ABSTRACT

The research work entitled, "Synthetic and biological activity studies of Heterocyclic compounds containing Nitrogen and Sulphur" is divided into two sections and these includes eight chapters. The first section deals with the synthesis of heterocyclic Compounds like pyrimidine-2-thiones/ones, pyrimidines-2-ones/ols, benzimidazoles, 4-thiazolidinones and pyrazolines derivatives. The second section deals with the biological activities like antimicrobial (antibacterial and antifungal), anthelmintic and insecticidal activities of synthesised heterocycles.

Chapter One : Introduction

This is a introductory chapter and it incorporates, in brief about the importance of heterocyclic compounds and their classification. Literature survey of previously prepared pyrimidines, benzimidazoles, thiazolidinones and pyrazolines are cited in this chapter. Structure elucidation of new synthesised heterocyclic compounds can be made by modern spectroscopic techniques viz. infrared, nuclear magnetic resonance, ultraviolet spectroscopy and Mass spectrometry. Chromatographic techniques like TLC and Gas chromatography can be used for checking the purity of compounds. Some of the applications of these physical methods are briefly reviewed in this chapter.

Infrared absorption spectroscopy is based on the differential absorption of infrared radiations by molecules leading to vibrations of bonds. Different bonds (C - C, C = C, C ≡ C, C=O, O-H, N-H, etc.) have different vibrational frequencies and we can detect the presence of these bonds in an organic molecule by identifying this characteristic frequency as an absorption band in the infrared spectrum.

Nuclear magnetic resonance spectroscopy is based on the magnetic properties of certain atomic nuclei, notably the nucleus of the hydrogen atom the proton. Studying an organic molecule by NMR spectroscopy enables us to record difference in the magnetic properties of the various
nuclei present, and deduce in large measure what are the positions of these nuclei within the molecule.

Ultraviolet absorption spectroscopy is based on the differential absorption of ultraviolet radiation by molecules, leading to transitions of energy levels of molecules. The strength of ultraviolet spectroscopy lies in its ability to measure the extent of multiple bond or aromatic conjugation within molecules.

Mass spectrometry is used in two principal ways

(a) To Measure relative molecular masses (molecular weights) with very high accuracy; from these can be deduced exact molecular formulae;

(b) To detect within a molecule the places at which it prefers to fragment, from this it can be deduced the presence of recognisable groupings within the molecule.

Chromatographic Techniques:

Among all the different type of separation methods available, chromatography has the unique position of being applicable to all types of problems in all areas of science. The technique of chromatography is based on the difference in the rate at which the components of mixture move through a porous medium (stationary phase) under the influence of some solvent or gas (moving phase). Based on the nature of the stationary and moving phase, chromatography is divided into (a) Partition chromatography (b) Absorption chromatography (c) Gas chromatography (d) Paper chromatography (e) Thin layer chromatography and (f) Column chromatography.

Biological Activities Studies:

To evaluate the pharmacological importance, the new synthesised heterocycles are tested for their curative properties against various
diseases. The biological activity studies carried are (1) **antimicrobial** (2) **anthelmintic** and (3) **insecticidal activities**.

**(1) Antimicrobial Activity Studies:**

Microbes like bacteria and fungi are used to develop the culture using a suitable culture media and new synthesised heterocycle compounds are tested, *in-vitro*, for their activity on microbes against a known standard substance. The antimicrobial activity is measured, *in-vitro*, in order to determine the potency of antimicrobial agent and the sensitivity of the given microorganism to the known concentration of the drug.

**(2) Anthelmintic activity Studies :**

The organisms like *Phretima posthuma* are used for the anthelmintic, *in-vitro*, evaluation of the new synthesised heterocyclic compounds by calculating the paralysis time and death time of the organism against a known standard substance.

**(3) Insecticidal Activity Studies :**

The ultimate practical objective of insect control is to lessen the extent of insect damage to human possessions or health by suppression or prevention of insect out break. Insecticidal activity is determined by injecting the acetone solution of new heterocyclic compounds into the abdominal region of insects, and the observations are recorded in terms of knock down values in minutes.
SECTION – A SYNTHESIS OF HETEROCYCLIC COMPOUNDS

Chapter – two:

Synthesis and structure elucidation of substituted pyrimidine-2-thiones/ones and 1-acetyl pyrimidine-2-thiols/ols derivatives.

Pyrimidines form a part of potential biological active compounds like antimicrobial, anticancer and antileishmanial activities. Pyrimidines form a base constituent of DNA and RNA double helix structure. Some naturally occurring alkaloids; caffeine; theobromine; vitamin-B₁; barbiturates and uric acid are containing a pyrimidine ring and possess diverse biological activities.

The synthesis involves the condensation of various acetophenones (e.g. p-hydroxy acetophenone and p-methoxy acetophenone) derivatives with various aromatic aldehydes to yield subsequent chalcone derivativies, which on treatment with thiourea and urea gives pyrimidine-2-thiones and pyrimidine-2-ones respectively, and these on further reaction with acetyl chloride give 1-acetyl-pyrimidine-2-thiols and 1-acetyl-pyrimidine-2-ols respectively. Structures of the compounds are determined using IR and NMR spectras.

\[ X - \text{OH, -OCH}_3 \]
\[ R = \text{H, 4-Cl, 4-OCH}_3, \text{furyl} \]
\[ Y = \text{-S, -O} \]

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\[ R = \text{H, 4-Cl, 4-OCH}_3, \text{furyl} \]
\[ Y = \text{-SH, -OH} \]
**Chapter Three:**

**Synthesis and structure elucidation of substituted benzimidazole derivatives.**

Benzimidazoles show a great biological activity like antifungal, antibacterial, anti-inflammatory, antiviral etc. Benzimidazole ring is present in vitamin-B_{12} structure.

The synthesis involves the condensation of O-phenyl diamine with various amino acids like glycine, alanine, valine, leucine and isoleucine. The structure is elucidated by IR and NMR spectras.
Chapter-Four:

**Synthesis and structure elucidation of substituted 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 thiazolidine nucleus. Sulfathiazole an important bacteriostatic sulfadrug, acetazolamide and methazolamide are powerful diuretics and all these are thiazole derivatives. Vitamin-B₁ (thiamine) an important thiazole derivative is used to cure beriberi.

The synthesis includes the preparation of Schiff bases by reacting various sulfonamides like sulphaguanidine and sulphadiazine with various aromatic aldehydes, which on further reacting with mercapto acetic acid (thioglycolic acid) gives the 4-thiazolidinones whose structures have been confirmed by IR and NMR spectras.
Chapter-Five:

**Synthesis and structure elucidation of substituted 2-pyrazoline derivatives.**

Substituted pyrazoles attracted considerable attention due to their antimicrobial, insecticidal, antiinflammatory and antidiabetic properties. Substituted pyrazoles are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate, phosphodiesterase, having utility in a variety of therapeutic areas, including the treatment of various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis. It is also known that some of the pyrazole derivatives exhibit selectivity for inhibition for CGMP PDE 's rather than cyclic adenosine 3',5'-monophosphate diesterases (CAMP.PDE's) and as a consequence of this selective PDE inhibition, CGMP levels are elevated, which in turn can give rise to beneficial anti-aggregatory, antivasopastic and vasodilatory activity as well as potentiation of the effects of endothelium-derived relaxing factors (EDRA) and nitrovasodilators.

The synthesis involves condensation of various acetophenones like p-hydroxy and p-methoxy acetphenone with various aromatic aldehydes to yield substituted chalcones which on cyclisation with hydrazine hydrate gives 2-pyrazolines which on further reacting with glacial acetic acid gives 1-acetyl 2-pyrazolines whose structures are confirmed by IR and NMR spectras.
SECTION - B BIOLOGICAL ACTIVITY STUDIES OF SYNTHESISED HETEROCYCLIC COMPOUNDS

Chapter-Six: Antimicrobial Activity Studies

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

On going through the results of antimicrobial activity of pyrimidines, it was observed that chlorophenyl and methoxyphenyl derivatives of all the four series shows good activity against all tested organisms. Among the benzimidazoles, derivatives containing ethyl amine group shows highest activity while their isobutyl amine derivative shows good to moderate activity against all tested organisms.

The comparision of the results of antimicrobial activity of both series of thiazolidinones, it was observed that methoxyphenyl and furyl derivatives show good to moderate activity on all tested organisms.

The antimicrobial activity of pyrazolines of first series containing methoxyphenyl and chlorophenyl moiety shows highest activity while methoxyphenyl and furyl derivative of the second series shows highest activity against all tested organisms.
Chapter-Seven : Anthelmintic activity Studies

This chapter deals with the anthelmintic activity of synthesised heterocycles. The activities were determined using earthworms by 'Watkins' method.

Among the synthesised compounds, methoxy derivatives show good to moderate activity in all four series of pyrimidines; isopentylamine derivatives of benzimidazole; chlorophenyl derivative of both series of thiazolidinones and both serirs of 2- pyrazolines have shown highest anthelmintic activity.

Chapter- Eight : Insecticidal Activity Studies

The insecticidal activity of synthesised pyrimidine, benzimidazole, thiazolidinone and pyrazoline derivatives were determined on cockroaches and $K_D$ values are noted.

The results of insecticidal activity revealed that chlorophenyl derivatives of all series of pyrimidines; 2- isopentylamine benzimidazole; chlorophenyl and phenyl derivatives of both series of thiazolidinone and 2-pyrazolines possess moderate to good insecticidal activity compared to the standard.