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Synthesis and Evaluation of New N-GlucosylatedIsothiobiurets as Antimicrobial Agents

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ABSTRACT

Several 1-Tetra-*O*-acetyl-β-D-glucopyranosyl-5-aryl-isothiobiurets were synthesized by the interaction of tetra-*O*-acetyl-β-D-glucopyranosylthiocarbamides with various aryl isocyanatesand were evaluated for their antibacterial and antifungal activities. The identities of these new *N*-glucosides have been established on the basis of elemental analysis, IR, ^{1}HNMR, ^{13}CNMR and MS spectral studies.

Keywords: Glucopyranosylthiocarbamides, GlucosylIsothiobiurets, Synthesis, Antimicrobial Activity.

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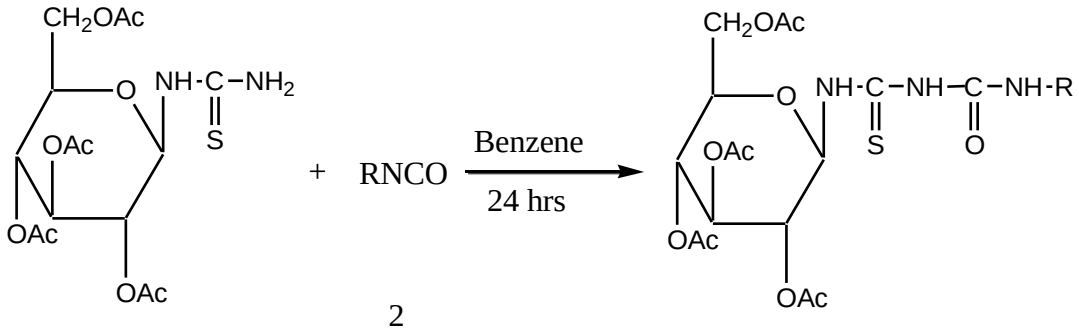
INTRODUCTION

Carbohydrate derivatives mostly having thiourea structure show broad spectrum biological & pharmaceutical activities. Numerous antiviral, antibacterial and antitumor agents have been prepared by reaction of glycosylisothiocyanates with biologically active amines. At the same time glycosylthiocarbamides are compounds of antiviral and antitumor interests, so they have become an important subject of research in the field of organic and pharmaceutical chemistry due to the successful treatment of many infectious diseases, in particular for the therapy of AIDS[1]. Isothiobiuret is important derivative of thiourea, which reportedly increases the biological activity of thiourea. Thiobiuret derivatives demonstrated growth regulating[2], analgesic[3], anticonvulsant and hypnotic activity[4,5]. In view of the advantage conferred by glycosylisothiobiurets it was interesting to carry out synthesis of various 1-tetra-*O*-acetyl-β-D-glucopyranosyl-5-aryl-isothiobiurets by interaction of 1-tetra-*O*-acetyl-β-D-glucopyranosylthiocarbamide with various aryl isocyanates.

MATERIALS AND METHODS:

Melting points of the synthesized compounds were recorded on electro thermal melting point apparatus are uncorrected. Specific rotations of the newly synthesized compounds were measured on Equip-Tronic digital polarimeter model no. EQ 800 at 30^0C in $CHCl_3$. IR spectra were recorded on a Shamazdu FTIR spectrometer. ^{1}HNMR were obtained on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as an internal reference. The MS spectra were recorded on a Jeol SX -102 FAB mass spectrometer and ^{13}CNMR were recorded in $CDCl_3$. Purity of the compounds was checked by thin layer chromatography using Merck silica gel coated aluminum plates and petroleum ether: ethyl acetate as eluent. The synthetic strategy involved the interaction of 1-Tetra-*O*-acetyl-β-D-glucopyranosyl-thiocarbamide with aryl isocyanates. The required 1-Tetra-*O*-acetyl-β-D-glucopyranosyl-thiocarbamidewas prepared by earlier known method[6-8] by interaction of Tetra-*O*-acetyl-β-D-glucopyranosylisothiocyante with ammonia in benzene medium. The various aryl isocyanates were purchased from Sigma-Aldrich.



1 2 3

Where, Ac - $COCH_3$

R = a) *o-Tolyl*, b) *m-Tolyl*, c) *p-Tolyl*, d) *m-Cl-Phenyl*, e) *p-Cl-Phenyl*, f*) o-Anisyl*, g*) m-Anisyl*, h*) p-Anisyl*, i) *1-Naphthyl*.

1-Tetra-*O* -acetyl- β -D -glucopyranosyl-5-aryl-isothiobiurets (3a-i)

1-Tetra-*O*-acetyl-β-D-glucopyranosyl-5-aryl-isothiobiurets **(3a-i)** were synthesized by mixing 1-tetra-O-acetyl-β-D-glucopyranosyl-thiocarbamide**(1)** (0.005M, 2.03gm) with aryl isocyanateS (0.005M) (**2a-i)** in dry benzene medium and stirring at room temperature for 24 hr while monitoring the reaction by TLC. Benzene was distilled off and the resultant syrupy mass was triturated several times with petroleum ether ($60\text{-}80^0$), to afford white granular solid **(3a-i) (Table-1)**. Crystallized from ethanol. The characterization of products **(3a-g)** was established by IR[9], ^{1}HNMR[10-14], ^{13}CNMR and MS[15]spectral studies.

Table 1-Synthesis of 1-Tetra-*O* -acetyl- β -D -glucopyranosyl-5-aryl-isothiobiurets (3a-i)

Sr. No.	Product (3a-i)	Reactants (2a-i)	Yield (%)	M.P. (^oC)	α_D^{32} (0.1, in $CHCl_3$)	Found (Required)		Rf(Pet.Ether: EtOAc)(1:1)
						N	S	
1	3a	-5-*o-tolyl*-	81	173	-101	7.42 (7.79)	5.95 (5.93)	0.67
2	3b	-5-*m-tolyl*-	84	150	-150	7.38 (7.79)	5.98 (5.93)	0.91
3	3c	-5-*p-toly*l-	78	220	+121	7.31 (7.79)	5.99 (5.93)	0.56
4	3d	-5- *m-Cl-phenyl*-	82	164	+215	7.23 (7.51)	5.84 (5.72)	0.93
5	3e	-5-*p-Cl-phenyl*-	76	184	-205	7.49 (7.51)	5.83 (5.72)	0.48
6	3f	-5-*o-anisyl*-	99	168	-204	7.33 (7.56)	5.84 (5.76)	0.86
7	3g	-5-*m-anisyl*-	88	172	-160	7.45 (7.56)	5.85 (5.76)	0.66
8	3h	-5-*p-anisyl*-	94	169	-138	7.30 (7.56)	5.79 (5.76)	0.89
9	3i	-5-*α-naphthyl*-	91	193	+226	7.22 (7.30)	5.98 (5.64)	0.84

Satisfactory C and H analysis were found in all cases.

ANTIMICROBIAL ACTIVITY:

Newly synthesized isothiobiurets were tested against following pathogenic microbes for their antibacterial and antifungal activities using cup plate agar diffusion method[16-18]. *Escherichia Coli*, *Staphalococcusaureus*, *Proteus vulgaris*, *Psudomonasaeruginosa*, *Bacillus cereus* in nutrient agar medium and for antifungal activity against *Candida albicancs*and *Aspergillusniger*in potato

dextrose agar medium. The compounds were taken at a concentration of 1mg/ml using dimethyl sulphoxide as solvent and in MIC also. Gentamycine (100µg/ml) was used as a standard for antibacterial and Nystatin (100µg/ml) as a standard for antifungal activity. Most of the synthesized compounds exhibited mild to moderate anti-microbial activity against the tested microorganisms. Compounds were found to possess significant antibacterial and antifungal activity when compared to standard drug (*Gentamycine and Nystatin* for antibacterial and antifungal respectively).The entire synthesized compounds exhibited mild to moderate activity are shown in **Table 2.**

Table 2- Antibacterial and Antifungal Activities of Compounds 3a – i

Inhibition zone diameter in mm*							
Compounds	**Bacteria**					**Fungi**	
	E. coli	***P. vulgaris***	***S. aureus***	***P.aeruginosa***	***B. cereus***	***A. niger***	**C. albicans**
3a	16	13	14	12	16	18	17
3b	17	12	12	16	18	20	19
3c	16	15	15	17	12	19	17
3d	19	14	16	14	19	18	20
3e	18	16	14	12	16	17	16
3f	14	12	13	13	13	20	18
3g	13	14	15	14	19	18	20
3h	12	13	16	17	19	19	17
3i	---	11	13	---	11	16	15
Gentamycine	19	19	19	19	19	---	---
Nystatin	---	---	---	---	---	20	20

** Values are the average of three readings / --- No activity was observed.*

RESULTS AND DISCUSSION:

Thus novel 1-tetra-*O*-acetyl-β-D-glucopyranosyl-5-aryl-isothiobiuretsexhibits comparable antibacterial and antifungal activities against the organism tested. The method adopted in the synthesis and investigation is simple, efficient and inexpensive in synthesizing pharmacologically important molecules.

SPECTRAL ANALYSIS:

3c 1-Tetra-*O* -acetyl- β -D -glucopyranosyl-5-*p*-tolyl-isothiobiurets

IR(KBr) 3304.14 (NH), 3022 (Ar-H), 1750.71 (C=O), 1373 (C-N), 929.16 (C=S), 931 (char. of D-glucose), 761.87 (para substituted). **1HNMR (CDCl3)**δ 7.268-7.025 (t, 3H, Ar-H), δ 5.446-3.740 (.m, 7H, glucose unit), δ 2.190-2.027 (m, 13H –OAc), δ 1.692-1.253 (t, 3H, NH).**MS** 541 [M+2], 413, 327, 503, 387, 263, 279. **^{13}CNMR** (CDCl3, 90 MHz) δ 20.86 (4× CH3-CO), δ 61.72-77.65 (C of glucose ring), δ 130.17-122.34 (Ph-C).Anal.Calcd. For $C_{23}H_{29}O_{10}N_3S$: C 51.20, H 5.38, O 29.68, N 7.79, S 5.93, Found C 51.17, H 5.34, O 29.66, N 7.31, S 5.95%.

3d 1-Tetra-*O* -acetyl- β -D -glucopyranosyl-5-*m*-chloro-isothiobiurets

IR (KBr) 3450.7 (NH), 3024.27 (Ar-H), 1752.8 (C=O), 1532.85 (C=N), 1374.19 (C-N) 669 (C=S), 1041(char. of D-glucose), 758 (meta substituted). **1HNMR (CDCl3)**δ 7.271-7.225 (s, 1H, Ar-H)), δ 2.190-2.026 (m, 17H –OAc), δ 6.342-6.330 (s, 1H, NH), δ 1.661 (s, NH).**MS** 559 M+, 573, 429, 327, 803, 413, 414.^{13}**CNMR** (CDCl3, 90 MHz) ppm δ 21.05-20.62 (CH3CO), δ 77.65-61.70 (Carbons of glucosyl ring), δ 89.30 (C=S), δ 169.85-168.94 (-C=O, 1C), δ 170.83-170.41 (-CH3C0)Anal. Calcd. For $C_{22}H_{26}O_{10}N_3SCl$: C, 47.22, H 4.65, O 28.62, N 7.51, S 5.72, Found C 47.19, H 4.58, O 28.59, N 7.23, S 5.84%.

3i1-Tetra-*O*-acetyl- β -D-glucopyranosyl-5-*1*-naphthyl-isothiobiurets

IR (KBr) 3473.32 (NH), 3023.66 (Ar-H), 1752.8 (C=O), 1523 (C=N), 1373.19 (C-N) 758.78 (para substituted), 1041.43 (char. of D-glucose). **1HNMR (CDCl3)** δ 7.2 (s, 1H, Ar-H)), δ 2.240 - 2.036 (m, 20H –OAc), δ 6.3 (s, 1H, NH), δ 1.671 (s, 1H, NH), δ 5.362-5.93 (m, 6H, glucose unit). **MS** 575 M+, 573, 803, 429,351, 413, 429, 415, 430. ^{13}**CNMR(CDCl3, 90 MHz**) δ 170.82-170.40 (-COCH3), δ 168.54 - 168.94 (-C=O), δ 89.29 (-C=S), δ 77.66-61.70 (carbons of glucosyl ring), δ 21.05-20.62 (-COCH3).Anal.Calcd. For $C_{26}H_{29}O_{10}N_3S$: C, 54.26, H 5.04, O 27.82, N 7.30, S 5.64, Found C 54.21, H 4.98, O 27.8, N 7.22, S 5.98%

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