“Medicinal Chemistry had its beginning when chemists, pharmacists and physicians isolated and purified active principles of plant and animal tissues and latter from micro organisms and their fermentation products. Some of these compounds have been associated with therapeutic properties in the disease during the last decades of the 20th century, the traditional lines between biological, chemical and physical sciences were erased, and new borderline investigations such as molecular biology, molecular pharmacology, biomedicine and others began to capture the medicinal interest. Medicinal Chemistry which had leaned on the classical field of chemistry, especially organic chemistry, biology and some areas of physics extended new roots into these emerging topics, problems in elevated to unapproachable chemical studies with therapeutic application became accessible and revised the choice of researches to the benefit of all scientific doctrines involved. Medicinal chemistry remains a challenging science, which provides profound satisfaction to its practitioners. It intrigues those of us who like to solve problems pose by nature. It inverses increasingly on biochemistry and on the physical, genetic and chemical riddles in animal physiology which bear on medicine. Chemists have a chance to participate in the fundamentals of prevention, therapy and understanding of diseases and thereby to contribute to a healthier and happier life” [1].

Medicinal Chemistry essentially it concerns with the understanding of mechanisms of action of drugs mechanism. It attempts to establish relationship between structure and activity and to link biodynamic behaviour with chemical reactivity and physical properties. Rightly, therefore, Medicinal Chemistry is also referred as therapeutic chemistry, pharmaceutical chemistry, pharmaco chemistry etc. (Fig. 1). Emphasis is laid on drugs, nevertheless, the interests of the chemists does not stop at drugs and include bioactive compounds in general. It encompasses discovery, development, identification and interpretation of mode of action at the molecular level. It is also concerned with the study, identification, and synthesis of the metabolic products of drugs and related compounds. Besides
this, it also involves the isolation, characterization and synthesis of compounds that can be used in medicine for the prevention, treatment and cure of diseases. Thus, it provides chemical basis for the interdisciplinary field of therapeutics.

Heterocyclic compounds have great applicability in pharmaceutics as they have specific chemical reactivity and provide false synthons in biosynthetic process as they block the normal functioning of biological receptors. The inhibition of amide resonance resulting in more susceptibility of $\beta$-lectam to nucleophile is considered at least in part responsible for antibacterial property, apparently by acetylated transpeptidase and thus inhibiting bacterial cell wall biosynthesis. Heterocyclic compounds containing nitrogen and sulphur atoms are of vital importance due to their variable biological activities and considerable diversity in the heterocyclic ring system.

The discoveries of the medicinal properties of compounds have always stimulated inquiry into the therapeutic chemical reactions and this has led to involve a view to develop methods of synthesis of similar substances. Chemists have made possible some of the proudest achievements of human and veterinary medicine as well as animal husbandry. The World Health Organization defines drug as “any substance used in a pharmaceutical product that is intended to modify or explore physiological system or pathological states for the benefit of the recipient”. A pharmaceutical product is defined as “a dosage form containing one or more drugs along with other substances included during the manufacturing process.” Many drugs are either organic acids or organic bases used as salts. These bring about: (a) modification of physiochemical properties, such as solubility, stability, photosensitivity and organoleptic characteristics; (b) improvement of bioavailability through modification of absorption, increase of potency and extension of effect and (c) reduction of toxicity.
Fig. 1  Ramifications of Medicinal Chemistry in different branches of other Sciences
INTRODUCTION OF THIENOPYRIMIDINE

Pyrimidines are the most important six member heterocyclic ring containing two nitrogen atoms on 1, 3 positions. This ring system is present in cytosine, adenine, guanine and thiamine, which form a part of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) and vitamins like riboflavin, pyridoxine and other purines [2].

The formation of novel fused heterocycles is an important task for heterocyclic chemists from various points of view for the development of living things. Furthermore, many condensed heterocyclic systems, especially when linked to a pyrimidine ring as quinazolines, pyridopyrimidines, triazolopyrimidines, pyrazolopyrimidines, pyrimidoazepines, furo-pyrimidines and pyrrolopyrimidines. Thienopyrimidines occupy a special position among these compounds. Bicyclic aromatic heterocycles are well-known pharmacophores in drug discovery. As a logical consequence of thiophene-phenyl isosterism, thienopyrimidines can be considered as bioisosteres of quinazolines.

Synthesis of thienopyrimidine derivatives as potential substitution for the quinazoline core structure has therefore become a routine strategy in modern drug design and development.

Quinazoline  Thienopyrimidine

The known approaches to the synthesis of thienopyrimidines can be divided into main two groups according to the starting material. Either, the synthesis starts from a pyrimidine derivative and a thiophene ring is then constructed, or a thiophene analogue is used as starting material followed by the formation of a pyrimidine.
Retrosynthetic analysis of thienopyrimidines

There are three isomeric thienopyrimidines corresponding to the three possible types of annulation of thiophene to the pyrimidine ring. Thieno[2,3-d]pyrimidine (1), thieno[3,2-d]pyrimidine (2), and thieno[3,4-d]pyrimidine (3). The structures and the conventional numbering of these heterocyclic systems are shown below [3]:

Isomeric thienopyrimidines

The similarity between the physicochemical properties of benzene and thiophene is striking. For example, the boiling point of benzene is 81.1 °C and the one of thiophene is 84.4 °C and therefore, thiophene and benzene are a well known example of bioisosterism. The change of a benzene moiety into a thiophene often results in superior pharmacodynamic, pharmacokinetic or toxicological properties. For example, the thiophene analogue of piroxicam (a non- steroid anti-inflammatory agent used in arthritis) has the same biological activity, with the same mechanism of action as piroxicam and even displayed a longer plasma half-life than piroxicam [4].
Synthesis:

Synthesis of thienopyrimidine derivatives involve following two routes:

(a) Synthesis of thienopyrimidines by thiophene ring closure.

Thienopyrimidine derivative (4) was synthesized by the reaction of 4,6-dichloro-2-(methylthio)pyrimidine-5-carbonitrile with 2-fluoroaniline and then treated with ethyl mercaptoacetate in the presence of NaOH [5].

![Reaction diagram](image)

Thienopyrimidinediones (5) can be synthesized by Claisen rearrangement of propargyl sulfide [6].

![Reaction diagram](image)

Synthesis of thienopyrimidine derivatives (6) involve substitution of the mercaptoacetic acid residue for the chlorine atom in 4-chloro-5-ethoxy-carbonylpyrimidines and cyclization in presence of base [7,8].

![Reaction diagram](image)

Z = CONHAr, CN, NO₂
(b) Synthesis of thienopyrimidines by pyrimidine ring closure.

Various substituted aminothiophenes, which are used as the main starting compounds for the preparation of thienopyrimidines by pyrimidine ring closure.

Starting compound 2- and 3-aminothiophenes are synthesized by Gewald aminothiophene synthesis (Page no. 69).

Amino(ethoxycarbonyl)thiophene reacts with isothiocyanate to form thienylthiourea derivative then treated with an ethanolic alkali followed by acidification of the reaction mixture with HCl to give thioxopyrimidinone (7) [9,10].

![Chemical structure of thioxopyrimidinone](image)

2-aminothienopyrimidin-4-imines (8) are synthesized by the reaction of 2-amino-3-cyanothiophenes with cyanamides in an acidic medium [11].

![Chemical structure of 2-aminothienopyrimidin-4-imines](image)

Di(methylthio)thienopyrimidines (9) can be synthesized from iminothienothiazinethiones [12].

![Chemical structure of di(methylthio)thienopyrimidines](image)
Thieno[3,2-d]pyrimidine derivatives (10) synthesized by reaction of methyl-3-aminothiophene-2-carboxylate with CSCl₂, NH₂CH₂CN and alkyl halides [13].

2-chloroacetylamino-3-ethoxycarbonylthiophene reacts with salts KXCN (X=S or Se) to give substituted thienopyrimidines (11) [14].
Biological Importance

Thienopyrimidines are important class of fused heterocycles that are of considerable interest on account of diverse range of their biological activities [15] such as; antibiotic [16], radioprotective [17,18], anticancer [19-21], antimicrobial [22-25], antiviral [26], antiproliferative [27], antifolate [28-30], anamesic [31], anaphylactic [32], antihistaminic [33,34], antiglaucoma [35], antioxidant [36,37], anticoccidial [38], thrombolytic [39] antifungal [40,41], neurotropic [42], molluscicidal and larvicidal [43,44], antipyretic [45-47], analgesic [48-52], antipsychotic [53], anticonvulsant [54-57], anti-inflammatory [58-60], ulcerogenic index [61], antihypertensive [62], antibacterial [63-65], antiallergic [66,67], antiarrhythmic [68], antidepresant [69].

Many thieno[2,3-d]pyrimidine derivatives were reported as phosphodiesterase inhibitors [70], also exhibit good H1 receptor antagonistic activities [71]. 4-amino thienopyrimidine derivatives show insecticidal, pesticidal and acaricidal activities [72]. Numerous thieno[2,3-d]pyrimidines have been proved useful for cerebral ischemia, malaria, tuberculosis, Alzheimer’s and Parkinson’s diseases [73-75].

Some thienopyrimidine derivatives have also found as fluorescent dyes for biomolecule detection and as novel ionophores in plasticized poly(vinyl chloride) matrix membrane sensors for uranyl ions [76].

Literature Review

Panico et al. synthesized thienopyrimidine derivatives (12) to report the effects of synthesized compounds on the prevention of cartilage destruction in articular disease [77].

(12)

Mkrtchyan et al. synthesized 2-R-substituted-3-amino-6,6-dimethyl-5,6-dihydro-8H-pyrano[4',3':4,5]-thieno[2,3-d]pyrimidin-4-ones (13) [78].

Shestopalov and co-workers synthesized 10-oxo-10H-pyrido[1,2-a]thieno[3,2-d]pyrimidines and 10-oxo-10H-pyrido[1,2-a]thieno[3,4-d] pyrimidines and all the synthesized compounds were evaluated for their antiallergic activity [80].

Sasaki et al. synthesized thieno[2,3-d]pyrimidine-2,4-dione derivatives (15) as highly potent and orally active non-peptide LHRH antagonist [81].

Thieno[2,3-d:5,4-d'] dipyrimidine-4,5-(3H,6H)-diones (16) synthesized by Ding and co-workers [82].
Oganisyan et al. synthesized novel condensed pyrano[4′,3′:4,5]thieno[3,2-e]triazolo[3,4-b]pyrimidine derivatives from 2-amino-3-carbethoxy-5,5-dimethyl-4,5-dihydro-7H-thieno[2,3-c]pyran and the structures of synthesized compounds have been identified by X-ray analysis [83].

Thieno[3,4-d], thieno[3,2-d] and thieno[2,3-d]pyrimidine-2,4-diones with (phenylpiperazinyl)alkyl substitution at N₃ position synthesized by Moustafa et al. for blood pressure lowering activity in the conscious spontaneously hypertensive rat. It was found that more potent compounds have [(2-methoxyphenyl)piperazinyl]ethyl moiety at N₃ position and hydrogen present at N₁ position [84].

Modica et al. synthesized piperazinyl-substituted thienopyrimidine derivatives (17) and binding properties on 5-HT₃ and 5-HT₄ serotonin receptors [85].

Munchhof et al. synthesized thienopyrimidine derivatives (18) as potent inhibitors of VEGFR-2 kinase [86].

Dai and co-workers discovered C₅ and C₆-substituted aminothieno pyrimidines (20) based multitargeted receptor tyrosine kinases inhibitors [87].
2,4-Diaminothieno[2,3-\textit{d}]pyrimidine (21) lipophilic antifolates synthesized by Gazzara \textit{et al.} as potent inhibitors of \textit{Pneumocystis carinii} and \textit{Toxoplasma gondii} dihydrofolate reductase [88].

Moore \textit{et al.} synthesized thienopyrimidine derivatives having structure (22) [89].

Tavares \textit{et al.} synthesized thieno[3,2-\textit{d}]pyrimidinone derivatives (23) as potent and selective MCHR1 antagonists. These antagonists provide to discovery of new therapies for the treatment of obesity [90].
Phoujdar and co-workers synthesized novel 2-unsubstituted-4-(substituted)anilinothieno[2,3-\(d\)] pyrimidines (24) under microwave irradiation [91].

Abu-Zieda synthesized thienopyrimidine and thiazolothienopyrimidine derivatives [92].

Alagarsamy et al. synthesized some novel 2-mercapto-3-(substituted amino)-5,6,7,8-tetrahydro-3\(H\)-benzo[4,5]thieno[2,3-\(d\)]pyrimidin-4-ones (25) from 2-amino-3-carbethoxy-4, 5, 6, 7-tetrahydrobenzo thiophene as starting compound [93]. All the synthesized compounds were investigated for analgesic and anti-inflammatory and ulcerogenic index activities. It was found that when R\(_1\) = -CH\(_3\) and R\(_2\) = -C\(_6\)H\(_5\) the compound showed more potent anti-inflammatory activity compared to the reference standard diclofenac sodium.

Prasad et al. synthesized some novel triazolothienopyrimidines (26). All the synthesized compounds were screened for their affinity towards A\(_1\) and A\(_{2A}\) receptors at 1 \(\mu\)M concentration. In the series, two compounds are most potent containing an ethyl side chain at C\(_5\)-position while increasing or decreasing the alkyl chain length, reduced affinity [94].
Rheault et al. synthesized novel thienopyrimidine cores (27) to show anti-proliferative activity with IC\textsubscript{50} values less than 1µM against human tumor cell in vitro [95].

Ouf et al. synthesized some thienopyrimidine derivatives and tested for analgesic and antiparkinsonian activities [96].

Modica et al. discovered [(arylpiperazinyl)alkyl]thieno[2,3-d]pyrimidine derivatives screened for in vitro 5-HT\textsubscript{1A} receptor affinity and noted the importance of an amino group in position-3 of thienopyrimidine system for the interaction with 5-HT\textsubscript{1A} receptor binding sites [97].

Bencsik et al. discovered a novel series of dihydrothienopyrimidine derivatives (28) as potent Akt inhibitors [98].
Luke et al. synthesized novel thienopyrimidine derivatives (29) as kinase inhibitors containing moderate potency in cellular assays of Tie-2 inhibition, good physical properties, Drug Metabolism and Pharmacokinetics (DMPK) and showed evidence of in vivo inhibition of Tie-2 [99].

![Image](29)

Gangjee et al. synthesized 2-amino-4-oxo-5-substituted-6-ethyl thieno[2,3-d]pyrimidines and evaluated as potent inhibitors of TS and DHFR [100].

Gillespie et al. synthesized 4-arylthieno[3,2-d]pyrimidine derivatives as potent adenosine A$_{2A}$ receptor antagonists to provide novel therapy for the treatment of Parkinson’s disease [101].

Kortum et al. synthesized thienopyrimidine derivatives (30) based P2Y12 platelet aggregation inhibitors [102].

![Image](30)

Bedford et al. discovered a novel class of antagonists (31) of the human adenosine A$_{2B}$ receptor to play a role in diverse indication such as nociception, diabetes, cancer and respiratory conditions [103].
Waterson et al. synthesized alkynyl thienopyrimidine derivatives (32) as inhibitors of EGFR and ErbB-2 kinases and also display potent, selective inhibition of cellular proliferation [104].

Dotsenko et al. synthesized 6-benzoyl-5-(2-chlorophenyl)-3-(4-methyl)-3,4,5,6-tetrahydro thieno [2,3-d] pyrimidine-4a(2H)-carbonitrile by Mannich reaction [105].

Wu et al. synthesized tetrahydropyridothieno[2,3-d]pyrimidine derivatives (33) evaluated for their antiproliferative activity [106].

Hacker et al. synthesized 2-alkylthio-4-aminothieno[2,3-d]pyrimidines (34) to investigate in a daunorubicin accumulation assay with the human ovarian cancer cell line A2780 [107].
Katada *et al.* synthesized a series of thienopyrimidine derivatives (35) and screened for their cytotoxic effects on several cell lines [108].

Verheijen *et al.* discovered 2-arylthieno[3,2-*d]*pyrimidines (36) containing 8-oxa-3-azabicyclo[3.2.1]octane by the replacement of the morpholine group in the 4th-position to enhance the mTOR activity with excellent selectivity (up>1000-fold) over PI3K and good potency in a cellular proliferation assay (IC$_{50}$<50nM) [109].

Sasikumar *et al.* synthesized tricyclic thienopyrimidine-pyrimidones and screening as potent and selective mGluR1 antagonists for neuropathic pain [110].

Sutherlin *et al.* discovered (thienopyrimidin-2-yl)aminopyrimidine derivatives (37) as potent PI3K and mTOR inhibitors [111].
El-Kashef and co-workers synthesized pyrido[4',3':4,5]thieno [2,3-d] pyrimidine derivatives (38) from thienopyridine aminoester [112].

![Image](38)

Heffron et al. synthesized 6-aryl morpholino thienopyrimidines derivatives (39) as potent and efficacious dual PI3K/ mTOR inhibitors [113].

![Image](39)

Kaplan and co-workers synthesized 2-ureidophenyl-thieno[3,2-d] pyrimidines (40). It was found that PI3K activity of the synthesized thienopyrimidines was similar to or slightly better and also mTOR potency was slightly lower than that of the corresponding pyrazolopyrimidines [114].

![Image](40)

Kumar et al. synthesized 4-(hetero)aryl substituted thieno[2,3-d] pyrimidines (41) and (42) from 4-chloro-thieno[2,3-d]pyrimidines in good to excellent yields [115].
Shirisha et al. synthesized novel N-and O-perfluoroalkyl triazole tagged thienopyrimidines (43). All newly synthesized compounds evaluated for their binding affinities towards adenosine receptors. It was found that the aryl substitution at second position to influence the binding properties, where selectivity towards \( A_{2A} \) receptor was increased and reduced with alkyl and aralkyl substitution [116].

Rashad et al. discovered some novel fused thieno[2,3-d] pyrimidine derivatives (44) from 2-amino-4,5-dihydronaphtho[2,1-b]thiophene-1-carbonitrile and the synthesized compounds were screened for antiviral activity against anti-avian influenza virus (H5N1) [117].

Brough et al. synthesized 2-aminothieno[2,3-d]pyrimidine derivatives as a class of H$_{sp}$90 inhibitor [118].

Tasler et al. synthesized thienopyrimidine derivatives having following structure (45) as human \( \beta3 \)-adrenoceptor agonists [119].
Thieno[2,3-\(d\)] and thieno[3,2-\(d\)]pyrimidines synthesized by Snegaroff \textit{et al.} using a mixed lithium-cadmium base and all some target compounds were screened for their anticancer activities [120].

Gorja \textit{et al.} synthesized novel 4-alkynylthieno[2,3-\(d\)]pyrimidine derivatives (46) in good to excellent yields and screened for their cytotoxic activity against chronic myelogenous leukemia (CML) cell line \textit{in vitro} [121].

Deng \textit{et al.} synthesized thienopyrimidine derivatives (47) in high yields. All the newly synthesized compounds were evaluated for activity against DPP-4 enzyme and for selectivity against DPP-8 and DPP-9. Among them, one compound has 10 times more active than Alogliptin \textit{in vitro} [122].
Golub et al. synthesized substituted (thieno[2,3-\textit{d}]pyrimidin-4-ylthio)carboxylic acids (48) and tested \textit{in vitro} towards human protein kinase CK2. It was found that $R^4=\text{propionic acid}$ showed highest inhibitory activity of the synthesized compounds. The most active compounds have IC$_{50}$ values of 0.1 $\mu$M and 0.125 $\mu$M [123].

![Chemical structure of the synthesized compounds] (48)
INTRODUCTION OF BENZOTHIAZOLE

Thiazoles are found in a variety of specialized products, often fused with benzene derivatives, are so-called benzothiazoles. Thus, benzothiazoles are a large family of compounds and their chemical structure containing a benzene ring fused with a thiazole ring is rather stable and is quite intractable towards microorganisms and direct photolysis.

The history of the true thiazole series begins in 1879 with the work of Hofmann, who synthesized derivatives of benzothiazole such as 2-chloro benzothiazole and 2-phenylbenzothiazole.

There are various methods for synthesis of benzothiazole derivatives [124-128], some of them are described here.

The reaction below the example for the synthesis of 2-amino-4,5\textit{b}-substituted thiazole (49) via the pathway of first synthesized substituted thiouride derivatives of substituted-1’-amines and followed by the cyclization with bromine [129].

\[ \begin{align*}
R &= 6-\text{NO}_2, 6-\text{Cl}, 6-\text{CH}_3, 6-\text{H}, 6-\text{OCH}_3, 6-\text{OH}, 6-\text{NCOCH}_3 
\end{align*} \]
Benzothiazole (50) can also be synthesized by direct thiocyanation (KSCN/CuSO₄) of substituted anilines [130].

\[
\begin{align*}
\text{R} & \quad \text{NH}_2 \\ 
\text{H}_2\text{C} &
\end{align*}
\quad \xrightarrow{\text{KSCN/CuSO}_4} 
\begin{align*}
\text{R} & \quad \text{NH}_2 \\ 
\text{H}_2\text{C} &
\end{align*}
\quad (50)
\]

It has also been found that acetyl phenyl thiourea on treatment with nitric acid produces 2-acetylamino-6-nitrophenylbenzothiazole which on hydrolysis with NaOH to give 2-amino-6-nitrophenylbenzothiazole (51) [131].

\[
\begin{align*}
\text{R} & \quad \text{S} & \quad \text{C} & \quad \text{NHCOCH}_3 \\ 
\text{H}_2\text{C} &
\end{align*}
\quad \xrightarrow{\text{Conc HNO}_3} 
\begin{align*}
\text{R} & \quad \text{O}_2\text{N} & \quad \text{NHCOCH}_3 \\ 
\text{H}_2\text{C} &
\end{align*}
\quad \text{Hydrolysis} \\
\begin{align*}
\text{R} & \quad \text{O}_2\text{N} & \quad \text{NH}_2 \\ 
\text{H}_2\text{C} &
\end{align*}
\quad (51)
\]
Biological Importance

Benzothiazole derivatives exhibit a wide range of biological activities [132,133], Benzothiazole moiety exhibits activity such as antiallagesic [134], antiparastic [135], antitumour [136-138], anti-glutamate [139], antifungal [140], vasdilator [141], anticancer [142], brest cancer [143], anti tubercular [144], CNS [145], photosynthesis inhibiting activity [146,147], anti-inflammatory [148,149], antibacterial [150], etc.

Literature Review

Mohomad et al. synthesized 2-(substituted phenyl)-3-(6-chloro-2-benzothiazol-2-yl)-5H-thiazolidinones (52) showed significant antibacterial and antifungal activity [151].

![Image](52)

Gurupadaiah et al. have synthesized 6-fluoro-7-[aniline/morpholino/piperazino]-2-[N-p-tolylsulfonamido]-benzo-thiazoles (53). Some of these have found to exhibit antibacterial activity [152].

![Image](53)

Vasselin et al. synthesized (54 & 55) a new series of -F, -OCH$_3$ and -NH$_2$ substituted isoflavones as a potential antitumor agents based on structural similarities to known flavones and isoflavones and antitumor 2-phenyl benzothiazoles [153].
Mahran and co-workers synthesized (56) and *in vitro* evaluation of new benzothiazole derivatives as schistosomicidal agents [154].

Siddiqui and co-workers synthesized a series of sulphonamide derivatives (57) in good yield and evaluated for their possible anticonvulsant activity and neurotoxic study [155].

Nah *et al.* synthesized various lanthanide complexes with benzothiazole derivatives (58) and investigated their photophysical properties [156].
Alang et al. synthesized different benzothiazole derivatives (59) and evaluated their antibacterial activity [157].

![Chemical Structure](image1)

(59)

Korman synthesized number of aryl substituted benzothiazole-2-sulfonamides (60), all of which are potent carbonic anhydrase inhibitors. Among these compounds 6-ethoxybenzothiazole-2-sulfonamide found to be clinically useful diuretics [158].

![Chemical Structure](image2)

(60)

Srivastava et al. synthesized 2-aminobenzothiazole derivatives (61) and evaluated their antibacterial and antifungal activity [159].

![Chemical Structure](image3)

(61)

Nagarajan et al. synthesized thiazolidinone derivatives (62) and evaluated their antibacterial activities [160].
Moghaddam et al. investigated facile and efficient one-pot protocol for the synthesis of benzoxazole and benzothiazole derivatives using molecular iodine as catalyst [161].

A. Hassan studied important reactions of 2-cyanomethyl-1,3-benzothiazole (63) and evaluated their antitumor activity [162].

Fadda et al. reviewed various methods for the synthesis of 2-cyano methylbenzothiazole, its chemical reactivity towards different electrophiles and nucleophiles and its use for the synthesis of heterocyclic compounds. Its biological activity and applications were also reported [163].
INTRODUCTION OF CHALCONE

Chalcones [164] are the compounds where aromatic substituent are introduced at the terminal position of the system -C=C-C=O. So, chalcones are characterized by their position of an Ar (A)-CO-CH=CH-Ar (B) (63) in which two aromatic rings A and B are linked by an aliphatic three carbon chain.

Chalcones or 1,3-diaryl-2-propen-1-ones, belong to the flavonoid family. Chemically they consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α, β -unsaturated carbonyl system. Chalcones are the precursors in the biosynthesis of anthocyanins and flavones. Chalcones and substituted chalcones can be synthesized in laboratory by Claisen-Schmidt condensation of acetophenone or substituted acetophenones with aldehydes. The first condensation was reported by Kestanecki [165, 166] and he gave the name “Chalcones”.

The chemistry of chalcone has been recognized as a significant field of study. The phenomenal growth of publications in this area is undoubtedly a reflection of the interest in this field throughout the world. An interesting feature of chalcones is that they serve as starting materials for the synthesis of various heterocyclic compounds such as pyrimidines, pyrazolines, flavones, flavonols, flavanones, aurones and benzoylcoumarones as well as certain compounds like deoxybenzoins and hydantions which are of some therapeutic importance.

The chalcones have a carbon skeleton made of two aromatic rings A and B which are linked by an aliphatic three carbon chain.

![Diagram of chalcone structure](image)

(63)

The chalcones or phenyl styryl ketones are α, β -unsaturated ketones containing the reactive keto-ethylenic group (-COCH=CH-). The chalcones are coloured compounds because of the presence of the chromophore (-COCH=CH-).
In fact, the pharmacological properties of chalcones are due to the presence of both $\alpha$, $\beta$-unsaturation.

Chalcones are natural compounds that are largely distributed in plants, fruits, and vegetables. They belong to the flavonoid group of molecules and some of them exhibit numerous biological activities. They are precursors in flavonoid biosynthesis. The enzymatic cyclization of the 6'-hydroxychalcones leads to the formation of flavanones and subsequently to a large number of flavonoid groups including flavones, flavonols, dihydroflavonols, aurones and isoflavones [167].

**Biological Importance**

Chalcones are essential intermediate compounds in flavonoid biosynthesis, and they are easily found in arboreal or smaller plants. They can be obtained by several chemical methods and Claisen–Schmidt's condensation is most important. Many studies have shown that they are compounds of great chemical and pharmacological interest because they exhibit many biological activities such as antimicrobial [168-170], antitumor [171-173], antimalarial [174-176], cytotoxic [177,178], antidepressant [179], anti-inflammatory [180], anti HIV [181], anticancer [182] and inhibitor [183,184].

Chalcone are potential biocides, because of some naturally occurring antibiotics [185] and aminochalcones [186,187] probably own their biological activity in presence of $\alpha$, $\beta$-unsaturated carbonyl group.
Literature Review

Boumendjel *et al.* reported chalcones (64) and their antimitotic and antiproliferative activities [188].

![Image of chalcone structure](image)

Yadav *et al.* synthesized N and S containing furanoflavonoids and thiophenylflavonoids (65), which have been screened for their antifungal and antibacterial activity [189].

![Image of furanoflavonoid structure](image)

Meng *et al.* discovered some novel heteroaryl substituted chalcones (66), as inhibitors of TNF-alpha-induced VCAM-1 expression [190].

![Image of heteroaryl substituted chalcone structure](image)
Shafiee et al. synthesized azachalcones (67) and studied their antimycobacterial and antifungal agents [191].

![azachalcones](image67)

Kumar and co-workers synthesized heterocyclic indoles (68) and their anti-inflammatory activity [192].

![heterocyclic indoles](image68)

Jadhav and Ramaa synthesized fluorinated chalcones (69) and studied their anti-inflammatory activities [193].

![fluorinated chalcones](image69)

Chiaradia et al. synthesized chalcones (70) from 2,4,6-trimethoxy acetophenone and studied their anti-inflammatory activity [194].

![chalcones](image70)
Cheng et al. synthesized 2,5-dialkoxylchalcones (71) and studied their cytotoxic, anti-inflammatory and anti-oxidant activities [195].

![Image of 2,5-dialkoxylchalcones](image)

(71)

Dominguez et al. synthesized sulfonamide chalcone derivatives (72) and studied their antimalarial activity [196].

![Image of sulfonamide chalcone derivatives](image)

(72)

Mishra et al. synthesized 1,3-diaryl propenone (73) and studied their *in vitro* antimalarial activity [197].

![Image of 1,3-diaryl propenone](image)

(73)

Ferrer et al. synthesized [(7-chloroquinolin-4-yl)amino]chalcones (74) as a potential antimalarial and anticancer agents [198].

![Image of [(7-chloroquinolin-4-yl)amino]chalcones](image)

(74)
Xia et al. synthesized novel 2-amino chalcones (75) as antitumor agents [199].

Khan et al. synthesized novel boronic-chalcones having structure (76) and screened for their antitumor activity [200].

Midiwo and co-workers synthesized 9-hydroxy homo-isoflavanone chalcones (77) and screened for their anti-plasmodial activity [201].
Kalirajan and co-workers synthesized some chalcones (78) and their antibacterial and anti-inflammatory activities [202].

![Chemical structure of chalcone (78)](image)

Boeck et al. synthesized novel chalcone analogues (79) with antileishmanial activity. Analogues containing nitro, fluorine or bromine group respectively displayed increased selectivity against the parasites as compared with natural chalcone [203].

![Chemical structure of chalcone analogues (79)](image)

\[
R=\text{NO}_2, \ R'=\text{H}, \ R''=\text{H} \\
R=\text{H}, \ R'=\text{F}, \ R''=\text{H} \\
R=\text{NO}_2, \ R'=\text{H}, \ R''=\text{Br}
\]

Desai et al. synthesized chalcones (80) and studied their antimicrobial activities [204].

![Chemical structure of chalcones (80)](image)

Fathalla et al. have synthesized chalcones (81) and studied their antimicrobial activity [205].
Swamy and Agasimundin synthesized certain substituted chalcones (82) and studied their antimicrobial activity [206].

Alcaraz and co-workers described the role of nuclear factor-kappa B and heme oxygenase-1 in the mechanism of action of an anti-inflammatory activity [207]. Nerya et al. synthesized chalcones as potent tyrosinase inhibitors [208].

Purohit et al. synthesized 2-(4′-chlorophenyl)-6- methyl-3-[1”-aryl-2”- propene-1”-one-3-yl]-imadazo[1,2-a]pyridine derivatives (83) and evaluated their antimicrobial activity [209].

Rana et al. synthesized chalcone derivatives (84) and found to be shown good as anti-inflammatory [210].
Joshi synthesized some chalcones (85) and evaluated antitubercular, antibacterial and antifungal activities [211].

Rathod and co-workers synthesized novel chalcones derivatives of phthalimidoester (86). All the synthesized compounds were screened for their antimicrobial and anti-inflammatory activities [212].
INTRODUCTION OF SCHIFF BASE

Schiff bases, named for Hugo Schiff, are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. They are organic compounds with the general formula $RR'C=NR''$, where $R$ and $R'$ represent hydrogen, an alkyl or an aryl and $R''$ is an alkyl or aryl; in the latter case, Schiff bases are also called anils. Schiff bases are crystalline or oily substances that are insoluble in water and soluble in organic solvents. They are weak bases, forming salts with acids in an anhydrous medium; in aqueous acid solutions undergo hydrolysis to yield an amine and aldehyde. The majority of Schiff bases are stable in alkaline solutions. Schiff bases undergo hydrogenation to give secondary amines ($RR' \text{CH-NHR''}$) and add on many compounds containing mobile hydrogen, such as β-dicarbonyl compounds, ketones, and imines. They are produced mainly by the condensation of aldehydes or ketones with primary amines. The reaction was first completed by H. Schiff in 1864 (hence the name of the compounds). Schiff bases are valuable intermediate products of organic synthesis, for example, in the preparation of secondary amines and various heterocyclic compounds. The Schiff bases known as azomethine dyes are used for dyeing acetate and synthetic fibers; they are also used in colour photography to reduce the photosensitivity of photographic emulsions.

Structurally, a Schiff base (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group has been replaced by an imine or azomethine group [213]. Many methods for the synthesis of Schiff bases [214-216] developed and the simplest method appears is to condense by boiling them into alcohols. Aldehydes and ketones react with primary amine ($R-NH_2$) and with other ammonia derivatives ($Z-NH_2$) to form Schiff base (imine) (87). An imine is a compound with a carbon-nitrogen double bond (-CH=N-).
Biological Importance

Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and polymer stabilisers. Schiff bases also shown to exhibit a broad range of biological activities including antimicrobial [217-222], anti-inflammatory [223-226], antitubercular [227-229], antimycobacterial [230,231], antioxidant [232], antiviral [233] and inhibitors [234].

Thiacetazone and Nitrofuryrazone are the drugs which have Schiff base in their structures which are responsible for their biological activities.

Literature Review

Panneerselvam and co-workers have synthesized schiff base of 4-(2-aminophenyl)-morpholines (88) synthesized and studied their analgesic, anti-inflammatory, antibacterial and antifungal activities [235].

Sinha and co-workers synthesized N-arylidene-N-[2-oxo-2-(4-aryl-piperazin-1-yl)ethyl]hydrazide derivatives (89) containing isonicotinic acid hydrazide-hydrazone and evaluated their antimycobacterial activity [236].
Mamolo and co-workers synthesized [5-(pyridine-2-yl)-1,3,4-thiadiazole-2-yl]acetic acid (3,4-diaryl-3H-thiazole-2-ylidene)hydrazide (90) and tested for their in vitro antimycobacterial activity [237].

Kucukguzel and co-workers synthesized $N\'-(4$-methoxybenzamido)benzoyl]-$N^2$-[(5-nitro-2-furyl)methylene]hydrazine (91) inhibited the growth of several bacteria and fungi [238].
Sriram et al. have synthesized various diclofenac acid hydrazones (92) and evaluated their in vitro and in vivo antimycobacterial activities [239].

\[ \text{Hydrazone Structure (92)} \]

Lima and co-workers synthesized [(4-N,N-dimethylamino benzylidene-3-(3,4-methylenedioxyphenyl)propionylhydrazine] (93) was more potent than dipyrone and indomethacin are used as standard anti-inflammatory/antinociceptive drugs [240].

\[ \text{Hydrazone Structure (93)} \]

Turan-Zitouni et al. synthesized some 5-bromoimidazo[1,2-a]pyridine-2-carboxylic acid benzylidenehydrazide (94) and screened their antimicrobial activity [241].

\[ \text{Hydrazone Structure (94)} \]
Terzioglu and Gursoy synthesized some novel 2,6-dimethyl-N'-substituted-phenylmethyleneimidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazides (95) showed the most favorable cytotoxicity [242].

![Formula 95]

Dimmock et al. synthesized acetylhydrazones (96) provided good protection against convulsions, while the oxamoylhydrazones (97) were significantly less active [243].

![Formula 96]

![Formula 97]

Gursoy and Guzeldemirci-Ulusoy synthesized 6-amino-4-aryl-2-oxo-1-(1-pyrid-3-yl- or 4-yl-ethylidene-amino)-1,2-dihydro pyridine-3,5-dicarbonitrile (98) and studied their antitumor activity [244].

![Formula 98]
4-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the mammalian brain. Ragavendran et al. have synthesized GABA hydrazones (99) and evaluated their anticonvulsant properties in different animal models [245].

![Chemical Structure](image)

Xu Li and Xu Shiping synthesized a series of Schiff bases of indol-2-carboxaldehydes (100), which reported useful for anticancer agents [246].

![Chemical Structure](image)

Kamel et al. synthesized a series of sulfapyridine-polyhydroxyalkylidene (or arylidene)-imino derivatives (101) and reported their antitumor activity [247].

![Chemical Structure](image)

Krishnanand Singh and co-workers synthesized N-acetyl and N-methyl isatin derivatives (102) which showed an anticonvulsant activity [248].
Bhandari *et al.* have synthesized Schiff bases derived from 2-[(2,6-dichloroanilino) phenyl] acetic acid (diclofenac acid) (103) and studied their anti-inflammatory, analgesic and ulcerogenicity activities [249].

![Schiff base](image1)

(103)

Bawa and Kumar synthesized Schiff base of 8-methyl-tetrazolo[1,5-a] quinoline (104) and evaluated their anti-inflammatory and antimicrobial activities [250].

![Schiff base](image2)

(104)

Demirbas *et al.* synthesized new hydrazide-hyrazones containing 5-oxo-[1,2,4]triazole ring (105) and studied their antitumor activity in breast cancer [251].

![Schiff base](image3)

(105)
Valentina et al. synthesized some substituted 1,2,4-triazol-5-thione Schiff base (106) and studied their antioxidant activity [252].
INTRODUCTION OF AZETIDINONE

The azetidinone or $\beta$-lactams have been known as products of the reaction of certain ketenes with anils. It was discovered during the Second World War, as important antibiotics known as the penicillin contained a fused ring systems of which one part was a $\beta$-lactams ring.

The systematic name assigned to the conjugated doubly unsaturated ring made up of three carbon atoms and one nitrogen atom is azete [253], accordingly, the dihydro derivatives is named azetine and the saturated ring system is name azetidine.

The 2-carbonyl derivative of azetidine is known as 2-azetidinones. The development of the chemistry of the $\beta$-lactams was initiated by Staudinger and his co-worker during his classical studies of ketenes [254]. For several years these researches stood as only important contribution to this field of heterocyclic chemistry. However, since 1940 a tremendous impetus has been given to the reactivity of these compounds because of their relation to the structure of the naturally occurring penicillin. The 2-azetitinone ($\beta$-lactams) ring is a common structural feature of a number of broad spectrum $\beta$-lactam antibiotics including penicillins (107), cephalosporins (108), carbapenems (109), nocardicin A (110) and monobactams which have been widely used as chemotherapeutic agents to treat bacterial infection and microbial diseases [255,256].

(107)  (108)
These molecules operate by forming a covalent adducts with membrane bound bacterial transpeptidases which are also known as penicillin binding proteins (PBPs) involved in the biosynthesis of cell wall [257]. These mechanism based inhibitors prevent the construction of cell wall and eventually lead to cell lysis and death. Moreover due to their $\beta$-lactamase inhibitory action 2-azetidinones based heterocycles represent an attractive target of contemporary organic synthesis [258].

**Ketene-imine cycloaddition**

The ketene-imine cycloaddition was reported by Staudinger to be a smooth well-documented route to the synthesis of substituted $\beta$-lactam derivatives. In an effort to investigate a suitably substituted monocyclic $\beta$-lactam as a minimum requirement for biological activity, many scientists reported the *trans* stereoselective synthesis of butadienyl azetidinones and their Diels-Alder cycloaddition. This included the preparation of a series of Schiff’s bases and their reaction with dienylketene to produce a *trans* azetidinone. This involved the *in situ* formation of the ketene and its subsequent addition to the imine (111).
Biological importance

2-azetidinones commonly known as $\beta$-lactams are well-known heterocyclic compounds among organic and medicinal chemists. The activity of famous antibiotics such as penicillins, cephalosporins, nocardicins and carbapenems are attributed to the presence of 2-azetidinone ring in them. Azetidinones are very important class of compounds possessing wide range of biological activities such as antimicrobial [259-265], pesticidal [266], antitumor [267], antitubercular [268], anticancer [269], cytotoxic [270-272], enzyme inhibitors [273], elastase inhibitors [274] and cholesterol absorption inhibitors [275].

Literature Review

Halve et al. synthesized 2-hydroxy-5-(substituted phenylazo)-chloro-N-(substitutedphenyl)azetidin-2-one (112) and 2-hydroxy-5-(substituted phenylazo)-N-(1,3-diketo-substitutedphenylamine)-3-chloro-azetidin-2-one (113) as anti-microbial agent [276].
Havaldar and Khatri synthesized new azetidinones (112) as antibacterial and antifungal agent [277].

P. S. Reddy and co-workers synthesized novel bisquinazoline β-lactam derivatives (114) having following structure [278].

P. S. Reddy and co-workers synthesized novel bisquinazoline β-lactam derivatives (115) having following structure [278].
Synthesis and biological active compounds 1-[5'-{(2,4-dichloro-5-fluorophenyl)}-6-\(H\)1,3,4-thiadiazin-2-yl]-4-(substitutedphenyl)-3-chloro-2-oxo-azetidines (116) given by Patel and Desai [279].

![Chemical Structure 116](image)

Vasoya et al. synthesized 4-(substitutedphenyl)-3-chloro-1-(3'-chloro-5'-phenoxy-2-benzo[b]thiophenoylamino)-2-azetidinones (117) as a potent biological active agent [280].

![Chemical Structure 117](image)

Patel and Mistry synthesized novel azetidinones (118) and studied their antibacterial activity [281].

![Chemical Structure 118](image)

Bis heterocyclic synthesis and antimicrobial studies of biologically significant 2-[\(N\)-(3'-chloro-4'-substitutedazetidinone-2)]amino-4-hydroxy purines (119) given by Sharma et al. [282].
Some azetidinone derivatives with the \( p \)-anisidine moiety (120) synthesized and studied their antimicrobial activity by Bhat \textit{et al.} [283].

Gurupadayya \textit{et al.} synthesized 1-(7-chloro-6-fluorobenzothiazol-2-yl)-3,4-substituted-aryl-azetidin-2-ones (121) and studied their anti-inflammatory, analgesic, CNS depressant, muscle relaxant activities [284].

Novel azetidinones (122) synthesized and studied their antimicrobial activity by Arunkumar \textit{et al.} [285].
Mulwad and Mir synthesized coumarin based azetidinones (123) and screening their antimicrobial activity [286].

Desai et al. synthesized new azetidinones (124) and studied their antimicrobial activity [287].

Nagaraja and co-workers discovered azetidinones (125) and studied their antimicrobial activity [288].
Wadher et al. synthesized 2-azetidinones of 4,4-diamino diphenyl sulphone \((126)\) and reported their antimicrobial activities [289].

\[ \text{(126)} \]

Ansari and Lal synthesized novel azetidinone \((127)\) and studied their antimicrobial activity [290].

\[ \text{(127)} \]

Natarajan et al. synthesized novel 2-azetidinone \((128)\) and evaluate their leptospirocidal study [291].

\[ \text{(128)} \]
Srivastava *et al.* discovered \( N_{\gamma}-[\text{hydrazinoacetyl-(2-oxo-3-chloro-4-substituted aryl azetidine})]-\text{carbazoles (129)} \) and studied their antibacterial and antifungal activities [292].

![Diagram](image1)

(129)

Raga *et al* synthesized azetidinone derivatives from 5-chloro-3-methyl benzofuran (130) and studied their antitubercular activity [293].

![Diagram](image2)

(130)

Sharma *et al.* synthesized 1-(nicotinylamino)-2 substituted azetidine-4-ones (131) and reported as antibacterial agent [294].

![Diagram](image3)

(131)

Kumar and Rajput synthesized 3-(3-chloro-2-oxo-4-substituted-aryl-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanyl)methyl)-substituted-3\(H\)-quinazolin-4-ones (132) and screened their anti-inflammatory activities [295].
Kumar et al. synthesized 2-[(4’-oxo-3’-chloro-2’-phenylazetidin-1’-yl)aminomethyl]-3-[4’’-(p-chlorophenyl)thiazol-2’’-yl]-6-bromoquinazolin-4-ones (133) and showed as anti-inflammatory agents [296].

Valarmathy et al. synthesized new 3-chloro-4-phenyl substituted)-1-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2yl] azetidine 2-one (134) and evaluate their antibacterial activity [297].

Rajasekaran et al. synthesized novel azetidinones (135) and studied their anti-tubercular, antibacterial, anti-fungal, inflammation activities [298].
Sinh and co-workers synthesized two different azetidinones (136, 137) and studied their antibacterial activity [299].

Shanmugapandiyam et al. have synthesized a new series of 2-[4-(azetidin-2-one)-3-chloro-4-phenyl]-1H-phenyl benzimidazoles (138) and screened their analgesic, anti-inflammatory, antibacterial and antifungal activities [300].
INTRODUCTION OF THIAZOLIDINONE

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds. 4-thiazolidinone derivatives exhibit a vital role in many biological processes and synthetic drugs. They also exhibit a vital role owing to their wide range of pharmacological activities and industrial importance as stabilizers for polymeric materials. Numerous reports have appeared in the literature which highlights their chemistry and use.

Thiazolidinones are five membered aliphatic heterocycles containing sulphur and nitrogen at 1<sup>st</sup> and 3<sup>rd</sup> and carbonyl group at 4<sup>th</sup> position in the ring. It is also known as 4-oxothiazolidinone. Thiazolidinone are synthesized by the condensation of β-aminomercaptans with aldehydes or ketones and may also be synthesized by reducing 2-thiazolines with aluminium amalgam. The stability of thiazolidine depends greatly on substituents present.

There are numerous biologically active molecules with five member rings, containing two hetero atoms. Thiazolidinone (139) is an important scaffold known to be associated with several biological activities. 1,3-thiazolidin-4-ones are heterocycles that have an atom of sulphur at 1<sup>st</sup> position, an atom of nitrogen at 3<sup>rd</sup> position and a carbonyl group at 4<sup>th</sup> position. Numerous methods for the synthesis of thiazolidinones and also their diverse reactions offer enormous scope in the field of medicinal chemistry.

![Chemical Structure](image)

(139)

The chemistry of 4-thiazolidinones was reviewed in depth by Brown F. [301] in 1962 and by Newkome G. and Nayak A. [302] in 1977. 4-thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4<sup>th</sup> position (140). Substituents in the 2<sup>nd</sup>, 3<sup>rd</sup> and 5<sup>th</sup> positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to
the carbon atom in the 2\textsuperscript{nd} position (R and R’ in (141) or X in (142)). Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by (141) and (142).

\[
\begin{align*}
(140) & \quad (141) & \quad (142)
\end{align*}
\]

X = O, S

An improved protocol has been reported wherein \textit{N,N}-dicyclohexyl carbodiimide/2-(1\textit{H}-benzotriazo-1-yl)-1,1,3,3-tetramethyl uranium hexafluorophosphate is used as a dehydrating agent to accelerate the intramolecular cyclization resulting in faster reaction and improved yields [303,304]. The dicyclohexyl carbodiimide / 2-(1\textit{H}-benzotriazo-1-yl)-1,1,3,3-tetramethyl uranium hexafluorophosphate mediated protocol has the advantage of mild reaction conditions, a very short reaction time and product formation in almost quantitative yields. More importantly, yields of the 4-thiazolidinones are independent of the nature of the reactants. This modification is compatible with a solid-phase combinatorial approach to generate a library of compounds.
Several investigators [305-312] reported the various synthesis of thiazolidine derivatives.

**Biological importance**

4-thiazolidinone derivatives, an important group of heterocyclic compounds, have been the subject of extensive study in the recent past. Numerous reports have highlighted their chemistry and use. It has also been reported in literature that certain compounds bearing 4-thiazolidinone nucleus possess antimicrobial [313-323], anti-HIV [324-327], anti-inflammatory [328-330], antitubercular [331-333], anticonvulsant [334,335] and antioxidant activity [336].

**Literature Review**

Ottana *et al.* synthesized 5-arylidene-3-hydroxyalkyl-2-phenylimino 4-thiazolidinones (144) and studied their *in vitro* antidegenerative activity on human chondrocyte cultures [337].

![Diagram of 5-arylidene-3-hydroxyalkyl-2-phenylimino 4-thiazolidinones](image)

(144)

Archana and her co-workers synthesized newer thiadiazoaryl and thiazolidinonyl quinazolin-4(3H)-ones (145) as potential anticonvulsant agents [338].

![Diagram of thiadiazoaryl and thiazolidinonyl quinazolin-4(3H)-ones](image)

(145)
Imran et al. synthesized 2-(substitutedphenyl)-3-[[4-(1-naphthyl)-1,3-thiazol-2-yl] amino]-4-oxo-1, 3-thiazolidin-5-ylacetic acid (146) and reported their antihyperglycemic activity [339].

![Chemical Structure](image)

(146)

Agarwal et al. synthesized some potential thiazolidinonyl-2-oxo/thio barbituric acids (147) and studied their anticonvulsant activity [340].

![Chemical Structure](image)

(147)

Shingalapur et al. have synthesized 4-thiazolidinones (148) containing 2-mercapto benzimidazole moiety and studies their anticonvulsant, antidiabetic and DNA cleavage activities [341].

![Chemical Structure](image)

(148)

Chen et al. synthesized novel pyrimidines containing thiazolidinones (149, 150) and studied their HIV-RT inhibitory activity [342].
Hafez and El-Gazzar synthesized new thiazolidinone derivatives (151) and studied their antitumor activity [343].

Kamel et al. synthesized 2-aryl thiazolidin-4-one (152) and studied their antitumor activity [344].

Tatar et al. synthesized novel 2-isonicotinoylhydrazono-5-arylidene-4-thiazolidinones (153) and studied their anti-tuberculosis and antiviral activity [345].
Omar et al. synthesized novel 4-thiazolidinones (154) as potential antifungal and antibacterial drugs [346].

![Image of 154]

Barreca et al. synthesized 2,3-diaryl-1,3-thiazolidin-4-ones (155) and studied their anti-HIV activity [347].

![Image of 155]

Rao et al. synthesized 2-(2,6-dihalophenyl)-3-(pyrimidin-2-yl)-1,3-thiazolidin-4-ones (156) as non-nucleoside HIV-1 reverse transcriptase inhibitors [348].

![Image of 156]

Vazzana et al. synthesized 2,3-disubstituted-1,3-thiazolidin-4-one (157) as anti-inflammatory agents [349].

![Image of 157]
Bhati and Kumar synthesized 2-aryl-3-\{5-\{[1,3,4] thiadiazino[6,5-b]indol-3-ylamino\}methyl\}-1,3,4-thiadiazol-2-yl\}-1,3-thiazolidin-4-one (158) and studied their anti-inflammatory activities [350].

Banday and Rauf synthesized thiazolidinones (159) from fatty acids and evaluated their antimicrobial activity [351].

Gurupadayya et al. synthesized 3-(7-chloro-6-fluoro-benzothiazol-2-yl)-2-substituted-aryl-thiazolidin-4-ones (160) and studied their anti-inflammatory analgesic, CNS depressant, muscle relaxant activity [352].
Bhovi et al. synthesized thiazolidinone derivatives (161) by the condensation of Schiff bases and thioacetic acid [353]. All the synthesized compounds were screened in vitro for their antimicrobial activity by the cup plate method.

Kumar and Rajput discovered 3-(4-oxo-2-substituted-aryl-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanyl methyl)-substituted-3H-quinazolin-4-ones (162) and studied their anti-inflammatory activity [354].

Lesyk et al. synthesized twenty one new 2-thioxo-4-thiazolidinone derivatives (98) and screened for in vitro anticancer activity [355].
Rawal et al. discovered different 1,3-thiazolidin-4-ones (164) derivatives as anti-HIV agents [356-358].

(164)

Srivastava and Sen synthesized [(2''-substituted aryl)-4”-oxo-1””,3”-thiazolidine-3”-imino-acetyl]-2-aminobenzothiazole (165) and studied their antimicrobial activity [359].

(165)

Tatar et al. synthesized new 1,3-thiazolidine-4-ones derived from 1-[2-(benzoylamino)-4-(methylthio)butyryl]-4-alkyl/arylalkyl thiosemi carbazides (166, 167) and screening their antimicrobial, anti-tuberculosis, antiviral and anticancer activity [360].

(166)
Geronikaki *et al.* synthesized 2-thiazolylimino/heteroarylimino-5-arylidene-4-thiazolidinones derivatives (168) tested for SHP-2 inhibitory action using human recombinant GST-fusion SHP-2. Most of the tested compounds exhibit good inhibitory activity [361].

Havrylyuk *et al.* synthesized novel nonfused bicyclic thiazolidinone derivatives (169) and tested for antitumor activity at a single concentration of $10^{-5}$M against 57 cancer cell lines [362].

Sharma *et al.* synthesized various isoniazidothiazolidinones (170) and imidoxy derivatives (171) and studied their antimicrobial activities [363].
Sayyed et al. synthesized new 2,3-diaryl-1,3-thiazolidin-4-ones (172) and screened their antimicrobial activity [364].

Kavitha et al. synthesized bioactive venlafaxine analogs such as 2,3-disubstituted 1,3-thiazolidin-4-ones (173) as antimicrobial agents [365].

Rana et al. have synthesized various thiazolidinone derivatives from 3-\{[(1E)-(2'-chloro-7'-methoxyquinoline-3'-yl)methylene]amino\}-4-(substituted phenyl diazenyl)phenol (174) and studied their antimicrobial activities [366].
Palekar et al. synthesized new bis-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and bis-4-thiazolidinone derivatives (175) from terephthalic dihydrazide and studied their antimicrobial activities [367].

Ramalakshmi et al. synthesized thiazolidinone derivatives (176) of nicotinic acid and reported their antimicrobial, analgesic, anti-inflammatory activities [368].

Vicini et al. synthesized novel 2-thiazolylimino-5-arylidene-4-thiazolidinones (177) and screened their antimicrobial activity [369].
Saeed *et al.* synthesized some novel 2-arylimino-3-aryl-thiazolidin-4-ones and studied their antibacterial activity[370].
GEWALD AMINOTHIOPHENE SYNTHESIS

The chemistry of 2-aminothiophenes has received much attention upon their convenient availability through the most versatile synthetic method developed by Gewald and his co-workers [371].

Historical Perspective:

In 1966, German chemist Karl Gewald reported that aliphatic ketones, aldehydes or 1,3-dicarbonyl compounds (179) reacted with activated nitriles (180) and sulphur in the presence of an amine at room temperature to give 2-amino thiophenes (181) [372].

R₁, R₂ = H, alkyl, aryl, heteroaryl, COOR
X = CN, COOR, COPh, CO-heteroaryl, CONH₂

Mechanism:

The first step of the Gewald reaction is a Knoevenagel condensation of an activated nitrile with an oxo component (ketone or aldehyde) to produce an acrylonitrile, which is then thiolated at the methylene group with elemental sulphur. The sulphurated compound undergoes ring closure via nucleophilic mercaptide attack at the cyano carbon to provide intermediate. Finally, a prototropic rearrangement affords the 2-aminothiophene [373].