

FIBROBLAST ACTIVATION PROTEIN LIGAND AND USE THEREOF

Technical Field

[0001] The present disclosure relates to a fibroblast activation protein ligand and the use thereof, and belongs to the field of pharmaceuticals.

Background Art

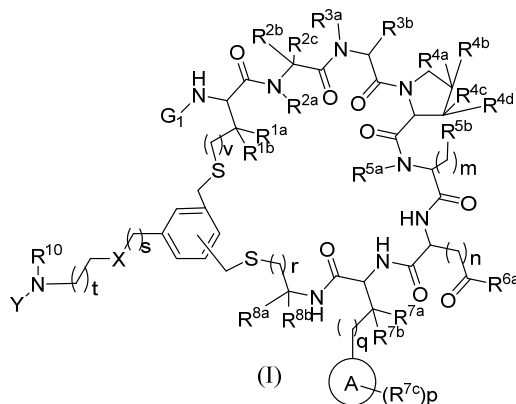
[0002] In recent years, the tumor microenvironment has attracted interest as a therapeutic target for cancer treatment. The tumor microenvironment can account for a large portion of a tumor. For example, in pancreatic ductal carcinoma, the tumor microenvironment has been reported to constitute up to 80% of the tumor mass. Cancer-associated fibroblasts are a component of the tumor microenvironment and are abundantly present in the stroma of tumor entities such as breast cancer and colon cancer. Fibroblast activation protein (FAP) is a type II transmembrane serine protease, which can serve as a tumor-associated fibroblast marker. FAP is not expressed or is expressed at low levels in normal tissues, but is highly expressed in over 90% of epithelial-derived tumor tissues, such as breast cancer, colorectal cancer, lung cancer, ovarian cancer and pancreatic cancer. Due to the limited expression in normal tissues, FAP has been identified as a potential pan-tumor target for cancer treatment. In cancer indications of mesenchymal origin, especially sarcomas and mesotheliomas, FAP is expressed on tumor cells in addition to cancer-associated fibroblasts. FAP expression is also found in chronic inflammatory diseases such as rheumatoid arthritis and osteoarthritis, and cardiac remodeling after myocardial infarction.

[0003] The first method of targeting FAP for cancer treatment involves the use of the monoclonal antibody sibrotuzumab, which is tested in the treatment of colorectal cancer in both unconjugated and ¹³¹I-conjugated forms. Other methods targeting FAP, including bispecific antibodies, antibody fragment constructs, chimeric antigen receptor T cells and antibody-drug conjugates, are currently under investigation, most of which are in preclinical development or phase I clinical trials. In addition, small molecule FAP inhibitors (FAPIs) have been found, and conjugated with radionuclides to produce excellent imaging agents suitable for various cancer indications (*J Nucl Med* 2022; 63: 415-423).

[0004] FAP-2286 contains a peptide that effectively and selectively binds to FAP, and is attached to DOTA via a linker. This compound is currently in the clinical stage. More FAP inhibitors have been developed, showing broad application prospects.

Summary of the Invention

[0005] The present disclosure provides a compound as shown in formula (I) or a pharmaceutically acceptable salt thereof,



wherein the R^{1a} and R^{1b} are each independently selected from hydrogen or methyl;

the v is selected from 0 or 1;

the G₁ is selected from -(CO)-L-R^{1c}, the L is selected from C₃₋₂₀ alkylene, the R^{1c} is selected from methyl or -NH-(C=NH)-NR^{1d}R^{1f}, and the R^{1d} and R^{1f} are each independently selected from

hydrogen or methyl; or the G_1 is selected from , and the u is selected from an integer from 1 to 5;

the R^{2a}, R^{2b} and R^{2c} are each independently selected from hydrogen or C₁₋₃ alkyl;

the R^{3a} and R^{3b} are each independently selected from hydrogen and C₁₋₃ alkyl, or the R^{3a} and R^{3b} together with the atom to which each is attached form 5- to 6-membered nitrogen-containing heterocycloalkyl, the C₁₋₃ alkyl or 5- to 6-membered nitrogen-containing heterocycloalkyl is optionally substituted with 1, 2 or 3 R^A, and the R^A groups are the same or different, and are selected from hydroxyl, amino, halogen, C₁₋₃ alkyl or C₁₋₃ haloalkyl;

the R^{4a}, R^{4b}, R^{4c} and R^{4d} are each independently selected from hydrogen, hydroxyl, amino, halogen, C₁₋₃ alkyl or C₁₋₃ haloalkyl;

the R^{5a} is selected from hydrogen or methyl;

the R^{5b} is selected from C₁₋₆ alkyl, 6- to 10-membered aryl or 5- to 6-membered heteroaryl, the C₁₋₆ alkyl, 6- to 10-membered aryl or 5- to 6-membered heteroaryl is optionally substituted with

1 or 2 R^B , and the R^B groups are the same or different, and are selected from hydroxyl, amino, halogen and $-\text{CONH}_2$;

the m is selected from 1, 2 or 3; the hydrogen on CH_2 is optionally substituted with one or more groups selected from hydroxyl, halogen, C_{1-3} alkyl, 6- to 10-membered aryl or 5- to 6-membered



heteroaryl (i.e., in R^{5b}), m is selected from 1, 2 or 3, the hydrogen on CH_2 is optionally substituted with one or more groups selected from hydroxyl, halogen, C_{1-3} alkyl, 6- to 10-membered aryl or 5- to 6-membered heteroaryl);

the R^{6a} is selected from hydroxyl or amino;

the n is selected from 1, 2 or 3;

the R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-3} alkyl;

the q is selected from 0 or 1;

the ring A is selected from phenyl, pyridyl, naphthyl or thienyl;

each R^{7c} is independently selected from halogen, nitro, amino, cyano, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy C_{1-6} alkyl, trifluoromethyl, difluoromethyl and trifluoroethyl;

the p is selected from 0, 1, 2 or 3;

the R^{8a} and R^{8b} are each independently selected from hydrogen, $-\text{COOH}$, $-\text{CONH}_2$, $\text{CH}_2\text{-OH}$, $-\text{CONHR}^{8c}$ and $-(\text{CO})-(\text{NR}^{8c})-\text{R}^{8d}$, and the R^{8c} and R^{8d} are each independently selected from C_{1-6} alkyl;

the r is selected from 0 or 1;

the s is selected from 0 or 1;

the X is selected from O, S or NR^9 , and the R^9 is selected from hydrogen or C_{1-6} alkyl;

the t is selected from 1, 2, 3, 4, 5 or 6;

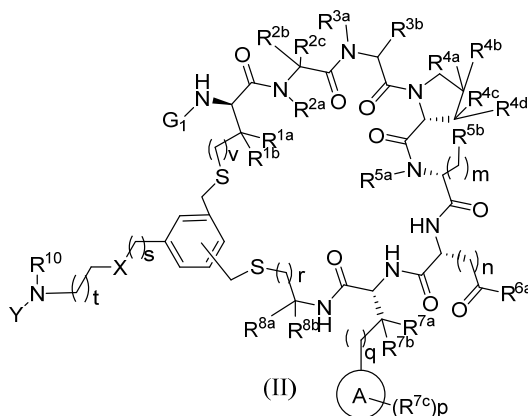
the R^{10} is selected from hydrogen or C_{1-6} alkyl;

the Y is a chelating agent or hydrogen, and the chelating agent optionally complexes a nuclide.

[0006] In an alternative embodiment, the Y is a chelating agent, and the chelating agent optionally complexes a nuclide.

[0007] In an alternative embodiment, the Y is hydrogen.

[0008] In an alternative embodiment, the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof is a compound as shown in formula (II) or a pharmaceutically acceptable salt thereof,



wherein the R^{1a} , R^{1b} , v , G_1 , R^{2a} , R^{2b} , R^{2c} , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{5a} , R^{5b} , m , R^{6a} , n , R^{7a} , R^{7b} , q , ring A, R^{7c} , p , R^{8a} , R^{8b} , r , s , X , t , R^{10} and Y are as defined in formula (I).

[0009] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{2a} is hydrogen or methyl, and the R^{2b} and R^{2c} are each independently selected from hydrogen or methyl; optionally, the R^{2b} is hydrogen, the R^{2c} is methyl, or the R^{2b} and R^{2c} are both methyl.

[0010] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{4a} and R^{4b} are each independently selected from hydrogen and hydroxyl; optionally, the R^{4a} is hydrogen, and the R^{4b} is hydroxyl.

[0011] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{2a} is hydrogen or methyl; the R^{2b} and R^{2c} are each independently selected from hydrogen or methyl, with at least one being methyl; the R^{4a} is hydrogen, and the R^{4b} is hydroxyl; the R^{4c} and R^{4d} are each independently selected from hydrogen.

[0012] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{3a} and R^{3b} are each independently selected from hydrogen and C_{1-3} alkyl, the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R^A , and the R^A groups are the same or different, and are selected from hydroxyl, amino, halogen, C_{1-3} alkyl or C_{1-3} haloalkyl.

[0013] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{3a} is methyl, and the R^{3b} is hydrogen.

[0014] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{3a} and R^{3b} together with the atom to which each is attached form 5-membered nitrogen-containing heterocycloalkyl, the 5-membered nitrogen-containing heterocycloalkyl is optionally substituted with 1, 2 or 3 R^A, and the R^A groups are the same or different, and are selected from hydroxyl, amino, halogen, C₁₋₃ alkyl or C₁₋₃ haloalkyl.

[0015] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{3a} and R^{3b} together with the atom to which each is attached form 5-membered nitrogen-containing heterocycloalkyl, and the 5-membered nitrogen-containing heterocycloalkyl is unsubstituted.

[0016] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{7a} and R^{7b} are each independently selected from hydrogen and C₁₋₃ alkyl;
the q is selected from 0 or 1;
the ring A is selected from phenyl or naphthyl;
each R^{7c} is independently selected from halogen, nitro, amino, cyano, hydroxyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy C₁₋₆ alkyl, trifluoromethyl, difluoromethyl and trifluoroethyl;
the p is selected from 0, 1, 2 or 3.

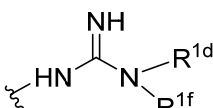
[0017] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{7a} and R^{7b} are each independently selected from hydrogen;
the q is 0;
the ring A is phenyl;

each R^{7c} is independently selected from fluorine, chlorine, bromine and iodine, or trifluoromethyl, difluoromethyl and trifluoroethyl;
the p is selected from 0, 1 or 2.

[0018] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{1a} and R^{1b} are each independently selected from hydrogen or methyl;
the v is selected from 0 or 1;
the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{3-20} alkylene, and the R^{1c} is selected from methyl.

[0019] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{1a} and R^{1b} are each independently selected from hydrogen;
the v is selected from 0;
the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{4-14} alkylene, and the R^{1c} is selected from methyl;

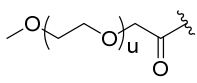
[0020] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{1a} and R^{1b} are each independently selected from hydrogen or methyl;
the v is selected from 0 or 1;
the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{3-20} alkylene, the R^{1c} is selected from -

$NH-(C=NH)-NR^{1d}R^{1f}$, i.e., , and the R^{1d} and R^{1f} are each independently selected from hydrogen or methyl.

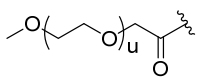
[0021] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure,
the R^{1a} and R^{1b} are each independently selected from hydrogen;
the v is selected from 0;

the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{4-14} alkylene, the R^{1c} is selected from $-NH(C=NH)-NR^{1d}R^{1f}$, and the R^{1d} and R^{1f} are each independently selected from hydrogen or methyl.

[0022] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{1a} and R^{1b} are each independently selected from hydrogen or methyl;
the v is selected from 0 or 1;

the G_1 is selected from , and the u is selected from an integer from 1 to 5.

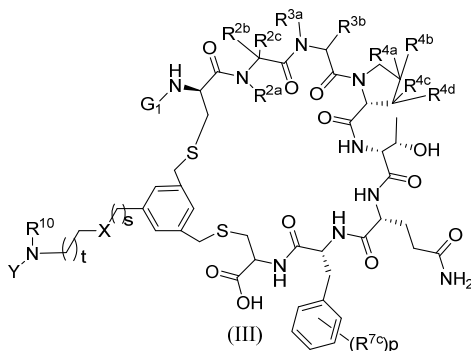
[0023] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{1a} and R^{1b} are each independently selected from hydrogen;
the v is selected from 0;

the G_1 is selected from  ;
the u is selected from 1 or 2.

[0024] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof provided by the present disclosure,
the R^{5a} is selected from hydrogen;
the R^{5b} is selected from C_{1-6} alkyl, the C_{1-6} alkyl is optionally substituted with 1 or 2 R^B , and the R^B groups are the same or different, and are selected from hydroxyl or halogen;
the m is selected from 0 or 1; the hydrogen on CH_2 is optionally substituted with one or more groups selected from hydroxyl, halogen, hydroxyl and C_{1-3} alkyl;
the n is 2;
the R^{6a} is amino;
the R^{8a} and R^{8b} are each independently selected from hydrogen, $-COOH$ and $-CONH_2$, with at least one being $-COOH$ or $-CONH_2$, and the r is 1.

[0025] In an alternative embodiment, the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, or the compound as shown in formula (II) or the

pharmaceutically acceptable salt thereof provided by the present disclosure is a compound as shown in formula (III) or a pharmaceutically acceptable salt thereof,



wherein the R^{2a} is hydrogen or methyl;

the R^{2b} and R^{2c} are each independently selected from hydrogen or methyl, with at least one being methyl;

the R^{3a} and R^{3b} are each independently selected from hydrogen and C₁₋₃ alkyl, the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R^A, and the R^A groups are the same or different, and are selected from hydroxyl, amino, halogen, C₁₋₃ alkyl or C₁₋₃ haloalkyl; or the R^{3a} and R^{3b} together with the atom to which each is attached form 5-membered nitrogen-containing heterocycloalkyl, the 5-membered nitrogen-containing heterocycloalkyl is optionally substituted with 1, 2 or 3 R^A, and the R^A groups are the same or different, and are selected from hydroxyl, amino, halogen, C₁₋₃ alkyl or C₁₋₃ haloalkyl;

the R^{4a} is hydrogen, fluorine or trifluoromethyl, and the R^{4b} is fluorine or hydroxyl;

the R^{4c} and R^{4d} are each independently selected from hydrogen;

each R^{7c} is independently selected from fluorine, chlorine, bromine and iodine, or trifluoromethyl, difluoromethyl and trifluoroethyl;

the p is selected from 0, 1 or 2;

the G₁, s, X, t, R¹⁰ and Y are as defined in formula (I).

[0026] In an alternative embodiment, in the compound as shown in formula (III) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{4a} is hydrogen, and the R^{4b} is hydroxyl.

[0027] In an alternative embodiment, in the compound as shown in formula (III) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{3a} is hydrogen, and the R^{3b} is methyl.

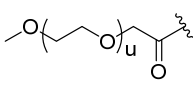
[0028] In an alternative embodiment, in the compound as shown in formula (III) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the R^{3a} and R^{3b} together with the atom to which each is attached form 5-membered nitrogen-containing heterocycloalkyl, and the 5-membered nitrogen-containing heterocycloalkyl is unsubstituted.

[0029] In an alternative embodiment, in the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof, the compound as shown in formula (II) or the pharmaceutically acceptable salt thereof, and the compound as shown in formula (III) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the s is 1; X is S; R^{10} is hydrogen.

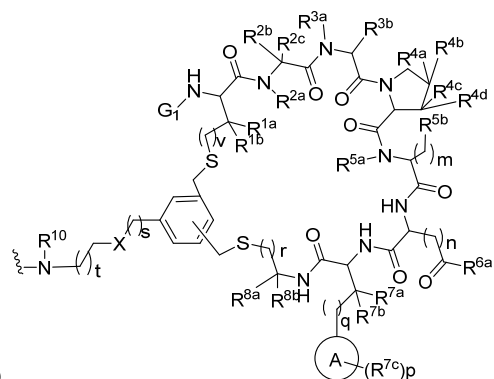
[0030] In an alternative embodiment, in the compound as shown in formula (III) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{4-14} alkylene, the R^{1c} is selected from methyl, and the L may be selected from, for example, C_4 alkylene, C_6 alkylene, C_8 alkylene, C_{10} alkylene, C_{12} alkylene or C_{14} alkylene.

[0031] In an alternative embodiment, in the compound as shown in formula (III) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{4-14} alkylene, the R^{1c} is selected from $-NH-(C=NH)-NR^{1d}R^{1f}$, the R^{1d} and R^{1f} are each independently selected from hydrogen or methyl, and the L may be selected from, for example, C_4 alkylene, C_5 alkylene or C_6 alkylene.

[0032] In an alternative embodiment, in the compound as shown in formula (III) or the pharmaceutically acceptable salt thereof provided by the present disclosure, the G_1 is selected

from , and the u is selected from 1 or 2.

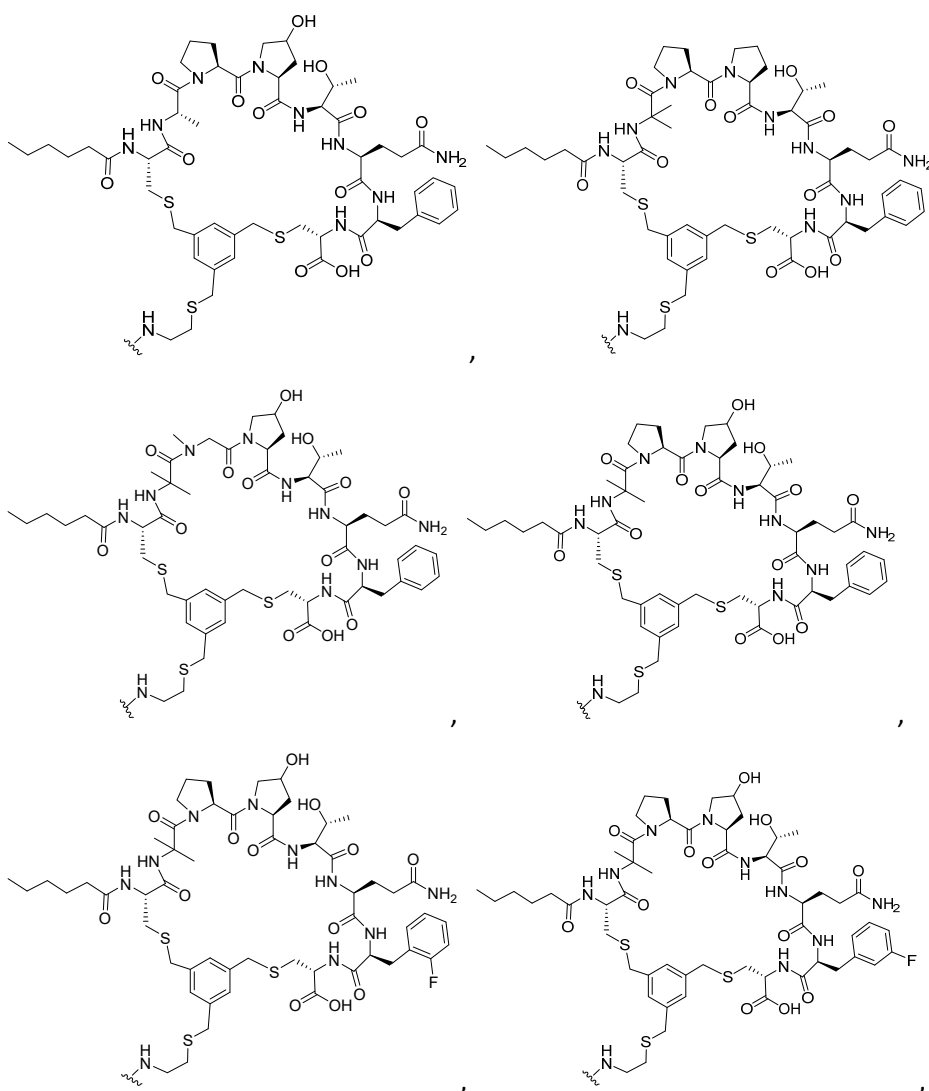
[0033] In the compound provided by the present disclosure, the fragment attached to Y

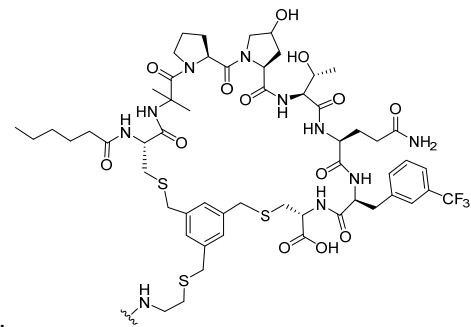
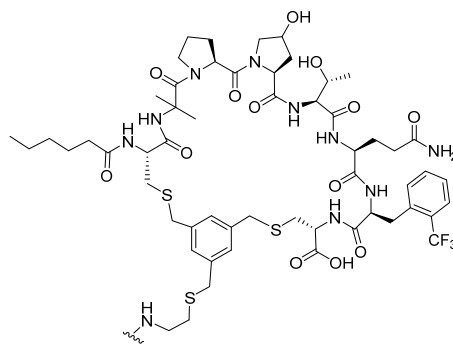
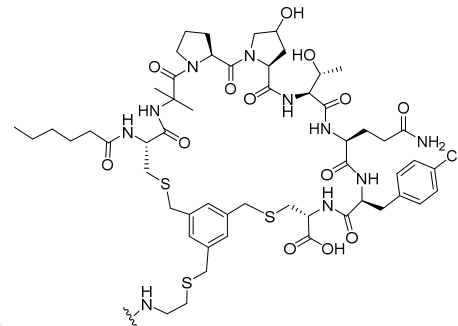
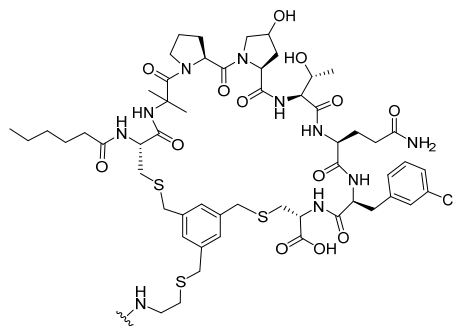
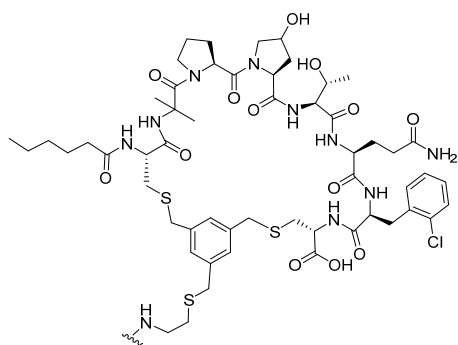
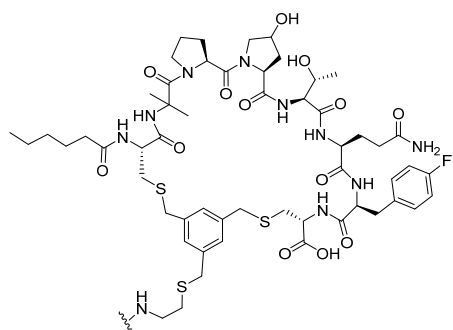


specifically refers to the fragment corresponding to

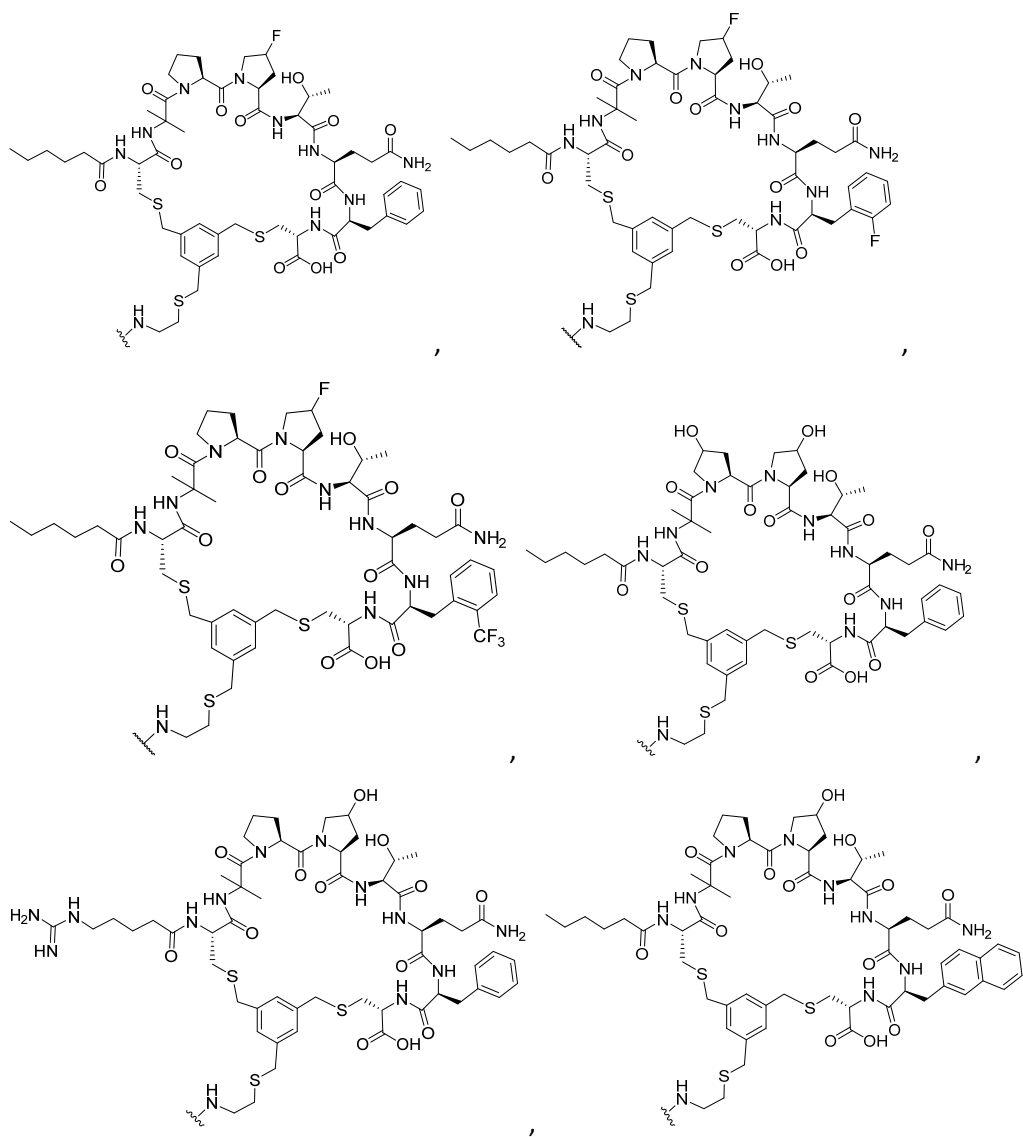
and is selected from:

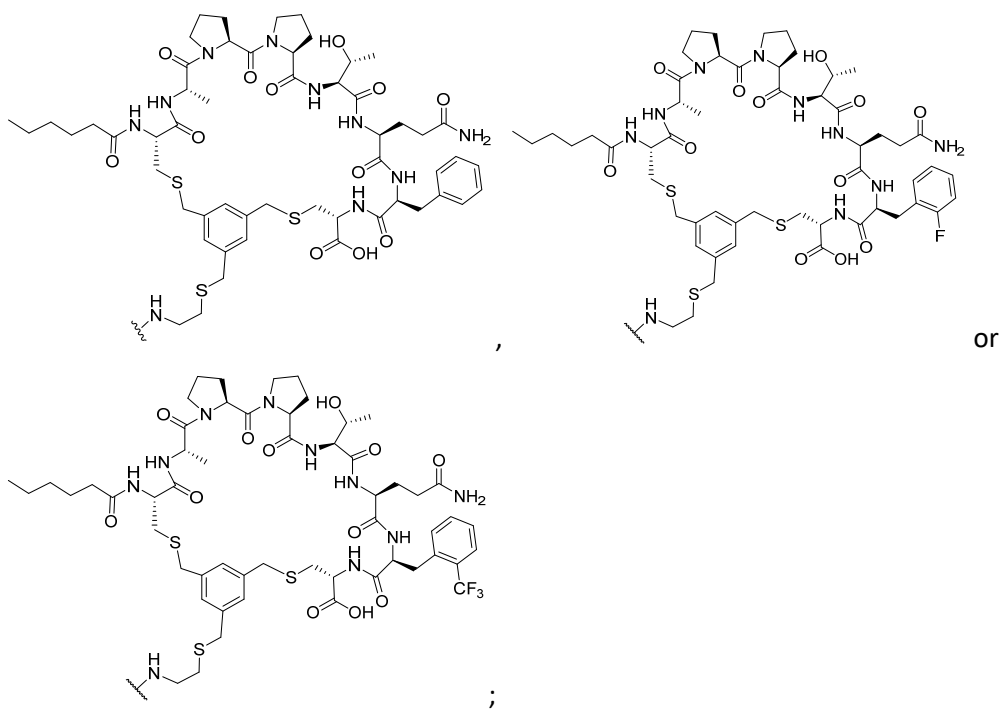
group 1:



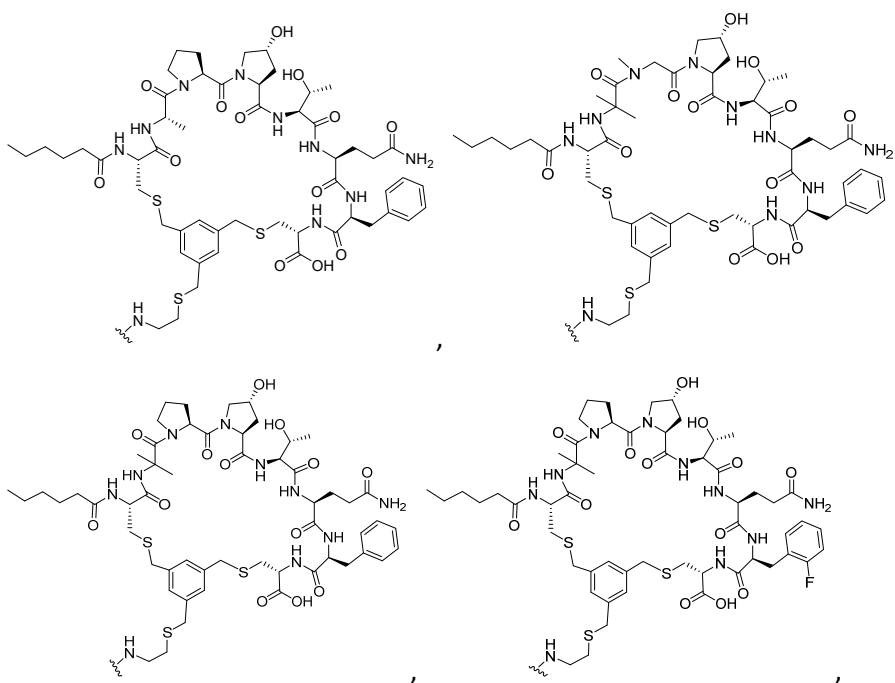


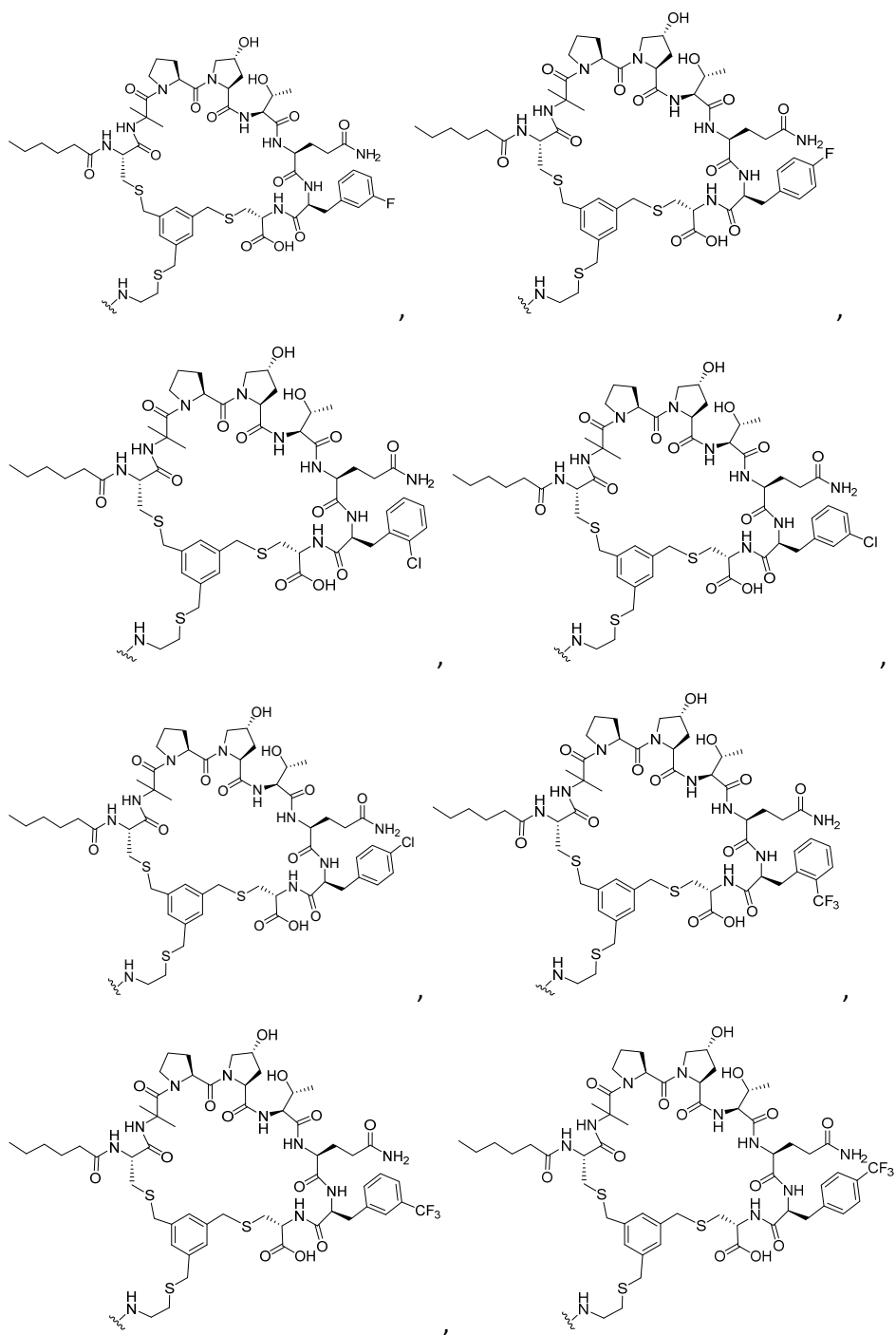


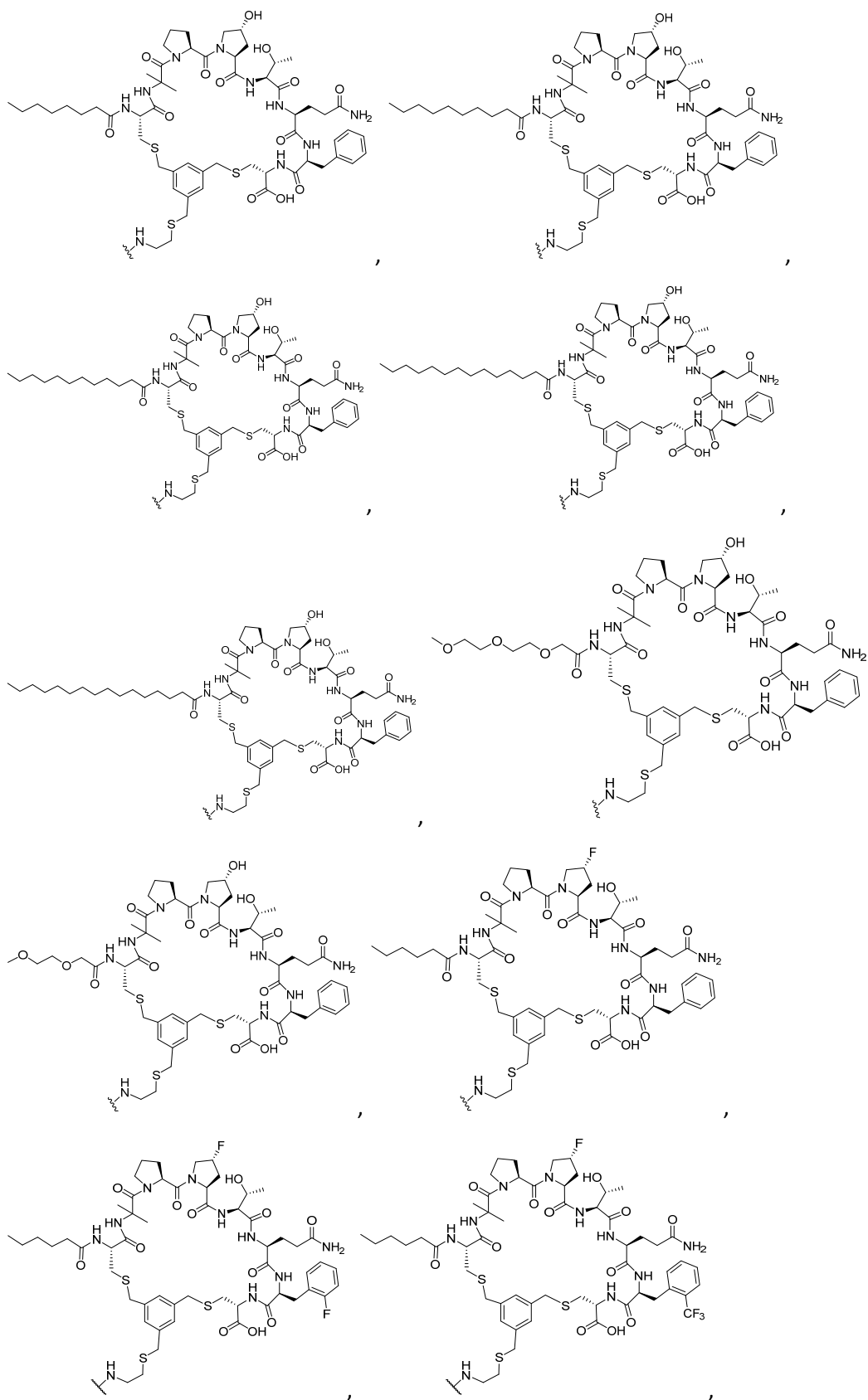


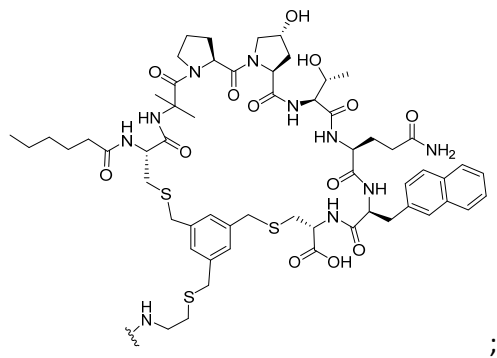
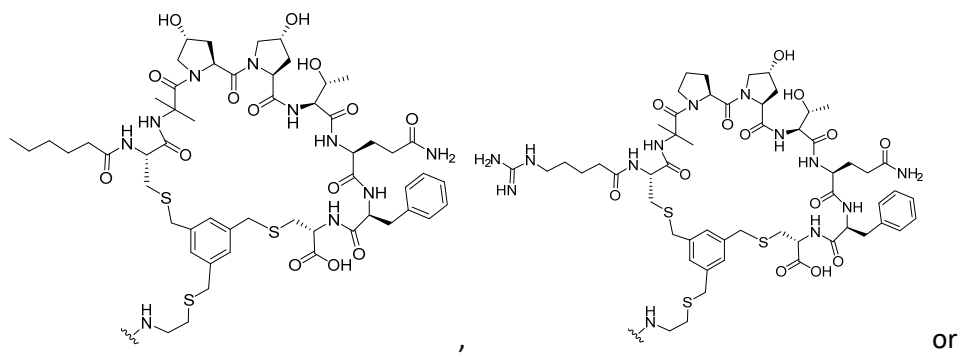


group 2:

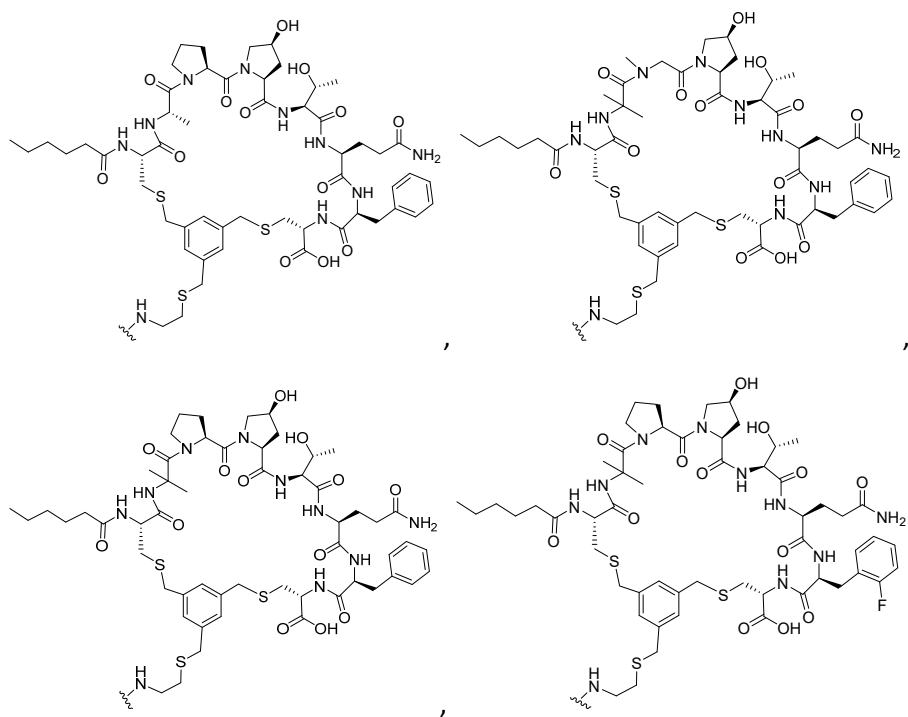


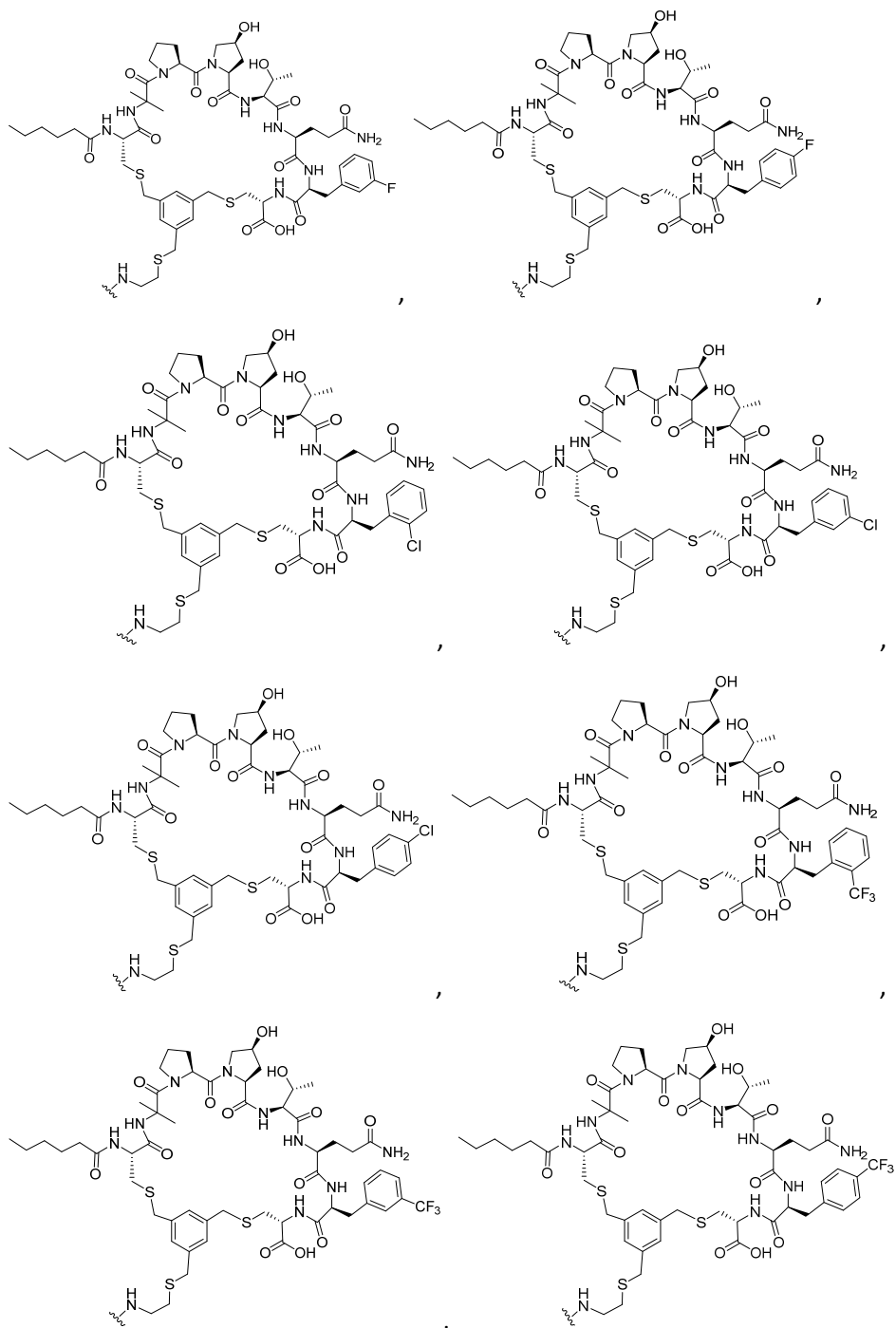


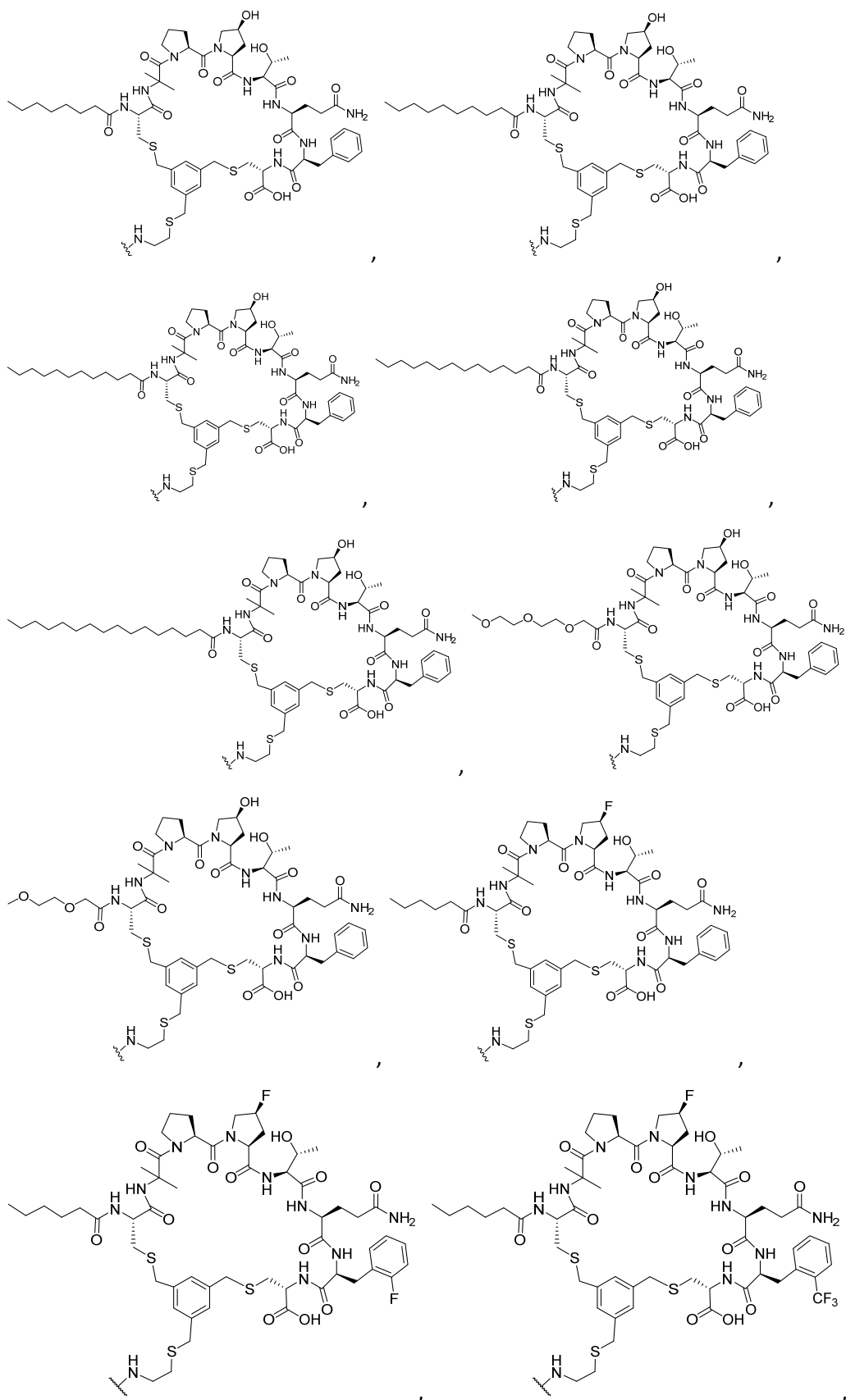


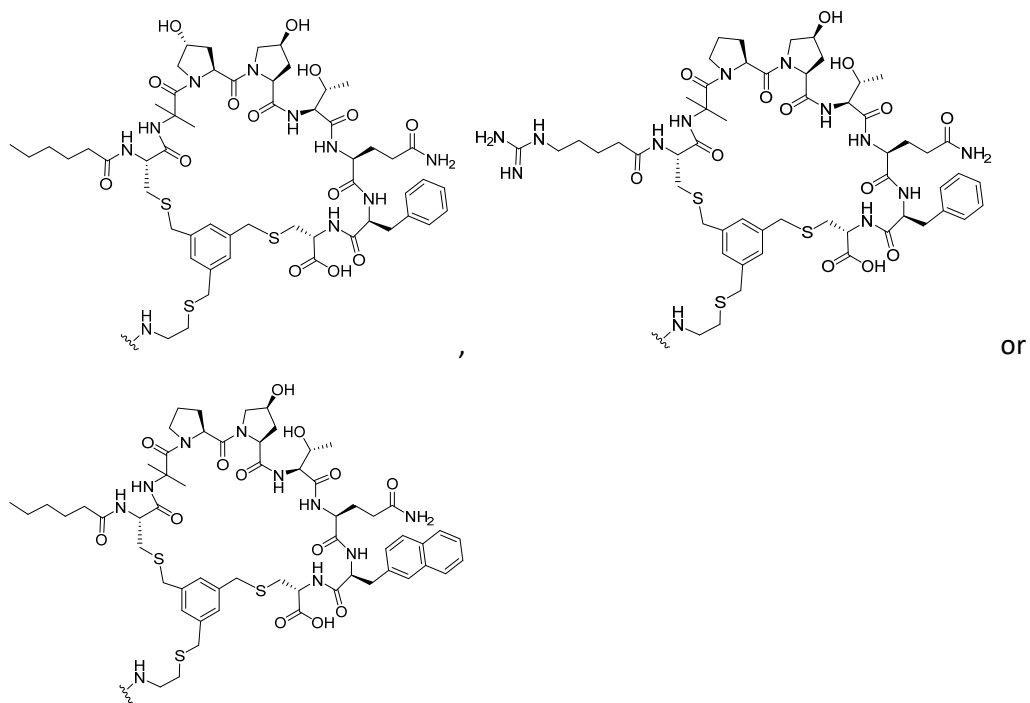


group 3:

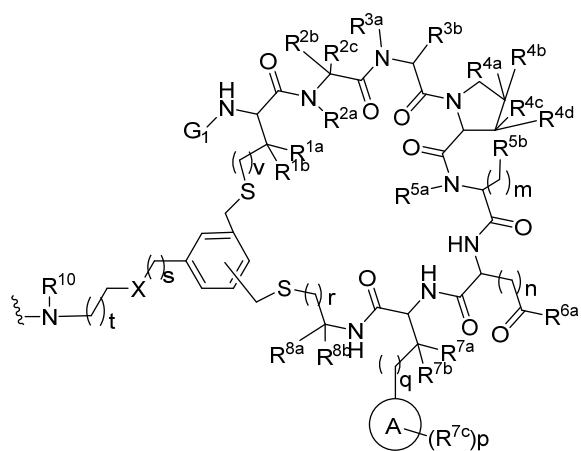




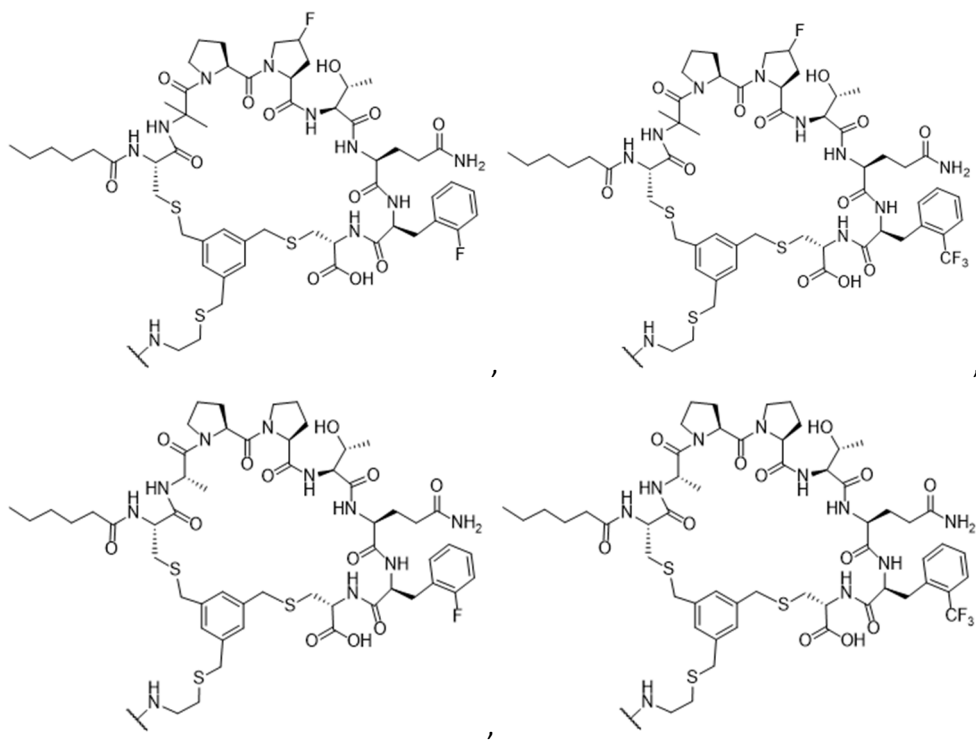




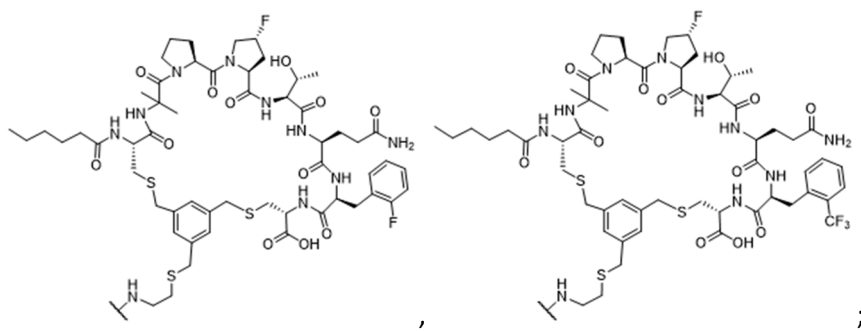
[0034] In the compound provided by the present disclosure, the fragment attached to Y specifically refers to:



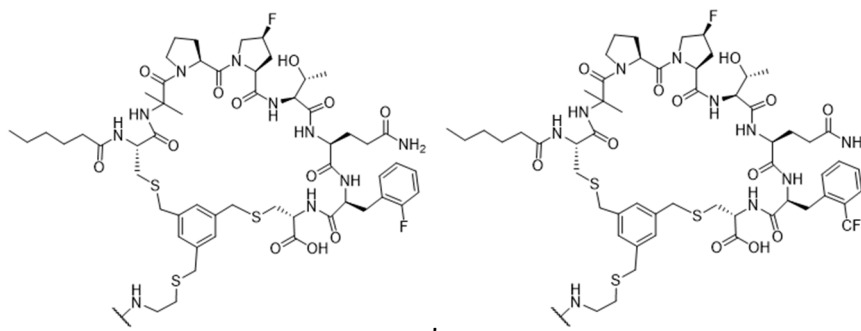
the fragment corresponding to
from:
group 1'



group 2':

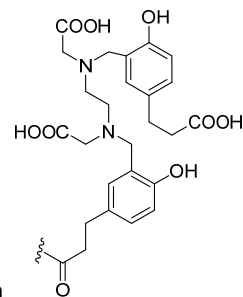


group 3':

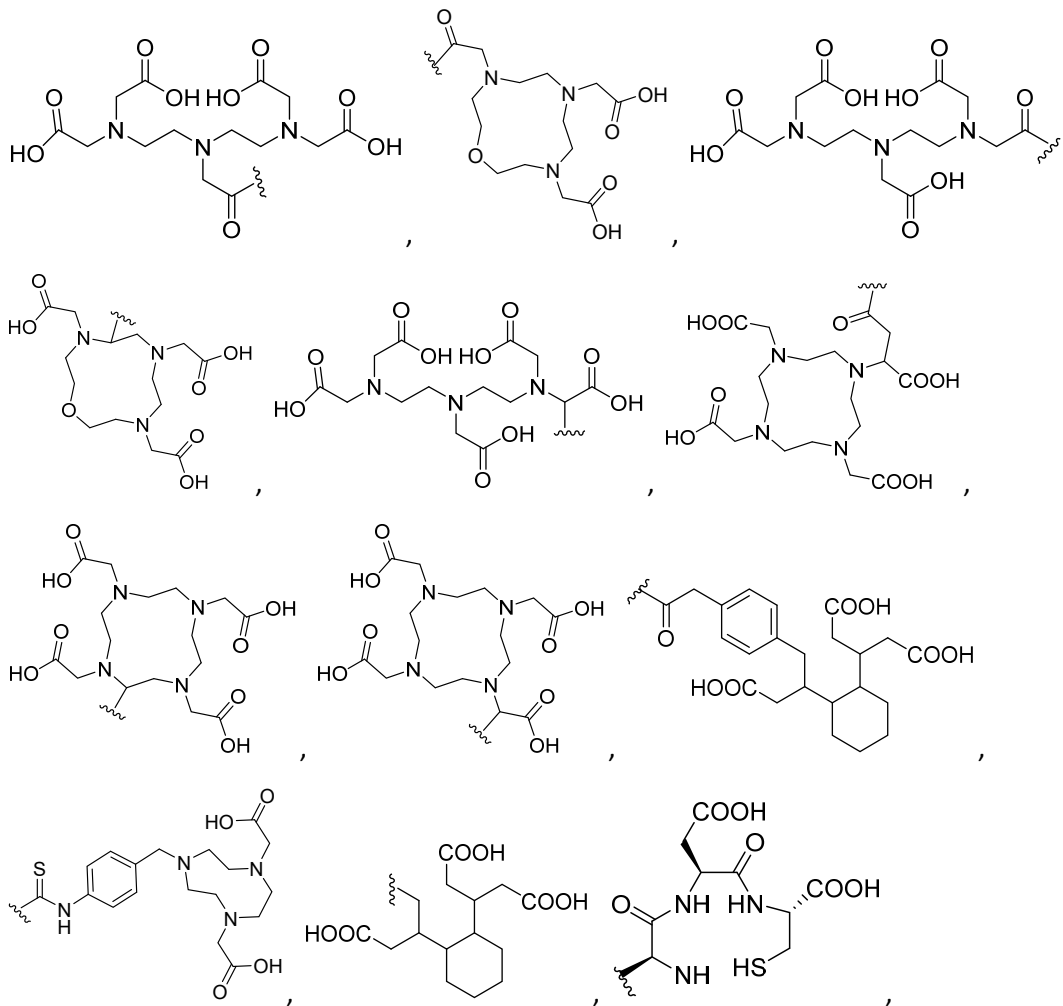


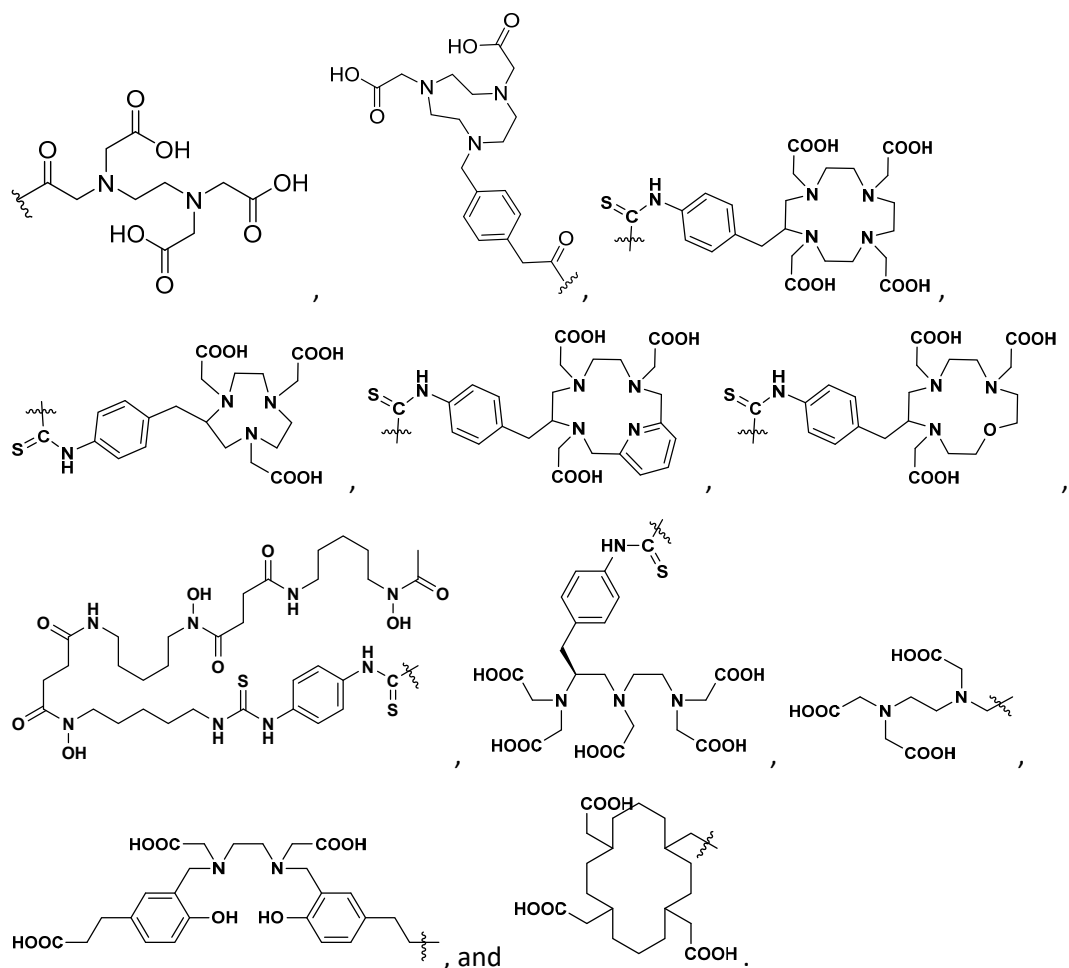
[0035] The chelating agent described in the present disclosure is selected from DOTA, DOTAGA, NOTA, NODAGA, NODA-MPAA, HBED, TETA, CB-TE2A, DTPA, DFO, Macropa, HOPO, TRAP, THP,

DATA, NOTP, sarcophagine, FSC, NETA, H4octapa, Pycup, $\text{NxS}_4\text{-x}(\text{N}_4, \text{N}_2\text{S}_2, \text{N}_3\text{S})$, Hynic, and $^{99\text{m}}\text{Tc}(\text{CO})_3$ -chelating agent.



[0036] In an alternative embodiment, the chelating agent is selected from



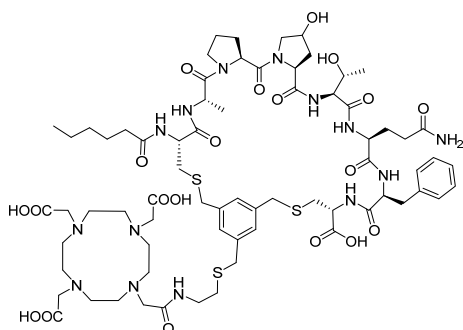


[0037] In some embodiments, the chelating agent is selected from DOTA, DOTAGA, NOTA, NODAGA, NODA-MPAA, HBED, CB-TE2A, DFO, THP and N_4 .

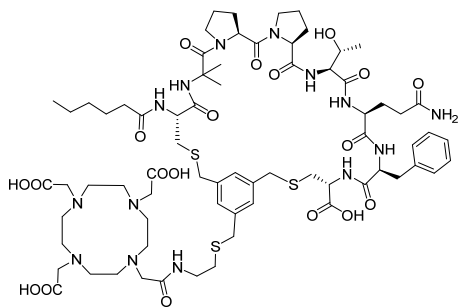
[0038] In some embodiments, the chelating agent is selected from DOTA, DOTAGA, NOTA and NODAGA.

[0039] The present disclosure provides a compound as shown below or a pharmaceutically acceptable salt thereof, which is selected from:

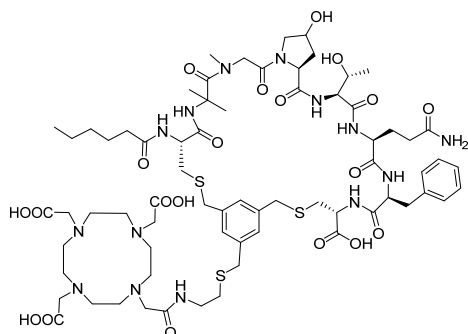
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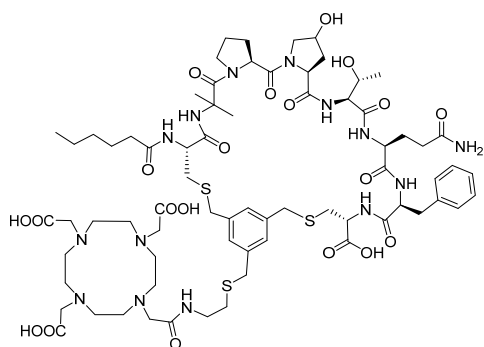
Hex-[Cys-(tMeBn(DOTA-AET))-Ala-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



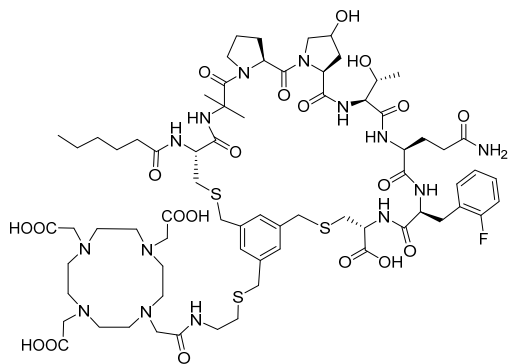
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-Pro-Thr-Gln-Phe-Cys]-OH,



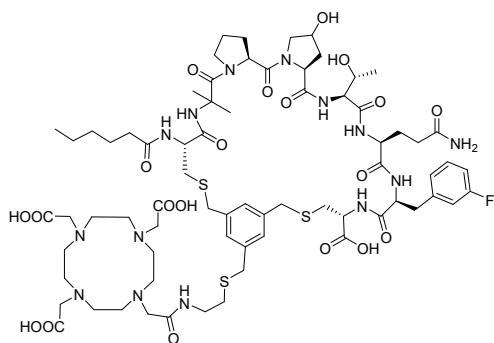
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Sar-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



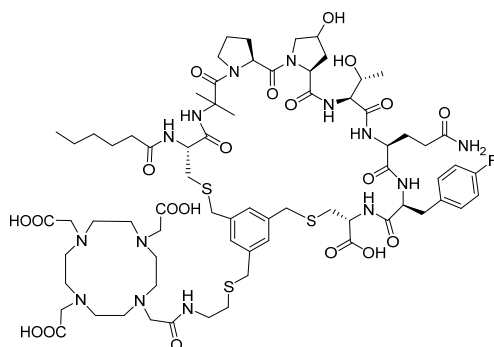
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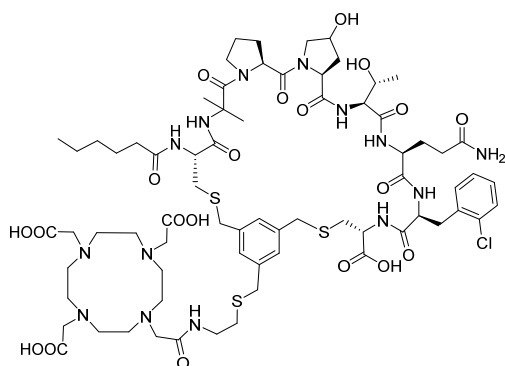
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-(2-F-Phe)-Cys]-OH,



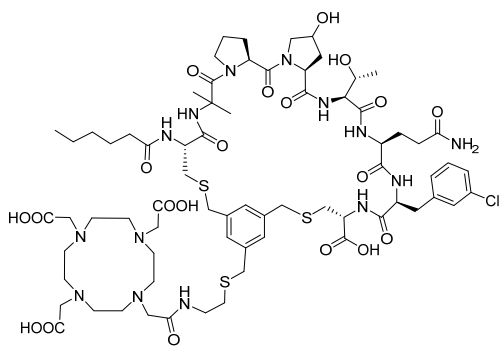
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-(3-F-Phe)-Cys]-OH,



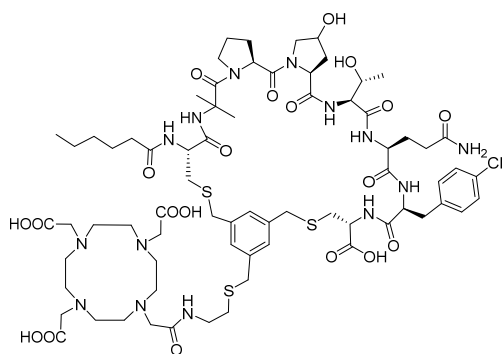
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-(4-F-Phe)-Cys]-OH,



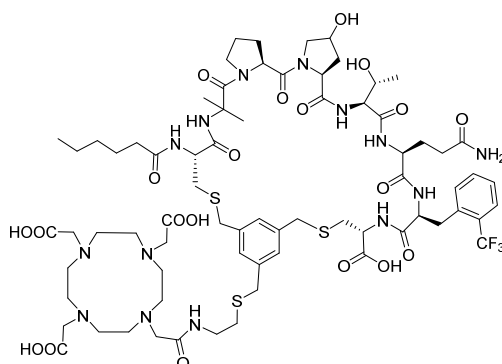
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-(2-Cl-Phe)-Cys]-OH,



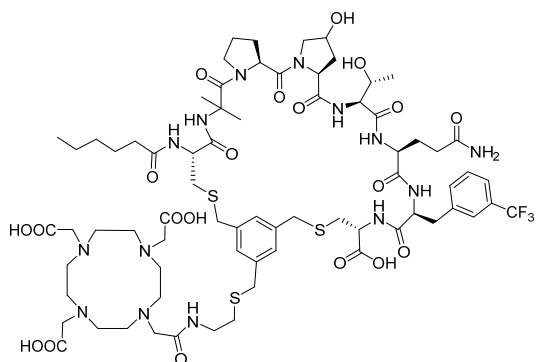
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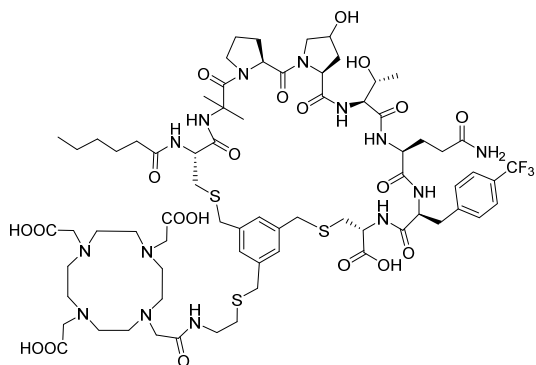
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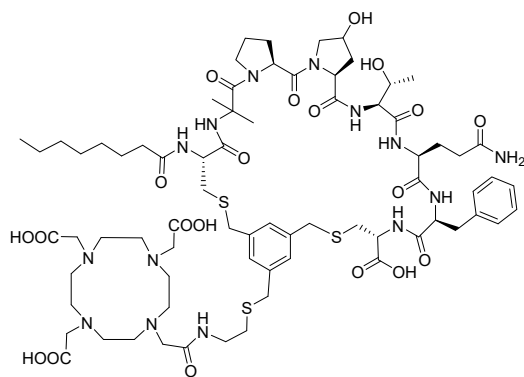
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-(2-CF₃-Phe)-Cys]-OH,



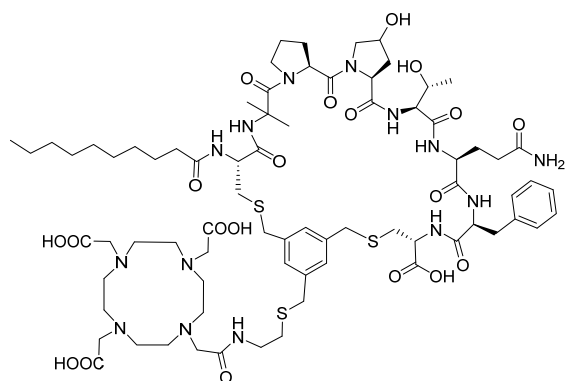
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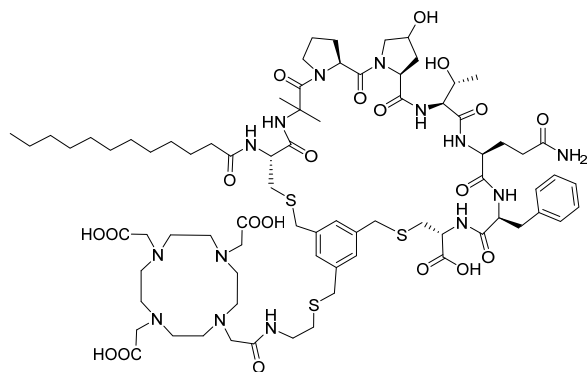
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-(4-CF₃-Phe)-Cys]-OH,



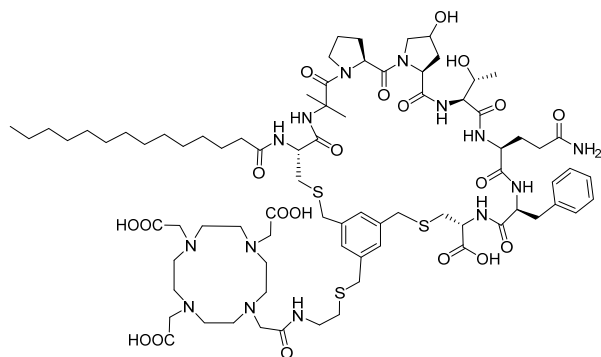
Oct-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



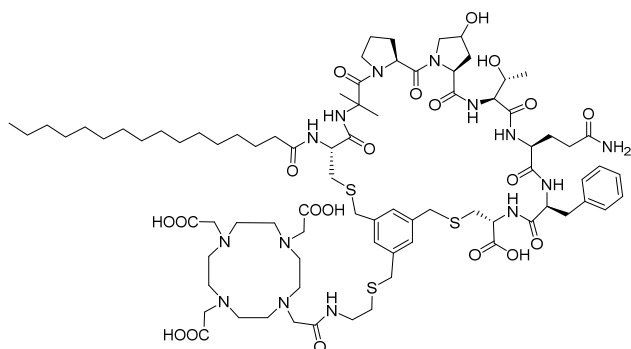
Dec-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



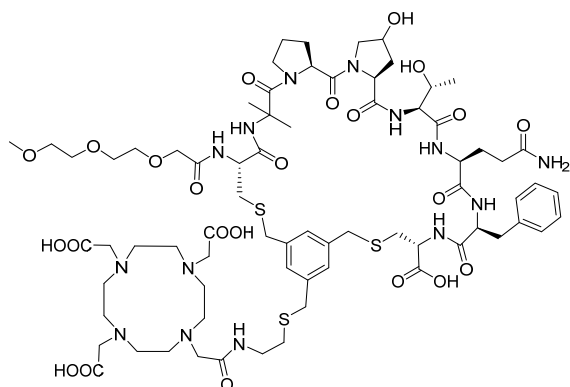
Dod-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



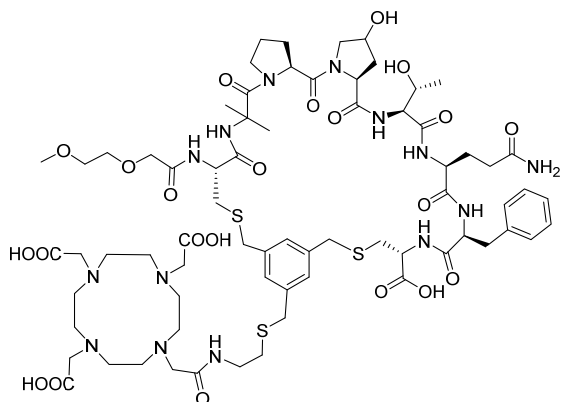
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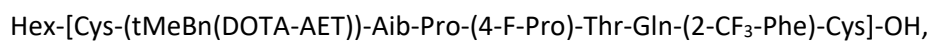
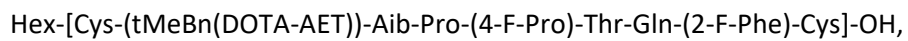
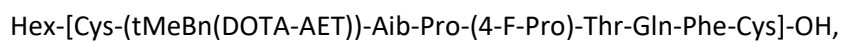
Pal-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,

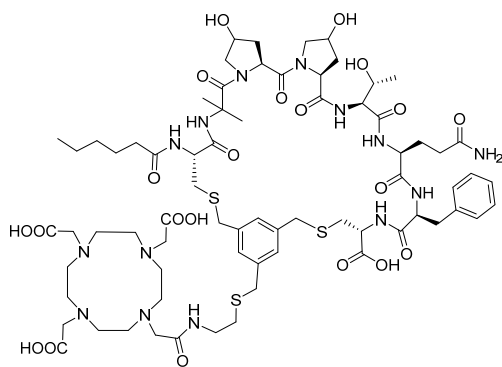


{2-[2-(2-Methoxyethoxy)ethoxy]-Ace}-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,

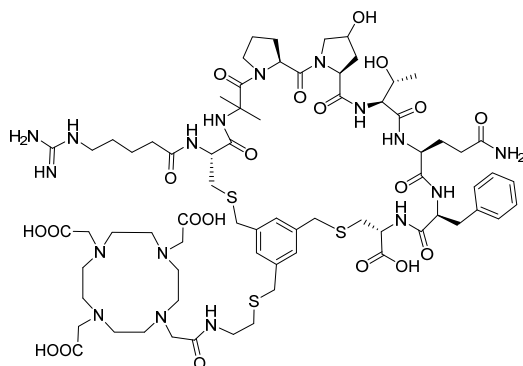


[2-(2-Methoxyethoxy)-Ace]-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,

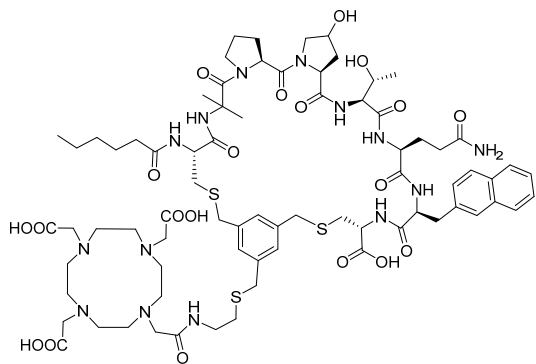




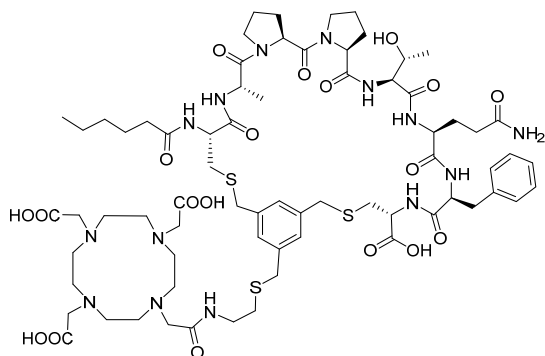
Hex-[Cys-(tMeBn(DOTA-AET))]-Aib-(4-OH-Pro)-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



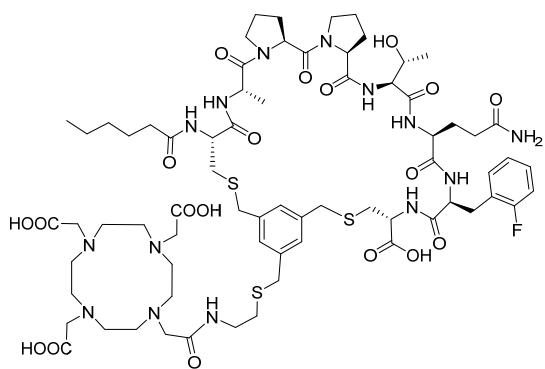
(5-guanidineValy)-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



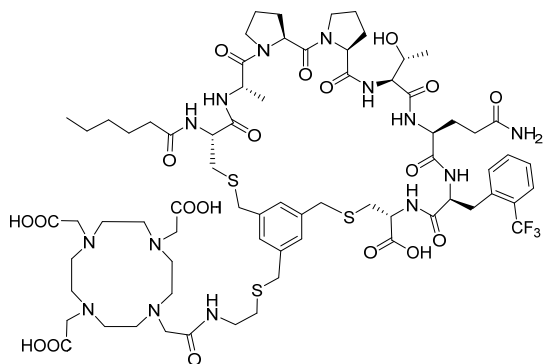
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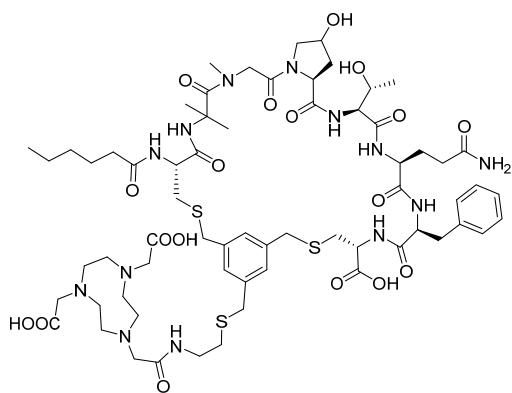
Hex-[Cys-(tMeBn(DOTA-AET))]-Ala-Pro-Pro-Thr-Gln-Phe-Cys]-OH,



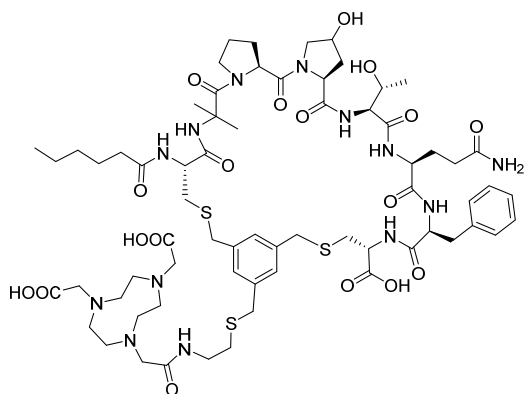
Hex-[Cys-(tMeBn(DOTA-AET))-Ala-Pro-Pro-Thr-Gln-(2-F-Phe)-Cys]-OH,



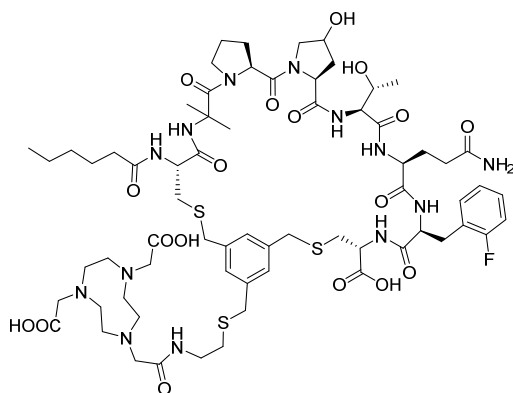
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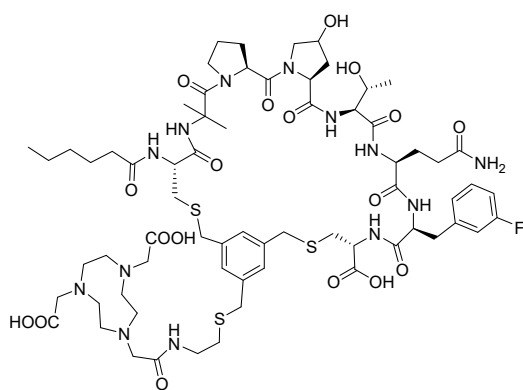
Hex-[Cys-(tMeBn(NOTA-AET))-Aib-Sar-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



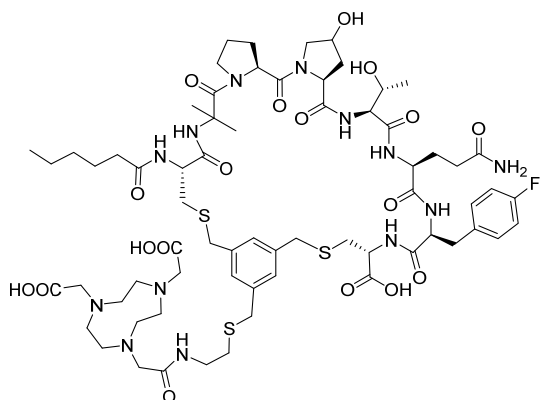
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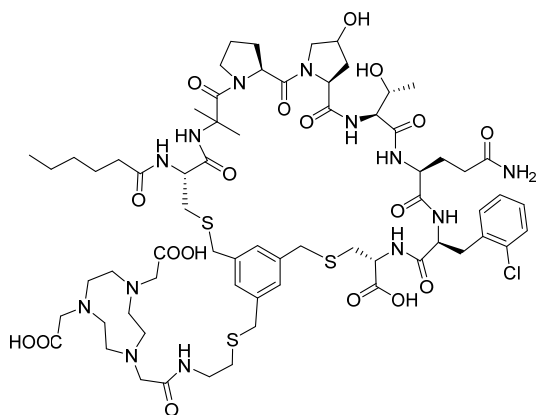
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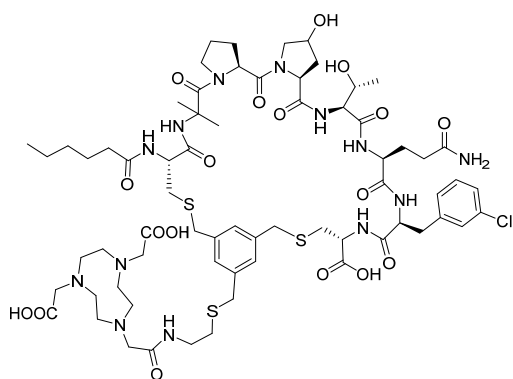
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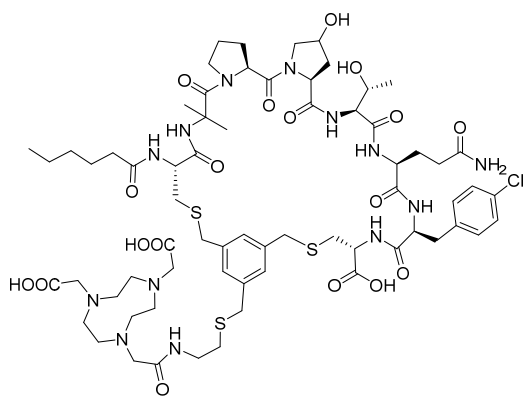
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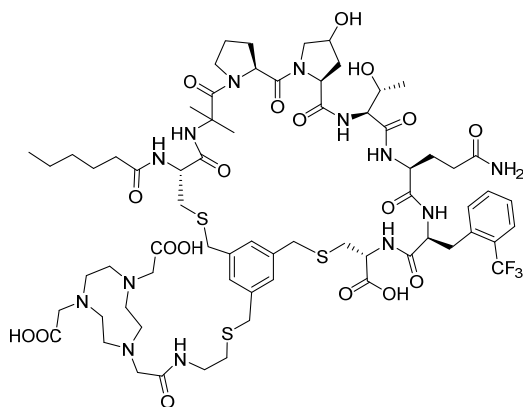
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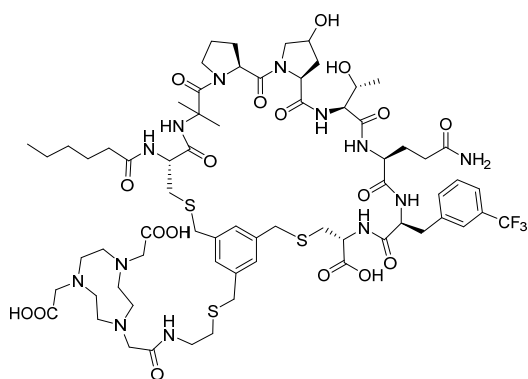
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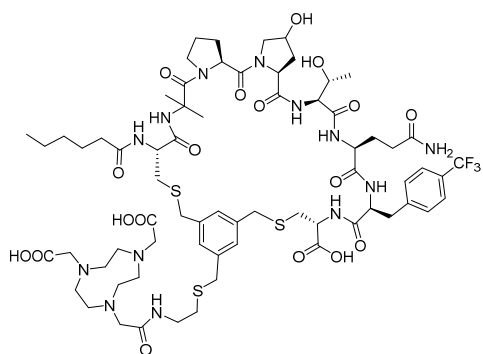
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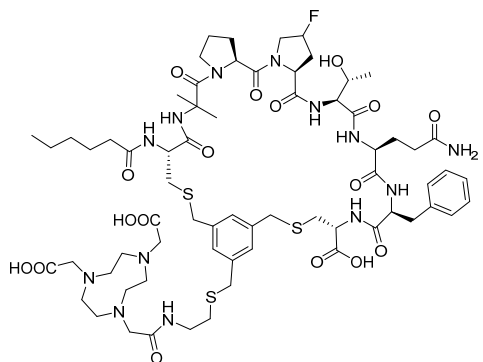
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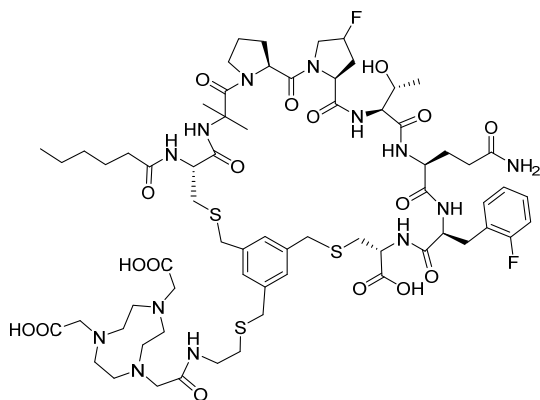
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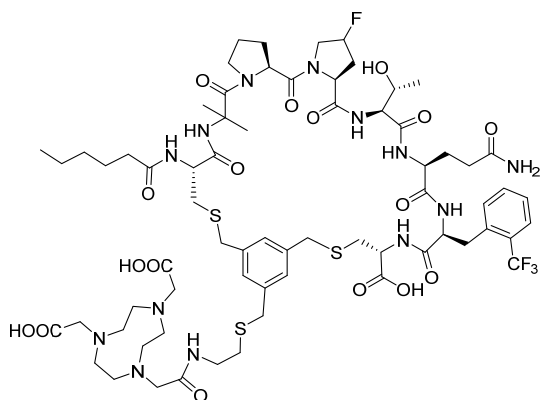
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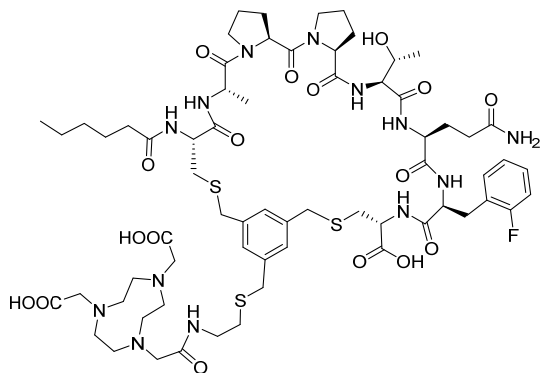
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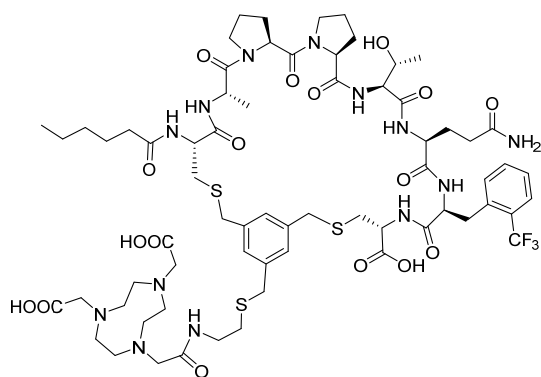
Hex-[Cys-(tMeBn(NOTA-AET))-Aib-Pro-(4-F-Pro)-Thr-Gln-(2-F-Phe)-Cys]-OH,



Hex-[Cys-(tMeBn(NOTA-AET))-Aib-Pro-(4-F-Pro)-Thr-Gln-(2-CF₃-Phe)-Cys]-OH,

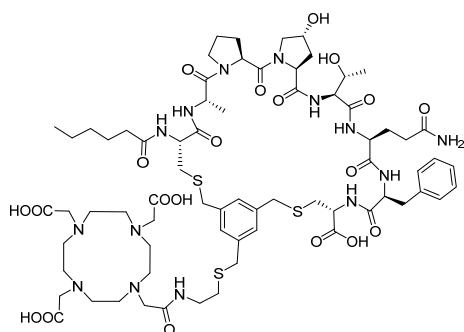


Hex-[Cys-(tMeBn(NOTA-AET))-Ala-Pro-Pro-Thr-Gln-(2-F-Phe)-Cys]-OH, and

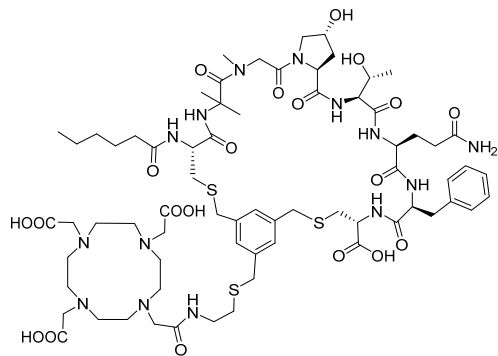


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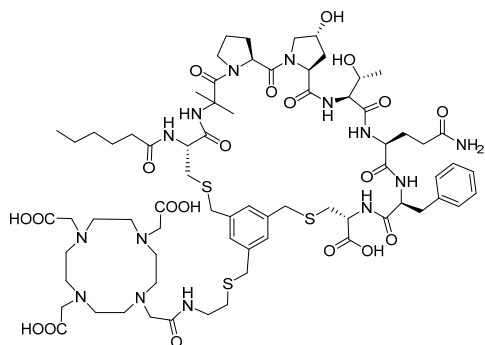
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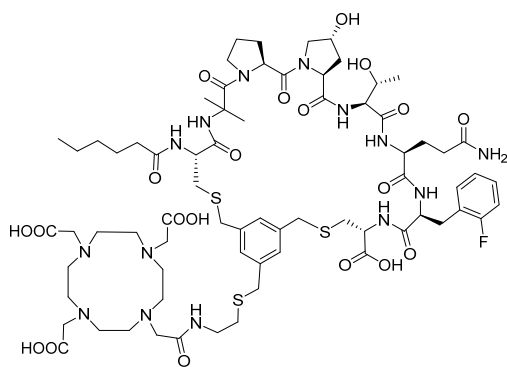
Hex-[Cys-(tMeBn(DOTA-AET))-Ala-Pro-((4R)-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



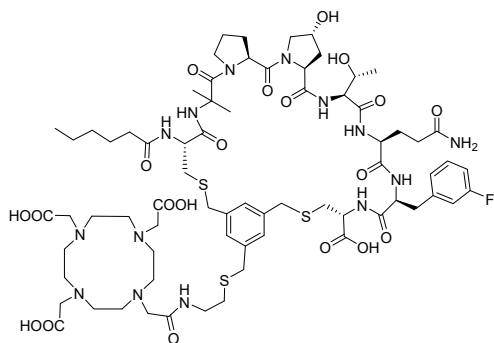
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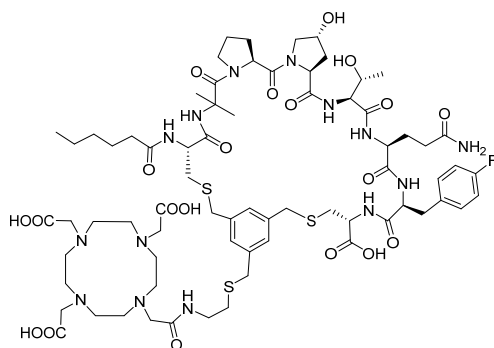
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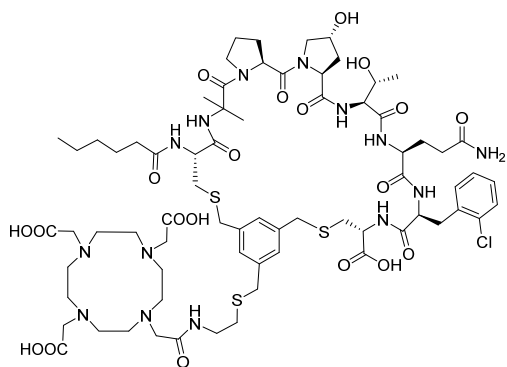
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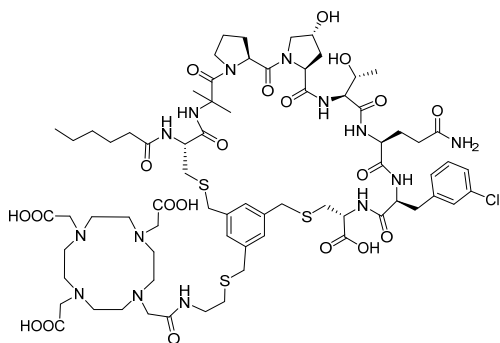
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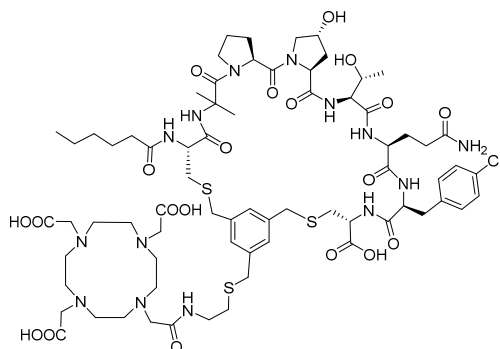
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-((4R)-OH-Pro)-Thr-Gln-(4-F-Phe)-Cys]-OH,



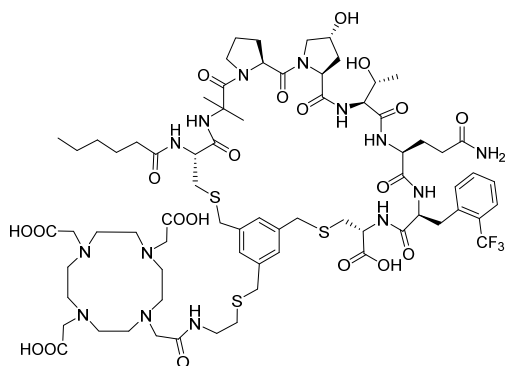
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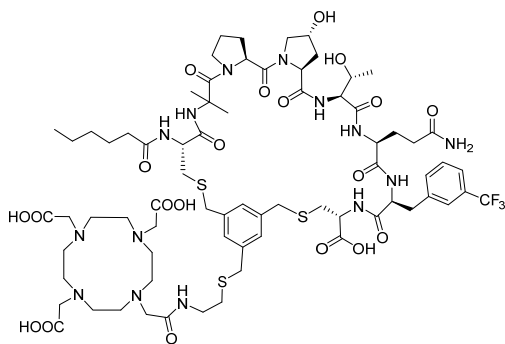
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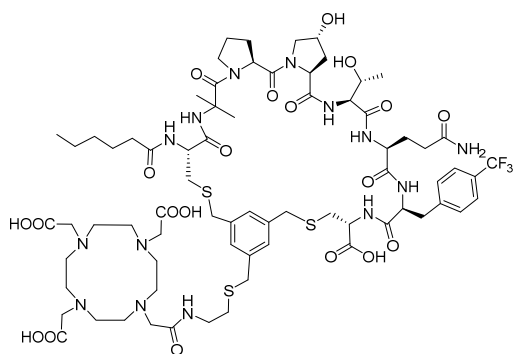
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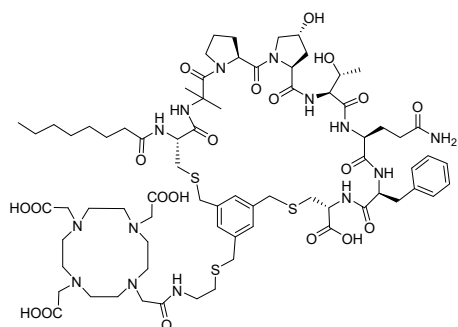
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-((4R)-OH-Pro)-Thr-Gln-(2-CF₃-Phe)-Cys]-OH,



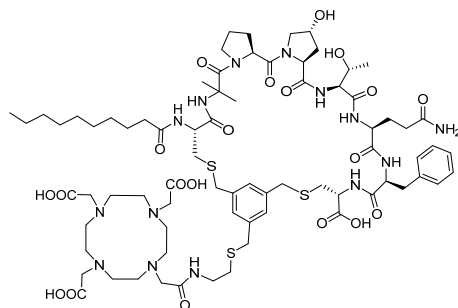
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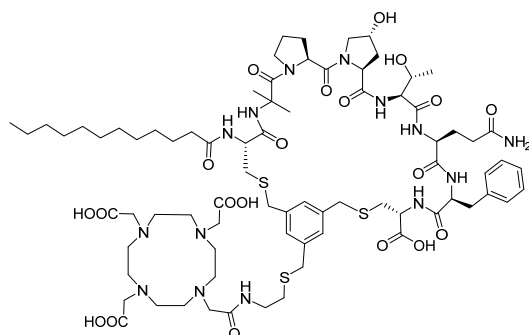
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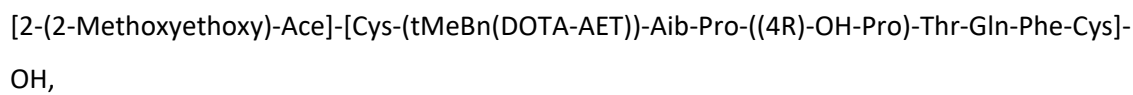
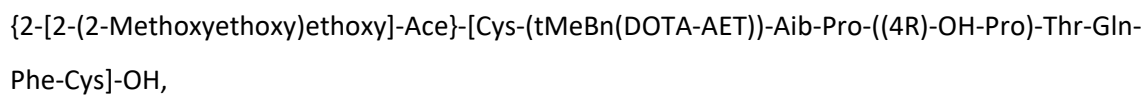
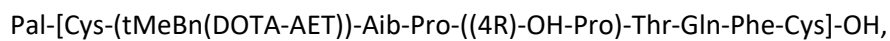
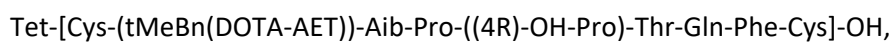
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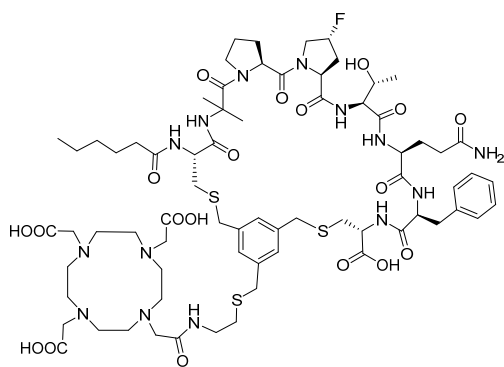


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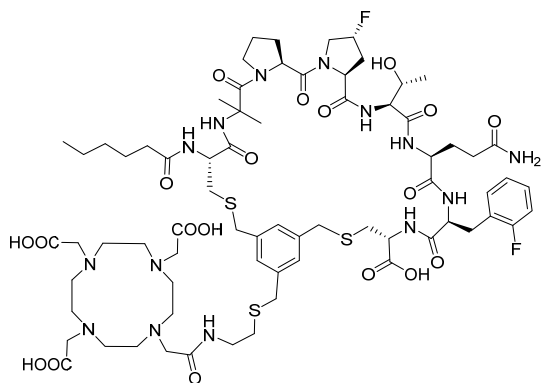


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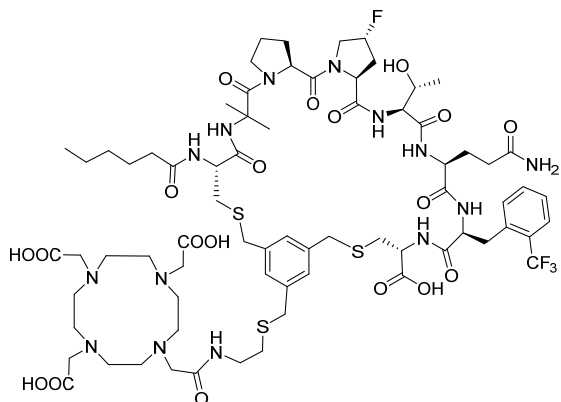




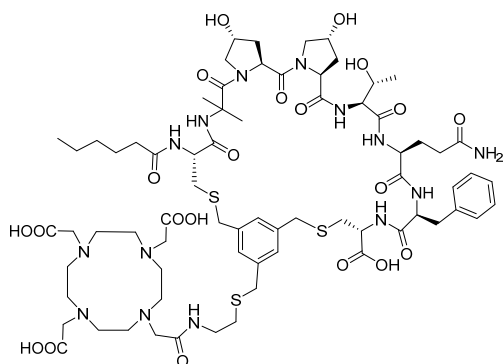
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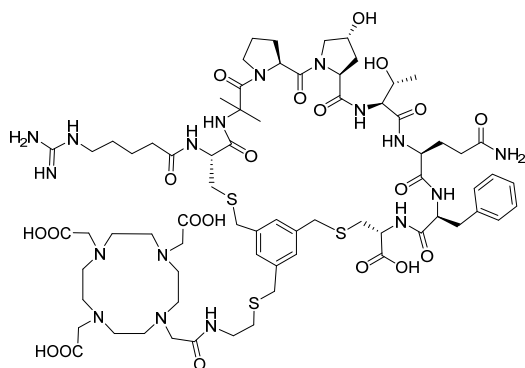
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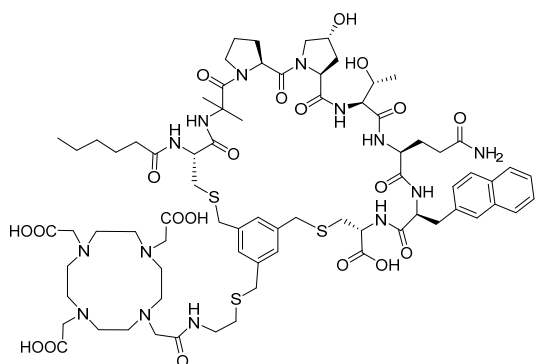
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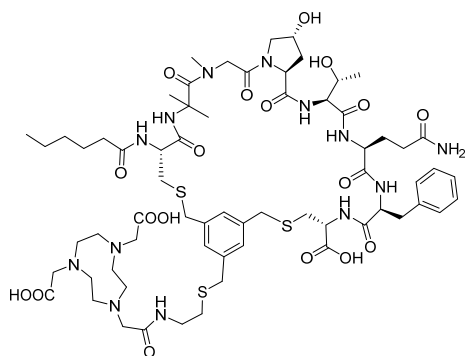
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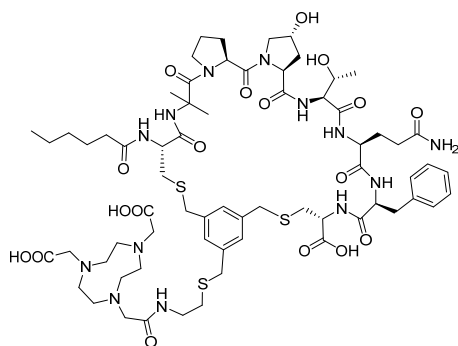
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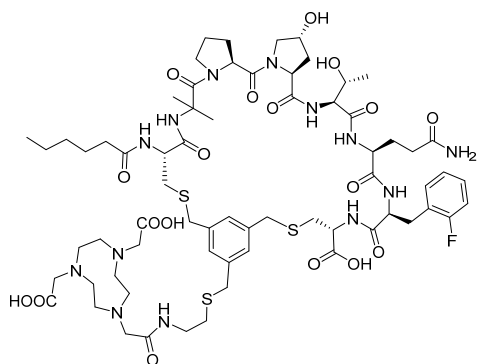
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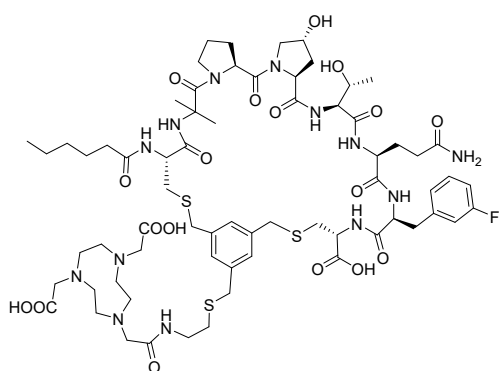
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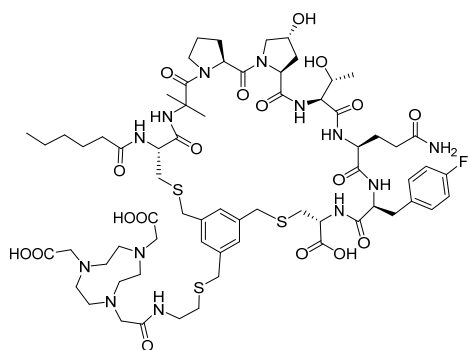
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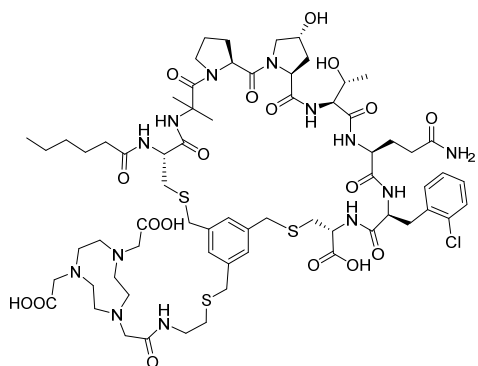
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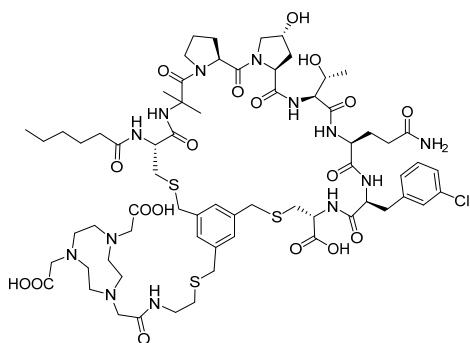
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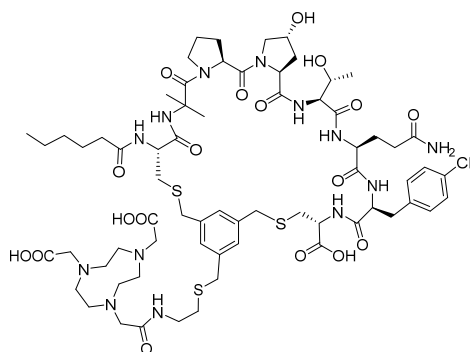
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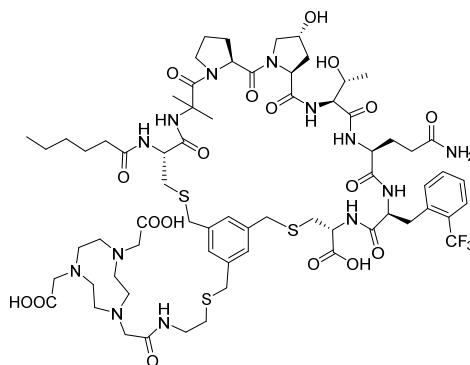
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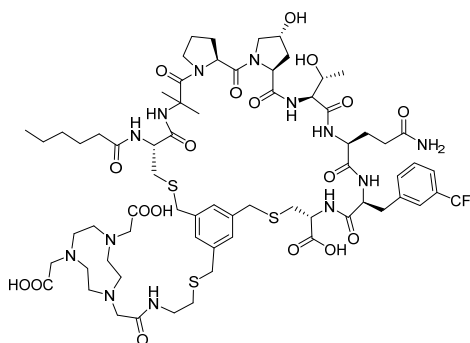
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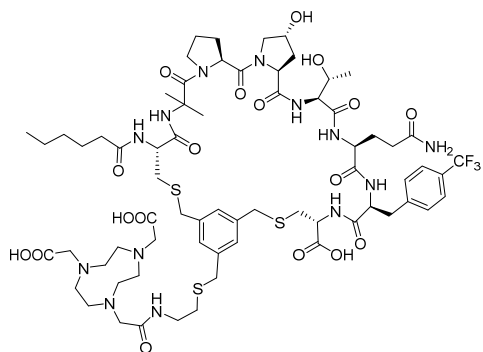
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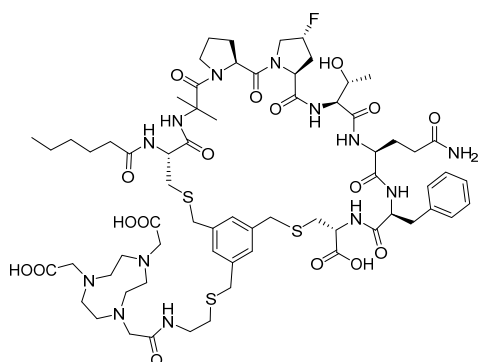
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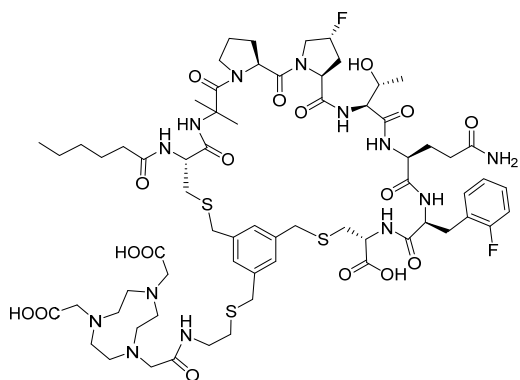
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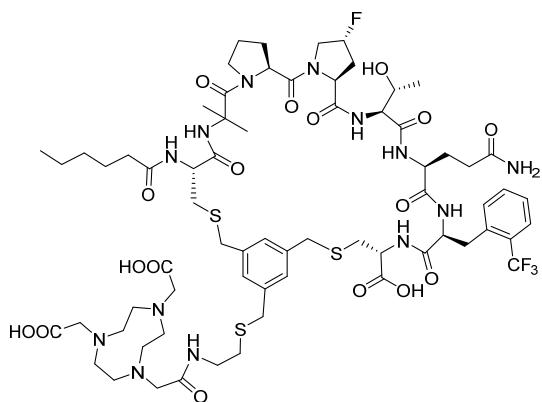
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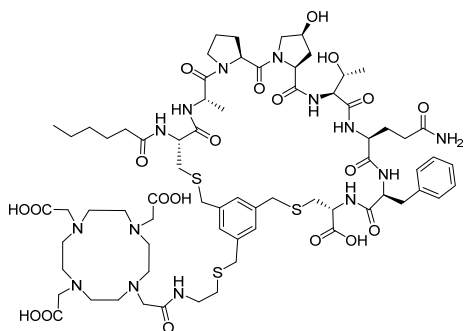
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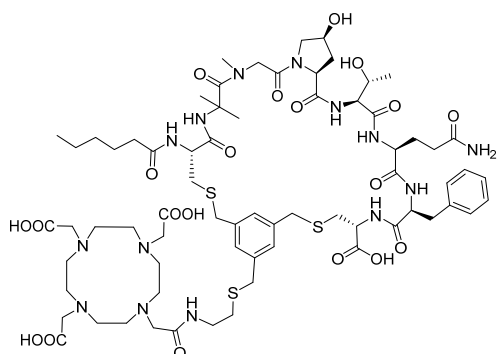
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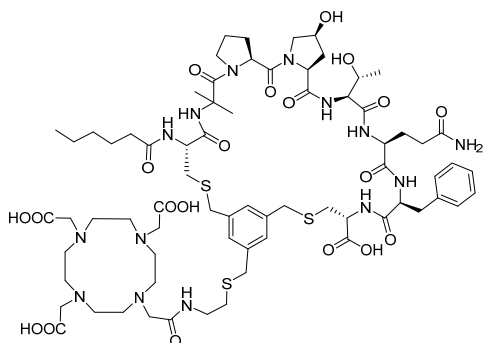
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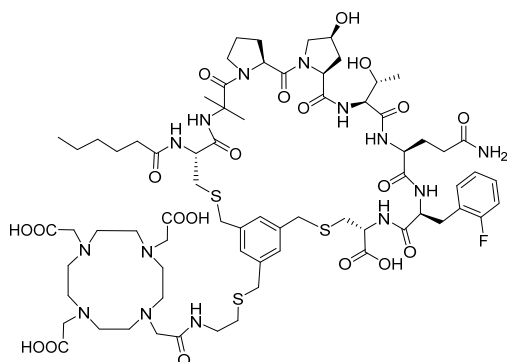
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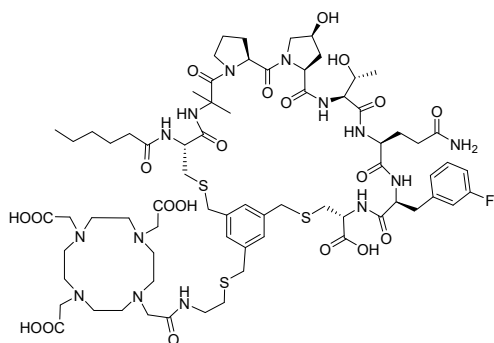
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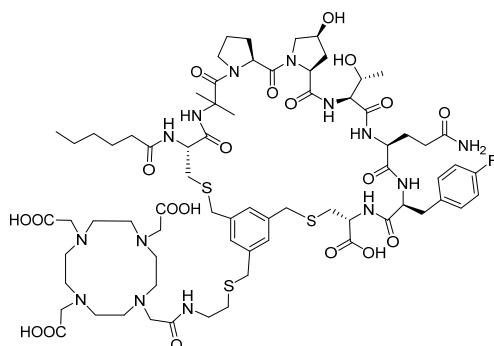
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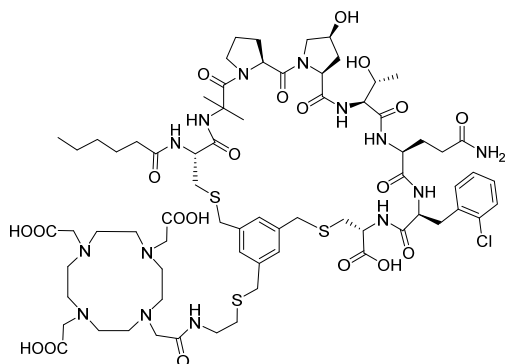
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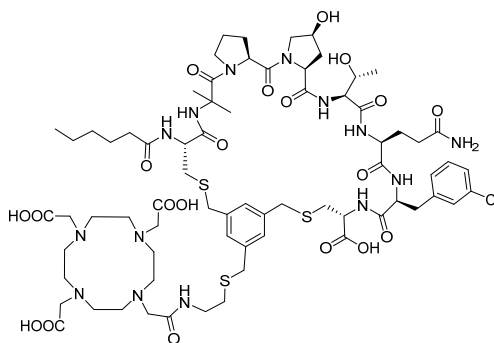
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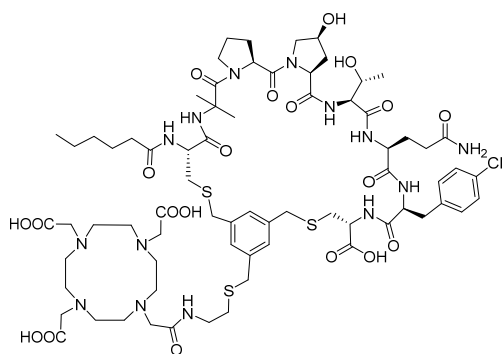
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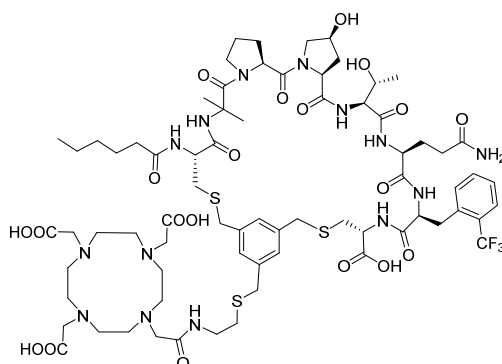
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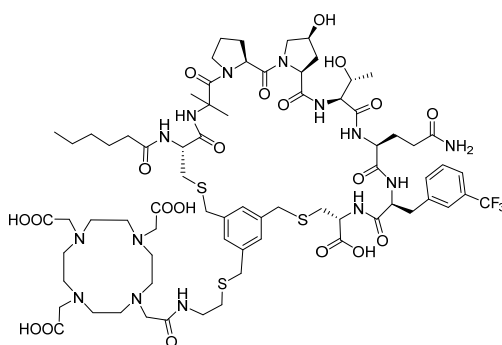
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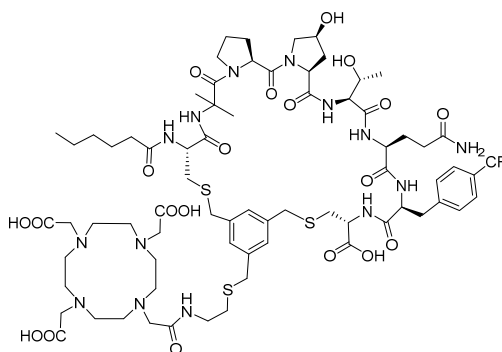
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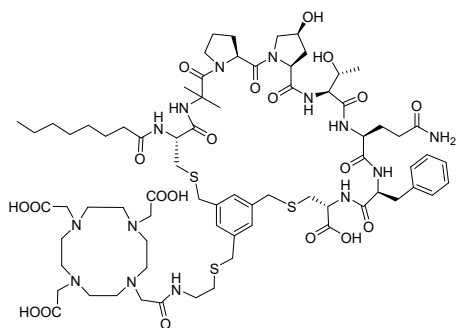
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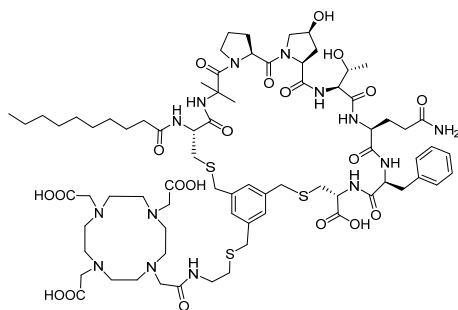
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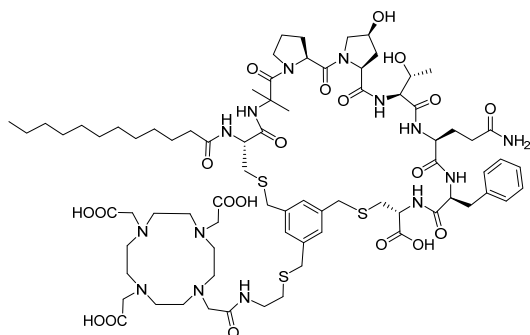
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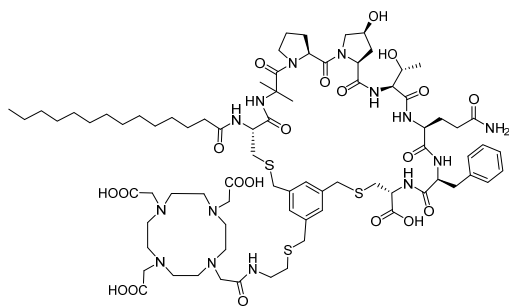
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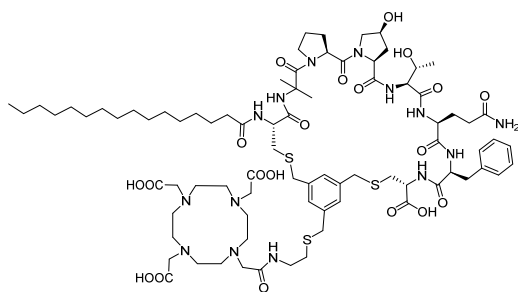
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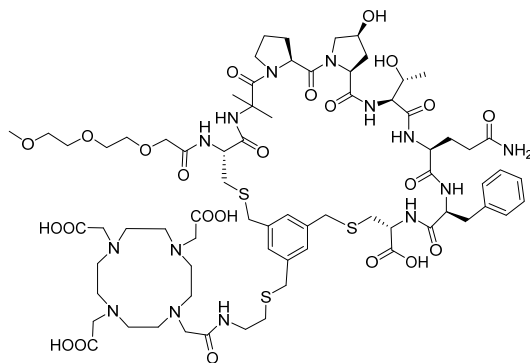
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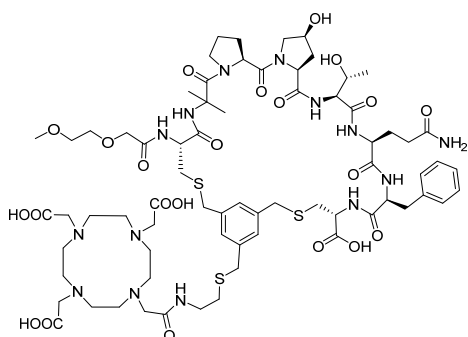
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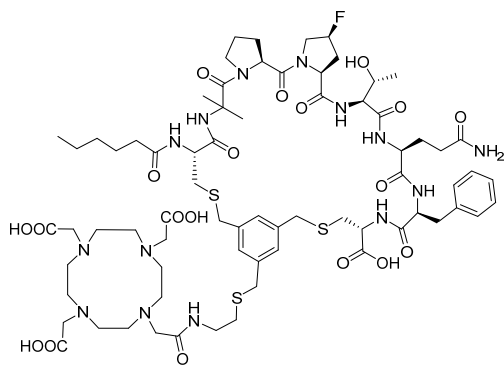
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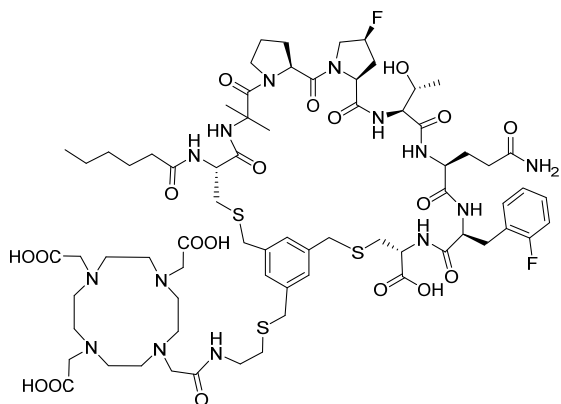
{2-[2-(2-Methoxyethoxy)ethoxy]-Ace}-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-((4S)-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



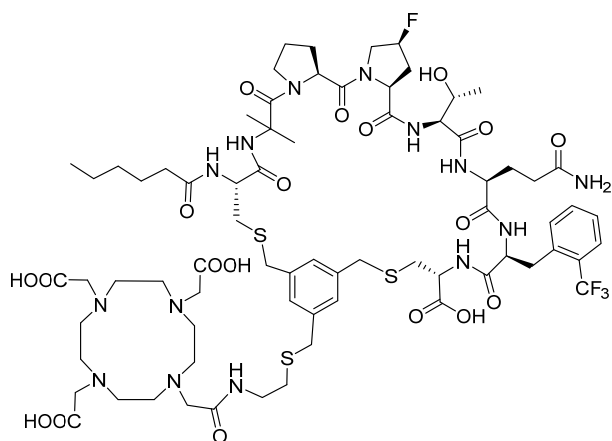
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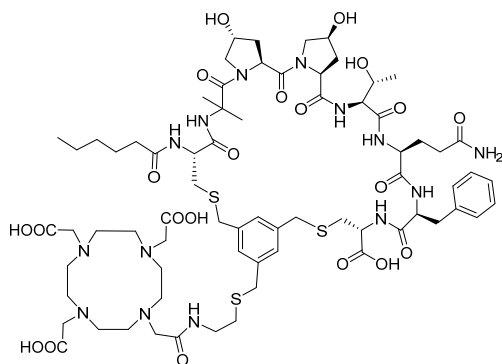
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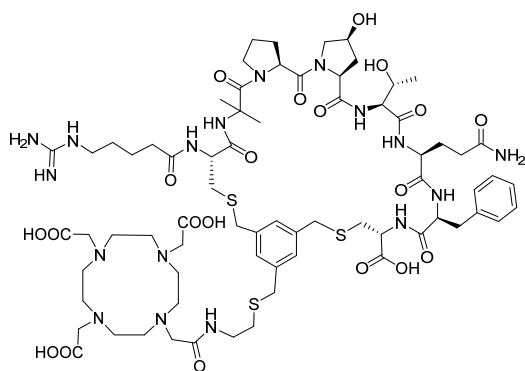
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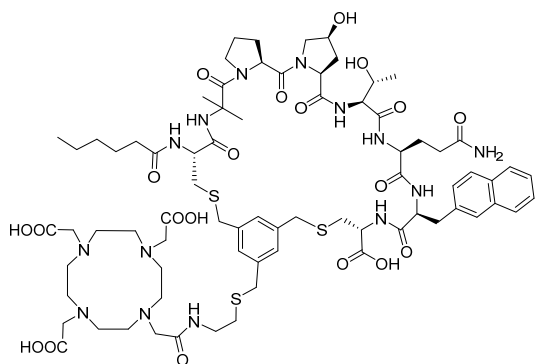
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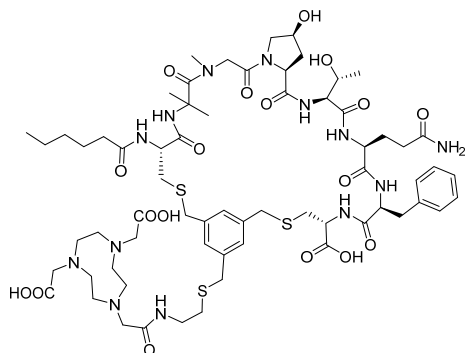
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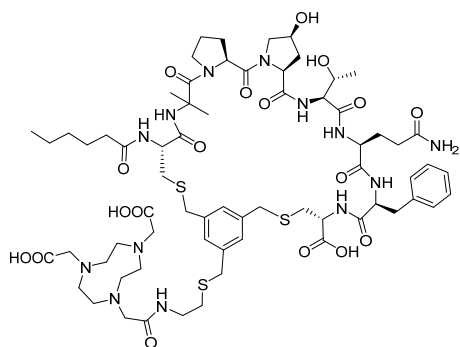
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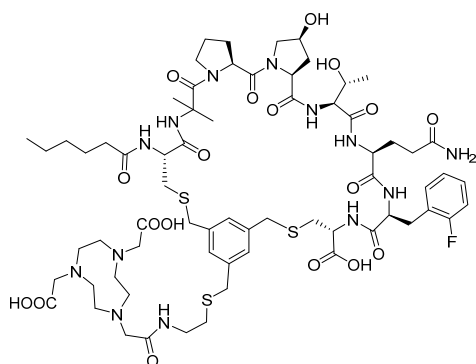
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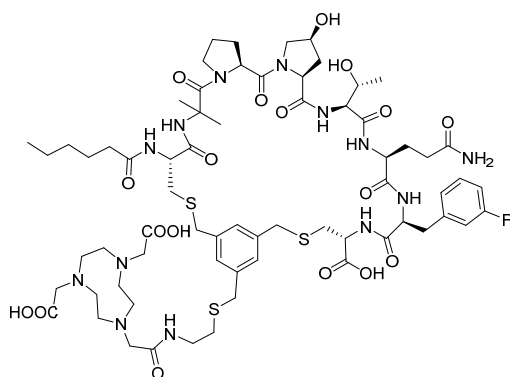
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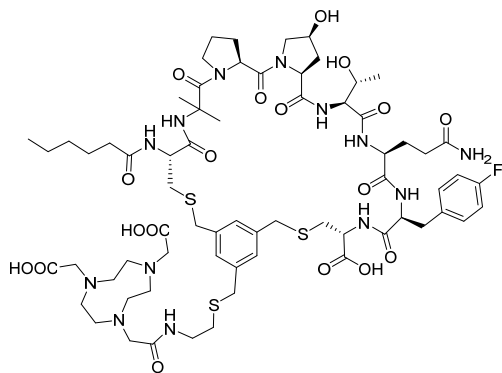
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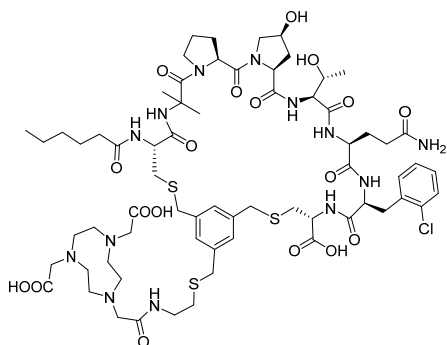
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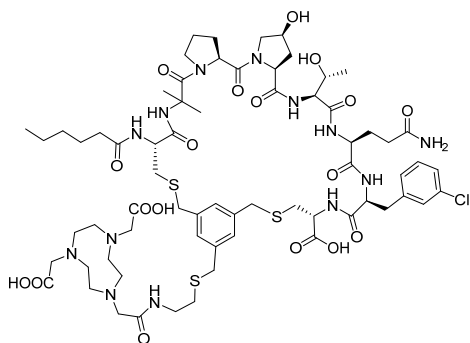
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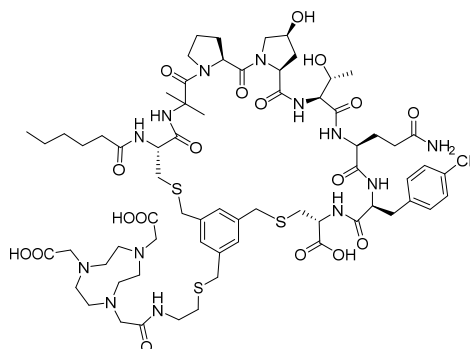
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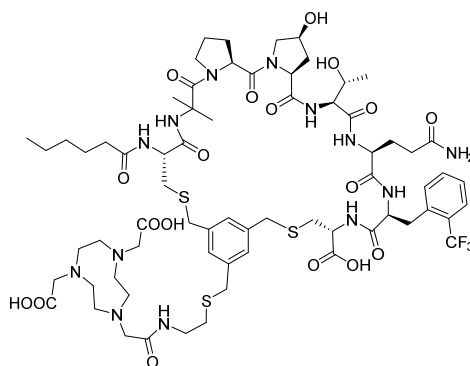
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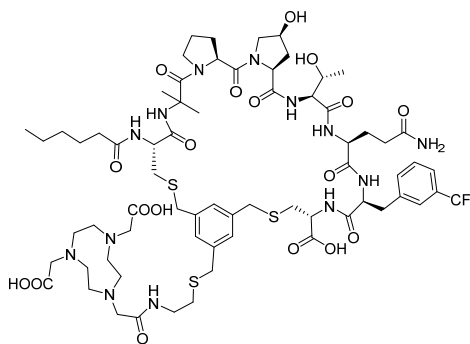
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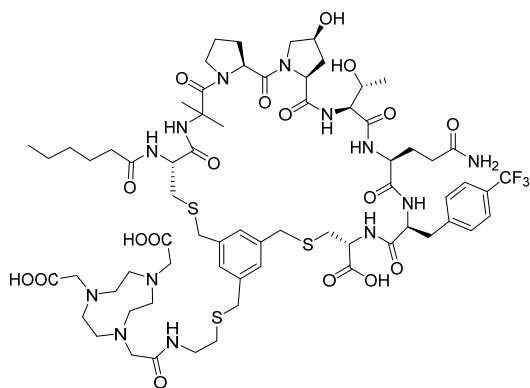
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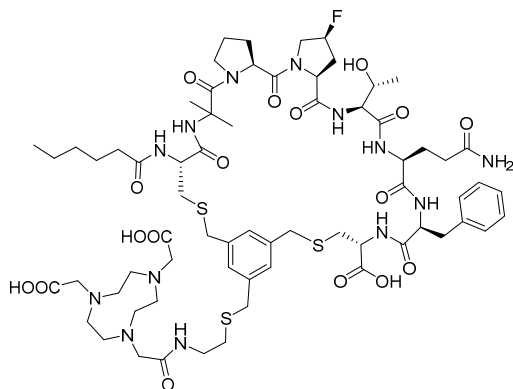
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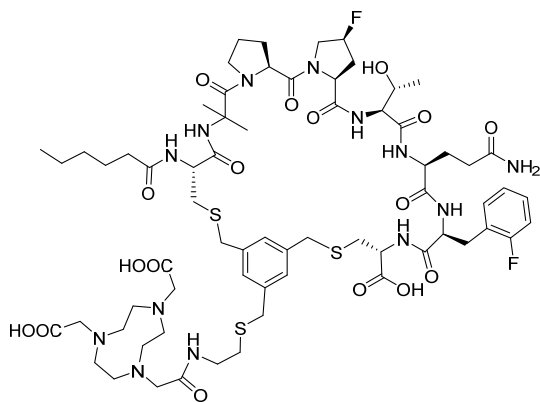
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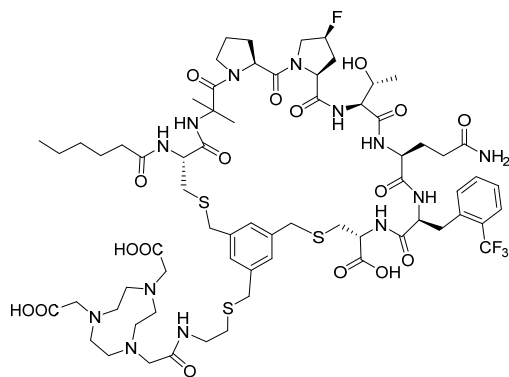
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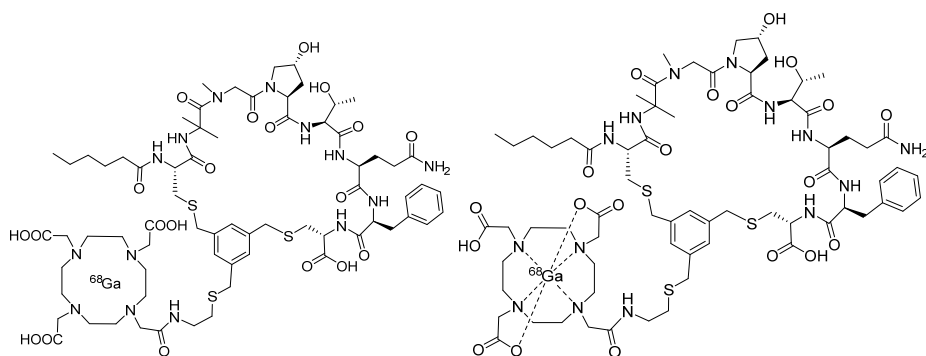


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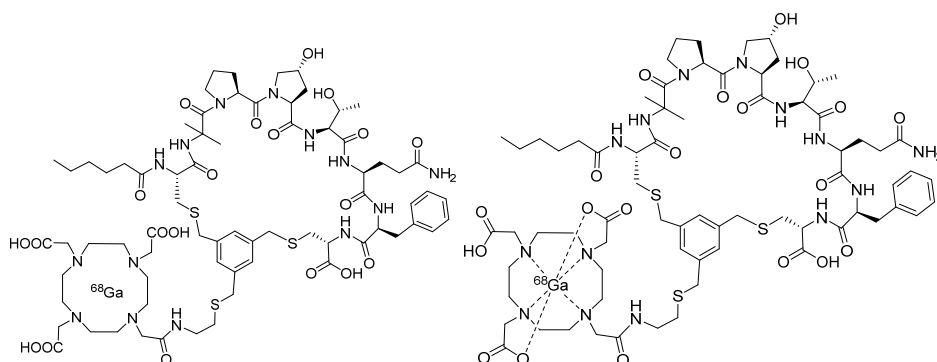


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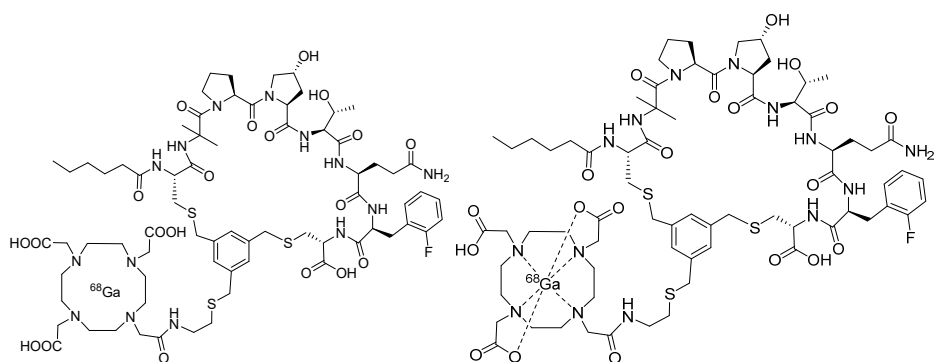
- [0040] In the compound or the pharmaceutically acceptable salt thereof provided by the present disclosure, the chelating agent complexes a nuclide, the nuclide is a diagnostically active nuclide, and the diagnostically active nuclide is selected from ⁴³Sc, ⁴⁴Sc, ⁵¹Mn, ⁵²Mn, ⁶⁴Cu, ⁶⁷Ga, ⁶⁸Ga, ⁸⁶Y, ⁸⁹Zr, ^{94m}Tc, ^{99m}Tc, ¹¹¹In, ¹⁵²Tb, ¹⁵⁵Tb, ²⁰¹Tl, ²⁰³Pb, ¹⁸F, ⁷⁶Br, ⁷⁷Br, ¹²³I, ¹²⁴I and ¹²⁵I.
- [0041] In some embodiments, the diagnostically active nuclide is selected from ⁴³Sc, ⁴⁴Sc, ⁶⁴Cu, ⁶⁷Ga, ⁶⁸Ga, ⁸⁶Y, ⁸⁹Zr, ^{99m}Tc, ¹¹¹In, ¹⁵²Tb, ¹⁵⁵Tb, ²⁰³Pb, ¹⁸F, ⁷⁶Br, ⁷⁷Br, ¹²³I, ¹²⁴I and ¹²⁵I.
- [0042] In some embodiments, the diagnostically active nuclide is selected from ⁶⁴Cu, ⁶⁸Ga, ⁸⁹Zr, ^{99m}Tc, ¹¹¹In, ¹⁸F, ¹²³I and ¹²⁴I.
- [0043] In the compounds or the pharmaceutically acceptable salts thereof provided by the present disclosure, the chelating agent complexes a nuclide, and the nuclide is a therapeutically active nuclide selected from ⁴⁷Sc, ⁶⁷Cu, ⁸⁹Sr, ⁹⁰Y, ¹⁵³Sm, ¹⁴⁹Tb, ¹⁶¹Tb, ¹⁷⁷Lu, ¹⁸⁶Re, ¹⁸⁸Re, ²¹²Pb, ²¹³Bi, ²²³Ra, ²²⁵Ac, ²²⁶Th, ²²⁷Th, ¹³¹I and ²¹¹A.
- [0044] In an alternative embodiment, the therapeutically active radionuclide is selected from ⁴⁷Sc, ⁶⁷Cu, ⁹⁰Y, ¹⁷⁷Lu, ¹⁸⁸Re, ²¹²Pb, ²¹³Bi, ²²⁵Ac, ²²⁷Th, ¹³¹I and ²¹¹At.
- [0045] In an alternative embodiment, the therapeutically active radionuclide is selected from ⁹⁰Y, ¹⁷⁷Lu, ²²⁵Ac, ²²⁷Th, ¹³¹I and ²¹¹At.
- [0046] The present disclosure provides compounds as shown below or pharmaceutically acceptable salts thereof:



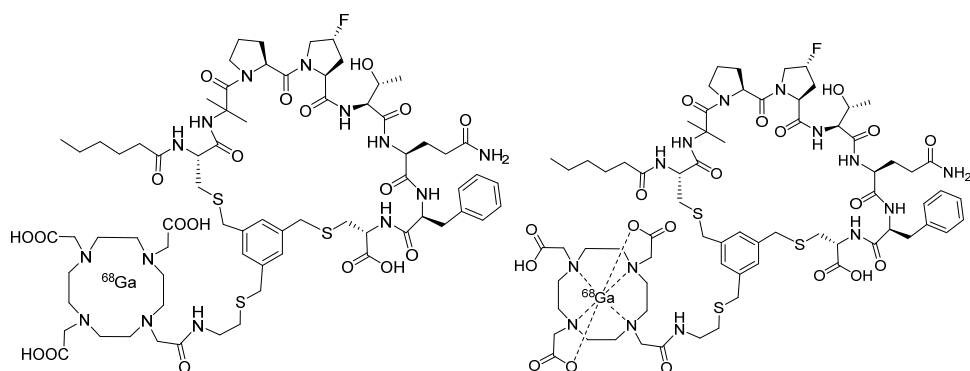
Hex-[Cys-(tMeBn(^{68}Ga -DOTA-AET))-Aib-Sar-((4R)-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



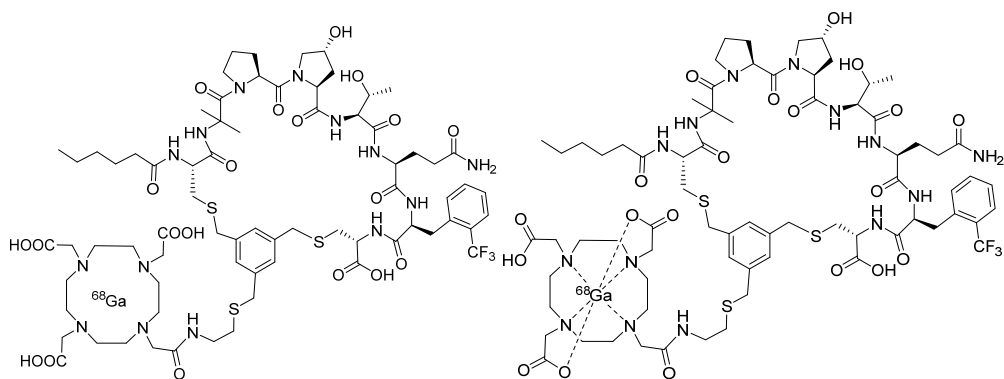
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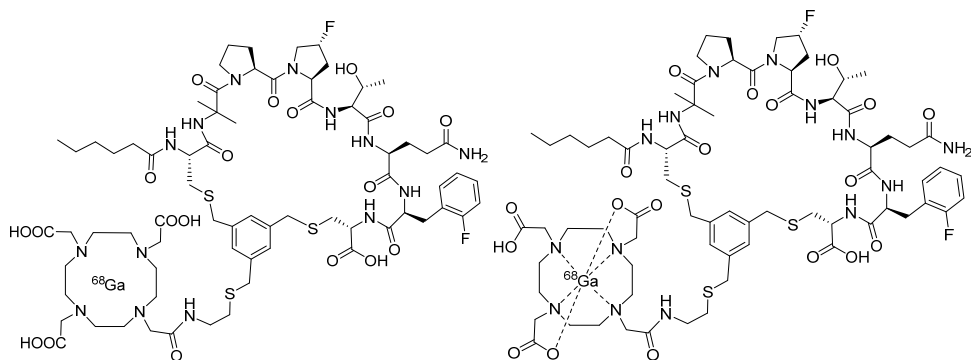
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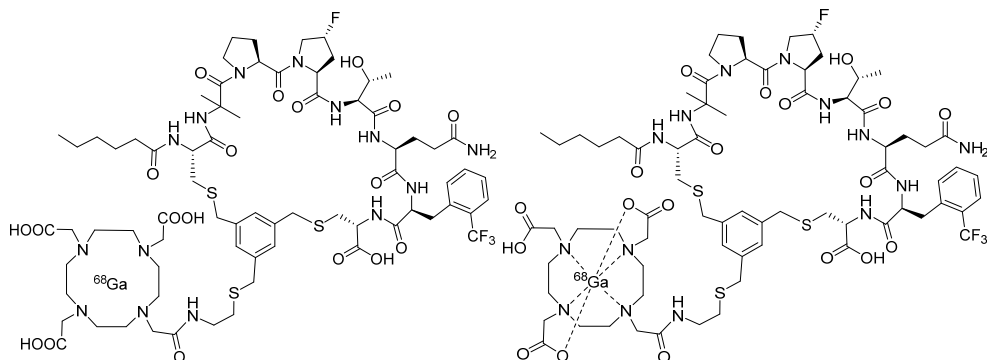
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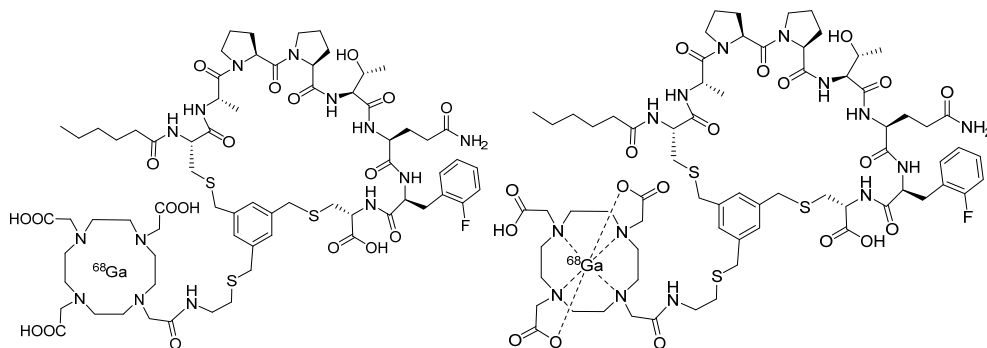
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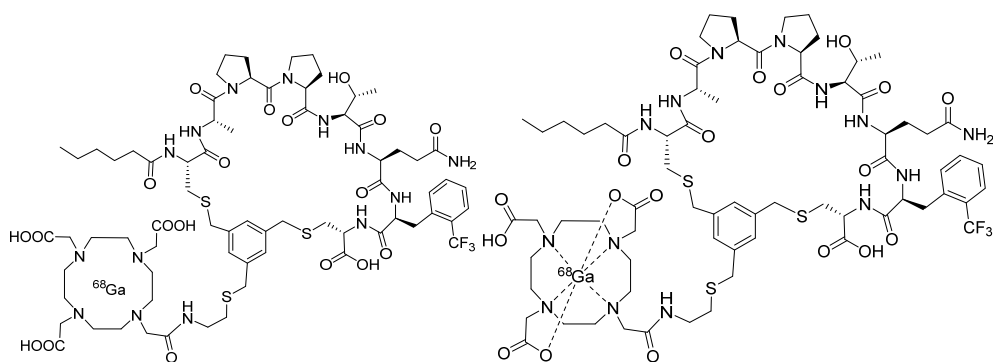
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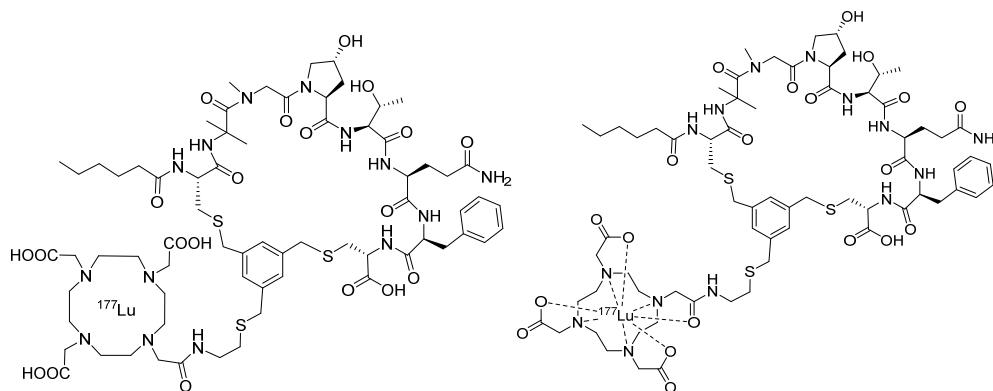
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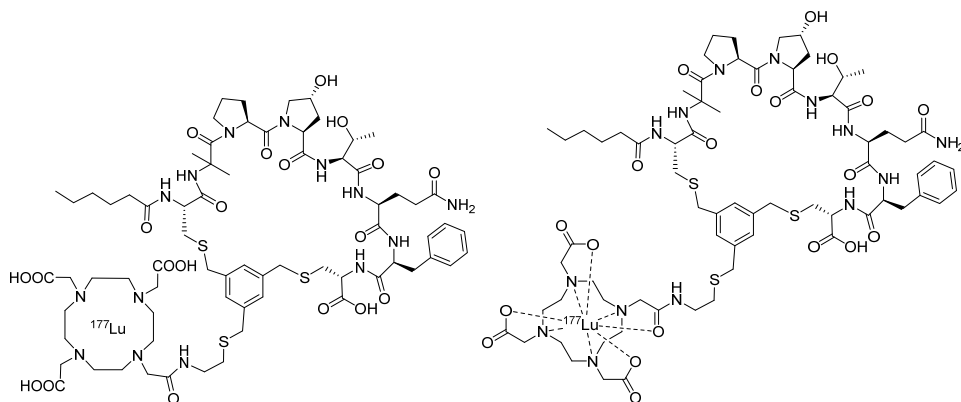
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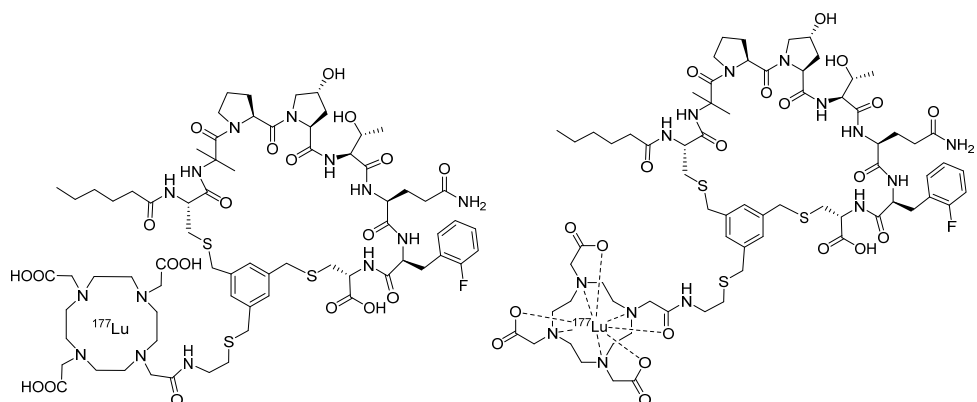
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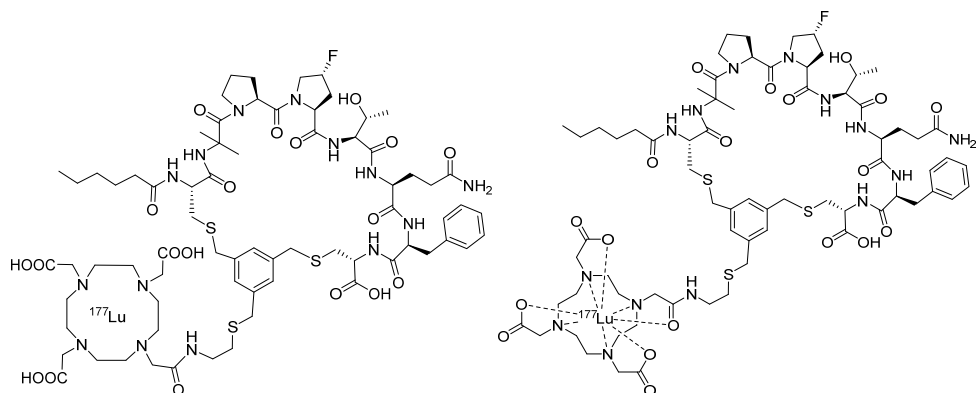
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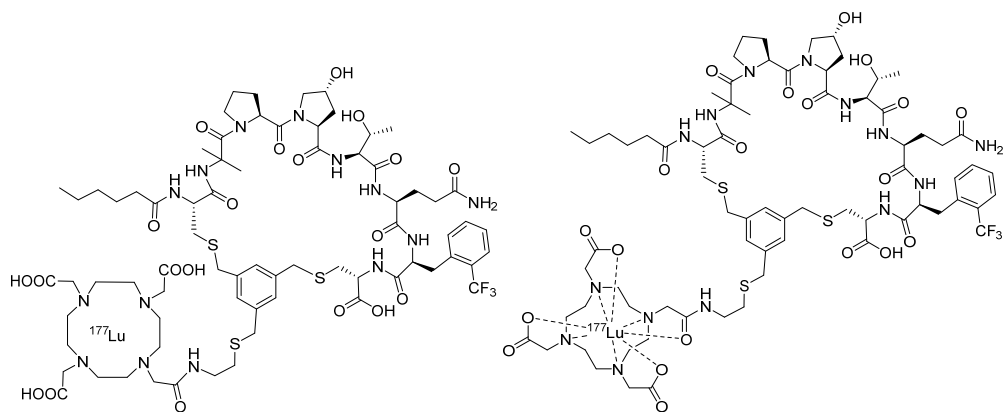
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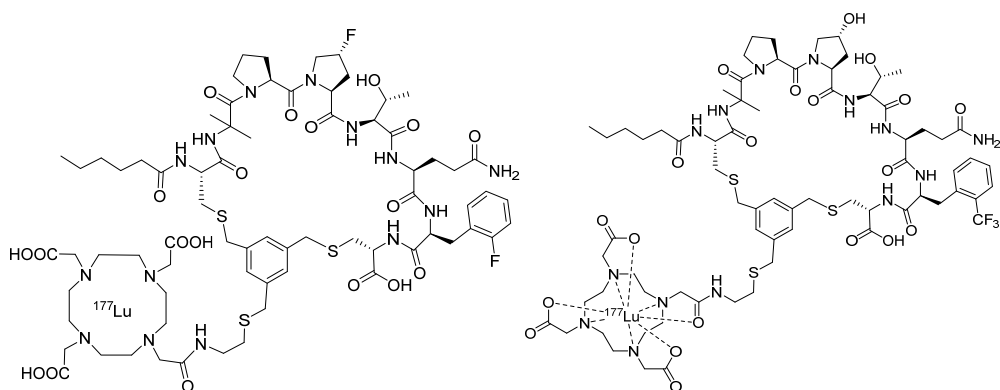
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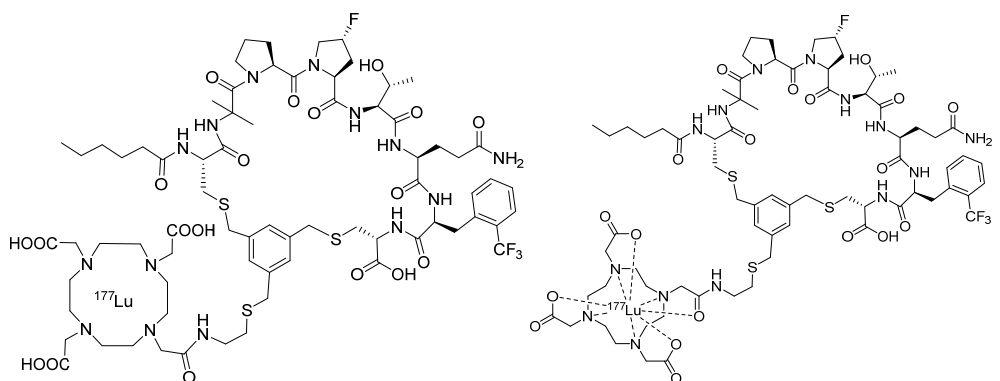
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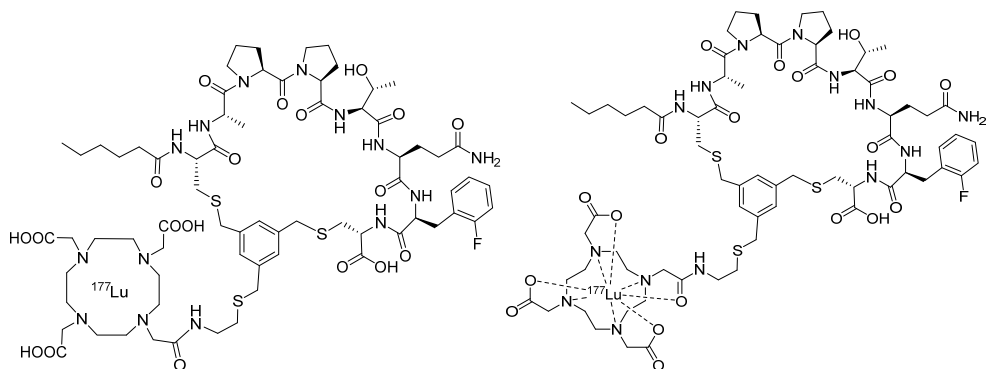
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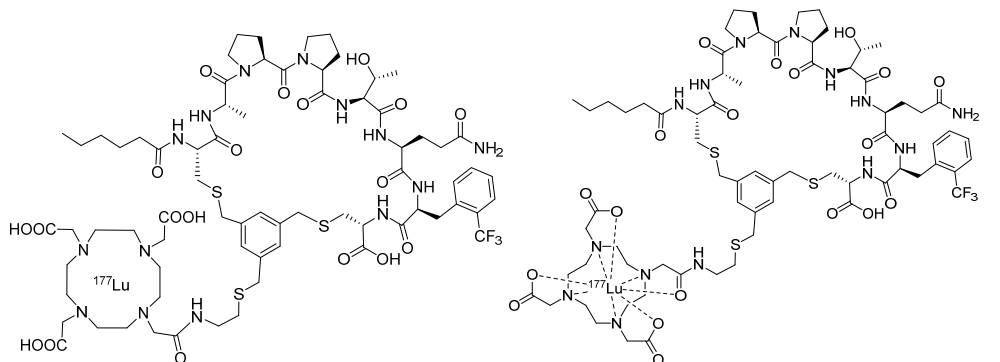
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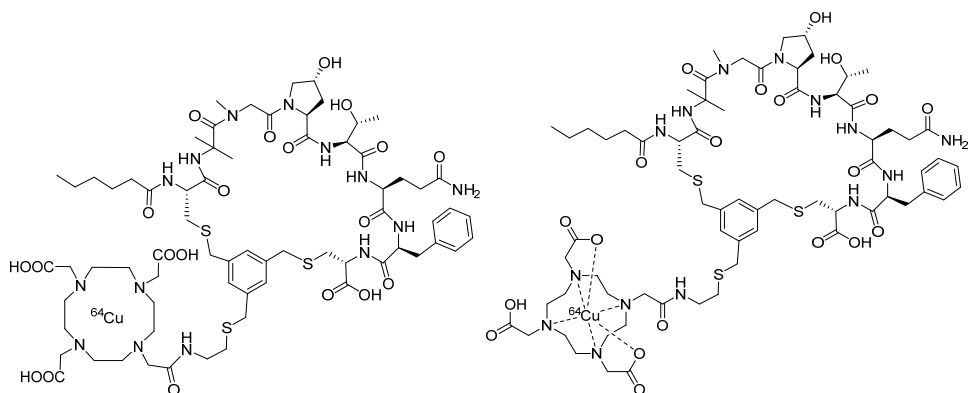
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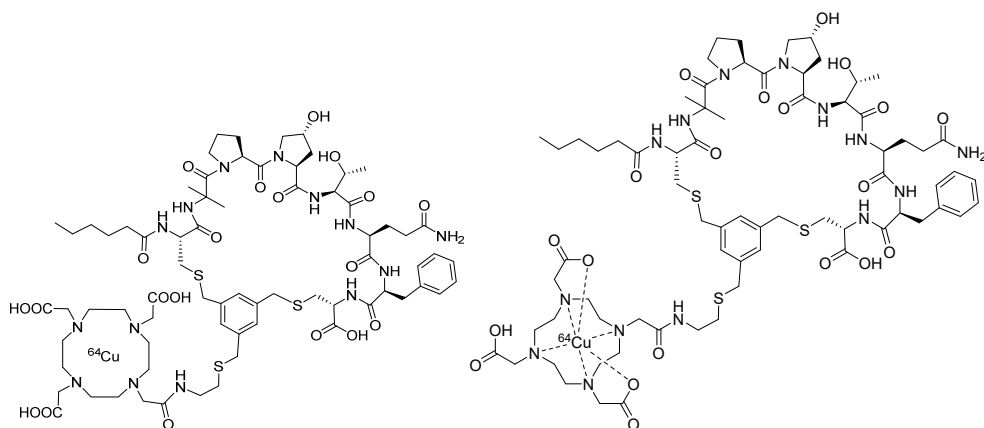
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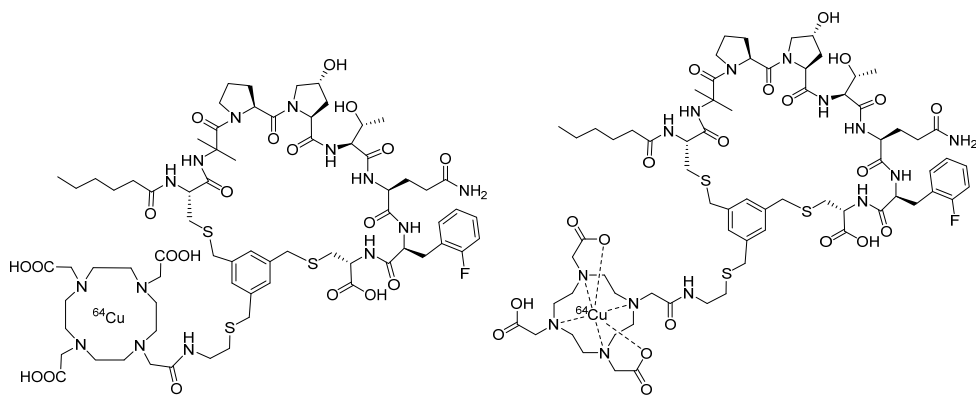
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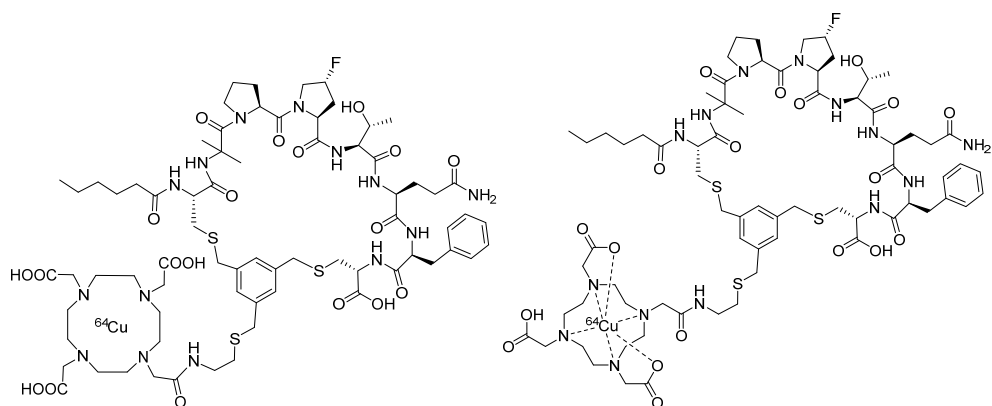
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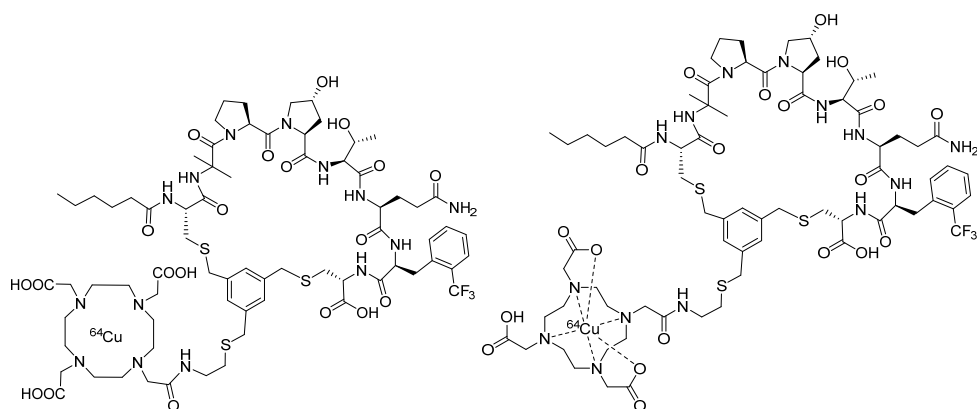
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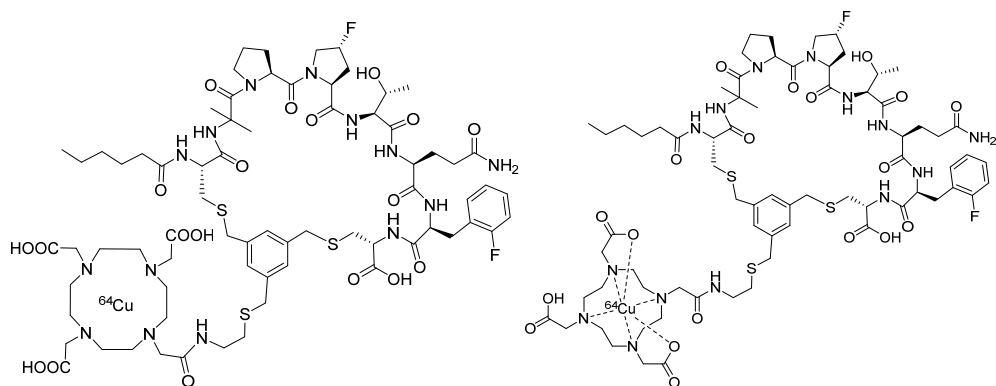
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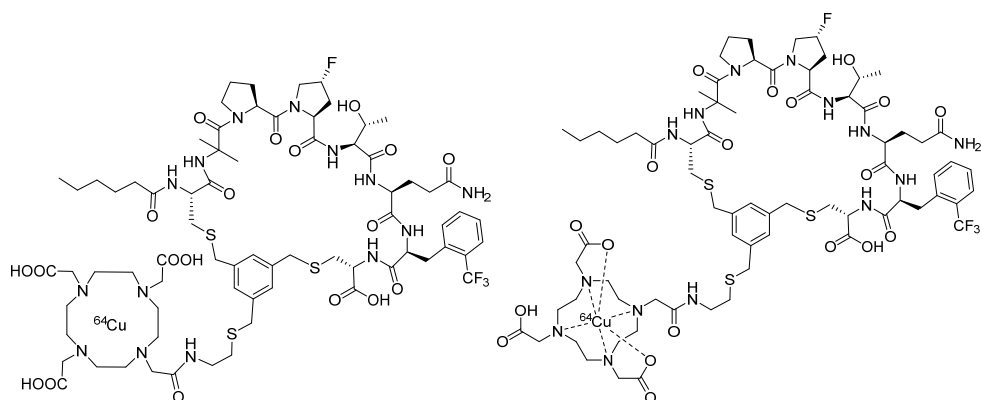
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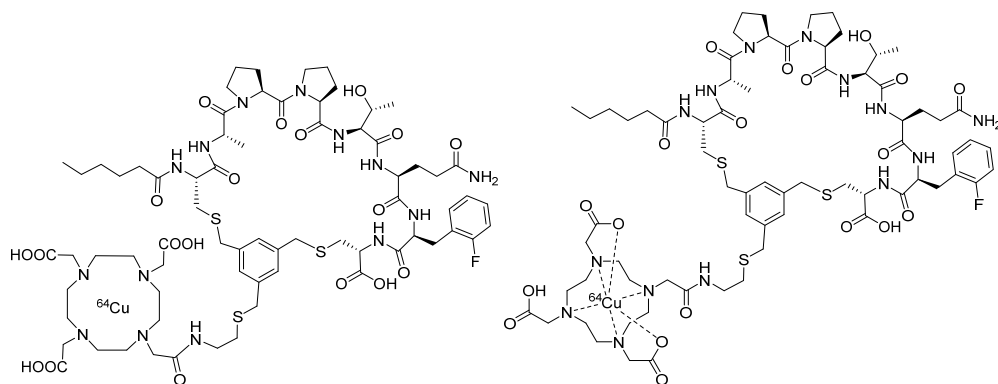
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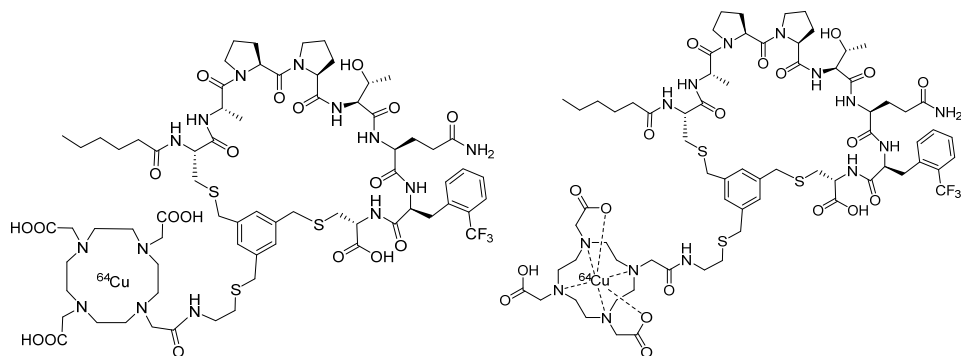
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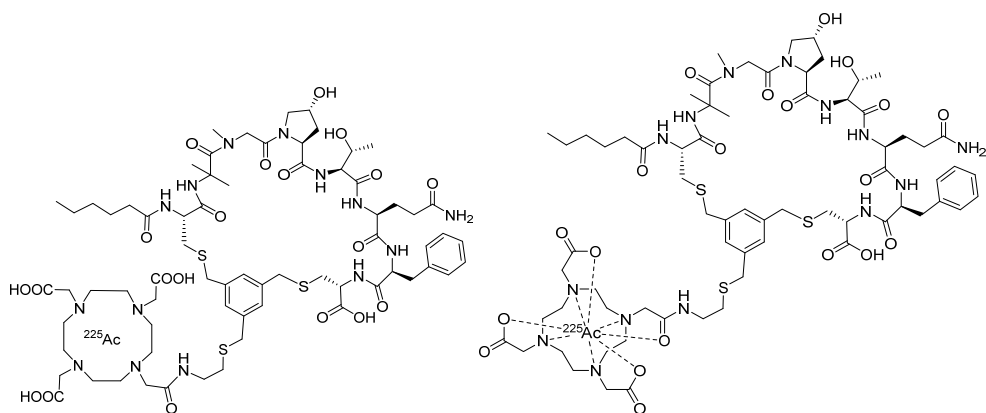
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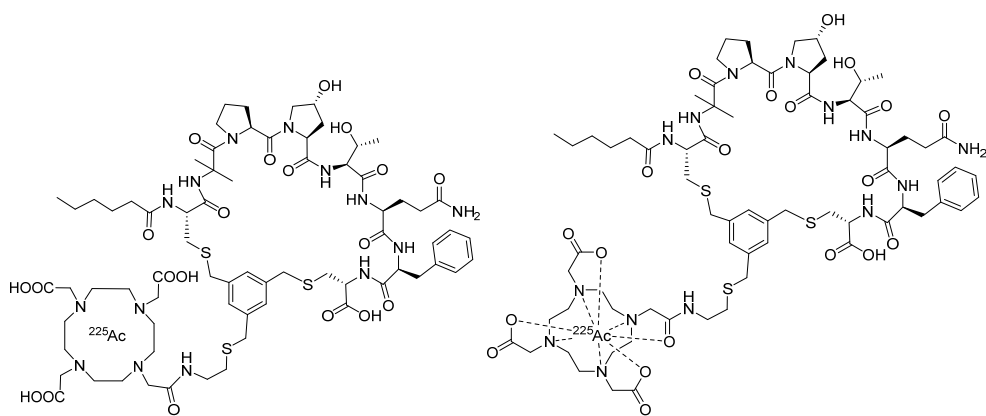
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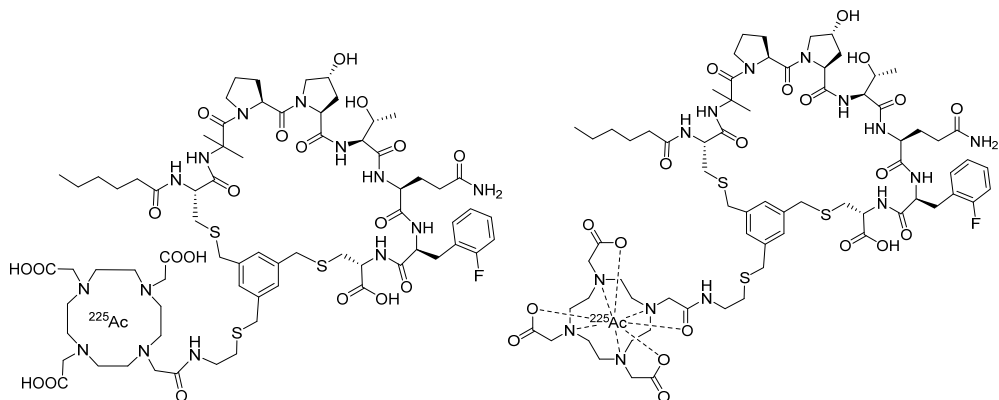
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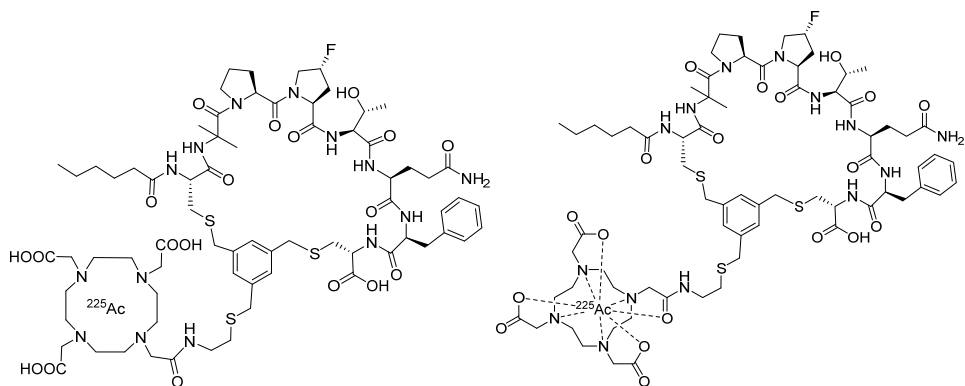
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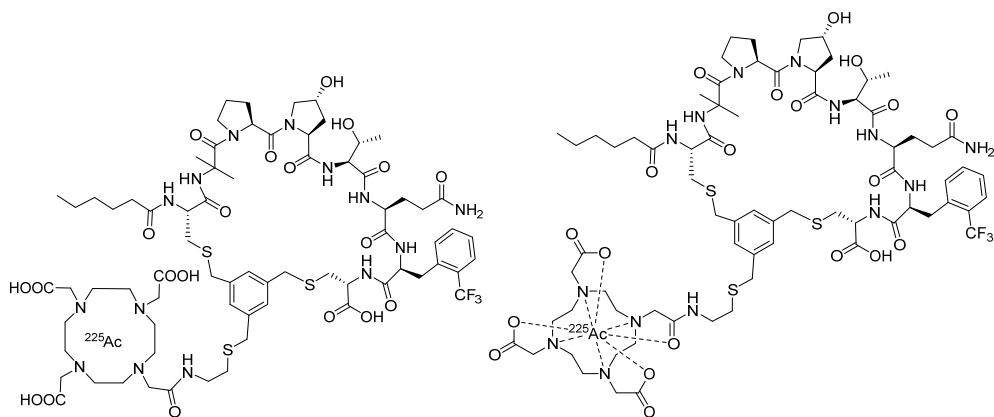
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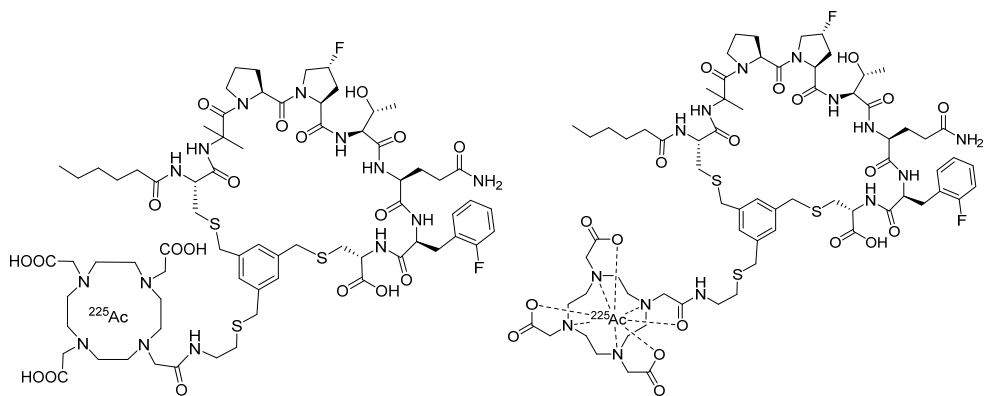
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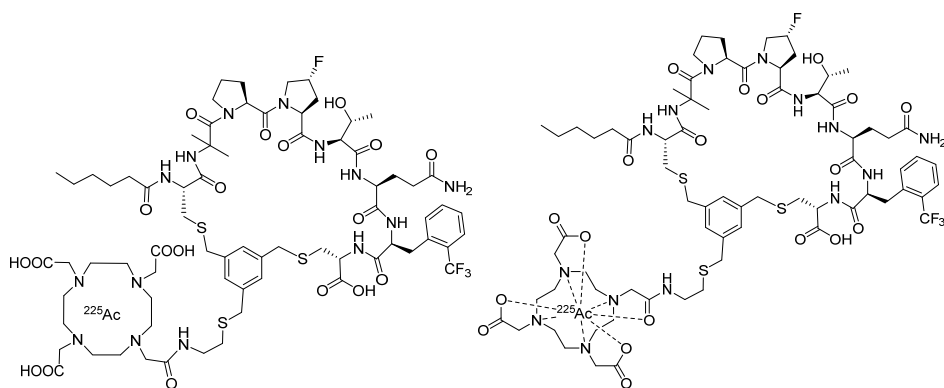
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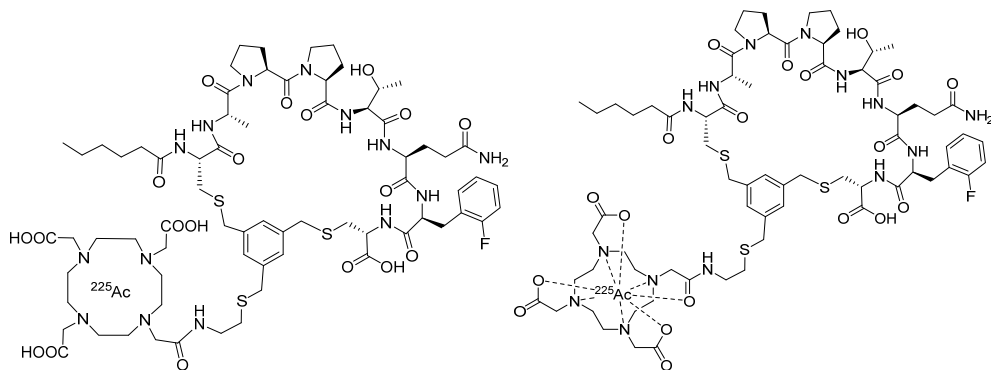
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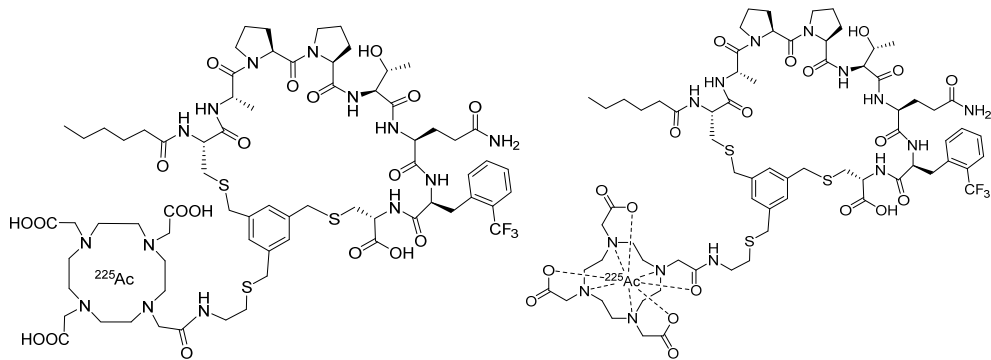
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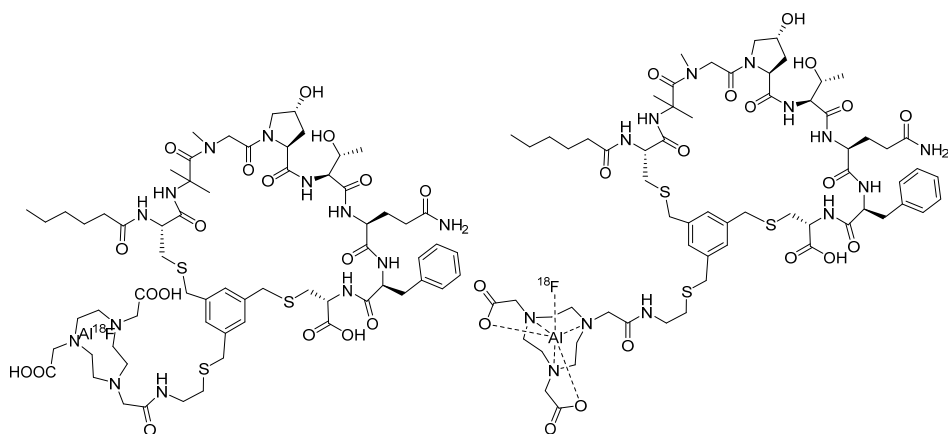
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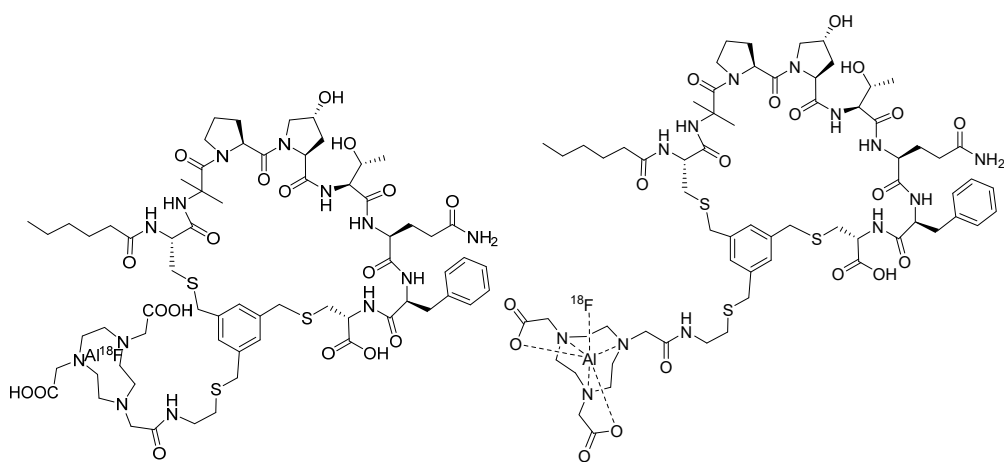
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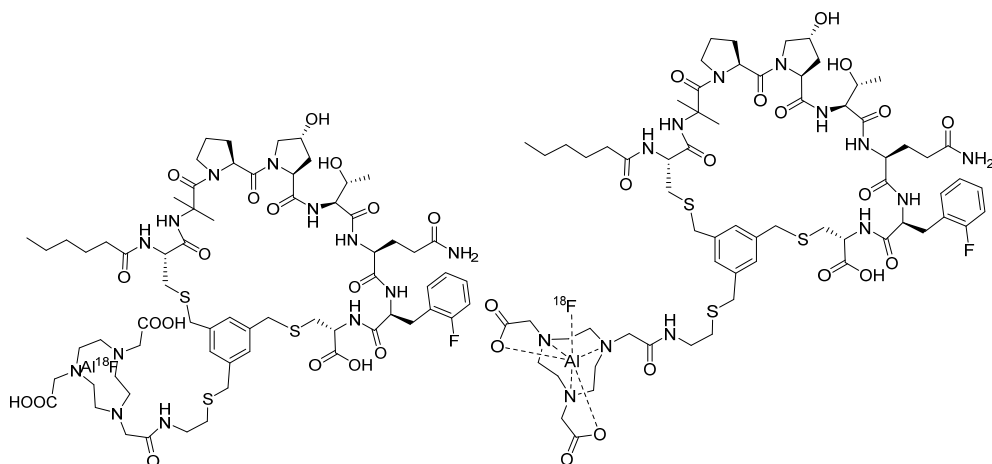
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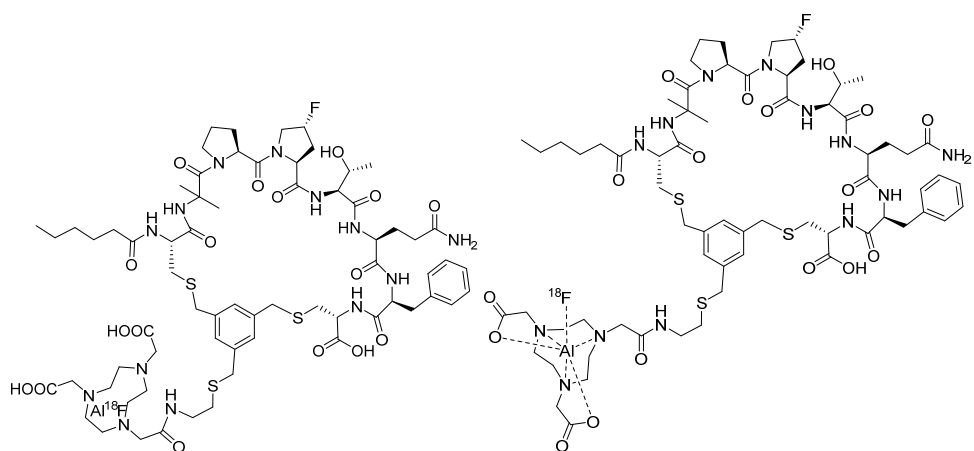
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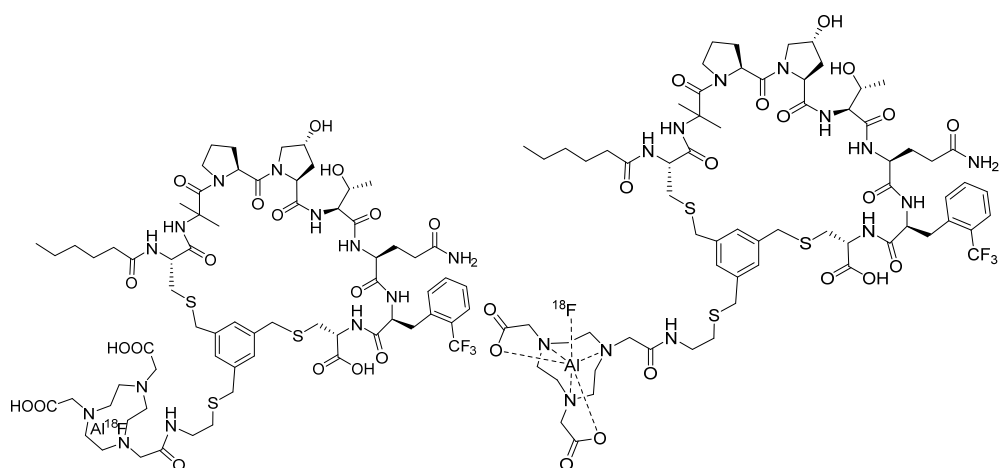
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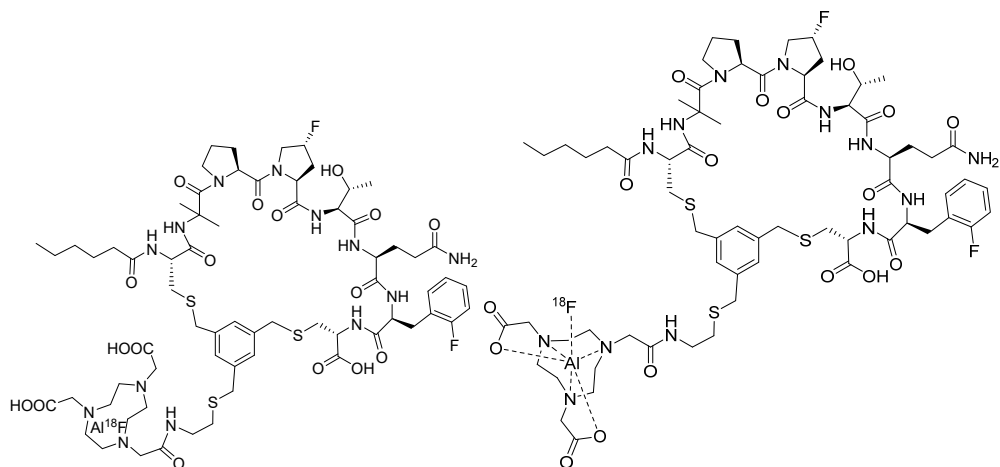
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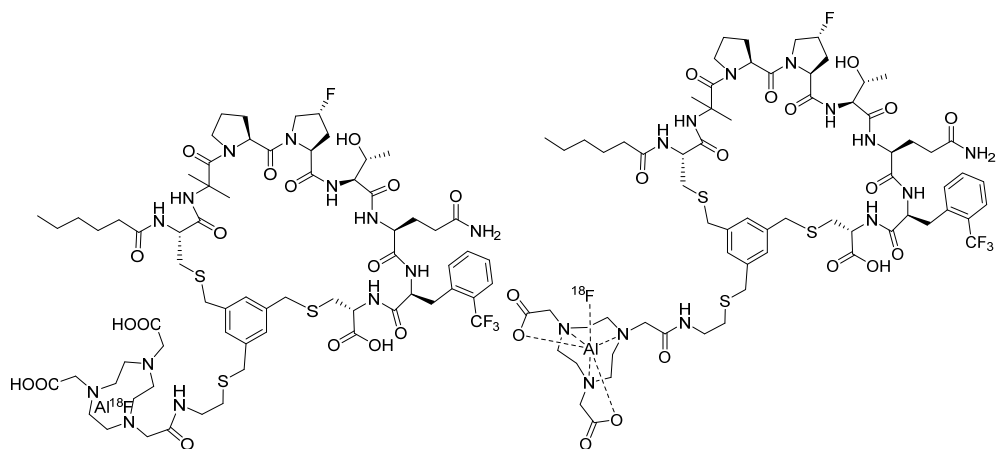
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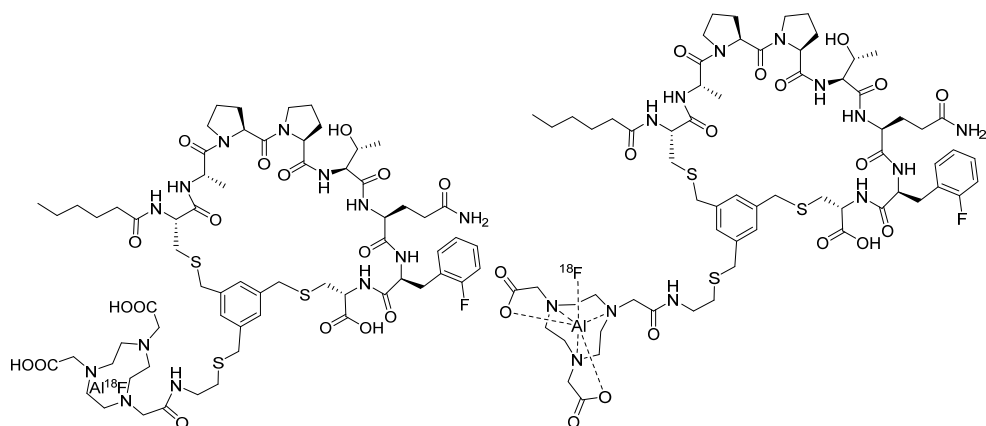
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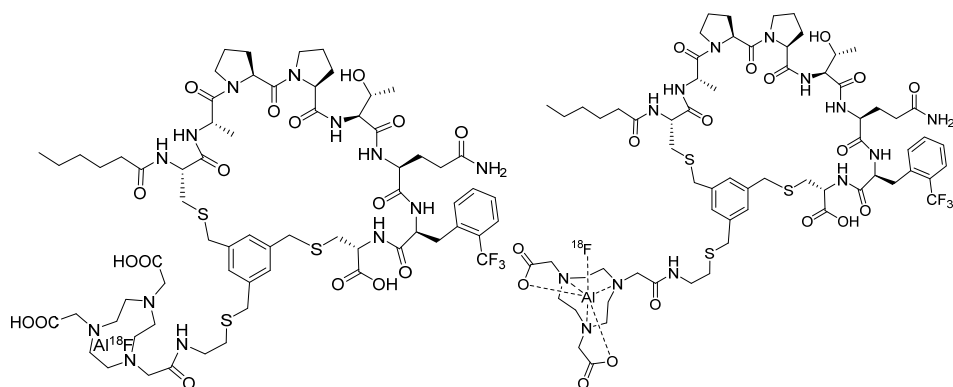
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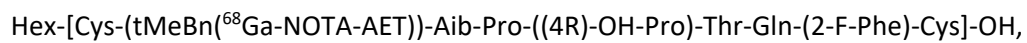
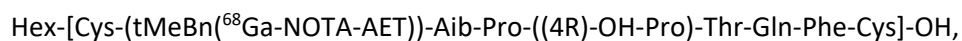
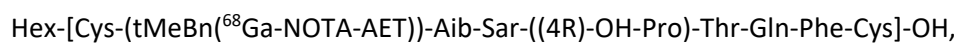
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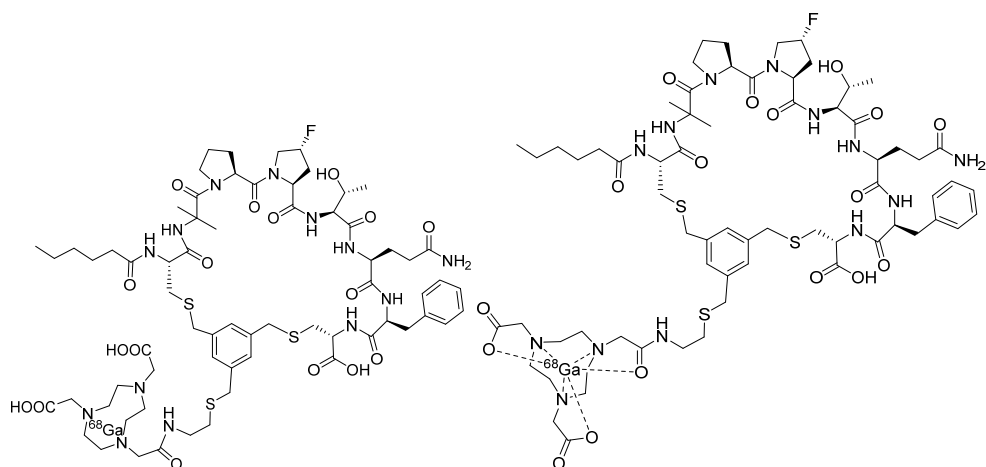


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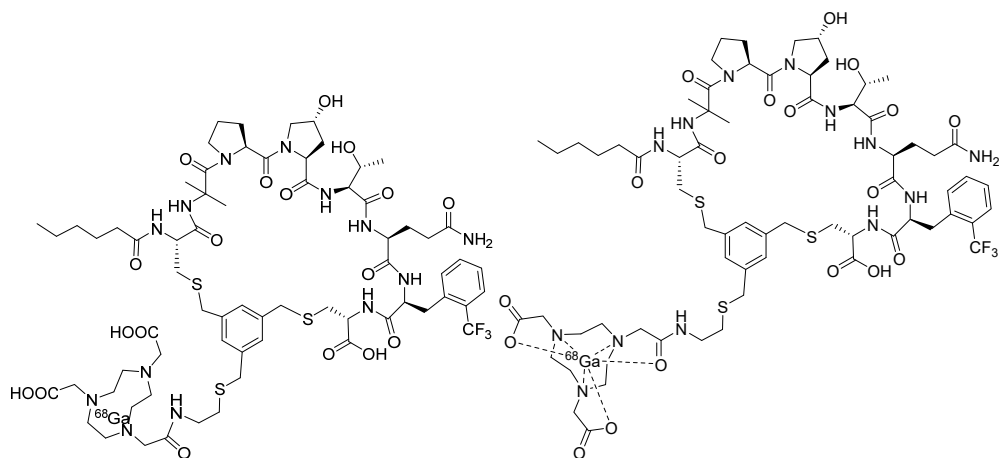


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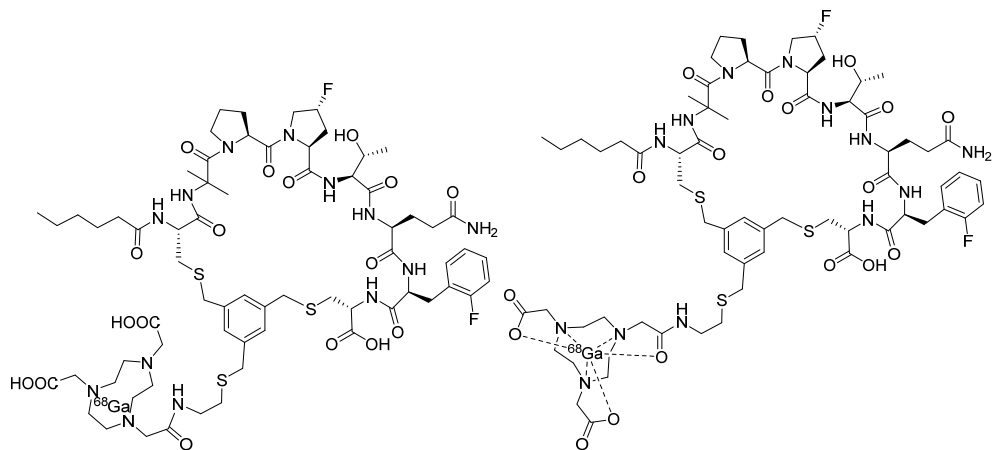




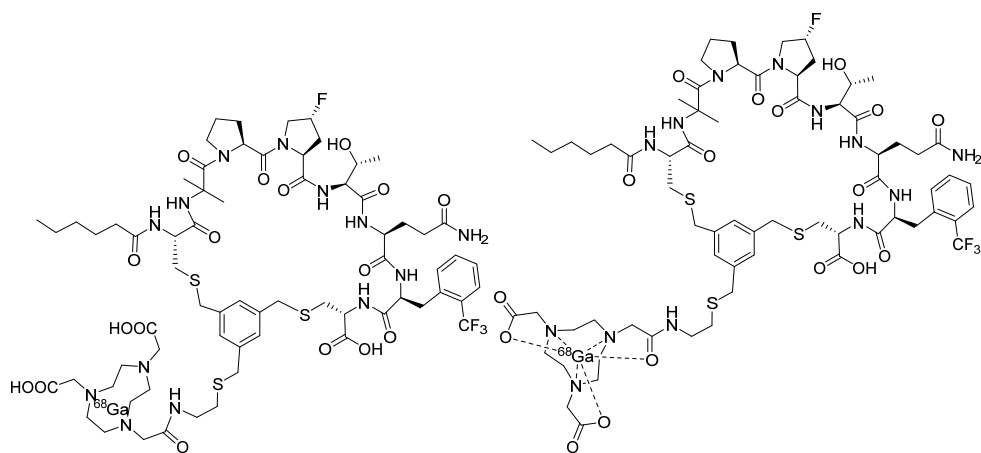
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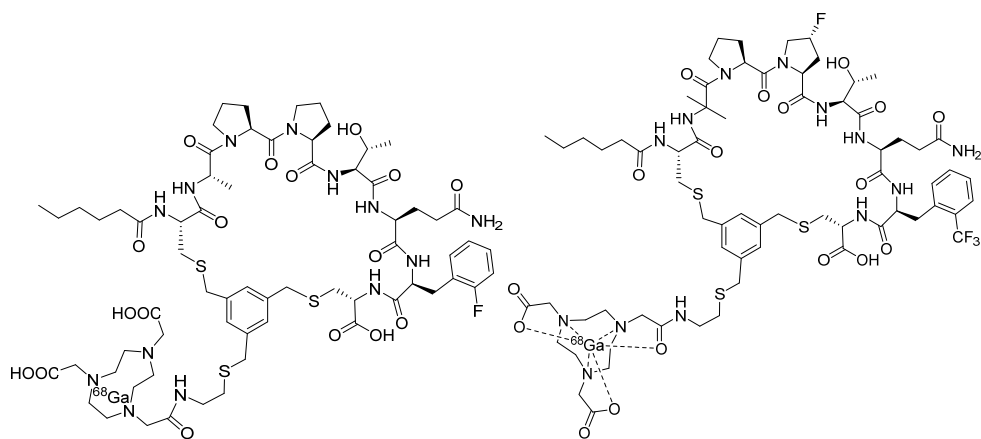
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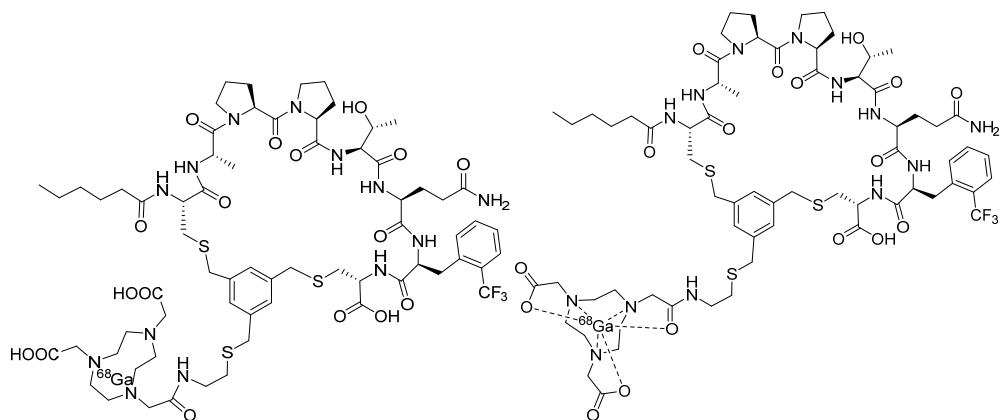
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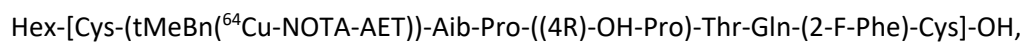
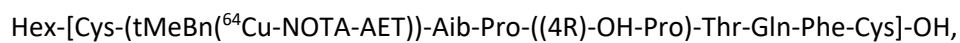
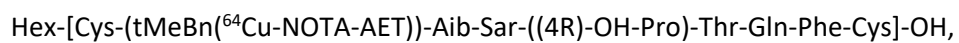
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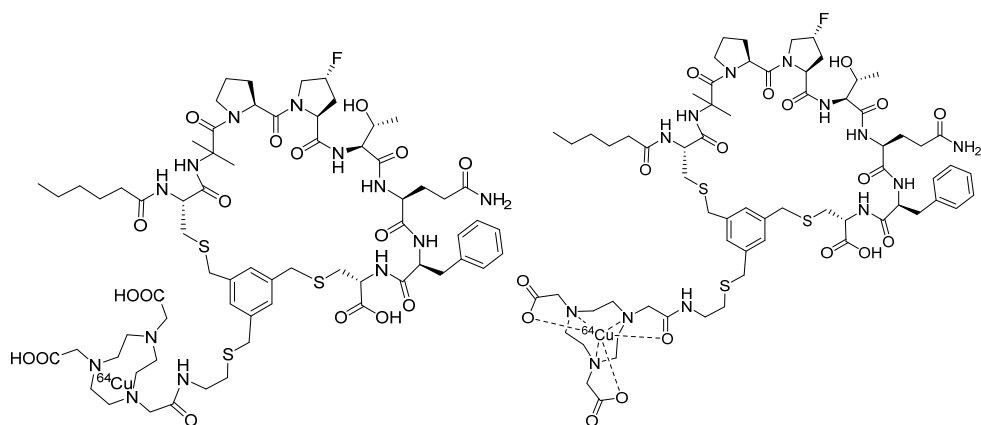


Hex-[Cys-(tMeBn(^{68}Ga -NOTA-AET))-Ala-Pro-Pro-Thr-Gln-(2-F-Phe)-Cys]-OH,

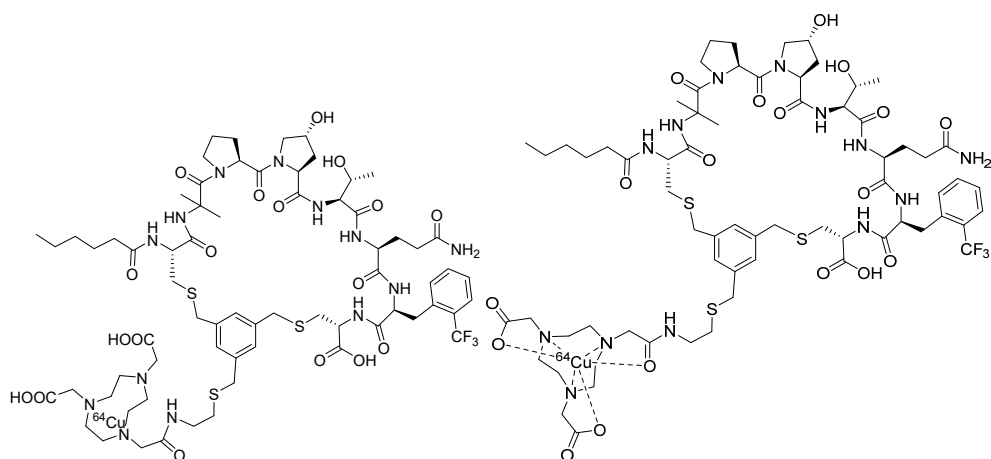


Hex-[Cys-(tMeBn(^{68}Ga -NOTA-AET))-Ala-Pro-Pro-Thr-Gln-(2- CF_3 -Phe)-Cys]-OH,

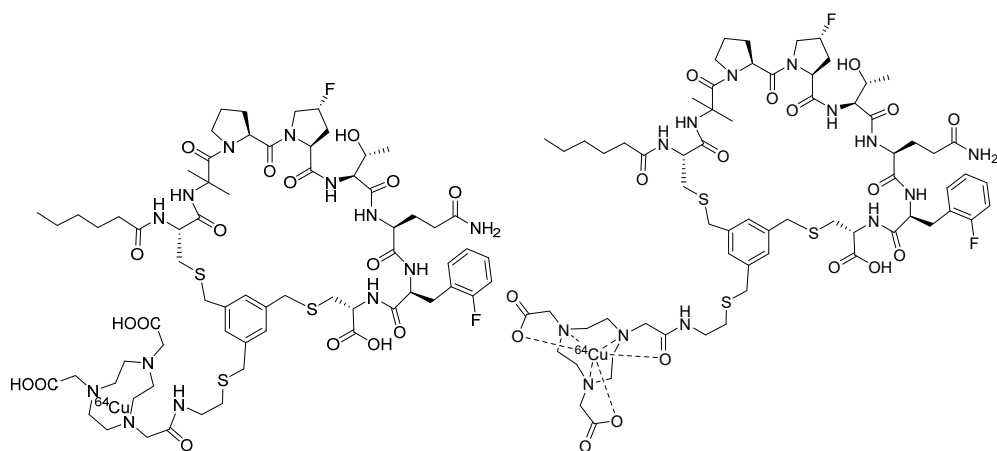




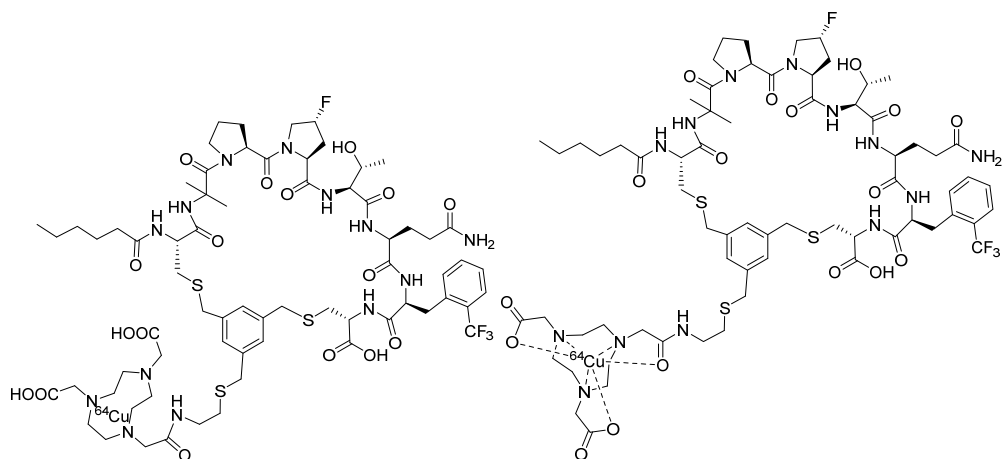
Hex-[Cys-(tMeBn(^{64}Cu -NOTA-AET))-Aib-Pro-((4R)-F-Pro)-Thr-Gln-Phe-Cys]-OH,



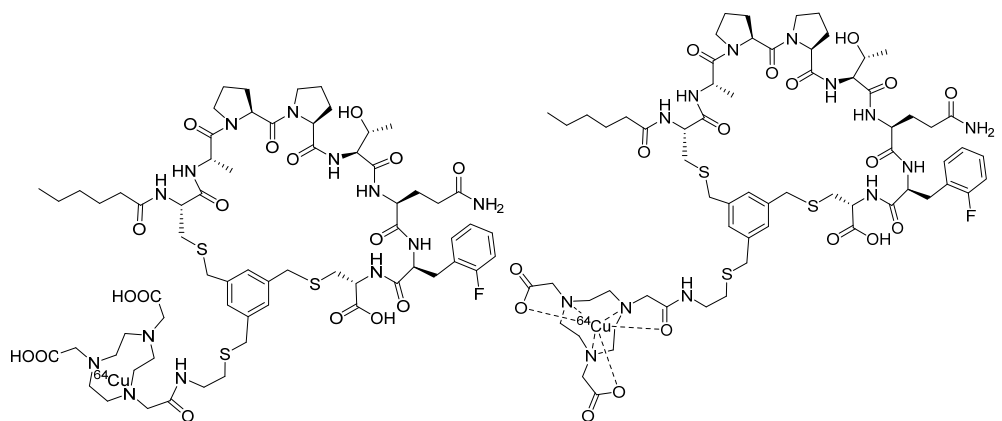
Hex-[Cys-(tMeBn(^{64}Cu -NOTA-AET))-Aib-Pro-((4R)-OH-Pro)-Thr-Gln-(2- CF_3 -Phe)-Cys]-OH,



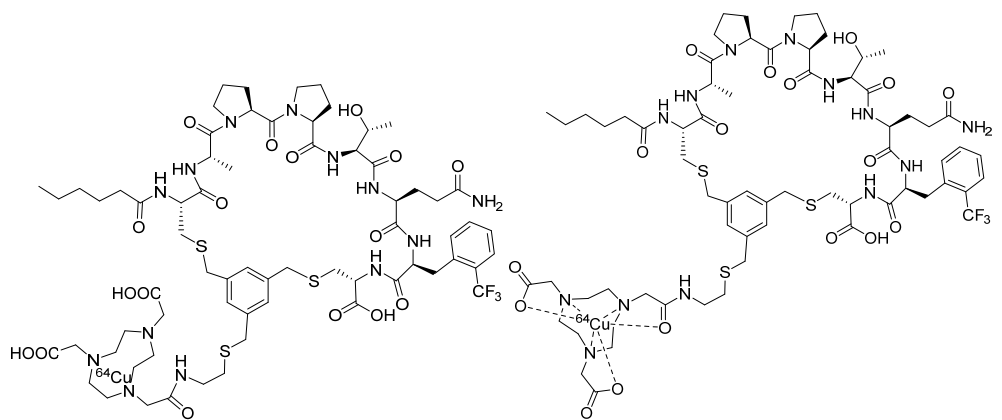
Hex-[Cys-(tMeBn(^{64}Cu -NOTA-AET))-Aib-Pro-((4R)-F-Pro)-Thr-Gln-(2-F-Phe)-Cys]-OH,



Hex-[Cys-(tMeBn(^{64}Cu -NOTA-AET))-Aib-Pro-((4R)-F-Pro)-Thr-Gln-(2- CF_3 -Phe)-Cys]-OH,



Hex-[Cys-(tMeBn(^{64}Cu -NOTA-AET))-Ala-Pro-Pro-Thr-Gln-(2-F-Phe)-Cys]-OH, and



Hex-[Cys-(tMeBn(^{64}Cu -NOTA-AET))-Ala-Pro-Pro-Thr-Gln-(2- CF_3 -Phe)-Cys]-OH.

[0047] The aforementioned compounds provided by the present disclosure may be used as medicaments.

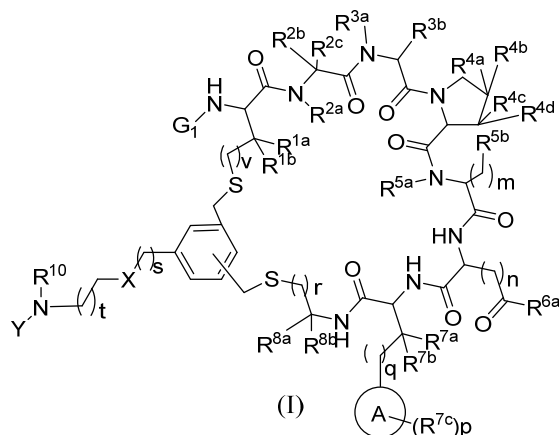
- [0048] Another aspect of the present disclosure provides a pharmaceutical composition comprising the aforementioned compound or the pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, diluents or excipients.
- [0049] Another aspect of the present disclosure provides a method for preparing the aforementioned compound or the pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition, which method comprises a step of complexing the compound or the pharmaceutically acceptable salt thereof with a nuclide.
- [0050] In another aspect, the present disclosure provides the use of the aforementioned compound or the pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition in the manufacture of a medicament for diagnosing or treating a disease, wherein the disease is a disease related to fibroblast activation protein (FAP).
- [0051] In an alternative embodiment, the disease related to fibroblast activation protein (FAP) is a disease associated with upregulation of fibroblast activation protein (FAP) expression.
- [0052] In an alternative embodiment, the disease is related to cells that exhibit upregulation of fibroblast activation protein (FAP) expression.
- [0053] In an alternative embodiment, the disease is related to a diseased tissue containing cells that exhibit upregulation of fibroblast activation protein (FAP) expression.
- [0054] In an alternative embodiment, the disease is a disease related to tumor-associated fibroblasts.
- [0055] In another aspect, the present disclosure further provides the use of the aforementioned compound or the pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition in the manufacture of a medicament for diagnosing or treating a disease, wherein the disease is a tumor or cancer.
- [0056] In another aspect, the present disclosure provides the use of the aforementioned compound or the pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition in the manufacture of a medicament for diagnosing or treating a disease, wherein the disease is selected from an inflammatory disease, a cardiovascular disease, an autoimmune disease and a fibrotic disease.
- [0057] In an alternative embodiment, the disease is an inflammatory disease, e.g., atherosclerosis, arthritis or rheumatoid arthritis.
- [0058] In an alternative embodiment, the disease is a cardiovascular disease.

- [0059] In an alternative embodiment, the disease is a cardiovascular disease related to atherosclerotic plaque.
- [0060] In an alternative embodiment, the disease is atherosclerotic lesion, acute coronary syndrome, myocardial infarction, thrombosis, or vascular occlusion caused by plaque rupture.
- [0061] In an alternative embodiment, the disease is a fibrotic disease, e.g., idiopathic pulmonary fibrosis, Crohn's disease and liver fibrosis.
- [0062] The tumor or cancer described in the present disclosure is selected from solid tumor, epithelioma, bladder cancer, breast cancer, cervical cancer, colorectal cancer, cholangiocarcinoma, endometrial cancer, esophageal cancer, gastric cancer, gastrointestinal stromal tumor, head and neck cancer, liver cancer, lung cancer, melanoma, mesothelioma, neuroendocrine tumor and carcinoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, salivary gland cancer, sarcoma, squamous cell carcinoma, glioma (e.g., human brain astrocytoma cells), and thyroid cancer (e.g., medullary thyroid carcinoma).
- [0063] In an alternative embodiment, the tumor or cancer described in the present disclosure is selected from breast cancer, colorectal cancer, cholangiocarcinoma, head and neck cancer, lung cancer, mesothelioma, neuroendocrine tumor and carcinoma, ovarian cancer, pancreatic cancer, prostate cancer, sarcoma and squamous cell carcinoma.
- [0064] The present disclosure further provides a method for diagnosing or treating a disease, which method comprises administering to a patient a diagnostically effective amount or a therapeutically effective amount of the aforementioned compound or the pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition, wherein the disease is selected from a disease related to fibroblast activation protein (FAP), a tumor or cancer, an inflammatory disease, a cardiovascular disease, an autoimmune disease and a fibrotic disease.
- [0065] The patient described in the present disclosure may be a mammal, e.g., human, dog, cat, horse and cow.
- [0066] In some embodiments, the method for diagnosing a disease using the compound provided by the present disclosure is imaging, wherein the imaging method is selected from scintigraphy, single-photon emission computed tomography (SPECT) and positron emission tomography (PET).
- [0067] In some embodiments, the unit dose of the pharmaceutical composition is 0.001 mg to 1000 mg.

[0068] In certain embodiments, the pharmaceutical composition comprises 0.01%-99.99% of the aforementioned compound or a pharmaceutically acceptable salt thereof, or an isotopic substitute thereof, on the basis of the total weight of the composition. In certain embodiments, the pharmaceutical composition comprises 0.1%-99.9% of the aforementioned compound or a pharmaceutically acceptable salt thereof, or an isotopic substitute thereof. In certain embodiments, the pharmaceutical composition comprises 0.5%-99.5% of the aforementioned compound or a pharmaceutically acceptable salt thereof, or an isotopic substitute thereof. In certain embodiments, the pharmaceutical composition comprises 1%-99% of the aforementioned compound or a pharmaceutically acceptable salt thereof, or an isotopic substitute thereof. In certain embodiments, the pharmaceutical composition comprises 2%-98% of the aforementioned compound or a pharmaceutically acceptable salt thereof, or an isotopic substitute thereof.

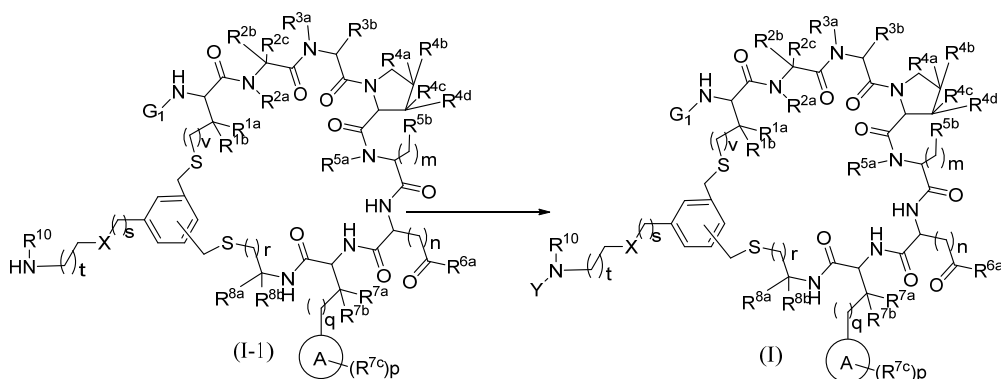
[0069] In certain embodiments, the pharmaceutical composition comprises 0.01%-99.99% of the pharmaceutically acceptable excipient, on the basis of the total weight of the composition. In certain embodiments, the pharmaceutical composition comprises 0.1%-99.9% of the pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition comprises 0.5%-99.5% of the pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition comprises 1%-99% of the pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition comprises 2%-98% of the pharmaceutically acceptable excipient.

[0070] The present disclosure further provides a method for preparing the aforementioned compound or a pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition, which method comprises a step of complexing the compound as shown in formula (I) or a pharmaceutically acceptable salt thereof with a nuclide,



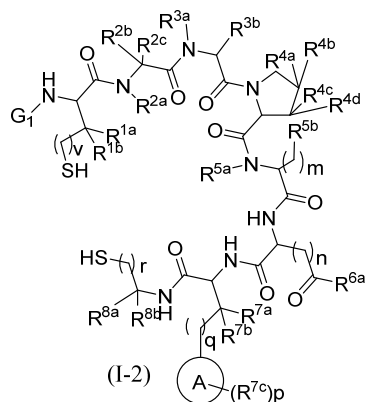
wherein the Y is a chelating agent, the chelating agent complexes a nuclide, and the R^{1a} , R^{1b} , v , G_1 , R^{2a} , R^{2b} , R^{2c} , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{5a} , R^{5b} , m , R^{6a} , n , R^{7a} , R^{7b} , q , ring A, R^{7c} , p , R^{8a} , R^{8b} , r , s , X , t and R^{10} are as defined in formula (I).

[0071] The present disclosure further provides a method for preparing the aforementioned compound or a pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition, which method comprises a step of reacting a compound as shown in formula (I-1) with a chelating agent,



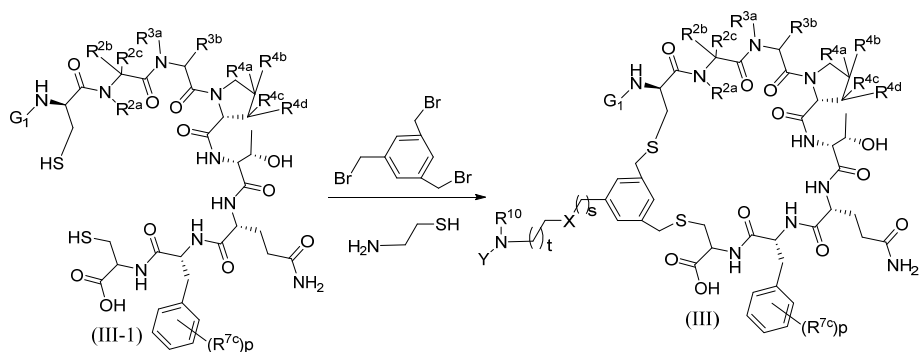
wherein the R^{1a} , R^{1b} , v , G_1 , R^{2a} , R^{2b} , R^{2c} , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{5a} , R^{5b} , m , R^{6a} , n , R^{7a} , R^{7b} , q , ring A, R^{7c} , p , R^{8a} , R^{8b} , r , s , X , t and R^{10} are as defined in formula (I).

[0072] The present disclosure provides a compound as shown in formula (I-2) or a pharmaceutically acceptable salt thereof,



wherein the R^{1a} , R^{1b} , v , G_1 , R^{2a} , R^{2b} , R^{2c} , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{5a} , R^{5b} , m , R^{6a} , n , R^{7a} , R^{7b} , q , ring A, R^{7c} , p , R^{8a} , R^{8b} and r are as defined in formula (I).

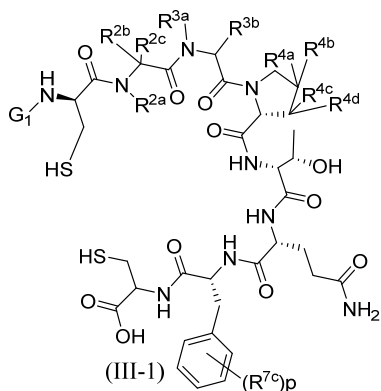
[0073] The present disclosure further provides a method for preparing the aforementioned compound as shown in formula (III) or a pharmaceutically acceptable salt thereof, which method comprises a step of reacting a compound as shown in formula (III-1) or a pharmaceutically acceptable salt thereof with 2-aminoethanethiol and 1,3,5-tris(bromomethyl)benzene,



wherein the Y is hydrogen; R^{10} is hydrogen; the t is 1; the X is a sulfur atom; the s is 1; the R^{2a} , R^{2b} , R^{2c} , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{7c} , p and G_1 are as defined in formula (III).

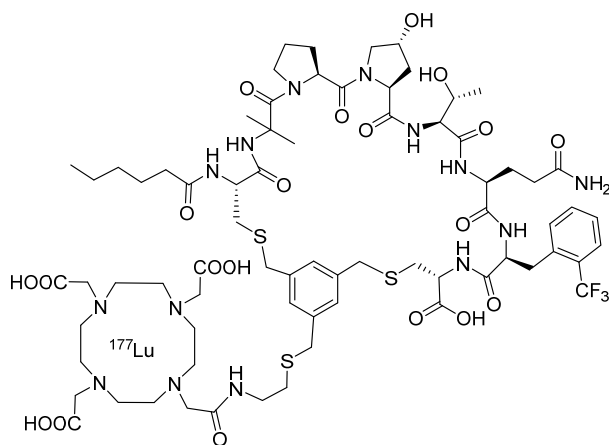
[0074] Alternatively, the method for preparing the aforementioned compound as shown in formula (I) or a pharmaceutically acceptable salt thereof provided by the present disclosure further comprises the step in the aforementioned method for preparing the compound as shown in formula (III) or a pharmaceutically acceptable salt thereof.

[0075] The present disclosure provides a compound as shown in formula (III-1) or a pharmaceutically acceptable salt thereof,

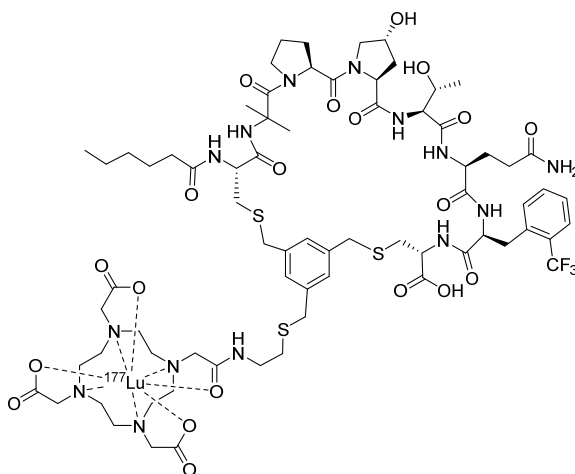


wherein the R^{2a} , R^{2b} , R^{2c} , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{7c} , p and G_1 are as defined in formula (III).

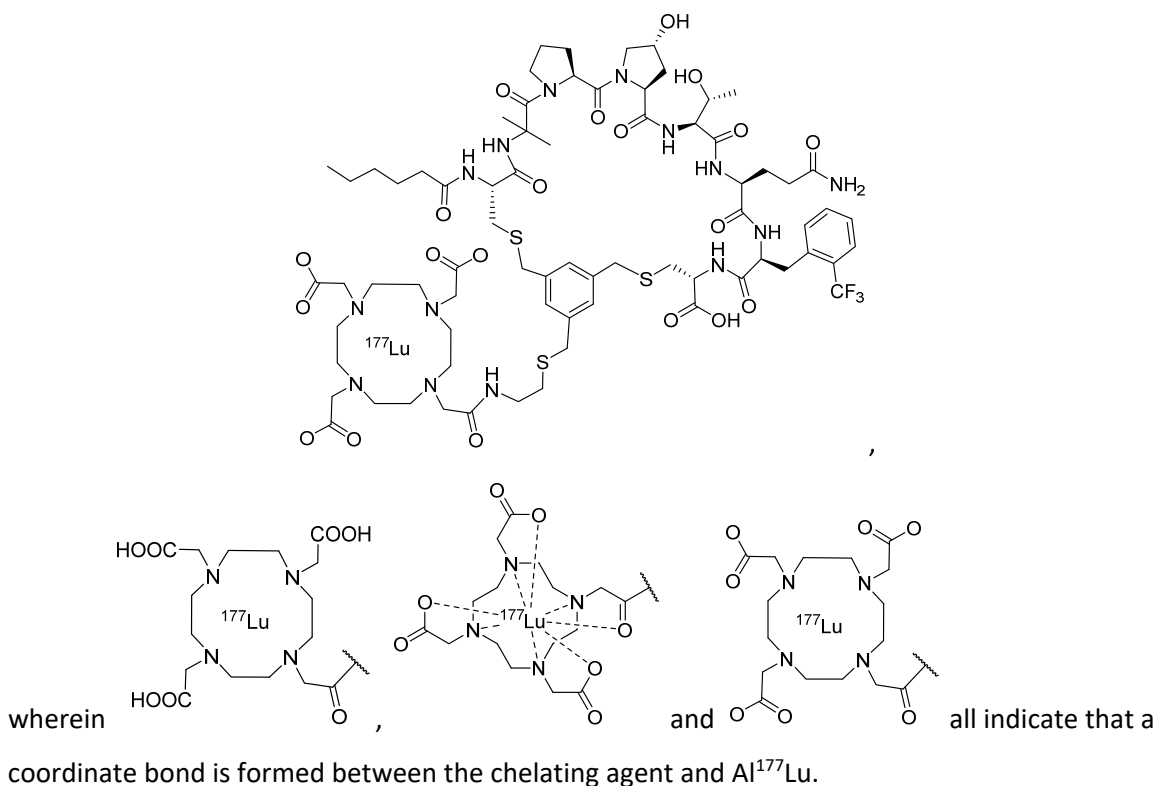
[0076] In the present disclosure, the representation of the attachment between the chelating agent and the radioactive element in the structure of the radiolabeled compound is not limited to one type. Taking ^{177}Lu -DOTA-09 as an example,



the structural formula may also be represented as:



or



[0077] The pharmaceutically acceptable salts of the compounds described in the present disclosure may be selected from inorganic salts or organic salts.

[0078] The compounds of the present disclosure may exist in specific geometric or stereoisomeric forms. The present disclosure contemplates all such compounds, including cis and trans isomers, (-)- and (+)-enantiomers, (*R*)- and (*S*)-enantiomers, diastereomers, (*D*)-isomers, (*L*)-isomers, and racemic mixtures and other mixtures thereof, such as enantiomerically or diastereomerically enriched mixtures, all of which fall within the scope of the present disclosure. Additional asymmetric carbon atoms may be present in substituents such as alkyl. All these isomers and mixtures thereof are encompassed within the scope of the present disclosure. The compound comprising asymmetric carbon atoms of the present disclosure can be isolated in optically active-pure or racemic forms. The optically active-pure form can be resolved from the racemic mixture or synthesized by using chiral raw materials or chiral reagents.

[0079] Optically active (*R*)- and (*S*)-isomers and *D* and *L* isomers can be prepared by using chiral synthesis or chiral reagents or other conventional techniques. If an enantiomer of a compound of the present disclosure is desired, it can be prepared by asymmetric synthesis or derivatization with a chiral auxiliary, wherein the resulting diastereomeric mixture is separated and the

auxiliary groups are cleaved to provide pure desired enantiomers. Alternatively, where the molecule contains a basic functional group (such as amino) or an acidic functional group (such as carboxyl), diastereomeric salts can be formed with an appropriate optically active acid or base, followed by resolution of the diastereomers using conventional methods well known in the art, and subsequent recovery of the pure enantiomers. In addition, separation of enantiomers and diastereomers is generally accomplished by using chromatography, which uses chiral stationary phases, optionally in combination with chemical derivatization methods (e.g., formation of carbamates from amines).

[0080] In the chemical structures of the compounds of the present disclosure, a bond "" represents an unspecified configuration; that is, if chiral isomers exist in the chemical structures, the bond "" may be "" or "", or both the configurations of "" and "" are included simultaneously. In the chemical structures of the compounds of the present disclosure, a bond "" does not specify a configuration; that is, the configuration for the bond "" can be an E configuration or a Z configuration, or includes both the E configuration and the Z configuration.

[0081] The compounds and intermediates of the present disclosure may also exist in different tautomeric forms, and all such forms are encompassed within the scope of the present disclosure.

[0082] The present disclosure further includes isotopically labeled compounds of the present disclosure that are identical to those recited herein, but have one or more atoms replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, iodine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{123}I , ^{125}I and ^{36}Cl , respectively.

[0083] Unless otherwise stated, when a position is specifically designated as deuterium (D), the position should be construed as having deuterium at an abundance at least 1000 times greater than the natural abundance of deuterium (which is 0.015%) (i.e., at least 10% incorporation of deuterium). The expression "having deuterium at an abundance greater than the natural abundance of deuterium" in the compounds in examples means having deuterium at an abundance at least 1000 times greater, at least 2000 times greater, at least 3000 times greater, at least 4000 times greater, at least 5000 times greater, at least 6000 times greater, or having

deuterium at a higher abundance. The present disclosure further includes various deuterated forms of the compound of formula (I). Each available hydrogen atom attached to a carbon atom can be independently replaced with a deuterium atom. Those skilled in the art can synthesize deuterated forms of the compound of formula (I) by referring to relevant literatures. The deuterated forms of the compound of formula (I) can be prepared using commercially available deuterated starting materials, or can be synthesized using deuterated reagents using conventional techniques. The deuterated reagents include, but are not limited to, deuterated borane, solution of trideuterated borane in tetrahydrofuran, deuterated lithium aluminum hydride, deuterated iodoethane and deuterated iodomethane.

Description of Terminology

[0084] The term "optionally" or "optional" means that the event or circumstance subsequently described may but need not occur, and the description includes the case where the event or circumstance occurs or does not occur. For example, the term " C_{1-6} alkyl optionally substituted with halogen or cyano" means that halogen or cyano may but need not be present. The description includes the case where the alkyl is substituted with halogen or cyano and the case where the alkyl is not substituted with halogen or cyano.

[0085] The term "pharmaceutical composition" denotes a mixture containing one or more compounds described herein or physiologically and pharmaceutically acceptable salts or prodrugs thereof and other chemical components, as well as other components, such as physiologically and pharmaceutically acceptable carriers and excipients. The purpose of pharmaceutical compositions is to facilitate administration to living organisms and facilitate the absorption of active ingredients to exert biological activity.

[0086] The term "pharmaceutically acceptable excipient" includes, but is not limited to, any adjuvant, carrier, glidant, sweetener, diluent, preservative, dye/colorant, flavoring agent, surfactant, wetting agent, dispersant, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier that has been approved by the U.S. Food and Drug Administration (FDA) as acceptable for use in humans or livestock animals.

[0087] The term "effective amount" or "therapeutically effective amount" described in the present disclosure includes an amount sufficient to ameliorate or prevent a symptom or disorder of a medical disorder. An effective amount also means an amount sufficient to allow or facilitate diagnosis. An effective amount for a particular patient or veterinary subject may vary depending on factors such as the condition to be treated, the general health of the patient, the

method, route and dose of administration, and the severity of side effects. An effective amount may be the maximum dosage or dosing regimen that avoids significant side effects or toxic effects.

[0088] The term "alkyl" refers to a saturated aliphatic hydrocarbon group. Non-limiting examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl and various branched-chain isomers thereof, etc.

[0089] The term "cycloalkyl" refers to a saturated or partially unsaturated monocyclic or polycyclic hydrocarbon. The cycloalkyl ring comprises 3 to 20 carbon atoms, preferably 3 to 6 carbon atoms. Non-limiting examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, etc.

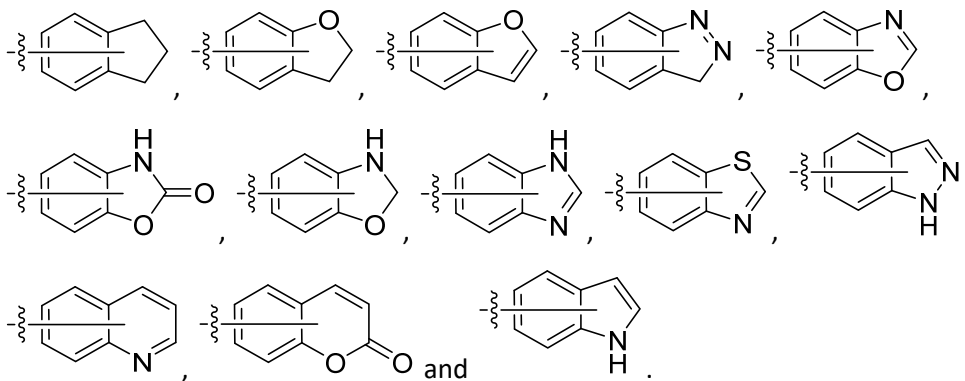
[0090] The term "heterocycloalkyl" refers to a saturated or partially unsaturated monocyclic or polycyclic hydrocarbon, which comprises 3 to 20 ring atoms, wherein one or more of the ring atoms are heteroatoms selected from nitrogen, oxygen or S(O)_m (wherein m is an integer from 0 to 2), but excluding ring moieties of -O-O-, -O-S- or -S-S-, and the remaining ring atoms are carbon.

[0091] The term "alkoxy" refers to -O-(alkyl), wherein the alkyl is as defined above. Non-limiting examples of alkoxy include: methoxy, ethoxy, propoxy and butoxy.

[0092] The term "alkylene" refers to the moiety remaining after removal of two hydrogen atoms from an alkane molecule, including linear and branched -ylene groups comprising 1 to 20 carbon atoms. Non-limiting examples include methylene (-CH₂-) and ethylene (e.g., -CH₂CH₂- or -CH(CH₃)-).

[0093] The term "aryl" refers to a 6- to 14-membered all-carbon monocyclic or fused polycyclic (i.e., rings sharing an adjacent pair of carbon atoms) group having a conjugated π electron system, preferably 6- to 12-membered aryl, e.g., phenyl and naphthyl.

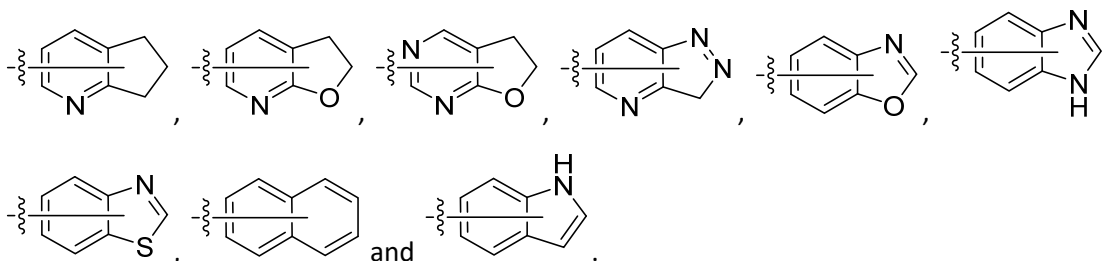
[0094] The aryl ring may be fused to a heteroaryl, heterocycloalkyl or cycloalkyl ring, wherein the ring attached to the parent structure is an aryl ring, and the non-limiting examples thereof include:



[0095] The term "heteroaryl" refers to a heteroaromatic system containing 1 to 4 heteroatoms and 5 to 14 ring atoms, wherein the heteroatoms are selected from oxygen, sulfur and nitrogen. The heteroaryl is preferably 6- to 12-membered, and more preferably 5- to 6-membered. Non-limiting examples thereof include: imidazolyl, furyl, thienyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyrrolyl, tetrazolyl, pyridyl, pyrimidinyl, thiadiazolyl, pyrazinyl, triazolyl, indazolyl,

benzimidazolyl, , , , etc.

[0096] The heteroaryl ring may be fused to an aryl, heterocycloalkyl or cycloalkyl ring, wherein the ring attached to the parent structure is a heteroaryl ring, and the non-limiting examples thereof include:



[0097] The term "hydroxyl" refers to -OH.

[0098] The term "halogen" refers to fluorine, chlorine, bromine or iodine.

[0099] The term "cyano" refers to -CN.

[0100] The term "amino" refers to -NH₂.

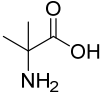
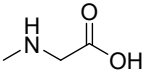
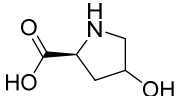
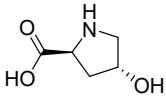
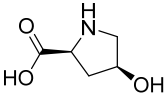
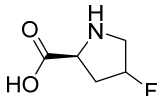
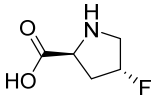
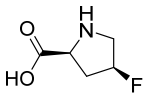
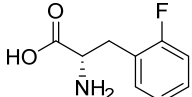
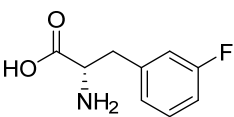
[0101] The term "nitro" refers to -NO₂.

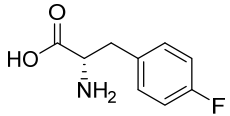
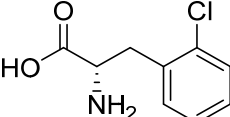
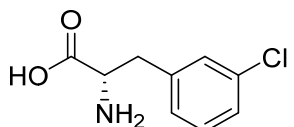
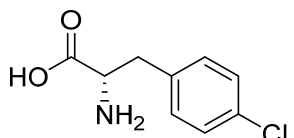
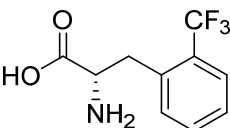
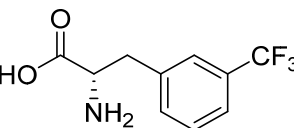
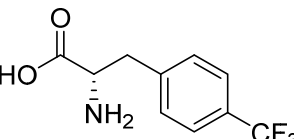
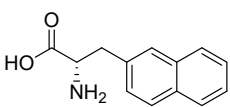
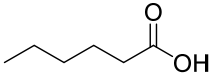
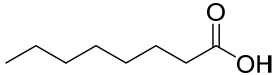
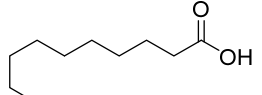
[0102] The term "oxo" refers to =O.

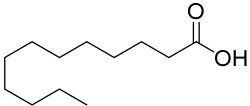
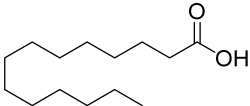
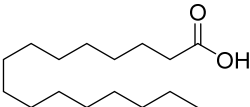
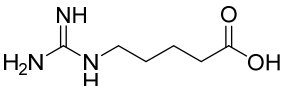
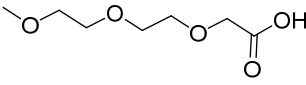
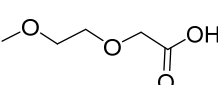
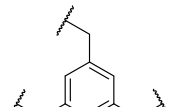
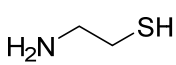
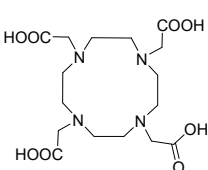
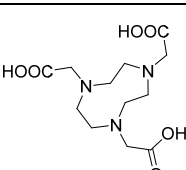
[0103] The term "substituted" refers to one or more hydrogen atoms in the group, preferably at most 5, more preferably 1 to 3 hydrogen atoms each independently substituted with a

corresponding number of substituents. When the substituent is a ketone or oxo (i.e., =O), two (2) hydrogens on the atom are replaced.

Abbreviations, names and structures for unnatural amino acids and other chemical moieties

Abbreviation	Name	Structure
Aib	2-Aminoisobutyric acid	
Sar	Sarcosine	
4-OH-Pro	4-Hydroxy-L-proline	
(4R)-OH-Pro	(2S,4R)-4-Hydroxypyrrolidine-2-carboxylic acid	
(4S)-OH-Pro	(2S,4S)-4-Hydroxypyrrolidine-2-carboxylic acid	
4-F-Pro	(2S)-4-Fluoropyrrolidine-2-carboxylic acid	
(4R)-F-Pro	(2S,4R)-4-Fluoropyrrolidine-2-carboxylic acid	
(4S)-F-Pro	(2S,4S)-4-Fluoropyrrolidine-2-carboxylic acid	
2-F-Phe	L-2-Fluorophenylalanine	
3-F-Phe	L-3-Fluorophenylalanine	

4-F-Phe	L-4-Fluorophenylalanine	
2-Cl-Phe	L-2-Chlorophenylalanine	
3-Cl-Phe	L-3-Chlorophenylalanine	
4-Cl-Phe	L-4-Chlorophenylalanine	
2-CF ₃ -Phe	L-2-Trifluoromethylphenylalanine	
3-CF ₃ -Phe	L-3-Trifluoromethylphenylalanine	
4-CF ₃ -Phe	L-4-Trifluoromethylphenylalanine	
2-Nal	3-(2-Naphthyl)-L-alanine	
Hex	Hexanoic acid	
Oct	Octanoic acid	
Dec	Decanoic acid	

Dod	Dodecanoic acid	
Tet	Tetradecanoic acid	
Pal	Palmitic acid	
5-guanidine Valy	5-Guanidinopentanoic acid	
2-[2-(2-Methoxyethoxy)ethoxy]-Ace	2-[2-(2-Methoxyethoxy)ethoxy]acetic acid	
2-(2-Methoxyethoxy)-Ace	2-(2-Methoxyethoxy) acetic acid	
tMeBn	1,3,5-Trimethylbenzylidene	
AET	2-Aminoethanethiol	
DOTA	1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid	
NOTA	1,4,7-Triazacyclononane-1,4,7-triacetic acid	

Brief Description of the Drawings

[0104] FIG. 1 shows the uptake of the compounds of the present disclosure in tumor and various tissues.

- [0105] FIG. 2 shows the tumor/kidney uptake ratio curves of the compounds of the present disclosure and ^{68}Ga -FAP-2286 (** indicates statistically significant difference).
- [0106] FIG. 3 shows the tumor uptake of the compounds of the present disclosure and ^{68}Ga -FAP-2286 at different time points.
- [0107] FIG. 4 shows the tumor/kidney uptake ratios of the compounds of the present disclosure and ^{68}Ga -FAP-2286 at different time points.
- [0108] FIG. 5 shows the tumor uptake of the compounds of the present disclosure and ^{177}Lu -FAP-2286 at different time points.
- [0109] FIG. 6 shows the tumor/kidney uptake ratios of the compounds of the present disclosure and ^{177}Lu -FAP-2286 at different time points.
- [0110] FIG. 7 shows the tumor uptake of the compounds of the present disclosure and ^{68}Ga -FAP-2286 at different time points.
- [0111] FIG. 8 shows the tumor/kidney uptake ratios of the compounds of the present disclosure and ^{68}Ga -FAP-2286 at different time points.
- [0112] FIG. 9 shows the tumor uptake of the compounds of the present disclosure and Al^{18}F -NOTA-2286 at different time points.
- [0113] FIG. 10 shows the tumor/kidney uptake of the compounds of the present disclosure and Al^{18}F -NOTA-2286 at different time points.
- [0114] FIG. 11 shows the tumor growth curves of U-87 MG model mice after administration of ^{177}Lu -DOTA-09 at different radioactive doses (n = 8, mean $\pm$ standard deviation).
- [0115] FIG. 12 shows the changes in body weight of mice during administration of ^{177}Lu -DOTA-09 at different radioactive doses (n = 8, mean $\pm$ standard deviation).
- [0116] FIG. 13 shows the survival time of U-87 MG model mice after administration of ^{177}Lu -DOTA-09 at different radioactive doses.

Detailed Description of Embodiments

Example

- [0117] The following synthetic descriptions or specific examples are for illustrative purposes only and shall not be construed as limiting, in any way, the preparation of the compounds of the present disclosure by other methods.
- [0118] The chromatographic conditions for HPLC/MS analysis are as follows:

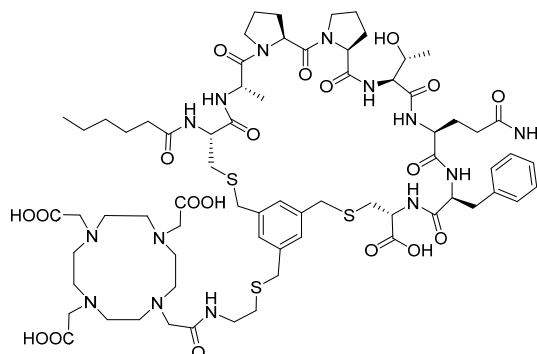
10 µl of each sample is injected automatically. Mobile phase: A: 0.1% formic acid in water, B: 0.1% formic acid in acetonitrile. Flow rate: 1.5 ml/min. Gradient: from 10% B to 95% B in 0-6 min, from 95% B to 100% B in 6-8 min, from 100% B to 10% B in 8-8.10 min, and 10% B maintained in 8.10-11.0 min.

- [0119] Device model: Thermo Scientific ULTIMATE3000 ISQEM.
- [0120] Chromatographic column: Eclipse Plus C18, 3.5 nm, 4.6 × 100 mm.
- [0121] UV detection wavelength: 220 nm.
- [0122] The purity data of the compounds is obtained by manual integration, and the molecular weight $[M+1]^+$ or $[M-1]^-$ is collected.
- [0123] The chromatographic conditions for preparative liquid chromatography are as follows:
Mobile phase: A: 0.1% trifluoroacetic acid in water, B: 0.1% trifluoroacetic acid in acetonitrile.
Flow rate: 60 ml/min. Gradient: from 25% B to 45% B in 0-20.0 min, from 45%B to 70% B in 20.0-30.0 min, and 70% B maintained in 30.0-40.0 min.
- [0124] Device model: Agilent AGILENT1260II.
- [0125] Chromatographic column: HPLCONE, 5.0 µm, 30 × 250 mm.
- [0126] UV detection wavelength: 220 nm.
- [0127] The chromatographic conditions for radio-HPLC analysis are as follows:
5-20 µl of each sample is injected automatically. Mobile phase: A: 0.1% formic acid in water, B: 0.1% formic acid in acetonitrile. Flow rate: 0.8 ml/min. Gradient: from 10% B to 50% B in 0-24 min, from 50% B to 10% B in 24-25 min, and 10% B maintained in 25-35 min.
- [0128] Device model: Thermo Scientific ULTIMATE3000 ISQEM.
- [0129] Chromatographic column: XBridge C18 3.5 µm, 4.6*150 mm.
- [0130] UV detection wavelength: 225 nm.
- [0131] Radiation detector: 30000 cps/V.
- [0132] The radiochemical purity is obtained by manual integration.
- [0133] Abbreviations and corresponding full names used in the examples:

Abbreviation	Full name
Fmoc-Cys(Trt)-OH	N-Fluorenylmethoxycarbonyl-S-trityl-L-cysteine
Fmoc-Cys(Mmt)-OH	N-Fluorenylmethoxycarbonyl-S-(4-methoxytrityl)-L-cysteine
DMF	N,N-Dimethylformamide
DCM	Dichloromethane

DIPEA	N,N-Diisopropylethylamine
HOBt	1-Hydroxybenzotriazole
DIC	N,N'-Diisopropylcarbodiimide
DMAP	4-Dimethylaminopyridine
TFA	Trifluoroacetic acid
DTT	Dithiothreitol
Tips	Triisopropylsilane
DOTA	1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTA-NHS	2,2',2''-(10-(2-((2,5-Dioxopyrrolidin-1-yl)oxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid
NOTA	1,4,7-Triazacyclononane-1,4,7-triacetic acid
NOTA-NHS	2,2'-(7-(2-((2,5-dioxopyrrolidin-1-yl)oxy)-2-oxoethyl)-1,4,7-triazacyclononane-1,4-diyl)diacetic acid

Example 1. Preparation of DOTA-01



[0134] can be performed by either of two solid-phase synthetic schemes.

Scheme I

a. Loading of first amino acid onto solid-phase support

[0135] CTC resin (degree of substitution = 1.09 mmol/g) was selected as a solid-phase support.

The resin was swollen with DMF for 1 h. Subsequently, an amino acid solution was prepared: 3.00 eq of Fmoc-Cys(Trt)-OH and 6.00 eq of DIPEA were dissolved in DMF (8 times the mass of the resin). After uniform stirring, the solution was reacted with the resin for 3 h. The resin was washed, and then capped with methanol and DIPEA. The capped resin was washed with DMF (8 times the mass of the resin) 4 to 6 times, and then washed and shrunk sequentially with

isopropyl ether, DCM and isopropyl ether (each 8 times the mass of the resin). After drying, the degree of substitution was measured for later use.

b. Amino acid coupling

[0136] In the synthesis, each amino acid was coupled using the general coupling method described below.

[0137] The Fmoc-Cys(Trt)-CTC resin obtained in the previous step was swollen with DMF (8 times the mass of the resin) for 1 h. The Fmoc protecting group was removed twice with a 20% piperidine/DMF solution (8 times the mass of the resin) (first time: 5 min, and second time: 20 min). After the deprotection was completed, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. The activated amino acid solution was prepared: 3.0 eq of amino acid and 3.0 eq of HOBT were dissolved in 8 Vol of DMF. 3.0 eq of DIC was added for activation for 2-5 min, and then the reaction was performed. After the reaction was completed and the deprotection was finished, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. After the coupling of the linear peptide resin was completed using the above method, the resin was washed, shrunk, and dried for later use.

c. Cleavage

[0138] The obtained peptide resin was cleaved using a cleavage solution with a ratio of TFA/DTT/H₂O/Tips of 94/2.5/2.5/1, wherein the cleavage solution was added in an amount 8 to 10 times the mass of the peptide resin. After 2 h of cleavage, filtration was performed to obtain the filtrate. The obtained filtrate was poured into isopropyl ether (80 to 100 times the mass of the peptide resin) for crystallization. The resulting product was filtered, rinsed with isopropyl ether, and dried to obtain a linear crude peptide.

d. Cyclization

[0139] The obtained linear crude peptide was dissolved in a mixture of acetonitrile/purified water = 1/1 (400 times the mass of the crude peptide). First, 7.2 eq of DIPEA was added, followed by the addition of 1.2 eq of 1,3,5-tris(bromomethyl)benzene. After the reaction was completed, 3.6 eq of mercaptoethylamine was directly added to the system. After the reaction was completed, purification was performed by preparative liquid chromatography, followed by lyophilization to obtain a cyclic peptide intermediate.

e. Conjugation with DOTA

[0140] The obtained lyophilized powder of the cyclic peptide was dissolved in DMF (10 times the mass of the lyophilized powder). 4.0 eq of DIPEA and 2.0 eq of DOTA-NHS were added. The

reaction was monitored by LCMS until completion. Purification was performed by preparative liquid chromatography, followed by lyophilization to obtain the target product. Purity: 98.2%, MS m/z (ESI): 1540.72 $[M-H]^-$.

Scheme II

1: Loading of first amino acid onto solid-phase support

[0141] Wang resin (degree of substitution = 1.08 mmol/g) was selected as a solid-phase support. The resin was swollen with DMF (8 times the mass of the resin) for 1 h. Subsequently, an amino acid solution was prepared: 3.00 eq of Fmoc-Cys(Mmt)-OH and 3.00 eq of HOBT were dissolved in DMF (8 times the mass of the resin). After uniform stirring, 3.00 eq of DIC was added for amino acid activation. After the activation was completed, the solution was added to the swollen resin. Bubbling was performed until uniform, 0.3 eq of DMAP was then added for catalysis. The reaction was performed for 3 hours. After the reaction was completed, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. 3.00 eq of acetic anhydride and 6.00 DIPEA were dissolved in DMF (8 times the mass of the resin) for capping for 1 h. The capped resin was washed with DMF (8 times the mass of the resin) 4 to 6 times, and then shrunk with isopropyl ether, DCM and isopropyl ether (each 8 times the mass of the resin). After drying, the degree of substitution was measured for later use.

2: Amino acid coupling

[0142] In the synthesis, each amino acid was coupled using the general coupling method described below.

[0143] The Fmoc-Cys(Mmt)-Wang resin obtained in the previous step was swollen with DMF (8 times the mass of the resin) for 1 h. The Fmoc protecting group was removed twice with a 20% piperidine/DMF solution (8 times the mass of the resin) (first time: 5 min, and second time: 20 min). After the deprotection was completed, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. The activated amino acid solution was prepared: 3.0 eq of amino acid and 3.0 eq of HOBT were dissolved in 8 Vol of DMF. 3.0 eq of DIC was added for activation for 2-5 min, and then the reaction was performed. After the reaction was completed and the deprotection was finished, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. After the coupling of the linear peptide resin was completed using the above method, the resin was washed, shrunk, and dried for later use.

3: Solid-phase cyclization

[0144] The side-chain protecting group Mmt for Cys was removed using 1% TFA/DCM (8 times the mass of the resin). The resin was washed with DMF (8 times the mass of the resin) 4 to 6 times, followed by addition of DMF (8 times the mass of the resin) as a solvent. 7.2 eq of DIPEA was added, followed by the addition of 1.2 eq of 1,3,5-tris(bromomethyl)benzene. After the cyclization was performed, 3.6 eq of mercaptoethylamine was directly added to the system. After the reaction was completed, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times.

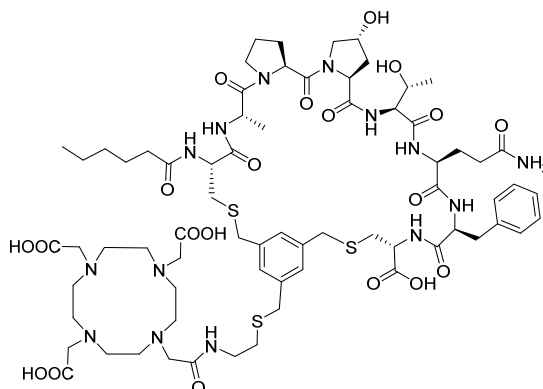
4: Conjugation with DOTA

[0145] 4.0 eq of DIPEA and 2.0 eq of DOTA-NHS were dissolved in DMF (8 times the mass of the resin) to prepare a reaction solution. The reaction solution was added to a solid-phase column for reaction. After the reaction was completed, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times, and then shrunk with isopropyl ether, DCM and isopropyl ether (each 8 times the mass of the resin). The resin was dried for later use.

5: Cleavage

[0146] The obtained peptide resin was cleaved using a cleavage solution with a ratio of TFA/DTT/H₂O/Tips of 94/2.5/2.5/1, wherein the cleavage solution was added in an amount 8 to 10 times the mass of the peptide resin. After 2 h of cleavage, filtration was performed to obtain the filtrate. The obtained filtrate was poured into isopropyl ether (80 to 100 times the mass of the peptide resin) for crystallization. The resulting product was filtered, rinsed with isopropyl ether, and dried to obtain a linear crude peptide. Purification was performed by preparative liquid chromatography, followed by lyophilization to obtain a lyophilized powder. Purity: 96.7%, MS m/z (ESI): 1540.72 [M-H]⁻.

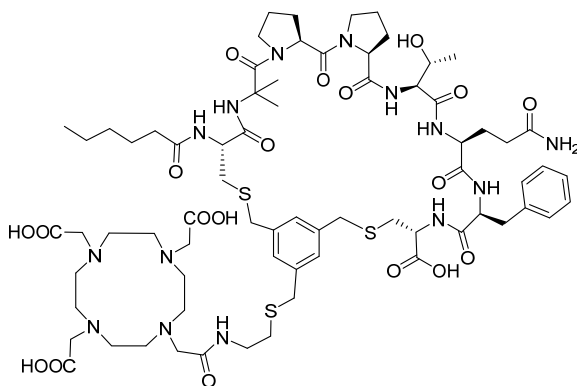
Example 2. Preparation of DOTA-02



[0147] The target compound DOTA-02 was obtained in a manner similar to that of scheme I in

Example 1. 97.7%, MS m/z (ESI): 1556.34 [M-H]⁻.

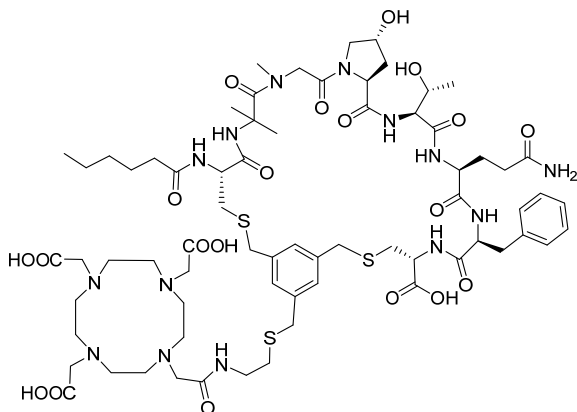
Example 3. Preparation of DOTA-03



[0148] The target compound DOTA-03 was obtained in a manner similar to that of scheme I in

Example 1. 96.3%, MS m/z (ESI): 1555.08 [M+H]⁺.

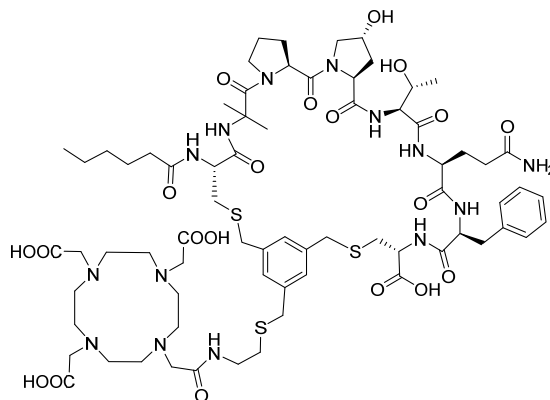
Example 4. Preparation of DOTA-04



[0149] The target compound DOTA-04 was obtained in a manner similar to that of scheme I in

Example 1. 95.2%, MS m/z (ESI): 1545.01 [M+H]⁺.

Example 5. Preparation of DOTA-05



[0150] The target compound DOTA-05 was obtained in a manner similar to that of scheme I in Example 1;

a. Loading of first amino acid onto solid-phase support

[0151] CTC resin (degree of substitution = 1.09mmol/g) was selected as a solid-phase support. The resin was swollen with DMF for 1 h. Subsequently, an amino acid solution was prepared: 3.00 eq of Fmoc-Cys(Trt)-OH and 6.00 eq of DIPEA were dissolved in DMF (8 times the mass of the resin). After uniform stirring, the solution was reacted with the resin for 3 h. The resin was washed, and then capped with methanol and DIPEA. The capped resin was washed with DMF (8 times the mass of the resin) 4 to 6 times, and then washed and shrunk sequentially with isopropyl ether, DCM and isopropyl ether (each 8 times the mass of the resin). After drying, the degree of substitution was measured for later use.

b. Amino acid coupling

[0152] In the synthesis, each amino acid was coupled using the general coupling method described below.

[0153] The Fmoc-Cys(Trt)-CTC resin obtained in the previous step was swollen in DMF (8 times the mass of the resin) for 1 h. The Fmoc protecting group was removed twice with a 20% piperidine/DMF solution (8 times the mass of the resin) (first time: 5 min, and second time: 20 min). After the deprotection was completed, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. The activated amino acid solution was prepared: 3.0 eq of amino acid and 3.0 eq of HBTU were dissolved in 8 Vol of DMF. 3.0 eq of DEPEA was added for activation for 2-5 min, and then the reaction was performed. After the reaction was completed and the deprotection was finished, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. After the coupling of the linear peptide resin was completed using the above method, the resin was washed, shrunk, and dried for later use.

c. Cleavage

[0154] The obtained peptide resin was cleaved using a cleavage solution with a ratio of TFA/DTT/H₂O/Tips of 94/2.5/2.5/1, wherein the cleavage solution was added in an amount 8 to 10 times the mass of the peptide resin. After 2 h of cleavage, filtration was performed to obtain the filtrate. The obtained filtrate was poured into isopropyl ether (80 to 100 times the mass of the peptide resin) for crystallization. The resulting product was filtered, rinsed with isopropyl ether, and dried to obtain a linear crude peptide.

d. Cyclization

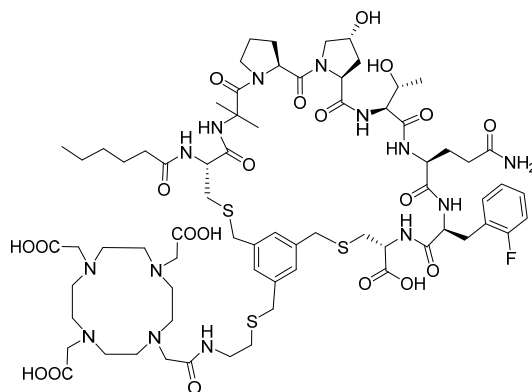
[0155] The obtained linear crude peptide was dissolved in a mixture of acetonitrile/purified water=1/1 (400 times the mass of the crude peptide). First, 7.2 eq of DIPEA was added, followed by the addition of 1.2 eq of 1,3,5-tris(bromomethyl)benzene. After the reaction was completed, 3.6 eq of mercaptoethylamine was directly added to the system. After the reaction was completed, purification was performed by preparative liquid chromatography, followed by lyophilization to obtain a cyclic peptide intermediate.

e. Conjugation with DOTA

[0156] The obtained lyophilized powder of the cyclic peptide was dissolved in DMF (10 times the mass of the lyophilized powder). 4.0 eq of DIPEA and 2.0 eq of DOTA-NHS were added. The reaction was monitored by LCMS until completion. Purification was performed by preparative liquid chromatography, followed by lyophilization to obtain the target product.

[0157] Purity: 97.8%, MS m/z (ESI): 1571.10 [M+H]⁺.

Example 6. Preparation of DOTA-06



a. Loading of first amino acid onto solid-phase support

[0158] CTC resin (degree of substitution = 1.09mmol/g) was selected as a solid-phase support. The resin was swollen with DMF for 1 h. Subsequently, an amino acid solution was prepared: 3.00 eq of Fmoc-Cys(Trt)-OH and 6.00 eq of DIPEA were dissolved in DMF (8 times the mass of the resin). After uniform stirring, the solution was reacted with the resin for 3 h. The resin was washed, and then capped with methanol and DIPEA. The capped resin was washed with DMF (8 times the mass of the resin) 4 to 6 times, and then washed and shrunk sequentially with isopropyl ether, DCM and isopropyl ether (each 8 times the mass of the resin). After drying, the degree of substitution was measured for later use.

b. Amino acid coupling

[0159] In the synthesis, each amino acid was coupled using the general coupling method described below.

[0160] The Fmoc-Cys(Trt)-CTC resin obtained in the previous step was swollen with DMF (8 times the mass of the resin) for 1 h. The Fmoc protecting group was removed twice with a 20% piperidine/DMF solution (8 times the mass of the resin) (first time: 5 min, and second time: 20 min). After the deprotection was completed, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. The activated amino acid solution was prepared: 3.0 eq of amino acid and 3.0 eq of HBTU were dissolved in 8 Vol of DMF. 3.0 eq of DIPEA was added for activation for 2-5 min, and then the reaction was performed. After the reaction was completed and the deprotection was finished, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. After the coupling of the linear peptide resin was completed using the above method, the resin was washed, shrunk, and dried for later use.

c. Cleavage

[0161] The obtained peptide resin was cleaved using a cleavage solution with a ratio of TFA/DTT/H₂O/Tips of 94/2.5/2.5/1, wherein the cleavage solution was added in an amount 8 to 10 times the mass of the peptide resin. After 2 h of cleavage, filtration was performed to obtain the filtrate. The obtained filtrate was poured into isopropyl ether (80 to 100 times the mass of the peptide resin) for crystallization. The resulting product was filtered, rinsed with isopropyl ether, and dried to obtain a linear crude peptide.

d. Cyclization

[0162] The obtained linear crude peptide was dissolved in a mixture of acetonitrile/purified water = 1/1 (400 times the mass of the crude peptide). First, 7.2 eq of DIPEA was added, followed by the addition of 1.2 eq of 1,3,5-tris(bromomethyl)benzene. After the reaction was completed, 3.6 eq of mercaptoethylamine was directly added to the system. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was purified by preparative liquid chromatography and lyophilized to obtain a cyclic peptide intermediate.

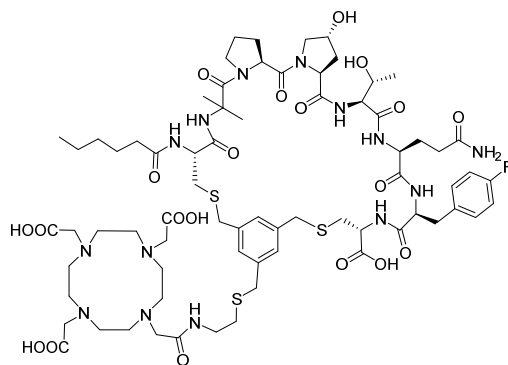
e. Conjugation with DOTA

[0163] The obtained lyophilized powder of the cyclic peptide was dissolved in DMF (10 times the mass of the lyophilized powder). 4.0 eq of DIPEA and 2.0 eq of DOTA-NHS were added. The reaction was monitored by LCMS until completion. Purification was performed by preparative liquid chromatography, followed by lyophilization to obtain the target product.

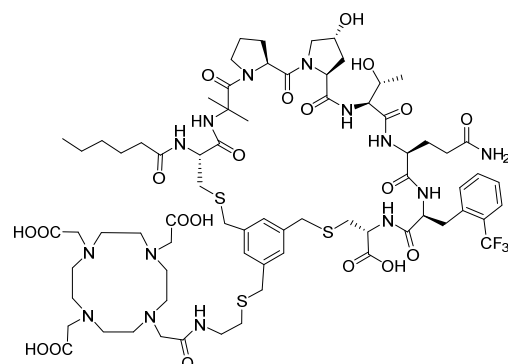
[0164] Purity: 96.9%, MS m/z (ESI): 1587.88 [M-H]⁻.

CCCCCCC(=O)N[C@@H](C)C(=O)N[C@@H](CS[C@@H](Cc1ccc(CS[C@@H](Cc2ccc(cc2)C(=O)O)cc2)cc1)C(=O)O)C(=O)O)C(=O)O)N1CCN(CC1)C(=O)N[C@@H](C)C(=O)N2C[C@H](O)[C@@H](C(=O)N[C@@H](Cc3ccc(cc3)C(=O)O)C(=O)O)C(=O)N2C[C@H](O)[C@@H](C(=O)N[C@@H](Cc4ccc(cc4)C(=O)O)C(=O)O)C(=O)N2C[C@H](O)[C@@H](C(=O)N[C@@H](Cc5ccc(cc5)C(=O)O)C(=O)O)C(=O)N2C[C@H](O)[C@@H](C(=O)N[C@@H](Cc6ccc(cc6)C(=O)O)C(=O)O)C(=O)N2

Example 8. Preparation of DOTA-08



Example 9. Preparation of DOTA-09



[0167] CTC resin (degree of substitution = 1.09mmol/g) was selected as a solid-phase support. The resin was swollen with DMF for 1 h. Subsequently, an amino acid solution was prepared:

3.00 eq of Fmoc-Cys(Trt)-OH and 6.00 eq of DIPEA were dissolved in DMF (8 times the mass of the resin). After uniform stirring, the solution was reacted with the resin for 3 h. The resin was washed, and then capped with methanol and DIPEA. The capped resin was washed with DMF (8 times the mass of the resin) 4 to 6 times, and then washed and shrunk sequentially with isopropyl ether, DCM and isopropyl ether (each 8 times the mass of the resin). After drying, the degree of substitution was measured for later use.

b. Amino acid coupling

[0168] In the synthesis, each amino acid was coupled using the general coupling method described below.

[0169] The Fmoc-Cys(Trt)-CTC resin obtained in the previous step was swollen with DMF (8 times the mass of the resin) for 1 h. The Fmoc protecting group was removed twice with a 20% piperidine/DMF solution (8 times the mass of the resin) (first time: 5 min, and second time: 20 min). After the deprotection was completed, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. The activated amino acid solution was prepared: 3.0 eq of amino acid and 3.0 eq of HBTU were dissolved in 8 Vol of DMF. 3.0 eq of DIPEA was added for activation for 2-5 min, and then the reaction was performed. After the reaction was completed and the deprotection was finished, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. After the coupling of the linear peptide resin was completed using the above method, the resin was washed, shrunk, and dried for later use.

c. Cleavage

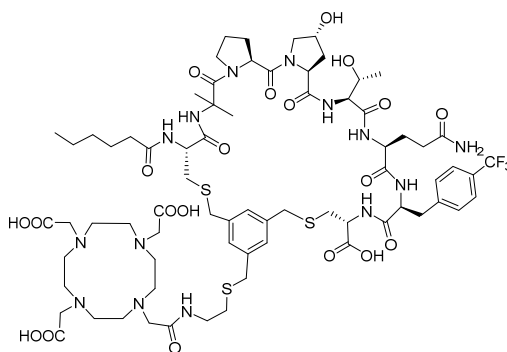
[0170] The obtained peptide resin was cleaved using a cleavage solution with a ratio of TFA/DTT/H₂O/Tips of 94/2.5/2.5/1, wherein the cleavage solution was added in an amount 8 to 10 times the mass of the peptide resin. After 2 h of cleavage, filtration was performed to obtain the filtrate. The obtained filtrate was poured into isopropyl ether (80 to 100 times the mass of the peptide resin) for crystallization. The resulting product was filtered, rinsed with isopropyl ether, and dried to obtain a linear crude peptide.

d. Cyclization

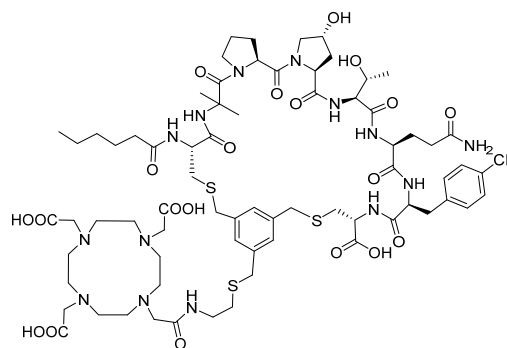
[0171] The obtained linear crude peptide was dissolved in a mixture of acetonitrile/purified water=1/1 (400 times the mass of the crude peptide). First, 7.2 eq of DIPEA was added, followed by the addition of 1.2 eq of 1,3,5-tris(bromomethyl)benzene. After the reaction was completed, 3.6 eq of mercaptoethylamine was directly added to the system. After the reaction was

e. Conjugation with DOTA

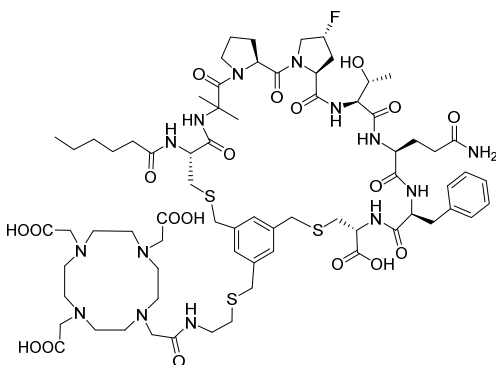
Example 10. Preparation of DOTA-10



Example 11. Preparation of DOTA-11

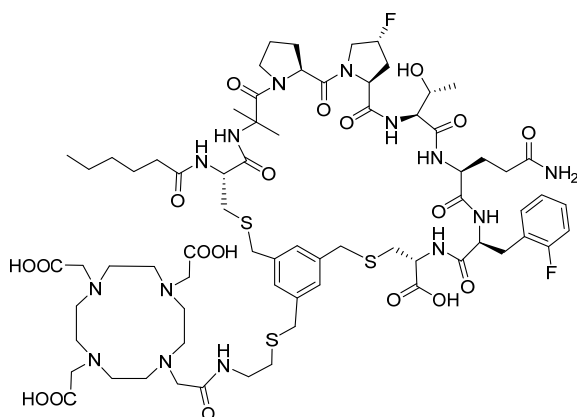


Example 12. Preparation of DOTA-12



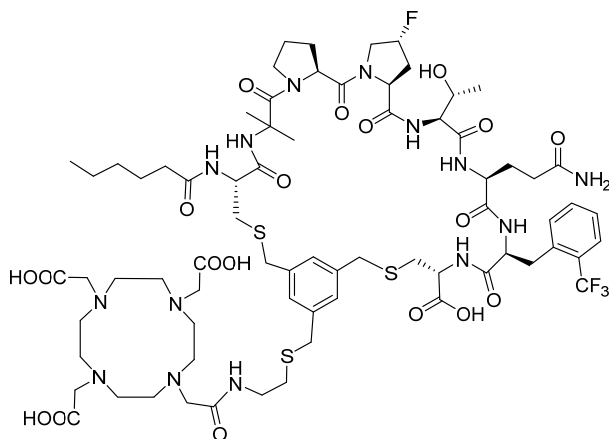
[0175] The target compound DOTA-12 was obtained in a manner similar to that of scheme I in Example 1. 99.1%, MS m/z (ESI): 1572.31 [M-H]⁻.

Example 13. Preparation of DOTA-13



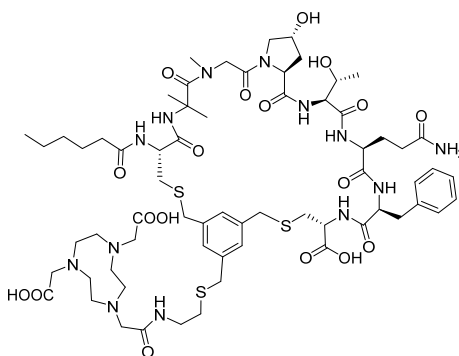
[0176] The target compound DOTA-13 was obtained in a manner similar to that of scheme I in Example 1. 98.9%, MS m/z (ESI): 1590.01 [M-H]⁻.

Example 14. Preparation of DOTA-14



[0177] The target compound DOTA-14 was obtained in a manner similar to that of scheme I in Example 1. 97.4%, MS m/z (ESI): 1589.87 [M-H]⁻.

Example 15. Preparation of NOTA-04



a. Loading of first amino acid onto solid-phase support

[0178] CTC resin (degree of substitution = 1.09mmol/g) was selected as a solid-phase support. The resin was swollen with DMF for 1 h. Subsequently, an amino acid solution was prepared: 3.00 eq of Fmoc-Cys(Trt)-OH and 6.00 eq of DIPEA were dissolved in DMF (8 times the mass of the resin). After uniform stirring, the solution was reacted with the resin for 3 h. The resin was washed, and then capped with methanol and DIPEA. The capped resin was washed with DMF (8 times the mass of the resin) 4 to 6 times, and then washed and shrunk sequentially with isopropyl ether, DCM and isopropyl ether (each 8 times the mass of the resin). After drying, the degree of substitution was measured for later use.

b. Amino acid coupling

[0179] In the synthesis, each amino acid was coupled using the general coupling method described below.

[0180] The Fmoc-Cys(Trt)-CTC resin obtained in the previous step was swollen with DMF (8 times the mass of the resin) for 1 h. The Fmoc protecting group was removed twice with a 20% piperidine/DMF solution (8 times the mass of the resin) (first time: 5 min, and second time: 20 min). After the deprotection was completed, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. The activated amino acid solution was prepared: 3.0 eq of amino acid and 3.0 eq of HBTU were dissolved in 8 Vol of DMF. 3.0 eq of DEPEA was added for activation for 2-5 min, and then the reaction was performed. After the reaction was completed and the deprotection was finished, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. After the coupling of the linear peptide resin was completed using the above method, the resin was washed, shrunk, and dried for later use.

c. Cleavage

[0181] The obtained peptide resin was cleaved using a cleavage solution with a ratio of TFA/DTT/H₂O/Tips of 94/2.5/2.5/1, wherein the cleavage solution was added in an amount 8 to 10 times the mass of the peptide resin. After 2 h of cleavage, filtration was performed to obtain the filtrate. The obtained filtrate was poured into isopropyl ether (80 to 100 times the mass of the peptide resin) for crystallization. The resulting product was filtered, rinsed with isopropyl ether, and dried to obtain a linear crude peptide.

d. Cyclization

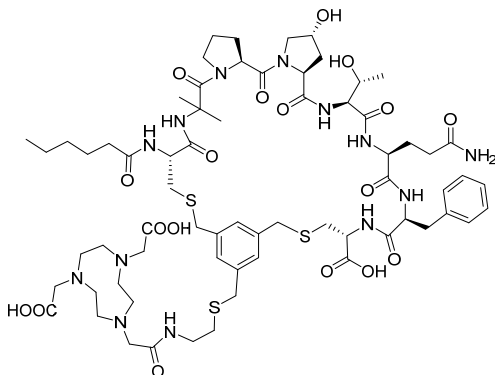
[0182] The obtained linear crude peptide was dissolved in a mixture of acetonitrile/purified water = 1/1 (400 times the mass of the crude peptide). First, 7.2 eq of DIPEA was added, followed by the addition of 1.2 eq of 1,3,5-tris(bromomethyl)benzene. After the reaction was completed, 3.6 eq of mercaptoethylamine was directly added to the system. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was purified by preparative liquid chromatography and lyophilized to obtain a cyclic peptide intermediate.

e. Conjugation with NOTA

[0183] The obtained lyophilized powder of the cyclic peptide was dissolved in DMF (10 times the mass of the lyophilized powder). 4.0 eq of DIPEA and 2.0 eq of NOTA-NHS were added. The reaction was monitored by LCMS until completion. Purification was performed by preparative liquid chromatography, followed by lyophilization to obtain the target product.

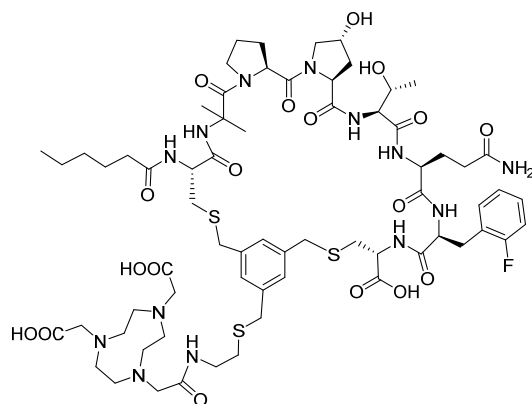
[0184] Purity: 97.20%, MS m/z (ESI): 1442.89 [M-H]⁻.

Example 16. Preparation of NOTA-05



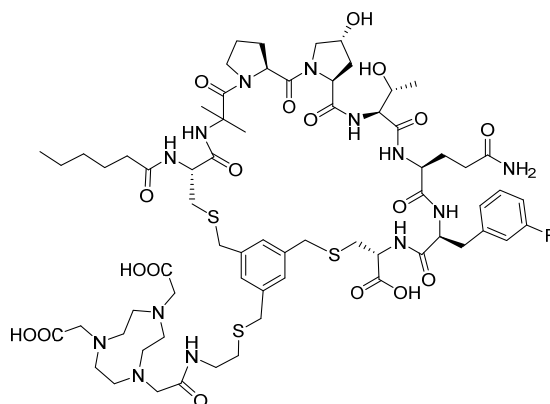
[0185] The target compound NOTA-05 was obtained in a manner similar to that in Example 15, purity: 97.20%, MS m/z (ESI): 1470.33 [M+H]⁺.

Example 17. Preparation of NOTA-06



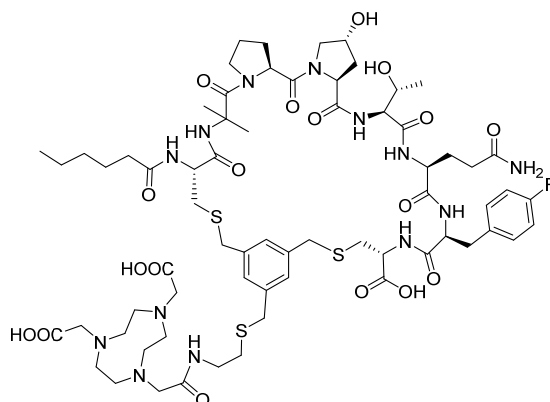
[0186] The target compound NOTA-06 was obtained in a manner similar to that in Example 15, purity: 99.2%, MS m/z (ESI): 1486.94 [M-H]⁻.

Example 18. Preparation of NOTA-07



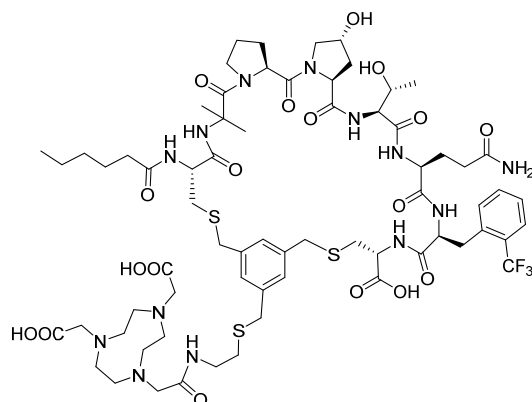
[0187] The target compound NOTA-07 was obtained in a manner similar to that in Example 15, purity: 99.0%, MS m/z (ESI): 1486.91 [M-H]⁻.

Example 19. Preparation of NOTA-08



[0188] The target compound NOTA-08 was obtained in a manner similar to that in Example 15, purity: 99.6%, MS m/z (ESI): 1486.86 [M-H]⁻.

Example 20. Preparation of NOTA-09



a. Loading of first amino acid onto solid-phase support

[0189] CTC resin (degree of substitution = 1.09mmol/g) was selected as a solid-phase support. The resin was swollen with DMF for 1 h. Subsequently, an amino acid solution was prepared: 3.00 eq of Fmoc-Cys(Trt)-OH and 6.00 eq of DIPEA were dissolved in DMF (8 times the mass of the resin). After uniform stirring, the solution was reacted with the resin for 3 h. The resin was washed, and then capped with methanol and DIPEA. The capped resin was washed with DMF (8 times the mass of the resin) 4 to 6 times, and then washed and shrunk sequentially with isopropyl ether, DCM and isopropyl ether (each 8 times the mass of the resin). After drying, the degree of substitution was measured for later use.

b. Amino acid coupling

[0190] In the synthesis, each amino acid was coupled using the general coupling method described below.

[0191] The Fmoc-Cys(Trt)-CTC resin obtained in the previous step was swollen with DMF (8 times the mass of the resin) for 1 h. The Fmoc protecting group was removed twice with a 20% piperidine/DMF solution (8 times the mass of the resin) (first time: 5 min, and second time: 20 min). After the deprotection was completed, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. The activated amino acid solution was prepared: 3.0 eq of amino acid and 3.0 eq of HBTU were dissolved in 8 Vol of DMF. 3.0 eq of DEPEA was added for activation for 2-5 min, and then the reaction was performed. After the reaction was completed and the deprotection was finished, the resin was washed with DMF (8 times the mass of the resin) 4 to 6 times. After the coupling of the linear peptide resin was completed using the above method, the resin was washed, shrunk, and dried for later use.

c. Cleavage

[0192] The obtained peptide resin was cleaved using a cleavage solution with a ratio of TFA/DTT/H₂O/Tips of 94/2.5/2.5/1, wherein the cleavage solution was added in an amount 8 to 10 times the mass of the peptide resin. After 2 h of cleavage, filtration was performed to obtain the filtrate. The obtained filtrate was poured into isopropyl ether (80 to 100 times the mass of the peptide resin) for crystallization. The resulting product was filtered, rinsed with isopropyl ether, and dried to obtain a linear crude peptide.

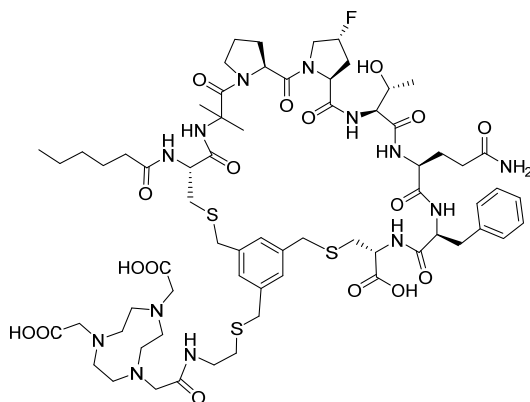
d. Cyclization

[0193] The obtained linear crude peptide was dissolved in a mixture of acetonitrile/purified water = 1/1 (400 times the mass of the crude peptide). First, 7.2 eq of DIPEA was added, followed by the addition of 1.2 eq of 1,3,5-tris(bromomethyl)benzene. After the reaction was completed, 3.6 eq of mercaptoethylamine was directly added to the system. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was purified by preparative liquid chromatography and lyophilized to obtain a cyclic peptide intermediate.

e. Conjugation with NOTA

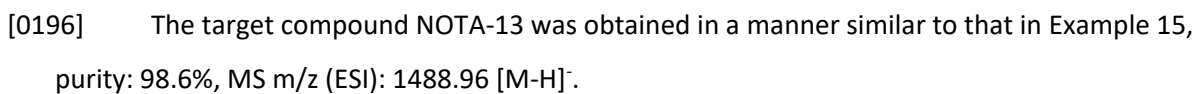
[0194] The obtained lyophilized powder of the cyclic peptide was dissolved in DMF (10 times the mass of the lyophilized powder). 4.0 eq of DIPEA and 2.0 eq of NOTA-NHS were added. The reaction was monitored by LCMS until completion. Purification was performed by preparative liquid chromatography, followed by lyophilization to obtain the target product. Purity: 99.7%, MS m/z (ESI): 1536.65 [M-H]⁻.

Example 21. Preparation of NOTA-12



[0195] The target compound NOTA-12 was obtained in a manner similar to that in Example 15, purity: 98.8%, MS m/z (ESI): 1470.88 [M-H]⁻.

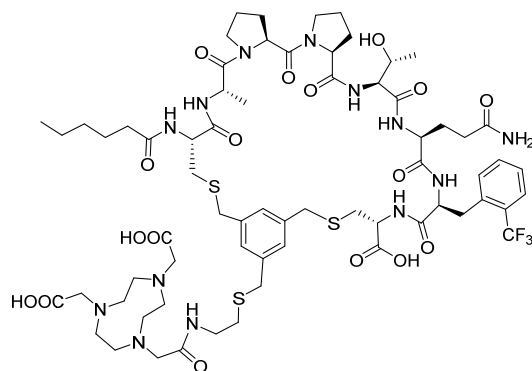
Example 22. Preparation of NOTA-13



[0197] The target compound NOTA-14 was obtained in a manner similar to that in Example 15, purity: 97.9%, MS m/z (ESI): 1538.94 [M-H]⁻.

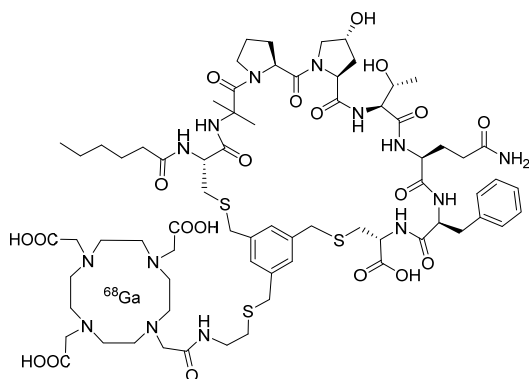
[0198] The target compound NOTA-15 was obtained in a manner similar to that in Example 15, purity: 97.3%, MS m/z (ESI): 1456.95 [M-H]⁻.

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[0199] The target compound NOTA-16 was obtained in a manner similar to that in Example 15, purity: 97.8%, MS m/z (ESI): 1506.90 [M-H]⁻.

Example 26. Preparation of ⁶⁸Ga-DOTA-05



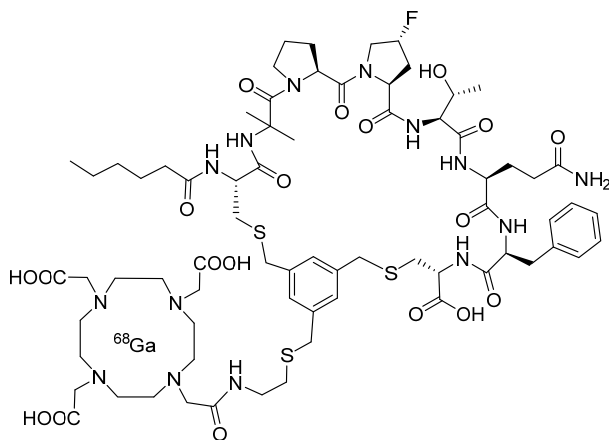
[0200] The ⁶⁸GaCl₃ solution was rinsed with 0.1 N hydrochloric acid. 0.1 ml of a 1 mM aqueous solution of sodium acetate was added to a reaction vessel; 0.9 ml of the above ⁶⁸GaCl₃ solution was then added. 5 μl of **DOTA-05** (1 mg/ml) solution and 67 μl of gentisic acid solution (15 mg/ml) were added and uniformly mixed. The reaction solution was adjusted to pH 3.5-5.0, and heated at 95°C for 15 min. The radiochemical purity was 97.54% as detected by radio-HPLC.

[0201] If the radiochemical purity is not less than 90%, the product can be directly used. If the radiochemical purity is less than 90%, purification is performed using a C18 cartridge. Then, the cartridge is rinsed with ethanol, and the eluate is diluted with physiological saline until the ethanol content is below 10%.

Example 27. Preparation of ⁶⁸Ga-DOTA-06

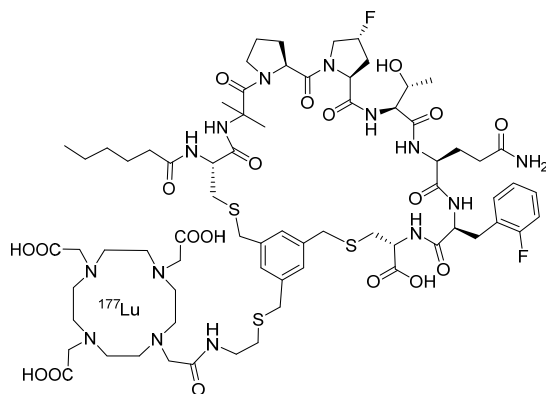
[0205] The $^{68}\text{GaCl}_3$ solution was rinsed with 0.1 N hydrochloric acid. 0.1 ml of a 1 mM aqueous solution of sodium acetate was added to a reaction vessel; 0.9 ml of the above $^{68}\text{GaCl}_3$ solution was then added. 5 μl of **DOTA-09** (1 mg/ml) solution and 67 μl of gentisic acid solution (15 mg/ml) were added and uniformly mixed. The reaction solution was adjusted to pH 3.5-5.0, and heated at 95°C for 15 min. The radiochemical purity was 93.38% as detected by radio-HPLC.

Example 31. Preparation of ^{68}Ga -DOTA-12



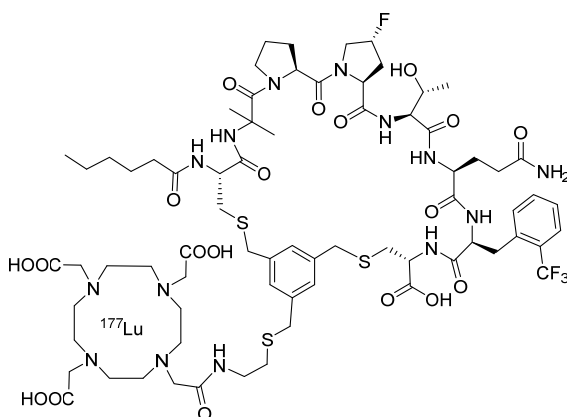
[0206] The target compound ^{68}Ga -DOTA-12 was obtained in a manner similar to that in Example 26, radiochemical purity: 97.57%.

Example 32. Preparation of ^{68}Ga -DOTA-13



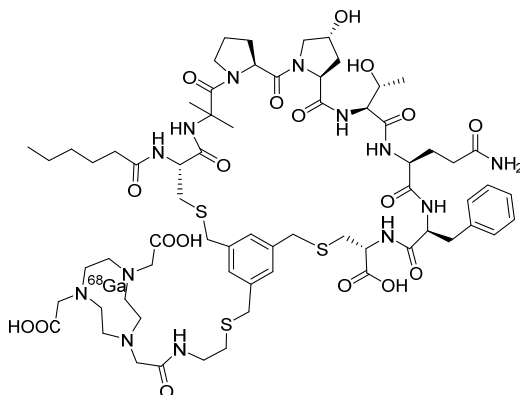
[0211] The target compound ^{177}Lu -DOTA-13 was obtained in a manner similar to that in Example 33, radiochemical purity: 95.95%.

Example 37. Preparation of ^{177}Lu -DOTA-14



[0212] The target compound ^{177}Lu -DOTA-14 was obtained in a manner similar to that in Example 33, radiochemical purity: 97.45%.

Example 38. Preparation of ^{68}Ga -NOTA-05

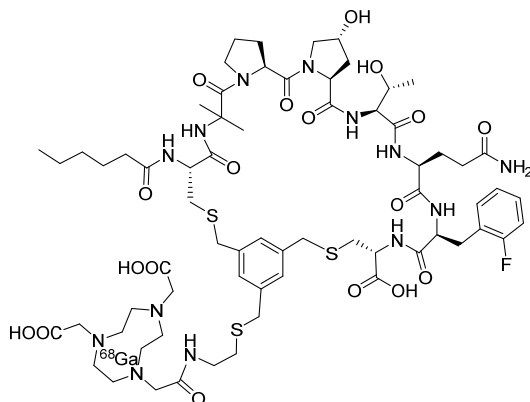


[0213] The $^{68}\text{GaCl}_3$ solution was rinsed with 0.1 N hydrochloric acid. 0.1 ml of a 1 mM aqueous solution of sodium acetate was added to a reaction vessel; 0.9 ml of the above $^{68}\text{GaCl}_3$ solution was then added. 5 μl of an aqueous solution of NOTA-05 (1 mg/ml) and 67 μl of an aqueous

solution of gentisic acid (15 mg/ml) were added, and uniformly mixed. The reaction solution was reacted at room temperature for 15 min under a pH condition of 3.5-5.0. The radiochemical purity was 91.07% as detected by radio-HPLC.

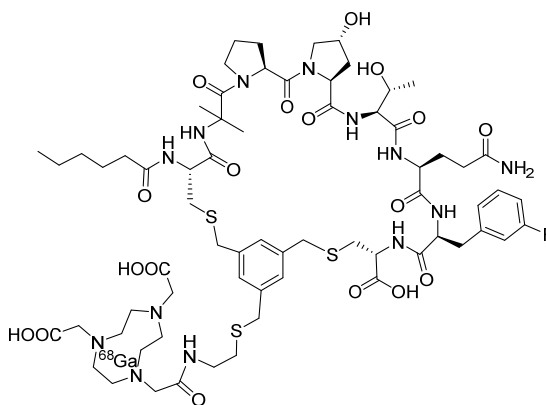
[0214] If the radiochemical purity is not less than 90%, the product can be directly used. If the radiochemical purity is less than 90%, purification is performed using a C18 cartridge. Then, the cartridge is rinsed with ethanol, and the eluate is diluted with physiological saline until the ethanol content is below 10%.

Example 39. Preparation of ^{68}Ga -NOTA-06



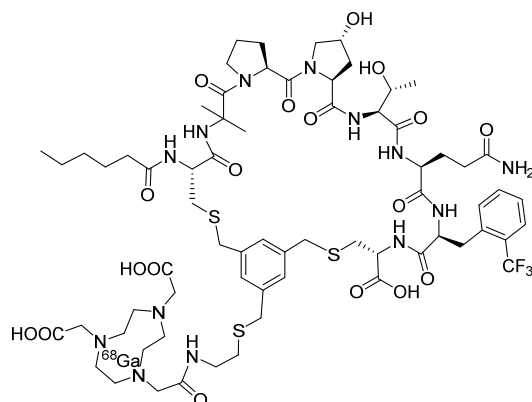
[0215] The target compound ^{68}Ga -NOTA-06 was obtained in a manner similar to that in Example 38, radiochemical purity: 91.38%.

Example 40. Preparation of ^{68}Ga -NOTA-07



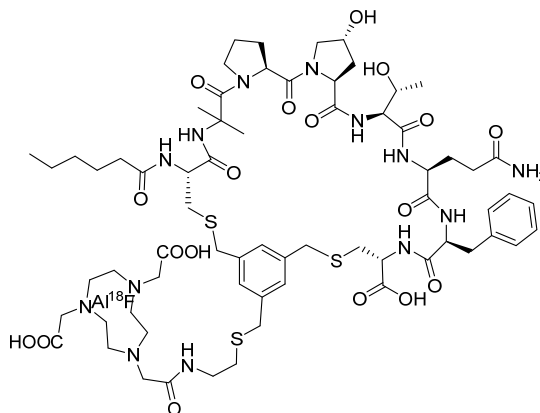
[0216] The target compound ^{68}Ga -NOTA-07 was obtained in a manner similar to that in Example 38, radiochemical purity: 92.54%.

Example 41. Preparation of ^{68}Ga -NOTA-09



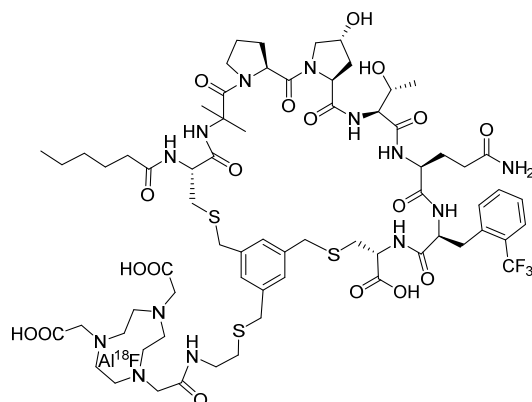
[0217] The $^{68}\text{GaCl}_3$ solution was rinsed with 0.1 N hydrochloric acid. 0.1 ml of a 1 mM aqueous solution of sodium acetate was added to a reaction vessel; 0.9 ml of the above $^{68}\text{GaCl}_3$ solution was then added. 5 μl of an aqueous solution of NOTA-09 (1 mg/ml) and 67 μl of an aqueous solution of gentisic acid (15 mg/ml) were added, and uniformly mixed. The reaction solution was reacted at room temperature for 15 min under a pH condition of 3.5-5.0. The radiochemical purity was 92.36% as detected by radio-HPLC.

Example 42. Preparation of Al^{18}F -NOTA-05



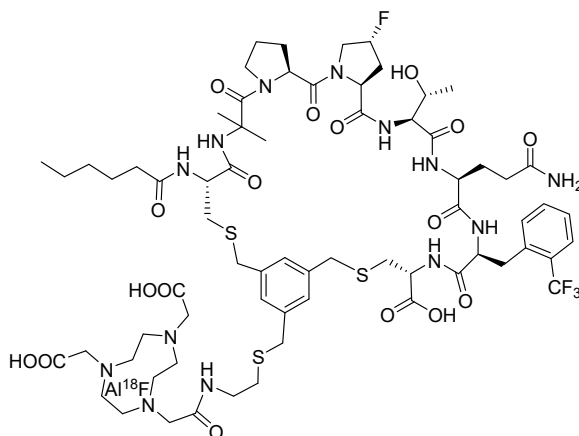
[0218] 1 μl of a 10 mM aqueous solution of NOTA-05 was dissolved in 50-100 μl of 0.5 M acetic acid/sodium acetate buffer at pH 4.0-4.4. A 2 mM aqueous solution of AlCl_3 was then added in a molar ratio of 2 : 1, followed by the addition of 50 μl of 1850 MBq QMA-purified ^{18}F ions. The mixture was reacted at 100°C for 10-15 min. Purification was performed using an HLB cartridge. The cartridge was rinsed with ethanol/water (1 : 1), and the eluate was diluted with physiological saline until the ethanol content was below 10%. The radiochemical purity was 92.37% as detected by radio-HPLC.

Example 43. Preparation of Al^{18}F -NOTA-09



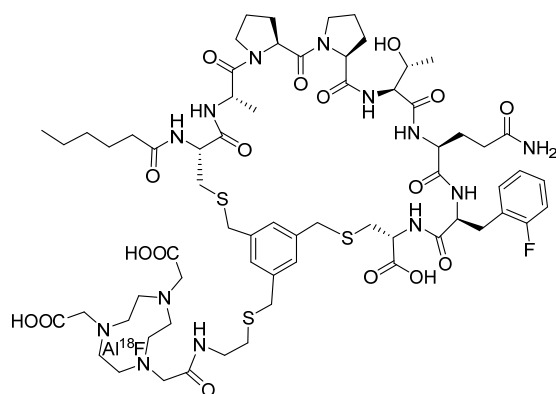
[0219] 1 μ l of a 10 mM aqueous solution of NOTA-09 was dissolved in 50-100 μ l of 0.5 M acetic acid/sodium acetate buffer at pH 4.0-4.4. A 2 mM aqueous solution of AlCl_3 was then added in a molar ratio of 2 : 1, followed by the addition of 50 μ l of 1850 MBq QMA-purified $^{18}\text{F}^-$ ions. The mixture was reacted at 100°C for 10-15 min. Purification was performed using an HLB cartridge. The cartridge was rinsed with ethanol/water (1 : 1), and the eluate was diluted with physiological saline until the ethanol content was below 10%. The radiochemical purity was 91.57% as detected by radio-HPLC.

Example 44. Preparation of Al^{18}F -NOTA-14



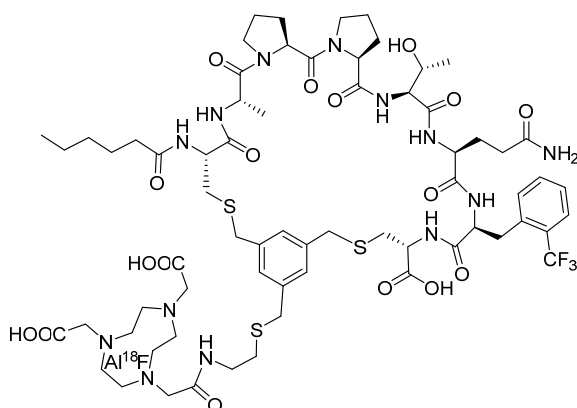
[0220] The target compound Al^{18}F -NOTA-14 was obtained in a manner similar to that in Example 42, radiochemical purity: 90.33%.

Example 45. Preparation of Al^{18}F -NOTA-15



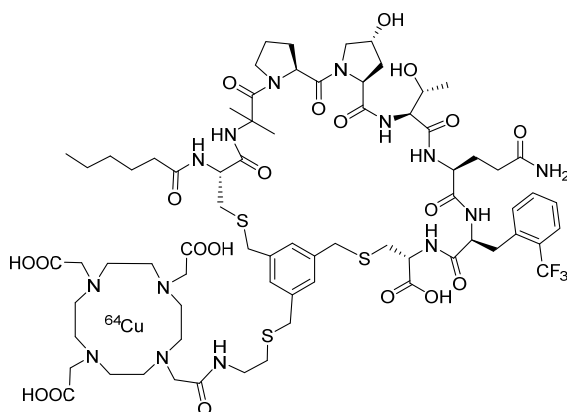
[0221] The target compound Al^{18}F -NOTA-15 was obtained in a manner similar to that in Example 42, radiochemical purity: 92.94%.

Example 46. Preparation of Al^{18}F -NOTA-16



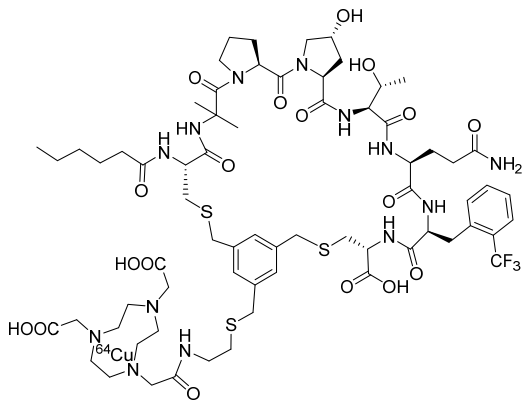
[0222] The target compound Al^{18}F -NOTA-16 was obtained in a manner similar to that in Example 42, radiochemical purity: 91.60%.

Example 47. Preparation of ^{64}Cu -DOTA-09

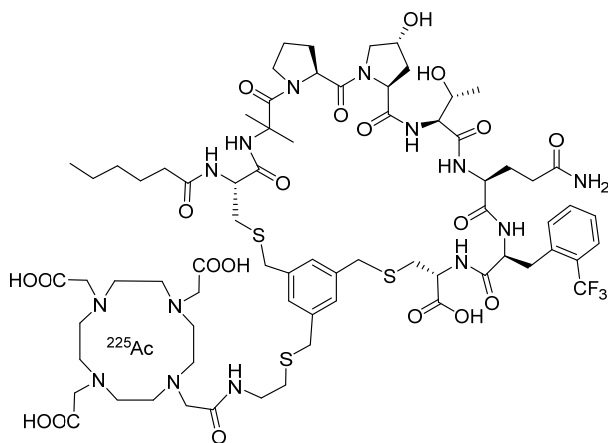


[0223] 5 μl of a 10 mM aqueous solution of DOTA-09 was dissolved in 100 μl of sodium acetate solution at pH 3.5-6.5. Then, 50 μl of 1850 MBq $^{64}\text{CuCl}_2$ solution, which had been dissolved in 0.1 M hydrochloric acid, was added. The mixture was reacted at 80°C for 15 min. Purification was

Example 48. Preparation of ⁶⁴Cu-NOTA-09



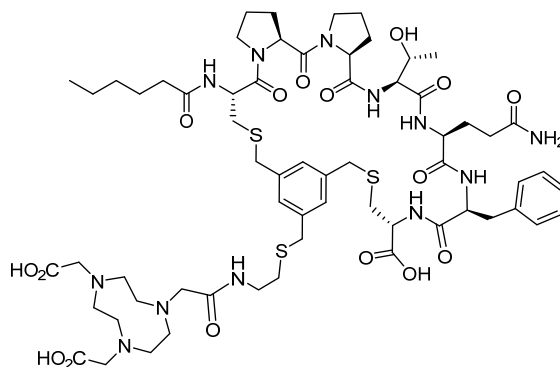
Example 49. Preparation of ^{225}Ac -DOTA-09



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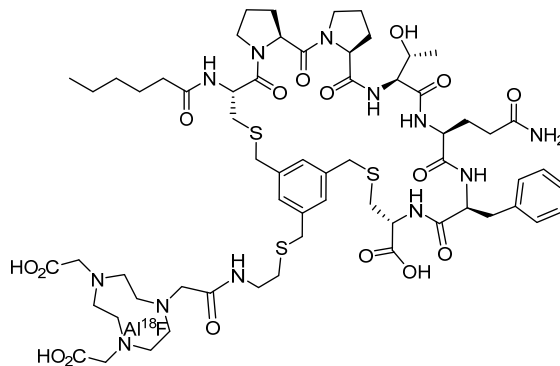
temperature, and 0.65 ml of 10 mg/ml sodium ascorbate in physiological saline was added. The radiochemical purity was greater than 90% as detected by radio-HPLC.

Comparative Example 1. Preparation of NOTA-2286



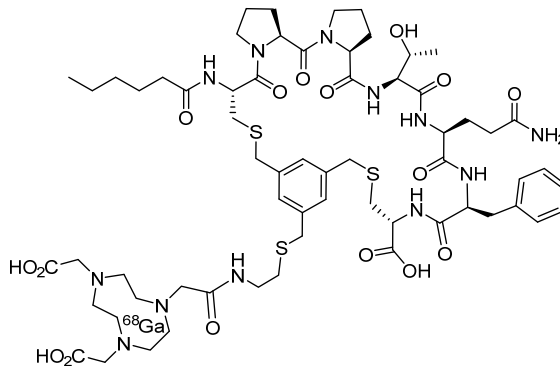
[0226] The target compound NOTA-2286 was obtained in a manner similar to that in Example 15, purity: 97.35%, MS m/z (ESI): 1367.78 [M-H]⁻.

Comparative Example 2. Preparation of Al¹⁸F-NOTA-2286



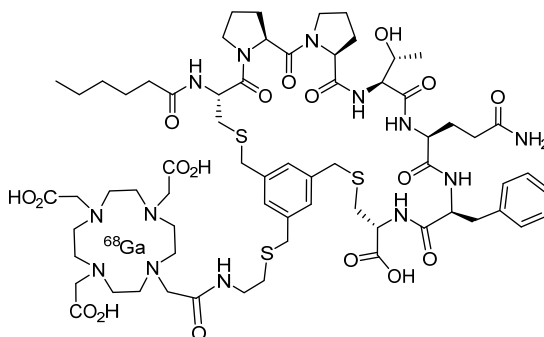
[0227] The target compound Al¹⁸F-NOTA-2286 was obtained in a manner similar to that in Example 42, radiochemical purity: 95.37%.

Comparative Example 3. Preparation of ⁶⁸Ga-NOTA-2286

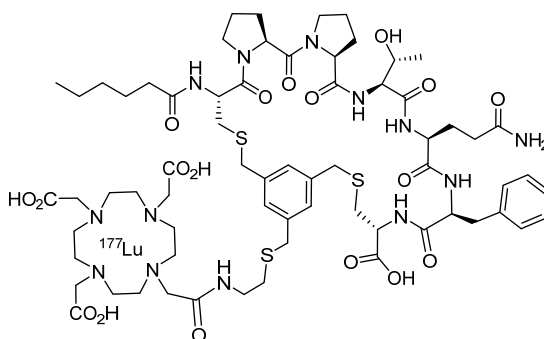


[0228] The target compound ⁶⁸Ga-NOTA-2286 was obtained in a manner similar to that in Example 38, radiochemical purity: 96.29%.

Comparative Example 4. Preparation of ^{68}Ga -FAP-2286



[0229] The target compound ^{68}Ga -FAP-2286 was obtained in a manner similar to that in Example 26, radiochemical purity: 94.98%.



Comparative Example 5. Preparation of ^{177}Lu -FAP-2286

[0230] The target compound ^{177}Lu -FAP-2286 was obtained in a manner similar to that in Example 33, radiochemical purity: 97.76%.

Biological evaluation

[0231] The present disclosure will be further described and explained below in conjunction with test examples, but these examples are not intended to limit the scope of the present disclosure.

Test Example 1. FAP α enzyme activity test

1.1 Experimental materials and instruments

Table 1. Source information of experimental materials and instruments

Experimental materials	Source
FAP α protein	TANJIN HENGRUI MEDICINE CO., LTD.
Z-Gly-Pro-AMC	GLPBIO, GA23817
PBS	Nanjing SenBeiJia Biological Technology Co., Ltd., BC-BPBS-01

DMSO	sigma, D5879-500ML
Microplate	675076
Microplate reader	TECAN, Spark

1.2 Experimental steps

[0232] The substrate (Z-Gly-Pro-AMC) was diluted with DMSO to prepare a 0.5 mM stock solution. Before each experiment, the 0.5 mM stock solution was diluted with PBS to 50 μ M for later use. The FAP α protein was diluted with PBS to 0.5 ng/ μ l for later use. The test compounds and positive control were diluted with PBS to a concentration of 100 nM or 200 nM for the determination of single-point inhibition rate. For compounds with a single-point inhibition rate comparable to that of the positive compound, further determination of IC₅₀ values was performed. The test compounds and positive control were subjected to a 5-fold serial dilution with PBS to obtain 8 gradients for later use, with the highest concentration being 10 μ M, and the lowest concentration being 0 nM. Test method: 85 μ l of the FAP α dilution and 10 μ l of the compound dilution were added to a microplate, uniformly mixed and incubated at 37°C for 10 min. Then, 5 μ l of 50 μ M substrate was added, uniformly mixed and incubated at 37°C for 10 min. The microplate was read on a microplate reader, with an excitation wavelength of 380 nm and an emission wavelength of 465 nm.

1.3 Experimental results

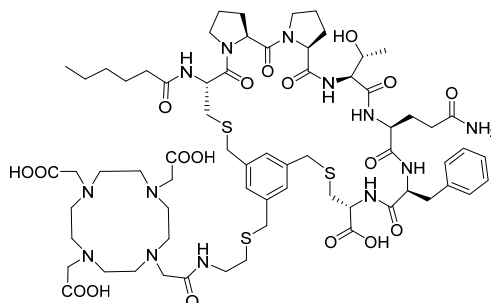
Table 2. IC₅₀ values of the compounds of the present disclosure against FAP α

Compound No.	IC ₅₀ (nM)	Compound No.	IC ₅₀ (nM)
DOTA-01	13.91	NOTA-04	0.47
DOTA-02	10.31	NOTA-05	0.45
DOTA03	4.05	NOTA-06	0.088
DOTA-04	1.84	NOTA-07	0.086
DOTA-05	1.16	NOTA-08	0.59
DOTA-06	0.93	NOTA-09	2.75
DOTA-07	1.50	NOTA-10	/
DOTA-08	0.53	NOTA-11	/
DOTA-09	0.28	NOTA-12	2.70
DOTA-10	11.20	NOTA-13	2.73
DOTA-11	4.04	NOTA-14	3.40

DOTA-12	1.08	NOTA-15	2.72
DOTA-13	1.09	NOTA-16	3.59
DOTA-14	0.53	NOTA-2286 (Comparative Example 1)	0.59
FAP-2286 (positive)	11.68		

Note: The structure of FAP-2286 is shown as follows:

References: European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:3651-3667



Test Example 2. PET/SPECT imaging test of labeled compounds

2.1 Experimental materials

- [0233] Cell information: U-87 MG cells (Wuhan Pricella Biotechnology Co., Ltd.); Culture conditions: U-87 MG cell specific medium (MEM + 10% FBS + 1% P/S); Number of passages: 6-9.
- [0234] Experimental animals: Germline: B-NDG (Biocytogen Jiangsu Co., Ltd.); Age: 5-8 weeks old; Body weight: 20-24 g.
- [0235] Reagent: PBS (Solarbio, P1020); Matrigel (ABW, 0827045); Trypsin-EDTA (Gibco, 25200-072); U-87 MG specific medium (Pricella, CM-0238).
- [0236] Instrument: Small animal PET/CT (ediso, nanoScan PET/CT 4heads); Activity meter (Capintec, activity meter); Electronic balance (Changzhou Shuangjie, DT100).

2.2 Experimental steps

Model construction

- [0237] A sufficient quantity of U-87 MG cells was prepared and inoculated into the posterior position of the right forelimb of B-NDG mice in an inoculation volume of 100 μ l, containing 50% Matrigel and 5×10^6 cells. After inoculation, the tumor volume and animal body weight were monitored twice a week. Model mice with a tumor volume between 200 and 500 m^3 were selected for enrollment in this experiment and randomly grouped on the basis of tumor volume.

Operation steps

- [0238] 1) The workbench surface was wiped with 75% medical alcohol and covered with a disposable sterile tablecloth.
- [0239] 2) 0.5 mL insulin syringes, alcohol swabs, cotton swabs and a marking pen were prepared in the injection room; and the mice were placed in a mouse restrainer, and the tails of the mice were disinfected with alcohol swabs.
- [0240] 3) The prepared test sample was injected into each mouse via the tail vein, with the time of each injection, the activity of the syringe and the activity of the empty syringe recorded.
- [0241] 4) Tumor-bearing mice were anesthetized with isoflurane, and then placed in a prone position on small animal PET/SPECT beds and fixed.
- [0242] 5) After administration, static PET/SPECT image acquisition was performed at different time points; prior to each static scan, a whole-body CT scan was performed to obtain whole-body distribution images of the labeled compound in the tumor-bearing mice, thereby obtaining PET/SPECT images for each experimental animal at different time points after administration; and major organs were selected and delineated, specifically including: parts such as tumor, muscle, bone, lung, brain, liver and kidney.
- [0243] 6) The radioactive accumulation and clearance of the labeled compounds in tumors and non-target tissues of tumor-bearing mice were observed.

2.3 Experimental results

Table 3. Uptake in tumors and various tissues and tumor/kidney ratios of the compounds of the present disclosure and ⁶⁸Ga-FAP-2286

Compound	⁶⁸ Ga-FAP-2286 ()		⁶⁸ Ga-DOTA-05		⁶⁸ Ga-DOTA-06	
	1 h	3 h	1 h	3 h	1 h	3 h
Tumor	10.99±0.90	4.96±0.87	9.44±1.39	6.72±1.44	17.43±0.88	13.53±1.89
Kidney	7.04±0.42	5.67±0.11	4.06±0.56	2.52±0.22	3.66±0.32	2.14±0.18
Liver	1.14±0.26	0.30±0.09	0.81±0.13	0.42±0.08	1.48±0.01	0.77±0.06
Brain	0.32 ± 0.09	0.11±0.06	0.50±0.08	0.26±0.03	1.14±0.12	0.60±0.04
Lung	0.90±0.14	0.26±0.05	0.91±0.21	0.39±0.13	1.84±0.05	0.93±0.21
Muscle	0.22±0.06	0.05±0.01	0.48±0.21	0.14±0.07	1.94±0.60	0.89±0.10
Joint	0.94±0.20	0.29±0.07	1.40±0.70	0.58±0.10	3.70±0.65	1.95±0.79
Gallbladder	1.26 ± 0.17	0.38±0.09	0.89±0.14	0.41±0.10	1.46±0.08	0.82±0.18
Tumor/kidney	1.56±0.11	0.87±0.14	2.37±0.62	2.65±0.34	4.78±0.18	6.31±0.34

[0244] ^{68}Ga -DOTA-05 and the positive control ^{68}Ga -FAP-2286 exhibited comparable tumor uptake in model mice, while ^{68}Ga -DOTA-06 showed significantly higher tumor uptake than that of ^{68}Ga -FAP-2286. ^{68}Ga -DOTA-05 and ^{68}Ga -DOTA-06 showed lower kidney uptake and higher tumor/kidney uptake ratios (FIG. 1). Moreover, with the increase of time, the tumor/kidney uptake ratios of ^{68}Ga -DOTA-05 and ^{68}Ga -DOTA-06 increased, whereas the tumor/kidney uptake ratio of ^{68}Ga -FAP-2286 decreased (FIG. 2).

Table 4. Tumor uptake and tumor/kidney ratios of the compounds of the present disclosure and ^{68}Ga -FAP-2286

Tissue	Tumor		Tumor/kidney	
Time	1 h	3h	1h	3h
^{68}Ga -FAP-2286	10.99±0.90	4.96±0.87	1.56±0.11	0.87±0.14
^{68}Ga -DOTA-05	9.44±1.39	6.72±1.44	2.37±0.62	2.65±0.34
^{68}Ga -DOTA-06	17.43±0.88	13.53±1.89	4.78±0.18	6.31±0.34
^{68}Ga -DOTA-07	14.92±5.18	10.82±3.04	4.36±0.85	6.73±0.65
^{68}Ga -DOTA-08	19.22±0.92	14.29±1.47	4.75±0.16	7.32±0.92
^{68}Ga -DOTA-09	/	12.44±2.78	/	3.79±1.05
^{68}Ga -DOTA-12	13.91±3.64	8.74±2.59	3.74±0.58	4.72±0.48
^{68}Ga -DOTA-13	/	12.15±2.59	/	8.97±3.15

[0245] In the mouse model, the tumor uptake (FIG. 3) and tumor/kidney ratios (FIG. 4) of ^{68}Ga -DOTA-06, ^{68}Ga -DOTA-07, ^{68}Ga -DOTA-08, ^{68}Ga -DOTA-09, ^{68}Ga -DOTA-12 and ^{68}Ga -DOTA-13 were significantly higher than those of the control ^{68}Ga -FAP-2286.

Table 5. Tumor uptake and tumor/kidney ratios of the compounds of the present disclosure and ^{177}Lu -FAP-2286

	Time	^{177}Lu -FAP-2286	^{177}Lu -DOTA-06	^{177}Lu -DOTA-09	^{177}Lu -DOTA-13	^{177}Lu -DOTA-14
Tumor	0.5 h	29.84±3.52	27.50±3.74	29.52±2.98	26.57±3.35	25.61±3.20
	1.5 h	28.49±3.49	28.71±2.44	30.88±3.14	26.96±1.84	26.71±2.44
	4.0 h	23.66±3.01	27.77±4.60	31.09±3.88	26.03±3.98	28.74±2.76
	24h	6.26±1.10	21.62±2.63	30.46±1.99	22.23±1.53	23.32±1.20
	48h	6.40±1.24	14.11±2.03	24.10±2.21	12.58±1.42	19.73±1.72
	72h	6.02±1.56	11.52±1.31	20.59±1.91	9.90±1.40	15.69±1.98
	168h	6.30±2.32	9.16±1.49	12.81±0.90	8.46±0.98	10.40±2.25

Tumor/kidney	0.5 h	3.29±0.78	7.30±1.05	6.08±1.62	8.01±1.82	4.88±1.29
	1.5 h	6.53±1.12	10.97±2.66	8.66±0.73	12.66±1.91	7.96±2.25
	4.0 h	9.82±4.79	11.42±1.75	11.79±2.62	13.93±4.74	10.09±1.62
	24h	2.75±0.90	15.45±3.12	19.38±5.84	15.46±3.17	15.89±3.71

[0246] In the mouse model, ¹⁷⁷Lu-DOTA-09 and ¹⁷⁷Lu-DOTA-14 decreased slowly in the tumor uptake, maintaining relatively stable intratumoral retention, whereas ¹⁷⁷Lu-FAP-2286 showed a rapid decrease in intratumoral retention after 4 hours (FIG. 5). The tumor/kidney ratios (FIG. 6) of ¹⁷⁷Lu-DOTA-09 and ¹⁷⁷Lu-DOTA-14 were higher than that of the control ¹⁷⁷Lu-FAP-2286.

Table 6. Tumor uptake and tumor/kidney ratios of the compounds of the present disclosure and ⁶⁸Ga-NOTA-2286

Tissue	Tumor			Tumor/kidney		
Time	0.5h	1.5h	3.0h	0.5h	1.5h	3.0h
⁶⁸Ga-NOTA-2286	6.27±1.03	4.37±1.03	2.85±0.83	1.59±0.55	1.77±0.31	2.43±1.04
⁶⁸Ga-NOTA-05	18.15±1.35	17.14±1.59	16.38±1.00	5.78±1.05	9.50±1.83	11.83±1.60
⁶⁸Ga-NOTA-06	24.98±6.33	23.33±4.71	21.71±4.88	6.81±2.29	9.79±3.33	18.51±10.73
⁶⁸Ga-NOTA-07	23.77±2.69	19.85±2.15	16.80±3.31	5.64±1.54	13.09±6.46	8.24±2.44
⁶⁸Ga-DOTA-09	15.32±1.14	15.09±0.53	13.24±1.21	2.81±0.21	5.34±0.92	10.17±2.53

[0247] In the mouse model, the tumor uptake (FIG. 7) and tumor/kidney ratios (FIG. 8) of ⁶⁸Ga-NOTA-05, ⁶⁸Ga-NOTA-06, ⁶⁸Ga-NOTA-07 and ⁶⁸Ga-DOTA-09 were significantly higher than those of the control ⁶⁸Ga-NOTA-2286.

Table 7. Tumor uptake and tumor/kidney ratios of the compounds of the present disclosure and Al¹⁸F-NOTA-2286

Tissue	Tumor			Tumor/kidney		
Time	0.5h	1.5h	3.0h	0.5h	1.5h	3.0h
Al¹⁸F-NOTA-2286	33.27±0.64	22.34±3.00	11.32±3.02	2.57±0.09	11.24±1.79	10.06±1.60
Al¹⁸F-NOTA-09	48.94±4.56	38.13±3.50	28.72±3.12	7.06±0.80	16.97±1.74	20.65±5.55
Al¹⁸F-NOTA-14	43.75±9.01	44.75±7.53	37.05±8.03	6.75±0.65	18.78±0.20	38.95±16.30
Al¹⁸F-NOTA-16	26.50±6.07	23.11±7.02	22.82±4.71	6.59±0.72	9.84±3.70	15.03±3.02

[0248] In the mouse model, the tumor uptake (FIG. 9) and tumor/kidney ratios (FIG. 10) of Al¹⁸F-NOTA-09 and Al¹⁸F-NOTA-14 were significantly higher than those of the control Al¹⁸F-NOTA-2286.

Test Example 3. Plasma concentration experiment of ¹⁷⁷Lu-labeled compound

3.1 Experimental materials

- [0249] Experimental animals: Germline: SD rat (Beijing Vital River Laboratory Animal Technology Co., Ltd.); Age: 5-6 weeks old; Body weight: 100-150 g.
- [0250] Reagent: Sodium Chloride Injection (SHANDONG QIDU PHARMACEUTICAL CO., LTD.).
- [0251] Instrument: Activity meter (Capintec); Analytical balance with 0.1 mg readability (Sartorius Scientific Instruments Co., Ltd.); Low-energy γ-counter (PerkinElmer Instruments Co., Ltd, USA).

3.2 Experimental steps

- [0252] 1) Empty tubes for γ-counting were weighed and labeled in advance.
- [0253] 2) After the test sample was injected into the tail vein of rats, animal blood samples were collected from the orbit at 2 min, 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 24 h, 48 h and 72 h. The sample tubes containing blood were weighed.
- [0254] 3) The net weight of the blood was calculated, and the radioactive count of the collected blood was determined using a γ-counter.
- [0255] 4) The distribution of the labeled compound in the blood of rats at different time points was determined. The test sample was accurately diluted 100-fold, and 0.5 ml of the dilution was added to a counting tube to serve as a 1% ID standard (i.e., one percent of the injected dose). The radioactive counts of both the 1% ID standard and the biological samples were simultaneously determined using the γ-counter.
- [0256] 5) The pharmacokinetic parameters were calculated using DAS software.
- [0257] Data obtained from rat blood was expressed as the percentage of radioactive count per gram of blood relative to the total dose (radioactive count) (%ID/g). Specific calculation formula: %ID/g = CPM organ or tissue / (CPM total administered dose × W organ or tissue) × 100%
Data for each sampling time point was expressed as mean ± standard deviation (mean±SD).
- [0258] At the same time, the drug concentration in the blood was calculated on the basis of the radioactive count in the blood. Specific calculation formula:

$$\text{Plasma concentration } (\mu\text{Ci/mL}) = \frac{(\text{CPM Blood} / \text{CPM Total administered dose}) \times D (\mu\text{Ci})_{\text{Administered dose}}}{W (\text{g})_{\text{Blood}} / 1 (\text{g/mL})_{\text{Blood density}}}$$

3.3 Experimental results

Table 8. Pharmacokinetic parameters of the compounds of the present disclosure and ¹⁷⁷Lu-FAP-

Pharmacokinetic parameter	Unit	¹⁷⁷ Lu-FAP-2286	¹⁷⁷ Lu-DOTA-09	¹⁷⁷ Lu-DOTA-06	¹⁷⁷ Lu-DOTA-13	¹⁷⁷ Lu-DOTA-14
t _{1/2}	h	1.29±0.43	9.12±4.69	5.43±3.22	7.43±5.58	10.29±6.22
C _{max}	%ID/g	0.73±0.27	0.89±0.21	1.42±0.18	1.42±0.18	0.61±0.06
AUC _{last}	h*%ID/g	0.96±0.14	5.04±0.94	7.31±0.86	7.31±0.86	3.45±0.55
AUC _{INF_obs}	h*%ID/g	0.97±0.14	5.28±1.07	7.53±0.85	7.53±0.85	3.67±0.61
Vz _{obs}	μCi/%ID/g	1.50±0.97	2.21±0.38	1.49±0.30	1.49±0.30	3.71±0.55
Cl _{obs}	μCi/h*%ID/g	0.53±0.08	0.10±0.02	0.07±0.01	0.07±0.01	0.14±0.03
MRT _{last}	h	2.52±0.34	15.49±0.36	14.19±0.40	14.19±0.40	16.77±0.59

[0259] *In vivo* pharmacokinetic experiments showed that the half-life (t_{1/2}) and mean residence time (MRT_{last}) of ¹⁷⁷Lu-DOTA-09, ¹⁷⁷Lu-DOTA-06, ¹⁷⁷Lu-DOTA-13, ¹⁷⁷Lu-DOTA-14 in rats were significantly longer than those of ¹⁷⁷Lu-FAP-2286, which was consistent with the longer intratumoral residence time observed in mouse imaging experiments.

Test Example 4. *In vivo* efficacy experiment of the compounds of the present disclosure in U-87 MG model mice

4.1. Cell information

- [0260] Name: U-87 MG cells
- [0261] Source: Wuhan Pricella Biotechnology Co., Ltd.
- [0262] Cat. No.: CL-0238
- [0263] Batch No.: YBMIL8BQH0
- [0264] Culture conditions: U-87 MG cell specific medium (90% MEM + 10% FBS + 1% P/S)
- [0265] Number of passages: 23-36

4.2. Experimental animals

- [0266] Germline: B-NDG
- [0267] Grade: SPF grade
- [0268] Age: 5 weeks old
- [0269] Body weight: 21-24 g
- [0270] Gender and number: Male; 90 mice were introduced for U-87 MG model construction, among which 40 were selected for study enrollment.
- [0271] Source: Biocytogen Jiangsu Co., Ltd.
- [0272] Production license No.: SCXK (Jiangsu) 2021-0005.
- [0273] Certificate No.: B202311200038

4.3. Experimental drug

[0274] Name: ^{177}Lu -DOTA-09 (see Example 35 for preparation method)

[0275] Specification and composition: 31 mCi/2.5 mL/37.5 nmol

[0276] ^{177}Lu -FAP-2286 (refer to Comparative Example 5)

[0277] Specification and composition: 15.87 mCi/1.25 mL/18.75 nmol

4.4. Instrument device information

Table 9. Instrument device information

Device name	Model	No.	Manufacturer
Activity meter	CRC-55tR	IEB-008-02	Capintec
Electronic balance	DT100	IEB-003-01	Changzhou Shuangjie
Electronic balance	DT100	IEB-003-02	Changzhou Shuangjie
Digital caliper	LR44	IEB-012-01	Shanghai Measuring & Cutting Tool Works Co., Ltd.

4.5. Reagent information

Table 10. Reagent information

Reagent name	Specification	Batch No.	Cat. No.	Storage condition	Manufacturer
PBS	500 mL	BC20230406	BC-BPBS-01	Room temperature	Bio-Channel
Matrigel	5 mL	20223127PHH	082704	2°C-8°C	ABW
Trypsin-EDTA	500 mL	2522739	25200-072	2°C-8°C	Gibco
U-87 MG cell specific medium	125 mL	WH3723K018	CM-0238	2°C-8°C	Procell

4.6. Experimental design

[0278] A suspension containing about 4.5×10^8 U-87 MG cells was prepared and inoculated into the posterior position of the right forelimb of B-NDG mice in an inoculation volume of 100 μL , containing 50% Matrigel and 5×10^6 cells. A total of 90 mice were inoculated. When the tumor in the mice grew to about 150 cm^3 , 40 mice with uniform tumor sizes were selected for study enrollment.

[0279] The administration regimen was as follows:

Route of administration: tail vein injection;

Administration volume: 0.03-0.07 mL/animal;

Administration frequency and dose: The control group was given PBS, the ^{177}Lu -FAP-2286 group was given a single dose of 0.8 mCi/animal, the ^{177}Lu -DOTA-09 0.4mCi group was given a single dose of 0.4 mCi/animal, the ^{177}Lu -DOTA-09 0.8 mCi group was given a single dose of 0.8 mCi/animal, the ^{177}Lu -DOTA-09 0.8mCi $\times$ 2 group was given two doses of 0.8 mCi/animal, with an administration interval of 35 days. Each group included eight animals. The administration time and administration activity of each mouse were recorded in detail.

4.7. Operation steps

[0280] After tumor modeling, the tumor size was observed. On the day before administration or the day of administration, the tumor volume was measured using a digital caliper, and the animal body weight was recorded. The animals were evenly divided into five groups on the basis of tumor volume, as follows: control group, ^{177}Lu -FAP-2286 0.8 mCi group, ^{177}Lu -DOTA-09 0.4 mCi group, ^{177}Lu -DOTA-09 0.8 mCi group, and ^{177}Lu -DOTA-09 0.8 mCi $\times$ 2 group, with eight animals in each group.

[0281] On the day of administration, the test sample was taken for preparation (the stock solution of the test sample was directly used), and the activity of the prepared solution was measured. The workbench surface was wiped with 75% medical alcohol and covered with a disposable sterile tablecloth. 0.5 mL insulin syringes, alcohol swabs, cotton swabs and a marking pen were prepared in the injection room. The mice were placed in a mouse restrainer, and the tails of the mice were disinfected with alcohol swabs. The prepared test sample was injected into each mouse via the tail vein, with the time of each injection recorded.

[0282] From the second day after administration, the stage of tumor and body weight measurement began. The tumor and body weight measurement was performed at least twice a week. During each measurement, the long and short diameters of the tumor were recorded. The measurements were kept at the same location as possible. The abnormalities and deaths of the animals were recorded in time. The animals were euthanized when the mean tumor diameter exceeded 20 mm, or when the tumors exhibited ulceration or necrosis. The tumor volume was calculated as follows: tumor volume (mm^3) = long diameter $\times$ short diameter $\times$ short diameter $\times$ 0.52.

4.8. Experimental results and discussion

Tumor growth curve

[0283] The experimental results showed that different doses of ^{177}Lu -DOTA-09 exhibited certain tumor growth inhibitory effect in U-87 MG model mice (FIG. 11).

[0284] The U-87 MG tumor grew rapidly. On day 20 after administration, the tumor size in the control group reached $3057.58 \pm 715.73 \text{ mm}^3$, the tumor size in the ^{177}Lu -FAP-2286 0.8 mCi group was $1833.89 \pm 338.00 \text{ mm}^3$, the tumor size in the ^{177}Lu -DOTA-09 0.4 mCi group was $790.09 \pm 618.40 \text{ mm}^3$, and the tumor sizes in the ^{177}Lu -DOTA-09 0.8 mCi group and the ^{177}Lu -DOTA-09 0.8 mCi*2 group were $314.25 \pm 65.57 \text{ mm}^3$ and $326.04 \pm 82.5 \text{ mm}^3$, respectively. On day 20 after administration, the tumor inhibition rates in the four administration groups were 40.02%, 74.16%, 89.72% and 89.34%, respectively.

[0285] On day 35 after the first administration, the ^{177}Lu -DOTA-09 0.8 mCi*2 group was subjected to a second administration, which continued to inhibit tumor growth.

[0286] On day 46 after administration, the tumor size in the ^{177}Lu -DOTA-09 0.8 mCi group was $3605.05 \pm 803.40 \text{ mm}^3$, and the tumor size in the ^{177}Lu -DOTA-09 0.8 mCi*2 group was $1735 \pm 482.69 \text{ mm}^3$.

Mouse body weight

[0287] During the administration of ^{177}Lu -DOTA-09, the body weights of the mice were monitored simultaneously. No significant body weight changes were observed in mice across all four dose groups, indicating that ^{177}Lu -DOTA-09 did not cause toxic side effects leading to weight loss in the tumor-bearing animals (FIG. 12).

Mouse survival time

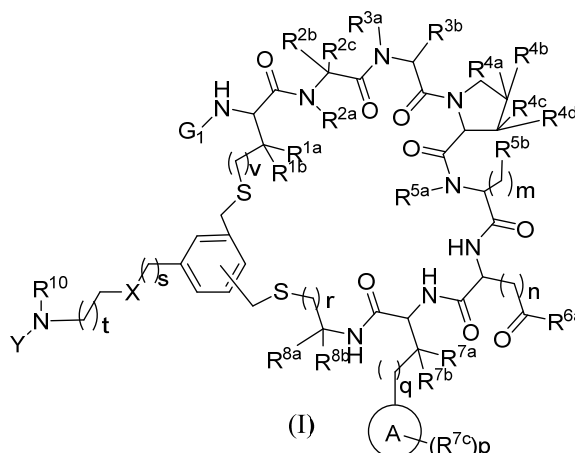
[0288] Statistical analysis showed that ^{177}Lu -DOTA-09 significantly improved the survival rate of U-87 MG model mice (FIG. 13). In the control group, excessive tumor burden appeared from day 20 after administration, and all mice died due to the tumor burden by day 42, with a median survival of 35 days, while in the ^{177}Lu -DOTA-09 0.8 mCi*2 group, about half of the mice remained alive by day 59 after administration, indicating that ^{177}Lu -DOTA-09 showed a significant improvement in the survival of tumor-bearing mice. Statistical analysis showed that the median survival times of the control group, the ^{177}Lu -FAP-2286 0.8 mCi group, the ^{177}Lu -DOTA-09 0.4 mCi group, the ^{177}Lu -DOTA-09 0.8 mCi group and the ^{177}Lu -DOTA-09 0.8 mCi*2 group were 35 days, 39 days, 42 days, 49 days and 57.5 days, respectively.

Experimental conclusion

[0289] ^{177}Lu -DOTA-09, as a ^{177}Lu -labeled radioactive targeted drug, can significantly inhibit the growth of FAP-positive tumors in U-87 MG model mice and prolong the survival time of the mice.

Claims

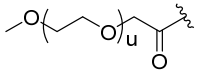
1. A compound as shown in formula (I) or a pharmaceutically acceptable salt thereof,



wherein the R^{1a} and R^{1b} are each independently selected from hydrogen or methyl;

the v is selected from 0 or 1;

the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{3-20} alkylene, the R^{1c} is selected from methyl or $-NH-(C=NH)-NR^{1d}R^{1f}$, and the R^{1d} and R^{1f} are each independently selected from

hydrogen or methyl; or the G_1 is selected from , and the u is selected from an integer from 1 to 5;

the R^{2a} , R^{2b} and R^{2c} are each independently selected from hydrogen or C_{1-3} alkyl;

the R^{3a} and R^{3b} are each independently selected from hydrogen and C_{1-3} alkyl, or the R^{3a} and R^{3b} together with the atom to which each is attached form 5- to 6-membered nitrogen-containing heterocycloalkyl, the C_{1-3} alkyl or 5- to 6-membered nitrogen-containing heterocycloalkyl is optionally substituted with 1, 2 or 3 R^A , and the R^A groups are the same or different, and are selected from hydroxyl, amino, halogen, C_{1-3} alkyl or C_{1-3} haloalkyl;

the R^{4a} , R^{4b} , R^{4c} and R^{4d} are each independently selected from hydrogen, hydroxyl, amino, halogen, C_{1-3} alkyl or C_{1-3} haloalkyl;

the R^{5a} is selected from hydrogen or methyl;

the R^{5b} is selected from C_{1-6} alkyl, 6- to 10-membered aryl or 5- to 6-membered heteroaryl, the C_{1-6} alkyl, 6- to 10-membered aryl or 5- to 6-membered heteroaryl is optionally substituted with 1 or 2 R^B , and the R^B groups are the same or different, and are selected from hydroxyl, amino, halogen and $-CONH_2$;

the m is selected from 1, 2 or 3; the hydrogen on CH₂ is optionally substituted with one or more groups selected from hydroxyl, halogen, C₁₋₃ alkyl, 6- to 10-membered aryl or 5- to 6-membered heteroaryl;

the R^{6a} is selected from hydroxyl or amino;

the n is selected from 1, 2 or 3;

the R^{7a} and R^{7b} are each independently selected from hydrogen and C₁₋₃ alkyl;

the q is selected from 0 or 1;

the ring A is selected from phenyl, pyridyl, naphthyl or thienyl;

each R^{7c} is independently selected from halogen, nitro, amino, cyano, hydroxyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy C₁₋₆ alkyl, trifluoromethyl, difluoromethyl and trifluoroethyl;

the p is selected from 0, 1, 2 or 3;

the R^{8a} and R^{8b} are each independently selected from hydrogen, -COOH, -CONH₂, CH₂-OH, -CONHR^{8c} and -(CO)-(NR^{8c})-R^{8d}, and the R^{8c} and R^{8d} are each independently selected from C₁₋₆ alkyl;

the r is selected from 0 or 1;

the s is selected from 0 or 1;

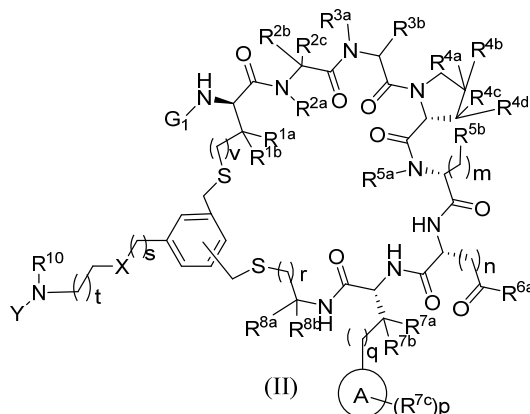
the X is selected from O, S or NR⁹, and the R⁹ is selected from hydrogen or C₁₋₆ alkyl;

the t is selected from 1, 2, 3, 4, 5 or 6;

the R¹⁰ is selected from hydrogen or C₁₋₆ alkyl;

the Y is a chelating agent or hydrogen, and the chelating agent optionally complexes a nuclide; preferably, the Y is a chelating agent.

2. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is a compound as shown in formula (II) or a pharmaceutically acceptable salt thereof,



wherein the R^{1a} , R^{1b} , v , G_1 , R^{2a} , R^{2b} , R^{2c} , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{5a} , R^{5b} , m , R^{6a} , n , R^{7a} , R^{7b} , q , ring A , R^{7c} , p , R^{8a} , R^{8b} , r , s , X , t , R^{10} and Y are as defined in claim 1.

3. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein the R^{2a} is hydrogen or methyl, and the R^{2b} and R^{2c} are each independently selected from hydrogen or methyl; preferably, the R^{2b} is hydrogen, the R^{2c} is methyl, or the R^{2b} and R^{2c} are both methyl.
4. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 3, wherein the R^{4a} and R^{4b} are each independently selected from hydrogen and hydroxyl; preferably, the R^{4a} is hydrogen, and the R^{4b} is hydroxyl.
5. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to either claim 3 or claim 4, wherein the R^{2a} is hydrogen or methyl; the R^{2b} and R^{2c} are each independently selected from hydrogen or methyl, with at least one being methyl; the R^{4a} is hydrogen, and the R^{4b} is hydroxyl; the R^{4c} and R^{4d} are each independently selected from hydrogen.
6. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein the R^{3a} and R^{3b} are each independently selected from hydrogen and C_{1-3} alkyl, the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R^A , and the R^A groups are the same or different, and are selected from hydroxyl, amino, halogen, C_{1-3} alkyl or C_{1-3} haloalkyl; preferably, the R^{3a} is methyl, and the R^{3b} is hydrogen.
7. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein the R^{3a} and R^{3b} together with the atom to which each is attached form 5-membered nitrogen-containing heterocycloalkyl, the 5-membered nitrogen-containing heterocycloalkyl is optionally substituted with 1, 2 or 3 R^A , and the R^A groups are the same or different, and are selected from hydroxyl, amino, halogen, C_{1-3} alkyl or C_{1-3} haloalkyl; preferably, the 5-membered nitrogen-containing heterocycloalkyl is unsubstituted.
8. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 7, wherein the R^{7a} and R^{7b} are each independently selected from hydrogen and C_{1-3} alkyl;
the q is selected from 0 or 1;
the ring A is selected from phenyl or naphthyl;
each R^{7c} is independently selected from halogen, nitro, amino, cyano, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy C_{1-6} alkyl, trifluoromethyl, difluoromethyl and trifluoroethyl;

the p is selected from 0, 1, 2 or 3;

preferably,

the R^{7a} and R^{7b} are each independently selected from hydrogen;

the q is 0;

the ring A is selected from phenyl;

each R^{7c} is independently selected from fluorine, chlorine, bromine and iodine, or

trifluoromethyl, difluoromethyl and trifluoroethyl;

the p is selected from 0, 1 or 2.

9. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 8, wherein the R^{1a} and R^{1b} are each independently selected from hydrogen or methyl;

the v is selected from 0 or 1;

the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{3-20} alkylene, and the R^{1c} is selected from methyl;

preferably, the R^{1a} and R^{1b} are each independently selected from hydrogen;

the v is selected from 0;

the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{4-14} alkylene, and the R^{1c} is selected from methyl.

10. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 8, wherein the R^{1a} and R^{1b} are each independently selected from hydrogen or methyl;

the v is selected from 0 or 1;

the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{3-20} alkylene, the R^{1c} is selected from $-NH-(C=NH)-NR^{1d}R^{1f}$, and the R^{1d} and R^{1f} are each independently selected from hydrogen or methyl;

preferably,

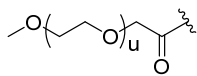
the R^{1a} and R^{1b} are each independently selected from hydrogen;

the v is selected from 0;

the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{4-14} alkylene, the R^{1c} is selected from $-NH-(C=NH)-NR^{1d}R^{1f}$, and the R^{1d} and R^{1f} are each independently selected from hydrogen or methyl.

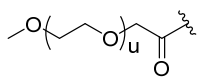
11. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 8, wherein the R^{1a} and R^{1b} are each independently selected from hydrogen or methyl;

the v is selected from 0 or 1;



the G_1 is selected from , and the u is selected from an integer from 1 to 5; preferably,

the R^{1a} and R^{1b} are each independently selected from hydrogen;



the G_1 is selected from ;

the v is selected from 0;

the u is selected from 1 or 2.

12. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 11, wherein

the R^{5a} is selected from hydrogen;

the R^{5b} is selected from C_{1-6} alkyl, the C_{1-6} alkyl is optionally substituted with 1 or 2 R^B , and the R^B groups are the same or different, and are selected from hydroxyl or halogen;

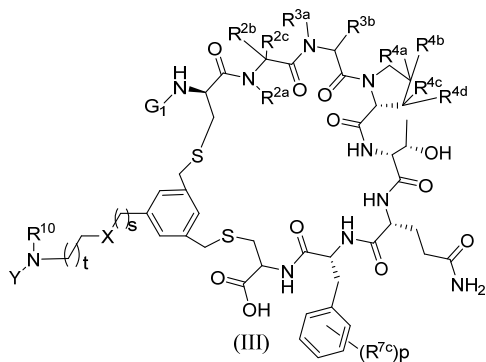
the m is selected from 0 or 1; the hydrogen on CH_2 is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-3} alkyl;

the n is 2;

the R^{6a} is amino;

the R^{8a} and R^{8b} are each independently selected from hydrogen, $-COOH$ and $-CONH_2$, with at least one being $-COOH$ or $-CONH_2$, and the r is 1.

13. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is a compound as shown in formula (III) or a pharmaceutically acceptable salt thereof,



wherein the R^{2a} is hydrogen or methyl;

the R^{2b} and R^{2c} are each independently selected from hydrogen or methyl, with at least one being methyl;

the R^{3a} and R^{3b} are each independently selected from hydrogen and C_{1-3} alkyl, the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R^A , and the R^A groups are the same or different, and are selected from hydroxyl, amino, halogen, C_{1-3} alkyl or C_{1-3} haloalkyl; or the R^{3a} and R^{3b} together with the atom to which each is attached form 5-membered nitrogen-containing heterocycloalkyl, the 5-membered nitrogen-containing heterocycloalkyl is optionally substituted with 1, 2 or 3 R^A , and the R^A groups are the same or different, and are selected from hydroxyl, amino, halogen, C_{1-3} alkyl or C_{1-3} haloalkyl;

the R^{4a} is hydrogen, fluorine or trifluoromethyl, and the R^{4b} is fluorine or hydroxyl;

the R^{4c} and R^{4d} are each independently selected from hydrogen;

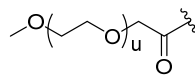
each R^{7c} is independently selected from fluorine, chlorine, bromine and iodine, or trifluoromethyl, difluoromethyl and trifluoroethyl;

the p is selected from 0, 1 or 2;

the G_1 , s , X , t , R^{10} and Y are as defined in claim 1.

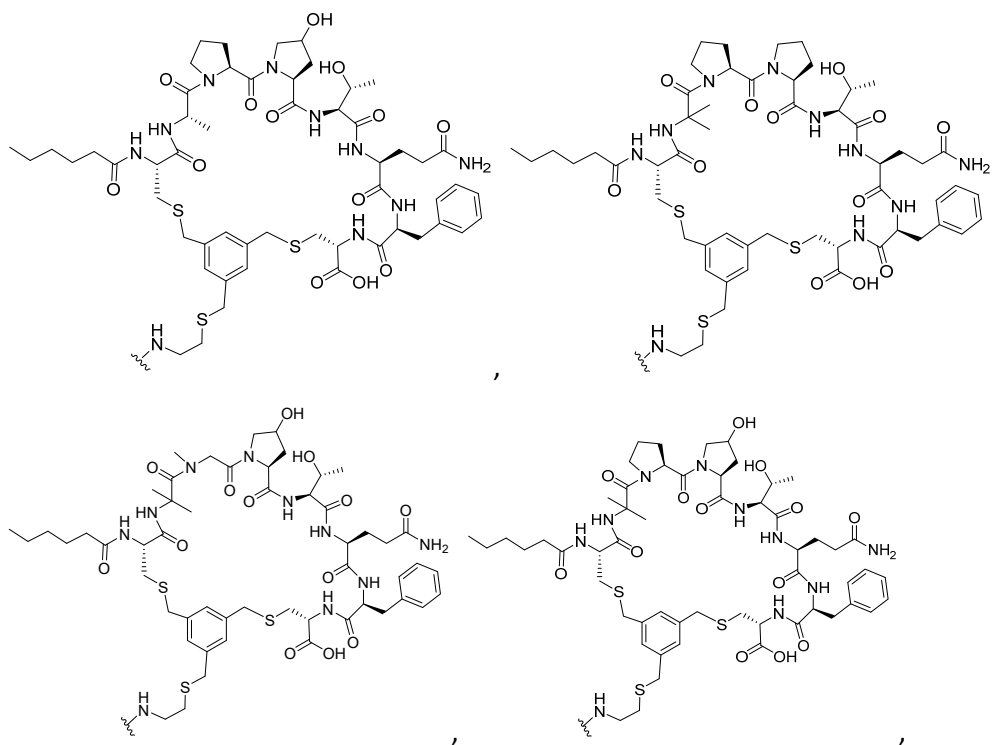
14. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to claim 13, wherein the R^{4a} is hydrogen, and the R^{4b} is hydroxyl.
15. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to claim 14, wherein the R^{3a} is methyl, and the R^{3b} is hydrogen.
16. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to claim 14, wherein the R^{3a} and R^{3b} together with the atom to which each is attached form 5-membered nitrogen-containing heterocycloalkyl, and the 5-membered nitrogen-containing heterocycloalkyl is unsubstituted.

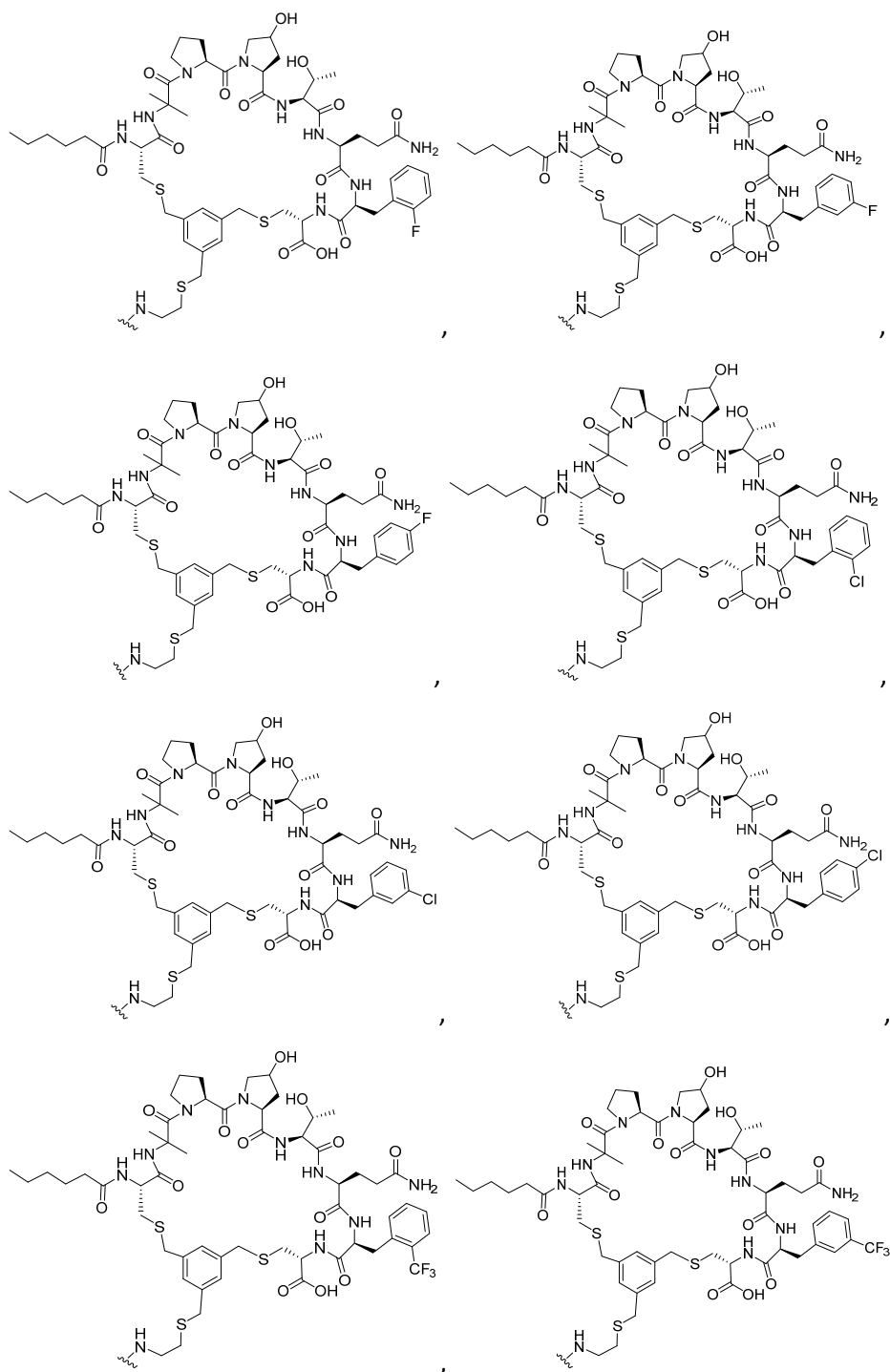
17. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 16, wherein the s is 1; X is S ; R^{10} is hydrogen.
18. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to 17, wherein the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{4-14} alkylene, and the R^{1c} is selected from methyl; preferably, the L is selected from C_4 alkylene, C_6 alkylene, C_8 alkylene, C_{10} alkylene, C_{12} alkylene or C_{14} alkylene.
19. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to 17, wherein the G_1 is selected from $-(CO)-L-R^{1c}$, the L is selected from $-(CO)-L-R^{1c}$, the L is selected from C_{4-14} alkylene, the R^{1c} is selected from $-NH(C=NH)-NR^{1d}R^{1f}$, and the R^{1d} and R^{1f} are each independently selected from hydrogen or methyl; preferably, the L is selected from C_4 alkylene, C_5 alkylene or C_6 alkylene.
20. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according

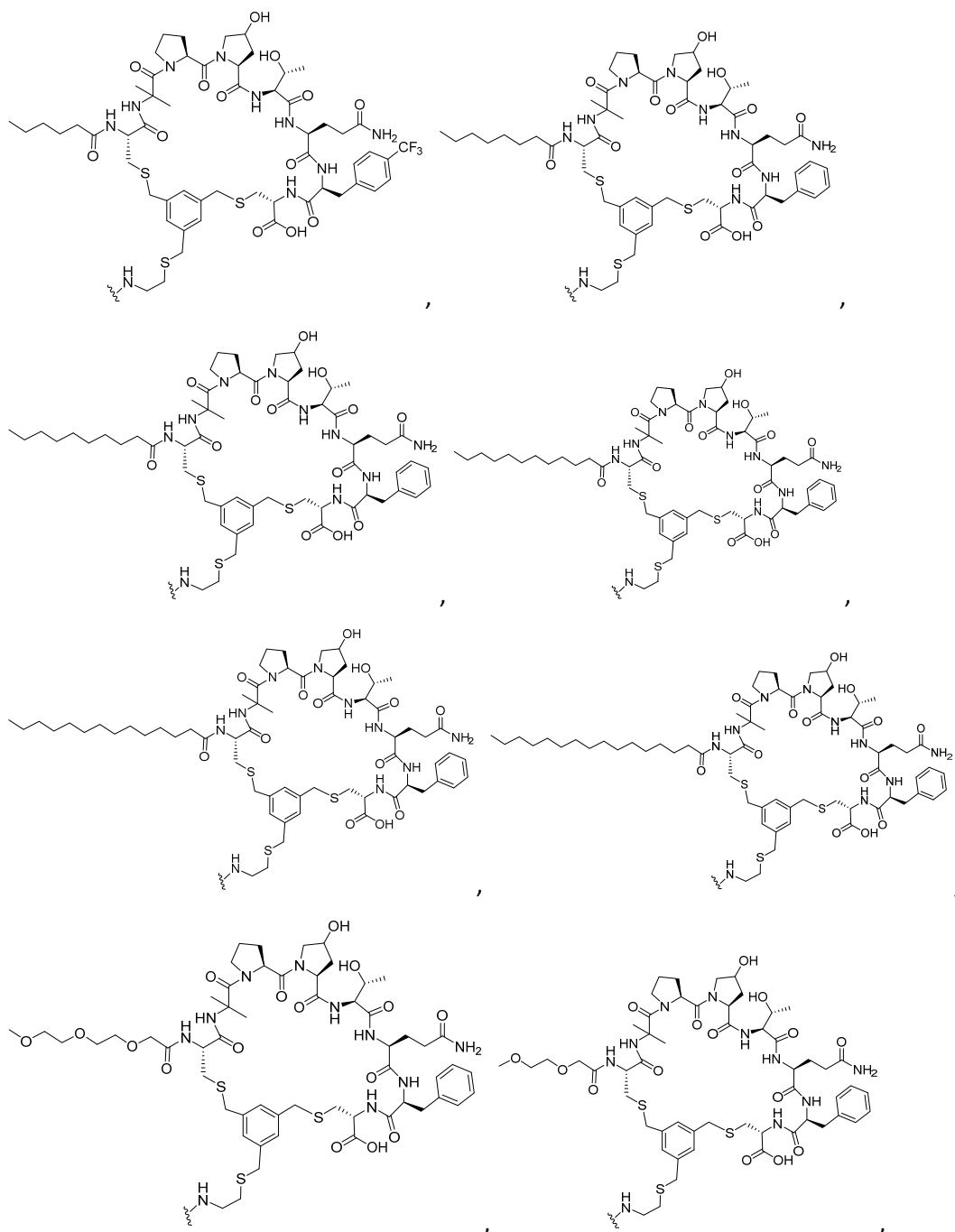


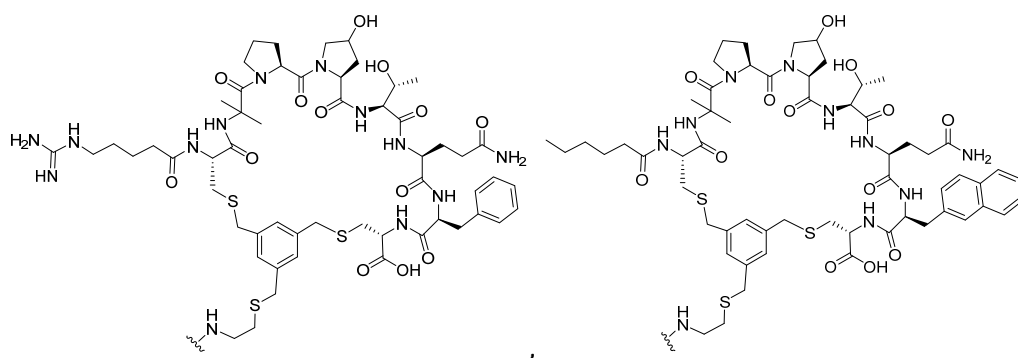
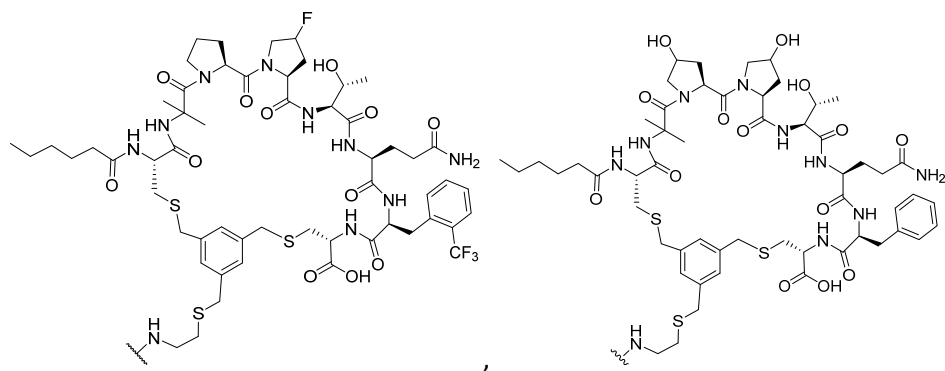
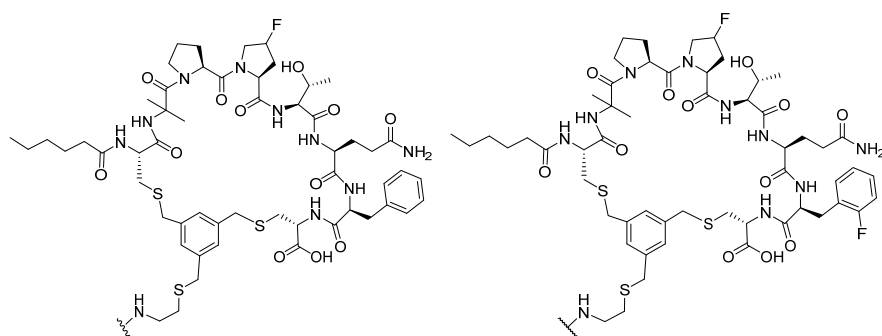
to claim 17, wherein the G_1 is selected from , and the u is selected from 1 or 2.

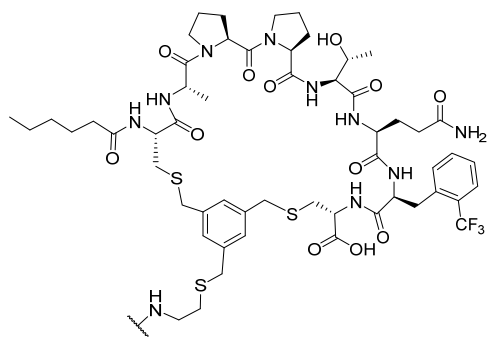
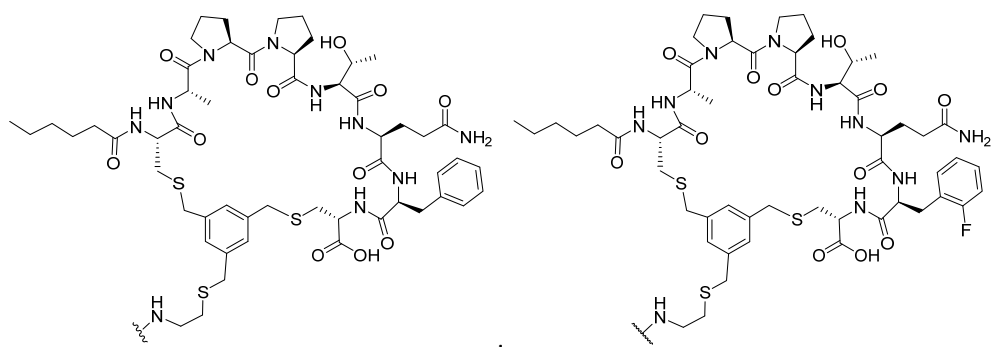
21. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 20, wherein the fragment attached to Y is selected from group 1:



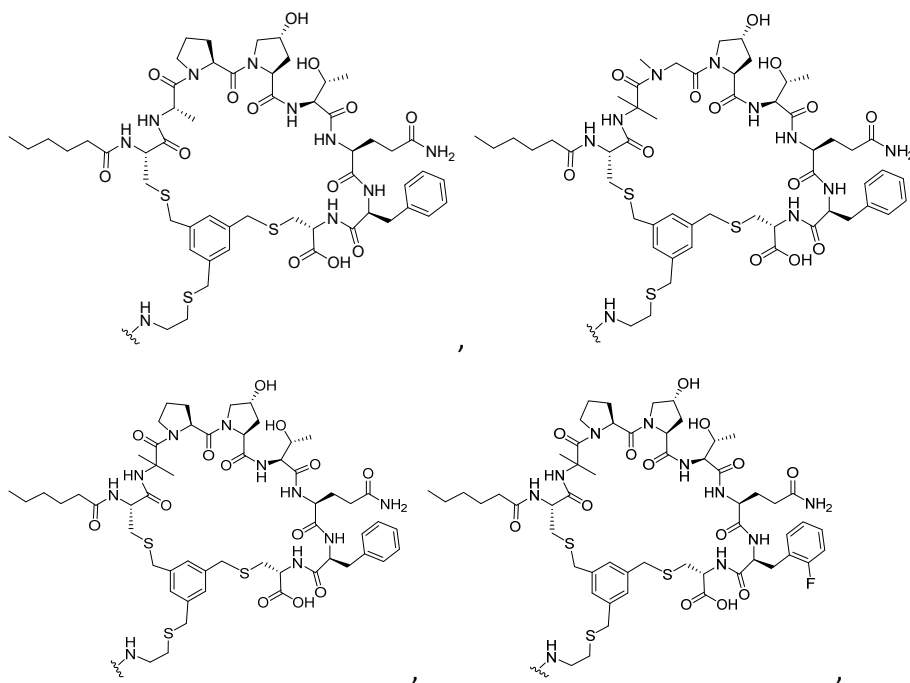


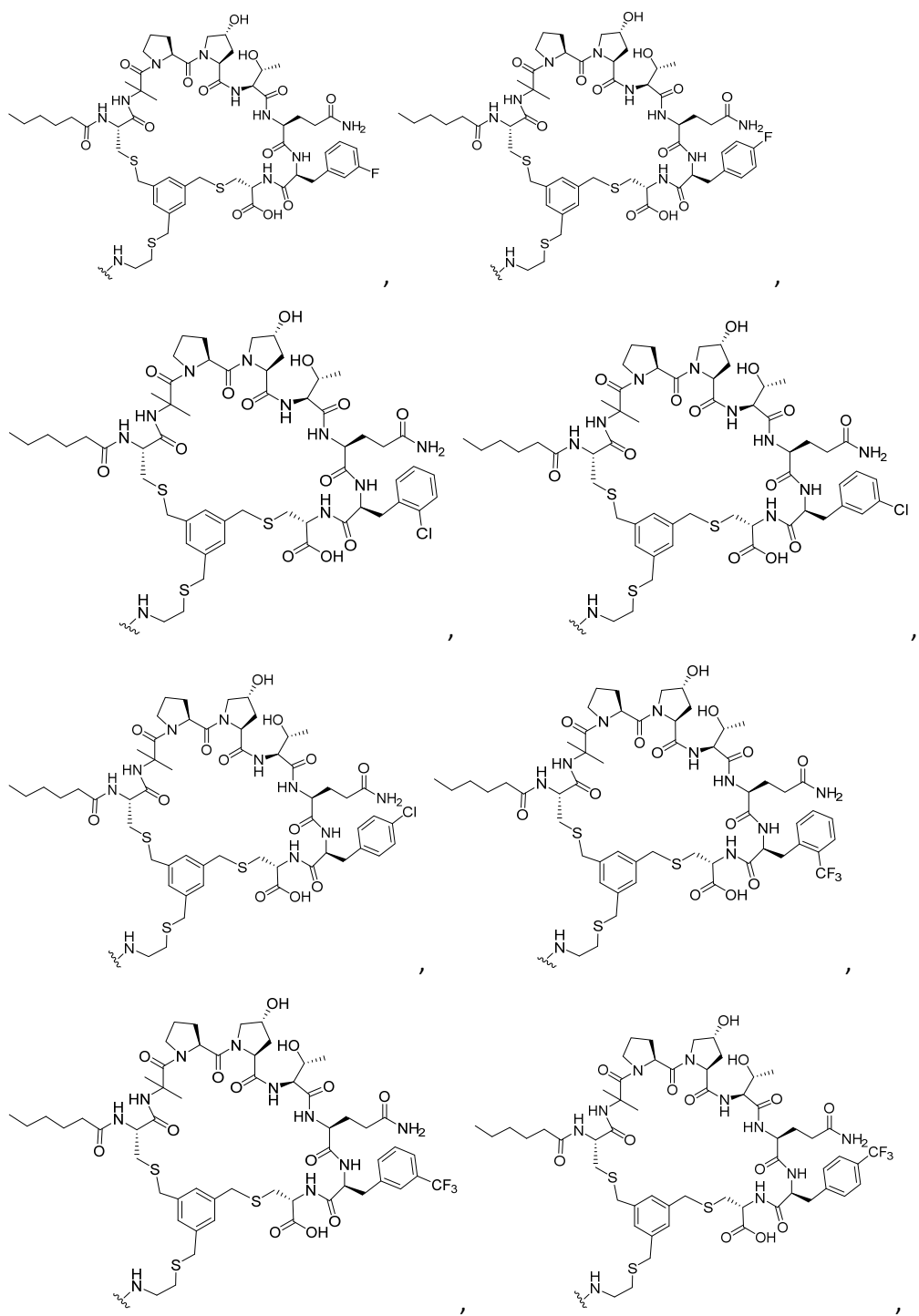


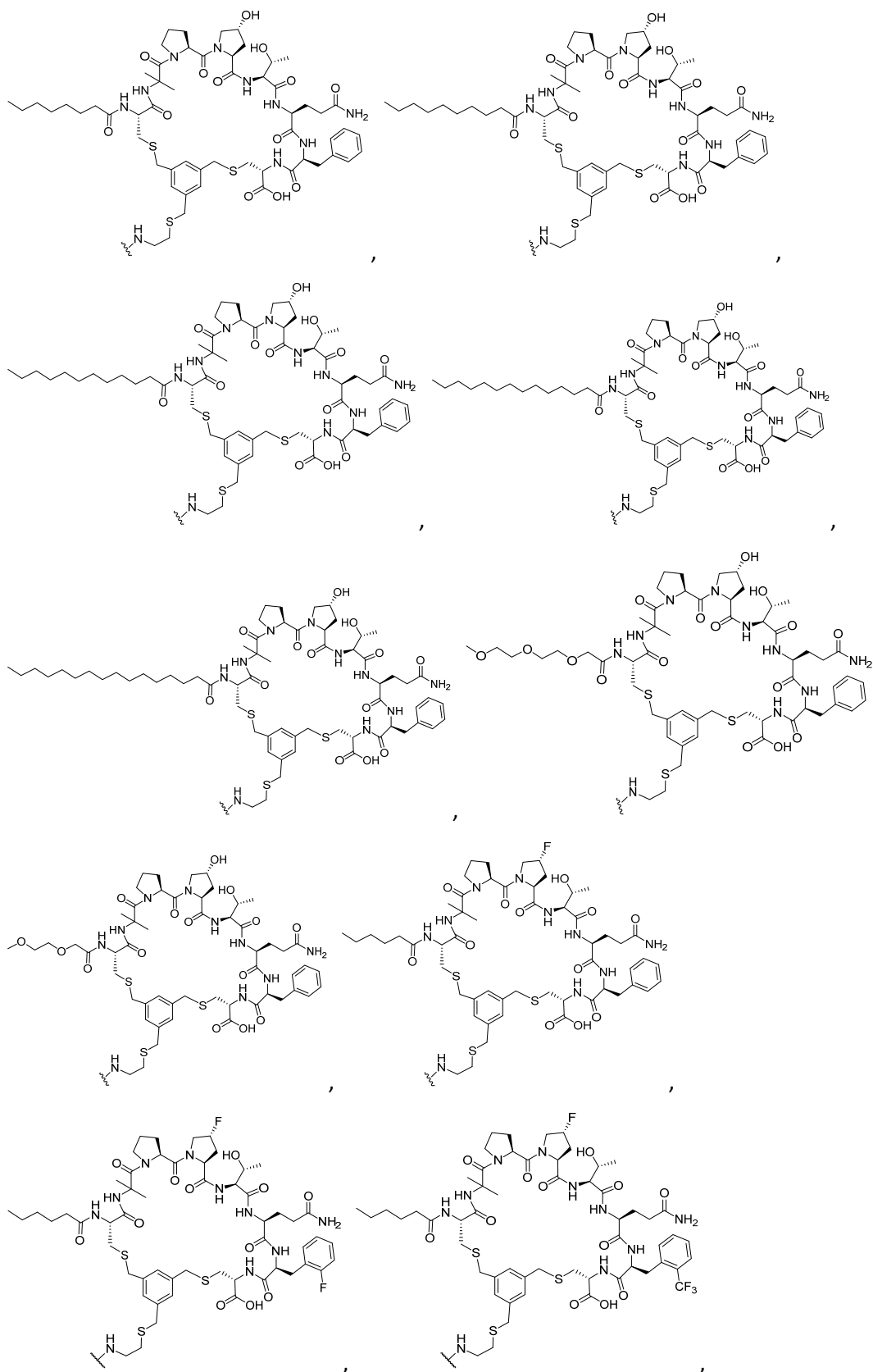


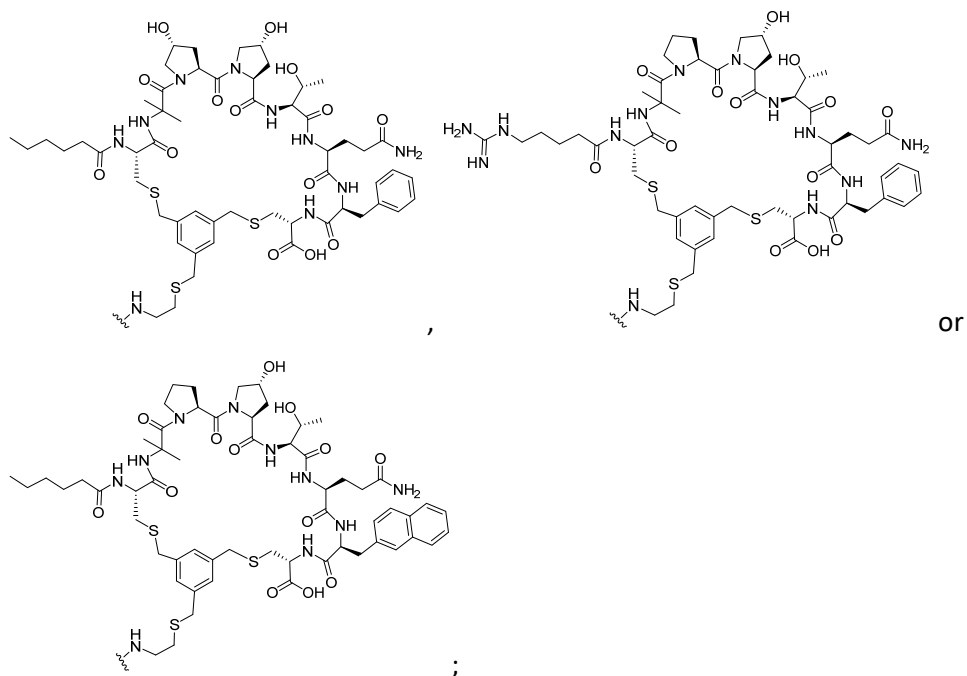


group 2:

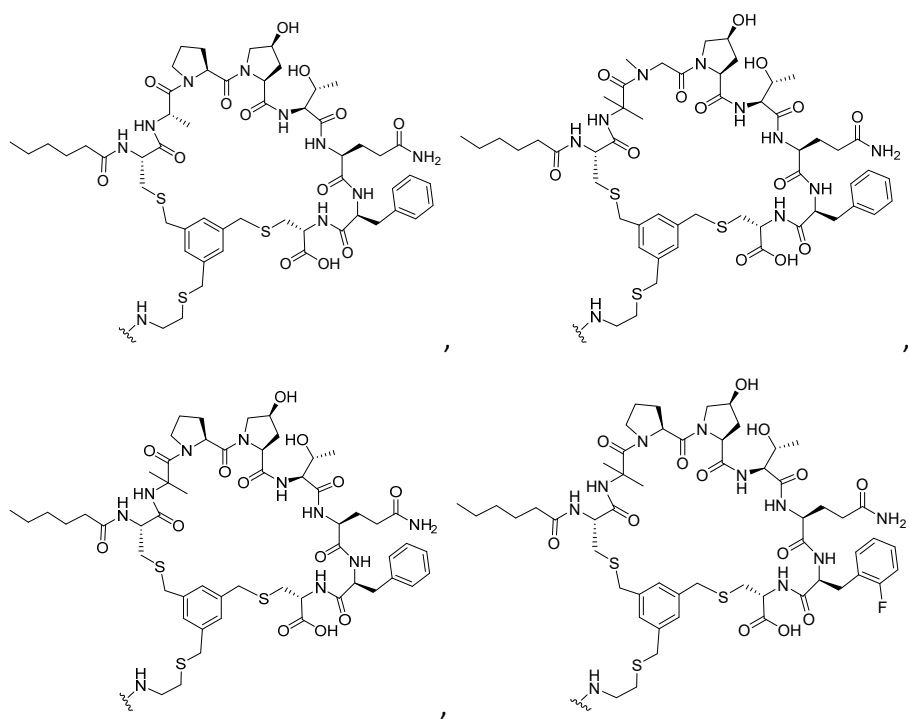


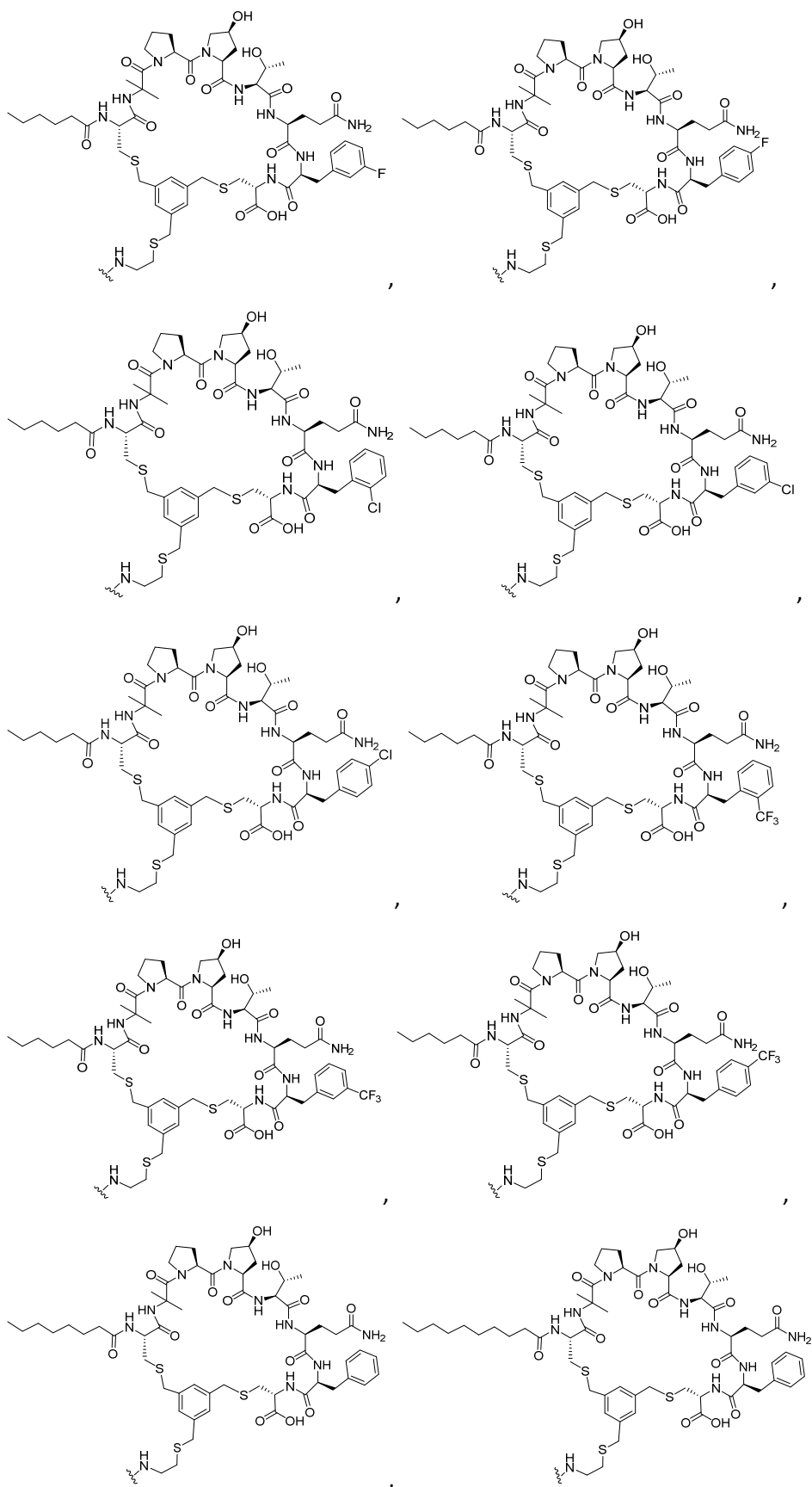


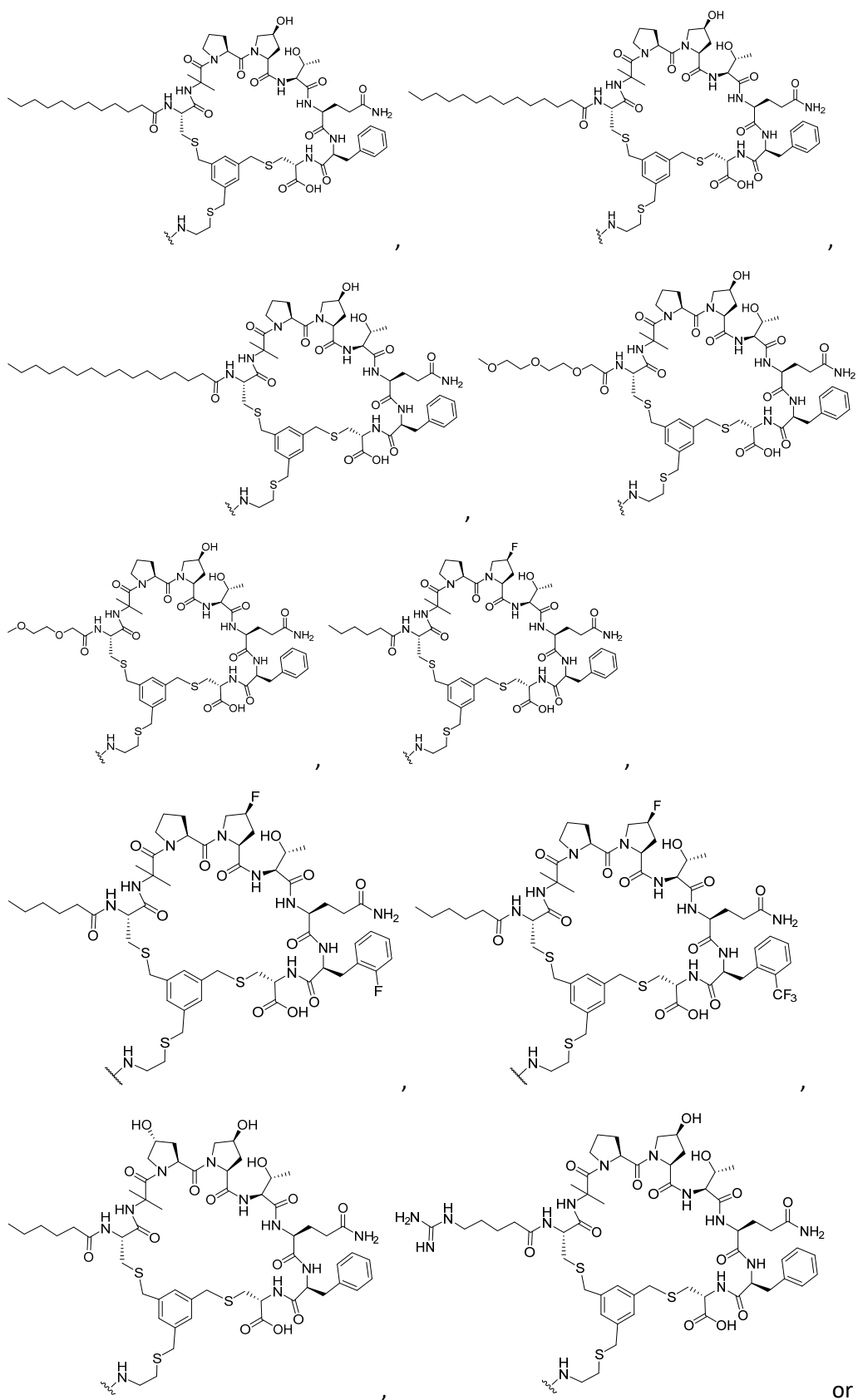


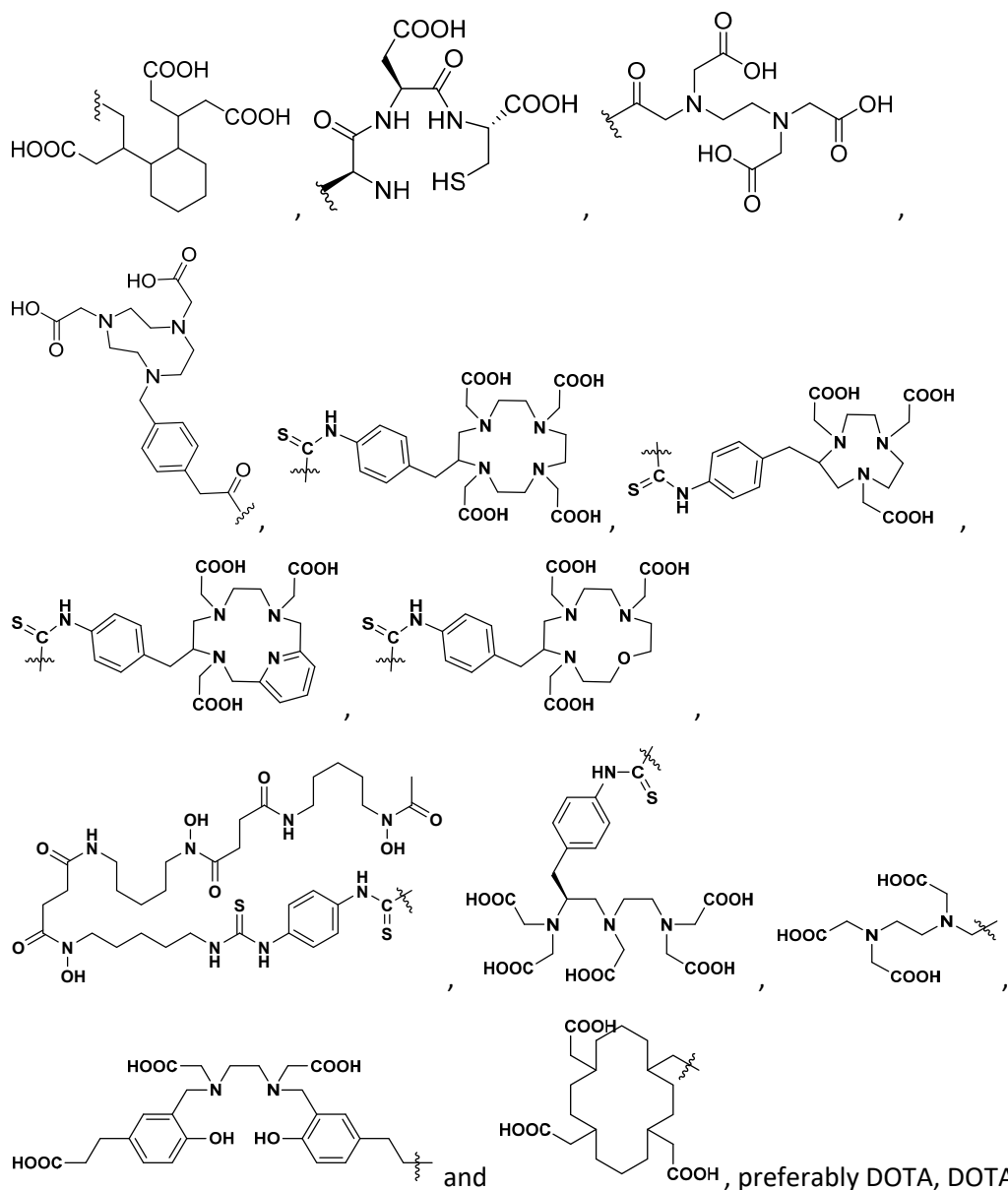


group 3:



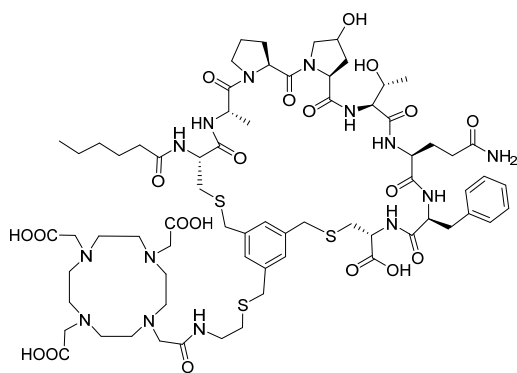




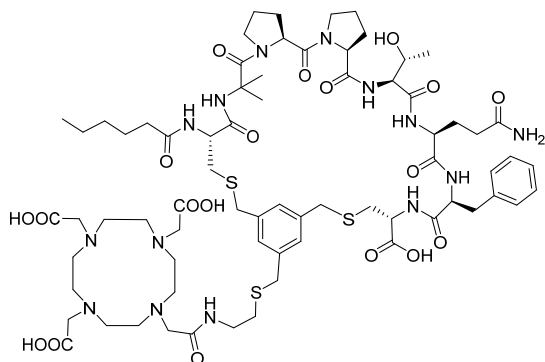


preferably DOTA, DOTAGA, NOTA, NODAGA, NODA-MPAA, HBED, CB-TE2A, DFO, THP and N_4 , and most preferably DOTA, DOTAGA, NOTA and NODAGA.

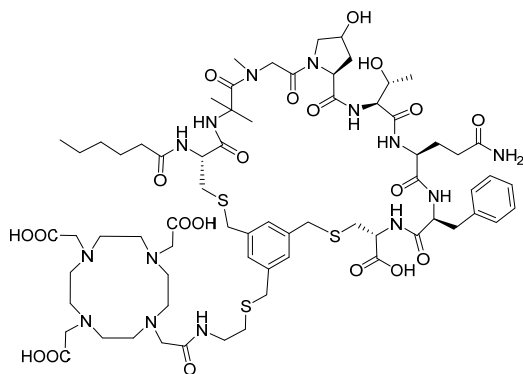
23. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 22, wherein the compound is selected from:
- group 4:



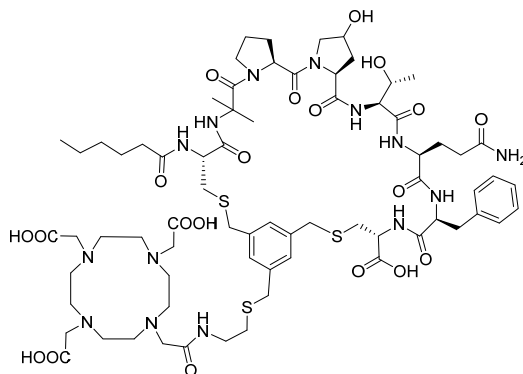
Hex-[Cys-(tMeBn(DOTA-AET))-Ala-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-Pro-Thr-Gln-Phe-Cys]-OH,



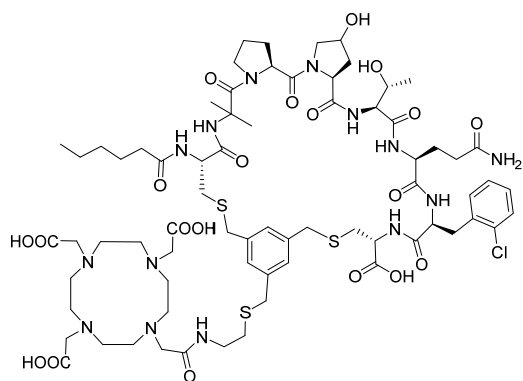
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Sar-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



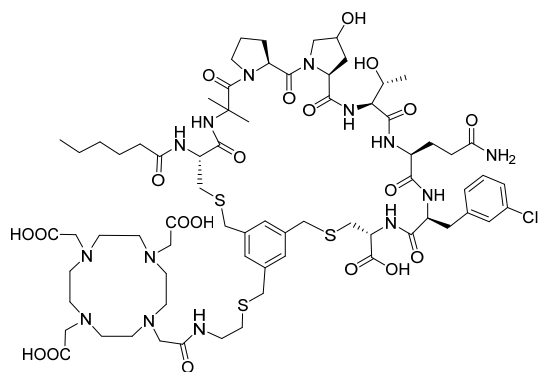
Chemical structure of compound 10, a macrocyclic peptide derivative. The structure shows a 14-membered macrocycle with four nitrogen atoms and four carboxylic acid groups. The macrocycle is substituted with a long alkyl chain, a thioether linkage, and a complex side chain containing a fluorophore (4-fluorophenyl) and a hydroxyl group.

CCCCCCC(=O)N[C@@H](C(=O)N[C@@H](CS[C@@H](c1ccc(CS[C@@H](c2ccc(cc2)NC(=O)O)cc2)cc1)C(=O)O)C(=O)O[illegible]

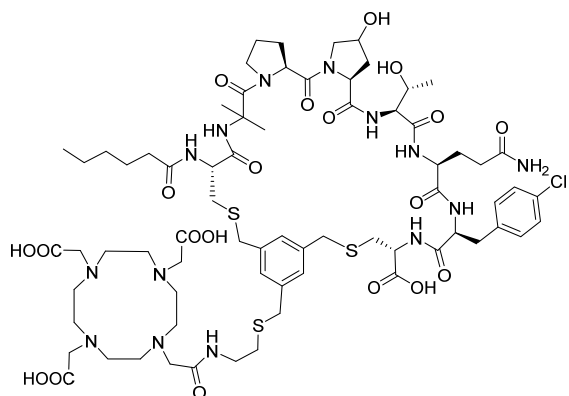
154



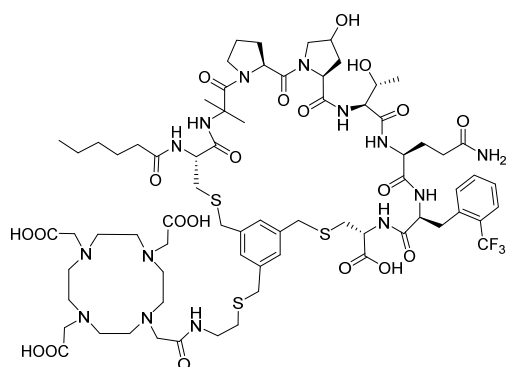
Hex-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-(4-OH-Pro)-Thr-Gln-(2-Cl-Phe)-Cys]-OH,



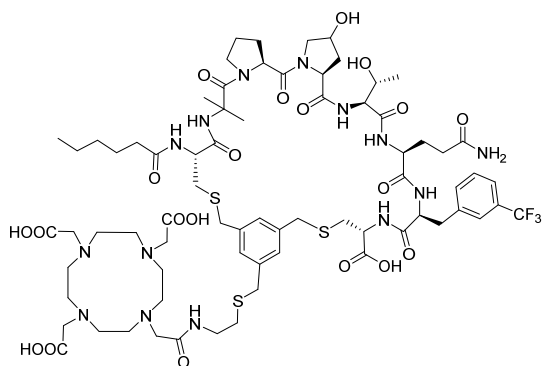
Hex-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-(4-OH-Pro)-Thr-Gln-(3-Cl-Phe)-Cys]-OH,



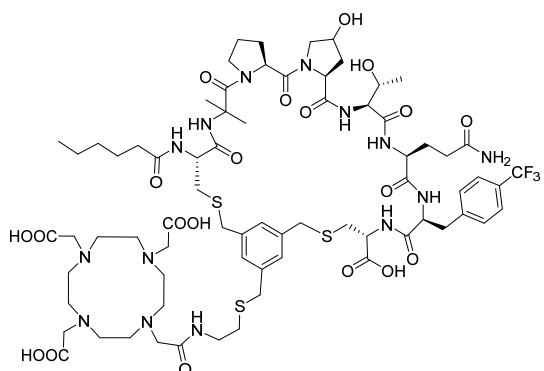
Hex-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-(4-OH-Pro)-Thr-Gln-(4-Cl-Phe)-Cys]-OH,



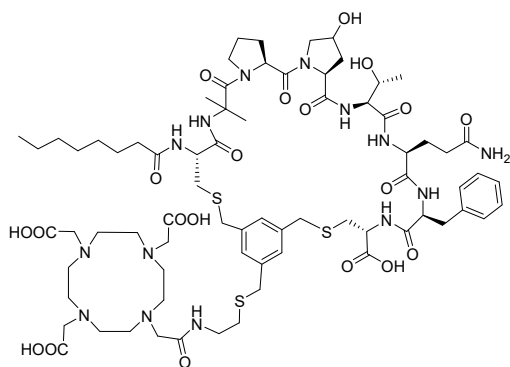
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-(2-CF₃-Phe)-Cys]-OH,



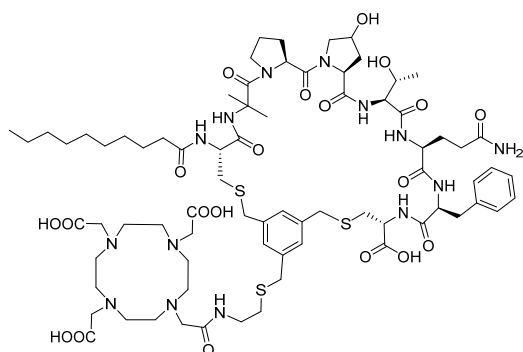
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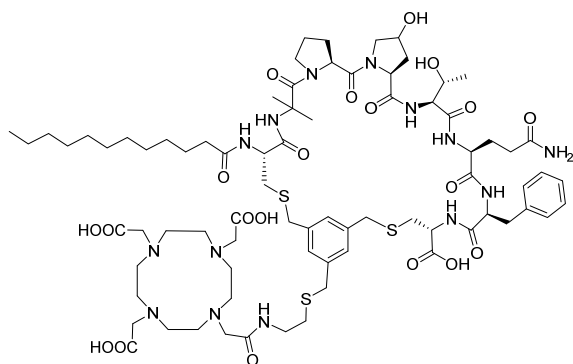
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-(4-CF₃-Phe)-Cys]-OH,



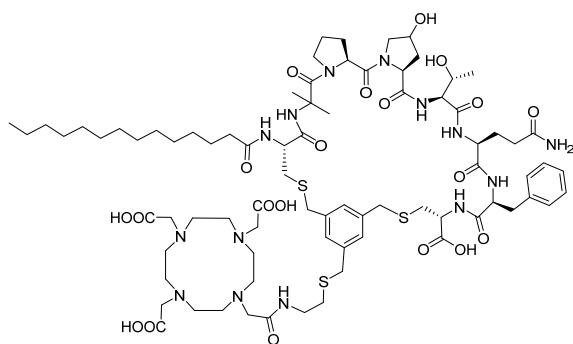
Oct-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



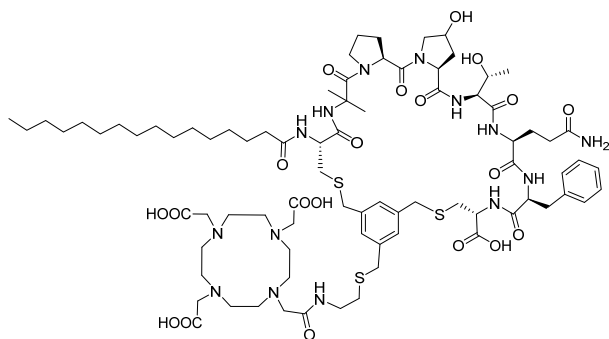
Dec-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



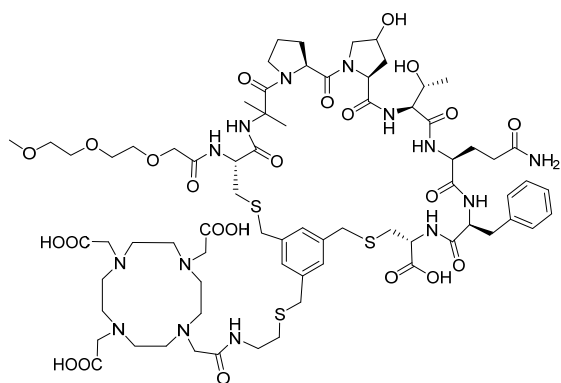
Dod-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



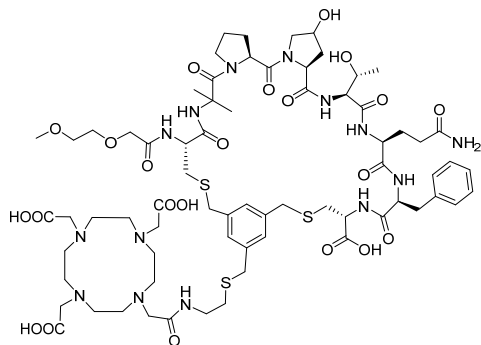
Tet-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



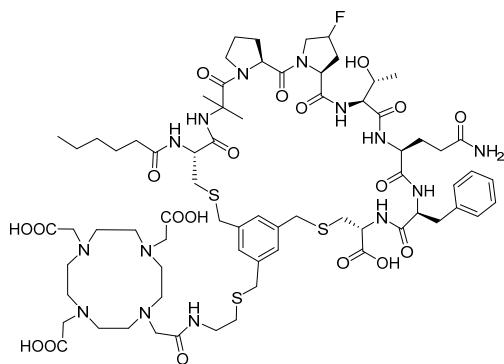
Pal-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



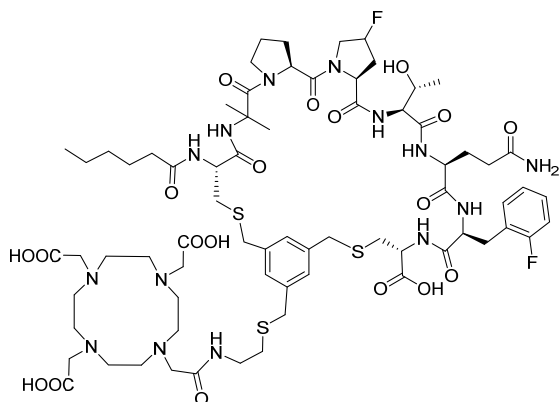
{2-[2-(2-Methoxyethoxy)ethoxy]-Ace}-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



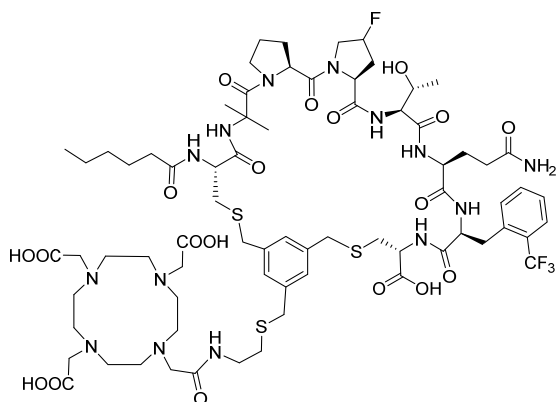
[2-(2-Methoxyethoxy)-Ace]-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



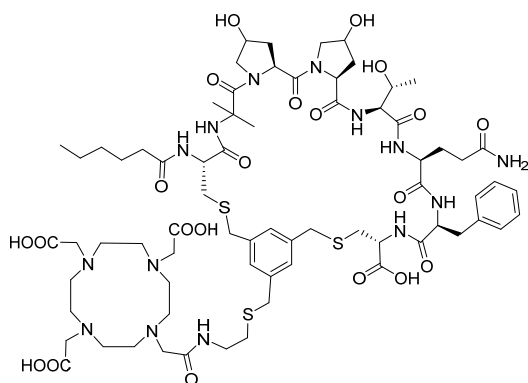
Hex-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-(4-F-Pro)-Thr-Gln-Phe-Cys]-OH,



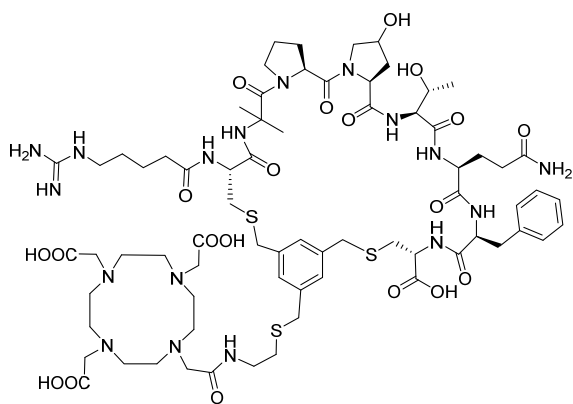
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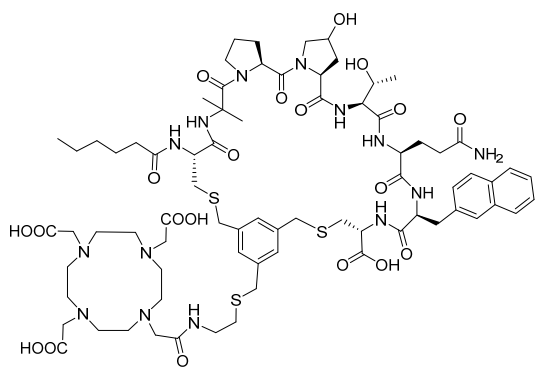
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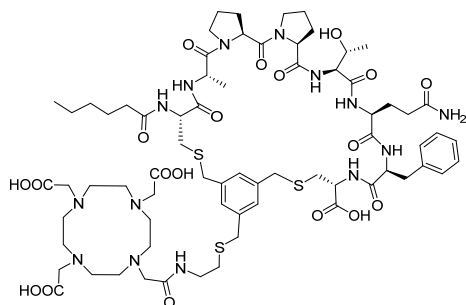
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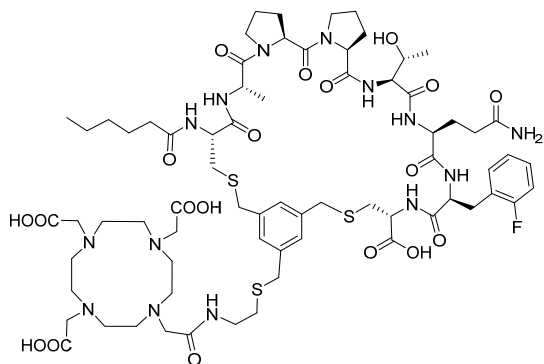
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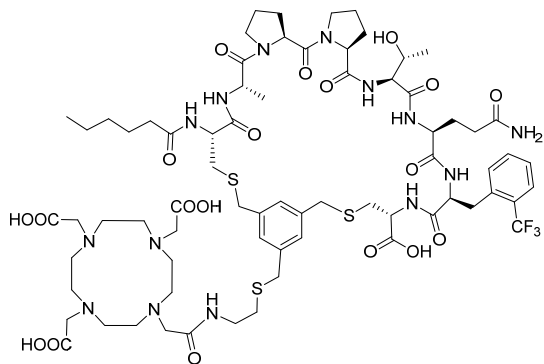
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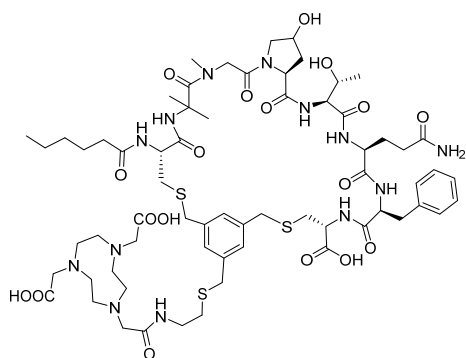
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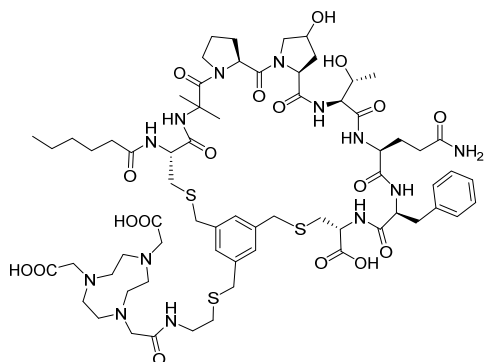
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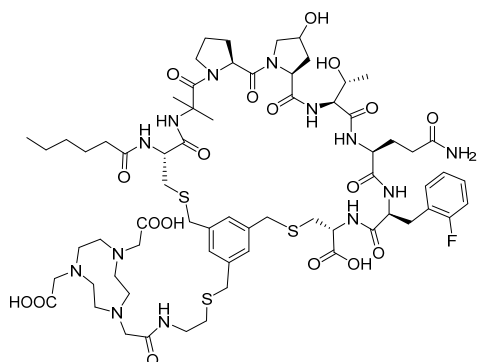
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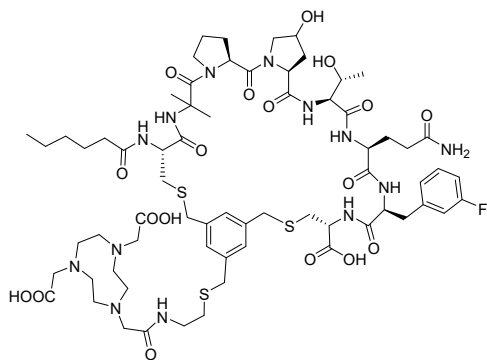
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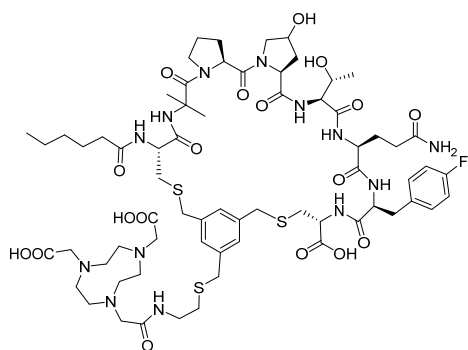
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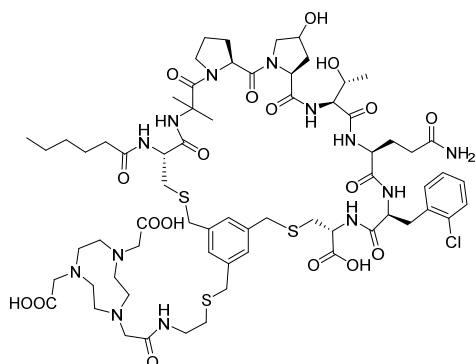
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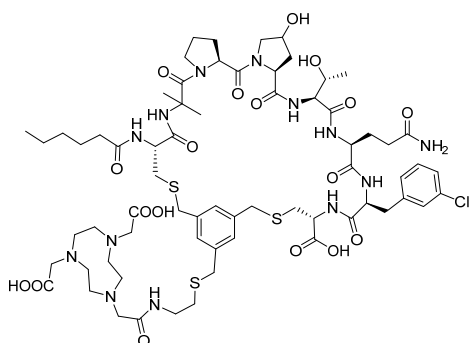
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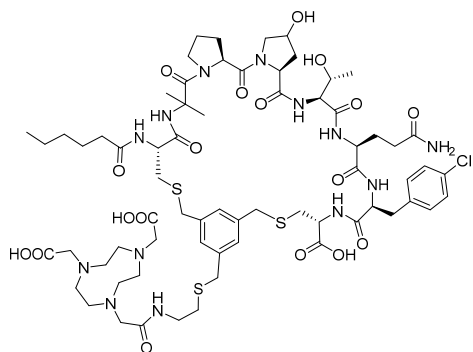
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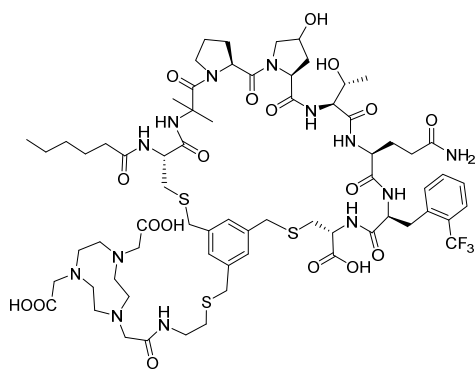
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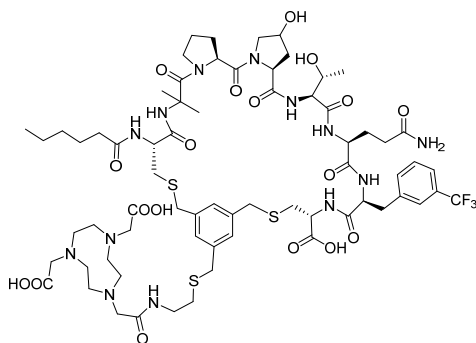
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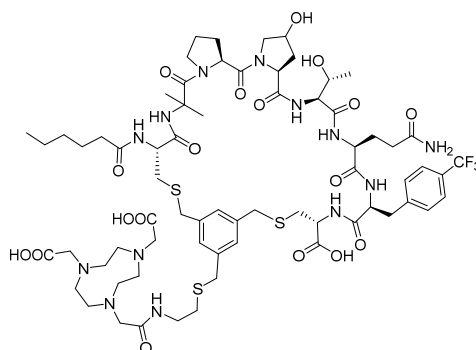
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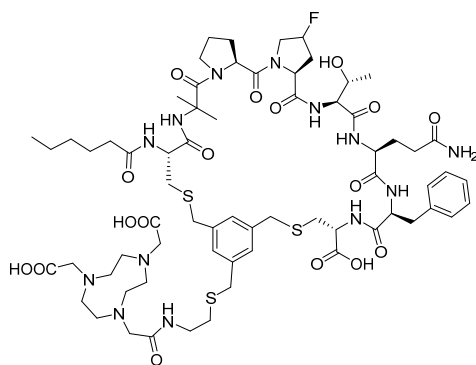
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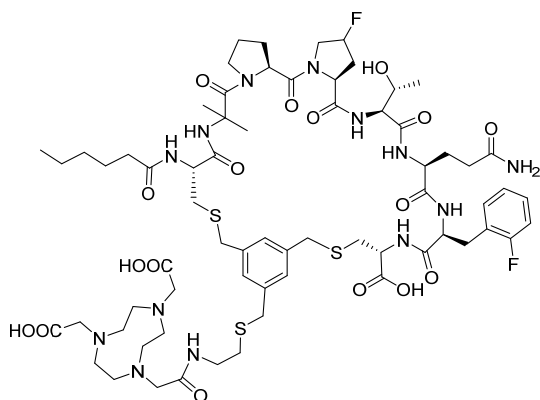
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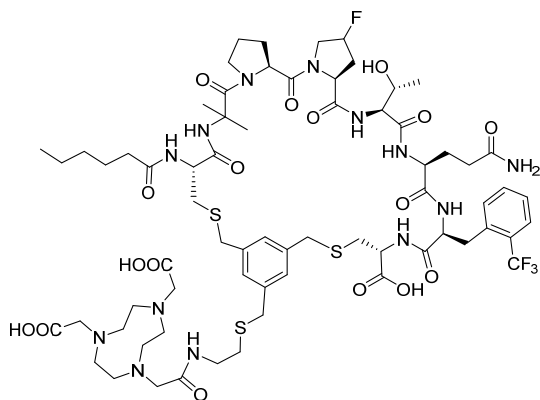
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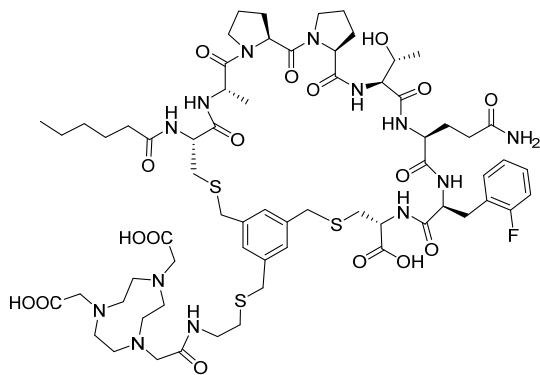
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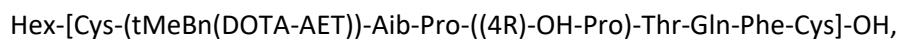
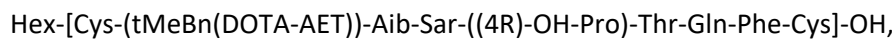
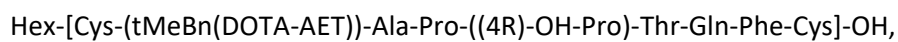
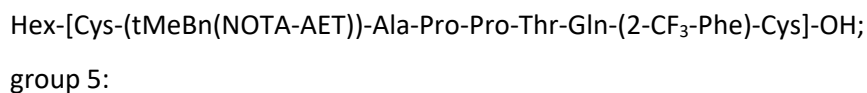
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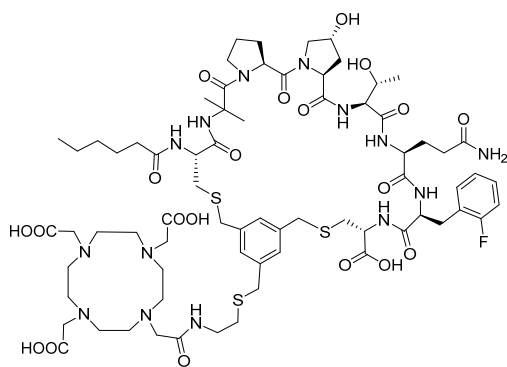


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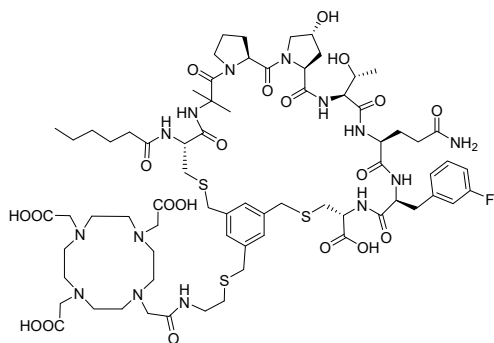


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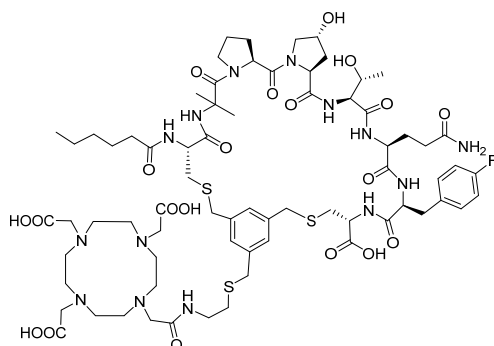




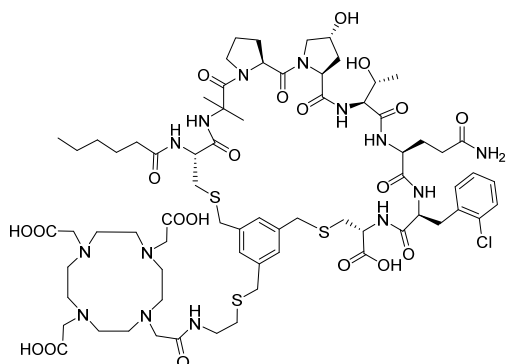
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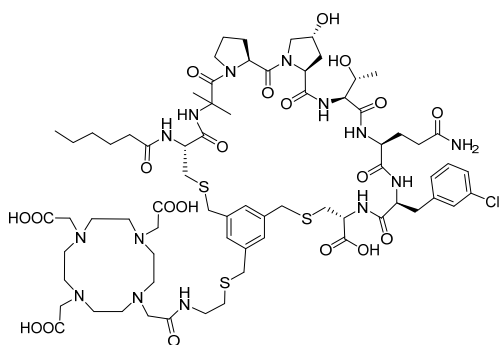
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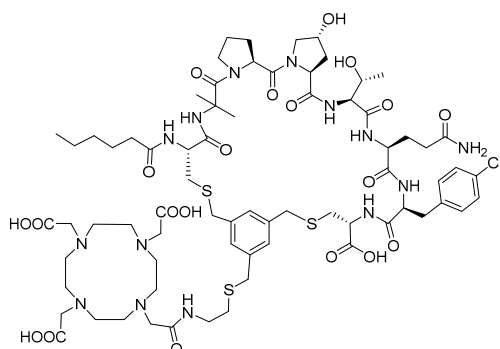
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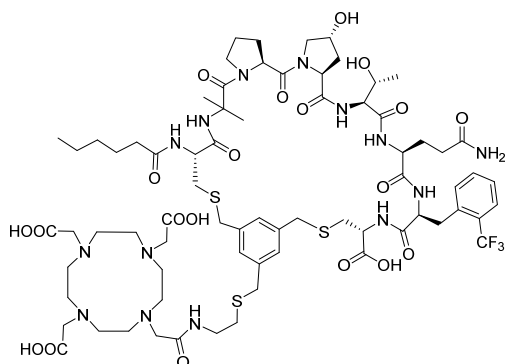
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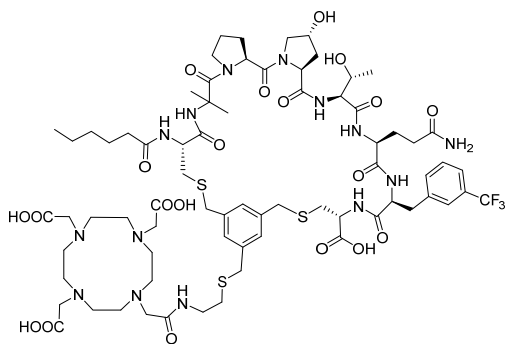
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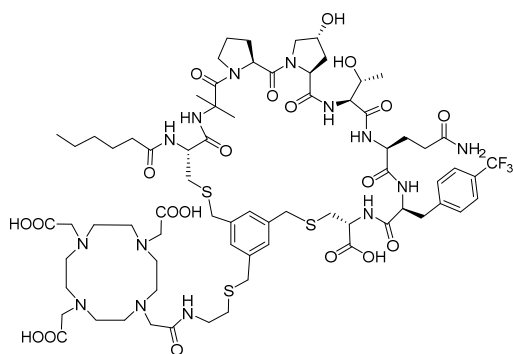
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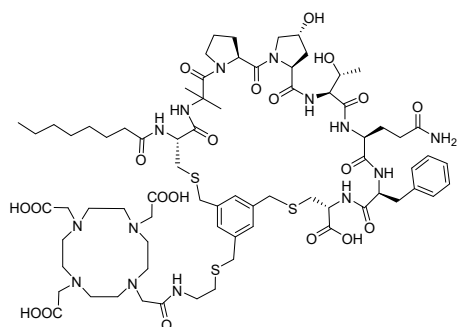
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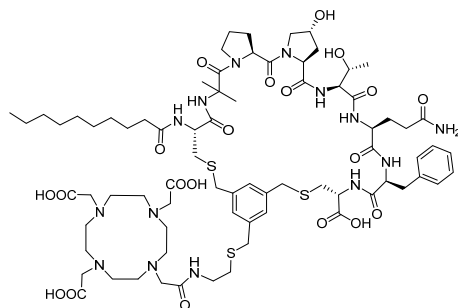
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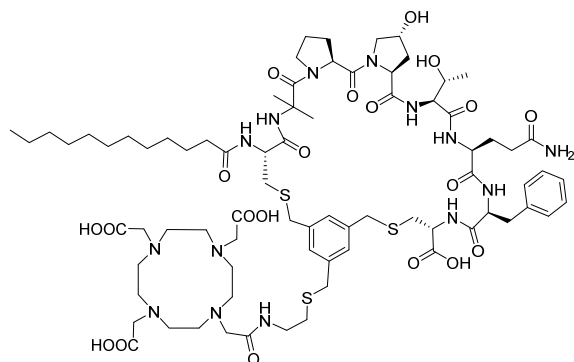
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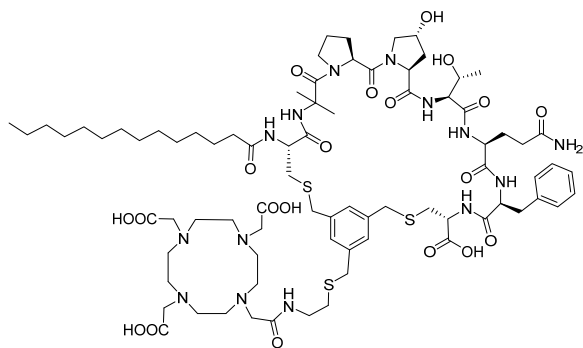
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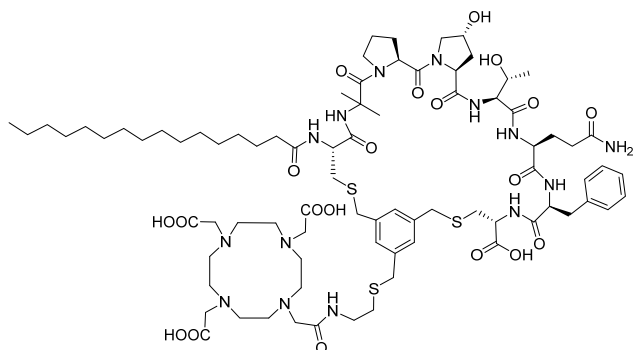
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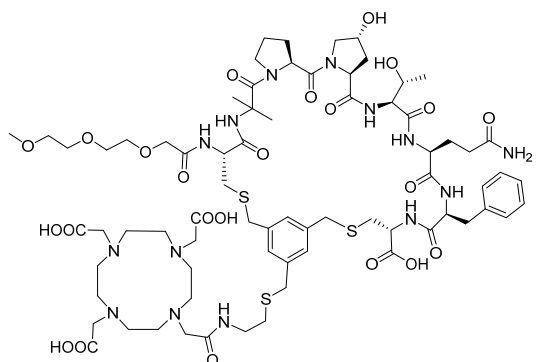
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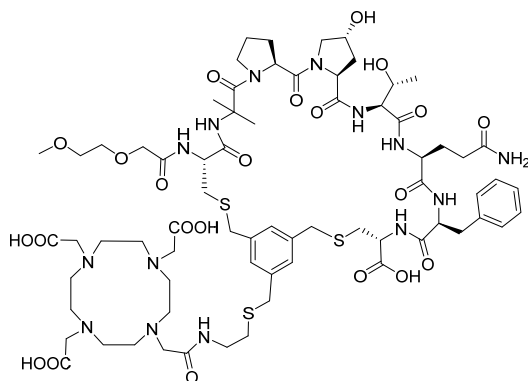
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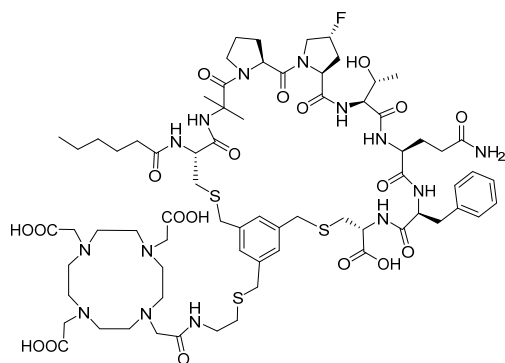
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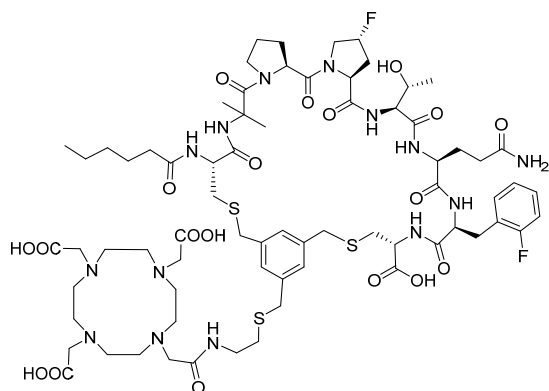
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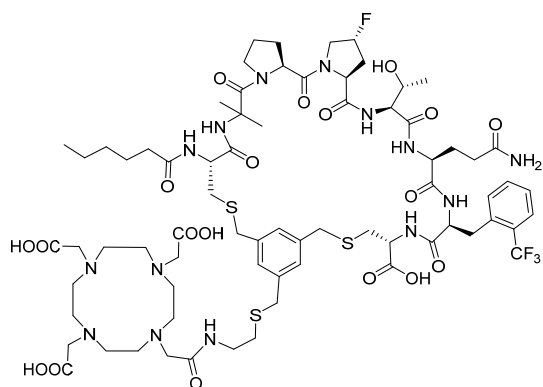
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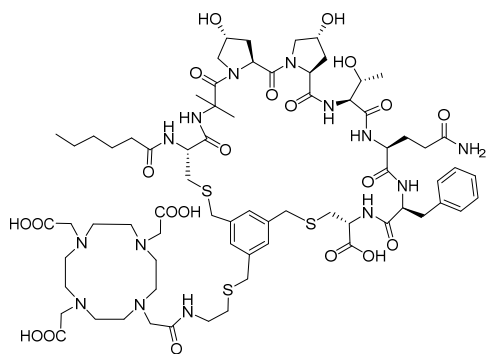
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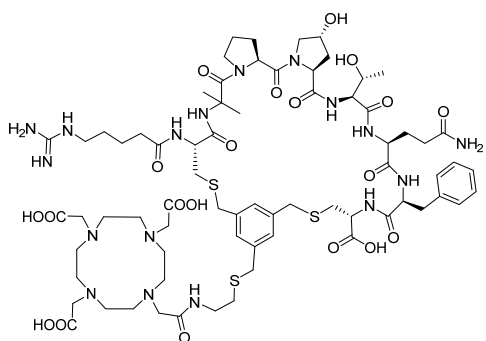
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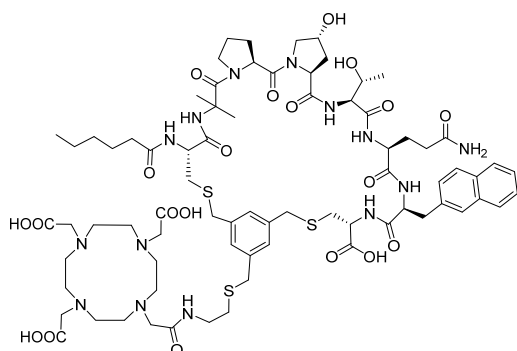
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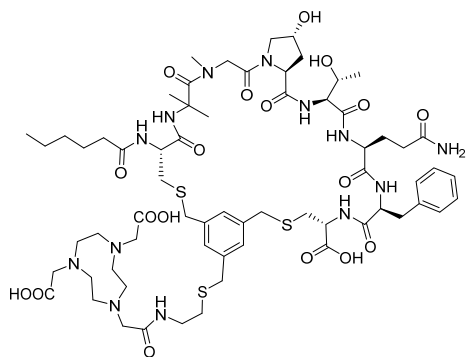
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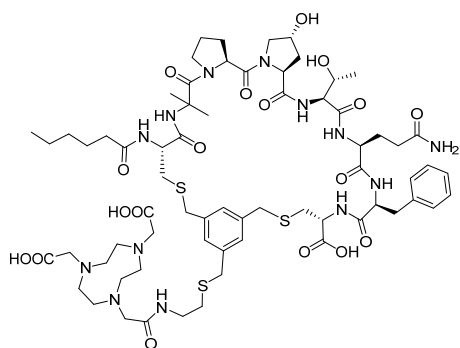
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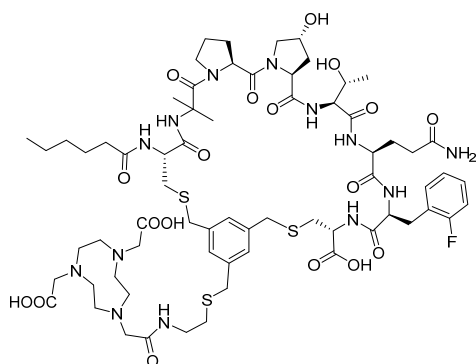
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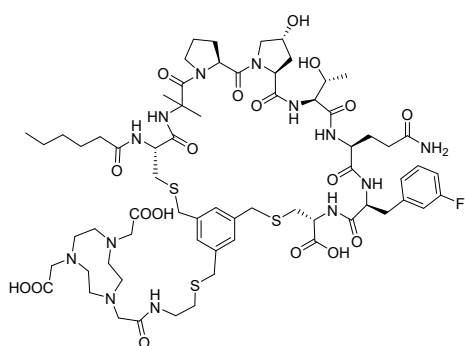
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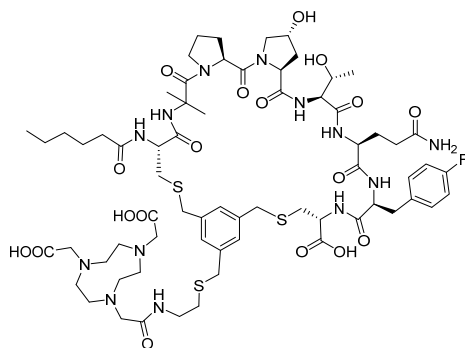
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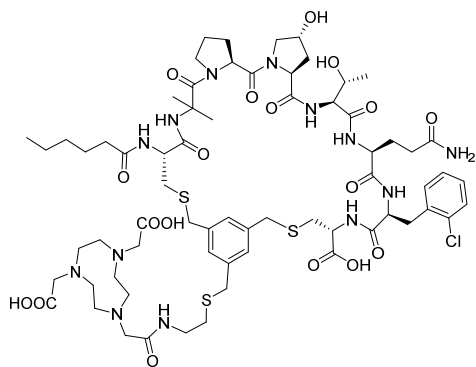
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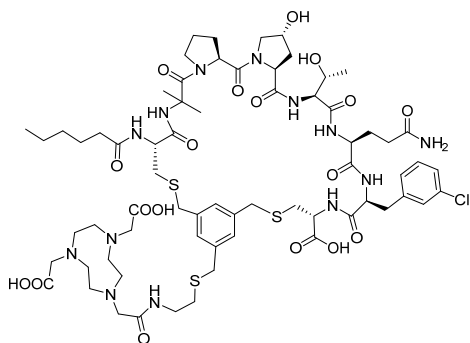
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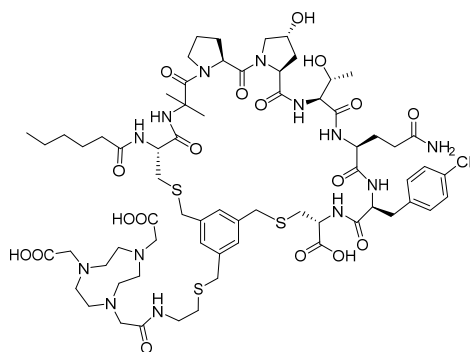
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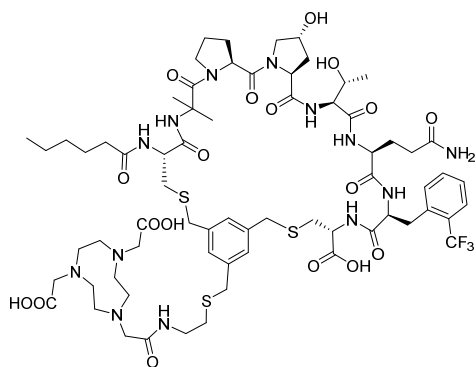
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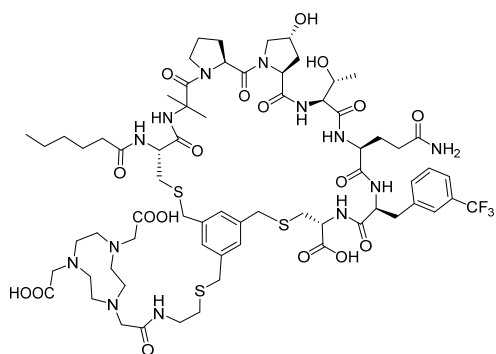
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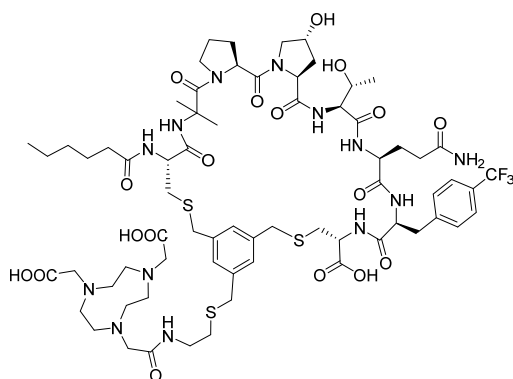
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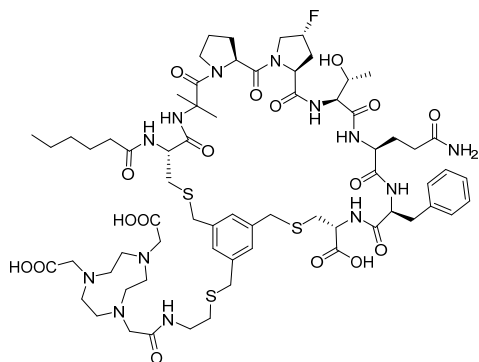
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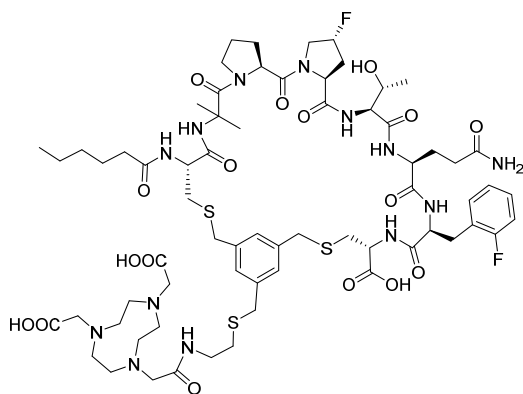
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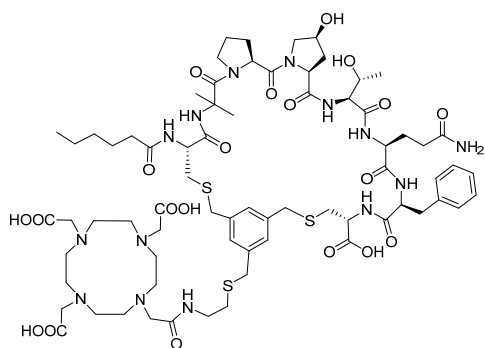


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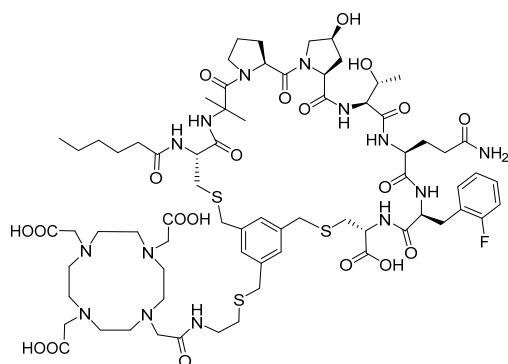


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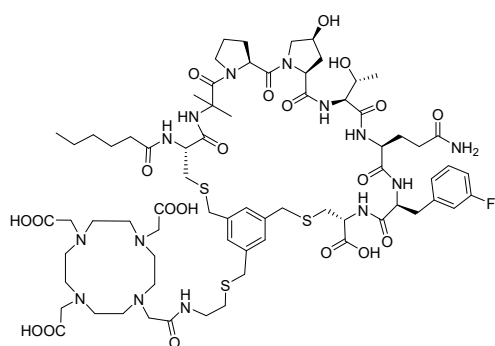
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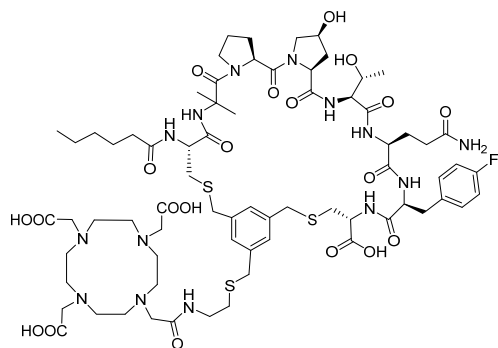
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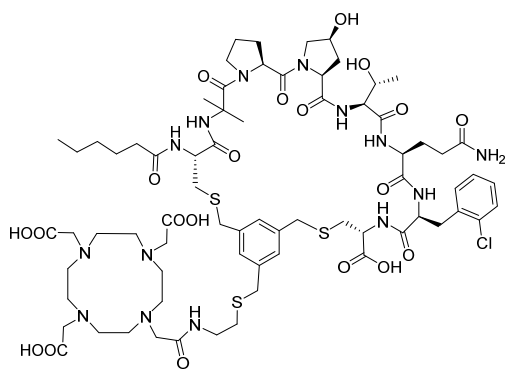
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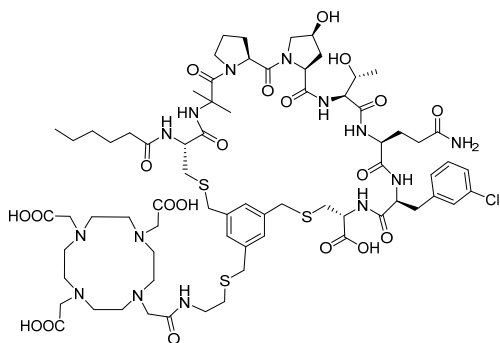
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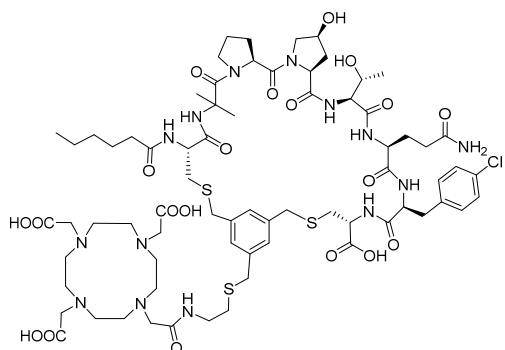
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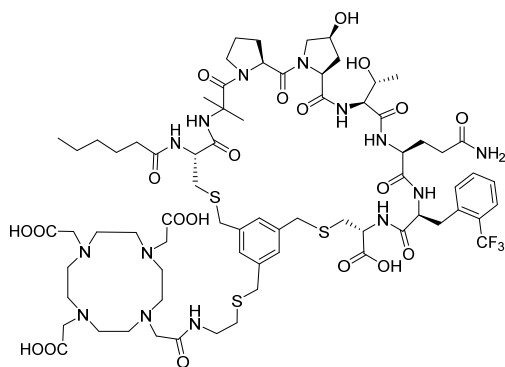
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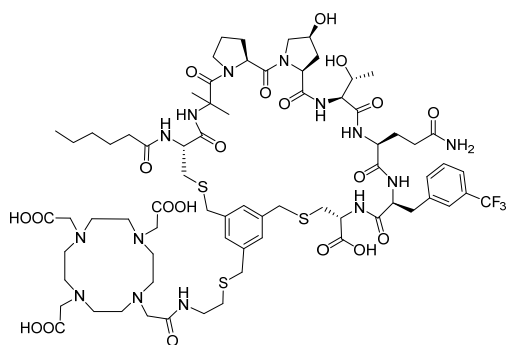
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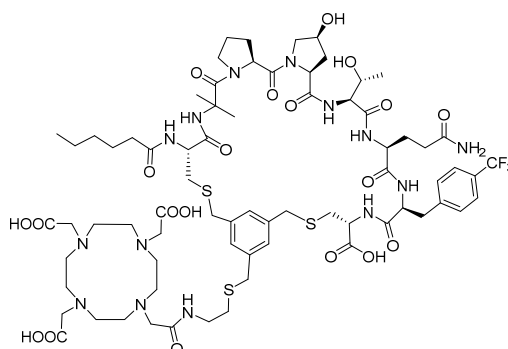
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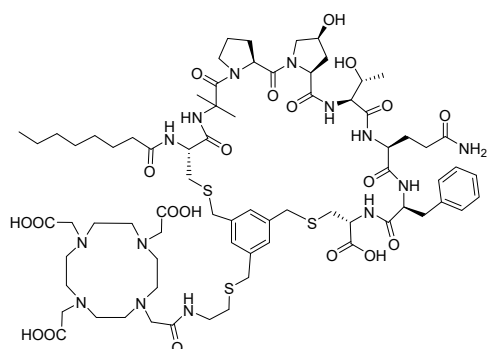
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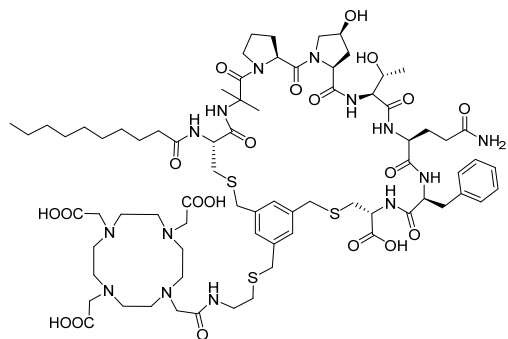
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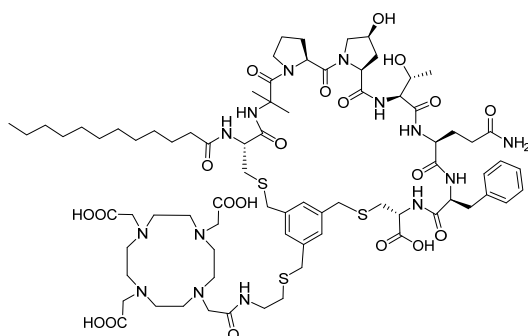
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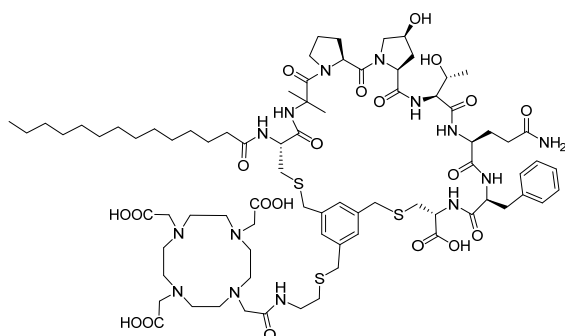
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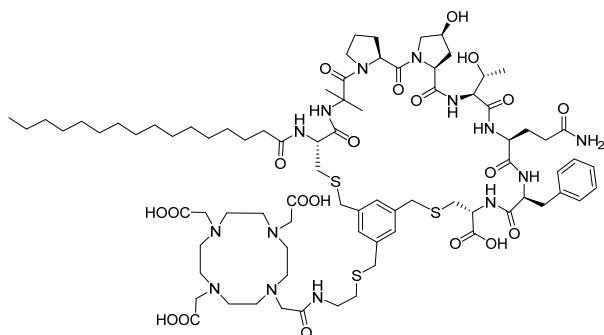
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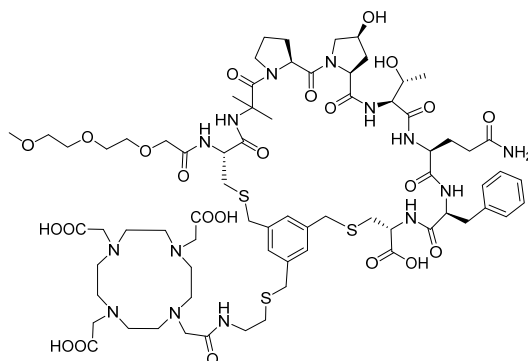
Dod-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-((4S)-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



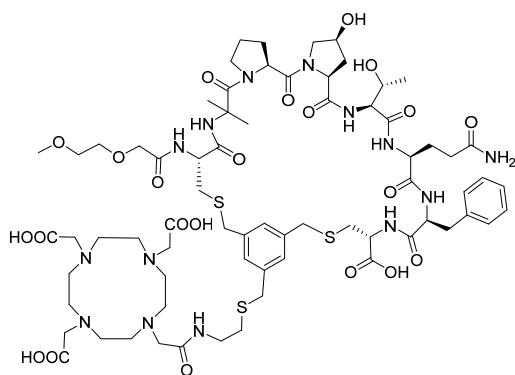
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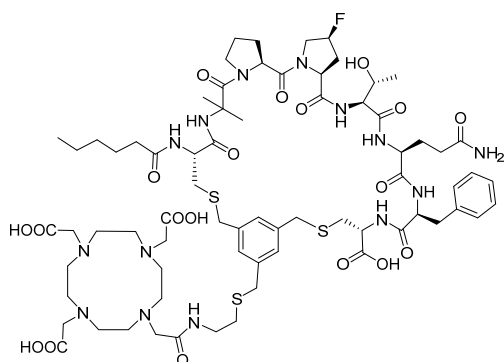
Pal-[Cys-(tMeBn(DOTA-AET))-Aib-Pro-((4S)-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



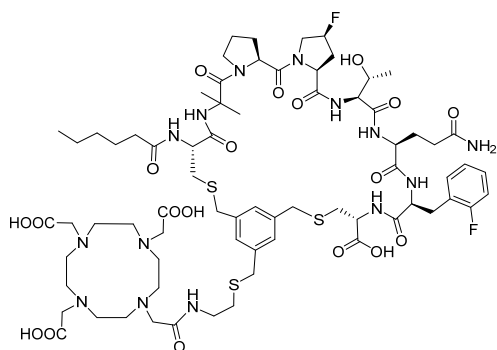
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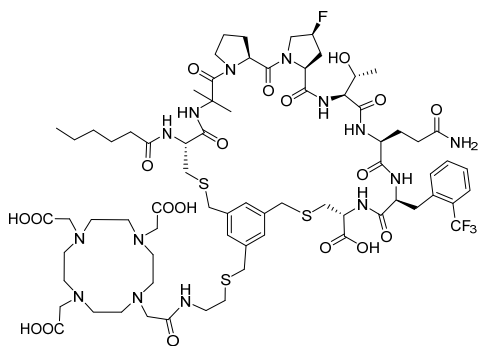
[2-(2-Methoxyethoxy)-Ace]-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-((4S)-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



Hex-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-((4S)-F-Pro)-Thr-Gln-Phe-Cys]-OH,



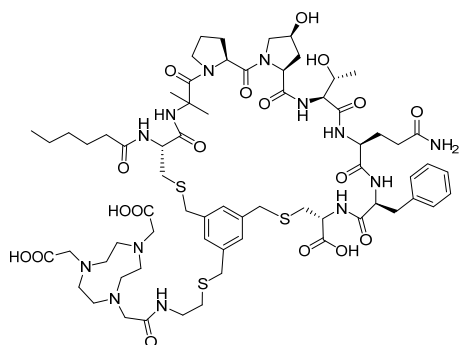
Hex-[Cys-(tMeBn(DOTA-AET))]-Aib-Pro-((4S)-F-Pro)-Thr-Gln-(2-F-Phe)-Cys]-OH,



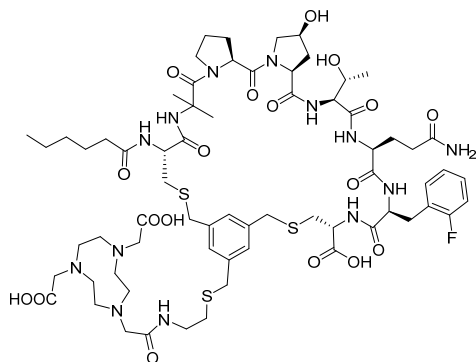
Chemical structure of compound 10, a complex macrocyclic molecule. The structure features a 12-membered ring with four nitrogen atoms. The ring is substituted with various side chains, including a long alkyl chain, a thioether-linked chain, and a complex polycyclic amide system.

The chemical structure of compound 10 is a complex macrocyclic molecule. It features a central macrocycle with four nitrogen atoms. Attached to this core are several side chains: a long chain with a terminal guanidino group (H₂N-C(=NH)-NH-), a chain with a terminal carboxylic acid group (HOOC-), and a chain with a terminal amide group (NH-C(=O)-). A thioether linkage (-S-) connects the macrocycle to a side chain that includes a benzyl group and a carboxylic acid group. The molecule is highly functionalized with various amide, ester, and carboxylic acid groups.

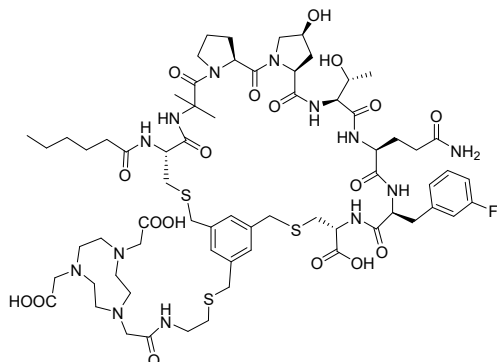
Hex-[Cys-(tMeBn(NOTA-AET))-Aib-Sar-((4S)-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



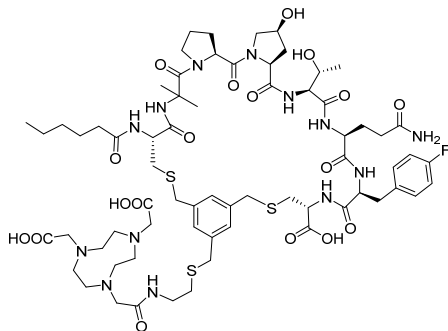
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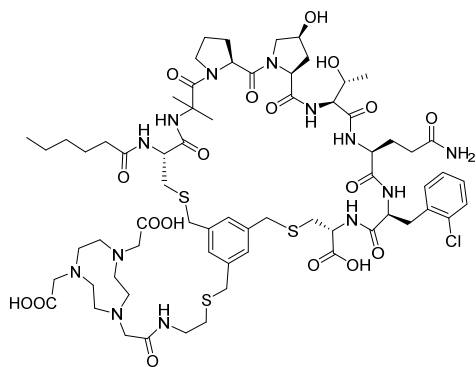
Hex-[Cys-(tMeBn(NOTA-AET))-Aib-Pro-((4S)-OH-Pro)-Thr-Gln-(2-F-Phe)-Cys]-OH,



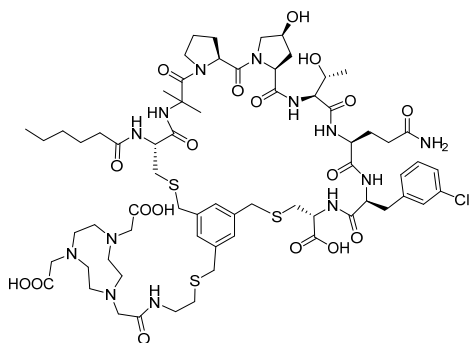
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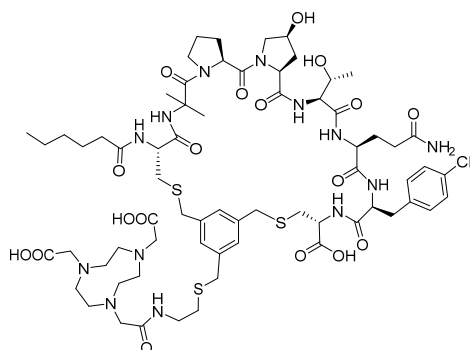
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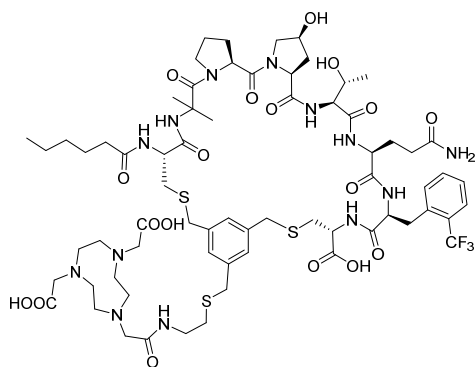
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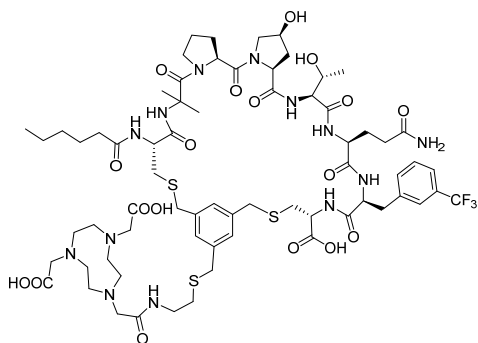
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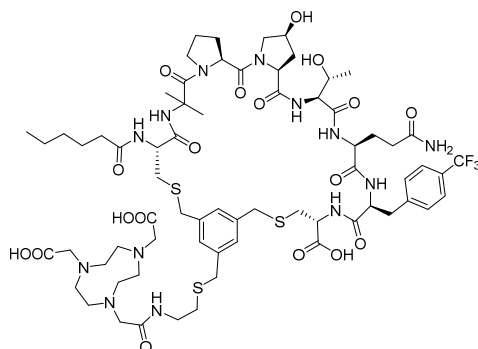
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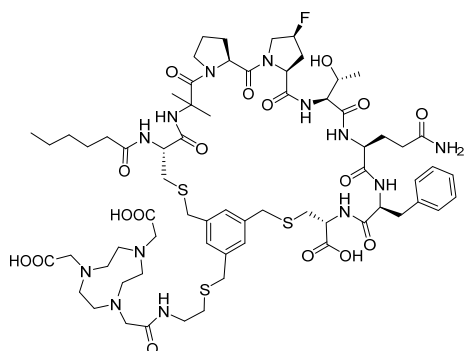
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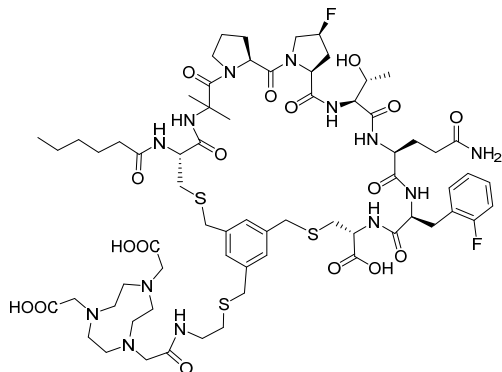
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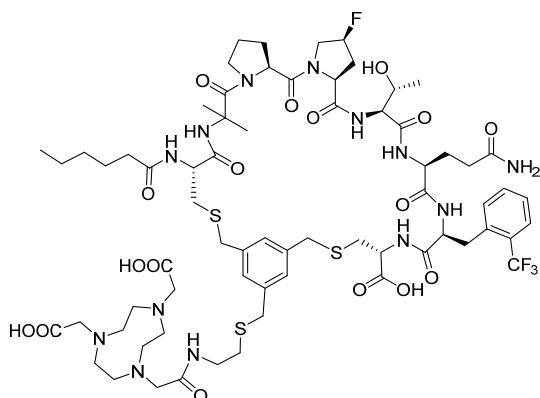
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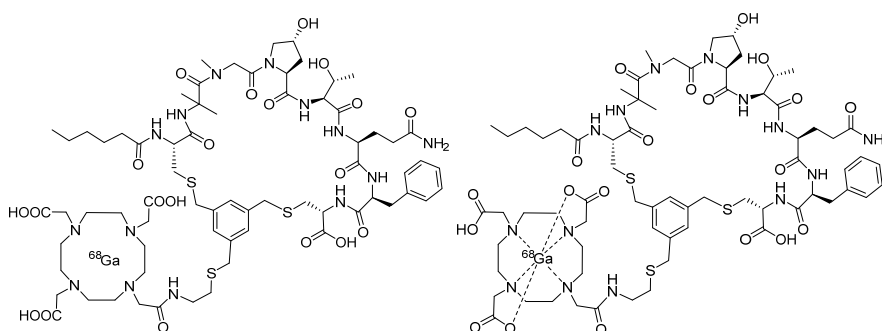
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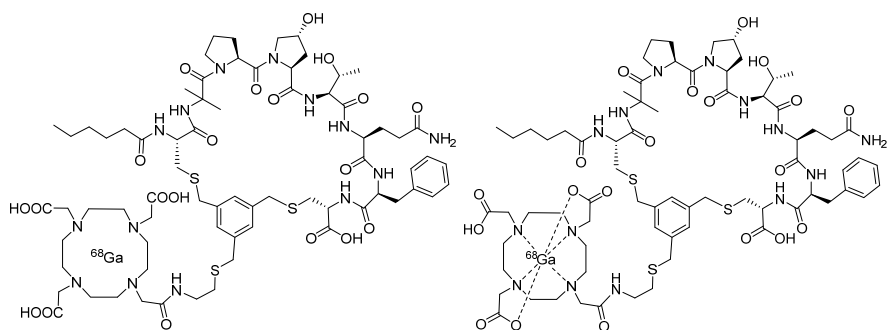
Hex-[Cys-(tMeBn(NOTA-AET))-Aib-Pro-((4S)-F-Pro)-Thr-Gln-(2-CF₃-Phe)-Cys]-OH.

24. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 23, wherein the chelating agent complexes a nuclide, the nuclide comprises a diagnostically active nuclide or a therapeutically active nuclide, and the diagnostically active nuclide is selected from ⁴³Sc, ⁴⁴Sc, ⁵¹Mn, ⁵²Mn, ⁶⁴Cu, ⁶⁷Ga, ⁶⁸Ga, ⁸⁶Y, ⁸⁹Zr, ^{94m}Tc, ^{99m}Tc, ¹¹¹In, ¹⁵²Tb, ¹⁵⁵Tb, ²⁰¹Tl, ²⁰³Pb, ¹⁸F, ⁷⁶Br, ⁷⁷Br, ¹²³I, ¹²⁴I and ¹²⁵I, preferably ⁴³Sc, ⁴⁴Sc, ⁶⁴Cu, ⁶⁷Ga, ⁶⁸Ga, ⁸⁶Y, ⁸⁹Zr, ^{99m}Tc, ¹¹¹In, ¹⁵²Tb, ¹⁵⁵Tb, ²⁰³Pb, ¹⁸F, ⁷⁶Br, ⁷⁷Br, ¹²³I, ¹²⁴I and ¹²⁵I, and most preferably ⁶⁴Cu, ⁶⁸Ga, ⁸⁹Zr, ^{99m}Tc, ¹¹¹In, ¹⁸F, ¹²³I and ¹²⁴I; the therapeutically active nuclide is selected from ⁴⁷Sc, ⁶⁷Cu, ⁸⁹Sr, ⁹⁰Y, ¹⁵³Sm, ¹⁴⁹Tb, ¹⁶¹Tb, ¹⁷⁷Lu, ¹⁸⁶Re, ¹⁸⁸Re, ²¹²Pb, ²¹³Bi, ²²³Ra, ²²⁵Ac, ²²⁶Th, ²²⁷Th, ¹³¹I and ²¹¹At, preferably ⁴⁷Sc, ⁶⁷Cu, ⁹⁰Y, ¹⁷⁷Lu, ¹⁸⁸Re, ²¹²Pb, ²¹³Bi, ²²⁵Ac, ²²⁷Th, ¹³¹I and ²¹¹At, and most preferably ⁹⁰Y, ¹⁷⁷Lu, ²²⁵Ac, ²²⁷Th, ¹³¹I and ²¹¹At.

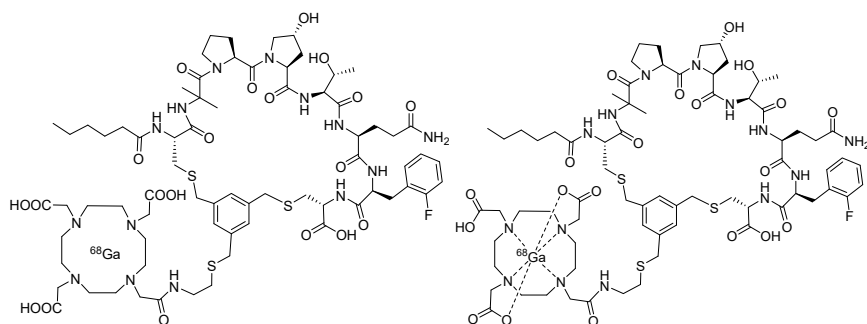
25. The compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 24, wherein the compound is selected from:



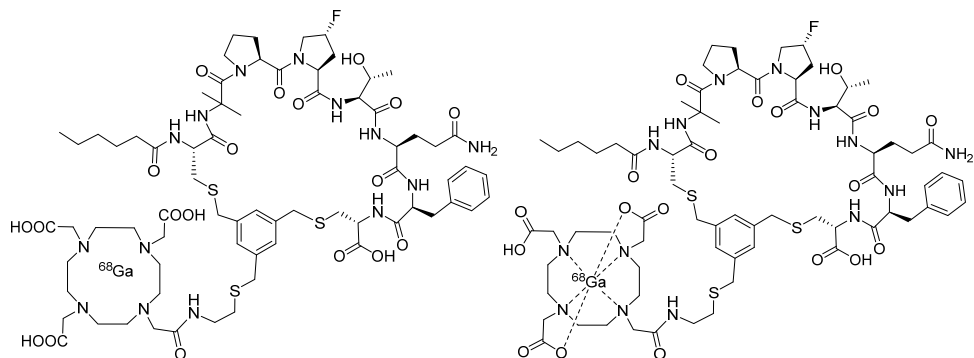
Hex-[Cys-(tMeBn(⁶⁸Ga-DOTA-AET))-Aib-Sar-((4R)-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



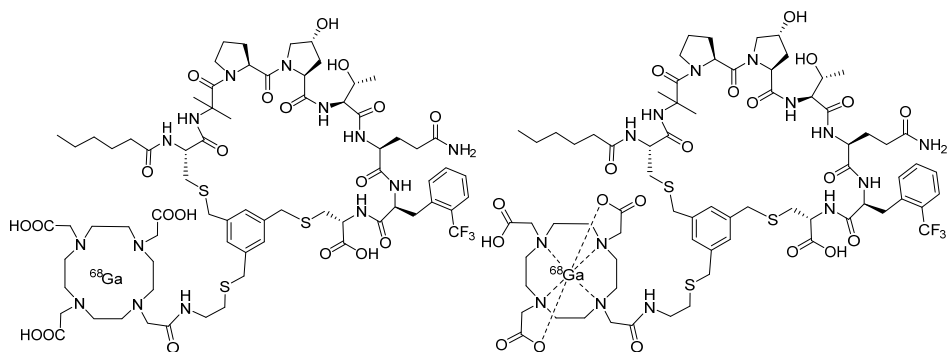
Hex-[Cys-(tMeBn(^{68}Ga -DOTA-AET))-Aib-Pro-((4R)-OH-Pro)-Thr-Gln-Phe-Cys]-OH,



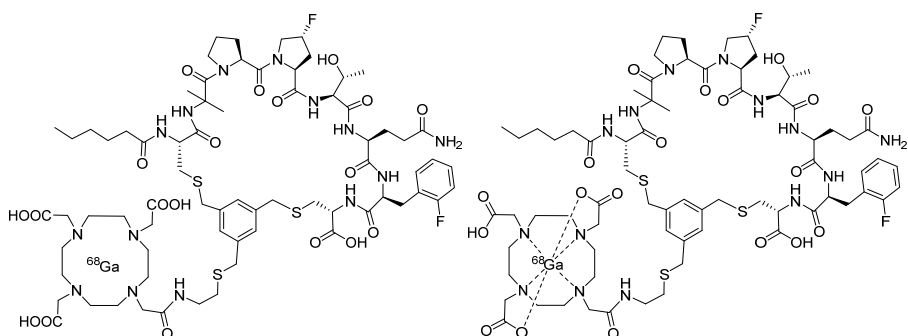
Hex-[Cys-(tMeBn(^{68}Ga -DOTA-AET))-Aib-Pro-((4R)-OH-Pro)-Thr-Gln-(2-F-Phe)-Cys]-OH,



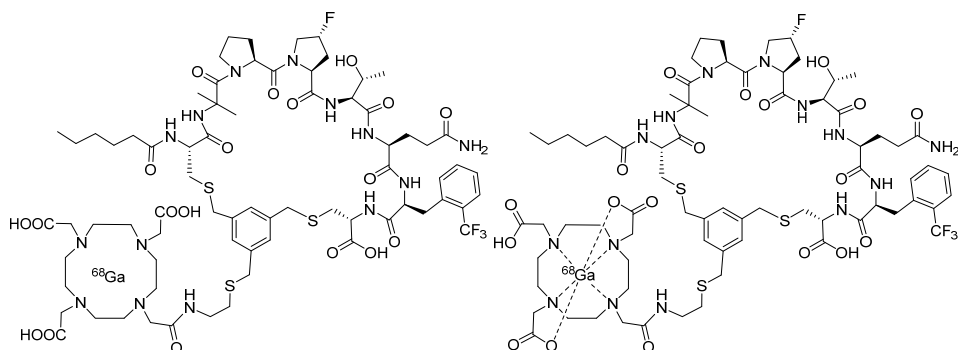
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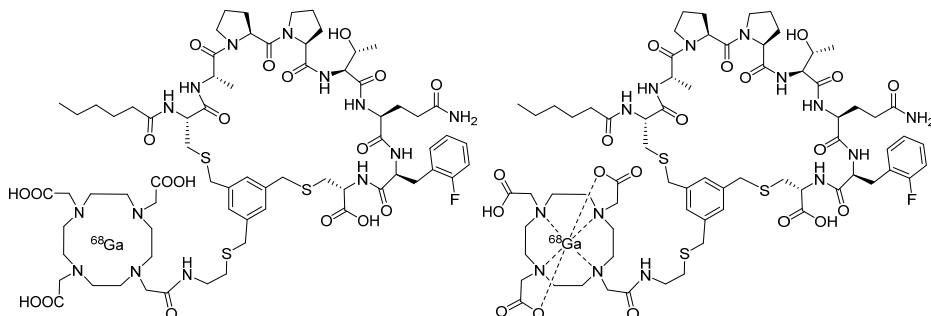
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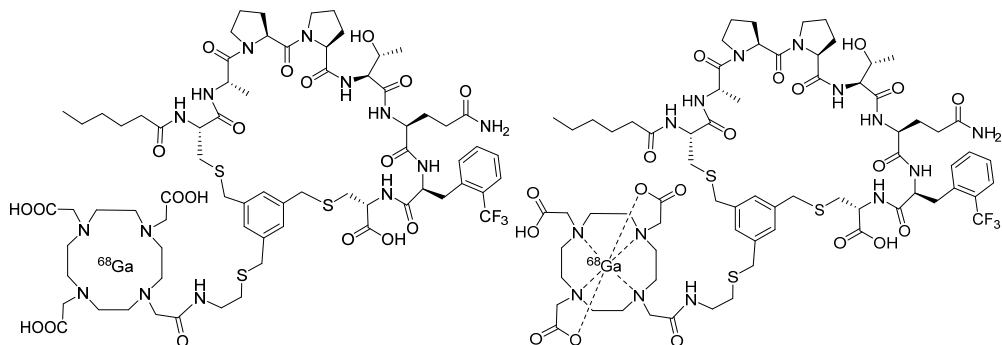
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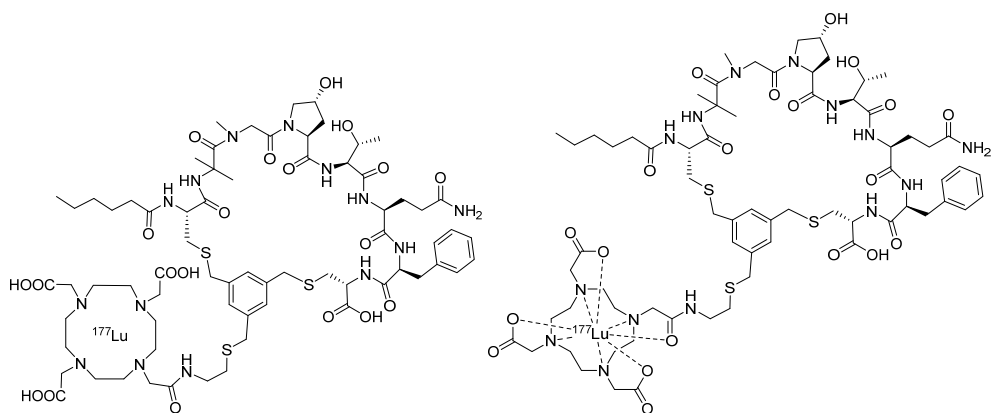
Hex-[Cys-(tMeBn(^{68}Ga -DOTA-AET))-Aib-Pro-((4R)-F-Pro)-Thr-Gln-(2- CF_3 -Phe)-Cys]-OH,



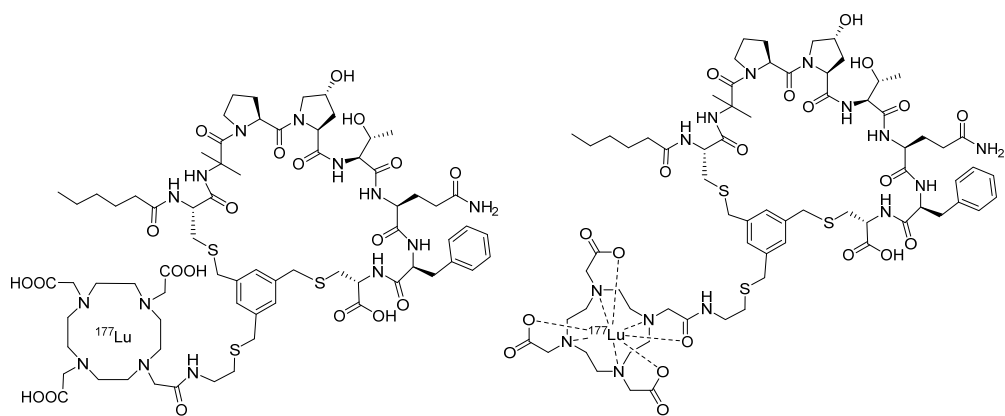
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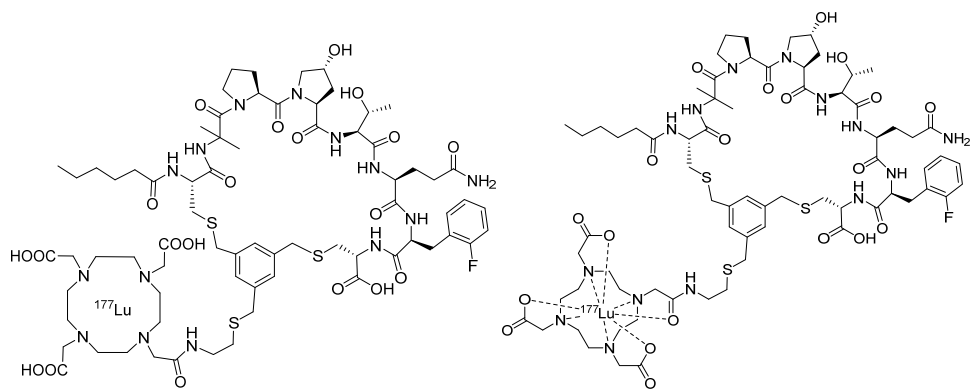
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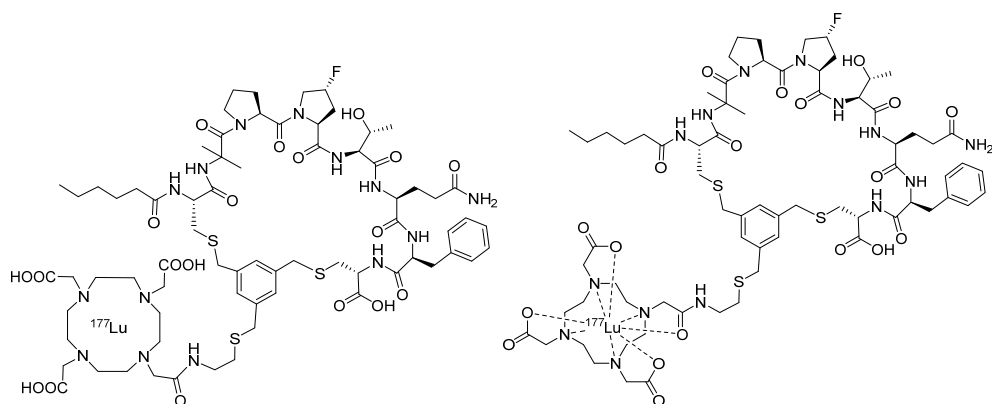
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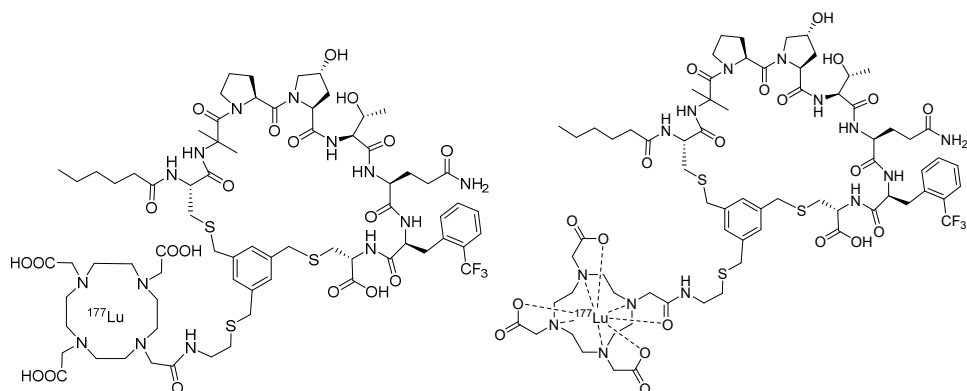
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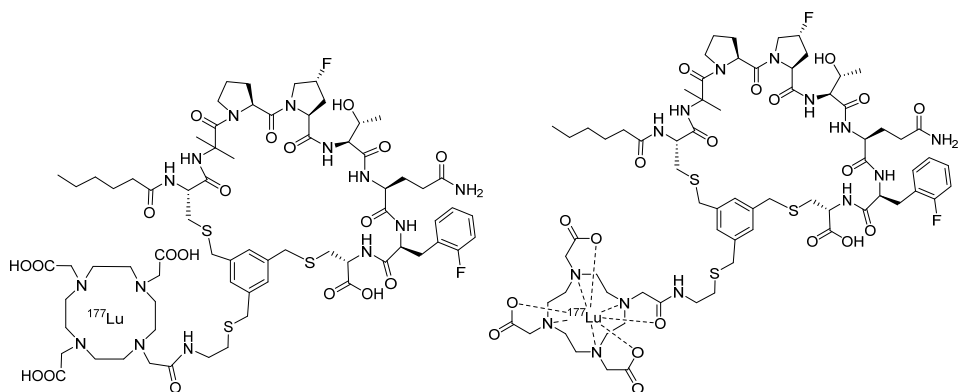
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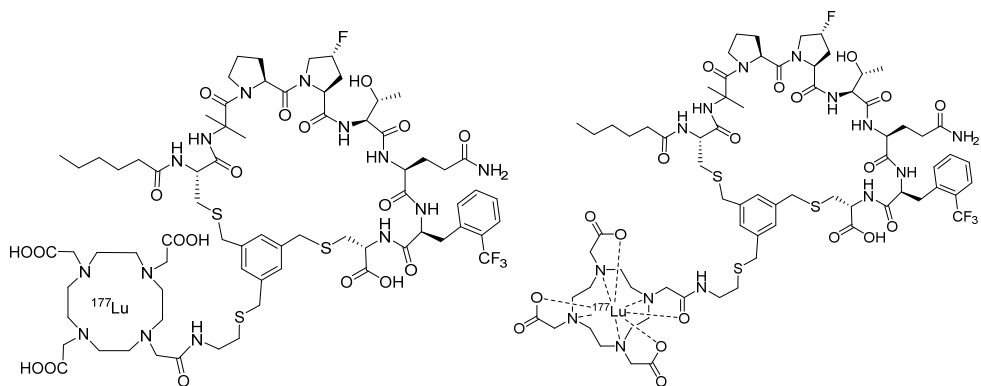
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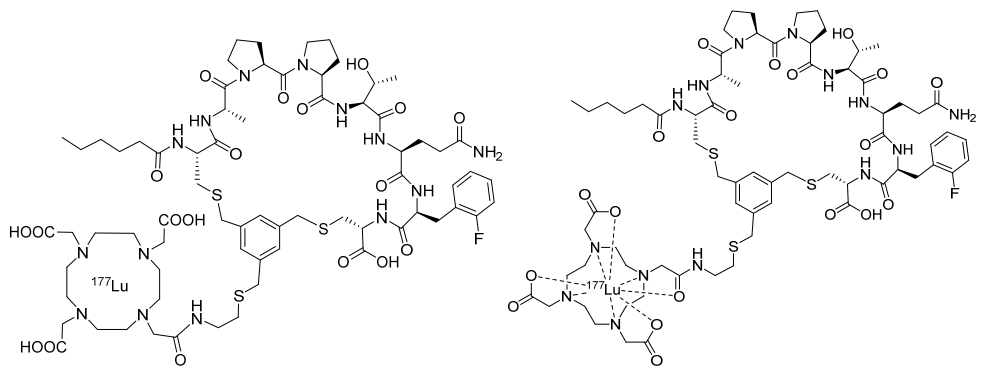
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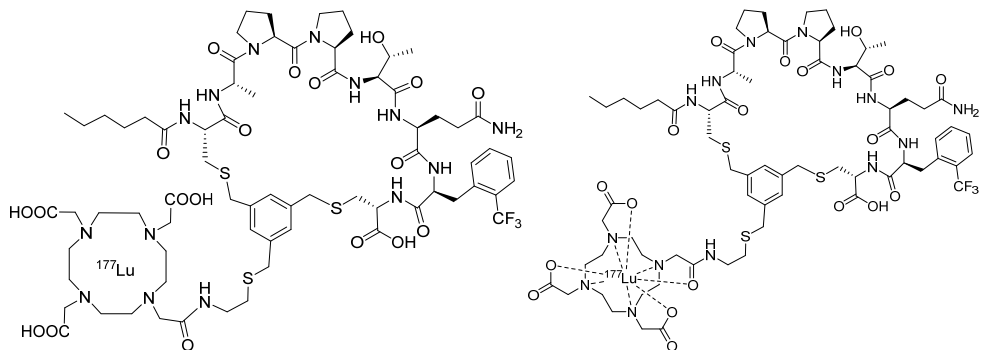
Hex-[Cys-(tMeBn(^{177}Lu -DOTA-AET))-Aib-Pro-((4R)-F-Pro)-Thr-Gln-(2-F-Phe)-Cys]-OH,



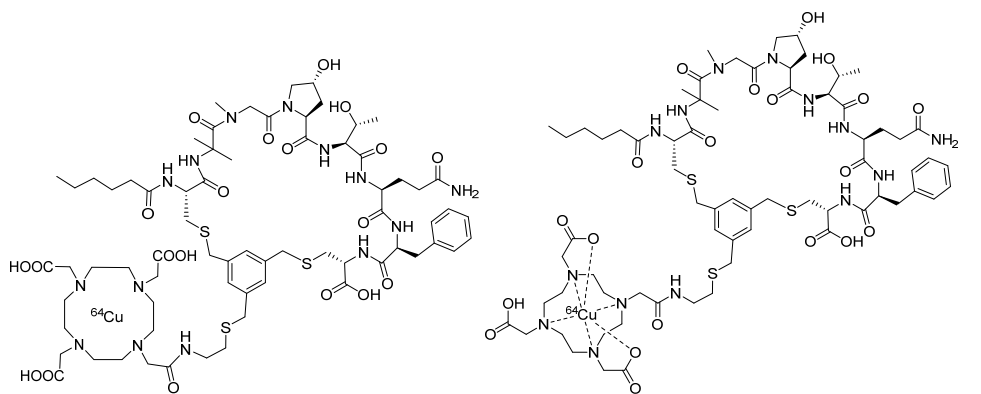
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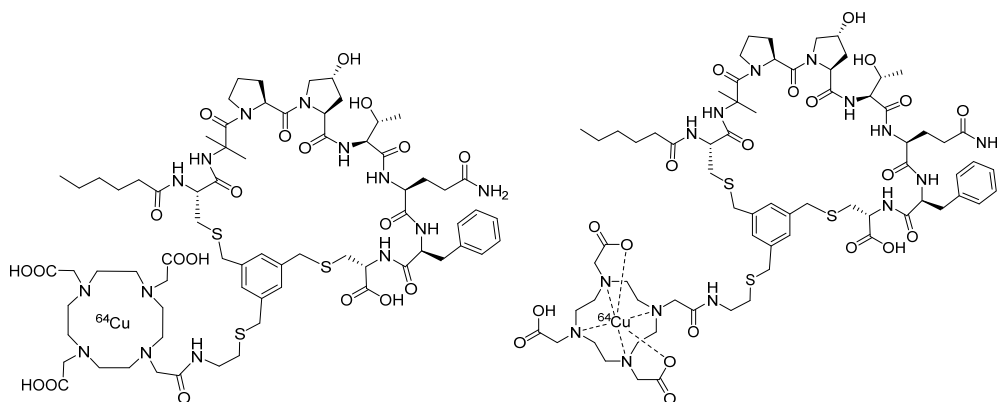
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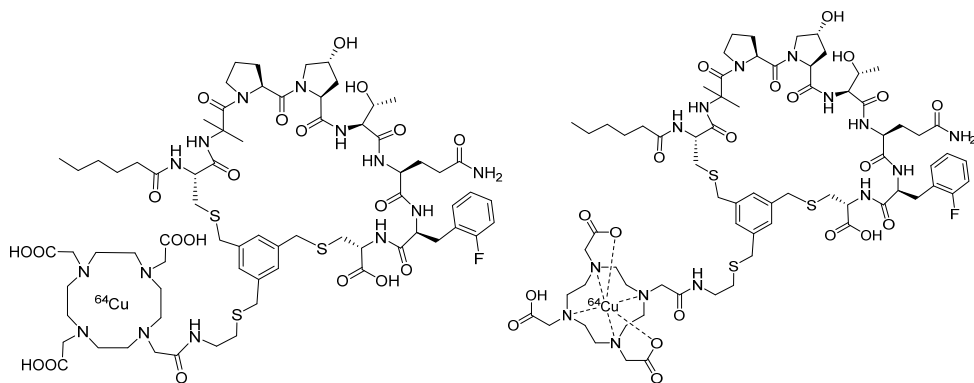
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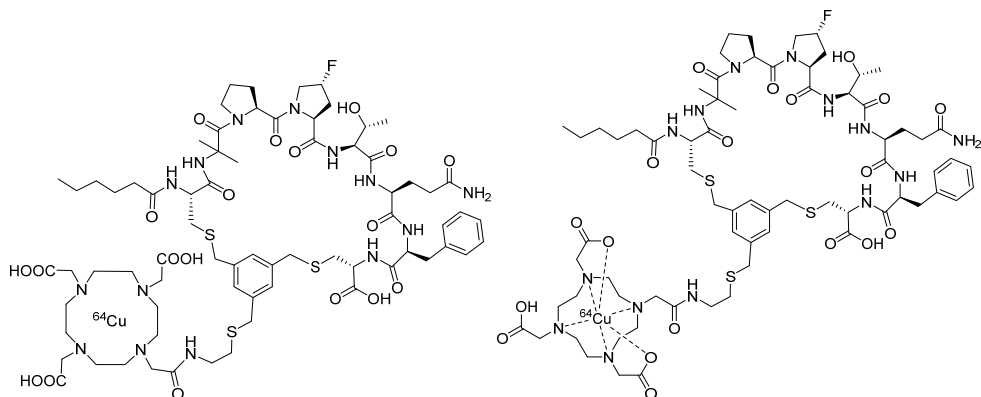
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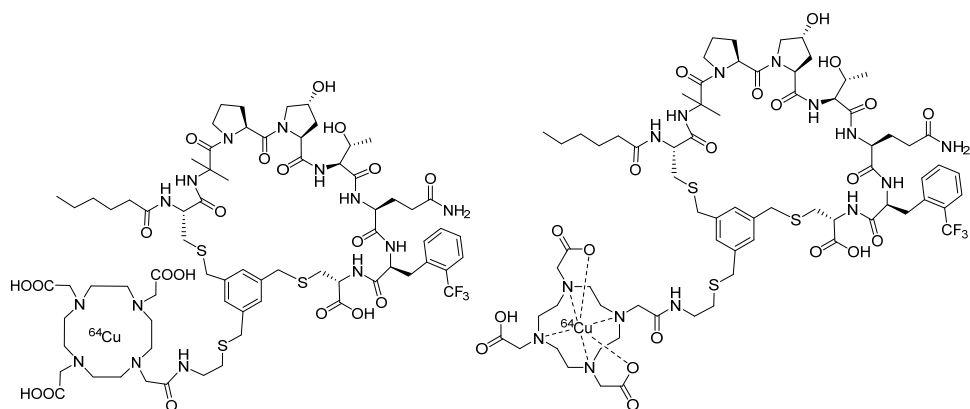
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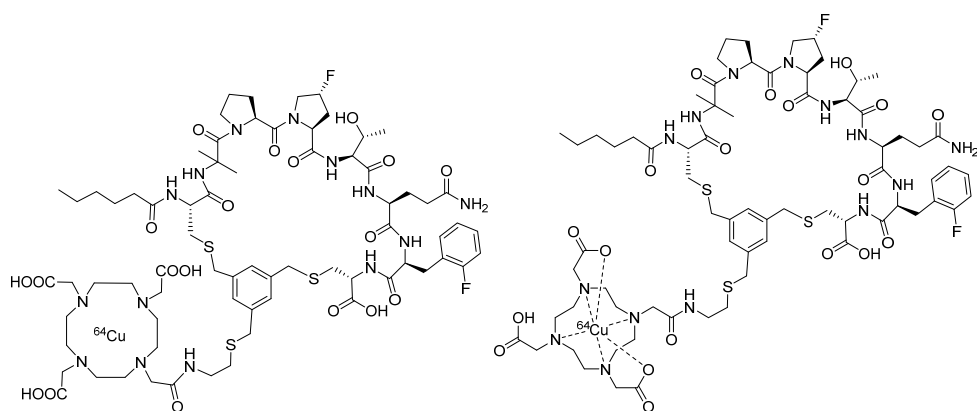
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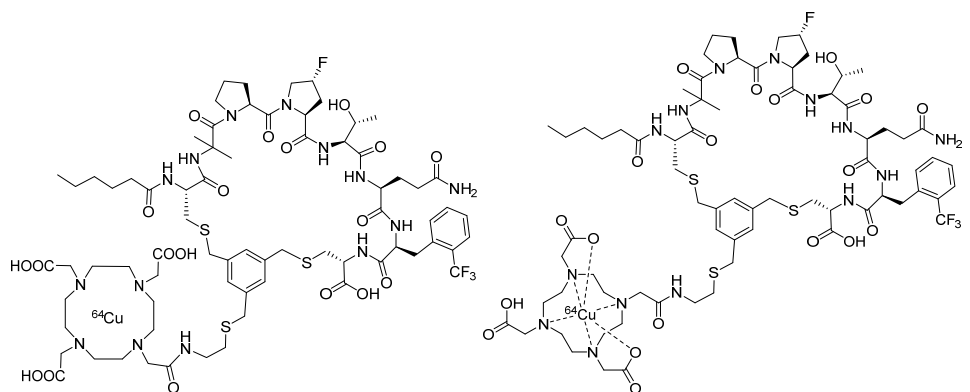
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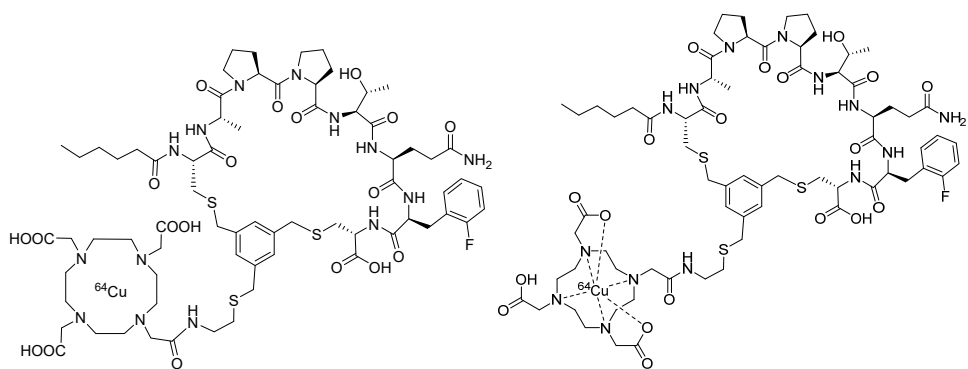
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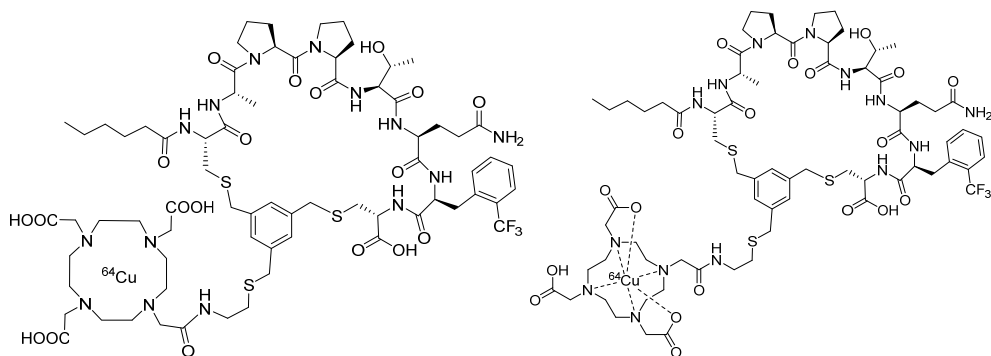
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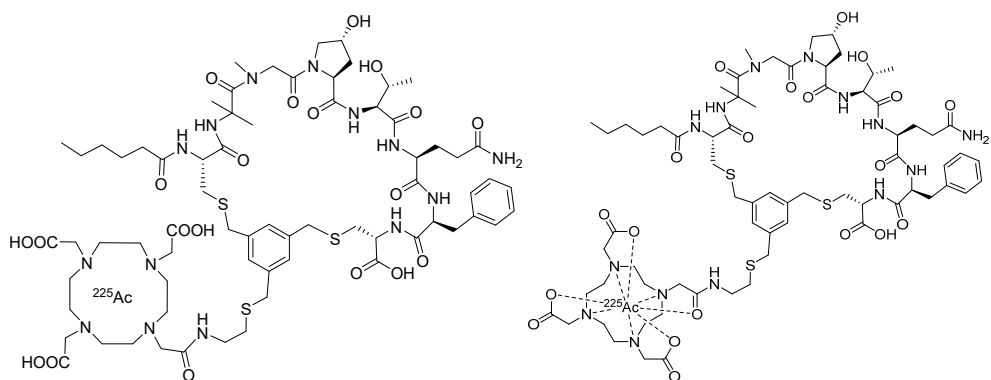
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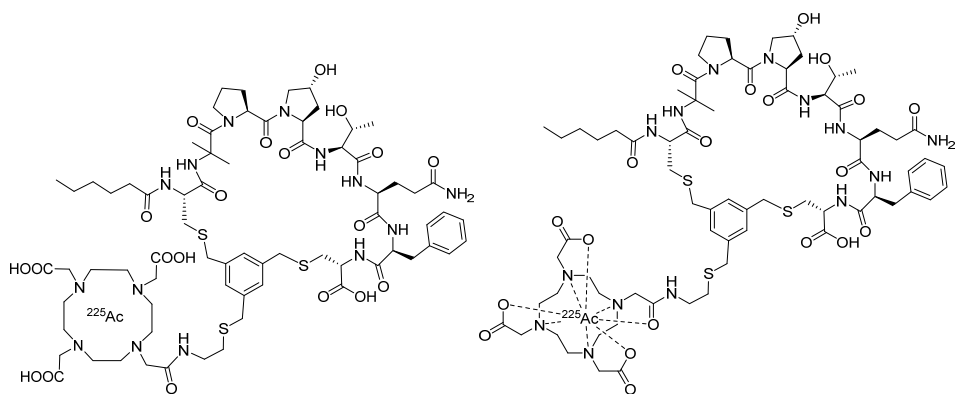
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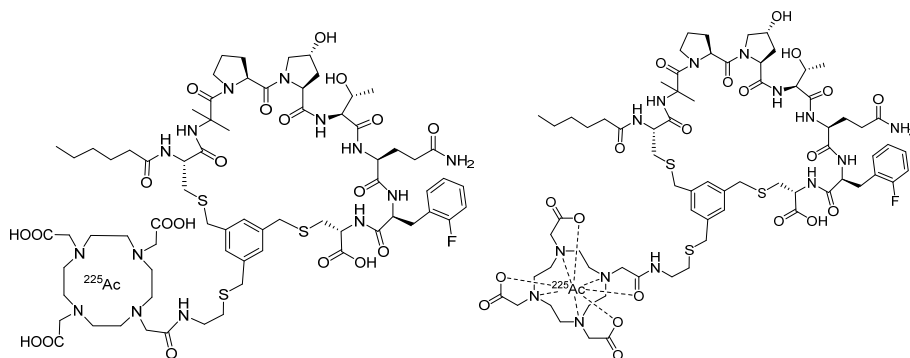
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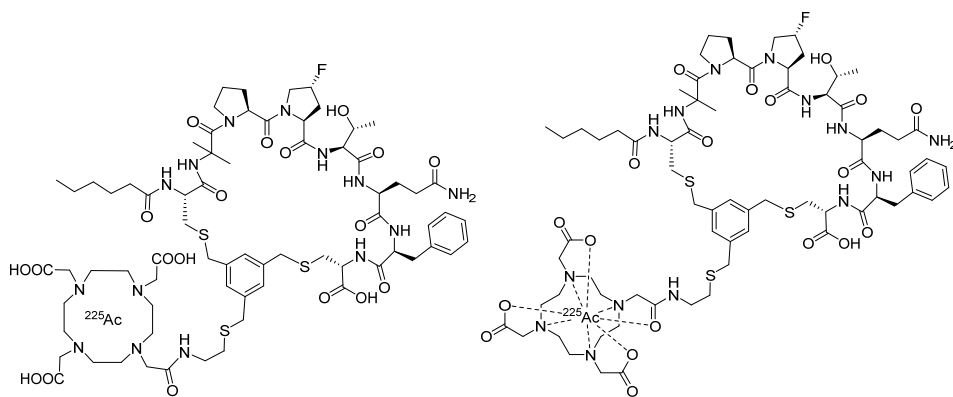
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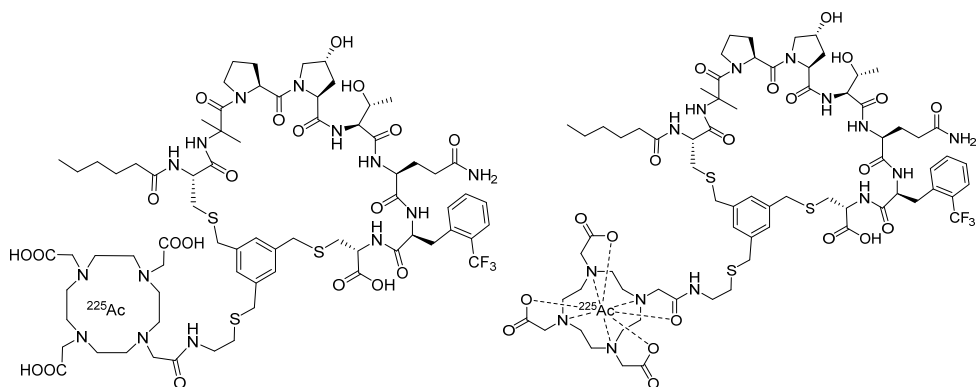
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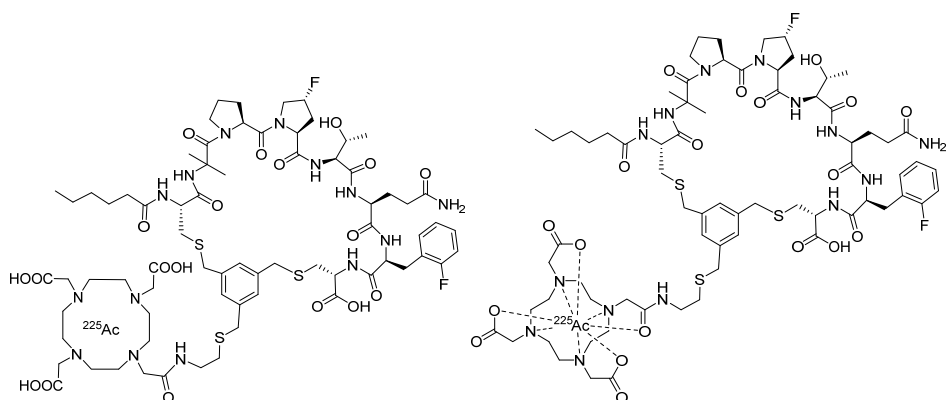
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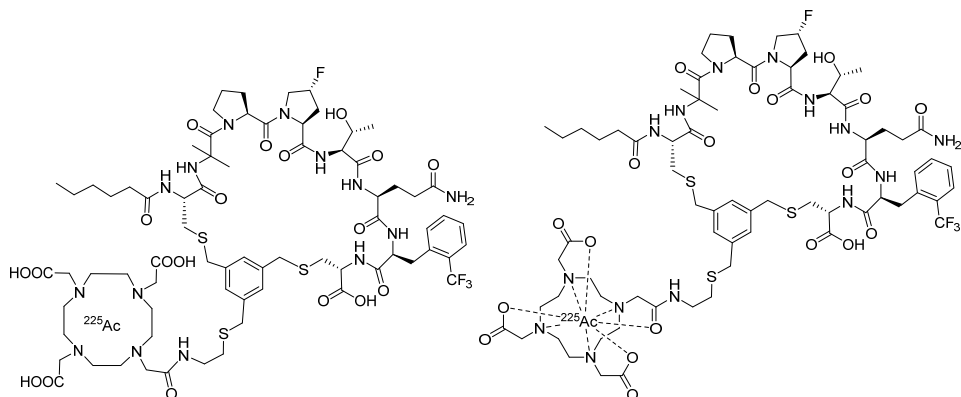
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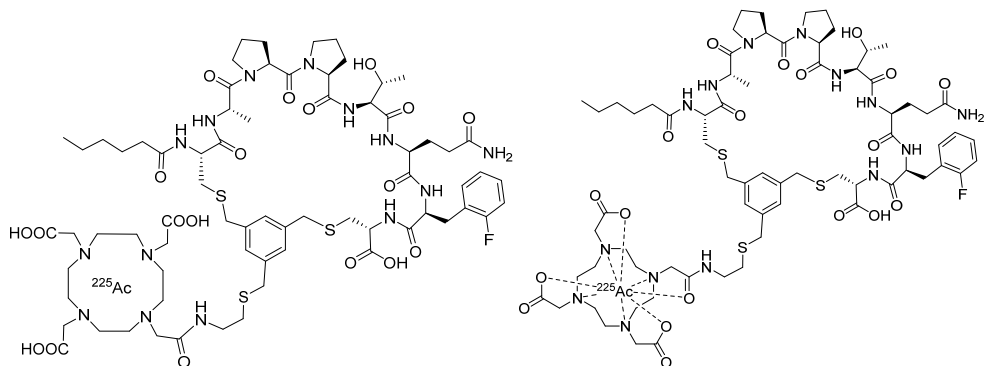
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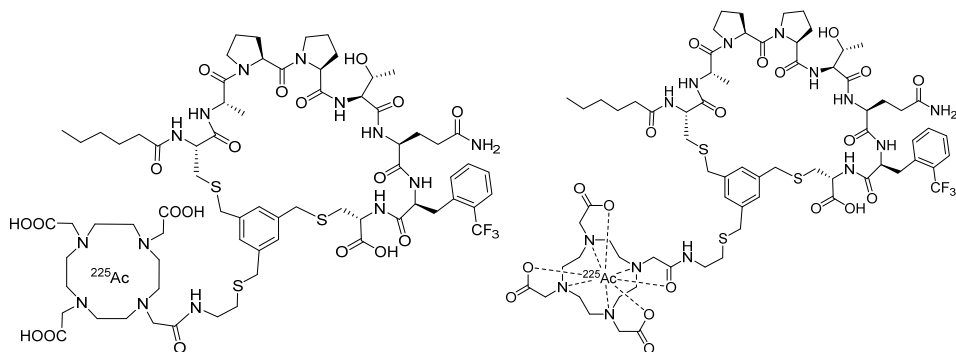
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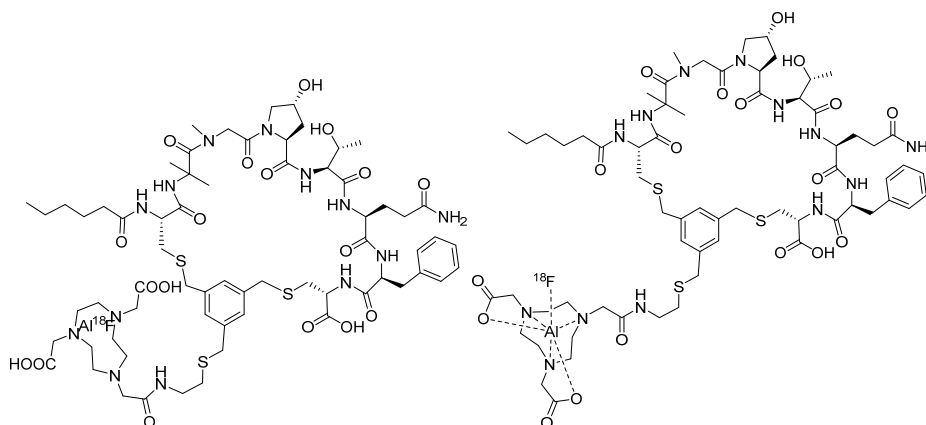
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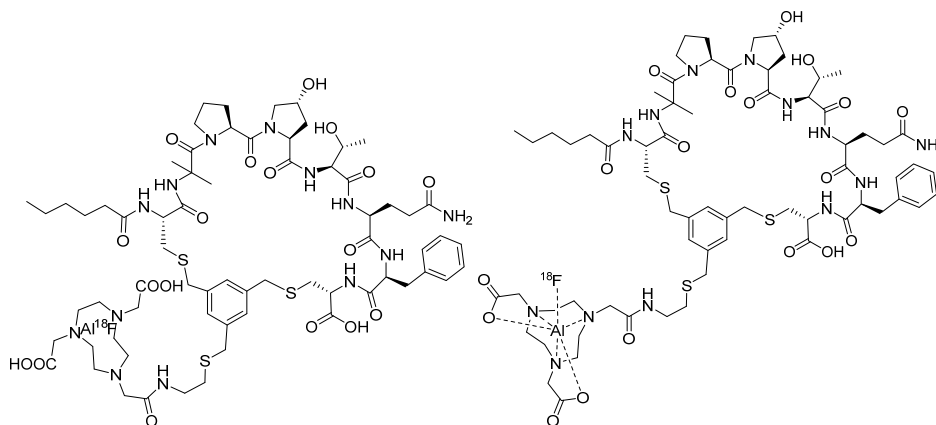
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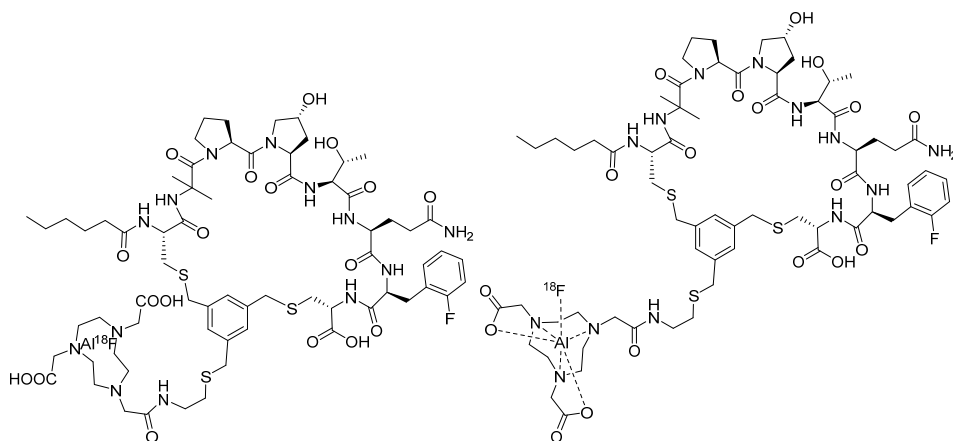
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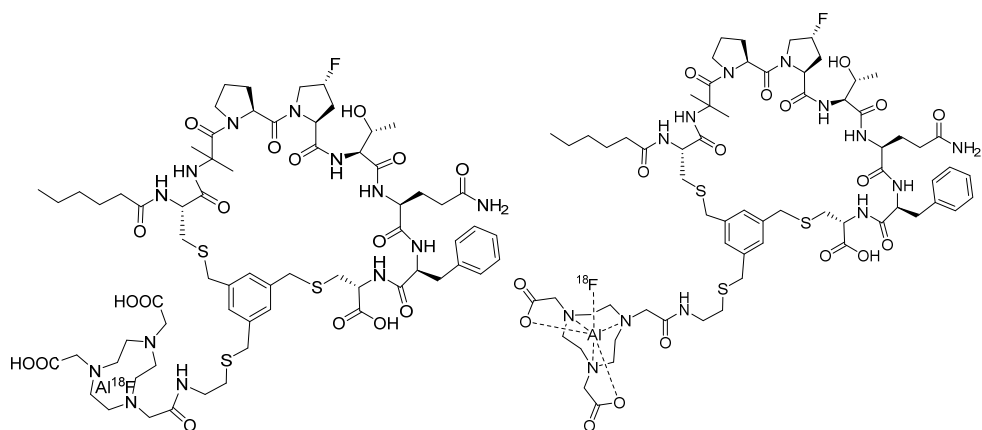
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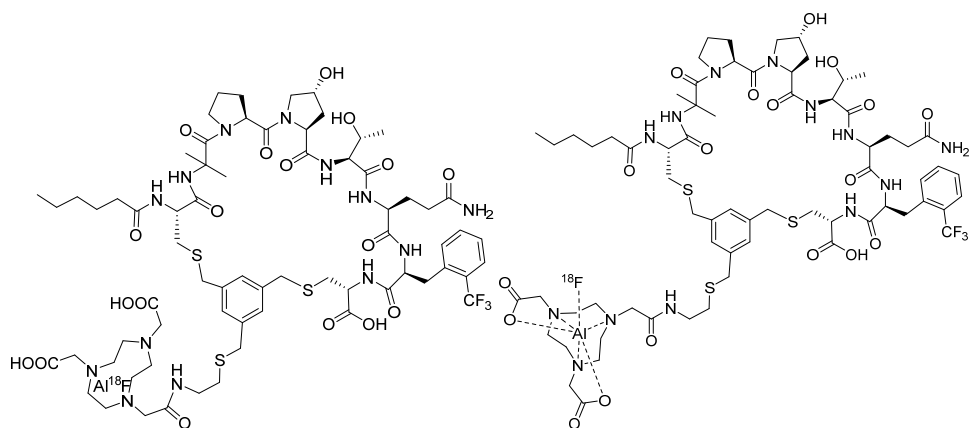
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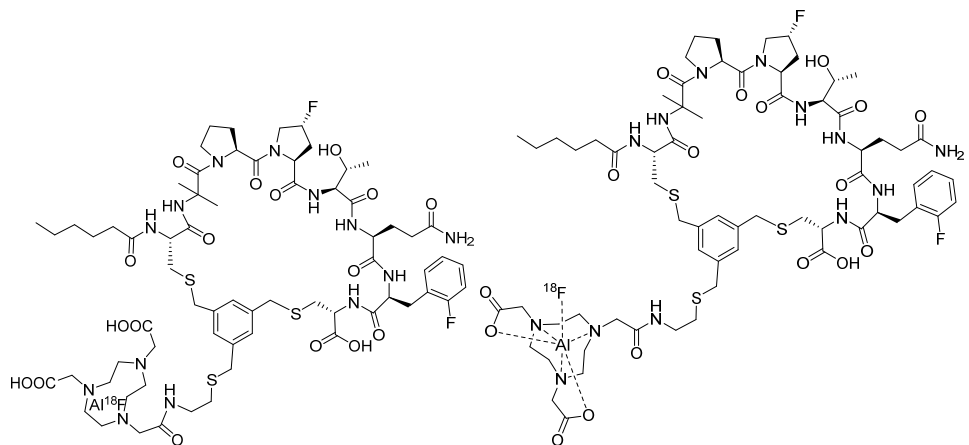
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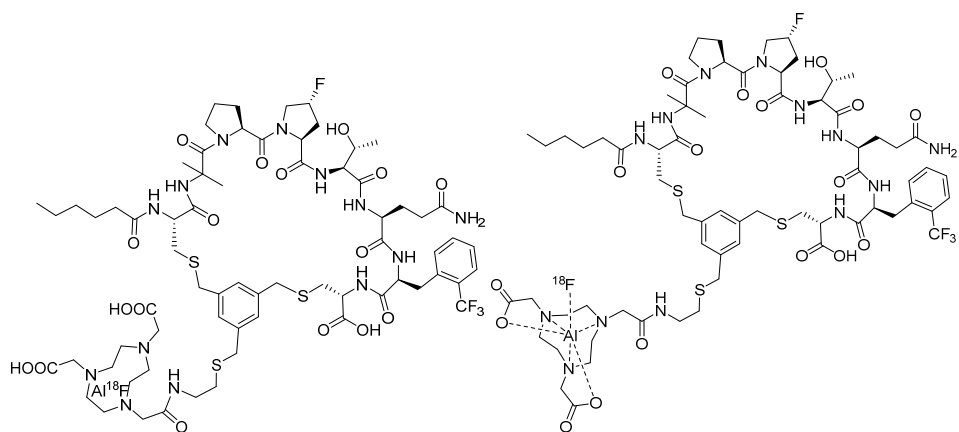
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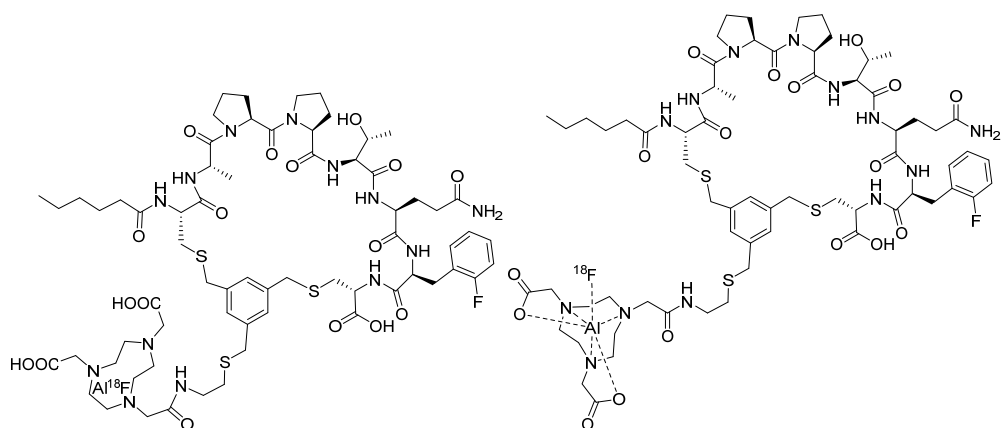
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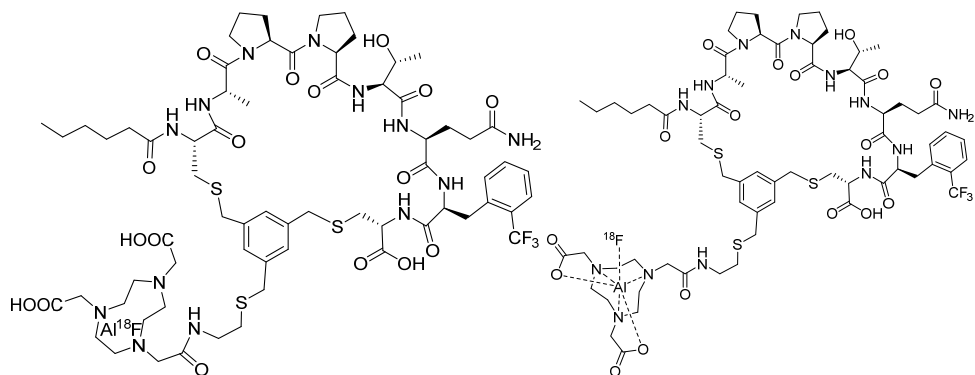
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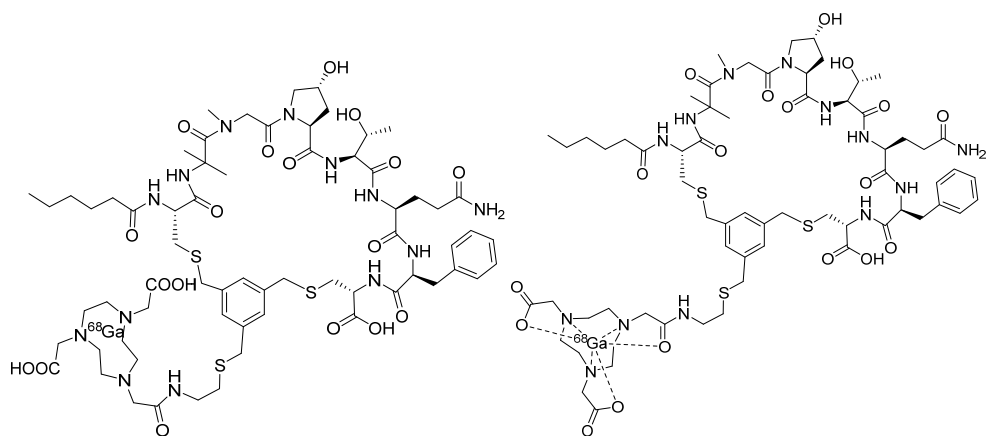
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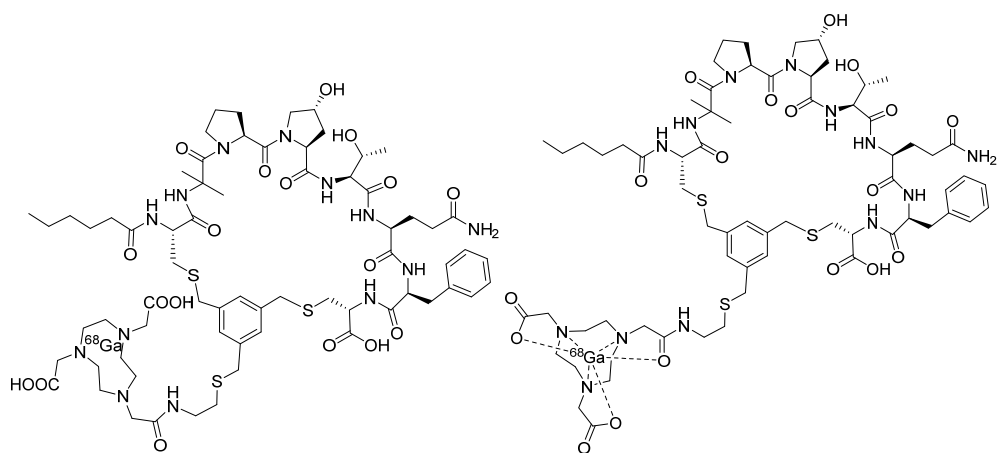
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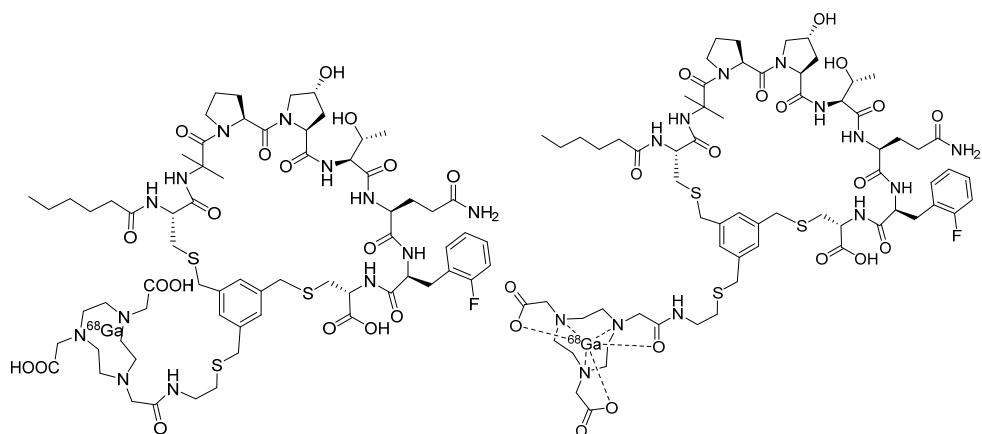
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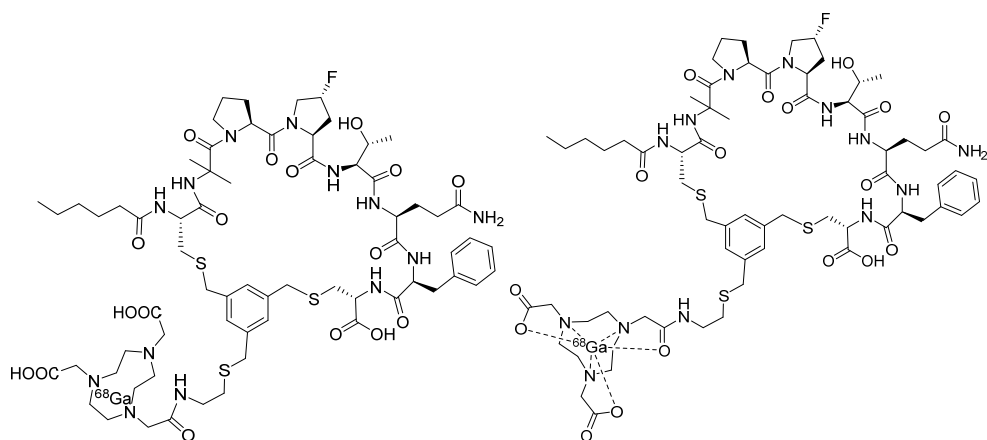
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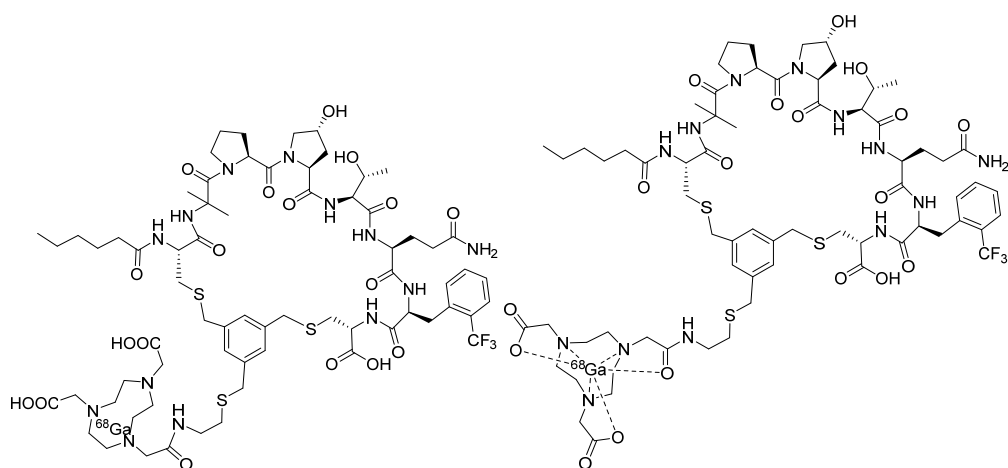
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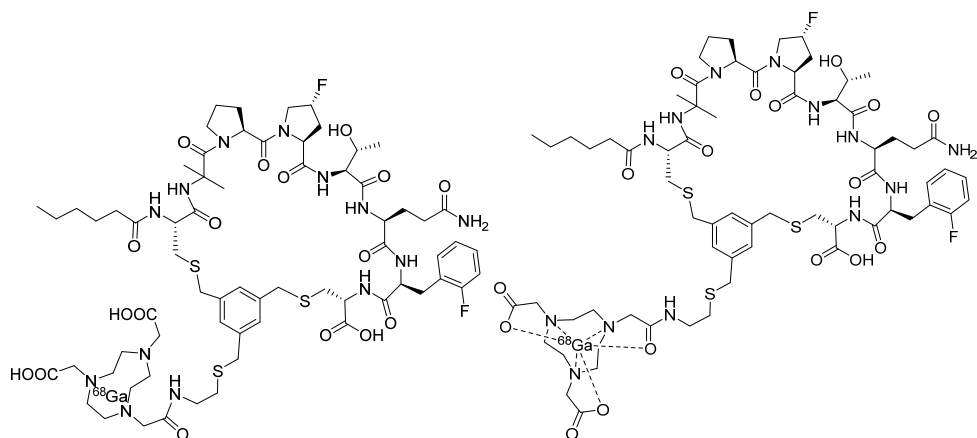
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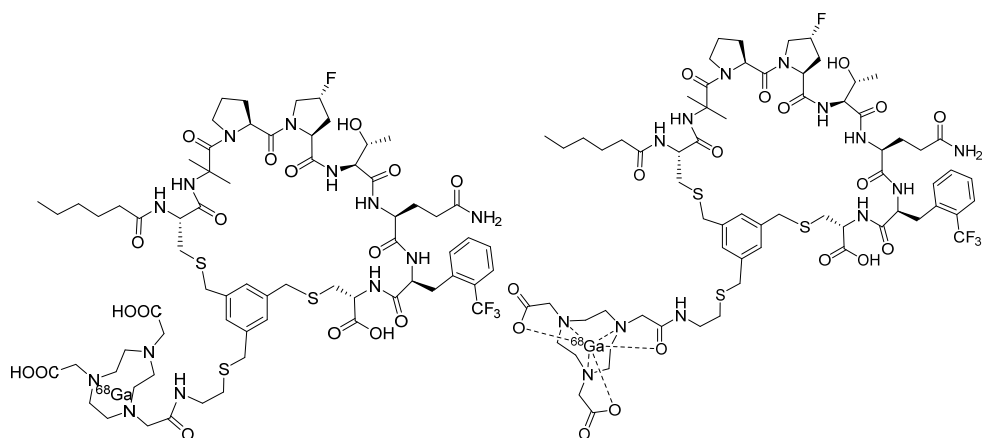
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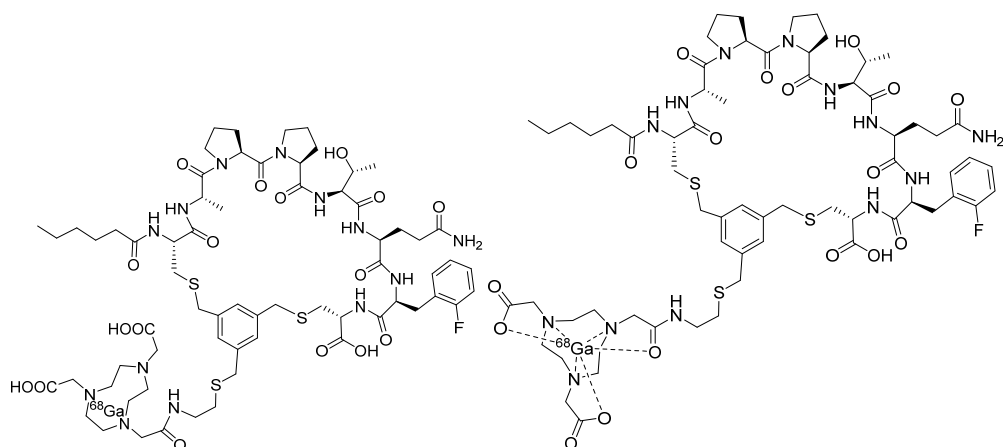
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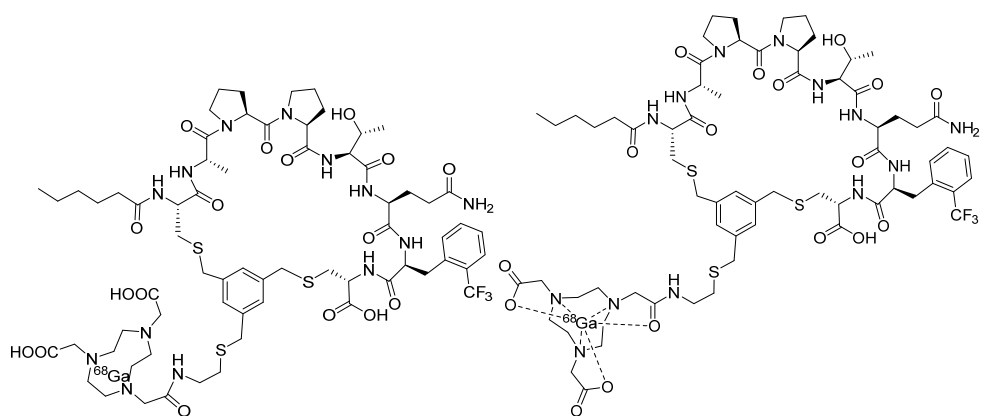
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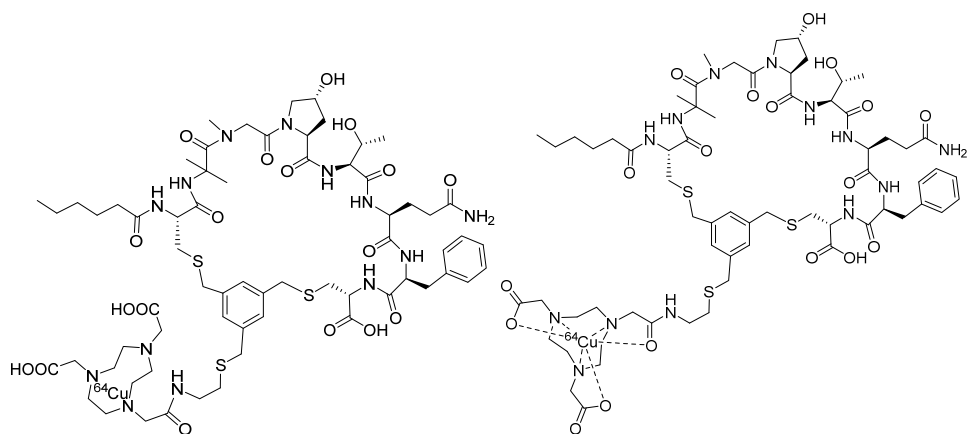
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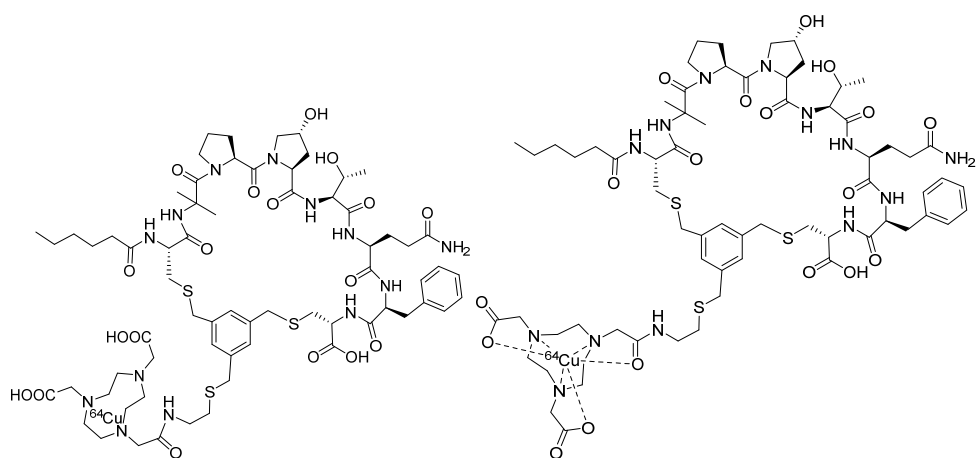
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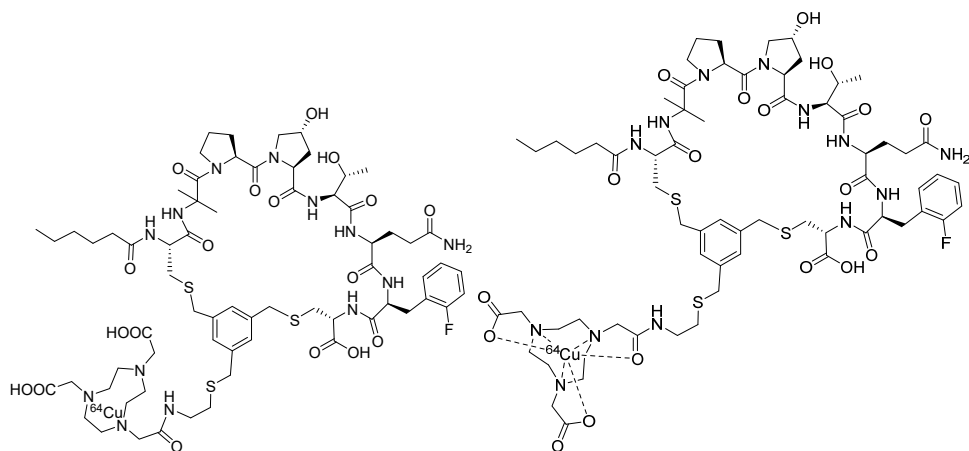
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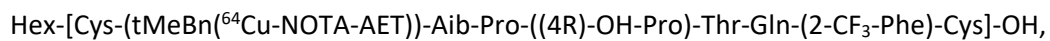
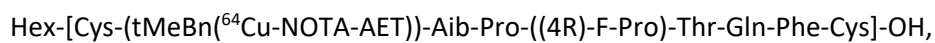
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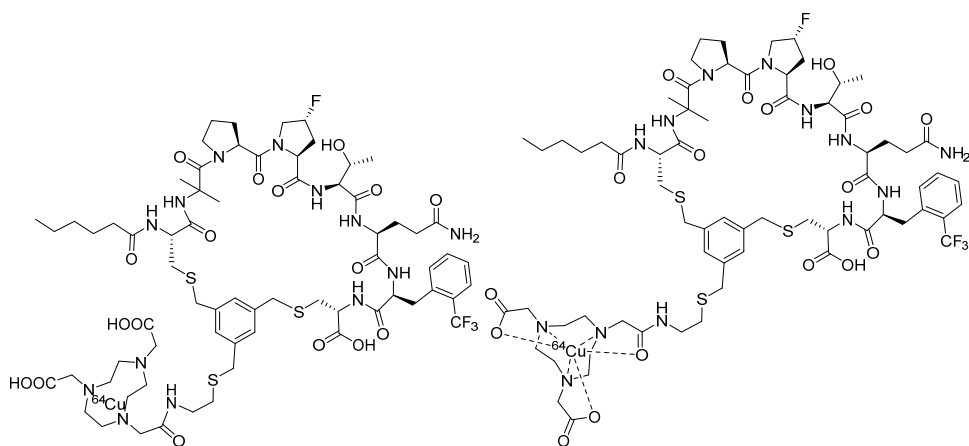


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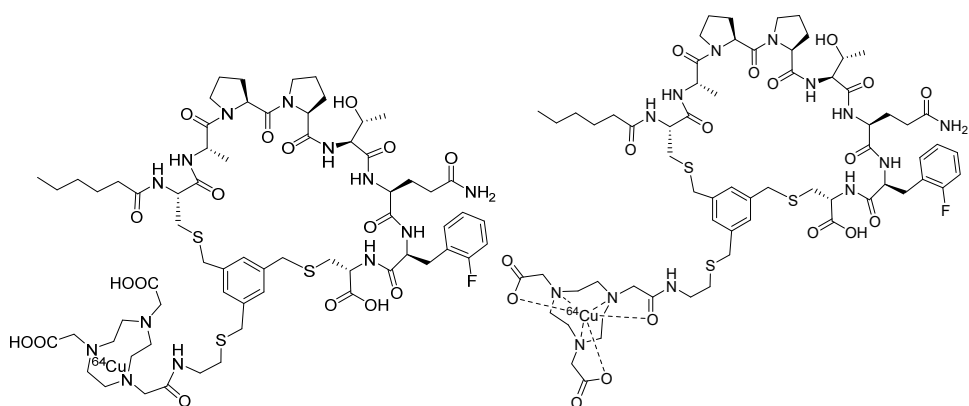


Hex-[Cys-(tMeBn(^{64}Cu -NOTA-AET))-Aib-Pro-((4R)-OH-Pro)-Thr-Gln-(2-F-Phe)-Cys]-OH,

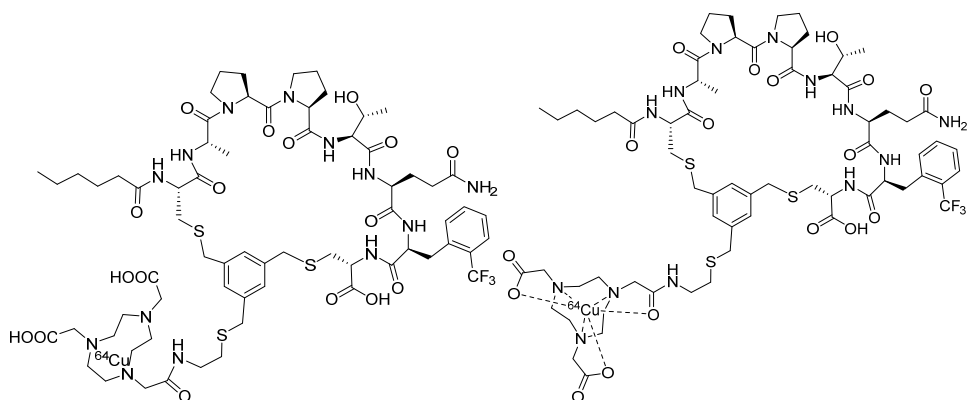




Hex-[Cys-(tMeBn(^{64}Cu -NOTA-AET))-Aib-Pro-((4R)-F-Pro)-Thr-Gln-(2-CF₃-Phe)-Cys]-OH,



Hex-[Cys-(tMeBn(^{64}Cu -NOTA-AET))-Ala-Pro-Pro-Thr-Gln-(2-F-Phe)-Cys]-OH, and

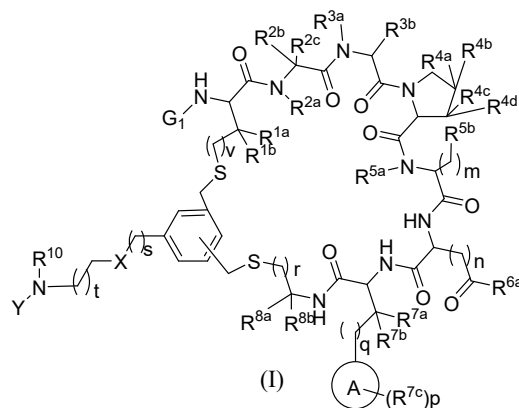


Hex-[Cys-(tMeBn(^{64}Cu -NOTA-AET))-Ala-Pro-Pro-Thr-Gln-(2-CF₃-Phe)-Cys]-OH.

26. A pharmaceutical composition, comprising the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 25, and one or more pharmaceutically acceptable carriers, diluents or excipients.
27. A method for preparing the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 25 or the pharmaceutical

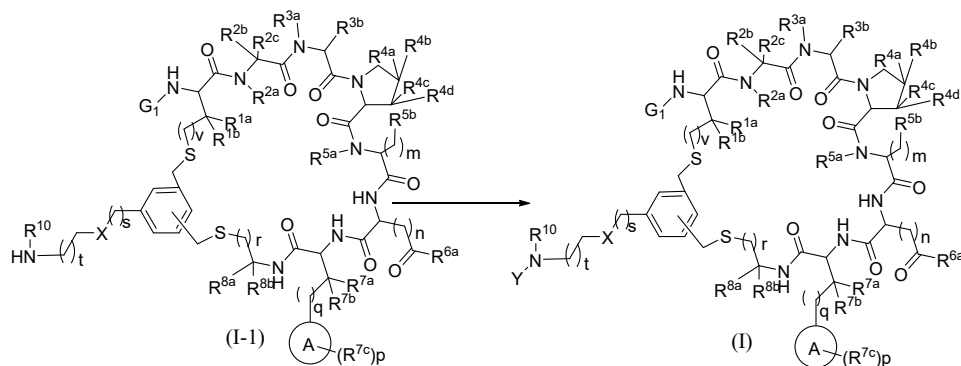
composition according to claim 26, wherein the method comprises a step of complexing the compound or the pharmaceutically acceptable salt thereof with a nuclide.

28. Use of the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 25 or the pharmaceutical composition according to claim 26 in the manufacture of a medicament for diagnosing or treating a disease, wherein the disease is a disease related to fibroblast activation protein (FAP); preferably, the disease related to fibroblast activation protein (FAP) is a disease associated with upregulation of fibroblast activation protein (FAP) expression; and more preferably, the disease is related to cells that exhibit upregulation of fibroblast activation protein (FAP) expression or a diseased tissue containing cells that exhibit upregulation of fibroblast activation protein (FAP) expression, e.g., a tumor or cancer.
29. Use of the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 25 or the pharmaceutical composition according to claim 26 in the manufacture of a medicament for diagnosing or treating a disease, wherein the disease is a tumor or cancer selected from solid tumor, epithelioma, bladder cancer, breast cancer, cervical cancer, colorectal cancer, cholangiocarcinoma, endometrial cancer, esophageal cancer, gastric cancer, gastrointestinal stromal tumor, head and neck cancer, liver cancer, lung cancer, melanoma, mesothelioma, neuroendocrine tumor and carcinoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, salivary gland cancer, sarcoma, squamous cell carcinoma, glioma (e.g., human brain astroglia cells), and thyroid cancer (e.g., medullary thyroid carcinoma).
30. Use of the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 25 or the pharmaceutical composition according to claim 26 in the manufacture of a medicament for diagnosing or treating a disease, wherein the disease is selected from an inflammatory disease, a cardiovascular disease, an autoimmune disease and a fibrotic disease.
31. A method for preparing the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to either claim 24 or claim 25, or the pharmaceutical composition according to claim 26, wherein the method comprises a step of complexing the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof with a nuclide,



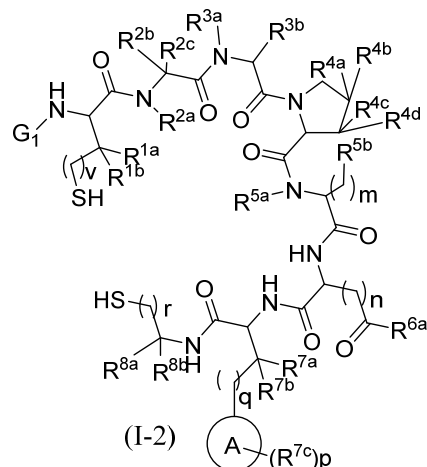
wherein the Y is a chelating agent, the chelating agent complexes a nuclide, and the R^{1a} , R^{1b} , v , G_1 , R^{2a} , R^{2b} , R^{2c} , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{5a} , R^{5b} , m , R^{6a} , n , R^{7a} , R^{7b} , q , ring A, R^{7c} , p , R^{8a} , R^{8b} , r , s , X , t and R^{10} are as defined in claims 1 to 25.

32. A method for preparing the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 25 or the pharmaceutical composition according to claim 26, wherein the method comprises a step of reacting a compound as shown in formula (I-1) with a chelating agent,



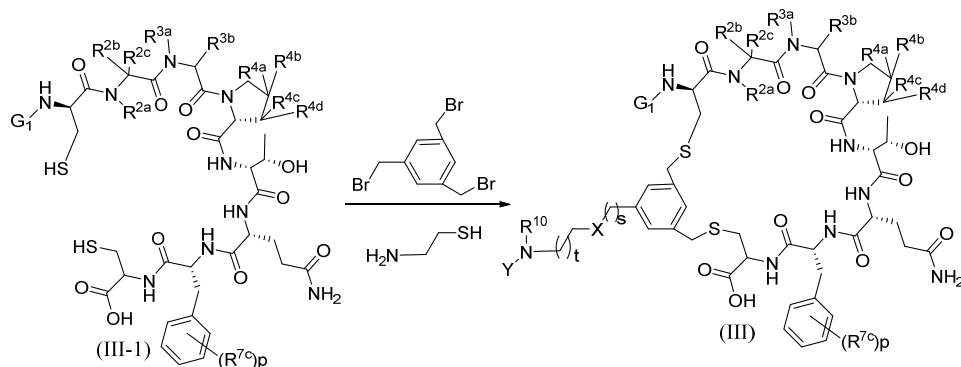
wherein the R^{1a} , R^{1b} , v , G_1 , R^{2a} , R^{2b} , R^{2c} , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{5a} , R^{5b} , m , R^{6a} , n , R^{7a} , R^{7b} , q , ring A, R^{7c} , p , R^{8a} , R^{8b} , r , s , X , t and R^{10} are as defined in claims 1 to 25.

33. A compound as shown in formula (I-2) or a pharmaceutically acceptable salt thereof,



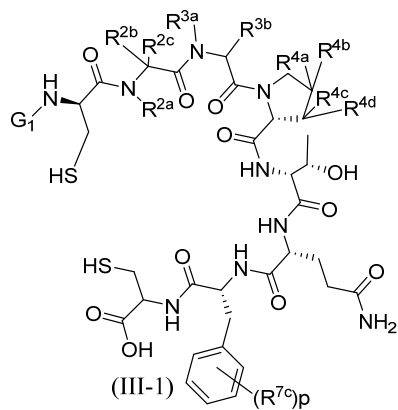
wherein the R^{1a} , R^{1b} , v , G_1 , R^{2a} , R^{2b} , R^{2c} , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{5a} , R^{5b} , m , R^{6a} , n , R^{7a} , R^{7b} , q , ring A, R^{7c} , p , R^{8a} , R^{8b} and r are as defined in claims 1 to 25.

34. A method for preparing the compound as shown in formula (I) or the pharmaceutically acceptable salt thereof according to any one of claims 13 to 25, wherein the method comprises a step of reacting a compound as shown in formula (III-1) or a pharmaceutically acceptable salt thereof with 2-aminoethanethiol and 1,3,5-tris(bromomethyl)benzene,



wherein the Y is hydrogen; R^{10} is hydrogen; the t is 1; the X is a sulfur atom; the s is 1; the R^{2a} , R^{2b} , R^{2c} , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{7c} , p and G_1 are as defined in claims 13 to 25.

35. The preparation method according to claim 31 or 32, wherein the method further comprises the step in the preparation method according to claim 34.
36. A compound as shown in formula (III-1) or a pharmaceutically acceptable salt thereof,



wherein the R^{2a}, R^{2b}, R^{2c}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{7c}, p and G₁ are as defined in claims 13 to 25.