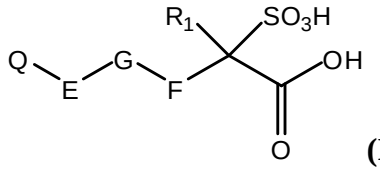
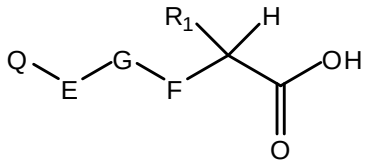
Claims:

1. A process for the preparation of a compound of formula **(III)**:



(III),

or a salt thereof, comprising the step of reacting a compound of formula **(II)**:



(II),

or a salt thereof, with a sulfonating agent, wherein:

Q represents a thiol-reactive moiety;

E represents a linear, branched or cyclic alkyl, alkenyl or alkynyl bearing 1 to 10 carbon atoms, a phenyl group, a three to six membered heterocycloalkyl group or a five or six-membered heteroaromatic group, containing 1, 2 or 3 heteroatoms selected from O, N or S;

F is an optional moiety that has the same definition as E; or when G is absent, F and R_1 together with the carbon atom from which they are attached can form a three to seven membered cycloalkyl group;

G is absent or represents -G'-$(OCH_2CH_2)_n$-, -G'-$(CH_2–CH_2-O)_n$- or -$(AA)_m$-;

G' is absent, -C(=O)-NH- or -NH-C(=O)-,

AA represents an amino acid residue;

R_1 is -H or a linear, branched or cyclic alkyl, alkenyl or alkynyl bearing 1 to 10 carbon atoms;

n is 0 or an integer from 1 to 24; and

m is 0 or an integer from 1 to 6.

2. The process of claim 1, wherein:

Q represents a thiol-reactive moiety which is a disulfide group selected from alkyl disulfide, phenyl disulfide, ortho or para-nitrophenyl disulfide, 2,4-dintrophenyl disulfide, pyridyl disulfide, nitropyridyl disulfide;

E represents a linear or branched alkyl bearing 1 to 4 carbon atoms;

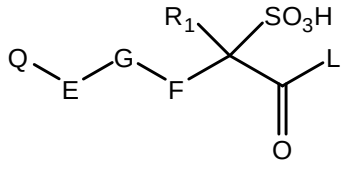
F is absent or F and R_1 together with the carbon atom from which they are attached can form a three to seven membered cycloalkyl group;

G is absent; and

R_1 is -H or a linear or branched alkyl bearing 1 to 4 carbon atoms.

3. The process of claim 2, wherein (i) the sulfonating reaction is carried out in the presence of a base; (ii) the sulfonating reaction is carried out in the presence of a base, wherein the base is triethyl amine, diisopropylethyl amine or tributyl amine; or (iii) the sulfonating reaction is carried out in the presence of a base that is diisopropylethyl amine.

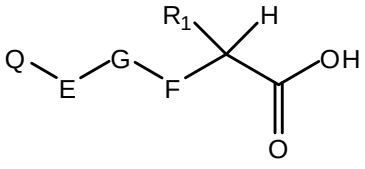
4. A process for the preparation of a compound of formula **(I)**:



(I)

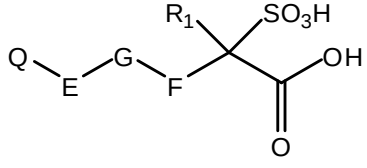
or a salt thereof, comprising the steps of:

a) reacting a compound of formula (II):



(II),

or a salt thereof, with a sulfonating agent to form a compound of formula **(III)**



(III),

or a salt thereof;

b) reacting the compound of formula **(III)** or a salt thereof with a hydroxy or mercapto compound to form a compound of formula **(I)**, wherein:

Q represents a thiol-reactive moiety;

E represents a linear, branched or cyclic alkyl, alkenyl or alkynyl bearing 1 to 10 carbon atoms, a phenyl group, a three to six membered heterocycloalkyl group or a five or six-membered heteroaromatic group, containing 1, 2 or 3 heteroatoms selected from O, N or S;

F is an optional moiety that has the same definition as E; or when G is absent, F and R_1 together with the carbon atom from which they are attached can form a three to seven membered cycloalkyl group;

G is absent or represents -G'-$(OCH_2CH_2)_n$-, -G'-$(CH_2–CH_2-O)_n$- or -$(AA)_m$-;

G' is absent, -C(=O)-NH- or -NH-C(=O)-,

AA represents an amino acid residue;

C(=O)L represents a reactive ester or thioester group;

R_1 is -H or a linear, branched or cyclic alkyl, alkenyl or alkynyl bearing 1 to 10 carbon atoms;

n is 0 or an integer from 1 to 24; and

m is 0 or an integer from 1 to 6.

5. The process of claim 4, wherein:

Q represents a thiol-reactive moiety which is a disulfide group selected from alkyl disulfide, phenyl disulfide, ortho or para-nitrophenyl disulfide, 2,4-dintrophenyl disulfide, pyridyl disulfide, nitropyridyl disulfide;

E represents a linear or branched alkyl bearing 1 to 4 carbon atoms;

F is absent or F and R_1 together with the carbon atom from which they are attached can form a three to seven membered cycloalkyl group;

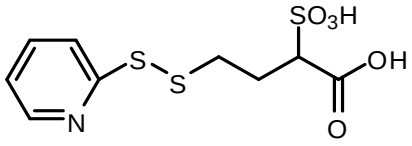
G is absent;

C(=O)L represents a reactive ester or thioester group selected from N-hydroxysuccinimide ester, N-hydroxy sulfosuccinimide ester, nitrophenyl ester, tetrafluoro phenyl ester, pentafluorophenyl ester, thiopyridyl ester and thionitrophenyl ester; and

R_1 is -H or a linear or branched alkyl bearing 1 to 4 carbon atoms.

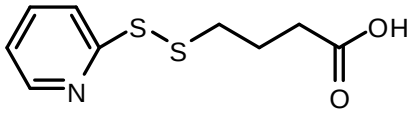
6. The process of any one of claims 1 to 5, wherein the process further comprises the step of purifying, optionally by reverse phase chromatography, the compound of formula (III) or the salt thereof.

7. The process of claim 1, which is for the preparation of a compound of formula **(IV)**:



(IV)

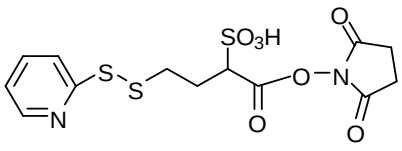
or a salt thereof, comprising the step of reacting a compound of formula **(2a)**:



(2a),

or a salt thereof, with a sulfonating agent.

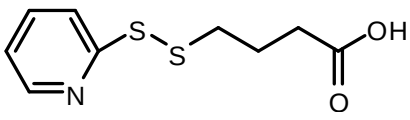
8. The process of claim 4, which is for the preparation of a compound represented by formula **(V)**:



(V),

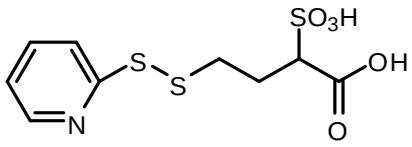
or a salt thereof, comprising the steps of:

a) reacting a compound of formula (2a):



(2a)

or a salt thereof, with a sulfonating agent to form a compound of formula **(IV)**:



(IV), or a salt thereof; and

b) reacting the compound of formula (IV), or a salt thereof, with N-hydroxysuccinimide to form the compound of formula **(V)**.

9. The process of claim 7 or claim 8, wherein the process further comprises the step of purifying, optionally by reverse phase chromatography, the compound of formula (IV) or the salt thereof.

10. The process of any one of claims 1 to 6, wherein:
(i) G and F are both absent;
(ii) G and F are both absent; and E is $–CH_2-CH_2-$;
(iii) G is absent, and F and R_1 together with the carbon atom from which they are attached form a cyclohexyl group;
(iv) G is absent, and F and R_1 together with the carbon atom from which they are attached form a cyclohexyl group; or
(iv) G is absent, and F and R_1 together with the carbon atom from which they are attached form a cyclohexyl group, and E $–CH_2-$.

11. The process of any one of claims 1 to 6 or 8, wherein Q is pyridyl disulfide.

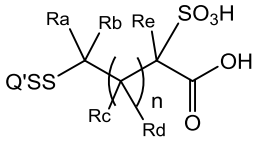
12. The process of claim 7 or claim 8, wherein (i) the sulfonating reaction is carried out in the presence of 1,2-di(pyridin-2-yl)disulfane (PySSPy); or (ii) the sulfonating reaction is carried out in the presence of 0.5 equivalent of 1,2-di(pyridin-2-yl)disulfane (PySSPy).

13. The process of claim 4 or claim 8, wherein:
(i) step b) is carried out in the presence of a coupling agent;
(ii) step b) is carried out in the presence of a coupling agent selected from *N,N'*-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), *N,N'*-diisopropyl carbodiimide (DIC) and 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ); or

(iii) step b) is carried out in the presence of a coupling agent that is EDC.

14. The process of any one of claims 1-13, wherein (i) the sulfonating agent is chlorosulfonic acid or sulfur trioxide; or (ii) the sulfonating agent is chlorosulfonic acid.

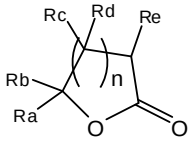
15. A process for the preparation of a compound of formula **(3)**:



(3),

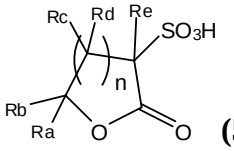
or a salt thereof, comprising the step of:

a) reacting a lactone of formula (4):



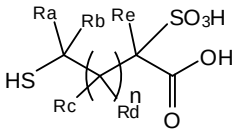
(4)

with a sulfonating agent to form a compound of formula **(5):**



(5) or a salt thereof;

b) reacting the compound of formula **(5)** or a salt thereof with a sulfur-bearing nucleophile, optionally followed by deprotection, to form a compound of formula **(6)**:



(6) or a salt thereof;

c) reacting the compound of formula **(6)** or a salt thereof with a disulfide compound to form the compound of formula **(3)**, wherein:

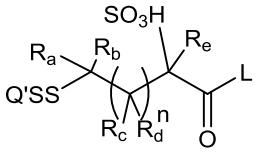
n is 0, 1, 2, 3 or 4;

Q' is a linear, branched or cyclic alkyl having 1 to 10 carbon atoms, phenyl, ortho or para-nitrophenyl, dinitrophenyl, pyridyl or nitropyridyl; and

R_a, R_b, R_c, R_d and R_e, each independently, is H or a linear, branched or cyclic alkyl having 1 to 10 carbon atoms.

16. The process of claim 15, wherein the sulfur-bearing nucleophile is selected from hydrogen sulfide or a salt thereof, thiourea, thioacetic acid, 2-(trimethylsilyl)ethanethiol and thiophenol.

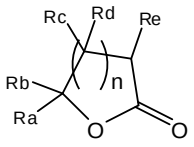
17. A process for the preparation of a compound of formula **(Ia)**:



(**Ia**)

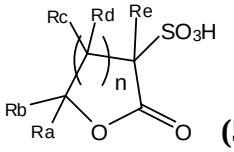
or a salt thereof, comprising the steps of :

a) reacting a lactone of formula (4):



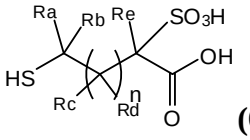
(4)

with a sulfonating agent to form a compound of formula **(5)**:



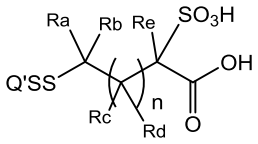
(5) or a salt thereof;

b) reacting the compound of formula (5) or a salt thereof with a sulfur-bearing nucleophile, optionally followed by deprotection, to form a compound of formula (6):



(6) or a salt thereof;

c) reacting the compound of formula (6) or a salt thereof with a disulfide compound to form a compound of formula (3)



(3), or a salt thereof

reacting the compound of formula **(3)** with a hydroxy or mercapto compound to form the compound of formula **(Ia)**, wherein:

n is 0, 1, 2, 3 or 4;

Q' is a linear, branched or cyclic alkyl having 1 to 10 carbon atoms, phenyl, ortho or para-nitrophenyl, dinitrophenyl, pyridyl or nitropyridyl;

R_a, R_b, R_c, R_d and R_e, each independently, is H or a linear, branched or cyclic alkyl having 1 to 10 carbon atoms; and

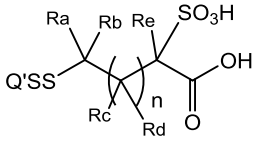
C(=O)L is a reactive ester or thioester group.

18. The process of claim 17, wherein:

the sulfur-bearing nucleophile is selected from hydrogen sulfide or a salt thereof, thiourea, thioacetic acid, 2-(trimethylsilyl)ethanethiol and thiophenol; and

C(=O)L is a reactive ester or thioester group selected from N-hydroxysuccinimide ester, N-hydroxy sulfosuccinimide ester, nitrophenyl ester, tetrafluoro phenyl ester, pentafluorophenyl ester, thiopyridyl ester and thionitrophenyl ester.

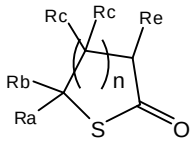
19. A process for the preparation of a compound of formula **(3)**:



(3)

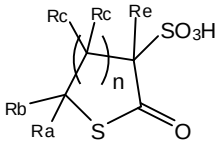
or a salt thereof, comprising the step of:

a) reacting a thiolactone of formula **(7)**:



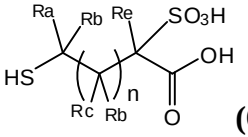
(7)

with a sulfonating agent to form a compound of formula **(8)**:



(8) or a salt thereof;

b) hydrolyzing the compound of formula **(8)** or a salt thereof to a compound of formula (6)



(6) or a salt thereof;

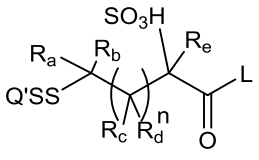
c) reacting the compound of formula **(6)** or a salt thereof with a disulfide compound to form the compound of formula **(3)**, wherein:

n is 0, 1, 2, 3 or 4;

Q' is a linear, branched or cyclic alkyl having 1 to 10 carbon atoms, phenyl, ortho or para-nitrophenyl, dinitrophenyl, pyridyl or nitropyridyl; and

R_a, R_b, R_c, R_d and R_e, each independently, is H or a linear, branched or cyclic alkyl having 1 to 10 carbon atoms.

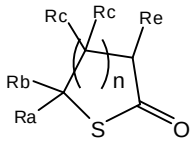
20. A process for the preparation of a compound of formula **(Ia)**:



(**Ia**),

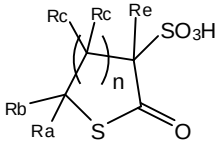
or a salt thereof, comprising the steps of:

a) reacting a thiolactone of formula (7):



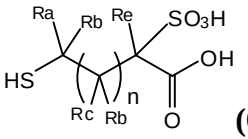
(7)

with a sulfonating agent to form a compound of formula **(8)**:



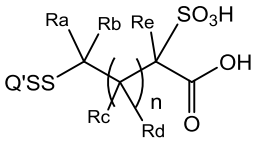
(8) or a salt thereof;

b) hydrolyzing the compound of formula **(8)** or a salt thereof to a compound of formula (6)



(6) or a salt thereof;

c) reacting the compound of formula **(6)** or a salt thereof with a disulfide compound to form a compound of formula **(3)**,



(3)

or a salt thereof,

d) reacting the compound of formula **(3)** with a hydroxy or mercapto compound to form the compound of formula **(Ia)** or a salt thereof, wherein:

n is 0, 1, 2, 3 or 4;

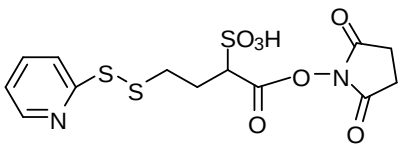
Q' is a linear, branched or cyclic alkyl having 1 to 10 carbon atoms, phenyl, ortho or para-nitrophenyl, dinitrophenyl, pyridyl or nitropyridyl;

R_a, R_b, R_c, R_d and R_e, each independently, is H or a linear, branched or cyclic alkyl having 1 to 10 carbon atoms; and

C(=O)L is a reactive ester or thioester group.

21. The process of claim 1, wherein C(=O)L is a reactive ester or thioester group selected from N-hydroxysuccinimide ester, N-hydroxy sulfosuccinimide ester, nitrophenyl ester, tetrafluoro phenyl ester, pentafluorophenyl ester, thiopyridyl ester and thionitrophenyl ester.

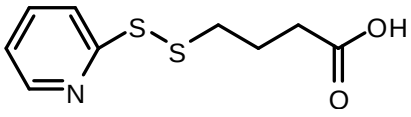
22. The process of claim 4, which is for the preparation of a compound represented by formula **(V)**:



(V),

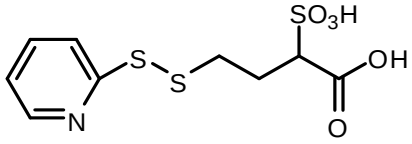
or a salt thereof, comprising the steps of:

a) reacting a compound of formula (2a):



(2a)

or a salt thereof, with a sulfonating agent to form a compound of formula **(IV)**:



(IV), or a salt thereof; and

b) reacting the compound of formula (IV), or a salt thereof, with N-hydroxysuccinimide to form the compound of formula **(V)**; and

c) purifying the salt of the compound of formula **(V)**, by crystallization of the salt of the compound of formula (**V**) in an organic solvent or a mixture of an organic solvent and water in the presence of an acid to form the neutral form of the compound of formula (**V**).

23. The process of claim 22, wherein the sulfonating agent is chlorosulfonic acid or sulfur trioxide.

24. The process of claim 23, wherein the sulfonating agent is chlorosulfonic acid.

25. The process of claim any one of claims 22-24, wherein the sulfonating reaction is carried out in the presence of PySSPy.

26. The process of claim 25, wherein about 0.5 equivalent of PySSPy is present.

27. The process of any one of claims 22-26, wherein the reaction between the compound of formula **(IV)** and N-hydroxysuccinimide is carried out in the presence of a coupling agent.

28. The process of claim 27, wherein the coupling agent is selected from *N,N'*-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), *N,N'*-diisopropyl carbodiimide (DIC) and 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ).

29. The process of claim 28, wherein the coupling agent is EDC.

30. The process of any one of claims 22-29, wherein the base is diisopropylethylamine (DIPEA).

31. The process of claim 22, wherein the process comprises the steps of:

a) reacting the compound of formula **(2a)** or a salt thereof with chlorosulfonic acid to form the compound of formula **(IV)**; and

b) reacting the compound of formula **(IV)** with N-hydroxysuccinimide in the presence of EDC to form the compound of formula **(V)**.

32. The process of any one of claims 22-31, wherein the acid is HCl or H_2SO_4.

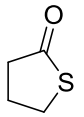
33. The process of claim 32, wherein the acid is HCl.

34. The process of any one of claims 22-33, wherein the crystallization is carried out in a mixture of an organic solvent and water.

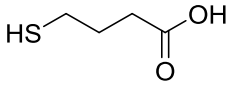
35. The process of claim 14, wherein the mixture of an organic solvent and water is acetone/water, DMF/water, DMSO/water or acetonitrile/water.

36. The process of any one of claims 7-9, 11-14 and 22-35, wherein the compound of formula (**2a**), or a salt thereof, is prepared by a method comprising the steps of:

a) reacting a compound of the following formula:



with sodium hydroxide to form a compound of formula **(1a)**:



(**1a**)

or a salt thereof; and

b) reacting the compound of formula **(1a)** or a salt thereof with 1,2-di(pyridin-2-yl)disulfane (PySSPy) to form the compound of formula (**2a**), or a salt thereof.