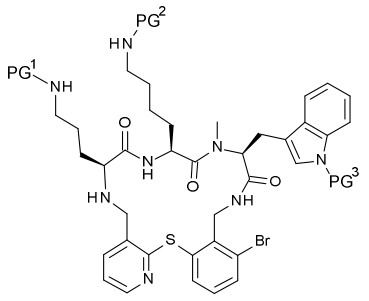
CLAIMS

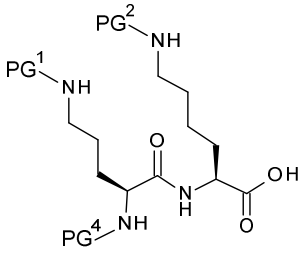
1. A process for manufacturing a compound of formula (I), or a salt thereof,



(I)

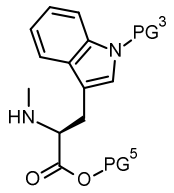
comprising:

(a) reacting a carboxylic acid of formula (II)



(II)

with a secondary amine of formula (III)



(III)

using reagents selected from:

(i) HOAt and DIC;

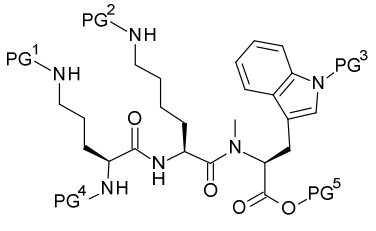
(ii) HODhat and DIC;

(iii) HOPO and DIC;

(iv) HOPO and DCC; and

(v) HOPO and EDC;

to form a compound of formula (IV)



(IV)

wherein PG^1, PG^2, PG^3 and PG^4 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

2. The process according to claim 1, wherein the process is performed in a solvent selected from:

(i) a mixture of *tert*-butyl methyl ether, *n*-heptane and dimethylacetamide;

(ii) isopropylacetate with or without 1,3-dimethyl-2-imidazolidinone;

(iii) *tert*-butyl methyl ether with or without 1,3-dimethyl-2-imidazolidinone;

(iv) dichloromethane with or without 1,3-dimethyl-2-imidazolidinone;

(v) THF with or without 1,3-dimethyl-2-imidazolidinone;

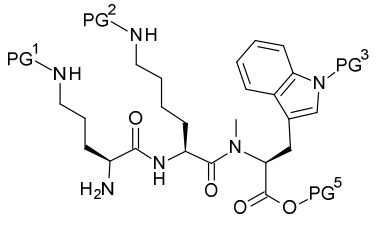
(vi) 2-methyl-THF with or without 1,3-dimethyl-2-imidazolidinone;

(vii) toluene with or without 1,3-dimethyl-2-imidazolidinone; and

(viii) acetonitrile.

3. The process according to any one of claims 1 or 2, further comprising:

(b1) reacting said compound of formula (IV), wherein PG^4 is Fmoc, with N-acetylcysteine and $tAmNH_2$ or $tBuNH_2$, to form a compound of formula (V):



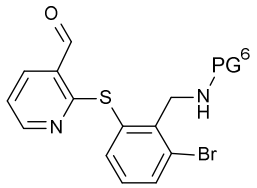
(V);

wherein PG^1, PG^2, and PG^3 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl; and

(b2) washing the reaction mixture obtained in (b1) with a basic aqueous solution.

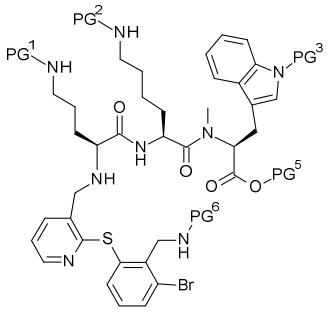
4. The process according to claim 3, further comprising:

(c) reacting said compound of formula (V), with a compound of formula (VI):



(VI);

wherein PG^6 is an amino protective group selected from BOC, Adoc, Moz, and Fmoc; in the presence of (i) a reducing agent selected from $NaBH_3CN$ and $NaBH(OAc)_3$; and (ii) a carboxylic acid selected from acetic acid and propionic acid; to form a compound of formula (VII):

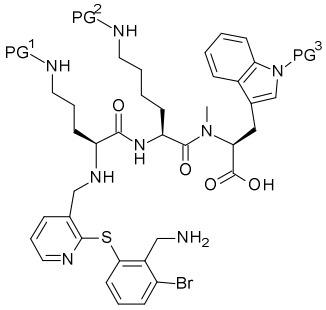


(VII)

wherein PG^1, PG^2, PG^3 and PG^6 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

5. The process according to claim 4, further comprising:

(d) reacting said compound of formula (VII), wherein PG^5 is an allyl group, with a transition metal catalyst in the presence of a secondary amine, to form a compound of formula (IX):



(IX)

wherein PG^1, PG^2 and PG^3 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc.

6. The process according to claim 5, wherein the secondary amine is Et_2NH and the transition metal catalyst is $(PPh_3)_4Pd$.

7. The process according to claim 5 or 6, wherein step (d) is performed in acetonitrile and further comprises working up the reaction mixture obtained from step (d) by:

(d2) adding N-acetylcysteine to said reaction mixture obtained from step (d);

(d3) adding Cy_2NH to the reaction mixture obtained from step (d2);

(d4) distilling off the secondary amine from step (d); and

(d5) filtering the reaction mixture obtained from step (d4).

8. The process according to any one of claims 5 to 7, further comprising:

(e) reacting said compound of formula (IX) with:

(i) a mixture of HOBt and EDCI;

(ii) a mixture of DIC and oxyma;

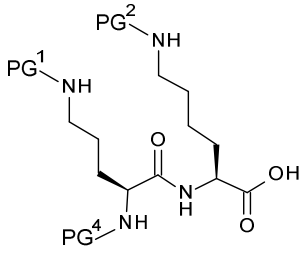
(iii) COMU;

(iv) 2,4,6-trichloro-1,3,5-triazine (TCT); or

(v) 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM);

to form a compound of formula (I).

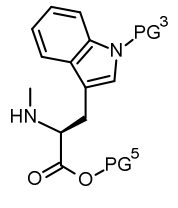
9. A compound of formula (II),



(II)

or a salt thereof, wherein PG^1, PG^2 and PG^4 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc.

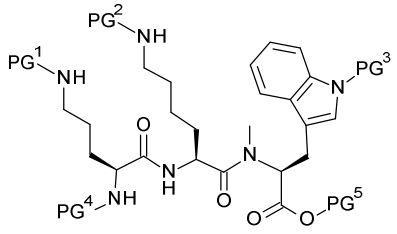
10. A compound of formula (III),



(III)

or a salt thereof, wherein PG^3 is an amino protective group selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

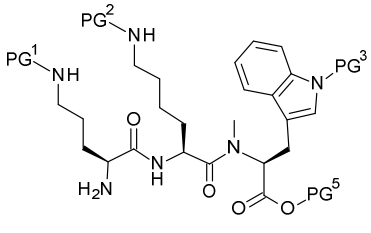
11. A compound of formula (IV),



(IV)

or a salt thereof, wherein PG^1, PG^2, PG^3 and PG^4 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

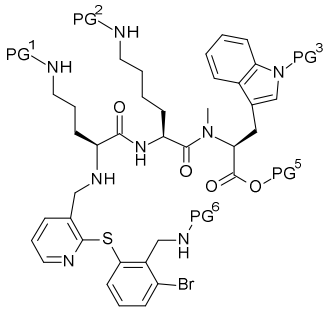
12. A compound of formula (V),



(V)

or a salt thereof, wherein PG^1, PG^2 and PG^3 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

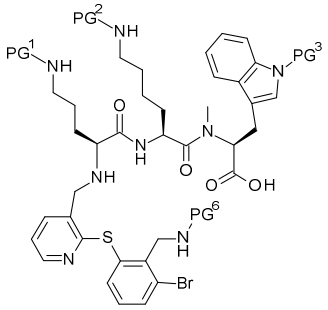
13. A compound of formula (VII),



(VII)

or a salt thereof, wherein PG^1, PG^2, PG^3 and PG^6 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc, and PG^5 is a carboxylic acid protective group selected from allyl and 9-fluorenylmethyl.

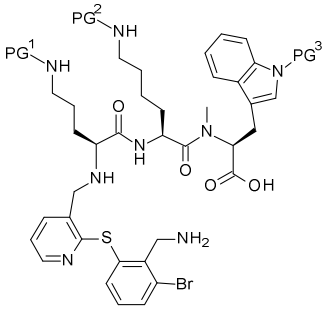
14. A compound of formula (VIII),



(VIII)

or a salt thereof, wherein PG^1, PG^2 and PG^3 and PG^6 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc.

15. A compound of formula (IX),



(IX)

or a salt thereof, wherein PG^1, PG^2 and PG^3 are amino protective groups independently selected from BOC, Adoc, Moz, and Fmoc.

16. The process according to claim 1 or the compound of formula (IV) according to claim 11, wherein PG^1, PG^2 and PG^3 are BOC; PG^4 is Fmoc; and PG^5 is allyl.

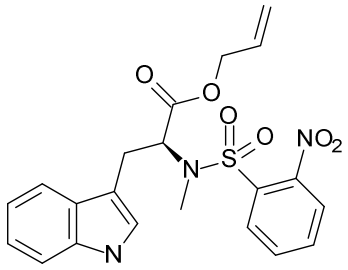
17. The process according to claim 3 or the compound of formula (V) according to claim 12, wherein PG^1, PG^2 and PG^3 are BOC; and PG^5 is allyl.

18. The process according to claim 4 or the compound of formula (VII) according to claim 13, wherein PG^1, PG^2 and PG^3 are BOC; PG^5 is allyl; and PG^6 is Fmoc.

19. The process according to claim 6 or the compound of formula (VIII) according to claim 14, wherein PG^1, PG^2 and PG^3 are BOC; and PG^6 is Fmoc.

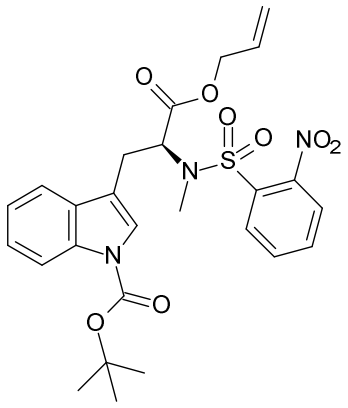
20. The process according to claim 7 or the compound of formula (IX) according to claim 15, wherein PG^1, PG^2 and PG^3 are BOC.

21. A compound, which is N-NBS-N-Me-Trp-OAll



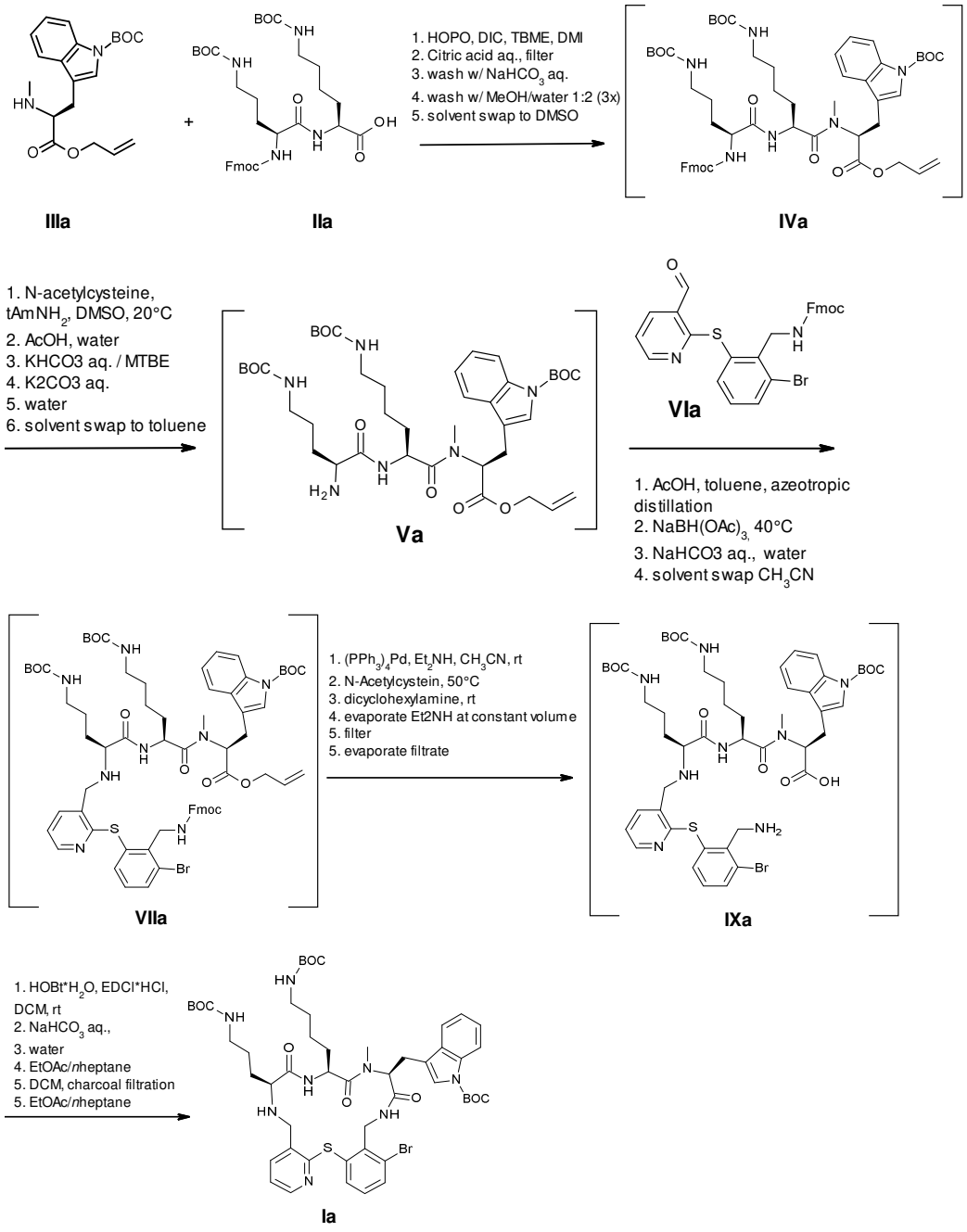
or a salt thereof.

22. A compound, which is N-NBS-N-Me-Trp(Boc)-OAll

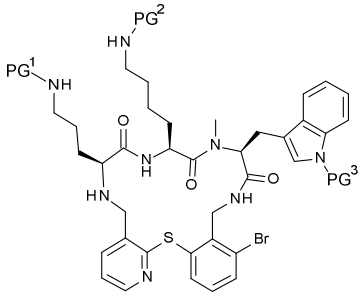


or a salt thereof.

23. The process according to any one of claims 1 to 8, and 16 to 20, which is:



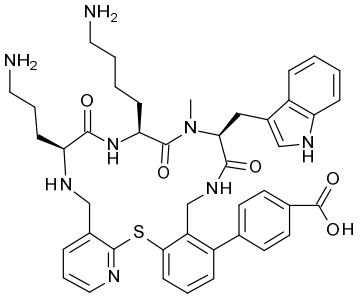
24. A compound of formula (I), or a salt thereof,



(I)

wherein PG^1, PG^2 and PG^3 are amino protective groups, when manufactured according to the process of any one of claims 1 to 8 or 16 to 21.

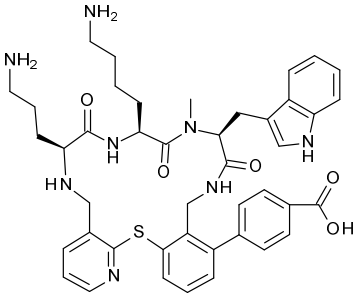
25. A process for manufacturing a compound of formula (1), or a salt thereof,



(1)

comprising a process according to any one of claims 1 to 8 or 16 to 21.

26. Use of the process according to any one of claims 1 to 8 or 16 or 21 in the manufacture of the compound of formula (1)



(1)

or a salt thereof.

27. A method for removing an Fmoc protective group from a compound comprising an Fmoc protected amine, comprising:

(a) reacting said compound comprising an Fmoc protected amine with a base;

(b) adding N-acetylcysteine to the reaction mixture obtained from step (a);

(c) provided the base in step (a) was not Cy_2NH or t-amylamine, adding a base selected from Cy_2NH and t-amylamine to the reaction mixture obtained from step (b);

(d) optionally distilling off the base from step (a); and

(e) filtering the reaction mixture obtained from step (b), (c) or (d).

28. The method of claim 27, wherein the method is performed in acetonitrile as a solvent.

29. The method according to any one of claims 27 or 28, wherein the base used in step (a) is diethylamine.

30. The method according to any one of claims 27 to 29, wherein ≥10 equivalents of base are used relative to compound comprising an Fmoc protected amine in step (a).

31. The method according to claim 30, wherein steps (a)-(c) are performed at room temperature.

32. The method according to any one of claims 27 to 31, wherein the base used in step (c) is Cy_2NH.

33. The method according to any one of claims 27 to 32, comprising step (d), distilling off the base from step (a).

34. The method according to any one of claims 27 to 29, 32 and 33, wherein the reaction mixture obtained in step (b) is heated to 30 °C to reflux.

35. The method of claim 34, wherein the reaction mixture obtained in step (b) is heated to 30 °C to 70 °C.

36. The method of claim 35, wherein the reaction mixture obtained in step (b) is heated to 40 °C to 60 °C.

37. The method of claim 36, wherein the reaction mixture obtained in step (b) is heated to 50 °C.

38. The method according to any one of claims 27 to 37, wherein said compound comprising an Fmoc protected amine further comprises at least one carboxylic acid moiety.