Synthesis, Characterization, of 2H-3-Aryl-3, 4-Dihydro-1,3-Chlorobenzoxazine Derivatives of Benzoxazoline, antimicrobial activity and PC model Computational Studies

Indorkar Dilesh, Chourasia O.P. and Limaye S.N.
Department of Chemistry, Dr. H.S. Gour Central University Sagar, MP, 470 003, INDIA

Available online at: www.isca.in, www.isca.me
Received 19th October 2014, revised 21st November 2014, accepted 13th December 2014

Abstract
The invention comprises benzoxazole-2-carboxylic acid derivatives of the general formula wherein R represents a chlorine atom or an alkyl radical containing 1 to 4 carbon atoms, n is 0 or an integer of 1 to 4, and Y represents -OR1 or -NR112, wherein R1 represents an alkyl, aralkyl, cycloalkyl, aryl or chloroaryl radical and R11 represents a hydrogen atom or an alkyl, aralkyl or cycloalkyl radical, or -NR112 represents a heterocyclic ring. They may be prepared by causing a 3-chlorobenzoxazine-(1,4)-one-(2) of the general formula to react with ammonia, a strong basic primary or secondary amine, an alcohol, a phenol or a chlorophenol in the presence of an acid binding agent.; The reaction is expeditiously performed in an inert organic solvent or diluent at -30 DEG to + 200 DEG C. and when one of the reactants is an alcohol it can advantageously be used in excess as the diluent. Specified acid binding agents are the alkali metal and alkaline earth metal hydroxides, carbonates and bicarbonates, but in the case of the reaction with ammonia or an amine an excess thereof can be used instead of the binding agent.; The compounds of the invention may be isolated from the reaction mixture, which may contain the corresponding 3-substituted-benzoxazine-(1,4)-ones-(2) as by-products (see Specification 1,008,266), by, for example, fractional crystallization or preparative chromatography. ALSO:Herbicidal compositions comprise benzoxazole-2-carboxylic acid derivatives of the general formula wherein R represents a chloric atom or an alkyl radical containing 1 to 4 carbon atoms, n is 0 or an integer of 1 to 4, and 7 represents -OR1 or -NR112, where in R1 represents an alkyl, aralkyl, cycloalkyl, aryl or chloroaryl radical and R11 represents a hydrogen atom or an alkyl, aralkyl or cycloalkyl radical, or -NR112 represents a heterocyclic ring.; The compositions may be prepared by causing the reaction mixture to react with ammonia, a strong basic primary or secondary amine, an alcohol, a phenol or a chlorophenol in the presence of an acid binding agent.; The compounds of the invention may be isolated from the reaction mixture, which may contain the corresponding 3-substituted-benzoxazine-(1,4)-ones-(2) as by-products (see Specification 1,008,266), by, for example, fractional crystallization or preparative chromatography. ALSO:Herbicidal compositions comprise benzoxazole-2-carboxylic acid derivatives of the general formula wherein R represents a chloric atom or an alkyl radical containing 1 to 4 carbon atoms, n is 0 or an integer of 1 to 4, and Y represents -OR1 or -NR112, wherein R1 represents an alkyl, aralkyl, cycloalkyl, aryl or chloroaryl radical and R11 represents a hydrogen atom or an alkyl, aralkyl or cycloalkyl radical, or -NR112 represents a heterocyclic ring.; The compositions may be in the form of p emulsifiable concentrates, spray powders, pastes, soluble powders, dusts or granulates and contain 0.1 to 95% by weight of the active compounds.

Keywords: Synthesis, characterization, chlorobenzoxazine derivatives, antimicrobial, PC model, computational studies.

Introduction
The present new heterocyclic esters are therapeutically useful as such or can be employed in the form of salts with a wide variety of acids, inorganic and organic, including therapeutically-acceptable acids. The strobilurins, derived from fermentations of Strobilus tenacellus by Anke and coworkers in 1977, are one of the most important classes of agricultural fungicides. Their primary mechanism of action is the inhibition of mitochondrial respiration by blocking electron transfer at the ubiquinol oxidation center (Qo site) of the cytochrome 1 complex (complex III). Strobilurin derivatives have attracted significant attention of the agricultural chemists owing to their outstanding characteristics and uniquemode of action, broader antifungal spectrum, long-lasting effects, high antifungal activity, and low toxicity toward mammalian cells. The strobilurins were first commercialized in 1996 with the launch of azoxystrobin and kresoxim-methyl (figure-1). Till date, over ten strobilurin derivatives are commercially available. However, following the use of strobilurin fungicides in a short period of field applications, significant increase in resistance to fungicide has been observed. Recently, significant research efforts focusing on structural modification of strobilurins have been devoted to overcoming the above-mentioned problem. Moreover, according to the literature, the methoxyiminoacetate is an effective pharmaphore which is indispensable for antifungal activity of strobilurin fungicides. The aromatic bridge helps to stabilize the molecule and the molecule also exhibits photo stability. Therefore, numerous studies have reported that modification of the side chain is the most effective method to obtain novel strobilurin derivatives with higher biological activities. In general, 1,2,4-triazole and similar Schiff bases exhibit diverse biological activities, such as pesticides, fungicides, herbicidal, anticancer, anti-inflammatory, antiviral, and antimicrobial properties. So far, over twenty triazole fungicides have been commercialized, like triadimefon and triadimenol. Therefore, based on the active substructure combination and biososeteric replacement, the intermediate derivatization method was employed to synthesize a series of novel strobilurin derivatives containing 1,2,4-triazole.

Methodology
Step: I Preparation of 2-(arylimino)-5—Chloromethyl
**phenols:** 5-Chlorosalicilaldehyde(I) 2 gm and appropriate aromatic amine 2 gm were refluxed in ethanol (20 ml) for 30 min crystalline residue deposited on cooling was further purified by crystallization from chloroform-petroleum ether (2:8 v/v) to furnish (II) the amines taken were aniline (Clbenz.1), p-Chloro-aniline, (Clbenz.2), o-nitroaniline, (Clbenz.3), m-nitro aniline (Clbenz.4), p-nitro aniline and (Cbenz.5), p-bromo-aniline.

Step II Preparation of 2-(Arylamino)-5-Chloromethyl phenols: Sodium borohydride (0.5 gm) was added to solution of 2-(arylimino)-5-Chloromethyl phenol (2 gm) in methanol (10 ml) and the mixture stirred for 30 min at room temperature. The residue obtained on pouring the solution in to cold water was further crystallized from ethanol to afford (III).

Step III Preparation of 2H-3-Aryl-3, 4-Dihydro-1,3-Chlorobenzoxazine: 2-(arylimino)-5-Chloromethyl phenol 2 gm and formalin (35% 10 ml) were refluxed in ethanol (10 ml) for 6 h. The residue obtained after pouring the reaction mixture into cold water was crystallized from ethanol to give the yields and melting points of the 1, 3-oxazines are given in table-1. The molecular formulae of these compounds were calculated from their elemental analysis (table-2). The structure of 1,3-oxazines were confirmed by their IR spectra. IR spectra of compounds have been scanned with Perkin-Elmer spectrophotometer using KBr pellets.

\[ \text{Cl} \quad \text{OH} \quad + \quad \text{NH}_2 \quad \rightarrow \quad \text{Cl} \quad \text{OH} \quad \text{N} \quad \text{NH} \quad \text{R} \]

\[ \text{Cl} \quad \text{O} \quad \text{Cl} \quad \text{N} \quad \text{OH} \quad \text{R} \]

\[ \text{R= 1 p- chloro-aniline, 2 o-nitro-aniline, 3 m-nitro-aniline, 4 p-nitro-aniline, 5 p-bromo-aniline.} \]

**Scheme-1**

**Reaction Sequences**

![Figure-1](Figure-1)

**Ball and stick model Chloro-Benzoxazine**
Table 1
Physical Data Compound Code Clbenzx

<table>
<thead>
<tr>
<th>Name</th>
<th>2H-3(p-bromophenyl)-3,4-dihydro-Chloro-1,3-benzoxazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. Wt.</td>
<td>356.7</td>
</tr>
<tr>
<td>M.P. °C</td>
<td>165</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>75</td>
</tr>
<tr>
<td>Mol. For.</td>
<td>C14H11NO3ClBr</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elemental Analysis</th>
<th>C %</th>
<th>H %</th>
<th>N %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>47.10</td>
<td>3.06</td>
<td>13.44</td>
</tr>
<tr>
<td>Calcu.</td>
<td>47.12</td>
<td>3.08</td>
<td>13.46</td>
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</table>

Table 2
Characterization of IR data

<table>
<thead>
<tr>
<th>Group type</th>
<th>Vibration mode</th>
<th>Frequency (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxazine ring</td>
<td>-CH (str.) in –OCH₂</td>
<td>2916.64</td>
</tr>
<tr>
<td></td>
<td>-CH (str.) in –NCH₂</td>
<td>2842.54</td>
</tr>
<tr>
<td></td>
<td>-C-N (str.) in –NCH₂</td>
<td>1278.78</td>
</tr>
<tr>
<td></td>
<td>C-O(str.) in –OCH₂</td>
<td>1062.96</td>
</tr>
<tr>
<td></td>
<td>-CH (bend.) in–OCH₂</td>
<td>1510.65</td>
</tr>
<tr>
<td></td>
<td>-CH (bend.) in –NCH₂</td>
<td>1473.97</td>
</tr>
<tr>
<td>Aromatic ring</td>
<td>-CH (str.)</td>
<td>3056.54, 3012.13</td>
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<tr>
<td></td>
<td>C=C (str.)</td>
<td>1597.60</td>
</tr>
<tr>
<td></td>
<td>-CH (bend.)</td>
<td>1026.65</td>
</tr>
<tr>
<td>Ar-Cl</td>
<td>C-Cl(str.) in Ar-Cl</td>
<td>760.90</td>
</tr>
<tr>
<td>Ar-Br</td>
<td>C-Br(str.) in Ar-Br</td>
<td>621.80</td>
</tr>
</tbody>
</table>

Table 3
Characterization of H¹ NMR data

<table>
<thead>
<tr>
<th>Signal No.</th>
<th>Chemical shift (in δ ppm)</th>
<th>Multiplicity</th>
<th>Relativeno. of protons</th>
<th>Inference</th>
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<tbody>
<tr>
<td>1.</td>
<td>7.16-7.71</td>
<td>Multiplet</td>
<td>7</td>
<td>Ar-H</td>
</tr>
<tr>
<td>2.</td>
<td>4.68</td>
<td>Singlet</td>
<td>2</td>
<td>-OCH₂ of Benzoxazine ring</td>
</tr>
<tr>
<td>3.</td>
<td>3.63</td>
<td>Singlet</td>
<td>2</td>
<td>-NCH₂ of Benzoxazine ring</td>
</tr>
</tbody>
</table>

Table 4
Variation in PC Model simulated data for substituted Chlorobenzoxazine derivatives of series

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clbenzx.1</td>
<td>13</td>
<td>4 – Cl</td>
<td>1.463</td>
<td>120.82</td>
<td>165.82</td>
<td>280</td>
<td>9.24</td>
<td>1.89</td>
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<td>11</td>
<td>2-NO₂</td>
<td>1.459</td>
<td>112.26</td>
<td>156.94</td>
<td>276</td>
<td>11.7</td>
<td>5.03</td>
</tr>
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<td>12</td>
<td>3-NO₂</td>
<td>1.457</td>
<td>111.60</td>
<td>160.096</td>
<td>276</td>
<td>11.7</td>
<td>3.93</td>
</tr>
<tr>
<td>Clbenzx 4</td>
<td>13</td>
<td>4-NO₂</td>
<td>1.464</td>
<td>120.81</td>
<td>166.19</td>
<td>275</td>
<td>10.1</td>
<td>2.51</td>
</tr>
<tr>
<td>Clbenzx .5</td>
<td>13</td>
<td>4 – Br</td>
<td>1.463</td>
<td>120.82</td>
<td>165.82</td>
<td>356</td>
<td>9.36</td>
<td>1.95</td>
</tr>
</tbody>
</table>
Table-5
Z-matrix in PC Model simulated data for substituted Chlorobenzoxazine derivatives of series

<table>
<thead>
<tr>
<th>Compound code Clbenz – 20</th>
<th>PC Model Values</th>
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</thead>
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<tr>
<td></td>
<td>MMXEnergy</td>
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<td></td>
<td>27.582</td>
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<tr>
<td>Structure:</td>
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<tr>
<td></td>
<td>Str 0.642</td>
</tr>
<tr>
<td></td>
<td>Bnd 1.32</td>
</tr>
<tr>
<td></td>
<td>Str Bnd 0.052</td>
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<tr>
<td></td>
<td>Tor 14.47</td>
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<td></td>
<td>VDW 9.363</td>
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<tr>
<td></td>
<td>QQ 1.743</td>
</tr>
<tr>
<td></td>
<td>DM 1.954</td>
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<tr>
<td></td>
<td>HF 16.85</td>
</tr>
<tr>
<td></td>
<td>SE 3.15</td>
</tr>
</tbody>
</table>

Table-6
IR Characterization data for specific bonds in substituted Chlorobenzoxazine derivatives

<table>
<thead>
<tr>
<th>Compound code</th>
<th>Substituent</th>
<th>C=N</th>
<th>C-O</th>
<th>C-H(str) in NCH₂</th>
<th>C-H(bend) in N-CH₂</th>
<th>C=C</th>
<th>Ar-Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clbenzx.-1</td>
<td>4 – Cl</td>
<td>1279.5</td>
<td>1056.8</td>
<td>2846.1</td>
<td>1472.4</td>
<td>1610.7</td>
<td>767.4</td>
</tr>
<tr>
<td>Clbenzx.-2</td>
<td>2 – NO₂</td>
<td>1269.6</td>
<td>1062.8</td>
<td>2843.1</td>
<td>1441.4</td>
<td>1605.6</td>
<td>769.9</td>
</tr>
<tr>
<td>Clbenzx.-3</td>
<td>3 – NO₂</td>
<td>1271.5</td>
<td>1056.7</td>
<td>2840.2</td>
<td>1452.4</td>
<td>1608.7</td>
<td>770.9</td>
</tr>
<tr>
<td>Clbenzx.-4</td>
<td>4 – NO₂</td>
<td>1277.5</td>
<td>1058.6</td>
<td>2838.12</td>
<td>1456.4</td>
<td>1604.7</td>
<td>774.8</td>
</tr>
<tr>
<td>Clbenzx.-5</td>
<td>4 – Br</td>
<td>1278.6</td>
<td>1062.8</td>
<td>2842.2</td>
<td>1473.5</td>
<td>1597.7</td>
<td>621.4</td>
</tr>
</tbody>
</table>

The deviations may be due to the steric hinderance in these cases. On similar lines, the NMR shift values showed the following trend. 4-Br, 2-NO₂, 3-NO, 4-NO₂, 4-Cl

Table-7
Variation in the ¹H-NMR spectra for substituted Chlorobenzoxazine derivatives of series III

<table>
<thead>
<tr>
<th>Compound code</th>
<th>Substituent</th>
<th>Cl-Subs ring</th>
<th>-OCH₂ of benzoazine ring</th>
<th>-NCH₂ of benzoazine ring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clbenzx.-1</td>
<td>4 – Cl</td>
<td>7.19-7.77</td>
<td>4.60</td>
<td>3.59</td>
</tr>
<tr>
<td>Clbenzx.-2</td>
<td>2 – NO₂</td>
<td>7.00-7.73</td>
<td>4.66</td>
<td>3.56</td>
</tr>
<tr>
<td>Clbenzx.-3</td>
<td>3 – NO₂</td>
<td>7.02-7.72</td>
<td>4.62</td>
<td>3.52</td>
</tr>
<tr>
<td>Clbenzx.-4</td>
<td>4 – NO₂</td>
<td>7.39-7.64</td>
<td>4.63</td>
<td>3.67</td>
</tr>
<tr>
<td>Clbenzx.-5</td>
<td>4 – Br</td>
<td>7.16-7.71</td>
<td>4.68</td>
<td>3.63</td>
</tr>
</tbody>
</table>

This may be the expected trend on account of the PC Model data obtained for these compounds (table-7)

Table-8
Computer simulated PC Model data for marked bonds and their subsequent angles Series III

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clbenzx.-1</td>
<td>4 – Cl</td>
<td>1.463</td>
<td>120.82</td>
<td>165.82</td>
<td>280</td>
<td>9.245</td>
<td>1.899</td>
<td>27.338</td>
</tr>
<tr>
<td>Clbenzx.-2</td>
<td>2 – NO₂</td>
<td>1.459</td>
<td>112.26</td>
<td>156.94</td>
<td>276.5</td>
<td>11.76</td>
<td>5.033</td>
<td>44.908</td>
</tr>
<tr>
<td>Clbenzx.-3</td>
<td>3 – NO₂</td>
<td>1.457</td>
<td>111.60</td>
<td>160.96</td>
<td>276.5</td>
<td>11.74</td>
<td>3.938</td>
<td>29.41</td>
</tr>
<tr>
<td>Clbenzx.-4</td>
<td>4 – NO₂</td>
<td>1.464</td>
<td>120.81</td>
<td>166.19</td>
<td>275</td>
<td>10.13</td>
<td>2.516</td>
<td>22.208</td>
</tr>
<tr>
<td>Clbenzx.-5</td>
<td>4 – Br</td>
<td>1.463</td>
<td>120.82</td>
<td>165.82</td>
<td>356.7</td>
<td>9.363</td>
<td>1.954</td>
<td>27.582</td>
</tr>
</tbody>
</table>

B.L. – Bond Length, B.A.- Bond angle, D.A.- Dihedral angle

Results and Discussion

The overall correlation between the experimental characterization and PC model data justify the results obtained in spectral characterization and also certify the potential of the PC model simulation. The reliability of the PC model simulated data was further justified by correlating PC model values with the electrical polarizability values as described by Hansch for different substituents at different positions (ortho, Meta, para) for the present series of synthesized compounds. The following table (table-8) records the electrical polarizability for the set substituents of series III along with their dipole moment values.
Biological Studies: A general perusal of the biological studies made on four bacteria (E. coli, Bacillus subtilis, Pseudomonas alcaligen, Salmonella sp.) and four fungi (Penicillium citrinum, Aspergillus flavus, Rhizoctonia bataticola, Aspergillus niger) for 8 different samples indicates a significant biological activity for the synthesized compounds with respect to a common fungal (Griseofulvin) and bacterial (Streptomycin) control taken for the present study. This indicates that the synthesized samples possess good bactericidal and fungicidal activity.

The biological activities for these samples have been compared within the series. In persuasion with the results obtained in QSPR, the author is of the opinion that a greater asymmetry in the molecule may lead to greater distribution of charges leading to higher dipole values which are responsible for the higher hydrophobicity values. The hydrophobicity (lipophilicity) on its turn is responsible for the penetration of the drug through the biological (lipid) membrane thereby causing the exact cidal activity. Therefore, a direct dependence in biological activity and dipole moment values may be sort.

Variations in the biological activities (measure of the zone of inhibition in mm) with the dipole moment values have been attempted. The following tables record the dipole and zone of inhibition for some selected cases (where the activity is significant and large) for the azine and chlorobenzoxazine compound.

Table-9

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Clbenzx.17</th>
<th>Clbenz.18</th>
<th>Clbenz.19</th>
<th>Clbenz.20</th>
<th>Clbenz.21</th>
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</thead>
<tbody>
<tr>
<td>Elec. pol.</td>
<td>2.78</td>
<td>2.34</td>
<td>3.03</td>
<td>3.23</td>
<td>2.78</td>
</tr>
<tr>
<td>Dip. Mom.</td>
<td>1.899</td>
<td>5.033</td>
<td>3.938</td>
<td>2.516</td>
<td>1.954</td>
</tr>
</tbody>
</table>

The almost linear dependence between the electrical polarizability values and dipole moment values justifies the various correlations carried out in present study.

Table-10

<table>
<thead>
<tr>
<th>Compound code</th>
<th>Dip. Mom</th>
<th>E. coli</th>
<th>Klebsiella pneumoniae</th>
<th>Pseudomonas alcaligen</th>
<th>Salmonella sp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clbenzx.1</td>
<td>1.899</td>
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<td>13</td>
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<td>Clbenzx.2</td>
<td>1.954</td>
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<td>Clbenzx.3</td>
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<td>17</td>
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<tr>
<td>Clbenzx.4</td>
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<td>Clbenzx.5</td>
<td>5.033</td>
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<td>13</td>
<td>12</td>
<td>14</td>
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</tbody>
</table>

Figure-1

Variations in the biological activities (measure of the zone of inhibition in mm) with the dipole moment.
Table-11

Antifungal activity of Clbenzoxazine derivatives and its variation with Dipole moment values

<table>
<thead>
<tr>
<th>Compound code</th>
<th>Dip.Mom</th>
<th>Penicillium citrinum 2%</th>
<th>Penicillium citrinum 4%</th>
<th>Aspergillus flavus 2%</th>
<th>Aspergillus flavus 4%</th>
<th>Rhizoctonia bataticola 2%</th>
<th>Rhizoctonia bataticola 4%</th>
<th>Aspergillus niger 2%</th>
<th>Aspergillus niger 4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clbenx.1</td>
<td>1.899</td>
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<td>12</td>
<td>13</td>
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<td>10</td>
<td>13</td>
<td>15</td>
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<tr>
<td>Clbenx.2</td>
<td>1.954</td>
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![Figure-2](image-url)

Variations in the biological activities (measure of the zone of inhibition in mm) with the dipole moment

**Acknowledgement**

The authors are thankful to SAIF, CDRI Lukhnow providing the NMR spectra and analytical data of the compounds. The authors are thankful to Department of Chemistry, Dr. H. S. Gour central University, Sagar for providing IR spectral data and laboratory facilities.

**Conclusion**

The biological activities for these samples have been compared within the series. In persuation with the results obtained in QSAR, the author is of the opinion that a greater asymmetry in the molecule may lead to greater distribution of charges leading to higher dipole values which are responsible for the higher hydrophobicity values. The hydrophobility (lipophilicity) on its turn is responsible for the penetration of the drug through the biological (lipid) membrane thereby causing the exact cidal activity. Therefore, a direct dependence in biological activity and dipole moment values may be sort.

Variations in the biological activities (measure of the zone of inhibition in mm) with the dipole moment values have been attempted. The following tables record the dipole and zone of inhibition for some selected cases (where the activity is significant and large) for the azine and chlorobenzoxazine compound.

**Reference**

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