Carbohydrate Research 417 (2015) 66–71

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Antimicrobial and cytotoxic activities of 1,2,3-triazole-sucrose derivatives

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ARTICLE INFO

Article history:
Received 4 July 2015
Received in revised form 3 September 2015
Accepted 4 September 2015
Available online 15 September 2015

Keywords:
1,2,3-Triazoles
Sucrose
Antibacterial activity
Antifungal activity
Cytotoxic activity

ABSTRACT

A library of 1-(1′,2,3,3′,4,4′,6-hepta-*O*-acetyl-6′-deoxy-sucros-6′-yl)-1,2,3-triazoles have been investigated for their antibacterial, antifungal and cytotoxic activities. Most of the target compounds showed good inhibitory activity against a variety of clinically and food contaminant important microbial pathogens. In particular, 1-(1′,2,3,3′,4,4′,6-hepta-*O*-acetyl-6′-deoxy-sucros-6′-yl)-4-(4-pentylphenyl)-1,2,3-triazole (**5**) was highly active against all the tested bacteria with minimal inhibitory concentrations (MICs) ranging between 1.1 and 4.4 μM and bactericidal concentrations (MBCs) from 2.2 and 8.4 μM. The compound 1-(1′,2,3,3′,4,4′,6-hepta-*O*-acetyl-6′-deoxy-sucros-6′-yl)-4-(4-bromophenyl)-1,2,3-triazole (**3**) showed antifungal activity with MICs from 0.6 to 4.8 μM and minimal fungicidal concentrations (MFCs) ranging between 1.2 and 8.9 μM. Furthermore, some of the compounds possessed moderate cytotoxicity against human breast, lung, cervical and hepatocellular carcinoma cell lines, without showing toxicity for non-tumor liver cells. The above mentioned derivatives represent promising leads for the development of new generation of sugar-triazole antifungal agents.

1. Introduction

The alarming rates of emerging and reemerging microbial threats coupled with the growing antimicrobial resistance to current antibiotics are major concerns to the public health and scientific communities worldwide.[1,2] These trends have emphasized the urgent need for designing and developing new classes of antimicrobial agents with different chemical structures and mechanism of action compared with traditional drugs, in order to improve their activities while retaining good bioavailability and safety profiles.[3]

1,2,3-Triazole derivatives are an important class of heterocyclic compounds with various potential applications,[4] which have aroused growing attention in recent years with the introduction of 'click chemistry' for their easy and efficient synthesis.[5] The triazole is an attractive bridge group, which could connect two pharmacophores to produce novel bifunctional molecules,[6] while it is almost impossible to be hydrolyzed, oxidized or reduced. Though 1,2,3-triazole units are not present in natural products, they are remarkably stable to metabolic transformations and are present in many drugs such as tazobactam, cefatrizine, fluconazole, voriconazole, itraconazole and posaconazole.[7] New triazoles with improved pharmacological and pharmacokinetic profiles are emerging rapidly.[8]

Various glycosides can be found in natural resources, mainly in the form of glycoconjugates, such as glycopeptides, glycolipids, and nucleic acids, where the saccharide moiety plays important role for their biological activity.[9] Considering that sugar moieties with polyhydroxyl groups have been extensively employed in drug design with the view to improve water solubility and to increase the interaction between receptors and guests for molecular recognition,[10,11] various novel monosaccharide-derived 1,2,3-triazoles were synthesized and their inhibiting activities for glycosidases, such as α-glucosidase, isomaltase, amyloglucosidase and β-glucosidase,[12] sweet almond β-glucosidase and yeast α-glucosidase,[13] or a-glucosidase (*Saccharomyces cerevisiae*), β-glucosidase (almonds), α-galactosidase (green coffee beans), β-galactosidase (*Aspergillus oryzae*), α-mannosidase (*Canavalia ensiformis*), β-mannosidase (snail acetone powder), and β-N-acetylglucosaminidase,[14] were tested. Others were tested against fucosidases,[15] trans-sialidase,[16] glycogen phosphorylase,[17] etc. Members of the sugar-triazole conjugates family were investigated for other biological activities, such as receptor interactions,[18] antitubercular activity,[19] nucleoside mimetics,[20]

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http://dx.doi.org/10.1016/j.carres.2015.09.003
0008-6215/

and antiviral agents.[21] Many of them have shown strong antibacterial and antifungal activities, for example glycal-derived tetrahydrofuran 1,2,3-triazoles,[22] pyranoid derivatives comprising both triazole and conjugated carbonyl system,[23] D-glucose-derived benzyl and alkyl 1,2,3-triazoles,[24] 6-triazolyl 2,3,6-trideoxy sugars,[25] and triazoles with substituted triazole-piperidine side chains.[26]

Antitumor agents for chemotherapy also attract much attention, since cancer is responsible for many lethal outcomes worldwide.[27] Derivatives of 4β-(1,2,3-triazol-1-yl)podophyllotoxin have been obtained and their cytotoxicity toward human cancer cell lines HL-60, A-549, HeLa and HCT-8 were assessed, showing potent anticancer activity toward HL-60 and moderate cytotoxicities against the rest of the studied cell lines.[28]

Sucrose, being a biorenewable, biocompatible and biodegradable raw material with relatively low cost,[29] is a promising starting material for the synthesis of new compounds with biological activity.[30] Our research group has been focused on the applications of sucrose for the synthesis of new compounds with potential applications either industrial or in academia. In this sense, we have developed sucrose chemoselective derivatization methods,[31,32] the synthesis of sucrose-based biodegradable polymers[33–35] and nanoparticles.[36] To the best of our knowledge, the only other example in the literature of the synthesis of sucrose triazoles was reported by Jarosz et al. for the construction of sucrose macrocycles with complexation properties.[37,38]

Based on these literature data and the features described previously, we have created a small library of 1,2,3-triazoles of sucrose[39] to be screened for their biological activities.[40] Their antimicrobial and antifungal activities were tested and compared with the ones of some commercial antibiotics. Cytotoxicity against a number of human tumor cell lines and non-tumor liver cell primary culture was studied as well.

2. Results and discussion

2.1. Chemistry

The library of 1,2,3-triazole-sucrose derivatives is presented in Fig. 1 and have been synthesized as previously described.[39] Briefly, the series of 1-(1′,2,3,3′,4,4′,6-hepta-*O*-acetyl-6′-deoxy-sucros-6′-yl)-1,2,3-triazoles were obtained by microwave assisted copper catalyzed 1,3-dipolar cycloaddition of sucrose derived azides with terminal alkynes in excellent yields and in short reaction times. The compound 1′,2,3,3′,4,4′,6-hepta-*O*-acetyl-6′-azido-6′-deoxy-sucrose was regioselectively synthesized from sucrose by improved procedure and used for the cycloadditions.

The antimicrobial and cytotoxic activities of the synthesized library of compounds have been studied in their peracetylated form. There are indications in the literature that hydrophobic groups as acetyls increase the molecule's tendency to aggregate on the cell membrane and facilitate its permeability. On the other hand, the presence of the acetyl groups can influence the enzymatic activity, triggering higher or lower affinity of the compound toward various enzymes involved in the processes.[41]

2.2. Antibacterial activity

The results of the antibacterial activity, evaluated by the microdilution method, of the 1,2,3-triazole-sucrose derivatives and standard antibiotics are presented in Table 1. All derivatives showed antibacterial activity against all the tested bacteria with minimal inhibitory concentrations (MICs) ranging between 1.1 and 38 μM and bactericidal concentrations (MBCs) from 2.2 and 57.2 μM. The antibacterial activity could be presented as follows: **5** > **3** > **7** > **6** > **9** > **1** > **10** > **4** > **2** > **8**, but higher than the tested commercial drugs streptomycin and ampicillin. The most resistant bacteria to these compounds were *Listeria monocytogenes*, while the most susceptible bacteria were *Bacillus cereus* and *Staphylococcus aureus*. The obtained results are in agreement with Isloor et al.,[26] who have synthesized 1,2,4-triazole-3(4H)-thione derivatives and reported higher antibacterial activity for the compounds with *p*-substitutions.

2.3. Antifungal activity

All the triazole-sucrose derivatives showed antifungal activity (also evaluated by a microdilution method) with MICs from 0.6 to 26 μM and minimal fungicidal concentrations (MFCs) ranging between 2.2 and 39 μM (Table 2). The antifungal activity could be presented as follows: **3** > **1** > **5** > **7** > **9** > **4** > **2** > **6** > **8** > **10** and once more, higher than the tested standards, bifonazole and ketoconazole. The highest activity was verified for *Trichoderma viride*, while *Aspergillus fumigatus* was the most resistant fungi.

Fungi were in general more sensitive than bacterial species. The antifungal activity exhibited by many potent antifungal agents has

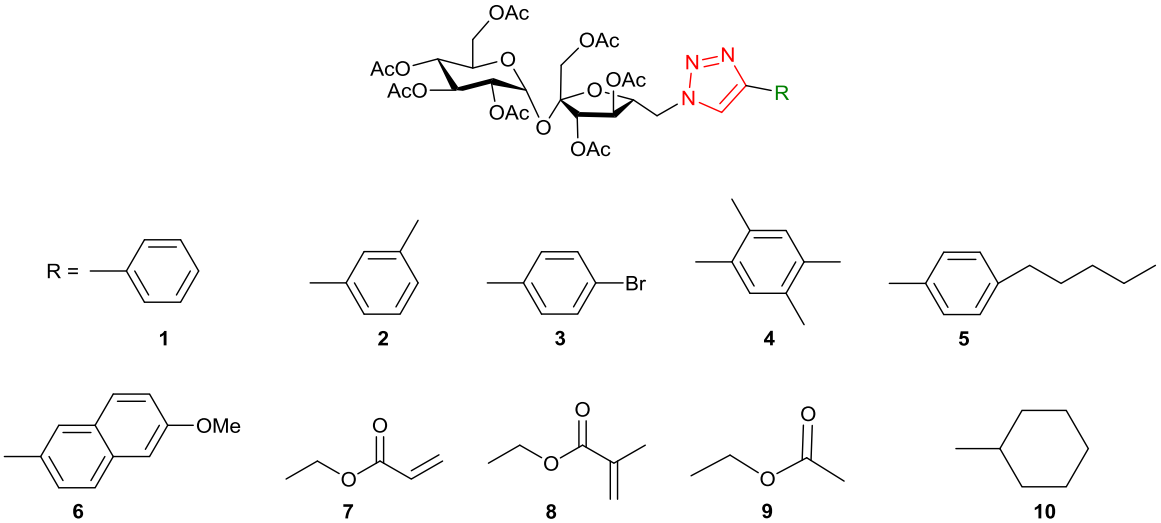

Fig. 1. General structure and library of the synthesized 1-(1′,2,3,3′,4,4′,6-hepta-*O*-acetyl-6′-deoxy-sucros-6′-yl)-1,2,3-triazoles.[39]