CHAPTER-I

SECTION-A: BIOLOGICAL ACTIVITY OF HETEROCYCLIC COMPOUNDS

-A BRIEF REVIEW

Introduction:

Heterocyclic systems are encountered in many groups of organic compounds possessing great applicability in industry as well as in our life in various ways i.e. most of the sugars and their derivatives, including vitamin C, for instance, exist largely in the form of five membered or six membered ring containing one oxygen atom. Most members of the vitamin B group possess heterocyclic rings containing nitrogen; one example is vitamin B6 (Pyridoxine), which is a derivative of the pyridine, essential in amino acid metabolism. Natural products containing heterocyclic compounds such as alkaloids and glycosides have been used since old age, as remedial agents. Febrifagl alkaloid from ancient Chinese drug, Chang Shan, reserpine from Indian rouwopifia, Curen alkaloid from arrow poison, codeine, tropine and strychnine are all examples of heterocyclic compounds. Many antibiotics including penicillin, cephalosporin, norfloxacin, streptomycin etc. also contain heterocyclic ring systems. Majority of the drugs being introduced in pharmacopeias in recent years are heterocyclic compounds.

Taking in view of the applicability of heterocyclic compounds, we have undertaken the synthesis of heterocycles bearing 1,2,3-triazole, pyrazole, pyrazoline, 1,5-benzodiazepene, indole, quinoline, piperidine, and pyrrolidine nuclei. The placements of a wide variety of substituents on these nuclei have been designed in order to evaluate their pharmacological profile against several strains of bacteria and fungi. Biological activity of some of the heterocyclic compounds related to my research work is given in the following tables.
Table-1: Biological activity of 1,2,3-triazole derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rufinamide</td>
<td><img src="image" alt="Rufinamide Structure" /></td>
<td>Anticonvulsant activity</td>
</tr>
<tr>
<td>Carboxyamidotriazole (CAI)</td>
<td><img src="image" alt="CAI Structure" /></td>
<td>Anticancer activity</td>
</tr>
</tbody>
</table>

Table-2: Biological activity of 1,2,3-triazole with chalcones derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-(1-{4-[3-(4-Hydroxy-phenyl)-3-oxo-propenyl]-phenoxy-methyl}-1H-[1,2,3]triazol-4-ylmethoxy)-7-methoxy-1,2,3,11α-tetrahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one</td>
<td><img src="image" alt="Compound Structure" /></td>
<td>Anticancer activity</td>
</tr>
</tbody>
</table>
Table-3: Biological activity of pyrazole derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td><img src="" alt="Structure" /></td>
<td>Nonsteroidal anti-inflammatory activity</td>
</tr>
<tr>
<td>Rimonabant</td>
<td><img src="" alt="Structure" /></td>
<td>Cannabinoid receptor type 1 antagonist</td>
</tr>
</tbody>
</table>

Table-4: Biological activity of pyrazoline derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibipinabant</td>
<td><img src="" alt="Structure" /></td>
<td>Cannabinoid receptor type 1 antagonist</td>
</tr>
<tr>
<td>Phenazone</td>
<td><img src="" alt="Structure" /></td>
<td>Anaesthetic activity</td>
</tr>
</tbody>
</table>
Table-5: Biological activity of indole derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td><img src="image1" alt="Structure" /></td>
<td>Multiple Myeloma activity</td>
</tr>
<tr>
<td>Demethylasterriquinone</td>
<td><img src="image2" alt="Structure" /></td>
<td>Antidiabetic activity</td>
</tr>
</tbody>
</table>

Table-6: Biological activity of diazepine derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorazepate</td>
<td><img src="image3" alt="Structure" /></td>
<td>Anticonvulsant activity</td>
</tr>
<tr>
<td>2-Methyl-2,4-di-thiophen-3-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine</td>
<td><img src="image4" alt="Structure" /></td>
<td>Anti-inflammatory activity</td>
</tr>
</tbody>
</table>
### Table-7: Biological activity of quinoline derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinchonine</td>
<td><img src="image1" alt="Structure" /></td>
<td>Antimalarial activity</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td><img src="image2" alt="Structure" /></td>
<td>Antibacterial activity</td>
</tr>
</tbody>
</table>

### Table-8: Biological activity of piparidine derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td><img src="image3" alt="Structure" /></td>
<td>Antiprotozoal activity</td>
</tr>
</tbody>
</table>

### Table-9: Biological activity of pyrrolidine derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td><img src="image4" alt="Structure" /></td>
<td>Antibacterial activity</td>
</tr>
</tbody>
</table>
SECTION-B: GREEN CHEMISTRY-A BRIEF REVIEW

Introduction:

Over the past few years, the chemistry community has been mobilized to develop new strategies that are less hazardous to human health and the environment. This new approach has received extensive attention and goes by many names including Green Chemistry, Environmentally Benign Chemistry, Clean Chemistry, Atom Economy and Benign by Design Chemistry. The green chemistry is the use of techniques and methodologies that reduce or eliminate the use or generation of feedstock, products, by-products, solvents, reagents, etc., that are hazardous to human health or the environment.

Applications of new methodologies used in the green synthesis

- Solvent-free / neat reactions
- Microwave assisted synthesis
- Ultrasound assisted synthesis
- Ionic liquids in organic synthetic routes
- Organic synthesis in water

In these methodologies our research concern we have taken up to discussed three methodologies, following.

Solvent-free / neat reactions:

Solvent-free reactions, has gained special attention from synthetic organic chemists. As a result, many reactions are newly found to proceed cleanly and efficiently in the solid state or under solvent-free conditions. Less chemical pollution, lower expenses, and easier procedures are the main reasons for the recent increase in the popularity of solvent-free reactions. While an obvious approach to chemical synthesis, there are many problems associated with this approach, the chief of which is the role of diffusion/interactions between reactants. Further, it is clear that the reactions in the solid state will generate the same products as those found in the presence of solvents.
1) Sivasubramanian Muthusaravanan et. al., have synthesized 3-Aroyl-3a,8b-dihydroxy-1-aryl-1,8b-dihydroindeno[1,2-b]pyrrol-4(3aH)-ones from a mixture of enaminone, ninhydrin and aniline in AcOH was thoroughly ground using a pestle and mortar at room temperature for 5-8 min.

**Scheme-1:** Synthesis of 3-aroyl-3a,8b-dihydroxy-1-aryl-1,8b-dihydroindeno[1,2-b]pyrrol-4(3aH)-ones (4)

![Scheme-1](image)

**Microwave assisted synthesis:**

Microwave reactions involve selective absorption of electromagnetic waves by polar molecules, non-polar molecules being inert to microwaves. When molecules with a permanent dipole are submitted to an electric field, they become aligned and as the field oscillates their orientation changes, this rapid reorientation produces intense internal heating. The main difference between classical heating and microwave heating lies in core and homogenous heating associated with microwaves, whereas classical heating is all about heat transfer by preheated molecules.

2) M. G. Gündüz et al., have synthesised 9-(1H-Indol-3-yl)-3,3,6,6-tetramethyldecahydro acridine-1,8(2H,8aH)-dione a one pot multicomponent mixture of 4,4-dimethyl-1,3-cyclohexanedione, indole carboxaldehyde and ammonium acetate was filled into 10 mL-microwave pressure vial and heated under microwave irradiation (power 50 W, maximum temperature 120 °C) for 10 min in 5 ml methanol.
Scheme-2: Synthesis of 9-\((1H\text{-indol-3-yl})\)-3,3,6,6-tetramethyldecahydroacridine-1,8(2H,8aH)-dione (8).

\[
\begin{align*}
\text{CHO} + \text{MeOH} &\rightarrow \text{O} \\
\text{NH} + \text{O} &\rightarrow \text{O} \\
\text{HN} &\rightarrow \text{O} \\
\text{H} &\rightarrow \text{O} \\
\text{MeO} &\rightarrow \text{O} \\
\text{MWI, 50 W, 120 }^\circ\text{C.}
\end{align*}
\]

Ultrasound assisted synthesis:

Ultrasonic waves are propagated via alternating compressions and rarefactions induced in the transmitting medium through which they pass. During the rarefaction cycle of the sound wave, the molecules of the liquid are separated, generating bubbles that subsequently collapse in the compression cycle. These rapid and violent implosions generate short-lived regions with local temperatures of roughly 5000 °C, pressures of about 1000 atm and heating and cooling rates that can exceed 10 billion °C per second. Such localized hot spots can be thought of as micro reactors in which the mechanical energy of sound is transformed into a useful chemical form. In addition to the generation of such hot spots, there can also be mechanical effects produced as a result of the violent. In the ensuing four decades, numerous efficient and innovative applications of ultrasound in organic synthesis have appeared which have established sonochemistry as an important tool in the arsenal of Green Chemistry.

3) K. C. Prousis et al., have synthesized 4-substituted coumarins from a mixture of the appropriate phenol, β-ketoester and anhydrous FeCl₃ was placed in a 10 ml glass tube and was sonicated (20 KHz, 130 watts nominal power) for 1-20 min.

Scheme-3: Synthesis of 4-substituted coumarins (11).
Comparative study of conventional and nonconventional methods in synthetic heterocyclic chemistry:

The advantages obtained by the use of microwave irradiation in relation to a conventional heating method were demonstrated.

4) Dandia et. al., have reported the synthesis of Spiro[1,5-benzothiazepin-2,3’[3’H]-indol]-2’(1’H)-ones form \((E)\)-3-(2-oxo-2-(4-substitutedphenyl)ethylidene)indolin-2-ones and 2-amino-5-substitutedbenzenethiols under conventional heating and microwave irradiation method.

**Scheme-4: Synthesis of Spiro[1,5-benzothiazepin-2,3’[3’H]-indol]-2’(1’H)-ones (14).**

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Reaction time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MWI (min)</td>
<td>MWI</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>5</td>
<td>91</td>
</tr>
<tr>
<td>Allyl</td>
<td>H</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>Me</td>
<td>Cl</td>
<td>5</td>
<td>97</td>
</tr>
<tr>
<td>Allyl</td>
<td>Cl</td>
<td>5</td>
<td>85</td>
</tr>
<tr>
<td>Me</td>
<td>Br</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>Allyl</td>
<td>Br</td>
<td>5</td>
<td>60</td>
</tr>
</tbody>
</table>

5) Dandia et. al., have reported the synthesis of Spiro [Indoline-3,2’-[1,3]thiazinane]-2,4’-diones by the reaction of substituted isatin, substituted anilines and 3-mercaptopropanoic acid under conventional heating and microwave irradiation method.
Scheme-5: Synthesis of Spiro[Indoline-3,2’-[1,3]thiazinane]-2,4’-diones (17).

<table>
<thead>
<tr>
<th>X</th>
<th>R</th>
<th>Reaction time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MWI Conventional MWI Conventional</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(min) (hr)</td>
<td></td>
</tr>
<tr>
<td>5-Cl</td>
<td>2-CF$_3$</td>
<td>14 15</td>
<td>72 68</td>
</tr>
<tr>
<td>5-Cl</td>
<td>3-CF$_3$</td>
<td>13 14</td>
<td>76 61</td>
</tr>
<tr>
<td>5-NO$_2$</td>
<td>4-F</td>
<td>18 16</td>
<td>68 55</td>
</tr>
</tbody>
</table>

Objective of the present investigation:

From recent literature review it is evident that a number of natural and synthetic heterocyclic compounds possess biological activity. Therefore the aim of the present work is to synthesize some novel heterocyclic compounds and evaluate their biological activity. Our ongoing research program towards the green chemistry to the experimental set ups. The green chemistry is the use of chemistry techniques and methodologies that reduce or eliminate the use or generation of feedstock, products, by-products, solvents, reagents, etc., that are hazardous to human health or the environment.

Chapter-I is divided into two sections.

Section-A: Biological activity of heterocyclic compounds-A brief review

Section-B: Green chemistry- A brief review

Chapter-II is divided into two sections.

Section-A: Synthesis of (E)-3-(3-Aryl-1-phenyl-1H-pyrazol-4-yl)-1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-2-yl)prop-2-en-1-ones
Section-B: Synthesis of \((E)-3-(3-Aryl-1-phenyl-1H-pyrazol-4-yl)-1-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)prop-2-en-1-ones.\)

Chapter-III is divided into two sections.

Section-A: Synthesis of \((2E.2'E)-1,1'-(4,6-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis-3-aryl-prop-2-en-1-one\) from bis-chalcones.

Section-B: Synthesis of \((2E.2'E)-1,1'-(4,6-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis-3-aryl-prop-2-en-1-one\) from bis-triazole

Chapter-IV is divided into two sections.

Section-A: Synthesis of 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrrole and 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrrole

Section-B: Synthesis of 3'-Aryl-5-(2-methoxynaphthalen-1-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrrole and 3'-Aryl-5-(2-methoxynaphthalen-1-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrrole.

Chapter-V is divided into two sections.

Section-A: Synthesis of 4,6-Bis-(4-aryl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzene-1,3-diols

Section-B: Synthesis of 4,6-Bis-(5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-benzene-1,3-diols.

Chapter-VI is divided into three sections.

Section-A: Synthesis of \((E)-1-Aryl-3-(2-substituted-quinolin-3-yl)prop-2-en-1-ones,\)

Section-B: Synthesis of \(2\{4-[3-(1-Phenyl-3-aryl-1H-pyrazol-4-yl)-acryloyl]-phenyl\}-isoindole-1,3-diones\)

Section-C: Synthesis of 2-(2-Ethoxy-5-substituted-indol-3-ylidene)-1-aryl-ethanones

Chapter-VII is divided into two sections.

Section-A: Evaluation of antimicrobial activity

Section-B: Evaluation of aldose reductase inhibition and antioxidant scavenging activity
Structures of all the synthesized compounds were established on the basis of spectral data such as IR, $^1$H & $^{13}$C NMR, mass and elemental analysis.

**CHAPTER-II**

**SYNTHESIS OF (E)-3-(3-ARYL-1-PHENYL-1H-PYRAZOL-4-YL)-1-(1-((1-BENZYL-1H-1,2,3-TRIAZOL-4-YL)METHOXY)NAPHTHALEN-2-YL)PROP-2-EN-1-ONES AND (E)-3-(3-ARYL-1-PHENYL-1H-PYRAZOL-4-YL)-1-(2-((1-BENZYL-1H-1,2,3-TRIAZOL-4-YL)METHOXY)NAPHTHALEN-1-YL)PROP-2-EN-1-ONES**

**Introduction:**
1,2,3-Triazoles have not been isolated in any naturally occurring compounds, however the 1,2,3-triazole moiety has been utilized in many applications ranging from industrial to pharmaceutical uses. Derivatives of 1,2,3-triazole have been found to have anti-HIV, anti-allergenic, antimicrobial, cytostatic, virostatic, anti-inflammatory and anti-bacterial activities. Triazoles are also being studied for the treatment of obesity and osteoarthritis. Pyrazole derivatives have been reported in the literature to exhibit various pharmacological activities such as antimicrobial, anti-inflammatory, antitubercular, antitumor, antiangiogenesis, antiparasitic, antiviral, and also possess analgesic and anxiolytic activity. Chalcones are widely distributed in nature and are known to have multipronged activity, they exhibit wide spectrum of biological activities, such as antibacterial, antifungal, anti-inflammatory, antioxidant and antitumor activities.

**Present work:**
Recent literature survey revealed that the 1,2,3-triazole and pyrazole compounds are found to exhibit various biological activities. The synthesis and study of biological activity of 1,2,3-triazole with pyrazolylchalcone back bone is a relatively unexplored area. Therefore we have taken up the synthesis of (E)-3-(3-Aryl-1-phenyl-1H-pyrazol-4-yl)-1-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-2-yl)prop-2-en-1-ones and (E)-3-(3-Aryl-1-phenyl-1H-pyrazol-4-yl)-1-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)prop-2-en-1-ones with a view to study their ease of formation and also to evaluate their antimicrobial activity.
Section-A: Synthesis of \((E)-3-(3\text{-Aryl-1-phenyl-1}H\text{-pyrazol-4-yl)-1-(1-(1-benzyl-1}H\text{-1,2,3-triazol-4-yl)methoxy}naphthalen-2-yl)prop-2-en-1-ones\)

Synthesis of \((E)-3-(3\text{-Aryl-1-phenyl-1}H\text{-pyrazol-4-yl)-1-(1-(1-benzyl-1}H\text{-1,2,3-triazol-4-yl)methoxy}naphthalen-2-yl)prop-2-en-1-ones\) involves five steps.

1) Synthesis of Benzyl azide

Benzyl bromide on reaction with sodium azide in acetone:water at room temperature for 24 hr to afford benzyl azide.

2) Synthesis of 1-(1-Prop-2-ynyloxy-naphthalen-2-yl)-ethanone under conventional heating and microwave irradiation methods

**Conventional heating method:**

A mixture of 1-(1-Hydroxy-naphthalen-2-yl)-ethanone and propargyl bromide in acetone was refluxed to afford 1-(1-Prop-2-ynyloxy-naphthalen-2-yl)-ethanone

**Microwave irradiation method:**

A mixture of 1-(1-Hydroxy-naphthalen-2-yl)-ethanone and propargyl bromide was adsorbed on potassium carbonate and subjected to microwave irradiation to give 1-(1-Prop-2-ynyloxy-naphthalen-2-yl)-ethanone

3) Synthesis of \(1-(1-(1\text{-Benzyl-1}H\text{-1,2,3-triazol-4-yl)methoxy}naphthalen-2-yl)ethanone\) under conventional and microwave irradiation methods.
Conventional method using Copper (II) sulphate:
A mixture of 1-(1-Prop-2-ynyl oxy-naphthalen-2-yl)-ethanone, benzyl azide, sodium ascorbate and CuSO₄·5H₂O in t-butanol:water (2:1) was stirred at room temperature for 24 hr to afford 1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-2-yl)ethanone.

Microwave irradiation method using Copper (II) sulphate:
A mixture of 1-(1-Prop-2-ynyl oxy-naphthalen-2-yl)-ethanone, benzyl azide, sodium ascorbate and CuSO₄·5H₂O in DMF was subjected to microwave irradiation at 180 watts for 8 min to afford 1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-2-yl)ethanone.

Conventional method using Copper (I) iodide:
A mixture of 1-(1-Prop-2-ynyl oxy-naphthalen-2-yl)-ethanone reacts with benzyl azide in presence of diisopropylethylamine and CuI in DMF was stirred at room temperature for 18 hr to afford 1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-2-yl)ethanone.

Microwave irradiation method using Copper (I) iodide:
A mixture of 1-(1-Prop-2-ynyl oxy-naphthalen-2-yl)-ethanone, benzyl azide, diisopropylethylamine and CuI and DMF was subjected to microwave irradiation at 180 watts for 6 min to give 1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-2-yl)ethanone in good yields.

4) Synthesis of 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes
3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes are the key starting materials for the synthesis of title compounds, were synthesized by the Vilsmeir-Haack reaction of N-phenyl-N'(1-arylethylidene)hydrazones.

5) Synthesis of (E)-3-(3-Aryl-1-phenyl-1H-pyrazol-4-yl)-1-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)napththalen-2-yl)prop-2-en-1-ones under conventional heating and microwave irradiation methods.
**Conventional heating method:**

1-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-2-yl)ethanone (18) on condensation with 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (19 a-g) in the presence of alcoholic KOH gave corresponding (E)-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-1-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-2-yl)prop-2-en-1-ones (20 a-g).

**Microwave Irradiation method:**

1-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-2-yl)ethanone (18) on condensation with 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (19 a-g) in the presence of alcoholic KOH under microwave irradiation yielded corresponding (E)-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-1-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-2-yl)prop-2-en-1-ones (20 a-g).

**Scheme-6: Synthesis of (E)-3-(3-Aryl-1-phenyl-1H-pyrazol-4-yl)-1-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-2-yl)prop-2-en-1-ones (20 a-g)**

**Section-B: Synthesis of (E)-3-(3-Aryl-1-phenyl-1H-pyrazol-4-yl)-1-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)prop-2-en-1-ones**

Synthesis of (E)-3-(3-Aryl-1-phenyl-1H-pyrazol-4-yl)-1-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)prop-2-en-1-ones involves five steps.
ABSTRACT

1) Synthesis of Benzyl azide
2) Synthesis of 1-(2-Prop-2-ynyloxy-naphthalen-1-yl)-ethanone
3) Synthesis of 1-(2-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)ethanone
4) Synthesis of 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes
5) Synthesis of (E)-3-(3-Aryl-1-phenyl-1H-pyrazol-4-yl)-1-(2-((1-benzyl-1H-1,2,3-triazol-4-yl) methoxy)naphthalen-1-yl)prop-2-en-1-ones

1) Synthesis of Benzyl azide (already discussed in section-A of chapter-II)

2) Synthesis of 1-(2-Prop-2-ynyloxy-naphthalen-1-yl)-ethanone under conventional heating and microwave irradiation methods

Conventional heating method:
A mixture of 1-(2-Hydroxy-naphthalen-1-yl)-ethanone and propargylbromide in acetone was refluxed to afford 1-(2-Prop-2-ynyloxy-naphthalen-1-yl)-ethanone.

Microwave irradiation method:
A mixture of 1-(2-Hydroxy-naphthalen-1-yl)-ethanone and propargyl bromide was adsorbed on potassium carbonate and subjected to microwave irradiation to give 1-(2-Prop-2-ynyloxy-naphthalen-1-yl)-ethanone.

3) Synthesis of 1-[2-(1-Benzyl-1H-[1,2,3]triazol-4-ylmethoxy)-naphthalen-1-yl]-ethanone under conventional and microwave irradiation methods.

Conventional method using Copper (II) sulphate:
A mixture of 1-(2-Prop-2-ynyloxy-naphthalen-1-yl)-ethanone, benzyl azide, sodium ascorbate and CuSO₄·5H₂O in t-butanol:water (2:1) medium to afford 1-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)ethanone.
Microwave irradiation method using Copper (II) sulphate:
A mixture of 1-(2-Prop-2-ynyloxy-naphthalen-1-yl)-ethanone, benzyl azide, sodium ascorbate and CuSO$_4$.5H$_2$O in DMF was subjected to microwave irradiation to afford 1-(2-((1-benzyl-1$H$-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)ethanone.

Conventional method using Copper (I) iodide:
1-(2-Prop-2-ynyloxy-naphthalen-1-yl)-ethanone reacts with benzyl azide in presence of diisopropylethylamine and CuI in DMF at room temperature to afford 1-(2-((1-benzyl-1$H$-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)ethanone.

Microwave irradiation method using Copper (I) iodide:
A mixture of 1-(2-Prop-2-ynyloxy-naphthalen-1-yl)-ethanone, benzyl azide, diisopropylethylamine and CuI and DMF was subjected to microwave irradiation to give 1-(2-((1-benzyl-1$H$-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)ethanone in good yields.

4) Synthesis of 3-Aryl-1-phenyl-1$H$-pyrazole-4-carbaldehyde (already discussed in section-A of chapter-II)

5) Synthesis of (E)-3-(3-Aryl-1-phenyl-1$H$-pyrazol-4-yl)-1-(2-((1-benzyl-1$H$-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)prop-2-en-1-ones under conventional heating and microwave irradiation methods.

Conventional heating method:
1-(2-((1-Benzyl-1$H$-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)ethanone (21) on condensation with 3-aryl-1-phenyl-1$H$-pyrazole-4-carbaldehydes (19 a-g) in the presence of alcoholic KOH gave corresponding (E)-3-(3-aryl-1-phenyl-1$H$-pyrazol-4-yl)-1-(2-((1-benzyl-1$H$-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)prop-2-en-1-ones (22 a-g).

Microwave Irradiation method:
1-(2-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)ethanone (21) on condensation with 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (19 a-g) in the presence of alcoholic KOH under microwave irradiation yielded corresponding (E)-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-1-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)prop-2-en-1-ones (22 a-g).

**Scheme-7:** Synthesis of (E)-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-1-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)prop-2-en-1-ones (22 a-g).
CHAPTER-III

Synthesis of \((2E,2'E)-1,1'-(4,6-\text{Bis}((1\text{-benzyl}-1H-1,2,3-\text{triazol}-4-\text{yl})\text{methoxy})-1,3-\text{phenylene})\text{bis}(3\text{-arylprop-2-en-1-one})\)s

Introduction:

Bis-heterocyclic compounds are gaining increased interest in the recent past as the dimeric analogues have proven to be having better and potential biological activity than the corresponding monomer. Bis-heterocyclic compounds also show biological activities such as antimicrobial, antifungal, anti-inflammatory, antiviral, anti-HIV. Literature on 1,2,3-triazole moiety is also a part of number of drugs such as \(\beta\)-lactum antibiotic of Tazobactam, Carboxyamidotriazole (CAI) and Cefatrizine. Chalcones are widely distributed in nature and are known to have multipronged activity, they exhibit wide spectrum of biological activities, such as antibacterial, antifungal, antioxidant and antitumor activities.

Present work:

Literature survey revealed that the bis-heterocyclic compounds are found to exhibit various biological activities. Therefore we have taken up the synthesis of \((2E,2'E)-1,1'-(4,6-\text{Bis}((1\text{-benzyl}-1H-1,2,3-\text{triazol}-4-\text{yl})\text{methoxy})-1,3-\text{phenylene})\text{bis}(3\text{-arylprop-2-en-1-one})\)s with a view to study their ease of formation and also to evaluate their biological activity. All these compounds were synthesized under both conventional heating and microwave irradiation methods. The reaction time and yields are compared in both the methods.

Section-A: Synthesis of \((2E,2'E)-1,1'-(4,6-\text{Bis}((1\text{-benzyl}-1H-1,2,3-\text{triazol}-4-\text{yl})\text{methoxy})-1,3-\text{phenylene})\text{bis}(3\text{-arylprop-2-en-1-one})\)s form bis-chalcones

Synthesis of \((2E,2'E)-1,1'-(4,6-\text{Bis}((1\text{-benzyl}-1H-1,2,3-\text{triazol}-4-\text{yl})\text{methoxy})-1,3-\text{phenylene})\text{bis}(3\text{-arylprop-2-en-1-one})\)s (route-a) involves five steps.

1) Synthesis of Benzyl azide
2) Synthesis of 1,1'-(4,6-Dihydroxy-1,3-phenylene)diethanone
3) Synthesis of \((2E,2'E)-1,1'-(4,6\text{-Dihydroxy}-1,3\text{-phenylene})\text{bis}(3\text{-arylprop}-2\text{-en-1-one})s\)

4) Synthesis of \((2E,2'E)-1,1'-(4,6\text{-Bis(prop-2-yn-1-yl}oxy)-1,3\text{-phenylene})\text{bis}(3\text{-arylprop}-2\text{-en-1-one})s\)

5) Synthesis of \((2E,2'E)-1,1'-(4,6\text{-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy})-1,3\text{-phenylene})\text{bis}(3\text{-arylprop}-2\text{-en-1-one})s\)

1) Synthesis of Benzyl azide (already discussed in chapter-II, section-A)

2) Synthesis of 1,1'-(4,6-Dihydroxy-1,3-phenylene)diethanone under conventional heating and microwave irradiation

**Conventional heating method:**

4,6-Diacetyl resorcinol is the key starting materials for the synthesis of title compounds was prepared in excellent yield by condensing resorcinol with acetic anhydride in the presence of anhydrous ZnCl\(_2\).

**Microwave irradiation method:**

4,6-Diacetyl resorcinol was also prepared by microwave irradiation of a mixture of resorcinol and acetic anhydride in the presence of anhydrous ZnCl\(_2\).

3) Synthesis of \((2E,2'E)-1,1'-(4,6\text{-Dihydroxy}-1,3\text{-phenylene})\text{bis}(3\text{-arylprop}-2\text{-en-1-one})s\) under conventional heating and microwave irradiation methods.

**Conventional heating method:**

A mixture of 1,1'-(4,6-Dihydroxy-1,3-phenylene)diethanone, aromatic aldehydes in alcoholic potassium hydroxide was stirred for 8-10 hr to afford \((2E,2'E)-1,1'-(4,6\text{-Dihydroxy}-1,3\text{-phenylene})\text{bis}(3\text{-arylprop}-2\text{-en-1-one})s\).
Microwave irradiation method:

A mixture of 1,1’-(4,6-Dihydroxy-1,3-phenylene)diethanone, aromatic aldehydes in alcoholic potassium hydroxide was subjected to microwave irradiation at 320 watts for 5-7 min to afford (2E,2’E)-1,1’-(4,6-dihydroxy-1,3-phenylene)bis(3-arylprop-2-en-1-one)s.

4) Synthesis of (2E,2’E)-1,1’-(4,6-Bis(prop-2-yn-1-yl)oxy)-1,3-phenylene)bis(3-arylprop-2-en-1-one)s under conventional heating and microwave irradiation methods.

Conventional heating method:

A mixture of (2E,2’E)-1,1’-(4,6-Dihydroxy-1,3-phenylene)bis(3-arylprop-2-en-1-one)s and propargyl bromide, K₂CO₃ in acetone was refluxed for 8-10 hr to afford 1,1’-(4,6-bis(prop-2-yn-1-yl)oxy)-1,3-phenylene)diethanones.

Microwave Irradiation method:

A mixture of (2E,2’E)-1,1’-(4,6-Dihydroxy-1,3-phenylene)bis(3-arylprop-2-en-1-one)s, propargyl bromide were adsorbed on potassium carbonate and subjected to microwave irradiation at 180 watts for 5-6 min. to afford 1,1’-(4,6-bis(prop-2-yn-1-yl)oxy)-1,3-phenylene)diethanones.

5) Synthesis of (2E,2’E)-1,1’-(4,6-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis(3-arylprop-2-en-1-one)s (25 a-e) under conventional heating and microwave irradiation methods.

Conventional method using CuSO₄.5H₂O & Sodium ascorbate:

A mixture of (2E,2’E)-1,1’-(4,6-Bis(prop-2-yn-1-yl)oxy)-1,3-phenylene)bis(3-arylprop-2-en-1-one)s (23 a-e), benzyl azide (24), CuSO₄. 5H₂O and sodium ascorbate in t-BuOH: H₂O (2:1, v/v) was stirred at room temperature for 24 hr to give compound (2E,2’E)-1,1’-(4,6-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis(3-arylprop-2-en-1-one)s (25 a-e).

Microwave irradiation method using CuSO₄.5H₂O & Sodium ascorbate:
A mixture of \((2E,2'E)-1,1'-(4,6\text{-Bis(prop-2-yn-1-yl}oxy)-1,3\text{-phenylene})\text{bis(3-arylprop-2-en-1-one)s (23 a-e)}\), benzyl azide (24), \(\text{CuSO}_4\cdot5\text{H}_2\text{O}\) and sodium ascorbate in \(t\text{-BuOH}: \text{H}_2\text{O (2:1, v/v)}\) was subjected microwave irradiation to afford corresponding \((2E,2'E)-1,1'-(4,6\text{-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene})\text{bis(3-arylprop-2-en-1-one)s (25 a-e)}\).

**Conventional method using CuI:**

A mixture of \((2E,2'E)-1,1'-(4,6\text{-Bis(prop-2-yn-1-yl}oxy)-1,3\text{-phenylene})\text{bis(3-arylprop-2-en-1-one)s (23 a-e)}\), benzyl azide (24), CuI, triethylamine in DMF was stirred at room temperature for 24 hr to give \((2E,2'E)-1,1'-(4,6\text{-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene})\text{bis(3-arylprop-2-en-1-one)s (25 a-e)}\).

**Microwave irradiation method using CuI:**

A mixture of \((2E,2'E)-1,1'-(4,6\text{-Bis(prop-2-yn-1-yl}oxy)-1,3\text{-phenylene})\text{bis(3-arylprop-2-en-1-one)s (23 a-e)}\), benzyl azide (24), CuI, triethylamine in DMF was subjected to microwave irradiation to afford corresponding \((2E,2'E)-1,1'-(4,6\text{-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene})\text{bis(3-arylprop-2-en-1-one)s (25 a-e)}\).

**Scheme-8:** *Synthesis of \((2E,2'E)-1,1'-(4,6\text{-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene})\text{bis(3-arylprop-2-en-1-one)s (38 a-e)}\).*

**Section-B:** *Synthesis of \((2E,2'E)-1,1'-(4,6\text{-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene})\text{bis(3-arylprop-2-en-1-one)s from bis-triazole}.*
ABSTRACT

Synthesis of \((2E,2'E)-1,1'-(4,6\text{-Bis((1\text{-benzyl}-1H-1,2,3\text{-triazol-4-yl})methoxy})-1,3\text{-phenylene})\text{bis(3-arylprop-2-en-1-one)s (route-b)}\) involves five steps

1) Synthesis of Benzyl azide
2) Synthesis of 1,1'-(4,6-Dihydroxy-1,3-phenylene)diethanone
3) Synthesis of 1,1'-(4,6-Bis(prop-2-yn-1-yloxy)-1,3-phenylene)diethanone
4) Synthesis of 1,1'-(4,6-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)diethanone
5) Synthesis of \((2E,2'E)-1,1'-(4,6\text{-Bis((1\text{-benzyl}-1H-1,2,3\text{-triazol-4-yl})methoxy})-1,3\text{-phenylene})\text{bis(3-arylprop-2-en-1-one)s}.

1) Synthesis of Benzyl azide (already discussed in chapter-II, section-A)

2) Synthesis of 1,1'-(4,6-Dihydroxy-1,3-phenylene)diethanone (already discussed in chapter-III, section-A)

3) Synthesis of 1,1'-(4,6-Bis(prop-2-yn-1-yloxy)-1,3-phenylene)diethanone under conventional heating and microwave irradiation methods.

Conventional heating method:
A mixture of 1,1'-(4,6-Dihydroxy-1,3-phenylene)diethanone and propargyl bromide, K\(_2\)CO\(_3\) in acetone were refluxed for 8 hr to afford 1,1'-(4,6-bis(prop-2-yn-1-yloxy)-1,3-phenylene)diethanone.

Microwave Irradiation method:
A mixture of 1,1'-(4,6-Dihydroxy-1,3-phenylene)diethanone, propargyl bromide was adsorbed on potassium carbonate and subjected to microwave irradiation at 180 watts for 6 min. to afford 1,1'-(4,6-bis(prop-2-yn-1-yloxy)-1,3-phenylene)diethanone.

4) Synthesis of 1,1'-(4,6-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)diethanone under conventional heating and microwave irradiation methods.
Conventional conditions using CuSO$_4$.5H$_2$O & Sodium ascorbate method:

A mixture of 1,1'-(4,6-Bis(prop-2-yn-1-yn-1-yl)-1,3-phenylene)diethanone, benzyl azide, CuSO$_4$.5H$_2$O and sodium ascorbate in t-BuOH:H$_2$O (2:1, v/v) was stirred at room temperature for 24 hr to give compound 1,1'-(4,6-bis(1-benzyl-1H-1,2,3-triazol-4-yl) methoxy)-1,3-phenylene)diethanone.

Microwave irradiation using CuSO$_4$.5H$_2$O & Sodium ascorbate method:

A mixture of 1,1'-(4,6-Bis(prop-2-yn-1-yn-1-yl)-1,3-phenylene)diethanone, benzyl azide, CuSO$_4$.5H$_2$O and sodium ascorbate in t-BuOH:H$_2$O (2:1, v/v) was subjected to microwave irradiation to afford corresponding 1,1'-(4,6-bis(1-benzyl-1H-1,2,3-triazol-4-yl) methoxy)-1,3-phenylene)diethanone.

Conventional conditions using CuI method:

A mixture of 1,1'-(4,6-Bis(prop-2-yn-1-yn-1-yl)-1,3-phenylene)diethanone, benzyl azide, CuI, triethylamine in DMF was stirred at room temperature for 24 hr to give 1,1'-(4,6-bis(1-benzyl-1H-1,2,3-triazol-4-yl) methoxy)-1,3-phenylene)diethanone.

Microwave irradiation using CuI method:

A mixture of 1,1'-(4,6-Bis(prop-2-yn-1-yn-1-yl)-1,3-phenylene)diethanone, benzyl azide, CuI, triethylamine in DMF was subjected to microwave irradiation to afford corresponding 1,1'-(4,6-bis(1-benzyl-1H-1,2,3-triazol-4-yl) methoxy)-1,3-phenylene)diethanone.

5) Synthesis of (2\text{E},2'\text{E})-1,1'-(4,6-Bis((1-benzyl-1H-1,2,3-triazol-4-yl) methoxy)-1,3-phenylene)bis(3-arylprop-2-en-1-one)s under conventional heating and microwave irradiation methods.

Conventional heating method:

A mixture of 1,1'-(4,6-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)diethanone (26), aromatic aldehydes (27 a-l) in alcoholic potassium hydroxide was stirred for 8-10 hr to afford (2\text{E},2'\text{E})-1,1'-(4,6-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis(3-arylprop-2-en-1-one)s (25 a-l).
**Microwave irradiation method:**

A mixture of 1,1’-(4,6-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)diethanone (26), aromatic aldehydes (27 a-l) in alcoholic potassium hydroxide was subjected to microwave irradiation at 320 watts for 5-7 min to afford (2E,2’E)-1,1’-(4,6-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis(3-arylprop-2-en-1-one)s (25 a-l).

**Scheme-9:** Synthesis of (2E,2’E)-1,1’-(4,6-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis(3-arylprop-2-en-1-one)s (25 a-l).
SYNTHESIS OF (i) 3'-ARYL-5-(1-METHOXYNAPHTHALEN-2-YL)-1'-PHENYL-3,4-DIHYDRO-1'H,2'H-3,4'-BIPYRAZOLES, (ii) 3'-ARYL-5-(1-METHOXYNAPHTHALEN-2-YL)-1',2-DIPHENYL-3,4-DIHYDRO-1'H,2'H-3,4'-BIPYRAZOLES, (iii) 3'-ARYL-5-(2-METHOXYNAPHTHALEN-1-YL)-1'-PHENYL-3,4-DIHYDRO-1'H,2'H-3,4'-BIPYRAZOLES AND (iv) 3'-ARYL-5-(2-METHOXY NAPHTHALEN-1-YL)-1',2-DIPHENYL-3,4-DIHYDRO-1'H,2'H-3,4'-BIPYRAZOLES

Introduction:

Pyrazole refers to the class of simple aromatic ring organic compounds of the heterocyclic series. Derivatives of pyrazole are used for their analgesic, anti-inflammatory, antipyretic, anticonvulsant, monoamineoxidase inhibiting, antidiabetic and antibacterial activities. The pyrazole ring is present as the core in a variety of leading nonsteroidal anti-inflammatory drugs (NSAIDs) and antihypertensive drugs. They have also found use as bifunctional ligands for metal catalysis, and in various building blocks for pharmaceutical and agricultural research. The pyrazole ring is present as the core in a variety of leading drugs such as Celebrex, Viagra or Rimonabant. Moreover, 2-Pyrazolines display a broad spectrum of potential pharmacological activities and are present in a number of pharmacologically active molecules such as phenazone/amidopyrene/methampyrone (analgesic and antipyretic), azolid/tandearil (anti-inflammatory), indoxacarb (insecticidal), anturane (uricosuric), etc. Considerable interest has been focused on the pyrazoline structure.

Present work:

Encouraged by the biological activities of 2-pyrazoline and pyrazole moieties, we have taken up the synthesis of 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1'-phenyl-3,4-dihydro-1'H,2'H-3,4'-bipyrazoles, 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1',2-diphenyl-3,4-dihydro-1'H,2'H-3,4'-bipyrazoles, 3'-Aryl-5-(2-methoxynaphthalen-1-yl)-1'-phenyl-3,4-dihydro-1'H,2'H-3,4'-bipyrazoles and 3'-Aryl-5-(2-methoxynaphthalen-1-yl)-1',2-diphenyl-3,4-dihydro-1'H,2'H-3,4'-bipyrazoles with a view to test their antimicrobial activity.
Section-A: Synthesis of 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles and 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles.

Synthesis of 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles and 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles involve three steps

1) Synthesis of 1-(1-Methoxynaphthalen-2-yl)ethanone
2) Synthesis of 3-Aryl-1-phenyl-1'H-pyrazole-4-carbaldehyde
3) Synthesis of 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles and 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles

1) Synthesis of 1-(1-Methoxynaphthalen-2-yl)ethanone.

A mixture of 1-(1-Hydroxynaphthalen-2-yl)ethanone, potassium carbonate and dimethyl sulfate in DMF was stirred at room temperature for 6 hr to yield 1-(1-methoxynaphthalen-2-yl)ethanone.

2) Synthesis of 3-Aryl-1-phenyl-1'H-pyrazole-4-carbaldehydes (already discussed in chapter-II, section-A)

3) Synthesis of 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (29 a-g) and 3'-Aryl-5-(1-methoxynaphthalen-2-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (29 h-m) under conventional heating, microwave irradiation and ultrasound irradiation methods
Conventional heating method:

A solution of KOH, 1-(1-Methoxynaphthalen-2-yl)ethanone (28) and 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (19 a-g) in ethanol was refluxed until the starting materials have completely disappeared, then hydrazine hydrate / phenylhydrazine hydrochloride is added and reflux continued to afford corresponding 3'-aryl-5-(1-methoxynaphthalen-2-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (29 a-g) / 3'-aryl-5-(1-methoxynaphthalen-2-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (29 h-m).

Microwave irradiation method:

A solution of KOH, 1-(1-Methoxynaphthalen-2-yl)ethanone (28) and 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (19 a-g) in ethanol was irradiated under microwave until the starting materials have completely disappeared, then hydrazine hydrate / phenylhydrazine hydrochloride is added and irradiation continued to yield corresponding 3'-aryl-5-(1-methoxynaphthalen-2-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (29 a-g) / 3'-aryl-5-(1-methoxynaphthalen-2-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (29 h-m).

Ultrasound irradiation method:

A solution of KOH, 1-(1-Methoxynaphthalen-2-yl)ethanone (28) and 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (19 a-g) in ethanol was irradiated under ultrasound until the starting materials have completely disappeared, then hydrazine hydrate / phenylhydrazine hydrochloride is added and irradiation continued to yield corresponding 3'-aryl-5-(1-methoxynaphthalen-2-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (29 a-g) / 3'-aryl-5-(1-methoxynaphthalen-2-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (29 h-m).
Scheme-10: Synthesis of 3’-Aryl-5-(1-methoxynaphthalen-2-yl)-1’-phenyl-3,4-dihydro-1’H,2H-3,4’-bipyrazoles (29 a-g) & 3’-Aryl-5-(1-methoxynaphthalen-2-yl)-1’,2-diphenyl-3,4-dihydro-1’H,2H-3,4’-bipyrazoles (29 h-m).

Section-B: Synthesis of 3’-Aryl-5-(2-methoxynaphthalen-1-yl)-1’-phenyl-3,4-dihydro-1’H,2H-3,4’-bipyrazoles and 3’-Aryl-5-(2-methoxynaphthalen-1-yl)-1’,2-diphenyl-3,4-dihydro-1’H,2H-3,4’-bipyrazoles.

Synthesis of 3’-Aryl-5-(2-methoxynaphthalen-1-yl)-1’-phenyl-3,4-dihydro-1’H,2H-3,4’-bipyrazoles and synthesis of 3’-Aryl-5-(2-methoxynaphthalen-1-yl)-1’,2-diphenyl-3,4-dihydro-1’H,2H-3,4’-bipyrazoles involve three steps

1) Synthesis of 1-(2-Methoxynaphthalen-1-yl)ethanone
2) Synthesis of 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes
3) Synthesis of 3’-Aryl-5-(2-methoxynaphthalen-1-yl)-1’-phenyl-3,4-dihydro-1’H,2H-3,4’-bipyrazoles and 3’-Aryl-5-(2-methoxynaphthalen-1-yl)-1’,2-diphenyl-3,4-dihydro-1’H,2H-3,4’-bipyrazoles

1) Synthesis of 1-(2-Methoxynaphthalen-1-yl)ethanone
A mixture of 1-(2-Hydroxynaphthalen-1-yl)ethanone, potassium carbonate and dimethylsulfate in DMF was stirred for room temperature to yield 1-(2-methoxynaphthalen-1-yl)ethanone.

2) Synthesis of 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (already discussed in chapter-I, section-A)

3) Synthesis of 3'-Aryl-5-(2-methoxynaphthalen-1-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (31 a-f) and 3'-Aryl-5-(2-methoxynaphthalen-1-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (31 g-k) under conventional heating, microwave irradiation and ultrasound irradiation methods

Conventional heating method:

A solution of KOH, 1-(2-Methoxynaphthalen-1-yl)ethanone (30), 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (19 a-f) in ethanol was refluxed until the starting materials have completely disappeared, then hydrazine hydrate / phenylhydrazine hydrochloride is added and reflux continued to afford corresponding 3'-aryl-5-(2-methoxynaphthalen-1-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (31 a-f) / 3'-aryl-5-(2-methoxynaphthalen-1-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (31 g-k).

Microwave irradiation method:

A solution of KOH, 1-(2-Methoxynaphthalen-1-yl)ethanone (30), 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (19 a-f) in ethanol was irradiated under microwave until the starting materials have completely disappeared, then hydrazine hydrate / phenylhydrazine hydrochloride is added and irradiation continued to yield corresponding 3'-aryl-5-(2-methoxynaphthalen-1-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (31 a-f) / 3'-aryl-5-(2-methoxynaphthalen-1-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (31 g-k).

Ultrasound irradiation method:
A solution of KOH, 1-(2-Methoxynaphthalen-1-yl)ethanone (30), 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (19 a-f) in ethanol was irradiated under ultrasound until the starting materials have completely disappeared, then hydrazine hydrate / phenylhydrazine hydrochloride is added and irradiation continued to yield corresponding 3'-aryl-5-(2-methoxynaphthalen-1-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (31 a-f) / 3'-aryl-5-(2-methoxynaphthalen-1-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (31 g-k).

Scheme-10: Synthesis of 3'-Aryl-5-(2-methoxynaphthalen-1-yl)-1'-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (31 a-f) & 3'-Aryl-5-(2-methoxynaphthalen-1-yl)-1',2-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (31 g-k).
CHAPTER-V

SYNTHESIS OF 4,6-BIS-(4-ARYL-4,5-DIHYDRO-3H-BENZO[b][1,4] DIAZEPIN-2-YL)-BENZENE-1,3-DIOLS AND 4,6-BIS-(5-ARYL-4,5-DIHYDRO-1H-PYRAZOL-3-YL)-BENZENE-1,3-DIOLS

Introduction:

Heterocyclic moiety is a pivotal core of many biologically and pharmacologically interesting compounds. Any synthetic approach for these compounds depends upon the availability and cast of the starting material, selection of ring closure steps and the tolerance of the functional group present in the molecule. A vast number of nitrogen containing heterocyclic building blocks have application in pharmaceutical and agrochemical research and drug discovery. Further, more bis-heterocyclic compounds are gaining increased interest in the recent past as the dimeric analogues have proven to be better and potential biological activity than the corresponding monomers.

Section-A: Solvent-free synthesis of 4,6-Bis-(4-aryl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzene-1,3-diols

Introduction:

Benzodiazepines are very important compounds because of their pharmacological properties, and have become increasingly interesting since they are used as tranquilizing, anti-inflammatory and anticonvulsant agents. In addition, benzodiazepines are used as starting materials for the preparation of fused ring compounds such as triazolo- and oxadiazolo-benzodiazepines. Bis-heterocyclic compounds are gaining increased interest in the recent past as the dimeric analogues have proven to be having better and potent biological activity than the corresponding monomers. The condensation reactions of o-phenylenediamine with α, β-unsaturated carbonyl compounds, β-haloketones, or ketones in the presence of polyphosphoric acid and silica gel, Yb(OTf)₃, MgO and POCl₃, Amberlyst-15 and acetic acid under microwave irradiation produces benzodiazepines.
Present work:

Encouraged by the biological activities of 1,5-benzodiazepines and bis-heterocyclic moieties, we have made considerable efforts for designing and carrying out more eco-sustainable synthetic approach. As a part of our research, we found that solvent-free microwave irradiation can promote reactive pathways in very convenient way from green chemical point of view. We have taken up the synthesis of 4,6-Bis-(4-aryl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzene-1,3-diols under microwave irradiation and conventional heating methods.

Synthesis of 4,6-Bis-(4-aryl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzene-1,3-diols involves three stages

1) Synthesis of 4,6-Diacetyl resorcinol
2) Synthesis of 4,6-Dicinnamoyl resorcinols
3) Synthesis of 4,6-Bis-(4-aryl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzene-1,3-diols

1. Synthesis of 4,6-Diacetyl resorcinol (already discussed in chapter-III, section-B)

2. Synthesis of 4,6-Dicinnamoyl resorcinols (already discussed in chapter-III, section-B)

3) Synthesis of 4,6-Bis-(4-aryl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzene-1,3-diols under conventional heating and microwave irradiation.

Conventional heating method

A mixture of 4,6-Dicinnamoyl resorcinols (32 a-g) and o-phenylenediamine (33) was adsorbed on basic alumina and heated to 80 °C for 3.5-4.5 hr to give 4,6-bis-(4-aryl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzene-1,3-diols (34 a-g).

Microwave irradiation method:

A mixture of 4,6-Dicinnamoyl resorcinols (32 a-g) and o-phenylenediamine (33) was adsorbed on basic alumina and subjected to microwave irradiation at 480 W for 7-8 min to afford 4,6-bis-(4-aryl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzene-1,3-diols (34 a-g).
**ABSTRACT**

**Scheme-11:** Synthesis of 4,6-Bis-(4-aryl-4,5-dihydro-3H-benzo[6][1,4]diazepin-2-yl)-benzene-1,3-diols (34 a-g).

![Scheme-11](image)

**Introduction:**
Pyrazolines and their derivatives have been gaining prominence because of their potential biological activities. Most of the members of this family have wide spectrum of biological activities such as antibacterial, analgesic, anti-inflammatory, antiviral, antifungal, antiarthritic, cerebroprotective effect and antidepressant activities. There are several substituted pyrazolines having bleaching property and also act as luminescent and fluorescent agents. They are also used in the synthesis of biodegradable agrochemicals. On the other hand bis-heterocyclic compounds are gaining increased interest in the recent past as the dimeric analogues have proven to be better and potential biological activity than the corresponding monomers. Bis-pyrazoles show biological activities such as antimicrobial, antifungal, anti-inflammatory, antiviral and cytotoxicity activities.

**Present work:**
A variety of methods reported for the preparation of pyrazoline derivatives. Most common method is the cyclization of chalcones with hydrazine hydrate. Many of these cyclization procedures are catalyzed by AcOH, HCl, Et₃N, C₅H₅N, Ba(OH)₂ or NaOH. However, many of these processes suffer from one or other limitations such as drastic reaction conditions, low yields, tedious work-up procedures, relatively long reaction times and co-occurrence of several side reactions. Therefore the need for an alternate method for the synthesis of pyrazolines is imperative. Therefore we have taken up the synthesis of 4,6-bis-(5-aryl-4,5-dihydro-1H-
pyrazol-3-yl)-benzene-1,3-diols with a view to study their ease of formation and also evaluate their biological activity.

Synthesis of 4,6-Bis-(5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-benzene-1,3-diols involves three steps.

1) Synthesis of 4,6-Diacetyl resorcinol
2) Synthesis of 4,6-Dicinnamoyl resorcinols
3) Synthesis of 4,6-Bis-(5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-benzene-1,3-diols

1) Synthesis of 4,6-Diacetyl resorcinol (already discussed in chapter-III, Section-A).

2) Synthesis of 4,6-Dicinnamoyl resorcinols (already discussed in chapter-III, Section-B).

3) Synthesis of 4,6-Bis-(5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-benzene-1,3-diols under ultrasound and microwave irradiation methods.

Ultrasound irradiation method:
A mixture of 4,6-dicinnamoyl resorcinols (32 a-i), hydrazine hydrate, sodium acetate and 2-3 drops of glacial acetic acid in ethanol was irradiated under ultrasonic cleaner in water bath gave corresponding bis-pyrazolines (35 a-i).

Microwave irradiation method:
A mixture of 4,6-dicinnamoyl resorcinols (32 a-i), hydrazine hydrate, sodium acetate and 2-3 drops of glacial acetic acid in ethanol was irradiated under microwave gave corresponding bis-pyrazolines (35 a-i).

Scheme-12: Synthesis of 4,6-Bis-(5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-benzene-1,3-diols (35 a-i).
SYNTHESIS OF (i) \((E)-1\text{-aryl-3-}\text{(2-substituted-quinolin-3-yl)}\text{prop-2-en-1-ones}\), (ii) \(2\{-4\{-3\{-1\text{-phenyl-3-aryl-1H-pyrazol-4-yl}\text{-acyryloyl}\}\text{-phenyl}\}\text{-isoindole-1,3-diones}\) and (iii) \(2\{-2\text{-ethoxy-5-substituted-indol-3-ylidene}\}\text{-1-aryl-ethanones}\)

Introduction:

The chemistry of chalcones has generated intensive scientific interest due to their synthetic, biological and industrial applications. Chalcones are natural biocides and are well known intermediates in the synthesis of various heterocyclic compounds. Presence of a reactive \(\alpha,\beta\)-unsaturated ketones in their structures, chalcones have a preferential reactivity towards thiols in contrast to amino and hydroxyl groups. Therefore, chalcones are less likely to interact with nucleic acids and hence avoid the problems of mutagenicity associated with certain alkylating agents in cancer chemotherapy. In addition, chalcone are susceptible to the Michael addition at enone, which can cause binding to particular receptors and lead to the induction of phase II enzymes against carcinogens.

Section-A: Synthesis of \((E)-1\text{-aryl-3-}\text{(2-piperidin-1-yl)quinolin-3-yl)}\text{prop-2-en-1-ones}\) and \((E)-1\text{-aryl-3-}\text{(2-pyrrolidin-1-yl)quinolin-3-yl)}\text{prop-2-en-1-ones}\)

Introduction:

The quinolines scaffold and its derivatives represent a major class of heterocycles and are widely found in natural products, drugs and exhibit significant role in medicinal chemistry. Several quinoline derivatives have been reported to exhibit biological activities such as antibactericidal, antimalarial, antiallergenic anti-inflammatory and antitumor. Piperidine derivatives were reported for various pharmacological activities such as antimicrobials, anticonvulsants, antihypertensives, antidepressants, antiinflammatory, antidepressant (Paroxetine) and attention-deficit hyperactivity disorder (ADHD) (Methylphenidate) agents. Pyrrolidines are well known for their versatile pharmacological activities such as antimicrobial, antiarrrhythmic,
antitumor, anti-HIV, antineoplastic, anticonvulsant and antifungal. Moreover, Chalcones are a class of privileged structures that have a wide range of biological properties such as antimicrobial, anti-inflammatory, antioxidant, anticancer and analgesic activities etc. Sofalcone is a gastroprotective chalcone based drug promotes healing of gastric ulcer and they inhibit many types of enzymes.

**Present work:**

A survey of literature revealed that several quinoline derivatives exhibit a wide variety of biological activities. It was also observed from the literature that chalcones are associated with various biological activities. This leads to the conclusion that the combined effect of both quinoline and chalcone moieties play an important role in imparting various biological activities to title compounds. The microwave and ultrasound irradiation were proved to be extremely simple and high efficient. The advantages obtained by the use of microwave and ultrasound irradiation in relation to a conventional heating method were demonstrated. These prompted us to taken up the microwave and ultrasound irradiation synthesis of (E)-1-aryl-3-(2-substitutedquinolin-3-yl)prop-2-en-1-ones.

Synthesis of (E)-1-aryl-3-(2-(piperidin-1-yl)quinolin-3-yl)prop-2-en-1-ones and (E)-1-aryl-3-(2-(pyrrolidin-1-yl)quinolin-3-yl)prop-2-en-1-ones involve three steps

1) Synthesis of 2-chloroquinoline-3-carbaldehyde
2) Synthesis of 2-(piperidin-1-yl)quinoline-3-carbaldehyde and 2-(pyrrolidin-1-yl)quinoline-3-carbaldehyde
3) (E)-1-aryl-3-(2-(piperidin-1-yl)quinolin-3-yl)prop-2-en-1-ones and (E)-1-aryl-3-(2-(pyrrolidin-1-yl)quinolin-3-yl)prop-2-en-1-ones

1) **Synthesis of 2-Chloroquinoline-3-carbaldehyde**

To a solution of acetanilide in dry DMF at 0-5 °C with stirring POCl$_3$ was added drop wise and the mixture stirred at room temperature for 12 hr to yield 2-chloroquinoline-3-carbaldehyde.

2) **Synthesis of 2-Substitutedquinoline-3-carbaldehyde**
A mixture of 2-Chloroquinoline-3-carbaldehyde, piperidine / pyrrolidine and K$_2$CO$_3$ in DMF was heated at 80-90 °C for 10-12 hr to yield corresponding 2-(piperidin-1-yl)quinoline-3-carbaldehyde / 2-(pyrrolidin-1-yl)quinoline-3-carbaldehyde.

3) Synthesis of (E)-1-aryl-3-(2-(piperidin-1-yl)quinolin-3-yl)prop-2-en-1-ones and (E)-1-aryl-3-(2-(pyrrolidin-1-yl)quinolin-3-yl)prop-2-en-1-ones.

Conventional stirring method:

A mixture of 2-(piperidin-1-yl)quinoline-3-carbaldehyde (36 a) /2-(pyrrolidin-1-yl)quinoline-3-carbaldehyde (36 b), aryl methyl ketones (37 a-i) and potassium hydroxide in ethanol was stirred at room temperature for 5-6 hr to afforded (E)-1-aryl-3-(2-(piperidin-1-yl)quinolin-3-yl)prop-2-en-1-ones (38 a-i) / (E)-1-aryl-3-(2-(pyrrolidin-1-yl)quinolin-3-yl)prop-2-en-1-ones (39 a-g).

Ultrasound irradiation method:

A mixture of 2-(piperidin-1-yl)quinoline-3-carbaldehyde (36 a) / 2-(pyrrolidin-1-yl)quinoline-3-carbaldehyde (36 b), aryl methyl ketones (37 a-i) and potassium hydroxide in ethanol was subjected to ultrasound irradiation for 40-50 min at 60 °C to afforded (E)-1-aryl-3-(2-(pyrrolidin-1-yl)quinolin-3-yl)prop-2-en-1-ones (38 a-i) / (E)-1-aryl-3-(2-(pyrrolidin-1-yl)quinolin-3-yl)prop-2-en-1-ones (39 a-g).

Microwave irradiation method:

A mixture of 2-(piperidin-1-yl)quinoline-3-carbaldehyde (36 a) /2-(pyrrolidin-1-yl)quinoline-3-carbaldehyde (36 b), aryl methyl ketones (37 a-i) and potassium hydroxide in ethanol was subjected to microwave at 160 watts for 3-4 min with 30 sec intervals to afforded (E)-1-aryl-3-(2-(pyrrolidin-1-yl)quinolin-3-yl)prop-2-en-1-ones (38 a-i)/(E)-1-aryl-3-(2-(pyrrolidin-1-yl)quinolin-3-yl)prop-2-en-1-ones (39 a-g).

Scheme-13: Synthesis of (E)-1-aryl-3-(2-(piperidin-1-yl)quinolin-3-yl)prop-2-en-1-ones (38 a-i).
**ABSTRACT**

Scheme-14: *Synthesis of (E)-1-aryl-3-(2-(pyrrolidin-1-yl)quinolin-3-yl)prop-2-en-1-ones (39 a-g).*

**Section-B: Solvent-free microwave assisted synthesis of 2-{4-[3-(1-Phenyl-3-aryl-1H-pyrazol-4-yl)-acryloyl]-phenyl}-isoindole-1,3-diones**

**Introduction:**

Isoindole1,3-diones exhibit important biological and pharmacological activities such as antimicrobial, antihypertensive, antiviral, anti-inflammatory. They also act as inhibitors of HIV-I integrase and sedatives. Chalcones are well known intermediates for the synthesis of various heterocycles of biological interest. Compounds having chalcone backbone have been found to possess various biological activities such as antimicrobial, anti-inflammatory, antioxidant, anticancer and analgesic activities.

**Present work:**

In view of the potential bioactivity of pyrazole, chalcone and isoindole1,3-diones, we have taken up the solvent-free microwave assisted synthesis of new 2-{4-[3-(1-Phenyl-3-aryl-1H-pyrazol-4-yl)-acryloyl]-phenyl}-isoindole-1,3-diones.

**Synthesis of 2-{4-[3-(1-phenyl-3-aryl-1H-pyrazol-4-yl)-acryloyl]-phenyl}-isoindole-1,3-diones involves three steps.**

1) Synthesis of 2-(4-acetyl-phenyl)-isoindole-1,3-dione
2) Synthesis of 3-aryl-1-phenyl-1\textit{H}-pyrazole-4-carbaldehyde

3) Synthesis of 2-{4-[3-(1-phenyl-3-aryl-1\textit{H}-pyrazol-4-yl)-acryloyl]-phenyl}-isoindole-1,3-diones

1) Synthesis of 2-(4-Acetyl-phenyl)-isoindole-1,3-dione

2-(4-Acetyl-phenyl)-isoindole-1,3-dione was synthesized from Isobenzofuran-1,3-dione by reacting with 4-Amino-acetophenone in the presence of acetic acid.

2) Synthesis 3-Aryl-1-phenyl-1\textit{H}-pyrazole-4-carbaldehydes (already discussed in chapter-II, section-A)

3) Synthesis of 2-{4-[3-(1-phenyl-3-aryl-1\textit{H}-pyrazol-4-yl)-acryloyl]-phenyl}-isoindole-1,3-diones under conventional heating and microwave irradiation

Conventional heating method:

A mixture of 2-(4-Acetyl-phenyl)-isoindole-1,3-dione (40) and 3-aryl-1-phenyl-1\textit{H}-pyrazole-4-carbaldehydes (19 a-j) was adsorbed on basic alumina and heated 80 °C for 9 hr to afford corresponding 2-{4-[3-(1-phenyl-3-aryl-1\textit{H}-pyrazol-4-yl)-acryloyl]-phenyl}-isoindole-1,3-diones (41 a-j).

Microwave irradiation method:

A mixture of 2-(4-Acetyl-phenyl)-isoindole-1,3-dione (40) and 3-aryl-1-phenyl-1\textit{H}-pyrazole-4-carbaldehyde (19 a-j) was adsorbed on basic alumina and irradiated under microwave at 160 watts for 4-5 min to yield 2-{4-[3-(1-phenyl-3-aryl-1\textit{H}-pyrazol-4-yl)-acryloyl]-phenyl}-isoindole-1,3-diones (41 a-j).

Scheme-15: Synthesis of 2-{4-[3-(3-Aryl-1-phenyl-1\textit{H}-pyrazol-4-yl)-acryloyl]-phenyl}-isoindole-1,3-diones (41 a-j).
Section-C: Synthesis of 2-(2-Ethoxy-5-substituted-indol-3-ylidene)-1-aryl-ethanones

Introduction:

The Indole ring system has become an important structural component in many pharmaceutical agents. Indole and its analogs possess wide spectrum of biological activities such as anti-inflammatory, anti-microbial, anti-bacterial, anticonvulsant and cardiovascular activities. Furthermore, Isatin(1H-Indole-2,3-dione) has important applications in synthetic organic chemistry and some of its derivatives show their biological activities such as antibacterial, antifungal, antiviral, anti-HIV, antiprotozoal, anticancer, muscle relaxant and antiallergic activities.

Present work:

Encouraged by the biological activities of indole and chalcone moieties, we have taken up the synthesis of 2-(2-Ethoxy-5-substituted-indol-3-ylidene)-1-aryl-ethanones with a view to test their antimicrobial activity. Microwave Assisted Organic Synthesis (MAOS) and ultrasound method has gained popularity as a non-conventional technique for rapid organic synthesis it is eco-friendly, economical and is believed to be a step towards Green chemistry. In order to provide a method that is economic, eco-friendly, we have taken up the synthesis of 2-(2-Ethoxy-5-substituted-indol-3-ylidene)-1-aryl-ethanones under microwave and ultrasound irradiation. The advantages obtained by the use of microwave irradiation and ultrasound method in relation to a conventional method were demonstrated.

Synthesis of 2-(2-Ethoxy-5-substituted-indol-3-ylidene)-1-aryl-ethanones (45 a-s) under conventional heating, microwave and ultrasound irradiation method.
Conventional heating method:

A mixture of 5-Substituted-1H-indole-2,3-diones (42 a,b), 1-(aryl)ethanones (44 a-k) and 3-4 drops of conc. H2SO4 in ethyl alcohol (43) was refluxed for 5-6 hr to yield 2-(2-ethoxy-5-substituted-indol-3-ylidene)-1-aryl-ethanones (45 a-s).

Ultrasonic irradiation method:

A mixture of 5-Substituted-1H-indole-2,3-diones (42 a,b), 1-(aryl)ethanones (44 a-k), ethyl alcohol (43) and 3-4 drops of conc. H2SO4 was irradiated under ultrasonic cleaner in water bath for 40-50 min at 60 °C to yield 2-(2-ethoxy-5-substituted-indol-3-ylidene)-1-aryl-ethanones (45 a-s).

Microwave irradiation method:

A mixture of 5-Substituted-1H-indole-2,3-diones (42 a,b), 1-(aryl)ethanones (44 a-k), ethyl alcohol (43) and 3-4 drops of conc. H2SO4 was subjected to microwave irradiation at 160 watts for 4-6 min with 30 sec intervals to yield 2-(2-ethoxy-5-substituted-indol-3-ylidene)-1-aryl-ethanones (45 a-s).

Scheme-16: Synthesis of 2-(2-Ethoxy-5-substituted-indol-3-ylidene)-1-aryl-ethanones (45 a-s)
CHAPTER-VII

Section-A: Evaluation of antimicrobial activity

Introduction:

The treatment of microbial infections still remains an important and challenging therapeutic problem because of factors that include emerging infectious diseases and the increasing number of multidrug-resistant microbial pathogens. Ancient era human being struggles for existence against the infection of disease, decay and death. It is the continuous requirement of human to retain healthy and cure from his surroundings. In the ancient era, millions of people died from various infectious diseases like tuberculosis, cholera, diarrhea and plague etc, in epidemic form, which has initiated the man for remedy from their sufferings. Some of the example of antimicrobial drug such as Penicillin antibiotics were among the first drugs to be effective against many previously serious diseases, such as syphilis and infections caused by staphylococci and streptococci.

Biological activity may be defined as the final result of a series of interlinked chemical reaction or the observed manifestations of an interference with a delicately balanced system of interdependent chemical and physical process. Various factors contribute to the biological activity of the molecule. Among these the texophore determining the type of physiological activity, position of substituents, optimum carbon skeleton, membranes permeability, lipid solubility, stereo chemical configurations etc., of the molecule play an important role in determining the activity but also on the species selectively. The problem therefore is complex and the molecules as a whole has to be taken into account and the physiological activity should not be attributed to any one single factor. As many heterocyclic compounds exhibit antimicrobial activity, it is considered worthwhile to assess the antibacterial and antifungal activity of the compounds synthesized in the present investigation by the standard disc sensitivity testing method (Kirby-Bauer method). Antibacterial activity was tested against *Escherichia coli* (gram -ve strain) and *Staphylococcus aureus* (gram +ve, strain), and antifungal was tested against *Candida metapsilosis* and *Aspergillus niger*.

All the compounds were tested at different concentrations such as 100 µg/ml, 50 µg/ml and 25 µg/ml. sample solution were prepared by employing dilution method and sterile agar nutrient
was used as medium. Ampicillin and Greseofulvin were used as for the comparison of the antimicrobial activity of compounds under study.

Among the compound synthesized in the present investigation, the highest antibacterial activity shown by \((E)-1-(1-((1\text{-benzyl}-1H-1,2,3\text{-triazol-4-yl})\text{methoxy})\text{naphthalen-2-yl})-3-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)\text{prop-2-en-1-one},\ 5-(1\text{-methoxynaphthalen-2-yl})-3'-(4-nitrophenyl)-1'\text{-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazole},\ 4,6\text{-bis}(2-(\text{thiophen-2-yl})-2,3\text{-dihydro-1H-benzo}[b][1,4]\text{diazepin-4-yl})\text{benzene-1,3-diol},\ 4,6\text{-bis}(5-(4\text{-methoxyphenyl})-4,5\text{-dihydro-1H-pyrazol-3-yl})\text{benzene-1,3-diol},\ (E)-1-(4\text{-bromophenyl})-3-(2-(piperidin-1-yl)\text{quinolin-3-yl})\text{prop-2-en-1-one},\ (E)-1-(4\text{-chlorophenyl})-3-(2-(pyrrolidin-1-yl)\text{quinolin-3-yl})\text{prop-2-en-1-one},\ (E)-2-(4-(3-(1,3\text{-diphenyl-1H-pyrazol-4-yl})\text{acryloyl})\text{phenyl})\text{isoindoline-1,3-dione},\ (E)-2-(2\text{-ethoxy-3H-indol-3-ylidene})-1-(4\text{-nitrophenyl})\text{ethanone}\) towards \textit{Escherichia coli} and \textit{Staphylococcus aureus}.

Among the compound synthesized in the present investigation, the highest antifungal activity shown by \((E)-1-(1-((1\text{-benzyl}-1H-1,2,3\text{-triazol-4-yl})\text{methoxy})\text{naphthalen-2-yl})-3-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)\text{prop-2-en-1-one},\ 5-(1\text{-methoxynaphthalen-2-yl})-3'-(4-nitrophenyl)-1'\text{-phenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazole},\ 4,6\text{-bis}(2-(\text{thiophen-2-yl})-2,3\text{-dihydro-1H-benzo}[b][1,4]\text{diazepin-4-yl})\text{benzene-1,3-diol},\ 4,6\text{-bis}(5-(4\text{-methoxyphenyl})-4,5\text{-dihydro-1H-pyrazol-3-yl})\text{benzene-1,3-diol},\ (E)-1-(4\text{-bromophenyl})-3-(2-(piperidin-1-yl)\text{quinolin-3-yl})\text{prop-2-en-1-one},\ (E)-1-(4\text{-chlorophenyl})-3-(2-(pyrrolidin-1-yl)\text{quinolin-3-yl})\text{prop-2-en-1-one},\ (E)-2-(4-(3-(1,3\text{-diphenyl-1H-pyrazol-4-yl})\text{acryloyl})\text{phenyl})\text{isoindoline-1,3-dione},\ (E)-2-(2\text{-ethoxy-3H-indol-3-ylidene})-1-(4\text{-nitrophenyl})\text{ethanone}\) towards \textit{Candida metapsilosis} and \textit{Aspergillus niger}.

\textbf{Section-B: Evaluation of Aldose reductase inhibition and antioxidant scavenging activity}

\textbf{Introduction:}

Free radicals are any species that contain one or more unpaired electrons and will take an electron from fat, proteins, or DNA for its full complement. Normal metabolic processes, pollution, solar, and cosmic radiation and smoking all affect our bodies by forming highly reactive cells. Antioxidants are molecules that prevent free radicals from doing harm to our DNA, proteins, and cells by donating an electron. The most popular and abundant antioxidant vitamins are ascorbic acid (vitamin C), tocopherol (vitamin E) and beta-carotene. Medical studies show
that antioxidants can help prevent certain diseases such as arteriosclerosis which can be brought on by free radicals oxidizing the low-density lipoprotein (LDL) cholesterol damaging the artery lining. There are also studies being done to find out if antioxidants can help prevent damaging affects of visible light on the retina and the lens epithelium.

The free radical scavenging activity of title compounds on the DPPH radical was determined according to the Brand-Williams method. Various concentrations of each compound (10, 20, 50, 100, 200, 300 and 500 µg/ml) was added to 3.9 ml of DPPH solution (25 mg/l in methanolic solution). An equal amount of methanol and DPPH served as control. After the mixture was shaken and allowed to stand at ambient temperature for 30 min, the absorbance at 517 nm was measured. Lower absorbance of the reaction mixture indicates higher free radical scavenging activity. The IC$_{50}$ value, defined as the amount of antioxidant necessary to decrease the initial DPPH concentration by 50%, was calculated from the results and used for comparison. The capability to scavenge the DPPH radical was calculated using the following equation: DPPH scavenging effect (%) = [(A1–A2)/A1] ×100

Where A1 = the absorbance of the control reaction; A2 = the absorbance in the presence of the sample. Ascorbic acid was used as standards.

Our investigation of antioxidant activity revealed that, the compounds (2$E$,2$'E$)-1,1'-(4,6-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis(3-phenylprop-2-en-1-one), (2$E$,2$'E$)-1,1'-(4,6-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis(3-(p-tolyl)prop-2-en-1-one), (2$E$,2$'E$)-1,1'-(4,6-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis(3-(thiophen-2-yl)prop-2-en-1-one) exhibited maximum inhibitory activity indicate that those compounds more potency towards DPPH scavenger activity.

Diabetes mellitus has become a major health threat as a global rise in it has been seen. The chronic disease has afflicted over 171 million people worldwide in 2000 and the incidence is expected to grow steadily to 366 million by 2030. As of May 2008, an estimated 92 million adults in China of the most populous country were living with diabetes and 148 million adults with prediabetes. Diabetes mellitus is one of the leading causes of death across the globe particularly in the developing world. Most diabetic patients suffer from so-called long-term complications such as neuropathy, nephropathy, retinopathy, cataracts and even stroke. These complications arise from chronic hyperglycemia, which causes damage to blood vessels and peripheral nerves, greatly increasing the risk of heart attack.
For inhibition studies compounds stock solutions were prepared ranging from 0.1 mg to 1 mg and Quercetin (1 mg/ml) was prepared in DMSO as known inhibitor. Various concentrations of extracts were added to the assay mixture and incubated for 5 min before initiating the reaction by NADPH as described above and corresponding blanks have been maintained. The percent of inhibition with test compounds was calculated by taking into account of the AR activity as 100% in the absence of inhibitor. The concentration of each test sample with 50% inhibition (IC$_{50}$) was then estimated.

Our investigation of aldose reductase inhibition revealed that, the compounds (2$E,2'E$)-1,1'-(4,6-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis(3-phenylprop-2-en-1-one), (2$E,2'E$)-1,1'-(4,6-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis(3-(p-tolyl)prop-2-en-1-one), (2$E,2'E$)-1,1'-(4,6-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1,3-phenylene)bis(3-(thiophen-2-yl)prop-2-en-1-one) exhibited minimum inhibitory activity indicate that those compounds more potency towards aldose reductase inhibition.