SYNTHESIS, CHARACTERIZATION OF 4\{2-\{4-[(PHENOThIAZeNE 10YL-PHENYL-Methyl)-AMINO]2,3-
DihydROBenZimidazoL-1-yl]phenyl-Methyl\}AMino\}-BENZOIC ACID DERIVATIVES

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ABSTRACT
Novel compounds have been synthesized combining Phenothiazine ring and Benzimidazole. Phenothiazine (I) was synthesized by reacting diphenylamine, sulfur, and iodine which subsequently reacted with p-amino benzoic acid and aromatic aldehydes in ethanol produces 10-(α-p-carboxyphenyl-aminobenzyl)phenothiazines (II). Phenothiazines (II) was further treated with o-phenylene diamine in pyridine resulted in the formation of 10-(α-p-benzimidazolyl aminobenzyl) phenothiazines(III). A Series of compounds like 4\{2-\{4-[(Phenothiazine 10yl-Phenyl-methyl)-amino]2,3-
dihydrobenzimidazol-1-yl]Phenyl-methyl\}amino\}-benzoic acid (IVa-j) were synthesized by refluxing intermediate compound III with Paramino benzoic acid& Different Aromatic Benzaldehyde in presence of ethanol. The yield of novel compound was recorded 56-80%. All compounds were characterized on the basis of Melting point, I.R spectra, N.M.R spectra and Mass spectra.

Key words: Phenothiazines, Benzimidazole, Benzaldehyde

INTRODUCTION

Synthetic phenothiazines (with aliphatic, methylpiperazine, piperazine-ethanol, piperazine-ethyl, or piperidine side-chain) and phenothiazine-derived agents e.g., (thioxanthenes, benzepines, imonostilbenes, tricyclic antidepressants, dimethothiazine, and cyproheptadine) have been reported effective in the treatment of a number of medical condition like antihistamic, antipsychotic, anticholinergic (antiparkinson), antipruritic¹.

Paul Ehrlich [2] found in vitro antimicrobial activity of phenothiazine methylene blue. The potential use of chlorpromazine derivatives of this phenothiazine as an antimicrobial, increasing activity of antibiotics to which bacteria are susceptible [3-4] and reverse resistance of *Staphylococcus aureus* and corynebacteria to penicillin [5] strongly supports that phenothiazine can be exploited for the management of bacterial infections.

It was hypothesized that since Phenothiazine and Benzimidazole rings showed antimicrobial activity [6-7] individually; combination of these two rings may produce compounds which may have potent antimicrobial activity. Henceforth, this study was focused on the synthesis and antimicrobial activity of molecules combining Phenothiazine and Benzimidazole rings.
MATERIALS AND METHODS

Materials

Benzaldehyde, 2-ChloroBenzaldehyde, 4-ChloroBenzaldehyde, 4-Hydroxy Benzaldehyde, 2-Hydroxy Benzaldehyde, 2-Nitro Benzaldehyde, Para-amino benzoic acid, Diphenylamine, 2-Methoxy Benzaldehyde, Pyridine, o-phenylenediamine, Sulfur powder purified, 4-Methoxy Benzaldehyde, 3-Hydroxy Benzaldehyde, 2-Methoxy-4-Hydroxy Benzaldehyde.

Synthesis of Phenothiazine Derivatives

All the melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked on silica gel plates by using appropriate solvents. The IR spectra (KBr) were recorded on a Shimadzu spectrophotometer. 1H- NMR spectra were recorded on Bruker spectrophotometer. (AMX 400 MHz) using CDCl3, DMSO as internal standard. The chemical shift values are expressed in δ ppm (parts per million). The MASS spectrum was recorded on Autospec Mass spectrometer.

General procedure: A mixture of 10-(α-benzimidazolyl-amino benzyl)phenothiazine benzaldehyde (III) (0.02 mol), (0.02 mol) of Paraamino benzoic acid and (0.02 mol) of different Aromatic benzaldehyde in ethanol 50 ml was heated under reflux for 4-8 hours on a steam bath subsequently ethanol was distilled off and the pasty mass obtained was triturated with petroleum ether the product which was isolated and dried in vaccum desicator it was recrystallized from different organic and inorganic solvent. [8]

RESULT & DISCUSSION

4-[2-{4-[(Phenothiazine 10yl-Phenyl-methyl)-amino]2,3-dihydrobenzimidazol-1-yl}Phenyl-methylamino]-benzoic acid. (IVa)

The characteristic peaks in IR and NMR are as follows:

IR(KBr)- 3693, 1691, 1101, 1338, 3338, 1483, 700, 3042 cm⁻¹

1H-NMR(CDCl3)- 7.05(d, 2H Phenothiazine), 6.67 (t, 3H Phenothiazine), 7.10 (t, 3H Phenothiazine), 6.61 (d, , 2H Phenothiazine), 7.21 (d, 2H Methylene group), 7.24 (t, 3H Methylene group), 5.04 (t, 3H Methylene group), 4.0 (d, 2H amino group), 7.25 (d, 2H Benzimidazole), 7.29 (d, , 2H Benzimidazole), 7.31 (d, 2H Benzimidazole), 10.9 (s, 1H hydroxyl group).6.61-7.98(m,10H Aromatic Proton)7.05-7.68 (m,10H Aromatic Proton)

Mass-m/z-723.8
4 {[(2-Chloro-PhenyI) -(2-{4-[(Phenothiazine 10yl-Phenyl-methyl)-amino]2,3-ihydrobenzimidazol-1-yl)Phenyl-methyl]amino}-benzoic acid. (IVb)

The characteristic peaks in IR are as follows:

\[
\text{IR (KBr)} - 3041, 1606, 1164, 1284, 3361, 1471, 686 \text{ cm}^{-1}
\]

\[
\text{HNMR (CDCl}_3\text{)} - 7.14 (d, 2H Phenothiazine), 6.98 (t, 3H Phenothiazine), 7.21 (t, 3H Phenothiazine), 6.98 (d, 2H Phenothiazine), 7.21 (d, 2H Methylene group), 7.24 (t, 3H Methylene group), 5.04 (t, 3H Methylene group), 4.18 (d, 2H amino group), 7.25 (d, 2H Benzimidazole), 7.28 (d, 2H Benzimidazole), 7.31 (d, 2H Benzimidazole), 10.99 (s, 1H hydroxyl group).

\[
6.98-7.98 (m, 10H Aromatic Proton) 7.14-7.31 (m, 10H Aromatic Proton)
\]

\[
\text{Mass-m/z-758.3}
\]

4 {[(4-Chloro-PhenyI) -(2-{4-[(Phenothiazine 10yl-Phenyl-methyl)-amino]2,3-ihydrobenzimidazol-1-yl)Phenyl-methyl]amino}-benzoic acid. (IVc)

The characteristic peaks in IR are as follows:

\[
\text{IR (KBr)} - 3093, 1616, 1193, 1382, 3390, 1440, 1080, 640 \text{ cm}^{-1}
\]

\[
\text{HNMR (DMSO)} - 7.14 (d, 2H Phenothiazine), 6.98 (t, 3H Phenothiazine), 7.21 (t, 3H Phenothiazine), 6.98 (d, 2H Phenothiazine), 7.21 (d, 2H Methylene group), 7.24 (t, 3H Methylene group), 5.11 (t, 3H Methylene group), 4.18 (d, 2H amino group), 7.25 (d, 2H Benzimidazole), 7.28 (d, 2H Benzimidazole), 7.31 (d, 2H Benzimidazole), 10.9 (s, 1H hydroxyl group).

\[
6.98-7.98 (m, 10H Aromatic Proton) 7.14-7.31 (m, 10H Aromatic Proton)
\]

\[
\text{Mass-m/z-738.3}
\]

4 {[(2-Hydroxy-PhenyI) -(2-{4-[(Phenothiazine 10yl-Phenyl-methyl)-amino]2,3-ihydrobenzimidazol-1-yl)Phenyl-methyl]amino}-benzoic acid. (IVd)

The characteristic peaks in IR are as follows:

\[
\text{IR (KBr)} - 3085, 1045, 1278, 3375, 1498, 1598, 1369, 644 \text{ cm}^{-1}
\]

\[
\text{HNMR (DMSO)} - 7.14 (d, 2H Phenothiazine), 6.98 (t, 3H Phenothiazine), 7.21 (t, 3H Phenothiazine), 6.98 (d, 2H Phenothiazine), 7.21 (d, 2H Methylene group), 7.24 (t, 3H Methylene group), 5.11 (t, 3H Methylene group), 4.11 (d, 2H amino group), 7.25 (d, 2H Benzimidazole), 7.28 (d, 2H Benzimidazole), 7.31 (d, 2H Benzimidazole), 10.9 (s, 1H hydroxyl group).

\[
6.98-7.98 (m, 10H Aromatic Proton) 7.14-7.74 (m, 10H Aromatic Proton)
\]

\[
\text{Mass-m/z-739.8}
\]
4 \{(4-Hydroxy-Phenyl) -\(2-{4-[\text{Phenothiazine \(10y\)-Phenyl-methyl]-amino}\)2,3-ihydrobenzimidazol-1-yl\)Phenyl-methyl\[amino\]-benzoic acid. (IVe)

The characteristic peaks in IR are as follows:

IR (KBr)- 3089, 1081, 1272, 3379, 1488, 1612, 1323, 875, 624 cm\(^{-1}\)

\(^1\text{HNMR(DMSO)}-\)

\[7.14(d, \ 2H \ \text{Phenothiazine}), 6.92 \ (t, \ 3H \ \text{Phenothiazine}), 7.21 \ (t, \ 3H \ \text{Phenothiazine}), 6.87 \ (d, \ , \ 2H \ \text{Phenothiazine}), 7.21 \ (d, \ 2H \ \text{Methylene group}), 7.25 \ (t, \ 3H \ \text{Methylene group}), 5.12 \ (t, \ , \ 3H \ \text{Methylene group}), 4.11 \ (d, \ 2H \ \text{amino group}), 7.25 \ (d, \ 2H \ \text{Benzimidazole}), 7.29(d, \ , \ 2H \ \text{Benzimidazole}), 7.31 \ (d, \ 2H \ \text{Benzimidazole}), 10.9 \ (s, \ 1H \ \text{hydroxyl group}).6.81-7.97(m,10H \ Aromatic Proton)7.05-7.68 (m,10H \ Aromatic Proton)

Mass-\(m/z\)-729.8

4 \{(2-Nitro-Phenyl) -\(2-{4-[\text{Phenothiazine \(10y\)-Phenyl-methyl]-amino}\)2,3-ihydrobenzimidazol-1-yl\)Phenyl-methyl\[amino\]-benzoic acid (IVf)

The characteristic peaks in IR are as follows:

IR(KBr)- 3062, 1614, 1201, 1380, 3367, 1444, 1085,649 cm\(^{-1}\)

\(^1\text{HNMR(DMSO)}-\)

\[7.13(d, \ 2H \ \text{Phenothiazine}), 6.93 \ (t, \ 3H \ \text{Phenothiazine}), 7.22 \ (t, \ 3H \ \text{Phenothiazine}), 6.69 \ (d, \ , \ 2H \ \text{Phenothiazine}), 7.23 \ (d, \ 2H \ \text{Methylene group}), 7.29 \ (t, \ 3H \ \text{Methylene group}), 5.11 \ (t, \ , \ 3H \ \text{Methylene group}), 4.15 \ (d, \ 2H \ \text{amino group}), 7.30 \ (d, \ 2H \ \text{Benzimidazole}), 7.31 \ (d, \ , \ 2H \ \text{Benzimidazole}), 7.41 \ (d, \ 2H \ \text{Benzimidazole}), 11.30 \ (s, \ 1H \ \text{hydroxyl group}).6.62-7.93(m,10H \ Aromatic Proton)7.1-7.6 (m,10H \ Aromatic Proton)

Mass-\(m/z\)-768.8

4 \{(2-Methoxy-Phenyl) -\(2-{4-[\text{Phenothiazine \(10y\)-Phenyl-methyl]-amino}\)2,3-ihydrobenzimidazol-1-yl\)Phenyl-methyl\[amino\]-benzoic acid. (IVg)

The characteristic peaks in IR are as follows:

IR(KBr)- 3045, 1625, 1105, 1282, 3388, 1500, 1026, 699 cm\(^{-1}\)

\(^1\text{HNMR(DMSO)}-\)

\[7.18(d, \ 2H \ \text{Phenothiazine}), 6.62 \ (t, \ 3H \ \text{Phenothiazine}), 7.22 \ (t, \ 3H \ \text{Phenothiazine}), 6.69 \ (d, \ , \ 2H \ \text{Phenothiazine}), 7.23 \ (d, \ 2H \ \text{Methylene group}), 7.29 \ (t, \ 3H \ \text{Methylene group}), 5.11 \ (t, \ , \ 3H \ \text{Methylene group}), 4.15 \ (d, \ 2H \ \text{amino group}), 7.30 \ (d, \ 2H \ \text{Benzimidazole}), 7.31 \ (d, \ , \ 2H \ \text{Benzimidazole}), 7.41 \ (d, \ 2H \ \text{Benzimidazole}), 11.30 \ (s, \ 1H \ \text{hydroxyl group}).6.62-7.93(m,10H \ Aromatic Proton)7.1-7.6 (m,10H \ Aromatic Proton)

Mass-\(m/z\)-733.9
4 {[(4-Methoxy-Phenyl) -(2-{4-[(Phenothiazine 10yl-Phenyl-methyl)-amino]2,3-ihydrobenzimidazol-1-yl})Phenyl-methyl]amino}-benzoic acid. (IVh)

Characteristic peaks in IR are as follows:

**IR (KBr)** - 3026, 1593, 1070, 1253, 3357, 1481, 3643, 615 cm$^{-1}$

$^1$HNMR(DMSO) - 7.18(d, 2H Phenothiazine), 6.69 (t, 3H Phenothiazine), 7.23 (t, 3H Phenothiazine), 6.09 (d, , 2H Phenothiazine), 7.23 (d, 2H Methylene group), 7.29 (t, 3H Methylene group), 5.11(t, , 3H Methylene group), 4.15 (d, 2H amino group), 7.30 (d, 2H Benzimidazole), 7.31 (d, , 2H Benzimidazole), 7.41 (d, 2H Benzimidazole), 11.30 (s, 1H hydroxyl group).6.62-7.55(m,10H Aromatic Proton)7.1-7.9 (m,10H Aromatic Proton)

**Mass-m/z-753.9**

4 {[(3-Hydroxy-Phenyl) -(2-{4-[(Phenothiazine 10yl-Phenyl-methyl)-amino]2,3-ihydrobenzimidazol-1-yl})Phenyl-methyl]amino}-benzoic acid. (IVi)

The characteristic peaks in IR are as follows:

**IR (KBr)** - 3060, 1600, 1081, 1276, 3369, 1406, 3612, 700 cm$^{-1}$

$^1$HNMR(DMSO) - 7.18(d, 2H Phenothiazine), 6.69 (t, 3H Phenothiazine), 7.23(t, 3H Phenothiazine), 6.09 (d, , 2H Phenothiazine), 7.23 (d, 2H Methylene group), 7.30(t, 3H Methylene group), 5.18(t, , 3H Methylene group), 4.25(d, 2H amino group), 7.30 (d, 2H Benzimidazole), 7.31 (d, , 2H Benzimidazole), 7.41 (d, 2H Benzimidazole), 11.30 (s, 1H hydroxyl group).6.62-7.55(m,10H Aromatic Proton)7.11-7.93 (m,10H Aromatic Proton)

**Mass-m/z-709.8**

4 {[(4-Hydroxy-2-Methoxy-Phenyl) -(2-{4-[(Phenothiazine 10yl-Phenyl-methyl)-amino]2,3-ihydrobenzimidazol-1-yl})Phenyl-methyl]amino}-benzoic acid. (IVj)

The characteristic peaks in IR are as follows:

**IR(KBr)**- 3078, 1600, 1122, 1303, 3367, 1431, 929,692 cm$^{-1}$,

$^1$HNMR(DMSO) 7.22(d, 2H Phenothiazine), 6.62 (t, 3H Phenothiazine), 7.18 (t, 3H Phenothiazine), 6.09 (d, , 2H Phenothiazine), 7.29 (d, 2H Methylene group), 7.30 (t, 3H Methylene group), 5.11 (t, , 3H Methylene group), 4.25 (d, 2H amino group), 7.41(d, 2H Benzimidazole), 7.31 (d, , 2H Benzimidazole), 7.45 (d, 2H Benzimidazole), 11.30 (s, 1H hydroxyl group).6.62-7.52(m,10H Aromatic Proton)7.11-7.93 (m,10H Aromatic Proton)

**Mass-m/z-739.9**
Table 1: Physicochemical data of 4[2-{4-[(Phenothiazine 10yl-Phenyl-methyl)-amino]2,3-dihydrobenzimidazol-1-yl)Phenyl-methyl]amino}-benzoic acid. (IVa-j)

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Compound</th>
<th>R</th>
<th>M.P (°C)</th>
<th>Yield (%)</th>
<th>Molecular weight</th>
<th>Molecular formula</th>
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<tr>
<td>1</td>
<td>IVa</td>
<td>H</td>
<td>181-183</td>
<td>62.2</td>
<td>723.88</td>
<td>C₄₆H₃₇N₅O₂S</td>
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<tr>
<td>2</td>
<td>IVb</td>
<td>o-Cl</td>
<td>190-192</td>
<td>65.5</td>
<td>758.33</td>
<td>C₄₆H₃₆ClN₅O₂S</td>
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<tr>
<td>3</td>
<td>IVc</td>
<td>p-Cl</td>
<td>162-164</td>
<td>56.9</td>
<td>758.33</td>
<td>C₄₆H₃₆ClN₅O₂S</td>
</tr>
<tr>
<td>4</td>
<td>IVd</td>
<td>o-OH</td>
<td>195-197</td>
<td>75.5</td>
<td>739.88</td>
<td>C₄₆H₃₇N₅O₂S</td>
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<tr>
<td>5</td>
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<td>p-OH</td>
<td>175-177</td>
<td>77.6</td>
<td>739.88</td>
<td>C₄₆H₃₇N₅O₂S</td>
</tr>
<tr>
<td>6</td>
<td>IVf</td>
<td>o-NO₂</td>
<td>156-158</td>
<td>79.5</td>
<td>768.88</td>
<td>C₄₆H₃₆N₆O₄S</td>
</tr>
<tr>
<td>7</td>
<td>IVg</td>
<td>o-OCH₃</td>
<td>169-171</td>
<td>58.9</td>
<td>753.91</td>
<td>C₄₇H₃₉N₅O₃S</td>
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<tr>
<td>8</td>
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<td>p-OCH₃</td>
<td>203-205</td>
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<td>753.91</td>
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<td>C₄₆H₃₇N₅O₃S</td>
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<tr>
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<td>o-OCH₃ p-OH</td>
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<td>C₄₇H₃₉N₅O₄S</td>
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CONCLUSION

From all these studies, it is apparent that the phenothiazine and structurally related compounds possessing three benzene rings are often endowed with potent antimicrobial action. Compounds IVc, IVf, IVi shows good activity against *E.Coli* (gram negative) *B.subtilis, S.aureus*. compound IVb, IVd, IVh shows moderate activity against *E.Coli, B.subtilis, S.aureus*. The structures of the synthesized compounds were characterized with the help of TLC, IR and NMR, MASS.
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