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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 5-ARYL-6-[TETRA(O-BENZOYL)-β-*D*-GLUCO-PYRANOSYLIMINO]-4-BENZYLTHIO-2-PHENYLIMINO-5,6-DIHYDRO-2H-1,3,5-THIADIAZINES

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Certain 5-aryl-6-[tetra(O-benzoyl)-β-D-glucopyranosylimino]-4-benzylthio-2-phenylimino-5,6-dihydro-2H-1,3,5-thiadiazines have been prepared by interaction of N-[tetra(O-benzoyl)-β-D-glucopyranosyl] isocyanodichloride and 1-aryl-5-phenyl-2-(S-benzyl)-2,4-isodithiobiurets. The products have been characterized through the usual chemical transformations, IR, NMR and mass spectral analyses. The compounds have been screened for their antibacterial activities against various bacteria.

Keywords: isodithiobiurets, isocyanodichlorides, 1,3,5-thiadiazines, synthesis.

Benzoylated glucosyl nucleoside analogs having 1,3,5-thiadiazine moieties as heterocyclic bases have not been earlier synthesized. We now report the synthesis of 5-aryl-6-[tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-2-phenylimino-5,6-dihydro-2H-1,3,5-thiadiazines using N-[tetra(O-benzoyl)-β-*D*-glucopyranosyl] isocyanodichloride (**1**) as a key reagent. The latter has been prepared in our laboratory for the first time by interaction of N-[tetra(O-benzoyl)-β-*D*-glucopyranosyl] isothiocyanate with excess of chlorine gas.

The reaction of compound **1** and 1-aryl-5-phenyl-2-(S-benzyl)-2,4-isodithiobiurets (**2**) was carried out in cold dry chloroform for 24 h. The solvent was distilled off and sticky mass was isolated as a residue. When triturated several times with petroleum ether it was converted to a granular yellow solid. This solid was dissolved in ethanol and basified with cold ammonium hydroxide solution to give 5-aryl-6-[tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-2-phenylimino-5,6-dihydro-2H-1,3,5-thiadiazines **3** (Scheme). Compounds **3** were purified by recrystallization from ethanol, their purity was checked by TLC. The products were found to be non-desulfurisable when boiled with alkaline plumbite solution (Scheme 1).

The compounds were screened for their antibacterial activities against various pathogenic bacteria such as *E. coli*, *S. aureus*, *Pr. mirabilis*, *S. typhi* by disc method at concentration 10 μg·ml^{-1} in DMF. Amongst the compounds tested for the antibacterial activity, compounds **3b**,**d**,**g**, and **3i** showed higher activity against *E. coli*, *S. typhi* and *S. aureus*, compounds **3e**,**j**, and **3k** demonstrated higher activity against *Pr. mirabilis*, while other compounds revealed good to moderate activity.

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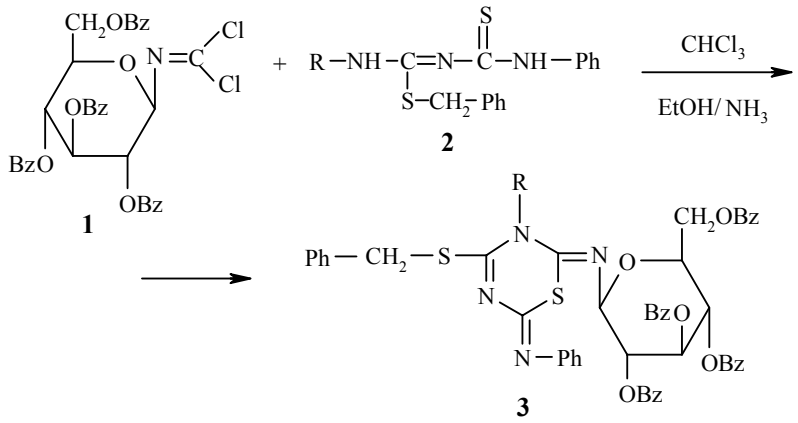
Scheme 1



a R = Ph, **b** R = *o*-Tol, **c** R = *m*-Tol, **d** R = *p*-Tol, **e** R = *o*-ClC_6H_4, **f** R = *m*-ClC_6H_4, **g** R = *p*-ClC_6H_4, **h** R = *m*- $O_2NC_6H_4$, **i** R = *p*-$O_2NC_6H_4$, **j** R = *o*-$MeOC_6H_4$, **k** R = *p*-$MeOC_6H_4$; Bz = benzoyl

EXPERIMENTAL

Melting points are uncorrected, optical rotation was measured at 38°C. IR spectra [1-3] recorded for 4.0 cm^{-1} flat, smooth, abex in 4000-200 cm^{-1} range. ^1H NMR spectra [2, 4, 5] (300 MHz) were obtained for solutions in deuteriochloroform using traces of $CHCl_3$ as internal standard, chemical shifts were given in δ scale relative to TMS. The FAB mass spectra [6, 7] were recorded on JEOL SX 102/DA-6000 Mass spectrometer/Data system using Argon/Xenon (6 kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV and the spectra were recorded at room temperature. *m*-Nitrobenzyl alcohol (NBA) was used as a matrix unless specified otherwise. Thin layer chromatography was conducted on Merck TLC Aluminium sheet Silica gel 60 F_{254}.

N-[Tetra(O-benzoyl)-β-*D*-glucopyranosyl] isocyanodichloride (**1**) was prepared from N-[tetra(O-benzoyl)-β-*D*-glucopyranosyl] isothiocyanate with excess of chlorine gas similar to the synthesis of phenyl isocyanodichloride [8]. 1-Aryl-5-phenyl-2-(S-benzyl)-2,4-isodithiobiurets **2** were prepared by the method [9].

N-[Tetra(O-benzoyl)-β-*D*-glucopyranosyl] Isocyanodichloride (**1**). Through a solution of N-[tetra(O-benzoyl)-β-*D*-glucopyranosyl] isothiocyanate [10] (6.37 g) in chloroform (20 ml) excess chlorine gas (generated from 10 g of $KMnO_4$ and 70 ml of concentrated hydrochloric acid) was passed maintaining the temperature below 10°C. After complete addition of chlorine, a pale yellow reaction mixture was diluted with dry petroleum ether (40 ml) and filtered to remove suspended impurities. After vacuum evaporation a pale yellow solid was obtained (6.3 g); mp 165-167°C. Found, %: C 61.88; H 3.75; N 2.11; Cl 10.53. $C_{35}H_{27}Cl_2NO_9$. Calculated, %: C 62.10; H 3.99; N 2.07; Cl 10.50.

6-[Tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-5-phenyl-2-phenylimino-5,6-dihydro-2H-1,3,5-thiadiazine (3a). The reaction of compound **1** (3.38 g, 0.005 mol; R_f 0.28; EtOAc–CCl_4 = 1:2 as an eluent) and 1,5-diphenyl-2-(S-benzyl)-2,4-isodithiobiuret (**2a**) (1.9 g, 0.005 mol) was carried out in cold dry chloroform for 24 hr. The solvent was then removed to leave a sticky syrup which was triturated with petroleum ether until a yellow solid resulted. The solid was dissolved in ethanol and basified with cold ammonium hydroxide solution to give compound **3a** (4.5 g, 91.8%); mp 140°C (ethanol), $[\alpha]_D^{38}$ = -6.66° (*c* 0.0014 in $CHCl_3$). The purity of product was checked by TLC and R_f value 0.92 (EtOH–$CHCl_3$–Me_2CO = 1:2:3 as an eluent) was recorded. IR spectrum, ν, cm^{-1}: 3062.7 (Ar–H), 2893.0 (C–H, aliphatic), 1728.1 (C=O), 1596.9 (C=N), 1380.9 (C–N), 1265.2 (C–O), 856.3 (β-*D*-glucopyranosyl ring deformation), 756.0 (C–S), 709.8

(monosubstituted ring), 614.5 (C–S–C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.05-7.2 (35H, m, Ar–H); 5.3-4.2 (5H, m, β-*D*-glucopyranosyl ring); 4.5-4.0 (2H, br. d, CH_2–O); 4.52-4.40 (2H, br. s, S–CH_2–Ph). Mass spectrum, *m/z* (*I*, %): 997 [M^+ + OH]; 980 [M]$^+$; 935 [M – C_2H_5O]; 907 [M – C_4H_9O]; 873 [M – $PhCH_2O$]; 595 [TBG – NH_2^+]; 579 [TBG]$^+$; 462 [TBG – C_8H_5O]; 401 [M – TBG]; 376 [M – TBGNC]; 361 [M – TBGNCN]; 286 [M – $TBGNCNC_6H_3$]; 220 [M – $TBGNCHPh_2$]; 105 [PhCO]$^+$. Found, %: C 68.26; H 4.32; N 5.60; S 6.90. $C_{56}H_{44}N_4O_9S_2$. Calculated, %: C 68.57; H 4.48; N 5.71; S 6.53.

The reaction of compound **1** was extended to several other 1-aryl-5-phenyl-2-(S-benzyl)-2,4-isodithiobiurets and corresponding products **3b-k** were prepared.

6-[Tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-2-phenylimino-5-(*o*-tolyl)-5,6-dihydro-2H-1,3,5-thiadiazine (3b). Obtained from compound **1** (3.38 g, 0.005 mol) and compound **2b** (1.95 g, 0.005 mol). Yield 4.1 g, 82.5%; mp 159°C; $[\alpha]_D^{38}$ = -140.0° (*c* 0.0015 in $CHCl_3$), R_f 0.52 (*n*-BuOH–$CHCl_3$–Me_2CO = 1:2:3). Found, %: C 68.44; H 4.32; N 5.39; S 6.75. $C_{57}H_{46}N_4O_9S_2$. Calculated, %: C 68.81; H 4.62; N 5.63; S 6.43.

6-[Tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-2-phenylimino-5-(*m*-tolyl)-5,6-dihydro-2H-1,3,5-thiadiazine (3c). Obtained from compound **1** (3.38 g, 0.005 mol) and compound **2c** (1.95 g, 0.005 mol). Yield 3.2 g, 64.4%; mp 160°C; $[\alpha]_D^{38}$ = -84.6° (*c* 0.0013 in $CHCl_3$), R_f 0.68 (*n*-BuOH–$CHCl_3$–Me_2CO = 1:2:3). Found, %: C 68.52; H 4.34; N 5.48; S 6.65. $C_{57}H_{46}N_4O_9S_2$. Calculated, %: C 68.81; H 4.62; N 5.63; S 6.43.

6-[Tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-2-phenylimino-5-(*p*-tolyl)-5,6-dihydro-2H-1,3,5-thiadiazine (3d). Obtained from compound **1** (3.38 g, 0.005 mol) and compound **2d** (1.95 g, 0.005 mol). Yield 4.0 g, 80.6%; mp 172°C; $[\alpha]_D^{38}$ = -35.71° (*c* 0.0014 in $CHCl_3$), R_f 0.72 (*n*-BuOH–$CHCl_3$–Me_2CO = 1:2:3). IR spectrum, ν, cm^{-1}: 3062.7 (Ar–H), 2977.9 (C–H, CH_3), 2885.3 (C–H, CH_2), 1728.1 (C=O), 1596.9 (C=N), 1404.1 (C–N), 1265.2 (C–O), 854.1 (β-*D*-glucopyranosyl ring deformation), 825.5 (1,4-disubstituted ring), 750 (C–S), 619.7 (C–S–C), 709.8 (monosubstituted ring). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.0-7.25 (34H, m, Ar–H); 5.3-4.2 (5H, m, β-*D*-glucopyranosyl ring); 4.49-4.30 (2H, br. s, S–CH_2–Ph); 4.5-4.0 (2H, br. d, CH_2O); 2.4-1.7 (3H, br. s, Ar–CH_3). Mass spectrum, *m/z* (*I*, %): 994 [M]$^+$; 967 [M – CHN]; 923 [M – C_4H_7O]; 887 [M – PhCHOH]; 847 [M – C_8H_5NS]; 827 [M – $C_{12}H_9N$]; 805 [M – $C_{12}H_{13}S$]; 767 [M – $C_{15}H_{15}S$]; 728 [M – $C_{20}H_{12}N$]; 639 [TBGNH–CHS]$^+$; 596 [TBG – NH_2^+]; 579 [TBG]$^+$; 475 [TBG – C_6H_4CO]; 300 [$C_{17}H_{16}O_5^+$]; 231 [$C_{13}H_{11}O_4^+$]; 105 [PhCO$^+$]. Found, %: C 68.84; H 4.47; N 5.27; S 6.62. $C_{57}H_{46}N_4O_9S_2$. Calculated, %: C 68.81; H 4.62; N 5.63; S 6.43.

6-[Tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-5-(*o*-chlorophenyl)-2-phenylimino-5,6-dihydro-2H-1,3,5-thiadiazine (3e). Obtained from compound **1** (3.38 g, 0.005 mol) and compound **2e** (2.04 g, 0.005 mol). Yield 4.0 g, 80%; mp 141°C; $[\alpha]_D^{38}$ = -141.66° (*c* 0.0012 in $CHCl_3$), R_f 0.82 (EtOH–$CHCl_3$–Me_2CO = 1:2:3). Found, %: C 65.95; H 3.93; Cl 3.00; N 5.16; S 6.34. $C_{56}H_{43}ClN_4O_9S_2$. Calculated, %: C 66.27; H 4.24; Cl 3.50; N 5.52; S 6.31.

6-[Tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-5-(*m*-chlorophenyl)-2-phenylimino-5,6-dihydro-2H-1,3,5-thiadiazine (3f). Obtained from compound **1** (3.38 g, 0.005 mol) and of compound **2f** (2.04 g, 0.005 mol). Yield 4.4 g, 88%; mp 145°C; $[\alpha]_D^{38}$ = -77.77° (*c* 0.0018 in $CHCl_3$), R_f 0.79 (EtOH–$CHCl_3$–Me_2CO = 1:2:3). IR spectrum, ν, cm^{-1}: 3065.5 (Ar–H), 2916.2 (C–H, aliphatic), 1728.1 (C=O), 1596.9 (C=N), 1380.9 (C–N), 1265.2 (C–O), 854.1 (β-*D*-glucopyranosyl ring deformation), 802.0 (1,3-disubstituted ring), 755.2 (C–S), 709.8 (monosubstituted ring), 625 (C–S–C), 578 (C–Cl). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.0-7.0 (34H, m, Ar–H); 5.25-4.38 (5H, m, β-*D*-glucopyranosyl ring); 4.52-4.35 (2H, br. s, S–CH_2–Ph); 4.44-4.05 (2H, br.d, CH_2O). Mass spectrum, *m/z* (*I*, %): 1014 [M]$^+$; 986 [M – CO]; 941 [M – $C_3H_5O_2$]; 909 [M – PhCO]; 895 [M – $PhCOCH_2$]; 867 [M – $PhCOOC_2H_2$]; 850 [M – $PhNHC(=S)N=CH_2$]; 639 [TBG–NH–CH=S]$^+$; 604 [TBGCN]$^+$; 579 [TBG]$^+$; 231 [$C_{14}H_{15}O_3$]$^+$; 149 [$PhCOOCH_2H_4$]; 106 [PhCHO]$^+$. Found, %: C 66.05; H 4.23; Cl 3.21; N 5.36; S 6.00. $C_{56}H_{43}ClN_4O_9S_2$. Calculated, %: C 66.27; H 4.24; Cl 3.50; N 5.52; S 6.31.

6-[Tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-5-(*p*-chlorophenyl)-2-phenylimino-5,6-dihydro-2H-1,3,5-thiadiazine (3g). Obtained from compound **1** (3.38 g, 0.005 mol) and compound **2g** (2.04 g, 0.005 mol). Yield 4.2 g, 84%; mp 165°C; $[\alpha]_D^{38}$ = -111.76° (*c* 0.0017 in $CHCl_3$), R_f, 0.70 (EtOH–$CHCl_3$–Me_2CO = 1:2:3). Found, %: C 66.09; H 4.01; Cl 2.97; N 5.28; S 5.95. $C_{56}H_{43}ClN_4O_9S_2$. Calculated, %: C 66.27; H 4.24; Cl 3.50; N 5.52; S 6.31.

6-[Tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-5-(*m*-nitrophenyl)-2-phenylimino-5,6-dihydro-2H-1,3,5-thiadiazine (3h). Obtained from compound **1** (3.38 g, 0.005 mol) and compound **2h** (2.1 g, 0.005 mol). Yield 4.1 g, 79.9%; mp 156°C; $[\alpha]_D^{38}$ = 166.66° (*c* 0.0009 in $CHCl_3$), R_f 0.42 (EtOH–$CHCl_3$–Me_2CO = 1:1:2). IR spectrum, ν, cm^{-1}: 3028.8 (Ar–H), 2900.1 (C–H, aliphatic), 1728.1 (C=O), 1596.9 (C=N), 1527.5 (C–NO_2), 1373.2 (C–N), 1265.2 (C–O), 852 (β-*D*-glucopyranosyl ring deformation), 801 (1,3-disubstituted ring), 780 (C–S), 709.8 (monosubstituted ring), 625 (C–S–C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.95-7.15 (34H, m, Ar–H); 5.31-4.25 (5H, m, β-*D*-glucopyranosyl ring); 4.52-4.0 (2H, br. s, S–CH_2–Ph); 4.40-4.0 (2H, br. d, CH_2O). Mass spectrum, *m/z* (*I*, %): 1025 $[M]^+$; 932 [M – $PhNH_2$]; 886 [M – Ph–NH–CH_2–SH]; 638 $[TBGNH{=}C{=}S]^+$; 579 $[TBG]^+$; 475 [TBG – C_6H_4CO]; 424 [TBG – $C_{12}H_{11}$]; 335 [TBG – 2PhCOOH]; 105 $[PhCO]^+$. Found, %: C 65.21; H 3.98; N 6.52; S 6.15. $C_{56}H_{43}N_5O_{11}S_2$. Calculated, %: C 65.56; H 4.19; N 6.82; S 6.24.

6-[Tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-5-(*p*-nitrophenyl)-2-phenylimino-5,6-dihydro-2H-1,3,5-thiadiazine (3i). Obtained from compound **1** (3.38 g, 0.005 mol) and compound **2i** (2.1 g, 0.005 mol). Yield 4.6 g, 89.7%; mp 125°C; $[\alpha]_D^{38}$ = 100.00° (*c* 0.0012 in $CHCl_3$), R_f 0.54 (EtOH–$CHCl_3$–Me_2CO = 1:1:2). Found, %: C 65.41; H 4.00; N 6.69; S 6.45. $C_{56}H_{43}N_5O_{11}S_2$. Calculated, %: C 65.56; H 4.19; N 6.82; S 6.24.

6-[Tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-5-(*o*-methoxyphenyl)-2-phenylimino-5,6-dihydro-2H-1,3,5-thiadiazine (3j). Obtained from compound **1** (3.38 g, 0.005 mol) and compound **2j** (1.97 g, 0.005 mol). Yield 4.6 g, 85.1%; mp 154°C (decomp.); $[\alpha]_D^{38}$ = -76.92° (*c* 0.0013 in $CHCl_3$), R_f 0.59 (*n*-BuOH–$CHCl_3$–Me_2CO = 1:2:3). IR spectrum, ν, cm^{-1}: 3062.7 (Ar–H), 2977.9 (C–H, OCH_3), 2885.3 (C–H, CH_2), 1728.1 (C=O), 1596.9 (C=N), 1373.2 (C–N), 1265.2 (C–O), 848.6 (β-*D*-glucopyranosyl ring deformation), 802.0 (C–S), 749.0 (1,2-disubstituted ring), 709.8 (monosubstituted ring), 635.4 (C–S–C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.0-7. 15 (34H, m, Ar–H); 5.3-4.0 (5H, m, β-*D*-glucopyranosyl ring); 4.45-4.1 (2H, br. s, S–CH_2–Ph); 4.25-4.12 (2H, br. d, CH_2–O); 3.7-3.65 (3H, br. s, CH_3–O–Ar). Mass spectrum, *m/z* (*I*, %): 1010 $[M]^+$; 937 [M – C_4H_9O]; 914 [M – C_6H_8O]; 843 [M – $C_{13}H_{11}$]; 831 [M – $C_{14}H_{11}$]; 744 [M – $C_{15}H_{12}N_3S$]; 664 [M – $C_{21}H_{20}N_3S$]; 648 [M – $C_{21}H_{20}N_3OS$]; 579 $[TBG]^+$; 350 [TBG – $C_{14}H_{13}O_3$]; 333 [TBG – $C_{14}H_{14}O_4$]; 231 $[C_{14}H_{15}O_3]^+$; 106 $[PhCHO]^+$. Found, %: C 67.54; H 4.29; N 5.55; S 6.67. $C_{57}H_{46}N_4O_{10}S_2$. Calculated, %: C 67.72; H 4.55; N 5.54; S 6.33.

6-[Tetra(O-benzoyl)-β-*D*-glucopyranosylimino]-4-benzylthio-5-(*p*-methoxyphenyl)-2-phenylimino-5,6-dihydro-2H-1,3,5-thiadiazine (3k). Obtained from compound **1** (3.38 g, 0.005 mol) and compound **2k** (1.97 g, 0.005 mol). Yield 4.5 g, 87.7%; mp 240°C (decomp.); $[\alpha]_D^{38}$ = 60.00° (*c* 0015 in $CHCl_3$), R_f 0.48 (*n*-BuOH–$CHCl_3$–Me_2CO = 1:2:3). Found, %: C 67.49; H 3.99; N 5.33; S 6.43. $C_{57}H_{46}N_4O_{10}S_2$. Calculated, %: C 67.72; H 4.55; N 5.54; S 6.33.

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