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Synthesis and *in vitro* biological studies of *N*-glycosylated semicarbazides

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ABSTRACT

A series of new 1-Glycosyl-4-(2,4-dinitrophenyl) semicarbazides have been synthesized by the interaction of various Glycosyl isocyanates and 2,4-Dinitrophenyl hydrazine. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformations and IR, ^{1}H NMR and Mass spectral studies and these compounds were screened for their antibacterial activity against pathogens like E. coli, S. aureus, P. vulgaris, S. typhi, Ps. aeruginosa, K. pneumoniae and for antifungal activity against T. harzianum and Verticillium species to get potent bioactive molecule.

Keywords: Glycosyl isocyanates, 2,4-Dinitrophenyl hydrazine, 1-Glycosyl-4-(2,4-dinitrophenyl) semicarbazides, antimicrobial activity.

INTRODUCTION

The biological role of glycosyl derivatives have been intensively studied over a number of decades. Frequently, the syntheses of nitrogen heterocycles from saccharide derivatives have attracted great interest due to their important pharmaceutical applications, leading to the development and discovery of numerous therapeutic[1-6].

Similarly semicarbazides are an importantclass of molecules with a large spectrum of biological properties. These compounds have been studied as anticonvulsant[7], antitubercular[8] and antinociceptive[9] agents. Aryl semicarbazides are reported to display excellent anticonvulsant activity in mice and rats compared to that of phenytoin[10]. It is known that the biological activity of the molecules is related to theirstructure and physicochemical properties. These results promoted us to design new analogues with further modification of semicarbazide. In the present work, we report the synthesis and results of antimicrobial investigation of newly synthesized Glycosyl dinitrophenyl semicarbazides.

MATERIALS AND METHODS

General

The reagent grade chemicals were obtained from commercial sources and purified by either distillation or recrystallization before use. 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 ^{1}H NMR spectra in $CDCl_3$ on Bruker DRX-300 of NMR spectrometer 300 MHz. The Mass spectra were recorded on Waters UPLC-TQD Mass Spectrometer. Optical rotations were measured on Equip-Tronics EQ 800 Digital Polarimeter in $CHCl_3$. Purity of synthesized compounds has been checked by thin layer chromatography. It was performed on E. Merck precoated silica gel plates.

Starting material

Synthesis of Glycosyl isocyanate (1a-f)

Various glycosyl isocyanate were synthesized by the condensation of glycosyl bromide (5.0 mmol) and lead cyanate (5.0 mmol) in boiling sodium dried xylene (25 mL) for 3 h with frequent shaking. Solution then filtered and the filtrate was concentrated to get the syrupy mass. It was triturated with petroleum benzine (40-60 ^{o}C) and purified by dissolving it in minimum quantity of chloroform and reprecipitating with petroleum ether (1a-f).

Synthesis of 1-Tetra-*O*-acetyl-β-D-glucosyl-4-(2,4-dinitrophenyl) semicarbazides (3a-f)

A chloroform solution of glycosyl isocyanate (1a-f) (0.003 M, in 20 mL) was mixed with chloroform solution of 2,4-Dinitrophenyl hydrazine (2) (0.003 M, in 10 mL). The reaction mixture was shaken for some time and heated under reflux at 60°C for 9 h. The progress of reaction was monitored by TLC. Chloroform was distilled off to obtained sticky residue. This residue was triturated several times with petroleum ether (60-80°C) to afford a light coloured solid (3a-f). The crude product was crystallized from ethanol **(Scheme-I)**.

RESULTS AND DISCUSSION

All products were crystallized from ethanol before recording the physical data (Table-1). The purity of compounds was checked by TLC. The spectral analysis[11-13] IR, ^{1}H NMR and Mass spectra of the product were observed. Optical rotation of the product was also recorded**.** All the compounds have been screen for both antibacterial and antifungal activity using cup plate agar diffusion method[14-15] by measuring the inhibition zone in mm. Amikacin (100 µg/ml) was used as standard for antibacterial activity and Fluconazole (100 µg/ml) as standard for antifungal activity. Antibacterial studies of synthesized compounds indicated that compound 3b exhibited most significant activity against *E. coli*, 3c was found to be active against *S. aureus*, 3a and 3d active towards *P. vulgaris*, compound 3c effective towards *S. typhi*, 3f exhibited most significant activity against *P. aeruginosa* and compound 3b active towards *K. pneumoniae*. All the other compounds exhibited low to moderate activity. It was observed that most of the compounds were exhibited potent antifungal activity. The results of antifungal activities showed that compounds 3b, 3e and 3f are most effectively active against *T. harzianum* and compounds 3c and 3e actively inhibited *Verticillium species*. While other compounds inhibited moderate activity. (Table-2)

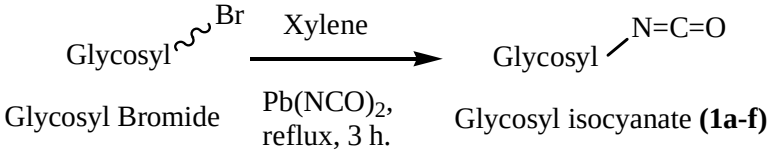
Spectral Data

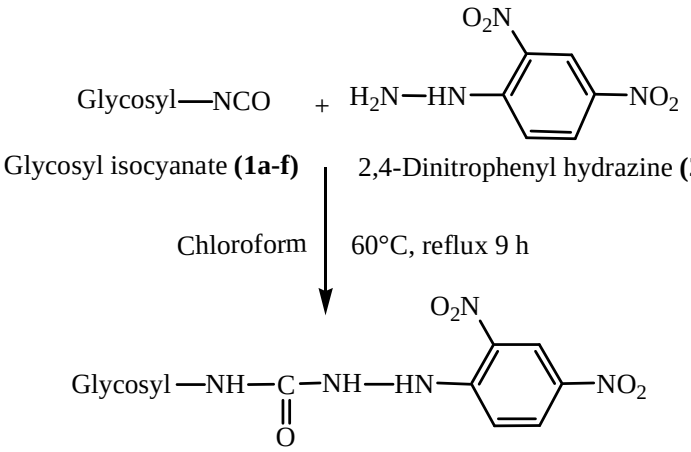
3a) IR (KBr, cm^{-1}): υ 3479 (N-H stretch), 3064 (Aromatic C-H stretch), 2968 (Aliphatic C-H stretch), 1730 (C=O), 1450 (-C-NO_2), 1271 (C-O), 1149 (C-N), 856 (characteristic of glucose); ^{1}H NMR ($CDCl_3$, ppm): δ 9.130 (1H, d, NH), 8.309-7.264 (3H, m, aromatic protons), 8.304 (1H, d, NH), 7.974 (1H, s, NH), 5.089-4.104 (7H, m, glucosyl ring protons), 2.182 (3H, s, $COCH_3$), 2.160 (3H, s, $COCH_3$), 2.128 (3H, s, $COCH_3$), 1.956(3H, s, $COCH_3$); Mass (m/z): 572 ($M^{\dagger}$+1), 540, 519, 449, 346 (100%), 286, 238, 208. Anal. Calcd. for $C_{21}H_{25}O_{14}N_5$: C, 44.13; H, 4.37; N, 12.26. Found: C, 44.09; H, 4.31; N, 12.22 %.

3d) IR (KBr, cm^{-1}): υ 3373 (N-H stretch), 3066 (Aromatic C-H stretch), 2958 (Aliphatic C-H stretch), 1732 (C=O), 1450 (-C-NO_2), 1273 (C-O), 1155 (C-N), 1024 & 937 (characteristic of lactose); ^{1}H NMR ($CDCl_3$, ppm): δ 9.134 (1H, d, NH), 8.088 (1H, d, NH), 8.072-7.181 (38H, m, Ar-H), 7.476 (1H, s, NH), 6.136-3.803 (14H, m, lactosyl ring protons); Mass (m/z): 1295 ($M^{\dagger}$+2), 813, 701, 659 (100%), 636, 559. Anal. Calcd. for $C_{68}H_{55}O_{22}N_5$: C, 63.11; H, 4.25; N, 5.41. Found : C, 62.92; H, 4.22; N, 5.39 %.

3e) IR (KBr, cm^{-1}): υ 3379 (N-H stretch), 3016 (Aromatic C-H stretch), 2962 (Aliphatic C-H stretch), 1759 (C=O), 1433 (-C-NO_2), 1257 (C-O), 1159 (C-N), 1060 & 901 (characteristic of maltose); ^{1}H NMR ($CDCl_3$, ppm): δ 9.134 (1H, d, NH), 8.313 (1H, d, NH), 8.307-7.977 (3H, m, Ar-H), 7.953 (1H, s, NH), 5.611-3.243 (14H, m, maltosyl ring protons), 2.182 (3H, s, $COCH_3$), 2.151 (3H, s, $COCH_3$), 2.103 (3H, s, $COCH_3$), 2.090 (3H, s, $COCH_3$), 2.064 (3H, s, $COCH_3$), 2.028 (3H, s, $COCH_3$), 2.005 (3H, s, $COCH_3$); Mass (m/z): 859 ($M^{\dagger}$), 669, 627, 465,407 (100%), 365, 296. Anal. Calcd. for $C_{33}H_{41}O_{22}N_5$: C, 46.10; H, 4.77; N, 8.15. Found : C, 46.05; H, 4.71; N, 8.04 %.

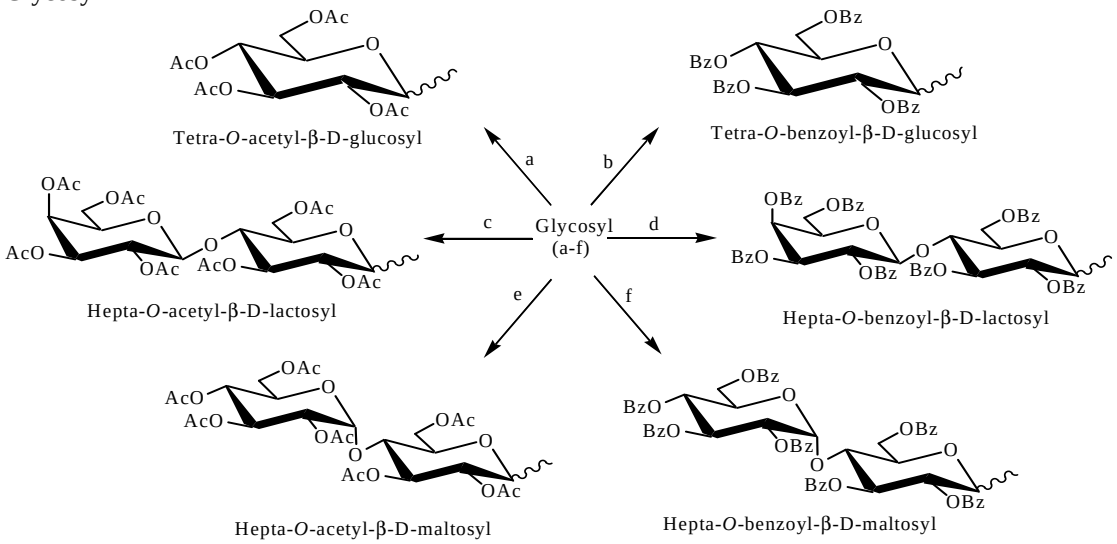
Scheme for synthesis shown as follows:





1-Glycosyl-4-(2,4-dinitrophenyl) semicarbazides **(3a-f)**

Where, Glycosyl =



Where, OAc = $OCOCH_3$ and OBz = $OCOC_6H_5$

Table 1: Physical characterisation of 1-Glycosyl-4-(2,4-dinitrophenyl) semicarbazides (3a-f)

Sr. No.	Compd.	Yield g (%)	m. p. (°C)	Elemental Analysis Found (Required) N	$[\alpha]_D^{32}$ (c, $CHCl_3$)	R_f Value
1.	3a	1.42 (83)	122-124	12.22 (12.26)	+34° (1.013)	0.78
2.	3b	1.35 (79)	131-132	8.50 (8.55)	+256° (1.013)	0.73
3.	3c	1.38 (80)	151-153	8.09 (8.15)	+29° (1.020)	0.69
4.	3d	1.57 (81)	138-141	5.39 (5.41)	+207° (1.015)	0.75
5.	3e	1.67 (78)	152-154	8.04 (8.15)	+306° (1.017)	0.72
6.	3f	1.84 (84)	147-149	5.36 (5.41)	+394° (1.013)	0.79

Table 2: Antimicrobial activities of 1-Glycosyl-4-(2,4-dinitrophenyl) semicarbazides (3a-f)

Compounds	Antibacterial**						Antifungal**	
	E. c.	*S. a.*	*P. v.*	*S. t.*	*Ps. a*	*K. p.*	*T. h.*	*V. sp.*
3a	18	14	21	16	19	12	17	19
3b	23	13	13	12	15	22	21	17
3c	19	22	10	21	17	13	18	23
3d	12	17	22	10	13	17	16	19
3e	13	19	12	18	23	15	24	22
3f	16	15	17	14	21	16	20	18
Amikacin	24	27	25	26	29	28	-	-
Fluconazole	-	-	-	-	-	-	28	29

***zone of inhibition in mm (15 or less) resistance, (16-20mm) moderate and (more than 20mm) sensitive. Escherichia coli (E. c.), Staphalococcus aureus (S. a.), Proteus vulgaris (P. v.), Salmonella typhi (S. t.), Psudomonas auriginosa (Ps. a.), Klebsiyella pneumonia (K. p.), Thrycoderma harzianum (T. h.) and Verticillium species (V. sp.).*

CONCLUSION

We have synthesized new Glycosyl semicarbazides (**3a-f**) and isolated in good yields. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformations and spectral studies. Most of the synthesized compounds showed promising antibacterial and antifungal activities against the highly pathogenic organisms.

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