CHAPTER-I

Introduction
1.0. Introduction

Heterocyclic chemistry persists an interesting psychology these days. Commonly majority of the published work in organic chemistry involves at least one heterocyclic ring. Moreover, in providing us with a wealth of fascinating molecular arrays, over half of which posses heterocyclic constitution, nature presents a most cogent argument for developing an appreciation for this area. Heterocyclic chemistry is a vast and expanding area of chemistry because of the obvious applications of compounds derived from heterocyclic rings in pharmacy, medicine, agriculture and other fields. The chemistry of heterocyclic compounds is as relevant as that of aliphatic or aromatic compounds. Their study is of great interest both from the theoretical as well as practical stand point. An important application of small molecule libraries is the preparation of a directed or focused combinatorial library for assay against a specific biological target. Heterocyclic compounds play a vital role in organic chemistry, especially in the field of medicinal chemistry. More than half of the naturally occurring compounds and a high proportion of drugs contain heterocycles. Heterocyclic compounds may be classified in to aliphatic and aromatic heterocyclic compounds. The aliphatic heterocycles are the cycles analogues of amines, ethers, thioethers, amides etc. Heterocyclic compounds are organic compounds with incorporation of nitrogen, sulfur, oxygen, or an atom of a related element into an organic ring structure in place of a carbon atom gives rise to a heterocyclic compound. A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbolic compound. If at least one atom other than carbon forms a part of the ring system then it is designed as a heterocyclic compound [1-4].
These are containing at least one atom of carbon, and at least one element other than carbon, such as nitrogen, oxygen or sulfur within a ring structure. These structures may comprise either simple aromatic rings or non aromatic rings. Nitrogen, oxygen, and sulfur are the most common hetero atoms, but heterocyclic rings containing other hetero atoms are also widely known. A heterocyclic ring may comprise of three or more atoms which may be saturated or unsaturated. Also the ring may contain more than one heteroatom which may be similar or dissimilar. Some heterocyclic compounds are shown below.

![Chemical structures](attachment:image.png)

**Figure:** Some examples of heterocyclic compounds.
1.1. Significance of heterocyclic compounds

There are a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Some of these are natural products, for example antibiotics such as penicillin and cephalosporin, alkaloids such as vinblastine, ellipticine, morphine, and reserpine and cardiac glycosides such as those of digitals. However, the large majority are synthetic heterocycles which found widespread use, for example as anticancer agents, analeptics, analgesics, hypnotics and vasopressin modifiers and as pesticides, insecticides, weed killers and rodenticides. There are also a large number of synthetic heterocyclic compounds with other important practical applications, as dye stuffs, copolymers, solvents, photographic sensitizers and developers, as antioxidants and vulcanization acceleration in the rubber industry, and many are valuable intermediates in synthesis.

The successful application of heterocyclic compounds in these and many other ways and their appeal as materials in applied chemistry and in more fundamental and theoretical studies, stems from their very complexity; this ensures a virtually limitless series of structurally novel compounds with a wide range of physical, chemical and biological properties, spanning a broad spectrum of reactivity and stability. Another consequence of their varied chemical reactivity, including the possible destruction of the heterocyclic ring is their increasing use in the synthesis of specifically functionalized non-heterocyclic structures.

More important is the recognition that, heterocycles can play a pivotal role not only as goals in synthesis, but as mediators of synthetic transformations since the appearance of the benchmark monograph by Meyers [5], which formally legitimised the use of heterocycles as a viable and occasionally superior means of arriving at the
functionalized materials. Just as the synthetic organic chemistry has blossomed since that time, so has the use of heterocycles in synthesis.

The number of possible heterocyclic systems is almost limitless. An enormous number of heterocyclic compounds are known and this number is increasing very rapidly. The literature of the subject is correspondingly vast and of the three major divisions of organic chemistry aliphatic, aromatic and heterocyclic, the last is much the biggest. Over six million compounds are recorded in chemical abstracts and approximately half of these are heterocyclic.

1.2. Introduction to pyrimidinones

One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures [6], with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry [7-10]. Pyrimidine is the most important member of all the diazines as this ring system occurs widely in living organisms. Purines, uric acid, alkoxyan, barbutiric acid and a mixture of anti-malarial and anti-bacterials also contain the pyrimidine ring. The chemistry of pyrimidine has been widely studied [11, 12]. Pyrimidine was first isolated by Gabriel and Colman in 1899. The derivatives of fused pyrimidinones have been the focus of great interest over many years due to the fact that many compounds containing a fused pyrimidinone ring play an important role in the biochemistry of living cell [13-16]. Heterofused pyrimidines exhibit promising antiviral [17], antibacterial [18], anti-AIDS [19], and antinociceptive [20] activities. The group of pyrido [1,2-a] pyrimidin-4-ones is a well-known class of aza-bridgehead fused heterocyclic compounds which have miscellaneous pharmaceutical applications [21].
This kind of structural pattern is present in the known psychotropic agents risperidone and paliperidone [22, 23], the human leukocyte elastase inhibitor SSR69071 [24], the antiallergic agent ramastine [25], and antioxidants [26]. Fused pyrimidines are extensively used in neurology, particularly in the treatment of neurodegenerative disorders such as Parkinson’s disease [27], anxiety disorders [28] and depression [29]. Fused pyrimidines are selective inhibitors for multidrug resistance (MDR) [30]. Folate metabolism has long been recognized as an attractive target for cancer chemotherapy because of indispensable role of fused pyrimidines antifolates as antitumor agents [31]. Risperidone a derivative of pyrido[1,2-a]pyrimidines [32, 33] and derivatives showed antipsychotic activity [34] which were used as α-2 antagonists [35-37]. They exhibit high affinity for α-2 adrenoceptor with high selectivity versus the α-receptor and posses potent in vivo central activity [38, 39]. Many other examples of pyrimidine based derivative have been investigated as potential antitumor agents, including 2-phenyl amino derivatives [40-43], 4-phenyl amino derivatives [44, 45], 2,4-bis(phenylamino)derivatives [46], 4,6-bis(phenylamino)derivatives [47, 48], and 4-aryl substituted derivatives [49]. All these observations point out that pyrimidinones occupies distant and remarkable place in medicinal chemistry. Keeping in view of these above facts, it was thought of synthesizing some pyrimidinone derivatives to explore their biological significance.

1.3. Biological significance of pyrimidinones

Signal transduction, angiogenesis and cancer activity

In 1996 Pfizer researchers reported the first selective Src-family inhibitors, named PP1, (1) and PP2 (2) [50], endowed with good potency, but poor selectivity toward the different members of SFKs. A very large amount of biological data is reported for PP1 and PP2; they inhibited Lck, Fyn, c-Src and Hck activity kinase with IC₅₀ values
ranging from 4 to 170 nM, while were essentially inactive against other non-Src family TK, such as ZAP-70 or JAK 2. Some inhibition of EGFR was also observed with IC\(_{50}\) values of 250 and 480 nM for PP1 and PP2, respectively. The compounds appeared to be ATP competitive inhibitors. The library of compounds (3) and (4) 4-amino-substituted pyrazolo [3,4-\(d\)] pyrimidines bearing a 2-chloro-2-phenyl N1 side chain showed a submicromolar to nanomolar activity toward isolated Src as well as antiproliferative activity toward the epidermoid (A431) and breast cancer (BC-8701) cell lines (that overexpress Src) blocking Src phosphorylation and inducing apoptosis with potency about two-fold higher than that of the reference compound 4-amino-5-(4-chlorophenyl)-7-(tert-butyl)pyrazolo[3,4-\(d\)] pyrimidine (PP2) (2).

In 1997, Parke-Davis reported a family of pyrido[2,3-\(d\)]pyrimidines, belonging to the important class of urea TK inhibitors [51], as potent, but non-selective inhibitors of several kinases, acting with an ATP - competitive mechanism [52]. The most interesting compounds are represented by the soluble 2-substituted aminopyrido
[2,3-$d$]pyrimidin-7-yl ureas, such as (5) that showed $IC_{50}$ values of 18, 210 and 49 nM, toward Src, PDGFR, FGFR, respectively, in enzymatic assays. Compound (6) (PD 166285) is a tyrosine kinase inhibitor with moderate selectivity for Src, PDGFR, FGFR and EGFR, respectively [53, 54]. This derivative has been also reported to inhibit tumor cell growth particularly of human leukemic cell lines and leukemic blasts [55]. Compound (7) (PD 173955) has been found to be a more selective Src inhibitor with $IC_{50}$ values of 22, 1600 and 1600 nM, for Src, PDGFR, FGFR, respectively. Treatment of MDA-MB-468 cells, a breast cancer line with this compound causes a loss in Src activity, with a reduction in the tyrosine phosphorylation of the enzymes; the cell growth of this tumor line resulted also blocked, for the ability of (7) to cause mitotic arrest [56]. PD 173955 also inhibits Bcr-Ab1 and c-Kit, with $IC_{50}$ values of 2 and 50 nM, respectively [57]. Compound (8) (PD 166326) [58] is a potent dual inhibitor of Src and Abl with $IC_{50}$ values of 6 and 8 nM, respectively moreover, it is a picomolar inhibitor of K562 cells growth, showing an $IC_{50}$ of 300 pM, and leading to apoptotic G1 arrest, PD 0166326 is also effective against imatinib-resistant Brc-Ab1 mutants and could represent a prototype of a new generation of potential agents useful in the treatment of CML [59]. Compound (9) (PD 180970) is one of the most recent member of this class, and shows a similar biological behaviour to that of (8), inducing apoptosis in K562 cells and of CD34-positive leukemic cells from patients with imatinib-resistant CML [60, 61].
Gangjee et al., [62] synthesized 2-amino-4-\textit{m}-bromoanilino-6-arylmethyl-7\textit{H}-pyrrolo[2,3-\textit{d}] pyrimidines (10). Embarked on the design of RTK inhibitors using the pyrrolo[2,3-\textit{d}] pyrimidine scaffold with an additional 2-NH\textsubscript{2} moiety which is not present in most other 6-6 or 6-5 ring system RTK inhibitors. The 2-NH\textsubscript{2} group in our compounds provides a third H-bonding moiety in the Hinge region of RTKs, and was anticipated to increase binding and consequently potency against RTKs. This has recently been shown to be true in most instances, but is dependent on the nature of the scaffold and its substitutions [63].
An initial series of 2-amino-4-(3-bromoanilino)-6-(aryl methyl)-pyrrolo[2,3-d]pyrimidine derivatives 10 (a-c) indicated that substitution on the 6-aryl moiety dictates both the selectivity and potency against a variety of RTKs.

The pyrimidine moiety with some substitution shows promising antitumor activity as there is a large number of pyrimidine-based antimetabolites. Early metabolite prepared was 5-flurouracil (11) [64] a pyrimidine derivative followed by 5-thiouracil (12) which also exhibits some useful antineoplastic activities [65].

Palwinder Singh et al., [66] reported the synthesis of 5-substituted-1,3-dimethylpyrimidine-2,4,6-trione derivatives (13) reacted with amines provided enamines. The investigation for anticancer activity of molecule with 59 human tumor cell lines was done representing leukemia, melanoma and cancer of lung, colon, brain, ovary, breast as well as kidney.
CHAPTER-I

**Pyrimidin-4-one derivatives**

et al

and screened them for analgesic and anti-inflammatory activities equivalent to those of acetysalicylic acid.

3,5,6-trisubstituted-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimido[2,3-d]pyrimidin-4-one derivatives (14) and screened them for analgesic and anti-inflammatory activity.

Cannito et al., [68] investigated analgesic and anti-inflammatory activity of some of 3,5,6-trisubstituted-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4-one derivatives (15). The i.p. administration of these products at a dose of 1000 mg/kg shows that they are not toxic (one excepted). Some compounds showed analgesic and anti-inflammatory activities equivalent to those of acetylsalicylic acid.

F. Russo et al., [69] described new thienopyrimido benzothiazole and thienopyrimidobenzo oxazoles (16) and screened them for analgesic and anti-inflammatory activities.
Nargund et al., [70] synthesised substituted 2-mercapto-3-(N-alkyl)pyrimido[5,4-C] cinnolin-4-(3H)-ones (17) refluxing 4-aminocinnoline, 3-carboxylic acids, with aryl isothiocyanates in anhydrous pyridine. These derivatives were evaluated for their anti-microbial and anti-inflammatory activities. Some of the compounds possessed potent anti-microbial activity.

Ishwaarsingh S. Rathod et al., [71] studied the analgesic activity of thieno[2,3-d]pyrimidine-4-(3H)-ones (18), 2-aryl amino-3-aryl-5-methyl-6-(substituted)thieno[2, 3- d] pyrimidin-4(3H)-ones (19) by tail flick method in albino rats and by writhing method in albino mice.
A series of 3-substituted amino-2-methyl thieno[2,3-d]pyrimidin-4-(3H)-ones (20) were synthesized and screened for acute (30mg/kg p.o) and chronic (10mg/kg p.o) anti-inflammatory activity using carrageenan induced rat paw edema model and carrageenan-induced granuloma air pouch model respectively. The tested compounds have exhibited significant ($P<0.05$) anti-inflammatory activity in acute model while in chronic model only compounds 20(a-g) have exhibited significant activity ($P < 0.05$) [72].

![Chemical Structure](image-url)
Proquazone (21) a non-steroidal anti-inflammatory agent (NSAID) which, unlike most other NSAIDs, does not have a free acid group in its structure. It is advocated for use in rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, musculoskeletal disorders, acute inflammatory conditions and acute pain states such as dysmenorrhea, post-operative pain and headache. Preliminary studies have confirmed the efficacy of proquazone in acute inflammatory disorders, and shown that it provides useful analgesic relief in acute pain states such as dysmenorrhea,
headache and after minor surgery produces a high incidence of gastrointestinal symptoms such as diarrhoea [73].

**Platelet aggregation inhibition activity**

1,2,3,5-tetrahydroimidazo[l,2-a]thieno pyrimidin-2-one (22) derivatives have been prepared and tested for platelet aggregation inhibitory activity in rats *in vitro* and *ex vivo*. Few of the compounds are identified potent inhibitors of blood platelet aggregation. Compounds 1,2,3,5,6,7,8,9-octahydro-[1]benzothieno[2,3-\(d\)] imidazo[1,2-a]pyrimidin-2-one exhibited the most favourable activity [74].

**Antihypertensive activity**

Mery Press *et al.*, [75] synthesized of 3-substituted-thieno[2,3-\(d\)]pyrimidine-2,4-dione (23) and for their antihypertensive activity.
Russell et al., [76] evaluated the antihypertensive activity of thienopyrimidine derivatives (24).

\[ R = \text{2-OCH}_3, \text{3-OCH}_3, \text{H} \]

Atwal et al., [77] synthesized dihydropyrimidinone derivatives (25). Where as the modifications of the substituent at N3 led to the development of orally long-lasting antihypertensive activity. Furthermore, it has been established that the absolute stereochemistry at the C4 carbon atom is very important. For example, the desired antihypertensive effect was observed only with the (R)-enantiomer of the compound.
Ketanserin (26) a serotonin receptor antagonist, reduces blood pressure appears as a new and important alternative in the treatment of mild and moderate essential hypertension [78].

![Chemical Structure of Ketanserin (26)](image)

**CNS activity**

Howard et al., [79] screened Risoperidone (27) for CNS activity, its structural hybrid is of butyrophenone and can be used as anxiolytic, antidepressant and antiparkinsonian drug.

![Chemical Structure of Risoperidone (27)](image)

Abott et al., [80] synthesized and checks the anesthetic activity of pyrimidine analogue, thimylal (28).
Sugiyama et al., [81] condensed thieno[3,2-\textit{d}], [3,4-\textit{d}], and [2,3-\textit{d}]pyrimidin-5-one derivatives (29) in which the oxygen atom of the oxazolidine moiety in 29 was replaced by a sulfur atom or methylene groups, and evaluated for their gastric antisecretory activity in pylorus-ligated rats.

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\text{29}
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**Sedative/hypnotic/antiepileptic agents**

Agents of the anxiolytic, sedative and hypnotic group include a wide variety of barbiturates 30(a-i) used as sedative and hypnotics and are classified as drugs having short, intermediate and long duration of action [82]. Allobarbital 30(a), aprobarbital 30(b), pentobarbital 30(e), phenobarbital 30(g) and secobarbital 30(i) are frequently used clinically as hypnotic barbiturates [83]. Hexobarbital 30(c), cyclobarbital 30(d) and propallylonal 30(f) are some of the current drugs in the market used as sedative hypnotics [84]. Barbiturates as sedative hypnotics have a long and fascinating history. Eli Lilly patented secbutabarbital 30(h) in 1932 [85].

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Flucytosine (31) is a fluorinated pyrimidene used as nucleosidal anti-fungal agent for the treatment of serious systemic infections caused by susceptible strains of candida and Cryptococcus [86].

Non-peptide Luteinizing Hormone-Releasing Hormone (LHRH) Antagonists

Sasaki et al., [87] designed, synthesized, and evaluated a new class of non-peptide luteinizing hormone-releasing hormone (LHRH) receptor antagonists, the 2-phenylimidazo[1,2-a]pyrimidin-5-ones, a heterocyclic 5-6 ring (32). This study resulted in the identification of a new class of potent LHRH antagonists, represented by the methoxyurea ‘32 g’ possessing high binding affinity and potent in vitro antagonism, with IC_{50} values of 0.4 and 7 nM, respectively. These results conclude that the imidazopyrimidin-5-one provide a new scaffold for small molecule LHRH antagonists devoid of a thiophene ring. Taking this finding into consideration, it is suggested that the heterocyclic 5-6 ring system bearing a pendant phenyl group attached to the five-membered ring is the key structural motif for a LHRH antagonist scaffold system (32) in which an imidazole ring is embedded, as a novel scaffold for non-peptide LHRH antagonists.
Stadler et al., [88] described nitrofuryl-substituted DHPM derivative Nitracin (33) and the compound displayed activity against viruses of the trachoma group and modest antibacterial activity.

Calcium channel blocking activity

Rovnyak et al., [89] investigated 2-(methylthio)-4-(2-(methylthio)-3-nitrophenyl)-4,7-dihydrofuro[3,4-d]pyrimidin-5(1H)-one (34). Alajarin et al., [90] investigated a monocyclic dihydropyrimidine (35). Besides the monocyclic DHMP derivatives, some fused analogs, which incorporate hetero- or carbocyclic rings attached to either C2/N3 or the C5/C6 positions of dihydropyrimidine such as (34) and (35) possess calcium channel blocking activity.
1.4. Introduction to Thiazoles

Thiazoles \(36\) are structurally related to thiopene and pyridine, but in most of its properties it resembles to the latter. Thiazole was first described by Hantzch and Waber in 1889. The numbering in thiazole starts from the sulphur atom. Structure \(37\) is benzothiazole. The basic structure of benzothiazole consists of benzene ring fused with 4, 5 position of thiazole. The two rings together constitute the basic nucleus 1,3-benzothiazole.

Thiazole is a five-membered ring containing one nitrogen and one sulfur. Benzothiazole is a heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Benzothiazole moieties are part of compounds showing numerous biological activities such as antimicrobial [91-95], anticancer [96-98], anthelmentic [99], antidiabetic [100], activities. They have also found application in industry as anti-oxidants, vulcanization accelerators. Various benzothiazoles such as 2-arylbenzothiazole received much attention due to unique structure and its uses as radioactive amyloid imaging agents [101], and anticancer agents [102]. Benzothiazoles are bicyclic ring system with
multiple applications. In the 1950’s, a number of 2-aminobenzothiazoles were intensively studied, as the 2-aminobenzothiazole scaffold is one of privileged structure in medicinal chemistry [101-103] and reported cytotoxic on cancer cells [103]. It must be emphasized that combination of 2-aminobenzothiazoles with other heterocyclic is a well known approach to design new drug like molecules, which allows achieving new pharmacological profile, action, toxicity lowering. The 2-(4-aminophenyl) benzothiazoles are novel class of potent and selective antitumor agents and display characteristic profile of cytotoxic response across the cell lines. In addition, benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological properties. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds.

1.5. Biological significance of Thiazoles

Antimicrobial activity

Yadav et al., [104] synthesized a series of fluoro, chloro 2-(a-substituted aryl amino acetamido)benzothiazole (38) and screened for antibacterial activity against B. subtilis, S. typhi, E. coli, and S. aureus bacterial strains. The fluoro, and chloro substituents showed a significant antibacterial activity.

![Chemical structure of 38](image)

\[ R = p\text{-Bromo/ nitro/ methyl aniline} \]

Basavaraja K. M. et al., [105] described 2-[1-aryl azo]methyleneimino-6-chloro benzothiazole derivatives (39) and tested for antimicrobial activity against B. subtilis,
S. typhi, E. coli, and S. aureus bacterial strains. The compounds showed a significant antibacterial activity.

Murthy Y. et al., [106] evaluated some new 2-mercaptobenzothiazoles (40) and correlated the effect on antimicrobial potency by varying the substituents in benzene part of the benzothiazole ring system. Anti-microbial screening was performed against E. coli, S. aureus, C. albicans and antifungal activity against Aspergillus flavus and Candida albicans at conc. 100 µg/mL using agar plate Kirby-Bauer disc diffusion method.

Pandurangan A. et al., [107] reported N-2-benzothiazolylthiourea derivatives (41) as good antimicrobial agents against Gram-positive and Gram-negative bacteria such as S. aureus, P. aeruginosa, E. coli, and a yeast (C. albicans) and a mould (Microsporum gypseum).
Maharan M. et al., [108] discussed a series of benzothiazole-2-yl-dithiocarbamates (42) along with copper complexes via reaction of suitable alkyl or heteroaryl halide with sodium salt of benzothiazole-2-yl-dithiocarbamic acid followed by complexation with copper sulphate and selected derivatives checked for their schistosomicidal activity against Schistosoma mansoni.

![Image](image1)

Amir M. et al., [109] examined thiadiazole derivatives containing benzothiazole (43) and screened for both antibacterial and antifungal activities using cup-plate agar diffusion method. Anti-microbial screening was performed against E. coli, S. aureus, C. albicans and antifungal activity against Aspergillus flavus and Candida albicans.

![Image](image2)

Soni B. et al., [110] reported newer Schiff bases of benzothiazole derivatives (44) and they tested for antibacterial activity. The synthesized derivatives exhibited moderate antibacterial activity against Gram-positive (S. aureus and S. pyrogenus), Gram-negative bacteria (E. coli and P. aeruginasa) and Fungi (C. albicans, A. niger and A. clavatus). The results demonstrated that compounds with a 4-hydroxy, 4-dimethylamino and 3,4-dimethoxy group on the aromatic ring showed good antibacterial activity.
Alang et al., [111] studied seven new derivatives of 2-substituted benzothiazole (45) and found them as good antibacterial agent against Gram-positive bacteria (S. aureus, S. epidermis) and Gram-negative bacteria (P. aeruginosa and E. coli).

Malik et al.,[112] synthesized some new 2-amino substituted benzothiazoles (46) and evaluated for in vitro antifungal activity against fungal strains such as C. albicans, A. niger and A. flavus.

Barot H. K. et al., [113] evaluated nitrogen mustards of fluorobenzothiazoles (47, 48) and was determined for antibacterial and antifungal activities against S. aureus, B. subtilis, C. tropicans, A. niger, and F. heterosporium. The synthesized compounds showed an excellent inhibition at a conc. of 50µg/0.1mL.
Anthelmintic activity

Sreenivasa M. et al., [114] synthesized fluorobenzothiazole comprising sulphanamide pyrazole derivatives (49). The synthesized compounds were screened for anthelmintic activity by using earthworms (Peritumaposthum). The compounds were evaluated by time taken for complete paralysis and death of worms.

4-Fluoro-3-chloroaniline treated with potassium thiocyanate in presence of glacial acetic acid and bromine was converted into 2-amino-6-fluoro-7-chlorobenzothiazole. The synthesized compound in presence of p-dimethylaminobenzaldehyde refluxed in ethanol to obtain a corresponding 6-fluoro benzothiazole Schiff’s base (50) the above said compound was treated with ortho, meta and para nitroanilines, ortho, meta, para chloroanilines, morpholino, piperazine, diphenylamine in the presence of DMF to obtain different new moieties. Some new moieties showed promising anthelmintic activity [115].
Anti-inflammatory activity

Shashank et al. [116] described synthesis of 2-substituted benzothiazole derivatives (51) and evaluated for anti-inflammatory activity. The maximum activity may be due to presence of -F and -OCH₃ groups. The same series of compounds also showed good anticancer activity.

A series of 2-(benzo[d]thiazol-2-ylthio)-N-(2-oxoindolin-3-ylidene)acetohydrazide 52(a-g), 2(benzo[d]thiazol-2-ylthio)-N-(2,4-dioxospiro[indolin-3,2-thiazolidin]-3’-yl) acetamide 53(a-g) and 2’-((benzo[d]thiazol-2-ylthio)methyl)spiro[indoline-3,5’-thiazolo [4,3-b][1,3,4]oxadiazol]-2-ones 54(a-g) have been synthesized and screened for their anti-inflammatory, analgesic and anti-bacterial activities. The most potent anti-inflamm
atory and anti-bacterial compound of this series was compound 54d and most potent analgesic compound was compound 54e [117].

Oketani et al., [118] studied the in vitro pharmacological profiles of 6-hydroxy-5, 7-dimethyl-2-(methylamino)-4-(3-pyridylmethyl)benzothiazole (55) against the 5 lipoxygenase activity of rat basophilic leukemia cells. This result indicated that the compound effectively inhibited 5-lipoxygenase and thromboxane B₂ production in rat peritoneal and human blood vessels.

Cyclooxygenase inhibitor activity

Gurupadaya B. et al., [119] synthesized azatidin-2-ones and thiazoline-4-ones (56) encompassing benzothiazole derivatives and evaluated for anti-inflammatory activity using carrageenan induced rat hind paw edema method.
Anti-cancer activity

The 2-arylsulfonated benzothiazole derivatives (57) were synthesized by refluxing o-aminothiophenol with substituted benzoic acids in the presence of polyphosphoric acid at 220 °C. 2-Mercaptothiazole was used along with thionyl chloride to get the carbethioates. The screening for antitumour activity was done as per the National Cancer Institute drug screening strategy. 3 compounds were found to be significantly cytotoxic as compared to [2-(3-bromo-4-aminophenyl)benzothiazole] against the human cervical cancer cell lines [120].

Fluorinated 2-arylbenzothiazoles (58) are new potential antitumor drugs, which show potent and selective inhibitory activity against breast, lung, and colon cancer cell lines. Carbon-11 labeled fluorinated 2-arylbenzothiazoles may serve as novel probes for positron emission tomography (PET) to image tyrosine kinase in cancers [121].

Gupta S. et al., [122] synthesized benzothiazole derivatives (59) and screened for in vitro cytotoxic activity against HL-60 and U-937 cell lines. In silico pharmacokinetic study revealed that benzothiazole dimere were free from teratogenicity, irritation and sensitivity properties than monomers. The QSAR study showed that increase in
hydrogen donor count is conductive for cytotoxic activity of benzothiazole derivatives against HL-60 cell lines.

![MTP inhibition activity](image)

**MTP inhibition activity**

A series of triamide derivatives bearing a benzothiazole (60) core is shown to be potent microsomal triglyceride transfer protein (MTP) inhibitors. In order to minimize liver toxicity, these compounds have been optimized to have activity only in the enterocytes and have limited systemic bioavailability. Upon oral administration, selected analogs within this series have been further demonstrated to reduce food intake along with body weight and thereby improve glucose homeostasis and insulin sensitivity in a 28 day mice induced obesity (Dio) model [123].

![Amyloid imaging agent in Alzheimer’s disease](image)

**Amyloid imaging agent in Alzheimer’s disease**

Serdons K. *et al.*, [124] examined F-labelled 2-(4-fluorophenyl)benzo[d]thiazoles (61) evaluated it as amyloid imaging agent in Alzheimer’s disease and they showed good affinity for amyloid plaques present in human Alzheimer’s disease.
**Antimalarial activity**

Hout S. *et al.*, [125] synthesized 2-substituted-6-nitro (62) and 6-aminobenzothiazoles (63) and their anthranilic acids were carried out on W2 and 3D7 strains of *P. falciparum*. The results revealed the potency of compounds 62 and 63 as the antimalarial agents of clinical and biological research.

![Chemical structures of compounds 62 and 63](image)

**PPAR δ activity**

To find novel PPAR δ-selective agonists, Fujida *et al.*, [126] designed and synthesized phenylpropanoic acid derivatives bearing 6-substituted benzothiazole derivatives. Optimization of this series led to the identification of a potent and selective PPAR δ-agonist. Among the synthesized compounds, compound (65) has shown PPAR δ activity and selectivity. The introduction of Cl group at the C-6 position of the benzothiazole ring and methyl group at the ortho position of phenyl propanoic acid further improved PPAR δ transcriptional activity. Compound (65) was found to be the most potent and selective PPAR δ agonist.

![Chemical structures of compounds 64 and 65](image)
Anti convulsive activity

Several benzothiazoles containing sulphanamide derivatives (66) [127], benzothiazolyl guanidones (67) [128], benzothiazolamines (68) [129], were synthesized and evaluated for their activity against electro shock and phenyl tetrazolone induced seizures. The review of these literatures revealed the benzothiazole moiety as a dynamic agent against convulsive seizures.

Siddiqui et al., [130] reported N-(6-substituted-1, 3-benzothiazole-2-yl)-4-sulphanamides (69) and screened for anticonvulsive activity. The tested compound showed an anticonvulsive effect in MES and PTZ induced seizures.

Amnerkar N. et al., [131] investigated prop-2-eneamido and 1-acetyl-pyrazolin derivative of aminobenzothiazole (70) and the compound was evaluated for anticonvulsive activity. The screened compound showed anticonvulsive activity in MES and PTZ induced seizures.
Anti-diabetic activity

Pattan S. R. et al., [132] described a series of 2-amino[5′(4-sulphonylbenzylidene)-2,4-thiazolidinone]-6-flurobenzothiazoles (71) and examined for anti-diabetic activity. All the compounds of this series showed promising anti-diabetic activity.

Paoli and co-workers [133] prepared a small library of 2-arylsulphonyl aminobenzothiazoles (72, 73) and screened them for protein tyrosine phosphatase 1B inhibition. The most active compounds (72) and (73) were observed as rapid reversible inhibitors of PTP-1B and significantly lowered plasma glucose concentration.
1.6. Scope of the present work

Heterocyclic chemistry is a vast and expanding area of chemistry, because of the obvious applications of compounds derived from heterocyclic rings in pharmacy, medicine, agriculture and other fields. This study is of great interest both from theoretical as well as practical standpoint. In five-membered and six-membered ring systems, the presence of nitrogen, oxygen, and sulphur heteroatom defines an interesting class of compounds. An important application of small molecule libraries is the preparation of a directed or focused combinatorial library for assay against a specific biological target. Pyrimidinone and thiazole is among the most important heterocyclic compounds, which exhibit their therapeutic activity is due to their conformationally flexible nature. The accentuated interest in the pyrimidinone and thiazoles class of opiate analgesics continues to be expressed in the pharmaceutical community and biological properties of these agents have been the subject of ongoing investigations. In this connection the present investigation is undertaken and is divided into three chapters. Chapter-I gives the introduction to pyrimidinone and benzothiazole derivatives. Pyrimidinones and benzothiazoles were proven to be biologically very potent and selective. A wide spectrum of pharmacological activities has been reported for these compounds. These include anti-cancer, anti-inflammatory, platelet aggregation inhibition, C.N.S activity, antimicrobial, anthelmentic, anti-inflammatory, cyclooxygenase inhibitor activity, anti-diabetic, antimalarial, MTP inhibition activity, PPAR-δ activity. Such varieties of interesting biological activity for this class of compounds prompted us to synthesize pyrimidinone and thiazole derivatives and investigate their biological importance. It is expected that these would result in highly potent and selective pharmaceutical agents.
Chapter-II deals with the synthesis of 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one derivatives 6(a-s) and investigate for antimicrobial activity. From the results obtained compounds 6c and 6i showed inhibitory activity against tested bacterial strains. Synthesis of 2-methyl-3-(2-(piperazin-1-yl)ethyl)-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one derivatives 8(a-g) and 9(a-f) and investigate for antimicrobial activity. From the results obtained compounds 8a and 9d showed inhibitory activity against tested bacterial strains. Synthesis of 2-methyl-3-(2-(piperazin-1-yl)ethyl)-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one derivatives 8(a-d) and 9(a-e) and screened for anti-angiogenesis by EAT cells in vivo. From the results obtained compounds 8d and 9a showed potent activity against EAT cells in vivo.

Chapter III contains the evaluation of 1-(substituted phenyl)-3-(6-ethoxybenzo[d]thiazol-2-yl)thiourea derivatives 5(a-i) and evaluated for anti-angiogenesis by EAT cells in vivo. From the results obtained compounds 5e and 5g can be considered as anti-angiogenic compounds against EAT cells in vivo.

Synthesis of N-(benzyl)-6-ethoxybenzo[d]thiazol-2-amine derivatives 7(a-i) and screened for anti-angiogenesis by EAT cells in vivo. From the results obtained compounds 7b and 7g have shown good anti-angiogenic effects against mouse Ehrlich Ascites Tumour. Synthesis of N-(benzylidene)-6-ethoxybenzo[d]thiazol-2-amine derivatives 9(a-i) and tested for anti-diabetic agents. From the results obtained compounds 9a and 9d can be considered as anti-diabetic agents against sucrase, maltase, glucosidase, and amylase of in vitro activity.
CHAPTER-I

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