Thiadiazolyl quinazolines as potential antiviral and antihypertensive agents

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Phthalic anhydride on treatment with β-ethanol amine gives N-hydroxy ethylphthalimide 1 which reacts with anthranilic acid in presence of ethanol containing concentrated hydrochloric acid affording 5-(N-ethylphthalimido)-anthranilic acid 2. This on treatment with benzoyl chloride in pyridine gives 6-(N-ethyl phthalimido)-2-phenyl-4-oxo-3,4-dihydrobenzoxazine 3 which on reaction with 2-amino-5-aralkyl-1, 3, 4-thiadiazoles 4 in pyridine results in the formation of 6-(N-ethylphthalimido)-3-[2-(5'-aralkyl-1', 3', 4'-thiadiazolyl)-2-phenyl-4-oxo-(3H)-quinazolines 5. The antiviral and antihypertensive activities of 5 have been reported.

The diverse pharmacological properties exhibited by quinazolines have been of much significance in recent years. 2, 3-Disubstituted quinazolines have been demonstrated to be associated with antiviral 1 and antifungal activities 2. In addition, some quinazoline derivatives containing sulphonamido group caused antihypertensive effect probably due to the initial reduction of blood volume because of Na+ depletion and subsequently on account of direct relaxation of arteriolar smooth muscle 3. Some compounds were generally effective in lowering blood pressure in the spontaneous hypertensive rats model and showed α-adrenergic blocking activity 4. These valid observations led the authors to undertake the synthesis of some 6-(N-ethylphthalimido)-3-[2-(5'-aralkyl-1', 3', 4'-thiadiazolyl)]-2-phenyl-4-oxo-(3H)-quinazolines 5 to evaluate their antihypertensive and antiviral activities.

6-(N-Ethylphthalimido)-3-[2-(5'-aralkyl-1', 3', 4'-thiadiazolyl)]-2-phenyl-4-oxo-(3H) quinazolines 5 were prepared (Scheme 1) by heating a mixture of 6-(N-ethylphthalimido)-2-phenyl-4-oxo-3,4-dihydrobenzoxazine 3 and 2-amino-5-aralkyl-1,3,4-thiadiazoles 4 in anhydrous pyridine under anhydrous reaction conditions 5. The synthesized compounds were characterized with the help of elemental analysis, IR and 1H NMR spectral data.

Pharmacological activity

Compounds 5 were evaluated for their antiviral activity against two animal viruses viz. Japanese encephalitis virus (JEV) (P20778) and Herpes simplex virus (HSV-1) (753166) in vitro. JEV was maintained by intracerebral passages in 1-3-days-old suckling albino Swiss mice. The brains of the infected mice with specific paralytic symptoms were triturated and 10% homogenate was made in phosphate buffered saline (PBS) pH 7.2. The mean lethal dose (LD50) of the virus in mice was calculated before each experiment. HSV-1 was maintained in 5-6 g of albino Swiss mice by the same route as JEV. Vero cells were maintained in minimum essential medium (Sigma USA) with 10% foetal bovine serum (Gibco, USA) and 100 units of gentamycin/ml were added. Cytotoxicity and antiviral assay of the compounds were performed by the standard method of Sidwell and Huffman 6.

Amongst six thiadiazolyl quinazolines only two such compounds 5a having R = phenyl and 5e having R = n-propyl showed anti-viral activity to the magnitude of 50%, each at the same dose level with same EC50 value against JEV in vitro. A qualitative structure activity relationship study reveals the fact that substituted phenyl group in such compounds has little role to play as far as anti-JEV activity is concerned. Thus, compounds 5b and 5c containing R = p-chlorophenyl and o-hydroxy phenyl substituents respectively, were unable to exhibit any noticeable degree of anti-JEV activity in vitro. Secondly, a group larger than ethyl is required in such compounds to display anti-JEV activity. Thus, compounds 5d and 5f having R = methyl and ethyl respectively, were found inactive while compound 5e containing n-propyl group was found to inhibit the multiplication of virus
Thiadiazolyl quinazolones were assayed for their effects on cardiovascular system (CVS) at two dose levels. Only one compound was found to show some noticeable antihypertensive activity at 5.0 mg/kg, i.v. Thus compound 5c containing R = 2-hydroxyphenyl substituent attached with the thia diazole nucleus was found to cause a depletion in blood pressure to the extent of 60 mm Hg for more than 30 minutes at 5.0 mg/kg, i.v. However, the same compound at a dose level of 1.0 mg/kg, i.v., decreased the blood pressure to the extent of 25 mm Hg only transitory. It is interesting to observe here that compound 5b containing a p-chlorophenyl substituent attached with the thia diazole nucleus increased, the blood pressure to an extent of 16 mm Hg for a period of 2 minutes at a dose of 5.0 mg/kg, i.v. and at 1.0 mg/kg, i.v. the same compound decreased the blood pressure to the extent of 10 mm Hg transitory. Another compound of this category (compound 5e, R = n-propyl) was also found to increase the blood pressure at 5.0 mg/kg i.v., to the extent of 20 mm Hg for 11 minutes and at 1.0 mg/kg i.v. it did not show any observable activity (decrease or increase in blood pressure) while compound 5f (R = ethyl) showed a fall of 1.0 mm Hg transitory and 16 mm Hg at 5.0 mg/kg for a period of 2 minutes.

Experimental Section

Melting points were determined in open capillaries using a Toshniwal melting point apparatus and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 157 spectrophotometer (νmax in cm⁻¹) and ¹H NMR spectra in MeOH on a Varian A-60 instrument using TMS as internal standard (chemical shifts in δ, ppm).

N-Hydroxy ethyl phthalimide 1. Phthalic anhydride (14.8 g, 0.1 mole) and β-ethanol amine (7.3 mL, 0.12 mole) were heated together at 210°C for 0.5 hr. Subsequently, the contents were cooled and diluted hydrochloric acid (50 mL) was added slowly with constant stirring. A white solid separated out which was filtered off and dried at 100°C. The crude N-hydroxy ethyl-phthalimide was recrystallized from ethanol as white crystalline solid, m.p. 127°C [127-28°C]², yield 80%.

5-(N-Ethylphthalimido)-anthranilic acid 2. This is an example of amidodialkylation reaction, which has been attempted employing the procedure of Einhorn³. Thus, a mixture of N-hydroxy ethyl phthalimide 1 (11.4g, 0.06 mole) and anthranilic acid (8.2 g, 0.06 mole) in ethanol (50 mL) containing 2 mL of concentrated hydrochloric acid was heated under
The pasty mass so obtained was diluted with water. The solution was cooled to 0°C and benzoyl chloride (4.6 mL, 0.04 mole) was added to this solution slowly with constant stirring. When the addition was complete, the reaction mixture was further stirred for 0.5 hr at room temperature and set aside for 1 hr. The pasty mass so obtained, was diluted with water (50 mL) and treated with 5% sodium bicarbonate solution (50 mL) to remove any unreacted acid. When the effervescence ceased, it was filtered and washed with water to remove the adhered pyridine and the inorganic materials. The crude benzoxazine thus obtained was dried in vacuo and recrystallized from ethanol.

2-Amino-5-aralkyl-1, 3, 4-thiadiazoles 4. A mixture of a carboxylic acid (0.1 mole) and thiosemicarbazide (0.1 mole) in 100 mL concentrated sulfuric acid was heated under reflux for 6 hr. The solution was allowed to cool at room temperature. It was further cooled to 0°C and then neutralized cautiously and slowly with ammonium hydroxide solution. Initially, a solid separated out which dissolved on stirring. On adding more ammonia solution, a thick mass separated out which was allowed to settle down. It was filtered off and washed repeatedly with water. The crude thiadiazole thus obtained was dried in vacuo and recrystallized from ethanol.

2-Amino-5-aralkyl-1, 3, 4-thiadiazoles thus synthesized, are recorded in Table I.

Table I – Characterization data of 2-amino-5-aralkyl-1, 3, 4-thiadiazoles 4 and 6-(N-ethylphthalimido)-3-[2'-(5'-aralkyl-1', 3', 4'-thiadiazolyl)]-2-phenyl-4-oxo-(3H)-quinazolines 5.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Calcd.</th>
<th>Found</th>
<th>Mass (m/z)</th>
<th>1H NMR (MeOH) (δ, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Phenyl</td>
<td>220-24</td>
<td>70</td>
<td>23.72</td>
<td>23.68</td>
<td>555(M+), 381, 174, 161</td>
<td>3.30-3.61(m, 4H, CH2-CH3), 7.2-8.0 (m, 17H, Ar-H)</td>
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<tr>
<td>4b</td>
<td>p-Chloro phenyl</td>
<td>230[d]</td>
<td>65</td>
<td>19.85</td>
<td>19.80</td>
<td>591(M++), 589(M+), 417, 415, 195, 174</td>
<td>3.30-3.61(m, 4H, CH2-CH3), 7.2-8.0(m, 16H, Ar-H)</td>
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<tr>
<td>4c</td>
<td>α-Hydroxy phenyl</td>
<td>229-30</td>
<td>66</td>
<td>21.76</td>
<td>21.71</td>
<td>571(M+), 397, 177, 174</td>
<td>3.31-3.61(m, 4H, CH2-CH3), 6.5 (s, 1H, OH), 7.1-8.2 (m, 16H, Ar-H)</td>
</tr>
<tr>
<td>4d</td>
<td>Methyl</td>
<td>233[d]</td>
<td>30</td>
<td>36.52</td>
<td>36.48</td>
<td>396(M+), 174, 146</td>
<td>3.71 (t, 2H, N-CH2)</td>
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<tr>
<td>4e</td>
<td>n-Propyl</td>
<td>240</td>
<td>60</td>
<td>29.37</td>
<td>29.34</td>
<td>3400-3672(OH str.), 1640 (C=O str.), 1632 (C=N str.), 319, 174, 99</td>
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<tr>
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<td>199-01</td>
<td>70</td>
<td>32.55</td>
<td>32.50</td>
<td>3.30(t, J= 7.5Hz, 2H, C-CH2), 7.01-7.98 (m, 12H Ar-H); (Mass): (m/z) 396(M+), 174, 146</td>
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<tr>
<td>5a</td>
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<td>65</td>
<td>12.61</td>
<td>12.58</td>
<td>555(M+), 381, 174, 161</td>
<td>3.30-3.61(m, 4H, CH2-CH3), 7.2-8.0 (m, 17H, Ar-H), 5.30(t, J= 7.5Hz, 2H, C-CH2), 7.01-7.98 (m, 12H Ar-H); (Mass): (m/z) 396(M+), 174, 146, 3.30(t, J= 7.5Hz, 2H, C-CH2), 7.01-7.98 (m, 12H Ar-H)</td>
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<tr>
<td>5b</td>
<td>p-Chloro phenyl</td>
<td>197</td>
<td>62</td>
<td>11.87</td>
<td>11.84</td>
<td>591(M++), 589(M+), 417, 415, 195, 174</td>
<td>3.30-3.61(m, 4H, CH2-CH3), 7.2-8.0(m, 16H, Ar-H)</td>
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<tr>
<td>5c</td>
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<td>63</td>
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<td>12.20</td>
<td>571(M+), 397, 177, 174</td>
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<tr>
<td>5d</td>
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<td>14.19</td>
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<td>493(M+), 319, 174, 99</td>
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<td>74-75</td>
<td>54</td>
<td>13.43</td>
<td>13.40</td>
<td>3.30-3.61(m, 4H, CH2-CH3), 7.2-8.0 (m, 17H, Ar-H)</td>
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</tr>
<tr>
<td>5f</td>
<td>Ethyl</td>
<td>62-63</td>
<td>63</td>
<td>13.80</td>
<td>13.76</td>
<td>3.30-3.61(m, 4H, CH2-CH3), 7.2-8.0 (m, 17H, Ar-H)</td>
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tallization from diluted ethanol resulted in crystalline substance. The compounds, thus synthesized are presented in Table I along with their characterization data.

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References