Synthesis And Biological Importance Of -1,3,5-Thiadiazines As Antibacterial And Antifungal Agents

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Abstract - Variety of 3-Aryl-4S-benzyl-6p-tolylimino-2-phenylimino-2,3-dihydro-1,3,5-thiadiazines were synthesized by the interaction of phenyl isocyanodichloride with various 1-Aryl-5p-tolyl-2S-benzyl-2,4-isodithiobiuretes respectively in refluxing chloroform medium and were screened for their antibacterial and antifungal activities against some selected pathogenic organisms like Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhimurium, Klebsiella pneumoniae, Psudomonas aeruginosa, Aspergillus Niger and Candida albicance. These compounds show appreciable activity towards these microorganisms. The identities of these newly synthesized -1,3,5-thiadiazines have been established on the basis of elemental analysis, IR, ¹HNMR and MASS spectral studies.

The literature survey reveals that the heterocyclic compounds having 1, 3, 5-thiadiazines nucleus enhanced pharmaceutical, medicinal, agricultural and industrial values. The high synthetic versatility exhibited by the isothiocyanate moiety has allowed its use as a building block in the preparation of a variety of derivatives. In carbohydrates, the strong electrophilicity shown by isothiocyanates, together with the possibility of undergoing cyclization reaction has made it possible to access a broad spectrum of heterocyclic compounds, of either synthetic or pharmaceutical interest.

Key words - Phenyl isocyanodichloride, 2,4-isodithiobiuretes, 1,3,5-thiadiazines, Antimicrobial activity
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Introduction

1, 3, 5-thiadiazines and their rearranged product 1, 3, 5-triazines have been shown to possess brightening and fiber finishing properties in textile industry¹², symmetric triazines have also been used as chain lengthening agents in polyurethane, polymerization¹, azodye, paints, plastic and rubber⁴. They are also used as fungicidal³, insecticidal⁵, and as medicinal compounds. The literature survey reveals that the heterocyclic compounds having 1, 3, 5-thiadiazines nucleus enhanced pharmaceutical, medicinal, agricultural and industrial values.

The chemistry of heterocyclic compounds continues to explore the field of carbohydrate chemistry. Literature survey also revealed that the heterocyclic derivatives of sugar possess antimicrobial⁷⁹, and antitumor activity¹⁰¹². Thiadiazines and their derivatives acts as antifibrinolytic¹³, cardiotonic¹⁴, anesthetic, cardiovascular and hypometabolic agents¹⁵. It is also used as fungicidal¹⁶, insecticidal¹⁷ as well as medicinal compounds.

Results and discussion

Several 3-Aryl-4-benzyl-6-p-tolylimino-2-phenylimino-2,3-dihydro-[1,3,5] thiadiazine [Hydrochloride] (3a-j) have been synthesized by the interaction of 1-Aryl-5-p-tolyl-2-S-benzyl-2,4-isodithiobiurets (2a-j) and phenyl isocyanodichloride (1). To the chloroform suspension of Phenyl isothiocyanate chlorinated on chlorination assembly. This chlorinated solution was added to 1-Aryl-5-p-tolyl-2-S-benzyl-2,4-isodithiobiuret in chloroform medium. Then the reaction mixture was reflux for 3 hrs. and a sticky mass obtained as a residue was triturated several times with petroleum ether (60-80°C). A product will separate out.
The IR spectra of products shows bands due to Ar-H, N-H, C=N, C-N, C-S stretching and ¹H NMR spectra of products distinctly displayed signals due to aromatic protons and aliphatic Protons. The Mass spectrum of product was also observed. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformations and also IR, ¹H NMR and Mass spectral studies.

METHODOLOGY

General Methods

All chemicals were research grade. Melting points determined are uncorrected. IR spectra were recorded in KBr on a FT-IR Perkin-Elmer RXI(4000-450cm⁻¹) spectrophotometer. ¹H NMR measurements were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in CDCl₃ solution with TMS as internal reference. The Mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap Mass spectrometer. Thin layer chromatography (TLC) was performed on silica Gel G and spots were visualized by iodine vapour. The compounds were screened for their antibacterial and antifungal activities by the disc diffusion assay method. The compounds describe in this paper were first time synthesized by the multistep reaction protocol.

1|Synthesis of 3-Aryl-4-S-benzyl-6-p-tolylimino-2-phenylimino-2,3-dihydro-[1,3,5] thiadiazine[Hydrochloride] (Scheme 3)

3-Aryl-4-S-benzyl-6-p-tolylimino-2-phenylimino-2,3-dihydro-[1,3,5] thiadiazine[Hydrochloride] was prepared by the interaction of 1-Aryl-5-p-tolyl-2-S-benzyl-2,4-isodithiobiurets and phenyl isocyanodichloride in chloroform medium. A chloroform solution of Phenyl isocyanodichloride was mixed with the chloroform solution of 1-Aryl-5-p-tolyl-2-S-benzyl-2,4-isodithiobiuret. Then the reaction mixture was reflux on boiling water bath for 3 hr during which evolution of HCl was noticed. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was brought to room temperature and the solvent removed under reduced pressure to obtain residue. This residue was triturated several times with petroleum ether (60-80°C) to afford a pale yellow solid.

Scheme 1-

\[
\text{Ph-N=C=S} \xrightarrow{\text{KMnO}_4} \text{Ph-N=C-Cl} \xrightarrow{\text{HCl}} \text{Ph-N=C-Cl}
\]

Scheme 2-

[Chemical structures of 1-Aryl-5-p-tolyl-2-S-benzyl-2,4-isodithiobiurets]

Scheme 3-

[Chemical structures of 3-Aryl-4-S-benzyl-6-p-tolylimino-2-phenylimino-2,3-dihydro-[1,3,5] thiadiazine[Hydrochloride]]
When the reaction of phenyl isocyanodichloride was extended to several other 1-dihydro-
6.91 (19H, m, Ar. H), δ 4.27

Where, R= (a) Phenyl, (b) o-Cl-phenyl, (c) m-Cl-phenyl, (d) p-Cl-phenyl, (e) o-NO₂-phenyl, (f) m-NO₂-phenyl, (g) p-NO₂-phenyl

3a: IR (KBr):υ 3201 (Ar-H), 2877 (Ali-H), 1523 (C=N), 1450 (C-C), 1323 (C-N), 694 (C-S). H NMR (δ in ppm, CDCl₃): δ 7.63 - 6.91 (19H, m, Ar. H), δ 4.27 - 2.26 (5H, m, Ali. H) Mass (m/z): 490 (M⁺), 477, 387, 300, 91; Anal. Calcd for C₂₉H₂₃N₆S₂: C, 70.73; H, 4.87; N, 11.38; S, 13.00; Found: C, 70.70; H, 4.85; N, 11.40; S, 13.04.

On the basis of all above facts the product with m. p. 98°C was assigned the structure 3-Phenyl-4-S-benzyl-6-p-tolylimino-2-phenylimino-2,3-dihydro- [1,3,5] thiadiazine [Hydrochloride]

When the reaction of phenyl isocyanodichloride was extended to several other 1-Aryl-5-p-tolyl-2-S-benzyl-2,4-isothiobiurets corresponding 3-Aryl-4-S-benzyl-6-p-tolylimino-2-phenylimino 2,3-dihydro- [1,3,5] thiadiazine [Hydrochloride] has been synthesized.

3c: IR (KBr):υ 3030 (Ar-H), 2872 (Ali-H), 1566 (C=N), 1475 (C-C), 1267(C-N), 792 (C-S). H NMR (δ in ppm, CDCl₃): δ 7.62-7.21 (18H, m, Ar. H), δ 4.57- 2.38 (5H, m, Ali. H) Mass (m/z): 526 (M⁺), 425, 403, 91; Anal. Calcd for C₂₉H₂₃N₆S₂Cl: C, 66.09; H, 4.36; N, 10.63; S, 12.15; Found: C, 66.05; H, 4.33; N, 10.67; S, 12.18.

3g: IR (KBr):υ 3062 (Ar-H), 2895 (Ali-H), 1504 (C=N), 1481 (C-C), 1303(C-N), 754(C-S). H NMR (δ in ppm, CDCl₃): δ8.08-6.56 (18H, m, Ar. H), δ 4.42- 1.59 (5H, m, Ali. H) Mass (m/z): 537 (M⁺), 490, 462, 404, 390, 91; Anal. Calcd for C₂₉H₂₃N₆S₂O₂: C, 64.80; H, 4.28; N, 13.03; S, 11.91; Found: C, 64.85; H, 4.25; N, 13.08; S, 11.95;.

Table -1: Physical data for characterization of compounds (3a-g)

<table>
<thead>
<tr>
<th>Compd</th>
<th>Yield %</th>
<th>Rf</th>
<th>M.P. °C</th>
<th>Analysis (%)</th>
<th>Found (calc)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>S</td>
</tr>
<tr>
<td>3a</td>
<td>80.00</td>
<td>0.67</td>
<td>98</td>
<td>11.40(11.38)</td>
<td>13.04(13.00)</td>
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</table>
Antimicrobial activity:
All the compounds have been screened for both; antimicrobial and antifungal activity by using disc diffusion assay. For this, sterlial filter paper disc (6 mm) impregnated with fixed doses of compounds was placed on pre-inneculated surface. The disc bearing plates were incubated at 37°C for 24 h. After incubation, zone diameter were measured. The compounds were taken at a concentration or 1 mg/mL using dimethyl sulphoxide as a solvent. Amikacin (100 μg/mL) was used as standard for antibacterial and fluconazole (100μg/mL) as a standard for antifungal activity. The compound were screened for antibacterial activity against Eschrichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhi, and Psudomonas aeruginosa in nutrient agar medium and for, antifungal activity against Aspergillus niger and Candida albicance in potato dextrose agar medium. It has been observed that all the compounds showed good activity against both; bacteria and fungi.

C and H analysis was found satisfactory in all cases.

### Table

<table>
<thead>
<tr>
<th>Compound</th>
<th>E. coli</th>
<th>S. aureus</th>
<th>P. vulgaris</th>
<th>P. aeruginosa</th>
<th>S. typhi</th>
<th>A. niger</th>
<th>C. albicance</th>
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<tbody>
<tr>
<td>1(3a)</td>
<td>17</td>
<td>16</td>
<td>20</td>
<td>19</td>
<td>18</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>2(3b)</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>12</td>
<td>20</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>3(3c)</td>
<td>18</td>
<td>14</td>
<td>19</td>
<td>17</td>
<td>15</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>4(3d)</td>
<td>14</td>
<td>19</td>
<td>--</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>5(3e)</td>
<td>16</td>
<td>19</td>
<td>17</td>
<td>14</td>
<td>18</td>
<td>20</td>
<td>21</td>
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<tr>
<td>6(3f)</td>
<td>11</td>
<td>08</td>
<td>19</td>
<td>15</td>
<td>16</td>
<td>21</td>
<td>--</td>
</tr>
<tr>
<td>7(3g)</td>
<td>18</td>
<td>16</td>
<td>16</td>
<td>--</td>
<td>20</td>
<td>18</td>
<td>--</td>
</tr>
<tr>
<td>Amikacin</td>
<td>18</td>
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<td>23</td>
<td>19</td>
<td>20</td>
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<tr>
<td>Fluconazole</td>
<td>24</td>
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### Table

<table>
<thead>
<tr>
<th>Sample</th>
<th>Disc content</th>
<th>Resistant</th>
<th>Intermediate</th>
<th>Sensitive</th>
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<tbody>
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<td>Amikacin</td>
<td>100ug/ml</td>
<td>≤ 15 mm</td>
<td>16-20 mm</td>
<td>≥ 21 mm</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>100ug/ml</td>
<td>≤ 15 mm</td>
<td>16-20 mm</td>
<td>≥ 21 mm</td>
</tr>
</tbody>
</table>

Acknowledgement
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References: