Int. J. Chem. Sci.: 7(3), 2009, 2158-2164

SYNTHESIS AND *IN VITRO* ANTIMICROBIAL ACTIVITY OF 3-HEPTA-*O*-BENZOYL-β-D-MALTOSYLIMINO-4-ARYL-5-PHENYLIMINO-1, 2, 4-DITHIAZOLIDINES (HYDROCHLORIDE)

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ABSTRACT

A series of 3-hepta-*O*-benzoyl-β-D-maltosylimino-4-aryl-5-phenylimino-1, 2, 4-dithiazolidines (hydrochloride) have been synthesized by the interaction of various 1-hepta-*O*-benzoyl-β-D-maltosyl-3-aryl thiocarbamides with *N*-phenyl-*S*-chloroisothiocarbamoyl chloride. All the compounds investigated for their antimicrobial activities against *Proteus vulgaries, Escherichia coli, Salmonella typhimurium, Staphylococcus aureus, Pseudomonas aeruginosar, Riazoctomia and Aspergilus niger.* The newly synthesized compounds have been characterized by analytical and IR, ^{1}H NMR and Mass spectral studies. The purity of these was confirmed by TLC.

Key words: Maltosyl thiocarbamides, *N*-Phenyl-*S*-Chloroisothiocarbamoyl Chloride, 1, 2, 4-Dithiazolidines (Hydrochloride), Antimicrobial activity.

INTRODUCTION

Nitrogen containing heterocycles with sulphur atom are an important class of existing drugs. Azoles, triazoles, 4-thiazolidinones, substituted thiazoles, thiadiazoles and dithiazolidines have been known to possess wide spectrum of activities like antiviral[1], anti-HIV[2], anti-inflammatory[3] and antimicrobial[4,5], selective PDE7 inhibitors[6] in the field of pharmaceutical industry. Similarly, many studies have been reported on the synthesis of 1, 2, 4-dithiazolidines attached to different carbohydrate templates[7-9]. In continuation of our work on biologically active 1, 2, 4-dithiazolidines and search for more potent derivatives. We report herein the first time synthesis of 3-hepta-*O*-benzoyl-β-D-maltosylimino-4-aryl-5-phenylimino-1, 2, 4-dithiazolidines (hydrochloride) **Scheme 1 (3a-g).** These were synthesized by the reaction of 1-hepta-*O*-benzoyl-β-D-maltosyl-3-aryl thiocarbamides with

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N-phenyl-*S*-chloroisothiocarbamoyl chloride was prepared by extension of earlier method[10,11]. The required 1-hepta-*O*-benzoyl-β-D-maltosyl-3-arylthiocarbamides[12,13] were obtained by known method by the interaction of 1-hepta-*O*-benzoyl-β-D-maltosyl isothiocyanate[14-18] with various aryl amines. This maltosyl isothiocyanate remain very important starting material for the construction of heterocycles and also potent irreversible inhibitors of glucose transport in human erythrocytes[19].

EXPERIMENTAL

General procedure

Melting points were determined and are uncorrected. IR spectra were recorded in Nujol, KBr on a FT- IR Perkin- Elmer RXI (4000-450 cm^{-1}) spectrophotometer. ^1H NMR measurements were performed on a Bruker DRX- 300 (300 MHz FT NMR) NMR Spectrometer in $CDCl_3$ solution with TMS as internal reference. The mass spectra FAB were recorded on a JEOL SX-102 Mass spectrometer. Optical rotation $[\alpha]_D^{31}$ measured on a Equip- Tronics Digital Polarimeter EQ-800 at 31°C in $CHCl_3$. Thin layer chromatography (TLC) was performed on Silica gel G for TLC (Merck) and spots were visualized by iodine vapour.

3-Hepta-O-benzoyl-β-D-maltosylimino-4-aryl-5-phenylimino-1, 2, 4-dithiazolidines (hydrochloride) (3a-g)

A mixture of 1-hepta-*O*-benzoyl-β-D-maltosyl-3-phenyl thiocarbamides **(1a)** with *N*-phenyl-*S*-chloroisothiocarbamoyl chloride **(2)** (3.09 g, 0.0025 mmol in 15 mL $CHCl_3$) in chloroform (0.515 g, 0.0025 mmol in 5 mL $CHCl_3$) was gently refluxed for 6h. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was brought to room temperature and the solvent was removed under reduced pressure to obtain sticky residue. This residue was triturated with petroleum ether (60-80°C) to afford a granular pale yellow solid **(3a)** (2.8 g, 79.77 %). The crude product was purified by chloroform-ether and recrystallized by ethanol-water, m. p. 130-132°C. **(Scheme 1).** The physical characterization results are summarized in Table 1 **(3a-g)**. Compounds **(3b-g)** were also prepared by similar method.

3a. Yield 2.8 g, (79.77 %); m. p. 130-132°C; $[\alpha]_D^{31}$ +40° (c, 1.00 in $CHCl_3$); R_f 0.71; (1 : 1, Petroleum ether : EtOAc); IR (KBr) : ν 3065.9 (Ar-H), 2959.4 (ali. C-H), 1728.9 (C=O), 1536.5 (C=N), 1378.4 (C-N), 1269.9 (C-O), 1096.7, 1068.6, 1027 and 936.6 (characteristic of maltose), 756.1 (C-S) cm^{-1}; ^1H NMR (δ in ppm, $CDCl_3$) : δ 8.09-6.52 (45H, m, $7COC_6H_5$, $2C_6H_5$), 6.27-4.02 (14H, m, maltose ring protons); FABMS (m/z)

: 1410(M^+), 1337, 1202, 1188, 1053 (HBM^+), 976, 948, 932, 918, 827, 579 (TBG^+), 474, 353, 232, 135, 105 , 77.Anal. Calcd. for $C_{75}H_{59}O_{17}N_3S_2$, 2HCl Requires : C, 63.82; H, 4.18; N, 2.97; S, 4.53; Found : C, 64.22; H, 4.35; N, 2.91; S, 4.71 %.

3b : Yield 3.11 g, (89.11 %); m. p. 135-139°C; $[\alpha]_D^{31}$ +90° (c, 1.00 in $CHCl_3$); R_f 0.75; (1 : 1, Petroleum ether : EtOAc); IR (KBr) : ν 3067.1 (Ar-H), 2959.6 (ali. C-H), 1729.4 (C=O), 1530.2 (C=N), 1378 (C-N), 1270.4 (C-O), 1100.4, 1028.6 and 936.6 (characteristic of maltose), 757.2(C-S) cm^{-1}; ^1H NMR (δ in ppm, $CDCl_3$) : δ 7.67-6.66 (44H, m, $7COC_6H_5$, C_6H_5, C_6H_4), 6.24-4.52 (14H, m, maltose ring protons); FABMS (m/z) : 1444 (M^+), 1371, 1250, 1173, 1038, 1053 (HBM^+), 976, 948, 932, 918, 827, 579 (TBG^+), 474, 353, 232, 135, 105, 77; Anal. Calcd. for $C_{75}H_{58}O_{17}N_3S_2Cl$, 2HCl. Requires : C, 62.32; H, 4.01; N, 2.90; S, 4.43; Found : C, 63.09; H, 4.20; N, 2.89; S, 4.59 %.

3c : Yield 2.96 g, (84.81 %); m. p. 139-142 °C; $[\alpha]_D^{31}$ -130° (c, 1.00 in $CHCl_3$); R_f 0.62; (1 : 1, Petroleum ether : EtOAc); ^1H NMR (δ in ppm, $CDCl_3$) : δ 8.11-6.66 (44H, m, $7COC_6H_5$, C_6H_5, C_6H_4), 6.19-4.45 (14H, m, maltose ring protons); Anal. Calcd. for $C_{75}H_{58}O_{17}N_3S_2Cl$, 2HCl. Requires : C, 62.32; H, 4.01; N, 2.90; S, 4.43; Found : C, 63.41; H, 4.14; N, 2.84; S, 4.51 %.

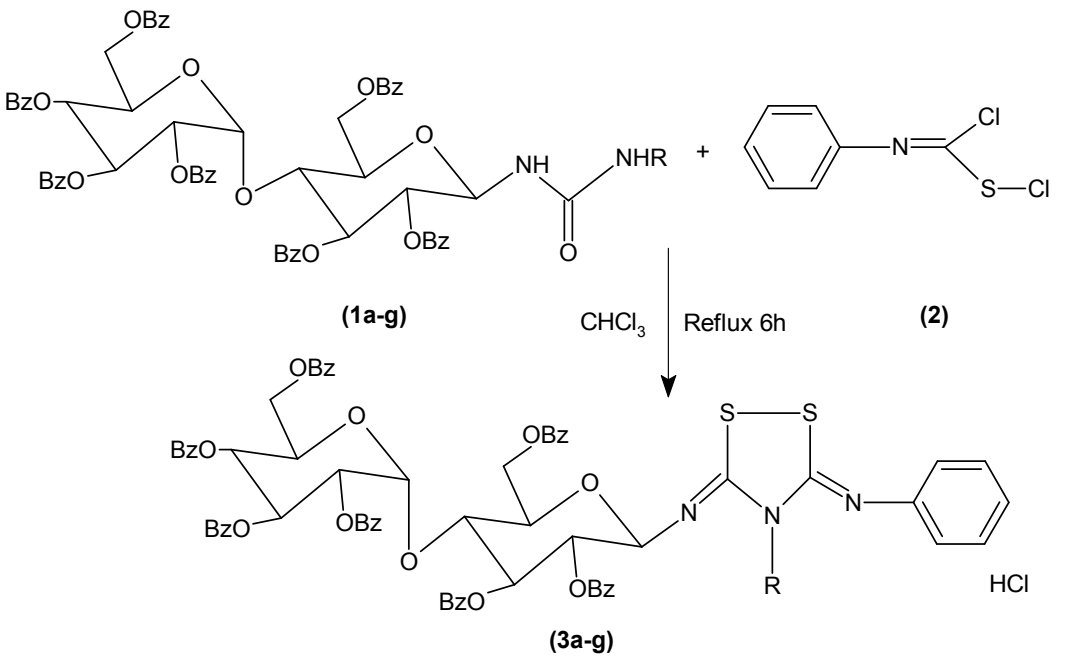
3d : Yield 3 g, (85.95 %); m. p. 130(d) °C; $[\alpha]_D^{31}$ +60° (c, 1.04 in $CHCl_3$); R_f 0.54; ^1H NMR (δ in ppm, $CDCl_3$) : δ 8.11-6.66 (44H, m, $7COC_6H_5$, C_6H_5, C_6H_4), 6.20-4.29 (14H, m, maltose ring protons); (1 : 1, Petroleum ether : EtOAc); Anal. Calcd. for $C_{75}H_{58}O_{17}N_3S_2$, 2HCl Requires : C, 62.32; H, 4.01; N, 2.90; S, 4.43; Found : C, 63.78; H, 4.03; N, 2.86; S, 4.58 %.

3e : Yield 3.27 g, (93.42 %); m. p. 125-130°C; $[\alpha]_D^{31}$ +50° (c, 1.00 in $CHCl_3$); R_f 0.66; (6 : 4, Petroleum ether : EtOAc); ^1H NMR (δ in ppm, $CDCl_3$) : δ 8.11-6.66 (44H, m, $7COC_6H_5$, C_6H_5, C_6H_4), 6.16-4.29 (14H, m, maltose ring protons), 2.36 (3H, s, Ar-CH_3); Anal. Calcd. for $C_{76}H_{61}O_{17}N_3S_2Cl$, 2HCl. Requires : C, 64.04; H, 4.28; N, 2.94; S, 4.49; Found : C, 64.12; H, 4.18; N, 2.90; S, 4.69 %.

3f : Yield 3.19 g, (91.14 %); m. p. 137-140°C; $[\alpha]_D^{31}$ -40° (c, 1.00 in $CHCl_3$); R_f 0.80; (6 : 4, Petroleum ether : EtOAc); ^1H NMR (δ in ppm, $CDCl_3$) : δ 8.11-7.07 (44H, m, $7COC_6H_5$, C_6H_5, C_6H_4), 6.20-3.91 (14H, m, maltose ring protons) 2.44 (3H, s, Ar-CH_3); Anal. Calcd. for $C_{76}H_{61}O_{17}N_3S_2$, 2HCl. Requires : C, 64.04; H, 4.28; N, 2.94; S, 4.49; Found : C, 64.08; H, 4.13; N, 2.92; S, 4.61%.

3g : Yield 2.89 g, (82.57 %); m. p. 141(d) °C; $[\alpha]_D^{31}$ +100° (c, 1.00 in $CHCl_3$); R_f 0.59; (6 : 4, Petroleum ether : EtOAc); IR (KBr) : ν3065.8 (Ar-H), 2958.5 (ali. C-H), 1728.5 (C=O), 1529.8 (C=N), . 1377.2 (C-N), 1270.2 (C-O), 755.2 (C=S), 1096.8, 1068.4, 1026.6 and 936.2 (characteristic of maltose), 757.6 (C-S) cm^{-1}; ^1H NMR (δ in ppm, $CDCl_3$) : δ 8.11-6.66 (44H, m, $7COC_6H_5$, C_6H_5, , C_6H_4), 6.16-4.29 (14H, m, maltose ring protons,), 2.36 (3H, s, Ar-CH_3); FABMS(m/z) : 1424 (M^+), 1351, 1216, 1169, 1048, 1053 (HBM^+), 976, 948, 932, 918, 827, 579 (TBG^+), 474, 353, 232, 135, 105, 77.Anal. Calcd. for $C_{76}H_{61}O_{17}N_3S_2$, 2HCl. Requires : C, 64.04; H, 4.28; N, 2.94; S, 4.49; Found : C, 65.64; H, 4.76; N, 2.93; S, 4.64 %.

HBM^+ = Hepta-O–benzoyl–β-D-maltosyl, TBG^+ = Tetra-O-benzoyl-β-glucosyl



Where, Bz = COC_6H_5;
R = (a) Phenyl; (b) o-Cl-phenyl; (c) m-Cl-phenyl; (d) p-Cl-phenyl; (e) o- Tolyl; (f) m-Tolyl; (g) p-Tolyl.

Scheme 1

RESULTS AND DISCUSSION

3-Hepta-*O*-benzoyl-β-D-maltosylimino-4-aryl-5-phenylimino-1,2,4-dithiazolidines

(hydrochloride) **(3a-g)** were prepared by the reaction of 1-hepta-*O*-benzoyl-β-D-maltosyl-3-aryl thiocarbamides **(1a-g)** with *N*-phenyl-*S*-chloroisothiocarbamoyl chloride **(2)** in $CHCl_3$. After condensation, the solvent was distilled off to obtain a sticky residue. This residue was triturated with petroleum ether (60-80°C) to afford a pale yellow solid **(3a-g).** The product was found non-desulphurizable, when boiled with alkaline lead acetate solution. The specific rotation was measured in chloroform. The reaction can be easily monitored by TLC and the R_f values were also recorded.

In spectral analysis[20-22], IR spectrum of product shows absorption bands due to N-H, Ar-H, Ali. C-H, C=O, C=N, C-N, C-O, C-S and glycosidic C-O-C (symmetrical and asymmetrical)[23] str. at 1100.4, 1068.6, 1028.6 and 1271 cm^{-1} and the ^1H NMR spectrum distinctly displayed signals at 6.27-3.91[24,25] due to carbohydrate portion. The coupling constant of the anomeric protons ranged between 9-10 Hz, which indicated the β-configuration of glycosidic bond[26,27]. The Mass spectrum of product was also observed.

Antimicrobial activity

Antimicrobial activities of compounds were tested by using cup plate[28] method at 100 μg mL^{-1} concentration in DMSO as solvent. The zone of inhibition was measured in mm. Tested micro-organism strains were *Proteus vulgaries, Escherichia coli, Salmonella typhimurium, Staphylococcus aureus, Pseudomonas aeruginosa, Riazoctomia and Aspergilus niger*. The observed data on the antimicrobial activity of the compounds and control drugs (100) μg mL^{-1} are given in the Table 1.

Table 1: Antimicrobial activity of 3-hepta-O-benzoyl-β-D-maltosylimino-4-aryl-5-phenylimino-1, 2, 4-dithiazolidines (hydrochloride) (4a-g)

Comp.	*P. vulgaries*	*S. typhim-urium*	*P. aerug-inosa*	*E. coli*	*S. aureus*	*A. niger*	*Riazoct-omia*
3a	13	12	-	11	11	21	11
3b	10	13	-	12	13	20	12
3c	12	14	-	12	13	21	12
3d	18	13	-	12	12	21	14
3e	12	19	-	-	12	18	12

Cont…

Comp.	*P. vulgaries*	*S. typhim-urium*	*P. aerug-inosa*	*E. coli*	*S. aureus*	*A. niger*	*Riazoct-omia*
3f	15	18	-	-	16	17	11
3g	20	19	-	15	15	17	13
Amikacin	24	21	-	19	18	24	19
Griseofulvin	-	-	-	-	-	21	23
DMSO	-		-	-	-	-	-

Concentration required for tested compounds **(3a-g)** and control drugs (Amikacin and Griseofulvin) is 100 μg mL^{-1}. Zone of inhibition in mm

ACKNOWLEDGEMENT

The authors thank Sophisticated Analytical Instrumentation Facility (SAIF), a division of Central Drug Research Institute (CDRI), Lucknow for recording the spectra and the Principal, Dr. S. G. Bhadange for providing necessary facilities.

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Accepted : 21.05.2009