Claims

1. Use of a pharmaceutical composition comprising at least one controlled-release CNP agonist and at least one human growth hormone moiety or drug for the manufacture of a medicament for the treatment of a disorder that benefits from stimulating growth selected from the group comprising achondroplasia, hypochondroplasia, short stature, dwarfism, osteochondrodysplasias, thanatophoric dysplasia, osteogenesis imperfecta, achondrogenesis, chondrodysplasia punctata, homozygous achondroplasia, camptomelic dysplasia, congenital lethal hypophosphatasia, perinatal lethal type of osteogenesis imperfecta, short-rib polydactyly syndromes, rhizomelic type of chondrodysplasia punctata, Jansen-type metaphyseal dysplasia, spondyloepiphyseal dysplasia congenita, atelosteogenesis, diastrophic dysplasia, congenital short femur, Langer-type mesomelic dysplasia, Nievergelt-type mesomelic dysplasia, Robinow syndrome, Reinhardt syndrome, acrodysostosis, peripheral dysostosis, Kniest dysplasia, fibrochondrogenesis, Roberts syndrome, acromesomelic dysplasia, micromelia, Morquio syndrome, Kniest syndrome, metatrophic dysplasia, and spondyloepimetaphyseal dysplasia, wherein the controlled-release CNP agonist is of formula (Ia) or (Ib)

$$Z-\left(L^2-L^1-D\right)_x \quad \text{(Ia)}$$

$$D-\left(L^1-L^2-Z\right)_y \quad \text{(Ib)},$$

wherein

-D is a CNP moiety of SEQ ID NO:1 to SEQ ID NO:95;

-L^1- is a reversible prodrug linker moiety from which the CNP moiety is released with a release half-life of at least 48 hours;

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

-Z is a water-soluble carrier moiety;

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 or 16; and

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

2. The use of claim 1, wherein the CNP moiety has the sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:38, SEQ ID

NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:91 or SEQ ID NO:92.

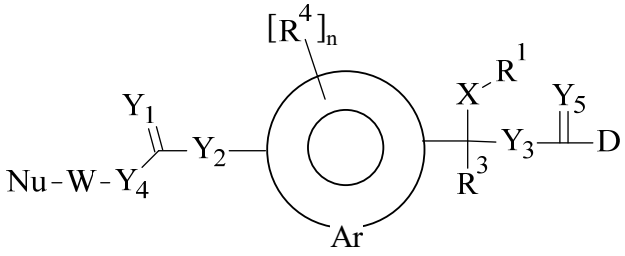
3. The use of claim 1 or 2, wherein the CNP moiety has the sequence of SEQ ID NO:24.

4. The use of any one of claims 1 to 3, wherein the at least one human growth hormone moiety or drug is human growth hormone in its free form.

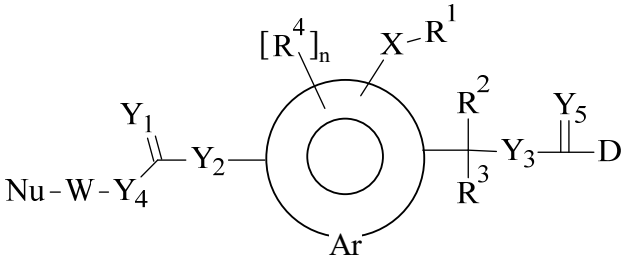
5. The use of any one of claims 1 to 4, wherein the at least one human growth hormone moiety or drug has the sequence of SEQ ID NO:99.

6. The use of any one of claims 1 to 3 or 5, wherein the at least one human growth hormone moiety is in the form of a controlled-release compound.

7. The use of any one of claims 1 to 3, 5 or 6, wherein the human growth hormone moiety is of formula (1a) or (1b):



(1a),



(1b),

wherein

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

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-, -Y_5- are independently of each other selected from the group consisting of -O- and -S-;

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

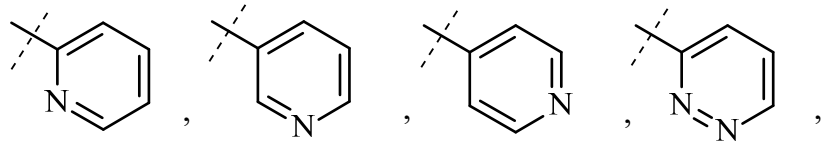
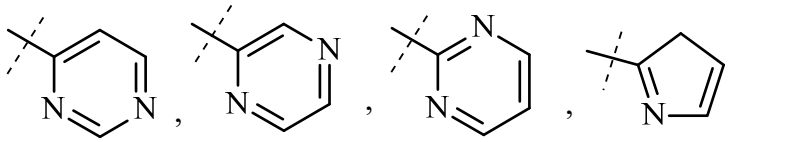
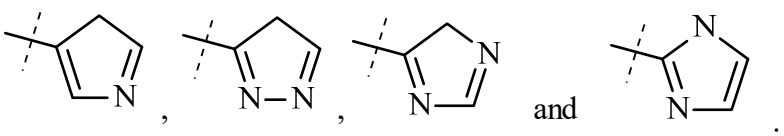
-R^1 is a carrier, preferably a water-soluble PEG-based moiety comprising at least 40% PEG;

-R^2, -R^3, -R^5, -R^6, and -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;

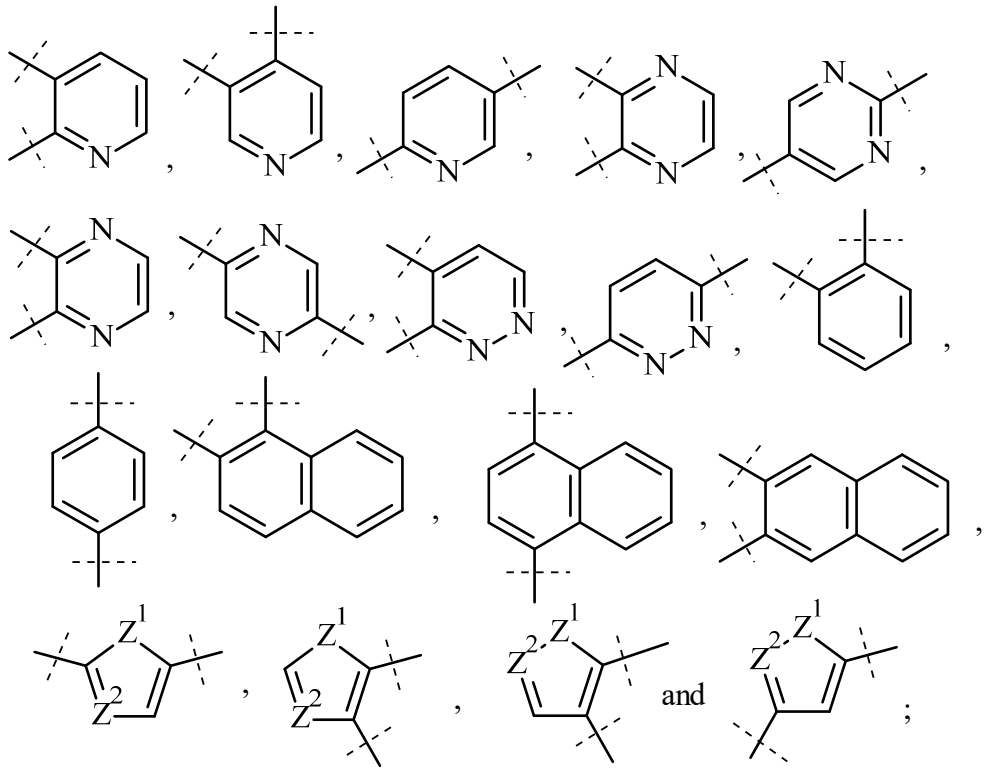
-W- is selected from the group consisting of C_{1-20} alkyl optionally interrupted by one or more groups selected from the group consisting of C_{3-10} cycloalkyl, 8- to 30-membered carbopolycyclyl, 3- to 10-membered heterocyclyl, -C(O)-, -$C(O)N(R^7)$-, -O-, -S- and -$N(R^7)$-;

-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 compound,

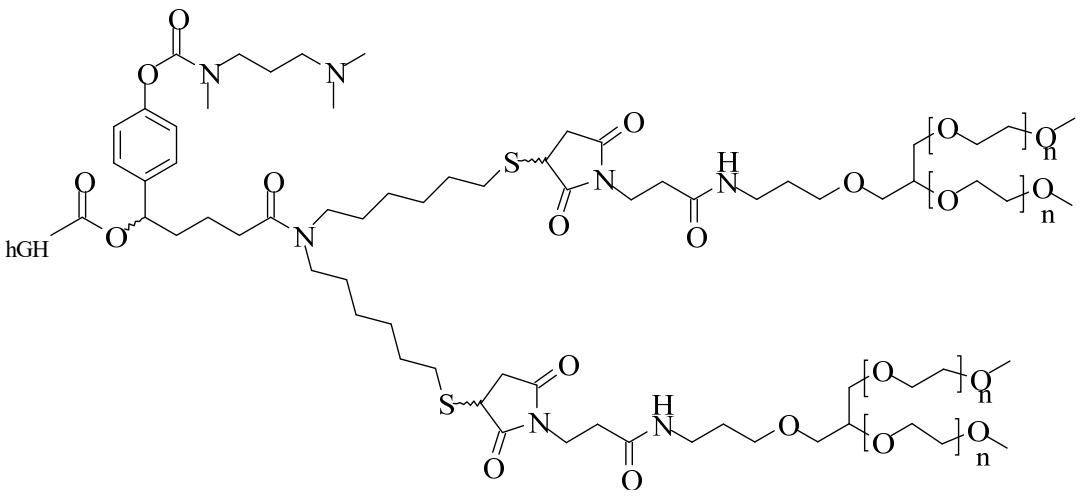
$-Z^1-$ is selected from the group consisting of -O-, -S- and $-N(R^7)-$,

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

$-R^7$, $-R^{7a}$ and $-R^{7b}$ 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 compound of formula (1a) or (1b) is optionally further substituted.

8. The use of any one of claims 1 to 3, or 5 to 7, wherein the human growth hormone moiety is of formula (A1)



(A1),

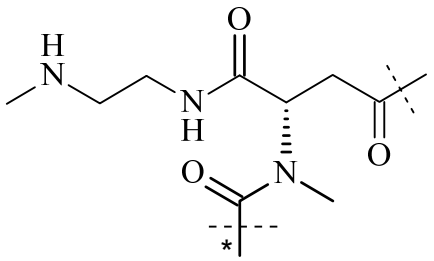
wherein n ranges from 200 to 250.

9. The use of any one of claims 1 to 8, wherein the controlled-release CNP agonist and the at least one human growth hormone moiety or drug are formulated for simultaneous, separate or sequential administration.

10. The use of any one of claims 1 to 9, wherein the controlled-release CNP agonist and the at least one human growth hormone moiety or drug are formulated in one pharmaceutical composition for simultaneous administration.

11. The use of any one of claims 1 to 9, wherein the controlled-release CNP agonist and the at least one human growth hormone moiety or drug are formulated for sequential administration.

12. The use of any one of claims 1 to 10, wherein the controlled-release CNP agonist is of formula (IIf a')

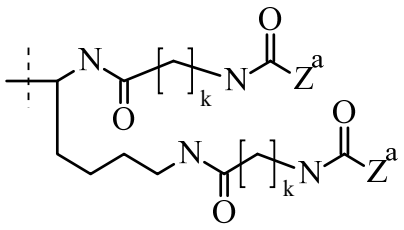


(IIfa'),

wherein

the unmarked dashed line indicates the attachment to the 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

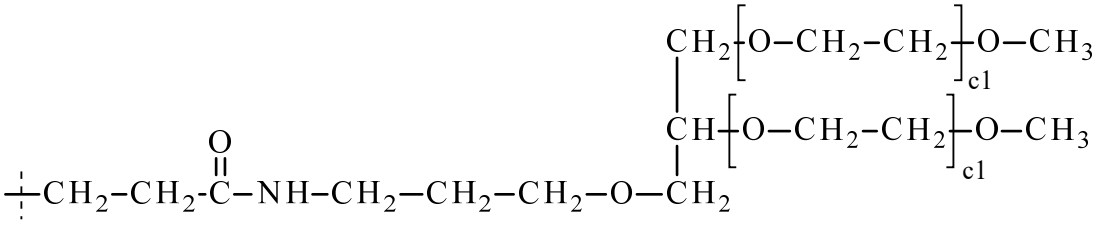


,

wherein

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

each Z^a is



wherein

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

13. The use of any one of claims 1 to 12, wherein the controlled-release CNP agonist is to be administered every week.

14. The use of claim 4, wherein the human growth hormone in its free form is to be administered every 24 hours.

15. The use of any one of claims 6 to 14, wherein the human growth hormone in the form of a controlled-release compound is to be administered every week.

16. The use of any one of claims 1 to 15, wherein the treatment is to be administered to a mammalian patient.

17. The use of any one of claims 1 to 16, wherein the treatment is to be administered to a human patient.

18. The use of any one of claims 1 to 15, wherein the disorder that benefits from stimulating growth is achondroplasia.