SYNTHESIS, ANTIFUNGAL AND ANTI BACTERIAL ACTIVITY OF N-(4-CHLORO-2-TRIFLUOROACTYL PHENYL) - AMINOTHIAZOLE DERIVATIVES

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DOI: 10.7897/2230-8407.1004141

ABSTRACT

In this study, 1-(2-amino-5-chlorophenyl)-2,2,2-trifluoroethane was synthesized by reacting p-chloroaniline with ethyl trifluoroacetate in presence of n-butyl lithium, further reacting with ammonium thiocyanate with hydrochloric acid leads to 1-(4-chloro-2-(2,2,2-trifluoroacetyl)phenyl)urea. Then reacted with ArCOCH3Br and sodium acetate gave 1:-(5-chloro-2-(4-substituted-1, 3-thiazol-2-yl) amino) phenyl)-2,2,2-trifluoroethanone derivatives. The chemical structure of newly synthesized compounds has been confirmed on the basis of elemental analysis, IR, 1H NMR and Mass spectral data. The newly synthesized compounds were screened for their antibacterial activity invitro against Gram-positive bacteria namely Escherichia coli, Staphylococcus aureus, and Gram-negative bacteria namely Pseudomonas aeruginosa, Bacillus subtilis and the fungus namely Candida albicans by disc diffusion method. Among the synthesized compounds 5b, 5f, 5g, 5h, 5j were found to have a very good antibacterial and antifungal activity.

Key words: Aminothiazole, trifluoroethanone, thiosemicarbazone, antibacterial, antifungal.

INTRODUCTION

Now days due to increase in no of multi-disease, consumption of antibiotic drugs quantity is increasing because of this reason abnormal side effects have become predominant, therefore, pathogenic bacteria has developed resistance to beta lactam antibiotics. The thiazole and its derivatives are playing a very important role in medicinal chemistry. Its intermediates are used as synthetic drugs, dyes and fungicides. Due to the Therapeutic importance of heterocyclic compounds, chemists are showing more interest in the preparation of new heterocyclic compounds in order to explore their biodynamic properties. Nitrogen and sulfur containing organic compounds show wide range of biological activity. According to the literature survey 2-amino thiazole nucleus have been incorporated into a wide variety of therapeutically interesting candidates. Thiazoles Particularly are showing effective antimicrobial activity. Fungal infections are caused by microscopic organism that can invade the epithelial cells in immune compromised patients. Simple 2-aminothiazole is known as thyroid inhibitor. In market many 2-aminothiazole derivatives such as sulfathiazole and cefotibuten encouraging us to synthesize aminothiazole derivatives. Ritonavir is an anti-HIV agent, Nizatidine is an antacid used for the treatment of gastroesophageal reflux disease, dasatinib is an antineoplastic agent and rauvustanol is an antifungal agent. Thiazole derivatives not only show potent FabIl and FabK inhibitory activity, but also have an antibacterial effect. Abafungin is the low toxic thiazole containing antimicrobial present in market, which unlike imidazole and triazole antifungals directly impairs the fungal cell membrane and in addition inhibits stereo-2,4-methyl transformation modifying the composition of cell membrane, it also acts as antibiotic against Gram +ve bacteria. 5-fluorocytosine is an antifungal used along with amphotericin –B specifically for serious candida infection. Cefdinir is broad spectrum cephalosporin antibiotic used for treatment of pneumonia, chronic bronchitis, sinusitis, pharyngitis, tonsillitis. 4-Chloro-2-(trifluoroacetyl)aniline is one of the important pharmacophore found in the anti HIV Effavirenz, the fluorine containing moiety are most widely found in active pharma ingredients due its high biological activity. Due to the demand of the trend for more safe and effective antifungal agents made us to bring two different biologically active scaffolds like 2-aminothiazole and 4-Chloro-2-(trifluoroacetyl)aniline in one frame to synthesis new and novel thiazole derivative having very good antimicrobial activity.

MATERIALS AND METHODS

The general method to prepare the title compounds is outlined in scheme 1. The synthesis of 2-mercaptothiazoles was first attempted in a stepwise manner via the isolation of intermediate, Phenacyl bromides (1a-k) employed in the preparation of 2,4-disubstituted-1,3-thiazoles (5) are prepared by the reaction of various substituted acetophenones with bromine in chloroform at 0°C. However in few cases readily available phenacyl chlorides were used instead of phenacyl bromides. Further reaction of 4-Chloro-2-(trifluoroacetyl)aniline hydrochloride with ammonium thiocyanate was carried out by heating the mixture of 4-Chloro-2-(trifluoroacetyl)aniline hydrochloride with ammonium thiocyanate in presence of Hydrochloric acid and water yielded 1-[4-Chloro-2-(trifluoroacetyl) substituted phenyl] thiourea (4). 4-Chloro-2-(trifluoroacetyl)aniline (3) was in turn obtained by the reaction of p-chloroaniline with ethyl trifluoroacetate in presence of n-butyl lithium at -70°C. The Hantz reaction of 1-[4-Chloro-2-(trifluoroacetyl)phenyl] thiourea (4) with appropriate phenacyl bromides (1a-k) in aqueous alcoholic medium employing sodium
EXPERIMENTAL

Phenacyl bromides (1)

To a cold solution of substituted acetophenone (0.1mol) in chloroform (30mL), bromine (0.12mol) in chloroform (10mL) was gradually added (30 minutes) with continuous stirring and maintaining the temperature of the reaction mixture at 0°C. Then the reaction mixture was slowly brought to room temperature and stirring was continued for another 60 minutes until the evolution of hydrogen bromide gas ceased. Solvent was removed under reduced pressure. The solid that formed was washed with petroleum ether and collected by filtration, which is then recrystallized from minimum quantity of ethanol. Compounds prepared by this procedure are

a. Phenacyl bromide, m.p. 50°C (Lit50, 50°C).

b. 4-Nitropheny lacetyl)aniline

c. 4-Chloro phenacyl bromide, m.p. 98°C (Lit51, 98-99°C).

d. 2, 4-Dichlorophenacyl bromide, m.p. 103°C (Lit52, 105-107°C).

e. 4-Methyl phenacyl bromide, m.p. 61°C (Lit53, 61°C).

f. 4-Methoxy phenacyl bromide, m.p. 75°C (Lit53, 75-76°C).

g. 4-Hydroxy phenacyl bromide, m.p. 125°C (Lit55, 125-126°C).

h. 3-Androstene-3,17-dione, m.p. 176°C (Lit54, 176°C).

1-(4-Chloro-2-(trifluoroacetyl) substituted phenyl) thiourea (4)

A mixture of substituted aniline (0.1mol), concentrated hydrochloric acid (0.01mol), ammonium thiocyanate (0.015mol) and water (20mL) were mixed well with constant stirring for one hour at room temperature, and then refluxed for about four hours for completion of reaction. The reaction mixture was then poured on to crushed ice. The precipitate formed was collected by filtration, washed with water and recrystallized from ethanol.

1-(5-Chloro-2(4-substituted-1, 3-thiazol-2-yl) amino phenyl)-2, 2-trifluoroethanone (5a-k)

A mixture of 1-[4-Chloro-2-(trifluoroacetyl) substituted phenyl] thiourea (0.01mol), a pinch of sodium acetate in ethanol (10mL) and suitable bromoacetyl derivatives (0.01mol) was refluxed for 1-3 hours. The reaction mixture was then cooled to RT and the solid separated was collected by filtration, dried and recrystallized from ethanol. The yield, melting point and other characterization data of compounds prepared by this procedure are given in Table-1

**Table 1**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR ( νmax, cm⁻¹):</th>
<th>¹H-NMR (DMSO-d₆): δ, ppm, (s, 1H, NH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 5k</td>
<td>IR ((vmax, cm⁻¹): 3047(N-H), 2913 (C-H), 1564 (C=N); The ¹H-NMR(300 Hz DMSO-d₆): δ, 4.97 (s, 1H, NH)</td>
<td>7.57-7.72 (m, 2H, ArH), 7.73 (s, 1H, thiazole) 8.027-8.039 (m, 2H protons of p-fluoro phenyl), 7.72 (s, 1H)</td>
</tr>
<tr>
<td>Compound 5g</td>
<td>IR ((vmax, cm⁻¹): 3199(N-H), 2953 (C-H), 1584 (C=N), 1724 cm⁻¹ (c=O); The ¹H-NMR(300 Hz DMSO-d₆): δ, 8.027-8.039 (m, 2H, ArH), 7.827, (s, 1H, ArH), 7.796 (s, 1H, thiazole), 7.605-7.640 (2d, 2H ArH), 8.027-8.039 (m, 2H, ArH), 7.827 (s, 1H, ArH), 7.796 (s, 1H, thiazole), 7.54 (s, 1H ArH), 4.807 (s, 1H, NH) Mass: m/z, 382 (molecular formula C₁₇H₁₄Cl₂N₂SO)</td>
<td></td>
</tr>
<tr>
<td>Compound 5b</td>
<td>¹H NMR (DMSO-d₆): δ, 7.15 (1H, s), 7.158 (1H, NH), 4.0 (s, 1H, ArH), 7.35 (m, 2H, Ar-H), 7.358 (d, 2H, ortho protons of p-fluoro phenyl), 7.580 (d, 2H meta protons of p-fluoro phenyl)</td>
<td></td>
</tr>
</tbody>
</table>

RESULTS AND DISCUSSION

Antimicrobial studies

The newly synthesized compounds were screened for their antibacterial activity in vitro against Gram-positive bacteria namely Escherichia coli, Staphylococcus aureus, and Gram-negative bacteria namely Pseudomonas aeruginosa, Bacillus subtilis and the fungus namely Candida albicans by disc diffusion method19. The test compounds were dissolved in N, N-Dimethylformamide (DMF) to obtain a solution of 10mg/ml concentration. The inhibition zones of microbial growth produced by different compounds were measured at the end of an incubation period of 48 hours at 37°C. DMF alone showed no inhibition. Penicillin and Fluconazole were used as reference standards to evaluate the potency of the tested compounds. The results are presented in the Table 2.

This study reports the successful synthesis of the title compounds. The antimicrobial activity study revealed that some of the thiazoles possess significant antifungal activity.

The compounds 5a-k synthesized as per the outlined scheme (1) were purified by recrystallization and the purity was ascertained by TLC using Silica Gel Gas stationary phase. The instrumental data suggested the formation of the compounds as desired. Antimicrobial screening of the compounds was performed using four different strains of bacteria and one strain of fungi. Compounds 5b, 5c, 5f, 5g, 5h, 5j showed good activity against three different Microbial strains (bacteria). The structural make up of the compounds were thought of to be responsible of their antimicrobial activities.

The compounds 5b, 5f, 5g, 5h, 5j showed very good activity against microbial fungal strains even better than the standard, the structural makeup of the compounds were thought of to be responsible for their antimicrobial activities. Compounds 5b, 5f, 5h, 5j are having a 4-Chloro-2-(trifluoroacetyl)aniline at 2nd position and 4-fluorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 4-nitrophenyl, 2-chloro-2-sulphanidimethane thiophene and 2,4-dibromocoumarin group as aromatic substituent.

Due to the presence of 4-Chloro-2-(trifluoroacetyl)aniline at 2nd position of 1, 3-thiazole nucleus. The aryl group gives the compound extra stability while entering the bacterial cell membrane and the thiol group enhances penetration into fungal cell wall. Introduction of chloro (Cl) moiety at 4-position into the aromatic ring attached to the thiazole nucleus resulted in poor antimicrobial activity with less antifungal activity, i.e. compound 5d showed poor activity. Further substituted aniline attached to the thiazole nucleus leads very good antimicrobial activity. Compound containing a 5-Chlorothiophene-2-sulfonamide moiety attached to the thiazole nucleus further enhances the lipophilicity of the molecule enabling it to penetrate the microbial cell more easily, thus showing good activity.
Table 1: Characterization data of compound 5a-k

<table>
<thead>
<tr>
<th>Compd No</th>
<th>Ar</th>
<th>M.P (°C)</th>
<th>Yield %</th>
<th>Color</th>
<th>Molecular Formula (M. W)</th>
</tr>
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<tbody>
<tr>
<td>5a</td>
<td>Methyl phenyl</td>
<td>225-28</td>
<td>68</td>
<td>Cream</td>
<td>C_{18}H_{12}ClF_3N_2OS</td>
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<tr>
<td>5b</td>
<td>4-Fluorophenyl</td>
<td>230-231</td>
<td>55</td>
<td>Light yellow</td>
<td>C_{17}H_{11}ClF_3N_2OS</td>
</tr>
<tr>
<td>5c</td>
<td>4-Chlorophenyl</td>
<td>196-198</td>
<td>60</td>
<td>Yellowish brown</td>
<td>C_{17}H_{11}ClF_3N_2OS</td>
</tr>
<tr>
<td>5d</td>
<td>4-Amino-2-hydroxyphenyl</td>
<td>198-200</td>
<td>72</td>
<td>Yellow</td>
<td>C_{17}H_{11}ClF_3N_2OS</td>
</tr>
<tr>
<td>5e</td>
<td>5-Aminophenyl</td>
<td>140-42</td>
<td>67</td>
<td>Yellow</td>
<td>C_{17}H_{11}ClF_3N_2OS</td>
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<tr>
<td>5f</td>
<td>4-Nitrophenyl</td>
<td>150-52</td>
<td>76</td>
<td>Yellow crystalline</td>
<td>C_{17}H_{11}ClF_3N_2OS</td>
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<tr>
<td>5g</td>
<td>2,4-Dichlorophenyl</td>
<td>104-06</td>
<td>78</td>
<td>Pale yellow</td>
<td>C_{17}H_{11}ClF_3N_2OS</td>
</tr>
<tr>
<td>5h</td>
<td>5-Chloro-2-sulphanamide thiophene</td>
<td>184-86</td>
<td>64</td>
<td>Yellowish orange</td>
<td>C_{16}H_{8}ClF_3N_2OS</td>
</tr>
<tr>
<td>5i</td>
<td>9h-Carbazole</td>
<td>168-70</td>
<td>65</td>
<td>Yellow</td>
<td>C_{17}H_{11}ClF_3N_2OS</td>
</tr>
<tr>
<td>5j</td>
<td>2,4-Dibromocoumarine</td>
<td>194-96</td>
<td>56</td>
<td>Deep yellow</td>
<td>C_{21}H_{9}BrClF_3N_2OS</td>
</tr>
<tr>
<td>5k</td>
<td>Phenyl</td>
<td>169-70</td>
<td>65</td>
<td>White</td>
<td>C_{17}H_{10}ClF_3N_2OS</td>
</tr>
</tbody>
</table>

Solvent for recrystallization: ethanol.

Table 2: Antibacterial and antifungal data of compounds (5a-k)

<table>
<thead>
<tr>
<th>Compd No</th>
<th>E.coli (MIC in µg/mL)</th>
<th>Aures (MIC in µg/mL)</th>
<th>P.aeruginosa (MIC in µg/mL)</th>
<th>B.subtitis (MIC in µg/mL)</th>
<th>C.albicans (MIC in µg/mL)</th>
</tr>
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<tbody>
<tr>
<td>5a</td>
<td>12.5</td>
<td>25</td>
<td>6.25</td>
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<tr>
<td>5b</td>
<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
<td>3.12</td>
</tr>
<tr>
<td>5c</td>
<td>6.25</td>
<td>3.12</td>
<td>6.25</td>
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<tr>
<td>5d</td>
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<td>12.5</td>
<td>6.25</td>
<td>6.25</td>
<td>12.5</td>
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<tr>
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<td>6.25</td>
<td>12.5</td>
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<td>6.25</td>
<td>6.25</td>
<td>3.12</td>
<td>3.12</td>
<td>3.12</td>
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<tr>
<td>5i</td>
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<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
</tr>
<tr>
<td>5j</td>
<td>6.25</td>
<td>12.5</td>
<td>3.12</td>
<td>12.5</td>
<td>3.12</td>
</tr>
<tr>
<td>5k</td>
<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
</tr>
</tbody>
</table>

Standard: Penicillin
- 0.12

Standard: Fluconazole
- 8.0

Reaction scheme 1

(1) \( \text{Ar-COCH}_3 \xrightarrow{\text{Br}_2/\text{Acetic acid}} 0 \, ^\circ \text{C} \xrightarrow{} \text{Ar-COCH}_2\text{Br} \)

(2) \( \text{Cl-} \text{NH}_2 \xrightarrow{\text{CF}_3\text{CO}_2\text{C}_2\text{H}_5/\text{nButLi}} \text{Cl-} \text{CF}_3 \text{CF}_3 \text{NH}_2 \)

(3) \( \text{Cl-} \text{CF}_3 \text{CF}_3 \text{NH}_2 \xrightarrow{\text{NH}_2\text{SCN/cone.HCl}} \text{Cl-} \text{CF}_3 \text{CF}_3 \text{NH}_2 \)

(4) \( \text{Cl-} \text{CF}_3 \text{CF}_3 \text{NH}_2 \xrightarrow{\text{ArCOCH}_2\text{Br/sodiumacetate}} \text{Cl-} \text{CF}_3 \text{CF}_3 \text{NH}_2 \text{Ar} \)

(5a-k) \( \text{Cl-} \text{CF}_3 \text{CF}_3 \text{NH}_2 \xrightarrow{} \text{Cl-} \text{CF}_3 \text{CF}_3 \text{NH}_2 \text{Ar} \)

Figure: 01. 5g-2-4 chlorophenyl

Figure: 02.5b-4-Flurophenyl
CONCLUSION

This work describe the synthesis of 2-aminothiazole derivatives. The synthesized compounds were characterized by IR, HNMR and mass spectral studies, all compounds were screened for antibacterial and antifungal activity. Out of the sixteen compounds hereby reported that compound Sh, Sf, Sh, Sj showed the best activity against microbial strains Candida albicans with an MIC of 3.12 mg/ml. The activity is found to be better than standard.

ACKNOWLEDGEMENTS

We are grateful to the management of Sequent Scientific Ltd., New Mangalore. The authors are thankful to IISC Bangalore and CDRI, Lucknow, India for providing spectral data.

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Cite this article as:

Source of support: Nil, Conflict of interest: None Declared

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