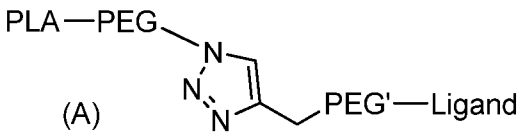
CLAIMS

1. A compound of formula (A)



(A)

where:

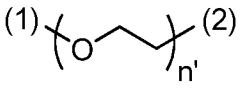
PLA represents a polylactic acid rest;

PEG represents a polyethylene glycol rest;

The linker PEG' is a polyethylene glycol rest; and

Ligand is a functional ligand rest.

2. The compound of formula (A) according to claim 1, wherein PEG' is of formula



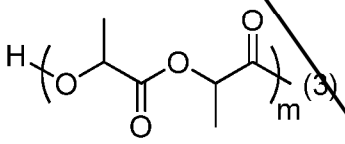
where:

n' is the number of units and is comprised between 1 to 10

(1) is the attachment of the bond to the –(CH_2)-triazole group;

(2) is the attachment of the bond to the ligand.

3. The compound of formula (A) according to claim 1 or 2, wherein PLA is of formula:

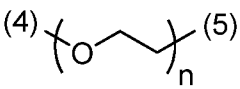


where:

(3) is the attachment of the bond to the PEG moiety; and

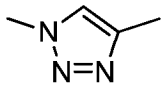
m is the number of units and is comprised between 1 and 500.

4. The compound of formula (A) according according to anyone of claims 1 to 3, wherein PEG is of formula:



where:

(4) is the attachment of the bond to –PLA;

(5) is the attachment of the bond to the nitrogen atom of  ; and

n is the number of units and is comprised between 1 and 300.

5. The compound of formula (A) according to anyone of claims 1 to 4, wherein Ligand is chosen from rests of homing devices, diagnostic agents, imaging agents, stimuli-sensitive agents, docking agents, cell penetrating agents, detoxifying agents and drugs.

6. The compound of formula (A) according to anyone of claim 5, wherein said homing device is a membrane recognition ligand.

7. The compound of formula (A) according to anyone of claims 1 to 5 wherein Ligand is chosen from :

a membrane recognition ligands selected from an oestrogen receptor antagonist, an androgen receptor antagonist, folic acid, anisamide, an antibody cabable of recognising the corresponding surface antigen, a RGD sequence that binds to $\alpha_v\beta_3$ integrins overexpressed on tumor angiogenic endothelium, hyaluronic acid, transferrin, peptide targeted gene vectors, aptamers, or tumor necrosis factor,

diagnostic/imaging agents selected from iron oxide, gadolinium complexes, indocyanin green, near infra-red fluorescent probes, or positron emitters,

stimuli responsive substances selected from iron oxide nanoparticles, gold nanoparticles, or any radiation-activable substances,

docking agents selected from oligopeptides,

a cell penetrating agent selected from Transactivator of transcription (TAT) sequences, penetratin, polyarginine sequences, or VP22 protein sequences,

a detoxifying agent selected from cobalamin, cobinamide, rhodanese enzyme, an organophosphorus hydrolyzing enzyme, naloxone, atropine, or antibodies/antibody fragments recognizing a specific toxin; or

a drug selected from an antibiotic, anti-cancer agent, antiviral agent, anti-inflammatory agent, a vaccine antigen or a nutraceutical.

8. A nanoparticle comprising one or more identical or different compounds of formula (A) according to anyone of claims 1 to 7.

9. The nanoparticle according to claim 8 which further comprises one or more compounds of formula (I'):



PLA—PEG—OR (I')

where PLA and PEG are defined as in formula (A) and R is H or a C_1-C_6 alkyl.

10. The nanoparticle according to claim 8 or 9 which comprises a drug.

11. The nanoparticle according to claim 10, wherein the drug is a cytotoxic agent.

12. The nanoparticle according to claim 10 or 11, wherein the drug is a taxoid.

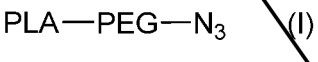
13. The nanoparticle according to claim 10, 11 or 12, wherein the drug is docetaxel.

14. The nanoparticle according to anyone of claims 10 to 13, wherein the drug is non-covalently encapsulated with the nanoparticle.

15. The nanoparticle according to anyone of claims 1 to 14, wherein the drug is covalently conjugated to the nanoparticle.

16. A process for the preparation of a compound of formula (A) according to anyone of claims 1 to 7 comprising coupling:

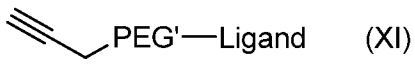
- a compound of formula (I):



PLA—PEG—N_3 (I)

with

- a compound of formula (XI):



PEG'—Ligand (XI)

where PLA, PEG, PEG' and Ligand are defined as in anyone of claims 1 to 7.

17. The process according to claim 16, wherein said coupling is made by click chemistry.

18. The process according to claim 16 or 17, wherein said coupling reaction is carried out according to the Huisgen reaction, in organic or aqueous conditions.

19. The process according to anyone of claims 16, 17 or 18, wherein said click chemistry coupling reaction is carried out in the presence of CuBr and PMDETA (N, N, N', N', N''-pentamethyldiethylenetriamine).

20. The process according to anyone of claims 16, 17 or 18, wherein said click chemistry coupling reaction is carried out in the presence of water, $CuSO_4$-$5H_2O$ and sodium ascorbate.

21. A compound of formula (I):

$$PLA—PEG—N_3 \qquad (I)$$

where PLA and PEG are defined according to anyone of claims 1, 3 and 4.

22. A nanoparticle comprising one or more identical or different compounds of formula (I) according to claim 21.

23. The nanoparticle according to claim 22 which further comprises one or more compounds of formula (I'):

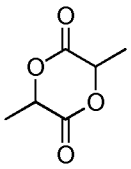
$$PLA—PEG—OR \qquad (I')$$

where PLA and PEG are defined as in anyone of claims 1, 3 and 4 and R is H or a C_1-C_6 alkyl.

24. A process for the preparation of a compound of formula (I) according to claim 21, comprising the step of reacting a compound of formula (II):

$$H—PEG—X \qquad (II)$$

where PEG is defined as in anyone of claims 1 and 4 and X is a halogen atom or an azide (N_3) with the compound of formula:



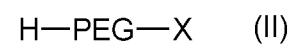
by ring opening polymerization (ROP), followed when X is a halogen atom, by reacting the obtained compound of formula (III):

$$PLA—PEG—Hal \qquad (III)$$

where PLA and PEG are defined as in formula (A), and Hal represents an halogen atom, with NaN_3.

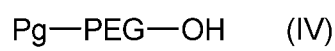
25. The process according to claim 24, wherein said reaction is carried out in the presence of $Sn(Oct)_2$.

26. The process according to claim 24 or 25, which further comprises the preparation of the compound of formula (II):



(II)

from a compound of formula (IV):



(IV)

where Pg represents an hydroxyl protecting group, X is a halogen atom or an azide (N_3) and PEG is defined as in anyone of claims 1 and 4

by

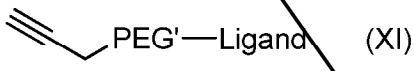
- a substitution reaction of OH with X, followed by
- a deprotection reaction

27. The process according to claim 26 wherein, where X is an azide group, the substitution reaction comprises :

1) substituting the OH group of the compound of formula (IV) with a leaving group,

2) substituting the leaving group of the obtained compound in step 1) with an azide (N_3) group.

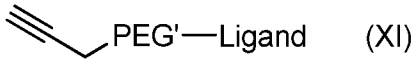
28. A compound of formula (XI):



(XI)

where PEG' is defined as in anyone of claims 1 and 2 and Ligand is defined as in anyone of claims 5, 6 and 7.

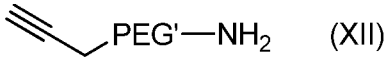
29. A process for the preparation of the compound of formula (XI) according to claim 28:



(XI)

comprising reacting

- a compound of formula (XII);



(XII)

with

- a Ligand Precursor

where PEG' is defined as in anyone of claims 1 and 2.

30. The process according to claim 29, wherein said coupling is carried out in the presence of a peptide coupling reagent, in the presence of a base.

31. The process according to claim 30, wherein said peptide coupling reagent is chosen from PyBOP (benzothiazol-1-yl-oxytripyrrolidinophosphoniuhexafluorophosphate) and the base is N,N-diisopropylethylenediamine (DIPEA).

32. The process according to claim 30, wherein said peptide coupling reagent is EDC/NHS (1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride / N-hydroxy sulfosuccinimide) and the base is triethylamine.

33. A process for the preparation of the nanoparticle according to anyone of claims 8 to 15 comprising reacting a nanoparticle according to claim 22 or 23 with one or more compounds of formula (XI) according to claim 28, optionally followed by non-covalent encapsulation or covalent conjugation of a drug.

34. A process for the preparation of the nanoparticle according to anyone of claims 8 to 15 comprising nanoprecipitating one or more compounds of formula (A) according to anyone of claims 1 to 7, optionally in the presence of a compound of formula (I') as defined in claim 9, optionally followed by non-covalent encapsulation or covalent conjugation of a drug.

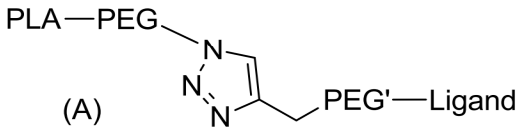
35. A process for the preparation of the nanoparticle according to claim 22 or 23 comprising nanoprecipitating one or more compounds of formula (I) according to claim 21, optionally in the presence of a compound of formula (I') as defined in claim 10.

36. A medicament, which comprises at least one compound of formula (A) according to anyone of claims 1 to 7, optionally in the form of a nanoparticle according to anyone of claims 8 to 15.

37. A pharmaceutical composition, which comprises, as active principle, a compound of formula (A) according to anyone of claims 1 to 7, optionally in the form of a nanoparticle according to anyone of claims 8 to 15 and at least one pharmaceutically acceptable excipient.

CLAIMS

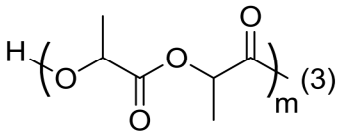
1. A compound of formula (A)



(A)

where:

PLA represents a polylactic acid rest of formula:

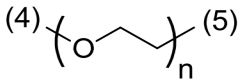


where:

(3) is the attachment of the bond to the PEG moiety; and

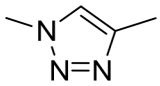
m is the number of units and is comprised between 1 and 500;

PEG represents a polyethylene glycol rest of formula:



where:

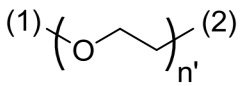
(4) is the attachment of the bond to –PLA;

(5) is the attachment of the bond to the nitrogen atom of 

; and

n is the number of units and is comprised between 1 and 300;

The linker PEG' is a polyethylene glycol rest of formula:



where:

n' is the number of units and is comprised between 1 to 10

(1) is the attachment of the bond to the–(CH_2)-triazole group;

(2) is the attachment of the bond to the ligand;

Ligand is a functional ligand rest chosen from homing devices, diagnostic agents, imaging agents, stimuli-sensitive agents, docking agents, cell penetrating agents, detoxifying agents and drugs.

2. The compound of formula (A) according to claim 1, wherein said homing device is a membrane recognition ligand.

3. The compound of formula (A) according to claim 1 or 2 wherein Ligand is chosen from :

a membrane recognition ligands selected from an oestrogen receptor antagonist, an androgen receptor antagonist, folic acid, anisamide, an antibody cabable of recognising the corresponding surface antigen, a RGD sequence that binds to $\alpha_v\beta_3$ integrins overexpressed on tumor angiogenic endothelium, hyaluronic acid, transferrin, peptide targeted gene vectors, aptamers, or tumor necrosis factor,

diagnostic/imaging agents selected from iron oxide, gadolinium complexes, indocyanin green, near infra-red fluorescent probes, or positron emitters,

stimuli responsive substances selected from iron oxide nanoparticles, gold nanoparticles, or any radiation-activable substances,

docking agents selected from oligopeptides,

a cell penetrating agent selected from Transactivator of transcription (TAT) sequences, penetratin, polyarginine sequences, or VP22 protein sequences,

a detoxifying agent selected from cobalamin, cobinamide, rhodanese enzyme, an organophosphorus hydrolyzing enzyme, naloxone, atropine, or antibodies/antibody fragments recognizing a specific toxin; or

a drug selected from an antibiotic, anti-cancer agent, antiviral agent, anti-inflammatory agent, a vaccine antigen or a nutraceutical.

4. A nanoparticle comprising one or more identical or different compounds of formula (A) according to anyone of claims 1 to 3.

5. The nanoparticle according to claim 4 which further comprises one or more compounds of formula (I'):

PLA—PEG—OR (I')

where PLA and PEG are defined as in formula (A) and R is H or a C_1-C_6 alkyl.

6. The nanoparticle according to claim 4 or 5 which comprises a drug.

7. The nanoparticle according to claim 6, wherein the drug is a cytotoxic agent.

8. The nanoparticle according to claim 6 or 7, wherein the drug is a taxoid.

9. The nanoparticle according to claim 6, 7 or 8, wherein the drug is docetaxel.

10. The nanoparticle according to anyone of claims 6 to 9, wherein the drug is non-covalently encapsulated with the nanoparticle.

11. The nanoparticle according to anyone of claims 1 to 10, wherein the drug is covalently conjugated to the nanoparticle, where ligand represents said drug.

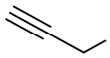
12. A process for the preparation of a compound of formula (A) according to anyone of claims 1 to 3 comprising coupling:

- a compound of formula (I):

$$PLA—PEG—N_3 \qquad (I)$$

with

- a compound of formula (XI):



(XI)

where PLA, PEG, PEG' and Ligand are defined as in anyone of claims 1 to 7.

13. The process according to claim 12, wherein said coupling is made by click chemistry.

14. The process according to claim 12 or 13, wherein said coupling reaction is carried out according to the Huisgen reaction, in organic or aqueous conditions.

15. The process according to anyone of claims 12, 13 or 14, wherein said click chemistry coupling reaction is carried out in the presence of CuBr and PMDETA (N, N, N', N', N''-pentamethyldiethylenetriamine).

16. The process according to anyone of claims 12, 13 or 14, wherein said click chemistry coupling reaction is carried out in the presence of water, $CuSO_4$-$5H_2O$ and sodium ascorbate.

17. A compound of formula (I):

$$PLA—PEG—N_3 \qquad (I)$$

where PLA and PEG are defined according to claim 1.

18. A nanoparticle comprising one or more identical or different compounds of formula (I) according to claim 17.

19. The nanoparticle according to claim 18 which further comprises one or more compounds of formula (I'):

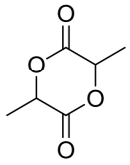
PLA—PEG—OR (I')

where PLA and PEG are defined as in claim 1 and R is H or a C_1-C_6 alkyl.

20. A process for the preparation of a compound of formula (I) according to claim 17, comprising the step of reacting a compound of formula (II):

H—PEG—X (II)

where PEG is defined as in claim 1 and X is a halogen atom or an azide (N_3) with the compound of formula:



by ring opening polymerization (ROP), followed when X is a halogen atom, by reacting the obtained compound of formula (III):

PLA—PEG—Hal (III)

where PLA and PEG are defined as in formula (A), and Hal represents an halogen atom, with NaN_3.

21. The process according to claim 20, wherein said reaction is carried out in the presence of $Sn(Oct)_2$.

22. The process according to claim 20 or 21, which further comprises the preparation of the compound of formula (II):

H—PEG—X (II)

from a compound of formula (IV):

Pg—PEG—OH (IV)

where Pg represents an hydroxyl protecting group, X is a halogen atom or an azide (N_3) and PEG is defined as in claim 1

by

- a substitution reaction of OH with X, followed by

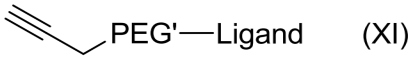
- a deprotection reaction.

23. The process according to claim 22 wherein, where X is an azide group, the substitution reaction comprises:

1) substituting the OH group of the compound of formula (IV) with a leaving group,

2) substituting the leaving group of the obtained compound in step 1) with an azide (N_3) group.

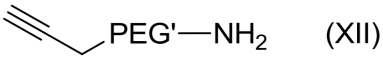
24. The process according to anyone of claims 12 to 23, which further comprises the process for the preparation of the compound of formula (XI):



(XI)

comprising reacting

- a compound of formula (XII);



(XII)

with

- a Ligand Precursor

where PEG' is defined as in anyone of claims 1 and 2.

25. The process according to claim 24, wherein said coupling is carried out in the presence of a peptide coupling reagent, in the presence of a base.

26. The process according to claim 25, wherein said peptide coupling reagent is chosen from PyBOP (benzothiazol-1-yl-oxytripyrrolidinophosphoniuhexafluorophosphate) and the base is N,N-diisopropylethylenediamine (DIPEA).

27. The process according to claim 25, wherein said peptide coupling reagent is EDC/NHS (1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride / N-hydroxy sulfosuccinimide) and the base is triethylamine.

28. A process for the preparation of the nanoparticle according to anyone of claims 8 to 15 comprising reacting a nanoparticle according to claim 18 or 19 with one or more compounds of formula (XI) according to claim 24, optionally followed by non-covalent encapsulation or covalent conjugation of a drug.

29. A process for the preparation of the nanoparticle according to anyone of claims 4 to 11 comprising nanoprecipitating one or more compounds of formula (A) according to anyone of claims 1 to 3, optionally in the presence of a compound of formula (I') as defined in claim 9, optionally followed by non-covalent encapsulation or covalent conjugation of a drug.

30. A process for the preparation of the nanoparticle according to claim 18 or 19 comprising nanoprecipitating one or more compounds of formula (I) according to claim 17, optionally in the presence of a compound of formula (I') as defined in claim 6.

31. A medicament, which comprises at least one compound of formula (A) according to anyone of claims 1 to 3, optionally in the form of a nanoparticle according to anyone of claims 4 to 11.

32. A pharmaceutical composition, which comprises, as active principle, a compound of formula (A) according to anyone of claims 1 to 3, optionally in the form of a nanoparticle according to anyone of claims 4 to 11 and at least one pharmaceutically acceptable excipient.