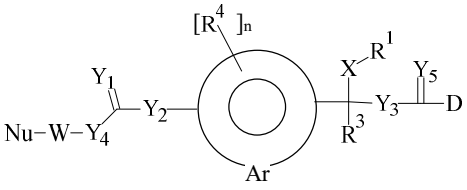
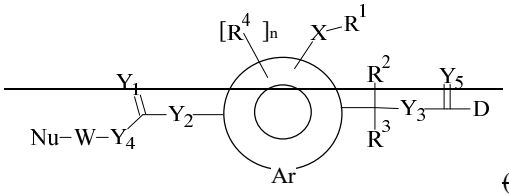
Claims

1. A container comprising a polymeric human growth hormone (hGH) prodrug or a pharmaceutically acceptable salt thereof of formula (Ia) ~~or (Ib)~~



(Ia),



~~(Ib),~~

wherein

-D is a hGH moiety connected to the rest of the molecule through an amine functional group;

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

-X- is a chemical bond or a spacer;

$=Y_1$ is selected from the group consisting of =O and =S;

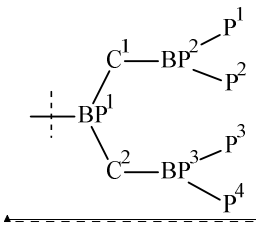
$-Y_2-$ is selected from the group consisting of -O- and -S-;

$-Y_3-$ is selected from the group consisting of -O- and -S-;

$-Y_4-$ is selected from the group consisting of -O-, $-NR^5-$ and $-C(R^6R^{6a})-$;

$=Y_5$ is selected from the group consisting of =O and =S;

$-R^1$ is ~~is~~ a water-soluble PEG-based moiety comprising ~~at least 40% PEG having a molecular weight ranging from 30 to 50 kDa~~ a moiety of formula (II)



(II),

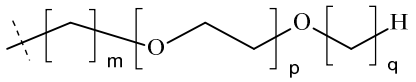
wherein

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-BP^1<, -BP^2<, -BP^3< are independently of each other selected from the group consisting of -N< and -C(R^8)<;

R^8 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

-P^1, -P^2, -P^3, -P^4 are independently of each other of formula (IIb)



(IIb),

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wherein

the dashed line indicates attachment the remainder of R^1, i.e. to BP^2 or BP^3, respectively,

m is 0 or 1,

p is an integer ranging from 180 to 240,

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

-C^1-, -C^2- are independently of each other 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^9, 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^{10})-, -S(O)$_2$N(R^{10})-, -S(O)N(R^{10})-, -S(O)$_2$-, -S(O)-, -N(R^{10})S(O)$_2$N(R^{10a})-, -S-, -N(R^{10})-, -OC(OR^{10})(R^{10a})-, -N(R^{10})C(O)N(R^{10a})-, and -OC(O)N(R^{10})-;

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^9, which are the same or different;

each -R^9 is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{11}, -OR^{11}, -C(O)R^{11}, -C(O)N($R^{11}R^{11a}$), -S(O)$_2$N($R^{11}R^{11a}$), -S(O)N($R^{11}R^{11a}$), -S(O)$_2R^{11}$, -S(O)R^{11}, -N(R^{11})S(O)$_2$N($R^{11a}R^{11b}$), -SR^{11}, -N($R^{11}R^{11a}$), -NO$_2$, -OC(O)R^{11}, -N(R^{11})C(O)R^{11a}, -N(R^{11})S(O)$_2R^{11a}$, -N(R^{11})S(O)R^{11a}, -N(R^{11})C(O)OR^{11a}, -N(R^{11})C(O)N($R^{11a}R^{11b}$), -OC(O)N($R^{11}R^{11a}$), 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

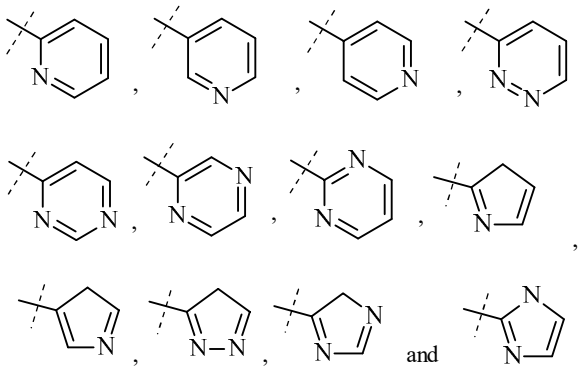
each -R^{10}, -R^{10a}, -R^{11}, -R^{11a} and -R^{11b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

~~-R^{2},~~ -R^{3}, -R^{5}, -R^{6}, -R^{6a} are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

-R^{4} is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

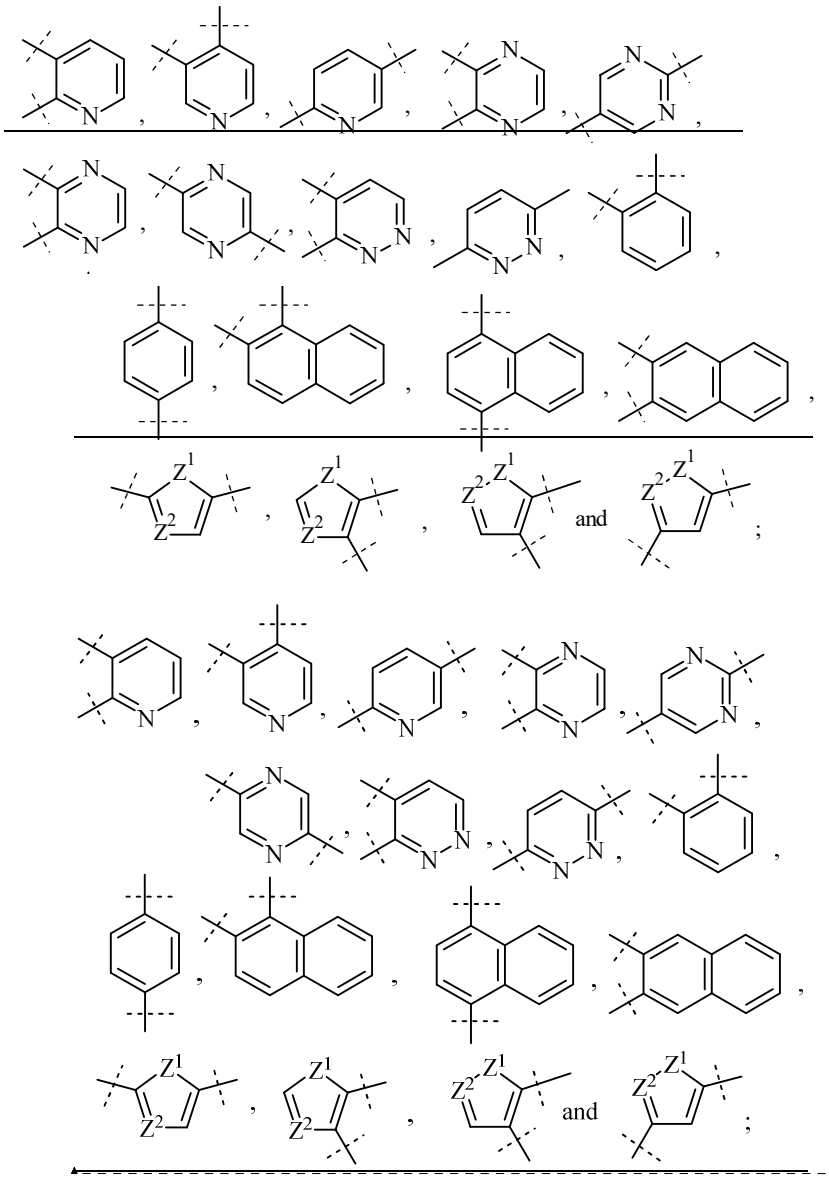
-W- is selected from the group consisting of C_{1-20} alkyl optionally interrupted by one or more groups selected from the group consisting of C_{3-10} cycloalkyl, 8- to 30-membered carbopolycyclyl, 3- to 10-membered heterocyclyl, -C(O)-, -C(O)N(R^{7})-, -O-, -S- and -N(R^{7})-;

-Nu is a nucleophile selected from the group consisting of -N($R^{7}R^{7a}$), -N(R^{7}OH), -N(R^{7})-N($R^{7a}R^{7b}$), -S(R^{7}),-COOH,



;

-Ar- is selected from the group consisting of



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wherein

dashed lines indicate attachment to the rest of the prodrug,

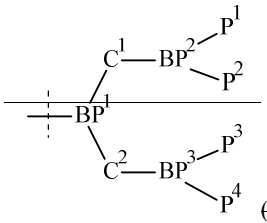
$-Z^1-$ is selected from the group consisting of -O-, -S- and $-N(R^7)-$, and

$-Z^2-$ is $-N(R^7)-$; and

-R^7, -R^{7a}, -R^{7b} are independently of each other selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

wherein the prodrug of formula (Ia) and (Ib) is optionally further substituted.

2. The container of claim 1, wherein BP^1 of formula (II) is –N<. -R^1 comprises a moiety of formula (II)



(II),

wherein

-BP^1<, -BP^2<, -BP^3< are independently of each other selected from the group consisting of -N< and -C(R^8)<;

-R^8 is selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

-P^1, -P^2, -P^3, -P^4 are independently of each other a PEG-based chain comprising at least 40% PEG and having a molecular weight ranging from 8 to 12 kDa;

-C^1-, -C^2- are independently of each other 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^9, 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^{10})-, -$S(O)_2N(R^{10})$-, -S(O)N(R^{10})-, -$S(O)_2$-, -S(O)-, -N(R^{10})$S(O)_2N(R^{10a})$-, -S-, -N(R^{10})-, -OC(OR^{10})(R^{10a})-, -N(R^{10})C(O)N(R^{10a})-, and -OC(O)N(R^{10})-;

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^9, which are the same or different;

each -R^9 is independently selected from the group consisting of halogen, -CN, oxo (=O), -$COOR^{11}$, -OR^{11}, -C(O)R^{11}, -C(O)N($R^{11}R^{11a}$), -$S(O)_2N(R^{11}R^{11a})$, -S(O)N($R^{11}R^{11a}$), -$S(O)_2R^{11}$, -S(O)R^{11}, -N(R^{11})$S(O)_2N(R^{11a}R^{11b})$, -SR^{11},

~~$-N(R^{11}R^{11a})$, $-NO_2$, $-OC(O)R^{11}$, $-N(R^{11})C(O)R^{11a}$, $-N(R^{11})S(O)_2R^{11a}$, $-N(R^{11})S(O)R^{11a}$, $-N(R^{11})C(O)OR^{11a}$, $-N(R^{11})C(O)N(R^{11a}R^{11b})$, $-OC(O)N(R^{11}R^{11a})$, 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~~

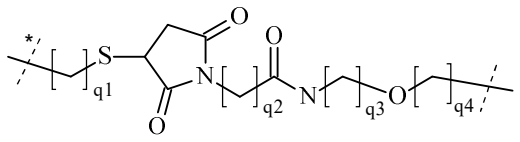
~~each R^{10}, R^{10a}, R^{11}, R^{11a} and R^{11b} is independently selected from the group consisting of H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.~~

3. The container of claim 1 or 2, wherein BP^2 and BP^3 of formula (II) are both –CH<.

4. The container of any one of claims 1 to 3, wherein the first branching point BP^1 and the attachment site of X are separated by no more than 60 atoms.

5. The container of any one of claims 1 to 4, wherein C^1 and C^2 of formula (II) are C_{1-50} alkyl interrupted by one or more of the groups selected from the group consisting of -O-, $-C(O)N(R^{10})-$ and 3- to 10 membered heterocyclyl; wherein the 3- to 10 membered heterocyclyl is substituted with at least one oxo (=O).

6. The container of any one of claims 1 to 5, wherein C^1 and C^2 are of formula (IIa)



(IIa),

wherein

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

the unmarked dashed line indicates attachment to BP^2 or BP^3, respectively;

q1 is 1, 2, 3, 4, 5, 6, 7 or 8;

q2 is 1, 2, 3, 4, or 5;

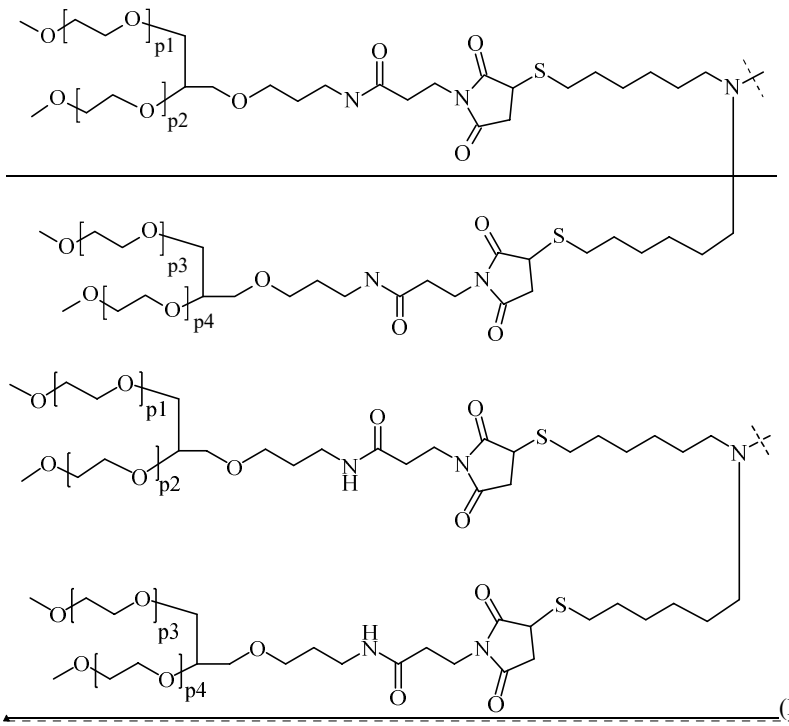
q3 is 1, 2, 3, 4, 5, 6, 7 or 8;

q4 is 1, 2 or 3.

7. The container of any one of claims 1 to 6, wherein p is an integer ranging from 210 to 240.

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~~3.~~8.The container of any one of claims 1 ~~or 2~~to 7, wherein -R^1 comprises a moiety of formula (IIc):



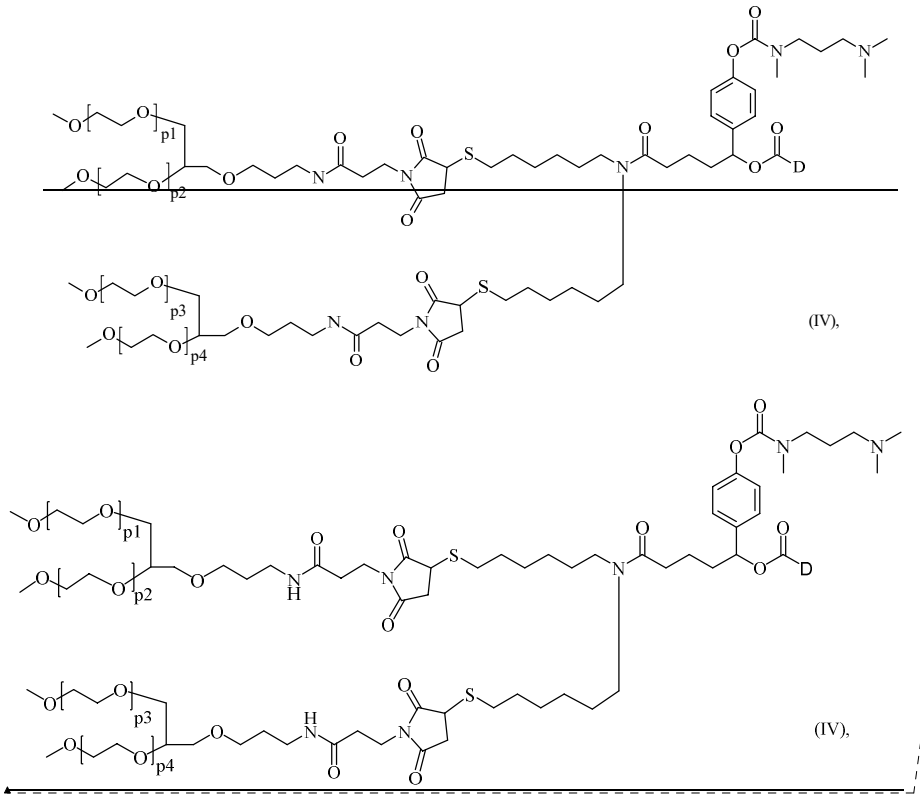
(IIc),

wherein

p1, p2, p3, p4 are independently an integer ranging from 180 ~~to 270, preferably from 200 to 250, even more preferably from 210~~ to 240 ~~and most preferably from 220 to 240~~.

9. The container of one of claims 1 to 8, wherein p is an integer ranging from 210 to 240.

~~4.~~10. The container of any one of claims 1 to ~~3~~9, wherein the polymeric hGH prodrug is of formula (IV)



(IV),

(IV),

Field Code Changed

wherein

D is an hGH moiety connected to the rest of the molecule through an amine functional group; and

p1, p2, p3, p4 are independently an integer ranging from 180 to ~~270~~240.

~~5.~~11. The container of claim ~~4~~10, wherein pl, p2, p3, and p4 are independently an integer ranging from 200 to 240.

~~6.~~12. The container of any one of claims 1 to ~~5~~11, wherein-D is connected to the rest of the molecule through an amine provided by a lysine side chain.

~~7.~~13. The container of any one of claims 1 to ~~6~~12, wherein the-D is an hGH moiety of SEQ ID NO: 1.

~~8.~~14. The container of any one of claims 1 to ~~7~~13, which further comprises at least one excipient.

~~9.~~15. The container of any one of claims 1 to ~~8~~14, which comprises a liquid formulation and from 3 to 300 mg/ml of the prodrug.

~~10.~~16. The container of claim ~~9~~15, wherein the liquid formulation comprises

polymeric hGH prodrug	3-300 mg/ml
succinic acid	5-50 mM
optionally trehalose dihydrate	25-150 mg/ml
optionally methionine	1-50 mM;

and has a pH ranging from pH 4.0 to 6.0 which is titrated using a suitable buffer.

~~11.~~17. The container of any one of claims 1 to ~~8~~14, which comprises a dry formulation and from 1 to 99.9% (w/w) of the prodrug.

~~12.~~18. The container of claim ~~11~~17, wherein the dry formulation comprises from 9 to 71% (w/w) of the prodrug.

~~13.~~19. The container of claim ~~11~~ 17 or ~~12~~18, wherein the dry formulation comprises from 32 to 34% (w/w) or 50 to 54% (w/w) of the prodrug.

~~14.~~20. The container of any one of claims ~~11~~ 17 to ~~13~~19, wherein the dry formulation is obtained by a process comprising the steps of

(a) providing a liquid formulation comprising

polymeric hGH prodrug	3-300 mg/ml
succinic acid	5-50 mM
optionally trehalose dihydrate	25-150 mg/ml

and having a pH ranging from pH 4.0 to pH 6.0 which is titrated using a suitable buffer, and

(b) drying the liquid formulation of step (a).

~~15.~~21. The container of any one of claims ~~11~~ 17 to ~~14~~20, wherein the dry formulation comprises based on the total weight of the formulation:

polymeric hGH prodrug	14-65% (w/w)
succinic acid	0.5-2.5% (w/w)
trehalose dihydrate	31-84% (w/w)
Tris	0.4-4% (w/w)

~~16.~~22. The container of any one of claims 1 to ~~15~~21, wherein the container is selected from the group consisting of syringes, dual-chamber syringes, vials, vials with stopper and seal, ampoules, cartridges, and dual-chamber cartridges.

~~17.~~23. The container of claim ~~16~~22, wherein the vial is a glass vial.

~~18.~~24. The container of claim ~~16~~22, wherein the container is a dual-chamber cartridge.