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Original article

Efficient synthesis of (6-deoxy-glycopyranosid-6-yl) sulfone derivatives and their effect on Ca^{2+}-ATPase

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ABSTRACT

Synthesis of a series of novel (6-deoxy-glycopyranosid-6-yl) sulfone derivatives has been achieved using a general synthetic strategy. Yields were excellent in every case. The synthetic compounds were evaluated for their biological potential against Ca^{2+}-ATPase, an important enzyme involves in tranporting Ca^{2+} across the cell membranes.

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1. Introduction

Variation in the intracellular calcium levels (Ca^{2+}) is essential for the normal cellular activities related to the development of cells, immune response, muscle movement, modulation of neuronal processes etc. Calcium ATPase (Ca^{2+}-ATPase) and its isoforms control the level of Ca^{2+} ion in cells, which has strong influence on calcium homeostasis [1]. In animal cells, Ca^{2+} homeostasis depends on the function of ATP-driven Ca^{2+}-pump that transports cytosolic free calcium into the intracellular storage compartments. Ca^{2+}-ATPase is a vesicular integral membrane protein located in the sarcoplasmic reticulum (SR), plays significant role for pumping out of calcium ion from the cytoplasm to lumen. The existence of a number of Ca^{2+}-ATPases have been reported earlier whose activities depend on the presence Mg^{2+} ion [2]. Earlier, Sen et al. and others reported a Ca^{2+}-ATPase from rat testicular membranes [3a], brain [3b] and goat spermatozoa membranes [4] that could be activated by Ca^{2+} ion alone without the requirement of Mg^{2+} ion in contrast to the classical Mg^{2+} dependent Ca^{2+}-ATPases [2c,d]. The enzyme belongs to the family of P-type ATPases and couple ATP hydrolysis with cation transport [4], which is essential in cellular calcium homeostasis. Like most other Ca^{2+}-ATPases, it is involved in ATP-dependent Ca^{2+}-transport and undergoes phosphorylation–dephosphorylation in the transport cycle [5] with transient phosphorylation of the enzyme by ATP on an active aspartyl group being the key step in Ca^{2+} translocation. Inhibition of this enzyme activity using vanadate and lanthanum chloride suggested its similarity with the SERCA family of Ca^{2+}-ATPases [4]. A considerable number of stimulators as well as inhibitors for Ca^{2+}-ATPase have been reported and their mechanism of actions has also been well established [6]. Several peptide toxins have shown strong inhibitory activity on this enzyme [7]. In the past several carbohydrate derivatives and pseudodisaccharide derivatives were reported to act as inhibitors for a number of important enzymes [8]. It was envisaged that the development of novel sulfone-linked pseudodisaccharide derivatives acting as stimulators and/or inhibitors of Mg^{2+} independent Ca^{2+}-ATPase would be beneficial in this context. Carbohydrate derivatives could serve as better stimulators or inhibitors because of their less toxic nature, hydrophilicity and presence of chirality in the structure.

Replacement of ether linkage between two sugar units with a sulfur atom or sulfone group could provide useful glycomimetics to study their potential as enzyme inhibitors. A number reports appeared in the literature for the synthesis of thioether linked disaccharide derivatives having biological activities [9–13]. Although sulfur-linked pseudodisaccharides are reported earlier [14,15], preparation of sulfone-linked pseudodisaccharides and their biological evaluation are rather scarce [16]. In an ongoing program for the development of carbohydrate derived small molecule stimulators and/or inhibitors of Mg^{2+} independent Ca^{2+}-ATPase, we

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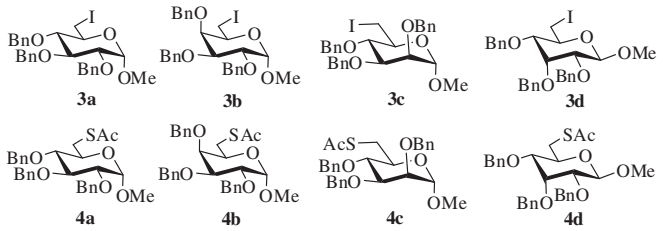


Fig. 1. Suitably functionalized monosaccharide intermediates.

report herein, efficient synthesis of a series of novel (6-deoxy-glycopyranosid-6-yl) sulfone derivatives and their effect on Mg^{2+} independent Ca^{2+}-ATPase.

2. Chemistry

Synthesis of a series of bis-(6-deoxy-glycopyranosid-6-yl) sulfone derivatives (**7a**–**h**) starting from a range of suitably functionalized monosaccharide derivatives was achieved using a general synthetic strategy. Methyl α-D-glucopyranoside (**1a**) was converted to methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside (**3a**) [17] using a reaction sequence involving selective tritylation [18] of 6-hydroxy group using trityl chloride in pyridine, per-*O*-benzylation [19] using benzyl bromide and sodium hydroxide and acidic removal [20] of trityl group followed by treatment with iodine in the presence of triphenylphosphine and imidazole [21]. Compound **3a** [17] was treated with potassium thioacetate to furnish methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-thioacetyl-α-D-glucopyranoside (**4a**) [22] in 88% yield. Following similar reaction conditions, compounds **3b**–**d** [17] and **4b**, **4c** [23] and **4d** were synthesized from methyl glycosides of D-galactose, D-mannose and D-allose respectively (Fig. 1, Scheme 1).

Synthesis of (6-deoxy-glycopyranosid-6-yl) sulfide derivatives was carried out by coupling compounds **3a**–**d** [17] with **4a**–**d**. After a series of experimentations, it was observed that treatment of compound **3a** with compound **4a** in the presence of solid sodium hydroxide (2 equiv.) in dimethylformamide at room temperature furnished compound **5a** in 86% yield. Following similar reaction condition, a series of symmetric and asymmetric (6-deoxy-glycopyranosid-6-yl) sulfide derivatives (**5a**–**h**) have been synthesized in excellent yield (Fig. 2, Scheme 2). Compounds **5a**–**h** were treated with excess 3-chloroperbenzoic acid (*m*-CPBA) [24] to give (6-deoxy-glycopyranosid-6-yl) sulfone derivatives (**6a**–**h**) in excellent yield. Conventional hydrogenolysis [25] of compounds **6a**–**h** over Pearlman's catalyst furnished symmetric and asymmetric (6-deoxy-glycopyranosid-6-yl) sulfone (**7a**–**h**) in excellent yield (Fig. 3, Scheme 2).

3. Biology

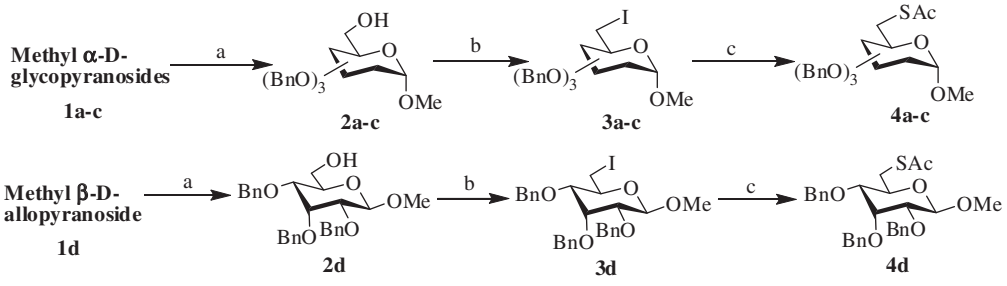
In order to examine the bioactivity of the synthetic compounds (**7a**–**h**), their effects were tested against an important enzyme known as Mg^{2+} independent Ca^{2+}-ATPase. Since all compounds (**7a**–**h**) were found to stimulate Ca^{2+}-ATPase, they were tested in the presence of a number of calcium channel blockers like verapamil, thapsigargin and vanadate to examine their effect. Biological activities of compounds **7a**–**h** alone and in combination with known calcium blockers against Mg^{2+} independent Ca^{2+}-ATPase are presented in Table 1. The Mg^{2+} independent Ca^{2+}-ATPase activity assay was performed in the microsomal membranes of goat spermatozoa according to Sikdar et al. [4]. In the present study, all compounds (**7a**–**h**) have been found to stimulate the enzyme and 30–50% stimulation was observed at an average concentration of about 20 μg/L (70 nM) (Fig. 4).

4. Results and discussion

The biological experiments using synthetic compounds **7a**–**h** in the presence of known calcium blockers revealed that the inhibitory effect of Thapsigargin predominates over the stimulating effect of target compounds **7a**–**7h** on Ca^{2+}-ATPase, whereas the inhibitory effect of Verapamil on Ca^{2+}-ATPase was effectively compensated by the presence of disaccharides **7b**–**7d** and **7f**–**7h**. In the case of orthovanadate, a reasonable reduction in the inhibitory effect on Ca^{2+}-ATPase was observed in the presence of disaccharides **7b** and **7c** only (Table 1). These findings suggest that even the modification of one stereocenter may exert a considerable influence on the ability of the (6-deoxy-glycopyranosid-6-yl)sulfone target compounds to compensate the effect of various Ca-ATPase inhibitors. Since Mg^{2+} independent Ca^{2+}-ATPase is involved in calcium transport, the stimulatory effects on this enzyme by these synthetic compounds and subsequent competition with some known calcium blockers support their biological significance.

5. Conclusion

In summary, a series of a new class of symmetric and asymmetric (6-deoxy-glycopyranosid-6-yl) sulfone have been synthesized by coupling a set of sugar iodides with sugar thiols in a very straightforward and high yielding reaction condition. The reaction condition can be applied in a scale-up synthesis. The synthetic intermediates (**3a**–**d** and **4a**–**d**) were prepared from the same starting material. Furthermore compounds **7a**–**h** are found to be biologically important as evident from their stimulatory effects on Mg^{2+} independent Ca^{2+}-ATPase. Further optimization for the development of Ca^{2+}-ATPase stimulators are currently in progress in our laboratory.



Sugars: a: D-glucose, b: D-galactose, c: D-mannose.

Scheme 1. Reagents: (a) (i) Trityl chloride, pyridine, 70 °C; (ii) BnBr, NaOH, r. t.; (iii) 80% aq. AcOH, 70 °C (75% for **2a**; 72% for **2b**; 72% for **2c** and 70% for **2d**); (b) I_2, PPh_3, Imidazole, toluene, 60 °C (84% for **3a**; 79% for **3b**; 82% for **3c** and 79% for **3d**); (c) KSAc, DMF, r. t. (88% for **4a**; 82% for **4b**; 88% for **4c** and 85% for **4d**).

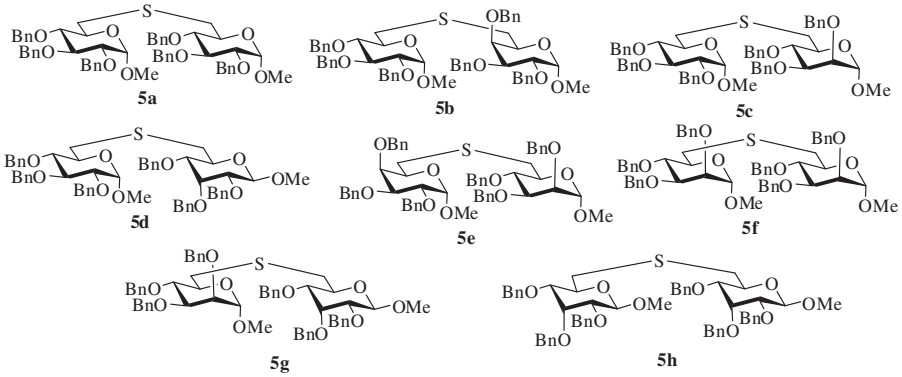


Fig. 2. Synthesized (6,6′)-thiolinked protected pseudodisaccharide derivatives (**5a**–**h**).

6. Experimental section

6.1. General remarks

All reactions were monitored by thin layer chromatography over silica gel coated TLC plates. The spots on TLC were visualized by warming ceric sulphate (2% $Ce(SO_4)_2$ in 2 N H_2SO_4) sprayed plates on a hot plate. Silica gel 230–400 mesh was used for column chromatography. ^1H and ^{13}C NMR, 2D COSY, HMQC spectra were recorded on Brucker DRX 500 MHz spectrometer using $CDCl_3$ and D_2O as solvents and TMS as internal reference unless stated otherwise. Chemical shift values are expressed in ppm. ESI-MS were recorded on a Micromass Quattro II triple quadrupole mass spectrometer. Elementary analysis was carried out on Carlo Erba-1108 analyzer. Optical rotations were measured at 25 °C on a Perkin Elmer 341 polarimeter. Biological experiments were carried out in a Shimadzu UV-2401PC spectrophotometer. Commercially available grades of organic solvents of adequate purity are used in all reactions.

6.1.1. General experimental procedure for the preparation of methyl 2,3,4-tri-O-benzyl-6-deoxy-6-iodo-α/β-D-glycopyranoside (**3a**–**d**)

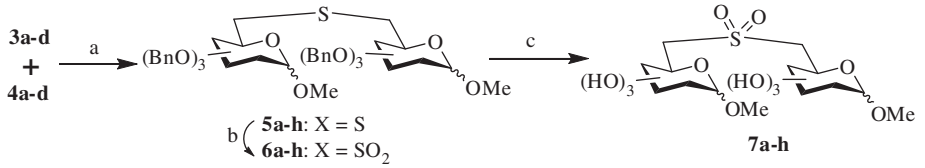
To a solution of compound **2a**–**d** (3 g, 6.5 mmol) in dry toluene (30 mL) were added triphenylphosphine (3.4 g, 12.9 mmol) and imidazole (2.2 g, 32.3 mmol) respectively, followed by the addition of iodine (2.5 g, 9.7 mmol) and the reaction mixture was stirred at 60 °C for 1 h. Methanol (10 mL) was added to the reaction mixture and the entire solvent was evaporated out. The crude reaction mixture was then diluted with CH_2Cl_2 (40 mL) and the organic layer was then washed with 10% aq. $Na_2S_2O_3$ solution (2 × 15 mL) and brine (2 × 15 mL) respectively. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure and the crude product was purified over SiO_2 using hexane–EtOAc (8:1) as eluant to give pure product as syrup.

6.1.2. General experimental procedure for the preparation of methyl 6-S-acetyl-2,3,4-tri-O-benzyl-6-deoxy-α/β-D-glycopyranoside (**4a**–**d**)

To a solution of compound **3a** (1.5 g, 2.6 mmol) in dry DMF (15 mL) was added potassium thioacetate (600 mg, 5.2 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then concentrated under reduced pressure, diluted with CH_2Cl_2 (25 mL) and washed with water (2 × 10 mL) and 10% aq. $Na_2S_2O_3$ (2 × 10 mL) solution respectively. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure and the crude product was purified over SiO_2 using hexane–EtOAc (6:1) as eluant to give pure product as syrup.

*6.1.2.1. Methyl 6-S-acetyl-2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranoside (**4a**).* Yellowish oil (1.2 g, 88%); R_f: 0.7 (hexane–EtOAc, 2:1); IR (neat): 2914, 2363, 1695, 1358, 1114, 1071, 1003, 740, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.29–7.24 (m, 15H, Ar-H), 4.95 (d, J = 10.9 Hz, 1H, PhCH_2), 4.86 (d, J = 10.8 Hz, 1H, PhCH_2), 4.79 (d, J = 10.9 Hz, 1H, PhCH_2), 4.76 (d, J = 12.1 Hz, 1H, PhCH_2), 4.63 (d, J = 12.1 Hz, 1H, PhCH_2), 4.60 (d, J = 10.7 Hz, 1H, PhCH_2), 4.51 (d, J = 3.5 Hz, 1H, H-1), 3.94 (t, J = 9.2 Hz each, 1H, H-3), 3.73–3.69 (m, 1H, H-5), 3.47 (dd, J = 9.7, 3.5 Hz, 1H, H-2), 3.41 (dd, J = 13.8, 3.0 Hz, 1H, H-6_a), 3.34 (s, 3H, OCH_3), 3.26 (t, J = 9.1 Hz each, 1H, H-4), 2.98 (dd, J = 13.6, 7.7 Hz, 1H, H-6_b), 2.31 (s, 3H, COCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.2 (*C*OCH$_3$), 138.6–127.5 (Ar-C), 97.8 (C-1), 81.7, 80.5, 80.0, 75.6, 75.0, 73.2, 69.4, 55.1, 30.8, 30.4; ESI-MS: m/z = 545.3 $[M + Na]^+$; $[\alpha]_D^{25}$ + 30.3 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{30}H_{34}O_6S$ (522.21): C, 68.94; H, 6.56. Found: C, 68.75; H, 6.80.

*6.1.2.2. Methyl 6-S-acetyl-2,3,4-tri-O-benzyl-6-deoxy-α-D-galactopyranoside (**4b**).* Yellowish oil (1.1 g, 82%). R_f: 0.6 (hexane–EtOAc, 3:1); IR (neat): 3021, 2357, 1678, 1595, 1425, 1216, 1043, 764, 672 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.22 (m, 15H, Ar-H), 4.99 (d, J = 11.3 Hz, 1H, PhCH_2), 4.86 (d, J = 11.8 Hz, 1H, PhCH_2), 4.80



Scheme 2. Reagents: (a) Solid NaOH, DMF, r. t. (86% for **5a**, 85% for **5b**, 88% for **5c**, 86% for **5d**, 83% for **5e**, 86% for **5f**, 88% for **5g** and 84% for **5h**); (b) *m*-CPBA, CH_2Cl_2, 0 °C–r. t. (83% for **6a**, 80% for **6b**, 84% for **6c**, 79% for **6d**, 80% for **6e**, 83% for **6f**, 80% for **6g** and 76% for **6h**); (c) 20% $Pd(OH)_2$/C, CH_3OH-EtOAc (3:1), r. t. (78% for **7a**, 75% for **7b**, 80% for **7c**, 76% for **7d**, 75% for **7e**, 76% for **7f**, 78% for **7g** and 73% for **7h**).

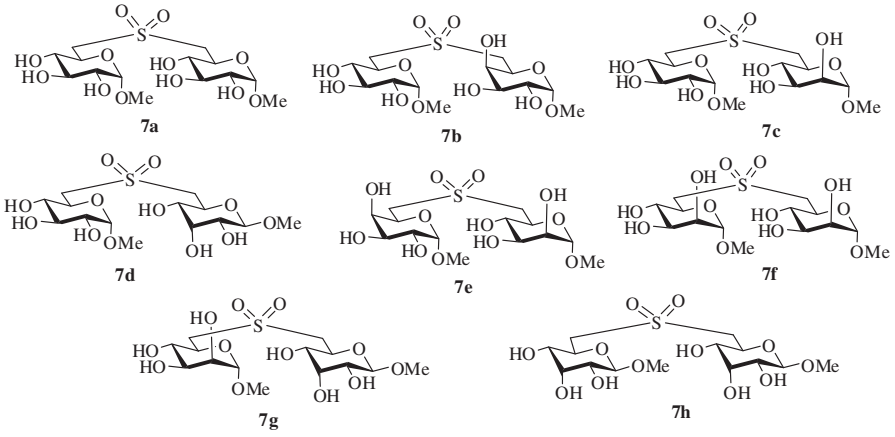


Fig. 3. Synthesized (6,6′)-sulfonyl linked pseudodisaccharides (**7a**–**h**).

(d, J = 12.0 Hz, 1H, PhCH_2), 4.73 (d, J = 11.8 Hz, 1H, PhCH_2), 4.66 (d, J = 12.1 Hz, 1H, PhCH_2), 4.62–4.57 (m, 2H, H-1, PhCH_2), 3.99 (dd, J = 9.9, 3.5 Hz, 1H, H-2), 3.89 (dd, J = 10.0, 2.7 Hz, 1H, H-3), 3.87–3.85 (m, 1H, H-4), 3.64 (t, J = 6.6 Hz, 1H, H-5), 3.35 (s, 3H, OCH_3), 3.06–2.94 (m, 2H, H-6_{ab}), 2.30 (s, 3H, COCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.8 (*C*OCH$_3$), 138.7–127.4 (Ar-C), 98.7 (C-1), 79.1, 77.2, 76.3, 76.1, 74.8, 73.5, 69.7, 55.2, 30.4, 29.9; ESI-MS: m/z = 545.2 [M + Na]$^+$; $[\alpha]_D^{25}$ + 23.4 (*c* 1.0, $CHCl_3$); Anal. Calcd. for $C_{30}H_{34}O_6S$ (522.21): C, 68.94; H, 6.56. Found: C, 68.78; H, 6.70.

*6.1.2.3. Methyl 6-S-acetyl-2,3,4-tri-O-benzyl-6-deoxy-α-D-mannopyranoside (**4c**).* Yellowish oil (1.2 g, 86%). R_f: 0.6 (hexane–EtOAc, 2:1); IR (neat): 3028, 2352, 1676, 1595, 1425, 1216, 1045, 764, 675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86–7.22 (m, 15H, Ar-H), 4.93 (d, J = 10.8 Hz, 1H, PhCH_2), 4.74 (d, J = 12.4 Hz, 1H, PhCH_2), 4.69 (d, J = 12.4 Hz, 1H, PhCH_2), 4.66 (br s, 1H, H-1), 4.65 (d, J = 10.9 Hz, 1H, PhCH_2), 4.60 (br s, 2H, PhCH_2), 3.85 (dd, J = 9.1, 3.0 Hz, 1H, H-3), 3.79–3.75 (m, 2H, H-2 and H-4), 3.68 (ddd, J = 10.9, 8.2, 2.7 Hz, 1H, H-5), 3.57 (dd, J = 13.5, 2.8 Hz, 1H, H-6_a), 3.28 (s, 3H, OCH_3), 3.07 (dd, J = 13.5, 8.1 Hz, 1H, H-6_b), 2.33 (s, 3H, COCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.1 (*C*OCH$_3$), 138.3–127.5 (Ar-C), 98.9 (C-1), 80.0, 77.5, 75.2, 74.6, 72.7, 72.1, 70.8, 54.7, 31.2, 30.4; ESI-MS: m/z = 545.3 [M + Na]$^+$; $[\alpha]_D^{25}$ + 36.9 (*c* 1.0, $CHCl_3$); Anal. Calcd. for $C_{30}H_{34}O_6S$ (522.21): C, 68.94; H, 6.56. Found: C, 68.75; H, 6.82.

*6.1.2.4. Methyl 6-S-acetyl-2,3,4-tri-O-benzyl-6-deoxy-β-D-allopyranoside (**4d**).* Yellowish oil (1.15 g, 85%). R_f: 0.6 (hexane–EtOAc, 3:1); IR (neat): 3273, 2925, 2360, 1651, 1218, 1088, 769, 674 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.22 (m, 15H, Ar-H), 4.83 (d, J = 10.6 Hz, 1H, PhCH_2), 4.82 (d, J = 12.1 Hz, 1H, PhCH_2), 4.75 (d, J = 11.4 Hz, 1H, PhCH_2), 4.74 (d, J = 8.0 Hz, 1H, H-1), 4.58 (d, J = 12.2 Hz, 1H, PhCH_2), 4.48 (d, J = 11.5 Hz, 1H, PhCH_2), 4.33 (d, J = 11.5 Hz, 1H, PhCH_2), 4.06–3.96 (m, 2H, H-3 and H-5), 3.51 (s, 3H, OCH_3), 3.53–3.46 (m, 1H, H-6_a), 3.17–3.12 (m, 2H, H-2 and H-4), 2.98 (dd, J = 13.6, 7.7 Hz, 1H, H-6_b), 2.34 (s, 3H, COCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.5 (*C*OCH$_3$), 138.8–127.4 (Ar-C), 101.8 (C-1), 79.0, 78.3, 74.5, 74.3, 73.0, 71.4, 71.2, 56.6, 31.1, 30.5; ESI-MS: m/z = 545.2 [M + Na]$^+$; $[\alpha]_D^{25}$ + 32.6 (*c* 1.0, $CHCl_3$); Anal. Calcd. for $C_{30}H_{34}O_6S$ (522.21): C, 68.94; H, 6.56. Found: C, 68.72; H, 6.78.

*6.1.3. General experimental procedure for the preparation of (methyl 2,3,4-tri-O-benzyl-6-deoxy-α/β-D-glycopyranosid-6-yl)-(methyl 2,3,4-tri-O-benzyl-6-deoxy-α/β-D-glycopyranosid-6-yl) sulfide (**5a**-**h**)*

To a solution of compound **3a**–**d** (300 mg, 0.52 mmol) and compound **4a**–**d** (275 mg, 0.52 mmol) in dry DMF (6 mL) was added crushed NaOH (125 mg, 3.1 mmol) and the resulting reaction mixture was then stirred at room temperature for 3 h. The reaction mixture was then concentrated under reduced pressure, diluted with saturated aq. NH_4Cl solution (8 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure and the crude product was purified over SiO_2 using hexane–EtOAc (5:1) as eluant to give pure product as colorless oil.

*6.1.3.1. Bis-(methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranosid-6-yl) sulfide (**5a**).* Yellowish oil (420 mg, 86%). R_f: 0.5 (hexane–EtOAc, 2:1); IR (neat): 3020, 2359, 1595, 1216, 1052, 761, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30–7.22 (m, 15H, Ar-H), 4.94 (d, J = 10.9 Hz, 1H, PhCH_2), 4.86 (d, J = 11.1 Hz, 1H, PhCH_2), 4.77

Table 1
Effects of pseudosacchrides (**7a**–**h**) on Mg^{2+} independent Ca^{2+}-ATPase in absence and presence of different calcium blockers.

Concentration of compounds	Control	Compound No.							
		7a	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	**7h**
Thapsigargin (TG) (25 nM)	−50	NA	NA	NA	NA	NA	NA	NA	NA
Compounds (20 μg)	NA	+36	+32	+43	+30	+53	+49	+45	+30
TG (25 mM) + Compound (20 μg)	NA	−28	−38	−35	−31	−36	−29	−27	−33
Verapamil (300 μM)	−25	NA	NA	NA	NA	NA	NA	NA	NA
Verapamil (300 μM) + Compound (20 μg)	NA	−14	−5	−3	−9	−21	−2	−5	−8
Orthovanadate (1 mM)	−30	NA	NA	NA	NA	NA	NA	NA	NA
Orthovanadate (1 mM) + Compound (20 μg)	NA	−24	−8	+4	−17	−25	−27	−19	−21

Enzyme activity: percent stimulation (+) or inhibition (−). NA: Not applicable. Enzyme activity was measured either in the presence of a fixed concentration of any calcium blocker, or in the presence of a fixed concentration of a pseudosaccharide alone or in combination of any of specific calcium blocker and pseudodisaccharide. The results shown are the average of four separate assays.

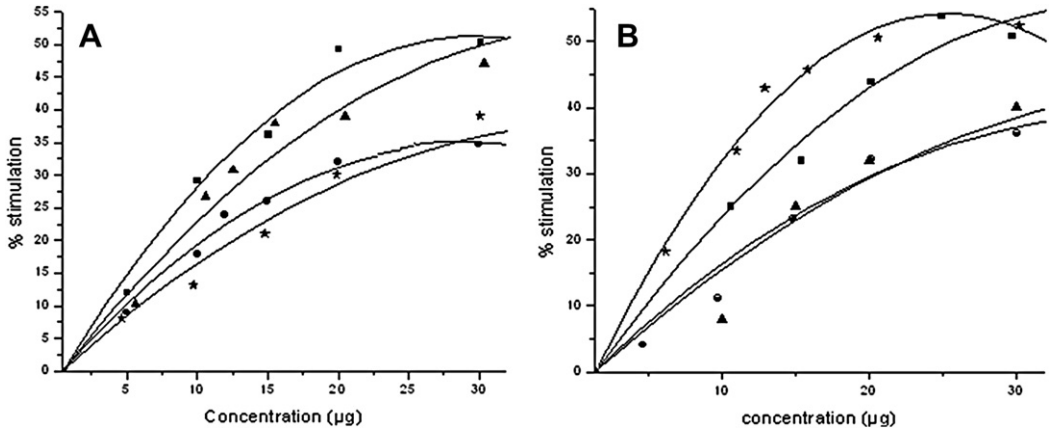


Fig. 4. Effect of different concentrations of pseudosaccharides on Mg^{2+} independent Ca^{2+}-ATPase. Activity was assayed in presence of varying concentrations of each of the compound as described in methods. In plot A: ■: compound **7a**;*: compound **7b**; ●: compound **7c** and ▲: compound **7d**. In plot B: ■: compound **7e**; *: compound **7f**; ●: compound **7g** and ▲: compound **7h**.

(d, J = 10.9 Hz, 1H, PhCH_2), 4.71 (d, J = 12.1 Hz, 1H, PhCH_2), 4.59 (d, J = 12.1 Hz, 1H, PhCH_2), 4.58 (d, J = 11.2 Hz, 1H, PhCH_2), 4.49 (d, J = 3.5 Hz, 1H, H-1), 3.91 (t, J = 9.2 Hz each, 1H, H-3), 3.73 (ddd, J = 9.6, 7.9, 1.7 Hz, 1H, H-5), 3.44 (dd, J = 9.6, 3.5 Hz, 1H, H-2), 3.35 (dd, J = 8.4, 3.5 Hz, 1H, H-4), 3.34 (s, 3H, OCH_3), 2.90 (dd, J = 13.6, 2.2 Hz, 1H, H-6_a), 2.60 (dd, J = 13.6, 7.7 Hz, 1H, H-6_b); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.7–127.4 (Ar-C), 97.6 (C-1), 81.8, 80.4, 80.1, 75.5, 74.8, 73.0, 71.0, 54.9, 34.9; The proton integration in the ^{1}H NMR and carbon signals in the ^{13}C NMR spectra appeared as monomer because of the symmetric nature of the molecule; ESI-MS: m/z = 949.6 $[M + Na]^+$; $[\alpha]_D^{25}$ + 43.4 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{10}S$ (926.41): C, 72.54; H, 6.74. Found: C, 72.35; H, 6.90.

*6.1.3.2. (Methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranosid-6-yl)-(methyl 2′,3′,4′-tri-O-benzyl-6-deoxy-α-D-galactopyranosid-6-yl) sulfide (**5b**).* Yellowish oil (415 mg, 85%). R_f: 0.4 (hexane–EtOAc, 3:1); IR (neat): 3020, 2926, 2360, 1594, 1216, 1049, 760, 671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.19 (m, 30H, Ar-H), 4.96 (d, J = 11.4 Hz, 1H, PhCH_2), 4.95 (d, J = 10.9 Hz, 1H, PhCH_2), 4.86 (d, J = 11.2 Hz, 1H, PhCH_2), 4.84 (d, J = 11.8 Hz, 1H, PhCH_2), 4.79 (d, J = 12.1 Hz, 1H, PhCH_2), 4.77 (d, J = 10.9 Hz, 1H, PhCH_2), 4.74 (d, J = 12.1 Hz, 1H, PhCH_2), 4.71 (d, J = 11.8 Hz, 1H, PhCH_2), 4.65 (d, J = 11.9 Hz, 1H, PhCH_2), 4.62 (d, J = 12.0 Hz, 1H, PhCH_2), 4.59 (d, J = 2.8 Hz, 1H, H-1′), 4.57 (d, J = 11.2 Hz, 1H, PhCH_2), 4.55 (d, J = 11.2 Hz, 1H, PhCH_2), 4.51 (d, J = 3.5 Hz, 1H, H-1), 4.00–3.85 (m, 4H, H-3, H-2′, H-3′ and H-4′), 3.74–3.68 (m, 2H, H-5 and H-5′), 3.45 (dd, J = 9.6, 3.5 Hz, 1H, H-2), 3.38–3.28 (m, 1H, H-4), 3.34 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 2.84 (dd, J = 13.4, 2.1 Hz, 1H, H-6_a), 2.73 (dd, J = 13.5, 7.3 Hz, 1H, H-6_a′), 2.61–2.44 (m, 2H, H-6_b and H-6_b′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8–127.5 (Ar-C), 98.7 (C-1′), 97.8 (C-1), 81.9, 80.5, 80.2, 79.3, 76.4, 76.0, 75.7, 75.0, 74.8, 73.5, 73.4, 73.3, 71.1, 70.9, 55.2, 55.1, 34.9, 33.9; ESI-MS: m/z = 949.6 $[M + Na]^+$; $[\alpha]_D^{25}$ + 23.3 (c 1.2, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{10}S$ (926.41): C, 72.54; H, 6.74. Found: C, 72.32; H, 7.0.

*6.1.3.3. (Methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranosid-6-yl)-(methyl 2′,3′,4′-tri-O-benzyl-6-deoxy-α-D-mannopyranosid-6-yl) sulfide (**5c**).* Yellowish oil (430 mg, 88%). R_f: 0.5 (hexane–EtOAc, 2:1); IR (neat): 3020, 2361, 1593, 1216, 1052, 761, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.23 (m, 30H, Ar-H), 4.94 (d, J = 10.9 Hz, 1H, PhCH_2), 4.91 (d, J = 11.1 Hz, 1H, PhCH_2), 4.84 (d, J = 11.2 Hz, 1H, PhCH_2), 4.77 (d, J = 11.0 Hz, 1H, PhCH_2), 4.72 (d, J = 12.1 Hz, 1H, PhCH_2), 4.67 (d, J = 3.7 Hz, 1H, H-1′), 4.63–4.56 (m, 7H, PhCH_2), 4.51 (d, J = 3.4 Hz, 1H, H-1), 3.92 (t, J = 9.1 Hz each, 1H, H-3), 3.82–3.62 (m, 5H, H-5, H-2′, H-3′, H-4′ and H-5′), 3.46 (dd, J = 9.6, 3.5 Hz, 1H, H-2), 3.34 (s, 3H, OCH_3), 3.32–3.29 (m, 1H, H-4), 3.27 (s, 3H, OCH_3), 3.02–2.95 (m, 2H, H-6_{ab}′), 2.73–2.59 (m, 2H, H-6_{ab}); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8–127.5 (Ar-C), 98.8 (C-1′), 97.7 (C-1), 81.9, 80.7, 80.3, 80.2, 77.6, 75.6, 75.0, 74.9, 74.7, 73.2, 72.8, 72.7, 72.1, 71.0, 55.0, 54.6, 35.0, 34.9; ESI-MS: m/z = 949.5 $[M + Na]^+$; $[\alpha]_D^{25}$ + 38.7 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{10}S$ (926.41): C, 72.54; H, 6.74. Found: C, 72.36; H, 6.98.

*6.1.3.4. (Methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranosid-6-yl)-(methyl 2′,3′,4′-tri-O-benzyl-6-deoxy-β-D-allopyranosid-6-yl) sulfide (**5d**).* Yellowish oil (420 mg, 86%). R_f: 0.7 (hexane–EtOAc, 1:1); IR (neat): 3019, 2359, 1596, 1215, 1080, 760, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.19 (m, 30H, Ar-H), 4.93 (d, J = 10.9 Hz, 1H, PhCH_2), 4.87–4.70 (m, 7H, H-1′ and PhCH_2), 4.63–4.52 (m, 4H, H-1 and PhCH_2), 4.46 (d, J = 11.5 Hz, 1H, PhCH_2), 4.32 (d, J = 11.5 Hz, 1H, PhCH_2), 4.08–4.03 (m, 2H, H-3′ and H-5′), 3.91 (t, J = 9.1 Hz each, 1H, H-3), 3.78–3.74 (m, 1H, H-5), 3.49–3.44 (m, 1H, H-2), 3.45 (s, 3H, OCH_3), 3.39–3.33 (m, 1H, H-4), 3.36 (s, 3H, OCH_3), 3.28 (dd, J = 9.4, 2.2 Hz, 1H, H-4′), 3.14 (dd, J = 7.9, 2.4 Hz, 1H, H-2′), 3.02–2.94 (m, 2H, H-6_a and H-6_a′), 2.79–2.64 (m, 2H, H-6_b and H-6_b′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.9–127.3 (Ar-C), 101.9 (C-1′), 97.8 (C-1), 82.0, 80.4, 80.2, 79.2, 78.1, 77.2, 75.6, 74.9, 74.5, 74.4, 73.2, 73.0, 71.3, 70.9, 56.6, 55.0, 35.4, 35.1; ESI-MS: m/z = 949.4 $[M + Na]^+$; $[\alpha]_D^{25}$ + 46.5 (c 1.2, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{10}S$ (926.41): C, 72.54; H, 6.74. Found: C, 72.35; H, 6.95.

*6.1.3.5. (Methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-galactopyranosid-6-yl)-(methyl 2′,3′,4′-tri-O-benzyl-6-deoxy-α-D-mannopyranosid-6-yl) sulfide (**5e**).* Yellowish oil (405 mg, 83%). R_f: 0.5 (hexane–EtOAc, 4:1); IR (neat): 3020, 2359, 1596, 1216, 760, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31–7.19 (m, 30H, Ar-H), 4.93–4.56 (m, 14H, H-1, H-1′ and PhCH_2), 4.02–3.60 (m, 8H, H-2, H-3, H-4, H-5, H-2′, H-3′, H-4′ and H-5′), 3.35 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3), 2.95–2.64 (m, 4H, H-6_{ab} and H-6_{ab}′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8–127.3 (Ar-C), 98.8 (C-1′), 98.6 (C-1), 80.1, 79.2, 77.5, 76.4, 75.9, 75.0, 74.8, 74.6, 73.3, 73.2, 72.7, 72.6, 71.9, 70.5, 55.1, 54.6, 34.9, 33.6; ESI-MS: m/z = 949.6 $[M + Na]^+$; $[\alpha]_D^{25}$ + 31.8 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{10}S$ (926.41): C, 72.54; H, 6.74. Found: C, 72.32; H, 7.0.

*6.1.3.6. Bis (methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-mannopyranosid-6-yl) sulfide (**5f**).* Yellowish oil (420 mg, 86%). R_f: 0.6 (hexane–EtOAc, 3:1); IR (neat): 3020, 2360, 1522, 1216, 762, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.20 (m, 15H, Ar-H), 4.90 (d, J = 11.2 Hz, 1H, PhCH_2), 4.71–4.56 (m, 6H, H-1, PhCH_2), 3.82–3.63 (m, 4H, H-2, H-3, H-4 and H-5), 3.27 (s, 3H, OCH_3), 3.06

(dd, $J = 13.6, 1.6$ Hz, 1H, H-6_a), 2.72 (dd, $J = 13.5, 8.6$ Hz, 1H, H-6_b); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.7–127.4 (Ar-C), 98.8 (C-1), 80.3, 77.8, 75.0, 74.8, 72.8, 72.7, 72.1, 54.6, 34.9; The proton integration in the ^{1}H NMR and carbon signals in the ^{13}C NMR spectra appeared as monomer because of the symmetric nature of the molecule; ESI-MS: m/z = 949.4 $[M + Na]^+$; $[\alpha]_D^{25}$ + 42.6 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{10}S$ (926.41): C, 72.54; H, 6.74. Found: C, 72.35; H, 6.98.

*6.1.3.7. (Methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-mannopyranosid-6-yl)-(methyl 2′,3′,4′-tri-O-benzyl-6-deoxy-β-D-allopyranosid-6-yl) sulfide (**5g**).* Yellowish oil (430 mg, 88%). R_f: 0.6 (hexane–EtOAc, 3:2); IR (neat): 3020, 2363, 1594, 1216, 761, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.21 (m, 30H, Ar-H), 4.90 (d, J = 11.1 Hz, 1H, PhCH_2), 4.84 (d, J = 11.8 Hz, 1H, PhCH_2), 4.82 (d, J = 12.2 Hz, 1H, PhCH_2), 4.76–4.55 (m, 9H, H-1, H-1′ and PhCH_2), 4.46 (d, J = 11.5 Hz, 1H, PhCH_2), 4.34 (d, J = 11.5 Hz, 1H, PhCH_2), 4.10–4.04 (m, 2H, H-3′ and H-5′), 3.80–3.66 (m, 4H, H-2, H-3, H-4 and H-5), 3.44 (s, 3H, OCH_3), 3.32–3.28 (m, 1H, H-4′), 3.29 (s, 3H, OCH_3), 3.16 (dd, J = 7.9, 2.5 Hz, 1H, H-2′), 3.11–3.00 (m, 2H, H-6_a and H-6_a′), 2.85–2.69 (m, 2H, H-6_b and H-6_b′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.0–127.3 (Ar-C), 101.9 (C-1′), 98.8 (C-1), 80.3, 79.2, 78.2, 77.6, 75.0, 74.8, 74.6, 74.4, 73.1, 73.0, 72.7, 72.6, 72.1, 71.4, 56.5, 54.6, 35.5, 35.1; ESI-MS: m/z = 949.5 $[M + Na]^+$; $[\alpha]_D^{25}$ + 35.6 (c 1.2, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{10}S$ (926.41): C, 72.54; H, 6.74. Found: C, 72.36; H, 7.0.

*6.1.3.8. Bis (methyl 2,3,4-tri-O-benzyl-6-deoxy-β-D-allopyranosid-6-yl) sulfide (**5h**).* Yellowish oil (410 mg, 84%). R_f: 0.6 (hexane–EtOAc, 2:1); IR (neat): 3021, 2359, 1594, 1216, 1039, 761, 671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.24 (m, 15H, Ar-H), 4.88–4.73 (m, 4H, H-1 and PhCH_2), 4.59 (d, J = 12.2 Hz, 1H, PhCH_2), 4.48 (d, J = 11.6 Hz, 1H, PhCH_2), 4.36 (d, J = 11.6 Hz, 1H, PhCH_2), 4.11–4.06 (m, 2H, H-3 and H-2), 3.48 (s, 3H, OCH_3), 3.30 (dd, J = 9.5, 2.2 Hz, 1H, H-4), 3.20 (dd, J = 9.8, 7.3 Hz, 1H, H-5), 3.09 (dd, J = 13.9, 2.5 Hz, 1H, H-6_a), 2.77 (dd, J = 13.9, 7.4 Hz, 1H, H-6_b); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.9–127.3 (Ar-C), 101.8 (C-1), 79.1, 78.1, 74.4, 74.3, 73.1, 72.8, 71.3, 56.6, 35.2. The proton integration in the ^{1}H NMR and carbon signals in the ^{13}C NMR spectra appeared as monomer because of the symmetric nature of the molecule; ESI-MS: m/z = 949.4 $[M + Na]^+$; $[\alpha]_D^{25}$ + 21.6 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{10}S$ (926.41): C, 72.54; H, 6.74. Found: C, 72.38; H, 6.98.

*6.1.4. General experimental procedure for the preparation of (methyl 2,3,4-tri-O-benzyl-6-deoxy-α/β-D-glycopyranosid-6-yl)-(methyl 2,3,4-tri-O-benzyl-6-deoxy-α/β-D-glycopyranosid-6-yl) sulfone (**6a**–**h**)*

To a solution of compound **5a**–**h** (350 mg, 0.38 mmol) in dry CH_2Cl_2 (5 mL) was added *m*-CPBA (325 mg, 1.89 mmol) at 0 °C and the reaction mixture was then stirred at room temperature for 2 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and washed with 10% aq. $Na_2S_2O_3$ solution (2 × 8 mL), saturated aq. Na_2CO_3 solution (2 × 8 mL) and brine (2 × 8 mL) respectively. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure and the crude product was purified over SiO_2 using hexane–EtOAc (4:1) as eluant to give pure product as syrup.

*6.1.4.1. Bis (methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranosid-6-yl) sulfone (**6a**).* Yellowish oil (300 mg, 83%). R_f: 0.6 (hexane–EtOAc, 2:1); IR (neat): 2908, 2371, 1631, 1453, 1360, 1313, 1127, 1090, 1037, 739, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31–7.18 (m, 15H, Ar-H), 4.95 (d, J = 10.9 Hz, 1H, PhCH_2), 4.84 (d, J = 11.5 Hz, 1H, PhCH_2), 4.76 (d, J = 10.9 Hz, 1H, PhCH_2), 4.71 (d, J = 12.1 Hz, 1H, PhCH_2), 4.60 (d, J = 12.2 Hz, 1H, PhCH_2), 4.51 (d, J = 11.5 Hz, 1H, PhCH_2), 4.41 (d, J = 3.4 Hz, 1H, H-1), 4.13 (t, J = 9.9 Hz each, 1H, H-5), 3.95 (t, J = 9.1 Hz each, 1H, H-3), 3.42 (dd, J = 9.6, 3.5 Hz, 1H, H-2), 3.33 (s, 3H, OCH_3), 3.26–3.21 (m, 1H, H-6_a), 3.11 (t, J = 9.2 Hz each, 1H, H-4), 2.96–2.87 (m, 1H, H-6_b); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4–127.6 (Ar-C), 97.8 (C-1), 81.6, 79.7, 79.1, 75.6, 74.5, 73.0, 65.9, 56.3, 55.8; The proton integration in the ^{1}H NMR and carbon signals in the ^{13}C NMR spectra appeared as monomer because of the symmetric nature of the molecule; ESI-MS: m/z = 981.5 $[M + Na]^+$; $[\alpha]_D^{25}$ + 76.5 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{12}S$ (958.40): C, 70.12; H, 6.52. Found: C, 70.0; H, 6.78.

*6.1.4.2. (Methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranosid-6-yl)-(methyl 2′,3′,4′-tri-O-benzyl-6-deoxy-α-D-galactopyranosid-6-yl) sulfone (**6b**).* Yellowish oil (290 mg, 80%). R_f: 0.5 (hexane–EtOAc, 3:1); IR (neat): 3020, 2359, 1726, 1594, 1216, 1046, 760, 671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27–7.18 (m, 30H, Ar-H), 4.98 (d, J = 11.4 Hz, 1H, PhCH_2), 4.96 (d, J = 10.8 Hz, 1H, PhCH_2), 4.86 (d, J = 11.7 Hz, 1H, PhCH_2), 4.84 (d, J = 11.5 Hz, 1H, PhCH_2), 4.78 (d, J = 12.3 Hz, 1H, PhCH_2), 4.77 (d, J = 10.4 Hz, 1H, PhCH_2), 4.73 (d, J = 11.9 Hz, 1H, PhCH_2), 4.70 (d, J = 11.6 Hz, 1H, PhCH_2), 4.63 (d, J = 12.1 Hz, 1H, PhCH_2), 4.61 (d, J = 12.2 Hz, 1H, PhCH_2), 4.52–4.45 (m, 4H, H-1, H-1′ and PhCH_2), 4.22–4.10 (m, 2H, H-5 and H-5′), 3.99–3.88 (m, 3H, H-3, H-2′ and H-3′), 3.65–3.56 (m, 2H, H-6_a and H-4′), 3.45 (dd, J = 9.6, 3.5 Hz, 1H, H-2), 3.36 (s, 3H, OCH_3), 3.29–3.20 (m, 4H, H-6_b and OCH_3), 3.12 (t, J = 9.2 Hz each, 1H, H-4), 3.01–2.92 (m, 1H, H-6_a′), 2.55–2.49 (m, 1H, H-6_b′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4–127.6 (Ar-C), 98.8 (C-1′), 98.0 (C-1), 81.8, 79.7, 78.9, 78.6, 76.1, 75.7, 74.7, 74.5, 73.8 (2C), 73.4, 73.2, 66.3, 66.0, 56.8, 56.1, 55.9, 55.7; ESI-MS: m/z = 981.4 $[M + Na]^+$; $[\alpha]_D^{25}$ + 74.5 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{12}S$ (958.40): C, 70.12; H, 6.52. Found: C, 69.95; H, 6.80.

*6.1.4.3. (Methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranosid-6-yl)-(methyl 2′,3′,4′-tri-O-benzyl-6-deoxy-α-D-mannopyranosid-6-yl) sulfone (**6c**).* Yellowish oil (305 mg, 84%). R_f: 0.4 (hexane–EtOAc, 3:1); IR (neat): 3020, 2363, 1666, 1596, 1216, 1071, 760, 671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.20 (m, 30H, Ar-H), 4.97 (d, J = 10.9 Hz, 1H, PhCH_2), 4.92 (d, J = 11.5 Hz, 1H, PhCH_2), 4.87 (d, J = 11.5 Hz, 1H, PhCH_2), 4.78–4.47 (m, 11H, H-1, H-1′ and PhCH_2), 4.18 (t, J = 9.6 Hz each, 1H, H-3), 4.13–4.06 (m, 1H, H-5′), 3.97 (t, J = 9.2 Hz each, 1H, H-3′), 3.84 (dd, J = 9.3, 3.0 Hz, 1H, H-2′), 3.74–3.71 (m, 1H, H-5), 3.62 (t, J = 9.5 Hz each, 1H, H-4′), 3.45 (dd, J = 9.7, 3.5 Hz, 1H, H-2), 3.39–3.28 (m, 5H, H-4, H-6_a and OCH_3), 3.24–3.10 (m, 5H, H-6_b, H-6_a′ and OCH_3), 3.05–2.96 (m, 1H, H-6_b′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5–127.6 (Ar-C), 99.0 (C-1′), 97.8 (C-1), 81.7, 80.1, 79.8, 79.4, 75.9, 75.7, 74.8, 74.6 (2C), 73.1, 73.0, 72.1, 67.3, 65.7, 56.6, 56.5, 55.8, 55.3; ESI-MS: m/z = 981.5 $[M + Na]^+$; $[\alpha]_D^{25}$ + 86.6 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{12}S$ (958.40): C, 70.12; H, 6.52. Found: C, 69.96; H, 6.75.

*6.1.4.4. (Methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranosid-6-yl)-(methyl 2′,3′,4′-tri-O-benzyl-6-deoxy-β-D-allopyranosid-6-yl) sulfone (**6d**).* Yellowish oil (285 mg, 79%). R_f: 0.6 (hexane–EtOAc, 2:1); IR (neat): 3021, 2360, 1727, 1589, 1216, 1080, 761, 671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.15 (m, 30H, Ar-H), 4.95 (d, J = 10.8 Hz, 1H, PhCH_2), 4.88–4.70 (m, 7H, PhCH_2), 4.63–4.39 (m, 6H, H-1, H-1′ and PhCH_2), 4.22–4.14 (m, 2H, H-3′ and H-5′), 4.07–4.06 (m, 1H, H-5), 3.97 (t, J = 9.1 Hz each, 1H, H-3), 3.44 (dd, J = 9.6, 3.5 Hz, 1H, H-2), 3.42–3.39 (m, 1H, H-4), 3.29–3.24 (m, 1H, H-6_a), 3.17–3.06 (m, 5H, H-6_b, H-2′, H-4′ and H-6_{ab}′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5–127.5 (Ar-C), 102.1 (C-1′), 97.9 (C-1), 81.7, 79.8, 79.3, 78.6, 77.3, 75.7, 74.5 (2C), 73.6, 73.2, 73.0, 70.8, 68.3, 66.1, 57.2, 56.8, 56.5, 55.8; ESI-MS: m/z = 981.6 $[M + Na]^+$; $[\alpha]_D^{25}$ + 44.3 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{12}S$ (958.40): C, 70.12; H, 6.52. Found: C, 69.95; H, 6.80.

6.1.4.5. (Methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-galactopyranosid-6-yl)-(methyl 2′,3′,4′-tri-O-benzyl-6-deoxy-α-D-mannopyranosid-6-yl)

*sulfone (**6e**).* Yellowish oil (290 mg, 80%). R_f: 0.5 (hexane–EtOAc, 2:1); IR (neat): 3023, 2365, 1668, 1596, 1216, 1073, 760, 675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.21 (m, 30H, Ar-H), 5.01 (d, J = 11.4 Hz, 1H, PhCH_2), 4.94 (d, J = 11.3 Hz, 1H, PhCH_2), 4.87 (d, J = 11.8 Hz, 1H, PhCH_2), 4.77 (d, J = 12.1 Hz, 1H, PhCH_2), 4.72 (d, J = 11.8 Hz, 1H, PhCH_2), 4.67–4.51 (m, 9H, H-1, H-1′ and PhCH_2), 4.32–4.24 (m, 1H, H-5′), 4.18–4.10 (m, 1H, H-3), 3.96 (br s, 2H, H-2 and H-4), 3.87 (dd, J = 9.2, 3.0 Hz, 1H, H-3′), 3.77–3.58 (m, 4H, H-5, H-2′, H-4′ and H-6_a′), 3.45–3.38 (m, 1H, H-6_a), 3.28–3.20 (m, 7H, H-6_b′ and 2 OCH_3), 2.78–2.72 (m, 1H, H-6_b); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4–127.5 (Ar-C), 98.9 (C-1′), 98.6 (C-1), 79.9, 78.5, 77.0, 75.9, 75.8, 74.8, 74.7, 74.4, 73.6, 73.3, 72.8, 71.9, 67.0, 65.9, 56.7, 56.2, 55.7, 55.1; ESI-MS: m/z = 981.4 $[M + Na]^+$; $[\alpha]_D^{25}$ + 62.5 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{12}S$ (958.40): C, 70.12; H, 6.52. Found: C, 69.92; H, 6.75.

*6.1.4.6. Bis (methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-mannopyranosid-6-yl) sulfone (**6f**).* Yellowish oil (300 mg, 83%). R_f: 0.7 (hexane–EtOAc, 1:1); IR (neat): 3021, 2923, 2361, 1664, 1596, 1216, 1124, 1067, 761, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.20 (m, 15H, Ar-H), 4.94 (d, J = 11.4 Hz, 1H, PhCH_2), 4.65 (br s, 2H, PhCH_2), 4.57–4.53 (m, 4H, H-1 and PhCH_2), 4.14 (t, J = 9.8 Hz each, 1H, H-5), 3.85 (dd, J = 9.3, 3.0 Hz, 1H, H-3), 3.74–3.72 (m, 1H, H-2), 3.65 (t, J = 9.5 Hz each, 1H, H-4), 3.46–3.41 (m, 1H, H-6_a), 3.29–3.21 (m, 4H, H-6_b and OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.1–127.6 (Ar-C), 98.8 (C-1), 80.1, 76.1, 74.8, 74.6, 72.8, 72.0, 67.1, 56.6, 55.3; The proton integration in the ^1H NMR and carbon signals in the ^{13}C NMR spectra appeared as monomer because of the symmetric nature of the molecule; ESI-MS: m/z = 981.5 $[M + Na]^+$; $[\alpha]_D^{25}$ + 64.9 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{12}S$ (958.40): C, 70.12; H, 6.52. Found: C, 70.0; H, 6.80.

*6.1.4.7. (Methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-mannopyranosid-6-yl)-(methyl 2′,3′,4′-tri-O-benzyl-6-deoxy-β-D-allopyranosid-6-yl) sulfone (**6g**).* Yellowish oil (290 mg, 80%). R_f: 0.6 (hexane–EtOAc, 2:1); IR (neat): 3025, 2363, 1726, 1596, 1216, 1045, 760, 675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.18 (m, 30H, Ar-H), 4.94–4.43 (m, 14H, H-1, H-5, H-1′ and PhCH_2), 4.23 (d, J = 11.6 Hz, 1H, PhCH_2), 4.18–4.10 (m, 2H, H-3′ and H-5′), 3.88 (dd, J = 9.2, 3.0 Hz, 1H, H-3), 3.77–3.75 (m, 1H, H-2), 3.64 (t, J = 9.5 Hz each, 1H, H-4), 3.60–3.55 (m, 1H, H-6_a), 3.42 (s, 3H, OCH_3), 3.37–3.34 (m, 2H, H-2′ and H-6_a′), 3.26–3.13 (m, 6H, H-6_b, H-4′, H-6_b′ and OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.6–127.4 (Ar-C), 101.8 (C-1′), 98.7 (C-1), 80.0, 78.5, 75.9, 74.6, 74.5, 74.4, 73.7, 72.9 (3C), 72.0, 70.8, 67.9, 67.4, 56.8 (2C), 56.5, 55.2; ESI-MS: m/z = 981.5 $[M + Na]^+$; $[\alpha]_D^{25}$ + 34.3 (c 1.2, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{12}S$ (958.40): C, 70.12; H, 6.52. Found: C, 69.95; H, 6.82.

*6.1.4.8. Bis (methyl 2,3,4-tri-O-benzyl-6-deoxy-β-D-allopyranosid-6-yl) sulfone (**6h**).* Yellowish oil (275 mg, 76%). R_f: 0.5 (hexane–EtOAc, 2:1); IR (neat): 3023, 2357, 1726, 1594, 1216, 1046, 765, 674 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.16 (m, 15H, Ar-H), 4.86 (d, J = 11.6 Hz, 1H, PhCH_2), 4.82 (d, J = 10.7 Hz, 1H, PhCH_2), 4.80 (d, J = 7.9 Hz, 1H, H-1), 4.75 (d, J = 11.9 Hz, 1H, PhCH_2), 4.59 (d, J = 12.2 Hz, 1H, PhCH_2), 4.53–4.44 (m, 2H, H-5 and PhCH_2), 4.21 (d, J = 11.8 Hz, 1H, PhCH_2), 4.09–4.08 (m, 1H, H-3), 3.48–3.43 (m, 1H, H-6_a), 3.37 (s, 3H, OCH_3), 3.34–3.25 (m, 1H, H-6_b), 3.17 (dd, J = 7.9, 2.4 Hz, 1H, H-2), 3.12 (dd, J = 9.6, 2.1 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5–127.4 (Ar-C), 102.0 (C-1), 78.6, 77.2, 74.4, 73.4, 73.0, 70.6, 68.3, 57.1, 56.8; The proton integration in the ^1H NMR and carbon signals in the ^{13}C NMR spectra appeared as monomer because of the symmetric nature of the molecule; ESI-MS: m/z = 981.4 $[M + Na]^+$; $[\alpha]_D^{25}$ + 38 (c 1.0, $CHCl_3$); Anal. Calcd. for $C_{56}H_{62}O_{12}S$ (958.40): C, 70.12; H, 6.52. Found: C, 69.90; H, 6.75.

*6.1.5. General experimental procedure for the preparation of (methyl 6-deoxy-α/β-D-glycopyranosid-6-yl)-(methyl 6-deoxy-α/β-D-glycopyranosid-6-yl) sulfone (**7a**–**h**)*

To the solution of compound **6a**–**h** (200 mg, 0.21 mmol) in methanol and ethyl acetate (3:1, 12 mL) was added 20% $Pd(OH)_2/C$ (50 mg) and the reaction mixture was allowed to stir at room temperature under a positive pressure of hydrogen for 24 h. The reaction mixture was filtered through a Celite® bed and evaporated to dryness to give compound **7a**–**h** as a white powder, which was further purified by passing through a column of Sephadex-LH-20 using CH_3OH as eluant.

*6.1.5.1. Bis(methyl 6-deoxy-α-D-glucopyranosid-6-yl) sulfone (**7a**).* Glass (85 mg, 78%). R_f: 0.4 (CH_2Cl_2–CH_3OH, 6:1); ^1H NMR (D_2O, 300 MHz): δ 4.86 (d, J = 3.6 Hz, 1H), 4.19 (t, J = 9.2 Hz each, 1H), 3.86–3.68 (m, 3H), 3.64 (dd, J = 9.7, 3.5 Hz, 1H), 3.50 (s, 3H), 3.36 (t, J = 9.2 Hz each, 1H); ^{13}C NMR (D_2O, 75 MHz): δ 99.4, 72.7, 71.9, 70.9, 66.4, 55.7, 55.6; The proton integration in the ^1H NMR and carbon signals in the ^{13}C NMR spectra appeared as monomer because of the symmetric nature of the molecule; ESI-MS: m/z = 441.3 $[M + Na]^+$; $[\alpha]_D^{25}$ + 111.4 (c 1.0, H_2O); Anal. Calcd. for $C_{14}H_{26}O_{12}S$ (418.11): C, 40.19; H, 6.26. Found: C, 40.0; H, 6.50.

*6.1.5.2. (Methyl 6-deoxy-α-D-glucopyranosid-6-yl)-(methyl 6′-deoxy-α-D-galactopyranosid-6-yl) sulfone (**7b**).* Glass (82 mg, 75%). R_f: 0.5 (CH_2Cl_2–CH_3OH, 6:1); ^1H NMR (D_2O, 300 MHz): δ 4.83–4.81 (m, 2H), 4.42 (d, J = 9.8 Hz, 1H), 4.13 (t, J = 9.5 Hz each, 1H), 3.91–3.76 (m, 5H), 3.70–3.55 (m, 4H), 3.46–3.41 (m, 7H); ^{13}C NMR (D_2O, 75 MHz): δ 99.7, 99.3, 72.7, 71.9, 70.9, 70.7, 69.1, 67.6, 66.3, 65.6, 55.7 (2C), 55.6, 55.5; ESI-MS: m/z = 441.3 $[M + Na]^+$; $[\alpha]_D^{25}$ + 148.3 (c 1.0, H_2O); Anal. Calcd. for $C_{14}H_{26}O_{12}S$ (418.11): C, 40.19; H, 6.26. Found: C, 39.95; H, 6.45.

*6.1.5.3. (Methyl 6-deoxy-α-D-glucopyranosid-6-yl)-(methyl 6′-deoxy-α-D-mannopyranosid-6-yl) sulfone (**7c**).* Glass (87 mg, 80%). R_f: 0.4 (CH_2Cl_2–CH_3OH, 6:1); ^1H NMR (D_2O, 300 MHz): δ 4.82–4.80 (m, 2H), 4.18–4.07 (m, 2H), 3.97–3.95 (m, 1H), 3.84–3.75 (m, 3H), 3.71–3.53 (m, 5H), 3.46 (s, 3H), 3.44 (s, 3H), 3.35–3.32 (m, 1H); ^{13}C NMR (D_2O, 75 MHz): δ 101.0, 99.4, 72.8, 71.9, 71.0, 70.2, 69.7, 68.7, 67.2, 66.4, 55.8 (2C), 55.6, 55.3; ESI-MS: m/z = 441.2 $[M + Na]^+$; $[\alpha]_D^{25}$ + 90.0 (c 1.0, H_2O); Anal. Calcd. for $C_{14}H_{26}O_{12}S$ (418.11): C, 40.19; H, 6.26. Found: C, 40.0; H, 6.48.

*6.1.5.4. (Methyl 6-deoxy-α-D-glucopyranosid-6-yl)-(methyl 6′-deoxy-β-D-allopyranosid-6-yl) sulfone (**7d**).* Glass (83 mg, 76%). R_f: 0.4 (CH_2Cl_2–CH_3OH, 5:1); ^1H NMR (D_2O, 300 MHz): δ 4.82–4.80 (m, 1H), 4.65 (d, J = 8.2 Hz, 1H), 4.26–4.15 (m, 3H), 3.79–3.55 (m, 7H), 3.56 (s, 3H), 3.47 (s, 3H), 3.35–3.28 (m, 2H); ^{13}C NMR (D_2O, 75 MHz): δ 101.2, 99.4, 72.9, 72.2, 71.0, 70.7, 70.1, 69.1, 68.5, 66.3, 57.4, 56.4, 55.7 (2C); ESI-MS: m/z = 441.2 $[M + Na]^+$; $[\alpha]_D^{25}$ + 35.0 (c 1.0, H_2O); Anal. Calcd. for $C_{14}H_{26}O_{12}S$ (418.11): C, 40.19; H, 6.26. Found: C, 39.96; H, 6.50.

*6.1.5.5. (Methyl 6-deoxy-α-D-galactopyranosid-6-yl)-(methyl 6′-deoxy-α-D-mannopyranosid-6-yl) sulfone (**7e**).* Glass (82 mg, 75%). R_f: 0.5 (CH_2Cl_2–CH_3OH, 5:1); ^1H NMR (D_2O, 300 MHz): δ 4.82–4.80 (m, 2H), 4.41 (d, J = 9.9 Hz, 1H), 4.13–4.06 (m, 1H), 3.96–3.50 (m, 10H), 3.43 (br s, 6H); ^{13}C NMR (D_2O, 75 MHz): δ 101.0, 99.7, 70.7, 70.1, 69.7, 69.1, 68.7, 67.6, 67.1, 65.6, 55.7 (3C), 55.2; ESI-MS: m/z = 441.3 $[M + Na]^+$; $[\alpha]_D^{25}$ + 122 (c 1.0, H_2O); Anal. Calcd. for $C_{14}H_{26}O_{12}S$ (418.11): C, 40.19; H, 6.26. Found: C, 40.28; H, 6.50.

*6.1.5.6. Bis(methyl 6-deoxy-α-D-mannopyranosid-6-yl) sulfone (**7f**).* Glass (83 mg, 76%). R_f: 0.4 (CH_2Cl_2–CH_3OH, 6:1); ^1H NMR (D_2O, 300 MHz): δ 4.76 (d, J = 3.5 Hz, 1H), 4.10 (t, J = 9.3 Hz each, 1H),

3.96–3.94 (m, 1H), 3.84–3.64 (m, 3H), 3.56 (t, $J = 9.7$ Hz each, 1H), 3.45 (s, 3H); ^{13}C NMR (D_2O, 75 MHz): δ 101.1, 70.1, 69.7, 68.7, 67.3, 55.8, 55.4; The proton integration in the ^{1}H NMR and carbon signals in the ^{13}C NMR spectra appeared as monomer because of the symmetric nature of the molecule; ESI-MS: $m/z = 441.1$ $[M + Na]^+$. $[\alpha]_D^{25} + 56.6$ (c 1.0, H_2O); Anal. Calcd. for $C_{14}H_{26}O_{12}S$ (418.11): C, 40.19; H, 6.26. Found: C, 40.0H, 6.50.

*6.1.5.7. (Methyl 6-deoxy-α-D-mannopyranosid-6-yl)-(methyl 6′-deoxy-β-D-allopyranosid-6-yl) sulfone (**7g**).* Glass (85 mg, 78%). R_f: 0.5 (CH_2Cl_2–CH_3OH, 5:1); ^{1}H NMR (D_2O, 300 MHz): δ 4.82–4.81 (m, 1H), 4.68 (d, $J = 8.3$ Hz, 1H), 4.34–4.27 (m, 1H), 4.23–4.15 (m, 2H), 4.01–3.99 (m, 1H), 3.84–3.68 (m, 5H), 3.66–3.58 (m, 5H), 3.53–3.49 (m, 4H); ^{13}C NMR (D_2O, 75 MHz): δ 101.2, 101.0, 70.7, 70.2, 70.1, 69.8, 69.0, 68.8, 68.5, 67.0, 57.4, 56.3, 55.7, 55.3; ESI-MS: $m/z = 441.3$ $[M + Na]^+$; $[\alpha]_D^{25} + 20$ (c 1.0, H_2O); Anal. Calcd. for $C_{14}H_{26}O_{12}S$ (418.11): C, 40.19; H, 6.26. Found: C, 40.05; H, 6.50.

*6.1.5.8. Bis (methyl 6-deoxy-β-D-allopyranosid-6-yl) sulfone (**7h**).* Glass (80 mg, 73%). R_f: 0.4 (CH_2Cl_2–CH_3OH, 6:1); ^{1}H NMR (D_2O, 300 MHz): δ 4.62 (d, $J = 7.8$ Hz, 1H), 4.26–4.15 (m, 2H), 3.72–3.33 (m, 7H); ^{13}C NMR (D_2O, 75 MHz): δ 101.1, 70.8, 70.1, 69.2, 68.3, 57.4, 56.2; The proton integration in the ^{1}H NMR and carbon signals in the ^{13}C NMR spectra appeared as monomer because of the symmetric nature of the molecule; ESI-MS: $m/z = 441.2$ $[M + Na]^+$; $[\alpha]_D^{25} - 25.7$ (c 1.0, H_2O); Anal. Calcd. for $C_{14}H_{26}O_{12}S$ (418.11): C, 40.19; H, 6.26. Found: C, 39.96; H, 6.50.

6.2. Assay of ATPase activity

ATPase activity was assayed in the microsomal membranes isolated from goat spermatozoa which was reported to be enriched with this enzyme. The microsomal membranes were isolated from goat spermatozoa following the method reported before by Sikdar et al. [4]. In a typical experiment, 2 μg of the enzyme preparation and 3 mM ATP were added to the reaction buffer containing 50 mM imidazole in 25 mM sucrose, 0.5 mM EDTA, 1 mM 2-mercaptoethanol, with and without 4 mM $CaCl_2$ in a total volume of 250 μl. After incubation for 30 min at 37 °C, the reaction was terminated with the addition of 7% ice-cold trichloroacetic acid (TCA). To determine the amount of enzymatically released inorganic phosphate (Pi), a solution containing 1.75% ammonium molybdate and 2% ascorbic acid was added. The blue colour developed was measured at 820 nm using a spectrophotometer. The amount of inorganic phosphate (Pi) released was quantitated from a standard phosphate curve. The Ca^{2+}-ATPase activity was expressed as the difference of activity in the presence and absence of Ca^{2+} ion. To examine the effect of different synthetic compounds and/or calcium blockers, the enzyme activity was measured in the presence of different concentrations of each of them under above mentioned standard conditions. It is noteworthy that all synthetic compounds, verapamil and orthovanadate are water soluble, whereas thapsigargin is ethanol soluble. Appropriate experiment in presence of equal concentration of ethanol was run as control.

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Appendix. Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.ejmech.2010.09.069.

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