Contents

Water-Solubilization by Using Symmetrically Branched Oligoglycerol Trimers

Abstract

As a water-solubilizing fragment, branched glycerol trimer (BGL003) has been conjugated here with several lipophilic molecules to increase the hydrophilicity.

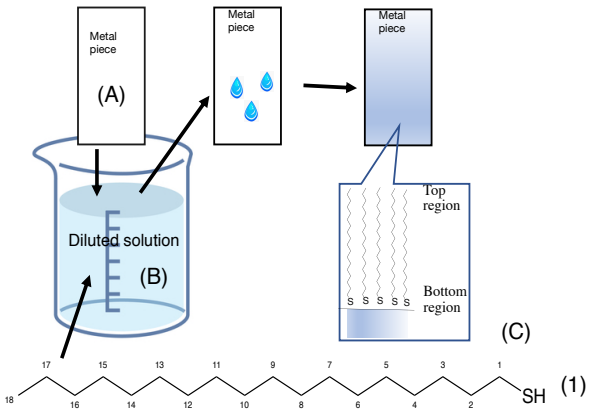
Alkanethiols have been chemically modified by BGL003 to develop a lipophilic-thiolate-chemisorbed "Self-assembled Monolayers" (SAM) on metal surface in an aqueous solution. Octadecanethiol (ODT) which is used with organic solvent for depositing a molecular layer on the expensive metal surfaces. Herein, lipophilic thiols have been connected with BGL003 through succinyl residue and converted to a water-soluble derivative. The chemically modified octadecanethiol derivative has been applied for novel transition metal coating in water and the anticorrosive effect of metal piece was as high as with lipophilic thiol in organic solvent. Thus, an environmentally friendly coating method has been established from this project.

Next, a couple of branched glycerol trimers with new apex were synthesized. Using *N*-acyl tyrosine methylamide as a smallest model of peptides and SN38 as an antineoplastic drug, the new BGL003 was connected with side chain of tyrosine and A-ring of SN38, respectively, via one additional linker molecule. Paclitaxel and docetaxel are also a chemotherapy medication and another new BGL003 has been conjugated with 3′-debenzoylated paclitaxel and 3′-de(*tert*-butyloxycarbonyl) docetaxel, respectively, without any linker molecule. I believe these BGL003 modified drugs will be more hydrophilic and increase absorption amount in the human body. The efficiency (*in vitro and in vivo*) of these modified drugs will be tested later on.

Chapter 1. Water-Solubilization of Alkanethiol

Introduction

The surface properties of metals and metal oxides can be altered by adding a single layer of organic molecules. A most widespread route for depositing such a molecular layer is via the formation of self-assembled monolayers (SAMs). Since Nuzzo *et al.* found the disulfide adsorption on a gold surface [1], a lipophilic organothiol (RSH) has been often used as an anticorrosive for metal [2]. Among various RSH, octadecane-1-thiol (**1**) has been one of the most representative chemicals [3] (**Scheme 1**). A target such as a piece of metal (**A**), is dipped into a diluted solution of **1** (**B**). During this operation, a strong coordination is generated between zero-valent metal surface and the thiolate generated from **1** to afford "self-assembled monolayers" (SAM) [3], as shown in (**C**). No further layers are assembled on the surface of metal after the SAM is created, because the top region shown in (**C**) is occupied with only chemically inert alkyl chains, which can generate no strong chemical bond such as covalent, ionic or dipole moment interaction. Accordingly, a very thin and stable coating completes via the simple procedure illustrated in **Scheme 1**. Due to such a thin layer, electroconductivity of the target metal is often retained after the coating procedure, in general. In contrast, required property of rust anticorrosive is often satisfied, in spite of such a thin layer [3].



Scheme 1. Major coating procedure by using octadecane-1-thiol (**1**).

Due to high lipophilicity of **1**, organic solvents*, a lipophilic and volatile liquid,* has been required for the coating procedure. If such an organic solvent could be displaced to water, it would be *environmentally friendly*. In addition, total cost, including purchased price and waste

disposal costs, would be reduced, because the solute occupies major weight and volume of the commercial package such as (**B**). However, RSH possessing a long hydrocarbon chain is extremely insoluble in water. Although it has been reported that a large amount of surfactant was used to prepare a micellar solution [4], it means a top priority backwards since surfactant often facilitates rust.

Although a commercially available water-affinitive RSH such as oligoethylene-alkanethiols (**2**) [5–7] can be an alternative idea, property of the top region with **2** can be totally different from that with **1** (**Fig 1**). Accordingly, **2** can be incompatible to lipophilic thiol and use of organic solvent has been indispensable for lipophilic thiolate coating.

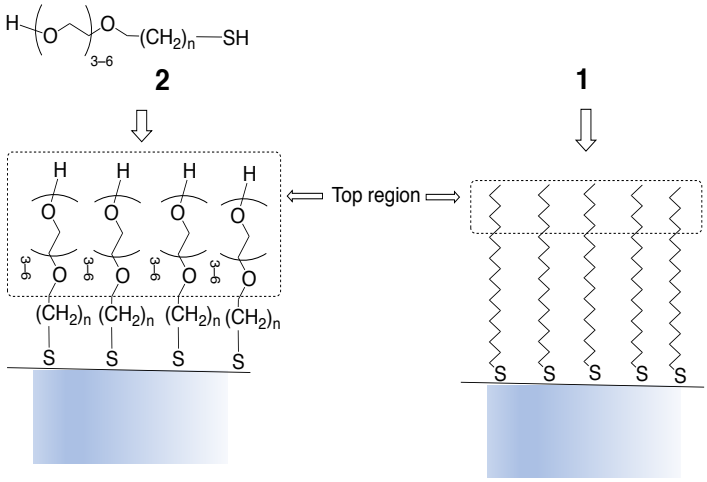
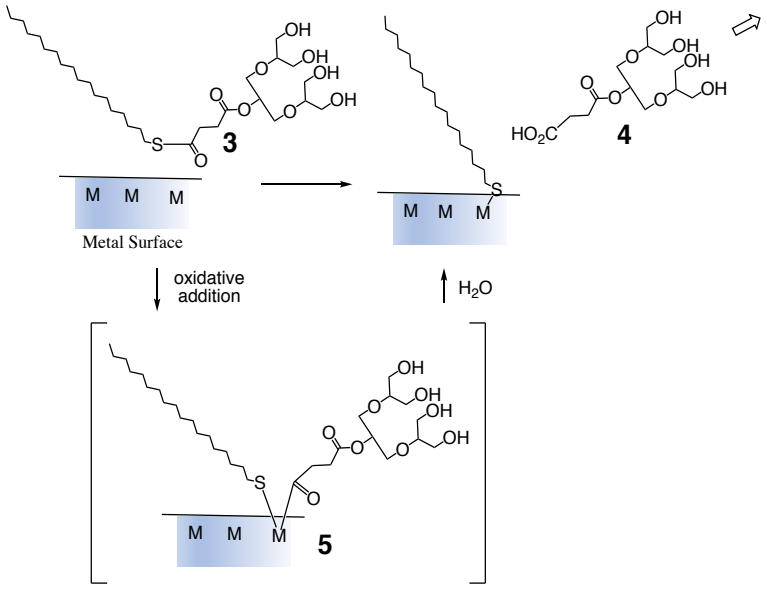


Figure 1. Comparison between **1** and a commercially available water-affinitive thiol **2** after coating procedure.

In this research, I designed a preparation method of lipophilic-thiolate-chemisorbed SAM on metal ((**C**) in **Scheme 1**) *in an aqueous solution*. In this method, original lipophilic thiol was modified to a water-soluble derivative such as **3** [8] (**Scheme 2**). Due to the result in a previous paper [9], it is anticipated that the thioester moiety of **3** is cleaved to afford the corresponding oxidative adduct **5**, followed by releasing the water-solubilizing fragment **4** into an aqueous solution. The fragment **4** can be finally converted to succinic acid [10] and BGL003 [11,12] (**Fig 2**), both of which are known to have extremely low toxicity. Accordingly, the released fragment **4** is also designed to be environmentally friendly.



Scheme 2. Proposed mechanism of metal surface coating with thioester **3**.

As a water-solubilizing fragment, originally developed molecules, glycerol trimer BGL003 [13,14] and heptamer BGL007 [14] were used. Various functional groups X at apex have been used for the covalent bond formation with poorly water-soluble compounds [15–17] such as **1**. Primary hydroxy groups, four in BGL003 and eight in BGL007, respectively (terminal side of the dendric structure), have stronger water-affinitive property than another polyhydroxylated molecules such as cyclic carbohydrates, due to the high conformational flexibility and three-dimensional spread.

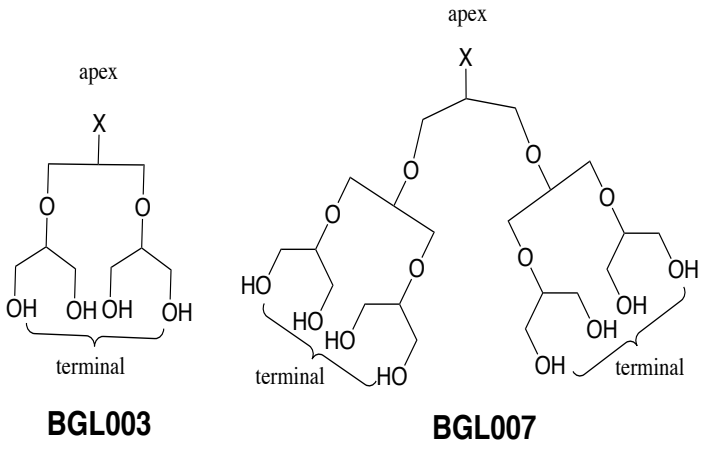
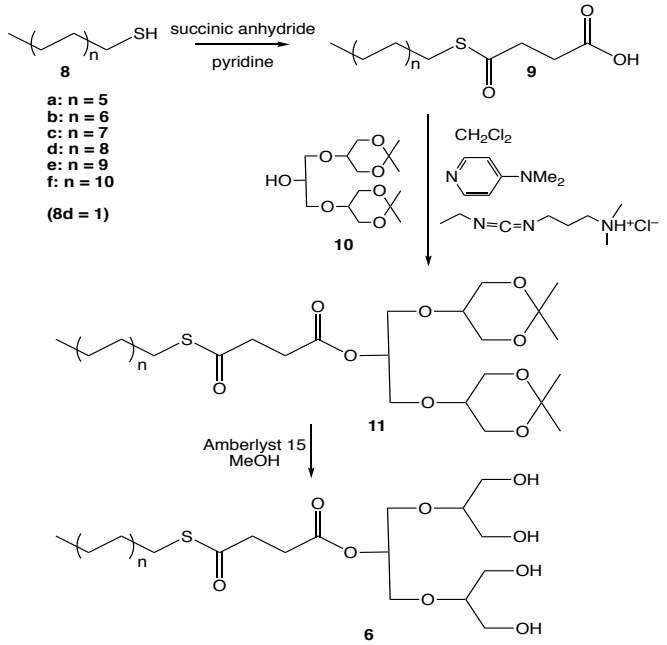


Figure 2. Originally designed symmetrically branched glycerol trimer and heptamer.

Results and Discussion

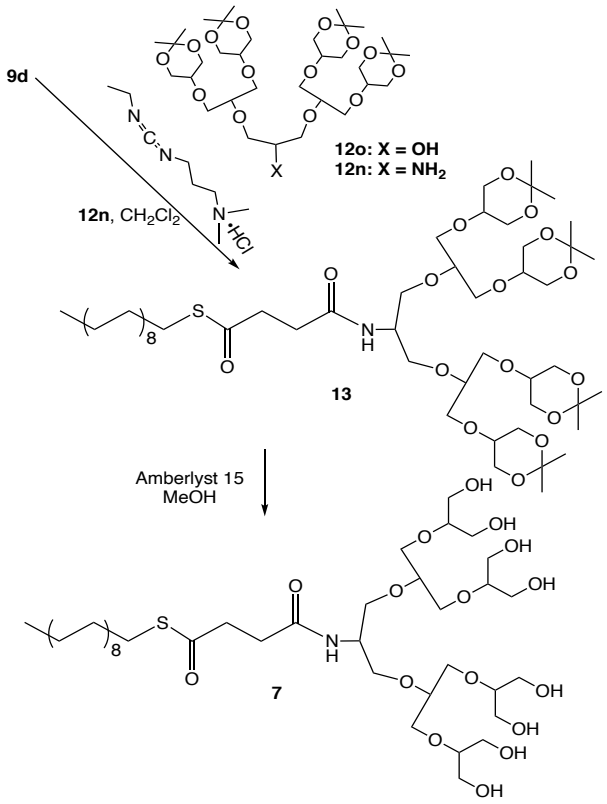
Synthesis

In Scheme 3, the detail of the synthetic procedure of **3** (=**6d**) as well as the related derivatives **6a–6c**, **6e** and **6f** has been illustrated. The reaction of **8** with succinic anhydride in pyridine afforded thioester **9** in a range of 87–96% chemical yield. Condensation between the alcohol **10**, and carboxylic acid **9** was carried out in dichloromethane with 3-(((ethylimino)methylene)amino)-*N*,*N*- dimethylpropan-1-aminium chloride (EDC•HCl) and 4-(N,N-dimethyl)pyridine (DMAP) to give the corresponding ester **11** in a range of 75–88% yield. Finally, **11** in anhydrous methanol was stirred for several hours in the presence of Amberlyst-15®, an acidic polystyrene polymer, to afford tetraol **6** in a range of 83–98% yield.



Scheme 3. Synthesis of various alkanethiol–BGL003 **6a–6f**.

Next, instead of BGL trimer **10**, condensation of BGL heptamer **12o** [14] and **9d** was examined (**Scheme 4**). However, chemical yield of the corresponding ester was extremely low with almost quantitative recovery of both **12o** and **9d**. Therefore, more nucleophilic amine **12n** [14] was used instead to afford **13** in 25% yield. This step was not further optimized, because water-solubility of smaller BGL derivative **6d** was high enough as mentioned later in this paper. Methanolic deprotection of **13** under acidic condition was carried out with Amberlyst-15® to afford octaol **7** in 93% yield.



Scheme 4. Synthesis of octadecane-1-thiol–BGL007 **7**.

Property and performance of a water-soluble thiol

Water-solubility of the final product was examined as follows. Water after distillation and deionization (50.09 g) and **6d** (0.320 g, 0.526 mmol) and was mixed. Although small drops of **6d** were visibly observed in the initial mixture, homogeneous solution was afforded after stirring for 6h at 60˚C. After the solution was cooled to room temperature, homogeneity of the solution was maintained. Accordingly, water-solubility of **6d** was recorded to be over 10.0 mmol/L with a large margin. ^{1}H NMR analysis indicated that pure **6d** was observed after the aqueous solution was stocked for three months at room temperature in a simple screw-capped plastic bottle [18].

For usual anticorrosive treatment in an organic solvent, less than 5.00 mmol/L of thiol has been usually reported [3,4]. Therefore, the prepared solution (10.0 mmol/L) was diluted with water again. By using the diluted aqueous solution of **6d**, various examinations such as observation by digital microscope, reflection of visible light (380–780 nm), measurement of the contact angle of small water-droplet, and resistance against hydrogen sulfide gas was carried out. Among these comparisons, the results with aqueous potassium sulfide solution (K_2Saq) were representatively [19] described (**Fig 3**).

Three pieces of silver-plating metal (30 mm length) were prepared from commercially available long strings (20 mm width, 0.2 mm thickness). The three pieces were washed with deionized water, and dried at 100–120˚C for 5 sec to afford **Xn**, **X1** and **X6d**. The pieces **X1** and **X6d** were dipped into **1** in ethanol (0.1 wt% = 3.50 mmol/L) [20] and **6d** in water (0.2 wt% = 3.30 mmol/L) at 55˚C for 30 sec, respectively, and washed with deionized water, and dried at 100–120˚C. No pre-treatment was carried out for **Xn**. After being cooled to room temperature, all the three pieces **Xn**, **X1** and **X6d** were soaked with K_2Saq (0.6 wt%) at 22˚C for 1 min. Then, these surfaces were washed with deionized water at 22˚C and dried at 100–120˚C for 5 sec to afford **Yn**, **Y1** and **Y6d**, respectively.

The color of **Yn** was dark yellow, which indicated the direct effect from K_2Saq. In contrast, color change from **X1** to **Y1**, as well as from **X6d** to **Y6d**, was highly suppressed. It is noteworthy that mottled pattern was partially observed in **Y1** [21] but smooth surface was observed in all the area of **Y6d**.

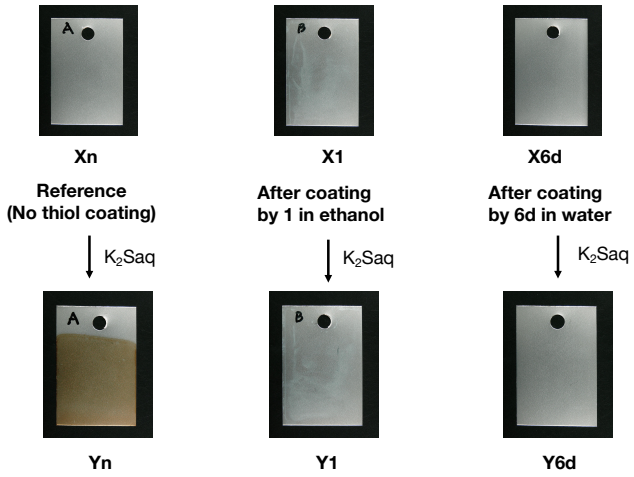


Figure 3. Color change of silver plates after aqueous K_2S (0.6 wt%) soaking.

Conclusion and perspective

In conclusion, synthesis of organothiol–BGL003 was successfully carried out within a few steps in high chemical yields. A thioester of each synthetic intermediate was stable during the following chemical reactions (carbodiimide condensation and methanolic solvolysis under acidic condition). In contrast, the thioester in the organothiol–BGL003 was probably cleaved to release original organothiol *in situ* at the metal surface. Accordingly, predictable result after coating with organothiol–BGL003 in water was as exactly same as with organothiol in organic solvent, due to the molecular design of organothiol–BGL003.

In fact, anticorrosive performance of organothiol–BGL003 in water was as high as, or slightly higher than, that of organothiol in organic solvent. I believe that the result reported in this research will solve one of the environmental problems. To deploy this result for the practical use, the synthetic process in a large scale is under optimization.

Chapter 2. Water-Solubilization of Peptide-model, SN-38 and Taxol derivatives

Introduction

As a water-solubilization fragment, branched glycerol trimer (BGL003) and heptamer (BGL007) with various apex groups (–OH, $–NH_2$) have been reported [13,14]. Earlier BGLation method in several drug molecules required the special synthetic skills, linker molecules, activating agents, and vigorous conditions [15–17]. Protected BGLs were used in the previous cases and protecting groups were necessarily deprotected after BGLation in acidic or harsh conditions. Very often, these are not practicable conditions in case of several medicinal molecules, proteins or peptides. Hence, new apex groups in BGL were searched and I designed to develop new functionality in BGL003, alkoxylamine ($–ONH_2$) and isothiocyanate (–NCS). Accordingly, herein I have developed the reagents with new apex group, branched glycerol trimer alkoxylamine (BGL003–ONH_2) and branched glycerol trimer isothiocyanate (BGL003–NCS). The advantages of these reagents from the previous BGL reagents are– (1) stable and storable for long time, (2) BGLation can be carried out in aqueous condition without dehydrating and /or activating reagent, (3) BGLation condition is around pH=7 under biologically mild temperature, and (4) BGLation is simply completed without special synthetic skill. The detail structure of BGL003–ONH_2 (**4**) and BGL003–NCS (**7**) have been shown (**Fig 1)**.

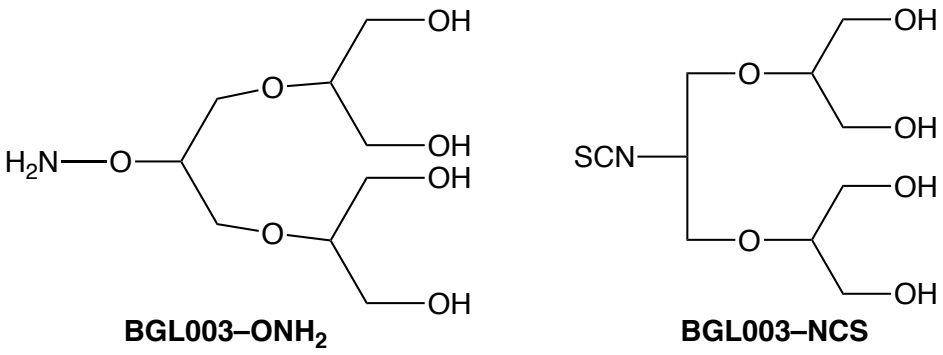


Figure 1. Branched glycerol alkoxylamine (**4**) and branched glycerol isothiocyanate (**7**).

Lipophilic-hydrophilic balance is a quite important determinant of Absorption, Distribution, Metabolism, and Excretion (ADME) properties of pharmaceuticals. For optimum ADME of a drug molecule, the use of a chemically single molecule is preferable because quality control of a single molecule is generally simple and highly reproducible. Using branched glycerol trimer

(BGL003), some medicinal molecules were converted to the corresponding water-soluble derivatives, in which water-solubility was increased 1000–5000 times [13,16,17], and molecular weight was increased only 1.5–2 times [8,16,17]. The cytotoxicity of BGL003 was evaluated and did not exhibit any significant cytotoxicity [11,12]. Consequently, BGL003 should be safe and suitable water-solubilizing fragment for hydrophobic drug molecules. In this research, I planned to conjugate branched glycerol alkoxylamine (**4**) and branched glycerol isothiocyanate (**7**) with some lipophilic molecules to enhance water-solubilization.

A tyrosine residue is expected to be a good target for protein functionalization due to having a polar phenolic hydroxyl group that is often exposed on a protein's surface [22]. Metal-free and mild tyrosine modification reactions [23–29] are an attractive alternative to the commonly used lysine and cysteine modification protocols. The high abundance of lysine in a typical protein or antibody significantly complicates control of the stoichiometry and specificity of bioconjugation reactions. Although cysteines are less abundant, but require reductive pretreatment before bioconjugation. Tyrosines are less common than lysine and do not form stabilizing linkages like cysteine. Diazonium reagents have been used for selective modification of tyrosine [23,24,30], but are often not extensively due to several limitations for the modification of proteins or antibodies. Earlier reported diazonium labeling reagents are unstable and the use of these reagents require in situ preparation just prior to use. Diazonium reagents are generally prepared in situ under strongly acidic conditions which is not feasible for the diazo coupling reaction with protein. Barbas *et al.* have developed a novel bench-stable bifunctional diazonium reagent, 4-formylbenzene diazonium hexafluorophosphate (FBDP) for selective modification of tyrosine [31]. The authors successfully connected the diazonium reagent (FBDP) with the tyrosine residue of *N*-acyl tyrosine methylamide taken as a smallest model of peptide. This reagent (FBDP) was stable, maintained excellent reactivity and selectivity after more than six months of storage at 4 ˚C under air. The modifications by this reagent was taken place rapidly at mild conditions with a high chemical yield. The authors applied this reagent (FBDP) for tyrosine-selective modification of peptides or proteins to introduce biorthogonal aldehyde tags suitable for classical oxime and hydrazide ligations (**Fig 2**). Accordingly, herein I designed to conjugate the new BGL reagent, **4** (BGL003–ONH_2) with *N*-acyl tyrosine methylamide via this additional linker molecule (FBDP).

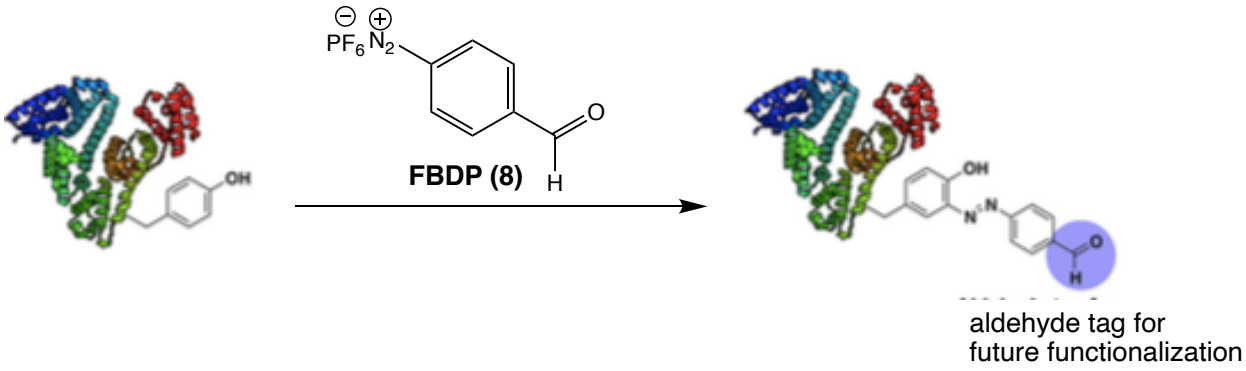


Figure 2. Selective modification of tyrosine residue in protein by FBDP.

SN-38 (7-ethyl-10-hydroxycamptothecin) is an antineoplastic drug and it is the active metabolite of irinotecan (CPT-11). It is effective against numerous malignant tumors including lung, colorectal, gastric, lymph, cervical, and ovarian cancers [32]. SN-38 is 100–1,000 times more potent than CPT-11 in terms of antitumor effect [33]. The presence of the lactone ring in SN-38 mainly influence the inhibition activity, which undergoes hydrolysis depending on pH [34,35]. The active lactone ring is stable at pH ≤ 4.5, but converts to the inactive carboxylate form completely at pH>9.0 [36]. Hence, the therapeutic effect of SN-38 reduces significantly at physiological pH (pH 7.4) [35]. In addition, it is extremely insoluble in water (11–38 μg/mL) and is poorly solubilized at 0.5% (w/w) in most physiologically compatible and pharmaceutically acceptable solvents [32,37,38]. As a result, this drug molecule cannot be administered directly and is given by slow injection into a vein. To enhance the solubility of SN-38, a variety of drug delivery systems have been extensively investigated, including polymeric implants [39], micelles [40–42], liposomes [43,44], polymeric conjugates [34,45], antibody conjugates [46] and nanoparticles [37,47]. Unfortunately, there were many limitations though these techniques enhanced the solubility. For example, low encapsulation efficiency and low drug loading [38,43], poor stability, and low final yield of polymer conjugates [48], and adverse side effects. Several studies have focused on enabling oral SN-38 delivery by synthesizing prodrugs and/ or nanomedicines; these have shown different degrees of success [49,50]. Earlier reported prodrug modifications were done through hydroxyl functionality at C20 and/ or C10 position, as a result hydroxyl functionality isn't survived (**Fig 3**). From the literature survey, no chemical modifications were performed via diazo linker with SN-38 and no SN38–BGL conjugates were known yet. Herein, I designed to connect the FBDP (**8**) reagent

at C9 position in the A-ring, so that hydroxyl functionality remain survived. Finally, the reagent, **4** (BGL003–ONH_2) were conjugated with SN-38 via this additional linker molecule.

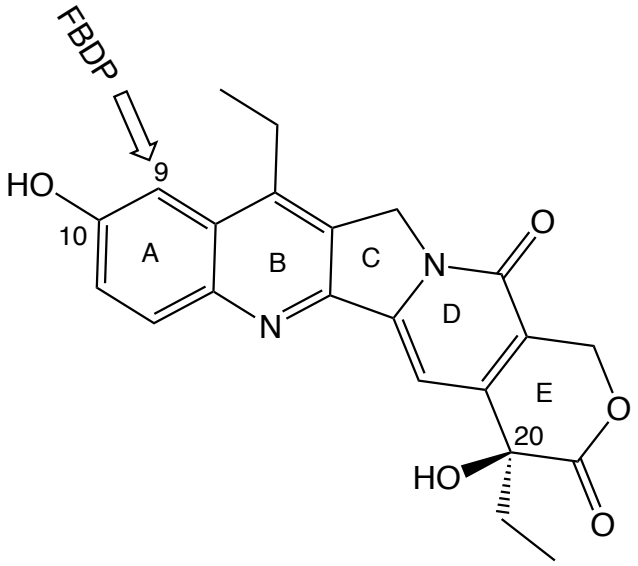


Figure 3. The linking point with FBDP is illustrated using white arrows in SN-38.

Paclitaxel and Docetaxel, both are chemotherapy medications and used to treat a number of types of cancer [51,52]. These drugs are used for the treatment of breast, ovarian, lung, stomach, prostate, head and neck, cervical and pancreatic cancer. These are given as an injection or infusion into a vein due to its poor water-solubility (paclitaxel 0.25 μg/mL [53], docetaxel 6–7 μg/mL). So, oral administration of these drugs are clinically ineffective and must be administered via injection as an aqueous solution containing a surfactant and ethanol, which often cause undesired clinical side effects [54]. Several chemically modified paclitaxel derivatives were reported to overcome the above limitations [55]. For example, Battaglia *et al.* reported a succinic derivative, although water-solubility was not specifically mentioned [55a]. Greenwald *et al.* reported a derivative possessing a polyethylene glycol region, with a distributed molecular weight of more than 5–50 times that of paclitaxel. Therefore, appropriate doses of the entire drug package would be nonsensically increased if this derivative were to be clinically used [55b]. Mandai et al. reported derivatives of a diastereomeric mixture of sugars with a glucolate linker [55c], which may be prohibited due to guidelines adopted by governments of advanced countries. Though, numerous inclusion complexes of paclitaxel by a protein [56], a micelle [57], or a liposome [58] have also been developed, but these were not the chemically single compound. Several docetaxel prodrugs were also synthesized to solve the problem of low water solubility. These are docetaxel-lauroyl conjugates [59], 2′-malyl docetaxel [60], docetaxel-glycosyl derivatives [61,62] and docetaxel-amino acid conjugates

[63]. Although some of the prodrugs enhanced the solubility, unexpectedly showed several drawbacks like low drug loading and adverse side effects. All of the modifications were occurred through the introduction of solubilizing moieties to C2′, C7 and/ or C10 positions [**Fig 4**].

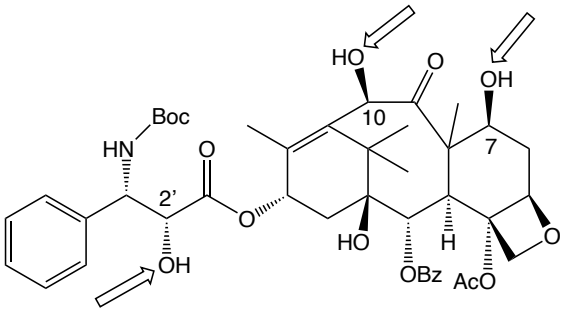


Figure 4. White arrows show the linking points in docetaxel.

Chemical derivatization of free hydroxyl groups on paclitaxel has been well studied [64,65]. For example, the hydroxyl group at C2′ is most reactive for acylation or silylation, that at C7 is the second most reactive, and that at C1 is hardly reactive. It has been reported that activity as an anti-tumor agent was similar even if the C3′-benzoyl moiety was substituted with other large acyl groups [66], and a method for the preparation of C3′-debenzoylated paclitaxel is known [67]. Following this information, previously five kinds of paclitaxel-BGL conjugates were synthesized by Nemoto *et al.* [15]. Each of which was a chemically single compound of less than two times the molecular weight of paclitaxel and BGL were linked at C2′, C3′ and C7 position. The three linking points have been illustrated using white arrows (**Fig 5**).

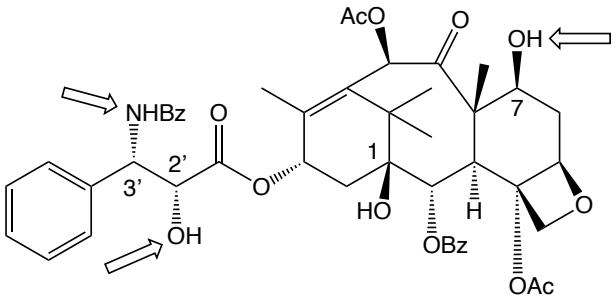


Figure 5. White arrows show the BGLating points in paclitaxel.

BGLation location unexpectedly influenced the water-solubilization and among these, 3′-debenzoylated paclitaxel–BGL003 conjugate [**Fig 6**] was the most water-soluble one. The anti-

tumor activity of 3′-debenzoylated paclitaxel possessing BGL003 was studied and found to be preserved in spite of chemical modification [15].

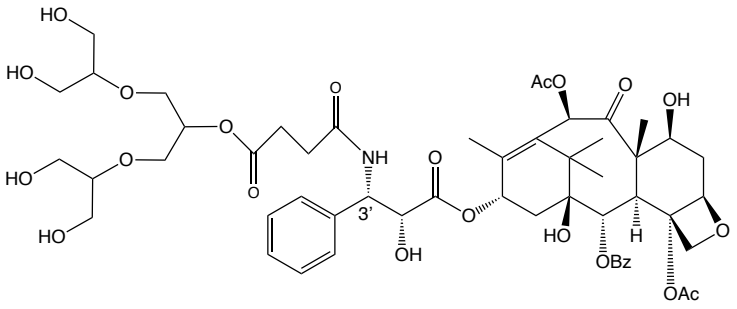


Figure 6. Structure of 3′-debenzoylated paclitaxel–BGL003 conjugate.

The protecting groups on BGL were removed prior to BGLation in case of conjugation at C3′, because conjugation happened more faster via amino group in 3′-debenzoylated paclitaxel [**Fig 7**]. BGLation at C2′ and C7, protecting groups were deprotected after conjugation, whereas prior deprotection would generate the others competing hydroxyl groups on the terminus. This BGLation process required a linker possessing two carboxylates such as succinate or glutarate and involved several complicated synthetic steps under harsh conditions. Hence, easier BGLation method was searched by using BGL isothiocyanate reagent (**7**). Bingaman *et al.* reported that fluorescein isothiocyanate (FITC) modification of proteins through amine terminal in microvascular research [68]. Accordingly herein, I designed to conjugate the new isothiocyanate reagent, **7** (BGL003–NCS) with 3′-debenzoylated paclitaxel to overcome the drawbacks in the previous BGLation method. In addition, 3′-de(*tert*-butyloxycarbonyl) docetaxel was also taken as a target molecule being the taxane class of drugs.

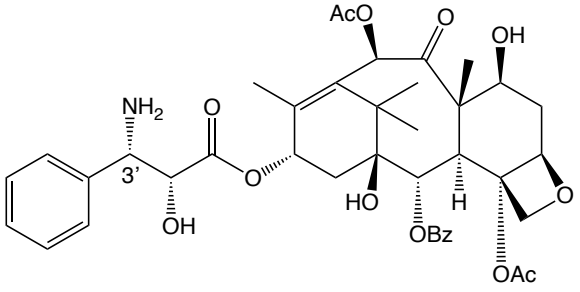
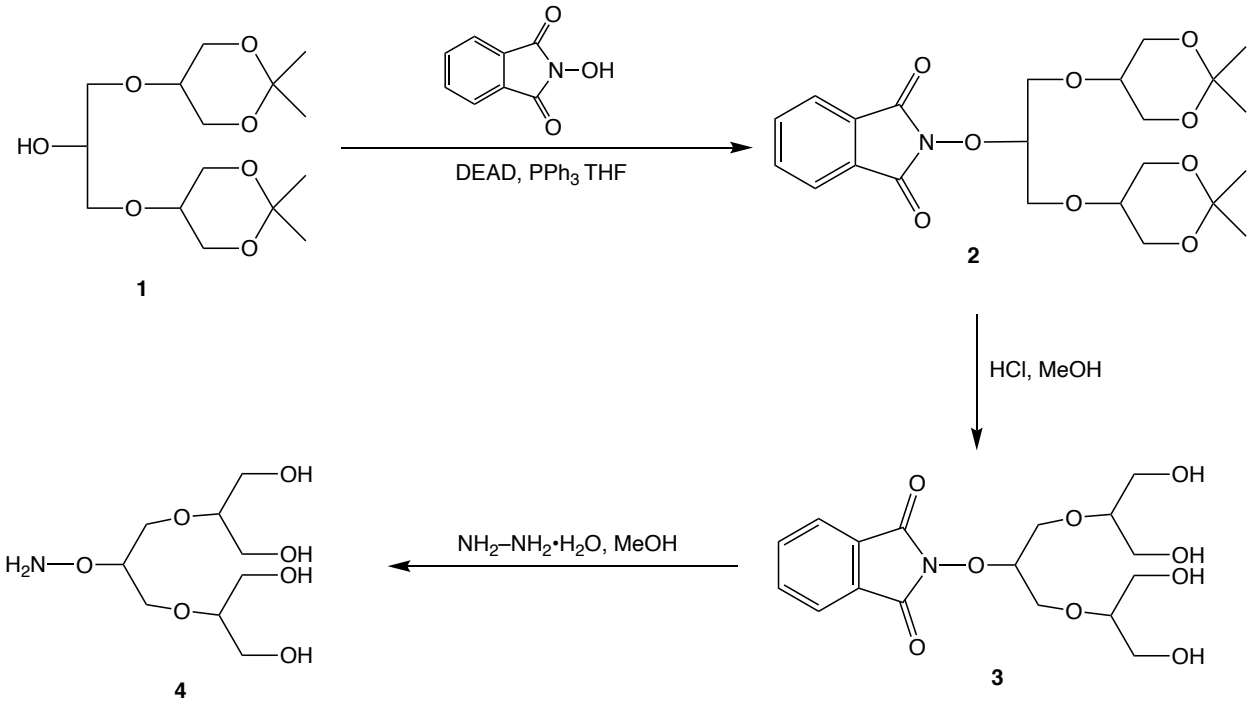


Figure 7. Structure of 3′-debenzoylated paclitaxel.

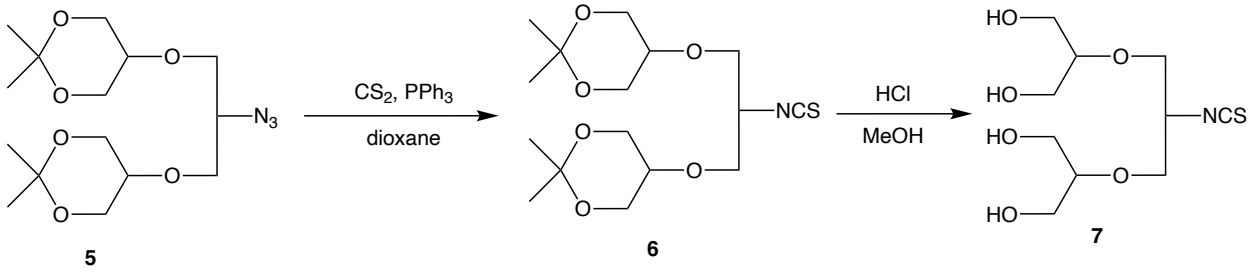
Results and discussion

The detail of the synthetic procedure of **4** (BGL003–ONH_2) has been illustrated in **Scheme 1**. Condensation between **1** and N-hydroxyphthalimide was carried out in tetrahydrofuran (THF) with diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh_3) to afford **2** in 96% yield. This intermediate product, **2** was stirred with anhydrous hydrogen chloride in methanol to give **3** in 78% yield. Finally, **3** in anhydrous methanol (MeOH) was stirred with hydrazine monohydrate to afford the final product **4** in 74% yield.



Scheme 1. Synthesis of BGL alkoxylamine (BGL003–ONH_2) **4**

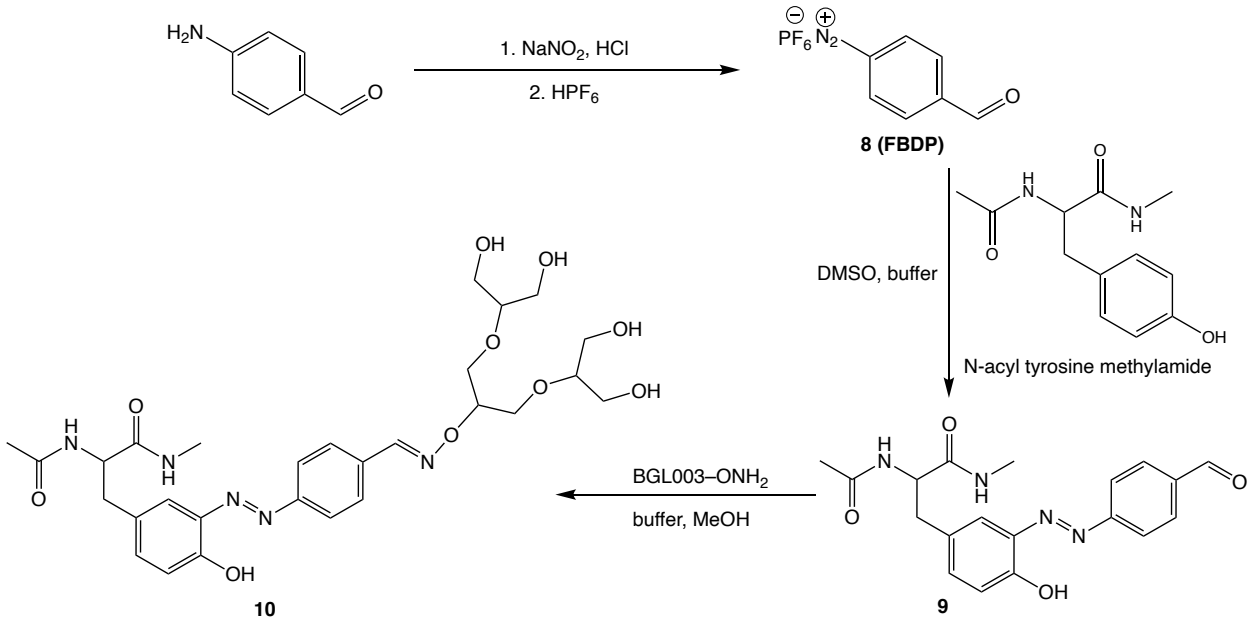
In **Scheme 2**, the detail of the synthetic procedure of **7** (BGL003–NCS) has been shown here. The reagent **5** was synthesized following the reported method [17]. The reaction of **5** with carbon disulfide in presence of triphenylphosphine in dioxane afforded **6** in 89% yield. Finally, **6** was stirred with anhydrous hydrogen chloride in methanol to afford **7** in 89% yield.



Scheme 2. Synthesis of BGL isothiocyanate (BGL003–NCS) **7**

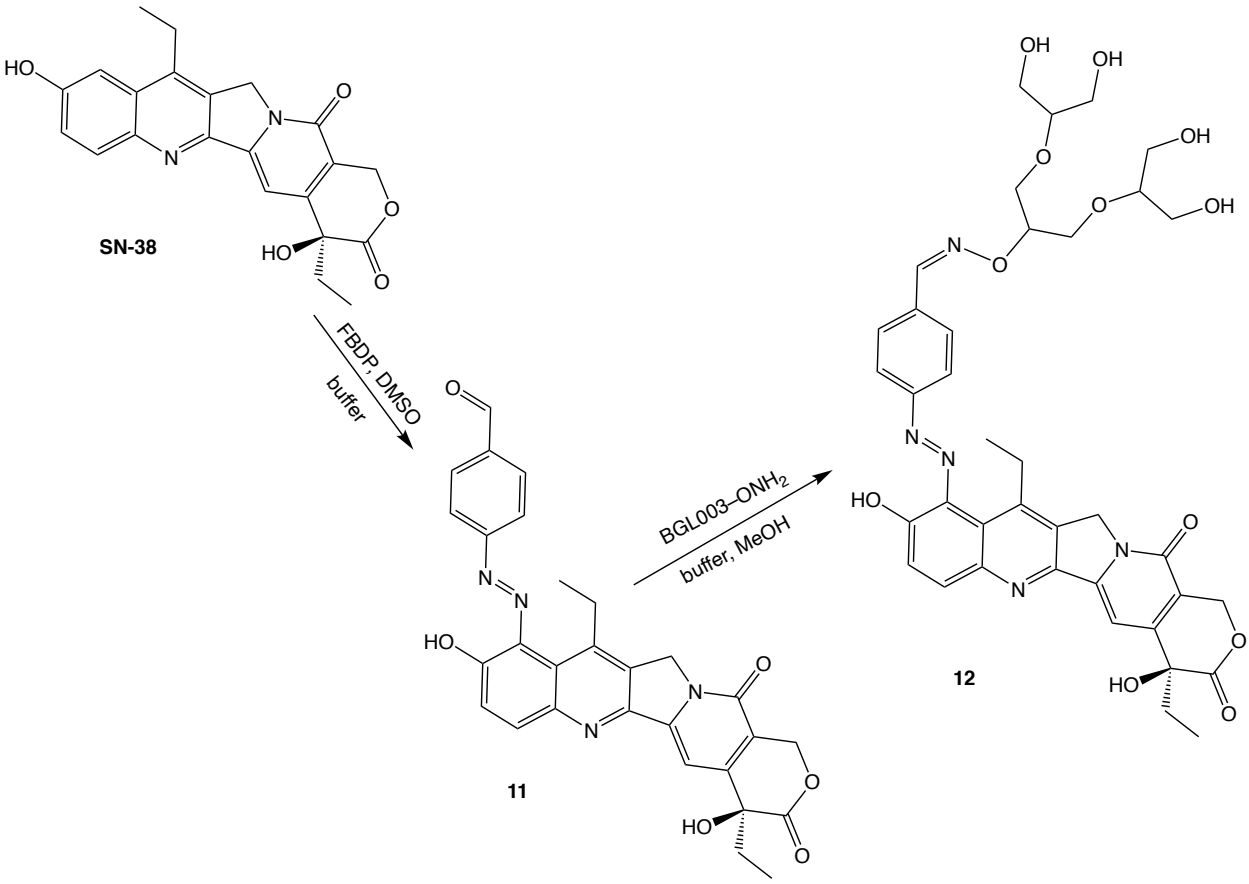
Herein, BGL003–ONH_2 (**4**) was used for BGLation of *N*-acyl tyrosine methylamide and SN-38 via an additional linker molecule. BGL003–NCS (**7**) was applied for BGLation of 3′-debenzoylated paclitaxel and 3′-de(*tert*-butyloxycarbonyl) docetaxel without any linker molecule.

The detail of the synthetic procedure of **10** (Tyrosine peptide–BGL conjugate) has been presented here in **Scheme 3**. The reagent **8** [(4-Formylbenzene diazonium hexafluorophosphate (FBDP)] was synthesized as the reported procedure [31]. The compound **9** was also prepared from the reaction of *N*-acyl tyrosine methylamide with **8**, following the reported procedure [31]. Finally, condensation reaction between **9** and **4** (BGL003–ONH_2) in NaH_2PO_4/Na_2HPO_4 buffer (pH 7.0)–methanol afforded **10** in 93% yield. Here, BGLation occurred around the physiological conditions (pH ≅ 7.4, aqueous media and mild temperature).



Scheme 3. Synthesis of Tyrosine peptide–BGL conjugate **10**

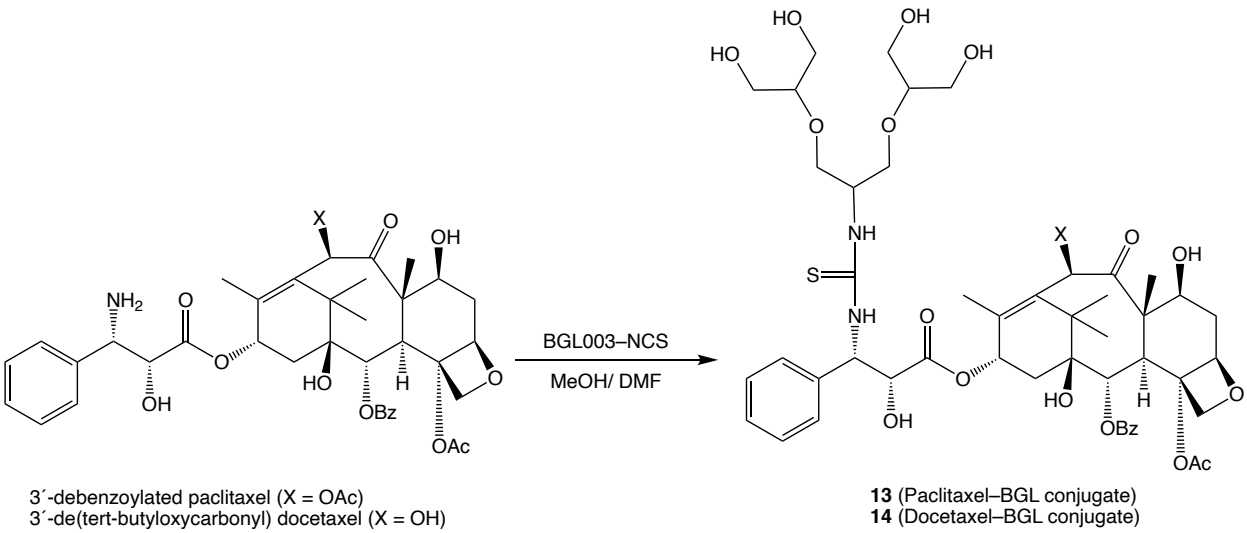
In **Scheme 4**, the detail of the synthetic procedure of **12** (SN38–BGL conjugate) has been displayed here. The diazo coupling reaction between SN-38 and **8** (FBDP) was carried out in the mixture of NaH_2PO_4/Na_2HPO_4 buffer (pH 7.0) and dimethyl sulfoxide (DMSO) to afford **11** in 95% yield. Then, the reaction between **11** and **4** ($BGL003–ONH_2$) in NaH_2PO_4/Na_2HPO_4 buffer (pH 7.0)–methanol afforded **12** in 73% yield. BGLation also occurred here around the physiological conditions (pH ≅ 7.4, aqueous media and mild temperature).



Scheme 4. Synthesis of SN38–BGL conjugate **12**

The detail of the synthetic procedure of **13 and 14** (Taxol–BGL conjugates) has been illustrated in **Scheme 5**. The condensation between 3′-debenzoylated paclitaxel and **7** (BGL003–NCS) in methanol afforded **13** in 80% yield. The reaction of 3′-de(*tert*-butyloxycarbonyl) docetaxel with **7** (BGL003–NCS) in dimethylformamide (DMF) gave **14** in 80% yield. Here, deprotected BGL003–NCS (**7**) was conjugated successfully with 3′-debenzoylated paclitaxel and 3′-de(*tert*-butyloxycarbonyl) docetaxel, respectively. So acidic/ or harsh conditions required for

deprotection could be avoided. This isothiocyanate modification involve only one easy synthetic step, avoided linker molecules and occurred under mild conditions in high chemical yield.



Scheme 5. Synthesis of Taxol–BGL conjugates **13, 14**

Conclusion and Perspective

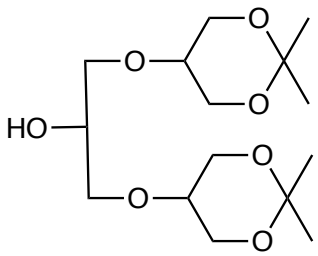
In this project, two important BGL trimer reagents, branched glycerol alkoxylamine (BGL003–ONH_2) and branched glycerol isothiocyanate (BGL003–NCS) have been developed. BGL003–ONH_2 was conjugated with tyrosine residue of a simplest peptide and A-ring of SN-38, respectively, via one additional linker molecule. BGL003–NCS was also connected with 3′-debenzoylated paclitaxel and 3′-de(*tert*-butyloxycarbonyl) docetaxel without any linker molecule. All the synthetic steps involved here occurred under mild conditions and gave a high chemical yield. I believe these BGL–conjugated drugs will be more water-soluble and more effective in the human body. *In vitro and in vivo* analysis of these modified drugs will be tested later on. I expect, in future more pharmaceutically important molecules might be conjugated with these BGL trimer reagents to enhance water-solubilization.

Experimental

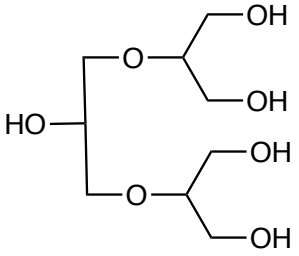
General Information

IR spectra were measured by Nihon Bunko FT-IR 6200 spectrometer. ^{1}H NMR spectra were recorded by Bruker FT-NMR AV400N at 400 MHz or Bruker FT-NMR AV500 at 500 MHz, and ^{13}C NMR spectra were recorded by Bruker FT-NMR AV500 at 125 MHz in deuteriated chloroform or methanol or dimethyl sulfoxide ($CDCl_3$ or CD_3OD or DMSO-d_6). Chemical shifts were indicated by d value in ppm with tetramethylsilane as an internal standard. Multiplicities are abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), brs (broaded singlet). Coupling constants, *J,* were reported in Hz (Hertz). High resolution mass spectra (HRMS) were measured by Waters LCT PRIMIER using Electronically Sprayed Injection–Time-of-Fight (ESI-TOF). All the reactions were carried out under nitrogen atmosphere. Reactions were monitored by thin layer chromatography of Merck Silica gel 60 F_{254} (0.25 mm) when it was applicable. Purifications were performed with Silica gel 60 N purchased from KANTO. Thiols, succinic anhydride, diethyl azodicarboxylate (DEAD), hydrazine monohydrate, N-hydroxyphthalimide, 4-aminobenzaldehyde polymer, SN-38 were purchased from TCI. 4-(Dimethylamino)pyridine (DMAP), carbon disulfide (CS_2), triphenyl phosphine (PPh_3), hexafluorophosphoric acid, dehydrated tetrahydrofuran (THF) and 1,4-dioxane, dimethylformamide (DMF) and pyridine were purchased from Wako. *N*-acyl tyrosine methylamide from Watanabe Chemical Co., Ltd., dimethyl sulfoxide (DMSO) from Nacalai Tesque, 3-(((ethylimino)methylene)amino)-*N*,*N*-dimethylpropan-1-aminium chloride (EDC•HCl) from Combi-Blocks were purchased. Dichloromethane (DCM), dimethylformamide (DMF) and methanol (MeOH) were distilled over calcium hydride. Pyridine was distilled over potassium hydroxide. All other chemicals and solvents were purchased as analytical grade and used as directly unless otherwise specified.

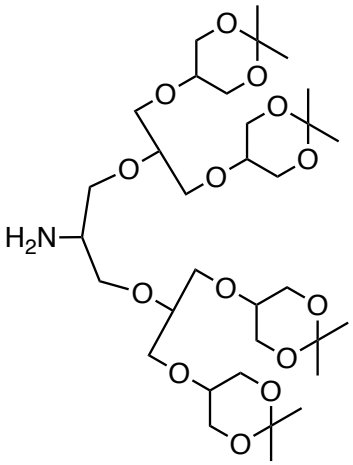
Schematic representation of glycerol trimer (BGL003) and heptamer (BGL007)



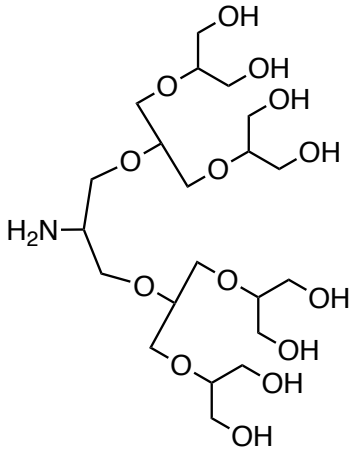
BGL003 (protected)



BGL003



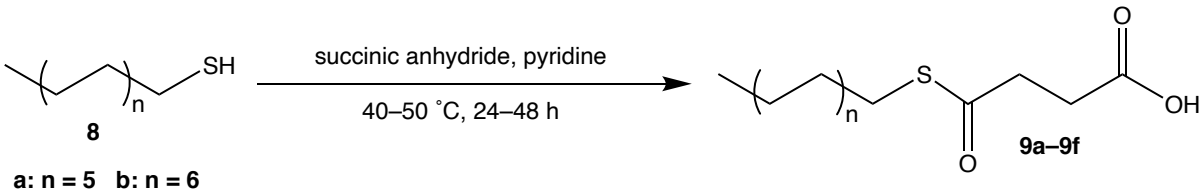
BGL007–NH_2 (protected)



BGL007–NH_2

Experimental for Chapter 1

General Procedure for the synthesis of compounds 9a–9f:



a: n = 5 b: n = 6
c: n = 7 d: n = 8
e: n = 9 f: n = 10
(8d = 1)

To a stirred solution of alkane-1-thiol (4.90 mmol, 1.00 eq) in pyridine (9.80 mL, 0.50 M) was added succinic anhydride (0.73 g, 7.30 mmol, 1.50 eq) at room temperature and the resulting mixture was stirred for 24–48 h at 40–50 ˚C. The reaction mixture was allowed to cool to room temperature and poured into aqueous potassium hydrogen sulfate (5%, 100 mL). The resulting

reaction mixture was extracted with DCM (50 mL × 2). The combined organic layers were washed with brine (100 mL × 2), dried over sodium sulfate, and concentrated *in vacuo.* The residue was purified by recrystallization from DCM (20 mL) or chloroform (20 mL) at 35 ˚C and allowed to cool at 4 ˚C to afford 4-(alkylthio)-4-oxobutanoic acid (**9a–9f**) in 87–96% yield as a colorless solid or crystal.

Compound 9a

FT-IR (KBr) 3422, 2926, 2844, 1719, 1688, 1612, 1556, 1506, 1462, 1412, 1311, 1217, 1104 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.93–2.90 (m, 4H), 2.73 (t, J = 6.8 Hz, 2H), 1.59 (quint, J = 7.2 Hz, 2H), 1.38–1.28 (m, 18H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8 (C, **C**OS), 178.0 (C, **C**O_2H), 38.1 (CH_2), 31.9 (CH_2), 29.6 (CH_2 × 2), 29.57 (CH_2), 29.5 (CH_2 × 2), 29.3 (CH_2), 29.1 (CH_2 × 2), 29.0 (CH_2), 28.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{16}H_{30}O_3SNa$ $[M + Na]^+$ 325.1813, found 325.1837.

Compound 9b

FT-IR (KBr) 3359, 2951, 2920, 2850, 1713, 1688, 1462, 1412, 1305, 1217, 1079, 1003, 897, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.93–2.89 (m, 4H), 2.73 (t, J = 7.0 Hz, 2H), 1.59 (quint, J = 7.0 Hz, 2H), 1.38–1.28 (m, 22H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8 (C, **C**OS), 177.6 (C, **C**O_2H), 38.1 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2 × 2), 29.6 (CH_2), 29.57 (CH_2), 29.5 (CH_2 × 2), 29.4 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{18}H_{35}O_3S$ $[M + H]^+$ 331.2307, found 331.2325.

Compound 9c

FT-IR (KBr) 3422, 2954, 2919, 2850, 1714, 1693, 1633, 1608, 1458, 1408, 1320, 1227, 1087, 1001, 654, 533 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.93–2.90 (m, 4H), 2.73 (t, J = 6.5 Hz, 2H), 1.59 (quint, J = 7.0 Hz, 2H), 1.38–1.28 (m, 26H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8 (C, **C**OS), 177.7 (C, **C**O_2H), 38.1 (CH_2), 31.9 (CH_2), 29.7 (CH_2 × 3), 29.65 (CH_2), 29.63 (CH_2), 29.6 (CH_2), 29.5 (CH_2 × 2), 29.4 (CH_2 × 2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{20}H_{38}O_3S$ $[M]^+$ 358.2542, found 358.2505.

Compound 9d

FT-IR (neat) 3417, 2921, 2850, 1716, 1693, 1635, 1462, 1411, 1321, 1222, 1087, 1004 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.79 (brs, 1H, CO_2**H**), 2.90–2.87 (m, 4H), 2.70 (t, J = 7.0 Hz, 2H), 1.56 (quint, J = 7.5 Hz, 2H), 1.37–1.25 (m, 30H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.9 (C, **C**OS), 176.1 (C, **C**O_2H), 38.2 (CH_2), 31.9 (CH_2), 29.7 (CH_2 ×

5), 29.68 (CH_2 × 2), 29.6 (CH_2), 29.59 (CH_2), 29.5 (CH_2 × 2), 29.4 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.8 (CH_2 × 2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{22}H_{42}O_3SNa$ $[M + Na]^+$ 409.2752, found 409.2766.

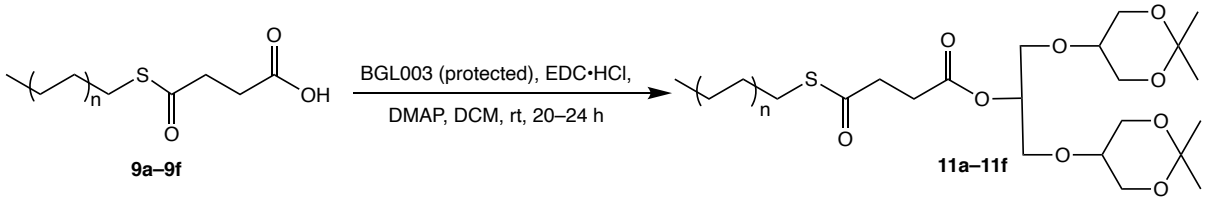
Compound 9e

FT-IR (KBr) 3406, 2961, 2920, 2842, 1721, 1693, 1462, 1420, 1320, 1227, 1086, 1000, 901, 788, 731, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.93–2.90 (m, 4H), 2.73 (t, J = 7.2 Hz, 2H), 1.59 (quint, J = 7.6 Hz, 2H), 1.38–1.28 (m, 34H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8 (C, **C**OS), 176.6 (C, **C**O_2H), 38.2 (CH_2), 31.9 (CH_2), 29.7 (CH_2 × 6), 29.67 (CH_2 × 2), 29.6 (CH_2), 29.58 (CH_2), 29.5 (CH_2 × 2), 29.4 (CH_2), 29.1 (CH_2 × 2), 29.0 (CH_2), 28.8 (CH_2 × 2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{24}H_{47}O_3S$ $[M + H]^+$ 415.3246, found 415.3245.

Compound 9f

FT-IR (KBr) 3406, 2954, 2917, 2848, 1714, 1689, 1646, 1621, 1465, 1445, 1408, 1320, 1220, 1087, 1001, 901, 788, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.92 (t, J = 7.2 Hz, 2H), 2.92 (t, J = 7.2 Hz, 2H), 2.73 (t, J = 7.2 Hz, 2H), 1.59 (quint, J = 6.8 Hz, 2H), 1.38–1.28 (m, 38H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8 (C, **C**OS), 175.6 (C, **C**O_2H), 38.2 (CH_2), 31.9 (CH_2), 29.7 (CH_2 × 8), 29.64 (CH_2 × 2), 29.6 (CH_2), 29.57 (CH_2), 29.5 (CH_2 × 2), 29.3 (CH_2 × 2), 29.1 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{26}H_{50}O_3S$ $[M]^+$ 442.3481, found 442.3495.

General Procedure for the synthesis of compounds 11a–11f:



To a stirred solution of 4-(alkylthio)-4-oxobutanoic acid (0.662 mmol, 1.00 eq), BGL003 (protected) **10** (254.5 mg, 0.794 mmol, 1.20 eq) and DMAP (8 mg, 0.066 mmol, 0.10 eq) in DCM (3.31 mL, 0.20 M) was added EDC•HCl (152.3 mg, 0.794 mmol, 1.20 eq) at room temperature and the resulting mixture was stirred for 20–24 h at room temperature. The reaction mixture was poured into aqueous ammonium chloride (5%, 50 mL) and extracted with DCM (50 mL × 2). The combined organic layers were washed with brine (50 mL × 2), dried over sodium sulfate, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography, eluted with DCM/acetone (95/5) as an eluent to afford 1,3-bis((2,2-dimethyl-

1,3-dioxan-5-yl)oxy)propan-2-yl 4-(alkylthio)-4-oxobutanoate (**11a–11f**) in 75–88% yield as a colorless sticky oil.

Compound 11a

FT-IR (neat) 2995, 2925, 2855, 1740, 1692, 1461, 1372, 1251, 1227, 1199,1155, 1086, 985, 939, 831, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.05 (quint, J = 5.0 Hz, 1H, OC**H(**$CH_2)_2$), 3.97–3.93 (m, 4H, CHC**H₂**O), 3.74–3.70 (m, 4H, CHC**H₂**O), 3.68–3.61 (m, 4H, CHC**H₂**O), 3.46–3.42 (m, 2H, OC**H(**$CH_2)_2$), 2.89–2.86 (m, 4H), 2.67 (t, J = 7.0 Hz, 2H), 1.55 (quint, J = 7.0 Hz, 2H), 1.42 and 1.39 (s, 12H, CC**H₃**), 1.35–1.25 (m, 18H), 0.87 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.7 (C, **C**OS), 171.4 (C, **C**O_2), 98.1 (C × 2, **C**$(CH_3)_2$), 71.9 (CH), 70.9 (CH × 2), 67.0 (CH_2 × 2), 62.5 (CH_2 × 2), 62.4 (CH_2 × 2), 38.4 (CH_2), 31.9 (CH_2), 29.63 (CH_2), 29.6 (CH_2), 29.54 (CH_2), 29.5 (CH_2), 29.46 (CH_2), 29.3 (CH_2), 29.1 (CH_2 × 2), 28.9 (CH_2), 28.8 (CH_2), 24.2 and 22.9 (CH_3 × 4, C(**C**$H_3)_2$), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{31}H_{56}O_9S^+$ $[M]^+$ 604.3645, found 604.3652.

Compound 11b

FT-IR (neat) 2991, 2922, 2852, 1737, 1686, 1459, 1364, 1252, 1226, 1195, 1150, 1088, 980, 936, 828, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.06 (quint, J = 5.0 Hz, 1H, OC**H**$(CH_2)_2$), 3.97–3.93 (m, 4H, CHC**H₂**O), 3.74–3.70 (m, 4H, CHC**H₂**O), 3.69–3.61 (m, 4H, CHC**H₂**O), 3.47–3.43 (m, 2H, OC**H**$(CH_2)_2$), 2.89–2.86 (m, 4H), 2.67 (t, J = 7.0 Hz, 2H), 1.56 (quint, J = 7.5 Hz, 2H), 1.43 and 1.40 (s, 12H, CC**H₃**), 1.34–1.25 (m, 22H), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.7 (C, **C**OS), 171.4 (C, **C**O_2), 98.2 (C × 2, **C**$(CH_3)_2$), 71.9 (CH), 71.0 (CH × 2), 67.1 (CH_2 × 2), 62.5 (CH_2 × 2), 62.4 (CH_2 × 2), 38.4 (CH_2), 31.9 (CH_2), 29.6 (CH_2 × 3), 29.5 (CH_2), 29.48 (CH_2), 29.46 (CH_2), 29.3 (CH_2 × 2), 29.1 (CH_2 × 2), 28.9 (CH_2), 28.8 (CH_2), 24.3 and 22.9 (CH_3 × 4, C(**C**$H_3)_2$), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{33}H_{60}O_9S$ $[M]^+$ 632.3958, found 632.3929.

Compound 11c

FT-IR (neat) 2995, 2926, 2850, 1744, 1688, 1462, 1367, 1248, 1223, 1192, 1154, 1092, 978, 940, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.07 (quint, J = 5.0 Hz, 1H, OC**H**$(CH_2)_2$), 3.98–3.94 (m, 4H, CHC**H₂**O), 3.75–3.71 (m, 4H, CHC**H₂**O), 3.69–3.62 (m, 4H, CHC**H₂**O), 3.48–3.44 (m, 2H, OC**H**$(CH_2)_2$), 2.90–2.87 (m, 4H), 2.68 (t, J = 7.0 Hz, 2H), 1.57 (quint, J = 7 Hz, 2H), 1.44 and 1.41 (s, 12H, CC**H₃**), 1.36–1.26 (m, 26H), 0.89 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.7 (C, **C**OS), 171.4 (C, **C**O_2), 98.2 (C × 2, **C**$(CH_3)_2$), 71.9 (CH), 70.9 (CH × 2), 67.1 (CH_2 × 2), 62.5 (CH_2 × 2), 62.4 (CH_2 × 2), 38.4 (CH_2), 31.9 (CH_2), 29.7 (CH_2 × 3), 29.65 (CH_2), 29.6 (CH_2), 29.57 (CH_2), 29.5 (CH_2 × 2), 29.34 (CH_2), 29.3 (CH_2),

29.1 (CH_2), 28.9 (CH_2 × 2), 28.8 (CH_2), 24.2 and 22.9 (CH_3 × 4, C(**C**H_3)$_2$), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{35}H_{64}O_9SNa$ $[M + Na]^+$ 683.4169, found 683.4177.

Compound 11d

FT-IR (neat) 2918, 2850, 1737, 1692, 1469, 1372, 1251, 1200, 1086, 985, 938, 830, 721 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.08 (quint, J = 5.0 Hz, 1H, OC**H**(CH_2)$_2$), 4.00–3.96 (m, 4H, CHC**H$_2$**O), 3.77–3.73 (m, 4H, CHC**H$_2$**O), 3.71–3.64 (m, 4H, CHC**H$_2$**O), 3.49–3.45 (m, 2H, OC**H**(CH_2)$_2$), 2.92–2.88 (m, 4H), 2.70 (t, J = 7.0 Hz, 2H), 1.58 (quint, J = 7.5 Hz, 2H), 1.45 and 1.42 (s, 12H, CC**H$_3$**), 1.37–1.27 (m, 30H), 0.90 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8 (C, **C**OS), 171.5 (C, **C**O_2), 98.2 (C × 2, **C**(CH_3)$_2$), 72.0 (CH), 71.0 (CH × 2), 67.1 (CH_2 × 2), 62.5 (CH_2 × 2), 62.4 (CH_2 × 2), 38.4 (CH_2), 31.9 (CH_2), 29.7 (CH_2 × 5), 29.69 (CH_2), 29.67 (CH_2 × 2), 29.6 (CH_2), 29.5 (CH_2 × 2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.98 (CH_2), 28.9 (CH_2), 24.3 and 23.0 (CH_3 × 4, C(**C**H_3)$_2$), 22.7 (CH_2), 14.2 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{37}H_{68}O_9SNa$ $[M+Na]^+$ 711.4482, found 711.4492.

Compound 11e

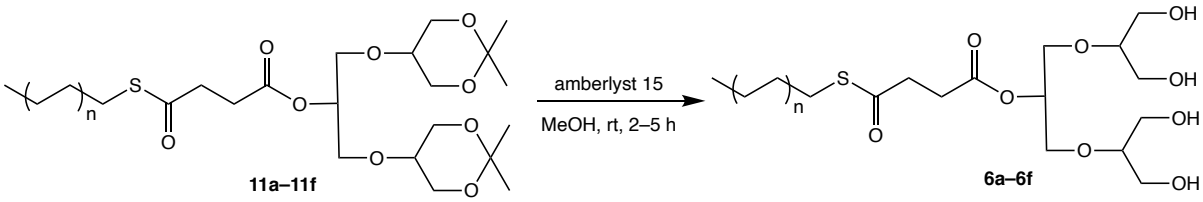
FT-IR (neat) 2991, 2922, 2852, 1737, 1686, 1459, 1371, 1245, 1195, 1156, 1088, 980, 936, 828, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.08 (quint, J = 5.2 Hz, 1H, OC**H**(CH_2)$_2$), 3.99–3.95 (m, 4H, CHC**H$_2$**O), 3.76–3.72 (m, 4H, CHC**H$_2$**O), 3.71–3.63 (m, 4H, CHC**H$_2$**O), 3.50–3.44 (m, 2H, OC**H**(CH_2)$_2$), 2.90 (t, J = 7.6 Hz, 2H), 2.90 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 6.8 Hz, 2H), 1.58 (quint, J = 6.8 Hz, 2H), 1.45 and 1.42 (s, 12H, CC**H$_3$**), 1.38–1.28 (m, 34H), 0.90 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.7 (C, **C**OS), 171.4 (C, **C**O_2H), 98.2 (C × 2, **C**(CH_3)$_2$), 72.0 (CH), 71.0 (CH × 2), 67.0 (CH_2 × 2), 62.5 (CH_2 × 2), 62.4 (CH_2 × 2), 38.4 (CH_2), 31.9 (CH_2), 29.7 (CH_2 × 7), 29.6 (CH_2 × 2), 29.56 (CH_2), 29.5 (CH_2 × 2), 29.34 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2 × 2), 28.8 (CH_2), 24.2 and 22.9 (CH_3 × 4, C(**C**H_3)$_2$), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{39}H_{72}O_9S$ $[M]^+$ 716.4897, found 716.4899.

Compound 11f

FT-IR (neat) 2991, 2922, 2859, 1737, 1686, 1466, 1377, 1245, 1195, 1150, 1093, 1037, 980, 936, 828, 753, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.05 (quint, J = 5.0 Hz, 1H, OC**H**(**C**H_2)$_2$), 3.96–3.92 (m, 4H, CHC**H$_2$**O), 3.73–3.69 (m, 4H, CHC**H$_2$**O), 3.68–3.61 (m, 4H, CHC**H$_2$**O), 3.46–3.42 (m, 2H, OC**H**(CH_2)$_2$), 2.88–2.85 (m, 4H), 2.66 (t, J = 7.0 Hz, 2H), 1.55 (quint, J = 7 Hz, 2H), 1.42 and 1.38 (s, 12H, CC**H$_3$**), 1.35–1.25 (m, 38H), 0.87 (t, J = 7.0 Hz, 3H, C**H$_3$**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.7 (C, **C**OS), 171.4 (C, **C**O_2), 98.2 (C × 2, **C**(CH_3)$_2$), 72.0 (CH), 71.0 (CH × 2), 67.0 (CH_2 × 2), 62.5 (CH_2 × 2), 62.4 (CH_2 × 2), 38.4

(CH_2), 31.9 (CH_2), 29.7 (CH_2 × 8), 29.64 (CH_2), 29.62 (CH_2 × 2), 29.6 (CH_2), 29.5 (CH_2), 29.47 (CH_2), 29.3 (CH_2 × 2), 29.28 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 24.2 and 22.9 (CH_3 × 4, C(**C**H_3)$_2$), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{41}H_{77}O_9S$ [M + H]$^+$ 745.5288, found 745.5281.

General Procedure for the synthesis of compounds 6a–6f:



To a stirred solution of 1,3-bis((2,2-dimethyl-1,3-dioxan-5-yl)oxy)propan-2-yl 4-(alkylthio)-4-oxobutanoate (0.537 mmol) in methanol (5.37 mL, 0.10 M) was added Amberlyst 15® (100 mg) at room temperature and the resulting suspension was stirred for 2–5 h at room temperature. After filtration, the filtrate was concentrated *in vacuo* to afford 1,3-bis((1,3-dihydroxypropan-2-yl)oxy)propan-2-yl 4-(alkylthio)-4-oxobutanoate (**6a–6f**) in 83–98% yield as a colorless sticky oil or gummy solid.

Compound 6a

FT-IR (neat) 3401, 3010, 2928, 2852, 1737, 1680, 1459, 1409, 1377, 1220, 1170, 1119, 1068, 1043, 986, 760 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 5.13 (quint, J = 5.0 Hz, 1H, OC**H(**CH_2)$_2$), 3.85–3.76 (m, 4H, CHC**H$_2$**O), 3.67–3.64 (m, 4H, CHC**H$_2$**O), 3.61–3.58 (m, 4H, CHC**H$_2$**O), 3.45 (quint, J = 5.0 Hz, 2H, OC**H(**CH_2)$_2$), 2.94–2.90 (m, 4H), 2.69 (t, J = 7.0 Hz, 2H), 1.59 (quint, J = 7.5 Hz, 2H), 1.40–1.32 (m, 18H), 0.92 (t, J = 7.0 Hz, 3H, C**H$_3$**); ^{13}C NMR (CD_3OD, 125 MHz) δ 198.4 (C, **C**OS), 172.1 (C, **C**O_2), 81.8 (CH × 2), 72.7 (CH), 68.3 (CH_2 × 2), 61.1 (CH_2 × 2), 61.07 (CH_2 × 2), 38.0 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 29.36 (CH_2 × 2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.4 (CH_2), 28.3 (CH_2), 22.3 (CH_2), 13.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{25}H_{48}O_9S$ [M]$^+$ 524.3019, found 524.3051.

Compound 6b

FT-IR (neat): 3411, 2974, 2923, 2859, 1738, 1686, 1465, 1408, 1211, 1174, 1122, 1072, 1046 755 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz): δ 5.12 (quint, J = 5.2 Hz, 1H, OC**H(**CH_2)$_2$), 3.85–3.76 (m, 4H, CHC**H$_2$**O), 3.68–3.64 (m, 4H, CHC**H$_2$**O), 3.61–3.57 (m, 4H, CHC**H$_2$**O), 3.45 (quint, J = 5.2 Hz, 2H, OC**H(**CH_2)$_2$), 2.94–2.89 (m, 4H), 2.69 (t, J = 6.8 Hz, 2H), 1.58 (quint, J = 7.2 Hz, 2H), 1.40–1.31 (m, 22H), 0.92 (t, J = 6.8 Hz, 3H, C**H$_3$**). ^{13}C NMR (CD_3OD, 125

MHz): δ 198.3 (C, **C**OS), 174.2 (C, **C**O_2), 81.8 (CH × 2), 71.1 (CH), 70.0 (CH_2 × 2), 61.1 (CH_2 × 4), 38.0 (CH_2), 31.7 (CH_2), 29.4 (CH_2 × 3), 29.3 (CH_2), 29.28 (CH_2), 29.2 (CH_2), 29.1 (CH_2 × 2), 28.8 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 22.35 (CH_2), 13.06 (CH_3). HRMS (ESI-TOF) m/z calcd for $C_{27}H_{53}O_9S$ $[M + H]^+$ 553.3410, found 553.3438.

Compound 6c

FT-IR (neat) 3401, 2960, 2922, 2852, 1737, 1692, 1466, 1409, 1339, 1207, 1131, 1088, 1062, 700 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 5.12 (quint, J = 5.6 Hz, 1H, OC**H(**$CH_2)_2$), 3.85–3.76 (m, 4H, CHC**H₂**O), 3.68–3.64 (m, 4H, CHC**H₂**O), 3.61–3.57 (m, 4H, CHC**H₂**O), 3.45 (quint, J = 5.2 Hz, 2H, OC**H(**$CH_2)_2$), 2.94–2.89 (m, 4H), 2.69 (t, J = 7.2 Hz, 2H), 1.59 (quint, J = 7.6 Hz, 2H), 1.41–1.31 (m, 26H), 0.92 (t, J = 7.2 Hz, 3H, C**H₃**); ^{13}C NMR (CD_3OD, 125 MHz) δ 198.4 (C, **C**OS), 172.1 (C, **C**O_2), 81.8 (CH × 2), 72.7 (CH), 68.3 (CH_2 × 2), 61.1 (CH_2 × 2), 61.09 (CH_2 × 2), 38.0 (CH_2), 31.7 (CH_2), 29.4 (CH_2 × 5), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.4 (CH_2 × 2), 28.3 (CH_2 × 2), 22.3 (CH_2), 13.0 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{29}H_{57}O_9S$ $[M + H]^+$ 581.3723, found 581.3704.

Compound 6d

FT-IR (KBr) 3403, 2918, 2850, 1734, 1686, 1468, 1127, 1073, 474, 448, 421, 411 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.15 (quint, J = 5.0 Hz, 1H, OC**H(**$CH_2)_2$), 3.87–3.82 (m, 4H, CHC**H₂**O), 3.79–3.73 (m, 4H, CHC**H₂**O), 3.71–3.65 (m, 4H, CHC**H₂**O), 3.55–3.51 (m, 2H, OC**H**$(CH_2)_2$), 2.99 (brs, 2H, CH_2O**H**), 2.93–2.87 (m, 4H), 2.93–2.86 (brs (hidden), 2H, CH_2O**H**), 2.67 (t, J = 7.0 Hz, 2H), 1.56 (quint, J = 7.0 Hz, 2H), 1.34–1.25 (m, 30H), 0.88 (t, J = 7.0 Hz, 3H, C**H₃**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.6 (C, **C**OS), 171.8 (C, **C**O_2), 81.2 (CH × 2), 72.0 (CH), 68.1 (CH_2 × 2), 62.4 (CH_2 × 2), 62.2 (CH_2 × 2), 38.4 (CH_2), 32.0 (CH_2), 29.8 (CH_2 × 6), 29.7 (CH_2 × 2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.42 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{31}H_{60}O_9SNa$ $[M+Na]^+$ 631.3856, found 631.3913.

Compound 6e

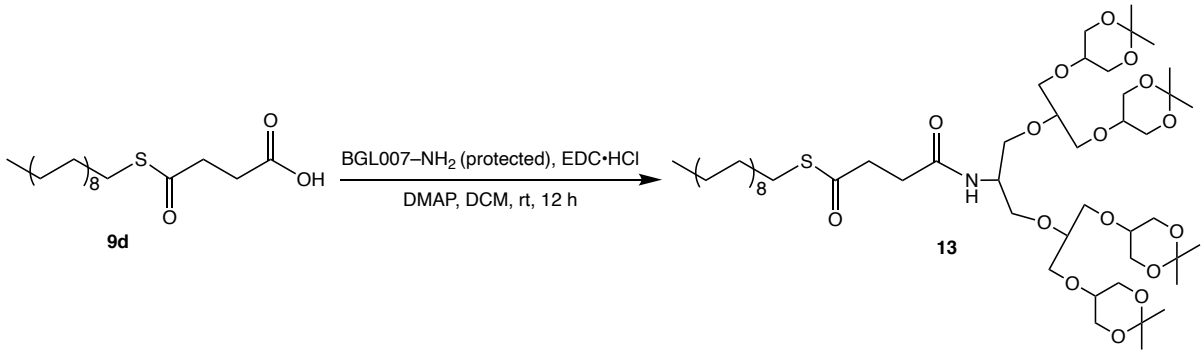
FT-IR (neat) 3403, 3020, 2920, 2857, 1739, 1688, 1462, 1417, 1380, 1210, 1122, 1066, 777, 745, 664 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.17 (quint, J = 5.2 Hz, 1H, OC**H(**$CH_2)_2$), 3.87 (d, J = 5.2 Hz, 4H, CHC**H₂**O), 3.82–3.76 (m, 4H, CHC**H₂**O), 3.73–3.67 (m, 4H, CHC**H₂**O), 3.58–3.53 (m, 2H, OC**H**$(CH_2)_2$), 2.95–2.89 (m, 4H), 2.79 (brs, 2H, CH_2O**H),** 2.71–2.66 (m, 2H), 2.71–2.66 (brs (hidden), 2H, CH_2O**H**), 1.58 (quint, J = 7.6 Hz, 2H), 1.37–1.28 (m, 34H), 0.90 (t, J = 7.2 Hz, 3H, C**H₃**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.5 (C, **C**OS), 171.7 (C, **C**O_2), 81.2 (CH × 2), 71.9 (CH), 68.1 (CH_2 × 2), 62.4 (CH_2 × 2), 62.2 (CH_2 × 2), 38.4 (CH_2), 31.9

(CH_2), 29.7 (CH_2 × 7), 29.67 (CH_2 × 3), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.38 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.06 (CH_2), 28.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{33}H_{64}O_9S$ $[M]^+$ 636.4271, found 636.4233.

Compound 6f

FT-IR (neat) 3408, 3016, 2916, 2846, 1737, 1692, 1471, 1409, 1377, 1213, 1131, 1068, 974, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.17 (quint, J = 5.0 Hz, 1H, OC**H**$(CH_2)_2$), 3.89–3.83 (m, 4H, CHC**H₂**O), 3.81–3.76 (m, 4H, CHC**H₂**O), 3.72–3.67 (m, 4H, CHC**H₂**O), 3.56–3.53 (m, 2H, OC**H**$(CH_2)_2$), 3.20–2.60 (brs (hidden), 4H, CH_2O**H**), 2.95–2.89 (m, 4H), 2.69 (t, J = 7.5 Hz, 2H), 1.58 (quint, J = 7.0 Hz, 2H), 1.38–1.28 (m, 38H), 0.90 (t, J = 7.0 Hz, 3H, C**H₃**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.5 (C, **C**OS), 171.7 (C, **C**O_2), 81.2 (CH × 2), 72.0 (CH), 68.1 (CH_2 × 2), 62.4 (CH_2 × 2), 62.2 (CH_2 × 2), 38.4 (CH_2), 31.9 (CH_2), 29.7 (CH_2 × 9), 29.65 (CH_2 × 3), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.35 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.06 (CH_2), 28.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{35}H_{69}O_9S$ $[M + H]^+$ 665.4662, found 665.4633.

Procedure for the synthesis of compound 13:

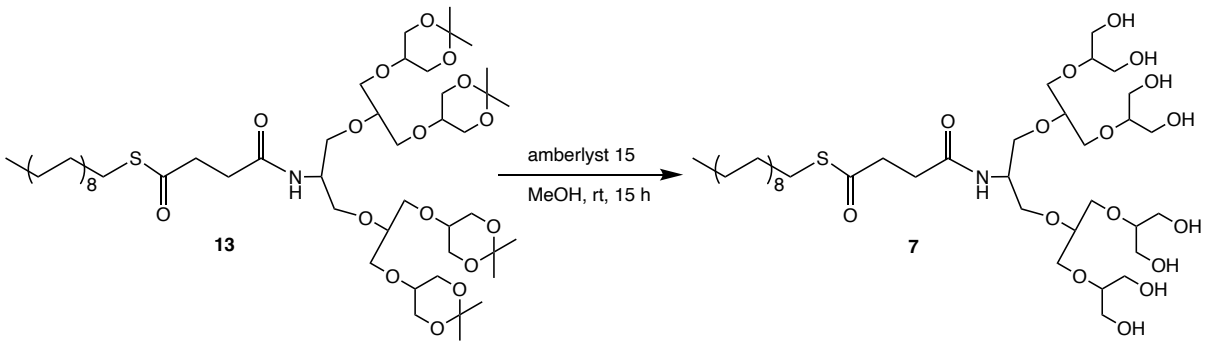


To a stirred solution of **9d** (309.5 mg, 0.8 mmol) in DCM (5 mL) was added BGL007–NH_2 (protected) **12n** (459.3 mg, 0.66 mmol), DMAP (7.3 mg, 0.06 mmol) and EDC•HCl (164.5 mg, 0.86 mmol) and the mixture was stirred for 12 h at room temperature. The resulting mixture was poured into aqueous potassium hydrogen sulfate(1%, 50 mL). (15 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel eluted by DCM/acetone (5/1) to afford **13** (210.0 mg, 0.20 mmol) in 25% yield as a colorless oil.

Compound 13

FT-IR (neat) 3336, 2925, 2854, 1679, 1533, 1467, 1372, 1251, 1228, 1199, 1096, 985, 940, 831, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.66 (d, J = 8.5 Hz, 1H, N**H**), 4.13 (quint, J = 4.5 Hz, 1H, NC**H(**$CH_2)_2$), 3.98–3.93 (m, 8H), 3.76–3.70 (m, 10H), 3.63–3.49 (m, 12H), 3.44–3.39 (m, 4H), 2.90–2.85 (m, 4H), 2.54 (t, J = 7.0 Hz, 2H), 1.55 (quint, J = 7.5 Hz, 2H), 1.42, 1.41 and 1.40 (s, 24H, CC**H₃**), 1.35–1.25 (m, 30H), 0.88 (t, J = 7.0 Hz, 3H, C**H₃**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.5 (C, **C**OS), 170.9 (C, **C**ONH), 98.24 and 98.2 (C × 4, **C**$(CH_3)_2$), 78.8 (CH × 2), 71.2 (CH × 2), 71.1 (CH × 2), 68.9, 68.7, 62.6, 62.4, 62.35 (CH_2 × 14), 49.5 (CH, N**C**H$(CH_2)_2$), 39.1 (CH_2), 31.9 (CH_2), 30.9 (CH_2), 29.7 (CH_2 × 5), 29.69 (CH_2), 29.67 (CH_2 × 2), 29.6 (CH_2), 29.5 (CH_2 × 2), 29.4 (CH_2), 29.2 (CH_2), 28.9 (CH_2 × 2), 24.0, 23.7, 23.6 and 23.3 (CH_3 × 8, C(**C**$H_3)_2$), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{55}H_{101}NO_{16}SNa$ $[M+Na]^+$ 1086.6739, found 1086.6738.

Procedure for the synthesis of compound 7:



To a stirred solution of **13** (210.0 mg, 0.20 mmol) in methanol (2 mL) was added Amberlyst 15® (19.8 mg). The resulting suspension was stirred for 15 h at room temperature, and filtered through filter paper. The filtrate was concentrated in *vacuo* to afford **7** (168.3 mg, 0.186 mmol) in 93% yield as a white amorphous.

Compound 7

FT-IR (KBr) 3735, 3649, 3417, 2919, 2850, 2360, 234, 1653, 1558, 1541, 1457, 1121, 1074, 668cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 4.11 (quint, J = 5.0 Hz, 1H, NC**H(**$CH_2)_2$), 3.79–3.57 (m, 30H), 3.43 (quint, J = 5.0 Hz, 4H), 2.89–2.86 (m, 4H), 2.55 (t, J = 7.0 Hz, 2H), 1.56 (quint, J = 7.5 Hz, 2H), 1.40–1.29 (m, 30H), 0.90 (t, J = 7.0 Hz, 3H, C**H₃**); ^{13}C NMR (CD_3OD, 125 MHz) δ 199.8 (C, **C**OS), 173.9 (C, **C**O_2), 83.2 (CH × 4), 83.1 (CH_2 × 2), 80.4 (CH × 2), 70.8, 69.9, 62.6, 62.5 (CH_2 × 12), 51.1 (CH, N**C**H$(CH_2)_2$), 40.0 (CH_2), 33.1 (CH_2), 31.8 (CH_2), 30.8 (CH_2 × 2), 30.76 (CH_2 × 5), 30.74 (CH_2 × 2), 30.7 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.3 (CH_2),

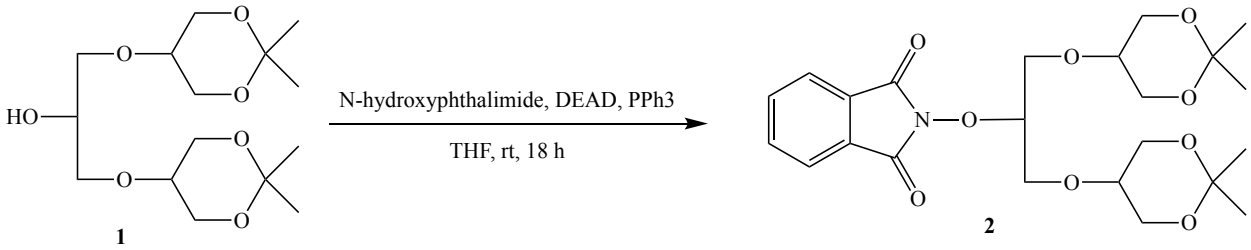
29.9 (CH_2), 29.7 (CH_2), 23.7 (CH_2), 14.4 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{43}H_{85}O_{16}SNa$ $[M+Na]^+$ 926.5487, found 926.5487.

Table 1: Physical data for all the products

Compound No.	Temperature [˚C]	Reaction time [h]	Physical state	Yield [%]	m.p. [˚C] and recrystallized solvent
9a	40	24	colorless solid	96	
9b	50	48	colorless crystal	92	81–83, DCM
9c	50	48	colorless crystal	95	88–90, DCM
9d	45	24	colorless crystal	93	90–92, $CHCl_3$
9e	45	30	colorless crystal	87	94–96, $CHCl_3$
9f	50	40	colorless solid	96	
11a	rt	22	colorless sticky oil	81	
11b	rt	24	colorless sticky oil	88	
11c	rt	24	colorless sticky oil	85	
11d	rt	20	colorless sticky oil	86	
11e	rt	24	colorless sticky oil	80	
11f	rt	21	colorless sticky oil	75	
6a	rt	5	colorless sticky oil	98	
6b	rt	4	colorless sticky oil	95	
6c	rt	4	colorless sticky oil	96	
6d	rt	4	colorless sticky oil	98	
6e	rt	2	colorless gummy solid	83	
6f	rt	5	colorless gummy solid	90	
13	rt	12	colorless oil	25	
7	rt	15	white amorphous	93	

Experimental for Chapter 2

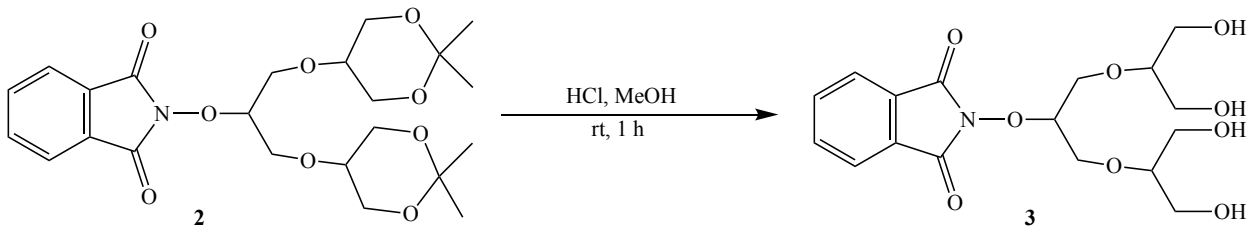
Procedure for the synthesis of compound 2:



To a stirred solution of **1** [BGL003 (protected)] (560 mg, 1.75 mmol, 1.00 eq), N-hydroxyphthalimide (428 mg, 2.62 mmol, 1.50 eq) and triphenyl phosphine (687 mg, 2.62 mmol, 1.50 eq) in THF (8.75 mL, 0.2 M) was added diethyl azodicarboxylate (DEAD) (456.3 mg, 2.62 mmol, 1.50 eq) at 0 ˚C over 10 min. The ice bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for further 18 h. Then the resulting reaction mixture was concentrated *in vacuo* and the residue was recrystallized from DCM (20 mL) to afford diethyl hydrazine-1,2-dicarboxylate as a crystal (otherwise column purification was troublesome). After filtration, the filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography, eluted with DCM/methanol (95/5) to give **2** (775 mg, 1.67 mmol, 96%) as a colorless oil.

FT-IR (neat) 2992, 2940, 2873, 1791, 1735, 1468, 1456, 1374, 1285, 1252, 1227, 1191, 1125, 1080, 1041, 1016, 979, 940, 878, 830, 789, 758, 732, 702, 668 and 646 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86–7.80 (m, 2H), 7.78–7.72 (m, 2H), 4.50 (quint, J = 4.4 Hz, 1H, OC**H(**$CH_2)_2$), 4.00–3.83 (m, 8H, CHC**H₂**O), 3.74–3.65 (m, 4H, CHC**H₂**O), 3.53 (quint, J = 4.4 Hz, 2H, OC**H(**$CH_2)_2$), 1.38 and 1.37 (s, 12H, CC**H₃**). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5 (**C**O), 134.5 (CH), 128.9 (C), 123.5 (CH), 98.2 (C), 85.8 (CH), 71.2 (CH), 67.6 (CH_2), 62.3 (CH_2), 62.3 (CH_2), 24.1 (CH_3) and 23.0 (CH_3). HRMS (ESI-TOF) m/z calcd for $C_{23}H_{31}NO_9Na$ $[M + Na]^+$ 488.1897, found 488.1893.

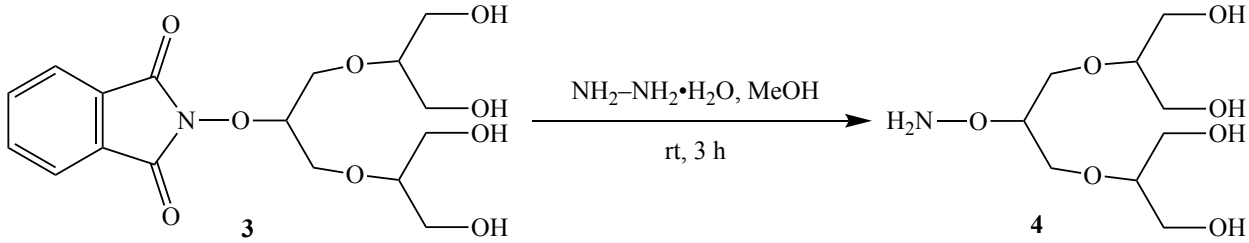
Procedure for the synthesis of compound 3:



In methanol (0.1N of anhydrous hydrogen chloride, 1.0 mL, 0.1 mmol, 0.60 eq) was added **2** (78 mg, 0.168 mmol, 1.00 eq) at room temperature and the resulting solution was stirred for 1 h at room temperature. The resulting solution was concentrated *in vacuo* and the residue was purified by silica gel column chromatography, eluted with DCM/methanol (7/3) as an eluent to give **3** (50 mg, 78%) as a colorless oil.

FT-IR (neat) 3400, 2950, 2875, 1790, 1740, 1480, 1460, 1374, 1280, 1250, 1230, 1190, 1080, 1040, 1020, 980, 950, 875, 825, 780, 730, 700 and 645 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz) δ 7.89–7.85 (m, 4H), 4.54 (quint, J = 4.5 Hz, 1H, OC**H(**$CH_2)_2$), 4.00 (d, J = 5.0 Hz, 4H, CHC**H₂**O), 3.68–3.55 (m, 8H, CHC**H₂**O), 3.48 (quint, J = 5.0 Hz, 2H, OC**H(**$CH_2)_2$). ^{13}C NMR (CD_3OD, 125 MHz) δ 164.1 (**C**O × 2), 134.5 (CH × 2), 128.9 (C × 2), 123.0 (CH × 2), 86.4 (CH), 81.8 (CH × 2), 68.4 (CH_2 × 2), 61.0 (CH_2 × 4). HRMS (ESI-TOF) m/z calcd for $C_{17}H_{23}NO_9Na$ $[M + Na]^+$ 408.1271, found 408.1290.

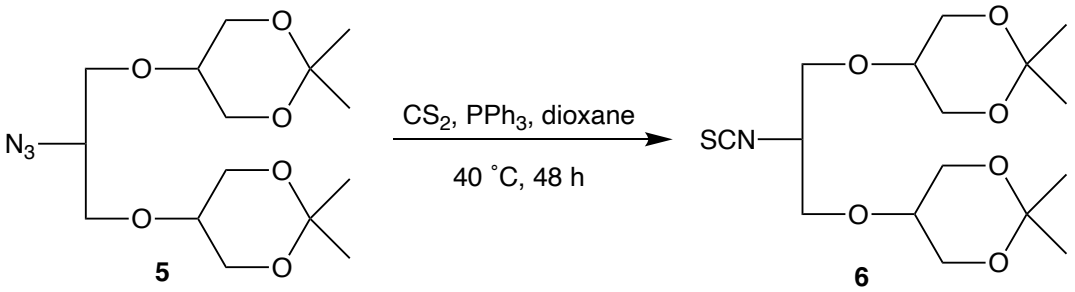
Procedure for the synthesis of compound 4:



To a stirred solution of **3** (119 mg, 0.309 mmol, 1.00 eq) in methanol (1.54 mL, 0.2 M) was added hydrazine monohydrate (20.11 mg, 0.402 mmol, 1.30 eq) at room temperature and the resulting solution was stirred for 3 h at room temperature. The resulting reaction mixture was filtered off and the filtrate was concentrated *in vacuo*. Then the residue was purified by silica gel column chromatography, eluted with DCM/methanol/acetic acid (100/100/5) as an eluent to give **4** (58 mg, 74%) as a colorless oil.

FT-IR (KBr) 3387, 2946, 2882, 1646, 1465, 1412, 1353, 1220, 1114, 1055, 996, 975, 911, 831, 677 and 571 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz) δ 3.89 (quint, J = 4.5 Hz, 1H), 3.81–3.73 (m, 4H), 3.67 (dd, J = 11.5 and 4.5 Hz, 4H), 3.60 (dd, J = 12.0 and 6.0 Hz, 4H) and 3.45 (quint, J = 5.0 Hz, 2H). ^{13}C NMR (CD_3OD, 125 MHz) δ 82.5 (CH), 81.8 (CH), 68.8 (CH_2) 61.1 (CH_2) and 61.0 (CH_2). HRMS (ESI-TOF) m/z calcd for $C_9H_{21}NO_7Na$ $[M + Na]^+$ 278.1216, found 278.1238.

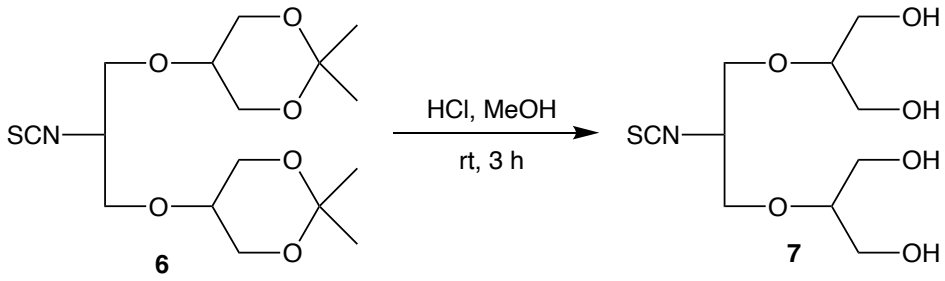
Procedure for the synthesis of compound 6:



To a stirred solution of **5** (134.0 mg, 0.388 mmol, 1.0 eq) in 1,4-dioxane (7.80 mL, 0.05 M), was added triphenylphosphine (122.1 mg, 0.466 mmol, 1.2 eq) and carbon disulfide (470 µL, 7.76 mmol, 20.0 eq) at room temperature. The resulting mixture was stirred at 40 ˚C for 48 h in a sealed flask. Then the reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography, eluted with ethyl acetate/hexane (1/1) as an eluent to afford **6** (125.0 mg, 89%) as a white solid.

FT-IR (neat) 2992, 2968, 2945, 2906, 2874, 2114, 1740, 1471, 1373, 1309, 1252, 1199, 1141, 1087, 1040, 1001, 968, 940, 887, 856 and 824 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.99 (dd, J = 12.0, 4.0 Hz, 4H), 3.93 (quint, J = 4.8 Hz, 1H), 3.77 (dd, J = 12.4, 6.0 Hz, 4H), 3.70 (dd, J = 9.6, 5.2 Hz, 2H), 3.67 (dd, J = 10.0, 5.6 Hz, 2H), 3.48 (quint, J = 5.2 Hz, 2H), 1.44 and 1.41 (s, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.5 (N**C**S), 98.3 (C), 71.4 (CH), 68.0 (CH_2), 62.4 (CH_2), 57.9 (CH), 23.8 (CH_3) and 23.4 (CH_3). HRMS (ESI-TOF) m/z calcd for $C_{16}H_{27}NNaO_6S$ $[M + Na]^+$ 384.1457, found 384.1433.

Procedure for the synthesis of compound 7:

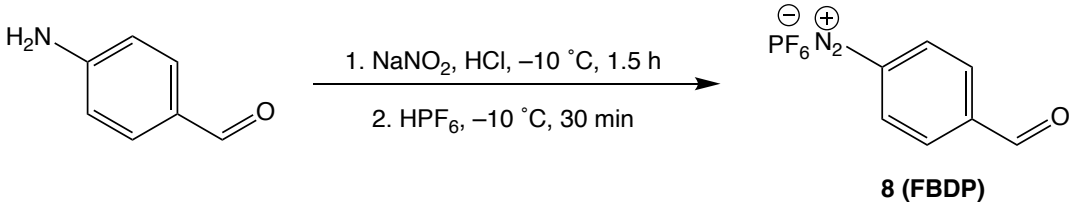


In methanol (0.1N of anhydrous hydrogen chloride, 3.0 mL) was added **6** (116.0 mg, 0.321 mmol) at room temperature and the resulting solution was stirred for 3 h at room temperature.

The resulting reaction mixture was concentrated *in vacuo* to afford **7** (80 mg, 0.284 mmol, 89%) as a colorless oil.

FT-IR (KBr) 3393, 2932, 2882, 2097, 1641, 1459, 1344, 1122, 1051, 970, 848, 672 and 496 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz) δ 4.04 (quint, J = 5.4 Hz, 1H), 3.84 (dd, J = 10.0, 4.8 Hz, 2H), 3.80 (dd, J = 10.0, 6.0 Hz, 2H), 3.66 (dd, J = 11.6, 4.8 Hz, 4H), 3.60 (dd, J = 11.6, 5.6 Hz, 4H) and 3.46 (quint, J = 5.6 Hz, 2H). ^{13}C NMR (CD_3OD, 125 MHz) δ 135.9 (N=C=S), 83.4 (CH), 70.5 (CH_2), 62.6 (CH) and 59.6 (CH_2). HRMS (ESI-TOF) m/z calcd for $C_{10}H_{19}NO_6SNa$ $[M + Na]^+$ 304.0831, found 304.0803.

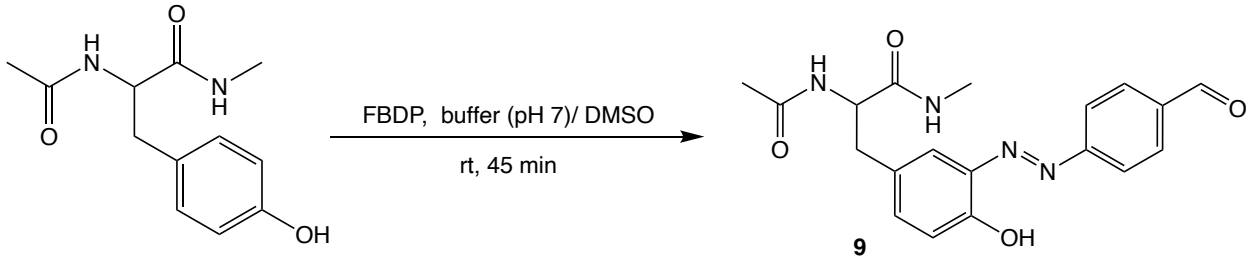
Procedure for the synthesis of compound 8 **[**Barbas *et al.*, *Bioconjugate Chem.,* **2012**, 23, 2321–2328]:



8 (FBDP)

To a stirred suspension of 4-aminobenzaldehyde polymer (5.00 g, 41.3 mmol. 1.00 eq) in 12N HCl (85 mL) was added the solution of sodium nitrite (3.42 g, 49.5 mmol, 1.20 eq) in water (67 mL) at –10 ˚C. The resulting solution was stirred at –10 ˚C. After 1.5 h, 60% hexafluorophosphoric acid in water (10.3 mL, 70.2 mmol, 1.70 eq) was added at –10 ˚C and stirred for 30 min. Then the reaction mixture was further stirred at room temperature for 30 min. The resulting solids were collected by filtration, and washed with water and ethyl acetate, dried *in vacuo* to afford 4-Formylbenzene diazonium hexafluorophosphate (FBDP) **8** (4.14 g, 36%) as an off-white solid.

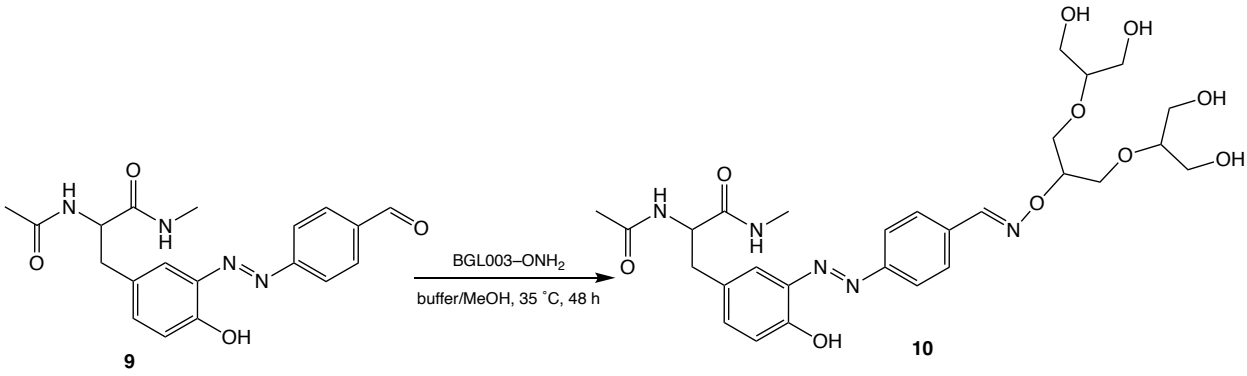
Procedure for the synthesis of compound 9 **[**Barbas *et al.*, *Bioconjugate Chem.,* **2012**, 23, 2321–2328]:



9

To a stirred solution of *N*-acyl tyrosine methylamide (20 mg, 0.0846 mmol, 1.00 eq) in 100 mM pH 7.0 NaH_2PO_4/Na_2HPO_4 buffer (2.83 mL) – DMSO (1.41 mL) was added **8 (FBDP)** (26 mg, 0.0931 mmol, 1.10 eq) at room temperature. The resulting solution was stirred at room temperature for 45 min and water (2.82 mL) was added into the reaction mixture. The generated solid was filtered and washed with water and ethyl acetate. The collected solid was dried *in vacuo* to afford **9** (30 mg, 95%) as a yellow solid.

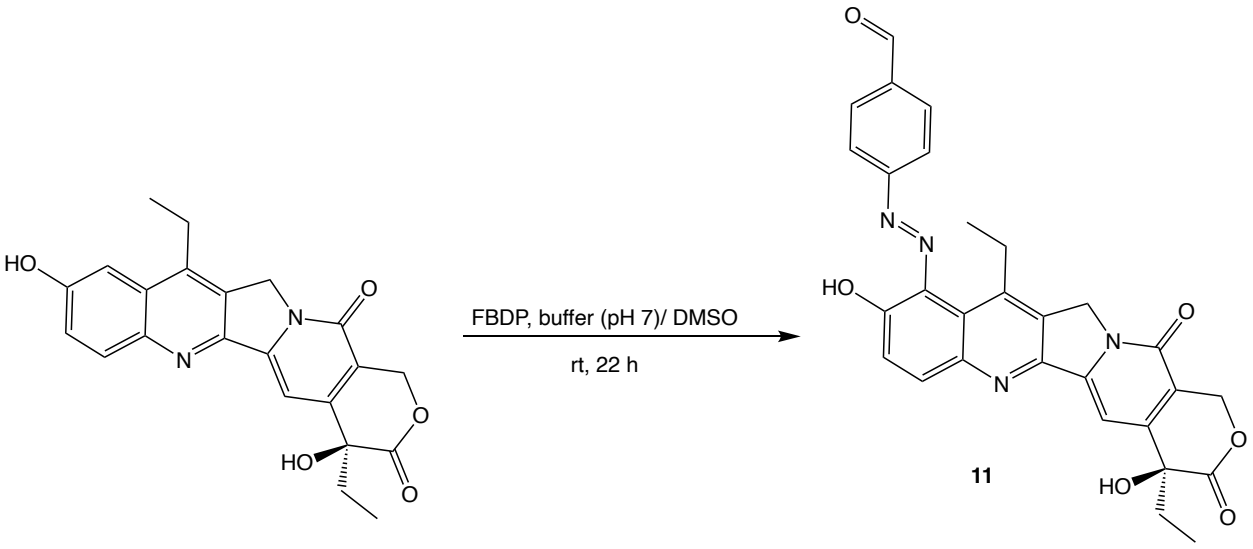
Procedure for the synthesis of compound 10:



To a stirred solution of **4** (BGL003–ONH_2) (30 mg, 0.1175 mmol, 1.50 eq) in 100 mM pH 7.0 NaH_2PO_4/Na_2HPO_4 buffer (0.978 mL) – methanol (2.936 mL) was added **10** (28 mg, 0.0783 mmol, 1.00 eq) at room temperature and the resulting solution was stirred for 96 h at 35 ˚C. The resulting reaction mixture was filtered off and the filtrate was concentrated *in vacuo*. Then the residue was purified by diaion column chromatography, eluted with ethanol/water (1/3) as an eluent to afford **10** (44 mg, 93%) as an orange solid.

FT-IR (KBr) 3401, 3281, 2924, 2878, 1635, 1552, 1491, 1453, 1424, 1373, 1281, 1207, 1118, 1069, 969, 841, 678 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) (E:Z isomer ratio = 9:1) δ 8.27 (s, 1H, C**H**=N), 7.96 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 7.82 (s, 1H), 7.30 (dd, J = 8.4, 2.4 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 4.61–4.54 (m, 2H), 4.00–3.95 (m, 4H, CHC**H₂**O), 3.71–3.61 (m, 8H, CHC**H₂**O), 3.50 (quint, J = 5.6 Hz, 2H, OC**H**$(CH_2)_2$), 3.16 (dd, J = 14.0, 6.4 Hz, 1H), 2.93 (dd, J = 14.0, 8.8 Hz, 1H), 2.71 (s, 3H, CH_3), 1.95 (s, 3H, CH_3); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.6 (**C**O), 171.8 (**C**O), 151.9 (C), 151.7 (C), 148.3 (CH=N), 137.5(C), 134.9 (C), 134.4 (CH), 130.5 (CH), 129.0 (C), 127.8 (CH), 122.4 (CH), 117.7 (CH), 82.2 (CH), 81.8 (CH), 68.6 (CH_2 × 2), 61.12 (CH_2 × 2), 61.1 (CH_2 × 2), 54.9 (CH), 36.7 (CH_2), 24.9 (CH_3), 21.1 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{28}H_{39}N_5O_{10}$ $[M]^+$ 628.2595, found 628.2592.

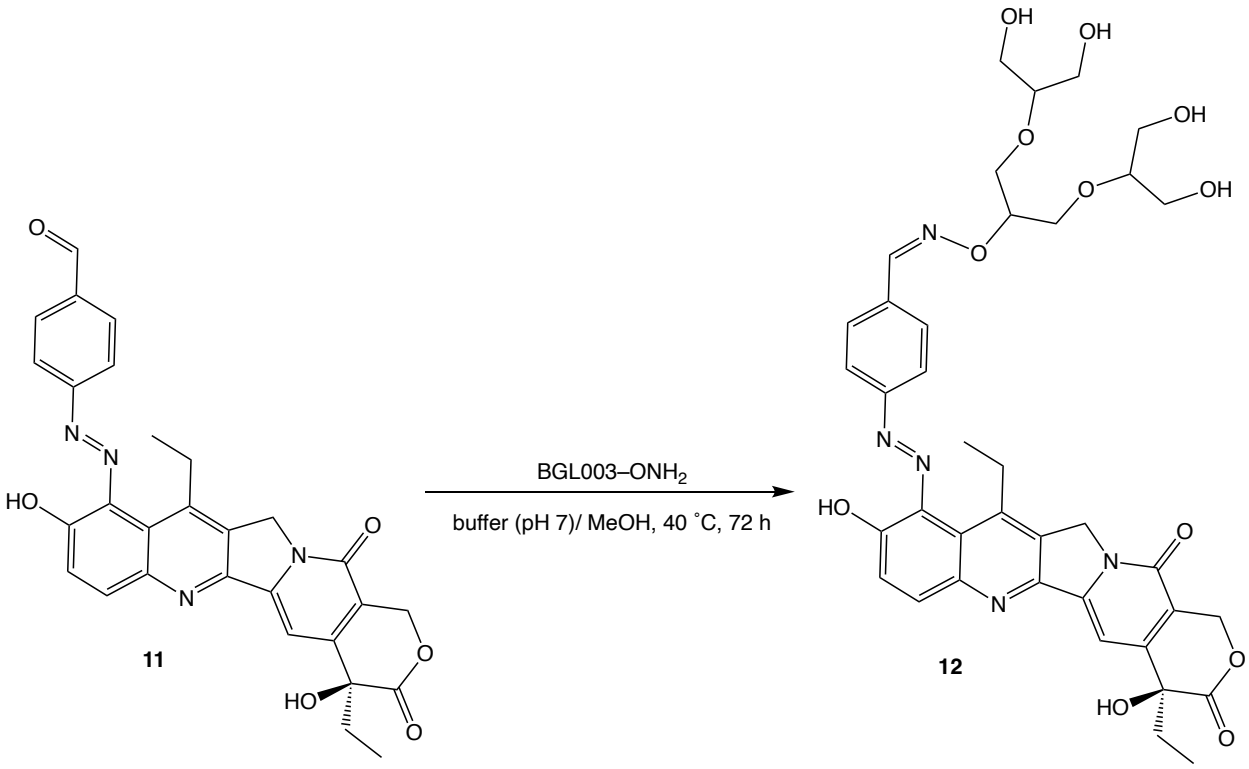
Procedure for the synthesis of compound 11:



To a stirred solution of SN38 (100 mg, 0.255 mmol, 1.00 eq) in 100 mM pH 7.0 NaH_2PO_4/Na_2HPO_4 buffer (8.50 mL) – DMSO (4.25 mL) was added **8 (FBDP)** (106 mg, 0.382 mmol, 1.50 eq) at room temperature. The resulting mixture was stirred at room temperature for 22 h and water (15 mL) was added into the reaction mixture. The generated solid was filtered and then washed with water and ethyl acetate, dried *in vacuo* to afford **11** (132 mg, 95%) as a red solid.

FT-IR (KBr) 3437, 2973, 2935, 2876, 2735, 1747, 1692, 1655, 1599, 1489, 1456, 1407, 1341, 1301, 1213, 1153, 1043, 1009, 941, 834, 809, 690, 647, 617, 494 cm^{-1}; ^1H NMR (DMSO-d6, 500 MHz) δ 9.90 (s, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 9.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.15 (s, 1H), 6.94 (d, J = 10 Hz, 1H), 6.53 (s, 1H), 5.37 (d, J = 5.5 Hz, 2H), 5.17 (s, 2H), 3.30 (q, J = 7.5 Hz, 2H), 1.92–1.83 (m, 2H), 1.30 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (DMSO-d6, 125 MHz) δ 191.9 (**C**HO), 179.5(O**C**O), 172.9 (N**C**O), 157.0, 150.5, 149.7, 148.2, 146.8, 146.1,145.5, 144.3, 134.1, 134.0, 132.2, 131.9, 131.9, 130.6, 126.8, 118.7, 117.7, 96.6 (CH), 72.8 (C), 65.6 (CH_2), 50.6 (CH_2), 30.8 (CH_2), 26.7 (CH_2), 12.6 (CH_3), 8.2 (CH_3); HRMS (ESI-TOF) m/z: calcd for $C_{29}H_{24}N_4O_6Na^+$ $[M + Na]^+$, 547.1594; found, 547.1599.

Procedure for the synthesis of compound 12:

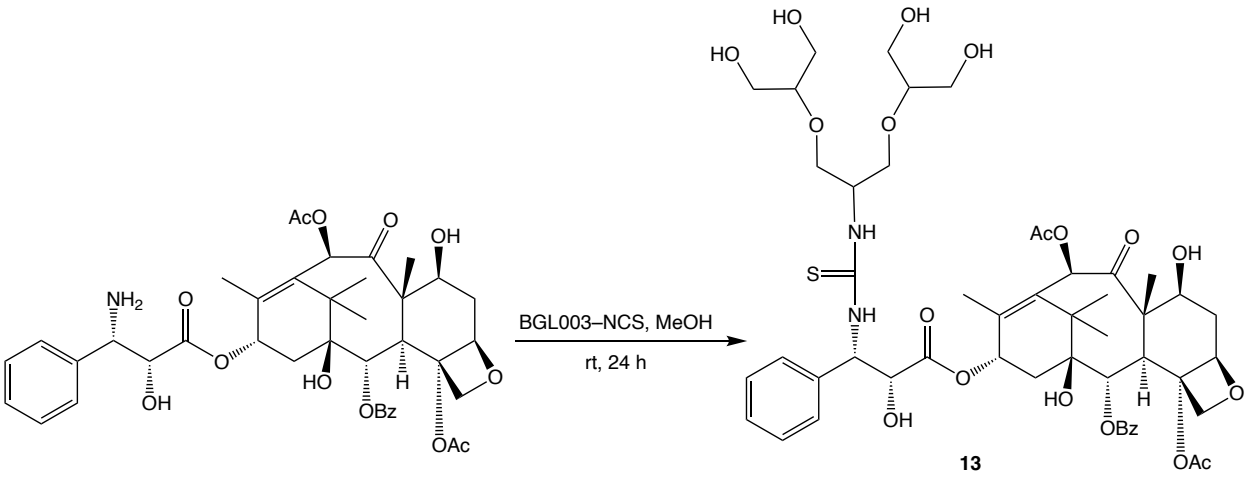


To a stirred solution of **4** (BGL003–ONH_2) (30 mg, 0.1175 mmol, 1.50 eq) in 100 mM pH 7.0 NaH_2PO_4/Na_2HPO_4 buffer (0.978 mL) – methanol (2.936 mL) was added **11** (41 mg, 0.0783 mmol, 1.00 eq) at room temperature. The resulting solution was stirred at 40 ˚C for 120 h. The reaction mixture was filtered off and the filtrate was concentrated *in vacuo*. Then the residue was washed with water (2.0 mL) and methanol (2.0 mL), the solid residue was collected, dried *in vacuo* to afford **12** (43.0 mg, 73%) as a deep red solid.

FT-IR (KBr) 3404, 3237, 2934, 2878, 1744, 1651, 1635, 1602, 1559, 1483, 1459, 1409, 1342, 1217, 1161, 1112, 1069, 964, 827, 604, 512 cm^{-1}; ^1H NMR (DMSO-d6, 500 MHz) (E:Z isomer ratio = 9:1) δ 8.31 (s, 1H), 8.06 (d, *J* = *9.5* Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.24 (s, 1H), 7.15 (d, *J* = *9*.5 Hz, 1H), 6.53 (brs,1H), 5.43 (s, 2H), 5.34 (s, 2H), 4.55 (brs, 4H), 4.38 (quint, *J* = 5.5 Hz, 1H), 3.79 (d, *J* = 5 Hz, 4H), 3.49–3.39 (m, 8H), 3.40 (quint, overlapped with HOD, 2H), 3.33 (q, *J* = 5 Hz, 2H), 1.92–1.83 (m, 2H), 1.38 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (DMSO-d6, 125 MHz) δ176.1 (O**C**O), 172.9 (N**C**O), 157.0, 150.5, 149.4, 148.4, 147.5, 146.2, 145.1, 143.9, 143.0, 133.8, 131.4, 131.3, 129.9, 128.9, 126.8, (118.6, 118.6 overlapped), 96.5, (82.6, 82.6 overlapped), 72.8, 68.8, 65.7, 61.3, 61.26 (CH_2),

49.1 (CH_2), 30.8 (CH_2), 26.8 (CH_2), 12.8 (CH_3), 8.3 (CH_3); HRMS (ESI-TOF) m/z calcd for $C_{38}H_{43}N_5O_{12}Na$ $[M + Na]^+$ 784.2806, found 784.2797.

Procedure for the Synthesis of compound 13:

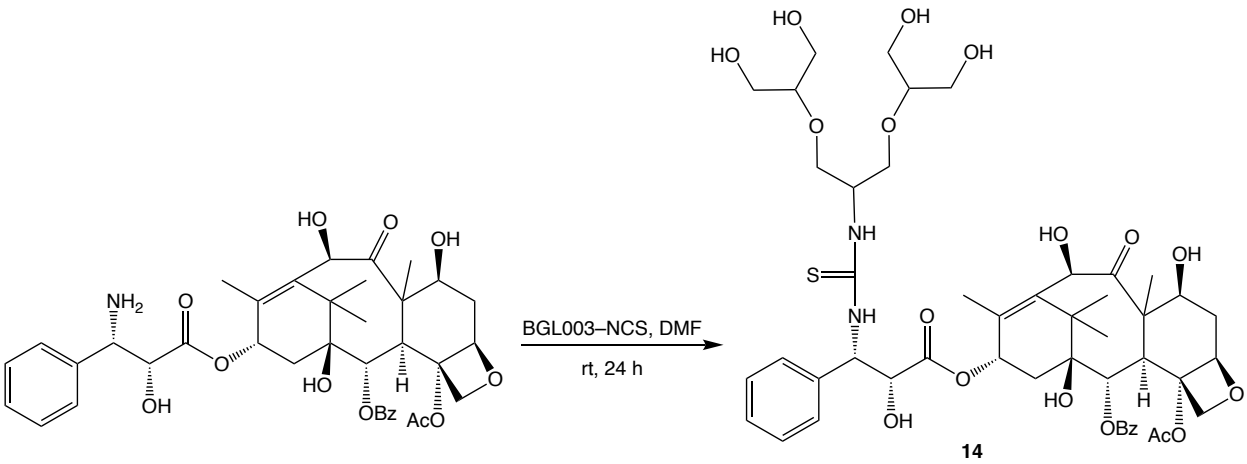


To a stirred solution of 3′-debenzoylated paclitaxel (50 mg, 0.067 mmol, 1.00 eq) in methanol (0.30 mL) was added **7** (BGL003–NCS) (25 mg, 0.089 mmol, 1.30 eq) at room temperature and the resulting solution was stirred for 24 h at room temperature. Then the reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography, eluted with DCM/methanol (4/1) to give **13** (55 mg, 80%) as a white solid.

FT-IR (KBr) 3425, 3073, 3031, 2938, 2893, 1719, 1637, 1541, 1454, 1373, 1310, 1247, 1183, 1114, 1070, 1023, 979, 906, 852, 805, 784, 712 and 672 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz) δ 8.15 (d, J = 7.2 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 8.0 Hz, 2H), 7.46–7.38 (m, 4H), 7.30 (t, J = 7.6 Hz, 1H), 6.50 (s, 1H), 6.34 (t, J = 9.6 Hz, 1H), 6.30 (brs, 1H), 5.68 (d, J = 7.6 Hz, 1H), 5.02 (d, J = 8.0 Hz, 1H), 4.79 (brs, 1H), 4.60 (brs, 1H), 4.37 (dd, J = 10.8, 6.4 Hz, 1H), 4.26 (d, J = 8.4 Hz, 1H), 4.20 (d, J = 8.4 Hz, 1H), 3.91 (d, J = 7.6 Hz, 1H), 3.89–3.79 (m, 2H), 3.70–3.40 (m, 12H), 2.55–2.46 (m, 2H), 2.50 (s, 3H), 2.36–2.29 (m, 1H), 2.20 (s, 3H), 1.97 (s, 3H), 1.88–1.80 (m, 1H), 1.70 (s, 3H), 1.23 (s, 3H) and 1.19 (s, 3H). ^{13}C NMR (CD_3OD, 125 MHz) δ 205.2 (**C**=O), 184.4 (N–**C**=S), 174.4 (**C**=O), 172.2 (**C**=O), 171.4 (**C**=O), 167.9 (**C**=O), 142.4 (C), 140.8 (C), 135.0 (C), 134.5 (CH), 131.4 (C), 131.3 (CH), 129.8 (CH), 129.5 (CH), 128.5 (CH), 128.2 (CH), 85.9 (CH), 82.9 (CH), 82.4 (C), 79.4 (C), 77.6 (CH_2), 76.9 (CH), 76.6 (CH), 74.4 (CH), 72.5 (CH), 72.4 (CH), 69.2 (CH_2), 62.7 (CH_2), 62.6 (CH_2), 62.5 (CH_2), 62.4 (CH_2), 60.6 (CH), 59.3 (C), 55.5 (CH), 48.0 (CH), 44.7 (C), 37.5 (CH_2), 37.4 (CH_2),

27.1 (CH_3), 23.4 (CH_3), 22.6 (CH_3), 20.8 (CH_3), 14.9 (CH_3) and 10.5 (CH_3). HRMS (ESI-TOF) m/z calcd for $C_{50}H_{66}N_2O_{19}NaS$ $[M + Na]^+$ 1053.3878, found 1053.3900.

Procedure for the Synthesis of compound 14:



To a stirred solution of 3′-de(*tert*-butyloxycarbonyl) docetaxel (77 mg, 0.108 mmol, 1.00 eq) in DMF (0.30 mL) was added **7** (BGL003–NCS) (30 mg, 0.108 mmol, 1.00 eq) at room temperature and the resulting solution was stirred for 24 h at room temperature. Then the reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography, eluted with DCM/methanol (4/1) to afford **14** (85 mg, 80%) as a white solid. FT-IR (KBr) 3414, 2933, 2882, 1718, 1636, 1541, 1460, 1372, 1321, 1272, 1177, 1108, 1067, 985, 709 and 667 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz) δ 8.13 (d, J = 7.2 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.44–7.36 (m, 4H), 7.28 (t, J = 7.2 Hz, 1H), 6.34 (t, J = 9.2 Hz, 1H), 6.28 (brs, 1H), 5.64 (d, J = 7.2 Hz, 1H), 5.28 (s, 1H), 5.00 (d, J = 7.6 Hz, 1H), 4.76 (brs, 1H), 4.56 (brs, 1H), 4.27–4.21 (m, 2H), 4.18 (d, J = 8.4 Hz, 1H), 3.93 (d, J = 7.2 Hz, 1H), 3.85–3.77 (m, 2H), 3.69–3.36 (m, 12H), 2.51–2.41 (m, 2H), 2.48 (s, 3H), 2.32–2.25 (m, 1H), 1.93 (s, 3H), 1.87–1.80 (m, 1H), 1.71 (s, 3H), 1.21 (s, 3H) and 1.13 (s, 3H). ^{13}C NMR (CD_3OD, 125 MHz) δ 211.2 (**C**=O), 178.1 (N–**C**=S), 174.4 (**C**=O), 172.1 (**C**=O), 167.9 (**C**=O), 140.8 (C), 139.5 (C), 137.9 (C), 134.5 (CH), 131.5 (C), 131.3 (CH), 129.8 (CH), 129.6 (CH), 128.5 (CH), 128.2 (CH), 86.0 (CH), 82.9 (CH), 82.4 (C), 79.5 (C), 77.7 (CH_2), 76.8 (CH), 75.7 (CH), 74.4 (CH), 72.7 (CH), 72.7 (CH), 69.2 (CH_2), 62.7 (CH_2), 62.6 (CH_2), 62.5 (CH_2), 62.4 (CH_2), 60.5 (CH), 58.9 (C), 55.5 (CH), 48.0 (CH), 44.6 (C), 37.6 (CH_2), 37.5 (CH_2), 27.2 (CH_3), 23.5 (CH_3), 21.9 (CH_3), 14.5 (CH_3) and 10.6 (CH_3). HRMS (ESI-TOF) m/z calcd for $C_{48}H_{64}N_2O_{18}NaS$ $[M + Na]^+$ 1011.3773, found 1011.3748.

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19. Detail of other examinations are planning to be submitted to the more suitable journals such as *Surface & Coating Technology.*
20. At early period, lipophilic thiol was used as a solution of halogenated hydrocarbons such as 1,2-dichloroethane [3], which is negative impact on the environment. After the use of such a solvent was strictly prohibited under the law in various countries, ethanol has been used instead.
21. When the experiment reported in Figure 3 was carried out, the solution of **1** in ethanol was slightly cloudy. The solubility of **1** in ethanol was not as high as expected. Due to the inhomogeneity, the mottled pattern may be generated on the surface of **Y1**.
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