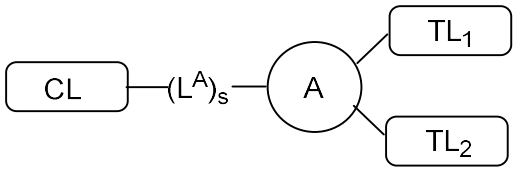
CLAIMS

WHAT IS CLAIMED:

1. A conjugate of Formula (A), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (A);

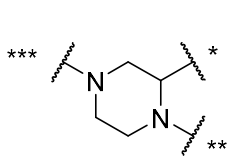
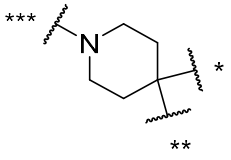
wherein:

TL_1 represents a 1st targeting moiety that binds to carbonic anhydrase IX;

TL_2 represents a 2nd targeting moiety that binds to carbonic anhydrase IX;

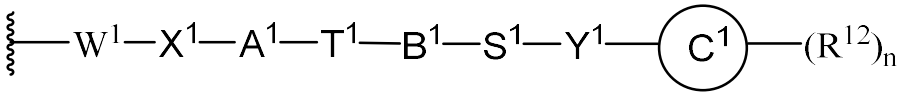
L^A represents a linker;

s is 0 or 1;

Ring A is  or  ; and

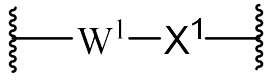
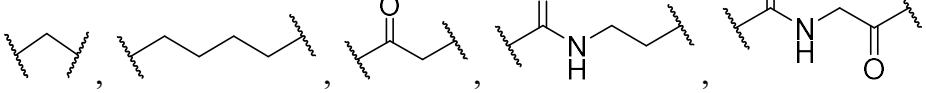
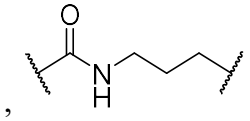
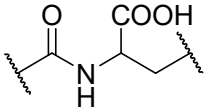
CL represents a metal chelator.

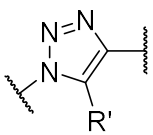
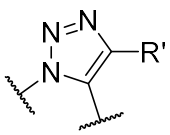
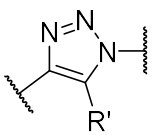
2. The conjugate of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein TL_1 is of Formula (IA):

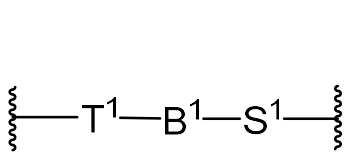
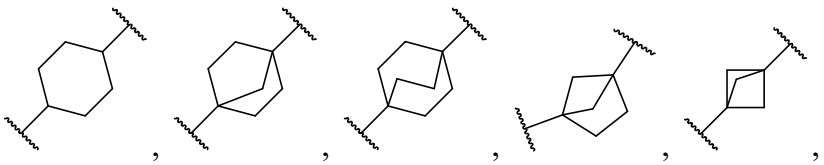
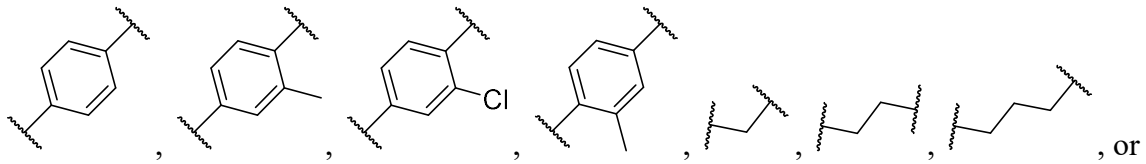
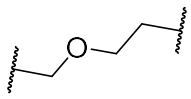


Formula (IA);

wherein:

 is  ,  , or  ;

A^1 is  ,  , or  , wherein R' is hydrogen or R;


is 


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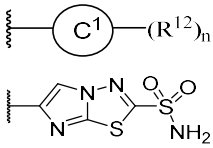
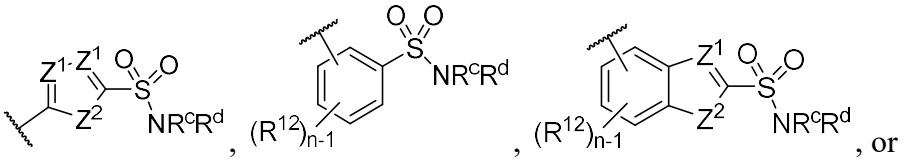
Y^1 is absent, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -NR^{11}-, -C(=O)-, -C(=O)NR^{11}-, -NR^{11}C(=O)-, -S(=O)$_2$NR^{11}-, or -NR^{11}S(=O)$_2$;

R^{11} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

n is 0, 1, 2, 3, 4, 5, or 6;


is 

;

wherein each Z^1 is independently -N- or -C$R^{12'}$-;

Z^2 is -O-, -S-, or -N$R^{12''}$-;

each $R^{12'}$ is independently hydrogen, halogen, -CN, -OH, -OR^a, -N$R^c$$R^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl, or heterocycloalkyl;

$R^{12''}$ is hydrogen, -S(=O)R^a, -S(=O)$_2$$R^a$, -S(=O)$_2NR^c$$R^d$, -C(=O)$R^a$, -C(=O)O$R^b$, -C(=O)N$R^c$$R^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl, or heterocycloalkyl;each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

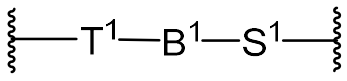
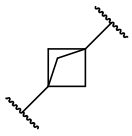
or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R;

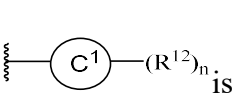
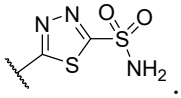
L is absent or C_1-C_3alkylene optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, $-SF_5$, -SH, $-S(=O)C_1$-C_3alkyl, $-S(=O)_2C_1$-C_3alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NHC_1$-C_3alkyl, $-S(=O)_2N(C_1$-C_3alkyl$)_2$, $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl$)_2$, $-C(=O)C_1$-C_3alkyl, -C(=O)OH, $-C(=O)OC_1$-C_3alkyl, $-C(=O)NH_2$, $-C(=O)NHC_1$-C_3alkyl, $-C(=O)N(C_1$-C_3alkyl$)_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, C_3-C_6cycloalkyl, or 3- to 6-membered heterocycloalkyl;

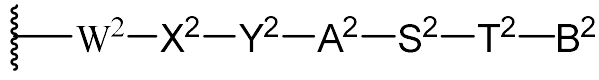
or two R on the same atom form an oxo;

or two R on the same or different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

3. The conjugate of claim 2, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein  is  .

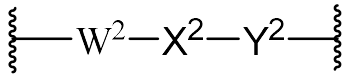
4. The conjugate of claim 2 or 3, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein  is  .

5. The conjugate of any one of claims 1-4, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein TL_2 is of Formula (IIA):



Formula (IIA);

wherein: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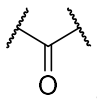
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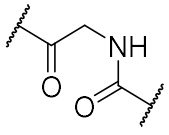
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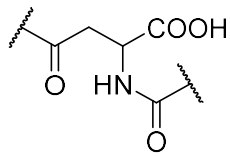
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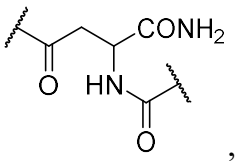
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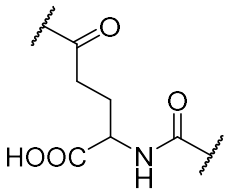
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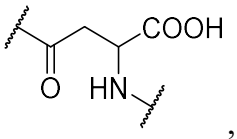
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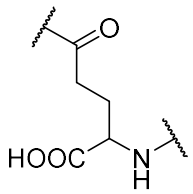
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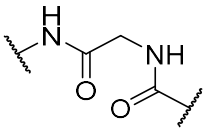
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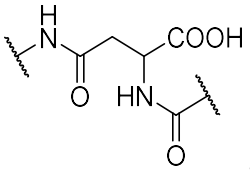
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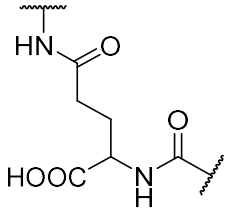
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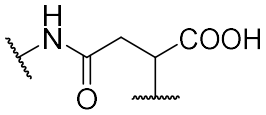
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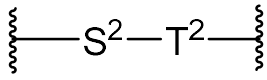
A^2 is absent, C_1-C_{10}alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substitued with one or more R^{22};

each R^{22} is independently -C(=O)OR^b or -C(=O)NR^{c}R^d;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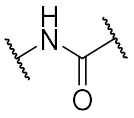
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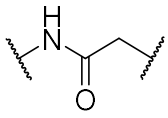
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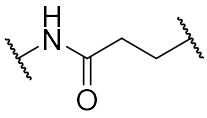
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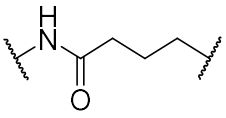
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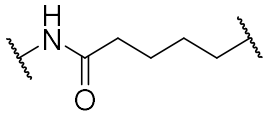
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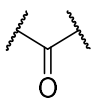
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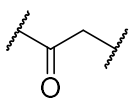
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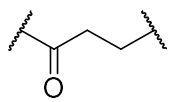
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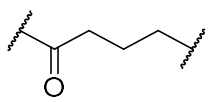
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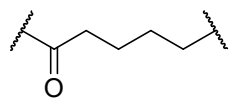
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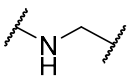
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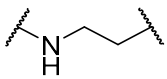
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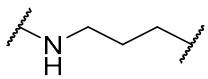
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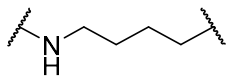

;(i) B^2 is absent;

or

(ii) B^2 is -N(R^{23})$_2$;

each R^{23} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or

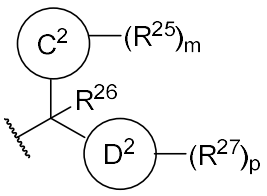
(iii) B^2 is -CF_3;

or

(iv) B^2 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substitued with one or more R^{24};

each R^{24} is independently halogen, -OH, C_1-C_6alkyl, or C_1-C_6haloalkyl;

or

(v) B^2 is  ;

Ring C^2 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{25} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SF_5, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

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

R^{26} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

Ring D^2 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{27} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SF_5, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

p is 0, 1, 2, 3, or 4;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

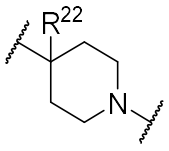
or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R;

L is absent or C_1-C_3alkylene optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, -SF_5, -SH, -S(=O)C_1-C_3alkyl, -S(=O)$_2$$C_1$-$C_3$alkyl, -S(=O)$_2$$NH_2$, -S(=O)$_2NHC_1$-$C_3$alkyl, -S(=O)$_2$N($C_1$-$C_3$alkyl)$_2$, -$NH_2$, -NH$C_1$-$C_3$alkyl, -N($C_1$-$C_3$alkyl)$_2$, -C(=O)$C_1$-$C_3$alkyl, -C(=O)OH, -C(=O)O$C_1$-$C_3$alkyl, -C(=O)$NH_2$, -C(=O)NH$C_1$-$C_3$alkyl, -C(=O)N($C_1$-$C_3$alkyl)$_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, C_3-C_6cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo;

or two R on the same or different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

6. The conjugate of claim 5, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein A^2 is 

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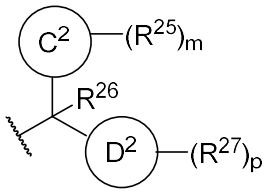
7. The conjugate of claim 5 or 6, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B^2 is 

wherein:

Ring C^2 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{25} is independently halogen, -CN, -NO_2, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF_5, -SH, -SR^a, -S(=O)R^a, -S(=O)$_2$$R^a$, -S(=O)$_2$$NR^cR^d$, -$NR^cR^d$, -$NR^b$C(=O)$NR^cR^d$, -$NR^b$C(=O)$R^a$, -$NR^b$C(=O)$OR^b$, -$NR^b$S(=O)$_2$$R^a$, -C(=O)$R^a$, -C(=O)$OR^b$, -C(=O)$NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

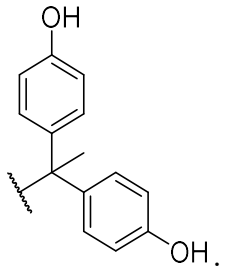
m is 0, 1, 2, 3, or 4;

R^{26} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

Ring D^2 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{27} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SF_5, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R; and

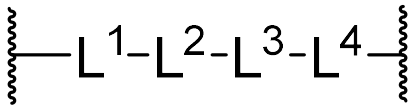
p is 0, 1, 2, 3, or 4.

8. The conjugate of any one of claims 5-7, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B^2 is  .

9. The conjugate of any one of claims 1-8, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein s is 0.

10. The conjugate of any one of claims 1-8, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein s is 1.

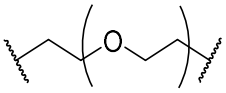
11. The conjugate of any one of claims 1-8 and 10, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the linker L^A has a structure of Formula (L-1a),



Formula (L-1a);

wherein:

L^1 is absent, -O-, -NR^L-, -$N(R^L)_2^+$-, -S-, -S(=O)-, -$S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -$C(=O)NR^L$-, -$NR^LC(=O)$-, -$OC(=O)NR^L$-, -$NR^LC(=O)O$-, -$NR^LC(=O)NR^L$-, -$NR^LS(=O)_2$-, -$S(=O)_2NR^L$-, -$C(=O)NR^LS(=O)_2$-, or -$S(=O)_2NR^LC(=O)$-;

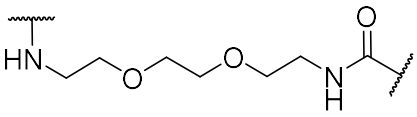
L^2 is  , C_1-C_{10}alkylene, or heterocycloalkylene optionally substituted with one or more R;

L^3 is absent or C_1-C_{10}alkylene; and

L^4 is absent, -O-, -NR^L-, -$N(R^L)_2^+$-, -S-, -S(=O)-, -$S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LS(=O)$_2$-, -S(=O)$_2NR^L$-, -C(=O)NR^LS(=O)$_2$-, or -S(=O)$_2NR^L$C(=O)-;

each R^L is independently hydrogen, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

12. The conjugate of any one of claims 8, 10, and 11, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the linker L^A is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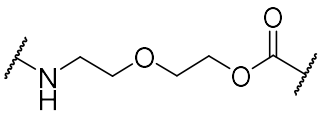
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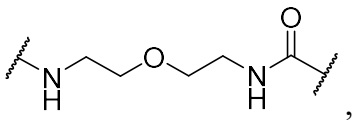
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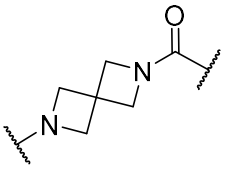
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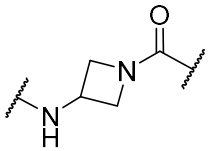
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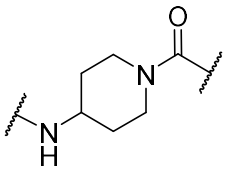
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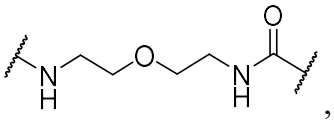
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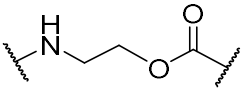
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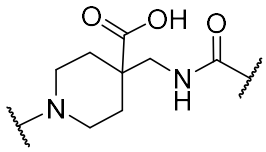
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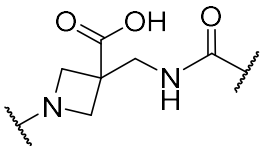
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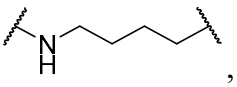
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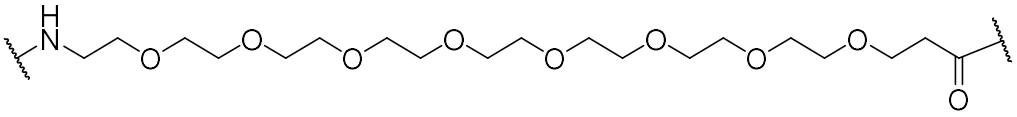
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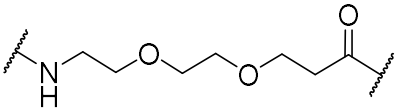
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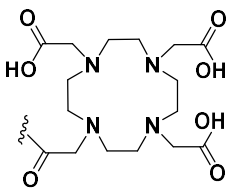
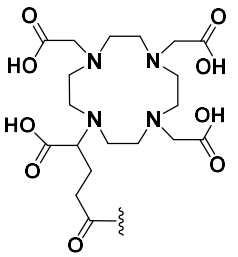
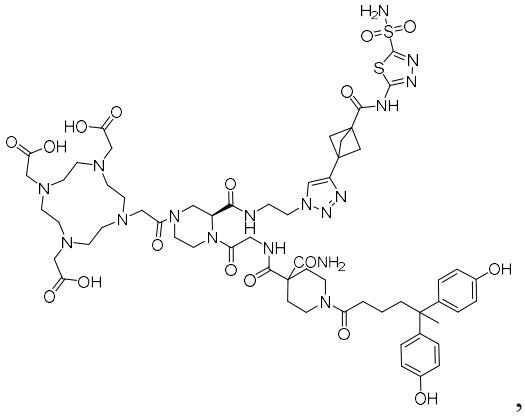
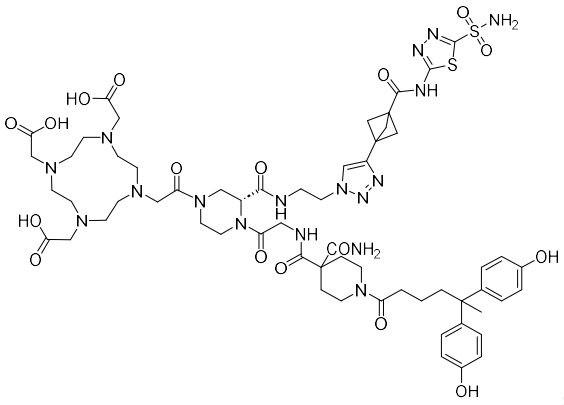
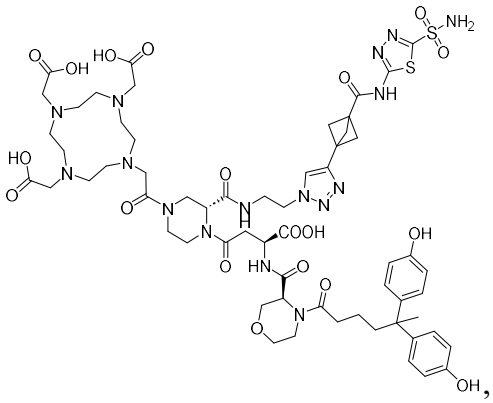
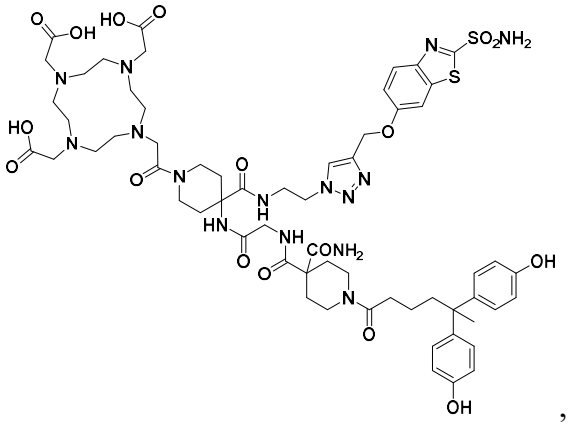
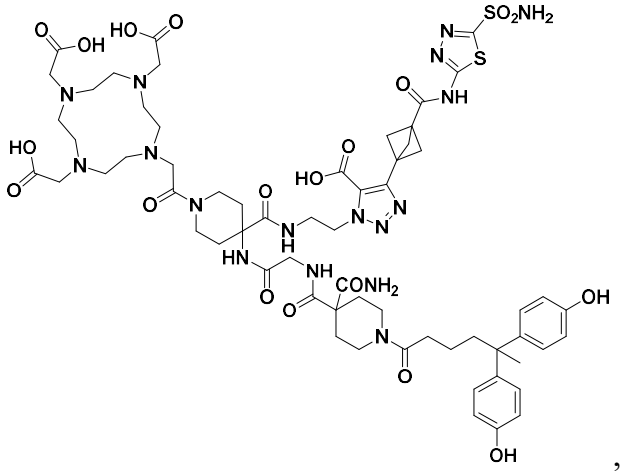
13. The conjugate of any one of claims 1-12, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein CL is DOTA, DOTA-GA, pBn-DOTA, pBn-SCN-DOTA, NH2-DOTA, NH2-DOTA-GA, p-NCS-Bn-DOTA-GA, p-NH2-Bn-oxo-DO3A, p-SCN-Bn-oxo-DO3A, NOTA, NODA-GA, NH2-NODA-GA, p-NCS-Bn-NODA-GA, p-NH2-Bn-NOTA, p-SCN-Bn-NOTA, NCS-MP-NODA, NH2-MPAA-NODA, PCTA, p-NH2-Bn-PCTA, p-SCN-Bn-PCTA, p-SCN-Bn-HEHA, H2-MACROPA-NCS, H1-MACROPA, H2-MACROPA-NH2, H4-OCTAPA, tetra-(S, S, S, S)-Me-DOTA, tetra-(S, S, S, S)-Et-DOTA, tetra-(S, S, S, S)-iBu-DOTA, or maleimide-nBu-DOTA.

14. The conjugate of any one of claims 1-13, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein CL is  DOTA or  DOTA-GA .

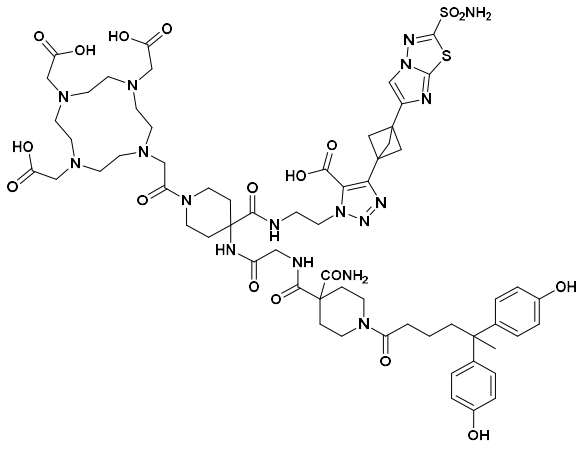
15. The conjugate of any one of claims 1-14, wherein the conjugate is:

 ,  ,

 ,  , or

 , or a pharmaceutically acceptable salt thereof.

16. The conjugate of claim 1, wherein the conjugate is:



, or a pharmaceutically acceptable salt thereof.

17. The conjugate of any one of claims 1-16, or a pharmaceutically acceptable salt or stereoisomer thereof, further comprising a radionuclide bound to the metal chelator.

18. The conjugate of claim 17, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the radionuclide is an alpha particle-emitting radionuclide.

19. The conjugate of claim 18, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the alpha particle-emitting radionuclide is Ac-225.

20. The conjugate of claim 17, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the radionuclide is a beta particle-emitting radionuclide.

21. The conjugate of claim 20, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the beta particle-emitting radionuclide is lutetium-177.

22. The conjugate of claim 17, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the radionuclide is a positron-emitting radionuclide.

23. The conjugate of claim 22, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the positron-emitting radionuclide is gallium-68, copper-61, copper-62, copper-64, zirconium-89, or terbium-152.

24. A pharmaceutical composition comprising the conjugate of any one of claims 18-23, or pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable excipient or carrier.

25. Use of the conjugate of any one of claims 18-23, or pharmaceutically acceptable salt or stereoisomer thereof, or the pharmaceutical composition of claim 24 in the manufacture of a medicament for diagnosing or imaging a disease or disorder in a subject in need thereof, wherein the conjugate, or pharmaceutically acceptable salt or stereoisomer thereof, or the pharmaceutical composition is to be administered to the subject.

26. Use of the conjugate of any one of claims 18-23, or pharmaceutically acceptable salt or stereoisomer thereof, or the pharmaceutical composition of claim 24 in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof, wherein the conjugate, or pharmaceutically acceptable salt or stereoisomer thereof, or the pharmaceutical composition is to be administered to the subject.
27. The use of claim 25 or 26, wherein the disease or disorder is a cancer.
28. The use of claim 27, wherein the cancer is hypoxic.
29. The use of any one of claim 27 or 28, wherein the cancer is clear cell renal cell carcinoma (ccRCC).