AN ABSTRACT OF THE THESIS ENTITLED
“SYNTHESIS AND PHARMACOLOGICAL SCREENING OF SOME
HETEROCYCLIC COMPOUNDS”

The present work entitled “Synthesis and Pharmacological screening of some Heterocyclic Compounds” describes synthesis of varied classes such as substituted Schiff bases, imidazole, pyrrole, oxazole, pyrazolone, thiozolidone, piperazine, 2-oxo-cyclohex-3-ene and nitrone derivatives.

Pyrazole chemistry has been the focus of high attention for more than three decades due to versatile biological activities of pyrazole derivatives appearing as antimicrobial, antiviral, antitumor, anti-inflammatory, antihistaminic, anticonvulsant, antidepressant agents. The attachment of pyrazole ring in an organic structure is of significant interest because of its easy accessibility and diverse properties that are associated with it. The selection of pyrazole derivative in the field of clinical medicine is undoubtedly the principal practical application that one can come across.

Schiff bases and azo compounds are important structures in the medicinal and pharmaceutical fields. A series of chemically modified aryl-aldehyde Schiff bases have been synthesized and tested for their antioxidant activity and radiation protection. We know that disulfide-containing aryl-aldehyde Schiff base exhibited potent free radical scavenging, antioxidation, and radioprotection activities.

Substituted imidazoles exhibit different biological activities such as antimicrobial, antimuscarinic, antifungal, antineoplastics, leishmanicidal, analgesic and anti-platelet aggregation activities. Similarly, substituted pyrazoles also display antimicrobial, cytoprotective, antiulcer and antitumor activities. Knowing the importance of imidazole and the pyrazole containing ring system, in this project, it was decided to prepare derivatives of pyrazole containing 3,4,5-trisubstituted imidazoles as a new class of antimicrobial agents.

A large number of natural flavonoids with biological activity have been identified in recent decades. One group of these products, the polihydroxylated chalcones, exhibit antiviral, antitumoral, anti-inflammatory, antimicrobial.
activities and applications of therapeutic effects \(^{21}\) have been reported. Synthesis of 2-\ni\-cyclohex-3-ene derivatives is important key intermediate in today's chemistry.

Substituted pyrroles and their analogues have been used as precursors for synthesis of various biologically active molecules, such as antitumor agents,\(^ {22}\) antioxidative agents\(^ {23}\) and antimicrobial agents.\(^ {24}\)

Recently, it has been reported that acryl amide monomer may be formed in certain foods cooked at high temperatures. The highest concentrations of acryl amide have been identified in potato and grain-based foods that are cooked at very high temperatures (e.g., frying, grilling or baking) (Tareke et al. 2002). Acryl amide levels as high as 3500 g/kg has been reported in potato chips and French fries. Acryl amide is thought to form in food principally from the interaction of the amino acid asparagines with glucose or other carbohydrates.

Di-substituted oxazole and their analogues exhibit various biological activities, however, in literature; methods are available for the facile synthesis of disubstituted oxazole. Oxazoles and Oxazolidinones have attracted attention as a new class of orally active synthetic antibiotics with a unique mechanism of bacterial protein synthesis inhibition.\(^ {25,26}\)

In the recent years many methods have been reported for the synthesis of various pyrazolones derivatives.\(^ {27-30}\) Synthesis and application of 1, 3, 4, 5-tetrasubstituted pyrazoles.\(^ {31}\)

Molecular chirality's plays a very important role in science and technology. Chiral molecules may exist in either left-handed or right-handed form depending on the absolute configuration of the molecule.

Substituted pyrazol, thiazolidone and their analogues have been a great success in the field of modern drug discovery processes, both are powerful biding blocks for forming heterocyclic combinatorial rows for modeling of potential biological active compounds. The members of this series of 2, 3-diaryl-1, 3-thiazolidin-4-ones were reported to be highly effective in inhibiting the cytopathic effect of HIV-1 in human T-lymphocyte cells.\(^ {32}\)

Stable nitrones are experiencing expanding application today as spin trapper,\(^ {33}\) as potential therapeutic agents,\(^ {34}\) and as synthetic intermediates.\(^ {35}\) N-tert-butyl-\(\alpha-\)
phenyl nitrone (PBN) is a commonly used free-radical spin trap. It has been shown to reduce the number of emboli-induced cerebral microinfarction in the rabbit cortex and prevent neoplasia by its radical scavenging activity and its ability to inhibit cyclooxygenase-2-activity at the catalytic level. Reported to inhibit the induction of nitric oxide synthase (iNOS), thereby preventing the overproduction of nitric oxide (NO). Green sock and Wiebe studied the effect of substituents on the rate at which C-aryl nitrones reacted with various radical species generated from the pulse radiolysis of water.\(^{36}\)

A series of compounds 3-aryl-piperazinone inhibitors of protein geranylgeranyltransferase-I (PGGTase-I)\(^{37}\) 4, 5-disubstituted-thiazolyl amides, derivatives of 4-hydroxy-piperidine and of 4-$N$-methyl piperazine, were synthesized and tested as anti-inflammatory agents, 3D-QSAR studies of aryl-piperazines as $\alpha_1$-adrenoceptor antagonists.

Having successfully synthesized the derivatives of Schiff bases, imidazol, pyrrole, oxazole, pyrazolone, thiazolidone and nitrone series. We planned to evaluate their anti-microbial activities by agar diffusion method.\(^{38}\)

In the recent years, microwave-assisted organic synthesis has shown significant improvement in the generation of combinatorial libraries of small molecules.\(^{39}\) In general, microwave irradiation was found to be very useful to accelerate the rate of reaction of various thermally conducted reactions and also this technique was found to be very useful to improve an overall yield and reaction selectivity.\(^{40}\) Moreover, microwave chemistry assure safe and reproducible experimental procedures.

Keeping these factors in view, it was thought worthwhile to synthesize a series of compounds having different heterocyclic moieties with variety of substituents at different positions.
The present work is broadly divided into five parts.

**PART-I**

This part is divided into three sections.

**Section- A**

**Synthesis of 4-formyl pyrazoles.**

4-formyl pyrazoles are synthesized by Vilsmeier-Haack formylation of phenyl hydrazones.

Formyl pyrazoles are important key intermediate for synthesis of different heterocycles.$^{41}$

![Chemical structure of 4-formyl pyrazoles](attachment:image.png)

Where $R=R_1=\text{Cl, Br, OMe, H, NO}_2, \text{CH}_3, \text{etc.}$

*Reagents and conditions:*

a) Cat. $\text{H}_2\text{SO}_4$, EtOH, Reflux, 2-6 hr, 85-95%

b) DMF- $\text{POCl}_3, 0^\circ\text{C}-\text{RT}$, Overnight stirring, 83-90%

**Section- B**

**Synthesis of Schiff’s Bases:**

Schiff bases are important intermediates for the synthesis of some bioactive compounds such as $\beta$-lactams.$^{42-44}$ Schiff bases are prepared by condensation of heteroaromatic amines with formyl pyrazoles.
Section- C

Synthesis of Substituted Imidazoles.

Earlier, Olofson et al\textsuperscript{45} reported synthesis of 1, 5-disubstitued imidazoles by N-alkylation of 4(5)-aryl- or 4(5)-alkyl-imidazoles, which gives a mixture of 1, 4- and 1, 5-disubstituted imidazoles.

Reagents and conditions:

Method A: TOSMIC, DMF: methanol, potassium carbonate, 0°C-RT, 2hr. 65-74%.

Method B: Microwave-Irradiation, TOSMIC, DMF: methanol, potassium carbonate, 100°C, 10-15 min. 82-92%.

Microwave assisted synthesis of substituted imidazoles facilitates rapid synthesis of wide range of imidazole derivatives along with several advantages.
PART-II

This part is divided into four sections.

Section- A

Synthesis of chalcones (α-β unsaturated ketones)

A large number of natural flavonoids with biological activity have been identified in recent decades. One group of these products, the polyhydroxylated chalcones, exhibits antimicrobial activity.

\[
\begin{align*}
\text{Ar} & \quad \text{H} + \quad \text{Ar}_1 & \quad \xrightarrow{\text{aq. NaOH, MeOH}} & \quad \text{Ar} & \quad \text{Ar}_1 \\
0^\circ \text{C} - \text{RT}, 2-6 \text{ hr}
\end{align*}
\]

Where \( \text{Ar} = \text{Ar}_1 \) = Aromatic (unsubstituted, substituted), Heteroaromatic (unsubstituted, substituted).

Section- B

Synthesis of 2-oxo-cyclohex-3-ene derivatives from chalcones

\[\text{Ar} - \text{H} + \text{Ar}_1 \xrightarrow{\text{Method A}} \begin{array}{c}
\text{Method A: Ethyl acetoacetate, aq. NaOH, MeOH, 0^\circ \text{C}- \text{RT}, 2-6 \text{ hr. This method gives mixture of products [1 (50%), 2 (20%) and 3 (30%)].}} \\
\text{Method B: Ethyl acetoacetate, MeCN, MgCl}_2, \text{Et}_3\text{N, 10-25^\circ \text{C, 2.5 hr. This method gives only one product (1 with 80-90% yield).}}
\end{array}\]

Section- C

Synthesis of 1, 3, 4-trisubstituted pyrroles from chalcones.
Substituted pyroles & their analogs have been used as precursors for synthesis of various biologically active molecules.

Section- D

Synthesis of acryl amide derivatives.

Where Q is aromatic, heteroaromatic (unsubstituted, substituted)

Reagents and conditions:

a) THF, HOBT, EDCI, DIEA, 0°C-RT, 2-6 hr. 70-81%.

Acryl amide was synthesized by using cinnamic acid, aromatic amine and coupling agents such as HOBT and EDCI.46
Synthesis of 1, 3, 4-trisubstituted pyrroles from acryl amides.

Where Q is aromatic, heteroaromatic (unsubstituted, substituted)

Reagents and conditions:

a) DMSO: ether, NaH, 0°C-RT, 1-2hr, 70-90%.

b) Acid derivatives (Ar), THF, HOBt, EDCI, DIEA, 0°C-RT, 3-6 hr. 74-90%.

PART-III

This part is divided into three sections.

Section- A

Synthesis of oxazole derivatives.

Oxazoles and oxazolidinones have attracted attention as a new class of orally active synthetic antibiotics.
Reagents and conditions:

**Method A**: CH$_3$COONa, Ac$_2$O, reflux, 2-3 hr, 50-75%.

**Method B**: Microwave Irradiation, CH$_3$COONa, Ac$_2$O, reflux, 10-15 min, 72-92%.

Section- B

Condensation of 4-formyl pyrazoles with pyrazolone and reduction.
Reagents and conditions:
a) Cat. amount CH₃COONa, CH₃COOH, reflux, 2-3 hr, 70-90%.
b) NaBH₄, THF, CH₃COOH (cat.), -10°C to RT, 2-3 hr, 62-90%.

Section C

Condensation of 4-formyl pyrazoles with 2-thioxo-thiazolidin-4-ones.

\[
\text{Conditions: a) Cat. amount CH}_3\text{COONa, CH}_3\text{COOH, reflux, 2-3 hr, 82%. b) SnCl}_2\cdot\text{H}_2\text{O, EtOH, reflux, 2-3 hr, 90%. c) (I) Acid chlorides, THF, DIEA, 0°C-RT, 2-6 hr. 74-80%. (II) Different chloroformates, DIEA, THF, 0°C-RT, 2-3 hr. 80-89%. (III) Different isocyanates, toluene, reflux, 2-8 hr, 65-80%.}
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PART-IV

This part is divided into three sections.

Section- A

Synthesis of Schiff’s bases of formyl pyrazoles.
**Section-B**

**Synthesis of nitrone derivatives:**

Stable Nitrones are experiencing expanding applications as spin traps, potential therapeutic agents, and as synthetic intermediates. N-tert-butyl-α-phenyl nitrone (PBN) is a commonly used free-radical spin trap.

**Reagents and conditions:**

a) Oxone, MeOH, H₂O, reflux, 2-3hr, 60-82%.

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**Section-C**

**Synthesis of piperazin-2-one derivatives:**

A series of compounds 3-aryl-piperazinone inhibitors of protein geranylgeranyltransferase-I (PGGTase-I) 4, 5-disubstituted-thiazolyl amides, derivatives of 4-hydroxy-piperidine and of 4-N-methyl piperazine, were synthesized and tested as anti-inflammatory agents, 3D-QSAR studies of aryl-piperazines as α₁-adrenoceptor antagonists.
**Reagents and conditions**

a) DIEA, THF, 0°C-RT, 2-4 hr, 82%.

b) BrCH$_2$COOEt, DIEA, THF, 0°C - RT, 2-4 hr, 80%.

c) aq. NaOH, EtOH, 0°C - RT, 2 hr, 90%

d) THF, HOBr, EDCI, DIEA, 0°C - RT, 2-6 hr. 85%.

e) SnCl$_2$ .2H$_2$O, EtOH, reflux, 2-3 hr, 90%.

f) (I) Acid chlorides, THF, DIEA, 0°C-RT, 2-6 hr. 74-80%. (II) Different chloroformates, DIEA, THF, 0°C-RT, 2-3 hr. 80-89%. (III) Different isocynates, toluene, reflux, 2-8 hr. 80%. (IV) Different sulphonyl chlorides, DIEA, THF, 0°C-RT, 2-3 hr. 80-89%.

**PART-V**

Activity evaluation of Imidazoles, Pyrrole, Oxazole, Pyrazolone, Thiazolidone and Nitrone series.
Having successfully synthesized the derivatives of Imidazol, Pyrrole, Oxazole, Pyrazolone, Thiazolidone and Nitrone series. We planned to evaluate their biological activities. These were evaluated for the antifungal activity against the strains of *Candida albicans* ATCC 10231 (Fluconazole, Ketaconazole, clotrimazole sensitive) by agar diffusion method. For the antibacterial testing the compounds were screened against *Staphylococcus aureus* (gram positive bacteria), *E Coli* (gram negative bacteria) and *Pseudomonas aeruginosa* (gram negative) by agar diffusion method. Ampicillin, Streptomycin again a broad-spectrum antibiotic active against both gram positive and gram-negative organisms were taken as a standard for antibacterial testings. The evaluation of the synthesized compounds for antifungal activity was carried out by standard literature procedure using broth dilution method and minimum inhibitory concentration was determined by visual comparison with the negative control tubes.

Abbreviation:

**TOSMIC**: p-Tolunesulphonylmethyl isocyanide.

**DMF**: Dimethyl formamide.

**PTSA**: p-Toluene sulphonic acid

**HOBt**: 1-Hydroxybenzotriazole hydrates.

**EDCI**: 1-ethyl-3- (3-dimethyl-aminopropyl) carbodiimide

**DIEA**: N-Ethyldiisopropylamine.
REFERENCES:


