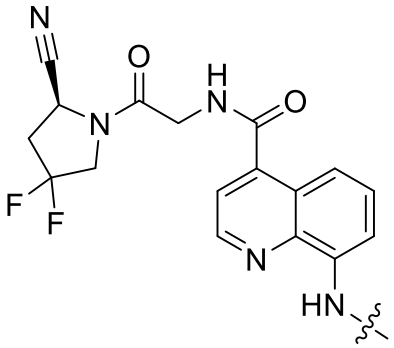
imaging tracers of atherosclerotic plaques. Dvořáková et al. (J Med Chem 2017) describe the preparation of a polymer conjugate containing a FAP-specific inhibitor for targeting applications. Loktev et al. (J Nucl Med 2018) describe the development of an iodinated and a DOTA-coupled radiotracer based on a FAP-specific enzyme inhibitor. Lindner et al. (J Nucl Med 2018) describe the modification and optimization of FAP inhibitors for use as theranostic tracers. Giesel et al. (J Nucl Med 2019) describe the clinical imaging performance of quinoline-based PET tracers that act as FAP inhibitors.

PROBLEMS TO BE SOLVED BY THE INVENTION

The present invention aims at the problem of providing improved binders (ligands) of fibroblast activation protein (FAP) suitable for targeting applications. The binders should be suitable for inhibition of FAP and/or targeted delivery of a payload, such as a therapeutic or diagnostic agent, to a site afflicted by or at risk of disease or disorder characterized by overexpression of FAP. Preferably, the binder should form a stable complex with FAP, display an increased affinity, increased inhibitory activity, a slower rate of dissociation from the complex, and/or prolonged residence at a disease site.

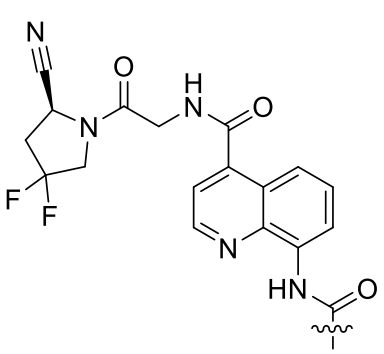
SUMMARY ~~OF THE INVENTION~~

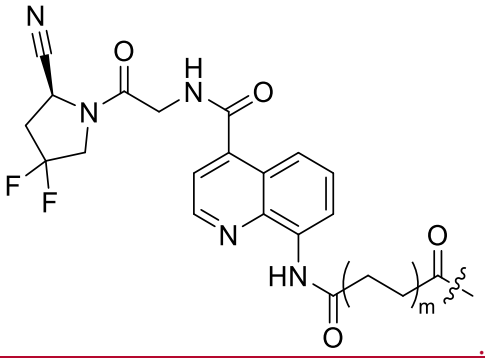
The present inventors have found novel organic ligands of fibroblast activation protein (FAP) suitable for targeting applications. The compounds according to the present ~~invention~~disclosure (also referred to as ligands or binders) comprise a small binding moiety **A** having the following structure:



A

In an aspect of the present disclosure, there is provided a compound, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof, wherein the compound comprises a moiety having the following structure $\mathbf{A^1}$ or $\mathbf{A^2}$, wherein *m* is 0, 1, 2, 3, 4 or 5:

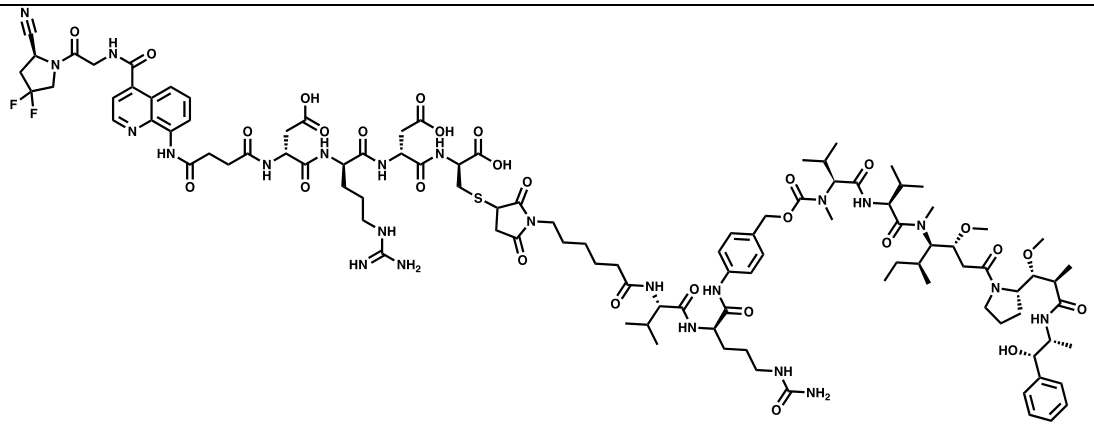
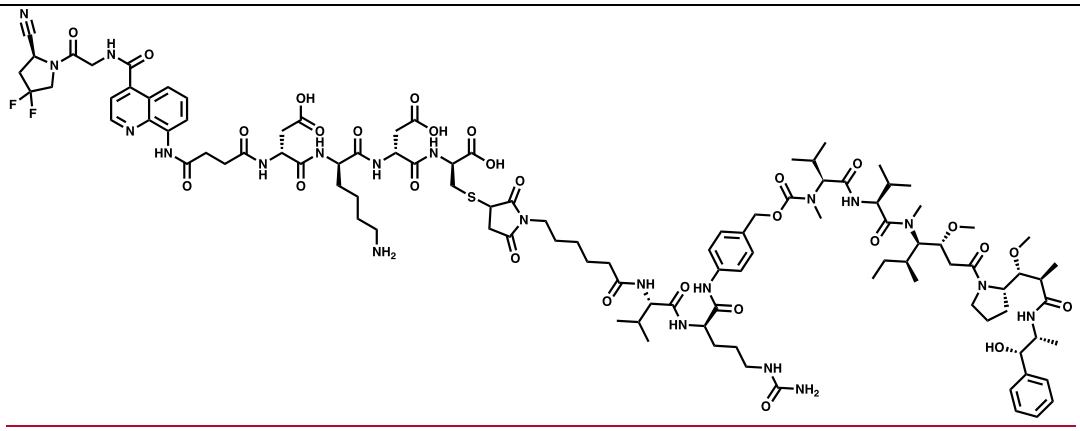


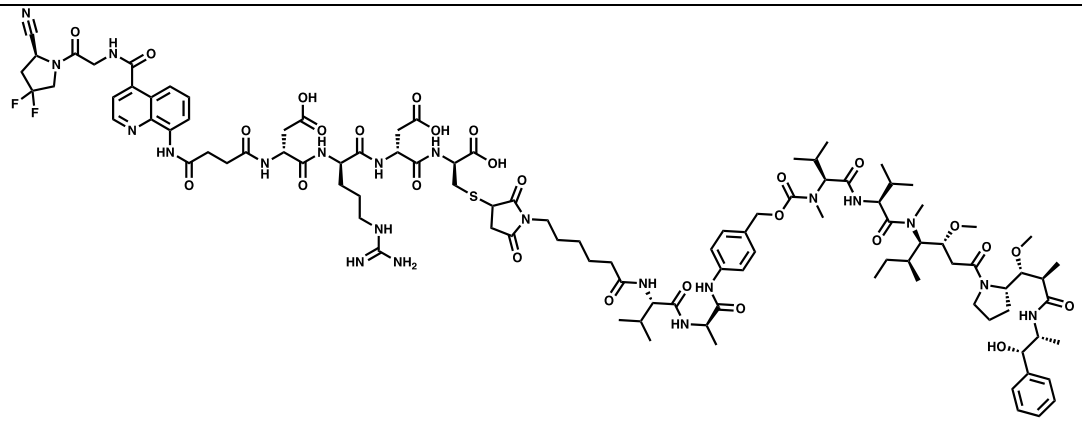
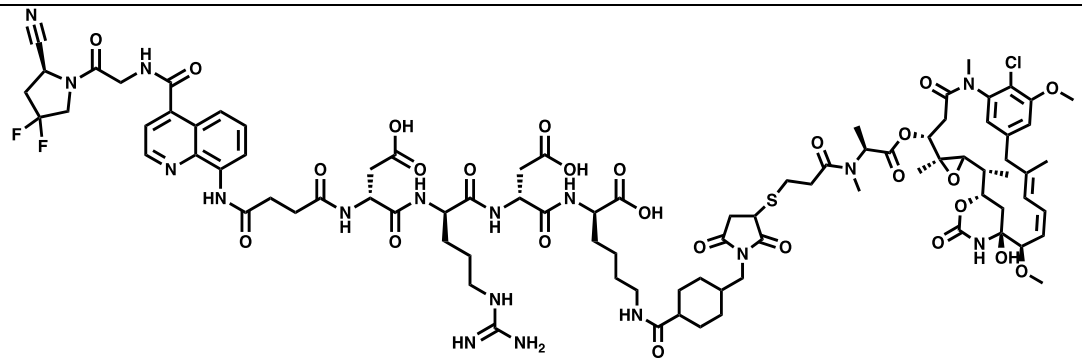
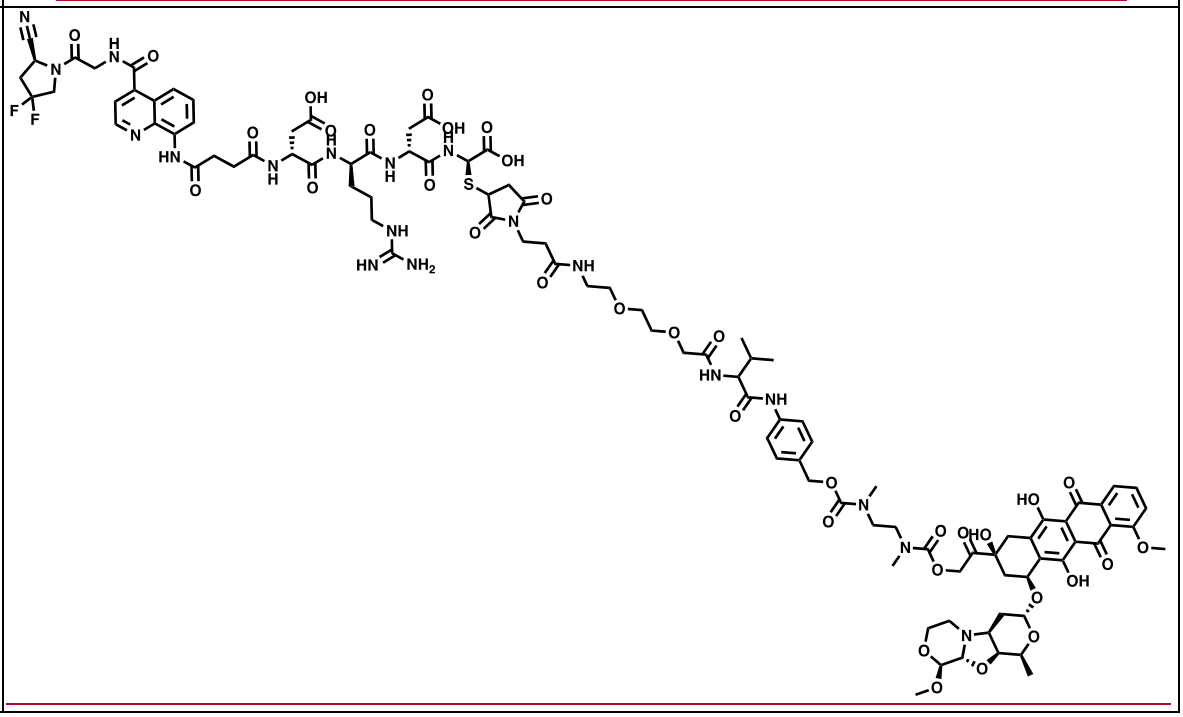


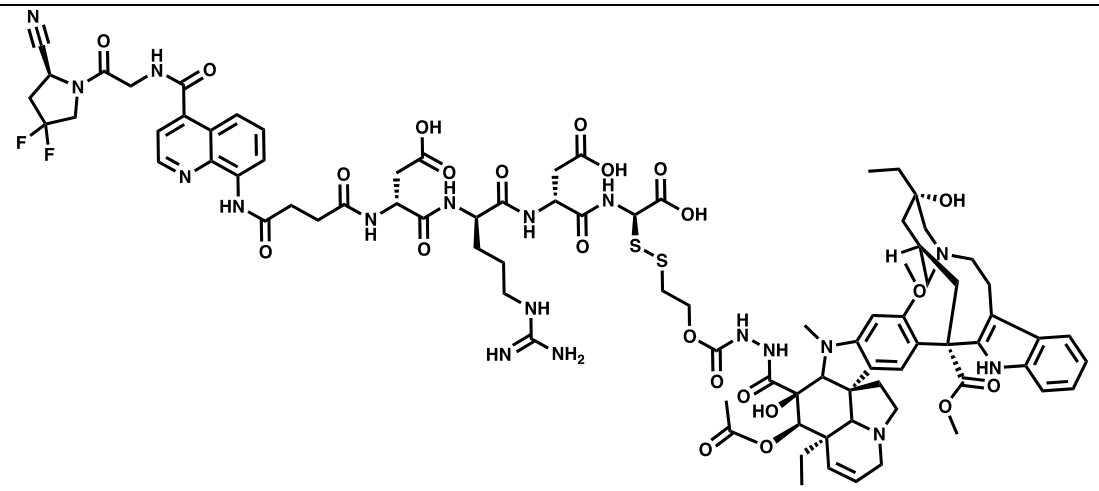
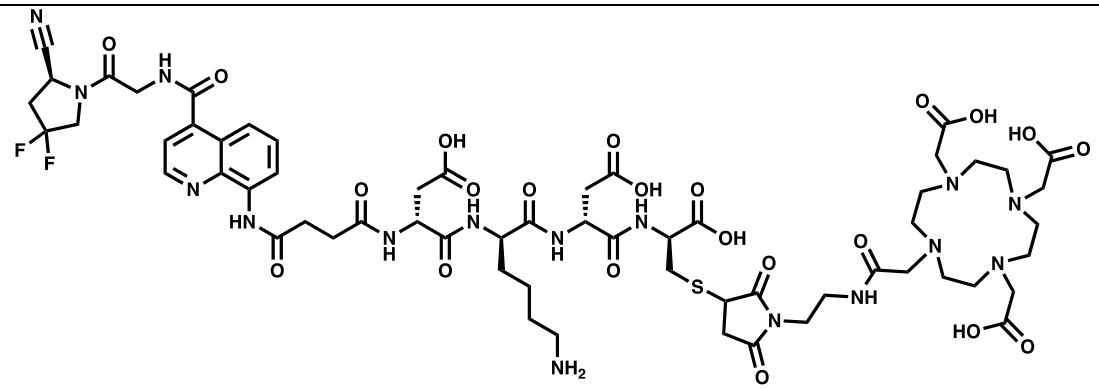
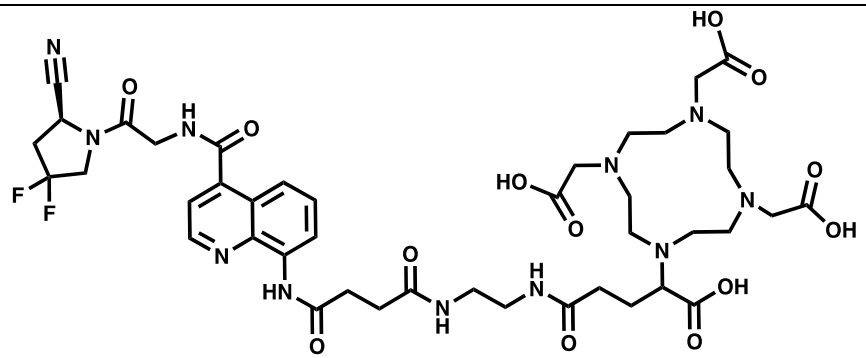
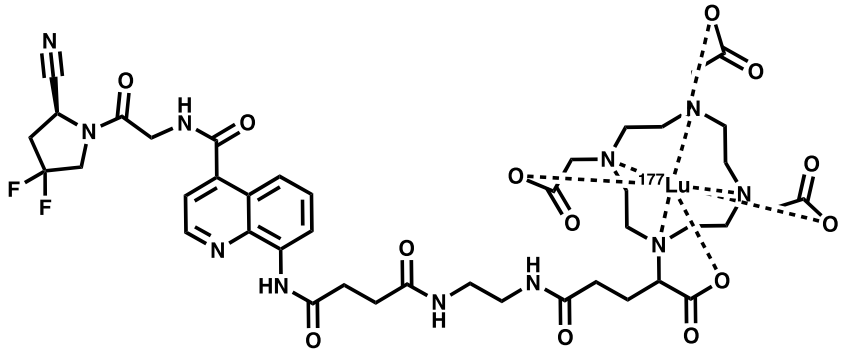
.

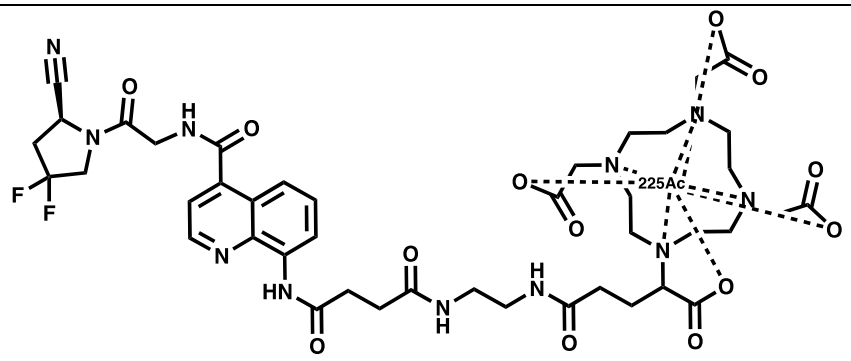
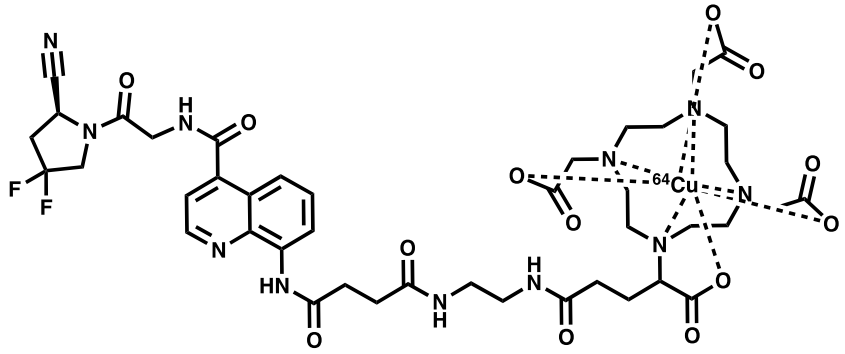
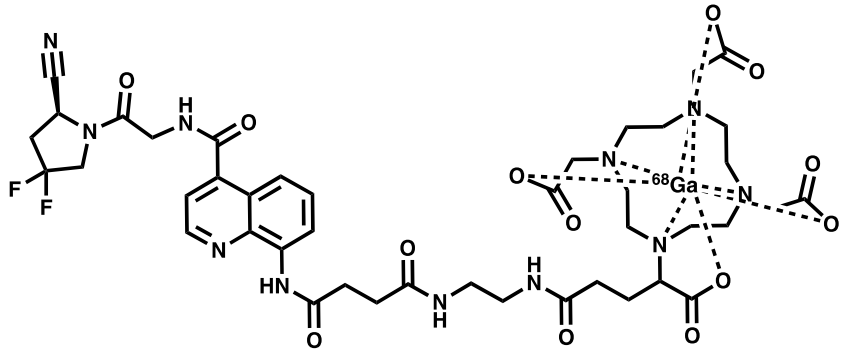
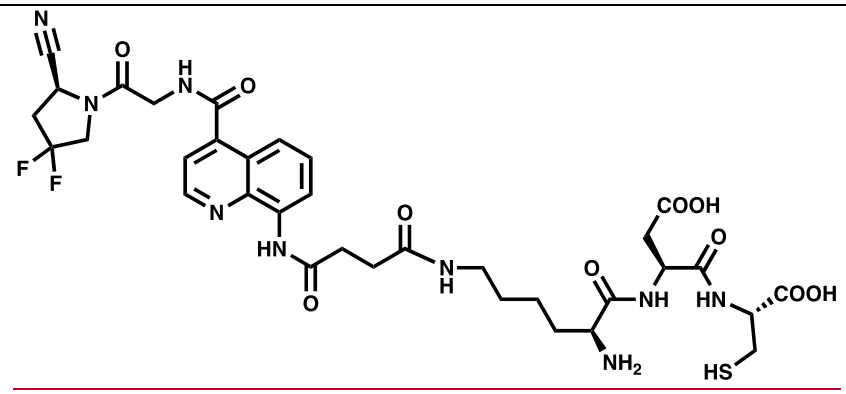
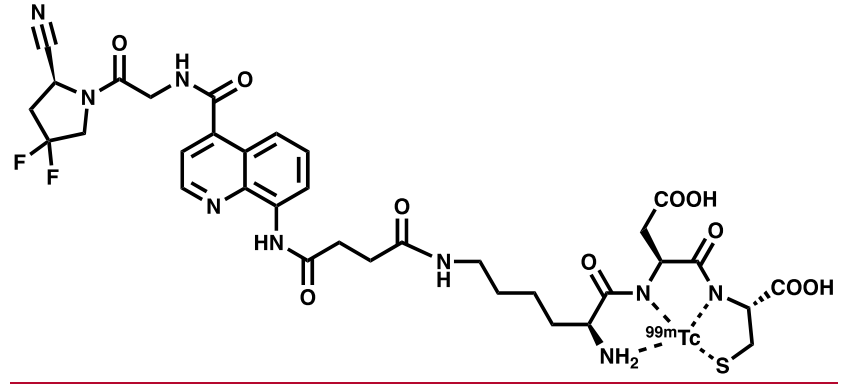
A[1] **A[2]**

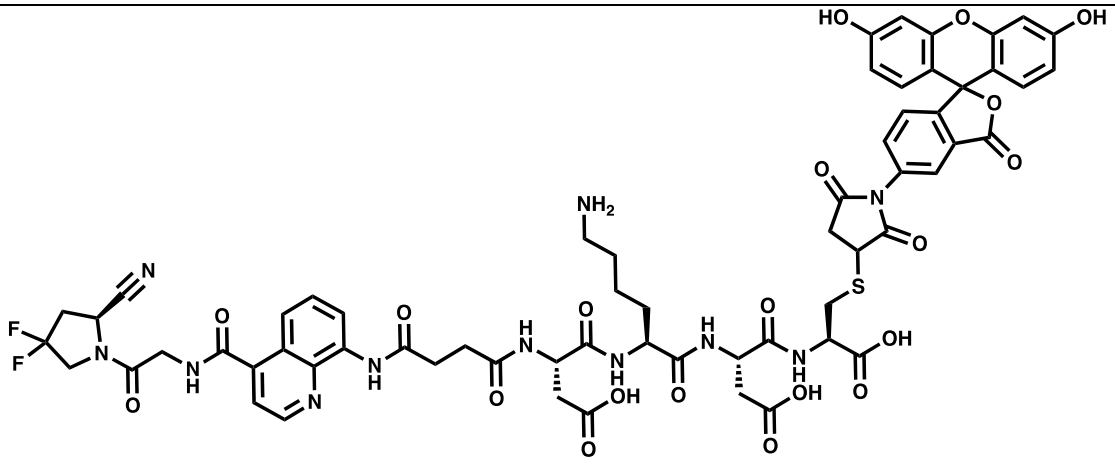
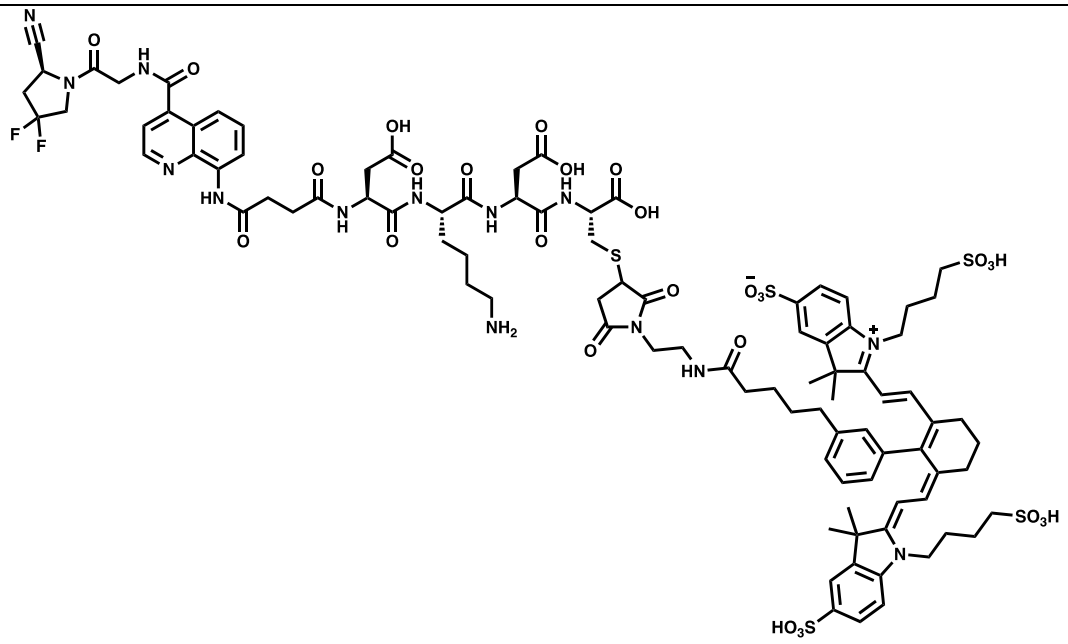
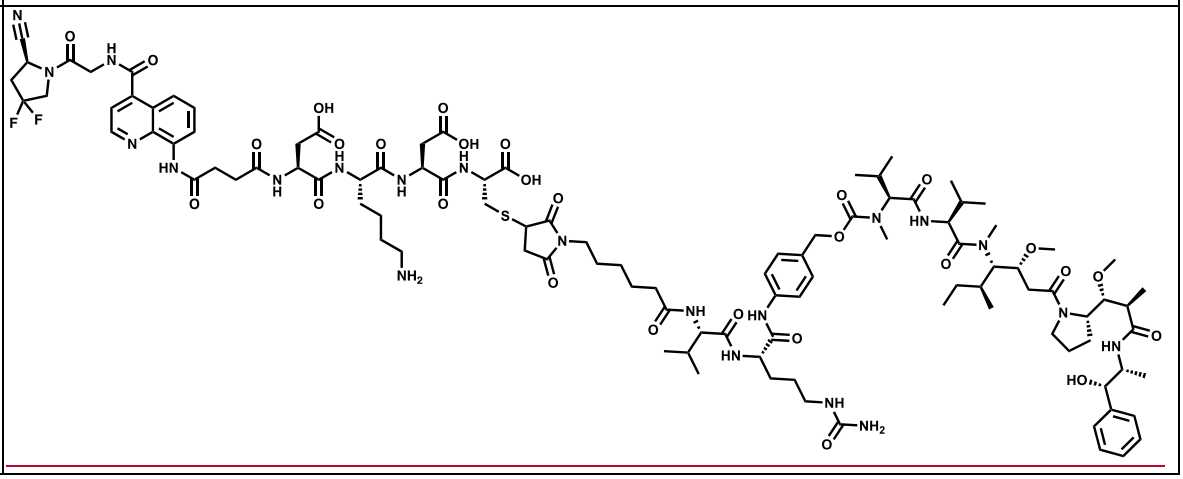
In another aspect of the present disclosure, there is provided a compound having one the following structures, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof:

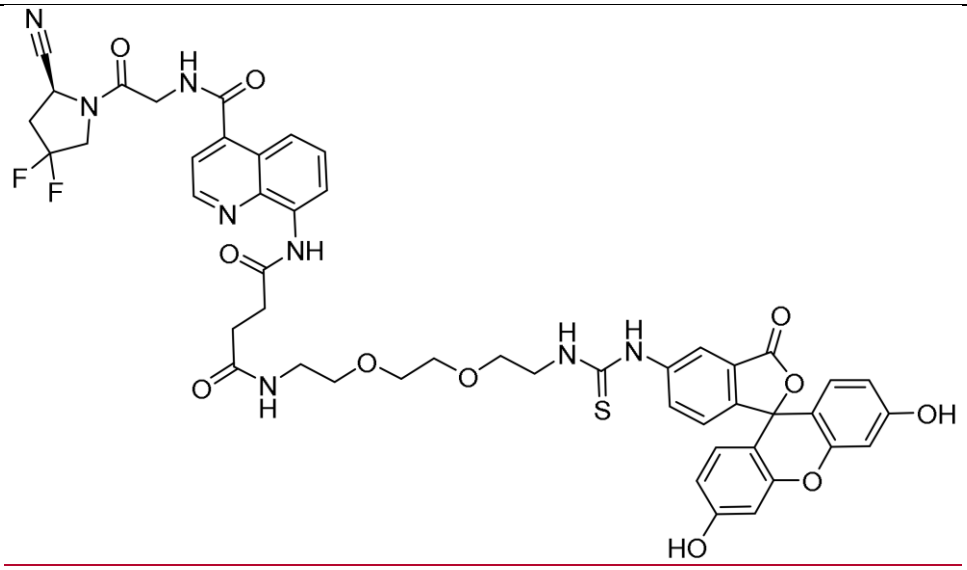
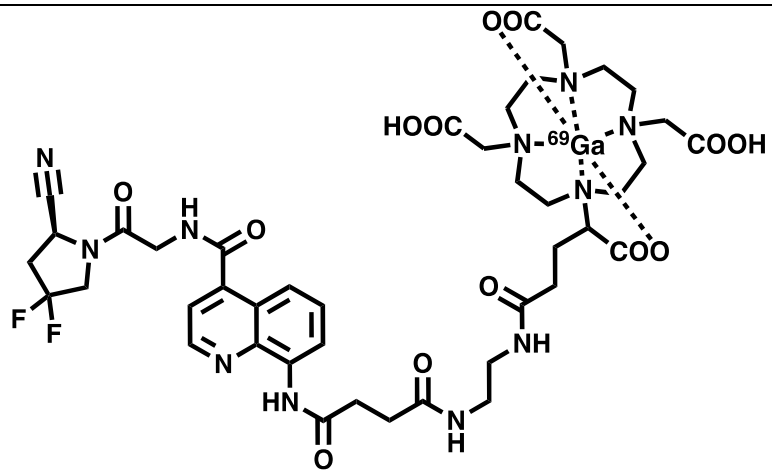
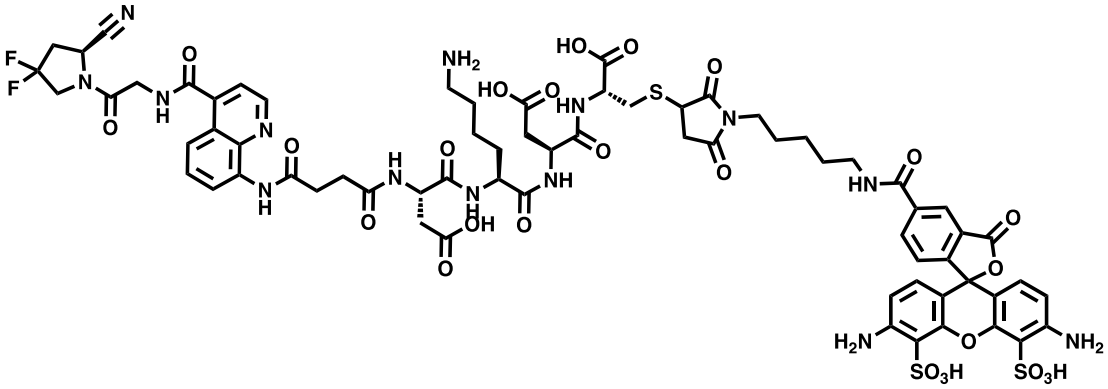
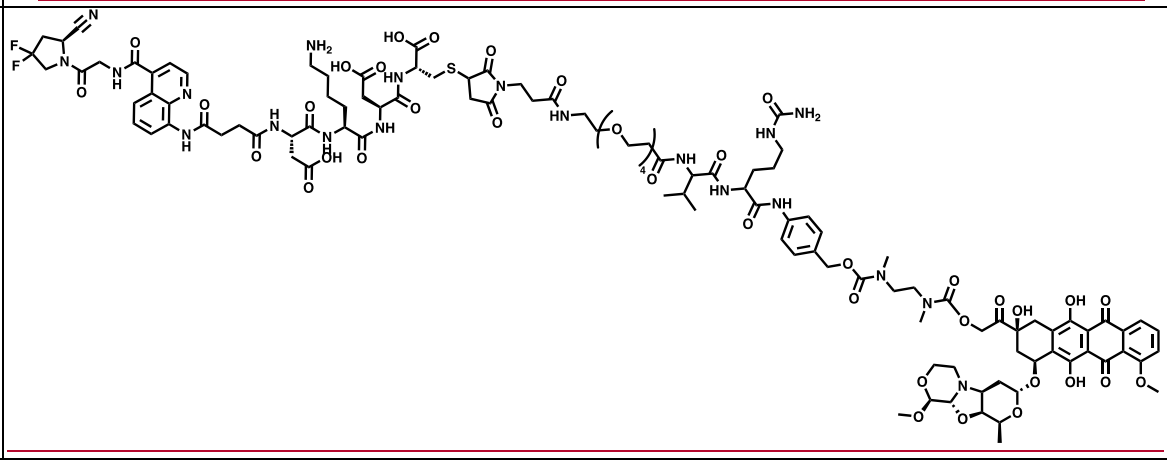
#	Structure
1	
2	

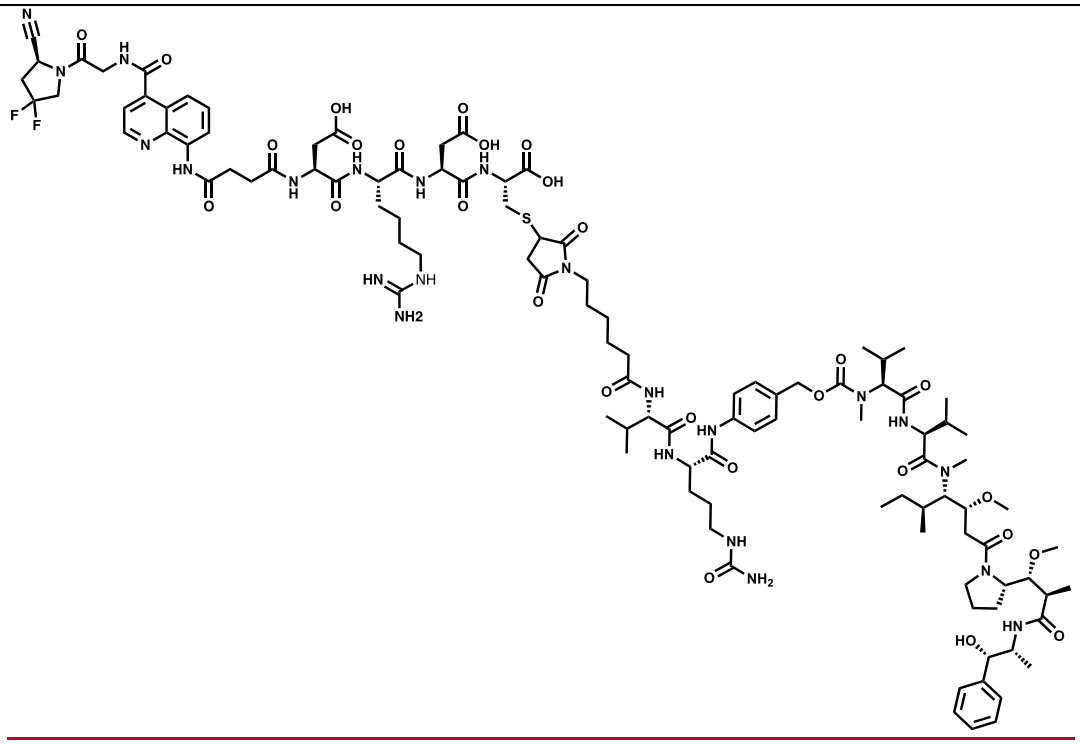
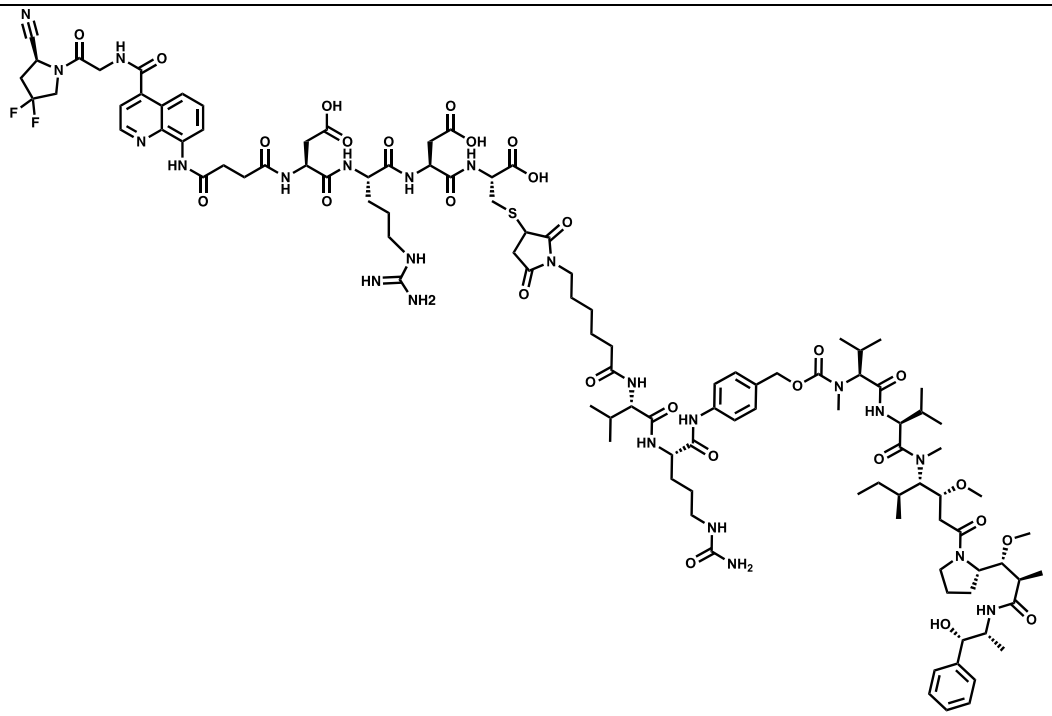
3	
4	
5	

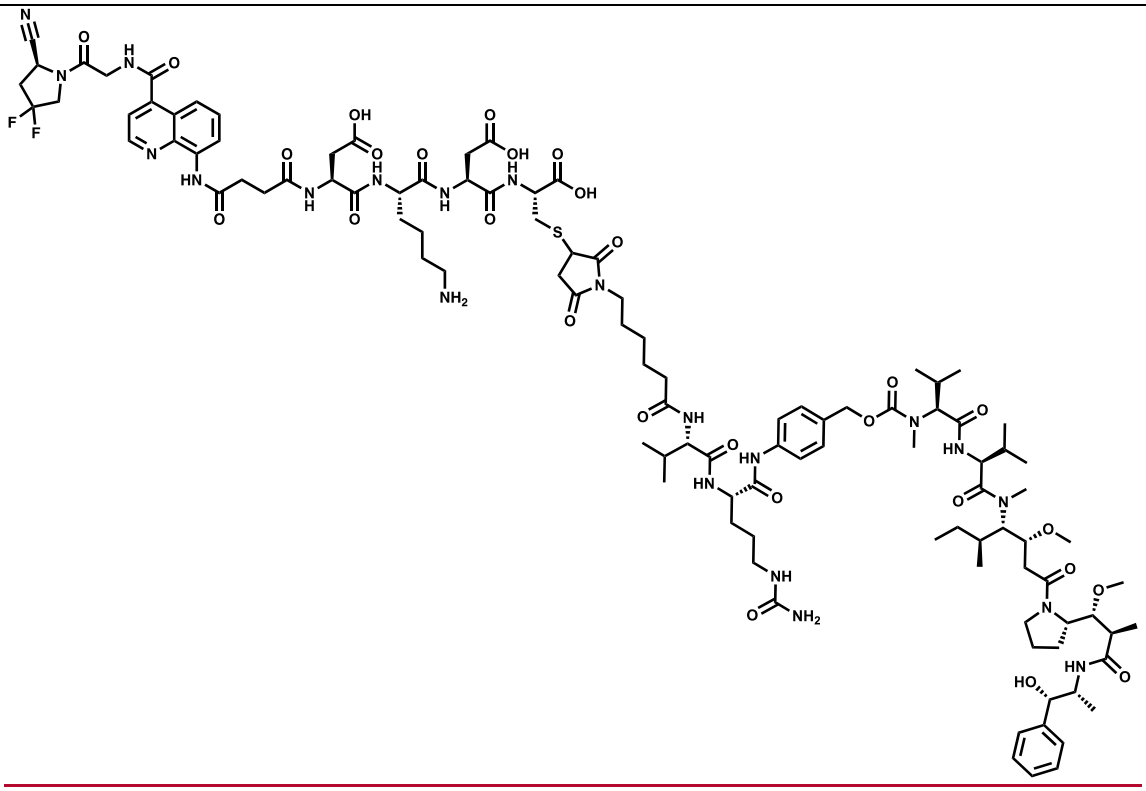
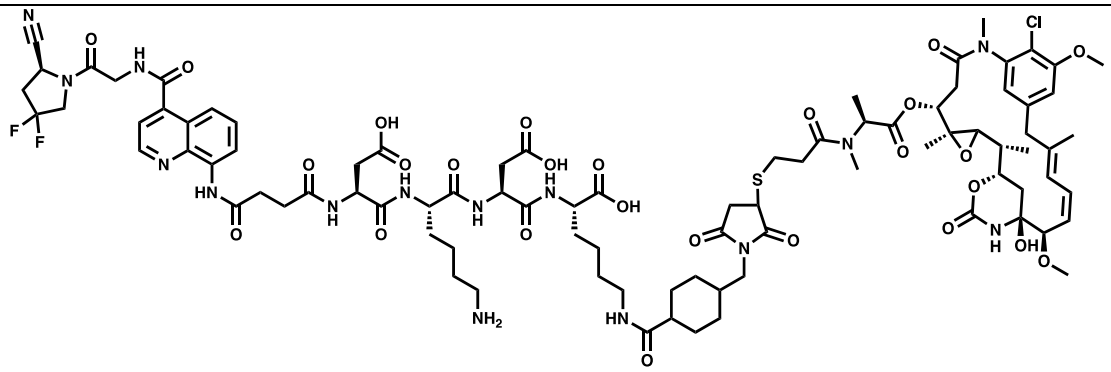
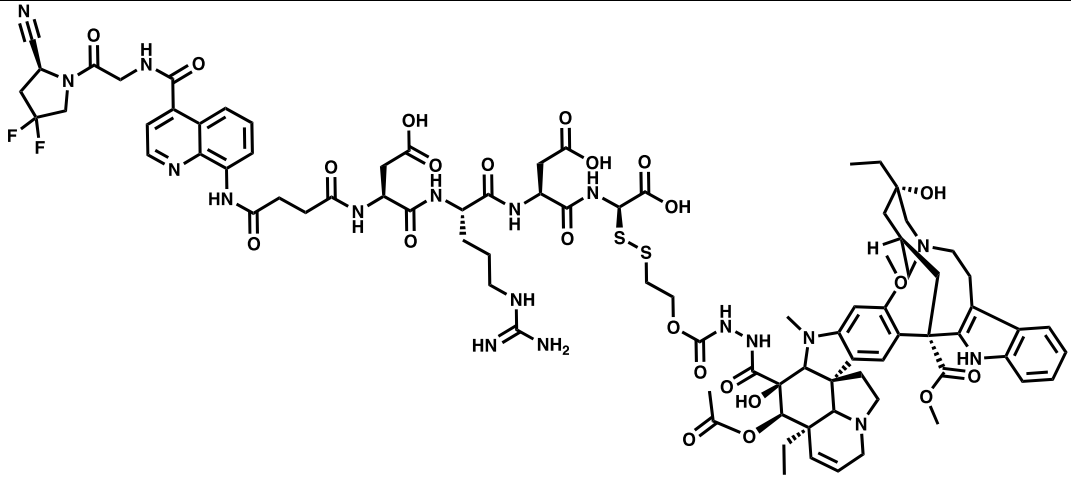
6	
7	
8	
9	

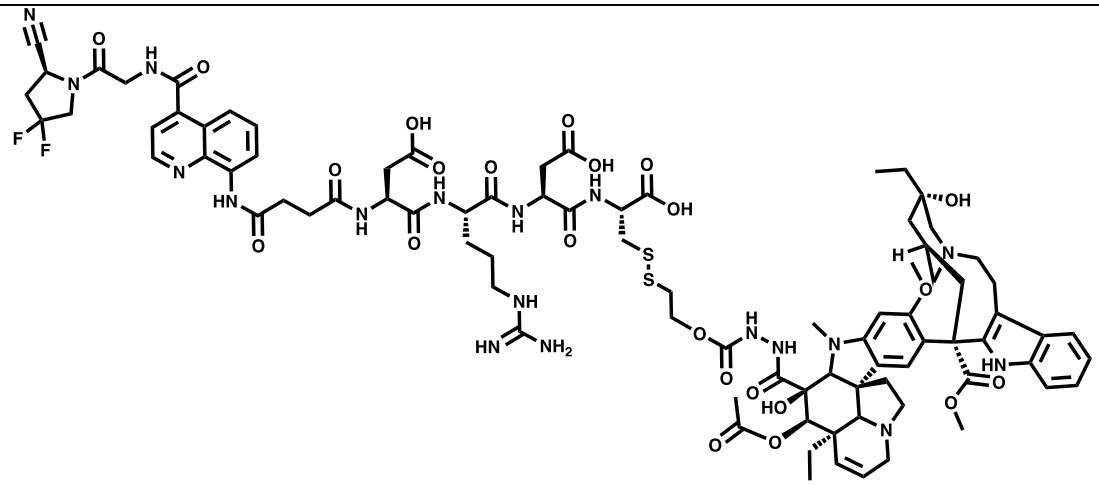
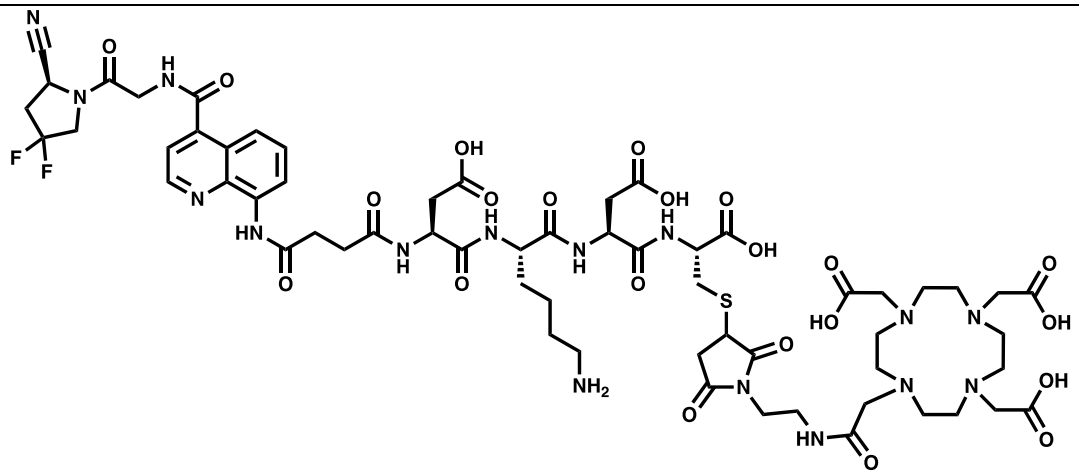
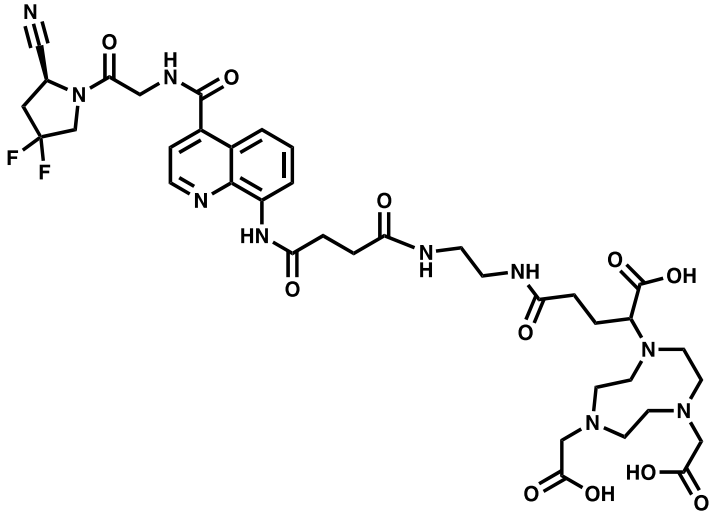
10	
11	
12	
13	
14	

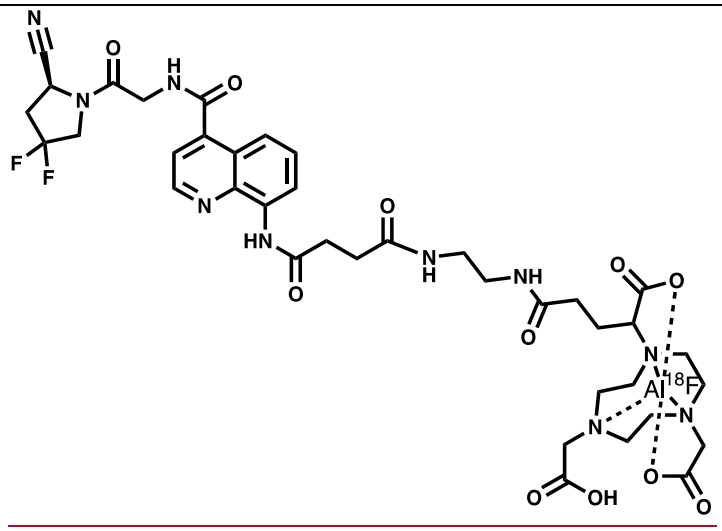
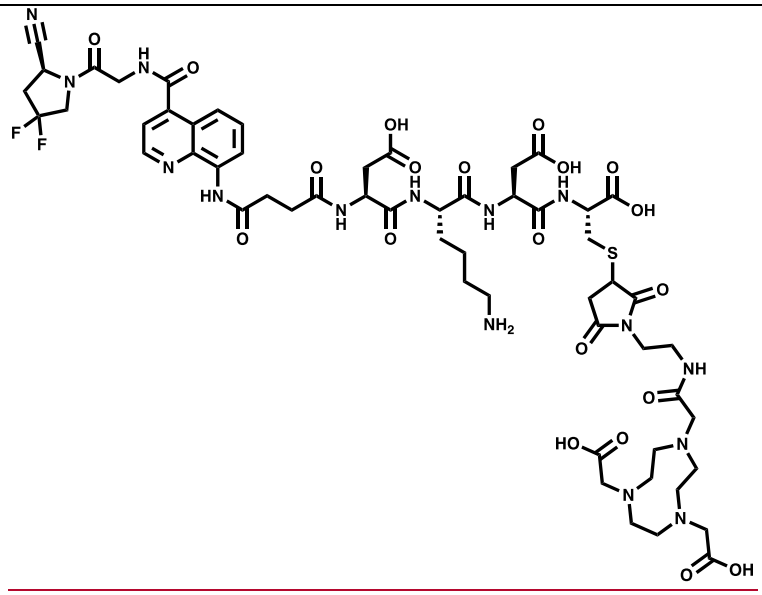
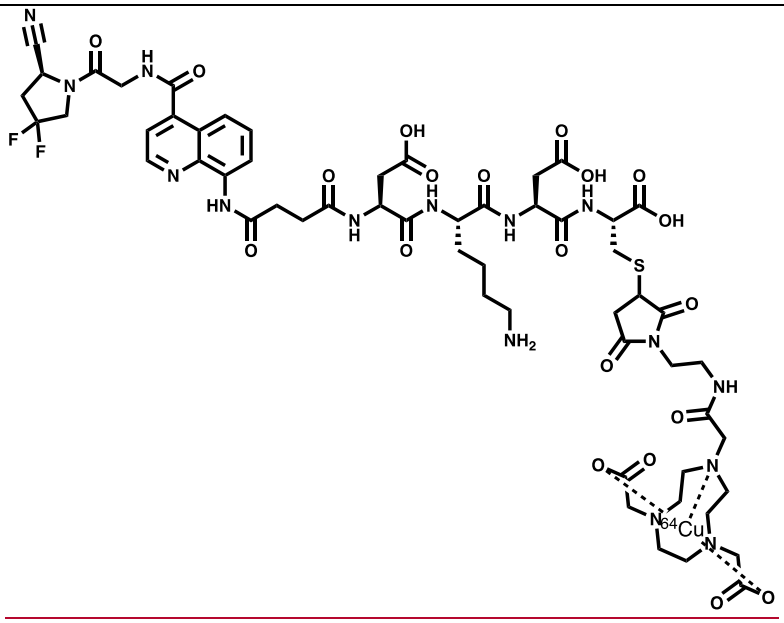
15	
18	
21	

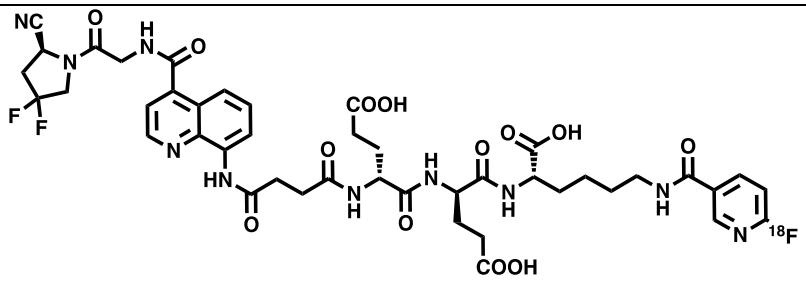
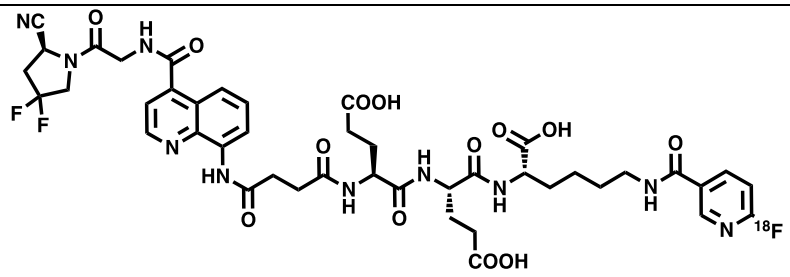
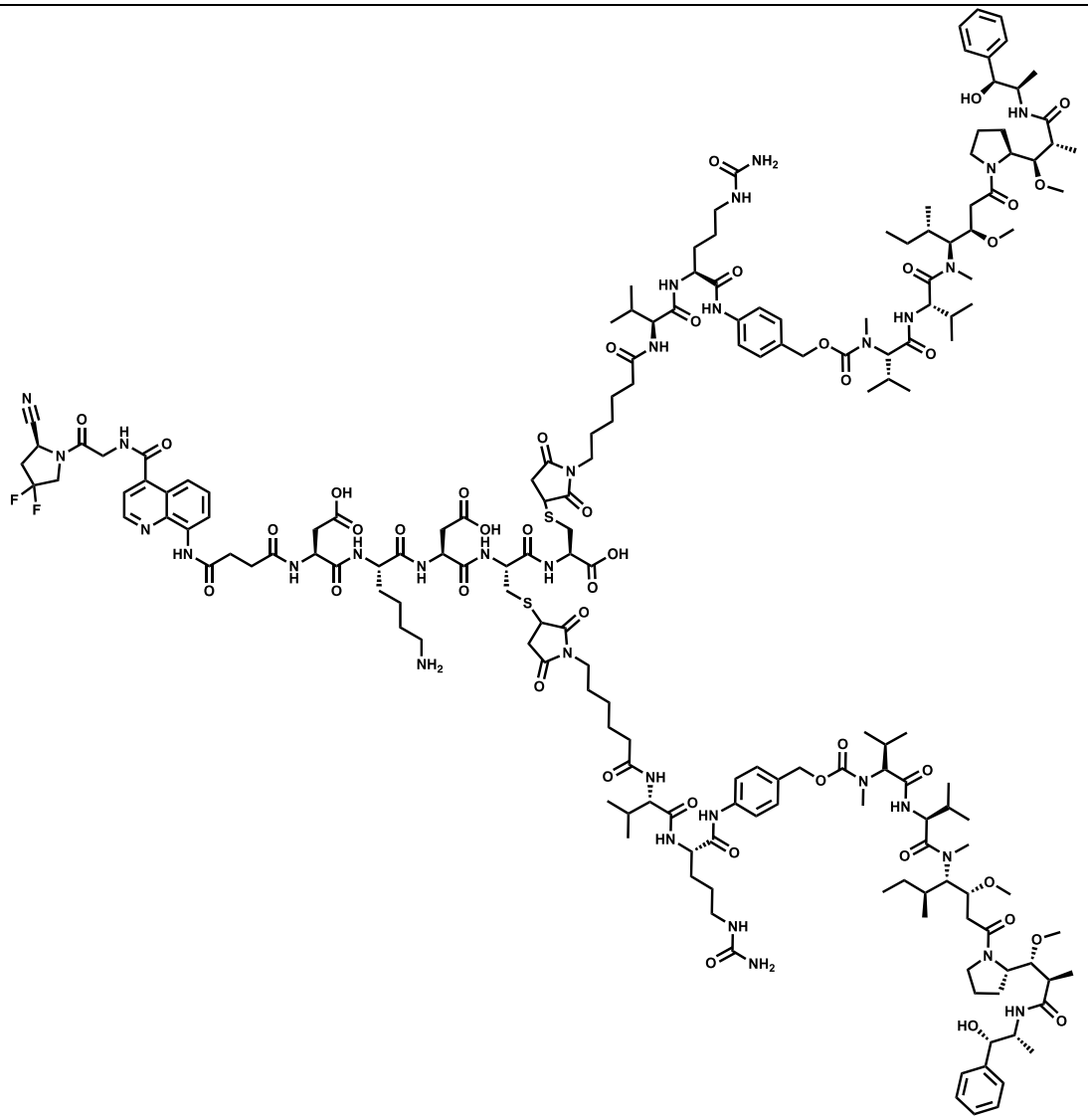
26	
27	
30	
31	

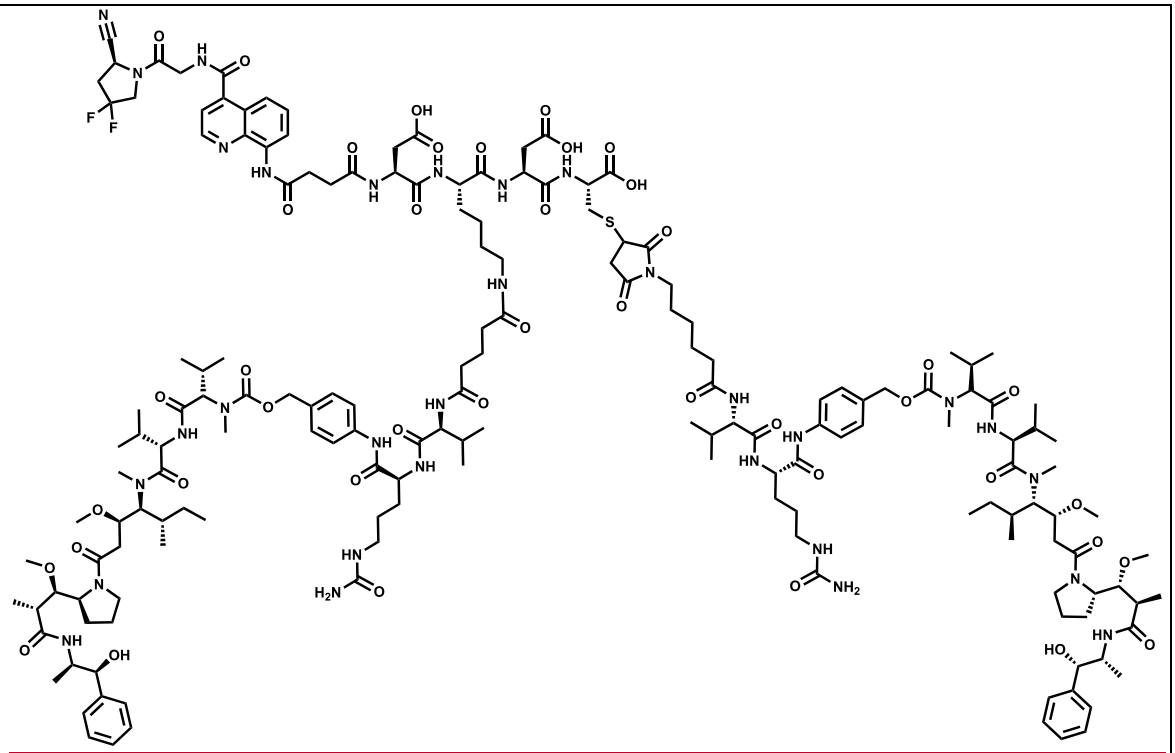
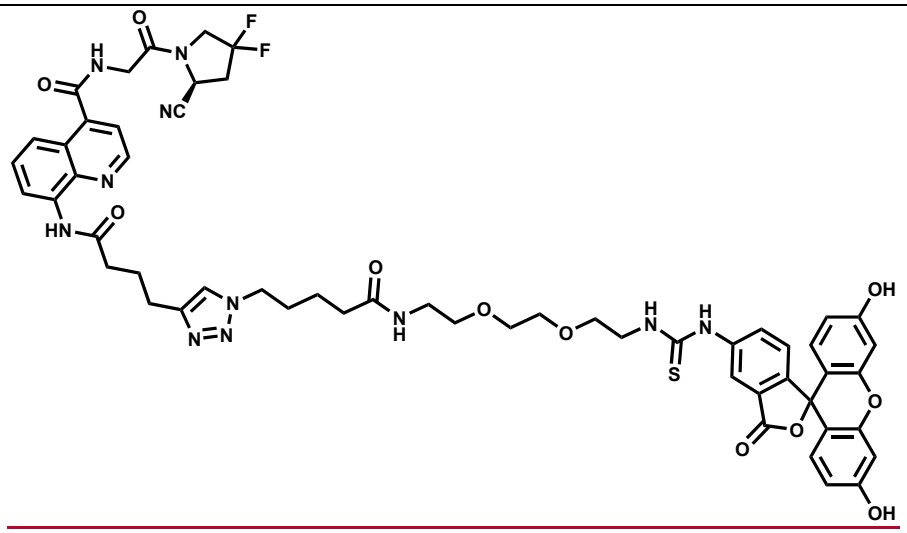
34	
34a	

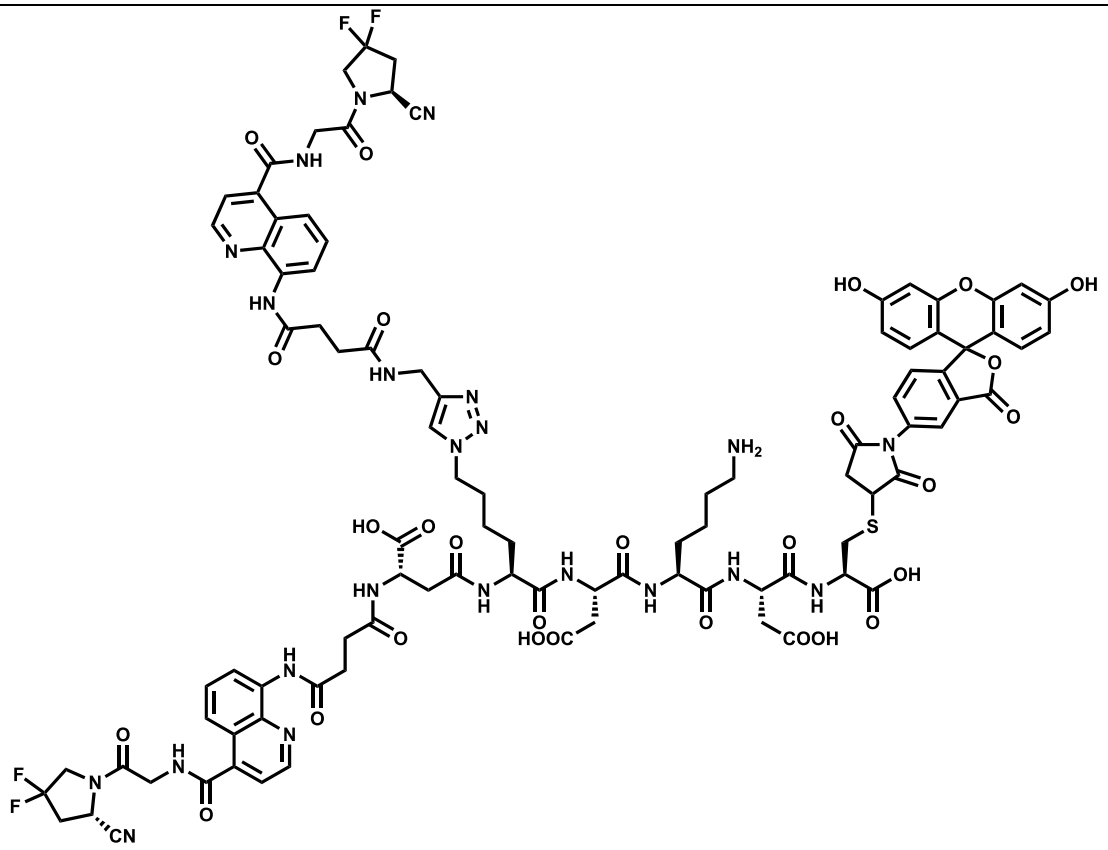
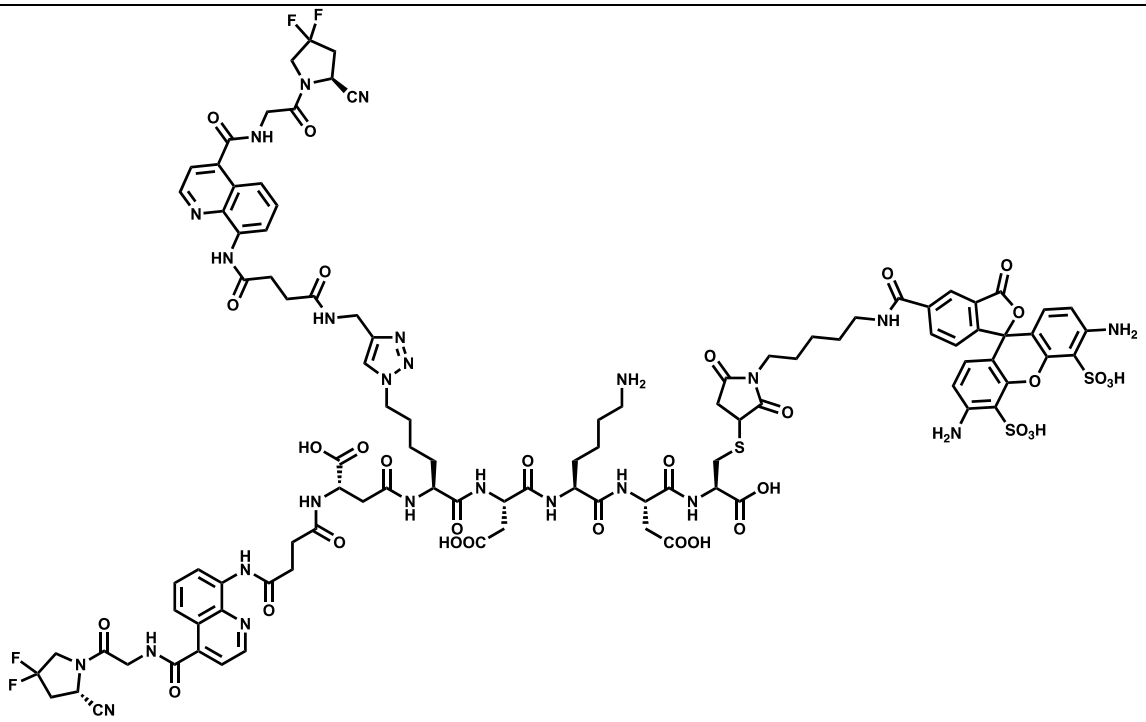
35	
36	
37	

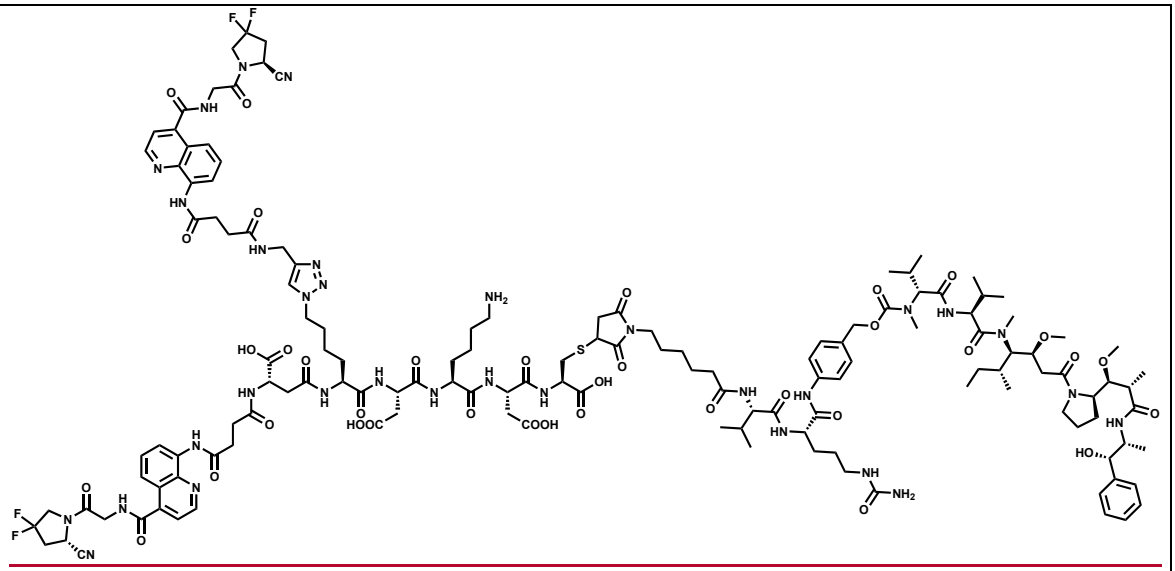
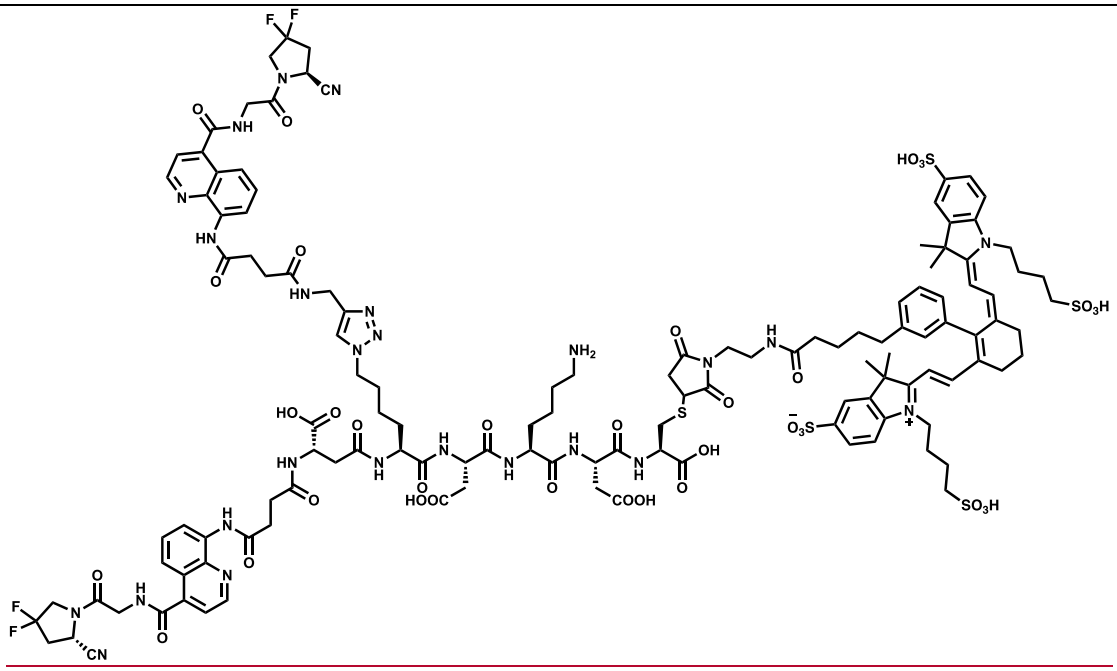
37a	
38	
39	

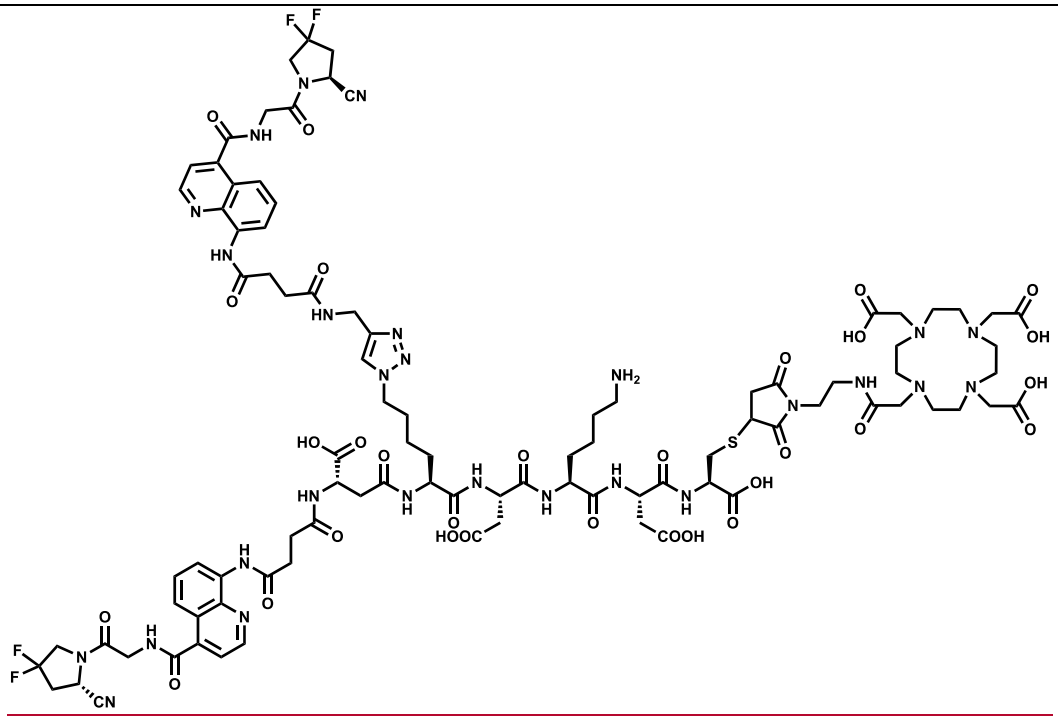
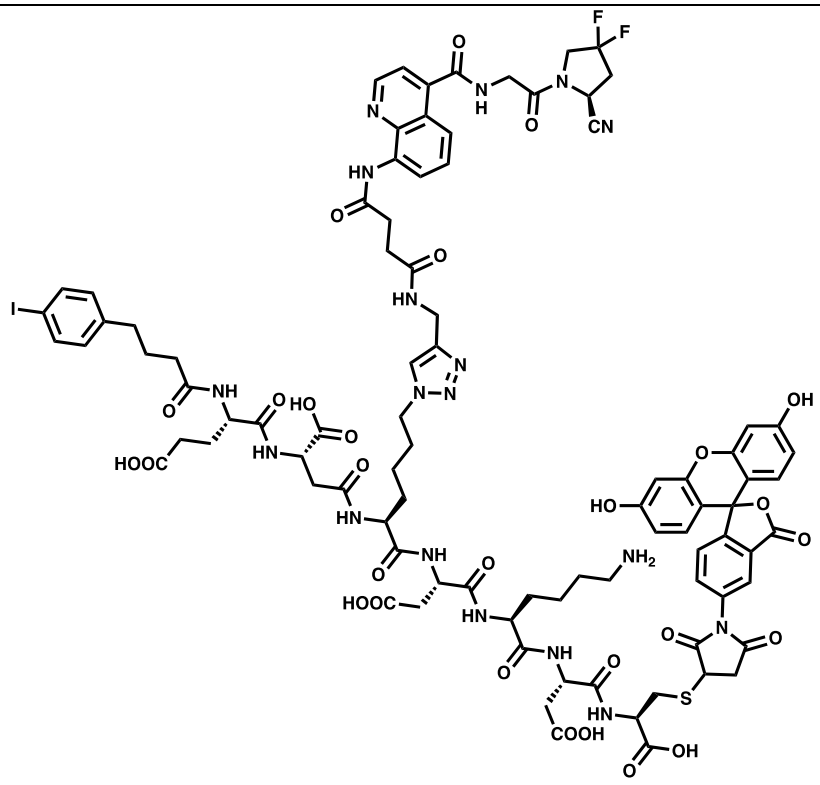
40	
41	
42	

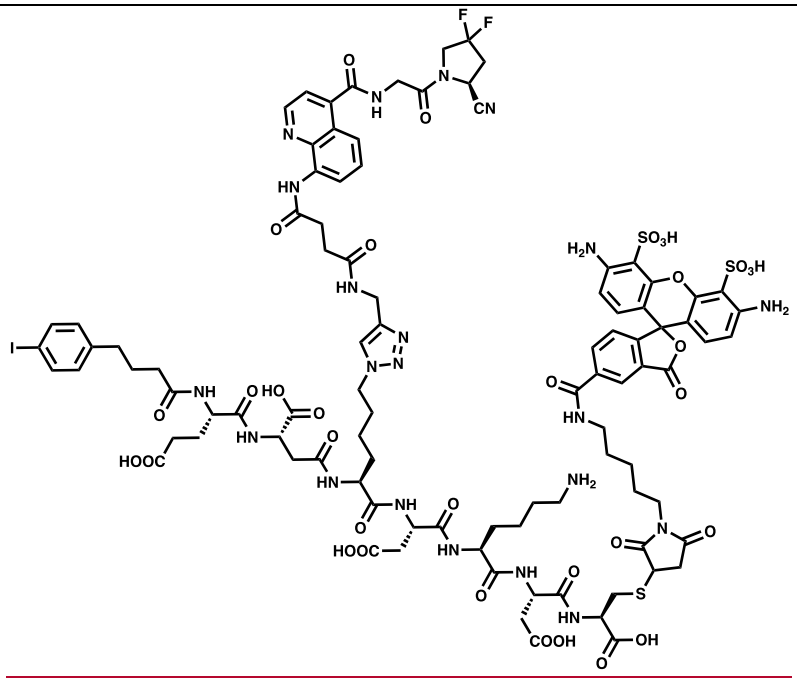
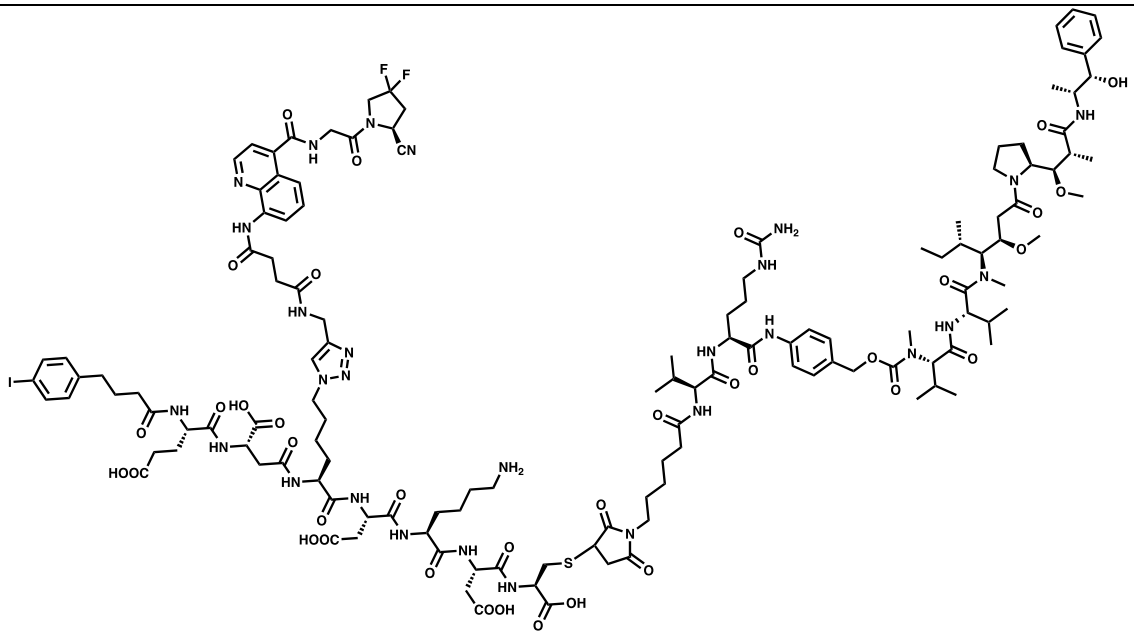
43	
43a	
44	

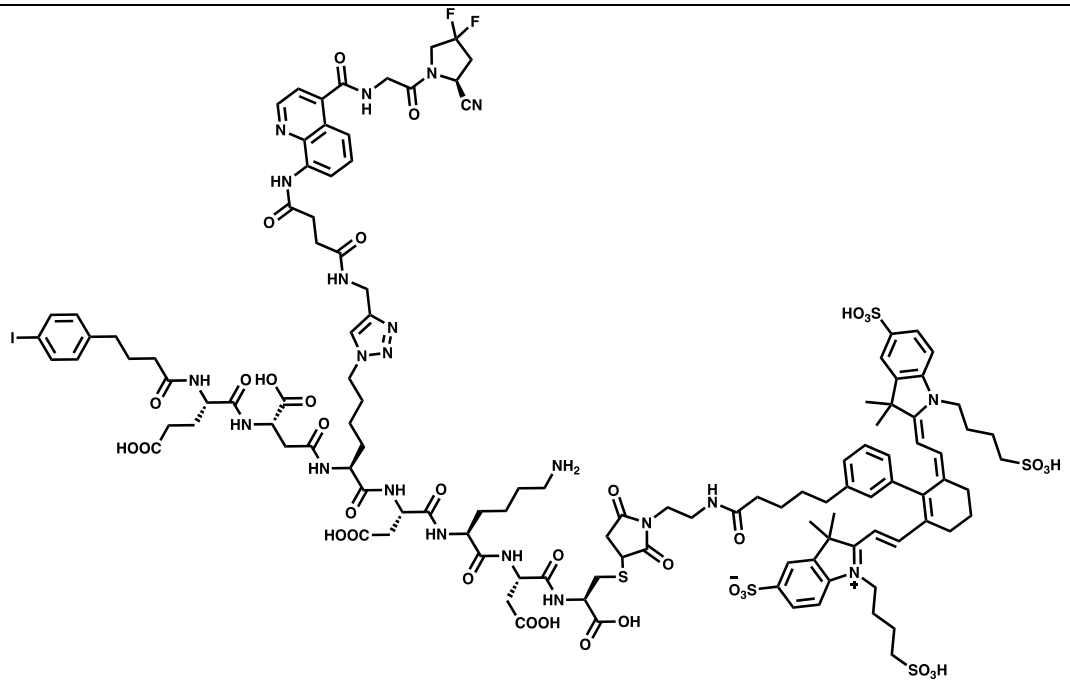
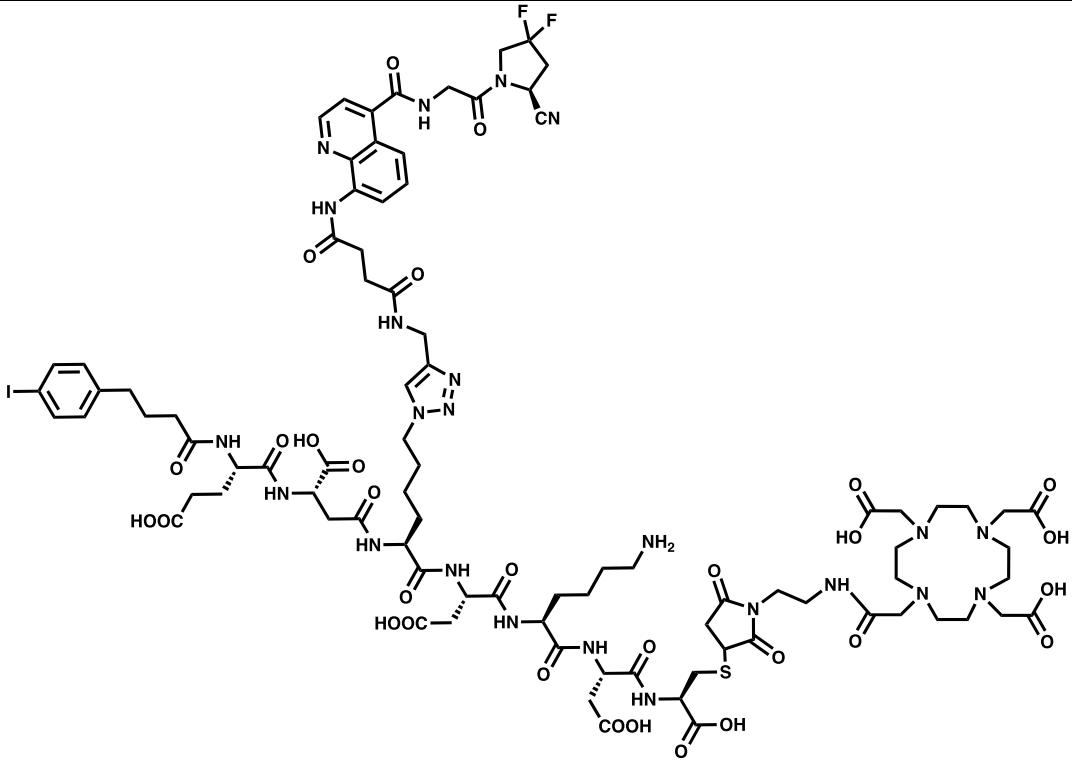
45	
46	

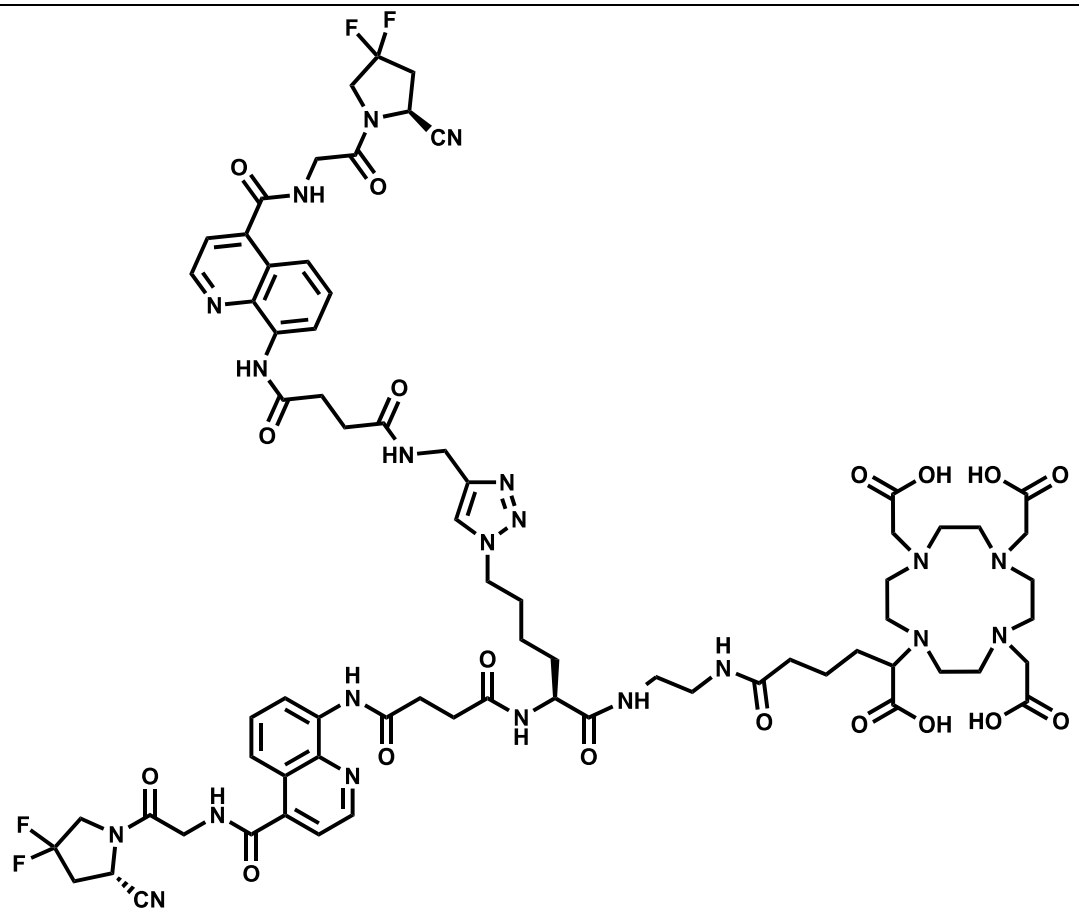
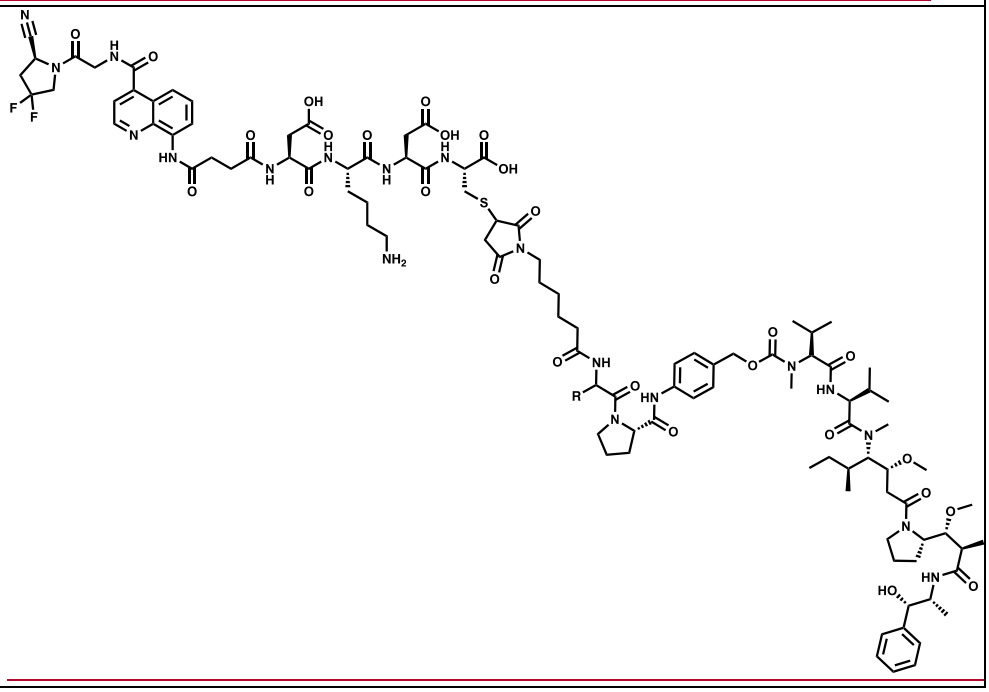
47	
48	

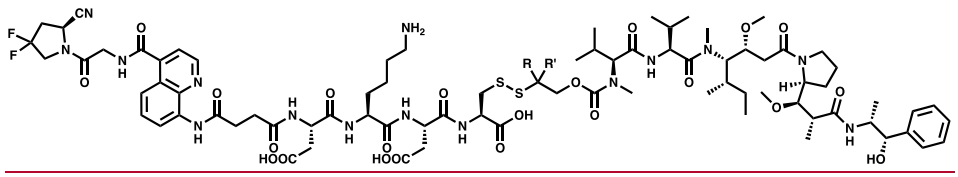
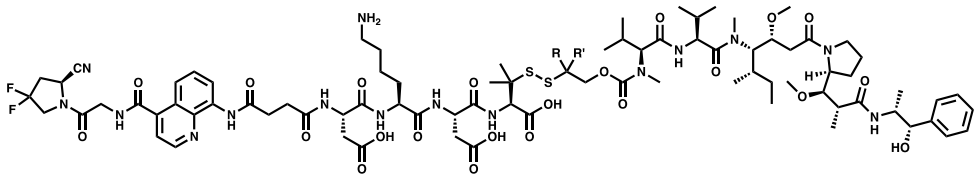
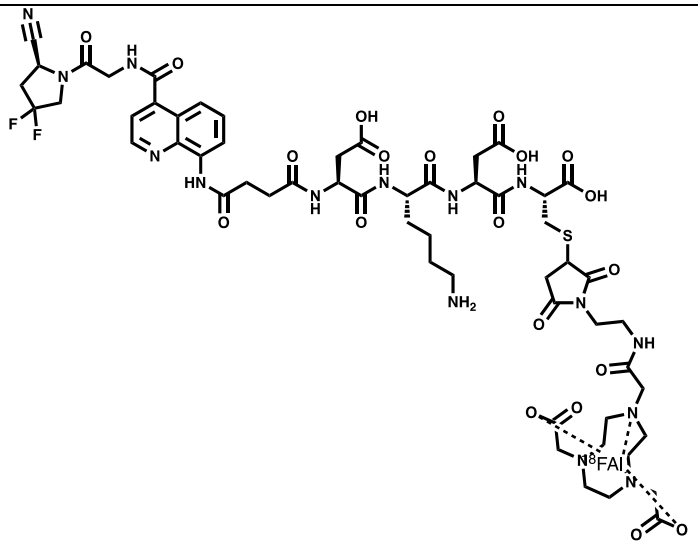
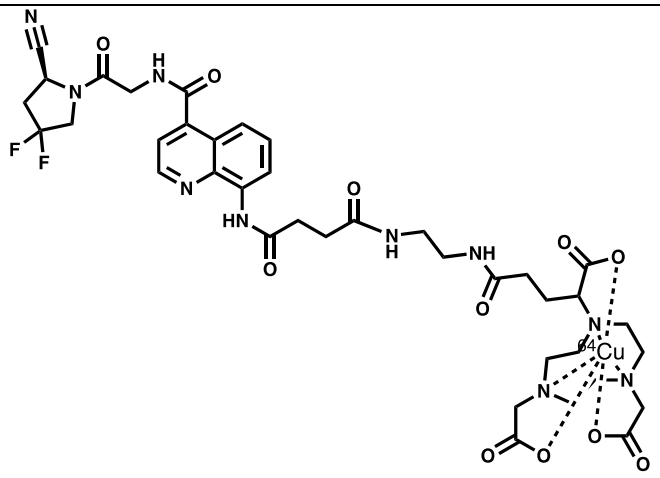
49	
50	

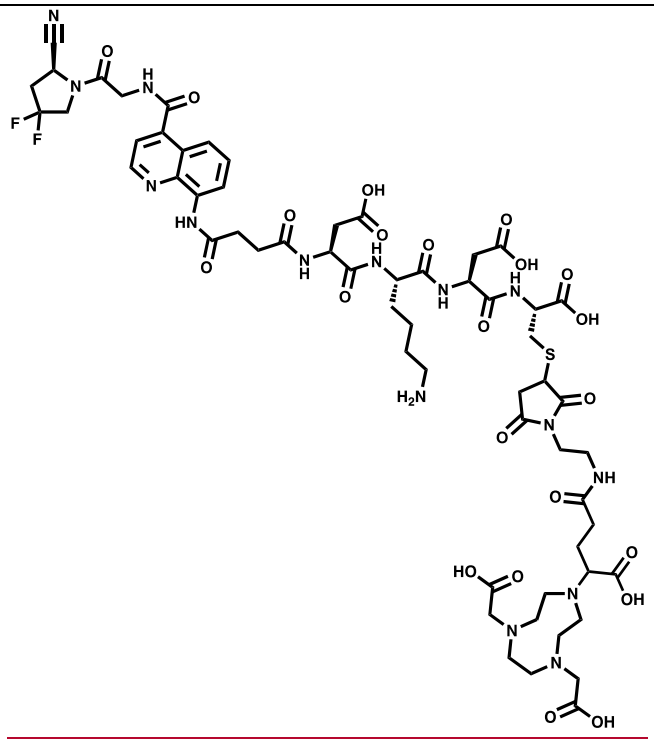
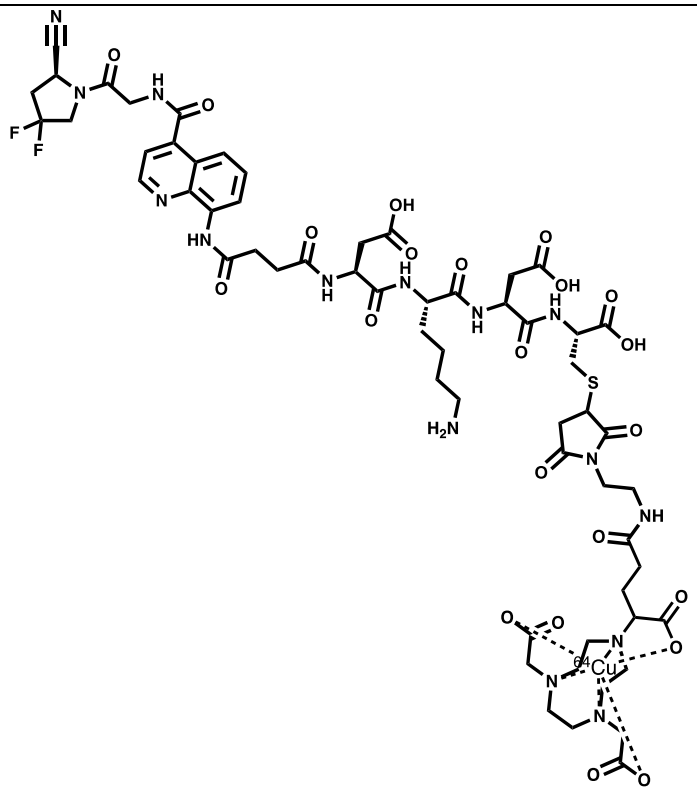
51	
52	

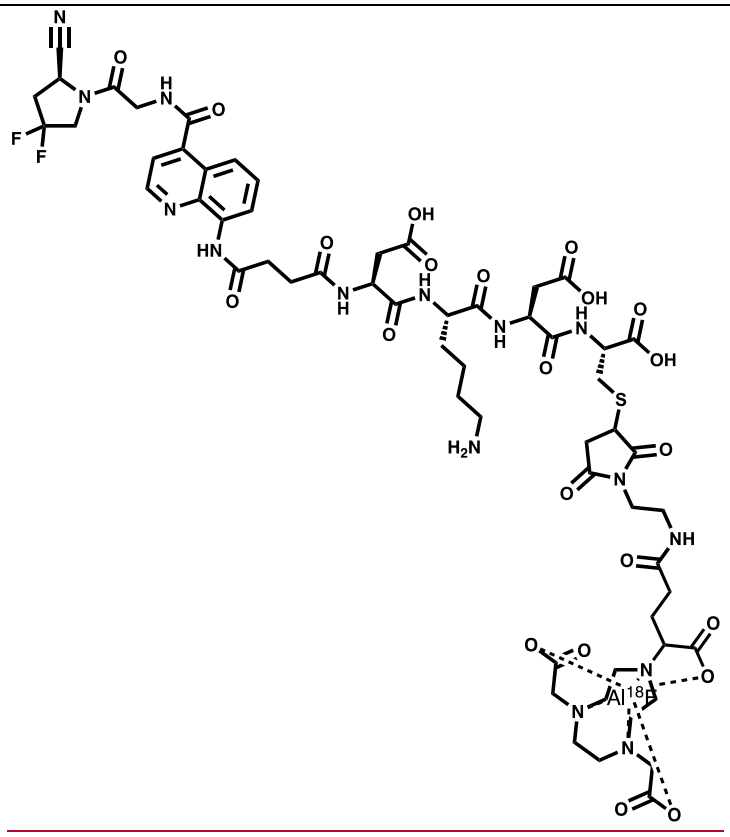
53	
54	

55	
56	

57		
58		
	R derived from AA:	
58a	Glycine	
58b	Alanine	
58c	Valine	
58d	Isoleucine	
58e	Proline	
58f	Arginine	

59			
	R	**R‘**	
59a	H	H	
59b	CH_3	H	
59c	CH_3	CH_3	
60			
	R	**R‘**	
60a	H	H	
60b	CH_3	H	
60c	CH_3	CH_3	
64			
65			

66	
67	

68	

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein and a pharmaceutically acceptable excipient.

In another aspect of the present disclosure, there is provided a diagnostic composition comprising the compound disclosed herein.

In a further aspect of the present disclosure, there is provided a compound disclosed herein or the composition disclosed herein for use in medicine.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein or the composition disclosed herein in the manufacture of a cancer diagnostic agent.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or the composition disclosed herein in the manufacture of a medicament for treatment of cancer.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein or the pharmaceutical composition disclosed herein or the diagnostic composition disclosed herein, in the manufacture of a medicament or diagnostic agent for:

(a) the treatment of the human or animal body by surgery or therapy or a diagnostic method practised on the human or animal body; or

(b) therapy or prophylaxis of a subject suffering from or having risk for a disease or disorder; or

(c) guided surgery practised on a subject suffering from or having risk for a disease or disorder; or

(d) diagnosis of a disease or disorder, wherein the diagnosis is to be practised on the human or animal body and involves a nuclear medicine imaging technique, such as Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT); or

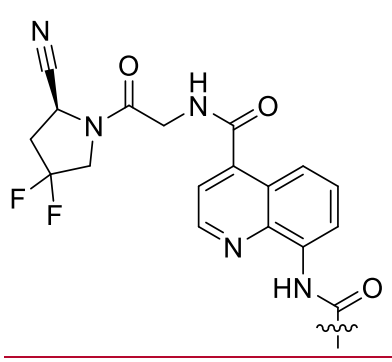
(e) targeted delivery of a therapeutic or diagnostic agent to a subject suffering from or having risk for a disease or disorder,

wherein in each of the preceding (b)–(e), said disease or disorder is independently selected from cancer, inflammation, atherosclerosis, fibrosis, tissue remodelling and keloid disorder, preferably wherein the cancer is selected from the group consisting of breast cancer, pancreatic cancer, small intestine cancer, colon cancer, multi-drug resistant colon cancer, rectal cancer, colorectal cancer, metastatic colorectal cancer, lung cancer, non-small cell lung cancer, head and neck cancer, ovarian cancer, hepatocellular cancer, oesophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocarcinoma, clear cell renal carcinoma, neuroendocrine tumour, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus cancer, desmoid tumours, glioma, astrocytoma, cervix cancer, skin cancer, kidney cancer and prostate cancer;

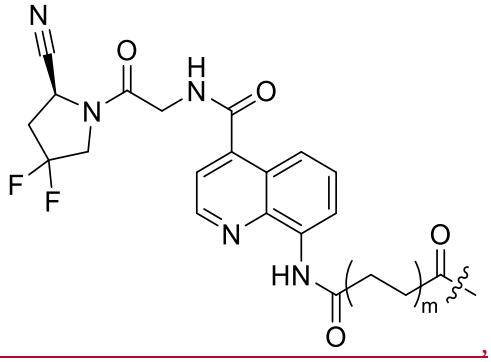
preferably wherein the compound has a prolonged residence at the disease site at a therapeutically or diagnostically relevant level, preferably beyond 1 h, more preferably beyond 6 h post injection.

In a further aspect of the present disclosure, there is provided a compound, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a salt thereof, wherein the compound comprises:

a moiety having the following structure **A¹** or **A²**, wherein *m* is 0, 1, 2, 3, 4 or 5:



A¹



A²

and a reactive moiety **L** capable of reacting and forming a covalent bond with a conjugation partner.

In another aspect of the present disclosure, there is provided a method for preparing a conjugate comprising the step of conjugating with a compound disclosed herein with a conjugation partner, wherein preferably:

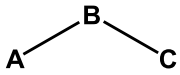
(a) the compound is conjugated by reacting with the conjugation partner to form a covalent bond;

(b) the conjugate is a compound as disclosed herein;

(c) the conjugation partner is a therapeutic or diagnostic agent; and/or

(d) the method further comprises formulating the conjugate as a pharmaceutical composition or as a diagnostic composition.

A compound according to the present ~~invention~~disclosure may be represented by following general Formula I,



Formula I

its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof, wherein **A** is a binding moiety; **B** is a covalent bond or a moiety comprising a chain of atoms that covalently attaches the moieties **A** und **C**; and **C** is a payload moiety.

The present ~~invention~~disclosure further provides a pharmaceutical composition comprising said compound and a pharmaceutically acceptable excipient.

The present ~~invention~~disclosure further provides said compound or pharmaceutical composition for use in a method for treatment of the human or animal body by surgery or therapy or a diagnostic method practised on the human or animal body; as well as a method for treatment of the human or animal body by surgery or therapy or a diagnostic method practised on the human or animal body comprising administering a therapeutically or diagnostically effective amount of said compound or pharmaceutical composition to a subject in need thereof.

The present ~~invention~~disclosure further provides said compound or pharmaceutical composition for use in a method for therapy or prophylaxis of a subject suffering from or having risk for a disease or disorder; as well as a method for treatment therapy or prophylaxis of a disease or disorder comprising administering a therapeutically or diagnostically effective amount of said compound or pharmaceutical composition to a subject suffering from or having risk for said disease or disorder.

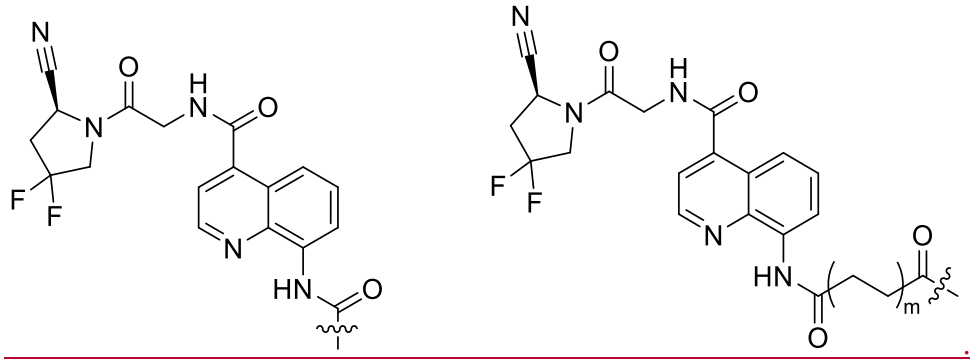
The present ~~invention~~disclosure further provides said compound or pharmaceutical composition for use in a method for guided surgery practised on a subject suffering from or having risk for a disease or disorder; as well as a method for guided surgery comprising administering a therapeutically or diagnostically effective amount of said compound or pharmaceutical composition to a subject suffering from or having risk for a disease or disorder.

The present ~~invention~~disclosure further provides said compound or pharmaceutical composition for use in a method for diagnosis of a disease or disorder, the method being practised on the human or animal body and involving a nuclear medicine imaging technique, such as Positron Emission Tomography (PET); as well as a method for diagnosis of a disease or disorder, the method being practised on the human or animal body and involving a nuclear medicine imaging technique, such as Positron Emission Tomography (PET), and comprising administering a therapeutically or diagnostically effective amount of said compound or pharmaceutical composition to a subject in need thereof.

The present ~~invention~~disclosure further provides said compound or pharmaceutical composition for use in a method for targeted delivery of a therapeutic or diagnostic agent to a subject suffering from or having risk for a disease or disorder; as well as a method for targeted delivery of a therapeutically or diagnostically effective amount of said compound or pharmaceutical composition to a subject suffering from or having risk for a disease or disorder.

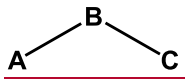
CLAIMS

1. A compound, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof, wherein the compound comprises a moiety having the following structure **A**[1] or **A**[2], wherein *m* is 0, 1, 2, 3, 4 or 5:



A[1] **A**[2]

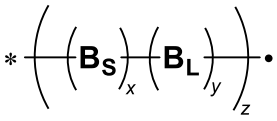
2. The compound of claim 1, wherein the compound is represented by the following Formula I:



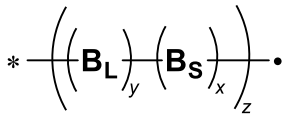
Formula I

wherein **A** has the structure **A**[1] or **A**[2]; **B** is a covalent bond or a moiety comprising a chain of atoms covalently attaching **A** to **C**; and **C** is an atom, a molecule or a particle, and/or is a therapeutic or diagnostic agent.

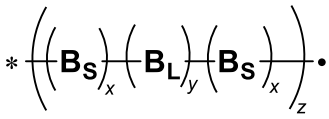
3. The compound according to claim 2, wherein **B** is represented by any of the following general Formulae II–V, wherein:



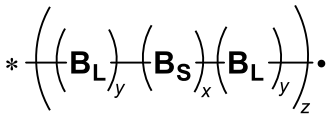
Formula II



Formula III



Formula IV



Formula V

each *x* is an integer independently selected from the range of 0 to 100, preferably 0 to 50, more preferably 0 to 30, yet more preferably selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20;

each *y* is an integer independently selected from the range of 0 to 30, preferably selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20;

each *z* is an integer independently selected from the range of 0 to 5, preferably selected from selected from 0, 1, 2, 3 and 4; and

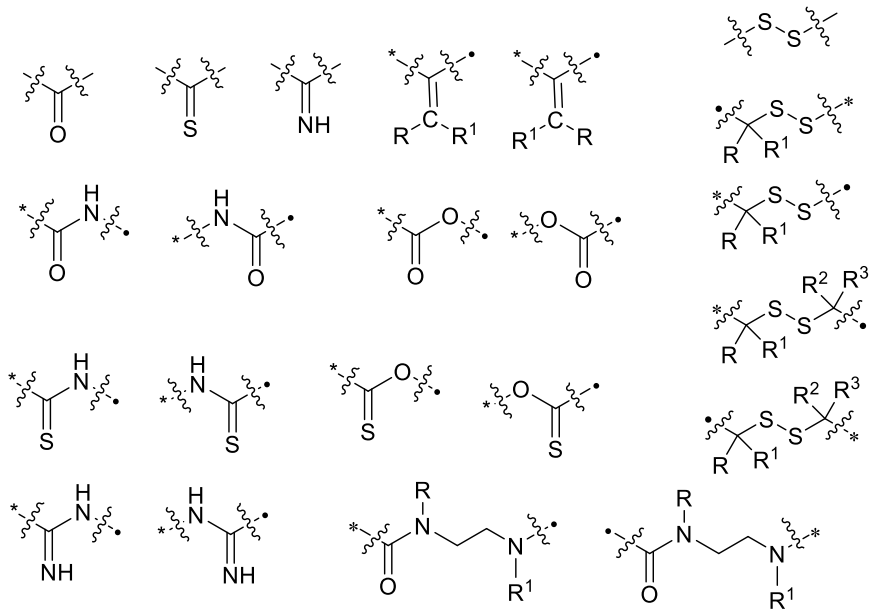
* represents a point of attachment to moiety **A**; and

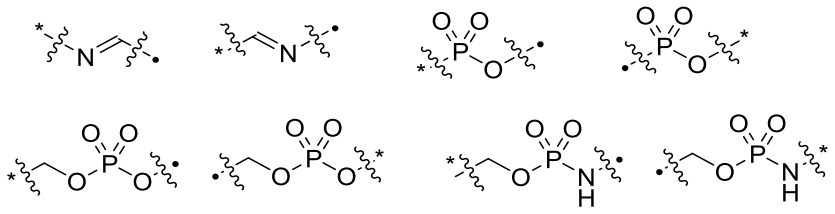
• represents a point of attachment to moiety **C**, wherein

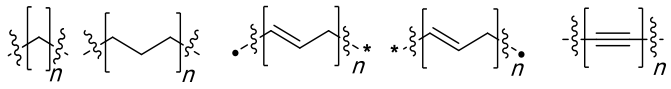
$\mathbf{B_S}$ and/or $\mathbf{B_L}$ is a group comprising or consisting of a structural unit independently selected from the group consisting of alkylene, cycloalkylene, arylalkylene, heteroarylalkylene, heteroalkylene, heterocycloalkylene, alkenylene, cycloalkenylene, arylalkenylene, heteroarylalkenylene, heteroalkenylene, heterocycloalenkylene, alkynylene, heteroalkynylene, arylene, heteroarylene, aminoacyl, oxyalkylene, aminoalkylene, diacid ester, dialkylsiloxane, amide, thioamide, thioether, thioester, ester, carbamate, hydrazone, thiazolidine, methylene alkoxy carbamate, disulfide, vinylene, imine, imidamide, phosphoramide, saccharide, phosphate ester, phosphoramide, carbamate, dipeptide, tripeptide, tetrapeptide, each of which is substituted or unsubstituted.

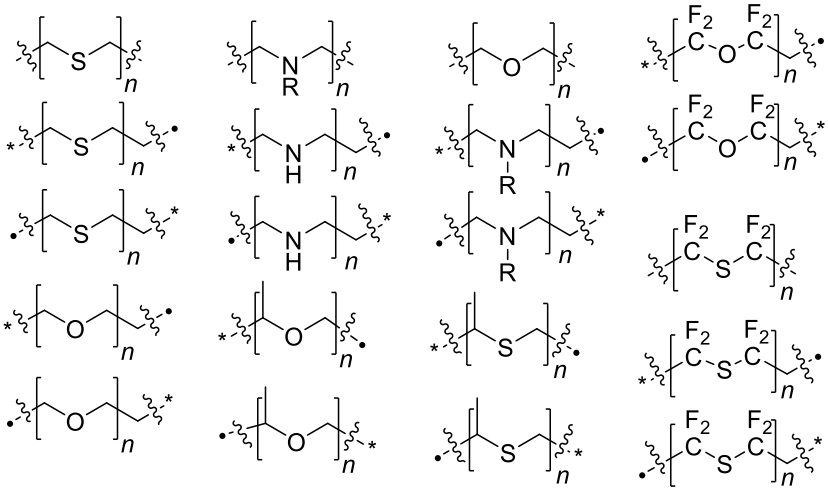
4. The compound according to claim 3, wherein:

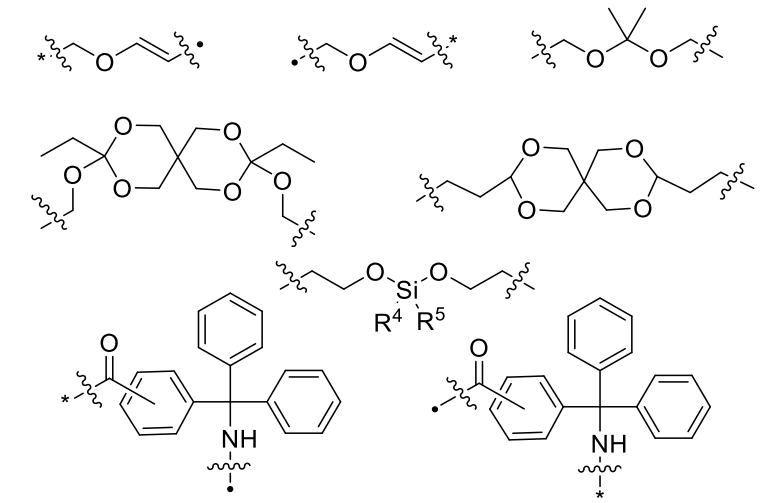
(a) $\mathbf{B_S}$ and/or $\mathbf{B_L}$ is a group comprising or consisting of a structural unit independently selected from the group consisting of:

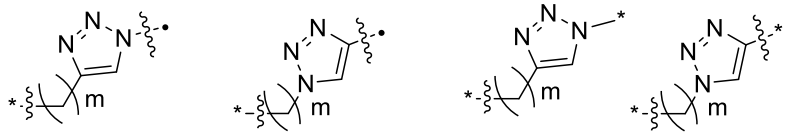


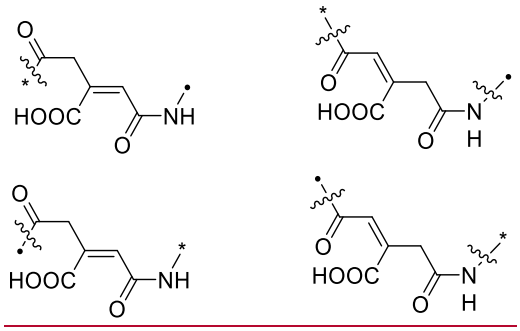


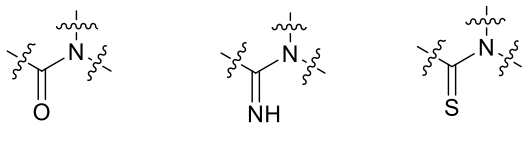


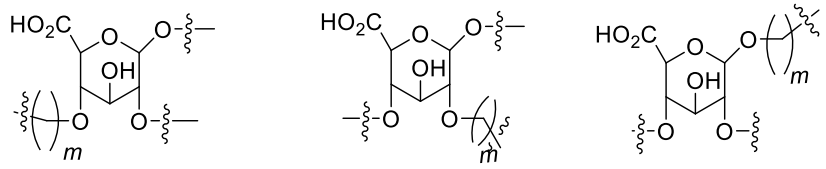


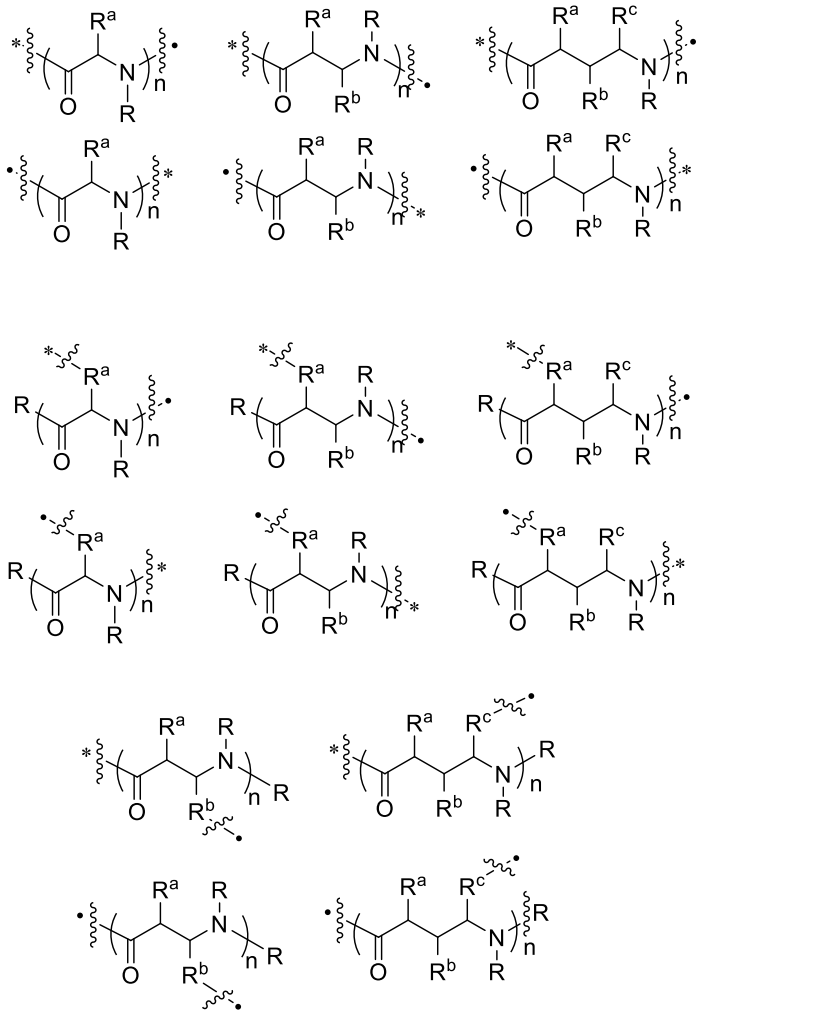


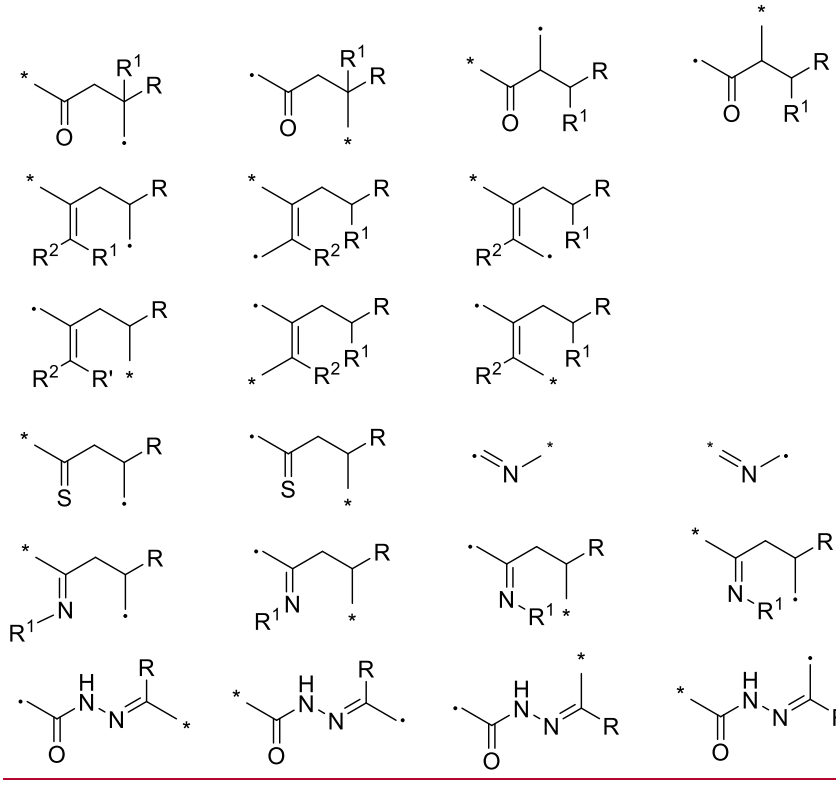


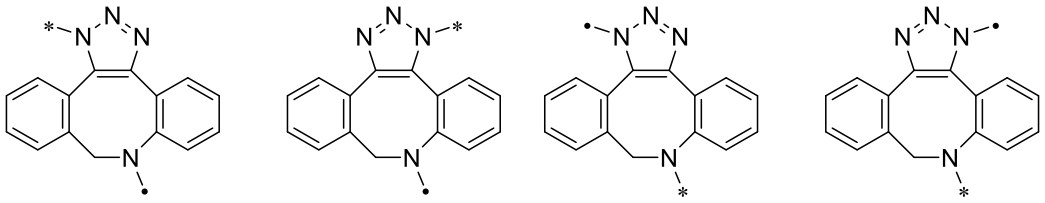


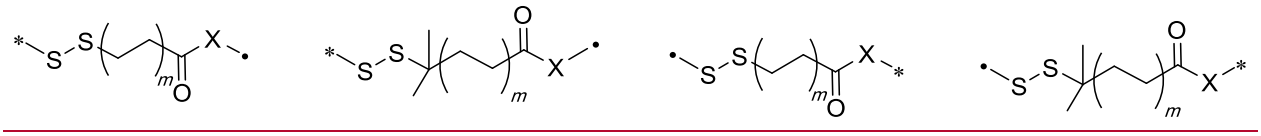


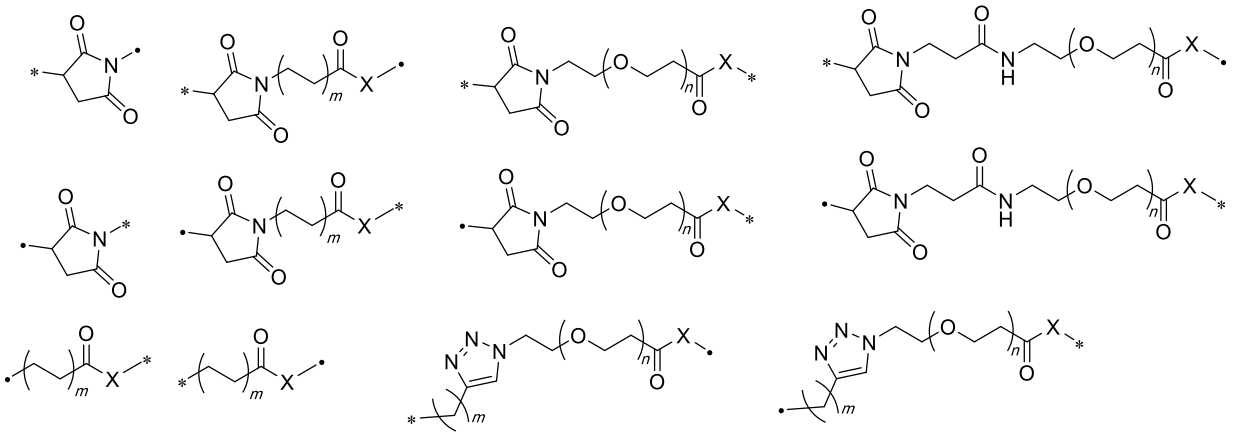












wherein each of R, R^1, R^2 and R^3 is independently selected from H, OH, SH, NH_2, halogen, cyano, carboxy, alkyl, cycloalkyl, aryl and heteroaryl, each of which is substituted or unsubstituted;

each of R^4 and R^5 is independently selected from alkyl, cycloalkyl, aryl and heteroaryl, each of which is substituted or unsubstituted;

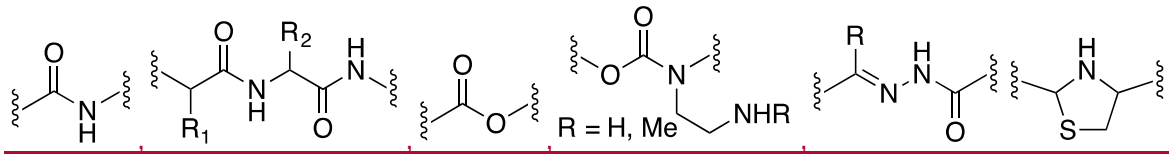
each of R^a, R^b and R^c is independently selected from side-chain residues of a proteinogenic or a non-proteinogenic amino acid, each of which can be further substituted;

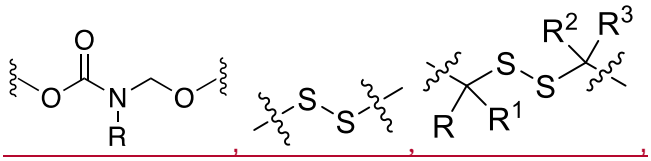
each X is independently selected from NH, NR, S, O and CH_2, preferably NH;

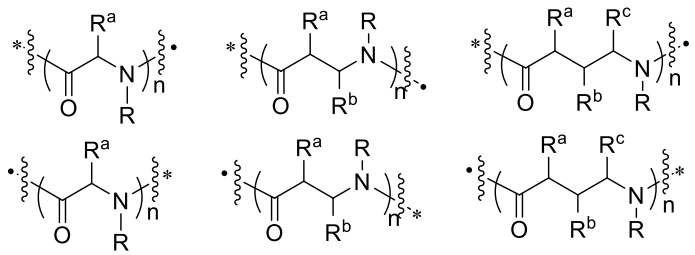
each of *n* and *m* is independently an integer from 0 to 100, preferably 0 to 50, more preferably 0 to 30, yet more preferably selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20; and

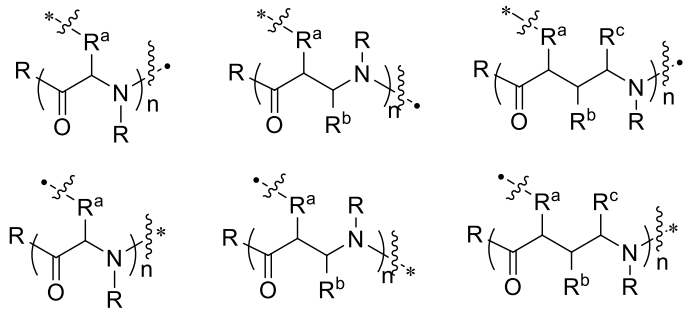
wherein each * represents a point of attachment for which the shortest path to moiety **A** comprises less atoms than that for •; and each • represents a point of attachment for which the shortest path to moiety **C** comprises less atoms than that for *;

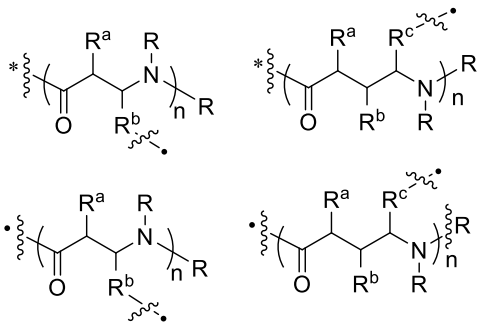
(b) one or more $\mathbf{B}_L$ independently comprises or consists of one or more of the following structural units:







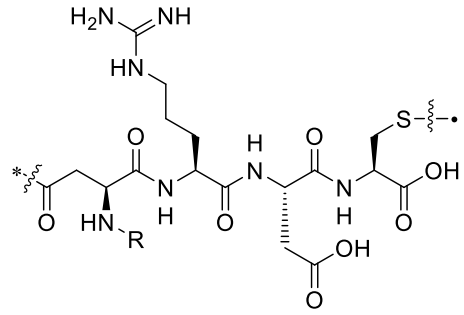
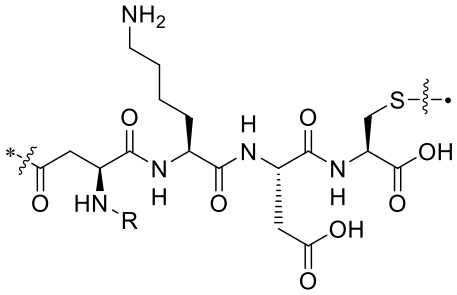
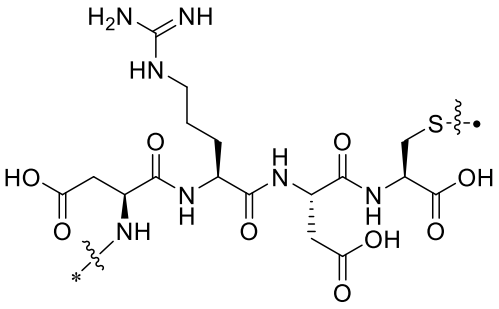
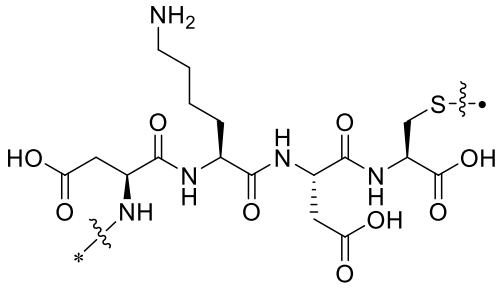




wherein in each of the above structures, *n* is 1, 2, 3 or 4; and

each * represents a point of attachment for which the shortest path to moiety **A** comprises less atoms than that for •; and each • represents a point of attachment for which the shortest path to moiety **C** comprises less atoms than that for *, with the proviso that when n is > 1 and a respective point of attachment is indicated on any one of R^a, R^b and R^c, then it can be independently present in one or more of the peptide monomeric units, preferably in one peptide monomeric unit most distant from the other point of attachment indicated in the respective structure;

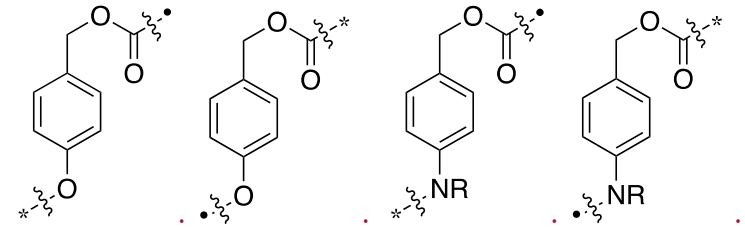
(c) one or more of $\mathbf{B_L}$ and $\mathbf{B_S}$ is independently selected from the following structures:

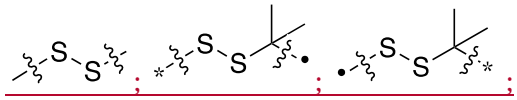





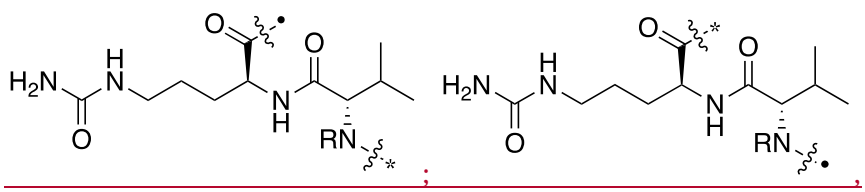
*–Val-Ala–•; *–Val-Lys–•; *–Val-Arg–•,

wherein each * represents a point of attachment for which the shortest path to moiety **A** comprises less atoms than that for •; and each • represents a point of attachment for which the shortest path to moiety **C** comprises less atoms than that for *; and/or

(d) y is 1, 2 or 3; and/or at least one $\mathbf{B_L}$ further comprises a cleavable linker group independently selected from the following structures:

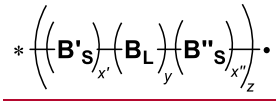




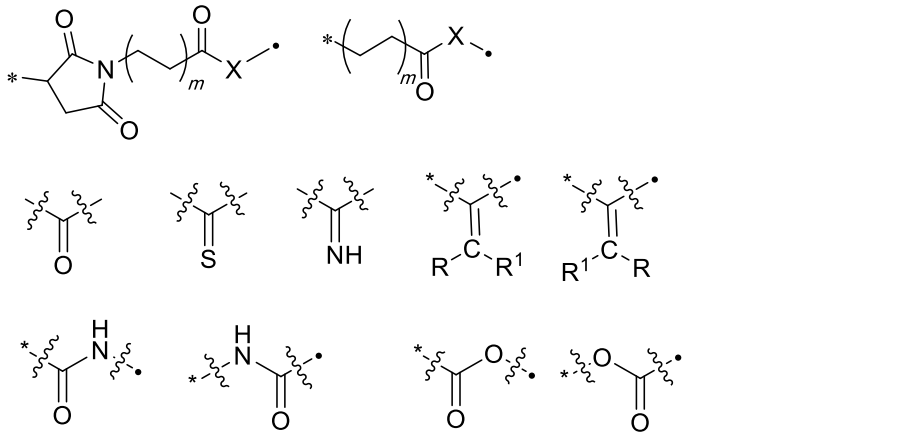


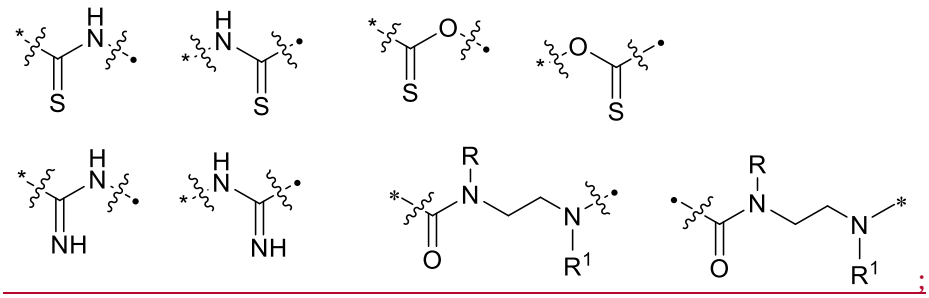
each * represents a point of attachment for which the shortest path to moiety **A** comprises less atoms than that for •; and each • represents a point of attachment for which the shortest path to moiety **C** comprises less atoms than that for *.

5. The compound according to any one of claims 2–4, wherein **B** has the following structure:



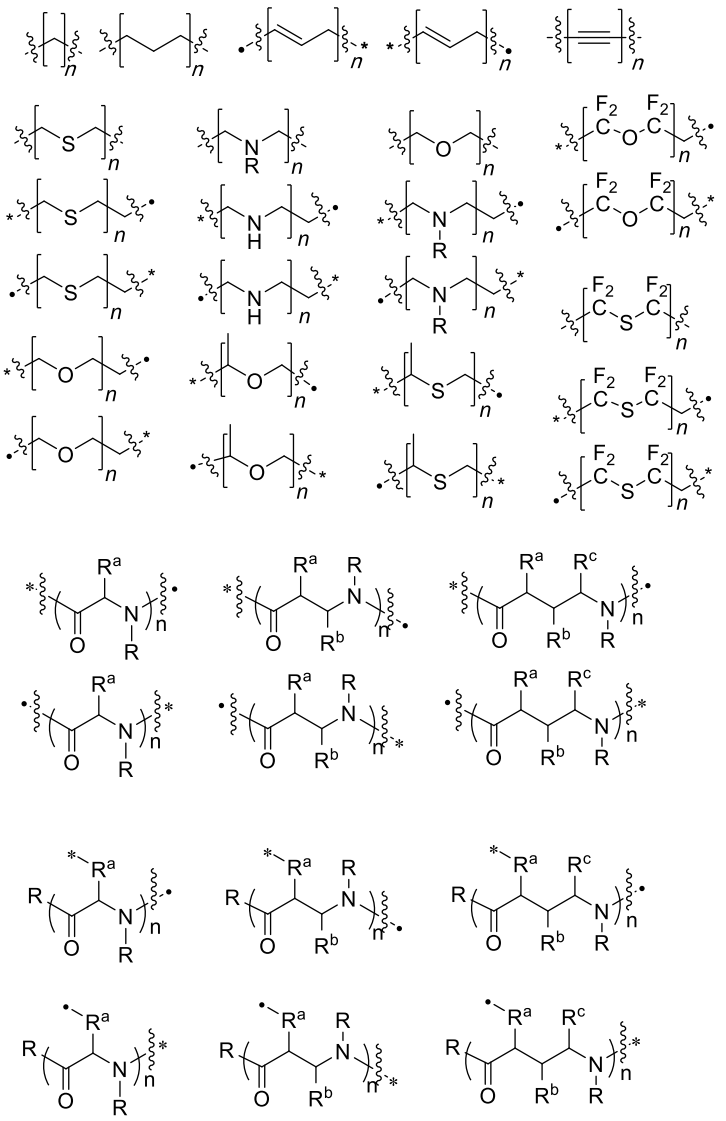
wherein **B'$_S$** and **B''$_S$** are each independently selected from the group consisting of:

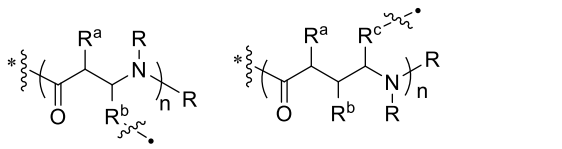


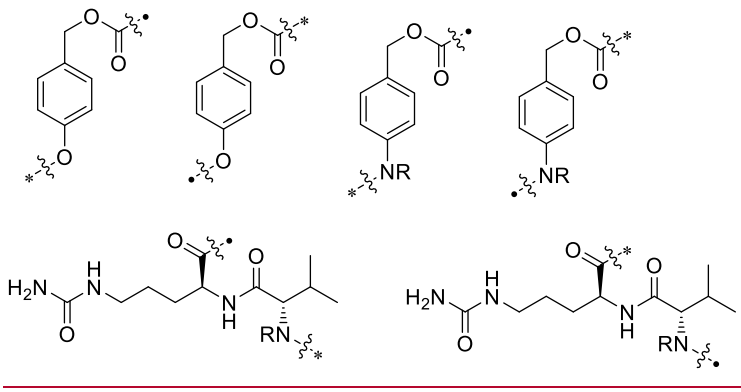


;

each **B$_L$** is independently selected from the group consisting of:







each *n* is 0, 1, 2, 3, 4 or 5;

each *m* is 0, 1, 2, 3, 4 or 5;

each *x′* is 0, 1 or 2;

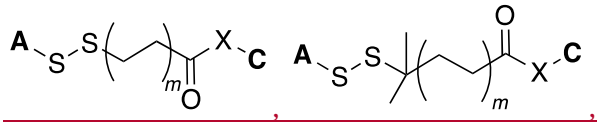
each *x″* is 0, 1 or 2;

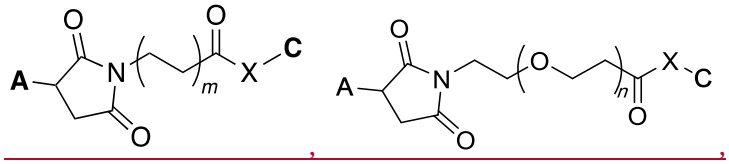
each *y* is 0, 1 or 2; and

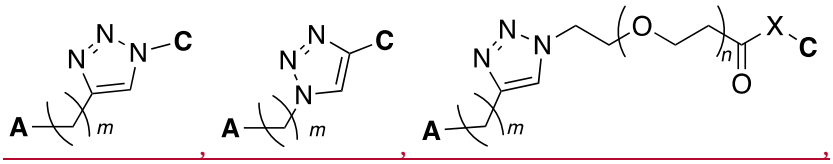
z is 1 or 2,

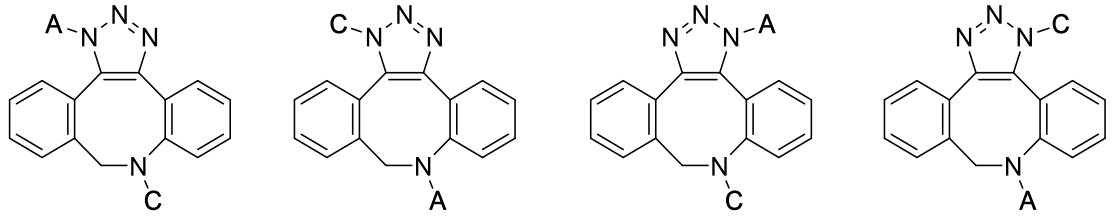
wherein R, R^1, R^2, R^3, R^a, R^b, R^c, X, * and • are defined as in any one of the preceding claims.

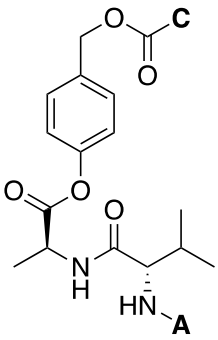
6. The compound according to any one of claims 1–5 having a structure represented by one of the following formulae:



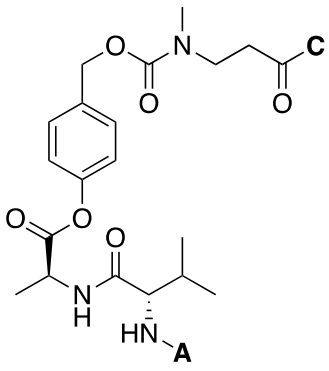




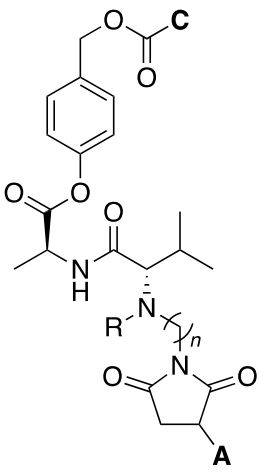




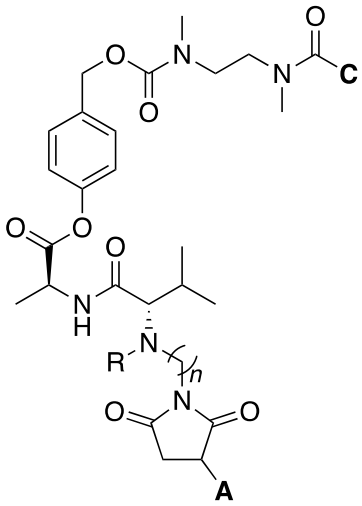
Val-Ala-PAB



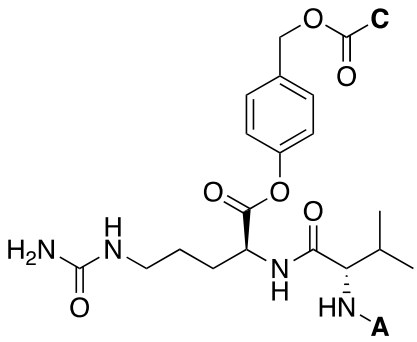
Val-Ala-PAB



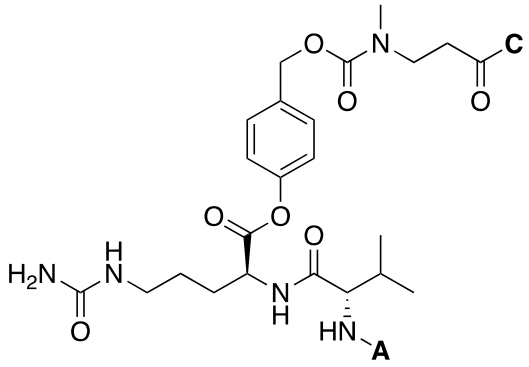
MC-Val-Ala-PAB



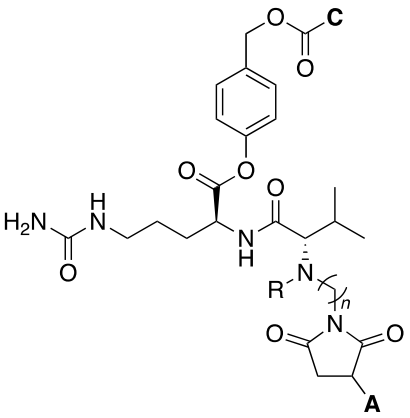
MC-Val-Ala-PAB



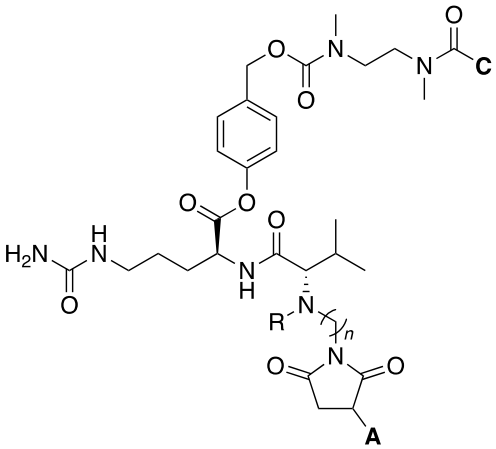
Val-Cit-PAB



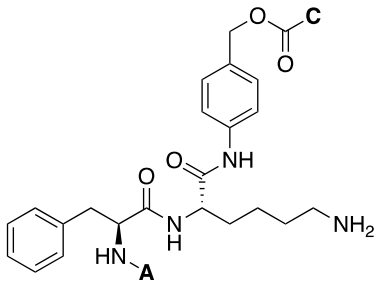
Val-Cit-PAB



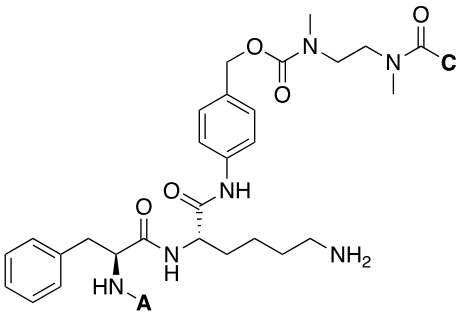
MC-Val-Cit-PAB



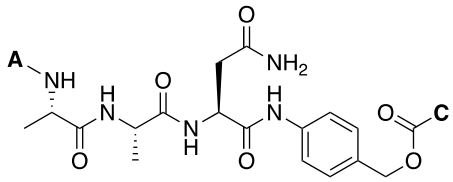
MC-Val-Cit-PAB



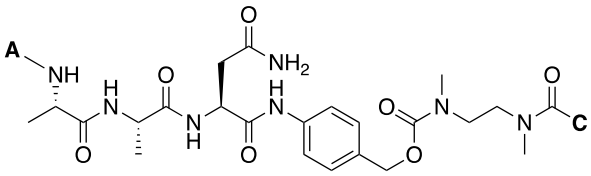
Phe-Lys-PAB



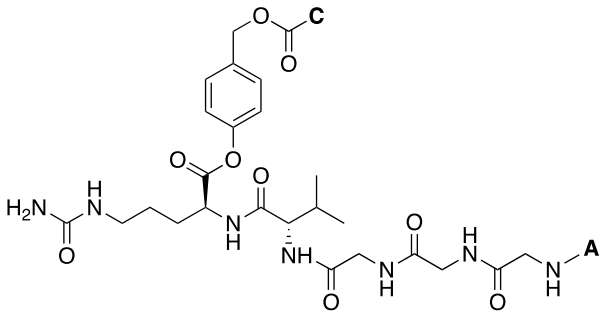
Phe-Lys-PAB



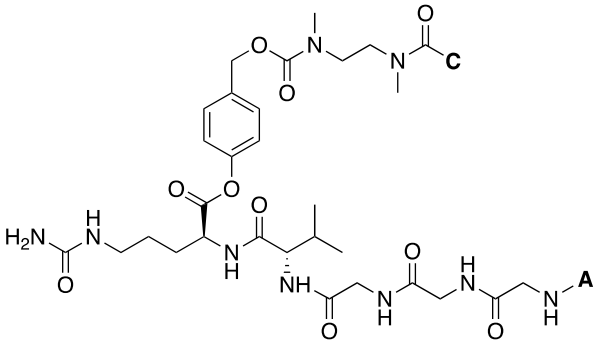
Ala-Ala-Asn-PAB



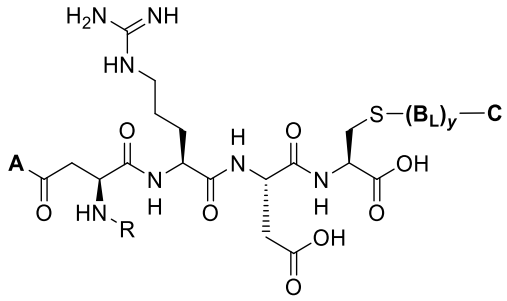
Ala-Ala-Asn-PAB

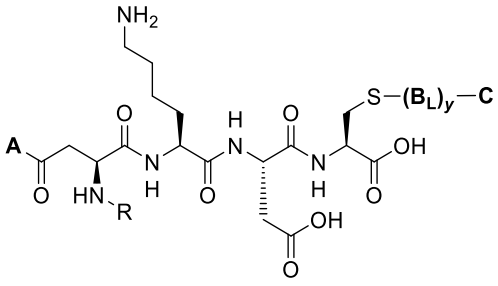


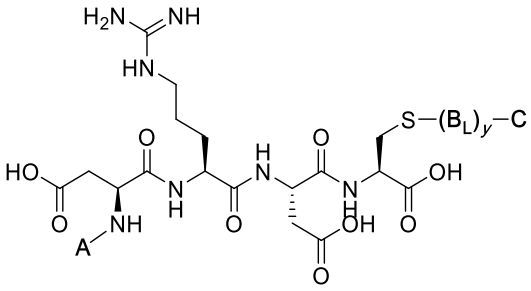
gly-gly-gly-Val-Cit-PAB

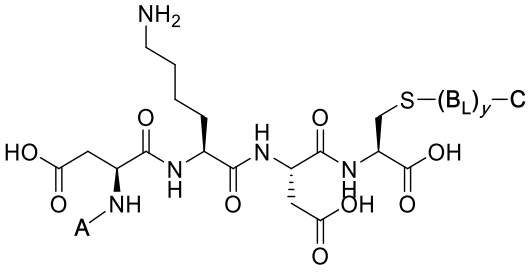


gly-gly-gly-Val-Cit-PAB

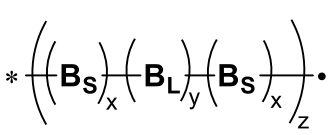




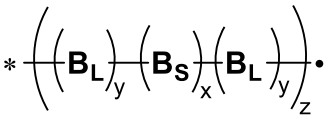




7. The compound according to any one of claims 2–6, wherein **B** is represented by the Formula **IV** or **V**,

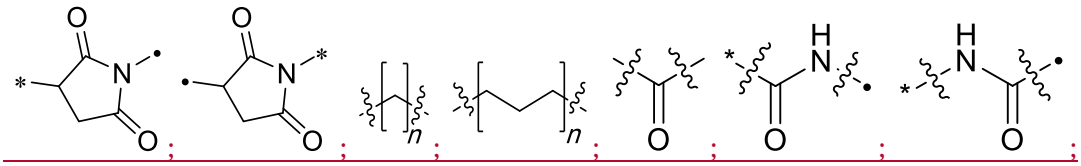


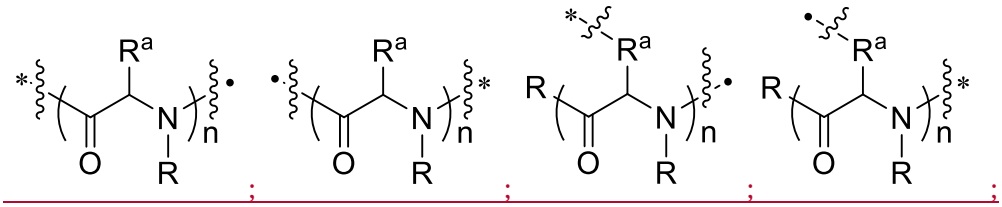
Formula IV



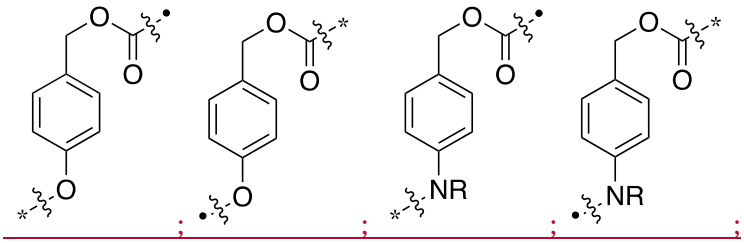
Formula V

wherein each $\mathbf{B_S}$ and $\mathbf{B_L}$ is independently selected from:





and wherein optionally at least one $\mathbf{B_L}$ further comprises a cleavable linker group independently selected from the following structures:

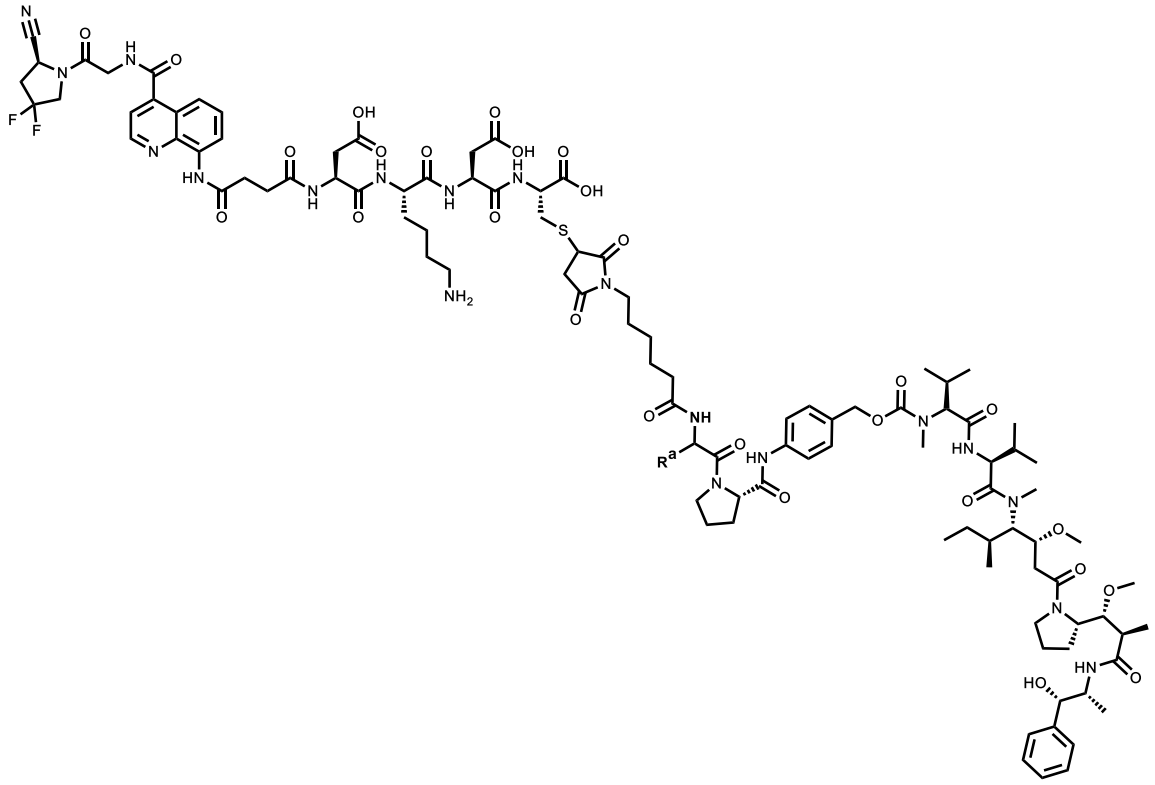


wherein each of R is independently selected from H, OH, SH, NH_2, halogen, cyano, carboxy, alkyl, cycloalkyl, aryl and heteroaryl, each of which is substituted or unsubstituted;

each R^a is independently selected from side-chain residues of a proteinogenic or a non-proteinogenic amino acid, each of which can be further substituted, wherein side-chain residues of a proteinogenic or a non-proteinogenic amino acid represented by any of R^a can be part of a 3-, 4-, 5-, 6- or 7-membered ring, optionally wherein the side chain of said proteinogenic or non-proteinogenic amino acid can be part of a cyclic structure selected from an azetidine ring, pyrrolidine ring and a piperidine ring, such as in proline or hydroxyproline; and wherein each R^a may independently be part of an unsaturated structure; and

wherein each * represents a point of attachment for which the shortest path to moiety **A** comprises less atoms than that for •; and each • represents a point of attachment for which the shortest path to moiety **C** comprises less atoms than that for *;

preferably wherein the compound is represented by the following formula:



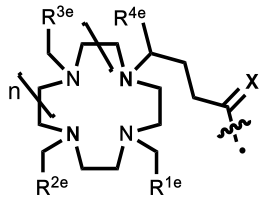
in which R^a is an amino acid side chain derived from glycine, alanine, valine, isoleucine, proline, or arginine.

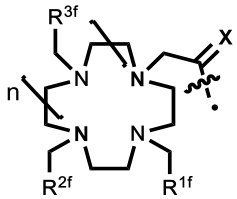
8. The compound according to any one of claims 2–7, wherein the moiety **C** is selected from: (a) a chelating agent group suitable for radiolabelling; (b) a radioactive group comprising a radioisotope; (c) a chelate of a radioactive isotope with a chelating agent; (d) a fluorophore group; (e) a cytotoxic and/or cytostatic agent; (f) immunomodulator agent; or (g) a protein.

9. The compound according to claim 8, wherein:

(a) the chelating agent group suitable for radiolabelling:

(i) has a structure according one of the following formulae:





wherein:

n is 0, 1, 2, 3, 4 or 5; preferably 1;

R^{1e} is independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH;

R^{2e} is independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH;

each R^{3e} is independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH;

R^{4e} is independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH;

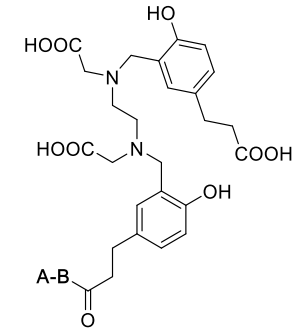
R^{1f} is independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH;

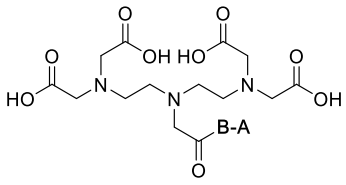
R^{2f} is independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH;

R^{3f} is independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH; and

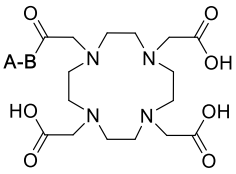
X is O, NH or S; preferably O; or

(ii) is selected from sulfur colloid, diethylenetriaminepentaacetic acid (DTPA), ethylenediaminetetraacetic acid (EDTA), 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), 1,4,7-triazacyclononane-N,N',N"-triacetic acid (NOTA), 1,4,8,11-tetraazacyclotetradecane-N,N',N",N"'-tetraacetic acid (TETA), iminodiacetic acid, bis(carboxymethylimidazole)glycine, 6-Hydrazinopyridine-3-carboxylic acid (HYNIC),

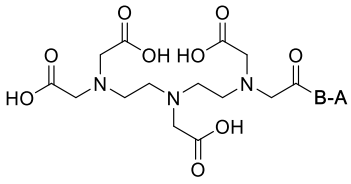




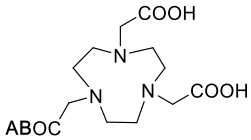
DTPA (1)



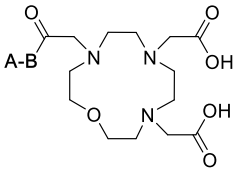
DOTA (1)

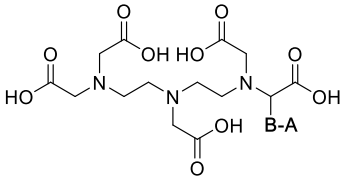


DTPA (2)

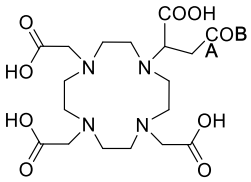


NOTA

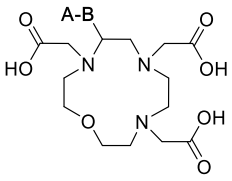


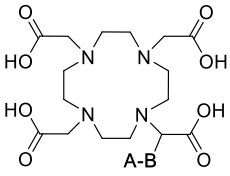


DTPA (3)

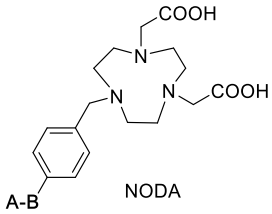


DOTA-GA

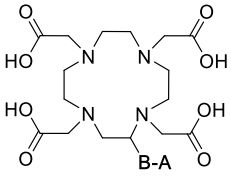




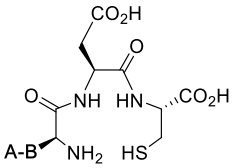
DOTA (2)



NODA



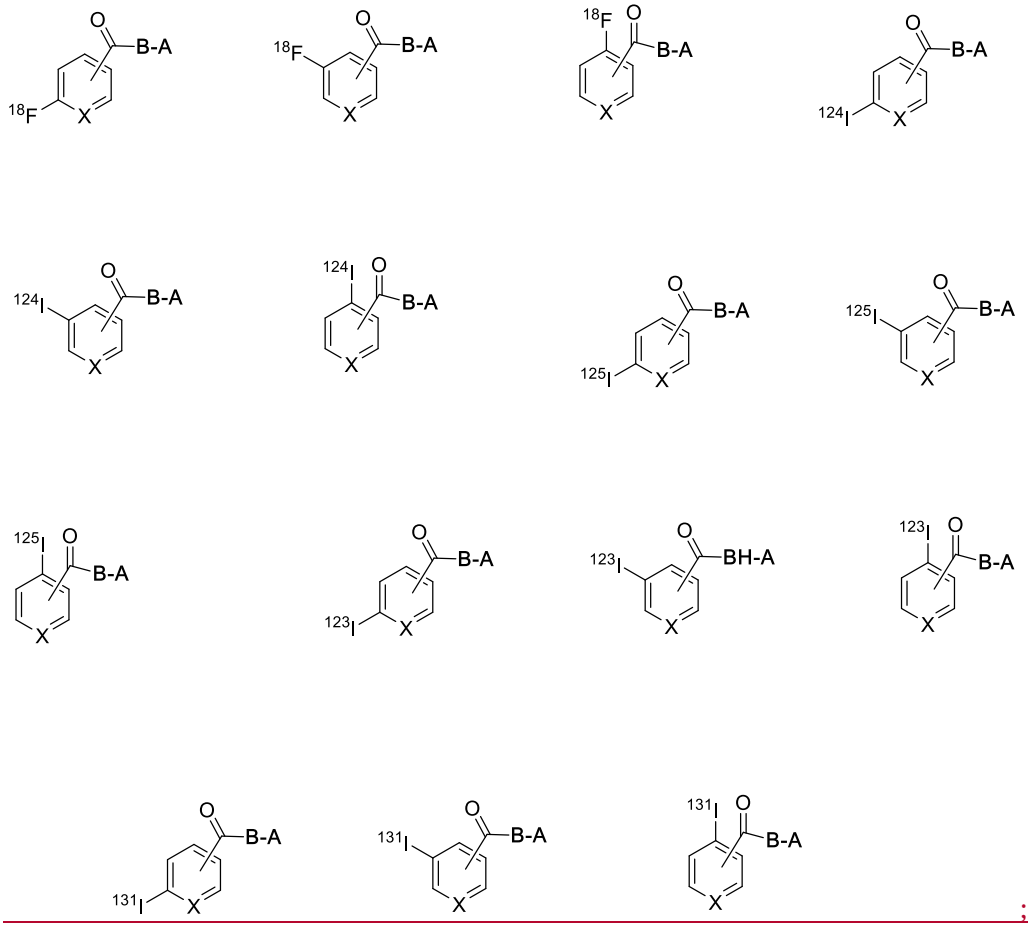
DOTA (3)



;

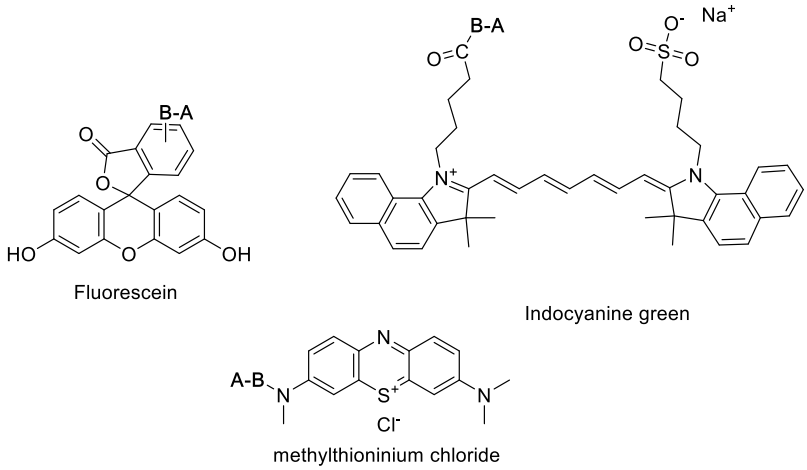
(b) the radioactive group comprising a radioisotope is selected from ^{223}Ra, ^{89}Sr, ^{94m}Tc, ^{99m}Tc, ^{186}Re, ^{188}Re, ^{203}Pb, ^{67}Ga, ^{68}Ga, ^{47}Sc, ^{111}In, ^{97}Ru, ^{62}Cu, ^{64}Cu, ^{86}Y, ^{88}Y, ^{90}Y, ^{121}Sn, ^{161}Tb, ^{153}Sm, ^{166}Ho, ^{105}Rh, ^{177}Lu, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{18}F, ^{211}At, ^{225}Ac, ^{89}Sr, ^{225}Ac, ^{117m}Sn and ^{169}Er;

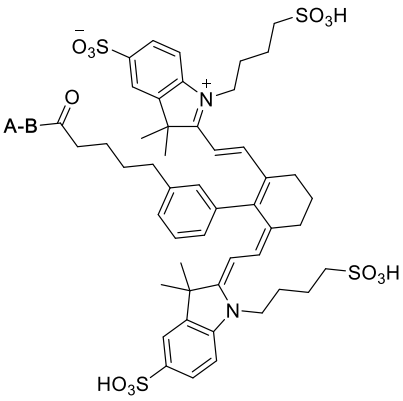
(c) the chelate of a radioactive isotope is a chelate of an isotope listed under (b) above and/or with a chelating agent listed under (a) above; or moiety **C** is a group selected from any of the following structures:



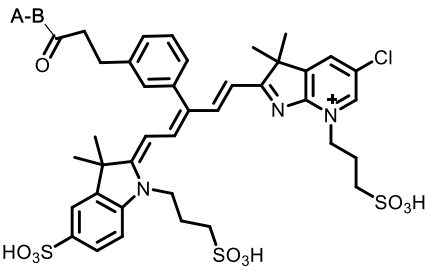
;

(d) the fluorophore group is selected from a xanthene dye, acridine dye, oxazine dye, cyanine dye, styryl dye, coumarine dye, porphine dye, fluorescent metal-ligand-complex, fluorescent protein, nanocrystals, perylene dye, boron-dipyrromethene dye and phtalocyanine dye, preferably selected from the following structures:

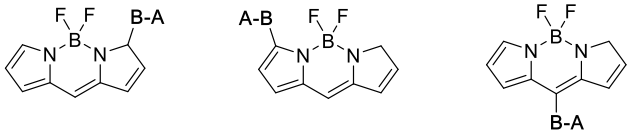




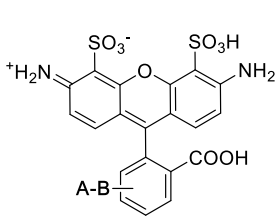
IRDye 760



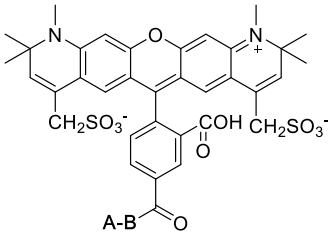
IRDye 680



BodyPY



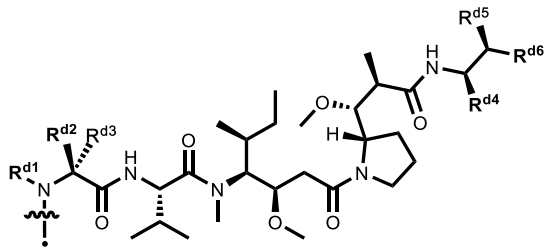
Alexa Fluor 488



Alexa Fluor 594 ;

(e) the cytotoxic and/or cytostatic agent:

(i) has a structure according to the following formula:



wherein:

R^{1d} is independently H or C_1-C_6 alkyl; preferably H or CH_3;

R^{2d} is independently C_1-C_6 alkyl; preferably CH_3 or iPr;

R^{3d} is independently H or C_1-C_6 alkyl; preferably H or CH_3;

R^{4d} is independently H, C_1-C_6 alkyl, COO(C_1-C_6 alkyl), CON(H or C_1-C_6 alkyl), C_3-C_{10} aryl

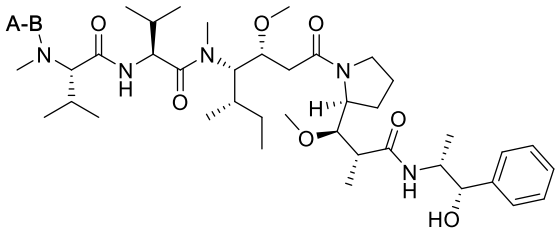
or C_3-C_{10} heteroaryl; preferably H, CH_3, COOH, $COOCH_3$ or thiazolyl;

R^{5d} is independently H, OH, C_1-C_6 alkyl; preferably H or OH; and

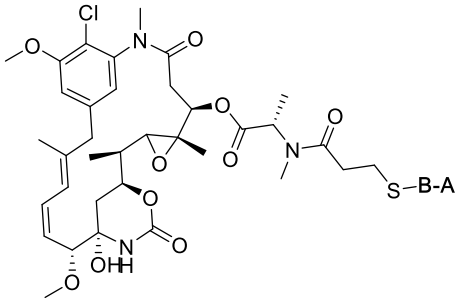
R^{6d} is independently C_3-C_10 aryl or C_3-C_10 heteroaryl; preferably optionally substituted phenyl or pyridyl; or

(ii) is selected from chemotherapeutic agent selected from the group consisting of topoisomerase inhibitors, alkylating agents, antimetabolites, antibiotics, mitotic disrupters, DNA intercalating agents, DNA synthesis inhibitors, DNA-RNA transcription regulator, enzyme inhibitors, gene regulators, hormone response modifiers, hypoxia-selective cytotoxins, epidermal growth factor inhibitors, anti-vascular agents and a combination of two or more thereof; or

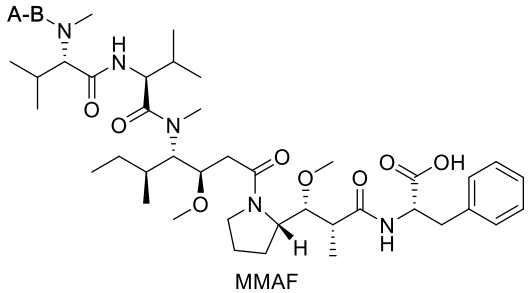
(iii) is selected from the following structures:



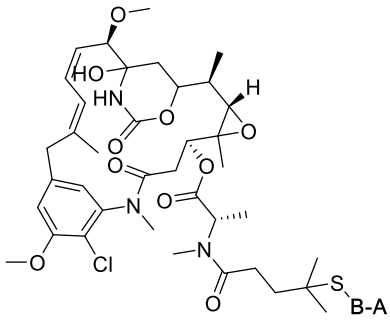
MMAE



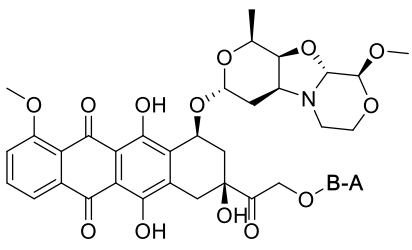
DM1



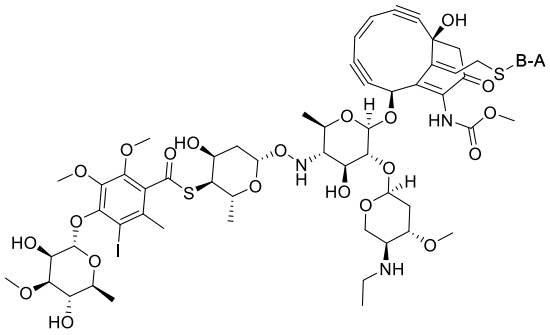
MMAF



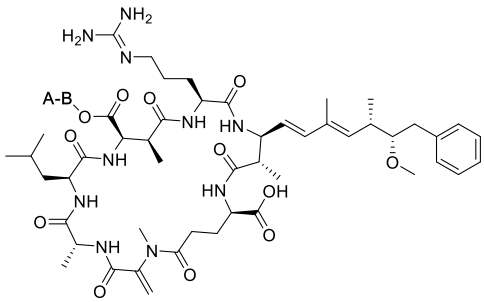
DM4



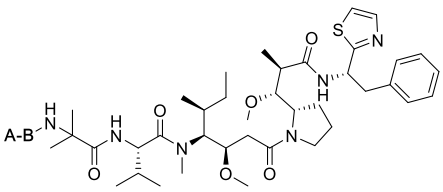
PNU-159682



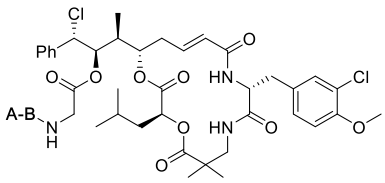
calicheamicin



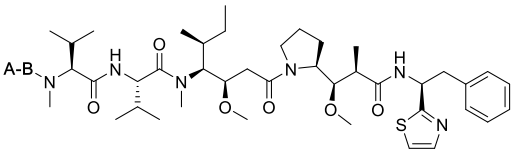
MC-LR



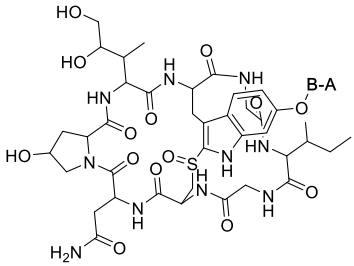
PF-06380101



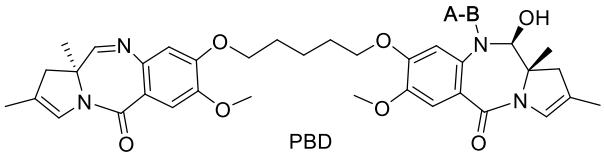
Cryptophycin-55



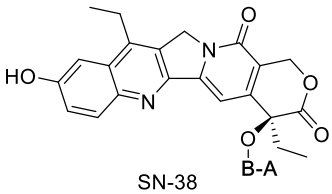
MMAD



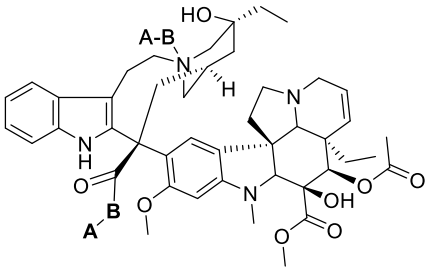
Alpha-Amanitin

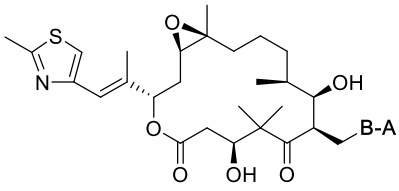


PBD

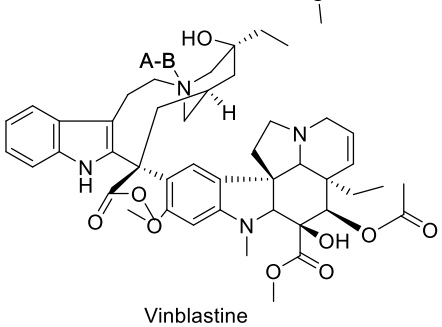


SN-38

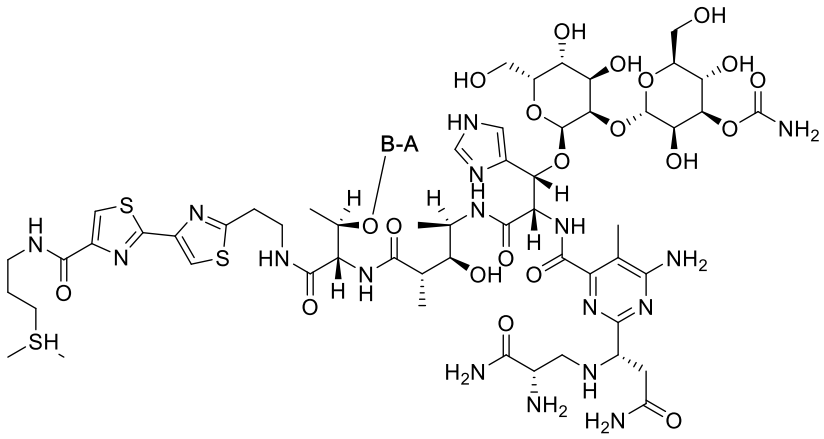




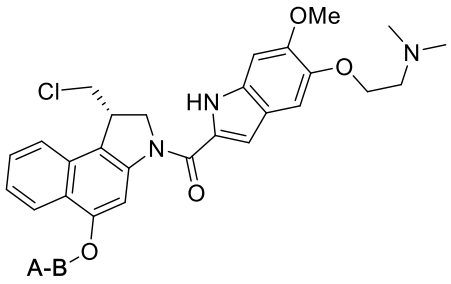
Epothilone B



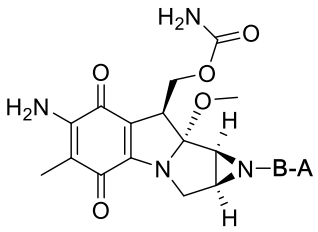
Vinblastine



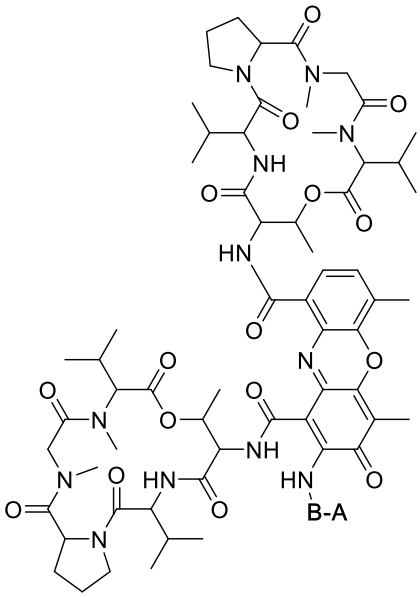
Bleomycin A2



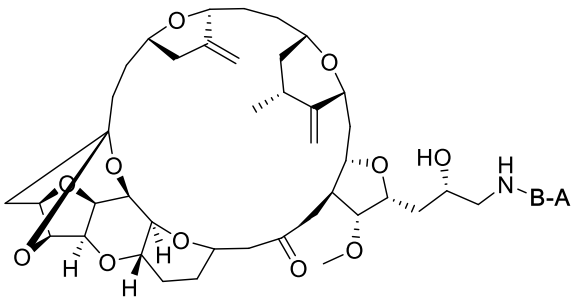
Duocarmycin



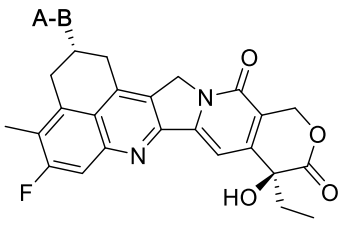
Mitomycin C



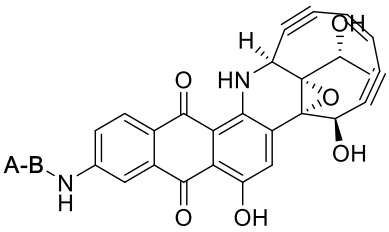
Dactinomycin D



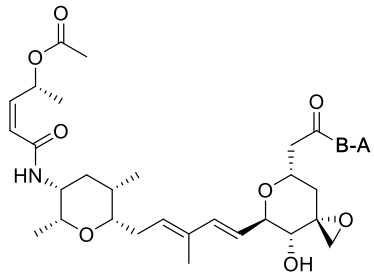
Eribulin



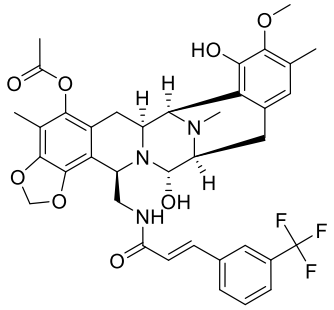
Camptothecin derivative



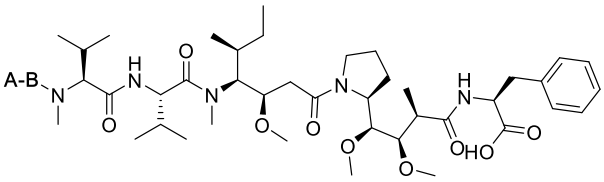
Uncialamycin



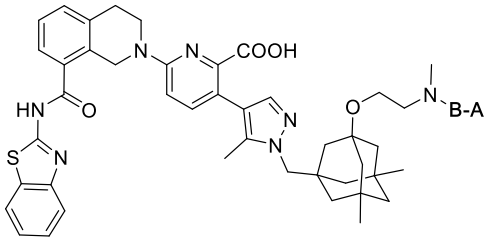
thailanstatin A



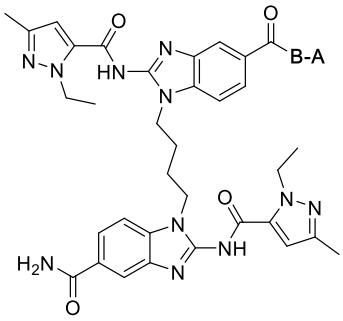
PM00104



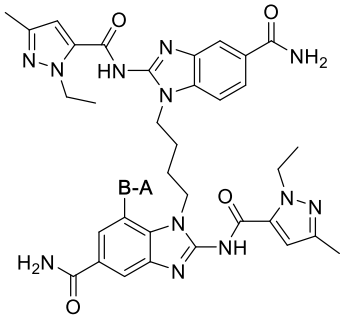
AS269



Bcl-x_L inhibitor



STING agonist 1



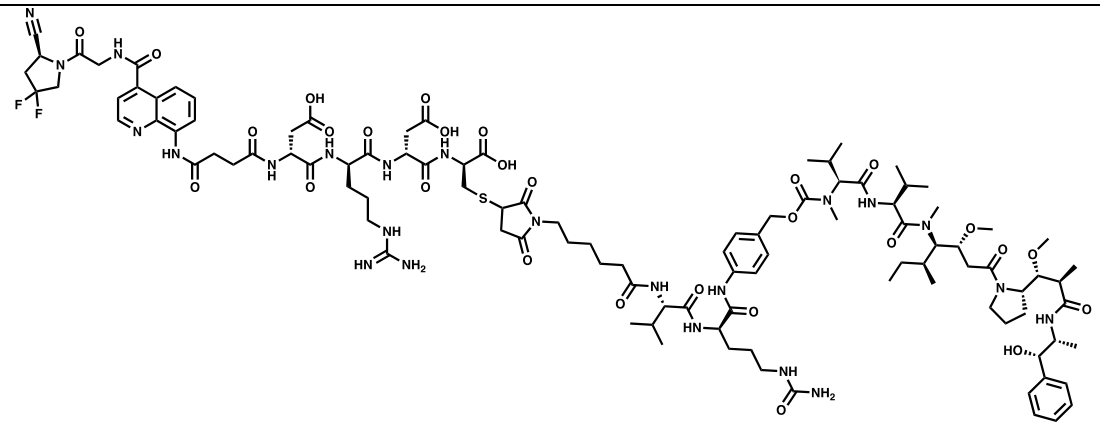
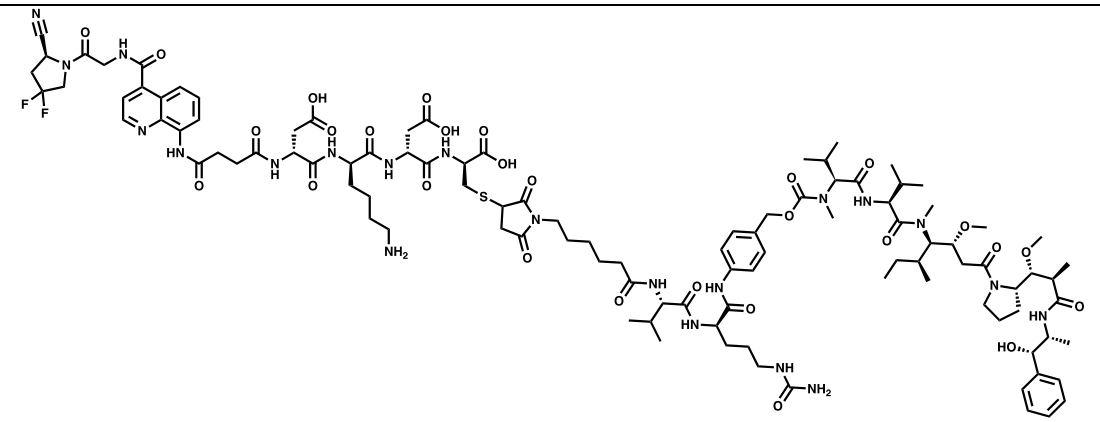
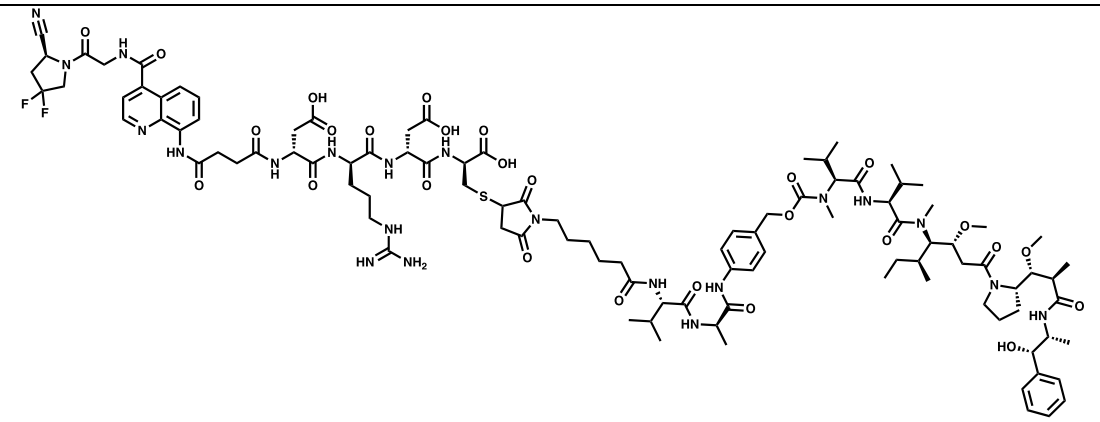
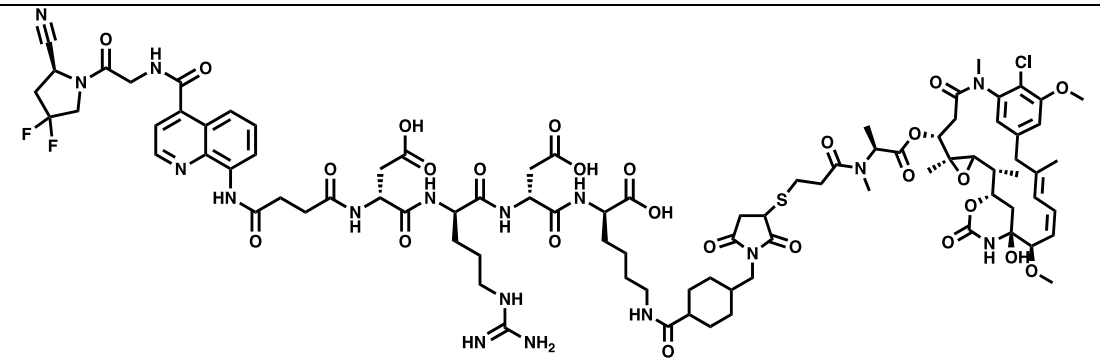
STING agonist 2 ;

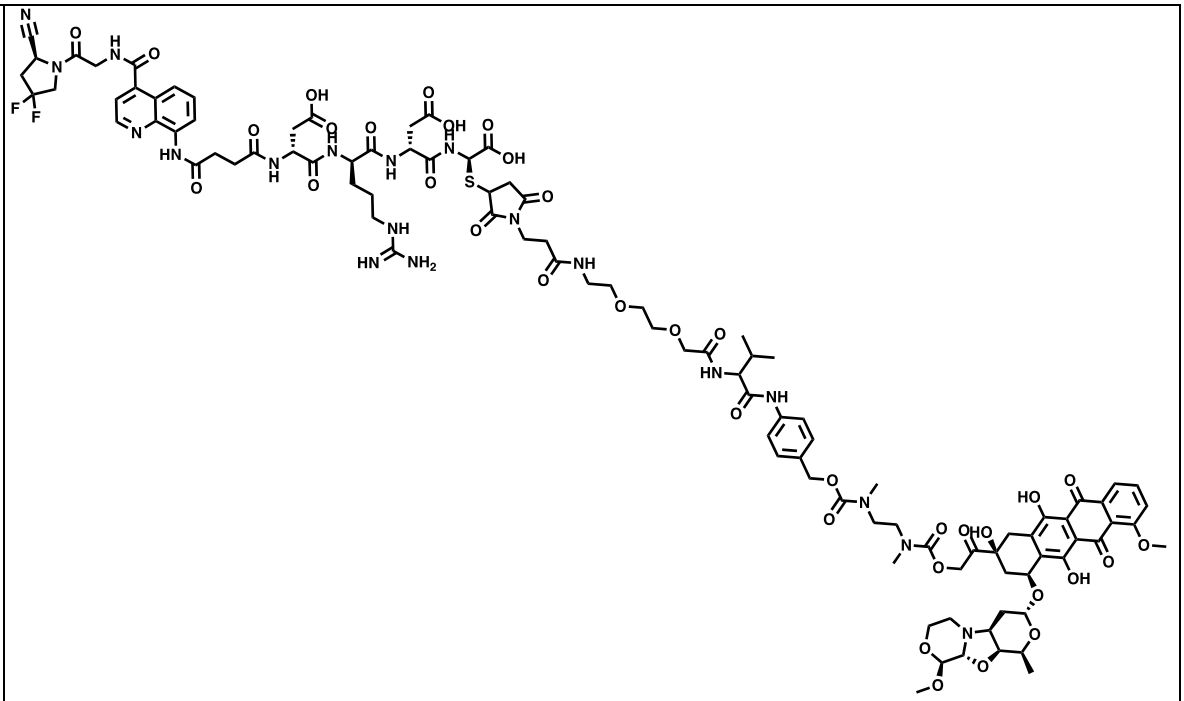
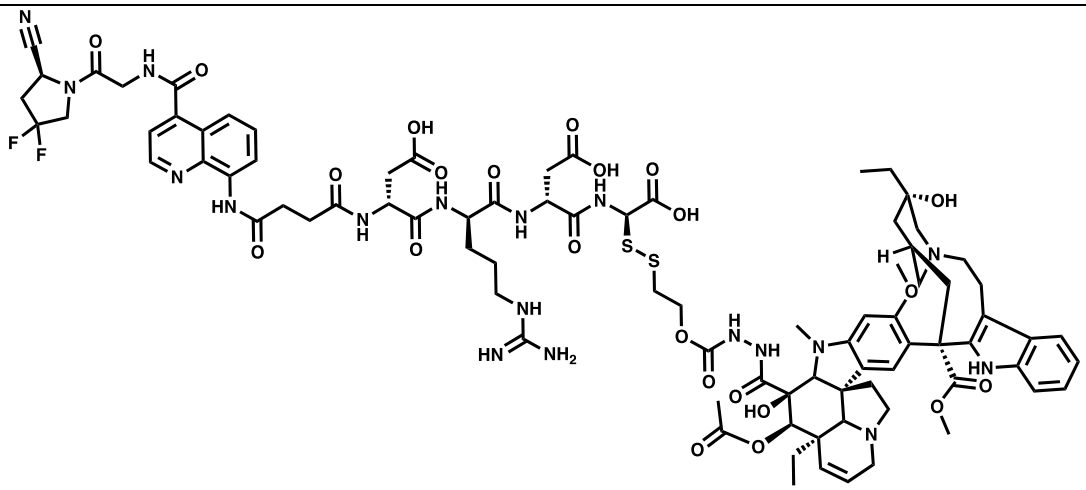
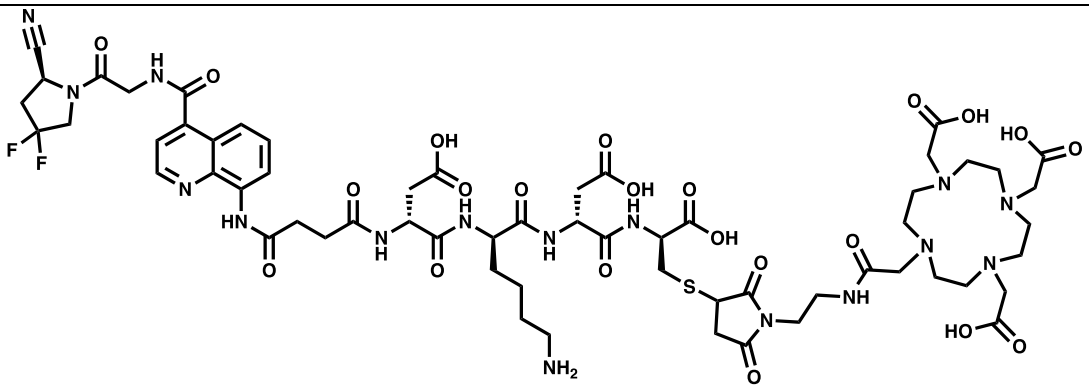
(f) the immunomodulator agent is selected from molecules known to be able to modulate the immune system, such as ligands of CD3, CD25, TLRs, STING, 4-1BBL, 4-1BB, PD-1, mTor, PDL-1, NKG-2D IMiDs, wherein ligands can be agonists and/or antagonist; or

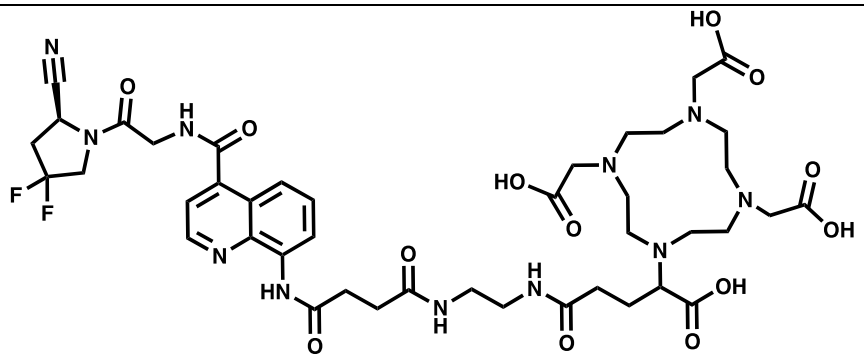
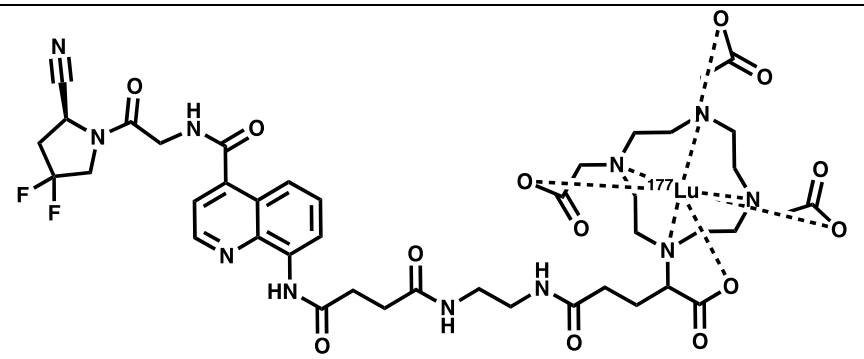
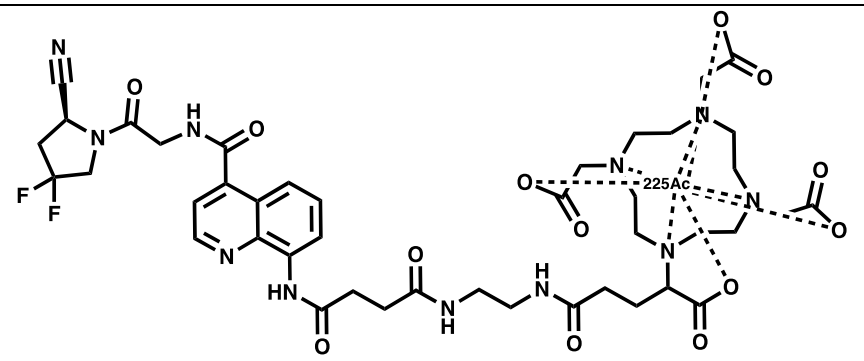
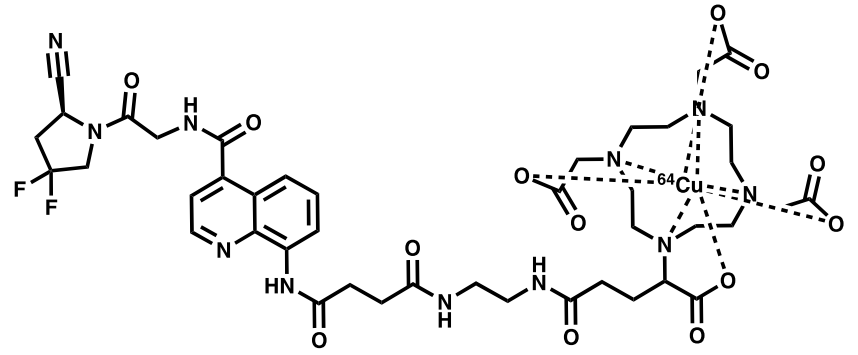
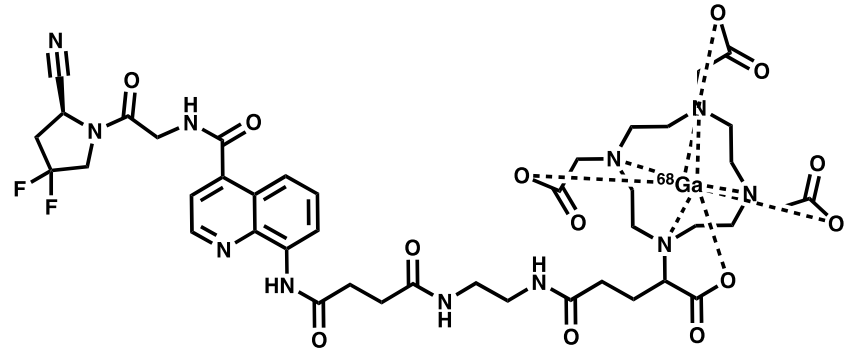
(g) the protein is selected from cytokines, such as IL2, IL10, IL12, IL15, TNF, Interferon Gamma, or is an antibody.

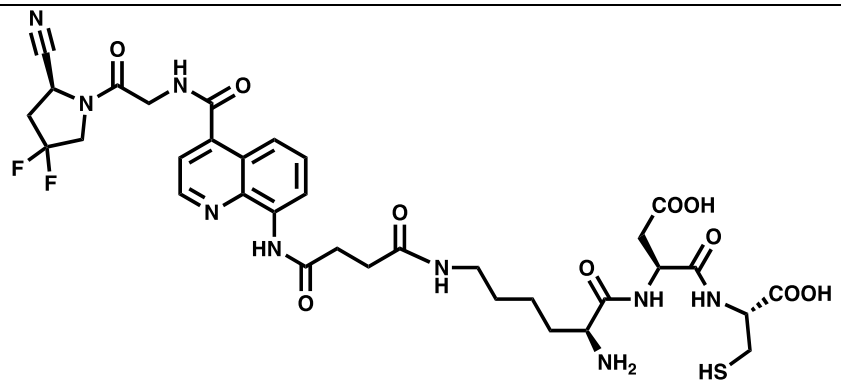
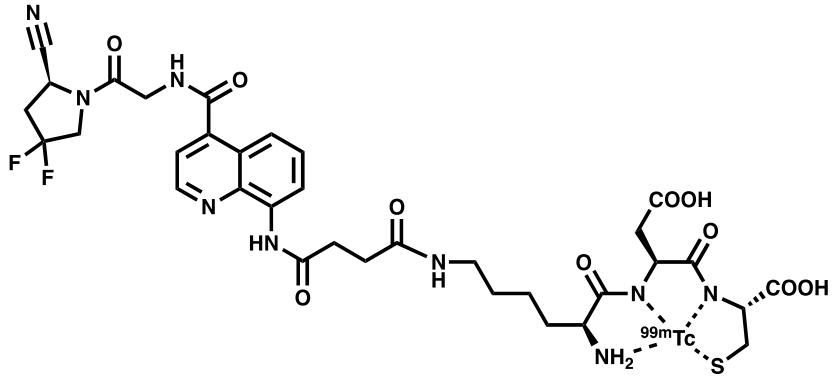
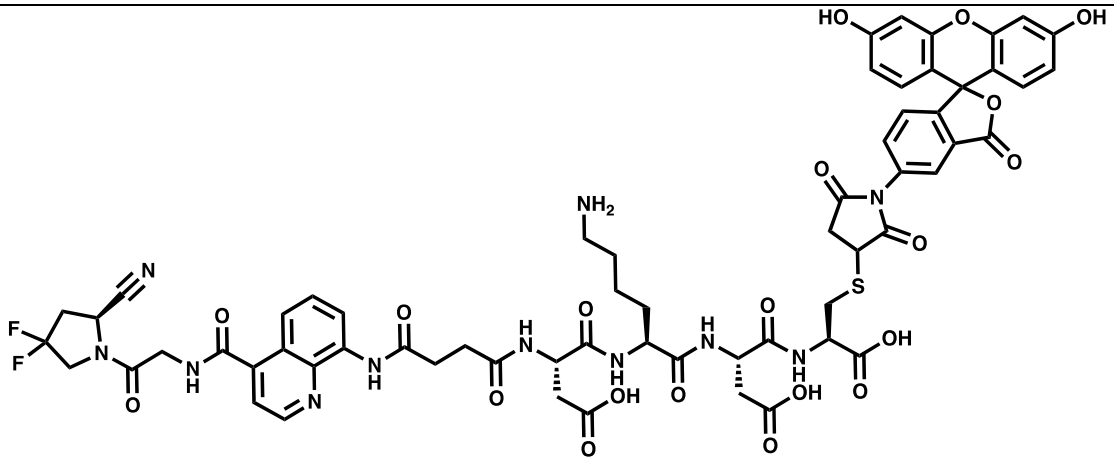
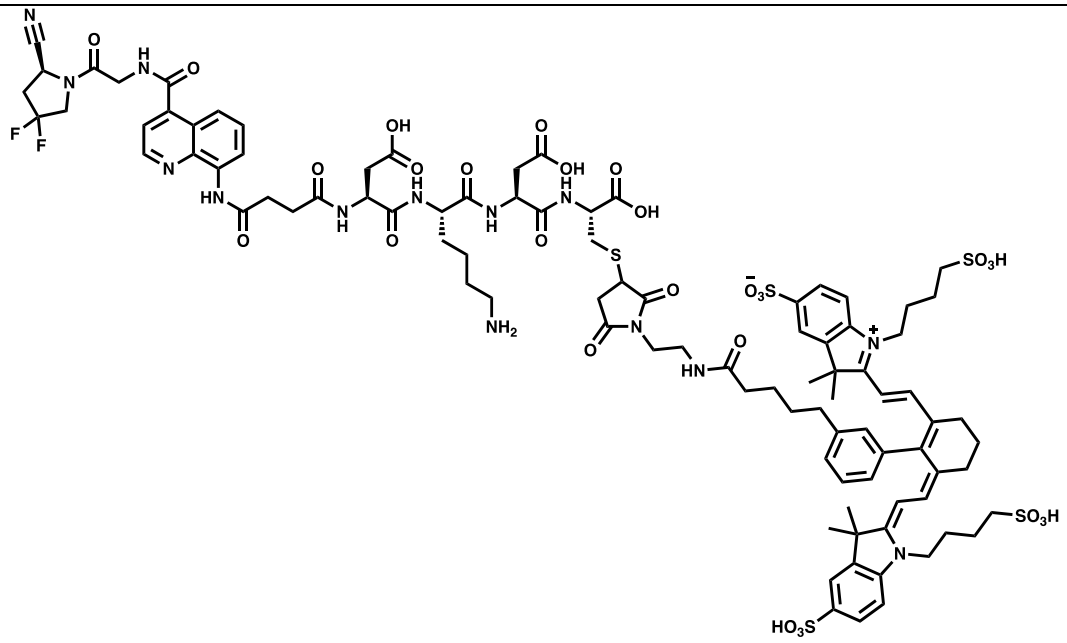
10. A compound having one the following structures, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof:

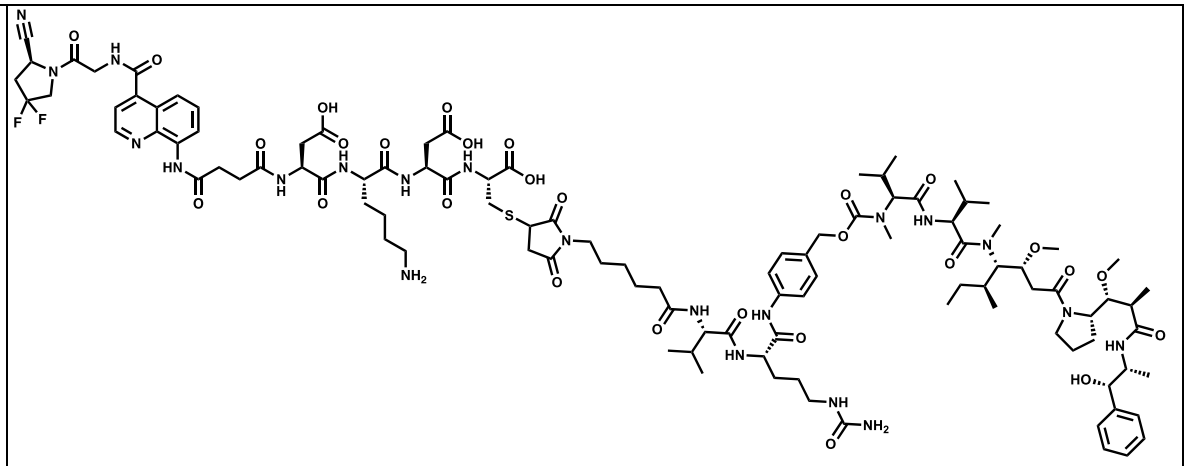
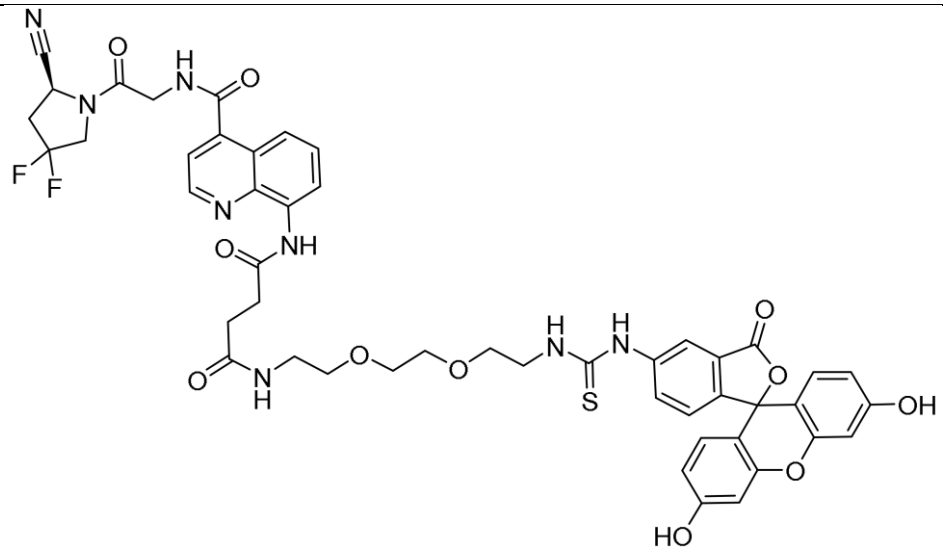
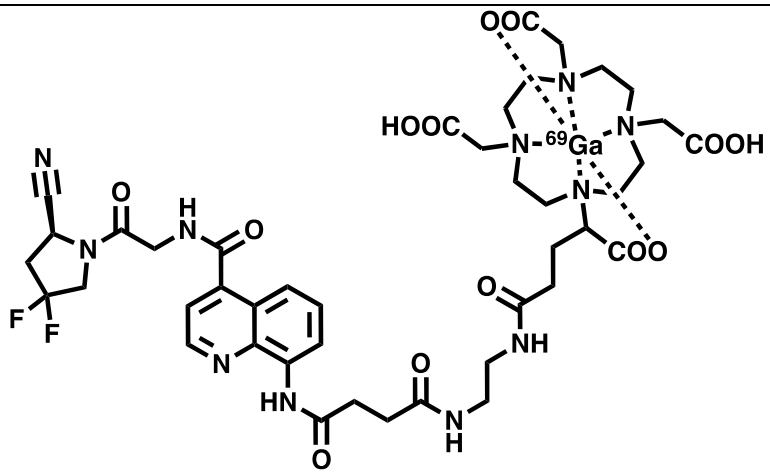
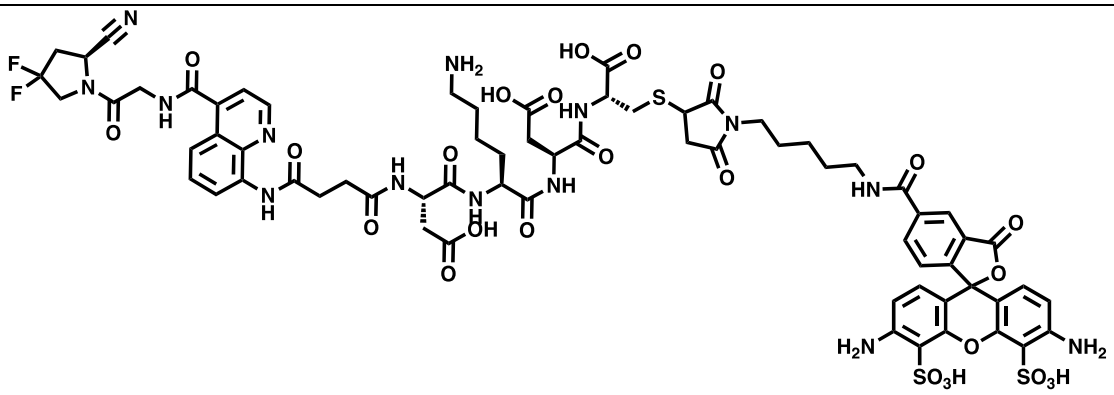
#	Structure

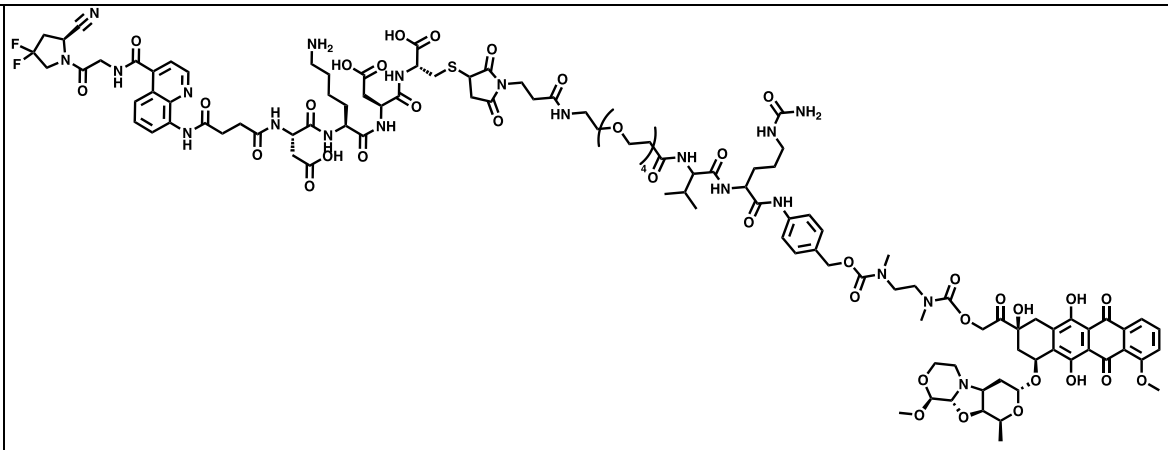
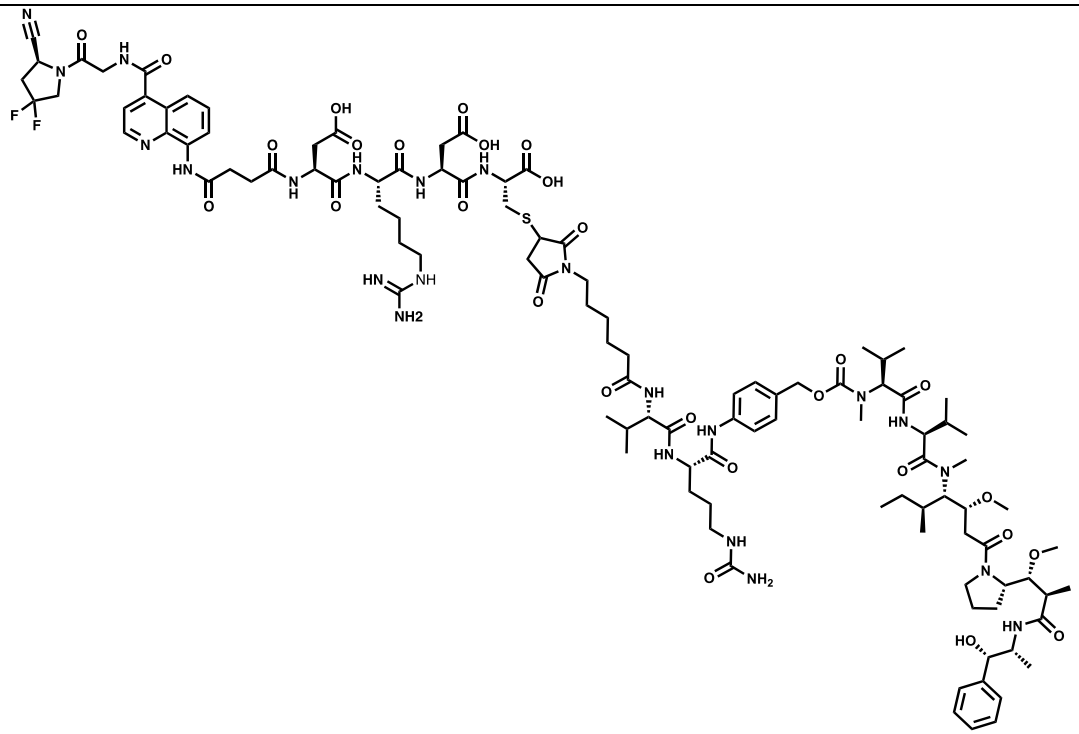
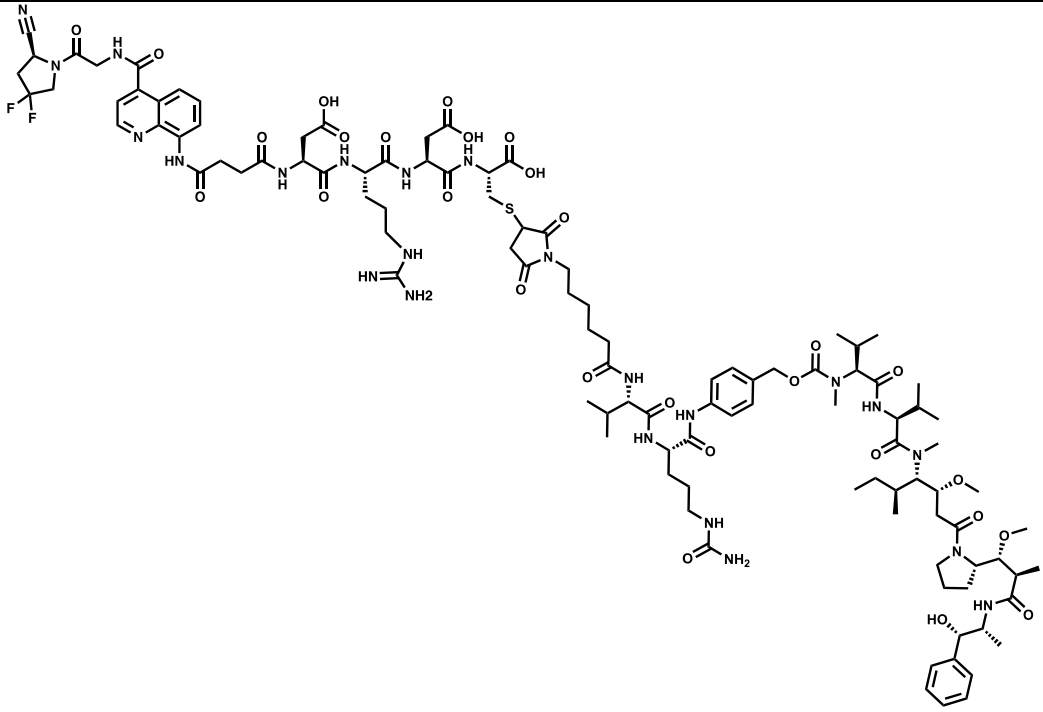
1	
2	
3	
4	

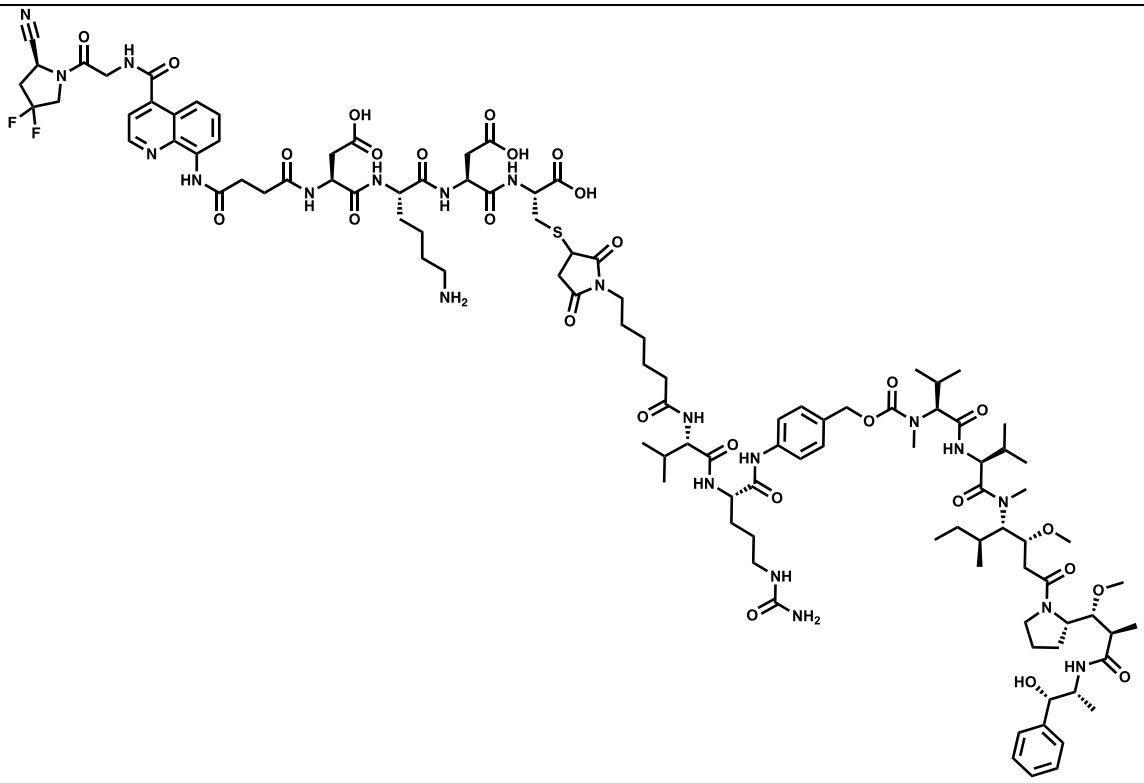
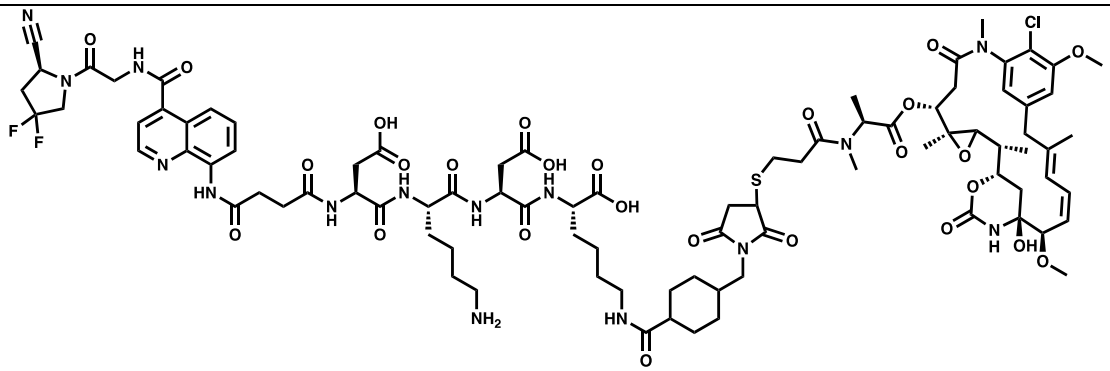
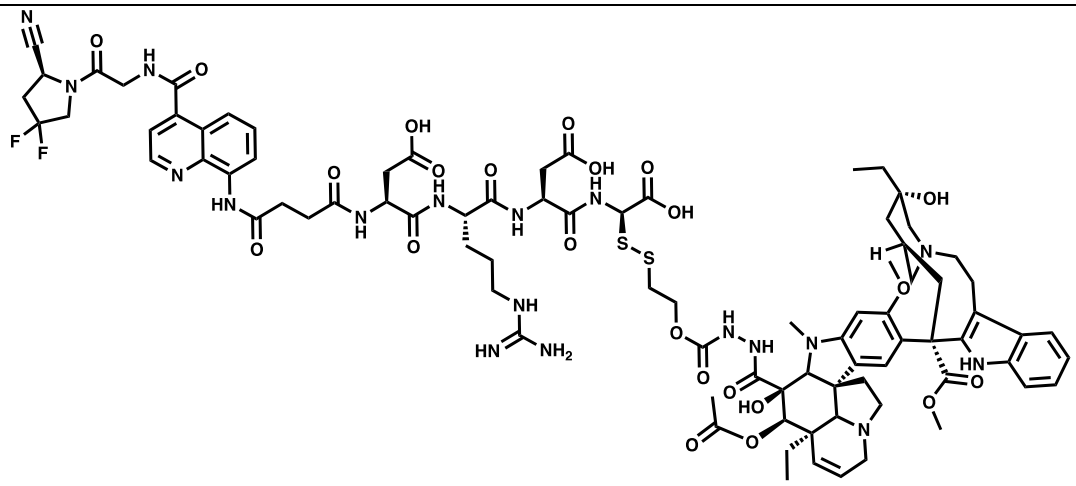
5	
6	
7	

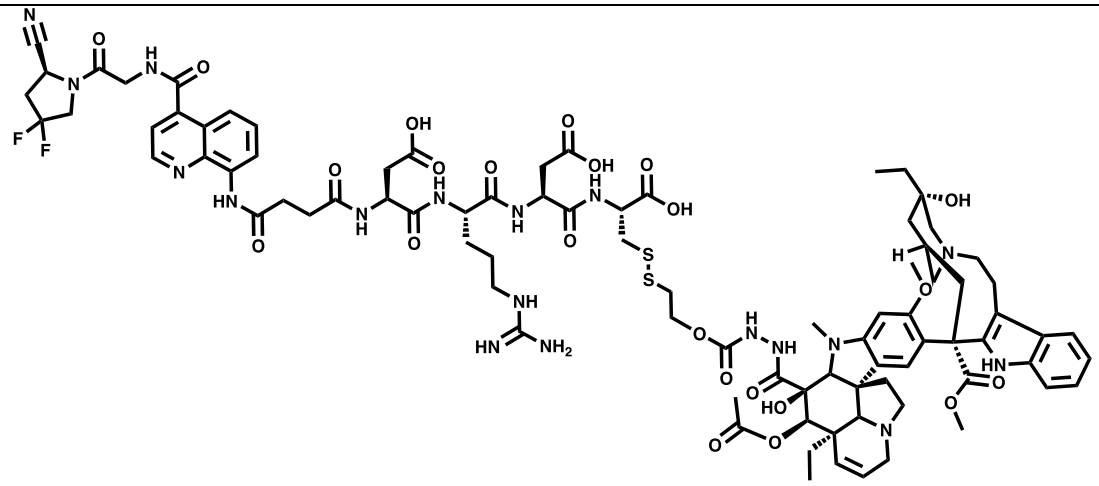
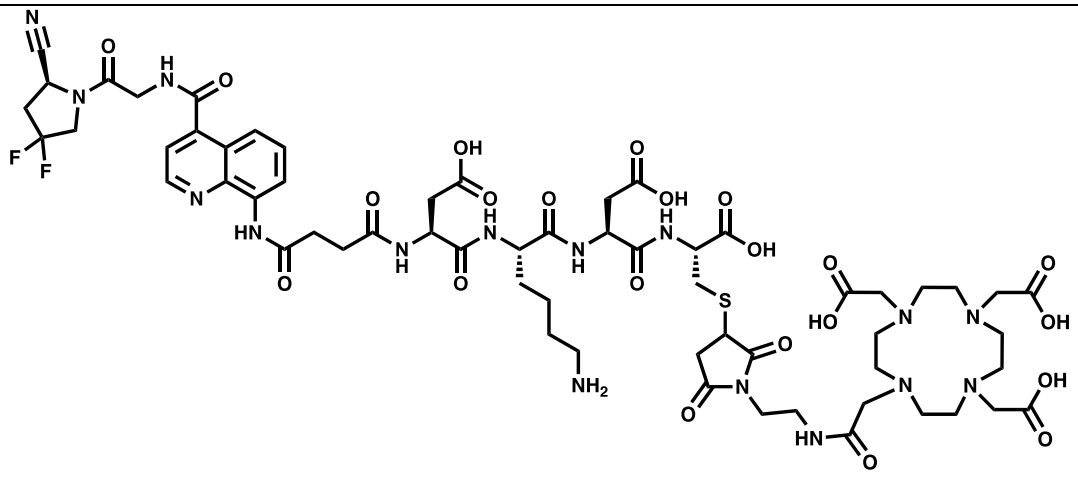
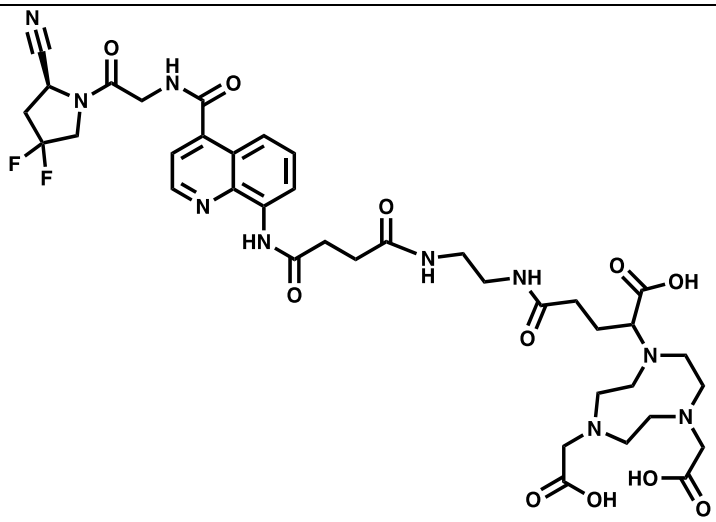
8	
9	
10	
11	
12	

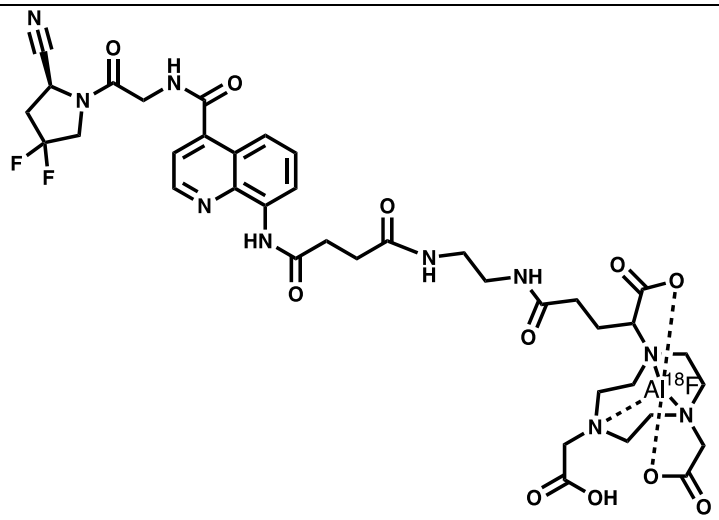
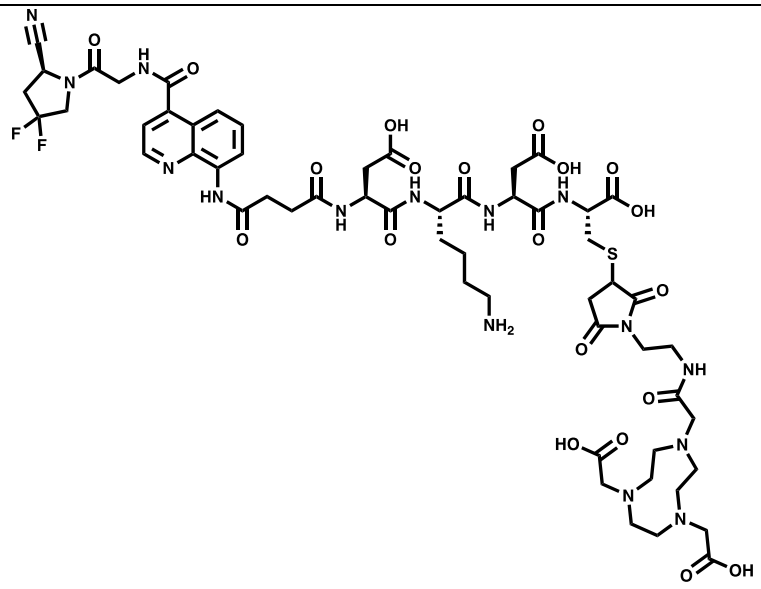
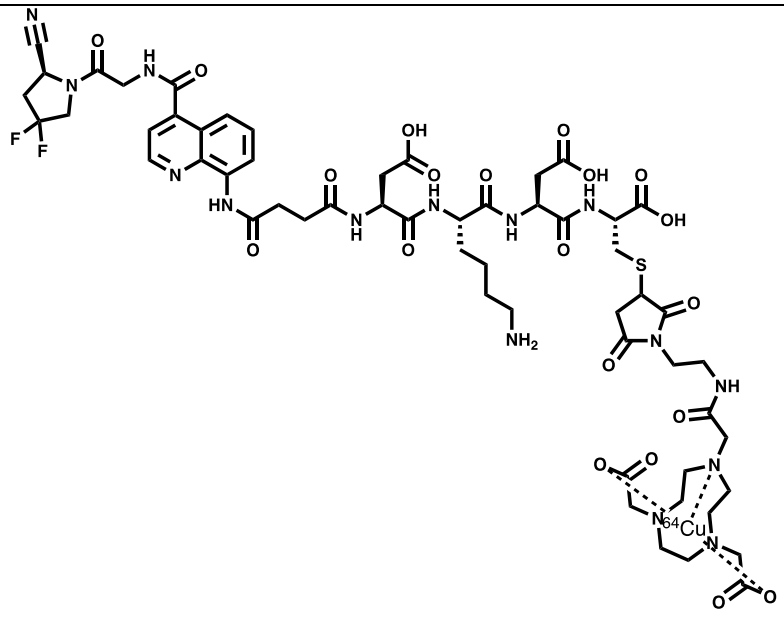
13	
14	
15	
18	

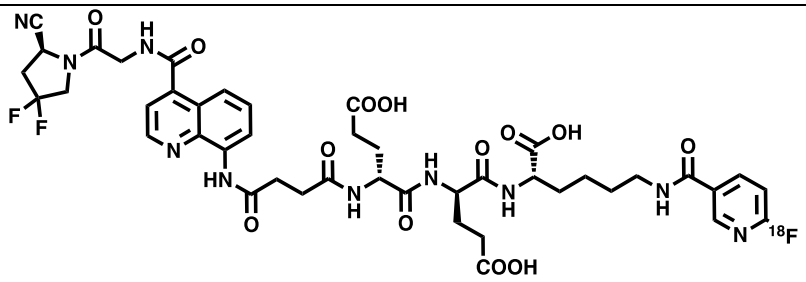
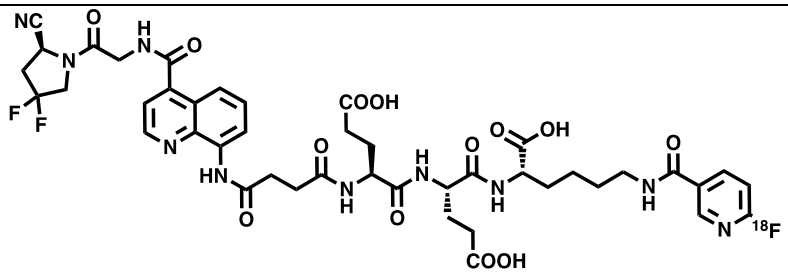
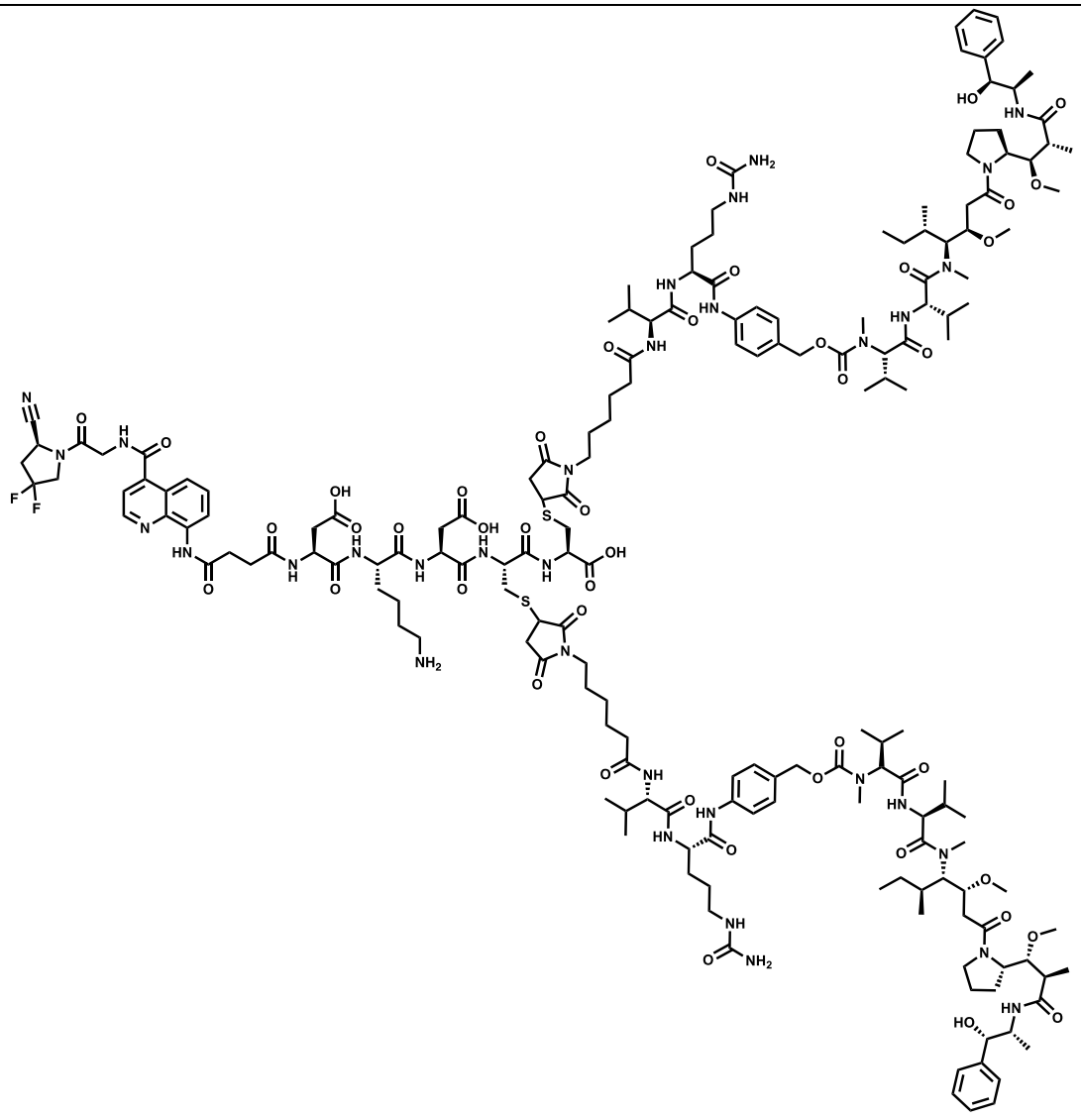
21	
26	
27	
30	

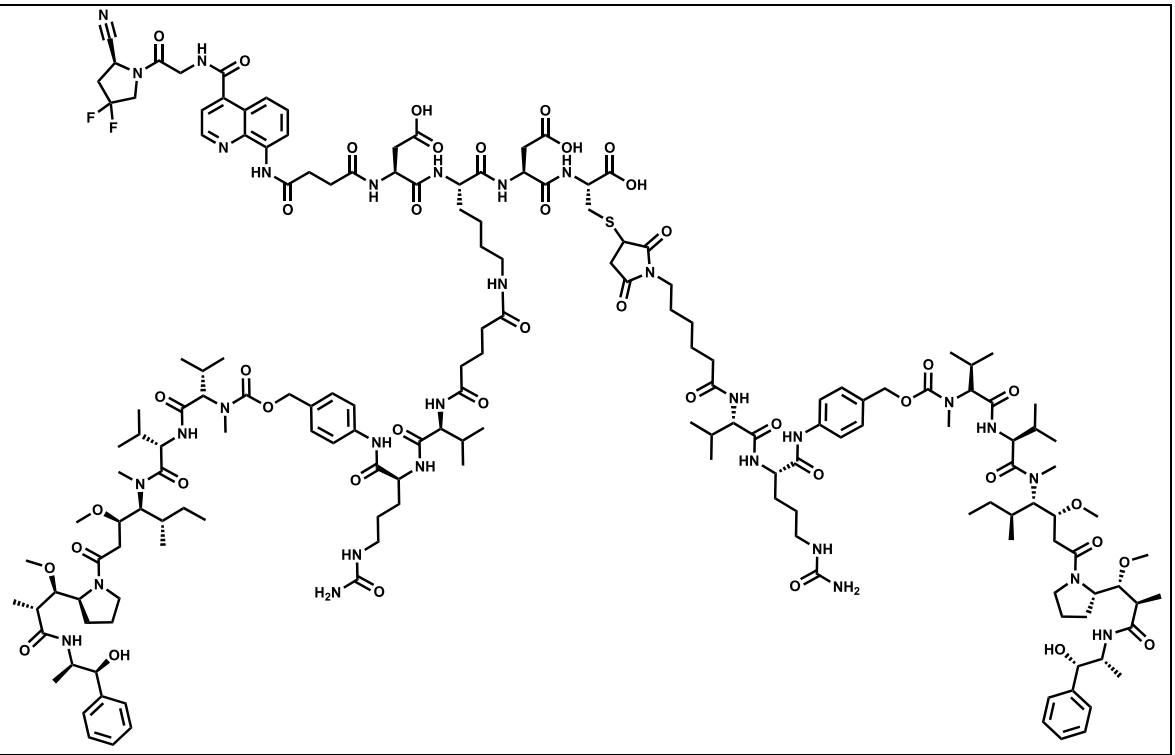
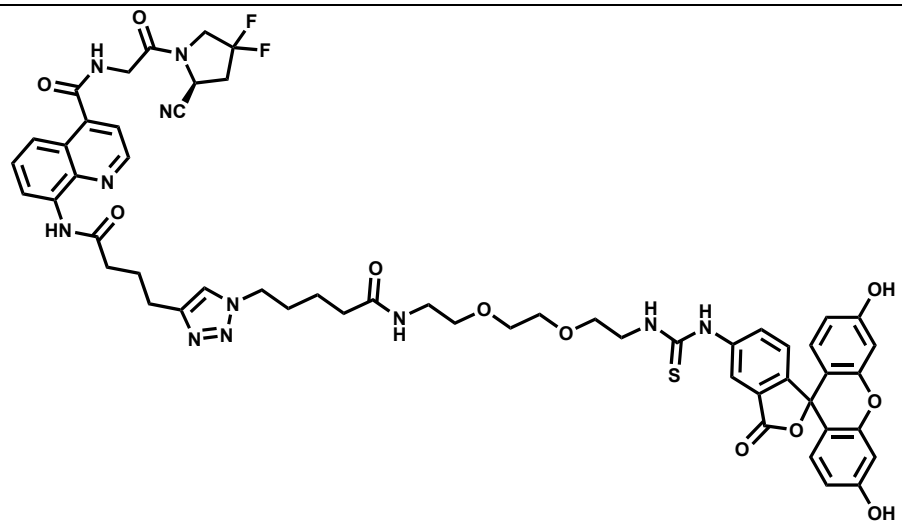
31	
34	
34a	

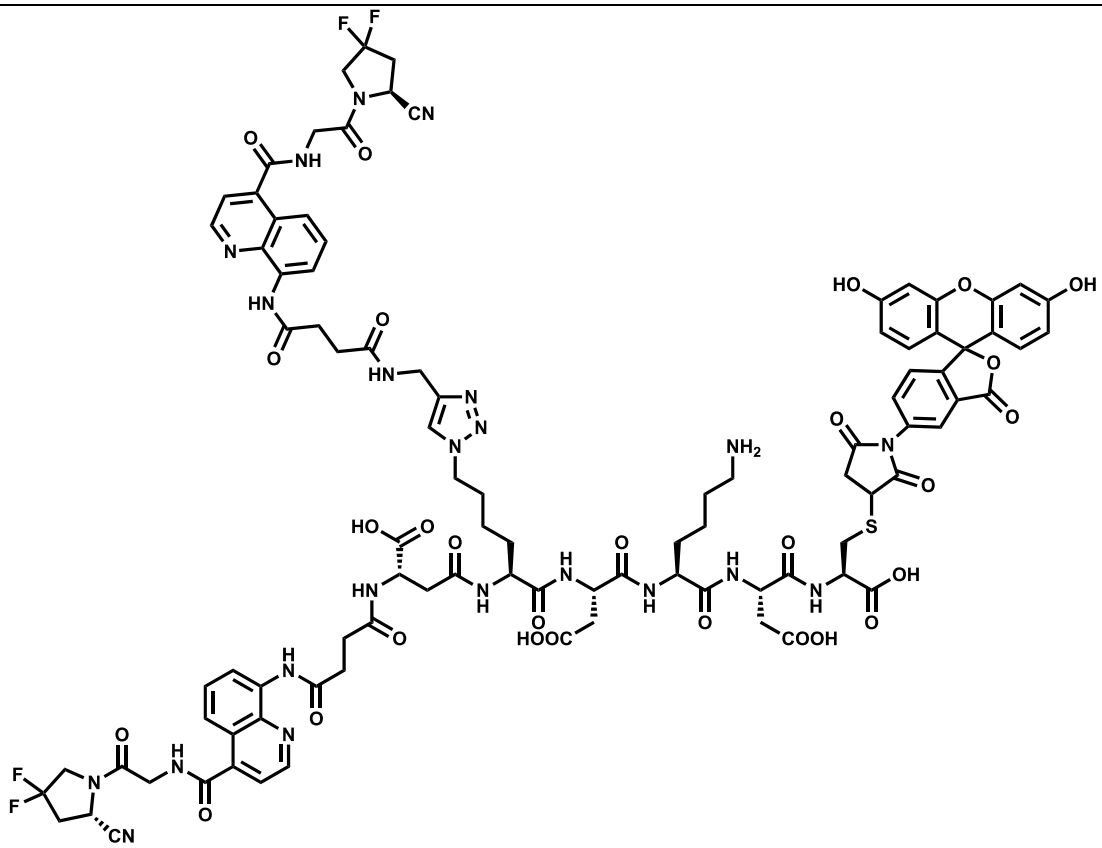
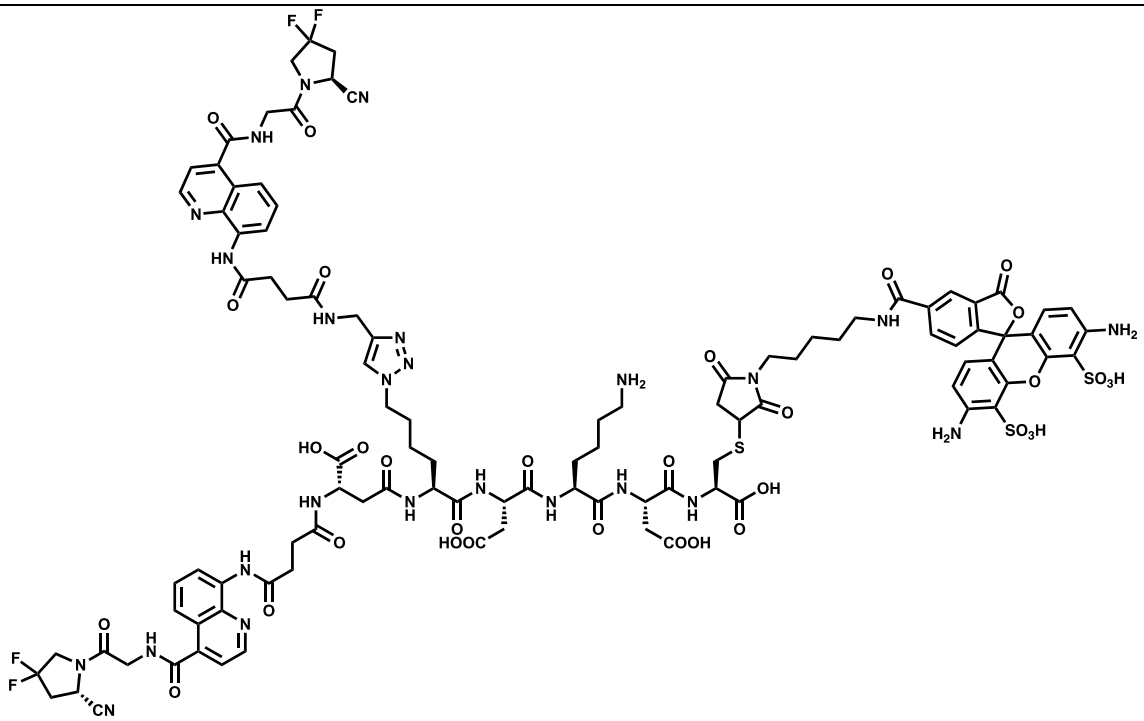
35	
36	
37	

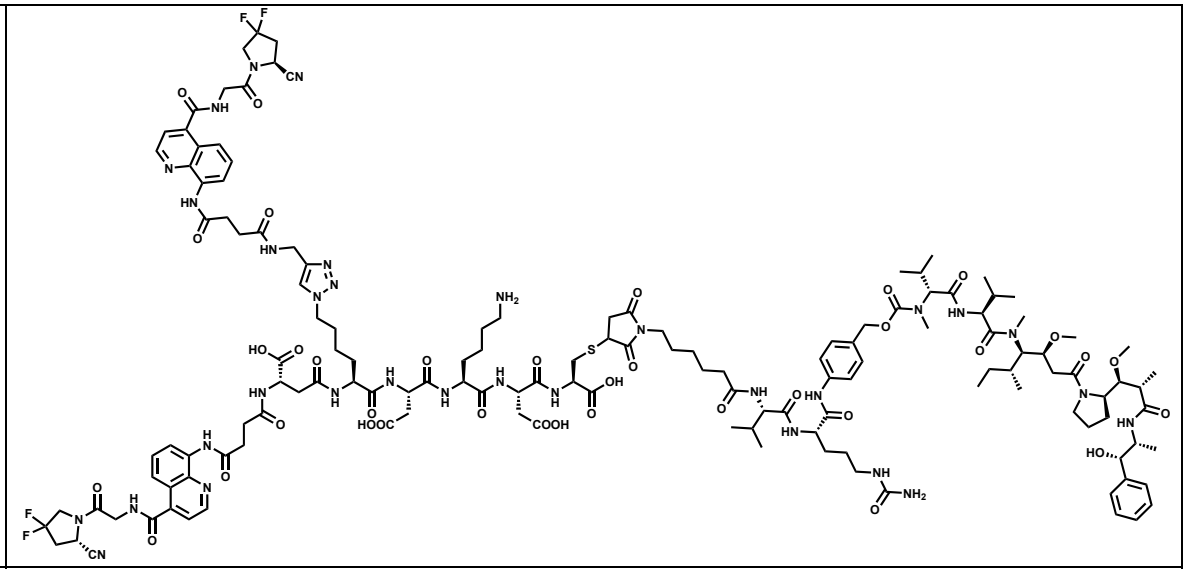
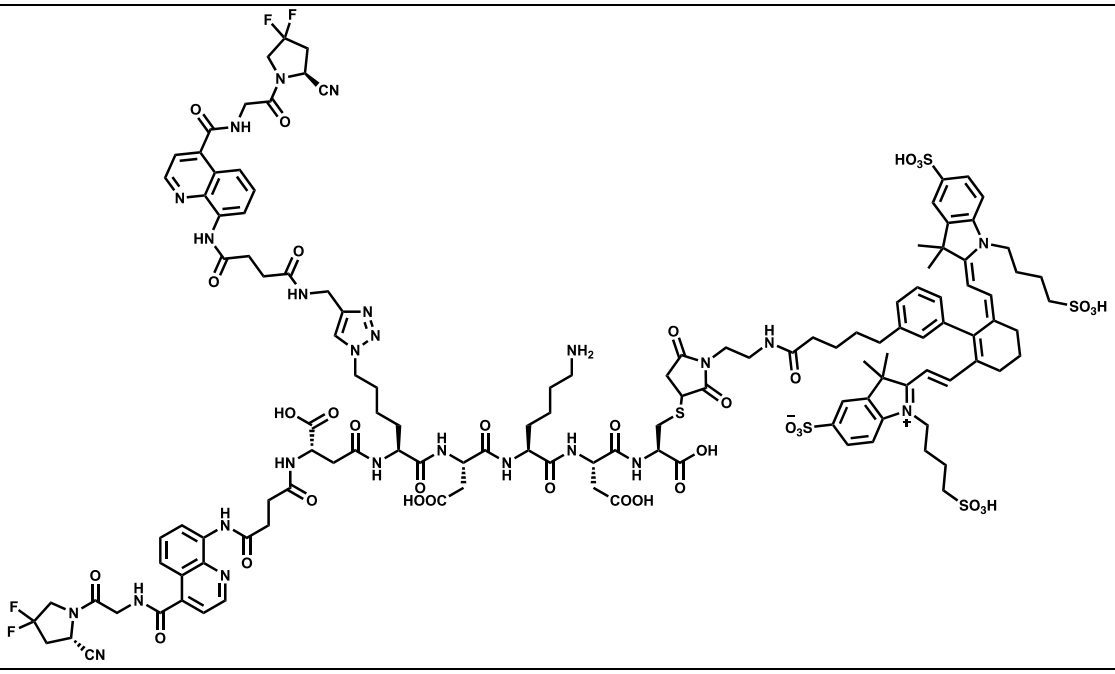
37a	
38	
39	

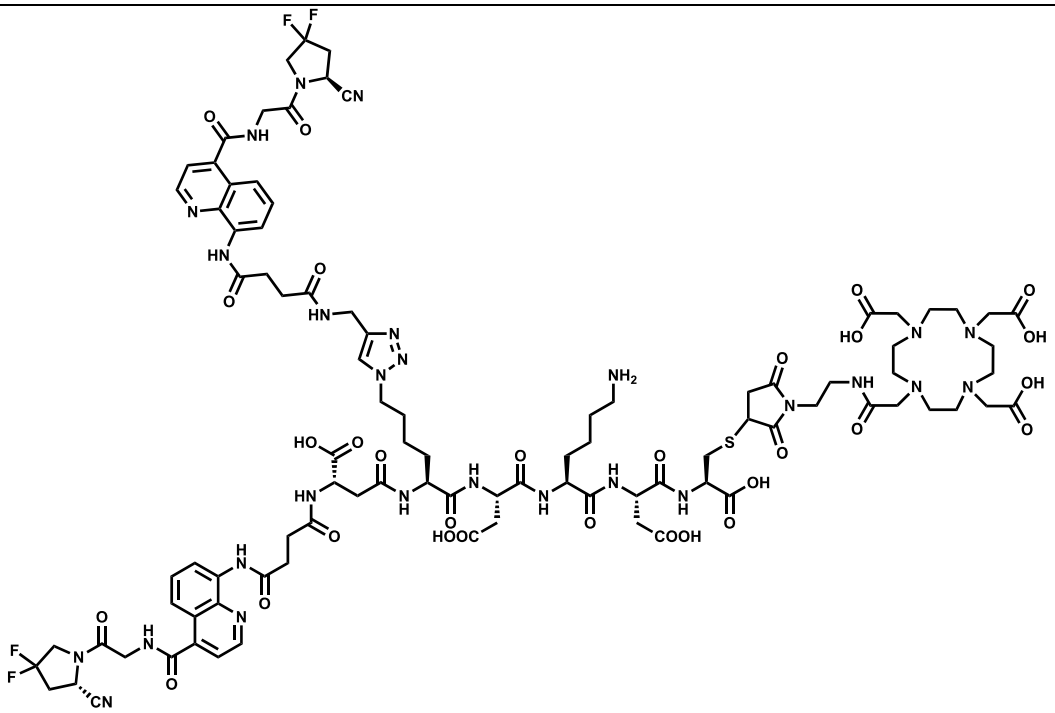
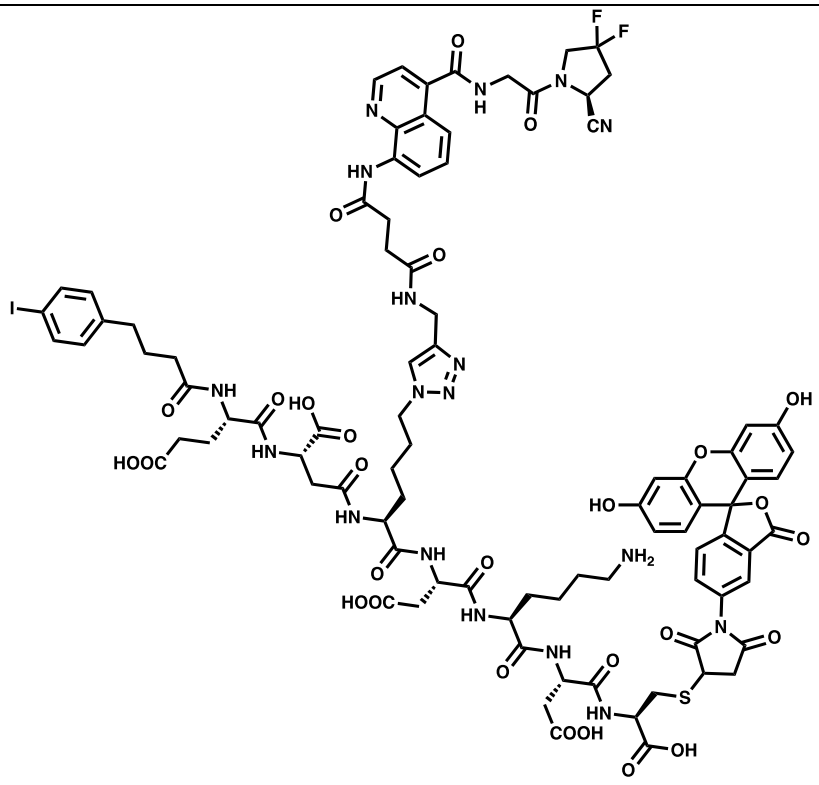
40	
41	
42	

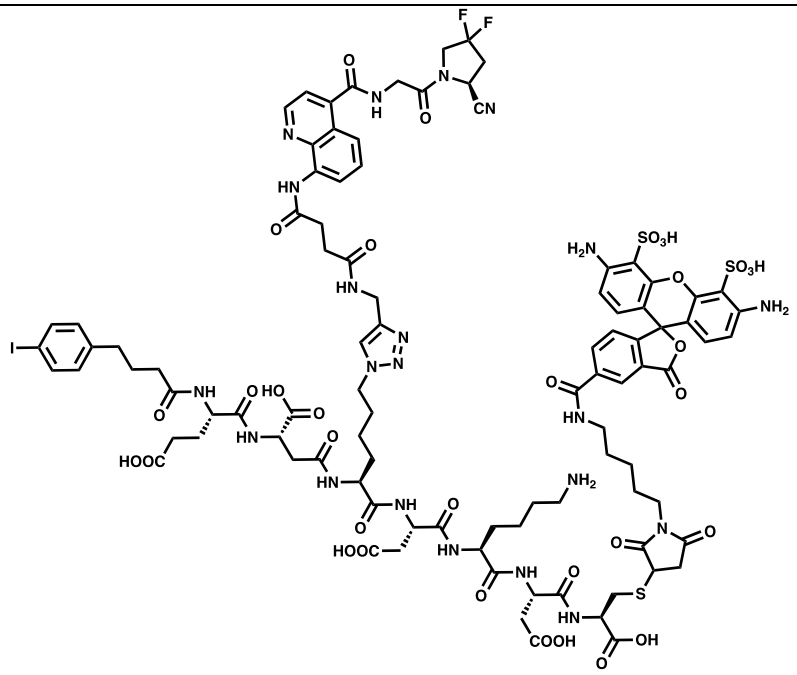
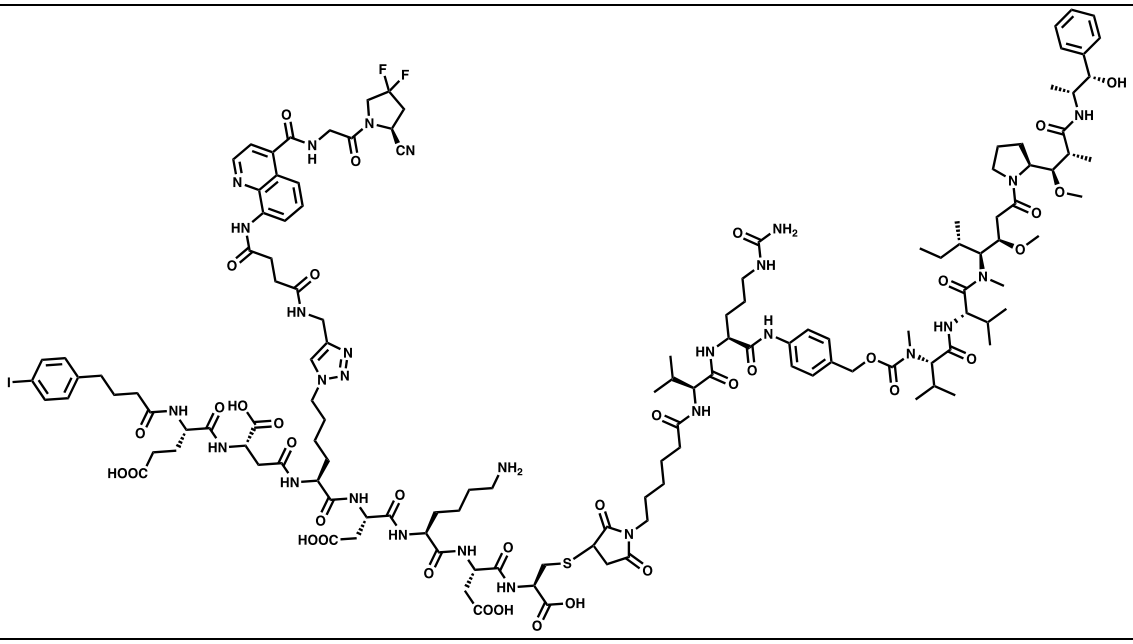
43	
43a	
44	

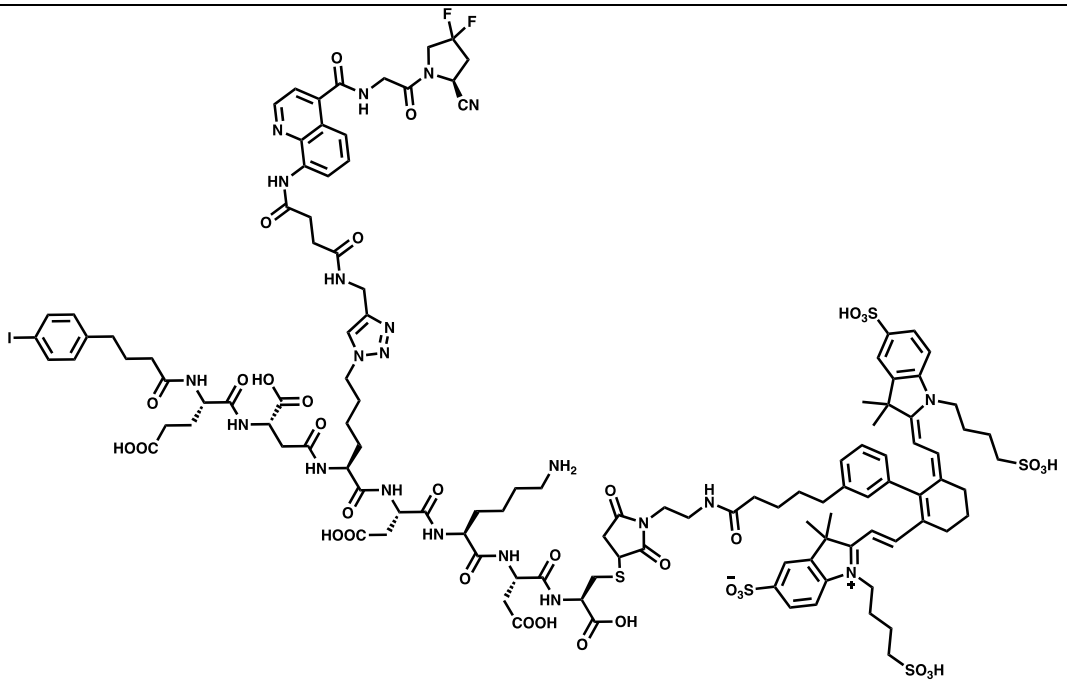
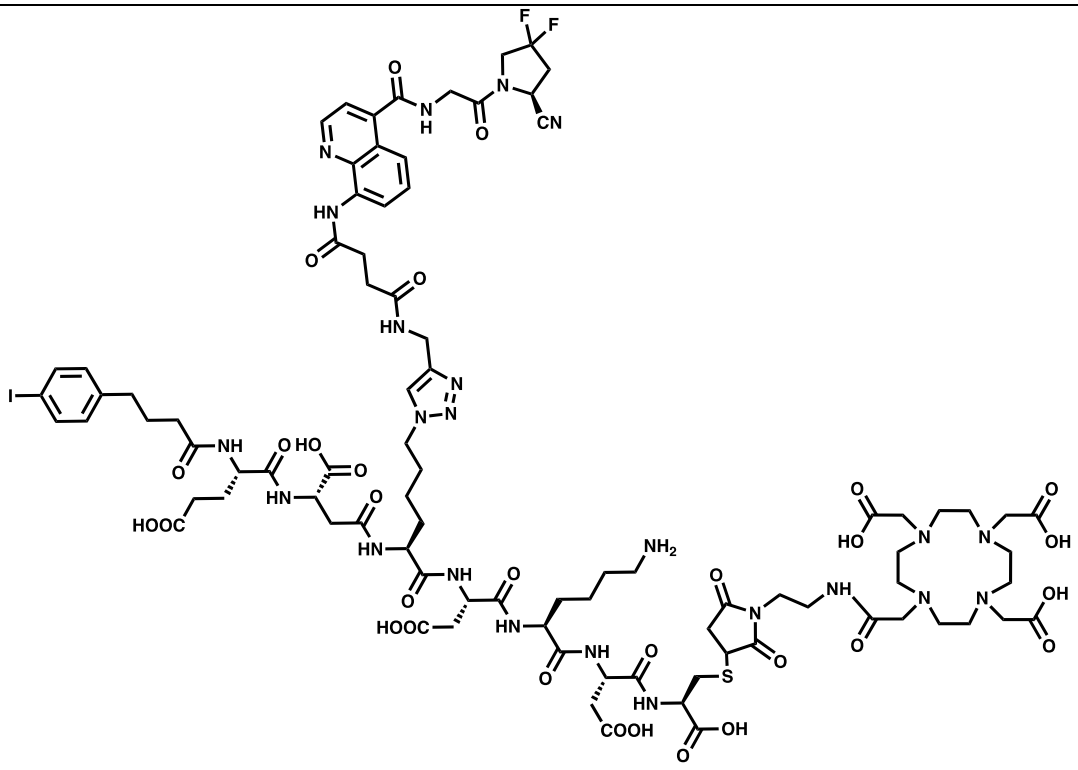
45	
46	

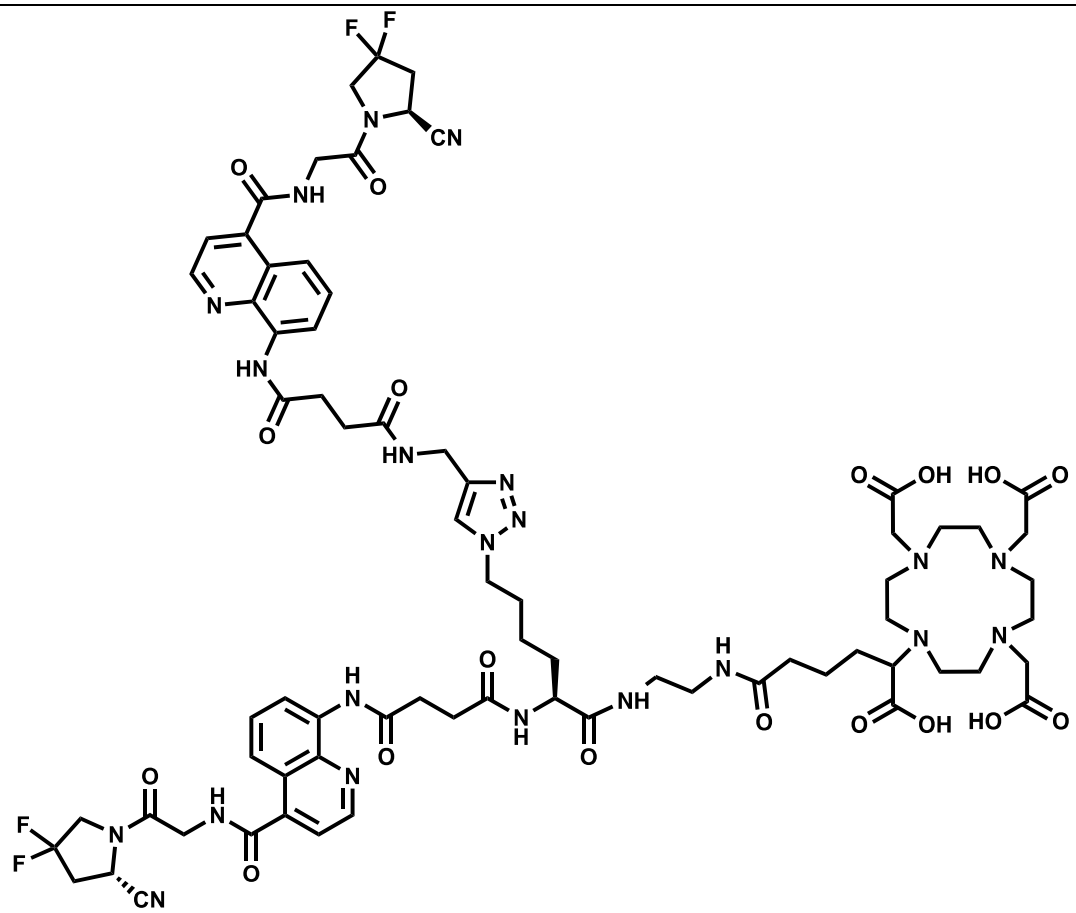
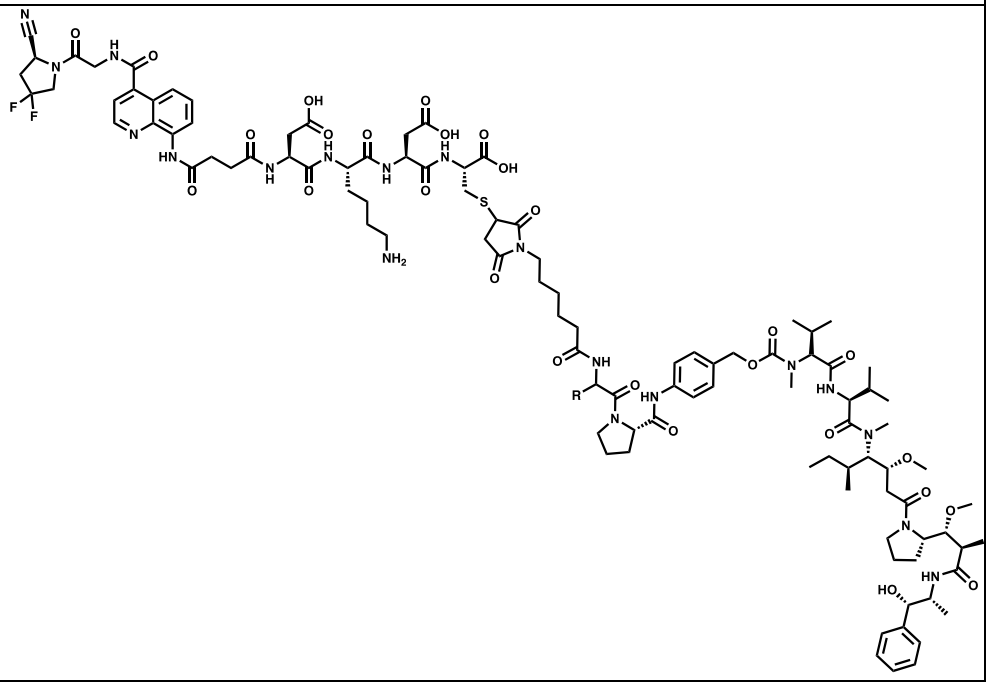
47	
48	

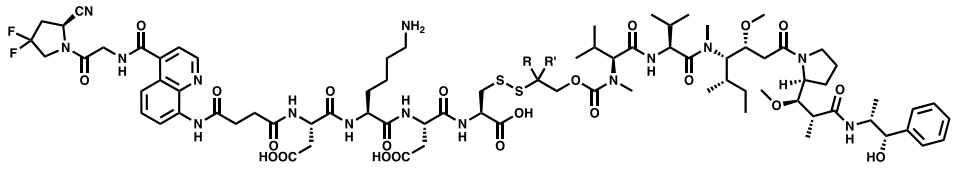
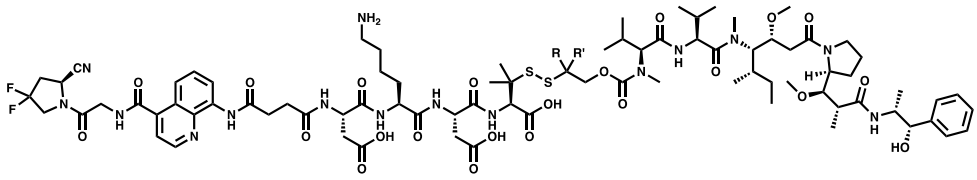
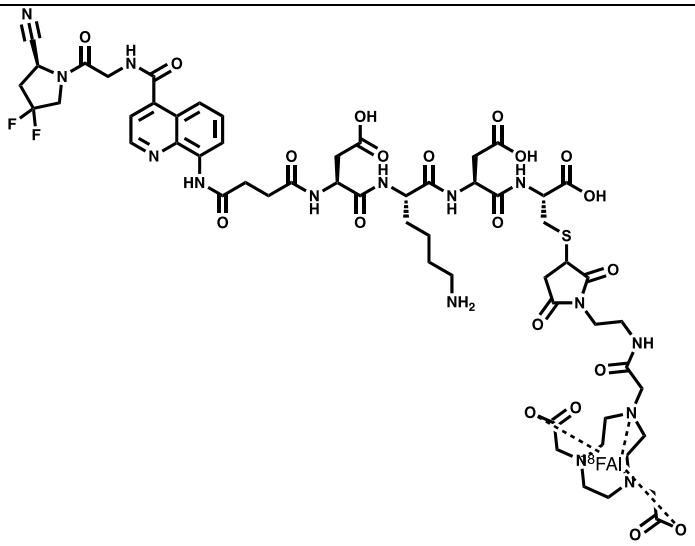
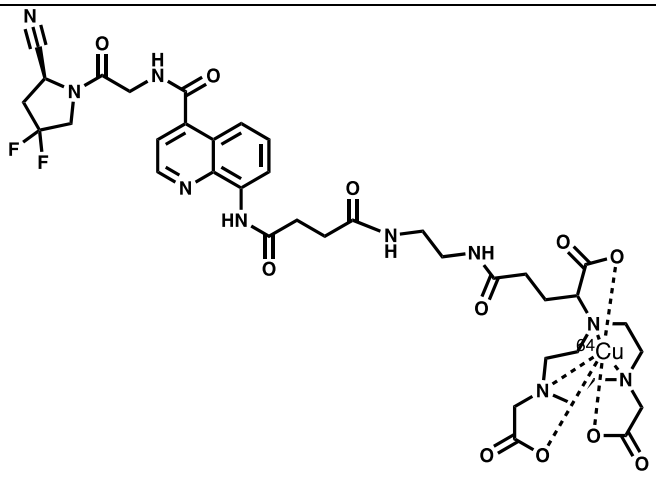
49	
50	

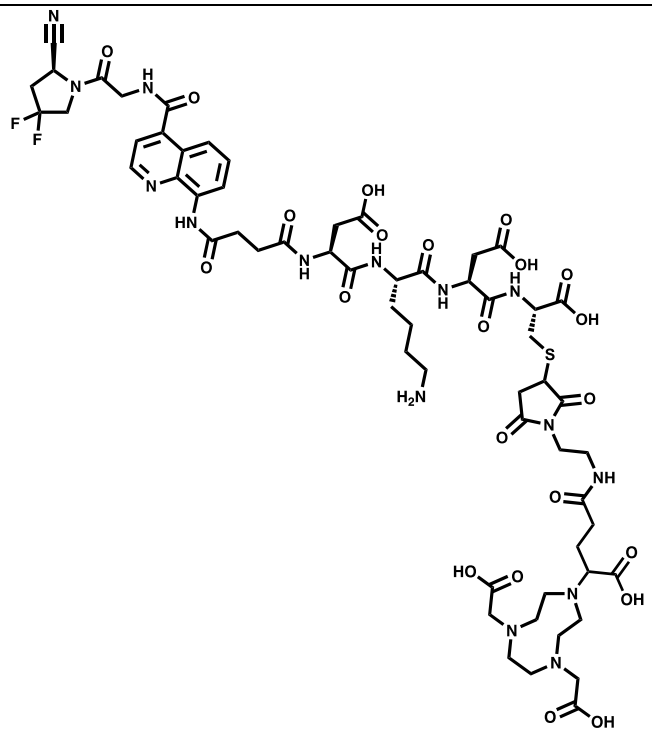
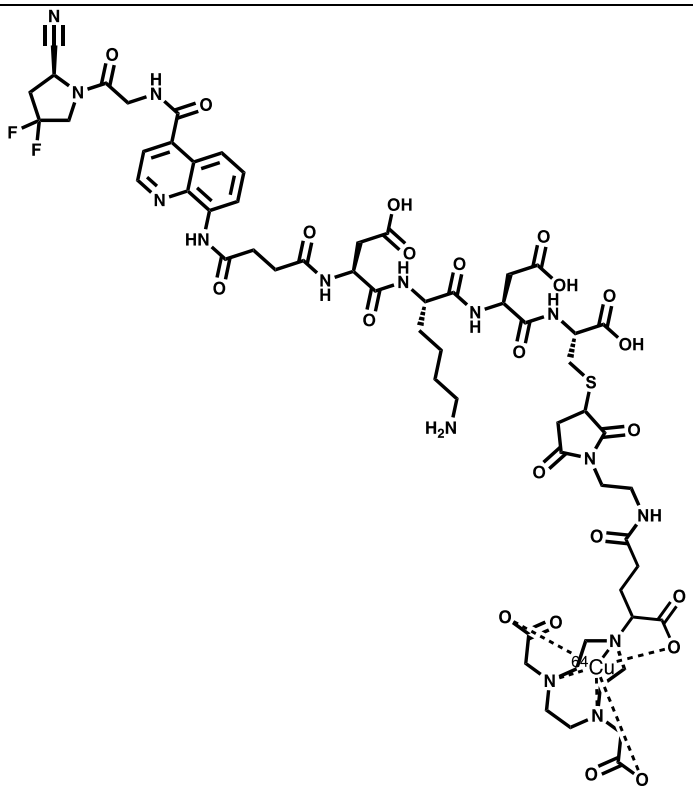
51	
52	

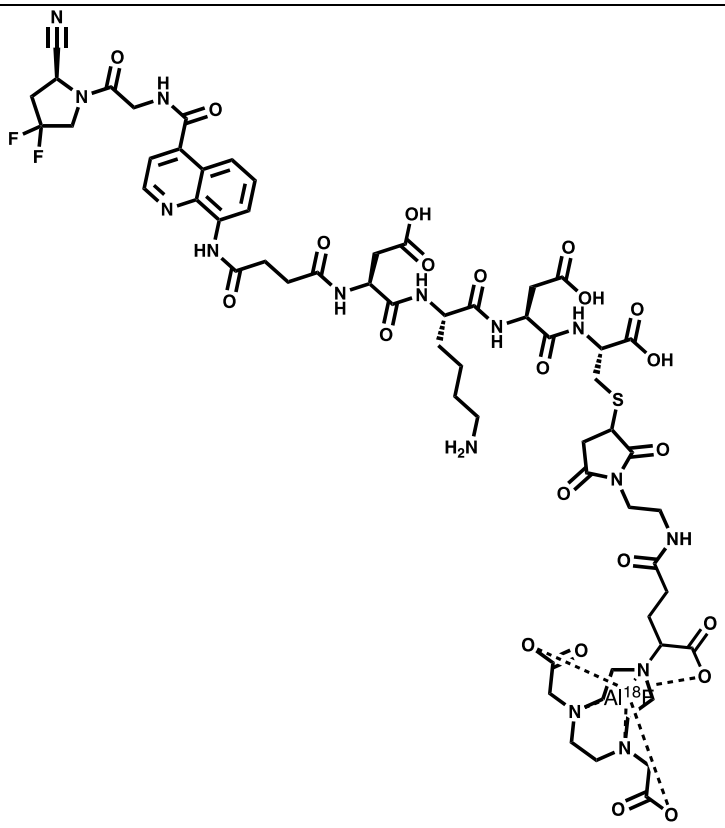
53	
54	

55	
56	

57		
58		
	R derived from AA:	
58a	Glycine	
58b	Alanine	
58c	Valine	
58d	Isoleucine	
58e	Proline	
58f	Arginine	

59			
	R	**R‘**	
59a	H	H	
59b	CH_3	H	
59c	CH_3	CH_3	
60			
	R	**R‘**	
60a	H	H	
60b	CH_3	H	
60c	CH_3	CH_3	
64			
65			

66	
67	

68	

211. The compound according to claim 10, wherein the structure is selected from those with numbers **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **18**, **21**, **26**, **27**, **30**, **31**, **34a**, **35**, **36**, **37a**, **38**, **39**, **40**, **41**, **42**, **43**, **43a**, **44**, **45**, **47**, **48**, **49**, **50**, **51**, **52**, **53**, **54**, **55**, **56**, **57**, **58a**, **58b**, **58c**, **58d**, **58e**, **58f**, **59a**, **60a**, **64**, **65**, **66**, **67**, and **68**.

312. The compound according to claim 10, wherein the structure is selected from those with numbers **2**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **18**, **21**, **26**, **27**, **30**, **31**, **34a**, **35**, **36**, **37a**, **38**, **39**, **40**, **41**, **42**, **43**, **43a**, **44**, **45**, **47**, **48**, **49**, **50**, **51**, **52**, **53**, **54**, **55**, **56**, **57**, **58a**, **58b**, **58c**, **58d**, **58e**, **58f**, **59a**, **60a**, **64**, **65**, **66**, **67**, and **68**.

413. The compound according to claim 10, wherein the structure is selected from those with numbers **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **18**, **21**, **26**, **27**, **30**, **35**, **38**, **39**, **40**, **41**, **42**, **43a**, **58a**, **58b**, **58c**, **59a**, **60a**, **64**, **65**, **66**, **67**, and **68**.

514. The compound according to claim 10, wherein the structure is selected from those with numbers **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, and **26**.

615. The compound according to claim 10 having the structure **8**.

16. A pharmaceutical composition comprising the compound according to any one of claims 1 to 15 and a pharmaceutically acceptable excipient.

17. A diagnostic composition comprising the compound according to any one of claims 1 to 15.

18. The compound according to any one of claims 1 to 15 or the composition as claimed in claim 16 or 17 for use in medicine.

19. Use of a compound according to any one of claims 1 to 15 or the composition as claimed in claim 17 in the manufacture of a cancer diagnostic agent.

20. Use of a compound according to any one of claims 1 to 15 or the composition as claimed in claim 16 in the manufacture of a medicament for treatment of cancer.

21. Use of a compound according any one of claims 1 to 15 or the pharmaceutical composition according to claim 16 or the diagnostic composition of claim 17, in the manufacture of a medicament or diagnostic agent for:

(a) the treatment of the human or animal body by surgery or therapy or a diagnostic method practised on the human or animal body; or

(b) therapy or prophylaxis of a subject suffering from or having risk for a disease or disorder; or

(c) guided surgery practised on a subject suffering from or having risk for a disease or disorder; or

(d) diagnosis of a disease or disorder, wherein the diagnosis is to be practised on the human or animal body and involves a nuclear medicine imaging technique, such as Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT); or

(e) targeted delivery of a therapeutic or diagnostic agent to a subject suffering from or having risk for a disease or disorder,

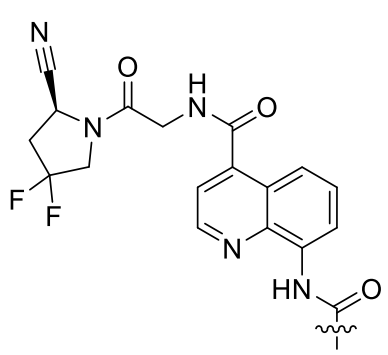
wherein in each of the preceding (b)–(e), said disease or disorder is independently selected from cancer, inflammation, atherosclerosis, fibrosis, tissue remodelling and keloid disorder, preferably wherein the cancer is selected from the group consisting of breast cancer, pancreatic cancer, small intestine cancer, colon cancer, multi-drug resistant colon cancer, rectal cancer, colorectal cancer, metastatic colorectal cancer, lung cancer, non-small cell lung cancer, head and neck cancer, ovarian cancer, hepatocellular cancer, oesophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocarcinoma, clear cell renal carcinoma, neuroendocrine tumour, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus cancer, desmoid tumours, glioma, astrocytoma, cervix cancer, skin cancer, kidney cancer and prostate cancer;

preferably wherein the compound has a prolonged residence at the disease site at a therapeutically or diagnostically relevant level, preferably beyond 1 h, more preferably beyond 6 h post injection.

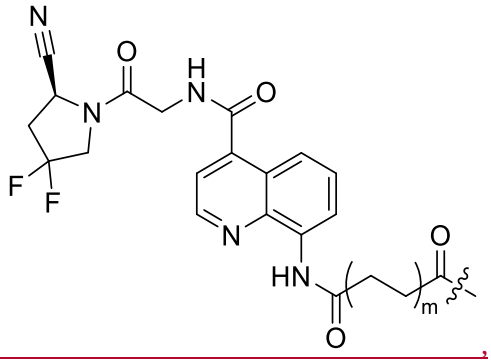
22. A compound, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its

individual tautomers or a salt thereof, wherein the compound comprises:

a moiety having the following structure **A**[1] or **A**[2], wherein *m* is 0, 1, 2, 3, 4 or 5:



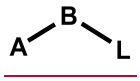
A[1]



A[2]

and a reactive moiety **L** capable of reacting and forming a covalent bond with a conjugation partner.

23. The compound of claim 22, wherein the compound is represented by the following Formula VI:

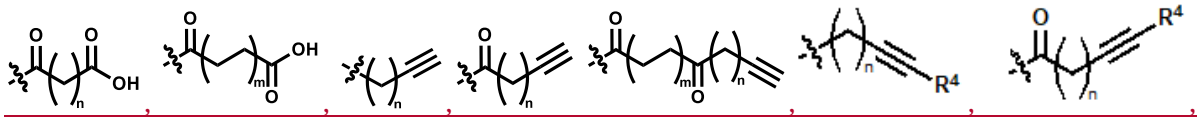
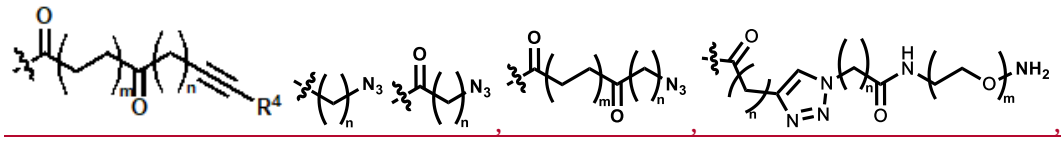
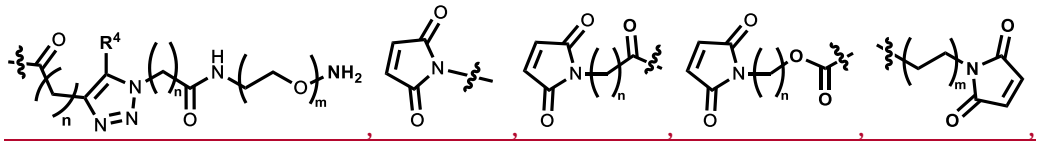
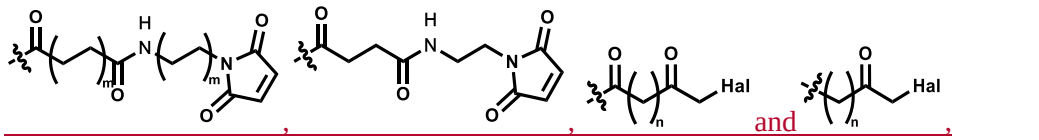
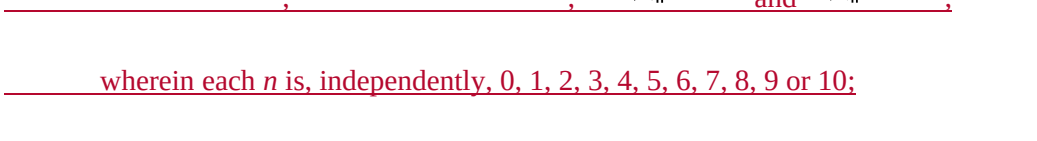
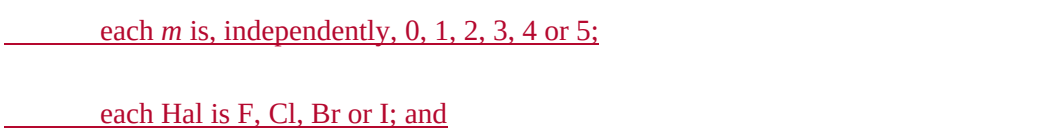
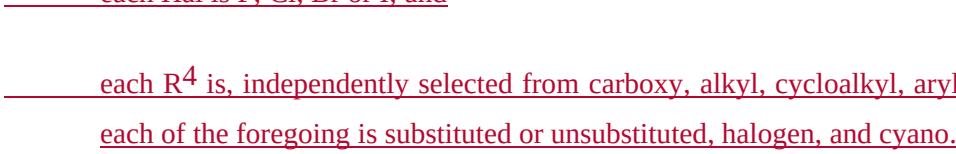


Formula VI

wherein **B** is a covalent bond or a moiety comprising a chain of atoms covalently attaching **A** to **L**, preferably wherein moiety **B** is as defined in claim 3, 4, 5 or 6.

24. The compound according to any one of claims 22 or 23, wherein **L** is capable of forming, upon reacting, an amide, ester, carbamate, hydrazone, thiazolidine, methylene alkoxy carbamate, disulphide, alkylene, cycloalkylene, arylalkylene, heteroarylalkylene, heteroalkylene, heterocycloalkylene, alkenylene, cycloalkenylene, arylalkenylene, heteroarylalkenylene, heteroalkenylene, heterocycloalenkylene, alkynylene, heteroalkynylene, arylene, heteroarylene, aminoacyl, oxyalkylene, aminoalkylene, diacid ester, dialkylsiloxane, amide, thioamide, thioether, thioester, ester, carbamate, hydrazone, thiazolidine, methylene alkoxy carbamate, disulfide, vinylene, imine, imidamide, phosphoramide, saccharide, phosphate ester, phosphoramide, carbamate, dipeptide, tripeptide or tetrapeptide linking group,

preferably wherein moiety **L** is selected from: H, NH_2, N_3, COOH, SH, Hal,

, , , , , , and ,

wherein each *n* is, independently, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

each *m* is, independently, 0, 1, 2, 3, 4 or 5;

each Hal is F, Cl, Br or I; and

each R^4 is, independently selected from carboxy, alkyl, cycloalkyl, aryl and heteroaryl, wherein each of the foregoing is substituted or unsubstituted, halogen, and cyano.

25. A method for preparing a conjugate comprising the step of conjugating with a compound according to any one of claims 22–24 with a conjugation partner, wherein preferably:

(a) the compound is conjugated by reacting with the conjugation partner to form a covalent bond;

(b) the conjugate is a compound according to any one of claims 1–9;

(c) the conjugation partner is a therapeutic or diagnostic agent; and/or

(d) the method further comprises formulating the conjugate as a pharmaceutical composition or as a diagnostic composition.