CHAPTER - 1


Since last two decades a rapid progress in synthetic organic chemistry is associated with a search for new compounds with desired properties. Such compounds are widely used in pharmaceutical industries. Among these, the heterocycles form the largest of the classical division of organic chemistry and are of immense biological and industrial importance. The majority of biologically active compounds are heterocycles also applicative as additives and modifiers used in industries of cosmetics, photography, information storage and plastics.

Heterocyclic compounds are also used in pharmacy and agriculture. Analysis of scientific papers in the last two decades revealed that there is a general trend in research for new drugs involving modification of existing biologically active matrices and molecular design of the structures of compounds.

In the recent years much attention has been focused on the synthesis of heterocycles containing nitrogen atom because of their biological and medicinal importance including ontological research. They are widely distributed in nature and are essential for life.

Nitrogen Heterocycles play a major part in the biochemical processes in living cells, DNA and RNA containing pyrimidine [cytosine and uracil] and thymine and purine [adenine and guanine ] bases are aromatic heterocycles. Most of enzymes have aromatic heterocycles as major constituents while coenzymes incorporate non-amino acids moieties, most of them are aromatic nitrogen heterocycles. Some important vitamins are constructed on aromatic heterocyclic scaffold.

Observations of life in nature by primitive communities led humans to the discovery of many healing materials. Majority pharmaceutical products are mimics of natural products with good biological activity which includes many
heterocycles. The efforts are being made to synthesize heteroaromatic bioactive molecules which is of through need. The routinely used antibiotics like penicillin and cephalosporin’s, alkaloids such as vinblastine, elliptine, morphine, reserpine and cardiac glucoside such as the class of digitalis are heterocyclic natural products of significance for human being and animal health. Modern life and civilization opened the way to other important practical applications of heterocycles for example dyestuffs, copolymers, solvent extraction, photographic sensitizers, vulcanization accelerators and antioxidants in the rubber industry.

Heterocyclic Chemistry is an inexhaustible resources of novel compounds. Almost unlimited combinations of carbon, hydrogen and heteroatoms can be designed, making available compounds with the most diverse physical, chemical and biological properties. Since diverse organic molecules of animal and plant origins have predominance of nitrogen and oxygen heterocycles proved their utility in different fields.

In the present thesis, we explore the methods of synthesis and biological properties of new pyran, indole, phthalazine and pyrazole derivatives.

**LITERATURE SURVEY**

### 1.1 PYRAZOLE

Pyrazole is a five member heterocyclic compound containing two nitrogen atoms adjacent to each other. In 1883, Knorr et al\(^1\) gave the generic name pyrazole to above class of the compounds, which is a five member unsaturated ring compound with two adjacent nitrogen atoms.

**Pyrazolone**

There are three possible heteropyrazolines \([1, 2, 3]\) in which carbonyl group is adjacent to nitrogen.

\[
\begin{align*}
\text{[1]} & \quad \text{[2]} & \quad \text{[3]}
\end{align*}
\]
The carbonyl at position five leads to 5-hydroxyl pyrazoles [4], since the 5-hydroxy compound exhibits pronounced enol character, tautomeric forms shown below for the 1-phenylderivative are the fundamental structures involved in the pyrazolone reactions.

\[
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{N} \\
\text{N} \\
\end{array} \quad \begin{array}{c}
\text{Ph} \\
\text{OH} \\
\text{N} \\
\text{N} \\
\end{array} \quad \begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{N} \\
\text{NH} \\
\end{array}
\]

1-Phenyl-5-pyrazolone [4]

**Derivatives of Pyrazole**

Most of the drug in this chemical category are structurally related to the aromatic compound pyrazole [5]. If one of the double bonds in pyrazole is saturated then resultant compound is pyrazoline [6]. However, if both are saturated, then it is known as pyrazolidine [7].

\[
\begin{array}{c}
\text{NH} \\
\text{NN} \\
\end{array} \quad \begin{array}{c}
\text{NH} \\
\text{NN} \\
\end{array} \quad \begin{array}{c}
\text{H} \\
\text{NN} \\
\end{array}
\]


**Physical properties**

Pyrazole melts at 69-70 °C; it is very stable to heat.\[^{[2]}\] Hydrophobic substituents reduce the solubility of pyrazole in water, at 20 °C.

**Electron densities.**

The electron density distribution of pyrazole [8] as follows.

\[
\begin{array}{c}
\text{1.086} \\
\text{1.109} \\
\text{1.162} \\
\text{1.656} \\
\text{1.031} \\
\text{N} \\
\text{N} \end{array}
\]

[8]

In UV-spectrum of pyrazole, the bands observed at 211 nm in ethanol and at 203.2 nm in the vapour phase.\[^{[3]}\]
Infrared Absorption Spectrum

Pyrazole rings without carbonyl group shows C-H stretching modes near 3000 cm\(^{-1}\). Some such frequencies range from about 1800 to 1600 cm\(^{-1}\). Some of them are so low that they fail to be recognized as carbonyl absorption e.g. carbonyl joined to a heterocyclic ring via an exocyclic double bond. Low frequencies \(\nu\) (C=O) bands are widespread because the five membered heterocyclic rings is inherently \(\Pi\) electron donar. The transfer of electron to the exocyclic double bond is extensive when both adjacent atoms are electron donors.[4]

\(^1\)H Magnetic Resonance Spectrum

At a room temperature, 5-hydroxy-4,5-dihydroxy-pyrazole in the case of diketones possessing terminal perfluoroalkyl substituents show non-equivalent protons at the 4-position of the ring.[5]

If the strong electron withdrawing substituent is present e.g. diketone, the interaction leads to the desired 5-hydroxy-4,5–dihydropyrazole. The \(^1\)H NMR spectrum of AB type of diastereotopic protons in 4-position of the ring are observed. The inclusion of the strong electron withdrawing substituent into the hydrazine component, acyl group is known to stabilize the 5-hydroxy-4,5–dihydropyrazole structure or its linear tautomer.[6] The \(\text{CH}_2\) protons at the 4\(^{th}\) position of the ring displayed a broad singlet at \(\delta\) 2.78 proved the arrangement of the perfluoroalkyl and hydroxyl groups. The proton chemical shift for ring \(\text{CH}\) of fully aromatic neutral pyrazoles was displayed at \(\delta\) \(H_3=7.61\), \(H_4=7.31\), \(H_5=7.61\) and spin coupling constant \(J\) (Hz) =2.1.[7-8] Similarly, \(^1\)H NMR spectra of N-methyl pyrazole, tetrahydropyrazole,[9] 3H and 4H-pyrazole,[10] pyrazolin-3-one[11] were studied extensively.

\(^{13}\)C Magnetic Resonance

The observed \(^{13}\)C NMR shift of different carbons have been presented below.
Mass Spectroscopy

Nishiwaki et al studied the behavior of pyrazole under electron impact.\textsuperscript{[12]} Pyrazoles, due to their aromatic character are extremely stable under electron impact.\textsuperscript{[13]} The most important fragmentation pathways of the molecular ions of pyrazole occur because of loss of RCN or HCN.

\[ \text{m/e 68} \quad \text{m/e 41} \]

The photoelectron spectroscopy of pyrazole reported by Baker et al.\textsuperscript{[14]} The ionization energies of pyrazole are 9.5, 10.1 and 10.8 ev. The PE spectrum of pyrazole in the gas phase showed a series of bands at 9.15, 14.7, 17.5 ev.\textsuperscript{[15]} The pKa of pyrazole is 2.5. The inductive effect is predominating over mesomeric effect in the pyrazole, N-Methyl group has base weakening effect in pyrazole, probably because of steric hindrance to hydration.

The dipole moment of pyrazole calculated from variable electronegativity self consistent field (VESCf) procedure, which is 2.20 (G=gas phase), 2.30,\textsuperscript{[16]} 5.05 (CEHT),\textsuperscript{[17]} 2.50 (ILCAO)\textsuperscript{[18]} Dipole moment of pyrazole in the solution showed that pyrazole forms non-polar cyclic dimer.\textsuperscript{[19]} X-ray data for pyrazole was first analyzed by Ehrlich.\textsuperscript{[20]} However, it was later proved to be wrong. The definitive structure of pyrazole was established by
Ramussen et al\cite{21}\ dealing with neutron diffraction and X-ray diffraction study at 295 and 168 °K.

In the ESR spectroscopy of pyrazole, Kasai and Mcleod\cite{22}\ generated radical anions in Argan matrices at 4K by the reaction of the parent heterocycles with sodium atoms. The photo induced radical anion of pyrazole shows an ESR spectrum with the characteristic triplet of doublet features, assigned to a non-aromatic tautomeric form. The triplet features with a spacing of a 50G attributed to the two protons at C-5, the doublet with spacing of a 15G to proton C-4. The radical formed by the reaction of ‘OH’ with pyrazole has the structure according to the ESR spectrum (hyperfine constant (G); H-3, H-1, 1.5, H-4, 10, H-5, 31).

Because of the diverse properties, easily accessible path and the wide range of biological activities are centre of attraction for organic chemist. The literature survey reveals the importance of pyrazole derivatives as an intermediate in the medicines. They are used in dye industries, useful as biodegradable agrochemicals,\cite{23}\ effective chemical bleaching agent as luminescent and fluorescent substances\cite{24-25}\ in the development of cine films.\cite{26}

**Methods of Synthesis**

Cyclocondensation of 3-aryl(heteroaryl)pyrazole-4-cabaldehyde with ethylacetoacetate and urea in the presence of FeCl$_3$.6H$_2$O extrudes 3-aryl (heteryl)-4-(4-pyrazolyl)-1,2,3,4tetrahydropyridine2-ones/(thiones)\cite{9}\ (Scheme 1.1) reported by M. K. Brantenko and co-workers.\cite{27}
Jairo Quiroga et al\textsuperscript{[28]} have synthesized a series of 6-(2-hydroxybenzoyl)-5-methyl-7-phenylpyrazolo[1,5-\textit{a}]pyrimidines \textsuperscript{[10]} and 5-amino-1\textit{H}-pyrazoles and 3-benzoyl-2-methyl-4\textit{H}-chromen-4-one under solvent free condition. This solvent-free reaction proceeds in a regiospecific fashion by intramolecular opening of the \(\gamma\)-pyrone ring in a Michael type addition reaction, followed by cyclization via nucleophilic attack of endocyclic pyrazole nitrogen toward benzoyl group to give the pyrazolo[1,5-\textit{a}]pyrimidines. The use of this method offers high yields in short reaction time.

![Scheme 1.2](image)

**Scheme 1.2**

Application of Vilsmeier Haack method for the synthesis of 2-(3-aryl-4-formyl pyrazole-1-yl)-3-phenyl1,8-naphthyridines \textsuperscript{[11]} from acetophenone hydrazones to give 3-phenyl-1,8 naphthapyridine-2-ylhydrazones with POCl\textsubscript{3} and DMF has been reported by Rao et al.\textsuperscript{[29]}

![Scheme 1.3](image)

**Scheme 1.3**

O. V. Kokoreva et al\textsuperscript{[30]} have carried out the synthesis of 3, 5-dimethyl-4(2-N-substituted amino ethyl) pyrazoles \textsuperscript{[12]} (**Scheme 1.4**) by the reaction of hydrazine hydrate with diketone. The said molecules have been formed after the ring opening of cyclopropane (**Scheme 1.4**).
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[12]

Scheme 1.4

The good ligand properties of the pyrazole [13] utilized for the synthesis of carbonyl complexes by the photochemical reaction. The synthesis of metal carbonyls of transition metals like Cr and W are found to be effective in THF at room temperature, reported by W. jia et al [31] (Scheme 1.5).

[13]

Scheme 1.6

Ahluwalia et al [32] have demonstrated ring closing reaction of hydrazones of 1-phenyl-2-chloro pyrazole [14] under thermal condition. In this reaction the chlorine atom on pyrazole ring leads to formation of 3,6-disubstituted-1-phenyl-1H, 6H pyrazolo pyrazoles (Scheme 1.7).

[14]

Scheme 1.7

Three component condensation of 4-piperidinones, 5-pyrazolones and malononitrile demonstrated by A. M. Shestopolar [33] and associates, which proceeds chemically as well as electrochemically to give 6-amino-5-cyanospiro-4-(piperidine-4)-2H,4H-dihydropyrazolo[3,4-b]pyran [15] (Scheme
The electrochemical reaction proceeds under milder conditions and with yield ranging between 12-15%.

**Scheme 1.8**

Microwave assisted synthesis of pyrazoles [17] reported by R. Atir et al [34] through 1, 3–dipolar cycloaddition of diphenyl nitrilimine [16] on olefins under solvent free condition (Scheme 1.9). The corresponding pyrazoline obtained requires less time period as compared to conventional heating.

**Scheme 1.9**

Nucleophilic aromatic substitution reaction on 5-chloropyrazoles activated by the electron withdrawing formyl group, is a useful method to introduce a wide range of N-containing heterocycles. The rate of SNAr reaction was greatly affected by the electronic nature of N-1 substituted pattern [35] (Scheme 1.10).
Pyrazole[3,4-d]pyridazine [18] have been synthesized from hydrazonoyl chloride. Treatment of ethyl,4-methyl-6-[2-(thienyl)]-2-thioxo-1,3,6 trihydro-pyrimidine-5-carboxylate with methoxy-N-phenylhydrazonoyl chloride and triethylamine in chloroform under reflux to give the 1, 2, 4 triazolo [4, 3-a] pyrimidine 5-carboxylate. Similarly, A. O. Abdelhamid et al [36] reacted the appropriate hydrazonoyl halide with of 2-methylthio-4-oxo-6-(2-thienyl)-3-hydrapyrimidine 5-carbinitrile in ethanol under reflux to give 1,2,4 trizolino[4,3-a] pyrimidine derivatives (Scheme 1.11).

![Scheme 1.11](image)

Oxidative aromatization of pyrazolines with oxidizing reagents provides an efficient method for the preparation of pyrazole derivatives. For this oxidative conversion of pyrazolines, a limited number of reports exists in the literature, which includes Pd/C, Co(II) and oxygen, iodobenzene diacetate, lead tetracetate, MnO2, KMnO4 and NBS. These reactions requires severe reaction conditions or their use is accompanied by the formation of biproducts due to decomposition and ring scission. R. Ghorbani–Vaghei [37] and co-workers have developed a mild route for the oxidative dehydrogenation of 1,3,5 trisubstituted pyrazolines to the corresponding pyrazoles [19] using the new reagent N, N, N, N–tetrabromobenzene1,3-disulfonylamide (TBBDA), which is relatively easy to drive the reaction under heterogeneous and solvent free conditions (Scheme 1.12).
Addition of diazomethane across carbon-carbon triple bond has been demonstrated by V. A. Lopyrev et al.\cite{38} to synthesize 3(5)-trimethylsilylpyrazole\cite{20} by the reaction of trimethylsilylacetylene with diazomethane in quantitative yields.

M. M. Mojtahedi et al.\cite{39} have synthesized a series of substituted 1H, 6H pyrano[2,3-C]pyrazol-6-one derivatives\cite{21} from one pot cyclocondensation of hydrazine derivatives or 1H-pyrazole-5-one derivatives with various β-keto esters under solvent free condition using microwave irradiation in short time with an excellent yields (Scheme 1.15).

Microwave induced reaction reported by N. L. Nam\cite{40} and co-workers for the synthesis of pyrano [2,3-C] pyrazol-6-ones in good yields by reaction of 1H-pyrazol-5-one with β-keto esters.
Addition of hydrazine across the chalcone is well known method for the synthesis of pyrazolines. B. A. Bhat\cite{22} have reported the synthesis of pyrazoles \cite{22} by reaction of hydrazine with epoxide of chalcone followed by dehydration (Scheme 1.16)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{NhNH2} & \\
\text{NH2NH2} & \\
\text{N} & \\
\text{N} & \\
\end{align*}
\]

[22]

Scheme 1.16

R. S. Varma\cite{23} et al have accomplished the direct synthesis of N-aryl pyrazole derivatives \cite{23} via double-alkylation of hydrazine by alkylhalide or ditosylation in aqueous media under microwave irradiation.

\[
\begin{align*}
\text{R} & \quad \text{NHNH2} \\
\text{Cl} & \\
\text{ArB(OH)2} & \\
\text{Na2CO3, CH3CN} & \\
\text{Pd catalyst} & \\
\text{MW} & \\
\end{align*}
\]

[23]

Scheme 1.17

Hong-Jun Wang et al\cite{43} have reported the coupling of 3-chloro-1-phenyl-2-pyrazoline with arylboronic acids in good yields under microwave heating (Scheme 1.18).

\[
\begin{align*}
\text{Cl} & \\
\text{ArB(OH)2} & \\
\text{1M Na2CO3, CH3CN} & \\
\text{Pd catalyst} & \\
\text{microwave} & \\
\end{align*}
\]

Scheme 1.18

Synthesis of 4-methylthiopyrazolo[1,5-a]-1,3,5-triazene \cite{24} via reaction of dimethyl N-cyanodithioiminocarbonate with 5-amino pyrazole have
been reported by G. H. Elgemeie.\cite{44} Thus, it has been found that dimethyl N-cyanodithioiminocarbonate reacts with 5-aminopyrazoles in refluxing ethanol containing catalytic amount of piperidine to give the corresponding 4-methylthiopyrazole[1, 5-a]-1, 3, 5-triazines. Derivatives of this ring system have useful properties as an antimetabolites in purine biochemical reactions (Scheme 1.19).

\begin{Scheme1.19}
\begin{center}
\begin{tikzpicture}
\node at (0,0) {NH$_2$} node[below left] at (0,0) {Ar} node[above right] at (0,0) {NH} node[below right] at (0,0) {SCH$_3$} node[above] at (0,0) {NC- N} node[below] at (0,0) {SCH$_3$} node[below right] at (0,0) {R} node[below left] at (0,0) {NH$_2$} node[below] at (0,0) {Ethanol} node[below] at (0,0) {Piperidine} ;
\end{tikzpicture}
\end{center}
\end{Scheme1.19}

\textbf{Scheme 1.19}

Sulfonyl ureas are most common oral hypoglycemic agents but some times their major drawbacks is formation of serious hypoglycemia. Thus, use of nonsulfonyl urea class of compounds are desirable which do not increase insulin secretion but enhance the action of insulin. Ashoke Sharon and co-workers\cite{45} synthesized a series of 5-[(5-aryl-1H-pyrazol-3-yl) methyl]-1H-tetrazoles \cite{27} by reaction between 5-aryl-3-cyanomethyl-1H-pyrazoles \cite{26} and sodium azide (Scheme 1.20). The precursor 5-aryl-3-cyanomethyl-1H-pyrazoles obtained from ring opening transformation of 6-aryl-4-ethylsulfanyl-2H-pyran-2-one-3-carbonitrile \cite{25} by hydrazine hydrate and further reaction of \cite{26} with sodium azide offers tetrazole derivative and further evaluation for their in-vivo antihyperglycemic activity revealed that some of the synthesized compounds have shown significant glucose lowering activity in male Sprague–Dawley rats in sucrose loaded model.

\begin{Scheme1.20}
\begin{center}
\begin{tikzpicture}
\node at (0,0) {SCH$_3$} node[below] at (0,0) {Ar} node[above] at (0,0) {CN} node[below] at (0,0) {O} node[below left] at (0,0) {O} ;
\end{tikzpicture}
\end{center}
\end{Scheme1.20}

\textbf{Scheme 1.20}
An efficient one pot synthesis of pyrazolo[4,3,5,6]pyrido[2,3-d]pyrimidine-dione \([30]\) by coupling 4-amino-1,3-biphenyl imidazole \([28]\), barbutiric acid \([29]\) and arylaldehyde under solvent free condition have been reported by Ayoob Bazgira in the presence of para toluenesulfonic acid as catalyst\(^{46}\) (Scheme 1.21). The reaction took four hours for completion. The synthesized compounds were screened for their antibacterial activity against Bacillus subtilis, Bacillus pumilus, Micrococcus luteus, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mutan, Escherichia coli, Enterococcus feacalis, Pseudomonas aeruginosa bacterial strain. Almost all of the compounds were found to be intensly active against all bacterial strains.

![Scheme 1.21](image)

1.2 INDOLE

It is aromatic bicyclic heterocycles in which benzene ring fused to a five member pyrole ring. It is one of the important constituent of perfumes and precursor of many pharmaceuticals. The indole is a common name. The systematic nomenclature of the indole is 1-benzo\([b]\)pyrole. The well known indole derivative is tryptophan. Other indolic compounds include plant hormone, indole acetic acid and anti-inflammatory agent, indomethazine. The chemistry of indole starts with the study of dye indigo. Some of the indole derivatives are important dyestuff. The research in indole intensified when it was acknowledged that the indole nucleus is present in many important alkaloids, as well in tryptophan and auxin. The Indole is major constituent of coal tar and fraction obtained at 220-260 °C is the main industrial source of the
material. There are some other important routes reported for synthesis of indole derivatives.\[47-49\]

**Methods of Synthesis**

The most important method for synthesis of substituted indole is the Fischer Indole synthesis. Indole can be synthesized by reacting phenylhydrazine with pyruvic acid followed by decarboxylation to form an indole. This has also been accomplished in a one pot synthesis using microwave irradiations.\[50\] (Scheme 1.22).

![Scheme 1.22]

Synthesis of indole in large scale is carried out by vapour phase reaction between aniline and ethylene glycol\[51\] at the temperature between 200-500 °C (Scheme 1.23).

![Scheme 1.23]

The Leimgruber-Batcho\[52\] indole synthesis is an efficient method of synthesizing indole and substituted indoles. Originally disclosed in a patent in 1976, this method is high-yielding and can generate substituted indoles. This method is especially popular in the pharmaceutical industry, where many pharmaceutical drugs are made from substituted indoles (Scheme 1.24).

![Scheme 1.24]
In Bartoli indole synthesis,[53] nitroarenes with vinyl grignards reagent at low temperature to form substituted indoles [31]. The reaction found to be unsuccessful in the absence of ortho substituent and it requires three equivalent of Grignards reagent for good yield of the products (Scheme 1.25). Advantage of this method is to synthesize substituted indole both on carbocyclic ring as well as on pyrole ring.

![Scheme 1.25](image)

**Scheme 1.25**

Bischler- Mohlau et al[54] developed a simple method for synthesis of 2-arylindole [32] by use of simple starting material, α-bromoacetophenone and excess aniline (Scheme 1.26).

![Scheme 1.26](image)

**Scheme 1.26**

The Fukuyama synthesis[55] involves the chemical reaction of alkenylthioanilide to offer 2, 3 disubstituted indole [33]. In this reaction tributyltinhydride has been used as reducing agent, with azobisisobutylnitrile (AIBN) as radical initiator (Scheme 1.27). The important synthetic aspect of this reaction is the synthesis of poly-substituted indoles and thus it often utilized in the synthesis of natural products including asidophytine, vinblastine and strychine.
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Thermal decomposition of 3-aryl-2-azido-propenoic acid ester into an indole-2-carboxylic acid ester [34] has been reported by Hemetsberger et al. [56]. The yield of this reaction is good more than 70%, but due to the less thermal stability of starting material this method has less synthetic importance (Scheme 1.28). The mechanistic path towards the formation of the final product is still unknown but aziridine have been isolated as an intermediate, on the basis of postulated formation of indole through nitrene intermediate.

The one step synthesis of substituted indole [35] have been reported by Larock et al. [57] by palladium-catalyzed coupling of 2-iodoaniline with a wide variety of internal alkynes provides 2,3-disubstituted indoles to an excellent yields (Scheme 1.29). The best results are obtained by employing an excess of the alkyne and sodium or potassium acetate or carbonate base and one equiv of either LiCl or n-Bu₄NCl, occasionally adding 5 mol % PPh₃. The yields with LiCl appear to be higher and more reproducible than those obtained with n-Bu₄NCl. The reaction drives towards the good yield of the product. Considering the regeoselectivity, it is assumed that the alkyl group with large steric bulk will orient at R₂ position.
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Scheme 1.29

The Madelung synthesis\textsuperscript{[58]} is a chemical reaction that produces substituted or unsubstituted indoles \textsuperscript{[36]} by the intramolecular cyclization of N-phenylamides using strong base at a high temperature. This method is essentially confined to the preparation of 2-alkenylindoles (not easily accessible through electrophile aromatic substitution) because of the vigorous reaction conditions(Scheme 1.30).

Scheme 1.30

Raed A. Al-Qawasmeh\textsuperscript{[59]} and associates have reported new series of antimicrobial derivatives, [3-(4, 5-diaryl-1H-imidazol-2-yl)-1H-indole)] \textsuperscript{[37]} which showed potent activity against bacterial strain of *Staphylococcus aureus*, including methicillin-resistant strains (MRSA). The compound, [3-[4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl]-5-bromo-1H-indole] was found to be the most active derivative inhibiting the growth of all Gram-positive strains tested, including vancomycin resistant *Enterococcus faecalis* and *Enterococcus faecium.*
Synthesis, biological evaluation and structure–activity relationships for a series of novel 5-styryl and 5-phenethyl analogues of dimebolin are reported by Alexandre V. Ivachtchenko. The novel derivatives and dimebolin share a broad spectrum of activities against therapeutically relevant targets. Among all synthesized derivatives, 2,8-dimethyl-5-[(Z)-2-phenylvinyl]-2,3,4,5-tetrahydro-1\(H\)-pyrido[4,3-\(b\)]indole and its 5-phenethyl analogues are the most potent blockers of 5-HT\(_7\), 5-HT\(_6\), 5-HT\(_{2C}\), Adrenergic \(\alpha_2\) and \(H_1\) receptors.

Because of multiple factors, the burden of malaria is currently increasing, the most important limiting factor here is the development of resistance by \textit{P. falciparum} against the cheap and relatively ineffective drugs like chloroquine. One of the innovative approaches to antimalarial drug discovery is the identification of new drug targets and attendant inhibitor design. However, as recently reviewed most of clinically available antimalarial drugs were developed using pregene technology-era pharmacochemical approaches and the action mechanisms for the majority has not yet been clarified. Franc-oise Never et al\(^[61]\) undertook the synthesis and study of in-vitro
and in-vivo antiparasitic activity of indolone N-oxides [41] (Scheme 1.31) against *Plasmodium spp.*

![Scheme 1.31](image)

Reagents and conditions: (i) Ph₃PCH₂R₂Br, NaOH, CH₂Cl₂, Bu₄N Br (ii) KMnO₄, acetic anhydride, 0°C (iii) Zn, NH₄Cl, tetrahydrofuran, CH₂Cl₂.

**Scheme 1.31**

In-vitro antimalarial activities of 6-trifluoromethyl-1,2,4-triazino[5,6-b]indole and 5H-1,2,4-triazolo[1,5,2,3]-1,2,4-triazino[5,6-b] indole [42] were examined against the *Plasmodium falciparum* by Joseph L. Kgokong [62] (Scheme 1.32). The 1,2,4-triazino [5,6,b] indole derivative with a trifluoromethyl group at position 6 exhibit increased in-vitro activity when compared to the unsubstituted analogues. The presence of the trifluoromethyl group in the 5H-1,2,4-triazolo[1',5',2,3]-1,2,4-triazino[5,6-b] indole ring system leads to compounds with diminished antimalarial activity when compared to the corresponding unsubstituted analogues.

![Scheme 1.32](image)
A series of 2 and 3-aryl substituted indoles and 1,3,4,5-tetrahydropyranopyrano [4, 3-b]indoles [43] have been synthesized from indole and 5-methoxyindole. A number of the 2 and 3-aryl indoles displayed noteworthy antimicrobial activity (3.9 μg/mL) against the Gram-positive micro-organism, Bacillus cereus reported by Tlabo C. Leboho et al[^63] (Scheme1.33).

![Scheme1.33](image)

**Scheme1.33**

### 1.3 PYRAN

Benzopyran is a very interesting class of heterocyclic compounds, having wide range of applications in medicinal chemistry. In this category a benzene ring fused with pyran ring. Two classes of benzopyrans are 1-benzopyrans [44] and 2-benzopyrans [45].

![1-benzopyran](image)

![2-benzopyran](image)

[^43]: Reference number
[^44]: Reference number
[^45]: Reference number
Out of these two classes of benzopyrans, 1-benzopyrans of various levels of saturation such as chromen [46], 2H-chromene [47], 4H-chromene [48], 3-chromene [49], 4-chromene [50], 2, 4 chromandione [51] are given below.

Since, the common name chromene still acceptable under the IUPAC rules, name derived from chroman are used frequently.

These compounds are important because many of them occur in plants and have considerable biological importance, especially as drugs. The common name ‘Chromene’ for 2H and 4H-1-benzopyran was probably coined in 1904 by Houben.[64] Although chromen was first prepared[65] in 1905, little interest was shown in the compounds until studies on the tocopherols (vit. E) began to indicate that they were derivatives of chroman. Many of them occur in plants, and have considerable biological importance.

Since, the discovery of benzopyran in the late 19th century, their nomenclature has been changed several times. Both 2H and 4H–benzopyrans have many names eg-2H-1- benzopyran has been called β-chromene and Δ³ 0-chromene[66] called as 4H-chromene and benzo-γ–pyran α-chromene[67] and in the ring index.
Method of Synthesis

Various methods of preparations of 2, 3-dihydro-4H-1-benzopyran-4-ones or 4-chromanone ring [52] have been reported in literature. Most successful and widely used method for the synthesis of 4-chromanone ring system is the cyclization of 3-phenoxypropionic acids and related preparation of β-phenoxypropionic acid or 3-phenoxypropionic acid is earlier reported by Bischoff.[68] 3-Phenoxypropionic acids undergoes dehydration with a variety of dehydrating agents, mainly phosphorous pentoxide or polyphosphoric acid (PPA) (Scheme 1.34).

![Scheme 1.34](image)

The most widely used reagent for cyclising 3-phenoxy propionic acids was phosphorus pentoxide which has been rendered by this method.[69] The use of a mixture of phosphorus pentoxide and phosphoric acid have rapidly found widespread applications.[69-70] One of the earliest technique used to prepare chromanone from 3-Phenylpropionic acid was the use of phosphorous pentachloride and aluminium chloride.[71]

The second method, normally used for the synthesis of 4-chromanone [54] with one or two substituted groups in the 2-position, involves the reaction of phenol or its methyl ether and unsaturated acid e.g. 3, 3-dimethyl acrylic [53] acid in the presence of dehydrating agent (Scheme 1.35).
Simple chromenes and their derivatives are useful as thermoplastic resins, antioxidant for fats and oils, in anticorrosive treatment of sheet metals,\textsuperscript{[72]} estrogenic and antifertility agents.\textsuperscript{[73]} They have shown Vit. E activity\textsuperscript{[74]} and are useful in angina pectoris\textsuperscript{[75]}. The 2H-1-benzopyrans were considered to be analgesics, antidepressant, antianxietal,\textsuperscript{[76-77]} antihypertensive,\textsuperscript{[78]} antioxidant,\textsuperscript{[79]} antitumor\textsuperscript{[80-82]} and hypoglycemic agents.\textsuperscript{[83]}

Klaus Urbahns\textsuperscript{[84]} and co-workers have been identified 4-Phenyl-4H-pyran\textsuperscript{[55]} as potent and specific IK\textsubscript{Ca} channel blockers. A selected derivative reduces the infarct volume in a rat subdural hematoma model of traumatic brain injury after administration.

The synthesis of furo-[3,2-c]isochroman-2-trione \textsuperscript{[56]} which possess antibiotic activity of the pyranonaphthoquinones have been reported by Darío A. Bianchi et al\textsuperscript{[85]} (\textbf{Scheme 1.36}). One of the derivative was found to be active against \textit{Staphylococcus aureus} and \textit{Bacillus subtilis} with MIC of 64 and 32 \textmu g/mL respectively.
Reagents and conditions: (a) NaCNBH₃, AcOH, EtOH, rt, overnight (96%) (b) CSA (0.5 equiv), MeOH, 40 °C, 6 h (89%); (c) TBDMSCl, imidazole, DMAP, DMF, rt, 4 h (87%); (d) DIBAL-H, toluene, 78 °C, 10 min (93%); (e) Ph₃C=CHCO₂Et, MeCN, reflux, 40 min; (f) KtBuO (0.1 equiv), 2 min (76%, overall) TBAF, THF, rt, 1 h (90%) (h) TEA, CH₂Cl₂, rt, overnight (80%) (i) AgO, 6 N HNO₃, 5 min (55%).

Scheme 1.36

Kenneth O. Eyong et al\textsuperscript{[86]} found unexpected formation of 2-acetylfuranonaphthoquinone \textsuperscript{[59]} along with the expected aldehyde \textsuperscript{[58]} while ozonolysis reaction on lapachol \textsuperscript{[57]} (Scheme 1.37). This side product is known to be as a potent antitumor agent (25 lg/ml). All the tested samples showed dose-dependent activity.

Scheme 1.37

An efficient, green protocol has been developed by Raju Ranjith Kumar\textsuperscript{[87]} and co-workers for the synthesis of 2-amino-6-methyl-4-aryl-8-[(E)-
aryl methylidene]-5,6,7,8-tetrahydro-4H-pyra no[3,2-c]pyridine-3-carbonitriles [61] from 1-methyl-3,5-bis[(E)-aryl methylidene]-tetrahydro-4(1H)-pyridinones [60] and malononitrile in presence of solid sodium ethoxide under solvent-free condition (Scheme1.38). The synthesized compounds have been examined for their in-vitro activity against *Mycobacterium tuberculosis* and *Mycobacterium smegmatis* using agar dilution method. 2-Amino-4-[4-(dimethylamino)phenyl]-8-(E)-[4-dimethylamino)phenyl]methylidene-6-methyl-5,6,7,8-tetrahydro-4H-pyr ano[3,2-c]-pyridine-3-carbonitrile found to be the most potent compound in the series.

![Scheme1.38](image)

Fractionation of the ethanolic extract of all the plants of *Lespedeza virgata* (Thunb.) DC resulted in the isolation of a novel flavonoid bearing pyran nucleus [62] along with some other constituents. The superoxide anion scavenging activities of all isolated compounds have been evaluated by the hypoxanthine nitro blue tetrazolium [88] and ESR method. The isolated new compound showed the strongest antioxidative property with IP50 0.14 mg/mL.
Carbohydrate derivatives bearing a fused pyran or furan ring have also been prepared by intramolecular Heck cyclization.\cite{89} Thus, the reaction of hex-2-enopyranosides [63] with catalytic Pd(OAc)$_2$/PPh$_3$, Et$_3$N and MeCN or toluene as solvent give the cis-fused pyran derivatives [64] in good yield. The configuration at C(4) was crucial for the cyclization and only 1,4-trans-hex-2-enopyranosides could be cyclized efficiently (Scheme 1.39).

Guillou and co-workers\cite{90} utilized an intramolecular Heck cyclization reaction to prepare a benzopyran ring in their synthesis of the alkaloid lycoramine (Scheme 1.40). The tricyclic benzopyran [66] was obtained from iododerivative [65] in 50% yield using catalytic Pd(OAc)$_2$/dppe in the presence of 1,2,2,6,6-pentamethylpiperidine (PMP), tetrabutylammonium acetate and toluene as solvent.

The antioxidants are the organic compounds having capacity to quench free radicals. Medicinal mushrooms produce various classes of secondary metabolites with potent antioxidant activity. In-Kyoung Lee and co-workers\cite{91} isolated some polyphenols, inonoblins A (1), B (2), and C (3) [67-69] from the
methanolic extract of the fruiting body of Inonotus obliquus, I. obliquus, Pil. Syn and Fuscoporia obliqua.

![Chemical structures](image)

Anticonvulsant activities of alkanoamine and amide derivatives [70] of xanthone have been evaluated by Henryk Marona and co-workers [92] (Scheme 1.41) using maximal electroshock (MES) and subcutaneous pentylenetetrazole (sc-Met) induced seizures and for the neurotoxicity (TOX) using the rotorod test on mice and rats.

![Scheme 1.41](image)

Scheme 1.41

Xanthone derivative [71] with extended \( \pi \)-systems and there some other structurally perturbed analogues have been synthesized by Yan Liu et al [93] (Scheme 1.42). These synthesized derivatives were found to be working as \( \alpha \)-glucosidase inhibitors. It is found that the xanthone derivative with least conjugated system are less effective, thus it is proved that extended conjugation plays an crucial role in the inhibition process.
Reagents and conditions: (a) ZnCl₂, POCl₃, 70–80°C; (b) LiAlH₄, THF, rt.

Scheme 1.42

Several new S-euglobalgs synthesized by Sandip B. Bharate et al⁹⁴ from suitably substituted phloroglucinol and different monoterpenes via three-component reaction involving Knoevenagel condensation followed by [4+2] cycloaddition. Some of these analogues were found to have antileishmanial activity. Robustadials also showed moderate antileishmanial activity and weak antimalarial activity against Plasmodium falciparum [⁷²,⁷³].

The synthesis and trypanosomatic behavior of a new series of 1,4-bis(alkylamino)benzo[g]phthalazines [⁷⁴] is reported by Robert W. Carling⁹⁵ (Scheme 1.44). In-vitro antiparasitic activity against Trypanosoma cruzi epimastigotes is remarkable, whereas toxicity against Vero cells is very low. Conversion of epimastigotes to metacyclic forms in the presence of the tested compounds causes significant decrease in the amastigote and trypomastigote numbers. Fe-SOD inhibition is noteworthy, whereas effect on human Cu/Zn-SOD is negligible.
One of the important synthetic routes via rearrangement of phthalazine have been reported by Kwok P. Chan et al. Phthalazine on heating at 360 °C for 30 min. offers quinoxaline derivatives in good yields [75], (Scheme 1.45).

Scheme 1.44

Scheme 1.45
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CHAPTER 1

Introduction – Structure, reactivity, synthesis and applications of pyrazole, indole, pyran and phthalazine.


Introduction – Structure, reactivity, synthesis and applications of pyrazole, indole, pyran and phthalazine.


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CHAPTER 1

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