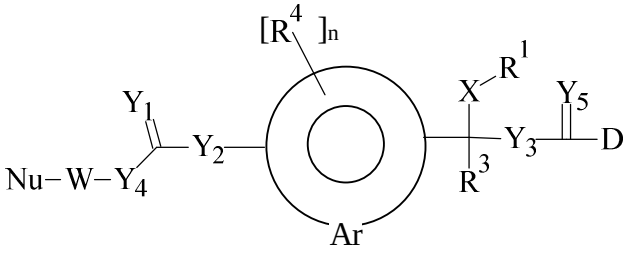
Claims

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



(Ia),

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;

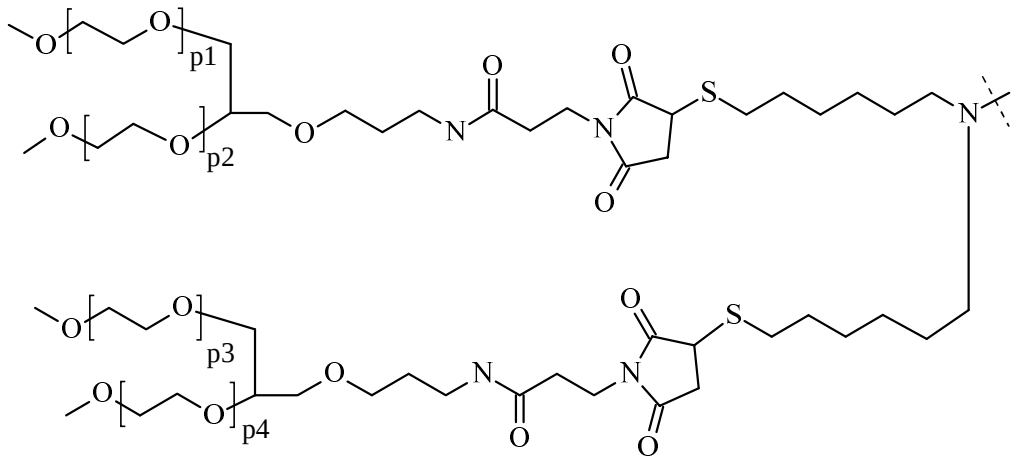
$-Y_2-$ is selected from the group consisting of -O- and -S-;

$-Y_3-$, 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 a water-soluble PEG-based moiety comprising at least 40% PEG having a molecular weight ranging from 30 to 50 kDa and comprising a moiety of formula (IIc):



(IIc),

wherein

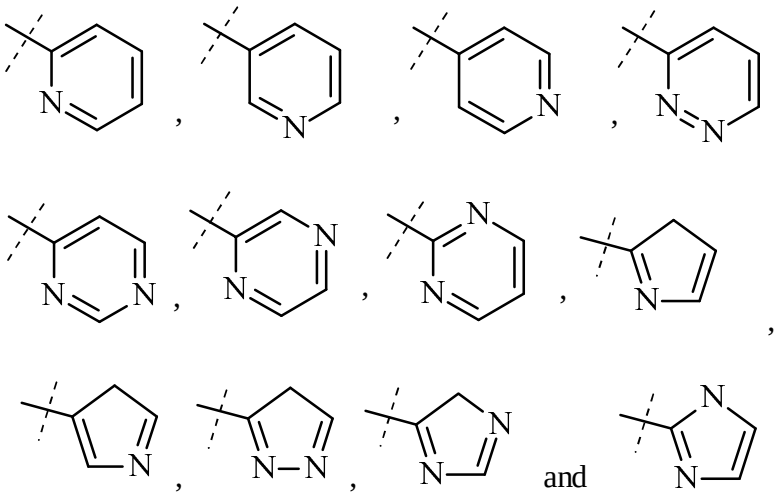
p1, p2, p3, p4 are independently an integer ranging from 210 to 240;

-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;

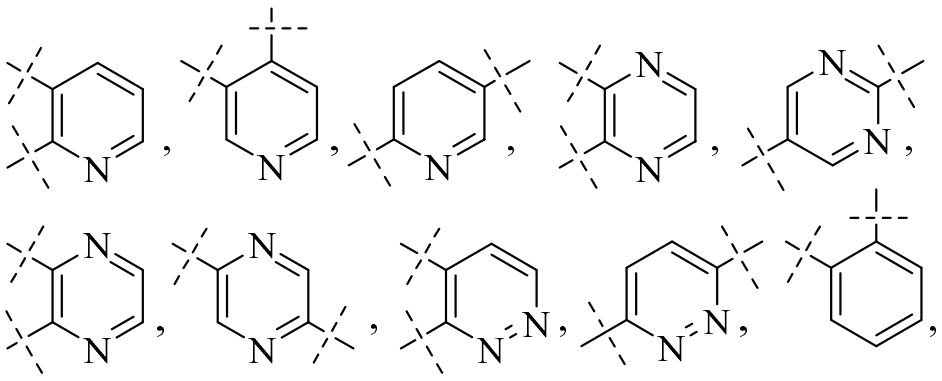
-W- is selected from the group consisting of C_{1-20} alkyl optionally interrupted by one or more groups selected from the group consisting of C_{3-10} cycloalkyl, 8- to 30-membered carbopolycyclyl, 3- to 10-membered heterocyclyl, -C(O)-, -C(O)N(R^7)-, -O-, -S- and -N(R^7)-;

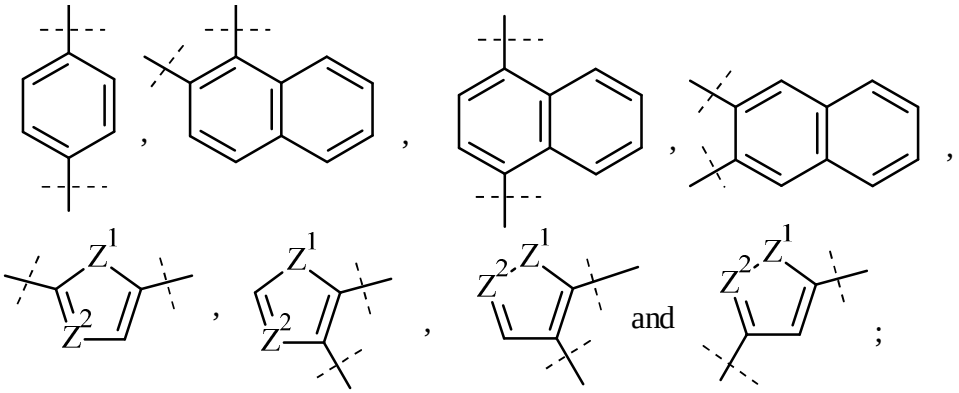
-Nu is a nucleophile selected from the group consisting of -N(R^7R^{7a}), -N(R^7OH), -N(R^7)-N($R^{7a}R^{7b}$), -S(R^7),-COOH,



;

-Ar- is selected from the group consisting of





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; and

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

2. The prodrug of claim 1, wherein $=Y^1$ is =O.

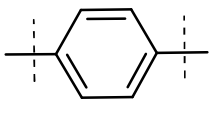
3. The prodrug of claim 1 or 2, wherein $-Y^2-$ is -O-.

4. The prodrug of any one of claims 1 to 3, wherein $-Y^3-$ is -O-.

5. The prodrug of any one of claims 1 to 4, wherein $-Y^4-$ is $-NR^5-$..

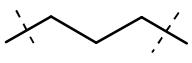
6. The prodrug of any one of claims 1 to 5, wherein $=Y^5$ is =O.

7. The prodrug of any one of claims 1 to 6, wherein Ar is



wherein the dashed lines indicate attachment to the remainder of the prodrug.

8. The prodrug of any one of claims 1 to 7, wherein W is



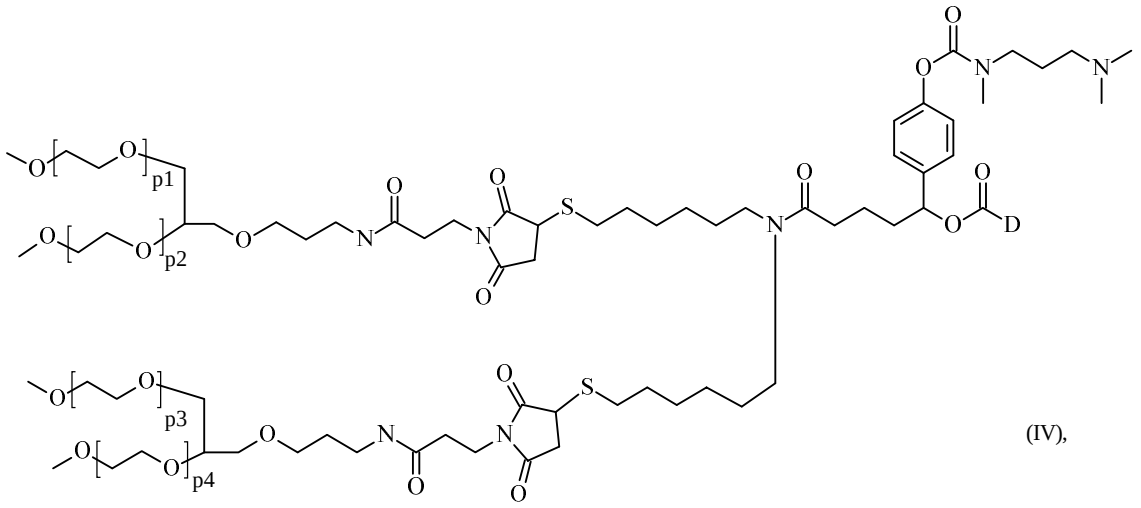
wherein

the dashed lines indicate attachment to the rest of the molecule.

9. The prodrug of any one of claims 1 to 8, wherein -Nu is -N(R^7R^{7a}).

10. The prodrug of any one of claims 1 to 9, wherein -R^3 is -H.

11. The prodrug of any one of claims 1 to 10, wherein the polymeric hGH prodrug is of formula (IV)



(IV),

wherein

-D is a 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 210 to 240.

12. The prodrug of any one of claims 1 to 11, wherein p1, p2, p3, p4 are independently an integer ranging from 220 to 240.

13. The prodrug of any one of claims 1 to 12, wherein -D has the sequence of SEQ ID NO:1.

14. The prodrug of any one of claims 11 to 13, wherein -D is connected to the rest of the molecule through an amine provided by a lysine side chain.

15. A pharmaceutical formulation comprising the prodrug of any one of claims 1 to 14 and at least one excipient.

16. The pharmaceutical formulation of claim 15, wherein the pharmaceutical formulation is a dry formulation and comprises from 1 to 99.9% (w/w) of the prodrug of any one of claims 1 to 14.

17. The pharmaceutical formulation of claim 16, wherein the pharmaceutical formulation comprises from 9 to 71% (w/w) of the prodrug of any one of claims 1 to 14.

18. The pharmaceutical formulation of claim 16 or 17, wherein the pharmaceutical formulation comprises from 32 to 34% (w/w) or 50 to 54% (w/w) of the prodrug of any one of claims 1 to 14.

19. The pharmaceutical formulation of any one of claims 16 to 18, 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 wherein the polymeric hGH prodrug is the prodrug of any one of claims 1 to 14; and

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

20. The pharmaceutical formulation of any one of claims 16 to 19, 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)

wherein the polymeric hGH prodrug is the prodrug of any one of claims 1 to 14.

21. A method of reconstituting the pharmaceutical formulation of any one of claims 16 to 20, wherein the method comprises the step of

- contacting the dry pharmaceutical formulation of any one of claims 16 to 20 with a reconstitution solution.

22. A reconstituted formulation obtainable from the method of claim 21.

23. The reconstituted formulation of claim 22, wherein the reconstituted formulation comprises

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

and has a pH ranging from pH 4.0 to pH 6.0; and wherein the polymeric hGH prodrug is the prodrug of any one of claims 1 to 14.

24. The prodrug of any one of claims 1 to 14, the pharmaceutical formulation of any one of claims 15 to 20 or the reconstituted formulation of claim 22 or 23 for use as a medicament.

25. Use of the prodrug of any one of claims 1 to 14, the pharmaceutical formulation of any one of claims 15 to 20 or the reconstituted formulation of claim 22 or 23 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of growth hormone deficiency in children, idiopathic short stature, short stature homeobox gene mutations, Turner syndrome, Noonan syndrome, Prader-Willi syndrome, children born small for gestational age, chronic renal insufficiency, growth hormone deficiency in adults, wasting due to HIV or AIDS or other malignancies, short bowel syndrome, sarcopenia, and frailty.

26. The use of claim 25, wherein the disease is growth hormone deficiency in children.

27. The use of claim 25, wherein the disease is growth hormone deficiency in adults.

28. The use of claim 25, wherein the disease is small for gestational age.

29. The use of any one of claims 25 to 28, wherein the medicament is to be administered via topical, enteral or parenteral administration or by methods of external application, injection or infusion, including intraarticular, periarticular, intradermal, subcutaneous, intramuscular, intravenous, intraosseous, intraperitoneal, intrathecal, intracapsular,

intraorbital, intravitreal, intratympanic, intravesical, intracardiac, transtracheal, subcuticular, subcapsular, subarachnoid, intraspinal, intraventricular, intrasternal injection or infusion, direct delivery to the brain via implanted device allowing delivery of the invention or the like to brain tissue or brain fluids, direct intracerebroventricular injection or infusion, injection or infusion into brain or brain associated regions, injection into the subchoroidal space, retro-orbital injection and ocular instillation.