SCH_2OMe); or R^7 together with R^5 or R^6 and the carbons to which they are attached, form an optionally substituted ring (e.g., a cyclopropyl ring);

R^{7a} H or OH;

R^8 is OH or a leaving group (e.g., a mesylate, or halo); or R^8 taken together with R^{9a} and the carbons to which they are attached form a ring;

R^{9a} is an activated alkyl (e.g.CH_2I); or R^{9a} taken together with R^8 and the carbons to which they are attached form a ring; or R^{9a}, together with R^{9b} and the carbon to which it is attached, forms a ring (forming a spirocyclic ring);

R^{9b} is OH, OC(O)alkyl (e.g., Oacyl), OC(O)Oalkyl (e.g., OC(O)OMe), or OC(O)cycloalkyl; or R^{9b}, taken together with R^1 and the carbons to which they are attached, form a ring; or R^{9b}, together with R^{9a} and the carbon to which it is attached, forms a ring (forming a spirocyclic ring);

R^{10} is OH, OC(O)aryl (e.g., wherein aryl is optionally substituted for example with halo, alkoxy, or N_3) or OC(O)alkyl; or R^{10} taken together with R^1 or R^{11} and the carbons to which they are attached, forms a ring;

R^{11} H or OH; or R^{11} taken together with R^{10} or R^{12} and the carbons to which they are attached, forms a ring;

R^{12} is H, or OH; or R^{12} taken together with R^{11} and the carbons to which they are attached, forms a ring;

each R^{1a} is independently halo (e.g., fluro), alkyl (e.g., methyl)

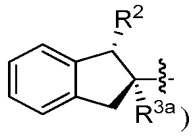
each R^{2a} and R^{2b} is independently H, C(O)aryl (e.g, C(O)phenyl), C(O)alkyl (e.g., acyl), C(O)H, C(O)Oalkyl; wherein C(O)aryl (e.g, C(O)phenyl), C(O)alkyl (e.g., acyl), and C(O)Oalkyl is each optionally further substituted, for example, with a substituent as descdribed in R^{1a}; and

R^{2c} is H or C(O)NHalkyl.

In some embodiments, R^1 is phenyl (e.g., optionally substituted for example with halo such as fluoro). In some embodiments, R^1 is heteroaryl, for example, furanyl, thiophenyl, or pyridyl (e.g., an optionally substituted pyridyl).

In some embodiments, R^1 is alkyl, e.g., butyl such as isobutyl or tert-butyl.

In some embodiments, R^1 is heterocyclcoalkyl (e.g., epoxyl optionally substituted, for example, with one or more alkyl groups such as methyl).

In some embodiments, R^1, taken together with R^{3b} and the carbons to which they are attached form a bicyclic ring system (e.g., ).

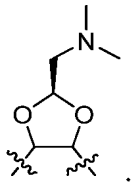
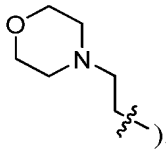
In some embodiments, R^1, taken together with R^{10} and the carbons to which they are attached, form a ring, e.g., a mono- or bi-cyclic ring system).

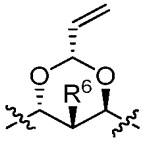
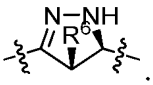
In some embodiments, R^1, taken together with R^{9b} and the carbons to which they are attached, form a ring, e.g., a mono- or bi-cyclic ring system).

In some embodiments, R^2 is $NR^{2a}R^{2b}$. In some embodiments, at least one of R^{2a} or R^{2b} is H. In some embodiments, R^{2a} is H and R^{2b} is C(O)aryl (e.g, C(O)phenyl), C(O)alkyl (e.g., acyl), C(O)H, or C(O)Oalkyl. In some embodiments, R^2 is NHC(O)aryl or NHC(O)Oalkyl.

In some embodiments, R^{3a} is OH. In some embodiments, R^{3a} is Opolymer. In some embodiments, polymer is polyglutamic acid. In some embodiments, R^{3a} is $OC(O)C_{21}$alkenyl.

In some embodiments, one of R^{3a} or R^{3b} is H and the other of R^{3a} or R^{3b} is OH.

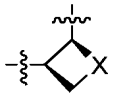
In some embodiments, R^4 is OAcyl. In some embodiments, R^4 is OH. In some embodiments, R^4 is methoxy. In some embodiments, R^4 together with R^5 and the carbons to which they are attached forms  . In some embodiments, R^4, together with the carbon to which it is attached, forms  . In some embodiments, R^4, together with the carbon to which it is attached, forms an oxo. In some embodiments, R^4 is heterocycloalkylalkyl (e.g., ).

In some embodiments, R^5, together with the carbon to which it is attached, forms an oxo. In some embodiments, R^5 together with R^7 and the carbons to which they are attached forms  or  .

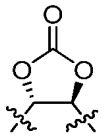
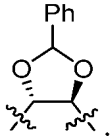
In some embodiments, R^6 is methyl. In some embodiments, R^6 together with R^7 and the carbons to which they are attached form a ring (e.g., cyclopropyl).

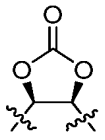
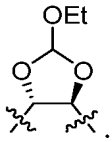
In some embodiments, R^7 is OH. In some embodiments, R^7 is H. In some embodiments, when R^7 is H, R^{7a} is OH.

In some embodiments, R^{7a} is H. In some embodiments, R^{7a} is OH.

In some embobodiments, R^8 together with R^{9a} and the carbons to which they are attached form  , wherein X is O, S, Se, or NR^{8a} (e.g., O), wherein R^{8a} is H, alkyl, arylalkyl (e.g., benzyl), C(O)alkyl, or C(O)H.In some embobodiments, R^8 together with R^{9a} and the carbons to which they are attached form a cyclopropyl ring.

In some embodiments, R^{9b} is OAc.

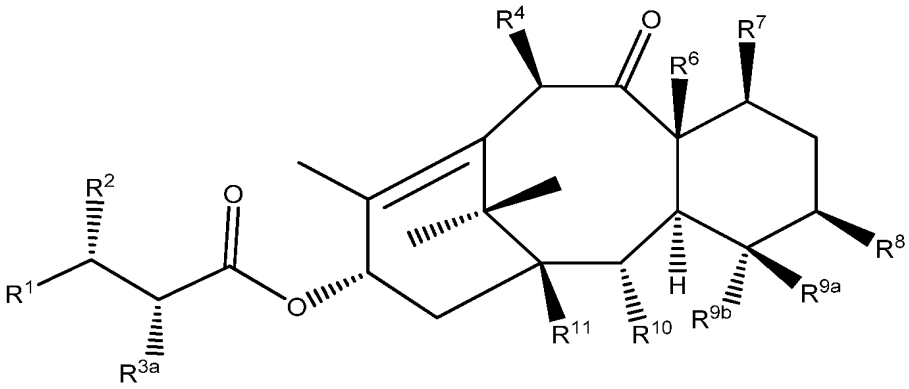
In some embodiments, R^{10} is OC(O)phenyl. In some embodiments, R^{10} taken together with R^{11} and the carbon to which it is attached, forms a ring such as  or  .

In some embodiments, R^{11} is OH. In some embodiments, R^{11} taken together with R^{12} and the carbon to which it is attached, forms a ring such as  or  .

In some embodiments, R^{12} is H.

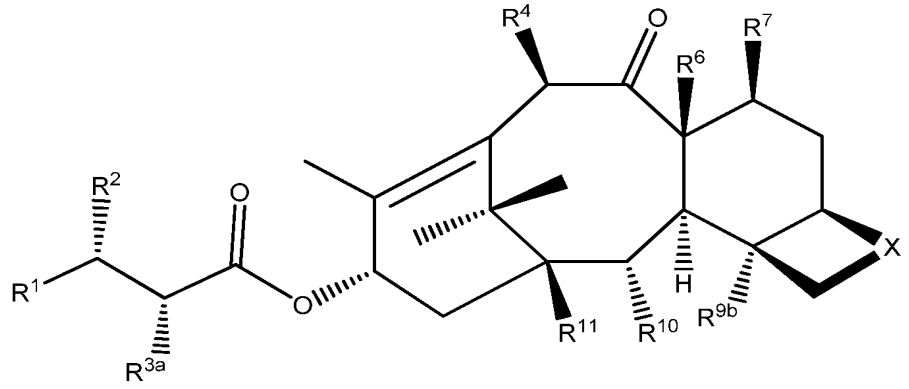
In some embodiments, the variables defined above are chosen so as to form docetaxel, paclitaxel, larotaxel, or cabazitaxel or a structural analogue therof.

In some embodiments, the taxane is a compound of formula (Xa)



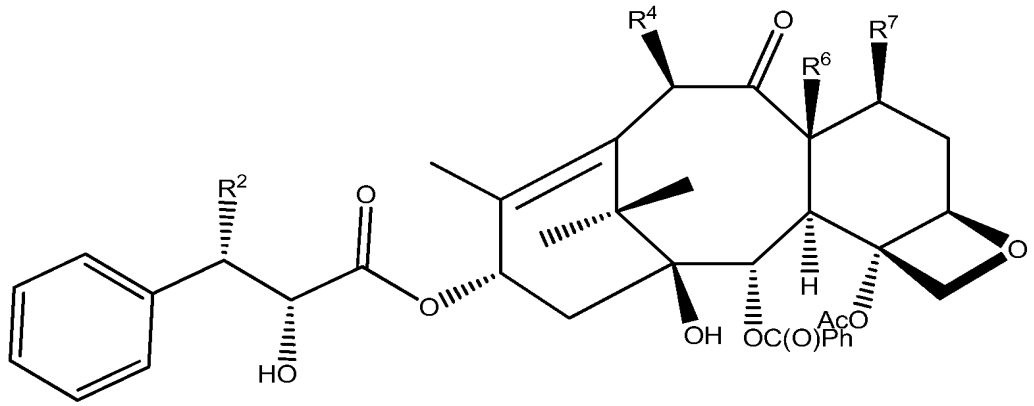
formula (Xa).

In some embodiments, the taxane is a compound of formula (Xb)



formula (Xb).

In some embodiments, the compound is a compound of formula Xc



(Xc).

In some embodiments, R^2 is NHC(O)aryl or NHC(O)Oalkyl.

In some embodiments, R^4 is OH or OAc.

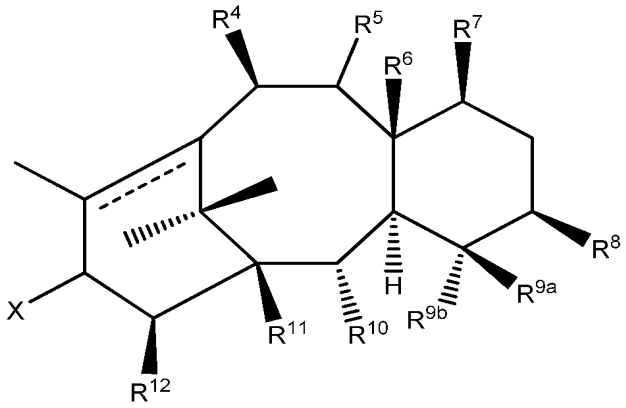
In some embodiments, R^6 is methyl.

In some embodiments, R^7 is OH or OMe.

In some embodiments, R^6 and R^7, together with the carbons to which they are attached, form a ring.

In some embodiments, the variables defined above are chosen so as to form docetaxel, paclitaxel, larotaxel, or cabazitaxel or a structural analogue therof.

In one embodiment, the taxane is a compound of formula (XI)



formula (XI)

wherein

X is OH, oxo (i.e., when forming a double bond with the carbon to which it is attached), alkoxy, OC(O)alkyl (e.g., Oacyl), or OPg;

R^4 is OH, alkoxy (e.g., methoxy), OC(O)alkyl (e.g., Oacyl), OC(O)cycloalkyl, OPg, heterocycloalkylalkyl; or R^4 together with R^5 and the carbons to which they are attached, form an optionally substituted ring; or R^4, together with the carbon to which it is attached, forms a ring (forming a spirocyclic ring) or an oxo;

R^5 is OH, OC(O)alkyl (e.g., Oacyl), or OPg; or R^5 together with R^4 and the carbons to which they are attached, form an optionally substituted ring; or R^5, together with the carbon to which it is attached, forms an oxo;

R^6 is alkyl (e.g., methyl);

R^7 is H, OH, alkoxy (e.g., methoxy), OC(O)alkyl (e.g., OAc); OPg (e.g., OTES or OTroc), or OC(O)alkenyl (wherein alkenyl is substituted, e.g., with aryl (e.g., napthyl) (e.g., OC(O)CHCHnapthyl), or R^7, together with the carbon to which it is attached, forms an oxo;

R^8 is OH, optionally substituted OC(O)arylalkyl (e.g., OC(O)CHCHphenyl), $OC(O)(CH_2)_{1\text{-}3}$aryl (e.g., $OC(O)CH_2CH_2$phenyl), or a leaving group (e.g., a mesylate, or halo); or R^8 taken together with R^{9a} and the carbons to which they are attached form a ring;

R^{9a} is an activated alkyl (e.g.CH_2I); or R^{9a} taken together with R^8 and the carbons to which they are attached form a ring; or R^{9a}, together with R^{9b} and the carbon to which

it is attached, forms a ring (forming a spirocyclic ring)or R^{9a} taken together with R^{9b} and the carbon to which they are attached form an alylenyl;

R^{9b} is OH, alkoxy, OC(O)alkyl (e.g., Oacyl), OC(O)Oalkyl (e.g., OC(O)OMe), OC(O)cycloalkyl, or OPg; or R^{9b}, together with R^{9a} and the carbon to which it is attached, forms a ring (forming a spirocyclic ring); or R^{9b} taken together with R^{9a} and the carbon to which they are attached form an alylenyl;

R^{10} is OH, OC(O)aryl (e.g., wherein aryl is optionally substituted for example with halo, alkoxy, or N_3) or OC(O)alkyl; or R^{10} taken together with R^{11} and the carbons to which they are attached, forms a ring;

R^{11} H, OH; or R^{11} taken together with R^{10} or R^{12} and the carbons to which they are attached, forms a ring;

R^{12} is H, OH, or OC(O)alkyl, wherein alkyl is substituted with 1-4 substituents; or R^{12} taken together with R^{11} and the carbons to which they are attached, forms a ring;

Pg is a protecting group for a heteroatom such as O or N (e.g., Bn, Bz, TES, TMS, DMS, Troc, or Ac); and

 is a single or double bond

In some embodiments, X is OH. In some embodiments, X is oxo. In some embodiments, X is OAc.

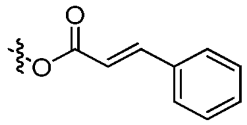
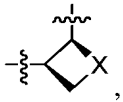
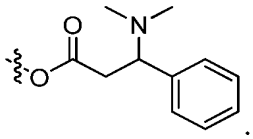
In some embodiments,  is a single bond.

In some embodiments, R^4 is OAcyl. In some embodiments, R^4 is OH. In some embodiments, R^4 is methoxy. In some embodiments, R^4 is OPg (e.g., OTroc or OAc). In some embodiments, R^4 together with R^5 and the carbons to which they are attached forms a ring.

In some embodiments, R^5, together with the carbon to which it is attached, forms an oxo. In some embodiments, R^5 is OH or OPg.

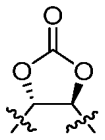
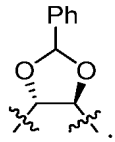
In some embodiments, R^6 is methyl.

In some embodiments, R^7 is H. In some embodiments, R^7 is OH or OPg. In some embodiments, R^7, together with the carbon to which it is attached, forms an oxo.

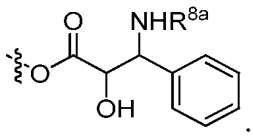
In some embodiments, R^8 is  . In some embodiments, R^8 together with R^{9a} and the carbons to which they are attached form  , wherein X is O, S, Se, or NR^{8a} (e.g., O), wherein R^{8a} is H, alkyl, arylalkyl (e.g., benzyl), C(O)alkyl, Pg, or C(O)H. In some embodiments, R^8 together with R^{9a} and the carbons to which they are attached form a cyclopropyl ring. In some embodiments,  .

In some embodiments, R^{9a} and R^{9b}, together with the carbon to which they are attached form  .

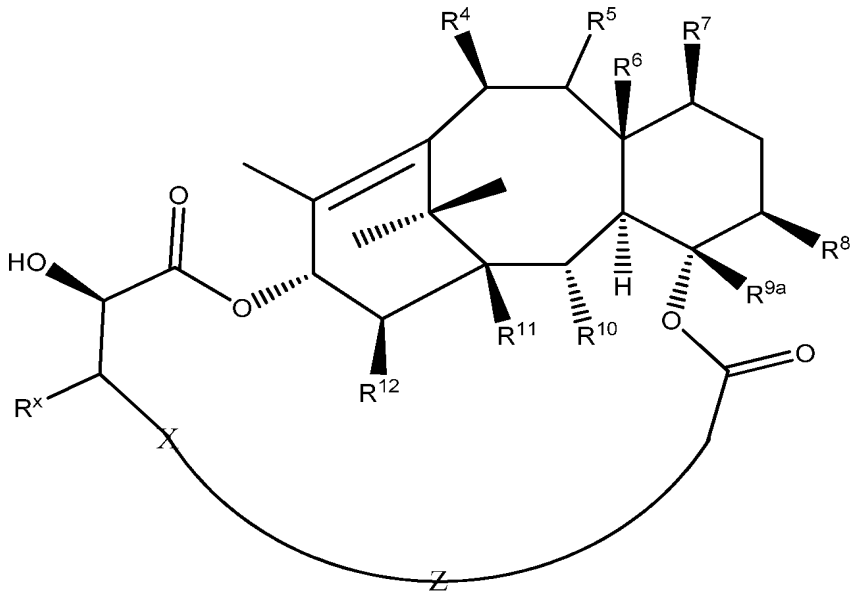
In some embodiments, R^{9b} is OAc.

In some embodiments, R^{10} is OC(O)phenyl. In some embodiments, R^{10} taken together with R^{11} and the carbon to which it is attached, forms a ring such as  or  .

In some embodiments, R^{11} is H. In some embodiments, R^{11} is OH.

In some embodiments, R^{12} is H. In some embodiments, R^{12} is OH. In some embodiments, R^{12} is  .

In one embodiment, the taxane is a compound of formula (XIIa)



formula (XIIa)

wherein

Z forms a ring by linking O with the atom X attached to $-CHR^x$;

R^4 is OH, alkoxy (e.g., methoxy), OC(O)alkyl (e.g., Oacyl), OC(O)cycloalkyl, heterocycloalkylalkyl; or R^4 together with R^5 and the carbons to which they are attached, form an optionally substituted ring; or R^4, together with the carbon to which it is attached, forms a ring (forming a spirocyclic ring) or an oxo;

R^5 is OH, OC(O)alkyl (e.g., Oacyl); or R^5 together with R^4 or R^7 and the carbons to which they are attached, form an optionally substituted ring; or R^5, together with the carbon to which it is attached, forms a ring (forming a spirocyclic ring) or an oxo;

R^6 is alkyl (e.g., methyl); or R^6 together with R^7 and the carbons to which they are attached, form an optionally substituted ring (e.g., a cyclopropyl ring);

R^7 is H, OH, alkoxy (e.g., methoxy), OC(O)Oalkyl, OalkylSalkyl (e.g., OCH_2SMe), or OalkylOalkyl (e.g., OCH_2OMe), thioalkyl, SalkylOalkyl (e.g., SCH_2OMe); or R^7 together with R^5 or R^6 and the carbons to which they are attached, form an optionally substituted ring (e.g., a cyclopropyl ring);

R^{7a} H or OH;

R^8 is OH or a leaving group (e.g., a mesylate, or halo); or R^8 taken together with R^{9a} and the carbons to which they are attached form a ring;

R^{9a} is an activated alkyl (e.g.CH_2I); or R^{9a} taken together with R^8 and the carbons to which they are attached form a ring;

R^{10} is OH, OC(O)aryl (e.g., wherein aryl is optionally substituted for example with halo, alkoxy, or N_3) or OC(O)alkyl; or R^{10} taken together with R^1 or R^{11} and the carbons to which they are attached, forms a ring;

R^{11} H or OH; or R^{11} taken together with R^{10} or R^{12} and the carbons to which they are attached, forms a ring;

R^{12} is H, or OH; or R^{12} taken together with R^{11} and the carbons to which they are attached, forms a ring;

R^x is NHPg or aryl;

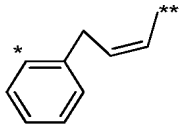
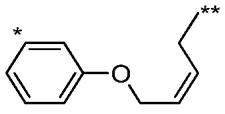
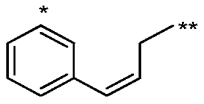
X is C or N; and

Pg is a protecting group for a heteroatom such as O or N (e.g., Bn, Bz, TES, TMS, DMS, Troc, Boc or Ac).

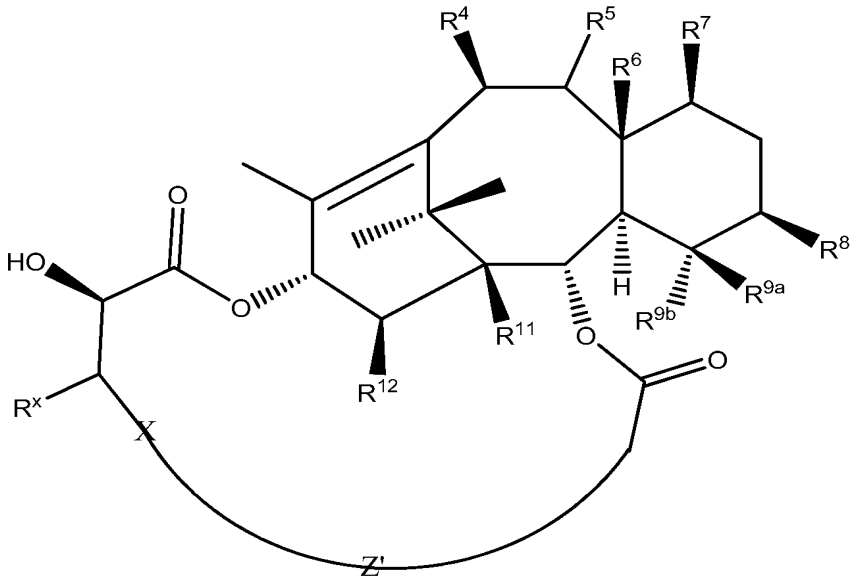
In some embodiments, Z includes one or more phenyl rings.

In some embodiments, Z includes one or more double bonds.

In some embodiments, Z includes one or more heteroatoms.

In some embodiments, Z is  , wherein * indicates the atom X attached to CHR^x and ** indicates the carbon attached to C(O). In some embodiments, Z is  , wherein * indicates the atom X attached to CHR^x and ** indicates the carbon attached to C(O). In some embodiments, Z is  , wherein * indicates the atom X attached to CHR^x and ** indicates the carbon attached to C(O).

In some embodiments, the taxane is a compound of formula (XIIb)



formula(XIIb)

wherein

Z' forms a ring by linking O with the atom X, which is attached to $-CHR^x$;

R^4 is OH, alkoxy (e.g., methoxy), OC(O)alkyl (e.g., Oacyl), OC(O)cycloalkyl, heterocycloalkylalkyl; or R^4 together with R^5 and the carbons to which they are attached, form an optionally substituted ring; or R^4, together with the carbon to which it is attached, forms a ring (forming a spirocyclic ring) or an oxo;

R^5 is OH, OC(O)alkyl (e.g., Oacyl); or R^5 together with R^4 or R^7 and the carbons to which they are attached, form an optionally substituted ring; or R^5, together with the carbon to which it is attached, forms a ring (forming a spirocyclic ring) or an oxo;

R^6 is alkyl (e.g., methyl); or R^6 together with R^7 and the carbons to which they are attached, form an optionally substituted ring (e.g., a cyclopropyl ring);

R^7 is H, OH, alkoxy (e.g., methoxy), OC(O)Oalkyl, OalkylSalkyl (e.g., OCH_2SMe), or OalkylOalkyl (e.g., OCH_2OMe), thioalkyl, SalkylOalkyl (e.g., SCH_2OMe); or R^7 together with R^5 or R^6 and the carbons to which they are attached, form an optionally substituted ring (e.g., a cyclopropyl ring);

R^{7a} H or OH;

R^8 is OH or a leaving group (e.g., a mesylate, or halo); or R^8 taken together with R^{9a} and the carbons to which they are attached form a ring;

R^{9a} is an activated alkyl (e.g.CH_2I); or R^{9a} taken together with R^8 and the carbons to which they are attached form a ring; or R^{9a}, together with R^{9b} and the carbon to which it is attached, forms a ring (forming a spirocyclic ring);

R^{9b} is OH, OC(O)alkyl (e.g., Oacyl), OC(O)Oalkyl (e.g., OC(O)OMe), or OC(O)cycloalkyl; or R^{9b}, together with R^{9a} and the carbon to which it is attached, forms a ring (forming a spirocyclic ring);

R^{11} H or OH; or R^{11} taken together with R^{10} or R^{12} and the carbons to which they are attached, forms a ring;

R^{12} is H, or OH; or R^{12} taken together with R^{11} and the carbons to which they are attached, forms a ring;

R^x is NHPg or aryl;

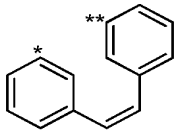
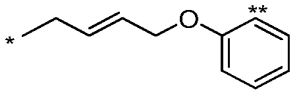
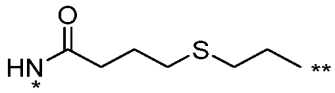
X is C or N; and

Pg is a protecting group for a heteroatom such as O or N (e.g., Bn, Bz, TES, TMS, DMS, Troc, Boc or Ac).

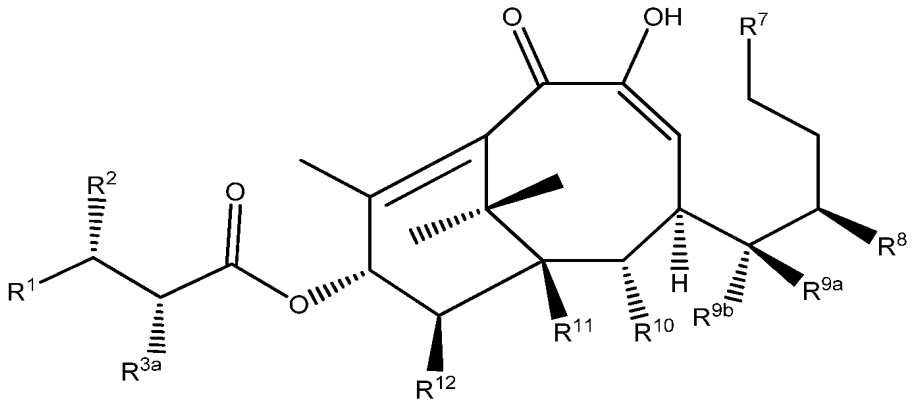
In some embodiments, Z' includes one or more phenyl rings.

In some embodiments, Z' includes one or more double bonds.

In some embodiments, Z' includes one or more heteroatoms.

In some embodiments, Z' is  , wherein * indicates the atom X attached to CHR^x and ** indicates the carbon attached to C(O). In some embodiments, Z' is  , wherein * indicates the atom X attached to CHR^x and ** indicates the carbon attached to C(O). In some embodiments, Z' is  , wherein * indicates the atom X attached to CHR^x and ** indicates the carbon attached to C(O).

In some embodiments, the taxane is a compound of formula (XIII)



formula (XIII)

wherein;

R^1 is aryl (e.g., phenyl), heteroaryl (e.g., furanyl, thiophenyl, or pyridyl), alkyl (e.g., butyl such as isobutyl or tert-butyl), cycloalyl (e.g., cyclopropyl), heterocycloalkyl (epoxyl), or R^1, when taken together with one of R^{3b}, R^{9b}, or R^{10} and the carbons to which they are attached, forms a mono- or bi-cyclic ring system; wherein R^1 is optionally substituted with 1-3 R^{1a};

R^2 is $NR^{2a}R^{2b}$ or OR^{2c};

R^{3a} is H, OH, Opolymer, OC(O)alkyl, or OC(O)alkenyl;

R^7 is OH, alkoxy (e.g., methoxy), OC(O)Oalkyl;

R^8 is OH or a leaving group (e.g., a mesylate, or halo); or R^8 taken together with R^{9a} and the carbons to which they are attached form a ring;

R^{9a} is an activated alkyl (e.g.CH_2I); or R^{9a} taken together with R^8 and the carbons to which they are attached form a ring; or R^{9a}, together with R^{9b} and the carbon to which it is attached, forms a ring (forming a spirocyclic ring)

R^{9b} is OH, OC(O)alkyl (e.g., Oacyl), OC(O)Oalkyl (e.g., OC(O)OMe), or OC(O)cycloalkyl; or R^{9b}, taken together with R^1 and the carbons to which they are attached, form a ring; or R^{9b}, together with R^{9a} and the carbon to which it is attached, forms a ring (forming a spirocyclic ring);

R^{10} is OH, OC(O)aryl (e.g., wherein aryl is optionally substituted for example with halo, alkoxy, or N_3) or OC(O)alkyl; or R^{10} taken together with R^1 or R^{11} and the carbons to which they are attached, forms a ring;

R^{11} H or OH; or R^{11} taken together with R^{10} or R^{12} and the carbons to which they are attached, forms a ring;

R^{12} is H, or OH; or R^{12} taken together with R^{11} and the carbons to which they are attached, forms a ring;

each R^{1a} is independently halo (e.g., fluro), alkyl (e.g., methyl)

each R^{2a} and R^{2b} is independently H, C(O)aryl (e.g, C(O)phenyl), C(O)alkyl (e.g., acyl), C(O)H, C(O)Oalkyl; wherein C(O)aryl (e.g, C(O)phenyl), C(O)alkyl (e.g., acyl), and C(O)Oalkyl is each optionally further substituted, for example, with a substituent as descdribed in R^{1a};

R^{2c} is H or C(O)NHalkyl; and

R^{8a} is H, alkyl, arylalkyl (e.g., benzyl), C(O)alkyl, or C(O)H.

In some embodiments, R^7 is OH.

In some preferred embodiments, the taxane is docetaxel, larotaxel, milataxel, TPI-287, TL-310, BMS-275183, BMS-184476, BMS-188797, ortataxel, tesetaxel, or cabazitaxel. Additional taxanes are provided in Fan, Mini-Reviews in Medicinal Chemistry, 2005, 5, 1-12; Gueritte, Current Pharmaceutical Design, 2001, 7, 1229-1249; Kingston, J. Nat. Prod., 2009, 72, 507-515; and Ferlini, Exper Opin. Invest. Drugs, 2008, 17, 3, 335-347; the contents of each of which is incorporated herein by reference in its entirety.

Exemplary CDP-taxane conjugates

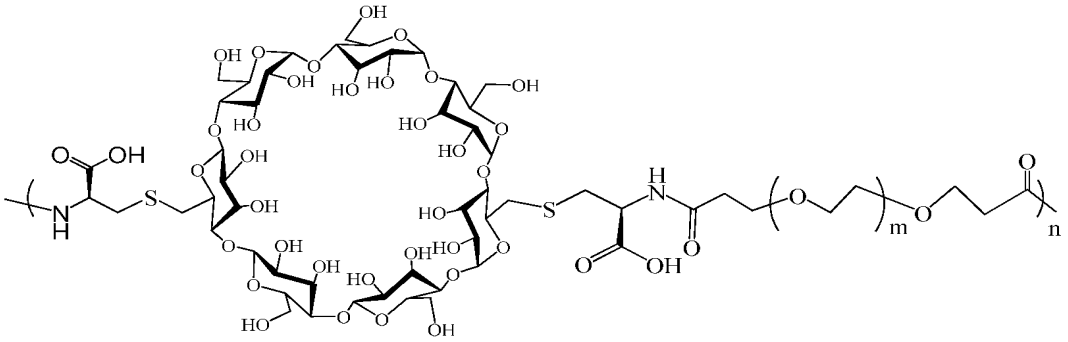
CDP-taxane conjugates can be made using many different combinations of components described herein. For example, various combinations of cyclodextrins (e.g., beta-cyclodextrin), comonomers (e.g., PEG containing comonomers), linkers linking the cyclodextrins and comonomers, and/or linkers tethering the taxane to the CDP are described herein.

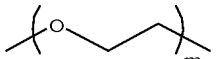
Fig. 2 is a table depicting examples of different CDP-taxane conjugates. The CDP-taxane conjugates in Fig. 2 are represented by the following formula:

CDP-CO-ABX-Taxane

In this formula,

CDP is the cyclodextrin-containing polymer shown below (as well as in Figure 1):



wherein the group  has a Mw of 3.4kDa or less and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. Note that the taxane is conjugated to the CDP through the carboxylic acid moieties of the polymer as provided above. Full loading of the taxane onto the CDP is not required. In some embodiments, at least one, e.g., at least 2, 3, 4, 5, 6 or 7, of the carboxylic acid moieties remains unreacted with the taxane after conjugation (e.g., a plurality of the carboxylic acid moieties remain unreacted).

CO represents the carbonyl group of the cysteine residue of the CDP;

A and B represent the link between the CDP and the taxane. Position A is either a bond between linker B and the cysteine acid carbonyl of CDP (represented as a "-" in Fig. 2), a bond between the taxane and the cysteine acid carbonyl of CDP (represented as a "-"in Fig. 2) or depicts a portion of the linker that is attached via a bond to the cysteine acid carbonyl of the CDP. Position B is either not occupied (represented by "-" in Fig. 2) or represents the linker or the portion of the linker that is attached via a bond to the taxane; and

X represents the heteroatom to which the linker is coupled on the taxane.

As provided in Fig. 2, the column with the heading "Taxane" indicates which taxane is included in the CDP-taxane conjugate.

The three columns on the right of the table in Fig. 2 indicate respectively, what, if any, protecting groups are used to protect the indicated position of the taxane, the process for producing the CDP-taxane conjugate, and the final product of the process for producing the CDP-taxane conjugate.

The processes referred to in Fig. 2 are given a letter representation, e.g., Process A, Process B, etc. as seen in the second column from the right. The steps for each these processes respectively are provided below.

Process A: Couple the protected linker of position B to the taxane, deprotect the linker and couple to CDP via the carboxylic acid group of the CDP to afford the 2'-taxane linked to CDP.

Process B: Couple the activated linker of position B to the 2'-hydroxyl of taxane, and couple to CDP containing linker of position A via the linker of A to afford the 2'- taxane linked to CDP.

Process C: Protect the C2' hydroxy group of the taxane, couple the protected linker of position B to the taxane, deprotect the linker and the C2' hydroxy group, and couple to CDP via the carboxylic acid group of the CDP to afford the 7-taxane linked to CDP.

Process D: Protect the C2' hydroxy group of the taxane, couple the activated linker of position B to the 7-hydroxyl of the taxane, deprotect the C2' hydroxy group and couple to CDP containing linker of position A via the linker of A to afford afford the 7-taxane linked to CDP.

As shown specifically in Fig. 2, the CDP-taxane conjugates can be prepared using a variety of methods known in the art, including those described herein. In some embodiments, the CDP-taxane conjugates can be prepared using no protecting groups on the taxane (see, e.g., examples 1, 3 and 4). For taxanes having hydroxyl groups at both the 2' and the 7-positions, one of skill in the art will understand that the 2'-position is more reactive, and therefore when using no protecting groups, the major product of the reaction(s) will be that which is linked via the 2' position.

One or more protecting groups can be used in the processes described above to make the CDP-taxane conjugates described herein. A protecting group can be used to control the point of attachment of the taxane and/or taxane linker to position A. In some embodiments, the protecting group is removed and, in other embodiments, the protecting group is not removed. If a protecting group is not removed, then it can be selected so that it is removed *in vivo* (e.g., acting as a prodrug). An example is hexanoic acid which has been shown to be removed by lipases *in vivo* if used to protect a hydroxyl group in doxorubicin. Protecting groups are generally selected for both the reactive groups of the taxane and the reactive groups of the linker that are not targeted to be part of the coupling reaction. The protecting group should be removable under conditions which will not degrade the taxane and/or linker material. Examples include t-butyldimethylsilyl ("TBDMS") and TROC (derived from 2,2,2-trichloroethoxy chloroformate). Carboxybenzyl ("CBz") can also be used in place of TROC if there is selectivity seen for removal over olefin reduction. This can be addressed by using a group which is more readily removed by hydrogenation such as –methoxybenzyl OCO-. Other protecting groups may also be acceptable. One of skill in the art can select suitable protecting groups for the products and methods described herein.

CDP-taxane conjugate characteristics

In some embodiments, the CDP and/or CDP-taxane conjugates as described herein have polydispersities less than about 3, or even less than about 2.

One embodiment of the present invention provides an improved delivery of certain taxanes by covalently conjugating them to a CDP. Such conjugation improves the aqueous solubility and hence the bioavailability of the taxane. Accordingly, in one embodiment of the invention, the taxane is a hydrophobic compound with a log P >0.4, >0.6, >0.8, >1, >2, >3, >4, or even >5. In other embodiments, a taxane may be attached to another compound, such as an amino acid, prior to covalently attaching the conjugate onto the CDP.

The CDP-taxane conjugates described herein preferably have molecular weights in the range of 10,000 to 500,000; 30,000 to 200,000; or even 70,000 to 150,000 amu. In certain embodiments as disclosed herein, the compound has a number average (M_n)

molecular weight between 1,000 to 500,000 amu, or between 5,000 to 200,000 amu, or between 10,000 to 100,000 amu. One method to determine molecular weight is by gel permeation chromatography ("GPC"), e.g., mixed bed columns, CH_2Cl_2 solvent, light scattering detector, and off-line dn/dc. Other methods are known in the art.

In certain embodiments as disclosed herein, the CDP-taxane conjugate is biodegradable or bioerodable.

In certain embodiments as disclosed herein, the taxane or prodrug thereof makes up at least 3% (e.g., at least about 5%, 10%, 15%, or 20%) by weight of the compound. In certain embodiments, the taxane or prodrug thereof makes up at least 15% or 20% by weight of the compound (e.g., from 17-21% by weight).

In other embodiments, the CDP-taxane conjugate may be a flexible or flowable material. When the CDP used is itself flowable, the CDP composition of the invention, even when viscous, need not include a biocompatible solvent to be flowable, although trace or residual amounts of biocompatible solvents may still be present.

When a solvent is used to facilitate mixing or to maintain the flowability of the CDP-taxane conjugate, it should be non-toxic, otherwise biocompatible, and should be used in relatively small amounts. Examples of suitable biocompatible solvents, when used, include N-methyl-2-pyrrolidone, 2-pyrrolidone, ethanol, propylene glycol, acetone, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide, dimethylsulfoxide, tetrahydrofuran, caprolactam, oleic acid, or 1-dodecylazacylcoheptanone. Preferred solvents include N-methylpyrrolidone, 2-pyrrolidone, dimethylsulfoxide, and acetone because of their solvating ability and their biocompatibility.

In certain embodiments, the CDP-taxane conjugates are soluble in one or more common organic solvents for ease of fabrication and processing. Common organic solvents include such solvents as chloroform, dichloromethane, dichloroethane, 2-butanone, butyl acetate, ethyl butyrate, acetone, ethyl acetate, dimethylacetamide, N-methylpyrrolidone, dimethylformamide, and dimethylsulfoxide.

In certain embodiments, the CDP-taxane conjugates described herein, upon contact with body fluids, undergo gradual degradation. The life of a biodegradable

polymer *in vivo* depends upon, among other things, its molecular weight, crystallinity, biostability, and the degree of crosslinking. In general, the greater the molecular weight, the higher the degree of crystallinity, and the greater the biostability, the slower biodegradation will be.

If a subject composition is formulated with a taxane or other material, release of the taxane or other material for a sustained or extended period as compared to the release from an isotonic saline solution generally results. Such release profile may result in prolonged delivery (over, say 1 to about 2,000 hours, or alternatively about 2 to about 800 hours) of effective amounts (e.g., about 0.0001 mg/kg/hour to about 10 mg/kg/hour, e.g., 0.001 mg/kg/hour, 0.01 mg/kg/hour, 0.1 mg/kg/hour, 1.0 mg/kg/hour) of the taxane or any other material associated with the polymer.

A variety of factors may affect the desired rate of hydrolysis of CDP-taxane conjugates, the desired softness and flexibility of the resulting solid matrix, rate and extent of bioactive material release. Some of such factors include the selection/identity of the various subunits, the enantiomeric or diastereomeric purity of the monomeric subunits, homogeneity of subunits found in the polymer, and the length of the polymer. For instance, the present invention contemplates heteropolymers with varying linkages, and/or the inclusion of other monomeric elements in the polymer, in order to control, for example, the rate of biodegradation of the matrix.

To illustrate further, a wide range of degradation rates may be obtained by adjusting the hydrophobicities of the backbones or side chains of the polymers while still maintaining sufficient biodegradability for the use intended for any such polymer. Such a result may be achieved by varying the various functional groups of the polymer. For example, the combination of a hydrophobic backbone and a hydrophilic linkage produces heterogeneous degradation because cleavage is encouraged whereas water penetration is resisted.

One protocol generally accepted in the field that may be used to determine the release rate of a therapeutic agent such as a taxane or other material loaded in the CDP-taxane conjugates of the present invention involves degradation of any such matrix in a 0.1 M PBS solution (pH 7.4) at 37 °C, an assay known in the art. For purposes of the present invention, the term "PBS protocol" is used herein to refer to such protocol.

In certain instances, the release rates of different CDP-taxane conjugates of the present invention may be compared by subjecting them to such a protocol. In certain instances, it may be necessary to process polymeric systems in the same fashion to allow direct and relatively accurate comparisons of different systems to be made. For example, the present invention teaches several different methods of formulating the CDP-taxane conjugates. Such comparisons may indicate that any one CDP-taxane conjugate releases incorporated material at a rate from about 2 or less to about 1000 or more times faster than another polymeric system.

Alternatively, a comparison may reveal a rate difference of about 3, 5, 7, 10, 25, 50, 100, 250, 500 or 750 times. Even higher rate differences are contemplated by the present invention and release rate protocols.

In certain embodiments, when formulated in a certain manner, the release rate for CDP-taxane conjugates of the present invention may present as mono- or bi-phasic.

Release of any material incorporated into the polymer matrix, which is often provided as a microsphere, may be characterized in certain instances by an initial increased release rate, which may release from about 5 to about 50% or more of any incorporated material, or alternatively about 10, 15, 20, 25, 30 or 40%, followed by a release rate of lesser magnitude.

The release rate of any incorporated material may also be characterized by the amount of such material released per day per mg of polymer matrix. For example, in certain embodiments, the release rate may vary from about 1 ng or less of any incorporated material per day per mg of polymeric system to about 500 or more ng/day/mg. Alternatively, the release rate may be about 0.05, 0.5, 5, 10, 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, or 500 ng/day/mg. In still other embodiments, the release rate of any incorporated material may be 10,000 ng/day/mg, or even higher. In certain instances, materials incorporated and characterized by such release rate protocols may include therapeutic agents, fillers, and other substances.

In another aspect, the rate of release of any material from any CDP-taxane conjugate of the present invention may be presented as the half-life of such material in the matrix.

In addition to the embodiment involving protocols for in vitro determination of release rates, *in vivo* protocols, whereby in certain instances release rates for polymeric systems may be determined *in vivo*, are also contemplated by the present invention. Other assays useful for determining the release of any material from the polymers of the present system are known in the art.

Physical Structures of the CDP-taxane conjugates

The CDP-taxane conjugates may be formed in a variety of shapes. For example, in certain embodiments, the CDP-taxane conjugates may be presented in the form of a nanoparticle. In one embodiment, the CDP-taxane conjugate self assembles into a nanoparticle. In one embodiment, the CDP-taxane conjugate self assembles into a nanoparticle in an aqueous solution, e.g., water.

In addition to intracellular delivery of a taxane, it also possible that nanoparticles of the CDP-taxane conjugates may undergo endocytosis, thereby obtaining access to the cell. The frequency of such an endocytosis process will likely depend on the size of any nanoparticle.

In one embodiment, the surface charge of the molecule is neutral, or slightly negative. In some embodiments, the zeta potential of the particle surface is from about -80 mV to about 50 mV.

CDPs, methods of making same, and methods of conjugating CDPs to Taxanes

Generally, the CDP-taxane conjugates described herein can be prepared in one of two ways: monomers bearing taxanes, targeting ligands, and/or cyclodextrin moieties can be polymerized, or polymer backbones can be derivatized with taxanes, targeting ligands, and/or cyclodextrin moieties.

Thus, in one embodiment, the synthesis of the CDP-taxane conjugates can be accomplished by reacting monomers M-L-CD and M-L-D (and, optionally, M-L-T), wherein

CD represents a cyclic moiety, such as a cyclodextrin molecule, or derivative thereof;

L, independently for each occurrence, may be absent or represents a linker group;

D, independently for each occurrence, represents the same or different taxane or prodrug thereof;

T, independently for each occurrence, represents the same or different targeting ligand or precursor thereof; and

M represents a monomer subunit bearing one or more reactive moieties capable of undergoing a polymerization reaction with one or more other M in the monomers in the reaction mixture, under conditions that cause polymerization of the monomers to take place.

In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

In certain embodiments, the reaction mixture may further comprise monomers that do not bear CD, T, or D moieties, e.g., to space the derivatized monomer units throughout the polymer.

In an alternative embodiment, the invention contemplates synthesizing a CDP-taxane conjugate by reacting a polymer P (the polymer bearing a plurality of reactive groups, such as carboxylic acids, alcohols, thiols, amines, epoxides, etc.) with grafting agents X-L-CD and/or Y-L-D (and, optionally, Z-L-T), wherein

CD represents a cyclic moiety, such as a cyclodextrin molecule, or derivative thereof;

L, independently for each occurrence, may be absent or represents a linker group;

D, independently for each occurrence, represents the same or different taxane or prodrug thereof;

T, independently for each occurrence, represents the same or different targeting ligand or precursor thereof;

X, independently for each occurrence, represents a reactive group, such as carboxylic acids, alcohols, thiols, amines, epoxides, etc., capable of forming a covalent bond with a reactive group of the polymer; and

Y and Z, independently for each occurrence, represent inclusion hosts or reactive groups, such as carboxylic acids, alcohols, thiols, amines, epoxides, etc., capable of

forming a covalent bond with a reactive group of the polymer or inclusion complexes with CD moieties grafted to the polymer, under conditions that cause the grafting agents to form covalent bonds and/or inclusion complexes, as appropriate, with the polymer or moieties grafted to the polymer.

In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

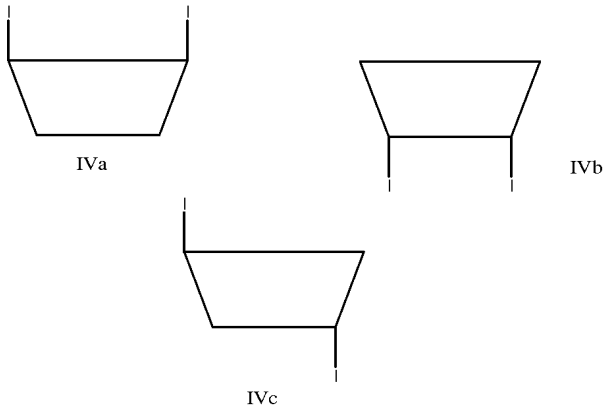
For example, if the CDP includes alcohols, thiols, or amines as reactive groups, the grafting agents may include reactive groups that react with them, such as isocyanates, isothiocyanates, acid chlorides, acid anhydrides, epoxides, ketenes, sulfonyl chlorides, activated carboxylic acids (e.g., carboxylic acids treated with an activating agent such as PyBrOP, carbonyldiimidazole, or another reagent that reacts with a carboxylic acid to form a moiety susceptible to nucleophilic attack), or other electrophilic moieties known to those of skill in the art. In certain embodiments, a catalyst may be needed to cause the reaction to take place (e.g., a Lewis acid, a transition metal catalyst, an amine base, etc.) as will be understood by those of skill in the art.

In certain embodiments, the different grafting agents are reacted with the polymer simultaneously or substantially simultaneously (e.g., in a one-pot reaction), or are reacted sequentially with the polymer (optionally with a purification and/or wash step between reactions).

Another aspect of the present invention is a method for manufacturing the linear or branched CDPs and CDP-taxane conjugates as described herein. While the discussion below focuses on the preparation of linear cyclodextrin molecules, one skilled in the art would readily recognize that the methods described can be adapted for producing branched polymers by choosing an appropriate comonomer precursor.

Accordingly, one embodiment of the invention is a method of preparing a linear CDP. According to the invention, a linear CDP may be prepared by copolymerizing a cyclodextrin monomer precursor disubstituted with one or more appropriate leaving groups with a comonomer precursor capable of displacing the leaving groups. The leaving group, which may be the same or different, may be any leaving group known in the art which may be displaced upon copolymerization with a comonomer precursor. In a

preferred embodiment, a linear CDP may be prepared by iodinating a cyclodextrin monomer precursor to form a diiodinated cyclodextrin monomer precursor and copolymerizing the diiodinated cyclodextrin monomer precursor with a comonomer precursor to form a linear CDP having a repeating unit of formula I or II, provided in the section entitles "CDP-Taxane conjugates" or a combination thereof, each as described above. In some embodiments, the cyclodextrin moiety precursors are in a composition, the composition being substantially free of cyclodextrin moieties having other than two positions modified to bear a reactive site (e.g., 1, 3, 4, 5, 6, or 7). While examples presented below discuss iodinated cyclodextrin moieties, one skilled in the art would readily recognize that the present invention contemplates and encompasses cyclodextrin moieties wherein other leaving groups such as alkyl and aryl sulfonate may be present instead of iodo groups. In a preferred embodiment, a method of preparing a linear cyclodextrin copolymer of the invention by iodinating a cyclodextrin monomer precursor as described above to form a diiodinated cyclodextrin monomer precursor of formula IVa, IVb, IVc or a mixture thereof:

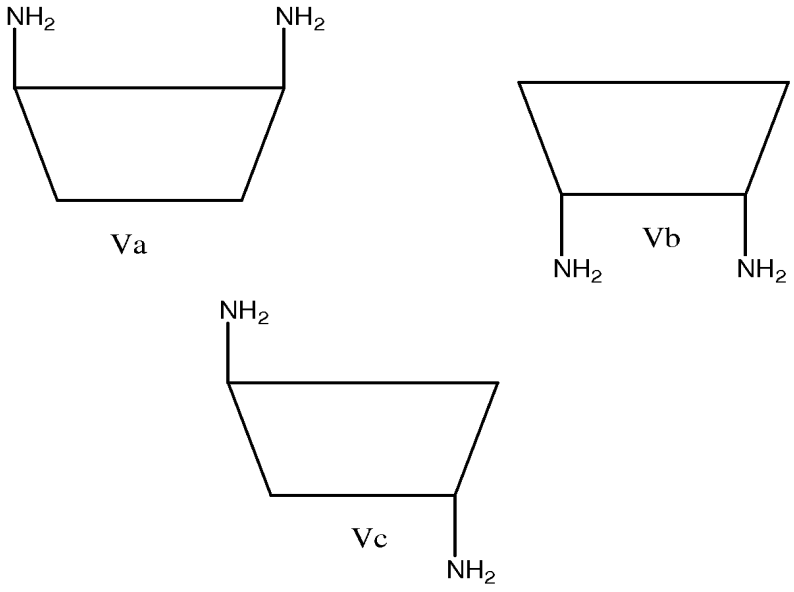


In some embodiments, the iodine moieties as shown on the cyclodextrin moieties are positioned such that the derivatization on the cyclodextrin is on the A and D glucopyranose moieties. In some embodiments, the iodine moieties as shown on the cyclodextrin moieties are positioned in such that the derivatization on the cyclodextrin is on the A and C glucopyranose moieties. In some embodiments, the iodine moieties as shown on the cyclodextrin moieties are positioned in such that the derivatization on the cyclodextrin is on the A and F glucopyranose moieties. In some embodiments, the iodine

moieties as shown on the cyclodextrin moieties are positioned in such that the derivatization on the cyclodextrin is on the A and E glucopyranose moieties.

The diiodinated cyclodextrin may be prepared by any means known in the art. (Tabushi et al. J. Am. Chem. 106, 5267-5270 (1984); Tabushi et al. J. Am. Chem. 106, 4580-4584 (1984)). For example, β–cyclodextrin may be reacted with biphenyl-4,4'-disulfonyl chloride in the presence of anhydrous pyridine to form a biphenyl-4,4'-disulfonyl chloride capped β-cyclodextrin which may then be reacted with potassium iodide to produce diiodo-β-cyclodextrin. The cyclodextrin monomer precursor is iodinated at only two positions. By copolymerizing the diiodinated cyclodextrin monomer precursor with a comonomer precursor, as described above, a linear cyclodextrin polymer having a repeating unit of Formula Ia, Ib, or a combination thereof, also as described above, may be prepared. If appropriate, the iodine or iodo groups may be replaced with other known leaving groups.

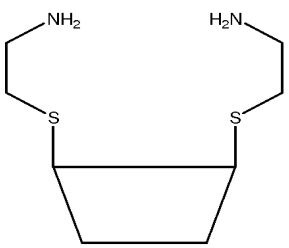
Also according to the invention, the iodo groups or other appropriate leaving group may be displaced with a group that permits reaction with a comonomer precursor, as described above. For example, a diiodinated cyclodextrin monomer precursor of formula IVa, IVb, IVc or a mixture thereof may be aminated to form a diaminated cyclodextrin monomer precursor of formula Va, Vb, Vc or a mixture thereof:



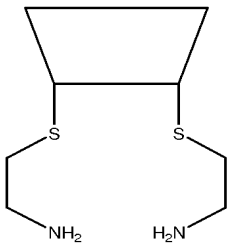
In some embodiments, the amino moieties as shown on the cyclodextrin moieties are positioned such that the derivatization on the cyclodextrin is on the A and D glucopyranose moieties. In some embodiments, the amino moieties as shown on the cyclodextrin moieties are positioned in such that the derivatization on the cyclodextrin is on the A and C glucopyranose moieties. In some embodiments, the amino moieties as shown on the cyclodextrin moieties are positioned in such that the derivatization on the cyclodextrin is on the A and F glucopyranose moieties. In some embodiments, the amino moieties as shown on the cyclodextrin moieties are positioned in such that the derivatization on the cyclodextrin is on the A and E glucopyranose moieties.

The diaminated cyclodextrin monomer precursor may be prepared by any means known in the art. (Tabushi et al. Tetrahedron Lett. 18:11527-1530 (1977); Mungall et al., J. Org. Chem. 16591662 (1975)). For example, a diiodo-β-cyclodextrin may be reacted with sodium azide and then reduced to form a diamino-β-cyclodextrin). The cyclodextrin monomer precursor is aminated at only two positions. The diaminated cyclodextrin monomer precursor may then be copolymerized with a comonomer precursor, as described above, to produce a linear cyclodextrin copolymer having a repeating unit of formula I-II provided in the section entitles "CDP-Taxane conjugates" or a combination thereof, also as described above. However, the amino functionality of a diaminated cyclodextrin monomer precursor need not be directly attached to the cyclodextrin moiety. Alternatively, the amino functionality or another nucleophilic functionality may be introduced by displacement of the iodo or other appropriate leaving groups of a cyclodextrin monomer precursor with amino group containing moieties such as, for example, $HSCH_2CH_2NH_2$ (or a di-nucleophilic molecule more generally represented by $HW\text{-}(CR_1R_2)_n\text{-}WH$ wherein W, independently for each occurrence, represents O, S, or NR_1; R_1 and R_2, independently for each occurrence, represent H, (un)substituted alkyl, (un)substituted aryl, (un)substituted heteroalkyl, (un)substituted heteroaryl) with an appropriate base such as a metal hydride, alkali or alkaline carbonate, or tertiary amine to form a diaminated cyclodextrin monomer precursor of formula Vd, Ve, Vf or a mixture thereof:

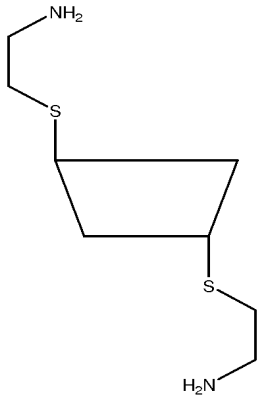
Vd



Ve



Vf

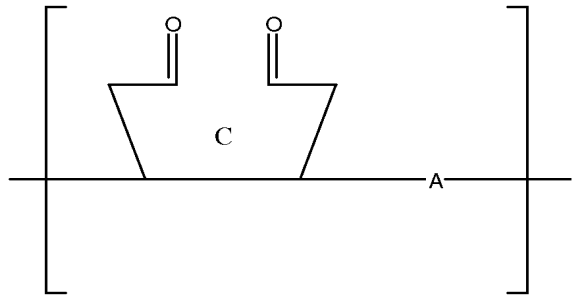


In some embodiments, the -$SCH_2CH_2NH_2$ moieties as shown on the cyclodextrin moieties are positioned such that the derivatization on the cyclodextrin is on the A and D glucopyranose moieties. In some embodiments, the -$SCH_2CH_2NH_2$ moieties as shown on the cyclodextrin moieties are positioned in such that the derivatization on the cyclodextrin is on the A and C glucopyranose moieties. In some embodiments, the -$SCH_2CH_2NH_2$ moieties as shown on the cyclodextrin moieties are positioned in such that the derivatization on the cyclodextrin is on the A and F glucopyranose moieties. In some embodiments, the -$SCH_2CH_2NH_2$ moieties as shown on the cyclodextrin moieties are positioned in such that the derivatization on the cyclodextrin is on the A and E glucopyranose moieties.

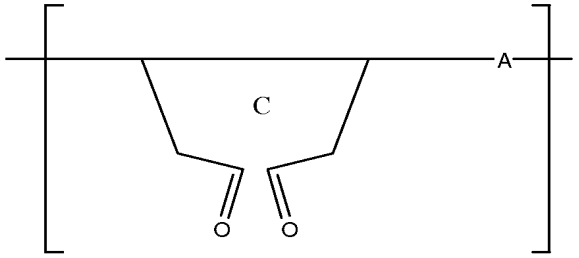
A linear oxidized CDP may also be prepared by oxidizing a reduced linear cyclodextrin-containing copolymer as described below. This method may be performed as long as the comonomer does not contain an oxidation sensitive moiety or group such as, for example, a thiol.

A linear CDP of the invention may be oxidized so as to introduce at least one oxidized cyclodextrin monomer into the copolymer such that the oxidized cyclodextrin monomer is an integral part of the polymer backbone. A linear CDP which contains at least one oxidized cyclodextrin monomer is defined as a linear oxidized cyclodextrin copolymer or a linear oxidized cyclodextrin-containing polymer. The cyclodextrin monomer may be oxidized on either the secondary or primary hydroxyl side of the cyclodextrin moiety. If more than one oxidized cyclodextrin monomer is present in a linear oxidized cyclodextrin copolymer of the invention, the same or different

cyclodextrin monomers oxidized on either the primary hydroxyl side, the secondary hydroxyl side, or both may be present. For illustration purposes, a linear oxidized cyclodextrin copolymer with oxidized secondary hydroxyl groups has, for example, at least one unit of formula VIa or VIb:



VIa



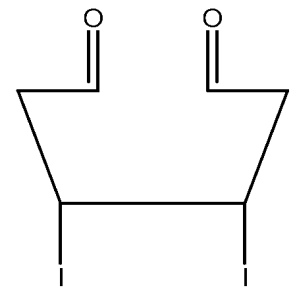
VIb

In formulae VIa and VIb, C is a substituted or unsubstituted oxidized cyclodextrin monomer and the comonomer (i.e., shown herein as A) is a comonomer bound, i.e., covalently bound, to the oxidized cyclodextrin C. Also in formulae VIa and VIb, oxidation of the secondary hydroxyl groups leads to ring opening of the cyclodextrin moiety and the formation of aldehyde groups.

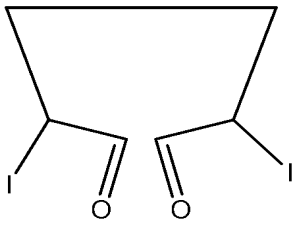
A linear oxidized CDP copolymer may be prepared by oxidation of a linear cyclodextrin copolymer as discussed above. Oxidation of a linear cyclodextrin copolymer of the invention may be accomplished by oxidation techniques known in the art. (Hisamatsu et al., Starch 44:188-191 (1992)). Preferably, an oxidant such as, for example, sodium periodate is used. It would be understood by one of ordinary skill in the art that under standard oxidation conditions that the degree of oxidation may vary or be varied per copolymer. Thus in one embodiment of the invention, a CDP may contain one

oxidized cyclodextrin monomer. In another embodiment, substantially all cyclodextrin monomers of the copolymer would be oxidized.

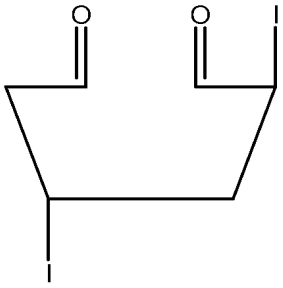
Another method of preparing a linear oxidized CDP involves the oxidation of a diiodinated or diaminated cyclodextrin monomer precursor, as described above, to form an oxidized diiodinated or diaminated cyclodextrin monomer precursor and copolymerization of the oxidized diiodinated or diaminated cyclodextrin monomer precursor with a comonomer precursor. In a preferred embodiment, an oxidized diiodinated cyclodextrin monomer precursor of formula VIIa, VIIb, VIIc, or a mixture thereof:



VIIa

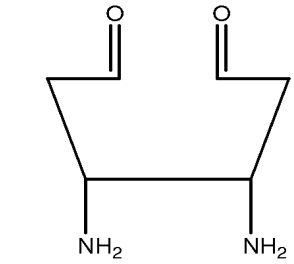


VIIb

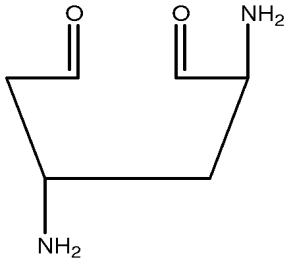


VIIc

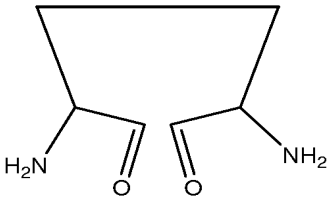
may be prepared by oxidation of a diiodinated cyclodextrin monomer precursor of formulae IVa, IVb, IVc, or a mixture thereof, as described above. In another preferred embodiment, an oxidized diaminated cyclodextrin monomer precursor of formula VIIIa, VIIIb, VIIIc or a mixture thereof:



VIIIa

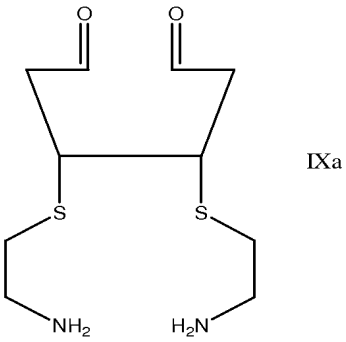


VIIIc

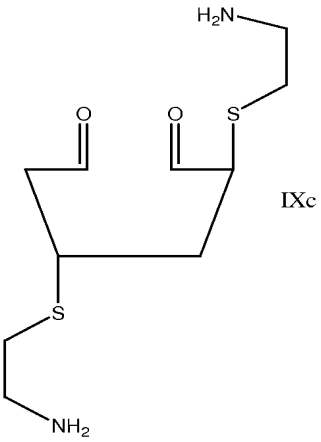


VIIIb

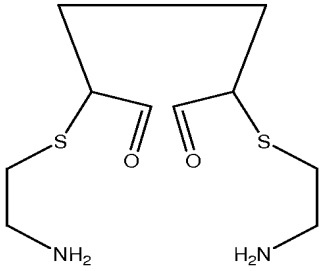
may be prepared by amination of an oxidized diiodinated cyclodextrin monomer precursor of formulae VIIa, VIIb, VIIc, or a mixture thereof, as described above. In still another preferred embodiment, an oxidized diaminated cyclodextrin monomer precursor of formula IXa, IXb, IXc or a mixture thereof:



IXa



IXc



IXb

may be prepared by displacement of the iodo or other appropriate leaving groups of an oxidized cyclodextrin monomer precursor disubstituted with an iodo or other appropriate leaving group with the amino or other nucleophilic group containing moiety such as, e.g. $HSCH_2CH_2NH_2$ (or a di-nucleophilic molecule more generally represented by HW-$(CR_1R_2)_n$-WH wherein W, independently for each occurrence, represents O, S, or NR_1; R_1 and R_2, independently for each occurrence, represent H, (un)substituted alkyl, (un)substituted aryl, (un)substituted heteroalkyl, (un)substituted heteroaryl) with an appropriate base such as a metal hydride, alkali or alkaline carbonate, or tertiary amine.

Alternatively, an oxidized diiodinated or diaminated cyclodextrin monomer precursor, as described above, may be prepared by oxidizing a cyclodextrin monomer precursor to form an oxidized cyclodextrin monomer precursor and then diiodinating and/or diaminating the oxidized cyclodextrin monomer, as described above. As discussed above, the cyclodextrin moiety may be modified with other leaving groups other than iodo groups and other amino group containing functionalities. The oxidized diiodinated or diaminated cyclodextrin monomer precursor may then be copolymerized with a comonomer precursor, as described above, to form a linear oxidized cyclodextrin copolymer of the invention.

A linear oxidized CDP may also be further modified by attachment of at least one ligand to the copolymer. The ligand is as described above.

In some embodiments, a CDP comprises: cyclodextrin moieties, and comonomers which do not contain cyclodextrin moieties (comonomers), and wherein the CDP comprises at least four, five six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen or twenty cyclodextrin moieties and at least four, five six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen or twenty comonomers.

In some embodiments, the at least four, five six, seven, eight, etc., cyclodextrin moieties and at least four, five six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen or twenty comonomers alternate in the water soluble linear polymer.

In some embodiments, the cyclodextrin moieties comprise linkers to which therapeutic agents may be further linked.

In some embodiments, the CDP has no taxanes attached. In some embodiments, the CDP has a plurality (i.e., more than one) of taxanes attached (e.g., through a linker). In some embodiments, the taxanes are attached via a second linker.

In some embodiments, the comonomer is a compound containing residues of least two functional groups through which reaction and thus linkage of the cyclodextrin monomers is achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer comprise an amino, acid, imidazole, hydroxyl, thio, acyl halide, -HC=CH-, —C≡C— group, or derivative thereof. In some embodiments, the residues of the two functional groups are the same and are located at termini of the comonomer. In some embodiments, a comonomer contains one or more pendant groups with at least one functional group through which reaction and thus linkage of a taxane can be achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer pendant group comprise an amino, acid, imidazole, hydroxyl, thiol, acyl halide, ethylene, ethyne group, or derivative thereof. In some embodiments, the pendant group is a substituted or unsubstituted branched, cyclic or straight chain C_1-C_{10} alkyl, or arylalkyl optionally containing one or more heteroatoms within the chain or ring.

In some embodiments, the cyclodextrin moiety comprises an alpha, beta, or gamma cyclodextrin moiety.

In some embodiments, the CDP is suitable for the attachment of sufficient taxane such that up to at least 5%, 10%, 15%, 20%, 25%, 30%, or even 35% by weight of the water soluble linear polymer, when conjugated, is taxane.

In some embodiments, the molecular weight of the CDP is 10,000-500,000 Da, e.g., about 30,000 to about 100,000 Da.

In some embodiments, the cyclodextrin moieties make up at least about 2%, 5%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 30%, 50% or 80% of the polymer by weight.

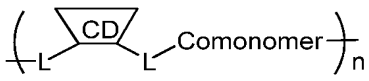
In some embodiments, the CDP is made by a method comprising providing cyclodextrin moiety precursors modified to bear one reactive site at each of exactly two

positions, and reacting the cyclodextrin moiety with comonomer precursors having exactly two reactive moieties capable of forming a covalent bond with the reactive sites under polymerization conditions that promote reaction of the reactive sites with the reactive moieties to form covalent bonds between the comonomers and the cyclodextrin moieties, whereby a CDP comprising alternating units of a cyclodextrin moiety and comonomer is produced.

In some embodiments, the CDP comprises a comonomer selected from the group consisting of: an alkylene chain, polysuccinic anhydride, poly-L-glutamic acid, poly(ethyleneimine), an oligosaccharide, and an amino acid chain. In some embodiments, a comonomer comprises a polyethylene glycol chain. In some embodiments, the CDP comprises a comonomer selected from the group consisting of: polyglycolic acid and polylactic acid chain.

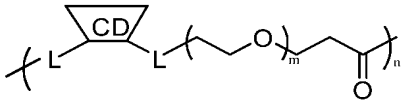
In some embodiments, a comonomer comprises a hydrocarbylene group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR_1, O or S), -OC(O)-, -C(=O)O, -NR_1-, -NR_1CO-, -C(O)NR_1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR_1, -NR_1-C(O)-NR_1-, -$NR_1$1-C(NR_1)-NR_1-, and -B(OR_1)-; and R_1, independently for each occurrence, represents H or a lower alkyl.

In some embodiments, the CDP is a polymer of the following formula:

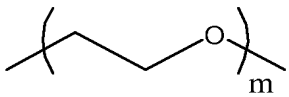


wherein each L is independently a linker, each comonomer is independently a comonomer described herein, and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. In some embodiments, the molecular weight of the comonomer is from about 2000 to about 5000 Da (e.g., from about 3000 to about 4000 Da (e.g., about 3400 Da).

In some embodiments, the CDP is a polymer of the following formula:



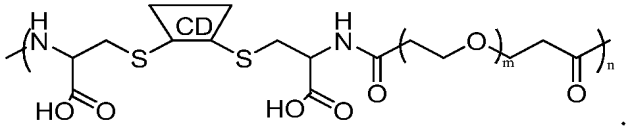
wherein each L is independently a linker,

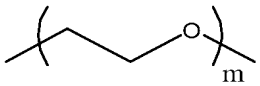
wherein the group  has a Mw of 3.4kDa or less and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

In some embodiments,  is alpha, beta or gamma cyclodextrin, e.g., beta cyclodextrin.

In some embodiments, each L independently comprises an amino acid or a derivative thereof. In some embodiments, at least one L comprises cysteine or a derivative thereof. In some embodiments, each L comprises cysteine. In some embodiments, each L is cysteine and the cysteine is connected to the CD by way of a thiol linkage.

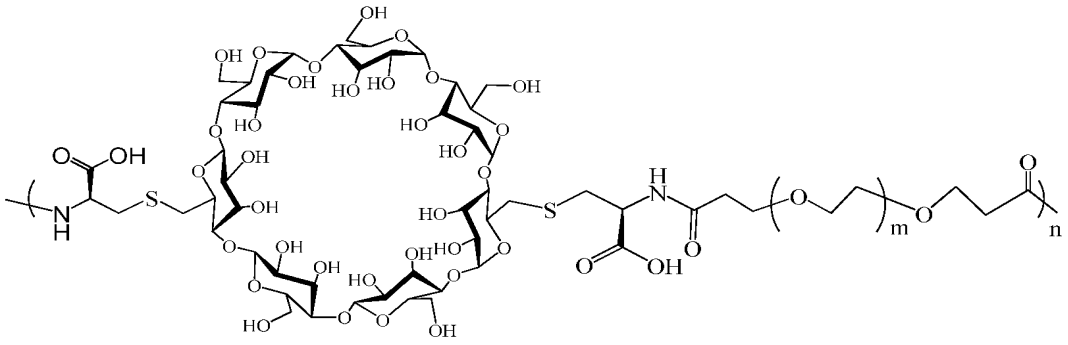
In some embodiments, the CDP is a polymer of the following formula:

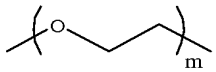


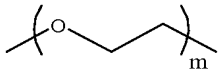
wherein the group  has a Mw of 3.4kDa or less and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

In some embodiments,  is alpha, beta or gamma cyclodextrin, e.g., beta cyclodextrin.

In some embodiments, the CDP is a polymer of the following formula:



wherein the group  has a Mw of 3.4kDa or less and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

In some embodiments, the group  has a Mw of 3.4kDa and the Mw of the compound as a whole is from 27kDa to 99.6kDa.

The CDPs described herein can be made using a variety of methods including those described herein. In some embodiments, a CDP can be made by: providing cyclodextrin moiety precursors; providing comonomer precursors which do not contain cyclodextrin moieties (comonomer precursors); and copolymerizing the said cyclodextrin moiety precursors and comonomer precursors to thereby make a CDP wherein CDP comprises at least four, five six, seven, eight, or more, cyclodextrin moieties and at least four, five six, seven, eight, or more, comonomers.

In some embodiments, the at least four, five, six, seven, eight, or more cyclodextrin moieties and at least four, five, six, seven, eight, or more comonomers alternate in the water soluble linear polymer. In some embodiments, the method includes providing cyclodextrin moiety precursors modified to bear one reactive site at each of exactly two positions, and reacting the cyclodextrin moiety precursors with comonomer precursors having exactly two reactive moieties capable of forming a covalent bond with the reactive sites under polymerization conditions that promote reaction of the reactive sites with the reactive moieties to form covalent bonds between the comonomers and the

cyclodextrin moieties, whereby a CDP comprising alternating units of a cyclodextrin moiety and a comonomer is produced.

In some embodiments, the cyclodextrin comonomers comprise linkers to which taxanes may be further linked. In some embodiments, the taxanes are linked via second linkers.

In some embodiments, the comonomer precursor is a compound containing at least two functional groups through which reaction and thus linkage of the cyclodextrin moieties is achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer precursor comprise an amino, acid, imidazole, hydroxyl, thio, acyl halide, -HC=CH-, —C≡C— group, or derivative thereof. In some embodiments, the two functional groups are the same and are located at termini of the comonomer precursor. In some embodiments, a comonomer contains one or more pendant groups with at least one functional group through which reaction and thus linkage of a therapeutic agent can be achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer pendant group comprise an amino, acid, imidazole, hydroxyl, thiol, acyl halide, ethylene, ethyne group, or derivative thereof. In some embodiments, the pendant group is a substituted or unsubstituted branched, cyclic or straight chain C_1-C_{10} alkyl, or arylalkyl optionally containing one or more heteroatoms within the chain or ring.

In some embodiments, the cyclodextrin moiety comprises an alpha, beta, or gamma cyclodextrin moiety.

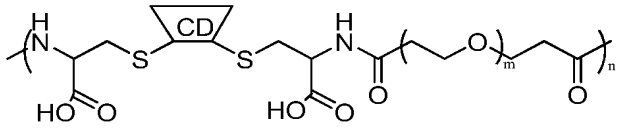
In some embodiments, the CDP is suitable for the attachment of sufficient taxane such that up to at least 3%, 5%, 10%, 15%, 20%, 25%, 30%, or even 35% by weight of the CDP, when conjugated, is taxane.

In some embodiments, the CDP has a molecular weight of 10,000-500,000. In some embodiments, the cyclodextrin moieties make up at least about 2%, 5%, 10%, 20%, 30%, 50% or 80% of the CDP by weight.

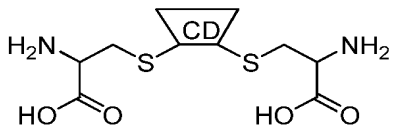
In some embodiments, the CDP comprises a comonomer selected from the group consisting of: an alkylene chain, polysuccinic anhydride, poly-L-glutamic acid, poly(ethyleneimine), an oligosaccharide, and an amino acid chain. In some embodiments, a comonomer comprises a polyethylene glycol chain. In some

embodiments, the CDP comprises a comonomer selected from the group consisting of: polyglycolic acid and polylactic acid chain. the CDP comprises a comonomer selected from the group consisting of a comonomer comprises a hydrocarbylene group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR_1, O or S), -OC(O)-, -C(=O)O, -NR_1-, -NR_1CO-, -C(O)NR_1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR_1, -NR_1-C(O)-NR_1-, -NR_1-C(NR_1)-NR_1-, and -B(OR_1)-; and R_1, independently for each occurrence, represents H or a lower alkyl.

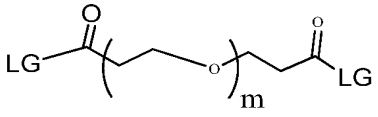
In some embodiments, a CDP of the following formula can be made by the scheme below:



providing a compound of formula A and formula B:



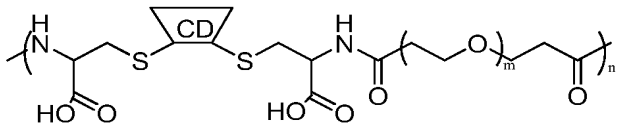
and

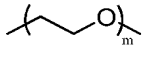


Formula A Formula B

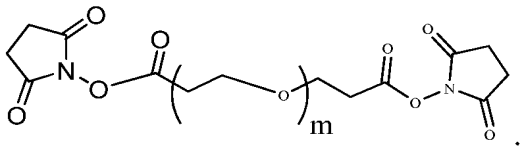
wherein LG is a leaving group;

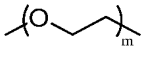
and contacting the compounds under conditions that allow for the formation of a covalent bond between the compounds of formula A and B, to form a polymer of the following formula:



wherein the group  has a Mw of 3.4kDa or less and n is at least four.

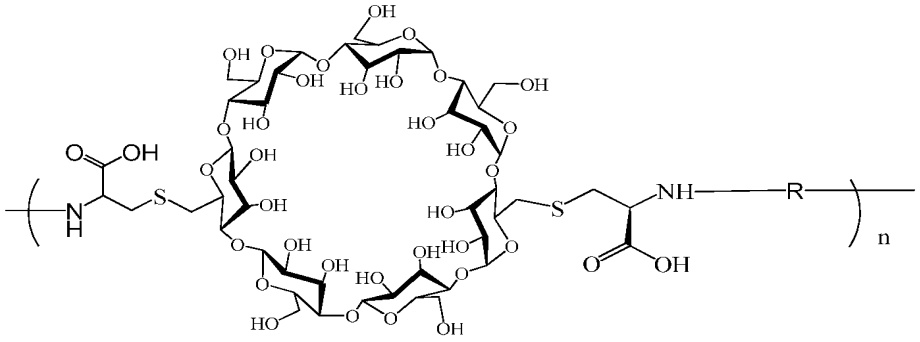
In some embodiments, Formula B is



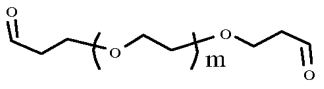
In some embodiments, the group  has a Mw of 3.4kDa and the Mw of the compound is from 27kDa to 99.6kDa.

In some embodiments, the compounds of formula A and formula B are contacted in the presence of a base. In some embodiments, the base is an amine containing base. In some embodiments, the base is DEA.

In some embodiments, a CDP of the following formula can be made by the scheme below:

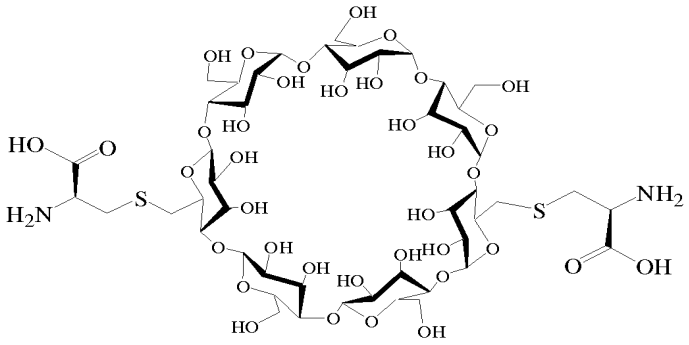


wherein R is of the form:

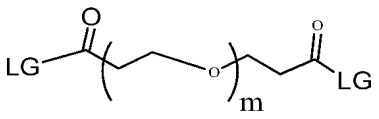
 :

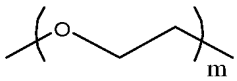
comprising the steps of:

reacting a compound of the formula below:

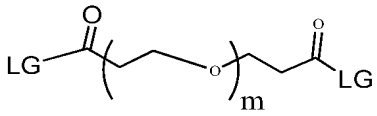
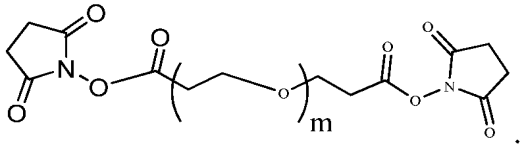


with a compound of the formula below:



wherein the group  has a Mw of 3.4kDa or less and n is at least four,

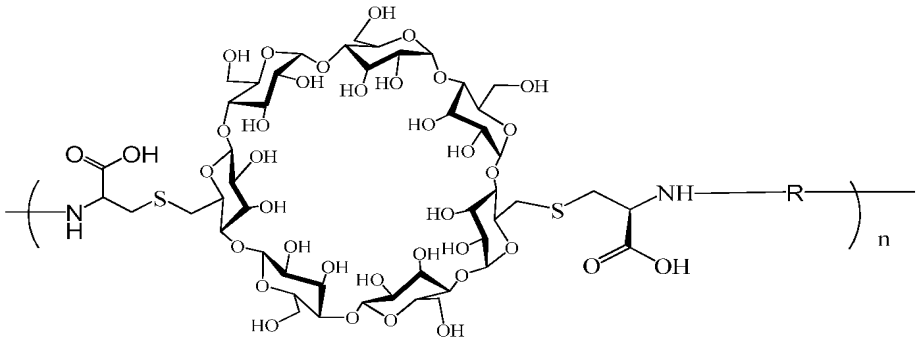
in the presence of a non-nucleophilic organic base in a solvent.

In some embodiments,  is  .

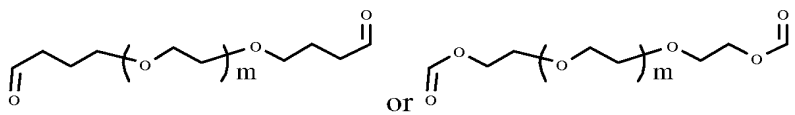
In some embodiments, the solvent is a polar aprotic solvent. In some embodiments, the solvent is DMSO.

In some embodiments, the method also includes the steps of dialysis; and lyophylization.

In some embodiments, a CDP provided below can be made by the following scheme:

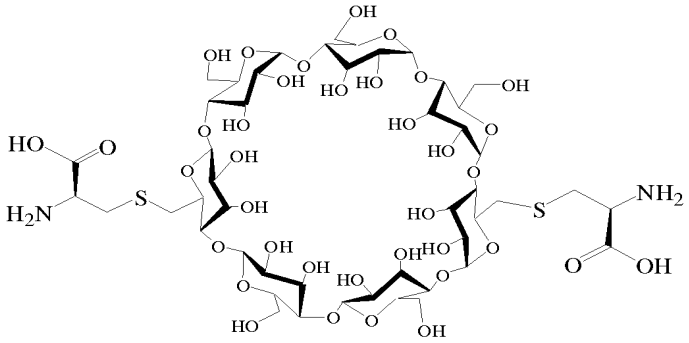


wherein R is of the form:

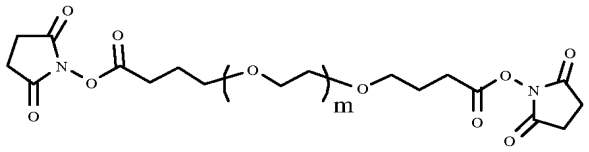


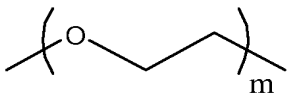
comprising the steps of:

reacting a compound of the formula below:

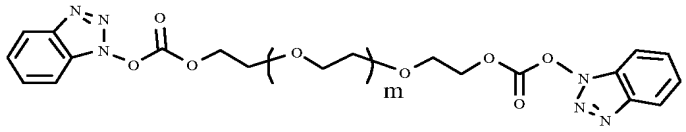


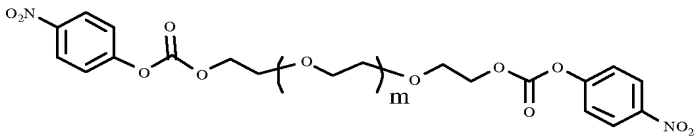
with a compound of the formula below:

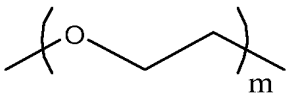


wherein the group  has a Mw of 3.4kDa or less and n is at least four,

or with a compound provided below:

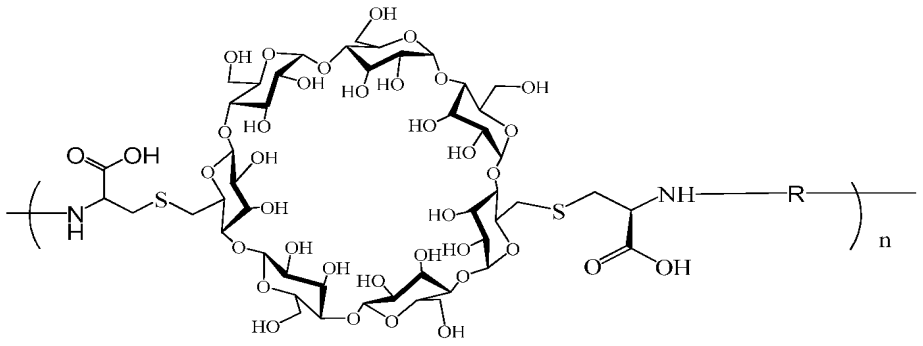




wherein the group  has a Mw of 3.4kDa;

in the presence of a non-nucleophilic organic base in DMSO;

and dialyzing and lyophilizing the following polymer



A CDP described herein may be attached to or grafted onto a substrate. The substrate may be any substrate as recognized by those of ordinary skill in the art. In another preferred embodiment of the invention, a CDP may be crosslinked to a polymer to form, respectively, a crosslinked cyclodextrin copolymer or a crosslinked oxidized cyclodextrin copolymer. The polymer may be any polymer capable of crosslinking with a CDP (e.g., polyethylene glycol (PEG) polymer, polyethylene polymer). The polymer may also be the same or different CDP. Thus; for example, a linear CDP may be crosslinked to any polymer including, but not limited to, itself, another linear CDP, and a linear oxidized CDP. A crosslinked linear CDP may be prepared by reacting a linear CDP with a polymer in the presence of a crosslinking agent. A crosslinked linear oxidized CDP may be prepared by reacting a linear oxidized CDP with a polymer in the presence of an appropriate crosslinking agent. The crosslinking agent may be any crosslinking agent known in the art. Examples of crosslinking agents include dihydrazides and disulfides. In a preferred embodiment, the crosslinking agent is a labile group such that a crosslinked copolymer may be uncrosslinked if desired.

A linear CDP and a linear oxidized CDP may be characterized by any means known in the art. Such characterization methods or techniques include, but are not limited to, gel permeation chromatography (GPC), matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF Mass spec), ^{1}H and ^{13}C NMR, light scattering and titration.

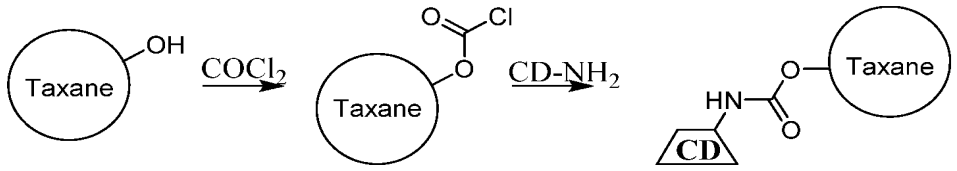
The invention also provides a cyclodextrin composition containing at least one linear CDP and at least one linear oxidized CDP as described above. Accordingly, either or both of the linear CDP and linear oxidized CDP may be crosslinked to another

polymer and/or bound to a ligand as described above. Therapeutic compositions according to the invention contain a taxane and a linear CDP or a linear oxidized CDP, including crosslinked copolymers. A linear CDP, a linear oxidized CDP and their crosslinked derivatives are as described above. The taxane may be any synthetic, semi-synthetic or naturally occurring biologically active taxane, including those known in the art.

One aspect of the present invention contemplates attaching a taxane to a CDP for delivery of a taxane. The present invention discloses various types of linear, branched, or grafted CDPs wherein a taxane is covalently bound to the polymer. In certain embodiments, the taxane is covalently linked via a biohydrolyzable bond, for example, an ester, amide, carbamates, or carbonate.

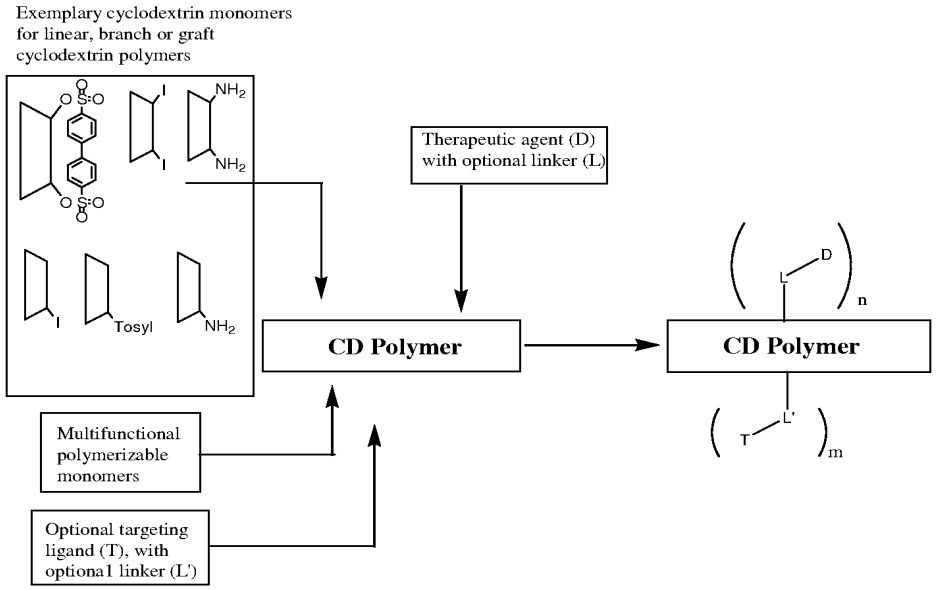
An exemplary synthetic scheme for covalently bonding a derivatized CD to a taxane is shown in Scheme I.

Scheme I



A general strategy for synthesizing linear, branched or grafted cyclodextrin-containing polymers (CDPs) for loading a taxane, and an optional targeting ligand is shown in Scheme II.

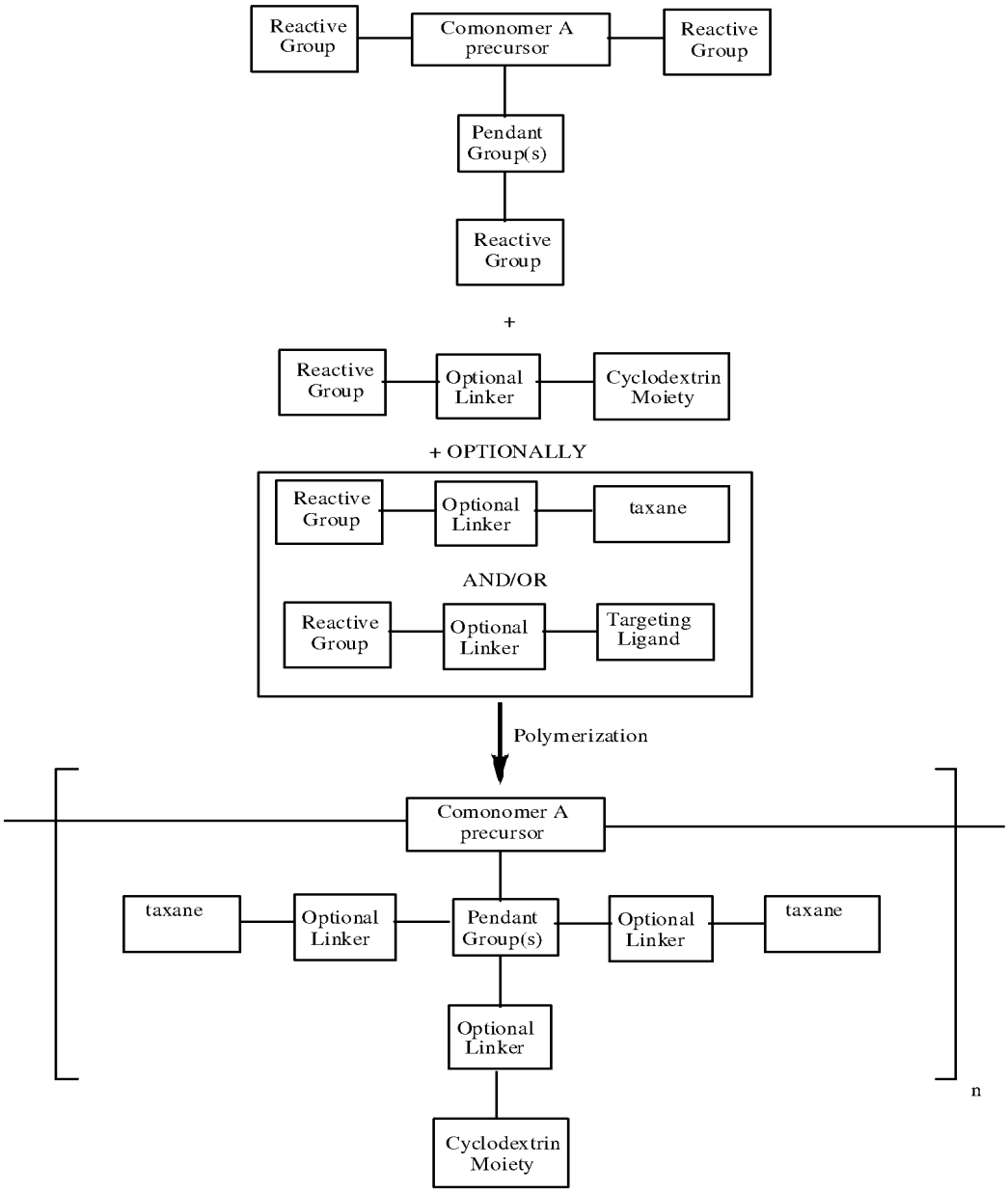
Scheme II



To illustrate further, comonomer precursors (shown in the scheme below as A), cyclodextrin moieties, taxanes, and/or targeting ligands may be assembled as shown in Schemes IIa-IIb below. Note that in schemes IIa-IIb, in any given reaction there may be more than one comonomer precursor, cyclodextrin moiety, therapeutic agent or targeting ligand that is of the same type or different. Furthermore, prior to polymerization, one or more comonomer precursor, cyclodextrin moiety, therapeutic agent or targeting ligand may be covalently linked with each other in one or more separate step. The scheme as provided above includes embodiments, where not all available positions for attachment of the taxane are occupied on the CDP. For example, in some embodiments, less than all of the available points of attachments are reacted, leaving less than 100% yield of the taxane onto the polymer. Accordingly, the loading of the taxane onto the polymer can vary. This is also the case regarding a targeting agent when a targeting agent is included.

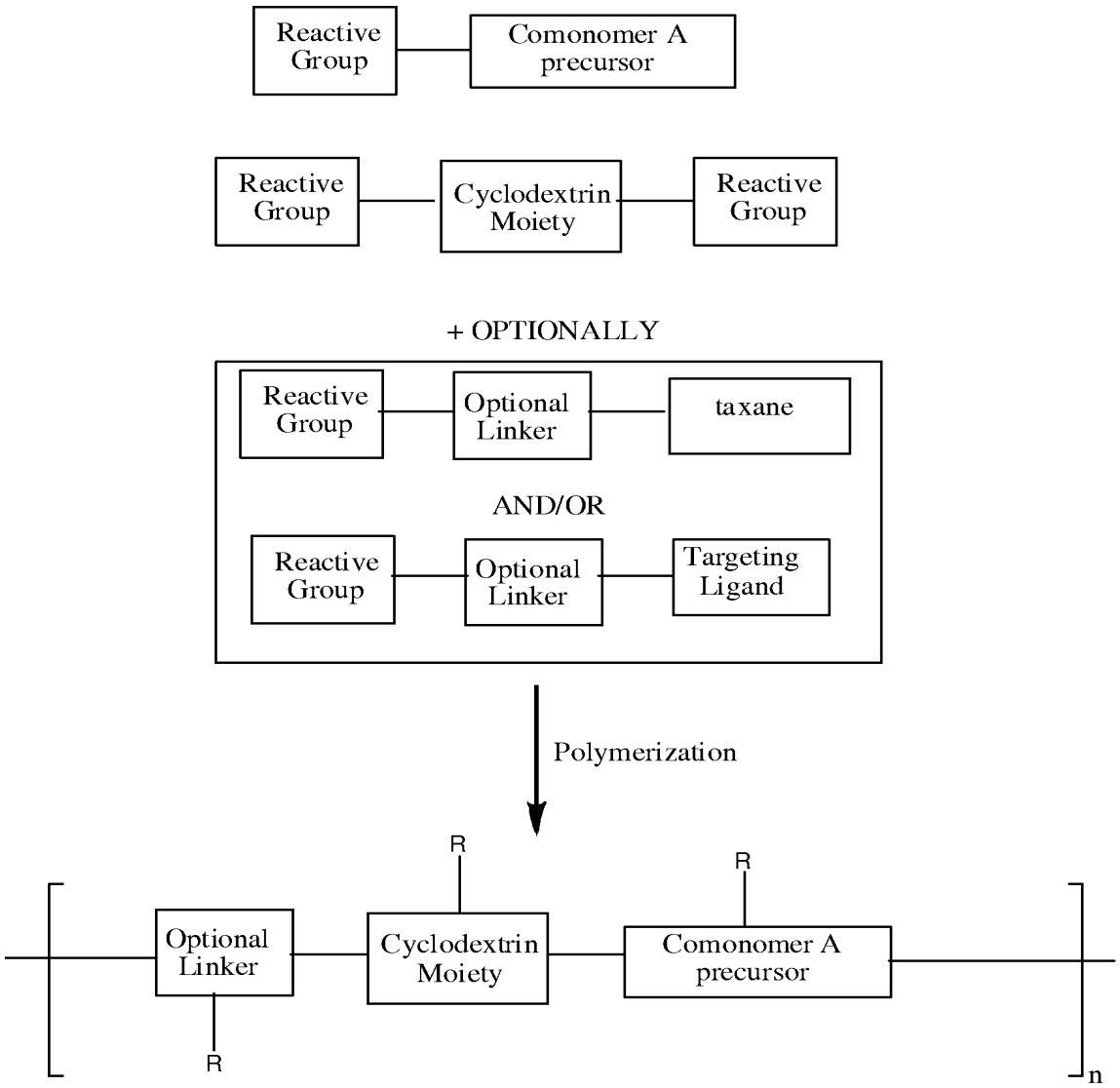
Scheme IIa: General scheme for graft polymers. The comonomer A precursor, cyclodextrin moiety, taxane and optional targeting ligand are as defined above. Furthermore, one skilled in the art may choose from a variety of reactive groups, e.g., hydroxyls, carboxyls, halides, amines, and activated ethenes, ethynes, or aromatic groups

in order achieve polymerization. For further examples of reactive groups are disclosed in Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th Edition, 2000.



In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

Scheme IIb: General scheme of preparing linear CDPs. One skilled in the art would recognize that by choosing a comonomer A precursor that has multiple reactive groups polymer branching can be achieved.

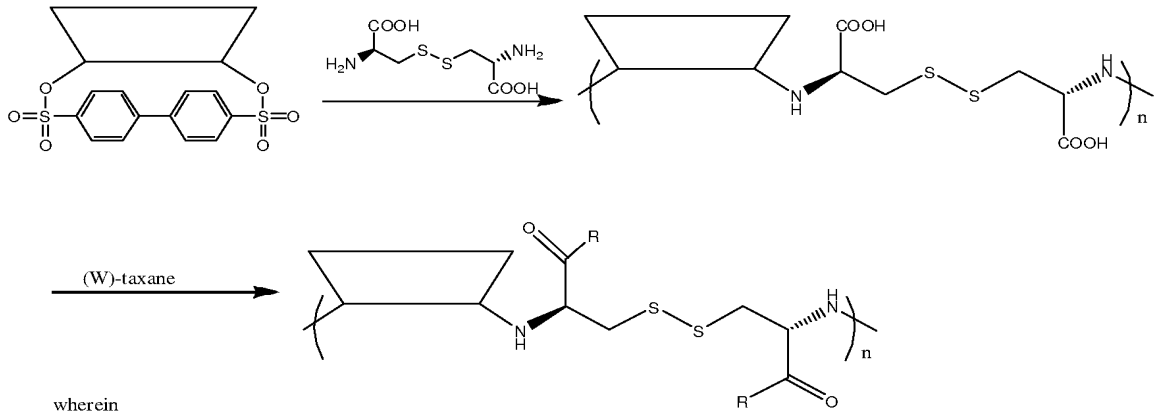


Wherein R is a taxane and/or targeting ligand, either of which may be absent or present.

In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

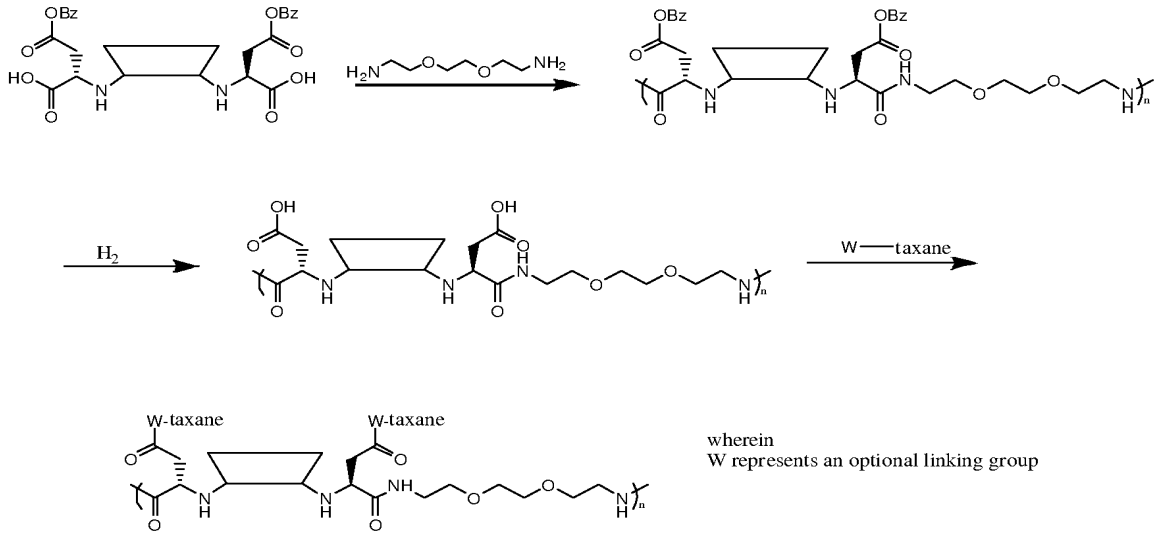
Examples of different ways of synthesizing CDP-taxane conjugates are shown in Schemes III-VIII below. In each of Schemes III-VIII, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

Scheme III



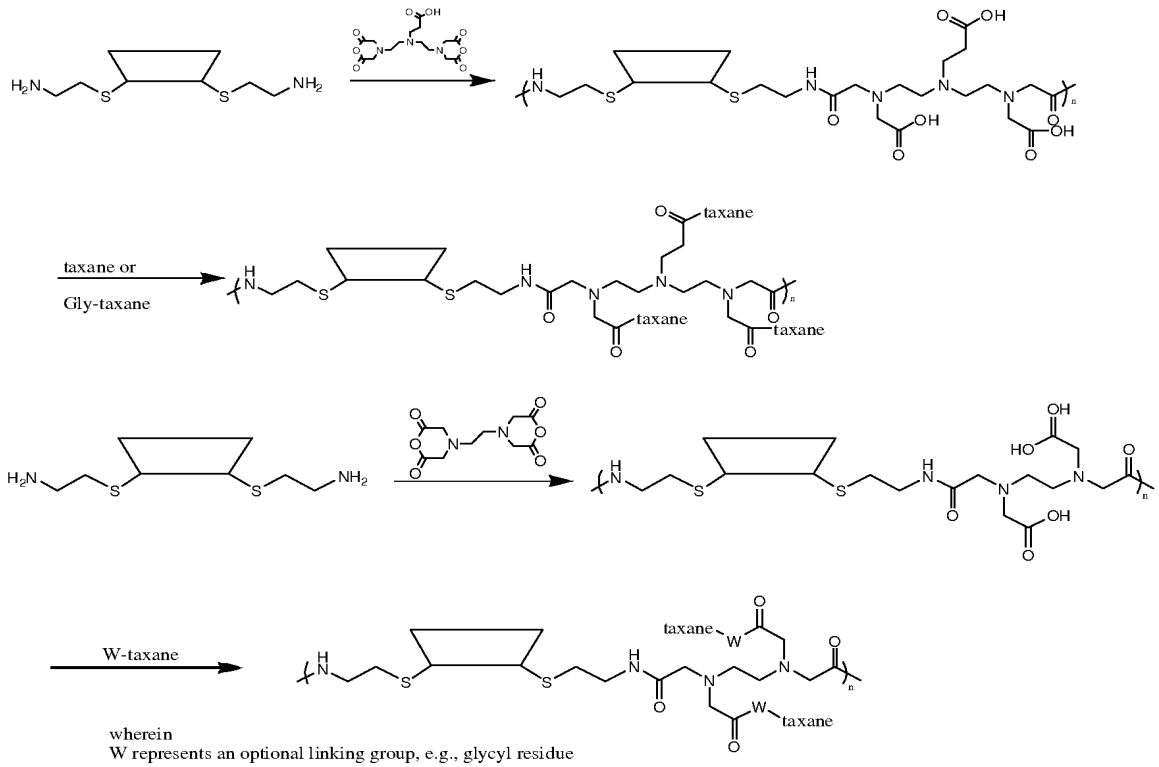
wherein
W represents an optional linking group; and
R represents OH or taxane.

Scheme IV



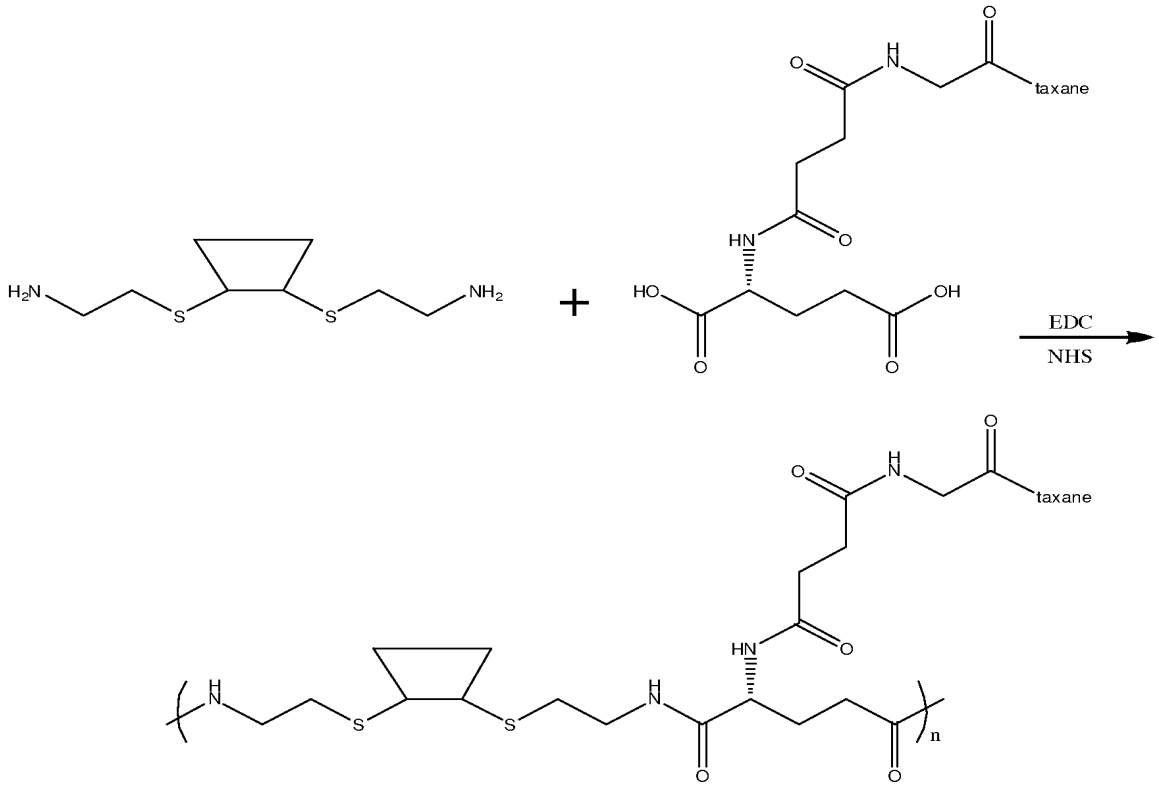
Scheme IV, as provided above, includes embodiments where W-taxane is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane to the polymer and/or when less than an equivalent amount of taxane is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary.

Scheme V



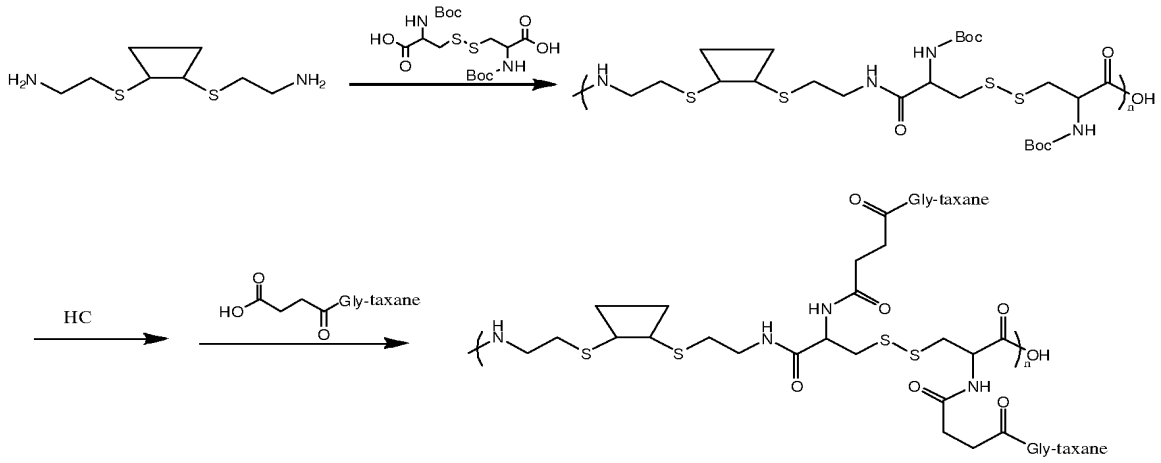
Scheme V, as provided above, includes embodiments where W-taxane is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane to the polymer and/or when less than an equivalent amount of taxane is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary.

Scheme VI



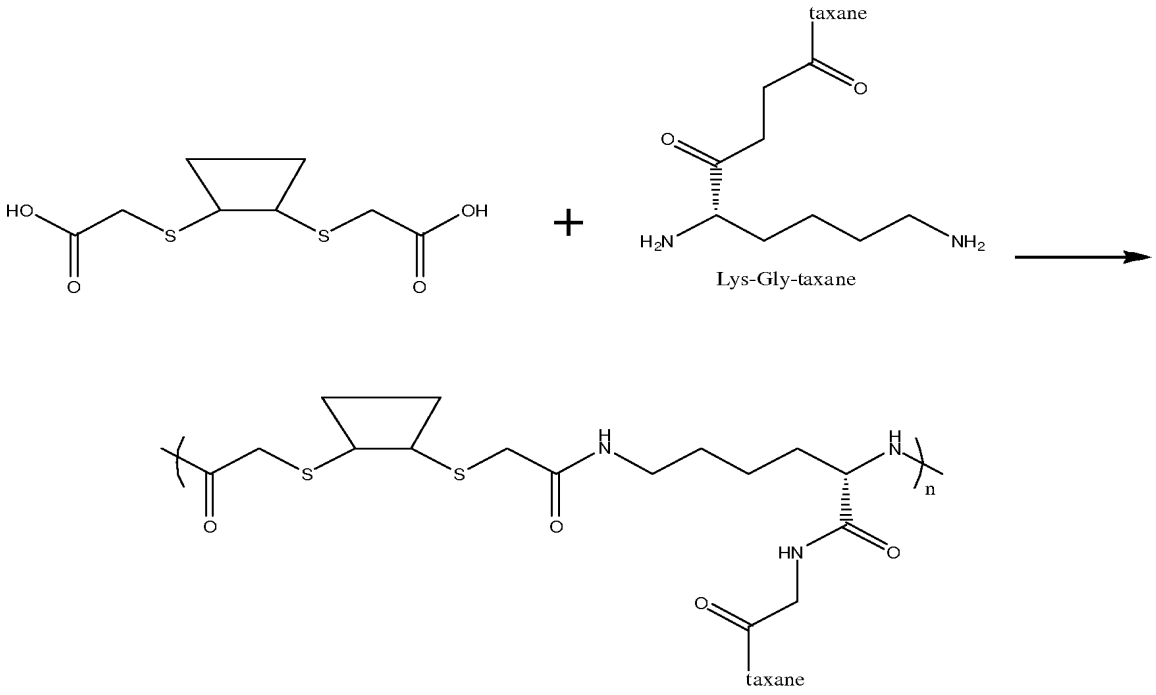
Scheme VI, as provided above, includes embodiments where taxane is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane to the polymer and/or when less than an equivalent amount of taxane is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary.

Scheme VII



Scheme VII, as provided above, includes embodiments where gly-taxane is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane to the polymer and/or when less than an equivalent amount of taxane is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary.

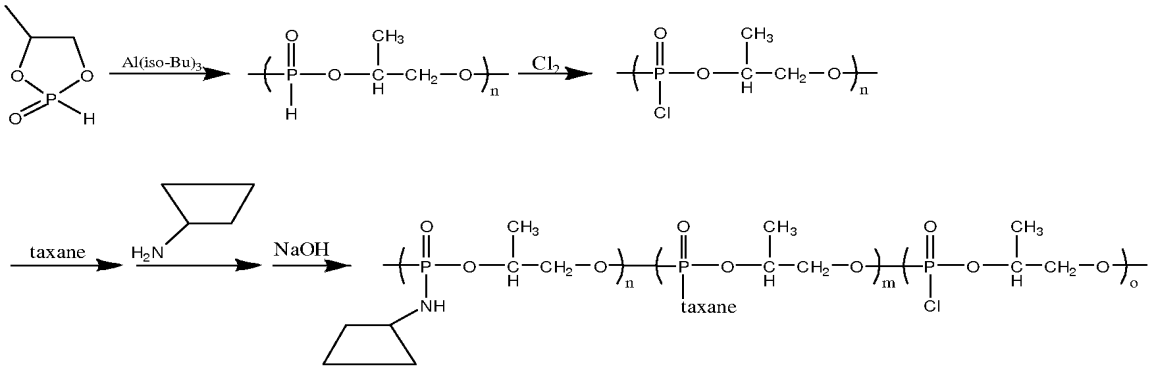
Scheme VIII



Scheme VIII, as provided above, includes embodiments where taxane is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane to the polymer and/or when less than an equivalent amount of taxane is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary.

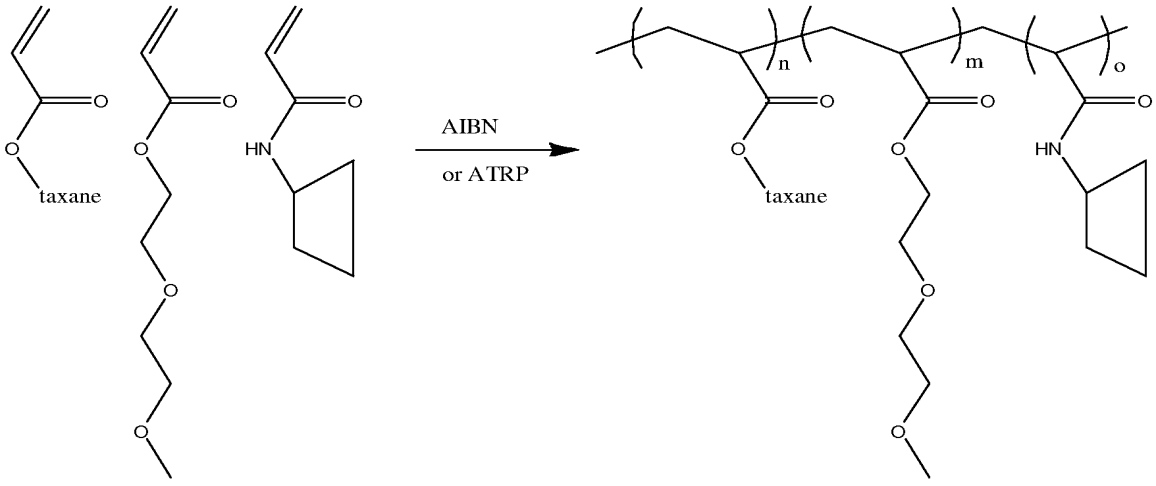
Additional examples of methods of synthesizing CDP-taxane conjugates are shown in Schemes IX-XIV below. In each of Schemes IX-XIV, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

Scheme IX

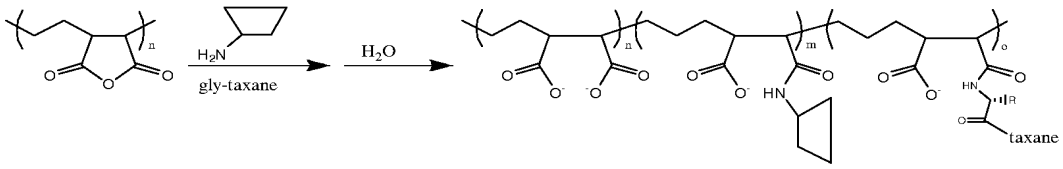


Scheme IX, as provided above, includes embodiments where taxane is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane to the polymer and/or when less than an equivalent amount of taxane is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary.

Scheme X

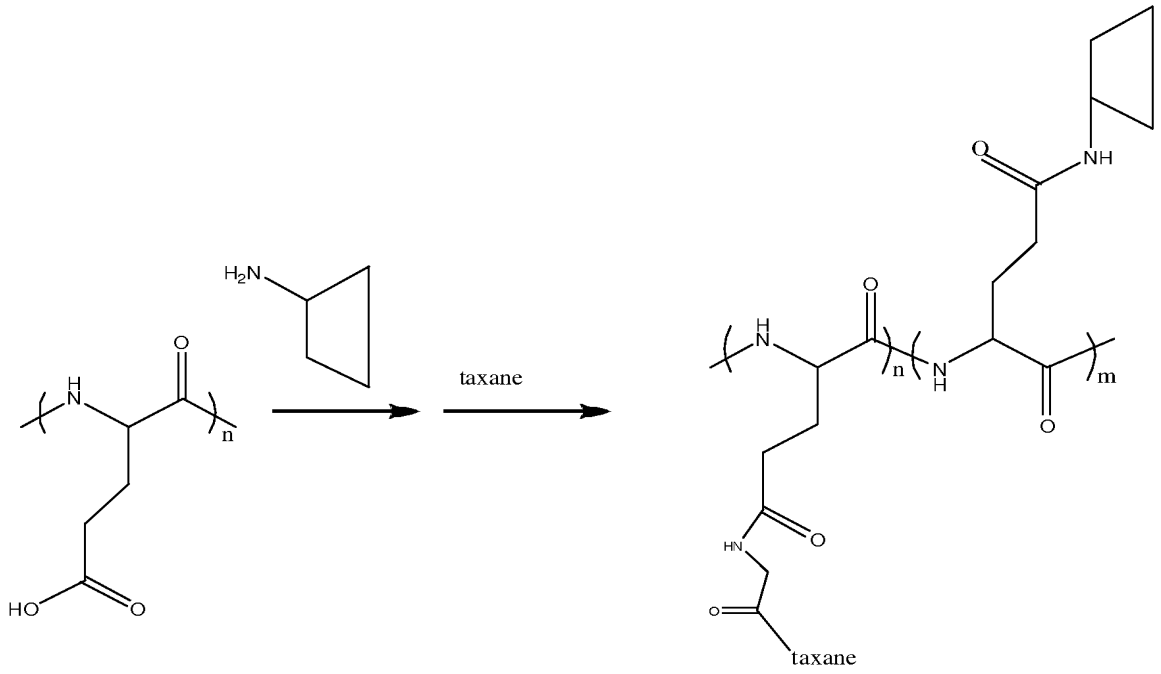


Scheme XI



Scheme XI, as provided above, includes embodiments where gly-taxane is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane to the polymer and/or when less than an equivalent amount of taxane is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary.

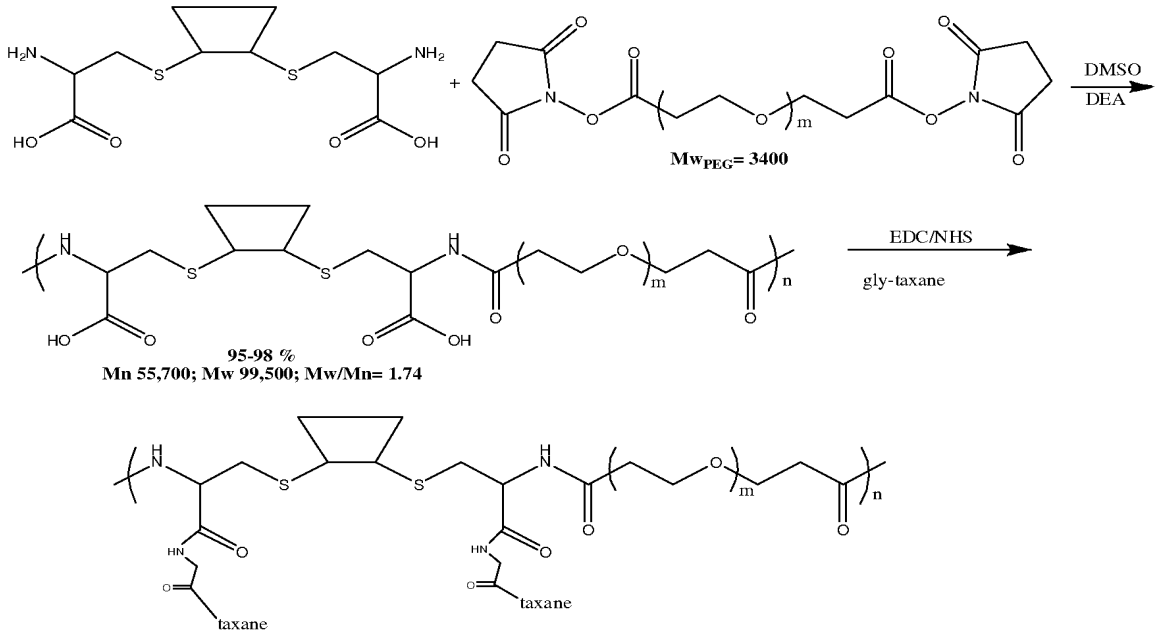
Scheme XII



Scheme XII, as provided above, includes embodiments where taxane is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane to the polymer and/or when less than an equivalent amount of taxane is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary.

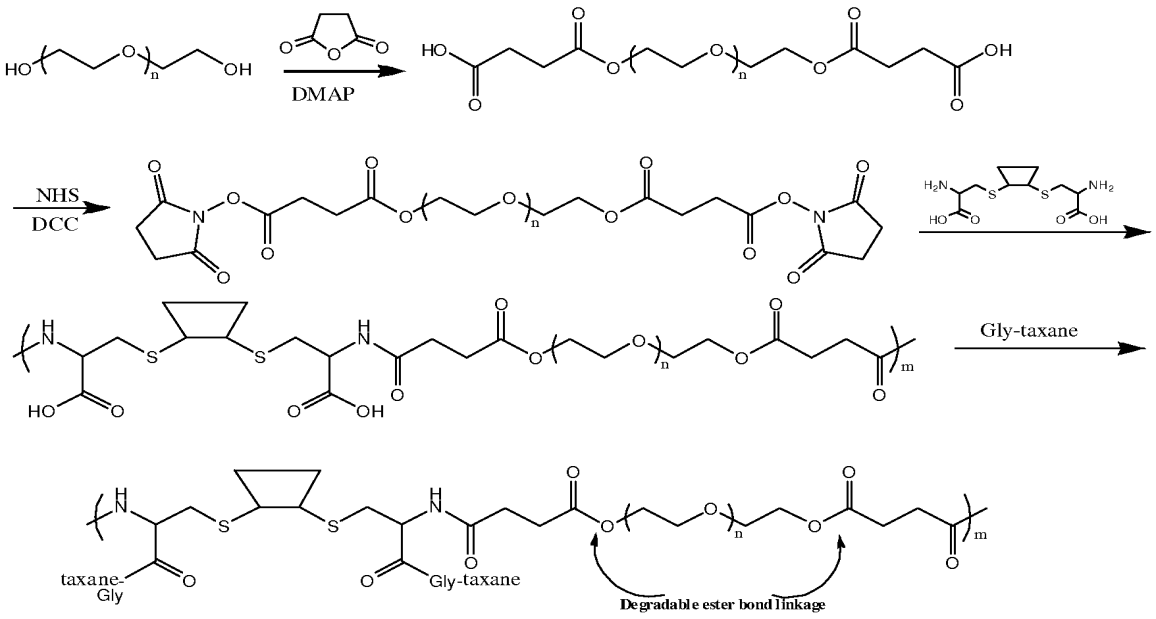
The present invention further contemplates CDPs and CDP-conjugates synthesized using CD-biscysteine monomer and a di-NHS ester such as PEG-DiSPA or PEG-BTC as shown in Schemes XIII-XIV below.

Scheme XIII



Scheme XIII, as provided above, includes embodiments where gly-taxane is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane to the polymer and/or when less than an equivalent amount of taxane is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary.

Scheme XIV



Scheme XIV, as provided above, includes embodiments where gly-taxane is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane to the polymer and/or when less than an equivalent amount of taxane is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary.

In some embodiments, a CDP-taxane conjugate can be made by providing a CDP comprising cyclodextrin moieties and comonomers which do not contain cyclodextrin moieties (comonomers), wherein the cyclodextrin moieties and comonomers alternate in the CDP and wherein the CDP comprises at least four, five, six, seven, eight, etc. cyclodextrin moieties and at least four, five, six, seven, eight, etc. comonomers; and attaching a taxane to the CDP.

In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

In some embodiments, the taxane is attached via a linker. In some embodiments, the taxane is attached to the water soluble linear polymer through an attachment that is cleaved under biological conditions to release the taxane. In some embodiments, the taxane is attached to the water soluble linear polymer at a cyclodextrin moiety or a comonomer. In some embodiments, the taxane is attached to the water soluble linear polymer via an optional linker to a cyclodextrin moiety or a comonomer.

In some embodiments, the cyclodextrin moieties comprise linkers to which therapeutic agents are linked. In some embodiments, the cyclodextrin moieties comprise linkers to which therapeutic agents are linked via a second linker.

In some embodiments, the CDP is made by a process comprising: providing cyclodextrin moiety precursors, providing comonomer precursors, and copolymerizing said cyclodextrin moiety precursors and comonomer precursors to thereby make a CDP comprising cyclodextrin moieties and comonomers. In some embodiments, the CDP is conjugated with a taxane to provide a CDP-taxane conjugate.

In some embodiments, the method includes providing cyclodextrin moiety precursors modified to bear one reactive site at each of exactly two positions, and reacting the cyclodextrin moiety precursors with comonomer precursors having exactly two reactive moieties capable of forming a covalent bond with the reactive sites under polymerization conditions that promote reaction of the reactive sites with the reactive moieties to form covalent bonds between the comonomers and the cyclodextrin moieties, whereby a CDP comprising alternating units of a cyclodextrin moiety and a comonomer is produced.

In some embodiments, the taxane is attached to the CDP via a linker. In some embodiments, the linker is cleaved under biological conditions.

In some embodiments, the taxane makes up at least 5%, 10%, 15%, 20%, 25%, 30%, or even 35% by weight of the CDP-taxane conjugate. In some embodiments, at least about 50% of available positions on the CDP are reacted with a taxane and/or a linker taxane (e.g., at least about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%).

In some embodiments, the comonomer comprises polyethylene glycol of molecular weight 3,400 Da, the cyclodextrin moiety comprises beta-cyclodextrin, the theoretical maximum loading of taxane on the CDP-taxane conjugate is 19%, and taxane

is 17-21% by weight of the CDP-taxane conjugate. In some embodiments, about 80-90% of available positions on the CDP are reacted with a taxane and/or a linker taxane.

In some embodiments, the comonomer precursor is a compound containing at least two functional groups through which reaction and thus linkage of the cyclodextrin moieties is achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer precursor comprise an amino, acid, imidazole, hydroxyl, thio, acyl halide, -HC=CH-, —C≡C— group, or derivative thereof. In some embodiments, the two functional groups are the same and are located at termini of the comonomer precursor. In some embodiments, a comonomer contains one or more pendant groups with at least one functional group through which reaction and thus linkage of a therapeutic agent is achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer pendant group comprise an amino, acid, imidazole, hydroxyl, thiol, acyl halide, ethylene, ethyne group, or derivative thereof. In some embodiments, the pendant group is a substituted or unsubstituted branched, cyclic or straight chain C1-C10 alkyl, or arylalkyl optionally containing one or more heteroatoms within the chain or ring.

In some embodiments, the cyclodextrin moiety comprises an alpha, beta, or gamma cyclodextrin moiety.

In some embodiments, the taxane is poorly soluble in water.

In some embodiments, the solubility of the taxane is <5 mg/ml at physiological pH.

In some embodiments, the taxane is a hydrophobic compound with a log P>0.4, >0.6, >0.8, >1, >2, >3, >4, or >5. In some embodiments, the taxane is hydrophobic and is attached via a second compound.

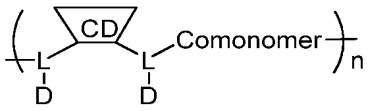
In some embodiments, administration of the CDP-taxane conjugate to a subject results in release of the taxane over a period of at least 6 hours. In some embodiments, administration of the CDP-taxane conjugate to a subject results in release of the taxane over a period of 6 hours to a month. In some embodiments, upon administration of the CDP-taxane conjugate to a subject the rate of taxane release is dependent primarily upon the rate of hydrolysis as opposed to enzymatic cleavage.

In some embodiments, the CDP-taxane conjugate has a molecular weight of 10,000-500,000.

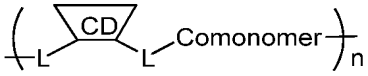
In some embodiments, the cyclodextrin moieties make up at least about 2%, 5%, 10%, 20%, 30%, 50% or 80% of the polymer by weight.

In some embodiments, a the CDP includes a comonomer selected from the group consisting of: an alkylene chain, polysuccinic anhydride, poly-L-glutamic acid, poly(ethyleneimine), an oligosaccharide, and an amino acid chain. In some embodiments, a comonomer comprises a polyethylene glycol chain. In some embodiments, a comonomer comprises a polyglycolic acid or polylactic acid chain. In some embodiments, a comonomer comprises a hydrocarbylene group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR_1, O or S), -OC(O)-, -C(=O)O, -NR_1-, -NR_1CO-, -C(O)NR_1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR_1, -NR_1-C(O)-NR_1-, -NR_1-C(NR_1)-NR_1-, and -B(OR_1)-; and R_1, independently for each occurrence, represents H or a lower alkyl.

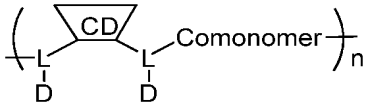
In some embodiments, a CDP-polymer conjugate of the following formula can be made as follows:



providing a polymer of the formula below:



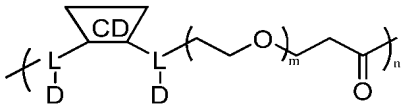
and coupling the polymer with a plurality of D moieties, wherein each D is independently absent or a taxane, to provide:



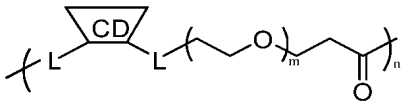
wherein the comonomer has a Mw of 2000 to 5000 Da (e.g., 3000 to 4000 Da, e.g., 3200 kDa to about 3.8 kDa, e.g., about 3.4 kDa) and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

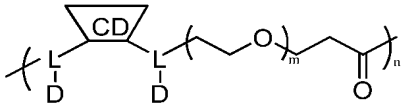
In some embodiments, a CDP-polymer conjugate of the following formula can be made as follows:

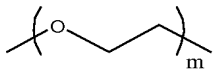


providing a polymer of the formula below:



and coupling the polymer with a plurality of D moieties, wherein each D is independently absent or a taxane, to provide:



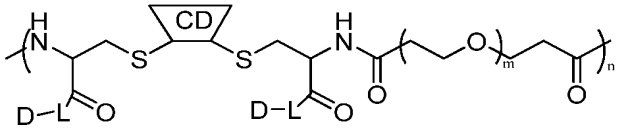
wherein the group  has a Mw of 4.0 kDa or less, e.g., 3.2 to 3.8 kDa, e.g., 3.4 kDa and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

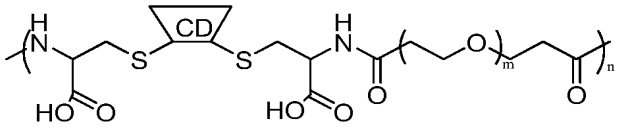
The reaction scheme as provided above includes embodiments where D is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane to the polymer (e.g., 80-90%) and/or when less than an equivalent amount of taxane is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary, for example, the loading of the taxane can be at least about 3% by weight, e.g., at least about 5%, at

least about 8%, at least about 10%, at least about 13%, at least about 15%, or at least about 20%.

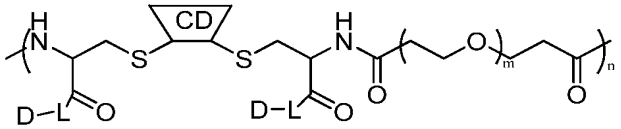
In some embodiments, a CDP-polymer conjugate of the following formula can be made as follows:

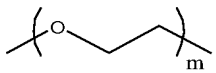


providing a polymer below:



and coupling the polymer with a plurality of L-D moieties, wherein L is a linker or absent and D is a taxane, to provide:



wherein the group  has a Mw of 4.0 kDa or less, e.g., 3.2 to 3.8 kDa, e.g., 3.4 kDa and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

The reaction scheme as provided above includes embodiments where L-D is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the taxane-linker to the polymer (e.g., 80-90%) and/or when less than an equivalent amount of taxane-linker is used in the reaction. Accordingly, the loading of the taxane, by weight of the polymer, can vary, for example, the loading of the taxane can be at least about 3% by weight, e.g., at least about 5%, at least about 8%, at least about 10%, at least about 13%, at least about 15%, or at least about 20%.

In some embodiments, at least a portion of the L moieties of L-D is absent. In some embodiments, each L is independently an amino acid or derivative thereof (e.g., glycine).

In some embodiments, the coupling of the polymer with the plurality of L-D moieties results in the formation of a plurality of amide bonds.

In certain instances, the CDPs are random copolymers, in which the different subunits and/or other monomeric units are distributed randomly throughout the polymer chain. Thus, where the formula X_m-Y_n-Z_o appears, wherein X, Y and Z are polymer subunits, these subunits may be randomly interspersed throughout the polymer backbone. In part, the term "random" is intended to refer to the situation in which the particular distribution or incorporation of monomeric units in a polymer that has more than one type of monomeric units is not directed or controlled directly by the synthetic protocol, but instead results from features inherent to the polymer system, such as the reactivity, amounts of subunits and other characteristics of the synthetic reaction or other methods of manufacture, processing, or treatment.

Pharmaceutical Compositions

In another aspect, the present invention provides a composition, e.g., a pharmaceutical composition, comprising a CDP-taxane conjugate and a pharmaceutically acceptable carrier or adjuvant.

In some embodiments, a pharmaceutical composition may include a pharmaceutically acceptable salt of a compound described herein, e.g., a CDP-taxane conjugate. Pharmaceutically acceptable salts of the compounds described herein include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, benzoate, benzenesulfonate, butyrate, citrate, digluconate, dodecylsulfate, formate, fumarate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, tosylate and undecanoate. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-$(alkyl)_4^+$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the

compounds described herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gailate, aipha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

A composition may include a liquid used for suspending a CDP-taxane conjugate, which may be any liquid solution compatible with the CDP-taxane conjugate, which is also suitable to be used in pharmaceutical compositions, such as a pharmaceutically acceptable nontoxic liquid. Suitable suspending liquids including but are not limited to suspending liquids selected from the group consisting of water, aqueous sucrose syrups, corn syrups, sorbitol, polyethylene glycol, propylene glycol, and mixtures thereof.

A composition described herein may also include another component, such as an antioxidant, antibacterial, buffer, bulking agent, chelating agent, an inert gas, a tonicity agent and/or a viscosity agent.

In one embodiment, the CDP-taxane conjugate is provided in lyophilized form and is reconstituted prior to administration to a subject. The lyophilized CDP-taxane conjugate can be reconstituted by a diluent solution, such as a salt or saline solution, e.g., a sodium chloride solution having a pH between 6 and 9, lactated Ringer's injection solution, or a commercially available diluent, such as PLASMA-LYTE A Injection pH 7.4® (Baxter, Deerfield, IL).

In one embodiment, a lyophilized formulation includes a lyoprotectant or stabilizer to maintain physical and chemical stability by protecting the CDP-taxane conjugate from damage from crystal formation and the fusion process during freeze-

drying. The lyoprotectant or stabilizer can be one or more of polyethylene glycol (PEG), a PEG lipid conjugate (e.g., PEG-ceramide or D-alpha-tocopheryl polyethylene glycol 1000 succinate), poly(vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP), polyoxyethylene esters, poloxomers, Tweens, lecithins, saccharides, oligosaccharides, polysaccharides and polyols (e.g., trehalose, mannitol, sorbitol, lactose, sucrose, glucose and dextran), salts and crown ethers.

In some embodiments, the lyophilized CDP-taxane conjugate is reconstituted with a mixture of equal parts by volume of Dehydrated Alcohol, USP and a nonionic surfactant, such as a polyoxyethylated castor oil surfactant available from GAF Corporation, Mount Olive, N.J., under the trademark, Cremophor EL. The lyophilized product and vehicle for reconstitution can be packaged separately in appropriately light-protected vials. To minimize the amount of surfactant in the reconstituted solution, only a sufficient amount of the vehicle may be provided to form a solution having a concentration of about 2 mg/mL to about 4 mg/mL of the CDP-taxane conjugate. Once dissolution of the drug is achieved, the resulting solution is further diluted prior to injection with a suitable parenteral diluent. Such diluents are well known to those of ordinary skill in the art. These diluents are generally available in clinical facilities. It is, however, within the scope of the present invention to package the subject CDP-taxane conjugate with a third vial containing sufficient parenteral diluent to prepare the final concentration for administration. A typical diluent is Lactated Ringer's Injection.

The final dilution of the reconstituted CDP-taxane conjugate may be carried out with other preparations having similar utility, for example, 5% Dextrose Injection, Lactated Ringer's and Dextrose Injection, Sterile Water for Injection, and the like. However, because of its narrow pH range, pH 6.0 to 7.5, Lactated Ringer's Injection is most typical. Per 100 mL, Lactated Ringer's Injection contains Sodium Chloride USP 0.6 g, Sodium Lactate 0.31 g, Potassium chloride USP 0.03 g and Calcium Chloride2H2O USP 0.02 g. The osmolarity is 275 mOsmol/L, which is very close to isotonicity.

The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration.

The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Routes of Administration

The pharmaceutical compositions described herein may be administered orally, parenterally (e.g., via intravenous, subcutaneous, intracutaneous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional or intracranial injection), topically, mucosally (e.g., rectally or vaginally), nasally, buccally, ophthalmically, via inhalation spray (e.g., delivered via nebulzation, propellant or a dry powder device) or via an implanted reservoir.

Pharmaceutical compositions suitable for parenteral administration comprise one or more CDP-taxane conjugate(s) in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal

agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the agent from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the CDP-taxane conjugate then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the CDP-taxane conjugate in an oil vehicle.

Pharmaceutical compositions suitable for oral administration may be in the form of capsules, cachets, pills, tablets, gums, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouthwashes and the like, each containing a predetermined amount of an agent as an active ingredient. A compound may also be administered as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered peptide or peptidomimetic moistened with an inert liquid diluent.

Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may

also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the CDP-taxane conjugate, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the CDP-taxane conjugate may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Pharmaceutical compositions suitable for topical administration are useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be

formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the a particle described herein include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active particle suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions described herein may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included herein.

The pharmaceutical compositions described herein may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The pharmaceutical compositions described herein may also be administered in the form of suppositories for rectal or vaginal administration. Suppositories may be prepared by mixing one or more CDP-taxane conjugate described herein with one or more suitable non-irritating excipients which is solid at room temperature, but liquid at body temperature. The composition will therefore melt in the rectum or vaginal cavity and release the CDP-taxane conjugate. Such materials include, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate. Compositions of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of the invention.

Dosages and Dosage Regimens

The CDP-taxane conjugate can be formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular subject, composition, and mode of administration, without being toxic to the subject.

In one embodiment, the CDP-taxane conjugate is administered to a subject at a dosage of, e.g., about 0.1 to 300 mg/m^2, about 5 to 275 mg/m^2, about 10 to 250 mg/m^2, e.g., about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290 mg/m^2 of the taxane. Administration can be at regular intervals, such as every 1, 2, 3, 4, or 5 days, or weekly, or every 2, 3, 4, 5, 6, or 7 or 8 weeks. The administration can be over a period of from about 10 minutes to about 6 hours, e.g., from about 30 minutes to about 2 hours, from about 45 minutes to 90 minutes, e.g., about 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours or more. In one embodiment, the CDP-taxane conjugate is administered as a bolus infusion or intravenous push, e.g., over a period of 15 minutes, 10 minutes, 5 minutes or less. In one embodiment, the CDP-taxane is administered in an amount such the desired dose of the agent is administered. Preferably the dose of the CDP-taxane conjugate is a dose described herein.

In one embodiment, the subject receives 1, 2, 3, up to 10 treatments, or more, or until the disorder or a symptom of the disorder is cured, healed, alleviated, relieved, altered, remedied, ameliorated, palliated, improved or affected. For example, the subject receive an infusion once every 1, 2, 3 or 4 weeks until the disorder or a symptom of the disorder are cured, healed, alleviated, relieved, altered, remedied, ameliorated, palliated, improved or affected. Preferably, the dosing schedule is a dosing schedule described herein.

The CDP-taxane conjugate can be administered as a first line therapy, e.g., alone or in combination with an additional agent or agents. In other embodiments, a CDP-taxane is administered after a subject has developed resistance to, has filed to respond to or has relapsed after a first line therapy. The CDP-taxane conjugate can be administered

in combination with a second agent. Preferably, the CDP-taxane is administered in combination with a second agent described herein.

Kits

A CDP-taxane described herein may be provided in a kit. The kit includes a CDP-taxane conjugate described herein and, optionally, a container, a pharmaceutically acceptable carrier and/or informational material. The informational material can be descriptive, instructional, marketing or other material that relates to the methods described herein and/or the use of the CDP-taxane conjugate for the methods described herein.

The informational material of the kits is not limited in its form. In one embodiment, the informational material can include information about production of the CDP-taxane conjugate, physical properties of the CDP-taxane conjugate, concentration, date of expiration, batch or production site information, and so forth. In one embodiment, the informational material relates to methods for administering the CDp-taxane.

In one embodiment, the informational material can include instructions to administer a CDP-taxane conjugate described herein in a suitable manner to perform the methods described herein, e.g., in a suitable dose, dosage form, or mode of administration (e.g., a dose, dosage form, or mode of administration described herein). In another embodiment, the informational material can include instructions to administer a CDP-taxane conjugate described herein to a suitable subject, e.g., a human, e.g., a human having or at risk for a disorder described herein. In another embodiment, the informational material can include instructions to reconstitute a CDP-taxane conjugate described herein into a pharmaceutically acceptable composition.

In one embodiment, the kit includes instructions to use the CDP-taxane conjugate, such as for treatment of a subject. The instructions can include methods for reconstituting or diluting the CDP-taxane conjugate for use with a particular subject or in combination with a particular chemotherapeutic agent. The instructions can also include methods for reconstituting or diluting the CDP-taxane conjugate for use with a particular means of administration, such as by intravenous infusion.

In another embodiment, the kit includes instructions for treating a subject with a particular indication, such as a particular cancer, or a cancer at a particular stage. For example, the instructions can be for a cancer or cancer at stage described herein. The instructions may also address first line treatment of a subject who has a particular cancer, or cancer at a stage described herein. The instructions can also address treatment of a subject who has been non-responsive to a first line therapy or has become sensitive (e.g., has one or more unacceptable side effect) to a first line therapy, such as a taxane, an anthracycline, an alkylating agent, a platinum based agent, a vinca alkaloid. In another embodiment, the instructions will describe treatment of selected subjects with the CDP-taxane conjugate. For example, the instructions can describe treatment of one or more of: a subject who has received an anticancer agent (e.g., a taxane) and has a neutrophil count less than a standard; a subject who has moderate to severe neutropenia; a subject who has experienced one or more symptom of neuropathy from treatment with an anticancer agent, e.g., a taxane, a vinca alkaloid, an alkylating agent, an anthracycline, a platinum-based agent or an epothilone; a subject who has experienced an infusion site reaction or has or is at risk for having hypersensitivity to treatment with an anticancer agent (e.g., a taxane); a subject having hepatic impairment, e.g., having transaminase (ALT and/or AST levels) greater than the upper limit of normal (ULN) and/or bilirubin levels greater than ULN; a subject havinghepatic impairment, e.g., ALP levels greater than the upper limit of normal (ULN), SGOT and/or SGPT levels greater the upper limit of normal (ULN) and/or bilirubin levels greater than the ULN; a subject who is currently being administered or will be administered a cytochrome P450 isoenzyme inhibitor; a subject who has experienced or is at risk for renal impairment, a subject who has or is at risk of having a gastroinstinal disorder (e.g., vomiting, nausea and/or diarrhea, e.g., associated with the administration of a chemotherapeutic agent (e.g., a taxane)),and a subject who has or is at risk for having fluid retention and/or effusion.

The informational material of the kits is not limited in its form. In many cases, the informational material, e.g., instructions, is provided in printed matter, e.g., a printed text, drawing, and/or photograph, e.g., a label or printed sheet. However, the informational material can also be provided in other formats, such as Braille, computer readable material, video recording, or audio recording. In another embodiment, the

informational material of the kit is contact information, e.g., a physical address, email address, website, or telephone number, where a user of the kit can obtain substantive information about a CDP-taxane conjugate described herein and/or its use in the methods described herein. The informational material can also be provided in any combination of formats.

In addition to a CDP-taxane conjugate described herein, the composition of the kit can include other ingredients, such as a surfactant, a lyoprotectant or stabilizer, an antioxidant, an antibacterial agent, a bulking agent, a chelating agent, an inert gas, a tonicity agent and/or a viscosity agent, a solvent or buffer, a stabilizer, a preservative, a flavoring agent (e.g., a bitter antagonist or a sweetener), a fragrance, a dye or coloring agent, for example, to tint or color one or more components in the kit, or other cosmetic ingredient, a pharmaceutically acceptable carrier and/or a second agent for treating a condition or disorder described herein. Alternatively, the other ingredients can be included in the kit, but in different compositions or containers than a CDP-taxane described herein. In such embodiments, the kit can include instructions for admixing a CDP-taxane conjugate described herein and the other ingredients, or for using a CDP-taxane conjugate described herein together with the other ingredients.

In another embodiment, the kit includes a second therapeutic agent, such as a second chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein. In one embodiment, the second agent is in lyophilized or in liquid form. In one embodiment, the CDP-taxane conjugate and the second therapeutic agent are in separate containers, and in another embodiment, the CDP-taxane conjugate and the second therapeutic agent are packaged in the same container.

In some embodiments, a component of the kit is stored in a sealed vial, e.g., with a rubber or silicone enclosure (e.g., a polybutadiene or polyisoprene enclosure). In some embodiments, a component of the kit is stored under inert conditions (e.g., under Nitrogen or another inert gas such as Argon). In some embodiments, a component of the kit is stored under anhydrous conditions (e.g., with a desiccant). In some embodiments, a component of the kit is stored in a light blocking container such as an amber vial.

A CDP-taxane described herein can be provided in any form, e.g., liquid, frozen, dried or lyophilized form. It is preferred that a particle described herein be substantially

pure and/or sterile. When a CDP-taxane conjugate described herein is provided in a liquid solution, the liquid solution preferably is an aqueous solution, with a sterile aqueous solution being preferred. In one embodiment, the CDP-taxane conjugate is provided in lyophilized form and, optionally, a diluent solution is provided for reconstituting the lyophilized agent. The diluent can include for example, a salt or saline solution, e.g., a sodium chloride solution having a pH between 6 and 9, lactated Ringer's injection solution, D5W, or PLASMA-LYTE A Injection pH 7.4® (Baxter, Deerfield, IL).

The kit can include one or more containers for the composition containing a CDP-taxane conjugate described herein. In some embodiments, the kit contains separate containers, dividers or compartments for the composition and informational material. For example, the composition can be contained in a bottle, vial, IV admixture bag, IV infusion set, piggyback set or syringe, and the informational material can be contained in a plastic sleeve or packet. In other embodiments, the separate elements of the kit are contained within a single, undivided container. For example, the composition is contained in a bottle, vial or syringe that has attached thereto the informational material in the form of a label. In some embodiments, the kit includes a plurality (e.g., a pack) of individual containers, each containing one or more unit dosage forms (e.g., a dosage form described herein) of a CDP-taxane conjugate described herein. For example, the kit includes a plurality of syringes, ampules, foil packets, or blister packs, each containing a single unit dose of a particle described herein. The containers of the kits can be air tight, waterproof (e.g., impermeable to changes in moisture or evaporation), and/or light-tight.

The kit optionally includes a device suitable for administration of the composition, e.g., a syringe, inhalant, pipette, forceps, measured spoon, dropper (e.g., eye dropper), swab (e.g., a cotton swab or wooden swab), or any such delivery device. In one embodiment, the device is a medical implant device, e.g., packaged for surgical insertion.

Combination therapy

The CDP-taxane conjugate may be used in combination with other known therapies. Administered "in combination", as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject's affliction with the disorder, e.g., the two or more treatments are delivered after the subject

has been diagnosed with the disorder and before the disorder has been cured or eliminated or treatment has ceased for other reasons. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery". In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, e.g., an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

The CDP-taxane conjugate and the at least one additional therapeutic agent can be administered simultaneously, in the same or in separate compositions, or sequentially. For sequential administration, the CDP-taxane conjugate can be administered first, and the additional agent can be administered second, or the order of administration can be reversed.

In some embodiments, the CDP-taxane conjugate is administered in combination with other therapeutic treatment modalities, including surgery, radiation, cryosurgery, and/or thermotherapy. Such combination therapies may advantageously utilize lower dosages of the administered agent and/or other chemotherapeutic agent, thus avoiding possible toxicities or complications associated with the various monotherapies. The phrase "radiation" includes, but is not limited to, external-beam therapy which involves three dimensional, conformal radiation therapy where the field of radiation is designed to conform to the volume of tissue treated; interstitial-radiation therapy where seeds of radioactive compounds are implanted using ultrasound guidance; and a combination of external-beam therapy and interstitial-radiation therapy.

In some embodiments, the CDP-taxane conjugate is administered with at least one additional therapeutic agent, such as a chemotherapeutic agent. In certain embodiments, the CDP-taxane is administered in combination with one or more additional chemotherapeutic agent, e.g., with one or more chemotherapeutic agents described herein. Exemplary classes of chemotherapeutic agents include, e.g., the following:

alkylating agents (including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): uracil mustard (Aminouracil Mustard®, Chlorethaminacil®, Demethyldopan®, Desmethyldopan®, Haemanthamine®, Nordopan®, Uracil nitrogen mustard®, Uracillost®, Uracilmostaza®, Uramustin®, Uramustine®), chlormethine (Mustargen®), cyclophosphamide (Cytoxan®, Neosar®, Clafen®, Endoxan®, Procytox®, Revimmune™), ifosfamide (Mitoxana®), melphalan (Alkeran®), Chlorambucil (Leukeran®), pipobroman (Amedel®, Vercyte®), triethylenemelamine (Hemel®, Hexalen®, Hexastat®), triethylenethiophosphoramine, Temozolomide (Temodar®), thiotepa (Thioplex®), busulfan (Busilvex®, Myleran®), carmustine (BiCNU®), lomustine (CeeNU®), streptozocin (Zanosar®), and Dacarbazine (DTIC-Dome®).

anti-EGFR antibodies (e.g., cetuximab (Erbitux®), panitumumab (Vectibix®), and gefitinib (Iressa®)).

anti-Her-2 antibodies (e.g., trastuzumab (Herceptin®) and other antibodies from Genentech).

antimetabolites (including, without limitation, folic acid antagonists (also referred to herein as antifolates), pyrimidine analogs, purine analogs and adenosine deaminase inhibitors): methotrexate (Rheumatrex®, Trexall®), 5-fluorouracil (Adrucil®, Efudex®, Fluoroplex®), floxuridine (FUDF®), cytarabine (Cytosar-U®, Tarabine PFS), 6-mercaptopurine (Puri-Nethol®)), 6-thioguanine (Thioguanine Tabloid®), fludarabine phosphate (Fludara®), pentostatin (Nipent®), pemetrexed (Alimta®), raltitrexed (Tomudex®), cladribine (Leustatin®), clofarabine (Clofarex®, Clolar®), mercaptopurine (Puri-Nethol®), capecitabine (Xeloda®), nelarabine (Arranon®), azacitidine (Vidaza®) and gemcitabine (Gemzar®). Preferred antimetabolites include, e.g., 5-fluorouracil (Adrucil®, Efudex®, Fluoroplex®), floxuridine (FUDF®), capecitabine (Xeloda®), pemetrexed (Alimta®), raltitrexed (Tomudex®) and gemcitabine (Gemzar®).

vinca alkaloids: vinblastine (Velban®, Velsar®), vincristine (Vincasar®, Oncovin®), vindesine (Eldisine®), vinorelbine (Navelbine®).

platinum-based agents: carboplatin (Paraplat®, Paraplatin®), cisplatin (Platinol®), oxaliplatin (Eloxatin®).

anthracyclines: daunorubicin (Cerubidine®, Rubidomycin®), doxorubicin (Adriamycin®), epirubicin (Ellence®), idarubicin (Idamycin®), mitoxantrone (Novantrone®), valrubicin (Valstar®). Preferred anthracyclines include daunorubicin (Cerubidine®, Rubidomycin®) and doxorubicin (Adriamycin®).

topoisomerase inhibitors: topotecan (Hycamtin®), irinotecan (Camptosar®), etoposide (Toposar®, VePesid®), teniposide (Vumon®), lamellarin D, SN-38, camptothecin (e.g., CRLX101).

taxanes: paclitaxel (Taxol®), docetaxel (Taxotere®), larotaxel, cabazitaxel.

antibiotics: actinomycin (Cosmegen®), bleomycin (Blenoxane®), hydroxyurea (Droxia®, Hydrea®), mitomycin (Mitozytrex®, Mutamycin®).

immunomodulators: lenalidomide (Revlimid®), thalidomide (Thalomid®).

immune cell antibodies: alemtuzamab (Campath®), gemtuzumab (Myelotarg®), rituximab (Rituxan®), tositumomab (Bexxar®).

proteosome inhibitors: bortezomib (Velcade®).

interferons (e.g., IFN-alpha (Alferon®, Roferon-A®, Intron®-A) or IFN-gamma (Actimmune®))

interleukins: IL-1, IL-2 (Proleukin®), IL-24, IL-6 (Sigosix®), IL-12.

HSP90 inhibitors (e.g., geldanamycin or any of its derivatives). In certain embodiments, the HSP90 inhibitor is selected from geldanamycin, 17-alkylamino-17-desmethoxygeldanamycin ("17-AAG") or 17-(2-dimethylaminoethyl)amino-17-desmethoxygeldanamycin ("17-DMAG").

anti-androgens which include, without limitation nilutamide (Nilandron®) and bicalutamide (Caxodex®).

antiestrogens which include, without limitation tamoxifen (Nolvadex®), toremifene (Fareston®), letrozole (Femara®), testolactone (Teslac®), anastrozole (Arimidex®), bicalutamide (Casodex®), exemestane (Aromasin®), flutamide

(Eulexin®), fulvestrant (Faslodex®), raloxifene (Evista®, Keoxifene®) and raloxifene hydrochloride.

anti-hypercalcaemia agents which include without limitation gallium (III) nitrate hydrate (Ganite®) and pamidronate disodium (Aredia®).

apoptosis inducers which include without limitation ethanol, 2-[[3-(2,3-dichlorophenoxy)propyl]amino]-(9Cl), gambogic acid, embelin and arsenic trioxide (Trisenox®).

Aurora kinase inhibitors which include without limitation binucleine 2.

Bruton's tyrosine kinase inhibitors which include without limitation terreic acid.

calcineurin inhibitors which include without limitation cypermethrin, deltamethrin, fenvalerate and tyrphostin 8.

CaM kinase II inhibitors which include without limitation 5-Isoquinolinesulfonic acid, 4-[{2S)-2-[(5-isoquinolinylsulfonyl)methylamino]-3-oxo-3-{4-phenyl-1-piperazinyl)propyl]phenyl ester and benzenesulfonamide.

CD45 tyrosine phosphatase inhibitors which include without limitation phosphonic acid.

CDC25 phosphatase inhibitors which include without limitation 1,4-naphthalene dione, 2,3-bis[(2-hydroxyethyl)thio]-(9Cl).

CHK kinase inhibitors which include without limitation debromohymenialdisine.

cyclooxygenase inhibitors which include without limitation 1H-indole-3-acetamide, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-N-(2-phenylethyl)-(9Cl), 5-alkyl substituted 2-arylaminophenylacetic acid and its derivatives (e.g., celecoxib (Celebrex®), rofecoxib (Vioxx®), etoricoxib (Arcoxia®), lumiracoxib (Prexige®), valdecoxib (Bextra®) or 5-alkyl-2-arylaminophenylacetic acid).

cRAF kinase inhibitors which include without limitation 3-(3,5-dibromo-4-hydroxybenzylidene)-5-iodo-1,3-dihydroindol-2-one and benzamide, 3-(dimethylamino)-N-[3-[(4-hydroxybenzoyl)amino]-4-methylphenyl]-(9Cl).

cyclin dependent kinase inhibitors which include without limitation olomoucine and its derivatives, purvalanol B, roascovitine (Seliciclib®), indirubin, kenpaullone, purvalanol A and indirubin-3'-monooxime.

cysteine protease inhibitors which include without limitation 4-morpholinecarboxamide, N-[(1S)-3-fluoro-2-oxo-1-(2-phenylethyl)propyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-(9Cl).

DNA intercalators which include without limitation plicamycin (Mithracin®) and daptomycin (Cubicin®).

DNA strand breakers which include without limitation bleomycin (Blenoxane®).

E3 ligase inhibitors which include without limitation N-((3,3,3-trifluoro-2-trifluoromethyl)propionyl)sulfanilamide.

EGF Pathway Inhibitors which include, without limitation tyrphostin 46, EKB-569, erlotinib (Tarceva®), gefitinib (Iressa®), lapatinib (Tykerb®) and those compounds that are generically and specifically disclosed in WO 97/02266, EP 0 564 409, WO 99/03854, EP 0 520 722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and WO 96/33980.

farnesyltransferase inhibitors which include without limitation A-hydroxyfarnesylphosphonic acid, butanoic acid, 2-[(2S)-2-[[(2S,3S)-2-[[(2R)-2-amino-3-mercaptopropyl]amino]-3-methylpentyl]oxy]-1-oxo-3-phenylpropyl]amino]-4-(methylsulfonyl)-1-methylethylester (2S)-(9Cl), and manumycin A.

Flk-1 kinase inhibitors which include without limitation 2-propenamide, 2-cyano-3-[4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-(2E)-(9Cl).

glycogen synthase kinase-3 (GSK3) inhibitors which include without limitation indirubin-3'-monooxime.

histone deacetylase (HDAC) inhibitors which include without limitation suberoylanilide hydroxamic acid (SAHA), [4-(2-amino-phenylcarbamoyl)-benzyl]-carbamic acid pyridine-3-ylmethylester and its derivatives, butyric acid, pyroxamide, trichostatin A, oxamflatin, apicidin, depsipeptide, depudecin, trapoxin and compounds disclosed in WO 02/22577.

I-kappa B-alpha kinase inhibitors (IKK) which include without limitation 2-propenenitrile, 3-[(4-methylphenyl)sulfonyl]-(2E)-(9Cl).

imidazotetrazinones which include without limitation temozolomide (Methazolastone®, Temodar® and its derivatives (e.g., as disclosed generically and specifically in US 5,260,291) and Mitozolomide.

insulin tyrosine kinase inhibitors which include without limitation hydroxyl-2-naphthalenylmethylphosphonic acid.

c-Jun-N-terminal kinase (JNK) inhibitors which include without limitation pyrazoleanthrone and epigallocatechin gallate.

mitogen-activated protein kinase (MAP) inhibitors which include without limitation benzenesulfonamide, N-[2-[[[3-(4-chlorophenyl)-2-propenyl]methyl]amino]methyl]phenyl]-N-(2-hydroxyethyl)-4-methoxy-(9Cl).

MDM2 inhibitors which include without limitation trans-4-iodo, 4'-boranyl-chalcone.

MEK inhibitors which include without limitation butanedinitrile, bis[amino[2-aminophenyl)thio]methylene]-(9Cl).

MMP inhibitors which include without limitation Actinonin, epigallocatechin gallate, collagen peptidomimetic and non-peptidomimetic inhibitors, tetracycline derivatives marimastat (Marimastat®), prinomastat, incyclinide (Metastat®), shark cartilage extract AE-941 (Neovastat®), Tanomastat, TAA211, MMI270B or AAJ996.

mTor inhibitors which include without limitation rapamycin (Rapamune®), and analogs and derivatives thereof, AP23573 (also known as ridaforolimus, deforolimus, or MK-8669), CCI-779 (also known as temsirolimus) (Torisel®) and SDZ-RAD.

NGFR tyrosine kinase inhibitors which include without limitation tyrphostin AG 879.

p38 MAP kinase inhibitors which include without limitation Phenol, 4-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]-(9Cl), and benzamide, 3-(dimethylamino)-N-[3-[(4-hydroxylbenzoyl)amino]-4-methylphenyl]-(9Cl).

p56 tyrosine kinase inhibitors which include without limitation damnacanthal and tyrphostin 46.

PDGF pathway inhibitors which include without limitation tyrphostin AG 1296, tyrphostin 9, 1,3-butadiene-1,1,3-tricarbonitrile, 2-amino-4-(1H-indol-5-yl)-(9Cl), imatinib (Gleevec®) and gefitinib (Iressa®) and those compounds generically and specifically disclosed in European Patent No.: 0 564 409 and PCT Publication No.: WO 99/03854.

phosphatidylinositol 3-kinase inhibitors which include without limitation wortmannin, and quercetin dihydrate.

phosphatase inhibitors which include without limitation cantharidic acid, cantharidin, and L-leucinamide.

protein phosphatase inhibitors which include without limitation cantharidic acid, cantharidin, L-P-bromotetramisole oxalate, 2(5H)-furanone, 4-hydroxy-5-(hydroxymethyl)-3-(1-oxohexadecyl)-(5R)-(9Cl) and benzylphosphonic acid.

PKC inhibitors which include without limitation 1-H-pyrollo-2,5-dione,3-[1-[3-(dimethylamino)propyl]-1H-indol-3-yl]-4-(1H-indol-3-yl)-(9Cl), Bisindolylmaleimide IX, Sphinogosine, staurosporine, and Hypericin.

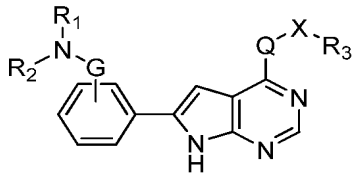
PKC delta kinase inhibitors which include without limitation rottlerin.

polyamine synthesis inhibitors which include without limitation DMFO.

proteasome inhibitors which include, without limitation aclacinomycin A, gliotoxin and bortezomib (Velcade®).

PTP1B inhibitors which include without limitation L-leucinamide.

protein tyrosine kinase inhibitors which include, without limitation tyrphostin Ag 216, tyrphostin Ag 1288, tyrphostin Ag 1295, geldanamycin, genistein and 7H-pyrollo[2,3-d]pyrimidine derivatives of formula I as generically and specifically described in PCT Publication No.: WO 03/013541 and U.S. Publication No.: 2008/0139587:



(I)

Publication No.: 2008/0139587 discloses the various substituents, e.g., R_1, R_2, etc.

SRC family tyrosine kinase inhibitors which include without limitation PP1 and PP2.

Syk tyrosine kinase inhibitors which include without limitation piceatannol.

Janus (JAK-2 and/or JAK-3) tyrosine kinase inhibitors which include without limitation tyrphostin AG 490 and 2-naphthyl vinyl ketone.

retinoids which include without limitation isotretinoin (Accutane®, Amnesteem®, Cistane®, Claravis®, Sotret®) and tretinoin (Aberel®, Aknoten®, Avita®, Renova®, Retin-A®, Retin-A MICRO®, Vesanoid®).

RNA polymerase II elongation inhibitors which include without limitation 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole.

serine/Threonine kinase inhibitors which include without limitation 2-aminopurine.

sterol biosynthesis inhibitors which include without limitation squalene epoxidase and CYP2D6.

VEGF pathway inhibitors, which include without limitation anti-VEGF antibodies, e.g., bevacizumab, and small molecules, e.g., sunitinib (Sutent®), sorafinib (Nexavar®), ZD6474 (also known as vandetanib) (Zactima™), SU6668, CP-547632 and AZD2171 (also known as cediranib) (Recentin™).

Examples of chemotherapeutic agents are also described in the scientific and patent literature, see, e.g., Bulinski (1997) J. Cell Sci. 110:3055-3064; Panda (1997) Proc. Natl. Acad. Sci. USA 94:10560-10564; Muhlradt (1997) Cancer Res. 57:3344-3346; Nicolaou (1997) Nature 387:268-272; Vasquez (1997) Mol. Biol. Cell. 8:973-985; Panda (1996) J. Biol. Chem 271:29807-29812.

In some embodiment, the CDP-taxane conjugate is administered instead of another microtubule affecting agent, e.g., instead of a microtubule affecting agent as a first line therapy or a second line therapy. For example, the CDP-taxane conjugate can be used instead of any of the following microtubule affecting agents allocolchicine (NSC 406042), halichondrin B (NSC 609395), colchicine (NSC 757), colchicine derivatives (e.g., NSC 33410), dolastatin 10 (NSC 376128), maytansine (NSC 153858), rhizoxin (NSC 332598), paclitaxel (Taxol®, NSC 125973), taxol derivatives (e.g., derivatives (e.g., NSC 608832), thiocolchicine (NSC 361792), trityl cysteine (NSC 83265), vinblastine sulfate (NSC 49842), vincristine sulfate (NSC 67574).

In some cases, a hormone and/or steriod can be administered in combination with a CDP-taxane conjugate. Examples of hormones and steroids include: 17a-ethinylestradiol (Estinyl®, Ethinoral®, Feminone®, Orestralyn®), diethylstilbestrol (Acnestrol®, Cyren A®, Deladumone®, Diastyl®, Domestrol®, Estrobene®,

Estrobene®, Estrosyn®, Fonatol®, Makarol®, Milestrol®, Milestrol®, Neo-Oestronol I®, Oestrogenine®, Oestromenin®, Oestromon®, Palestrol®, Stilbestrol®, Stilbetin®, Stilboestroform®, Stilboestrol®, Synestrin®, Synthoestrin®, Vagestrol®), testosterone (Delatestryl®, Testoderm®, Testolin®, Testostroval®, Testostroval-PA®, Testro AQ®), prednisone (Delta-Dome®, Deltasone®, Liquid Pred®, Lisacort®, Meticorten®, Orasone®, Prednicen-M®, Sk-Prednisone®, Sterapred®), Fluoxymesterone (Android-F®, Halodrin®, Halotestin®, Ora-Testryl®, Ultandren®), dromostanolone propionate (Drolban®, Emdisterone®, Masterid®, Masteril®, Masteron®, Masterone®, Metholone®, Permastril®), testolactone (Teslac®), megestrolacetate (Magestin®, Maygace®, Megace®, Megeron®, Megestat®, Megestil®, Megestin®, Nia®, Niagestin®, Ovaban®, Ovarid®, Volidan®), methylprednisolone (Depo-Medrol®, Medlone 21®, Medrol®, Meprolone®, Metrocort®, Metypred®, Solu-Medrol®, Summicort®), methyl-testosterone (Android®, Testred®, Virilon®), prednisolone (Cortalone®, Delta-Cortef®, Hydeltra®, Hydeltrasol®, Meti-derm®, Prelone®), triamcinolone (Aristocort®), chlorotrianisene (Anisene®, Chlorotrisin®, Clorestrolo®, Clorotrisin®, Hormonisene®, Khlortrianizen®, Merbentul®, Metace®, Rianil®, Tace®, Tace-Fn®, Trianisestrol®), hydroxyprogesterone (Delalutin®, Gestiva™), aminoglutethimide (Cytadren®, Elipten®, Orimeten®), estramustine (Emcyt®), medroxyprogesteroneacetate (Provera®, Depo-Provera®), leuprolide (Lupron®, Viadur®), flutamide (Eulexin®), toremifene (Fareston®), and goserelin (Zoladex®).

In certain embodiments, the CDP-taxane conjugate is administered in combination with an anti-microbial (e.g., leptomycin B).

In another embodiment, the CDP-taxane conjugate is administered in combination with an agent or procedure to mitigate potential side effects from the agent compositions such as diarrhea, nausea and vomiting.

Diarrhea may be treated with antidiarrheal agents including, but not limited to opioids (e.g., codeine (Codicept®, Coducept®), oxicodeine, percocet, paregoric, tincture of opium, diphenoxylate (Lomotil®), diflenoxin), and loperamide (Imodium A-D®), bismuth subsalicylate, lanreotide, vapreotide (Sanvar®, Sanvar IR®), motiln antagonists, COX2 inhibitors (e.g., celecoxib (Celebrex®), glutamine (NutreStore®), thalidomide

(Synovir®, Thalomid®), traditional antidiarrhea remedies (e.g., kaolin, pectin, berberine and muscarinic agents), octreotide and DPP-IV inhibitors.

DPP-IV inhibitors employed in the present invention are generically and specifically disclosed in PCT Publication Nos.: WO 98/19998, DE 196 16 486 A1, WO 00/34241 and WO 95/15309.

Nausea and vomiting may be treated with antiemetic agents such as dexamethasone (Aeroseb-Dex®, Alba-Dex®, Decaderm®, Decadrol®, Decadron®, Decasone®, Decaspray®, Deenar®, Deronil®, Dex-4®, Dexace®, Dexameth®, Dezone®, Gammacorten®, Hexadrol®, Maxidex®, Sk-Dexamethasone®), metoclopramide (Reglan®), diphenylhydramine (Benadryl®, SK-Diphenhydramine®), lorazepam (Ativan®), ondansetron (Zofran®), prochlorperazine (Bayer A 173®, Buccastem®, Capazine®, Combid®, Compazine®, Compro®, Emelent®, Emetiral®, Eskatrol®, Kronocin®, Meterazin®, Meterazin Maleate®, Meterazine®, Nipodal®, Novamin®, Pasotomin®, Phenotil®, Stemetil®, Stemzine®, Tementil®, Temetid®, Vertigon®), thiethylperazine (Norzine®, Torecan®), and dronabinol (Marinol®).

In some embodiments, the CDP-taxane conjugate is administered in combination with an immunosuppressive agent. Immunosuppressive agents suitable for the combination include, but are not limited to natalizumab (Tysabri®), azathioprine (Imuran®), mitoxantrone (Novantrone®), mycophenolate mofetil (Cellcept®), cyclosporins (e.g., Cyclosporin A (Neoral®, Sandimmun®, Sandimmune®, SangCya®), cacineurin inhibitors (e.g., Tacrolimus (Prograf®, Protopic®), sirolimus (Rapamune®), everolimus (Afinitor®), cyclophosphamide (Clafen®, Cytoxan®, Neosar®), or methotrexate (Abitrexate®, Folex®, Methotrexate®, Mexate®)), fingolimod, mycophenolate mofetil (CellCept®), mycophenolic acid (Myfortic®), anti-CD3 antibody, anti-CD25 antibody (e.g., Basiliximab (Simulect®) or daclizumab (Zenapax®)), and anti-TNFα antibody (e.g., Infliximab (Remicade®) or adalimumab (Humira®)).

In some embodiments, a CDP-taxane conjugate is administered in combination with a CYP3A4 inhibitor (e.g., ketoconazole (Nizoral®, Xolegel®), itraconazole (Sporanox®), clarithromycin (Biaxin®), atazanavir (Reyataz®), nefazodone (Serzone®, Nefadar®), saquinavir (Invirase®), telithromycin (Ketek®), ritonavir (Norvir®),

amprenavir (also known as Agenerase, a prodrug version is fosamprenavir (Lexiva®, Telzir®), indinavir (Crixivan®), nelfinavir (Viracept®), delavirdine (Rescriptor®) or voriconazole (Vfend®)).

When employing the methods or compositions, other agents used in the modulation of tumor growth or metastasis in a clinical setting, such as antiemetics, can also be administered as desired.

When formulating the pharmaceutical compositions featured in the invention the clinician may utilize preferred dosages as warranted by the condition of the subject being treated. For example, in one embodiment, a CDP-taxane conjugate may be administered at a dosing schedule described herein, e.g., once every one, two three four, five, or six weeks.

Also, in general, a CDP-taxane conjugate and an additional chemotherapeutic agent(s) do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, the CDP-taxane conjugate may be administered intravenously while the chemotherapeutic agent(s) may be administered orally. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

In one embodiment, a CDP-taxane conjugate is administered once every three weeks and an additional therapeutic agent (or additional therapeutic agents) may also be administered every three weeks for as long as treatment is required. Examples of other chemotherapeutic agents which are administered one every three weeks include: an antimetabolite (e.g., floxuridine (FUDF®), pemetrexed (ALIMTA®), 5FU (Adrucil®, Efudex®, Fluoroplex®)); an anthracycline (e.g., daunorubicin (Cerubidine®, Rubidomycin®), epirubicin (Ellence®), idarubicin (Idamycin®), mitoxantrone (Novantrone®), valrubicin (Valstar®)); a vinca alkaloid (e.g., vinblastine (Velban®, Velsar®), vincristine (Vincasar®, Oncovin®), vindesine (Eldisine®) and vinorelbine (Navelbine®)); a topoisomerase inhibitor (e.g., topotecan (Hycamtin®), irinotecan

(Camptosar®), etoposide (Toposar®, VePesid®), teniposide (Vumon®), lamellarin D, SN-38, camptothecin (e.g., CRLX101)); and a platinum-based agent (e.g., cisplatin (Platinol®), carboplatin (Paraplat®, Paraplatin®), oxaliplatin (Eloxatin®)).

In another embodiment, the CDP-taxane conjugate is administered once every two weeks in combination with one or more additional chemotherapeutic agent that is administered orally. For example, the CDP-taxane conjugate can be administered once every two weeks in combination with one or more of the following chemotherapeutic agents: capecitabine (Xeloda®), estramustine (Emcyt®), erlotinib (Tarceva®), rapamycin (Rapamune®), SDZ-RAD, CP-547632; AZD2171, sunitinib (Sutent®), sorafenib (Nexavar®) and everolimus (Afinitor®).

The actual dosage of the CDP-taxane conjugate and/or any additional chemotherapeutic agent employed may be varied depending upon the requirements of the subject and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached.

In some embodiments, when a CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, the additional chemotherapeutic agent (or agents) is administered at a standard dose. For example, a standard dosage for cisplatin is 75-120 mg/m^2 administered every three weeks; a standard dosage for carboplatin is within the range of 200-600 mg/m^2 or an AUC of 0.5-8 mg/ml x min; e.g., at an AUC of 4-6 mg/ml x min; a standard dosage for irinotecan is within 100-125 mg/m^2, once a week; a standard dosage for gemcitabine is within the range of 80-1500 mg/m^2 administered weekly; a standard dose for UFT is within a range of 300-400 mg/m^2 per day when combined with leucovorin administration; a standard dosage for leucovorin is 10-600 mg/m^2 administered weekly.

The disclosure also encompasses a method for the synergistic treatment of cancer wherein a CDP-taxane conjugate is administered in combination with an additional chemotherapeutic agent or agents.

The particular choice of conjugate and anti-proliferative cytotoxic agent(s) or radiation will depend upon the diagnosis of the attending physicians and their judgment of the condition of the subject and the appropriate treatment protocol.

If the CDP-taxane conjugate and the chemotherapeutic agent(s) and/or radiation are not administered simultaneously or essentially simultaneously, then the initial order of administration of the CDp-taxane conjugate, and the chemotherapeutic agent(s) and/or radiation, may be varied. Thus, for example, the CDP-taxane conjugate may be administered first followed by the administration of the chemotherapeutic agent(s) and/or radiation; or the chemotherapeutic agent(s) and/or radiation may be administered first followed by the administration of the CDP-taxane conjugate. This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the subject.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a component (CDP-taxane conjugate, anti-neoplastic agent(s), or radiation) of the treatment according to the individual subject's needs, as the treatment proceeds.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the subject as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

Indications

The disclosed CDP-taxane conjugates are useful in evaluating or treating proliferative disorders, e.g., treating a tumor and metastases thereof wherein the tumor or metastases thereof is a cancer described herein. The methods described herein can be

used to treat a solid tumor, a soft tissue tumor or a liquid tumor. Exemplary solid tumors include malignancies (*e.g.,* sarcomas and carcinomas (e.g., adenocarcinoma or squamous cell carcinoma)) of the various organ systems, such as those of brain, lung, breast, lymphoid, gastrointestinal (*e.g.,* colon), and genitourinary (*e.g.,* renal, urothelial, or testicular tumors) tracts, pharynx, prostate, and ovary. Exemplary adenocarcinomas include colorectal cancers, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, and cancer of the small intestine. The disclosed methods are also useful in evaluating or treating soft tissue tumors such as those of the tendons, muscles or fat, and liquid tumors.

The methods described herein can be used with any cancer, for example those described by the National Cancer Institute. The cancer can be a carcinoma, a sarcoma, a myeloma, a leukemia, a lymphoma or a mixed type. Exemplary cancers described by the National Cancer Institute include:

Digestive/gastrointestinal cancers such as anal cancer; bile duct cancer; extrahepatic bile duct cancer; appendix cancer; carcinoid tumor, gastrointestinal cancer; colon cancer; colorectal cancer, childhood; esophageal cancer; esophageal cancer, childhood; gallbladder cancer; gastric (stomach) cancer; gastric (stomach) cancer, childhood; hepatocellular (liver) cancer, adult (primary); hepatocellular (liver) cancer, childhood (primary); extrahepatic; pancreatic cancer; pancreatic cancer, childhood; sarcoma, rhabdomyosarcoma; pancreatic cancer, islet cell; rectal cancer; and small intestine cancer;

Endocrine cancers such as islet cell carcinoma (endocrine pancreas); adrenocortical carcinoma; adrenocortical carcinoma, childhood; gastrointestinal carcinoid tumor; parathyroid cancer; pheochromocytoma; pituitary tumor; thyroid cancer; thyroid cancer, childhood; multiple endocrine neoplasia syndrome, childhood; and carcinoid tumor, childhood;

Eye cancers such as intraocular melanoma; and retinoblastoma;

Musculoskeletal cancers such as Ewing's family of tumors; osteosarcoma/malignant fibrous histiocytoma of the bone; rhabdomyosarcoma, childhood; soft tissue sarcoma, adult; soft tissue sarcoma, childhood; clear cell sarcoma of tendon sheaths; and uterine sarcoma;

Breast cancer such as breast cancer and pregnancy; breast cancer, childhood; and breast cancer, male;

Neurologic cancers such as brain stem glioma, childhood; brain tumor, adult; brain stem glioma, childhood; cerebellar astrocytoma, childhood; cerebral astrocytoma/malignant glioma, childhood; ependymoma, childhood; medulloblastoma, childhood; pineal and supratentorial primitive neuroectodermal tumors, childhood; visual pathway and hypothalamic glioma, childhood; other childhood brain cancers; adrenocortical carcinoma; central nervous system lymphoma, primary; cerebellar astrocytoma, childhood; neuroblastoma; craniopharyngioma; spinal cord tumors; central nervous system atypical teratoid/rhabdoid tumor; central nervous system embryonal tumors; andsupratentorial primitive neuroectodermal tumors, childhood and pituitary tumor;

Genitourinary cancers such as bladder cancer; bladder cancer, childhood; kidney cancer; ovarian cancer, childhood; ovarian epithelial cancer; ovarian low malignant potential tumor; penile cancer; prostate cancer; renal cell cancer, childhood; renal pelvis and ureter, transitional cell cancer; testicular cancer; urethral cancer; vaginal cancer; vulvar cancer; cervical cancer; Wilms tumor and other childhood kidney tumors; endometrial cancer; and gestational trophoblastic tumor;

Germ cell cancers such as extracranial germ cell tumor, childhood; extragonadal germ cell tumor; ovarian germ cell tumor; and testicular cancer;

Head and neck cancers such as lip and oral cavity cancer; oral cancer, childhood; hypopharyngeal cancer; laryngeal cancer; laryngeal cancer, childhood; metastatic squamous neck cancer with occult primary; mouth cancer; nasal cavity and paranasal sinus cancer; nasopharyngeal cancer; nasopharyngeal cancer, childhood; oropharyngeal cancer; parathyroid cancer; pharyngeal cancer; salivary gland cancer; salivary gland cancer, childhood; throat cancer; and thyroid cancer;

Hematologic/blood cell cancers such as a leukemia (e.g., acute lymphoblastic leukemia, adult; acute lymphoblastic leukemia, childhood; acute myeloid leukemia, adult; acute myeloid leukemia, childhood; chronic lymphocytic leukemia; chronic myelogenous leukemia; and hairy cell leukemia); a lymphoma (e.g., AIDS-related lymphoma; cutaneous T-cell lymphoma; Hodgkin's lymphoma, adult; Hodgkin's lymphoma,

childhood; Hodgkin's lymphoma during pregnancy; non-Hodgkin's lymphoma, adult; non- Hodgkin's lymphoma, childhood; non-Hodgkin's lymphoma during pregnancy; mycosis fungoides; sezary syndrome; T- cell lymphoma, cutaneous; Waldenstrom's macroglobulinemia; and primary central nervous system lymphoma); and other hematologic cancers (e.g., chronic myeloproliferative disorders; multiple myeloma/plasma cell neoplasm; myelodysplastic syndromes; and myelodysplastic/myeloproliferative disorders);

Lung cancer such as non-small cell lung cancer; and small cell lung cancer;

Respiratory cancers such as malignant mesothelioma, adult; malignant mesothelioma, childhood; malignant thymoma; thymoma, childhood; thymic carcinoma; bronchial adenomas/carcinoids; pleuropulmonary blastoma; non-small cell lung cancer; and small cell lung cancer;

Skin cancers such as Kaposi's sarcoma; Merkel cell carcinoma; melanoma; and skin cancer, childhood;

Other childhood cancers and cancers of unknown primary site;

and metastases of the aforementioned cancers can also be treated or prevented in accordance with the methods described herein.

The CDP-taxane conjugates described herein are particularly suited to treat accelerated or metastatic cancers of the bladder cancer, pancreatic cancer, prostate cancer, renal cancer, non-small cell lung cancer, ovarian cancer, melanoma, colorectal cancer, and breast cancer.

In one embodiment, a method is provided for a combination treatment of a cancer, such as by treatment with a CDP-taxane conjugate and a second therapeutic agent. Various combinations are described herein. The combination can reduce the development of tumors, reduces tumor burden, or produce tumor regression in a mammalian host.

In some embodiments, the proliferative disorder is a disease or disorder associated with inflammation. A CDP-taxane conjugate described herein may be administered prior to the onset of, at, or after the initiation of inflammation. When used prophylactically, the CDP-taxane is preferably provided in advance of any inflammatory response or

symptom. Administration of the CDP-taxane conjugate may prevent or attenuate inflammatory responses or symptoms. Exemplary inflammatory conditions include, for example, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, degenerative joint disease, spondouloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, diabetes (e.g., insulin dependent diabetes mellitus or juvenile onset diabetes), menstrual cramps, cystic fibrosis, inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, mucous colitis, ulcerative colitis, gastritis, esophagitis, pancreatitis, peritonitis, Alzheimer's disease, shock, ankylosing spondylitis, gastritis, conjunctivitis, pancreatis (acute or chronic), multiple organ injury syndrome (e.g., secondary to septicemia or trauma), myocardial infarction, atherosclerosis, stroke, reperfusion injury (e.g., due to cardiopulmonary bypass or kidney dialysis), acute glomerulonephritis, vasculitis, thermal injury (i.e., sunburn), necrotizing enterocolitis, granulocyte transfusion associated syndrome, and/or Sjogren's syndrome. Exemplary inflammatory conditions of the skin include, for example, eczema, atopic dermatitis, contact dermatitis, urticaria, schleroderma, psoriasis, and dermatosis with acute inflammatory components.

The CDP-taxane conjugate can be administered to a subject undergoing or who has undergone angioplasty. In one embodiment, the CDP-taxane conjugate is administered to a subject undergoing or who has undergone angioplasty with a stent placement. In some embodiments, the CDP-taxane conjugate can be used as a strut of a stent or a coating for a stent.

The CDP-taxane can be used during the implantation of a stent, e.g., as a separate intravenous administration, as coating for a stent or as the strut of a stent.

Stent

The CDP-taxane conjugates described herein can be used as or be part of a stent. As used herein, the term "stent" refers to a man-made 'tube' inserted into a natural passage or conduit in the body to prevent or counteract localized flow constriction. Types of stents include, e.g., coronary stent, urinary tract stent, urethral/prostatic stent, vascular stent (e.g., peripheral vascular stent, or stent graft), esophageal stent, duodenal stent, colonic stent, biliary stent, and pancreatic stent. Types of stents that can be used in

coronary arteries include, e.g., bare-metal stent (BMS) and drug-eluting stent (DES). A coronary stent can be placed within the coronary artery during an angioplasty procedure.

Bare-metal stent (BMS)

In one embodiment, the CDP-taxane conjugate can be used in combination with a BMS. As used herein, BMS refers to a stent without a coating that is made or a metal or combination of metals. BMS can be made from, e.g., stainless steel (e.g., BxVelocity™ stent, Express2 ™ stent, R stent™, and Matrix® coronary stent), cobalt-chromium alloy (e.g., Driver® coronary stent, ML Vision® stent, and Coronnium® stent), or nickel titanium (Nitinol® stent). A CDP-taxane conjugate described herein can be used as a coating of a BMS, e.g., to coat the luminal and/or abluminal surface of a BMS.

Drug-eluting stent (DES)

In one embodiment, the CDP-taxane conjugate can be a DES or can be part of a DES. As used herein, DES refers to a stent placed into a natural passage or conduit of the body (e.g., a narrowed coronary artery) that releases (e.g., slowly releases) one or more agents to treat one or more symptoms associated with the constricted flow to the passage or conduit and/or one or more effect caused by or associated with the stent. For example, the DES can release one (or more) agent that reduces or inhibits the migration and/or proliferation of vascular smooth muscle cells (SMCs), that promotes or increases epithelialization, that reduces or inhibits a hypersensitivity reaction, that reduces or inhibits inflammation, that reduces or inhibits thrombosis, that reduces the risk of restenosis, and/or that reduces or inhibits other unwanted effects due to the stent.

One type of DES includes a stent strut and a polymer, on which an agent is loaded. Thus, in one embodiment, a CDP-taxane conjugate described herein can be used in combination with other polymeric struts (e.g., other biocompatible or bioasorbable polymers). For example, a CDP-taxane conjugate described herein can be coated on a polymeric strut, e.g., on the luminal and/or abluminal surface of a polymeric strut.

In another embodiment, the CDP-taxane conjugates described herein can be used as a polymeric strut, with out without an additional polymer and/or agent.

In one embodiment, the rate of major adverse cardiac events (MACE) of a subject having a stent made of a CDP-taxane conjugate described herein or a strut coated with a CDP-taxane conjugate described herein is reduced by at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 95% or more, as compared to the rate of MACE of a subject having a stent made of a different material (e.g., a metal or polymer) or a stent not coated or coated with a polymer and/or agent other than the CDP-taxane conjugate. In another embodiment, the need for target vessel revascularization (TVR) of a subject having a stent made of a CDP-taxane conjugate described herein or a strut coated with a CDP-taxane conjugate described herein is reduced by at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 95% or more, compared to the TVR of a subject having a stent made of a different material (e.g., a metal or polymer) or a stent not coated or coated with a polymer and/or agent other than the CDP-taxane conjugate. In yet another embodiment, the rate for target lesion revascularization (TLR) of a subject having a stent made of a CDP-taxane conjugate described herein or a strut coated with a CDP-taxane conjugate described herein is reduced by at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 95% or more, compared to the TLR of a subject having a stent made of a different material (e.g., a metal or polymer) or a stent not coated or coated with a polymer and/or agent other than the CDP-taxane conjugate.

Agents

Agents that can be loaded onto a DES include, for example, antiproliferative agents, e.g., anticancer agents (e.g., a taxane (e.g., docetaxel, paclitaxel, larotaxel and cabazitaxel) and an anthracycline (e.g., doxorubicin); pro-endothelial cell agents, anti-restenotic agents; anti-inflammatory agents; statins (e.g., simovastatin); immunosuppresants (e.g., mycophenolic acid); somatostatin receptor agonists (e.g., angiopeptin); and dimethyl sulfoxide.

Exemplary anti-proliferative agents include, e.g., an anticancer agent, e.g., a taxane (e.g., docetaxel, paclitaxel, larotaxel and cabazitaxel) and an anthracycline (e.g., doxorubicin); and an immunosuppressive agent, e.g., a rapamycin analogue (e.g., everolimus, zotarolimus, biolimus), pimecrolimus, or tacrolimus.

One or more of the pro-endothelial agents can be loaded on the stents, e.g., to promote, accelerate or increase endothelial healing. Exemplary pro-endothelial agents include, e.g., agents that diminish platelet adhesion and/or fibrinogen binding (e.g., titanium-nitride-oxide or titanium-nitride), agents that capture endothelial progenitor cells (EPCs) (e.g., antibodies (e.g., anti-CD34 antibody) or peptides (e.g., integrin-binding cyclic Arg-Gly-Asp peptide)), or estradiol.

One or more of anti-restenotic agent can also be loaded on or in the stents, e.g., anti-inflammatory agents (e.g., dexamethasone), immunosuppressive agents (e.g., mycophenolic acid), antisense agents (e.g., an advanced six-ring morpholino backbone c-myc antisense (AVI-4126)), inhibitors of vascular smooth muscle cell proliferation and/or tissue factor expression (e.g., 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)-reductase-inhibitors (statins), simvastatin, angiopeptin or dimethyl sulfoxide (DMSO)), or anti-hyperlipidemic agents (e.g., probucol).

In one embodiment, the agent (or agents) is loaded on the luminal side of the stent. In another embodiment, the agent (or agents) is loaded on the abluminal side of the stent. In yet another embodiment, the agent (or agents) is loaded on both the luminal and abluminal sides of the stent. In another embodiment, an agent (or agents) is loaded on the luminal side of the stent and a different agent (or combination of agents) is loaded on the abluminal side of the stent. Thus, different agents (e.g., an anti-proliferation agent and a pro-endothelial agent) can be loaded on different sides (luminal or abluminal) of the stent, e.g., to allow for differential agent elution, or different agents can be loaded on the same side (luminal or abluminal side) of the stent, e.g., to allow for dual local agent elution.

In one embodiment, the agent is present at a concentration of at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, or 100 μg/mm. In one embodiment, more than about 50, 60, 70, 80, 90, 95, 99% of the agent is released over a period of one month. In one embodiment, the release of the agent (e.g., a pro-endothelial agent) is delayed for at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days. In one embodiment, the release of the agent sustains for at least 7, 14, 21, 28, 35, or 42 days.

Polymeric Stents

Stents described herein can be made of biocompatible and/or bioabsorbable polymers. A CDP-taxane conjugate described herein can be the stent, the strut of a stent or the CDP-taxane conjugate can coat a strut made of a polymeric material.

An example of a biocompatible stent is the Endeavor Rsolute® stent. This system is composed of three elements: one hydrophobic polymer ('C10') to retain the drug and control drug release, another polymer ('C19') to provide improved biocompatibility, and finally (on the outer-most side of the stent) a polyvinyl pyrrolidinone (PVP) hydrophilic polymer which increases the initial drug burst and further enhances biocompatibility. Thus, in one embodiment, the CDP-taxane conjugate can be coated on an Endeavor Rsolute® stent. In other embodiments, a CDP-taxane conjugate described herein can replace one or more of the elements of the Endeavor Rsolute® stent.

Bioabsorbable polymers (e.g., inert bioabsorbable polymer) can also be used in a DES, e.g., to reduce prothrombogenic potential and/or allow non-invasive imaging. In some embodiments, the bioabsorbable polymer has a degradation time of at least about 14, 21, 28, 35, 42, 49, 56, 63, 70 days.

Exemplary bioasorbable stents include, e.g., a polymeric stent (e.g., a poly-L-lactide stent, a tyrosine poly(desaminotyrosyl-tyrosine ethyl ester) carbonate stent, and a poly(anhydride ester) salicyclic acid stent). For example, Igaki-Tamai stent is constructed from a poly-L-lactic acid polymer and contains either the tyrosine kinase antagonist ST638 or paclitaxel. REVA® stent is a tyrosine poly(desaminotyrosyl-tyrosine ethyl ester) carbonate stent. It is radio-opaque and has slide and lock mechanism designed to allow for substantial reductions in stent-strut thickness. IDEAL™ stent is a poly(anhydride ester) salicyclic acid stent. Infinnium® stent is composed of two biodegradable polymers with different paclitaxel-release kinetics. Other exemplary bioasorbable stents include, e.g., BVS®, Sahajanand®, Infinnium®, BioMATRIX®, Champion®, and Infinnium®. In one embodiment, a CDP-taxane conjugate described herein can be coated onto any of these bioabsorbable stents. In other embodiments, a CDP-taxane conjugate described herein can replace one or more elements of one of these bioabsorbable stents.

Biosorbable Metallic Stents

The CDP-taxane conjugates described herein can be used to coat a bioabsorbable metallic stent. An exemplary bioabsorbable stent is the Absorbable Metal Stent (AMS®) which is an alloy stent made of 93% magnesium and 7% rare-earth metals.

Reservoir stents

As described herein, reservoir stents can be used, e.g., to decrease the "thickness" of the stent or reduce the unwanted effect due to microfragmentation of the polymer and/or the agent. For example, the drug can be loaded in one or more reservoirs or wells in the stent, compared to, e.g., more or less uniformly spread over the stent.

In one embodiment, a CDP-taxane conjugate described herein is loaded in the reservoirs or wells located on the stent, e.g., the CDP-taxane conjugate described herein is loaded in the reservoirs or wells located on the luminal side or the abluminal side of the stent. In yet another embodiment, the CDP-taxane conjugate described herein is loaded in the reservoirs or wells located on both the luminal and abluminal sides of the stent.

In one embodiment, different agents (e.g., an anti-proliferation agent and a pro-endothelial agent) can be loaded into the reservoirs or wells on different sides (luminal or abluminal) of the stent, e.g., to allow for differential agent elution. In another embodiment, different agents can be loaded into adjacent reservoirs or wells of the same side (luminal or abluminal side) of the stent, e.g., to allow for dual local drug elution.

Strut

In one embodiment, the strut thickness is at least about 25, 50, 100, 150, 200, 250 μm. In another embodiment, the strut wideness is at least about 0.002, 0.004, 0.006, 0.008, or 0.01 inch. In yet another embodiment, the number of struts is at least about 4, 8, 12, 16, or 18 in its cross-section.

Various shapes of struts such as a zig zag coil, a ratchet log design, circumferential loops, etc. are known in the art and can be employed in the stents described herein.

In one embodiment, the strut can be made of a CDP-taxane conjugate described herein.

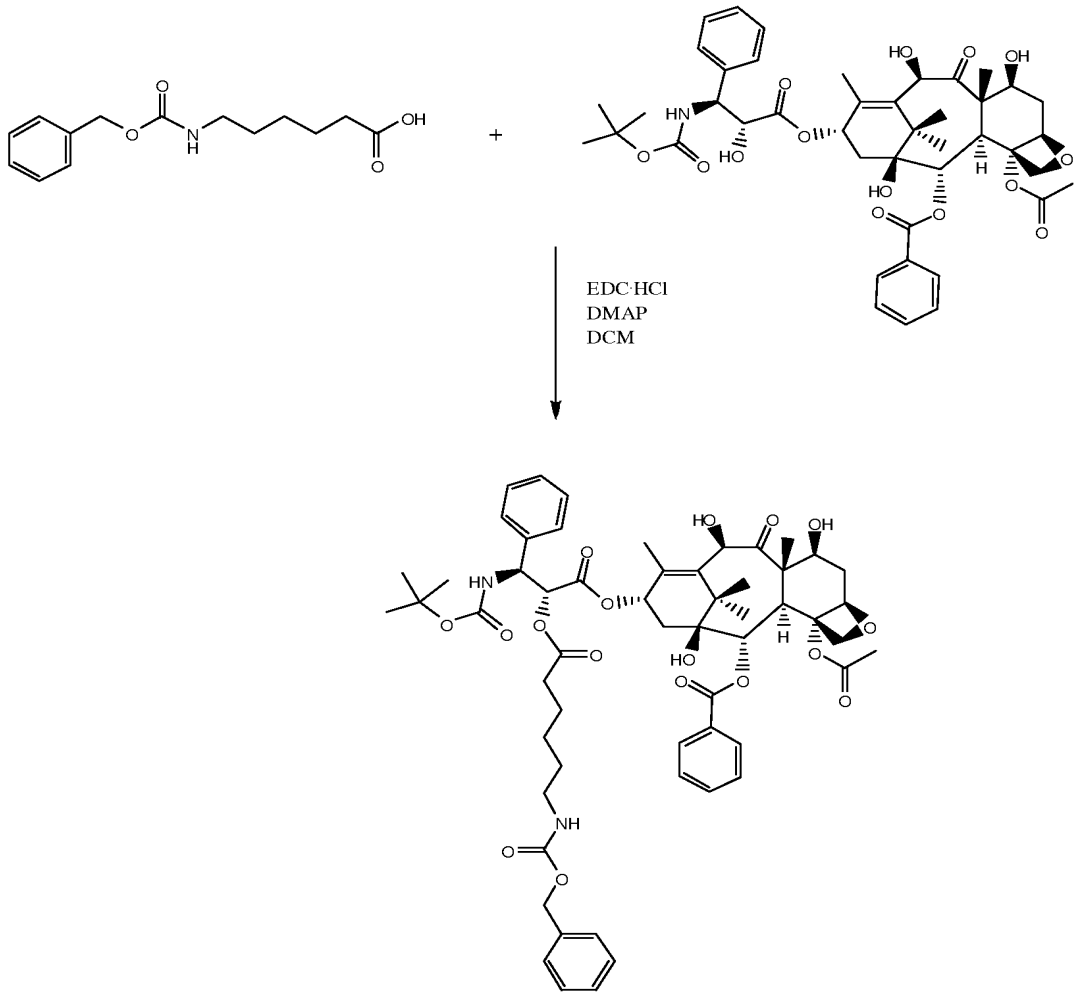
Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

EXAMPLES

Example 1. Synthesis 2'-(6-(carbobenzyloxyamino) caproyl) docetaxel

A 500-mL round-bottom flask equipped with a magnetic stirrer was charged with 6-(carbobenzyloxyamino) caproic acid (4.13 g, 15.5 mmol), docetaxel (12.0 g, 14.8 mmol), and dichloromethane (240 mL). The mixture was stirred for 5 min to produce a clear solution, to which 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (EDC•HCl) (3.40 g, 17.6 mmol) and 4 dimethylaminopyridine (DMAP) (2.15 g, 17.6 mmol) were added. The mixture was stirred at ambient temperature for 3 h at which time, IPC analysis showed a 57% conversion along with 34% residual docetaxel. An additional 0.2 equivalents of EDC•HCl and DMAP were added and the reaction was stirred for 3 h, at which time IPC analysis showed 63% conversion. An additional 0.1 equivalents of 6-(carbobenzyloxyamino) caproic acid along with 0.2 equivalents of EDC•HCl and DMAP were added. The reaction was stirred for 12 h and IPC analysis indicated 74% conversion and 12% residual docetaxel. To further increase the conversion, an additional 0.1 equivalents of 6-(carbobenzyloxyamino) caproic acid and 0.2 equivalents of EDC•HCl and DMAP were added. The reaction was continued for another 3 h at which time, IPC analysis revealed 82% conversion and the residual docetaxel dropped to 3%. The reaction was diluted with DCM (200 mL) and washed with 0.01% HCl (2× 150 mL) and brine (150 mL). The organic layer was separated, dried over sodium sulfate, and filtered. The filtrate was concentrated to a residue and dissolved in ethyl acetate (25 mL). The solution was divided into two portions, each of which was passed through a 120-g silica column (Biotage F40). The flow rate was adjusted to 20 mL/min and 2000 mL of 55:45 ethyl acetate/heptanes was consumed for each of the column purifications. The fractions containing minor impurities were

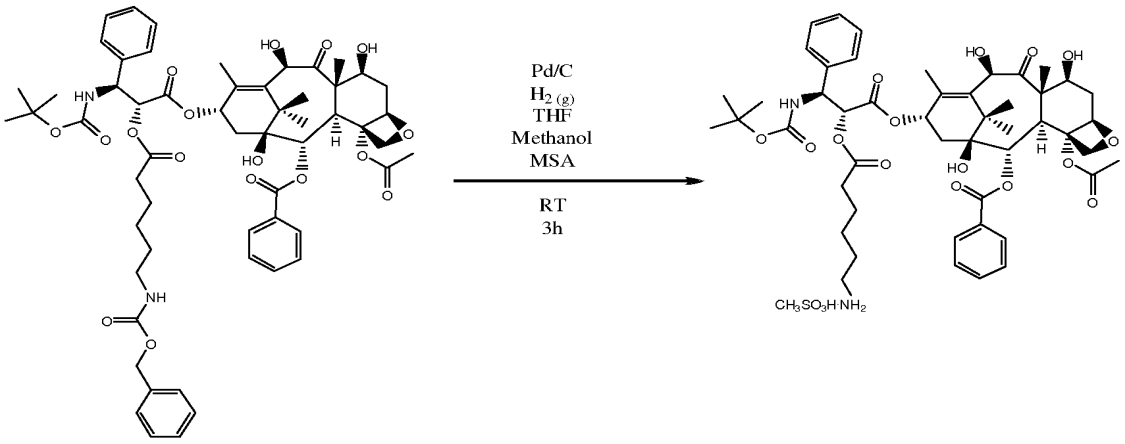
combined, concentrated, and passed through a column a third time. The fractions containing product (shown as a single spot by TLC analysis) from all three column purifications were combined, concentrated to a residue, vacuum-dried at ambient temperature for 16 h to afford the product, 2'-(6-(carbobenzyloxyamino) caproyl) docetaxel as a white powder [10 g, yield: 64%]. The ^{1}H NMR analysis was consistent with the assigned structure of the desired product; however, HPLC analysis (AUC, 227 nm) indicated only a 97% purity along with 3% of bis-adducts. To purify the 2'-(6-(carbobenzyloxyamino) caproyl) docetaxel product, ethyl acetate (20 mL) was added to dissolve the batch to produce a clear solution. The solution was divided into two portions, each of which was passed through a 120-g silica column. The fractions containing product were combined, concentrated to a residue, vacuum-dried at ambient temperature for 16 h to afford the desired product (2'-(6-(carbobenzyloxyamino) caproyl) docetaxel) as a white powder [8.6 g, recovery yield: 86%]. HPLC analysis (AUC, 227 nm) indicated >99% purity.



Example 2. Synthesis of 2'-(6-amino caproyl) docetaxel.$MeSO_3H$

A 1000-mL round-bottom flask equipped with a magnetic stirrer was charged with 2'-(6-(carbobenzyloxyamino) caproyl) docetaxel product [5.3 g, 5.02 mmol] and THF (250 mL). To the resultant clear solution, MeOH (2.5 mL) and 5% Pd/C (1.8 g, 10 mol% of Pd) were added. The mixture was cooled to 0 °C and methanesulfonic acid (316 μL, 4.79 mmol) was added. The flask was evacuated for 10 seconds and filled with hydrogen using a balloon. After 3 h, IPC analysis indicated 62% conversion. The ice-bath was removed and the reaction was allowed to warm up to ambient temperature. After an additional 3 h, IPC analysis indicated that the reaction was complete. The

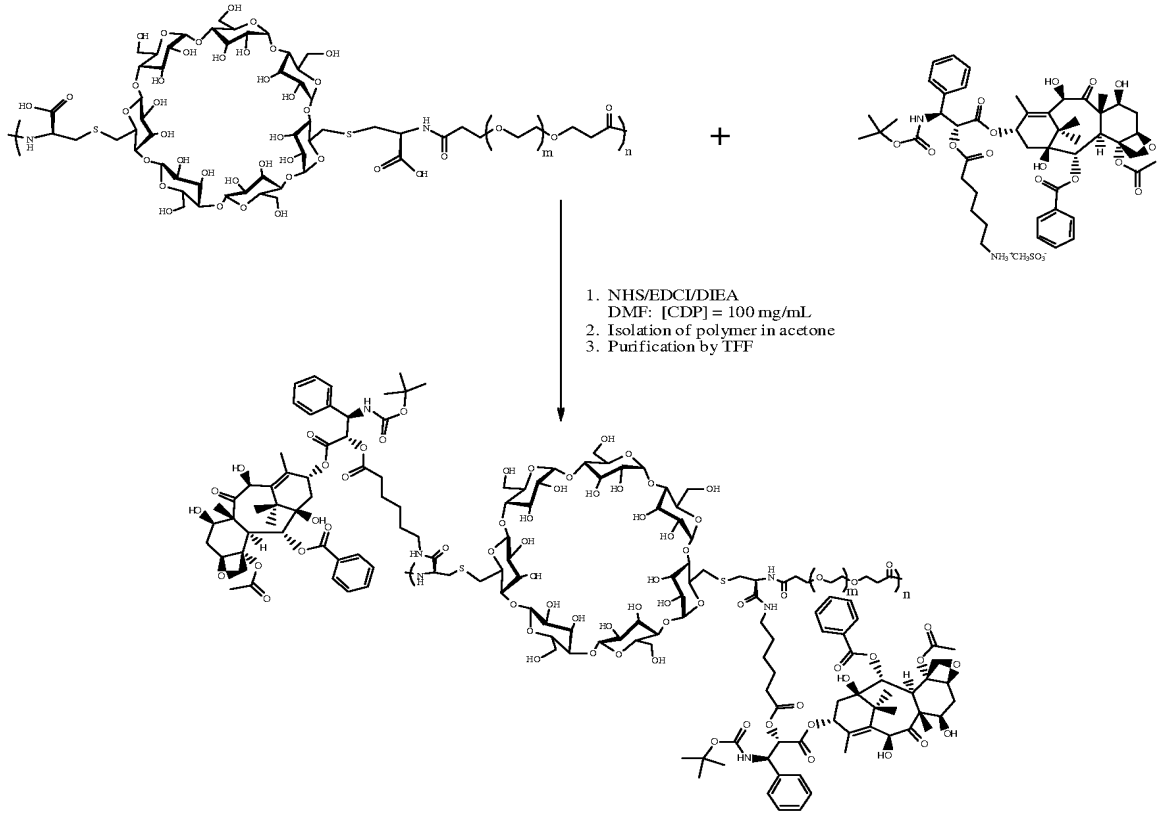
solution was filtered through a Celite® pad and the filtrate was black in appearance. To remove the possible residual Pd, charcoal (5 g, Darco®) was added and the mixture was placed in a fridge overnight and filtered through a Celite® pad to produce a clear colorless solution. This was concentrated at < 20°C under reduced pressure to a volume of ~100 mL, to which methyl tert-butyl ether (MTBE) (100 mL) was added. The resultant solution was added to a solution of cold MTBE (1500 mL) with vigorous stirring over 0.5 h. The suspension was left at ambient temperature for 16 h, the upper clear supernatant was decanted off and the bottom layer was filtered through a 0.45 μm filter membrane. The filter cake was vacuum-dried at ambient temperature for 16 h to afford the desired product 2'-(6-amino caproyl) docetaxel.$MeSO_3H$ as a white solid [4.2 g, yield: 82%]. HPLC analysis indicated >99% purity and the ^1H NMR analysis indicated the desired product.



Example 3. Synthesis of CDP-hexanoate-docetaxel

CDP (4.9 g, 1.0 mmol) was dissolved in dry N,N-dimethylformamide (DMF, 49 mL). 2'-(6-aminohexanoyl) docetaxel·$MeSO_3H$ (2.0 g, 2.2 mmol), N,N-Diisopropylethylamine (290 mg, 2.2 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (580 mg, 3.0 mmol), and N-Hydroxysuccinimide (250 mg, 2.2 mmol) were added to the polymer solution and stirred for 4 h. The polymer was precipitated with acetone (500 mL). It was then rinsed with acetone (100 mL). The product contained CD-hexanoate-docetaxel and could contain free CDP and traces of free docetaxel.

The CDP hexanoate-docetaxel was dissolved in water (490 mL). The solution was dialyzed using a tangential flow filtration system (30 kDa MW cutoff, membrane area = 50 cm^2). It was then concentrated to 20 mg of CDP-hexanoate-docetaxel/mL. It was then formulated with mannitol and filtered through 0.2 μm filters (Nalgene) and lyophilized to yield white solid.



Example 4. Formulation of CDP-hexanoate-docetaxel nanoparticles

CDP-hexanoate-docetaxel (100 mg) as prepared in example 3 above was dissolved in water (10 mL). Particle solution properties were characterized by dynamic light scattering (DLS) spectrometer.

Particle properties, evaluated by using the resulting plurality of particles made in the method above:

Zavg = 47.0 nm

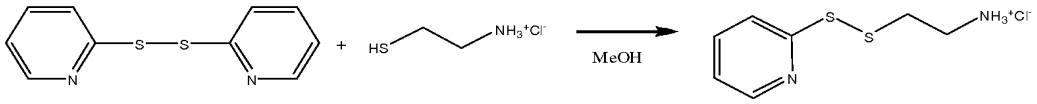
Particle PDI = 0.587

Dv50 = 11.2 nm

Dv90 = 18.2 nm

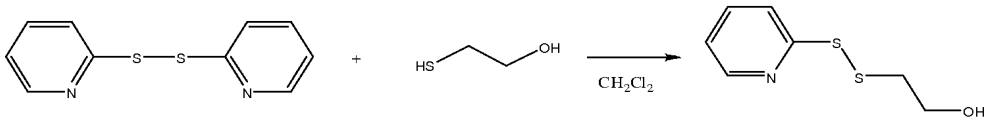
Example 5. Synthesis of 2-(2-(pyridin-2-yl)disulfanyl)ethylamine

In a 25 mL round bottom flask, 2,2′-dithiodipyridine (2.0 g, 9.1 mmol) was dissolved in methanol (8 mL) with acetic acid (0.3 mL). Cysteamine hydrochloride (520 mg, 4.5 mmol) was dissolved in methanol (5 mL) and added dropwise into the mixture over 30 minutes. The mixture was then stirred overnight. It was then reduced under vacuum to yield a yellow oil. The oil was dissolved in methanol (5 mL) and then precipitated into diethyl ether (100 mL). The precipitate was filtered off and dried. It was then redissolved in methanol (5 mL) and reprecipitated in diethyl ether (100 mL). This procedure was repeated twice. The pale yellow solid was filtered off and dried to produce the final product, 2-(2-(pyridin-2-yl)disulfanyl)ethylamine (0.74g, 74% yield) which was used without further purification.



Example 6. Synthesis of 2-(2-(pyridin-2-yl)disulfanyl)ethanol

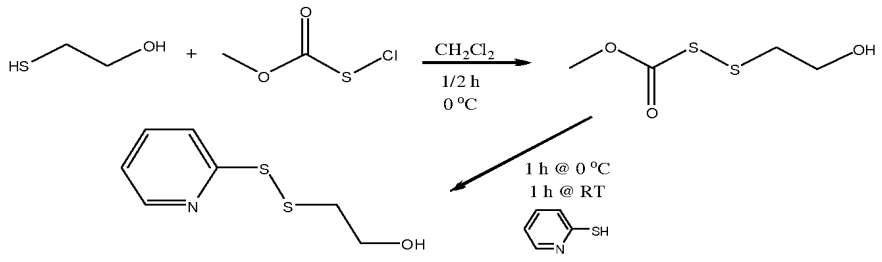
In a 50 mL round bottom flask, 2,2′-dithiodipyridine (0.50 g, 2.3 mmol) was dissolved in dichloromethane (5 mL). 2-Mercaptoethanol (90 mg, 1.1 mmol) was dissolved in dichloromethane (5 mL) and added to the mixture dropwise over 30 minutes. The mixture was stirred for an additional 30 minutes. It was then concentrated under vacuum to yield a yellow oil (200 mg, 91%). The oil was then used without further purification.



Example 7. Synthesis of 2-(2-(Pyridin-2-yl)disulfanyl)ethanol (alternate route)

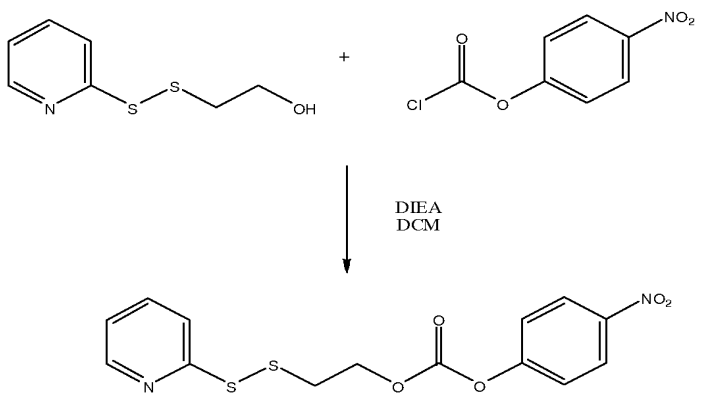
In a 250 mL round bottom flask, methoxycarbonylsulfenyl chloride (7.0 g, 55 mmol) was dissolved in dichloromethane (50 mL) and stirred in ice bath. To the mixture, 2-mercaptoethanol (4.5 g, 55 mmol) was added dropwise over 30 minutes. 2-Mercaptopyridine (6.1 g, 55 mmol) was dissolved in dichloromethane (80 mL) and it was added dropwise to the mixture over 1 h in an ice bath. It was then brought to room temperature and stirred for one additional hour. The mixture was concentrated down to approximately. 60 mL of dichloromethane in which a precipitate started to form. The precipitate was filtered off and washed with dichloromethane (25 mL) twice. It was then dried under vacuum to produce a yellow solid (9.6 g, 78% yield).

In a 50 mL round bottom flask, the crude yellow solid (2.5 g, 11 mmol) and 4-(dimethylamino)pyridine (1.4 g, 11 mmol) was dissolved in dichloromethane (20 mL). It was then purified by flash columnchromatography (dichloromethane:acetone = 15:1) to produce a yellow oil (1.9 g, 90% yield).



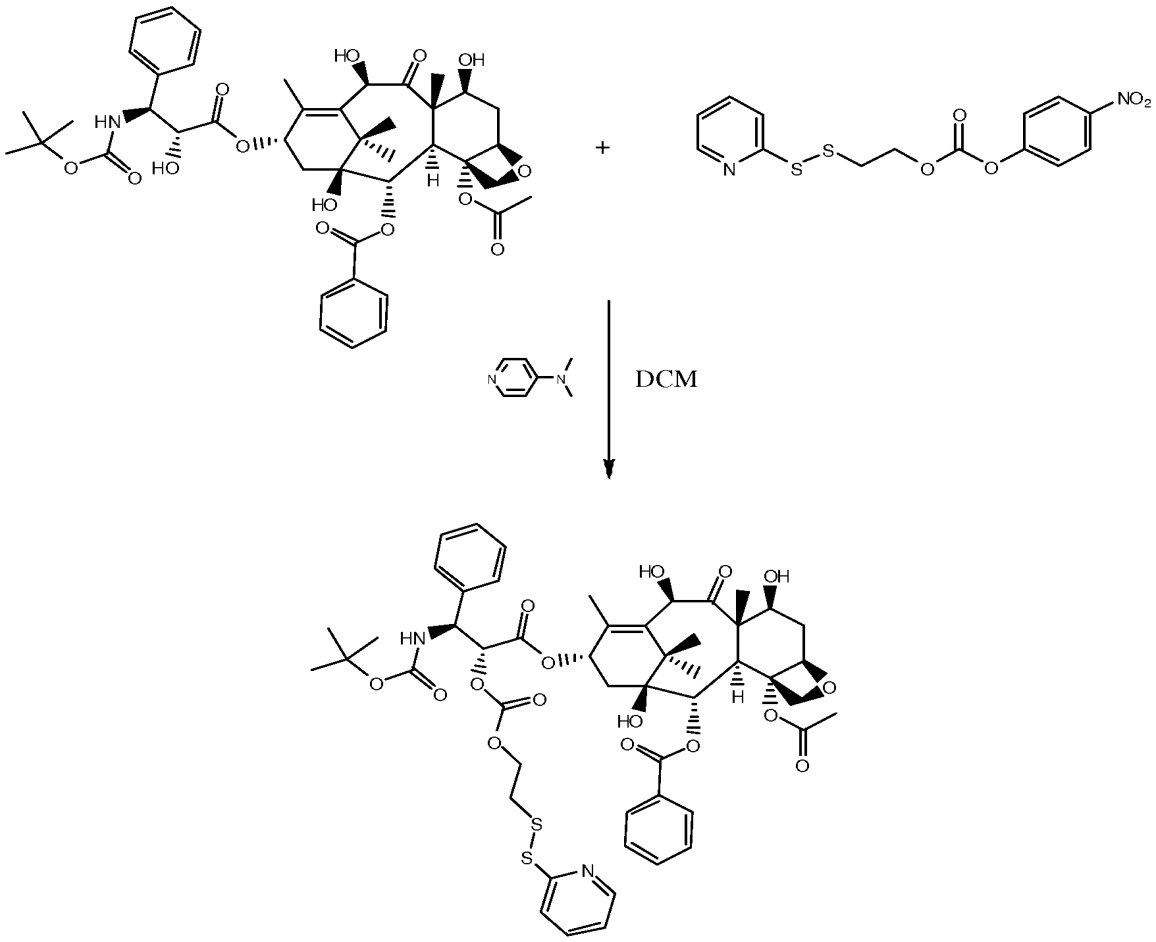
Example 8. Synthesis of 4-nitrophenyl 2-(2-(Pyridin-2-yl)disulfanyl)ethyl carbonate

In a 250 mL round bottom flask, 4-nitrophenyl chloroformate (2.0 g, 10 mmol) was dissolved in dichloromethane (20 mL). 2-(2-(Pyridin-2-yl)disulfanyl)ethanol (1.9 g, 10 mmol) and N,N-diisopropylethylamine (1.0 g, 10 mmol) were dissolved in dichloromethane (100 mL) and added dropwise to the mixture and stirred overnight. The solution was then pumped down to dryness to yield a yellow oil. The crude product was purified by flash column chromatography (dichloromethane:acetone = 30:1) to produce a yellow oil (2.9 g, 81% yield).



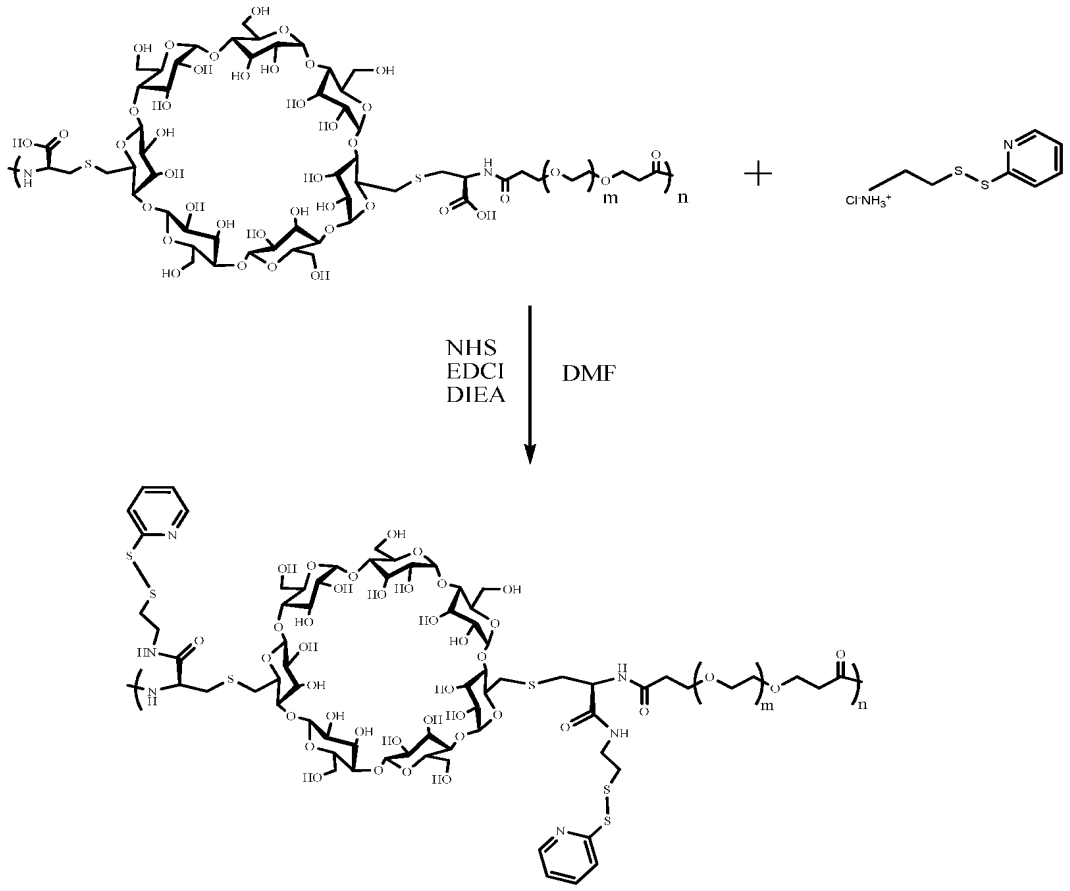
Example 9. Synthesis of 2'-(2-(2-(Pyridin-2-yl)disulfanyl)ethylcarbonate) Docetaxel

In a 50 mL round bottom flask, 4-nitrophenyl 2-(2-(pyridin-2-yl)disulfanyl)ethyl carbonate (200 mg, 0.56 mmol), docetaxel (500 mg, 0.62 mmol) and 4-(dimethylamino)pyridine (140 mg, 1.1 mmol) were dissolved in dichloromethane (50 mL) and stirred overnight. It was washed with 0.1N hydrochloric acid (10 mL) twice, dried over magnesium sulfate, and pumped down to yield a white solid. It was then purified by column chromatography (dichloromethane:methanol = 15:1) to yield a light yellow solid (210 mg, 36% yield).



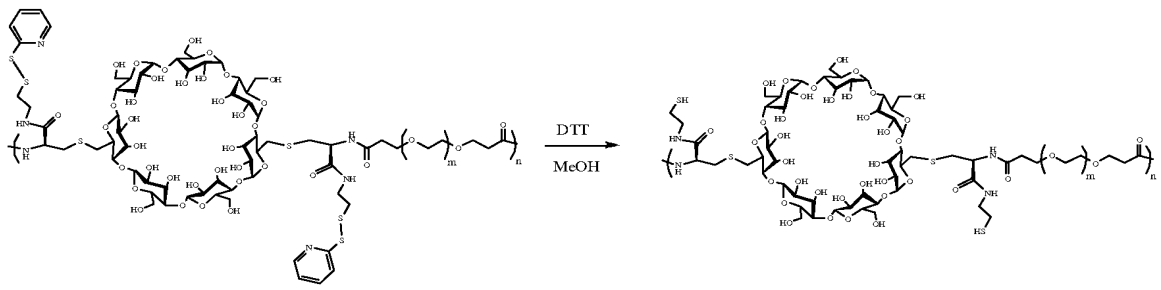
Example 10. Synthesis of CDP-NHEtSSPyridine

In a 25 mL round bottom flask, CDP (CDP, 0.50 g, 0.10 mmol) was dissolved in N,N-dimethylformamide (5 mL). To the solution, the following was added: 2-(2-(pyridin-2-yl)disulfanyl)ethylamine (51 mg, 0.23 mmol), N-hydroxysuccinimide (26 mg, 0.23 mmol), N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (60 mg, 0.31 mmol) and N,N-diisopropylethylamine (29 mg, 0.23 mmol). The mixture was stirred for 4 h. Isopropanol (10 mL) was added followed by diethyl ether (50 mL) to precipitate out the polymer. The polymer was then rinsed with acetone (20 mL) and dissolved in water (50 mL). The product was purified by dialysis against water by using dialysis tube membrane (25k MWCO) for 24 h. It was then filtered through a 0.2 μm filter and lyophilized to yield a white solid polymer (360 mg, 72% yield).



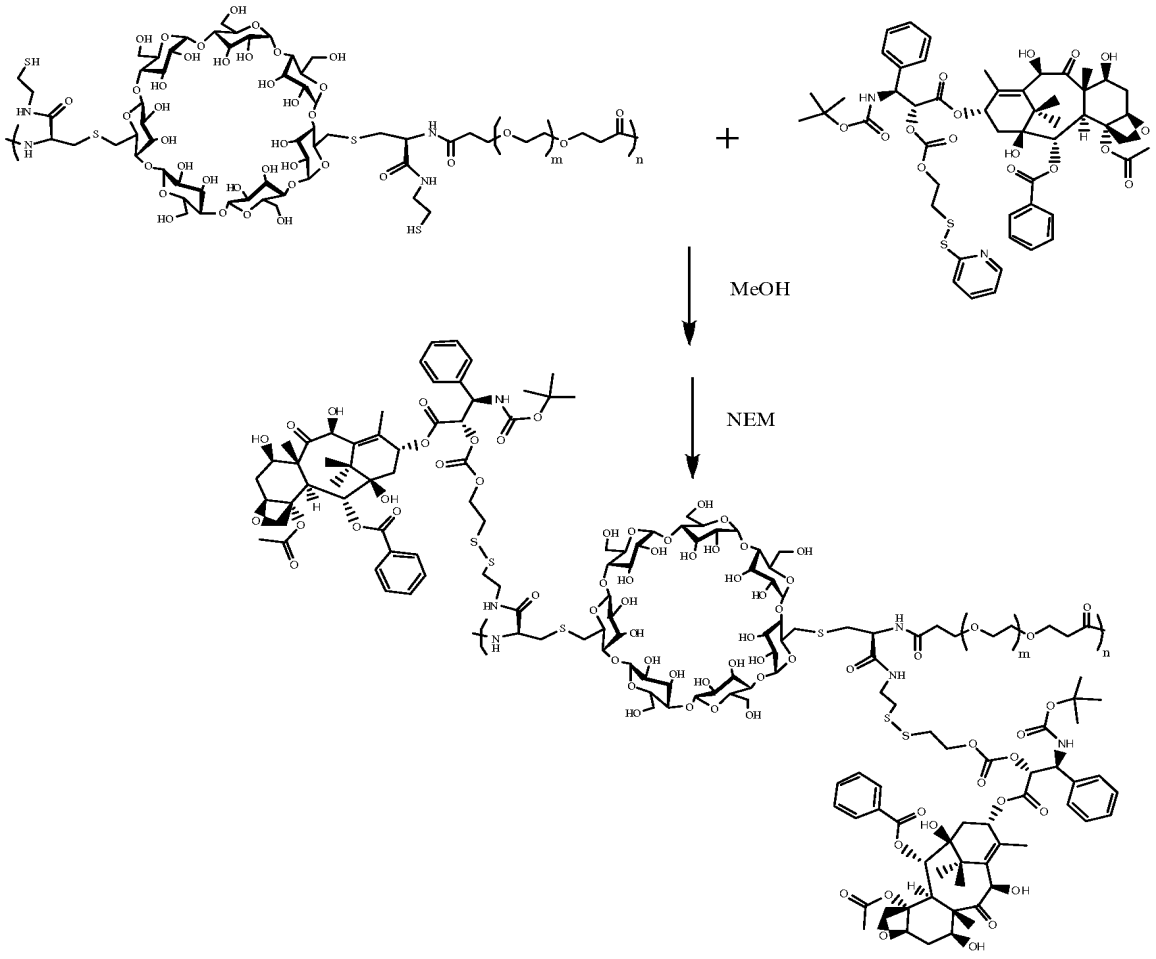
Example 11. Synthesis of CDP-NHEtSH

In a 10 mL round bottom flask, CDP-NHEtSSPyridine (120 mg, 0.023 mmol) was dissolved in methanol (2 mL). D,L-Dithiothreitol (36 mg, 0.23 mmol) was added to the mixture and stirred at room temperature for 1h. The polymer was then precipitated out in diethyl ether (20 mL). It was then dried under vacuum for 2 min. The polymer was then redissolved in methanol (2 mL) and precipitated out in diethyl ether (20 mL). This reprecipitation procedure was repeated once more. It was then dried under vacuum for 1 h to yield a white solid (88 mg, 73% yield).



Example 12. Synthesis of CDP-NHEtSSEtOCO-2'-O-docetaxel

In a 10 mL round bottom flask, CDP-NHEtSH (88 mg, 0.018mmol) was dissolved in methanol (1.8 mL). The solution was then mixed with 2'-(2-(2-(pyridin-2-yl)disulfanyl)ethylcarbonate) docetaxel (32 mg, 0.031 mmol) and stirred at room temperature for 1 h. N-Ethylmaleimide (4.4 mg, 0.035 mmol) was added to the mixture and stirred for an additional hour. The polymer was then precipitated out in diethyl ether (20 mL). It was then rinsed with acetone (10 mL). The polymer was dissolved in water (9 mL) and then purified by dialysis against water by using dialysis tube membrane (25k MWCO) for 24 h. It was then filtered through 0.2 μm and lyophilized to yield a white solid polymer (CDP-NHEtSSEtOCO-2'-O-docetaxel). The product could also contain free CDP and some traces of free docetaxel.



Example 13. Formulation of CDP-NHEtSSEtOCO-2'-O-docetaxel nanoparticles

CDP-NHEtSSEtOCO-2'-O-docetaxel (100 mg) as prepared in example 12 above was dissolved in water (10 mL). Particle solution properties were characterized by dynamic light scattering (DLS) spectrometer.

Particle properties, evaluated by using the resulting plurality of particles made in the method above:

Zavg = 16.4 nm

Particle PDI = 0.507

Dv50 = 4.41 nm

Dv90 = 8.30 nm

Example 14. Synthesis of docetaxel aminoethyldithioethyl carbonate

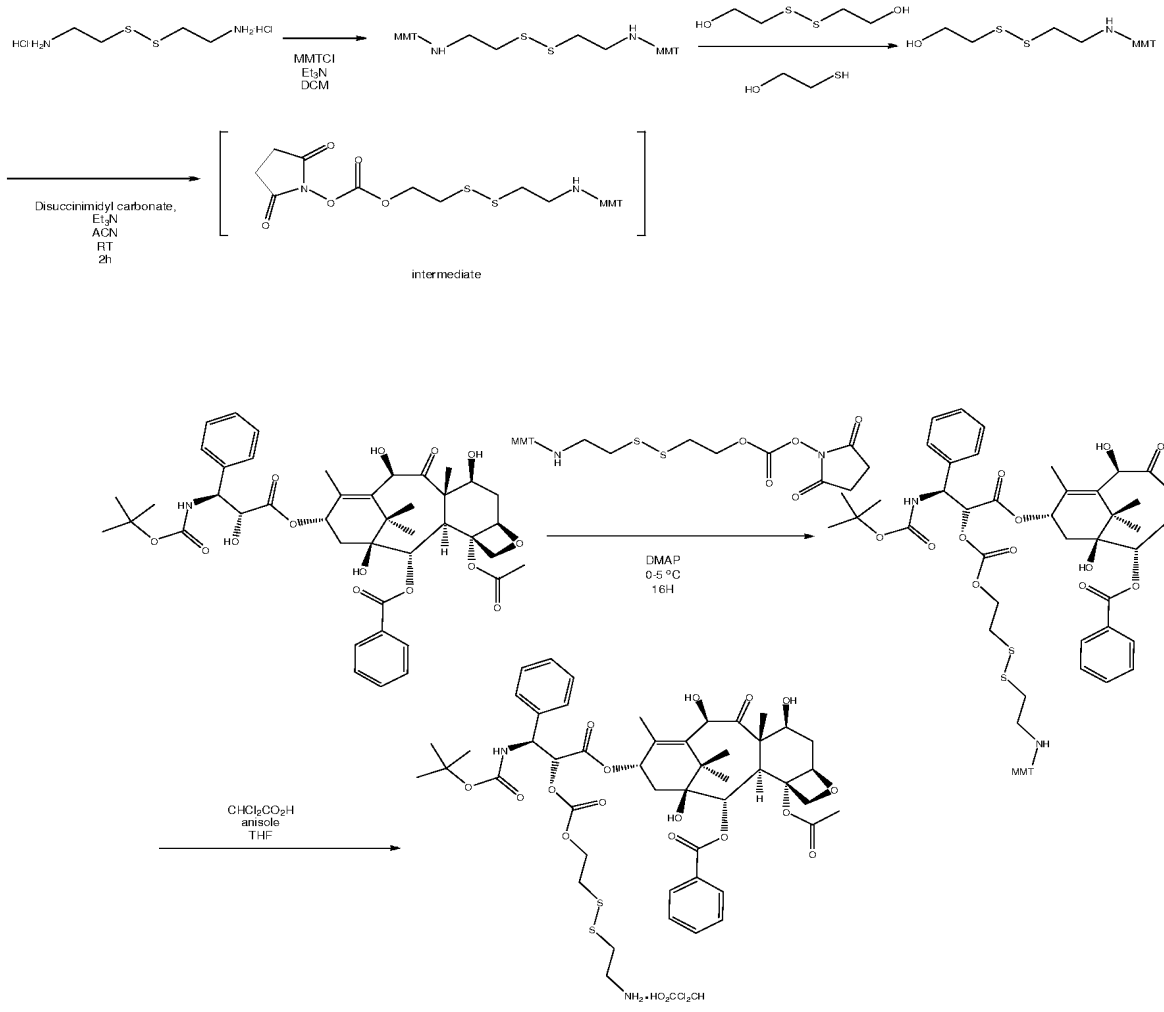
Triethylamine (15.0 mL, 108 mmol) was added to a mixture of cystamine•2HCl (5.00 g, 22.2 mmol) and MMTCl (14.1 g, 45.6 mmol, 2.05 equiv) in CH_2Cl_2 (200 mL) at ambient temperature. The mixture was stirred for 90h and 200 mL of 25% saturated $NaHCO_3$ was added, stirred for 30 min, and removed. The mixture was washed with brine (200 mL) and concentrated to produce a brown oil (19.1 g). The oil was dissolved in 20 – 25 mL CH_2Cl_2 and purified by flash chromatography to yield a white foam (diMMT-cyteamine, 12.2 g, 79% yield)

Bis(2-hydroxyethyldisulfide) (11.5mL, 94 mmol, 5.4 equiv) and 2-mercaptoethanol (1.25 mL, 17.8 mmol, 1.02 equiv) were added to a solution of diMMT-cyteamine (12.2 g, 17.5 mmol) in 1:1 CH_2Cl_2/MeOH (60 mL) and the mixture was stirred at ambient temperature for 42.5 h. The mixture was concentrated to an oil, dissolved in EtOAc (150 mL), washed with 10% saturated NaHCO3 (3 × 150 mL) and brine (150 mL), dried over Na2SO4, and concentrated to an oil (16.4 g). The oil was dissolved in 20 mL CH_2Cl_2 and purified by flash chromatography to yield clear thick oil (MMT-aminoethyldithioethanol, 5.33 g, 36% yield).

A 250 mL round bottom flask equipped with a magnetic stirrer was charged with MMT-aminoethyldithioethanol (3.6 g, 8.5 mmol) and acetonitrile (60 mL). Disuccinimidyl carbonate (2.6 g) was added and the reaction was stirred at ambient temperature for 3 h. It was used for the next reaction without isolation. Succinimidyl MMT-aminoethyldithioethyl carbonate was transferred to a cooled solution of docetaxel (6.14 g, 7.61 mmol) and DMAP (1.03 g) in DCM (60 mL) at 0-5 °C with stirring for 16 h. It was then purified by column chromatography.

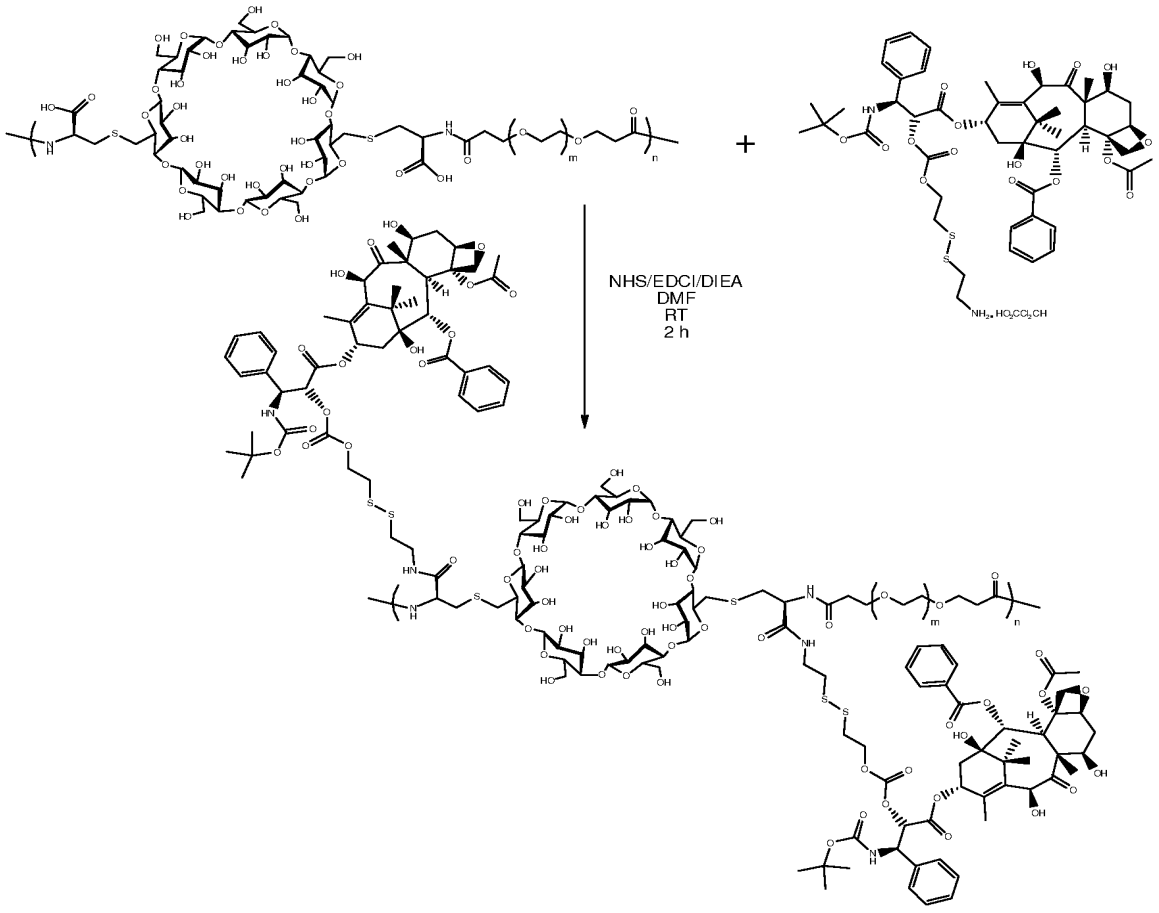
A 1000 mL round bottom flask equipped with a magnetic stirrer was charged with docetaxel Cbz-aminoethyldithioethyl carbonate (12.6 g) and DCM (300 mL). Anisole (10.9 mL, 10 equiv.) was added to this clear solution and stirred for a few minutes. Dichloroacetic acid (8.3 mL, 10 equiv.) was added over 5 min and the reaction was stirred at ambient temperature for 1h. The mixture was concentrated down to ~100 mL,

to which heptanes (800 mL) was slowly added resulting in a suspension. The suspension was stirred for 15 min and the supernatant was decanted. The orange residue was washed with heptanes (200 mL) and vacuum-dried at ambient temperature for 1 h. THF (30 mL) was added to dissolve the orange residue producing a red solution. Heptanes (500 mL) was slowly added to precipitate out the product. The resulting suspension was stirred at ambient temperature for 1 h and filtered. The filter cake was washed with heptanes (300 mL) and dried under vacuum to yield docetaxel aminoethyldithioethyl carbonate.



Example 15. Synthesis of CDP-NHEtSSEtOCO-2'-O-docetaxel

CDP (1.5 g, 0.31 mmol) was dissolved in dry N,N-dimethylformamide (DMF, 15 mL). Docetaxel aminoethyldithioethyl carbonate (760 mg, 0.68 mmol), N,N-Diisopropylethylamine (88 mg, 0.68 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (130 mg, 0.68 mmol), and N-Hydroxysuccinimide (79 mg, 0.68 mmol) were added to the polymer solution and stirred for 2 h. The polymer was precipitated with isopropanol (225 mL) and then rinsed with acetone (150 mL). The precipitate was dissolved in nanopure water (150 mL). It was purified by TFF with nanopure water (1.5 L). It was filtered through 0.2 μm filter and kept frozen.



Example 16. Formulation of CDP-NHEtSSEtOCO-2'-O-docetaxel nanoparticles

CDP-NHEtSSEtOCO-2'-O-docetaxel as prepared in Example 15 above (1 mg) was dissolved in water (1 mL). Particle solution properties were characterized by dynamic light scattering (DLS) spectrometer.

Particle properties, evaluated by using the resulting plurality of particles made in the method above:

Zavg = 26.67 nm

Particle PDI = 0.486

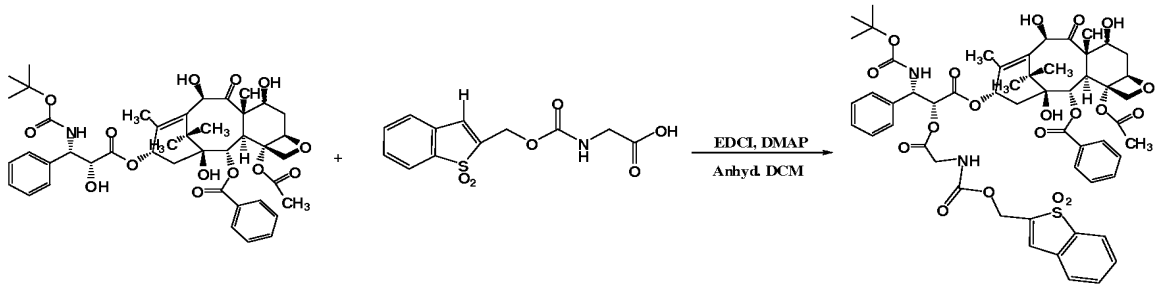
Dv50 = 8.55 nm

Dv90 = 14.6 nm

Example 17. Synthesis of docetaxel-2'-glycine bsmoc

A 50 ml round-bottom flask was charged with a solution of docetaxel (1 g, 1.23mmol), BsmocGlycine (0.4184 g, 1.4 mmol) and 4-dimethylaminopyridine (0.0487 g, 0.398 mmol) in anhydrous methylene chloride (20 mL) under nitrogen. The solution was cooled to 10°C and EDC.HCl (0.3589 g, 1.87 mmol) was added to the solution, while stirring. The reaction was stirred for 1 h at 10°C, resulting in a clear solution. The reaction was stirred for an additional hour at ambient temperature. TLC analysis in $CHCl_3$ and MeOH (14:1) showed a presence of small amount of unreacted docetaxel. The reaction was continued to stir for another 30 minutes and then washed with 0.1 M hydrochloric acid (2 x 200 mL) and water (200 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered. The organic solvent was then evaporated under reduced pressure to give a white powder (1.38 g). HPLC and LC/MS analysis of the final product showed a mixture of compounds – docetaxel, docetaxel-2'-glycine Bsmoc, docetaxel-7-glycine Bsmoc, docetaxel-2',7-bis(glycine Bsmoc) and another bis(Glycine Bsmoc) derivative of docetaxel. The crude product was separated by silica gel column chromatography. The products were eluted with $CHCl_3$/MeOH and with increasing MeOH concentration from 2% (200 ml) to 3% (600 ml). The TLC was monitored in $CHCl_3$ and MeOH (14:1). The fractions containing docetaxel-2'-Glycine Bsmoc were collected and concentrated to provide 93% pure product with docetaxel-7-

glycine Bsmoc as an impurity. ^{1}H NMR and LC/MS analysis confirmed the desired product.



Example 18. Synthesis and formulation of CDP-glycine-docetaxel nanoparticles

To a solution of docetaxel-2'-glycine Bsmoc (0.052 g, 0.0478 mmol) in anhydrous DMF (2 mL), 4-piperidinopiperidine (0.008g, 0.0478 mmol) was added and the reaction mixture was stirred at ambient temperature. 4-piperidinopiperidine was dried under vacuum before use. The TLC was monitored $CHCl_3$ and MeOH (14:1) and after ~2 h of stirring, no starting material was observed. A mass of 0.106 g (0.0217 mmol) of CDP polymer was then added to the reaction mixture and stirring was continued until the polymer dissolved, i.e., for approx. 15 min. The reagents EDC.HCl (0.0126 g, 0.0651 mmol) and NHS (0.0059g, 0.0477 mmol) were added followed by the addition of DIEA (0.0062g, 0.0477 mmol) and the stirring was continued for another 4 h. The polymer was precipitated in 5 volumes of acetone (10 ml), which resulted in a turbid solution. The acetone-DMF solution was then transferred into 5 volumes of diethyl ether (~60 ml). The polymer precipitated together as a lump. Diethyl ether was then decanted and the precipitated polymer product was washed with acetone. The product could contain some amounts of free CDP and trace amounts of drug present.

After decanting the acetone, the polymer was dissolved in 10 ml of water to make ~10 mg/mL polymer solution. The solution was then dialyzed against 4 L water using 25 kDa MWCO dialysis tube. The sample was dialyzed for 72 h and the water was changed once on the third day. A small amount of precipitate was observed in the dialysis bag.

The solution, ~13 mL volume, was filtered through a 0.22 µm filter. The filtered solution was then analyzed for size by dynamic light scattering (DLS) spectrometer.

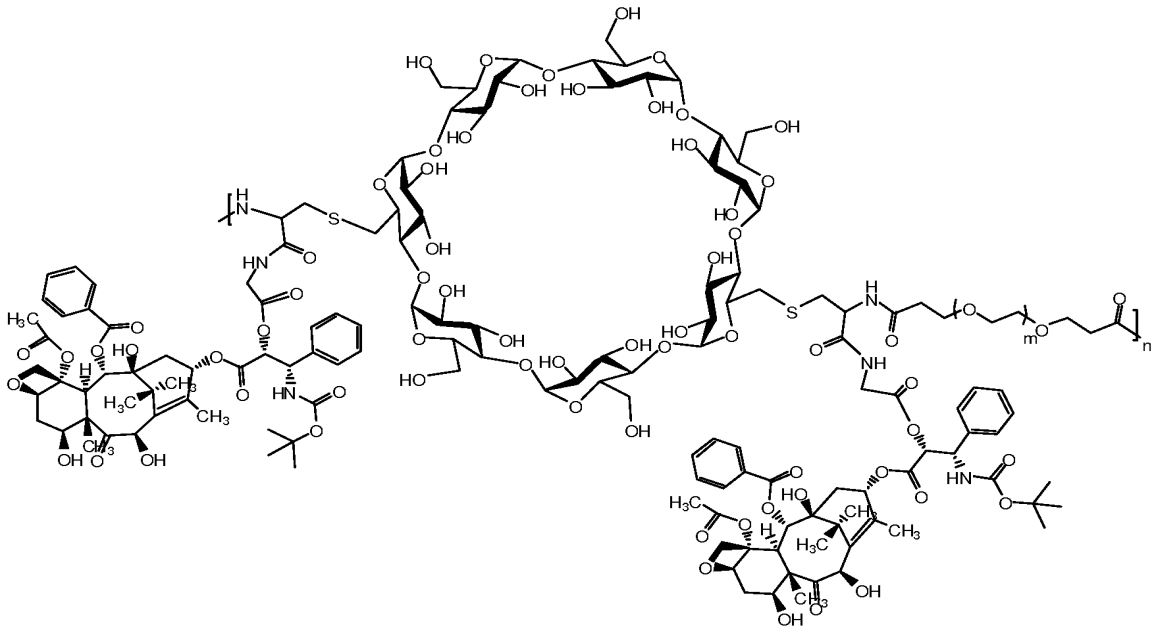
Particle properties, evaluated by using the resulting plurality of particles made in the method above:

Zavg = 55.11 nm

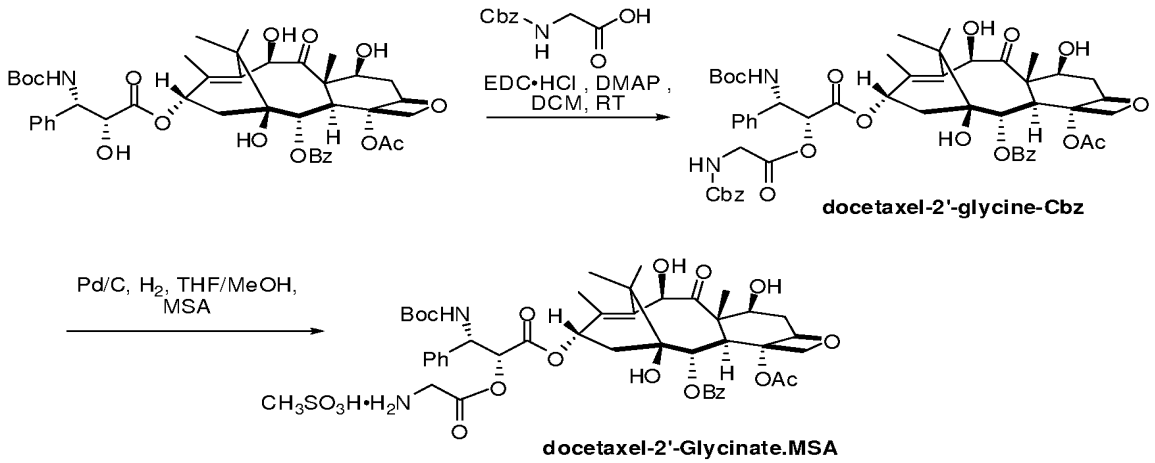
Particle PDI = 0.706

Dv50 = 13.2 nm

Dv90 = 23.9 nm



Example 19. Synthesis of Docetaxel-2'-Glycinate.Methanesulfonic acid



Docetaxel (15.0 g, 18.6 mmol) and dichloromethane (CH_2Cl_2, 300 mL) were added to a 1 litre round bottom flask and the mixture was stirred for 5 min using an overhead stirrer. N-Carbobenzyloxy-glycine (N-Cbz-glycine, 2.92 g, 13.9 mmol, 0.75 equiv), 4-(dimethylamino)pyridine (DMAP, 1.82 g, 15.0 mmol, 0.80 equiv) and N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC•HCl, 2.87 g, 14.9 mmol, 0.80 equiv) were then added. The mixture was stirred at ambient temperature for 3 h and an additional amount of N-Cbz-glycine (1.57 g, 7.5 mmol, 0.40 equiv), DMAP (1.04 g, 8.5 mmol, 0.46 equiv), and EDC•HCl (1.62 g, 8.4 mol, 0.45 equiv) were added. After stirring the mixture for an additional 2.75 h, it was washed twice with 0.5% HCl (2 × 150 mL) and brine (150 mL). The organics were dried over sodium sulfate, and the supernatant was concentrated to a residue (21.6 g). The residue was dissolved in 60 mL of chloroform and purified by flash chromatography to produce docetaxel-2'-glycine-Cbz [12.3 g, 66% yield, 98.5%] as a white solid.

In a 1 litre round bottom flask, 5% palladium on activated carbon (Pd/C, 4.13 g) was slurried in a mixture of tetrahydrofuran (THF, 60 mL), methanol (MeOH, 12.5 mL), and methanesulfonic acid (MSA, 0.75 mL, 11.5 mmol, 0.93 equiv). The mixture was stirred under hydrogen (balloon pressure) at ambient temperature for 1 h. A solution of docetaxel-2'-glycine-Cbz (12.3 g, 12.3 mmol) in THF (60 mL) was added with an additional 60 mL THF wash. The mixture was stirred for 2.5 h, then the hydrogen was removed and the mixture was filtered using a 40 mL THF wash. The filtrate was

concentrated and then diluted to about 80 mL with THF. Heptanes (700 mL) were then added drop wise over 20 min. The resulting slurry was filtered using a 150 mL heptanes wash and dried under vacuum to produce docetaxel-2'-glycinate.MSA as a white solid [11.05 g, 94%, 95.8% AUC by HPLC].

Example 20. Synthesis and Formulation of CDP-Glycine-Docetaxel Nanoparticles

CDP polymer (1 g, 0.207 mmol) was dissolved in anhydrous dimethylformamide (DMF, 10 mL) and stirred for 30 min to dissolve the polymer. Docetaxel-2'-glycinate.methanesulfonic acid (0.430 g, 0.455 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, 0.0597 g, 0.311 mmol) and N-Hydroxysuccinimide (NHS, 0.0263 g, 0.228 mmol) was added to the polymer solution. While stirring, N,N-diisopropylethylamine (DIEA, 0.0294 g, 0.228 mmol) was added and the stirring was continued for 2 h.

The reaction was worked up by precipitating the polymer in 15 volumes of acetone (150 mL). The polymer precipitated out immediately as a lump. The solution was stirred for 15 minutes and then the slightly turbid supernatant was decanted. The polymer precipitate was stirred in 10 volumes of acetone (100 mL) for 30 min and then added into 50 mL of water to produce an approximate 20 mg/mL polymer concentration. The solution was then dialyzed against 4 litres of water using a 25 kDa MWCO dialysis tube for 24 h. The water was changed once during that period. The final solution (volume ~52 mL) was filtered through a 0.22 μm filter and the filtered solution was analyzed for particle size.

Particle properties, evaluated by using the resulting plurality of particles made in the method above:

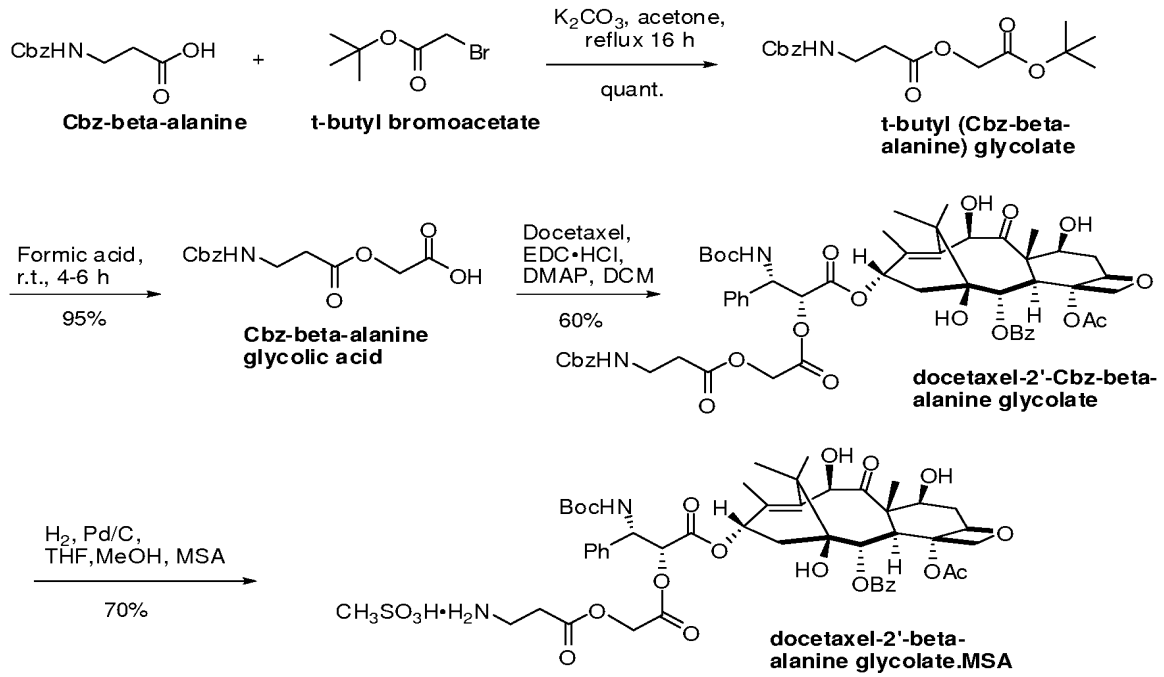
Zavg = 13.34 nm

Particle PDI = 0.332

Dv50 = 4.82 nm

Dv90 = 9.57 nm

Example 21. Synthesis of Docetaxel-2'-β-Alanine Glycolate



A 1000 mL round-bottom flask equipped with a magnetic stirrer was charged with carbobenzyloxy-β-alanine (Cbz-β-alanine, 15.0 g, 67.3 mmol), tert-butyl bromoacetate (13.1 g, 67.3 mmol), acetone (300 mL), and potassium carbonate (14 g, 100 mmol). The mixture was heated to reflux at 60 °C for 16 h, cooled to ambient temperature and then the solid was removed by filtration. The filtrate was concentrated to a residue, dissolved in ethyl acetate (EtOAc, 300 mL), and washed with 100 mL of water (three times) and 100 mL of brine. The organic layer was separated, dried over sodium sulfate and filtered. The filtrate was concentrated to clear oil [22.2 g, yield: 99%]. HPLC analysis showed 97.4% purity (AUC, 227 nm) and ^{1}H NMR analysis confirmed the desired intermediate product, t-butyl (carbobenzyloxy-β-alanine) glycolate.

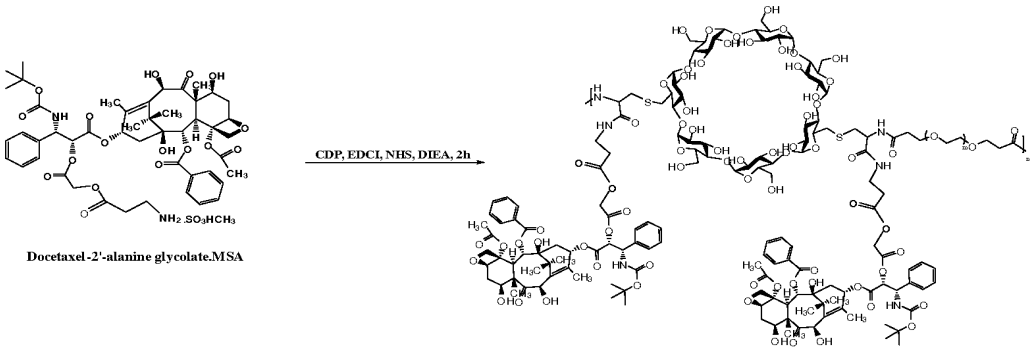
To prepare the intermediate product, carbobenzyloxy-β-alanine glycolic acid (Cbz-β-alanine glycolic acid), a 100 mL round-bottom flask equipped with a magnetic stirrer was charged with t-butyl (Cbz-β-alanine) glycolate [7.5 g, 22.2 mmol] and formic acid (15 mL, 2 vol). The mixture was stirred at ambient temperature for 3 h to give a red-wine color and HPLC analysis showed 63% conversion. The reaction was continued stirring for an additional 2 h, at which point HPLC analysis indicated 80% conversion. An additional portion of formic acid (20 mL, 5 vol in total) was added and the reaction was stirred overnight, at which time HPLC analysis showed that the reaction was complete. The reaction was concentrated under vacuum to a residue and redissolved in ethyl acetate (7.5 mL, 1 vol.). The solution was added to the solvent heptanes (150 mL, 20 vol.) and this resulted in the slow formation of the product in the form of a white suspension. The mixture was filtered and the filter cake was vacuum-dried at ambient temperature for 24 h to afford the desired product, Cbz-β-alanine glycolic acid as a white powder [5.0 g, yield: 80%]. HPLC analysis showed 98% purity. The ^{1}H NMR analysis in DMSO-d6 was consistent with the assigned structure of Cbz-β-alanine glycolic acid [δ 10.16 (s, 1H), 7.32 (bs, 5H), 5.57 (bs, 1H), 5.14 (s, 2H), 4.65 (s, 2H), 3.45 (m, 2H), 2.64 (m, 2H)].

To prepare the intermediate, docetaxel-2'-carbobenzyloxy-β-alanine glycolate (docetaxel-2'-Cbz- β-alanine glycolate), a 250-mL round-bottom flask equipped with a magnetic stirrer was charged with docetaxel (5.03 g, 6.25 mmol), Cbz-β-alanine glycolic acid [1.35 g, 4.80 mmol] and dichloromethane (DCM, 100 mL). The mixture was stirred for 5 min to produce a clear solution, to which N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC•HCl, 1.00 g, 5.23 mmol) and 4-(dimethylamino)pyridine (DMAP, 0.63 g, 5.23 mmol) were added. The mixture was stirred at ambient temperature for 3 h, at which point HPLC analysis showed 48% conversion along with 46% of residual docetaxel. A second portion of Cbz-β-alanine glycolic acid (0.68 g, 2.39 mmol), EDC•HCl (0.50 g, 1.04 mmol) and DMAP (0.13 g, 1.06 mmol) were added and the reaction was allowed to stirred overnight. At this point, HPLC analysis showed 69% conversion along with 12% of residual docetaxel. The solution was diluted to 200 mL with DCM and then washed with 80 mL of water (twice) and 80 mL of brine. The organic layer was separated, dried over sodium sulfate, and then

filtered. The filtrate was concentrated to a residue, re-dissolved in 10 mL of chloroform, and purified using a silica gel column. The fractions containing product (shown as a single spot by TLC analysis) were combined, concentrated to a residue, vacuum-dried at ambient temperature for 16 h to produce docetaxel-2'-Cbz- β-alanine glycolate as a white powder [3.5 g, yield: 52%]. HPLC analysis (AUC, 227 nm) indicated > 99.5% purity. The ^{1}H NMR analysis confirmed the corresponding peaks.

To prepare the intermediate, docetaxel-2'-β-alanine glycolate.methanesulfonic acid, a 250 mL round-bottom flask equipped with a magnetic stirrer was charged with docetaxel-2'-Cbz-β-alanine glycolate [3.1 g, 2.9 mmol] and tetrahydrofuran (THF, 100 mL). To the clear solution methanol (MeOH, 4 mL), methanesulfonic acid (172 µL, 2.6 mmol), and 5% palladium on activated carbon (Pd/C, 1.06 g, 10 mol% of Pd) were added. The mixture was evacuated for 15 seconds and filled with hydrogen using a balloon. After 3 h, HPLC analysis indicated that the reaction was complete. Charcoal (3 g, Aldrich, Darco®#175) was then added and the mixture was stirred for 15 min and filtered through a Celite® pad to produce a clear colorless solution. It was concentrated under reduced pressure at < 20°C to ~5 mL, to which 100 mL of heptanes was added slowly resulting in the formation of a white gummy solid. The supernatant was decanted and the gummy solid was vacuum-dried for 0.5 h to produce a white solid. A volume of 100 mL of heptanes were added and the mixture was triturated for 10 min and filtered. The filter cake was vacuum-dried at ambient temperature for 16 h to produce docetaxel-2'-β-alanine glycolate.MSA as a white powder [2.5 g, yield: 83%]. The HPLC analysis indicated >99% purity (AUC, 230 nm). MS analysis revealed the correct molecular mass (m/z: 936.5).

Example 22. Synthesis and Formulation of CDP-Alanine Glycolate-Docetaxel Nanoparticles



Docetaxel-2'-alanine glycolate.MSA

CDP (0.3 g, 0.062 mmol) was dissolved in anhydrous dimethylformamide (DMF, 3 mL) for 30 min with stirring. Docetaxel-2'-alanine glycolate.methanesulfonic acid (0.141 g, 0.137 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, 0.036 g, 0.186 mmol) and N-Hydroxysuccinimide (NHS, 0.016 g, 0.137 mmol) was then added to the polymer solution. While stirring, N,N-diisopropylethylamine (DIEA, 0.0177 g, 0.137 mmol) was added and the stirring was continued for 2 h.

The reaction was worked up by precipitating the polymer in 15 volumes of acetone (45 mL), which occurred immediately in the form of a lump. The solution was stirred for 15 minutes and then a slightly turbid supernatant was decanted. The polymer precipitate was stirred in 10 volumes (30 mL) of acetone for 30 min and then added into added into 50 mL of water to produce an approximate 20 mg/mL polymer concentration.. The solution was then dialyzed against 4 litres of water using a 25 kDa MWCO dialysis tube for 24 h. During this period, the water was changed once. The resulting solution (~16.5 mL), was filtered through a 0.22 μm filter and the filtered solution was analyzed for particle size.

Particle properties, evaluated by using the resulting plurality of particles made in the method above:

Zavg = 35.81 nm

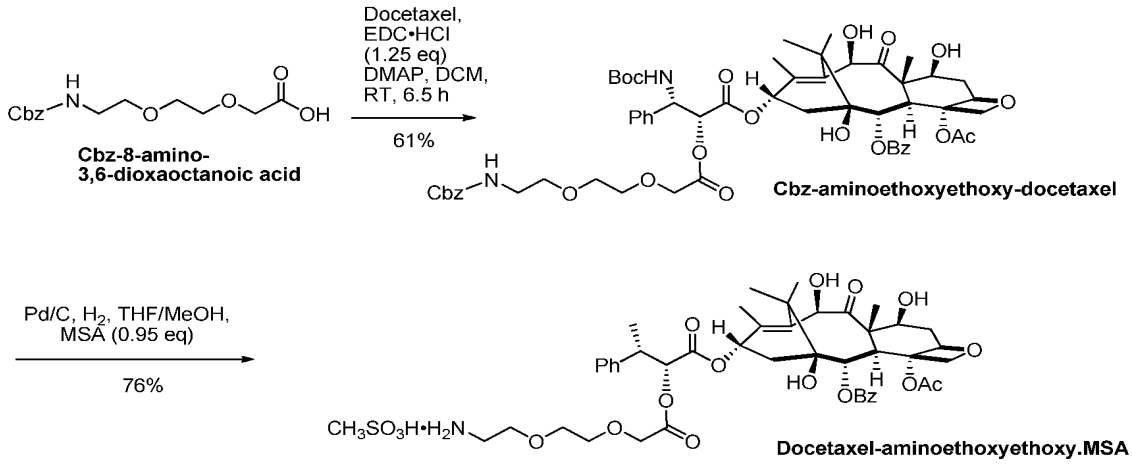
Particle PDI = 0.280

Dv50 = 12.9 nm

Dv90 = 26.1 nm

Example 23. Synthesis of Docetaxel-2-(2-(2-aminoethoxy)ethoxy)acetic acetate.Methanesulfonic acid.

As used herein, the linker "2-(2-(2-aminoethoxy)ethoxy)acetic acetate" can also be referred to shorthand as "aminoethoxyethoxy"

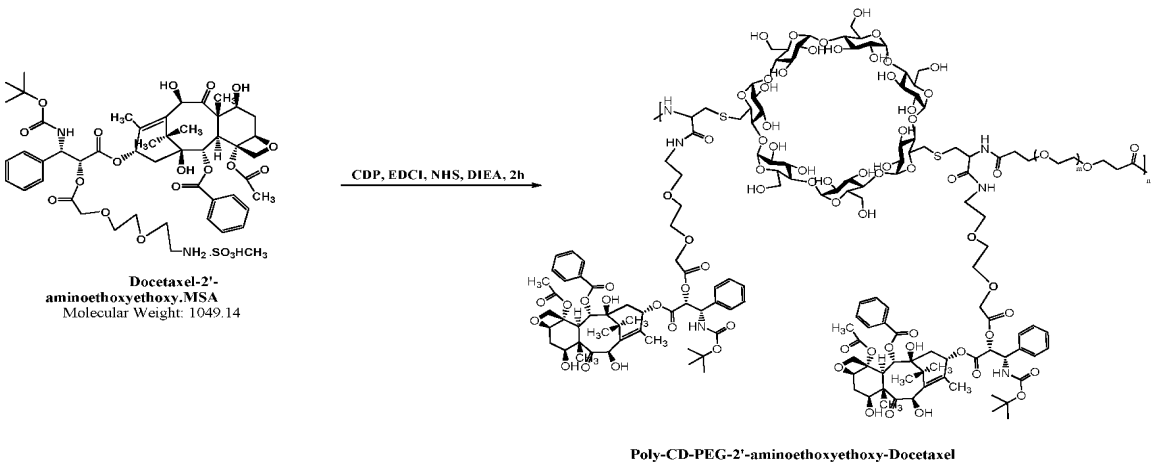


Carbobenzyloxy-8-amino-3,6-dioxaoctanoic acid (3.97 g, 13.3 mmol, 1.19 equiv) was dissolved in dichloromethane (CH_2Cl_2, 10 mL). A portion of this solution (9 mL, about 8.6 mmol, 0.77 equiv) was added to a solution of docetaxel (9.03 g, 11.2 mmol) in CH_2Cl_2 (180 mL) at ambient temperature. 4-(dimethylamino)pyridine (DMAP, 1.23 g, 10.1 mmol, 0.90 equiv) and N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC•HCl, 1.94 g, 10.1 mmol, 0.91 equiv) were added to the mixture and the contents were stirred at ambient temperature for 2.75 h. An additional amount of cbz-8-amino-3,6-dioxaoctanoic acid (5 mL, about 4.7 mmol, 0.42 equiv), DMAP (830 mg, 6.80 mmol, 0.61 equiv), and EDC•HCl (1.28 g, 6.67 mmol, 0.60 equiv) were added to the mixture and stirred for an additional 4.75 h. The mixture was then washed twice with 0.1 % HCl (2 × 100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate and concentrated to a residue (16.6 g). The residue was dissolved in chloroform ($CHCl_3$, 40 mL) and purified by flash chromatography to produce carbobenzyloxy-

aminoethoxyethoxy-docetaxel as a white solid in two portions [4.2 g, 35%, 97.0% AUC by HPLC] and [1.4 g, 12%, 97.2% AUC by HPLC].

In a 250 mL flask, 5% palladium on activated carbon (Pd/C, 1.95 g) was slurried in tetrahydrofuran (THF, 25 mL) with overhead stirring. The slurry was stirred under hydrogen at ambient temperature for 45 min. A solution of Cbz- aminoethoxyethoxy-docetaxel (5.6 g, 5.2 mmol) in THF (25 mL) and MeOH (5 mL) was added with an additional 25 mL THF wash. After 4.25 h, 5.0 g of activated carbon was added and stirred under nitrogen for 15 min. The slurry was filtered using a 25 mL THF wash and the filtrate was concentrated to about 20 mL. The solution was added drop wise into 200 mL heptanes to form a sticky precipitate. Both THF and MeOH solvents were added until dissolution of the precipitate occurred. A solvent swap into THF was then performed and the solution was concentrated to about 40 mL. Heptanes (500 mL) were subsequently added drop wise. The resulting slurry was filtered using a 250 mL heptanes wash and dried under vacuum overnight to produce docetaxel;- aminoethoxyethoxy.MSA as a white solid [4.55 g, 84%, 97.9% AUC by HPLC]. Pd analysis showed 69 ppm of residual Pd.

Example 24. Synthesis and Formulation of CDP-2'- aminoethoxyethoxy -Docetaxel Nanoparticles



Docetaxel-2'-aminoethoxyethoxy.MSA
Molecular Weight: 1049.14

Poly-CD-PEG-2'-aminoethoxyethoxy-Docetaxel

CDP (2 g, 0.414 mmol) was dissolved in anhydrous dimethylformamide (20 mL) and stirred for 30 minutes to dissolve the polymer. Docetaxel-2'- aminoethoxyethoxy .MSA (0.955 g, 0.911 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 0.174 g, 0.911 mmol) and N-hydroxysuccinimide (NHS, 0.1048 g, 0.911 mmol) were added to the polymer solution. While stirring, N,N-diisopropylethylamine (DIEA, 0.117 g, 0.911 mmol) was added and the stirring was continued for 2 h.

The reaction was worked up by precipitating the polymer in 15 volumes of acetone (300 mL). The polymer precipitated out immediately as a lump. The solution was stirred for 30 min. and then the slightly turbid supernatant was decanted. The polymer precipitate was stirred in 10 additional volumes of acetone (200 mL) for 30 min and then poured into 200 mL of water to prepare a ~10 mg/mL polymer concentration. The polymer dissolved smoothly in water and the polymer solution was then filtered through a 0.22 μm PES membrane. This solution was then washed using TFF (3 × 30K capsules) using 10 volumes of ultrapure water. After diafiltration, the solution was concentrated down to approximately half the volume and the concentrated solution was filtered with a 0.22 μm cellulose nitrate membrane. The filtered solution was analyzed for particle size using a particle sizer and docetaxel concentration using HPLC.

Particle properties, evaluated by using the resulting plurality of particles made in the method above:

Zavg = 18.85 nm
Particle PDI = 0.510
Dv50 = 8.78 nm
Dv90 = 15.4 nm

Example 25. Cytotoxicity of nanoparticles formed from CDP-linker-Docetaxel compounds

To measure the cytotoxic effect of CDP-linker-docetaxel compounds, the CellTiter-Glo Luminescent Cell Viability Assay (CTG) was used. Briefly, ATP and

oxygen in viable cells reduce luciferin to oxyluciferin in the presence of luciferase to produce energy in the form of light. B16.F10 cells, grown to 85-90% confluency in 150 cm2 flasks (passage <30), were resuspended in media (MEM-alpha, 10% HI-FBS, 1X antibiotic-antimycotic solution) and added to 96-well opaque-clear bottom plates at a concentration of 1500 cells/well in 200 µL/well. The cells were incubated at 37°C with 5% CO_2 for 24 hours. The following day, serial dilutions of 2X concentrated particles and 2X concentrated free drug were made in 12-well reservoirs with media to specified concentrations. The media in the plates was replaced with 100 µL of fresh media and 100 µL of the corresponding serially diluted drug. Three sets of plates were prepared with duplicate treatments. Following 24, 48 and 72 hours of incubation at 37°C with 5% CO2, the media in the plates was replaced with 100 µL of fresh media and 100 µL of CTG solution, and then incubated for 5 minutes on a plate shaker at room temperature set to 450 rpm and allowed to rest for 15 minutes. Viable cells were measured by luminescence using a microtiter plate reader. The data was plotted as % viability vs. concentration and standardized to untreated cells. The CDP-linker-docetaxel compounds inhibited the growth of B16.F10 cells in a dose and time dependent manner. Also, in comparison to the corresponding free drug, the CDP-linker-docetaxel compounds exhibited a slower release profile. IC_{50}: IC_{50} values 72 hours after treatment are shown in the table below

Group	IC_{50} (nM)
Free docetaxel	0.2-2
CDP-2'-hexanoate-docetaxel	325-440
CDP-2'-glycine-docetaxel	1.2-3.7
CDP-dithiolethyloxy-carbonate-docetaxel	23
CDP-2'-alanine glycolate-docetaxel	0.4-2.0
CDP-2'- aminoethoxyethoxys-Docetaxel	NA

Example 26. Drug release and stability method for the CDP-linker-Docetaxel compounds

The drug release and stability method experiment was run using the following CDP-linker-docetaxel nanoparticles: CDP-2'-glycine-docetaxel (CDP-Gly-DTX), CDP-2'-alanine glycolate-docetaxel (CDP-Ala Gly-DTX), CDP-2'-hexanoate-docetaxel (CDP-Hex-DTX), CDP-dithiolethyloxy-carbonate-docetaxel (CDP-ethane-S-S-ethane-DTX) and CDP-2'- aminoethoxyethoxy -Docetaxel (CDP-aminoethoxyethoxy-DTX).

A 10 mg/mL (with regard to polymer) solution of each CDP-linker-DTX nanoparticle was prepared in water (pH<5) or in 0.1x PBS buffer (pH=7.4). An aliquot of 100 μL was transferred into corresponding HPLC vials. A vial containing each CDP-linker-DTX nanoparticle in water for each designated time point was placed in both: 1) a water bath at 37°C and 2) kept at room temperature at 25°C. Samples were mixed using a water bath shaker at 100 rpm during the experiments. At each designated time point, a vial was removed for each CDP-linker-DTX nanoparticle and processed for HPLC using a sample preparation procedure.

To prepare a sample for HPLC analysis, each vial containing 100μL of sample was mixed with 25 μL of 0.1 % formic acid in ACN, which is a good solvent for both docetaxel and the CDP polymer. If there was any precipitated material in the vial, the contents were also stirred to dissolve the precipitate. If the sample was still opaque, an additional 25 μL of 0.1 % formic acid in ACN was added. HPLC analysis was used to determine the amount of free docetaxel and the amount of conjugated docetaxel in the sample for a given time point.

For the HPLC analysis at each time point, the peak areas of all relevant peaks from the chromatograms were retrieved and the concentration of free and conjugated docetaxel was calculated. The sample degradation was calculated based on the percentage of the amount of conjugated drug with regard to the initial starting point of the experiment (at t=0). The drug release was calculated based on the sum of free docetaxel and docetaxel main degradants at each time point. The drug release and degradation of given conjugate at 37 °C in 0.1x PBS after 24 h are presented in Table 1.

Table 1. Drug Release for Different CDP-linker-Docetaxel products at 37°C in 0.1x PBS at pH=7.4

CPX#	*In vitro* release of free drug (24 hrs in PBS at 37°C)	*In vitro* degradation of conjugate (24 hrs in PBS at 37°C)
CDP-Glycine-DTX	88 %	84 %
CDP-Ala Gly-DTX	95 %	96 %
CDP-Hex-DTX	8 %	7 %
CDP-Ethane-S-S-Ethane-Doce	7 %	4 %
CDP- aminoethoxyethoxy-Doce	71 %	74 %

The data indicates that the hexanoate linker and the disulfide linker are relatively stable toward hydrolysis in vitro, whereas the glycine linker, alanine-glycolate linker, and aminoethoxyethoxylinker are more susceptible to hydrolysis.

Relative stability of different CDP-linker-DTX nanoparticles:

CDP-hex-DTX, CDP-ethane-S-S-ethane-DTX >> CDP- aminoethoxyethoxy-DTX > CDP-Gly-DTX, CDP-Ala Gly-DTX

Example 27. Efficacy and tolerability of CDP – docetaxel nanoparticles in a murine melanoma model

B16.F10 cells were grown in culture to 85-90% confluency in MEM-alpha medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin. Cells were removed from the flask using 0.05% trypsin (passage = 4), re-suspended in PBS (density = 10×10^6 cells/mL) and were implanted subcutaneously (1×10^6 cells in 100 µL of PBS/mouse) into the right flank of male C57BL/6 mice on day 1.

The six treatment groups that were administered to the mice included: 1) Docetaxel formulation prepared at 10 mg/mL stock solution (with 20 mg of docetaxel, 0.2 mL ethanol, 0.5 mL Tween 80 and 1.3 mL water, added in that specific order and vortexed to ensure proper mixing) and diluted further with PBS to 1.5 and 3 mg/mL concentrations for a corresponding dose of 15 and 30 mg/kg respectively. 2) CDP-2'-glycine-docetaxel (CDP-Gly-DTX) nanoparticle formulation administered at 15 and 30 mg/kg. 3) CDP-2'-alanine glycolate-docetaxel (CDP-Ala Gly-DTX) nanoparticle formulation administered at 15 and 30 mg/kg. 4) CDP -2'-hexanoate-docetaxel (CDP-Hex-DTX) nanoparticle formulation administered at 30 mg/kg. (5) CDP-dithiolethyloxy-carbonate-docetaxel (CDP-ethane-S-S-ethane-DTX) nanoparticle formulation administered at 15 and 30 mg/kg. (6) CDP -2'- aminoethoxyethoxy-docetaxel (CDP-aminoethoxyethoxy-DTX) nanoparticle formulation administered at 15 and 30 mg/kg.

The treatments were administered IV into the tail vein at a dose volume of 10 mL/kg, beginning on post-implantation day 5, when the mean tumor volume was *ca.* 60 mm^3. Animals were monitored for any morbidity and adverse effect three times a week. In addition, body weight and tumor volume were also measured three times a week.

Tumor volume was calculated with a (width × width × length) / 2 mm^3 formula. Efficacy was determined by tumor growth inhibition (TGI), tumor growth delay (TGD) and survival. Tumor growth inhibition (TGI) was represented as % and calculated as (1 – (treated tumor volume/control tumor volume)) × 100 when the control group mean tumor volume reached ≥ 3000mm^3. Tumor growth delay (TGD) was calculated by subtracting the day when the vehicle treated group reached the maximum tumor size 3000mm^3 from the day when the treatment group tumor size reached 3000mm^3. The criterion at which a mouse was removed from the study was tumor volume ≥ 3000mm^3.

Tolerability was determined by changes in body weight, expressed as a percent of the initial body weight on post-implantation day 5. Health monitoring was conducted three times a week to evaluate lethargy, tremors, hypothermia, ataxia, hind limb paralysis etc. The criteria at which a mouse was removed from the study were > 20% body weight loss or severe morbidity or hind limb paralysis. When one of these criteria are seen, such

as greater than or equal to 20% body weight loss, the method of administering the CDP-taxane conjugates to the subject can be modified by, for example, decreasing the dose of the CDP-taxane conjugates to the subject, or increasing the interval between doses of the CDP-taxane conjugates to the subject.

1. CDP -2'-glycine-docetaxel (CDP-Gly-DTX) nanoparticle formulation

1.1. The CDP-Gly-DTX formulation was administered at a dose of 15 mg/kg with a schedule of three injections over 2 weeks at a dosing frequency of twice per week. Free docetaxel administered at the same dose and schedule of CDP-Gly-DTX formulation showed similar TGI. At 15 mg/kg, the TGI was 97% for the free docetaxel group and 98% for the CDP-Gly-DTX formulation group. CDP-Gly-DTX formulation showed better TGD as compared to the free docetaxel group. The free docetaxel group reached the mean tumor volume endpoint ($\geq 3000mm^3$) on day 34 and exhibited 15 days TGD (79% increase in TGD). In comparison, the CDP-Gly-DTX formulation had mean tumor volumes of $233mm^3$ and $374mm^3$ on day 33 and day 36 respectively and the group continued beyond day 36 whereas the free docetaxel group ended because the mean tumor volume reached the endpoint ($\geq 3000mm^3$). On day 52, the mean tumor volume of the CDP-Gly-DTX formulation group was 1556 mm^3 and the TGD was greater than 33 days as the mean tumor volume of the group did not reach the endpoint ($\geq 3000mm^3$) on day 52. For the free docetaxel group, 50% survival was observed on day 33 and 0% survival on day 40 compared to the CDP-Gly-DTX formulation which showed 86% survival on day 40, 50% on day 94 and 43% survival on day 115. Both the free docetaxel and CDP-Gly-DTX nanoparticle formulation did not cause any significant body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	15	97%	15 days	3%
CDP-Gly-DTX formulation	15	98%	> 33 days	7%

1.2. The CDP-Gly-DTX formulation was administered at a dose of 30 mg/kg with a schedule of three injections over 2 weeks at a dosing frequency of twice per week. Free docetaxel administered at a dose of 15 mg/kg, on a biweekly schedule for 3 injections showed similar TGI as compared to CDP-Gly-DTX formulation. At 15 mg/kg, the TGI was 97% for the free docetaxel group whereas TGI was 98% for the CDP-Gly-DTX formulation group at 30 mg/kg. CDP-Gly-DTX formulation showed better TGD as compared to the free docetaxel group. The free docetaxel group reached the mean tumor volume endpoint ($\geq 3000mm^3$) on day 34 and exhibited 15 days TGD (79% increase in TGD). In comparison, the CDP-Gly-DTX formulation had mean tumor volumes of $63mm^3$ on both day 33 and day 36 and the group continued beyond day 36 whereas the free docetaxel group ended because the mean tumor volume reached the endpoint ($\geq 3000mm^3$). On day 82, the mean tumor volume of the CDP-Gly-DTX formulation was 1979 mm^3 and the TGD was greater than 63 days as the mean tumor volume of the group did not reach the endpoint ($\geq 3000mm^3$) on day 82. 50% survival was observed on day 33 in the free docetaxel group and 0% survival on day 40 compared to the CDP-Gly-DTX formulation which showed 100% survival on day 40 and 50% survival on day 115. The CDP-Gly-DTX formulation caused 20% body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	15	97%	15 days	3%
CDP-Gly-DTX formulation	30	98%	> 63 days	20%

1.3. The CDP-Gly-DTX formulation was administered at a dose of 15 mg/kg, on a weekly schedule for 3 injections. The free docetaxel group administered at the same dose and schedule was less efficacious than the CDP-Gly-DTX formulation. At 15 mg/kg, the TGI was 68% for the free docetaxel group compared to 82% TGI for the CDP-Gly-DTX formulation. The free docetaxel group reached the mean tumor volume endpoint ($\geq$ 3000mm^3) on day 26 and exhibited 7 days TGD (37% increase in TGD). In contrast, the CDP-Gly-DTX formulation reached mean tumor volume endpoint on day 31 and exhibited 12 days TGD (63% increase in TGD). Both free docetaxel and CDP-Gly-DTX formulation groups did not cause any body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	15	68%	7 days	0%
CDP-Gly-DTX formulation	15	82%	12 days	0%

1.4 The CDP-Gly-DTX formulation was administered at a dose of 30 mg/kg, on a weekly schedule for 3 injections. The free docetaxel group administered at the same dose and schedule was less efficacious than the CDP-Gly-DTX formulation. At 30 mg/kg, the TGI was 84% for the free docetaxel group compared to 96% TGI for the CDP-Gly-DTX formulation. The free docetaxel group reached the mean tumor volume endpoint (≥ 3000mm^3) on day 31 and exhibited 12 days TGD (63% increase in TGD). In comparison, the CDP-Gly-DTX formulation reached the mean tumor volume endpoint on day 47 and exhibited 28 days TGD (147% increase in TGD). For the free docetaxel group, 50% survival was observed on day 29 and 0% survival on day 38 compared to the CDP-Gly-DTX formulation which showed 50% survival on day 47 and 25% survival on day 59. Both free docetaxel and CDP-Gly-DTX formulation groups did not cause any significant body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	30	84%	12 days	8%
CDP-Gly-DTX formulation	30	96%	28 days	14%

1.5 The CDP-Gly-DTX formulation was administered at a dose of 30 mg/kg, on a weekly schedule for 3 injections. The free docetaxel group administered at the same dose and schedule was less efficacious than the CDP-Gly-DTX formulation. At 30 mg/kg, the TGI was 92% for the free docetaxel group compared to 99% TGI for the CDP-Gly-DTX formulation. The free docetaxel group reached the mean tumor volume endpoint (≥ 3000mm^3) on day 41 and exhibited 21 days TGD (105% increase in TGD). In comparison, the CDP-Gly-DTX formulation did not yet reach the mean tumor volume endpoint (≥ 3000mm^3) on day 80 and exhibited >60 days TGD (>300% increase in

TGD). For the free docetaxel group, 50% survival was observed on day 40 and 0% survival on day 45 compared to the CDP-Gly-DTX formulation which showed 62.5% survival on day 127, which was the last day of the experiment.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	30	92%	21 days	12%
CDP-Gly-DTX formulation	30	99%	>60 days	15%

1.6. The CDP-Gly-DTX formulation was administered at a dose of 30 mg/kg on a biweekly schedule for 3 injections. The free docetaxel group administered at 30 mg/kg on a biweekly schedule for 2 injections was less efficacious than CDP-Gly-DTX formulation. At 30 mg/kg, the TGI was 73% for the free docetaxel in contrast to 93% TGI for the CDP-Gly-DTX formulation. The free docetaxel group reached the mean tumor volume endpoint ($\geq 3000mm^3$) on day 26 and exhibited 7 days TGD (37% increase in TGD). In comparison, the CDP-Gly-DTX formulation reached the mean tumor volume endpoint on day 43 and exhibited 24 days TGD (126% increase in TGD). The free docetaxel group did not receive the 3rd injection (on day 33) because the group exited on day 26. 50% survival was observed on day 24 in the free docetaxel group and 0% survival on day 31 whereas the CDP-Gly-DTX formulation showed 50% survival on day 40 and 13% survival on day 59. Both the free docetaxel and CDP-Gly-DTX formulation groups did not cause any significant body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition	Tumor growth delay	Maximum body weight

		(% TGI)	(TGD)	loss (%)
Free docetaxel	30	73%	7 days	5%
CDP-Gly-DTX formulation	30	93%	24 days	4%

2. CDP-2'-alanine glycolate-docetaxel (CDP-Ala Gly-DTX) nanoparticle formulation

2.1. The CDP-Ala Gly-DTX formulation was administered at 15 mg/kg, three injections over a 2 week schedule. Free docetaxel administered at the same dose and schedule of CDP-Ala Gly-DTX formulation showed similar TGI. At 15 mg/kg, the TGI was 97% for the free docetaxel group and 98% for the CDP-Ala Gly-DTX formulation group. CDP-Ala Gly-DTX formulation however showed better TGD as compared to the free docetaxel group. The mean tumor volume endpoint ($\geq 3000mm^3$) was reached at day 35 for the free docetaxel group compared to day 43 for CDP-Ala Gly-DTX formulation. The free docetaxel group exhibited 15 days TGD (79% increase in TGD) whereas CDP-Ala Gly-DTX formulation showed 24 days TGD (126% increase in TGD). 50% survival was observed on day 33 in the free docetaxel group and 0% survival on day 40 whereas CDP-Ala Gly-DTX formulation showed 75% survival on day 40 and 38% survival on day 43. Both free docetaxel and CDP-Ala Gly-DTX formulation groups did not cause any significant body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)

Free docetaxel	15	97%	15 days	3%
CDP-Ala Gly-DTX formulation	15	98%	24 days	6%

2.2. The CDP-Ala Gly-DTX formulation was administered at a dose of 15 mg/kg on a weekly schedule for 3 injections. The free docetaxel group administered at the same dose and schedule was less efficacious than CDP-Ala Gly-DTX formulation. The free docetaxel and CDP-Ala Gly-DTX formulation groups resulted in 68% TGI and 85% TGI respectively. On day 26, the free docetaxel group reached the mean tumor volume endpoint ($\geq 3000mm^3$) and exhibited 7 days TGD (37% increase in TGD). In comparison, on day 33, CDP-Ala Gly-DTX formulation reached the mean tumor volume endpoint on day 33 and exhibited 14 days TGD (74% increase in TGD). Both free docetaxel and CDP-Ala Gly-DTX formulation groups did not cause any significant body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	15	68%	7 days	0%
CDP-Ala Gly-DTX formulation	15	85%	14 days	3%

2.3. The CDP-Ala Gly-DTX formulation was administered at 30 mg/kg on a weekly schedule for 3 injections. Free docetaxel administered at the same dose and schedule was less efficacious than CDP-Ala Gly-DTX formulation. At 30 mg/kg, the free docetaxel and CDP-Ala Gly-DTX formulation groups caused 84% TGI and 96% TGI respectively. On day 31, the free docetaxel group reached the mean tumor volume endpoint ($\geq 3000mm^3$) and exhibited 12 days TGD (63% increase in TGD). In comparison, on day 43, CDP-Ala Gly-DTX formulation reached the mean tumor volume endpoint and showed 24 days TGD (126% increase in TGD). 50% survival was observed on day 29 in the free docetaxel group and 0% survival on day 38 whereas CDP-Ala Gly-DTX formulation showed 50% survival on day 40 and 0% survival on day 54. Both free docetaxel and CDP-Ala Gly-DTX formulation groups did not cause any significant body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	30	84%	12 days	8%
CDP-Ala Gly-DTX formulation	30	96%	24 days	7%

2.4. The CDP-Ala Gly-DTX formulation was administered at 30 mg/kg on a biweekly schedule for 2 injections. Free docetaxel administered at the same dose and schedule showed similar TGI but less TGD as compare to CDP-Ala Gly-DTX formulation. Free docetaxel caused 73% TGI whereas CDP-Ala Gly-DTX formulation caused 77% TGI. The free docetaxel group reached the mean tumor volume endpoint ($\geq 3000mm^3$) on day 26 and exhibited 7 days TGD (37% increase in TGD) whereas CDP-Ala Gly-DTX formulation reached the mean tumor volume endpoint on day 29 and exhibited 10 days TGD (53% increase in TGD). For the free docetaxel, 50% survival was observed on day 24 and 0% survival on day 31. In comparison, CDP-Ala Gly-DTX formulation showed 50% survival on day 29 and 0% survival on day 36. Both free docetaxel and CDP-Ala Gly-DTX formulation groups did not cause any significant body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	30	73%	7 days	5%
CDP-Ala Gly-DTX formulation	30	77%	10 days	2%

3. CDP-2'-hexanoate-docetaxel (CDP-Hex-DTX) nanoparticle formulation

3.1. The CDP-Hex-DTX formulation was administered at a dose of 30 mg/kg, three injections over a 2 week schedule. Free docetaxel administered at 15 mg/kg, three injections over a 2 week schedule was more efficacious than CDP-Hex-DTX formulation. At 15 mg/kg, the free docetaxel resulted in a 97% TGI compared to CDP-Hex-DTX formulation at 30 mg/kg, resulted in a 66% TGI. On day 34, the free docetaxel group reached the mean tumor volume endpoint ($\geq 3000mm^3$) and exhibited 15 days TGD (79% increase in TGD). The CDP-Hex-DTX formulation showed 10 days TGD (53% increase in TGD). Both free docetaxel and CDP-Hex-DTX formulation groups did not cause any significant body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	15	97%	15 days	3%
CDP-Hex-DTX formulation	30	66%	10 days	0%

4. CDP-dithiolethyloxy-carbonate-docetaxel (CDP-ethane-S-S-ethane-DTX) nanoparticle formulation

4.1. The CDP-ethane-S-S-ethane-DTX formulation was administered at a dose of 15 mg/kg, on a weekly schedule for 3 injections. Free docetaxel administered at the same dose and schedule was found to be more efficacious than CDP-ethane-S-S-ethane-DTX formulation. Free docetaxel caused 68% TGI whereas CDP-ethane-S-S-ethane-DTX formulation caused 24% TGI. On day 26, the free docetaxel group reached the mean tumor volume endpoint ($\geq 3000mm^3$) and exhibited 7 days TGD (37% increase in TGD) compared to CDP-ethane-S-S-ethane-DTX formulation which reached the mean tumor volume endpoint on day 21 and exhibited 2 days TGD (11% increase in TGD). Both free docetaxel and CDP-ethane-S-S-ethane-DTX formulation groups did not cause any body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	15	68%	7 days	0%
CDP-ethane-S-S-ethane-DTX formulation	15	24%	2 days	0%

4.2. The CDP-ethane-S-S-ethane-DTX formulation was administered at a dose of 30 mg/kg, on a weekly schedule for 3 injections. The free docetaxel administered at the same dose and schedule was less efficacious than CDP-ethane-S-S-ethane-DTX formulation. At 30 mg/kg, free docetaxel resulted in 84% TGI compared to 46% TGI for the CDP-ethane-S-S-ethane-DTX formulation. On day 31, the free docetaxel group reached the mean tumor volume endpoint ($\geq 3000mm^3$) and showed 12 days TGD (63% increase in TGD) compared to CDP-ethane-S-S-ethane-DTX formulation which reached the mean tumor volume endpoint on day 24 and exhibited 5 days TGD (26% increase in TGD). Both free docetaxel and CDP-ethane-S-S-ethane-DTX formulation groups did not cause any significant body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	30	84%	12 days	8%
CDP-ethane-S-S-ethane-DTX formulation	30	46%	5 days	0%

5. CDP-2'- aminoethoxyethoxy-Docetaxel (CDP- aminoethoxyethoxy-DTX) nanoparticle formulation

5.1. The CDP- aminoethoxyethoxy-DTX formulation was administered at a dose of 15 mg/kg on a weekly schedule for 3 injections. Free docetaxel administered at the same dose and schedule was less efficacious than the CDP- aminoethoxyethoxy-DTX formulation. Free docetaxel resulted in 68% TGI compared to CDP- aminoethoxyethoxy-DTX formulation which resulted in a 87% TGI. On day 26, the free docetaxel group reached the mean tumor volume endpoint ($\geq 3000mm^3$) and showed 7 days TGD (37% increase in TGD). In comparison, CDP- aminoethoxyethoxy-DTX formulation reached the mean tumor volume endpoint on day 33 and exhibited 14 days TGD (74% increase in TGD). Both free docetaxel and CDP- aminoethoxyethoxy-DTX formulation groups did not cause any significant body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	15	68%	7 days	0%
CDP- aminoethoxyethoxy-DTX formulation	15	87%	14 days	7%

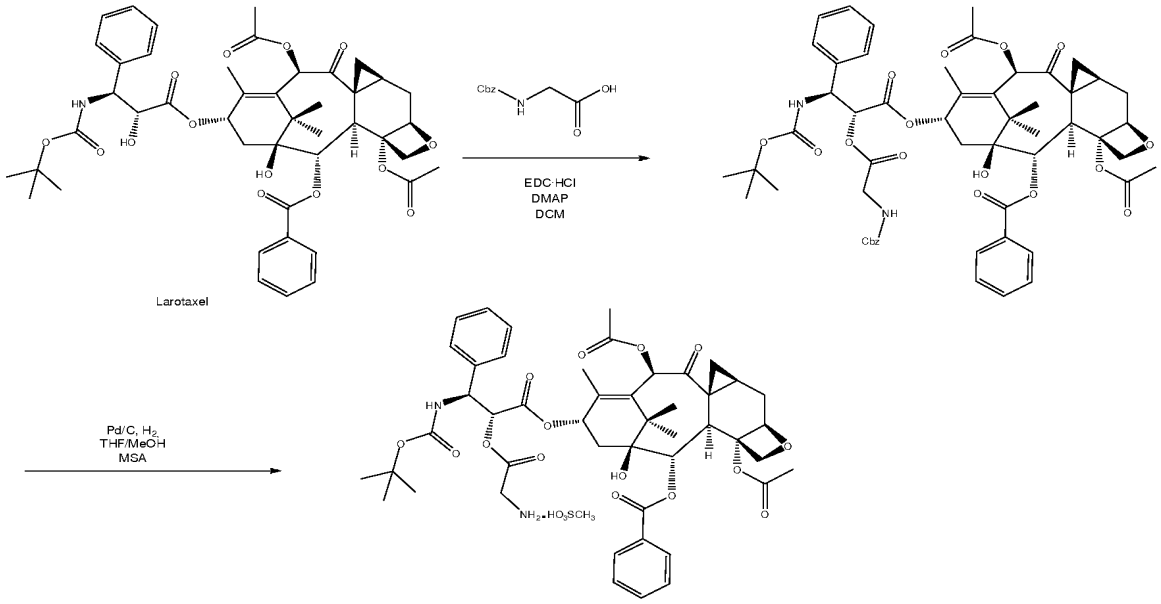
5.2. The CDP- aminoethoxyethoxy-DTX formulation was administered at a dose of 30 mg/kg on a weekly schedule for 3 injections. Free docetaxel administered at the same dose and schedule was less efficacious than the CDP- aminoethoxyethoxy-DTX formulation. At 30 mg/kg, free docetaxel resulted in a 84% TGI compared to 97% TGI for CDP- aminoethoxyethoxy-DTX formulation. The free docetaxel group reached the mean tumor volume endpoint ($\geq 3000mm^3$) on day 31 and exhibited 12 days TGD (63% increase in TGD) whereas the mean tumor volume of the CDP- aminoethoxyethoxy-DTX formulation was 1442 mm^3 on day 59 and the TGD was more than 40 days. 50% survival was observed on day 29 for the free docetaxel group and 0% survival on day 38. In comparison, CDP- aminoethoxyethoxy-DTX formulation showed 88% survival on day 59. The CDP- aminoethoxyethoxy-DTX formulation caused 23% body weight loss.

Formulation	Dose (mg/kg)	Tumor growth inhibition (% TGI)	Tumor growth delay (TGD)	Maximum body weight loss (%)
Free docetaxel	30	84%	12 days	8%
CDP- aminoethoxyethoxy-DTX formulation	30	97%	>40 days	23%

Example 28. Synthesis of larotaxel glycinate

A 1000 mL, three-neck jacketed reactor equipped with an addition funnel, overhead stirrer, J-KEM probe, and N_2 inlet will be charged with larotaxel (22.3 g, 26.7 mmol), *N*-Cbz-glycine (5.6 g, 26.7 mmol), DMAP (3.3 g, 26.7 mmol) and DCM (150 mL). The mixture will be stirred for a few minutes to produce a clear solution. It will be cooled from – 2 to 2 °C with a TCM. A suspension of EDCI (10.2 g, 53.4 mmol) and DMAP (1.6 g, 13.3 mmol) in DCM (100 mL) will be added dropwise over 2 h. The reaction will be stirred from – 2 to 2°C for 12 h and subsequently the temperature will be lowered to –5 °C. Additional *N*-Cbz-glycine (2.2 g, 10.7 mmol) will be added, followed by addition of EDCI (5.1 g, 26.7 mmol) and DMAP (1.6 g, 13.3 mmol) in DCM (50 mL) over 1 h. The reaction will be stirred at –5 °C for 16 h and then at 0 °C for 4 h, at which time IPC analysis will be done to check for the consumption of larotaxel. Once the reaction completion is confirmed, the reaction mixture will be diluted with DCM to 500 mL and washed with 1% HCl (2 × 150 mL), saturated $NaHCO_3$ (2 × 100 mL) and brine (150 mL). The organic layer will be separated, dried over Na_2SO_4, and filtered. The filtrate will be concentrated to a residue to produce a crude product. The crude product will then be purified by column chromatography to yield pure Cbz-glycinate larotaxel.

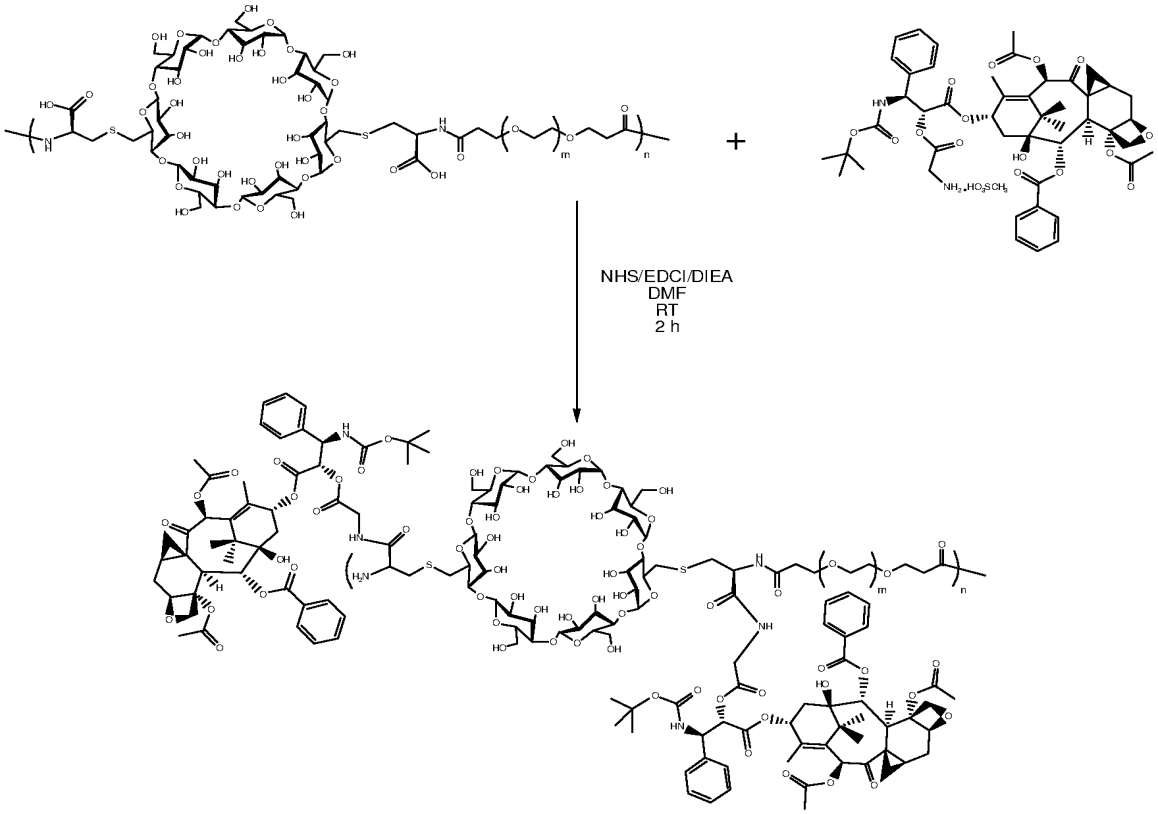
A 1000 mL round-bottom flask equipped with a magnetic stirrer will be charged with THF (160 mL), methanesulfonic acid (980 μL), and 5% Pd/C (5.9 g). The suspension will be evacuated and back filled with H_2 three times and stirred under H_2 for 0.5 h. A solution of Cbz-glycinate larotaxel (17.5 g, 17.0 mmol) in THF (170 mL) and MeOH (10 mL) will be added. The reaction will be monitored by HPLC. After the reaction is completed, charcoal (10 g) will be added to the reaction and the mixture will be stirred for 10 min and filtered through a Celite pad to produce a clear solution. It will be concentrated to ~50 mL, to which heptanes (500 mL) will be added to precipitate out the product. It will then be dried under vacuum to yield larotaxel glycinate.



Example 29. Synthesis of CDP Larotaxel glycinate conjugate

CDP (1.0 g, 0.21 mmol) will be dissolved in dry N,N-dimethylformamide (DMF, 10 mL). Larotaxel glycinate (400 mg, 0.46 mmol), N,N-Diisopropylethylamine (59 mg, 0.46 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (87 mg, 0.46 mmol), and N-Hydroxysuccinimide (52 mg, 0.46 mmol) will then be added to the

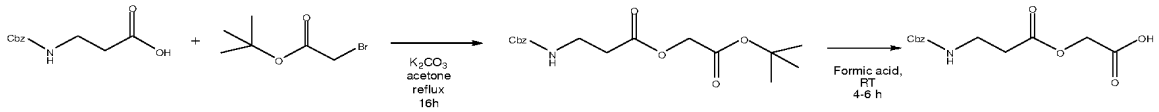
polymer solution and stirred for 2 h. The polymer will be precipitated with isopropanol (150 mL) and then rinsed with acetone (100 mL). The precipitate will be dissolved in nanopure water (100 mL). It will be purified by TFF with nanopure water (1L). Finally it will be filtered through 0.2 μm filter and kept frozen.



Example 30. Synthesis of larotaxel β-alanine glycolate

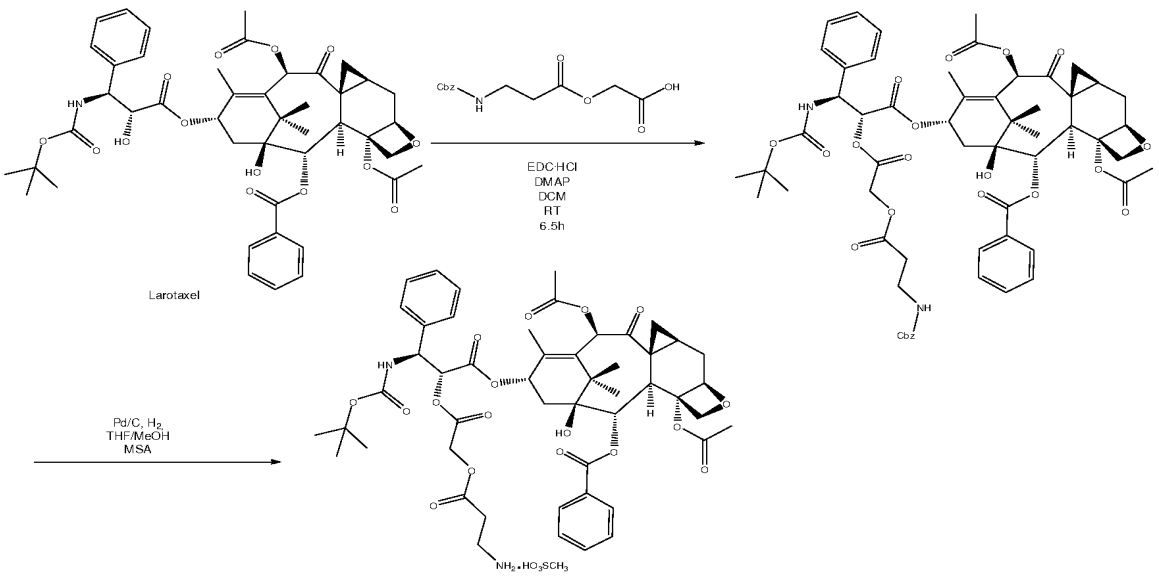
N-Cbz-β-alanine (15.0 g, 67.3 mmol), tert-butyl bromoacetate (13.1 g, 67.3 mmol), acetone (300 mL), and K_2CO_3 (14 g, 100 mmol) was added to a 1000 mL round bottom flask equipped with a magnetic stirrer. The mixture was heated to reflux (60 °C) for 16 h. The mixture was cooled to ambient temperature and the solid was filtered. The filtrate was concentrated to a residue, dissolved in EtOAc (300 mL), and washed with water (3 × 100 mL) and brine (100 mL). The organic layer was separated, dried over Na_2SO_4, and filtered. The filtrate was concentrated to produce a clear oil, tert-butyl N-Cbz-β-alanine glycolate (22.2 g, yield: 99%) with 97.4% purity.

A 100 mL round-bottom flask equipped with a magnetic stirrer was charged with tert-butyl N-Cbz-β-alanine glycolate (7.5 g, 22.2 mmol) and formic acid (35 mL). The mixture was stirred at ambient temperature overnight. The reaction was concentrated under vacuum to a residue and redissolved in EtOAc (7.5 mL). The solution was added to heptanes (150 mL). The product slowly precipitated out to give a white suspension. The mixture was filtered and the filter cake was vacuum-dried at ambient temperature for 24 h to produce the desired product as a white powder, N-Cbz-β-alanine glycolate (5.0 g, yield: 80%) with 98% purity.



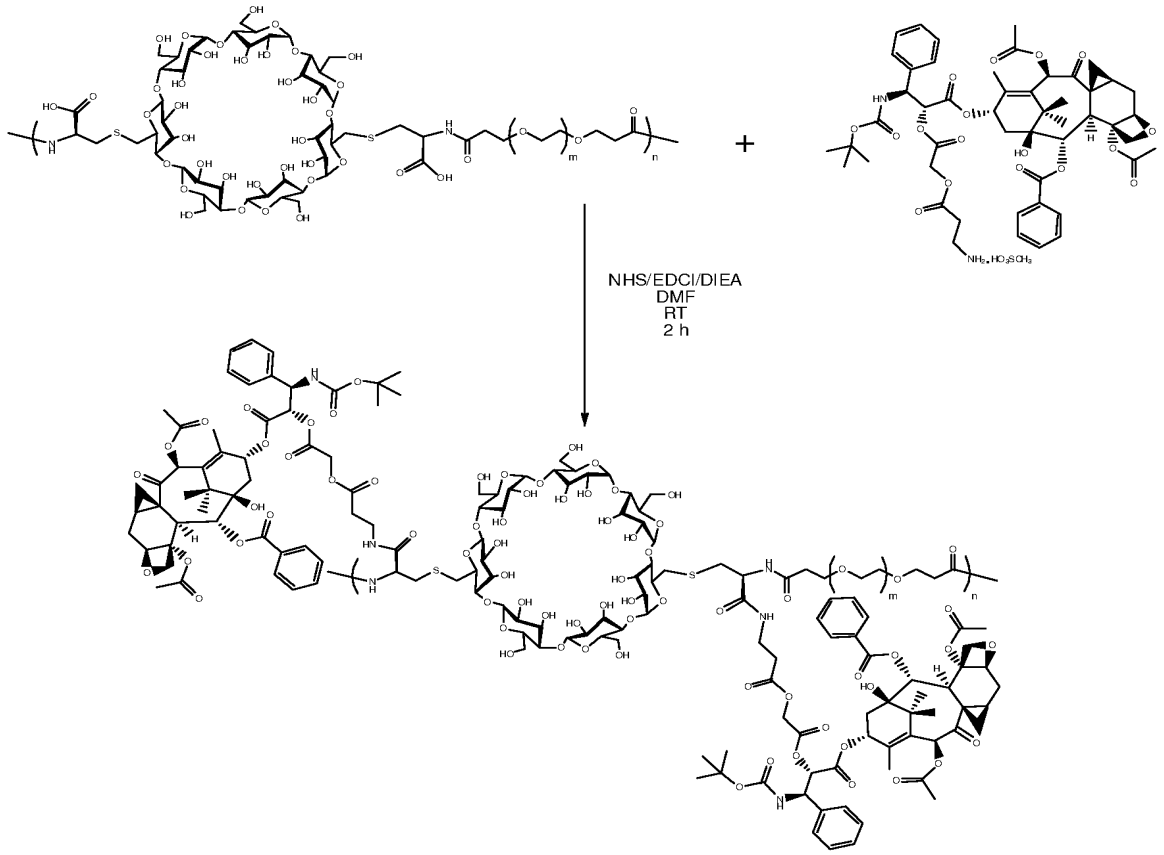
N-Cbz-β-alanine glycolate (1.8 g, 6.5 mmol), DMAP (850 mg, 6.9 mmol) and EDCI (1.4 g, 7.1 mmol) will be added to a solution of larotaxel (7.2 g, 8.7 mmol) in dichloromethane(140 mL) and the mixture will be stirred at ambient temperature for 2.5 h. N-Cbz-β-alanine glycolate (1.1 g, 3.9 mmol), DMAP (480 mg, 3.9 mmol), and EDCI (1.2 g, 6.1 mmol) will be added and the mixture will be stirred for an additional 2.5 h. The mixture will be washed twice with 1% HCl (2 × 100 mL) and brine (100 mL). The organics will be dried over sodium sulfate and concentrated under vacuum. The crude product will be purified by column chromatography.

5% Pd/C (2.80 g) will be slurried in 40 mL THF and 4 mL MeOH in a 250 mL flask with overhead stirring. Methanesulfonic acid (0.46 mL, 7.0 mmol) will be added and the slurry will be stirred under hydrogen at ambient temperature for 30 min. A solution of larotaxel Cbz-β-alanine glycolate (8.5 g, 7.7 mmol) in THF (40 mL) will be added (10 mL THF wash). After 2.0 h, the slurry will be filtered (50 mL THF wash) and the filtrate will be concentrated to a minimum volume, diluted with THF (100 mL) and concentrated to about 40 mL. Heptanes (400 mL) will be added dropwise to this mixture over 15 min and stirred 20 min. The resulting slurry will be filtered (100 mL heptanes wash) and the solid will be dried under vacuum to yield larotaxel β-alanine glycolate.



Example 31. Synthesis of CDP Larotaxel β-alanine glycolate

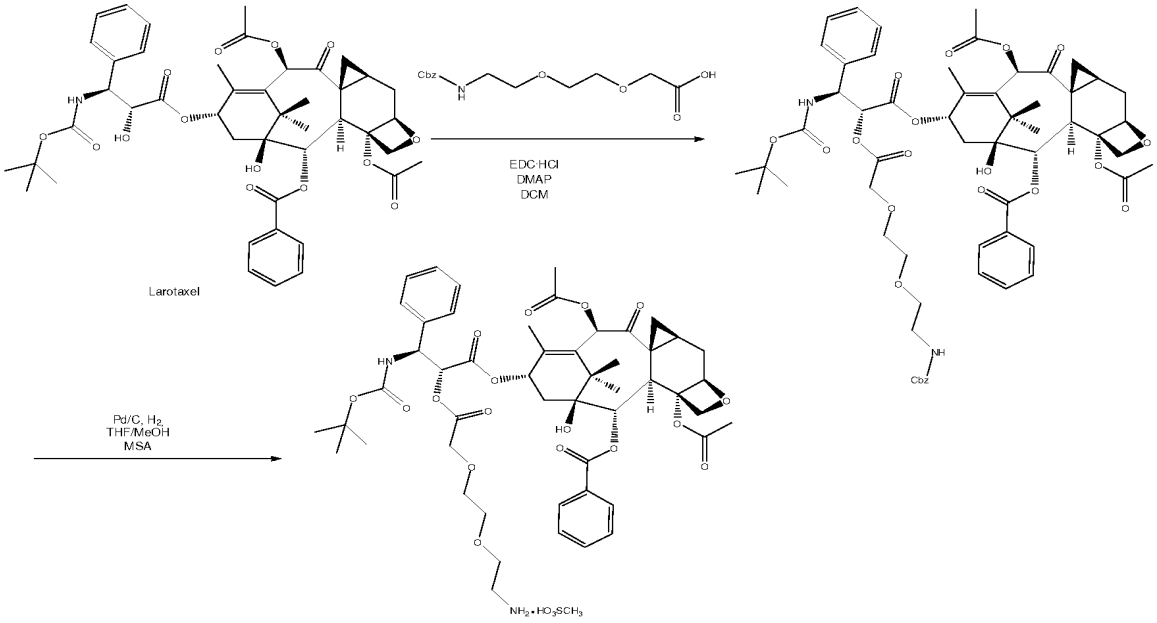
CDP (1.0 g, 0.21 mmol) will be dissolved in dry N,N-dimethylformamide (DMF, 10 mL). Larotaxel β-alanine glycolate (440 mg, 0.46 mmol), N,N-Diisopropylethylamine (59 mg, 0.46 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (87 mg, 0.46 mmol), and N-Hydroxysuccinimide (52 mg, 0.46 mmol) will then be added to the polymer solution and stirred for 2 h. The polymer will be precipitated with isopropanol (150 mL) and then rinsed with acetone (100 mL). The precipitate will be dissolved in nanopure water (100 mL). It will be purified by TFF with nanopure water (1L). Consequently, it will be filtered through 0.2 μm filter and kept frozen.



Example 32. Synthesis of larotaxel aminoethoxyethoxy acetate

Cbz-aminoethoxyethoxy acetic acid (3.97 g, 13.3 mmol) will be dissolved in dichloromethane (10 mL). A portion of this solution (9 mL, about 8.6 mmol) will be added to a solution of larotaxel (9.36 g, 11.2 mmol) in dichloromethane (180 mL) at ambient temperature. DMAP (1.23 g, 10.1 mmol) and EDCI (1.94 g, 10.1 mmol) will be added and the mixture will be stirred at ambient temperature for 2.75 h. The remaining solution of Cbz-aminoethoxyethoxy acetic acid (5 mL, about 4.7 mmol), DMAP (830 mg, 6.80 mmol), and EDCI (1.28 g, 6.67 mmol, 0.60 equiv) will be added. The mixture will be stirred for approximately 5 hours, and the mixture will be washed twice with 0.1 % HCl (2 × 100 mL) and brine (100 mL). The organic layer will be dried over sodium sulfate and concentrated to a residue. The crude product will be purified by column chromatography to yield larotaxel Cbz-aminoethoxyethoxy acetate.

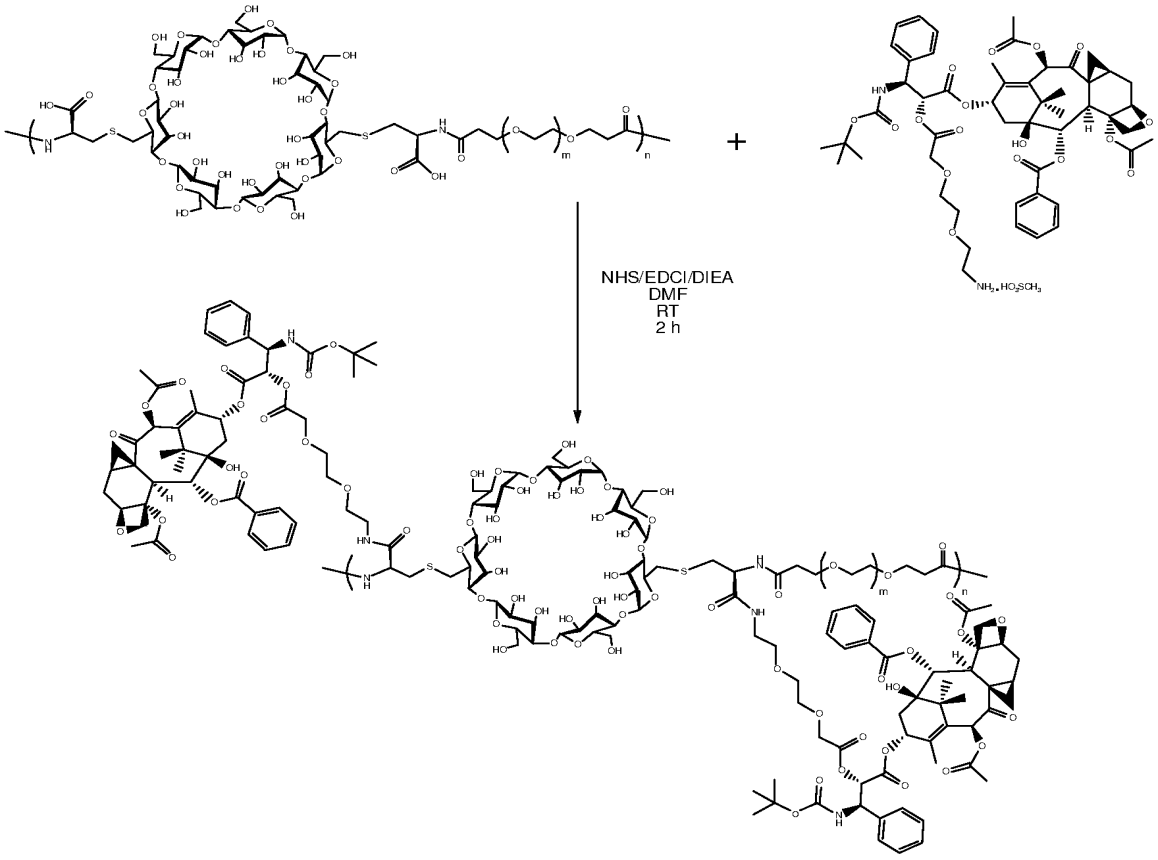
5% Pd/C (2.0 g) will be slurried in 25 mL THF in a 250 mL flask with overhead stirring. The slurry will be stirred under hydrogen at ambient temperature for 45 min. A solution of larotaxel Cbz-aminoethoxyethoxy acetate (5.8 g, 5.2 mmol) in THF (25 mL) and MeOH (5 mL) will be added (25 mL THF wash). After 4.25 h, 5.0 g of activated carbon will be added and stirred under nitrogen for 15 min. The slurry will be filtered (25 mL THF wash) and the filtrate will be concentrated to about 20 mL. The solution will be added dropwise into 200 mL heptanes. THF and MeOH will be added until dissolution of the precipitate has occurred. A solvent exchange with THF will be performed and the solution concentrated to about 40 mL. Heptanes (500 mL) will be added dropwise to precipitate out the product. It will be filtered and dried under vacuum to yield the final product, larotaxel aminoethoxyethoxy acetate.



Example 33. Synthesis of CDP Larotaxel aminoethoxyethoxy acetate

CDP (1.0 g, 0.21 mmol) will be dissolved in dry N,N-dimethylformamide (DMF, 10 mL). Larotaxel aminoethoxyethoxy acetate (440 mg, 0.46 mmol), N,N-Diisopropylethylamine (59 mg, 0.46 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (87 mg, 0.46 mmol), and N-Hydroxysuccinimide (52 mg, 0.46 mmol) will then be added to the polymer solution and stirred for 2 h. The polymer will be precipitated with isopropanol (150 mL) and then rinsed with acetone

(100 mL). The precipitate will be dissolved in nanopure water (100 mL). It will be purified by TFF with nanopure water (1L). In addition, it will be filtered through 0.2 μm filter and kept frozen.

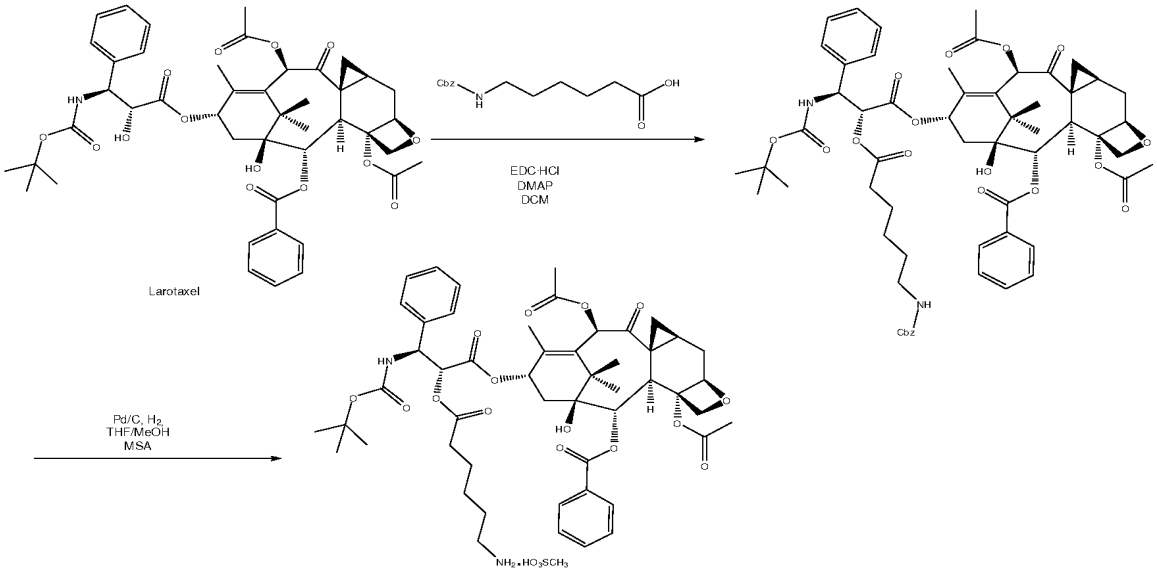


Example 34. Synthesis of larotaxel aminohexanoate

A 1000 mL, three-neck jacketed reactor equipped with an addition funnel, overhead stirrer, J-KEM probe, and N_2 inlet will be charged with larotaxel (22.3 g, 26.7 mmol), *N*-Cbz-aminohexanoic acid (7.08 g, 26.7 mmol), DMAP (3.3 g, 26.7 mmol) and DCM (150 mL). The mixture will be stirred for a few minutes to produce a clear solution. It will be cooled from –2 to 2 °C with a TCM. A suspension of EDCI (10.2 g, 53.4 mmol) and DMAP (1.6 g, 13.3 mmol) in DCM (100 mL) will be added dropwise over 2 h. The reaction will be stirred from –2 to 2 °C for 12 h and the temperature will be lowered to –5 °C. Additional Cbz-aminohexanoic acid (2.83 g, 10.7 mmol) will be

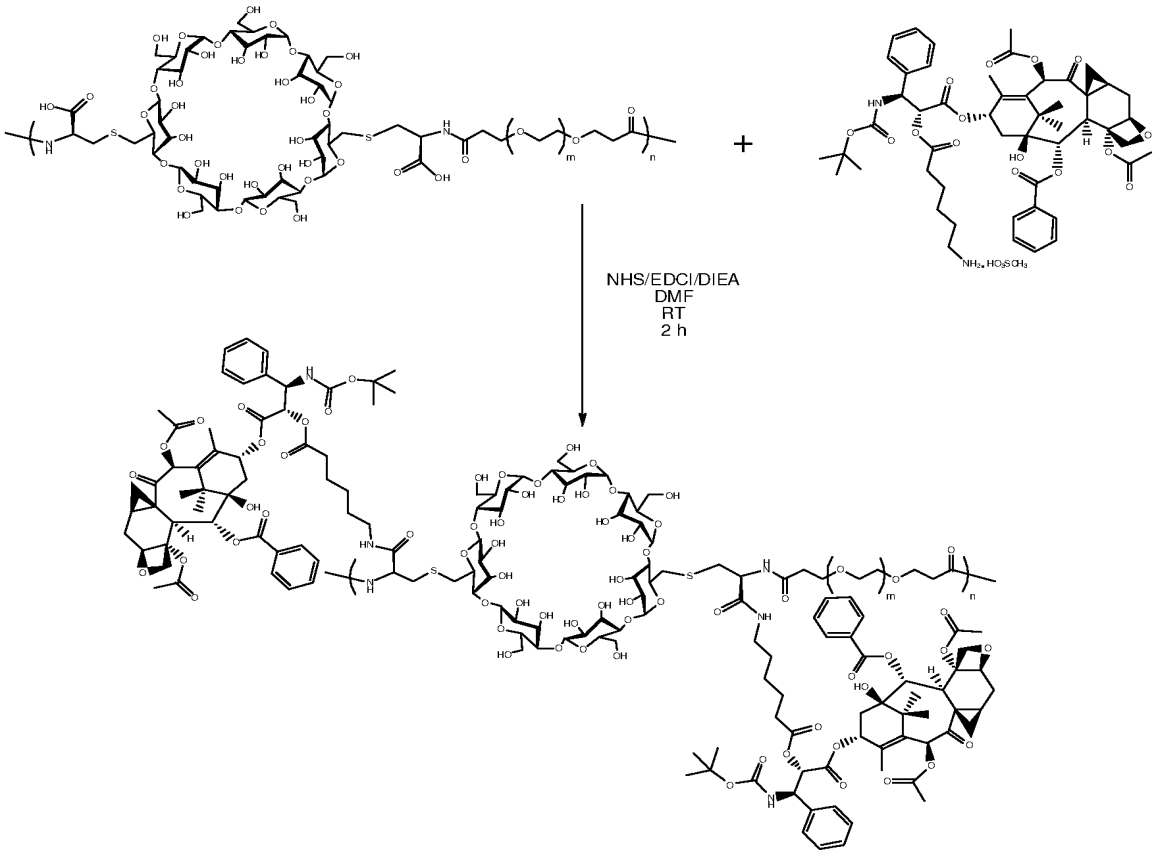
added, followed by addition of EDCI (5.1 g, 26.7 mmol) and DMAP (1.6 g, 13.3 mmol) in DCM (50 mL) over 1 h. The reaction will be stirred at –5 °C for 16 h and then at 0 °C for 4 h, at which time IPC analysis will be done to check for the consumption of larotaxel. Once the reaction completion is confirmed, the reaction mixture will be diluted with DCM to 500 mL and washed with 1% HCl (2 × 150 mL), saturated $NaHCO_3$ (2 × 100 mL) and brine (150 mL). The organic layer will be separated, dried over Na_2SO_4, and filtered. The filtrate will be concentrated to a residue to produce a crude product. Subsequently, the crude product will be purified by column chromatography to yield pure larotaxel Cbz-aminohexanoate.

A 1000 mL round-bottom flask equipped with a magnetic stirrer will be charged with THF (160 mL), methanesulfonic acid (980 µL), and 5% Pd/C (5.9 g). The suspension will be evacuated and back filled with H_2 three times and stirred under H_2 for 0.5 h. A solution of larotaxel Cbz-aminohexanoate (18.4 g, 17.0 mmol) in THF (170 mL) and MeOH (10 mL) will be added. The reaction will be monitored by HPLC. After the reaction is completed, charcoal (10 g) will be added to the reaction and the mixture will be stirred for 10 min and filtered through a Celite pad to produce a clear solution. It will be concentrated to ~50 mL, to which heptanes (500 mL) will be added to precipitate out the product. It will then be dried under vacuum to yield larotaxel aminohexanoate.



Example 35. Synthesis of CDP Larotaxel aminohexanoate conjugate

CDP (1.0 g, 0.21 mmol) will be dissolved in dry N,N-dimethylformamide (DMF, 10 mL). Larotaxel aminohexanoate (430 mg, 0.46 mmol), N,N-Diisopropylethylamine (59 mg, 0.46 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (87 mg, 0.46 mmol), and N-Hydroxysuccinimide (52 mg, 0.46 mmol) will then be added to the polymer solution and stirred for 2 h. The polymer will be precipitated with isopropanol (150 mL) and then rinsed with acetone (100 mL). The precipitate will be dissolved in nanopure water (100 mL). Then it will be purified by TFF with nanopure water (1L). Followed by filtration through a 0.2 μm filter and kept frozen.



Example 36. Synthesis of larotaxel aminoethyldithioethyl carbonate

Triethylamine (15.0 mL, 108 mmol) was added to a mixture of cystamine•2HCl (5.00 g, 22.2 mmol) and MMTCl (14.1 g, 45.6 mmol, 2.05 equiv) in CH_2Cl_2 (200 mL) at

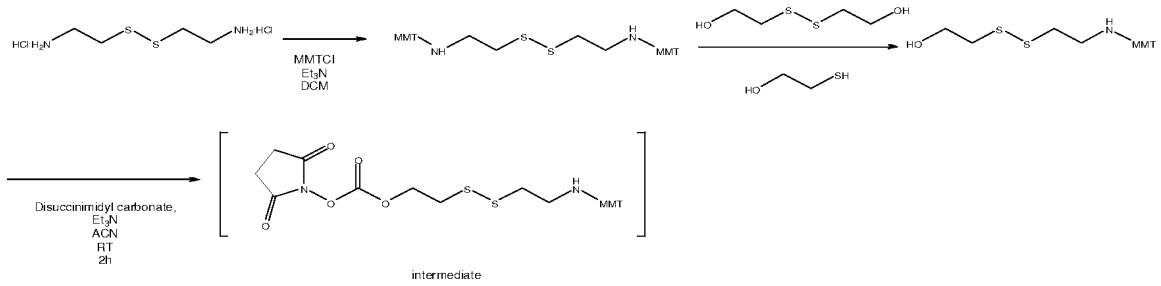
ambient temperature. The mixture was stirred for 90h and 200 mL of 25% saturated $NaHCO_3$ was added, stirred for 30 min, and removed. The mixture was washed with brine (200 mL) and concentrated to produce a brown oil (19.1 g). The oil was dissolved in 20 – 25 mL CH_2Cl_2 and purified by flash chromatography to yield a white foam (diMMT-cyteamine, 12.2 g, Yield: 79%)

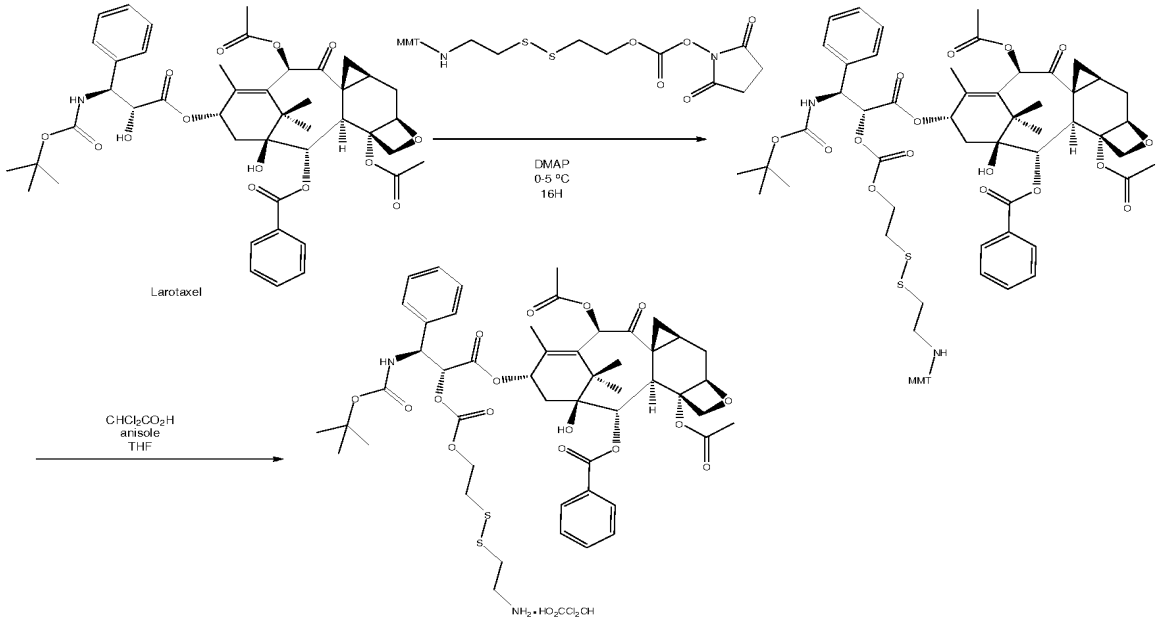
Bis(2-hydroxyethyldisulfide) (11.5mL, 94 mmol, 5.4 equiv) and 2-mercaptoethanol (1.25 mL, 17.8 mmol, 1.02 equiv) were added to a solution of diMMT-cyteamine (12.2 g, 17.5 mmol) in 1:1 CH_2Cl_2/MeOH (60 mL) and the mixture was stirred at ambient temperature for 42.5 h. The mixture was concentrated to an oil, dissolved in EtOAc (150 mL), washed with 10% saturated NaHCO3 (3 · 150 mL) and brine (150 mL), dried over Na2SO4, and concentrated to an oil (16.4 g). The oil was dissolved in 20 mL CH_2Cl_2 and purified by flash chromatography to yield clear thick oil (MMT-aminoethyldithioethanol, 5.33 g, Yield: 36%).

A 250 mL round bottom flask equipped with a magnetic stirrer was charged with MMT-aminoethyldithioethanol (3.6 g, 8.5 mmol) and acetonitrile (60 mL). Disuccinimidyl carbonate (2.6 g) was added and the reaction was stirred at ambient temperature for 3 h. It will be used for the next reaction without isolation. Succinimidyl MMT-aminoethyldithioethyl carbonate from Scheme 9(a) will be transferred to a cooled solution of larotaxel (6.36 g, 7.61 mmol) and DMAP (1.03 g) in DCM (60 mL) at 0-5 °C with stirring for 16 h. It will be then purified by column chromatography.

A 1000 mL round bottom flask equipped with a magnetic stirrer will be charged with larotaxel Cbz-aminoethyldithioethyl carbonate (12.6 g) and DCM (300 mL). Anisole (10.9 mL, 10 equiv.) will be added to this clear solution and stirred for a few minutes. Dichloroacetic acid (8.3 mL, 10 equiv.) will be added over 5 min and the reaction will be stirred at ambient temperature for 1h. The mixture will be concentrated down to ~100 mL, to which heptanes (800 mL) will be slowly added resulting in a suspension. The suspension will be stirred for 15 min and the supernatant will be decanted. The orange residue will be washed with heptanes (200 mL) and vacuum-dried at ambient temperature for 1 h. THF (30 mL) will be added to dissolve the orange

residue producing a red solution. Heptanes (500 mL) will be slowly added to precipitate out the product. The resulting suspension will be stirred at ambient temperature for 1 h and filtered. The filter cake will be washed with heptanes (300 mL) and dried under vacuum to yield larotaxel aminoethyldithioethyl carbonate.

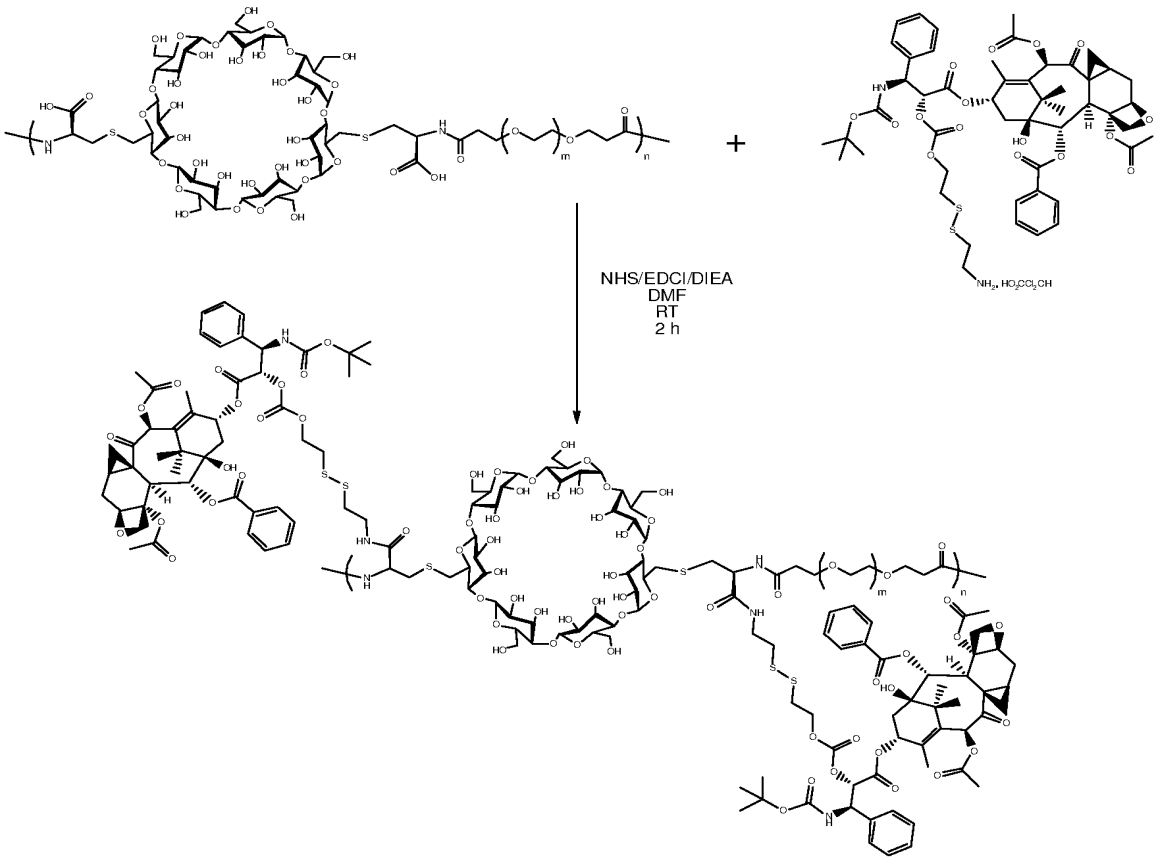




Example 37. Synthesis of CDP Larotaxel aminoethyldithioethyl carbonate

CDP (1.0 g, 0.21 mmol) will be dissolved in dry N,N-dimethylformamide (DMF, 10 mL). Larotaxel aminoethyldithioethyl carbonate (460 mg, 0.46 mmol), N,N-Diisopropylethylamine (59 mg, 0.46 mmol), N-(3-Dimethylaminopropyl)-N'-

ethylcarbodiimide hydrochloride (87 mg, 0.46 mmol), and N-Hydroxysuccinimide (52 mg, 0.46 mmol) will then be added to the polymer solution and stirred for 2 h. The polymer will be precipitated with isopropanol (150 mL) and then rinsed with acetone (100 mL). The precipitate will be dissolved in nanopure water (100 mL). It will be purified by TFF with nanopure water (1L). It will then be filtered through 0.2 μm filter and kept frozen.

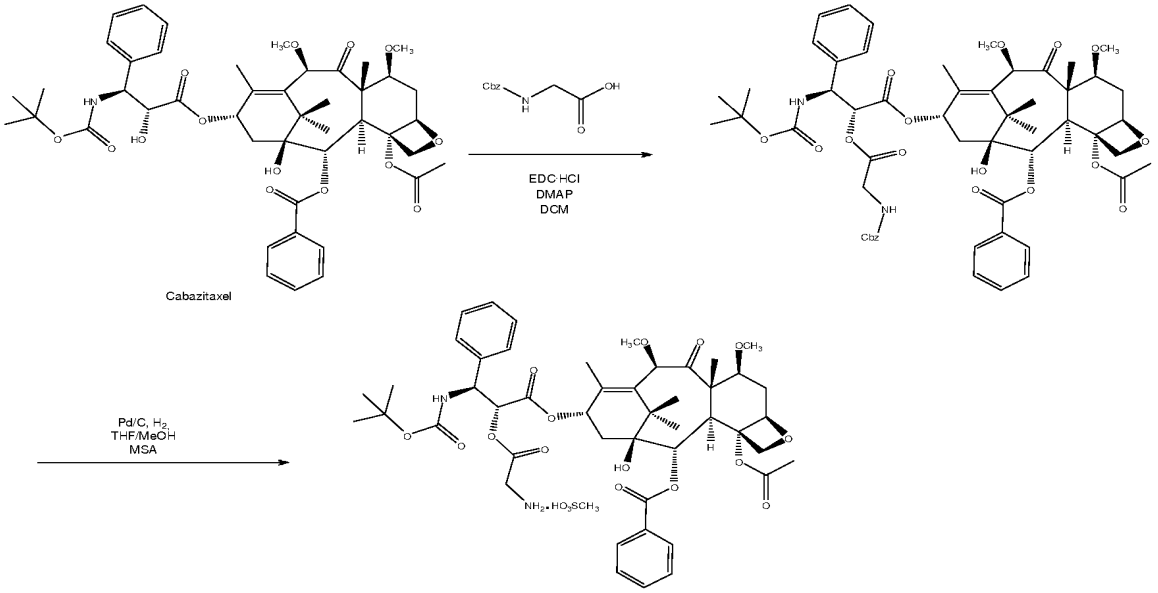


Example 38. Synthesis of Cabazitaxel glycinate

A 1000 mL, three-neck jacketed reactor equipped with an addition funnel, overhead stirrer, J-KEM probe, and N_2 inlet will be charged with cabazitaxel (22.3 g, 26.7 mmol), *N*-Cbz-glycine (5.6 g, 26.7 mmol), DMAP (3.3 g, 26.7 mmol) and DCM (150 mL). The mixture will be stirred for a few minutes to produce a clear solution. It will be cooled from −2 to 2 °C with a TCM. A suspension of EDCI (10.2 g, 53.4 mmol) and

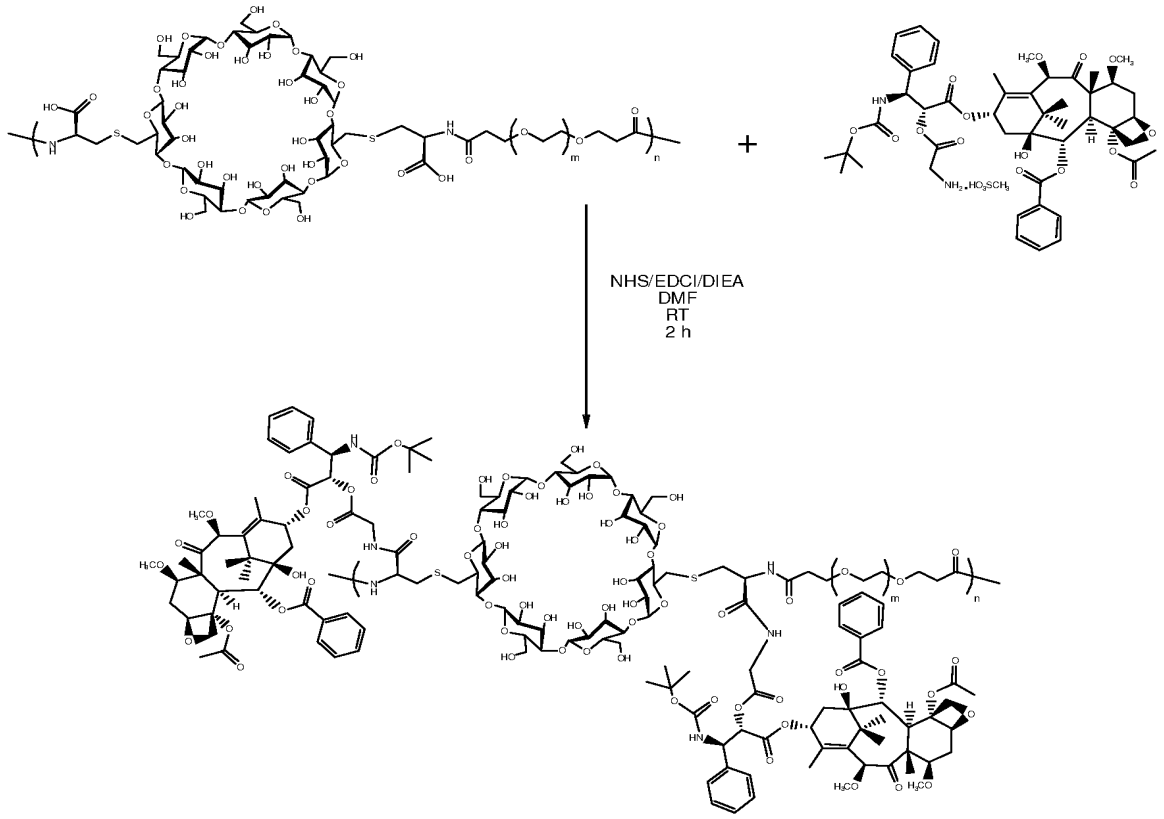
DMAP (1.6 g, 13.3 mmol) in DCM (100 mL) will be added dropwise over 2 h. The reaction will be stirred at –2 to 2 °C for 12 h and the temperature will be lowered to –5 °C. Additional *N*-Cbz-glycine (2.2 g, 10.7 mmol) will be added, followed by addition of EDCI (5.1 g, 26.7 mmol) and DMAP (1.6 g, 13.3 mmol) in DCM (50 mL) over 1 h. The reaction will be stirred at –5 °C for 16 h and then at 0 °C for 4 h, at which time IPC analysis will be done to check for the consumption of cabazitaxel. Once the reaction completion is confirmed, the reaction mixture will be diluted with DCM to 500 mL and washed with 1% HCl (2 × 150 mL), saturated $NaHCO_3$ (2 × 100 mL) and brine (150 mL). The organic layer will be separated, dried over Na_2SO_4, and filtered. The filtrate will be concentrated to a residue to produce a crude product. The crude product will then be purified by column chromatography to yield pure cabazitaxel Cbz-glycinate.

A 1000 mL round-bottom flask equipped with a magnetic stirrer will be charged with THF (160 mL), MSA (980 μL), and 5% Pd/C (5.9 g). The suspension will be evacuated and back filled with H_2 three times and stirred under H_2 for 0.5 h. A solution of cabazitaxel Cbz-glycinate (17.5 g, 17.0 mmol) in THF (170 mL) and MeOH (10 mL) will be added. The reaction will be monitored by HPLC. After the reaction is completed, charcoal (10 g) will be added to the reaction and the mixture will be stirred for 10 min and filtered through a Celite pad to produce a clear solution. It will be concentrated to ~50 mL, to which heptanes (500 mL) will be added to precipitate out the product. It will then be dried under vacuum to yield cabazitaxel glycinate.



Example 39. Synthesis of CDP Cabazitaxel glycinate conjugate

CDP (1.0 g, 0.21 mmol) will be dissolved in dry N,N-dimethylformamide (DMF, 10 mL). Cabazitaxel glycinate (400 mg, 0.46 mmol), N,N-Diisopropylethylamine (59 mg, 0.46 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (87 mg, 0.46 mmol), and N-Hydroxysuccinimide (52 mg, 0.46 mmol) will then be added to the polymer solution and stirred for 2 h. The polymer will be precipitated with isopropanol (150 mL) and then rinsed with acetone (100 mL). The precipitate will be dissolved in nanopure water (100 mL). It will be purified by TFF with nanopure water (1L). It will then be filtered through 0.2 μm filter and kept frozen.

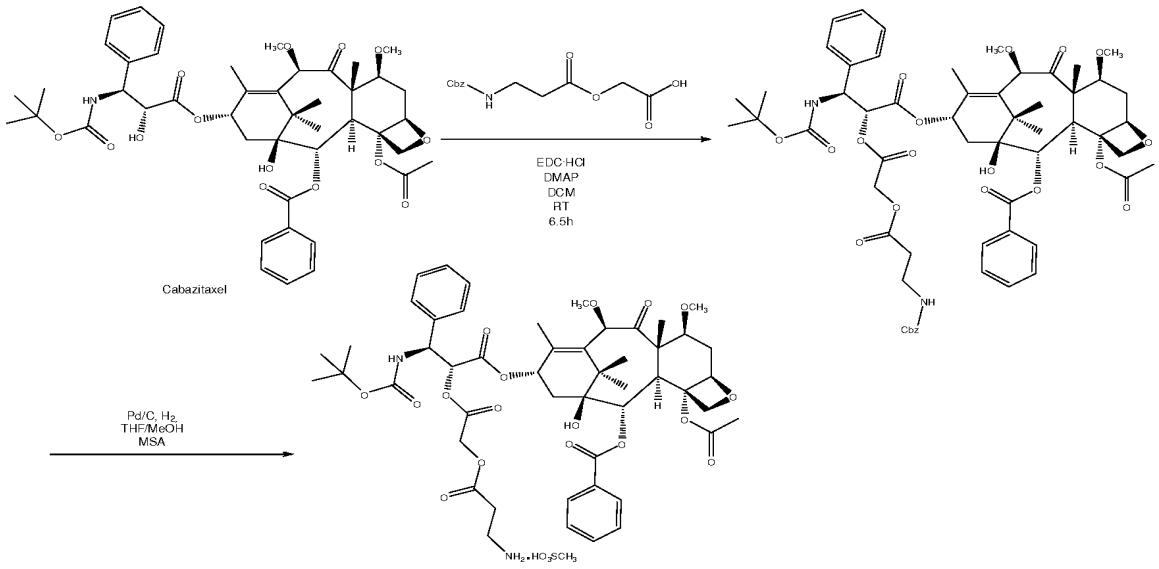


Example 40. Synthesis of cabazitaxel β-alanine glycolate

N-Cbz-β-alanine glycolate (1.8 g, 6.5 mmol), DMAP (850 mg, 6.9 mmol) and EDCI (1.4 g, 7.1 mmol) will be added to a solution of cabazitaxel (7.2 g, 8.7 mmol) in CH_2Cl_2 (140 mL) and the mixture will be stirred at ambient temperature for 2.5 h. N-Cbz-β-alanine glycolate (1.1 g, 3.9 mmol), DMAP (480 mg, 3.9 mmol), and EDCI (1.2 g, 6.1 mmol) will be added and the mixture was stirred for an additional 2.5 h. The mixture will be washed twice with 1% HCl (2 × 100 mL) and brine (100 mL). The organics will be dried over sodium sulfate and concentrated under vacuum. The crude product will be purified by column chromatography.

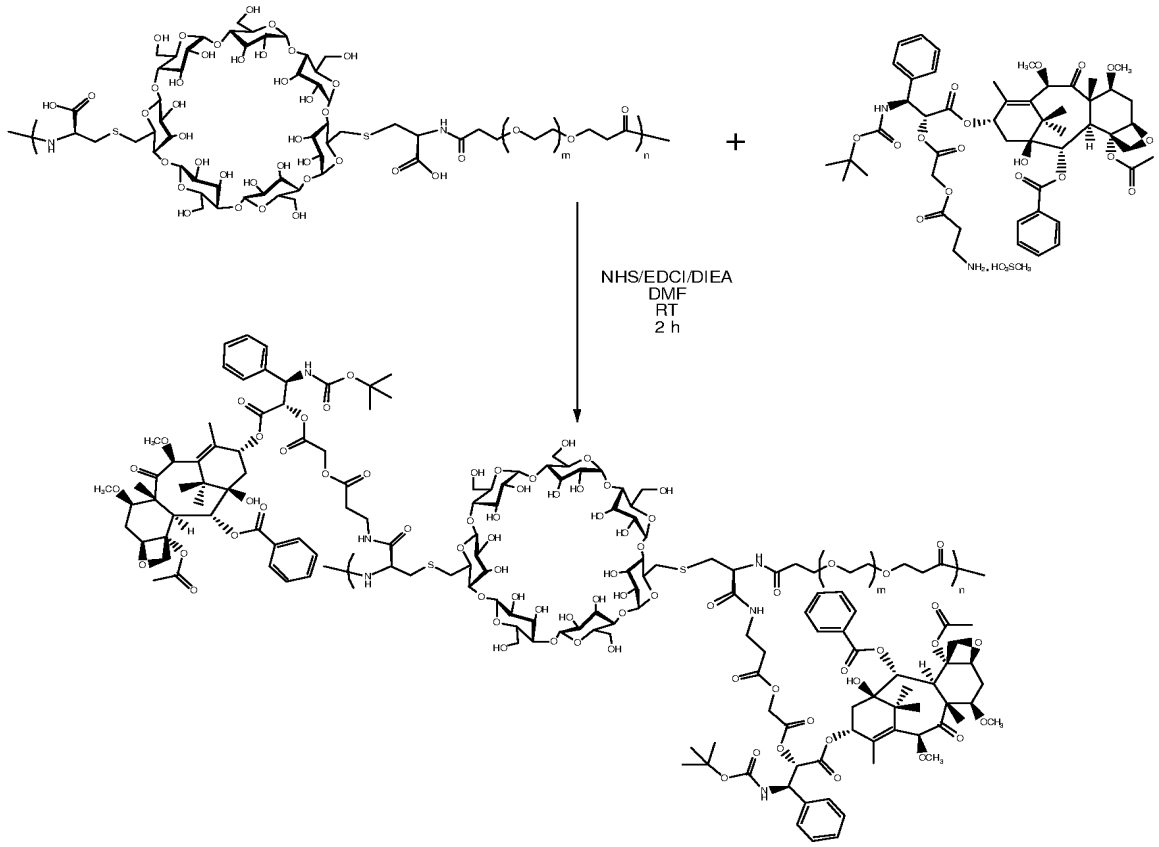
5% Pd/C (2.80 g) will be slurried in 40 mL THF and 4 mL MeOH in a 250 mL flask with overhead stirring. Methanesulfonic acid (0.46 mL, 7.0 mmol) will be added and the slurry will be stirred under hydrogen at ambient temperature for 30 min. A solution of cabazitaxel Cbz-β-alanine glycolate (8.5 g, 7.7 mmol) in THF (40 mL) will be

added (10 mL THF wash). After 2.0 h, the slurry will be filtered (50 mL THF wash) and the filtrate will be concentrated to a minimum volume, diluted with THF (100 mL) and concentrated to about 40 mL. Heptanes (400 mL) will be added dropwise to this mixture over 15 min and stirred 20 min. The resulting slurry will be filtered (100 mL heptanes wash) and the solid will be dried under vacuum to yield cabazitaxel β-alanine glycolate.



Example 41. Synthesis of CDP Cabazitaxel β-alanine glycolate

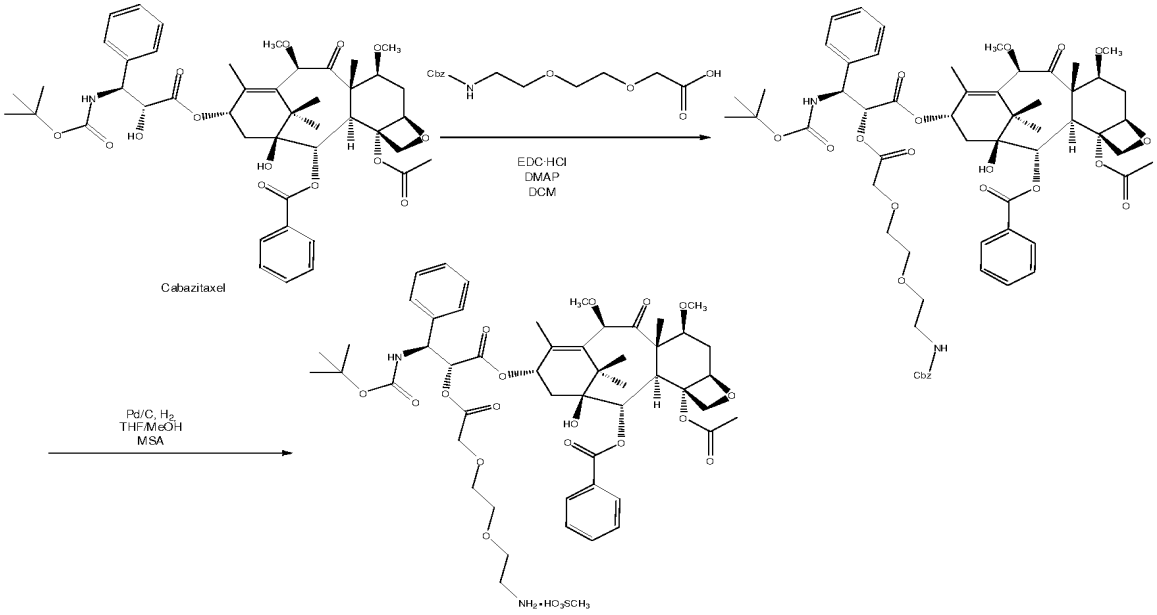
CDP (1.0 g, 0.21 mmol) will be dissolved in dry N,N-dimethylformamide (DMF, 10 mL). Cabazitaxel β-alanine glycolate (440 mg, 0.46 mmol), N,N-Diisopropylethylamine (59 mg, 0.46 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (87 mg, 0.46 mmol), and N-Hydroxysuccinimide (52 mg, 0.46 mmol) will then be added to the polymer solution and stirred for 2 h. The polymer will be precipitated with isopropanol (150 mL) and then rinsed with acetone (100 mL). The precipitate will be dissolved in nanopure water (100 mL). It will be purified by TFF with nanopure water (1L). It will then be filtered through 0.2 μm filter and kept frozen.



Example 42. Synthesis of cabazitaxel aminoethoxyethoxy acetate

Cbz-aminoethoxyethoxy acetic acid (3.97 g, 13.3 mmol) will be dissolved in dichloromethane (10 mL). A portion of this solution (9 mL, about 8.6 mmol) will be added to a solution of cabazitaxel (9.36 g, 11.2 mmol) in CH_2Cl_2 (180 mL) at ambient temperature. DMAP (1.23 g, 10.1 mmol) and EDCI (1.94 g, 10.1 mmol) will be added and the mixture will be stirred at ambient temperature for 2.75 h. The remaining solution of Cbz-aminoethoxyethoxy acetic acid (5 mL, about 4.7 mmol), DMAP (830 mg, 6.80 mmol), and EDCI (1.28 g, 6.67 mmol, 0.60 equiv) will be added. The mixture will be stirred for an additional 4.75 h, and the mixture will be washed twice with 0.1 % HCl (2 × 100 mL) and brine (100 mL). The organic layer will be dried over sodium sulfate and concentrated to a residue. The crude product will be purified by column chromatography to yield cabazitaxel Cbz-aminoethoxyethoxy acetate.

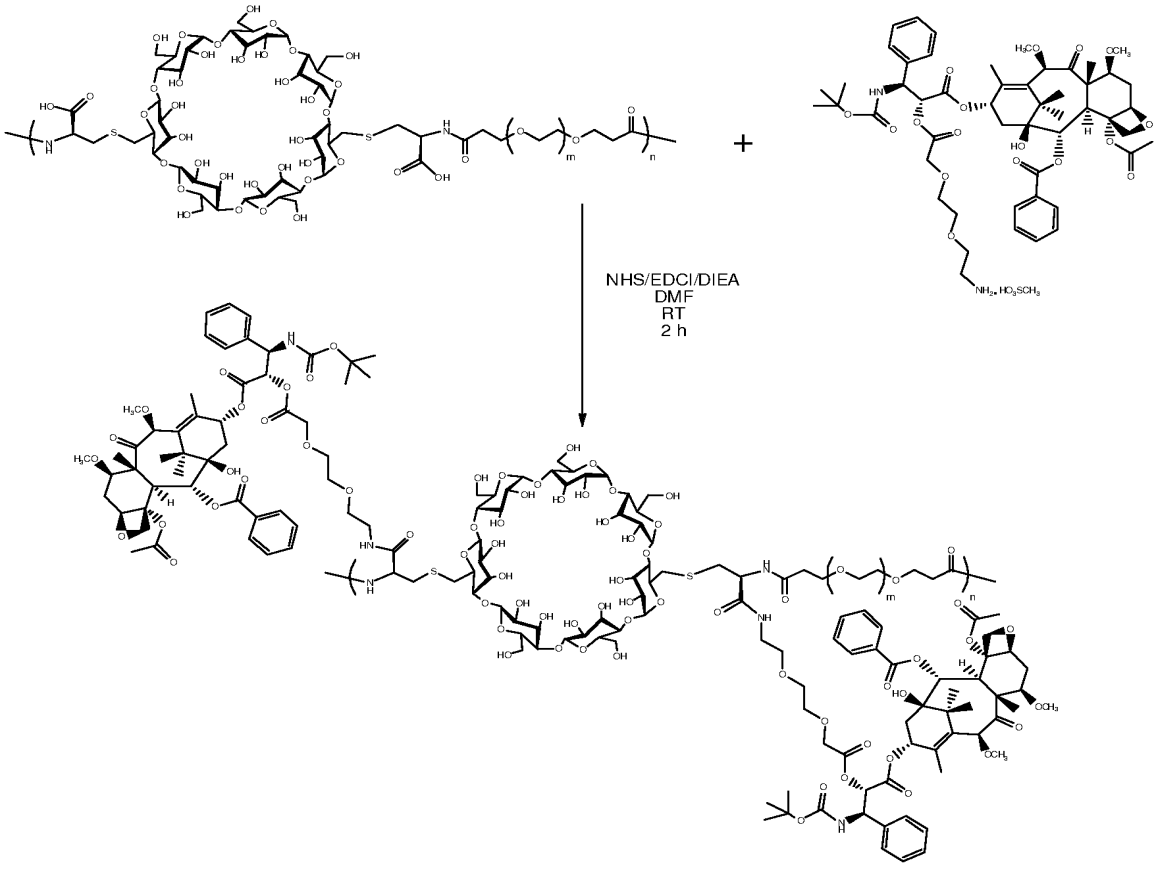
5% Pd/C (2.0 g) will be slurried in 25 mL THF in a 250 mL flask with overhead stirring. The slurry will be stirred under hydrogen at ambient temperature for 45 min. A solution of cabazitaxel Cbz-aminoethoxyethoxy acetate (5.8 g, 5.2 mmol) in THF (25 mL) and MeOH (5 mL) will be added (25 mL THF wash). After 4.25 h, 5.0 g of activated carbon will be added and stirred under nitrogen for 15 min. The slurry will be filtered (25 mL THF wash) and the filtrate will be concentrated to about 20 mL. The solution will be added dropwise into 200 mL heptanes. THF and MeOH will be added until dissolution of the precipitate has occurred. A solvent exchange with THF will be performed and concentrated to about 40 mL. Heptanes (500 mL) will be added dropwise to precipitate out the product. It will be filtered and dried under vacuum to yield the final product, cabazitaxel aminoethoxyethoxy acetate.



Example 43. Synthesis of CDP Cabazitaxel aminoethoxyethoxy acetate

CDP (1.0 g, 0.21 mmol) will be dissolved in dry N,N-dimethylformamide (DMF, 10 mL). Cabazitaxel aminoethoxyethoxy acetate (440 mg, 0.46 mmol), N,N-Diisopropylethylamine (59 mg, 0.46 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (87 mg, 0.46 mmol), and N-Hydroxysuccinimide (52 mg, 0.46 mmol) will then be added to the polymer solution and stirred for 2 h. The polymer will be precipitated with isopropanol (150 mL) and then rinsed with acetone

(100 mL). The precipitate will be dissolved in nanopure water (100 mL). It will be purified by TFF with nanopure water (1L). It will then be filtered through 0.2 μm filter and kept frozen.

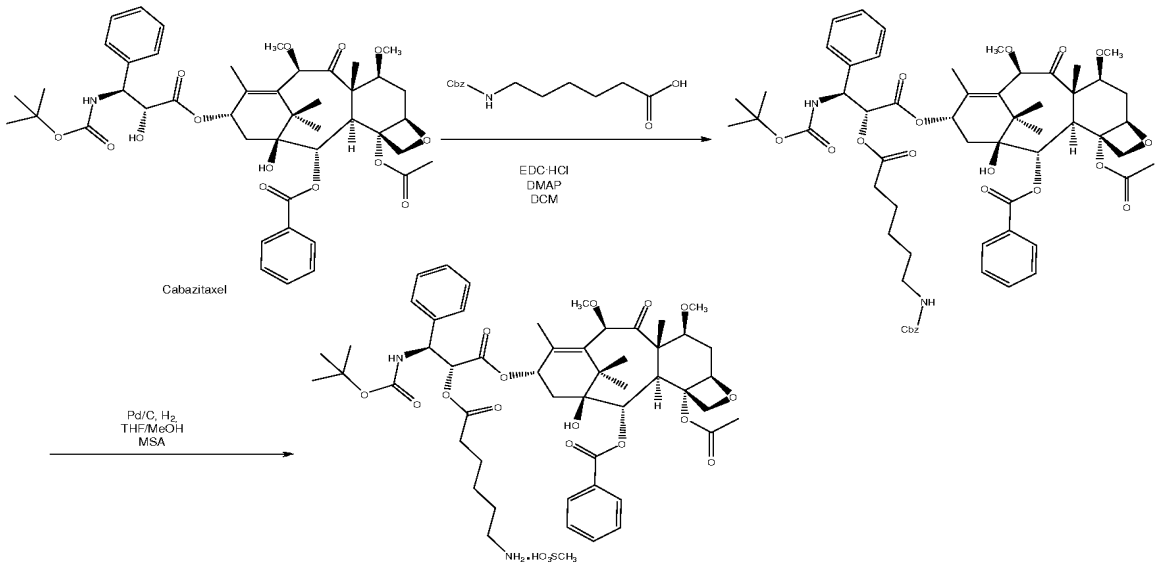


Example 44. Synthesis of cabazitaxel aminohexanoate

A 1000 mL, three-neck jacketed reactor equipped with an addition funnel, overhead stirrer, J-KEM probe, and N_2 inlet will be charged with cabazitaxel (22.3 g, 26.7 mmol), *N*-Cbz-aminohexanoic acid (7.08 g, 26.7 mmol), DMAP (3.3 g, 26.7 mmol) and DCM (150 mL). The mixture will be stirred for a few minutes to produce a clear solution. It will be cooled from –2 to 2 °C with a TCM. A suspension of EDCI (10.2 g, 53.4 mmol) and DMAP (1.6 g, 13.3 mmol) in DCM (100 mL) will be added dropwise over 2 h. The reaction will be stirred from –2 to 2 °C for 12 h and the temperature will be lowered to –5 °C. Additional Cbz-aminohexanoic acid (2.83 g, 10.7 mmol) will be

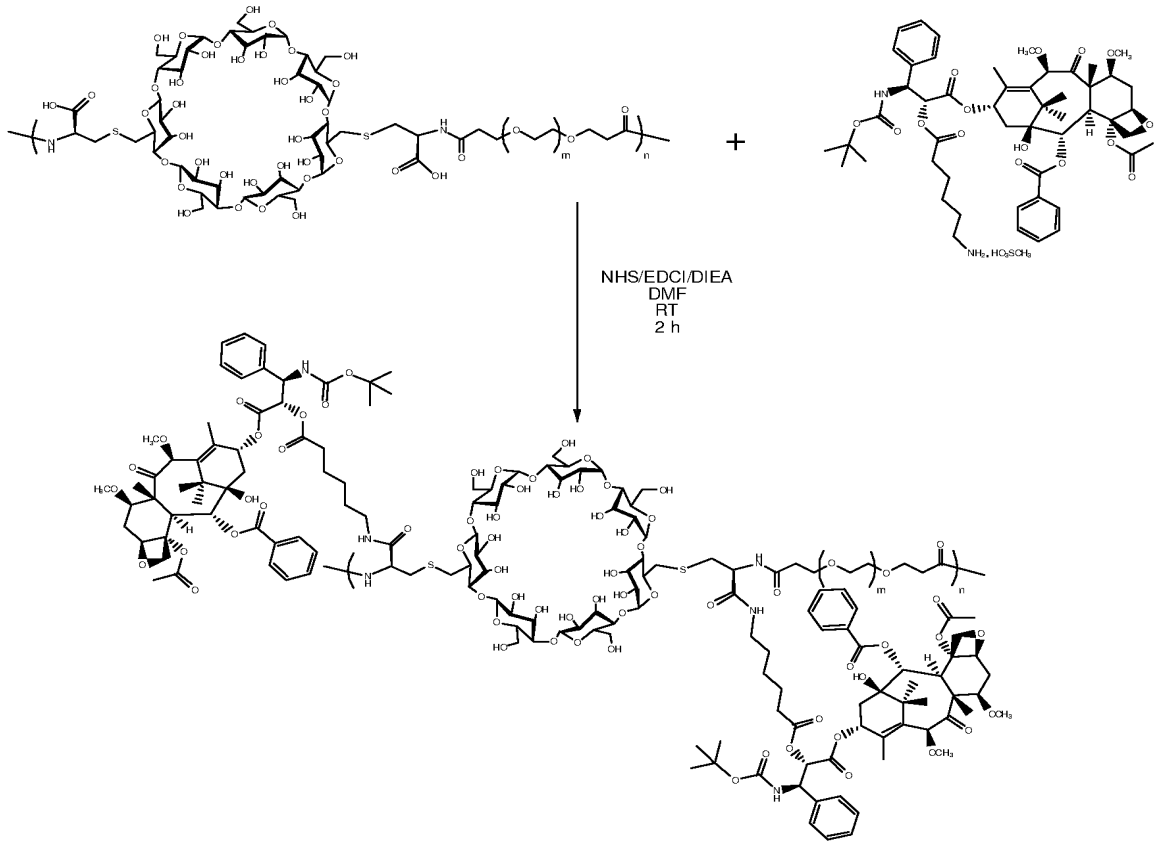
added, followed by addition of EDCI (5.1 g, 26.7 mmol) and DMAP (1.6 g, 13.3 mmol) in DCM (50 mL) over 1 h. The reaction will be stirred at –5 °C for 16 h and then at 0 °C for 4 h, at which time IPC analysis will be done to check for the consumption of cabazitaxel. Once the reaction completion is confirmed, the reaction mixture will be diluted with DCM to 500 mL and washed with 1% HCl (2 × 150 mL), saturated $NaHCO_3$ (2 × 100 mL) and brine (150 mL). The organic layer will be separated, dried over Na_2SO_4, and filtered. The filtrate will be concentrated to a residue to produce a crude product. The crude product will then be purified by column chromatography to yield pure cabazitaxel Cbz-aminohexanoate.

A 1000 mL round-bottom flask equipped with a magnetic stirrer will be charged with THF (160 mL), methanesulfonic acid (980 μL), and 5% Pd/C (5.9 g). The suspension will be evacuated and back filled with H_2 three times and stirred under H_2 for 0.5 h. A solution of cabazitaxel Cbz-aminohexanoate (18.4 g, 17.0 mmol) in THF (170 mL) and MeOH (10 mL) will be added. The reaction will be monitored by HPLC. After the reaction is completed, charcoal (10 g) will be added to the reaction and the mixture will be stirred for 10 min and filtered through a Celite pad to produce a clear solution. It will be concentrated to ~50 mL, to which heptanes (500 mL) will be added to precipitate out the product. It will then be dried under vacuum to yield cabazitaxel aminohexanoate.



Example 45. Synthesis of CDP Cabazitaxel aminohexanoate conjugate

CDP (1.0 g, 0.21 mmol) will be dissolved in dry N,N-dimethylformamide (DMF, 10 mL). Cabazitaxel aminohexanoate (430 mg, 0.46 mmol), N,N-Diisopropylethylamine (59 mg, 0.46 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (87 mg, 0.46 mmol), and N-Hydroxysuccinimide (52 mg, 0.46 mmol) will then be added to the polymer solution and stirred for 2 h. The polymer will be precipitated with isopropanol (150 mL) and then rinsed with acetone (100 mL). The precipitate will be dissolved in nanopure water (100 mL). It will be purified by TFF with nanopure water (1L). It will then be filtered through 0.2 μm filter and kept frozen.

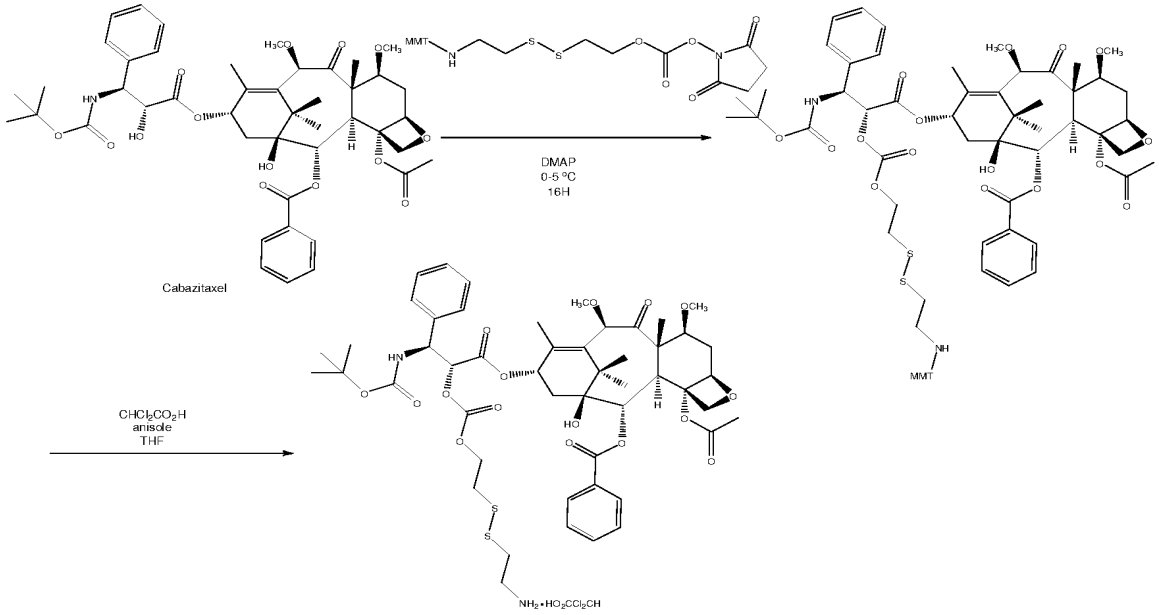


Example 46. Synthesis of cabazitaxel aminoethyldithioethyl carbonate

Succinimidyl MMT-aminoethyldithioethyl carbonate from Scheme 9(a) will then be transferred to a cooled solution of cabazitaxel (6.36 g, 7.61 mmol) and DMAP (1.03 g) in DCM (60 mL) at 0-5 °C with stirring for 16 h. It will be purified by column chromatography.

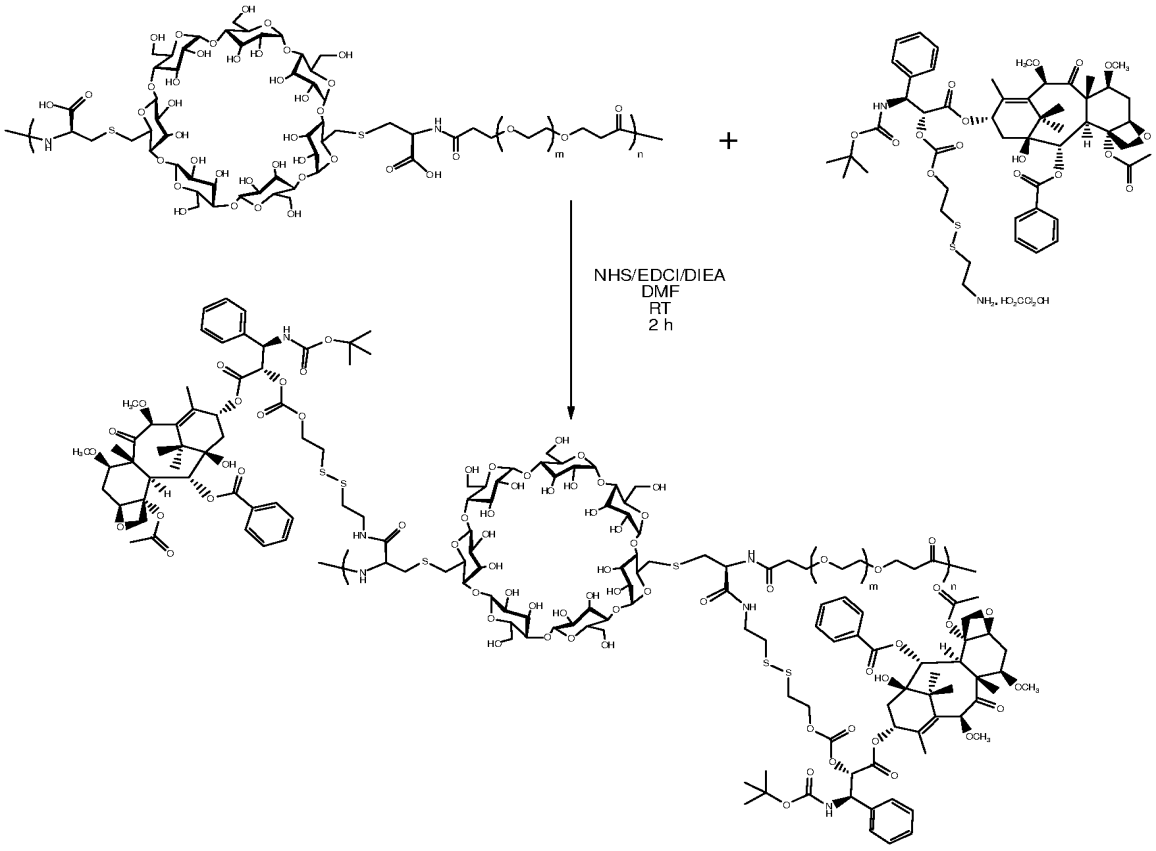
A 1000 mL round bottom flask equipped with a magnetic stirrer will be charged with cabazitaxel Cbz-aminoethyldithioethyl carbonate (12.6 g) and DCM (300 mL). Anisole (10.9 mL, 10 equiv.) will be added to this clear solution and stirred for a few minutes. Dichloroacetic acid (8.3 mL, 10 equiv.) will be added over 5 min and the reaction will be stirred at ambient temperature for 1h. The mixture will be concentrated down to ~100 mL, to which heptanes (800 mL) will be slowly added resulting in a suspension. The suspension will be stirred for 15 min and the supernatant will be

decanted off. The orange residue will be washed with heptanes (200 mL) and vacuum-dried at ambient temperature for 1 h. THF (30 mL) will be added to dissolve the orange residue producing a red solution. Heptanes (500 mL) will be slowly added to precipitate out the product. The resulting suspension will be stirred at ambient temperature for 1 h and filtered. The filter cake will be washed with heptanes (300 mL) and dried under vacuum to yield cabazitaxel aminoethyldithioethyl carbonate.



Example 47. Synthesis of CDP Cabazitaxel aminoethyldithioethyl carbonate

CDP (1.0 g, 0.21 mmol) will be dissolved in dry N,N-dimethylformamide (DMF, 10 mL). Cabazitaxel aminoethyldithioethyl carbonate (460 mg, 0.46 mmol), N,N-Diisopropylethylamine (59 mg, 0.46 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (87 mg, 0.46 mmol), and N-Hydroxysuccinimide (52 mg, 0.46 mmol) will then be added to the polymer solution and stirred for 2 h. The polymer will be precipitated with isopropanol (150 mL) and then rinsed with acetone (100 mL). The precipitate will be dissolved in nanopure water (100 mL). It will be purified by TFF with nanopure water (1L). It will then be filtered through 0.2 μm filter and kept frozen.



Other embodiments are in the claims.

We claim:

1. A method of treating cancer in a subject, wherein the subject has cancer and has received an anticancer agent, the method comprising administering to the subject a CDP-taxane conjugate in an amount effective to treat the disorder, to thereby treat the proliferative disorder.

2. The method of claim 1, wherein the subject has received a taxane.

3. The method of claim 1 or 2, wherein the taxane is not paclitaxel.

4. The method of any of claims 1-3, wherein the taxane is docetaxel, larotaxel, or cabazitaxel.

5. The method of any of claims 1-4, wherein the subject is a human.

6. The method of any of claims 1-5, wherein the taxane is coupled to the CDP via a linker.

7. The method of any of claims 1-6, wherein the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent.

8. The method of any of claims 1-7, wherein the CDP-taxane conjugate administered by intravenous administration.

9. The method of any of claims 1-8, wherein the cancer is a chemotherapeutic sensitive, a chemotherapeutic refractory, a chemotherapeutic resistant, and/or a relapsed cancer.

10. A method of identifying a subject for treatment with a CDP-taxane conjugate, the method comprising identifying a subject having cancer who has received an anticancer agent; and administering a CDP-taxane conjugate to a subject in an amount effective to treat the disorder, to thereby treat the cancer.

11. The method of claim 10, wherein the subject has received a taxane.

12. A method of treating a chemotherapeutic sensitive, a chemotherapeutic refractory, a chemotherapeutic resistant, and/or a relapsed cancer in a subject, the method comprising administering a CDP-taxane conjugate to a subject in an amount effective to treat a chemotherapeutic sensitive, a chemotherapeutic refractory, a chemotherapeutic resistant, and/or a relapsed cancer, to thereby treat the chemotherapeutic sensitive, the chemotherapeutic refractory, the chemotherapeutic resistant, and/or the relapsed cancer.

13. The method of claim 12, wherein the subject has received a taxane.

14. The method of claim 12 or 13, wherein the taxane is not paclitaxel.

15. The method of any of claims 12-14, wherein the taxane is docetaxel, larotaxel, or cabazitaxel.

16. The method of any of claims 12-15, wherein the subject is a human.

17. The method of any of claims 12-16, wherein the taxane is coupled to the CDP via a linker.

18. The method of any of claims 12-17, wherein the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent.

19. The method of any of claims 12-18, wherein, the cancer is refractory to, resistant to and/or relapsed during or after, treatment with, one or more of: an anthracycline, an alkylating agent, an antimetabolite, a vinca alkaloid, a topoisomerase inhibitor, a taxane or a platinum-based agent.

20. The method of any of claims 12-19, wherein the cancer is resistant to more than one chemotherapeutic agent.

21. A method of treating metastatic or locally advanced breast cancer in a subject, the method comprising administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

22. The method of claim 21, wherein the subject has received a taxane.

23. The method of claim 21 or 22, wherein the breast cancer is estrogen receptor positive breast cancer; estrogen receptor negative breast cancer; HER-2 positive breast cancer; HER-2 negative breast cancer; progesterone receptor positive breast cancer; progesterone receptor negative breast cancer; estrogen receptor negative, HER-2 negative and progesterone receptor negative breast cancer or inflammatory breast cancer.

24. The method of any of claims 21-23, wherein the CDP-taxane conjugate is administered in combination with a HER-2 pathway inhibitor, e.g., a HER-2 inhibitor or a HER-2 receptor inhibitor.

25. The method of any of claims 21-24, wherein, the CDP-taxane conjugate is administered in combination with a second chemotherapeutic agent.

26. A method of treating metastatic or locally advanced breast cancer in a subject, the method comprising

providing a subject who has metastatic or locally advanced breast cancer and has been treated with a chemotherapeutic agent which did not effectively treat the cancer or which had an unacceptable side effect, and

administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

27. The method of claim 26, wherein the subject has received a taxane.

28. The method of claim 26 or 27, wherein the subject has a chemotherapeutic refractory, a chemotherapeutic resistant and/or a relapsed cancer.

29. The method of any of claims 26-28, the subject has a chemotherapeutic sensitive cancer.

30. The method of any of claims 26-29, wherein, the cancer is refractory to, resistant to and/or relapsed during or after, treatment with, one or more of: an anthracycline, an alkylating agent, an antimetabolite, a vinca alkaloid, a topoisomerase inhibitor, a taxane or a platinum-based agent.

31. The method of any of claims 26-30, wherein the cancer is resistant to more than one chemotherapeutic agent.

32. The method of any of claims 26-31, wherein the composition is administered in combination with a pyrimidine analogue.

33. A method of treating hormone refractory prostate cancer in a subject, the method comprising administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

34. The method of claim 33, wherein the subject has received a taxane.

35. The method of claim 33 or 34, wherein, the CDP-taxane conjugate is administered in combination with prednisone or estramustine.

36. The method of any of claims 33-35, wherein the CDP-taxane conjugate is administered in combination with an anthracenedione and prednisone.

37. A method of treating hormone refractory prostate cancer in a subject, the method comprising:

providing a subject who has hormone refractory prostate cancer and has been treated with a chemotherapeutic agent that did not effectively treat the cancer or who had an unacceptable side effect, and

administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

38. The method of claim 37, wherein the subject has received a taxane.

39. The method of claim 37 or 38, wherein the subject has a chemotherapeutic refractory, chemotherapeutic resistant and/or relapsed cancer.

40. The method of any of claims 37-39, wherein the subject has a chemotherapeutic sensitive cancer.

41. A method of treating metastatic or advanced ovarian cancer in a subject, the method comprising: administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

42. The method of claim 41, wherein the subject has received a taxane.

43. The method of claim 41 or 42, wherein the metastatic or advanced ovarian cancer is peritoneal or fallopian tube cancer.

44. The method of any of claims 41-43, wherein the CDP-taxane conjugate is administered in combination with a platinum-based agent.

45. The method of any of claims 41-44, wherein the CDP-taxane conjugate is administered in combination with an alkylating agent.

46. The method of any of claims 41-45, wherein the CDP-taxane conjugate is administered in combination with a platinum-based agent and an alkylating agent.

47. A method of treating metastatic or advanced ovarian cancer in a subject, the method comprising:

providing a subject who has advanced ovarian cancer and has been treated with a chemotherapeutic agent that did not effectively treat the cancer or who had an unacceptable side effect, and

administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

48. The method of claim 47, wherein the subject has received a taxane.

49. The method of claim 47 or 48, wherein the metastatic or advanced ovarian cancer is peritoneal or fallopian tube cancer.

50. The method of any of claims 47-49, wherein the subject has a chemotherapeutic refractory, a chemotherapeutic resistant and/or a relapsed cancer.

51. The method of any of claims 47-50, wherein the subject has a chemotherapeutic sensitive cancer.

52. The method of any of claims 47-51, wherein the subject has been treated with a platinum-based agent that did not effectively treat the cancer.

53. The method of any of claims 47-52, wherein the CDP-taxane conjugate is administered in combination with a pyrimidine analog.

54. The method of any of claims 47-53, wherein the CDP-taxane conjugate is administered in combination with capecitabine and gemcitabine.

55. A method of treating non-small cell lung cancer in a subject, the method comprising: administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

56. The method of claim 55, wherein the subject has received a taxane.

57. The method of claim 55 or 56, wherein the non-small cell lung cancer is unresectable, locally advanced or metastatic non-small cell lung cancer.

58 The method of any of claims 55-57, wherein the CDP-taxane conjugate is administered in combination with a vascular endothelial (VEGF) pathway inhibitor.

59. The method of any of claims 55-58, wherein the CDP-taxane conjugate is administered in combination with an epidermal growth factor (EGF) pathway inhibitor.

60. The method of any of claims 55-59, wherein the CDP-taxane conjugate is administered in combination with radiation.

61. A method of treating unresectable, advanced or metastatic non-small cell lung cancer in a subject, the method comprising:

providing a subject who has unresectable, advanced or metastatic non-small cell lung cancer and has been treated with a chemotherapeutic agent that did not effectively treat the cancer or who had an unacceptable side effect, and

administering a CDP-taxane conjugate to the subject in an amount effective to treat the cancer, to thereby treat the cancer.

62. The method of claim 61, wherein the subject has received a taxane.

63. The method of claim 61 or 62, wherein the subject has a chemotherapeutic refractory, a chemotherapeutic resistant and/or a relapsed cancer.

64. The method of any of claims 61-63, wherein the subject has a chemotherapeutic sensitive cancer.

65. The method of any of claims 61-64, wherein the subject has been treated with a vascular endothelial growth factor (VEGF) pathway inhibitor which did not effectively treat the cancer.

66. The method of any of claims 61-65, wherein the subject has been treated with an endothelial growth factor (EGF) pathway inhibitor which did not effectively treat the cancer.

67. The method of any of claims 61-66, wherein the subject has been treated with a platinum-based agent which did not effectively treat the cancer.

68. A method of treating multiple myeloma in a subject, the method comprising: administering a composition comprising a CDP-taxane conjugate to a subject in an amount effective to treat the myeloma, to thereby treat the myeloma.

69. The method of claim 68, wherein the subject has received a taxane.

70. The method of claim 68 or 69, wherein the CDP-taxane conjugate is administered as a primary treatment for multiple myeloma.

71. The method of any of claims 68-70, wherein the CDP-taxane conjugate is administered in combination with dexamethasone.

72. The method of any of claims 68-71, wherein the CDP-taxane conjugate is administered in combination with an anthracycline, thalidomide or thalidomide derivative.

73. The method of any of claims 68-72, wherein the CDP-taxane conjugate is administered in combination with a proteasome inhibitor and dexamethasone.

74. The method of any of claims 68-73, wherein after the subject has received a primary treatment, the subject is further administered a high dose treatment.

75. The method of any of claims 68-74, wherein after the primary treatment stem cells are transplanted into the subject.

76. A method of treating multiple myeloma in a subject, the method comprising:

providing a subject who has multiple myeloma and has been treated with a chemotherapeutic agent that did not effectively treat the myeloma or who had an unacceptable side effect, and

administering a CDP-taxane conjugate to a subject in an amount effective to treat the myeloma, to thereby treat the myeloma.

77. The method of claim 76, wherein the subject has received a taxane.

78. The method of claim 76 or 77, wherein the subject has a chemotherapeutic refractory myeloma, a chemotherapeutic resistant myeloma and/or a relapsed myeloma.

79. The method of any of claims 76-78, wherein the subject has a chemotherapeutic sensitive myeloma.

80. The method of any of claims 76-79, wherein the subject has been treated with a proteosome inhibitor, which did not effectively treat the myeloma.

81. The method of any of claims 76-80, wherein the subject has been treated with an anthracycline which did not effectively treat the cancer.

82. The method of any of claims 76-81, wherein the subject has been treated with a thalidomide or thalidomide derivative which did not effectively treat the myeloma.

83. A method of treating AIDS-related Kaposi's Sarcoma in a subject, the method comprising: administering a CDP-taxane conjugate to a subject in an amount effective to treat the sarcoma, to thereby treat the sarcoma.

84. The method of claim 83, wherein the subject has received a taxane.

85. The method of claim 83 or 84, wherein the CDP-taxane conjugate is administered in combination with an antiviral agent.

86. The method of any of claims 83-85, wherein the CDP-taxane conjugate is administered in combination with cryosurgery.

87. A method of treating AIDS-related Kaposi's Sarcoma, in a subject, e.g., a human, the method comprising:

providing a subject who has AIDS-related Kaposi's Sarcoma and has been treated with a chemotherapeutic agent which did not effectively treat the sarcoma or which had an unacceptable side effect, and

administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

88. The method of claim 87, wherein the subject has received a taxane.

89. The method of claim 87 or 88, wherein the subject has a chemotherapeutic refractory, a chemotherapeutic resistant and/or a relapsed sarcoma.

90. The method of any of claims 87-89, wherein the subject has a chemotherapeutic sensitive sarcoma.

91. A method of treating gastric cancer in a subject, the method comprising: administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

92. The method of claim 91, wherein the subject has received a taxane.

93. The method of claim 91 or 92, wherein the gastric cancer is gastroesophageal junction adenocarcinoma.

94. The method of any of claims 91-93, wherein the CDP-taxane conjugate is administered prior to surgery, after surgery or before and after surgery to remove the cancer.

95. A method of treating gastric cancer in a subject, the method comprising:

providing a subject who has gastric cancer and has been treated with a chemotherapeutic agent which did not effectively treat the cancer or which had an unacceptable side effect, and

administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

96. The method of claim 95, wherein the subject has received a taxane.

97. The method of claim 95 or 96, wherein the gastric cancer is gastroesophageal junction adenocarcinoma,

98. The method of any of claims 95-97, wherein the subject has a non-resectable cancer, a chemotherapeutic refractory, a chemotherapeutic resistant and/or a relapsed cancer.

99. The method of any of claims 95-98, wherein the subject has a chemotherapeutic sensitive cancer.

100. A method of treating a soft tissue sarcoma in a subject the method comprising: administering a CDP-taxane conjugate to a subject in an amount effective to treat the sarcoma, to thereby treat the sarcoma.

101. The method of claim 100, wherein the subject has received a taxane.

102. The method of claim 100 or 101, wherein the soft tissue sarcoma is non-resectable, advanced, metastatic or relapsed soft tissue sarcoma.

103. The method of any of claims 100-102, wherein the soft tissue sarcoma is rhabdomyosarcoma, leiomyosarcoma, hemangiosarcoma, lymphangiosarcoma, synovial sarcoma, neurofibrosarcoma, liposarcoma, fibrosarcoma, malignant fibrous histiocytoma and dermatofibrosarcoma.

104. The method of any of claims 100-103, wherein the CDP-taxane conjugate is administered in combination with an anthracycline.

105. The method of any of claims 100-104, wherein the CDP-taxane conjugate is administered in combination with an alkylating agent.

106. A method of treating a soft tissue sarcoma in a subject, the method comprising:

providing a subject who has a soft tissue sarcoma and has been treated with a chemotherapeutic agent which did not effectively treat the sarcoma or which had an unacceptable side effect, and

administering a CDP-taxane conjugate to a subject in an amount effective to treat the sarcoma, to thereby treat the sarcoma.

107. The method of claim 106, wherein the subject has received a taxane.

108. The method of claim 106 or 107, wherein the subject has a chemotherapeutic refractory, a chemotherapeutic resistant and/or a relapsed sarcoma.

109. The method of any of claims 106-108, wherein the subject has a chemotherapeutic sensitive sarcoma.

110. The method of any of claims 106-109, wherein the sarcoma is refractory to, resistant to, and/or relapsed with treatment with one or more of: a taxane, an anthracycline, a vinca alkaloid, or an alkylating agent.

111. The method of any of claims 106-110, wherein the sarcoma is a multidrug resistant cancer.

112. The method of any of claims 106-111, wherein the soft tissue sarcoma is rhabdomyosarcoma, leiomyosarcoma, hemangiosarcoma, lymphangiosarcoma, synovial sarcoma, neurofibrosarcoma, liposarcoma, fibrosarcoma, malignant fibrous histiocytoma and dermatofibrosarcoma.

113. A method of treating pancreatic cancer in a subject, the method comprising: administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

114. The method of claim 113, wherein the subject has received a taxane.

115. The method of claim 113 or 114, wherein the pancreatic cancer is locally advanced or metastatic pancreatic cancer.

116. The method of any of claims 113-115, wherein the CDP-taxane conjugate is administered after surgery or before and after surgery to remove the cancer.

117. A method of treating pancreatic cancer in a subject, the method comprising:

providing a subject who has pancreatic cancer and has been treated with a chemotherapeutic agent which did not effectively treat the cancer or which had an unacceptable side effect, and

administering a CDP-taxane conjugate, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

118. The method of claim 117, wherein the subject has received a taxane.

119. The method of claim 117 or 118, wherein the pancreatic cancer is locally advanced or metastatic pancreatic cancer.

120. The method of any of claims 117-119, wherein the subject has a non-resectable cancer, a chemotherapeutic refractory, a chemotherapeutic resistant and/or a relapsed cancer.

121. The method of any of claims 117-120, wherein the subject has a chemotherapeutic sensitive cancer.

122. The method of any of claims 117-121, wherein the cancer is refractory to, resistant to, and/or relapsed with treatment with one or more of: a taxane, an anthracycline, an anti-metabolite, or a platinum-based agent.

123. The method of any of claims 117-122, wherein the cancer is a multidrug resistant cancer.

124. A method of treating advanced or metastatic colorectal cancer in a subject, the method comprising: administering a composition comprising a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

125. The method of claim 124, wherein the CDP-taxane conjugate is administered in combination with an antimetabolite.

126. A method of treating advanced or metastatic colorectal cancer in a subject, the method comprising:

providing a subject who has advanced or metastatic colorectal cancer and has been treated with a chemotherapeutic agent that did not effectively treat the cancer or who had an unacceptable side effect, and

administering a CDP-taxane conjugate to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

127. The method of claim 126, wherein the subject has received a taxane.

128. The method of claim 126 or 127, wherein the subject has a chemotherapeutic refractory cancer, a chemotherapeutic resistant cancer and/or a relapsed cancer.

129. The method of any of claims 126-128, wherein the subject has a chemotherapeutic sensitive cancer.

130. The method of any of claims 126-129, wherein the subject has been treated with an anti-metabolite, e.g., a pyrimidine analogue which did not effectively treat the cancer.

131. The method of any of claims 126-130, wherein the subject has been treated with a pyrimidine analog which did not effectively treat the cancer.

132. A method of identifying a subject having cancer for treatment with a CDP-taxane conjugate, the method comprising

identifying a subject having cancer who has received an anticancer agent and has a neutrophil count less than a standard; and

identifying the subject as suitable for treatment with a CDP-taxane conjugate.

133. The method of claim 132, wherein the subject has received a taxane.

134. The method of claim 132 or 33, wherein the subject has received a taxane or a proteosome inhibitor.

135. The method of any of claims 132-134, the method further comprising administering a CDP-taxane conjugate in an amount effective to treat the disorder.

136. The method of any of claims 132-135, wherein the standard is a neutrophil count below or equal to 1500 cells/mm^3.

137. The method of any of claims 132-136, wherein the standard is based on a neutrophil count prior to receiving an anticancer agent.

138. A method of treating a subject having cancer, the method comprising

selecting a subject having cancer who has received an anticancer agent and has a neutrophil count less than a standard; and

administering a CDP-taxane conjugate to the subject in an amount effective to treat the cancer, to thereby treat the cancer.

139. The method of claim 138, wherein the subject has received a taxane.

140. The method of claim 138 or 139, wherein the standard is a neutrophil count below or equal to 1500 cells/mm^3.

141. The method of any of claims 138-140, wherein the standard is based on a neutrophil count prior to receiving an anticancer agent.

142. A method for selecting a subject having cancer for treatment with a CDP-taxane conjugate, the method comprising:

determining whether a subject with a proliferative disorder has moderate to severe neutropenia; and

selecting a subject for treatment with a CDP-taxane conjugate on the basis that the subject has moderate to severe neutropenia.

143. The method of claim 142, wherein the subject has received a taxane.

144. The method of claim 142 or 143, wherein the subject experienced moderate to severe neutropenia from treatment with an anticancer agent.

145. The method of any of claims 142-144, wherein the subject has one or more symptom of febrile neutropenia.

146. The method of any of claims 142-145, wherein the standard for moderate neutropenia is a neutrophil count of 1000 to 500 cells/mm^3.

147. A method for treating a subject having cancer, the method comprising:

selecting a subject with cancer who has moderate to severe neutropenia; and

administering a CDP-taxane conjugate to the subject in an amount effective to treat the disorder, to thereby treat the proliferative disorder.

148. The method of claim 147, wherein the subject has received a taxane.

149. The method of claim 147 or 148, wherein the subject experienced moderate to severe neutropenia from treatment with an anticancer agent.

150. The method of any of claims 147-149, wherein the subject has one or more symptom of febrile neutropenia.

151. The method of any of claims 147-150, wherein the standard for moderate neutropenia is a neutrophil count of 1000 to 500 cells/mm^3.

152. A method for selecting a subject having cancer for treatment with a CDP-taxane conjugate, the method comprising:

determining whether a subject with cancer, has experienced neuropathy from treatment with an anticancer agent; and

selecting a subject for treatment with a CDP-taxane conjugate, on the basis that the subject has experienced neuropathy from treatment with an anticancer agent.

153. The method of claim 152, wherein the anticancer agent is a taxane, a vinca alkaloid, an alkylating agent, a platinum-based agent or an epothilone.

154. The method of claim 152 or 153, wherein the subject has received a taxane.

155. The method of any of claims 152-154, wherein the subject experienced moderate to severe neuropathy from treatment with a chemotherapeutic agent.

156. The method of any of claims 152-155, wherein the neuropathy is peripheral neuropathy.

157. The method of any of claims 152-156, wherein the neuropathy is sensory neuropathy, motor neuropathy or both.

158. A method for treating a subject having cancer, the method comprising:

selecting a subject with cancer who has experienced one or more symptom of neuropathy from treatment with a anticancer agent; and

administering a CDP-taxane conjugate, to the subject in an amount effective to treat the disorder, to thereby treat the proliferative disorder.

159. The method of claim 158, wherein the anticancer agent is a taxane, a vinca alkaloid, an alkylating agent, a platinum-based agent or an epothilone.

160. The method of claim 158 or 159, wherein the subject has received a taxane.

161. The method of any of claims 158-160, wherein the subject experienced moderate to severe neuropathy from treatment with a chemotherapeutic agent.

162. The method of any of claims 158-161, wherein the neuropathy is peripheral neuropathy.

163. The method of any of claims 158-162, wherein the neuropathy is sensory neuropathy, motor neuropathy or both.

164. The method of any of claims 158-163, wherein the subject has experienced neuropathy after two, three, four or five cycles of treatment with an anticancer agent.

165. A method for selecting a subject having cancer for treatment with a CDP-taxane conjugate, the method comprising:

determining whether a subject with cancer has experienced an infusion site reaction or has or is at risk for having hypersensitivity to treatment with an anticancer agent, and

selecting a subject for treatment with a CDP-taxane conjugate on the basis that the subject is in need of a reduced infusion site reaction or the subject has or is at risk for having hypersensitivity to treatment with an anticancer agent.

166. The method of claim 165, wherein the subject has received a taxane.

167. The method of claim 165 or 166, wherein the subject experienced an infusion site reaction during or within 12 hours of infusion of an anticancer agent.

168. The method of any of claims 165-167, wherein the infusion site reaction is reduced as compared to the reaction associated with or caused by the treatment with an anticancer agent.

169. The method of any of claims 165-168, wherein the subject has exhibited one or more symptom of infusion site reaction to a previous treatment with the anticancer agent.

170. The method of any of claims 165-169, wherein the subject has exhibited one or more symptom of hypersensitivity to a previous treatment with the anticancer agent or to a treatment formulated with Cremaphor and/or polysorbate.

171. A method of treating a subject having cancer, the method comprising:

selecting a subject with cancer, who has experienced an infusion site reaction to treatment with an anticancer agent or has or is at risk for having hypersensitivity to an anticancer agent; and

administering a CDP-taxane conjugate to the subject in an amount effective to treat the disorder, to thereby treat the cancer.

172. The method of claim 171, wherein the anticancer agent is a taxane.

173. The method of claim 171 or 172, wherein the subject has exhibited one or more symptom of infusion site reaction to a previous treatment with the anticancer agent.

174. The method of any of claims 171-173, wherein the subject has exhibited one or more symptom of hypersensitivity to a previous treatment with the anticancer agent or a treatment formulated with Cremaphor and/or polysorbate.

175. A method of treating a subject having cancer, the method comprising:

administering a CDP-taxane conjugate to a subject with cancer in an amount effective to treat the cancer and in the absence of administration of one or more of an antihistamine, an antiemetic, a corticosteroid, an H1 antagonist and an H2 antagonist, to thereby treat the cancer.

176. The method of claim 175, wherein the CDP-taxane conjugate is administered in the absence of administration of dexamethasone.

177. A method of treating a subject having cancer, the method comprising:

administering a CDP-taxane conjugate to a subject with cancer in an amount effective to treat the cancer and in combination with a corticosteroid, wherein the corticosteroid is administered at a dose less than 60 mg, 55 mg, 50 mg, 45 mg, 40 mg, 35 mg, 30 mg, to thereby treat the cancer.

178. The method of claim 177, wherein the corticosteroid is dexamethasone.

179. A method of treating a subject having cancer, the method comprising:

administering a CDP-taxane conjugate to a subject having cancer in an amount effective to treat the disorder and in combination with an antihistamine, an antiemetic, a corticosteroid, an H1 antagonist and/or an H2 antagonist, wherein the corticosteroid is administered at a dose less than 20 mg, 15 mg, 10 mg, 5 mg; the H1 antagonist is administered at a dose of less than 50 mg, 45 mg, 30 mg, 20 mg, 15 mg, 10 mg, 5 mg; and/or the H2 antagonist is administered at a dose of less than 300 mg, 275 mg, 250 mg, 225 mg, 200 mg, 175 mg, 150 mg, 125 mg, 100 mg and/or the H2 antagonist is administered at a dose less than 50 mg, 45 mg, 40 mg, 35 mg, 30 mg, 25 mg, 20 mg, to thereby treat cancer.

180. A method of selecting a subject having cancer, for treatment with a CDP-taxane conjugate, the method comprising:

determining if a subject having cancer has or is at risk of having hepatic impairment, e.g., determining alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin levels in a subject having cancer; and

selecting a subject having hepatic impairment, e.g., a subject having ALT and/or AST levels greater than 1.5 times the upper limit of normal (ULN) and/or bilirubin levels greater than 2 times the ULN, for treatment with a CDP-taxane conjugate.

181. The method of claim 180, wherein the subject has received a taxane.

182. A method of treating a subject having cancer, the method comprising:

selecting a subject with cancer who has or is at risk of having hepatic impairment, e.g., a subject having alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels greater than 1.5 times the upper limit of normal (ULN) and/or bilirubin levels greater than 2 times the ULN; and

administering a CDP-taxane conjugate to the subject in an amount effective to treat the disorder, to thereby treat the cancer.

183. The method of claim 182, wherein the subject has received a taxane.

184. A method of selecting a subject having cancer, for treatment with a CDP-taxane conjugate, the method comprising:

determining if a subject having cancer has or is at risk of having hepatic impairment, e.g., determining alkaline phosphatase (ALP), serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and/or bilirubin levels in the subject having cancer; and

selecting a subject having or at risk of having hepatic impairment, e.g., a subject having ALP levels greater than 2.5 times the upper limit of normal (ULN), SGOT and/or SGPT levels greater than 1.5 times the upper limit of normal (ULN) and/or bilirubin levels greater than the ULN for treatment with a CDP-taxane conjugate.

185. The method of claim 184, wherein the subject has received a taxane.

186. A method of treating a subject having cancer, the method comprising:

selecting a subject with cancer who has or is at risk of having hepatic impairment, e.g., a subject having alkaline phosphatase (ALP) levels greater than 2.5 times the upper limit of normal (ULN), serum glutamate oxaloacetate transaminase (SGOT) and/or serum glutamate pyruvate transaminase (SGPT) levels greater than 1.5 times the ULN and/or bilirubin levels greater than the ULN; and

administering a CDP-taxane conjugate to the subject in an amount effective to treat the disorder, to thereby treat the cancer.

187. The method of claim 186, wherein the subject has received a taxane.

188. A method of selecting a subject having cancer, for treatment with a CDP-taxane conjugate, the method comprising:

determining if a subject having cancer is currently being administered or will be administered a cytochrome P450 isoenzyme and/or a CYP2C8 inhibitor; and

selecting a subject with cancer who is currently being administered or will be administered a cytochrome P450 isoenzyme and/or a CYP2C8 inhibitor, for treatment with a CDP-taxane conjugate.

189. The method of claim 188, wherein the subject has received a taxane.

190. The method of claim 188 or 189, wherein the subject has been administered a cytochrome P450 isoenzyme inhibitor, the same day as chemotherapy treatment or within 1, 2, 3, 4, 5, 6, or 7 days before chemotherapy treatment.

191. The method of any of claims 188-190, wherein the subject will be administered on the same day as the chemotherapy treatment or within 1, 2, 3, 4, 5, 6, or 7 days after chemotherapy treatment.

192. A method of treating a subject having cancer, the method comprising:

selecting a subject having cancer who is currently being administered or will be, administered a cytochrome P450 isoenzyme, and/or a CYP2C8 inhibitor; and

administering a CDP-taxane conjugate to the subject at a dose described herein, to thereby treat the disorder.

193. The method of claim 192, wherein the subject has received a taxane.

194. A method of selecting a subject having cancer for treatment with a CDP-taxane conjugate, the method comprising:

determining if a subject having a proliferative disorder has or is at risk for having fluid retention and/or effusion and

selecting a subject with cancer, who has or is at risk for having fluid retention, for treatment with a CDP-taxane conjugate.

195. The method of claim 194, wherein the subject has received a taxane.

196. A method of treating a subject having cancer, the method comprising:

selecting a subject with cancer who has or is at risk for having fluid retention;

administering a CDP-taxane conjugate to the subject, to thereby treat the disorder.

197. The method of claim 196, wherein the subject has one or more of the following symptoms of fluid retention: edema and effusion.

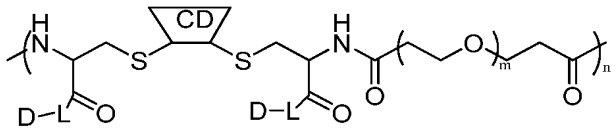
198. A method of selecting a subject having cancer, for treatment treating the subject with a CDP-taxane conjugate, the method comprising:

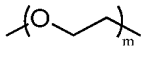
determining if a subject with cancer is at risk for or has diarrhea or has experienced diarrhea from treatment with an anticancer agent, and

selecting a subject who is at risk for or has diarrhea or has experienced diarrhea from treatment with an anticancer agent for treatment with treating the subject with a CDP-taxane conjugate.

199 The method of claim 199, wherein the subject has received a taxane.

200. A CDP-taxane conjugate of the following formula:



wherein each L is independently a linker or absent and each D is independently a taxane, a prodrug derivative thereof, or absent and wherein the group  has a Mw of 3.4kDa or less and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, provided that the polymer comprises at least one taxane.

201. The CDP-taxane conjugate of claim 200, wherein each L is indepdendently an amino acid derivative or absent.

202. The CDP-taxane conjugate of claim 200 or 201, wherein the taxane is docetaxel, larotaxel, or cabazitaxel.

203. The CDP-taxane conjugate of any of claims 200-202, wherein the taxane is paclitaxel.

204. The CDP-taxane conjugate of any of claims 200-203, wherein the taxane conjugated to the CDP is more water soluble when conjugated to the CDP, than when not conjugated to the CDP.

205. A composition comprising the CDP-taxane conjugate of any of claims 200-204.

206. A pharmaceutical composition comprising the CDP-taxane conjugate of any of claims 200-204.

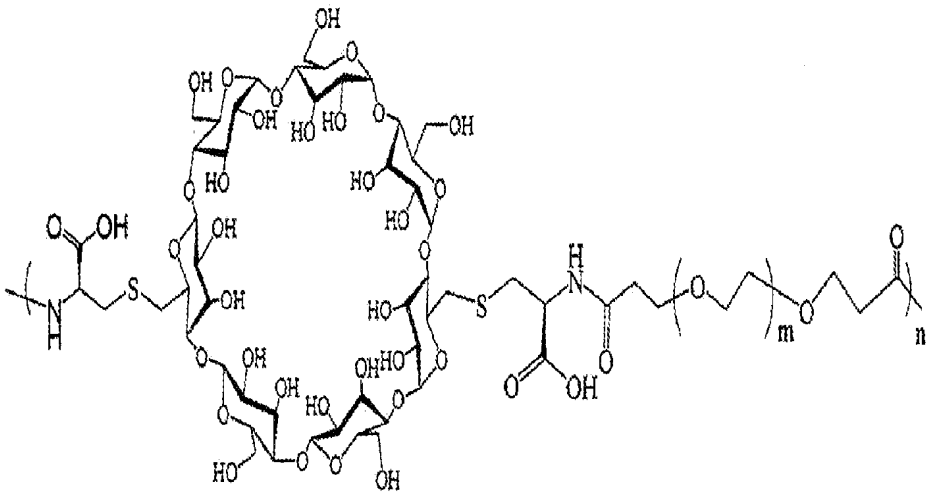
207. The composition of claim 205 or 206, wherein the composition comprises a population, mixture or plurality of CDP-taxane conjugates.

208. A dosage form comprising the CDP-taxane conjugate of any of claims 200-204.

209. A kit comprising the CDP-taxane conjugate of any of claims 200-204.

Figure 1

The CDP as shown in Figure 1 is provided below:



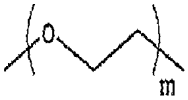
wherein the group  has a Mw of 3.4 kDa or less and n is at least 4. Note that the taxane is conjugated to the CDP through the carboxylic acid moieties of the polymer as provided above. Full loading of the taxane on to the CDP is not required. In some embodiments, at least one of the carboxylic acid moieties remains unreacted with the taxane after conjugation (e.g., a plurality of the carboxylic acid moieties remain unreacted).

Figure 2

Example	A	B	X	Taxane	Hydroxy Protecting Groups	Process for Preparation of taxane linker CDP molecules	Final Product
1.	-	$-NH(CH_2)_5CO-$	2'-OH	docetaxel	None	Process A	2'-docetaxel linked to CDP
2.	-	$-NH(CH_2)_5CO-$	7-OH	docetaxel	2' TBDMS or TROC	Process C	7-docetaxel linked to CDP
3.	-	$-NH(CH_2)_5CO-$	2'-OH	larotaxel	None	Process A	2'-larotaxel linked to CDP
4.	-	$-NH(CH_2)_5CO-$	2'-OH	cabazitaxel	None	Process A	2'-cabazitaxel linked to CDP
5.	-	$-NH(CH_2)_5CO-$	2'-OH	paclitaxel	None	Process A	2'-paclitaxel linked to CDP
6.	-	$-NH(CH_2)_5CO-$	7-OH	paclitaxel	2' TBDMS or TROC	Process C	7-paclitaxel linked to CDP
7.	-	$-NH(CH_2)_3OCH_2CO-$	2'-OH	docetaxel	None	Process A	2'-docetaxel linked to CDP
8.	-	$-NH(CH_2)_3OCH_2CO-$	7-OH	docetaxel	2' TBDMS or TROC	Process C	7-docetaxel linked to CDP
9.	-	$-NH(CH_2)_3OCH_2CO-$	2'-OH	larotaxel	None	Process A	2'-larotaxel linked to CDP
10.	-	$-NH(CH_2)_3OCH_2CO-$	2'-OH	cabazitaxel	None	Process A	2'-cabazitaxel linked to CDP
11.	-	$-NH(CH_2)_3OCH_2CO-$	2'-OH	paclitaxel	None	Process A	2'-paclitaxel linked to CDP
12.	-	$-NH(CH_2)_3OCH_2CO-$	7-OH	paclitaxel	2' TBDMS or TROC	Process C	7-paclitaxel linked to CDP
13.	-	$-NHCH_2CH_2COOCH_2CO-$	2'-OH	docetaxel	None	Process A	2'-docetaxel linked to CDP
14.	-	$-NHCH_2CH_2COOCH_2CO-$	7-OH	docetaxel	2' TBDMS or TROC	Process C	7-docetaxel linked to CDP

Figure 2

Example	A	B	X	Taxane	Hydroxy Protecting Groups	Process for Preparation of taxane linker CDP molecules	Final Product
15.	-	$-NHCH_2CH_2COOCH_2CO-$	2'-OH	larotaxel	None	Process A	2'-larotaxel linked to CDP
16.	-	$-NHCH_2CH_2COOCH_2CO-$	2'-OH	cabazitaxel	None	Process A	2'-cabazitaxel linked to CDP
17.	-	$-NHCH_2CH_2COOCH_2CO-$	2'-OH	paclitaxel	None	Process A	2'-paclitaxel linked to CDP
18.	-	$-NHCH_2CH_2COOCH_2CO-$	7-OH	paclitaxel	2' TBDMS or TROC	Process C	7-paclitaxel linked to CDP
19.	-	$-NHCH_2CH_2SSCH_2CH_2QCO-$ Q is O or NH	2'-OH	docetaxel	None	Process A	2'-docetaxel linked to CDP
20.	-	$-NHCH_2CH_2SSCH_2CH_2QCO-$ Q is O or NH	7-OH	docetaxel	2' TBDMS or TROC	Process C	7-docetaxel linked to CDP
21.	-	$-NHCH_2CH_2SSCH_2CH_2QCO-$ Q is O or NH	2'-OH	larotaxel	None	Process A	2'-larotaxel linked to CDP
22.	-	$-NHCH_2CH_2SSCH_2CH_2QCO-$ Q is O or NH	2'-OH	cabazitaxel	None	Process A	2'-cabazitaxel linked to CDP
23.	-	$-NHCH_2CH_2SSCH_2CH_2QCO-$ Q is O or NH	2'-OH	paclitaxel	None	Process A	2'-paclitaxel linked to CDP
24.	-	$-NHCH_2CH_2SSCH_2CH_2QCO-$ Q is O or NH	7-OH	paclitaxel	2' TBDMS or TROC	Process C	7-paclitaxel linked to CDP
25.	$-NH(CH_2)_2S-$	$-S(CH_2)_2NHCO-$	2'-OH	docetaxel	None	Process B	2'-docetaxel linked to CDP
26.	$-NH(CH_2)_2S-$	$-S(CH_2)_2NHCO-$	7-OH	docetaxel	2' TBDMS or TROC	Process D	7-docetaxel linked to CDP
27.	$-NH(CH_2)_2S-$	$-S(CH_2)_2NHCO-$	2'-OH	larotaxel	None	Process B	2'-larotaxel linked to CDP
28.	$-NH(CH_2)_2S-$	$-S(CH_2)_2NHCO-$	2'-OH	cabazitaxel	None	Process B	2'-cabazitaxel linked to CDP

Figure 2

Example	A	B	X	Taxane	Hydroxy Protecting Groups	Process for Preparation of taxane linker CDP molecules	Final Product
29.	$-NH(CH_2)_2S-$	$-S(CH_2)_2NHCO-$	2'-OH	paclitaxel	None	Process B	2'-paclitaxel linked to CDP
30.	$-NH(CH_2)_2S-$	$-S(CH_2)_2NHCO-$	7-OH	paclitaxel	2' TBDMS or TROC	Process D	7-paclitaxel linked to CDP
31.	-	$-NH(CH_2)_2SS(CH_2)_2NHCO-$	2'-OH	docetaxel	None	Process A	2'-docetaxel linked to CDP
32.	-	$-NH(CH_2)_2SS(CH_2)_2NHCO-$	7-OH	docetaxel	2' TBDMS or TROC	Process C	7-docetaxel linked to CDP
33.	-	$-NH(CH_2)_2SS(CH_2)_2NHCO-$	2'-OH	larotaxel	None	Process A	2'-larotaxel linked to CDP
34.	-	$-NH(CH_2)_2SS(CH_2)_2NHCO-$	2'-OH	cabazitaxel	None	Process A	2'-cabazitaxel linked to CDP
35.	-	$-NH(CH_2)_2SS(CH_2)_2NHCO-$	2'-OH	paclitaxel	None	Process A	2'-paclitaxel linked to CDP
36.	-	$-NH(CH_2)_2SS(CH_2)_2NHCO-$	7-OH	paclitaxel	2' TBDMS or TROC	Process C	7-paclitaxel linked to CDP
37.	$-NH(CH_2)_2S-$	$-S(CH_2)_2OCO-$	2'-OH	docetaxel	None	Process B	2'-docetaxel linked to CDP
38.	$-NH(CH_2)_2S-$	$-S(CH_2)_2OCO-$	7-OH	docetaxel	2' TBDMS or TROC	Process D	7-docetaxel linked to CDP
39.	$-NH(CH_2)_2S-$	$-S(CH_2)_2OCO-$	2'-OH	larotaxel	None	Process B	2'-larotaxel linked to CDP
40.	$-NH(CH_2)_2S-$	$-S(CH_2)_2OCO-$	2'-OH	cabazitaxel	None	Process B	2'-cabazitaxel linked to CDP
41.	$-NH(CH_2)_2S-$	$-S(CH_2)_2OCO-$	2'-OH	paclitaxel	None	Process B	2'-paclitaxel linked to CDP
42.	$-NH(CH_2)_2S-$	$-S(CH_2)_2OCO-$	7-OH	paclitaxel	2' TBDMS or TROC	Process D	7-paclitaxel linked to CDP

Figure 2

Example	A	B	X	Taxane	Hydroxy Protecting Groups	Process for Preparation of taxane linker CDP molecules	Final Product
43.	-	-NH(CH_2)$_n$CO- n is 1, 2, or 3	2'-OH	docetaxel	None	Process A	2'-docetaxel linked to CDP
44.	-	-NH(CH_2)$_n$CO- n is 1, 2, or 3	7-OH	docetaxel	2' TBDMS or TROC	Process C	7-docetaxel linked to CDP
45.	-	-NH(CH_2)$_n$CO- n is 1, 2, or 3	2'-OH	larotaxel	None	Process A	2'-larotaxel linked to CDP
46.	-	-NH(CH_2)$_n$CO- n is 1, 2, or 3	2'-OH	cabazitaxel	None	Process A	2'-cabazitaxel linked to CDP
47.	-	-NH(CH_2)$_n$CO- n is 1, 2, or 3	2'-OH	paclitaxel	None	Process A	2'-paclitaxel linked to CDP
48.	-	-NH(CH_2)$_n$CO- n is 1, 2, or 3	7-OH	paclitaxel	2' TBDMS or TROC	Process C	7-paclitaxel linked to CDP
49.	-	-NHZCO- Z is a mono, di, or tripeptide or other peptide or derivative thereof where NH and CO represent the amino and acid terminus of the amino acid or peptide	2'-OH	docetaxel	None	Process A	2'-docetaxel linked to CDP
50.	-	-NHZCO- Z is a mono, di, or tripeptide or other peptide or derivative thereof where NH and CO represent the amino and acid terminus of the amino acid or peptide	7-OH	docetaxel	2' TBDMS or TROC	Process C	7-docetaxel linked to CDP

Figure 2

Example	A	B	X	Taxane	Hydroxy Protecting Groups	Process for Preparation of taxane linker CDP molecules	Final Product
51.	-	-NHZCO- Z is a mono, di, or tripeptide or other peptide or derivative thereof where NH and CO represent the amino and acid terminus of the amino acid or peptide	2'-OH	larotaxel	None	Process A	2'-larotaxel linked to CDP
52.	-	-NHZCO- Z is a mono, di, or tripeptide or other peptide or derivative thereof where NH and CO represent the amino and acid terminus of the amino acid or peptide	2'-OH	cabazitaxel	None	Process A	2'-cabazitaxel linked to CDP
53.	-	-NHZCO- Z is a mono, di, or tripeptide or other peptide or derivative thereof where NH and CO represent the amino and acid terminus of the amino acid or peptide	2'-OH	paclitaxel	None	Process A	2'-paclitaxel linked to CDP
54.	-	-NHZCO- Z is a mono, di, or tripeptide or other peptide or derivative thereof where NH and CO represent the amino and acid terminus of the amino acid or peptide	7-OH	paclitaxel	2' TBDMS or TROC	Process C	7-paclitaxel linked to CDP

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/57913

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/02; A61K 31/335 (2010.01)
USPC - 514/449
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/49, 217, 492; 435/4, 6, 7.1, 69.1, 193, 198, 320.1, 325; 536/23.2 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Database Searched: PUBWEST (PGPUB,EP,JPAB,USPT). Search Terms Used cyclodextrin near5 taxane conjugate , docetaxel or larotaxel or cabazitaxel, chemotherapeutic, neutrophil, hormone refractory, chemotherapeutic agent, breast, lung, cancer, colorectal, myeloma

C. *DOCUMENTS CONSIDERED TO BE RELEVANT*

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0146598 A1 (Bianco) 19 June 2008 (19.06.2008) entire document, especially abstract; para [0001], [0003], [0006], [0012], [0016]-[0018], [0055]-[0056], [0084], [0087]-[0088], [0091], [0096], [0098], [0101], [0113], [0142], [0145]-[0146]	1-3, 10-14, 21-23, 26-28, 33-35, 37-39, 41-43, 47-49, 55-57, 61-63, 68-70, 76-78, 83-85, 87-89, 91-93, 95-97, 100-102, 106-108, 113-115, 117-119, 124-128, 132-134, 138-140, 142-144, 147-149, 152-154, 158-160, 165-167, 171-173, 175-190 and 192-202
Y	US 2009/0163574 A1 (Kim et al.) 25 June 2009 (25.06.2009) especially para [0012], [0018]	1-3, 10-14, 21-23, 26-28, 33-35, 37-39, 41-43, 47-49, 55-57, 61-63, 68-70, 76-78, 83-85, 87-89, 91-93, 95-97, 100-102, 106-108, 113-115, 117-119, 124-128, 132-134, 138-140, 142-144, 147-149, 152-154, 158-160, 165-167, 171-173, 175-190 and 192-202

☒ Further documents are listed in the continuation of Box C. ☐

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"&" document member of the same patent family

Date of the actual completion of the international search	*Date of mailing of the international search report*
15 January 2011 (15.01.1011)	26 JAN 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/57913

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/0129262 A1 (Epner et al.) 10 July 2003 (10.07.2003) especially para [0267]-[0268], [0307]	180-187
Y	US 2008/0171744 A1 (Danter et al.) 17 July 2008 (17.07.2008) especially para [0105]-[0106], [0164], [0166], [0168]	188-190 and 192-193
A	US 2008/0113031 A1 (Moodley et al.) 15 May 2008 (15.05.2008) entire document	1-3, 10-14, 21-23, 26-28, 32-35, 37-39, 41-43, 47-49, 55-57, 61-63, 68-70, 76-78, 83-85, 87-89, 91-93, 95-97, 100-102, 106-108, 113-115, 117-119, 124-128, 132-134, 138-140, 142-144, 147-149, 152-154, 158-160, 165-167, 171-173, 175-190 and 192-202

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/57913

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 4-9, 15-20, 24-25, 29-32, 36, 40, 44-46, 50-54, 58-60, 64-67, 71-75, 79-82, 86, 90, 94, 98-99, 103-105, 109-112, 116, 120-123, 129-131, 135-137, 141, 145-146, 150-151, 155-157, 161-164, 168-170, 174, 191, and 203-209 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

3. ☒ Claims Nos.: see above
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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Published
With international search report.

(54) Title: PROCESS FOR PREPARATION OF TAXANE DERIVATIVES AND β-LACTAM INTERMEDIATES THEREFOR

(57) Abstract

Taxol (I) is a complex diterpene which is currently considered the most exciting lead in cancer chemotherapy. Taxol possesses high cytotoxicity and strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs. However, taxol has a problem with solubility in aqueous media, which may impose some serious limitation in its use. TAXOTERE (III) seems to have antitumor activity superior to taxol with better bioavailability. Taxotère has a modified taxol structure with a modified C-13 side chain. This fact strongly indicates that modification on the C-13 side chain would provide a new series of taxol and TAXOTERE analogues which may have higher potency, better bioavailability and less unwanted toxicity. The present invention provides efficient and practical methods for the syntheses of TAXOTERE and its analogues through β-lactam intermediates and their coupling with baccatin III.

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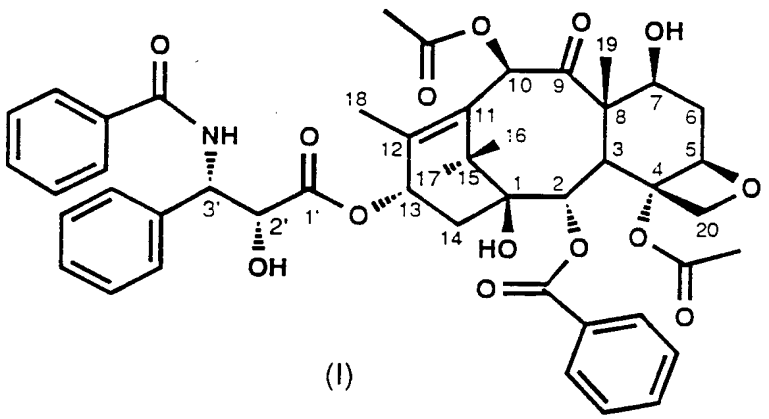
PROCESS FOR PREPARATION OF TAXANE DERIVATIVES AND ß-LACTAM INTERMEDIATES THEREFOR

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of taxoid(s) including TAXOTÈRE and its analogs and the ß-lactam intermediates useful in this process.

BACKGROUND OF THE INVENTION

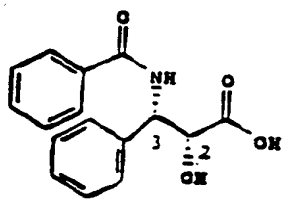
Taxol (I) is a complex diterpene which is currently considered the most exciting lead in cancer chemotherapy. Taxol possesses high cytotoxicity and strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs. For example, taxol is currently in phase III clinical trials for advanced ovarian cancer, phase II for breast cancer, and phase I for lung cancers, colon cancer and acute leukemia.



(I)

Although taxol is an extremely important "lead" in cancer chemotherapy, taxol has a problem with solubility in aqueous media, which may impose some serious limitation in its use. It is common for improved drugs to be derived from naturally occurring lead compounds. In fact, French researchers, Potier, Guéritte-Voegelein,

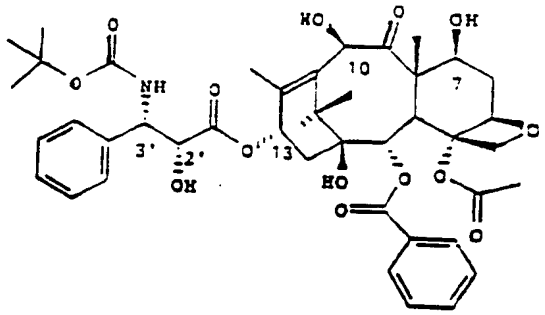
Guénard et al. have discovered that a modification of the C-13 side chain of taxol brought about a new anticancer agent which seems to have antitumor activity superior to taxol with better bioavailability. This synthetic compound was named "TAXOTÈRE (II)", which has t-butoxycarbonyl instead of benzoyl on the amino group of (2R,3S)-phenylisoserine moiety at the C-13 position and a hydroxyl group instead of an acetoxy group at C-10. [Colin, M. et al. Eur. Pat. Appl. EP253,738 (1988)]. Taxotère is currently in phase II clinical trial in both United States and Europe. TAXOTÈRE has been synthesized by a semisynthetic process, including a coupling of N-tert-butoxycarbonyl-(2R,3S)-3-phenylisoserine with 10-deacetylbaccatin III with proper protecting groups. (Denis, J.-N. recently reported (Commercon, A. et al., Tetrahedron Letters, 1992, 33 5185)).



(II)

It is known that the C-13 side chain of taxol, i.e., N-benzoyl-(2R, 3S)-3-phenylisoserine (III) moiety, is crucial for the strong antitumor activity of taxol. (Senilh et al., C.R. Séancas Acad. Sci. Ser. 2 1984, 299, 1039; Guéritte-Voegelein et al., Tetrahedron, 1986, 42, 4451, and Mangatal et al., Tetrahedron, 1989, 45, 4177; Guéritte-Voegelein et al. J. Med. Chem. 1991, 34, 992; and Swindell et al., J. Med. Chem. 1992, 35, 145; Mathew, A.E. et al., J. Med. Chem. 1992, 35, 145). Moreover, some modification of the C-13 side chain can provide a new series of taxol analogs which may have higher potency, better bioavailability and less unwanted toxicity, as

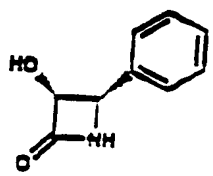
exemplified by the discovery of TAXOTÈRE (II).



(III)

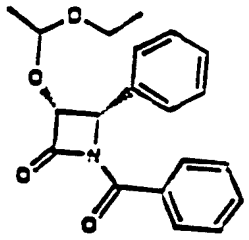
Accordingly, the development of an efficient method which can be applied to various analogs of taxol and TAXOTÈRE and analogs thereof, i.e., a method having flexibility and wide applicability, is extremely important and of current demand. It has been shown that such a new and efficient method with flexibility can be developed by using enantiomerically pure ß-lactams as key-intermediates [Ojima, I. et al., J. Org. Chem., 1991, 56, 1681; Ojima et al., Tetrahedron, 1992, 48, 6985; Holton, R.A., Eur. Patent Appl. EP 400,971 (1990)].

Lithium chiral ester enolate-imine cyclocondensation strategy has been applied to the asymmetric synthesis of the side chain of taxol via a (3*R*,4*S*)-3-hydroxy-4-phenylazotidin-2-one (IV) as the key-intermediate. (Ojima, I. et al., J. Org. Chem., 1991, 56, 1681; Ojima et al., Tetrahedron, 1992, 48, 6985)

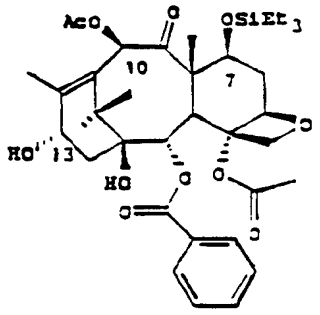


(IV)

Based on this protocol, the side chain can be obtained in 3 steps in high yield with virtually 100% e.e. (Ojima, I. et al. J. Org. Chem. 1991 56, 1681). Recently, it was found that 1-benzoyl-(3*R*,4*S*)-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one (V), readily derived from the hydroxy-ß-lactam (IV), served as the key-intermediate for the synthesis of taxol [Holton, R.A. Eur. Pat. Appl. EP 400,971 (1990)]. Therefore, this ß-lactam intermediate serves as the key-intermediate for both coupling methods.



(V)

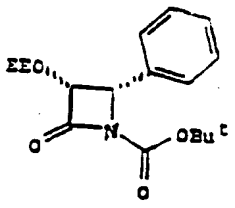


7-TES-baccatin III (VI)

In the published European application to Holton (hereinafter Holton), the ß-lactam intermediate (V) was

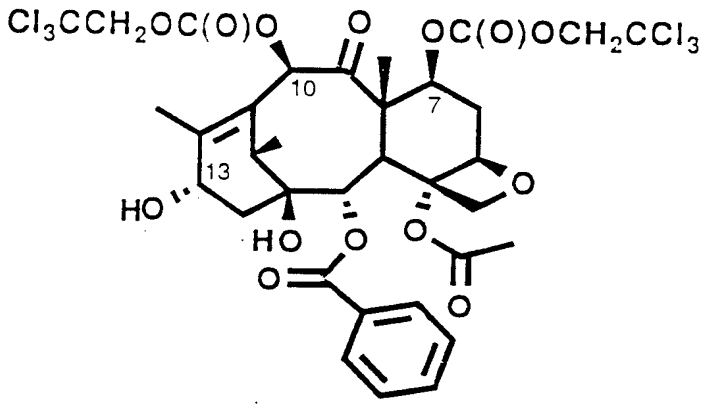
obtained through tedious optical resolution of the racemic cis-3-hydroxy-ß-lactam. According to Holton's procedure, the coupling of the ß-lactam (V) with 7-triethylsilylbaccatin III (VI) (7-TES-baccatin III) proceeds at 25°C in the presence of dimethylaminopyridine (DMAP) and pyridine for 12 hours to give protected taxol in 92% yield, which was deprotected with 0.5% hydrochloric acid in ethanol at 0°C to afford taxol in ca. 90% yield.

However, the Holton procedure did not work at all when 1-tert-butoxycarbonyl-(3*R*,4*S*)-3-(1-ethoxylethoxy)-4-phenylazetidin-2-one (VII) was used for the attempted synthesis of TAXOTÈRE (II) by the present inventors.



(VII)

It is believed that this may be due to the lack of reactivity of the 1-tert-butoxycarbonyl-ß-lactam (VII) toward the C-13 hydroxyl group of a protected baccatin III (VI or VIII) under the conditions used by Holton. The lack of reactivity may be ascribed to the substantially weaker electron-withdrawing ability of tert-butoxycarbonyl group than that of benzoyl group.



7.10-di-Troc-10-deacetylbaccatin III (VIII)

Therefore, it was an objective of the present invention to develop a new method which can achieve the coupling of the 1-tert-butoxycarbonyl-ß-lactam (VII) with the protected baccatin III (VIII) for the synthesis of TAXOTÈRE (II).

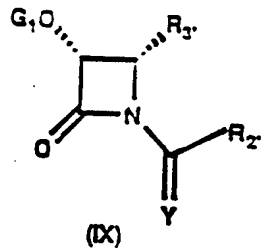
All of the references cited above and any reference which may be mentioned herein below are expressly incorporated into the present disclosure.

It is an object of the present invention to provide new ß-lactams useful in the syntheses of TAXOTÈRE (II) and analogs thereof.

It is further object of the present invention to provide a new coupling method for the syntheses of TAXOTÈRE (II) and analogs thereof.

SUMMARY OF THE INVENTION

A ß-lactam of the formula (IX)



(IX)

in which

$R_{2'}$ represents an RO-, RS- or RR'N- in which R represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, carbocyclic aryl or heteroaryl, wherein substituents bearing one or more active hydrogens such as hydroxyl, amino, marcapto and carboxyl groups are protected; R' is a hydrogen or R as defined above; R and R' can be connected to form a cyclic structure; Examples of $R_{2'}$ include methoxy, ethoxy, isopropoxy, tert-butoxy, neopentyloxy, cyclohexyloxy, allyloxy, propargyloxy, adamantyloxy, phenyoxy, 4-methoxyphenoxy, 2-fluorophenoxy, 4-methoxycarbonylphenoxy, methylthio, ethylthio, isopropylthio, tert-butylthio, neopentylthio, cyclohexylthio, phenylthio, 3,4-dimethoxyphenylthio, methylamino, ethylamino, isopropylamino, tert-butylamino, neopentylamino, cyclohexylamino, dimethylamino, pyrrolidino, piperidino and morpholino group.

$R_{3'}$ represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl

radical, an unsubstituted or substituted cycloalkyl, or cycloalkenyl radical, an unsubstituted or substituted aryl radical wherein substituents bearing one or more active hydrogens such as hydroxy, amino, mercapto and carboxyl groups are protected; Examples of R_3, include phenyl, 4-methoxyphenyl, 3,4-dimethoxylphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, cyclohexyl, cyclohexylmethyl, 2-phenylethenyl, 2-phenylethyl, benzyl, neopentyl, tert-butyl, isobutyl, isopropyl, allyl and proparagyl;

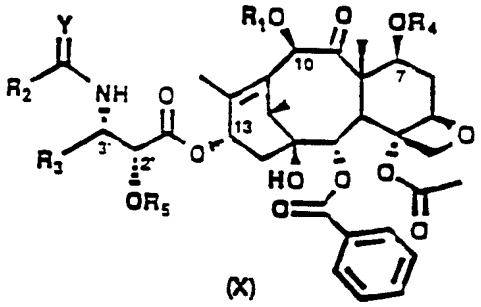
G_1 represents a hydrogen or hydroxyl protecting group such as methoxymethyl (MOM), methoxylethyl (MEM), 1-ethoxyethyl (EE) benzyloxymethyl, (ß-trimethylsilylethoxyl)methyl, tetrahydropyranyl, 2,2,2-trichloroethoxycarbonyl (Troc), tert-butoxycarbonyl (t-BOC), 9-fluorenylmethoxycarbonyl (Fmoc), 2,2,2-tricholoroethoxymethyl, trimethylsilyl, triethylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl and diphenylmethylsilyl;

Y is oxygen or sulfur.

The present inventor investigated the ß-lactam coupling reaction with protected Baccatin III in detail and found that the coupling could be achieved by increasing the nucleophilicity of the 13-hydroxyl group of a protected baccatin III (VI or VIII) through transformation of the hydroxyl group to the corresponding metal alkoxide. Such a C-13 metal alkoxide of a baccatin III was readily generated by reacting the baccatin III (VI or VIII) with an alkali or alkaline earth metal base. This finding is the basis of the present invention. The method of the present invention not only enables the coupling of the ß-lactam (VII) and its derivatives and analogs with a protected baccatin III, but also requires only a stoichiometric amount of the ß-lactams. The latter makes a sharp contrast with the Holton procedure for taxol

synthesis which needs 5-6 equivalents of the more reactive ß-lactam (V). Moreover, the coupling reactions of the present invention proceeds very smoothly and complete typically within 30 minutes at -30°C - 0°C.

The present invention also relates to a process for the preparation of taxane derivatives of the formula (X)



(X)

in which

R_1 represents a hydrogen atom or an acyl or an alkyl or an alkenyl or an alkynyl or carbocyclic aryl or a heteroaryl radical or a hydroxyl protecting group (G_1 defined above);

R_2 represents an RO-, RS- or RR'N- in which R represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, carbocyclic aryl or heteroaryl; R' is a hydrogen or R as defined above; R and R' can be connected to form a cyclic structure;

Y is oxygen or sulfur;

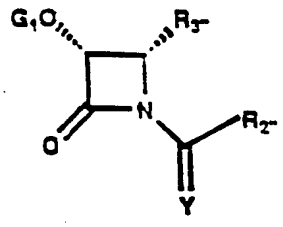
R_3 represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl radical, an

unsubstituted or substituted cycloalkyl, cycloalkenyl radical or an unsubstituted or substituted carbocyclic aryl radical;

R_4 represents a hydrogen or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical, or a hydroxyl group protecting group (G_1 defined above);

R_5 represents a hydrogen or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical, or a hydroxyl protecting group (G_1 defined above);

which comprises condensing a ß-lactam of the formula



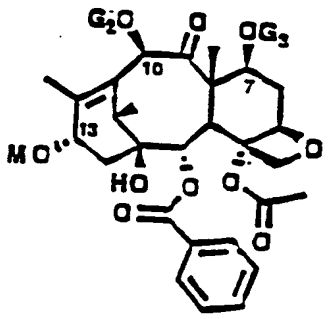
in which

Y and G_1 are defined above;

$R_{2'}$ represents a radical R_2 as defined above or a protected R_2 whenever R_2 includes one or more active hydrogens such as hydroxyl, amino, mercapto and carboxyl groups;

$R_{3'}$ represents a radical as R_3 defined above or a protected R_3 whenever R_3 includes one or more active

hydrogens such as hydroxyl, amino, mercapto and carboxyl groups; with a baccatin III derivative of the formula:



in which

M is an alkali metal or alkaline earth metal atom (ion);

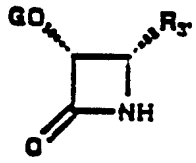
G_2 represents a hydroxyl protecting group (G_1 defined above) or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heteroycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical;

G_3 represents a hydroxyl group protecting group (G_3 defined above) or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or

substituted carbocyclic aryl or heteroaryl radical.

DETAILED DESCRIPTION OF THE INVENTION

The new ß-lactams of the formula (IX) herein above are synthesized by modifying the ß-lactams of the formula (XI)

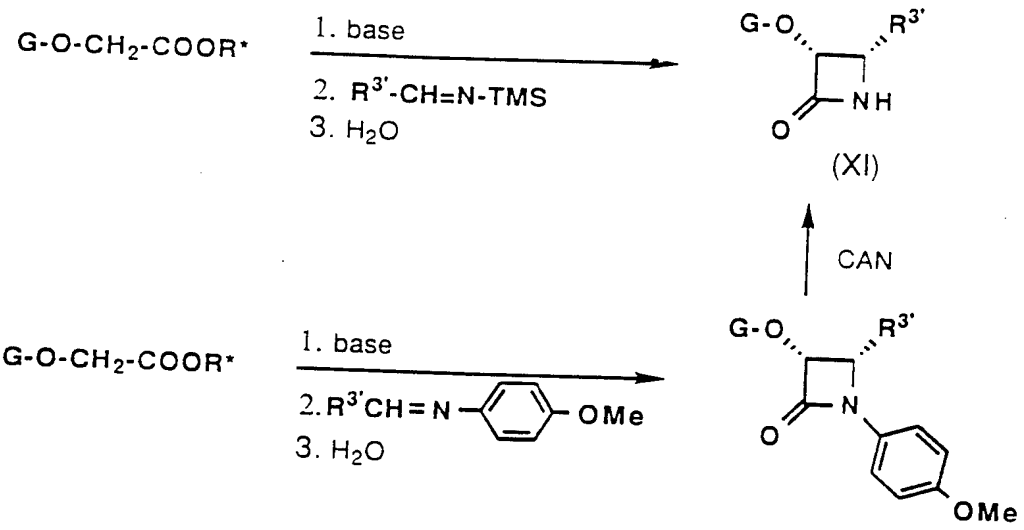


(XI)

wherein G is a hydroxyl protecting group such as triisopropylsilyl (TIPS) and dimethyl(tert-butyl) silyl (TBDMS), and R_3' has been defined hereinabove.

The ß-lactams (XI) are readily prepared by using the chiral enolate - imine cyclocondensation method which has been developed in the present inventor's laboratory as shown in Scheme 1 (Ojima, I. et al., Tetrahedron, 1992, 48, 6985; Ojima, I. et al., J. Org. Chem. 1991, 56, 1681). In this preparation the ß-lactams (XI) with extremely high enantiomeric purities are obtained in high yields. In Scheme 1, R* is a chiral auxiliary moiety which is (-)-trans-2-phenyl-1-cyclohexyl, TMS is a trimethylsilyl radical, and base is lithium diisopropylamide or lithium hexamethyldisilazide; G and R_3' have been defined hereinabove.

Scheme 1



The ß-lactams (VI) are converted to the 3-hydroxy-ß-lactams (XII), followed by protection with ethoxyethyl group (EE) to give the ß-lactams (XIII). The ß-lactams (XIII) are reacted with chloroformates or formic anhydrides or thiocholorformates or thioformic anhydrides in the presence of a base to yield the ß-lactams (XIV) (or thioanalogs thereof) which are used for the coupling with protected 10-deacetylbaccatin III to produce TAXOTÈRE and its analogs. The ß-lactams (XIV) are deprotected under weakly acidic conditions to afford the ß-lactams (XV) which can serve as very useful intermediates to the ß-lactams (XVI) bearing a variety of protecting groups (G_1) at the C-3 position of ß-lactam skeleton. The ß-lactams (XVI) can also be used for the coupling with a protected 10-deacetylbaccatin III to produce Taxotère and its analogs after deprotection.

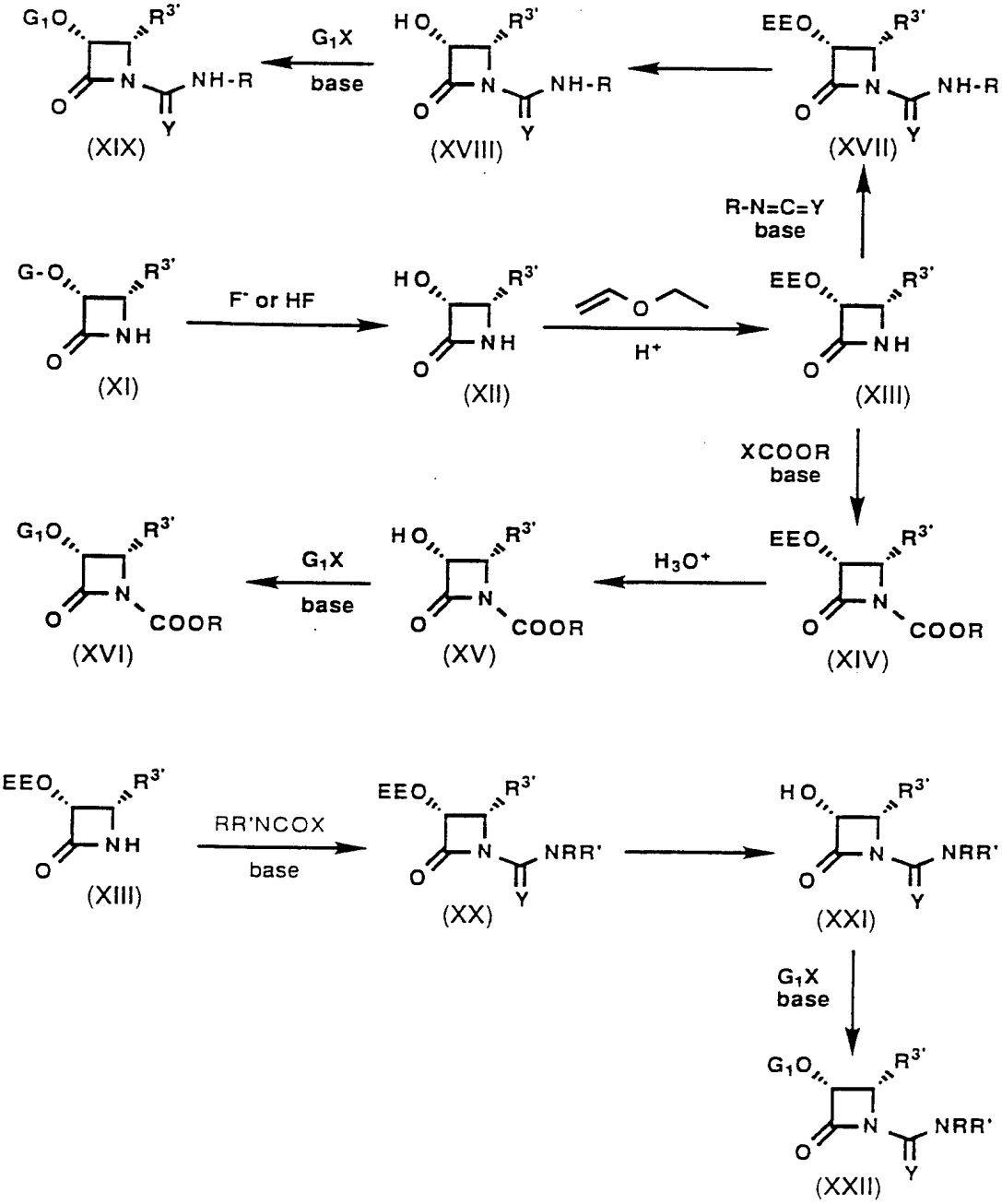
In a similar manner, the ß-lactams (XVII) are prepared by reacting the ß-lactams (XIII) with isocyanates or isothiocyanates in the presence of a base which can be used for the protection of other potent anticancer agents of formula (X) in which R_2 represents RRN-. The ß-lactams (XVII) are deprotected under weakly acidic conditions to give the ß-lactams (XVIII) which can serve as very useful intermediates to a variety of protected 3-hydroxyl-ß-

lactams (XIX). The ß-lactams (XVII and XIX) can also be used for the coupling with a protected 10-deacetylbaccatin III to yield a compound of formula (X) in which R_2 represents RR'N- after deprotection.

In a manner similar to that described above, the ß-lactams (XX) are prepared by reacting the ß-lactams (XIII) with N,N-disubstituted carbamoyl halides in the presence of a base. The ß-lactams (XX) are deprotected under weakly acidic conditions to give the 3-hydroxy-ß-lactams (XXI), which can serve as very useful intermediates to various protected 3-hydroxy-ß-lactams (XXII). The ß-lactams (XX and XXII) can readily be used for the coupling with a protected baccatin III to afford a compound of formula (X) after deprotection.

The transformations described above are illustrated in Scheme 2. In Scheme 2, X represents a leaving group such as fluoride, chloride, bromide, iodide, tosylate, mesylate and trifluoromesylate. G_1 represents a group protecting the hydroxyl function selected from methoxylmethyl (MOM), methoxyethyl (MEM), 1-ethoxyethyl (EE), benzyloxymethyl, (ß-trimethylsilylethoxyl) methyl, tetrahydropyranyl, 2,2,2-trichloroethoxylcarbonyl (TROC), benzyloxycarbonyl (CBZ), tert-butoxycarbonyl (t-BOC), 9-fluorenyl methoxycarbonyl (FMOC) 2,2,2-trichloroethoxymethyl, trimethyl silyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethyl phenylsilyl and diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl. $R^{2'}$, $R^{3'}$, R, and R' are defined hereinabove.

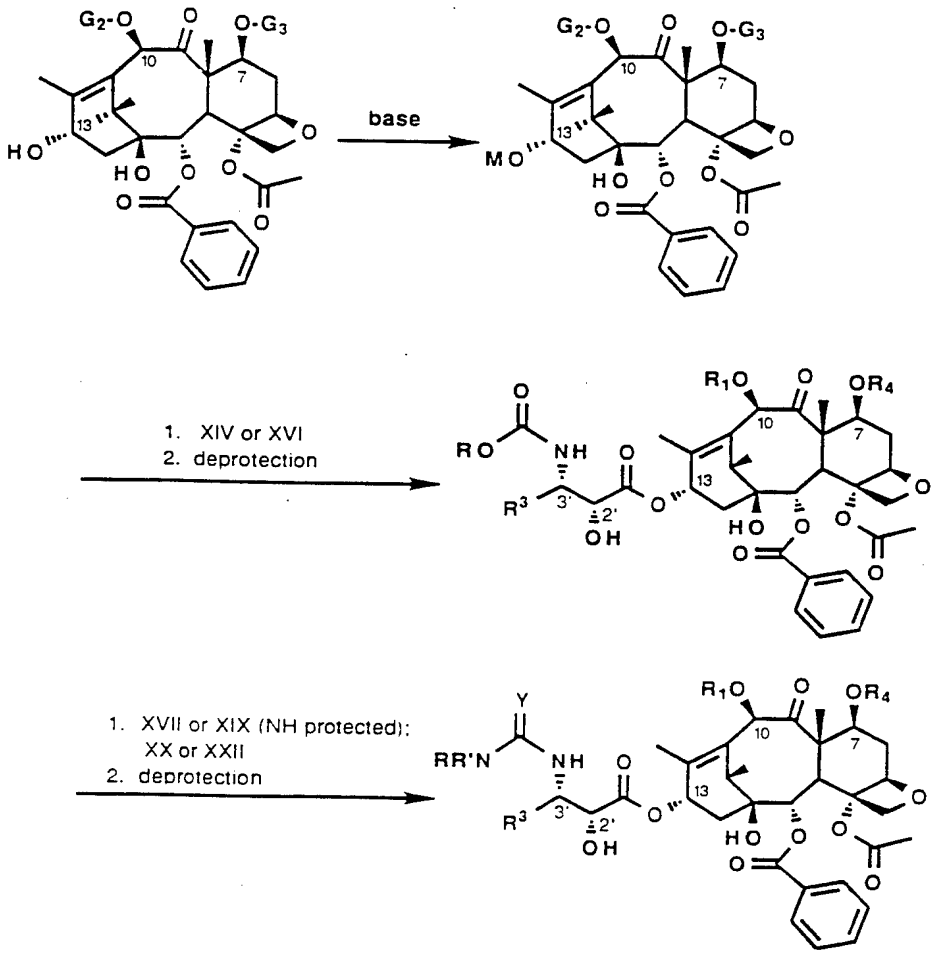
Scheme 2



The ß-lactams (XIV) and (XVI) are readily used for the coupling with protected baccatin IIIs in the presence of base, followed by deprotection to give TAXOTÈRE and its analogs in high yields (Scheme 3). In a similar manner, the ß-lactams (XVII and XIX; with

protection of -NH- moiety) and the ß-lactams (XX and XXII) can be used for the coupling with protected baccatin IIIs, followed by deprotection to give a compound of formula (X) in which R_2 represents RR^1N- (Scheme 3).

Scheme 3



G_2 and G_3 represents an hydroxyl protecting group or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical.

When G_2 and G_3 are hydroxyl protecting groups [G_3 defined above and 1-ethoxyethoxyl (EE)], these protecting

groups can be attached to the hydroxyl groups of 10-deacetylbaccatin III and its analogs by methods which are generally known to those skilled in the art.

The coupling reaction of the protected baccatin III and the ß-lactam is carried out via an alkali metal or alkaline earth metal alkoxide of the protected baccatin III at the C-13 hydroxyl group. The alkoxide can readily be generated by reacting the protected baccatin III with an alkali metal or alkaline earth metal base such as sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium hexamethyldisilazide, sodium diisopropylamide, potassium diisopropylamide, lithium diisopropylamide, sodium hydride, potassium hydride, lithium hydride, calcium hydride, magnesium hydride, in a dry nonprotic organic solvent such as tetrahydrofuran (THF), dioxane, ether, dimethoxyethane (DME), diglyme, dimethylformamide (DMF), mixtures of these solvents with hexane, toluene, an xylene, in a preferred temperature range from about -100°C to about 50°C, more preferably at about -78°C to about 25°C. This reaction is preferably carried out under inert atmosphere such as nitrogen and argon. The amount of the base used for the reaction is preferably approximately equivalent to the amount of the protected baccatin III when soluble bases such as sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium hexamethyldisilazide, sodium diisopropylamide, potassium diisopropylamide, lithium diisopropylamide are used. The use of a slight excess of the base does not adversely affect the reaction. When heterogeneous bases such as sodium hydride and potassium hydride are used, 5-10 equivalents of the base (to the amount of the protected baccatin III) is preferably employed.

The coupling reaction of the metal alkoxide of the protected baccatin III thus generated with the ß-lactam is typically carried out by adding the solution of the ß-lactam in a dry organic solvent exemplified above in

a preferred temperature range from about -100°C to 50°C, more preferably at about -35°C to 25°C. The mixture of reactants is stirred for 15 minutes to 24 hours and the progress and the completion of the reaction is monitored by thin layer chromatography (TLC), for example. When the limiting reactant is completely consumed, the reaction is quenched by addition of a brine. The crude reaction mixture is worked up using the standard isolation procedures which are generally known to those skilled in the art to give the corresponding protected taxoid. The proportion of the ß-lactam and the protected baccatin III is in a range from 2:1 to 1:2, more preferably approximately 1:1 for purposes of economy and efficiency, but the ratio is not critical for the reaction.

The protecting groups, EE, G_1, G_2 and G_3, can then be removed by using the standard procedures which are generally known to those skilled in the art to give the desired taxane derivatives. For example, EE and triethylsilyl groups can be removed with 0.5 N HCl at room temperature for 36 h, and Troc group can be removed with zinc and acetic acid in methanol at 60°C for 1 hour without disturbing the other functional groups and the skeleton of the taxoid.

The following non-limiting examples are illustrative of the present invention. It should be noted that various changes would be made in the above examples and processes therein without departing from the scope of the present invention. For this reason, it is intended that the illustrative embodiments of the present application should be interpreted as being illustrative and not limiting in any sense.

Examples 1-2

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-phenyl-2-azetidinone (1a): To a solution of 645 mL (4.6 mmol) of diisopropylamine in 10 mL of THF, was added 1.85 mL (4.6

mmol, 2.5M) of n-BuLi at 0°C. The solution was stirred 1 h at 0°C followed by the addition of 1.5 g (3.8 mmol) of (-) TIPS ester in 15 mL of THF over a 1 h period (using a cannula) at -78°C. The reaction was stirred 2 h at this temperature followed by the addition of 817 mg (4.6 mmol) of N-TMS benzaldimine in 15 mL of THF over a 2 h period at -95°C. The reaction was stirred overnight at this temperature and allowed to slowly warm up at room temperature. The reaction was quenched by addition of sat. NH_4Cl. The aqueous layer was extracted with ether. The organic layer was washed with 3% HCl and brine, dried over $MgSO_4$ and concentrated. The crude oil was purified by chromatography on silica gel using 1:5 EtAcO/hexanes to give 1.03 g (84%) of ß-lactam as a white solid: Mp 76-77°C; $[\alpha]D^{20}$ +52.7° (C 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86-0.93 (m, 21H), 4.81 (d, J = 4.7 Hz, 1H), 5.17 (dd, J = 4.7, 2.6 Hz, 1H), 6.18 (bs, 1H), 7.17-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$ δ 11.8, 17.4, 17.5, 59.6, 79.9, 127.9, 128.0, 128.1, 136.4, 170.0; IR (KBr) 3234, 2946-2866, 1760, 1458 cm^{-1}. Anal. Calcd for $C_{18}H_{29}NO_2Si$: C 67.66%, H 9.15%, N 4.38%. Found: C 67.64%, H 9.25%, N 4.44%.

In the same manner, ß-lactam **1b** was obtained in good yield.

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(2-phenylethenyl)-2-azetidinone (1b): 72%; colorless liquid; $_1H$ NMR (300 MHz, $CDCl_3$) δ 0.98-1.02 (m, 21H), 4.36 (dd, J = 4.6, 8.3 Hz, 1H), 5.09 (dd, J = 2.3, 4.6 Hz, 1H), 6.29 (dd, J = 8.3, 16.0 Hz, 1H), 6.59 (d, J = 16.0 Hz, 1H), 6.83, (bs, 1H), 7.23-7.39 (m, 5H); NMR (75 MHz,$CDCl_3$) δ 11.79, 17.61, 17.66, 58.34, 79.86, 126.05, 126.45, 127.90, 128.56, 134.41, 136.30, 169.69; IR (neat) 3262, 3032, 2944, 2865, 1748, 1672, 1623 cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_2Si$: C, 69.52; H, 9.04; N, 4.05. Found: C, 69.75; H, 9.02; N, 3.89.

Examples 3-4

To a solution of 2.51 mmol of diisopropylamine in 15 mL of THF was added 2.51 mL of n-butyllithium (2.5M in THF) at -10°C. After 30 min, the lithium diisopropylamide (LDA) was generated and the solution was cooled to -95°C. A solution of 2.17 mmol of chiral ester in 5 mL of THF was added. After 1 hr, a solution of 2.5 mmol of the appropriate imine in 3mL of THF was added. The mixture was stirred at -95°C overnight, and the progress of the reaction was monitored by TLC or ^1H NMR. The reaction was quenched with sat. NH_4Cl and THF was removed using a rotary evaporator. Ether (10 mL) was added and the aqueous layer was extracted with ether (10 mL x3). Drying and removal of the solvent gave the crude product which was purified by silica gel column chromatography (hexane/ethyl acetate=10:1) to afford the corresponding pure ß-lactam. The enantimeric excess was determined by HPLC using a CHIRALCEL OD column using n-hexane/i-PrOH (90/10) as the eluent.

(3*R*,4*S*)-4-(2-Methylpropyl)-1-(4-methoxyphenyl)-3-triisopropylsilyloxy-2-azetidinone (2a): 87%; pale yellow solid; mp 59-60°C; $[\alpha]D^{20}$ +60.46° (c 1.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J = 6.4 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H), 1.10-1.30 (m, 21H), 1.60-1.68 (m, 1H), 1.70-1.92 (m, 2H), 3.75 (s, 3H), 4.16-4.22 (m, 1H), 5.06 (d, J = 5.1 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.34, 17.82, 17.91, 22.18, 23.37, 25.34, 35.89, 55.50, 57.33, 76.34, 114.52, 118.73, 131.00, 156.29, 165.58; IR (KBr) 2946, 1742, 1513, 1458, 1249 cm^{-1}. Anal. Calcd for $C_{23}H_{39}NO_3Si$: C, 68.10; H, 9.70; N, 3.45. Found: C, 68.26; H, 9.85; N, 3.35.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-1-(4-methoxyphenyl)-3-triisophropylsilyloxy-2-azetidinone (2b): 83%; low melting point solid; $[\alpha]D^{20}$ +43.7° (c 0.92,

$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85-1.95 (m, 34H), 3.78 (s, 3H), 4.19-4.25 (m, 1H), 5.05 (d, J = 5.1 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, CDC_{13}) δ 12.15, 17.76, 17.83, 26.12, 26.22, 26.47, 32.84, 34.22, 34.51, 55.36, 56.41, 76.13, 114.30, 118.45, 130.81, 155.99, 165.55; IR (neat) 2925-2865, 1749, 1513, 1464, 1448, 1389, 1246, 1174, 1145, 1128, 939, 882, 828, 684 cm^{-1}. Anal. Calcd for $C_{26}H_{43}NO_3Si$: C, 70.06; H, 9.72; N, 3.14. Found: C, 69.91; H, 9.71; N, 3.02.

Examples 5-6

To a solution of 0.24 mmol of 1-(4-methoxyphenyl)-β-lactam in CH_3CN (20 mL) was added 0.65 mmol of CAN in 10 mL CH_3CN and 20 mL of water in 20 min at -15°C. After stirring for 1 hr, it was diluted with water (20 mL), and the mixture was then extracted with ethyl acetate (15 mL x2). The combined organic layer was washed with $NaHSO_3$ water (7 mL), 5% (10 mL x 2), 5% Na_2CO_3 (10 mL) and brine (5 mL) in sequence. Drying, removal of the solvent in vacuo followed by decolorization with activated charcoal afforded the crude product. It was further purified by silica gel column chromatography (hexanes/ethyl acetate, 3/1) to furnish N-deprotected β-lactam.

(3*R*,4*S*)-4-(2-Methylpropyl)-3-triisopropylsilyloxy-2-azetidinone (1c): 83%; yellow oil; $[\alpha]D^{20}$+35.45° (c 1.33, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 1.05-1.25 (m, 22H), 1.52 (M, 1H), 1.67 (m, 1H), 3.78 (m, 1H), 4.96 (dd, J = 4.8, 2.4 Hz, 1H), 6.02 (bs, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 12.12, 17.72, 17.80, 22.29, 23.08, 25.35, 39.08, 54.45, 78.04, 170.00; IR (neat) 3238, 1759, 1465, 1184 cm^{-1}. Anal. Calcd for $C_{16}H_{33}NO_2Si$: C, 64.16; H, 11.1; N, 4.68. Found: C, 64.17; H, 10.96; N, 4.47.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-3-

triisopropylsilyloxy-2-azetidinone (1d): 85%; yellow oil; $[\alpha]D^{20}$+12.44° (c 1.46, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.97-1.25 (m, 32H), 1.40-1.70 (m, 2H), 3.80 (dt, J = 8.4, 4.8 Hz, 1H), 4.95 (dd, J = 4.8, 2.4 Hz, 1H), 6.05 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.06, 17.77, 17.82, 26.16, 26.25, 26.46, 33.15, 33.82, 34.85, 37.72, 53.89, 77.98, 169.98; IR (neat) 3238, 1759, 1465, 1184 cm^1. Anal. Calcd for $C_{19}H_{37}NO_2Si$: C, 67.20; H, 10.98; N, 4.12. Found: C, 67.40; H, 10.79; N, 3.98.

Examples 7-11

To a solution of 2.6 mmol of 3-triisopropylsilyloxy-4-substituted-2-azetidinone in 20 mL of THF, was added at room temperature 3.1 mmol (1M in THF) of NBu_4F. After 5 h, the solvent was evaporated and the crude oil was directly purified by chromatography on silica gel using 5:1 EtAcO/hexanes to afford of 3-hydroxy-4-substituted-2-azetidinone:

(3*R*,4*S*)-3-Hydroxy-4-phenyl-2-azetidinone (3a): 100%; white solid; mp 189-190°C; $[\alpha]D^{20}$ +181.6° (c 0.5, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 4.84 (d, J = 4.7 Hz, 1H), 5.04 (d, J = 4.7 Hz, 1H), 7.25-7.35 (m, 5H); IR (KBr) 3373, 3252, 1732, 1494 cm^{-1}. Anal. Calcd for $C_9H_9NO_2$: C 66.25%, H 5.56%, N 8.58%. Found: C 66.42%, H 5.74%, N 8.62%.

(3*R*,4*S*)-3-Hydroxy-4-(2-phenylethenyl)-2-azetidinone (3b): 82%; white solid; mp 143-144°C; $[\alpha]D^{20}$ +21.9° (c 1.05, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 4.35 (ddd, J = 0.8, 4.7, 7.7 Hz, 1H), 4.93 (d, J = 4.7 Hz, 1H), 6.28 (dd, J = 7.7, 16.0 Hz, 1H), 7.18-7.43 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD) δ 58.95, 79.63, 126.83, 127.58, 128.88, 129.61, 135.28, 137.96, 172.79; IR (KBr) 3320,

3276, 1754, 1464 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.72; H, 5.92; N, 7.24.

(3*R*,4*S*)-3-Hydroxy-4-(2-methylpropyl)-2-azetidinone (3c): 94%; white solid; mp 141-142°C; $[\alpha]D^{20}$ +26.6° (c 0.70, MeOH); ^1H NMR (300 MHz, MeOH-d4) d 0.94 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.45 (m, 2H), 1.71 (sept, J = 6.6 Hz, 1H), 3.75 (m, 1H), 4.79 (d, J = 4.7 Hz, 1H); ^{13}C NMR (75 MHz, MeOH-d4) δ 22.62, 23.48, 26.53, 39.90, 55.47, 77.76, 173.18; IR (KBr) 3274, 3178, 1762, 1685, 1155 cm^{-1}. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.55; H, 9.41; N, 9.69.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-3-hydroxy-2-azetidinone (3d): 92%; white solid; mp 147-148°C; $[\alpha]D^{20}$ + 8.73° (c, 0.573, CH_3OH); ^1H NMR (300 MHz, MeOH-d4) δ 0.88-1.82 (m, 13H), 3.78 (m, 1H), 4.79 (d, J = 4.7 Hz, 1H); ^1H NMR (300 MHz, DMSO-d6) δ 0.86-1.72 (m, 13H), 3.58 (m, 1H), 4.63 (m, 1H), 5.82 (d, J = 7.6 Hz, 1H), 8.13 (d, J = 5.6, 1H); ^{13}C NMR (75 MHz, MeOH-d4) δ 27.29, 27.41, 27.48, 34.07, 35.06, 36.11, 38.52, 55.02, 77.65, 173.22; IR (KBr) 3301, 3219, 2915, 2847, 1754, 1694, 1168 cm^{-1}. Anal.Calcd for $C_{10}H_{17}NO_2$: C, 65.54, H, 9.35, N, 7.64. Found: C, 65.72, H, 9.46, N, 7.42.

(3*R*,4*S*)-4-cyclohexyl-3-hydroxy-2-azetidinone (3e): A suspension of 500 mg (3.06 mmol) of 4-phenyl-3-hydroxy-2-azetidinone **1a** and 15 mg of Rh-C in 10 mL of methanol was heated at 90°C under 800 psi in an autoclave. After 5 days, the hydrogen pressure was released and the catalyst filtrated on celite. Evaporation of the solvent afforded a solid which was recrystallized in ethyl acetate to give 440 mg (85%) of **3e** as a white solid: White solid; mp 140-140.5°C; $[\alpha]_D^{20}$ + 65.1° (c 0.66, CH_3OH); ^1H NMR (250

MHz, MeOH-d_4) δ 0.75-1.10 (m, 2H), 1.12-1.35 (m, 3H), 1.40-2.00 (m, 6H), 3.28 (dd, J = 9.7, 4.6 Hz, 1H), 4.81 (d, J = 4.6 Hz, 1H); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.75-1.00 (m, 2H), 1.10-1.35 (m, 3H), 1.37-1.55 (m, 1H), 1.58-1.85 (m, 5H), 3.10 (dd, J = 9.6, 4.7 Hz, 1H), 4.67 (m, 1H), 5.87 (d, J = 7.8 Hz, 1H), 8.21 (bs, 1H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 25.08, 25.36, 26.07, 28.83, 29.17, 37.51, 59.04, 76.41, 170.21; IR (KBr) 3312, 3219, 2928, 1726 cm^{-1}. Anal.Calcd for $C_9H_{15}NO_2$: C, 63.88, H, 8.93, N, 8.28. Found: C, 63.70, H, 9.00, N, 8.06.

Examples 12-16

To a solution of 1.9 mmol of 3-hydroxy-4-substituted-2-azetidinone in 20 mL of THF, was added at 0°C 3.9 mmol of ethylvinylether. After 2 h, at 0°C, the reaction mixture was diluted with ether and washed with sat. $NaHCO_3$. The organic layer was dried over Na_2CO_3, filtered and concentrated to yield of 3-(1-ethoxyethoxy)-4-substituted-2-azetidinone:

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-phenyl-2-azetidinone (4a): 100%; white solid; mp 78-80°C; ^{1}H NMR ($CDCl_3$) δ [0.98 (d, J = 5.4 Hz), 1.05 (d, J = 5.4 Hz), 3H], [1.11 (t, J = 7.1 Hz), 1.12 (t, J = 7.1 Hz), 3H], [3.16-3.26 (m), 3.31-3.42 (m), 3.59-3.69 (m), 2H], [4.47 (q, J=5.4 Hz), 4.68 (q, J = 5.4 Hz), 1H], [4.82 (d, J = 4.7 Hz), 4.85 (d, J = 4.7 Hz), 1H], 5.17-5.21 (m, 1H), 6.42 (bd, 1H), 7.35 (m, 5H); IR (KBr) 3214, 2983, 2933, 1753, 1718, 1456 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.46; H, 7.11; N, 5.88.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(2-phenylethenyl)-2-azetidinone (4b): 98%; white solid; mp 98-99°C; ^{1}H NMR

(300 MHz, $CDCl_3$) δ [1.17 (t, J = 7.1 Hz), 1.18 (t, J = 7.1 Hz), 3H], [1.26 (d, J = 5.4 Hz), 1.35 (d, J = 5.4 Hz), 3H], [3.44-3.52 (m), 3.60-3.68 (m), 3.75-3.82 (m), 2H], 4.41 (dd, J = 4.9, 8.5 Hz, 1H), [4.81 (q, J = 5.4 Hz), 4.90 (q, J = 5.4 Hz), 1H], [5.11 (d, J = 4.9 Hz), 5.12 (d, J = 4.9 Hz), 1H], 6.01 (bs, 1H), [6.27 (dd, J = 8.5, 15.9 Hz), 6.28 (dd, J = 8.5, 15.9 Hz), 1H], [6.61 (d, J = 15.9 Hz), 6.63 (d, J = 15.9 Hz), 1H], 7.27-7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.04, 20.37, 20.42, 57.22, 57.81, 61.23, 62.22, 78.77, 79.29, 99.50, 99.82, 125.56, 125.79, 126.59, 128.12, 128.65, 134.47, 134.58, 136.15, 168.59, 168.77; IR (KBr) 3310, 3030, 2963, 1770 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.13; H, 7.44; N, 5.16.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(2-methylpropyl)-2-azetidinone (4c): 100%; colorless oil: $[\alpha]D^{20}$ +20.93° (c 1.72, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H), [1.29 (d, J = 5.3 Hz), 1.34 (d, J = 5.3 Hz), 3H], 1.46 (m, 2H), 1.62 (m, 1H), [3.49 (m), 3.69 (m), 2H)], 3.80 (m, 1H), [4.79 (q, J = 5.4 Hz), 4.90 (q, J = 5,4 Hz), 1H], 4.87 (m, 1H), 6.78 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.08, 20.42, (21.98, 22.06), (23.15, 23.22), 25.35, (39.01, 39.10), (53.35, 53.69), (61.24, 62.24), (77.79, 77.92), (99.75, 100.05), (169.56, 169.65); IR (neat) 3269, 2956, 2871, 1758, 1468, 1382, 1340, 1152, 1115, 1083, 1052, 936, 893 cm^{-1}.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-3-(1-ethoxyethoxy)-2-azetidinone (4d): 100%; colorless oil; $[\alpha]D^{20}$ + 10.92° (c 1.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84-1.71 (m, 13H), 1.16 (t, J = 7.0 Hz, 3H), [1.28 (d, J = 5.3 Hz), 1.33 (d, J = 5.3 Hz), 3H], 3.48 (m, 1H), [3.72 (m), 3.8 (m), 2H], [4.78 (q, J = 5.4 Hz), 4.85 (q, J=5.4 Hz), 1H],

4.82 (m, 1H), 6.76 (bs, 1H); ^{13}C NMR (75 MHz, CDC_{13}) δ 14.37, 19.72, 25.30, 25.44, 25.63, (32.02, 32.13), (33.09, 33.17), (34.03, 34.07), (36.98, 37.07), (52.15, 52.49), (60.49, 61.52), (75.97, 76.39), (99.00, 99.35), (168.98, 169.05); IR (neat) 3278, 2924, 2852, 1758, 1448, 1382, 1150, 1114, 1086, 938, 886 cm^{-1}. Anal. Calcd for $C_{14}H_{25}NO_3$: C,65.85; H, 9.87; N, 5.49. Found: C, 66.03; H, 9.71; N, 5.30.

(3*R*,4*S*)-4-Cyclohexyl-3-(1-ethoxyethoxy)- 2-azetidinone (4e): 100%; white solid; mp 87-89°C; $[\alpha]_D^{20}$ + 83° (c 0.76, CH_3OH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.84 (m, 2H), 1.07-1.34 (m, 9H), 1.66 (m, 6H), 3.32 (m, 1H), [3.42 (q, J = 7.7 Hz), 3.54 (q, J = 7.7 Hz), 3.65 (q, J = 7.7 Hz), 3.74 (q, J = 7.7 Hz), 2H], 4.81 (m, 1H), [4.80 (m), 4.90 (q, J = 5.2 Hz), 1H], 6.92 (bs, 1H); IR ($CHCl_3$) 3412, 2989, 2931, 1760, 1443, 1155, 1114 cm^{-1}. Anal. Calcd for $C_{13}H_{27}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.82; H, 9.66; N, 5.64.

Examples 17-32

To a solution of 2.2 mmol of 3-(1-ethoxyethoxy)-4-substituted-2-azetidinone, 5 mg of DMAP, 4.5 mmol of triethylamine in 20 mL of dichloromethane, was added dropwise at 0°C 3.3 mmol of alkylchloroformate dissolved in 5 mL of dichloromethane. The reaction mixture was stirred overnight at room temperature. The organic layer was washed several times with brine, dried over Na_2CO_3 and concentrated. The crude solid was purified by chromatography on silica gel to yield N-protected β-lactam:

(3*R*,4*S*)-1-Methoxycarbonyl-3-(1-ethoxyethoxy)-

4-phenyl-2-azetidinone (5a): 62%; pale yellow oil; $[\alpha]D^{20}$ +98.2° (c 1.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.97 (d, J = 5.4 Hz), 1.08 (d, J = 5.4 Hz), 3H], 1.10 (bt, J = 7.3 Hz, 3H), [3.21 (dq, J = 9.5, 7.1 Hz), 3.32 (q, J = 7.1 Hz), 3.64 (dq, J = 9.5, 7.1 Hz), 2H], [3.76 (s), 3.77 (s), 3H], [4.48 (q, J = 5.4 Hz), 4.69 (q, J = 5.4 Hz), 1H], [5.11 (d, J = 5.9 Hz), 5.14 (d, J = 5.9 Hz), 1H], 5.23 (d, J = 5.9 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.96, 15.07), (19.84, 20.69), 53.59, (60.74, 62.36), (61.14, 61.92), (76.21, 77.21), (99.16, 99.56), (127.73, 128.03, 128.31, 128.36, 128.62, 128.85), (133.41, 133.58), (149.51, 149.57), (165.21, 165.67); IR (neat) 3033, 2979, 2957, 1821, 1738, 1654, 1440, 1336, 1101 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.55; H, 6.51; N, 4.90.

(3*R*,4*S*)-1-Ethoxycarbonyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (5b): 82%; colorless oil; $[\alpha]D^{20}$ +100.9° (c 1.08, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.95 (d, J = 5.4 Hz), 1.06 (d, J = 5.4 Hz), 3H], 1.08 (bt, J = 7.3 Hz, 3H), [1.19 (t, J = 7.1 Hz), 1.20 (t, J = 7.1 Hz), 3H], [3.20 (dq, J = 9.4, 7.1 Hz), 3.31 (q, J = 7.1 Hz), 3.32 (q, J = 7.1 Hz), 3.63 (dq, J = 9.4, 7.1 Hz), 2H], [4.18 (q, J = 7.1 Hz), 4.19 (q, J = 7.1 Hz), 2H], [4.47 (q, J = 5.4 Hz), 4.67 (q, J = 5.4 Hz), 1H], [5.09 (d, J = 5.8 Hz), 5.13 (d, J = 5.8 Hz), 1H], 5.21 (d, J = 5.8 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.14, (14.95, 15.07), (19.86, 20.05), (60.76, 62.35), 62.36, (61.14, 61.90), (76.18, 77.20), (99.17, 99.53), (127.73, 128.02, 128.25, 128.30, 128.50, 128.63), (133.59, 133.77), (148.99, 149.05), (165.33, 165.79); IR (neat) 2978, 2934, 1814, 1731, 1646, 1540, 1456, 1323, 1175, 1096 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.45; H, 6.63; N, 4.83.

(3*R*,4*S*)-1-*n*-Butoxycarbonyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (5c): 83%; colorless oil; $[\alpha]D^{20}$ +70.4° (c 1.25, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.79 (t, J = 7.3 Hz, 3H), [0.94 (d, J = 5.1 Hz), 1.07 (d, J = 5.1 Hz), 3H], 1.07 (t, J = 7.4 Hz, 3H), 1.20 (m, 2H), 1.51 (quint, J = 6.7 Hz, 2H), [3.21 (m), 3.30 (q, J = 7.1 Hz), 3.61 (m), 2H], 4.09 (m, 2H), [4.46 (q, J = 5.2 Hz), 4.66 (q, J = 5.2 Hz), 1H], [5.07 (d, J = 5.8 Hz), 5.11 (d, J = 5.8 Hz), 1H], 5.19 (d, J = 5.8 Hz, 1H), 7.28 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.50, (14.95, 15.29), 18.71, (19.84, 20.05), 30.42, (60.77, 62.33), (61.25, 62.02), 66.51, (76.24, 77.26), (99.17, 99.52), (127.76, 128.03, 128.22, 128.27, 128.50, 128.60), (133.61, 133.80), (148.96, 149.02), (165.40, 165.85); IR (neat) 2961, 2933, 1817, 1732, 1653, 1456, 1394, 1250, 1099 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.44; H, 7.57; N, 4.24.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (5d): 83%; white solid; mp 90-91°C; $[\alpha]D^{20}$ +70.4° (c 1.25, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.96 (d, J = 5.4 Hz), 1.08 (d, J = 5.4 Hz), 3H], [1.09 (t, J = 7.0 Hz), 1.10 (t, J = 7.0 Hz), 3H], [1.36 (s), 1.37 (s), 9H], [3.23 (dq, J = 9.5, 7.1 Hz), 3.32 (q, J = 7.1 Hz), 3.65 (dq, J = 9.5, 7.1 Hz), 2H], [4.48 (q, J = 5.4 Hz), 4.69 (q, J = 5.4 Hz), 1H], [5.03 (d, J = 5.8 Hz), 5.07 (d, J = 5.8 Hz), 1H], 5.18 (d, J = 5.8 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.98, 15.08), (19.89, 20.10), 27.84, (60.74, 62.32), (61.28, 62.08), (75.91, 76.54), 83.48 (99.10, 99.41), (127.76, 128.07, 128.20, 128.42, 128.85), (133.98, 134.16), 147.56, (165.61, 166.04); IR ($CHCl_3$) 3025, 2982, 2932, 1809, 1725, 1601, 1497, 1331, 1256, 1152 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.50; H, 7.41; N, 4.17.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-phenoxycarbonyl-4-phenyl-2-azetidinone (5e): 79%; white solid; mp 50-52°C; $[\alpha]D^{20}$ +64.9° (c 0.94, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [1.00 (d, J = 5.3 Hz), 1.11 (m), 3H], [1.14 (m), 3H], [3.27 (m), 3.35 (q, J = 7.1 Hz), 3.70 (m), 2H], [4.54 (q, J = 5.3 Hz), 4.74 (q, J = 5.3 Hz), 1H], [5.25 (d, J = 5.8 Hz), 5.29 (d, J = 5.8 Hz), 1H], 5.34 (d, J = 5.8 Hz, 1H), 7.03-7.39 (m, 10H); IR ($CHCl_3$) 3028, 2981, 2934, 1815, 1744, 1591, 1486, 1327, 1192 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.33; H, 6.06; N, 3.75.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-phenyl-1-phenylmethoxycarbonyl-2-azetidinone (5f): 44%; white solid; mp 58-60°C; $[\alpha]D^{20}$ +91.4° (c 1.16, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.97 (d, J = 5.3 Hz), 1.09 (d, J = 5.3 Hz), 3H], [1.10 (t, J = 7.0 Hz), 1.11 (t, J = 7.0 Hz), 3H], [3.23 (dq, J = 9.5, 7.1 Hz), 3.33 (q, J = 7.1 Hz), 3.66 (dq, J = 9.5, 7.1 Hz), 2H], [4.50 (q, J = 5.4 Hz), 4.70 (q, J = 5.4 Hz), 1H], [5.13 (d, J = 5.6 Hz), 5.15 (d, J = 5.6 Hz), 1H], [5.19 (s), 5.20 (s), 2H], 5.23 (d, J = 5.6 Hz, 1H), 7.21 (m, 2H), 7.26-7.37 (m, 8H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.99, 15.10), (19.90, 20.10), (60.83, 62.41), (61.64, 62.14), 68.01, (76.31, 77.28), (99.19, 99.53), (127.37, 127.86, 128.07, 128.16, 128.36, 128.52, 128.63, 128.85), (133.49, 133.68), 134.89, (148.72, 148.78), (165.37, 165.81); IR ($CHCl_3$) 3028, 2981, 2934, 1815, 1733, 1604, 1450, 1380, 1004 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.07; H, 6.43; N, 3.72.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-4-cyclohexyl-3-(1-ethoxyethoxy)-2-azetidinone (5g): 91%; colorless oil; $[\alpha]_D^{20}$ +62.5° (c 1.12, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.10-1.28 (m, 6H), 1.15 (t, J = 7.0 Hz, 3H), [1.27 (d, J =

5.4 Hz), 1.31 (d, J = 5.4 Hz), 3H], [1.45 (s), 1.46 (s), 9H], 1.63-1.70 (m, 5H), [3.43 (dq, J = 9.2, 7.0 Hz), 3.62 (m), 3.75 (d, J = 7.0 Hz), 3.78 (d, J = 7.0 Hz), 2H], 3.85 (t, J = 6.1 Hz, 1H), [4.78 (q, J = 5.4 Hz), 4.88 (m), 1H], [4.85 (d, J = 6.1 Hz), 4.86 (d, J = 6.1 Hz), 1H]; ^{13}C NMR (63 MHz, $CDCl_3$) δ 15.07, (20.25, 20.37), (26.05, 26.14), 26.26, (27.33, 27.95), (29.05, 29.20), (30.04, 30.23), (37.54, 37.64), (61.19, 62.53), (62.06, 62.32), (75.42, 75.85), 83.06, 100.11, 148.72, (166.70, 166.76); IR (neat) 2980, 2931, 2854, 1807, 1725, 1450, 1370, 1329, 1212, 1118 cm^{-1}. Anal. Calcd for $C_{18}H_{31}NO_5$: C, 63.32; H, 9.15; N, 4.10. Found: C, 63.15; H, 8.97; N, 3.96.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-(1-ethoxy ethoxy)-4-(2-phenylethenyl)-2-azetidinone (5h): 86%; white solid; mp 69-73°C; ^1H NMR (300 MHz, $CDCl_3$) δ [1.16 (t, J = 7.1 Hz), 1.18 (t, J = 7.1 Hz), 3H], [1.25 (d, J = 5.4 Hz), 1.36 (d, J = 5.4 Hz), 3H], 1.48 (s, 9 H), [3.47 (m), 3.62 (m), 3.80 (m), 2H], 4.68 (dd, J = 5.8, 8.8 Hz, 1H), [4.82 (q, J = 5.4 Hz), 4.91 (q, 5.4 Hz), 1H], [5.09 (d, J = 5.8 Hz), 5.11 (d, J = 5.8 Hz), 1H], [6.23 (dd, J = 8.8, 15.8 Hz), 6.25 (dd, J = 8.8, 15.8 Hz), 1H], [6.72 (d, J = 15.8 Hz), 6.73 (d, J = 15.8 Hz), 1H], 7.27-7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.98, 20.31, 27.98, 60.24, 60.85, 61.46, 62.36, 63.58, 83.38, 99.63, 99.87, 122.45, 122.63, 126.69, 128.20, 128.61, 136.15, 136.34, 136.38, 147.74, 147.79, 165.33, 165.53; IR (KBr) 3027, 3020, 2984, 2933, 1809, 1723 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.60; H, 7.50; N, 3.87.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-(1-ethoxy ethoxy)-4-(2-methylpropyl)-2-azetidinone (5i): 80%; yellow oil; $[\alpha]D^{20}$ +77.45° (c 0.216, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 5.7 Hz, 6H), 1.41 (t, J = 7.1

Hz, 3H), [1.25 (d, J = 5.3 Hz), 1.31 (d, J = 5.3 Hz), 3H], 1.45 (s, 9H), 1.51-1.67 (m, 3H), [3.48 (dq, J = 9.3, 7.1 Hz), 3.55-3.71 (m, 1H), 3.80 (dq, J = 9.3, 7.1 Hz), 2H], 4.08 (q, J = 6.1 Hz, 1H), [4.70 (q, J = 5.3 Hz), 4.90 (q, J = 5.3 Hz), 1H], 4.85 (d, J = 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.95, (20.11, 20.28), (22.42, 22.59), 22.70, (24.89, 25.07), 27.83, (37.03, 37.31), (56.14, 56.38), (61.07, 62.27), (75.65, 75.92), 82.98, 99.91, 148.1, (166.1, 165.9); IR (neat) 2931, 2960, 2872, (1790, 1807), (1708, 1726), (1454, 1465), 1332, 1256, 1048, 1158, 996, 955, 857, 834, 770 cm^{-1}. Anal. Calcd for $C_{16}H_{26}NO_5$: C, 60.93; H, 9.27; N, 4.44. Found: C, 61.19; H, 9.41; N, 4.37.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-4-cyclohexyl methyl-3-(1-ethoxyethoxy)-2-azetidinone (5j): 93%; yellow oil; $[\alpha]D^{20}$ +75.64° (c 0.78, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.81-1.74 (m, 13H), 1.19 (t, J = 7.1 Hz, 3H), 1.48 (s, 9H), [1.30 (d, J = 5.3 Hz), 1.35 (d, J = 5.3 Hz), 3H], [3.45 (dq, J = 9.3, 7.1 Hz), 3.62-3.71 (m), 3.78 (dq, J = 9.3, 7.1Hz), 2H], 4.01 (m, 1H), [4.81 (q, J = 5.3 Hz), 4.91 (q, J = 5.3 Hz), 1H], [4.86 (d, J = 6.1 Hz), 4.87 (d, J = 6.1 Hz), 1H]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.03, 20.19, 20.36, 26.10, 26.36, 27.91, (33.17, 33.31), (33.35, 33.49), (34.33, 34.58), (35.39, 35.68), (55.77, 55.99), (61.14, 62.21), (75.74, 75.90), 82.96, (99.86, 99.95), 147.96, 166.13; IR (neat) 2979, 2923, 2850, 1719, 1807, 1449, 1336, 1154 cm^{-1}. Anal. Calcd. for $C_{19}H_{33}NO_5$: C, 64.20; H, 9.36; N,3.94. Found: C, 64.00; H, 9.17; N, 4.02.

Examples 28-32

To a solution of 0.5 mmol of 3-(1-ethoxyethoxy)-4-phenyl-

2-azetidinone in 6 mL of tetrahydrofuran, was added dropwise at -78°C 0.6 mmol of n-BuLi. After 5 min, 1 mmol of an isocyanate or an isothiocyanate was added. The reaction mixture was stirred 30 min at -78°C and quenched by addition of 2 mL sat. NH_4Cl solution. The reaction mixture was diluted with 30 mL of ether and the organic layer was washed several times with brine, dried over Na_2CO_3 and concentrated. The crude solid was purified by chromatography on silica gel to yield N-protected β-lactam:

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-phenylcarbamoyl-4-phenyl-2-azetidinone (7a): 66%; pale yellow solid; mp 152-155°C; $[\alpha]D^{20}$ +87.8° (c 0.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [1.07 (d, J = 5.4 Hz), 1.13 (d, J = 5.4 Hz), 3H], 1.16 (t, J = 7.1 Hz, 3H), [3.26 (dq, J = 9.5, 7.1 Hz), 3.37 (q, J = 7.1 Hz), 3.39 (q, J = 7.1Hz), 3.67 (dq, J = 9.5, 7.1 Hz), 2H], [4.53 (q, J = 5.4 Hz), 4.72 (q, J = 5.4 Hz), 1H], 5.28 (m, 2H), [6.59 (bs), 6.60 (bs), 1H], 7.10-7.55 (m, 10H), 8.68 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (15.04, 15.16), (19.98, 20.11), (60.99, 62.53), 61.80, (76.05, 76.66), (99.34, 99.70), (119.63, 120.69, 124.37, 127.67, 127.95, 128.40, 128.45, 128.67, 128.85, 129.04, 129.12, 130.49), 133.48, (137.03, 137.28), (147.23, 147.29), (168.12, 168.52); IR ($CHCl_3$) 3342, 3017, 2982, 2932, 1773, 1719, 1602, 1548, 1445, 1312, 1224, 1210 cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.92; H, 5.98; N, 8.17.

(3*R*,4*S*)-1-*tert*-Butylcarbamoyl-3-(1-ethoxy ethoxy)-4-phenyl-2-azetidinone (7b): 74%; pale yellow viscous oil; $[\alpha]D^{20}$ +144.3° (c 0.7, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.96 (d, J = 5.3 Hz), 1.05 (d, J = 5.3 Hz), 3H], 1.10 (t, J = 7.1 Hz, 3H), [1.33 (s), 1.34 (s), 9H], [3.21 (dq, J = 9.3, 7.0 Hz), 3.30 (q, J = 7.0 Hz), 3.33

(q, J = 7.1Hz), 3.62 (dq, J = 9.1, 7.0 Hz), 2H], [4.46 (q, J = 5.4 Hz), 4.66 (q, J = 5.4 Hz), 1H], 5.10-5.19 (m, 2H), [6.59 (bs), 6.60 (bs), 1H], 7.23-7.36 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.86, 14.99), (19.75, 19.95), (28.81, 29.30), (60.62, 61.20), (60.80, 62.29), (75.57, 76.76), (98.91, 99.34), (127.07, 127.40, 127.70, 128.17, 128.29, 128.53), (133.71, 133.86), (148.54, 148.59), (167.67, 168.13); IR ($CHCl_3$) 3362, 3035, 2977, 2932, 1767, 1710, 1605, 1537, 1457, 1366, 1320, 1282, 1217, 1100 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.46; H, 7.75; N, 8.39.

(3*R*,4*S*)-1-Benzylcarbamoyl-3-(1-ethoxy ethoxy)-4-phenyl-2-azetidinone (7c): 50%; pale yellow viscous oil; $[\alpha]D^{20}$ +66.2° (c 0.8, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.99 (d, J = 5.5 Hz), 1.08 (d, J = 5.5 Hz), 3H], 1.12 (m, 3H), [3.16-3.40 (m), 3.63 (m), 2H], [4.35-4.55 (m), 4.69 (q, J = 5.5 Hz), 3H], 5.21 (m, 2H), [7.03 (bs), 7.05 (bs), 1H], 7.32 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (15.01, 15.14), (19.90, 20.11), 43.83, (60.66, 62.44), (60.75, 61.54), (75.93, 77.04), (99.16, 99.56), (127.25, 127.64, 127.69, 128.17, 127.93, 128.35, 128.55, 128.64, 128.74), (133.59, 133.76), 137.80, 150.02, (167.73, 168.19); IR ($CHCl_3$) 3379, 3090, 3033, 2980, 2930, 1773, 1707, 1604, 1536, 1455, 1319, 1270, 908 cm^{-1}. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.30; H, 6.66; N, 7.51.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-ethylcarbamoyl-4-phenyl-2-azetidinone (7d): 63%; pale yellow oil; $[\alpha]D^{20}$ +96.7° (c 0.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) d [0.96 (d, J = 5.3 Hz), 1.04 (d, J = 5.3 Hz), 3H], 1.05-1.18 (m, 3H), [3.13-3.39 (m), 3.59 (m), 4H], [4.45 (q, J = 5.3 Hz), 4.65 (q, J = 5.3 Hz), 1H], 5.16 (m, 2H), [6.60 (bs), 6.62 (bs), 1H], 7.27 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.98, (19.84,

29.93), 34.79, (60.56, 61.35), (60.72, 62.35), (75.91, 77.03), (99.14, 99.54), (127.28, 127.55, 127.85, 128.27, 128.40), (133.74, 133.89), (149.87, 149.93), (167.62, 168.07); IR ($CHCl_3$) 3378, 3035, 2980, 2934, 1774, 1704, 1537, 1455, 1321, 1271, 1112, 1025 cm^{-1}.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-phenylthio carbamoyl-4-phenyl-2-azetidinone (7e): 82%; yellow solid; mp 108-112°C; $[\alpha]D^{20}$ +68° (c 1.14, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [1.02 (d, J = 5.5 Hz), 1.11 (d, J = 5.5 Hz), 3H], 1.16 (t, J = 7.3 Hz, 3H), [3.20-3.44 (m), 3.66 (dq, J = 9.4, 7.3 Hz), 2H], [4.52 (q, J = 5.5 Hz), 4.72 (q, J = 5.5 Hz), 1H], [5.30 (d, J = 5.5 Hz), 5.32 (d, J = 5.5 Hz), 1H], [5.49 (d, J = 5.5 Hz), 5.52 (d, J = 5.5 Hz), 1H], 7.36 (m, 8H), 7.67 (d, J = 7.8 Hz, 2H), 10.37 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (15.04, 15.17), (19.95, 20.13), (60.96, 62.57), (63.92, 64.75), (74.75, 75.84), (99.34, 99.68), (123.43, 126.58, 127.91, 128.28, 128.49, 128.86, 128.91), (133.10, 133.25), (137.36), (166.55, 166.52), (174.812); IR ($CHCl_3$) 3288, 3024, 2983, 1760, 1497, 1385, 1222 cm^{-1}.

Examples 33-34

(3*R*,4*S*) -1-Morpholinecarbonyl-3-(-1-ethoxyethoxy)-4-phenyl-2-azetidinone (7f): To a solution of 30 mg (0.13 mmol) of 3-(1-ethoxyethoxy)-4-phenyl-2-azedinone 6 in 2 mL of CH_2Cl_2, 2 mg of DMAP and 0.05 mL of triethylamine was added at room temperature. After 5 min. 22.9 mg (0.15 mmol) of morpholinecarbonyl chloride was added. The reaction mixture was stirred for 2h at room temperature. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and the organic layer was washed two times with brine, dried over Na_2CO_3 and concentrated. The crude solid product was purified by chromatography on silica gel to yield pure 7f: 87%; pale yellow oil; ^1H NMR (250 MHz,

$CDCl_3$) δ [0.90 (d, J = 5.3 Hz), 1.01 (d, J = 5.3 Hz) (3H)], [1.04 (t, J = 7.1 Hz), 1.18 (t, J = 7.1 Hz)] (3H), 3.20 (m, 4H), [3.28 (m), 3.53 (m), 3.67 (m), (2H)], 3.60 (m, 4H), [4.41 (q, J = 5.3 Hz), 4.63 (q, J = 5.3 Hz) (1H), [5.07 (d, J = 5.8 Hz), 5.08 (d, J = 5.8 Hz) (1H), [5.29 (d, J = 5.8 Hz), 5.32 (d, J = 5.8 Hz) (1H)], 7.23-7.27 (m, 5H).

Examples 35-53

To a solution of 0.37 mmol of O-EE β-lactam in 4 mL THF was added 4 mL of 0.5 N HCl. The completion of reaction was monitored by TLC. After 1-3 hr, the reaction mixture was concentrated in vacuo to remove THF. The residue was dissolved in 30 mL ether and washed with 10 mL saturated $NaHCO_3$ solution. The ether layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 3-hydroxy β-lactam:

(3*R*,4*S*)-3-Hydroxy-1-methoxycarbonyl-4-phenyl-2-azetidinone (6a): 66%; white solid; mp ; 91-92°C $[\alpha]D^{20}$ +108° (c 0.63, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.13 (d, J = 6.0 Hz, 1H), 5.22 (d, J = 6.0 Hz, 1H), 7.25-7.42 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 53.77, 61.44, 77.33, 127.16, 128.94, 132.65, 149.20, 166.04; IR ($CHCl_3$) 3432, 3024, 2996, 1806, 1730, 1440, 1333, 1188 cm^{-1}. MS(FAB) m/z (%) 222 (M+1, 38), 194(29), 164(100).

(3*R*,4*S*)-1-Ethoxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6b): 59%; white solid; mp 112-113°C; $[\alpha]D^{20}$ +181° (c 0.97, CHCl3); ^1H NMR (250 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 4.25 (q, J = 7.1 Hz, 2H), 5.14 (d, J = 6.0 Hz, 1H), 5.22 (d, J = 6.0 Hz, 1H), 7.27-7.39 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.08, 61.36, 63.00, 77.26, 127.08, 128.83, 132.75, 149.08, 165.79; IR ($CHCl_3$)

3605, 3017, 2985, 1815, 1732, 1684, 1396, 1373, 1268, 1020 cm^{-1}; MS (FAB) m/z (%) 236 (M+1,98), 208(23), 178(100).

(3*R*,4*S*)-1-*n*-Butoxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6c): 69%; white solid; mp 88-89°C; $[\alpha]D^{20}$ +159.1° (c 0.71, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.78 (t, J = 7.3 Hz, 3H), 1.14 (m, 2H), 1.50 (m, 2H), [4.07 (q, J = 8.9 Hz), 4.10 (q, J = 8.9 Hz), 2H), 5.05 (d, J = 5.9 Hz, 1H), 5.11 (d, J = 5.9 Hz, 1H), 7.22-7.36 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.44, 18.71, 30.44, 61.54, 66.72, 77.31, 127.21, 128.80, 132.89, 149.15, 166.06; IR ($CHCl_3$) 3562, 3018, 2962, 1813, 1730, 1456, 1395, 1324, 1222, 1099 cm^{-1}. MS (FAB) m/z (%) 264(M+1,62), 236(20), 208(40), 206(100).

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6d): 88%; white solid; mp 131.5-132°C; $[\alpha]D^{20}$ +173.5° (c 0.98, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.70 (bs, 1H), 5.08 (d, J = 5.9 Hz, 1H), 5.14 (d, J = 5.9 Hz, 1H), 7.27 (d, J = 6.1 Hz, 2H), 7.38 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.87, 61.56, 77.00, 83.85, 127.20, 128.77, 128.82, 133.13, 147.72, 169.49; IR ($CHCl_3$) 3616, 3019, 2976, 1807, 1726, 1601, 1522, 1422, 1333, 1212, 1152 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.71; H, 6.38; N, 5.12.

(3*R*,4*S*)-3-Hydroxy-1-phenoxycarbonyl-4-phenyl-2-azetidinone (6e): 72%; white solid; mp 125-126°C; $[\alpha]D^{20}$ +107° (c 1.45, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.21 (d, J = 6.1 Hz, 1H), 5.34 (d, J = 6.1 Hz, 1H), 7.07-7.45 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 61.83, 73.24, 121.15, 125.46, 126.80, 127.22, 128.09, 128.80, 129.11, 129.30, 132.40, 138.49, 154.05; IR ($CHCl_3$) 3615, 3020, 2976, 1821, 1740, 1506, 1487, 1332, 1219 cm^{-1}.

(3*R*,4*S*)-1-Benzyloxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6f): 85%; white solid; mp 105-106°C; $[\alpha]D^{20}$ +177° (c 0.6, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.12 (d, J = 6.2 Hz, 1H), 5.22 (m, 3H), 7.24-7.40 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 61.53, 68.30, 77.43, 127.19, 128.13, 128.58, 129.06, 132.55, 134.74, 148.90, 165.92; IR ($CHCl_3$) 3557, 3018, 2924, 1814, 1731, 1383, 1273, 1162, 1004 cm^{-1}. MS (FAB) m/z (%) 298(M+1,14), 273(4).

(3*R*,4*S*)-1-tert-Butoxycarbonyl-4-cyclohexyl-3-hydroxy-2-azetidinone (6g): 96%; white solid; mp 121-122°C; $[\alpha]D^{20}$+78° (c 0.68, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.17-1.75 (m, 11H), 1.48 (s, 9H), 3.83 (t, J+6.5 Hz, 1H), 4.96 (d, J=6.5 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.87, 25.99, 26.24, 27.96, 29.69, 29.90, 37.45, 63.30, 75.24, 83.43, 148.80, 168.60; IR ($CHCl_3$) 3354, 2931, 2848, 1801, 1724, 1324, 1154 cm^{-1}.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-4-(2-phenylethenyl)-2-azetidinone (6h): 96%; white solid; mp 132-133°C; $[\alpha]D^{20}$ +122.0° (c 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 3.88 (bs, 1H), 4.71 (dd, J = 4.8, 8.0 Hz, 1H), 5.07 (d, J = 4.8 Hz, 1H), 6.26 (dd, J = 8.0, 15.9 Hz, 1H), 6.72 (d, J = 15.9 Hz, 1H), 7.24-7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.94, 60.78, 76.58, 83.77, 121.41, 126.75, 128.26, 128.59, 135.94, 136.62, 147.85, 166.95; IR (KBr) 3242, 3039, 2954, 1812, 1726 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.31; H, 6.71; N, 4.76.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-4-(2-methylpropyl)-2-azetidinone (6i): 98%; pale yellow solid; mp 108°C; $[\alpha]D^{20}$ +76.14° (c 0.88, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.3 Hz, 6H), 1.48 (s, 9H),