Chapter-1

Introduction
Two hundred years ago, the chemical science was an undivided field; around 1900 a division into inorganic, organic and physical chemistry became necessary. The increase of factual material enforced a progressive segmentation into sub disciplines. A map shows countries and regions neatly separated; similarly, the uninformed observer may regard chemistry as a side-by-side of numerous disciplines and specialties. The comparison is fallacious, however, because broad overlap is thwarting clear divisions.

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.

A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbocyclic compound. If at least one atom other than carbon, forms a part of the ring system then it is designated as a heterocyclic compound. Nitrogen, oxygen and sulfur are the most common hetero atoms but heterocyclic rings containing other hetero atoms are also widely known. An enormous number of heterocyclic compounds are known and this number is increasing rapidly. Accordingly the literature on the subject is very vast, heterocyclic compounds may be classified into aliphatic and aromatic. The aliphatic heterocyclic compounds are the cyclic analogues of amines, ethers, thioethers, amides, etc. Their properties are
particularly influenced by the presence of strain in the ring. These compounds generally consist of small (3- and 4- membered) and common (5 to 7 membered) ring systems. The aromatic heterocyclic compounds, in contrast are those which have a hetero atom in the ring and behave in a manner similar to benzene in some of their properties.

**Benzimidazole derivatives – a brief review of literature**

Benzimidazoles are a class of heterocyclic, aromatic chemical compounds which share a fundamental structural characteristic of six-membered benzene fused to five-membered imidazole.

![Benzimidazole structure](image)

Bilge Eren *et al.*\(^1\) reported a new convenient method for preparation of 2-substituted benzimidazoles and bis-benzimidazoles. In this method, o-phenylenediamines were condensed with bisulfite adducts of various aldehydes and di-aldehydes under neat conditions by microwave heating.

![Reaction scheme](image)

Changiz Karami *et al.*\(^2\) reported a highly selective synthesis of benzimidazoles from the reaction of o-phenylenediamines and aromatic aldehydes in the presence of PVP- trifluoromethanesulfonic acid. The reactions were
performed in solvent-free conditions and the catalyst could be reused for several runs.

Satish S Birajdar et al.\textsuperscript{3} reported a mild and efficient approach for the synthesis of benzimidazole ring through oxidative cyclization of o-phenylenediamine and different aldehydes using dioxane dibromide, as a user-friendly reagent. This is a new, convenient and facile methodology for the synthesis of 2-substituted-1\textit{H}-benzo[\textit{d}]imidazoles.

Mohammad Reza Poor Heravi and Marjan Ashori\textsuperscript{4} reported the synthesis of benzimidazoles by the reaction of o-phenylenediamine with aldehydes using boric acid, an efficient catalyst under mild reaction conditions in aqueous media. Yekkirala Venkateswarlu et al.\textsuperscript{5} reported the synthesis of benzimidazoles using lanthanum chloride as an efficient catalyst. One-pot synthesis of 2-substituted benzimidazole derivatives from o-phenylenediamine and a variety of aldehydes were developed under mild reaction conditions. D Kathirvelan et al.\textsuperscript{6} reported the synthesis of various 2-substituted benzimidazole derivatives in moderate to good yield in a one-pot reaction by the condensation of o-phenylenediamine and an
aldehyde in the presence of ammonium chloride as a catalyst at 80-90°C. Salahuddin et al.\textsuperscript{7} reported the synthesis of commercially available benzimidazole involving condensation of o-phenylenediamine with formic acid.

Hossein Eshghi et al.\textsuperscript{8} reported the synthesis of a series of substituted benzimidazoles and benzothiazoles through the one-pot reaction of o-phenylenediamine and o-aminothiophenol with various aldehydes in the presence of ferric hydrogensulfate both in EtOH and water as solvent.

Novel 2-amino-1-thiazolyl imidazoles were synthesized and demonstrated cytotoxicity against human cancer cells. 1-\((\text{4-phenylthiazol-2-yl})\)-4-(thiophen-2-yl)-1\textsubscript{H}-imidazol-2-amine, a 2-amino-1-thiazolyl imidazole, inhibited tubulin polymerization, interacted with the colchicine-binding sites of tubulins and caused cell cycle arrest at the G(2)/M phase in human gastric cancer cells. Disruption of the microtubule structure in cancer cells was also observed. Their concentration-dependently inhibited the proliferation of cancer cells in histocultured human gastric and colorectal tumors. Given orally, these compounds prolonged the lifespans of leukemia mice intraperitoneally inoculated with the murine P388 leukemic cells and reported 2-amino-1-thiazolyl imidazoles as novel class of orally active microtubule-destabilizing anticancer agents.\textsuperscript{9}
Sugumaran et al.\textsuperscript{10} reported the synthesis of new series of 2, 5 di-substituted benzimidazole derivatives. The antibacterial and antifungal activity of the synthesized compounds against the tested organisms was found to be less than that of respective standard drug at tested dose level.

The three component synthesis of 2-phenylimidazo [4,5-f] [1,10]phenanthroline derivatives, a typical acid catalyzed reaction, could be conducted successfully with good to excellent yields in a neutral ionic liquid, 1-methyl-3-heptyl-imidazolium tetrafluoroborate [(HeMIM) BF\textsubscript{4}], under solvent free and microwave assisted conditions. The combined merits of microwave irradiation and ionic liquid make the three-component condensation with safe operation, low pollution, rapid access to products and simple workup.\textsuperscript{11}
Parmender Singh Rathee et al.\textsuperscript{12} reported the synthesis of substituted 2-phenylbenzimidazole derivatives by introducing different substituents at different positions and screened for antimicrobial activity. These compounds showed appreciable antifungal inhibition.

A series of azole derivatives have been synthesized from (2,4,5-triphenyl-imidazole-1-yl)-acetic acid anhydride under various reaction conditions. All the synthesized azole derivatives showed moderate to good anti-inflammatory, antibacterial and antifungal activities.\textsuperscript{13}

Nannapaneni et al.\textsuperscript{14} synthesized benzimidazoles from the condensation reaction between \textit{o}-phenylenediamine and various carbonyl compounds, in the presence of ammonium chloride as a catalyst. The synthesized compounds showed potent anti-anxiety activity when compared to the standard Diazepam.

Benzimidazole derivatives have been synthesized using a catalytic amount of Zinc acetate at room temperature with excellent yields. The remarkable
selectivity under mild, neutral and solvent free conditions, commercially available inexpensive catalyst is an attractive feature of this method.\textsuperscript{15}

An efficient and simple procedure was developed for the green synthesis of various 2-aryl-1-(aryl methyl)-1\textit{H}-benzimidazoles in high yields by acetic acid-promoted condensation of o-phenylenediamine with aldehydes in air under microwave irradiation and transition metal catalyst-free conditions.\textsuperscript{16}

Direct, efficient syntheses of the benzimidazo[2,1-\textit{a}]isoquinolines have been achieved with 2-bromoarylaldehydes, terminal alkynes and 1,2-phenylenediamines by a microwave-accelerated tandem process in which a Sonogashira coupling, 5-endo cyclization, oxidative aromatization and 6-endo cyclization could be performed in a single synthetic operation\textsuperscript{17}.

![Chemical Structure](image)

2-(\textit{o}-arylideneaminophenyl)benzimidazoles were synthesized \textit{via} the condensation between 2-(\textit{o}-aminophenyl)benzimidazole and various aldehydes in refluxing ethanol in the presence of catalytic amount of acetic acid. Oxidative cyclization of 2-(\textit{o}-arylideneaminophenyl)-benzimidazoles using potassium permanganate in refluxing acetone resulted in the formation of 6-arylbenzimidazo[1,2-\textit{c}]quinazolines\textsuperscript{18}. 
Heating a mixture of 2-(2-aminophenyl)benzimidazole and chloroacetylchloride in glacial acetic acid on water-bath at 60°C gave 6-chloromethylbenzimidazo[1,2-c]quinazoline in 68% yield\(^\text{19}\).

Treatment of 1,8-naphthoic anhydride derivative with o-phenylenediamine in glacial acetic acid gave the pentacyclic fused system, 7H-benzimidazo[2,1-a]benzo[d,e]isoquinolin-7-ones\(^\text{20}\).

7-Methoxy-11H-isoindolo[2,1-a]benzimidazole was prepared in 90% yield from palladium-catalyzed annulation of 2-(4-methoxy-2-nitrophenyl)-2,3-dihydro-1H-isoindole by heating in DMF using bis-(dibenzylideneacetone)palladium
[Pd(dba)$_2$] and 1,10-phenanthroline at 120°C and the solution was saturated with CO under pressure$^{21}$.

Benzimidazo[1,2-c]quinazolines were readily prepared in high yield by reduction of 2-(2-nitrophenyl)benzimidazole followed by reaction of the obtained 2-(2-aminophenyl)benzimidazole with aldehydes in ethanol/acetic acid mixture$^{22}$.
Oxadiazole derivatives – a brief review of literature

Oxadiazole is a heterocyclic aromatic chemical compound with the molecular formula C₂H₂N₂O. It is a heterocycle characterized by a 5-membered ring of two carbon atoms, two nitrogen atoms and one oxygen atom. Among them, the structure of 1,3,4-oxadiazole is as follows.

Amar Patil et al.²³ reported the synthesis of oxadiazole derivatives and evaluated for their in vitro antifungal activity. The compound containing methyl group as the substituent was the most promising antifungal agent.

Aryl bromides were successfully transformed into their corresponding N,N'-diacylhydrazines via a Pd-catalyzed carbonylative coupling with amidoximes or hydrazides. Furthermore, dehydration conditions were identified that could be used in a compatible one-pot synthesis of 1,3,4-oxadiazoles²⁴.
Efficient palladium-catalyzed sequential isocyanide insertions into N-H and O-H bonds of hydrazides followed by oxidative annulation provide a convenient access to valuable 2-amino-1,3,4-oxadiazoles and their derivatives\textsuperscript{25}.

A 2-iodoxybenzoic acid/tetraethylammonium bromide mediated oxidative cyclization of hydrazide-hyrazones generated \textit{in situ} from aryl glyoxal and hydrazides enables an efficient and high-yielding protocol for the preparation of \(\alpha\)-keto-1,3,4-oxadiazoles under mild conditions in short reaction times\textsuperscript{26}.

A series of new 1,3,4-oxadiazole derivatives, containing 5-chloro-2-methoxy benzohydrazide moiety were synthesized by the reaction of 5-chloro-2-methoxybenzoate with different aromatic carboxylic acids. Antimicrobial studies revealed that compounds showed significant activity against tested strains\textsuperscript{27}. 
A practical and transition-metal-free oxidative cyclization of acylhydrazones into 1,3,4-oxadiazoles has been developed by employing stoichiometric molecular iodine in the presence of potassium carbonate. A series of symmetrical and asymmetrical 2,5-disubstituted (aryl, alkyl and vinyl) 1,3,4-oxadiazoles can be conveniently generated in an efficient and scalable fashion.28

The preparation of 1,3,4-oxadiazoles from 1,2-diacylhydrazines using XtalFluor-E ([Et₂NSF₂]BF₄) as cyclodehydration reagent is described. Various functionalized 1,3,4-oxadiazoles were synthesized and it was found that the use of acetic acid as an additive generally improved the yields.29

Singh et al.30 have synthesized substituted derivatives of 1,3,4-oxadiazole, a versatile hydrophobic molecule possessing preliminary CNS properties, with the hope to potentiate the biological activities with lesser or limited amount of toxicities. All the synthesized compounds were evaluated for their potential CNS depressant activities. Among the synthesized compounds, it was found that incorporation of electron withdrawing group at C₂ and C₅ position of the
oxadiazole ring led to high degree of pharmacological activity. Thus compounds 5-(4-nitrophenyl)-2-(4-chlorophenyl)-1,3,4-oxadiazole and 5-(4-nitrophenyl)-2-(4-nitrophenyl)-1,3,4-oxadiazole showed excellent CNS depressant activities.

An oxidative desulfurization approach enables the construction of oxadiazole and thiadiazole heterocycles in the presence of iodobenzene and oxone. The use of iodobenzene and the inexpensive readily available oxidant oxone makes the reaction system simple and versatile for desulfurization.\textsuperscript{31}

![Chemical Reaction](image)

The reaction of \(p\)-bromoanilino acetohydrazide with aromatic aldehydes in alcohol yielded 2-[4-bromoaniline] N-substituted benzyldine hydrazides, which in presence of yellow mercuric oxide and iodine in DMF, yielded corresponding 4-bromo[(N-5-substituted 1,3,4-oxadiazole-2-yl)methyl]aniline. Some of the compounds showed remarkable antibacterial, antifungal and anti-inflammatory activities.\textsuperscript{32}

A simple and straightforward method for the direct carboxylation of aromatic heterocycles such as oxazoles, thiazoles and oxadiazoles using CO\(_2\) as the carbon source requires no metal catalyst and only Cs\(_2\)CO\(_3\) as the base. A good functional group tolerance is achieved.\textsuperscript{33}
Suresh Kumar *et al.* synthesized a series of 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazole derivatives. Some of the compounds exhibited good to moderate antibacterial inhibition and excellent antifungal activity.

Propylphosphonic anhydride (T3P®) has been demonstrated to be an efficient and mild reagent for the one-pot synthesis of 1,2,4-oxadiazoles, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles from carboxylic acids.

A series of new 1-(2-aryl-5-phenethyl-1,3,4-oxadiazol-3(2\(H\))-yl)ethanones were synthesized by the cyclization of imines using acetic anhydride. The products were evaluated for anti-bacterial and anti-fungal activity. Among the newly synthesized compounds, 1-(2-(4-(dimethylamino)phenyl)-5-phenethyl-1,3,4-oxadiazol-3(2\(H\))-yl) ethanone and 1-(2-(4-chlorophenyl)-5-phenethyl-1,3,4-oxadiazol-3(2\(H\))-yl) ethanone were found to possess maximum activity against the tested strains. It was concluded that para-substitution enhances the activity of synthesized oxadiazoles.

Four novel stilbene derivatives containing 1,3,4-oxadiazole unit have been synthesized in four steps with overall yields (27~35\%). The synthetic route involved one-step installation of 2,5-di-p-tolyl-1,3,4-oxadiazole via the direct coupling of p-toluic acid with hydrazine hydrate promoted by PPA, benzylic bromination, conventional phosphonate formation and Wittig-Horner olefination.
A novel series of 2-[3-(4-bromophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles have been synthesized from 3-(4-bromobenzoyl)propionic acid with the aim to get better anti-inflammatory and analgesic agents with minimum or without side effects (ulcerogenicity). A fair number of compounds were found to have significant anti-inflammatory and analgesic activities, while a few compounds showed appreciable antibacterial activity. The newly synthesized compounds showed very low ulcerogenic action.\textsuperscript{38}

Synthesis and biological evaluation of various arylpropionic acid derivatives containing 1,3,4-oxadiazole nucleus is reported. The compounds were synthesized by cyclization of 3-arylpropionic acids into 1,3,4-oxadiazole nucleus by treating with various aryl acid hydrazides in the presence of POCl$_3$. The study showed that the cyclization of carboxylic group of arylpropionic acids into an oxadiazole nucleus resulted in compounds having good anti-inflammatory and analgesic effects with reduced gastric irritation.\textsuperscript{39}

![Diagram of the cyclization process](image)

A mild and efficient one-pot protocol for the synthesis of 1,3,4-oxadiazoles from carboxylic acids and acylhydrazides was developed. Diacylhydrazide formation via HATU coupling followed by addition of Burgess reagent afforded the corresponding 1,3,4-oxadiazoles in 63–96% yields at room temperature.\textsuperscript{40}
1,4-Bis(5-aryl-1,3,4-oxadiazole-2yl) benzene derivatives were synthesized from terephthalic dihydrazide by cyclization with various aromatic acids and aldehydes. Several of these compounds showed potential antibacterial activity\textsuperscript{41}.

An efficient and convenient method for the synthesis of 1-(5-aryl-[1,3,4]-oxadiazol-2ymethyl)-3-(3-trifluoromethyl-phenyl)-1H-[1,8]-naphthyridin-2-ones by the oxidation of [2-oxo-3-(3-trifluoromethyl-phenyl)-2H-[1,8]-naphthyridin-1-yl] acetic acid arylidene hydrazides with iodobenzene diacetate [PhI(OAc)\textsubscript{2}] under microwave irradiation in solvent-free conditions was reported\textsuperscript{42}. 
The mixture of hydrazide and appropriate ketone namely acetophenone, p-methyl acetophenone, p-chloro acetophenone, p-bromo acetophenone, p-nitro acetophenone was refluxed in methanol containing catalytic amount of glacial acetic acid to get the hydrazones. Cyclization of hydrazones with excess of acetic anhydride resulted in the corresponding 2-(4-acetyl-5-methyl-5-phenyl-4,5-dihydro-[1,3,4]oxadiazol-2-methyl)-5-methyl-4-(4’-substituted aryl hydrazono)-2,4-dihydro-pyrozol-3-one.

2,5-disubstituted 1,3,4-oxadiazoles have been synthesized as a one pot procedure from the reaction of acid hydrazide, acyl halides and phosphorus pentoxide in acetonitrile at room temperature. High yield, short reaction time (10–15 min), mild condition and easy work-up are advantages of this methodology.

2,5-disubstituted 1,3,4-oxadiazoles were prepared by the reaction of different acyl hydrazides and orthoesters in the presence of silica sulfuric acid under solvent-free conditions.
A series of substituted 1,3,4-oxadiazoles were synthesized by the cyclization of 2,6-pyridine dicarboxylic acid, 5-(4′-carboxyl-phenyl)-2-furanylcarboxylic acid or p-phthalic acid and aryl hydrazines in the presence of phosphorus oxychloride under the condition of microwave irradiation\(^{46}\).

A convenient one pot method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from carboxylic acids and acyl hydrazides was reported. Acid activation with CDI and coupling with the desired acylhydrazide followed by dehydration in the same pot with \(\text{Ph}_3\text{P}\) and \(\text{CBr}_4\) affords the corresponding 1,3,4-oxadiazoles in good yield\(^{47}\).

\[
\begin{array}{c}
\text{O} \quad \text{O} \\
\text{R}_1^\text{H} \quad \text{R}_2^\text{H} \\
\text{i) CDI} \quad \text{ii) Ph}_3\text{P, CBr}_4
\end{array}
\]

A microwave-assisted expeditious synthetic route to novel carbazole-based 1,3,4-oxadiazoles was described\(^{48}\).

\[
\begin{array}{c}
\text{N} \\
\text{R} \\
\text{R}_2^\text{H}
\end{array}
\]

A series of novel 2-{4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl}-5-substituted-1,3,4-oxadiazoles were synthesized by the oxidative cyclization of
hydrazones derived from 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde and aroylhydrazines using chloramine-T as oxidant. The compounds demonstrated potent to weak antimicrobial activity<sup>49</sup>.

![Chemical Structure](image)

Aromatic aldehyde N-acylhydrazones were oxidized into 2,5-disubstituted 1,3,4-oxadiazoles with bis(trifluoroacetox)iodobenzene in CHCl<sub>3</sub> or DMSO at room temperature in good to excellent yields<sup>50</sup>.

![Chemical Reaction](image)

A series of 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives were synthesized and thirteen of them were selected by the National Cancer Institute (NCI) and evaluated for their <i>in vitro</i> anticancer activity. Seven of the investigated compounds displayed high anticancer activity in the primary assay. Two of these compounds were identified as promising lead compounds<sup>51</sup>.

A facile and general protocol for the preparation of 2-amino-1,3,4-oxadiazoles relies on a tosyl chloride/pyridine-mediated cyclization of
thiosemicarbazides that consistently outperforms the analogous semicarbazide cyclizations\textsuperscript{52}.

2-chloro-1,4-phenylenedioxy-bis-acetyl hydrazine on reacting with aromatic carboxylic acid in the presence of phosphorus oxychloride afford 2-chloro-bis-1,3,4-oxadiazoles and the same on reacting with carbon disulfide under basic condition gave oxadiazole-2-thione. Two of these compounds showed significant anticancer activity\textsuperscript{53}.
Pyrazole derivatives – a brief review of literature

Pyrazole is an organic compound with the formula C$_3$H$_3$N$_2$H. It is a heterocycle characterized by a 5-membered ring of three carbon atoms and two adjacent nitrogen atoms. Pyrazole is a weak base.

Hemant Raundal et al.$^{54}$ reported the synthesis of novel 1,5-disubstituted pyrazole derivatives like aryl 5-(3-fluoro-4-methoxyphenyl)-1$H$-pyrazole-3-carboxylic acids. All the synthesized compounds exhibit good antibacterial and antifungal activity.

Amar Patil et al.$^{55}$ synthesized a series of eight derivatives of 5-bistrifluoromethyl phenyl pyrazole substituted thiazoles. Three of these compounds exhibited good antibacterial and antifungal activity.
Karale et al. synthesized substituted pyrazoles from 2-substituted chromones and these compounds exhibited antibacterial and antifungal activity.

2-substituted chromones on reaction with hydrazine hydrate gives 2-(5-(4-chloro-2,5-difluorophenyl)-1H-pyrazol-3-yl)phenols. These compounds exhibited good antimicrobial activity against tested strains.

Various pyrazoline and pyrimidine derivatives were synthesized by the reaction of thiosemicarbazide or phenyl hydrazine or hydrazine hydrate or thiourea or urea with 3-(3,4-dimethoxy-phenyl-1-(2,5-dimethyl-thiophen-3-yl)-propenone
under microwave irradiation. The corresponding pyrazoline and pyrimidine derivatives were obtained in good to excellent yields. The results showed that one of the pyrazoline derivatives is better at inhibiting the growth as compared to chloramphenicol against two types of the bacteria\textsuperscript{58}.

![Pyrazoline derivative](image)

A new series of novel derivatives of pyrazole were synthesized. All derivatives exhibited significant to moderate antibacterial activity\textsuperscript{59}.

![Pyrazole derivative](image)

Simpal Kumari \textit{et al.}\textsuperscript{60} reported the synthesis of 1\textit{H}-pyrazole, N-substituted pyrazoles, pyrazolopyrazoles and pyrazoles fused with a naturally occurring moiety. Some of these reported compounds have passed the preclinical or initial-phase clinical trials for their anticancer activity.

A series of 3-aryl-1-phenyl-1\textit{H}-pyrazole derivatives were synthesized in good yield and assayed \textit{in vitro} as inhibitors of the mice acetylcholinesterase (AChE) and two goat liver monoamine oxidase (MAO) isoforms, MAO-A and
MAO-B. Most of the compounds demonstrated a good AChE and selective MAO-B inhibitory activities in the nanomolar or low micromolar range.\(^6\)

Synthesis of highly diverse pyrano[2,3-c]pyrazoles was achieved by one pot multicomponent reaction using piperidine as catalyst. Some of these compounds showed significant antibacterial and antifungal activity.\(^6\)

Chankantha \textit{et al.}\(^3\) synthesized N-cyclohexyl-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide, N-(2,6-dimethylphenyl)-5-phenyl-1-(quinolin-2-yl)-1H pyrazole-4-carboxamide and N,N-diethyl-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide and these compounds showed good antibacterial activity.

Priyadersini \textit{et al.}\(^4\) synthesized 3-(2-hydroxyphenyl)-5-(4-chlorostyryl)-1-phenylpyrazole and 3-(2-hydroxyphenyl)-5-(4-chlorostyryl)-1H-pyrazole and found them to be having good antifungal activity against \textit{Aspergillus niger}. 
The key intermediate acetohydrazide cyclization with aryl substituted acids in presence of phosphorous oxychloride (POCl₃) under microwave irradiation resulted in the formation of the 2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-(5-phenyl-2,3-dihydro-1,3,4-oxadiazol-2-yl)ethyl)acetamide in excellent yields⁶⁵.

Yousef et al.⁶⁶ synthesized a series of some new thiazole and pyrazole derivatives using diarylpoxypropanone as precursor. The antimicrobial activity of compound considered was tested on *Escherichia coli*, *Pseudomonas puticide*, *Bacillus subtilis*, *Streptococcus lactus* and *Aspergillus niger*. All synthesized compounds showed good activity.

Nishida et al.⁶⁷ worked on isopropyl-2-[(10Z)-5{(2,5-dihydro-2,3-dimethyl-5-methyl-1-phenyl-1H-pyrazol-4-yl)methylene}-2,4-dioxothiazolidin-3-yl]acetate and showed that it posses good anticancer activity.
Dias et al. synthesized (isoindolin-2-yl) (3,5-dimethyl-1H-pyrazol-1-yl) methanone and the synthesized compound showed good antitumour activity.

Synthesis of three new tripodal ligands: 3-[bis-(3,5-dimethyl-pyrazol-1-ylmethyl)-amino]-propan-1-ol, \( L_1 \), 3-[bis-(5-methyl-3-carbomethoxy-pyrazol-1-ylmethyl)-amino]-propan-1-ol, \( L_2 \) and 3-[bis-(5-methyl-3-carboethoxy-pyrazol-1-ylmethyl)-amino]-propan-1-ol, \( L_3 \) was reported. The \textit{in situ} generated copper(II) complexes of three new compounds (\( L_1 \)–\( L_3 \)) were examined for their catalytic activities and were found to catalyse the oxidation reaction of catechol to \( o \)-quinone with the atmospheric dioxygen. These activities depend on the nature of the ligand and the copper salts.
Shilpa Ailawadi et al.\textsuperscript{70} synthesized a series of new substituted 3,5-dimethyl pyrazoles, 3-methyl pyrazole-5-one derivatives, 3-methyl-1-(substituted phenyl) pyrazole-5-ones and 2,3-dimethyl-1-(substituted phenyl) pyrazol-5-one derivatives. All the newly synthesized compounds tested for their \textit{in vivo} anti-inflammatory and analgesic activity by bioassay namely Corriganan induced paw Edema method and acetic acid induced method respectively. The compounds exhibited promising and significant inhibitory activity against COX2 enzyme.

Twelve derivatives of 4-pyrazolyl-N-arylquinoline-2,5-dione were synthesized by one pot base catalyzed cyclocondensation reaction of 1-aryl-5-chloro-3-methyl-1\textit{H}-pyrazole-4-carbaldehyde, Meldrum’s acid and 3-arylamino-5,5-disubstitutedcyclohex-2-enone. Some of the compounds were found to be equipotent or more potent than commercial drugs, against most of the employed strains, as evident from the screening data\textsuperscript{71}. 

![Diagram of a chemical structure](image-url)
Peng-cheng et al.\textsuperscript{72} synthesized a series of pyrazole derivatives that exhibited high antiproliferative activity against MCF-7 with IC\textsubscript{50} 0.08 µM.

Kalirajan et al.\textsuperscript{73} synthesized a series of pyrazole derivatives and these derivatives showed anticancer activity.

Bhaskar et al.\textsuperscript{74} synthesized a series of pyrazole derivatives and examined for their anti-inflammatory activity. All the compounds exhibited weak to potent anti-inflammatory activity. Derivative bearing a methoxy group exhibited very good anti-inflammatory activity.
Xiao Hong Wang et al.\textsuperscript{75} synthesized a series of pyrazole derivatives that were reported to have potent cytotoxicity against some tumour cells.

![Pyrazole Derivative](image1)

Pasin et al.\textsuperscript{76} synthesized a series of pyrazole derivatives and screened for antioxidant activity. All the compounds showed good activity.

![Pyrazole Derivative](image2)

Sivakumar et al.\textsuperscript{77} synthesized a series of (4Z)-3-methyl-1-[2-oxo-2H-chromen-4yl]carbonyl]-1H-pyrazole-4,5-dione-4-[(4-substituted phenyl)hydrazones]. All the compounds were screened for anti-inflammatory and analgesic activity.

![Pyrazole Derivative](image3)

Osama et al.\textsuperscript{78} synthesized 4,5-disubstituted pyrazole derivatives. The derivative containing R = Cl group showed potent antiviral activity against a broad panel of viruses in different cell cultures (HEL Cell cultures).
Sreenivasa *et al.*\(^79\) synthesized a series of pyrazole derivatives and evaluated for their antihelminitic activity. Synthesized compounds of pyrazole derivative were tested for antihelminitic activity against earthworms, *Peritoma poshuma* and were compared to standard albendazole.

Vijay V. Dabholkar *et al.*\(^80\) synthesized a series of fused isooxazoles and pyrazoles and the newly synthesized compounds were screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Corynebacterium diphtheriae* and *Proteus aeruginosa*. All the synthesized compounds showed good activity against *S. aureus* and *C. Diphtheriae* as compared to other derivatives.
A novel series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines were synthesized by reacting various substituted 3-aryl-1-(3-coumarinyl)propan-1-ones with phenylhydrazine in the presence of hot pyridine. Among the 12 prepared compounds, some compounds exhibited significant anti-inflammatory activity in model of acute inflammation such as carrageenan-induced rat edema paw while some compounds showed considerable activity in model of chronic inflammation such as adjuvant-induced arthritis and were compared with diclofenac as a standard drug.

Kini et al. synthesized a novel series of heterocyclic o/m/p- substituted diphenyl ether derivatives and determined their activity against H37Rv strain of Mycobacterium. All 10 compounds inhibited the growth at concentration as low as 1 µgml⁻¹.

Mohammad S. M. Al-Saadi, et al. synthesized a series of pyrazole and pyrazoline fused ring systems substituted with variable biologically-active chemical species and concluded that some of the synthesized compounds are significantly active in anticancer activity.
1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-4-yl)-1H-imidazole derivatives were synthesized and tested for their in vitro antifungal and antimycobacterial activities. These imidazole derivatives showed an excellent antifungal activity against a clinical strain of *Candida albicans* and an interesting antitubercular activity against *Mycobacterium tuberculosis* H(37)Rv reference strain.84

A variety of 3-(3-bromophenyl)-5-phenyl-1-(thiazolo[4,5-b]quinoxaline-2-yl)-2-pyrazolines were obtained by the refluxing of 1-N-thiocarbamoyl-3,5-diphenyl-2-pyrazoline with 2,3-dichloroquinoxaline. The antiamoebic activity of these compounds was evaluated by micro dilution method against HMI:IMS S strain of *Entamoeba histolytica*. Some of the quinoxaline derivatives showed less IC(50) values than metronidazole.85

A novel series of 1-acetyl-3-(4-hydroxy- and 2,4-dihydroxyphenyl)-5-phenyl-4,5-dihydro-[1H]-pyrazole derivatives have been synthesized and investigated for the ability to selectively inhibit the activity of the A and B isoforms of monoamine oxidase (MAO). The new synthesized compounds were proved to be more reversible, potent and selective inhibitors of MAO-A than of MAO-B.86

A series of 5-(-(substituted)phenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1H-1-pyrazolyl-2-toluidino methane thiones and 5-(substituted)phenyl-3-
(4-hydroxy-3-methylphenyl)-4,5-dihydro-1H-1-pyrazolyl-2-methoxyanilino methane thiones were synthesized by the reaction between hydrazine hydrate and chalcones followed by condensation with appropriate aryl isothiocyanate which yielded \( N \)-substituted pyrazoline derivatives. Among the synthesized compounds, anilino-3-(4-hydroxy-3-methylphenyl)-5-(2,6-dichlorophenyl)-4,5-dihydro-1H-1-pyrazolylmethanethione was found to be more active agent against \( M. tuberculosis \) H37Rv with minimum inhibitory concentration\(^{87}\).

A series of substituted chalcones and their corresponding pyrazoles were synthesized and evaluated for \textit{in vitro} cytotoxic activity against a panel of human cancer cell lines. Out of 93 compounds screened, 8 compounds show marked activity\(^{88}\).
Pyrazolin-5-one derivatives – a brief review of literature

A novel series of pyrazoline and thiazole derivatives incorporating 2-pyrazolin-5-one moiety were synthesized starting from \( \alpha,\beta \)-unsaturated ketones under the effect of hydrazine derivatives and thiosemicarbazide\(^{89}\).

New thiazolidine-4-one derivatives based on the 4-aminophenazone (4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) scaffold have been synthesized as potential anti-inflammatory drugs\(^{90}\).

![Diagram](image1)

3-methyl-1-\([\text{(5-substituted-1H-indol-2-yl)} \text{ carbonyl}] - 4-\{(4-(\text{substituted thiazol-2-yl})\text{iminoethyl})\text{phenyl} \text{hydrazono}\}\)-2-pyrazolin-5-one derivatives were synthesized by conventional and microwave methods. The synthesized compounds were tested for their antimicrobial activity against six strains of bacteria and three fungal strains. Most of the compounds showed varying antimicrobial activity\(^{91}\).

![Diagram](image2)

The key intermediate acetohydrazide on cyclization with aryl substituted acids in presence of phosphorous oxychloride (POCl\(_3\)) under microwave irradiation resulted in the formation of the 2-(5-oxo-4-(2-phenylhydrazono)-3-
(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-(5-phenyl-2,3-dihydro-1,3,4-oxadiazol-2-yl)ethyl)acetamide in excellent yields\cite{65}.

A convenient route to the synthesis of pyrazolo[3,4-b]pyridin-3-one and pyrazolo[1,5-a]pyrimidin-2(1H)-one via condensation of 3-amino-1-phenylpyrazolin-5-one with 2-pyrone derivatives followed by the alkylation of prepared compounds is described\cite{92}.

Based on the literature survey, the author in the present research investigation has focused on the synthesis, characterization and antimicrobial activity of benzimidazole, oxadiazole and pyrazole derivatives with the following objectives which will add new dimensions to the existing literature.
Objectives of the present investigations

In view of the diverse biological activities of benzimidazole, oxadiazole and pyrazole derivatives as mentioned above, the author has taken up the synthesis and biological evaluation of a series of

(i) $5$-($2$-(substituted phenoxymethyl)-$1H$-benzo[$d$]imidazol-$1$-yl)methyl)-
1,3,4-oxadiazole-$2$-thiols,

(ii) $3$-methyl-$4$-($2$-substituted phenylhydrazono)-$1$-($2$-($p$-tolyl)-
$1H$-benzo[$d$]imidazol-$1$-yl)acetyl)-$1H$-pyrazol-$5(4H)$-ones and
$1$-($3,5$-Dimethyl-$4$-(substituted phenylazanyl)-$1H$-pyrazol-$1$-yl)-
$2$-($2$-($p$-tolyl)-($p$-tolyl)methyl)-$1H$-benzo[$d$]imidazol-$1$-yl)ethanones,

(iii) $1$-(substituted $3,5$-diphenyl-$4,5$-dihydro-$1H$-pyrazol-$1$-yl)-
$2$-(quinolin-$8$-yloxy)ethanones and

(iv) $4$-(substituted benzylidene)-$3$-methyl-$1$-($2$-(quinolin-$8$-yloxy)acetyl)-
$1H$-pyrazol-$5(4H)$-ones.
References


