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Synthesis of 2,3,6-trideoxy sugar triazole hybrids as potential new broad spectrum antimicrobial agents

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ABSTRACT

Here, we describe a molecular hybridization inspired design and synthesis of novel 6-triazolyl 2,3,6-trideoxy sugars as promising new broad-spectrum antimicrobial agents using click chemistry in key step. These compounds showed MIC between 0.39 and 50 μg/mL against different native and resistant bacteria and fungi with no toxicity. Among them, compound **29** was the most active molecule with MIC 0.78 μg/mL against *Staphylococcus aureus* and *Klebsiella pneumoniae* and 3.12 μg/mL against methicillin- and vancomycin-resistant *S. aureus*. Compound **26** was the most potent anti-fungal candidate with MIC 0.39 μg/mL against *Trichophyton mentagrophytes*. Compound **46** was found to be promising with broad-spectrum activity against both bacterial and fungal strains. The bioinformatic studies involving bacteria's protein co-crystals prompted penicillin binding protein-2 as the most likely target of these compounds.

1. Introduction

The discovery of antibiotics revolutionized the treatment of surgical and non-surgical infections [1]. Their overwhelming benefits carried away almost everyone to believe that the infectious diseases would soon be a thing of the past [2]. However the accumulation of drug resistant bacterial strains and slow pace of new antibiotics development turned the situation from one of exhilarating optimism to growing pessimism with a warning of impending return to pre-antibiotic era [2]. The falling numbers of FDA approved antibiotics since 1980 substantiate this scenario [3]. The situation is dim as limited new leads are added to give diversity to the search of potential drugs [4]. Out of the twenty antibiotics approved since 2000, only three – linezolid, daptomycin and retapamulin – originated from new scaffolds [1]. The picture is more grim in case of drugs of Gram-negative bacteria. Adding to the woes, now they are posing more threat than Gram-positive bacteria [5]. Furthermore, recently bedaquiline, a novel diarylquinoline based analogue, is approved by the FDA for multidrug resistant tuberculosis [6].

Fungal infections are another serious health concern. They are mounting pressure on health-care system over the past two decades. The ever increasing immuno-compromised patients and emergence of drug resistance fungal strains has led to this scenario. The existing antifungal drugs e.g., amphotericin-B, flucytosine, azoles etc suffer from severe side effects and/or resistance [7]. Thus, the situation is warranting discovery of alternative drugs involving new molecules with broad-spectrum activity [8]. Natural products with some desirable activity, pathogens' metabolites and/or their critical functional components often serve as good starting point for exploring new prototypes as drug leads. Nevertheless, merging or joining two or more such skeletons, also referred to as molecular hybridization, offer scope for scaffold hopping and open avenues for discovering novel drug molecules [9–12].

The cell walls of bacteria and fungi respectively carry large proportion of peptidoglycan and glucosamine moieties which share similarity in their sugar units. During the past two decades different sugar like scaffolds which include hex-2-enopyranosid-4-ulose [13–15], 4,6-*O*-butylidene-β-D-glucopyraosyl-3-phthalimido-4-styryl-azetidin-2-one [16] and 9-chloro-8-hydroxy-8,9-deoxyspyrone [17] have been recognized as privileged structure in antibacterial and antifungal drug discovery.

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We recently synthesized 2,3-dideoxy hex-2-enopyranosid-4-uloses which showed very mild antibacterial and antifungal activity in *in vitro* screening [18,19]. Furthermore, in medicinal chemistry heterocycles have drawn considerable attention at all times. Here, 1,2,3-triazoles have attracted us due to their facile synthesis through click chemistry [20] and wide biological profiles which include antibacterial and antifungal activities [21–23]. It also mimics the amide features of penicillin antibiotics [24].

Glycoconjugates having a carbohydrate and traizoles moieties are involved in important biological functions, including those on the cell surface, such as the recognition of host compounds, immunological responses, inflammation, cell–cell recognition, bacterial and viral infection, cell communication, metastasis, and many important functions inside cells [25]. Also, many recent reports suggested that different triazole carbohydrate conjugates are endowed with antimicrobial activity [26–30]. In this gamut, we conceptualized the hybridization of our previously reported 2,3-dideoxy hex-2-enopyranosid-4-uloses and 1,2,3-triazole derivatives to result in a new lead to serve as probable broad-spectrum agent with antibacterial and antifungal properties. The synthesis was implemented by choosing the C-6 position of the 2,3,6-trideoxy hex-2-enopyranosid-4-ulose for integration with the 1,2,3-triazole moiety to result in 2,3,6-trideoxy sugar–triazole conjugates [31,32].

2. Chemistry

The synthesis of the target molecules are envisaged as shown in Scheme 1. The intermediates 2,3-dideoxy hex-2-enopyranosid-4-uloses **1a**–**c** were synthesized from D-glucal as reported in our earlier work [18]. Tosylation of the hydroxy group at C-6 led to the 6-*O*-tosyl derivative **2a**–**c**. Luche reduction of **2a**–**c** furnished their 4-hydroxy derivatives **3a**–**c** which were then treated with NaN_3 in DMF at 120 °C to obtain 6-azido-4-*O*-hydroxy 2,3,6-trideoxy hex-2-enopyranosides **4a**–**c** in near quantitative yield. The 6-azido derivatives were now reacted with different terminal alkynes using click chemistry to afford 6-triazolo derivatives **5**–**23**. Oxidation of the 4-hydroxy group of the 6-triazolo derivatives furnished the target sugar triazole conjugates (Table 1).

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3. Biological evaluation

The synthesized sugar triazole conjugates **10**, **24**–**42**, **46**, **50**, **51** and **53** were evaluated for *in vitro* antibacterial activity (MIC; the minimum concentration of drug/compound that produced 90% of growth inhibition) by Muller-Hinton broth dilution method against Gram-positive bacteria *Staphylococcus aureus* (Sa) (ATCC 25923) and Gram-negative bacteria *Klebsiella pneumoniae* (Kp) (ATCC 27736), *Escherichia coli* (Ec) (ATCC 9637), and *Pseudomonas aeruginosa* (Pa) (ATCC BAA-427). They showed activity in the range of 0.78–50 μg/mL against the mentioned bacterial strains.

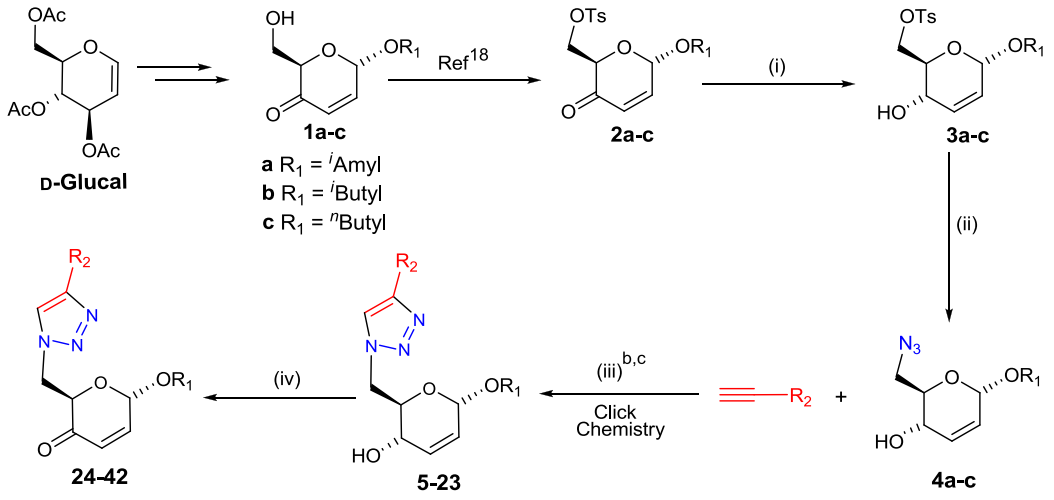
4. Result and discussion

4.1. Antimycobacterial activity

Among the compounds, **29**, **38** and **53** showed MIC 0.78 μg/mL against Sa which make them sixteen-folds more active than standard drugs ampicillin and vancomycin (Table 1). For Kp the MIC of compounds **29** and **46** is 0.78 μg/mL. It makes them as sixteen-, eight- and two-folds more active than ampicillin (also vancomycin), methicillin and gentamycin, respectively (Table 1).

In these analogues structure–activity relationships (SARs) revealed that the antibacterial activity against Sa and Kp improved by increasing the number of carbons in the alkyl chain at C-4 position of triazole ring (compounds **27** to **29**, 3.12 μg/mL to 0.78 μg/mL; Table 1).

In comparison to compound **29**, compound **30** showed eight- and sixty-four-folds less activity against Sa and Kp, respectively, and suggested the unfavourable nature of n-butyl substituent at anomeric position for the activity. Compound **29** with a high CLog*P* value (4.164) showed better activity indicating that lipophilicity as an important parameter for antibacterial activity, though



Scheme 1. General synthetic strategy[a]. [a]Reagents and Conditions: (i) $NaBH_4$, $CeCl_3.7H_2O$, EtOH, 1 h, 0 → 10 °C (ii) NaN_3, DMF, 2–5 h, 80–120 °C, yield:~60% (iii) Sodium ascorbate, $CuSO4{\cdot}5H_2O$, tBuOH: H_2O, yield:~75% ([b]For compound **22** and **23** MeOH:H_2O was used as solvent. [c]In case of preparation of compound **23** K_2CO_3 was also used along with other reagents) (iv) DMP, DCM, 3–6 h, −5–10 °C, yield: ~50%; for compound **6**, **25** R_1 = ^{i}Butyl, **7**, **11**, **26**, **30** R_1 = ^{n}Butyl and for remaining R_1=^{i}Amyl.