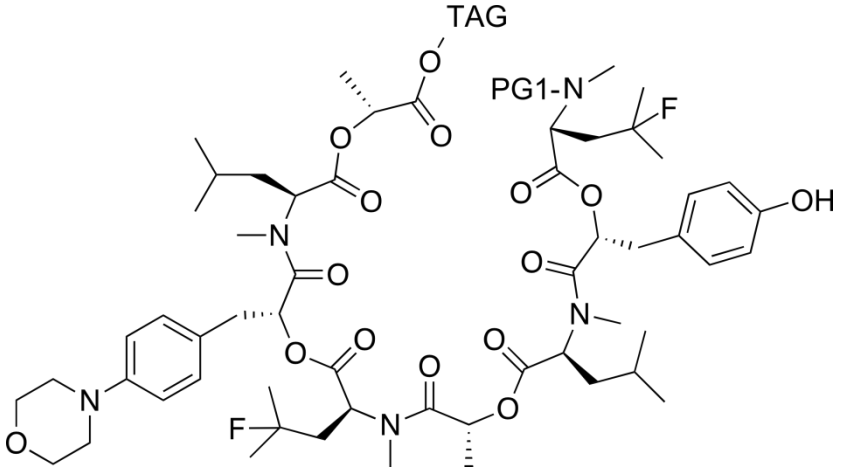
(II-8)



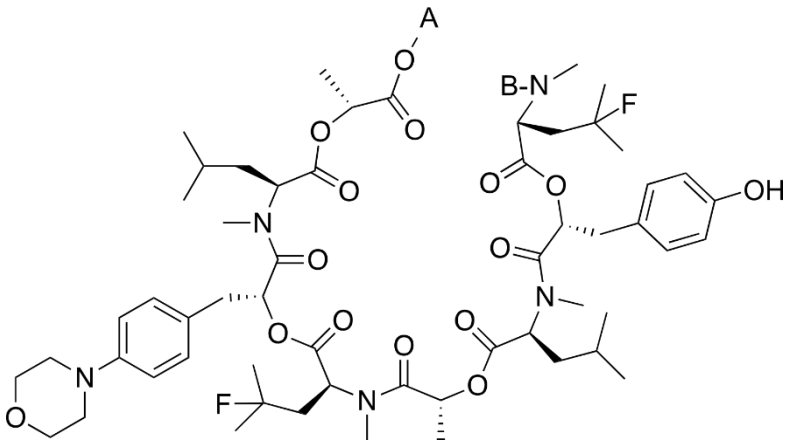
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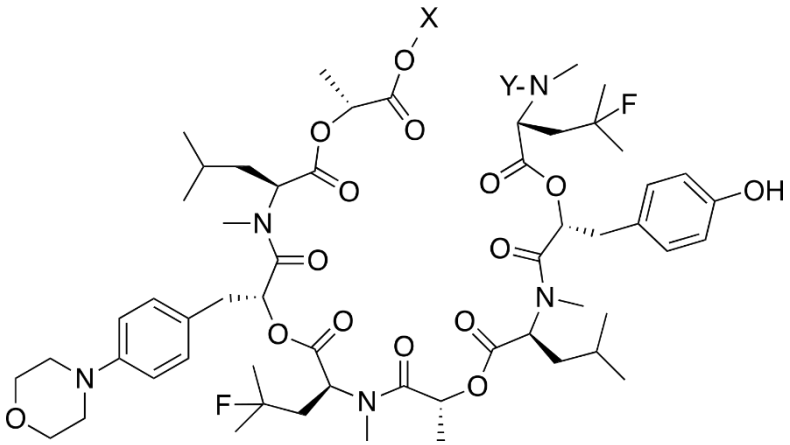
(II-8b)



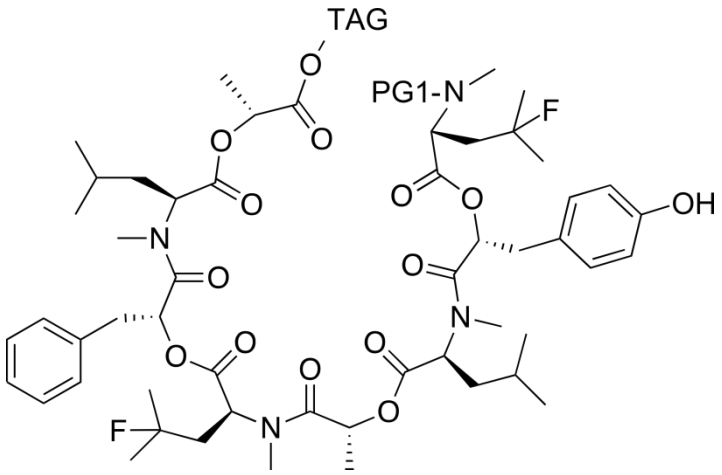
(II-9)



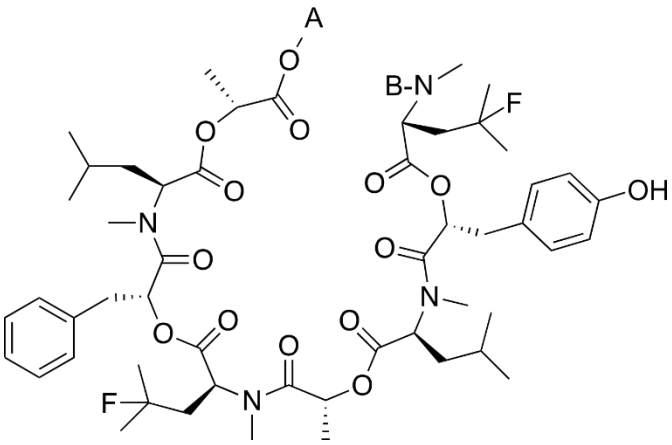
(II-9a)



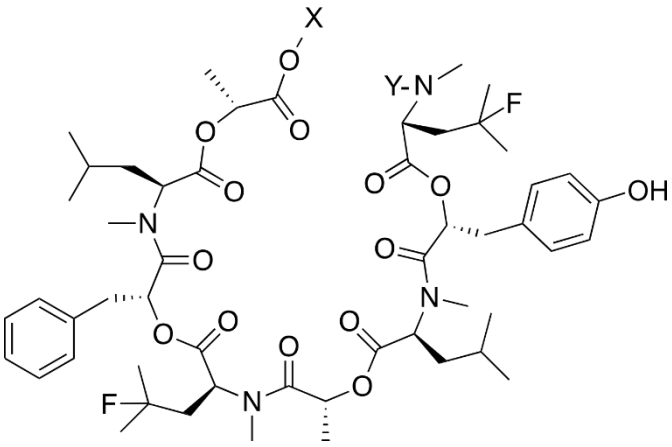
(II-9b)



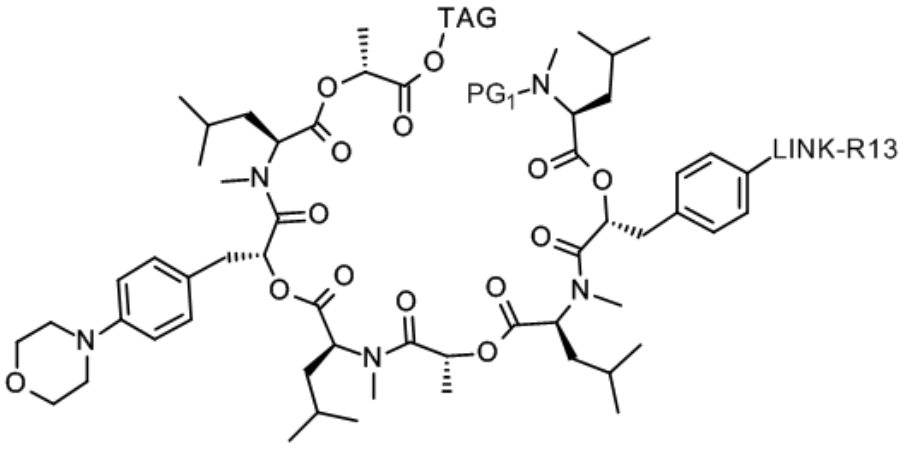
(II-10)



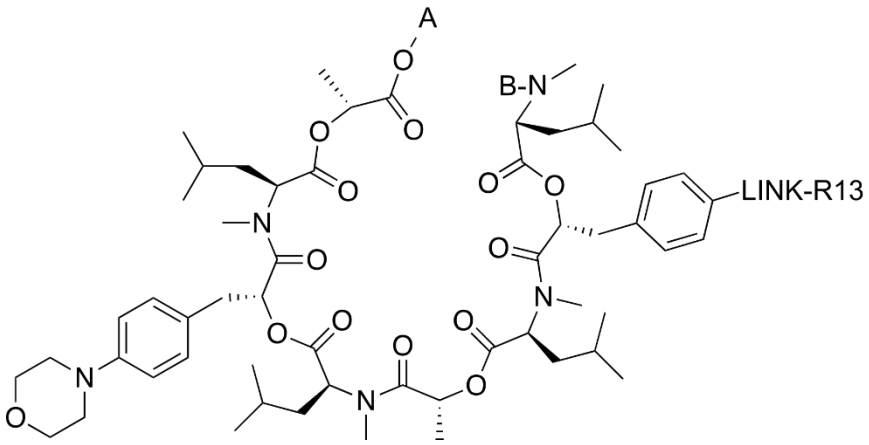
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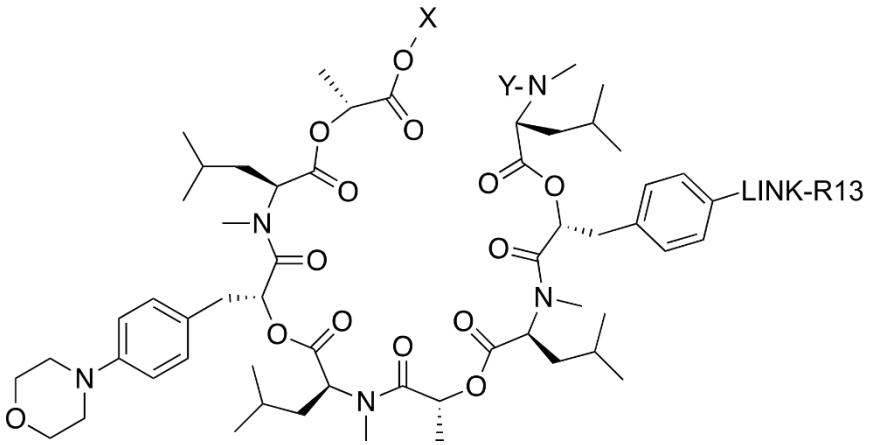
(II-10b)



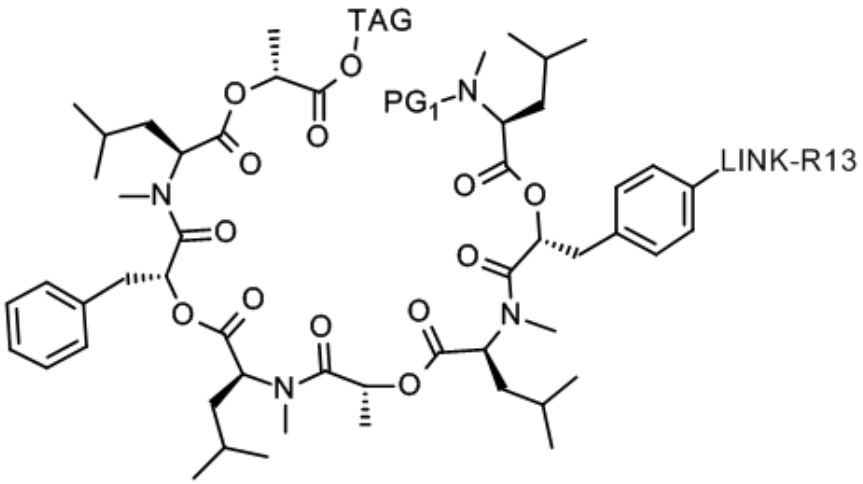
(II-11)



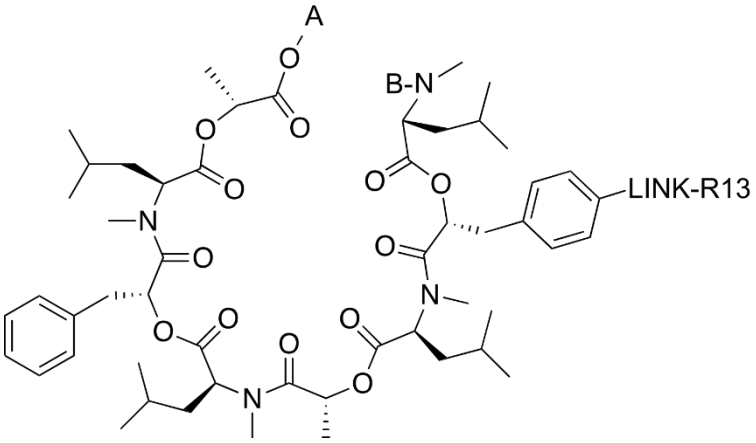
(II-11a)



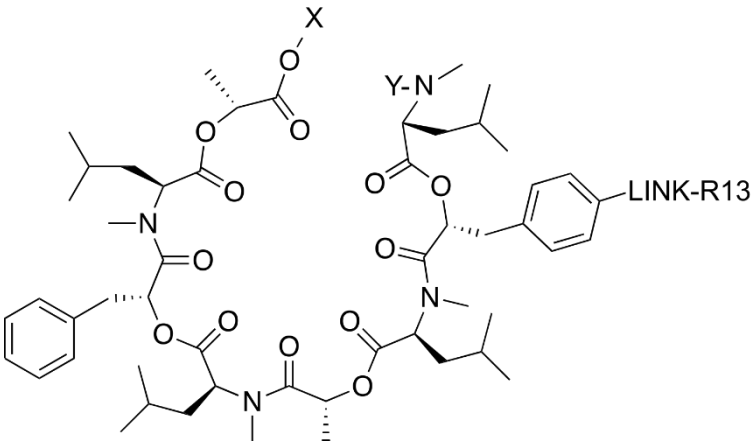
(II-11b)



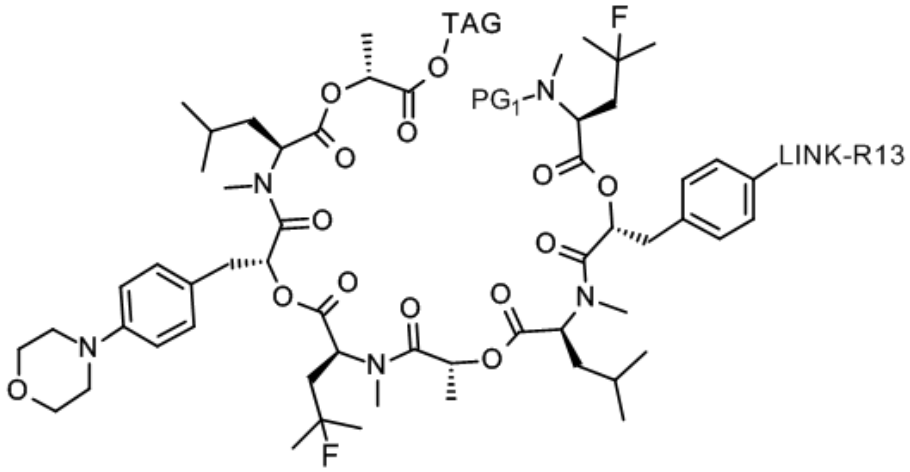
(II-12)



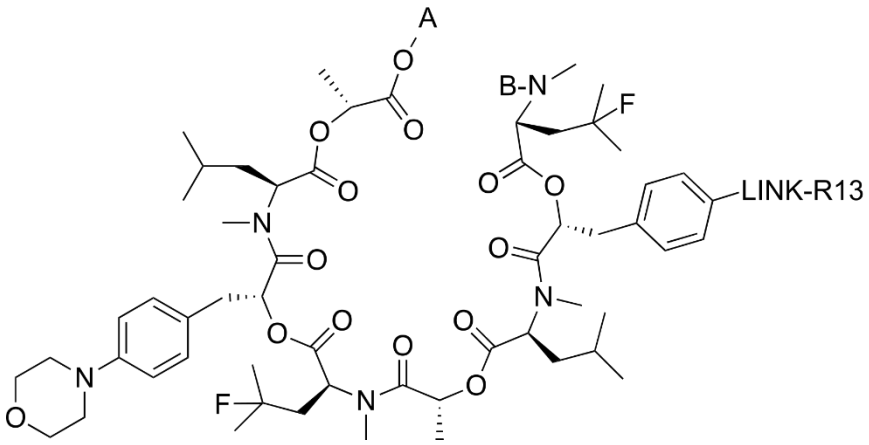
(II-12a)



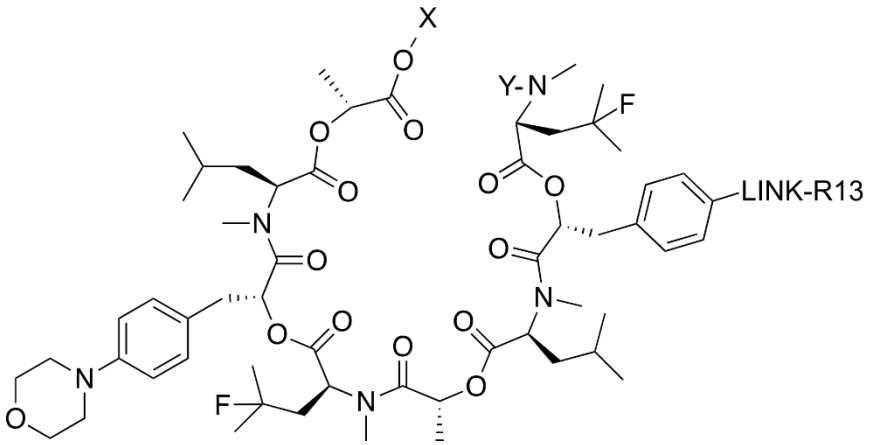
(II-12b)



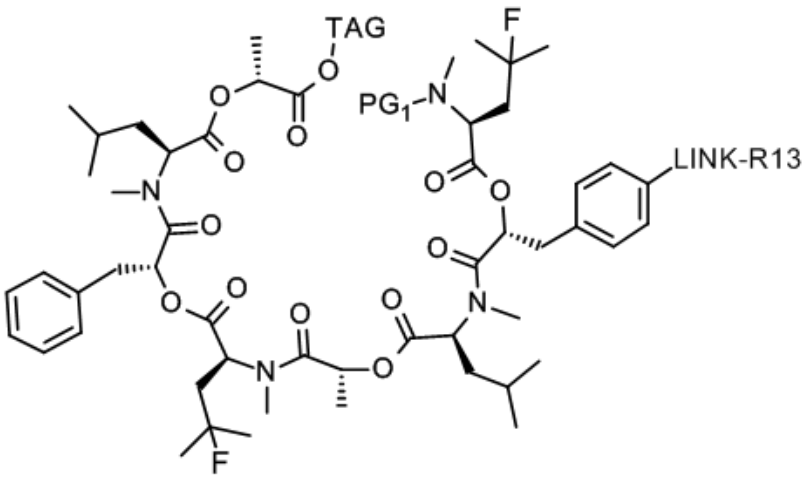
(II-13)



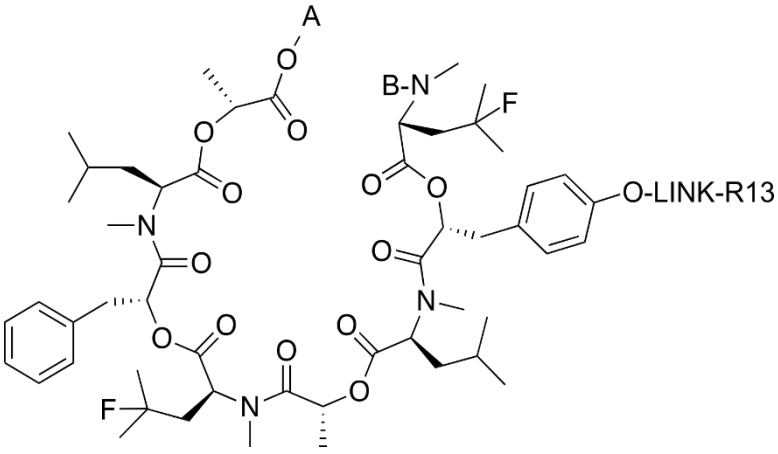
(II-13a)



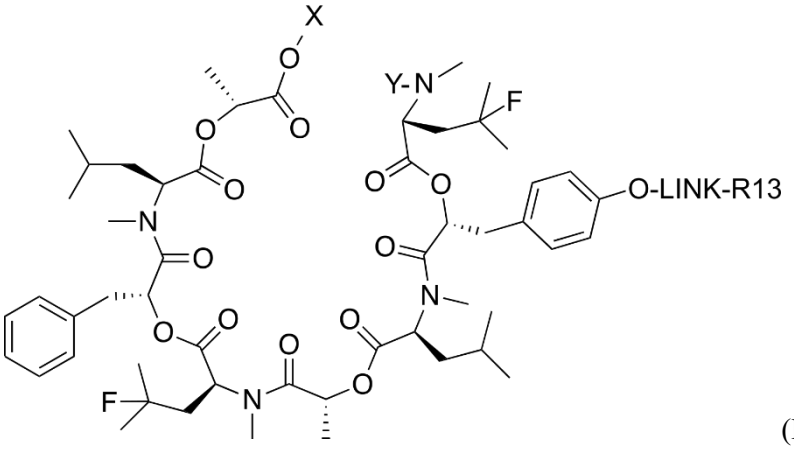
(II-13b)



(II-14)

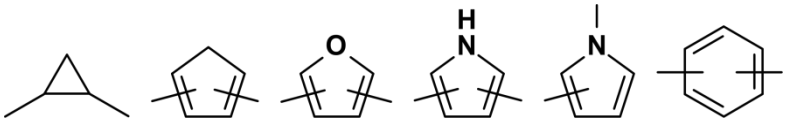


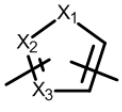
(II-14a)



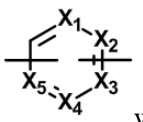
(II- 14b)

wherein in formulas (II-11) to (II-14b) –LINK– is selected from:

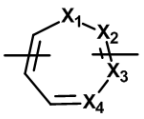




wherein X1 can be C, N, S, O, X2 and X3 can be C or N;



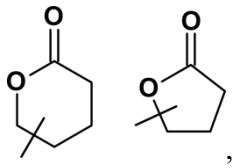
wherein X1 can be C, N, S, O, X2, X3 and X4 can be C or N;



wherein X1, X2, X3 and X4 can be C or N;

and wherein R13 is selected from $SO_2NH(CH_3)$, SO_2NH_2, $OC(O)CH_3$, CF_3 or one the following

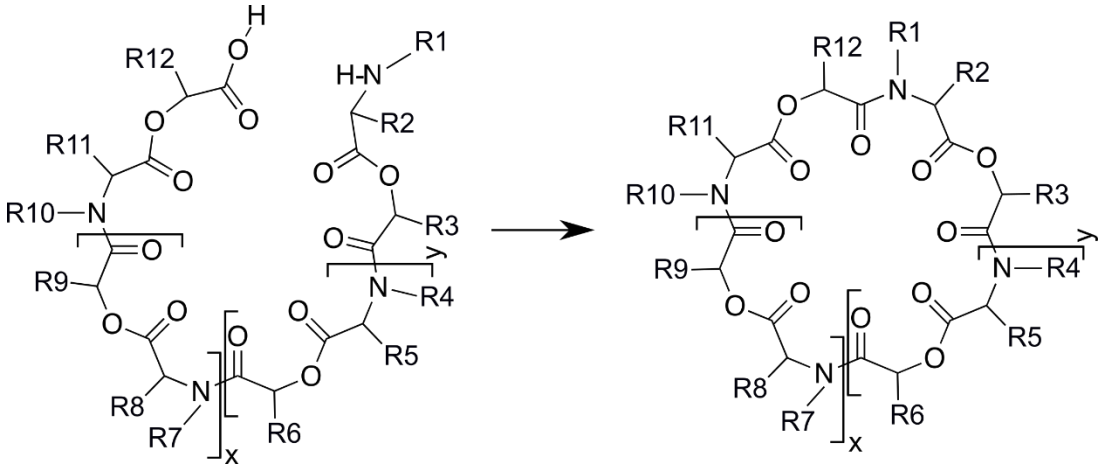
lactone structures:



,

and wherein TAG and PG1 are defined as in claim 15, X and Y are defined as in claim 3, and A and B are defined as in claim 1.

26. A method for the synthesis of cyclic depsipeptides according to the general formula (I) from depsipeptides according to the general formula (IIc):



(IIc) (I)

comprising the steps of

- Providing a mixture of compound (IIc) and a base in a solvent having an $E_T(30)$-value of ≥30 and ≤ 43

- Slow, preferably dropwise addition of a solution of a coupling agent in the solvent to form the cyclic depsipeptide (I)

whereby R2 and R8 each, independent of each other, represent hydrogen, straight-chain or branched C1-C8-alkyl, in particular methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, sec-pentyl, hexyl, isohexyl, sec-hexyl, heptyl, isoheptyl, sec-heptyl, tert-heptyl, octyl, isooctyl, sec-octyl, straight-chain or branched halogenated C1-C8 alkyl, in particular fluorinated sec-butyl, hydroxy-C1-C6-alkyl, in particular hydroxymethyl, 1-hydroxyethyl, C1-C4-alkanoyloxy-C1-C6-alkyl, in particular acetoxymethyl, 1-acetoxyethyl, C1-C4-alkoxy-C1-C6-alkyl,

in particular methoxymethyl, 1-methoxyethyl, aryl-C1-C4-alkyloxy-C1-C6-alkyl, in particular benzyloxymethyl, 1-benzyloxyethyl, mercapto-C1-C6-alkyl, in particular mercaptomethyl, C1-C4-alkylthio-C1-C6-alkyl, in particular methylthioethyl, C1-C4-alkylsulphinyl-C1-C6-alkyl, in particular methylsulphinylethyl, C1-C4-alkylsulphonyl-C1-C6-alkyl, in particular methylsulphonylethyl, carboxy-C1-C6-alkyl, in particular carboxymethyl, carboxyethyl, C1-C4-alkoxycarbonyl-C1-C6-alkyl, in particular methoxycarbonylmethyl, ethoxycarbonylethyl, C1-C4-arylalkoxycarbonyl-C1-C6-alkyl, in particular benzyloxycarbonylmethyl, carbamoyl-C1-C6-alkyl, in particular carbamoylmethyl, carbamoylethyl, amino-C1-C6-alkyl, in particular aminopropyl, aminobutyl, C1-C4-alkylamino-C1-C6-alkyl, in particular methylaminopropyl, methylaminobutyl, C1-C4-dialkylamino-C1-C6-alkyl, in particular dimethylaminopropyl, dimethylaminobutyl, guanidino-C1-C6-alkyl, in particular guanidinopropyl, C1-C4-alkoxycarbonylamino-C1-C6-alkyl, in particular tert-butoxycarbonylaminopropyl, tert-butoxycarbonylaminobutyl, 9-fluorenylmethoxycarbonyl(Fmoc)amino-C1-C6-alkyl, in particular 9-fluorenylmethoxycarbonyl(Fmoc)aminopropyl, 9-fluorenylmethoxycarbonyl(Fmoc)aminobutyl, C2-C8-alkenyl, in particular vinyl, allyl, butenyl, C3-C7-cycloalkyl, in particular cyclopentyl, cyclohexyl, cycloheptyl, C3-C7-cycloalkyl-C1-C4-alkyl, in particular cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, benzyl, substituted benzyl, phenyl, phenyl-C1-C4-alkyl, in particular phenylmethyl which may optionally be substituted by radicals from the group consisting of halogen, in particular fluorine, chlorine, bromine or iodine,

wherein x is 1, y is 1, R1, R4, R7 and R10 are methyl, R6 and R12 are methyl, R5 and R11 are, independent of each other, straight-chain or branched C1-C4-alkyl or straight-chain or branched halogenated C1-C4-alkyl and R3 and R9 are, independent of each other, benzyl or substituted benzyl, and

wherein the coupling agent is T3P® (Propylphosphonic anhydride, 2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide, PPACA).

27. The method according to Claim 26, whereby the $E_T(30)$-value of the solvent is ≥ 34 and ≤ 39.

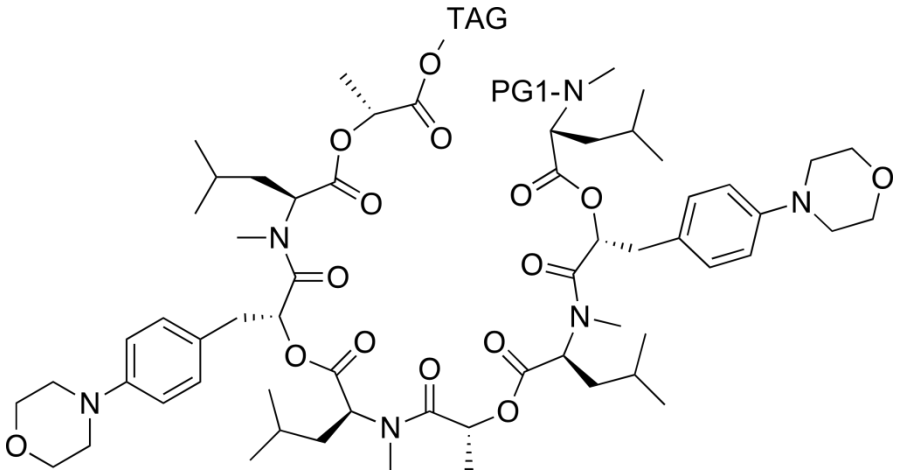
28. The method according to Claim 26 or 27 whereby the addition of the solution of the coupling agent is at a rate of ≤ 2 (mol)-% per minute.

29. The method according to any of the Claims 26 to 28, whereby the ratio of base to compound (IIb) prior to the reaction (in mol:mole) is $\geq 2:1$ to $\leq 10:1$.

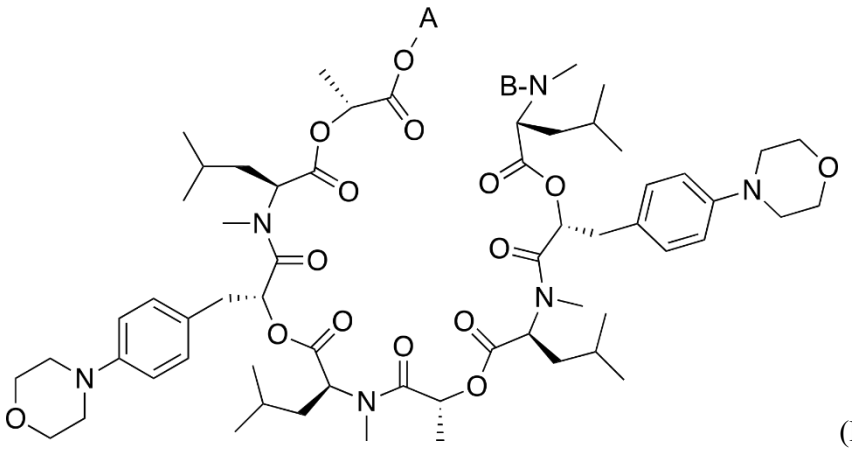
30. The method according to any of the Claims 26 to 29, whereby the ratio of coupling agent to compound (IIb) prior to the reaction (in mol:mole) is $\geq 1:1$ to $\leq 5:1$.

31. The method according to any of the claims 26 to 30, whereby during the addition of the coupling agent the temperature is kept ≤ 25°C.

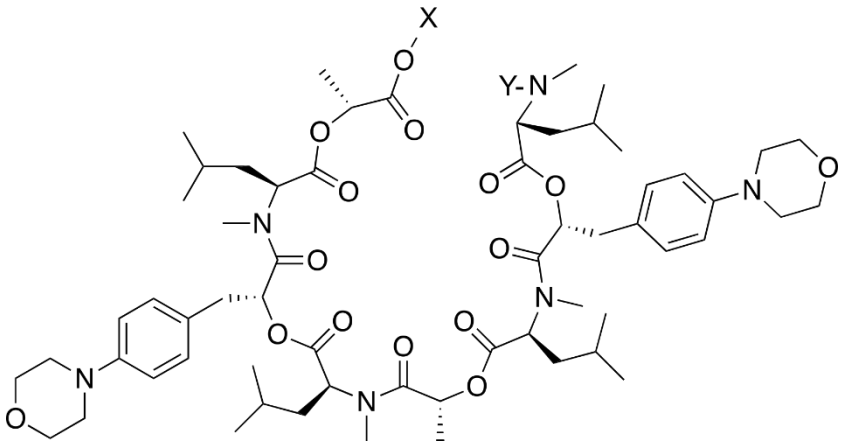
32. A linear or cyclic depsipeptide selected from one of the general formulas (II-1) to (II-14b) or (I-1) to (I-9) or a pharmaceutically or veterinarily acceptable salt thereof:



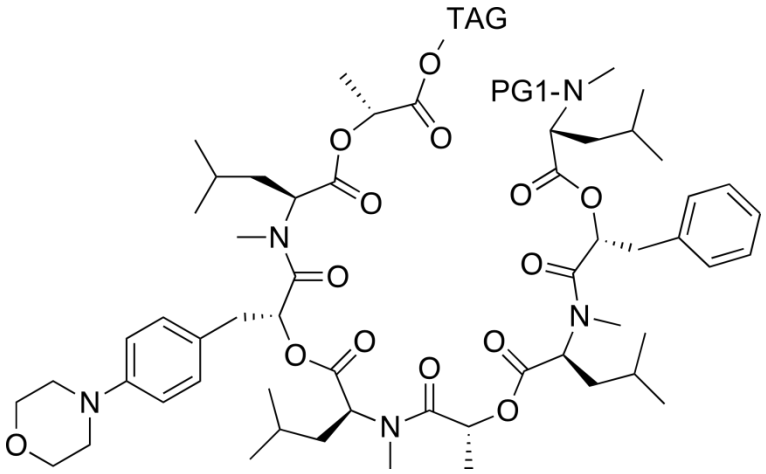
(II-1)



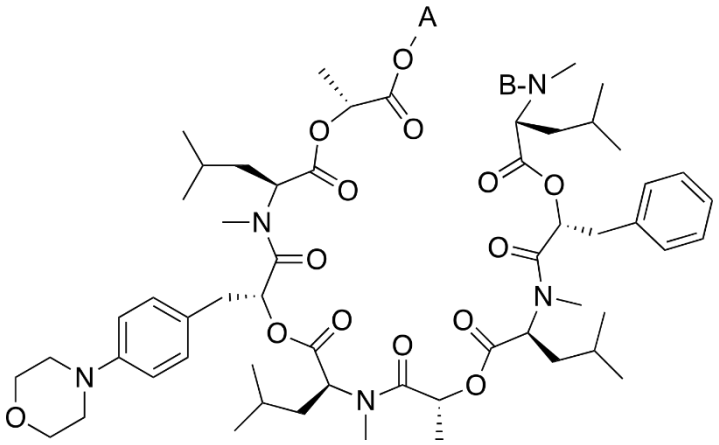
(II- 1a)



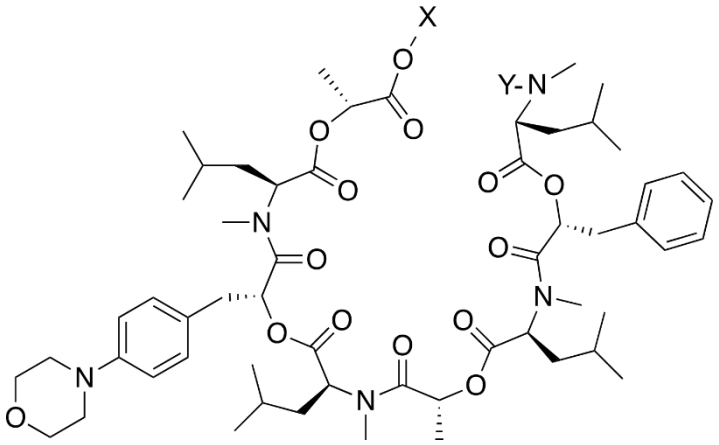
(II- 1b)



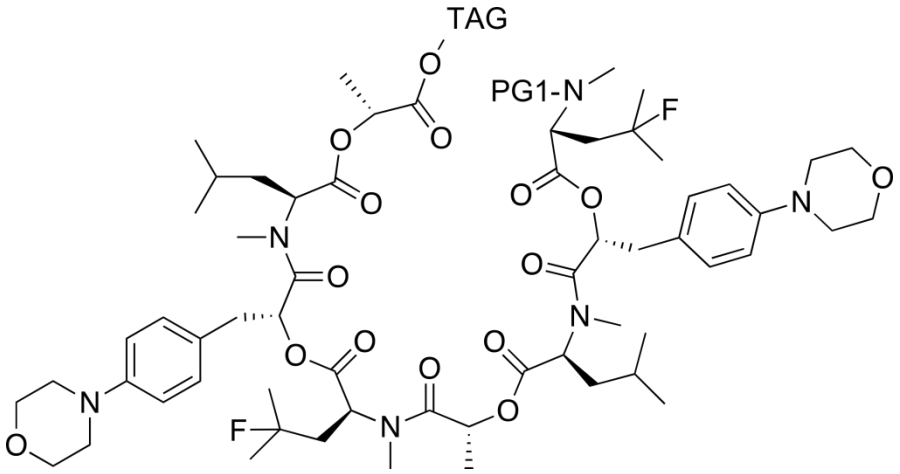
(II-2)



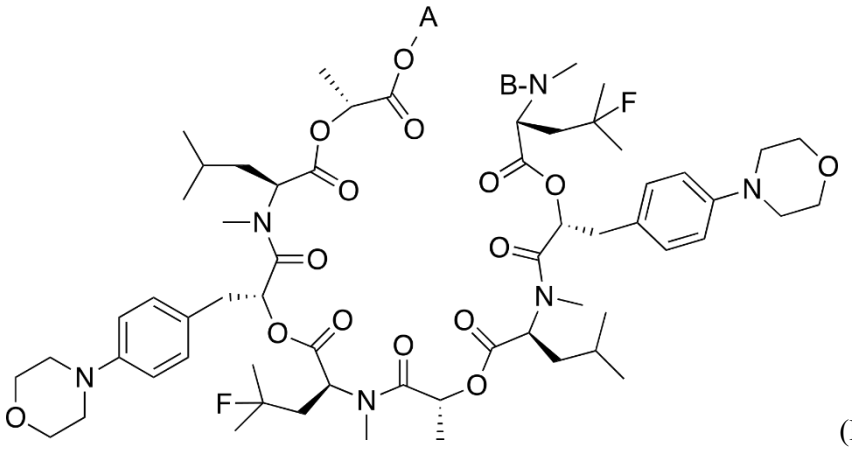
(II-2a)



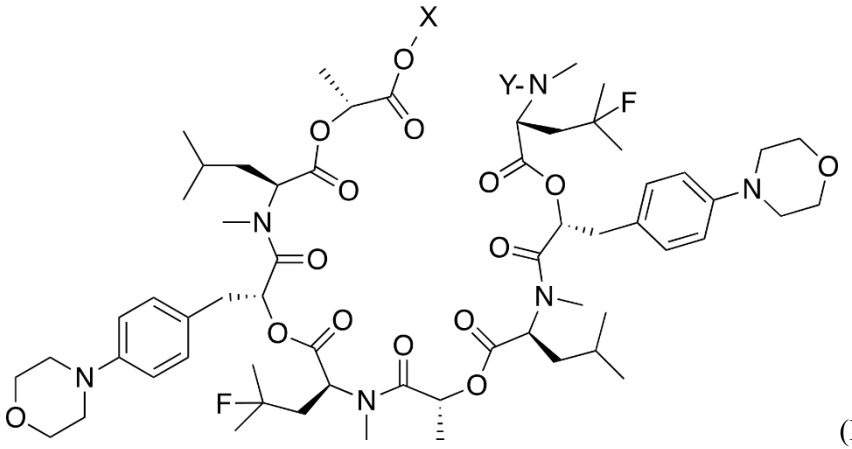
(II- 2b)



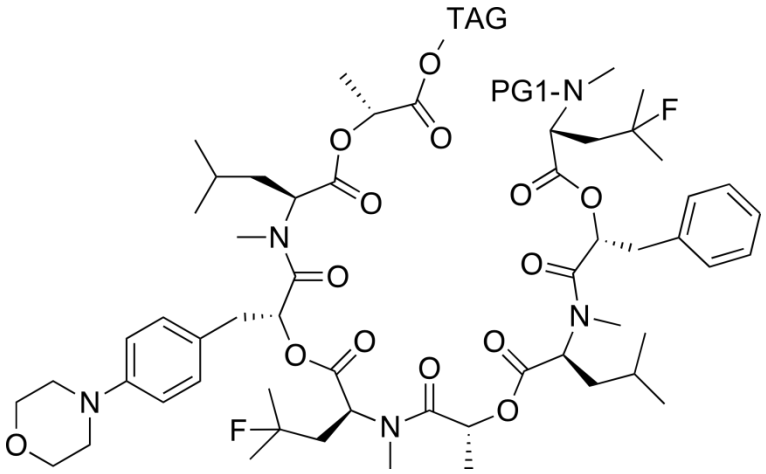
(II-3)



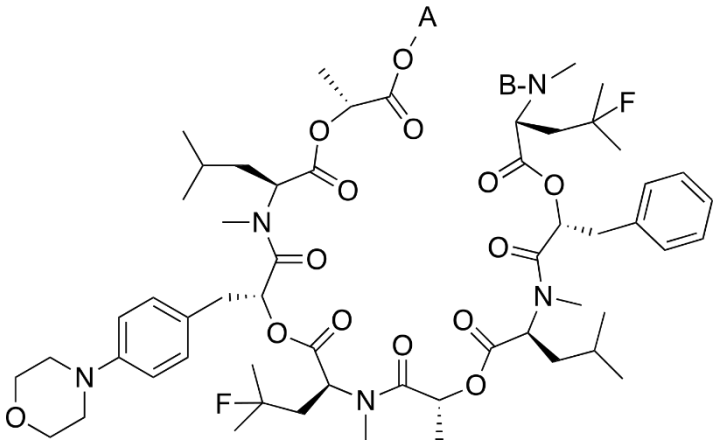
(II-3a)



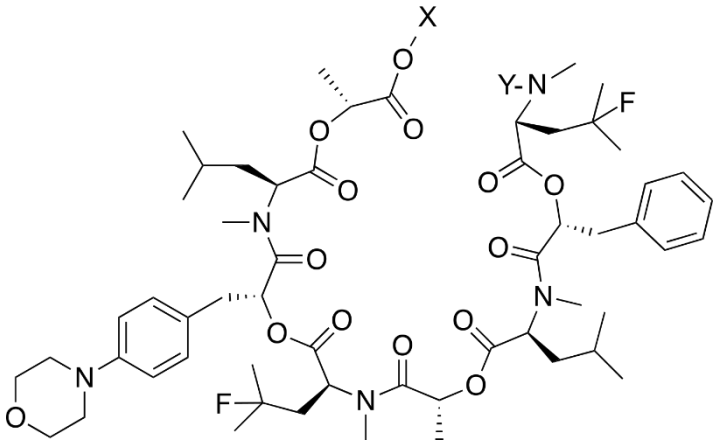
(II-3b)



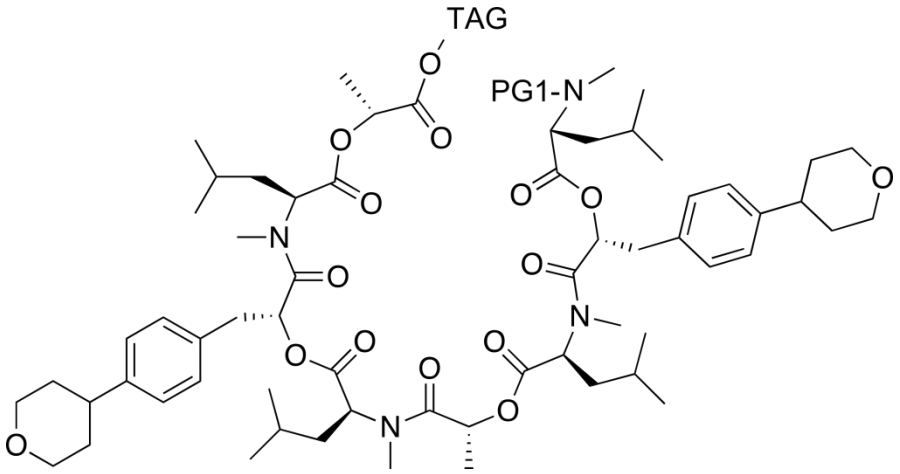
(II-4)



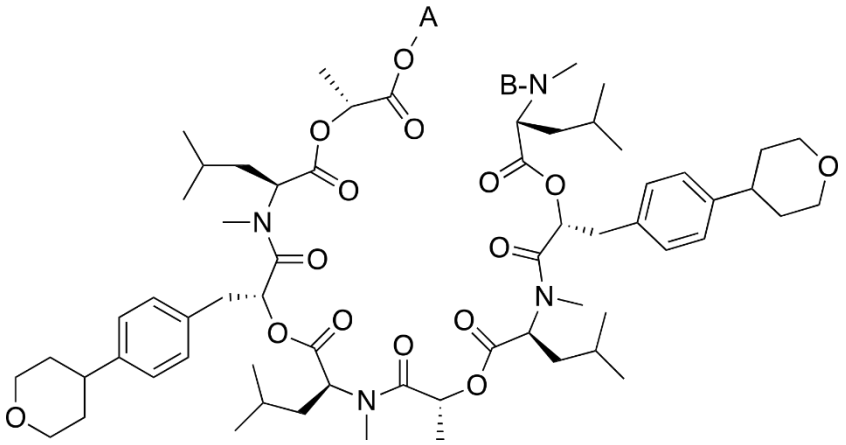
(II-4a)



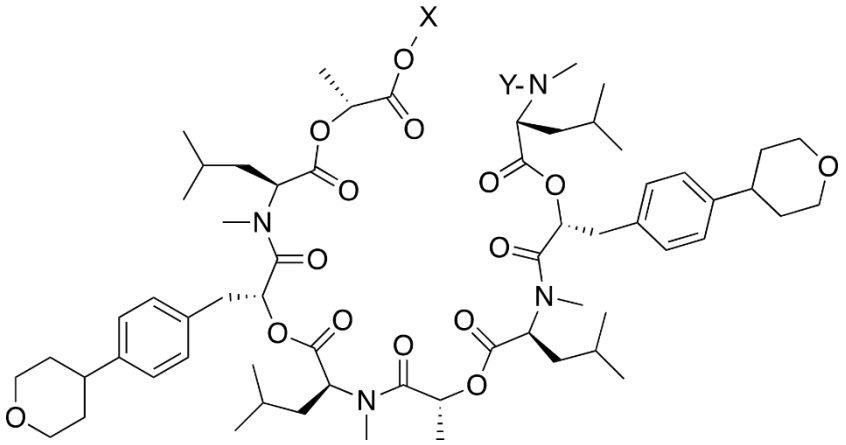
(II- 4b)



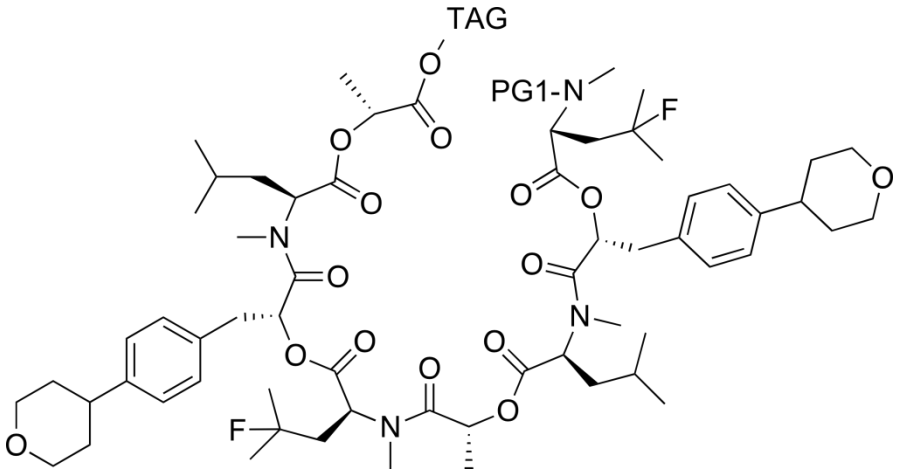
(II-5)



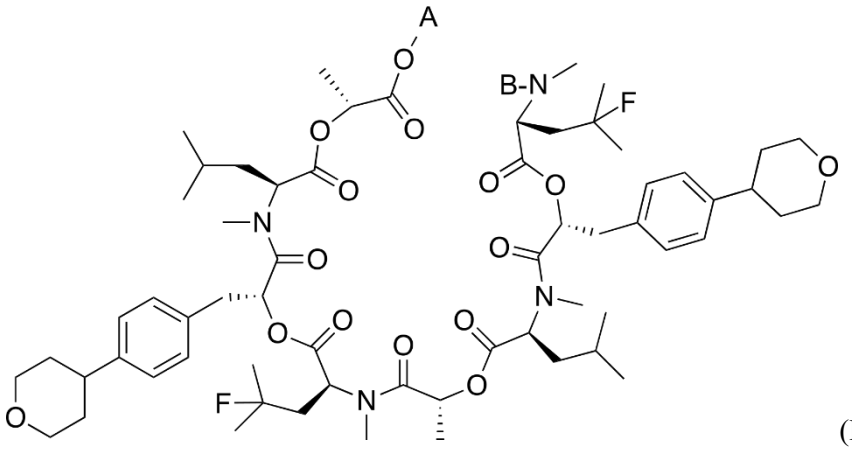
(II-5a)



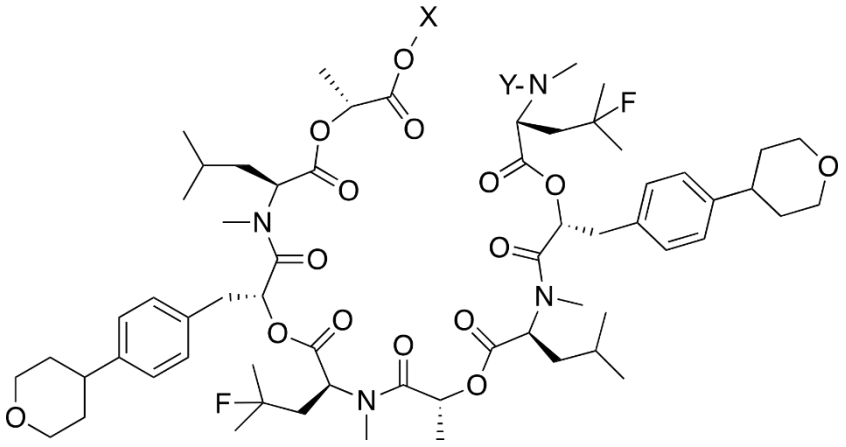
(II-5b)



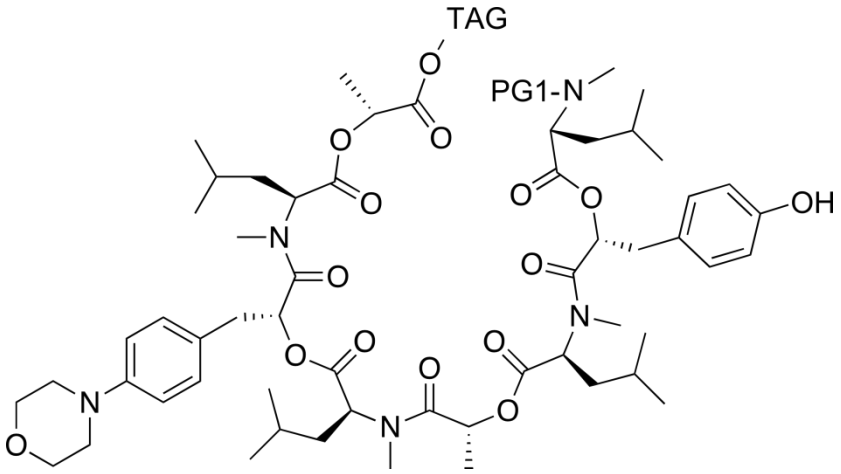
(II-6)



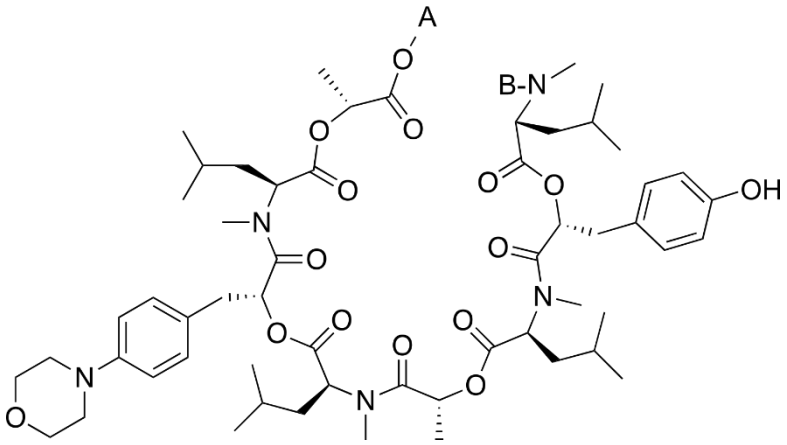
(II- 6a)



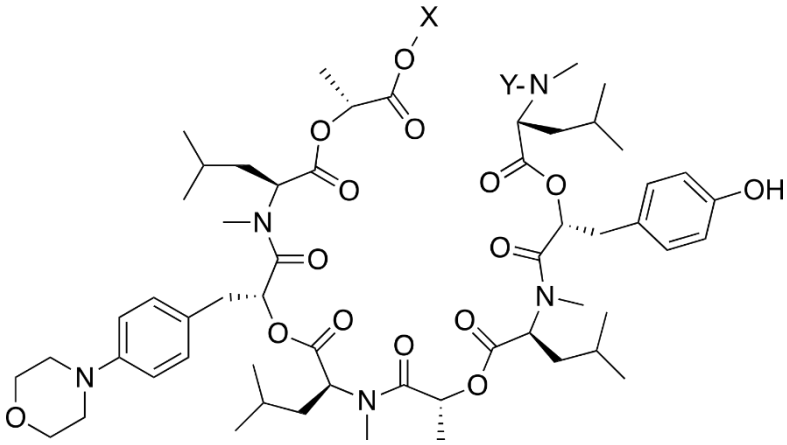
(II-6b)



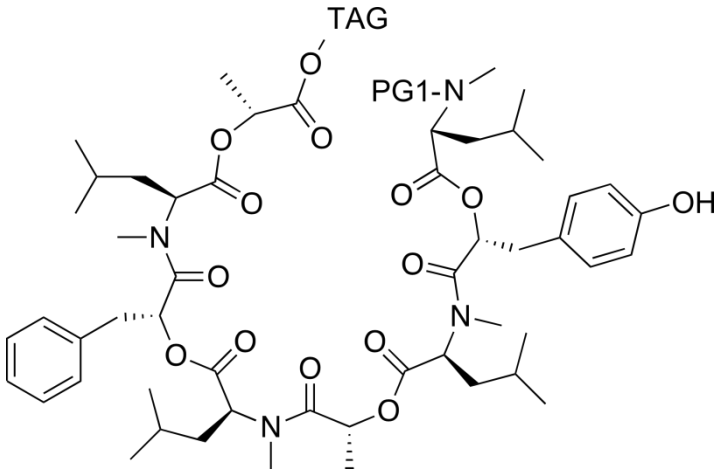
(II-7)



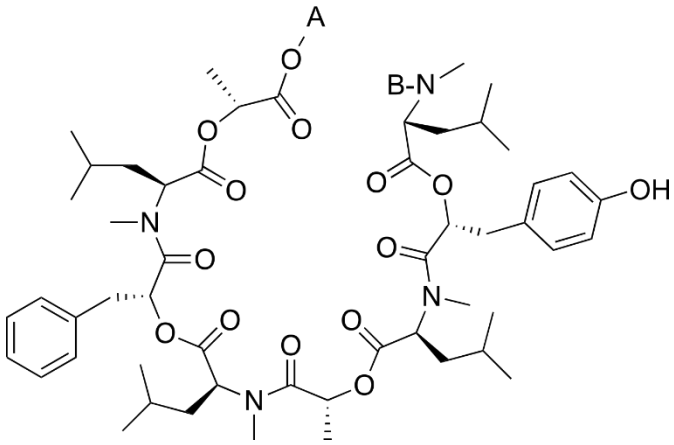
(II-7a)



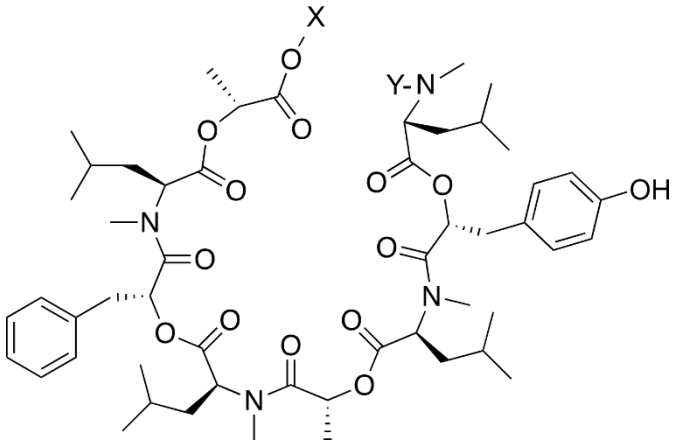
(II-7b)



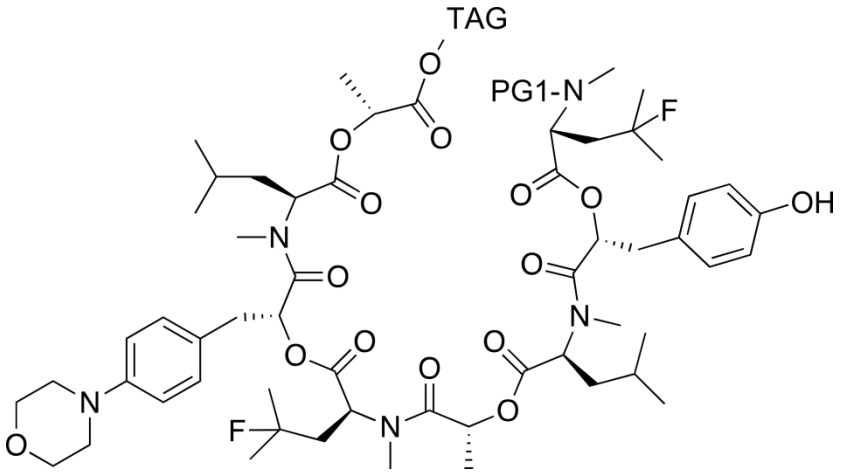
(II-8)



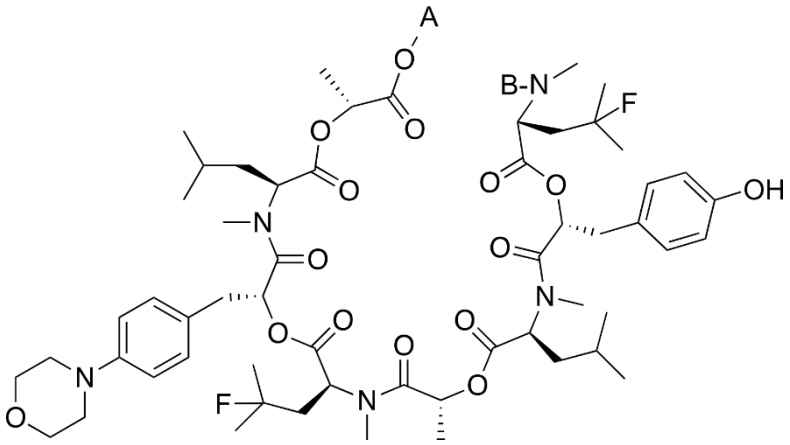
(II-8a)



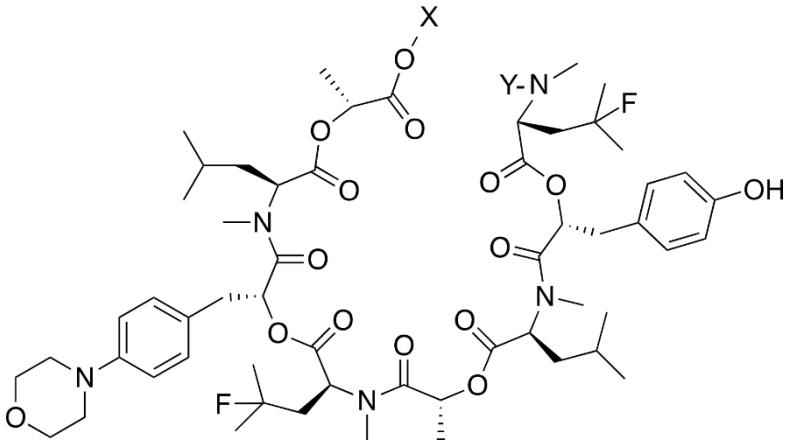
(II-8b)



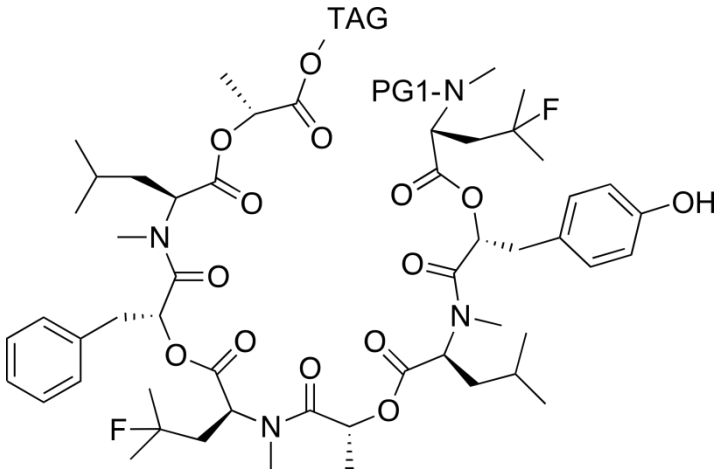
(II-9)



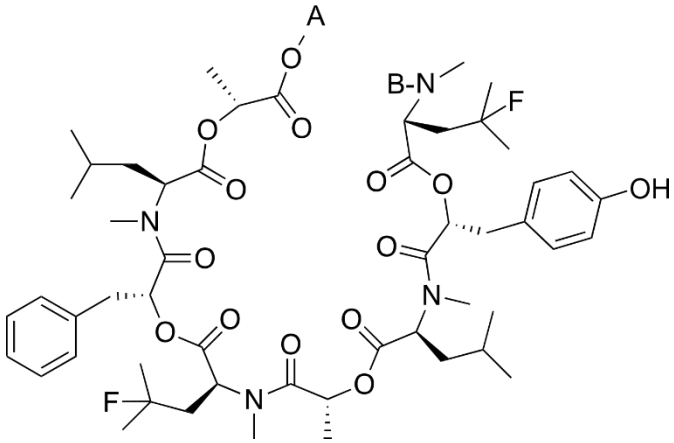
(II-9a)



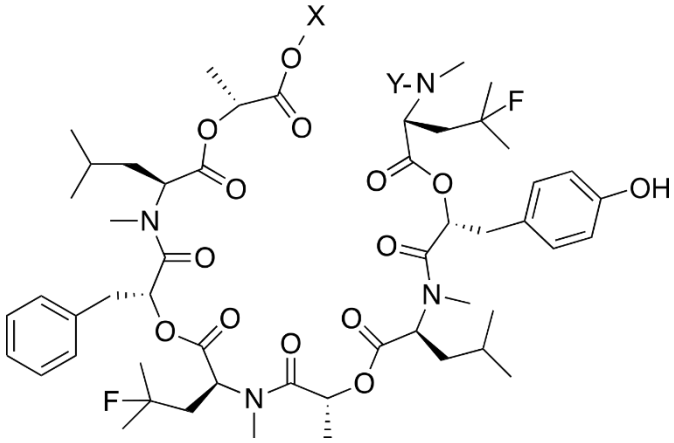
(II-9b)



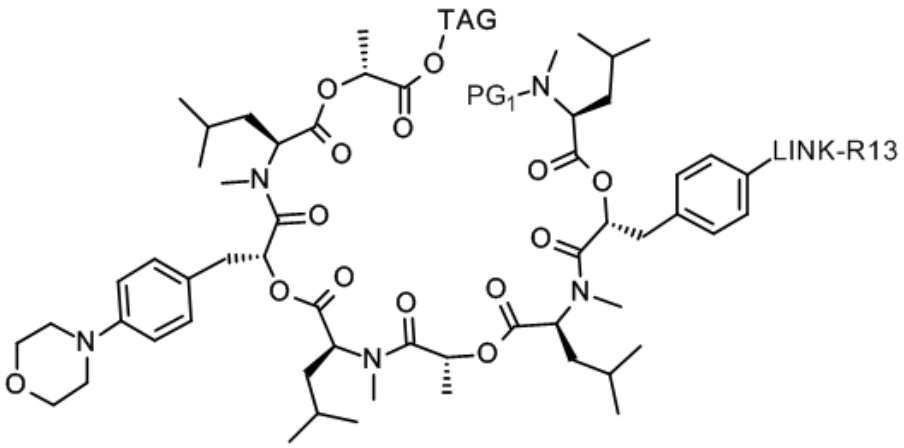
(II-10)



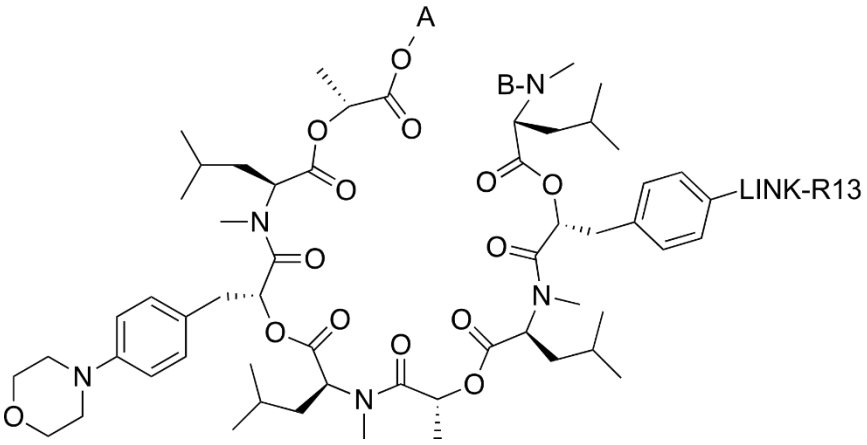
(II-10a)



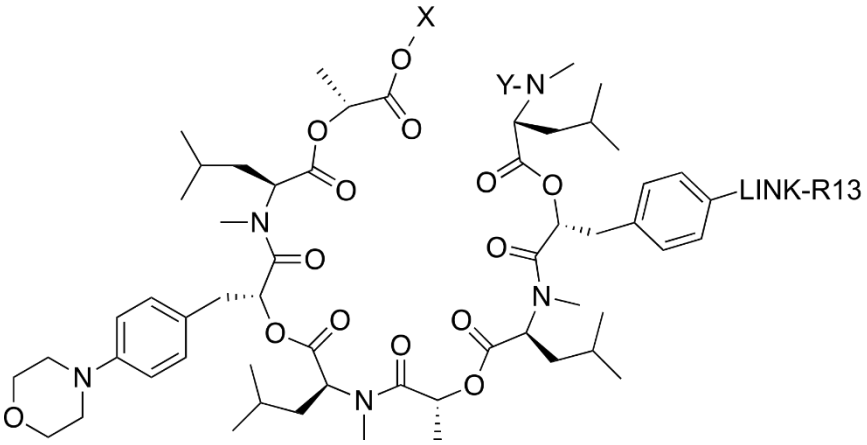
(II-10b)



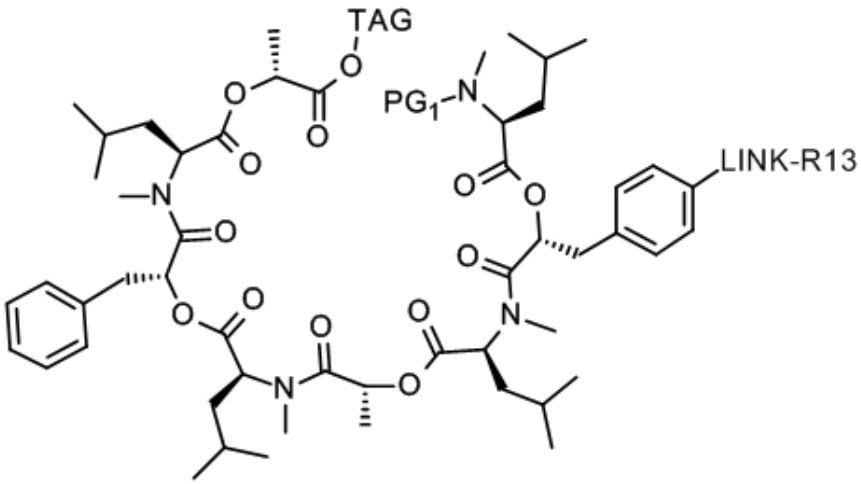
(II-11)



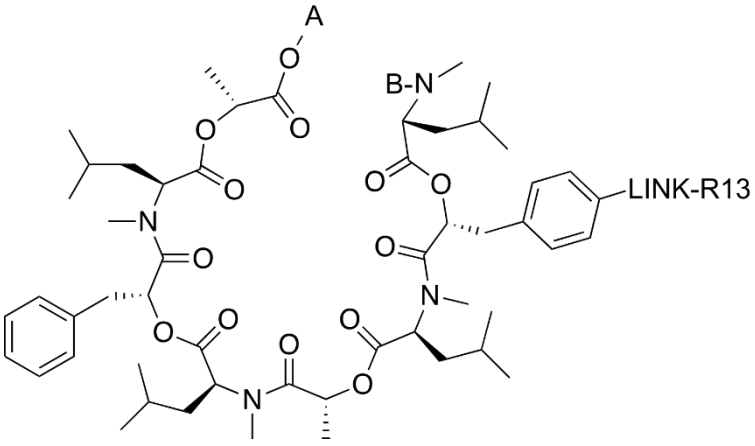
(II-11a)



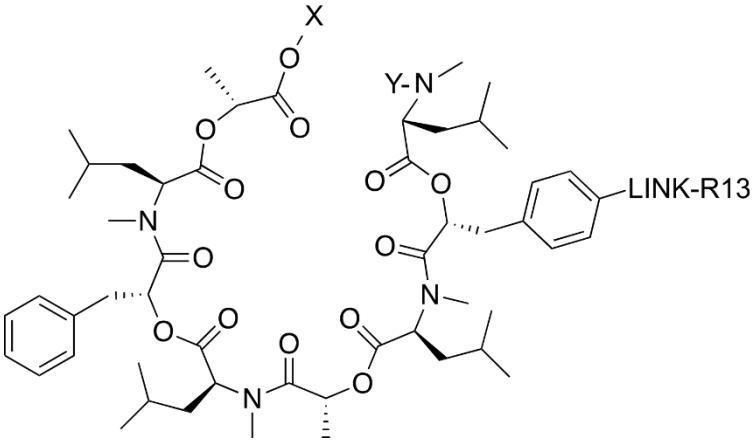
(II-11b)



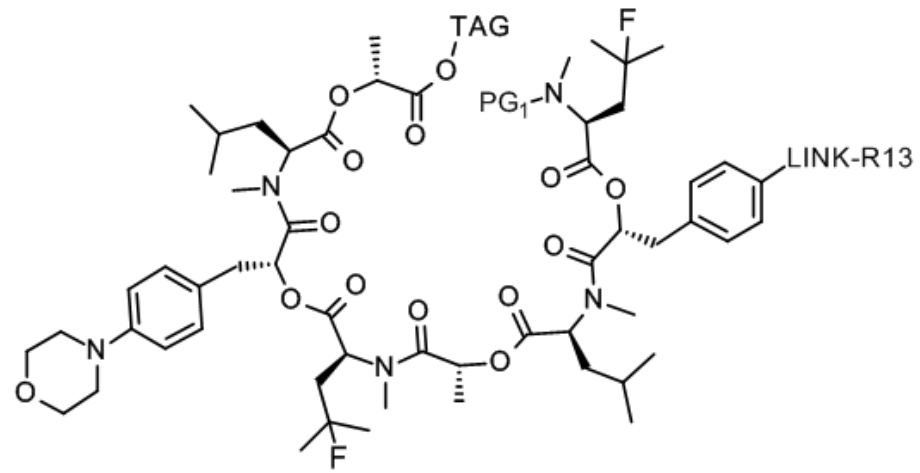
(II-12)



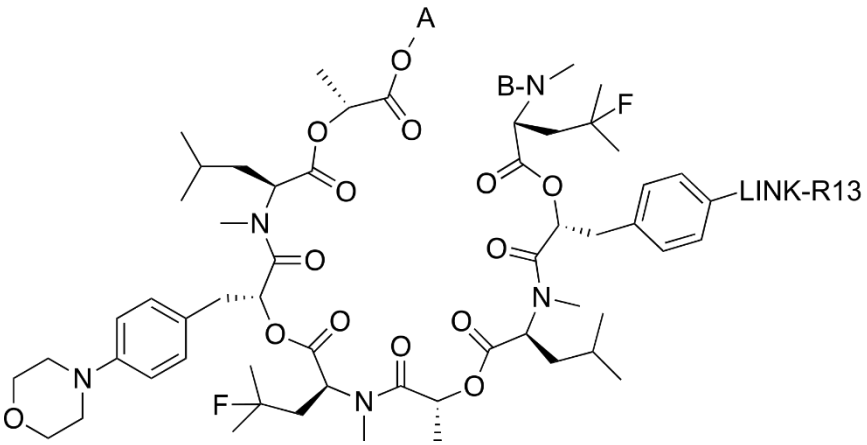
(II-12a)



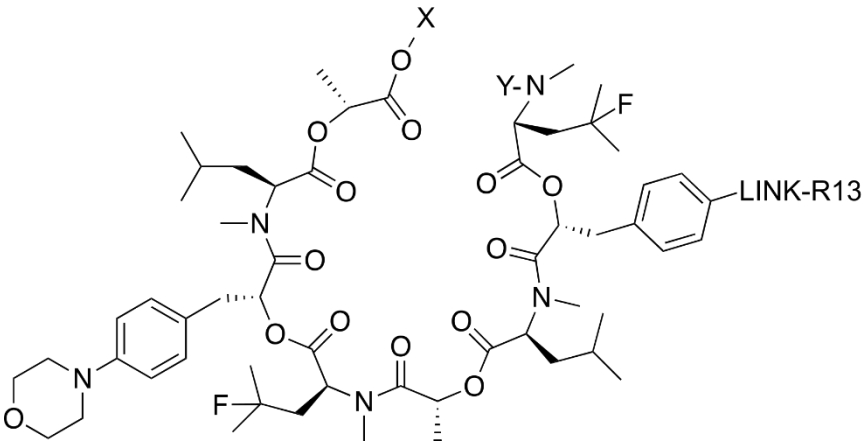
(II-12b)



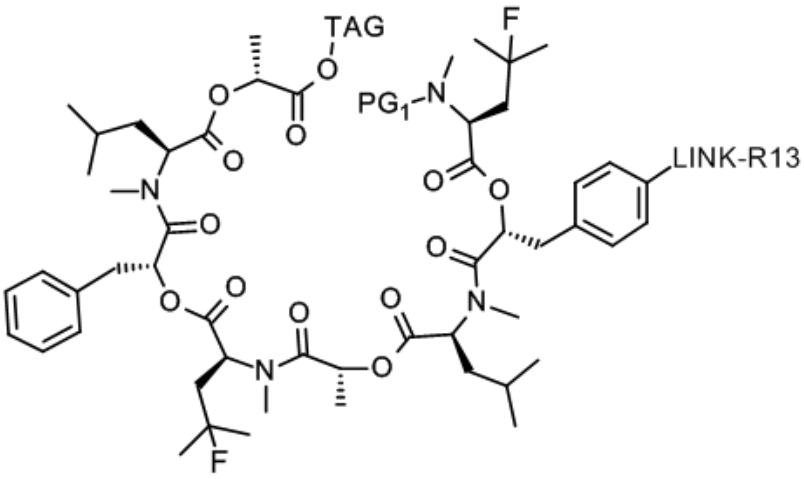
(II-13)



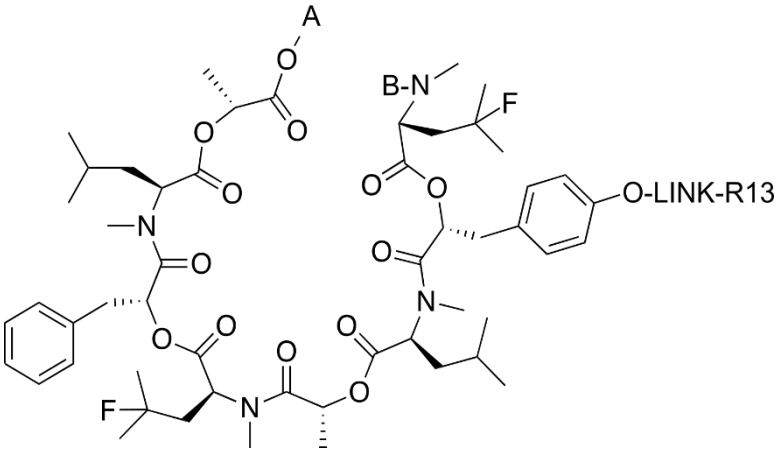
(II-13a)



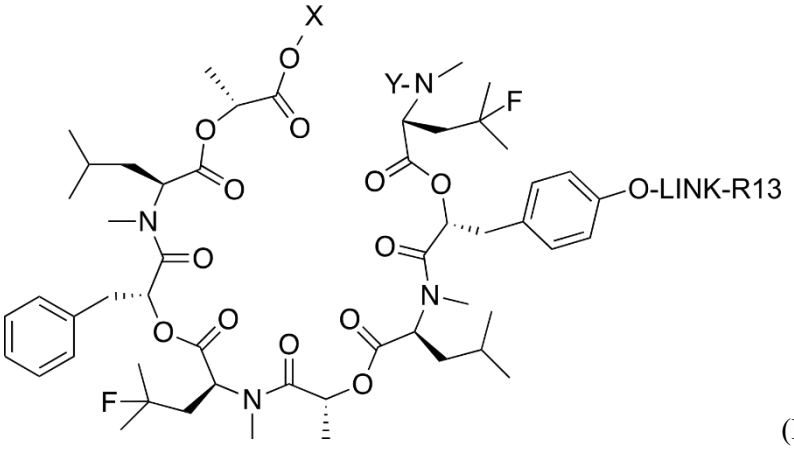
(II-13b)



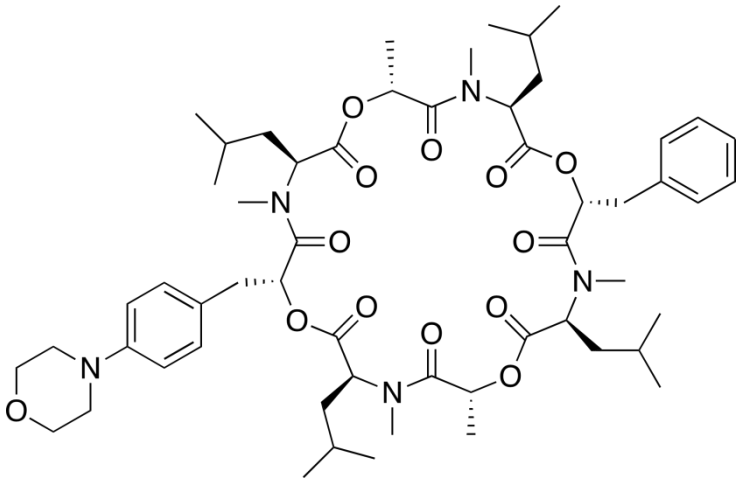
(II-14)



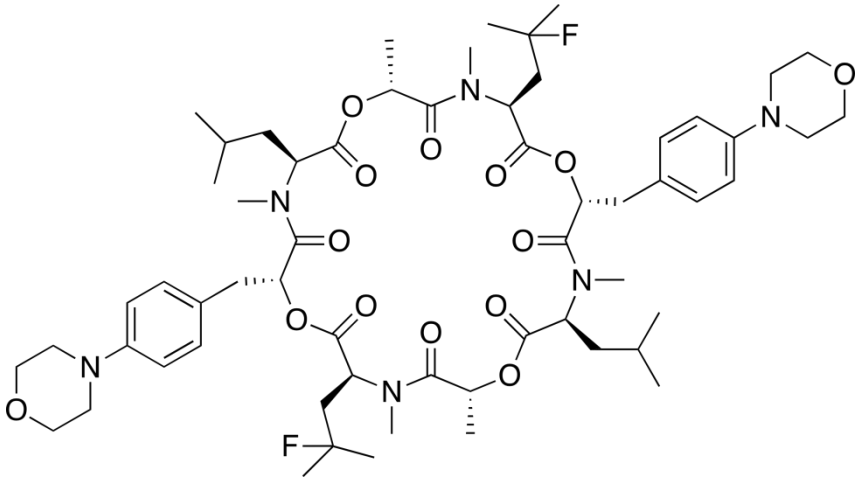
(II-14a)



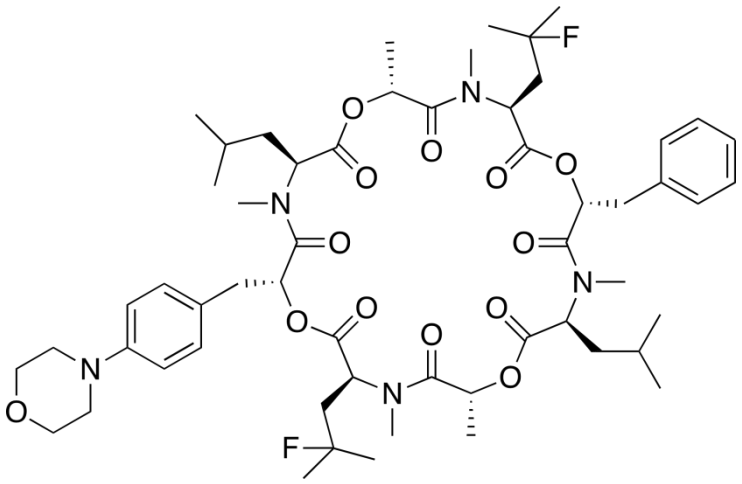
(II- 14b)



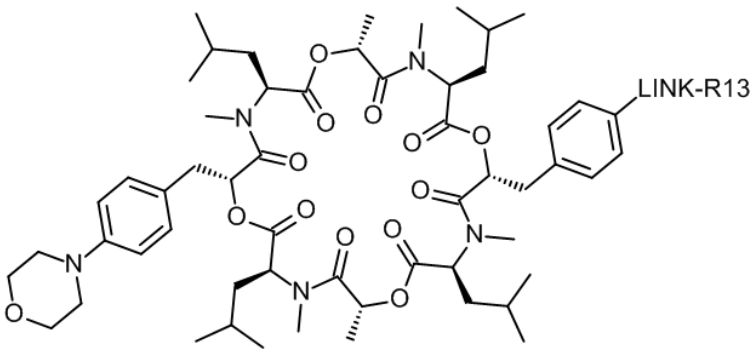
(I-1)



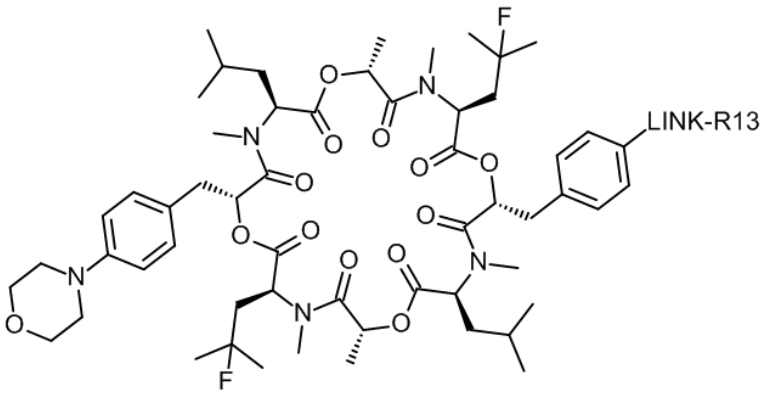
(I-2)



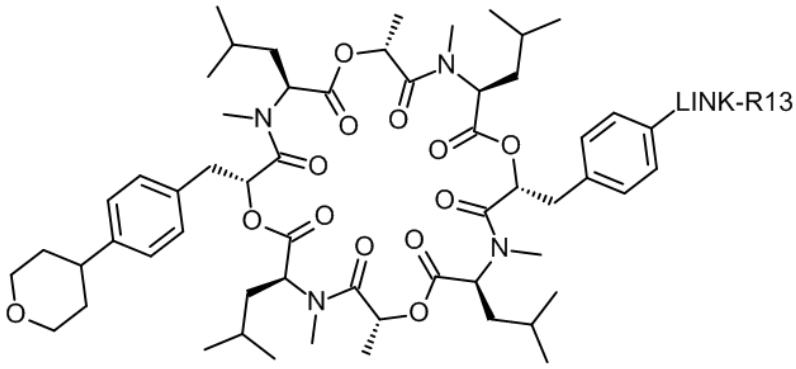
(I-3)



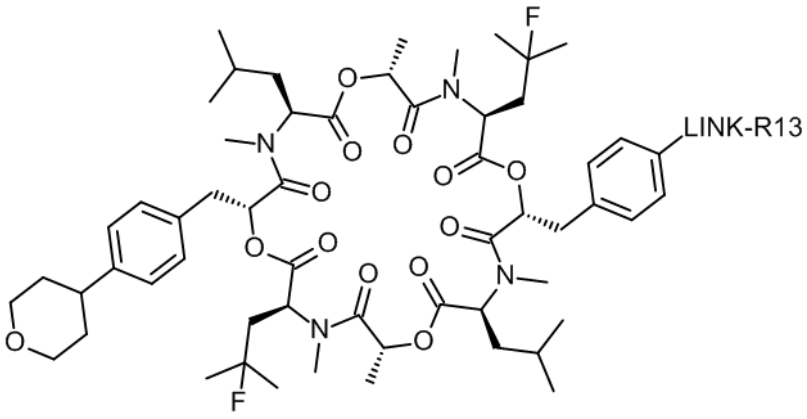
(I-4)



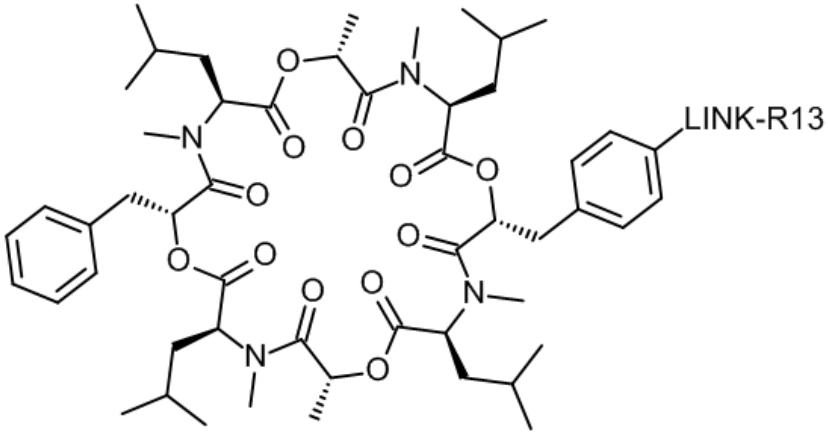
(I-5)



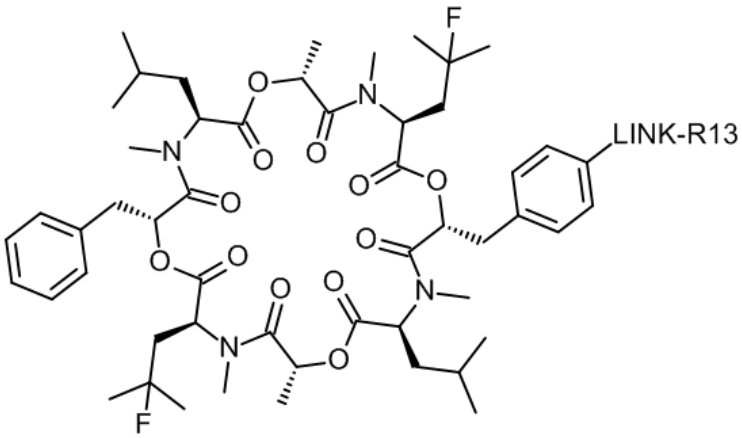
(I-6)



(I-7)



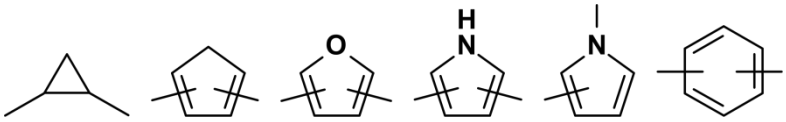
(I-8)



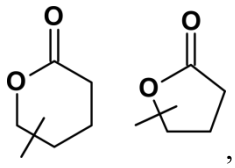
(I-9)

wherein in formulas (II-11) to (II-14b) and (I-4) to (I-9), respectively:

–LINK– is selected from:



and R13 is selected from $SO_2NH(CH_3)$, SO_2NH_2, $OC(O)CH_3$, CF_3 or one the following lactone structures:



,

and wherein TAG and PG1 are defined as in claim 15, X and Y are defined as in claim 3, and A and B are defined as in claim 1.