Chapter-1: LITERATURE OVERVIEW

1.1. Introduction

Medicinal chemistry is the science that deals with the discovery and design of new therapeutic chemicals and its uses as medicines. The main objective of the medicinal chemistry is to synthesize the compounds that show promising activity as therapeutic agents with lower toxicity. Over the last few decades, compounds bearing heterocyclic nuclei have received much more attention of the chemist, due to their broad chemotherapeutic activities such as anti-inflammatory, anthelmintic, anti-tubercular, anti-fungal and anti-microbial activities. Due to such widespread applications of heterocyclic compounds in medicinal chemistry, present research work compiles synthesis and biological activities of heterocycles containing important pharmacophors such as thiazolidine-4-one, Pyrimidine, Pyrazoline, and 1,5-benzothiazepine with promising anti-bacterial, anti-fungal and anti-inflammatory activity.

Schiff bases and thiazolidinone have been proved to be the most useful framework for biological activities. They have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them.

From the last decade a lot of work is going on the thiazolidinone ring. Scientist had developed a lot of new compound related to this moiety. They have screened them for different biological activities to get a molecule which have good pharmacological activity with least adverse effects. The thiazolidinone is not only synthetically important scaffold but also possesses a wide range of promising biological activities [1]. Thiazolidinones are the derivatives of thiazolidine which
belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. Thiazolidine-4-one is the derivative of thiazole which belongs to five member heterocyclic ring system with multiple applications [2]. 4-Thiazolidinone ring system contains sulphur and nitrogen heterogeneous at position 1 and 3 respectively and keto group at position 4.

Thiazolidinones, with a carbonyl group at position 2 (a, Fig. 1) and position 4 or 5 (b, c, Fig. 1) have been widespread studied in last few decades. Numerous examples have appeared in the literature which describes their chemistry and uses [3-11].

![Fig. 1](image)

Among the 4-thiazolidinone derivatives (b, Fig. 1), substituents at the 2, 3 and 5 positions enhances the medicinal properties of thiazolidinone, thiazole with carbonyl group on fourth carbon has been considered as a magic moiety (wonder nucleus) which possess wide range of biological activities[12].

The synthesis of compounds belonging to thiazolidinone series constitute an important research area due to their interesting diverse pharmacological activities such as antibacterial, antifungal, anti-inflammatory, anticancer, and anticonvulsant properties[13-17].

2-(N,N-dimethylaminophenyl)-3-(6-chloro-2-benzothiazole-2-yl)-5H-thiazolidinone (Fig. 2) synthesized by the reaction between 4-{(Z)-[(6-chloro-1,3-benzothiazol-2-yl)imino]methyl}-N,N-dimethylaniline and thioglycolic acid was reported to be an excellent antibacterial agent [18].
D. S. Kundariya et al. synthesized 2-(substituted phenyl)-3-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (Fig. 3) by the reaction between N-benzylidene-1H-pyrazolo[3,4-b]pyridin-3-amine and mercaptoacetic acid which exhibited potent antifungal activity [19].

3-(6-chloro-1,3-benzothiazol-2-yl)-2-(2-nitrophenyl)-1,3-thiazolidin-4-one (Fig. 4) prepared by the reaction between (Z)-N-(6-chloro-1,3-benzothiazol-2-yl)-1-(2-nitrophenyl) methanimine and mercaptoacetic acid was revealed to be a potent anti-inflammatory agent possessing a thiazolidinone ring [18].

2-(4-nitrophenyl)-3-(4H-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-one (Fig. 5) synthesized by the reaction between (E)-1-(4-nitrophenyl)-N-(4H-1,2,4-triazol-4-yl)
Thioglycolic acid was reported to be an excellent anticonvulsant agent showing no signs of neurological deficit [19].

Kumar et al. synthesized a group of (E)-2-(4-chlorophenyl)-3-(((3-(4-(4-chlorophenyl)thiazol-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)methylene)amino)thiazolidin-4-one (Fig. 6) and screened them for anti-inflammatory and analgesic activities. They found that the presence of thiazolidinone ring have shown much better anti-inflammatory and analgesic activity [20].

Shih et al. synthesized a series of sydnonyl substituted thiazolidinone and thiazoline derivatives and evaluated for their antioxidant activity[21]. The antioxidant activity of derivatives of compound (Fig. 7) have been found to exhibit the significant DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging activity, comparable to that of vitamin E.
The thiazolidinone is not only synthetically important scaffold but also possesses a wide range of promising biological activities. Some thiazolidinone derivatives have better activity than standard drugs and could become a new drug for the market in future.

Chalcone is the soul of number of pharmacologically active heterocyclic compounds; many heterocyclic compounds can be synthesized starting from chalcones. The most common compounds of chalconoid group are the chalcones, which provide new class of medicines due to the physiologically and pharmacologically active moiety. Chalcones are 1,3-diarylprop-2-en-1-one, form a broad class of compounds containing two aromatic rings which are connected by a three carbon chain. Chalcones were found to have broad spectrum of biological properties such as antiviral, antimalarial, antimicrobial etc. Hence the synthesis of chalcones has generated huge interest for researcher and chemist to organic as well as medicinal. Chemically they are open-chain flavonoids in which the two aromatic rings are joined by a three carbon α, β-unsaturated carbonyl system as illustrated below.

Chalcones are abundantly present in nature starting from ferns to higher plants [22] and a number of them are polyhydroxylated in the aryl rings. In plants, chalcones are converted to the corresponding (2S)-flavanones in a stereospecific reaction.
catalyzed by the enzyme *chalconeisomerase*. This close structural and biogenetic relationship between chalcones and flavanones explains why they often co-occur as natural products.

Isolation of chalcone derivatives from nature requires a long and usually complicated procedure and time consuming, hence many research groups either isolated or synthesized or modified chalcones that possess antimicrobial activity. Given below is a brief account of various modifications reported on chalcones.

Prasad *et al.* synthesized 3-[1-oxo-3-(2,4,5-trimethoxyphenyl)-2-propenyl]-2H-1-benzopyran -2-ones (Fig. 8), that showed significant antimicrobial activity[23]. The study revealed that, substituted groups such as hydroxyl and methoxyl groups enhancing the activity. Similarly, Chalcones with halogen substituents like bromine and chlorine contributed favorably to the antifungal activity.

![Fig. 7- 3-[1-oxo-3-(2,4,5-trimethoxyphenyl)-2-propenyl]-2H-1-benzopyran -2-ones](image)

Karthikeyan *et al.* synthesized 3-aryl-1-(2,4-dichloro-5- fluorophenyl)-2-propen-1-ones (Fig. 8) showing antimicrobial activity, it was observed that halogens possess favorable lipophilic character required for antimicrobial activity[24].

![Fig. 8- 3-aryl-1-(2,4-dichloro-5- fluorophenyl)-2-propen-1-ones](image)

Stevaz *et al.* isolated a 2',4'-dihydroxy-3'-methoxychalcone (Fig. 9) from the methanolic extract of *Zuccagnia punctata* which exhibited antifungal activity[25].
Literature survey reveals that there are number of efficient and novel methods for synthesis of chalcones. The Claisen-Schmidt is one of the methods for synthesis of Chalcone in which aliphatic or aromatic ketone is condense with an aldehyde in the presence of alkaline hydroxide or EtONa[26] (Fig. 10).

Chalcones have been synthesized by V. Calvino and M. Picallo under sonochemical irradiation by Claisen-Schmidt condensation between benzaldehyde and acetophenone. A green method (combination of alkaline doped carbon catalyzed and ultrasound waves) have been applied to the synthesis of several chalcones with antibacterial properties two basic activated carbon (Na and Cs-Norit) have been used as catalysts [27].
There are number of biologically active heterocyclic compounds have been synthesized by chalcones.

Fig. 10- Different Heterocyclic Compounds from Chalcones

In medicinal chemistry, the chemist attempts to design and synthesize a medicine or a pharmaceutical agent which will benefit humanity. The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease [28]. The chemistry of heterocyclic compounds is the most important in the discovery of new drugs. The study of these compounds is of great interest both in theoretical as well as practical aspects [29]. Various compounds such as alkaloids, essential amino acids, vitamins, hemoglobin, hormones, large number of synthetic drugs and dyes also contain heterocyclic ring systems. Nitrogen containing heterocycles play an important role in medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes [30]. Among all heterocyclic compounds, Pyrimidines are one of the most important heterocycles exhibiting remarkable pharmacological activities because it is an essential constituent of all cells and thus of all living matter [31].
Pyrimidines [32] are the heterocyclic aromatic compounds similar to benzene and pyridine; it contains two nitrogen atoms at positions 1 and 3 of the six membered rings. Pyrimidine is a much weaker base than pyridine and soluble in water. Several Pyrimidines have been isolated from the nucleic acid hydrolyses. The metabolism of these Pyrimidines is unique and important to understand both biochemical utilization of these compounds and drug metabolism of pyrimidine derivatives [33].

In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. The presence of a pyrimidine uracil [34] and thymine [35] being constituents of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) and with cytosine [36] is one of the possible reasons for their activities [37]. In addition to this, Pyrimidines skeleton is also present in many natural products such as vitamin B$_1$ (thiamine), riboflavin and many synthetic compounds, such as barbituric acid [38] and Veranal [39] which are used as hypnotics [40].

Over the years Pyrimidine system turned out to be an important pharmacophors, interacting with the synthesis and function of nucleic acid e.g. HIV
drug Zidovudin [41], barbiturates such as thiopental sodium (Pentothal)[42] are often used as general anesthetics. Some diaminopyrimidines, such as trimethoprim [43] are powerful antimalarial drugs.

Khanage et.al, studied and reported the antimicrobial, anticonvulsant and anticancer properties of some new pyrimidine derivatives containing 1,2,4-triazole (Fig. 11). The compound 6-(2,4-dimethylophenyl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydro pyridine-2-thiol (Ar = 2,4-dimethoy phenyl) possess good antibacterial activity and Anticonvulsant activity[44].

Sridhar et.al; 2011, reported the synthesis and anticancer activity of novel pyrimidine derivatives, i.e. 4-(4-chlorophenyl)-6-(2,5-dimethylfuran-3-yl)pyrimidin-2-amine (Fig. 12) derivatives, from which chlorophenyl derivatives attained maximum activity [45].
Mohamed; 2011, reported the thesis on 2,4-disubstituted pyrimidine derivatives and evaluated its potential for the treatment of alzheimers disease. IC$_{50}$ values of the various synthesized compounds were compared with donepezil and galantamine. 2-(pyrrololidin-1-yl)-N-(3,4,5-trimethoxy benzyl) pyrimidin-4- amine (Fig.13) was found as the most potent drug [46].

Padmashri et al., reported the synthesis of 2- (2', 5' substituted indolideneamino- 3'- yl) - 4, 6- diarylpyrimidines (I) and 2 [2', 5'-substitutedindole-3'- yl) (phenyl azo)methylene imino]- 4, 6- Diaryl pyrimidine (II) (Fig.14) and screen them for their antimicrobial activity against the gram negative Bacteria possess good antibacterial activity[47].
Recently Monica Kachroo et al., reported 6-(4-substitutedphenyl)-4-pyridin-4-yl-1,6-dihydropyrimidin-2-thiol, 4-(4-substitutedphenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine and 6-(4-substitutedphenyl)-4-pyridin-4-yl-1,6-dihydropyrimidin-2-ol, which exhibit excellent anti-tubercular activity at the concentration of 3.12 μg/ml, moreover it has also exhibited good anti-inflammatory and antioxidant activities[48].

A large number of organic reactions can be carried out with higher yields, shorter reaction time or milder conditions and green protocol under microwave irradiation. S. Karpov et. al, describes a convenient procedure for the synthesis of pyrimidine from β-formyl enamide involves samarium chloride catalyzed cyclisation of β-formyl enamides using urea as source of ammonia under microwave irradiation(Fig.15)[49].

Pyrimidines are synthetically versatile substrates and hence can be used for the synthesis of a large variety of heterocyclic compounds. Pyrimidines occupy a distinct and unique place in our life. This heterocyclic moiety has great biological and medicinal significance. The versatile synthetic applicability and biological activity of these heterocycles will help the medicinal chemists to plan, organize and implement new approaches towards discovery of novel drugs.

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. Heterocyclic compounds [50] promote the life on earth as they are widely distributed in nature and essential for sustains of life. Many heterocyclic compounds due to their specific activity are employed in the treatment of many
infectious diseases. Their use in the treatment is attributed to their inherent toxicity to various pathogens. Among a wide range of heterocyclic compounds five membered heterocyclic compounds have been explored for the development of pharmaceutically important molecules. Five membered heterocycles like Pyrazolines have been found to display wide application as pharmaceutical and agrochemical agents.

Pyrazolines are well-known important nitrogen containing five membered heterocyclic bioorganic molecules. Pyrazole is a π-excessive aromatic monocyclic heterocycle containing two nitrogen atoms in a five membered 1,2-diazole ring. It was in the late nineteenth century that Fischer and Knoevenagel described the reaction of acrolein with phenylhydrazine [51] to provide a 2-pyrazoline type compound (a). Their experiment seems to be the first example of pyrazoline formation by the reaction of an α,β-enone with a hydrazine derivative. Later, Auwers et al. [52,53] corroborated that the product of this reaction was 1-phenyl 2-pyrazoline. During the last century, after these pioneering studies, numerous 2-pyrazolines were synthesized by the reaction of α,β-enones with hydrazines. This simple and convenient procedure has remained one of the most popular methods for the preparation of 2-pyrazolines.

![Pyrazoline Structure](image)

Pyrazoles exhibit aromatic character with properties resembling those of both pyrrole and pyridine. 1-Pyrazoline, 2-pyrazoline and 3-pyrazoline are the three partially reduced forms of the pyrazole structure with different positions of the double bonds and exists in equilibrium one with the other (Fig. 16). 2-pyrazoline exhibits the monoimino character and hence more stable than the rest even though all the three types have been synthesized [54].
FIG. 16- ALL THE THREE PARTIALLY REDUCED FORMS OF PYRAZOLINE

Pyrazoles and its derivatives, a class of well-known nitrogen heterocycles, occupy an prime position in medicinal and pesticide chemistry for their diverse biological activities. The pyrazoline ring is present as the core in a variety of leading drugs such as Celebrex, Sildenafil (Viagra), Ionazlac, Rimonabant and Difenamizole etc. Pyrazoline analogues have found use as building blocks in organic synthesis for designing pharmaceutical and agrochemicals.

In recent years, attention has increasingly been given to the synthesis of pyrazoline derivatives as a source of new antibacterial agents. Pyrazoline derivatives have been reported to possess diverse biological activities such as antibacterial [55], antifungal [56], analgesic [57], anticancer [58], anti-tubercular [59], anti-inflammatory [60], antidepressant [61], anticonvulsant [62], tranquilizing [63],
immunosuppressive [64], diuretic [65], antioxidant [66] and herbicidal [67] properties. Literature survey reveals several synthetic protocols for the synthesis of these compounds and the presence of this core in any molecule plays a key role in enhancing its pharmacological activity some are illustrated below.

Sivakumar et al. synthesized some novel 1,3,5-triphenyl-2-pyrazolines (Fig. 17) and evaluated their antimicrobial activity. All the compounds showed good activity against *E.coli* and poor activity against *S.aureus*. Compounds possessing chloro, methoxy, dimethoxy and bromo as substituents exhibited reasonable activity against all the organisms tested (< 0.309 μm) except against *S.aureus*. Compounds possessing halogens (-F and -Cl) as substituents showed very good activity (<88% reduction) against the fungi studied at 2 mg/mL. The results proved the importance of halogen substituents for antibacterial and antifungal activities [68].

![1,3,5-triphenyl-2-pyrazolines](image17)

Deshmukh et al. synthesized chloro substituted Δ^2-2-pyrazolines (Fig. 18) that showed antibacterial activity when assayed against some human pathogens [69].

![Chloro substituted Δ^2-2-pyrazoline](image18)
Prasad et al. synthesized 1, 3, 5-triphenyl-2-pyrazolines (a) and 3-(2”-hydroxyl naphthalene-1”-yl)-1,5-diphenyl-2-pyrazolines (b) (Fig. 19) which showed significant antidepressant activity [70].

![Fig. 19- 1, 3, 5-Substituted-2-pyrazolines](image)

Based on the biological activities exhibited by the pyrazoline compounds, Revanasiddappa et al., (2010) reported the synthesis and biological evaluation of some novel pyrazoline derivatives. The chalcones were converted into 1,3,5-trisubstituted pyrazoline derivatives (Fig. 20) by reacting with isoniazid (INH) in acidic medium (glacial acetic acid). The structures of newly synthesized compounds were established by spectroscopy. All the synthesized compounds were evaluated for their antibacterial and antifungal activities and it was found that most of the compounds were moderately active against both bacteria and fungi [71].

![Fig. 20- (3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone](image)

Madhav M. Kendre et al., reported the synthesis of 3-(2’-hydroxy-phenyl)-5-(4’-substituted phenyl)-2-Pyrazoline-\text{N}^1\text{-Carboxaldehydes} (Fig. 21) and screen them for their antimicrobial activity. From the results it is evident that most of chloro, bromo, iodo, hydroxyl and methyl groups exhibited good antimicrobial activity [72].
Dawane et al. synthesized some 1-(4-(4’-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1H-imidazo-5yl)-2-pyrazoline derivatives (Fig. 22) by the base catalyzed treatment of appropriate chalcones with 4-(4’-chlorophenyl)-2-hydrazone-thiazole in polyethylene glycol (PEG 400) as an alternative reaction solvent. All the synthesized compounds were tested for their antimicrobial activities. Most of the compounds showed potent antibacterial and antifungal activity [73].

Organic synthetic chemistry is now a fast growing research field in chemistry. Among the various organic compounds, heterocyclic compounds have been associated with various biologically activities. Due to bioactivity connected with heterocycle and ease of preparation, a number of researchers are takings keen interested into the study of this. Heterocyclic compounds containing nitrogen and sulphur have received considerable attention in recent years. Benzothiazepines are important nitrogen and sulfur containing seven member heterocyclic compounds,
which are of great interest in the area of drug discovery and development due to their broad spectrum of pharmacological activity.

1,5-Benzothiazepines are bicyclic heterocyclic compounds with one nitrogen and one sulphur atom at 1 and 5 positions in a seven membered ring fused to a benzene ring. Basically 1,5-benzothiazepines are the 2,3-benzo-annelated derivatives of 1,4-thiazepines. Benzothiazepines are numbered as shown in (Fig. 23).

![Fig. 23- 1,5-benzothiazepines](image)

The first molecule of 1,5-benzothiazepine used clinically was diltiazem (a), followed by clentiazem (b), for their cardiovascular action. Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim (c), clothiapine (d) and quetiapine (e). Therefore, the 1,5-benzothiazepines are useful compounds in the drug research which has stimulated the invention of a wide range of synthetic methods for their preparation and chemical transformations[74-78].

![Diltiazem (a)](image)
![Clentiazem (b)](image)
![Thiazesim (c)](image)
![Clothiapine (d)](image)
![Quetiapine (e)](image)
1,5-benzothiazepine moiety is a privileged class of pharmacophore, as compounds bearing this structural unit possess a broad spectrum of biological activities such as cardiovascular modulator[79] such as vasodilator[80,81] and anti-arrhythmic[82]. Recently, antifungal[83], antimicrobial[84] and anti HIV [85], Ca++ channel blockers [86], have also been reported. In the last decade, a series of monocyclic thiazepine inhibitors of the interleukin-1β converting enzyme (ICE) were synthesized [87] and also exhibited neuroprotective properties [88]. Literature survey revealed that different synthetic routes of thiazepine and its pharmacological activity have been reported by number of researchers illustrated below.

Recently Pragi Arora et al. synthesized 4-(2,4-substitutedphenyl)-2-(naphthalen-2-yl)-2,3-dihydrobenzo[1,5]thiazepine derivatives (Fig. 24) and evaluated for antimicrobial and antifungal properties. The results of antimicrobial studies have shown that all compounds were found to possess antimicrobial activity against all tested microorganisms [89].

Ganesh R. Mhaske et. al. reported the synthesis of 2-(-(2-(1-(4-chlorophenyl)-1H-pyrazol-4-yl)-2,3-dihydrobenzo[b][1,5]thiazepin-4-yl)-substitutedphenol (Fig. 25) and screened them for anti-inflammatory activity. They found considerable activity compared with diclofenac as a standard drug [90].
4-(1H-benzimidazol-2-yl)-2-phenyl-2,3-dihydro-1H-1,5-benzodiazepines (Fig. 26) have been synthesized by Janardan Singh Yadav et al. by employing microwave irradiation techniques and evaluated for their antimicrobial activities. The Microwave Assisted method is a very efficient Operative simplicity, easy work-up procedure; better yields are other advantages of this method. The reaction was clean and the products were obtained in excellent yields. The entire synthesized compounds exhibited moderate antibacterial activities and significant antifungal activities [91].

6-arylpyrrolo[2,1-d][1,5]benzothiazepine derivatives (Fig. 27), are the Most potent ligands specific for mitochondrial benzodiazepine receptor (MBR) [92].
Kamal synthesized a series of 4-(2-Chloro-6-substituted quinoline-3-yl)-2-(4-
substituted phenyl) 2,3-dihydro-benzo[b][1,5] thiazepine (Fig. 28), and their
antimicrobial activity was carried out. It was found that the presence of
pharmacophors such as quinoline have showed moderate degree of antimicrobial
activity [93].

![Fig. 28- 4-(2-Chloro-6-substituted quinoline-3-yl)-2-(4-substituted phenyl)
2,3-dihydro-benzo[b][1,5] thiazepine](image)

This promising moiety has much scope as a number of different molecular
targets are available for 1,5-benzothiazepines.

Keeping this goal in mind it was therefore planned to undertake research work
entitled, “Synthesis of Newer Heterocyclic Compounds and Study of Their
Biological Activity”. Using rapid synthetic method from easily available materials
and employing modern synthetic tools accordingly the work was planned, and finally
synthesized compounds were screened for anti-bacterial, anti-fungal and Anti-
Inflammatory (In-Vitro) activities.
1.2. References


Chapter 1 Literature Overview


