ABSTRACT

Heterocyclic chemistry is a branch in some quise has been inseparable from man kinds origin or history since it fulfils one of our basic needs. Heterocycles occupy a key position in the area of drugs and pharmaceuticals. Almost 80% of the drugs in clinical use are based on heterocyclic constitution. The cell which is the unit of human body, chooses heterocyclic substances for some of the most important functions as vitamins, coenzymes and components of nucleic acid.

There are vast number of pharmacologically active heterocyclic compounds and many of these are life saving drugs. Some of these are natural products like penicillin, cephalosporin and vinblastine. A large majority are the synthetic heterocyclics, have found wide spread use as drugs and pesticides. Some of them are valuable intermediates in organic synthesis. The successful application of heterocyclic compounds in many ways and their appeal as materials in applied chemistry in more fundamental and theoretical studies ensures a limitless scope of structurally novel compounds with a wide range of physical, chemical, biological properties and broad spectrum of chemical reactivity useful in the synthesis of specifically fictionalised structures.

The chemistry of heterocyclic compounds is challenging but at the same time a handsomely rewarding field for study. Each year witnesses the growing inclusion of many thousands of heterocyclic compounds in literature, on account of their intrinsic potential. The routes adopted for the synthesis of the new entrants to this large family vary from time honoured methods and variations of old themes to entirely novel procedures. Any modifications of an existing method or new synthetic route of these compounds is, therefore of interest, and merits for a detailed study.

The research work entitled, "Synthesis and Biological activity studies of some Nitrogen and Sulphur containing Heterocyclic compounds", is divided into two sections. The first section deals with the synthesis of heterocyclic compounds in 1,4-dihydro pyridines, pyrimidine-2-thiones/ones, 1-acety pyrimidine-2-thiole/ols pyrazines, 2-pyrazolines, and 4-thiazolidinones. The second section deals with the biological activities like anti microbial (antibacterial, and antifungal), anthelmintic and insecticidal activities of synthesized heterocyclics.
SECTION A: SYNTHESIS OF THE HETEROCYCLIC COMPOUNDS

CHAPTER TWO: *Synthesis and characterization of various 1,4-dihydro pyridine derivatives.*

Hantsch 1, 4-dihydopyridine (1,4-DHP:dialkyl 1, 4-dihydro-2,6-di-methyl pyridine-3, 5-dicarboxylates) are said to be the most important class of calcium modulators. Some of these, nifedipine, amiodipine, isradipine etc., have been commercialized and are known as vital drugs in the treatment of angina and hypertension due to their vasodilator properties. The 1,4-dihydopyridines are hydrogen transferring coenzymes of most importance in biological system. They have been reported to possess weak analgesic, curare like properties, antitumour and coronary dilating activities.

Methylacetoacetate on treatment with different aromatic aldehydes in the presence of ammonia and ethanol gave 1, 4-dihydro-2, 6-dimethyl-4-(aryl substituted) pyridine-3, 5-dicarboxylic acid dimethyl ester. The ester on treatment with α-naphthylamine in the presence of dioxane gave 1, 4-dihydro-2, 6-dimethyl-4-(aryl substituted) pyridine-3, 5 di α-naphthamide. In another series, the 1, 4-di hydro-2, 6-di methyl-4-(aryl substituted) pyridine-3, 5-di carboxylic acid di methyl ester on treatment with β-naphthyl amine in the presence of dioxane gave 1,4 di hydro-2, 6-di methyl-4-(aryl substituted) pyridine-3, 5-di β-naphthamide.

The structures of these compounds were confirmed by I.R. and H-NMR spectroscopy.

\[ R=\text{C}_6\text{H}_5, 4-\text{OCH}_3, \text{C}_6\text{H}_4, 4-\text{Cl. C}_6\text{H}_4, 2-\text{furyl, 4-OH-3-OCH}_3, \text{C}_6\text{H}_3 \]

\[ R=\text{C}_6\text{H}_5, 4-\text{OCH}_3, \text{C}_6\text{H}_4, 4-\text{Cl.C}_6\text{H}_4, 2-\text{furyl, 4-OH-3-OCH}_3, \text{C}_6\text{H}_3. \]

Pyrimidines from a part of potential biological activities like antimicrobial, anticancer, and antileishmanial activities. Pyrimidines forms a basic constituent of D.N.A. and R.N.A. double helix structure. Some naturally occurring alkaloids, terpenes vitamin-B₁, barbiturates and uric acid are containing a pyrimidine ring and possess diverse biological activities.

The synthesis involves the condensation of p-chloroacetophenone with various aromatic aldehydes to yield subsequent chalcone derivatives, which on treatment with thiourea and urea gives pyrimidine-2-thiones and pyrimidine-2-one respectively, and on further reaction with acetyl chloride give 1-acetyl pyrimidine-2-thiols and 1-acetyl pyrimidine-2-ols respectively. Structure of these compounds were determined by IR and N.M.R. spectras.

\[ Y = -S, -O \]
\[ R = C₆H₅, 4-OCH₃C₆H₄, 4-ClC₆H₄, 2-furyl, 4-OH-OCH₃, C₆H₃ \]

CHAPTER-FOUR: *Synthesis and Characterization of Various Pyrazine derivatives:*

Pyrazine or, 1,4 diazine is a symmetrical molecule as the nitrogen atoms occupy the 1,4- positions. Pyrazine occurs naturally though not in appreciable amounts but several polycyclic derivatives of pyrazine ring system such as pteridine and phenazine occur in nature. The pyrazines have long been of interest to medicinal chemists. Their derivatives, many of which are natural products have proven to be useful as antibiotics,
diuretics and anti-tumor agents. Structure of this compounds are determined by using the IR and NMR spectras.

\[ \text{CON=CH} - \text{R} \]

\[ \text{CON=CH} - \text{R} \]

R = C₆H₅, 4-OCH₃C₆H₄, 4-ClC₆H₄, 2-furyl, 4-OH-OCH₃, C₆H₄, C₆H₄OH

**CHAPTER- FIVE: Synthesis and characterization of various 2-pyrazoline derivatives:**

Pyrazolines are important nitrogen containing heterocycles possessing diverse biological activities. The pyrazolines are effective bleaching agents. The sulfonamides based on pyrazolines are of particular interest, for instance, orisul has bacteriostatic action in vivo. Substituted pyrazoles which are potent and selective inhibitors of cyclic guanosine 3', 5'-monophosphate phosphodiester having utility in a variety of therapeutic areas including the treatment of cardiovascular disorders such as angina, hypertension, heart failure and other sceleroses.

The synthesis involves the condensation of p-chloro acetophenone with various aromatic aldehydes in the presence of NaOH and ethanol to form chalcones. The chalcones on treatment with phenylhydrazine hydrochloride and 2, 4-dinitrophenylhydrazine cyclise to form various substituted pyrazolines and structure of compounds are determined by using the I.R. and N.M.R. spectras.

\[ \text{Cl} - \text{R} \]

\[ \text{Cl} - \text{R} \]

R = C₆H₅, 4-OCH₃, C₆H₄, 4-ClC₆H₄, 2-furyl, 4-OH-3-OCH₃C₆H₃
CHAPTER SIX: *Synthesis and characterization of various 4-thiazolidinone derivatives:*

Thiazole derivatives found to possess diverse biological activities like fungicides, antibiotics, vitamins and penicillin which are used in treatment of various infections. These are containing the thiazolidin nucleus. Sulfathiazole is an important bacteriostatic sulfadrug, acetazolamide and methazolamide are powerful diuretics and all these are thiazole derivatives. Vitamine-\(B_1\) (thiamine) an important thiazole derivative which is used in Beriberi.

The synthesis includes the preparation of Schiff bases by reacting various sulfonamides like dapsone and sulphadiazine with various aromatic aldehydes, which on further reacting with thiomalic acid gives the 4-thiazolidinones whose structures have been confirmed by IR and NMR spectra.

\[
\begin{align*}
\text{R}= & \text{C}_6\text{H}_5, 4\text{OCH}_3\text{C}_6\text{H}_4; 4\text{-ClC}_6\text{H}_4; 2\text{-furyl}; 4\text{-OH-3-OCH}_3\text{C}_6\text{H}_3
\end{align*}
\]

**SECTION B: BIOLOGICAL ACTIVITY STUDIES OF SYNTHESISED HETEROCYCCLIC COMPOUNDS**

CHAPTER SEVEN: *Anti-microbial activity studies:*

In this chapter, the result of antimicrobial activity of synthesised compounds have been reported. For this present study filter paper disc diffusion method was used. Activity of the compounds were determined in 2% and 4% solutions in DMF, against four bacteria and four fungi. The bacteria tested were *Streptococcus aureus, Escherichia coli, Bacillus subtilis,* and *Vibrio cholerae.* The fungi tested were *Aspergillus niger, Trichoderma sps.*,....
Aspergillus parasitica and Chrysosporium sps. The activity of these compounds were compared with standard drugs streptomycin for bacteria and gresiofulvin for fungi.

The synthesized compounds showed moderate to good antimicrobial activity. The pyrazine derivative showed good activity. The chlorophenyl and 2-furyl derivatives showed good activity. Almost maximum number of compounds in the pyrimidine and 4-thiazolene groups showed good activity.

CHAPTER-EIGHT: Anthelmintic activity studies.

4% and 2% solutions of synthesized heterocyclic compounds were prepared in ethylene glycol. Same concentrations (4% and 2%) of standard drug pyrazine hydrochloride is also prepared in ethylene glycol. Watkins method was adopted for evaluation of the anthelmintic activity. Earth worms were selected for the study 4% and 2% solutions. In petridish, 25 ml normal saline solution and 2 ml of test sample solutions are prepared. Two living earth worms of nearly equal size, washed with normal saline solution, are transferred into petridish. Same experiment is performed with the standard. The time taken by earth warms to become motionless was noted as paralytic time and the time of death was noted as lethal time. Among the synthesized compounds the p-chloro phenyl and pyrazine derivatives showed good activity.

CHAPTER NINE: Insecticidal Activity Studies.

Cockroaches were selected for the study. Acetone solution of the synthesized compounds was injected in the abdominal region of the cockroach. The time of death was noted as knock down value (K.D. Value) Cypermethrin 25% E.C. was used as standard. The synthesized compounds showed moderate to good activity.