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# Click Chemistry Inspired Synthesis of Morpholine-Fused Triazoles

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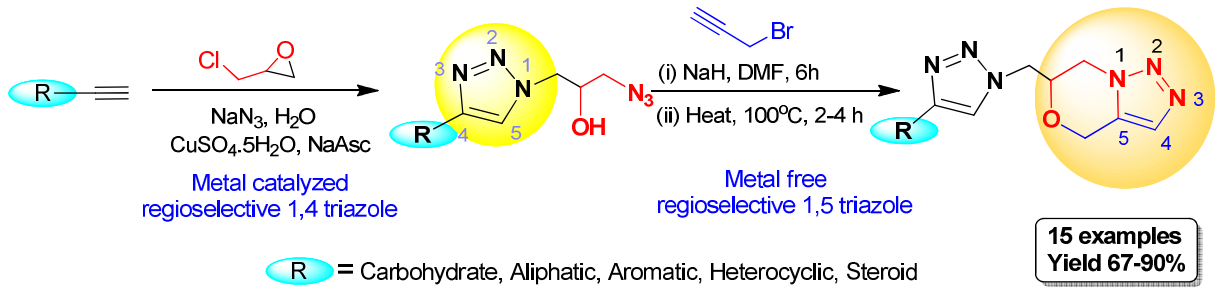
**Abstract:**




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 one-pot methodology. The developed triazolyl *azido* alcohols were further utilized for the synthesis of diverse range of morpholine fused triazoles of chemotherapeutic value. 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.

**Keywords:** Click Chemistry, cyclization, triazole, morpholine fused triazole, glycoconjugate

## 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] Towards this end, the triazolo-morpholine skeleton (Figure 1), a privileged bicyclic ring system in myriad compounds of chemotherapeutic values, is significant due to wide range of enzyme inhibitory activities such as glycosidase, galactosidase, SGLT2, gamma secretes modulators etc.[2] Also, a number of molecules possessing 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]

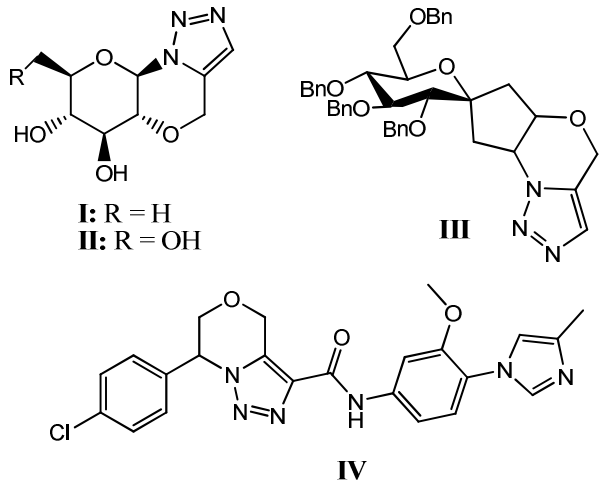



**Figure 1.** Biologically active morpholine-fused triazoles

Now-a-days, 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, method is limited to 2-aryl-ethynyl-1H-indole and related heteroaromatic skeletons and thus need to be investigated with wide range of substrate 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, has 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 subsequent intramolecular azide-alkyne cycloaddition under one-pot methodology is yet to be realized fully.

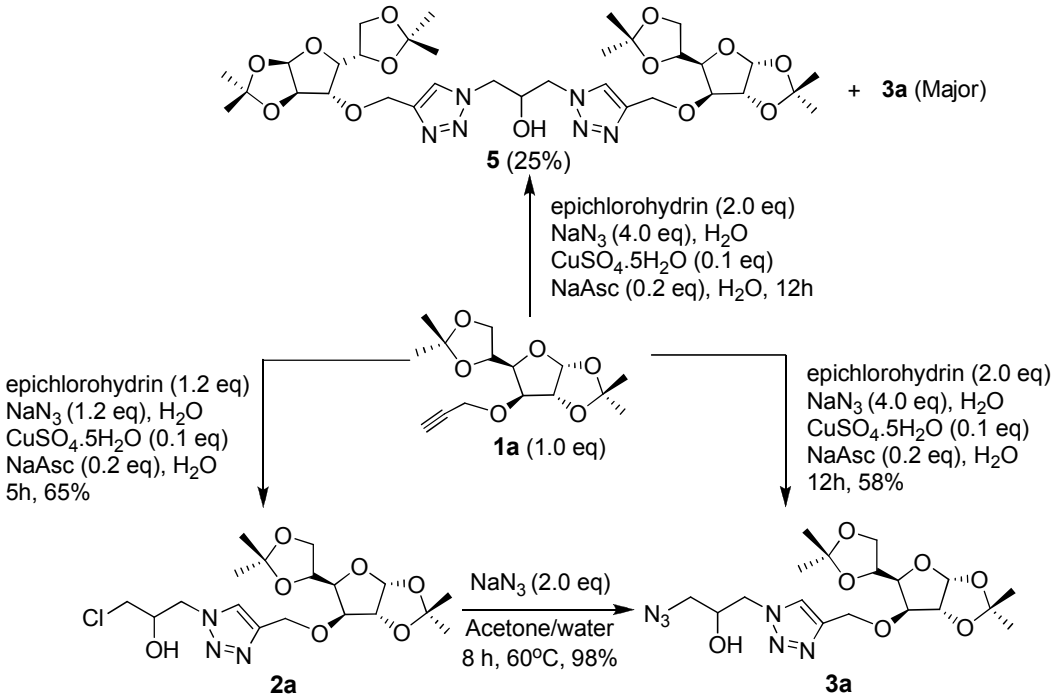
Because of an increased demand for new carbohydrate scaffolds for the numerous pharmacological investigations[17,18] and also with our previous experience,[19-22] we herein describe a novel two step protocol for an easy access to diverse range of morpholine-fused [5,1-*c*]-triazoles from terminal glycosyl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

## RESULTS AND DISCUSSION

Our synthetic strategy begins with orthogonally protected sugars which on propargylation under strong basic medium in dry DMF affords good yield of glycosyl alkynes (**1a-h**).[23] We further extended our investigation with *N*-propargylated and other commercially available alkynes (**1i-**

**o**), which on treatment with epichlorohydrin (a well-known versatile synthons),[24] and $NaN_3$ in presence of $CuSO_4.5H_2O$/NaAsc in $H_2O$ at room temperature under one-pot condition delivered triazolyl *azido* alcohols (**3a-o**) 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, $NaN_3$ in a ratio of 1:1.2:1.2 using Copper catalyst in $H_2O$ furnished **2a** in 65% yield after 5h. In reaction optimization study to measure the effect of reagent concentration and time on product yields, we reacted **1a** (1.0 eq.) with epichlorohydrin (2.0 eq), $NaN_3$ (4.0 eq) in presence of $CuSO_4.5H_2O$ (10 mol%) and NaAsc (20 mol%) for 12h, and isolated good yields of compound **3a** (58%) along with a side product *β*-hydroxy *bis*-triazole **5** (25%) (Scheme 1).

**Scheme 1.** Model reaction of glycosyl alkyne **1a**



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

**Scheme 2.** Synthesis of triazolyl azido alcohols (**3a-3o**)

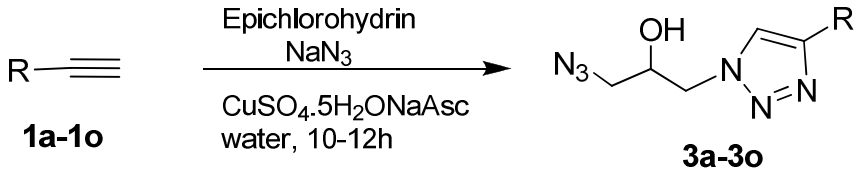
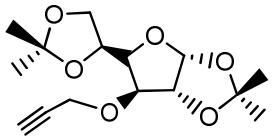
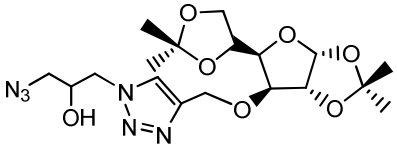
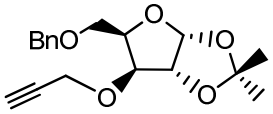
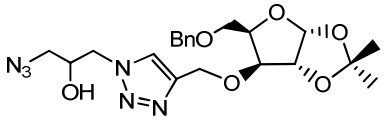
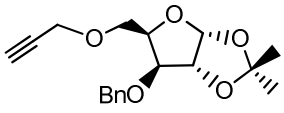
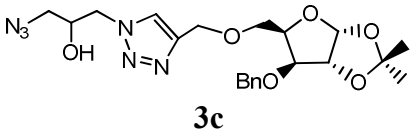
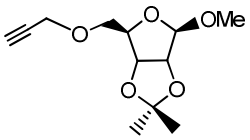
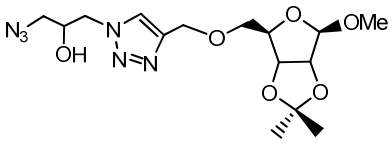
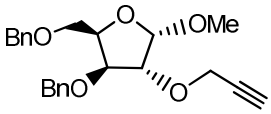
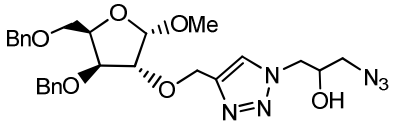
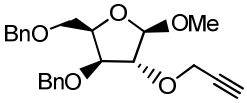
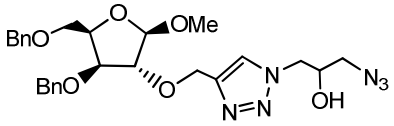
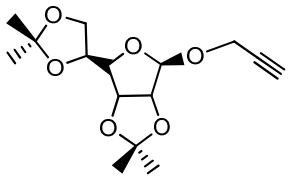
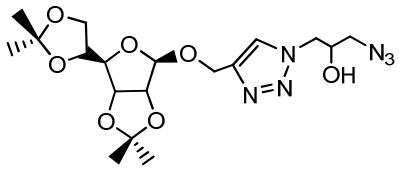
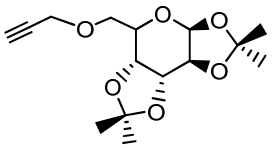
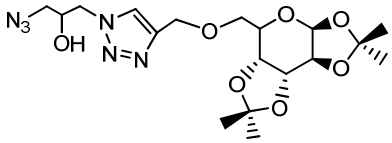
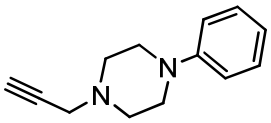
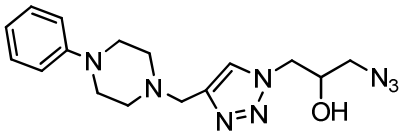
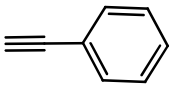
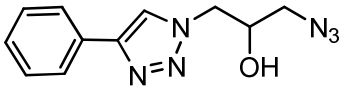
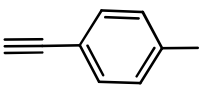
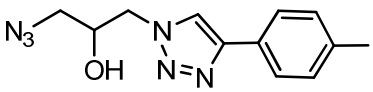
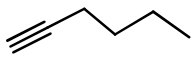
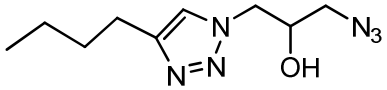
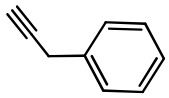
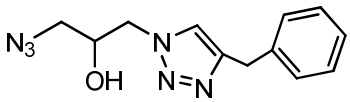
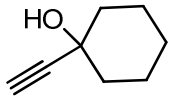
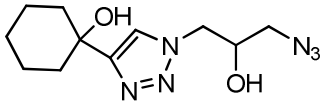
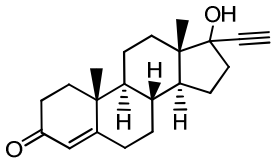
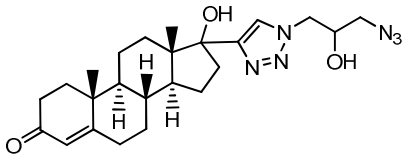



**Table 1.** Synthesis of various carbohydrates and other triazolyl azido alcohols (**3a-o)**

| entry[a] | Substrate | product[b] | time (h)[c] | yield (%)[d] |
|---|---|---|---|---|
| 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 alkyne (1 eq), epichlorohydrin (2 eq), $NaN_3$ (4 eq), $CuSO_4.5H_2O$ (10 mol%), NaAsc (20 mol%), [b]Carbohydrate and other triazolyl azido alcohols. [c]Reaction time. [d]Yield reported after purification by column chromatography.

Interestingly, the reaction of **1i** with epichlorohydrin, $NaN_3$ using $CuSO_4.5H_2O$ 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 in compared to glycosyl alkynes. Likewise, ethisterone, a steroidal alkyne showed poor performance, and required at least 3.0 equivalents of epichlorohydrin to afford desired steroidal *azido* alcohol **3o** in 42% yields.

The regioselectivity in both steps i.e. ring opening reaction of epichlorohydrin with azide nucleophile, and the cycloaddition with alkynes was evidenced by 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 an intramolecular CH···N and OH···N interactions with a measured distances of 2.648 Å and 2.473 Å, respectively. Out of the four conformers evidenced by single crystal X-ray, the intermolecular interaction were observed in between triazole-CH of the one conformer to triazole-*N*2 and oxygen-atom of the others, in an alternate manner as CH···N and CH···O interactions with a measured distance of 2.530 Å, 2.537 Å and 2.665 Å, 2.609 Å, respectively (Figure 2).

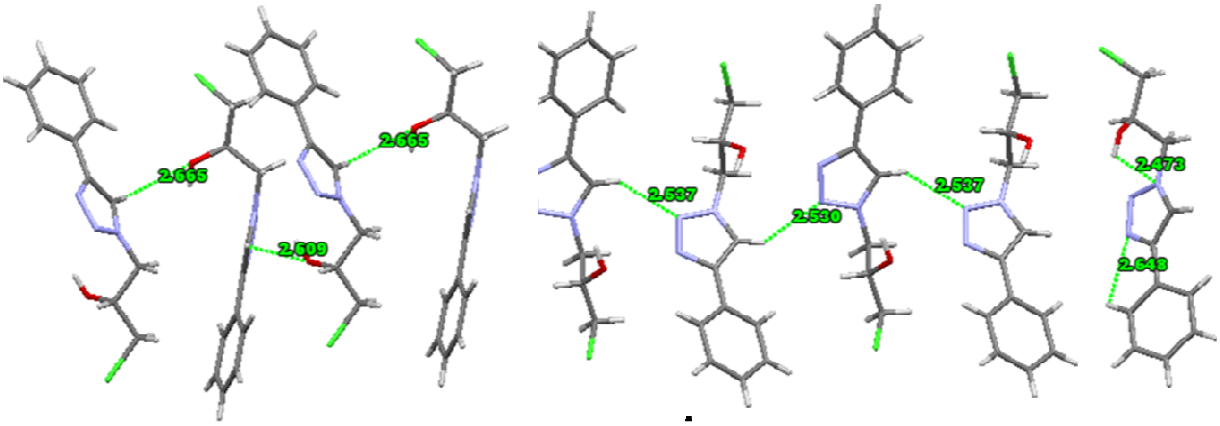



**Figure 2.** Inter molecular and intramolecular hydrogen bonding in **2j**

Regio-selectivity of all developed azido alcohols also supported by 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 same reaction conditions (Figure 3). Because of overlapping of peaks in $^{1}$H NMR spectrum of developed compound, $^{13}$C NMR is comparatively more clear and well suited for study on regioselectivity. C1 of **3a** is appeared at $\delta$ 53.06, which is shifted to $\delta$ 65.0 in **6,** indicates the presence of a up-field carbon due to $CH_2$-triazole in **3a** and favoring for predicted regioselectivity; Also a shifting in C2 carbon peak from $\delta$ 67.3 in **6** to $\delta$ 69.4 in **3a** supported to presence of secondary hydroxyl group in **3a**.

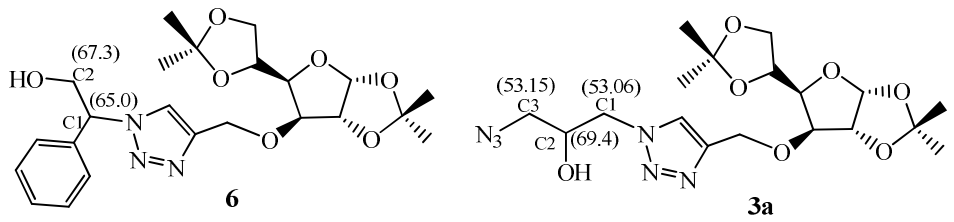



**Figure 3.** Regioselectivity of oxirane ring opening and triazole formation through $^{13}C$ NMR analysis of **3a** and **6**

The developed 1,2-*azido* hydroxyl triazoles (**3a-o**) were further successfully utilized for the synthesis of morpholine fused [5,1-*c*]triazoles (**4a-o**) in excellent yields ranging from 65 to 90% *via O*-propargylation using NaH in dry DMF at ambient temperature followed by metal free intramolecular cyclization of intermediate *azido* alkynes in DMF at $110^0$C for 12-16 hour (Scheme 3, Table 2). The structure of compounds **4a-o** was deduced from their extensive spectral studies (IR, NMR, and MS) and single crystal X-ray analysis.

**Scheme 3.** Synthesis of morpholine-fused [1,5-*c*]-Triazoles

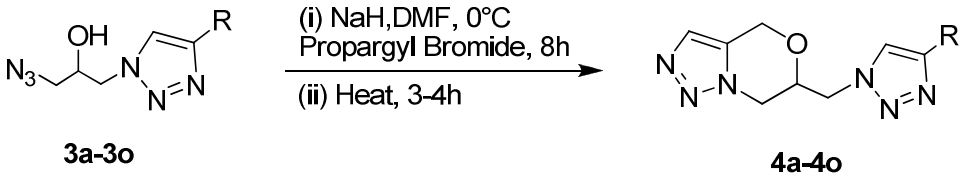
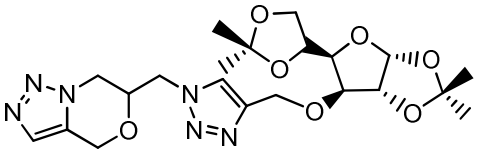
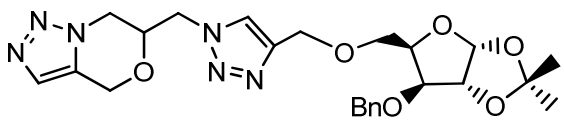
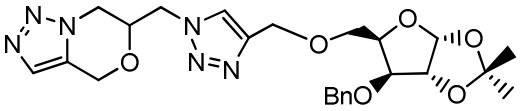
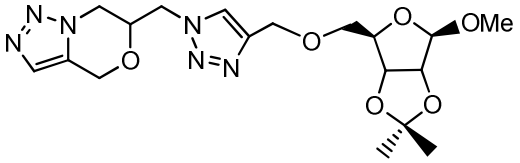
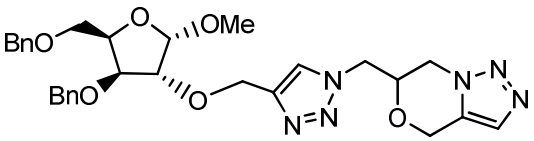
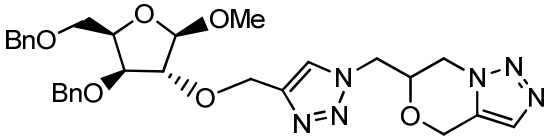
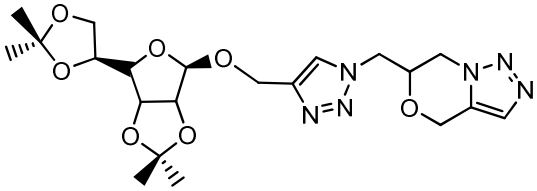
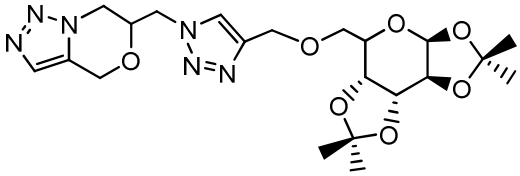
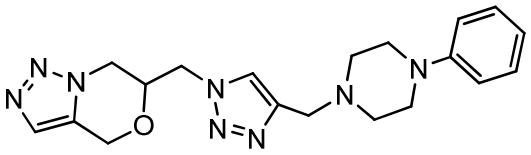
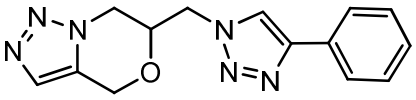
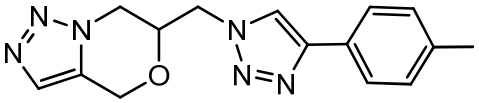
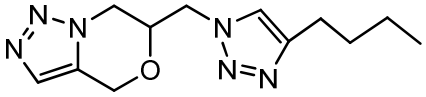
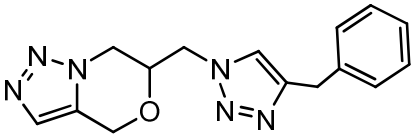
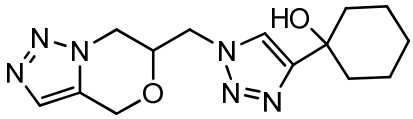
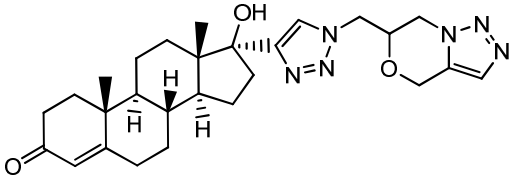



**Table 2: Synthesis of morpholine-fused Triazoles (4a-o)**

| 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 azidohydroxy triazoles (1.0 eq.), Propargyl Bromide (1.2 eq.), NaH (2.0 eq.), [b]Morpholine-fused triazoles. [c]Reaction time. [d]Yield reported after purification by column chromatography.

The $^{1}$H NMR spectrum of compound **4a** exhibited two singlets one proton each observed at $\delta$ 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 $\delta$ 5.13 and $\delta$ 4.70 ($J$ = 15.0 Hz) attributed for OC$H_2$ finally confirmed the precedence of thermal cyclization leading to the formation of morpholine fused skeleton. In $^{13}$C NMR, two resonances observed at $\delta$ 129.6 and $\delta$ 127.8 were assigned for [1,5] triazole-*C*. A shifting in the signal of $CH_2N_3$ from $\delta$ 53.1 to $\delta$ 46.7 corroborated the formation of desired cyclized morpholine 1,5-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-o** were elucidated. Furthermore, a single crystal X-ray analysis evidenced the unambiguous structure of compounds **4d**, **4j** and **4n** (see supporting information figure S2 to S4).

**Weak Interactions in crystals 4d, 4j & 4n and their role in the stabilization of geometrical conformations**

The presence of weak non-bonded 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 morpholine ring, methylene hydrogens besides the triazole ring and methyne hydrogen near the ethereal oxygen act as donor. Intramolecular and intermolecular CH···X (O, N), CH···π and OH···N interactions stabilizes 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 structural conformation of morpholine fused triazoles with respect to 1,4- triazole was investigated through the change of intramolecular

weak interactions observed in compounds **4d**, **4j** and **4n**. The methyne hydrogens of morpholine ring in **4n** and **4j** was involved in C-H10···N5 and C-H10···N1 interactions with measured distances of 2.822 Å and 2.716 Å, respectively, however, absent in **4d**. A methylene H18B of same ring in **4d** also involves C-H18B···N interaction which is absent in other two, thus forces the face of bicyclic system towards 1,4 triazole ring in **4d**. In addition, the resulted 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).

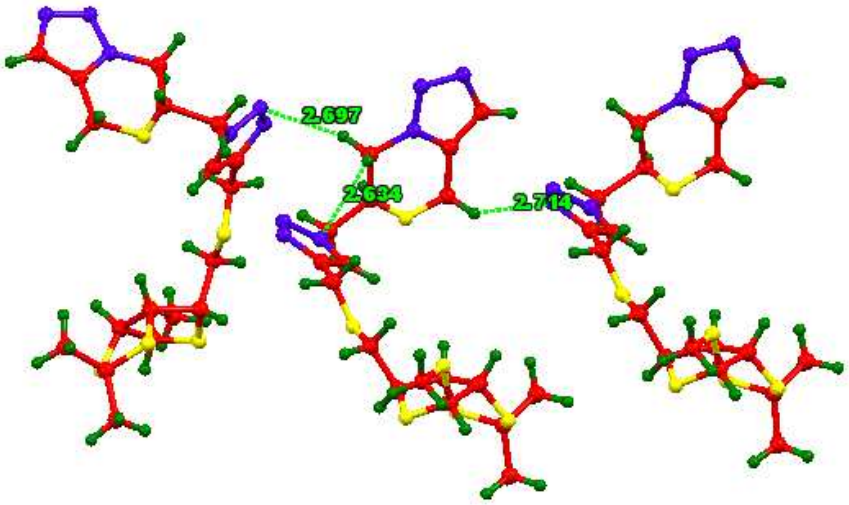



**Figure 4.** Stabilization of **4d** *via* intra and intermolecular weak interactions involving morpholine ring hydrogens

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

H1 of used alkynes is taking part in CH···N interaction in **4n** (2.784 Å) and **4j** (2.585 Å) responsible for rigidity of skeleton above the plane (Figure 5).

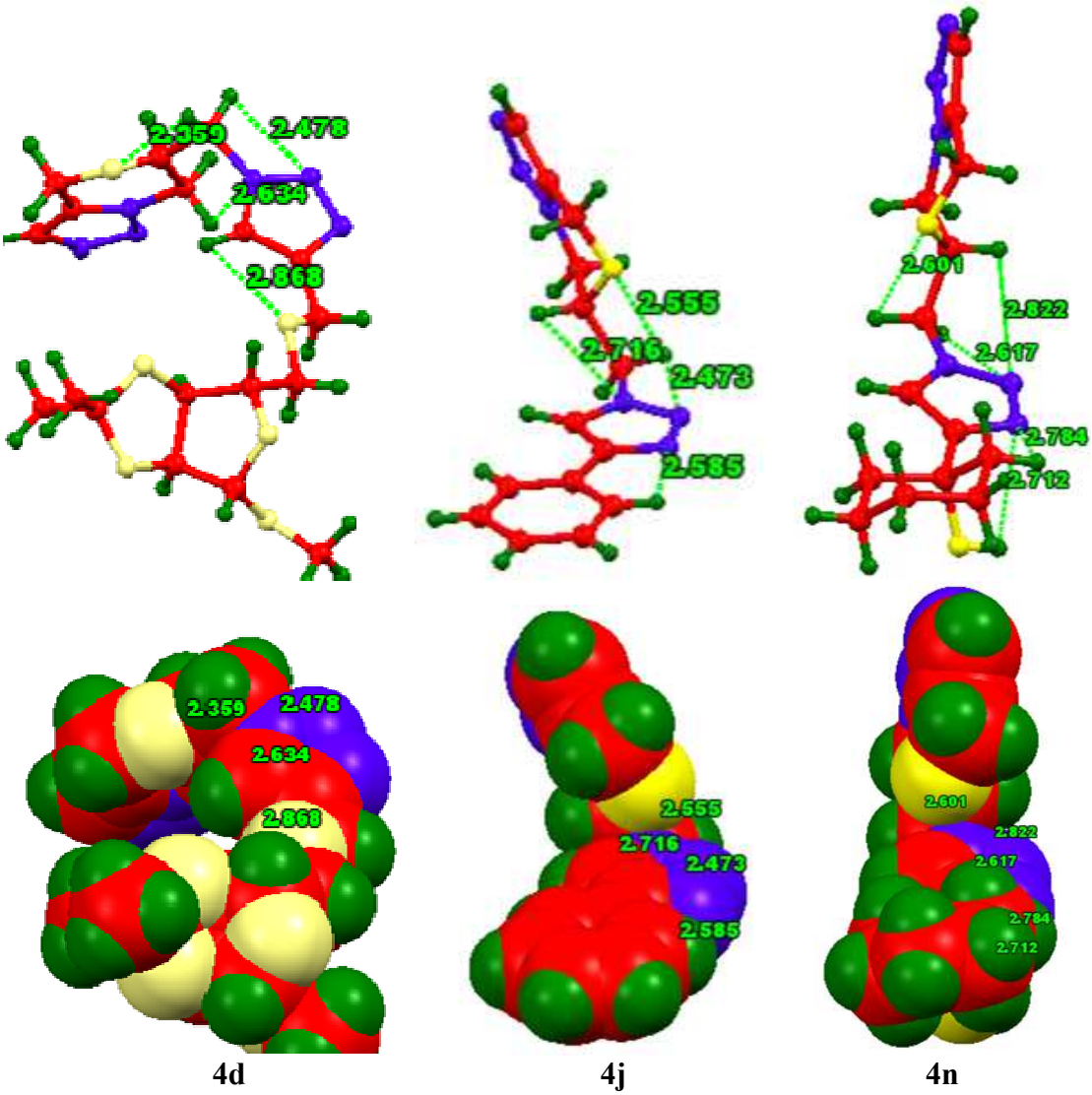
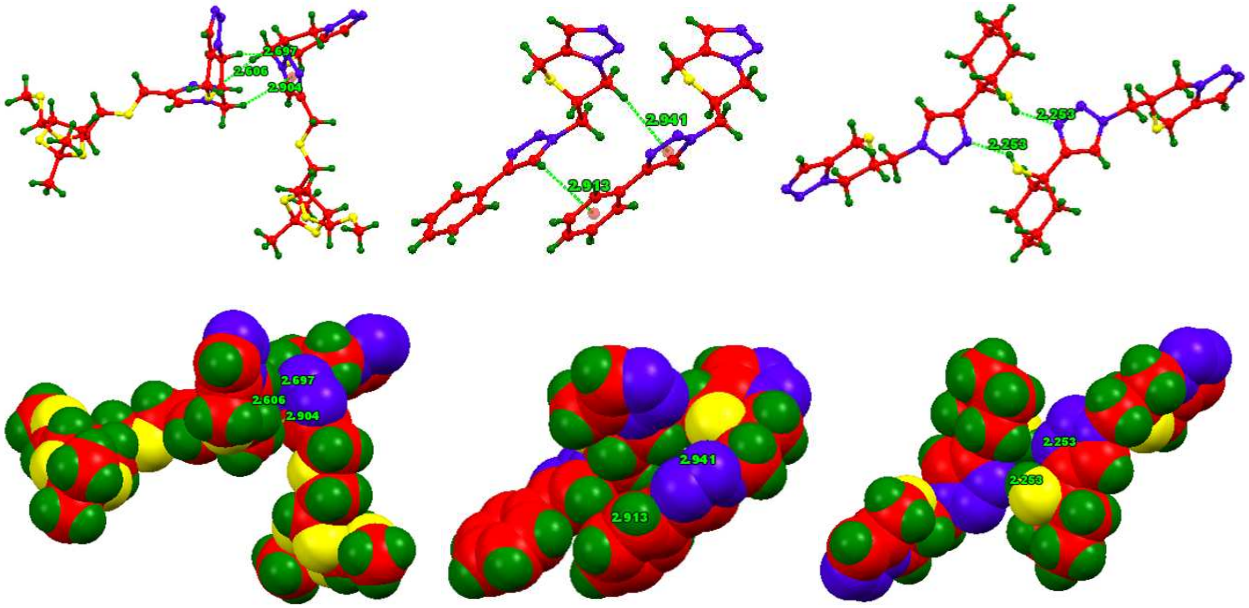



**Figure 5.** Ball stick and space fill diagram of crystals **4d**, **4j** and **4n** having intramolecular weak interactions. Hydrogen bonds are represented by broken light green lines. Carbon atoms are colored red, hydrogen atoms green, oxygen atoms yellow, and nitrogen atoms blue.

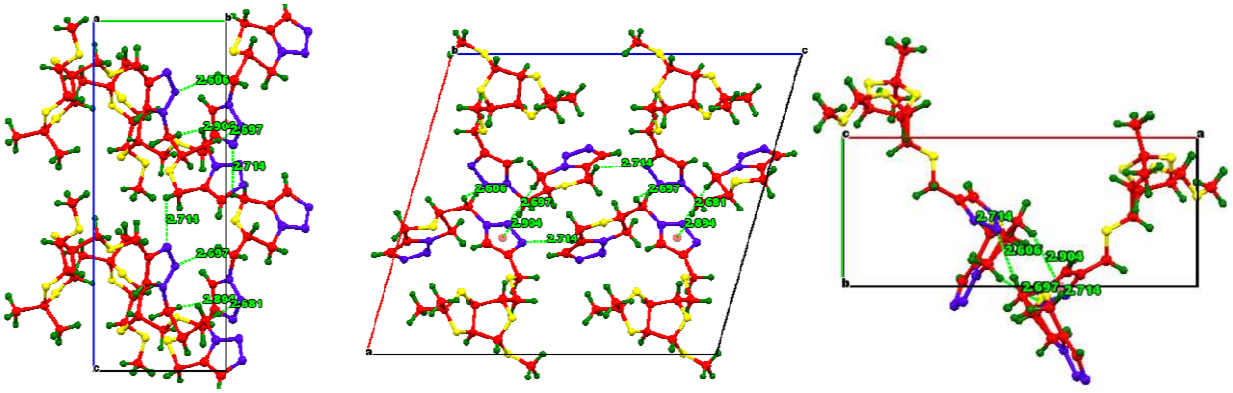
**Role of intermolecular weak interactions**

All these crystals also show weak intermolecular interactions and hydrogen bonding with in the crystal packing, which effect their geometrical conformations and responsible for originating the

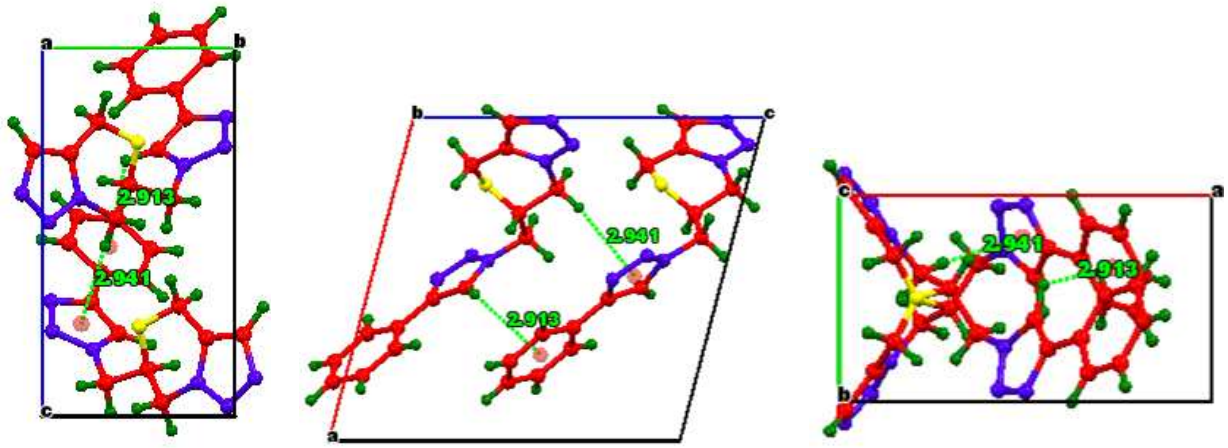
dimeric forms. The dimeric forms appeared in all of three crystals **4d**, **4j** and **4n** are originated from different CH···N, CH···$\pi$ and OH···N interactions, respectively. The **4d** dimer originates through CH···N (2.697 & 2.606 Å) and CH···$\pi$ (3.187 Å) interactions while CH···$\pi$ (2.828, 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 ten members (Figure 6).



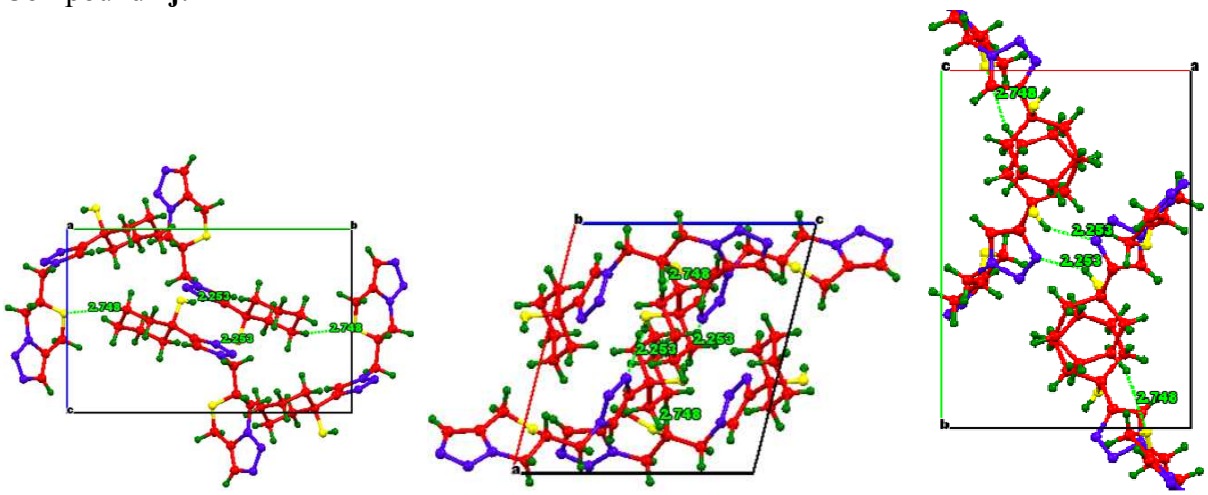

**4d** **4j** **4n**



Compound **4d:**




Compound **4j:**



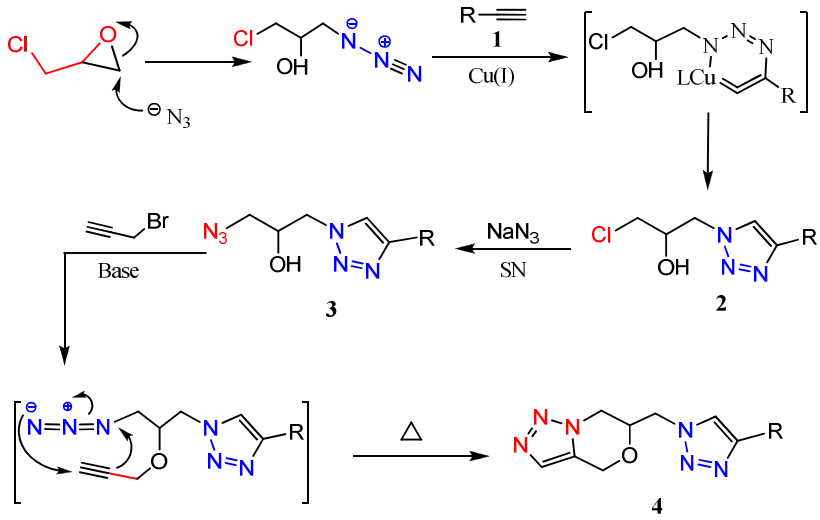

Compound **4n:**

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

Although a detailed investigation is required to establish the concern reaction mechanism, however we envisaged that the reaction may first involve the oxirane ring opening by azide nucleophile followed by 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 intermediate azidoalkyne affords **4** (Figure 7).

**Figure 7.** Proposed reaction mechanism




## 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 wide range biologically relevant skeletons. The protocol exhibits a wide substrate scope, uses cheap and readily available reagents, easy to perform, and high yielding copper free/copper catalyst reaction that creates rare and biologically relevant heterocyclic molecules, which could be difficult to synthesized by other ways. Furthermore, a discussion about changing in intra and inter-molecular weak interactions and their effect on conformations of 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 one hour 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, pre-coated on aluminum plates and revealed with either a UV lamp ($\lambda_{max}$ = 254 nm) or a specific colour reagent (*Draggendorff* reagent or iodine vapours) or by spraying with methanolic-$H_2SO_4$ solution and subsequent charring by heating at 80 °C. $^1H$ and $^{13}C$ NMR were recorded at 300 and 75 MHz, respectively. Chemical shifts given in ppm downfield from internal TMS and *J* values in Hz. Infrared spectra 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 TofMS/ES system. Single-crystal X-ray data collected on CCD-diffractometer.

### (A) 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 ºC and sodium hydride (3.0 mmol) was added. The reaction mixture was stirred at 0 ºC under argon atmosphere for 20 minutes. Propargyl bromide (1.2 mmol) was added at 0 ºC and allowed to stir for 12 hour at room temperature. Upon completion of the reaction, remaining sodium hydride quenched by water, the solvent was removed under reduced pressure, 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, concentrated under vacuum, which on flash chromatography (ethyl acetate: hexane) afforded desired sugar based alkyne.

**Methyl-3,5-di-*O*-benzyl-2-*O*-(prop-2-ynyl)-α-D-*xylo*furanose, 1e:** Methyl-3,5-di-*O*-benzyl-α-D-*xylo*furanose (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 procedure described above to afford **1e** (0.6 g, 78%) as colourless 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-*xylo*furanose, 1f :** Methyl-3,5-di-*O*-benzyl-β-D-*xylo*furanose (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 typical procedure described above to afford **1f** (0.55 g, 80%) as colourless 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, 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) $CuSO_4.5H_2O$ (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, 0.6mmol). The resulting solution was stirred for 5 hrs at room temperature. Reaction mixture was extracted with ethyl acetate (3 × 8ml), further purification was done by flash chromatography to afford **2a** (185 mg, 65%) as 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), $CuSO_4.5H_2O$ (0.073 g, 0.3 mmol) and sodium ascorbate (0.116 g, 0.5 mmol) phenyl acetylene (0.379 ml, 3.0 mmol) was added. The resulting solution was stirred for 5h at room temperature. After consumption of starting material (monitored by TLC), 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 white solid. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.63 (d, $J$ = 6.6Hz, 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.

**(B) 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), $CuSO_4.5H_2O$ (0.1 mmol), and sodium ascorbate (0.2 mmol) in water was reacted in a closed vessel after three subsequent flushes of argon in order to avoid the possible oxidation in 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 (3×15ml), 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 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), $CuSO_4.5H_2O$ (0.22 g, 0.8 mmol) and NaAsc (0.349 g ,1.6 mmol) were reacted in water (15 ml) using procedure described above to afford **3a** (2.2 g, 58%) as viscous; IR (KBr) $cm^{-1}$: 3429, 2988, 2934, 2105, 1634, 1260, 1217, 1076; $^1H$ 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), $NaN_3$ (0.816 g, 12.5 mmol), $CuSO_4.5H_2O$ (0.078 g, 0.3 mmol) and NaAsc (0.124 g, 0.6 mmol) were reacted in water (10 ml) 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, 2871, 2103, 1639, 1217, 1165; $^1H$ 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), $CuSO_4.5H_2O$ (0.117 g, 0.47 mmol) and NaAsc (0.186 g, 0.94 mmol) were reacted in water (12 ml) using procedure described above to afford **3c** liquid (1.25 g, 58%) as colorless viscous; IR (KBr) $cm^{-1}$: 3455, 2926, 2871, 2103, 1455, 1074; $^1H$ 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), $CuSO_4.5H_2O$ (0.137 g, 0.55 mmol) and NaAsc (0.218 g, 1.1 mmol) were reacted in water (10 ml) using procedure described above to afford **3d** (1.32 mg, 63%) as colourless viscous ; IR (KBr) $cm^{-1}$: 3416, 2989, 2939, 2865, 2105, 1633, 1274, 1212, 1107; $^1H$ 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-xylofuranose)-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), $CuSO_4.5H_2O$ (0.049 g, 0.2 mmol) and NaAsc (0.081 g, 0.42 mmol) were reacted in water (8 ml) using procedure described above to afford **3e** (0.569 g, 52%) as

colorless viscous; IR (KBr) $cm^{-1}$: 3432, 2924, 2104, 1710, 1454, 1055 ; $^1H$ 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-xylofuranose)-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), $CuSO_4.5H_2O$ (0.039 g, 0.15 mmol) and NaAsc (0.061 g, 0.31 mmol) were reacted in water (8 ml) using typical procedure described above to afford **3f** (0.46 g, 56%) as pale yellow liquid; IR (KBr) $cm^{-1}$ 3433, 2923, 2853, 2104, 1455, 1055: $^1H$ 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), $CuSO_4.5H_2O$ (0.115 g, 0.4 mmol) and NaAsc (0.184 g, 0.9 mmol) were reacted in water (10 ml) using procedure described above to afford **3g** (1.2 g, 60%) as viscous; IR (KBr) $cm^{-1}$3427, 2987, 2935, 2105, 1373, 1211, 1084: $^1H$ 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), $CuSO_4.5H_2O$ (0.101 g, 0.4 mmol) and NaAsc (0.161 g, 0.8 mmol) were reacted in water (10 ml) using procedure described above to afford **3h** (1.09 g, 62%) as viscous; IR (KBr) $cm^{-1}$ 3345, 2988, 2924, 2105, 1383, 1069: $^1H$ 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); a freshly prepared solution of $CuSO_4.5H_2O$ (0.069 g, 0.2 mmol), and sodium ascorbate (0.11 g, 0.5 mmol) in water (3 ml) was added. The resulting solution was stirred at room temperature for 4 h and then heated at $60^0C$ with constant stirring for next 4 h. After complete consumption of alkyne (monitored by TLC), the solvent was evaporated and residue was extracted with water (10 ml) and ethyl acetate (3×15 ml). Organic layer was washed with 10 ml brine solution. Further purification by flash chromatography afforded **3i** (0.387 g, 40%) as 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) $CuSO_4.5H_2O$ (0.122 g, 0.4 mmol) and sodium ascorbate (0.194 g, 0.9 mmol) phenyl acetylene (0.537 ml, 4.9 mmol) was added and stirred at room temperature for 9h. After complete consumption of acetylene (monitored by TLC), reaction mixture were extracted with ethyl acetate (3×10 ml). Organic layer were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Further purification by flash chromatography gave compound **3j** (0.717 g, 60%) as white crystalline solid; IR (KBr) cm$^{-1}$: $^1$H 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), $CuSO_4.5H_2O$ (0.107 g, 0.4 mmol) and NaAsc (0.170mg, 0.8 mmol) were reacted in water (8 ml) using procedure described above to afford **3k** (0.689 g, 62%) as white solid ; IR (KBr) cm$^{-1}$:$^1$H 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), $CuSO_4.5H_2O$ (0.149 g, 0.6 mmol) and NaAsc (0.237 g, 1.2 mmol) were reacted in water (10 ml) using procedure described above to afford **3l** (0.740 g, 55%) as 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), $CuSO_4.5H_2O$ (0.107 g, 0.4 mmol) and NaAsc (0.170 g, 0.8 mmol) were reacted in water (8 ml) using procedure described above to afford **3m** (622 mg, 56%) as 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), $CuSO_4.5H_2O$ (0.10 mg, 0.4 mmol) and NaAsc (0.159 g, 0.8 mmol) were reacted in water (10 ml) using procedure described above to afford **3n** as viscous (0.482 g, 45%); 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), $CuSO_4.5H_2O$ (0.047 g, 0.2mmol) and NaAsc (0.079 g, 0.4 mmol) were reacted in water (10 ml) using typical procedure described above to afford **3o** (0.362 g, 42%) as 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, 14.1ppm; 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.

**(C) General Procedure for the synthesis of 1,2 ,3-triazolo[5,1- *c*]morpholines (4a-o)**

A solution of azido alcohol (**3**, 1.0 mmol) in anhydrous DMF (10 ml) was cooled to 0 ºC and NaH (2 mmol) was added portion wise. The reaction mixture was stirred at 0 ºC under argon atmosphere for 20 minutes. Then at same temperature, propargyl bromide (1.2 mmol) was added and reaction mixture was further stirred for 12 hour at room temperature. After disappearance of starting materials (monitored by TLC), reaction was quenched by water and whole reaction mixture was allowed to heat at 110 ºC with constant stirring for 3-4 hour. 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 title compound **4**.

**6-(4-(1,2:5,6-Di-*O*-isopropylidene-3-*O*-methylene-α-D-glucofuranose)-1*H*-1,2,3-triazol-1-yl)-6,7-dihydro-4*H*-[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 procedure described above to give **4a** (1.0 g, 90%) as 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-4*H*-[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 procedure described above to give **4b** (0.169 g, 85%) as 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-4*H*-[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 procedure described above to give **4c** (0.215 g, 80%) as white solid; IR (KBr)

$cm^{-1}$ 3421, 3128, 2955, 2845, 1715, 1450, 1372, 1221, 1069: $^1$H 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* = 12.0Hz, 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-4*H*-[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 procedure described above to give **4d** (0.779 g, 84%) as white solid IR (KBr) $cm^{-1}$ 3444, 3137, 2976, 2938, 2865, 1735, 1489, 1244, 1109: $^1$H 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-4*H*-[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 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: $^1$H 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-4*H*-[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 procedure described above to afford **4f** (0.225g, 84%) as yellowish viscous material; IR (KBr) $cm^{-1}$ 3415, 3124, 2934, 2864, 1725, 1619, 1445, 1106, 1080, 1045: $^1$H 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-4*H*-[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 procedure described above to give **4g** (0.184 g, 85%) as red solid; IR (KBr) $cm^{-1}$ 3428, 2927, 1737, 1615, 1467, 1219, 1082: $^1$H 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-4*H*-[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 procedure described above to give **4h** (0.496 g, 88%) as white solid ; IR (KBr) $cm^{-1}$ 3444, 3142, 2988, 2933, 1721, 1457, 1383, 1212, 1068: $^1$H 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-4*H*-[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 procedure described above to give **4i** (0.275g, 45%) as solid; IR (KBr) $cm^{-1}$: $^1$H 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-4*H*-[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 procedure described above to give **4j** (0.311 g, 90 %) as white solid; IR (KBr) $cm^{-1}$ 3413, 3133, 2924, 2853, 1442, 1226, 1043: $^1$H 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-4*H*-[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 procedure described above to give **4k** (0.080 g, 82%) as 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-4*H*-[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 procedure described above to give **4l** (0.147g, 88%) 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-4*H*-[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 procedure described above to give **4m** (0.116 g, 86%) as yellowish crystalline solid; IR (KBr) $cm^{-1}$ 3433, 3138, 2924, 2854, 1603, 1454, 1199,

1048: $^{1}$H 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.

**6-(4-(1-Cyclohexanol)-1H-1,2,3-triazol-1-yl)-6,7-dihydro-4*H*-[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 procedure described above to give **4n** (124mg, 85%) as crystalline solid; IR (KBr) $cm^{-1}$ 3402, 3155, 2931, 2856, 1707, 1646, 1448, 1252, 1082: $^{1}$H 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-4*H*-[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 procedure described above to give **4o** (108 mg, 67%) as brown solid; $^{1}$H 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.

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**Supporting Information**

Copies of $^{1}H$ 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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