Chapter 3.

Ring Transformations of 1-Methyl-3- (substituted) phenacyl benzimidazolium cations.

As previously discussed, a broad spectrum of activities associated with sulphur and nitrogen containing heterocycles has prompted an unabated research in the development of their synthetic protocols (chapter-2). Similarly, owing to diverse pharmacological and biological properties of nitrogen containing heterocycles (pyrimidines, quinazolines, pyrazines, quinolines etc.), an extensive research has been carried out for their syntheses and numerous methodologies have been developed to synthesize these motifs. Besides, the multifarious applications in various fields, these compounds allow to understand the effect of nitrogen heteroatom on the ring cleavage and subsequent reactions which prompted us to extend the scope of our investigations to appropriately appended 1,3-heterocycles possessing two nitrogen atoms in the ring. Analogous to the base induced ring transformations of 3-phenacylbenzothiazolium cations to 1,4-benzothiazines (chapter-2), 3-phenacylbenzimidazolium cations would give six membered quinoxaline derivatives that imperatively prompts to reconnoiter their synthetic methodologies. Quinaxoline, a nitrogen containing heterocycle (benzene ring fused with pyrazine ring) is also called benzopyrazine. Quinoxaline derivatives, generally synthetic in origin exhibit different pharmacological activities viz. antibacterial, antifungal, antiviral, antimicrobial, antidepressant, anticonvulsant, anti-inflammatory, antithrombotic, NMDA (N-methyl-D-aspartate) antagonistic, antituberculosis, antimalarial and anti HIV etc. [Amin et al., 2012; Ali et al., 2000; Carta et al., 2001; Kumar et al., 2013]. Quinoxaline derivatives have been found to be as the core nuclei in various antibiotics
such as echinomycin, levomycin and actinolutin that inhibit the growth of gram positive bacteria [Waring et al., 1974; Kiran et al., 2017]. The manifold applications of quinaxoline derivatives have encouraged the researchers to synthesise these motifs through different reaction methodologies viz. cyclocondensation, oxidations, reductions, nucleophilic reactions, ring transformation via conventional routes and green routes (microwave, ultrasonication etc.). A brief review of literature on the synthetic procedures of quinoxalines and their derivatives precedes the investigations.

The presence of two amine groups in o-phenylenediamine proves to be a potent source of nitrogen atoms and remains a main precursor in most of the reactions for the synthesis of quinoxaline derivatives. Different reactions of o-phenylenediamine with alkynes, epoxides, dinucleophiles etc. follow the ring transformations for the synthesis of quinoxalines in the present review.

Benzofuroxanes (1) undergo Beirut reaction with 3-oxo-3-N-diphenyl-propionamide (2), N-benzyl-3-oxo-3-phenyl-propionamide (3), 3-oxo-N-phenethyl-3-phenyl-propionamide (4), N-ethyl-3-oxo-butyramide (5) to yield corresponding 7-chloro-6-fluoro-3-phenylquinaxoline-2-carboxylic acid phenylamide-1,4-di-N-oxide (6), 7-chloro-6-fluoro-3-phenylquinaxoline-2-carboxylicacid benzylamide1,4-N-oxide (7), 7-chloro-6-fluoro-3-phenylquinaxoline2-carboxylic acid (2-phenylethyl) amide-1,4-di-N-oxide (8) and 1,4-di-N-oxide-quinaxoline-2-carboxylic acid aryl amide derivatives (9). The latter exhibit good antimycobacterial activity (Table-1) [Moreno et al., 2010].
Similarly, substituted benzo[1,2,5]oxadiazole-1-oxide (10) with many reagents viz. enamines, β-diketone esters, aldehyde or ketone having α-H affords a series of quinoxaline 1, 4-di-N-oxide analogues (11) (Scheme-1) [Xu et al., 2011].

\[
\begin{align*}
\text{R} &= -\text{H}, \text{R}^1 = -\text{CH}_3; \\
\text{R} &= -\text{H}, \text{R}^1 = -\text{C}_2\text{H}_5; \\
\text{R} &= -\text{H}, \text{R}^1 = -\text{t-C}_4\text{H}_9; \\
\text{R} &= \text{R}^1 = -\text{CH}_3; \\
\text{R} &= -\text{CH}_3, \text{R}^1 = -\text{C}_2\text{H}_5; \\
\text{R} &= -\text{OCH}_3, \text{R}^1 = -\text{CH}_3; \\
\text{R} &= -\text{CH}_3, \text{R}^1 = -\text{OCH}_3; \\
\text{R} &= -\text{OCH}_3, \text{R}^1 = -\text{t-C}_4\text{H}_9.
\end{align*}
\]

Scheme-1

While, in the presence of piperidine or butylamine benzo[1,2,5]oxadiazole-1-oxide (12) condenses with 4-phenyl-but-3-en-2-one (13) to give 2-phenylquinoxaline 4-oxide (14) and 2-acetyl-3-phenylquinoxaline-4-oxide (15), respectively (Scheme-2) [Brown, 2004].

**Table-1. Synthesis of 1,4-di-N-oxide-quinoxaline-2-carboxylic acid aryl amide derivatives**

<table>
<thead>
<tr>
<th>Reactant A</th>
<th>Reactant B</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image 1" /></td>
<td><img src="image2.png" alt="Image 2" /></td>
<td><img src="image3.png" alt="Image 3" /></td>
</tr>
</tbody>
</table>

(1) | (2) | (6)
Scheme-2
An electrolytic reduction of 6-phenyl-5H-5,7(6H)-pyrrolo[3,4-b]pyrazine (16) in the presence of chlorotrimethylsilane gives an intermediate (17) which on reaction with methyl acrylate affords 6-acetyl-8-(phenyl amino)-1,2-dihydroquinoxalin-5(4aH)-one (18) (Scheme-3) [Brown, 2004].

Benzimidazole through ring expansion in chloroform produces a mixture (9:1) of chloroquinoxaline (19) and quinoxaline-2,3-dicarbonitrile (20) (Scheme-4) [Brown, 2004].

3-Azido-3-methyl-2-indolinone (21) when refluxed in xylene produces 3-methyl-2(1H)-quinoxalinone (22) (Scheme-5) [Brown, 2004]. The reaction of pyrrole substituted anilines (23) and alkynes with Au catalyst afford substituted pyrrolo[1,2-a]quinoxalines (24) (Scheme-6) [Liu et al., 2011].
Oxidation of alkynes by using different catalysts PdCl$_2$ and CuCl$_2$ in PEG-400 followed by reaction with o-phenylenediamine afford 2,3-disubstituted quinaxoline derivatives (25) (Scheme-7) [Chandrasekhar et al., 2010].
o-Phenylenediamine undergoes cyclocondensation with N-substituted aniline (26) in the presence of recyclable ionic liquid \( N, N, N\)-trimethyl \(-N\)- propane- sulfonyl acid ammonium hydrogen sulfate (TMPSA) and \( H_2SO_4 \) to give 2, 3-disubstituted quinoxaline derivatives (27). The reaction has been carried out both in water as well as organic solvent. The maximum yield has been obtained by using mild conditions (stirring in water) (Scheme-8) [Dong et al., 2008].

\[
\begin{align*}
\text{R} &= \text{p-H, p-F, p-Cl, p-I, p-Br, p-CH}_3, \text{p-OCH}_3, \text{p-NO}_2; \\
\text{R}^1 &= \text{-CH}_3, \text{-C}_6\text{H}_5, \text{t-C}_4\text{H}_9 \\
\end{align*}
\]

**Scheme-8**

Epoxides (28) undergo bi-catalyzed oxidative coupling with ene-1, 2-diamines (29) in the presence of Bi (5 mol %) to produce tetrahydroquinoxaline derivatives (30) (Scheme-9). Similarly, when epoxide (31) reacts with o-phenylenediamine, 2, 3-susbtstituted quinoxaline derivatives (32) have been obtained (Scheme-10) [Antoniottia et al., 2002].

\[
\begin{align*}
\text{R} &= \text{R}^1 = \text{R}^2 \text{-C}_6\text{H}_5; \\
\text{R}^1 &= \text{p-Cl-C}_6\text{H}_4, \text{R}^1 = \text{R}^2 = \text{-CN} \\
\end{align*}
\]

**Scheme-9**
While, *p*-tolylsulfone (33) on cyclocondensation with *o*-phenylenediamine in DMF without any catalyst gives 2-phenyl-quinoxaline (34) (Scheme-11) [Noorulla *et al.*, 2011].

Phenacyl bromide on reaction with *o*-phenylenediamine in the presence of *tetra*-butyl ammonium bromide (TBAB) yield 2-phenylquinaxoline (35) in basic medium (Scheme-12) [Sherman *et al.*, 2007] whereas, phenacyl chloride when refluxed with *o*-phenylenediamine in ethanol and by subsequent oxidation of intermediate (36) in the presence of H$_2$O$_2$, produces phenylquinoxaline (37) (Scheme-13) [Noorulla *et al.*, 2011].
Quinoxaline derivatives (38) have also been synthesized from glyoxal and o-phenylenediamine derivative (29) when stirred in the presence of mono dispersed and easily recyclable Ni-nanoparticles (Scheme-14) [Kumar et al., 2008].

![Chemical reaction diagram]

**Scheme-13**

Further, o-phenylenediamine derivatives (29) undergo one pot reaction with 1,2-dicarbonyl compounds (39) viz. oxaldehyde, biacetyl, oxalyldifluoride and dimethyl oxalate at room temperature.

**Scheme-14**

R= -CH₃, -NO₂, -CF₃.
temperature in the presence of iodine to furnish quinaxoline derivatives (40) (Scheme 15) [Kotharkar et al., 2006].

\[
\text{R}^1 = \text{-H, -CH}_3, \text{-F, -OCH}_3; \text{R}^1 = \text{-H, -NO}_2, \text{-CH}_3
\]

**Scheme-15**

Another ring-cyclocondensation of \(\alpha\)-phenylenediamine with 2-oxopropionaldehyde (41) in DMF affords 2-methyl-quinaxoline (42). The synthesised compounds show good antibacterial activity (Scheme-16) [Noorulla et al., 2011].

**Scheme-16**

In the presence of iodine, \(\alpha\)-phenylenediamine derivative (29) undergo condensation with 1, 2-dicarbonyl compounds (39) give quinaxoline derivatives (43) under microwave irradiation (Scheme-17) [Bandyopadhyay et al., 2010].
Further, quinoxaline derivatives (44) have been synthesized by the condensation reaction of 4-nitro-o-phenylenediamine with phenedione (39) (Scheme-18) [Kleineweischede et al., 2006].

In the presence of enzymatic catalyst S. Cereviciae (Saccharomyces Cereviciae) and under microwave radiation, 2, 3- diamine- naphthalene (45) reacts with α-ketoacids to yield quinoxalinone derivatives (46). The compound shows in vitro antitumor activity (Scheme-19) [Gris et al., 2008].
\[ \text{o-Phenylenediamine (29) undergoes cyclocondensation with carbonyl compounds (39) in the presence of phosphosulphonic acid at ambient temperature in ethanol to yield quinaxoline derivatives (47) (Scheme-20) [Rezaati et al., 2016].} \]

\[ \text{NH}_2 \text{NH}_2 + R \text{\textbullet\textbullet} \text{CO}_2 \text{R} \rightarrow \text{HO}_3\text{SO-P-O}_3\text{SO}_2\text{H} \rightarrow \text{N}=\text{N} \text{R} \text{R} \]

\( (29) \quad (39) \quad (47) \)

\( R= -\text{C}_6\text{H}_5, \text{p-Br- C}_6\text{H}_4, \text{p-Br- C}_6\text{H}_4. \)

**Scheme-20**

Similarly, 1,2-diamines (29), when reacted with 1,2-dicarbonyl compounds (39) in the presence of polymer supported sulphanilic acid in ethanol afford quinaxoline derivatives (48) (Scheme-21) [Tarpada et al., 2017]

\[ \text{R} \text{\textbullet\textbullet} \text{NH}_2 + R' \text{\textbullet\textbullet} \text{CO}_2 \text{R}' \rightarrow \text{ENPFSR, ethanol} \rightarrow \text{N}=\text{N} \text{R} \text{R}' \]

\( (29) \quad (39) \quad (48) \)

\( R= R'= -\text{C}_6\text{H}_5, \text{R} = \text{H}, R'= -\text{C}_6\text{H}_7\text{O}_2; R= -\text{CH}_3, R'= -\text{C}_6\text{H}_5; R= -\text{CH}_3, R'= \text{p-CH}_3\text{C}-\text{C}_6\text{H}_4; R= -\text{CH}_3, R= -\text{C}_6\text{H}_7\text{O}_2, R'= -\text{NO}_2, R'= -\text{C}_6\text{H}_5; R= -\text{NO}_2, R'= \text{p-CH}_3\text{C}-\text{C}_6\text{H}_4; R= -\text{NO}_2, R'= -\text{C}_6\text{H}_7\text{O}_2; R= -\text{Cl}, R'= -\text{C}_6\text{H}_5; R= \text{Cl}, R'= \text{p-CH}_3\text{C}-\text{C}_6\text{H}_4; R= -\text{Cl}, R'= -\text{C}_6\text{H}_7\text{O}_2. \)

**Scheme-21**

1,2-Diamine (29) on reaction with 1,2-diketone (39) in the presence of Lewis acid—surfactant combined Fe(DS\(_3\)) catalyst yields 2,3-diphenyl quinaxoline (49). The catalyst plays
dual nature in the reaction as it activates the substrate molecule and also acts as phase transfer
catalyst to solublize organic reactants in water (Scheme-22) [Singh et al., 2016]

\[
\begin{align*}
\text{NH}_2 & \text{NH}_2 + \text{Fe(DS}_3\text{)} (10\% \text{mol}) \text{ water} \\
\text{(29)} & \text{(39)} & \text{(49)}
\end{align*}
\]

Scheme-22

1,2-Diketones (39) when stirred with o-phenlenediamine in acetic acid in the presence of
different catalysts viz. o-iodoxbenzoic acid (IBX) or molybdophospho-vandates (MOVP catalyst)
yield quinaxoline derivatives (50) (Scheme-23) [Heravi et al., 2006; Ruiz et al., 2012].

\[
\begin{align*}
\text{NH}_2 & \text{NH}_2 + \text{R}_1\text{R} \text{R}_1 \text{R} \\
\text{(39)} & \text{(50)}
\end{align*}
\]

R= R\text{ }_1 = \text{-H}; R= \text{-H}, R\text{ }_1= \text{-CH}_3; R= \text{-H}, R\text{ }_1= \text{-NO}_2; R= \text{-OCH}_3, R\text{ }_1= \text{-H}; R= \text{-OCH}_3, R\text{ }_1= \text{-NO}_2; R= \text{-F}, R\text{ }_1= \text{-H}.

Scheme-23
\textit{o}-Phenylenediamine undergoes catalytic cyclocondensation with $5,5$-dialkyl-$2,3,4,5$-tetrahydropyrrolo[2,1-\textit{o}]isoquinoline-$2,3$-diones (51) in the presence of hydrochloric acid/$p$-toluene sulfonic acid and propan-$1$-ol to furnish quinoxalin-$2$-one derivatives (52) (Scheme-24) \cite{Surikova et al., 2008}.

\begin{align*}
\text{Phenylenediamine} + \text{Isoquinoline-2,3-diones} &\rightarrow \text{Quinoxalin-2-one derivatives} \\
(51) &\rightarrow (52)
\end{align*}

\begin{align*}
&\text{R}= -\text{H}, -\text{OCH}_3, R^1 = -\text{CH}_3, -(\text{CH}_2)_5.
\end{align*}

**Scheme-24**

A base induced cyclocondensation of $o$-phenylenediamine with $3, 4$-dihydro-$2\text{H}$-$1$-benzopyran-$2, 3$-dione (53) furnishes $3$-$o$-hydroxybenzyl-$2(1\text{H})$-quinoxalinone (54) (Scheme-25) \cite{Brown, 2004}.

\begin{align*}
\text{Phenylenediamine} + \text{Dihydro-1-benzopyran-2,3-dione} &\rightarrow \text{Quinoxalinone} \\
(53) &\rightarrow (54)
\end{align*}

\begin{align*}
\text{NaOH, 100 }^\circ\text{C, 15 min.} &\rightarrow \text{Quinoxalinone}
\end{align*}

**Scheme-25**

Condensation of $1, 3$-cyclohexanedione with $2$-nitroaniline produces $3$-($2$-nitrophenylamino)-cyclohex-1-enone (55) and its subsequent cyclization in the presence of catalyst (Pd(dba)$_2$, dppp, phen) in DMF affords $1$-hydroxyphenazine (56) (Scheme-26) \cite{Wallace et al., 2008}.
Further, in the acidic medium diaminomaleonitrile (57) cyclocondenses with 2-hydroxy-1, 4-naphthoquinone (58) to give 6-hydroxy-benzo[ff] - quinoxaline-2, 3-dicarbonitrile (59) (Scheme-27) [Ghadari et al., 2012].

Scheme-26

Quinaxoline and phenazines have been synthesized in good yield by the reaction of 1,2-dicarbonyl derivatives with substituted o-phenylenediamine in the presence of magnesium sulfate heptahydrate (MgSO₄·7H₂O) (Table- 2) [Karami et al., 2011].
Table- 2. Synthesis of quinaxoline and phenazine derivatives.

<table>
<thead>
<tr>
<th>Reactant A</th>
<th>Reactant B</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-NH₂</td>
<td>F-Ph₂</td>
<td>F-Ph₂</td>
</tr>
<tr>
<td></td>
<td>F-Ph₂</td>
<td>F-Ph₂</td>
</tr>
<tr>
<td></td>
<td>Ph₂</td>
<td>Ph₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph₂</td>
</tr>
</tbody>
</table>

R= -H, -NO₂, -CH₃

α-Phenylenediamine on reaction with 3-bromomethyl-4-methyl-2, 5-dihydro-2, 5-furandione (2-bromomethyl-3-methylmaleic anhydride) (60) produces 3-(1-carboxyvinyl)-3-methyl-3, 4-dihydro-2(1H)-quinoxalinone (61) (Scheme-28) whereas, with 4-benzoyl-5-phenyl-2, 3-dihydro-2, 3-thiophenedione (62) yields 3-(α-benzoyl-β-mercaptostyryl)-2(1H)-quinoxalinone (63) (Scheme-29) [Brown, 2004].
Hydroxyl ketones (64) have been oxidized in the presence of iodine to produce an intermediate (39). The latter cyclocondensed with o-phenylenediamine to produce quinaxoline derivatives (65). In the reaction, iodine plays a dual nature as it act as oxidant as well as Lewis acid for the cyclization whereas DMSO oxidizes HI produced in the reaction back into iodine (Scheme-30) [Xie et al., 2015].
Under microwave radiations, α-phenylenediamine reacts with α-hydroxyketone (64) to give quinoxaline derivatives (66) in better yield and less reaction time (Scheme-31) [Islami et al., 2008].

An acid derivative, 3-aryl-3-bromo-2-oxopropanoates (67) on reaction with α-phenylenediamine in acetic acid yields quinoxaline-2(1H)-one derivatives (68). The oxidation of latter in DMSO affords the quinoxaline-2(1H)-one derivatives (69) (Scheme-32) [Gorbunova et al., 2006].
R= -C₆H₅, p-H₃C-C₆H₄, p-H₃CO-C₆H₄

**Scheme-32**

Solvent free grinding of o-phenylenediamine (29) with oxalic acid affords 1,4-dihydro-quinoxaline-2,3-dione (70) with potential chemotherapic properties (Scheme-33) [Thakuria et al., 2006].

Further, 1,4-dihydro-quinoxaline-2,3-dione (71) on reaction with ethane-1,2-diamine give 3-(2-amino-ethylimino)-3,4-dihydro-1H-quinoxalin-2-one (72). The latter, when refluxed with aryl aldehyde derivatives yield 3-[2-(benzylidene-amino)-ethyl-imino]-3,4-dihydro-1H-quinoxalin-2-one derivatives (73), whereas, o-phenylenediamine on reaction α-keto-glutric acid (2-
oxopentanedioic acid) (74) produces 3-(3-oxo-3,4-dihydro-quinoxalin-2-yl) propionic acid (75), which when further treated with hydrazine hydrate in the presence of microwave radiations yields its hydrazone derivatives (76). Compound (76) shows excellent anti-virus activity (Scheme-34) [Ghadage et al., 2011; Khan et al., 2009].

o-Phenylenediamine when refluxed with oxalic acid dehydrate in acidic condition (conc. HCl) yields 1,4-dihydro-quinaxoline-2,3-dione (77) which show good antimicrobial activity (Scheme-35) [Alasmari et al., 2015].

Dichlorophenylenediamine (78) when refluxed with pyruvic acid yields 6,7-dichloro-3-methylquinaxolin-2(1H)-one (79) (Scheme-36) [Wiedermannova et al., 2002].

o-Phenylenediamine undergoes cyclocondensation with ethyl-2-oxo-propanoate to give 3-methylquinaxalin-2(1H)-one derivative (80). The latter on condensation with aromatic aldehyde produces 3-substituted styryl- quinoxalin-2(1H)-ones (81) which further, on refluxing with POCl₃ yield 2-chloro-3-substituted styrylquinaxoline derivative (82), while 81 on reaction with substituted piperazine give 2-(4-substituted piperazin-1-yl)-3-substituted styrylquinoxalines (83). These compounds exhibit good antimicrobial activity (Scheme-37) [Badran et al., 2007].
\[ \text{NH}_2 \text{NH}_2 + \text{COOH} \xrightarrow{\text{Stirring}} \text{NH}_2 \text{COOHH}_2 \text{NH}_2 \]

\[ \xrightarrow{\text{H}_2\text{N} - \text{CH}_2\text{NH}_2, \text{MW}} \text{NH}_2 \text{COOHH}_2 \text{NH}_2 \]

\[ \xrightarrow{\text{NH}_2\text{NH}_2, \text{MW}} \text{NH}_2 \text{COOHH}_2 \text{NH}_2 \]

\[ \text{R} = -\text{H}, -\text{NO}_2, -\text{CH}_3; \text{R}^1 = -\text{C}_6\text{H}_5, \text{p}-\text{H}_3\text{C}-\text{C}_6\text{H}_5. \]

\text{Scheme-34}

\[ \text{NH}_2 \text{NH}_2 + \text{COOH} \rightarrow \text{NH}_2 \text{COOHH}_2 \text{NH}_2 \]

\[ \text{Scheme-35} \]

\[ \text{ClNH}_2 \text{ClNH}_2 \rightarrow \text{CH}_2\text{COOH} \]

\[ \text{Scheme-36} \]
R= o-F, R1= p-CH3; R= o-F, R1= o-H5C2O-C6H4; R= o-Cl, R1= o-H5CO-C6H4; R= o-Cl, R1= p-IC-C6H4.

**Scheme-37**

Quinaxoline 2,3-diones (85) which exhibit property to act as NMDA (N-methyl-D-aspartate) receptor antagonists have been synthesized simply by the rotatory evaporation of substituted o-phenylenediamine (29) in diethyloxalate (84) at 50-80°C (Scheme-38) [Lin, 1996].
R= -H, R\textsuperscript{1} = -CH\textsubscript{3}; R= -H, R\textsuperscript{1} = -Cl; R= -C\textsubscript{6}H\textsubscript{5}, R\textsuperscript{1} = -H; R= -CH\textsubscript{2}CH\textsubscript{2}CN, R= -Cl; R= -CH\textsubscript{2}CH\textsubscript{2}CN, R\textsuperscript{1} = -CF\textsubscript{3}.

**Scheme-38**

o-Phenylendiamine derivatives (29), on stirring with maleic anhydride in THF and 10 mol% of butylated hydroxyl toluene (BHT) afford a mixture of 3-(carboxymethyl)-1,2,3,4-tetrahydroquinoxalin-2-one (86) and (Z)-3-(2-amino-substituted phenylcarbamoyl)propenoic acid (87) (Scheme-39) [Santos-Sancheza et al., 2008].

![Scheme-39](image)

R= -H, -NO\textsubscript{2}

**Scheme-39**

Diethyl-N-[(2,4-dinitrophenyl)amino]malonate (88) undergoes reduction and sequential cyclization in H\textsubscript{2}/Pd/C to give ethyl 6-amino-3,4-dihydro-3-oxoquinoxaline-2-carboxylate (89). The latter on reaction with CuCl\textsubscript{2} and t-BuONO produces ethyl 6-chloro-3,4-dihydro-3-oxoquinoxaline-2-carboxylate (90), a promising glycine/NMDA antagonist receptor (Scheme-40) [Varano, 2001].
Hexane-2, 3, 5-trione (91) and o-phenylenediamine in ethanol furnishes 3, 4-dihydroquinoxaline-2 (1H) -one (92) (Scheme-41) [Shabaan et al., 2011].

N-cyclohexyl-3-aryl-quinoxaline-2-aamines (94) have been procured by the reaction of o-phenylenediamine, cyclohexylisocyanide (93) and aromatic aldehyde in the presence of a catalyst (FeClO₄)₃ (Scheme-42) [Heravi et al., 2009].
Substituted o-phenylenediamine (29) with 2,3-O-isopropylidene-4-chloro-4-deoxy-hex-5-ulose di-methyl acetal (95) under neutral conditions provide quinoxaline derivatives (96) which shows excellent cytotoxic activities (Scheme-43) [Yan et al., 2007]

Under microwave, isatin (97) undergoes condensation with o-phenylenediamine in the presence of HCl to afford quinoxaline derivatives (98). The latter reacts with 4-amino-benzoic acid to give 4-[(indolo[2,3-b]quinoxalin-6-ylmethyl)-amino]-benzoic acid (99) which further condenses with o-phenylenediamine in acidic medium to produce [4-(1H-benzoimidazol-2-yl)-

\[
\text{R} = -\text{H, m-NO}_2, \text{p-Cl, p-NO}_2, \text{p-CH}_3.
\]

\[
\text{Scheme-42}
\]

\[
\text{Scheme-43}
\]
phenyl]-indolo [2, 3-b] quinoxalin-6-ylmethyl-amine derivative (100). All these compounds shows anti-virus property (Scheme-44) [Amin et al., 2012].

![Scheme-44](image)

4-Nitro- o-phenylenediamine, on reaction with acetic anhydride followed by coupling with thiophene-2-glyoxylic acid produces N- (2-acetylamino- 4- nitro- phenyl) - 2- oxo-2 -thiophen-2-yl-acetamide (101). The latter when refluxed in acidic medium affords 6-nitro-3-thiophen-2-yl-1H-quinoxalin-2-one (102) (Scheme-45) [Sherman et al., 2007].

2, 3-Bis (benzimidazol-2-yl) quinoxaline (104) has been synthesized from o-phenylenediamine and 3, 4, 5, 6-tetrachloropyridazine (103) when refluxed in N-methyl pyrrolidine at 115 °C for prolonged time (Scheme-46) [Brown, 2004].

N-hetero-annulation of enamine (105) in the presence of Pd (dba)₂ and dppp under carbon monoxide affords 1,2-dihydroquinoxaline (106) and 3,4-dihydroquinoxalinone (107) (Scheme-47) [Wallace et al., 2008].
The above review shows that the synthetic methodologies for quinoxalines primarily include cyclocondensations, additions etc. and a few ring transformations. Further, it has been noticed that green protocols has not much been put in use especially ring transformations. In view of these and to draw a comparison between the conventional and green strategies, the
syntheses of quinoxaline derivatives through ring transformations via green protocols have been undertaken in the present investigations.

Material and Method

3. Materials

3.1. Chemicals

The chemicals used in the research work were procured from various firms viz. Himedia, Sigma Aldrich, Rankem, Spectrochem, Alfa aesar etc. The solvents used for the synthesis of various compounds in the research work were of analytical grade and were used without further purification. Thin layer chromatography (TLC) was performed with glass plates coated with silica gel ‘G’ and were exposed to iodine vapors to check the progress of the reaction.

3.2. Instruments

- Melting points of the compounds were determined through melting point apparatus.
- Microwave synthesizer (Anton Paar, Monowave 300) was used for performing Microwave assisted reactions.
- Ultrasonication was done through ultrasonic cleaner model GB-2500 B (Microsil, India). It operates at a power of 500 W±15% and a frequency of 40 KHz. Operating voltage of the ultrasonic cleaner was 220-240 V. The temperature range of ultrasonic cleaner was 0-60°C.
- $^1$H and $^{13}$C NMR spectra were taken in CDCl$_3$ on a BRUKER ADVANCE II 400 NMR spectrometer using tetramethylsilane (TMS) as an internal reference (standard). The values have been given in ppm (δ). The coupling constant values have been given in Hertz (Hz). While citing $^1$H NMR data, following abbreviations have been used: s- singlet,
$d$-doublet, $t$-triplet, $q$-quartet and $m$-multiplet. $^{13}\text{C}$ NMR spectra were recorded on the same instrument with complete noise decoupling.

- Mass spectra were recorded on Waters Q-T Micromass (LC-MS) and Shimadzu GCMS-QP 2010 gas chromatogram mass spectrometer. The relative intensities of the peaks have been given in the parenthesis.
- Infrared spectra (IR) were recorded on IR Agilent Cary-660 with KBR pellets and the results have been reported in cm$^{-1}$. Only principle absorption peaks of interest have been reported.
- UV spectra were run on a UV-1800 (Shimadzu).
- Fluorescence spectra were recorded on a RF-5301 PC Spectro-fluorophotometer (Shimadzu).

3.3. General procedure for the synthesis of 1-methyl-3-(substituted) phenacylbenzimidazolium bromide (108):

N-methyl benzimidazole (1 mol, 1 equivalent) and phenacyl bromide (1.2 mol, 1.1 equivalent) or its derivatives were stirred at room temperature for 6-7 hours in dry toluene. The white solid (108) obtained was filtered and washed with diethyl ether to remove unreacted phenacyl bromide. The solid was dried and used without further purification.

3.4. Synthesis of Quinaxoline derivatives (109)

a). General procedure (Method A):

1-Methyl-3-phenacyl (substituted) benzimidazolium bromide (1 mol, 1 equivalent) (108) and TBAB (tetra butyl ammonium bromide, PTC) (0.5mmol) were dissolved in DMSO and NaOH
solution (2%, 9mL, 2.2 equivalent) was added dropwise. Further, the reaction mixture was refluxed with stirring. The progress of the reaction was monitored by TLC. After completion (2-2.5 hrs), the reaction mixture was poured into ice cold water. The solid, thus separated was filtered, washed with hexane and recrystallized in ethanol.

b). Ultrasonication (Method B):

To the solution of 1-methyl-3-phenacyl (substituted) benzimidazolium bromide (1 mol, 1 equivalent) (108) from methanol, 2 % NaOH solution (8 mL, 2.2 equivalent) was added dropwise during its ultrasonication in the ultrasonicator bath. The reaction was monitored with TLC. At the end of the reaction (20-45 minutes), it was worked up and the products were purified as mentioned in the above procedure.

c). Microwave assisted

A mixture of 1-methyl-3-phenacyl (substituted) benzimidazolium bromide (1 mol, 1 equivalent) (108), 2 % NaOH solution (8 mL, 2.2 equivalent) in water or ethanol was irradiated with microwave radiations for 10-20 minutes with a pulse time of 1 minute. The completion of the reaction was monitored with TLC after short intervals. The reaction was worked up and products were recrystallized as given in Method A.

3.4.1. 4-Methyl-3-phenylquinaxoline-1(4H)-carbaldehyde (109a; Ar= -H):

yellow colored solid; mp: 250 °C; yield: 40/72/85% (Mehtod A/B/C); M + m/z 251 (100%); ν = 1725cm⁻¹ (C=O, stretch); 2765 cm⁻¹ (C-H, stretch); ¹H NMR (CDCl₃, 400 MHz): δ= 3.13 (s, 3H, N-CH₃), 6.84-6.86 (d, 1H, –C₆H₅ of benzimidazole ring, J= 9.08 Hz), 7.01 (s, 1H, =CH), 7.47-7.67 (m, 6H, –C₆H₅ of benzimidazole and benzene ring), 7.83-7.85 (t, 2H, J= 6.28Hz, –C₆H₅ of benzene ring), 7.86 (s, 1H, -N-CHO); λₘₐₓ= 267 nm.
3.4.2. 3-(4-Chlorophenyl)-4-methylquinaxoline-1(4H)-carbaldehyde (109b; Ar= p-Cl-C₆H₄):

Yellowish orange colored solid; mp: 265 °C; yield: 42/74/ 87% (Method A/B/C); M⁺ m/z 284 286(1:1); ν = 1720cm⁻¹ (C=O, stretch); ¹H NMR (CDCl₃, 400 MHz): δ 3.84 (s, 3H, N−CH₃), 7.19-7.35 (m, 4H, −C₆H₅ of benzimidazole ring), 7.38-7.49 (m, 2H, −C₆H₅ of benzene ring), 7.61 (s, 1H, =CH), 7.78-7.80 (d, 2H, J= 7.80 Hz, −C₆H₅ of benzene ring), 7.88 (s, 1H, −N-CHO); ¹³C NMR (100 MHz, CDCl₃): δ 175.47 (-CHO), 142.83, 139.94, 135.78, 133.87, 133.81, 132.95, 131.55, 130.56, 129.51, 128.93, 128.85, 128.10, 127.51, 126.89, 126.80, 126.64, 126.61, 113.81, 113.57, 113.45, 65.96, 56.08, 48.55, 28.61, 26.68; λₓmult = 260 nm.

3.4.3. 3-(4-Bromophenyl)-4-methylquinaxoline-1(4H)-carbaldehyde (109c; Ar= p-Br-C₆H₄)

Yellowish brown colored solid; mp: 249°C; yield: 45/75/89% (Method A/B/C); M⁺ m/z 328, 330(1:1); ν = 1725cm⁻¹ (C=O, stretch); ¹H NMR (CDCl₃, 400 MHz): δ = 3.98 (s, 3H, N−CH₃), 6.05 (s, 2H, −C₆H₅ of benzimidazole ring), 7.69 (s, 1H, =CH), 7.70-7.83 (m, 3H, −C₆H₅ of benzene ring), 7.97-8.00 (m, 3H, −C₆H₅ of benzene ring), 9.01 (s, 1H, -N-CHO); ¹³C NMR (100 MHz, CDCl₃): δ 175.47 (-CHO), 148.54, 148.52, 135.54, 135.51, 131.63, 129.18, 128.60, 127.76, 126.73, 125.84, 125.72, 125.86, 66.71, 66.68, 49.24, 48.84; λₓmult = 265 nm.

3.4.4. 3-(4-Methoxyphenyl)-4-methylquinaxoline-1(4H)-carbaldehyde (109d; Ar= p-CH₃O-C₆H₄):

Light Yellowish colored solid; mp: 238 °C; yield: 50/79/82% (Method A/B/C); M⁺ m/z 281; ν = 1715 cm⁻¹ (C=O, stretch); ¹H NMR (CDCl₃, 400 MHz): δ 3.38 (s, 3H, N−CH₃), 3.70 (s, 3H, O−CH₃), 7.11-7.13 (t, 1H, J= 8.52 Hz, −C₆H₅ of benzimidazole ring), 7.18-7.20 (t, 1H, J= 2.28Hz, −C₆H₅ of benzimidazole ring), 7.30-7.32 (d, 2H, J= 8.12 Hz, −C₆H₅ of benzimidazole ring), 7.43-7.45 (t, 4H, J= 6.84 Hz, −C₆H₅ of benzene ring), 7.68 (s, 1H, =CH), 8.20 (s, 1H, -N-CHO); ¹³C NMR (100 MHz,
CDCl₃: 176.53 (-CHO); 142.60, 135.39, 128.46, 127.67, 127.06, 125.76, 118.32, 113.88, 112.87, 66.66, 55.15, 49.35, 35.83; λₘₐₓ = 263 nm.

3.4.5. 4-Methyl-3-p-tolylquinaxoline-1(4H)-carbaldehyde (109e; Ar= p-H₃C-C₆H₄):

Yellowish orange colored solid; mp: 230°C; yield: 48/78/84% (Method A/B/C); M⁺ m/z 265; ν = 1725 cm⁻¹ (C=O, stretch); ¹H NMR (CDCl₃, 400 MHz): δ 1.64 (s, 3H, -CH₃), 3.21 (s, 3H, N-CH₃), 7.15-7.17 (t, 1H, -C₆H₅ of benzimidazole ring, J= 7.64 Hz), 7.22-7.26 (m, 1H, -C₆H₅ of benzimidazole ring), 7.34-7.38(q, 1H, J= 7.96Hz, -C₆H₅ of benzimidazole ring) 7.40-7.40 (d, 1H, J= 0.96Hz, -C₆H₅ of benzimidazole ring); 7.42-7.42 (d, 1H, J= 1.00Hz, -C₆H₅ of benzene ring); 7.45-7.49 (t, 2H, J= 7.12Hz, -C₆H₅ of benzene ring); 7.56-7.60 (t, 1H, J= 7.40 Hz, -C₆H₅ of benzene ring); 7.92-7.94 (d, 2H, J= 7.44 Hz, -C₆H₅ of benzene ring); 8.11 (s, 1H, =CH); 8. 28 (s, 1H, N-CHO); λₘₐₓ = 263 nm.

3.5. Biological activities

3.5.1. Methodology for antioxidant activity (DPPH radical scavenging activity)

The methodology for DPPH radical scavenging activity was the same as adopted in chapter 2.

3.5.2. Antimicrobial activity

Agar Diffusion Method

The methodology for DPPH radical scavenging activity was the same as adopted in chapter 2.

3.6 Results and Discussion

Despite the development of numerous synthetic strategies involving different species, it has been observed from the literature that the quinoxalines have mostly been prepared by 1,2-diamines – their condensations with diketones, 1,4- additions with derivatized butenes, oxidative cyclisations with α-haloketones, oxidative couplings involving epoxides etc. [Brown,
2004; Antoniottia et al., 2002]. It has also been noticed that only a few ring expansions have been reported to procure the said motifs [Brown, 2004].

Further, the employment of the green synthetic protocols for the above said synthesis has been observed to be even more scarce. It was envisaged to extend the methodology adopted earlier for syntheses of the derivatives of 1,4-benzothiazines to the substituted benzimidizolium salts to procure the quinoxaline derivatives using green chemistry (ultrasonication, microwave etc.).

In the present investigations, in order to optimise the base induced ring expansions of 1-methyl-3-phenacyl (substituted) benzimidazolium salts (108) [prepared by reaction of 1-methyl benzimidazole with phenacyl bromide or its derivatives], different bases (Na₂CO₃, NaHCO₃, NEt₃, NaOH etc.) with varied concentrations (1-5%) and different equivalents have been employed. It has been observed that in weak bases the reaction does not initiate or if commences the percentage yield has been quite low, while at higher concentration decomposition could be observed (numerous spots observed on TLC). However, NaOH (2%, 2.2 equivalent) solution proved to be optimum which brings in the desired results.

A reaction of 1-methyl-3-phenacyl benzoimidazolium bromide with 2% NaOH (2.2 equiv) on refluxing or under ultrasonication or microwave radiations provides a light yellow colored solid (Scheme-48) M⁺ m/z 281 (100%) in 50/ 79/82% yield. Its IR shows an absorption band at 1725 cm⁻¹ stretch whereas UV exhibits a band at λ_max 263 nm due to C=O. The ¹H NMR spectrum displays signals at δ 3.38 (s, 3H, N-CH₃), 3.70 (s, 3H, O-CH₃), 7.11-7.13 (t, 1H, J= 8.52 Hz, –C₆H₅ of benzimidazole ring), 7.18-7.20 (t, 1H, J= 2.28Hz, –C₆H₅ of benzimidazole ring), 7.30-7.32 (d, 2H, J= 8.12 Hz, –C₆H₅ of benzimidazole ring), 7.43-7.45 (t, 4H, J= 6.84 Hz, –C₆H₅ of
benzene ring), 7.68 (s, 1H, -CH), 8.20 (s, 1H, -N-CHO) whereas its $^{13}$C NMR shows signals at δ 176.53 (-CHO), 142.60, 135.39, 128.46, 127.67, 127.06, 125.76, 118.32, 113.88, 112.87, 66.66, 55.15, 49.35, 35.83. From the above data the product has been assigned the structure 3-(4-methoxyphenyl)-4-methylquinoxaline-1(4H)-carbaldehyde (109d; Ar= p-CH$_3$O-C$_6$H$_4$).

The other quinoxaline derivatives (109 a-c,e) have been procured under similar reaction conditions. The structures of the quinoxaline derivatives synthesized through one pot ring expansion of corresponding benzimidazole salts in alkaline medium have been elucidated through $^1$H, $^{13}$C NMR and mass spectral data. The $^1$H NMR spectra of the synthesized compounds (109a-c,e) shows signals at δ 3.21-3.98 and δ 7.68-8.17 due to N-CH$_3$ and N-CHO, respectively (Table- 3). Further the $^{13}$C NMR spectra and mass spectrum (m/z) values clearly corroborates the assigned structures (109a-c,e) to the synthesized compounds.

The mechanism of the reaction has been envisaged to be identical with formation of 1,4-benzothiazines. Appropriately appended benzimidazolium salts undergo base induced ring C(2)-N(1) cleavage in 108 to form an intermediate (108A ) which alternately cyclises to give (108B). The latter undergoes dehydration to furnish the quinoxaline derivatives (109 a-e) (Scheme-49).

\[ \text{Ar} = \text{-C}_6\text{H}_5, \text{p-ClC}_6\text{H}_4, \text{p-BrC}_6\text{H}_4, \text{p-CH}_3\text{C}_6\text{H}_4, \text{p-OCH}_3\text{C}_6\text{H}_4 \]

\[ \text{Scheme-48.} \]
Table-3. Spectral data of the synthesised compounds (109a-e).

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>¹H NMR</th>
<th>Mass Spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>(109a)</td>
<td>3.13 (s, 3H, N-CH₃), 6.84-6.86 (d, 1H, -C₆H₅ of benzimidazole ring, J= 9.08 Hz), 7.01 (s, 1H, -CH), 7.47-7.67 (m, 6H, -C₆H₅ of benzimidazole and benzene ring), 7.83-7.85 (t, 1H, J= 6.28Hz, -C₆H₅ of benzene ring), 7.86 (s, 1H, -N-CHO)</td>
<td>251 (M⁺)</td>
</tr>
</tbody>
</table>
(109b) 3.84 (s, 3H, N-CH₃), 7.19-7.35 (m, 4H, -C₆H₅ of benzimidazole ring), 7.38-7.49 (m, 2H, -C₆H₅ of benzene ring), 7.61 (s, 1H, -CH), 7.78-7.80 (d, 2H, J = 7.80 Hz, -C₆H₅ of benzene ring), 7.88 (s, 1H, -N-CHO) 284, 286 (3:1)

(109c) 3.98 (s, 3H, N-CH₃), 6.05 (s, 2H, -C₆H₅ of benzimidazole ring), 7.69 (s, 1H, -CH), 7.70-7.83 (m, 3H, -C₆H₅ of benzene ring), 7.97-8.00 (m, 2H, -C₆H₅ of benzene ring), 9.01 (s, 1H, -N-CHO) 328-330 (1:1)

(109d) 3.38 (s, 3H, N-CH₃), 3.70 (s, 3H, O-CH₃), 7.11-7.13 (t, 1H, J = 8.52 Hz, -C₆H₅ of benzimidazole ring), 7.18-7.20 (t, 1H, J = 2.28 Hz, -C₆H₅ of benzimidazole ring), 7.30-7.32 (d, 2H, J = 8.12 Hz, -C₆H₅ of benzimidazole ring), 7.43-7.45 (t, 4H, J = 6.84 Hz, -C₆H₅ of benzene ring), 7.68 (s, 1H, -CH), 8.20 (s, 1H, -N-CHO) 281 (M⁺)

(109e) 1.64 (s, 3H, -CH₃), 3.21 (s, 3H, N-CH₃), 7.15-7.17 (t, 1H, -C₆H₅ of benzimidazole ring, J = 7.64 Hz), 7.22-7.26 (m, 1H, -C₆H₅ of benzimidazole ring), 7.34-7.38 (q, 1H, J = 7.96 Hz, -C₆H₅ of benzimidazole ring) 7.40-7.40 (d, 1H, J = 0.96 Hz, -C₆H₅ of benzimidazole ring); 7.42-7.42 (d, 1H, J = 1.00 Hz, -C₆H₅ of benzene ring); 7.45-7.49 (t, 2H, J = 7.12 Hz, -C₆H₅ of benzene ring); 7.56-7.60 (t, 1H, J = 7.40 Hz, -C₆H₅ of benzene ring); 7.92-7.94 (d,
2H, J = 7.44 Hz, -C₆H₅ of benzene ring); 8.11 (s, 1H, -CH); 8.28 (s, 1H, N-CHO)

Under the optimized conditions, the reactions have been performed through different synthetic routes (refluxing, ultrasonication and microwave). As reported in literature, pressure and temperature act as vital parameters in reaction processes which explains the high yield of compounds via microwave radiation/ultrasonication in comparison to simple refluxing.

It has been observed from the results that the microwave assisted reactions provided marginally more yield in less time in comparison to ultrasonication. A probable rationale is that in microwave, direct radiations fall on the reaction solvent which enhances the kinetic energy of the molecules of the precursors, whereas in ultrasonication the energy is supplied from acoustic cavitation which brings in marginal differences in both the non-conventional methodologies. A comparative data of all the three reaction routes has been summarized in Table 4.

**Table- 4.** Comparative yield and reaction time of conventional, Ultrasonication and microwave reaction.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Conventional</th>
<th>Ultrasonication</th>
<th>Microwave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time</td>
<td>Yield (%)</td>
<td>Time</td>
</tr>
<tr>
<td></td>
<td>(Hrs/min)</td>
<td></td>
<td>(Hrs/mins)</td>
</tr>
<tr>
<td>(109a)</td>
<td>2 hrs 45 min</td>
<td>40 %</td>
<td>30 min</td>
</tr>
</tbody>
</table>
(109b) 2 hrs 30 min  42 %  35 min  74 %  12 min  87 %

(109c) 2 hrs 30 min  45 %  35 min  75 %  15 min  89 %

(109d) 2 hrs 35 min  50 %  40 min  79 %  17 min  82%

(109e) 2 hrs 35 min  48%  42 min  78 %  17 min  84 %

3.6.1. Computational studies

For the molecular geometry optimization, Gaussian 09W software package [Frisch et al., 2009] integrated with DFT methods and B3LYP (Becke three parameter Lee-Yang-Parr) exchange correlation functional have been used which combines the hybrid exchange functional of Becke [Becke, 1988] with the gradient-correlation functional of Lee, Yang and Parr [Lee et al., 1988]. The 6-31G(d) basis set has been used for calculations in the gas phase of the compound (109c).

The DFT calculations have been carried out to predict the geometry of the molecules. The optimized bond lengths and bond angles as obtained by geometry optimization at B3LYP/6-31G(d) level of the theoretical structure (109c) have been reported in Table- 5. The calculated bond lengths: C=C, C-Br and C-N bonds of quinaxoline ring of (109c) have been found to be 1.201 Å, 1.4876 Å and 1.3896 Å, respectively whereas the calculated bond angles for N2-C3-C8, C4-N1-C9 and N1-C9-C8 bond have been 119.46°, 104.9° and 135.9°, respectively. The
optimized configuration of structure (109c) with atoms numbering scheme has been depicted in Figure 1.

![Optimized Structure of the compound (109c)](image)

**Figure 1. Optimized Structure of the compound (109c)**

The total energy that is the energy of highest occupied molecular orbitals and the energy of lowest unoccupied molecular orbitals for structure (109c) have been obtained by theoretical calculations. The localization of highest occupied molecular orbitals (HOMOs) on the six membered quinaxoline ring of compound (109c), makes this to be the most active part of the molecule. Stationary points for the molecule (109c) have been verified by the frequency calculations. In the absence of negative frequency, the assigned geometry to the molecules has been considered to be the energy minimum. The calculated total energy and the dipole moment of the compound (109c) have been found to be -1589.96 kcal/mol and 2.313 D, respectively.

**Table- 5. Theoretical Bond length and bond angles of the compound (109c)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.6.2. Fluorescence spectra

The emission spectra of compounds (109b), (109c) and (109d) show peaks at 444 nm, 438 nm, and 447 nm, respectively. These compounds represent the single fluorescence emission band.
which makes them fluorescence active. The spectrum in Figure-2 shows that compound 109c to be more fluorescence active than the other two (109c, 109d).

![Emission Spectra of the synthesized compounds (109b-d).](image)

**Figure 2.** Emission Spectra of the synthesized compounds (109b-d).

### 3.6.3. Antioxidant potential

The results of antioxidant potential have been depicted in Table-6. DPPH radical scavenging methodology, being simple and convenient, has extensively been employed to find the in vitro model antioxidant efficacy. In its radical form, DPPH shows absorbance at 517 nm which disappears, when DPPH gets reduced by an antioxidant compound or a radical species to become a stable diamagnetic molecule. As a result, the color changes from dark purple to light or yellow in case of excellent antioxidant potential. This physical change has been taken as an indication of the hydrogen releasing ability of the compounds under test.

Antioxidants react with DPPH to produce 1,1-diphenyl-2-picryl-hydrazine. The reducing ability of the examined compounds has been determined by their interaction with the free
stable radical 1,1-diphenyl-2-picryl-hydrazine (DPPH) at 5 different concentrations for 30 min. The highest scavenger activity has been observed in 109c probably due to presence of bromo group at the phenyl ring attached to quinaxoline ring. Generally, electron withdrawing substituents deactivates aromatic ring which does not allow it to bind the free radicals. From the results, brominated compound exhibited better activity than unsubstituted one and methyl derivatives (anomalous behavior is being investigated). It was also noteworthy that with the increase in concentration, antioxidant potential increases (Figure 3).

**Table- 6**: Antioxidant potential of the synthesized compounds (109a-e).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Concentration of Drugs (in μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200</td>
</tr>
<tr>
<td>(109a)</td>
<td>11</td>
</tr>
<tr>
<td>(109b)</td>
<td>17</td>
</tr>
<tr>
<td>(109c)</td>
<td>31</td>
</tr>
<tr>
<td>(109d)</td>
<td>15</td>
</tr>
<tr>
<td>(109e)</td>
<td>18</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>42</td>
</tr>
</tbody>
</table>

Above figures show percentage inhibition of DPPH radical
3.6.4. Antimicrobial activity

The antimicrobial activity of the synthesized compounds has been determined by the agar diffusion techniques. The results of antimicrobial activity test have been summarized in Table-7.

In case of the antibacterial activity assay, none of the synthesized compounds have been observed to be active against *E. Coli*. However, all the synthesized compounds also showed activity against *Staph. Aureus*. Compound (109a) shows moderate activity, (109b) & (109c) shows good antibacterial activity whereas 109d and 109e exhibit excellent antibacterial activity. The presence of incorporated aromatic ring and –CH₃ group increases the lipophilicity of the compound. Due to which 109e exhibit high activity. The increase in lipophilicity helps
permeability through microbial cell wall resulting in higher activity. (109b) and (109c) shows activity probably due to presence of electron withdrawing groups (-Cl, -Br).

The antifungal activity has tested against *A. Niger* and *C. Albicans*, using Amphotericin as standard antifungal. All the compounds exhibit good activity against *C. Albicans* and poor to moderate against *A. Niger* (Figure 4).

**Table- 7.** Antimicrobial activity of the synthesized compounds *(109a-e).*

<table>
<thead>
<tr>
<th>Compounds</th>
<th><em>Staph. Aureus</em></th>
<th><em>E. Coli</em></th>
<th><em>C. Albicans</em></th>
<th><em>A. Niger</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>(109a)</td>
<td>12.5</td>
<td>0.0</td>
<td>15.3</td>
<td>13</td>
</tr>
<tr>
<td>(109b)</td>
<td>13</td>
<td>0.1</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>(109c)</td>
<td>13.5</td>
<td>0.0</td>
<td>15.6</td>
<td>13.3</td>
</tr>
<tr>
<td>(109d)</td>
<td>15.5</td>
<td>0.2</td>
<td>18</td>
<td>13.5</td>
</tr>
<tr>
<td>(109e)</td>
<td>20</td>
<td>0.4</td>
<td>17.6</td>
<td>12</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>33</td>
<td>33</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Amphotericin</td>
<td>22</td>
<td>22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 4. Pictorial representation of antimicrobial activity of compounds (109a-e).

Further, Reaction of N,N-dimethyl benzimidazolium iodide with α-haloketone has been carried out to synthesise derivatized quinaxolines but to no avail, that has been attributed to the thermal stability of the ionic liquid N,N-dimethyl benzimidazolium iodide.

It has been concluded that 1-methyl-3-(substituted) phenacylbenzimidazolium cations undergo facile one pot ring expansions to the corresponding quinoxaline derivatives in the optimized basic medium. Further, the reactions through ecofriendly routes (ultrasonication and microwave) provided exceptionally better yields in less time. Furthermore, the synthesized compounds have been observed to be biologically active.

The ring expansions especially via green methodologies have been observed to be less explored in literature. Hence, in the present study, aqueous base induced ring transformations of the benzimidazolium salts (similar to benzothiazolium salts: chapter 2) through green protocols have been under taken.
Further, mostly the reactions have been performed through conventional procedures (stirring, refluxing etc.), with a few through green protocols.

**References**


Bandyopadhyay, D., Mukherjee, S., Rodriguez, R.R., Banik, B.K. 2010. An Effective Microwave-Induced Iodine-Catalyzed Method forthe Synthesis of Quinoxalines via Condensation of 1,2-Diamines with 1,2-Dicarbonyl Compounds. *Molecules*. 15: 4207-4212.


