CHAPTER 3

SYNTHESSES OF 1-[(4-ARYLPIPERAZIN-1-YL)/THIOARYLOXY] -3-[2-OXO-(PYRROLIDIN/PIPERIDIN)-1-YL]- PROPANES
3.1 BASIS OF WORK

In view of the diverse type of biological activities associated with arylpiperazines, as discussed in the preceding two chapters, and the nootropic, coognition enhancement, antiinflammatory and analgesic activities exhibited by pyrrolidine derivatives viz. I\(^1\), II\(^2\), III, IV\(^3\), V & VI\(^4\), it appeared of interest to synthesize the compounds in which combination of either of the two substructures from arylpiperazine, thioaryl and pyrrolidin-2-one are annealed together through 3-methylene unit spacer. The syntheses and pharmacological activities of such compounds viz. 1-[4-arylpiperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]propanes and 1-thioaryloxy-3-(2-oxopyrrolidine/piperdin-1-yl)propanes are presented in this chapter.

![Chemical structures]

- **I**: \( R = \text{NH}_2, \text{Pyrrolidono} \\
- **II**: \( R = \text{Me} \\
- **III**: \( R = \text{H} \\
- **IV**: \( R = \text{3-Cl} \\
- **V**: \( \text{CH}_2\text{CHCH}_2\text{N} \text{N-}\text{O} \text{OH} \\
- **VI**: \( \text{CH}_2\text{CHCH}_2\text{N} \text{N-}\text{O} \text{COCH}_3 \)
3.2 SYNTHESIS OF 1-[4-ARYLPiperazin-1-YL]-3-[2-OXOPYRROLIDIN-1-YL]PROPANES

The 1-[4-arylpiperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]-propanes (5-8) were synthesized by the condensation of 1-chloro-3-(2-oxopyrrolidin-1-yl)propane (3)\(^5\) and 1-arylpiperazines (4) in the presence of a base like Na\(_2\)CO\(_3\) or K\(_2\)CO\(_3\) and NaI/KI in DMF (Scheme 1). These compounds were also synthesized by another method in which 1-[4-arylpiperazin-1-yl]-3-chloropropanes\(^6\) (9-12) were condensed with 2-pyrrolidone (1) in the presence of a base like sodium, potassium metal or potassium tert. butoxide in different solvents such as xylene and toluene to yield 1-[4-arylpiperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]propane (13-16) (Scheme 2). The 1-[4-arylpiperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]-propanes (5-8 & 13-16), in general showed strong absorption band around 1650-1660 cm\(^{-1}\) in their IR spectra for carbonyl group. These compounds (5-8 & 13-16) in their \(^1\)H NMR spectra in CDCl\(_3\), in general exhibited a multiplet between \(\delta 1.50-2.80\) for methylene protons at 3' & 4' positions of pyrrolidine ring and 1 & 2 position of propane and 4 protons of piperazines. Rest of the aliphatic and aromatic protons appeared in the region \(\delta 3.00-3.60\) and \(\delta 6.70-7.20\) respectively. Structures of these compounds were further supported by their mass spectra which showed M\(^+\) as their molecular ion peak.
I. Pulverized Na or K metal or (CH₃)₂COK, toluene or xylene refluxing. II. Cl·C₂H₅₂CH₂Br (2).

III. HN—RX(4), Na₂CO₃-NaI or K₂CO₃-KI, dry DMF, 120°C.

**SCHEME 1**

\[
\text{Cl·C₂H₅₂CH₂Br} + \text{HN} \rightarrow \text{Cl·C₂H₅₂CH₂} - N - Ar
\]

1. aq. NaOH, acetone, r.t. 80 h. II. Pulverised Na or K, xylene refluxing. III. 9-12, xylene, refluxing.

**SCHEME 2**

I. \( R = 3\text{-F} \)
II. \( R = 4\text{-F} \)
III. \( R = 4\text{-C₆H₅} \)
IV. \( R = 2\text{-C₆H₅} \)
3.3 SYNTHESIS OF 1-THIOARYLOXY-3-[2-OXO- (PYRROLIDIN/PIPERIDIN)-1-YL]PROPANES

The title compounds (18-21 & 27-30) were synthesized either by the condensation of 1-thioaryloxy-3-chloropropane (22-25) and 2-piperidone (26) in the presence of sodium metal in xylene according to Scheme-4 or by the condensation of 1-chloro-3-[2-oxopyrrolidin-1-yl]propane (3) and substituted thiophenols (17) in the presence of sodium hydroxide in ethanol according to Scheme-3.

The 1-thioaryloxy-3-[2-oxopyrrolidin-1-yl]propanes (18-21), in general, showed strong absorption band between 1670-1675 cm⁻¹ in their IR spectra for carbonyl group. The ¹H NMR spectra of 18-21 in CDCl₃, in general exhibited a multiplet between δ 1.60-2.60 for methylene protons of 3' & 4' position of pyrrolidine ring and of 2 position of propane, triplet between δ 2.85-2.90 for methylene protons of 1 position of propane. Rest of the aliphatic and aromatic protons appeared as multiplets in the region δ 3.10-3.60 and δ 7.00-7.50 respectively. The structures of these compounds were also supported by their mass spectra.

The 1-thioaryloxy-3-[2-oxopiperidin-1-yl]propanes (27-30), in general, showed strong absorption band at 1630 cm⁻¹ in their IR spectra for carbonyl group. These compounds (27-30) in their ¹H NMR spectra in CDCl₃, generally, exhibited a multiplet between δ 1.50-2.60 for methylene protons of 3', 4' and 5' position of piperidine ring and of 2 position of propane, triplet between δ 2.90-2.95 for methylene protons of 1 position of propane, a broad
**SCHEME 3**

\[
\text{Cl-CH}_2\text{CH}_2\text{CH}_2\text{-Br} + \text{HS-}\text{C}_\text{H}_2\text{R} \xrightarrow{\text{aq. NaOH, EtOH, refluxing}} \text{Cl-CH}_2\text{CH}_2\text{CH}_2\text{-S-R}
\]

18, \( R = \text{H} \)
19, \( R = \text{4-Cl} \)
20, \( R = \text{3-Cl} \)
21, \( R = \text{4-Br} \)

**SCHEME 4**

\[
\text{HS-}\text{C}_\text{H}_2\text{R} \xrightarrow{\text{aq. NaOH, EtOH, refluxing}} \text{HS-}\text{C}_\text{H}_2\text{CH}_2\text{-S-R}
\]

22, \( R = \text{H} \)
23, \( R = \text{4-Cl} \)
24, \( R = \text{3-Cl} \)
25, \( R = \text{4-Br} \)
signal at $\delta$ 3.28 for methylene protons of 6' position of piperidine and triplet between $\delta$ 3.40-3.45 for methylene protons of 3 position of propane. Aromatic protons appeared as multiplet between $\delta$ 7.00-7.40. Structures of these compounds were further supported by their mass spectra which showed $M^+$ as their molecular ion peak.

### 3.4 EXPERIMENTAL

Melting points were taken in an electrically heated instrument and are uncorrected. Compounds were routinely checked for their purity on silica gel-G TLC plates and their spots were visualized by exposing them to iodine vapour by spraying with Dragendorff or KMnO$_4$ reagents. IR spectra ($\lambda_{\text{max}}$ in cm$^{-1}$) were recorded either on Perkin-Elmer 157 or Acculab-1 models and $^1$H NMR spectra were recorded on Perkin-Elmer R-32 (90 MHz) or EM-360L (60 MHz) or Bruker WM (400 MHz) instruments using TMS as internal reference and chemical shifts are in $\delta$ units. Mass spectra were run on Jeol JMS-D300 instrument using direct inlet system. All compounds were analysed for C, H and N contents on Carlo Erba Strum and DP 200.

1-Chloro-3-[2-oxopyrrolidin-1-yl]propane (3)

A mixture of 2-pyrrolidine (A) and base (B) in organic solvent was heated at different temperatures with vigorous stirring. 1-Bromo-3-chloropropane (C) was added to the stirred reaction mixture after specified time and the reaction mixture was heated with stirring for varied period (Table 1). The reaction mixture
Table 1:

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Molar ratio of reactants (mmol)</th>
<th>Solvent</th>
<th>Base</th>
<th>Reaction time (hrs.)</th>
<th>Temp. (°C)</th>
<th>Method of purification</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td></td>
<td>a</td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>23.0</td>
<td>25.0</td>
<td>23.0</td>
<td>Toluene (120 ml.)</td>
<td>6-7</td>
<td>7</td>
<td>120</td>
</tr>
<tr>
<td>2.</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
<td>Xylene (600 ml)</td>
<td>1/2</td>
<td>1</td>
<td>150</td>
</tr>
<tr>
<td>3.</td>
<td>12.0</td>
<td>12.0</td>
<td>12.0</td>
<td>Xylene (60 ml)</td>
<td>1/2</td>
<td>1</td>
<td>150</td>
</tr>
<tr>
<td>4.</td>
<td>12.0</td>
<td>12.0</td>
<td>12.0</td>
<td>Xylene (60 ml)</td>
<td>2</td>
<td>4</td>
<td>150</td>
</tr>
</tbody>
</table>

a- Reaction time required for salt formation before addition of 1-bromo-3-chloropropane
b- Reaction time required after addition of 1-bromo-3-chloropropane
was filtered and solvent was removed under reduced pressure to give 3 as an oil, which was purified by different methods as given in Table 1. IR (Neat): 2980, 2880, 1710, 1460, 1420, 1280, 1050. $^1$H NMR (CDCl$_3$): 1.92-2.18 (m, 4H, 4'&2-CH$_2$), 2.40 (t, 2H, J=6.0 Hz, 3'-CH$_2$), 3.42 (t, 4H, J=6.0 Hz, 5'&3-CH$_2$), 3.58 (t, 2H, J=6.0 Hz, 1-CH$_2$). MS: m/z 161(M$^+$).

1-[4-(3-Fluorophenyl)piperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]propane [5]

A mixture of 1-chloro-3-[2-oxopyrrolidin-1-yl]propane (3, 1 gm, 6.2 mmol), 1-(3-fluorophenyl)piperazine [4 (R=3-F), 1.12 gm, 6.2 mmol], anhydrous K$_2$CO$_3$ (0.434 gm, 3.1 mmol) and KI (0.10 gm, 0.6 mmol) in dry DMF (5 ml) was stirred at 90°C for 12 hours. The reaction mixture was cooled poured on water (25 ml) and the separated residue was extracted with CHCl$_3$ (2x25 ml), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give 5 as an oil which was purified by flash column chromatography over silica gel using chloroform as eluant, yield 1.32 gm (69.6%). IR (Neat): 2920, 2800, 1650, 1440, 1240, 1150, 740. $^1$H NMR (CDCl$_3$): 1.50-2.70 (m, 12H, 3',4',2,1-CH$_2$ & 2xN-CH$_2$), 3.00-3.60 (m, 8H 2xN-CH$_2$, 5' & 3-CH$_2$), 6.30-6.80 (m, 4H, ArH). MS: m/z 305 (M$^+$) 307 (M+2).

Analysis:

C$_{17}$H$_{24}$FN$_3$O

Found: C, 67.22; H, 7.72; N, 13.97
Calcd.: C, 66.86; H, 7.92; N, 13.76%.
1-[4-(4-Fluorophenyl)piperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]propane [6]

A mixture of 1-chloro-3-[2-oxopyrrolidin-1-yl]propane (3, 4.0 gm, 25.0 mmol), 1-(4-fluorophenyl)piperazine (4 (R=4-F), 4.47 gm, 25.0 mmol), anhydrous Na$_2$CO$_3$ (1.325 gm, 12.5 mmol) and NaI (0.38 gm, 2.5 mmol) in dry DMF (20 ml) was stirred at 120°C for 8 hours. The reaction mixture was worked up as described for 5 to give 6 as an oil which was purified by flash column chromatography over silica gel using chloroform as eluant, yield 5.72 gm (75.5%).

IR (Neat): 2920, 2820, 1660, 1500, 1250, 730. $^1$H NMR (CDCl$_3$): 1.50-2.80 (m, 12H, 3',4',2&1-CH$_2$, 2xN-CH$_2$), 3.00-3.60 (m, 8H, 2xN-CH$_2$, 5' & 3-CH$_2$), 6.70-7.10 (m, 4H, ArH). MS: m/z 305 (M$^+$).

Analysis:

C$_{17}$H$_{24}$FN$_3$O

Found: C, 66.55; H, 8.07; N, 13.69
Calcd.: C, 66.86; H, 7.92; N, 13.76%.

The compounds 7 & 8 were also prepared by the above procedure and their spectral and analytical data are given below:

1-[4-(4-Ethylphenyl)piperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]propane [7]

Yield 62.0%, oil. IR (Neat): 2940, 2800, 1660, 1440, 1000, 900, 800. $^1$H NMR (CDCl$_3$): 1.20 (t, 3H, J=6.0 Hz, CH$_2$-CH$_3$), 1.60-2.80 (m, 14H, 3',4',2,1,-CH$_2$, 2xN-CH$_2$, CH$_2$-CH$_3$), 3.00-3.60 (m, 8H, 2xN-CH$_2$, 5',3,-CH$_2$). MS: m/z 315 (M$^+$).
Analysis:

C$_{19}$H$_{29}$N$_3$O  
Found: C, 71.94; H, 9.16; N, 13.15  
Calcd.: C, 72.34; H, 9.27; N, 13.32%.

1-[4-(2-Ethylphenyl)piperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]propane [8]

Yield 63.6%, oil. IR (Neat): 2940, 2820, 1660, 1430, 1010, 900, 800. $^1$H NMR (CDCl$_3$): 1.24 (t, 3H, J=6.0 Hz, CH$_2$-C$\equiv$H), 1.68-1.85 (m, 2H, 4'-CH$_2$), 1.98-2.10 (m, 2H, 2-CH$_2$), 2.34-2.50 (m, 4H, 3'-CH$_2$, 1-CH$_2$), 2.62 (bs, 4H, 2xN-CH$_2$), 2.68 (q, 2H, CH$_3$-CH$_2$), 2.94 (t, 4H, J=6.0 Hz, 2xN-CH$_2$), 3.35 (t, 2H, J=6.0 Hz, 3-CH$_2$), 3.42 (t, 2H, J=6.0 Hz, 5'-CH$_2$), 7.0-7.28 (m, 4H, Ar-H).

MS: m/z 315 (M$^+$).

Analysis:

C$_{19}$H$_{29}$N$_3$O  
Found: C, 72.64; H, 9.11; N, 13.64  
Calcd.: C, 72.34; H, 9.27; N, 13.32%.

1-[4-(4-Chlorophenyl)piperazin-1-yl]-3-chloropropane (9)

1-Bromo-3-chloropropane (2, 3.68 gm, 23.0 mmol) was added dropwise to vigorously stirred solution of 4-chlorophenyl piperazine (4, R=4-Cl, 4.20 gm, 21.0 mmol) in acetone (5.36 ml) and 25% NaOH (4.02 ml). Stirring was continued at room temperature (30°C) for 60 hours. Mixture was extracted with chloroform (2x20 ml) and the CHCl$_3$ extracts were washed with water (2x20 ml), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give 9, it was
purified by column chromatography over silica gel using chloroform as eluant, yield 4.920 gm (77.12%); m.p. 60°C (lit. 7 m.p. 62°C). IR (KBr): 2980, 2820, 1590, 1490, 1240, 1180, 1000, 920, 810. \(^1\)H NMR (CDCl\(_3\)): 1.99 (quint, 2H, J=6.0 Hz, 2-CH\(_2\)), 2.54 (t, 2H, J=6.0 Hz, 1-CH\(_2\)), 2.61 (t, 4H, J=6.0 Hz, 2xN-CH\(_2\)), 3.65 (t, 2H, J=6.0 Hz, CH\(_2\)Cl), 6.84 (d, 2H, J=9.0 Hz, ArH, o to Cl), 7.20 (d, 2H, J=9.0 Hz, ArH, m to Cl). MS: m/z 272 (M\(^+\)) 274 (M+2).

Other 1-[4-aryl-piperazin-1-yl]-3-chloropropanes (10-12) were also prepared by the same method as described above and their spectral data are given below:

1-[4-(3-Chlorophenyl)piperazin-1-yl]-3-chloropropane [10]

Yield 68.2%, oil (lit. 6 10. 2HCl m.p. 203-207°C). IR (Neat): 2960, 2800, 1590, 1480, 1230, 930. \(^1\)H NMR (CDCl\(_3\)): 1.95 (quint, 2H, J=6.0 Hz, 2-CH\(_2\)), 2.40-2.78 (m, 6H, 1-CH\(_2\) & 2xN-CH\(_2\)), 3.18 (t, 4H, J=6.0 Hz, 2xN-CH\(_2\)), 3.60 (t, 2H, J=6.0 Hz, CH\(_2\)Cl), 6.60-7.25 (m, 4H, ArH). MS: m/z 272 (M\(^+\)) 274 (M+2).

1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-chloropropane [11]

Yield 65.0%, oil (lit. 7 b.p.152-155°C/0.25 mm.). IR (Neat): 2960, 2820, 1590, 1240, 1020, 920, 740. \(^1\)H NMR (CDCl\(_3\)): 2.00 (quint, 2H, J=6.0 Hz, 2-CH\(_2\)), 2.55 (t, 2H, J=6.0 Hz, 1-CH\(_2\)),
2.62-2.78 (m, 4H, 2xN-CH₂), 3.00-3.20 (m, 4H, 2xN-CH₂), 3.62 (t, 2H, J=6.0 Hz, CH₂Cl), 3.88 (s, 3H, OCH₃), 6.82-7.02 (m, 4H, ArH).

MS: m/z 268 (M⁺) 270 (M+2).

1-[4-(2-Pyridyl)piperazin-1-yl]-3-chloropropane [12]

Yield 60.0%, oil. IR (Neat): 2960, 2820, 1590, 1460, 1420, 1240, 960, 720. ¹H NMR (CDCl₃): 2.00 (quint, 2H, J=6.0 Hz, 2-CH₂), 2.30-2.70 (m, 6H, 1-CH₂ & 2xN-CH₂), 3.30-3.74 (m, 6H, 3-CH₂ & 2xN-CH₂), 6.35-6.70 (m, 2H, ArH, 3 & 5 pyridyl H), 7.35 (m, 1H, ArH, 4-pyridyl H), 8.10 (m, 1H, ArH, 6-pyridyl H). MS: m/z 239 (M⁺) 241 (M+2).

1-[4-(4-Chlorophenyl)piperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]propane [13]

Method A:

A mixture of 2 pyrrolidone (1, 1.0 gm, 12.0 mmol) and finely pulverized potassium metal (0.47 gm, 12.0 mmol) in dry xylene (60.0 ml) was heated at 150°C with vigorous stirring for 20 minutes. Thereafter 1-[4-(4-chlorophenyl)piperazin-1-yl]-3-chloropropane (9, 3.26 gm, 12.0 mmol) was added to this stirred reaction mixture at 150°C. The stirring and heating was continued for 1 hour. The reaction mixture was cooled, filtered, and xylene was removed under reduced pressure to give 13 which was purified by flash column chromatography over silica gel using chloroform as eluant, yield 2.78 gm (73.5%), m.p. 78-80°C.
Method B:

A mixture of 2 pyrrolidone (1, 1.0 gm, 12.0 mmol) and finely pulverized sodium metal (0.28 gm, 12.0 mmol) in dry xylene (60.0 ml) was heated at 150°C with vigorous stirring for 30 minutes. Thereafter 1-[4-(4-chlorophenyl)piperazin-1-yl]-3-chloropropane (13, 3.26 gm, 12.0 mmol) was added to this stirred reaction mixture. The stirring and heating was continued for 1 hour and the reaction mixture was worked up as above to give 13 which was purified by flash column chromatography over silica gel using chloroform as eluent, yield 2.83 gm (75.0%), m.p. 78-80°C. IR (KBr): 3440, 2820, 1660, 1490, 130, 810. \(^1\)H NMR (CDCl3): 1.50-2.80 (m, 12H, 3', 4', 2 & l-CH2, 2xN-CH2), 3.00-3.60 (m, 8H, 5' & 3-CH2 & 2xN-CH2), 6.80 (d, 2H, J = 9.0 Hz, ArH, o to Cl), 7.20 (2H, J = 9.0 Hz, ArH, m to Cl). MS: m/z 321 (M+1) 323 (M+2).

Analysis:

C\(_{17}\)H\(_{24}\)ClN\(_3\)O

Found: C, 63.84; H, 7.32; N, 13.12

Calcd.: C, 63.44; H, 7.52; N, 13.06%.

The compounds 14-16 were also prepared by the above procedure and their spectral and analytical data are given below.

1-[4-(3-Chlorophenyl)piperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]propane [14]

Yield (70.0%), oil. IR (Neat): 3020, 2820, 1660, 1590, 1450, 1210, 730. \(^1\)H NMR (CDCl3): 1.30-2.60 (m, 12H, 3',4', 2 & 1-CH2, 2xN-CH2), 2.40-3.50 (m, 8H, 5' & 3-CH2 & 2xN-CH2), 6.40-7.20 (m, 4H, ArH). MS: m/z 321 (M+1) 323 (M+2).
Analysis:
\[\text{C}_{17}\text{H}_{24}\text{ClN}_{3}\text{O}\]  
Found: C, 63.58; H, 7.82; N, 13.17  
Calcd.: C, 63.44; H, 7.52; N, 13.06%.

1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]propane [15]

Yield (68.0%), oil. IR (Neat): 3460, 2960, 2820, 1660, 1590, 1490, 1370, 1230, 1010, 910, 720. \(^1\)H NMR (CDCl\(_3\)): 1.50-2.80 (m, 12H, 3',4', 2 & \(\text{CH}_2\), 2xN-\(\text{CH}_2\)), 2.90-3.50 (m, 8H, 5' & 3-\(\text{CH}_2\) & 2xN-\(\text{CH}_2\)), 3.78 (s, 3H, \(\text{OCH}_3\)), 6.60-7.10 (m, 4H, \(\text{ArH}\)). MS: m/z 317 (M\(^+\)).

Analysis:
\[\text{C}_{18}\text{H}_{27}\text{N}_{3}\text{O}_2\]  
Found: C, 68.42; H, 8.43; N, 13.11  
Calcd.: C, 68.11, H, 8.58, N, 13.24%.

1-[4-(2-Pyridyl)]-3-[2-oxopyrrolidin-1-yl]propane [16]

Yield (52.0%), oil. IR (Neat): 3220, 2900, 2320, 1650, 1450, 1240. \(^1\)H NMR (CDCl\(_3\)): 1.50-2.80 (m, 12H, 3',4', 2 & \(\text{CH}_2\), 2xN-\(\text{CH}_2\)), 3.10-3.80 (m, 8H, 5' & 3-\(\text{CH}_2\), 2xN-\(\text{CH}_2\)), 6.50-6.80 (m, 2H, \(\text{ArH}\), 3,5-pyridyl \(\text{H}\)), 7.50 (m, 1H, \(\text{ArH}\), 4-pyridyl \(\text{H}\)), 8.20 (m, 1H, \(\text{ArH}\), 6-pyridyl \(\text{H}\)). MS: m/z 288 (M\(^+\)).

Analysis:
\[\text{C}_{16}\text{H}_{24}\text{N}_{4}\text{O}\]  
Found: C, 68.45; H, 8.42, N, 14.34  
Calcd.: C, 68.02; H, 8.39; N, 14.57%.
1-Phenylthio-3-[2-oxopyrrolidin-1-yl]propane [18]

A reaction mixture of NaOH (0.248 gm, 6.2 mmol), ethanol (20.0 ml) and thiophenol (17; R=H, 0.682 gm, 6.2 mmol) was refluxed for 5-6 hours at 80°C. The 1-chloro-3-[2-oxopyrrolidin-1-yl]propane (3, 1.0 gm, 6.2 mmol) was added to the above reaction mixture at room temperature (30°C) and was refluxed for 12 hours. Ethanol was evaporated under reduced pressure and water (20.0 ml) was added to the residue. The separated oil was extracted with chloroform (3x20 ml). The combined chloroform extracts were washed with water (2x30 ml), dried (Na₂SO₄) and concentrated at reduced pressure to yield 18 as an oil which was purified by column chromatography over silica gel using chloroform as eluent, yield 1.00 gm (68.49%). IR (Neat): 3480, 2960, 1670, 1430, 1280. ¹H NMR (CDCl₃): 1.60-2.60 (m, 6H, 3',4', & 2-CH₂), 2.90 (t, 2H, J=6.0 Hz, 1-CH₂), 3.10-3.60 (m, 4H, 5' & 3-CH₂), 7.00-7.50 (m, 4H, ArH). MS: m/z 235 (M⁺).

Analysis:

C₁₃H₁₇NOS

Found: C, 66.35; H, 7.51; N, 6.03
Calcd.: C, 66.34; H, 7.28; N, 5.95%.

The compounds 19-21 were also prepared by the same procedure as described above and their spectral and analytical data are given below:

1-[4-Chlorophenylthio]-3-[2-oxopyrrolidin-1-yl]-propane [19]

Yield 80.23%, oil. IR (Neat): 3460, 2920, 1670, 1420, 1260,
1090, 800. $^1$H NMR (CDCl$_3$): 1.60-2.60 (m, 6H, 3’,4’, & 2-CH$_2$), 2.90 (t, 2H, J=6.0 Hz, 1-CH$_2$), 3.20-3.60 (m, 4H, 5’ & 3-CH$_2$), 7.10-7.40 (m, 4H, ArH). MS: m/z 269 (M$^+$), 271 (M+2).

Analysis:
C$_{13}$H$_{16}$ClNOS  
Found: C, 58.08; H, 6.22; N, 5.43  
Calcd.: C, 57.87; H, 5.98; N, 5.19%.

1-[3-Chlorophenylthio]-3-[2-oxopyrrolidin-1-yl]-propane [20]

Yield 68.26%, oil. IR (Neat): 3220, 2920, 1675, 1580, 1460, 1210, 1060, 740. $^1$H NMR (CDCl$_3$): 1.60-2.50 (m, 6H, 3’,4’, & 2-CH$_2$), 2.85 (t, 2H, J=6.0 Hz, 1-CH$_2$), 3.20-3.50 (m, 4H, 5’ & 3-CH$_2$), 7.00-7.30 (m, 4H, ArH). MS: m/z 269 (M$^+$), 271 (M+2).

Analysis:
C$_{13}$H$_{16}$ClNOS  
Found: C, 57.31; H, 5.78; N, 4.77  
Calcd.: C, 57.87; H, 5.98; N, 5.19%.

1-[4-Bromophenylthio]-3-[2-oxopyrrolidin-1-yl]-propane [21]

Yield 52.60%, oil. IR (Neat): 3460, 3020, 1670, 1460, 1420, 1270, 1210, 1080, 1000, 720. $^1$H NMR (CDCl$_3$): 1.60-1.90 (m, 2H, 4’-CH$_2$), 1.92-2.10 (m, 2H, 2-CH$_2$), 2.35 (t, 2H, J=6.0 Hz, 3’-CH$_2$), 2.85 (t, 2H, J=6.0 Hz, 1-CH$_2$), 3.02-3.50 (m, 4H, 5’ & 3-CH$_2$), 7.18 (d, 2H, J=9.0 Hz, ArH, o to Br), 7.28 (d, 2H, J=9.0 Hz, ArH, m to Br). MS: m/z 314 (M$^+$), 316 (M+2).
Analysis:
C₁₃H₁₈BrNOS  Found: C, 50.02; H, 5.21; N, 4.31
Calcd.: C, 49.68; H, 5.13; N, 4.46%.

1-[4-Chlorophenylthio]-3-chloropropane [23]
A reaction mixture consisting of NaOH (1.64 gm, 41.0 mmol),
ethanol (30 ml) and 4-chlorothiophenol (17; R=4-Cl, 6.0 gm, 41.0
mmol) was refluxed for 5-6 hours. 1-Bromo-3-chloropropane (2,
6.54 gm, 41 mmol) was added to the above reaction mixture at room
temperature and refluxed for 12 hours. Ethanol was evaporated
under reduced pressure and water (30 ml) was added to the residue.
The separated oil was extracted with chloroform (3x30 ml). The
combined chloroform extracts were washed with water (2x40 ml),
dried (Na₂SO₄) and concentrated at reduced pressure to yield 23 as
an oil, which was purified by column chromatography over silica gel
using hexane chloroform (80:20) as eluant, yield 6.20 gm (67.69%)
(lit.¹⁰ b.p. 126°C/1.5 mm.). IR (Neat): 2940, 1570, 1460, 1440,
1260, 1020, 730. ¹H NMR (CDCl₃): 1.90-2.20 (m, 2H, 2-CH₂), 3.00
(t, 2H, J=6.0 Hz, S-CH₂), 3.52 (t, 2H, J=6.0 Hz, CH₂-Cl), 7.00-7.48
(m, 4H, ArH). MS: m/z 220 (M⁺), 222 (M+2).

1-[Phenylthio]-3-chloropropane [22]
Yield 40%, oil, (lit.⁸ b.p. 79-82°C/0.7 mm). IR (Neat): 2920,
1580, 1480, 1430, 1260, 1080, 1010, 720. ¹H NMR (CDCl₃): 1.90-
2.20 (m, 2H, 2-CH₂), 3.02 (t, 2H, J=6.0 Hz, S-CH₂), 3.60 (t, 2H,
J=6.0 Hz, CH₂Cl), 7.00-7.50 (m, 5H, ArH). MS: m/z 186 (M⁺), 188
1-[3-Chlorophenylthio]-3-chloropropane [24] \(^{10}\)

Yield 58.8\%, oil, (lit. b.p. 126\(^\circ\)C/1.5 mm). IR (Neat): 2940, 1580, 1470, 1270, 1120, 1080, 770, 670. \(^1\)H NMR (CDCl\(_3\)): 1.90-2.50 (m, 2H, 2-CH\(_2\)), 3.10 (t, 2H, S-CH\(_2\)), 3.68 (t, 2H, CH\(_2\)Cl), 7.10-7.30 (m, 4H, ArH). MS: m/z 220 (M\(^+\)), 222 (M+2).

1-[4-Bromophenylthio]-3-chloropropane [25]

Yield 60.0\%, oil, (lit.\(^{11}\) b.p. 149\(^\circ\)C/1.5 mm). IR (Neat): 2920, 1470, 1430, 1260, 1080, 1000, 800. \(^1\)H NMR (CDCl\(_3\)): 1.80-2.32 (m, 2H, 2-CH\(_2\)), 3.10 (t, 2H, S-CH\(_2\)), 3.65 (t, 2H, CH\(_2\)Cl), 7.10-7.60 (m, 4H, ArH). MS: m/z 265 (M\(^+\)), 267 (M+2).

1-[Phenylthio]-3-[2-oxopiperidine-1-yl]propane [27]

A mixture of 2-piperidone (26, 1.28 gm, 13.0 mmol) and finely pulverized sodium metal (0.3 gm, 13.0 mmol) in dry xylene (70 ml) was heated at 150\(^\circ\)C with vigorous stirring for 30 minutes. Thereafter 1-phenylthio-3-chloropropane (22, 2.40 gm, 13.0 mmol) was added to this reaction mixture and stirring with heating at 150\(^\circ\)C was continued for 1 hour. The reaction mixture was cooled, filtered, and xylene was removed under reduced pressure to give 27 as an oil, which was purified by column chromatography over silica gel using chloroform as eluant, yield 2.05 gm (63.66\%). IR (Neat):
3460, 2940, 1630, 1490, 1430, 1350, 1270, 1170, 730. \( ^1H \) NMR (CDCl\(_3\)): 1.40-2.60 (m, 8H, 3’,4’,5’ & 2-CH\(_2\)), 2.95 (t, 2H, J=6.0 Hz, 1-CH\(_2\)), 3.35 (bs, 2H, 6’-CH\(_2\)), 3.58 (t, 2H, J=6.0 Hz, 3-CH\(_2\)), 7.10-7.52 (m, 5H, ArH). MS: m/z 249 (M\(^+\)).

**Analysis:**

C\(_{14}H_{19}\)NOS

<table>
<thead>
<tr>
<th>Found</th>
<th>Calcd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, 67.83; H, 7.53; N, 5.34</td>
<td>C, 67.45; H, 7.68; N, 5.62%</td>
</tr>
</tbody>
</table>

The other compounds of this series (28-30) were also prepared by the same procedure as described above and their spectral and analytical data are given below:

1-[4-Chlorophenylthio]-3-[2-oxopiperidin-1-yl]-propane [28]

Yield 22.0%, oil. IR (Neat): 3460, 2940, 1630, 1540, 1450, 1320, 1260, 1160, 750. \( ^1H \) NMR (CDCl\(_3\)): 1.50-2.50 (m, 8H, 3’,4’,5’ & 2-CH\(_2\)), 2.85 (t, 2H, 1-CH\(_2\)), 3.20 (bs, 2H, 6’-CH\(_2\)), 3.40 (t, 2H, 3-CH\(_2\)), 7.00-7.30 (m, 4H, ArH). MS: m/z 283 (M\(^+\)), 285 (M+2).

**Analysis:**

C\(_{14}H_{18}\)ClNOS

<table>
<thead>
<tr>
<th>Found</th>
<th>Calcd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, 59.63; H, 6.32; N, 4.72</td>
<td>C, 59.25; H, 6.39; N, 4.93%</td>
</tr>
</tbody>
</table>

1-[3-Chlorophenylthio]-3-[2-oxopiperidin-1-yl]-propane [29]

Yield 68.0%, oil. IR (Neat): 3460, 2940, 1630, 1570, 1460, 1340, 1270, 1160, 790. \( ^1H \) NMR (CDCl\(_3\)): 1.50-2.60 (m, 8H, 3’,4’,5’ & 2-CH\(_2\)), 2.95 (t, 2H, J=6.0 Hz, 1-CH\(_2\)), 3.20 (bs, 2H, 6’-CH\(_2\)), 7.00-7.30 (m, 4H, ArH). MS: m/z 283 (M\(^+\)), 285 (M+2).
3.45 (t, 2H, J=6.0 Hz, 3-CH₂), 7.00-7.40 (m, 4H, ArH). MS: m/z 283 (M⁺), 285 (M+2).

**Analysis:**
C₁₄H₁₈ClNOS  
Found: C, 59.52; H, 6.39; N, 4.66  
Calcd.: C, 59.25; H, 6.39; N, 4.93%.

1-[4-Bromophenylthio]-3-[2-oxopiperidin-1-yl]-propane [30]

Yield 50.0%, oil. IR (Neat): 3460, 2920, 2860, 1630, 1460, 1350, 1230, 1160, 1090, 1000, 800. ¹H NMR (CDCl₃): 1.65-1.82 (m, 4H, 4',5'-CH₂), 1.85-2.00 (m, 2H, 2-CH₂), 2.36 (bs, 2H, 3-CH₂), 2.90 (t, 2H, J=6.0 Hz, 1-CH₂), 3.28 (bs, 2H, 6'-CH₂), 3.45 (t, 2H, J=6.0 Hz, 3-CH₂), 7.18 (d, 2H, J=9.0 Hz, ArH, o to Br), 7.38 (d, 2H, J=9.0 Hz, ArH, m to Br). MS: m/z 328 (M⁺), 330 (M+2).

**Analysis:**
C₁₄H₁₈BrNOS  
Found: C, 50.84; H, 5.59; N, 4.01  
Calcd.: C, 51.22; H, 5.53; N, 4.26%.

3.5 PHARMACOLOGICAL ACTIVITY

These compounds were tested for their pharmacological activities in the pharmacology division of Central Drug Research Institute, Lucknow.

The compounds were tested for their acute toxicity, gross, observational effects, reduction in spontaneous and forced
Table 1: Pharmacological activities of the compounds.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>CVS activity in µmol/kg i.v.</th>
<th>Other activitiesb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 µmol/kg</td>
<td>10 µmol/kg</td>
</tr>
<tr>
<td></td>
<td>Resting B.P.</td>
<td>Fall in B.P. (mm)</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>142</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>120</td>
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</tr>
<tr>
<td></td>
<td>124</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>110</td>
<td>10</td>
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<td>13</td>
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</tr>
<tr>
<td>14</td>
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</tr>
<tr>
<td></td>
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<tr>
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<td>140</td>
<td>75</td>
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<tr>
<td>16</td>
<td>120</td>
<td>26</td>
</tr>
<tr>
<td>18</td>
<td>110</td>
<td>10</td>
</tr>
</tbody>
</table>

Note: Al indicates the compound number.
<p>| | | | | | | | | |</p>
<table>
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<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
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<td>G</td>
<td>H</td>
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<tr>
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<td>Tr.</td>
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<tr>
<td>20</td>
<td>100</td>
<td>30</td>
<td>Tr.</td>
<td>30.00</td>
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<td>Tr.</td>
<td>18.18</td>
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<tr>
<td>27</td>
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<td>36</td>
<td>Tr.</td>
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<td>126</td>
<td>26</td>
<td>Tr.</td>
<td>20.63</td>
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</tr>
</tbody>
</table>

a- Fall in blood pressure  
b- Figure in parentheses indicate dose in µmol/kg p.o.  
c- Antiinflammatory activity against carrageenan induced oedema in mice.
locomotor activities, antagonism to amphetamine hyper activity and amphetamine toxicity in aggregated animals, electroshock seizures, antireserpine and anorexigenic activities in male mice, effect on conditioned and unconditioned avoidance response (CAR and UCR) in rats at 75 µmol/kg dose by standard methods.

The compounds were tested for their effect on blood pressure and respiration in anaesthetized cats and on spontaneous hypertensive (SHR) rats by administering different doses. The compounds were also tested for their antiinflammatory activity against carrageenin induced oedema in male mice at 100 µmol/kg dose. The significant results are described in Table 1.

Results and discussion

Most of the 1-[4-arylpiperazin-1-yl]-3-[2-oxopyrrolidin-1-yl]propanes showed interesting hypotensive activity. Among these compounds (5-8 & 13-16), the compound 6 having 4-fluoro substitution on the piperazinyl part, showed best profile of hypotensive activity. It was effective at 2 µmol/kg i.v. dose in cat as well as in SHR model and it was evaluated in detail (Table 2). The replacement of 4-fluoro group in phenylpiperazine moiety of 6 by 3-fluoro group (5) decreased the hypotensive activity. The replacement of 3-fluoro group in 5 by 4 or 2-ethyl groups (7 or 8) led to the enhancement of activity as compared to 5 but these compounds were less active than 6. The substitution of 4-ethyl by 4-chloro in 7 (13) was more active than the corresponding ethyl
compound 7. The replacement of chloro group from 4 to 3-position (14) further increased the hypotensive activity in 14 as compared to compounds 5, 7, 8 & 13. The substitution of different groups like 3-F (5), 4-C₂H₅ (7), 2-C₂H₅ (8), 4-Cl (13), 3-Cl (14) by 2-methoxy group (15) led to further enhancement of activity as compared to all compounds except 6. The replacement of substituted phenyl ring in 15 by pyridyl group (16) decreased the hypotensive activity.

Table 2: Pharmacological activity of compound 6.

<table>
<thead>
<tr>
<th>Species</th>
<th>Preparation</th>
<th>Dose (μmol/kg)</th>
<th>Hypotension (%)</th>
<th>Duration (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat</td>
<td>Normal</td>
<td>10 i.d.</td>
<td>18.87±7.78</td>
<td>73.33±8.33</td>
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<tr>
<td>Cat</td>
<td>Spinal transected</td>
<td>2 i.v.</td>
<td>17.02±4.15</td>
<td>28.61±8.76</td>
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<tr>
<td>Cat</td>
<td>Spinal transected</td>
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<td>14.09±1.07</td>
<td>15.00±3.06</td>
</tr>
<tr>
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<td>27.83±6.34</td>
<td>51.00±9.00</td>
</tr>
<tr>
<td>Rat</td>
<td>Hypertensive</td>
<td>10 i.d.</td>
<td>24.17±4.52</td>
<td>82.25±16.53</td>
</tr>
</tbody>
</table>

The replacement of phenylpiperazine part of above compounds by different thiophenols led to the formation of 1-thioaryloxy-3-[2-oxopyrrolidin-1-yl]propanes, which were either inactive as hypotensive agents or showed mild hypotensive activity.
However, these compounds showed noteworthy antiinflammatory activity in 18 & 19. The replacement of 5-membered ring by 6-membered ring (27-30) in these compounds (18-21) also neither improved hypotensive activity nor showed antiinflammatory activity.

REFERENCES

