

Novel Oxadiazole Thioglycosides as Potential Anti-*Acinetobacter* Agents

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Abstract

The glycosylation of 1,3,4-oxadiazole-2-thiones has been performed with peracetylated β -pyranosyl bromide in the presence of potassium carbonate. Deprotection of acetylated thioglycosides was necessary for increasing their antibacterial effects. The structures of nucleosides were confirmed by ¹H NMR, ¹³C NMR and HRMS. The anomeric protons of nucleosides c₁₋₄ were assigned to the doublet, confirming the β -configuration. The synthesized compounds were tested for their antimicrobial activity against *Acinetobacter calcoaceticus* (Gram-negative) strain *in-vitro* in comparison with Ampicillin as a reference drug which is normally used for treating such infections. The synthetic compounds showed different inhibition zones against tested bacterial strain. Thioglycoside derivatives of 1,3,4-oxadiazole-2-thiones (c set) were more active against *Acinetobacter calcoaceticus* ATCC 23055 than “parent” 1,3,4-oxadiazole-2-thiones (a set), confirming the relation between glyco-conjugation and increasing of antiproliferative activity of antibiotic agents. The best result belonged to nucleoside bearing 2-furyl moiety in its heterocyclic nucleus (c₄). The existence of *m*-PhNO₂ group as Ar in structures of a set and their corresponding sugar derivatives decreased the antibacterial activity of them in comparison with the rest of synthetic compounds.

Keywords: 1,3,4-Oxadiazole-2-thione; β -Pyranosyl; Thioglycoside; Nucleoside; *in-vitro*; *Acinetobacter calcoaceticus*; Antiproliferative activity.

Introduction

The resistance of infective bacteria to present antibiotics demands research assigned to the discovery of new drugs in the antibacterial drug field. The majority of carbohydrates found in nature or biological systems exist as glycoconjugates in which the monosaccharide units are joined via O-, N-, or S-glycosidic bonds. Thioglycosides have received considerable attention, because they are widely employed as biological

inhibitors, inducers and ligands for affinity chromatography of carbohydrate-processing enzymes and proteins (1-8). They have excellent chemoselectivity in glycosylation processes as both donors and acceptors particularly via reaction processes that involve active and latent glycosylation protocols (9). The thioglycosyl heterocycles are sufficiently stable under a variety of reaction conditions and have the ability to be readily converted into a variety of other functionalities (10, 11). Multivalent display of carbohydrates is frequently used as a method to increase affinities in various contexts such as the binding of bacteria, bacterial toxins, galectins and other lectins (12-24). These properties may

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affect medicinal effect of antibiotic agents.

On the other hand, oxadiazole derivatives, which belong to an important group of heterocyclic compounds, have been the subject of extensive study in the recent past. Numerous reports have highlighted their chemistry and use. Diverse biological activities, such as anti-inflammatory, antitumor, antimicrobial and anticonvulsant, have been found to be associated with oxadiazole derivatives (25-28). Moreover, sulfur-containing heterocycles represent an important group of sulfur compounds that are promising for use in practical applications.

Therefore, it is interesting to report the synthesis of a new series of compounds in which the glycosyl moieties have been used as carriers for the heterocycles having the oxadiazole ring.

In our previous work (29), we reported the synthesis of antibacterial properties of new series of thioglycoside derivatives of 1,2,4-triazole-5-thiones, whereas in the present work, we report the synthesis of new groups of anti-*Acinetobacter calcoaceticus* agents in which 1,3,4-oxadiazole-2-thiones moiety is coupled to monosaccharide unit.

Experimental

¹H and ¹³C NMR spectra were recorded on a Bruker AVANCE-300 spectrometer at 300 and 75 MHz, respectively in CDCl₃ using TMS as the internal standard. High-resolution mass spectra were obtained with a HPLC-Q-TOF system equipped with Q-TOF micromass spectrometer (dual ESI). Melting points were measured on a Philip Harris C4954718 apparatus without calibration. Optically active samples were analyzed by EHARTNACK apparatus (Paris, France) at 20 °C in dichloromethane. Thin layer chromatography (TLC) analyses were carried out on silica gel plates. All chemicals were purchased from Merck and used as received.

5-phenyl-1,3,4-oxadiazole-2(3H)-thione (a₁)

Yield: 74%; mp 158-160 °C; ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 7.52 (m, 3H, ArH), 7.96 (d, J = 6.9, 2H, ArH), 10.75 (bs, 1H, N-H); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 122.90, 126.47, 129.85, 132.67, 160.90 (Ar), 177.88 (C=S).

5-(2-hydroxyphenyl)-1,3,4-oxadiazole-2(3H)-thione (a₂)

Yield: 84%; mp 162-164 °C; ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 7.10 (m, 2H, ArH), 7.49 (t, 1H, J = 7.1, ArH), 7.72 (d, 1H, J = 8.1, ArH), 8.39 (bs, 1H, OH), 11.34 (bs, 1H, N-H); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 109.79, 111.17, 119.84, 129.50, 133.87, 156.78, 160.27 (Ar), 177.47 (C=S).

5-(3-nitrophenyl)-1,3,4-oxadiazole-2(3H)-thione (a₃)

Yield: 78%; mp 167-168 °C; ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 7.40-7.60 (m, 3H, ArH), 7.94 (d, J = 7.8, 1H, ArH), 11.10 (bs, 1H, OH); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 120.93, 124.43, 126.85, 131.76, 132.44, 148.53, 159.15 (Ar), 178.04 (C=S).

5-(2-furyl)-1,3,4-oxadiazole-2(3H)-thione (a₄)

Yield: 69%; mp 152-155 °C; ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 6.62 (bs, 1H, Furyl), 7.18 (bs, 1H, Furyl), 7.66 (bs, 1H, Furyl), 11.38 (bs, 1H, N-H); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 113.05, 115.37, 137.99, 147.61, 153.90 (Ar), 177.10 (C=S).

2-phenyl-5-(2,3,4,6-tetra-O-acetyl-β-D-1-thio-glucopyranose)-1,3,4-oxadiazole (b1)

Yield: 64%; mp 102-105 °C; ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 1.95 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.18 (s, 3H, OAc), 3.88-3.99 (m, 1H, H-6a), 4.12-4.20 (m, 1H, H-6b), 4.27-4.30 (m, 1H, H-5), 5.14-5.71 (m, 3H, H-2, -3, -4), 5.96 (d, 1H, J_{1,2} = 9.3, H-1), 7.52 (m, 3H, ArH), 7.94-8.04 (m, 2H, ArH); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 20.56 (2C), 20.72 (2C) (4 × OCOCH₃), 61.55 (C-6), 67.56 (C-4), 69.76 (C-2), 73.52 (C-3), 74.71 (C-5), 83.42 (C-1), 121.93, 126.80, 129.18, 132.03, 132.79 (Ar), 166.52 (C-S), 168.93, 168.37, 170.06, 170.58 (4 × OCOCH₃).

2-(2-hydroxyphenyl)-5-(2,3,4,6-tetra-O-acetyl-β-D-1-thio-glucopyranose)-1,3,4-

oxadiazole (b2)

Yield: 66%; mp 99-101 °C; ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 2.03 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.10 (s, 3H, OAc), 3.88-3.92 (m, 1H, H-6a), 4.13-4.17 (m, 1H, H-6b), 4.27-4.32 (m, 1H, H-5), 5.14-5.37 (m, 3H, H-2, -3, -4), 5.50 (d, 1H, J_{1,2} = 9.6, H-1), 7.02 (t, 1H, J = 7.8, ArH), 7.13 (d, 1H, J = 8.4, ArH), 7.47 (t, 1H, J = 6.9, ArH), 7.72 (d, 1H, J = 7.8, ArH), 9.87 (bs, 1H, OH); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 20.54 (2C), 20.60 (2C) (4 × OCOCH₃), 61.56 (C-6), 67.72 (C-4), 69.74 (C-2), 73.46 (C-3), 76.62 (C-5), 83.33 (C-1), 107.58, 117.66, 120.11, 126.54, 134.04, 157.34, 160.02 (Ar), 165.92 (C-S), 169.34, 169.43, 169.966, 170.54 (4 × OCOCH₃).

2-(3-nitrophenyl)-5-(2,3,4,6-tetra-O-acetyl-β-D-1-thio-glucopyranose)-1,3,4-oxadiazole (b3)

Yield: 58%; mp 112-113 °C; ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 2.04 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.10 (s, 3H, OAc), 3.88-4.05 (m, 1H, H-6a), 4.14-4.21 (m, 1H, H-6b), 4.28-4.33 (m, 1H, H-5), 5.16-5.67 (m, 3H, H-2, -3, -4), 5.97 (d, 1H, J_{1,2} = 9.3, H-1), 7.75 (t, J = 7.8, 1H, ArH), 8.27-8.43 (m, 2H, ArH), 8.84 (d, J = 8.1, 1H, ArH); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 20.53 (2C), 20.65 (2C) (4 × OCOCH₃), 61.50 (C-6), 67.70 (C-4), 69.71 (C-2), 73.49 (C-3), 74.83 (C-5), 83.32 (C-1), 121.80, 124.93, 126.36, 127.03, 130.52, 132.21, 148.67 (Ar), 164.50 (C-S), 169.33, 169.44, 169.97, 170.53 (4 × OCOCH₃).

2-(2-furyl)-5-(2,3,4,6-tetra-O-acetyl-β-D-1-thio-glucopyranose)-1,3,4-oxadiazole (b4)

Yield: 72%; mp 107-109 °C; ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 1.97 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.10 (s, 3H, OAc), 3.85-4.00 (m, 1H, H-6a), 4.13-4.21 (m, 1H, H-6b), 4.27-4.32 (m, 1H, H-5), 5.24 (t, 1H, J_{1,2} = J_{2,3} = 9.3, H-2), 5.42 (t, 1H, J_{2,3} = J_{3,4} = 9.3, H-4), 5.61 (t, 1H, J_{2,3} = J_{3,4} = 9.3, H-3), 6.34 (d, 1H, J_{1,2} = 9.3, H-1), 6.61 (bs, 1H, Furyl), 7.17 (bs, 1H, Furyl), 7.66 (bs, 1H, Furyl); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 20.49 (2C), 20.70 (2C) (4 × OCOCH₃),

61.54 (C-6), 67.51 (C-4), 69.40 (C-2), 73.04 (C-3), 74.75 (C-5), 83.17 (C-1), 112.36, 116.17, 137.41, 146.80, 152.37 (Ar), 159.98 (C-S), 168.97, 169.28, 170.04, 170.56 (4 × OCOCH₃).

2-phenyl-5-(β-D-1-thio-glucopyranose)-1,3,4-oxadiazole (c1)

Yield: 33%; mp 108-110 °C; [α]_D²⁰ = 3° (c = 1.0, CH₂Cl₂). ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 3.92-4.03 (m, 1H, H-6a), 4.12-4.22 (m, 1H, H-6b), 4.27-4.30 (m, 1H, H-5), 4.35-4.85 (m, 4H, OH), 5.12-5.70 (m, 3H, H-2, -3, -4), 5.99 (d, 1H, J_{1,2} = 9.3, H-1), 7.50 (m, 3H, ArH), 7.94-8.02 (m, 2H, ArH); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 61.76 (C-6), 67.64 (C-4), 69.26 (C-2), 73.59 (C-3), 74.78 (C-5), 83.37 (C-1), 122.23, 126.88, 129.40, 132.09, 132.99 (Ar), 166.45 (C-S); HRMS spectrum (ESI), *m/z*: Calculated, 340.0729. C₁₄H₁₆N₂O₆S [M+H]⁺. Found, 341.0817.

2-(2-hydroxyphenyl)-5-(β-D-1-thio-glucopyranose)-1,3,4-oxadiazole (c2)

Yield: 46%; mp 144-145 °C; [α]_D²⁰ = 4° (c = 1.0, CH₂Cl₂). ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 3.86-3.97 (m, 1H, H-6a), 4.11-4.16 (m, 1H, H-6b), 4.26-4.32 (m, 1H, H-5), 4.37-4.83 (m, 4H, OH), 5.13-5.37 (m, 3H, H-2, -3, -4), 5.57 (d, 1H, J_{1,2} = 9.6, H-1), 7.03 (t, 1H, J = 7.8, ArH), 7.12 (d, 1H, J = 8.4, ArH), 7.49 (t, 1H, J = 6.9, ArH), 7.74 (d, 1H, J = 7.8, ArH), 9.97 (bs, 1H, OH); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 62.46 (C-6), 68.02 (C-4), 69.86 (C-2), 73.65 (C-3), 76.69 (C-5), 83.04 (C-1), 109.18, 117.36, 121.01, 126.94, 133.84, 157.86, 160.23 (Ar), 165.57 (C-S); HRMS spectrum (ESI), *m/z*: Calculated, 356.0678. C₁₄H₁₆N₂O₇S [M+H]⁺. Found, 357.0762.

2-(3-nitrophenyl)-5-(β-D-1-thio-glucopyranose)-1,3,4-oxadiazole (c3)

Yield: 39%; mp 122-124 °C; [α]_D²⁰ = -2° (c = 1.0, CH₂Cl₂). ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 3.84-4.01 (m, 1H, H-6a), 4.17-4.25 (m, 1H, H-6b), 4.24-4.33 (m, 1H, H-5), 4.36-4.85 (m, 4H, OH), 5.16-5.68 (m, 3H, H-2, -3, -4), 6.07 (d, 1H, J_{1,2} = 9.3, H-1), 7.78 (t, J = 7.8, 1H, ArH), 8.27-8.46 (m, 2H, ArH), 8.81 (d, J = 8.4, 1H, ArH); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 62.20 (C-6), 67.74 (C-

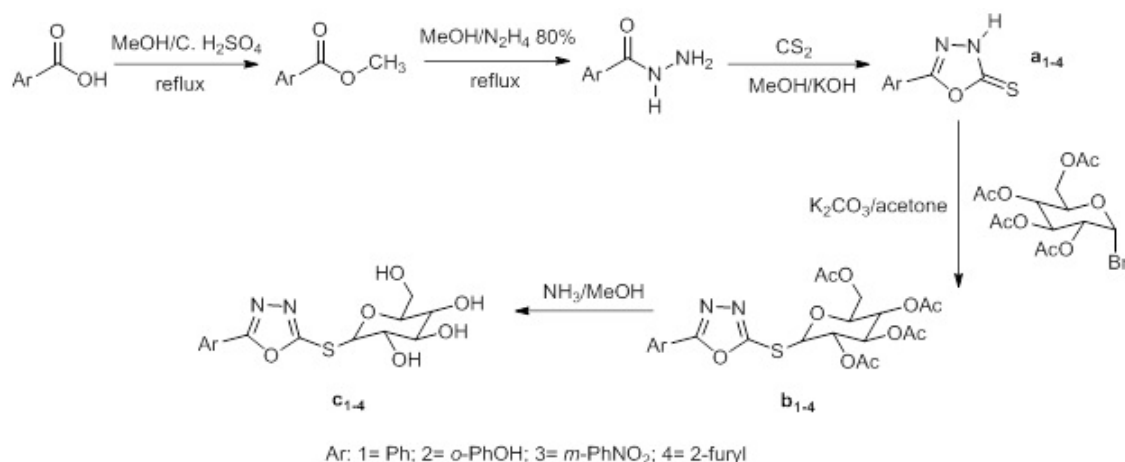


Figure 1. General synthetic pathway for the synthesis of thioglycosyl oxadiazoles.

4), 69.79 (C-2), 73.67 (C-3), 74.35 (C-5), 83.44 (C-1), 121.89, 123.90, 126.86, 127.43, 131.82, 132.28, 149.63 (Ar), 165.22 (C-S); HRMS spectrum (ESI), m/z : Calculated, 385.0580. C₁₄H₁₅N₃O₈S [M+H]⁺. Found, 386.0665.

2-(2-furyl)-5-(β-D-1-thio-glucopyranose)-1,3,4-oxadiazole (c4)

Yield: 52%; mp 111-113 °C; [α]_D²⁰ = -4° (c = 1.0, CH₂Cl₂). ¹H NMR spectrum, (300 MHz, CDCl₃), δ, ppm, (J, Hz): 3.82-4.08 (m, 1H, H-6a), 4.17-4.23 (m, 1H, H-6b), 4.24-4.39 (m, 1H, H-5), 4.35-4.89 (m, 4H, OH), 5.27 (t, 1H, J_{1,2}=J_{2,3} = 9.3, H-2), 5.45 (t, 1H, J_{2,3}=J_{3,4} = 9.3, H-4), 5.69 (t, 1H, J_{2,3}=J_{3,4} = 9.3, H-3), 6.31 (d, 1H, J_{1,2} = 9.3, H-1), 6.66 (bs, 1H, Furyl), 7.17 (bs, 1H, Furyl), 7.58 (bs, 1H, Furyl); ¹³C NMR spectrum, (75 MHz, CDCl₃), δ, ppm: 60.94 (C-6), 66.98 (C-4), 69.87 (C-2), 73.54 (C-3), 74.85 (C-5), 83.63 (C-1), 112.30, 117.20, 137.83, 146.88, 152.52 (Ar), 162.07 (C-S); HRMS spectrum (ESI), m/z : Calculated, 330.0522. C₁₂H₁₄N₂O₇S [M+H]⁺. Found, 331.0609.

Bacterial Strain

The antibacterial activity of compounds was assayed with our previous published method (30). The antibacterial activity of the compounds was tested against Gram-negative strain of *Acinetobacter calcoaceticus* ATCC 23055.

Results and Discussion

Thioglycosylation was performed according to our previous published method (29). 1-bromide sugar and 1,3,4-oxadiazole-2-thione nuclei a₁₋₄ were synthesized to the literature procedures (29,31). Deprotection of acetylated nucleosides was performed to the literature procedure (32). The synthesis of the final nucleosides is depicted in Figure 1.

The structure of thioglycosides was confirmed by appropriate spectroscopic methods such as ¹H NMR, ¹³C NMR, and high resolution mass spectroscopy (HRMS). The anomeric protons of nucleosides c₁₋₄ were assigned to the doublet at 5.57–6.31 ppm with J_{1,2} = 9.3–9.6 Hz, confirming the β-configuration.

In our recent published research (29), there was not any significant change in the antibacterial effect of the acetylated final thioglycosides in comparison with the parent heterocyclic nuclei. Therefore, in the present work, the deacetylated nucleosides c₁₋₄ have been compared to the parent heterocyclic nuclei a₁₋₄ against *Acinetobacter calcoaceticus*.

The *in vitro* antibacterial activity of the synthesized compounds in DMSO against *Acinetobacter calcoaceticus* shown in Tables 1. Diameter of inhibition zone for ampicillin as reference drug is 18 mm for 10 μg/μL concentration of drug in the same test conditions.

Table 1. *In-vitro* antibacterial activity of synthetic compounds against *Acinetobacter Calcoaceticus* ATCC 23055 (concentration = 10 µg/µL).

Compound	Diameter of inhib. zone (mm)	Compound	Diameter of inhib. zone (mm)
a ₁	19	c ₁	28
a ₂	18	c ₂	29
a ₃	16	c ₃	25
a ₄	22	c ₄	31

As shown in the Table 1. these compounds showed higher antibacterial effects in comparison with Ampicillin (18 mm) which is normally used for treating such infections.

In general, compounds from **c** set (nucleosides) showed more antimicrobial activity than the other set. Thioglycoside derivatives of 1,3,4-oxadiazole-2-thiones (**c** set) were more active against *Acinetobacter calcoaceticus* ATCC 23055 than “parent” 1,3,4-oxadiazole-2-thiones (**a** set), confirming the relation between glyco-conjugation and increasing of antiproliferative activity of antibiotic agents. The best results in the tables belonged to **c₄** that showing high activity against *A. calcoaceticus* (31 mm).

Going over the structure of these synthetic compounds confirmed that the existence of 2-furyl instead of *m*-PhNO₂ group as Ar increased their antibacterial activity against *A. calcoaceticus*. The existence of *m*-PhNO₂ group as Ar in structures of **a** set and their corresponding sugar derivatives decreased the antibacterial activity of them in comparison with the rest of synthetic compounds.

References

- (1) Marino C, Marino K, Miletto L, Manso Alves MJ, Colli W and de Lederkremer RM. 1-Thio-β-D-galactofuranosides: synthesis and evaluation as β-D-galactofuranosidase inhibitors. *Glycobiology* (1998) 8: 901-4.
- (2) Awad OME, Attia WE and El Ashry ESH. Comparative evaluation of D-glucosylthiuronium, glucosylthioheterocycles, Daonil and insulin as inhibitors for hepatic glycosidases. *Carbohydr. Res.* (2004) 339: 469-76.
- (3) El Ashry ESH, Awad LF and Atta IA. Synthesis and role of glucosylthioheterocycles in carbohydrate chemistry. *Tetrahedron* (2006) 62: 2943-98.
- (4) Apparu C, Driguez H, Williamson G and Svensson B. Chemoenzymatic synthesis of 6 ω -S- α -D-glucopyranosyl-6 ω -thiomaltooligosaccharides: their binding to *Aspergillus niger* glucoamylase G1 and its starch-binding domain. *Carbohydr. Res.* (1995) 277: 313-20.
- (5) Birk R, Ikan A, Bravdo B, Braun S and Shoseyov O. Synthesis of Isopropyl-1-thio-B-D-glucopyranoside (IPTGlc), an inducer of *Aspergillus niger* b1 B-glucosidase production. *Appl. Biochem. Biotechnol.* (1997) 66: 25-30.
- (6) Defaye J, Guillot JM, Biely P and Vrsanska M. Positional isomers of thioxylobiose, their synthesis and inducing ability for D-xylan-degrading enzymes in the yeast *Cryptococcus albidus*. *Carbohydr. Res.* (1992) 228: 47-64.
- (7) Schnaar RL and Lee YC. Polyacrylamide gels copolymerized with active esters. New medium for affinity systems. *Biochemistry* (1975) 14: 1535-41.
- (8) Orgeret C, Scillier E, Gautier C, Defaye J and Driguez H. 4-Thiocellooligosaccharides. Their synthesis and use as ligands for the separation of cellobiohydrolases of *Trichoderma reesei* by affinity chromatography. *Carbohydr. Res.* (1992) 224: 29-40.
- (9) Mereyala HB and Gurijala VR. Use of 2-pyridyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-1-thio-beta-D-glucopyranoside as a glycosyl donor and methyl iodide as an activator for the synthesis of 1,2-trans-linked saccharides. *Carbohydr. Res.* (1993) 242: 277-80.
- (10) Chen Q and Kong F. Stereoselective glycosylation using fully benzylated pyrimidin-2-yl 1-thio-β-D-glucopyranosides. *Carbohydr. Res.* (1995) 272: 149-57.
- (11) Ding X, Yang G and Kong F. Synthesis and glycosylation of pyrimidin-2-yl 1-thio- α -D-manno- and - α -L-rhamnopyranoside. *Carbohydr. Res.* (1998) 310: 135-9.
- (12) Mammen M, Choi SK and Whitesides GM. Polyvalent interactions in biological systems: implications for design and use of multivalent ligands and inhibitors. *Angew. Chem. Int. Ed.* (1998) 37: 2754-94.
- (13) Lee RT and Lee YC. Affinity enhancement by multivalent lectin-carbohydrate interaction. *Glycoconjugate J.* (2000) 17: 543-51.
- (14) Lindhorst TK, Dubber M, Krallmann-Wenzel U and Ehlers S. Cluster mannosides as inhibitors of type 1 fimbriae-mediated adhesion of *Escherichia coli*: pentaerythritol derivatives as scaffolds. *Eur. J. Org.*

- Chem.* (2000) 11: 2027-34.
- (15) Nagahori N, Lee RT, Nishimura SI, Pag' e D, Roy R and Lee YC. Inhibition of adhesion of type 1 fimbriated *Escherichia coli* to highly mannosylated ligands. *Chem. Bio. Chem.* (2002) 3: 836-44.
- (16) Autar R, Khan AS, Schad M, Hacker J, Liskamp RMJ and Pieters RJ. Adhesion inhibition of F1C-fimbriated *Escherichia coli* and *Pseudomonas aeruginosa* PAK and PAO by multivalent carbohydrate ligands. *Chem. Bio. Chem.* (2003) 4: 1317-25.
- (17) Joosten JAF, Loimaranta V, Appeldoorn CCM, Haataja S, El Maate FA, Liskamp RMJ, Finne J and Pieters RJ. Inhibition of *Streptococcus suis* adhesion by dendritic galabiose compounds at low nanomolar concentration. *J. Med. Chem.* (2004) 47: 6499-508.
- (18) Fan E, Zhang Z, Minke WE, Hou Z, Verlinde CLMJ and Hol WGJ. High-affinity pentavalent ligands of *Escherichia coli* heat-labile enterotoxin by modular structure-based design. *J. Am. Chem. Soc.* (2000) 122: 2663-4.
- (19) Kitov PI, Sadowska JM, Mulvey G, Armstrong GD, Ling H, Pannu NS, Read RJ and Bundle DR. Shiga-like toxins are neutralized by tailored multivalent carbohydrate ligands. *Nature* (2000) 403: 669-72.
- (20) Arosio D, Vrasidas I, Valentini P, Liskamp RMJ, Pieters RJ and Bernardi A. Synthesis and cholera toxin binding properties of multivalent GM1 mimics. *Org. Biomol. Chem.* (2004) 2: 2113-24.
- (21) Andr'e S, Pieters RJ, Vrasidas I, Kaltner H, Kuwabara I, Liu FT, Liskamp RMJ and Gabius HJ. Wedge like Glycodendrimers as inhibitors of binding of mammalian galectins to glycoproteins, lactose maxiclusters, and cell surface glycol conjugates. *Chem. Bio. Chem.* (2001) 2: 822-30.
- (22) Vrasidas I, Andr'e S, Valentini P, B'ock C, Lensch M, Kaltner H, Liskamp RMJ, Gabius HJ and Pieters RJ. Rigidified multivalent lactose molecules and their interactions with mammalian galectins: a route to selective inhibitors. *Org. Biomol. Chem.* (2003) 1: 803-10.
- (23) Wittmann V and Seeberger S. Spatial screening of cyclic neoglycopeptides: identification of polyvalent wheat-germ agglutinin ligands. *Angew. Chem. Int. Ed.* (2004) 43: 900-3.
- (24) Woller EK, Walter ED, Morgan JR, Singel DJ and Cloninger MJ. Altering the strength of lectin binding interactions and controlling the amount of lectin clustering using mannose/hydroxyl-functionalized dendrimers. *J. Am. Chem. Soc.* (2003) 125: 8820-6.
- (25) Tabatabai SA, Rezaee Zavareh E, Reyhanfard H, Alinezhad B, Shafaghi B, Sheikha M, Shafiee A and Faizi M. Evaluation of anxiolytic, sedative-hypnotic and amnesic effects of novel 2-phenoxy phenyl-1,3,4-oxadiazole derivatives using experimental models. *Iran. J. Pharm. Res.* (2015) 14: 51-7.
- (26) Obi K, Kojima A, Fukuda H and Hirai K. Synthesis and biological activity of a novel class of cephalosporins with a oxadiazolyl hydroxypyridone moiety at C-7. *Bioorg. Med. Chem. Lett.* (1995) 5: 2777-82.
- (27) Dilmaghani KA, Jazani NH, Nasuhi Pur F, Shokoufeh N, Ghadiri F and Mirfakhraee F. Synthesis of 5-(4-aminophenyl)-2-(arylamino)-1, 3, 4-thiadiazoles and their schiff base derivatives as antimycobacterial agents. *Chem. Heterocycl. Compd.* (2012) 48: 362-7.
- (28) Tabatabai SA, Lashkari SB, Zarrindast MR, Gholibeikian M and Shafiee A. Design, synthesis and anticonvulsant activity of 2-(2-phenoxy) phenyl-1,3,4-oxadiazole derivatives. *Iran. J. Pharm. Res.* (2013) 12: 105-11.
- (29) Dilmaghani KA, Nasuhi Pur F, Jazani NH, Alavi A, Niknam Z and Mirfakhraee F. Synthesis of new 1,2,4-triazole-5-thiones and their thioglycoside derivatives as potential antibacterial agents. *Phosphorus, Sulfur, and Silicon* (2014) 189: 81-7.
- (30) Dilmaghani KA, Nasuhi Pur F and Hatami Nezhad M. Synthesis and antibacterial evaluation of new thionesubstituted 1,2,4-triazole Schiff bases as novel antimicrobial agents. *Iran. J. Pharm. Res.* (2015) 14: 693-699.
- (31) Aydogan F, Turgut Z and Ocal N. Synthesis and electronic structure of new aryl- and alkyl-substituted 1,3,4-oxadiazole-2-thionederivatives. *Turk. J. Chem.* (2002) 26: 159-69.
- (32) Ahmad A, Iqbal R, Akhtar H, Hag ZU, Duddeck H, Stefaniak L and Sitkowski J. Synthesis and structure determination of some oxadiazole-2-thione and triazole-3-thione galactosides. *Nucleos. Nucleot. Nucl.* (2001) 20: 1671-82.