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ARTICLE TYPE

Click Chemistry route to tricyclic monosaccharide triazole hybrids: Design and Synthesis of Substituted Hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepines

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A click chemistry approach to novel tricyclic monosaccharide triazole hybrids, namely, aryl substituted hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine derivatives from an intramolecular 1,3-dipolar cycloaddition of 6-azido-4-*O*-propargyl glycopyranosides has been reported.

A carbohydrate inspired molecular hybridization approach incorporating natural chiral carbohydrate templates with heterocyclic rings offers an opportunity for the generation of an interesting array of structures and templates for drug discovery.[1] For instance, small molecule carbohydrate-triazole hybrids have been utilized either as drug candidates or as mechanistic probes to unravel intricate biological pathways (Figure 1).[2]

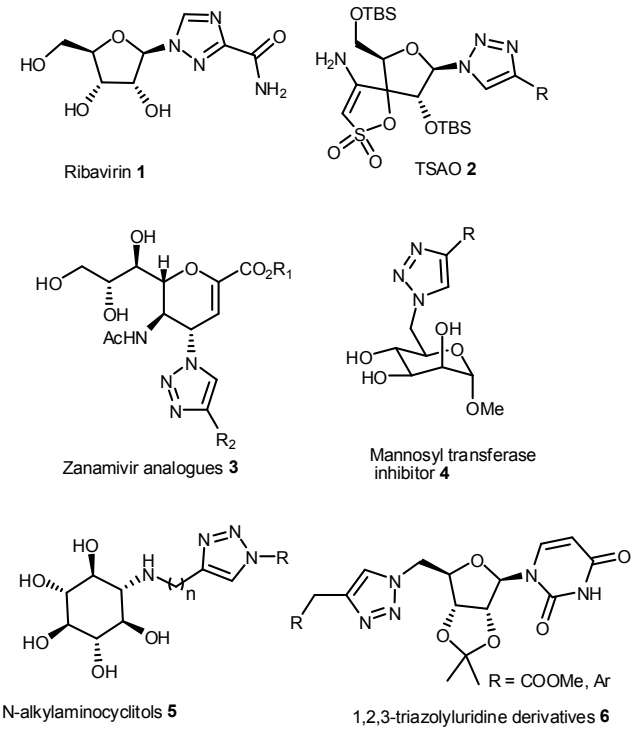


Figure 1: Representative examples of bioactive triazole carbohydrate hybrids

Against this background and given that the triazole moiety itself is present in many compounds exhibiting different biological properties such as antibacterial and anti-HIV,[3] we were interested to design and synthesize a set of tailor made tricyclic monosaccharide-derived analogues incorporating a pharmacophoric 1,2,3-triazole ring (Figure 2).

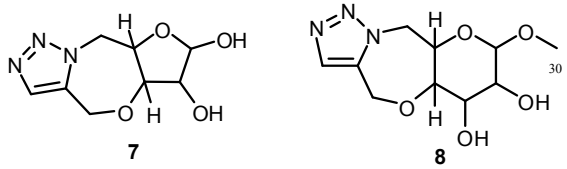


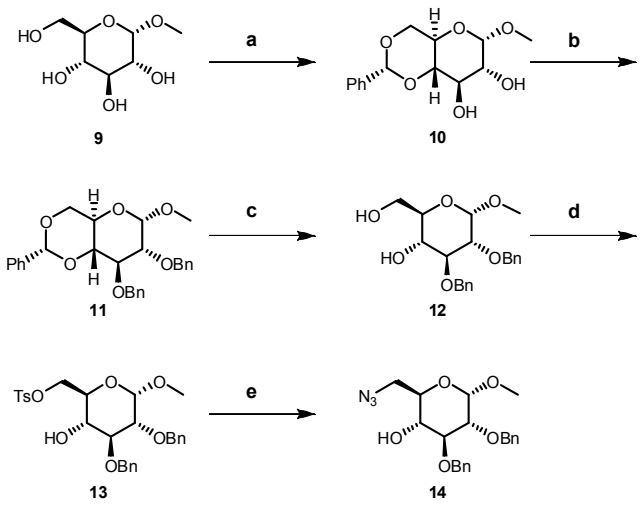
Figure 2: Typical tricyclic scaffold of 1,2,3-triazolyl furanose/pyranose hybrids

In this regard, construction of triazoles by Huisgen's 1,3-dipolar cycloaddition reaction[4] between alkynes and alkyl azides, termed as 'click-chemistry' by Sharpless,[5] appeared to us as a preferred means to rapidly assemble the tricyclic framework shown in **7** and **8**. Though similar approaches have been described earlier for the synthesis of triazole-carbohydrate analogues, [6,7] triazole moiety in these cases was invariably fused at the reducing end of the pentoses and hexoses. We were interested to synthesize fused carbohydrate aryl triazole hybrids, wherein the presence of aryl rings render the analogues drug-like with favourable ClogP values.

In the results described here-in, we have focussed on the introduction of a 4-aryl-triazole at the non-reducing end of the sugar by effecting an intramolecular [3+2] Huisgen's cycloaddition between a propargyl and an azide moiety anchored at the 4- and 6-OH groups of D-glucopyranoside derivative, to construct a triazole ring along with the concomitant formation of 1,4-oxazepine ring.

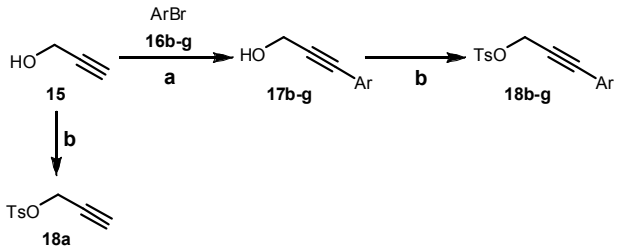
Starting from methyl α-D-glucopyranoside **9**, benzylidene protection using benzaldehyde dimethyl acetal in the presence of catalytic I_2 afforded 4,6-*O*-benzylidene derivative **10**[8] in good yield (Scheme 1). The 2- and 3-hydroxyl groups in **10** were protected as benzyl ethers using benzyl bromide/NaH milieu[9] to obtain **11** in quantitative yield. Deprotection of the benzylidene acetal **11** by treatment with *p*TSA in MeOH afforded diol **12**, which on regioselective tosylation of the primary hydroxyl using TsCl/Py gave **13**[11] in good yield. S_N2 displacement of the tosylate moiety in **13** with sodium azide afforded the 6-azido compound **14**[10] in 92% yield. The methyl 6-azido-2,3-*O*-benzyl-α-methyl-D-glucopyranoside **14** obtained was chosen as the key

carbohydrate precursor for further functionalization with the propargyl tosylate **18a** and various substituted aryl-propargyl alcohol tosylates **18b-g** (Schemes 2 and 3).



Scheme 1: *Reagents and conditions*: (a) $PhCH(OMe)_2$, cat. I_2, DMF, RT, 12 h, 75% (b) BnBr, NaH, DMF, RT, 12 h, 99%; (c) pTSA, MeOH, RT, 24 h, 90%; (d) TsCl, Py, CH_2Cl_2, RT, 2 h, 90%; (e) NaN_3, DMF, 80 ºC, 24 h, 92%.

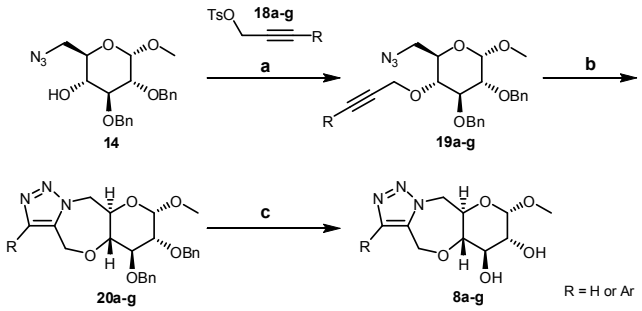
Substituted aryl-propargyl tosylates **18b-g** were synthesized from corresponding substituted aryl bromides and propargyl alcohol. Sonogashira coupling[11] of aryl bromides with propargyl alcohol **15** in the presence of $Pd(PPh_3)_4/CuI/K_2CO_3$ milieu (Scheme 2) afforded **17b–g**. Tosylation using TsCl/KOH[12] on **17b–g** gave the corresponding tosylates **18b-g** in good yields. Various propargyl tosylates **18a-g** synthesized are shown in Table 1 and were utilized for the proparglyation of the 4-OH in **14**.



Scheme 2: *Reagents and conditions*: (a) $Pd(PPh_3)_4$, CuI (cat), K_2CO_3, DMF, 80 ºC, 12 h, 80-90%; (b) TsCl, KOH, CH_2Cl_2, 0 ºC, 1 h, 80-90%.

Alkylation of **14** with the tosylates **18a-g** was achieved in the presence of NaH base to obtain azido-alkyne glucopyranosides **19a-g** (Scheme 3). This set the stage for [3+2] cyclization[13,14] and we initially attempted cycloaddition in **19a**. One of the concerns was whether the orientation of the azide and alkyne moieties was suited for the intramolecular reaction and any competing intermolecular products would dominate affording dimeric or oligomeric mixtures. Satisfactorily, intramolecular [3+2] cycloaddition afforded the desired product **20a**[6] in good yield and we did not observe products from intermolecular couplings when the reaction was monitored by LCMS. Subsequently debenzylation in **20a** afforded compound **8a**. The presence of a one proton singlet at δ 7.60 in ^{1}H NMR and carbon signals at δ 136.1 and 132.9 in ^{13}C NMR corresponding to the two carbon atoms of the triazole ring confirmed the formation of **8a**.

Encouraged by this result, cycloadditions were performed on **19b–g** to obtain **20b-g** in good yields (Table 2). Debenzylation of **20a-g** furnished the diols **8a-g** in excellent yields**.**

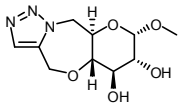
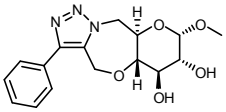
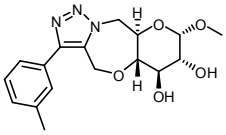
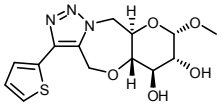
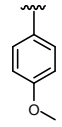
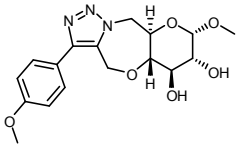
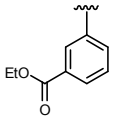
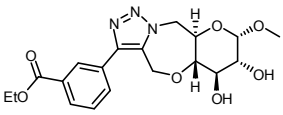
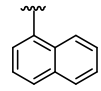
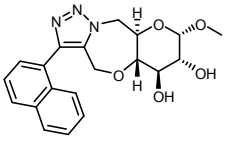


Scheme 3: *Reagents and conditions*: (a) NaH, DMF, 0 ºC – RT, 2 h; (b) DMF, 140 ºC, 12 h; (c) 10% Pd/C, MeOH, H_2 (1 atm), RT, 16 h.
*# Debenzylation of **8d** was very slow and completed over 2 days giving low yields of the product*

Table 1. 3-Arylprop-2-ynyl 4-tosylates **18b-g** used for the coupling *O*-propargylation of **14**

Entry	R (H or Ar)	Product
1	H	**18a**
2		**18b**
3		**18c**
4		**18d**
5		**18e**
6		**18f**
7		**18g**

Table 2. Aryl substituted hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepines **8a**–**g**.

Entry	R (H or Ar)	Product
1	H	 **8a**
2		 **8b**
3		 **8c**
4		 **8d**
5		 **8e**
6		 **8f**
7		 **8g**

The pivotal 'click-reaction' was therefore a one-step process for the construction of fused tricyclic system from a differentially derivatized glycopyranoside. In conclusion, we have developed a efficient route for the synthesis of tricyclic monosaccharide-triazole hybrids by employing 1,3-dipolar cycloaddition reaction. These new chemical motifs can serve as promising leads as drug candidates or probes for metabolic pathways.

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Notes and references

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Graphical Abstract

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