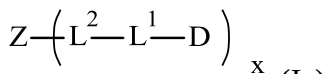
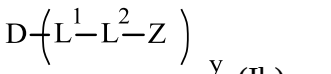
Claims

1. A CNP prodrug or a pharmaceutically acceptable salt thereof, wherein the prodrug is of formula (Ia) or (Ib)



(Ia)



(Ib),

wherein

-D is a CNP moiety having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:95;

-L^1- is a reversible prodrug linker moiety, which moiety -L^1- is conjugated to the side chain of an amino acid residue of the ring moiety of -D or to the backbone of the ring moiety of -D;

-L^2- is a single chemical bond or a spacer moiety;

-Z is a water-soluble branched polymer carrier moiety with a molecular weight of at least 10 kDa;

x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16; and

y is an integer selected from the group consisting of 1, 2, 3, 4 and 5;

from which CNP is released in the form of the free drug.

2. The CNP prodrug or a pharmaceutically acceptable salt thereof of claim 1, wherein the CNP prodrug is of formula (Ia).

3. The CNP prodrug or a pharmaceutically acceptable salt thereof of claim 1 or 2, wherein x is 1.

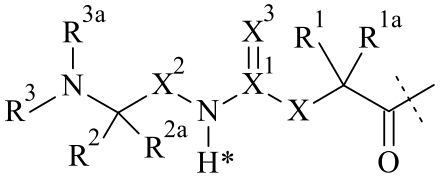
4. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 3, wherein CNP moiety has the sequence of SEQ ID NO:25 or SEQ ID NO:24.

5. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 4, wherein the CNP moiety has the sequence of SEQ ID NO:24.

6. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 5, wherein -L^1- is conjugated to the side chain of an amino acid residue of the ring moiety of -D selected from the group consisting of histidine, lysine, tryptophan, serine, threonine, tyrosine, aspartic acid, glutamic acid and arginine.

7. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 6, wherein -D has the sequence of SEQ ID NO:24 and -L^1- is conjugated to the lysine at position 26 of -D.

8. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 7, wherein the moiety -L^1- is of formula (II):


(II)

,

wherein the dashed line indicates the attachment to a nitrogen of -D which is a CNP moiety by forming an amide bond;

-X- is -C(R^4R^{4a})-; -N(R^4)-; -O-; -C(R^4R^{4a})-C(R^5R^{5a})-; -C(R^5R^{5a})-C(R^4R^{4a})-; -C(R^4R^{4a})-N(R^6)-; -N(R^6)-C(R^4R^{4a})-; -C(R^4R^{4a})-O-; -O-C(R^4R^{4a})-; or -C(R^7R^{7a})-;

X^1 is C; or S(O);

-X^2- is -C(R^8R^{8a})-; or -C(R^8R^{8a})-C(R^9R^{9a})-;

=X^3 is =O; =S; or =N-CN;

-R^1, -R^{1a}, -R^2, -R^{2a}, -R^4, -R^{4a}, -R^5, -R^{5a}, -R^6, -R^8, -R^{8a}, -R^9, -R^{9a} are independently selected from the group consisting of -H; and C_{1-6} alkyl;

-R^3, -R^{3a} are independently selected from the group consisting of -H; and C_{1-6} alkyl, provided that in case one of -R^3, -R^{3a} or both are other than -H they are connected to N to which they are attached through an SP^3-hybridized carbon atom;

-R^7 is -N($R^{10}R^{10a}$); or -NR^{10}-(C=O)-R^{11};

-R^{7a}, -R^{10}, -R^{10a}, -R^{11} are independently of each other -H; or C_{1-6} alkyl;

optionally, one or more of the pairs -R^{1a}/-R^{4a}, -R^{1a}/-R^{5a}, -R^{1a}/-R^{7a}, -R^{4a}/-R^{5a}, -R^{8a}/-R^{9a} form a chemical bond;

optionally, one or more of the pairs -R^1/-R^{1a}, -R^2/-R^{2a}, -R^4/-R^{4a}, -R^5/-R^{5a}, -R^8/-R^{8a},

$-R^9/-R^{9a}$ are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl; or 3- to 10-membered heterocyclyl;

optionally, one or more of the pairs $-R^1/-R^4$, $-R^1/-R^5$, $-R^1/-R^6$, $-R^1/-R^{7a}$, $-R^4/-R^5$, $-R^4/-R^6$, $-R^8/-R^9$, $-R^2/-R^3$ are joined together with the atoms to which they are attached to form a ring A;

optionally, R^3/R^{3a} are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle;

A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl; and

wherein $-L^1-$ is substituted with $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (II) is not replaced by $-L^2-Z$ or $-L^2-Z'$ or a substituent;

wherein

$-L^2-$ is a single chemical bond or a spacer;

$-Z$ is a water-soluble carrier; and

$-Z'$ is a water-insoluble carrier.

9. The CNP prodrug or a pharmaceutically acceptable salt thereof of claim 8, wherein $-X-$ is $-C(R^4R^{4a})-$ or $-N(R^4)-$.

10. The CNP prodrug or a pharmaceutically acceptable salt thereof of claim 8 or 9, wherein $-R^4$ is substituted with $-L^2-Z$ or $-L^2-Z'$.

11. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 8 to 10, wherein X^1 is C.

12. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 8 to 11, wherein $=X^3$ is =O.

13. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 8 to 12, wherein $-X^2-$ is $-C(R^8R^{8a})-$.

14. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 8 to 13, wherein -R^1 and -R^{1a} are -H.

15. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 8 to 14, wherein -R^2 and -R^{2a} are -H.

16. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 8 to 15, wherein -R^3 is -H and -R^{3a} is methyl.

17. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 8 to 16, wherein -R^4 and -R^{4a} are -H.

18. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 8 to 17, wherein -R^8 and -R^{8a} are -H.

19. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 18, wherein -L^2- is selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y1})-, -$S(O)_2$N(R^{y1})-, -S(O)N(R^{y1})-, -$S(O)_2$-, -S(O)-; -N(R^{y1})$S(O)_2$N(R^{y1a})-, -S-, -N(R^{y1})-, -OC(OR^{y1})(R^{y1a})-, -N(R^{y1})C(O)N(R^{y1a})-, -OC(O)N(R^{y1})-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y3})-, -$S(O)_2$N(R^{y3})-, -S(O)N(R^{y3})-, -$S(O)_2$-, -S(O)-, -N(R^{y3})$S(O)_2$N(R^{y3a})-, -S-, -N(R^{y3})-, -OC(OR^{y3})(R^{y3a})-, -N(R^{y3})C(O)N(R^{y3a})-, and -OC(O)N(R^{y3})-;

-R^{y1} and -R^{y1a} are independently of each other selected from the group consisting of -H, -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different, and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y4})-, -$S(O)_2$N(R^{y4})-, -S(O)N(R^{y4})-, -$S(O)_2$-,

-S(O)-, -N(R^{y4})S(O)$_2$N(R^{y4a})-, -S-, -N(R^{y4})-, -OC(OR^{y4})(R^{y4a})-, -N(R^{y4})C(O)N(R^{y4a})-, and -OC(O)N(R^{y4})-;

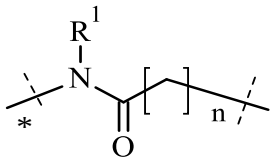
each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more -R^{y2}, which are the same or different;

each -R^{y2} is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{y5}, -OR^{y5}, -C(O)R^{y5}, -C(O)N($R^{y5}R^{y5a}$), -S(O)$_2$N($R^{y5}R^{y5a}$), -S(O)N($R^{y5}R^{y5a}$), -S(O)$_2R^{y5}$, -S(O)R^{y5}, -N(R^{y5})S(O)$_2$N($R^{y5a}R^{y5b}$), -SR^{y5}, -N($R^{y5}R^{y5a}$), -NO$_2$, -OC(O)R^{y5}, -N(R^{y5})C(O)R^{y5a}, -N(R^{y5})S(O)$_2R^{y5a}$, -N(R^{y5})S(O)R^{y5a}, -N(R^{y5})C(O)OR^{y5a}, -N(R^{y5})C(O)N($R^{y5a}R^{y5b}$), -OC(O)N($R^{y5}R^{y5a}$), and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

each -R^{y3}, -R^{y3a}, -R^{y4}, -R^{y4a}, -R^{y5}, -R^{y5a} and -R^{y5b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

20. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 19, wherein -L^2- is a C_{1-20} alkyl chain, which is optionally interrupted by one or more groups independently selected from -O-, -T- and -C(O)N(R^{y1})-; and which C_{1-20} alkyl chain is optionally substituted with one or more groups independently selected from -OH, -T and -C(O)N($R^{y6}R^{y6a}$); wherein -R^{y1}, -R^{y6}, -R^{y6a} are independently selected from the group consisting of H and C_{1-4} alkyl and wherein T is selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl.

21. The CNP prodrug or a pharmaceutical acceptable salt thereof of any one of claims 1 to 20, wherein -L^2- is of formula (i)



(i) ,

wherein

the dashed line marked with the asterisk indicates attachment to -L^1-;

the unmarked dashed line indicates attachment to -Z or -Z';

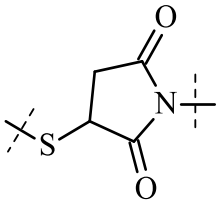
-R^1 is selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

n is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18; and

wherein the moiety of formula (i) is optionally further substituted.

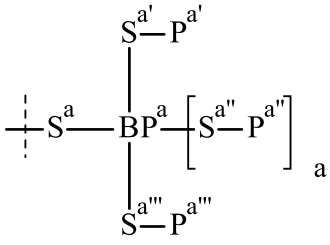
22. The prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 21, wherein -Z comprises a polymer selected from the group consisting of 2-methacryloyl-oxyethyl phosphoyl cholins, poly(acrylic acids), poly(acrylates), poly(acrylamides), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids), poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(ethyleneglycols), poly(ethylene oxides), poly(ethyl phosphates), poly(ethyloxazolines), poly(glycolic acids), poly(hydroxyethyl acrylates), poly(hydroxyethyl-oxazolines), poly(hydroxymethacrylates), poly(hydroxypropylmethacrylamides), poly(hydroxypropyl methacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids), poly(methacrylamides), poly(methacrylates), poly(methyloxazolines), poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(propylene glycols), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrins, gelatins, hyaluronic acids and derivatives, functionalized hyaluronic acids, mannans, pectins, rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

23. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 22, wherein -Z comprises a moiety



.

24. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 23, wherein -Z comprises a moiety of formula (a)



(a),

wherein

the dashed line indicates attachment to -L^2- or to the remainder of -Z;

BP^a is a branching point selected from the group consisting of -N<, -CR< and >C<;

-R is selected from the group consisting of -H and C_{1-6} alkyl;

a is 0 if BP^a is -N< or -CR< and n is 1 if BP^a is >C<;

-S^a-, -$S^{a'}$-, -$S^{a''}$- and -$S^{a'''}$- are independently of each other a chemical bond or are selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^1, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^2)-, -S(O)$_2$N(R^2)-, -S(O)N(R^2)-, -S(O)$_2$-, -S(O)-, -N(R^2)S(O)$_2$N(R^{2a})-, -S-, -N(R^2)-, -OC(OR^2)(R^{2a})-, -N(R^2)C(O)N(R^{2a})-, and -OC(O)N(R^2)-;

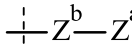
each -T- is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each -T- is independently optionally substituted with one or more -R^1, which are the same or different;

each -R^1 is independently selected from the group consisting of halogen, -CN, oxo (=O), -$COOR^3$, -OR^3, -$C(O)R^3$, -$C(O)N(R^3R^{3a})$, -$S(O)_2N(R^3R^{3a})$, -$S(O)N(R^3R^{3a})$, -$S(O)_2R^3$, -$S(O)R^3$, -$N(R^3)S(O)_2N(R^{3a}R^{3b})$, -$SR^3$, -$N(R^3R^{3a})$, -$NO_2$, -$OC(O)R^3$, -$N(R^3)C(O)R^{3a}$, -$N(R^3)S(O)_2R^{3a}$, -$N(R^3)S(O)R^{3a}$, -$N(R^3)C(O)OR^{3a}$, -$N(R^3)C(O)N(R^{3a}R^{3b})$, -$OC(O)N(R^3R^{3a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

each -R^2, -R^{2a}, -R^3, -R^{3a} and -R^{3b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

-$P^{a'}$, -$P^{a''}$ and -$P^{a'''}$ are independently a polymeric moiety.

25. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 24, wherein -Z is of formula (d)



(d),

wherein

the dashed line indicates attachment to -L^2-;

-Z^b- is selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^1, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -$C(O)N(R^2)$-, -$S(O)_2N(R^2)$-, -$S(O)N(R^2)$-, -$S(O)_2$-, -S(O)-, -$N(R^2)S(O)_2N(R^{2a})$-, -S-, -$N(R^2)$-, -$OC(OR^2)(R^{2a})$-, -$N(R^2)C(O)N(R^{2a})$-, and -$OC(O)N(R^2)$-;

each -T- is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each -T- is independently optionally substituted with one or more -R^1, which are the same or different;

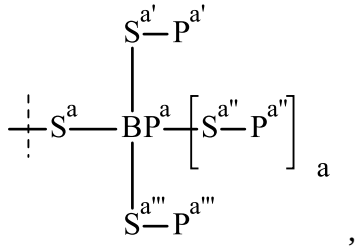
each -R^1 is independently selected from the group consisting of halogen, -CN, oxo (=O), -$COOR^3$, -OR^3, -$C(O)R^3$, -$C(O)N(R^3R^{3a})$, -$S(O)_2N(R^3R^{3a})$, -$S(O)N(R^3R^{3a})$, -$S(O)_2R^3$, -$S(O)R^3$, -$N(R^3)S(O)_2N(R^{3a}R^{3b})$, -$SR^3$, -$N(R^3R^{3a})$, -$NO_2$, -$OC(O)R^3$, -$N(R^3)C(O)R^{3a}$, -$N(R^3)S(O)_2R^{3a}$,

$-N(R^3)S(O)R^{3a}$, $-N(R^3)C(O)OR^{3a}$, $-N(R^3)C(O)N(R^{3a}R^{3b})$, $-OC(O)N(R^3R^{3a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

each $-R^2$, $-R^{2a}$, $-R^3$, $-R^{3a}$ and $-R^{3b}$ is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

and

$-Z^a$ is

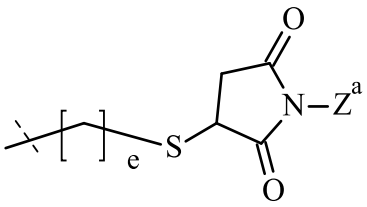


,

wherein

BP^a, $-S^a-$, $-S^{a'}-$, $-S^{a''}-$, $-S^{a'''}-$, $-P^{a'}$, $-P^{a''}$, $-P^{a'''}$ and a are used as defined in claim 24.

26. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 25, wherein -Z is of formula (e)



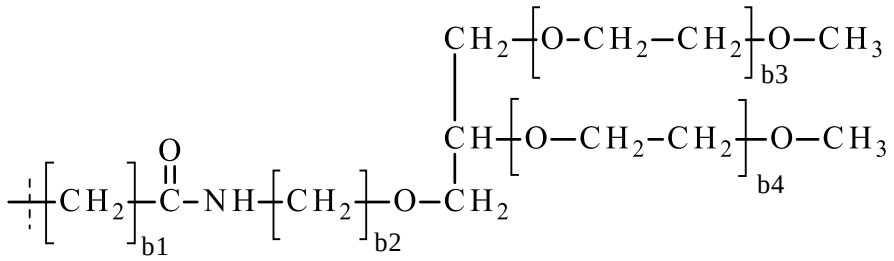
(e),

wherein

the dashed line indicates attachment to $-L^2-$;

e is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15; and

$-Z^a$ is



,

wherein

b1 is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7 and 8;

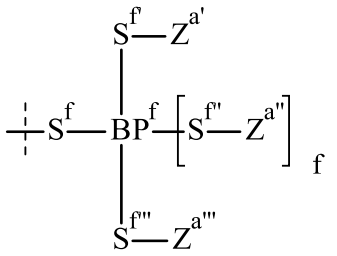
b2 is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7 and 8;

b3 is an integer ranging from and including 150 to 1000; and

b4 is an integer ranging from and including 150 to 1000.

27. The CNP prodrug or a pharmaceutically acceptable salt thereof of claim 26, wherein e is 5, b1 is 2, b2 is 3 and b3 and b4 are both about 450.

28. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 27, wherein -Z is of formula (f)



(f),

wherein

the dashed line indicates attachment to $-L^2-$;

BP^f is a branching point selected from the group consisting of -N<, -CR< and >C<;

-R is selected from the group consisting of -H and C_{1-6} alkyl;

f is 0 if BP^f is -N< or -CR< and f is 1 if BP^f is >C<;

$-S^f-$, $-S^{f'}-$, $-S^{f''}-$ and $-S^{f'''}-$ are independently either a chemical bond or are independently selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more $-R^1$, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^2)-$, $-S(O)_2N(R^2)-$, $-S(O)N(R^2)-$, $-S(O)_2-$, -S(O)-, $-N(R^2)S(O)_2N(R^{2a})-$, -S-, $-N(R^2)-$, $-OC(OR^2)(R^{2a})-$, $-N(R^2)C(O)N(R^{2a})-$, and $-OC(O)N(R^2)-$;

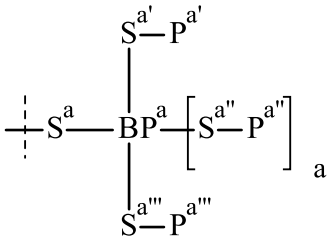
each -T- is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each –T- is independently optionally substituted with one or more $-R^1$, which are the same or different;

each R^1 is independently selected from the group consisting of halogen, -CN, oxo (=O), $-COOR^3$, $-OR^3$, $-C(O)R^3$, $-C(O)N(R^3R^{3a})$, $-S(O)_2N(R^3R^{3a})$, $-S(O)N(R^3R^{3a})$, $-S(O)_2R^3$, $-S(O)R^3$, $-N(R^3)S(O)_2N(R^{3a}R^{3b})$, $-SR^3$, $-N(R^3R^{3a})$, $-NO_2$, $-OC(O)R^3$, $-N(R^3)C(O)R^{3a}$, $-N(R^3)S(O)_2R^{3a}$, $-N(R^3)S(O)R^{3a}$, $-N(R^3)C(O)OR^{3a}$, $-N(R^3)C(O)N(R^{3a}R^{3b})$, $-OC(O)N(R^3R^{3a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

each $-R^2$, $-R^{2a}$, $-R^3$, $-R^{3a}$ and $-R^{3b}$ is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

and

$-Z^{a'}$, $-Z^{a''}$ and $-Z^{a'''}$ are independently

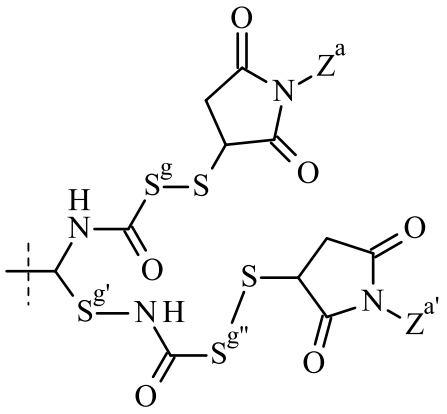


,

wherein

BP^a, $-S^a-$, $-S^{a'}-$, $-S^{a''}-$, $-S^{a'''}-$, $-P^{a'}$, $-P^{a''}$, $-P^{a'''}$ and a are used as defined in claim 24.

29. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 24 or 28, wherein -Z is of formula (g)



(g),

wherein

the dashed line indicates attachment to $-L^2-$;

$-S^g-$, $-S^{g'}-$ and $-S^{g''}-$ are independently selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50}

alkynyl are optionally substituted with one or more -R^1, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-,

-C(O)-, -C(O)N(R^2)-, -S(O)$_2$N(R^2)-, -S(O)N(R^2)-, -S(O)$_2$-, -S(O)-, -N(R^2)S(O)$_2$N(R^{2a})-, -S-, -N(R^2)-, -OC(OR^2)(R^{2a})-, -N(R^2)C(O)N(R^{2a})-, and -OC(O)N(R^2)-;

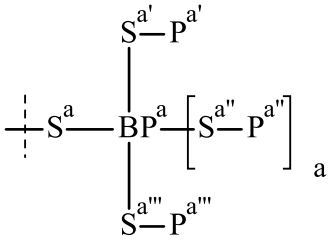
each -T- is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each -T- is independently optionally substituted with one or more -R^1, which are the same or different;

each R^1 is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^3, -OR^3, -C(O)R^3, -C(O)N(R^3R^{3a}), -S(O)$_2$N(R^3R^{3a}), -S(O)N(R^3R^{3a}), -S(O)$_2R^3$, -S(O)R^3, -N(R^3)S(O)$_2$N($R^{3a}R^{3b}$), -SR^3, -N(R^3R^{3a}), -NO$_2$, -OC(O)R^3, -N(R^3)C(O)R^{3a}, -N(R^3)S(O)$_2R^{3a}$, -N(R^3)S(O)R^{3a}, -N(R^3)C(O)OR^{3a}, -N(R^3)C(O)N($R^{3a}R^{3b}$), -OC(O)N(R^3R^{3a}), and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

each -R^2, -R^{2a}, -R^3, -R^{3a} and -R^{3b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

and

-Z^a and -$Z^{a'}$ are independently

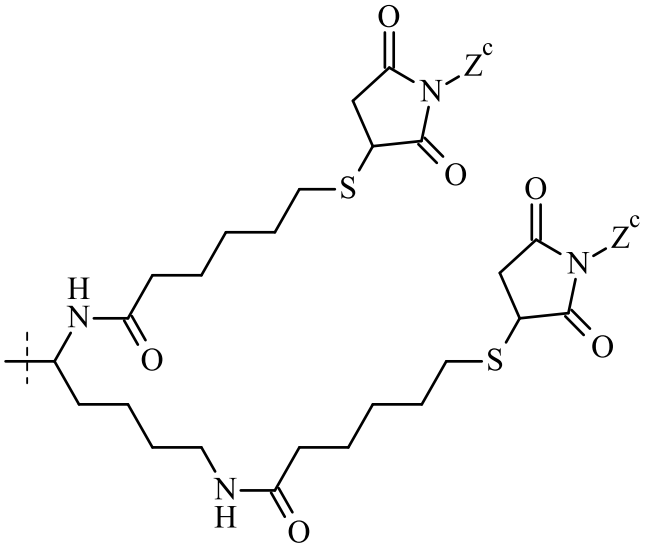


,

wherein

BP^a, -S^a-, -$S^{a'}$-, -$S^{a''}$-, -$S^{a'''}$-, -$P^{a'}$, -$P^{a''}$, -$P^{a'''}$ and a are used as defined in claim 24.

30. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 24, 28 or 29, wherein -Z is of formula (h)

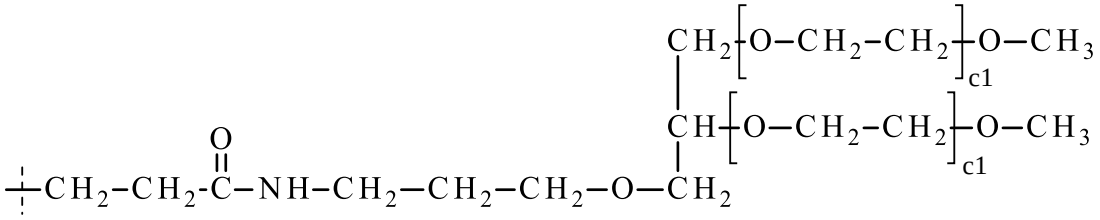


(h),

wherein

the dashed line indicates attachment to -L^2-; and

each -Z^c is a moiety

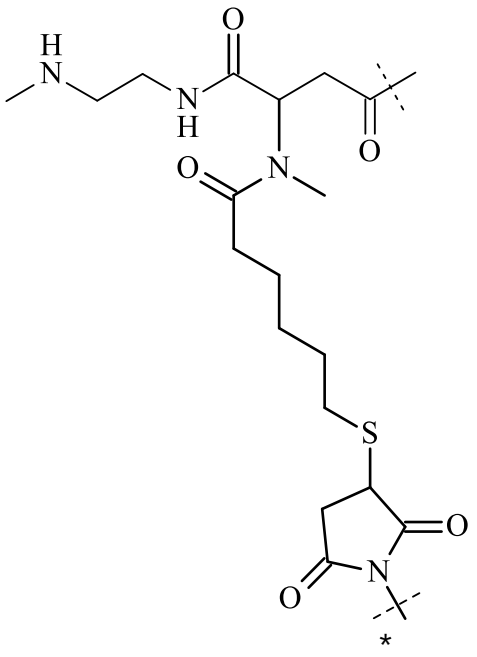


,

wherein

each c1 is an integer independently ranging from about 200 to 250.

31. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 27, wherein the CNP prodrug is of formula (IIe)

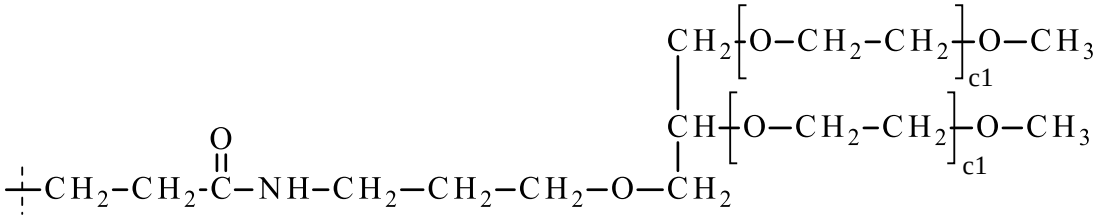


(IIe),

wherein

the unmarked dashed line indicates the attachment to a nitrogen of -D which is a CNP moiety by forming an amide bond; and

the dashed line marked with the asterisk indicates attachment to a moiety

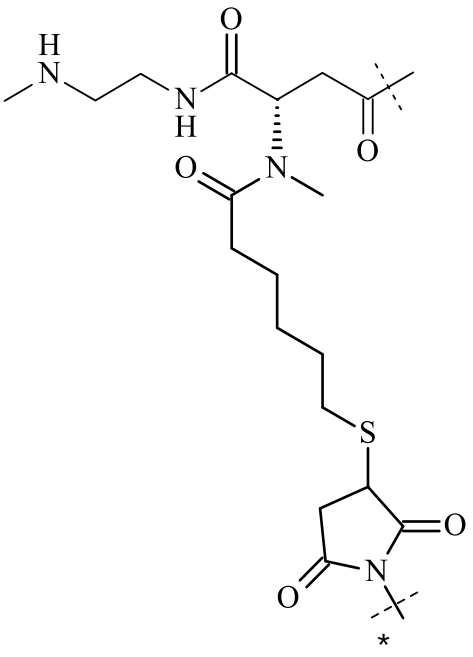


,

wherein

each c1 is an integer independently ranging from 400 to 500.

32. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 27 or 31, wherein the CNP prodrug is of formula (IIe')

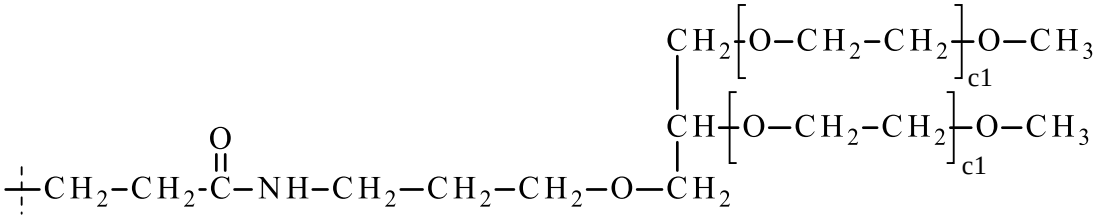


(IIe'),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond; and

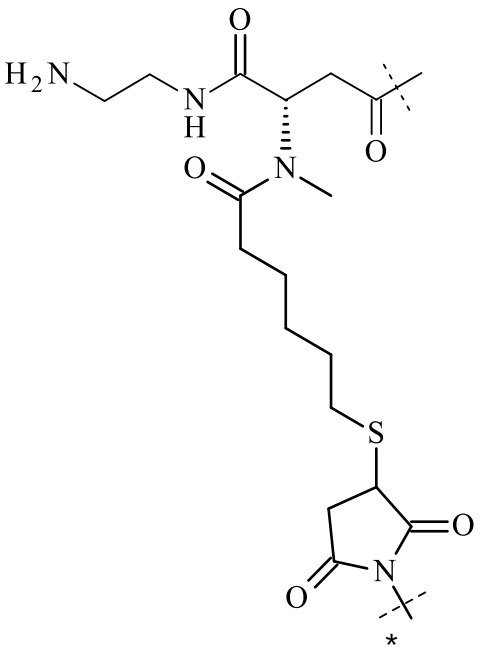
the dashed line marked with the asterisk indicates attachment to a moiety



wherein

each c1 is an integer independently ranging from 400 to 500.

33. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 27, wherein the CNP prodrug is of formula (IIe-i')

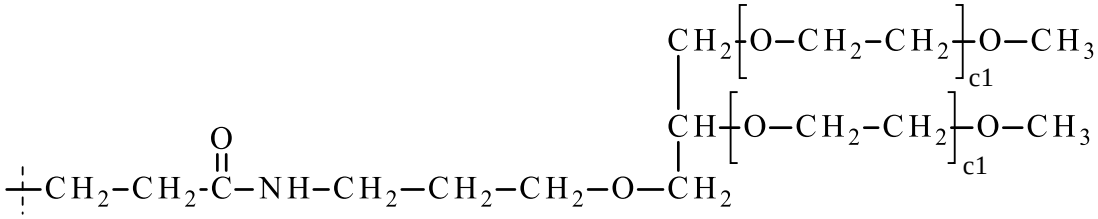


(IIe-i'),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond; and

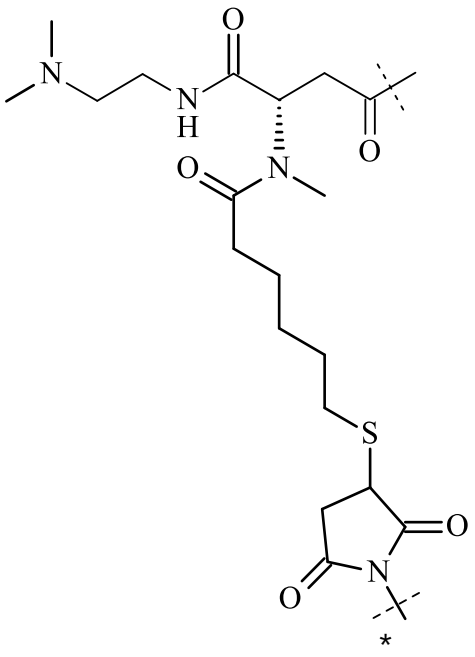
the dashed line marked with the asterisk indicates attachment to a moiety



wherein

each c1 is an integer independently ranging from 400 to 500.

34. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 27, wherein the CNP prodrug is of formula (IIe-ii')

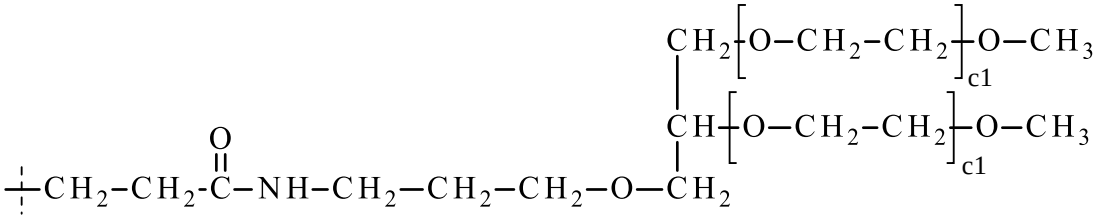


(IIe-ii'),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond; and

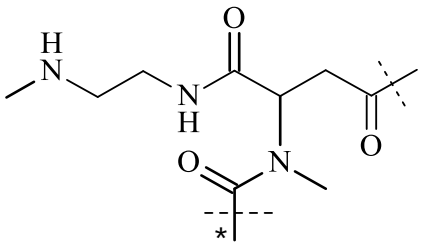
the dashed line marked with the asterisk indicates attachment to a moiety



wherein

each c1 is an integer independently ranging from 400 to 500.

35. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 24 or 28 to 30, wherein the CNP prodrug is of formula (IIf)

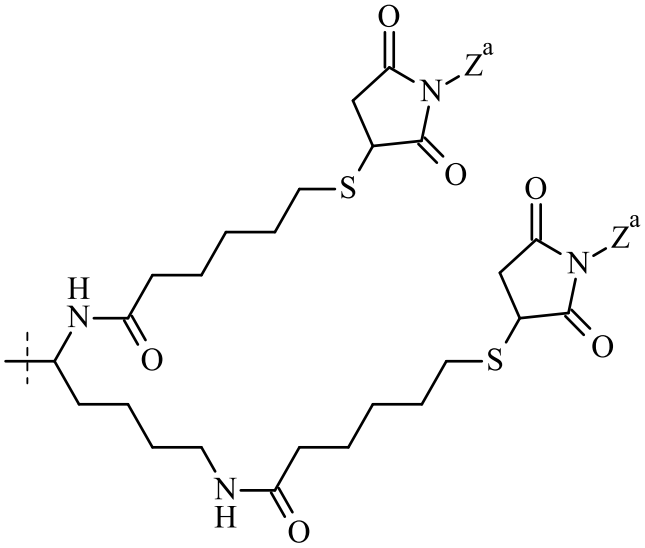


(IIf),

wherein

the unmarked dashed line indicates the attachment to a nitrogen of -D which is a CNP moiety by forming an amide bond; and

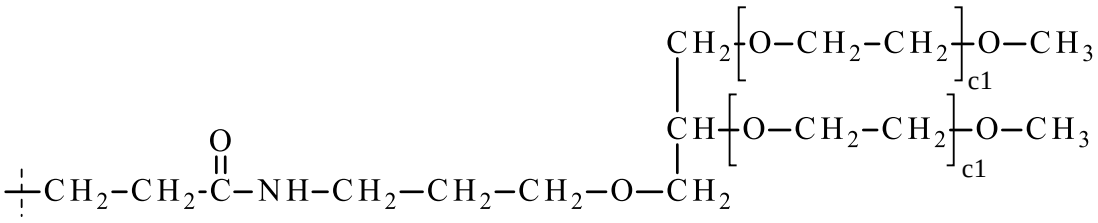
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

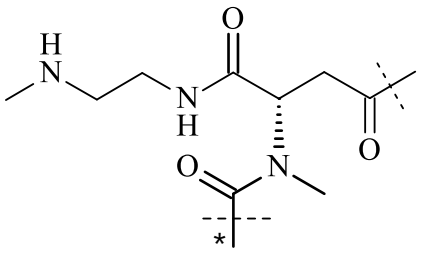
each -Z^a is



wherein

each c1 is an integer independently ranging from 200 to 250.

36. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 24, 28 to 30 or 35, wherein the CNP prodrug is of formula (IIf')

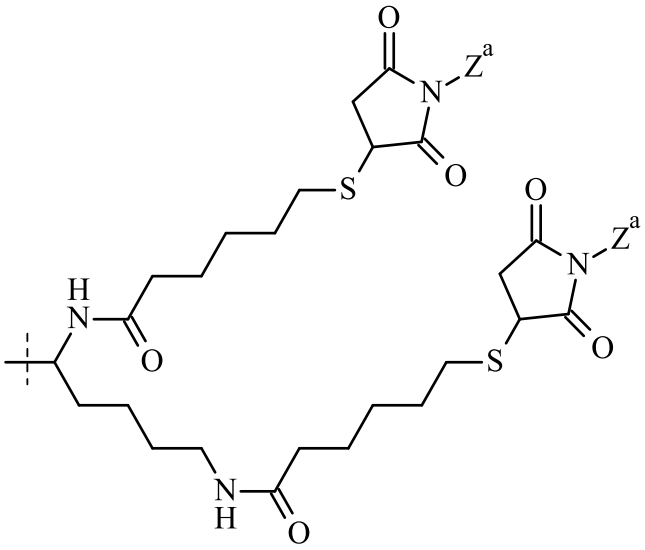


(IIf'),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond; and

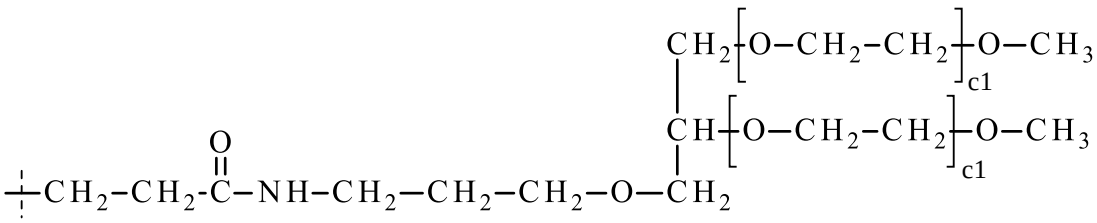
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

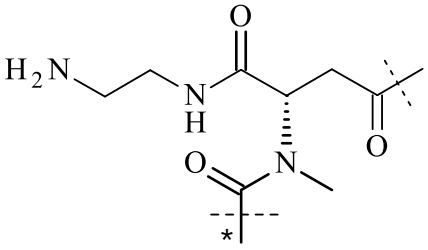
each Z^a is



wherein

each c1 is an integer independently ranging from 200 to 250.

37. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 24 or 28 to 30, wherein the CNP prodrug is of formula (IIf-i')

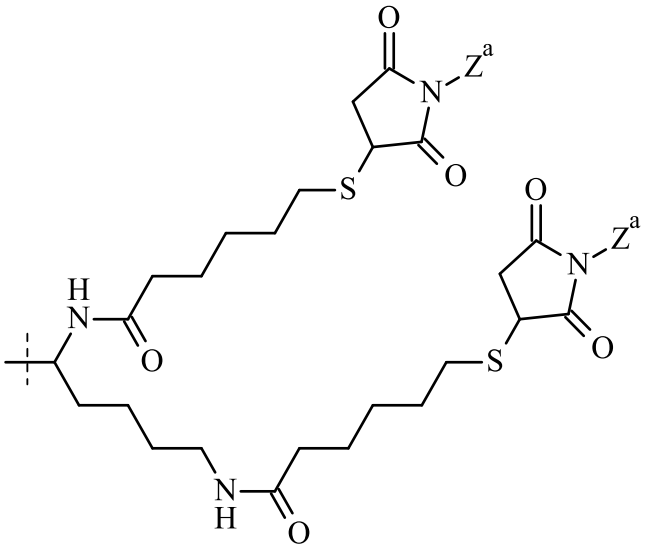


(IIf-i'),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond; and

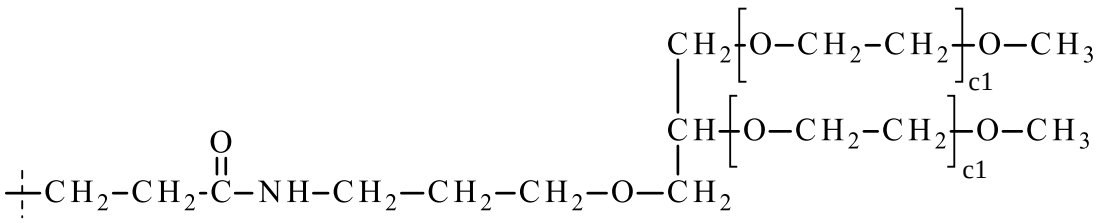
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

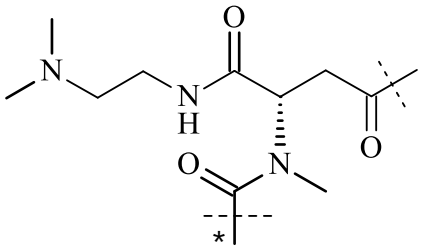
each Z^a is



wherein

each c1 is an integer independently ranging from 200 to 250.

38. The CNP prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 24 or 28 to 30, wherein the CNP prodrug is of formula (IIf-ii')

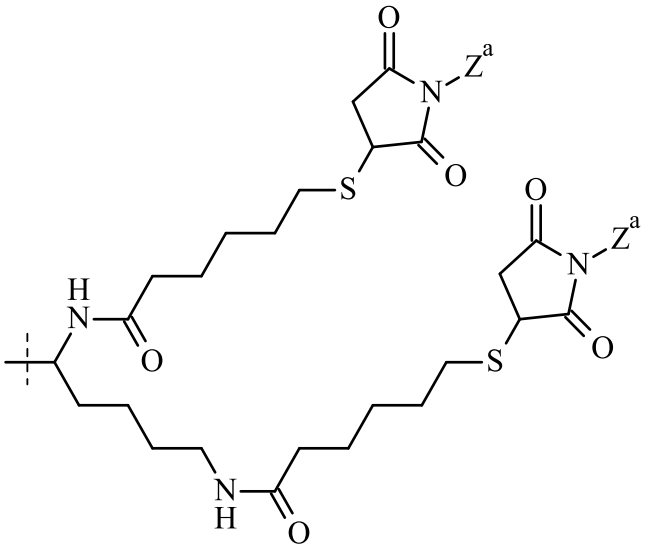


(IIf-ii'),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond; and

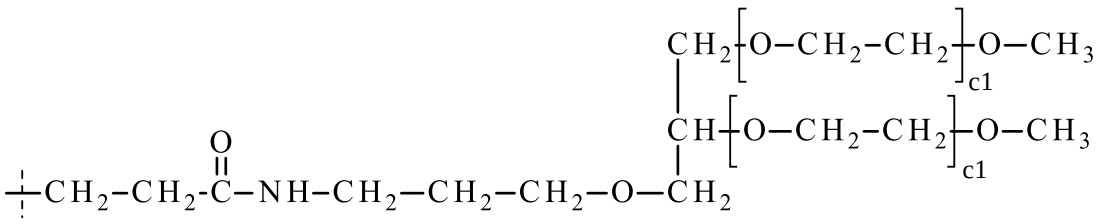
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

each Z^a is



wherein

each c1 is an integer independently ranging from 200 to 250.

39. The prodrug or pharmaceutically acceptable salt thereof of any one of claims 1 to 38, wherein the residual activity of the CNP prodrug is less than 10%.

40. A pharmaceutical composition comprising at least one CNP prodrug or pharmaceutically acceptable salt thereof of any one of claims 1 to 39 and at least one excipient.

41. The pharmaceutical composition of claim 40, wherein the pharmaceutical composition has a pH ranging from and including pH 4 to pH 6.