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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDY OF SOME BENZOYLATED GLUCOPYRANOSYL DISUBSTITUTED THIOCARBAMIDES

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ABSTRACT

A series of akyl/aryl/akyl-aryl thiocarbamides have been synthesized by the interaction of 1-tetra-*O*-benzoyl-β-D-glucopyranosyl isothiocyanate with sec. amines. The identities of these newly synthesized compounds have been established on the basis of chemical transformations, IR, ^{1}H NMR and Mass spectral studies. The antimicrobial study of these *N-glucosides* have been evaluated by using *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Candida albicance* and *Aspergillus niger*. The study reveals that most of the compounds shows satisfactory antimicrobial activities.

Key words: Glucopyranosyl isothiocyanate, Sec. amines, Thiocarbamides, Antimicrobial study.

INTRODUCTION

Thiourea and its derivatives represent well known important group of organic compounds due to the diverse applications in fields such as medicine, agriculture, coordination, and analytical chemistry[1].

N,N-Dialkyl-N-aroyl thioureas are efficient ligands for the separation of platinum group metals[2]. 1,3-Dialkyl or diaryl thioureas exhibit significant antifungal activity against the plant pathogens *Pyricularia oryzae* and *Drechslera oryzae*[3] N-Aryl N-phenylthioureas have been developed as anion binding sites in a hydrogen bonding receptor[4].

Some thioureas have been recently described as effective antitumor and nonnucleoside inhibitors of HIV reverse transcriptase[5]. Some dithiourea derivatives exhibited cytotoxicity against various cancer cells, and one of these indicated best inhibition activities against KB and CNE2 with IC_{50} values of 10.72 and 9.91 micrometer,

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respectively[6]. Thiourea moiety was described for dual inhibition of both cyclooxygenase isoforms 1 and 2 with a 4-fold selectivity towards COX-2 active site[7], pointing its anti-inflammatory properties. On the basis of knowledge gained on the work done on *N*-glucopyranosylated compouds, it was interesting to synthesize some new *N*-glucopyranosylated thioamides.

EXPERIMENTAL

General method

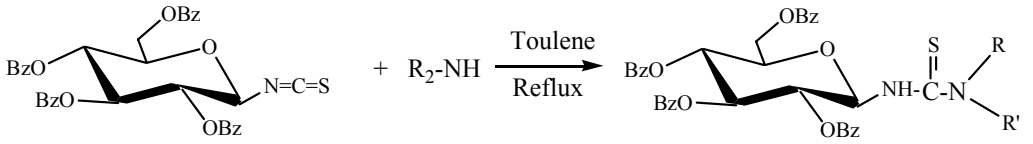
Melting points of all synthesized compounds were determined using open capillary tube on Mac digital melting point apparatus and were uncorrected. The IR spectrum was recorded in KBr Disks on Shimadzu IR affinity-1-FTIR spectrometer. The NMR spectrum was recorded in Brucker DRX-300 instruments operating at 300 MHz using $CDCl_3$ solution with TMS as internal standard. The mass spectrum was recorded on a THERMO Finnigan LCO Advantage max ion trop mass spectrometer. Specific rotations were measured on Equip-Tronics EQ-801 Digital Polarimeter. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) solvent system is ethyl acetate and pet. ether (7:3) and spot were visualized by iodine vapours.

Tetra-*O*-benzoyl–β-D-glucopyranosyl isothiocyanate (2)

Tetra-*O*-benzoyl-β-D-glucopyranosyl isothiocyanate (**2**) was prepared by interaction of tetra-*O*-benzoyl-α-D-glucopyranosyl bromide with lead thiocyanate in anhydrous xylene medium[8].

1-Tetra-*O*-benzoyl-β-D-glucopyranosyl-3,3-dimethyl thiocarbamides

Several 1-tetra-*O*-benzoyl-β-D-glucopyranosyl-3,3-disubstituted thiocarbamides **(3)** (**Scheme 1**) were prepared by the condensation of dialkyl amines **(1)** and tetra-*O*-benzoyl-β-D-glucopyranosyl isothiocyanate (**2**) in benzene for 4 hrs. The reaction was monitored by TLC. After complete reaction, the solvent was distilled off and the resultant sticky residue was triturated with petroleum ether (60-80^{o}C) to afford the products **(3)**.



1-Tetra-*O*-benzoyl-β-D-glucopyranosyl isothiocyanate **(1)**

Sec. amines **(2)**

1-Tetra–*O*–benzoyl–β–D-glucopyranosyl-3,3-disubstituted thiocarbamides **(3)**

Where, Bz = COC_6H_5

R = (a) Diethyl , (b) Dimethyl, (c) Diphenyl, (d) *N*-Methyl aniline, (e) Dibutyl (f) *N*-Ethyl aniline and (g) *N*-Benzyl anilne.

RESULTS AND DISCUSSION

Condensation of dimethyl amines (0.005 M, 0.95 mL) and tetra-*O*-benzoyl-β-D-glucopyranosyl isothiocyanate (0.005 M), in benzene (20 mL) was carried out on boiling water bath for 4 hr. The reaction was monitored by TLC. After completion of the reaction, the solvent was distilled off and the resultant sticky residue was triturated with petroleum ether (60-80^{o}C) to afford the solid with m.p. (100-101^{o}C). It was crystallized from water-alcohol. All the products were crystallized from ethanol-water. Similarly, when the condensation of tetra-*O*-benzoyl-β-D-glucopyranosyl isothiocyanate **(2)** was extended with other dialkyl amines **(1b-g)**, the corresponding 1-tetra-*O*-benzoyl-β-D-glucopyranosyl-3,3-disubstituted thiocarbamides (**3b-g**) were obtained.

Structures of all synthesized products were established on the basis of usual chemical transformations and IR, ^{1}H NMR and Mass spectral studies[9-13].

Spectral analysis

1- Tetra-*O*-benzoyl-β–D-glucopyranosyl-3, 3-diethyl thiocarbamide (3a)

IR (KBr): υ 3350 (N-H)str.; 3062 (Ar-H); 2958 (C-H ali-H); 1730 (C = O) str.; 1539, 1492, 1454 (C=C) str.; 1315 (C-N) str.; 1257 (C-O) str.; 852 (Char. D-Glucose); 1157 (C=S) str.; 767-705 (mono sub Ar-H Bending) ^{1}H NMR ($CDCl_3$) : δ 8.08-7.26 (m, 20H Ar-H); 6.8-5.8 (m, 7H, glucopyranosyl ring); δ 1.56-1.48 (t,3H, CH_3); δ 3.1-3.04 (q, 2H, CH_2); δ 3.46 (S, hump 1H, NH).

ESI Mass (M/z): 711 (M^+ pronated), 579, 351, 322, 245, 153, 105. Anal. Calcd. for:- $C_{39}H_{38}O_9N_2S$: C, 62.13; H, 5.62; N, 6.21; S, 4.73, found, C, 56.70; H, 5.40; N, 6.75; S, 5.25%.

1-Tetra-*O*-benzoyl-β–D-glucopyranosyl-3,3-diphenyl thiocarbamide (3c)

IR (KBr): υ 3394 (N-H); 3062 (Ar-H); 2958 (C-H ali); 1741 (C = O); 1492, 1452 (C=C); 1300 (C-N); 1282 (C-O); 852 (Char. D-Glucose); 1178 (C=S); 717, 748 (Mono sub Ar-H Bending). ^{1}H NMR ($CDCl_3$): δ 8.15-7.20 (m, 30 H Ar-H); δ 4.48 (s, 1H); 6.32-4.43 (m, 7 H, glucopyranosyl ring).

ESI Mass (M/z): 807 (M^+ Protonated), 579, 351, 322, 245, 153 Anal. Calcd. for:- $C_{47}H_{38}O_9N_2S$: C, 62.03; H, 5.50; N, 6.35; S, 4.70, found, C, 59.50; H, 5.23; N, 6.75; S, 5.65%.

1- Tetra-*O*-benzoyl-β–D-glucopyranosyl-3,3-methyl phenyl thiocarbamide (3d)

IR (KBr): υ 3373 (N-H)str; 3062 (Ar-H) str.; 2970 (C-H ali); 1728 (C = O); 1523, 1492, 1452 (C=C); 1313 (C-N); 1269 (C-O) str; 852 (Char. D-Glucose); 1176 (C=S) str.; 715 (Mono sub Ar-H Bending) ^{1}H NMR ($CDCl_3$): δ 8.10-7.20 (m, 25H, Ar-H); δ 4.2 (S, 1H, NH); 6.4-5.22 (m, 7H, glucopyranosyl ring); δ 3.58 (s, 3H, CH_3).

ESI Mass (M/z): 745 (M^+ Protonated), 579, 351, 322, 245, 153, 105. Anal. Calcd. for:- $C_{42}H_{36}O_9N_2S$: C, 62.13; H, 5.62; N, 6.21; S,4.73, found, C, 56.70; H, 5.40; N, 6.75; S,5.25%.

Table 1: Characterization of 1-tetra–*O*–benzoyl–β–D-glucopyranosyl-3,3-disubstituted thiocarbamides

Product	Yield (%)	R_f Value EtOAc : Pet. ether (7:3)	m. p. (^oC)	$[\alpha]_D^{39}$ (c in $CHCl_3$)	Analysis (%): Found (Required)	
					N	S
2a	76	0.95	127	+122..44^o (c,0.06)	3.02 (3.94)	4.32 (4.50)
2b	78.92	0.82	168	-97.82^o (c, 0.06)	4.10 (4.18)	3.55 (4.69)
2c	82.21	0.80	135	-212.12^o (c, 0.07)	2.98 (3.47)	3.79 (3.97)
2d	80.51	0.79	198	+210.52^o (c, 0.07)	3.02 (3.76)	4.01 (4.30)
2e	75.96	0.90	132	-195.87^o (c, 0.085)	3.23 (3.89)	4.19 (4.45)
2f	72.52	0.78	155	-173.46^o (c, 0.085)`	3.19 (3.69)	3.84 (4.22)
2g	79.89	0.69	182	+155.24^o (c, 0.065)	3.11 (3.41)	3.42 (3.90)

C and H analysis were found satisfactory in all cases.

Antimicrobial study

All the compounds have been screened for both antibacterial and antifungal activity using cup plate agar diffusion method[14,15] by measuring the inhibition zone in mm. The compounds were taken at a concentration of 1 mg/mL using dimethyl sulphoxide (DMSO) as solvent. The compounds were screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris* and *Pseudomonas aeruginosa* in nutrient agar medium. Amikacin (100 µg/mL) was used as standard for antibacterial activity. The compounds were screened for antifungal activity against *Aspergillus niger* and *Candida albicance* in potato dextrose agar medium. Fluconazole (100 µg/mL) as standard for antifungal activity. The results are presented in Table 2.

Table 2: Antimicrobial activities of 1-tetra–*O*–benzoyl–β–D-glucopyranosyl-3,3-disubstituted thiocarbamides

Compds.	Antibacterial**				Antifungal**	
	E. coli	***S. aureus***	***P. vulgaris***	***Ps. aeruginosa***	***C. albicance***	***A. niger***
2a	16	13	14	16	14	16
2b	17	18	16	16	14	16
2c	18	17	18	15	16	15
2d	20	16	15	15	15	17
2e	16	16	22	14	15	16
2f	16	13	16	15	16	17
Amikacin	19	23	22	24	-	-
Fluconazole	-	-	-	-	25	26

**Zone of inhibition in mm (15 or less) resistance, (16-20 mm) moderate and (more than 20 mm) sensitive. *Escherichia coli* (*E*. coli), *Staphalococcus aureus* (*S*. aureus), *Proteus vulgaris* (*P*. vulgaris), *Psudomonas auriginosa* (*Ps. auriginosa*), *Candida albicancs* (*C. albicancs*) and *Aspergillus niger* (*A*. *niger*)

It has been observed that some of these compounds exhibited interesting microbial activities. **(3c)** and **(3d)** exhibited most significant activity against *E. coli*, **(3b)** and **(3c)** exhibited most significant activity against *S. aureus*, **(3c)** and **(3e)** exhibited most significant activity against *P. vulgaris,* **(3a)** and **(3b)** exhibited most significant activity against *P. aeruginosa*, respectively. All the other compounds exhibited low to moderate activity.

The results of antifungal activities are also tabulated in Table 2. **(3c)** and **(3f)** are effective towards *C. albicance,* **(3d)** and **(3f)** inhibited *A. niger*. While other compounds inhibited moderate to low activity.

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