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Synthesis and antimicrobial screening some new glycosyl-3-*o*-tolyl carbamides

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ABSTRACT

In recent years area of sugar urea derivatives has established considerable attention because of the unique structural properties and activities that these compounds display. The urea-linkage at the anomeric center is a robust alternative to the naturally occurring O- and N-glycosidic linkages of oligosaccharides and glycoconjugates, and the natural products that have been identified to contain these structures show remarkable biological activity.With these approach a series of new glycosyl-3-o-tolyl carbamides were synthesized by the interaction of various glycosylamines with o-tolylisothiocyanate. The compounds obtained were identified and characterized by their physical, spectral and elemental analysis data. The synthesized compounds were screened for their in vitro antimicrobial activity against bacteria (S. aureus, E. coli, P. aeruginosa) and fungi (A. niger, T. viride). Some of these compounds exhibited moderate to good activity, whereas some were inactive.

Keywords: glycosylamines, *o*-tolylisocyanate,glycosyl-3-*o*-tolyl carbamides,antimicrobial activity.

INTRODUCTION

Carbamides and their derivatives are used as versatile reagent in organic synthesis [1]and also show effective antibacterial activity. A series of glucosylureas display strong inhibition action against α-glucosidase [2]in the field of carbohydrate chemistry. *N*-acyl-*N*'-β-D-glucopyranosylureas also used as anti-diabetic agents [3]and have been exposed to be strong glycogen phosphorylase inhibitors [4]. Urea acts as an important structural feature in many natural products, pharmaceutical and agricultural preparations [5-6].

Many compounds containing urea as a key moiety are of biological interest as antimycobacterial [7] and as HIV protease inhibitors [8]. *N*-nitrosourea has anti-tumoral activity [9]. These compounds are also used as plant growth regulators and agrochemicals [10]. The urea moiety is also useful in supramolecular chemistry [11] as it found in artificial receptors.

Glycosyl carbamides have countless pharmacological aspects [12]. Many of these derivatives have been found to own wide applications in industry as carbohydrate base detergent [13] and in medicine as anticancer [14] and antifungal agents [15-16]. Taking into account of these observations in the present work it is desired to explore the role of carbamides in comparison to other known substituted carbamidesby introducing glycosyl substitutions to observe the effect on antimicrobial activity and hence we designed and synthesized some newglycosyl-3-*o*-tolyl carbamides and were evaluated for their *in vitro* antimicrobial activity.

MATERIALS AND METHODS

All the solvents and chemicals used were of synthetic grade from SD fine chemicals Ltd., and E.Merck chemicals. Melting points of all synthesized compounds were determined using open capillary tube on Mac digital melting point apparatus and were uncorrected. IR spectra were recorded in solid phase KBr disks on SHIMADZU IR affinity-1 FTIR spectrometer and 1H NMR spectra in DMSO-d6 on AVANCE ll 400 NMR spectrometer 400 MHz.

The Mass spectra were recorded on WATERS, Q-TOF MICROMASS (LC-MS) instrument. Optical rotations were measured on Equip-Tronics EQ 801 Digital Polarimeter in DMSO. Purity of synthesized compounds has been checked by thin layer chromatography. It was performed on E.Merck pre-coated silica gel plates.

General procedure for glycosylamines (1a-d): A current of ammonia (generated by warming concentrated aqueous ammonia) was passed into a suspension of various sugars (0.01M) in cold anhydrous methanol (10 ml) until a clear solution was obtained. The reaction was carried out at 0-10°C in icecold condition. The reaction mixture was kept at room temperature to obtain a sticky mass which solidified into solid crystal in several days. It was recrystallized from methanol to furnish glycosylamines (1a-d) as white solid crystals.

General procedure for *o*-tolylisocyanate(2):The*o*-tolylisocyanateused was of commercial grades.

General procedure for 1-β-D-glucosyl-3-*o*-tolyl carbamides (3a-d): A pyridine solution of Glycosylamine (1a) (0.001M, 0.179g in 10 ml) was mixed with solution of *o*-tolylisocyanate (2) (0.001M, 0.119g in 10 ml) and mixture was kept at room temperature for 24 h. Afterwards, the pyridine was distilled off and resultant was triturated several times with petroleum ether 60-80°C) to afforded a white solid (3a). The product was crystallized from chloroform-petroleum ether, m.p. 175°C.

***In vitro* Antimicrobial activity:**
The antimicrobial activity of newly synthesized compounds were tested *invitro* against a selected gram positive, gram negative and fungi are presented in **Table.2** using cup plate agar diffusion method[17-19]by measuring the inhibition zone in mm. The compounds were screen for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* by using Muler Hinton agar medium and antifungal activity against *Aspergillusniger* and *Trichodermaviride*were determined by using Potato Dextrose Agar medium. The compounds were taken at a concentration of 1mg/mL using Dimethyl Sulphoxide (DMSO) as solvent. Amikacin (100µg/mL) was used as standard for antibacterial activity and Fluconazole (100µg/mL) as standard for antifungal activity. The results are presented in **Table 2.**

RESULTS AND DISCUSSION

The synthesis of title compounds was accomplished by reacting glycosylamines with *o*-tolylisocyanates in pyridine solvent for 24 h at room temperature. The progress of the reaction was monitored by TLC. The resulting title compounds **3a-d**were obtained in high yield. The chemical structures of the title compounds **3a-d** were deduced by IR, ^{1}H NMR, mass spectral analysis [20-21]& elemental analysis, the results of which are given below:

Spectral Characterization:
1-β-D-glucosyl-3- *o*-tolylcarbamide (3a):
IR: υ 3304 (O-H), 3176 (N-H), 3028 (Ar C-H), 2914 (Ali C-H), 1710 (C=O), 1309 (C-N), 1288 (C-O), 904 (characteristic of glucose). **^{1}H NMR**: δ 7.84-7.01 (4H, m, ArH), 8.25 and 6.11 (2H, s, NH), 5.10-4.03 (4H, m, hydroxyl proton), 3.72-3.13 (7H, m, glucosyl proton), 2.39 (3H, s, CH_3). **Mass (m/z)**: 312 (M^+), 298, 221, 206, 178. Found: C, 53.81; H, 6.40; N, 8.93calcd for $C_{14}H_{20}O_6N_2$; C, 53.84; H, 6.45; N, 8.97%.

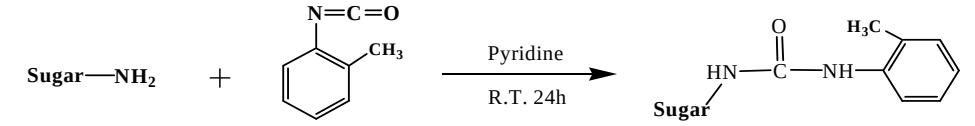
1-β-D-galactosyl-3- *o*-tolylcarbamide (3b):
IR (KBr cm^{-1}): υ 3396 (O-H), 3302 (N-H), 3028 (Ar C-H), 2937 (Ali C-H), 1710 (C=O), 1309 (C-N), 1238 (C-O), 896 (characteristic of galactose). **^{1}H NMR (DMSO-D_6, ppm)**: δ 7.26-7.20 (5H, m, ArH), 6.28 and 5.34 (2H, s, NH), 5.30-4.29(4H, m, hydroxyl proton), 4.25-3.98(7H, m, galactosyl proton), 2.35 (3H, s, CH_3). **Mass (m/z)**: 312 (M^+), 298, 294, 286, 221, 206, 178. Found: C, 53.83; H, 6.42; N, 8.91calcd for $C_{14}H_{20}O_6N_2$; C, 53.84; H, 6.45; N, 8.97%.

1-β-D-lactosyl-3- *o*-tolylcarbamide (3c):
IR (KBr cm^{-1}): υ 3482 (O-H), 3305 (N-H), 3032 (Ar C-H), 2879(Ali C-H), 1710 (C=O), 1290 (C-N), 1238 (C-O), 1076 and 893 cm^{-1} (characteristic of lactose). **^{1}H NMR (DMSO-D_6, ppm)**: δ 7.27-7.16 (5H, m, ArH), 6.68 and 5.59 (2H, s, NH), 5.84-3.67 (7H, m, hydroxyl proton), 3.65-3.48(14H, m, lactosyl proton), 2.36 (3H, s, CH_3). **Mass (m/z)**: 474 (M^+), 450, 415, 387, 373, 344, 329. Found: C, 40.60; H, 6.34; N, 5.87calcd for $C_{20}H_{30}O_{11}N_2$; C, 50.63; H, 6.37; N, 5.90%.

1-β-D-maltosyl-3- *o*-tolylcarbamide (3d):
IR (KBr cm^{-1}): υ 3537 (O-H), 3284 (N-H), 3035 (Ar C-H), 2897 (Ali C-H), 1712 (C=O), 1335 (C-N), 1290 (C-O), 1082 and 916 (characteristic of maltose). **^{1}H NMR (DMSO-D_6, ppm)**: δ 8.16-7.03 (4H, m, ArH), 8.44 and 6.66 (2H, s, NH), 4.46-4.34(4H, m, hydroxyl proton),3.72-3.03 (14H, m, maltosyl proton),2.39 (3H, s, CH_3). **Mass (m/z)**:

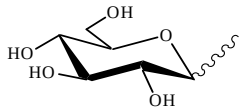
474 (M^+), 464, 450, 387, 373, 344, 329. Found: C, 50.62; H, 6.35; N, 5.85calcd for $C_{20}H_{30}O_{11}N_2$; C, 50.63; H, 6.37; N, 5.90%.

Scheme 1

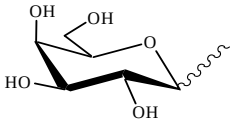


Glycosylamine **(1a-d)** *o*-tolyl isocyanate **(2)** 1-β-D-glycosyl-3-*o*-tolyl carbamides **(3a-d)**

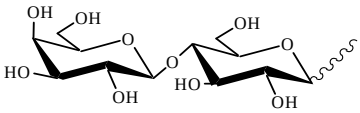
Where, Sugar =



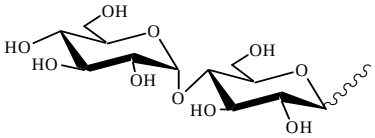
glucosyl (a)



galactosyl (b)



lactosyl (c)



maltosyl (d)

Table 1: Physical data characterization of compounds (3a-d)

Sr.no.	Compd.	Yield (%)	M. p. (°C)	Elemental analysis (%): Found (Req.) N	$[\alpha]^{32}_D$	R_f (7:3 EtOAc: pet. Ether)
1.	3a	78.2	175°C	8.93 (8.97)	- 119.10°	0.58
2.	3b	74.2	193°C	8.91 (8.97)	- 150.14°	0.73
3.	3c	80.95	151°C	5.87 (5.90)	- 108.18°	0.69
4.	3d	87.5	169°C	5.85 (5.90)	+ 98.75°	0.65

C and H are found to be satisfactory.

Antimicrobial Studies:

Antibacterial activity:

The compounds were screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*inmuller Hinton agar medium. Amikacin (100 µg/ml) was used as standard for antibacterial activity. The results are presented in **Table 2**.

Compounds **3c** and **3d** were found to be active against *Escherichia coli*, **3b**exhibited significant activity against *Staphylococcus aureus* and **3a** active towards *Pseudomonas aeruginosa*. All other compounds exhibited low to moderate activity.

Table 2: Antimicrobial activities of newly synthesized compounds (3a-d)

Compd.	Antimicrobial Activity**				
	Antibacterial Activity			Antifungal Activity	
	E.coli	*S. aureus*	*Ps. aeruginosa*	*A. niger*	*T. viride*
3a	8	8	16	10	15
3b	11	20	8	9	17
3c	20	16	7	20	17
3d	21	16	9	11	18
Amikacin	25	23	27	-	-
Fluconazole	-	-	-	24	25

***Zone of inhibition measured in mm, (15 or less) resistance, (16-20 mm) moderate and (more than 20 mm) sensitive.*
Escherichia coli (E. coli), Staphylococcus aureus(S. aureus), Psudomonasaeruginosa(Ps. Aeruginosa), Aspegillusniger (A.niger), Trichodermaviride (T. viride).

Antifungal activity:

The compounds were screened for antifungal activity against *Aspergillusniger* and *Trichodermaviride*in potato dextrose agar medium. Fluconazole (100 µg/ml) was used as standard for antifungal activity.

The results of antifungal activities are also tabulated in **Table 2**. Compound **3c** was most effective against *Aspergillusniger*. **3d** actively inhibited *Trichodermaviride*. The other compounds exhibited low to moderate activity.

CONCLUSION

The newly synthesized 1-β-D-glycosyl-3-aryl thiocarbamides exhibited comparable antibacterial and antifungal activities against the organisms tested. The method adopted in this investigation is simple, efficient and inexpensive and is useful in synthesizing pharmacologically important molecules.

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