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Der Pharmacia Lettre, 2014, 6 (3):286-289
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ISSN 0975-5071
USA CODEN: DPLEB4

Synthesis and microbial assay of maltosyl tetrazino benzothiazoles

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ABSTRACT

A new series of 3-oxo-4- hepta-O-benzoyl-β-D-maltosyl-(1,2,4,5)-tetrazino-(2,1b)-benzothiazoles by the oxidative cyclisation of 1-hepta-O-benzoyl-β-D-maltosyl-4-benzothiazolyl semicarbazides. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformations and IR, ^{1}H NMR, ^{13}C 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, K. pneumoniae, Ps. aeruginosa and for antifungal activity against T. harzianum and Verticillium species to get potent bioactive molecule.

Keywords: *Maltosyl benzothiazololyl semicarbazides, maltosyl tetrazino benzothiazoles, oxidative cyclisation, antimicrobial activity.*

INTRODUCTION

In recent years, we have witnessed significant improvements in the field of synthetic carbohydrate chemistry[1]. It seems, reasonable to support that an exhaustive investigation of *N*-maltosides and related compounds might result in the discovery of wide range of biological activity[2]. 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[3], antifungal agent[4] and antitumour agent[5]. Heterocycles bearing thiazole, sulphur and nitrogen moieties constitute the core structure of a number of pharmacologically and biologically active interesting compounds. Semicarbazides are valuable building blocks for the synthesis of heterocycles. Biologically active semicarbazide derivatives use as antibacterial[6], antifungal[7], anticonvulsant[8], antimicrobial[9] and antitumor agents[1]0. Tetrazines also possess a wide range of antiviral and antitumor properties and have been widely used as pesticides and herbicides[11].

These findings encouraged us to explore the synthesis and to examine antibacterial and antifungal properties of new synthesized maltosyl tetrazino benzothiazoles in a trial to obtain new derivatives with higher activity than that of the parent compounds.

MATERIALS AND METHODS

Genaral

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 1-hepta-*O*-benzoyl-β-D-maltosyl-4-benzothiazolyl semicarbazides[12] (1a-g)

A acetone solution of hepta-*O*-benzoyl-β-D-maltosyl isocyanate (0.0025M, 2.73g in 20 ml) was mixed with acetone solution of 2-hydrazino benzothiazole (0.0025M, 0.41g 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.

General Procedure for Synthesis of 3-oxo-4-hepta-*O*-benzoyl-β-D-maltosyl-(1,2,4,5)-tetrazino(2,1b)-benzothiazole (3a-g)

Slurry of 1-hepta-*O*-benzoyl-β-D-maltosyl-4-benzothiazolyl semicarbazide (**1a**) (2.52g, 0.002 M in 2 mL) was prepared in chloroform. To this, chloroformic bromine (2.0 mL, 20%) solution was added with constant stirring for 1 h. The reaction mixture was kept at room temperature for 24 h. The separated solid was crystallized from ethanol. It was acidic to litmus and on determination of equivalent weight, found to be dihydrobromide **(2a)**. It on basification with dilute ammonium hydroxide solution afforded a free base **(3a)**. It was recrystallized from aqueous 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[13-15] IR, ^{1}H NMR, ^{13}C 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[16-17] by measuring the inhibition zone in mm. Tetracycline (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. The results of antifungal activities are also tabulated in Table2. Almost all compounds are most effectively active against *Thrichoderma harzianum* and actively inhibited *Verticillium species*. (Table-2).

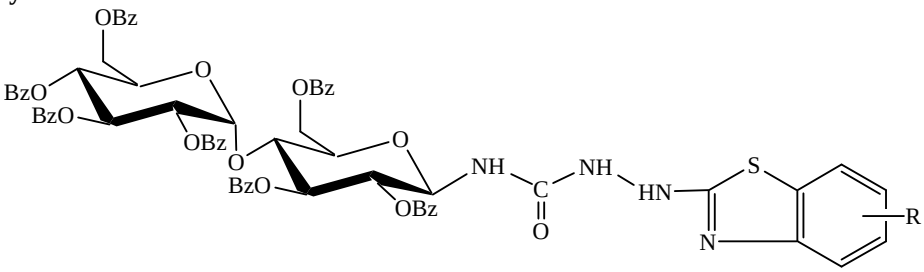
Spectral Data

3a) IR (KBr, cm^{-1}) : υ 3064 (Ar-H stretch), 2958 (Aliphatic C-H stretch), 1730 (C=O), 1598 (C=N), 1450 (C-N), 1174 (C-O), 1097 & 937 (characteristic of maltose unit), 711 (C-S); ^{1}H NMR ($CDCl_3$, ppm): δ 8.113-7.260 (39H, m, Ar-H), 6.276-3.959 (14H, m, maltosyl ring protons), 5.540 (s, 1H, NH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 165.86 (C=O), 133.37-128.36 (7COC_6H_5), 128.29-119.35 (6 Ar-C benzothiazole), 96.97 (C=N), 78.15-62.85 (maltosyl ring-C); Mass (m/z): M^+-1258, 1053, 579, 353, 151 (100%); Anal. Calcd. for $C_{69}H_{54}O_{18}N_4S$: C, 65.81; H, 4.29; N, 4.45; S, 2.54. Found : C, 65.78; H, 4.26; N, 4.41; S, 2.52%.

3b) IR (KBr, cm^{-1}) : υ 3064 (Ar-H stretch), 2956 (Aliphatic C-H stretch), 1732 (C=O), 1598 (C=N), 1448 (C-N), 1174 (C-O), 1099 & 937 (characteristic of maltose unit), 711 (C-S), 686 (C-Cl); ^{1}H NMR ($CDCl_3$, ppm): δ 8.033-7.188 (38H, m, Ar-H), 6.181-3.841 (14H, m, maltosyl ring protons), 5.530 (s, 1H, NH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 165.87 (C=O), 133.38-129.87 (7COC_6H_5), 129.69-120.76 (6 Ar-C benzothiazole), 96.98 (C=N), 78.16-62.86 (maltosyl ring-C); Mass (m/z): M^+-1292, 1054, 1011 (100%), 579, 243; Anal. Calcd. for $C_{69}H_{53}O_{18}N_4SCl$: C, 64.06; H, 4.10; N, 4.33; S, 2.47. Found : C, 64.01; H, 4.04; N, 4.26; S, 2.41%.

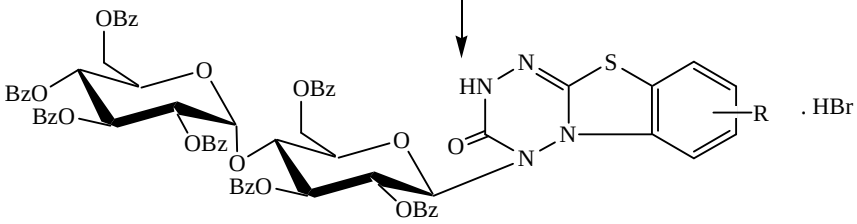
3e) IR (KBr, cm^{-1}) : IR (KBr, cm^{-1}) : υ 3064 (Ar-H stretch), 2956 (Aliphatic C-H stretch), 1730 (C=O), 1598 (C=N), 1450 (C-N), 1174 (C-O), 1097 & 937 (characteristic of maltose unit), 711 (C-S); ^{1}H NMR ($CDCl_3$, ppm): δ 8.110-7.199 (38H, m, Ar-H), 6.274-3.958 (14H, m, maltosyl ring protons), 5.541 (s, 1H, NH), 1.256 (s, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ 165.88 (C=O), 133.37-129.69 (7COC_6H_5), 128.57-128.30 (6 Ar-C benzothiazole), 90.07 (C=N), 78.23-62.85 (maltosyl ring-C), 23.11 (CH_3); Mass (m/z): M^+-1272, 1053, 1011 (100%), 579, 206; Anal. Calcd. for $C_{70}H_{56}O_{18}N_4S$: C, 66.03; H, 4.40; N, 4.40; S, 2.51. Found : C, 65.98; H, 4.35; N, 4.38; S, 2.49%.

Scheme for synthesis shown as follows:



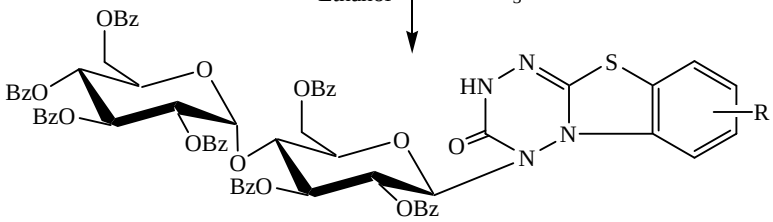
1-hepta-O-benzoyl-β-D-maltosyl-4-benzothiazolyl semicarbazides **1(a-g)**

[O] Br_2 in Chloroform



3-Oxo-4-hepta-*O*-benzoyl-β-D-maltosyl-(1,2,4,5)-tetrazino-(2,1b)-benzothiazole hydrobromides **2(a-g)**

Ethanol Dil. NH_3



3-Oxo-4-hepta-*O*-benzoyl-β-D-maltosyl-(1,2,4,5)-tetrazino-(2,1b)-benzothiazoles **3(a-g)**

Scheme-I

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.

Table: 1 Physial characterisation of 3-oxo-4-hepta-*O*-benzoyl-β-D-maltosyl-(1,2,4,5)-tetrazino(2,1b)-benzothiazoles (3a-g)

Sr. No.	Compd.	Yield g (%)	m. p. (°C)	Elemental Analysis Found (Required)		$[\alpha]_D^{28}$ (c, $CHCl_3$)	R_f Value
				N	S		
1.	3a	2.03 (81)	134-136	4.41 (4.45)	2.52 (2.54)	+90° (0.50)	0.45
2.	3b	2.01 (78)	141-142	4.28 (4.33)	2.43 (2.47)	+102° (0.53)	0.30
3.	3c	1.93 (75)	138-139	4.30 (4.33)	2.45 (2.47)	-89° (0.51)	0.27
4.	3d	2.06 (80)	133-135	4.26 (4.33)	2.41 (2.47)	+130° (0.51)	0.51
5.	3e	1.96 (77)	145-146	4.38 (4.40)	2.49 (2.51)	-98° (0.52)	0.40
6.	3f	1.85 (73)	148-149	4.34 (4.40)	2.47 (2.51)	+127° (0.50)	0.38
7.	3g	2.18 (86)	143-144	4.37 (4.40)	2.44 (2.51)	+119° (0.51)	0.34

Table : 2 Antimicrobial activities of newly synthesized 3-oxo-4-hepta-*O*-benzoyl-β-D-maltosyl-(1,2,4,5)-tetrazino(2,1b)-benzothiazoles (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.*

Acknowledgements
One of the authors (R.B.G.) is grateful to U. G. C., New Delhi, for Rajiv Gandhi National Fellowship. Authors are also grateful to SAIF, CDRI, Lucknow for providing the spectral data and to Dr. S. G. Bhadange, Principal, Shri Shivaji College, Akola for providing necessary facilities.

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