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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and biological evaluation of novel D-glucose-derived 1,2,3-triazoles as potential antibacterial and antifungal agents

Hui-Zhen Zhang · Jin-Jian Wei · Kannekanti Vijaya Kumar · Syed Rasheed · Cheng-He Zhou

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Abstract A series of novel D-glucose-derived 1,2,3-triazoles have been synthesized in excellent yields via Cu(I)-catalyzed 1,3-dipolar cycloaddition by using methyl α-D-glucopyranoside as starting material. All the new compounds were confirmed by ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectra, and their antimicrobial activities were screened against Gram-Positive, Gram-Negative bacteria, and fungi. Bioactive assay manifested that some of the synthesized glucose-derived 1,2,3-triazoles exhibited good antibacterial and antifungal activities. Notably, compound **5k** gave the most potent efficiency with MIC_{50} value of 6 μM against *Candida albicans*, which was nine-fold more active than the reference drug Fluconazole. It also exhibited good antibacterial activity against *Escherichia coli* with the MIC_{50} value of 10.8 μM compared to Chloramphenicol while the corresponding hydrochloride **4k** revealed remarkable inhibitory against *Bacillus subtilis* with an MIC_{50} value of 11 μM.

Keywords 1,2,3-Triazole · Glucoside · Antibacterial · Antifungal

Hui-Zhen Zhang and Jin-Jian Wei have contributed equally to this work.

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Introduction

The incidence of systemic microbial infections has been rapidly increasing and becoming a major threat to public health due to the dramatic upper-rising drug resistance in the past few decades. Especially, the occurrence of multi-drug resistant bacteria and fungi has emerged as a significant problem in both community and hospital acquired infections (De Marco *et al*., 2007; Dismukes, 2006). Among the various drugs responsible for antimicrobial activity, triazoles especially 1,2,4-triazole derivatives as an important type of nitrogen-containing aromatic heterocyclic compounds with excellent safety profile, favorable pharmacokinetic characteristics and wide biological activities showed wide range of potential applications (Peng *et al*., 2013a; Wang and Zhou, 2011a; Zhou and Wang 2012). This encouraged numerous researchers to engage in the development of novel 1,2,4-triazole-based antimicrobial agents with high efficiency, broad spectrum, and low toxicity in recent years (Fang *et al*., 2010; Wang *et al*., 2012; Zhang *et al*., 2013a). Up to now, a large number of 1,2,4-triazole antimicrobial agents (such as Itraconazole, Fluconazole, Voriconazole and Ravuconazole) have been successfully developed and widely used in clinic (Wang and Zhou, 2011a; Zhang *et al*., 2012). Nevertheless, the therapeutic use of these drugs is often accompanied with problems of drug resistance, undesired side effects, and limited bioavailability (Odd, 2010). Therefore, lots of efforts have been directed to optimize and modify the structure of well-known azole drugs according to the empirical development of structure–activity relationship

(SAR) and prodrug theory (Hecker and Erion, 2008; Zhang *et al*., 2011a; Zhang and Zhou, 2011b). Apart from this, another increasing prevalent and effective strategy is to design and develop new classes of antimicrobial agents with different chemical structures and new mechanism of action from traditional drugs to improve their activities while retaining good bioavailability and safety profiles (Shi and Zhou, 2011; Zhang *et al*., 2012; Zhang *et al*., 2010). Heterocyclic compounds with special structures have displayed interesting properties in medicinal aspects (Peng *et al*., 2013b; Zhang *et al*., 2014b), and their syntheses and researches have attracted numerous attentions (Zhang *et al*., 2014a).

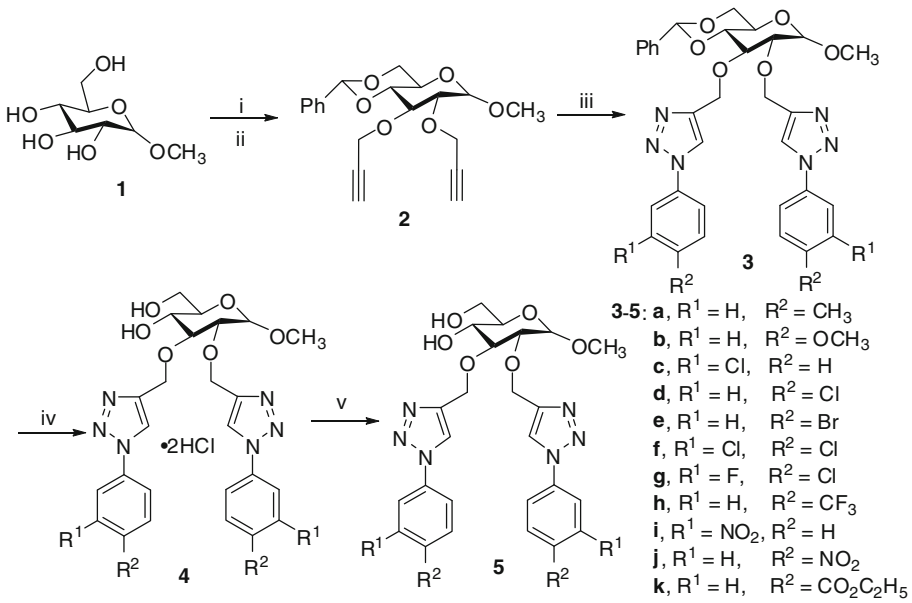
1,2,3-Triazole and its derivatives as another important class of triazoles possessing myriad potential applications in chemical synthesis, material science, and biology, have aroused progressive attention in recent years with the introduction of 'click chemistry' for its easy and efficient synthesis (Hawker and Wooley, 2005; Moses and Moorhouse, 2007; Wang *et al*., 2011b; Wang *et al*., 2010). In particular, 1,2,3-triazole serving as a potential pharmacophore, which was found to be potent antineoplastic (Wu *et al*., 2009), antibacterial (Phillips *et al*., 2009), antifungal (Aher *et al*., 2009), antitubercular (Gill *et al*., 2008), and anti-HIV agents (Giffin *et al*., 2008; Whiting *et al*., 2006), has occupied an important position in medicinal chemistry owing to its chemotherapeutic value (Somu *et al*., 2006; Tron *et al*., 2008; Wei *et al*., 2011). So far lots of 1,2,3-triazole drugs such as antibacterial cefatrizine and tazobactam as well as antiepileptic rufinamide have been extensively used in clinic, and some 1,2,3-triazole compounds as clinical candidates such as antibacterial radezolid have shown large potential (Mohebbi *et al*., 2014). It is especially noteworthy that 1,2,3-triazole derivatives may be considered as new entry to azole antifungal agents (Aher *et al*., 2009). Also, some 1,2,3-triazole derivatives were used as DNA cleaving agents (Kamal *et al*., 2008), potassium channel activator (Calderone *et al*., 2008), and cannabinoid CB1 receptor (Hou *et al*., 2009) and so on. 1,2,3-Triazole was stable to metabolic degradation and capable of forming hydrogen bonds, which was favoring in binding of biomolecular targets and improving solubility (Horne *et al*., 2004; Lv *et al*., 2014). Moreover, 1,2,3-triazole as an attractive bridge group, which could connect two pharmacophores to give an innovative bifunctional drug, has become increasingly useful and important in constructing bioactive molecules and functional molecules (Tron *et al*., 2008). Noticeably, the bioisosteric replacement between 1,2,3-triazole and its bioisoster 1,2,4-triazole, amide, or even other nitrogen-containing aromatic heterocycles is of special interest in medicinal chemistry, which represents an efficient concept for the discovery and development of novel triazole drugs. Furthermore, triazole scaffolds with extended chemical space could enhance biological activity effectively (Huber *et al*., 2009; Pokrovskaya *et al*., 2009). In addition, many investigations demonstrated that biological activity of azole derivatives was significantly influenced by the introduction of variable aromatic substituents. For example, halogen substitution or strong electron-withdrawing substitution were found to increase lipid solubility to a certain extent and could efficiently enhance the antimicrobial activity (Cui *et al*., 2013; Yin *et al*., 2014; Zhang *et al*., 2013b). The substitution of aromatic ring by fluorine or chlorine and other electron-withdrawing substituted aromatic rings represented a valuable strategy and were extensively employed in drug discovery.

Promoted by all above observations and considering that sugar moiety with polyhydroxyl groups has been extensively employed in drug design, frequently used to improve water solubility and usually introduced into artificial receptors to increase the interaction between receptors and guests for molecular recognition (Amblard *et al*., 2009; Thibodeaux *et al*., 2007), a series of novel D-glucose-derived 1,2,3-triazoles bearing various substituted phenyl rings were designed and synthesized in this contribution. All these newly synthesized compounds were evaluated for their antibacterial and antifungal activities. Incorporation of glucose was helpful to improve the water solubility of target molecules. Various substituted phenyl groups were introduced into the target compounds in order to investigate their SARs.

Results and discussion

Chemistry

The synthetic route for the preparation of D-glucose-derived 1,2,3-triaozles **3**–**5** was outlined in Scheme 1. The intermediate aryl azides were prepared from commercially available arylamines, which were treated with *t*-butyl nitrite and NaN_3 in *t*-BuOH to afford corresponding aryl azides with 75.2–90.0 % yields. Addition of small quantity of water increased the reaction rate considerably (Das *et al*., 2005). Compound **2** was synthesized in 80.9 % yield by the reaction of methyl 4,6-O-benzylidene-α-D-glucopyranoside with propargyl bromide in the presence of NaH using anhydrous Tetrahydrofuran (THF) as solvent. In the propargylation of methyl 4,6-O-benzylidene α-D-glucopyranoside, the reaction temperature, dropwise rate, and dosage of propargyl bromide as well as the nature of solvent exerted great influence on the reaction. Generally, slow addition of excess propargyl bromide (six equivalent of protected α-D-glucopyranoside) at low temperature such as ice-salt bath together with assurance of an anhydrous



Scheme 1 Synthetic route of novel glucose-derived 1,2,3-triazoles **5a–k** Reagents and conditions: (i) $PhCHO/ZnCl_2$; (ii) NaH/abs.THF, propargyl bromide; (iii) aryl azides (2 equiv), $CuSO_4 \bullet 5H_2O$ (0.1 equiv), sodium ascorbate (0.2 equiv), $DMSO/H_2O = 4:1$ (v/v); (iv) 5 % hydrochloric acid; (v) 25 % NH_3 aq

and anaerobic system facilitated the reaction and raised the yields apparently. No mono-propargyl-α-D-glucoside was obtained. Either the temperature higher than 50 °C or addition of all propargyl bromide at once resulted in a very complex system, which was difficult to separate. On the other hand, the effect of solvent was another quite important factor in the propargylation of glucoside. Our observation indicated that anhydrous aprotic solvent THF could give good reactivity and excellent yields.

The cycloaddition of acetylenic compound **2** with aryl azides using catalytic amount of copper sulfate and sodium ascorbate in *t*-$BuOH/H_2O$ at room temperature afforded 1,4-disubstituted triazole compounds **3a–k** in moderate to good yields ranging from 78.0 % to 97.4 %. The 4,6-O-benzylidene group of compounds **3a–k** were easily deprotected with 5 % hydrochloric acid. After the reaction was completed, the solvent was evaporated and the resulting residue was washed with petroleum ether (30–60 °C) in order to remove benzaldehyde. This afforded the pure hydrochlorides **4a–k** in almost quantitive yields. Subsequently, the salts **4a–k** were neutralized with 25 % analytic grade ammonium hydroxide to give compounds **5a–k**.

Analysis of spectra

All the new compounds were characterized by IR, ^1H NMR, ^{13}C NMR, MS, and HRMS spectra. Their spectral analyses were consistent with the assigned structures and listed in the experimental section. The mass spectra for benzimidazole compounds gave a major fragment of $[M + H]^+$ according to their molecular formula.

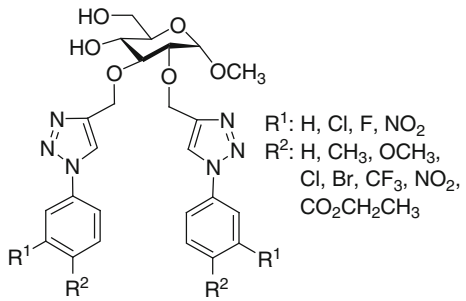


Fig. 1 Structures of some antimicrobial D-glucose-derived 1,2,3-triazole derivatives

The structures of the synthesized compounds **3a–k, 4a–k,** and **5a–k** were in accordance with their spectral analyses. MS of all the compounds displayed $[M + Na]^+$ and $[M + H]^+$ peaks corresponding to their molecular weights. Besides, triazole hydrochlorides **4a–k** showed a $[M + Na–2HCl]^+$ fragment ion peak in the mass spectra. (Fig. 1).

In the ^1H NMR of compound **3a**, triazole protons appeared as two distinct singlets at δ 8.23 and 8.02 ppm, indicating the different chemical environment of two triazole rings resulting from the chiral glucose. From the optimized 3D structure of compound **3a** (Fig. 2), the distance between the lone pair of triazole N-3 linked by glucoside C-2 position and triazole 5-H linked glucoside C-3 chain (3.341 Å) was closer than the distance between the one pair of triazole N-3 linked by glucoside C-3 position and triazole 5-H linked glucoside C-2 chain (7.860 Å). Electronic effects resulted in the large downfield of triazole 5-H linked glucoside C-3 chain (Fig. 3). From the ^{13}C NMR spectrum of compound **3a**, two set of signals of triazole

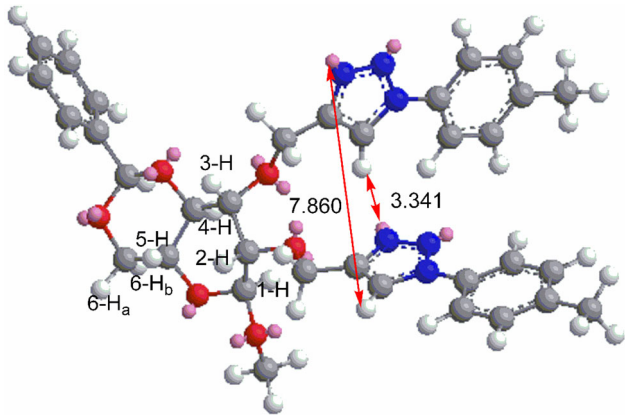


Fig. 2 The optimized 3D structure of compound **3a**

C-4 at δ 145.96 and 145.20 ppm or triazole C-5 at δ 120.62 and 120.13 ppm accounted for the above spatial influence of two triazole rings. Also, the ^{1}H NMR spectrum of compound **3a** showed a singlet at δ 5.57 ppm due to the presence of benzylidene group, which could be confirmed by the ^{13}C NMR signal of Ph-CH at δ 101.50 ppm. Similar patterns were observed in ^{1}H NMR and ^{13}C NMR spectra of compounds **3b**–**k** as well.

From the ^{1}H NMR of compound **4a**, the proton of Ph-CH, which appeared at δ 5.57 ppm of compound **3a**, disappeared. The proton of triazole ring in hydrochloroates **4a**–**k** showed large downfield shift of 0.3–0.9 ppm compared to the protected α-D-glucopyranoside derived bis-triazoles **3a**–**k**, which can be ascribed to the presence of positive charges in the triazole system. All the anomeric 1-H signals in compounds **5a**–**k** gave small coupling constants *J* values (2.9–3.6 Hz). This demonstrated that these D-glucose derivatives possessed α configuration. Thus, substitutions did not result in a change of the α-D-glucoside configuration.

In addition, the optical rotations of all the compounds showed a certain degree of regularity. All the compounds remained dextrorotation and the optical rotation pattern was observed that α values of hydrochlorides **4a**–**k** were larger than their corresponding α-D-glucopyranoside derived bis-triazoles **5a**–**k**, which were almost equal to compounds **3a**–**k**.

Biological activity

The in vitro antimicrobial screening for all the synthesized compounds was evaluated for two Gram-Positive bacteria (*Staphylococcus aureus* ATCC 29213, *Bacillus. subtilis*), three Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa, B. proteus*), and two fungi (*Candida albicans* ATCC 76615, *Aspergillus fumigatus*) using two-fold serial dilution technique recommended by National Committee for Clinical Laboratory

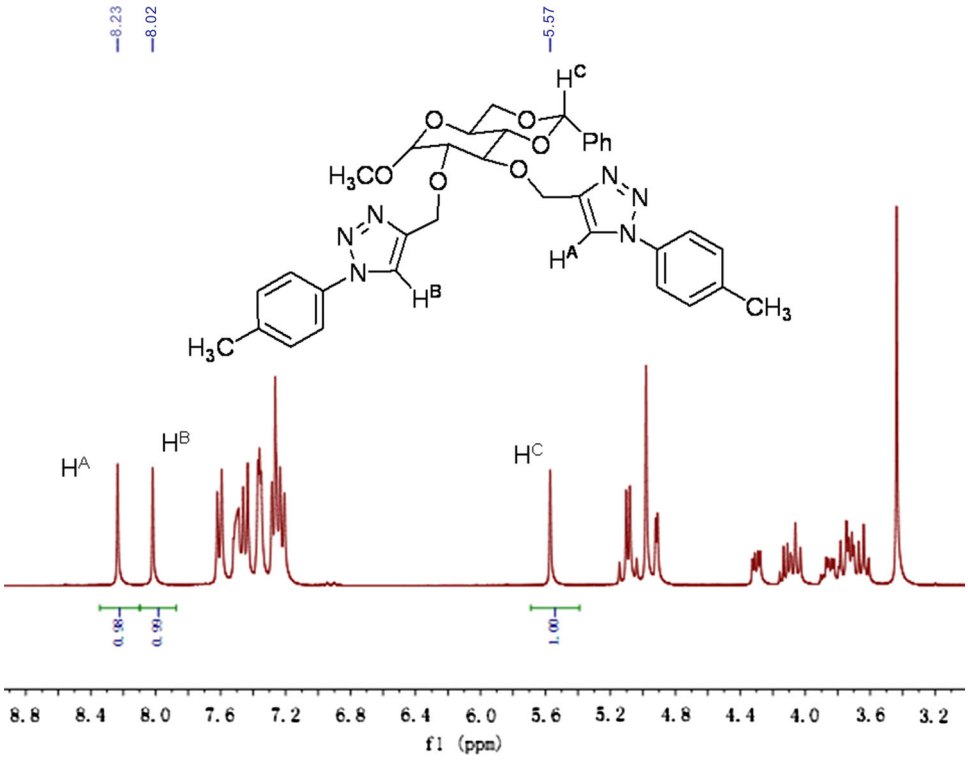


Fig. 3 The ^{1}H NMR spectrum of compound **3a**

Table 1 In vitro antimicrobial activity of compounds **3–5**

Compounds	MIC_{50} μM (μg/mL)						
	C.albicans ATCC 76615	*A.fumigatus*	*S. aureus* ATCC 29213	*P.aeruginosa*	*B.subtilis*	*B.proteus*	*E. coli* ATCC 25922
3a	820	820	820	820	820	820	820
3b	780	780	780	780	780	780	780
3c	770	770	770	770	770	770	770
3d	770	770	770	770	770	770	770
3e	680	680	680	680	680	680	680
3f	690	690	350	690	690	690	690
3g	730	730	730	730	730	730	730
3h	690	690	690	690	690	690	690
3i	750	750	750	750	750	750	750
3j	750	750	750	750	750	750	750
3k	690	690	690	690	173	690	345
4a	750	750	750	750	750	750	750
4b	800	750	750	750	750	750	750
4c	790	790	98.6	790	790	790	790
4d	790	790	790	790	790	790	790
4e	690	690	690	690	690	690	690
4f	50	800	800	800	800	100	50
4g	26	420	840	840	420	52	52
4h	50	100	800	800	400	12.5	50
4i	760	760	760	760	760	760	760
4j	760	760	760	760	760	760	760
4k	177	710	710	710	11	710	177
5a	960	960	960	960	960	960	960
5b	900	220	900	900	900	900	900
5c	890	890	27.8	890	890	890	890
5d	890	890	890	890	890	890	890
5e	770	770	770	770	770	770	770
5f	25	400	200	800	800	200	12.5
5g	13	210	840	840	840	26	26
5h	25	50	100	800	400	25	50
5i	860	860	860	860	860	860	860
5j	860	860	860	860	860	860	860
5k	6	780	196	780	196	390	10.8
A	52	837	–	–	–	–	–
B	–	–	1,590	1,590	1,590	50	50

Minimum inhibitory concentrations were determined by micro broth dilution method for microdilution plates

A = Fluconazole, **B** = Chloramphenicol

Candida albicans ATCC76615, *C. albicans* ATCC76615; *Aspergillus fumigatus*, *A. fumigatus*; *Staphylococcus aureus* ATCC 29213, *S. aureus* ATCC 29213; *Pseudomonas aeruginosa*, *P. aeruginosa*; *Bacillus proteus*, *B. proteus*; *Bacillus subtilis*, *B. subtilis*; *Escherichia coli* ATCC 25922, *E. coli* ATCC 25922

Standards (NCCLS) with the positive control of clinically antimicrobial drugs Chloromycin and Fluconazole. The results of all the tested compounds were reported as minimal inhibitory concentrations (MIC_{50}, μM), and were shown in Table 1.

Antibacterial activity

The antibacterial data revealed that most of the benzylidene protected glucose-derived bis-triazoles gave poor antibacterial activities. But some deprotected 1,2,3-triazoles and

their hydrochlorides showed moderate or even excellent antibacterial activity against tested strains.

The in vitro antibacterial evaluation demonstrated that benzylidene protected glucose triazole **3c** bearing chloro moiety at *meta* position of benzene showed moderate inhibitory against *S. aureus* ATCC 29213 among all the protected glucose 1,2,3-triazoles, whereas its corresponding deprotected glucose triazole **5c** exhibited excellent inhibitory activity against *S. aureus* with an MIC_{50} value of 27.8 μM superior to its hydrochloride **4c** and compound **3c**. While introduction of chloro substituent in C-4 position of aryl triazole **5c** afforded 3,4-dichloro substituted phenyl triazole **5f**, which showed dramatically decreased inhibitory against *S. aureus* with the MIC_{50} value of 200 μM in contrast to monochlorophenyl compound **5c**. Furthermore, compounds **5h** and **5k** gave moderate inhibitory against *S. aureus* compared to their antifungal activity, and the corresponding hydrochloride **4k** of compound **5k** showed excellent activity against *B. subtilis* with an MIC_{50} value of 11 μM superior to the protected glucose triazole **3k** and deprotected derivative **5k** with MIC_{50} values of 173 and 196 μM, respectively. Compounds **5g** and **5h** contaning 3-fluoro-4-chlorophenyl and trifluoromethyl, respectively, as well as their hydrochlorides **4g** and **4h** could significantly inhibit the growth of *B. proteus* and *E. coli* at concentrations ranging from 12.5 to 52 μM except for their efficient antifungal activity against *C. albicans*. In addition, 3,4-dichlorophenyl triazole **5f** and its hydrochloride **4f** also showed moderate inhibitory against *B. proteus* compared to Chloramphenicol. More importantly, the bioactive data revealed that deprotected glucose bis-triazoles **5k** possessed the most potent inhibitory against *E. coli* ATCC 25922 (MIC_{50} = 10.8 μM) superior to its hydrochloride **4k**.

From the overall results, it can be concluded that their antimicrobial activity was obviously influenced by substituents in benzene ring. As expected, some halogen-substituted or electron-withdrawing substituted aromatic compounds, which may result in the different electronic distribution of all listed compounds, really displayed good activity against tested strains. Especially, 1,2,3-triazoles **5f–h** and **5k** bearing 2,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, trifluoromethyl, as well as ethoxycarbonylphenyl, respectively, and their hydrochlorides showed good antimicrobial activity. While *meta*-chloro substituted phenyl triazole **5c** only gave excellent antibacterial activity against *S. aureus* in this study. As a result, it is necessary to further investigate these biologically active compounds as antimicrobial agents.

Antifungal activity

The antifungal tests indicated that some of the newly synthesized compounds showed potent activity in vitro. As seen in Table 1, glucose-derived 1,2,3-triaozles **5f**, **5g**, **5h**, and their corresponding hydrochlorides **4f**, **4g,** and **4h**, as well as compound **5k** exhibited efficient activities against *C. albicans* with MIC_{50} values ranging from 6 to 50 μM superior to reference drug Fluconazole. It was specially noted that deprotected glucose-derived bis-1,2,3-triazole **5k** bearing ethoxycarbonyl group at *para* position in substituted benzene showed better inhibitory against *C. albicans* than its hydrochloride **4k**, with an MIC_{50} value of 6 μM, nine-fold more potent than Fluconazole.

From the antifungal activity data in Table 1, it was also observed that compounds **5f**, **5g,** and **5h** exhibited better antifungal activity against *C. albicans* than their corresponding hydrochlorides. Triazole derivatives **4g** and **5g** with 3-fluoro-4-chlorophenyl moiety against *C. albicans* were superior to 3,4-dichlorophenyl triazoles **4f** and **5f**. The increased activity could be ascribed to the replacement of chloro substituent by fluoro moiety in C-3 position of phenyl triazoles **4f** and **5f**, which changed the electronic distribution and physical–chemical properties of the whole molecule and thereby influence the absorption, distribution, and metabolism of the bioactive molecules. Accordingly, strong electron withdrawing trifloromethyl substituted phenyl triazole **5h** possessed potent inhibitory activity against *C. albicans* with the MIC_{50} value of 25 μM, which was equivalent to that of compound **5f**. Meanwhile, compound **5h** possessed the best acitivity against *A. fumigatus* with the MIC_{50} value of 50 μM superior to the reference drug Fluconazole among all the tested compounds, while its hydrochloride **4h** gave a little weaker activity than compound **5h**. In addition, *para*-methoxyl substituted phenyl triazole **5b** and compound **5g** displayed moderate antifungal activity against *A. fumigatus*. Other 1,2,3-triazoles gave poor or no inhibitory against *A. fumigatus*.

The above discussion demonstrated that the substituents in 1,2,3-triazole ring played an important role in antifungal activity, they could not only broaden their antifungal spectrum but also greatly increase the potency. Glucose-derived bis-1,2,3-triazoles containing electron withdrawing substituents such as dichloro, 3-fluoro-4-chloro, trifluoromethyl, and ethoxycarbonyl moieties, were in favor of improving antifungal activity. Especially, bis-triazoles **5f**, **5g**, and **5h** along with their hydrochlorides, as well as compound **5k** exhibited equal or even better inhibitory compared to Fluconazole. This results manifested that 1,2,3-triazole and its derivatives are of biological importance. Further study in vivo of these bioactive compounds as antifungal agents is in progress.

Conclusion

In conclusion, we have successfully prepared a series of novel glucose-derived 1,2,3-triazoles through an easy, convenient,

and efficient synthetic route starting from commercially available methyl α-D-glucoside. All the new compounds were confirmed by NMR, IR, UV, and MS spectra, and their antimicrobial activities were evaluated against *S. aureus*, *E. coli*, *B. proteus*, *B. subtilis*, *P. aeruginosa, C. albicans,* and *A. fumigatus*. Based on the biological data, compound **5c** with chloro group at *meta* position of benzene exhibited excellent activity against *S. aureus* with an MIC_{50} value of 27.8 μM in comparison with Chloramphenicol. Compounds **5f–h** and **5k** as well as their corresponding hydrochlorides showed the most potent antimicrobial activity, even comparable or superior to the clinical drugs (Fluconazole and Chloramphenicol). The type of substituents in benzene ring had noticeable effect on the antimicrobial activity of glucose-derived 1,2,3-triazoles. These results showed that the present series containing 1,2,3-triazole as a lead is necessary to further investigate for new antimicrobial agents with potent activity and minimal toxicity.

Experimental

General methods

All air and moisture sensitive reactions were carried out in flame dried, N_2-flushed, double-neck round bottom flask sealed with rubber septa, and the reagents were injected with a syringe. THF was freshly distilled from sodium-benzophenone. Methyl 4,6-O-benzylidene α-D-glucopyranoside was prepared from methyl α-D-glucopyraoside (**1**). Aryl azides were prepared according to the procedure described as in the literature (Lv *et al*., 2014). All other chemicals and reagents were obtained from commercial suppliers and used without further purification. TLC analyses were done using pre-coated silica gel plates and visualization was done using UV lamp at 254 nm and I_2. ^1H and ^{13}C NMR spectra were recorded on Bruker AV-300 or Varian-Mercury 400 spectrometer instrument (Bruker Bioscience, Varian, Palo Alto, CA, respectively, both USA). The chemical shifts were given with respect to tetramethylsilane (^1H: δ 0 ppm) and $CDCl_3$ (^{13}C: δ 77.0 ppm). The following abbreviations were used to designate aryl groups: SUGAR = α-D-glucopyranoside, Ph = phenyl. Coupling constants were determined directly from ^1H NMR spectra. The mass spectra were recorded on FINIGAN TRACE GC/MS (Thermo Electron Corporation, Bremen, Germany). FT-IR spectra were carried out on Bruker RFS100/S spectrophotometer (Bio-Rad, Cambridge, MA, USA) using KBr pellets in the 400–4,000 cm^{-1} range. Absorption spectra were recorded on TU1901 UV–vis spectrometer (China). Melting points were recorded on X−6 melting point apparatus. Optical rotations were measured on a JASCO P-1010 Polarimeter (JASCO Corporation, Japan) at λ = 589 nm.

*Methyl 4,6-O-benzylidene-2,3-di-O-propargyl-α-D-glucopyranoside (**2**)*

To a solution of 5.0 g (17.7 mmol) methyl 4,6-O-benzylidene α-D-glucopyranoside (Tankam *et al*., 2007) in 80 mL anhydrous THF was added 3.3 g (0.14 mol) sodium hydride. The suspension was stirred for 45 min and cooled with an ice-salt bath. With vigorous stirring, 4.8 mL of propargyl bromide was added slowly, and the reaction mixture was stirred for 2 days at room temperature. Brash ice was added carefully until no gas was generated. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (40 mL × 3). The combined ethyl acetate solutions were washed with saturated NaCl solution, dried with anhydride sodium sulfate, and then concentrated under reduced pressure. The residue was subjected to column chromatography on flash chromatography on silica gel using ethyl acetate-petroleum (1:4, v/v) as eluent to give methyl 4,6-O-benzylidene-2,3-di-O-propargyl-α-D-glucopyranoside (**2**) as white solid (5.14 g, 80.9 %). Mp 75–77 °C. ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz): δ 7.42–7.40 (m, 2H, Ph 3-*H*, 5-*H*), 7.31–7.29 (m, 3H, Ph 2-*H*, 4-*H*, 6-*H*), 5.47 (s, 1*H*, Ph CH), 4.81 (d, 1H, $^3J_{1,2} = 3.7$, SUGAR 1-*H*), 4.40–4.35 (m, 4H, $2C\equiv CCH_2$), 4.21 (dd, 1*H*, $^3J_{6eq,5} = 4.1$, $^2J_{6eq,6ax} = 9.6$, SUGAR 6-H_{eq}), 3.93 (t, 1*H*, $^3J_{3,2} = {}^3J_{3,4} = 9.2$, SUGAR 3-*H*), 3.67 (ddd, 1*H*, $^3J_{5,6eq} = 4.1$, $^3J_{5,4} = 9.6$, $^3J_{5,6ax} = 10$, SUGAR 5-*H*), 3.66–3.62 (m, 2*H*, SUGAR 2-*H*, 6-H_{ax},), 3.55 (t, 1*H*, $^3J_{4,3} = 9.2$, $^3J_{4,5} = 9.6$, SUGAR 4-*H*), 3.38 (s, 3*H*, OCH_3), 2.39–2.36 (m, 1*H*, ≡CH), 2.10 (s, 1*H*, ≡C–*H*) ppm.

*General procedure for the Cu(I)-catalyzed synthesis of glucose-derived 1,2,3-triazoles **3a–k***

To a solution of 500 mg (1.40 mmol) methyl 4,6-O-benzylidene-2,3-di-O-propargyl-α-D-glucopyranoside **2** in 15 mL of a *t*-BuOH–water mixture (4:1, v/v) was added aryl azides. Hereafter, 55 mg (0.28 mmol) sodium ascorbate and 35 mg (0.14 mmol) of copper (II) sulfate pentahydrate was added successively, and the mixture was stirred for 1.5 days at room temperature. The reaction mixture was diluted with 20 mL of water and extracted with ethyl acetate (10 mL × 3). The combined ethyl acetate solutions were washed with saturated NaCl solution, dried with anhydride sodium sulfate, and then concentrated under reduced pressure. The residue was subjected to column chromatography on flash silica gel using ethyl acetate-petroleum (5:1, v/v) as eluent to give pure products **3a**–**k**.

*4,4′-(6-Methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl)bis(oxy)bis(methylene)bis(1-p-tolyl-1H-1,2,3-triazole) (**3a**)* Clay yellow solid. Yield: 97.4 %. Mp 106–107 °C. $[\alpha]_D^{25}$ +65.5° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 289 nm; IR (KBr) ν: 3,137, 3,037, 2,966, 2,919, 2,858,

1,634, 1,614, 1,522, 1,450, 1,368, 1,219, 1,189, 1,148, 1,107, 1,091.9, 1,049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.23 (s, 1*H*, triazole *H*), 8.02 (s, 1*H*, triazole *H*), 7.61 (d, 2*H*, $^3J = 8.3$, Ar *H*), 7.52–7.43 (m, 4*H*, Ar *H*), 7.36 (t, 3*H*, $^2J = 2.6$, Ph 2-*H*, 4-*H*, 6-*H*), 7.28–7.21 (m, 4*H*, Ph 3-*H*, 5-*H*, Ar *H*), 5.57 (s, 1*H*, Ph-CH), 5.11–5.07 (m, 2*H*, OCH_2), 4.98 (s, 2*H*, OCH_2), 4.91 (d, 1*H*, $^3J_{1,2} = 3.5$, SUGAR 1-*H*), 4.30 (dd, 1*H*, $^3J_{6eq,5} = 4.4$, $^2J_{6eq,6ax} = 9.8$, SUGAR 6-H_{eq}), 4.14 (t, 1*H*, $^3J_{4,3} = {}^3J_{2,3} = 9.2$, SUGAR 3-*H*), 3.86 (ddd, 1*H*, $^3J_{5,6eq} = 4.4$, $^3J_{5,4} = 9.6$, $^3J_{5,6ax} = 10$, SUGAR 5-*H*), 3.79–3.70 (m, 2*H*, SUGAR 2-*H*, 6-H_{ax}), 3.64 (t, 1*H*, $^3J_{4,3} = {}^3J_{4,5} = 9.2$, SUGAR 4-*H*), 3.44 (s, 3*H*, OCH_3), 2.39 (s, 6*H*, Ar-CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145. 96, 145.20, 138.64, 138.45, 137.19, 134.63, 130.11, 130.05, 129.01, 128.27, 126.06, 121.52, 120.82, 120.26, 120.13, 101.50, 98.42, 81.82, 79.19, 78.06, 68.99, 66.40, 64.72, 62.21, 55.25, 21.00 ppm; EI-MS *m/z*: 647 $[M + Na]^+$, 625 $[M + H]^+$.

4,4′-(6-Methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl)bis(oxy)bis(methylene)bis(1-(4-methoxyphenyl)-1H-1,2,3-triazole) (***3b***) Syrup. Yield: 92.1 %. $[\alpha]_D^{25}$ +47.5° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 288$ nm; IR (KBr) ν: 3,125, 3,043, 2,973, 2,919, 2,865, 1,645, 1,629, 1,530, 1,464, 1,363, 1,226, 1,146, 1,107, 1,045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.26 (s, 1*H*, triazole *H*), 8.00 (s, 1*H*, triazole *H*), 7.65 (d, 2*H*, $^3J = 8.8$, Ar *H*), 7.49–7.48 (m, 3*H*, Ar *H*), 7.45 (s, 1*H*, Ar *H*), 7.37 (d, 3*H*, $^4J = 2.6$, Ph 2-*H*, 4-*H*, 6-*H*), 7.00 (d, 2*H*, $^4J = 2.6$, Ph 3-*H*, 5-*H*), 6.95–6.87 (m, 2*H*, Ar *H*), 5.57 (s, 1*H*, Ph-CH), 5.16–5.04 (m, 2*H*, OCH_2), 4.99 (s, 2*H*, OCH_2), 4.93 (d, 1*H*, $^3J_{1,2} = 3.$ 3, SUGAR 1-*H*), 4.30 (dd, 1*H*, $^3J_{6eq,5} = 4.2$, $^2J_{6eq,6ax} = 9.$ 7, SUGAR 6-H_{eq}), 4.05 (t, 1*H*, $^3J_{2,3} = {}^3J_{4,3} = 9.2$, SUGAR 3-*H*), 3.85 (s, 6*H*, 2Ph-OCH_3), 3.80–3.70 (m, 3*H*, SUGAR 2-*H*, 5-*H*, 6-H_{ax}), 3.61 (t, 1*H*, $^3J_{4,3} = {}^3J_{4,5} = 9.2$, SUGAR 4-*H*), 3.44 (s, 3*H*, OCH_3) ppm; EI-MS *m/z*: 679 $[M + Na]^+$, 657 $[M + H]^+$.

4,4′-(6-Methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl)bis(oxy)bis(methylene)bis(1-(3-chlorophenyl)-1H-1,2,3-triazole) (***3c***) Light yellow solid. Mp 76–77 °C. Yield: 86.1 %. $[\alpha]_D^{25}$ +56.1° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 290$ nm; IR (KBr) ν: 3,425, 3,118, 3,100, 2,917, 2,871, 1,597, 1,493, 1,466, 1,377, 1,088, 1,044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.38 (s, 1*H*, triazole *H*), 8.08 (s, 1*H*, triazole *H*), 7.86 (s, 1*H*, Ar *H*), 7.73 (s, 1*H*, Ar *H*), 7.68 (d, $^3J = 6.2$, 1*H*, Ar *H*), 7.59 (t, 3*H*, $^3J = 6.2$, Ar *H*), 7.45–7.37 (m, 7*H*, Ar *H*), 5.57 (s, 1*H*, Ph-CH), 5.13–5.02 (m, 2*H*, OCH_2), 4.98 (s, 2*H*, OCH_2), 4.93 (d, 1*H*, $^3J_{1,2} = 2.9$, SUGAR 1-*H*), 4.31 (dd, 1*H*, $^3J_{6eq,5} = 4.3$, $^2J_{6eq,6ax} = 9.8$, SUGAR 6-H_{eq}), 4.05 (t, 1*H*, $^3J_{4,3} = {}^3J_{2,3} =$ 9.2, SUGAR 3-*H*), 3.87 (ddd, 1*H*, $^3J_{5,6eq} = 4.3$, $^3J_{5,4} = 9.6$, $^3J_{5,6ax} = 10$, SUGAR 5-*H*), 3.79–3.69 (m, 2*H*, SUGAR 2-*H*, 6-H_{ax}), 3.64 (t, 1*H*, $^3J_{4,3} = {}^3J_{4,5} = 9.2$, SUGAR 4-*H*), 3.45 (s, 3*H*, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.19, 145.57, 137.69, 137.13, 135.47, 135.40, 130.74, 130.69, 129.12, 128.68, 128.55, 128.31, 126.05, 121.61, 120.95, 120.58, 120.51, 118.29, 118.11, 101.55, 98.32, 81. 81, 77.99, 68.98, 66.13, 64.60, 62.21, 55.29 ppm; EI-MS *m/z*: 687 $[M + Na]^+$, 665 $[M + H]^+$.

4,4′-(6-Methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl)bis(oxy)bis(methylene)bis(1-(4-chlorophenyl)-1H-1,2,3-triazole) (***3d***) White solid. Mp 168–169 °C. Yield: 95.3 %. $[\alpha]_D^{25}$ +36.0° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 289$ nm; IR (KBr) ν: 3,144, 3,094, 2,918, 2,863, 1,503, 1,455, 1,404, 1,375, 1,230, 1,177, 1,044, 1,091, 1,044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.32 (s, 1*H*, triazole *H*), 8.05 (s, 1*H*, triazole *H*), 7.73 (d, 2*H*, $^3J = 8.9$, Ar *H*), 7.59 (t, 6*H*, $^3J = 8.9$, Ar *H*), 7.42–7.39 (m, 5*H*, Ar *H*), 5.57 (s, 1*H*, Ph-CH), 5.13–5.03 (m, 2*H*, OCH_2), 4.97 (s, 2*H*, OCH_2), 4.93 (d, 1*H*, $^3J_{1,2} = 3.5$, SUGAR 1-*H*), 4.31 (dd, 1*H*, $^3J_{6eq,5} = 4.3$, $^2J_{6eq,6ax} = 9.8$, SUGAR 6-H_{eq}), 4.04 (t, 1*H*, $^3J_{4,3} = {}^3J_{2,3} = 9.2$, SUGAR 3-*H*), 3.86 (ddd, 1*H*, $^3J_{5,6eq} = 4.$ 3, $^3J_{5,4} = 9.6$, $^3J_{5,6ax} = 10$, SUGAR 5-*H*), 3.78–3.69 (m, 2*H*, SUGAR 2-*H*, 6-H_{ax}), 3.64 (t, 1*H*, $^3J_{4,3} = {}^3J_{4,5} = 9.2$, SUGAR 4-*H*), 3.45 (s, 3*H*, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.37, 145.65, 137.23, 135.40, 134.42, 134.21, 129.86, 129.80, 129.13, 128.34, 126.12, 121.55, 121.35, 120.83, 101.61, 98.35, 81.84, 79.42, 78.01, 69.03, 66.29, 64.63, 62.26, 55.31 ppm; EI-MS *m/z*: 687 $[M + Na]^+$, 665 $[M + H]^+$.

4,4′-(6-Methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl)bis(oxy)bis(methylene)bis(1-(4-bromophenyl)-1H-1,2,3-triazole) (***3e***) White solid. Mp 87–89 °C. Yield: 85.7 %. $[\alpha]_D^{25}$ +60.5° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 287$ nm; IR (KBr) ν: 3,138, 3,012, 2,932, 2,914, 2,870, 1,638, 1,561, 1,498, 1,455, 1,401, 1,372, 1,230, 1,176, 1,152, 1,090, 1,044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.32 (s, 1*H*, triazole *H*), 8.06 (s, 1*H*, triazole *H*), 7.69–7.61 (m, 4*H*, Ar *H*), 7.57 (d, 2*H*, $^3J =$ 8.7, Ar *H*), 7.51–7.49 (m, 2*H*, Ph 3-*H*, 5-*H*), 7.45 (d, 2*H*, $^3J = 8.7$, Ar *H*), 7.38–7.3 (m, 3*H*, Ph 2-*H*, 4-*H*, 6-*H*), 5.57 (s, 1*H*, Ph-CH), 5.10–5.02 (m, 2*H*, OCH_2), 4.96 (s, 2*H*, OCH_2), 4.93 (d, 1*H*, $^3J_{1,2} = 3.5$, SUGAR 1-*H*), 4.31 (dd, 1*H*, $^3J_{6eq,5} = 4.3$, $^2J_{6eq,6ax} = 9.8$, SUGAR 6-H_{eq}), 4.02 (t, 1*H*, $^3J_{4,3} = {}^3J_{2,3} = 9.2$, SUGAR 3-*H*), 3.85 (ddd, 1*H*, $^3J_{5,6eq} = 4.3$, $^3J_{5,4} = 9.6$, $^3J_{5,6ax} = 10$, SUGAR 5-*H*), 3.79–3.69 (m, 2*H*, SUGAR 2-*H*, 6-H_{ax}), 3.64 (t, 1*H*, $^3J_{4,3} = {}^3J_{4,5} = 9.2$, SUGAR 4-*H*), 3.45 (s, 3*H*, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.38, 145.68, 137.22, 135.86, 132.82, 132.76, 129.12, 128.33, 126.11, 122.30, 122.09, 121.77, 121.58, 121.40, 120.76, 101.60, 98.34, 81.84, 79.40, 78.00, 69.02, 66.26, 64.61, 62.25, 55.30 ppm; EI-MS *m/z*: 777 $[M + Na]^+$, 755 $[M + H]^+$.

4,4′-((6S,7S,8S,8aR)-6-Methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl)bis(oxy)bis(methylene)bis(1-(3,4-dichlorophenyl)-1H-1,2,3-triazole) ***(3f)*** White solid. Mp 178 °C. $[\alpha]_D^{25}$ +33.9° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 294 nm; IR (KBr) ν: 3,179, 3,123, 2,935, 2,862, 1,546, 1,461, 1,380, 1,268, 1,106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *J* in Hz) *δ*: 8.40 (s, 1*H*, triazole *H*), 8.07 (s, 1*H*, triazole *H*), 7.98 (d, 1*H*, ^3J = 2.4, Ar *H*), 7.83 (d, 1*H*, ^3J = 2.4, Ar *H*), 7.69–7.65 (m, 1*H*, Ar *H*), 7.58 (d, 1*H*, ^3J = 8.8, Ar *H*), 7.53–7.42 (m, 4*H*, Ar *H*), 7.40–7.36 (m, 3*H*, Ph 2-*H*, 4-*H*, 6-*H*), 5.56 (s, 1*H*, Ph-CH), 5.10–5.00 (m, 2*H*, OCH_2), 4.97–4.92 (m, 3*H*, OCH_2, SUGAR 1-*H*), 4.30 (dd, 1*H*, $^3J_{6eq,5}$ = 4.8, $^2J_{6eq,6ax}$ = 10.4, SUGAR 6-H_{eq}), 4.02 (t, 1*H*, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.2, SUGAR 3-*H*), 3.83 (ddd, 1*H*, $^3J_{5,6eq}$ = 4.3, $^3J_{5,4}$ = 9.6, $^3J_{5,6ax}$ = 10, SUGAR 5-*H*), 3.78–3.68 (m, 2*H*, SUGAR 2-*H*, 6-H_{ax}), 3.63 (t, 1*H*, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.6, SUGAR 4-*H*), 3.45 (s, 3*H*, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 146.49, 145.92, 137.25, 135.99, 135.94, 133.98, 133.92, 132.82, 132.69, 131.43, 131.37, 129.17, 128.36, 126.13, 122.13, 122.06, 121.53, 120.93, 119.33, 119.13, 101.66, 98.37, 81.95, 79.42, 78.03, 69.06, 66.11, 64.62, 62.30, 55.35 ppm; EI-MS *m/z*: 755 $[M + Na]^+$, 733 $[M + H]^+$.

4,4′-((6S,7S,8S,8aR)-6-Methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl)bis(oxy)bis(methylene)bis(1-(4-chloro-3-fluorophenyl)-1H-1,2,3-triazole) ***(3g)*** White solid. Mp 137–139 °C. $[\alpha]_D^{25}$ +38.5° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 295 nm; IR (KBr) ν: 3,165, 3,036, 2,961, 2,885, 1,600, 1,531, 1,458, 1,376, 1,210, 1,035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *J* in Hz) *δ*: 8.38 (s, 1*H*, triazole *H*), 8.06 (s, 1*H*, triazole *H*), 7.92–7.91 (m, 1*H*, Ar *H*), 7.79–7.76 (m, 1*H*, Ar *H*), 7.71–7.67 (m, 1*H*, Ar ν), 7.50–7.48 (m, 2*H*, Ph 3-*H*, 5-*H*), 7.44–7.40 (m, 1*H*, Ar *H*), 7.37–7.34 (m, 3*H*, Ph 2-*H*, 4-*H*, 6-*H*), 7.30–7.26 (m, 1*H*, Ar *H*), 7.23–7.18 (m, 1*H*, Ar *H*), 5.55 (s, 1*H*, Ph-CH), 5.10–5.01 (m, 2*H*, OCH_2), 4.99–4.91 (m, 3*H*, OCH_2, SUGAR 1-*H*), 4.29 (dd, 1*H*, $^3J_{6eq,5}$ = 4.4, $^2J_{6eq,6ax}$ = 10, SUGAR 6-H_{eq}), 4.02 (t, 1*H*, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.2, SUGAR 3-*H*), 3.83 (ddd, 1*H*, $^3J_{5,6eq}$ = 4.4, $^3J_{5,4}$ = 9.2, $^3J_{5,6ax}$ = 10, SUGAR 5-*H*), 3.74–3.60 (m, 3*H*, SUGAR 2-*H*, 4-*H*, 6-H_{ax}), 3.44 (s, 3*H*, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 159.07, 158.96, 156.57, 156.46, 146.34, 145.74, 137.19, 133.50, 133.45, 133.41, 129.10, 128.28, 126.07, 122.82, 122.74, 122.53, 122.45, 122.33, 122.26, 121.69, 121.11, 120.14, 120.06, 119.92, 119.84, 117.64, 117.57, 117.42, 117.34, 101.57, 98.32, 81.84, 79.38, 77.99, 68.98, 66.08, 64.56, 62.24, 55.28 ppm; EI-MS *m/z*: 723 $[M + Na]^+$.

4,4′-((6S,7S,8S,8aR)-6-Methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl)bis(oxy)bis(methylene)bis(1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole) ***(3h)*** White solid. Mp 225–226 °C. $[\alpha]_D^{25}$ +34° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 298 nm; IR (KBr) ν: 3,112, 3,079, 2,976, 2,860, 1,580, 1,463, 1,352, 1,275, 1,016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *J* in Hz) *δ*: 8.44 (s, 1*H*, triazole *H*), 8.15 (s, 1*H*, triazole *H*), 7.94 (d, 2*H*, ^3J = 8.4, Ar *H*), 7.77 (d, 2*H*, ^3J = 8.4, Ar *H*), 7.70 (s, 4*H*, Ar *H*), 7.52–7.49 (m, 2*H*, Ph 3-*H*, 5-*H*), 7.38–7.35 (m, 3*H*, Ph 2-*H*, 4-*H*, 6-*H*), 5.57 (s, 1*H*, Ph-CH), 5.14–5.02 (m, 2*H*, OCH_2), 4.99–4.95 (m, 3*H*, OCH_2, 1-*H*), 4.31 (dd, 1*H*, $^3J_{6eq,5}$ = 4.8, $^2J_{6eq,6ax}$ = 10.0, SUGAR 6-H_{eq}), 4.05 (t, 1*H*, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.2, SUGAR 3-*H*), 3.85 (ddd, 1*H*, $^3J_{5,6eq}$ = 4.8, $^3J_{5,4}$ = 9.2, $^3J_{5,6ax}$ = 10, SUGAR 5-*H*), 3.78–3.71 (m, 2*H*, SUGAR 2-*H*, 6-H_{ax}), 3.64 (t, 1*H*, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.2, SUGAR 4-*H*), 3.45 (s, 3*H*, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 146.65, 145.99, 139.33, 139.28, 137.26, 131.16, 130.97, 130.83, 130.64, 130.50, 130.31, 130.17, 129.98, 129.17, 128.36, 127.10, 127.07, 127.03, 126.99, 126.96, 126.92, 126.16, 124.88, 122.17, 121.49, 120.90, 120.36, 120.13, 101.68, 98.34, 81.88, 79.58, 78.02, 69.05, 66.20, 64.60, 62.31, 55.34 ppm; EI-MS *m/z*: 733 $[M + H]^+$.

4,4′-(6-Methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl)bis(oxy)bis(methylene)bis(1-(3-nitrophenyl)-1H-1,2,3-triazole) ***(3i)*** Yellow solid. Mp 175–176 °C. Yield: 78.3 %. $[\alpha]_D^{25}$ +42.6° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 295 nm; IR (KBr) ν: 3,155, 3,012, 2,920, 2,871, 1,536, 1,455, 1,354, 1,225, 1,089, 1,048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) *δ*: 8.70 (s, 1*H*, Ar *H*), 8.60 (s, 1*H*, Ar *H*), 8.54 (s, 1*H*, triazole *H*), 8.31–8.25 (m, 4*H*, triazole *H*, Ar *H*), 8.00 (d, 1*H*, ^3J = 8.0, Ar *H*), 7.68 (t, 1*H*, ^3J = 8.2, Ar *H*), 7.51–7.50 (m, 2*H*, Ph 3-*H*, 5-*H*), 7.37–7.35 (m, 3*H*, Ph 2-*H*, 4-*H*, 6-*H*), 5.58 (s, 1*H*, Ph-CH), 5.15–5.08 (m, 2*H*, OCH_2), 5.04–5.00 (m, 2*H*, OCH_2), 4.96 (d, 1*H*, $^3J_{1,2}$ = 3.3, SUGAR 1-*H*), 4.32 (dd, 1*H*, $^3J_{6eq,5}$ = 4.3, $^2J_{6eq,6ax}$ = 9.8, SUGAR 6-H_{eq}), 4.06 (t, 1*H*, $^3J_{4,3}$ = $^3J_{2,3}$ = 9.2, SUGAR 3-*H*), 3.88 (ddd, 1*H*, $^3J_{5,6eq}$ = 4.3, $^3J_{5,4}$ = 9.2, $^3J_{5,6ax}$ = 9.9, SUGAR 5-*H*), 3.80–3.70 (m, 2*H*, SUGAR 2-*H*, 6-H_{ax}), 3.66 (t, 1*H*, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.2, SUGAR 4-*H*), 3.47 (s, 3*H*, OCH_3) ppm; ^{13}C NMR (75 M*H*z, $CDCl_3$) *δ*: 148.78, 146.60, 146.03, 137.60, 137.53, 137.12, 130.92, 130.86, 129.11, 128.31, 126.07, 125.85, 125.63, 123.11, 122.96, 121.81, 121.19, 115.26, 115.15, 101.56, 98.24, 81.84, 79.35, 77.98, 68.95, 65.95, 64.57, 62.20, 55.31 ppm; EI-MS *m/z*: 709 $[M + Na]^+$, 687 $[M + H]^+$.

4,4′-(6-Methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl)bis(oxy)bis(methylene)bis(1-(4-nitrophenyl)-1H-1,2,3-triazole) ***(3j)*** Light yellow solid. Mp 110 °C. Yield: 83.5 %. $[\alpha]_D^{25}$ +39.2° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 298 nm; IR (KBr) ν: 3,139, 2,923, 2,857, 1,599, 1,526, 1,451, 1,372, 1,344, 1,232, 1,089, 1,045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) *δ*: 8.56 (s, 1*H*, triazole *H*), 8.42 (d, 2*H*, ^3J = 8.9, Ar *H*), 8.32 (d, 2*H*, ^3J = 8.9, Ar *H*), 8.25 (s, 1*H*, triazole *H*), 8.09 (d, 2*H*, ^3J = 8.9, Ar *H*), 7.78 (d, 2*H*, ^3J = 8.9, Ar *H*), 7.53 (t, 2*H*, ^4J = 3.6, Ph 3-*H*, 5-*H*), 7.41 (t, 3*H*, ^4J = 3.6, Ph 2-*H*, 4-*H*, 6-*H*), 5.59 (s, 1*H*, Ph-CH),

5.17–5.06 (m, 2*H*, OCH_2), 5.01–4.96 (m, 3*H*, OCH_2, SUGAR 1-*H*), 4.32 (dd, 1*H*, $^3J_{6eq,5} = 4.3$, $^2J_{6eq,6ax} = 9.8$, SUGAR 6-H_{eq}), 4.04 (t, 1*H*, $^3J_{4,3} = {}^3J_{2,3} = 9.2$, SUGAR 3-*H*), 3.88 (ddd, 1*H*, $^3J_{5,6eq} = 4.3$, $^3J_{5,4} = 9.2$, $^3J_{5,6ax} = 9.9$, SUGAR 5-*H*), 3.80–3.71 (m, 2*H*, SUGAR 2-*H*, 6-H_{ax}), 3.66 (t, 1*H*, $^3J_{4,3} = {}^3J_{4,5} = 9.2$, SUGAR 4-*H*), 3.46 (s, 3*H*, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.92, 146.27, 137.18, 129. 28, 128.44, 126.18, 125.52, 125.46, 121.67, 121.08, 120.48, 120.18, 101.66, 98.16, 81.75, 79.62, 77.89, 68.99, 66.04, 64.53, 62.25, 55.35 ppm; EI-MS *m/z*: 709 $[M + Na]^+$.

*Diethyl 4,4′-(4,4′-(6-methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl)bis(oxy)bis (methylene)bis (1H-1,2,3-triazole-4,1-diyl))dibenzoate (**3k**)* White solid. Mp 183 °C. Yield: 78.0 %. $[\alpha]_D^{25}$ +50.0° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 296$ nm; IR (KBr) ν: 3,145, 2,991, 2,935, 2,868, 1,721, 1,609, 1,445, 1,409, 1,368, 1,291, 1,178, 1,088, 1,045, 1,004 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.44 (s, 1*H*, triazole *H*), 8.22–8.12 (m, 5*H*, triazole *H*, Ar *H*), 7.90 (d, 2*H*, $^3J = 8.6$, Ar *H*), 7.68 (d, 2*H*, $^3J = 8.6$, Ar *H*), 7.50 (t, 2*H*, $^4J = 3.3$, Ph 3-*H*, 5-*H*), 7.40 (t, 3*H*, $^4J = 3.3$, Ph 2-*H*, 4-*H*, 6-*H*), 5.60 (s, 1*H*, Ph-CH), 5.17–5.07 (m, 2*H*, OCH_2), 5.01 (s, 2*H*, OCH_2), 4.96 (d, 1*H*, $^3J_{1,2} = 3.5$, SUGAR 1-*H*), 4.45 (q, 4*H*, $^3J = 7.1$, $2CH_2CH_3$), 4.34 (dd, 1*H*, $^3J_{6eq,5} = 4.3$, $^2J_{6eq,6ax} = 9.8$, SUGAR 6-H_{eq}), 4.07 (t, 1*H*, $^3J_{4,3} = {}^3J_{2,3} = 9.2$, SUGAR 3-*H*), 3.87 (ddd, 1*H*, $^3J_{5,6eq} = 4.3$, $^3J_{5,4} = 9.2$, $^3J_{5,6ax} = 10$, SUGAR 5-*H*), 3.81–3.72 (m, 2*H*, SUGAR 2-*H*, 6-H_{ax}), 3.67 (t, 1*H*, $^3J_{4,3} = {}^3J_{4,5} = 9.2$, SUGAR 4-*H*), 3.47 (s, 3*H*, OCH_3), 1.45 (t, 6*H*, $^3J = 7.1$, $2CH_3CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.39, 146.50, 145.82, 139.89, 137.22, 131.24, 131.19, 130.49, 130.29, 129.18, 128.37, 126.13, 121.48, 120.81, 119.77, 119.56, 101.65, 98.37, 81.87, 79.42, 78.01, 69.04, 66.24, 64.63, 62.27, 61.36, 55.32, 14.29 ppm; EI-MS *m/z*: 779 $[M + K]^+$, 763 $[M + Na]^+$, 740 $[M]^+$.

*General procedure for the deprotection of compounds **3a–k***

A mixture of analytic grade concentrated hydrochloric acid (1 mL), distilled water (3 mL), and methyl 4,6-O-benzylidene α-D-glucopyranoside bis-1,2,3-triazoles (500 mg) was stirred at 50 °C for 2 h. The solvents were evaporated under reduced pressure. The residue was washed with petroleum ether (30–60 °C) to remove benzaldehyde and dried to afford corresponding α-D-glucopyranoside bis-1,2,3-triazoles hydrochloride.

*2-(Hydroxymethyl)-6-methoxy-4,5-bis((1-p-tolyl-1H-1,2,3-triazol-4-yl)methoxy)-tetrahydro-2H-pyran-3-ol hydrochloride (**4a**)* Syrup. Yield: 95.2 %. $[\alpha]_D^{25}$ +80.2° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 290$ nm; IR (KBr) ν: 3,409, 3,182, 3,015, 2,922, 2,876, 1,631, 1,519, 1,378, 1,243, 1,126, 1,047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz): δ 8.84 (s, 1*H*, triazole *H*), 8.60 (s, 1*H*, triazole *H*), 7.71 (s, 4*H*, Ar *H*), 6.45 (s, 4*H*, Ar *H*), 5.22–4.97 (m, 5*H*, $2OCH_2$, SUGAR 1-*H*), 3.96–3.84 (m, 4*H*, SUGAR 3-*H*, 5-*H*, 6-*H*), 3.58–3.47 (m, 2*H*, SUGAR 2-*H*, 4-*H*), 3.35 (s, 3*H*, OCH_3), 2.37 (s, 6*H*, 2Ph-CH_3) ppm; EI-MS *m/z*: 632 $[M\text{-}2HCl + Na]^+$, 610 $[M\text{-}2HCl + H]^+$.

*2-(Hydroxymethyl)-6-methoxy-4,5-bis((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-tetrahydro-2H-pyran-3-ol hydrochloride (**4b**)* Syrup. Yield: 92.1 %. $[\alpha]_D^{25}$ +76.2° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 289$ nm; IR (KBr) ν: 3,450, 3,200, 3,010, 2,933, 2,870, 1,636, 1,524, 1,382, 1,246, 1,131, 1,049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz): δ 8.91 (s, 1*H*, triazole *H*), 8.61 (s, 1*H*, triazole *H*), 7.74–7.64 (m, 4*H*, Ar *H*), 7.32 (d, 4*H*, Ar *H*), 5.81 (s, 6*H*, 2 CH_3O-Ph), 5.31–5.14 (m, 2*H*, OCH_2), 4.98–4.87 (m, 3*H*, OCH_2, SUGAR 1-*H*), 3.95 (d, 1*H*, $^2J_{6eq,6ax} = 11.2$, SUGAR 6-H_{eq}), 3.84 (s, 2H, SUGAR 3-*H*, 5-*H*), 3.73 (d, 1H, $^2J_{6eq,6ax} = 11.4$, SUGAR 6-H_{ax}), 3.57–3.49 (m, 2H, SUGAR 2-*H*, 4-*H*), 3.34 (s, 3*H*, OCH_3) ppm; EI-MS *m/z*: 591 $[M\text{-}2HCl + Na]^+$.

*4,5-Bis((1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(hydroxymethyl)-6-methoxy-tetrahydro-2H-pyran-3-ol hydrochloride (**4c**)* Light yellow solid. Mp 81–83 °C. Yield: 97.5 %. $[\alpha]_D^{25}$ +94.6° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 293$ nm; IR (KBr): ν: 3,407, 3,135, 3,026, 2,923, 2,891, 1,596, 1,552, 1,530, 1,512, 1,493, 1,465, 1,442, 1,345, 1,232, 1,192, 1,046.4 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz): δ 8.60 (s, 1*H*, triazole *H*), 8.48 (s, 1*H*, triazole *H*), 7.87–7.73 (m, 4*H*, Ar *H*), 7.48–7.44 (m, 4*H*, Ar *H*), 5.22–4.85 (m, 5*H*, $2OCH_2$, SUGAR 1-*H*), 3.96–3.79 (m, 4*H*, SUGAR 3-*H*, 5-*H*, 6-*H*), 3.63 (s, 2*H*, SUGAR 2-*H*, 4-*H*), 3.39 (s, 3*H*, OCH_3), 3.26 (bs, 7*H*, 2O*H* including water) ppm; EI-MS *m/z*: 672 $[M\text{-}2HCl + Na]^+$, 650 $[M\text{-}2HCl]^+$.

*4,5-Bis((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(hydroxymethyl)-6-methoxy-tetrahydro-2H-pyran-3-ol hydrochloride (**4d**)* White solid. Mp 102–103 °C. Yield: 98.1 %. $[\alpha]_D^{25}$ +87.2° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 290$ nm; IR (KBr) ν: 3,435, 3,126, 3,053, 2,920, 1,619, 1,561, 1,503, 1,459, 1,232, 1,193, 1,095, 1,047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz): δ 9.28 (s, 1*H*, triazole *H*), 8.92 (s, 1*H*, triazole *H*), 7.89–7.80 (m, 4*H*, Ar *H*), 7.48 (t, $^3J = 7.3$, Ar *H*), 5.32–4.86 (m, 6*H*, $2OCH_2$, SUGAR 1-*H*, O*H*), 3.97–3.85 (m, 3*H*, SUGAR 5-*H*, 6-*H*), 3.68–3.49 (m, 3*H*, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.31 (s, 3*H*, OCH_3), 2.42 (bs, 1*H*, O*H*) ppm; EI-MS *m/z*: 672 $[M\text{-}2HCl + Na]^+$, 650 $[M\text{-}2HCl]^+$.

*4,5-Bis((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(hydroxymethyl)-6-methoxy-tetrahydro-2H-pyran-3-ol hydrochloride (**4e**)* Light yellow solid. Mp 104–105 °C. Yield: 98.9 %. $[\alpha]_D^{25}$ +103.2° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 288 nm; IR (KBr) ν: 3,412.2, 3,156.7, 3,020.1, 2,970.8, 1,600.3, 1,560.2, 1,480.3, 1,470.8, 1,380.5, 1,335.2, 1,225.6, 1,159.7, 1,030.2, 1,011.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz): δ 8.50 (s, 1*H*, triazole *H*), 7.68 (s, 9*H*, triazole *H*, Ar *H*), 5.26 (s, 5*H*, $2OCH_2$, SUGAR 1-*H*), 3.91–3.83 (m, 4*H*, SUGAR 3-*H*, 5-*H*, 6-*H*), 3.63 (s, 2*H*, SUGAR 2-*H*, 4-*H*), 3.41 (s, 3*H*, OCH_3) ppm; EI-MS *m/z*: 689 $[M\text{-}2HCl + Na]^+$.

*(3R,4S,5S,6S)-4,5-Bis((1-(3,4-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(hydroxymethyl)-6-methoxy-tetrahydro-2H-pyran-3-ol hydrochloride (**4f**)* White solid. Mp 96–97 °C. Yield: 95.6 %. $[\alpha]_D^{25}$ +96.4° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 296 nm; IR (KBr) ν: 3,458.4, 3,123.7, 3,016.2, 2,989.1, 1,620.8, 1,566.1, 1,476.8, 1,438.2, 1,379.5, 1,346.1, 1,262.0, 1,146.2, 1,036.4, 1,009.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.78 (s, 1*H*, triazole *H*), 8.56 (s, 1*H*, triazole *H*), 7.91–7.89 (m, 3*H*, Ar *H*), 7.80–7.74 (m, 3*H*, Ar *H*), 5.11–5.01 (m, 2*H*, OCH_2), 5.00–4.95 (m, 3*H*, OCH_2, SUGAR 1-*H*), 3.85 (s, 3*H*, SUGAR 5-*H* 6-*H*), 3.68–3.62 (m, 3*H*, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.44 (s, 3*H*, OCH_3) ppm; EI-MS *m/z*: 645 $[M\text{-}2HCl + Na]^+$.

*(3R,4S,5S,6S)-4,5-Bis((1-(4-chloro-3-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(hydroxymethyl)-6-methoxy-tetrahydro-2H-pyran-3-ol hydrochloride (**4g**)* Syrup. Yield: 96.6 %. $[\alpha]_D^{25}$ +77.6° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 298 nm; IR (KBr) ν: 3,412.2, 3,156.7, 3,020.1, 2,970.8, 1,600.3, 1,560.2, 1,480.3, 1,470.8, 1,380.5, 1,335.2, 1,225.6, 1,159.7, 1,030.2, 1,011.4 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *J* in Hz) δ: 8.42 (s, 1*H*, triazole *H*), 8.28 (s, 1*H*, triazole *H*), 7.98–7.85 (m, 2*H*, Ar *H*), 7.83–7.79 (m, 2*H*, Ar *H*), 7.68–7.62 (m, 2*H*, Ar *H*), 5.10–5.01 (m, 2*H*, OCH_2), 4.99–4.93 (m, 3*H*, OCH_2, SUGAR 1-*H*), 3.83 (s, 3*H*, SUGAR 5-*H*, 6-*H*), 3.72–3.63 (m, 3*H*, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.46 (s, 3*H*, OCH_3) ppm; EI-MS *m/z*: 613 $[M\text{-}2HCl + Na]^+$.

*(3R,4S,5S,6S)-2-(Hydroxymethyl)-6-methoxy-4,5-bis((1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)-tetrahydro-2H-pyran-3-ol hydrochloride (**4h**)* White solid. Mp 120 °C. Yield: 98.9 %. $[\alpha]_D^{25}$ +92.8° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 301 nm; IR (KBr) ν: 3,423.0, 3,169.2, 3,013.2, 2,979.1, 1,631.8, 1,579.2, 1,476.5, 1,465.2, 1,384.2, 1,367.5, 1,320.2, 1,210.2.6, 1,167.1, 1,056.9, 1,010.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.56 (s, 1*H*, triazole *H*), 8.47 (s, 1*H*, triazole *H*), 7.96 (d, 4*H*, ^3J = 8.4, Ar *H*), 7.96 (d, 4*H*, ^3J = 8.4, Ar *H*), 5.11–5.00 (m, 2*H*, OCH_2), 4.10 (s, 3*H*, OCH_2, SUGAR 1-*H*), 3.94–3.81 (m, 4*H*, SUGAR 3-*H*, 5-*H*, 6-*H*), 3.63 (s, 2*H*, SUGAR 2-*H*, 4-*H*), 3.44 (s, 3*H*, OCH_3) ppm; EI-MS *m/z*: 733 $[M\text{-}2HCl + Na]^+$.

*2-(Hydroxymethyl)-6-methoxy-4,5-bis((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-tetrahydro-2H-pyran-3-ol hydrochloride (**4i**)* Yellow solid. Mp 114 °C. Yield: 98.6 %. $[\alpha]_D^{25}$ +89.7° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 286 nm; IR (KBr) ν: 3,479, 3,016, 2,985, 1,647, 1,562, 1,486, 1,351, 1,238, 1,200, 1,013 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz): δ 9.00 (s, 1*H*, triazole *H*), 8.92 (s, 1*H*, triazole *H*), 8.63–8.55 (m, 2*H*, Ar *H*), 8.31–8.21 (m, 4*H*, Ar *H*), 7.86–7.78 (m, 2*H*, Ar *H*), 4.93–4.81 (m, 5*H*, $2OCH_2$, SUGAR 1-*H*), 3.74–3.62 (m, 3*H*, SUGAR 5-*H*, 6-*H*), 3.50–3.32 (m, 3*H*, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.30 (s, 3*H*, OCH_3) ppm; EI-MS *m/z*: 694 $[M\text{-}2HCl + Na]^+$.

*2-(Hydroxymethyl)-6-methoxy-4,5-bis((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-tetrahydro-2H-pyran-3-ol hydrochloride (**4j**)* Syrup. Yield: 99.2 %. $[\alpha]_D^{25}$ +82.6° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 300 nm; IR (KBr) ν: 3,481, 3,015, 2,930, 1,626, 1,561, 1,489, 1,350, 1,241, 1,483, 1,056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz): δ 8.96 (s, 2*H*, 2triazole *H*), 8.40–8.25 (m, 4*H*, Ar *H*), 8.07–7.99 (m, 4*H*, Ar *H*), 5.17–4.95 (m, 5*H*, $2OCH_2$, SUGAR 1-*H*), 3.92–3.89 (m, 3*H*, SUGAR 5-*H*, 6-*H*), 3.74–3.60 (m, 3*H*, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.37 (s, 3*H*, OCH_3) ppm; EI-MS *m/z*: 694 $[M\text{-}2HCl + Na]^+$.

*Diethyl 4,4′-(4,4′-(5-hydroxy-6-(hydroxymethyl)-2-methoxy-tetrahydro-2H-pyran-3,4-diyl)bis(oxy)bis (methylene) bis (1H-1,2,3-triazole-4,1-diyl))dibenzoate hydrochloride (**4k**)* Yellow solid. Mp 93–94 °C. Yield: 99.1 %. $[\alpha]_D^{25}$ +110.3° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 294 nm; IR (KBr) ν: 3,409, 3,010, 2,993, 2,985, 1,719, 1,610, 1,519, 1,445, 1,381, 1,282, 1,109, 1,045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.76 (s, 1*H*, triazole *H*), 8.18 (s, 5*H*, triazole *H*, Ar *H*), 7.91 (s, 4*H*, Ar *H*), 5.15–4.95 (m, 5*H*, $2OCH_2$, SUGAR 1-*H*), 4.40 (q, 4*H*, ^3J = 6.5, $2CH_2CH_3$), 3.95–3.83 (m, 4*H*, SUGAR 3-*H*, 5-*H*, 6-*H*), 3.49 (s, 2*H*, SUGAR 2-*H*, 4-*H*), 3.37 (s, 3*H*, OCH_3), 1.42 (t, 6*H*, ^3J = 6.5, $2CH_3CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.13, 165.01, 145.03, 139.35, 139.02, 131.22, 130.78, 123.08, 122.62, 120.13, 119.99, 97.50, 81.66, 79.42, 71.35, 69.71, 65.02, 63.67, 61.40, 55.10, 14.19 ppm; EI-MS *m/z*: 675 $[M\text{-}2HCl + Na]^+$.

*General procedure for the synthesis of target compounds **5a–k***

The deprotected α-D-glucoside bis-1,2,3-triazole hydrochloride (100 mg) was dissolved in water (5 mL). The resulting solution was neutralized with 25 % analytic grade ammonium hydroxide under stirring, and then the mixture

was evaporated to dryness. The solid residue was washed with $CHCl_3$ (20 mL × 3). The combined $CHCl_3$ solution was evaporated to afford the pure compounds **5a–k**.

2-(Hydroxymethyl)-6-methoxy-4,5-bis((1-p-tolyl-1H-1,2,3-triazol-4-yl)methoxy)-tetrahydro-2H-pyran-3-ol ***(5a)*** Yellow solid. Mp 83–84 °C. Yield: 98.5 %. $[\alpha]_D^{25}$ +83.9° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 288$ nm; IR (KBr) ν: 3,425, 3,145, 3,099, 2,916, 2,868, 1,593, 1,502, 1,467, 1,371, 1,321, 1,229, 1,092, 1,045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.13 (s, 1*H*, triazole *H*), 8.07 (s, 1*H*, triazole *H*), 7.56 (t, 4*H*, $^3J = 7.9$, Ar *H*), 7.27 (t, 4*H*, $^3J = 3.7$, Ar *H*), 5.15 (d, 1*H*, $^2J = 12.4$, 1/2OCH_2), 5.00 (d, 1*H*, $^2J = 12.4$, 1/2OCH_2), 4.93 (s, 2*H*, OCH_2), 4.89 (d, 1*H*, $^3J_{1,2} = 3.3$, SUGAR 1-*H*), 3.92–3.86 (m, 3*H*, SUGAR 3-*H*, 6-*H*), 3.76–3.62 (m, 3*H*, SUGAR 2-*H*, 4-*H*, 5-*H*), 3.42 (s, 3*H*, OCH_3) 2.40 (s, 6*H*, $2CH_3$), 1.82 (bs, 1*H*, O*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.88, 145.26, 138.83, 134.59, 134.51, 130.15, 121.29, 120.88, 120.78, 120.32, 97.70, 81.98, 79.59, 71.11, 70.60, 70.49, 65.86, 64.28, 62.22, 55.05, 21.00 ppm; EI-MS *m/z*: 559 $[M + Na]^+$, 537 $[M + H]^+$.

2-(Hydroxymethyl)-6-methoxy-4,5-bis((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-tetrahydro-2H-pyran-3-ol ***(5b)*** Syrup. Yield: 96.8 %. $[\alpha]_D^{25}$ +69.6° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 289$ nm; IR (KBr) ν: 3,500, 3,113, 2,941, 2,875, 1,656, 1,503, 1,462, 1,441, 1,095, 1,049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz): δ 8.15 (s, 1*H*, triazole *H*), 8.05 (s, 1*H*, triazole *H*), 7.69–7.58 (t, 4*H*, Ar *H*), 7.20 (s, 4H, Ar *H*), 5.01–4.94 (m, 4H, $2OCH_2$), 4.89 (s, 1H, $^3J_{2,1} = 2.9$, SUGAR 1-*H*), 3.88 (s, 3H, SUGAR 5-*H*, 6-*H*), 3.85 (s, 6H, $2CH_3$O-Ph), 3.72–3.68 (m, 3H, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.42 (s, 3H, OCH_3) ppm; EI-MS *m/z*: 591 $[M + Na]^+$.

4,5-Bis((1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(hydroxymethyl)-6-methoxy-tetrahydro-2H-pyran-3-ol ***(5c)*** Light yellow solid. Mp 81–83 °C. Yield: 97.5 %. $[\alpha]_D^{25}$ +74.5° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 289$ nm; IR (KBr) ν: 3,416, 3,013, 2,995, 2,987, 1,641, 1,530, 1,597, 1,548, 1,512, 1,493, 1,467, 1,442, 1,047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.25 (s, 1*H*, triazole *H*), 8.23 (s, 1*H*, triazole *H*), 7.80 (s, 2*H*, Ar *H*), 7.63 (d, 2*H*, $^3J =$ 7.1, Ar *H*), 7.47–7.42 (m, 4*H*, Ar *H*), 5.15 (d, 1*H*, $^3J = 12.1$, 1/2OCH_2), 5.03–4.91 (m, 4*H*, 3/2OCH_2, SUGAR 1-*H*), 3.88 (s, 3*H*, SUGAR 3-*H*, 6-*H*), 3.76–3.61 (m, 3*H*, SUGAR 2-*H*, 4-*H*, 5-*H*), 3.42 (s, 3*H*, OCH_3), 3.02 (bs, 4*H*, 2O*H* including water) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.87, 145.44, 137.53, 137.40, 135.44, 130.77, 128.87, 128.80, 121.51, 120.53, 118.26, 97.49, 81.66, 79.48, 71.20, 70.05, 65.64, 63.92, 61.63, 55.05 ppm; EI-MS *m/z*: 599 $[M + Na]^+$, 577 $[M + H]^+$, 545 $[M\text{-}CH_3OH]^+$.

4,5-Bis((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(hydroxymethyl)-6-methoxy-tetrahydro-2H-pyran-3-ol ***(5d)*** White solid. Mp 97–98 °C. Yield: 98.8 %. $[\alpha]_D^{25}$ +67.2° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 288$ nm; IR (KBr) ν: 3,425, 3,107, 2,924, 2,871, 1,651, 1,503, 1,462, 1,441, 1,095, 1,049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.20 (s, 1*H*, triazole *H*), 8.08 (s, 1*H*, triazole *H*), 7.68 (t, 4*H*, $^3J = 8.8$, Ar *H*), 7.48 (t, 4*H*, $^3J = 7.3$, Ar *H*), 5.16 (d, 1*H*, $^3J = 12.5$, 1/2OCH_2), 5.00–4.89 (m, 4*H*, 3/2OCH_2, SUGAR 1-*H*), 4.52 (bs, 1*H*, O*H*), 3.88 (s, 3*H*, SUGAR 3-*H*, 6-*H*), 3.70–3.61 (m, 3*H*, SUGAR 2-*H*, 4-*H*, 5-*H*), 3.44 (s, 3*H*, OCH_3), 2.42 (bs, 1*H*, O*H*) ppm; EI-MS *m/z*: 617 $[M + K]^+$, 599 $[M + Na]^+$, 577 $[M + H]^+$.

4,5-Bis((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(hydroxymethyl)-6-methoxy-tetrahydro-2H-pyran-3-ol ***(5e)*** Light yellow solid. Mp 104–105 °C. Yield: 98.9 %. $[\alpha]_D^{25}$ +68.9° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 287$ nm; IR (KBr) ν: 3,388, 3,144, 3,083, 2,922, 1,593, 1,552, 1,490, 1,462, 1,409, 1,333, 1,222, 1,193, 1,051, 1,012 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.20 (s, 1*H*, triazole *H*), 8.07 (s, 1*H*, triazole *H*), 7.62 (d, 8*H*, $^3J = 6.4$, Ar *H*), 5.14–5.02 (m, 1*H*, 1/2OCH_2), 5.00–4.91 (m, 4H, 3/2OCH_2, SUGAR 1-*H*), 3.87 (s, 3H, SUGAR 5-*H*, 6-*H*), 3.68–3.66 (m, 3H, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.43 (s, 3H, OCH_3), 2.29 (bs, 5H, 2O*H* including water) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.16, 145.57, 135.68, 132.90, 122.57, 122.48, 121.78, 121.27, 120.74, 97.58, 81.87, 79.56, 70.97, 70.61, 65.79, 64.12, 62.29, 55.15 ppm; EI-MS *m/z*: 689 $[M + Na]^+$.

(3R,4S,5S,6S)-4,5-Bis((1-(3,4-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(hydroxymethyl)-6-methoxy-tetrahydro-2H-pyran-3-ol ***(5f)*** White solid. Mp 96–97 °C. Yield: 95.6 %. $[\alpha]_D^{25}$ +96.4° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 289$ nm; IR (KBr) ν: 3,562.8, 3,210.1, 3,176.3, 3,019.1, 2,979.5, 1,625.3, 1,567.9, 1,475.2, 1,463.4, 1,376.2, 1,346.2, 1,216.3, 1,172.5, 1,049.3, 1,057.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.27 (s, 1H, triazole *H*), 8.17 (s, 1*H*, triazole *H*), 7.92 (d, 2H, $^3J = 6.2$, Ar *H*), 7.59 (d, 4H, $^3J = 9.0$, Ar *H*), 5.13–5.01 (m, 2H, OCH_2), 5.00–4.91 (m, 3H, OCH_2, SUGAR 1-*H*), 3.87 (s, 3H, SUGAR 5-*H*, 6-*H*), 3.68–3.59 (m, 3H, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.44 (s, 3H, OCH_3) 2.69 (bs, 3H, 2O*H* including water) ppm; EI-MS *m/z*: 645 $[M + H]^+$.

(3R,4S,5S,6S)-4,5-Bis((1-(4-chloro-3-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(hydroxymethyl)-6-methoxy-tetrahydro-2H-pyran-3-ol ***(5g)*** Syrup. Yield: 96.6 %. $[\alpha]_D^{25}$ +77.6° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): $\lambda_{max} = 287$ nm; IR (KBr) ν: 3,512.6, 3,102.5, 3,016.9, 2,876.2, 1,613.5, 1,567.9, 1,476.8, 1,456.4, 1,372.6, 1,320.4, 1,249.9, 1,162.6, 1,029.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.24 (s, 1H, triazole *H*), 8.15 (s, 1H, triazole *H*), 7.87

(s, 2H, Ar *H*), 7.64 (d, 2H, ^4J = 2.8, Ar *H*), 7.33–7.30 (m, 2H, Ar *H*), 5.14–5.03 (m, 2H, OCH_2), 5.01–4.91 (m, 3H, OCH_2, SUGAR 1-*H*), 3.87 (s, 3H, SUGAR 5-*H*, 6-*H*), 3.70–3.62 (m, 3H, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.44 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.60, 156.27, 146.26, 145.67, 133.36, 122.90, 122.70, 122.41, 121.51, 121.08, 120.10, 117.76, 117.49, 97.56, 81.79, 79.58, 71.03, 70.56, 65.80, 63.98, 62.17, 55.14 ppm; EI-MS *m/z*: 613 $[M + H]^+$.

(3R,4S,5S,6S)-2-(Hydroxymethyl)-6-methoxy-4,5-bis((1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)-tetrahydro-2H-pyran-3-ol ***(5h)*** White solid. Mp 120 °C. Yield: 98.9 %. $[\alpha]_D^{25}$ +81.6° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 299 nm; IR (KBr) ν: 3,418.1, 3,179.2, 3,017.8, 2,975.2, 1,617.6, 1,564.1, 1,485.9, 1,443.5, 1,386.2, 1,373.7, 1,235.9, 1,167.2, 1,019.5 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.33 (s, 1H, triazole *H*), 8.26 (s, 1H, triazole *H*), 7.92–7.86 (m, 4H, Ar *H*), 7.77 (d, 4H, ^3J = 8.2, Ar *H*), 5.14–5.07 (m, 2H, OCH_2), 5.04–4.93 (m, 3H, OCH_2, SUGAR 1-*H*), 3.89 (s, 3H, SUGAR 5-*H*, 6-*H*), 3.74–3.66 (m, 3H, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.44 (s, 3H, OCH_3), 3.35 (bs, 1H, O*H*) ppm; EI-MS *m/z*: 733 $[M + H]^+$.

2-(Hydroxymethyl)-6-methoxy-4,5-bis((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-tetrahydro-2H-pyran-3-ol ***(5i)*** Yellow solid. Mp 95–96 °C. Yield: 97.8 %. $[\alpha]_D^{25}$ +73.6° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 291 nm; IR (KBr) ν: 3,400, 3,010, 2,929, 1,619, 1,535, 1,496, 1,352, 1,233, 1,193, 1,045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.63–8.60 (m, 2H, Ar *H*), 8.47 (s, 1H, triazole *H*), 8.41 (s, 1H, triazole *H*), 8.30–8.17 (m, 4H, Ar *H*), 7.78–7.73 (m, 2H, Ar *H*), 5.21–5.01 (m, 2H, OCH_2), 5.05–5.01 (m, 2H, OCH_2), 4.96 (d, 1H, $^3J_{1,2}$ = 3.3, SUGAR 1-*H*), 3.88 (t, 3H, ^3J = 6.5, SUGAR 5-*H*, 6-*H*), 3.74–3.63 (m, 3H, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.45 (s, 3H, OCH_3), 3.21 (bs, 2H, 2O*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.85, 146.55, 146.00, 137.45, 130.99, 125.81, 123.20, 121.55, 121.34, 121.26, 115.22, 115.16, 97.51, 81.73, 79.56, 71.08, 70.43, 70.32, 65.81, 63.90, 61.92, 55.17 ppm; EI-MS *m/z*: 621 $[M + Na]^+$.

2-(Hydroxymethyl)-6-methoxy-4,5-bis((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-tetrahydro-2H-pyran-3-ol ***(5j)*** White solid. Mp 97–98 °C. Yield: 99.6 %. $[\alpha]_D^{25}$ +86.3° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 289 nm; IR (KBr) ν: 3,416, 3,175, 3,011, 2,986, 1,596.6, 1,548, 1,512, 1,493, 1,467, 1,442, 1,047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.47–8.37 (m, 4H, triazole H, Ar *H*), 8.33 (s, 1H, triazole *H*), 8.07–7.99 (m, 3H, Ar *H*), 7.72 (s, 1H, Ar *H*), 7.55 (s, 1H, Ar *H*), 5.19 (d, 1H, ^3J = 12, 1/2OCH_2), 5.05–4.95 (m, 4H, 3/2OCH_2, SUGAR 1-*H*), 4.33–4.29 (bs, 3H, 2O*H* incuding water), 3.89 (s, 3H, SUGAR 5-*H*, 6-*H*), 3.70–3.63 (m, 3H, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.46 (s, 3H, OCH_3) ppm; EI-MS *m/z*: 637 $[M + K]^+$, 621 $[M + Na]^+$.

Diethyl 4,4′-(4,4′-(5-hydroxy-6-(hydroxymethyl)-2-methoxy-tetrahydro-2H-pyran-3,4-diyl)bis(oxy)bis (methylene) bis(1H-1,2,3-triazole-4,1-diyl))dibenzoate ***(5k)*** White solid. Mp 187 °C. Yield: 99.6 %. $[\alpha]_D^{25}$ +66.7° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$): λ_{max} = 293 nm; IR (KBr) ν: 3,436, 3,101, 3,010, 2,995, 2,864, 1,736, 1,719, 1,498, 1,283, 1,112, 1,049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ: 8.30 (s, 1H, triazole *H*), 8.18 (d, 5H, ^3J = 8.8, triazole *H*, Ar *H*), 7.83 (t, 4H, ^3J = 8.8, Ar *H*), 5.18 (d, 1H, ^2J = 12.5, 1/2OCH_2), 5.03–4.92 (m, 4H, 3/2OCH_2, SUGAR 1-*H*), 4.41 (q, 4H, ^3J = 6.5, 2CH_3CH_2), 3.88 (s, 3H, SUGAR 5-*H*, 6-*H*), 3.71–3.63 (m, 3H, SUGAR 2-*H*, 3-*H*, 4-*H*), 3.44 (s, 3H, OCH_3), 2.23 (bs, 1H, O*H*), 1.76 (bs, 1H, O*H*), 1.42 (t, 6H, ^3J = 6.5, 2CH_3CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.33, 146.30, 145.70, 139.70, 131.28, 130.58, 121.30, 120.76, 119.77, 97.59, 81.88, 79.60, 70.98, 70.63, 65.80, 64.11, 62.30, 61.44, 55.16, 14.28 ppm; EI-MS *m/z*: 675 $[M + Na]^+$.

Antibacterial and antifungal assays

The in vitro minimal inhibitory concentrations (MICs) of the target compounds were determined by broth microdilution assay method in 96-well microtest plates according to the NCCLS (Kadi *et al*., 2007; Özbek *et al*., 2007). The tested microorganism strains were provided by the School of Pharmaceutical Sciences, Southwest University. Fluconazole and Chloramphenicol were obtained from their respective manufacturers served as controls.

All compounds were evaluated for their antibacterial activity against *S. aureus* (ATCC29213) and *B. subtilis* as Gram-positive, *E. coli* (ATCC25922), *P. aeruginosa*, *Shigella* dysenteriae and *Eberthella typhosa* as Gram-negative bacteria, as well as their antifungal activity against *C. albicans* (ATCC76615) and *A. fumigatu*s. The minimum inhibitory concentration (MIC_{50}) values (in μM) were summarized in Table 1.

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