SYNOPSIS

Heterocyclic synthesis has emerged as powerful technique for generating new molecules useful for Drug Discovery. Heterocyclic compounds provides scaffolds on which pharmacophore can arrange to yield potent and selective drugs. Heterocyclic compounds containing two or more nitrogen atoms represent a very important group of organic compounds because many of them exhibit significant biological activity and pharmacological effects.

Pyrazole class of compounds are found to possess anti-hypertensive, antibacterial, anti-inflammatory and anti-tumor properties. Particularly, disubstituted pyrazoles have received immense attention in drug research after introduction of celocoxib in the market for various inflammatory conditions. Pyrimidines being an integral part of DNA and RNA, imparts to diverse pharmacological properties like bactericidal, anti-leishmenial, anti-hypertensive, anti-HIV, anti-cancer, anti-malarial and anti-filarial activities.

The importance of bridged pyrimidines with pyrazoles (pyrimidinylpyrazoles), is common source for the development of new potential therapeutic agents. Some of these derivatives are found to have anti-proliferative, anti-pyretic and anti-inflammatory activity. Pyrazolopyrimidines are also of considerable chemical and pharmacological importance, many of them are successfully used as anti-cancer agents and as hypnotics. Recent success of zaleplon and Indiplon as sedatives and hypnotics are the best results in the research of pyrazolopyrimidines as biodynamic molecules.
During the recent past tremendous upsurge in the study of metallo drugs has been done with ligands having different donor atoms. These metallo drugs offer unique advantage in overcoming problems associated pharmacodynamic properties of some organic moieties. It is reported that metal complexes of pyrimidines have anti-tumor, anti-leukemic and radiodiagnostic properties.

Many conventional heterocyclic syntheses involve longer reaction time, high temperature, unsatisfactory yield, cumbersome product isolation. Therefore, there is a need for versatile, simple and ecofriendly processes for the synthesis heterocyclic compounds. This can be achieved by using MORE (Microwave induced Organic Reaction Enhancement) chemistry.

Microwave-induced Organic Reaction Enhancement (MORE) Chemistry has received considerable attention in the recent years due to several advantages like short reaction time, ease work-up, excellent yields and cost-effectiveness. Moreover, it is environmentally friendly technique and is believed to be a step towards green chemistry. Since the appearance of pioneering reports on the application of microwaves for chemical synthesis in polar solvents, the approach has blossomed into useful technique for several reactions of synthetic importance.

Encouraged by these interesting reports on pyrazole-pyrimidine moieties, and applications of MORE chemistry in the synthesis of novel heterocyclics, in the present work, the author has synthesized some novel bridged /fused biheterocyclics comprised of pyrazole and pyrimidine moieties by conventional and microwave irradiation technique, which may be conveniently presented as follows.
1. Synthesis and biological activity of substituted pyrimidines and some of the metal complexes of Cu (II) and Ni (II).

2. Synthesis, biological and pharmacological activity of substituted pyrimidinylpyrazoles.

3. Synthesis, biological and pharmacological activity of pyrazolo(3,4-d) pyrimidines…, which are described in six different chapters.

Chapter one deals with general introduction and literature background, on pyrazoles and pyrimidines, and their biodynamic properties. Importance of microwave assisted synthesis of heterocyclic compounds was also dealt with. Metal complexes having biodynamic properties and their role in medicine is also discussed.

Second chapter begins with an detailed account of literature background, pharmacological activity of various pyrimidine derivatives followed by experimental procedure for the synthesis of pyrimidine derivatives. Ehtylcynoacetate, thiourea and different araldehydes were treated in the presence of potassium carbonate and ethanol to get 4-(substituted)-2-mercapto-5-cyno-6-oxo-1,6-dihydropyrimidine (PM$_1$ to PM$_{10}$). This reaction was carried out by conventional and MORE technique. By MORE technique enhanced yield, shorter reaction time have been reported. Further these pyrimidine derivatives were subjected for methylation in presence of methyl iodide to give 4-(substituted) -1-N-methyl-2-methylthio-5-cyno-6-oxo-1,6-dihydropyrimidine (PMM$_1$ to PMM$_{10}$). The synthesized compounds were characterized by various analytical techniques (UV, IR, $^1$HNMR and Mass Spectrometry) and screened for anti-microbial and anti-bacterial activity. Some compounds have shown promising activity against the organism tested.
Chapter three deals with and detailed account of pyrazole derivatives and their biodynamic properties, marketed products etc. It also describes a method for the synthesis of hydrazino compounds and its conversion into different pyrazole derivatives. 4- (substituted) -1 -N -methyl -2 -methylthio -5 -cyno -6 -oxo -1,6-dihydropyrimidine (PMM1 to PMM10) were treated with hydrazine hydrate to get 4- (substituted) -1 -N -methyl -2-hydrazino -5-cyno -6-oxo -1,6-dihydropyrimidine (PH1 to PH10), further this compound was converted into pyrazole derivative i.e., 5-amino -4-carbethoxy -1-[5 -cyano -4 - (substituted) -1 -N -methyl -6 -oxo -1,6 -dihydropyrimidin -2 -yl]-1H -pyrazole (PPA1 to PPA10). on treatment with ethyl -2-cyno -3-ethylacrylate. These reactions were carried out by both conventional and MORE technique. The synthesized compounds after their characterization were subjected for anti-inflammatory (invitro) and anthelmintic activity in addition to antibacterial and antifungal activities. Some of the compounds have shown promising activities.

Chapter four deals with the brief introduction of pyrimidinylpyrazoles followed by its synthesis. 4- (substituted) -1 -N -methyl -2-hydrazino -5-cyno -6-oxo -1,6-dihydropyrimidine (PH1 to PH10), was treated with acetyl acetone / ethyl acetoacetate in the presence of alcohol, yielded 2- (3,5- dimethyl -1H -pyrazol -1 -yl)-4- (Substituted) -1 -methyl -5-cyno -1,6 -dihydropyr -imidine -6-ones (PPAA1 to PPAA5) and 4-(Substituted) -1-methyl -2-(3-methyl -5-oxo -2,5 -dihydro -1H -pyrazol -1 -yl)-5-cyno -1,6 -dihydropyrimidine -6-ones (PPEA1 to PPEA5) respectively. The synthesized compounds were subjected for different analytical techniques for their characterization and screened for anti-bacterial, anti-fungal, anthelmintic and anti-inflammatory activity.
Chapter five describes pyrazolopyrimidines of pharmacological interest, and is divided into section A and section B.

Section A deals with the synthesis of \(3-\{(3-\text{Substituted})\text{amino}\}-4\text{-fluorophenyl} \text{amino}\)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (FPZPM\(_1\) to FPZPM\(_5\)). Ethylcyanoacetate was treated with ammonia to get cyanoacetamide, this was treated with KOH, DMS, CS\(_2\) in DMF to give bis-\(s\)-methylethylcyanoacetamide. This compound on reaction with fluorochloro aniline gave 1-\(s\)-methyl-1-[4-flouro 3-chloro-anilino] ethyleneacyanoacetamide (I). This compound was further treated with hydrazine hydrate to give 5-amino-3-\( (3-\text{chloro}-4-\text{fluorophenyl}) \text{amino}\) \(-1H\)-pyrazole-4-carboxamide (II), which was then converted to 3-\( (3-\text{chloro}-4-\text{fluorophenyl}) \text{-amino}\)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (III), on treatment with formamide. This compound on reaction with various aromatic amines in DMF yielded titled compounds.

Section B deals with synthesis of different \(N\)-(\(4\)-(2-oxoethoxy) phenyl)acetamido-5-(substituted)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (PZPM\(_1\) to PZPM\(_5\)). Paracetamol was treated with \(\alpha\)-chlooroethylacetate in presence of potassium carbonate and acetone to get \(p\)-acetamido (phenoxy) acetate (I), which was further treated with hydrazine hydrate to yield \(p\)-acetamido (phenoxy) acetyl hydrazide (II). Compounds (I) and (II) were also synthesized by MORE method. This intermediate was made to react with ethyl -2- cyan -3-ethylacrylate to get pyrazole derivatives. These compounds were reacted with various aromatic amines and triethyl orthoformate in acetic acid was yielded titled compounds.
Chapter six deals with introduction to coordination compounds, brief literature survey on metal complexes of pyrimidines, followed by synthesis of ligands and complexes. Some of these complexes were characterized by UV, IR, NMR, TGA/DTA and Magnetic susceptibility studies. The anti-bacterial and anti-fungal activity of these complexes were compared with ligands and some complexes were more active than ligands.

The related tables, results and discussions, summary and conclusions are reported in their respective chapters.

The work has resulted in the synthesis of biologically important heterocyclic compounds containing pyrazole-pyrimidine moieties.