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Antimicrobial screening of newly synthesized mono/poly chlorinated aryl, N-glucosylated-1,2,4-dithiazolidines

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ABSTRACT

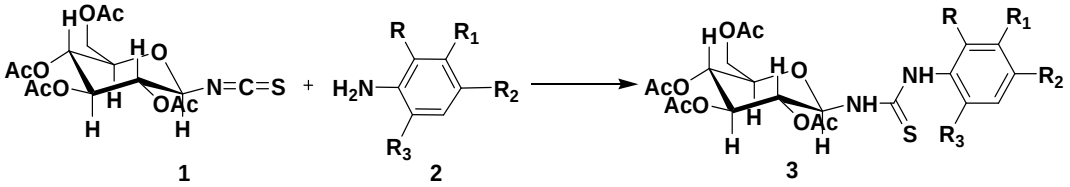
New series of chlorinated aryl, N-tetra-O-acetyl-β-D-glucopyranosylated 1,2,4-dithiazolidines,viz. 3-p-chlorophenyl imino-,4-phenyl,5-tetra-O-acetyl-β-D-glucopyranosylimino-,3-p-chlorophenylimino-, 4-chlorophenylimino-, 5-tetra-O-acetyl-β-D-glucopyranosylimino-, 3-p-chlorophenyl-4[2,4-dichlorophenyl]5-tetra-O-acetyl-β-D-glucopyranosylimino-, 3-p-chloropheylimino-, 4[2,4,6-trichlorophenyl]-5-tetra-O-acetyl-β-D-glucopyranosylimino-1,2,4-dithiazolidines have been synthesized by the interaction of S-chloro-N-aryl isothiocarbamoyl chloride and 1-tetra-O-acetyl-β-D-gluco-pyranosyl-3-p-chlorophenyl/ 2,4-dichlorophenyl/ 3,4-dichlorophenyl/ 2,4,6-trichlorophenyl-thiocarbamides in boiling benzene. The former has been prepared following the usual procedure, i.e. the controlled chlorination of p-chlorophenyl isothiocyanate, while the latter by the interaction of tetra-O-acetyl--β-D-glucopyranosyl isothiocyanate and p-chloroaniline/ 2,4-dichloroaniline/ 3,4-dichloroaniline/ 2,4,6-trichloroaniline, respectively. The structures of the compounds have been established by conventional chemical transformation and IR, ^{1}H NMR and Mass spectral analysis. The title compounds were screened for their antimicrobial activity against Gram Positive and Gram Negative microorganisms.

Keywords: N-glucopyranosylimino-1,2,4-dithiazolidines, S-chloro-N-aryl isothiocarbamoyl chloride, Tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate.

INTRODUCTION

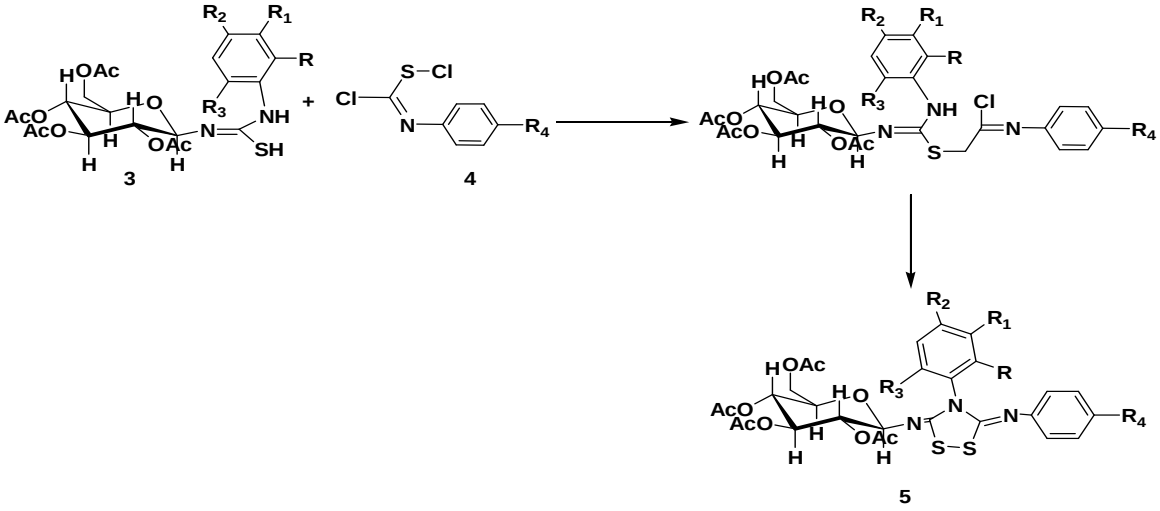
N-Glucosylated compounds have been shown to possess antiviral and antimicrobial activity [1]. They are reported to have anti-cancer activity also [2]. Glycosyl guanidine derivatives, glycosyl thiocarbamides have several medicinal applications such as antitumor agent [3], antilukemic agent [4], and antibacterial properties [5]. It has been already shown that halogenated derivatives possess promising activity [6-7]. In earlier communication we have reported synthesis of heterocycles with N atoms only [8]. Looking at the activity shown by different heterocycles, it was considered worthwhile to synthesize heterocyclic compounds containing both N and S atoms with various chloroaryl substituents and to carry out their antimicrobial study. The present communication describes the synthesis and antimicrobial screening of mono/polychlorinated aryl-N-glucosylated 1,2,4-dithiazolidines.

Reaction scheme:



1 2 3

Where (a) R=R$_1$=R$_3$=H, R$_2$=Cl (b) R$_1$=R$_3$=H, R=R$_2$=Cl, (c) R$_1$=R$_3$=H, R$_1$=R$_2$=Cl (d) R$_1$=H, R=R$_2$=R$_3$=Cl.



3 4 5

Where (a) R=R$_1$=R$_3$=H, R$_2$=R$_4$=Cl. (e) R=R$_1$=R$_3$=R$_4$=H R$_2$=Cl.
(b) R$_1$=R$_3$=H, R=R$_2$=R$_4$=Cl. (f) R=R$_1$=R$_2$=R$_3$=H, R$_4$=Cl.
(c) R=R$_3$=H, R$_1$=R$_2$=R$_4$=Cl. (g) R$_1$=R$_3$=R$_4$=H, R=R$_2$=Cl.
(d) R$_1$=R$_4$=H, R=R$_2$=R$_3$=Cl. (h) R=R$_3$=R$_4$=H, R$_1$= R$_2$=Cl.

MATERIALS AND METHODS

The melting points were recorded using open capillary method and are uncorrected. ^{1}HNMR spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvents. IR spectra were recorded on a Perkin-Elmer spectrophotometer in the range of 4000-400cm^{-1} in KBr pellet. Purity of compounds were checked using TLC plates. S-chloro-N-aryl isothiocarbamoyl chlorides were prepared by earlier known method [9].

Synthesis of 1-tetra-O-acetyl-β-D-glucopyranosyl-3-p-chlorophenyl thiocarbamide (3a).

The mixture of tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (1) (0.01mole), p-chloroaniline (2a) (0.01mole) and chloroform (15ml) was refluxed for 1.5hours. The solvent was distilled off and the residue was triturated with petroleum ether (60-80^0) 2-3times to give granular solid (3a). It was crystallized from 50% aqueous ethanol, m.p. 162^{o}C, yield (80%). The molecular formula of 3a was established as $C_{21}H_{25}N_2SO_9Cl$. It was optically active with $[\alpha]_D^{31}$ +3.61 (C= 0.20% in chloroform). IR (cm^{-1}): NH (3340), C-N (1360) and C=S (1210). The PMR Spectrum displayed the signals due to acetyl protons (δ 2.0), NH protons (δ7.2), aromatic protons at (δ7.4-7.6) and pyranosyl protons in the range δ4-4.5 & 4.8-5.5, a doublet due to β-glucopyranosyl proton at δ5.7. Similarly, other compounds have prepared from (1), **3b** yield (85%), m.p. 178^{o}C. IR(cm^{-1}): NH (3340), C-N (1370), C=S (1240) & Ar-Cl(1040). PMR=NH (δ7.2) ,Ar-H δ7.5,acetyl proton at δ2.02 and pyranosyl ring protons at δ4-4.5 & δ4.8-5.5 and β-glucopyranosyl proton as doublet at δ5.8ppm, **3c** yield (88%) 135^{o}C. IR(cm^{-1}): NH(3340), C-N(1370), C=S(1220), Ar-Cl(1030). PMR ($CDCl_3$): NH (δ7.8), ArH(δ7.4), acetyl proton at δ2.02, pyranosyl ring at δ3.8-4.3 & δ4.7-5.3, β-glucopyranosyl proton as doublet at δ6.02ppm. **3d** yield (82%) m.p.162^{o}C. IR (cm^{-1}): NH (3342),C-N(1370), C=S(1220), Ar-Cl (1030). PMR: NH (δ7.8), ArH(δ7.5), acetyl proton at δ2.02, pyranosyl ring at δ3.8-4.4 & δ4.7-5.3, β-glucopyranosyl proton as doublet at δ5.90ppm.

Synthesis of 3-p-chlorophenylimino-4-p-chlorophenyl-5-tetra-O-acetyl-β-D-glucopyranosylimino-1,2,4-dithiazolidine (5a).

A mixture of 1-tetra-O-acetyl-β-D-glucopyranosyl-3-p-chlorophenylthiocarbamide (3a, 0.01mole), S-chloro-N-p-chlorophenyl isothiocarbamoyl chloride (4a, 0.01mole) in 20ml benzene was refluxed for 4hours when evolution of hydrogen chloride gas was clearly noticed. After vacuum distilling the solvent, the sticky mass was isolated. It was triturated several times with petroleum ether followed by ethanol to afford a granular solid (5a), crystallized from ethanol, m.p. 190^{o}C, yield (79.24%). Its molecular formula was indicated as $C_{28}H_{27}N_3S_2O_9Cl_2$ (found N 5.89, S 9.13, $C_{28}H_{27}N_3S_2O_9Cl_2$ requires N 6.06, S 9.35%). It gave negative lead plumbite test. It was charred on heating with conc. H_2SO_4. It was optically active with $[\alpha]_D^{31}$ + 136.40 (C= 0.20% in $CHCl_3$). Its UV showed λmax at 240nm. IR (cm^{-1}): C=O (1735), C=N (1600), C-S (700), and S-S(480). The PMR of the **5a** showed the presence of the acetyl protons at δ2.05, Ar-H at δ6.60-7.05 and pyranosyl ring protons at δ3.8-4.2and δ4.6-5.3ppm. The mass spectrum of the product showed molecular ion peak at m/e 684 and other important fragment peaks at m/e 453, 393, 330, 263 and 169. **5b** m.p.174^{o}C, yield (78.11%). (Found C 46.38, H 4.45, N 5.86, S 8.69 $C_{28}H_{26}N_3S_2O_9Cl_3$ requires C 46.69, H 3.61, N 5.83, S 8.78 %) $[\alpha]_D^{30}$= -141.29 (C =0.12% in $CHCl_3$). IR (cm^{-1}): C=O (1735), C=N (1600), C-N(1350),C-S (690), and S-S (480). The PMR showed the acetyl protons at δ2.05, Ar-H at the δ6.7-7.4 and pyranosyl ring protons at δ3.8-4.3 and δ4.6-5.3ppm. The mass spectrum showed m/e values at 514,454,330,168, and 108. **5c** yield (79.15%), m.p. 223^{o}C (Found N 5.53, S 8.28, $C_{28}H_{26}N_3O_9S_2Cl_3$ requires N 5.84, S 8.92). $[\alpha]_D^{30}$= -122.7 (C 0.12% in $CHCl_3$). IR (cm^{-1}): C=O (1735), C=N(1550),C-N(1350), C-S (690), and S-S (480). The PMR showed the presence of the acetyl protons at δ2.05, Ar-H at δ6.7-7.5 and pyranosyl ring protons at δ3.7-4.4 and δ4.7-5.3ppm**. 5d** yield (81.31%), m.p.140^{o}C (found N 4.98, S 8.27 $C_{28}H_{25}N_3S_2Cl_4$ requires N 5.52 and S 8.47) $[\alpha]_D^{30}$= -126.67 (C= 0.13% in $CHCl_3$). IR (cm^{-1}): C=O (1735), C=N (1600), C-N (1360), C-S (700), and S-S (480). The PMR showed the signals due to presence of the acetyl protons at δ2.05, Ar-H at δ6.7-7.5 and pyranosyl ring protons at δ3.7-4.4 and δ4.7-5.3ppm. **5e** yield (75.19%), m.p.192^{o}C (found N 6.18, S 9.7, $C_{28}H_{28}N_3S_2O_9Cl$ requires N 6.36, S 9.7%). $[\alpha]_D^{30}$= +154.11 (C=0.15% in $CHCl_3$). IR (cm^{-1}): C=O (1750), C=N (1600), C-N(1330), C-S (690), and S-S (490) . The PMR showed the presence of the acetyl protons at δ2.05, Ar-H at δ6.7-7.5 and pyranosyl ring protons at δ3.8-4.2 and δ4.6-5.3ppm. **5f** yield (80.31%), m.p.180^{0}C, (found N 6.28, S 9.53, $C_{28}H_{28}N_3S_2O_9Cl$ requires N 6.46, S 9.7%). $[\alpha]_D^{30}$= +113.93 (C=0.12% in $CHCl_3$). IR (cm^{-1}): C=O (1740), C=N (1600), C-N (1330), C-S (680), and S-S (490). The PMR signals displayed for $COCH_3$ protons at δ2.05, Ar-H at δ6.7-7.3 and pyranosyl ring protons at δ3.8-4.2 and δ4.6-5.3ppm. **5g** yield (73.25%), m.p.145^{o}C, (found N 5.91, S 9.03, $C_{28}H_{27}N_3S_2O_9Cl_2$ requires N 6.06, S 9.35%). $[\alpha]_D^{30}$= +120.35 (C= 0.12% in $CHCl_3$). IR (cm^{-1}): C=O(1740), C=N(1590), C-N(1330), C-S(690), and S-S (460). The PMR signals displayed for $COCH_3$ protons at δ2.05, Ar-H at δ6.7-7.3 and pyranosyl ring protons at δ3.9-4.2 and δ4.6-5.2ppm. **5h** yield (78.65%), m.p.205^{o}C (found N 5.72, S 9.13, $C_{28}H_{27}N_3S_2O_9Cl_2$ requires N 6.06, S 9.35%). $[\alpha]_D^{30}$= +156.08 (C= 0.13% in $CHCl_3$). IR (cm^{-1}): C=O (1735), C=N (1580), C-N (1330), C-S (690), and S-S (470). The PMR signals displayed for $COCH_3$ protons at δ 1.09, Ar-H at δ6.7-7.6 and pyranosyl ring protons at δ3.9-4.2 and δ4.6-5.2ppm.

Antimicrobial activity:

To each sterilized test tube 5ml nutrient broth was transferred, stock solutions of different samples (0.1 or 0.05ml) were added. The resultant system was then inocculated with Staphylococcus aureus and E.coli. The second set of systems containing, 5ml nutrient broth and 1ml dimethyl sulphoxide was prepared. These reference systems were also inoculated by S.aureus and E.coli, respectively. Two sets of systems were kept in incubator at 37^{0}C at an interval of 24 hours. The growths of the microorganisms were recorded with respect to standard.

RESULTS AND DISCUSSION

Two series of compounds viz. 1-tetra-O-acetyl-β-D-glucopyranosyl-3-mono/di/trichlorophenyl thiocarbamides (3) and 3-phenyl/p-chlorophenyl, 4-mono/di/trichlorophenylimino,5-tetra-O-acetyl-β-D-glucopyranosylimino-1,2,4-dithiazolidines (5) were synthesized, the (3) by the interaction of tetra-O-acetyl-β-D-glucopyranosyl-isothiocyanate (1) and mono/di/trichloroanilines (2) and (5) were synthesized by the interaction of (3) and S-chloro-N-phenyl/p-chlorophenyl isothiocarbamoyl chlorides (4).

In a typical preparation of 3a, interaction of tetra-O-acetyl-β-D-glucopyranosyl isothiocynate (1) and p-chloroaniline (2a) has been carried out in boiling benzene medium for 3 hours. The solvent on distilling off gave sticky solid which on trituration with petroleum ether (60-80^{0}) gave granular solid. It was crystallized from 50% aqueous ethanol, m.p.162^{0}C. Its molecular formula was established as $C_{21}H_{25}N_2SO_9Cl$. It gave positive lead plumbite test

indicating the presence of C=S group. It was optically active. The IR of 3a indicated bands due to υNH, υ C=O and υC=S groups. The PMR spectrum displayed signals due to acetyl protons, NH protons, aromatic proton and pyranosyl proton as well as doublet due to β-glucopyranosyl ring proton. Similarly, other compounds (3a-3f) have been prepared from (1) by extending above reaction to other chloroanilines (2b-2f). In a typical preparation of 5a (where R=R1=R3=H and R2=R4=Cl), the interaction of a reagent S-chloro–N-p chlorophenyl isothiocarbamoyl chloride [9] (4a) and 1-p-chlorophenyl-3-tetra-O-acetyl -β-D-glucopyranosyl thiocarbamide (3a) in boiling benzene medium for 4 hours eliminated hydrogen chloride. On distilling off the solvent, the resultant viscous mass was triturated several times with petroleum ether (60-80) followed by ethanol, a white solid crystallized from ethanol, m.p. 190^0C was isolated. The elemental analysis of the product indicated the molecular formula as $C_{28}H_{27}N_3S_2O_9Cl_2$. It gave negative alkaline lead plumbite test indicating absence of C=S group. It was found optically active. The UV of the product showed λ max at 240nm. The IR indicated the presence of υC=O, υC=N, υC-S and υS-S bands. The PMR spectrum of the product distinctly displayed the signals due to aromatic, acetyl and pyranosyl ring protons. The mass spectrum [10] of the product showed presence of molecular ion peak at m/e = 684. Other important fragment peaks were located at m/e 330,263,200,169 etc.

On the basis of all the above facts the compound with m.p. 190^0C was assigned the structure 3-p-chloro-phenylimino-4-p-chlorophenyl-5-tetra-O-acetyl-β-D-glucopyranosylimino-1,2,4-diathiazolidine (5a).

The above reaction was extended to other dichloro-trichloro thiocarbamides (3b-3d) and S-chloro-N-p-chlorophenyl/ phenyl isothiocarbamoyl chlorides (4a,b) and corresponding (5b-h) have been isolated.

Antimicrobial study of the synthesized compounds (3and 5) were carried out using S.aureus and E.coli as the microorganism for study. 3C has shown some antimicrobial activity against S.aureus , while others were inactive.In the 1,2,4-dithiazolidine series the 5b has shown excellent activities against both S.aereus and E.coli while 5a has been found to be active against both organisms 5e and 5f were found to be active against S. aereus only while 5d was active against E.coli only. Ampicillin was used as standard drug during this work.

CONCLUSION

Synthesis of polyhalogenated aryl 1,2,4-dithiazolidines with N-glucosylatedimino group have been achieved and they have been shown to possess some antimicrobial activity against different antibacterial strains like S. aureus and E.coli.

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