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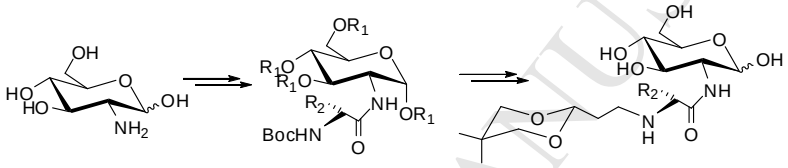
Graphic Abstract

Design, synthesis and evaluation of a novel class of glucosamine mimetic peptides containing 1,3-dioxane

Li Zeng [a], Pengchao Gao[b], Meng Zhang[a], Guichao Xu[a], Hong Li[a], and Jianwei Zhang* [a]

Some novel glucosamine mimetic peptides containing 1,3-dioxane were obtained and evaluated for their anti-inflammatory effect.



Inhibition ratio (%) : 64.3 Inhibition ratio (%) : 80.3- 88.7

Wherein R_1 = Ac or Bn; R_2 = $CH(CH_3)CH_2CH_3$, $CH_2C_6H_5$, $CH(CH_3)_2$, CH_3,  or $CH_2CH(CH_3)_2$.

Design, synthesis and evaluation of a novel class of glucosamine mimetic peptides containing 1,3-dioxane

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ABSTRACT

A number of novel 2-(*N*-(2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl)aminoacyl)amino-2-deoxy-D-glucopyranoside were synthesized from a readily available starting material, glucosamine, 2,2-dimethyl-1,3-propanediol and 1,1,3,3-tetramethoxypropane, and evaluated for their anti-inflammatory activity. Our results showed that all of the compounds tested exhibited a significant inhibition of xylene-induced inflammation in mice.

Keywords: Amino sugar; 1,3-Dioxane; Glucosamine; Inflammation

1. Introduction

Inflammatory diseases are widely prevalent throughout the world and affect many people's lifes. Inflammation is a normal protective response of mammalian tissues to a variety of hostile agents including infectious organisms, noxious chemicals, physical injury or tumor growth leading to local accumulation of plasmic fluid and blood cells. Although inflammation is a defense mechanism, the complex events and mediators involved in the inflammatory response can induce and aggravate many disorders. Inflammation is involved in various clinical conditions such as arthritis, cancer and vascular diseases.

Drugs used for the treatment of acute and chronic inflammatory disorders are usually directed at the inflammatory processes. Hence, the employment of anti-inflammatory agents may be helpful in the treatment of those conditions associated with inflammatory reactions. Many non-steroidal anti-inflammatory agents on the market have been of immense help in the management of various inflammatory conditions like rheumatism, arthritis and breast pain. However, there is always a need for the development of better anti-inflammatory agents.

The dioxane moiety is a common structural motif in a number of bioactive molecules. In 1966, the 1,3-dioxolane derivative dexoxadrol was synthesized and pharmacologically evaluated as a local anesthetic and general anesthetic drug [1]. Recently, 1,3-dioxanes have been evaluated as effective modulators for multi-drug resistance [2] and reported with anti-inflammatory activities [3]. Some 2,5-multisubstituted-1,3-dioxane derivatives have been identified to have significant biological activities or can be converted into active compounds [4-5]. Though promising anti-inflammatory agents substituted 1,3-dioxanes were prepared in some laboratories and the importance for both 2- and 5-position substitutions was explored [6-9], the diversity of substitutions at positions 2, 5 was still poor.

Glucosamine (GlcN), an amino monosaccharide, is the most common amino sugar and is generally

found as an *N*-acetylated and β-linked glycoside. It is found in connective tissues and gastrointestinal mucosal membranes. However, the ability to synthesize GlcN in the body declines with age. This, in turn, incapacitates the generation of proteoglycan, which is known to result in senile osteoarthritis (OA) [10-11]. Therefore, GlcN salts (sulfate and chloride) are thought to be beneficial in promoting the repair of damaged cartilage. Since the first publication of W. Bohne in 1969 showing that GlcN can be used to relieve the symptoms of OA, GlcN has received a great deal of attention from the public as a potential treatment for OA [12-13]. Furthermore, GlcN possesses antioxidant activities due to its pronounced reducing power, superoxide/hydroxyl-radical scavenging ability. It has been reported that GlcN possesses a unique anti-inflammatory activities and inhibits IL-1β and TNF-α-induced NO production in normal human articular chondrocytes [14]. It is also beneficial for inflammatory bowel diseases [15].

One of the successful and effective approaches in the search for new bioactive agents is to synthesize novel compounds by simple chemical modifications of lead compounds. In view of the pharmacological importance of glucosamine as well as 1,3-dioxolane it has been considerably worthwhile to prepare some new chemical entities containing glucosamine and 1,3-dioxolane moieties. All these observation encouraged us to explore the synthesis of glucosamine containing 1,3-dioxolane moieties and examine their activities as anti-inflammatory agents. Amide bond is stable in buffer solution at pH 7.4 and in culture medium. Amide structure is found in various natural products, pharmaceuticals, and polymers. Amides may be prepared by coupling reactions between carboxylic acids and amines [16-18]. The synthetic design used for preparation of glycosyl amides was based upon a number of reasons: (1) GlcN possesses some biological activity; (2) *N*-acetylglucosamine has several potential advantages over GlcN as a potential therapeutic anti-inflammatory agent [19]. In

addition, amino acid conjugates might target the gastrointestinal transporters involved in the absorption of amino acids and small peptides resulting in improved oral bioavailability [20]. Moreover, amino acids are attractive because they possess structurally diverse side chains. The various side chains of different amino acids allow the addition of amino acids to 1,3-dioxane to manipulate the pharmacokinetics profiles of the compounds. Furthermore, various amino acids can be introduced to enhance solubility. Therefore, in order to search for better anti-inflammatory agents, a novel class of glucosamine mimetic peptides containing 1,3 dioxane were designed and synthesized and evaluated for their anti-inflammatory activity.

2. Chemistry

The synthesis of the corresponding 2-(2,2-dimethoxylethyl)-5,5-dimethyl-1,3-dioxane (Compound **3**) has been achieved, as shown in Scheme 1, starting from the readily available 2,2-Dimethyl-1,3-propanediol (Compound **1**) with 1,1,3,3-tetramethoxypropane (Compound **2**) under acidic conditions in 65% yield as a major product [21]. The minor product, assigned as bis(5,5-dimethyl-1,3-dioxane-2-yl)-methane (Compound **3'**) was obtained in 20% yield. Then the reaction of Compound **3** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in aqueous acetonitrile afforded 3-(5,5-dimethyl-1,3-dioxane-2-yl)-propanal (Compound **4**) in 51% yield.

The synthetic routes for the preparation of glucosamine mimetic peptides containing 1,3 dioxane from glucosamine (GlcN) salt (chloride) **1** as starting material were presented in Schemes 2 and 3. Acylation of GlcN chloride with $(Boc)_2O$ resulted in *N*-Boc-glucosamine (Compound **6**). The free OH groups of *N*-Boc-glucosamine **6** were benzylated with NaH and BnBr to give 1,3,4,6-tetra-*O*-benzyl-2-(*tert*-butyloxycarbonylamino)-2-deoxy-D-glucopyranoside (Compound **7**) [22]. Subsequently, Boc groups of 7 were removed by subjecting 7 to trifluoroacetic acid in

dichloromethane to give *N*-terminal free intermediates (Compound **8**). **8** was further reacted with Boc-protected amino acids by the DCC/HOBt/*N*-methylmorpholine (NMM) procedure to give 1,3,4,6-Tetra-*O*-benzyl-2-(*N*-Boc-aminoacylamino)-2-deoxy-α-D-glucopyranoside (Compounds **9a-f**). The ^{1}H NMR spectra of **9a–f** showed signals for their anomeric protons as doublets with coupling constants of 3.6 Hz. In all cases, a noteworthy point is that sole the α-anomers are the products, which can be attributed to the anomeric effect. Subsequently, removal of the Boc group with hydrogen chloride in ethyl acetate led to a set of amine **10a-f** and subsequent coupling with the Compound **4** gave 2-(*N*-(2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl)aminoacyl)amino-1,3,4,6-tetra-*O*-benzyl-2-deoxy-α-D-glucopyranoside (Compounds **11a-f**) (chemical yields, 33–54%). ^{1}HNMR spectra indicated that **11a-f** were α-anomers. Effort was made with the aim of preparing 2-(*N*-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)aminoacyl)amino-2-deoxy-D-glucopyranoside (Compounds **16a-f**) through removal of the benzyl group from Compounds **11a-f** by palladium catalyzed hydrogenolysis. However, the attempt was unsuccessful. Another synthetic strategy was developed to remedy the failure of the previously adopted approach as shown in Scheme **3**. GlcN chloride was acetylated with acetic anhydride in sulfuric acid to give 2-amino-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucosamine (Compound **12**). **12** was further reacted with Boc-protected amino acids by the DCC/HOBt/*N*-methylmorpholine (NMM) procedure to afford 1,3,4,6-Tetra-*O*-acetyl -2-(*N*-Boc-aminoacylamino)-2-deoxy-α-D-glucopyranoside (Compounds **13a-f**) as single α-anomers (chemical yields, 31–56%). Subsequently, removal of the Boc group with hydrogen chloride in ethyl acetate led to a set of amine **14a-f** and subsequent coupling with the Compound **4** in the presence of $NaCNBH_3$ yielded 2-(*N*-(2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl)aminoacyl)amino-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-

glucopyranoside (Compounds **15a-f**) (chemical yields, 44–79%). The ^{1}H NMR spectra of **15a–f** showed signals for their anomeric protons as doublets with coupling constants of 3.6 Hz. ^{1}HNMR spectra indicated that **15a-f** were α-anomers. Finally, Compounds **15a-f** was deacetylated with sodium methoxide in methanol to give Compounds **16a-f** in 39–51% yield as a mixture of anomers. The structures of glucosamine mimetic peptides containing 1,3 dioxane are shown in Table 1. The structures of all new compounds were unambiguously characterized with ^{1}H NMR, ^{13}C NMR, mass spectrometry and high-resolution mass spectrometry and are in very good agreement with their analytical and spectroscopic data (see Experimental part).

3. Pharmacology

3.1. Anti-inflammatory activity of glucosamine mimetic peptides containing 1,3 dioxane

Compounds **5**, **11a-f, 15a-f** and **16a-f** were screened for their anti-inflammatory activity by using a xylene-induced ear edema model assay. [21]. The compounds **16a-f** used in the anti-inflammatory activity are a mixture of anomers. Mice administered orally by gavage with 0.5% carboxymethyl cellulose (CMC) suspension were used as negative control, and mice administered orally with Aspirin (at a dosage of 100 mg/kg) in CMC were used as positive control. The compounds tested were prepared as suspensions in 0.5% CMC at the concentration of 1 mM and were administered orally to the animals at a dosage of 10 μmol/kg 30 min before xylene was applied to both the anterior and posterior surfaces of the right ear. The left ear was considered as control. The extent of ear edema was evaluated by the weight difference between the right and the left ear biopsies of the same animal. The anti-inflammatory effect was defined by inhibition ratio (%) as:

$$\text{Inhibition ratio \%} = (1 - A/B) \times 100\%$$

A: The increase in weight caused by xylene

B: The weight of the untreated left ear section

The percentage of inhibition is used as an indication of anti-inflammatory activity. The anti-inflammatory activity of these derivatives is summarized in Table 2. The results showed that all of the compounds tested exhibited a significant inhibitory activity against xylene-induced ear edema in mice in comparison with the negative control group. The tested compounds showed inhibition ratio ranging from 70.6% to 90.3% ($P < 0.01$). It was found that most of tested compounds exhibited anti-inflammatory effect similar to or better than the positive control, aspirin. To understand the contribution of the 1, 3-dioxane to the anti-inflammatory activity observed, glucosamine GlcN (Compound **5**) was used as a reference compound. Comparison of the inhibition ratio values (70.6-90.3%) of tested compounds with that of GlcN (64.3%) showed that the presence of 1,3-dioxane increased the activity, suggesting that the 1,3-dioxane structure had a positive contribution to the activity. This research provided useful information for the further design of novel potent anti-inflammatory agents.

3.2. Effect of dose on anti-inflammatory activity

16a was selected to further explore the effect of dose on the anti-inflammatory activity. As shown in Table **3**, at 0.1, 1, and 10 μmol/kg, **16a** exhibited inhibition ratio of 44.3, 70.8 and 88.7%, respectively.

4. Conclusion

In summary, a novel class of glucosamine mimetic peptides containing 1,3 dioxane were designed, synthesized and evaluated for their anti-inflammatory effect. 1,3-Dioxane structure had a positive contribution to the activity. It was found that most of tested compounds exhibited anti-inflammatory effect similar to or better than the positive control, aspirin.

5. Experimental

5.1. Chemistry

5.1.1. General methods

Unless otherwise stated, all reactions were under a nitrogen atmosphere (1 bar). All reagents used were purchased from Sigma Chemical Co (USA). Optical rotations were determined with a Schmidt+Haensch Polartromic D instrument (Germany). IR spectra were recorded with an Avatar 330, Nicolet, USA spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300MHz on a VXR-300 instrument or at 500MHz on a Bruker Am-500 instrument in $CDCl_3$ or in DMSO-*d*6 with tetramethylsilane as internal standard and chemical shifts are expressed in ppm (δ). Chromatography was carried out using Qingdao silica gel H (Qingdao of China). The purity of the intermediates and the products was confirmed by TLC (Merck silica gel plates of type 60 F_{254}, 0.25 mm layer thickness, Germany) and HPLC (Waters, C_{18} column 4.6×150 mm, USA). Mass spectra (MS) were acquired on a Quattro Micro ZQ2000, Waters, USA instrument and m/z values are reported. High-resolution mass spectra were recorded with micrOTOF-Q mass spectrometer.

5.1.2. 1,3,4,6-Tetra-O-benzyl-2-(N-Boc-isoleucinylamino)-2-deoxy-α-D-glucopyranoside

HOBt (80.0 mg, 0.593 mmol) and DCC (124 mg, 0.602 mmol) were added to a solution of Boc-L-Ile-OH (127 mg, 0.550 mmol) in anhydrous THF (10 mL) at 0°C. The mixture was stirred at 0°C for 30 min. Compound **8** (270 mg, 0.500 mmol) in anhydrous THF (10 mL) was added and pH was adjusted to 9 with *N*-methylmorpholine. The mixture obtained was kept at 0°C for 1 h followed by at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50 mL). The mixture obtained was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under

reduced pressure, purification of the residue by recrystallization in petroleum ether-dichloromethane provided the title product, Compound **9a** (223 mg, 0.297 mmol, 59%). [α] $^{25}_{D}$ +36.9 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3315, 1683, 1654; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.38 ~ 7.27 (18H, m, Ar-H), 7.14 ~ 7.12 (2H, m, Ar-H), 6.16 (1H, d, *J* = 9.6 Hz, N-H), 4.94 (1H, d, *J* = 3.6 Hz, H-1), 4.82 ~ 4.50 (9H, m, H-2, CH_2), 4.36 (1H, m, CH), 3.95 ~ 3.67 (5H, m, H-3, H-4, H-5, H-6, H-6'), 1.97 ~ 1.87 (2H, m, CH, N-H), 1.45 (9H, s, CH_3), 1.39 ~ 1.32 (m, 1H, CH), 0.86 (3H, d, *J* = 6.9 Hz, CH_3), 0.78 (3H, t, *J* = 7.5 Hz, CH_3); ^{13}CNMR (75 MHz, $CDCl_3$): δ 171.4, 155.7, 138.3, 138.1, 138.0, 137.2, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.6, 127.4, 97.1, 80.5, 78.2, 75.0, 74.7, 73.5, 71.2, 69.8, 68.6, 52.9, 36.8, 33.9, 28.3, 25.6, 24.9, 24.3, 15.7, 11.3; ESIMS *m/z* 753.4 (M+1); HRMS calcd for: ($C_{25}H_{40}N_3O_{12}$ + 1), *m/z* (753.4109); found, *m/z* (753.3951).

5.1.3. 1,3,4,6-Tetra-O-benzyl-2-(N-Boc-phenylalanylamino)-2-deoxy-α-D-glucopyranoside

HOBt (80.0 mg, 0.593 mmol) and DCC (124 mg, 0.602 mmol) were added to a solution of Boc-L-Phe-OH (146 mg, 0.550 mmol) in anhydrous THF (10 mL) at 0℃. The reaction mixture was stirred at 0℃ for 30 min. Compound **8** (270 mg, 0.500 mmol) in anhydrous THF (10 mL) was added and pH was adjusted to 9 with *N*-methylmorpholine. The reaction mixture obtained was kept at 0℃ for 1 h followed by at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50 mL). The solution was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by recrystallization in petroleum ether-dichloromethane afforded the title product, Compound **9b** (130 mg, 0.165 mmol, 33%). [α] $^{25}_{D}$ +51.4 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3323, 1687, 1654; ^{1}HNMR (500 MHz, $CDCl_3$): δ7.38 ~ 7.14 (25H, m, Ar-H), 6.26

(1H, d, *J* = 9.3 Hz, N-H), 4.94 (1H, d, *J* = 3.6 Hz, H-1), 4.82 ~ 4.35 (10H, m, CH_2), 4.36 (1H, dt, J_1 = 3.3 Hz, J_2 = 9.3 Hz, CH), 3.95 ~ 3.67 (4H, m, H-2, H-3, H-4, H-5), 3.04 (2H, m, H-6, H-6'), 1.38 (9H, s, CH_3); ^{13}CNMR (125 MHz, $CDCl_3$): δ171.0, 155.3, 138.4, 138.1, 137.1, 136.6, 129.3, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.8, 127.7, 127.6, 127.0, 97.3, 80.9, 80.2, 78.0, 75.1, 75.0, 73.5, 71.2, 69.8, 68.6, 55.7, 52.9, 49.2, 37.8, 33.9, 28.2, 25.6, 25.0; ESIMS *m/z* 787 (M+1); HRMS calcd for: ($C_{25}H_{40}N_3O_{12}$ + 1), *m/z* (787.3953); found, *m/z* (787.3898).

5.1.4. 1,3,4,6-Tetra-O-benzyl-2-(N-Boc-valinylamino)-2-deoxy-α-D-glucopyranoside

HOBt (80.0 mg, 0.593 mmol) and DCC (124 mg, 0.602 mmol) were added to a solution of Boc-L-Val-OH (119 mg, 0.550 mmol) in anhydrous THF (10 mL) at 0℃. The mixture was stirred at 0℃ for 30 min. Compound **8** (270 mg, 0.500 mmol) in anhydrous THF (10 mL) was then added and pH was adjusted to 9 with *N*-methylmorpholine. The reaction mixture obtained was kept at 0℃ for 1 h followed by at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50 mL). The solution was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by recrystallization in petroleum ether-dichloromethane afforded the title product, Compound **9c** (177 mg, 0.240 mmol, 48%). [α] $^{25}_{D}$ +14.6 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3323, 2929, 1683; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.39 ~ 7.27 (18H, m, Ar-H), 7.15 ~ 7.12 (2H, m, Ar-H), 6.10 (1H, d, *J* = 9.3 Hz, N-H), 4.94 (1H, d, *J* = 3.6 Hz, H-1), 4.82 ~ 4.50 (8H, m, CH_2), 4.35 (1H, dt, J_1 = 3.3 Hz, J_2 = 9.6 Hz, CH), 3.92 ~ 3.66 (6H, m, CH), 1.45 (9H, s, CH_3), 0.89 (3H, d, *J* = 6.9 Hz, CH_3), 0.76 (3H, d, *J* = 6.6 Hz, CH_3); ^{13}CNMR (75 MHz, $CDCl_3$): δ171.5, 155.7, 138.3, 138.1, 138.0, 137.1, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.6, 127.5, 97.2, 80.5, 78.3, 77.2, 75.0,

74.8, 73.5, 71.2, 69.8, 68.6, 60.2, 52.9, 49.3, 33.9, 30.6, 28.3, 25.6, 24.9, 19.4, 17.1; ESIMS *m/z* 739 (M+1); HRMS calcd for: ($C_{25}H_{40}N_3O_{12}$ + 1), *m/z* (739.3953); found, *m/z* (739.3868).

5.1.5. 1,3,4,6-Tetra-O-benzyl-2-(N-Boc-alanylamino)-2-deoxy-α-D-glucopyranoside

HOBt (80.0 mg, 0.593 mmol) and DCC (124 mg, 0.602 mmol) were added to a solution of Boc-L-Ala-OH (105 mg, 0.550 mmol) in anhydrous THF (10 mL) at 0℃. The reaction mixture was stirred at 0℃ for 30 min. Compound **8** (270 mg, 0.500 mmol) in anhydrous THF (10 mL) was added and pH was adjusted to 9 with *N*-methylmorpholine. The reaction mixture obtained was kept at 0℃ for 1 h followed by at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50 mL). The mixture was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by recrystallization in petroleum ether-dichloromethane afforded the title product, Compound **9d** (203 mg, 0.286 mmol, 57%). $[\alpha]^{25}_D$ +54.4 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3331, 3316, 2929, 1687, 1658; ^{1}HNMR (300 MHz, $CDCl_3$): δ7.42 ~ 7.26 (18H, m, Ar-H), 7.18 ~ 7.15 (2H, m, Ar-H), 6.17 (1H, d, *J* = 9.3 Hz, N-H), 4.94 (1H, d, *J* = 3.6 Hz, H-1), 4.82 ~ 4.50 (8H, m, CH_2), 4.35 (1H, dt, J_1 = 3.6 Hz, J_2 = 9.6 Hz, CH), 4.06 (1H, t, *J* = 7.2 Hz, H-2), 3.90 ~ 3.66 (5H, m, CH), 1.44 (9H, s, CH_3), 1.27 (3H, d, *J* = 7.2 Hz, CH_3); ^{13}CNMR (75 MHz, $CDCl_3$): δ 172.2, 155.3, 138.4, 138.1, 138.0, 137.2, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 97.2, 81.0, 80.0, 78.2, 77.2, 75.1, 75.0, 73.5, 71.3, 69.8, 68.6, 52.9, 50.4, 49.2, 33.9, 30.6, 28.3, 25.6, 24.9, 18.4; ESIMS *m/z* 711 (M+1); HRMS calcd for: ($C_{25}H_{40}N_3O_{12}$ + 1), *m/z* (711.3640); found, *m/z* (711.3533).

5.1.6. 1,3,4,6-Tetra-O-benzyl-2-(N-Boc-tryptophanylamino)-2-deoxy-α-D-glucopyranoside

HOBt (80.0 mg, 0.593 mmol) and DCC (124 mg, 0.602 mmol) were added to a solution of Boc-L-Trp-OH (167 mg, 0.550 mmol) in anhydrous THF (10 mL) at 0℃. The reaction mixture was stirred at 0℃ for 30 min. Compound **8** (270 mg, 0.500 mmol) in anhydrous THF (10 mL) was then added and pH was adjusted to 9 with *N*-methylmorpholine. The reaction mixture obtained was kept at 0℃ for 1 h followed by at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50 mL). The mixture obtained was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by recrystallization in petroleum ether-dichloromethane afforded the title product, Compound **9e** (295 mg, 0.358 mmol, 72%). $[\alpha]_D^{25}$ +19.7 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3321, 1687, 1655; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.65 (1H, d, *J* = 7.5 Hz, Ar-H), 7.37 ~ 6.95 (24H, m, Ar-H), 6.20 (1H, d, *J* = 9.3 Hz, N-H), 5.00 (1H, m, N-H), 4.75 ~ 4.41 (9H, m, CH_2, H-1), 4.32 (1H, dt, J_1 = 3.6 Hz, J_2 = 9.6 Hz, CH), 4.09 (1H, d, *J* = 11.4 Hz, CH_2), 3.81 ~ 3.62 (5H, m, CH, CH_2), 3.36 (1H, dd, J_1 = 4.8 Hz, J_2 = 14.4 Hz, H-6), 3.14 (1H, dd, J_1 = 6.9 Hz, J_2 = 14.7 Hz, H-6'), 1.38 (9H, s, CH_3); ^{13}CNMR (75 MHz, $CDCl_3$) δ 171.6, 155.3, 138.6, 138.1, 137.2, 136.2, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 123.1, 122.4, 119.8, 119.0, 111.2, 110.5, 97.4, 80.8, 80.1, 77.9, 77.2, 75.0, 74.6, 73.5, 71.1, 69.8, 68.6, 52.9, 33.8, 28.2; ESIMS *m/z* 826 (M+1); HRMS calcd for: ($C_{25}H_{40}N_3O_{12}$ + 1), *m/z* (826.4062); found, *m/z* (826.3886).

5.1.7. 1,3,4,6-Tetra-O-benzyl-2-(N-Boc-leucylamino)-2-deoxy-α-D-glucopyranoside

HOBt (80.0 mg, 0.593 mmol) and DCC (124 mg, 0.602 mmol) were added to a solution of Boc-L-Leu-OH (127 mg, 0.550 mmol) in anhydrous THF (10 mL) at 0℃. The mixture was stirred at 0℃ for 30 min. Compound **8** (270 mg, 0.500 mmol) in anhydrous THF (10 mL) was added and pH

was adjusted to 9 with *N*-methylmorpholine. The reaction mixture obtained was kept at 0℃ for 1 h followed at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50 mL). The mixture obtained was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by recrystallization in petroleum ether-dichloromethane afforded the title product, Compound **9f** (244 mg, 0.324 mmol, 65%). $[\alpha]^{25}_{D}$ +30.3 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3331, 3319, 2933, 1687, 1654; ^{1}HNMR (300 MHz, $CDCl_3$): δ7.40 ~ 7.26 (18H, m, Ar-H), 7.16 ~ 7.13 (2H, m, Ar-H), 6.27 (1H, d, *J* = 9.3 Hz, N-H), 4.94 (1H, d, *J* = 3.6 Hz, H-1), 4.82 ~ 4.50 (8H, m, CH_2), 4.37 (1H, dt, J_1 = 3.6 Hz, J_2 = 9.6 Hz, CH), 4.06 (1H, m, H-5), 3.88 (1H, m, H-3), 3.87 ~ 3.74 (3H, m, H-2, H-4, H-6), 3.68 (1H, dd, J_1 = 1.5 Hz, J_2 = 10.5 Hz, H-6'), 1.60 (2H, m, CH_2), 1.44 (9H, s, CH_3), 1.38 (1H, m, CH), 0.86 (6H, d, *J* = 6.0 Hz, CH_3); ^{13}CNMR (75 MHz, $CDCl_3$) δ 172.3, 155.5, 138.4, 138.1, 137.2, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.4, 97.3, 80.9, 78.1, 77.5, 75.0, 74.9, 73.5, 71.2, 69.8, 68.6, 52.9, 41.1, 33.9, 28.3, 25.6, 24.9, 24.7, 22.9, 21.8; ESIMS *m/z* 753 (M+1); HRMS calcd for: ($C_{25}H_{40}N_3O_{12}$ + 1), *m/z* (753.4109); found, *m/z* (753.3983).

5.1.8. 1,3,4,6-Tetra-O-acetyl-2-(N-Boc-isoleucinylamino)-2-deoxy-α-D-glucopyranoside

HOBt (270 mg, 2.00 mmol) and DCC (412 mg, 2.00 mmol) were added to a solution of Boc-L-Ile-OH (462 mg, 2.00 mmol) in anhydrous THF (10 mL) at 0℃. The mixture was stirred at 0℃ for 30 min before Compound **12** (890 mg, 2.00 mmol) in anhydrous THF (10 mL) was added. The pH of the mixture was adjusted to 9 with *N*-methylmorpholine and the mixture obtained was kept at 0℃ for 1 h followed by at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50

mL). The mixture obtained was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by recrystallization in petroleum ether-ethyl acetate provided the title product, Compound **13a** (624 mg, 1.11 mmol, 56%). $[\alpha]^{25}_{D}$ +50.9 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3373, 2945, 1766, 1687; ^{1}HNMR (300 MHz, $CDCl_3$): δ 6.28 (1H, d, *J* = 9.0 Hz, N-H), 6.15 (1H, d, *J* = 3.6 Hz, H-1), 5.30 (1H, t, *J* = 9.6 Hz, H-3), 5.19 (1H, t, *J* = 9.6 Hz, H-4), 4.77 (1H, d, *J* = 6.9 Hz, N-H), 4.44 (1H, td, J_1 = 9.6 Hz, H-2), 4.28(1H, dd, J_1 = 12.6 Hz, J_2= 4.4 Hz, H-6), 4.08-3.91 (3H, m, H-6', H-5, CH), 2.22 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.59 (2H, m, CH, CH_2), 1.37 (1H, m, CH_2), 0.91 (6H, d, CH_3); ^{13}CNMR(75MHz, $CDCl_3$) δ 172.6, 171.2, 170.7, 169.2, 168.6, 155.6, 90.3, 80.3, 70.3, 69.6, 67.6, 61.6, 53.3, 50.9, 40.7, 28.3, 24.8, 22.6, 22.2, 20.9, 20.7, 20.6, 20.6; ESIMS *m/z* 583(M+Na), 645 (M); HRMS calcd for: ($C_{25}H_{40}N_3O_{12}$ + 1), *m/z* (561.2654); found, *m/z* (561.2766).

5.1.9. 1,3,4,6-Tetra-O-acetyl-2-(N-Boc-phenylalanylamino)-2-deoxy-α-D-glucopyranoside

HOBt (148 mg, 1.10 mmol) and DCC (227 mg, 1.10 mmol) were added to a solution of Boc-L-Phe-OH (291 mg, 1.10 mmol) in anhydrous THF (10 mL) at 0℃. The mixture was stirred at 0℃ for 30 min before Compound **12** (445 mg, 1.00 mmol) in anhydrous THF (10 mL) was added. The pH of the mixture was adjusted to 9 with *N*-methylmorpholine and the mixture obtained was kept at 0℃ for 1 h followed by at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50 mL). The mixture obtained was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was collected and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by recrystallization in petroleum ether-ethyl acetate

provided the title product, Compound **13b** (186 mg, 0.313 mmol, 31%). $[\alpha]^{25}_{D}$ +66.8 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3354, 1743, 1676, 1028; ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.32-7.23 (3H, m, Ar-H), 7.16 (2H, d, *J* = 7.3 Hz, Ar-H), 6.30 (1H, d, *J* = 8.3 Hz, N-H), 6.15 (1H, d, *J* = 3.6 Hz, H-1), 5.20 (2H, m, H-3, H-4), 4.79 (1H, d, *J* = 5.3 Hz, N-H), 4.41 (1H, m, CH), 4.28(2H, m, CH, H-6), 4.07 (1H, dd, J_1 = 12.4 Hz, J_2= 1.7 Hz, H-6'), 3.98 (1H, d, *J*= 9.0 Hz, H-5), 3.05 (2H, d, *J* = 6.6 Hz, CH_2), 2.14 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.04 (3H, s, CH_3), 1.91 (3H, s, CH_3), 1.42 (9H, s, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 171.6, 171.3, 170.6, 169.1, 168.5, 155.4, 136.2, 129.2, 128.8, 127.0, 90.3, 80.5, 70.1, 69.6, 67.7, 61.6, 55.7, 51.2, 37.5, 28.3, 20.9, 20.7, 20.6, 20.5; ESIMS *m/z* 594 (M); HRMS calcd for: ($C_{28}H_{38}N_2O_{12}$ + 1), *m/z* (595.2498); found, *m/z* (595.2588).

5.1.10 .1,3,4,6-Tetra-O-acetyl-2-(N-Boc-valinylamino)-2-deoxy-α-D-glucopyranoside

HOBt (1.48 g, 11.0 mmol) and DCC (2.27 g, 11.0 mmol) were added to a solution of Boc-L-Val-OH (2.33 g, 10.0 mmol) in anhydrous THF (20 mL) at 0℃. The mixture was stirred at 0℃ for 30 min before Compound **12** (4.45 g, 10.0 mmol) in anhydrous THF (20 mL) was added. The pH of the mixture was adjusted to 9 with *N*-methylmorpholine and the mixture was kept at 0℃ for 1 h followed by at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50 mL). The mixture obtained was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was collected and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by recrystallization in petroleum ether-ethyl acetate provided the title product, Compound **13c** (1.80 g, 3.30 mmol, 33%). $[\alpha]^{25}_{D}$ +45.8 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3358, 1747, 1697; ^{1}HNMR (500 MHz, $CDCl_3$): δ 6.18 (1H, d, *J* = 7.9 Hz, N-H), 6.17 (1H, d, *J* = 4.1 Hz, H-1), 5.31 (1H, t, *J* = 9.9 Hz, H-3), 5.20 (1H, t, *J* = 9.9 Hz, H-4), 4.93 (1H, d, *J* = 7.8 Hz, N-H),

4.45 (1H, m, H-2), 4.28 (1H, dd, J_1= 12.4 Hz, J_2= 4.1 Hz, H-6), 4.08 (1H, dd, J_1= 12.4 Hz, J_2= 2.05 Hz, H-6'), 4.02 (1H, m, H-5), 3.71 (1H, t, J = 7.4 Hz, CH), 2.21 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.05 (3H, s, CH_3), 2.04 (1H, m, CH), 2.03 (3H, s, CH_3), 1.43 (9H, s, CH_3), 0.90 (3H, d, J = 6.8 Hz, CH_3), 0.88 (3H, d, J = 6.8 Hz, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 172.0, 171.3, 170.7, 169.2, 168.6, 155.9, 90.2, 80.2, 70.2, 69.6, 67.7, 61.6, 60.5, 51.0, 33.7, 30.2, 20.8, 20.7, 20.6, 20.5; ESIMS *m/z* 547 (M+1), 569(M+Na); HRMS calcd for: ($C_{24}H_{38}N_2O_{12}$ + 1), *m/z* (547.2498); found, *m/z* (547.2616).

5.1.11. 1,3,4,6-Tetra-O-acetyl-2-(N-Boc-alanylamino)-2-deoxy-α-D-glucopyranoside

HOBt (1.35 g, 11.0 mmol) and DCC (2.06 g, 11.0 mmol) were added to a solution of Boc-L-Ala-OH (1.89 g, 10.0 mmol) in anhydrous THF (20 mL) at 0℃. The mixture was stirred at 0℃ for 30 min before Compound **12** (4.01 g, 9.01 mmol) in anhydrous THF (20 mL) was added. The pH of the mixture was adjusted to 9 with *N*-methylmorpholine and the mixture was then kept at 0℃ for 1 h followed by at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50 mL). The mixture obtained was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was collected and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by recrystallization in petroleum ether-ethyl acetate provided the title product, Compound **13d** (2.12 g, 4.09 mmol, 45%). [α] $^{25}_{D}$ +61.9 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3365, 1751, 1676; ^{1}HNMR (500 MHz, $CDCl_3$): δ 6.28 (1H, d, J =6.9 Hz, N-H), 6.16 (1H,d, J = 3.6 Hz, H-1), 5.29 (1H, t, J = 9.6 Hz, H-3), 5.20 (1H, t, J = 9.7 Hz, H-4), 4.91 (1H, d, J =6.5 Hz, N-H) , 4.45(1H, td, J_1 = 9.9 Hz, J_2= 3.7 Hz, H-2), 4.27 (1H, dd, J_1 = 12.5 Hz, J_2= 4.2 Hz, H-6), 4.07 (1H, dd, J_1 = 12.5 Hz, J_2= 2.3 Hz, H-6'), 4.02 (2H,m, H-5, CH), 2.21 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.05 (3H, s, CH_3), 2.04 (3H, s, CH_3), 1.44 (9H, s, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 172.8, 171.3,

170.7, 169.1, 168.6, 155.4, 90.4, 80.3, 70.5, 69.7, 67.6, 61.6, 51.0, 50.2, 28.3, 20.9, 20.7, 20.6, 20.5, 18.1; ESIMS *m/z* 541(M+Na); HRMS calcd for: ($C_{22}H_{34}N_2O_{12}$ + 1), *m/z* (519.2185); found, *m/z* (519.2313).

5.1.12. 1,3,4,6-Tetra-O-acetyl-2-(N-Boc-tryptophanylamino)-2-deoxy-α-D-glucopyranoside

HOBt (351 mg, 2.60 mmol) and DCC (536 mg, 2.60 mmol) were added to a solution of Boc-L-Trp-OH (790 mg, 2.60 mmol) in anhydrous THF (20 mL) at 0℃. The mixture was stirred at 0℃ for 30 min before Compound **12** (1.16 g, 2.60 mmol) in anhydrous THF (20 mL) was added. The pH of the mixture was adjusted to 9 with *N*-methylmorpholine and the reaction mixture was kept at 0℃ for 1 h followed by at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50 mL). The mixture obtained was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was collected and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by recrystallization in petroleum ether-ethyl acetate provided the title product, Compound **13e** (891 mg, 1.41 mmol, 54%). $[\alpha]_D^{25}$ +65.5 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3408, 1751, 1680, 738; ^{1}HNMR (300 MHz, $CDCl_3$): δ 8.27 (1H, brs, N-H), 7.63 (1H, d, Ar-H), 7.37 (1H, d, *J* = 7.8 Hz, Ar-H), 7.22 (1H, t, = 6.6 Hz, Ar-H), 7.16 (1H, t, = 6.9 Hz, Ar-H), 6.98 (1H, d, *J* =2.1 Hz, Ar-H), 6.25 (1H, d, *J* = 8.4 Hz, N-H), 6.01 (1H, d, *J* = 3.0 Hz, H-1), 5.17 (2H, m, H-3, H-4), 4.97 (1H, d, *J* = 5.1 Hz, N-H), 4.45 (2H, m, H-2, CH), 4.25(1H, dd, J_1 = 12.6 Hz, J_2= 3.9 Hz, H-6), 4.05 (1H, dd, J_1 = 12.6 Hz, J_2= 2.1 Hz, H-6'), 3.94 (1H, m, H-5), 3.32 (1H, dd, J_1 = 14.7 Hz, J_2= 5.4 Hz, CH_2), 3.17 (1H, dd, J_1 = 14.7 Hz, J_2= 6.3 Hz, CH_2), 2.09 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.98 (3H, s, CH_3), 1.90 (3H, s, CH_3), 1.43 (9H, s, CH_3); ^{13}CNMR(75MHz, $CDCl_3$) δ 172.2, 171.4, 170.7, 169.2, 168.9, 155.5, 136.1, 127.4, 123.4, 122.4, 120.0, 118.4, 111.3, 109.9, 90.3, 80.4, 70.0, 69.6, 67.6,

61.5, 55.4, 51.1, 28.3, 27.5, 20.9, 20.7, 20.6, 20.5, 20.4; ESIMS *m/z* 656(M+Na); HRMS calcd for: ($C_{30}H_{39}N_3O_{12}$ + 1), *m/z* (634.2607); found, *m/z* (634.2608).

5.1.13. 1,3,4,6-Tetra-O-acetyl-2-(N-Boc-leucylamino)-2-deoxy-α-D-glucopyranoside

HOBt (2.23g, 16.5 mmol) and DCC (3.40 mg, 16.5 mmol) were added to a solution of Boc-L-Leu-OH (3.81 g, 16.5 mmol) in anhydrous THF (20 mL) at 0℃. The mixture was stirred at 0℃ for 30 min. Compound **12** (6.67 g, 15.0 mmol) in anhydrous THF (20 mL) was then added and pH was adjusted to 9 with *N*-methylmorpholine. The mixture obtained was kept at 0℃ for 1 h followed by at room temperature for 15 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (50 mL). The mixture obtained was washed successively with saturated $NaHCO_3$, 5% $KHSO_4$ and saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by recrystallization in petroleum ether-ethyl acetate provided the title product, Compound **13f** (3.24 g, 5.79 mmol, 39%). $[\alpha]^{25}_{D}$ +49.5 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3365, 2972, 1751, 1676; ^{1}HNMR (300 MHz, $CDCl_3$): δ 6.29 (1H, d, *J* = 9.0 Hz, N-H), 6.15 (1H, d, *J* = 3.6 Hz, H-1), 5.23 (1H, t, *J* = 9.6 Hz, H-3), 5.19 (1H, t, *J* = 9.9 Hz, H-4), 4.78 (1H, d, *J* = 7.1 Hz, N-H), 4.43 (1H, td, J_1 = 9.9 Hz, J_2= 3.6 Hz, H-2), 4.28(1H, dd, J_1 = 12.3 Hz, J_2= 3.6 Hz, H-6), 4.08-3.91 (3H, m, H-6', H-5, CH), 2.22 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.03 (3H, s, CH_3), 1.60 (2H, m, CH_2), 1.42 (9H, s, CH_3), 1.38 (1H, m, CH), 0.91 (6H, d, *J* = 6.3 Hz, CH_3); ^{13}CNMR(75MHz, $CDCl_3$) δ 172.6, 171.2, 170.7, 169.2, 168.7, 155.6, 90.3, 80.3, 70.3, 69.6, 67.6, 61.6, 53.3, 50.9, 40.7, 28.3, 24.8, 22.6, 22.2, 20.9, 20.7, 20.6, 20.5; ESIMS *m/z* 583(M+Na); HRMS calcd for: ($C_{25}H_{40}N_2O_{12}$ + 1), *m/z* (561.2654); found, *m/z* (561.2763).

5.1.14. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl) isoleucinyl)amino-1,3,4,6-tetra-O-benzyl-2-

deoxy-α-D-glucopyranoside

The solution of Compound **9a** (104 mg, 0.138 mmol) in HCl in EtOAc (4 mL, 4 mol/L) was stirred at 0℃ for 2 h before solvent was removed by evaporation. The residue was dissolved in MeOH (5 mL), to which 76.0 mg of molecular sieve and 40.0 mg (0.253 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (18.0 mg, 0.286 mmol) was added and the reaction mixture obtained was kept at room temperature for 2 h. Molecular sieve was then removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The mixture obtained was washed with saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:1 petroleum ether-ethyl acetate) provided the title product, Compound **11a** (50.0 mg, 0.0630 mmol, 46%). $[\alpha]^{25}_{D}$ +47.1 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3302, 1635, 741, 694; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.60 (1H, d, *J* = 9.6 Hz, N-H), 7.38-7.13 (20H, m, Ar-H), 4.93 (1H, d, *J* = 3.6 Hz, H-1), 4.86-4.42 (8H, m, CH_2), 4.39 (2H, m, H-2, CH), 3.92 (1H, m, H-5), 3.81 (4H, m, CH_2), 3.53 (2H, m, H-3, H-6), 3.29 (2H, m, H-4, H-6'), 2.93 (1H, d, *J* = 3.6 Hz, CH), 2.54 (2H, t, *J* = 6.3 Hz, CH_2), 1.70 (4H, m, N-H, CH, CH_2), 1.39 (2H, m, CH_2), 1.16 (1H, m, CH_2), 1.14 (3H, s, CH_3), 0.93 (3H, d, *J* = 6.9 Hz, CH_3), 0.85 (3H, t, *J* = 7.5 Hz, CH_3), 0.67 (3H, s, CH_3); ^{13}CNMR(75MHz, $CDCl_3$) δ 173.6, 138.6, 138.2, 138.1, 137.2, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5, 127.2, 127.1, 101.1, 97.4, 81.0, 78.3, 77.2, 74.9, 74.5, 73.5, 71.3, 69.6, 68.7, 68.2, 52.5, 51.1, 44.9, 44.8, 38.0, 34.0, 30.0, 25.7, 25.0, 24.6, 23.0, 21.8; ESIMS *m/z* 795(M+1); HRMS calcd for: ($C_{48}H_{63}N_2O_8$ + 1), *m/z* (795.4579); found, *m/z* (795.4693).

5.1.15. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)phenylalanyl)amino-1,3,4,6-tetra-O-benzyl-2-deoxy-α-D-glucopyranoside

The solution of Compound **9b** (90.0 mg, 0.114 mmol) in HCl in EtOAc (4 mL, 4 mol/L) was stirred at 0℃ for 2 h before solvent was removed by evaporation. The residue was dissolved in MeOH (5 mL), to which 35.0 mg of molecular sieve and 18.0 mg (0.114 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (8.00 mg, 0.127 mmol) was added and the reaction mixture obtained was kept at room temperature for 2 h. Molecular sieve was then removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The mixture obtained was washed with saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:1 petroleum ether-ethyl acetate) provided the title product, Compound **11b** (45.0 mg, 0.0543 mmol, 47%). $[\alpha]^{25}_{D}$ +28.6 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3309, 1635, 694; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.64 (1H, d, *J* = 9.6 Hz, N-H), 7.41-7.13 (25H, m, Ar-H), 4.86 (1H, d, *J* = 3.9 Hz, H-1), 4.81-4.41 (8H, m, CH_2), 4.37 (1H, m, H-2), 4.16 (1H, t, *J* = 5.7 Hz, CH), 3.90 (1H, m, H-5), 3.92-3.70 (4H, m, CH_2), 3.40 (2H, m, H-3, H-4), 3.31 (1H, dd, J_1= 9.6 Hz, J_2= 3.6 Hz, H-6), 3.15 (3H, m, CH, CH_2, H-6'), 2.64 (1H, dd, J_1= 13.8 Hz, J_2= 9.6 Hz, CH_2), 2.47 (2H, m, CH_2), 1.56 (3H, m, N-H, CH_2), 1.04 (3H, s, CH_3), 0.62 (3H, s, CH_3); ^{13}CNMR(75MHz, $CDCl_3$) δ 173.7, 138.6, 138.2, 138.1, 137.7, 137.3, 129.2, 128.8, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 127.1, 126.8, 100.7, 97.4, 81.2, 78.3, 76.9, 74.9, 74.7, 73.5, 71.3, 69.6, 68.7, 64.1, 52.4, 43.9, 39.5, 34.4, 29.9, 22.9, 21.8; ESIMS *m/z* 829(M+1); HRMS calcd for: ($C_{51}H_{61}N_2O_8$ + 1), *m/z* (829.4422); found, *m/z* (829.4573).

5.1.16. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)valinyl)amino-1,3,4,6-tetra-O-benzyl-2-deoxy-α-D-glucopyranoside

The solution of Compound **9c** (143 mg, 0.194 mmol) in HCl in EtOAc (4 mL, 4 mol/L) was stirred

at 0℃ for 8 h before removing the solvent by evaporation. The residue was dissolved in MeOH (5 mL) to which 58.0 mg of molecular sieve and 31.0 mg (0.196 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (14.0 mg, 0.222 mmol) was added and the reaction mixture obtained was kept at room temperature for 2 h. Molecular sieve was then removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The mixture obtained was washed with saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:1 petroleum ether-ethyl acetate) provided the title product, Compound **11c** (50.0 mg, 0.0642 mmol, 33%). $[\alpha]^{25}_{D}$ +51.9 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3302, 1635, 740; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.68 (1H, d, *J* = 9.6 Hz, N-H), 7.40-7.26 (18H, m, Ar-H), 7.15 (2H, m, Ph), 4.93 (1H, d, *J* = 3.6 Hz, H-1), 4.87-4.46 (8H, m, CH_2), 4.39 (2H, m, H-3, CH), 3.90 (1H, m, H-5), 3.79 (4H, m, CH_2), 3.53 (2H, m, H-2, H-6), 3.29 (2H, m, H-4, H-6'), 2.91 (1H, d, *J* = 3.6 Hz, CH), 2.55 (1H, t, *J*= 6.3 Hz, CH_2), 2.16 (1H, m, CH), 1.71 (3H, m, N-H, CH_2), 1.15 (3H, s, CH_3), 0.98 (3H, d, *J* = 6.9 Hz, CH_3), 0.83 (3H, d, *J* = 6.9 Hz, CH_3), 0.67 (3H, s, CH_3); ^{13}CNMR(75MHz, $CDCl_3$) δ 173.6, 138.6, 138.2, 137.1, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.3, 127.1, 127.0, 101.1, 97.5, 81.0, 78.4, 77.0, 74.9, 74.6, 73.5, 71.3, 69.6, 68.7, 68.6, 52.5, 44.8, 34.5, 34.0, 31.1, 30.0, 23.0, 21.8, 19.8, 17.3; ESIMS *m/z* 781(M+1); HRMS calcd for: ($C_{47}H_{61}N_2O_8$ + 1), *m/z* (781.4422); found, *m/z* (781.4555).

5.1.17. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)alanyl)amino-1,3,4,6-tetra-O-benzyl-2-deoxy-α-D-glucopyranoside

The solution of Compound **9d** (170 mg, 0.239 mmol) in HCl in EtOAc (4 mL, 4 mol/L) was stirred at 0℃ for 2 h before removing the solvent by evaporation. The residue was dissolved in MeOH (5 mL)

to which 72.0 mg of molecular sieve and 38.0 mg (0.241 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (17.0 mg, 0.270 mmol) was added and the reaction mixture obtained was kept at room temperature for 2 h. Molecular sieve was then removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The mixture obtained was washed with saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:1 petroleum ether-ethyl acetate) provided the title product, Compound **11d** (98.0 mg, 0.130 mmol, 54%). $[\alpha]^{25}_{D}$ +48.0 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3287, 1634, 694; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.56 (1H, d, *J* = 9.6 Hz, N-H), 7.39-7.16 (20H, m, Ar-H), 4.92 (1H, d, *J* = 3.3 Hz, H-1), 4.88-4.53 (8H, m, CH_2), 4.44 (1H, t, *J* = 4.5 Hz, CH), 4.35 (1H, t, *J* = 9.9 Hz, H-2), 3.95 (1H, m, H-5), 3.83 (4H, m, CH_2), 3.56 (2H, m, H-3, H-4), 3.34 (2H, m, H-6, H-6'), 3.21 (1H, q, *J* = 6.9 Hz, CH), 2.65 (2H, m, CH_2), 1.76 (2H, dd, *J* = 5.7 Hz, CH_2), 1.28 (3H, d, *J* = 6.9 Hz, CH_3), 1.16 (3H, s, CH_3), 0.69 (3H, s, CH_3); ^{13}CNMR(75MHz, $CDCl_3$) δ 174.3, 138.6, 138.2, 137.2, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 100.8, 97.0, 81.1, 78.4, 77.1, 75.0, 74.8, 73.5, 71.3, 69.4, 68.7, 58.3, 52.5, 43.6, 34.3, 30.0, 23.0, 21.8, 19.4; ESIMS *m/z* 753(M+1); HRMS calcd for: ($C_{45}H_{57}N_2O_8$ + 1), *m/z* (753.4109); found, *m/z* (753.4251).

5.1.18. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)tryptophanyl)amino-1,3,4,6-tetra-O-benzyl-2-deoxy-α-D-glucopyranoside

The solution of **9e** (263 mg, 0.319 mmol) in HCl in EtOAc (4 mL, 4 mol/L) was stirred at 0℃ for 8 h following which solvent was removed by evaporation. The residue was dissolved in MeOH (5 mL), to which 96.0 mg of molecular sieve and 51.0 mg (0.323 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (23.0 mg, 0.365 mmol) was

added and the reaction mixture obtained was kept at room temperature for 2 h. Molecular sieve was then removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The mixture obtained was washed with saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:1 petroleum ether-ethyl acetate) provided the title product, Compound **11e** (125 mg, 0.144 mmol, 45%). $[\alpha]^{25}_{D}$ +29.9 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3310, 1659, 741; ^{1}HNMR (300 MHz, $CDCl_3$): δ 8.22 (1H, brs, N-H), 7.70 (2H, m, Ar-H), 7.41-7.04 (23H, m, Ar-H), 4.85-4.52 (7H, m, CH_2), 4.72 (1H, d, *J* = 3.6 Hz, H-1), 4.40 (1H, t, *J* = 9.9 Hz, H-2), 4.23 (1H, d, *J* = 11.7 Hz, CH_2), 4.11 (1H, t, *J* = 4.8 Hz, CH), 3.87(1H, m, H-5), 3.76 (4H, dd, *J* = 10.5 Hz, CH_2), 3.48-3.25 (4H, m, H-3, H-6, H-6', CH), 3.01 (3H, m, CH_2, H-4), 2.52 (2H, m, CH_2), 1.57 (2H, m, CH_2), 1.01 (3H, s, CH_3), 0.58 (3H, s, CH_3); ^{13}CNMR(75MHz, $CDCl_3$) δ 174.3, 138.6, 138.2, 138.1, 137.3, 136.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.3, 127.2, 122.9, 122.3, 119.7, 111.7, 111.2, 100.5, 97.5, 81.2, 78.3, 76.8, 76.7, 74.9, 74.7, 73.5, 71.2, 69.7, 68.7, 63.6, 52.4, 43.9, 34.6, 29.8, 29.1, 22.8, 21.7; ESIMS *m/z* 868(M+1); HRMS calcd for: ($C_{53}H_{62}N_3O_8$ + 1), *m/z* (868.4531); found, *m/z* (868.4657).

5.1.19. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)leucyl)amino-1,3,4,6-tetra-O-benzyl-2-deoxy-α-D-glucopyranoside

The solution of Compound **9f** (98.3 mg, 0.131 mmol) in HCl in EtOAc (4 mL, 4 mol/L) was stirred at 0℃ for 2 h following which solvent was removed by evaporation. The residue was dissolved in MeOH (5 mL), to which 80 mg of molecular sieve and 60 mg (0.380 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (40.0 mg, 0.634 mmol) was added and the reaction mixture obtained was kept at room temperature for 2 h. Molecular

sieve was then removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The solution was washed with saturated NaCl, and the organic phase was collected and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:1 petroleum ether-ethyl acetate) provided the title product, Compound **11f** (50.0 mg, 0.0630 mmol, 48%). $[\alpha]^{25}_{D}$ +46.4 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3302, 1636, 694; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.66 (1H, d, *J* = 9.9 Hz, N-H), 7.38-7.13 (20H, m, Ar-H), 4.91 (1H, d, *J* = 3.6 Hz, H-1), 4.87-4.50 (8H, m, CH_2), 4.34 (2H, m, CH, H-3), 3.92 (1H, m, H-5), 3.82 (4H, m, CH_2), 3.54(2H, m, H-2, H-4), 3.31 (1H, dd, J_1= 11.1 Hz, J_2= 5.4 Hz, H-6), 3.30 (1H, t, *J*= 5.7 Hz, CH), 3.06 (1H, dd, J_1= 11.4 Hz, J_2= 3.6 Hz, H-6'), 2.56 (2H, t, *J*= 6.3 Hz, CH_2), 1.67 (5H, m, N-H, CH_2), 1.33 (1H, m, CH), 1.15 (3H, s, CH_3), 0.95 (3H, d, *J*= 7.2 Hz, CH_3), 0.93 (3H, d, *J*= 6.9 Hz, CH_3), 0.68 (3H, s, CH_3); ^{13}CNMR(75MHz, $CDCl_3$) δ 175.1, 138.6, 138.2, 137.3, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 127.0, 101.2, 97.0, 81.0, 78.3, 77.2, 77.1, 74.9, 74.5, 73.5, 71.2, 69.4, 68.7, 61.8, 52.4, 44.1, 42.8, 34.6, 30.0, 25.1, 23.5, 22.9, 21.8, 21.6; ESIMS *m/z* 795(M+1); HRMS calcd for: ($C_{48}H_{63}N_2O_8$ + 1), *m/z* (795.4579); found, *m/z* (795.4705).

5.1.20. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)isoleucinyl)amino-1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-glucopyranoside

The solution of Compound **13a** (383 mg, 0.684 mmol) in HCl in EtOAc (10 mL, 4 mol/L) was stirred at 0℃ for 2 h before solvent was removed by evaporation. The residue was dissolved in MeOH (10 mL), to which 206 mg of molecular sieve and 108 mg (0.684 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (43.0 mg, 0.684 mmol) was added and the reaction mixture obtained was kept at room temperature for 1.5 h, following which molecular sieve was removed by filtration. The filtrate was subject to evaporation under reduced

pressure and the residue was dissolved in EtOAc (10 mL). The mixture obtained was washed with saturated NaCl, and the organic phase was collected and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:2 petroleum ether-ethyl acetate) provided the title product, Compound **15a** (290 mg, 0.482 mmol, 70%). $[\alpha]_D^{25}$ +47.0 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 2962, 1743, 1226; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.55 (1H, d, *J* = 8.7 Hz, N-H), 6.19 (1H, d, *J* = 3.6 Hz, H-1), 5.34 (1H, t, *J* = 9.1 Hz, H-3), 5.18 (1H, t, *J* = 9.9 Hz, H-4), 4.51 (1H, t, *J* = 3.5 Hz, CH), 4.40 (1H, m, H-2), 4.26 (1H, dd, J_1= 12.3 Hz, J_2= 3.6 Hz, H-6), 4.06 (1H, dd, J_1= 12.3 Hz, J_2= 2.1 Hz, H-6'), 3.99 (1H, m, H-5), 3.59 (2H, d, *J* = 10.8 Hz, CH_2), 3.41 (2H, d, *J* = 10.8 Hz, CH_2), 2.89 (1H, d, *J* = 4.2 Hz, CH), 2.59 (1H, m, CH_2), 2.47 (1H, m, CH_2), 2.15 (3H, s, CH_3), 2.08 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.01 (3H, s, CH_3), 1.81 (2H, m, CH_2), 1.72 (1H, m, CH), 1.30 (1H, m, CH_2), 1.17 (3H, s, CH_3), 1.09 (1H, m, CH CH_2), 0.87 (3H, d, *J* = 6.9 Hz, CH_3), 0.82 (3H, d, *J* = 7.2 Hz, CH_3), 0.72 (3H, s, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 174.0, 170.9, 170.7, 169.2, 168.6, 101.5, 90.2, 77.2, 77.0, 70.1, 69.6, 67.9, 67.8, 61.6, 50.6, 44.7, 38.1, 34.3, 30.1, 24.7, 23.0, 21.8, 20.7, 20.6, 20.5, 15.8, 11.7; ESIMS *m/z* 603(M+1). HRMS calcd for: ($C_{28}H_{46}N_2O_{12}$ + 1), *m/z* (603.3123); found, *m/z* (603.3218).

5.1.21. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)phenylalanyl)amino-1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-glucopyranoside

The solution of Compound **13b** (224 mg, 0.377 mmol) in HCl in EtOA (10 mL, 4 mol/L) was stirred at 0℃ for 2 h before solvent was removed by evaporation. The residue was dissolved in MeOH (8 mL), and 120 mg of molecular sieve and 63.0 mg (0.399 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (24.0 mg, 0.381 mmol) was added and the reaction mixture obtained was kept at room temperature for 2 h, following which molecular sieve

was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The mixture obtained was washed with saturated NaCl, and the organic phase was collected and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:2 petroleum ether-ethyl acetate) provided the title product, Compound **15b** (188 mg, 0.296 mmol, 79%). $[\alpha]^{25}_{D}$ +24.0 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 1751, 1226; ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.54 (1H, d, *J* = 8.1 Hz, N-H), 7.32-7.16 (5H, m, Ar-H), 6.20 (1H, d, *J* = 3.6 Hz, H-1), 5.33 (1H, t, *J* = 10.0 Hz, H-3), 5.21 (1H, t, *J* = 10.0 Hz, H-4), 4.43 (1H, m, H-2), 4.28 (1H, dd, J_1= 12.4 Hz, J_2= 4.1 Hz, H-6), 4.26 (1H, t, *J*= 4.0 Hz, CH), 4.09 (1H, dd, J_1= 12.4 Hz, J_2= 2.2 Hz, H-6'), 4.04 (1H, dt, J_1= 10.0 Hz, J_2= 2.4 Hz, H-5), 3.45 (2H, d, *J* = 11.1 Hz, CH_2), 3.28 (2H, d, *J* = 11.1 Hz, CH_2), 3.25 (1H, t, *J*= 11.2 Hz, CH), 3,14 (1H, dd, J_1= 13.8 Hz, J_2= 3.05 Hz, CH_2), 2.54 (1H, m, CH_2), 2.46 (2H, m, CH_2), 2.18 (3H, s, CH_3), 2.11 (3H, s, CH_3), 2.05 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.69 (3H, m, N-H, CH_2), 1.05 (3H, s, CH_3), 0.68 (3H, s, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 174.3, 170.8, 170.7, 169.2, 168.6, 137.3, 129.0, 128.8, 128.7, 126.9, 101.1, 90.5, 77.0, 70.2, 69.7, 67.9, 63.9, 61.6, 50.7, 43.9, 39.4, 34.1, 30.0, 22.9, 21.8, 20.9, 20.7, 20.6, 20.5; ESIMS *m/z* 637(M+1); HRMS calcd for: ($C_{31}H_{45}N_2O_{12}$ + 1), *m/z* (637.2967); found, *m/z* (637.3076).

5.1.22. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)valinyl)amino-1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-glucopyranoside

The solution of Compound **13c** (546 mg, 1.00 mmol) in HCl in EtOAc (10 mL, 4 mol/L) was stirred at 0℃ for 2 h before solvent was remove by evaporation. The residue was dissolved in MeOH (20 mL), to which 300 mg of molecular sieve and 158 mg (1.00 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (63.0 mg, 1.00 mmol) was added and

the reaction mixture obtained was kept at room temperature for 2 h. Molecular sieve was then removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The mixture obtained was washed with saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:2 petroleum ether-ethyl acetate) provided the title product, Compound **15c** (390 mg, 0.663 mmol, 66%). $[\alpha]^{25}_{D}$ +47.7 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3340, 1743; ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.55 (1H, d, *J* = 7.4 Hz, N-H), 6.20 (1H, d, *J* = 3.6 Hz, H-1), 5.35 (1H, t, *J* = 10.0 Hz, H-3), 5.19 (1H, t, *J* = 10.0 Hz, H-4), 4.53 (1H, t, *J* = 4.5 Hz, CH), 4.42 (1H, m, H-2), 4.27 (1H, dd, J_1 = 12.5 Hz, J_2 = 4.0 Hz, H-6), 4.07 (1H, dd, J_1 = 12.5 Hz, J_2 = 1.9 Hz, H-6'), 4.02 (1H, m, H-5), 3.60 (2H, d, *J* = 10.9 Hz, CH_2), 3.43 (2H, d, *J* = 10.9 Hz, CH_2), 2.84 (1H, s, CH), 2.54 (2H, m, CH_2), 2.16 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.82 (2H, m, CH_2), 1.73 (1H, m, CH),1.18 (3H, s, CH_3), 0.94 (3H, d, *J* = 7.0 Hz, CH_3), 0.79 (3H, d, *J* = 7.0 Hz, CH_3), 0.73 (3H, s, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 174.2, 170.9, 170.7, 169.2, 168.6, 101.5, 90.4, 77.2, 77.1, 70.1, 69.7, 68.4, 67.9, 61.6, 50.6, 44.7, 34.3, 31.2, 30.1, 29.7, 23.0, 21.8, 20.8, 20.7, 20.6, 19.5, 17.3; ESIMS *m/z* 589(M+1); HRMS calcd for: ($C_{27}H_{45}N_2O_{12}$ + 1), *m/z* (589.2967); found, *m/z* (589.3048).

5.1.23. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)alanyl)amino-1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-glucopyranoside

The solution of Compound **13d** (1.04 g, 2.00 mmol) in HCl in EtOAc (20 mL, 4 mol/L) was stirred at 0℃ for 2 h before solvent was removed by evaporation. The residue was dissolved in MeOH (20 mL), to which 600 mg of molecular sieve and 316 mg (2.00 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (126 mg, 2.00 mmol) was

added and the reaction mixture obtained was kept at room temperature for 2 h. Molecular sieve was then removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The mixture obtained was washed with saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:2 petroleum ether-ethyl acetate) provided the title product, Compound **15d** (556mg, 0.993 mmol, 50%). $[\alpha]^{25}_{D}$ +48.9 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3340, 1743; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.48 (1H, d, *J* = 9.0 Hz, N-H), 6.21 (1H, d, *J* = 3.6 Hz, H-1), 5.32 (1H, t, *J* = 9.5 Hz, H-3), 5.18 (1H, t, *J* = 9.9 Hz, H-4), 4.51 (1H, t, *J* = 4.5 Hz, CH), 4.39 (1H, m, H-2), 4.26 (1H, dd, J_1= 12.3 Hz, J_2= 4.2 Hz, H-6), 4.07 (1H, dd, J_1= 12.3 Hz, J_2= 2.1 Hz, H-6'), 4.01 (1H, m, H-5), 3.59 (2H, d, *J* = 10.8 Hz, CH_2), 3.41 (2H, d, *J* = 10.8 Hz, CH_2), 3.10 (1H, q, *J* = 6.9 Hz, CH), 2.67 (1H, m, CH_2), 2.49 (1H, m, CH_2), 2.16 (3H, s, CH_3), 2.18 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.80 (2H, m, CH_2), 1.20 (3H, d, *J* = 6.9 Hz, CH_3), 1.17 (3H, s, CH_3), 0.72 (3H, s, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 175.5, 170.9, 170.6, 169.2, 168.6, 101.2, 90.4, 77.2, 77.1, 70.1, 69.8, 68.4, 67.9, 61.6, 58.2, 50.6, 43.7, 34.4, 30.0, 22.9, 21.8, 20.8, 20.7, 20.5, 19.7; ESIMS *m/z* 561(M+1); HRMS calcd for: ($C_{25}H_{41}N_2O_{12}$ + 1), *m/z* (561.2654); found, *m/z* (561.2765).

5.1.24. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)tryptophanyl)amino-1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-glucopyranoside

The solution of Compound **13e** (695 mg, 1.10 mmol) in HCl in EtOAc (20 mL, 4 mol/L) was stirred at 0℃ for 2 h before solvent was removed by evaporation. The residue was dissolved in MeOH (20 mL) to which 330 mg of molecular sieve and 174 mg (1.10 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (69.0 mg, 1.10 mmol) was

added and the reaction mixture obtained was kept at room temperature for 2 h. Molecular sieve was then removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The mixture obtained was washed with saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:2 petroleum ether-ethyl acetate) provided the title product, Compound **15e** (376 mg, 0.557 mmol, 51%). $[\alpha]^{25}_{D}$ +31.8 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 1751, 1227; ^{1}HNMR (300 MHz, $CDCl_3$): δ 8.23 (1H, brs, N-H), 7.61 (2H, m, Ar-H, N-H), 7.37 (1H, d, *J* = 7.8 Hz, Ar-H), 7.20 (1H, t, *J* = 6.9 Hz, Ar-H), 7.15 (1H, t, *J* = 7.8 Hz, Ar-H), 7.00 (1H, d, *J* = 1.2 Hz, Ar-H), 6.15 (1H, d, *J* = 3.6 Hz, H-1), 5.33 (1H, t, *J* = 9.6 Hz, H-3), 5.21 (1H, t, *J* = 9.6 Hz, H-4), 4.46 (1H, td, J_1= 9.6 Hz, J_2= 3.6 Hz, H-2), 4.30 (1H, dd, J_1= 12.8 Hz, J_2= 4.2 Hz, H-6), 4.19 (1H, t, *J*= 4.5 Hz, CH), 4.09 (1H, dd, J_1= 12.3 Hz, J_2= 2.1 Hz, H-6'), 4.03 (1H, m, H-5), 3.36 (3H, m, CH, CH_2), 3.25 (1H, dd, J_1= 14.7 Hz, J_2= 3.6 Hz, CH_2), 3.13 (1H, dd, J_1= 15.3 Hz, J_2= 8.1 Hz, CH_2), 2.85 (1H, dd, J_1= 14.7 Hz, J_2= 5.7 Hz, CH_2), 2.51 (1H, m, CH_2), 2.11 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.01 (3H, s, CH_3), 1.81 (1H, m, N-H), 1.66 (2H, m, CH_2), 1.01(3H, s, CH_3), 0.63 (3H, s, CH_3); ^{13}CNMR(75MHz, $CDCl_3$) δ 174.7, 170.8, 170.7, 169.3, 168.8, 136.3, 127.6, 122.9, 122.2, 119.7, 118.6, 111.3, 100.8, 90.5, 76.9, 76.8, 70.1, 69.7, 67.9, 63.5, 61.6, 50.6, 43.9, 34.3, 29.9, 28.9, 22.8, 21.7, 20.8, 20.7, 20.6; ESIMS *m/z* 676(M+1); HRMS calcd for: ($C_{33}H_{46}N_3O_{12}$ + 1), *m/z* (676.3067); found, *m/z* (676.3186).

5.1.25. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)leucyl)amino-1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-glucopyranoside

The solution of Compound **13f** (560 mg, 1.00 mmol) in HCl in EtOAc (10 mL, 4 mol/L) was stirred at 0℃ for 2 h before solvent was removed by evaporation. The residue was dissolved in MeOH (20 mL)

to which 300 mg of molecular sieve and 158 mg (1.00 mmol) of Compound **4** were added. The reaction mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (63.0 mg, 1.00 mmol) was added and the reaction mixture obtained was kept at room temperature for 2 h. Molecular sieve was then removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (10 mL). The mixture obtained was washed with saturated NaCl, and the organic phase was separated and dried over Na_2SO_4. Following filtration and evaporation under reduced pressure, purification of the residue by chromatography (1:2 petroleum ether-ethyl acetate) provided the title product, Compound **15f** (262 mg, 0.436 mmol, 44%). $[\alpha]^{25}_{D}$ +41.6 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 2962, 1743; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.51 (1H, d, *J* = 7.8 Hz, N-H), 6.21 (1H, d, *J* = 3.6 Hz, H-1), 5.32 (1H, t, *J* = 9.9 Hz, H-3), 5.18 (1H, t, *J* = 9.6 Hz, H-4), 4.51 (1H, t, *J* = 4.5 Hz, CH), 4.38 (1H, m, H-2), 4.26 (1H, dd, J_1= 12.3 Hz, J_2= 3.9 Hz, H-6), 4.06 (1H, dd, J_1= 12.3 Hz, J_2= 2.1 Hz, H-6'), 4.03 (1H, m, H-5), 3.58 (2H, d, *J* = 11.1 Hz, CH_2), 3.40 (2H, d, *J* = 10.8 Hz, CH_2), 3.04 (1H, m, CH), 2.61 (1H, m, CH_2), 2.46 (1H, m, CH_2), 2.17 (3H, s, CH_3), 2.08 (3H, s, CH_3), 2.03 (3H, s, CH_3), 2.01 (3H, s, CH_3), 1.64 (1H, m, CH), 1.62 (1H, m, CH_2), 1.46 (1H, m, CH_2), 1.24 (1H, m, CH), 1.16 (3H, s, CH_3), 0.91 (3H, d, *J* = 4.5 Hz, CH_3), 0.89 (3H, d, *J* = 4.8 Hz, CH_3), 0.72 (3H, s, CH_3); ^{13}CNMR(75MHz, $CDCl_3$) δ 175.4, 170.9, 170.6, 169.2, 168.6, 101.5, 90.3, 77.2, 77.0, 70.1, 69.7, 67.9, 61.6, 61.5, 50.6, 44.1, 42.8, 34.3, 30.0, 24.9, 23.2, 22.9, 21.7, 20.8, 20.7, 20.5; ESIMS *m/z* 603(M+1). HRMS calcd for: ($C_{28}H_{46}N_2O_{12}$ + 1), *m/z* (603.3124); found, *m/z* (603.3231).

5.1.26. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)isoleucinyl)amino-2-deoxy-D-glucopyranoside

CH_3ONa (50.0 mg, 0.926 mmol) was added to a solution of Compound **15a** (100 mg, 0.166 mmol) in methanol (10 mL) at 0°C. The mixture was stirred at 0°C for 4 h and its pH was adjusted to 7 with 4 mol/L HCl in EtOAc. The reaction mixture was subject to evaporation to remove solvent and

purification of residue by chromatography (50:1 CH_2Cl_2-MeOH) provided the title product, Compound **16a** (37.0 mg, 0.0853 mmol, 51%). [α] $^{25}_{D}$ +28.0 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3368, 2959, 1655; ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.84 (1H, brs, N-H), 5.23 (1H, s, H-1), 4.70 (1H, m, H-3), 4.59 (1H, m, CH), 3.96-3.73 (3H, m, H-2, H-4, H-5), 3.61 (3H, m, H-6, CH_2), 3.49(3H, m, H-6', CH_2), 3.17 (1H, m, CH), 2.82 (2H, m, CH_2), 1.89 (3H, m, CH, CH_2), 1.51 (1H, m, CH_2), 1.24 (1H, m, CH_2), 1.18 (3H, s, CH_3), 0.95(6H, m, CH_3), 0.73 (3H, s, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 178.6, 101.3, 91.5, 76.2, 74.0, 71.2, 71.0, 67.2, 54.1, 53.4, 43.7, 37.2, 33.4, 30.1, 29.7, 25.2, 23.8, 23.1, 21.8; ESIMS *m/z* 435(M+1); HRMS calcd for: ($C_{20}H_{39}N_2O_8$ + 1), *m/z* (435.2701); found, *m/z* (435.2771).

5.1.27. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)phenylalanyl)amino-2-deoxy-D-glucopyranoside

CH_3ONa (50.0 mg, 0.926 mmol) was added to a solution of Compound **15b** (100 mg, 0.157 mmol) in methanol (10 mL) at 0°C. The mixture was stirred at 0°C for 4 h and its pH was adjusted to 7 with 4 mol/L HCl in EtOAc. The reaction mixture was subject to evaporation to remove solvent and purification of residue by chromatography (50:1 CH_2Cl_2-MeOH) provided the title product, Compound **16b** (34.0 mg, 0.0726 mmol, 46%). [α] $^{25}_{D}$ -11.6 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3314, 1678, 1543, 733; ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.34-7.09 (5H, m, Ar-H), 5.32 (1H, s, H-1), 4.51 (1H, m, CH), 4.38 (1H, m, H-5), 4.28 (2H, m, H-2, H-3), 4.08 (1H, m, CH), 3.77(2H, m, H-4, H-6), 3.64 (1H, m, H6'), 3.53 (2H, m, CH_2), 3.37 (2H, m, CH_2), 3.18 (2H, m, CH_2), 3.06 (1H, m, CH_2), 2.73 (1H, m, CH_2), 2.06 (2H, m, CH_2), 1.07 (3H, s, CH_3), 0.68 (3H, s, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 175.1, 135.5, 129.4, 129.0, 127.2, 117.8, 98.3, 77.2, 76.8, 74.5, 71.0, 65.8, 63.0, 53.4,53.1, 38.0, 34.7, 31.9, 29.9, 22.9, 21.6; ESIMS *m/z* 469(M+1). HRMS calcd for: ($C_{23}H_{37}N_2O_8$ + 1), *m/z* (469.2544); found, *m/z* (469.2553).

5.1.28. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)valinyl)amino-2-deoxy-D-glucopyranoside

CH_3ONa (50.0 mg, 0.926 mmol) was added to a solution of Compound **15c** (100 mg, 0.170 mmol) in methanol (10 mL) at 0°C. The mixture was stirred at 0°C for 4 h and its pH was adjusted to 7 with 4 mol/L HCl in EtOAc. The reaction mixture was subject to evaporation to remove solvent and purification of residue by chromatography (50:1 CH_2Cl_2-MeOH) provided the title product, Compound **16c** (30.0 mg, 0.0714 mmol, 42%). [α] $^{25}_{D}$ +43.0 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3302, 2924, 1655; ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.74 (1H, brs, N-H), 5.21 (1H, s, H-1), 4.58 (1H, s, CH), 3.94-3.79 (4H, m, H-2, H-3, H-5, CH), 3.72 (1H, dd, J_1= 14.0 Hz, J_2= 7.0 Hz, H-6), 3.61-3.44 (6H, m, H-4, H-6, CH_2), 2.94(1H, brs, N-H), 2.73 (2H, m, CH_2), 2.02 (1H, m, CH), 1.85 (2H, m, CH_2), 1.17 (3H, s, CH_3), 0.96 (3H, d, *J*= 5.5 Hz, CH_3), 0.89 (3H, d, *J*= 6.5 Hz, CH_3), 0.73 (3H, s, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 175.0, 101.5, 91.4, 77.1, 76.9, 71.8, 71.7, 68.6, 65.9, 61.4, 58.3, 43.9, 34.1, 30.9, 30.1, 23.1, 21.8, 19.5, 18.1; ESIMS *m/z* 419(M-1), 420 (M); HRMS calcd for: ($C_{19}H_{37}N_2O_8$ + 1), *m/z* (421.2544); found, *m/z* (421.2597).

5.1.29. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)alanyl)amino-2-deoxy-D-glucopyranoside

CH_3ONa (50.0 mg, 0.926 mmol) were added to a solution of Compound **15d** (100 mg, 0.179 mmol) in methanol (10 mL) at 0°C. The reaction mixture was stirred at 0°C for 4 h and its pH was adjusted to 7 with 4 mol/L HCl in EtOAc. The reaction mixture was subject to evaporation to remove the solvent. Purification of residue by chromatography (50:1 CH_2Cl_2-MeOH) provided the title product, Compound **16d** (34.0 mg, 0.0868 mmol, 49%). [α] $^{25}_{D}$ +0.545 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3302, 2924, 1655; ^{1}HNMR (500 MHz, $CDCl_3$): δ 5.32 (1H, s, H-1), 5.21-4.75 (3H, m, OH), 4.60 (1H, s, CH), 4.41 (2H, m, H-3, H-5), 4.06 (1H, m H-2), 3.74 (2H, m, H-6, CH), 3.61 (2H, m, CH_2), 3.42 (2H, m, CH_2), 2.97 (1H, m, H-6'), 2.61 (2H, m, CH_2), 2.20 (1H, brs, N-H), 2.02 (2H, m, CH_2), 1.17 (3H, s, CH_3), 1.13 (3H, s, CH_3), 0.74 (3H, s, CH_3), 0.73 (3H, d, *J*= 7.5 Hz, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 176.0, 99.6,

98.3, 77.1, 76.9, 74.5, 71.0, 62.8, 53.4, 38.4, 34.3, 30.2, 23.0, 21.8, 21.7; ESIMS *m/z* 393(M+1). HRMS calcd for: ($C_{17}H_{32}N_2O_8$ + 1), *m/z* (393.2231); found, *m/z* (393.2290).

5.1.30. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)tryptophanyl)amino2-deoxy-D-glucopyranoside

CH_3ONa (50.0 mg, 0.926 mmol) were added to a solution of Compound **15e** (100 mg, 0.148 mmol) in methanol (10 mL) at 0°C. The reaction mixture was stirred at 0°C for 4 h and its pH was adjusted to 7 with 4 mol/L HCl in EtOAc. The reaction mixture was subject to evaporation to remove the solvent and purified by chromatography (50:1 CH_2Cl_2-MeOH) to provide the title product Compound **16e** (31.0 mg, 0.0611 mmol, 41%). [α] $^{25}_{D}$ -3.14 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3279, 1654, 744; ^{1}HNMR (500 MHz, $CDCl_3$): δ 10.94 (1H, s, N-H), 7.63 (1H, d, *J*= 8.5 Hz, N-H), 7.56 (1H, d, *J*= 8.0 Hz, Ar-H), 7.36 (1H, d, *J*= 8.0 Hz, Ar-H), 7.23 (1H, s, Ar-H), 7.08 (1H, t, *J*= 7.5 Hz, Ar-H), 6.99 (1H, t, *J*= 7.5 Hz, Ar-H), 4.94 (1H, d, *J*= 3.0 Hz, H-1), 4.17 (1H, t, *J*= 5.0 Hz, CH) 3.65 (2H, m, CH_2), 3.51 (2H, m, CH_2), 3.43(1H, m, H-5), 3.32 (2H, m, H-3, CH), 3.29 (1H, m H-6), 3.19 (2H, m, H-2), 3.09 (3H, m, H-4, H-6', CH_2), 2.74 (1H, dd, J_1= 14.0 Hz, J_2= 9.0 Hz, CH_2), 2.59 (1H, m, CH_2), 2.39 (1H, m, CH_2), 1.53 (2H, m, CH_2), 0.94 (3H, s, CH_3), 0.59 (3H, s, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 174.1, 136.8, 127.8, 124.4, 121.4, 118.8, 118.7, 111.9, 110.8, 100.5, 91.2, 76.3, 76.2, 72.7, 71.6, 71.5, 63.2, 61.5, 54.3, 43.4, 34.5, 30.0, 29.5, 23.1, 21.8; ESIMS *m/z* 508 (M+1); HRMS calcd for: ($C_{25}H_{38}N_3O_8$ + 1), *m/z* (508.2653); found, *m/z* (508.2732).

5.1.31. 2-(N-(2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl)leucyl)amino-2-deoxy-D-glucopyranoside

CH_3ONa (50.0 mg, 0.926 mmol) was added to a solution of Compound **15f** (100 mg, 0.166 mmol) in methanol (10 mL) at 0°C. The mixture was stirred at 0°C for 4 h and its pH was adjusted to 7 with 4 mol/L HCl in EtOAc. The reaction mixture was subject to evaporation to remove the solvent. Purification of residue by chromatography (50:1 CH_2Cl_2-MeOH) provided the title product, Compound

16f (28.0 mg, 0.0645 mmol, 39%). [α] $^{25}_{D}$ -6.33 (c 0.1, $CHCl_3$); IR (cm^{-1}, KBr, neat): 3321, 2959, 1643; ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.24 (1H, s, N-H), 5.24 (1H, s, H-1), 4.61 (1H, m, CH), 4.42 (1H, m, H-3), 3.85 (3H, m H-2, H-5, H-6), 3.63 (3H, m, H-6', CH_2), 3.47 (3H, m, H-4, CH_2), 2.85 (2H, m, CH_2), 2.22 (1H, m, CH_2), 1.90 (2H, m, CH_2), 1.68 (1H, m, CH_2), 1.61 (1H, m, CH), 1.47 (1H, m, CH), 1.16 (3H, s, CH_3), 0.91 (3H, d, *J*= 7.0 Hz, CH_3) 0.90 (3H, d, *J*= 7.0 Hz, CH_3) 0.72 (3H, s, CH_3); ^{13}CNMR(125MHz, $CDCl_3$) δ 167.3, 101.2, 98.2, 77.2, 76.9, 74.5, 71.8, 60.9, 52.6, 43.1, 41.4, 35.2, 30.1, 28.1, 24.8, 23.0, 22.8, 21.8, 21.7; ESIMS *m/z* 435 (M+1); HRMS calcd for: ($C_{20}H_{39}N_2O_8$ + 1), *m/z* (435.2701); found, *m/z* (435.2767).

5.2. Pharmacology

5.2.1. Determination of anti-inflammatory activity

All animal experiments were conducted in accordance with China's National Guide for the Care and Use of Laboratory Animals. The animal protocol was approved by the Committee on Animal Care and Usage at the Capital Medical University. Male ICR mice (body weight, 18-20 g) were maintained on a 12/12 h light/dark cycle at constant temperature and humidity, and were provided with free access to food and water. They were allowed to acclimate to their new surroundings for 1 day before experiment. Mice were divided into twenty-one groups of twelve. Mice administered orally by gavage with 0.5% carboxymethyl cellulose (CMC) suspension were used as negative control, and mice administered orally with Aspirin (at a dosage of 100 mg/kg) in CMC were used as positive control. The compounds tested were prepared as suspensions in 0.5% CMC at the concentration of 1 mM and were administered orally to the animals at a dosage of 10 μmol/kg 30 min before xylene was applied to both the anterior and posterior surfaces of the right ear. The left ear was considered as control. Two hours after xylene application, all mice were decapitated and ear biopsies of 8.0 mm in diameter were punched out and

weighed. The extent of ear edema was evaluated by the weight difference between the right and the left ear biopsies of the same animal. The anti-inflammatory effect was defined by inhibition ratio (%) as:

$$\text{Inhibition ratio } \% = (1 - A/B) \times 100\%$$

A: The increase in weight caused by xylene

B: The weight of the untreated left ear section

The statistical analysis of the data was performed using an ANOVA test in which $p < 0.05$ was considered significant.

Acknowledgements

This work was supported by the National Natural Scientific Foundation of China (20642004), the Educational Council Foundation of Beijing (KM200710025012), Academic Human Resources Development in Institutions of Higher Learning under the Jurisdiction of Beijing Municipality (PHR201007114).

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Table 1. Structures of glucosamine mimetic peptides synthesized

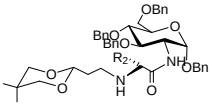
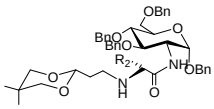
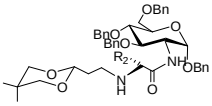
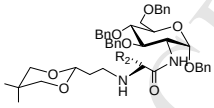
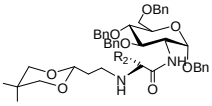
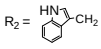
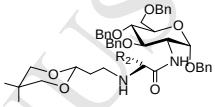
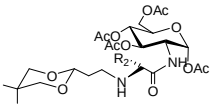
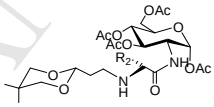
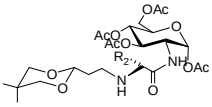
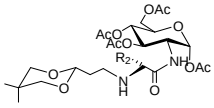
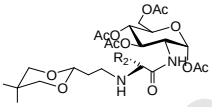
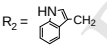
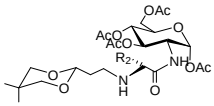
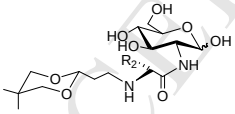
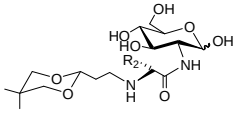
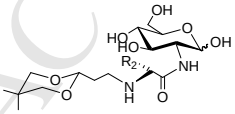
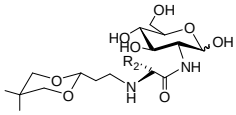
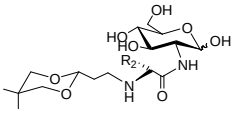
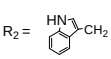
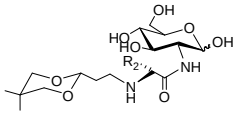
Compound No	Chemical structure	Compound No	Chemical structure
11a	 $R_2 = CH(CH_3)CH_2CH_3$	**11b**	 $R_2 = CH_2C_6H_5$
11c	 $R_2 = CH(CH_3)_2$	**11d**	 $R_2 = CH_3$
11e	 $R_2 =$ 	**11f**	 $R_2 = CH_2CH(CH_3)_2$
15a	 $R_2 = CH(CH_3)CH_2CH_3$	**15b**	 $R_2 = CH_2C_6H_5$
15c	 $R_2 = CH(CH_3)_2$	**15d**	 $R_2 = CH_3$
15e	 $R_2 =$ 	**15f**	 $R_2 = CH_2CH(CH_3)_2$
16a	 $R_2 = CH(CH_3)CH_2CH_3$	**16b**	 $R_2 = CH_2C_6H_5$
16c	 $R_2 = CH(CH_3)_2$	**16d**	 $R_2 = CH_3$
16e	 $R_2 =$ 	**16f**	 $R_2 = CH_2CH(CH_3)_2$

Table 2. Anti-inflammatory activity of glucosame mimetic peptides determined using an xylene-induced ear edema model

Compound [a] tested	Edema weight (X ± SD mg)	Inhibition ratio (%)	Compound tested	Edema weight (X ± SD mg)	Inhibition ratio (%)
CMC	7.6±2.8	31.8±23.9	**15c**	2.9±1.7	70.6±18.0 [b]
Aspirin	0.9±0.6	89.5±7.0 [c]	**15d**	1.9±2.1	84.2±16.5 [c, d]
5	3.5±2.2	64.3±23.0 [b]	**15e**	1.9±0.9	80.7±9.8 [c]
11a	2.3±2.3	81.6±17.5 [c, d]	**15f**	1.6±1.0	86.6±8.7 [c, d]
11b	1.8±1.3	87.1±15.4 [c, d]	**16a**	1.4±1.0	88.7±7.7 [c, d]
11c	1.5±1.3	86.2±11.9 [c, d]	**16b**	2.3±1.9	81.9±16.2 [c, d]
11d	1.2±1.1	90.3±9.3 [c, d]	**16c**	1.8±1.3	85.1±11.2 [c, d]
11e	2.4±1.7	80.1±14.1 [b]	**16d**	1.5±1.3	86.8±12.2 [c, d]
11f	2.8±2.4	76.7±19.2 [b]	**16e**	2.3±1.1	80.3±9.5 [c]
15a	2.5±2.5	79.8±20.4 [b]	**16f**	2.2±2.0	81.8±15.9 [c, d]
15b	1.6±2.0	86.8±16.6 [c, d]			

[a] Aspirin = Positive control, CMC = Vehicle, Dose of mimetic peptides derivatives = 10 μmol/kg, dose of aspirin = 100 mg/kg; n = 12.

[b] Compared to CMC $p < 0.01$.

[c] Compared to CMC $p < 0.01$, Compared to **5** $p < 0.05$.

[d] Compared to Aspirin $p > 0.05$.

Table 3. Inhibition ratio (%) by **16a** at different doses

Compound [a] tested	Dose (μmol/kg)	Edema weight (X ± SD mg)	Inhibition ratio (%)
CMC		7.6±2.8	31.8±23.9
16a	10	1.4±1.0	88.7±7.7[b]
16a	1	3.9±2.2	70.8±15.6[c]
16a	0.1	7.7±4.8	44.3±28.4

[a]CMC = Vehicle, n = 12.

[b]Compared to CMC $p < 0.01$, Compared to 1 μmol/kg $p < 0.01$.

[c]Compared to CMC $p < 0.01$, Compared to 0.1 μmol/kg $p < 0.05$.

Scheme captions

Scheme 1. Synthesis of 3-(5,5-dimethyl-1,3-dioxane-2-yl)-propanal (Compound **4**).

Reagents and conditions: (i) 6N HCl; (ii) DDQ, CH_3CN and H_2O.

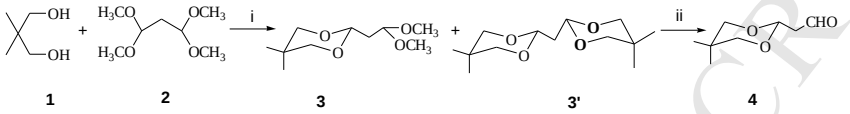
Scheme 2. Synthesis of glucosamine mimetic peptides, Compounds **11a-f** [a].

[a] For Compound **11a**: R_2 = $CH(CH_3)CH_2CH_3$; For Compound **11b**: R_2 = $CH_2C_6H_5$; For Compound **11c**: R_2 = $CH(CH_3)_2$; For Compound **11d**: R_2 = CH_3; For Compound **11e**: R_2 = 

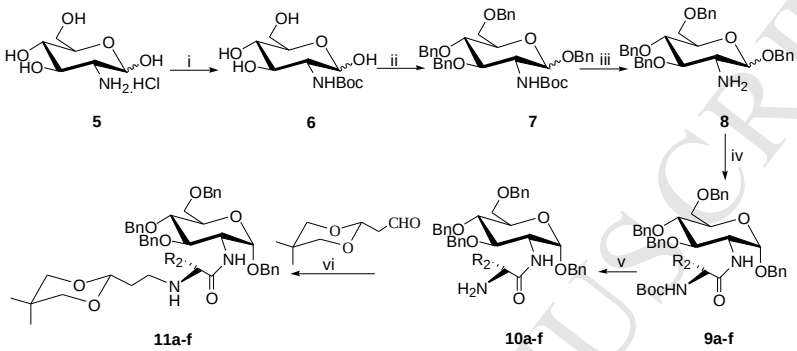
, **11f**: R_2 = $CH_2CH(CH_3)_2$. Reagents and conditions: (i) $(Boc)_2O$; (ii) BnBr, NaH; (iii) CF_3COOH; (iv) Boc-AA, HOBt, DCC, NMM; (v) 4N HCl/EtOAc; (vi) $NaCNBH_3$, MeOH.

Scheme 3. Synthesis of glucosamine mimetic peptides, Compounds **16a-f**.

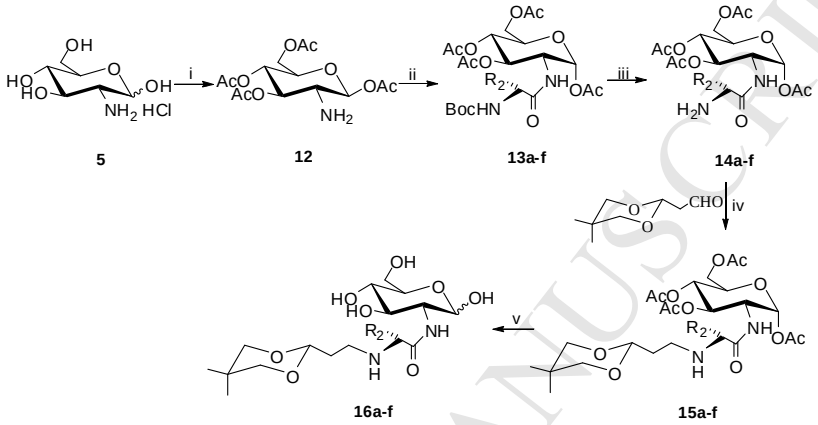
Reagents and conditions: (i) $(Ac)_2O$ and H_2SO_4; (ii) Boc-AA, HOBt, DCC, NMM; (iii) 4N HCl/EtOAc; (iv) $NaCNBH_3$, MeOH; (v) CH_3ONa, CH_3OH.



Scheme 1



Scheme 2



Scheme 3

Highlights

- Severa novel glucosamine mimetic peptides containing 1,3 dioxane were designed and synthesized.
- Most of compounds exhibited a significant inhibition against xylene-induced inflammation in mice.
- Some compounds show similar the anti-inflammatory effect in comparison to positive control aspirin.

SUPPORTING INFORMATION

Design, synthesis and evaluation of a novel class of glucosamine mimetic peptides containing 1,3-dioxane

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NMR and MS Spectra

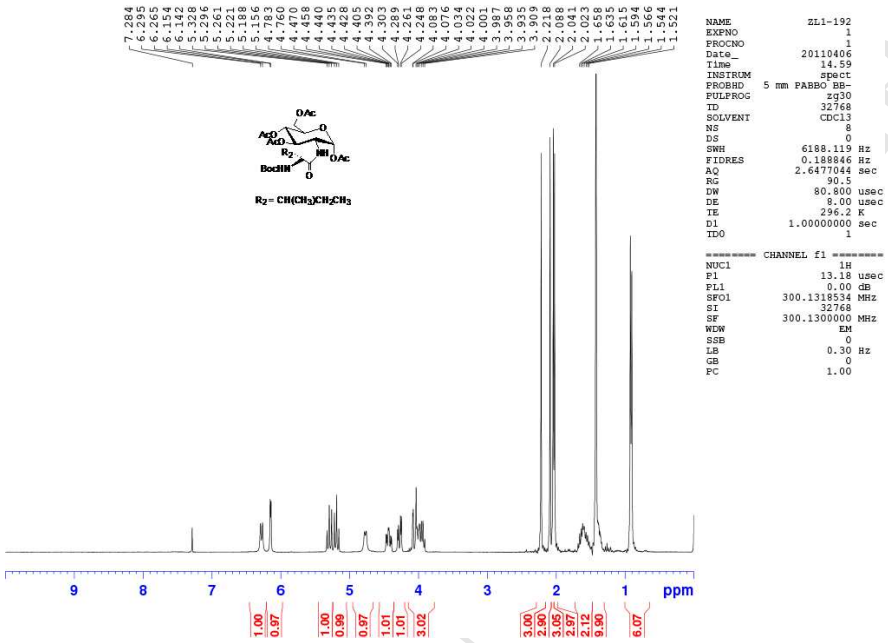
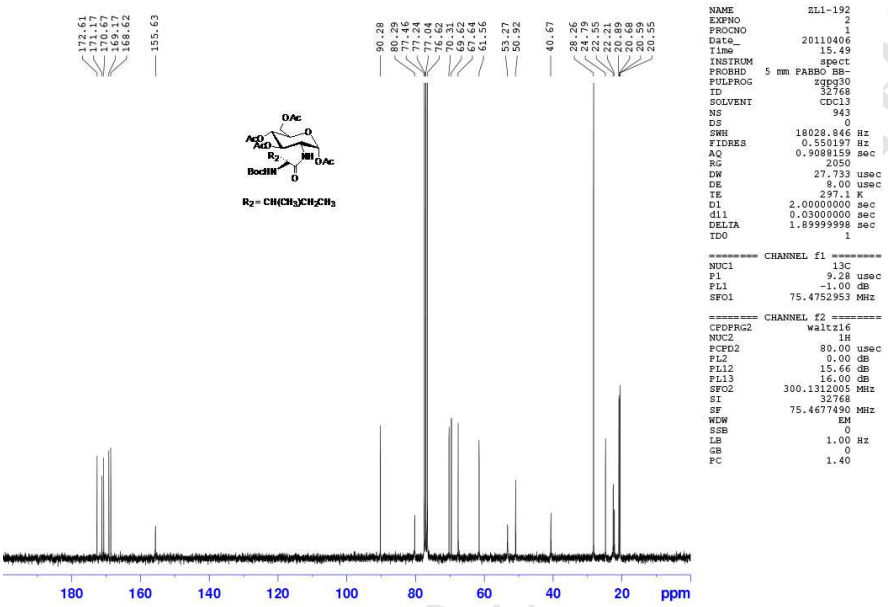


Figure S1 ^{1}H NMR spectrum of compound **13a** in $CDCl_3$ recorded at 25 □



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PROCNO	1
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SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	2050
DW	27.733 usec
DE	8.00 usec
TE	297.1 K
D1	2.00000000 sec
d11	0.03000000 sec
DELTA	1.89999998 sec
TD0	1
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PL1	-1.00 dB
SFO1	75.4752953 MHz
======== CHANNEL f2 ========	
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PL12	15.66 dB
PL13	16.00 dB
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Figure S2 ^{13}C NMR spectrum of compound **13a** in $CDCl_3$ recorded at 25 □

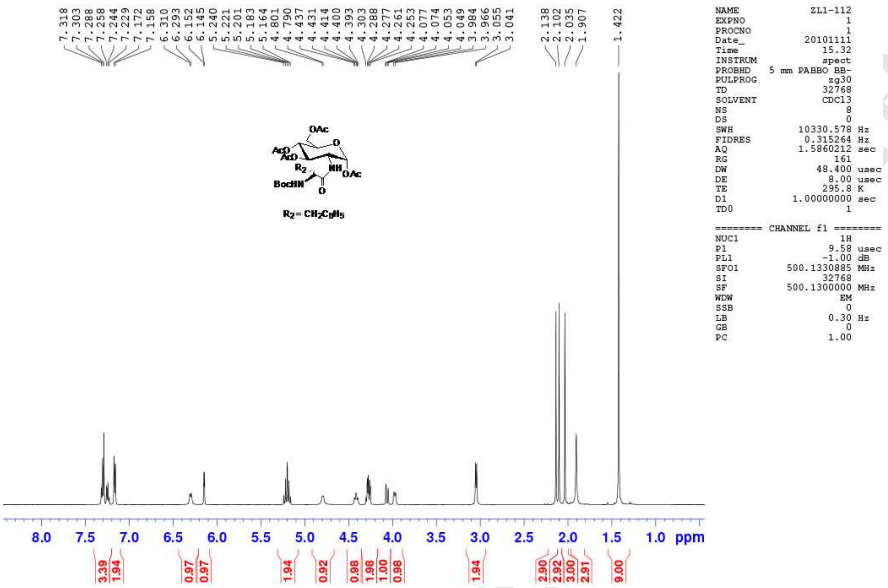


Figure S3 ^{1}H NMR spectrum of compound **13b** in $CDCl_3$ recorded at 25 □

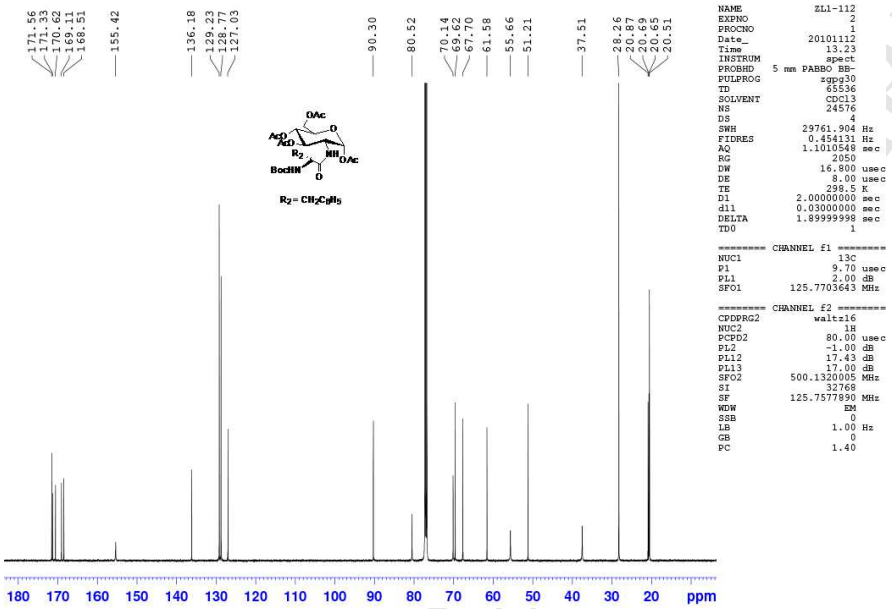


Figure S4 ^{13}C NMR spectrum of compound **13b** in $CDCl_3$ recorded at 25 □

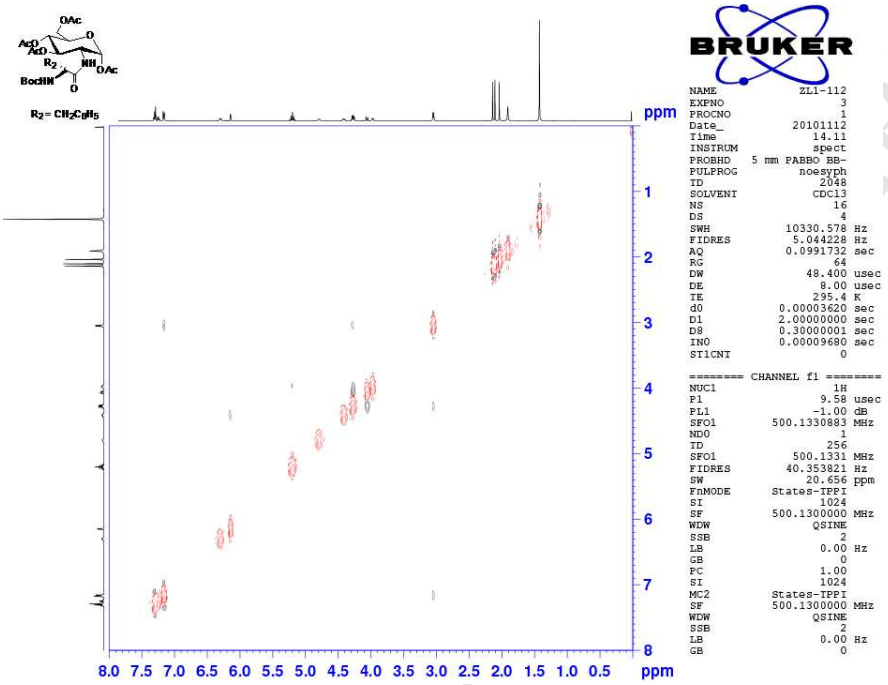


Figure S5 H-H Cosy spectrum of compound **13b** in $CDCl_3$ recorded at 25 □

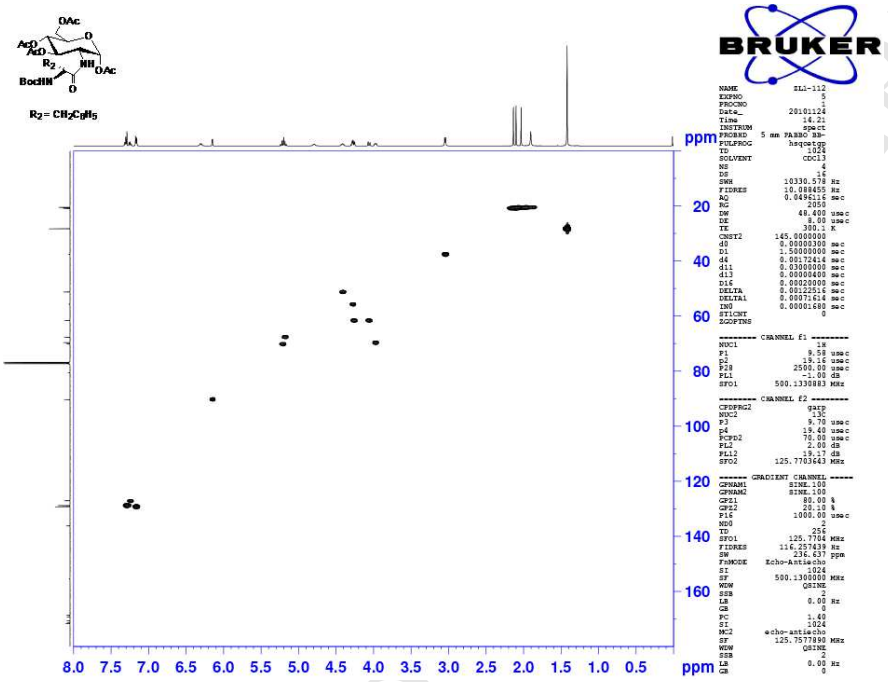


Figure S6 HMQC spectrum of compound **13b** in $CDCl_3$ recorded at 25 □

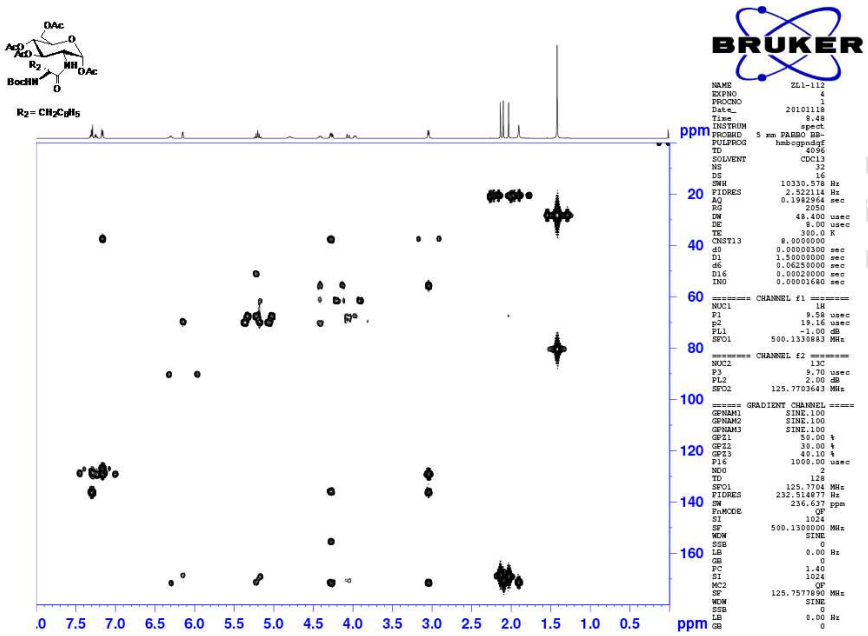


Figure S7 HMBC spectrum of compound **13b** in $CDCl_3$ recorded at 25 □

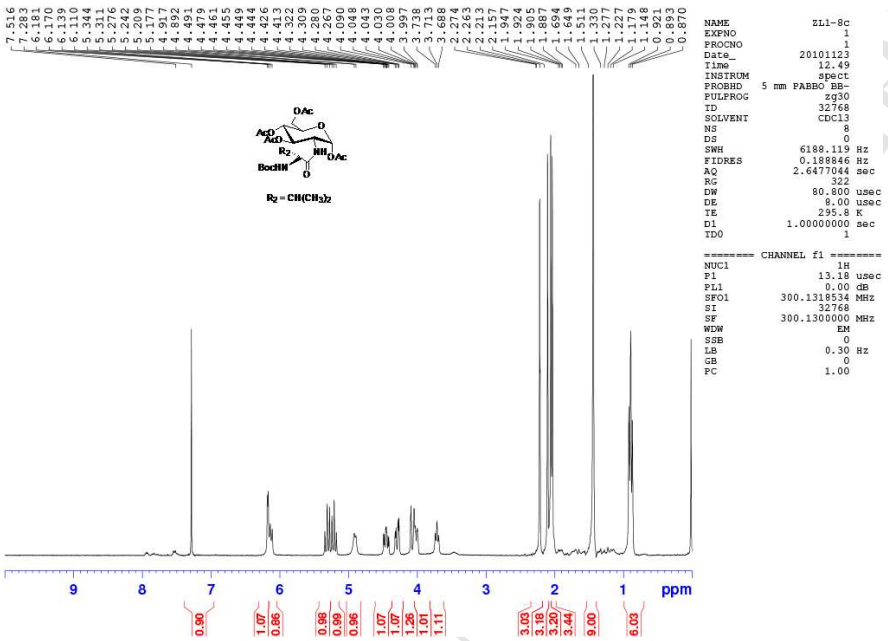


Figure S8 ^{1}H NMR spectrum of compound **13c** in $CDCl_3$ recorded at 25 □

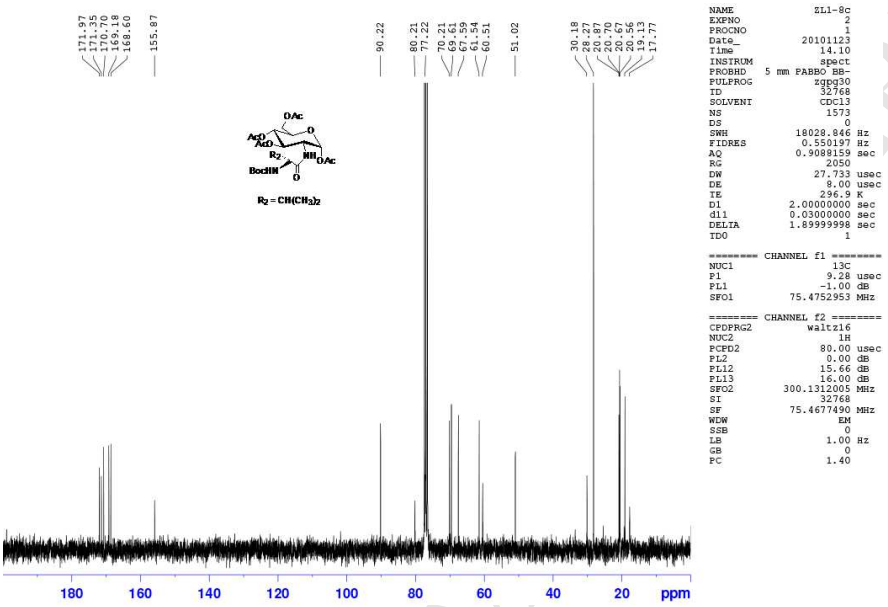


Figure S9 ^{13}C NMR spectrum of compound **13c** in $CDCl_3$ recorded at 25 □

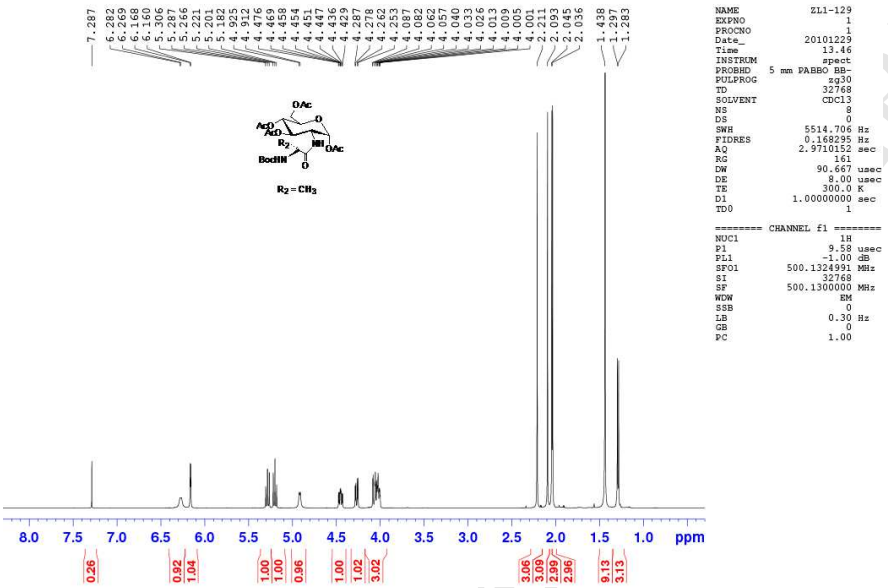


Figure S10 ^{1}H NMR spectrum of compound **13d** in $CDCl_3$ recorded at 25 □

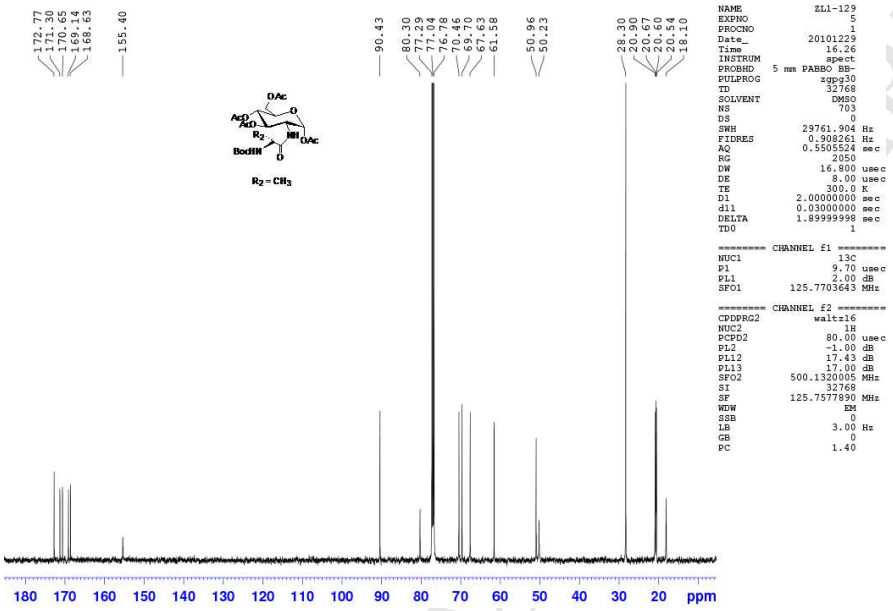


Figure S11 ^{13}C NMR spectrum of compound **13d** in $CDCl_3$ recorded at 25 □

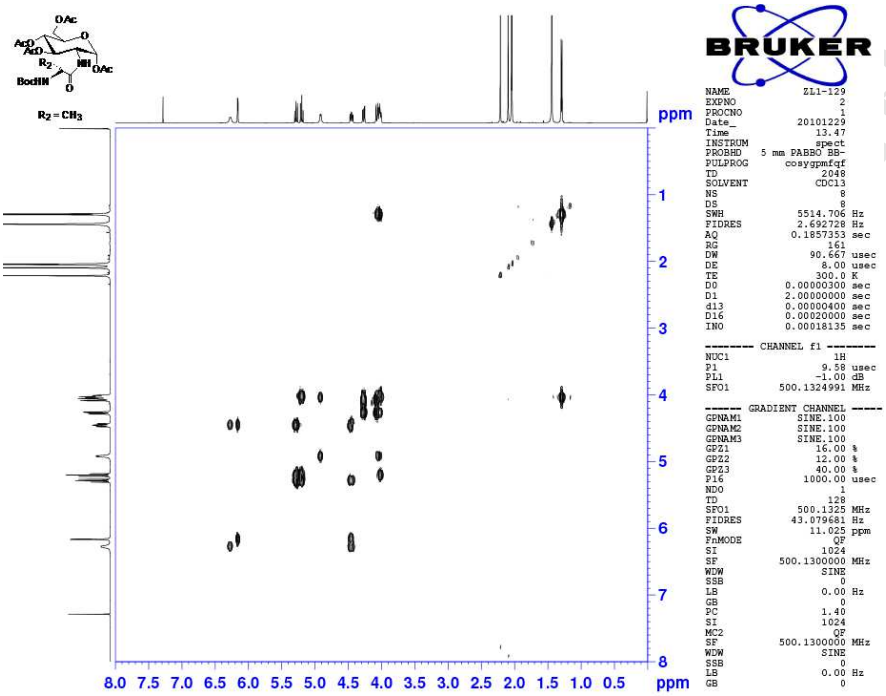


Figure S12 H-H Cosy spectrum of compound **13d** in $CDCl_3$ recorded at 25 □

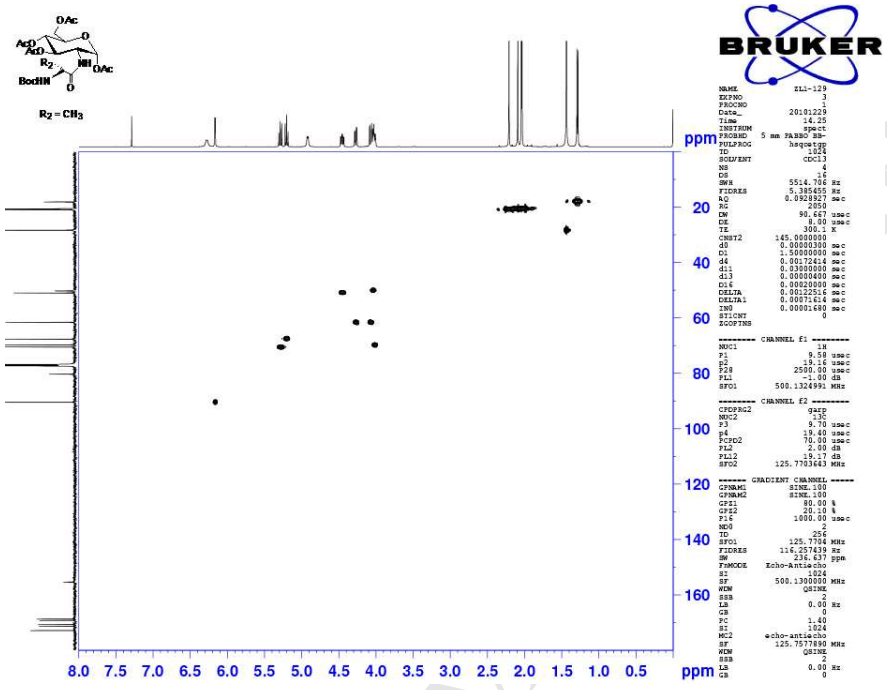


Figure S13 HMQC spectrum of compound **13d** in $CDCl_3$ recorded at 25 □

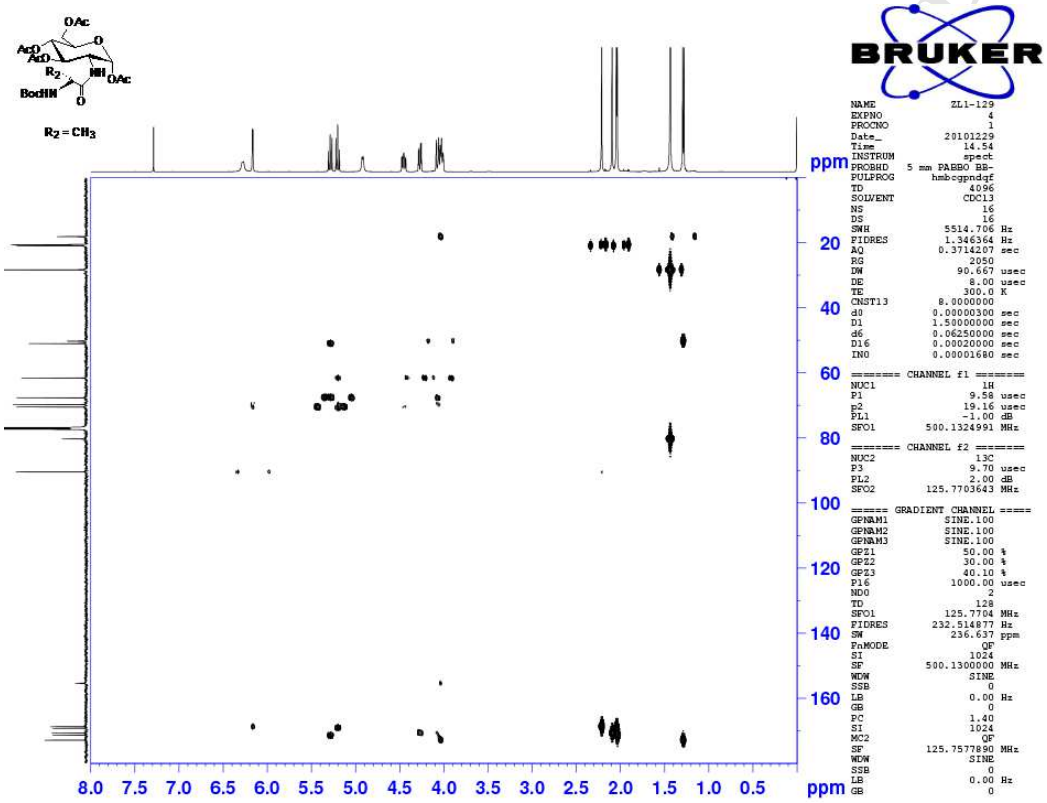


Figure S14 HMBC spectrum of compound **13d** in $CDCl_3$ recorded at 25 □

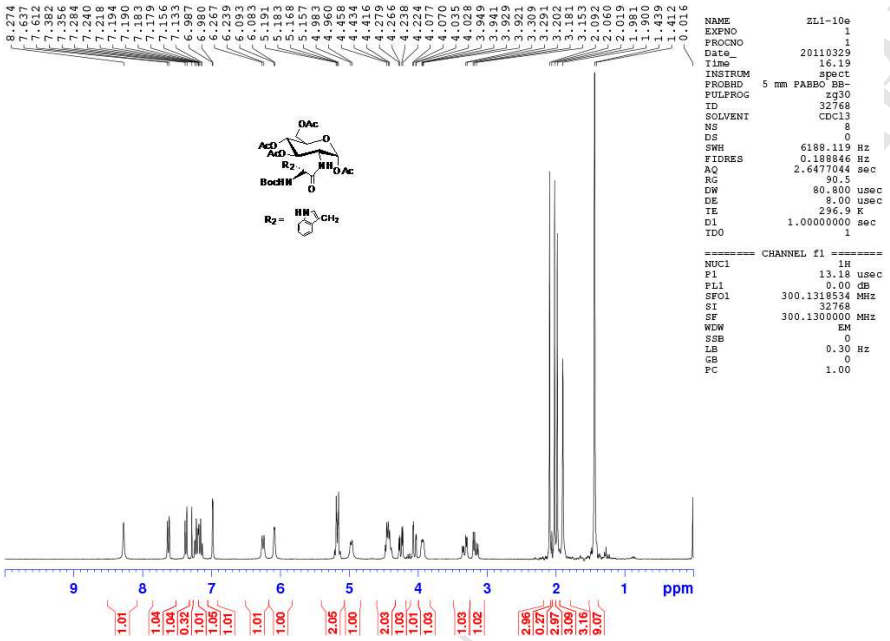


Figure S15 ^{1}H NMR spectrum of compound **13e** in $CDCl_3$ recorded at 25 □

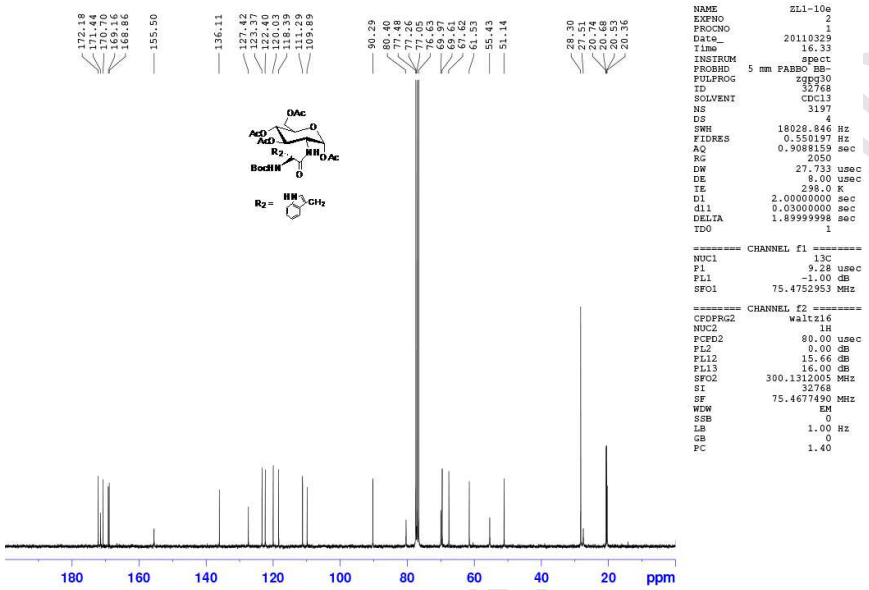


Figure S16 ^{13}C NMR spectrum of compound **13e** in $CDCl_3$ recorded at 25 □

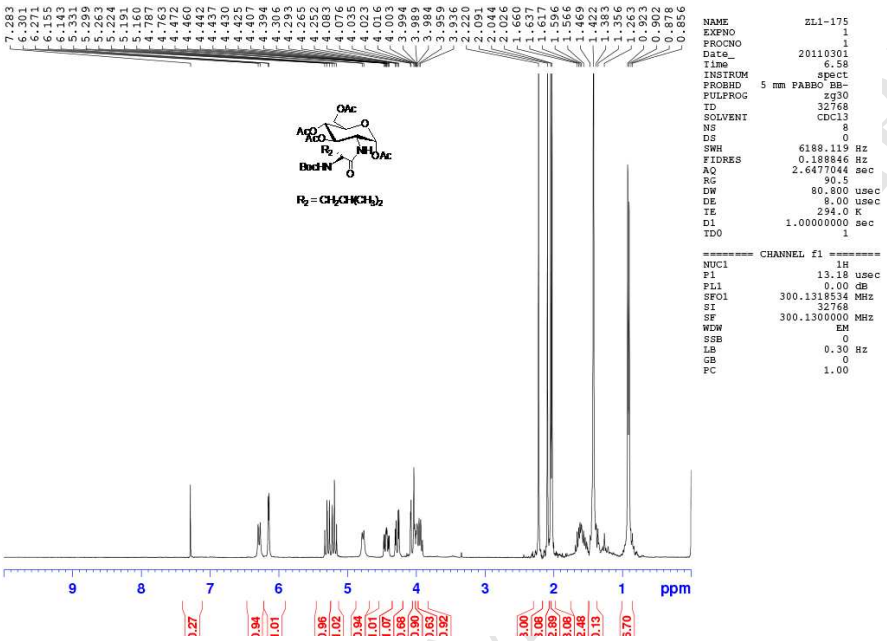


Figure S17 ^{1}H NMR spectrum of compound **13f** in $CDCl_3$ recorded at 25 □

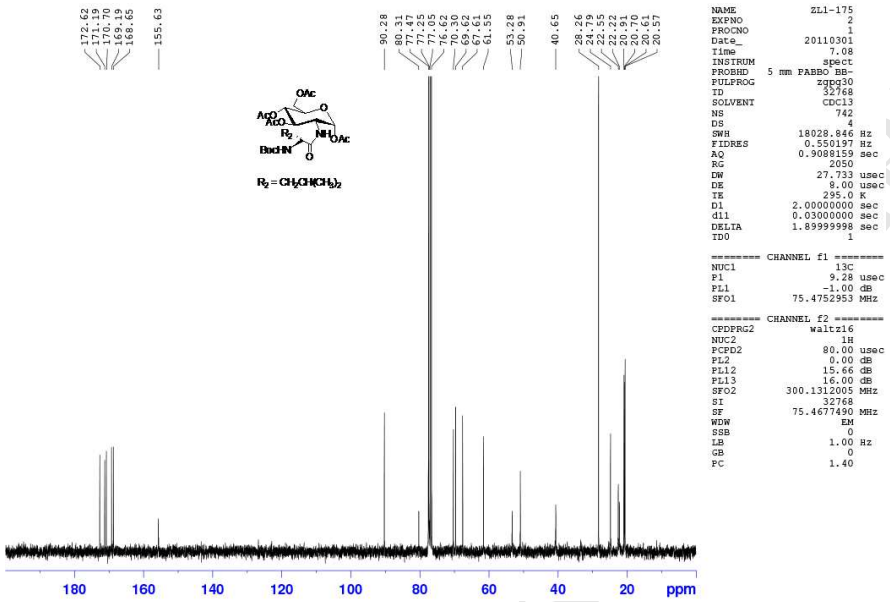


Figure S18 ^{13}C NMR spectrum of compound **13f** in $CDCl_3$ recorded at 25 □

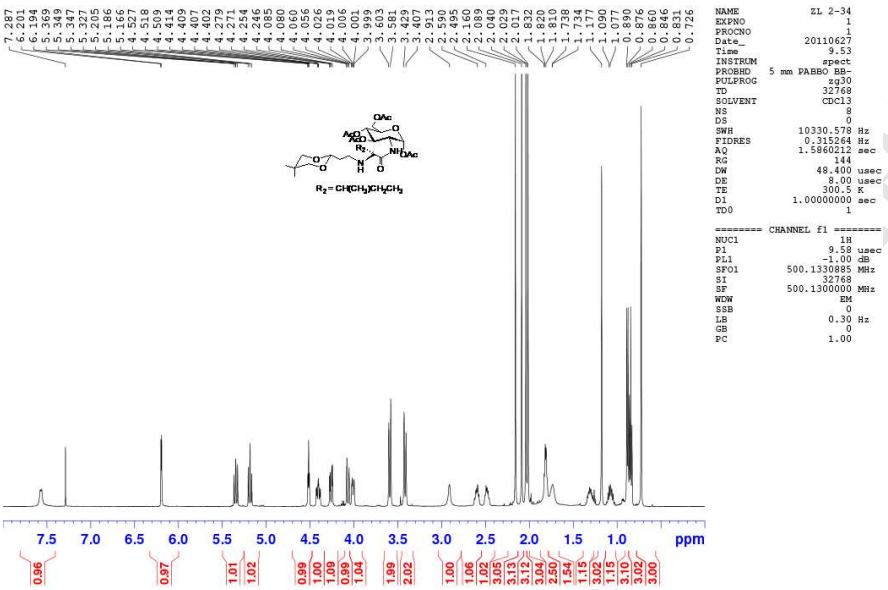


Figure S19 ^{1}H NMR spectrum of compound **15a** in $CDCl_3$ recorded at 25 □

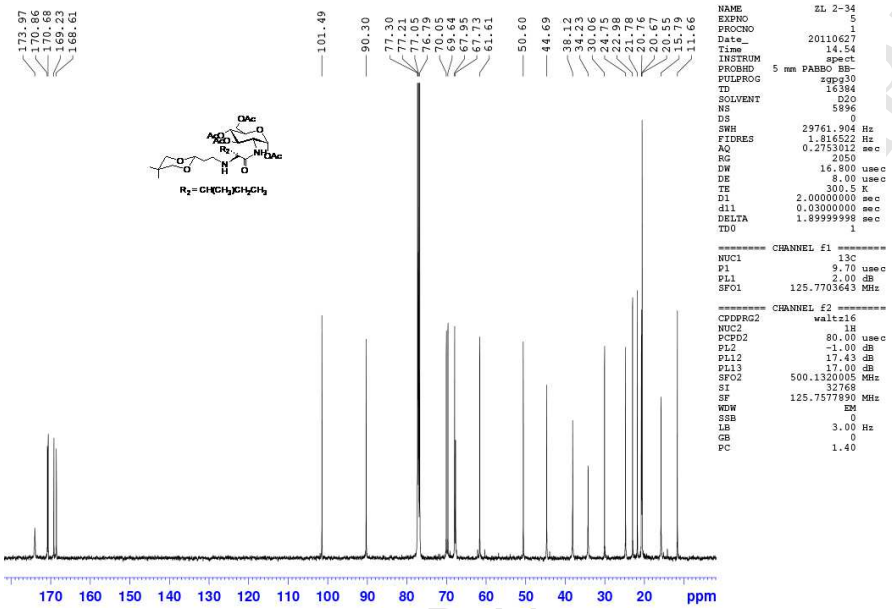


Figure S20 ^{13}C NMR spectrum of compound **15a** in $CDCl_3$ recorded at 25 □

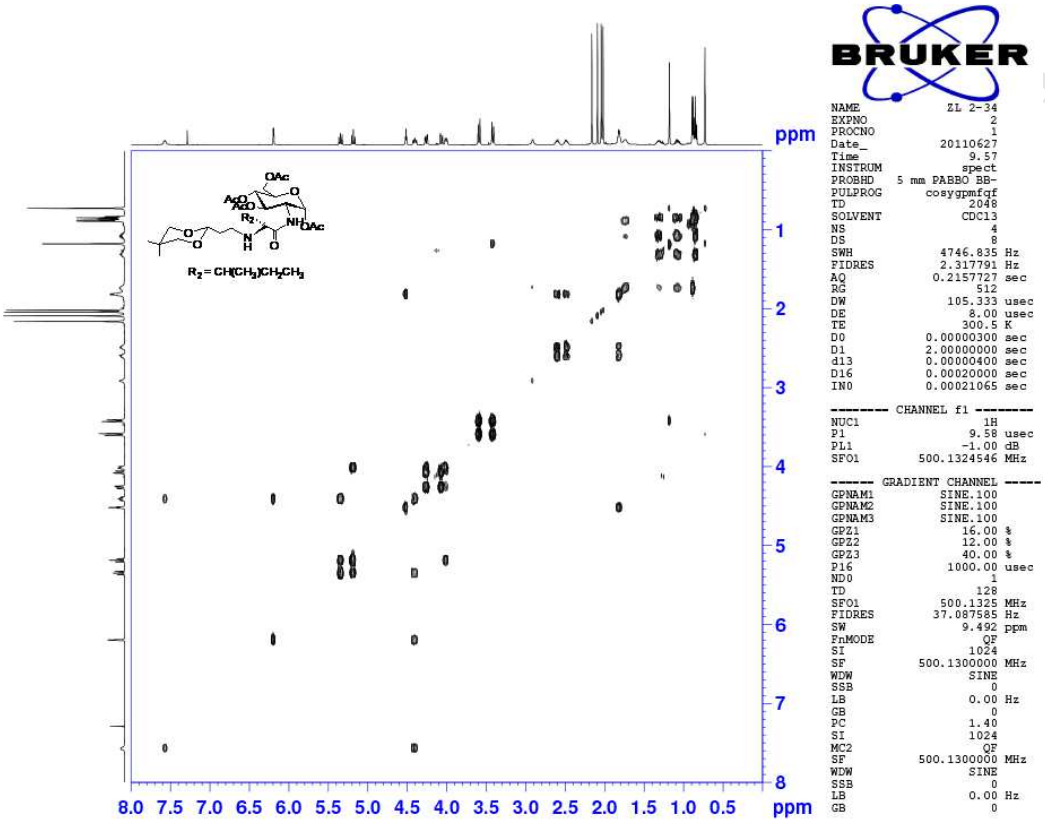


Figure S21 H-H Cosy spectrum of compound **15a** in $CDCl_3$ recorded at 25 □

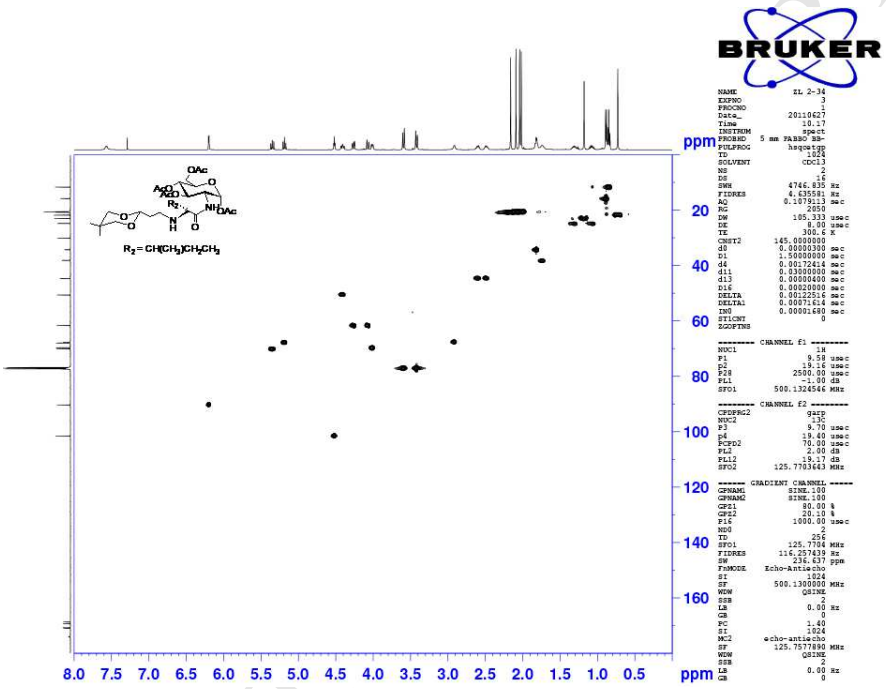


Figure S22 HMQC spectrum of compound **15a** in $CDCl_3$ recorded at 25 □

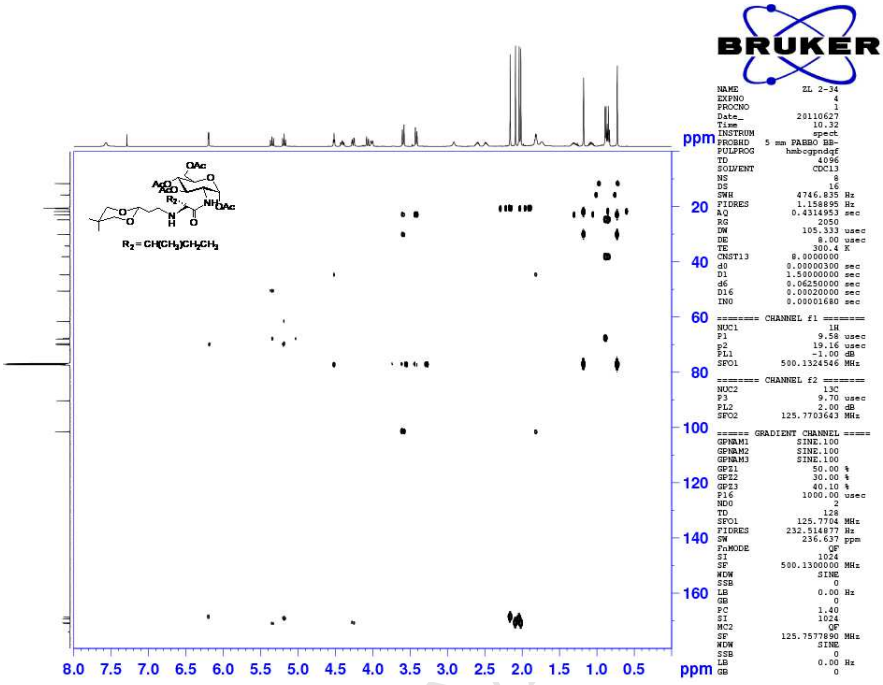


Figure S23 HMBC spectrum of compound **15a** in $CDCl_3$ recorded at 25 □

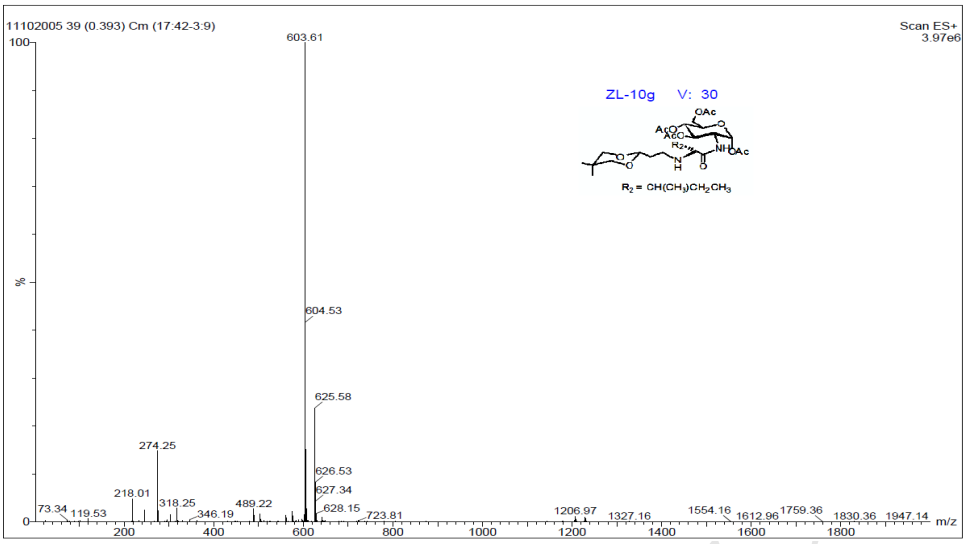
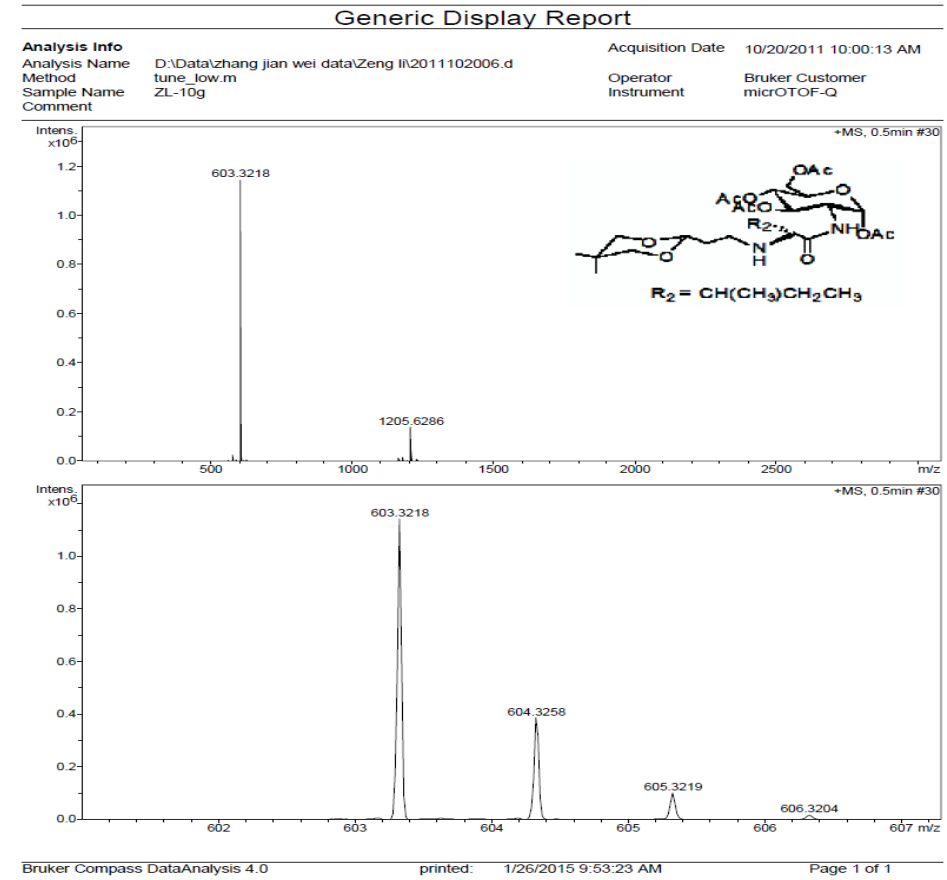


Figure S24 ESIMS spectrum of compound **15a**



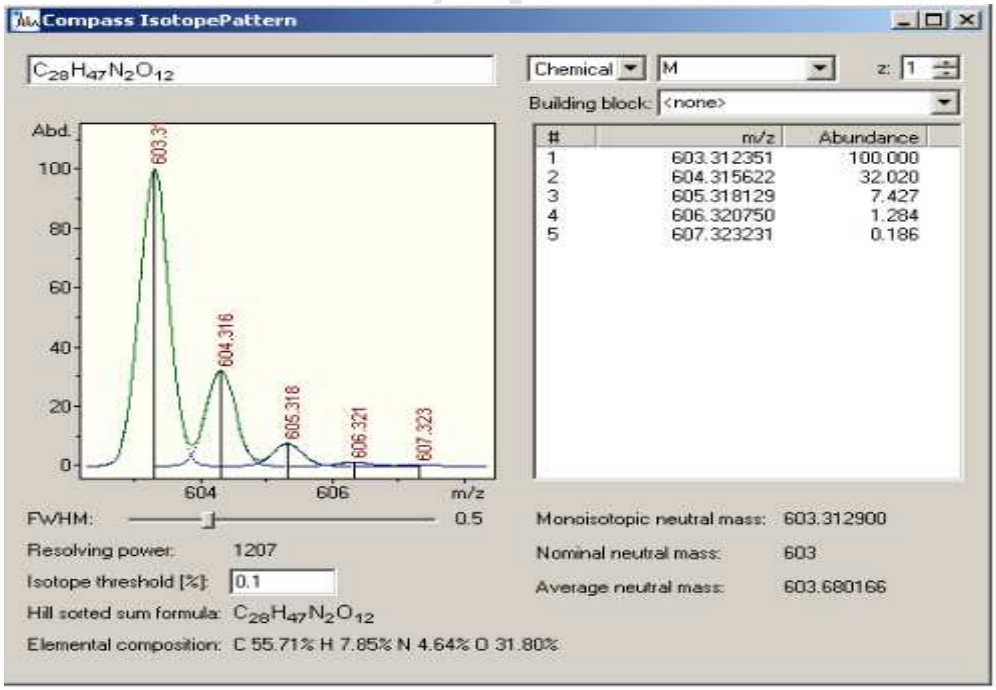


Figure S25 HRMS spectrum of compound **15a**

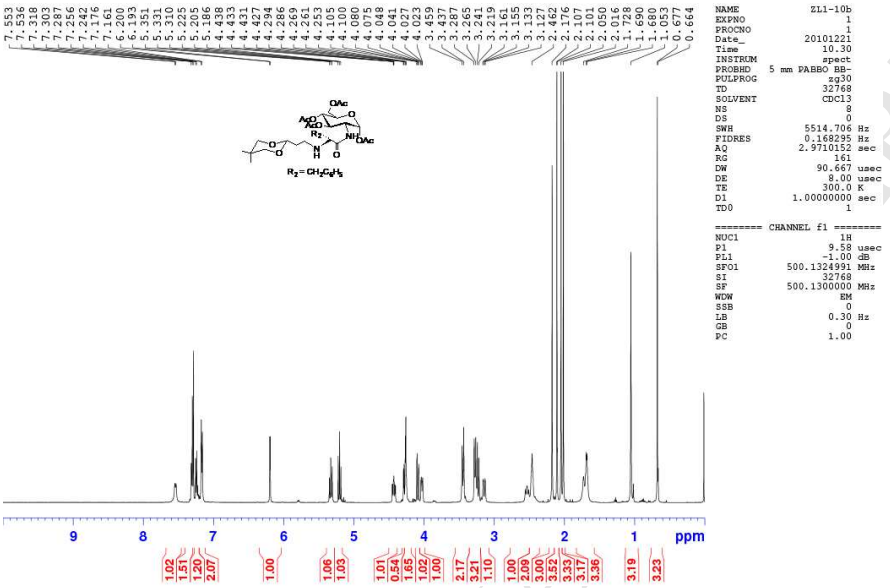


Figure S26 ^{1}H NMR spectrum of compound **15b** in $CDCl_3$ recorded at 25 □

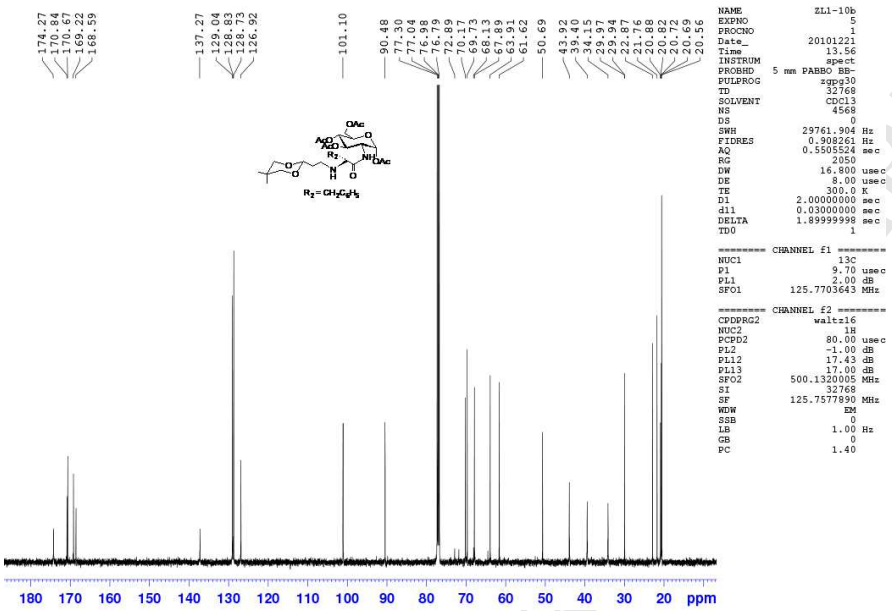


Figure S27 ^{13}C NMR spectrum of compound **15b** in $CDCl_3$ recorded at 25 □

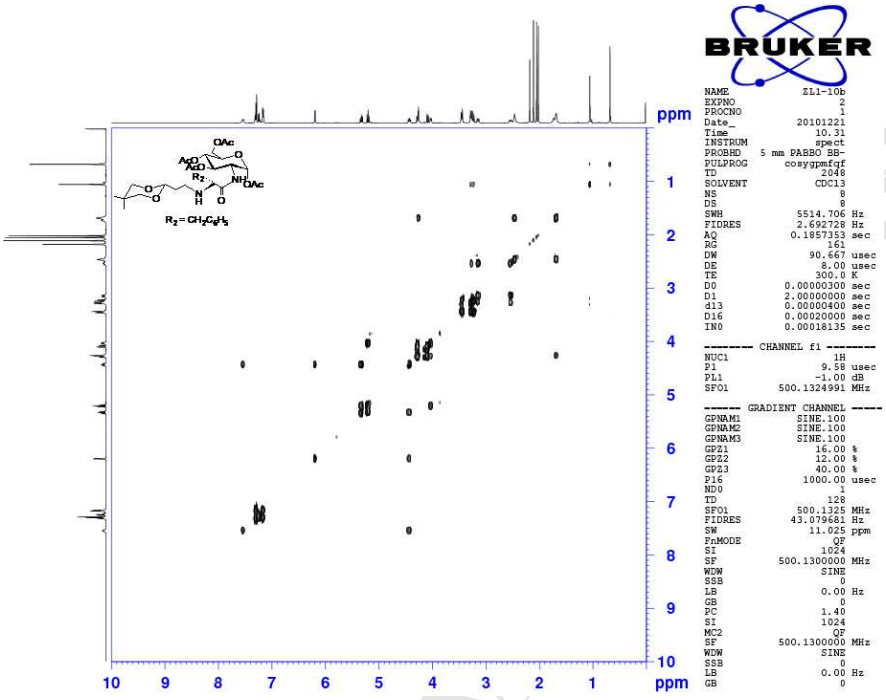


Figure S28 H-H Cosy spectrum of compound **15b** in $CDCl_3$ recorded at 25 □

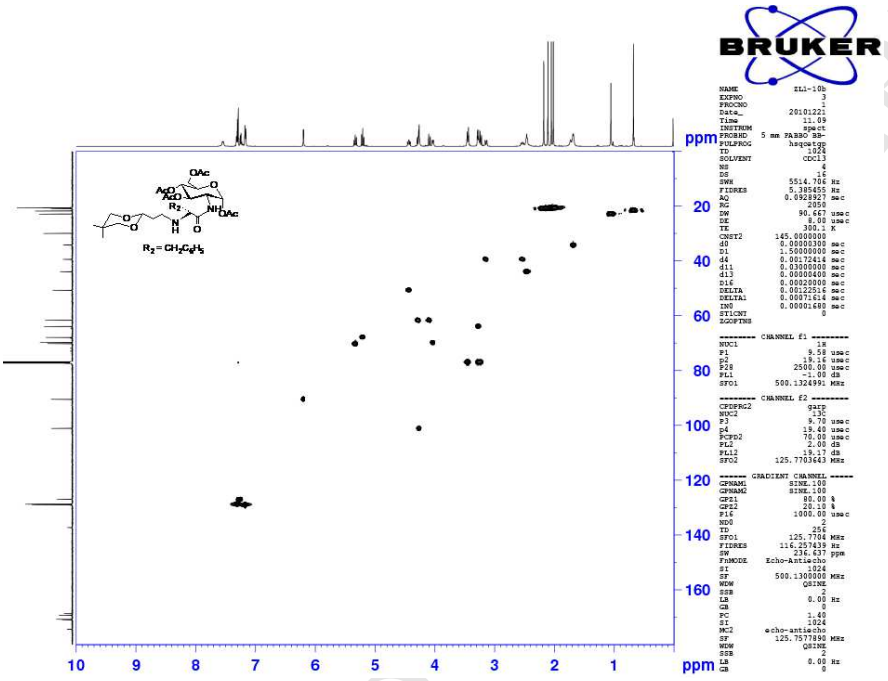


Figure S29 HMQC spectrum of compound **15b** in $CDCl_3$ recorded at 25 □

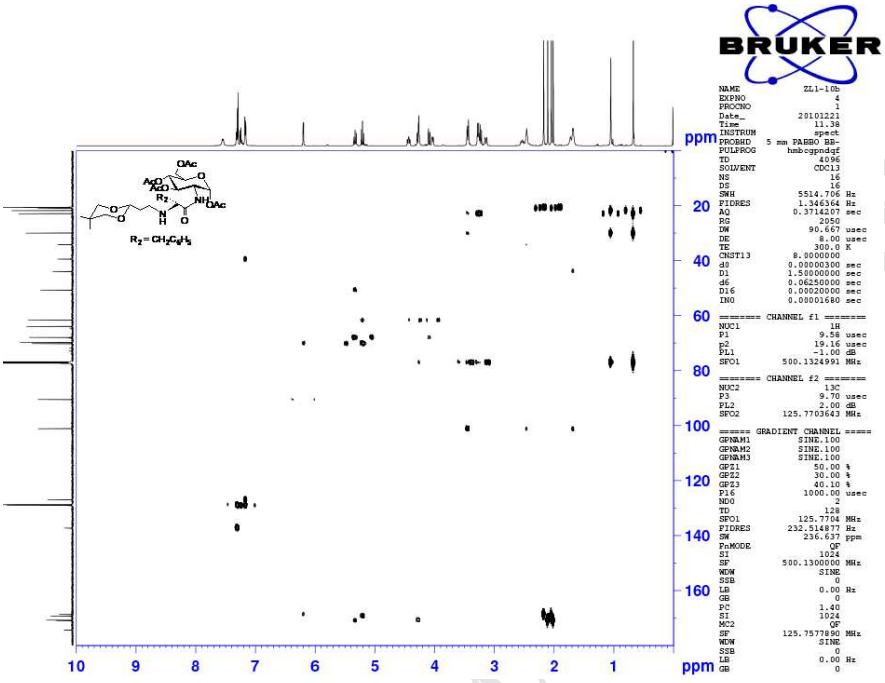


Figure S30 HMBC spectrum of compound **15b** in $CDCl_3$ recorded at 25 □

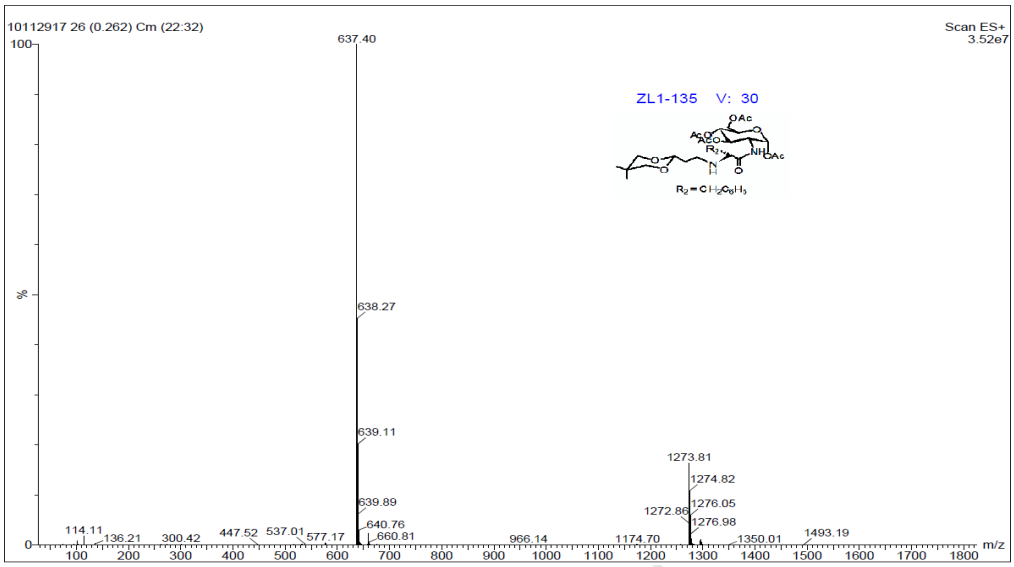
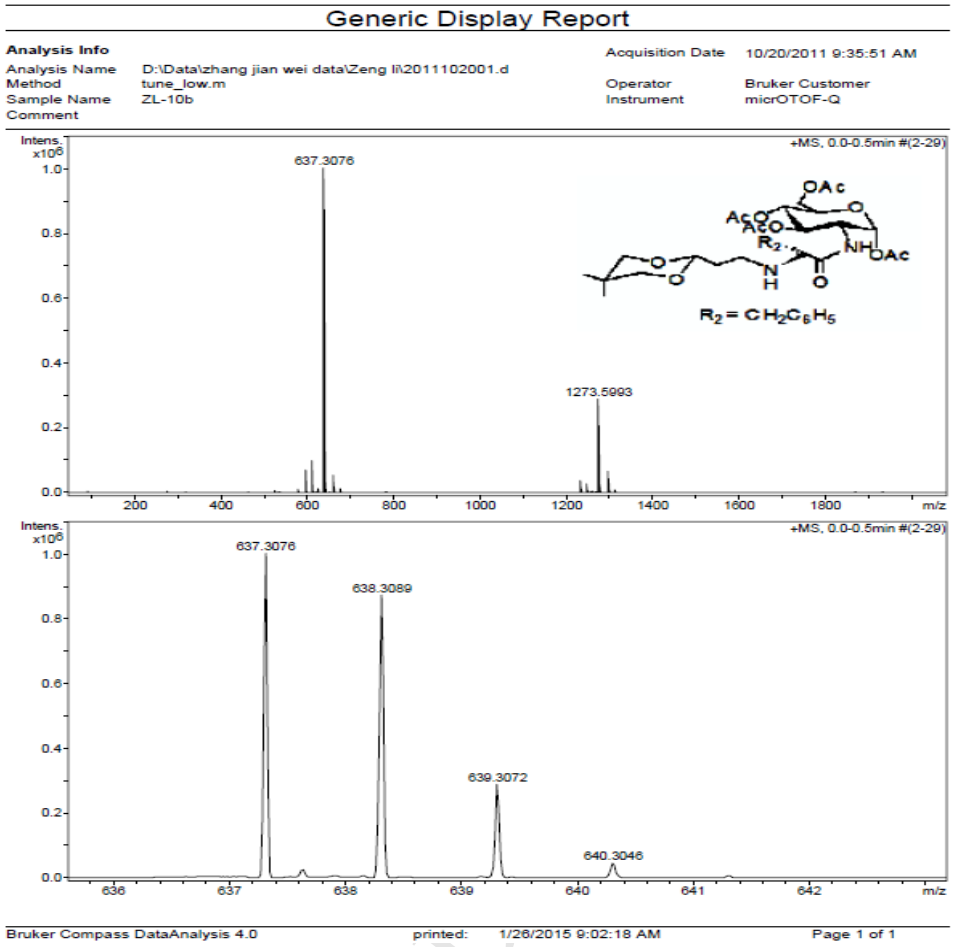


Figure S31 ESIMS spectrum of compound **15b**



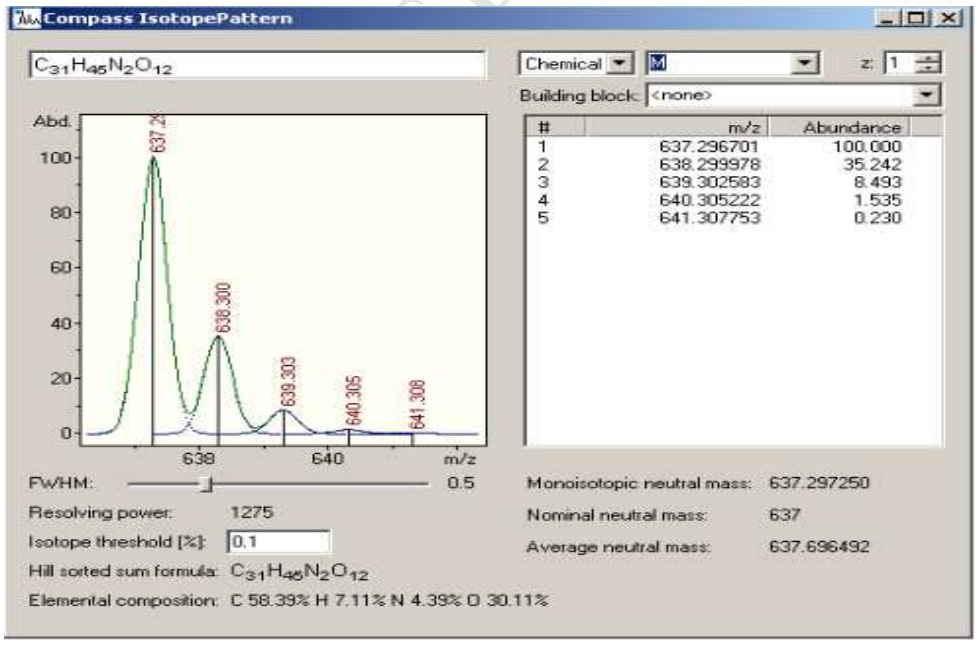


Figure S32 HRMS spectrum of compound **15b**

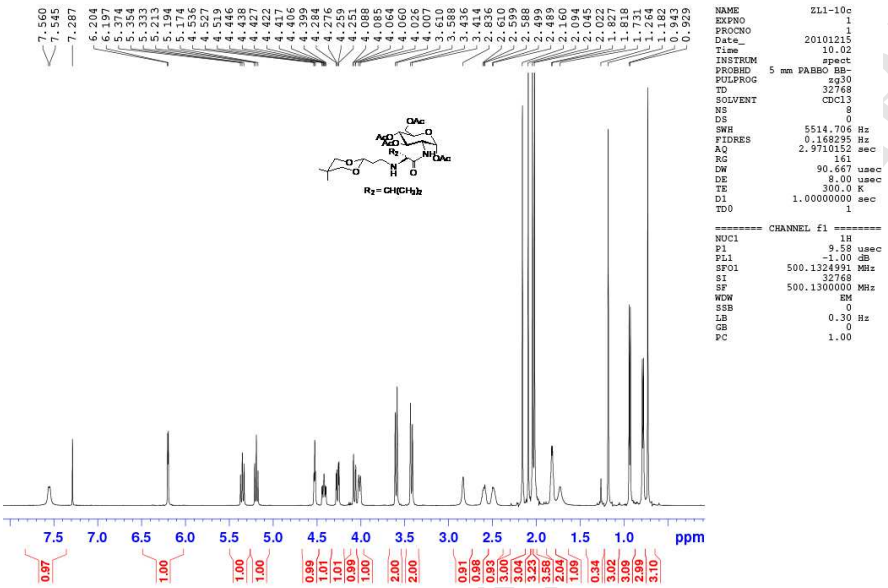


Figure S33 ^{1}H NMR spectrum of compound **15c** in $CDCl_3$ recorded at 25 □

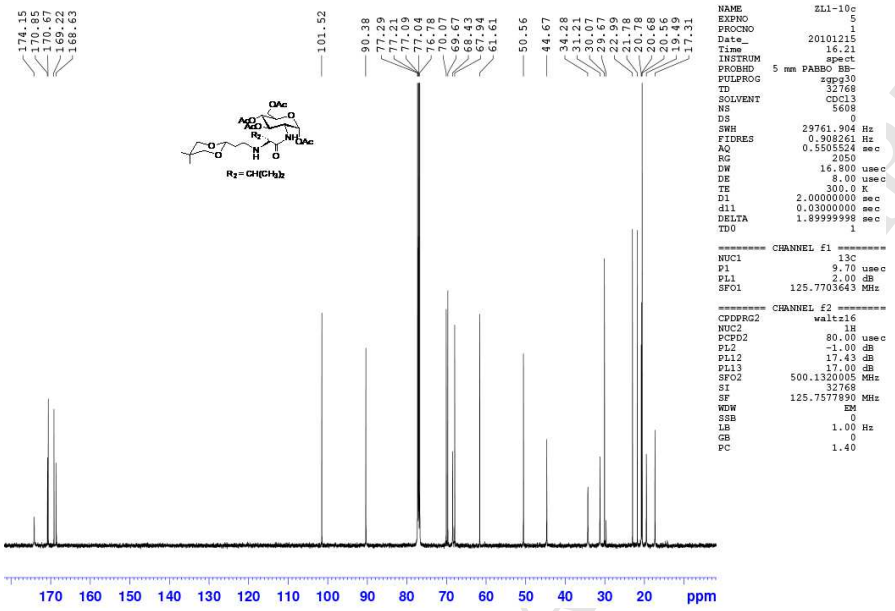


Figure S34 ^{13}C NMR spectrum of compound **15c** in $CDCl_3$ recorded at 25 □

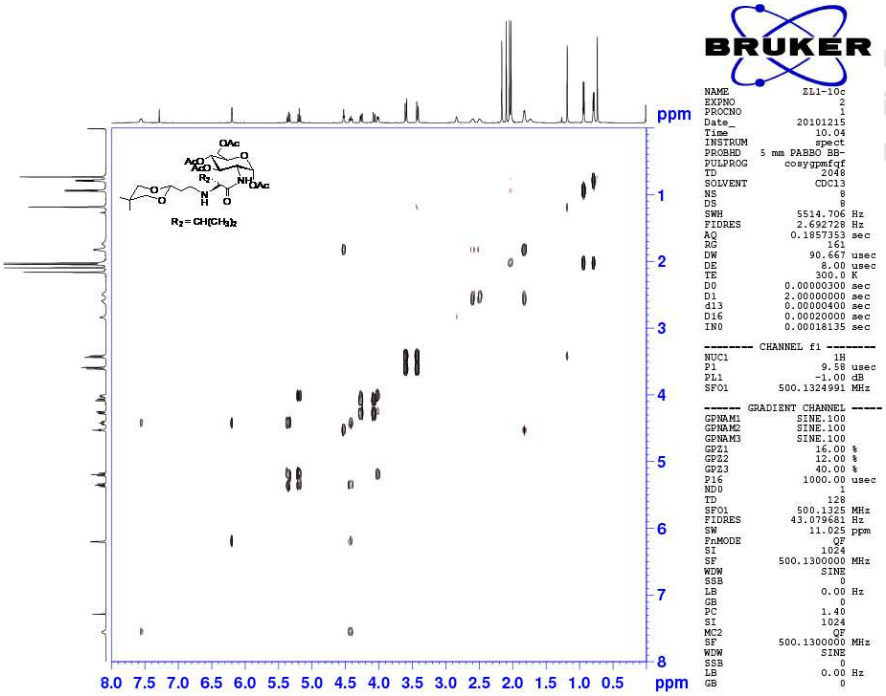


Figure S35 H-H Cosy spectrum of compound **15c** in $CDCl_3$ recorded at 25 □

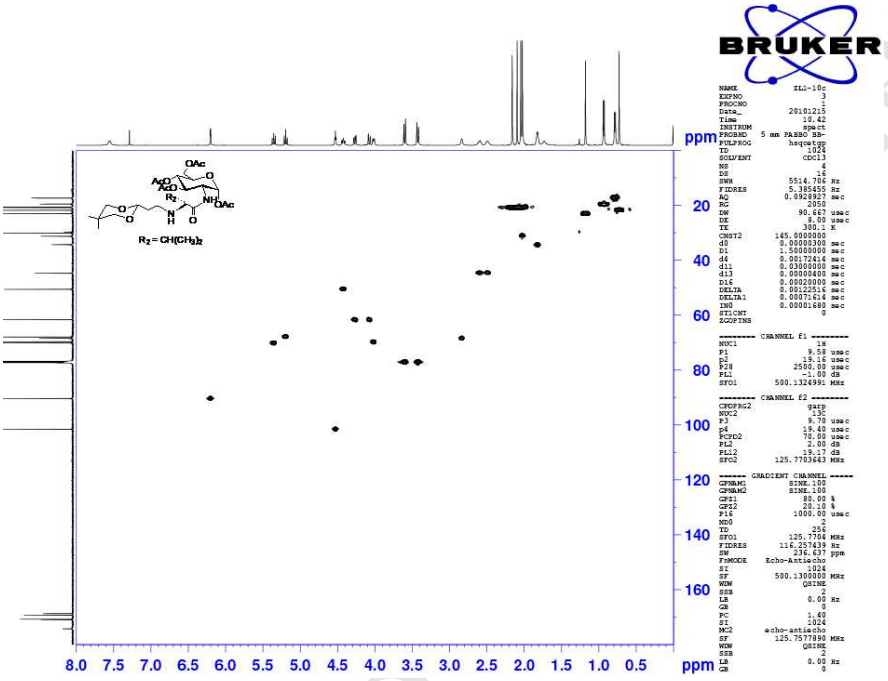


Figure S36 HMQC spectrum of compound **15c** in $CDCl_3$ recorded at 25 □

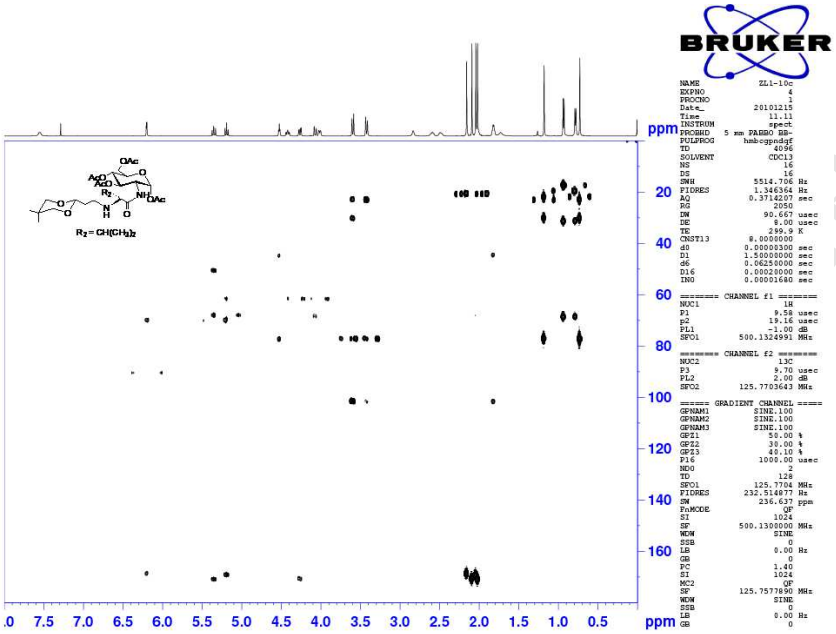


Figure S37 HMBC spectrum of compound **15c** in $CDCl_3$ recorded at 25 □

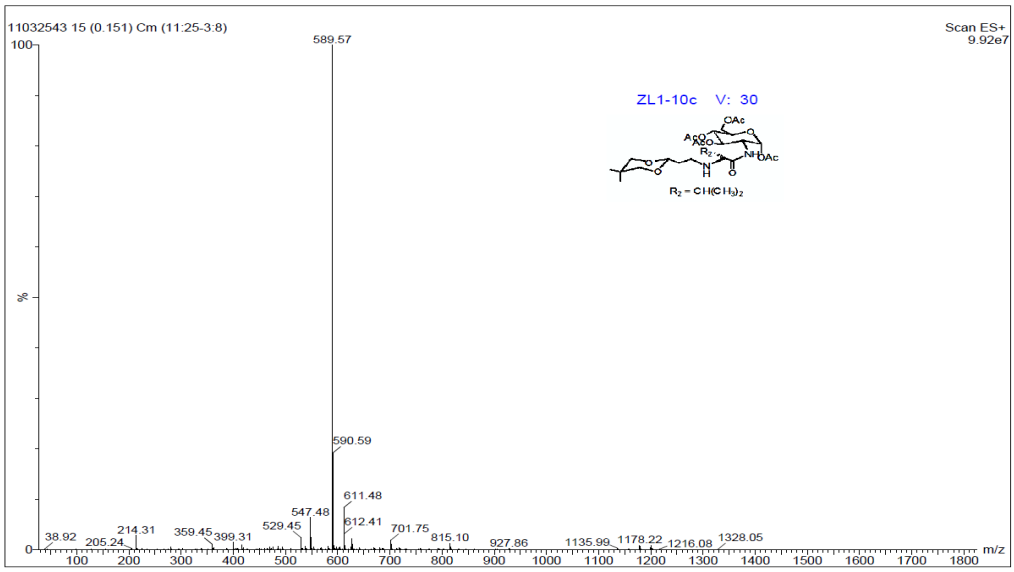
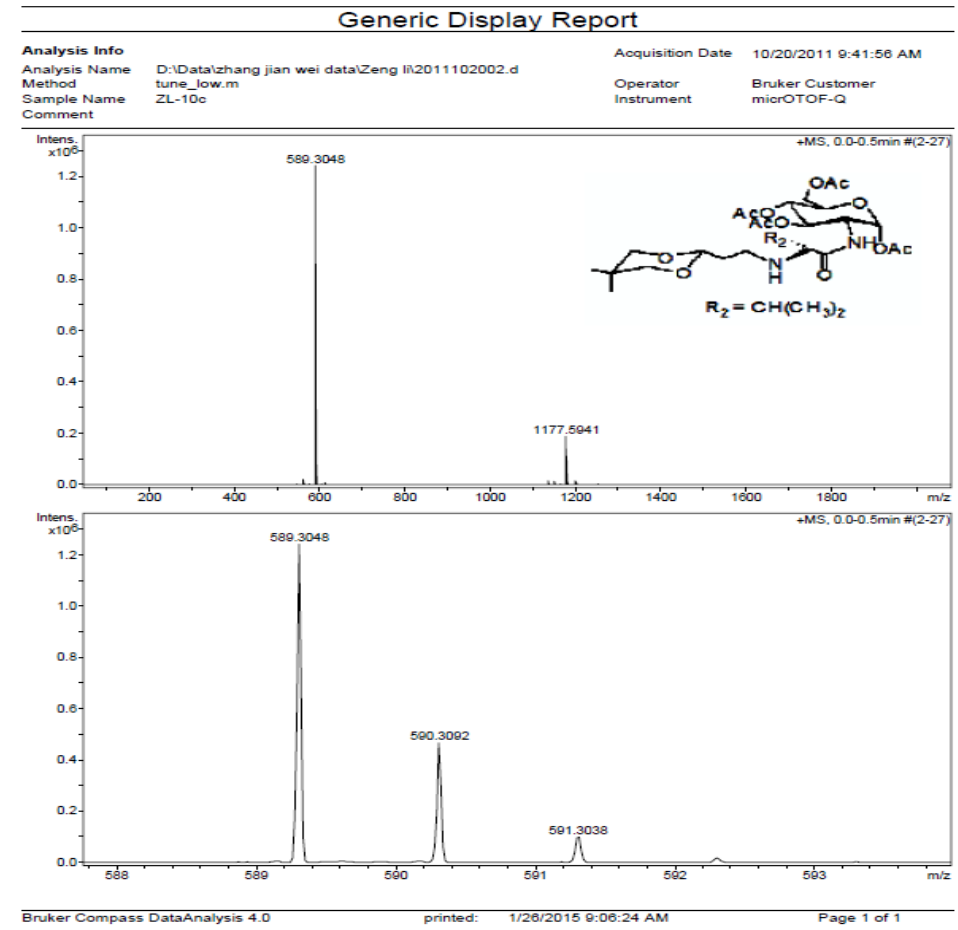


Figure S38 ESIMS spectrum of compound **15c**



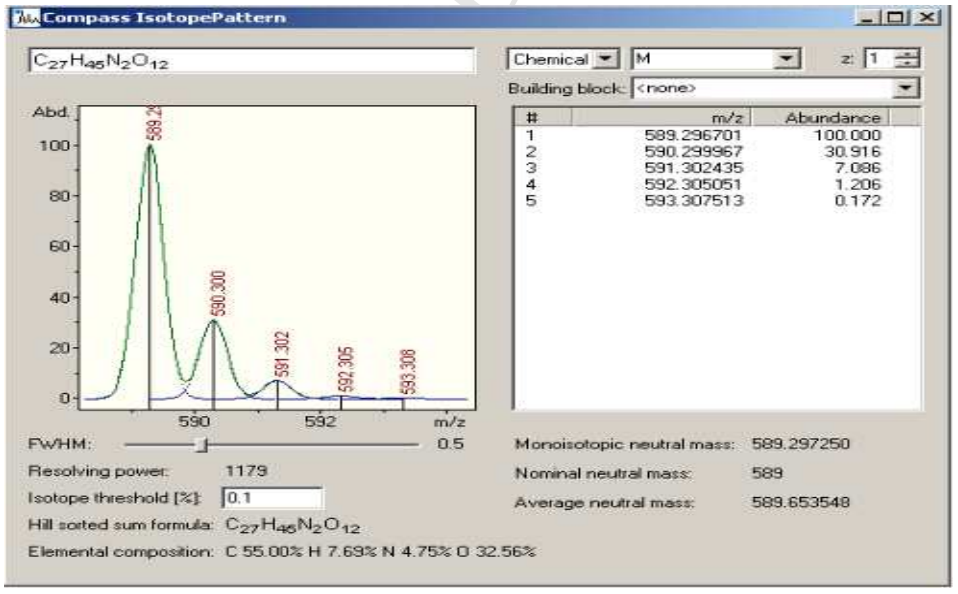


Figure S39 HRMS spectrum of compound **15c**

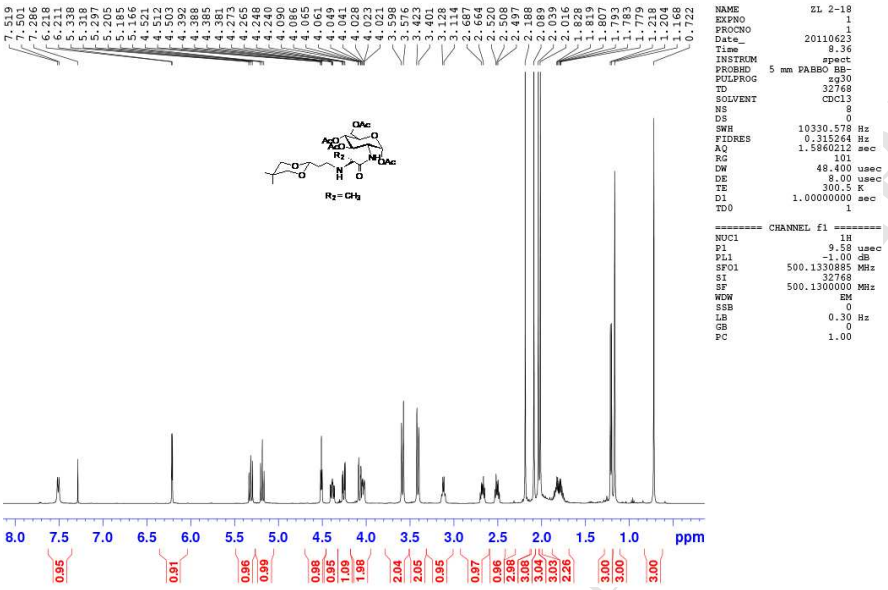


Figure S40 ^{1}H NMR spectrum of compound **15d** in $CDCl_3$ recorded at 25 □

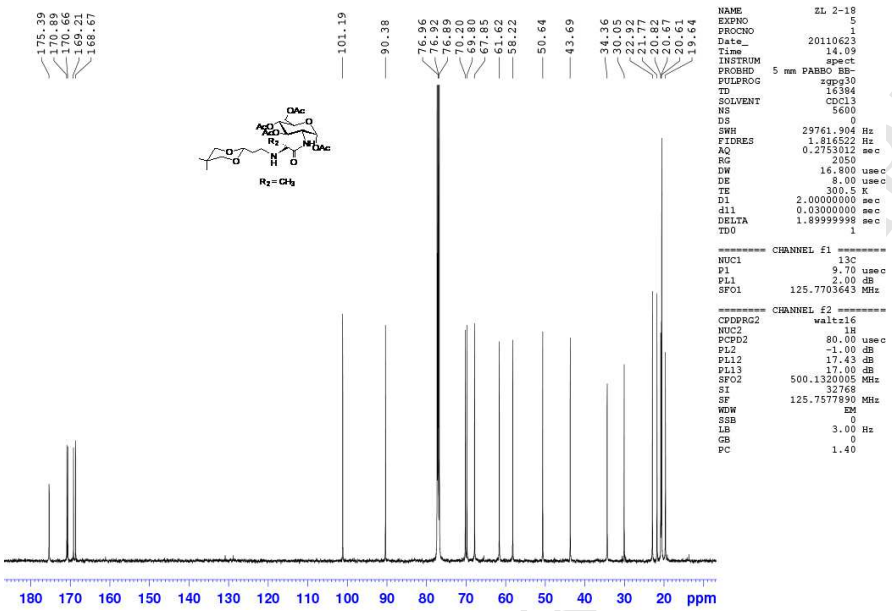


Figure S41 ^{13}C NMR spectrum of compound **15d** in $CDCl_3$ recorded at 25 □

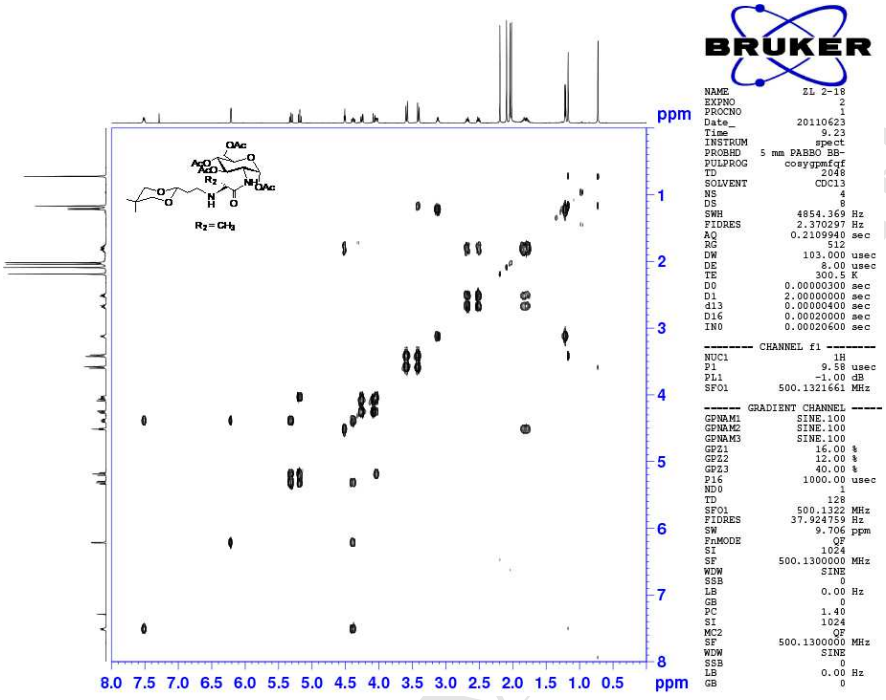


Figure S42 H-H Cosy spectrum of compound **15d** in $CDCl_3$ recorded at 25 □

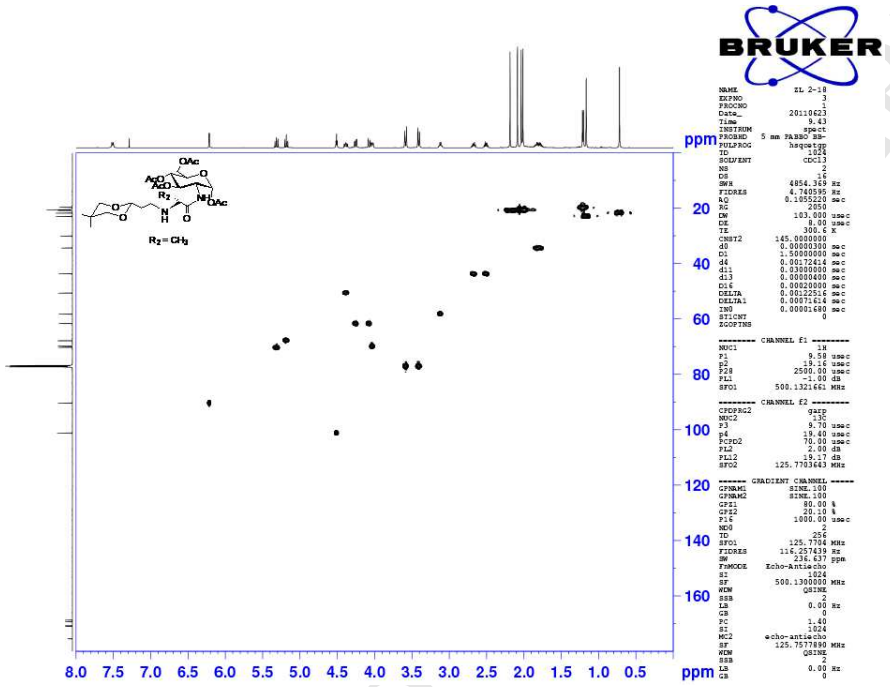


Figure S43 HMQC spectrum of compound **15d** in $CDCl_3$ recorded at 25 □

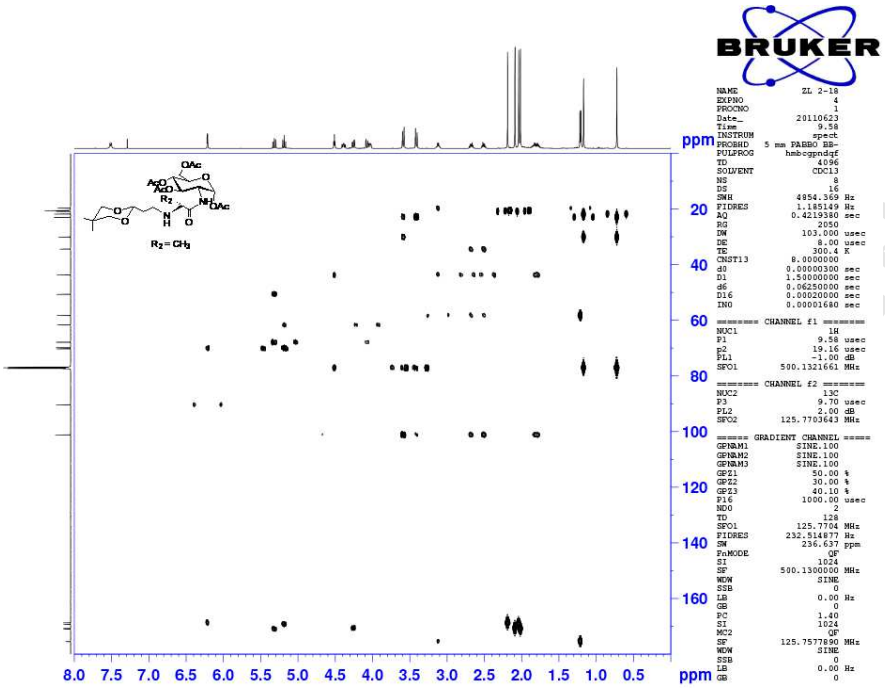


Figure S44 HMBC spectrum of compound **15d** in $CDCl_3$ recorded at 25 □

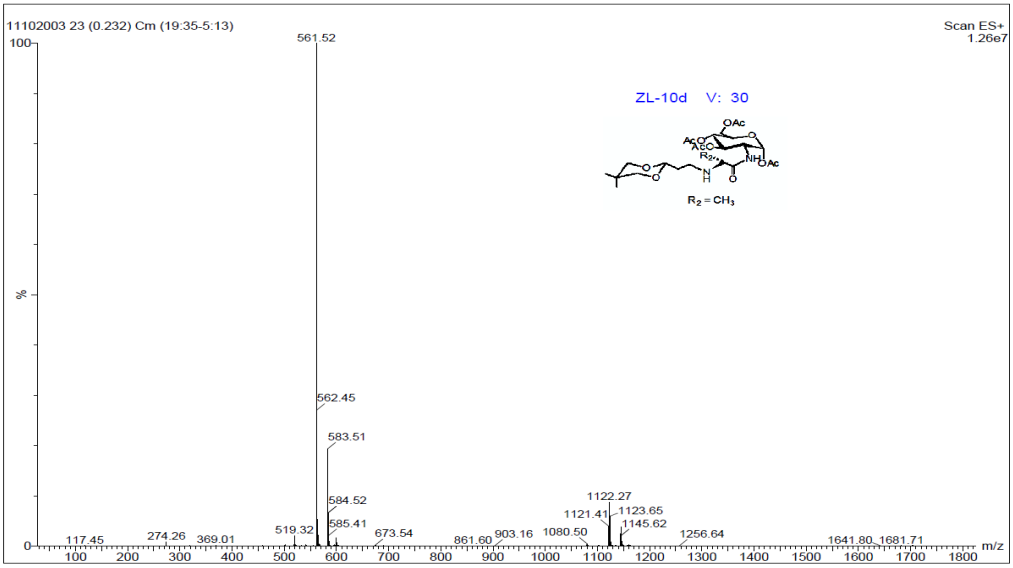
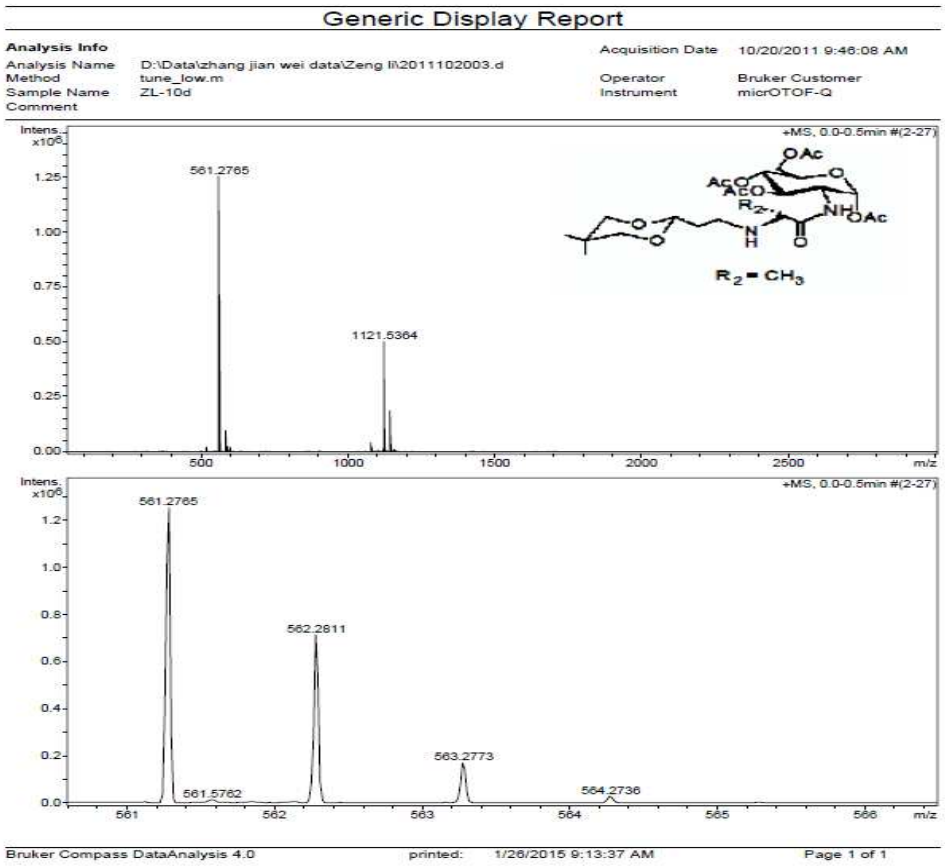


Figure S45 ESIMS spectrum of compound **15d**



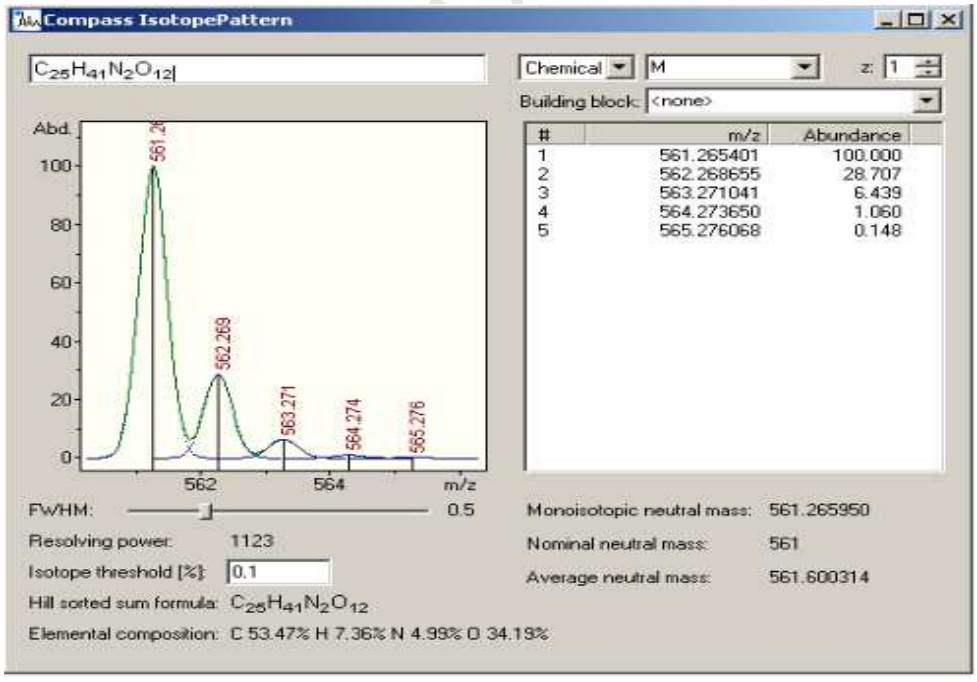


Figure S46 HRMS spectrum of compound **15d**

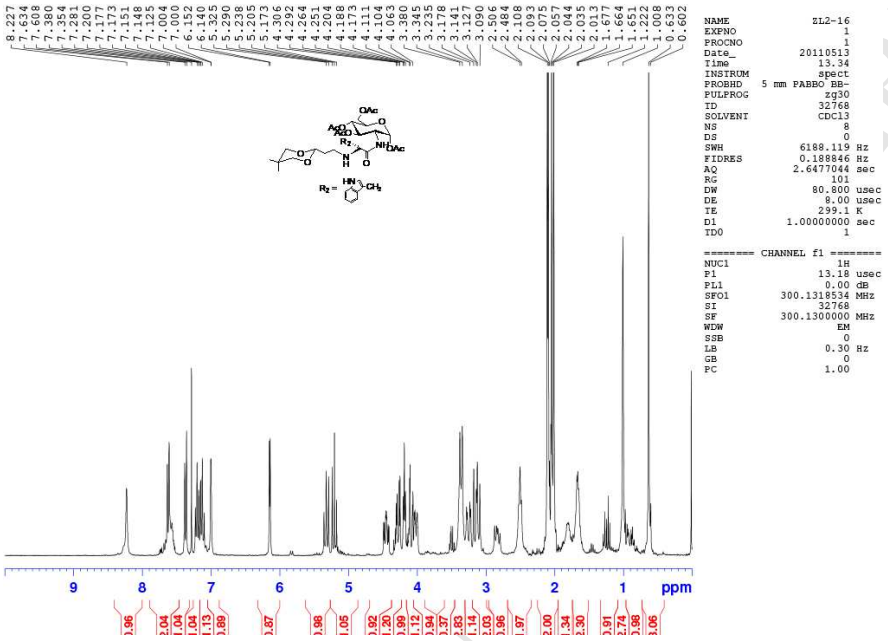
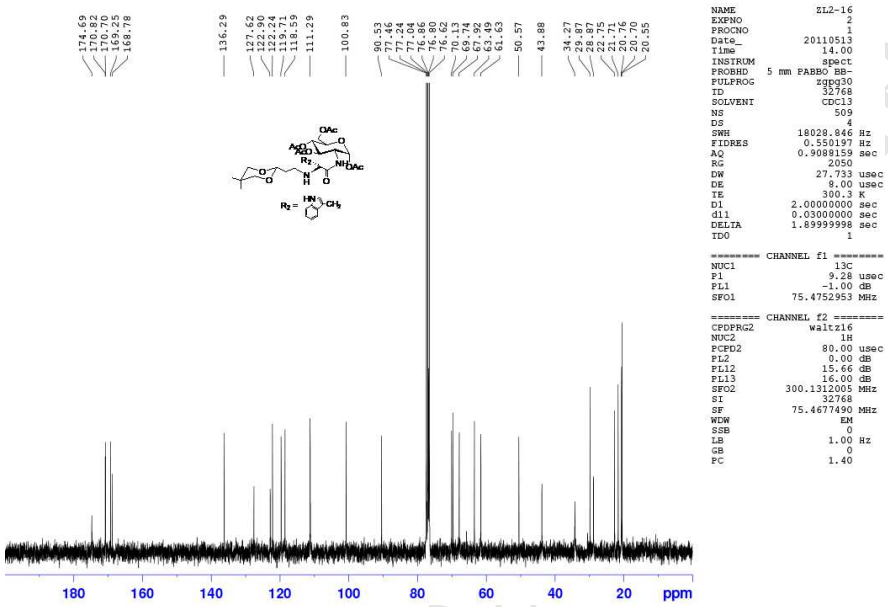


Figure S47 ^{1}H NMR spectrum of compound **15e** in $CDCl_3$ recorded at 25 □



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Time	14.00
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TD	32768
SOLVENT	CDCl3
NS	509
DS	4
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	2050
DW	27.733 usec
DE	8.00 usec
TE	300.3 K
D1	2.00000000 sec
d11	0.03000000 sec
DELTA	1.89999998 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.28 usec
PL1	-1.00 dB
SFO1	75.4752953 MHz
======== CHANNEL f2 ========	
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NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	15.66 dB
PL13	16.00 dB
SFO2	300.1312005 MHz
SI	32768
SF	75.4677490 MHz
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SSB	0
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GB	0
PC	1.40

Figure S48 ^{13}C NMR spectrum of compound **15e** in $CDCl_3$ recorded at 25 □

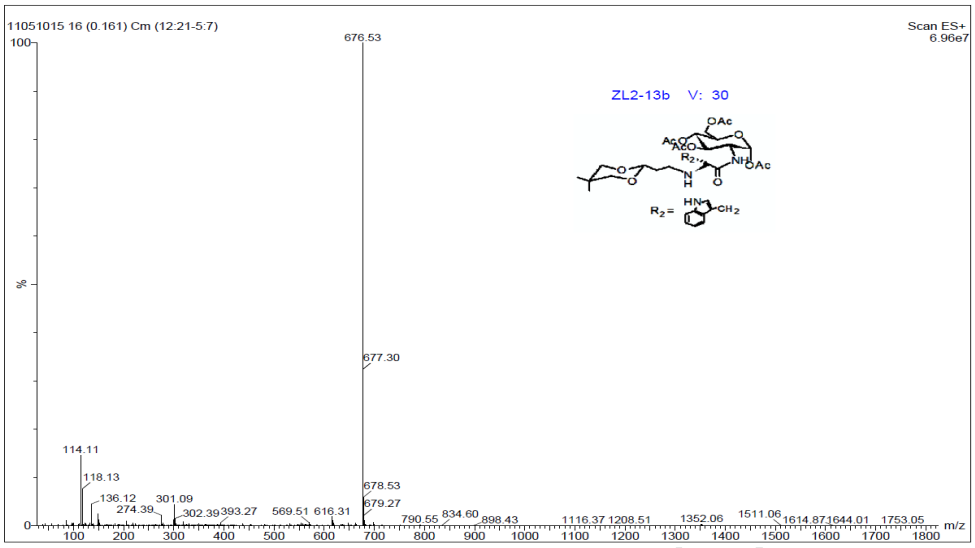
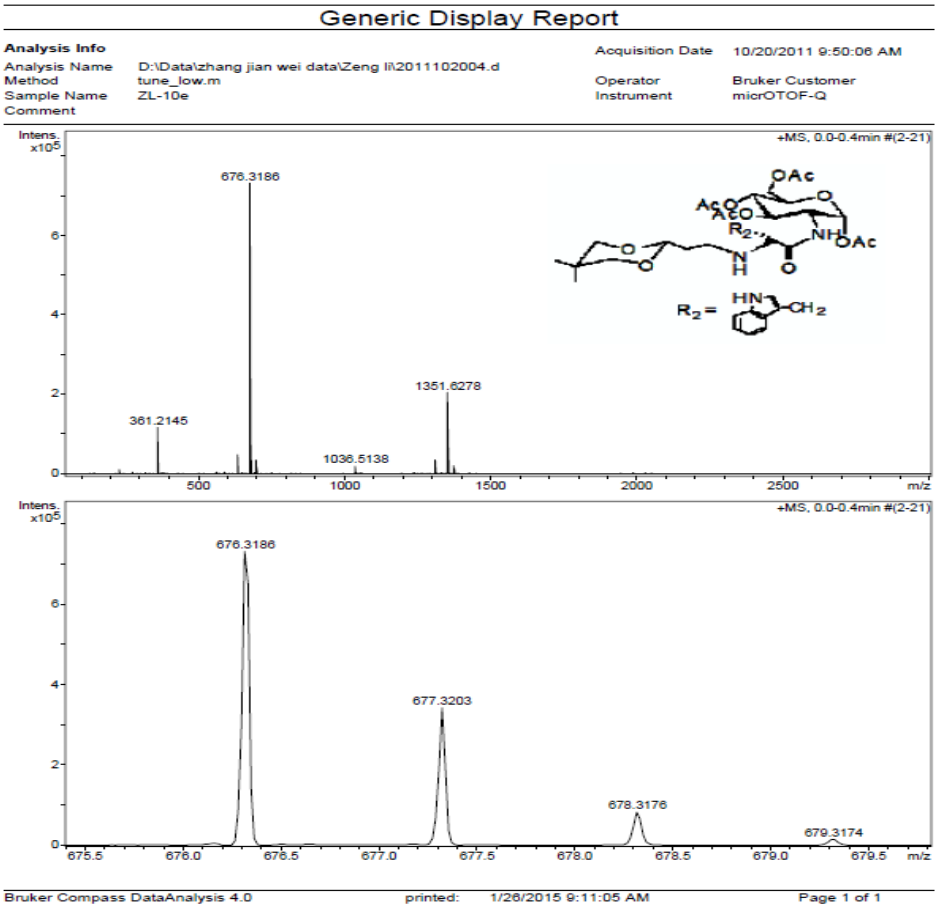


Figure S49 ESIMS spectrum of compound **15e**


Generic Display Report
Analysis Info
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Method tune_low.m
Sample Name ZL-10e
Comment
Acquisition Date 10/20/2011 9:50:06 AM
Operator Bruker Customer
Instrument micrOTOF-Q
Intens. x10^5
+MS, 0.0-0.4min #(2-21)
676.3186
1351.6278
361.2145
1036.5138
m/z
677.3203
678.3176
679.3174
Bruker Compass DataAnalysis 4.0
printed: 1/26/2015 9:11:05 AM
Page 1 of 1

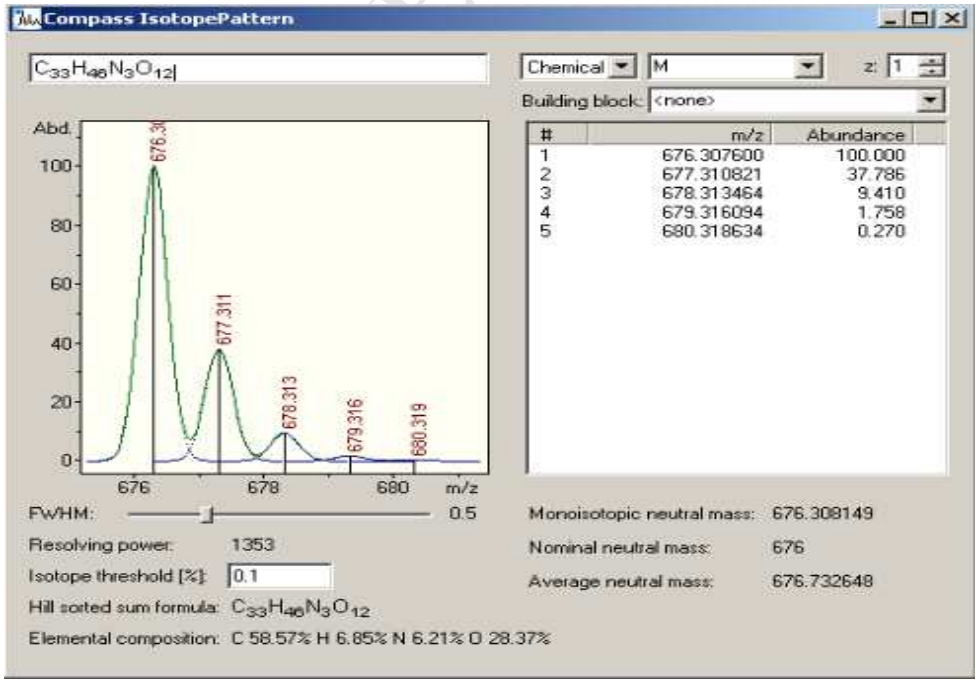
Compass IsotopePattern
C33H46N3O12
Chemical
M
z: 1
Building block: <none>
m/z Abundance
1 676.307600 100.000
2 677.310821 37.786
3 678.313464 9.410
4 679.316094 1.758
5 680.318634 0.270
Abd.
676.307
677.311
678.313
679.316
680.319
m/z
FWHM: 0.5
Resolving power: 1353
Isotope threshold [%]: 0.1
Hill sorted sum formula: C33H46N3O12
Elemental composition: C 58.57% H 6.85% N 6.21% O 28.37%
Monoisotopic neutral mass: 676.308149
Nominal neutral mass: 676
Average neutral mass: 676.732648

Figure S50 HRMS spectrum of compound **15e**

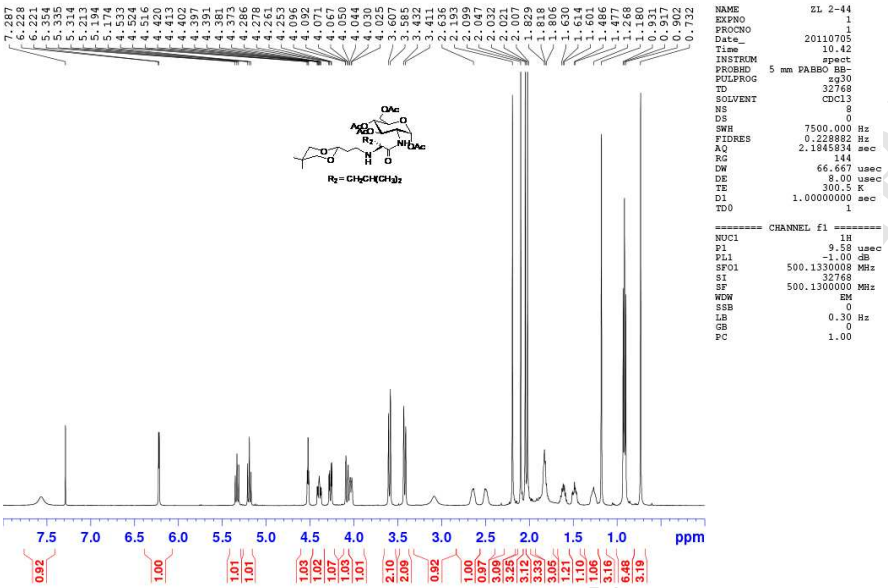

Figure S51 ^{1}H NMR spectrum of compound **15f** in $CDCl_3$ recorded at 25 □

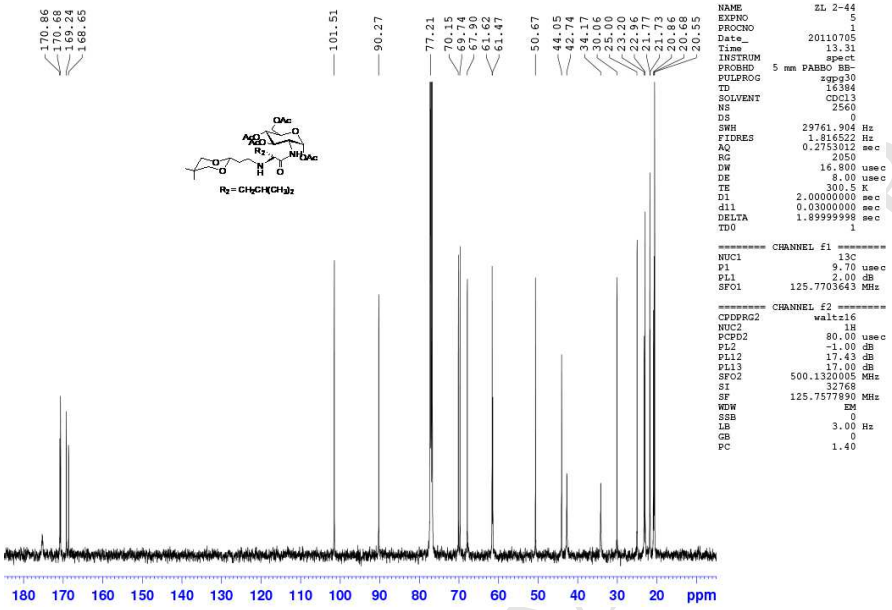

Figure S52 ^{13}C NMR spectrum of compound **15f** in $CDCl_3$ recorded at 25 □

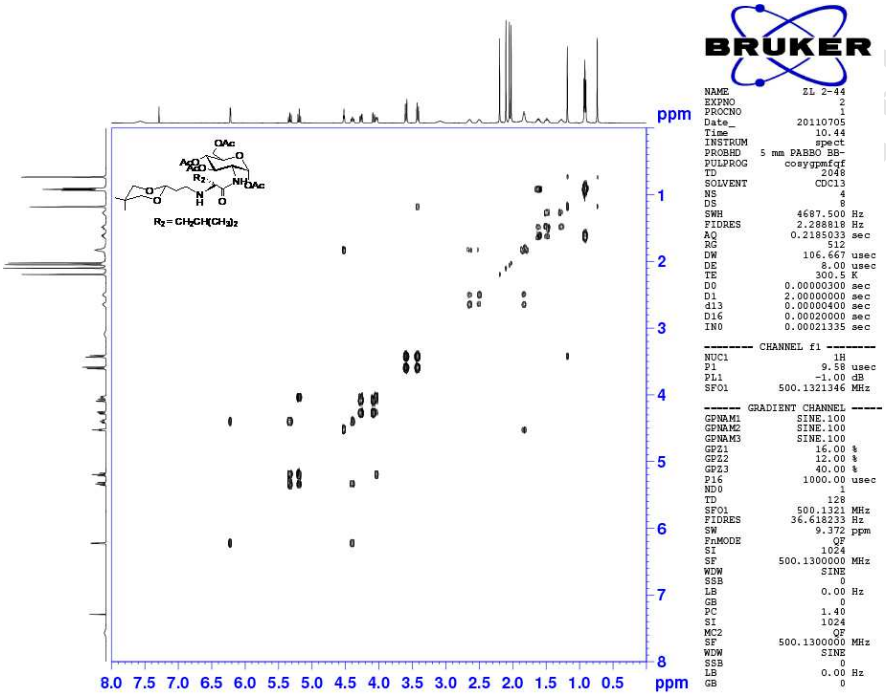

Figure S53 H-H Cosy spectrum of compound **15f** in $CDCl_3$ recorded at 25 □

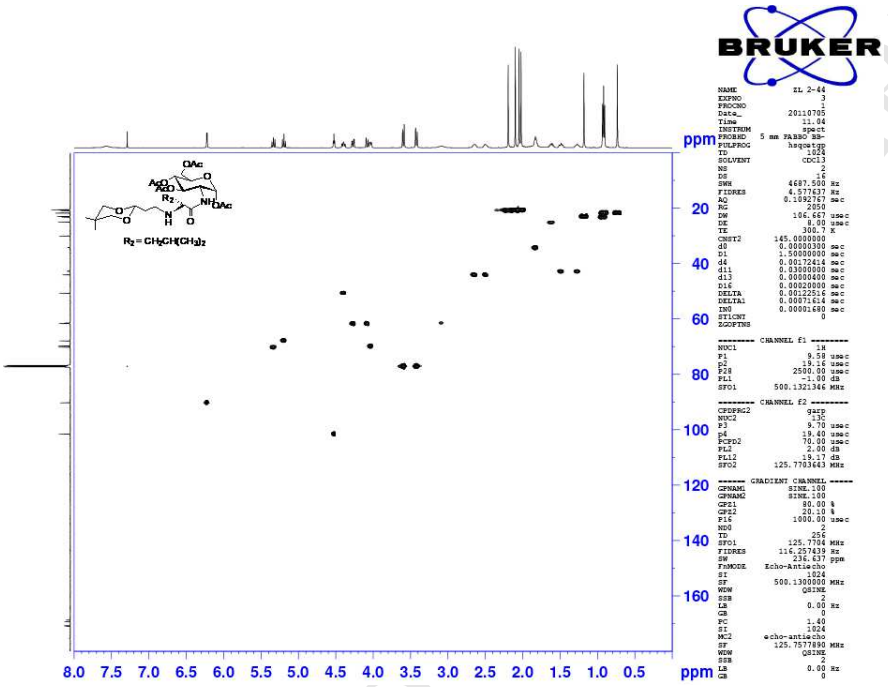

Figure S54 HMQC spectrum of compound **15f** in $CDCl_3$ recorded at 25 □

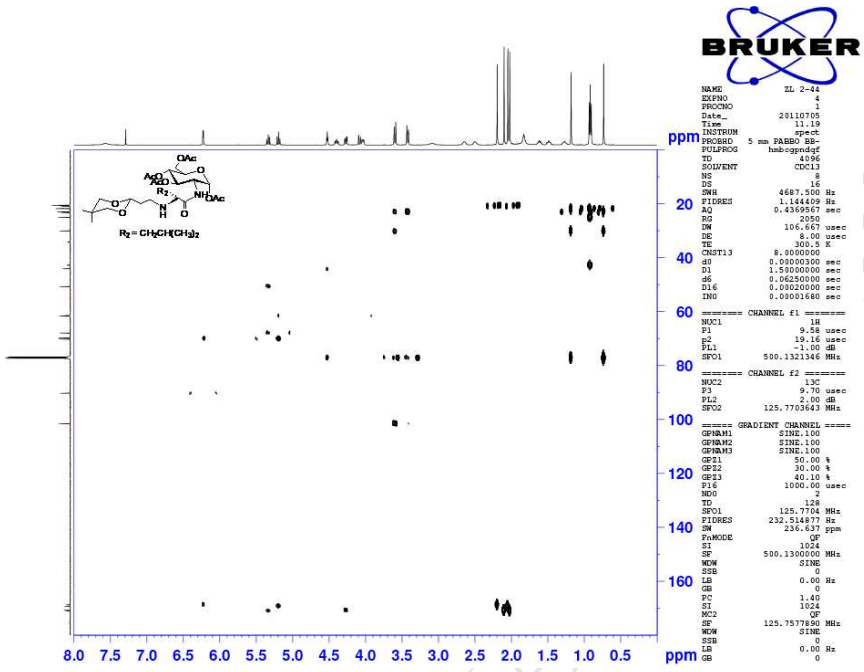

Figure S55 HMBC spectrum of compound **15f** in $CDCl_3$ recorded at 25 □

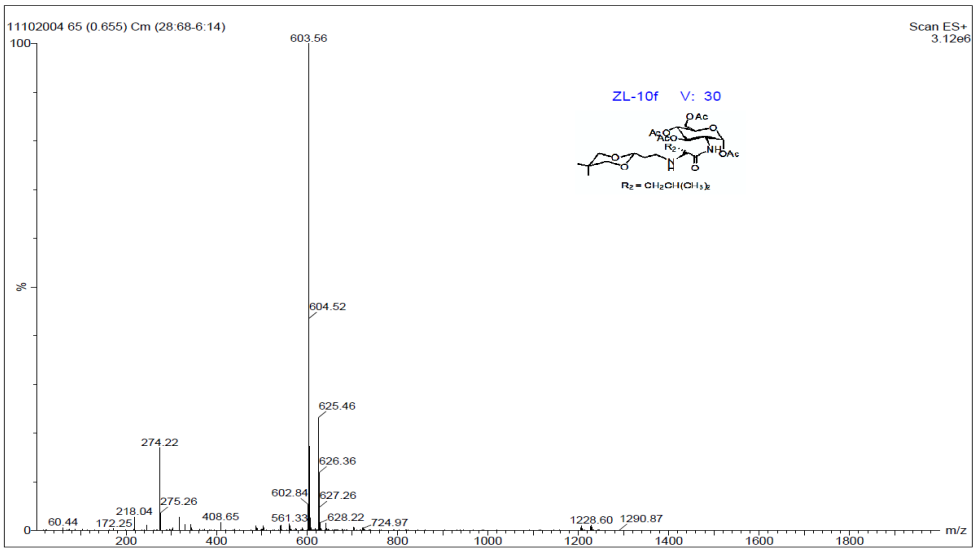

Figure S56 ESIMS spectrum of compound **15f**

Generic Display Report

Analysis Info

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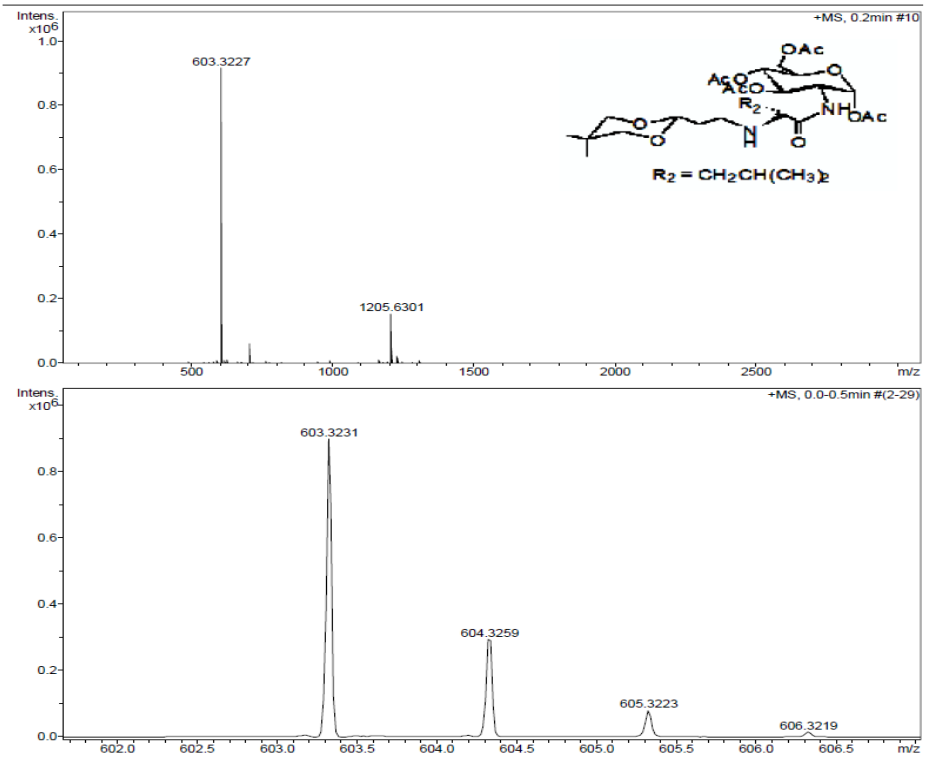
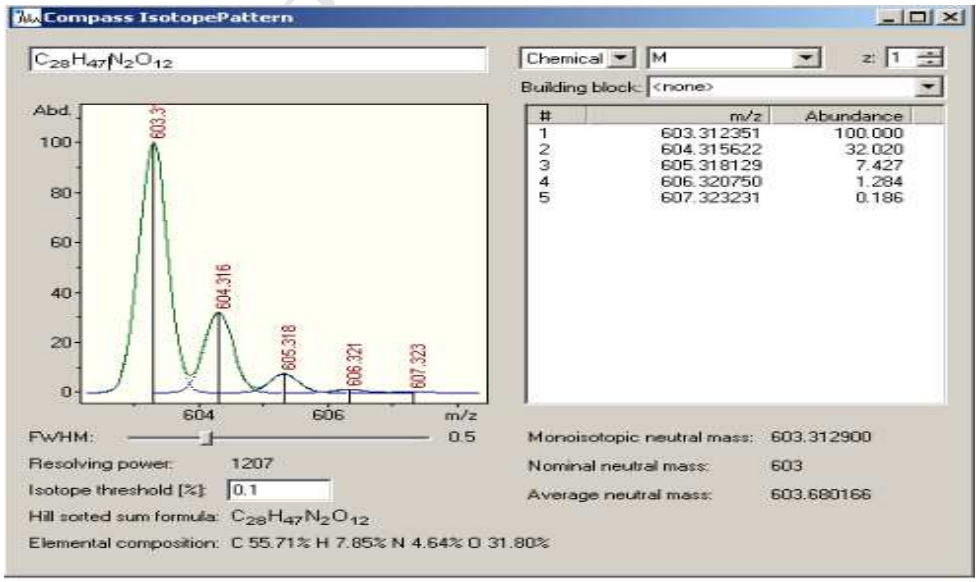
Method	tune_low.m	Operator	Bruker Customer
Sample Name	ZL-10f	Instrument	micrOTOF-Q
Comment			



Bruker Compass DataAnalysis 4.0 printed: 1/26/2015 9:40:59 AM Page 1 of 1



#	m/z	Abundance
1	603.312351	100.000
2	604.315622	32.020
3	605.318129	7.427
4	606.320750	1.284
5	607.323231	0.186

Figure S57 HRMS spectrum of compound **15f**

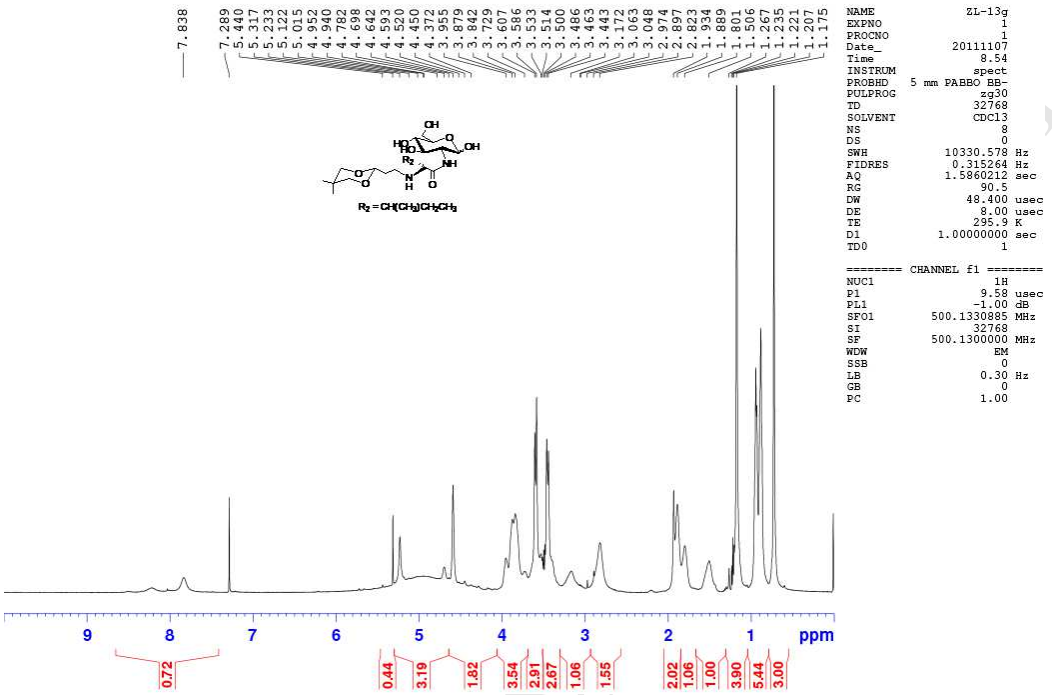


Figure S58 ^{1}H NMR spectrum of compound **16a** in $CDCl_3$ recorded at 25 □

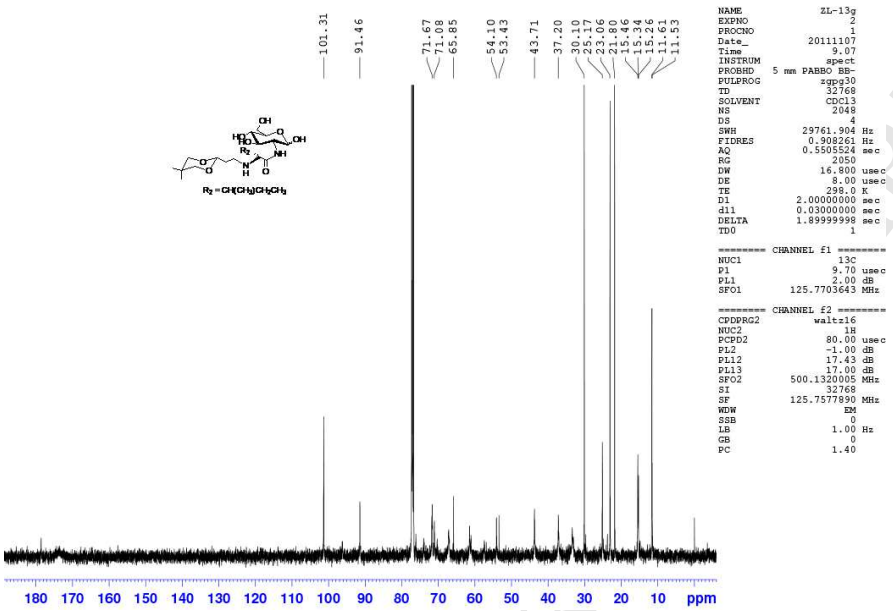


Figure S59 ^{13}C NMR spectrum of compound **16a** in $CDCl_3$ recorded at 25 □

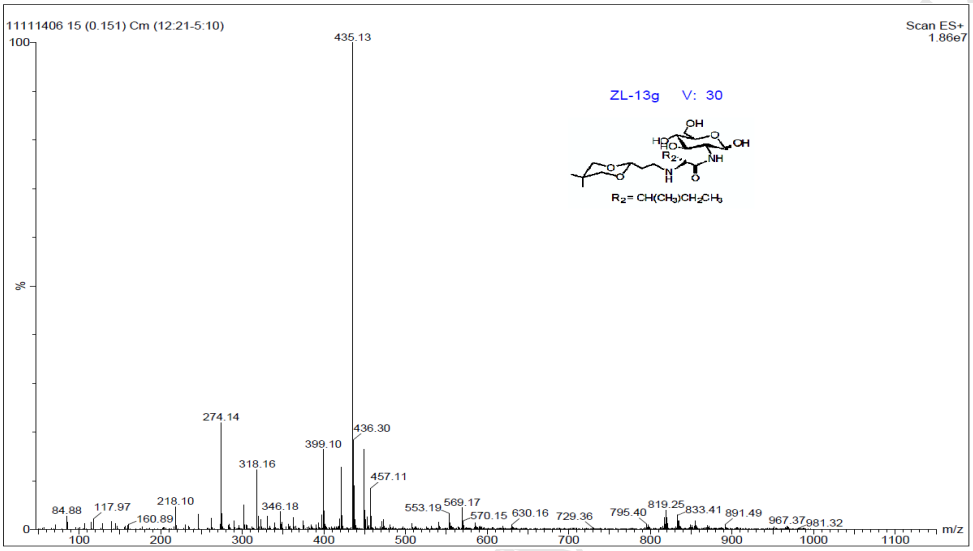
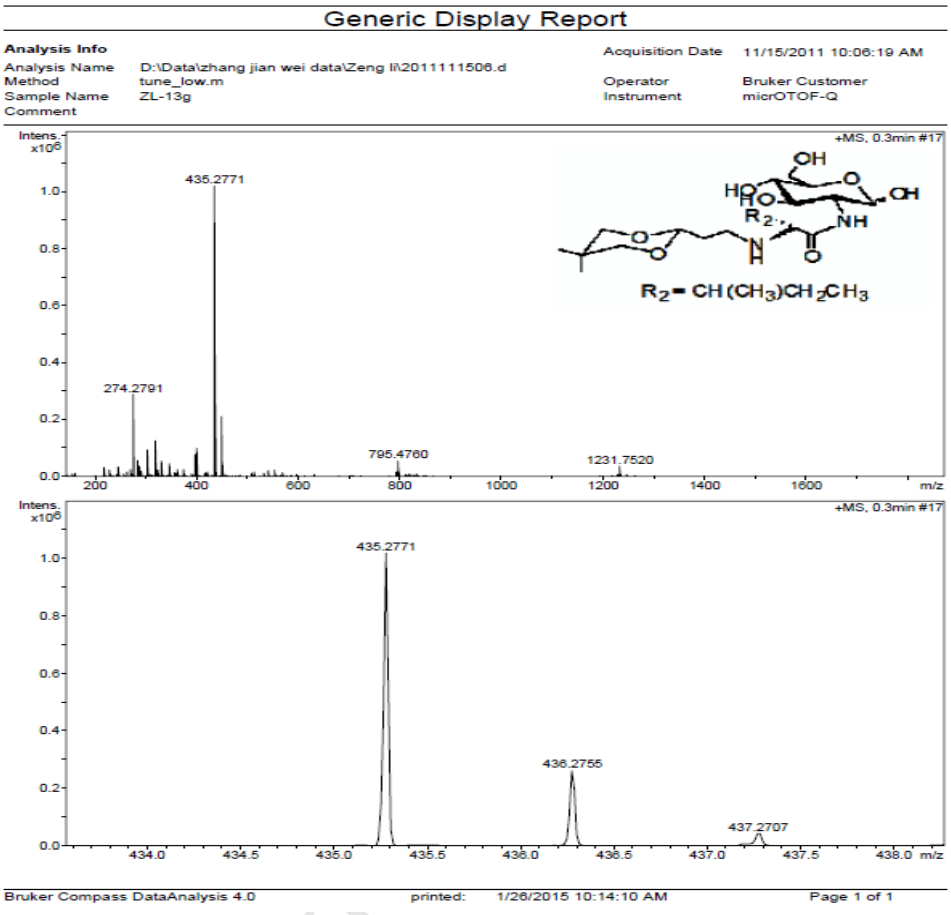


Figure S60 ESIMS spectrum of compound **16a**


Generic Display Report
Analysis Info
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Method tune_low.m
Sample Name ZL-13g
Comment
Acquisition Date 11/15/2011 10:06:19 AM
Operator Bruker Customer
Instrument micrOTOF-Q
Intens. x10^6
+MS, 0.3min #17
435.2771
274.2791
795.4760
1231.7520
m/z
R2 = CH(CH3)CH2CH3
Intens. x10^6
+MS, 0.3min #17
435.2771
436.2755
437.2707
m/z
Bruker Compass DataAnalysis 4.0
printed: 1/26/2015 10:14:10 AM
Page 1 of 1

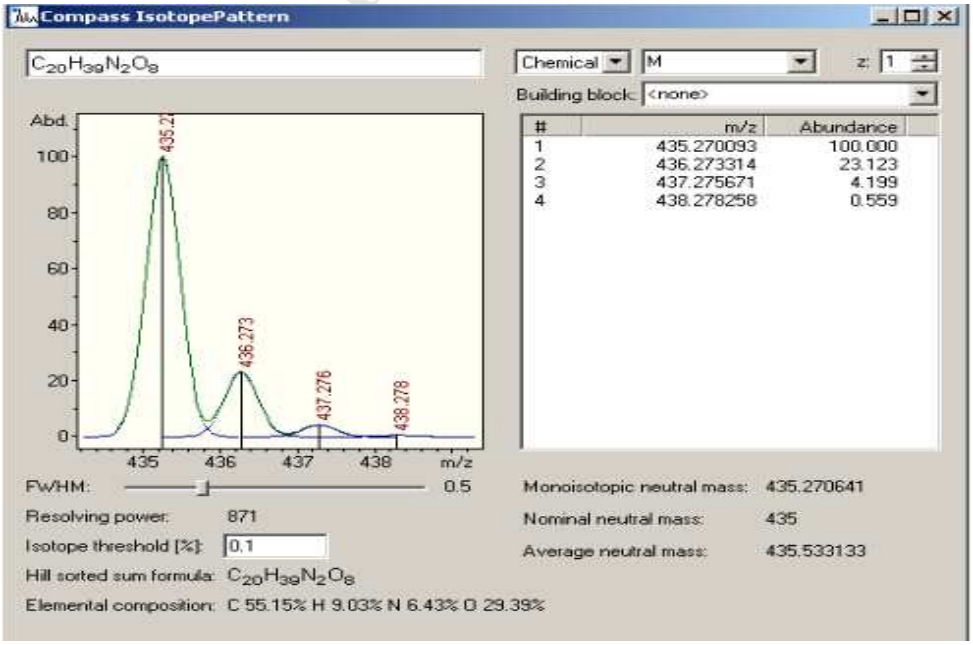

Compass IsotopePattern
C20H39N2O8
Chemical
M
z: 1
Building block: <none>
m/z Abundance
1 435.270093 100.000
2 436.273314 23.123
3 437.275671 4.199
4 438.278258 0.559
Abd.
435.27
436.273
437.276
438.278
m/z
FWHM: 0.5
Resolving power: 871
Isotope threshold [%]: 0.1
Hill sorted sum formula: C20H39N2O8
Elemental composition: C 55.15% H 9.03% N 6.43% O 29.39%
Monoisotopic neutral mass: 435.270641
Nominal neutral mass: 435
Average neutral mass: 435.533133

Figure S61 HRMS spectrum of compound **16a**

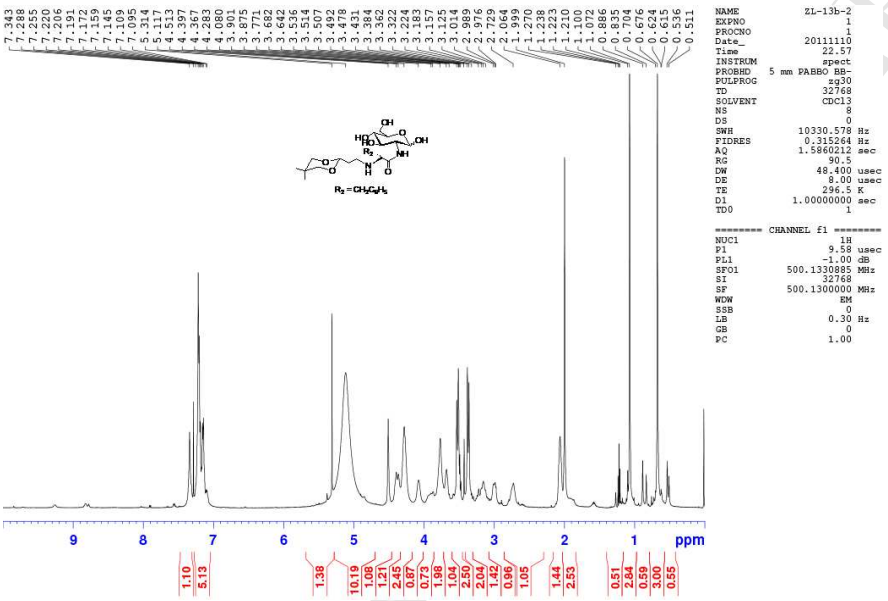


Figure S62 ^{1}H NMR spectrum of compound **16b** in $CDCl_3$ recorded at 25 □

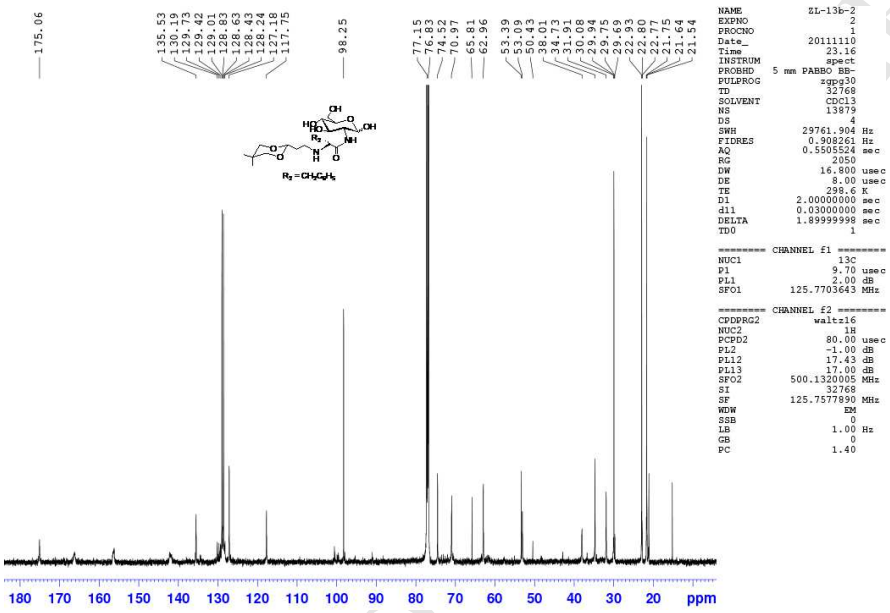


Figure S63 ^{13}C NMR spectrum of compound **16b** in $CDCl_3$ recorded at 25 □

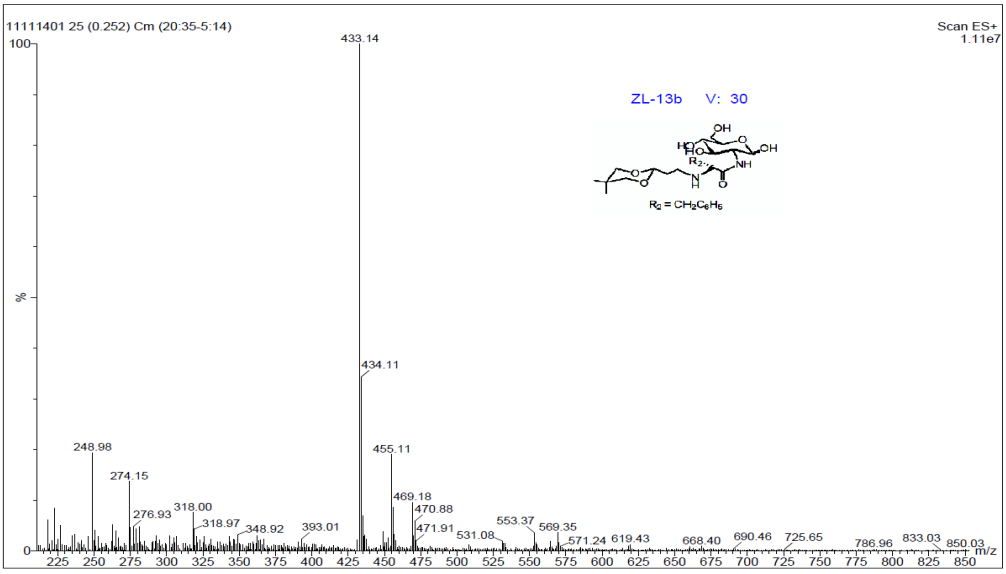
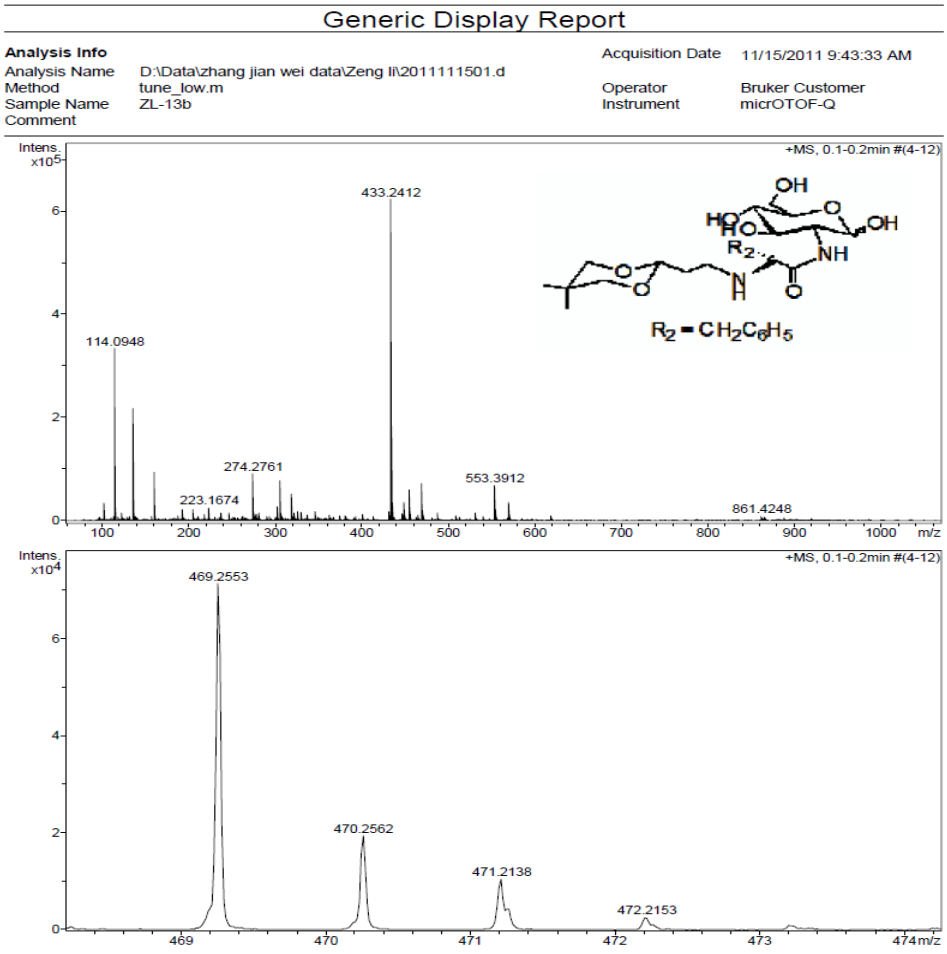


Figure S64 ESIMS spectrum of compound **16b**


Generic Display Report
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Method tune_low.m
Sample Name ZL-13b
Comment
Acquisition Date 11/15/2011 9:43:33 AM
Operator Bruker Customer
Instrument micrOTOF-Q
Intens.
x10^5
+MS, 0.1-0.2min #(4-12)
433.2412
114.0948
274.2761
223.1674
553.3912
861.4248
m/z
R2 = CH2C6H5
Intens.
x10^4
+MS, 0.1-0.2min #(4-12)
469.2553
470.2562
471.2138
472.2153
m/z
Bruker Compass DataAnalysis 4.0
printed: 1/28/2015 10:45:06 AM
Page 1 of 1

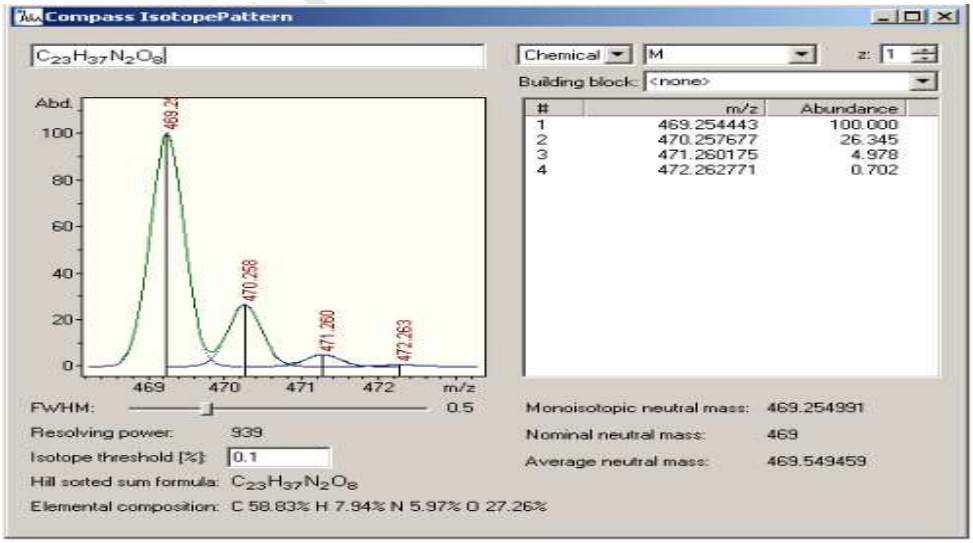

Compass IsotopePattern
C23H37N2O8
Chemical
M
z: 1
Building block: <none>
Abd.
469.254
470.258
471.260
472.263
m/z
m/z Abundance
1 469.254443 100.000
2 470.257677 26.345
3 471.260175 4.978
4 472.262771 0.702
FWHM: 0.5
Resolving power: 939
Isotope threshold [%]: 0.1
Hill sorted sum formula: C23H37N2O8
Elemental composition: C 58.83% H 7.94% N 5.97% O 27.26%
Monoisotopic neutral mass: 469.254991
Nominal neutral mass: 469
Average neutral mass: 469.549459

Figure S65 HRMS spectrum of compound **16b**

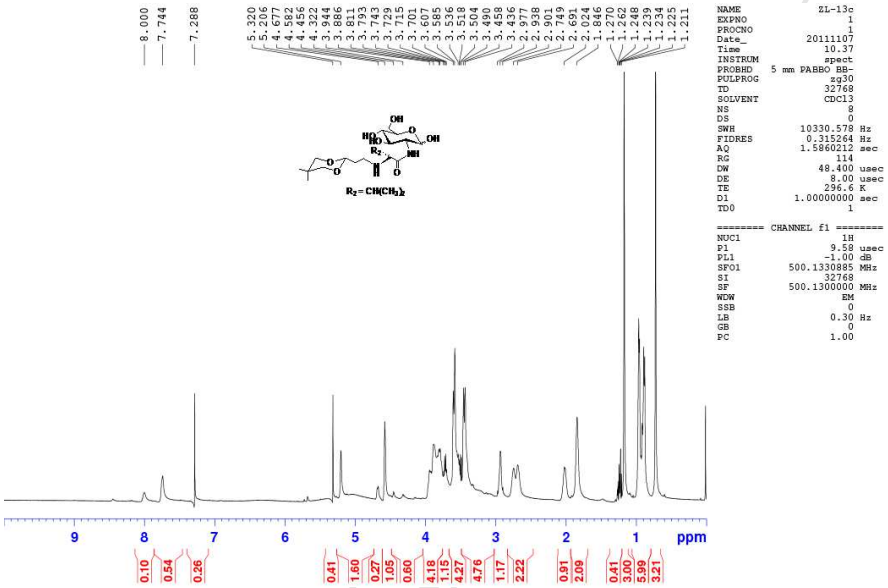


Figure S66 ^{1}H NMR spectrum of compound **16c** in $CDCl_3$ recorded at 25 □

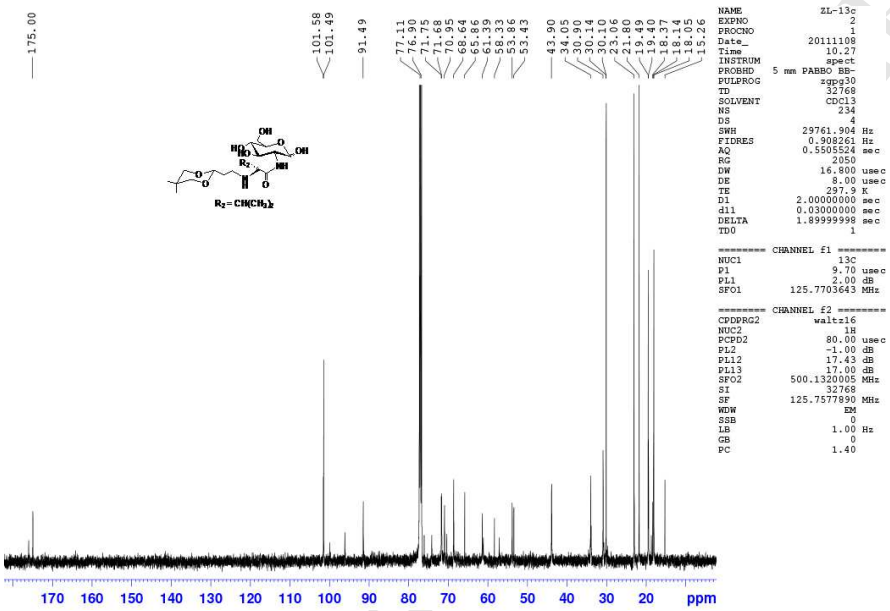


Figure S67 ^{13}C NMR spectrum of compound **16c** in $CDCl_3$ recorded at 25 □

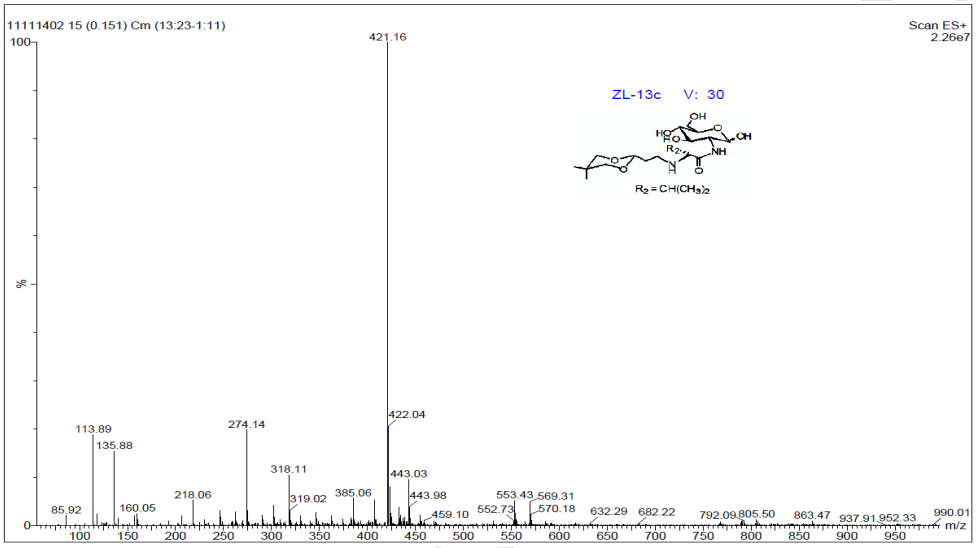
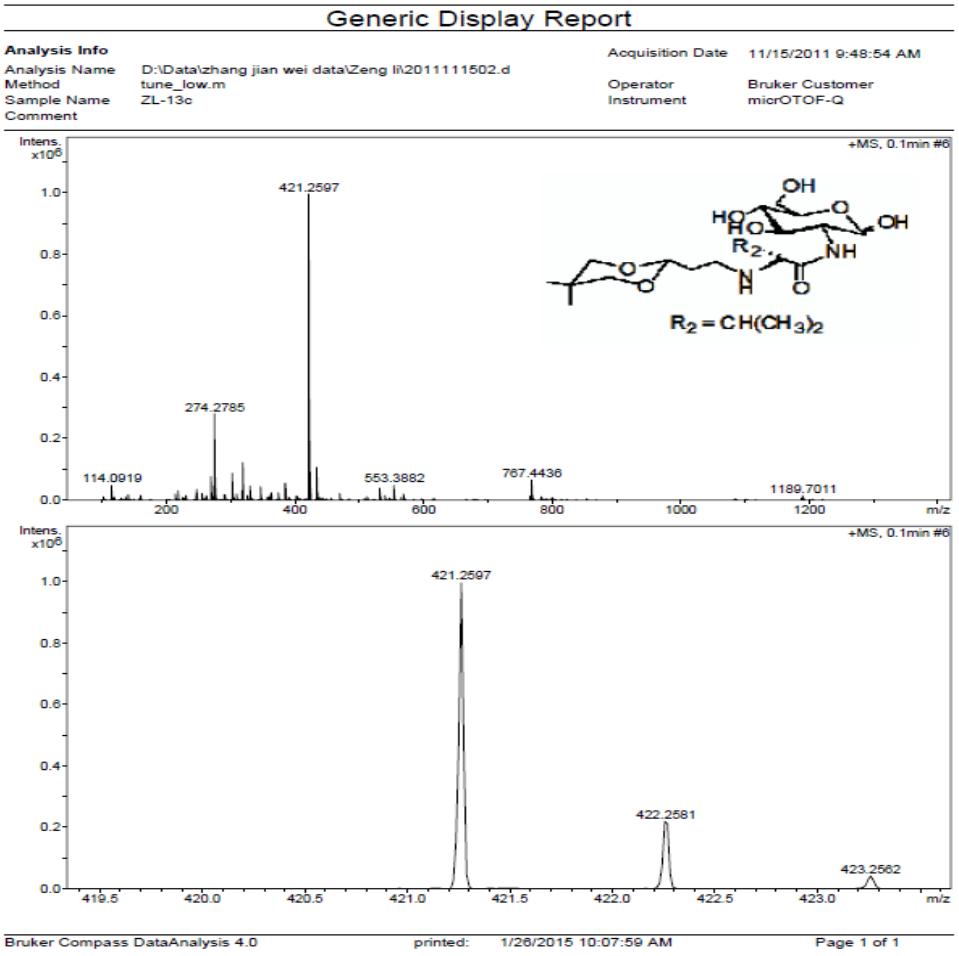


Figure S68 ESIMS spectrum of compound **16c**


Generic Display Report
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Sample Name ZL-13c
Comment
Acquisition Date 11/15/2011 9:48:54 AM
Operator Bruker Customer
Instrument micrOTOF-Q
Intens. x10^6
+MS, 0.1min #6
421.2597
274.2785
114.0919
553.3882
767.4436
1189.7011
m/z
R2 = CH(CH3)2
Intens. x10^6
+MS, 0.1min #6
421.2597
422.2581
423.2562
m/z
Bruker Compass DataAnalysis 4.0
printed: 1/26/2015 10:07:59 AM
Page 1 of 1

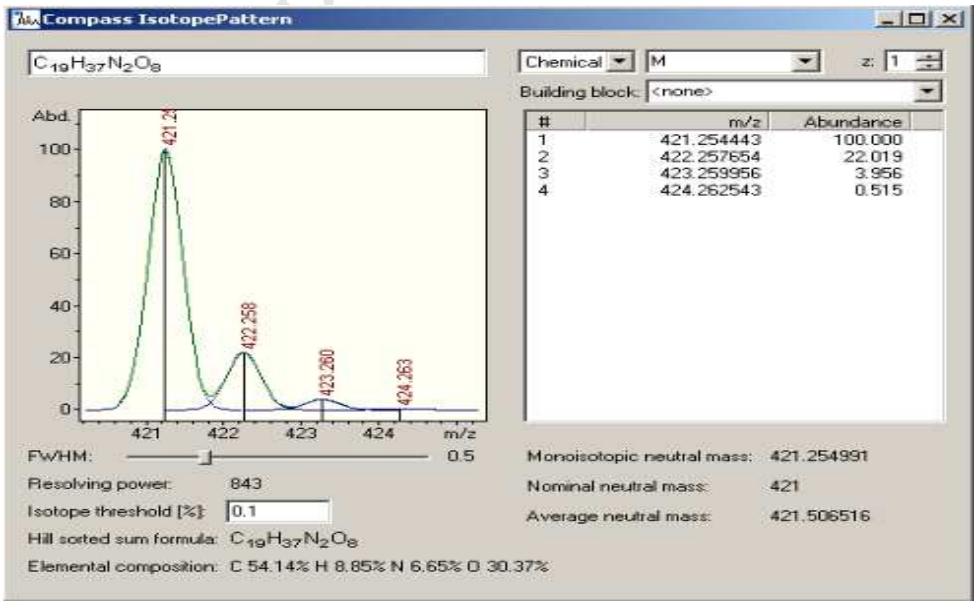
Compass IsotopePattern
C19H37N2O8
Chemical
M
z: 1
Building block: <none>
Abd.
421.254
422.258
423.260
424.263
m/z
m/z Abundance
1 421.254443 100.000
2 422.257654 22.019
3 423.259956 3.956
4 424.262543 0.515
FWHM: 0.5
Resolving power: 843
Isotope threshold [%]: 0.1
Hill sorted sum formula: C19H37N2O8
Elemental composition: C 54.14% H 8.85% N 6.65% O 30.37%
Monoisotopic neutral mass: 421.254991
Nominal neutral mass: 421
Average neutral mass: 421.506516

Figure S69 HRMS spectrum of compound **16c**

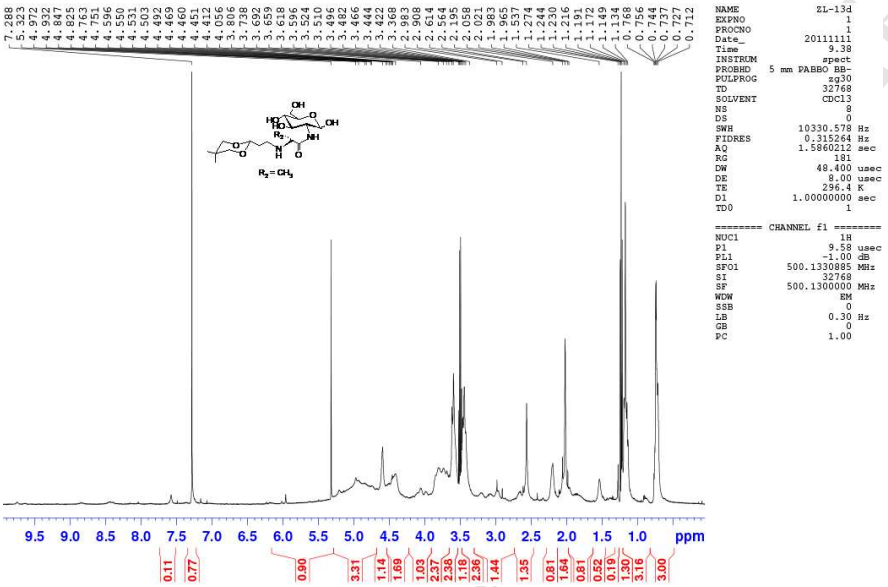

Figure S70 ^{1}H NMR spectrum of compound **16d** in $CDCl_3$ recorded at 25 □

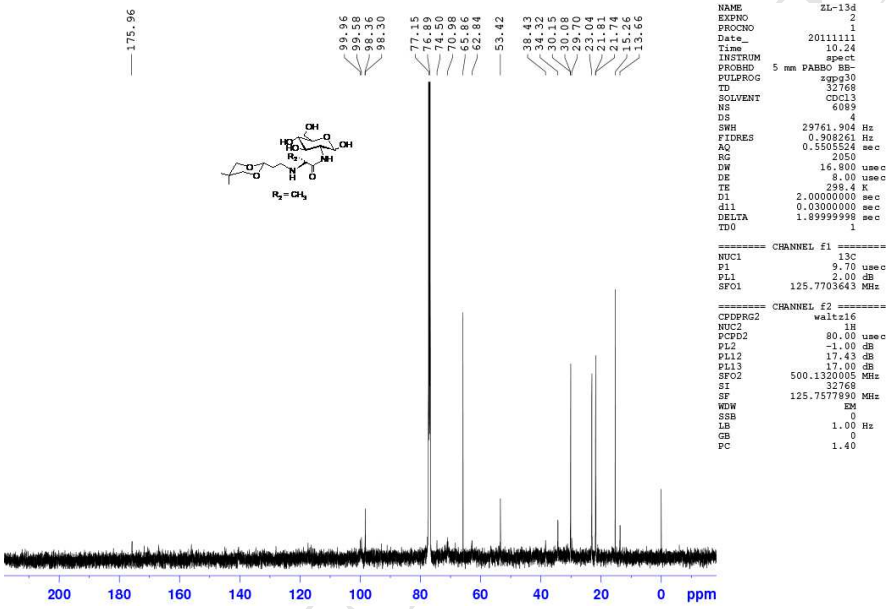

Figure S71 ^{13}C NMR spectrum of compound **16d** in $CDCl_3$ recorded at 25 □

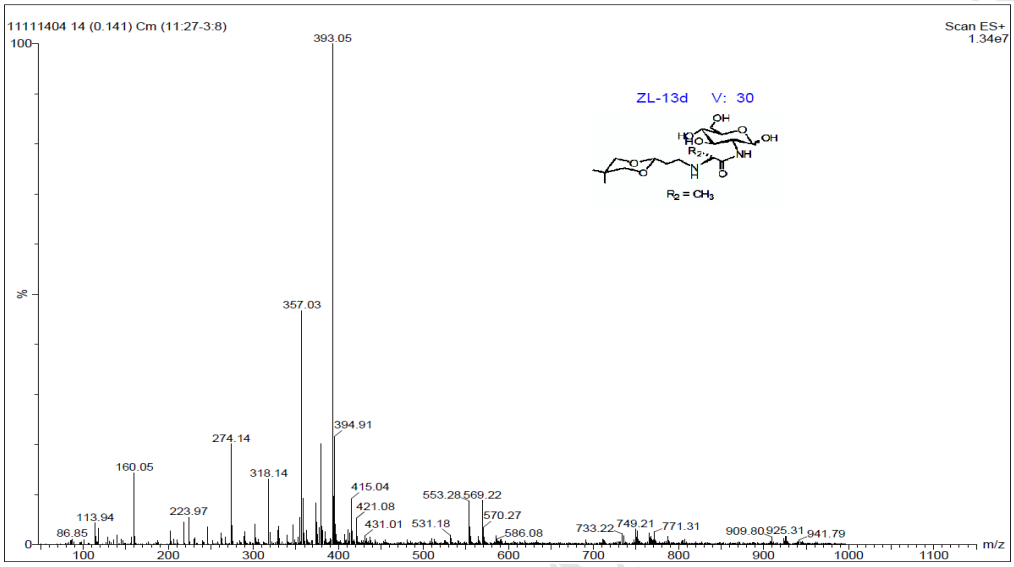

Figure S72 ESIMS spectrum of compound **16d**

Generic Display Report

Analysis Info

Analysis Name	D:\Data\zhang jian wei data\Zeng li\2011111503.d	Acquisition Date	11/15/2011 9:52:30 AM
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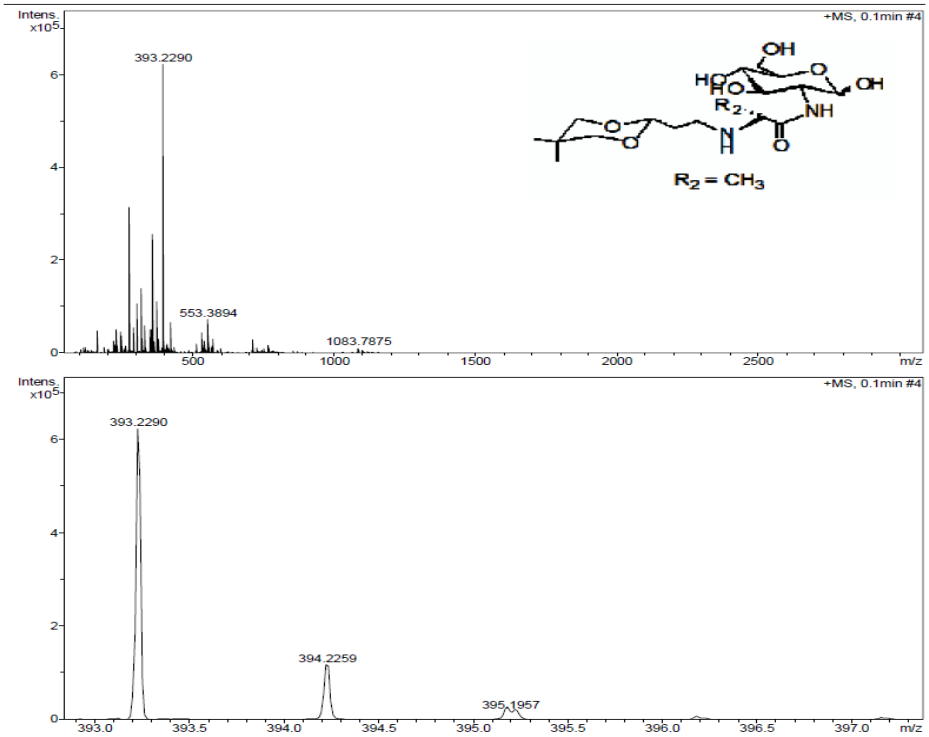
Sample Name	ZL-13d	Instrument	micrOTOF-Q
Comment			



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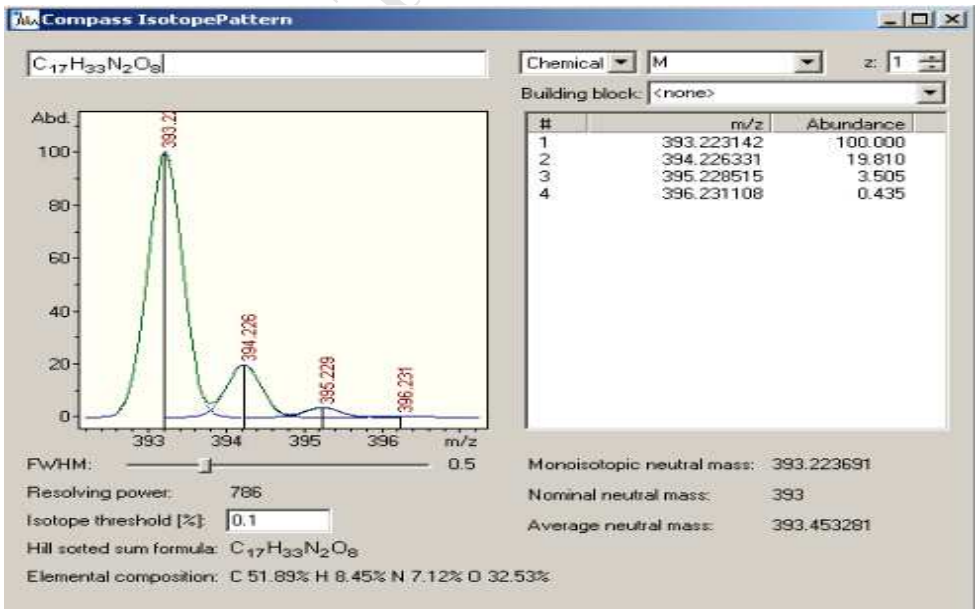

#	m/z	Abundance
1	393.223142	100.000
2	394.226331	19.810
3	395.228515	3.505
4	396.231108	0.435

Figure S73 HRMS spectrum of compound **16d**

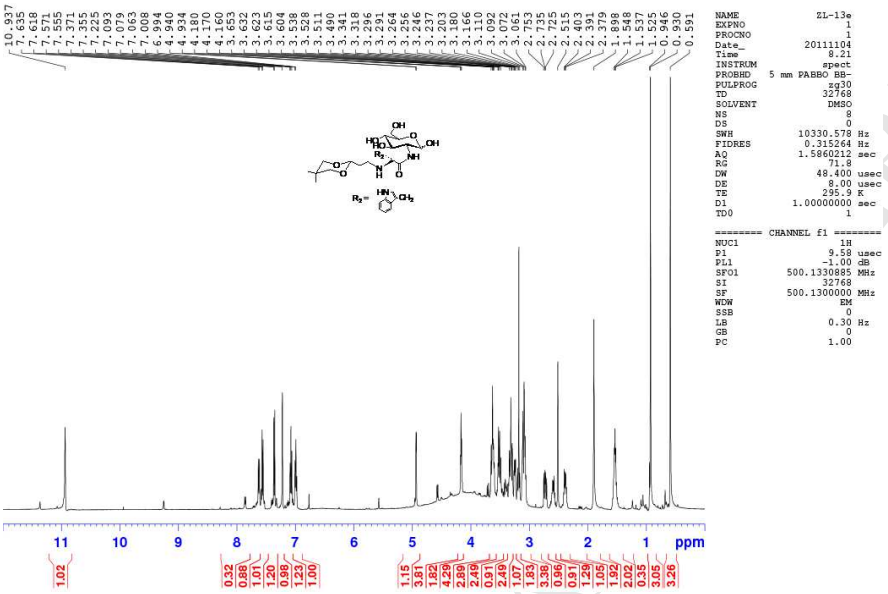

Figure S74 ^{1}H NMR spectrum of compound **16e** in DMSO-d_6 recorded at 25 □

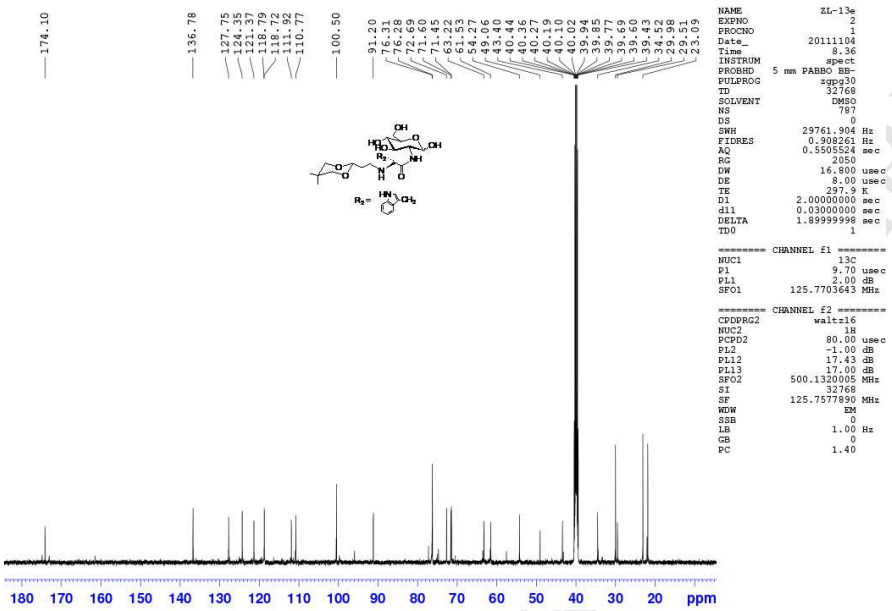

Figure S75 ^{13}C NMR spectrum of compound **16e** in DMSO-d_6 recorded at 25 □

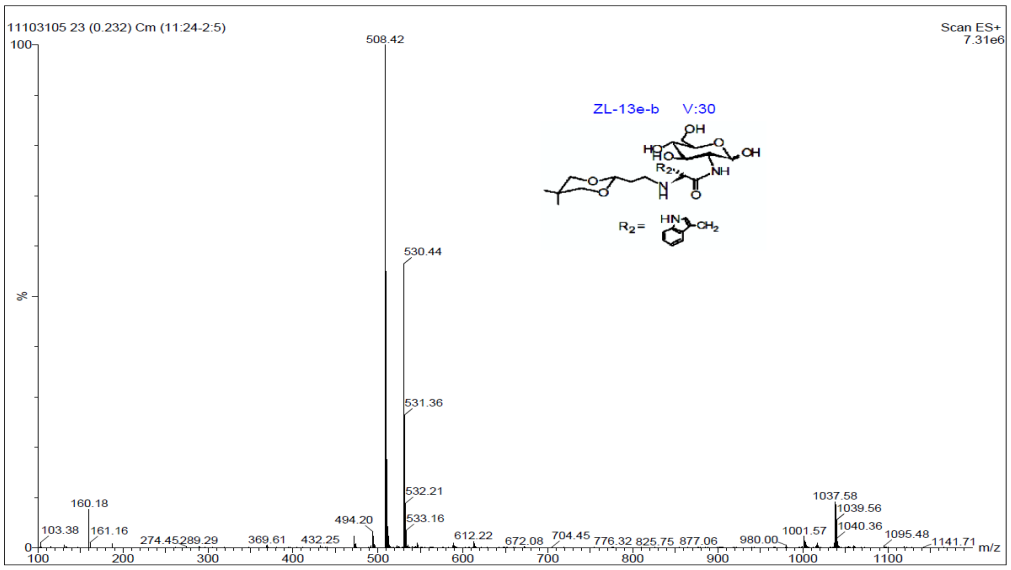

Figure S76 ESIMS spectrum of compound **16e**

Generic Display Report

Analysis Info

Analysis Name	D:\Data\zhang jian wei data\Zeng li\20111111504.d	Acquisition Date	11/15/2011 9:55:51 AM
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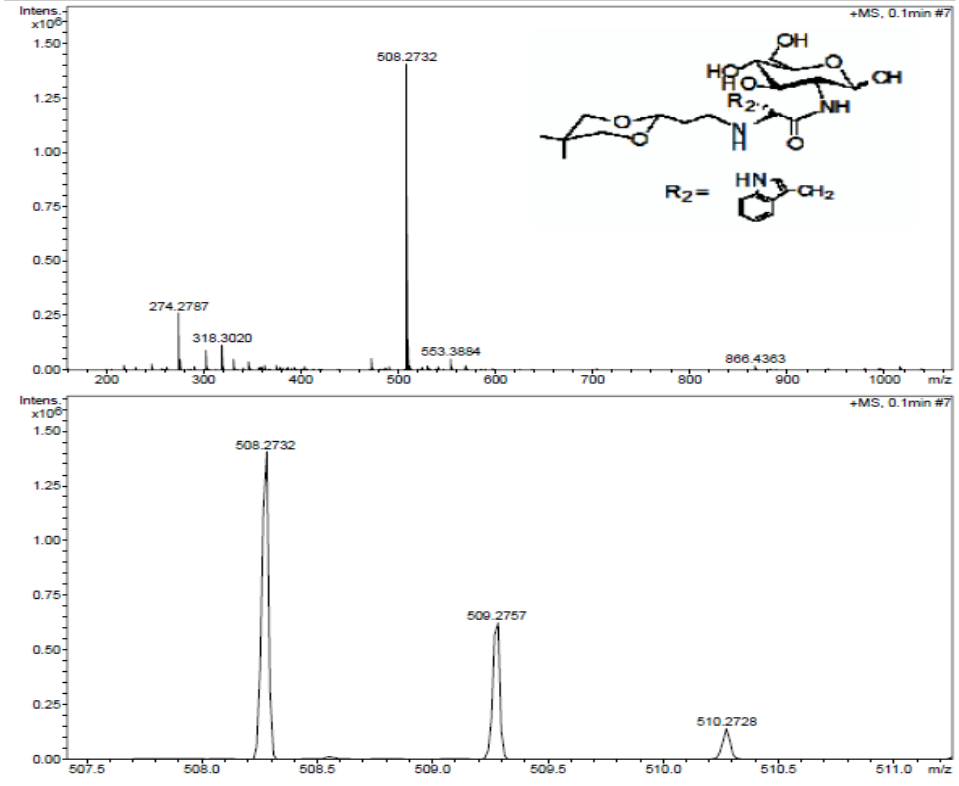
Sample Name	ZL-13e	Instrument	micrOTOF-Q
Comment			



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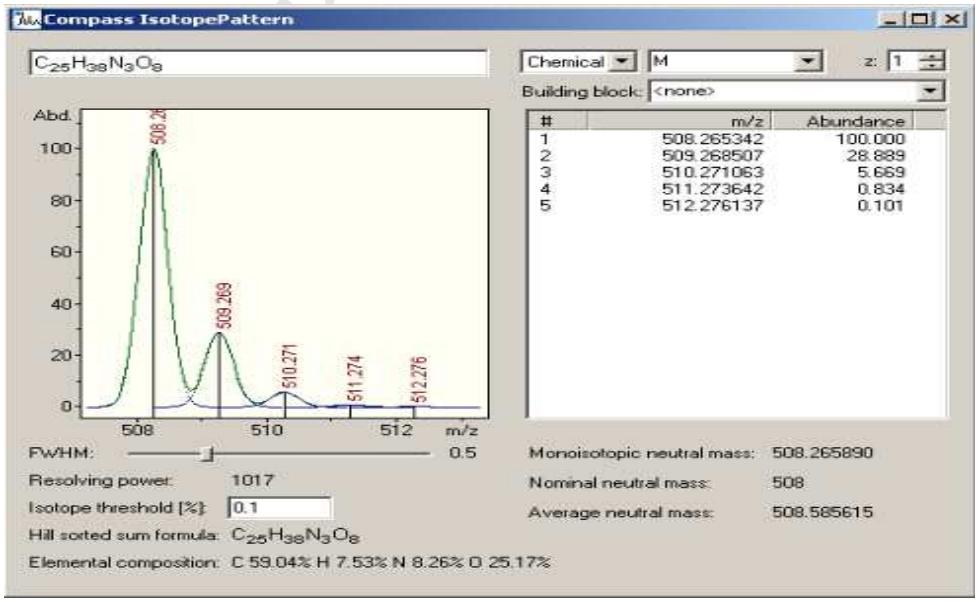


#	m/z	Abundance
1	508.265342	100.000
2	509.268507	28.889
3	510.271063	5.669
4	511.273642	0.834
5	512.276137	0.101

Figure S77 HRMS spectrum of compound **16e**

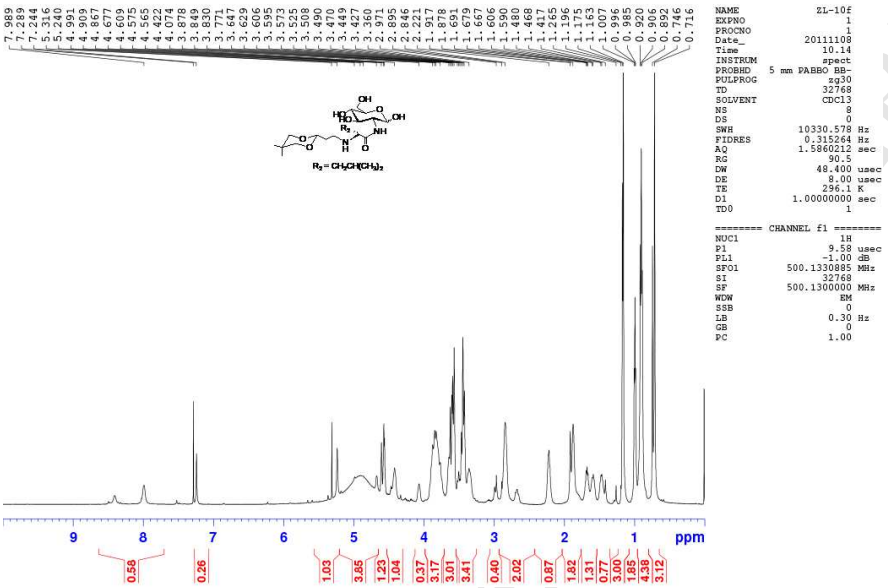


Figure S78 ^{1}H NMR spectrum of compound **16f** in $CDCl_3$ recorded at 25 □

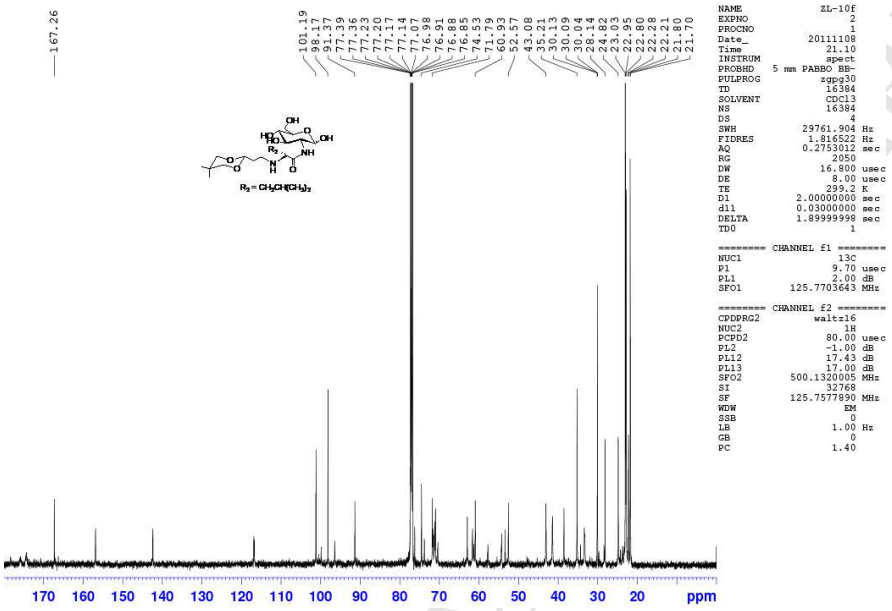


Figure S79 ^{13}C NMR spectrum of compound **16f** in $CDCl_3$ recorded at 25 □

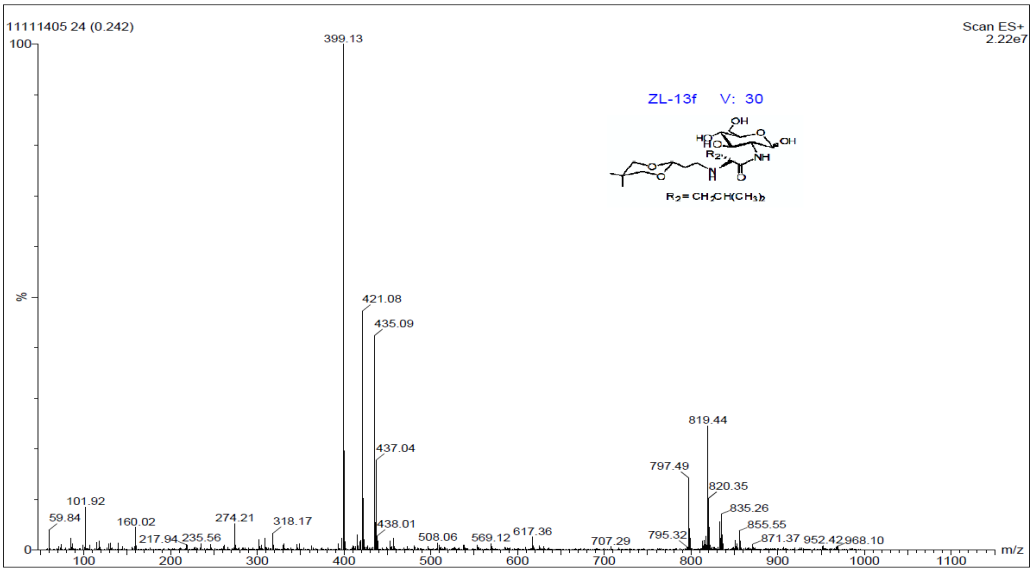
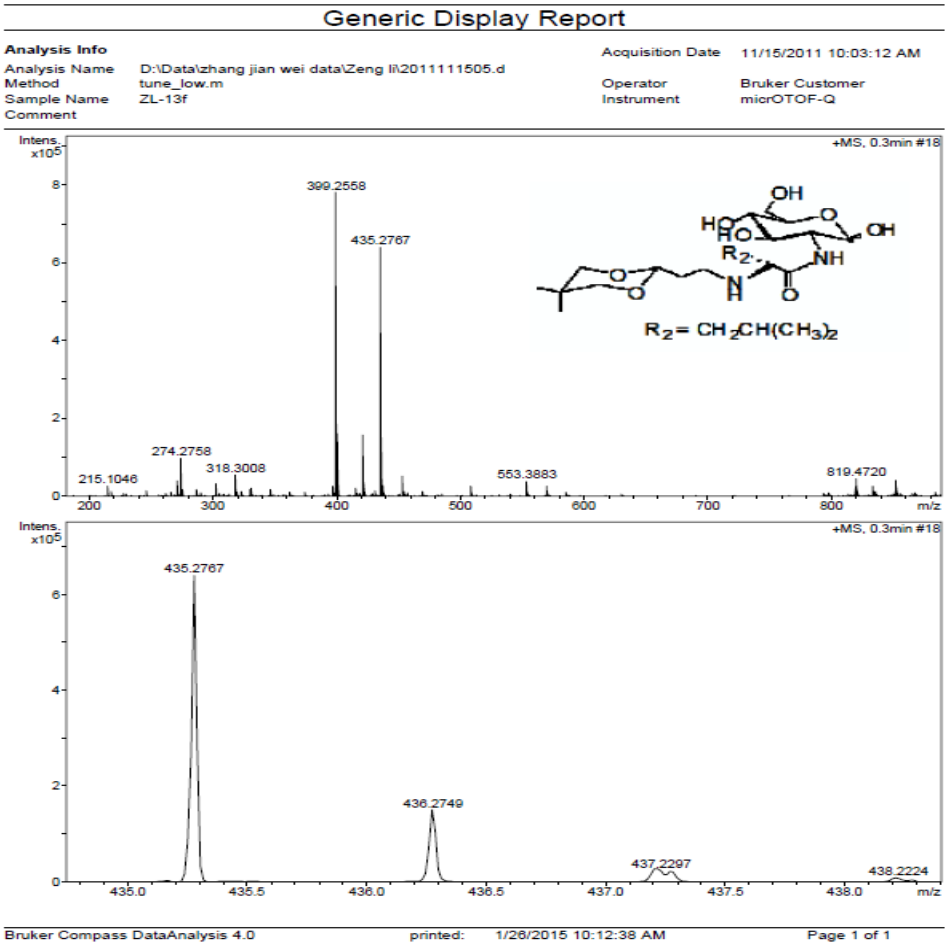


Figure S80 ESIMS spectrum of compound **16f**


Generic Display Report
Analysis Info
Analysis Name D:\Data\zhang jian wei data\Zeng li\2011111505.d
Method tune_low.m
Sample Name ZL-13f
Comment
Acquisition Date 11/15/2011 10:03:12 AM
Operator Bruker Customer
Instrument micrOTOF-Q
Intens. x10^5
+MS, 0.3min #18
399.2558
435.2767
274.2758
318.3008
215.1046
553.3883
819.4720
m/z
R2= CH2CH(CH3)2
Intens. x10^5
+MS, 0.3min #18
435.2767
436.2749
437.2297
438.2224
m/z
Bruker Compass DataAnalysis 4.0
printed: 1/26/2015 10:12:38 AM
Page 1 of 1

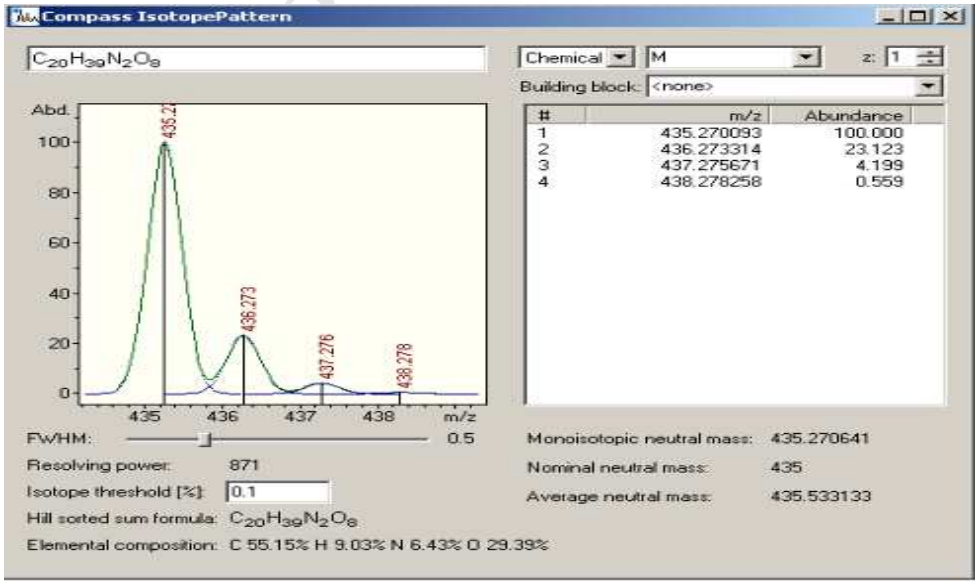

Compass IsotopePattern
C20H39N2O8
Chemical
M
z: 1
Building block: <none>
Abd.
435.27
436.273
437.276
438.278
m/z
m/z Abundance
1 435.270093 100.000
2 436.273314 23.123
3 437.275671 4.199
4 438.278258 0.559
FWHM: 0.5
Resolving power: 871
Isotope threshold [%]: 0.1
Hill sorted sum formula: C20H39N2O8
Elemental composition: C 55.15% H 9.03% N 6.43% O 29.39%
Monoisotopic neutral mass: 435.270641
Nominal neutral mass: 435
Average neutral mass: 435.533133

Figure S81 HRMS spectrum of compound **16f**

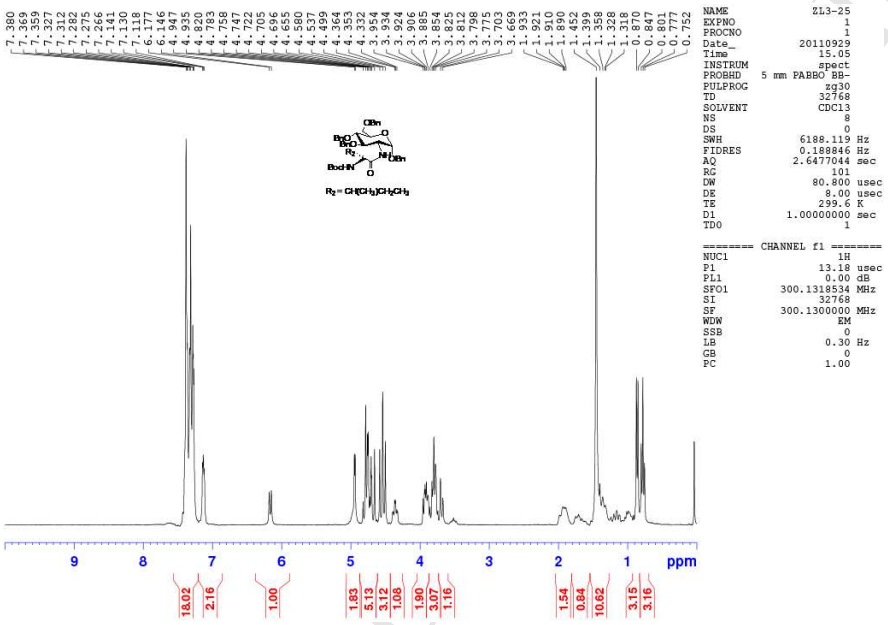
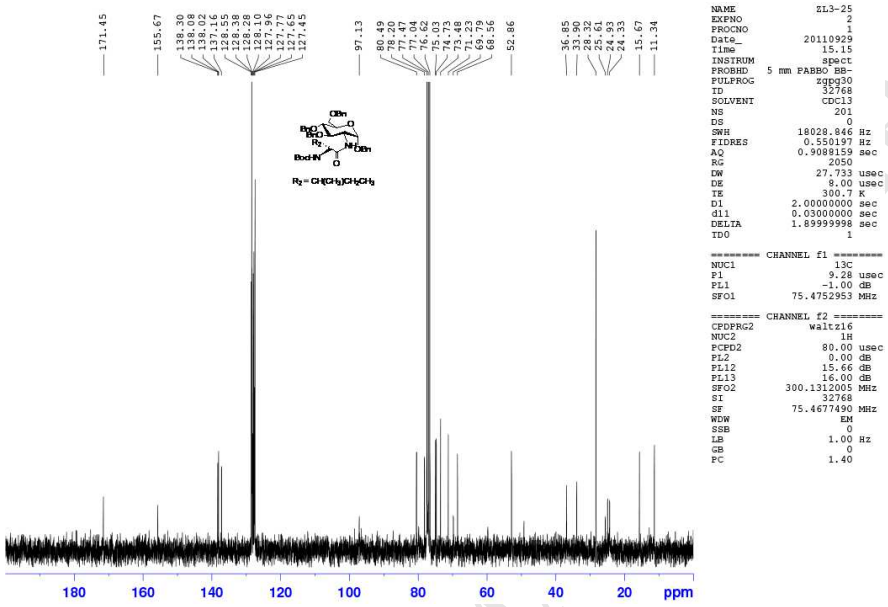


Figure S82 ^{1}H NMR spectrum of compound **9a** in $CDCl_3$ recorded at 25 □



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PROCNO	1
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PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	201
DS	0
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	2050
DW	27.733 usec
DE	8.00 usec
TE	300.7 K
D1	2.00000000 sec
d11	0.03000000 sec
DELTA	1.89999998 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.28 usec
PL1	-1.00 dB
SFO1	75.4752953 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	15.66 dB
PL13	16.00 dB
SFO2	300.1312005 MHz
SI	32768
SF	75.4677490 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

Figure S83 ^{13}C NMR spectrum of compound **9a** in $CDCl_3$ recorded at 25 □

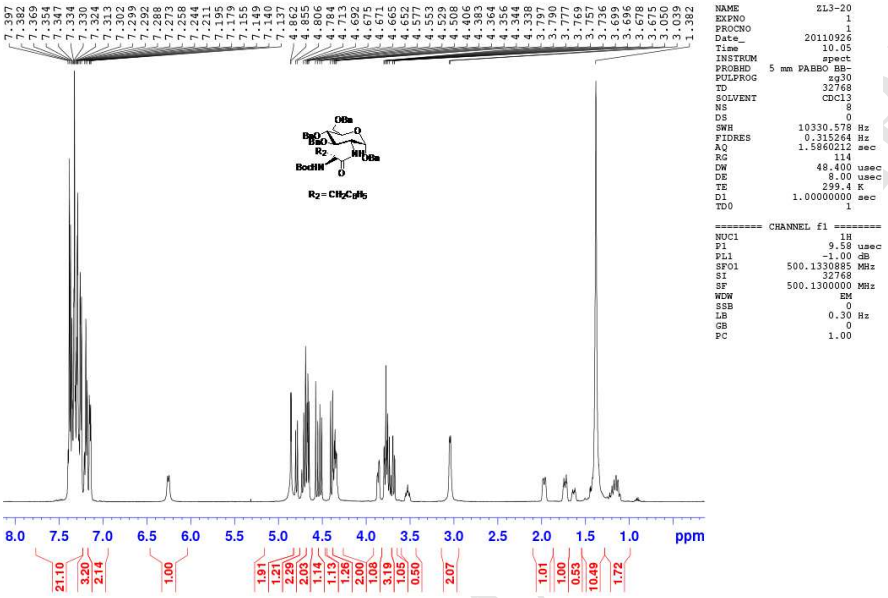


Figure S84 ^{1}H NMR spectrum of compound **9b** in $CDCl_3$ recorded at 25 □

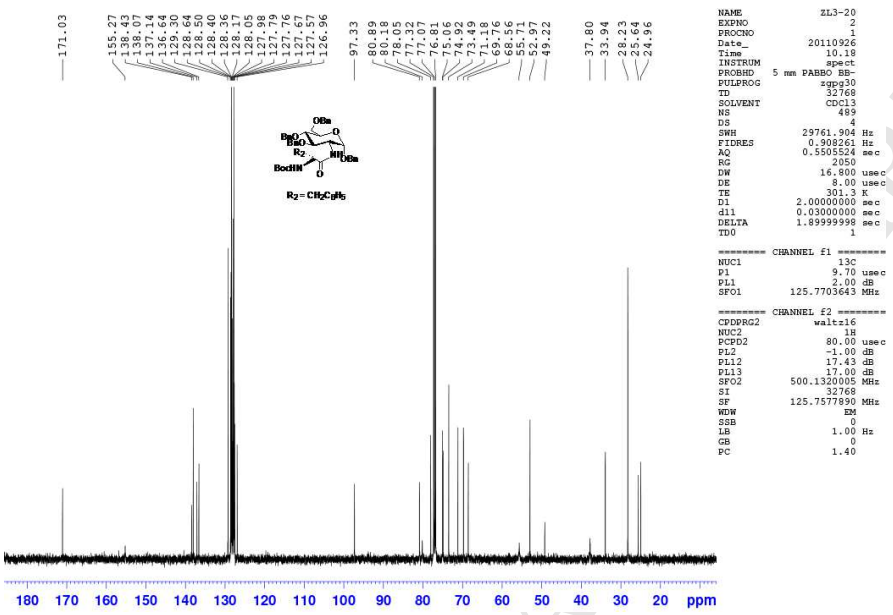


Figure S85 ^{13}C NMR spectrum of compound **9b** in $CDCl_3$ recorded at 25 □

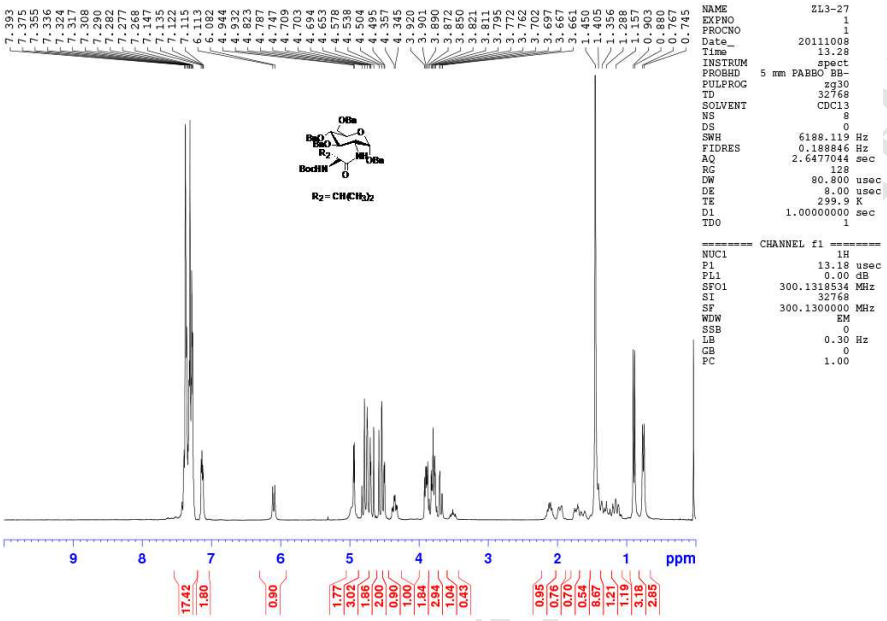


Figure S86 ^{1}H NMR spectrum of compound **9c** in $CDCl_3$ recorded at 25 □

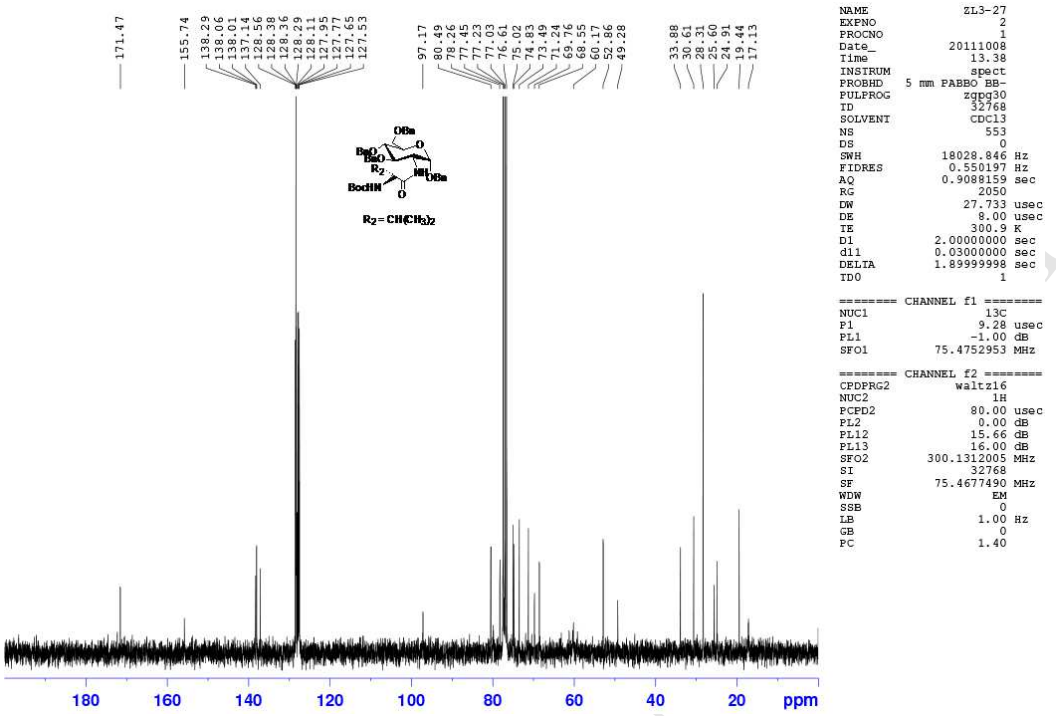


Figure S87 ^{13}C NMR spectrum of compound **9c** in $CDCl_3$ recorded at 25 □

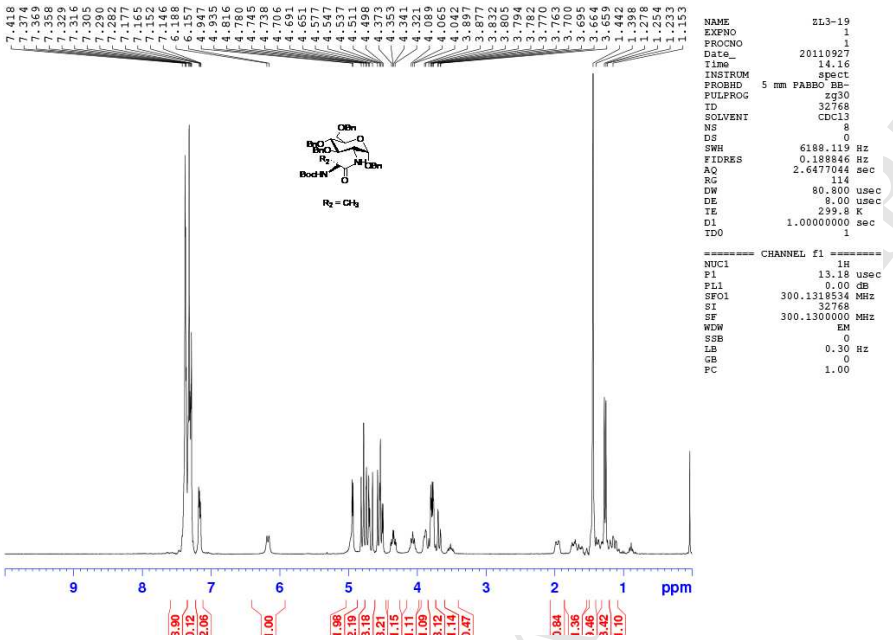
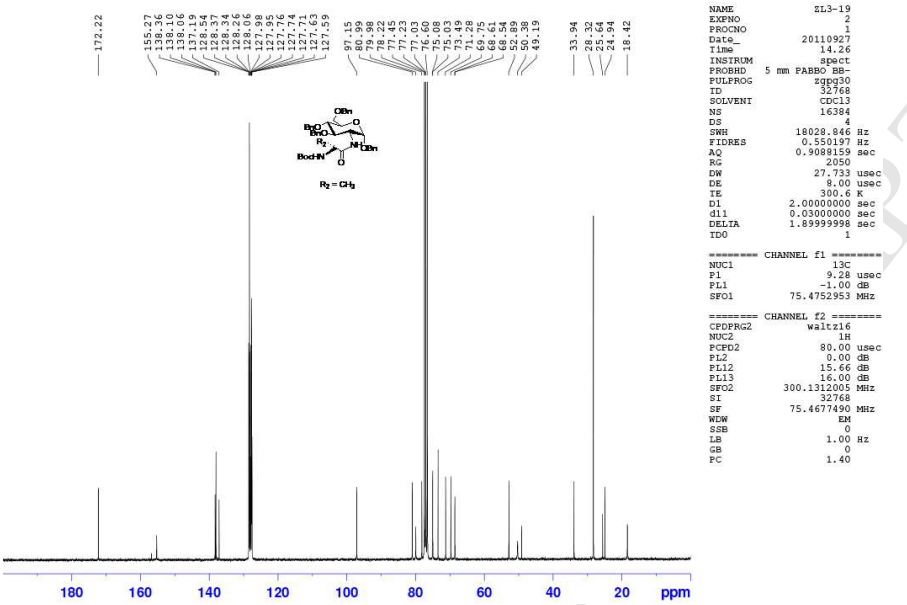


Figure S88 ^{1}H NMR spectrum of compound **9d** in $CDCl_3$ recorded at 25 □



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EXPNO	2
PROCNO	1
Date_	20110927
Time	14.26
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	16384
DS	4
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	2050
DW	27.733 usec
DE	8.00 usec
TE	300.6 K
D1	2.00000000 sec
d11	0.03000000 sec
DELTA	1.89999998 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.28 usec
PL1	-1.00 dB
SFO1	75.4752953 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	15.66 dB
PL13	16.00 dB
SFO2	300.1312005 MHz
SI	32768
SF	75.4677490 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

Figure S89 ^{13}C NMR spectrum of compound **9d** in $CDCl_3$ recorded at 25 □

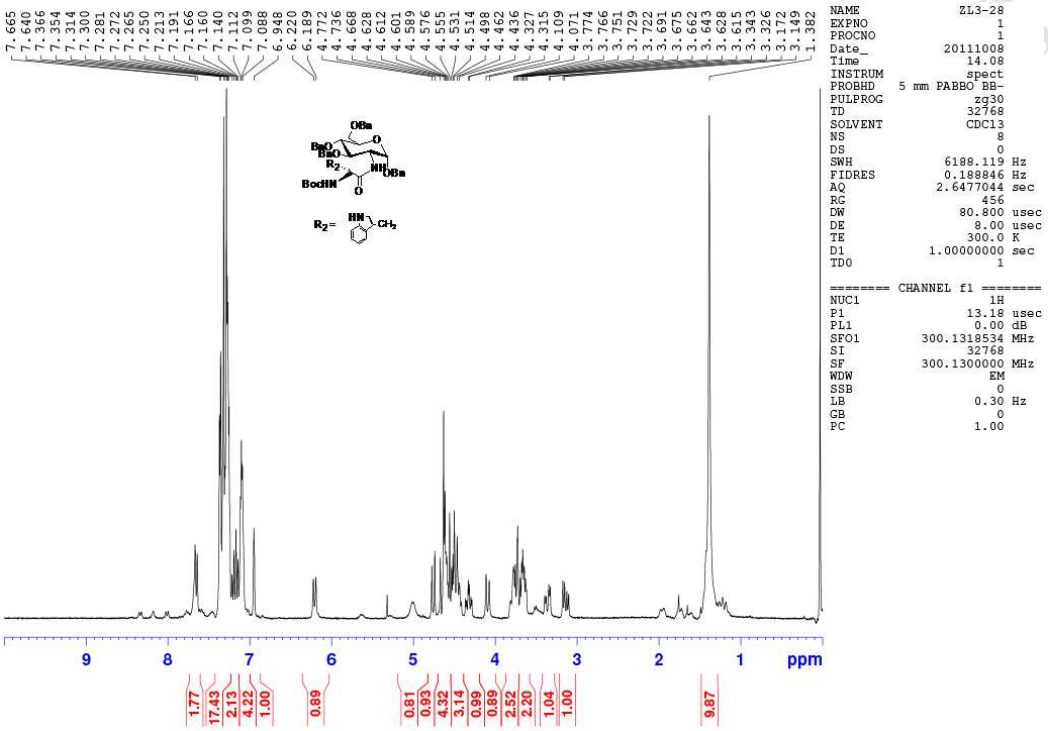


Figure S90 ^{1}H NMR spectrum of compound **9e** in $CDCl_3$ recorded at 25 □

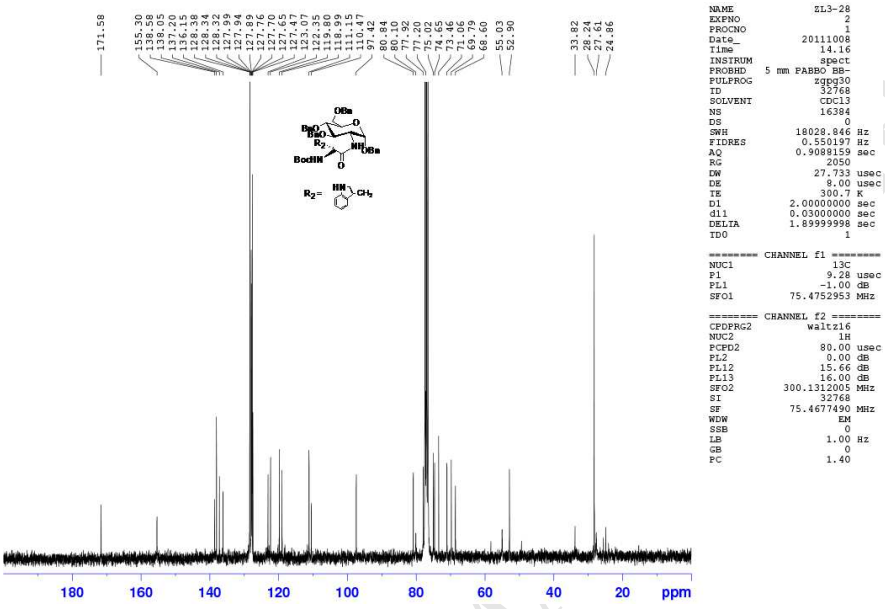


Figure S91 ^{13}C NMR spectrum of compound **9e** in $CDCl_3$ recorded at 25 □

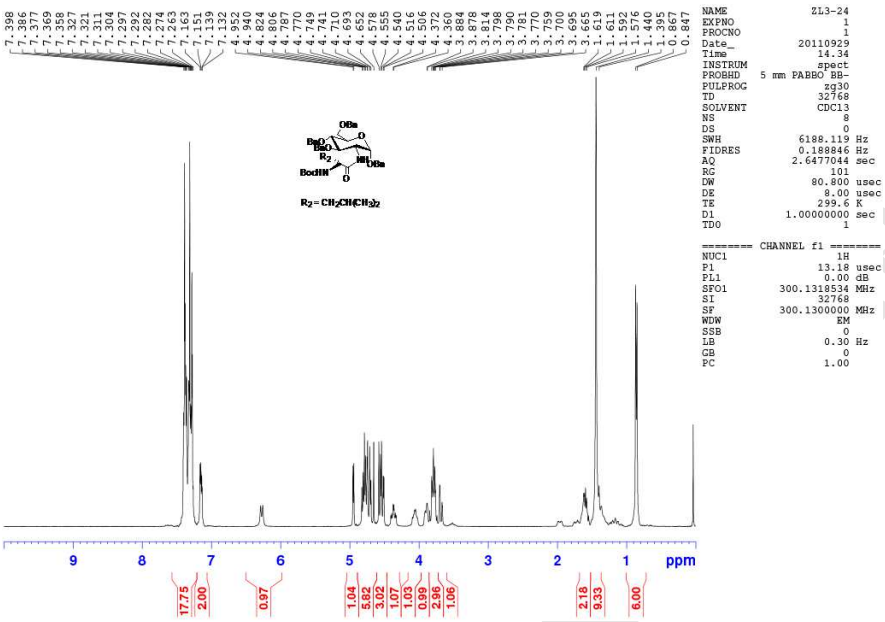


Figure S92 ^{1}H NMR spectrum of compound **9f** in $CDCl_3$ recorded at 25 □

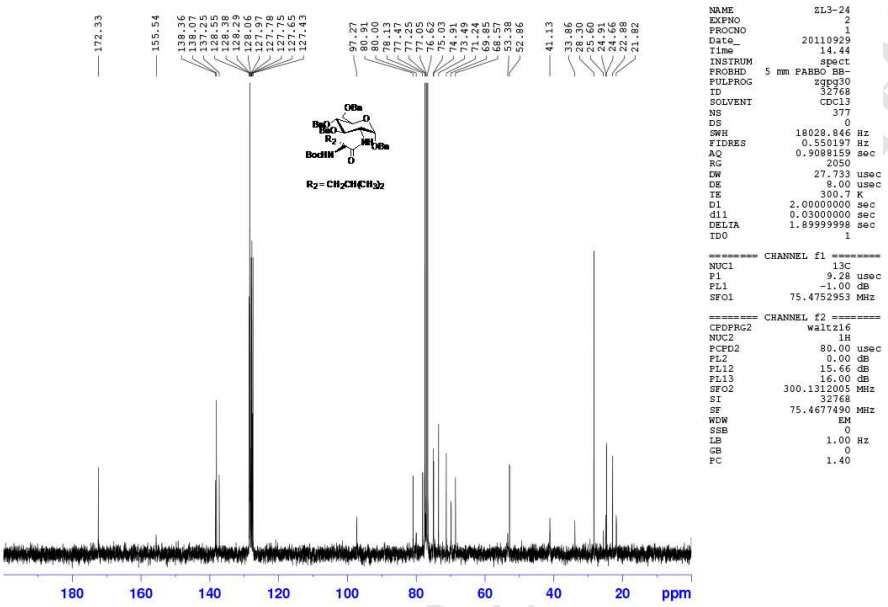


Figure S93 ^{13}C NMR spectrum of compound **9f** in $CDCl_3$ recorded at 25 □

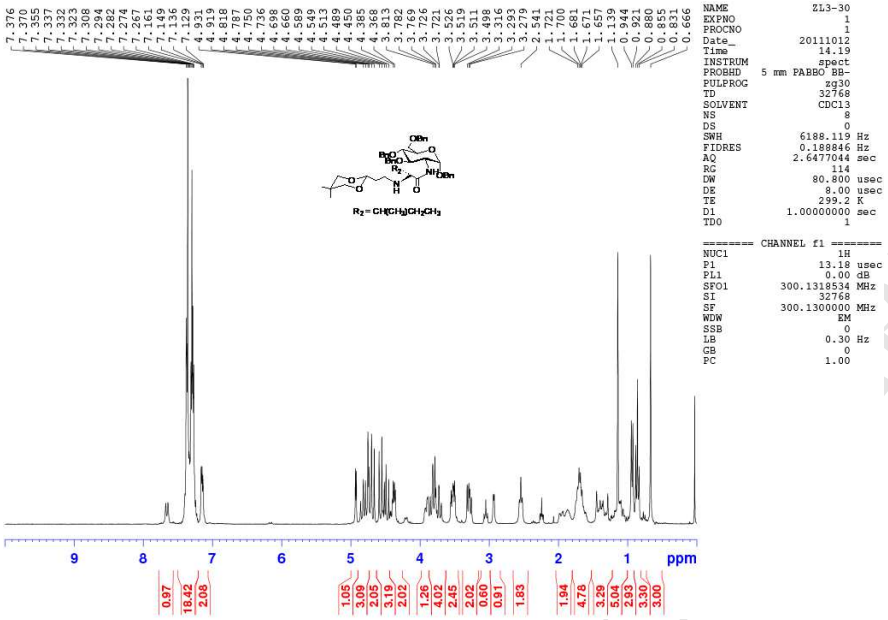


Figure S94 ^{1}H NMR spectrum of compound **11a** in $CDCl_3$ recorded at 25 □

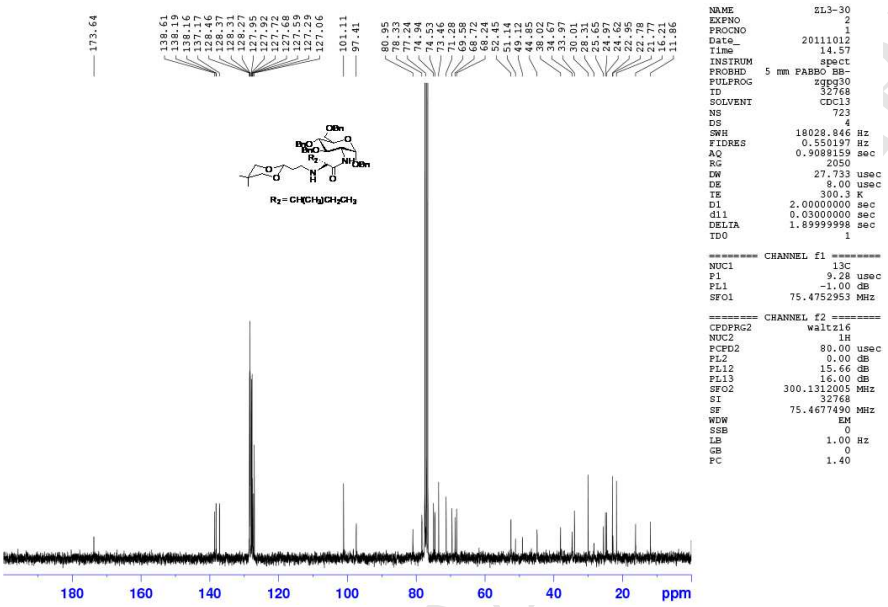


Figure S95 ^{13}C NMR spectrum of compound **11a** in $CDCl_3$ recorded at 25 □

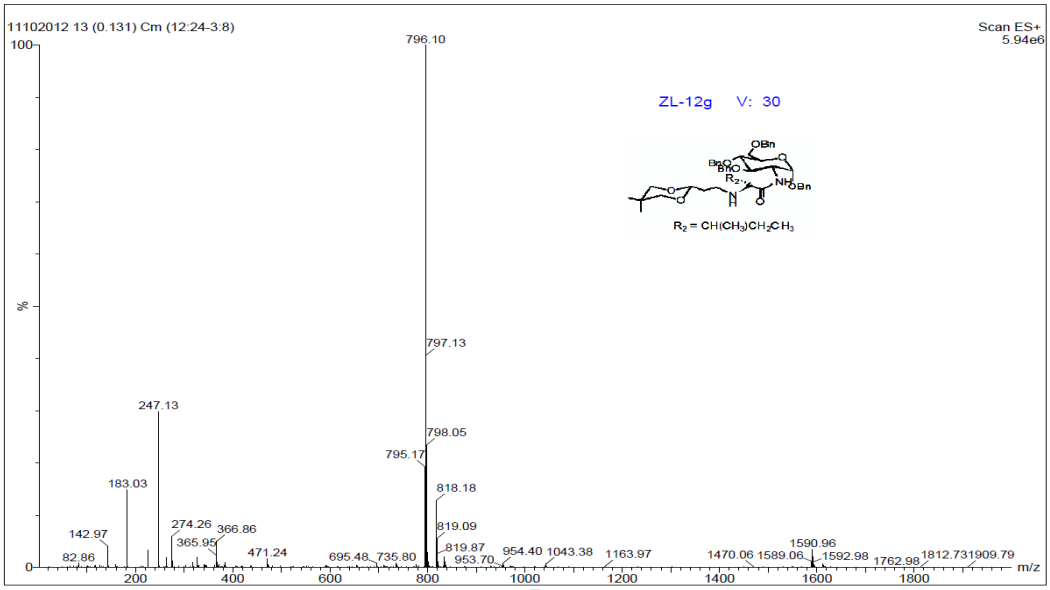
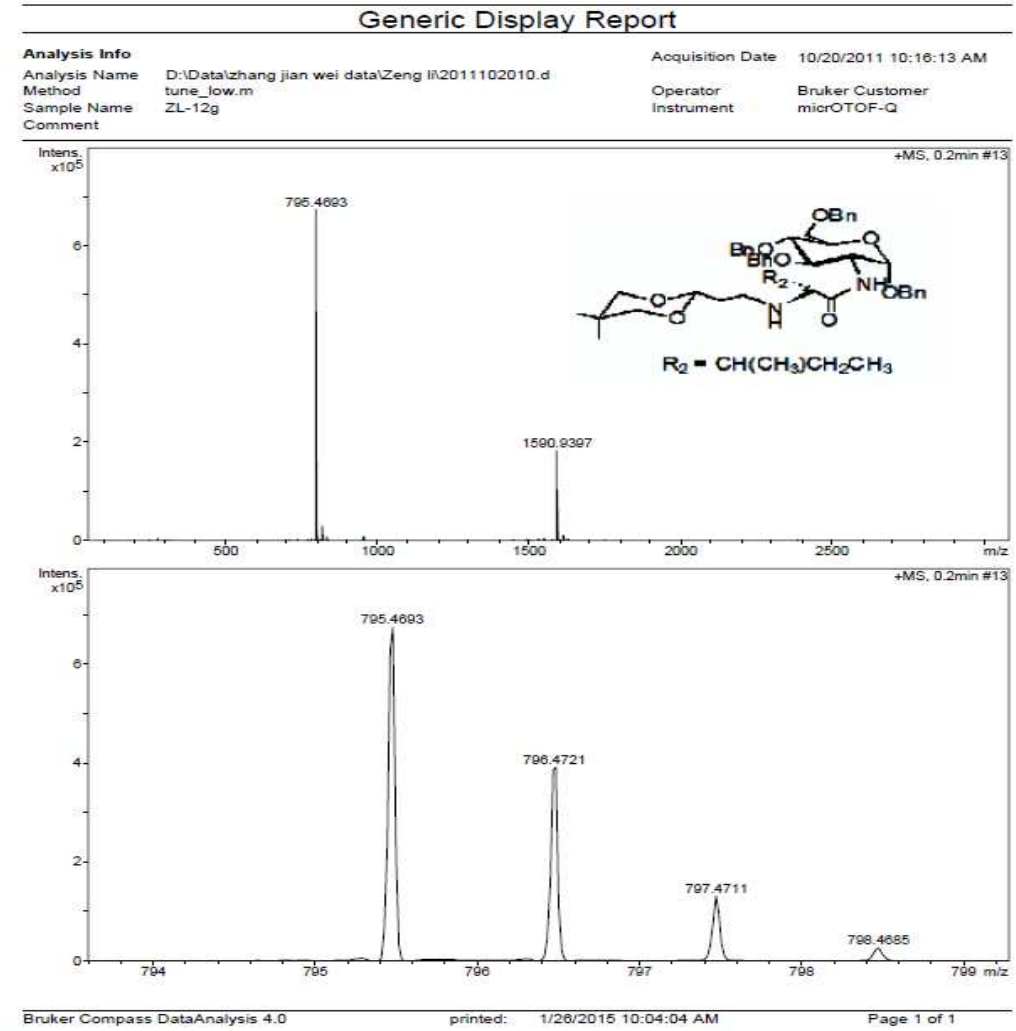


Figure S96 ESIMS spectrum of compound **11a**



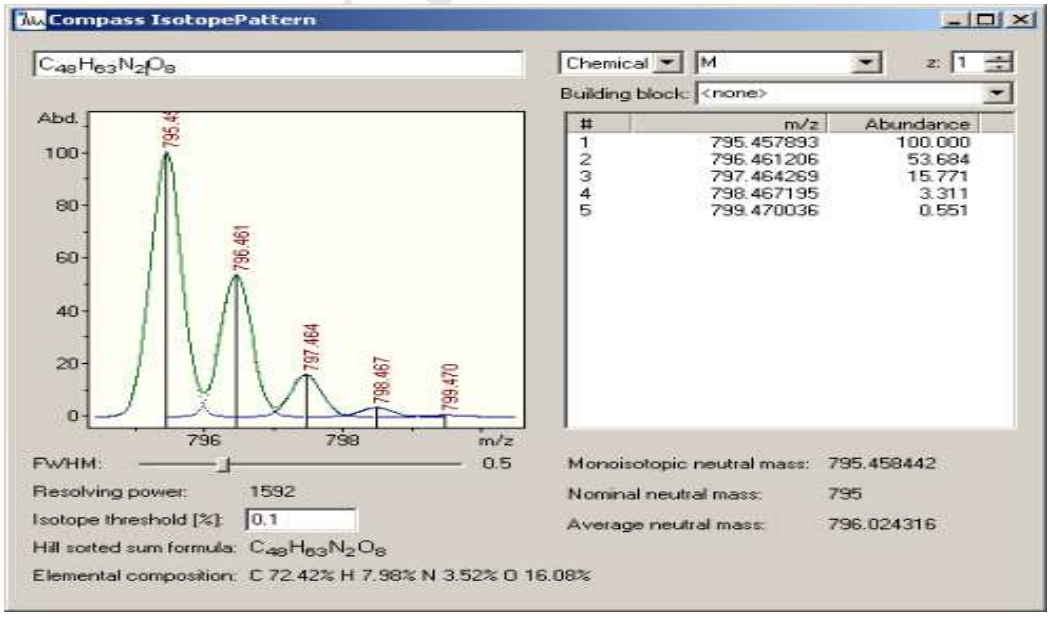


Figure S97 HRMS spectrum of compound **11a**

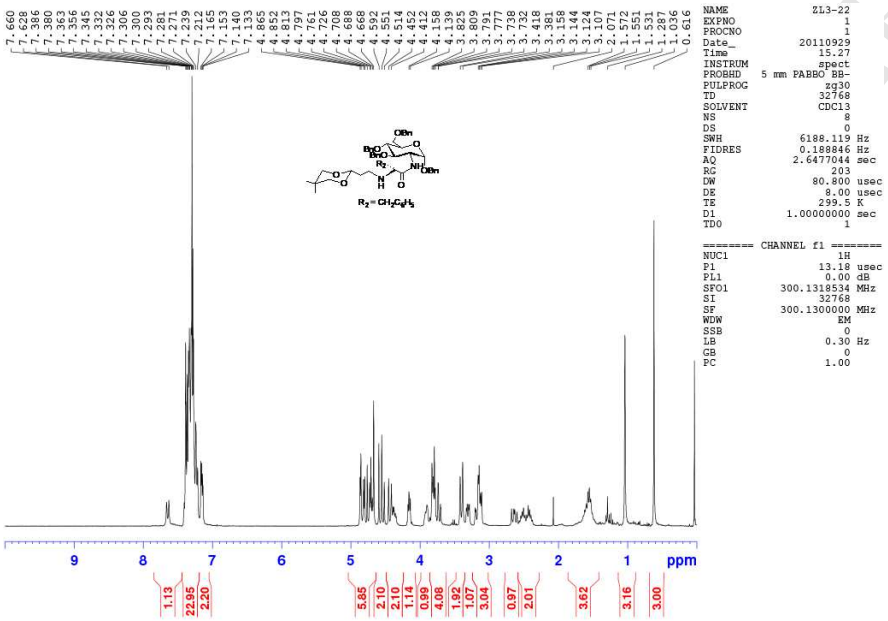


Figure S98 ^{1}H NMR spectrum of compound **11b** in $CDCl_3$ recorded at 25 □

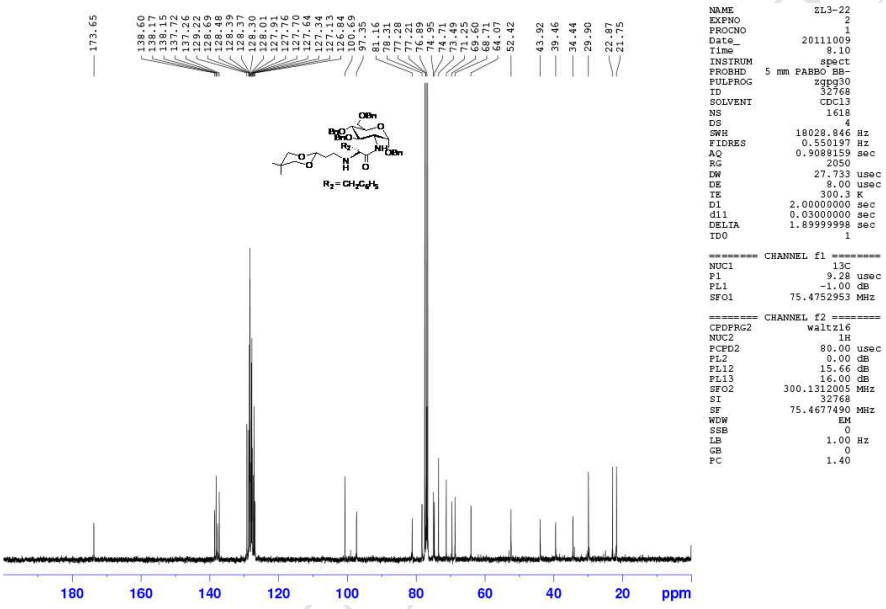


Figure S99 ^{13}C NMR spectrum of compound **11b** in $CDCl_3$ recorded at 25 □

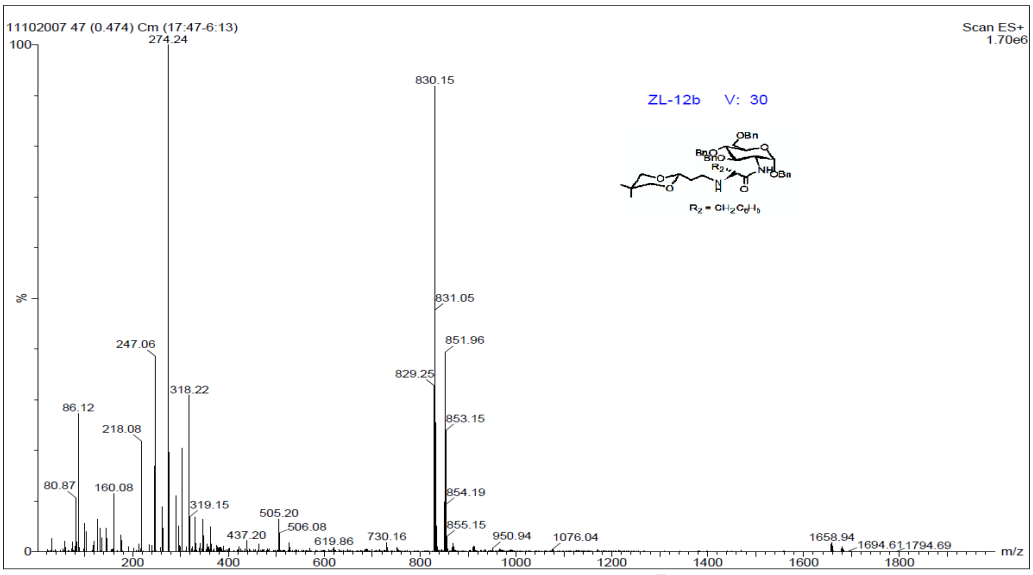


Figure S100 ESIMS spectrum of compound **11b**

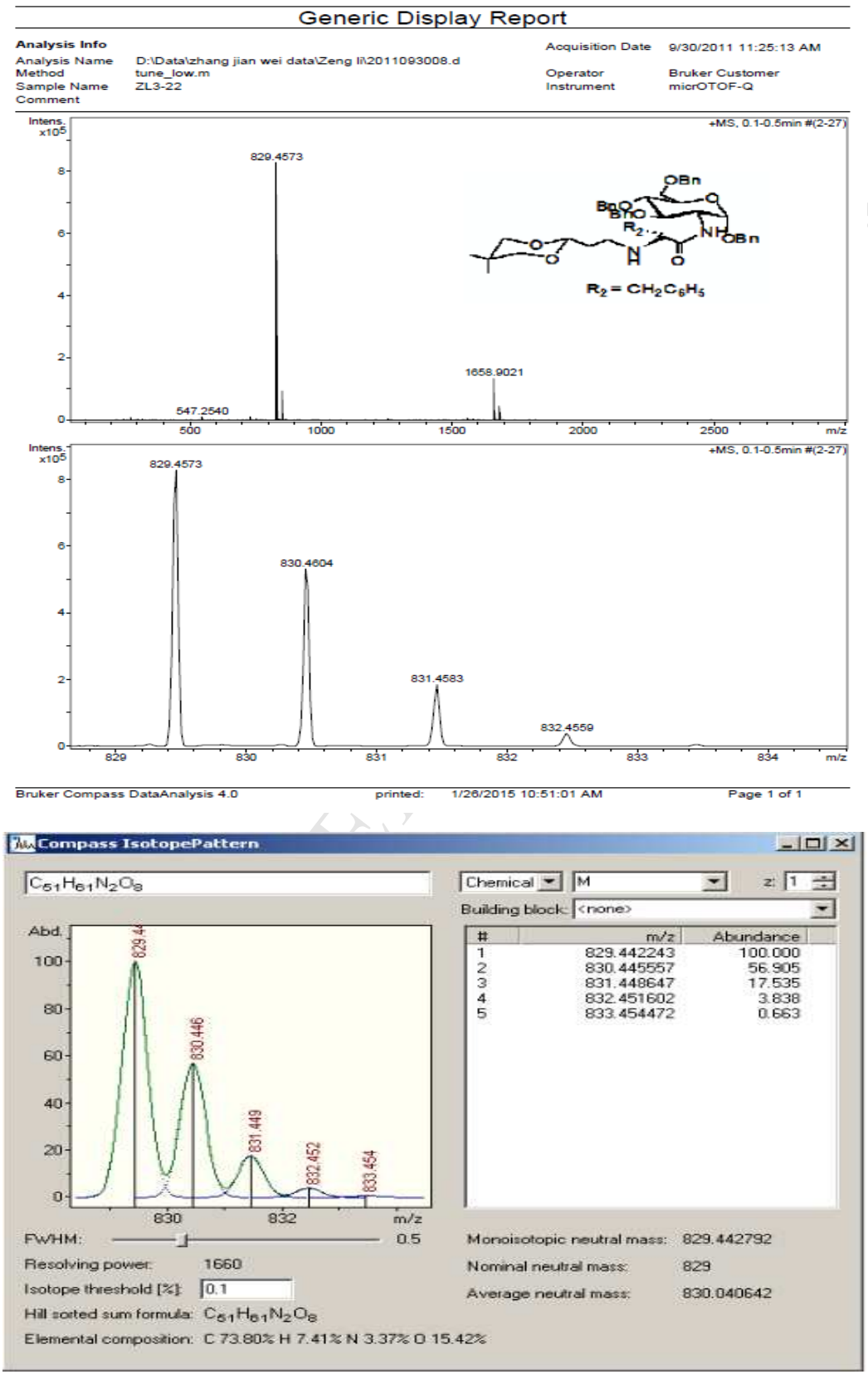


Figure S101 HRMS spectrum of compound **11b**

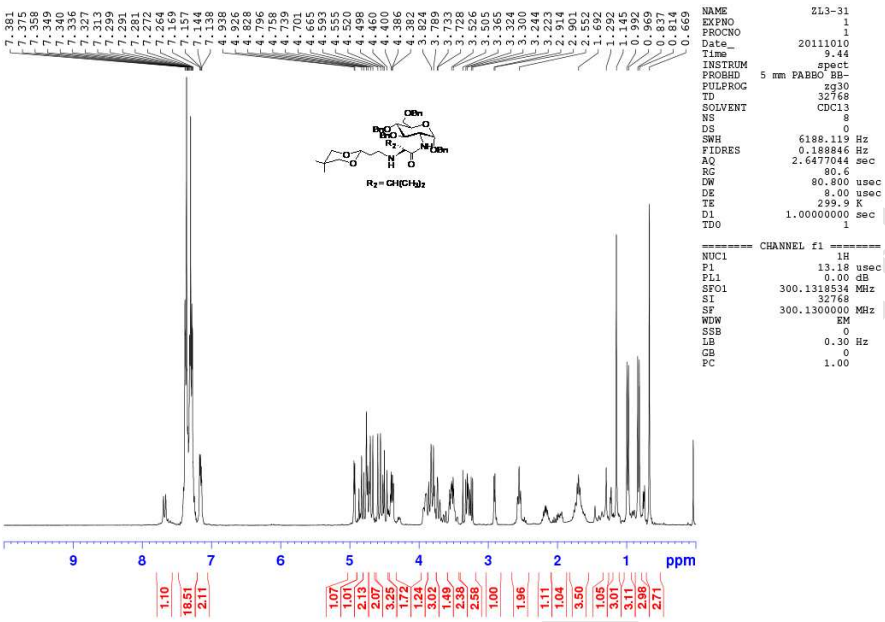


Figure S102 ^{1}H NMR spectrum of compound **11c** in $CDCl_3$ recorded at 25 □

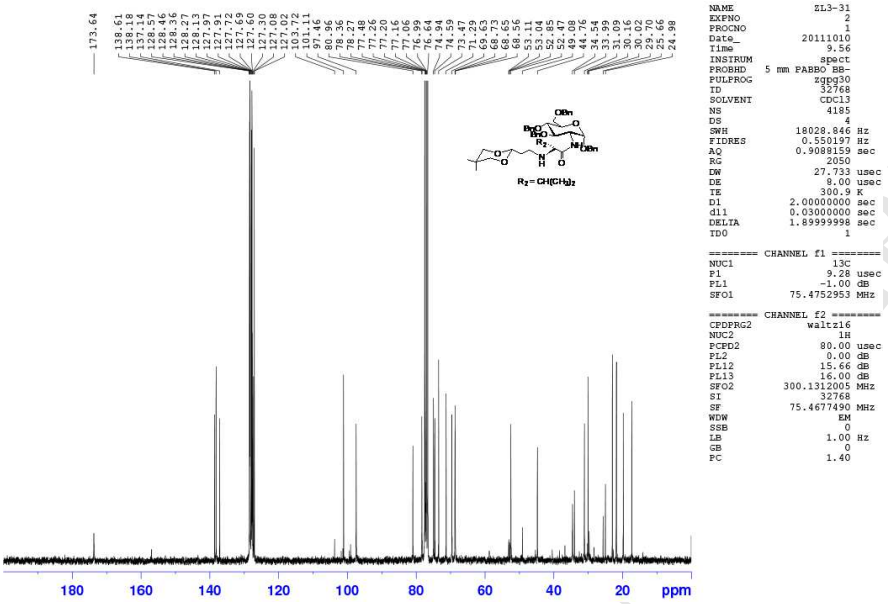


Figure S103 ^{13}C NMR spectrum of compound **11c** in $CDCl_3$ recorded at 25 □

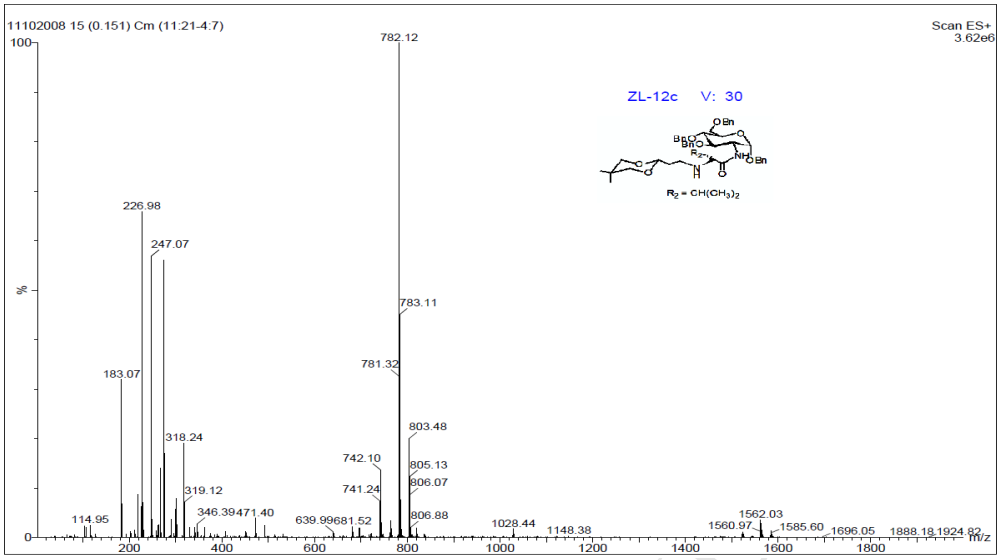


Figure S104 ESIMS spectrum of compound **11c**

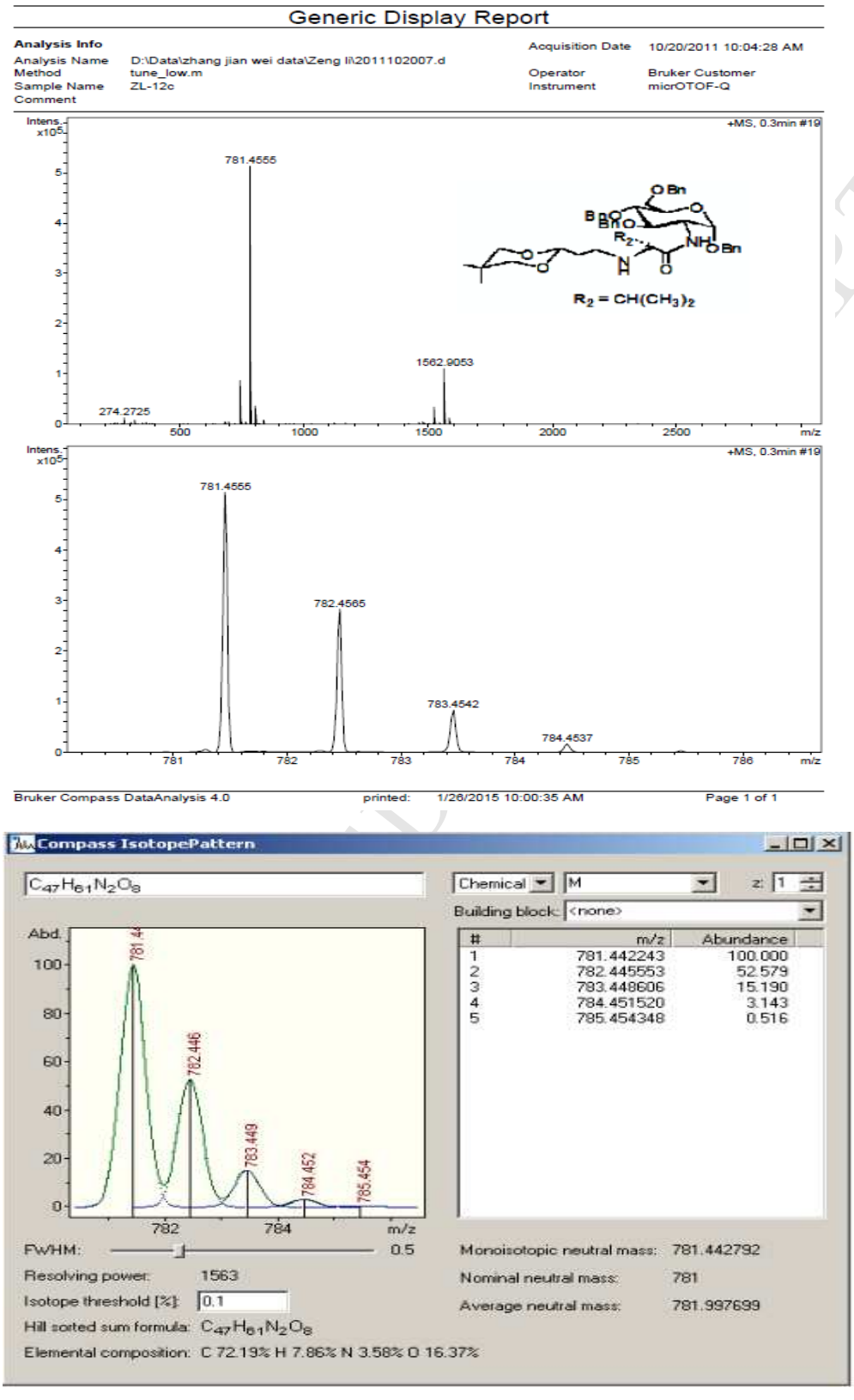


Figure S105 HRMS spectrum of compound **11c**

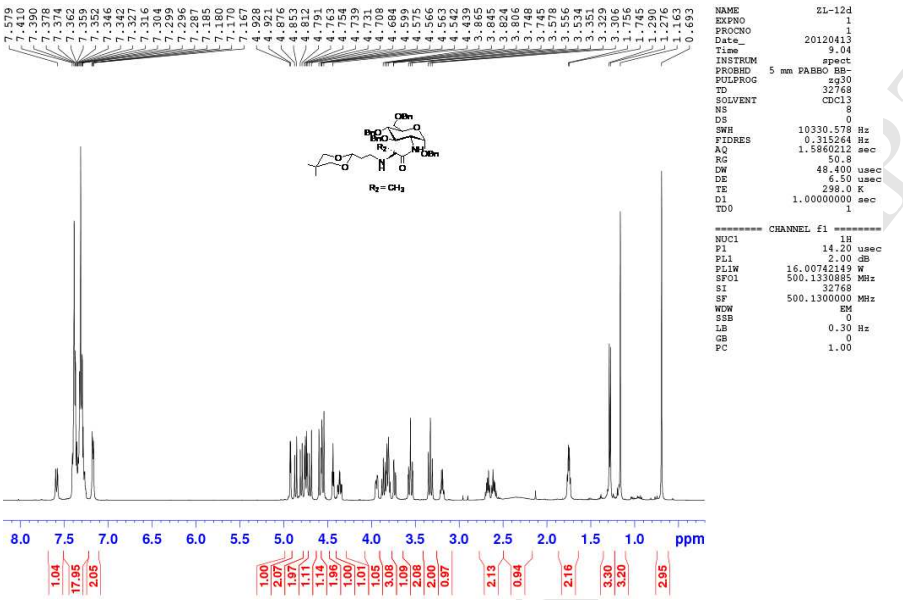
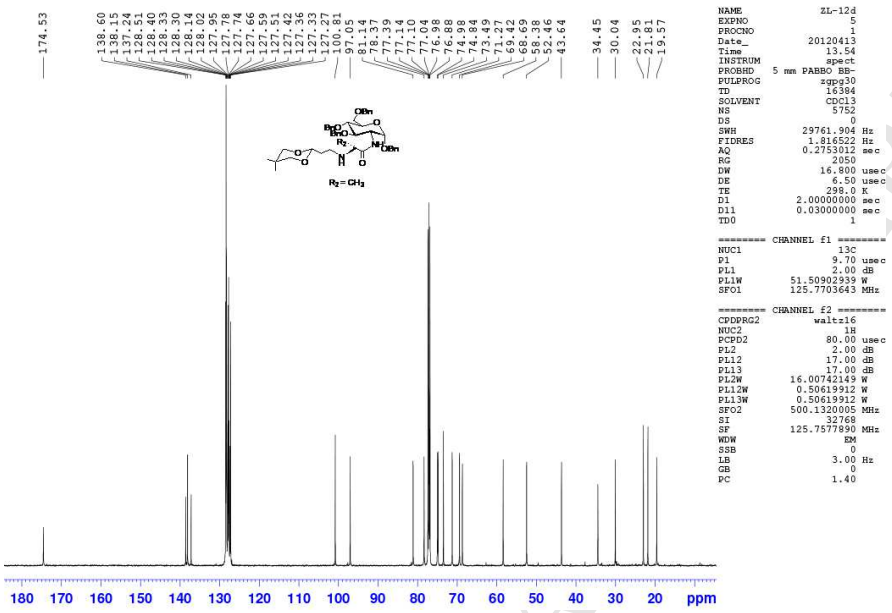


Figure S106 ^{1}H NMR spectrum of compound **11d** in $CDCl_3$ recorded at 25 □



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PROCNO	1
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FIDRES	1.816522 Hz
AQ	0.2753012 sec
RG	2050
DW	16.800 usec
DE	6.50 usec
TE	298.0 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.70 usec
PL1	2.00 dB
PL1W	51.50902939 W
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	2.00 dB
PL12	17.00 dB
PL13	17.00 dB
PL2W	16.00742149 W
PL12W	0.50619912 W
PL13W	0.50619912 W
SFO2	500.1320005 MHz
SI	32768
SF	125.7577890 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	1.40

Figure S107 ^{13}C NMR spectrum of compound **11d** in $CDCl_3$ recorded at 25 □

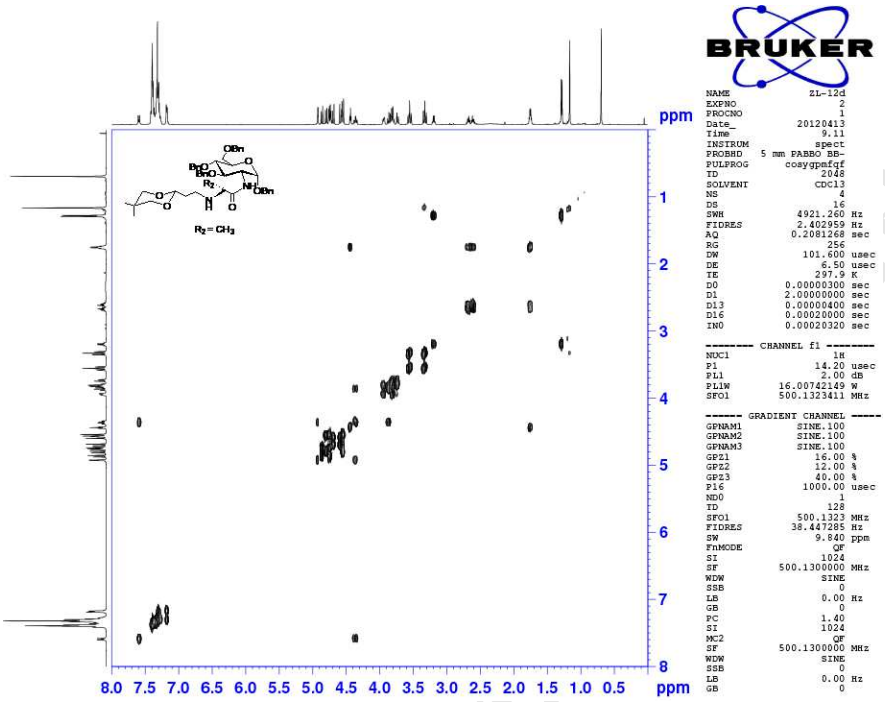


Figure S108 H-H Cosy spectrum of compound **11d** in $CDCl_3$ recorded at 25 □

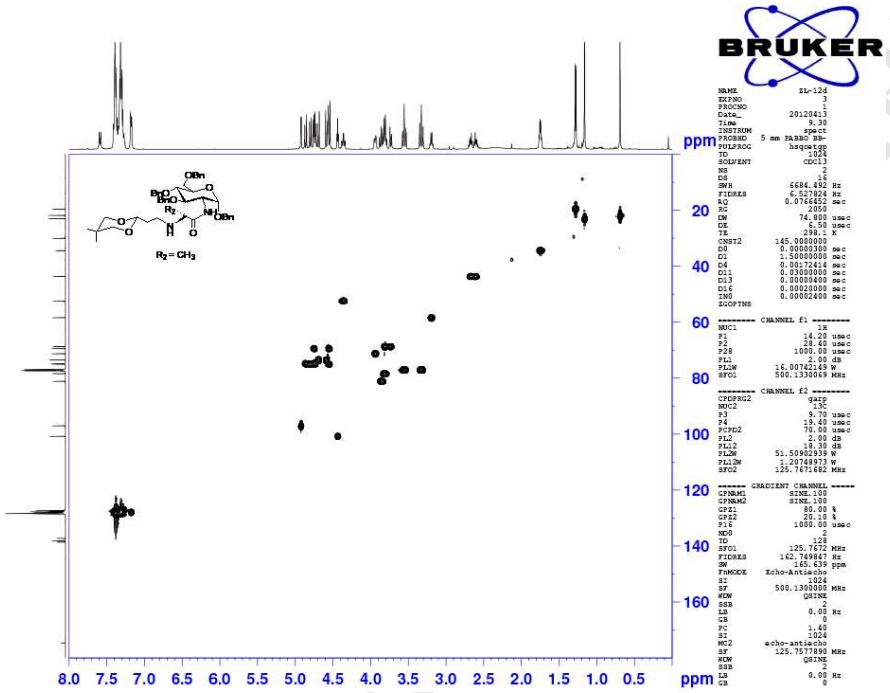


Figure S109 HMQC spectrum of compound **11d** in $CDCl_3$ recorded at 25 □

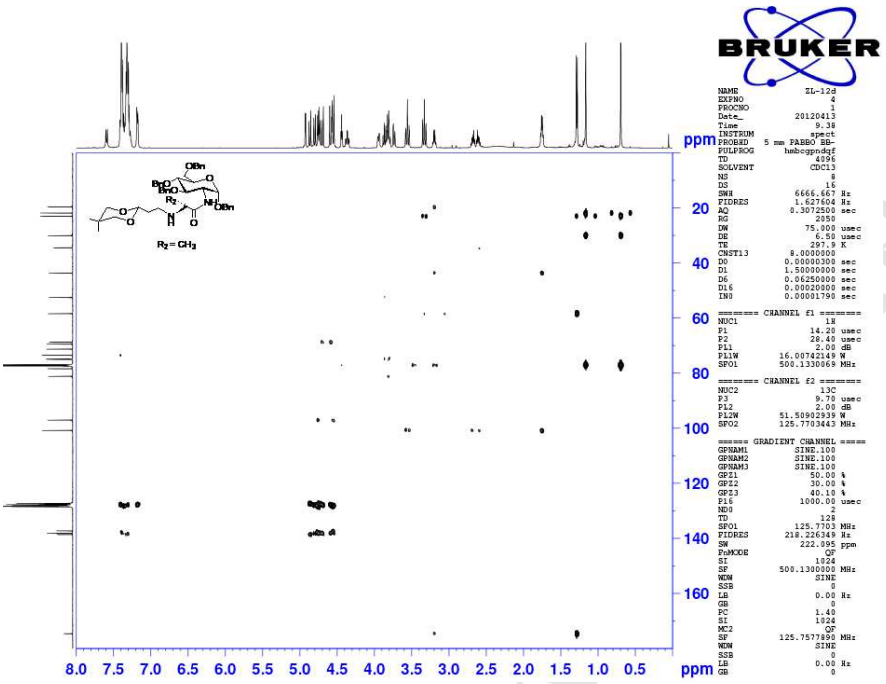


Figure S110 HMBC spectrum of compound **11d** in $CDCl_3$ recorded at 25 □

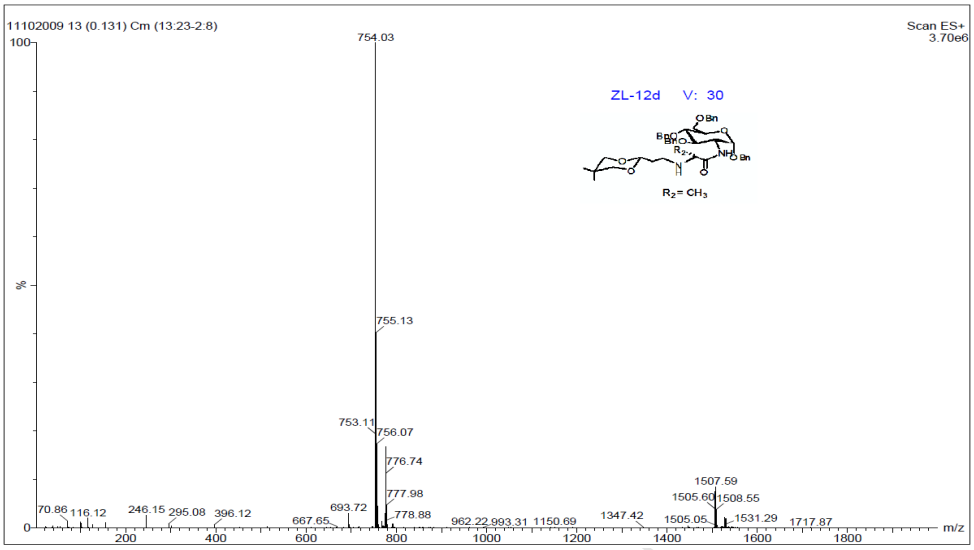
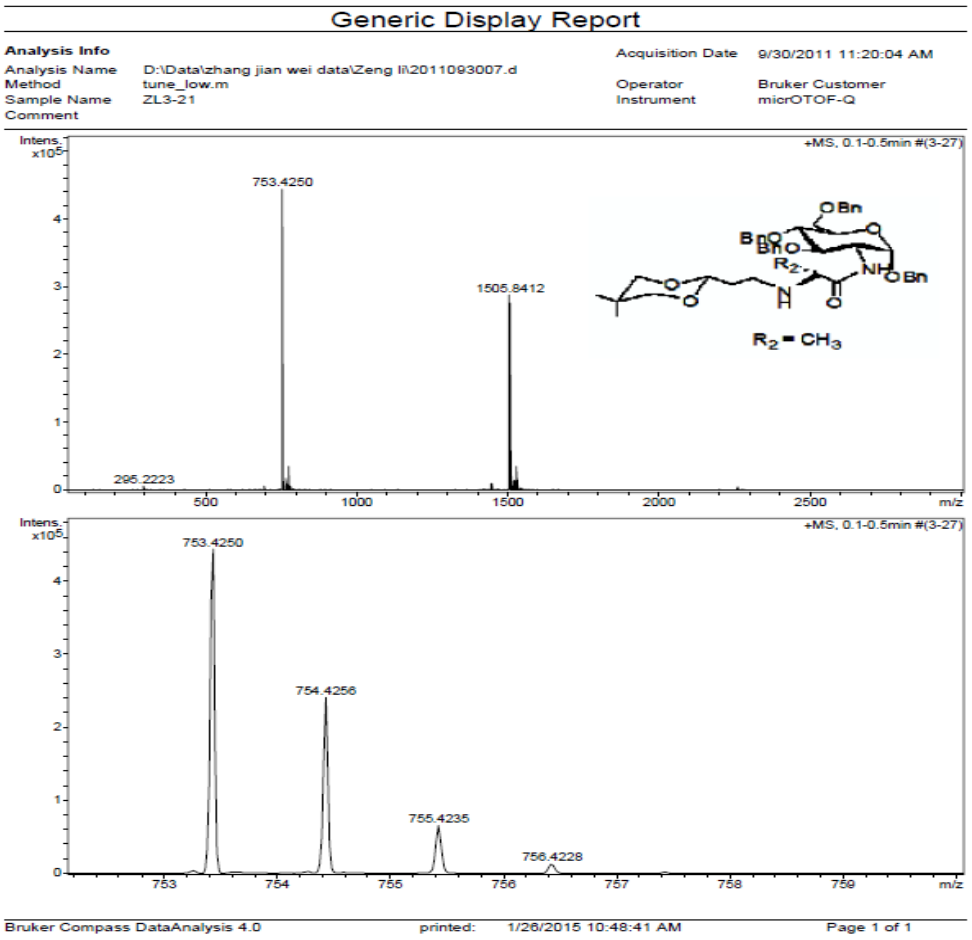


Figure S111 ESIMS spectrum of compound **11d**



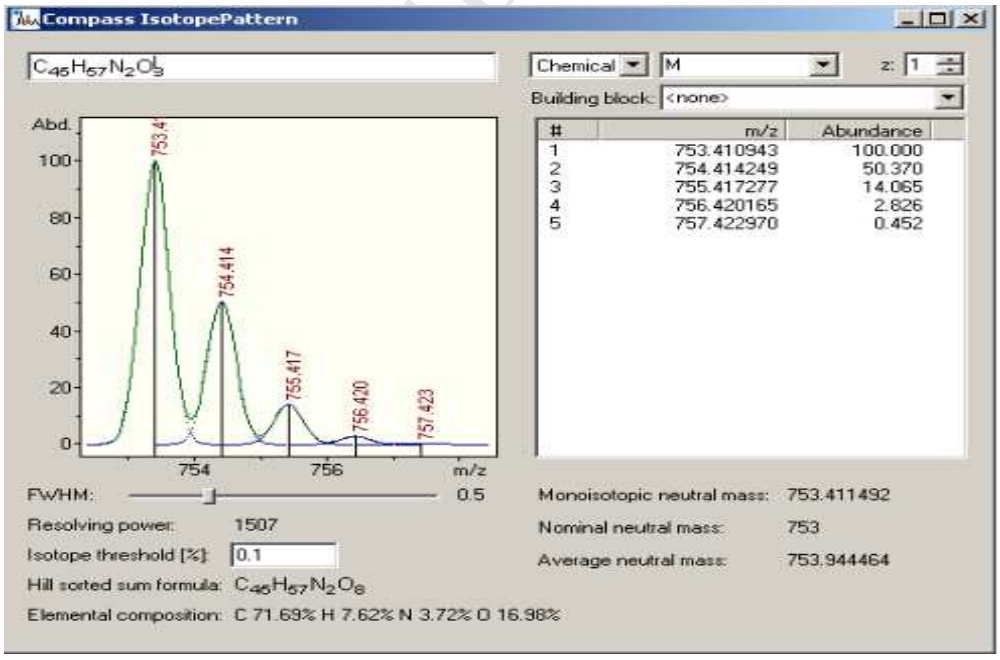


Figure S112 HRMS spectrum of compound **11d**

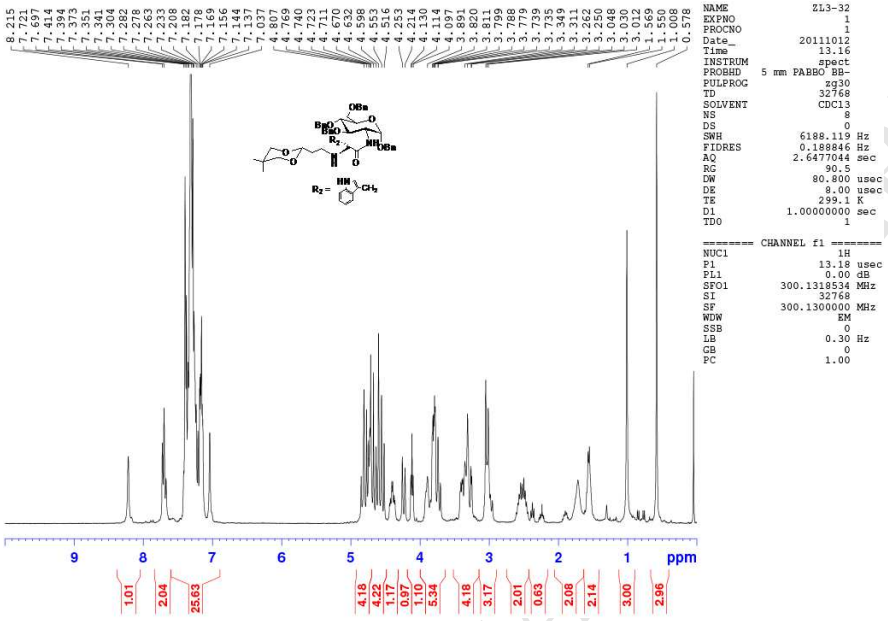
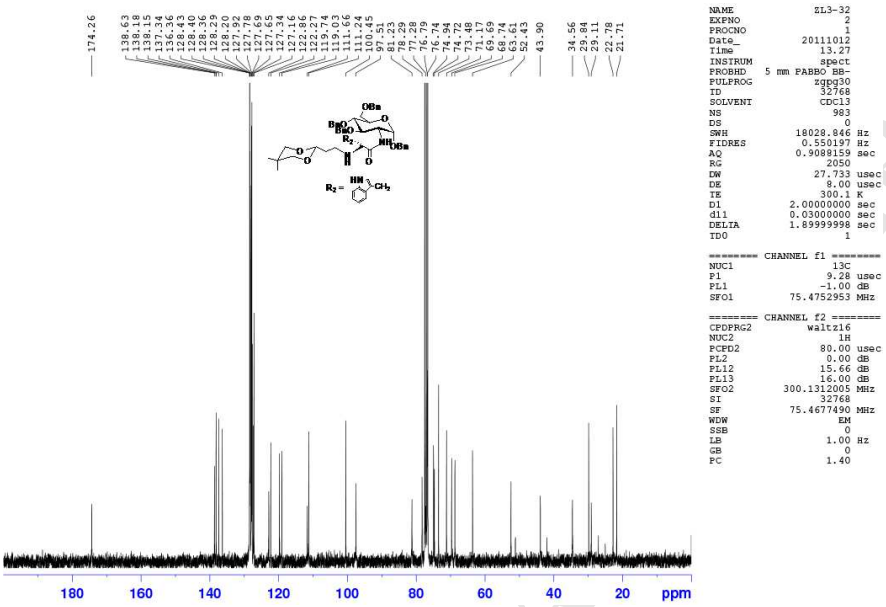


Figure S113 ^{1}H NMR spectrum of compound **11e** in $CDCl_3$ recorded at 25 □



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PROCNO	1
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PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	983
DS	0
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	2050
DW	27.733 usec
DE	8.00 usec
TE	300.1 K
D1	2.00000000 sec
d11	0.03000000 sec
DELTA	1.89999998 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.28 usec
PL1	-1.00 dB
SFO1	75.4752953 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	15.66 dB
PL13	16.00 dB
SFO2	300.1312005 MHz
SI	32768
SF	75.4677490 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

Figure S114 ^{13}C NMR spectrum of compound **11e** in $CDCl_3$ recorded at 25 □

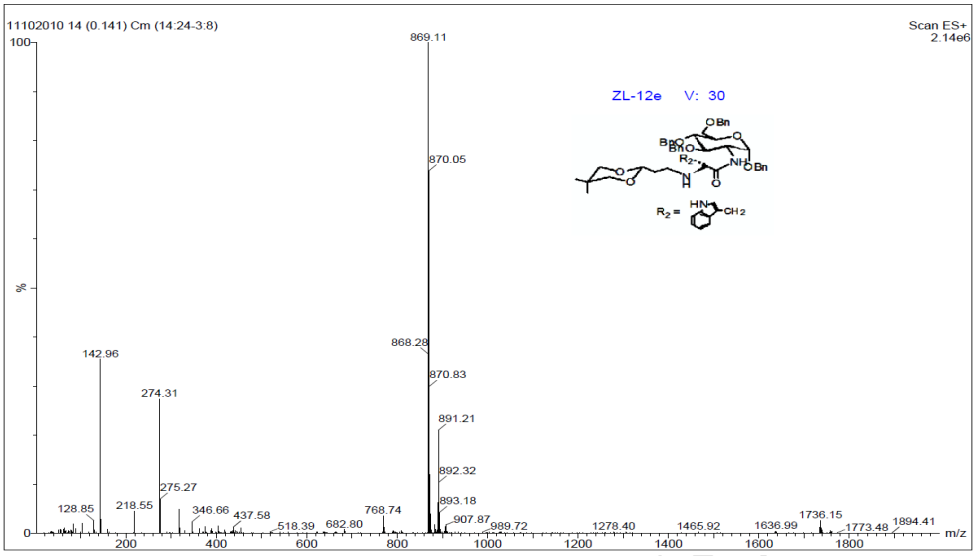
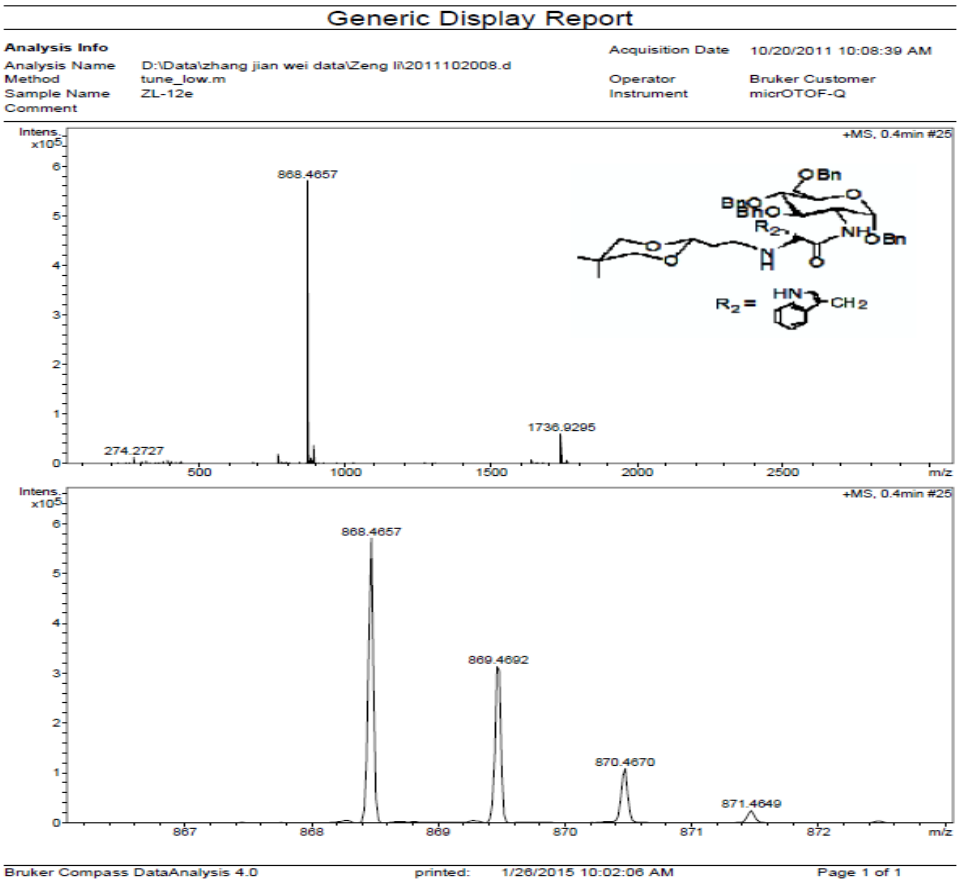


Figure S115 ESIMS spectrum of compound **11e**



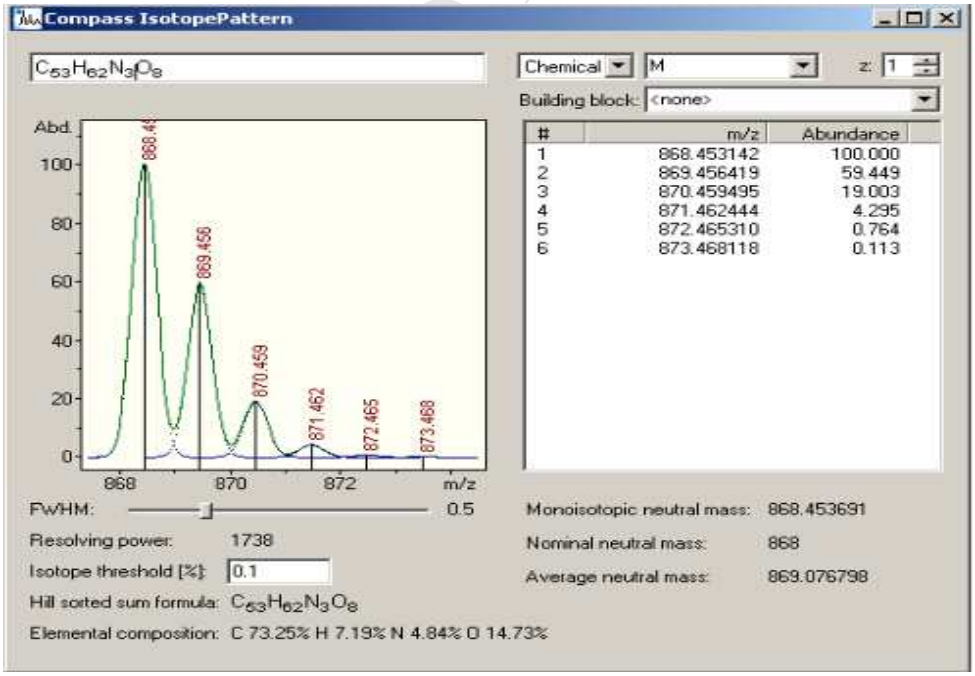


Figure S116 HRMS spectrum of compound **11e**

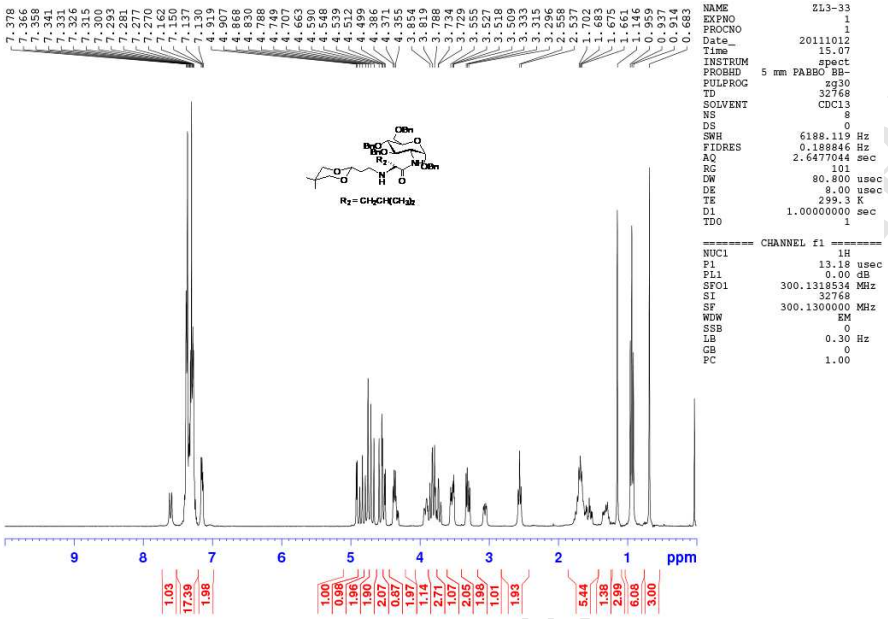


Figure S117 ^{1}H NMR spectrum of compound **11f** in $CDCl_3$ recorded at 25 □

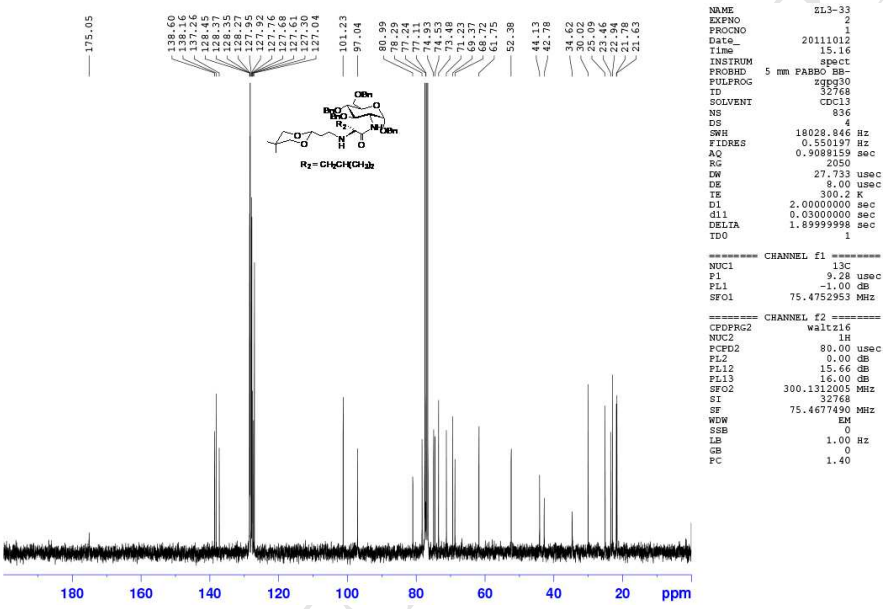


Figure S118 ^{13}C NMR spectrum of compound **11f** in $CDCl_3$ recorded at 25 □

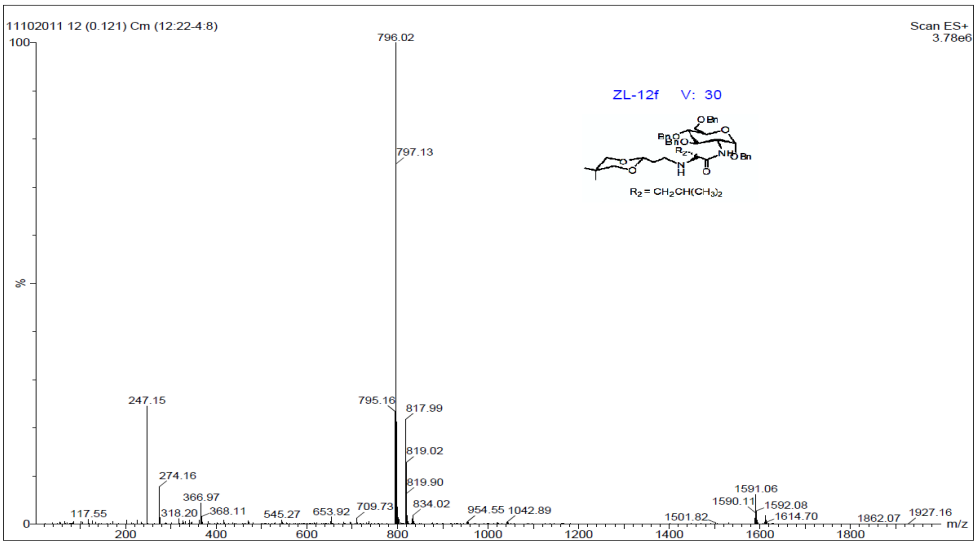
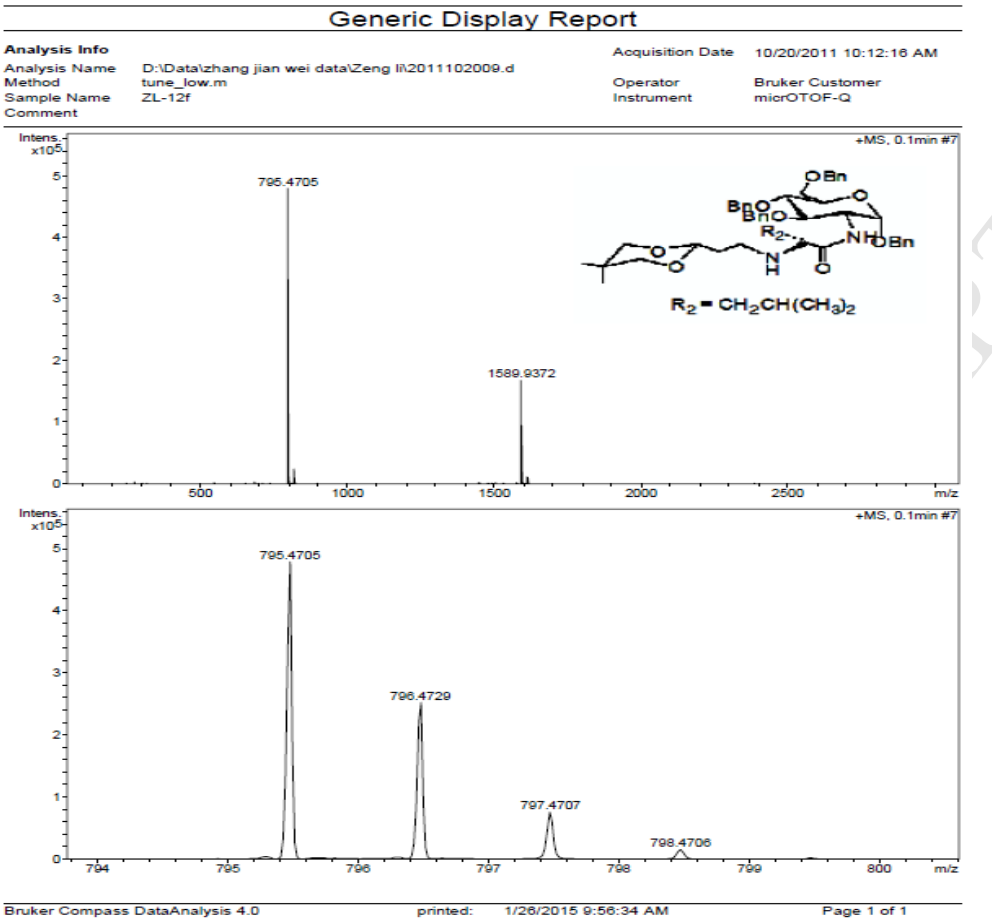


Figure S119 ESIMS spectrum of compound **11f**



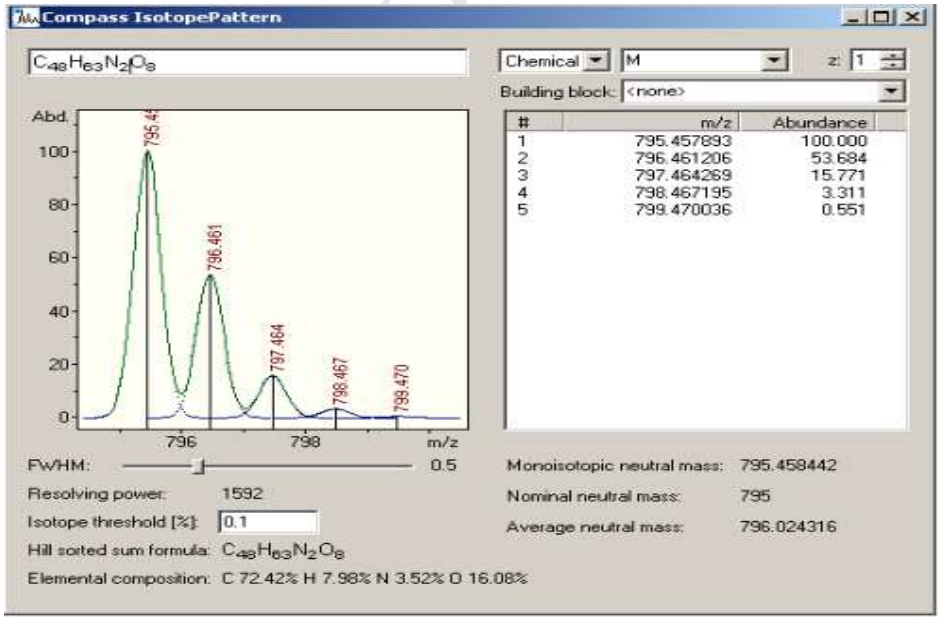


Figure S120 HRMS spectrum of compound **11f**