Anti-tubercular Activity of 6[6-fluoro-7-substituted-(1,3)benzothiazolyl-2-aminosulphonyl](5z)-5[2-hydroxybenzylidine-2-phenyl-3,5-dihydro-4H-4-imidazolonyl]-2-methyl-4-oxo-3,4-dihydroquinazolines.

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ABSTRACT

Some novel 6[6-fluoro-7-chloro-(1,3)benzothiazolyl-2-aminosulphonyl](5z)-5[2-hydroxybenzylidine-2-phenyl-3,5-dihydro-4H-4-imidazolonyl]-2-methyl-4-oxo-3,4-dihydroquinazoline containing different functional groups have been synthesized by treating substituted 2-amino benzothiazoles with 3-carboxy-4-N-acetylamine benzene sulphonyl chloride in presence of ethanol and pyridine, further it is treated with hydrazine hydrate then followed by oxazolone in presence of pyridine. The structure of these compounds was characterized by means of physical constants, elemental analysis, solubility tests, TLC and by UV, IR, NMR and Mass spectral studies. Some of the compounds were evaluated for in-vitro anti-tubercular activity. Compounds showed significant activity as comparing with that of standard.

KEY WORDS: Benzothiazole, Sulphonamide, Quinazoline, Anti-tubercular activity.

1. INTRODUCTION

The new generation antibiotics incorporated with fluorobenzene moiety proved their efficacy as potent bio active molecules [3]. Now a days vast number of compounds with Fluorobenzene moiety features in diverse areas like antibacterial, antifungal, anti-inflammatory, psychoactive agents, pesticides, herbicides etc [1]. Sulphonamides elicit wide varieties of anti-tubercular [1] and anti-microbial activity [14-17]. While quinazolines reported various activities [18-21]. Based on these observations we have synthesized some Fluoro-Benzothiazolo-sulphonamido quinazoline derivatives starting with fluorochloroaniline, in hope of getting pharmacological agents with broad spectrum of anti-tubercular activity [22].

2. MATERIAL AND METHODS

2.1. General

The melting points were recorded by open capillary method and are uncorrected. Analytical data is given in table 1. IR spectra (? max in cm-1) were recorded on a Shimadzu FTIR 8400 spectrophotometer, using KBr pellets. 1HNMR spectra were recorded on Bruker 300 MHz using tetramethyl silane (TMS) as an internal standard and CDCl3 as a solvent. Chemical shifts are given in parts per million (ppm). Mass spectra are recorded on LCMS.

2.2.1. Condensation of 2-amino-6-fluoro-7-chloro-(1,3)benzothiazole and 3-carbethoxy-4-N-acetylaminobenzene sulphonylchloride (II)

A mixture of 3-carboxy-4-N-acetylamino benzencesulphonyl chloride (2.77g, 0.01mol), 2-amino-6-fluoro-7-chloro(1,3)benzothiazole (1.71g, 0.01mol) in ethanol (10ml) and pyridine (0.05ml) was refluxed on a water bath for 3 hrs. The content was cooled and poured on crushed ice, filtered and washed with water. The isolated product was recrystallised from ethanol.

2.2.2. Synthesis of 3-amino-N-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)-2-methyl-4-oxo-3,4-dihydroquinazoline-6-sulphonamide (III)

A mixture of 2(acetylamino)-5-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)sulphanoylbenzoic acid (4.48g, 0.01 mol), hydrazine hydrate (0.5ml, 0.01 mol) in ethanol was refluxed on a water bath for 3 hrs. The content was cooled and poured on crushed ice, filtered and washed with water. The isolated product was recrystallized from ethanol.

2.2.3. Preparation of oxazolone: (4-o-hydroxy benzyliden-2-phenyl-oxazol-5-one)

Salicylaldehyde (0.25g) 35ml was treated with benzoylglycine (Hippuric acid) 0.25g 45gm in presence of dry acetic acid and anhydrous sodium acetate to get 4-o-hydroxy benzyliden-2-phenyl oxazol-5-one upon washing with ice cold alcohol and then with boiling water.

2.2.4. Synthesis of 6-fluoro-7-chloro-(1,3)benzothiazolyl-2-amino sulphonlf(5z)-5[2-hydroxy benzylidine-2-phenyl-3,5-dihydro-4H-4-imidazolonyl]-2-methyl-4-oxo-3,4-dihydroquinazoline (IV)

A mixture of 3-amino-N-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)-2-methyl-4-oxo-3,4-dihydroquinazoline-6-sulphonamide (4.44g, 0.01mol), 4-o-hydroxy benzyliden-2-phenyl-oxazol-5-one (2.59g, 0.01mol) in pyridine (10ml) was refluxed in an oil bath for 6 hrs at 120°C. The contents were cooled poured on crushed ice, filtered and washed with water. The isolated product was recrystallised from ethanol.

2.2.5. Synthesis of 6-fluoro-7-substituted-(1,3)benzothiazolyl-2-amino sulphonlf(5z)-5[2-hydroxy benzylidine-2-phenyl-3,5-dihydro-4H-4-imidazolonyl]-2-methyl-4-oxo-3,4-dihydroquinazoline (Vb1 – Vb13)

The 0.01 mol of 6-fluoro-7-chloro-(1,3)benzothiazolyl-2-amino sulphonlf(5z)-5[2-hydroxy benzylidine-2-phenyl-3,5-dihydro-4H-4-imidazolonyl]-2-methyl-4-oxo-3,4-dihydroquinazoline was treated with equimolar quantity of various substituted amines, substituted anisidines, PABA, morpholine, piperazine and refluxed in presence of N,N’-dimethyl formamide for 2 hrs. Then the contents were cooled and poured on crushed ice. The solid separated was filtered off. Dried and recrystallised from distilled water and alcohol (1:1).

3. RESULTS

3.1. Chemistry

The synthesis of our target compounds Vb1–Vb13 is outlined in Scheme. IR Spectral data (Table.2), NMR (Table 3) and Mass (Table 4) fully support the structures assigned to them.

3.2. In-vitro Anti – tubercular Screening

Sterile Kirchner’s medium was dispensed in each borosilicate test tube (150 x$\phi$10mm) and to this sterile horse serum (0.5 mL) was added. The stock solution
was sterile by passing through a 0.2 mm polycarbonate sterile membrane (Nuclepore) filters. Further the serial dilution of test compounds were carried out. Test compounds at various concentrations (250, 125, 62, 32, 16, 8, 4 and 1 µg/mL) were added to culture medium in a sterilized borosilicate test tube and strain of *M. tuberculosis* was inoculated at concentration (106 bacilli/mL). The tubes were incubated at 37°C for 21 days and then examined for the presence or absence of growth of the test organisms. All experiments were performed in triplicate. The lowest concentration, which showed no visible growth, was taken as the end point i.e. minimum inhibitory concentration (MIC). Rifampin and Isoniazide (INH) were used as standard for antimycobacterial activity.

\[
\text{Scheme: Synthetic Protocol of compounds}
\]

\[\text{R=O, MP-Nitro}\]
\[\text{R= O, MP-Chloro}\]
\[\text{R= H (Vb11, Vb12)}\]
\[\text{R= O, M, P - methoxy}\]
\[\text{R= p-carboxybenzilino}\]

(Vb1, Vb2, Vb3, Vb4, Vb5, Vb6, Vb7, Vb8, Vb9, Vb10, Vb13)
Table No. 1 Analytical Data of the Compounds (Vb1-Vb13)

<table>
<thead>
<tr>
<th>Comp</th>
<th>R</th>
<th>M.P (°C)</th>
<th>Yield (%)</th>
<th>Molecular Formula</th>
<th>Mol. Wt.</th>
<th>Elemental Analysis Data (Calculated in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vb1</td>
<td>NO2</td>
<td>166</td>
<td>84</td>
<td>C7H6O2SNF</td>
<td>313.2</td>
<td>3.08, 7.02, 7.02</td>
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<tr>
<td>Vb2</td>
<td></td>
<td>182</td>
<td>82</td>
<td>C7H6O2SNF</td>
<td>313.2</td>
<td>3.08, 7.02, 7.02</td>
</tr>
<tr>
<td>Vb3</td>
<td>NO2</td>
<td></td>
<td></td>
<td>C7H6O2S</td>
<td>212.1</td>
<td>2.90, 5.78, 5.78</td>
</tr>
<tr>
<td>Vb4</td>
<td>Cl</td>
<td>169</td>
<td>85</td>
<td>C7H6O2SNClF</td>
<td>407.8</td>
<td>3.08, 7.02, 7.02</td>
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</table>

Table 2. IR spectral assignments of synthesized compounds (Vb1-Vb13)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Compound code</th>
<th>Ar-NH H NMR Spectral Data</th>
<th>Ar-C=Ar H NMR Spectral Data</th>
<th>C=Ar C NMR Spectral Data</th>
<th>C-F C NMR Spectral Data</th>
<th>NBSO C NMR Spectral Data</th>
<th>C-Cl C NMR Spectral Data</th>
<th>ArNO2 C NMR Spectral Data</th>
<th>CH C NMR Spectral Data</th>
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<tr>
<td>1</td>
<td>Vb1</td>
<td>336.90</td>
<td>1606.57</td>
<td>1666.39</td>
<td>1159.80</td>
<td>1363.57</td>
<td>1529.84</td>
<td>1456.32</td>
<td>3.08, 7.02, 7.02</td>
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<tr>
<td>2</td>
<td>Vb2</td>
<td>3350.69</td>
<td>1607.66</td>
<td>1666.71</td>
<td>1159.36</td>
<td>1363.29</td>
<td>1536.77</td>
<td>1451.38</td>
<td>3.08, 7.02, 7.02</td>
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<tr>
<td>3</td>
<td>Vb3</td>
<td>3355.67</td>
<td>1608.50</td>
<td>1665.13</td>
<td>1159.54</td>
<td>1363.76</td>
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<tr>
<td>4</td>
<td>Vb4</td>
<td>3358.18</td>
<td>1607.23</td>
<td>1665.08</td>
<td>1158.90</td>
<td>1364.24</td>
<td>668579</td>
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<td>5</td>
<td>Vb5</td>
<td>3359.95</td>
<td>1606.71</td>
<td>1665.17</td>
<td>-</td>
<td>1364.03</td>
<td>668606</td>
<td>-</td>
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<td>6</td>
<td>Vb6</td>
<td>3363.58</td>
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<td>7</td>
<td>Vb7</td>
<td>3355.80</td>
<td>1608.57</td>
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<td>1160.12</td>
<td>1363.82</td>
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Table 3. 1H NMR Spectral Data

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Compound code</th>
<th>Hydrogen</th>
<th>δ (ppm)</th>
<th>Multiplicity</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Vb1</td>
<td>-1H-NH</td>
<td>7.3-7.91</td>
<td>Multiplet</td>
</tr>
<tr>
<td></td>
<td>-1H-CN</td>
<td>8.86</td>
<td>Singlet</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Vb2</td>
<td>-1H-CN</td>
<td>9</td>
<td>Singlet</td>
</tr>
</tbody>
</table>

Mass Spectra Information:

**Compd code Vb1:**

- Molecular formula: $C_7H_6O_2SNF$
- Calculated Molecular weight: 373.77

**Compd code Vb2:**

- Molecular formula: $C_7H_6O_2S$
- Calculated Molecular weight: 212.1

**Compd code Vb3:**

- Molecular formula: $C_7H_6O_2S$
- Calculated Molecular weight: 212.1

**Compd code Vb4:**

- Molecular formula: $C_7H_6O_2SNClF$
- Calculated Molecular weight: 407.8

**Compd code Vb5:**

- Molecular formula: $C_7H_6O_2S$
- Calculated Molecular weight: 212.1

The molecular ion base peak available M^+ available at m/z 202 which is the molecular weight of the parent compound 2-amino-6-flouro-chloro benzothiazole.

Table 4. Anti – tubercular activity (Vb1-Vb13)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Activity Data</th>
<th>3H7RV strain of M. tuberculosis 21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard 1</td>
<td>Rifampicin</td>
<td>0.25</td>
</tr>
<tr>
<td>Standard 2</td>
<td>Isoniazide</td>
<td>0.007</td>
</tr>
<tr>
<td>01</td>
<td>Vb1</td>
<td>25</td>
</tr>
<tr>
<td>02</td>
<td>Vb2</td>
<td>37</td>
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<tr>
<td>03</td>
<td>Vb3</td>
<td>19</td>
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<td>Vb4</td>
<td>30</td>
</tr>
<tr>
<td>05</td>
<td>Vb5</td>
<td>15</td>
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</tbody>
</table>

4. DISCUSSION

In present investigation synthesis of several novel Fluoro substituted benzothiazole comprised with quinazolines (Vb1-Vb13) is reported. The synthesized compounds exhibited significant anti-tubercular activity. In conclusion a novel fluoro benzothiazole comprised with sulfonamido quinazolines were synthesized.

5. ACKNOWLEDGEMENT

The authors express thanks to Dr. A.S. Bobde, Haffkine Institute, Mumbai for providing testing facilities for Anti-tubercular activity.

6. REFERENCES


12. Shierke V.G., Bobade A.S. Synthesis of 2(Substituted aryl amino)-5,6-disubstituted/6-substituted (1,3),benzothiazoles for antitubercular activity; *Chem Abstr* 1991; 11423845 r.