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Original article

Synthesis and cytotoxic profile of glycosyl–triazole linked to 1,2,4-oxadiazole moiety at C-5 through a straight-chain carbon and oxygen atoms

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ABSTRACT

The convergent synthesis of an unusual (but simple) class of compounds **5a–g** has been achieved by the copper-catalyzed [3 + 2] cycloaddition reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide **4** with propynyl 3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propionates **3a–g.** The formerly known azide **4** has been prepared according to the literature procedure; however, the synthesis of esters **3a–g** is being reported for the first time. The infrared as well as ^{1}H NMR spectra of all new products are in agreement with their proposed structures. By carrying out the nOe experiment of one of the final compounds **5a**, we have been able to establish that only the 1,4-regioisomers have been formed in the cycloaddition reaction. All final products presented weak cytotoxic activity, but **5e** and **5g** had somewhat better behaviour showing 22–25% cell growth inhibition against two cell strains: NCI-H_{292} (lung carcinoma) and HEp-2 (larynx carcinoma).

1. Introduction

The great cancer incidence worldwide increases the search for new, safer and efficient anticancer agents, aiming the prevention or the cure of this illness. In spite of all the efforts to combat cancer, the success of the treatment of certain types of tumors has shown little progress due their aggressiveness and to the mechanisms of malignant cell metastasis. In addition, anticancer agents show toxicity not only to cancer cells, but also to the non-neoplastic cells, showing no selectivity to the target and thus limiting the treatment [1]. Therefore, it would be interesting to discover more potent anticancer drugs for treating such a horrible disease.

Since our group has been involved in synthesizing and testing the biological activities of 1,2,4-oxadiazoles for a long time [2–9] and the recent findings that compounds carrying this heterocyclic ring possess antineoplastic properties [10,11] led us to conceptualize the incorporation of this heterocycle to a triazole nucleus which in turn contains a β-glucopyranosyl function at N-1. In fact, the 1,2,4-oxadiazole nucleus is present in many biologically active compounds [12–16], and is considered bioisoster of amide and ester functions [17]. Further, this heterocycle has found use in peptide chemistry and in the development of peptidomimetics [18–21]. Some compounds containing this ring in their structures have displayed, for example, anti-inflammatory [22], antimicrobial [23], antiviral [24], diuretic [25], anti-helmintic [26,27] and cytotoxic [11] activities.

1,2,3-Triazoles are also known to have antitumor properties [28]. Besides, they also possess other activities like anti-HIV [29,30], cytostatic [31] and anti-bactericidal [32] and can also act as GABA [33] and glycosidase inhibitors [34]. This heterocycle has been compared to amide bonds and may serve as bioisosters of peptide bonds due its electronic features [35,36].

Finally, the purpose of the glycosyl residue is that glycosides are relatively more water-soluble than their aglycones, and attaching this moiety into the molecule enhances its hydrophilicity, which in turn influences pharmacokinetic behaviour. The increased hydrophilicity of the molecule helps the membrane transport. Certain substances enter the cell because of the solubility within the membranal framework [37].

Considering the advantages of three heterocyclic rings contained in one molecule, we decided to synthesize seven such compounds **5a–g** in a convergent fashion. First, we prepared the prop-2-ynyl esters of 3-[3-(aryl)-1,2,4-oxadiazol-5-yl]propionic acids **2a–g** starting from arylamidoximes **1a–g** and succinic anhydride followed by the esterification of the acid using propargyl

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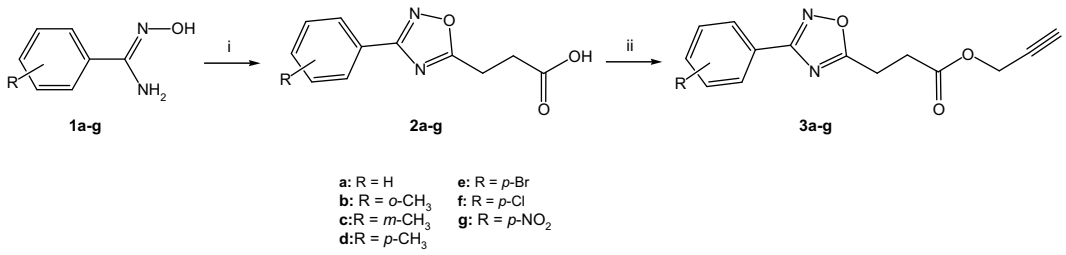


Scheme 1. Synthesis of 3-(1,2,4-oxadiazol-5-yl)propionic acids prop-2-ynyl esters **3a**–**g**. Reagents and conditions: (i) Succinic anhydride, 120–130 °C, neat, 3 h; (ii) Propargyl alcohol, H_2SO_4, 60 °C, 12 h.

alcohol to furnish **3a**–**g** (Scheme 1). Second, tetra-*O*-acetyl glucosylazide was prepared. Cycloaddition of azide to the acetylenic linkage easily afforded **5a**–**g**. These triheterocyclic compounds have not been found in the literature, and their complete synthesis is described in this paper. Further, they presented interesting cytotoxic activity.

1.1. Chemistry

The first step was the preparation of the 1,2,4-oxadiazoles containing a terminal acetylenic function, which involved the condensation of benzamidoximes **1a**–**g** [38] with succinic anhydride at 120–130 °C, under solvent-free conditions, to afford 3-[3-(aryl)-1,2,4-oxadiazol-5-yl]propionic acids **2a**–**g** in excellent yields [39]. Then, these acids were esterified with propargyl alcohol to furnish the unknown esters **3a**–**g** in 74–95% yields (Scheme 1).

Compounds **3a**–**g** were then submitted to the copper-catalyzed [3 + 2] cycloaddition with the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide **4** [40] using $Cu(OAc)_2$ and sodium ascorbate as catalyst in 1:1 dichloromethane:water [41,42] to give the products **5a**–**g** in good yields (Scheme 2 and Table 1).

In all cases, only 1,4-regioisomers were obtained, which is in agreement with earlier literature for this kind of copper-catalyzed dipolar cycloaddition [43,44]. Only one singlet was observed in the ^{1}H NMR spectra for the triazole ring (δ 8.47–8.49 ppm), which can be attributed to the proton in the C-5 position of the triazole ring. In fact, there are two possible regioisomers, which are shown in Fig. 1. In the first case (**A**), the triazole ring could adopt various conformations, where one of them might have the arrangement as indicated in **A**. In this arrangement, the H-5 of triazole and H-1 of the pyranosyl function are facing each other. In the other regioisomer (**B**), no matter how the conformations are arranged, the above-cited protons cannot acquire face-to-face arrangement. To verify this, the differential spectrum, using the nOe technique, clearly demonstrated the spatial effect between the two protons in question as shown in **5a.** This observation strongly supports the existence of 1,4-regioisomer and eliminates 1,5-regioisomer **B**.

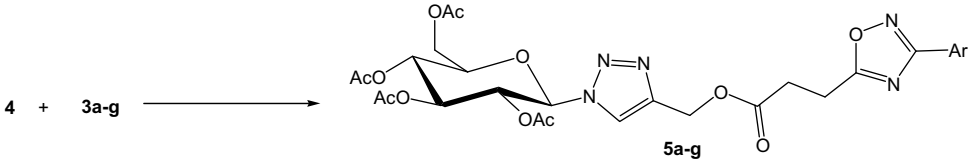
Fig. 2 shows the ^{1}H NMR spectrum including the nOe experiment. As we can see, the nOe differential spectrum of **5a** indicates that the irradiation of the anomeric proton increases the H-5 signal of triazole by 6.1%, showing the spatial interaction between the above-mentioned protons. With this experiment, we feel that all compounds were obtained as 1,4-regiomers.

In order to get more insight about the stable conformation of **5a**, we decided to carry out the *ab initio* molecular orbital calculations of this compound employing HF/6-31G(d) method [45]. Examining the geometry optimization of different possible conformations of **5a**, we found that the lowest energy for conformer **A** is close to the one shown in Fig. 1. The torsion angle between H-1 of the pyranosyl ring and H-5 of the triazole moiety was 24.70 degrees and the distance between these two protons in question was 2.53 Å, suitable for the spatial interaction between them. These data corroborate with our nOe experiment. The dihedral angle cited above may vary a little bit in the NMR experiment due to the solvent used for obtaining the spectrum, but the arrangement of the protons under consideration have reasonably the correct conformational arrangement for the nuclear Overhauser effect.

1.2. Biology

We evaluated the cytotoxic profile of **3a** and **5a**–**g** against two cell strains: NCI-H_{292} (lung carcinoma) and HEp-2 (larynx carcinoma). The cytotoxic assays were based on the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method [46–48]. Drugs **3a** and **5a**–**g** were tested in the following concentrations: 1.25; 2.5; 5.0; 6.25; 10.0; 12.5; 25.0 and 50.0 μg/mL. Compound **3a** presented extremely low inhibitory effect. However, **5a**–**g** showed 9–25% cell growth inhibition (Table 2). The percentage of inhibition is low except in **5e** and **5g**, but it does demonstrate that transformation of the triple bond of **3a**–**g** into a triazole moiety connected to glucosyl group does enhance the cytotoxic activity. In conclusion, compounds with electron withdrawing groups in the phenyl ring like bromine atom in **5e** and nitro group in **5g** presented the best cell growth inhibition percentages (more than 20% in both cell strains). Although this inhibition is still not sufficient, we feel that further research is needed to improve the inhibitory property. This could be done by putting one or more electron-attracting group(s) in the phenyl ring.

Compounds containing the 1,2,4-oxadiazole ring have already been reported as apoptosis inducers in cancer cell strains [11]. These substances act by activating a group of proteases, the caspase family. Once activated, the proteolytic degradation process occurs, leading to the programmed cell death [49]. Apoptosis inducers can



Scheme 2. Synthesis of *O*-{[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-[3-aryl-1,2,4-oxadiazol-5-yl] propanoates (**5a**–**g**). Reagents and conditions: (i) Copper acetate (5 mol%), Sodium ascorbate (15 mol%), CH_2Cl_2:H_2O, rt, 20 h.

Table 1
Synthesis of *O*-{[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-[3-aryl-1,2,4-oxadiazol-5-yl] propanoates (**5a**–**g**).

Entry	Product	Aryl	Yield (%)[a]
1	**5a**	Phenyl	83
2	**5b**	*o*-Tolyl	77
3	**5c**	*m*-Tolyl	74
4	**5d**	*p*-Tolyl	84
5	**5e**	*p*-Bromophenyl	73
6	**5f**	*p*-Chlorophenyl	66
7	**5g**	*p*-Nitrophenyl	69

[a] Isolated yields.

be selective cancer cell killers, once apoptosis is a consequence of various precise genetic events [50]. We believe that compounds **5e** and **5g**, for example, could also act by inducing the apoptotic process in the cancer cell strains.

2. Conclusion

In brief, we have accomplished the synthesis of seven distinctive heterocyclic compounds **5a**–**g** containing three such rings, a glycosyl function, a triazole moiety and an 1,2,4-oxadiazole ring. The triazole ring has substituents at N-1 and C-4 atoms. The molecular orbital calculations using *ab initio* method (HF/6-31G(d)) provided the optimized conformation of **5a,** where H-1 of the carbohydrate portion and H-5 of the triazole ring are facing each other. All seven compounds **5a**–**g** were tested against two neoplastic cell strains, among them **5e** and **5g** presented better inhibitory properties.

3. Experimental protocols

3.1. General methods

All commercially available reagents were used without any further purification. All reactions were monitored by TLC analysis (TLC plates GF_{254} E. Merck). Melting points were determined on a Büchi apparatus and are uncorrected. Column chromatography was performed on Silica Gel 60 (70–230 mesh, E. Merck). Optical rotations were recorded using a JASCO DIP 370 polarimeter. NMR spectra were recorded with a Varian Unity Plus 300 MHz spectrometer and referenced as following: ^{1}H (300 MHz), internal $SiMe_4$ at $\delta = 0.00$ ppm, ^{13}C (75 MHz), internal standard at $\delta = 77.23$ ppm. Benzamidoximes **1a**–**g** [38], oxadiazoles **2a**–**g** [39] and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**4**) [40] were prepared according to known literature procedures.

3.1.1. Synthesis of 3-[3-(aryl)-1,2,4-oxadiazol-5-yl]propionic acids prop-2-ynyl esters (*3a*–*g*)

An appropriate carboxylic acid **2a**–**g**, (2.3 mmol), propargyl alcohol (6.9 mmol) and 5 drops of sulphuric acid were taken in a round-bottom flask and the mixture was allowed to react for 12 h at 60 °C. The progress of the reaction was verified by TLC. The contents were allowed to cool to room temperature and then extracted with ethyl acetate (3×20 mL). The combined organic phase was washed with a saturated $NaHCO_3$ solution, brine and water. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to afford brown oil. The crude product was purified by column chromatography using 7:3 cyclohexane:ethyl acetate as eluant. The resulting crystals were recrystallized from methylene chloride:cyclohexane.

3-(3-Phenyl-1,2,4-oxadiazol-5-yl)propionic acid prop-2-ynyl ester (**3a**) prepared from **2a** (0.5 g); 95% (0.56 g); recrystallized from methylene chloride:cyclohexane (1:3, v/v); colorless crystals; m.p.: 66–67 °C; R_f 0.61 (EtOAc/cyclohexane 3:7); IR ν_{max} (KBr): 1185, 1328, 1590, 1752, 2920, 3253 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.50 (t, 1H, *J* 2.5 Hz, C≡CH), 3.00 (t, 2H, *J* 7.3 Hz, CH_2), 3.27 (t, 2H, *J* 7.3 Hz, CH_2), 4.26 (d, 2H, *J* 2.5 Hz, CH_2O), 7.43–7.50 (m, 3H, H_{arom}), 8.04–8.08 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 21.8, 30.1, 52.3, 75.1, 77.2, 126.6, 127.3, 128.7, 131.1, 168.1, 170.5, 177.9. Anal. Calcd. for $C_{14}H_{12}N_2O_3$ (C,H,N): C, 65.62%; H, 4.72%; N: 10.93%. Found: C, 65.81%; H, 4.49%; N, 11.33%.

3-[3-(2-Tolyl)-1,2,4-oxadiazol-5-yl]propionic acid prop-2-ynyl ester (**3b**). Prepared from **2b** (0.53 g); 84% (0.52 g); recrystallized from methylene chloride:cyclohexane (1:3, v/v); colorless crystals; m.p.: 50–51 °C; R_f 0.72 (EtOAc/cyclohexane 3:7); IR ν_{max} (KBr): 1161, 1344, 1590, 1751, 2948, 3262 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.49 (t, 1H, *J* 2.6 Hz, C≡CH), 2.61 (s, 3H, CH_3), 2.99 (t, 2H, *J* 7.3 Hz, CH_2), 3.28 (t, 2H, *J* 7.3 Hz, CH_2), 4.73 (d, 2H, *J* 2.6 Hz, CH_2O), 7.26–7.40 (m, 3H, H_{arom}); 7.96 (d, 1H, *J* 7.5 Hz, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 21.7, 22.0, 30.1, 52.3, 75.1, 77.2, 125.8, 129.9, 130.4, 131.2, 138.1, 168.7, 170.5, 176.9. Anal. Calcd. for $C_{15}H_{14}N_2O_3$ (C,H,N): C, 66.66%; H, 5.22%, N, 10.36%. Found: C, 66.74%; H, 5.20%; N, 10.57%.

3-[3-(3-Tolyl)-1,2,4-oxadiazol-5-yl]propionic acid prop-2-ynyl ester (**3c**). Prepared from **2c** (0.53 g); 79% (0.49 g); recrystallized from methylene chloride:cyclohexane (1:3, v/v); colorless crystals; m.p.: 44–45 °C; R_f 0.67 (EtOAc/cyclohexane 3:7); IR ν_{max} (KBr):

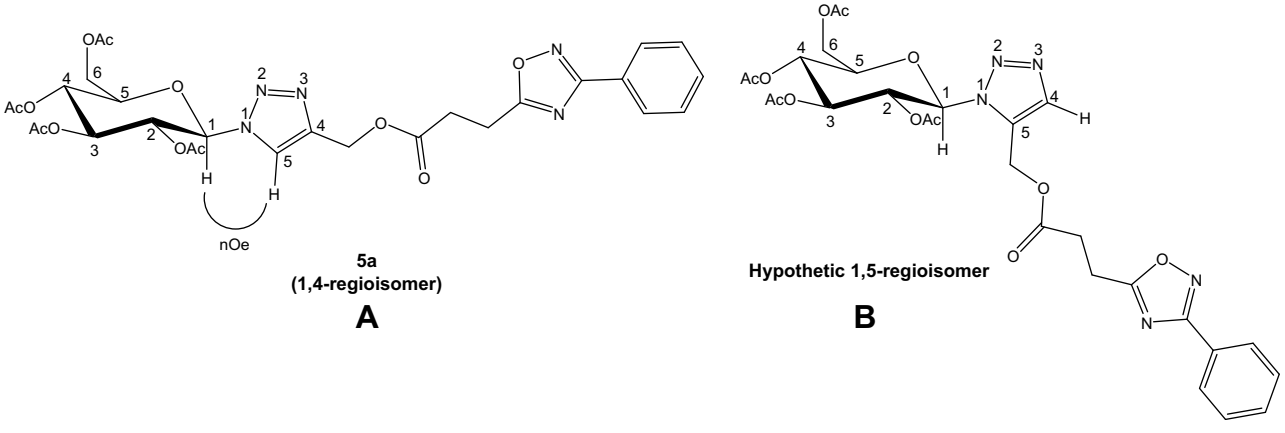


Fig. 1. Possible isomers formed in the copper-catalyzed [3 + 2] cycloaddition reaction between **4** and **3a**. The 1,4-regioisomer (left) was the only isolated product. No detection of the 1,5-regioisomer was found in the ^{1}H NMR and nOe difference spectra.

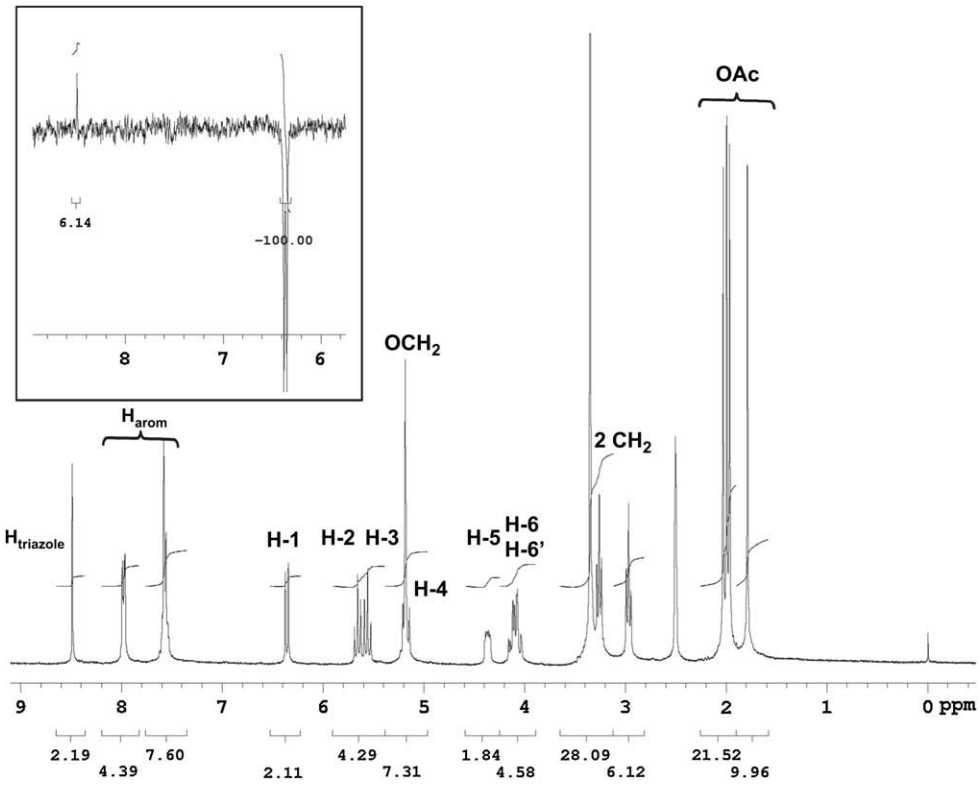


Fig. 2. ^{1}H NMR and nOe diff spectra of the compound **5a**, *O*-{[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-[3-phenyl-1,2,4-oxadiazol-5-yl] propanoate in $DMSO_{d6}$.

1173, 1343, 1590, 1752, 2930, 3243 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3), 2.50 (t, 1H, *J* 2.3 Hz, C≡CH), 3.00 (t, 2H, *J* 7.3 Hz, CH_2), 3.27 (t, 2H, *J* 7.3 Hz, CH_2), 4.73 (d, 2H, *J* 2.3 Hz, CH_2O); 7.29 (d, 1H, *J* 7.5 Hz, H_{arom}), 7.35 (d, 1H, *J* 7.5 Hz, H_{arom}); 7.86 (d, 2H, *J* 9.3 Hz, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 21.2, 21.8, 30.1, 52.4, 75.2, 77.2, 124.4, 126.4, 127.8, 128.6, 131.9, 138.5, 168.3, 170.5, 177.9. Anal. Calcd. for $C_{15}H_{14}N_2O_3$ (C,H,N): C, 66.66%; H, 5.22%, N, 10.36%. Found: C, 66.73%; H, 5.09%; N, 10.67%.

3-[3-(4-Tolyl)-1,2,4-oxadiazol-5-yl] propionic acid prop-2-ynyl ester (**3d**). Prepared from **2d** (0.53 g); 74% (0.46 g); recrystallized from methylene chloride:cyclohexane (1:3, v/v); colorless crystals; m.p.: 43–44 °C; R_f 0.64 (EtOAc/cyclohexane 3:7); IR ν_{max} (KBr): 1173, 1349, 1586, 1745, 2920, 3252 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.49 (t, 1H, *J* 2.4 Hz, C≡CH), 2.99 (t, 2H, *J* 7.3 Hz, CH_2), 3.26 (t, 2H, *J* 7.3 Hz, CH_2), 4.73 (d, 2H, *J* 2.4 Hz, CH_2O), 7.27 (d, 2H, *J* 8.4 Hz, $H_{arom,}$ AA′BB′ system), 7.94 (d, 2H, *J* 8.4 Hz, $H_{arom,}$ AA′BB′ system); ^{13}C NMR ($CDCl_3$): δ 21.5, 21.8, 30.1, 52.4, 75.1, 77.2, 123.7, 127.2, 129.4, 141.4, 168.2, 170.5, 177.7. Anal. Calcd. for $C_{15}H_{14}N_2O_3$ (C,H,N): C, 66.66%; H, 5.22%, N, 10.36%. Found: C, 66.67%; H, 5.15%; N, 10.65%.

Table 2
Neoplastic cell growth inhibition and IC_{50} of compounds **3a** and **5a**–**g**.

Compound	Cell Growth Inhibition (%)		IC_{50} (μg/mL)	
	NCI-H_{292}	HEp-2	NCI-H_{292}	HEp-2
3a	3.6	–	>50.0	
5a	10.4	4.5	>50.0	
5b	9.2	6.7	>50.0	
5c	9.5	7.5	>50.0	
5d	10.2	1.2	>50.0	
5e	24.8	24.1	>50.0	
5f	15.0	4.9	>50.0	
5g	23.1	22.4	>50.0	

3-[3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl]propionic acid prop-2-ynyl ester (**3e**). Prepared from **2e** (0.68 g); 93% (0.71 g); recrystallized from methylene chloride:cyclohexane (1:2, v/v); colorless crystals; m.p.: 61–62 °C; R_f 0.67 (EtOAc/cyclohexane 3:7); IR ν_{max} (KBr): 1186, 1363, 1591, 1744, 2941, 3252 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.50 (t, 1H, *J* 2.5 Hz, C≡CH), 3.00 (t, 2H, *J* 7.0 Hz, CH_2), 3.28 (t, 2H, *J* 7.0 Hz, CH_2), 4.74 (d, 2H, *J* 2.5 Hz, CH_2O), 7.60 (d, 2H, *J* 8.7 Hz, $H_{arom,}$ AA′BB′ system), 7.92 (d, 2H, *J* 8.7 Hz, $H_{arom,}$ AA′BB′ system); ^{13}C NMR ($CDCl_3$): δ 21.8, 30.1, 52.4, 75.2, 77.1, 125.5, 125.6, 128.8, 132.0, 167.5, 170.5, 178.2; Anal. Calcd. for $C_{14}H_{11}BrN_2O_3$ (C,H,N): C, 50.17%; H, 3.31%; N, 8.36%. Found: C, 50.09%; H, 3.18%; N, 8.47%.

3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]propionic acid prop-2-ynyl ester (**3f**). Prepared from **2f** (0.58 g); 93% (0.62 g); recrystallized from methylene chloride:cyclohexane (1:2, v/v); colorless crystals; m.p.: 49–50 °C; R_f 0.67 (EtOAc/cyclohexane 3:7); IR ν_{max} (KBr): 1186, 1357, 1586, 1743, 2934, 3243 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.49 (t, 1H, *J* 2.4 Hz, C≡CH), 3.00 (t, 2H, *J* 7.2 Hz, CH_2), 3.28 (t, 2H, *J* 7.2 Hz, CH_2), 4.74 (d, 2H, *J* 2.4 Hz, CH_2O), 7.45 (d, 2H, *J* 8.7 Hz, $H_{arom,}$ AA′BB′ system), 8.00 (d, 2H, *J* 8.4 Hz, $H_{arom,}$ AA′BB′ system); ^{13}C NMR ($CDCl_3$): δ 21.8, 30.1, 52.5, 75.2, 125.1, 128.7, 129.1, 137.3, 167.4, 170.5, 178.2. Anal. Calcd. for $C_{14}H_{11}ClN_2O_3$ (C,H,N): C, 57.84%; H, 3.81%; N: 9.64%. Found: C, 57.59%; H, 3.73%; N, 9.65%.

3-[3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-yl]propionic acid prop-2-ynyl ester (**3g**). Prepared from **2g** (0.6 g); 87% (0.6 g); recrystallized from methylene chloride:cyclohexane (1:3, v/v); yellow crystals; m.p.: 82–84 °C; R_f 0.55 (EtOAc/cyclohexane 3:7); IR ν_{max} (KBr): 1211, 1352, 1580, 1745, 2940, 3272 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.49 (t, 1H, *J* 2.4 Hz, C≡CH), 3.01 (t, 2H, *J* 7.2 Hz, CH_2), 3.30 (t, 2H, *J* 7.2 Hz, CH_2), 4.73 (d, 2H, *J* 2.4 Hz, CH_2O), 8.22 (d, 2H, *J* 9.0 Hz, $H_{arom,}$ AA′BB′ system), 8.30 (d, 2H, *J* 9.0 Hz, $H_{arom,}$ AA′BB′ system), ^{13}C NMR ($CDCl_3$): δ 21.8, 30.0, 52.5, 75.2, 77.1, 124.0, 128.3, 132.5, 149.3, 166.7, 170.4, 179.0. Anal. Calcd. for $C_{14}H_{11}N_3O_5$ (C,H,N): C, 55.82%; H, 3.68%; N, 13.95%. Found: C, 55.86%; H, 3.70%; N, 13.93%.

*3.1.2. Synthesis of glycosyl–triazole linked 1,2,4-oxadiazoles (**5a**–**g**)*

A solution of sodium ascorbate (14 mg, 0.072 mmol, 15 mol%) and copper acetate (5 mg, 0.024 mmol, 5 mol%) in water (3.0 mL) was added individually to a mixture of the corresponding acetylenic oxadiazole **3a**–**g** (0.53 mmol) and the azidosugar **4** (0.18 g, 0.48 mmol) in CH_2Cl_2 (3.0 mL). The contents were stirred for 20 h at room temperature. The progress of the reaction was monitored by TLC. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) followed by washing the organic layer with aqueous $NaHCO_3$, saturated brine solution and water. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The resulting yellow oil was chromatographed over silica gel using 1:1 cyclohexane:EtOAc as eluant, which after work-up furnished colorless crystals. The final product was recrystallized from methylene chloride:cyclohexane.

O-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-[3-phenyl-1,2,4-oxadiazol-5-yl] propanoate (**5a**). Prepared from **3a** (0.14 g); 83% (0.25 g); recrystallized from methylene chloride:cyclohexane (1:2, v/v); colorless crystals; m.p.: 140–141 °C; $[\alpha]_D^{20}$ −25 ± 1 (*c* 0.33, CH_2Cl_2); R_f 0.41 (EtOAc/cyclohexane 1:1); IR ν_{max} (KBr): 1038, 1236, 1374, 1590, 1751, 2948 cm^{-1}; ^1H NMR (DMSO$_{d6}$): δ 1.78 (s, 3H, OAc), 1.96 (s, 3H, OAc), 1.99 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.96 (t, 2H, *J* 6.9 Hz, CH_2), 3.25 (t, 2H, *J* 6.9 Hz, CH_2), 4.06 (dd, 1H, *J* 12.6, 2.4 Hz, H6), 4.13 (dd, 1H, *J* 12.6, 5.1 Hz, H6'), 4.36 (ddd, 1H, *J* 10.2, 5.1, 2.4 Hz, H5); 5.17 (dd, 1H, *J* 9.3, 10.2 Hz, H4), 5.18 (s, 2H, CH_2O), 5.55 (dd, 1H, *J* 9.3, 9.3 Hz, H3), 5.65 (dd, 1H, *J* 9.0, 9.3 Hz, H2), 6.34 (d, 1H, *J* 9.0 Hz, H1), 7.52–7.61 (m, 3H, H_{arom}), 7.98 (d, 2H, *J* 9.0 Hz, H_{arom}), 8.47 (s, 1H, $H_{triazole}$); ^{13}C NMR (DMSO$_{d6}$): δ 20.0, 20.3, 20.4, 20.6, 21.6, 29.7, 57.4, 61.8, 67.5, 70.1, 72.1, 73.3, 83.9, 124.0, 126.2, 127.0, 129.4, 131.6, 142.6, 167.5, 168.6, 169.5, 169.7, 170.1, 171.2, 179.4. Anal. Calcd. for $C_{28}H_{31}N_5O_{12}$ (C,H,N): C, 53.42%; H, 4.96%; N, 11.12%. Found: C, 53.46%; H, 4.94%; N, 10.79%.

O -{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-[3-(2-tolyl)-1,2,4-oxadiazol-5-yl]propanoate (**5b**). Prepared from **3b** (0.14 g); 77% (0.24 g); recrystallized from methylene chloride:cyclohexane (1:2, v/v); colorless crystals; m.p.: 125–126 °C; $[\alpha]_D^{20}$ −21 ± 2 (*c* 0.26, CH_2Cl_2); R_f 0.49 (EtOAc/cyclohexane 1:1); IR ν_{max} (KBr): 1038, 1233, 1370, 1598, 1747, 2960 cm^{-1}; ^1H NMR (DMSO$_{d6}$): δ 1.79 (s, 3H, OAc), 1.97 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.53 (s, 3H, CH_3), 2.97 (t, 2H, *J* 6.9 Hz, CH_2), 3.27 (t, 2H, *J* 6.9 Hz, CH_2), 4.07 (dd, 1H, *J* 12.6, 2.4 Hz, H6), 4.14 (dd, 1H, *J* 12.6, 5.4 Hz, H6′), 4.38 (ddd, 1H, *J* 9.9, 5.4, 2.4 Hz, H5), 5.18 (dd, 1H, *J* 9.9, 9.6 Hz, H4), 5.19 (s, 2H, CH_2O), 5.57 (dd, 1H, *J* 9.6, 9.3 Hz, H3), 5.67 (dd, 1H, *J* 9.3, 9.0 Hz, H2), 6.37 (d, 1H, *J* 9,0 Hz, H1), 7.34–7.49 (m, 3H, H_{arom}), 7.88 (dd, 1H, *J* 7.5, 1.5 Hz, H_{arom}), 8.49 (s, 1H, $H_{triazole}$); ^{13}C NMR (DMSO$_{d6}$): δ 19.9, 20.3, 20.4, 20.5, 21.6, 29.7, 57.4, 61.8, 67.5, 70.1, 72.1, 73.3, 83.8, 123.9, 125.5, 126.2, 129.7, 130.8, 131.4, 137.5, 142.5, 168.1, 168.5, 169.4, 169.6, 170.0, 171.1, 178.2. Anal. Calcd. for $C_{29}H_{33}N_5O_{12}$ (C,H,N): C, 54.12%; H, 5.17%; N, 10.88%. Found: C, 54.14%; H, 5.07%; N, 10.79%.

O -{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-[3-(3-tolyl)-1,2,4-oxadiazol-5-yl]propanoate (**5c**). Prepared from **3c** (0.14 g); 74% (0.23 g); recrystallized from methylene chloride:cyclohexane (1:2, v/v); colorless crystals; m.p.: 123–124 °C; $[\alpha]_D^{20}$ −28 ± 1 (*c* 0.22, CH_2Cl_2); R_f 0.46 (EtOAc/cyclohexane 1:1); IR ν_{max} (KBr): 1040, 1221, 1370, 1587, 1747, 2948 cm^{-1}; ^1H NMR (DMSO$_{d6}$): δ 1.79 (s, 3H, OAc), 1.97 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.40 (s, 3H, CH_3), 2.97 (t, 2H, *J* 6.9 Hz, CH_2), 3.26 (t, 2H, *J* 6.9 Hz, CH_2), 4.06 (dd, 1H, *J* 12.6, 2.4 Hz, H6), 4.14 (dd, 1H, *J* 12.6, 5.4 Hz, H6), 4.37 (ddd, 1H, *J* 9.9, 5.4, 2.4 Hz, H5), 5.18 (dd, 1H, *J* 9.9, 9.3 Hz, H4), 5.19 (s, 2H, CH_2O). 5.56 (dd, 1H, *J* 9.3, 9.3 Hz, H3), 5.66 (dd, 1H, *J* 9.3, 9.0 Hz, H2), 6.38 (d, 1H, *J* 9.0 Hz, H1), 7.41 (d, 2H, *J* 7.5 Hz, H_{arom}), 7.46 (d, 1H, *J* 7.5 Hz, H_{arom}), 7.79 (d, 1H, *J* 7.5 Hz, H_{arom}), 8.49 (s, 1H, $H_{triazole}$); ^{13}C NMR (DMSO$_{d6}$): δ 19.9, 20.3, 20.4, 20.9, 21.6, 29.7, 57.4, 61.8, 67.5, 70.1, 72.1, 73.3, 83.8, 123.9, 124.2, 126.1, 127.4, 129.2, 132.2, 138.7, 142.5, 167.5, 168.5, 169.4, 169.6, 170.1, 171.1, 179.2. Anal. Calcd. for $C_{29}H_{33}N_5O_{12}$ (C,H,N): C, 54.12%; H, 5.17%; N, 10.88%. Found: C, 53.83%; H, 5.12%; N, 10.92%.

O-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-[3-(4-tolyl)-1,2,4-oxadiazol-5-yl]propanoate (**5d**). Prepared from **3d** (0.14 g); 84% (0.26 g); recrystallized from methylene chloride:cyclohexane (1:2, v/v); colorless crystals; m.p.: 154–155 °C; $[\alpha]_D^{20}$ −20 ± 2 (*c* 0.26, CH_2Cl_2); R_f 0.46 (EtOAc/cyclohexane 1:1); IR ν_{max} (KBr): 1042, 1248, 1373, 1590, 1750, 2958 cm^{-1}; ^1H NMR (DMSO$_{d6}$): δ 1.78 (s, 3H, OAc), 1.96 (s, 3H, OAc), 1.99 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.37 (s, 3H, CH_3), 2.95 (t, 2H, *J* 6.9 Hz, CH_2), 3.24 (t, 2H, *J* 6.9 Hz, CH_2), 4.05 (dd, 1H, *J* 12.3, 2.4 Hz, H6), 4.13 (dd, 1H, *J* 12.3, 5.4 Hz, H6′), 4.36 (ddd, 1H, *J* 9.9, 5.4, 2.4 Hz, H5), 5.18 (dd, 1H, *J* 9.9, 9.3 Hz, H4), 5.18 (s, 2H, CH_2O), 5.55 (dd, 1H, *J* 9.3, 9.3 Hz, H3), 5.65 (dd, 1H, *J* 9.3, 9.0 Hz, H2), 6.34 (d, 1H, *J* 9.0 Hz, H1), 7.36 (d, 2H, *J* 8.1 Hz, H_{arom}, AA′BB′ system), 7.86 (d, 2H, *J* 8.1 Hz, H_{arom}, AA′′BB′ system), 8.47 (s, 1H, $H_{triazole}$); ^{13}C NMR (DMSO$_{d6}$): δ 20.0, 20.3, 20.5, 20.7, 21.2, 21.6, 29.7, 57.4, 61.8, 67.5, 70.2, 72.2, 73.3, 83.9, 123.5, 124.0, 127.0, 129.9, 141.5, 142.6, 167.5, 168.6, 169.5, 169.7, 170.1, 171.2, 179.2. Anal. Calcd. for $C_{29}H_{33}N_5O_{12}$ (C,H,N): C, 54.12%; H, 5.17%; N, 10.88%. Found: C, 54.34%; H, 5.16%; N, 10.72%.

O-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-[3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl]propanoate (**5e**). Prepared from **3e** (0.18 g); 73% (0.25 g); recrystallized from methylene chloride:cyclohexane (1:1, v/v); colorless crystals; m.p.: 105–107 °C; $[\alpha]_D^{20}$ −18 ± 2 (*c* 0.26, CH_2Cl_2); R_f 0.44 (EtOAc/cyclohexane 1:1); IR ν_{max} (KBr): 1040, 1231, 1368, 1585, 1745, 2945 cm^{-1}; ^1H NMR (DMSO$_{d6}$): δ 1.80 (s, 3H, OAc), 1.98 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.97 (t, 2H, *J* 6.9 Hz, CH_2), 3.27 (t, 2H, *J* 6.9 Hz, CH_2), 4.07 (dd, 1H, *J* 12.6, 2.4 Hz, H6), 4.14 (dd, 1H, *J* 12.6, 5.1 Hz, H6'), 4.38 (ddd, 1H, *J* 9.6, 5.1, 2.4 Hz, H5), 5.19 (dd, 1H, *J* 9.6, 9.6 Hz, H4), 5.19 (s, 2H, CH_2O), 5.57 (dd, 1H, *J* 9.6, 9.3 Hz, H3), 5.67 (dd, 1H, *J* 9.3, 9.0 Hz, H2), 6.37 (d, 1H, *J* 9.0 Hz, H1), 7.78 (d, 2H, *J* 8.7 Hz, H_{arom}, AA′BB′ system), 7.92 (d, 2H, *J* 8.4 Hz, H_{arom}, AA′BB′ system), 8.49 (s, 1H, $H_{triazole}$); ^{13}C NMR (DMSO$_{d6}$): δ 19.9, 20.3, 20.4, 20.5, 21.5, 29.7, 57.4, 61.8, 67.5, 70.1, 72.1, 73.3, 83.9, 123.9, 125.1, 125.4, 129.0, 132.4, 142.5, 166.8, 168.5, 169.4, 169.6, 170.1, 171.1, 179.6. Anal. Calcd. for $C_{28}H_{30}BrN_5O_{12}$ (C,H,N): C, 47.47%; H, 4.27%; N: 9.89%. Found: C, 47.25%; H, 4.32%; N, 9.86%.

O-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]propanoate (**5f**). Prepared from **3f** (0.15 g); 66% (0.21 g); recrystallized from methylene chloride:cyclohexane (1:1, v/v); colorless crystals; m.p.: 106–107 °C; $[\alpha]_D^{20}$ −17 ± 2 (*c* 0.31, CH_2Cl_2), R_f 0.39 (EtOAc/cyclohexane 1:1); IR ν_{max} (KBr): 1045, 1227, 1364, 1593, 1753, 2941 cm^{-1}; ^1H NMR (DMSO$_{d6}$): δ 1.79 (s, 3H, OAc), 1.97 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.97 (t, 2H, *J* 6.9 Hz, CH_2), 3.27 (t, 2H, *J* 6.9 Hz, CH_2), 4.07 (dd, 1H, *J* 12.6, 2.4 Hz, H6), 4.14 (dd, 1H, *J* 12.6, 5.3 Hz, H6'), 4.38 (ddd, 1H, *J* 9.9, 5.3, 2.4 Hz, H5), 5.19 (dd, 1H, *J* 9.9, 9.3 Hz, H4), 5.19 (s, 2H, CH_2O), 5.57 (dd, 1H, *J* 9.3, 9.3 Hz, H3), 5.67 (dd, 1H, *J* 9.3, 9.0 Hz, H2), 6.37 (d, 1H, *J* 9.0 Hz, H1), 7.65 (d, 2H, *J* 8.4 Hz, H_{arom}, AA′BB′ system), 7.99 (d, 1H, *J* 8.7 Hz, H_{arom}, AA′BB′ system), 8.49 (s, 1H, $H_{triazole}$); ^{13}C NMR (DMSO$_{d6}$): δ 19.9, 20.3, 20.4, 20.5, 21.5, 29.7, 57.4, 61.8, 67.5, 70.1, 72.1, 73.3, 83.8, 123.9, 125.0, 128.8, 129.4, 136.3, 142.5, 166.7, 168.5, 169.4, 169.6, 170.0, 171.1, 179.6. Anal. Calcd. for $C_{28}H_{30}ClN_5O_{12}$ (C,H,N): C, 50.65%; H, 4.55%; N, 10.55%. Found: C, 50.34%; H, 4.83%; N, 10.35%.

O-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]propanoate (**5g**). Prepared from **3g** (0.16 g); 69% (0.22 g); recrystallized from methylene chloride:cyclohexane (1:1, v/v); colorless crystals; m.p.: 124–125 °C; $[\alpha]_D^{20}$ −24 ± 1 (*c* 0.30, CH_2Cl_2); R_f 0.28 (EtOAc/cyclohexane 1:1); IR ν_{max} (KBr): 1042, 1225, 1362, 1579, 1750,

2950 cm^{-1}; ^1H NMR ($DMSO_{d6}$): δ 1.80 (s, 3H, OAc), 1.97 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.97 (t, 2H, *J* 6.9 Hz, CH_2), 3.31 (t, 2H, *J* 6.9 Hz, CH_2), 4.07 (dd, 1H, *J* 12.6, 2.4 Hz, H6), 4.14 (dd, 1H, *J* 12.6, 5.4 Hz, H6'), 4.38 (ddd, 1H, *J* 9.9, 5.4, 2.4 Hz, H5), 5.18 (dd, 1H, *J* 9.9, 9.3 Hz, H4), 5.20 (s, 2H, CH_2O), 5.57 (dd, 1H, *J* 9.3, 9.3 Hz, H3), 5.66 (dd, 1H, *J* 9.3, 9.0 Hz, H2), 6.36 (d, 1H, *J* 9.0 Hz, H1), 8.24 (d, 2H, *J* 9.0 Hz, $H_{arom,}$ AA′BB′ system), 8.41 (d, 1H, *J* 9.0 Hz, $H_{arom,}$ AA′BB′ system), 8.49 (s, 1H, $H_{triazole}$), ^{13}C NMR ($DMSO_{d6}$): δ 19.9, 20.3, 20.4, 20.5, 21.6, 29.7, 57.4, 61.8, 67.5, 70.1, 72.1, 73.3, 83.8, 123.9, 124.5, 128.4, 131.9, 142.5, 149.2, 166.2, 168.5, 169.4, 169.6, 170.1, 171.1, 180.2. Anal. Calcd. for $C_{28}H_{30}N_6O_{14}$ (C,H,N): C, 49.85%; H, 4.48%; N, 12.46%. Found: C, 49.41%; H, 4.53%; N, 12.00%.

3.2. Cytotoxic activity

For cytotoxicity evaluation, HEp-2 (larynx carcinoma) and NCI-H_{292} (lung carcinoma) cell strains with proven viability were used. The cells were cultivated in MEM – Minimal Essential Medium with 10% bovine fetal serum containing 1% antibiotics solution (penicillin 1000 UI/mL + streptomycin 250 mg/mL) and 1% glutamine solution (200 μM). A cell suspension containing 5.10^4 cells/mL was used and distributed in plates of 96 wells. The drugs **3a** and **5a–g** were diluted in DMSO (0.15 mL) and added into each well. The plates were incubated for 72 h at 37 °C in humid atmosphere enriched with 5% CO_2. After incubation, MTT (15 mL) in phosphate buffered saline solution (5 mg/mL) was added into each well. After 2 h, the culture medium was removed and DMSO (100 μL) were added in the wells for formazan quantification. The measurements were performed using a Multskan ELX 800 cell reader at 595 nm.

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Appendix. Supplementary materials

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2009.03.002.

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