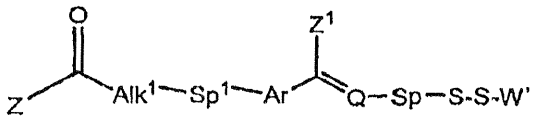
What is claimed is:

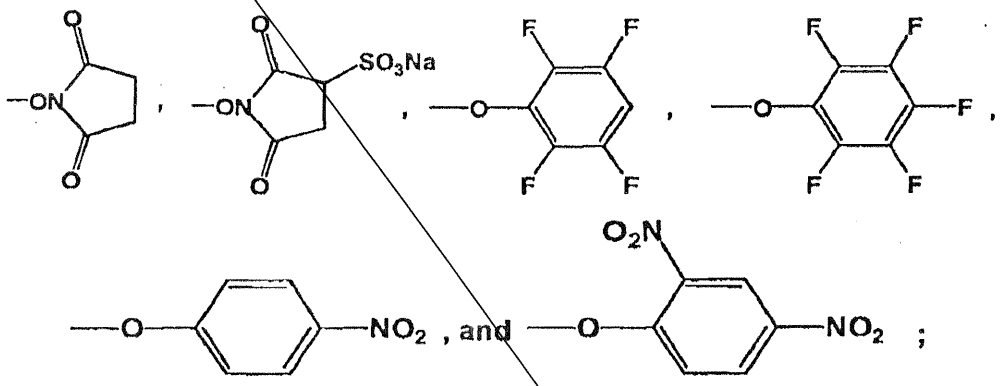
1. A process to prepare compounds of Formula (I):



Formula (I)

wherein:

Z is selected from the group consisting of



Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

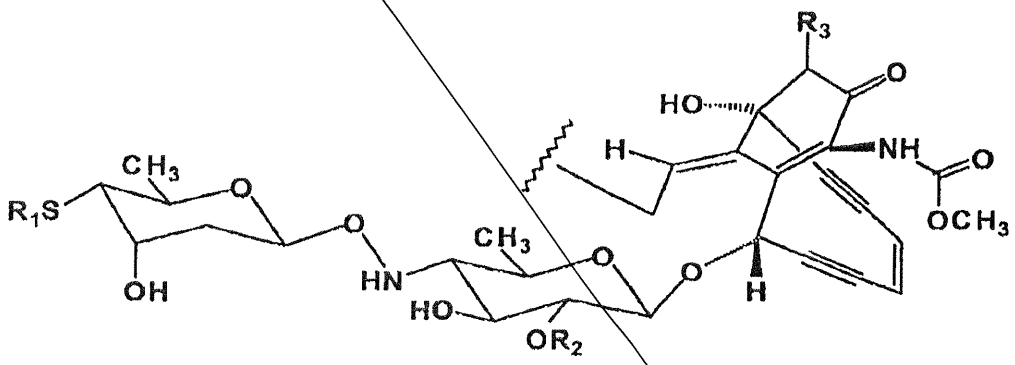
Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

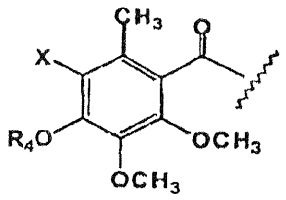
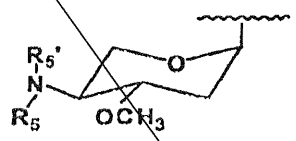
n is an integer from 0 to 5;

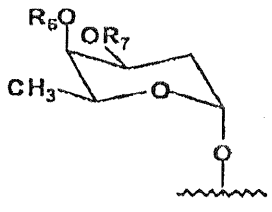
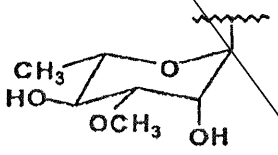
R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

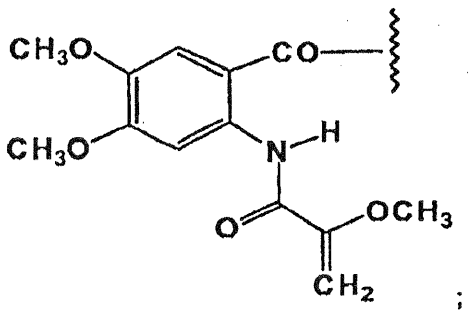
Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is  or H; R_4 is  or H;

R_6 or R_7 is H or 

;

R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)_2$;

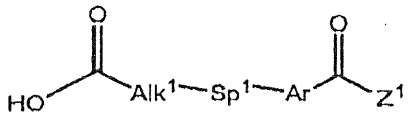
X is an iodine or bromine atom;

R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms; and

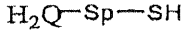
Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NNHCONH-, -NNHCSNH-, and -NO-;

comprising the steps of:

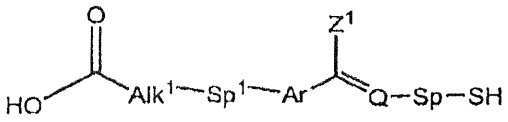
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula

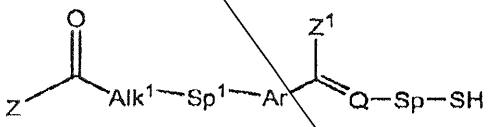


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula, wherein the mercapto compound and carboxylic acid are present in a ratio of about 1.2:1



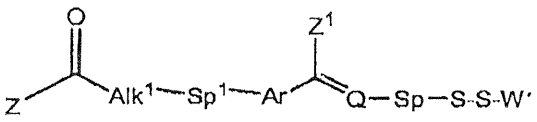
b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with an at least a 3 fold molar excess of N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate a trilinker-activated ester of the formula

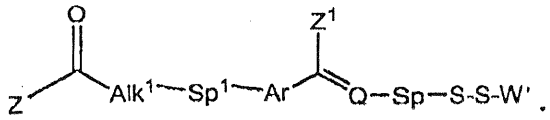


where Z is hereinbefore defined;

d. reacting the trilinker-activated ester formed in step c with a methyltrithio antitumor antiobiotic CH_3-S-S-S-W' in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent to generate an activated ester of the formula below, wherein the trilinker-activated ester in step c and the CH_3-S-S-S-W' are in a ratio of 3.3:1 and the temperature of the reaction is ≤5°C.



e. isolating the activated ester of step (d) and purifying to yield antitumor antibiotics of Formula (I)



Formula (I)

2. The process of claim 1 wherein the purifying of step (e) comprises the use of reverse phase high performance liquid chromatography having a mobile phase of about pH 7.0 to 9.0 followed by normal phase chromatography.

3. A process according to claim 1, wherein

alk^1 is 3 carbon atoms;

Sp^1 is –O-;

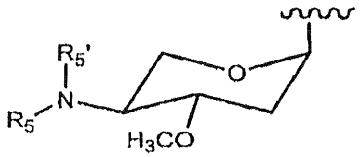
Z^1 is methyl;

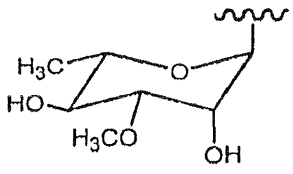
Ar is unsubstituted 1,4-phenylene;

Sp is 4 carbon atoms;

R_3 is H;

Q is NNHC(O)-;

R_2 is ;

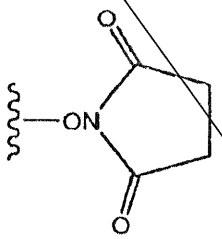
R_4 is ;

R_5 is C_2H_5;

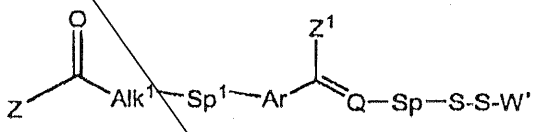
R_5' is –C(O)-R;

R is methyl; and

Z is



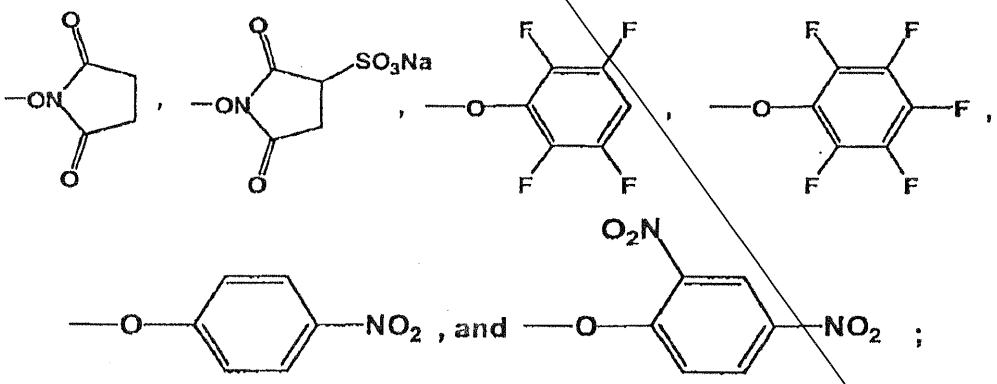
4. A process to prepare antitumor antibiotics of Formula (I):



Formula (I)

wherein:

Z is selected from the group consisting of



Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

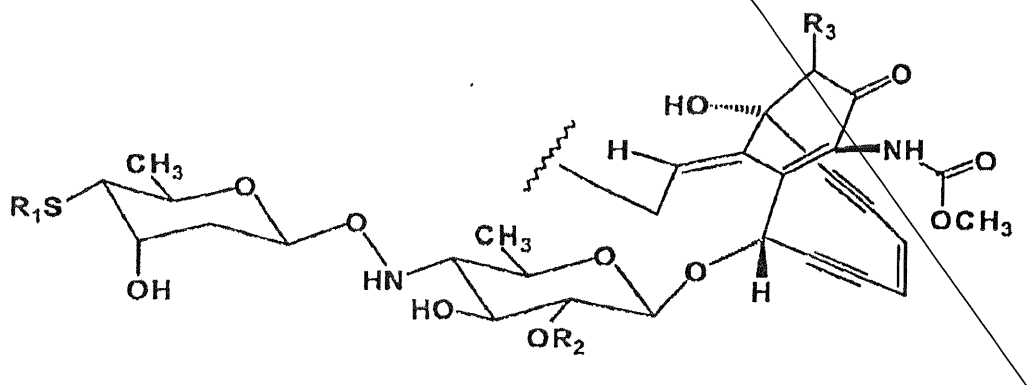
Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

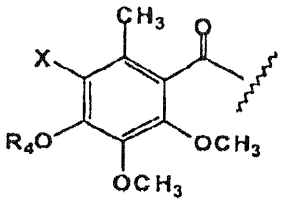
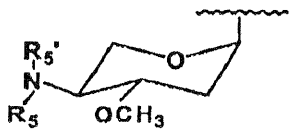
n is an integer from 0 to 5;

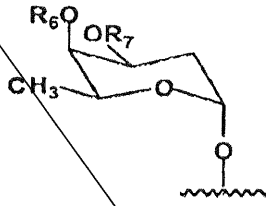
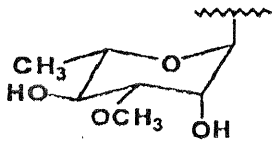
R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

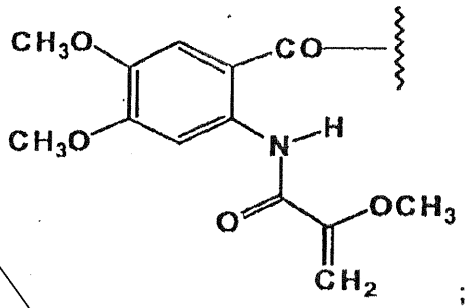
Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is  or H; R_4 is  or H;

R_6 or R_7 is H or ;

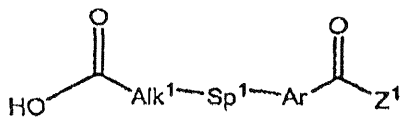
R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)_2$;

X is an iodine or bromine atom;

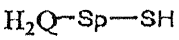
R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms;and

Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NNHCONH-, -NNHCSNH-, and -NO-;
comprising the steps of:

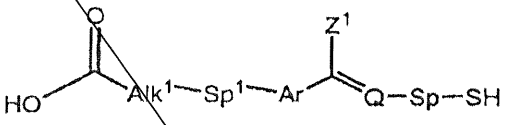
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula



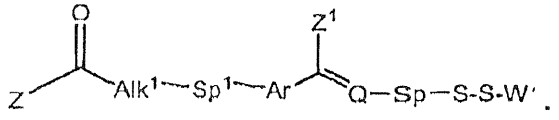
in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula, wherein the mercapto compound and carboxylic acid are present in a ratio of about 1.2:1



b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent;

d. reacting the compound of step (c) with an at least a 3 fold molar excess of N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) and purifying to yield antitumor antibiotics of Formula (I)



5. The process of claim 4 wherein the purifying of step (e) comprises the use of a reverse phase high performance liquid chromatography having a mobile phase of about pH 7.0 to 9.0 followed with a normal phase chromatography.

6. A process according to claim 4, wherein

alk^1 is 3 carbon atoms;

Sp^1 is –O-;

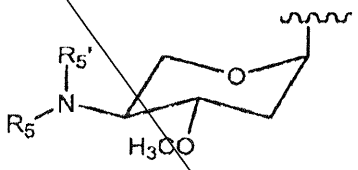
Z^1 is methyl;

Ar is unsubstituted 1,4-phenylene;

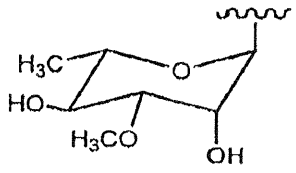
Sp is 4 carbon atoms;

R_3 is H;

Q is NNHC(O)-;

R_2 is 

;

R_4 is 

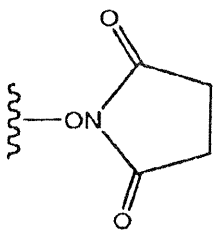
;

R_5 is C_2H_5;

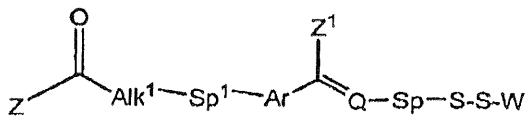
R_5' is –C(O)-R;

R is methyl; and

Z is



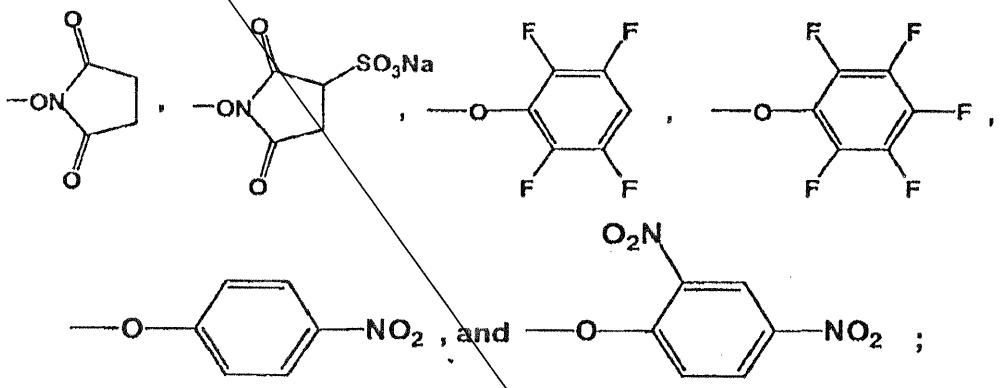
7. A process to prepare antitumor antibiotics of Formula (I):



Formula (I)

wherein:

Z is selected from the group consisting of



Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

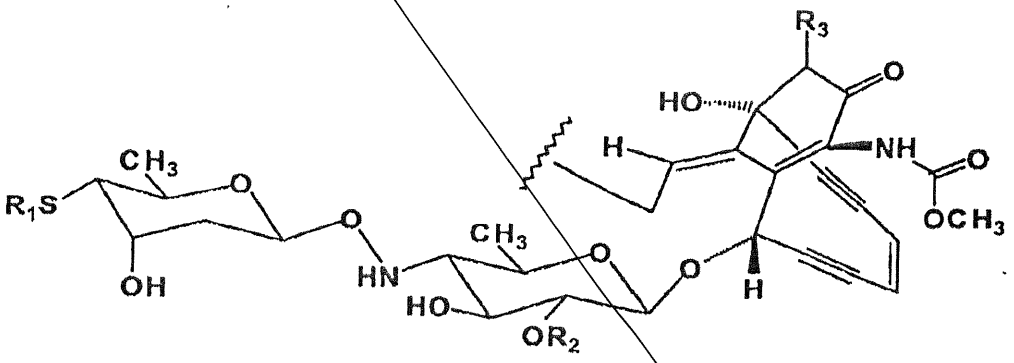
Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

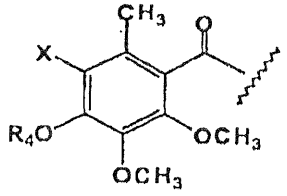
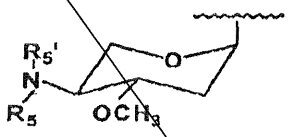
n is an integer from 0 to 5;

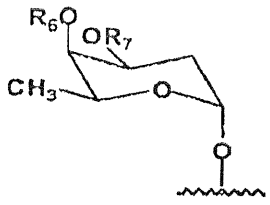
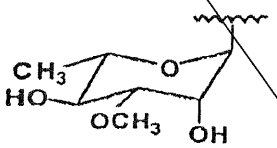
R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

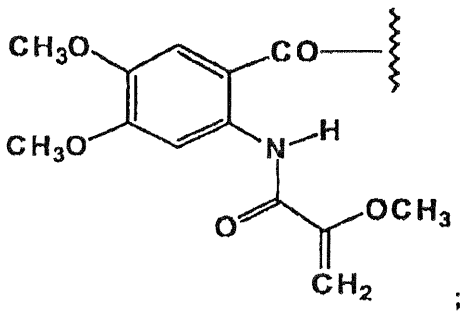
Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is  or H; R_4 is  or H;

R_6 or R_7 is H or 

;

R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)_2$;

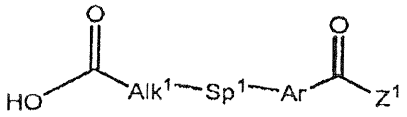
X is an iodine or bromine atom;

R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms;and

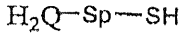
Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NNHCONH-, -NNHCSNH-, and -NO-;

comprising the steps of:

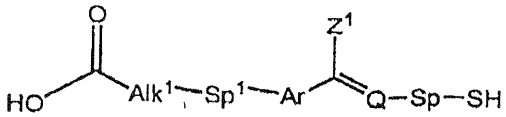
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula

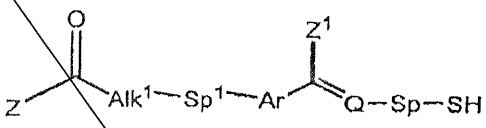


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula,



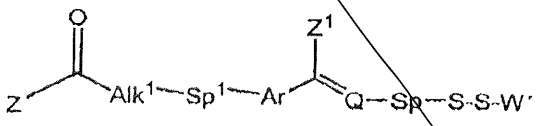
b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with an at least of N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate a trilinker-activated ester of the formula

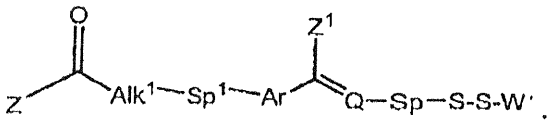


where Z is hereinbefore defined ;

d. reacting the trilinker-activated ester in step c in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent to generate an activated ester of the formula



e. isolating the activated ester of step (d) and purifying to yield antitumor antibiotics of Formula (I)



Formula (I)

8. A process according to claim 1, wherein

alk^1 is 3 carbon atoms;

Sp^1 is –O-;

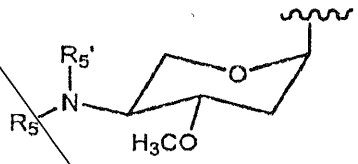
Z^1 is methyl;

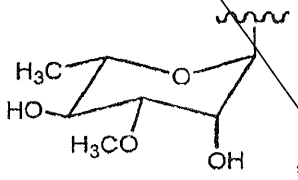
Ar is unsubstituted 1,4-phenylene;

Sp is 4 carbon atoms;

R_3 is H;

Q is NNHC(O)-;

R_2 is ;

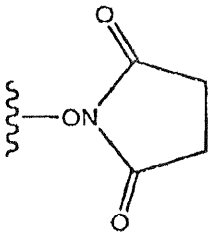
R_4 is ;

R_5 is C_2H_5;

R_5' is –C(O)-R;

R is methyl; and

Z is



9. A process according to claim 1, wherein Alk^1 is an alkylene of 2 to 5 carbon atoms, and Sp^1 is an oxygen atom.

10. A process according to claim 9, wherein Alk^1 is an alkylene of 3 carbon atoms.

11. A process according to claim 1, wherein Z^1 is alkyl of 1 to 3 carbon atoms.

12. A process according to claim 1, wherein Ar is 1,2-, 1,3-, or 1,4-phenylene, or 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene.

13. A process according to claim 12, wherein Ar is 1,4-phenylene.

14. A process according to claim 1, wherein Q is -NNHCO-.

15. A process according to claim 1, wherein Sp is straight or branched-chain divalent or trivalent alkyl radical of 1 to 12 carbon atoms.

16. A process according to claim 15, wherein Sp is straight or branched-chain divalent or trivalent alkyl radical of 1 to 6 carbon atoms.

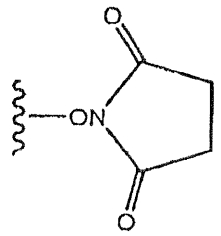
17. The process according to claim 1, wherein the alcohol solvent is methanol.

18. The process according to claim 1, wherein the inert solvent is acetonitrile.

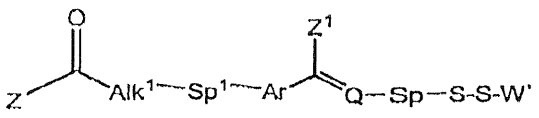
19. The process according to claim 1, wherein alkyl carboxylic acid is acetic acid.

20. The process according to claim 1, wherein the inert organic solvent is acetonitrile.

21. A process according to claim 1, wherein Z is

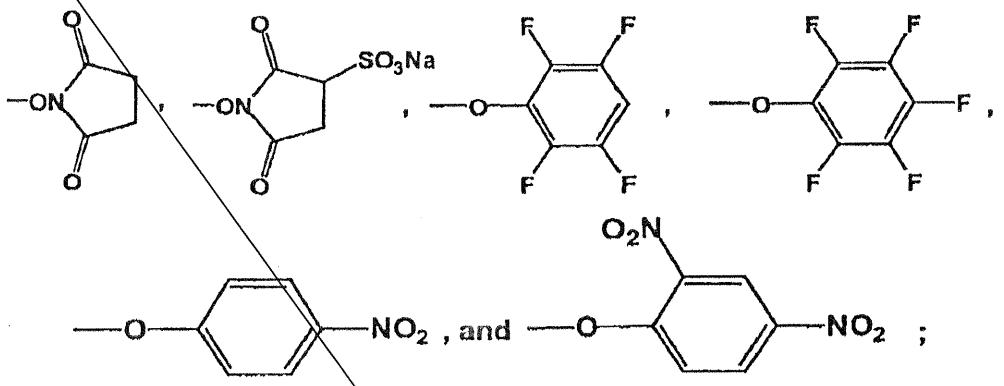


22. A process to prepare trilinker-activated esters of the formula:



wherein:

Z is selected from the group consisting of



Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

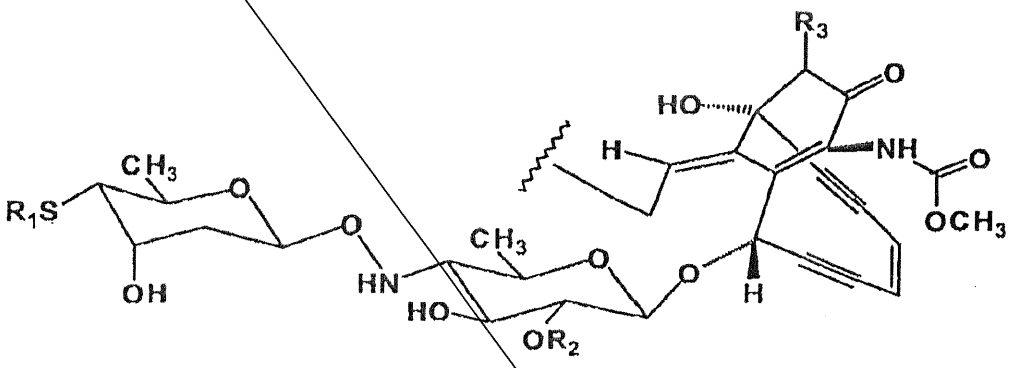
n is an integer from 0 to 5;

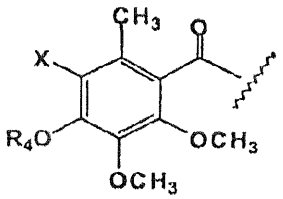
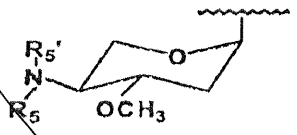
R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

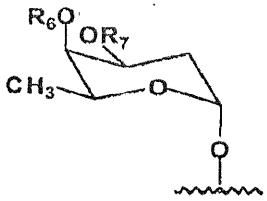
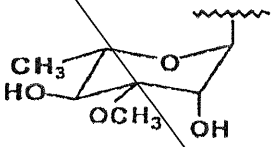
Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of

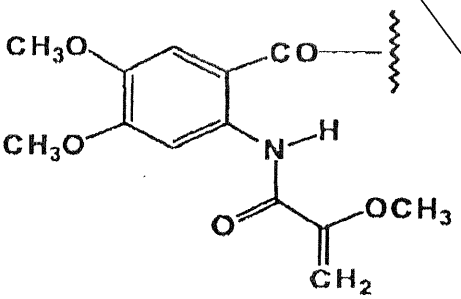
3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is  or H; R_4 is  or H;

R_6 or R_7 is H or 

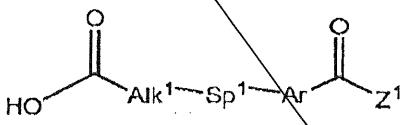
R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)_2$;

X is an iodine or bromine atom;

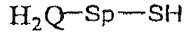
R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms;and
Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NHNCONH-, -NNCSNH-, and -NO-;

comprising the steps of:

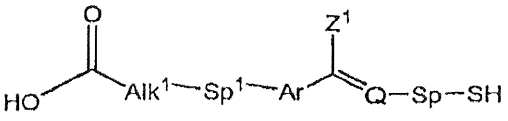
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula

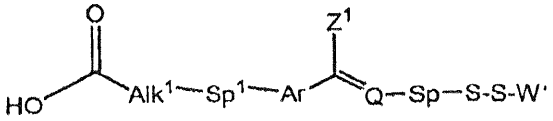


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula

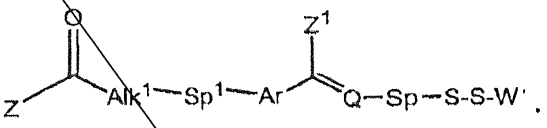


b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the bilinker-carboxylic acid from step (b) in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent to generate a bilinker-methyltrithio antitumor antibiotic of the formula

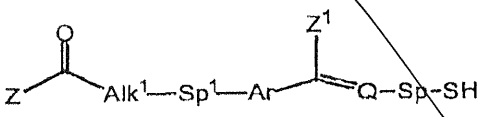


d. reacting the isolated bilinker-methyltrithio antitumor antibiotic of step (c) with N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate a trilinker-activated ester of the formula



23. The process according to claim 17, wherein Alk^1 is an alkylene of 2 to 5 carbon atoms, and Sp^1 is an oxygen atom.

24. A process for the preparation of trifunctional linker intermediates, of the formula



wherein:

Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR',

$-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

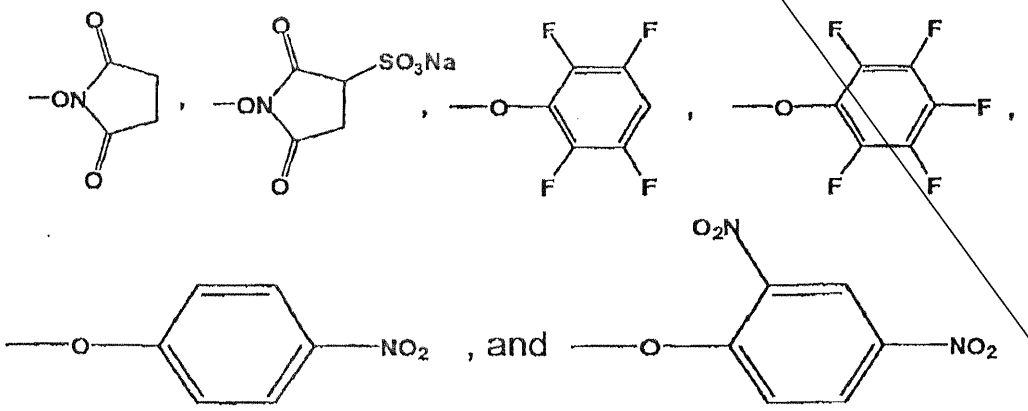
n is an integer from 0 to 5;

R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

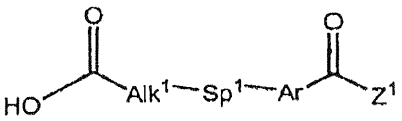
Q is selected from the group consisting of -NNHCO-, -NNHCS-, and -NNHCONH-;

Z is selected from the group consisting of

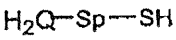


comprising the steps of:

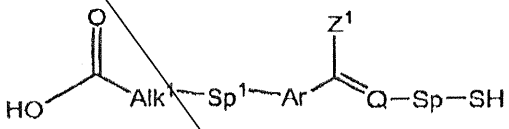
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula

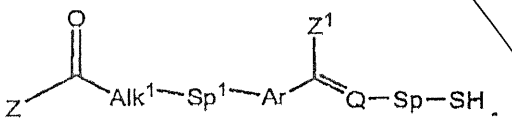


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H, where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula



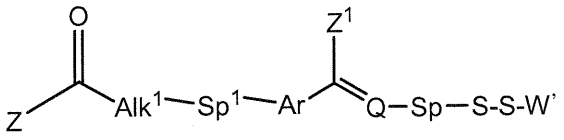
b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% DMF to generate trifunctional linker intermediates, of the formula



CLAIMS

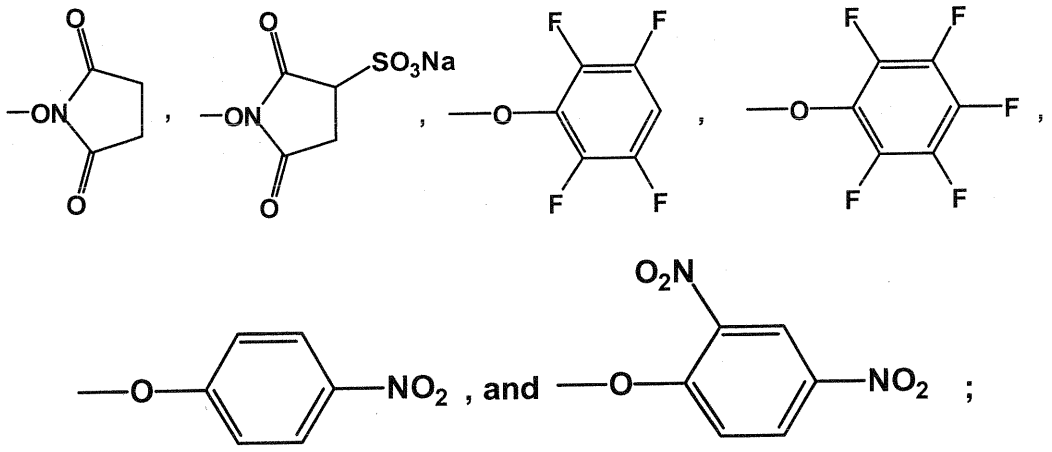
1. A process to prepare compounds of Formula (I):



Formula (I)

wherein:

Z is selected from the group consisting of



Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms,

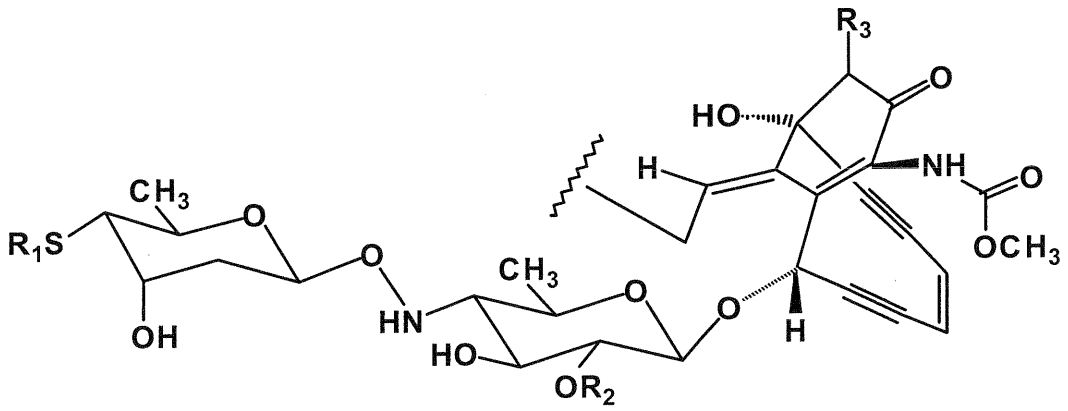
thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', -O$(CH_2)_n$COOR', -S$(CH_2)_n$COOR', -O$(CH_2)_n$CONHR', and -S$(CH_2)_n$CONHR' or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', -O$(CH_2)_n$COOR', -S$(CH_2)_n$COOR', -O$(CH_2)_n$CONHR', and -S$(CH_2)_n$CONHR';

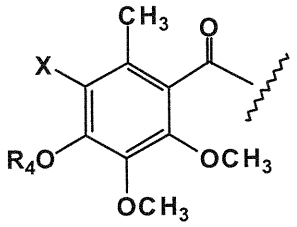
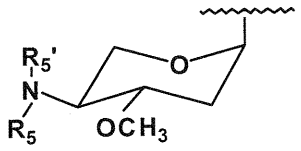
n is an integer from 0 to 5;

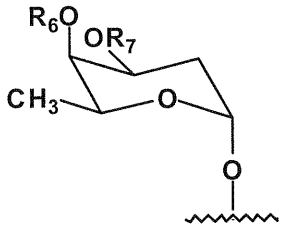
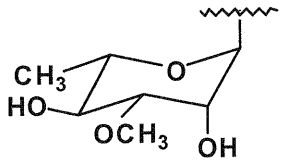
R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

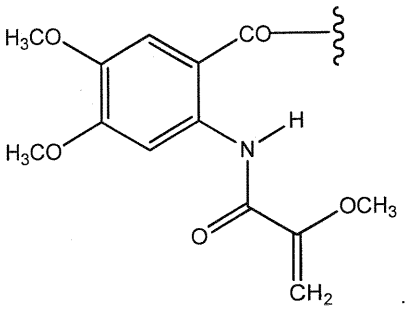
Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

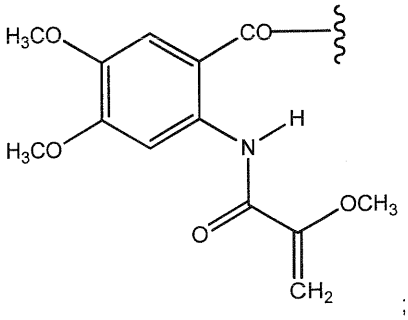
W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is  or H; R_4 is  or H;

R_6 is H or 

R_7 is H or 

R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)2$;

X is an iodine or bromine atom;

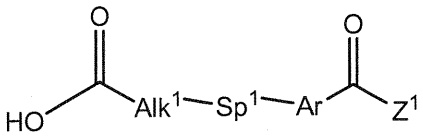
R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-,

or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms; and

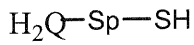
Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NNHCONH-, -NNHCSNH-, and -NO-;

comprising the steps of:

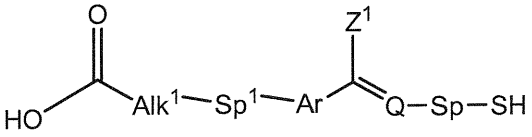
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula

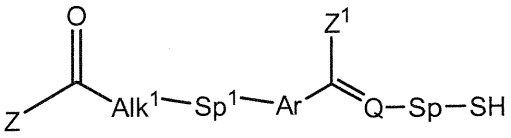


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula, wherein the mercapto compound and carboxylic acid are present in a ratio of about 1.2:1



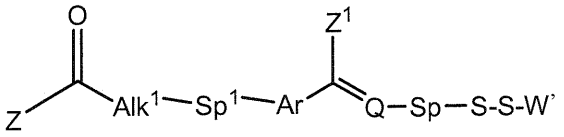
b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with an at least a 3 fold molar excess of N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate a trilinker-activated ester of the formula

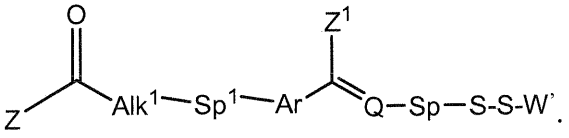


where Z is hereinbefore defined;

d. reacting the trilinker-activated ester formed in step c in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent to generate an activated ester of the formula below, wherein the trilinker-activated ester in step c and the CH_3-S-S-S-W' are in a ratio of 3.3:1 and the temperature of the reaction is ≤5°C.



e. isolating the activated ester of step (d) and purifying to yield antitumor antibiotics of Formula (I)



Formula (I)

2. The process of claim 1 wherein the purifying of step (e) comprises the use of reverse phase high performance liquid chromatography having a mobile phase of about pH 7.0 to 9.0 followed by normal phase chromatography.

3. A process according to claim 1, wherein

alk^1 is 3 carbon atoms;

Sp^1 is –O-;

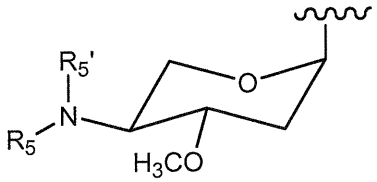
Z^1 is methyl;

Ar is unsubstituted 1,4-phenylene;

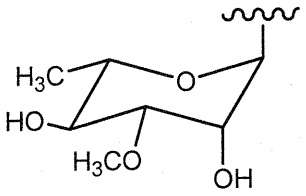
Sp is 4 carbon atoms;

R_3 is H;

Q is NNHC(O)-;

R_2 is 

;

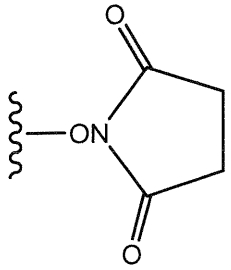
R_4 is 

;

R_5 is C_2H_5;

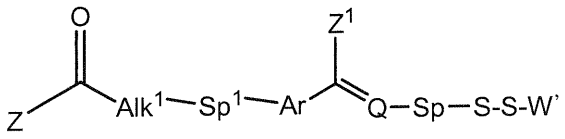
R_5' is –C(O)-R;

R is methyl; and

Z is 

.

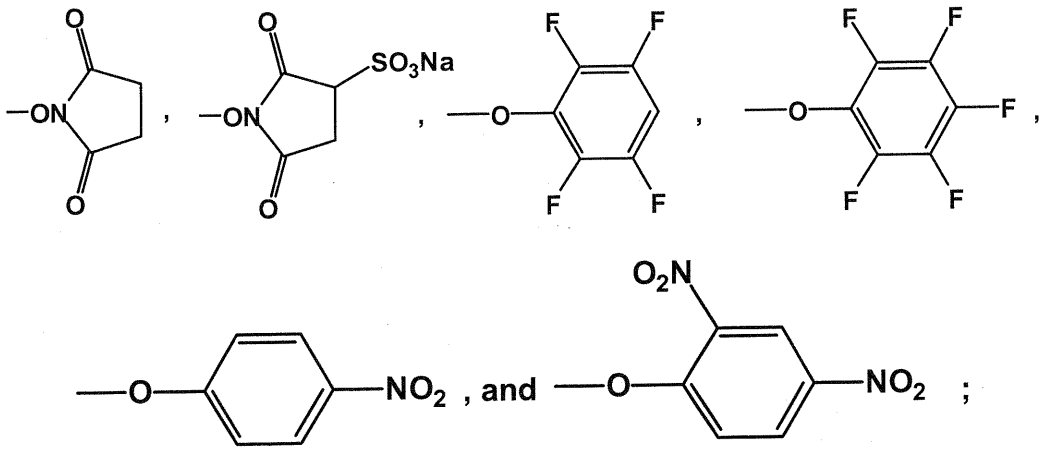
4. A process to prepare antitumor antibiotics of Formula (I):



Formula (I)

wherein:

Z is selected from the group consisting of



Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

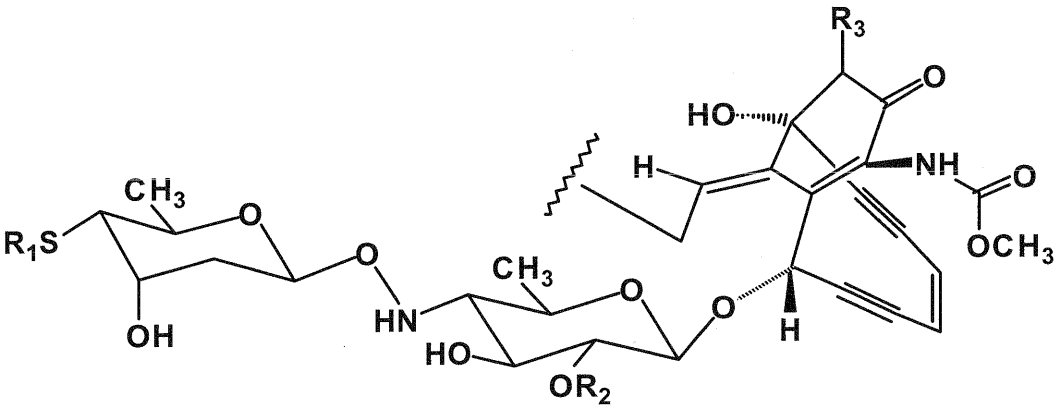
Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

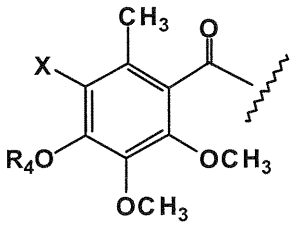
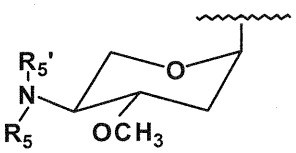
n is an integer from 0 to 5;

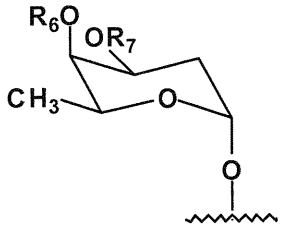
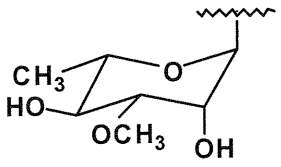
R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

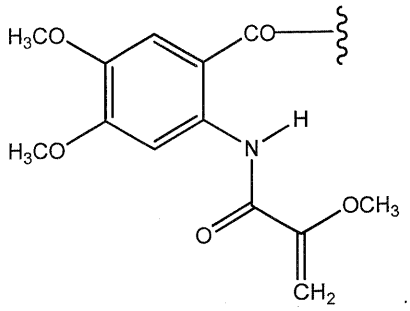
Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

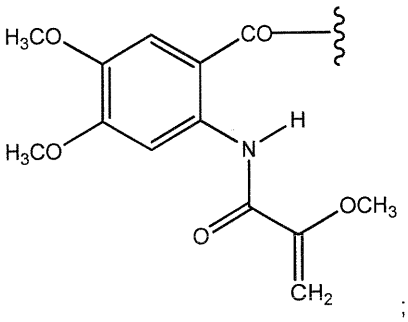
W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is  or H; R_4 is  or H;

R_6 is H or ;

R_7 is H or ;

R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)2$;

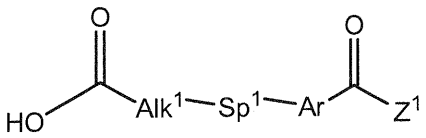
X is an iodine or bromine atom;

R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms;and

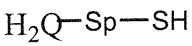
Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NNHCONH-, -NNHCSNH-, and -NO-;

comprising the steps of:

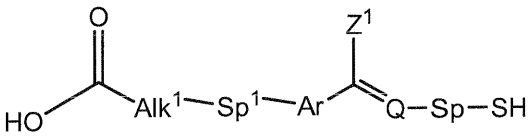
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula



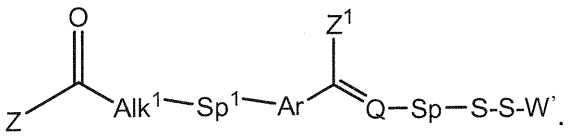
in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula, wherein the mercapto compound and carboxylic acid are present in a ratio of about 1.2:1



b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in the presence of a base or an organic base in an inter organic solvent;

d. reacting the compound of step (c) with an at least a 3 fold molar excess of N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) and purifying to yield antitumor antibiotics of Formula (I)



5. The process of claim 4 wherein the purifying of step (e) comprises the use of a reverse phase high performance liquid chromatography having a mobile phase of about pH 7.0 to 9.0 followed with a normal phase chromatography.

6. A process according to claim 4, wherein

alk^1 is 3 carbon atoms;

Sp^1 is –O-;

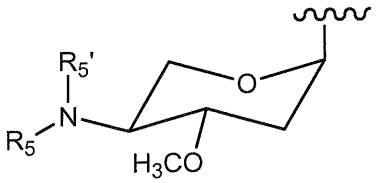
Z^1 is methyl;

Ar is unsubstituted 1,4-phenylene;

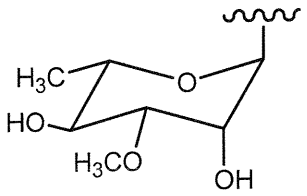
Sp is 4 carbon atoms;

R_3 is H;

Q is NNHC(O)-;

R_2 is 

;

R_4 is 

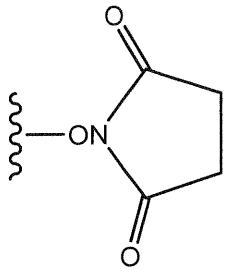
;

R_5 is C_2H_5;

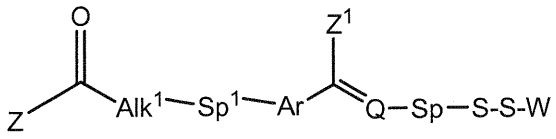
R_5' is –C(O)-R;

R is methyl; and

Z is



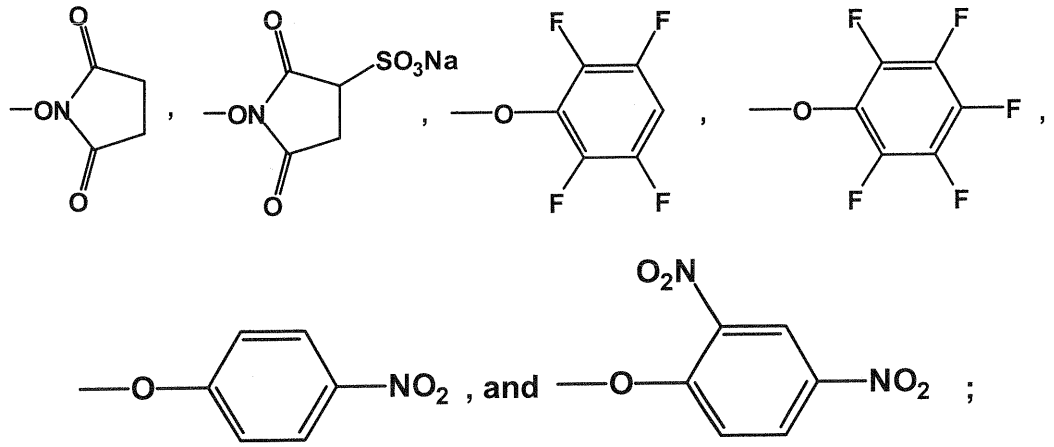
7. A process to prepare antitumor antibiotics of Formula (I):



Formula (I)

wherein:

Z is selected from the group consisting of



Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

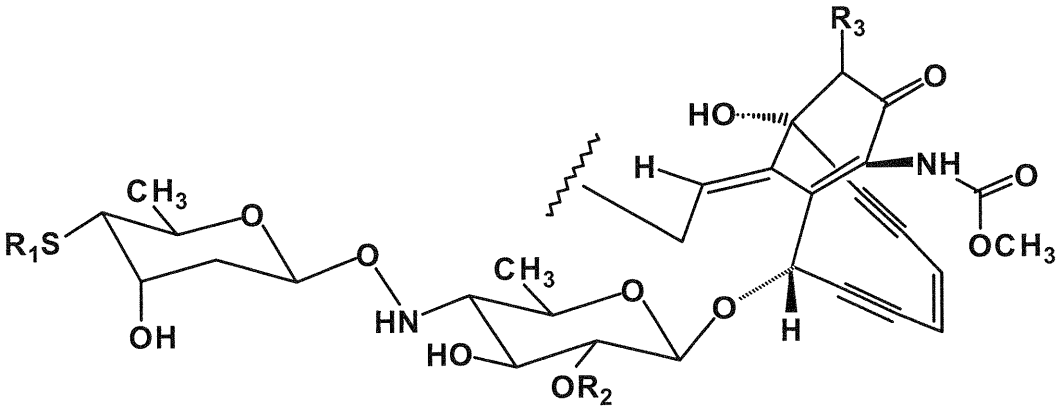
Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

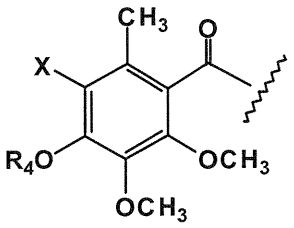
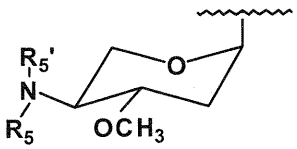
n is an integer from 0 to 5;

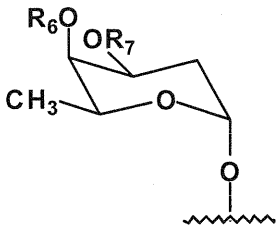
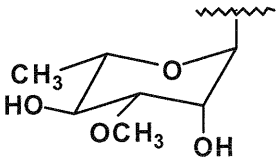
R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

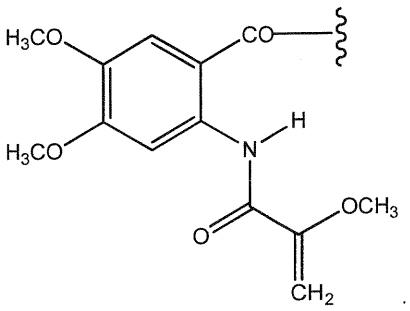
Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

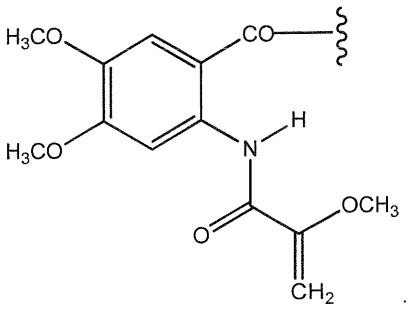
W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is  or H; R_4 is  or H;

R_6 is H or ;

R_7 is H or ;

R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)2$;

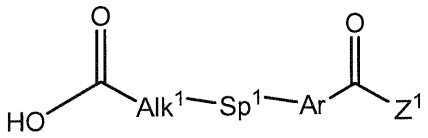
X is an iodine or bromine atom;

R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms;and

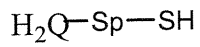
Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NNHCONH-, -NNHCSNH-, and -NO-;

comprising the steps of:

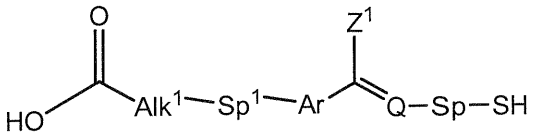
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula

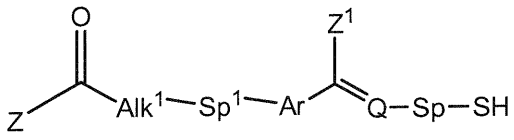


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula,



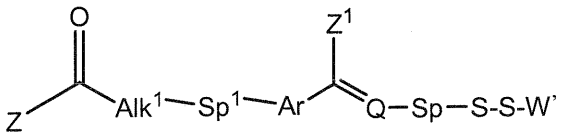
b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with an at least of N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate a trilinker-activated ester of the formula

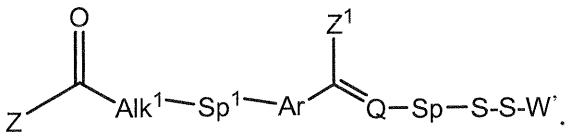


where Z is hereinbefore defined ;

d. reacting the trilinker-activated ester in step c in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent to generate an activated ester of the formula



e. isolating the activated ester of step (d) and purifying to yield antitumor antibiotics of Formula (I)



Formula (I)

8. A process according to claim 1, wherein

alk^1 is 3 carbon atoms;

Sp^1 is –O-;

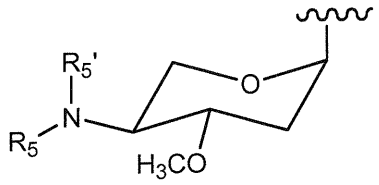
Z^1 is methyl;

Ar is unsubstituted 1,4-phenylene;

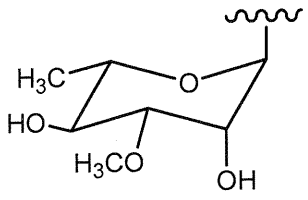
Sp is 4 carbon atoms;

R_3 is H;

Q is NNHC(O)-;

R_2 is 

;

R_4 is 

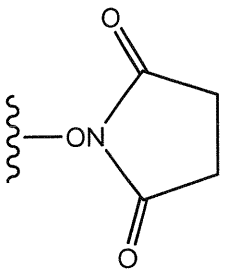
;

R_5 is C_2H_5;

R_5' is –C(O)-R;

R is methyl; and

Z is



.

9. A process according to claim 1, wherein Alk^1 is an alkylene of 2 to 5 carbon atoms, and Sp^1 is an oxygen atom.

10. A process according to claim 9, wherein Alk^1 is an alkylene of 3 carbon atoms.

11. A process according to claim 1, wherein Z^1 is alkyl of 1 to 3 carbon atoms.

12. A process according to claim 1, wherein Ar is 1,2-, 1,3-, or 1,4-phenylene, or 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene.

13. A process according to claim 12, wherein Ar is 1,4-phenylene.

14. A process according to claim 1, wherein Q is -NNHCO-.

15. A process according to claim 1, wherein Sp is straight or branched-chain divalent or trivalent alkyl radical of 1 to 12 carbon atoms.

16. A process according to claim 15, wherein Sp is straight or branched-chain divalent or trivalent alkyl radical of 1 to 6 carbon atoms.

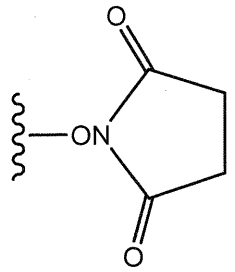
17. The process according to claim 1, wherein the alcohol solvent is methanol.

18. The process according to claim 1, wherein the inert solvent is acetonitrile.

19. The process according to claim 1, wherein alkyl carboxylic acid is acetic acid.

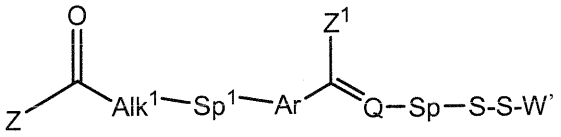
20. The process according to claim 1, wherein the inert organic solvent is acetonitrile.

21. A process according to claim 1, wherein Z is



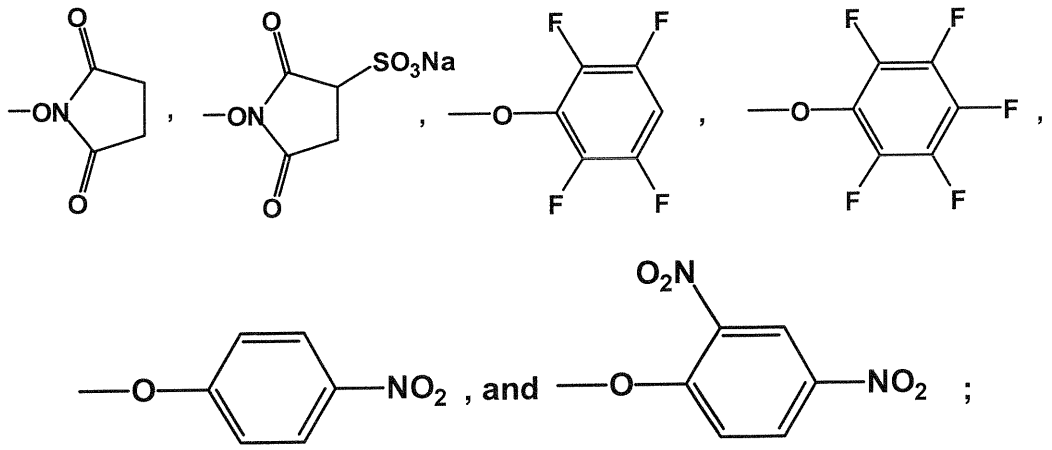
.

22. A process to prepare trilinker-activated esters of the formula:



wherein:

Z is selected from the group consisting of



Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

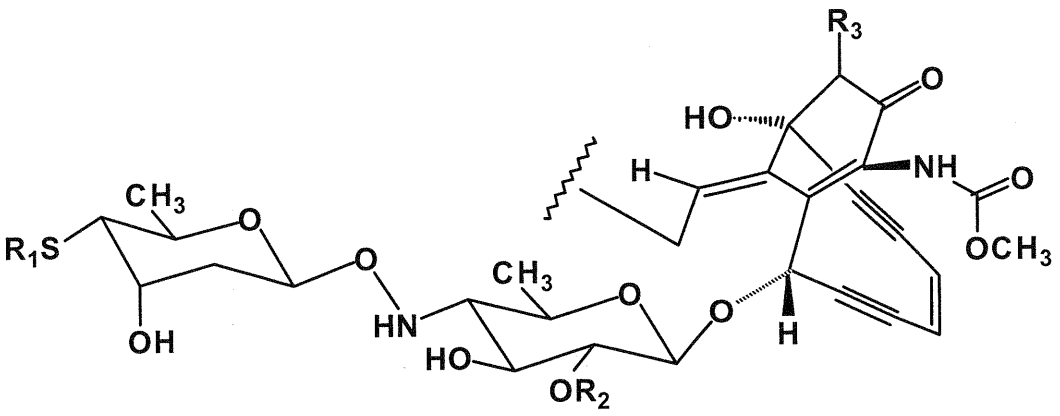
Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

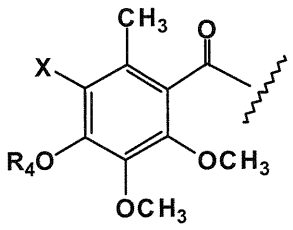
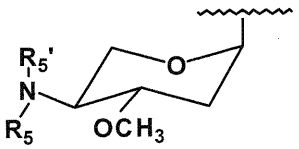
n is an integer from 0 to 5;

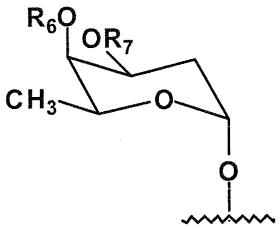
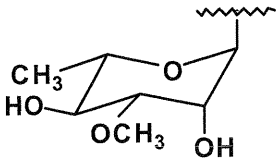
R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

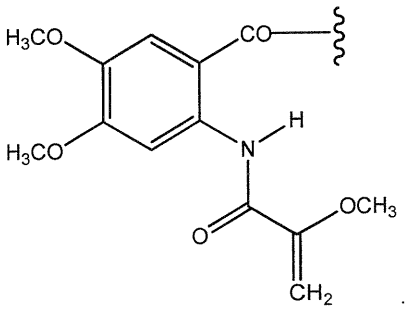
Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

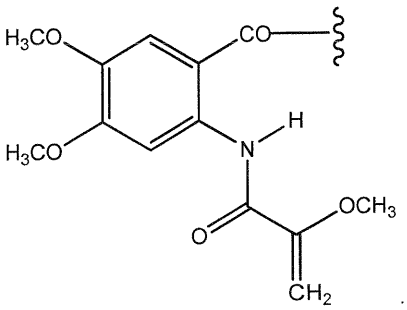
W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is  or H; R_4 is  or H;

R_6 is H or ;

R_7 is H or ;

R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)2$;

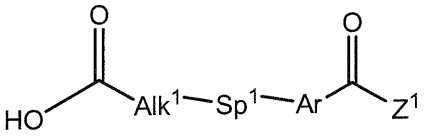
X is an iodine or bromine atom;

R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms;and

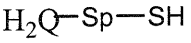
Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NHNCONH-, -NNCSNH-, and -NO-;

comprising the steps of:

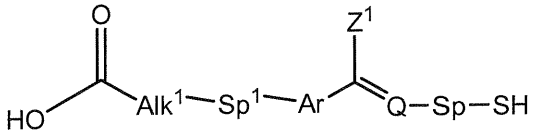
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula

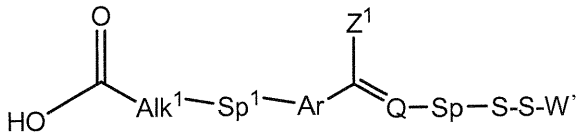


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula

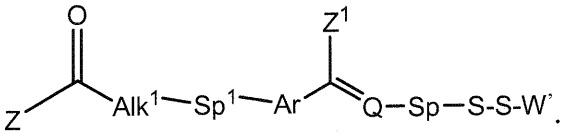


b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the bilinker-carboxylic acid from step (b) in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent to generate a bilinker-methyltrithio antitumor antibiotic of the formula

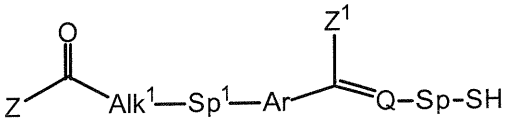


d. reacting the isolated bilinker-methyltrithio antitumor antibiotic of step (c) with N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate a trilinker-activated ester of the formula



23. The process according to claim 17, wherein Alk^1 is an alkylene of 2 to 5 carbon atoms, and Sp^1 is an oxygen atom.

24. A process for the preparation of trifunctional linker intermediates, of the formula



wherein:

Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', -$O(CH_2)_nCOOR'$, -$S(CH_2)_nCOOR'$, -$O(CH_2)_nCONHR'$, and -$S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', -$O(CH_2)_nCOOR'$, -$S(CH_2)_nCOOR'$, -$O(CH_2)_nCONHR'$, and -$S(CH_2)_nCONHR'$;

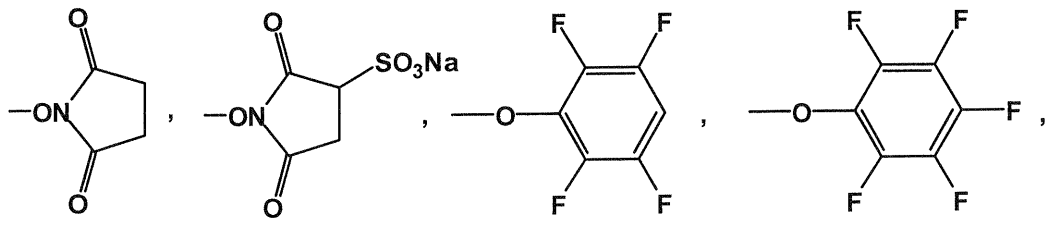
n is an integer from 0 to 5;

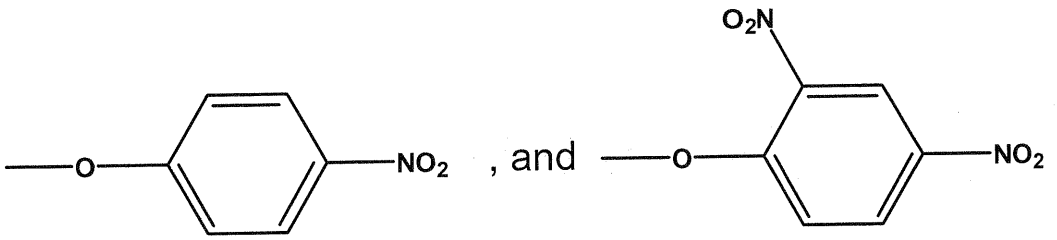
R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

Q is selected from the group consisting of -NNHCO-, -NNHCS-, and -NNHCONH-;

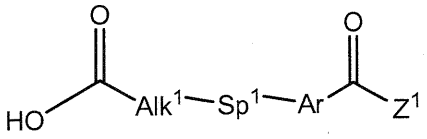
Z is selected from the group consisting of



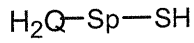


comprising the steps of:

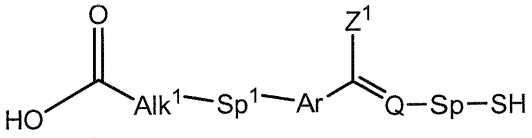
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula

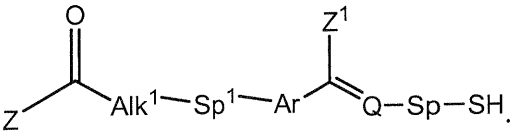


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H, where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula



b. isolating the bilinker-carboxylic acid of step (a);

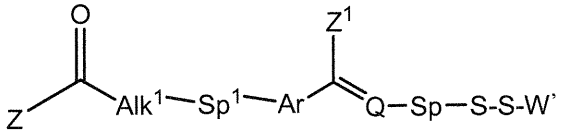
c. reacting the isolated bilinker-carboxylic acid of step (b) with N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% DMF to generate trifunctional linker intermediates, of the formula



25. The method of claim 1, wherein step c. comprises reacting the isolated bilinker-carboxylic acid with N-hydroxysuccinimide in the presence of DCC at ambient temperature in dioxane.

26. The method of claim 1, wherein the methyltrithio antitumor antiobiotic CH_3-S-S-S-W' comprises N-acetyl-LL-E33288 γ_1^I.

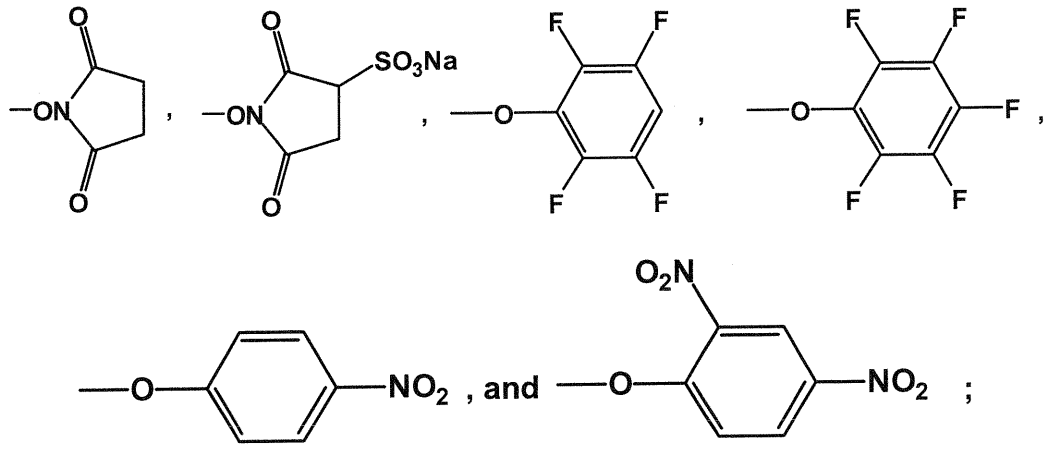
27. A process to prepare compounds of Formula (I):



Formula (I)

wherein:

Z is selected from the group consisting of



Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

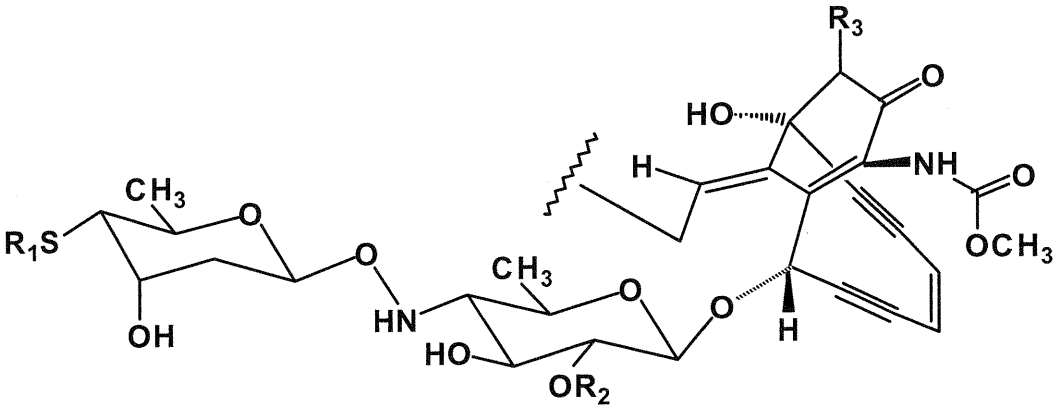
Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

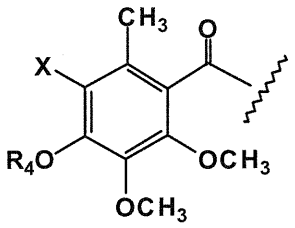
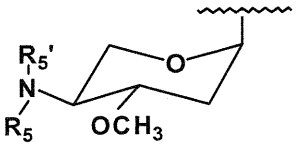
n is an integer from 0 to 5;

R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

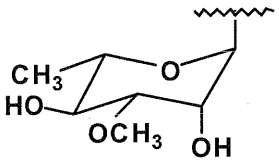
Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is H;

R_4 is  or H;

R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)2$;

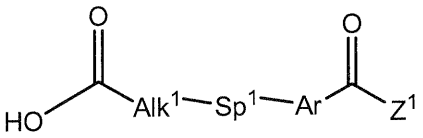
X is an iodine or bromine atom;

R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms; and

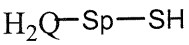
Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NNHCONH-, -NNHCSNH-, and -NO-;

comprising the steps of:

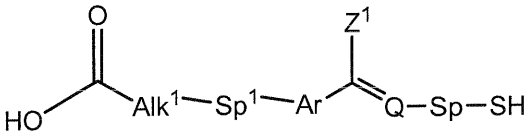
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula

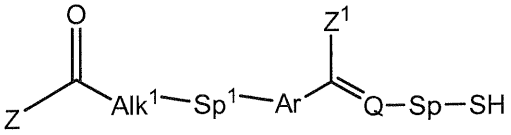


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula, wherein the mercapto compound and carboxylic acid are present in a ratio of about 1.2:1



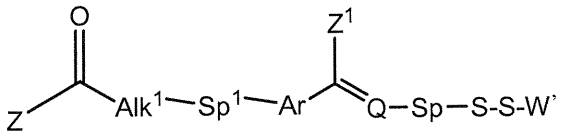
b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with an at least a 3 fold molar excess of N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate a trilinker-activated ester of the formula

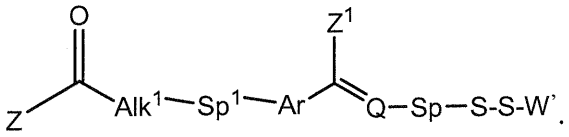


where Z is hereinbefore defined;

d. reacting the trilinker-activated ester formed in step c in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent to generate an activated ester of the formula below, wherein the trilinker-activated ester in step c and the CH_3-S-S-S-W' are in a ratio of 3.3:1 and the temperature of the reaction is ≤5°C.

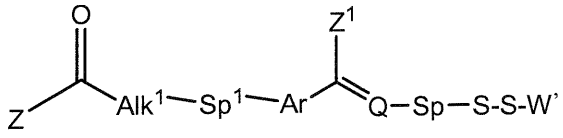


e. isolating the activated ester of step (d) and purifying to yield antitumor antibiotics of Formula (I)



Formula (I)

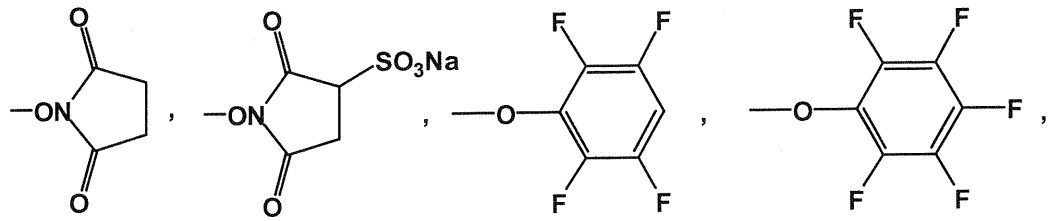
28. A process to prepare antitumor antibiotics of Formula (I):

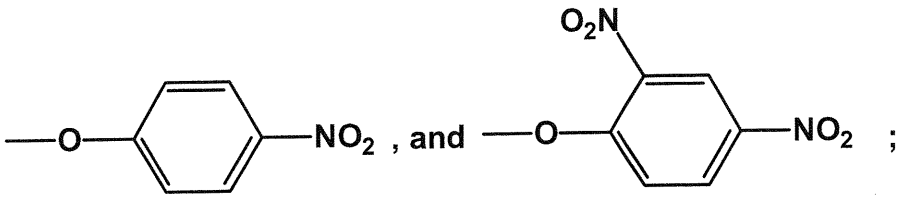


Formula (I)

wherein:

Z is selected from the group consisting of





Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

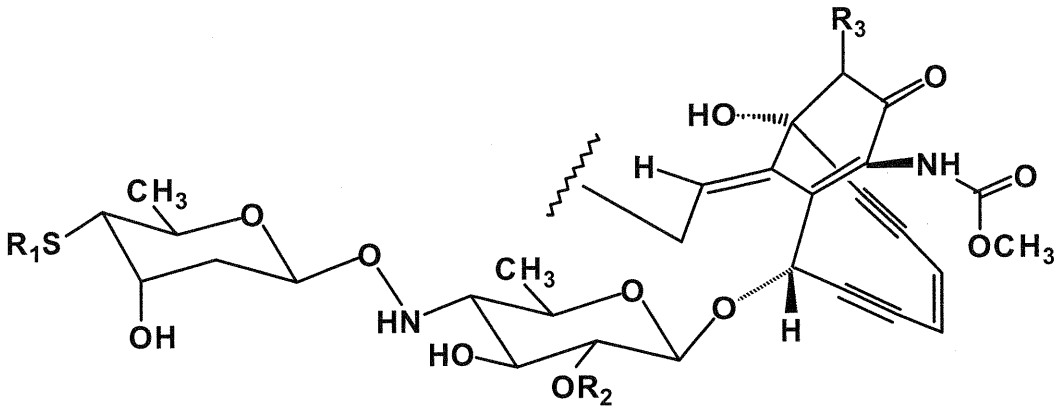
n is an integer from 0 to 5;

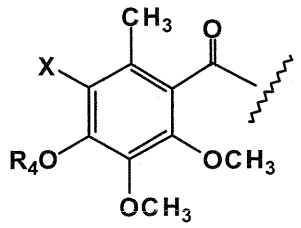
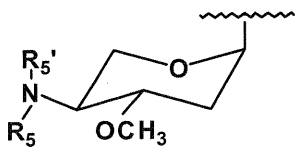
R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can

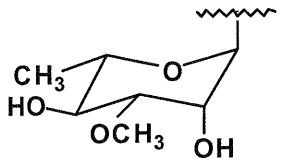
be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is H;

R_4 is  or H;

R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)2$;

X is an iodine or bromine atom;

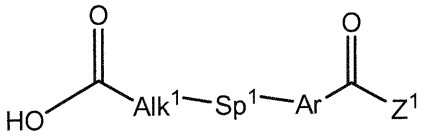
R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-,

or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms;and

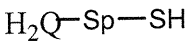
Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NNHCONH-, -NNHCSNH-, and -NO-;

comprising the steps of:

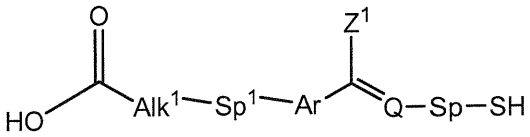
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula



in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula, wherein the mercapto compound and carboxylic acid are present in a ratio of about 1.2:1

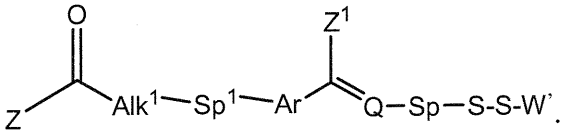


b. isolating the bilinker-carboxylic acid of step (a);

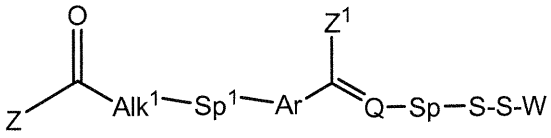
c. reacting the isolated bilinker-carboxylic acid of step (b) with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in the presence of a base or an organic base in an inert organic solvent;

d. reacting the compound of step (c) with an at least a 3 fold molar excess of N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl

carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) and purifying to yield antitumor antibiotics of Formula (I)



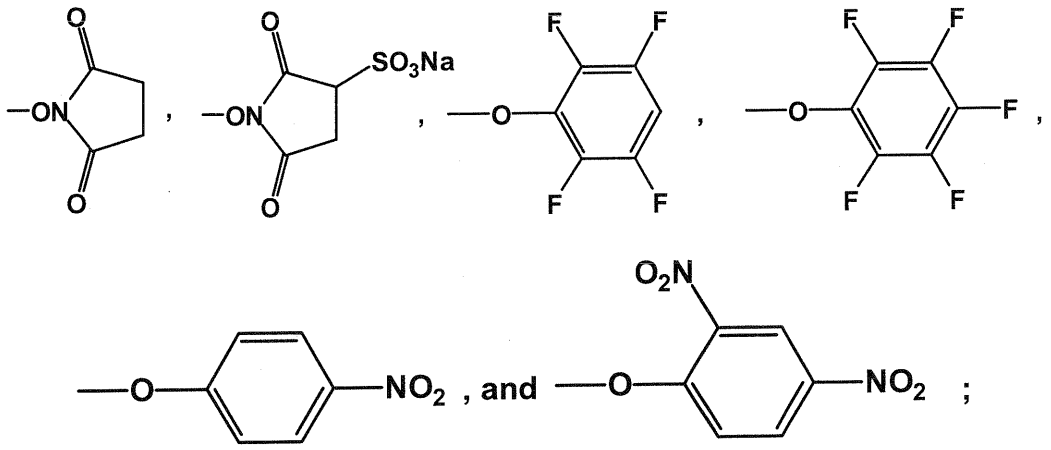
29. A process to prepare antitumor antibiotics of Formula (I):



Formula (I)

wherein:

Z is selected from the group consisting of



Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

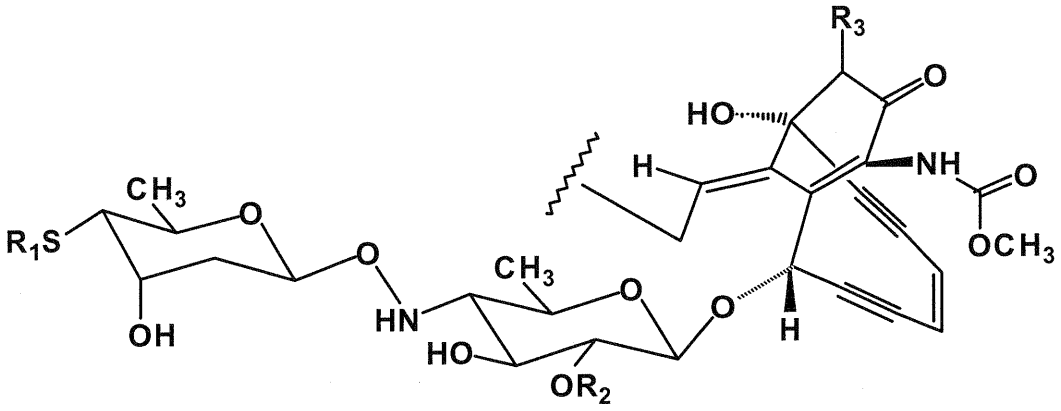
Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

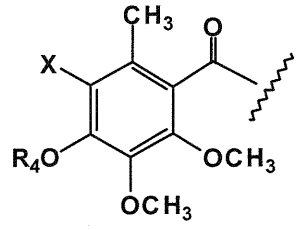
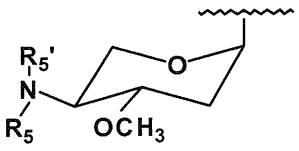
n is an integer from 0 to 5;

R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

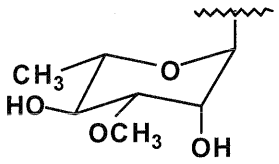
Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is H;

R_4 is  or H;

R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)_2$;

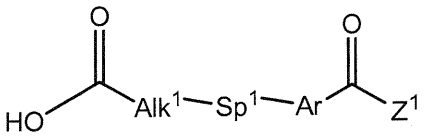
X is an iodine or bromine atom;

R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms;and

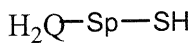
Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NNHCONH-, -NNHCSNH-, and -NO-;

comprising the steps of:

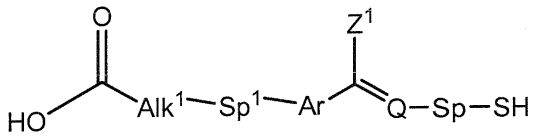
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula

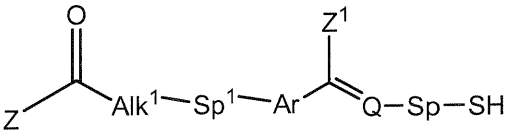


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula,



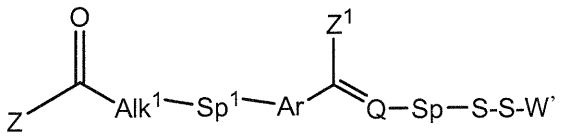
b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with an at least of N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate a trilinker-activated ester of the formula

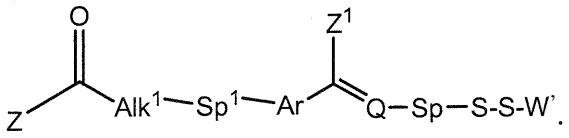


where Z is hereinbefore defined ;

d. reacting the trilinker-activated ester in step c in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent to generate an activated ester of the formula

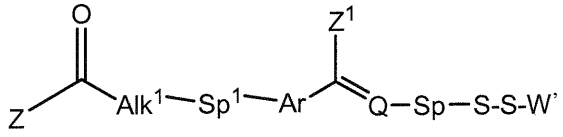


e. isolating the activated ester of step (d) and purifying to yield antitumor antibiotics of Formula (I)



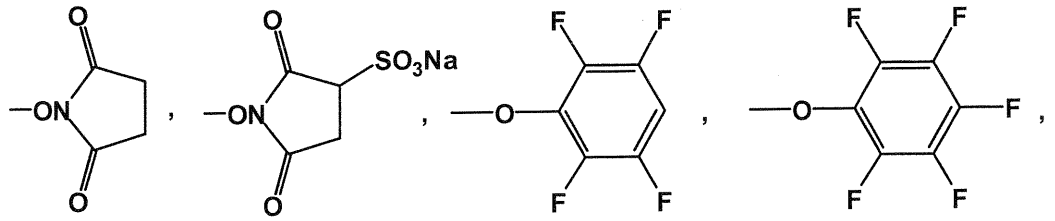
Formula (I)

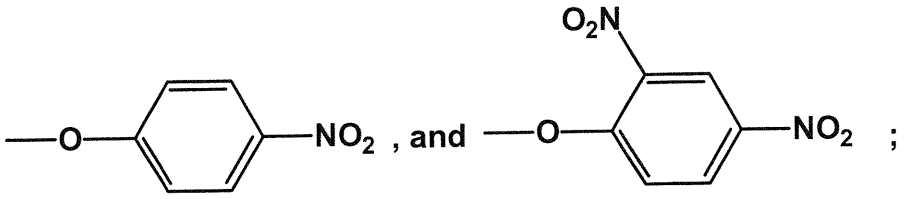
30. A process to prepare trilinker-activated esters of the formula:



wherein:

Z is selected from the group consisting of





;

Alk^1 is a branched or unbranched alkylene chain of 2 to 6 carbon atoms;

Sp^1 is selected from -S-, -O-, -CONH-, -NHCO-, and -NR'-;

Z^1 is H, or alkyl of 1 to 5 carbon atoms;

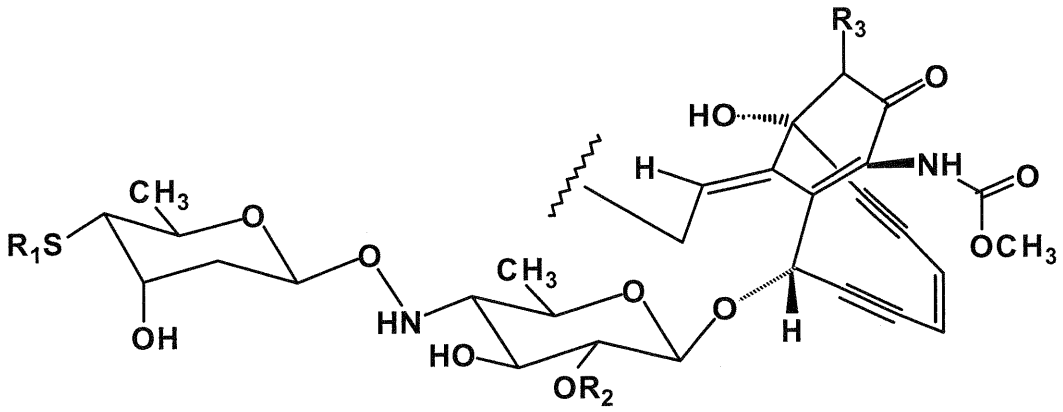
Ar is 1,2-, 1,3-, or 1,4-phenylene optionally substituted with one, two, or three groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$ or a 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3-, 2,6-, or 2,7-naphthylidene optionally substituted with one, two, three, or four groups independently selected from alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 5 carbon atoms, thioalkoxy of 1 to 4 carbon atoms, halogen, nitro, -COOR', -CONHR', $-O(CH_2)_nCOOR'$, $-S(CH_2)_nCOOR'$, $-O(CH_2)_nCONHR'$, and $-S(CH_2)_nCONHR'$;

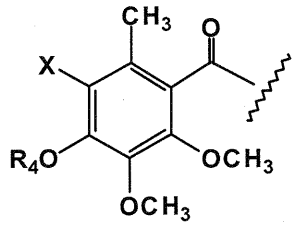
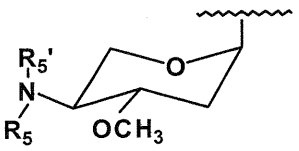
n is an integer from 0 to 5;

R' is a straight or branched alkyl of 1 to 5 carbon atoms optionally substituted by one or two groups of -OH, alkoxy of 1 to 4 carbon atoms, thioalkoxy of 1 to 4 carbon atoms;

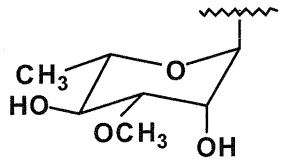
Sp is a straight or branched-chain divalent or trivalent alkyl radical of 1 to 18 carbon atoms, divalent or trivalent aryl or heteroaryl radical, divalent or trivalent cycloalkyl of 3 to 18 carbon atoms or heterocycloalkyl radical, divalent or trivalent aryl- or heteroaryl-alkyl (C_1-C_{18}) radical, divalent or trivalent cycloalkyl- or heterocyclo-alkyl-alkyl (C_1-C_{18}) radical or divalent or trivalent unsaturated alkyl radical of 2 to 18 carbon atoms, wherein heteroaryl is furyl, thienyl, N-methylpyrrolyl, pyridinyl, N-methylimidazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolyl, N-methylcarbazoyl, aminocoumarinyl, or phenazinyl and wherein if Sp is a trivalent radical, it can be additionally substituted by dialkylamino of 1 to 5 carbon atoms, alkoxy of 1 to 5 carbon atoms, hydroxy, or alkylthio of 1 to 5 carbon atoms groups;

W' is



R_1 is  or CH_3; R_2 is  or H;

R_3 is H;

R_4 is  or H;

R_5 is $-CH_3$, $-C_2H_5$, or $-CH(CH_3)2$;

X is an iodine or bromine atom;

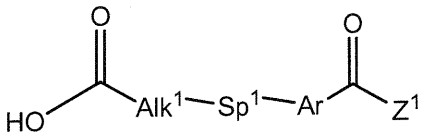
R_5' is a hydrogen or the group RCO, wherein R is hydrogen, branched or unbranched alkyl of 1 to 10 carbon atoms, alkylene of 2 to 10 carbon atoms, aryl of 6 to 11 carbon atoms, a (C_6-C_{11}) aryl-alkyl (C_1-C_5) group, or a heteroaryl or heteroaryl-alkyl (C_1-C_5) group wherein heteroaryl is defined as 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-(N-methylpyrrolyl), 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-(N-methylimidazolyl), 2-, 4-, or 5-oxazolyl, 2-, 3-, 5-, or 6-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl, or 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, all aryl and heteroaryl groups optionally

substituted by one or more hydroxy, amino, carboxy, halo, nitro, (C_1-C_3) alkoxy of 1 to 3 carbon atoms, or thioalkoxy of 1 to 5 carbon atoms;and

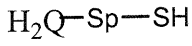
Q is selected from the group consisting of -NNHCO-, -NNHCS-, -NHNCONH-, -NNCSNH-, and -NO-;

comprising the steps of:

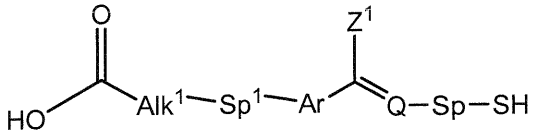
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula

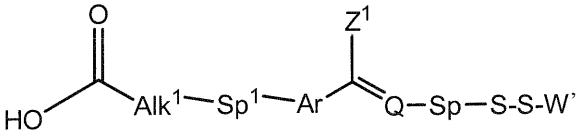


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein Alk^1, Sp^1, Ar, Z^1, Q, and Sp are as defined above, to produce a bilinker-carboxylic acid of the formula



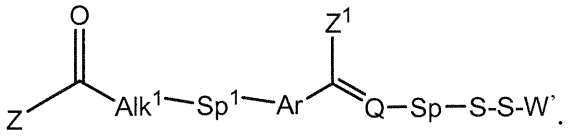
b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the bilinker-carboxylic acid from step (b) in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent to generate a bilinker-methyltrithio antitumor antibiotic of the formula

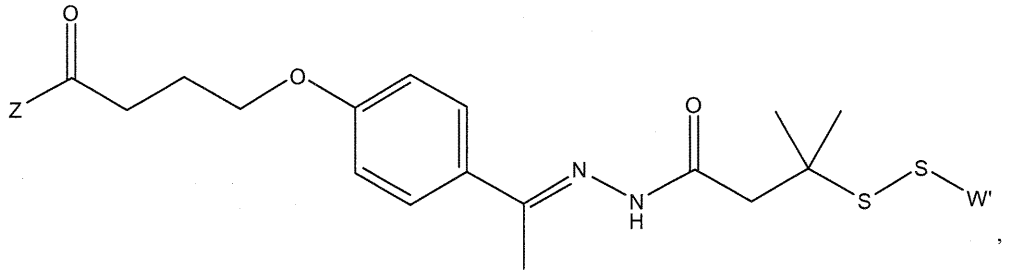


d. reacting the isolated bilinker-methyltrithio antitumor antibiotic of step (c) with N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide

(DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate a trilinker-activated ester of the formula

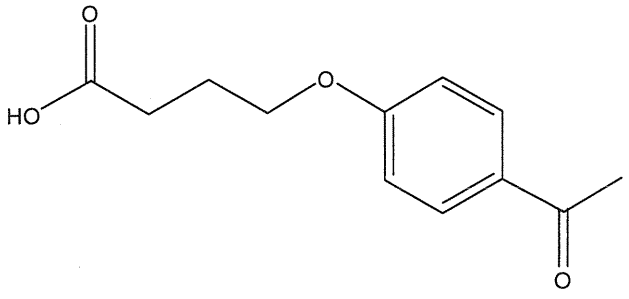


31. The method of claim 1, for preparing compounds of the following formula:

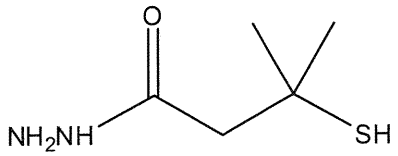


comprising the steps of:

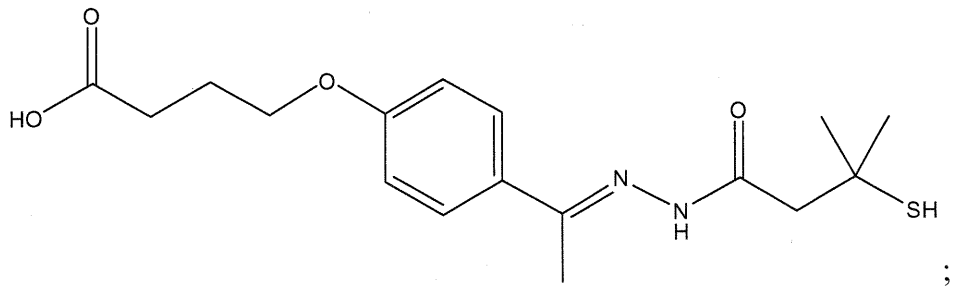
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula



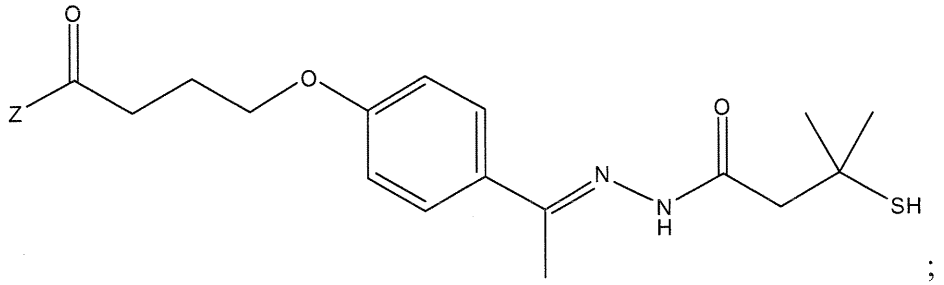
in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, to produce a bilinker-carboxylic acid of the following formula:



;

b. isolating the bilinker-carboxylic acid of step (a);

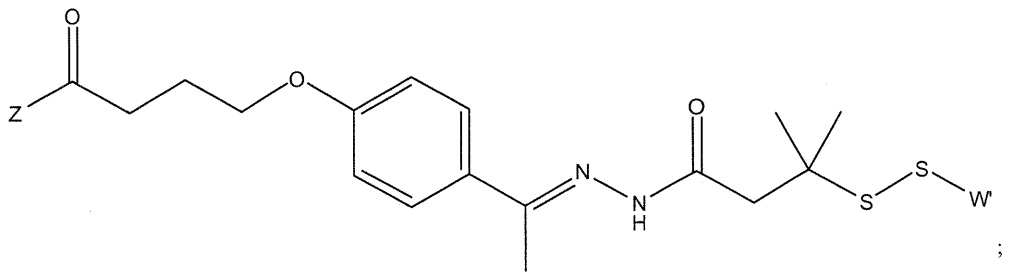
c. reacting the isolated bilinker-carboxylic acid of step (b) with N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimdyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate a trilinker-activated ester of the formula:



;

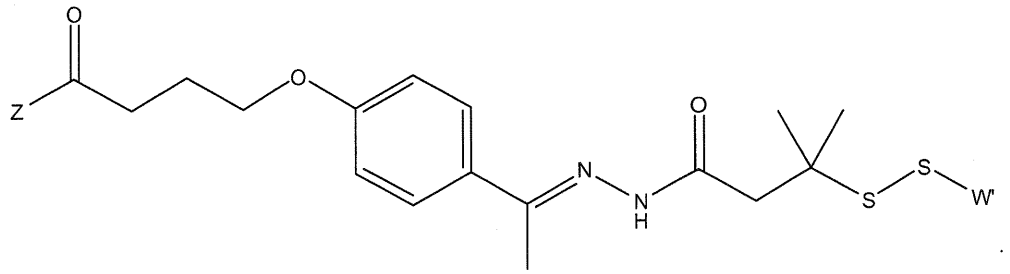
d. reacting the trilinker-activated ester formed in step c in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent to generate an activated ester of the formula below, wherein the trilinker-activated ester in step c and the CH_3-S-S-S-W' are in a ratio of 3.3:1 and the temperature of the reaction is ≤5°C and the

temperature of the reaction is ≤5°C and wherein the methyltrithio antitumor antibiotic CH_3-S-S-S-W' comprises N-acetyl-LL-E33288 γ_1^I:



;

e. isolating the activated ester of step (d) and purifying to yield antitumor antibiotics of the formula:



.

32. The method of claim 31, wherein the carboxylic acid and mercapto compound are present in a ratio of about 1.2:1.

33. The method of claim 31, wherein the alcohol solvent is methanol.

34. The method of claim 31, wherein the alkyl carboxylic acid is acetic acid.

35. The method of claim 31, wherein the isolated bilinker-carboxylic acid is reacted with N-hydroxysuccinimide in step (c).

36. The method of claim 35, wherein at least a 3 fold molar excess of N-hydroxysuccinimide is used.

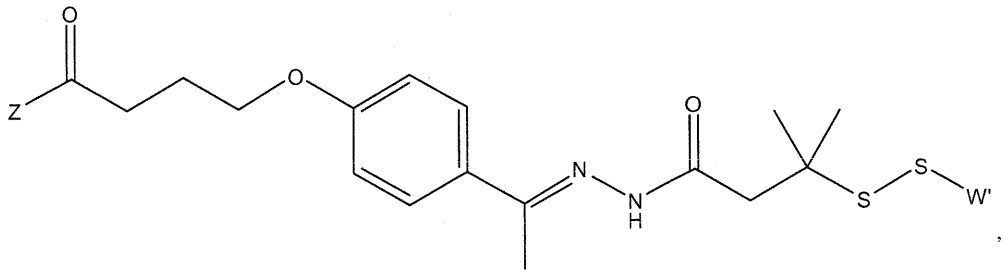
37. The method of claim 31, wherein the isolated bilinker-carboxylic acid is reacted in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) in step (c).

38. The method of claim 31, wherein the inert solvent is acetonitrile or dioxane.

39. The method of claim 31, wherein the inert organic solvent is acetonitrile.

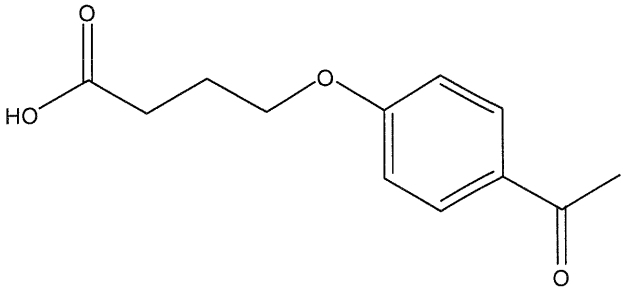
40. The method of claim 31 wherein the purifying of step (e) comprises the use of reverse phase high performance liquid chromatography having a mobile phase of about pH 7.0 to 9.0 followed by normal phase chromatography.

41. The method of claim 22, for preparing compounds of the following formula:

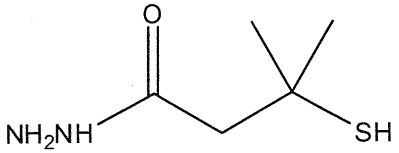


comprising the steps of:

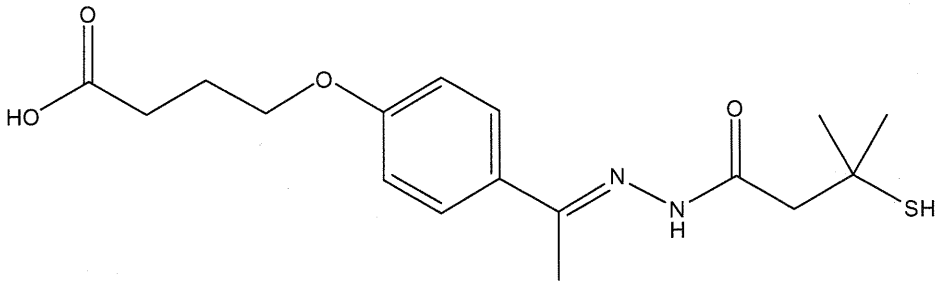
a. reacting a carboxylic acid of the formula:



with a mercapto compound of the formula:

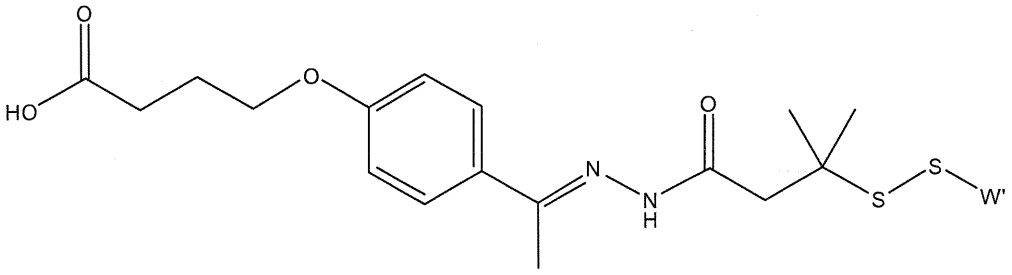


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, to produce a bilinker-carboxylic acid of the formula:

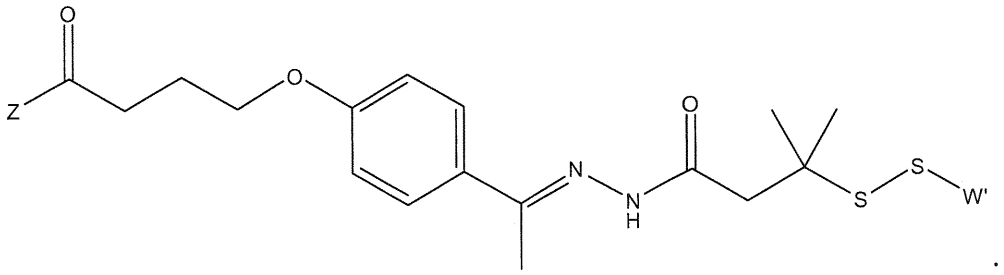


b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in the presence of a base or an organic base in an inert organic solvent wherein CH_3-S-S-S-W' comprises N-acetyl-LL-E33288 γ_1^I, to generate a bilinker-methyltrithio antitumor antibiotic of the formula:



d. reacting the compound of step (c) with N-hydroxysuccinimide, 2,3,5,6-tetrafluorophenol, pentafluorophenol, 4-nitrophenol, 2,4-dinitrophenol, or N-hydroxysulfosuccinimide in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), or N,N'-disuccinimidyl carbonate in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) and purifying to yield antitumor antibiotics of the following formula:



42. The method of claim 41, wherein the carboxylic acid and mercapto compound are present in a ratio of about 1.2:1.

43. The method of claim 4, wherein the alcohol solvent is methanol.

44. The method of claim 41, wherein the alkyl carboxylic acid is acetic acid.

45. The method of claim 41, wherein the bilinker-carboxylic acid and CH_3-S-S-S-W' in step (c) are in a ratio of 3.3:1

46. The method of claim 41, wherein the inert organic solvent is acetonitrile.

47. The method of claim 41, wherein the compound of step (c) is reacted with N-hydroxysuccinimide in step (d).

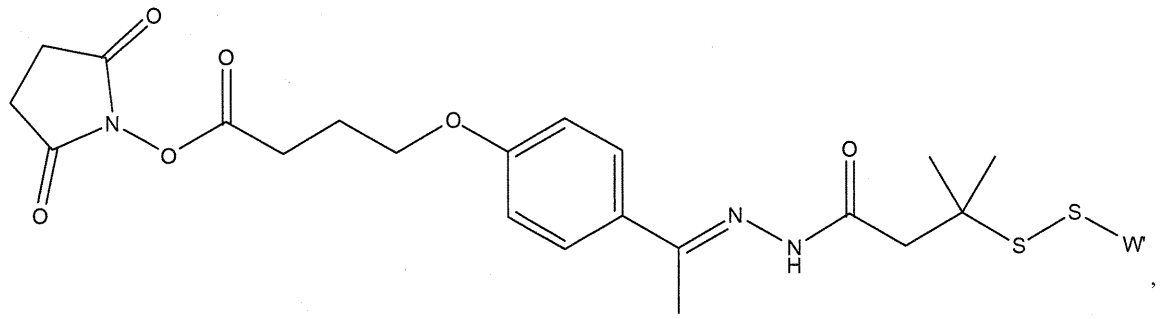
48. The method of claim 47, wherein at least a 3 fold molar excess of N-hydroxysuccinimide is used.

49. The method of claim 41, wherein the compound of step (c) is reacted in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) in step (d).

50. The method of claim 41, wherein the inert solvent is acetonitrile or dioxane.

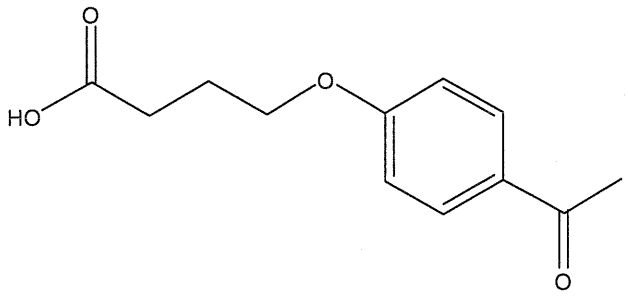
51. The method of claim 41, wherein the purifying comprises the use of reverse phase high performance liquid chromatography having a mobile phase of about pH 7.0 to 9.0 followed by normal phase chromatography.

52. The method of claim 7, for preparing compounds of the following formula:

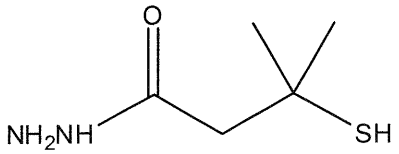


comprising the steps of:

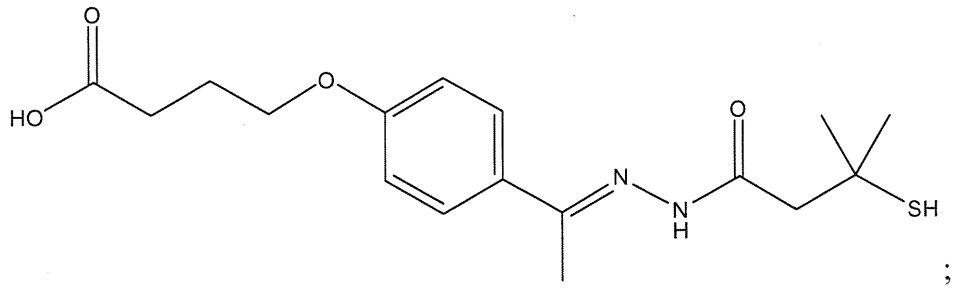
a. reacting a carboxylic acid of the formula



with a mercapto compound of the formula



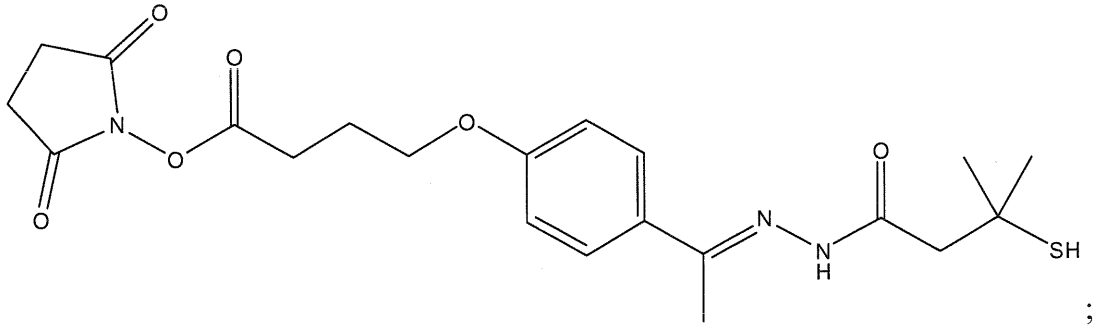
in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, to produce a bilinker-carboxylic acid of the following formula:



;

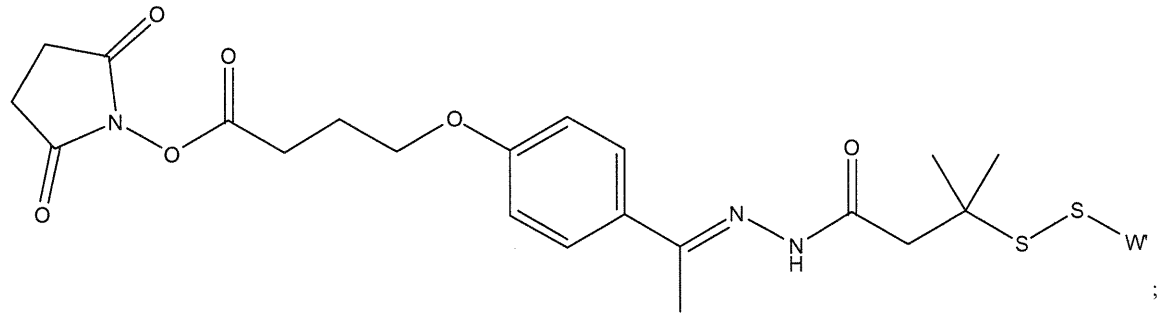
b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with at least a 3 fold molar excess of N-hydroxysuccinimide, in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate a trilinker-activated ester of the formula:

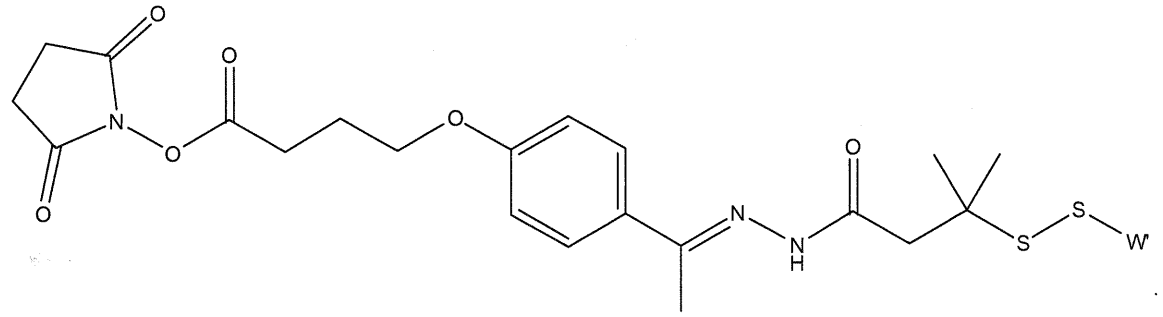


;

d. reacting the trilinker-activated ester formed in step c in the presence of a base or an organic base with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in an inert organic solvent to generate an activated ester of the formula below and the temperature of the reaction is ≤5°C and wherein the methyltrithio antitumor antibiotic CH_3-S-S-S-W' comprises N-acetyl-LL-E33288 γ_1^I:



e. isolating the activated ester of step (d) and purifying to yield antitumor antibiotics of the formula:



53. The method of claim 52, wherein the carboxylic acid and mercapto compound are present in a ratio of about 1.2:1.

54. The method of claim 52, wherein the alcohol solvent is methanol.

55. The method of claim 52, wherein the alkyl carboxylic acid is acetic acid.

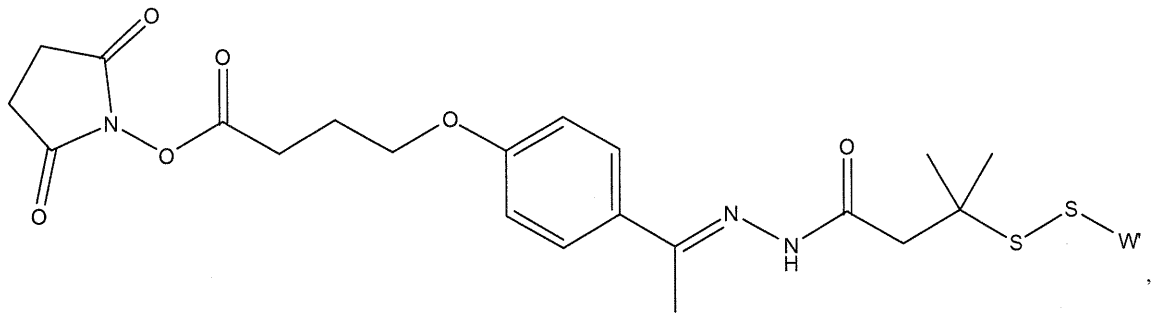
56. The method of claim 52, wherein the inert solvent is acetonitrile or dioxane.

57. The method of claim 52, wherein the trilinker-activated ester and CH_3-S-S-S-W' in step (d) are in a ratio of 3.3:1

58. The method of claim 52, wherein the inert organic solvent is acetonitrile.

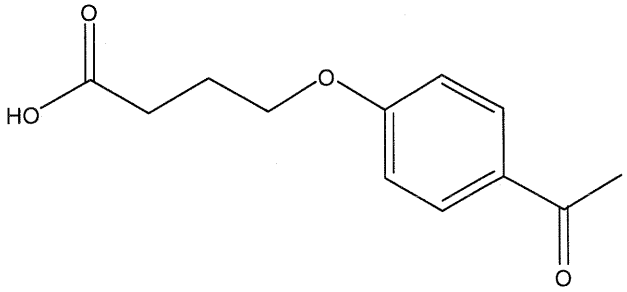
59. The method of claim 52 wherein the purifying of step (e) comprises the use of reverse phase high performance liquid chromatography having a mobile phase of about pH 7.0 to 9.0 followed by normal phase chromatography.

60. The method of claim 4, for preparing compounds of the following formula:

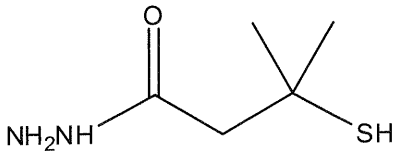


comprising the steps of:

a. reacting a carboxylic acid of the formula:

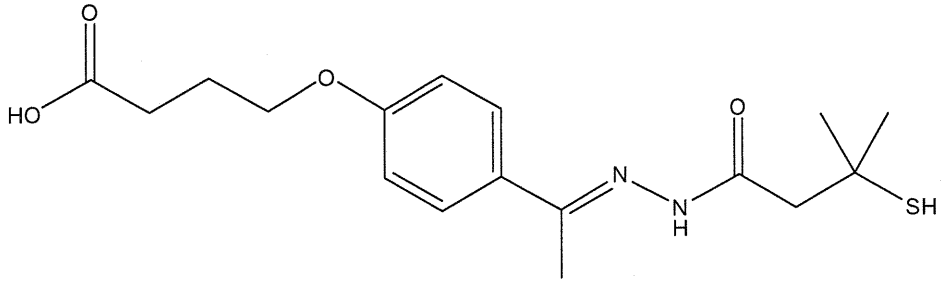


with a mercapto compound of the formula:



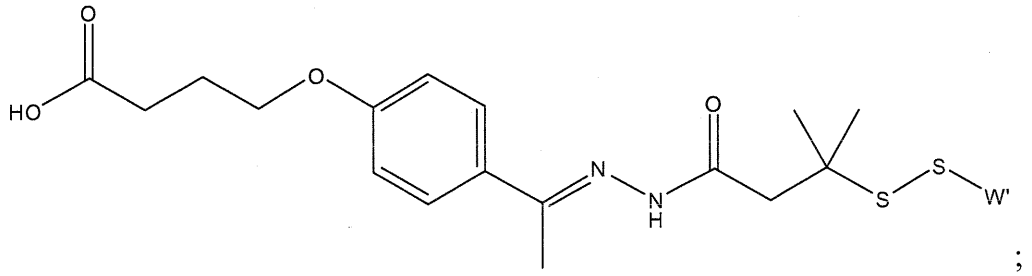
in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, wherein the mercapto compound and

carboxylic acid are present in a ratio of about 1.2:1, to produce a bilinker-carboxylic acid of the formula:



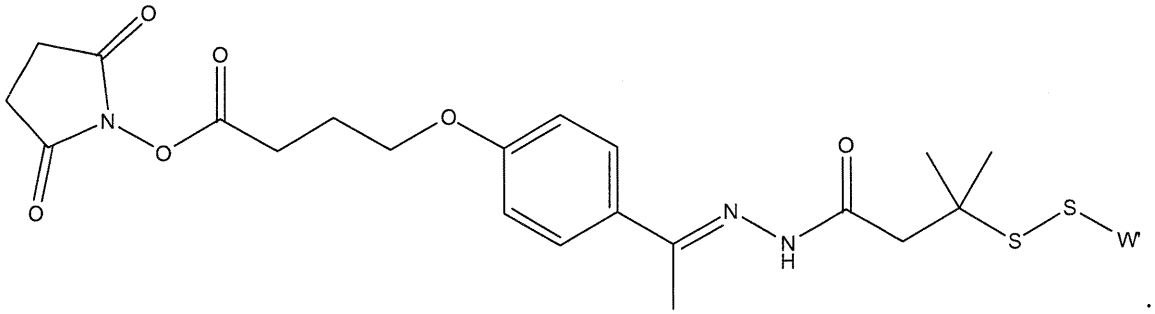
b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker-carboxylic acid of step (b) with a methyltrithio antitumor antibiotic CH_3-S-S-S-W' in the presence of a base or an organic base in an inert organic solvent wherein CH_3-S-S-S-W' comprises N-acetyl-LL-E33288γ_1^I to give a compound of formula:



;

d. reacting the compound of step (c) with at least a 3 fold molar excess of N-hydroxysuccinimide in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) and purifying to yield antitumor antibiotics of the following formula:



.

61. The method of claim 60, wherein the alcohol solvent is methanol.

62. The method of claim 60, wherein the alkyl carboxylic acid is acetic acid.

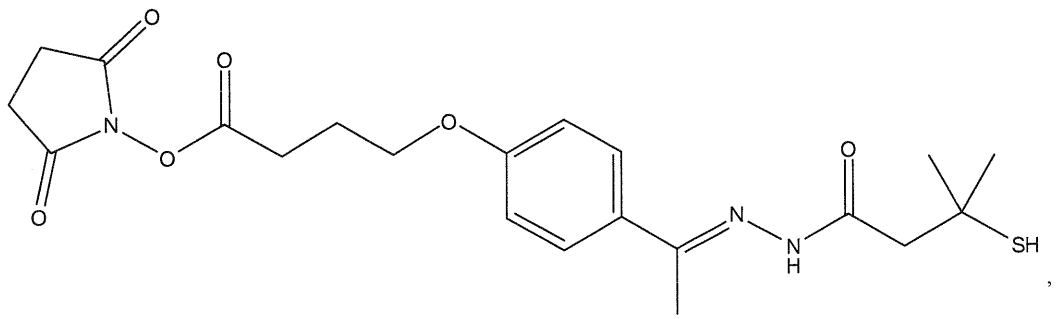
63. The method of claim 60, wherein the bilinker-carboxylic acid and CH_3-S-S-S-W' in step (c) are in a ratio of 3.3:1

64. The method of claim 60, wherein the inert organic solvent is acetonitrile.

65. The method of claim 60, wherein the inert solvent is acetonitrile or dioxane.

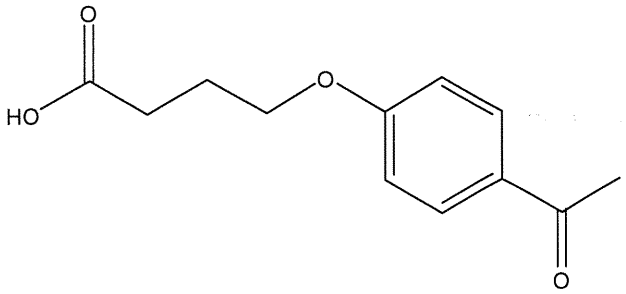
66. The method of claim 60, wherein the purifying comprises the use of reverse phase high performance liquid chromatography having a mobile phase of about pH 7.0 to 9.0 followed by normal phase chromatography.

67. The method of claim 24, for preparing trifunctional linker intermediates of the following formula:

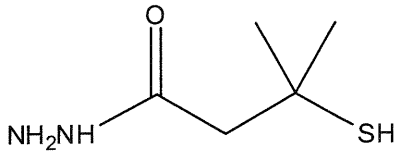


comprising the steps of:

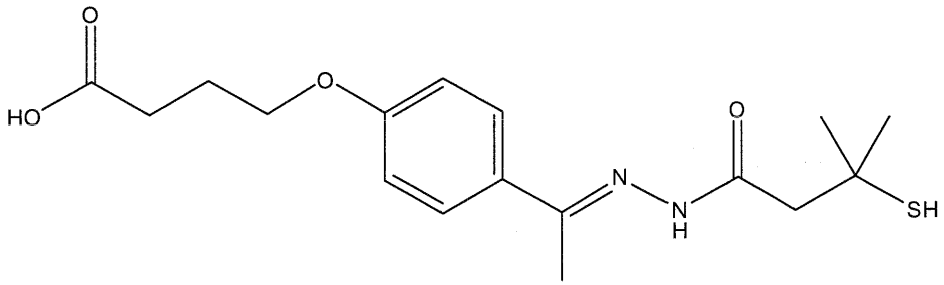
a. reacting a carboxylic acid of the formula:



with a mercapto compound of the formula:

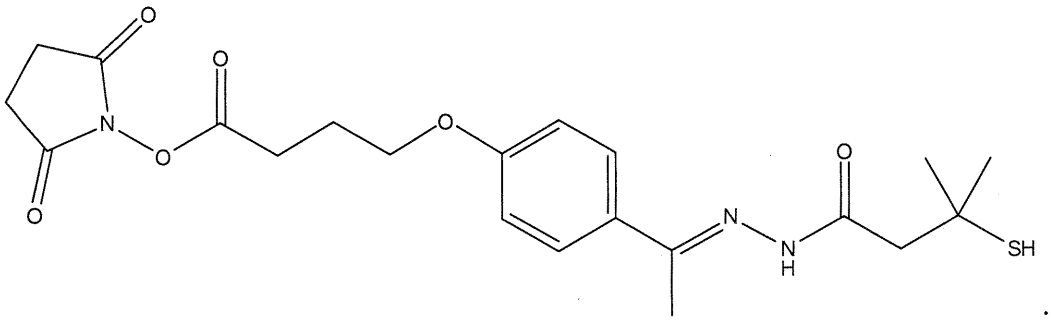


in an alcohol solvent in the presence of an alkyl carboxylic acid, alk^2CO_2H where alk^2 is 1 to 4 carbon atoms at about 20° to 70°C for about 1 to 24 hours, to produce a bilinker-carboxylic acid of the formula:



b. isolating the bilinker-carboxylic acid of step (a);

c. reacting the isolated bilinker of step (b) with N-hydroxysuccinimide in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) in an inert solvent containing 0-50% N,N-dimethylformamide (DMF) to generate trifunctional linker intermediates of the formula:


O
O
N
O
O
O
N
N
H
O
SH