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SYNTHESIS AND *IN VITRO* BIOLOGICAL EVALUATION OF 1-HEPTA-*O*-BENZOYL-β-D-MALTOSYL-4-BENZOTHIAZOLYL SEMICARBAZIDES

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ABSTRACT
The present work aims to synthesize and screen the antifungal and antibacterial activities of a series of new 1-hepta-*O*-benzoyl-β-D-maltosyl-4-benzothiazolyl semicarbazides by the interaction of hepta-*O*-benzoyl-β-D-maltosyl isocyanate and substituted 2-hydrazino benzothiazoles in acetone medium. The identities of these newly synthesised 1-hepta-*O*-benzoyl-β-D-maltosyl-4-benzothiazolyl semicarbazides have been established on the basis of usual chemical transformations and IR, H^1 NMR and Mass spectral studies. These synthesized products were evaluated for their antimicrobial activity against some selected organisms. Some of the products displayed promising activity.
Keywords: Maltosyl isocyanate, hydrazino benzothiazoles, maltosyl benzothiazolyl semicarbazides, antimicrobial activity.

INTRODUCTION

Isocyanates of sugars are one of the versatile reagents in the field of synthetic carbohydrate chemistry. Many of these derivatives have been found to possess wide applications in industry as carbohydrate base detergent and in medicine as anticancer and antifungal agents. The maltosylated derivatives show great potential in biological process and in medicinal chemistry. They act as bacteriostatic agent[1], antifungal agent[2] and antitumour agent[3]. Heterocycles bearing thiazole, sulphur and nitrogen moieties constitute the core structure of a number of pharmacologically and biologically active interesting compounds. A benzothiazole ring residues are reported to show antitumour[4], anti-inflammatory[5], analgesic[6], antidiabetic[7] and anticonvulsant[8] activities. These findings encouraged us to explore the synthesis and to examine antibacterial and antifungal properties of new synthesized semicarbazides.

EXPERIMENTAL

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.

General Procedures

Synthesis of hepta-*O*-benzoyl-β-D-maltosyl isocyanate (1)

To the suspension of hepta-*O*-benzoyl-α-D-maltosyl bromide (0.039 M, 15 g) in sodium dried xylene (60 ml) was added lead cyanate (0.039 M, 4.5 g). The mixture was refluxed gently for 3 h. The xylene filtrate was then treated with petroleum ether (60-80^{o}C) to afford a solid. It was purified by dissolving it in minimum quantity of chloroform and reprecipitating with petroleum ether (Scheme-1).

Synthesis of 2-hydrazino benzothiazoles (2a-g)

Concentrated HCl (1 ml) was added drop wise to hydrazine hydrate (0.2 M, 1 ml 80%) at 5-10°C followed by ethyleneglycol (20 ml). To the above solution 2-amino benzothiazole (0.01 M, 1.85g) was added in portions. It was then refluxed for 3 h, cooled and poured onto crushed ice. The separated solid was filtered, dried and recrystalized from ethanol(Scheme-2).

Synthesis of 1-hepta-*O*-benzoyl-β-D-maltosyl-4-benzothiazolyl semicarbazides

A acetone solution of hepta-*O*-benzoyl-β-D-maltosyl isocyanate (0.025M, 2.5g in 20 ml) was mixed with acetone solution of 2-hydrazino benzothiazole (0.025M, 0.37g in 10 ml) and mixture after shaking for sometime was refluxed on water bath for 3.30 h. Acetone was distilled off to obtained sticky residue. This residue was triturated several times with petroleum ether to afford a light coloured solid (Scheme-3).

Table-1: Physial characterisation of 1-hepta-*O*-benzoyl-β-D-maltosyl-4-benzothiazolyl semicarbazides (3a-g)

S. No.	Compd.	Yield g (%)	m. p. (°C)	Elemental Analysis Found (Required)		$[\alpha]_D^{28}$ (c, $CHCl_3$)	R_f Value
				N	S		
1.	3a	2.7 (84.63)	119-121	4.35 (4.44)	2.56 (2.53)	+70° (0.50)	0.66
2.	3b	2.6 (87.24)	124-126	4.19 (4.32)	2.69 (2.47)	+95° (0.53)	0.60
3.	3c	2.8 (77.56)	131-133	4.15 (4.32)	2.77 (2.47)	-108° (0.51)	0.59
4.	3d	2.5 (85.47)	126-128	4.17 (4.32)	2.58 (2.47)	+122° (0.51)	0.62
5.	3e	2.4 (72.39)	135-137	4.25 (4.39)	2.08 (2.51)	-89° (0.52)	0.54
6.	3f	2.7 (75.13)	129-130	4.30 (4.39)	2.91 (2.51)	+104° (0.50)	0.51
7.	3g	2.1 (89.22)	139-140	4.29 (4.39)	2.86 (2.51)	+97° (0.51)	0.63

Table-2: Antimicrobial activities of newly synthesized 1-hepta-*O*-benzoyl-β-D-maltosyl-4-benzothiazolyl semicarbazides (3a-g).

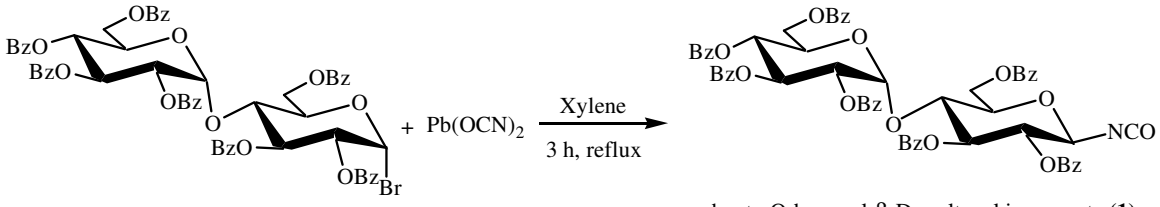
Compounds	Antibacterial**					Antifungal**	
	E. coli	*S. Aureus*	*P. vulgaris*	*Ps. aeruginosa*	*Klebsiyella species*	*T. harzianum*	*Verticillium species*
3a	21	24	17	24	19	21	22
3b	19	20	19	23	18	23	24
3c	17	18	-	12	13	19	23
3d	20	17	21	20	21	21	21
3e	15	-	13	-	12	25	25
3f	18	19	17	16	16	26	24
3g	19	21	22	19	19	24	23
Tetracycline	30	29	27	30	28	-	-
Fluconazole	-	-	-	-	-	31	30

**Including the well diameter of 6 mm. Zone of inhibition in mm (15 or less) resistant, (16-20 mm) moderate and (more than 20 mm) sensitive.

RESULTS AND DISCUSSION

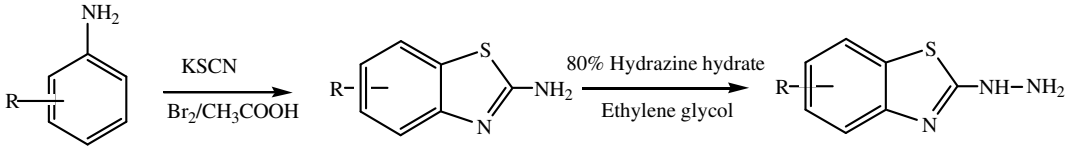
All products were crystallized from ethanol before recording the physical data (Table-1). The purity of compounds was checked by TLC. The spectral analysis[9-11] IR, ^{1}H NMR and Mass spectra of the product were observed. Optical rotation of the product was also recorded**.** All the compounds have been screen for both antimicrobial and antifungal activity using cup plate agar diffusion method[12-13] 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 these compounds indicated that compounds 3a and 3d were found to be active against *E.coli* and rest of were found to be

moderately active. Compound 3a, 3b and 3g exhibited most significant activity against *S.aureus* and compound 3a, 3b and 3d towards *Pseudomonas.* All the other compounds exhibited low to moderate activity. (Table-2). The results of antifungal activities are also tabulated in Table-2. Almost all compounds are most effectively active against *Thrichoderma harzianum* and actively inhibited *Verticillium species*. (Table-2).



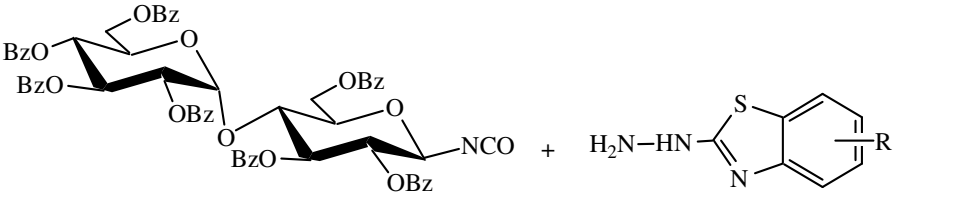
hepta-O-benzoyl-α-D-maltosyl bromide — hepta-O-benzoyl-β-D-maltosyl isocyanate **(1)**

Scheme-I

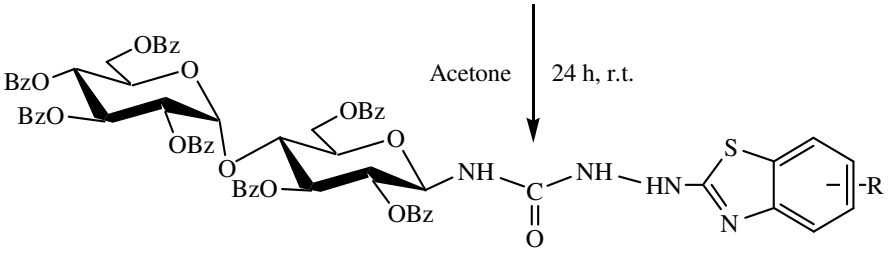


Substituted aromatic amines — 2-amino benzothiazoles — 2-hydrazino benzothiazoles **2(a-g)**

Scheme-II



hepta-O-benzoyl-β-D-maltosyl isocyanate **(1)** — 2-hydrazino benzothiazoles **2(a-g)**



1-hepta-O-benzoyl-β-D-maltosyl-4-benzothiazolyl semicarbazides **3(a-g)**

Scheme-III

Where, Bz = COC_6H_5, R = a) Hydrogen, b) 4-Chloro, c) 5-Chloro, d) 6-Chloro, e) 4-methyl, f) 5-methyl, g) 6-methyl.

Spectral Data

(3a) IR (KBr, cm^{-1}) : υ 3491 (N-H stretch), 3063 (Ar-H stretch), 1730 (C=O), 1643 (C=N), 1514 (N-H bend), 1452 (Ar C=C), 1315 (C-N), 1271 (C-O), 1095-937 (characteristic of maltose), 709 (C-S); ^{1}H NMR ($CDCl_3$, ppm): δ 8.123-7.262 (39H, m, Ar-H), 6.248-4.108 (14H, m, maltosyl protons), 5.897-5.673 (3H, m, NH); Mass (m/z): 1213, 1112, 1110, 1109 (100%), 1019, 1005, 943, 915. (Found : C, 65.52; H, 4.38; N, 4.35; S, 2.56%; Calcd. for $C_{69}H_{56}O_{18}N_4S$: C, 65.71; H, 4.44; N, 4.44; S, 2.53 %).

(3d) IR (KBr, cm^{-1}) : υ 3449 (N-H stretch), 3063 (Ar-H stretch), 1730 (C=O), 1601 (C=N), 1584 (N-H bend), 1451 (Ar C=C), 1315 (C-N), 1269 (C-O), 1095-937 (characteristic of maltose), 708 (C-S), 687 (C-

Cl); ^{1}H NMR ($CDCl_3$, ppm): δ 8.121-7.370 (38H, m, Ar-H), 6.945-4.228 (14H, m, maltosyl protons), 5.960-5.657 (3H, m, NH); Mass (m/z): 1213, 1110, 1109 (100%), 1019, 1005, 943, 915, 579. (Found : C, 63.09; H, 4.21; N, 4.17; S, 2.58%; Calcd. for $C_{69}H_{55}O_{18}N_4SCl$: C, 63.98; H, 4.25, N, 4.32; S, 2.47 %).
(3e) IR (KBr, cm^{-1}) : υ 3460 (N-H stretch), 3063 (Ar-H stretch), 1730 (C=O), 1601 (C=N), 1584 (N-H bend), 1450 (Ar C=C), 1315 (C-N), 1269 (C-O), 1093-937 (characteristic of maltose), 709 (C-S); ^{1}H NMR ($CDCl_3$, ppm): δ 8.124-7.217 (38H, m, Ar-H), 6.213-4.156 (14H, m, maltosyl protons), 5.895-5.672 (3H, m, NH), 1.601 (3H, s, CH_3 protons); Mass (m/z): 1112, 1110, 1109 (100%), 1019, 1005, 943, 915, 881. (Found : C, 64.83; H, 4.39; N, 4.25; S, 2.08 % Calcd. for $C_{70}H_{58}O_{18}N_4S$: C, 65.93; H, 4.55; N, 4.39; S, 2.51%).

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