CHAPTER –1
INTRODUCTION

1.1. General Introduction:

Organic chemistry plays a major role in the synthesis of chemical compounds and is concerned with the construction of organic compound via organic reactions. Medicinal chemistry is a specialized science, which involves the identification, synthesis and development of drugs like compounds for therapeutic use.

Carbocyclic compounds are the compounds, which are composed of carbons. E.g., Cyclohexane and benzene. If one or more of the carbon atoms in the carbocyclic ring is replaced by other elements like oxygen, sulfur or nitrogen then the product is a heterocycle. Biosynthesis of compounds of heterocycles takes place in animals and plants and are biologically active. Some heterocycles are fundamental to life, such as haem derivatives in the blood and the chlorophyll is essential for photosynthesis. Similarly, the paired bases found in RNA and DNA are heterocycles. The biological properties of heterocycles make them one of the prime interest of the pharmaceutical and biotechnology industries.

Kurasawa and Muramatsu et al [1] early types of antimicrobial substances were not specifically anti microbial but were usually toxic to all living cells, were of value only in so far as they could be employed without serious damage to the host. The search for more suitable anti microbial agents resulted in the preparation and testing of many substances of the widely different constitution, acute pain is generally well accounted for in terms of nociception, i.e., an excessive noxious stimulus giving risk to an intense and unpleasant sensation. Most chronic pain states are associated with aberrations of the normal physiological pathway giving rise to hyperalgesia. A variety of experimental pain models are available to demonstrate the antinociceptive activity of drugs which are used for the routine screening of analgesics. Since different classes of analgesics vary in their mechanisms of pain relief, it is recommended not to rely on any one form of nociceptive test during the determination of analgesic efficacies. A great variety of nociceptive tests are currently used differing from each other by the nature of the stimuli, parameters, site of application, and nature of responses, quantization and apparatus. Objectively, depending upon the
nature of the stimulus, they can be classified into chemical, electrical, mechanical and thermal methods.

In this work heterocyclics like quinoxaline and its derivatives were prepared. Different quinoxalines such as biphenyl quinoxaline, quinoxaline dione and quinoxaline-2-one were synthesized by different synthetic routes. In addition to the above (E) -1, 2-diphenylethylene ((E) -stilbene) and its derivatives were also synthesized.

1.2. Chemistry of Quinoxaline:


The above, antibiotics are active against transplantable tumors. There are several synthetic routes toward quinoxalines, other names for quinoxaline are 1, 4 – benzodiazine or benzopyrazine or1, 4-diazonaphthalene.
Quinoxalines possess antimicrobial activities and are prepared synthetically. Bicyclic desipeptide antibiotics contain quinoxaline ring and are found to be effective against certain tumors and gram-positive bacteria. Polymers and fluorescein dyes contain quinoxaline as an ingredient. Quinoxalines show low melting point and occur as solid with 99% purity. It is miscible with water and having melting point of 29-30°C. Finar [12] it is weekly basic (pka – 0.56).

(i) Quinazoline

\[
\begin{array}{c}
\text{1,3} - \text{diazonaphthalene} \\
\end{array}
\]

(ii) Cinnoline

\[
\begin{array}{c}
\text{1,2} - \text{diazonaphthalene} \\
\end{array}
\]

(iii) Phthallazine

\[
\begin{array}{c}
\text{2,3} - \text{diazonaphthalene} \\
\end{array}
\]

Cordes and James et al [139] the quinoxaline residue possesses a less electronegative system. They resist oxidation and undergo reduction.

1.3 Current Synthetic Approach on Quinoxaline Synthesis:

(i) Bansal [13] o-phenylene diamine can be combined with oxalic acid and glyoxal to give quinoxaline – 2, 3 – dione.

\[
\begin{array}{c}
\text{NH}_{2} \quad \text{NH}_{2} \\
\end{array} + \begin{array}{c}
\text{O} \\
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{N} \\
\end{array}
\]
(ii) Condensation of benzaldehyde with chloromethyl P-tolylsulfone forms 1-(P-tolyl sulfonyl) -2 phenyloxirane reported by Taylor. Reaction of chloromethyl P-tolylsulfone with o-phenylene diamine yields 2-phenyl quinoxaline.

(iii) Cai and Zou et al [14] quinoxalines are synthesized by the condensation reaction of o-phenylenediamine with α-dicarbonyl compounds in ethanol under microwave irradiation.


c) Shivajio and Sastry et al [17] synthesis of quinoxalines under microwave irradiation.
d) Goswami and Kumar [18] microwave-assisted region-specific synthesis of 2-substituted quinoxaline.

\[
\begin{array}{c}
\text{NH}_2 & \text{NH}_2 \\
\text{R} & \text{COOH} \\
\text{MW} & 150 \text{W, 62 s}
\end{array}
\]

\[
\begin{array}{c}
\text{R} & \text{COOH} \\
\text{MW} & 150 \text{W, 62 s}
\end{array}
\]

e) Noorulla and Sreenivasulu [119] Quinoxalines were prepared using magnetic material from coal fly ash.

f) Hajjaji and Zerga et al [120] synthesis of quinoxalines using Acid- and Metal-Free Catalyst.

\[
\begin{array}{c}
\text{NH}_2 & + & \text{NH}_2 \\
\text{NH}_2 & \text{NH}_2 & \text{O} \\
\text{NH}_2 & \text{NH}_2 & \text{NH}_2
\end{array}
\]

\[
\begin{array}{c}
\text{NH}_2 & + & \text{NH}_2 \\
\text{NH}_2 & \text{NH}_2 & \text{O} \\
\text{NH}_2 & \text{NH}_2 & \text{NH}_2
\end{array}
\]

g) Kirubavathy and Velmurugan et al [126] synthesis of quinoxalines from indolinone.

h) Kirubavathy and Velmurugan et al [126] synthesis of diphenyl quinoxaline by using iodine as a catalyst.

\[
\begin{array}{c}
\text{NH}_2 & + & \text{NH}_2 \\
\text{NH}_2 & \text{NH}_2 & \text{O} \\
\text{NH}_2 & \text{NH}_2 & \text{NH}_2
\end{array}
\]

\[
\begin{array}{c}
\text{NH}_2 & + & \text{NH}_2 \\
\text{NH}_2 & \text{NH}_2 & \text{O} \\
\text{NH}_2 & \text{NH}_2 & \text{NH}_2
\end{array}
\]

i) Soleymani an Niakan et al [130] condensation of Aryl-1,2-di amine with 1,2-di carbonyl in the acidic condition, used catalysts are CrCl2.6H2O, PbBr2 and CuSO4.5H2O

\[
\begin{array}{c}
\text{NH}_2 & \text{NH}_2 \\
\text{H}_2\text{N} & \text{X} \\
\text{X} & \text{NH}_2
\end{array}
\]

\[
\begin{array}{c}
\text{NH}_2 & \text{NH}_2 \\
\text{H}_2\text{N} & \text{X} \\
\text{X} & \text{NH}_2
\end{array}
\]
j) Thakuria and Das [133] synthesis of quinoxaline-2,3-dione by One-pot green synthesis by grinding under solvent-free conditions.

![Chemical structure](image)

Table 1.1: Green Synthesis of quinoxaline derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>A</th>
<th>b</th>
<th>Time(h)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>0.5</td>
<td>98</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>NO₂</td>
<td>3</td>
<td>82</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>Cl</td>
<td>2</td>
<td>87</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>CMe</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>n-Pr</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>Ph</td>
<td>0.5</td>
<td>96</td>
</tr>
<tr>
<td>g</td>
<td>Cl</td>
<td>Cl</td>
<td>5</td>
<td>76</td>
</tr>
</tbody>
</table>

Yield of isolated products

k) Kumar and Jeyakandan et al [137] synthesis of 2-Phenylquinoxaline by using phenylacylchloride.

![Chemical structure](image)

**Properties:**

Quinoxaline occurs as liquid in room temperature owing to its low melting point. It occurs at 99% purity and its oxygenated derivative are of higher melting solids exhibit low solubility in water, moderate solubility in ethanol and chloroform and high solubility in DMF and DMSO. It possesses a dipole moment of zero. Literature reported that quinoxaline derivatives like N-condensed, hydrazino,
Chalcones are nucleus targeted due to its optimum lipophilic nature and high receptor binding affinity. Bansal [13] hydroxy quinoxalines are known to exhibit good antibacterial properties due to its tautomeric imino-OH. Many quinoxaline derivatives with synthetic importance are obtained as reaction products.

2-hydroxy quinoxalines exhibit tautomeric forms, but not 2-amino quinoxaline.

\[
\begin{align*}
&\text{OH} \\
&\text{N} \\
&\text{N} \\
&\text{H} \\
&\text{O}
\end{align*}
\]

Shivajio and Sastry et al [19] the tautomerism of 3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline has been studied by means of \(^1\)H-NMR and UV spectroscopy tautomers. A and B co-exist in DMSO solution.

Burguete and Pontiki, et al [122] derivatives of quinoxalines showed the effect of inhibition on the mild steel corrosion in IM HCl.

**1.4. Synthesis of Quinoxaline and its Derivatives:**

Kroon and Iyer et al [20] the condensation of 1, 2-diaminobenzene (O-phenylene diamine) with benzil provides 2, 3-diphenyl quinoxaline which yields ranging from 34-85% depending on the reaction conditions. Different derivatives of 2, 3-diphenyl Quinoxaline were prepared by replacing hydrogen at 6th position of 2, 3-diphenyl quinoxaline by substituting different groups such as nitro, sulfonyl chloride, sulfonic acid amide etc.

Karger and Basel [21] quinoxaline-2,3(1H, 4H)-dione was prepared by treating ortho phenyldiamine with oxalic acid in 4N HCl. Quinoxalines 2,3-dione is nitrated with nitric acid and potassium nitrate in the presence of conc H\(_2\)SO\(_4\) results in the formation of 6- nitro–quinoxaline-2, 3 (1H,4H)-dione, 6, 7-dinitro quinoxaline-2,3(1H, 4H)-dione. The other derivative chloro sulphonyl compound was obtained up on treatment with chlorosulphonic acid. Both nitro derivatives on reduction in presence of Ni afforded 6, 7–diamino-quinoxaline-2, 3(1H, 4H)-dione. The compound
was refluxed with ammonia and was converted into sulphonamide derivatives. Various α,β unsaturated derivatives of quinoxaline-2,3(1H, 4H)-dione were prepared by using different aromatic aldehydes by Claisen-Schimdt condensation by conventional method.

\[
\text{benzene-1,2-diamine} + \frac{\text{oxalic acid}}{4N \text{ NaOH}} \xrightarrow{\text{reflux 4hr}} \text{quinoxaline-2,3(1H,4H)-dione}
\]

Quinoxaline-2-one was prepared by using chloroacetic acid. It was neutralized with 1N NaOH and then o-phenylenediamine was added to it. Then the mixture was subjected to microwave radiation for 2 minutes. The product was recrystallized by using water as a solvent.

\[
\text{benzene-1,2-diamine} + \text{2-chloroacetic acid} \xrightarrow{\text{microwave synthesis 3 minutes}} \text{quinoxaline-2(1H)-one}
\]

Acetylated derivative of quinoxalin-2(1H)-one was prepared by Fridel Craft’s acylation method. This was prepared by subjecting to microwave radiation for one minute. Various α,β unsaturated derivatives of quinoxalines were prepared by using different aromatic aldehydes by Claisen-Schimdt condensation by conventional method. The synthesized compounds after purification on column chromatography were identified by physical and spectral data.

Various compounds and their derivatives prepared were confirmed by IR, NMR, and Mass spectral studies. Antimicrobial activity was carried out by adopting the agar diffusion method. Anti-inflammatory activity was evaluated by applying carrageenan-induced paw edema test in rats. Analgesic activity was evaluated by acetic acid induced writhing in mice.

1.5. Stilbenes:

Fernandez et al [23] in cerebrovascular disorders and Ryoji and Akhiro et al, Mohamad and Fadzli et al [27,149] cytotoxic activities, Fernando and Pavan1 et al [146] antitubercular, Zhang and Do et al [150] antipsoriatic agent have been reported. Some of them, such as resveratrol, exert antioxidant activity which modulate the synthesis of lipids and it also inhibit ribonucleotide reductase and DNA polymerase increase the activity of map-kinase, an enzyme potentially related to neuro degenerative diseases such as Alzheimer’s and Parkinson’s inhibit platelet aggregation and after the eicosanoid synthesis. Both effects probably related to he inhibition of the cyclo oxygenase and hydroperoxidase activities. Sethi, Macickova and Pecivova et al [28,145] these findings have stimulated the study of these compounds as anti-inflammatory, Ashutosh [29] cardio tonic and anti-platelet aggregating agents and anti-convulsants. Although anti-convulsant activity is well known to hydantoin analogues, benzodiazepine structure. There are few reports about stilbene derivatives with anti-convulsant activity. A non-flavonoid polyphenol and resveratrol are present in the fresh skin of black grapes (Vitis vinifera). Al-Jumaily and Shafiq et al [142] 50-100 micro gram of pure resveratrol is present in each gram of fresh grape skin. Hong and Kim et al [147] stilbene derivative is suitable as fluorescence imaging agent to study Alzheimer’s disease. Lai and Herent et al [148] bioactive stilbene forms a major phenolic component in Rhodomyrtus tomentosa which acts as a source of health-promoting fruits.

**Stilbene chemistry:**

Stilbene is diarylethene and have the chemistry of a conjugated alkene. Two isomers are possible with Stilbene called (E) -stilbene or trans-stilbene is 1) trans-1,2-diphenylethylene 2) cis-1,2-diphenylethylene is called (Z)–stilbene or cis-stilbene. Cis-stilbene is less stable because the aromatic rings are forced out-of-plane due to steric interactions. The word stilbene is obtained from stilbos (Greek word) means shining.
<table>
<thead>
<tr>
<th>IUPAC Name</th>
<th>Other names</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E) -1,2-diphenylethylene</td>
<td>(E)-Stilbene, trans – Stilbene,</td>
</tr>
<tr>
<td></td>
<td>diphenylethylene</td>
</tr>
<tr>
<td>(Z) -1,2-diphenylethylene</td>
<td>(Z)-Stilbene, cis – Stilbene trans -</td>
</tr>
<tr>
<td></td>
<td>1,2-cis - 1,2-diphenylethylene</td>
</tr>
</tbody>
</table>

Stilbene shows the chemistry of conjugated alkene i.e., a diarylethene. Inter conversion of trans to cis-stilbene was observed in the presence of light. (Z) stilbene melts around 5-6°C and (E) stilbene has a melting point around 125°C indicating that two compounds differ in their physical properties.

Jung and Lee *et al* [140] the carbonyl compounds of 3,4 –dihydroxy stilbene inhibited protein tyrosine phosphatase. Karakusa and Nurioglua [141] trans-stilbene shows electrochromic properties.

Lefebvre and Jentsch *et al* [143] photocyclization of stilbene to phenanthrene.

![Chemical structure of stilbene and phenanthrene with reaction equations](image)
Kiselev and Dubrovina et al [144] the Resveretrol biosynthesis pathway in grape

![Resveretrol biosynthesis pathway diagram](image)

Table -1.2: Effect of different base combinations on the synthesis of 1b from 1a under microwave irradiation

<table>
<thead>
<tr>
<th>S.no</th>
<th>Base(B)</th>
<th>Yields(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Imidazole</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>Methylimidazole</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>Histidine</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>1-Buty-3-methylimidazoliumchloride</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>Pyridine</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>Triethylamine</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>Collidine</td>
<td>43</td>
</tr>
</tbody>
</table>

1.6. Synthesis of Stilbene and its Derivatives:

The objective of this research work is to synthesize various compounds and their derivatives, and characterizes by various spectral analysis and screen for antimicrobial, analgesic and antiinflammatory activities. Different stilbene derivatives are prepared as follows.
Pavia [30] stilbene was prepared by condensation of benzoin with HgCl₂/Zn. Macickova and Pecivova et al. [31] stilbene on Friedel - Craft’s acylation resulted in acetyl derivative of stilbene. Mark and Nagarathnam et al [32] different derivatives of stilbene were prepared by Claisen Schmidt condensation to get α, β unsaturated derivatives. The different compounds were recrystalised by suitable solvents such as ethanol and rectified spirit. Acetylation of stilbene was carried out in a microwave oven for 1 minute to get acetyl stilbene, whereas the time required for the same step by conventional method was about 1 hour.

1.7. Friedel-Crafts Acylation:

\[
\text{C}_6\text{H}_5 + X\text{C}_2\text{R} \xrightarrow{\text{Cat} \ - \ HX} X = \text{Cl} \ or \ RCOO
\]

This electrophilic aromatic substitution allows the synthesis of monoacylated products from the reaction between arenes and acyl chlorides or anhydrides. Normally, a stoichiometric amount of the Lewis acid catalyst is required, because both the substrate and the product form complexes.

1.8. Mechanism of the Friedel-Crafts Acylation:
1.9. Mechanism of Claisen-Schmidt condensation:

The mechanism for the base-catalyzed aldol condensation between 4-methoxyacetophenone and 4-chlorobenzaldehyde which involves the following steps.

**Step 1:** Formation of enolate ion first is an acid-base reaction. Hydroxide functions as a base and removes an acidic α-hydrogen, giving a reactive enolate.

**Step 2:** Alkoxide formation (nucleophilic addition). The nucleophilic enolate attacks the carbonyl carbon of 4-chlorobenzaldehyde in a nucleophilic addition process giving an intermediate alkoxide.

**Step 3:** Protonation of alkoxide. The alkoxide deprotonates a water molecule producing a hydroxide ion and a β-hydroxyketone, the aldol product.

**Step 4:** Dehydration. The hydroxide acts as a base and removes an acidic β-hydrogen giving the reactive enolates. The electrons associated with a negative charge of the enolate are used to form a carbon-carbon double bond (C=C) and displace a leaving group, regenerating the hydroxide giving the final product, the conjugated ketone.
Mark and Nagarathnam et al [34] synthesized stilbenoic acid derivatives were prepared by treating different benzaldehydes with phenyl acetic acid in the presence of acetic anhydride and triethyl amine.
Mark and Nagarathnam et al [34] (2E)-3-(substituted phenyl)-2-phenylacryloyl chloride from the (2E)-3-(phenyl)-2-phenylacrylic acid was obtained by treatment with thionyl chloride. Various derivatives of stilbenes were prepared by replacing chlorine atom by different amines to get the (2E)-3-(substituted phenyl)-N-substituted-2-phenylacrylamide.

Various compounds and their derivatives prepared were confirmed by IR, NMR, and Mass spectra. Studies confirmed the structure of quinoxaline and its derivatives. Antimicrobial activity was carried out by adopting the agar diffusion method. Carrageenan- induced paw edema method was adapted in rats for carrying anti-inflammatory activity. Acetic acid induced writhing method in mice was adapted to carry out analgesic activity.

1.10. Objectives of the Study:

1. To carry out a literature survey of Quinoxalines and Stilbene derivatives.
2. To establish the methods of synthesis for the proposed derivatives.
3. To synthesize some Quinoxalines and Stilbene derivatives.
4. To confirm the structure of the synthesized compounds by TLC, IR, $^1$HNMR, $^{13}$CNMR and Mass spectral data.
5. To evaluate the proposed derivatives for Pharmacological activity.