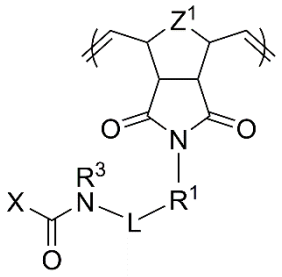
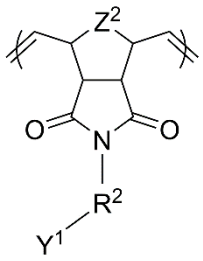
CLAIMS

1. A bioactive synthetic copolymer with a poly(norbornene) backbone comprising one or more repeating units represented by general formula (I) and one or more repeating units represented by general formula (II):



(I)



(II)

wherein

R^1 is optionally substituted alkyl;

R^2 is selected from a single bond, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxyalkyl, optionally substituted alkylcarbonyl or optionally substituted alkylcarbonylalkyl;

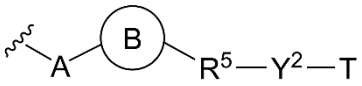
R^3 is selected from H, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl;

L is heteroalkylene;

X comprises a bioactive moiety selected from the group consisting of proteins, peptides, carbohydrates, therapeutic/drug molecules and derivatives thereof;

Z^1 and Z^2 are each independently selected from CR^aR^b, O, NR^c, SiR^aR^b, PR^a or S, wherein R^a, R^b and R^c are each independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl; and

Y^1 is represented by general formula (III):



(III)

wherein

A is selected from a single bond, oxy, carbonyl, oxycarbonyl, carboxyl, optionally substituted alkoxy, optionally substituted alkoxyalkyl, optionally substituted alkylcarbonyl, optionally substituted alkylcarbonylalkyl, optionally substituted carboxyalkyl, optionally substituted oxycarbonylalkyl, optionally substituted alkylcarboxylalkyl, or optionally substituted alkoxycarbonylalkyl;

B is optionally present as a ring selected from 1,2,3-triazole or succinimide;

R^5 is selected from a single bond, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxyalkyl, optionally substituted alkylcarbonyl or optionally substituted alkylcarbonylalkyl;

Y^2 is selected from the group consisting of polypropylene (PP), polyesters, poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(caprolactone) (PCL), polystyrene (PS), polyacrylates, poly(meth)acrylates, polyamides (PA), and parts thereof; and

T is a terminal group selected from the group consisting of hydrogen, halogen, hydroxyl, amino, acyl, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkoxyalkyl, optionally substituted alkylcarbonyl, optionally substituted alkylcarbonylalkyl, optionally substituted carboxyalkyl, optionally substituted oxycarbonylalkyl, optionally substituted alkylcarboxylalkyl or optionally substituted alkoxycarbonylalkyl.

2. The copolymer of claim 1, wherein the molecular weight of general formula (I) do not differ from the molecular weight of general formula (II) by more than 30% of the molecular weight of general formula (II).

3. The copolymer of any one of the preceding claims, wherein L is heteroalkylene having from 20 carbon atoms to 300 carbon atoms.

4. The copolymer of any one of the preceding claims, wherein L is polyethylene glycol (PEG).

5. The copolymer of any one of the preceding claims, wherein L is polyethylene glycol (PEG) having a number average molecular weight of between 500 and 7,000.

6. The copolymer of any one of the preceding claims, wherein R^1 is C_1-C_4 alkyl, and R^2 is selected from C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_1-C_{20} alkoxy, C_1-C_{20} alkoxyalkyl, C_2-C_{20} alkylcarbonyl or C_3-C_{20} alkylcarbonylalkyl.

7. The copolymer of any one of the preceding claims, wherein R^1 is straight or branched C_1-C_4 alkyl substituents independently selected from methyl, ethyl, n-propyl, 2-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or t-butyl, and R^2 is straight or branched C_1-C_{20} alkyl substituents independently selected from methyl, ethyl, n-propyl, 2-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, hexyl, amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, pentyl, isopentyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, 2-ethylpentyl, 3-ethylpentyl, heptyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, 5-methylheptyl, 1-methylheptyl, octyl, nonyl or decyl.

8. The copolymer of any one of the preceding claims, wherein Z^1 and Z^2 are both CR^aR^b wherein R^a and R^b are each independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl.

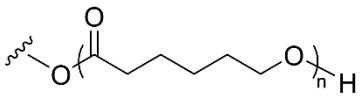
9. The copolymer of any one of the preceding claims, wherein X comprises protein, peptide or carbohydrate selected from the group consisting of peptide sequence, laminin-derived peptide, integrin binding peptide, cell-penetrating peptide, collagen mimics, collagen fragments, heparin sulfate, glycosaminoglycans (GAGs) and derivatives thereof.

10. The copolymer of any one of the preceding claims, wherein X is selected from the group consisting of RGD, SRGDS, RGDS, A5G81 (AGQWHRVSVRWGC), SVVYGLR, $(IRIK)_2$, $(IKKI)_3$, heparin oligosaccharide DP8, DP10, DP12, DP14, DP16, DGEA, $(PHypG)_n$ type sequence, $(PGHyp)_n$ type sequence, $(HypGP)_n$ type sequence, $(HypPG)_n$ type sequence, $(GHypP)_n$ type sequence, $(GPHyp)_n$ type sequence and hyaluronic acid.

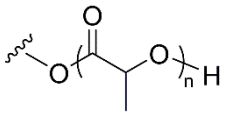
11. The copolymer of any one of the preceding claims, wherein X comprises an antibiotic, antimicrobial, antibacterial moiety, blood thinning agents or anti-inflammatory agents.

12. The copolymer of any one of the preceding claims, wherein X comprises antibiotic, antimicrobial, antibacterial, blood thinning agents or anti-inflammatory agents selected from the group consisting of penicillin, amoxicillin, amphotericin, ciprofloxacin (CIF), atorvastatin, aspirin, streptomycin, ribostamycin and gentamycin.

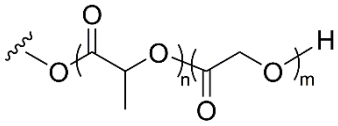
13. The copolymer of any one of the preceding claims, wherein Y^1 is selected from the following general formulae (IIIa), (IIIb), (IIIc), (IIId), (IIIe) or (IIIf):



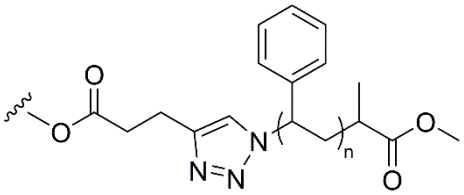
(IIIa)



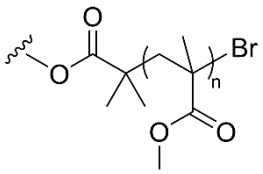
(IIIb)



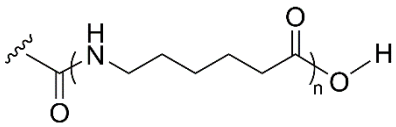
(IIIc)



(IIId)



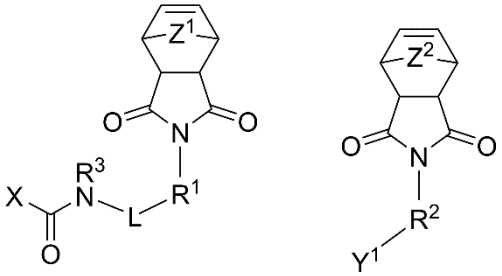
(IIIe)



(IIIf)

14. A method of preparing a bioactive synthetic copolymer of any one of claims 1 to 13, the method comprising:

polymerising one or more bioactive macromolecules represented by general formula (IV) with one or more synthetic macromolecules represented by general formula (V) in the presence of a catalyst to obtain the bioactive synthetic copolymer:



(IV) (V)

wherein

R^1 is optionally substituted alkyl;

R^2 is selected from a single bond, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxyalkyl, optionally substituted alkylcarbonyl or optionally substituted alkylcarbonylalkyl;

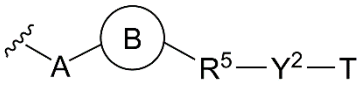
R^3 is selected from H, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl;

L is heteroalkylene;

X comprises a bioactive moiety selected from the group consisting of proteins, peptides, carbohydrates, therapeutic/drug molecules and derivatives thereof;

Z^1 and Z^2 are each independently selected from CR^aR^b, O, NR^c, SiR^aR^b, PR^a or S, wherein R^a, R^b and R^c are each independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl; and

Y^1 is represented by general formula (III):



(III)

wherein

A is selected from a single bond, oxy, carbonyl, oxycarbonyl, carboxyl, optionally substituted alkoxy, optionally substituted alkoxyalkyl, optionally substituted alkylcarbonyl, optionally substituted alkylcarbonylalkyl, optionally substituted carboxyalkyl, optionally substituted oxycarbonylalkyl, optionally substituted alkylcarboxylalkyl, or optionally substituted alkoxycarbonylalkyl;

B is optionally present as a ring selected from 1,2,3-triazole or succinimide;

R^5 is selected from a single bond, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxyalkyl, optionally substituted alkylcarbonyl or optionally substituted alkylcarbonylalkyl;

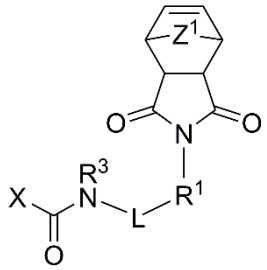
Y^2 is selected from the group consisting of polypropylene (PP), polyesters, poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(caprolactone) (PCL), polystyrene (PS), polyacrylates, poly(meth)acrylates, polyamides (PA), and parts thereof; and

T is a terminal group selected from the group consisting of hydrogen, halogen, hydroxyl, amino, acyl, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkoxyalkyl, optionally substituted alkylcarbonyl, optionally substituted alkylcarbonylalkyl, optionally substituted carboxyalkyl, optionally substituted oxycarbonylalkyl, optionally substituted alkylcarboxylalkyl or optionally substituted alkoxycarbonylalkyl.

15. The method according to claim 14, wherein the catalyst comprises a ruthenium complex.

16. The method according to any one of claims 14 to 15, wherein the method comprises ring opening metathesis polymerisation (ROMP).

17. A bioactive macromolecule represented by general formula (IV) for preparing the copolymer of any one of claims 1 to 13:



(IV)

wherein

R^1 is optionally substituted alkyl;

R^3 is selected from H, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl;

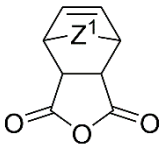
L is heteroalkylene;

X comprises a bioactive moiety selected from the group consisting of proteins, peptides, carbohydrates, therapeutic/drug molecules and derivatives thereof; and

Z^1 is selected from CR^aR^b, O, NR^c, SiR^aR^b, PR^a or S, wherein R^a, R^b and R^c are each independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl.

18. A method of preparing a bioactive macromolecule of claim 17, the method comprising:

(i) providing a dicarboxylic anhydride having general formula (VI):

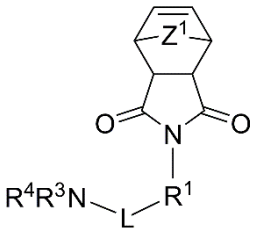


(VI)

wherein

Z^1 is selected from CR^aR^b, O, NR^c, SiR^aR^b, PR^a or S, wherein R^a, R^b and R^c are each independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

(ii) reacting said dicarboxylic anhydride having general formula (VI) with a diamine $R^4R^3N–L–R^1–NH_2$ to obtain an amine having general formula (VII):



(VII)

wherein

R^1 is optionally substituted alkyl;

R^3 and R^4 are each independently selected from H, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl, wherein at least one of R^3 and R^4 is H;

L is heteroalkylene; and

Z^1 is selected from CR^aR^b, O, NR^c, SiR^aR^b, PR^a or S, wherein R^a, R^b and R^c are each independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl;

(iii) reacting said amine having general formula (VII) with an acid-containing bioactive moiety X–C(=O)OH to obtain the bioactive macromolecule,

wherein X comprises a bioactive moiety selected from the group consisting of proteins, peptides, carbohydrates, therapeutic/drug molecules and derivatives thereof.

19. The method according to claim 18, wherein the method further comprises, prior to the step of reacting amine having general formula (VII) with X–C(=O)OH, purifying the amine having general formula (VII) to remove impurities.

20. The method according to claim 19, wherein the step of purifying comprises double neutralisation steps.

21. The method according to claim 20, wherein the double neutralisation steps comprises a first step of washing with acid and a second step of washing with base.

22. A material comprising a copolymer of any one of claims 1 to 13 for use in medicine.

23. The material according to claim 22, wherein the material is part of an apparatus selected from the group consisting of wound dressing, skin scaffold, bone scaffold, organoid scaffold, implants, and medical device.