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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF 1-ARYL-5-(1-NAPHTHYL)-2-*S*-HEPTA-*O*-BENZOYL-MALTOSYL ISOTHIOBIURETS

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ABSTRACT

A Series of *S*-maltosyl arylthioureas were condensed with naphthyl isocyanate to yield respective isothiobiuret derivatives. The newly synthesized compounds were characterized by ^{1}H-NMR, IR and Mass spectral studies. These compounds were also screened for their anti-microbial activities by comparing with the standard.

Keywords: *S*-Maltosyl arylthiourea, Isocyanates, Isothiobiuret, Antimicrobial activity.

INTRODUCTION

Thioureas are a group of compounds possessing a wide spectrum of biological activities, such as antimicrobial[1-3], antifungal[4], anticonvulsant[5], herbicidal[6,7], anticancer[8], as non nucleoside inhibitors of HIV-1 reverse transcriptase[9-11]. As a selective inhibitor of reverse mode of Na^+/Ca^{2+} exchange in cell expressing NCX1[12]. As influenza virus neuraminidase inhibitors[13]. Thompson et.al.[14] synthesized *N*-substituted isoquinolinl-*N*'-substituted phenyl thioureas, found useful for the treatment and / or propylaxis of anxiety, mania, depression, panic disorders, migraine and defects associated with AIDS

Whereas isocyanates are known as highly reactive species widely used in synthesis of ployurathens. The isocyanate group reacts with the hydroxyl group to form a urethane linkage, and with amine to form urea.

Thiobiuret is important derivative of thiourea, which reportedly increases the biological activity of thiourea. Thiobiuret derivatives demonstrated growth regulating[15], analgesic[16], anticonvulsant and hypnotic activity[17,18].

In quest for biologically more potent compounds we envisioned to synthesize series of isothiobiuret compounds by reacting *S*-maltosyl arylthiourea with naphthyl isocyanate and studied their antibacterial activity.

EXPERIMENTAL

Melting points were recorded on electro thermal melting point apparatus are uncorrected. Specific rotations 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}H NMR were obtained on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as an internal reference. The mass spectra were recorded on a Jeol SX -102 FAB mass spectrometer. Purity of the compounds was checked by thin layer chromatography using Merck silica gel coated aluminum plates and petroleum ether: ethyl acetate as eluent.

Synthetic Procedure

S-Maltosyl arylthioureas were synthesized as mentioned in prior art, starting from maltose. Hepta-*O*-benzoyl-maltose (Intermediate I) was prepared by the reaction of maltose with benzoylchloride in 1:1chloroform pyridine mixture below 10^0C. Hepta-*O*-benzoyl-maltosyl-bromide (Intermediate II) was prepared by reacting Hepta-*O*-benzoyl-maltose with bromine and catalytic amount of red phosphorous in cold condition. Arylthioureas (Intermediate III) were synthesized by refluxing substituted amine hydrochloride with ammonium thiocyanate in water. *S*-(*O*-benzoyl-maltosyl) arylthioureas (Intermediate

IV) were synthesized by refluxing arylthioureas with *O*-benzoyl maltosyl bromide in isopropyl alcohol for 3 hrs. 1-Aryl-5-(1-naphthyl)-2-*S*-hepta-*O*-benzoyl-maltosyl isothiobiurets (Molecules 1-6) were synthesised by condensing *S*-(*O*-benzoyl-maltosyl) arylthioureas (0.86 mmol) with naphthylisocyanate (0.86 mmol) under dry condition using dry benzene as solvent, and stirring at room temperature overnight.

Molecule Number 1: 1-Phenyl-5-(1-naphthyl)-2-*S*-hepta-*O*-benzoyl-maltosyl Isothiobiuret
Obtained as white solid in 63.6 % yield, m. p. 95-97 ^{0}C, TLC R_f 0.7 in EtOAc: Petether (3:7), $[\alpha]_D^{30}$ +89 [c,1, in $CHCl_3$], IR (KBr) in cm-1 υ 3300(N-H); 2960(Ar-H); 1741(C=O); 1590(C=N); 1372(C-N); 1235(C-O); 945(Carbohydrate ring deformation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.84-3.88(m, 3H), 4.34-4.70(m, 7H), 4.71-4.75(m, 3H), 5.30-5.50(m, 1H), 5.60-5.80(m, 1H), 5.80-5.90(m, 1H), 6.10-6.20(m, 1H), 7.10-7.15(m, 4H), 7.2-7.60(m, 26H), 7.70-8.10(m, 16H). MS, m/z: 1375[M^+.+1], Analytically calculated for $C_{79}H_{63}N_3O_{18}S$, Found C, 69.10; H, 4.56; N, 3.04; O, 21.00; S, 2.30%, Required C, 69.05; H, 4.59; N, 3.06; O, 20.97; S, 2.33%.

Molecule Number 2: 1-(*p*-Tolyl)-5-(1-naphthyl)-2-*S*-hepta-*O*-benzoyl-maltosyl Isothiobiuret
Obtained as white solid in 79.33 % yield, m.p. 98-103^{0}C, TLC R_f 0.63 in EtOAc: Petether (3:7), $[\alpha]_D^{30}$ +109 [c,1, in $CHCl_3$], IR (KBr) in cm-1 υ 3320(N-H); 2970(Ar-H); 1780(C=O); 1600(C=N); 1380(C-N); 1220(C-O); 945(Carbohydrate ring deformation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.21(s, 3H), 3.80-3.84(m, 3H), 4.31-4.50(m, 7H), 4.71-4.75(m, 3H), 5.21-5.45(m, 1H), 5.55-5.72(m, 1H), 5.80-5.92(m, 1H), 6.20-6.25(m, 1H), 7.10-7.12(m, 4H), 7.2-7.65(m, 25H), 7.70-8.20(m, 16H). MS, m/z: 1389[M^+.+1], Analytically calculated for $C_{80}H_{65}N_3O_{18}S$, Found C, 68.80; H, 5.1; N, 3.10; O, 20.70; S 2.30%, Required C, 69.21; H, 4.68; N, 3.03; O, 20.76; S, 2.31%.

Molecule Number 3: 1-(*o*-Tolyl)-5-(1-naphthyl)-2-*S*-hepta-*O*-benzoyl-maltosyl Isothiobiuret
Obtained as white solid in 79.33 % yield, m.p. 91-95^{0}C, TLC R_f 0.65 in EtOAc: Petether (3:7), $[\alpha]_D^{30}$ +100 [c,1, in $CHCl_3$], IR (KBr) in cm-1 υ 3290(N-H); 2930(Ar-H); 1730(C=O); 1580(C=N); 1359(C-N); 1220(C-O); 945(Carbohydrate ring deformation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.30(s, 3H), 3.84-3.92(m, 3H), 4.34-4.65(m, 7H), 4.68-4.70(m, 3H), 5.38-5.50(m, 1H), 5.55-5.75(m, 1H), 5.80-5.88(m, 1H), 6.20-6.25(m, 1H), 7.15-7.18(m, 4H), 7.23-7.68(m, 25H), 7.72-8.20(m, 16H). MS, m/z: 1389[M^+.+1], Analytically calculated for $C_{80}H_{65}N_3O_{18}S$, Found C, 69.20; H, 4.68; N, 3.00; O, 20.80; S 2.32%, Required C, 69.21; H, 4.68; N, 3.03; O, 20.76; S, 2.31%.

Molecule Number 4: 1-(*p*-Chlorophenyl)-5-(1-naphthyl)-2-*S*-hepta-*O*-benzoyl-maltosyl Isothiobiuret
Obtained as white solid in 73.2 % yield, m.p. 80-96^{0}C, TLC R_f 0.7 5 in EtOAc: Petether (3:7), $[\alpha]_D^{30}$ +115 [c,1, in $CHCl_3$], IR (KBr) in cm-1 υ 3285(N-H); 2890(Ar-H); 1730(C=O); 1565(C=N); 1365(C-N); 1210(C-O); 940(Carbohydrate ring deformation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.10-4.30(m, 3H), 4.34-4.65(m, 7H), 4.75-4.80(m, 3H), 5.40-5.50(m, 1H), 5.60-5.70(m, 1H), 5.80-5.85(m, 1H), 6.25-6.30(m, 1H), 7.10-7.15(m, 4H), 7.30-7.60(m, 23H), 7.70-8.15(m, 18H). MS, m/z: 1408[M^+.+1], Analytically calculated for $C_{79}H_{62}ClN_3O_{18}S$, Found C, 67.40; H, 4.35; Cl, 2.50; N, 3.00; O, 20.45; S 2.3%, Required C, 67.38; H, 4.406; Cl, 2.49; N, 2.98; O, 20.47; S, 2.27%.

Molecule Number 5: 1-(*o*-Chlorophenyl)-5-(1-naphthyl)-2-*S*-hepta-*O*-benzoyl-maltosyl Isothiobiuret
Obtained as white solid in 69.9 % yield, m.p. 90-93^{0}C, TLC R_f 0.8 in EtOAc: Petether (3:7), $[\alpha]_D^{30}$ +120 [c,1, in $CHCl_3$], IR (KBr) in cm-1 υ 3276(N-H); 2935(Ar-H); 1711(C=O); 1568(C=N); 1358(C-N); 1205(C-O); 935(Carbohydrate ring deformation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.95-4.25(m, 3H), 4.34-4.50(m, 7H), 4.70-4.80(m, 3H), 5.25-5.40(m, 1H), 5.50-5.65(m, 1H), 5.80-5.85(m, 1H), 6.20-6.25(m, 1H), 6.90-7.10(m, 4H), 7.25-7.68(m, 24H), 7.75-8.12(m, 17H). MS, m/z: 1408[M^+.+1], Analytically

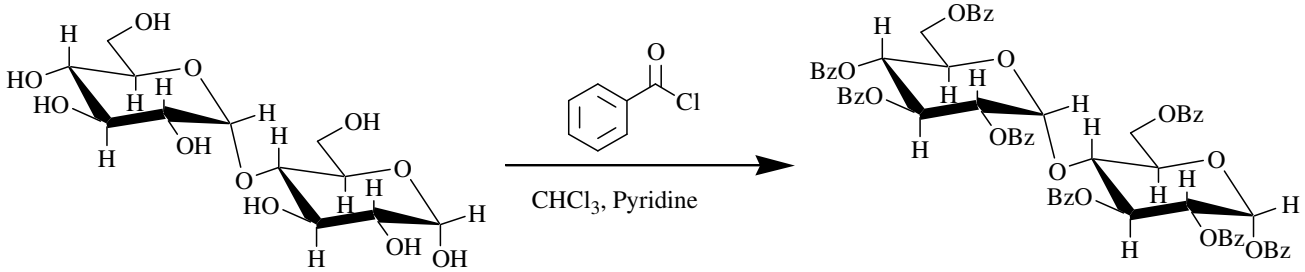
calculated for $C_{79}H_{62}ClN_3O_{18}S$, Found C, 67.40; H, 4.40; Cl, 2.50; N, 2.95; O, 20.45; S, 2.3%, Required C, 67.38; H, 4.406; Cl, 2.49; N, 2.98; O, 20.47; S, 2.27%.

Molecule Number 6: 1-(*m*-Chlorophenyl)-5-(1-naphthyl)-2-*S*-hepta-*O*-benzoyl-maltosyl Isothiobiuret

Obtained as white solid in 65.79% yield, m.p. 89-95^{0}C, TLC R_f 0.78 in EtOAc:Petether (3:7), $[\alpha]_D^{30}$ +108 [c,1, in $CHCl_3$], IR (KBr) in cm-1 υ 3290(N-H); 2860(Ar-H); 1695(C=O); 1575(C=N); 1359(C-N); 1255(C-O); 940(Carbohydrate ring deformation). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.78-3.85(m, 3H), 4.40-4.60(m, 7H), 4.70-4.78(m, 3H), 5.35-5.55(m, 1H), 5.60-5.78(m, 1H), 5.80-5.90(m, 1H), 5.92-6.20(m, 1H), 6.90-7.10(m, 3H), 7.30-7.70(m, 24H), 7.70-8.10(m, 18H). MS, m/z: 1408[M^++1], Analytically calculated for $C_{79}H_{62}ClN_3O_{18}S$, Found C, 67.40; H, 4.42; Cl, 2.48; N, 2.95; O, 20.50; S 2.25%, Required C, 67.38;H, 4.406;Cl, 2.49;N, 2.98;O, 20.47;S, 2.27%.

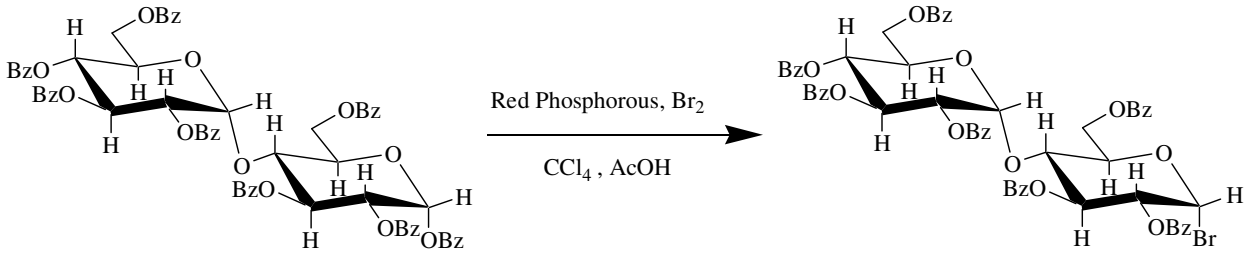
General Scheme of Synthesis

Step -I: Benzoylation



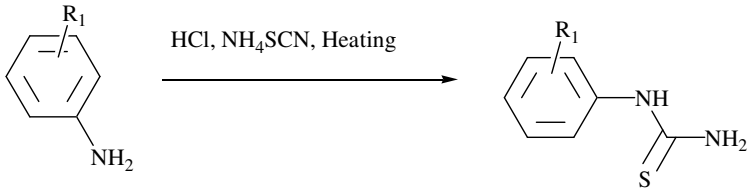
Intermediate I

Step -II: Bromination



Intermediate II

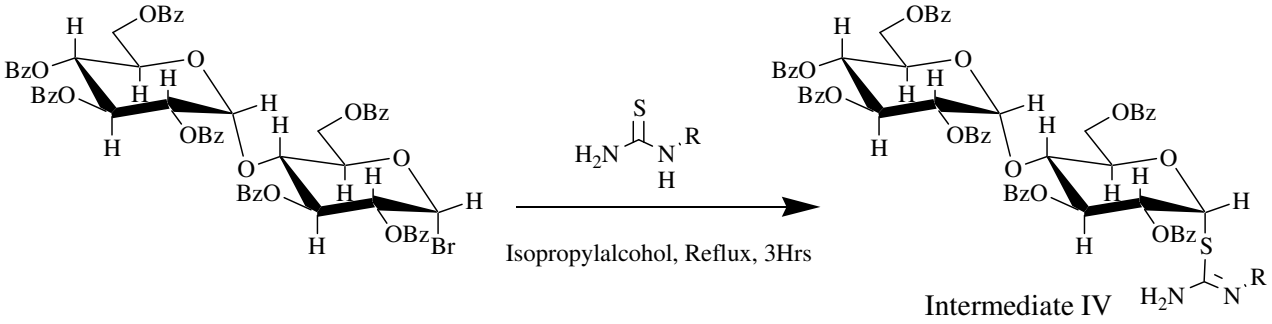
Step -III: Thiourea Synthesis



Intermediate III

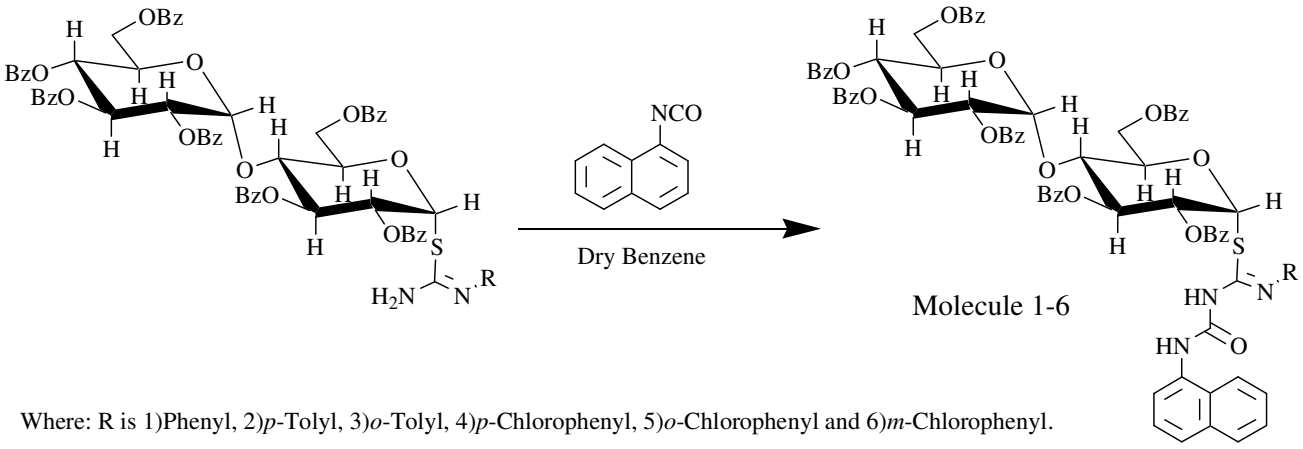
Where: R1 is H, 4-Cl, 3-Cl, 2-Cl, 2-Methyl, 4-Methyl

Step -IV: *S*-Alkylation



Where: R is 1)Phenyl, 2)*p*-Tolyl, 3)*o*-Tolyl, 4)*p*-Chlorophenyl, 5)*o*-Chlorophenyl and 6)*m*-Chlorophenyl.

Step- V: Thiourea isocyanate condensation



Where: R is 1)Phenyl, 2)*p*-Tolyl, 3)*o*-Tolyl, 4)*p*-Chlorophenyl, 5)*o*-Chlorophenyl and 6)*m*-Chlorophenyl.

Scheme-1

Antimicrobial Activity

All the compounds were screened for their antibacterial activity against pathogenic bacteria such as E. coli, S. aureus, and Klebsielleya by cup plate agar diffusion method at a concentration 100 µg/mL in DMSO. The zone of inhibition was measured in mm and is average of three readings. The readings are shown below in Table -1.

Table -1: Antimicrobial activities of compound number 1 to 6

Molecule Number	Antibacterial Activity		
	E. coli	S. aureus	Klebsielleya
1	18	14	15
2	14	12	15
3	14	12	14
4	14	12	18
5	10	10	10
6	10	10	10
Amikacin	25	23	23
Control(DMSO)	Nil	Nil	Nil

Including well diameter of 5 mm.

RESULTS AND DISUSSION

Molecule 1 showed good antimicrobial activity against E. coli and S. aureus, whereas molecule 4 showed good antimicrobial activity against Klebsielleya. Whereas remaining molecules showed moderate activity.

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