Synthesis, anxiolytic and antihypertensive activity of 1-aryloxy-3-(N⁴-substituted piperazinyl) propan-2-ols as aryloxypropanolamines

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ABSTRACT

Aryloxypropanolamines have an important role in the treatment of several cardiovascular disorders and are one of the most potent antihypertensive agents. A series of 1-aryloxy-3-(N⁴-substituted piperazinyl) propan-2-ols as aryloxypropanolamine were synthesized and evaluated for anxiolytic activity and antihypertensive activity. The structures of synthesized compounds were confirmed by IR, ¹H NMR and Mass spectroscopy. 1-aryloxy-3-(N⁴-substituted Piperazinyl) propan-2-ols were synthesized by reaction of various phenols (1a-c) with epichlorhydrin to form 1-aryloxy-2,3-epoxypropane. These epoxides on condensation with various substituted piperazines resulted in derivatives of aryloxypropanolamine compounds (4a-i) and were evaluated for anxiolytic activity by Elevated Plus Maze and antihypertensive activity by Tail Cuff technique. Out of nine (4a-i) compounds, Compound 4e [1-(2-naphthyloxy)-3-(N⁴-ethyl piperazinyl) propan-2-ol], 4i [1-(phenoxy)-3-(N⁴-hydroxyethyl piperazinyl)] propan-2-ol were found to be most active as anxiolytic agent whereas compound 4a [1-(1-Naphthoxy)-3-(N⁴-methyl piperazinyl) propan-2-ol] was possessing maximum antihypertensive activity.

Key Words: Aryloxypropanolamines, β-Adrenergic receptor antagonist, Anxiolytic activity, Antihypertensive activity, Enciprazine, Propranolol.

INTRODUCTION

The aryloxypropanolamine moiety is a general feature of various β-adrenoreceptor blocking drugs (β-blockers). β Adrenergic blocking agents [1-4], mostly comprising of β amino alcohols, are of pharmaceutical significance and have received major attention due to their utility in the management of cardiovascular disorders [5] including hypertension [6], angina pectoris, cardiac arrhythmias and other disorders [7] related to the sympathetic nervous system. However, some β-blockers readily access the brain because of their lipophilicity and can influence some central nervous system functions. Therefore, Propranolol has been used for the treatment of anxiety syndromes, prophylaxis of migraine headaches, schizophrenia, alcohol withdrawals, and tremors [8-11]. Biochemically, the mechanism of action involves the adrenergic system in which the hormonal system provides the communication link between the sympathetic nervous system and involuntary muscle[12]. Blocking of the β-receptor system reduces the overall activity of the sympathetic nervous system. β-blockers are thus used to increase life expectancy after heart attack. Drugs belonging to the class of aryloxypropanolamine are useful β-blockers [13]. In aryloxypropanolamines, there are two sites which play important role as per as the substitution is concerned. Those sites are aryloxy end and amine end. In this study, aryloxy and amine end had been considered for substitution. In case of aryloxy end, the nature of the aromatic ring and its substituents are the primary determinant of β-antagonistic activity of aryloxypropanolamines. The aryl group also affects the absorption, excretion, and metabolism of the β blockers[12]. In the course of studies on tranquilizers, Jurgen Engel et al synthesized new non-benzodiazepine like compounds & screened pharmacologically for antiaggressive & anxiolytic property & invented Enciprazine [1-(3,4,5-trimethoxy phenoxy)-3-[ 4-(2-methoxyphenyl) piperazinyl] propan-2-ol] which was selected for clinical investigation[8](Figure 1). In an attempt to find novel anxiolytic agents and antihypertensive agents we synthesized a novel class of
1-aryloxy-3-(N\textsuperscript{2}-substituted piperazinyl) propan-2-ols as arylxypropanolamine derivatives for the treatment of anxiety and hypertension. These synthesized compounds were tested for anxiolytic activity by Elevated Plus Maze and antihypertensive activity by Tail Cuff Technique.

MATERIALS AND METHODS

All reagents and solvents were of analytical grade and used directly. Melting points were determined by open capillary method and are uncorrected. The purity of compounds was confirmed by thin layer chromatography using Silica gel GF\textsubscript{254} as stationary phase and chloroform:methanol (9:1) as mobile phase.\textsuperscript{1}H NMR spectra were recorded in CDCl\textsubscript{3} on Brucker Advance-H 300MHz instrument. Chemical shift values are expressed in parts per million (ppm,\textdelta). IR spectra were recorded in KBr disc on Shimadzu FTIR 8400 spectrophotometer.

The synthetic pathway for preparation of title compounds is shown in scheme 1. 1-aryloxy-3-(N\textsuperscript{2}-substituted piperazinyl) propan-2-ols were synthesized by reaction of various phenols (1a-c) with epichlorhydrin in presence of 40\% sodium hydroxide solution to form 1-aryloxy-2,3-epoxypropane (3a-i). These epoxides on condensation with various substituted piperazines by refluxing the reaction mixture in isopropyl alcohol yielded derivatives of arylxypropanolamine compounds (4a-i). The purity of synthesized compounds was monitored by TLC and the structures of all the derivatives were assigned by IR,\textsuperscript{1}H NMR spectroscopic data, which are consistent with the proposed molecular structures.

Synthesis

A. Synthetic procedure for 1-aryloxy-2,3-epoxy propane (3a-c).

In a 250ml of 3-necked RBF suitable for azeotropic separation of water,(0.1M) of Ar-OH (1a-c) was boiled with 37gm (0.4M) of epichlorhydrin followed by dropwise addition of 10gm (0.1M) of 40\% sodium hydroxide over a period of 30 min. simultaneously, the water was removed azeotropically. After complete addition, the mixture was left to react for another hour at boiling temperature. Then it was diluted with 100ml of toluene, sodium chloride precipitates and was filtered off. The filtrate was then distilled to remove toluene and then in vacuum to get the 1-aryloxy-2,3-epoxy propane\[8\].

B. Synthetic procedure for 1-aryloxy-3-(N\textsuperscript{2}-substituted piperazinyl) propan-2-ols (4a-i).

In a 100ml RBF containing (0.05M) of 1-aryloxy-2,3-epoxy propane & (0.05M) of N-methyl/ethyl/hydroxyethyl piperazine was taken in 25ml of isopropyl alcohol and was refluxed on water bath for 5 hrs. The solvent was distilled off then, the residue was treated with excess of isopropyl alcohol saturated with anhydrous hydrochloride and the dihydrochloride of the product was precipitated by addition of diethyl ether\[8\]. Physico-chemical data of synthesized compounds is specified in Table 1 and the spectral analysis are as follows:

\textbf{4a} 1-(1-Naphthyloxy)-3-(N\textsuperscript{2}-methyl piperazinyl) propan-2-ols: IR (cm\textsuperscript{-1}) 3352, 2890, 1622, 1343, 1255; \textsuperscript{1}H NMR (\textdelta ppm): 2.1 (s, 3H, CH\textsubscript{3}), 2.4 (t, 8H, -CH\textsubscript{2} piperazinyl), 2.6-2.9 (d, 4H, O-CH\textsubscript{2} -CH\textsubscript{2}-N), 3.9 (m, 1H, -CH-), 4.8 (s, 1H, -OH), 6.6-8.30 (m, 7H, Ar-H).

\textbf{4b} 1-(1-Naphthyloxy)-3-(N\textsuperscript{2}-ethyl piperazinyl) propan-2-ols. IR (cm\textsuperscript{-1}) 3361,2989,1594,1459,1335,1259; \textsuperscript{1}H NMR (\textdelta ppm): 1.1 (t, 3H, CH\textsubscript{3}), 2.38 (q, 2H, -CH\textsubscript{2} -), 2.46 (t, 8H, -CH\textsubscript{2} piperazinyl), 2.6-3.1 (d, 4H, -O-CH\textsubscript{2} -CH\textsubscript{2}-N), 3.9 (m, 1H, -CH-), 4.81 (s, 1H, -OH), 6.7-8.30 (m, 7H, Ar-H).

\textbf{4c} 1-(1-Naphthyloxy)-3-(N\textsuperscript{2}-hydroxyethyl piperazinyl) propan-2-ols. IR (cm\textsuperscript{-1}) 3276,2933,1598,1390,1257; \textsuperscript{1}H NMR (\textdelta ppm): 2.39 (t, 8H, -CH\textsubscript{2} piperazinyl), 2.55 (t, 2H, -CH\textsubscript{2} -), 2.71-3.22 (d, 4H, -O-CH\textsubscript{2} -CH\textsubscript{2}-N), 3.6 (t, 2H, -CH\textsubscript{2} -N), 3.91 (m, 1H, -CH-), 4.81 (s, 2H, -OH), 6.24-8.15 (m, 7H, Ar-H).

\textbf{4d} 1-(2-Naphthyloxy)-3-(N\textsuperscript{2}-methylpiperazinyl) propan-2-ols. IR (cm\textsuperscript{-1}) 3217, 2918, 1597, 1385, 1300, 1255; \textsuperscript{1}H NMR (\textdelta ppm): 1.87 (s, 3H, CH\textsubscript{3}), 2.26 (t, 8H, -CH\textsubscript{2} piperazinyl), 2.56-3.17 (d, 4H, -O-CH\textsubscript{2} -CH\textsubscript{2}-N), 3.85 (m, 1H, -CH-), 4.64 (s, 2H, -OH), 7.04-7.98 (m, 7H, Ar-H).

\textbf{4e} 1-(2-Naphthyloxy)-3-(N\textsuperscript{2}-ethyl piperazinyl) propan-2-ols. IR (cm\textsuperscript{-1}) 3416, 1218, 1354, 1258, 1660; \textsuperscript{1}H NMR (\textdelta ppm): 1.09 (s, 3H, N-CH\textsubscript{3}), 2.28 (q, 2H, -CH\textsubscript{2} -), 2.43 (t, 8H, -CH\textsubscript{2} piperazinyl), 2.68-3.32 (d, 4H, -O-CH\textsubscript{2} -CH\textsubscript{2}-N), 3.91 (m, 1H, -CH-), 4.93 (s, 1H, -OH), 6.78-7.81 (m, 7H, Ar-H).

\textbf{4f} 1-(2-Naphthyloxy)-3-(N\textsuperscript{2}-hydroxyethyl piperazinyl) propan-2-ols. IR (cm\textsuperscript{-1}) 3435, 2963, 1587, 1365, 1259; \textsuperscript{1}H NMR (\textdelta ppm): 2.42 (t, 8H, -CH\textsubscript{2} piperazinyl), 2.50 (t, 2H, -CH\textsubscript{2} -), 2.74-3.07 (d, 4H, -O-CH\textsubscript{2} -CH\textsubscript{2}-N), 3.86 (t, 2H, -CH\textsubscript{2} -), 4.15 (m, 1H, -CH-), 4.97 (s, 2H, -OH), 7.04-7.98 (m, 7H, Ar-H); Mass 331.28 (M+1), 311.41 ,281.37,252.

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**4g** 1-((Phenoxy)-3-(N\(^4\)-methyl piperazinyl) propan-2-ols.
IR: (cm\(^{-1}\)) 3325, 2931, 1593, 1456, 1294, 1250; \(^1\)H NMR (\(\delta\) ppm): 2.07 (s, 3H, \(-\text{CH}_3\)), 2.26–2.76 (t, 8H, \(-\text{CH}_2\) piperazinyl), 2.88–3.17 (d, 4H, \(-\text{O-CH}_2, -\text{CH}_2\)-N), 3.90 (m, 1H, -CH-), 4.94 (s, 1H, -OH), 6.83–7.54 (m, 5H, Ar-H).

**4h** 1-((Phenoxy)-3-(N\(^4\)-ethyl piperazinyl) propan-2-ols.
IR: (cm\(^{-1}\)) 3336, 2939, 1599, 1462, 1340, 1244; \(^1\)H NMR (\(\delta\) ppm): 1.14 (s, 3H, \(-\text{CH}_3\)), 2.31 (q, 2H, \(-\text{CH}_2\)), 2.40 (t, 8H, \(-\text{CH}_2\) piperazinyl), 2.68–3.24 (d, 4H, \(-\text{O-CH}_2, -\text{CH}_2\)-N), 3.99 (m, 1H, -CH-), 4.97 (s, 1H, -OH), 6.93–7.27 (m, 5H, Ar-H).

**4i** 1-((Phenoxy)-3-(N\(^4\)-hydroxyethyl piperazinyl) propan-2-ols.
IR: (cm\(^{-1}\)) 3444, 3296, 2933, 1597, 1346, 1258; \(^1\)H NMR (\(\delta\) ppm): 2.46 (t, 8H, \(-\text{CH}_2\) piperazinyl), 2.59 (t, 2H, \(-\text{CH}_2\)), 2.63–3.24 (d, 4H, \(-\text{O-CH}_2, -\text{CH}_2\)-N), 3.66 (t, 2H, \(-\text{CH}_2\)), 3.85 (m, 1H, -CH-), 4.64 (s, 2H, \(-\text{OH}\)), 7.04–7.98 (m, 5H, Ar-H).

**Biological Evaluation**

All synthesized compounds were evaluated for anxiolytic activity by Elevated Plus Maze (EPM) test\[15,16\] and antihypertensive activity\[17\] by Tail Cuff Technique as racemates. The results were compared with standard anxiolytic like Diazepam and Propranolol as standard drug for antihypertensive activity.

Anxiolytic activity, mice (n=5) were treated with the compounds (50 mg/kg, p.o.) , and diazepam (1 mg/kg, i.p.) 30 min before placing individually in the centre of the EPM facing a closed arm and the time spent in both the open and closed arms was recorded for 5 min. The numbers of entries into open and closed arms were also counted during the test. If the drug has anxiolytic effect, then the mouse will spend more time in the open arm and the number of entries in the open arm shall also increase.

Antihypertensive activity, Adrenaline (0.5 mg/kg i.m) was administered into rats for 10 consecutive days to induce hypertension. After induction of hypertension, the synthesized compounds (50 mg/kg, p.o.) were administered orally for 20 days. Propranolol (10 mg/kg, i.p) was used as standard drug. During treatment schedule, systolic blood pressure (SBP), was measured by the Tail Cuff Technique in the conscious rat on PowerLab data acquisition system (AD Instruments, Australia). The details of results are given in table 1.

**RESULTS AND DISCUSSION**

In present work we synthesized 1-aryloxy-3-(N\(^4\)-substituted piperazinyl) propan-2-ols as derivatives of aryloxypropanolamine (Scheme 1) which gave about 60-75% yield.

The anxiolytic results of synthesized compounds is depicted in Table 2 , the results shows that all nine compounds (4a-i) were active as anxiolytic agent in EPM model by exhibiting significant (\(P < 0.01\)) increase in time spent and number of entries in open arm with decreased preference to the closed arm. The most active compound was shown by 4e [1-(2-naphthyloxy)-3-(N\(^4\)-ethyl piperazinyl) propan-2-ol] and 4i [1-(phenoxy)-3-(N\(^4\)-hydroxyethyl...
piperazinyl) propan-2-ol. Compound having aryloxy group as phenoxy and 2-naphthyloxy and amine group having N-ethyl and N-hydroxyethyl shown significant anxiolytic activity. The compound 4c and 4g were also shown good anxiolytic activity. The compound 4b and 4h are the least active.

Synthesized compounds were also evaluated for antihypertensive activity in Albino rats by Tail Cuff Technique. Results (Table 2) obtained shows that all the compounds except (4h) significantly decreased systolic blood pressure. The most active compound was 4a, [1-(1-naphthyloxy)-3-(N4-methyl piperazinyl) propan-2-ol]. Compound 4h, [1-(phenoxy)-3-(N4-ethyl piperazinyl) propan-2-ol] showed very less decrease in systolic blood pressure in rats.

Table 2: In vivo anxiolytic and antihypertensive activity of 1-aryloxy-3-(N4-substituted piperazinyl) propan-2-ols

<table>
<thead>
<tr>
<th>Compound</th>
<th>Anxiolytic activity</th>
<th>Antihypertensive activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Elevated Plus Maze</td>
<td>Tail Cuff Technique</td>
</tr>
<tr>
<td></td>
<td>Time Spent in Open</td>
<td>B.P before treatment</td>
</tr>
<tr>
<td></td>
<td>Arm [sec.]</td>
<td>B.P after treatment</td>
</tr>
<tr>
<td></td>
<td>Entries into Open</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm [sec.]</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>112.5 ± 4.5**</td>
<td>20.8 ± 2.7**</td>
</tr>
<tr>
<td>Vehicle</td>
<td>34.3 ± 1.2</td>
<td>7.5 ± 3.4</td>
</tr>
<tr>
<td>Control</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Propranolol</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4a</td>
<td>95.5 ± 5.5**</td>
<td>17.2 ± 1.8**</td>
</tr>
<tr>
<td>4b</td>
<td>89.2 ± 6.2**</td>
<td>15.7 ± 1.9**</td>
</tr>
<tr>
<td>4c</td>
<td>98.7 ± 5.5**</td>
<td>14.1 ± 1.3**</td>
</tr>
<tr>
<td>4d</td>
<td>92.6 ± 2.6**</td>
<td>15.8 ± 1.6**</td>
</tr>
<tr>
<td>4e</td>
<td>101.5 ± 2.8**</td>
<td>16.7 ± 2.6**</td>
</tr>
<tr>
<td>4f</td>
<td>95.8 ± 6.6**</td>
<td>18.1 ± 1.0**</td>
</tr>
<tr>
<td>4g</td>
<td>98.6 ± 5.5**</td>
<td>16.3 ± 2.5**</td>
</tr>
<tr>
<td>4h</td>
<td>89.7 ± 5.8**</td>
<td>13.7 ± 1.8 ns</td>
</tr>
<tr>
<td>4i</td>
<td>101.2 ± 6.1**</td>
<td>17.5 ± 2.9**</td>
</tr>
</tbody>
</table>

Scheme 1

In conclusion, synthesized compounds were obtained in good yields and were pure and stable. All the nine compounds shown significant anxiolytic activity, out of which compound 4e and 4i shown most active anxiolytic activity but are less potent than the standard drug Diazepam. Compounds tested for antihypertensive activity, compound 4a-g, and 4-i decreased systolic blood pressure significantly. Compound 4a and 4b are most active as antihypertensive agent and are less potent than the standard Propranolol drug.

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