Synthesis and biological evaluation of some new Schiff base 1,2,4-triazole derivatives

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Abstract

A series of substituted 1,2,4-Triazole derivatives were synthesized, and their anticonvulsant activity and antimicrobial activity were evaluated which include the MES model and by Cup-plate method. However, further studies need to be carried out to ascertain the precise mechanism of action of anticonvulsant activity of these molecules. The compounds 4-[1-(2-Bromo-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1,2,4] triazole-3-thione (SB-1) and 4-[1-(4-Fluoro-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1,2,4] triazole-3-thione (SB-2) showed significant anticonvulsant activity and antibacterial activity against *Escherichia coli.*

Keywords: 1,2,4-Triazole derivatives, Anticonvulsant activity and antibacterial activity.

1. Introduction

1, 2, 4-Triazole

There is significant and continuous concern in the chemistry of five-member N-heterocycle compounds, mainly tetrazole (CH$_2$N$_4$), triazoles (C$_2$H$_3$N$_3$), and their substituted derivatives. Triazole exists as two isomers, 1,2,3-triazoles and 1,2,4-triazoles, as shown in (Fig. 1).[1]

![Figure 1: Isomers of Triazole](image)

A large number of 1,2,4-triazole, a heterocyclic derivative exhibits important structural fragments and considered as biologically active compounds such as antifungal, anticonvulsant anti-tubercular, antioxidant, anti-inflammatory inhibition, anticancer, and antimicrobial activity,[2-7] corrosion inhibitors,[8] pesticides,[9] dyes,[10] acid-base indicator,[11] and other industrial chemicals[12]. At 1885, Bladin was the first scientist who gave the name of (triazole) to the carbon nitrogen ring system (C$_2$N$_3$H$_2$) and described triazoles derivatives.[13]

2. Experimental protocols

2.1 Chemistry

All the chemicals and solvents, purchased from Merck (India), Spectrochem (India), Sigma-Aldrich (India), CDH (India) and S.D. Fine were used without further purification. Thin layer chromatographic analysis of compounds was performed on silica gel G coated glass plates. The adsorbent silica gel G was coated to a thickness of about 0.25 mm on previously cleaned TLC plates of 20x5 cm using conventional spreader. The plates were placed in hot air oven at 105°C for 30 min. The solutions of compounds were applied as a spot on the activated plate about 2 cm above from the lower edge. The mobile phases were selected according to the polarity of compounds. Melting points were determined by using open capillary melting point apparatus and are reported uncorrected.

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Compounds were placed in one end of the sealed capillary and placed in the caves made for the capillary. Thermometer was placed in the cave. The temperature at which compound starts melting and the temperature at which it completely melts was recorded as a melting point range.

FT-IR spectra (KBr) were recorded on a Perkin-Elmer Spectrophotometer BX-II spectrophotometer. The 1H-NMR and spectra were recorded on Bruker 400 MHz High Resolution NMR spectrometer using TMS as an internal standard. Chemical shifts were reported in ppm (δ) and signals were described as singlet (s), doublet (d), triplet (t) and multiplet (m).

$$\text{NH}_2\text{NH}_2\text{H}_2\text{O} + \text{S} = \text{C}--\text{S} \rightarrow 1) \text{10-150C}$$

Hydrazine hydrate Carbon Disulphide

2.2.2 Synthesis of 4-Amino-5-(substituted-phenyl)-4H-[1,2,4]-triazole-3-thiol (2)

A mixture of substituted benzoic acid (0.01mol) and thiocarbohydrazide (0.015mol) were taken in a round bottomed flask and heated on a mantle until the content of the flask was melted. The product obtained on cooling was treated with sodium bicarbonate solution to neutralize the unreacted carboxylic acid, if any. It was then washed with water and collected by filtration. The product was recrystallized with ethanol to afford the title compounds. The physico-chemical data was calculated: Rf value 0.44, % yield 56.21, melting point 83-85°C, Cream color solid.

$$\text{S} = \text{NH}--\text{NH}_2$$

Nicotinic acid

$$\text{Melt, } \Delta$$

4-Amino-5-pyridin-3-yl-4H-[1,2,4]triazole-3-thiol

2.2.3 Procedure for 1,2,3-Triazole Derivative Preparation Containing Schiff base. (3)

To a suspension of substituted amino mercapto triazole (0.2 mol) in methanol, an equimolar amount of the corresponding substituted acetophenone with 3 to 4 drops of sulphuric acid was added. The reaction mixture was refluxed for 2-3 h at 80-90°C. The precipitate was obtained which was washed with water, filtered and dried.
Synthesis 1:
4-[1-(2-Bromo-phenyl)-ethyldeneamino]-5-pyridin-3-yl-2,4-dihydro-[1,2,4]triazole-3-thioe from 2-Bromoacetophenone. 3a (SB-1)

To a suspension of 4-Amino-5-pyridin-3-yl-4H-[1,2,4]triazole-3-thiol (0.2 mol) in methanol, an equimolar amount of the corresponding 2-Bromoacetophenone with 3 to 4 drops of sulphuric acid was added. The reaction mixture was refluxed for 2-3 h at 80-90 °C. The precipitate was obtained which was washed with water, filtered and dried. The physico-chemical data was calculated: Rf value 0.42, % yield 54.44, melting point 150-152^0C, Cream color solid.

Synthetic scheme

\[
\text{NH}_2\text{NH}_2\text{H}_2\text{O} \quad + \quad \text{S} \equiv \text{C} \equiv \text{S} \quad \xrightarrow{1) \ 10-15^0\text{C}} \quad \text{S} \equiv \text{C} \equiv \text{S} \quad \xrightarrow{2) \ 85^0\text{C}, \ 15\text{hr}} \quad \text{S} \equiv \text{C} \equiv \text{S} \\
\text{Hydrazine hydrate} \quad \text{Methanedithione} \quad \text{Thiocarboxyhydrazide (1)}
\]

To a suspension of 4-Amino-5-pyridin-3-yl-4H-[1,2,4]triazole-3-thiol (0.2 mol) in methanol, an equimolar amount of the corresponding 4-Fluoroacetophenone with 3 to 4 drops of sulphuric acid was added. The reaction mixture was refluxed for 2-3 h at 80-90 °C. The precipitate was obtained which was washed with water, filtered and dried. The physico-chemical data was calculated: Rf value 0.64, % yield 50.21, melting point 110-112^0C, Cream color solid.

Synthesis 2:
4-[1-(4-Fluoro-phenyl)-ethyldeneamino]-5-pyridin-3-yl-2,4-dihydro-[1,2,4]triazole-3-thione from 4-Fluoroacetophenone. 3b (SB-2)

4-Amino-5-pyridin-3-yl-4H-[1,2,4]triazole-3-thiol (2)

To a suspension of 4-Amino-5-pyridin-3-yl-4H-[1,2,4]triazole-3-thiol (0.2 mol) in methanol, an equimolar amount of the corresponding 4-Fluoroacetophenone with 3 to 4 drops of sulphuric acid was added. The reaction mixture was refluxed for 2-3 h at 80-90 °C. The precipitate was obtained which was washed with water, filtered and dried. The physico-chemical data was calculated: Rf value 0.64, % yield 50.21, melting point 110-112^0C, Cream color solid.

Figure 2: Synthesized compound is: SB-1 and SB-2
2.3 Characterization of the synthesized compounds

4-{1-[2-Bromo-phenyl]-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1,2,4]triazole-3-thione. (SB-1)

Cream colored flakes, M.F. C12H2BrN3S, M.P. 150-152 °C, Rf 0.42, % yield 54.44, IR (KBr, cm⁻¹): 2913.9(N-H); 1687.8(C=O); 1226.1(C=S); 1152.6(C=N); 647.3(-C-Br).¹H NMR (500 MHz, DMSO-d6), δ 10.214 (s, 1H, -NH), 7.352-8.143 (m, 8H, Ar-H), 1.312 (s, 3H, -CH3).

4-{1-[4-Fluoro-phenyl]-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1,2,4]triazole-3-thione. (SB-2)

Cream colored flakes, M.F. C13H2F2N3S, M.P. 110-112 °C, Rf 0.64, % yield 50.21, IR (KBr, cm⁻¹): 3276.6(-NH); 1606.5(-C=O); 1302.5(-C=O); 1232.5(-C-N); 1028(-F).¹H NMR (500 MHz, DMSO-d6), δ 10.014 (s, 1H, -NH).

3.1.1 Characterization of the synthesized compounds

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>Flexion</th>
<th>Extension</th>
<th>Stupor</th>
<th>Recovery</th>
<th>%Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Tween 80</td>
<td>4.416±0.31</td>
<td>14.88±0.31</td>
<td>80.68±0.19</td>
<td>122.1±0.91</td>
<td>33.33</td>
</tr>
<tr>
<td>Std.</td>
<td>25</td>
<td>0.592±0.12</td>
<td>1.22±0.13</td>
<td>29.01±0.92</td>
<td>61.47±0.46</td>
<td>100</td>
</tr>
<tr>
<td>SB-1</td>
<td>50</td>
<td>3.87±0.30</td>
<td>11.96±0.28</td>
<td>65.84±0.24</td>
<td>109.5±0.50</td>
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</tr>
<tr>
<td>SB-2</td>
<td>50</td>
<td>2.62±0.30</td>
<td>8.32±0.40</td>
<td>59.23±0.35</td>
<td>86.68±0.10</td>
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Values represent the mean ± SD of six animals each group (n=6). SB-1 and SB-2 test compounds. *indicates p<0.05, **indicates p<0.01 and when compared to the control group.(the mean difference was considered significant at 0.01 level).

3.1.2 Antibacterial activity

A compound 4-[1-(4-Fluoro-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1,2,4]triazole-3-thione (SB-2) showed stronger antimicrobial activity against MTCC-521 gram (-)ve bacteria were evaluated after Cup-plate method. The results are shown in Table 2. The studied products are still under investigation. Their antibiotic properties have promising applications in the control of infections.

Table 2: Antibacterial activity of compounds

<table>
<thead>
<tr>
<th>Compound code</th>
<th>Zone of inhibition in mm</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>E. coli (MTCC-521)</td>
</tr>
<tr>
<td></td>
<td>10 µg/ml</td>
</tr>
<tr>
<td>SB-1</td>
<td>2</td>
</tr>
<tr>
<td>SB-2</td>
<td>4</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>8</td>
</tr>
<tr>
<td>Control</td>
<td>-</td>
</tr>
</tbody>
</table>

3. Result and discussion

3.1.1 Anticonvulsant Activity

The compounds were primarily subjected for evaluating their anticonvulsant activity and then screened compounds were subjected to study various phases of MES. The results are shown in Table 1. The compounds 4-[1-(2-Bromo-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro [1,2,4]triazole-3-thione(SB-1)and 4-{1-[4-Fluoro-phenyl]-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1,2,4]triazole-3-thione (SB-2) i.e. 66.33% protection.

Table 1: Anticonvulsant activity of compounds

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4. Conclusion

The compounds 4-[1-(2-Bromo-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1, 2, 4]triazole-3-thione(SB-1) and 4-[1-(4-Fluoro-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro [1,2,4]triazole-3-thione (SB-2) showed significant anticonvulsant activity and show sufficient antibacterial activity against Escherichia coli. The Compound 4-[1-(4-Fluoro-phenyl)-ethylideneaminol]-5-pyridin-3-yl-2,4-dihydro[1, 2, 4]triazole-3-thione (SB-2) showed significant inhibitory characteristics with stronger antimicrobial activity against MTCC-521 gram(-)ve bacteria.

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References


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