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Click Chemistry Inspired Synthesis of Morpholine-Fused Triazoles

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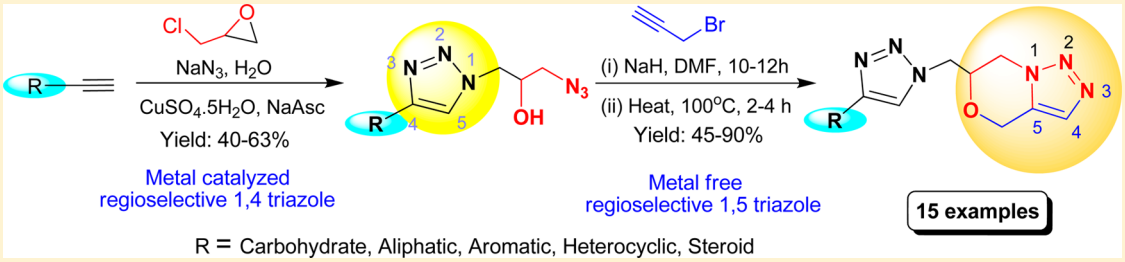
Supporting Information



ABSTRACT: The synthesis of triazolyl azido alcohols from terminal alkyne via oxirane ring-opening of epichlorohydrin, followed by click reaction with alkynes, and subsequent azidation of chlorohydroxy triazoles was achieved under a one-pot methodology. The developed triazolyl azido alcohols were further utilized for the synthesis of a diverse range of morpholine-fused triazoles of chemotherapeutic value. The structure of all developed compounds has been elucidated using IR, NMR, MS, and elemental analysis, where four of them have been characterized by single-crystal X-ray analysis.

INTRODUCTION

The development of new strategies for synthesis of medium-sized heterocycles found in numerous bioactive natural products and pharmaceutical molecules has remained a highly attractive, but challenging, proposition.[1] Toward this end, the triazolo−morpholine skeleton (Figure 1), a privileged bicyclic

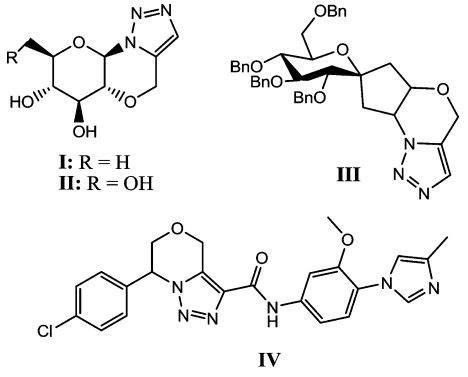


Figure 1. Biologically active morpholine-fused triazoles.

ring system in a myriad of compounds of chemotherapeutic value, is significant due to a wide range of enzyme inhibitory activities, such as glycosidase, galactosidase, SGLT2, gamma secretes modulators, etc.[2] Also, a number of molecules possessing a morpholine skeleton are the clinically approved drugs.[3,4] Furthermore, the triazolo−morpholine conjugation with carbohydrates would be effectively utilized for improving the enzyme inhibitory activities and, thus, may enhance the interaction of these ligands to carbohydrate-binding proteins.[2]

Nowadays, Cu(I)-catalyzed click reaction[5,6] has emerged as an important strategy for the discovery and optimization of lead along with its exploration as an effective drug candidate against various therapeutic strains.[7−12] Moreover, incorporation of an azide and/or an alkyne moiety in carbohydrate scaffolds unleashes the potential to access a new dimension of structural diversity to the molecules via click reaction.[13−15] Thus, we envisioned utilizing the click chemistry for induction of bicyclic systems in biologically relevant scaffolds. Recently, a library of triazole-fused polyheterocycles via a sequential $Yb(OTf)_3$-catalyzed intermolecular Michael addition, followed by an intramolecular azide−alkyne 1,3-dipolar cycloaddition reaction, has been reported.[1d] However, the method is limited to 2-aryl-ethynyl-1*H*-indole and related heteroaromatic skeletons and thus need to be investigated with a wide range of substrates including carbohydrates. Recently, glycosyl 1,2-azido alcohols, obtained from 1,2-anhydro sugars with the aid of $Ce(NH_4)_2(NO_3)_6$-mediated azidation, have successfully been utilized for the synthesis of structurally diverse sugar-based morpholine 1,5-disubstituted triazoles.[2a] Despite the tremendous biological significance of morpholine-fused triazoles, their heterocyclic, carbocyclic, and carbohydrate derivatives are relatively rare. To the best of our knowledge, the one-pot synthesis of triazolyl azido alcohols via oxirane ring-opening of epichlorohydrin, followed by click reaction with alkynes, and subsequent azidation of chlorohydroxy triazoles in water is not well-investigated.[16] Also, the application of triazolyl azido alcohols for the development of morpholine-fused triazoles by propargylation and subse-

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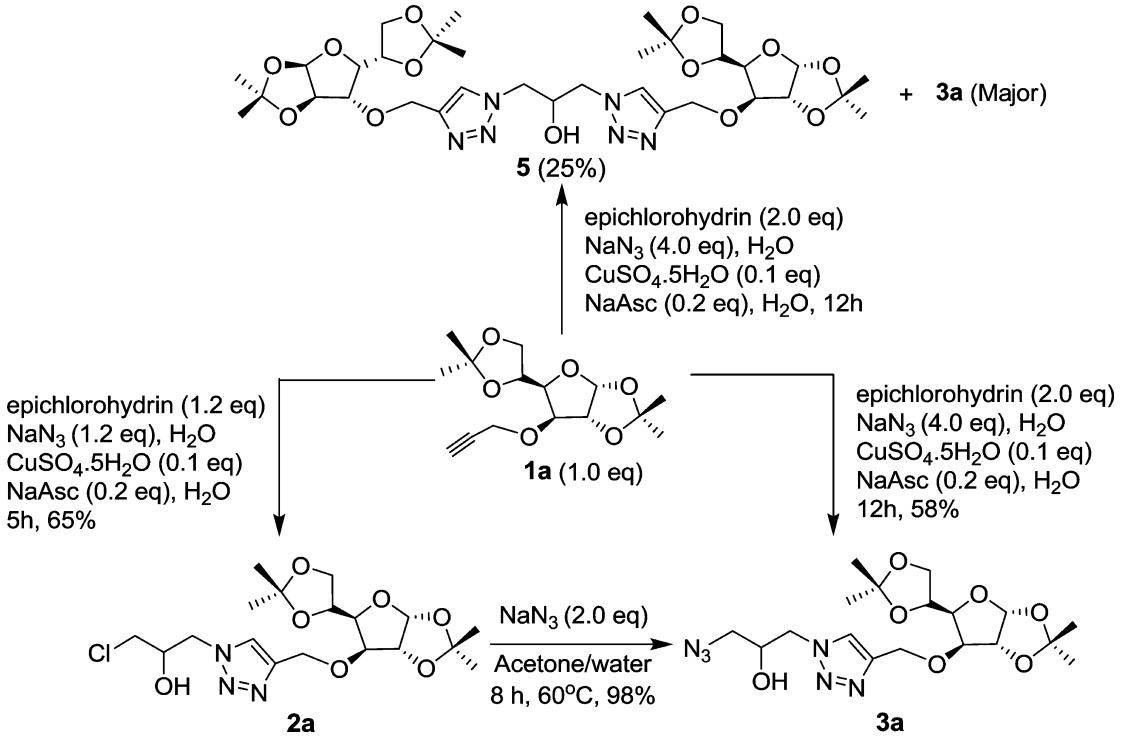
Scheme 1. Model Reaction of Glycosyl Alkyne 1a



quent intramolecular azide−alkyne cycloaddition under a one-pot methodology is yet to be realized fully.

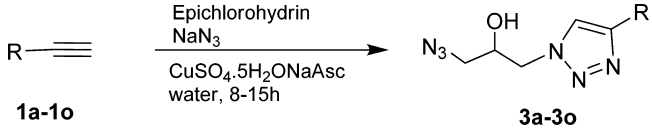
Because of an increased demand for new carbohydrate scaffolds for the numerous pharmacological investigations[17,18] and also with our previous experience,[19−22] we herein describe a novel two-step protocol for an easy access to a diverse range of morpholine-fused [5,1-*c*]-triazoles from terminal glycosyl and other alkynes.

RESULTS AND DISCUSSION

Our synthetic strategy begins with orthogonally protected sugars, which, on propargylation under a strong basic medium in dry DMF, afford good yields of glycosyl alkynes (**1a−1h**).[23] We further extended our investigation with *N*-propargylated and other commercially available alkynes (**1i−1o**), which, on treatment with epichlorohydrin (a well-known versatile synthons)[24] and NaN_3 in the presence of $CuSO_4{\cdot}5H_2O$/NaAsc in H_2O at room temperature under one-pot conditions, delivered triazolyl azido alcohols (**3a−3o**) in good yields. The regioselective ring-opening of epichlorohydrin under the influence of NaN_3 resulted in the formation of azido-hydroxy chloride in situ, which further underwent Cu(I)-catalyzed 1,3-dipolar cycloaddition with terminal alkynes to afford chlorohydroxy triazoles, isolated successfully in two cases (**2a** and **2j**). We investigated the reaction extensively and observed that the reaction of alkyne **1a**, epichlorohydrin, and NaN_3 in a ratio of 1:1.2:1.2 using copper catalyst in H_2O furnished **2a** in 65% yield after 5 h. In a reaction optimization study to measure the effect of reagent concentration and time on product yields, we reacted **1a** (1.0 equiv) with epichlorohydrin (2.0 equiv), and NaN_3 (4.0 equiv) in the presence of $CuSO_4{\cdot}5H_2O$ (10 mol %) and NaAsc (20 mol %) for 12 h and isolated good yields of compound **3a** (58%) along with a side product, *β*-hydroxy bis-triazole **5** (25%) (Scheme 1).

In the 300 MHz ^1H NMR spectrum of compound **3a**, the signal for the characteristic triazole-*H* proton was resonated at *δ* 7.74. The appearance of an intense absorption band at 2105 cm^{-1} in the IR spectrum was identified for the azide functionality in compound **3a**. Thus, under the optimized reaction conditions, a wide range of alkynes (**1a−1o**) were readily reacted with epichlorohydrin and NaN_3 in the presence of $CuSO_4{\cdot}5H_2O$ and NaAsc to afford azido-hydroxyl triazoles (**3a−3o**) in good yields (Scheme 2, Table 1).

Scheme 2. Synthesis of Triazolyl Azido Alcohols (3a−3o)



Interestingly, the reaction of **1i** with epichlorohydrin and NaN_3 using $CuSO_4{\cdot}5H_2O$ and NaAsc in H_2O led to the formation of **5i** as a major product, while compound **3i** only in traces. However, the same reaction, when carried out in DMF/H_2O (3:1) as a molecular solvent under heating condition, furnished **3i** in good yields. The reaction of aromatic acetylenes proceeded relatively faster compared to glycosyl alkynes. Likewise, ethisterone, a steroidal alkyne, showed poor performance and required at least 3.0 equiv of epichlorohydrin to afford the desired steroidal azido alcohol **3o** in 42% yields.

The regioselectivity in both steps, i.e., ring-opening reaction of epichlorohydrin with an azide nucleophile and the cycloaddition with alkynes, was evidenced by the NMR spectrum and single-crystal X-ray analysis of compound **2j** (see the Supporting Information, Figure S1).The X-ray crystallographic data of compound **2j** established the presence of intramolecular CH···N and OH···N interactions with

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Table 1. Synthesis of Various Carbohydrates and Other Triazolyl Azido Alcohols (3a−3o)[a,b,c,d]

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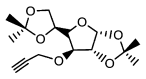
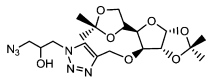
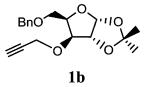
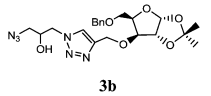
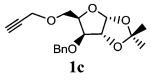
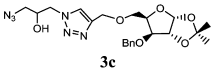
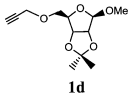
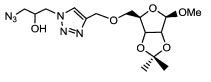
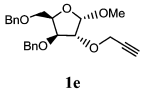
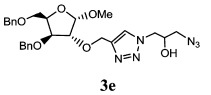
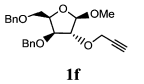
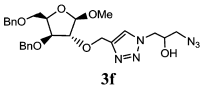
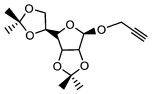
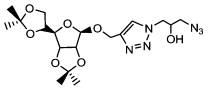
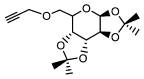
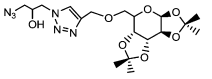
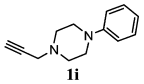
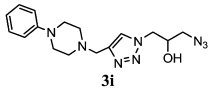
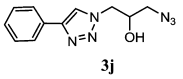
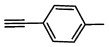
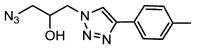
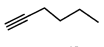
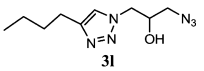
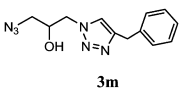
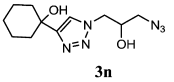
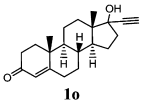
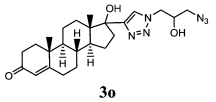
1	 1a	 3a	12	58
2	 1b	 3b	10	50
3	 1c	 3c	11	58
4	 1d	 3d	12	63
5	 1e	 3e	10	52
6	 1f	 3f	12	56
7	 1g	 3g	12	60
8	 1h	 3h	11	62
9	 1i	 3i	8	40
10	 1j	 3j	9	60
11	 1k	 3k	9	62
12	 1l	 3l	8	55
13	 1m	 3m	10	56
14	 1n	 3n	10	45
15	 1o	 3o	15	42

[a]Molar ratios: Carbohydrate and other alkynes (1 equiv), epichlorohydrin (2 equiv), NaN_3 (4 equiv), $CuSO_4·5H_2O$ (10 mol %), NaAsc (20 mol %), [b]Carbohydrate and other triazolyl azido alcohols. [c]Reaction time. [d]Yield reported after purification by column chromatography.

measured distances of 2.648 and 2.473 Å, respectively. Out of the four conformers evidenced by single-crystal X-ray, the intermolecular interactions were observed in between triazole-CH of the one conformer to triazole-*N*2 and an oxygen atom of the others, in an alternate manner as CH···N and CH···O interactions with measured distances of 2.530, 2.537 Å, and 2.665, 2.609 Å, respectively (Figure 2).

Regioselectivity of all developed azido alcohols was also supported by an NMR study of the two dissimilar regioisomers **3a** and **6** synthesized by treatment of model glycosyl alkyne and two different oxiranes via styrene oxide and epichlorohydrin individually under the same reaction conditions (Figure 3). Because of overlapping of peaks in the ^{1}H NMR spectrum of the developed compound, ^{13}C NMR is comparatively more clear and well-suited for the study on regioselectivity. C1 of **3a** appeared at δ 53.06, which is shifted to δ 65.0 in **6**, which indicates the presence of a upfield carbon due to CH_2-triazole in **3a** and favoring for the predicted regioselectivity; Also, a shifting in the C2 carbon peak from δ 67.3 in **6** to δ 69.4 in **3a** supported the presence of a secondary hydroxyl group in **3a**.

The developed 1,2-azido-hydroxyl triazoles (**3a−3o**) were further successfully utilized for the synthesis of morpholine-fused [5,1-*c*]-triazoles (**4a−4o**) in good yields ranging from 45% to 90% via *O*-propargylation using NaH in dry DMF at ambient temperature for 10−12 h, followed by metal-free intramolecular cyclization of intermediate azido alkynes in DMF at 110 °C for 2−4 h (Scheme 3, Table 2).

The ^{1}H NMR spectrum of compound **4a** exhibited two singlets; one proton each observed at δ 7.58 and 7.51 were assigned for the two triazole-*H* protons. In addition to other signals, the appearance of two double doublets at δ 5.13 and δ 4.70 (J = 15.0 Hz) attributed for OCH_2 finally confirmed the precedence of thermal cyclization leading to the formation of a morpholine-fused triazole skeleton. In ^{13}C NMR, two resonances observed at δ 129.6 and δ 127.8 were assigned to [1,5]-triazole-carbons. A shifting in the signal of CH_2N_3 from δ 53.1 to δ 46.7 corroborated the formation of the desired cyclized morpholine-fused [1,5-*c*]-triazole. The purity of compound **4a** was evidenced by HRMS spectra, which displayed a molecular ion peak at 501.2057 ($M + Na^+$).

Using extensive spectral studies (IR, MS, ^{1}H and ^{13}C NMR), the structures of all the developed compounds **4a−4o** were elucidated. Furthermore, a single-crystal X-ray analysis evidenced the unambiguous structure of compounds **4d**, **4j**, and **4n** (see the Supporting Information, Figures S2−S4).

Weak Interactions in Crystals 4d, 4j, and 4n and Their Role in the Stabilization of Geometrical Conformations. The presence of weak nonbonded interactions within the molecules **4d**, **4j**, and **4n** stabilized the conformational property. The molecules are rich in C-H donors and O, N, and π acceptors. In the morpholine ring, methylene hydrogens beside the triazole ring and methyne hydrogen near the ethereal oxygen act as donors. Intramolecular and intermolecular CH···X (O, N), CH···π, and OH···N interactions stabilize the geometry of the molecules and show their effects in relative changes in geometrical conformations of the molecules.

Role of Intramolecular Weak Interactions. The effect of variant (alkynes) and weak interactions on the structural conformation of morpholine-fused triazoles with respect to 1,4-triazoles was investigated through the change of intramolecular weak interactions observed in compounds **4d**, **4j**,

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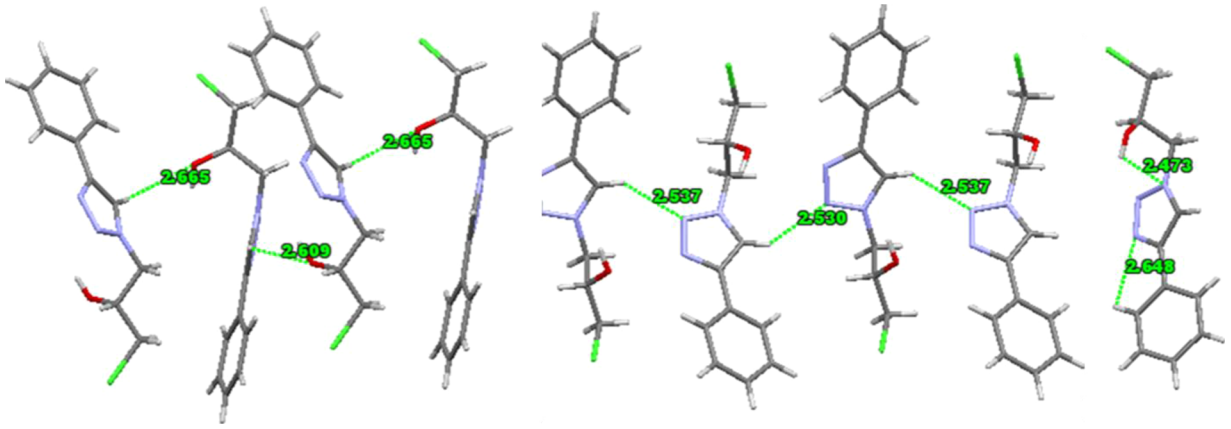


Figure 2. Intermolecular and intramolecular hydrogen bonding in **2j**.

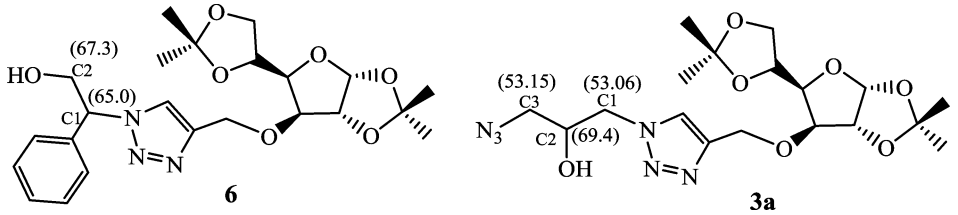
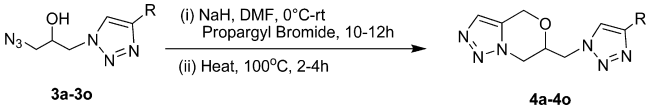


Figure 3. Regioselectivity of oxirane ring-opening and triazole formation through ^{13}C NMR analysis of **3a** and **6**.

Scheme 3. Synthesis of Morpholine-Fused [1,5-*c*]-Triazoles



and **4n**. The methyne hydrogens of the morpholine ring in **4n** and **4j** were involved in C−H10···N5 and C−H10···N1 interactions with measured distances of 2.822 and 2.716 Å, respectively; however, they were absent in **4d**. A methylene H18B of the same ring in **4d** also involves a C−H18B···N interaction, which is absent in the other two, and thus forces the face of the bicyclic system toward the 1,4-triazole ring in **4d**. In addition, the resultant conformation of **4d** was stabilized by intermolecular N−H hydrogen bonding, C−H18A···N11 (2.697 Å) and C−H15B···N12 (2.714 Å) (Figure 4).

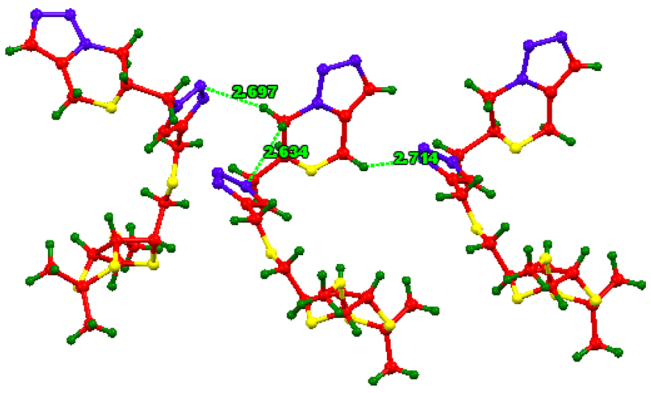


Figure 4. Stabilization of **4d** via intra- and intermolecular weak interactions involving morpholine ring hydrogens.

Likewise, the methylene hydrogen present between morpholine and the 1,4-triazole ring facilitates C−H···O and CH···N interactions in compounds **4d** (2.359 and 2.478 Å), **4j** (2.601 and 2.473 Å), and **4n** (2.555 and 2.617 Å), but the common hydrogen participating in both interactions was found only in the case of **4j**. This observation indicated a possible turn of the triazolo morpholine skeleton in **4j** compared to **4n** and **4d**. Similarly, the effect of variants appeared by the C−H12···O8 (2.868 Å) interaction responsible for below the plane of targeted scaffolds in **4d** wherever the ring hydrogen H1 of used alkynes is taking part in a CH···N interaction in **4n** (2.784 Å) and **4j** (2.585 Å) responsible for rigidity of the skeleton above the plane (Figure 5).

Role of Intermolecular Weak Interactions. All of these crystals also show weak intermolecular interactions and hydrogen bonding within the crystal packing, which affect their geometrical conformations and are responsible for originating the dimeric forms. The dimeric forms that appeared in all of the three crystals **4d**, **4j**, and **4n** are originated from different CH···N, CH···π, and OH···N interactions, respectively. The **4d** dimer originates through CH···N (2.697 and 2.606 Å) and CH···π (3.187 Å) interactions, while CH···π (2.828 and 3.233 Å) and OH···N (2.263 Å) interactions are involved in **4j** and **4n**, respectively. These intermolecular interactions form temporary big ring systems of more than 10 members (Figure 6).

Although a detailed investigation is required to establish the concerned reaction mechanism, we envisaged that the reaction may first involve the oxirane ring-opening by an azide nucleophile, followed by a Cu(I)-catalyzed click reaction with alkyne **1**, to afford product **2** that undergoes subsequent azidation to furnish triazole linked azido alcohol **3**. The base prompted propargylation of **3** and finally the metal-free thermal cycloaddition of the intermediate azido alkyne affords **4** (Figure 7).

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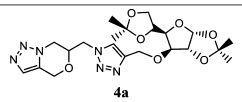
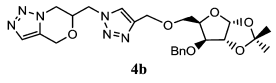
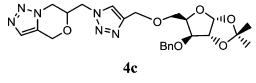
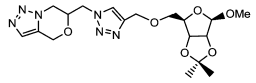
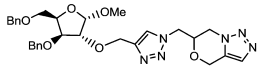
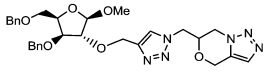
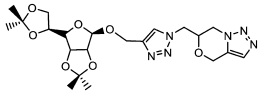
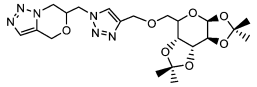
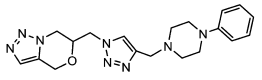
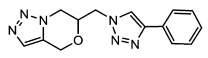
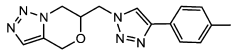
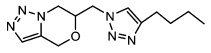
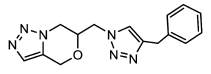
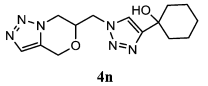
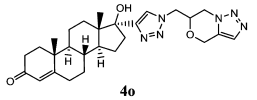
Table 2. Synthesis of Morpholine-Fused Triazoles (4a–4o)[a,b,c,d]

entry[a]	substrate	product[b]	time (h)[c]	yield (%)[d]
1	3a	 4a	16	90
2	3b	 4b	16	85
3	3c	 4c	15	80
4	3d	 4d	12	84
5	3e	 4e	14	82
6	3f	 4f	16	84
7	3g	 4g	15	85
8	3h	 4h	15	88
9	3i	 4i	14	45
10	3j	 4j	16	90
11	3k	 4k	14	82
12	3l	 4l	15	88
13	3m	 4m	15	86
14	3n	 4n	14	85
15	3o	 4o	16	67

[a]Molar ratios: Carbohydrate and other azido-hydroxy triazoles (1.0 equiv), propargyl bromide (1.2 equiv), NaH (2.0 equiv). [b]Morpholine-fused triazoles. [c]Reaction time. [d]Yield reported after purification by column chromatography.

CONCLUSION

In conclusion, we have developed a novel, short, and practical methodology for the synthesis of diverse morpholine-fused [5,1-*c*]-triazolyl heterocycles containing 1,4-triazoles in conjugation to a wide range biologically relevant skeletons. The protocol exhibits a wide substrate scope, uses cheap and readily available reagents, is easy to perform, and is a high-yielding copper-free/copper catalyst reaction that creates rare and biologically relevant heterocyclic molecules, which could be difficult to synthesize by other ways. Furthermore, a discussion about changing intra- and intermolecular weak interactions and their effect on conformations of the desired skeleton due to changing variant (alkynes) is presented, which may be recognized as a precise tool in drug discovery and development.

EXPERIMENTAL SECTION

General Remarks. All the reactions were executed in anhydrous solvents under an argon atmosphere in 1 h using oven-dried glassware at 100 °C. All reagents and solvents were of pure analytical grade. Thin-layer chromatography (TLC) was performed on 60 F_{254} silica gel, precoated on aluminum plates, and revealed with either a UV lamp (λ_{max} = 254 nm) or a specific color reagent (Draggendorff reagent or iodine vapors) or by spraying with methanolic–H_2SO_4 solution and subsequent charring by heating at 80 °C. ^{1}H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively. Chemical shifts are given in parts per million (ppm) downfield from internal TMS, and *J* values are in Hz. Infrared spectra were recorded as Nujol mulls in KBr plates. Elemental analysis was performed using a C, H, N analyzer, and results were found to be within ±0.4% of the calculated values. High-resolution mass spectra were recorded using a TofMS/ES system. Single-crystal X-ray data were collected on a CCD diffractometer.

General Procedure for Synthesis of Glycosyl Alkynes (1a–1h). A solution of orthogonally protected sugar having one free hydroxyl group (1.0 mmol) in anhydrous DMF (10 mL) was cooled to 0 °C, and sodium hydride (3.0 mmol) was added. The reaction mixture was stirred at 0 °C under an argon atmosphere for 20 min. Propargyl bromide (1.2 mmol) was added at 0 °C and allowed to stir for 12 h at room temperature. Upon completion of the reaction, the remaining sodium hydride was quenched with water, the solvent was removed under reduced pressure, and the resultant was extracted with ethyl acetate (3 × 15 mL) and water (10 mL). The organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum, which, on flash chromatography (ethyl acetate:hexane), afforded the desired sugar-based alkyne.

Methyl-3,5-di-O-benzyl-2-O-(prop-2-ynyl)-α-D-xylofuranose, ***1e.*** Methyl-3,5-di-*O*-benzyl-α-D-xylofuranose (0.69 g, 2.0 mmol), NaH (0.145 g, 6.0 mmol), and propargyl bromide (0.214 mL, 2.4 mmol) were reacted in DMF (15 mL) using the procedure described above to afford **1e** (0.6 g, 78%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.30 (m, 10H), 4.88 (s, 1H), 4.68–4.52 (m, 4H), 4.40 (m, 1H), 4.13–4.03 (m, 4H), 3.73–3.71(m, 2H), 3.41 (s, 3H), 2.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 128.6, 128.5, 127.9, 108.0, 86.4, 80.9, 80.2, 75.2, 73.6, 72.3, 69.9, 57.4, 55.9 ppm; Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6. 85; Found: C, 72.41; H, 6.57.

Methyl-3,5-di-O-benzyl-2-O-(prop-2-ynyl)-β-D-xylofuranose, ***1f.*** Methyl-3,5-di-*O*-benzyl-β-D-xylofuranose (0.62 g, 1.8 mmol), NaH (0.130 g, 5.4 mmol), and propargyl bromide (0.306 mL, 2.1 mmol) were reacted in DMF (15 mL) using the typical procedure described above to afford **1f** (0.55 g, 80%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.28 (m, 10H), 5.00 (d, *J* = 2.4 Hz, 1H), 4.71–4.50 (m, 4H), 4.39–4.17 (m, 5H), 3.75–3.43 (m, 2H), 3.43 (s, 3H), 2.45 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 137.9, 128.3, 128.2, 127.7, 127.6, 127.5, 127.5, 100.3, 83.1,

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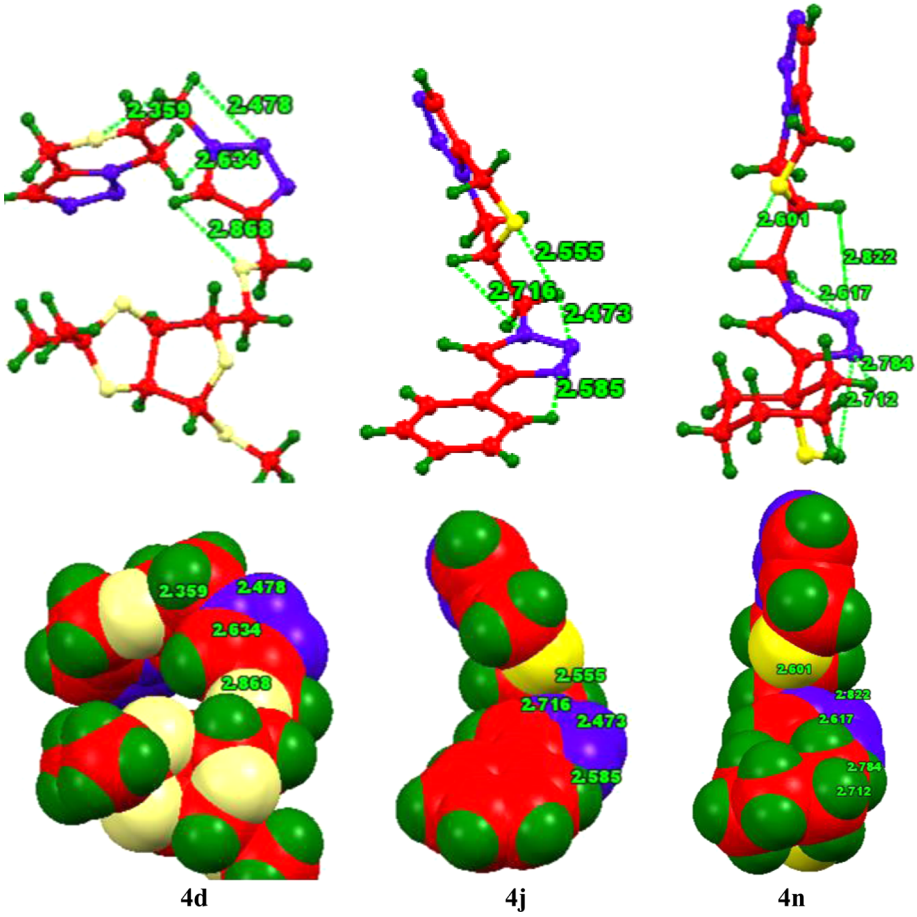

Figure 5. Ball-and-stick and space-filling diagrams of crystals **4d**, **4j**, and **4n** having intramolecular weak interactions. Hydrogen bonds are represented by broken light green lines. Carbon atoms are colored red, hydrogen atoms green, oxygen atoms yellow, and nitrogen atoms blue.

81.2, 79.2, 76.0, 75.1, 73.4, 72.4, 69.2, 57.6, 55.2 ppm; Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85; Found: C, 72.18; H, 6.92.

3-Chloro-1-(4-(1,2:3,4-di-O-isopropylidene-3-O-methylene-α-D-glucofuranose)-1H-1,2,3-triazol-1-yl)propan-2-ol, ***2a.*** A homogeneous solution of NaN_3 (0.046 g, 0.72 mmol), $CuSO_4{\cdot}5H_2O$ (0.016 g, 0.06 mmol), and sodium ascorbate (0.026 g, 0.13 mmol) in water (5 mL) was added in a mixture of epichlorohydrin (0.058 mL, 0.72 mmol) and sugar alkyne (0.197 g, 0.6 mmol). The resulting solution was stirred for 5 h at room temperature. The reaction mixture was extracted with ethyl acetate (3 × 8 mL), and further purification was done by flash chromatography to afford **2a** (185 mg, 65%) as a viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (s, 1H), 5.87 (d, J = 3.3 Hz, 1H), 4.79−4.78 (m, 2H), 4.64−4.48 (m, 3H), 4.29 (m, 2H), 4.10−3.96 (m, 4H), 3.57−3.55 (m, 2H), 1.48, 1.42, 1.36, 1.30 (each s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 124.2, 111.8, 109.0, 105.1, 82.5, 81.7, 80.9, 72.2, 69.8, 67.3, 63.8, 52.8, 45.7, 26.8, 26.7, 26.1, 25.4 ppm; Anal. Calcd for $C_{18}H_{28}ClO_7N_3$: C, 49.83; H, 6.50; N, 9.68; Found: C, 50.06; H, 6.33; N, 9.47.

3-Chloro-1-(4-phenyl-1H-1,2,3-triazol-1-yl)propan-2-ol, ***2j.*** To a stirring solution of epichlorohydrin (0.292 mL, 3.6 mmol) in water (8.0 mL), NaN_3 (0.229 g, 3.5 mmol), $CuSO_4{\cdot}5H_2O$ (0.073 g, 0.3 mmol), and sodium ascorbate (0.116 g, 0.5 mmol) was added phenyl acetylene (0.379 mL, 3.0 mmol). The resulting solution was stirred for 5 h at room temperature. After consumption of starting material (monitored by TLC), the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography in ethyl acetate/hexane (2:3) and afforded **2j** (0.477 g, 67%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.63 (d, J = 6.6 Hz, 2H), 7.35−7.29 (m, 3H), 4.64 (d, J = 10.2 Hz, 1H), 4.47−4.37 (m, 2H), 3.64−3.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 147.4, 129.8, 128.8, 128.2, 125.5, 121.4, 69.8, 53.3, 45.9 ppm.

General Procedure for the Synthesis of Triazole-Linked Sugar-Based Azido Alcohol. In a mixture of epichlorohydrin (2.0 mmol) and sugar alkyne (1.0 mmol), a solution of NaN_3 (4.0 mmol), $CuSO_4{\cdot}5H_2O$ (0.1 mmol), and sodium ascorbate (0.2 mmol) in water was added in a closed vessel after three subsequent flushes of argon in order to avoid the possible oxidation in the presence of molecular oxygen. The resulting solution was stirred for 10−12 h at room temperature. After consumption of starting material (monitored by TLC), the reaction mixture was extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum. The resulting residue was purified by flash chromatography (SiO_2) using EtOAc/hexane as the solvent system.

3-Azido-1-(4-(1,2:5,6-di-O-isopropylidene-3-O-methylene-α-D-glucofuranose)-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3a.*** Compound **1a** (2.63 g, 8.8 mmol), epichlorohydrin (1.4 mL, 17.6 mmol), NaN_3 (2.28 g, 35.2 mmol), $CuSO_4{\cdot}5H_2O$ (0.22 g, 0.8 mmol), and NaAsc (0.349 g, 1.6 mmol) were reacted in water (15 mL) using the procedure described above to afford **3a** (2.2 g, 58%) as viscous. IR (KBr) cm^{-1}: 3429, 2988, 2934, 2105, 1634, 1260, 1217, 1076; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (s, 1H), 5.87 (d, J = 3.0 Hz, 1H), 4.81−4.75 (m, 2H), 4.60−4.22 (m, 5H), 4.11−3.97 (m, 4H), 3.49−3.37 (m, 2H), 1.49, 1.42, 1.36, 1.30 (each s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.9, 124.2, 111.9, 109.1, 105.2, 82.6, 81.7, 80.9, 72.3, 69.3, 67.3, 63.9, 53.7, 53.0, 26.8, 26.7, 26.2, 25.4 ppm; Anal. Calcd for $C_{18}H_{28}O_7N_6$: C, 49.08; H, 6.41; N, 19.08; Found: C, 49.28; H, 6.57; N, 18.69.

3-Azido-1-(4-(5-O-benzyl-3-O-methylene-1,2-O-isopropylidene-α-D-xylofuranose)-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3b.*** Compound **1b** (1.0 g, 3.1 mmol), epichlorohydrin (0.509 mL, 6.2 mmol), NaN_3

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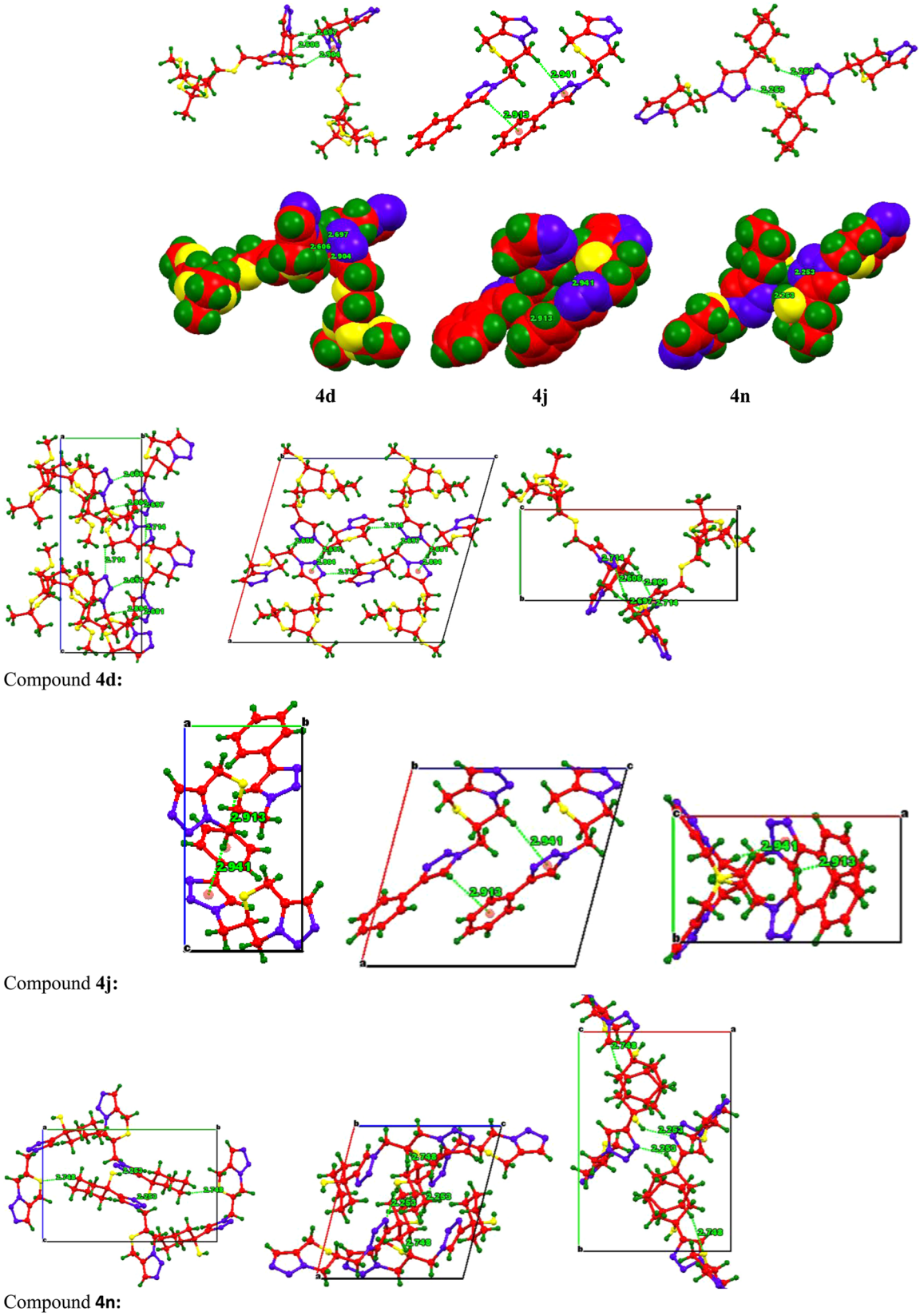

Figure 6. Dimeric forms of **4d**, **4j**, and **4n** and their crystal packings wih weak interactions along *a*, *b*, and *c* axes. Hydrogen bonds are represented by broken light green lines. Carbon atoms are red colored, hydrogen atoms green, oxygen atoms yellow, and nitrogen atoms blue (see the Supporting Information, Table S-13, for details of intra- and intermolecular interactions in compounds **4d**, **4j**, and **4n**).

(0.816 g, 12.5 mmol), $CuSO_4{\cdot}5H_2O$ (0.078 g, 0.3 mmol), and NaAsc (0.124 g, 0.6 mmol) were reacted in water (10 mL) using the procedure described above to afford **3b** (0.713 g, 50%) as viscous. IR (KBr) cm^{-1}: 3443, 2986, 2935, 2861, 2104, 1375, 1070: 3425, 2986,

dx.doi.org/10.1021/jo500890w | J. Org. Chem. 2014, 79, 5752−5762

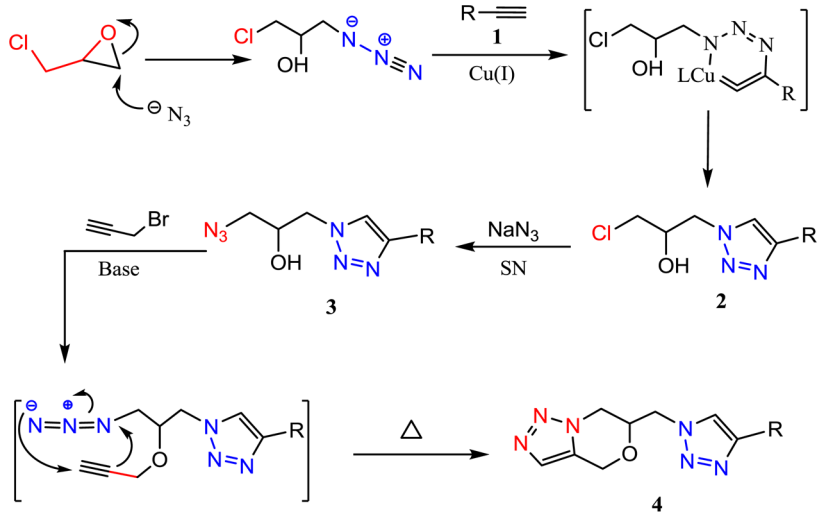

Figure 7. Proposed reaction mechanism.

2871, 2103, 1639, 1217, 1165; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59, (s, 1H), 7.31−7.27 (m, 5H), 5.88 (d, J = 3.6 Hz, 1H), 4.75−4.37 (m, 9H), 3.99 (s, 1H), 3.70−3.68 (m, 2H), 3.49 (d, J = 5.1 Hz, 1H), 3.33 (d, J = 5.7 Hz, 1H), 1.47, 1.30 (each s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.2, 137.8, 128.3, 127.6, 124.2, 111.7, 104.7, 82.2, 81.6, 78.6, 73.3, 69.6, 67.1, 63.3, 53.6, 52.8, 26.5, 26.1 ppm; Anal. Calcd for $C_{21}H_{28}O_6N_6$: C, 54.77; H, 6.13; N, 18.25; Found: C, 54.46; H, 6.32; N, 17.94.

3-Azido-1-(4-(3-O-benzyl-5-O-methylene-1,2-O-isopropylidene-α-D-xylofuranose)-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3c.*** Compound **1c** (1.5 g, 4.7 mmol), epichlorohydrin (0.738 mL, 9.4 mmol), NaN_3 (1.2 g, 18.8 mmol), $CuSO_4{\cdot}5H_2O$ (0.117 g, 0.47 mmol), and NaAsc (0.186 g, 0.94 mmol) were reacted in water (12 mL) using the procedure described above to afford **3c** (1.25 g, 58%) as a colorless, viscous liquid. IR (KBr) cm^{-1}: 3455, 2926, 2871, 2103, 1455, 1074; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.32−7.28 (m, 5H), 5.92 (d, J = 3.0 Hz, 1H), 4.72−4.59 (m, 4H), 4.50−4.20 (m, 5H), 3.94 (d, J = 3.0 Hz, 1H), 3.79−3.77 (m, 2H), 3.45−3.30 (m, 2H), 1.47, 1.31 (each S, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0, 137.4, 128.5, 127.9, 127.6, 124.1, 111.7, 105.0, 82.1, 81.7, 79.1, 71.8, 69.2, 68.2, 64.8, 53.7, 53.0, 26.7, 26.2 ppm; Anal. Calcd for $C_{21}H_{28}O_6N_6$: C, 54.77; H, 6.13; N, 18.25; Found: C, 54.65; H, 6.02; N, 17.94.

3-Azido-1-(4-(methyl-2,3-O-isopropylidene-5-O-methylene-β-D-ribofuranose)-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3d.*** Compound **1d** (1.33 g, 5.5 mmol), epichlorohydrin (0.864 mL, 11 mmol), NaN_3 (1.79 g, 22 mmol), $CuSO_4{\cdot}5H_2O$ (0.137 g, 0.55 mmol), and NaAsc (0.218 g, 1.1 mmol) were reacted in water (10 mL) using the procedure described above to afford **3d** (1.32 mg, 63%) as colorless, viscous. IR (KBr) cm^{-1}: 3416, 2989, 2939, 2865, 2105, 1633, 1274, 1212, 1107; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (s, 1H), 4.95 (s, 1H), 4.66−4.52 (m, 5H), 4.47−4.25 (m, 3H), 3.60−3.26 (m, 7H), 1.47, 1.30 (each s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 124.3, 112.4, 109.1, 85.0, 84.9, 81.9, 71.4, 69.1, 64.5, 54.8, 53.7, 53.2, 26.3, 24.8 ppm; Anal. Calcd for $C_{15}H_{24}O_6N_6$: C, 46.87; H, 6.29; N, 21.86; Found: C, 46.61; H, 6.11; N, 22.08.

3-Azido-1-(4-(methyl-3,5-di-O-benzyl-2-O-methylene-α-D-xylo-furanose)-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3e.*** Compound **1e** (0.80 g, 2 mmol), epichlorohydrin (0.339 mL, 4.1 mmol), NaN_3 (0.52 g, 8.2 mmol), $CuSO_4{\cdot}5H_2O$ (0.049 g, 0.2 mmol), and NaAsc (0.081 g, 0.42 mmol) were reacted in water (8 mL) using the procedure described above to afford **3e** (0.569 g, 52%) as colorless, viscous. IR (KBr) cm^{-1}: 3432, 2924, 2104, 1710, 1454, 1055; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.32−7.30 (m, 10H), 4.88 (s, 1H), 4.63−4.35 (m, 9H), 4.15−4.00 (m, 3H), 3.76−3.67 (m, 2H), 3.40−3.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 138.2, 137.6, 128.4, 128.3, 127.8, 127.5, 125.9, 124.2, 107.9, 86.8, 81.1, 79.9,73.4, 72.2, 69.2, 63.3, 60.4, 55.7, 53.7, 53.0 ppm; Anal. Calcd for $C_{26}H_{32}O_6N_6$: C, 59.53; H, 6.15; N, 16.02; Found: C, 59.91; H, 5.81; N, 16.29.

3-Azido-1-(4-(methyl-3,5-di-O-benzyl-2-methylene-β-D-xylo-furanose)-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3f.*** Compound **1f** (0.6 g, 1.5 mmol), epichlorohydrin (0.254 mL, 3.1 mmol), NaN_3 (0.406 g, 6.2 mmol), $CuSO_4{\cdot}5H_2O$ (0.039 g, 0.15 mmol), and NaAsc (0.061 g, 0.31 mmol) were reacted in water (8 mL) using the typical procedure described above to afford **3f** (0.46 g, 56%) as a pale yellow liquid. IR (KBr) cm^{-1}: 3433, 2923, 2853, 2104, 1455, 1055; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.30−7.29 (m, 10H), 4.95 (s, 1H), 4.80−4.49 (m, 6H), 4.46−4.08 (m, 6H), 3.72−3.56 (m, 2H), 3.41−3.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 138.1, 137.9, 128.3, 128.0, 127.7, 127.7, 127.5, 124.4, 100.2, 83.8, 81.4, 76.0, 73.5, 72.6, 69.2, 63.8, 60.4, 55.3, 53.7, 53.0 ppm; Anal. Calcd for $C_{26}H_{32}O_6N_6$: C, 59.53; H, 5.84; N, 16.02; Found: C, 59.26; H, 5.81; N, 16.23.

3-Azido-1-(4-(methylene-2,3:5,6-di-O-isopropylidene-β-D-mannofuranose)-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3g.*** Compound **1g** (1.38 g, 4.6 mmol), epichlorohydrin (0.728 mL, 9.2 mmol), NaN_3 (1.19 g, 18.4 mmol), $CuSO_4{\cdot}5H_2O$ (0.115 g, 0.4 mmol), and NaAsc (0.184 g, 0.9 mmol) were reacted in water (10 mL) using the procedure described above to afford **3g** (1.2 g, 60%) as viscous. IR (KBr) cm^{-1}: 3427, 2987, 2935, 2105, 1373, 1211, 1084; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (s, 1H), 5.12 (d, J = 7.2 Hz, 1H), 4.74−4.47 (m, 5H), 4.40−4.24 (m, 3H), 4.11−3.76 (m, 3H), 3.50−3.34 (m, 2H), 1.45, 1.37, 1.36, 1.31 (each s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.4, 124.1, 112,6, 109.2,106.2, 84.9, 80.1, 79.4, 73.1, 69.3, 66.6, 61.4, 60.5, 53.9, 53.2 ppm; Anal. Calcd for $C_{18}H_{28}O_7N_6$: C, 49.08; H, 6.41; N, 19.08; Found: C, 49.43; H, 6.67; N, 18.79.

3-Azido-1-(4-(1,2:3,4-di-O-isopropylidene-5-O-methylene-α-D-galactopyranose)-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3h.*** Compound **1h** (1.2 g, 4.0 mmol), epichlorohydrin (0.638 mL, 8.1 mmol), NaN_3 (1.05 g, 16.2 mmol), $CuSO_4{\cdot}5H_2O$ (0.101 g, 0.4 mmol), and NaAsc (0.161 g, 0.8 mmol) were reacted in water (10 mL) using the procedure described above to afford **3h** (1.09 g, 62%) as viscous. IR (KBr) cm^{-1}: 3345, 2988, 2924, 2105, 1383, 1069; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (s, 1H), 5.53 (d, J = 4.8 Hz, 1H), 4.65−4.21 (m, 8H), 3.97 (m, 1H), 3.71−3.68 (m, 2H), 3.45−3.35 (m, 2H), 1.51, 1.45, 1.43, 1.32 (each s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8, 124.3, 109.2, 108.5, 96.2, 71.1, 70.5, 70.3, 69.5, 69.1, 66.8, 64.6, 53.7, 53.2, 25.9, 25.9, 24.8, 24.3 ppm; Anal. Calcd for $C_{18}H_{28}O_7N_6$: C, 49.08; H, 6.41; N, 19.08; Found: C, 48.85; H, 6.04; N, 18.75.

3-Azido-1-(4-(4-N-methylene-1-N-phenyl piperazine)-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3i.*** In a solution of *N*-propargylated phenyl piperazine (0.56 g, 2.8 mmol), epichlorohydrin (0.46 mL, 5.6 mmol), and NaN_3 (0.73 g, 11.3 mmol) in DMF (7 mL) was added a freshly prepared solution of $CuSO_4{\cdot}5H_2O$ (0.069 g, 0.2 mmol) and sodium

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ascorbate (0.11 g, 0.5 mmol) in water (3 mL). The resulting solution was stirred at room temperature for 4 h and then heated at 60 °C with constant stirring for the next 4 h. After complete consumption of alkyne (monitored by TLC), the solvent was evaporated and residue the was extracted with water (10 mL) and ethyl acetate (3 × 15 mL). The organic layer was washed with 10 mL of brine solution. Further purification by flash chromatography afforded **3i** (0.387 g, 40%) as a white solid. IR (KBr) cm^{-1}: 3368, 2923, 2884, 2827, 2103, 1599, 1496, 1229; ^1H NMR (300 MHz, $CDCl_3$): δ 767 (s, 1H), 7.24 (visualize s, 2H), 6.89−6.87 (m, 3H), 4.50−4.26 (m, 3H), 3.69 (s, 2H), 3.39−3.34 (m, 2H), 3.16 (visualize s, 4H), 2.66 (visualize s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.9, 143.3, 129.0, 124.7, 119.9, 116.0, 69.0, 53.8, 53.3, 52.9, 52.7, 48.7 ppm; Anal. Calcd for $C_{16}H_{22}O_1N_8$: C, 56.12; H, 6.48; N, 32.73; Found: C, 55.92; H, 6.86; N, 32.99.

3-Azido-1-(4-phenyl-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3j.*** To a stirring solution of epichlorohydrin (0.768 mL, 9.8 mmol) in water (6 mL), NaN_3 (1.2 g, 19 mmol), $CuSO_4{\cdot}5H_2O$ (0.122 g, 0.4 mmol), and sodium ascorbate (0.194 g, 0.9 mmol) was added phenyl acetylene (0.537 mL, 4.9 mmol), and the mixture was stirred at room temperature for 9 h. After complete consumption of acetylene (monitored by TLC), reaction mixture were extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Further purification by flash chromatography gave compound **3j** (0.717 g, 60%) as a white crystalline solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.59 (d, J = 6.6 Hz, 2H), 7.34−7.29 (m, 3H), 4.51 (d, J = 10.8 Hz, 1H), 4.36−4.30 (m, 2H), 3.53−3.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.3, 129.8, 128.8, 128.2, 125.4, 121.3, 69.1, 53.8, 53.6 ppm.

3-Azido-1-(4-toluene-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3k.*** 4-Ethynyl toluene (0.545 mL, 4.3 mmol), epichlorohydrin (0.674 mL, 8.6 mmol), NaN_3 (1.12 g, 17.2 mmol), $CuSO_4{\cdot}5H_2O$ (0.107 g, 0.4 mmol), and NaAsc (0.170 mg, 0.8 mmol) were reacted in water (8 mL) using the procedure described above to afford **3k** (0.689 g, 62%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.49 (d, J = 7.8 Hz,1H), 7.14 (d, J = 7.8 Hz, 1H), 4.55−4.47 (m, 2H), 4.34−4.31 (m, 2H), 3.50−3.42 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 138.1, 129.4, 127.0, 125.4, 121.0, 69.2, 53.8, 53.5, 21.2 ppm; Anal. Calcd for $C_{12}H_{14}O_1N_6$: C, 55.80; H, 5.46; N, 32.54; Found: C, 55.62; H, 5.83; N, 32.45.

3-Azido-1-(4-butyl-1H-1,2,3-triazol-1yl)propan-2-ol, ***3l.*** 1-Hexyne (0.696 mL, 6.0 mmol), epichlorohydrin (0.940 mL, 12.1 mmol), NaN_3 (1.58 g, 24.3 mmol), $CuSO_4{\cdot}5H_2O$ (0.149 g, 0.6 mmol), and NaAsc (0.237 g, 1.2 mmol) were reacted in water (10 mL) using the procedure described above to afford **3l** (0.740 g, 55%) as a colorless liquid. IR (KBr) cm^{-1}: 3361, 2958, 2930, 2860, 2104, 1457, 1288; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (s, 1H), 4.47−4.30 (m, 3H), 3.94 (s, 1H), 3.48−3.33(m, 2H), 2.66 (t, J = 7.8 Hz, 2H), 1.60 (t, J = 7.8 Hz, 2H), 1.40−1.33 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 122.2, 69.2, 53.7, 53.0, 31.3, 25.1, 22.2, 13.7 ppm; Anal. Calcd for $C_9H_{16}O_1N_6$: C, 48.20; H, 7.19; N, 37.47; Found: C, 47.99; H, 6.88; N, 37.68.

3-Azido-1-(4-benzyl-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3m.*** 3-Phenyl-1-propyne (0.535 mL, 4.3 mmol), epichlorohydrin (0.674 mL, 8.6 mmol), NaN_3 (1.12 g, 17.2 mmol), $CuSO_4{\cdot}5H_2O$ (0.107 g, 0.4 mmol), and NaAsc (0.170 g, 0.8 mmol) were reacted in water (8 mL) using the procedure described above to afford **3m** (622 mg, 56%) as a pale yellow liquid. IR (KBr) cm^{-1}: 3361, 2958, 2930, 2860, 2104; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28−7.21 (m, 6H), 4.41−4.22 (m, 3H), 4.05−4.01 (m, 3H), 3.41−3.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.3, 138.6, 128.6, 126.5, 123.1, 69.1, 53.7, 53.1, 32.0 ppm; Anal. Calcd for $C_{12}H_{14}O_1N_6$: C, 55.80; H, 5.46; N, 32.54; Found: C, 56.15; H, 5.72; N, 32.25.

3-Azido-1-(4-(1-cyclohexanol)-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3n.*** 1-Ethynyl-1-cyclohexanol (0.5 g, 4.0 mmol), epichlorohydrin (0.627 mL, 8.0 mmol), NaN_3 (1.04 g, 16.0 mmol), $CuSO_4{\cdot}5H_2O$ (0.10 mg, 0.4 mmol), and NaAsc (0.159 g, 0.8 mmol) were reacted in water (10 mL) using the procedure described above to afford **3n** (0.482 g, 45%) as viscous. IR (KBr) cm^{-1}: 3383, 2934, 2857, 2104, 1707, 1447, 1061; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (s, 1H), 4.95 (s,1H), 4.48−4.43 (m, 1H), 4.30−4.24 (m, 2H), 3.48−3.42 (m, 3H), 1.96−1.29 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.5, 121.8, 69.2, 53.8, 53.6, 37.7, 37.5, 25.2, 21.9 ppm; Anal. Calcd for $C_{11}H_{18}O_2N_6$: C, 49.61; H, 6.18; N, 31.56; Found: C, 49.38; H, 5.81; N, 31.23.

3-Azido-1-(4-ethisteron-1H-1,2,3-triazol-1-yl)propan-2-ol, ***3o.*** Ethisteron (0.60 g, 1.9 mmol), epichlorohydrin (0.462 mL, 5.7 mmol), NaN_3 (0.617 g, 9.5 mmol), $CuSO_4{\cdot}5H_2O$ (0.047 g, 0.2 mmol), and NaAsc (0.079 g, 0.4 mmol) were reacted in water (10 mL) using the typical procedure described above to afford **3o** (0.362 g, 42%) as a white solid. IR (KBr) cm^{-1}: 3401, 2941, 2857, 2103, 1660, 1616; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (s, 1H), 5.68 (s, 1H), 4.50−4.23 (m, 3H), 3.46−3.39 (m, 2H), 2.37−2.28 (m, 5H), 2.09−1.86 (m, 4H), 1.60−1.04 (m, 14H), 0.70 (m, 1H), 0.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.6, 171.3, 153.0, 123.8, 82.1, 69.2, 53.8, 53.1, 48.9, 48.9, 46.7, 38.5, 37.6, 36.2, 35.5, 33.8, 32.7, 31.5, 29.6, 27.3, 23.5, 20.5, 17.3, 14.1 ppm; Anal. Calcd for $C_{24}H_{34}O_3N_6$: C, 63.41; H, 7. 54; N, 18.49; Found: C, 63.19; H, 7.92; N, 18.75.

General Procedure for the Synthesis of 1,2,3-Triazolo[5,1-*c*]morpholines (4a−4o). A solution of azido alcohol (**3**, 1.0 mmol) in anhydrous DMF (10 mL) was cooled to 0 °C, and NaH (2 mmol) was added portionwise. The reaction mixture was stirred at 0 °C under an argon atmosphere for 20 min. Then, at the same temperature, propargyl bromide (1.2 mmol) was added, and the reaction mixture was further stirred for 12 h at room temperature. After disappearance of starting materials (monitored by TLC), the reaction was quenched with water and whole reaction mixture was allowed to heat at 100 °C with constant stirring for 2−4 h. Upon completion of the reaction, the solvent was removed in vacuum; the residue was mixed with water (10 mL) and then extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine solution (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica gel 234−400 mesh, $CHCl_3/CH_3OH$ as eluent) to give the title compound **4**.

6-(4-(1,2:5,6-Di-O-isopropylidene-3-O-methylene-α-D-glucofuranose)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine, ***4a.*** Compound **3a** (1.03 g, 2.3 mmol), NaH (0.112 g, 4.6 mmol), and propargyl bromide (0.246 mL, 2.7 mmol) were reacted in DMF (15 mL) using the procedure described above to give **4a** (1.0 g, 90%) as a white solid. IR (KBr) cm^{-1}: 3457, 3142, 2988, 2936, 1640.456, 1374, 1217, 1078; ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.51 (s, 1H), 5.88 (d, J = 3.3 Hz, 1H), 5.13 (d, J = 15.0 Hz, 1H), 4.88−4.57 (m, 8H), 4.32−4.29 (m, 2H), 4.13−3.98 (m, 4H), 1.49, 1.42, 1.36, 1.30 (each s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8, 129.6, 127.8, 124.1, 111.6, 108.7, 105.0, 82.4, 81.7, 80.8, 72.1, 71.7, 67.0, 63.7, 61.8, 51.4, 46.7, 26.6, 26.5, 25.9, 25.2 ppm. HRMS: Calcd for $C_{21}H_{30}N_6O_7$ [M + Na] 501.2074; found 501.2057.

6-(4-(5-O-Benzyl-3-O-methylene-1,2-O-isopropylidene-α-D-xylofuranose)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine, ***4b.*** Compound **3b** (0.20 g, 0.43 mmol), NaH (0.02 mg, 0.8 mmol), and propargyl bromide (0.046 mL, 0.5 mmol) were reacted in DMF (6 mL) using the procedure described above to give **4b** (0.169 g, 85%) as a white solid. IR (KBr) cm^{-1}: 3428, 2925, 2855, 1710, 1454, 1375, 1221, 1079; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.47 (s, 1H), 7.29 (m, 5H), 5.90 (d, J = 3.3 Hz, 1H), 5.05 (d, J = 15.3 Hz, 1H), 4.81−4.40 (m, 10H), 4.17 (m, 1H), 4.02−3.94 (m, 2H), 3.79−3.70 (m, 2H), 1.48, 1.30 (each s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 144.7, 137.8, 129.7, 128.2, 127.9, 127.5, 124.0, 111.6, 104.7, 82,0, 81.6, 78.5, 73.2, 71.7, 67.0, 63.3, 61.8, 51.1, 46.8, 26.5, 26.0 ppm. HRMS: Calcd for $C_{24}H_{30}N_6O_6$ [M + Na] 521.2125; found 521.2123.

6-(4-(3-O-Benzyl-5-O-methylene-1,2-O-isopropylidene-α-D-xylofuranose)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine, ***4c.*** Compound **3c** (0.250 g, 0.54 mmol), NaH (0.026 g, 1.08 mmol), and propargyl bromide (0.062 mL, 0.7 mmol) were reacted in DMF (6 mL) using the procedure described above

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to give **4c** (0.215 g, 80%) as a white solid. IR (KBr) cm^{-1}: 3421, 3128, 2955, 2845, 1715, 1450, 1372, 1221, 1069; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.49 (s, 1H), 7.33−7.29 (m, 5H), 5.93 (d, J = 3.6 Hz, 1H), 5.09 (d, J = 15.0 Hz, 1H), 4.78−4.73 (m, 4H), 4.69−4.54 (m, 3H), 4.48 (d, J = 12.0 Hz, 1H), 4.39 (d, J = 3.3 Hz, 1H), 4.22 (m, 1H), 4.08−3.95 (m, 2H), 3.81−3.79 (m, 3H), 1.47, 1.31 (each s, 6H).); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 137.3, 129.7, 128.4, 128.1, 127.8, 127.5, 124.1, 111.6, 105.0, 82.1, 81.8, 79.1, 72.0, 71.8, 68.3, 64.8, 62.0, 51.4, 47.0, 26.7, 26.2 ppm. HRMS: Calcd for $C_{24}H_{30}N_6O_6$ [M + Na] 521.2125; found 521.2125.

6-(4-(Methyl-2,3-O-isopropylidene-5-O-methylene-β-D-ribofuranose)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine, ***4d.*** Compound **3d** (0.863 g, 2.2 mmol), NaH (0.107 g, 4.4 mmol), and propargyl bromide (0.235 mL, 2.6 mmol) were reacted in DMF (10 mL) using the procedure described above to give **4d** (0.779 g, 84%) as a white solid. IR (KBr) cm^{-1}: 3444, 3137, 2976, 2938, 2865, 1735, 1489, 1244, 1109; ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.50 (s, 1H), 5.13 (d, J = 15 Hz, 1H), 4.95 (s, 1H), 4.85−4.55 (m, 8H), 4.32−4.30 (m, 2H), 4.06 (t, J = 11.4 Hz, 1H), 3.63−3.51 (m, 2H), 3.30 (s, 3H), 1.47, 1.30 (each s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 129.7, 128.1, 124.1, 112.3, 109.1, 85.0, 82.0, 72.0, 71.6, 64.7, 62.1, 54.8, 54.7, 51..4, 47.0, 26.4, 26.9 ppm. HRMS: Calcd for $C_{18}H_{26}N_6O_6$ [M + Na] 445.1812; found 445.1806.

6-(4-(Methyl-3,5-di-O-benzyl-2-O-methylene-α-D-xylofuranose)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]-oxazine, ***4e.*** Compound **3e** (0.220 g, 0.4 mmol), NaH (0.020 g, 0.8 mmol), and propargyl bromide (0.044 mL, 0.5 mmol) were reacted in DMF (6 mL) using the procedure described above to give **4e** (0.193g, 82%) as viscous. IR (KBr) cm^{-1}: 3439, 3140, 2934, 2856, 1710, 1624, 1454, 1196, 1096, 1051; ^1H NMR (300 MHz, $CDCl_3$): δ 7.58 (s,1H), 7.40 (s, 1H), 7.24−7.21 (m, 10H), 4.99 (d, J = 15 Hz, 1H), 4.82 (s, 1H), 4.69−4.34 (m, 11H), 4.12 (m, 1H), 3.95 (m, 3H), 3.69−3.64 (m, 2H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 144.9, 138.1, 137.6, 129.7, 128.3, 128.2, 128.1, 127.7, 127.5, 124.2, 107.9, 86.8, 81.2, 80.0, 73.4, 72.2, 71.9, 69.6, 63.3, 62.0, 55.6, 51.4, 46.9 ppm. HRMS: Calcd for $C_{29}H_{34}N_6O_6$ [M + Na] 585.2438; found 585.2437.

6-(4-(Methyl-3,5-di-O-benzyl-2-O-methylene-β-D-xylofuranose)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]-oxazine, ***4f.*** Compound **3f** (0.25 g, 0.4 mmol), NaH (0.022 g, 0.9 mmol), and propargyl bromide (0.051 mL, 0.5 mmol) were reacted in DMF (6 mL) using the procedure described above to afford **4f** (0.225g, 84%) as a yellowish viscous material. IR (KBr) cm^{-1}: 3415, 3124, 2934, 2864, 1725, 1619, 1445, 1106, 1080, 1045; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.37−7.17 (m, 11H), 5.19 (s, 1H), 4.97−4.88 (m, 2H), 4.74−4.57 (m, 10H), 4.30−3.91 (m, 4H), 3.64−3.55(m, 2H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0, 138.0, 137.8, 129.6, 128.2, 127.9, 127.5, 127.4, 124.3, 100.3, 83.8, 81.3, 75.8, 73.3, 72.5, 71.8, 69.1, 63.7, 61.9, 55.1, 51.3, 46.8 ppm. HRMS: Calcd for $C_{29}H_{34}N_6O_6$ [M + Na] 585.2438; found 585.2435.

6-(4-(Methylene-2,3:5,6-di-O-isopropylidene-β-D-manofuranose)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]-oxazine, ***4g.*** Compound **3g** (0.20 g, 0.4 mmol), NaH (0.021g, 0.9 mmol), and propargyl bromide (0.036 mL, 0.5 mmol) were reacted in DMF (6 mL) using the procedure described above to give **4g** (0.184 g, 85%) as a red solid. IR (KBr) cm^{-1}: 3428, 2927, 1737, 1615, 1467, 1219, 1082; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.51 (s, 1H), 5.17−5.12 (m, 2H), 4.85−4.63 (m, 8H), 4.41−4.32 (m, 2H), 4.12−3.99 (m, 4H), 1.45, 1.37, 1.31, 1.25 (each s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 129.7, 128.1, 124.3, 112.6, 109.1, 106.0, 85.0, 80.3, 79.3, 73.0, 72.0, 66.6, 62.1, 60.3, 51.0, 47.0, 26.8, 25.7, 25.0, 24.4 ppm. HRMS: Calcd for $C_{21}H_{30}N_6O_7$ [M + Na] 501.2074; found 501.2078.

6-(4-(1,2:3,4-Di-O-isopropylidene-6-O-methylene-α-D-galactopyranose)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine, ***4h.*** Compound **3h** (0.52 g, 1.1 mmol), NaH (0.056 g, 2.3 mmol), and propargyl bromide (0.126 mL, 1.4 mmol) were reacted in DMF (8 mL) using the procedure described above to give **4h** (0.496 g, 88%) as a white solid. IR (KBr) cm^{-1}: 3444, 3142, 2988, 2933, 1721, 1457, 1383, 1212, 1068; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.51 (s, 1H), 5.54 (d, J = 4.8 Hz, 1H), 5.13 (d, J = 15 Hz, 1H), 4.84−4.58 (m, 7H), 4.32−4.23 (m,3H), 4.11−4.00 (m, 2H), 3.74−3.70 (m, 2H), 1.53, 1.43, 1.33, 1.33 (each s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.6, 129.7, 128.1, 124.2, 109.2, 108.5, 96.3, 72.0, 71.1, 70.6, 70.4, 69.5, 66.7, 64.7, 62.1, 53.2, 47.0. 26.0, 25.9, 24.8, 24.4 ppm. HRMS: Calcd for $C_{21}H_{30}N_6O_7$ [M + Na] 501.2074; found 501.2065.

6-(4-(4-N-Methylene-1-N-phenylpiperazine)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine, ***4i.*** Compound **3i** (0.55 g, 1.6 mmol), NaH (0.077g, 3.2 mmol), and propargyl bromide (0.171 mL, 1.9 mmol) were reacted in DMF (8 mL) using the procedure described above to give **4i** (0.275g, 45%) as a solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.51 (s, 1H), 7.34 (m, 1H), 7.09−7.06 (m, 1H), 6.92−6.86 (m, 3H), 5.13 (d, J = 14.7 Hz, 1H), 5.01−4.62 (m, 4H), 4.30 (m, 1H), 4.11−4.07 (m, 1H), 3.83 (m, 2H), 3.25 (s, 4H), 2.78 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.9, 145.5, 129.7, 129.1, 128.1, 124.4, 124.3, 123.4, 116.2, 72.0, 62.1, 52.9, 52.7, 52.5, 48.7, 48.7 ppm; MS m/z 381 $[M + H]^+$; Anal. Calcd for $C_{19}H_{24}N_8O_1$: C, 59.98; H, 6.36; N, 29.45; Found: C, 60.28; H, 6.62; N, 29.77.

6-(4-Phenyl-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo-[5,1-c][1,4]oxazine, ***4j.*** Compound **3j** (0.30 g, 1.2 mmol), NaH (0.059 g, 2.4 mmol), and propargyl bromide (0.131 mL, 1.4 mmol) were reacted in DMF (6 mL) using the procedure described above to give **4j** (0.311 g, 90%) as a white solid. IR (KBr) cm^{-1}: 3413, 3133, 2924, 2853, 1442, 1226, 1043; ^1H NMR (300 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.84−7.82 (m, 2H), 7.49−7.32 (m, 4H), 5.13 (d, J = 15.3 Hz, 1H), 4.84−4.79 (m, 2H), 4.70−4.63 (m, 2H), 4.31−4.30 (m, 1H), 4.12−4.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.0, 130.1, 129.7, 128.8, 128.3, 128.1, 125.6, 121.2, 72.0, 62.1, 51.5, 47.0 ppm. HRMS: Calcd for $C_{14}H_{14}N_6O_1$ [M + Na] 305.1127; found 305.1130.

6-(4-Toluene-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]-triazolo[5,1-c][1,4]oxazine, ***4k.*** Compound **3k** (0.096 g, 0.3 mmol), NaH (0.017 g, 0.7 mmol), and propargyl bromide (0.043 mL, 0.5 mmol) were reacted in DMF (5 mL) using the procedure described above to give **4k** (0.080 g, 82%) as a white solid. IR (KBr) cm^{-1}: 3407, 3142, 2940, 2871, 1432, 1232, 1056: ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.48 (s, 1H), 7.23 (d, J = 7.5 Hz, 2H), 5.13 (d, J = 15.0 Hz, 1H), 4.84−4.79 (m, 2H), 4.71−4.62 (m, 2H), 4.32−4.30 (m, 1H), 4.08 (t, J = 12.6 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9, 138.0, 129.7, 129.3, 127.9, 127.2, 125.4, 120.8, 71.9, 61.9, 51.3, 46.8, 21.1 ppm. HRMS: Calcd for $C_{15}H_{16}N_6O_1$ [M + Na] 319.1283; found 319.1287.

6-(4-Butyl-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo-[5,1-c][1,4]oxazine, ***4l.*** Compound **3l** (145 mg, 0.6 mmol), NaH (0.046 g, 1.9 mmol), and propargyl bromide (0.069 mL, 0.7 mmol) were reacted in DMF (5 mL) using the procedure described above to give **4l** (0.147g, 88%) as yellowish, viscous. IR (KBr) cm^{-1}: 3427, 3137, 2956, 2929, 2859, 1642, 1457, 1155, 1045; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49, 7.48 (merge two s, 2H), 5.13 (d, J = 15.0 Hz, 1H), 4.85−4.60 (m, 4H), 4.32−4.31 (m, 1H), 4.04 (t, J = 11.4 Hz, 1H), 2.72 (t, J = 7.5 Hz, 2H), 1.71−1.61 (m, 2H), 1.45−1.33 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.6, 129.8, 127.9, 127.9, 122.1, 71.9, 61.9, 51.1, 46.9, 31.2, 25.0, 22.1,13.6 ppm. HRMS: Calcd for $C_{12}H_{18}N_6O_1$ [M + Na] 285.1440; found 285.1430.

6-(4-Benzyl-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo-[5,1-c][1,4]oxazine, ***4m.*** Compound **3m** (0.120 g, 0.4 mmol), NaH (0.033 g, 1.3 mmol), and propargyl bromide (0.053 mL, 0.6 mmol) were reacted in DMF (6 mL) using the procedure described above to give **4m** (0.116 g, 86%) as a yellowish crystalline solid. IR (KBr) cm^{-1}: 3433, 3138, 2924, 2854, 1603, 1454, 1199, 1048; ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.36 (s, 1H), 7.30−7.24 (m, 5H), 5.09 (d, J = 15.0 Hz, 1H), 4.80−4.53 (m, 5H), 4.26−4.25 (m, 1H), 4.09−3.98 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9, 138.7, 132.0, 129.7, 128.6, 128.0, 126.5, 123.0, 71.9, 62.0, 51.3, 47.0, 32.0 ppm. HRMS: Calcd for $C_{15}H_{16}N_6O_1$ [M + Na] 319.1283; found 319.1287.

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6-(4-(1-Cyclohexanol)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine, ***4n****.* Compound **3n** (0.13 g, 0.4 mmol), NaH (40 mg, 1.4 mmol), and propargyl bromide (0.056 mL, 0.6 mmol) were reacted in DMF (6 mL) using the procedure described above to give **4n** (124 mg, 85%) as a crystalline solid. IR (KBr) cm^{-1}: 3402, 3155, 2931, 2856, 1707, 1646, 1448, 1252, 1082; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.47 (s, 1H), 5.11 (d, J = 15.0 Hz, 1H), 4.84−4.57 (m, 4H), 4.31 (m, 1H), 4.02 (t, J = 12.3 Hz, 1H), 2.03−1.33 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 156.0, 129.8, 128.0, 121.3, 71.9, 69.3, 61.9, 51.3, 46.9, 37.9, 25.2, 21.8 ppm. HRMS: Calcd for $C_{14}H_{20}N_6O_2$ [M + Na] 327.1545; found 327.1544.

6-(4-(Ethisteron)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4H-[1,2,3]-triazolo[5,1-c][1,4]oxazine, ***4o****.* Compound **3o** (0.15 g, 0.3 mmol), NaH (0.023 mg, 0.99 mmol), and propargyl bromide (0.038 mL, 0.39 mmol) were reacted in DMF (6 mL) using the procedure described above to give **4o** (108 mg, 67%) as a brown solid. ^1H NMR (300 MHz, DMSO): δ 7.43 (s, 1H), 7.15 (s, 1H), 5.32 (s, 1H), 4.68 (d, J = 15.3 Hz, 2H), 4.36−4.20 (m, 3H), 4.00 (s, 1H), 3.77−3.66 (m, 1H), 2.36 (s, 1H), 2.08−1.90 (m, 7H), 1.54−1.43 (m, 2H), 1.01−0.81 (m, 10H), 0.58−0.43 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 171.3, 148.2, 130.7, 127.9, 124.1, 81.0, 71.6, 61.2, 50.7, 47.6, 46.7, 46.0, 37.1, 35.5, 35.2, 34.5, 31.1, 29.8, 29.0, 23.8, 18.7, 14.3 ppm. MS m/z 493 $[M + H]^+$; Anal. Calcd for $C_{27}H_{36}N_6O_3$: C, 65.83; H, 7.37; N, 17.06; Found: C, 65.47; H, 7.72; N, 16.85.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all the developed compounds and X-ray crystallographic data for **2j**, **4d**, **4j**, and **4n** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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