Antibacterial and Antifungal Activities of Some Novel Thiolactosides

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A series of novel thiolactosides like S-hepta-O-acetyllactosyl-1-arylisothiocarbamides (1a-g) and hepta-O-acetyl lactosyl arylthiociarbamates (2a-g) were prepared by the interaction of hepta-O-acetyl lactosyl bromide with arylthiocarbamides and ammonium arylthiocarbamates respectively. Similarly (hepta-O-acetyl lactosyl)-1,5-disubstituted-2-isothiobiurets (3a-g), 1,5-disubstituted-2,4-isodithiobiurets (4a-g) and 1,2,4-thiadiazolines (5a-g) were synthesized by the interaction of (1a-g) with phenyl isocyanate, phenyl isothiocyanate and S-chloro-N-phenyl isothiocarbamoyl chloride respectively. The compounds 3-Aryl-2,6-diphenylimino 4-S-hepta-O-acetyl lactosyl-2,3dihydro-1,3,5-thiadiazines hydrochlorides (6a-g) were prepared by the interaction of (4a-g) with phenyl isocyanodichloride. In the present investigation activities of these thiolactosides against pathogenic bacteria and fungi such as E. coli, S. aureus, P. vulgaris, Salmonella typhi, Candida guillermondii and A. niger are discussed.

Thiolactosides are those compounds in which lactosyl group or its derivatives are attached to the sulphur of the sulphur containing compounds. This class of compounds has several applications in industries, medicinal chemistry and in many other ways1,2. Literature survey revealed that the heterocyclic derivatives of sugars possess antibacterial and antitumor activity3. Benzothiazole derivatives found to exhibit anticancer, antiHIV and antimalerial activity4-8. With this end in view, we recently reported the synthesis of several thiolactosides9-12. Scheme-1. In the present investigation, activities of these thiolactosides against pathogenic bacteria and fungi such as E. coli, S. aureus, P. vulgaris, Salmonella typhi, Candida guillermondii and A. niger are reported.

Melting points were determined on an electrothermal melting point apparatus and were uncorrected. The structures of the synthesized compounds were elucidated on the basis of elemental analysis and IR13-16. 1H NMR14,19 and Mass20-22 spectral studies (Table-1). IR spectra were recorded in KBr on a FT IR PerkinElmer (4000-450 cm-1) spectrophotometer. 1H NMR spectra are run on Brucker DRX 300 instrument operating at 300 MHz using CDCl3 solution with TMS as internal standard and mass spectra on Jeol SX 102 FAB instrument.

Solutions of hepta-O-acetyl lactosyl bromide and arylthiocarbamides in isopropyl alcohol were kept at room temperature for 18 h. It was mixed with distilled water and basified with aqueous ammonia to yield a sticky mass. The sticky mass was purified with ethanol-water furnished a granular solids of S-hepta-O-acetyl lactosyl-1-arylisothiocarbamides (1a -g)9.

Solutions of hepta-O-acetyl lactosyl bromide and ammonium arylthiocarbamates in isopropyl alcohol were kept at room temperature for 18 h. Upon adding distilled water, a sticky mass was separated. The sticky mass was purified with ethanol-water to give hepta-O-acetyl lactosyl arylthiocarbamates10 (2a-g).

An equimolar (0.0025 mol) mixture of S-hepta-O-acetyl lactosyl-1-arylisothiocarbamides (1a-g) and phenyl isocyanate in dry benzene was kept at room temperature for 24 h. The benzene was distilled off. The sticky mass thus obtained was triturated several times with petroleum ether to obtain S-hepta-O-acetyl lactosyl-1-aryl-5-phenyl-2-isothiobiurets11 in the form of granular solids (3a-g).

Condensation of S-hepta-O-acetyl lactosyl-1-arylisothiocarbamides (1a-g) with phenyl isothiocyanate in benzene was carried out for 9 h. The benzene was distilled off. The sticky mass obtained when triturated several times with petroleum ether furnished S-hepta-O-acetyl lactosyl-1-aryl-5-phenyl-2,4-isodithiobiurets11 as granular solids (4a-g).

Condensation of an equimolar (0.0025 mol) mixture of S-hepta-O-acetyl lactosyl-1,5-disubstituted-2,4-isodithiobiurets
<table>
<thead>
<tr>
<th>Comp</th>
<th>Mol. Formula</th>
<th>IR(KBr) cm⁻¹</th>
<th>¹H NMR (ppm)</th>
<th>Mass (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>C₂₆H₂₄O₇NS₂</td>
<td>3350,2970,1751,1635, 1439,1229,1050,758</td>
<td>δ 6.7-6.8 (m, 5H, Ar), δ 5.6-5.3 (2H, s, NH)</td>
<td>(M⁺)+1771,619,3</td>
</tr>
<tr>
<td>1b</td>
<td>C₂₆H₂₄O₇NS₃Cl</td>
<td>3348,2965,1751,1636, 1437,1229,1051,759</td>
<td>δ 7.5-7.0 (m, 5H, Ar), δ 6.5-6.1 (2H, s, NH)</td>
<td>31,229,169,127,109</td>
</tr>
<tr>
<td>1c</td>
<td>C₂₆H₂₄O₇NS₄</td>
<td>3458,2969,1751,1642, 1437,1228,1050,755</td>
<td>δ 7.2-6.9 (m, 4H, Ar), δ 5.3-5.2 (2H, s, NH)</td>
<td>(M⁺)+805,619,</td>
</tr>
<tr>
<td>1d</td>
<td>C₂₆H₂₄O₇NS₅</td>
<td>3408,2964,1753,1443, 1239,1722,1052,760</td>
<td>δ 7.9-7.1 (m, 5H, Ar), δ 6.8-6.6 (2H, s, NH)</td>
<td>31,229,169,127,109</td>
</tr>
<tr>
<td>2a</td>
<td>C₂₆H₂₄O₇NS₆</td>
<td>3465,3000,1752,1633, 1434,1228,1050,756</td>
<td>δ 7.8-7.0 (m, 10H, Ar), δ 5.8-5.2 (2H, s, NH)</td>
<td>(M⁺)+890,619,311</td>
</tr>
<tr>
<td>2b</td>
<td>C₂₆H₂₄O₇NS₇</td>
<td>3350,3000,1754,1630, 1442,1226,1049,750</td>
<td>δ 7.8-6.8 (m, 9H, Ar), δ 5.5-5.3 (2H, s, NH)</td>
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</tr>
<tr>
<td>2c</td>
<td>C₂₆H₂₄O₇NS₈</td>
<td>3458,2969,1751,1642, 1437,1228,1050,755</td>
<td>δ 7.5-6.9 (m,10H, Ar), δ 4.7-4.4 (2H, s, NH)</td>
<td>(M⁺)+905,619,311</td>
</tr>
<tr>
<td>2d</td>
<td>C₂₆H₂₄O₇NS₉</td>
<td>3488,2965,1752,1636, 1437,1228,1051,759</td>
<td>δ 7.5-7.2 (m,10H, Ar), δ 5.1-4.9 (2H, s, NH)</td>
<td>29,169,127,109</td>
</tr>
<tr>
<td>2e</td>
<td>C₂₆H₂₄O₇NS₁₀</td>
<td>3458,2969,1751,1642, 1437,1228,1050,755</td>
<td>δ 7.2-6.9 (m,10H, Ar), δ 5.3-5.2 (2H, s, NH)</td>
<td>(M⁺)+919,619,311</td>
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<tr>
<td>2f</td>
<td>C₂₆H₂₄O₇NS₁₁</td>
<td>2974,1749,1598,1542, 1231,1054,757</td>
<td>δ 7.6-7.2 (m,15H, Ar), δ 5.3-3.6 (2H, s, NH)</td>
<td>29,169,127,109</td>
</tr>
<tr>
<td>3a</td>
<td>C₂₆H₂₄O₇NS₁₂</td>
<td>2982,1750,1597,1493, 1231,1054,757</td>
<td>δ 7.6-7.2 (m,15H, Ar), δ 5.3-3.6 (2H, s, NH)</td>
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<tr>
<td>3b</td>
<td>C₂₆H₂₄O₇NS₁₃</td>
<td>2974,1749,1596,1512, 1230,1052,757</td>
<td>δ 7.6-6.9 (m,14H, Ar), δ 5.3-3.3 (2H, s, NH)</td>
<td>(M⁺)+1056,619,311,</td>
</tr>
</tbody>
</table>

R = a) phenyl, b) O-Cl-phenyl, c) m-Cl-phenyl, d) p-Cl-phenyl, e) o-tolyl, f) m-tolyl, g) p-tolyl and Ph = phenyl

All the compounds have been screened for both antibacterial and antifungal activity using cup plate agar diffusion method\textsuperscript{23,24} by measuring the inhibition zone in mm. The compounds were taken at a concentration of 1 mg/ml using dimethyl formamide (DMF) as solvent. Amikacin (100 µg/ml) was used as a standard for antibacterial activity and fluconazole (100 µg/ml) as a standard for antifungal activity. The compounds were screened for antibacterial activity against \textit{Escherichia coli}, \textit{Staphylococcus aureus}, \textit{Proteus vulgaris}, and \textit{Salmonella typhi} in nutrient agar medium and for antifungal activity against \textit{Candida guilliermondii} and \textit{Microsporum} in potato dextrose agar medium. These sterilized agar media were poured in to Petri dishes and allowed to solidify. On the surface of the media microbial suspensions were spread with the help of sterilized triangular loop. A stainless steel (4a-g) and phenyl isocyanodichloride in chloroform was carried out for 2.5 h. The excess of chloroform was distilled off. The sticky mass obtained was triturated with petroleum ether to separate 3-aryl-2,6-diphenylimino-4-hepta-O-acetyl lactosyl-2,3-dihydro-1,3,5-thiadiazine hydrochlorides\textsuperscript{12} as granular solids (5a-g).

Fig. 1: Scheme 1: Synthesis of several thiolactosides
R = a) Phenyl, b) O-Cl-phenyl, c) m-Cl-phenyl, d) p-Cl-phenyl, e) o-tolyl, f) m-tolyl, g) p-tolyl and Ph = Phenyl
It has been observed that some of these compounds exhibited interesting microbial activities. 1, 2, 3, 4, and 2 exhibited most significant activity against Salmonella. 1 inhibited E. coli while 3e inhibited S. aureus and P. vulgaris, respectively. All other compounds exhibited low to moderate activity (Table 2).

The results of antifungal activity are also tabulated in Table 2. 2, 3, 4, and 5 are effective towards Candida guilliermondii while other exhibited moderate to low activity. 1, 3, 3, 4, 4, 5, and 5 are effective against Microsporum while others exhibited moderate to low activity (Table 2).

Thus, the novel thiolactosides synthesized, exhibits comparable antibacterial and antifungal activities against the organisms tested. The method adopted in this investigation is simple, efficient, inexpensive, and is useful in synthesizing pharmacologically important molecules.

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