Claims

1. A polymeric prodrug for use in the prevention, diagnosis and/or treatment of a disease of the joint, wherein the polymeric prodrug comprises a water-insoluble polymeric carrier comprising at least one polymer, and wherein one or more biologically active moieties are reversibly conjugated through reversible prodrug linker moieties to said polymeric carrier and from which polymeric carrier the one or more biologically active moieties are released in their free form.

2. The polymeric prodrug of claim 1 for use for intra-articular injection.

3. The polymeric prodrug for use of claim 1 or 2, wherein the polymeric carrier comprises, preferably consists of, a hydrogel.

4. The polymeric prodrug for use of any one of claims 1 to 3, wherein the polymeric carrier comprises, preferably consists of, a PEG-based hydrogel.

5. The polymeric prodrug for use of any one of claims 1 to 3, wherein the polymeric carrier comprises, preferably consists of, a hyaluronic acid-based hydrogel.

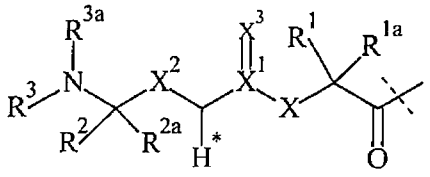
6. The polymeric prodrug for use of any one of claims 3 to 5, wherein the hydrogel is in the shape of microparticles.

7. The polymeric prodrug for use of any one of claims 3 to 6, wherein the hydrogel is in the shape of microparticulate beads having a diameter of 1 to 1000 µm.

8. The polymeric prodrug for use of any one of claims 1 to 7, wherein the polymeric prodrug is a conjugate D-L, wherein

-D is the primary amine- or secondary amine-comprising biologically active moiety; and

-L is a non-biologically active linker moiety -L^1 represented by formula (VII),



(VII),

wherein the dashed line indicates the attachment to a primary or secondary amino group of an amine-containing biologically active moiety D by forming an amide bond; and wherein X, X^1, X^2, R^1, R^{1a}, R^2, R^{2a}, R^3, and R^{3a} of formula (VII) have the following meaning:

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; or O-$C(R^4R^{4a})$;

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

X^2 is $C(R^7, R^{7a})$; or $C(R^7, R^{7a})$-$C(R^8, R^{8a})$;

X^3 is O·, S·, or N-CN;

R^1, R^{1a}, R^2, R^{2a}, R^3, R^{3a}, R^4, R^{4a}, R^5, R^{5a}, R^6, R^7, R^{7a}, R^8, R^{8a} are independently selected from the group consisting of H; and C_{1-4} alkyl; or

optionally, one or more of the pairs R^{1a}/R^{4a}, R^{1a}/R^{5a}, R^{4a}/R^{5a}, R^{4a}/R^{5a}, R^{7a}/R^{8a} 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^7/R^{7a}, R^8/R^{8a} are joined together with the atom to which they are attached to form a C_{3-7} cycloalkyl; or 4 to 7 membered heterocyclyl;

optionally, one or more of the pairs R^1/R^4, R^1/R^5, R^1/R^6, R^4/R^5, R^7/R^8, 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 4 to 7 membered heterocycle;

A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 4 to 7 membered heterocyclyl; and 9 to 11 membered heterobicyclyl; and

wherein L^1 is substituted with one group L^2-Z and optionally further substituted, provided that the hydrogen marked with the asterisk in formula (VII) is not replaced by a substituent and preferably provided that R^3 and R^{3a} are independently of each other H or are connected to N through an SP^3-hybridized carbon atom; and

wherein

L^2 is a single chemical bond or a spacer; and

Z is the polymeric carrier of the polymeric prodrug.

9. A pharmaceutical composition comprising a polymeric prodrug for use of any one of claims 1 to 8, and optionally one or more pharmaceutically acceptable excipients,
   a) for use in the prevention, diagnosis and/or treatment of a disease of the joint, and/or
   b) for use for intra-articular injection.

10. The polymeric prodrug or pharmaceutical composition for use of any one of claims 1 and 3 to 9, wherein the disease of the joint is selected from infectious arthropathies (M00-M03), inflammatory polyarthropathies (M05-M14), arthrosis (M15-M19), other joint disorders (M20-M25), and systemic connective tissue disorders (M30-M36), dorsopathies (M40-M54), soft tissue disorders (M60-M79), osteopathies and chondropathies (M80-M94).

11. The polymeric prodrug or pharmaceutical composition for use of any one of claims 1 to 10, wherein the one or more biologically active moieties are selected from the group consisting of (i) non-steroidal anti-inflammatory drugs (NSAIDs), (ii) disease modifying anti-rheumatic drugs (DMARDs), (iii) corticosteroids, and (iv) biologics.

12. The polymeric prodrug or pharmaceutical composition for use of any one of claims 1 to 11, wherein the one or more biologically active moiety is IL-1ra.

13. Use of the polymeric prodrug or pharmaceutical composition of any one of claims 1 to 12 for the manufacture of a medicament for preventing and/or treating a disease of the joint.

14. The use of claim 13, wherein the polymeric prodrug or pharmaceutical composition is administered by intra-articular injection.

Claims

1. Use of a polymeric prodrug in the preparation of a medicament for the treatment of a disease of the joint, wherein the polymeric prodrug comprises a water-insoluble polymeric hydrogel comprising at least one polymer, and wherein one or more biologically active moieties are reversibly conjugated through reversible prodrug linker moieties to said polymeric carrier and from which polymeric carrier the one or more biologically active moieties are released in their unmodified, pharmacologically active form.

2. The use of claim 1, wherein the polymeric prodrug is administered by intra-articular injection.

3. The use of claim 1 or 2, wherein the polymeric carrier comprises, preferably consists of, a PEG-based hydrogel.

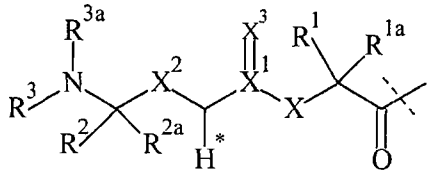
4. The use of claim 1 or 3, wherein the polymeric carrier comprises, preferably consists of, a hyaluronic acid-based hydrogel.

5. The use of any one of claims 1 to 4, wherein the hydrogel is in the shape of microparticles.

6. The use of any one of claims 3 to 5, wherein the hydrogel is in the shape of microparticulate beads having a diameter of 1 to 1000 µm.

7. The use of any one of claims 1 to 6, wherein the polymeric prodrug is a conjugate D-L, wherein

-D is the primary amine- or secondary amine-comprising biologically active moiety; and
-L is a non-biologically active linker moiety -L^1 represented by formula (VII),



(VII),

wherein the dashed line indicates the attachment to a primary or secondary amino group of an amine-containing biologically active moiety D by forming an amide bond; and wherein X, X^1, X^2, R^1, R^{1a}, R^2, R^{2a}, R^3, and R^{3a} of formula (VII) have the following meaning:

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; or O-$C(R^4R^{4a})$;

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

X^2 is $C(R^7, R^{7a})$; or $C(R^7, R^{7a})$-$C(R^8, R^{8a})$;

X^3 is O·, S·, or N-CN;

R^1, R^{1a}, R^2, R^{2a}, R^3, R^{3a}, R^4, R^{4a}, R^5, R^{5a}, R^6, R^7, R^{7a}, R^8, R^{8a} are independently selected from the group consisting of H; and C_{1-4} alkyl; or

optionally, one or more of the pairs R^{1a}/R^{4a}, R^{1a}/R^{5a}, R^{4a}/R^{5a}, R^{4a}/R^{5a}, R^{7a}/R^{8a} 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^7/R^{7a}, R^8/R^{8a} are joined together with the atom to which they are attached to form a C_{3-7} cycloalkyl; or 4 to 7 membered heterocyclyl;

optionally, one or more of the pairs R^1/R^4, R^1/R^5, R^1/R^6, R^4/R^5, R^7/R^8, 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 4 to 7 membered heterocycle;

A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 4 to 7 membered heterocyclyl; and 9 to 11 membered heterobicyclyl; and

wherein L^1 is substituted with one group L^2-Z and optionally further substituted, provided that the hydrogen marked with the asterisk in formula (VII) is not replaced by a substituent and preferably provided that R^3 and R^{3a} are independently of each other H or are connected to N through an SP^3-hybridized carbon atom; and

wherein

L^2 is a single chemical bond or a spacer; and

Z is the polymeric carrier of the polymeric prodrug.

8. The use of any one of claims 1 to 7, wherein the medicament comprises one or more pharmaceutically acceptable excipients.

9. The use of any one of claims 1 to 8, wherein the disease of the joint is selected from infectious arthropathies (M00-M03), inflammatory polyarthropathies (M05-M14), arthrosis (M15-M19), other joint disorders (M20-M25), and systemic connective tissue disorders (M30-M36), dorsopathies (M40-M54), soft tissue disorders (M60-M79), osteopathies and chondropathies (M80-M94).

10. The use of any one of claims 1 to 9, wherein the one or more biologically active moieties are selected from the group consisting of (i) non-steroidal anti-inflammatory drugs (NSAIDs), (ii) disease modifying anti-rheumatic drugs (DMARDs), (iii) corticosteroids, and (iv) biologics.

11. The use of any one of claims 1 to 10, wherein the one or more biologically active moiety is IL-1ra.

12. Use of any one of claims 1 to 11, wherein the disease of the joint is osteoarthritis or rheumatoid arthritis.

13. Use of any one of claims 1 to 12, wherein the medicament in addition to the polymeric prodrug comprises other biologically active moieties, either in their free form or as prodrugs.