Summary & Conclusions
Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature. One striking structural features inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three dimensional representations.

Heterocyclic chemistry always attracts the attention of scientists working not only in the area of natural products but also in synthetic organic chemistry. Moreover, in tune with the present trend, scientists to door steps of common man, there is always a challenging and rewarding task in search of more and more new scientific accomplishments. This is reflected by the voluminous data available in the literature of heterocyclic chemistry, many useful drug indeed have emerged from such investigations which strengthens the trend. Spectacular advances have been made in this field to furtherance the knowledge of relationship between chemical structure and biological activity. Thus, the successful application of this class of compounds in various fields ensures a limitless scope for the development of structurally novel compounds with a wide range of physico-chemical and biological properties.

Amongst different heterocyclic systems, benzimidazoles, 1,3,4-oxadiazoles, pyrazoles and pyrazolin-5-ones have gained importance because of their pronounced bioactive nature.
The research work embodied in this thesis is planned to synthesize some new heterocycles in order to assess their antimicrobial profile. The plan of work consists of synthesis, characterization and antimicrobial evaluation, which are incorporated in six chapters. At the end of each chapter literature citations are given.

CHAPTER-1: Introduction – A brief review of literature

This chapter deals with the general introduction, synthesis and biological applications of heterocyclic compounds containing hetero atoms like nitrogen and oxygen. A brief review of literature has been presented.

This literature comprises of innovations in the synthesis and biological applications of benzimidazole, 1,3,4-oxadiazole, pyrazole, pyrazolin-5-one derivatives in recent years. Based on this literature, the author of the present research investigation has focused on the synthesis, characterization and antimicrobial evaluation of benzimidazole, oxadiazole and pyrazole derivatives which will add new dimensions to the existing literature.

CHAPTER-2: Synthesis of 5-((2-(substituted phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiols

This chapter concerns with the synthesis and characterization of 2-(substituted phenoxy)methyl)-1H-benzo[d]imidazoles (3a-f), ethyl 2-(2-(substituted phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetates (4a-f), 2-(2-(substituted phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazides (5a-f), 5-((2-(substituted phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiols (6a-f).
Initially compounds 2a-f, aryloxy acetic acid derivative of substituted phenols were synthesized and these are the starting materials in our current chapter. Substituted 2-phenoxyacetic acids 2a-f on reaction with o-phenylenediamine yields 2-(substituted phenoxymethyl)-1H-benzo[d]imidazoles (3a-f). 2-(substituted phenoxymethyl)-1H-benzo[d]imidazoles (3a-f) on reaction with ethyl chloroacetate in DMSO yields ethyl 2-(2-(substituted phenoxymethyl)-1H-benzo[d]imidazol-1-yl)acetate (4a-f). Ethyl 2-(2-(substituted phenoxymethyl)-1H-benzo[d]imidazol-1-yl)acetate (4a-f) on reaction with hydrazine hydrate yields 2-(2-(substituted phenoxymethyl)-1H-benzo[d]imidazol-1-yl)acetohydrazides (5a-f). 2-(2-(substituted phenoxymethyl)-1H-benzo[d]imidazol-1-yl)acetohydrazides (5a-f) on reaction with carbon disulfide in KOH yields 5-((2-(substituted phenoxymethyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiols (6a-f). The synthetic route has been depicted in the SCHEME 2.1. IR, 1H NMR, 13C NMR, Mass and chemical analysis data are in agreement with the proposed structures of all newly synthesized compounds.
Summary and Conclusions

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\begin{align*}
\text{i) } \text{HCl, } \text{NaOH} & \\
\text{ii) } \text{HCl, KOH} & \\
\text{iii) } \text{CHOH, } \text{KOH} & \\
\text{iv) } \text{H}_2 \text{O, EtOAc} & \\
\text{v) } \text{CS}_2, \text{KOH} & \\
R = & \text{a) } -\text{H, b) } -\text{CH}_3, \text{ c) } -\text{CH}_2 \text{CH}_3, \text{ d) } -\text{CH}_2 \text{, e) } -\text{Cl, f) } -\text{Cl}
\end{align*}
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**SCHEME 2.1**
CHAPTER-3: Synthesis of 3-methyl-4-(2-substituted phenylhydrazono)-1-(2-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetyl)-1H-pyrazol-5(4H)-ones and 1-(3,5-Dimethyl-4-(substituted phenyldiazenyl)-1H-pyrazol-1-yl)-2-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)ethanones

This chapter concerns with the synthesis of 3-methyl-4-(2-substituted phenylhydrazono)-1-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetyl)-1H-pyrazol-5(4H)-ones (10a-i) and 1-(3,5-Dimethyl-4-(substituted phenyldiazenyl)-1H-pyrazol-1-yl)-2-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)ethanones (11a-i).

Initially 2-(p-tolyloxy)acetic acid 2 was prepared from p-cresol 1 as its aryloxyacetic acid derivative. 2-((p-tolyloxy)methyl)-1H-benzo[d]imidazole, 3 was prepared by treating 2-(p-tolyloxy)acetic acid 2 with o-phenylenediamine in 4N HCl. Ethyl 2-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate, 4 was prepared by agitating a mixture of 2-((p-tolyloxy)methyl)-1H-benzo[d]imidazole, 3 with ethyl chloro acetate in the presence of K$_2$CO$_3$ in DMF. Compound 4 was converted into corresponding acetohydrazide by heating with hydrazine hydrate to give 2-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide 5. On the other hand reaction of aryl diazonium chloride (7a-i) with ethyl acetoacetate and acetylacetone yield the corresponding ethyl-2-(substituted aryl hydrazono)-3-oxo butyrates (8a-i) and 3-(substituted aryldiazenyl)pentane-2,4-diones (9a-i).

Reaction of compound 5 with 8a-i in ethanol resulted in the formation of 3-methyl-4-(2-substituted arylhydrazono)-1-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetyl)-1H-pyrazol-5(4H)-ones (10a-i) in good yields. Reaction of compound 5 with 9a-i in ethanol resulted in the formation of 1-(3,5-dimethyl-4-
(substituted aryldiazenyl)-1H-pyrazol-1-yl)-2-(2-((p-tolyloxy)methyl)-1H-benzo[d]
imidazol-1-yl)ethanone (11a-i) in good yields. The synthetic route has been
depicted in the **SCHEME 3.1, SCHEME 3.2** and **SCHEME 3.3.** IR, $^{1}$H NMR,
$^{13}$C NMR, Mass and chemical analysis data are in agreement with the proposed
structures of all newly synthesized compounds.
Summary and Conclusions

Scheme 3.2

Scheme 3.3

R = a) -H, b) 4-CH₃, c) 2-CH₃, d) 4-Cl,
e) 2-Cl, f) 4-NO₂, g) 2-NO₂, h) 4-OCH₃, i) 2-OCH₃
CHAPTER-4: Synthesis of 1-(substituted 3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanones

This chapter concerns with the synthesis of 1-(substituted 3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanones (7a-o).

Quinolin-8-ol 1 on reaction with ethyl chloroacetate in DMSO yields ethyl 2-(quinolin-8-yloxy)acetate 2. Ethyl 2-(quinolin-8-yloxy)acetate 2 on reaction with hydrazine hydrate yields 2-(quinolin-8-yloxy)acetohydrazide 3. Substituted aromatic benzaldehyde 4 on reaction with substituted acetophenone 5 in ethanol yields 1,3-bis(substituted phenyl)prop-2-en-1-ones 6a-o (chalcones). Reaction of compound 3 with 6a-o in glacial acetic acid result in the formation of 1-(substituted 3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanones (7a-o). The synthetic route has been depicted in the SCHEME 4.1. IR, $^1$H NMR, $^{13}$C NMR, Mass and chemical analysis data are in agreement with the proposed structures of all newly synthesized compounds.
Summary and Conclusions

Scheme 4.1

(i) CH$_3$COOCH$_2$CH$_2$, K$_2$CO$_3$, DMF  (i)NH$_4$HCO$_2$, EtOH
(ii) NaOH, EtOH  (iv) Glacial acetic acid
R$_1$ = (a) 1 to (e) +H, (f) to (j) p-COCH$_3$, (k) to (o) o-C$_6$H$_5$OH
R$_2$ = (a), (f), (k) +H, (b), (g), (l) p-C$_6$H$_5$, (c), (h), (n) o-C$_6$H$_5$OH, (d), (i), (n) p-Cl, (e), (o) p-NO$_2$

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CHAPTER-5: Synthesis of 4-(substituted benzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1H-pyrazol-5(4H)-ones using Knoevenagel condensation

This chapter concerns with the synthesis of 4-(substituted benzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1H-pyrazol-5(4H)-ones (5a-i).

Quinolin-8-ol 1 on reaction with ethyl chloroacetate in DMSO yields ethyl 2-(quinolin-8-yloxy)acetate 2. Ethyl 2-(quinolin-8-yloxy)acetate 2 on reaction with hydrazine hydrate yields 2-(quinolin-8-yloxy)acetohydrazide 3. The precursor 3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1H-pyrazol-5(4H)-one 4 was obtained by condensing 2-(quinolin-8-yloxy)acetohydrazide 3 with ethyl acetoacetate in ethanol and refluxing for 8 hr. The next step involves Knoevenegel condensation of compound 4 containing active methylene group with various substituted aromatic aldehydes in presence of imidazole to yield 4-(substituted benzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1H-pyrazol-5(4H)-ones (5a-i). The synthetic route has been depicted in the SCHEME 5.1. IR, $^1$H NMR, $^{13}$C NMR, Mass and chemical analysis data are in agreement with the proposed structures of all newly synthesized compounds.
Summary and Conclusions

\begin{align*}
\text{Scheme 5.1}
\end{align*}
CHAPTER-6: Antimicrobial activity

All the synthesized compounds were screened for their antimicrobial activity by cup plate agar disc diffusion method and Minimum Inhibition Concentration (MIC) by serial dilution method respectively. The results and discussions are incorporated in this chapter.

All the synthesized compounds, 5-((2-(substituted phenoxymethyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiols 6a-f (SCHEME 2.1) and 3-methyl-4-(2-substituted phenylhydrazono)-1-(2-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetyl)-1H-pyrazol-5(4H)-ones 10a-i and 1-(3,5-Dimethyl-4-(substituted phenyldiazenyl)-1H-pyrazol-1-yl)-2-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)ethanones 11a-i (SCHEME 3.3) were screened for their antibacterial and antifungal activity by cup plate agar disc diffusion method against two Gram-positive bacteria, \textit{Staphylococcus aureus} and \textit{Bacillus subtilis} and three Gram-negative bacteria, \textit{Escherichia coli}, \textit{Pseudomonas aeruginosa} and \textit{Salmonella typhi}. Two kinds of fungi, \textit{A. Niger} and \textit{U. maydis} were chosen to test antifungal activity and compared with the standard drugs Gentamicin and Nystatin for bacterial and fungal growth respectively. The compounds exhibited moderate to good antibacterial activity and only few compounds exhibit significant antifungal inhibition.

The compounds 1-(substituted 3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanones 7a-o (SCHEME 4.1) and 4-(substituted benzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1H-pyrazol-5(4H)-ones 5a-i (SCHEME 5.1) have been screened for their antimicrobial activity by minimum inhibitory concentration. Following common standard strains were used for
screening of antibacterial and antifungal activities: *Staphylococcus aureus*, *Escherichia coli* and fungi *Aspergillus niger*. DMSO was used as diluent to get desired concentration of synthesized compounds to test upon standard bacterial strains. The results showed that some of the compounds exhibited moderate to good antibacterial activity against both the strains and a few compounds were active in antifungal activity.

The outstanding properties of this new class of antimicrobial substances deserves further investigation in order to clarify the mode of action at molecular level, responsible for the activity observed. More extensive study is also warranted to determine additional physicochemical and biological parameters to have a deeper insight into structure-activity relationship and to optimize the effectiveness of these series of molecules.