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Diversity Oriented Synthesis of Pyran Based Polyfunctional Stereogenic Macrocyles and Their Conformational Studies

Arya Ajay,[†] Shrikant Sharma,[‡] Munna Prasad Gupt,[†] Vikas Bajpai,[‡] Hamidullah,[§] Brijesh Kumar,[‡] Mahabir Prasad Kaushik,[∥] Rituraj Konwar,[§] Ravi Sankar Ampapathi,*[,‡] and Rama Pati Tripathi*[,†]

Medicinal and Process Chemistry Division, Sophisticated Analytical Instrumentation Facility, Endocrinology Division, CSIR-Central Drug Research Institute, Lucknow-226001, U.P., India, and Process Technology Division, Defence and Research Development Establishment, Jhansi Road, Gwalior-474011, M. P., India

ravi_sa@cdri.res.in; rpt.cdri@gmail.com

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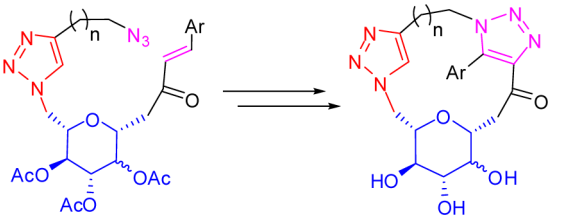
ABSTRACT



A new approach to synthesize a homologous series of 14-, 15-, and 16-membered drug-like, macrocyclic glycoconjugates involving TBAHS promoted azide-propenone intramolecular cycloaddition in designed *C*-glycopyranosyl butenones from a simple sugar D-glucose and D-mannose is reported.

Novel drug design and development relies on increased structural complexity, stereogenicity, and rigidity in molecules.[1] Macrocycles with chiral center(s) are often used as key molecules to address challenging problems such as protein−protein interfaces.[2] These structures are common in many biologically active natural products and synthetic compounds with important pharmacological properties.[3] The unique feature of these macrocycles originates from their structural complexity,[1] rigidity,[4] and ability to form stable, intramolecular H-bonds in solution.[5] In creating molecular diversity and complexity in terms of chirality and functionality, carbohydrates have played a significant role in medicinal chemistry. In this context several leading groups have reported the synthesis of carbohydrate derived macrocyles with interesting biological activity.[6] Rademann's group has reported an elegant synthesis of triazolyl cyclopeptides as privileged protein binders using dipolar cycloaddition.[7] Recently we have also reported 13-member cyclic tetrapeptides containing *C*-linked carbo-β-amino acids with preorganized conformations.[8] However, identification

[†] Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute.
[‡] Sophisticated Analytical Instrumentation Facility, CSIR-Central Drug Research Institute.
[§] Endocrinology Division, CSIR-Central Drug Research Institute.
[∥] Defence and Research Development Establishment.

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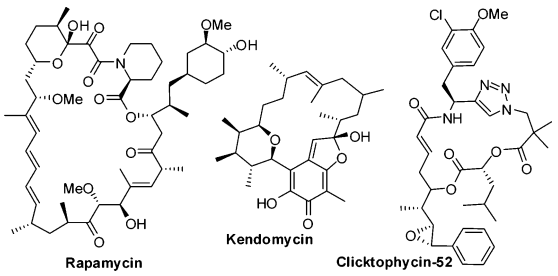

Figure 1. Pyran and triazole based biologically active macrocycles.

of nonpeptidic inhibitors are more significant than the peptidyl inhbibitors in drug design and may be achieved either by a natural substrate mimic or *via* isosteric replacement of the amide bond in the peptide backbone.[9] The 1,2,3-triazole unit is a surrogate of the peptide bond, and introduction of this motif offers improved stability, lipophilicity, and absorption to the molecules.[10]

In view of the continuous efforts to develop new chemotherapeutic agents from sugars,[11] we were inspired by the biologically active macrolides with pyran skeleton such as rapamycin,[12] bryostatin,[13] kendomycin,[14] spongistatine,[15] and triazole containing clicktophycin-52[16] (Figure 1) to undertake the synthesis, conformational studies, and preliminary biological activity of pyran based macrocycles as possible anticancer agents.

In spite of their remarkable properties, synthesis of macrocycles has serious limitations due to poor yields during intramolecular cyclization.[17] To alleviate these problems, solid supported Cu catalysts[18] and Cu tube flow reactors[19] have been used. These are mainly associated with the pseudodilution effect of heterogeneous catalysis. Recently, Hein et al.[20] reported a Cu-catalyzed, regiocontrolled synthesis of 5-iodo-1,2,3-triazole systems and used it as an intermediate in macrocyclization, while James et al.[21] synthesized the same intermediate using their flow reactor techniques to access a library of 1,4,5-trisubstituted macrocyclic triazoles *via* Pd-assisted coupling protocols. Marcaurelle et al.[22] reported the synthesis of 1,5-disubstituted triazoles by Ru catalysis. Several other methods for macrocylization using dipolar cycloaddition reactions were also reported.[23] Our protocol for intramolecular macrocylization is devoid of dilution techniques or heterogeneous catalysis. Moreover, we have synthesized both 1,4-di- and 1,4,5-trisubstituted triazoles within the same molecular framework without any postmodification in the preorganized structure.

Our synthetic strategy for structurally unique and diverse macrocyclic glycoconjugates is based upon three different scaffolds: (i) a polyfunctional pyran skeleton derived from readily available D-glucose and D-mannose, (ii) a 1,4-disubstituted triazole, and (iii) a 1,4,5-trisubstituted triazole. Stereochemical diversity in this collection is high as every molecule has five stereogenic centers, unaffected throughout the synthetic maneuver. Furthermore, the structural diversity and complexity were installed by altering the substituents in the phenyl ring and/or the length of the tether between the two triazole moieties.

The sugar based pyran substrates were prepared from readily available sugar, D-glucose (**1**) and D-mannose (**2**) (Schemes 1, 3). The glycopyranosyl butenones (**3a**−**c**, **4a**) were obtained by reaction of preformed 1-*C*-propanonyl β-D-glycopyranosides with different aromatic aldehydes in good yields (65−74%).[24] The latter (**3a**−**c**, **4a**) on reaction with tosyl chloride (TsCl) in presence of Et_3N at 0 °C in pyridine led to the formation of respective 6′-*O*-(tosyl)-β-D-*C*-glycopyranosyl aryl butenones chemoselectively, which on further acetylation (Ac_2O/pyridine) in the same pot afforded the corresponding 6′-*O*-(tosyl)-tri-*O*-acetyl-β-D-*C*-glycopyranosyl aryl butenones (**5a**−**c**, **6a**) in good yields (78−83%). Tosylated derivatives (**5a**−**c**, **6a**) were reacted separately with sodium azide in DMF at 80 °C to give the respective 6′-azido-6′-deoxy glycopyranosyl derivatives (**7a**−**c**, **8a**) in good yields (78−85%). At first, a Cu-catalyzed alkyne−azide cycloaddition was used to selectively combine the azide of the monosaccharide with different alkynols, to generate the desired triazolyl butenones (**9a**, **10a**, and **11b**) in very good yields (83−87%).

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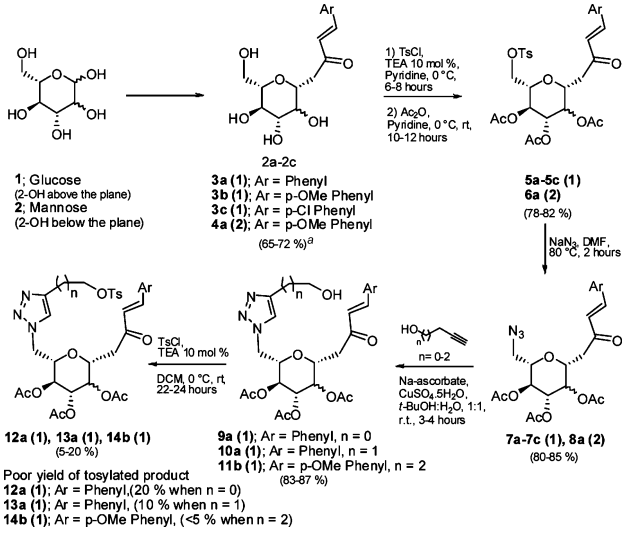
Scheme 1. Synthesis of Intermediate[a]

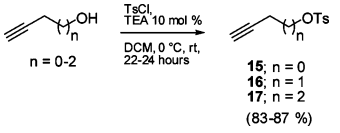


[a] Isolated yields.

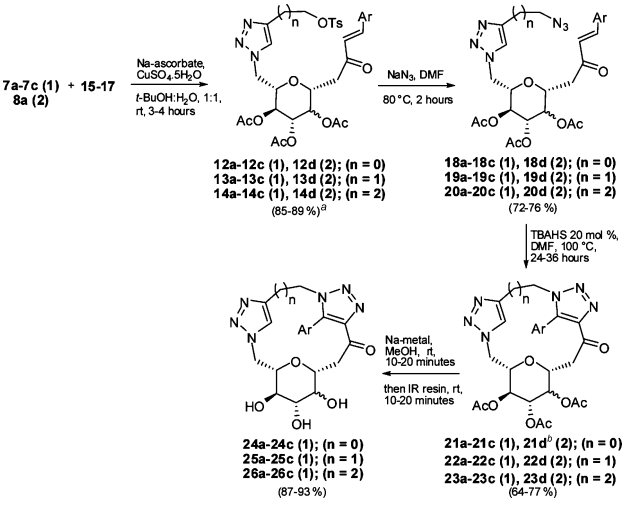
The tosylation of **9a**, **10a**, and **11b** with tosyl chloride in CH_2Cl_2 in the presence of Et_3N resulted in the desired compounds **12a**, **13a**, and **14b** only in very poor yields (5−20%) (Scheme 1).

To overcome the above-mentioned low yield problem, an alternative strategy was adopted, where the 6′-azido-6′-deoxy glycopyranosyl derivatives (**7a**−**c**, **8a**) were reacted with the preformed alkynyl tosylates (**15**−**17**) (Scheme 2) to get the respective tosyloxy triazoles (**12a**−**d**, **13a**−**d**, and **14a**−**d**) in very good yields (81−89%) (Scheme 3). These were then reacted separately with sodium azide in DMF at 80 °C to afford the requisite substrate 6′-(4″-azidoalkyl, triazolyl) β-D-glycopyranose derivatives (**18a**−**d**, **19a**−**d**, and **20a**−**d**) in good yields (70−77%). With these azido derivatives, we were ready to attempt the key 1,3-dipolar cycloaddition to generate the 1,4,5-trisubstituted triazoles with concomitant construction of the macrocyclic architecture. Finally, the tetrabutylammonium hydrogen sulfate (TBAHS) promoted intramolecular cycloaddition of the azide and alkenone in the above-mentioned bifunctional systems afforded the respective 1,4,5-trisubstituted triazolyl macrocyclic compounds (**21a**−**d**, **22a**−**d**, and **23a**−**d**) in good yields (61−76%).[25] The yield of the intramolecular macrocyclization is marginally dependent on the substrate concentration. At 0.34 M substrate concentration, we observed the maximum

Scheme 2. Synthesis of Alkynyl Tosylates



Scheme 3. Synthesis of Macrocyclic Glycoconjugates[a]



[a] Isolated yields. [b] Mannose derived macrocycles are not deacetylated.

macrocyclization (entry 2, Table S1). Furthermore, the yield of macrocylization is slightly time dependent as shown in Table S1.

From the HMBC spectra of **21b**, **22b**, and **23b** the long-range correlations between C1H,H′ with C3 and C7 with C8H,H′ confirmed that **18b**, **19b**, and **20b** undergo 1,4 intramolecular cycloaddition (Supporting Information (Figures S8, S9)). A reactivity comparison among **18a**−**c** for macrocyclization with H, OMe, and Cl as phenyl ring substituents in the glycosyl aryl butenones reveals that **18a** is more reactive and required less reaction time (Figure 2). The same trend was followed in the case of **19a**−**c** and **20a**−**c**. Yields of 14-membered macrocycles (**21a**−**d**) are lower as compared to 16-membered macrocycles (**23a**−**d**), suggesting that the linker size plays a role during macrocyclization and aromatic substituents are insignificant in controlling the yields of the macrocyles. The maximum yields of the macrocyles were achieved with the substrates **20a**−**d** having a 4-carbon tether to give the macrocyles **23a**−**d** (largest ring in the series) respectively in 69−75% yields (Figure 2). A notable trend in the cyclization reaction of the substrates **18a**−**d**, **19a**−**d**, and **20a**−**d** is the gradual increase of the ring-closure efficiency from 14- to 16-membered rings.

Conformational preferences of the synthesized macrocycles (**21b**, **22b**, and **23b**) were evaluated by extenisve NMR studies in $CDCl_3$ with a concentration of 5−10 mM at 300 K. Analysis of the NMR parameters suggest that the macrocyclic conformation remains stable and is similar for the major portion of the three macrocycles. For instance, $^3J_{C1'H-C2'H}$, $^3J_{C2'H-C3'H}$, $^3J_{C3'H-C4'H}$, and $^3J_{C4'H-C5'H}$ values of ∼10 Hz and the NOEs between C1′H↔C3′H, C3′H↔C5′H, and C2′H↔C4′H (Figures S1−S7) suggest that the pyranose ring exists in a chair conformation in all

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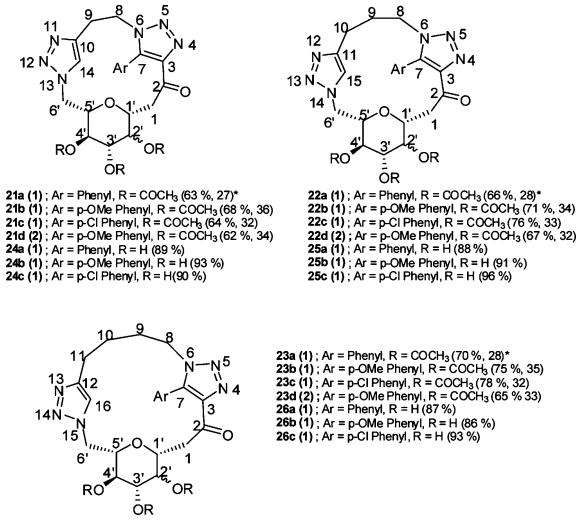

Figure 2. Structure of the synthesized macrocycles (*isolated yields).

three macrocycles. Further, $^{3}J_{C5'H-C6'H} > 10$ Hz and < 3 Hz and the NOE betweeen C4′H↔C6′H (Figures S1−S7) suggest the dihedral angle N−C6′−C5′−O is predominantly ∼60°.

Similarly, $^{3}J_{C1'H\text{-}C1H} > 10$ Hz and < 1 Hz and the NOE betweeen C2′H↔C1H′ indicate the preferred single conformation over the dihedral angle C(O)−C1−C1′−O. Further, both **21b** and **22b** have a similar set of NOEs as shown in Figures S1−S4 and S7 (A). Along with these, an additional NOE between Ar(*ortho*)↔Triazole ring CH (C16H) is characteristic for **23b** (Figure S7 (B)). It indicates that in **23b** the phenyl ring is oriented closer to the disubstituted triazole ring, creating more distance between the two triazole rings. The NOEs and coupling constant values used as distance and torsional constraints in the restrained MD calculations performed with the Discovery studio 3.0 version.[26] Figure 3 shows that, in **23b**, the orientation of the trisubstituted triazole ring moves away from the disubstituted triazole ring, compared to **21b** and **22b**.

Conformational studies on water-soluble compounds **24b**, **25b**, and **26b** in D_2O were also carried out to show the solvent dependency on the conformational preferences. In **25b** and **26b**, the coupling constants and the NOE pattern remained the same, compared to studies conducted in $CDCl_3$, and thus the conformations were also same. However for **24b** in D_2O, Ar(*ortho*) gave NOEs with C2′H and C4′H instead of C1′H as shown for the 14-membered cycle studied in $CDCl_3$. This was reflected in MD studies as well where the trisubstituted triazole ring was varied 180°

(26) See SI Tables S2−S4 for list of distance restriants.

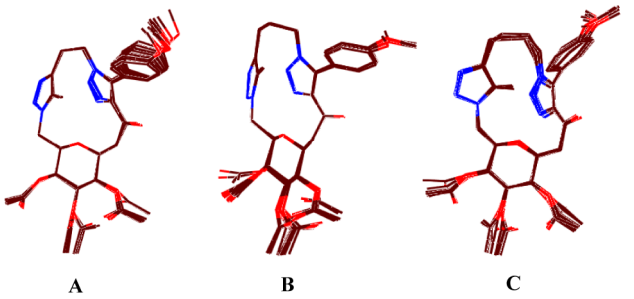

Figure 3. Restrained MD structures of macrocycles. 15 lowest-energy structures superimposed of (A) **21b**, (B) **22b**, and (C) **23b** respectively.

in its orientation between **21b** and **24b** and are represented as a superimposed in Figure S21.

The biological activity of a few macrocycles (**21a−c**, **23a−c**, **25a**) were evaluated against breast cancer (MCF-7 cell line), and compounds **21c**, **22c**, and **23c** were found to have good to moderate activity with IC_{50} values of 14.26, 11.22, and 23.15 μM respectively (SI Table S7).

Several key synthetic challenges were addressed in the synthesis of these macrocycles with the proposed route. The noteworthy observations include no *epi*/anomerization to attain the maximum stereochemical diversity and regioselectivity during 1,3-dipolar cycloaddition to give 1,4-di- and 1,4,5-trisubsituted triazoles by substrate manipulation for each macrocycle.

The current approach for the synthesis of these polyfunctional macrocyles with three points of stereochemical and scaffold diversity holds potential to access a library of biologically active macrocyles and natural product analogs. The presence of an isolated carbonyl group in these macrocyles enhances the potential in synthetic organic chemistry. The current molecules may allow a means for tuning the biological profile of any "hits" or enable labeling of the compounds for use as chemical probes.

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Supporting Information Available. Experimental procedures; ^{1}H, ^{13}C, 2D-NOESY and $^{1}H-^{13}C$ HMBC spectra; HRMS data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.