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Chapter 1

Significance of Thiazole-based Heterocycles for Bioactive Systems

Someshwar Pola

Abstract

Monocyclic and Bicyclic aromatic heterocycles such as imidazoles, thiazoles, thiadiazoles, oxazoles, oxadiazoles quinazolines, indoles, benzimidazoles, purines pyrido[4,3-d]pyrimidines, thiazolo[5,4-d]pyrimidines, thiazolo[4,5-d]pyrimidines, oxazolo[5,4-d]pyrimidines and thieno[2,3-d]pyrimidines are renowned pharmacophores in drug discovery. These special structures are well explained and exemplified in chemical compound libraries. In this chapter, several types of thiazole based heterocyclic scaffolds such as monocyclic or bicyclic systems synthesis and their biological activities studies are presented, which are not frequently present in books and reviews. We mention the first importance of synthetic route of various thiazole based compounds and their applications in medicinal chemistry in this chapter.

Keywords: Thiazole, privileged structures, thiazolopyridine, thiazolopyrimidines

1. Introduction

Currently, the whole pharmaceutical industry is encountered with the challenge of enhancing work rate and advancement. The key obstacles are the increasing expenses of exploration and expansion and a concurrent deteriorating amount of new chemical entities (NCEs). The source of this modernism shortfall is not the biology. Interpreting of the human genome has directed to a prosperity of drug targets. With the addition of more than 35,000 human genes, the hypothesis is that at least 2,000 are significantly tangled in the occurrence and progress of the illness. Moreover, since each of these genes is associated with the usefulness of between five and ten proteins, the deduction is that their potency be 5,000 – 10,000 aims for innovative drugs [1,2]. Even though the positive outline of protein therapeutics and the aptitude of gene therapy, key pharmaceutical establishments are even focused on research and growth of small molec-
ular mass compounds. Therefore, the challenge is to choose the greatest drugable objectives and formulate the conforming drug-like molecules. These materials are not only relative to the mark but also have precise pharmacokinetic and toxicological properties, which was allowed to be established as a drug. Medicinal chemistry as a scientific discipline has introduced several new techniques over the last few years to the rapidity of the drug discovery process, such as combinatorial chemistry, microwave-assisted organic synthesis, and high-output refinement [3]. Despite the stable rise in R & D, the total number of NCE successes in the market has reduced fundamentally. It appears clearly that choosing the suitable molecules to synthesize is one of the most difficult queries. It has been projected that the sum of potential compounds with molecular weight of lower than 500 Da is $10^{200}$, where only $10^{90}$ may retain drug-like applications. The percentage of molecules prepared until today has been projected as one part in $10^{95}$ or approximately the fraction of the mass of the proton to the mass of the sun. The concern is, therefore, the selection of new molecules from this vast universe that have the potential to be biologically active [4]. To build a new drug discovery mission and to discover the bioactive compounds, various possibilities are offered. Triumphs can be achieved via a virtual screening method or can be simulated from technical or manifest literature. Most often than not, drug innovation projects start with a high quantity screening operation of commercially accessible compound collections besides targeting curiosity. It became clear in recent years that combinatorial libraries are not distinct enough. As the core attention of the Laboratory of Medicinal Chemistry showed in the synthesis and biological evaluation of bicyclic aromatic heterocycles [5], it is scrutinized that the number of accessible bicyclic heterocycles is principally restricted to a well-known nitrogen enclosing compounds, such as pyrimidines, thiazoles, coumarins, thiazopyridines and benzothiazole (Figure 1).

![Figure 1. Examples of privileged structures](image)

In vision of the significance of thiazoles and their derivatives, numerous approaches for its synthesis were developed by various groups such as Hantzsch [6], Tchernic [7], Cook-Heilborn and Gabriel [8].

A thiazole ring system originates naturally in the crucial water soluble vitamin thiamin, also known as Vitamin B1, which supports the discharge of energy from carbohydrates through the course of metabolism. The occurrence of thiazole ring in vitamin B1 and its coenzyme play a significant role in the decarboxylation of alpha-keto acids and as an electron sink, respectively [9]. It also assist in the regular operational of the nervous system through its character in the synthesis of acetylcholine, a neurotransmitter.

Thiazole ring system appears in the bacitracin and penicillin antibiotics and various synthetic drugs. Synthetic drugs belonging to the thiazole family consist of the antimicrobial agents acinitrazole (1) and sulfathiazole [10], (2) antibiotic penicillin [11], (3) antidepressant prami-
pexole [12], (4) antineoplastic agents Bleomycin (5) and Tiazofurin [13], (6) anti-HIV drug Ritonavir [14], (7) the antiasthmatic drug cinalukast [15], (8) antiulcer agent Nizatidine [16] (9). Additionally, extensively used thiazole derivatives are the non-steroidal immunomodulatory drug Fanetizole [17] (10) and anti-inflammatory drug Meloxicam [18] (11). Thiazole derivatives with polyoxygenated phenyl module have exhibited encouraging anti-fungal activity [19]. Thiazoles found from microbial, and marine ancestries reveal antitumor and antiviral activities. Thiazole is recognized as ligand of estrogen receptors [20] and also as unique kind of antagonists for adenosine receptors [21].
Other substantial thiazoles take account of essential dyes and fungicides or nematicide, Tricyclazole 12, Thiabendazole 13, and Thifluzamide 14 are promoted for the switch of several agricultural pests [22,23]. Primuline yellow 15 and Rhodanine red 16 dyes are some of the best models of thiazole moiety containing dyes [24,25]. Numerous thiazoles are flavor materials and also originate in roasted peanuts. They materialized in foods by the exploit of sulfur-containing amino acids interacting with carbohydrates. Thiazoles are surrounded by some significant heterocyclic compounds that give the flavor of fermented coffee [26].

![Resonating Structures of Thiazole](image)

The exhilarating outcomes of the 2,4-disubstituted thiazoles as a unique class of Src Homology 2 (SH2) inhibitors for the behavior of osteoporosis and breast cancer have also been reported [27]. Selection of the 2,4-disubstituted thiazoles as concealed pharmacophores for diacylhydrazine of SC-51089, a prospective PGE2 antagonist have also been described [28]. With these results, the thiazole ring system proves to be a well-known structural motif that originate in several pharmaceutical agents and natural products extracted from various plants and marine systems.

2. Structure of Thiazole

The structure of thiazole is reflected as the resonance amalgam of the subsequent resonating structures (Figure 1). However, some of the resonating structures are also probable with the contribution of d-orbitals of the sulfur atom.

![Figure 2. Resonating Structures of Thiazole](image)

The p-bond orders quantified by molecular orbital methods have specified thiazole molecule to be aromatic with some dienic nature. Localization energies have projected reducing order of the nucleophilic reactivities following the order: 2 > 5 > 4 and the electrophilic reactivities
as: 5 > 2 > 4. Three hydrogen atoms present in the thiazole are anticipated to have the order of acidity as H2 >> H5 > H4.

3. Synthesis of Thiazole

In the assessment of the significance of thiazoles and their derivatives, numerous techniques for the synthesis of thiazole derivatives were established by various research groups such as Hantzsch [6], Tchernic [7], Cook-Heilborn and Gabriel [8]. Lately, thiazole derivatives were generated in the presence of various catalysts such as ammonium-12-molybdophosphate [29], cyclodextrins [30], iodine [31] and silica chloride [32] in organic solvents at higher temperature and solvents such as 1-methyl-2-pyrrolidinone [33], with the use of a microwave [34]. Numerous procedures for the synthesis of thiazole compounds are accessible, which can be categorized into the part structures demonstrated below. The earliest of these structures is observed to be the most significant and highly flexible of all the thiazole formation techniques. With a workable and first reactants, it approves alkyl, aryl, aralkyl or heterocycles to be taken in any one of the 2-, 3-, 4- or 5-carbons of the thiazole ring. This technique, better acknowledged by the name of the German chemist Hantzsch, who invented it in 1887, contains the condensation of a compound bearing the two heteroatoms on the same carbon with a compound attached one halogen and one carbonyl function on two adjacent carbon atoms. A boundless diversity of compounds may assist as nucleophilic reagent in this reaction, such as thiourea, thioamide, ammonium thiocarbamate or dithiocarbamate and its derivatives [35].

![Thiazole Structures](image1)

3.1. Synthesis from α-halocarbonyl compounds (Type Ia): Hantzsch’s synthesis.

First designated in 1887 by Hantzsch, the cyclization of α-halo carbonyl compounds by a wide diversity of reactants attached to the N-C-S portion of the ring is the most extensively popular process for formation of thiazoles.

![Hantzsch Reaction](image2)
3.1.1. Reactions with Thioamides

3.1.1.1. Chloroacetaldehyde and derivatives

Thiazole ready to obtain by condensing thioformamide and chloroacetaldehyde [36,37].

3.1.1.2. Condensation with higher thioamides (2,4-Disubstituted and 2,4,5-trisubstituted thiazoles)

The reaction between thioamide and various α-halocarbonyl compounds has been utilized broadly, and numerous thiazoles with alkyl, aryl, arylalkyl or heteroaryl of several functional groups at 2-, 4- or 5-positions have been published.

3.1.2. Reactions with N-substituted Thiourea

3.1.2.1. N-monosubstituted thioureas

The 2-monosubstituted or disubstituted aminothiazoles obtained reaction between Halo carbonyl and N-substituted thiourea compounds [38].

3.1.3. Reaction with salts and esters of thiocarbamic acid: 2-hydroxy thiazoles and derivatives

This technique, originated by Marchesini [39,40], in 1893 involves the condensation of a α-halocarbonyl compound with ammonium thiocarbamate to give 2-hydroxythiazole derivatives.
3.2. Thiazoles formation from reorganization of the α-thiocyanoacetophenones

The simple cyclic reaction of α-thiocyanoacetophenones in aqueous acid concentrated sulfuric acid in acetic acid, and water or alkaline solution gives to 2-hydroxy thiazoles after dilution in water. These reactions can be conceded out for various hours at room temperature or by refluxing for 1 or 2 hrs on a water bath [41-45].

α-Thiocyanoacetophenone reacts thiocid to yield 2-mercapto-4-phenyl thiazole.

α-Thiocyanoacetophenones highly react with alkyl amine or ammonium chloride to provide their N-substituted derivatives or 2-aminothiazoles [46].

3.3. Thiazoles from α-aminonitriles (Cook-Heilbron’s synthesis) (Type-II)

This category of synthesis, which was examined by Cook, Heilbron [47-49] give 5-aminothiazoles differently substituted in the 2-position by reacting with an aminonitrile with salts and esters of dithioacids, carbon oxysulfide, carbon disulfide, and isothiocyanates under remarkably very mild conditions.

3.3.1. Carbon disulfide: 2-mercapto-5-aminothiazole derivatives

Carbon disulfide freely reacts with α-aminonitriles giving 2-mercapto-5-amino thiazoles [50,51], which can be transformed into 5-amino thiazoles unsubstituted in the 2-position.

3.3.2. Esters and salts of dithioacids: 5-aminothiazole compounds and related condensations

By reducing the salts or the esters of both dithioformic and dithiophenacetic acids with α-aminonitriles, 5-aminothiazoles were achieved in better yields [52]. These reactions have agreed in aqueous ethereal solution at ambient temperature.
3.4. Thiazoles from acylaminocarbonyl compounds and phosphorus pentasulfide and related condensation (Gabriel’s synthesis) (Type III)

This reaction was originally designated by Gabriel [53] in 1910 phosphorus pentasulfide reacted with acylaminoketone (showed in below reaction) an equimolecular quantity to yield 2-phenyl-5-alkyl-thiazole. The reaction is analogous to the synthesis of additional five-membered oxygen and sulfur holding rings from 1,4-dicarbonyl compounds.

\[
\begin{align*}
\text{R}_2\text{NH} & + \text{R}_1\text{SH} \rightarrow \text{R}_2\text{N=S=R}_1 \\
\end{align*}
\]

3.5. Thiazoles from nitriles and α-mercaptoketones: 2,4-disubstituted and 2,4,5-trisubstituted derivatives

Also, α-halocarbonyl compounds and α-mercaptoketones react with nitriles and aldehyde oximes in the presence of an acid as catalyzed reaction for the synthesis of thiazoles.

3.5.1. 2,4,5-Trisubstituted thiazoles from α-mercaptoketones and nitriles

Miyatake and Yashikawa synthesized numerous 2,4,5-trisubstituted thiazoles and gave low yield (16 to 40%) by the interaction of α-mercaptoketones on nitriles. Asinger and Thiel [54] utilized an aldehyde and ammonia as an alternative for nitrile.

\[
\begin{align*}
\text{R}_1\text{O} & + \text{N} = \text{R}_2\text{SH} \rightarrow \text{R}_1\text{N=S=R}_2 \\
\text{R}_1, \text{R}_1, \text{and} \text{R}_2 \text{are different substituents} \\
\end{align*}
\]

3.5.2. 2,4-Diaminothiazole derivatives from α-halonitriles and thiourea

α-Halonitrile can substitute α-halogenocarbonyl compounds in the Hantzsch’s synthesis [55-57], thus, the reaction of thiourea with a α-halonitrile in refluxing alcohol provides 2,4-diaminothiazoles.

\[
\begin{align*}
\text{R} \equiv \text{X} & + \text{NH}_2\text{S} \rightarrow \text{NH}_2\text{N=S=NH}_2 \\
\text{R} & \text{Reflux} \\
\end{align*}
\]
3.6. Thiazoles from Vinyl Bromide

Thiazoles holding a variability of substituents such as aliphatic, aromatic, heterocyclic, or alkenyl groups can be synthesized by an intramolecular nucleophilic substitution reaction of \( N-(2\text{-bromoprop-2-enyl})\)thioamides [58]. This vinylc substitution technique would afford an exclusive synthetic method for a range of heterocycles.

![Chemical reaction diagram]

3.7. Synthesis of 2,4-disubstituted-5-acetoxythiazoles

From the viable existing methyl benzoate derivatives and with racemic phenyl glycine, a range of 2,4-disubstituted-5-acetoxythiazoles obtained in worthy to reasonable yields exhausting the succeeding scheme [59]. Due to the excellent thermal stability of the thiazole nucleus, the polymers integrating thiazole ring protocol have also been prepared.

![Chemical reaction diagram]

4. Biological importance of thiazoles

Thiazole moiety-containing compounds invention present an extensive range of applications in medicinal chemistry such as antibiotics, bacteriostatics, CNS regulators to high selling diuretics [60-64]. Thiazole framework has established wide application in drug growth for the treatment of hypertension [65], inflammation [66] and HIV infections [67]. Aminothiazoles are famous for being ligands of estrogen receptors [68] as well as a innovative type of adenosine receptor antagonists [69]. Other equivalents are utilized as fungicides, inhibiting \textit{in vivo} progress of Xanthomonas, as a component of herbicides or as schistosomicidal and anthelmintic drugs [70].

Sherif, et al. [71] syntheses of two series of compounds that is thiazolylantipyrines and thiadiazolylantipyrines, in which thiazolylantipyrine series exhibits better antibacterial potencies than the thiadiazolylantipyrine series of compounds. In thiazolylantipyrine series compounds 17 – 19 are well thought-out to be the better active antimicrobial members recognized in this study with a broad spectrum of antibacterial activity against both Gram positive and Gram negative bacteria.
Zablotskaya A et al. [72] prepared trimethylsilyl ethers of different hydroxyl group bearing thiazole compounds. All the compounds examined possess antihypoxic properties and extend the life of mice under conditions of hypoxia by 20-78%. The silylated and unsilylated derivatives in the preponderance of circumstances show antihypoxic activity.

Dae-Kee K et al. [73] produced a set of 5-(pyridin-2-yl)thiazoles enclosing a para or meta-carboxamide or carbonitrile-substituted phenylmethylamino moiety at the 2-position of the thiazole ring and was estimated for activating receptor-like kinase 5 (ALK5) inhibitory activity in cell-based luciferase publisher assays.

Rajan S G et al. [74] designed and synthesized a sequence of 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazoline-4-one 23 compounds. Synthesized molecules were estimated for their inhibitory activity in the course of record factors, nuclear factor-kB (NF-kB) and activating factor (AP-1) interceded transcriptional activation in a cell line based in vitro assay as well as for their anti-inflammatory activity in vivo model of severe inflammation.
Johan et al. [75] synthesized a unique sequence for Aurora kinase inhibitors enclosing thiozole moiety (SNS-314, 24). Also, key SAR as well as essential binding elements has been explained.

HI El-Subbagh et al. [76] synthesized a sequence of 2,4-disubstituted thiazole compounds containing N-n-butyl or N-cyclohexyl thioureido synthon at position-2 and N-substituted thiosemicarbazone moiety 25 at position-4 and verified for antitumor activity. All of the established derivatives revealed antineoplastic activity at concentrations less than 10^5 μM.

The unique model of a thiazole in the best 200 drugs citations is cefdinir 26 (Omnicef), a semi-synthetic third generation cephalosporin that is controlled orally and has a stretched antibacterial activity in contrast to both gram-positive and gram-negative bacteria. The key feature of cefdinir is that it exhibits outstanding activity against Staphylococcus species [77]. The thiazole ring in cefdinir reveals that the heterocyclic structure in a drug does not only affect its pharmacodynamic properties but can also affect its kinetics. It is hypothesized that the digestive tract iron (II) ions form chelate complexes with the oxime nitrogen atom and thiazole ring and, therefore, decrease the bioavailability of cefdinir [77].

The HIV-1 protease inhibitor ritonavir [78] (Norvir 7) contains two different substituted thiazole rings, which are presented at the advanced steps in the synthesis of this peptidomimetic antiviral compound. Remarkably, ritonavir is a consequence of advanced enhancements on earlier candidates for the action of AIDS [80].
The dopamine D2-agonist pramipexole 27 (Mirapex) contains a fused bicyclic tetrahydrobenzothiazole design, which is also easy to obtain by a Hantzsch-type condensation reaction between a α-brominated protected form of 4-aminocyclohexanone and thiourea [81].

Famotidine (28, Pepcidine) is one of the top an H2-receptor antagonists, which is equivalent to cimetidine that prevents various isoenzymes of the hepatic CYP450 system and the additional side effect (Swelling of the hands, feet or ankles) of enhancing the amount of gastric bacteria such as nitrate reducing bacteria. The arrangement of this ulcer therapeutic is very enthralling and contains a thiazole substituted guanidine and a sulfamoyl amidine. Current reports have performed designated famotidine as a significant ligand for numerous transition metals containing copper and cobalt developing tetradentate \[N, N, S, N\]-coordination spheres as revealed by single X-ray analysis [82]. Therefore, it seems viable that assured frequent bioavailable cations influence be included in the absorption and initiation of this thiazole involving compound. The formation of the thiazole ring [83,84] can be able again by condensation of thiourea with dichloroacetone.

One more example of a thiazole ring enclosing drug is known in the unique xanthine oxidase inhibitor febuxostat 29 (Uloric) which was accepted by the FDA in 2009 [85]. This inhibitor works by hindering xanthine oxidase in a non-competitive manner. Subsequently, the quantity of the oxidation product uric acid is decreased. Thus, it is an extremely well-organized action for hyperuricemia in gout.
Takeuchi et al. described the total synthesis of the cyclic tripeptide bistratamide H 30 established in the procedure of an extremely fluorous amino protecting group and multistep purifying by F-LPE using FC-72 in which 15 out of the 17 steps were purified by F-LPE [86].

The construction of two heterocyclic rings in one synthetic step has been developed for the preparation of coumarin derivatives. In this process, the thiazole ring (31–40) is accomplished by Hantzsch reaction monitored by fabrication of pyrazole by reacting a 3-(2-bromoacetyl) coumarin with thiosemicarbazide and acetylacetone at room temperature [87].

Adib et al. [88] described, in the latest work, a well-organized three component reaction that is significant to the formation of essential heterocycles titled by imidazo[1,2-a]thiazoles (41 & 42).

S. Zheng et al. [89] synthesized five series of thiazole derivatives (43–47) for fascin therapeutic target as emerged from cancer cells is thoroughly related to tumor progression and metastasis. The entire compounds based on thiazole derivatives examined anti-migration and anti-invasion activities via possible inhibition of fascin function. The five series of analogs with elongated alkyl chain substitutions on the thiazole nitrogen revealed better anti-migration activities than those with other structural motifs.
J. Zhu et al. [90] reported that Human dihydroorotate dehydrogenase (HsDHODH) is a flavin-dependent mitochondrial enzyme that has been specialized as a perspective therapeutic aim for the medication of rheumatoid arthritis and other autoimmune diseases. On the basis of the main compound 48, which was earlier recognized as potential HsDHODH inhibitor, a novel series of thiazole derivatives were designed and synthesized. The complex X-ray structures of the encouraging referents 49 and 50 established that these inhibitors bind at the recognized ubiquinone binding channel and directed us to explore additional potent inhibitors, such as compounds 44, 46, and 47 which exhibited double digit nanomolar activities of 26, 18, and 29 nM, respectively.

S. Singh et al. [91] P-glycoprotein (P-gp) works as a therapeutic target for the improvement of multidrug conflict reversal agents. In this study, we synthesized twenty-one novel derivatives by peptide coupling at equivalent carboxyl and amino termini of (S)-valine-based bis-thiazole and mono thiazole derivatives with different chemical scaffolds. Consuming calcein-AM efflux assay, we recognized compound 51 (IC$_{50}$ = 1.0 μM) containing 3,4,5-trimethoxybenzoyl and 2-aminobenzophenone groups, respectively, at the amino and carboxyl termini of the mono thiazole zwitterion. Compound 51 inhibited the photolabeling of P-gp with $^{[125]}$I- iodoaryla-zidoprazosin with IC$_{50}$ = 0.75 μM and motivated the basal ATP hydrolysis of P-gp in a concentration-dependent manner (EC$_{50}$ ATPase = 0.027 μM).
Oridonin 52, a complex molecule *ent*-kaurene diterpenoid obtained from the traditional Chinese herb *Isodon rubescens*, has demonstrated great potential in the treatment of various human cancers due to its unique and safe anticancer pharmacological profile. However, with oridonin’s poor solubility and poor bioavailability, hence C. Ding et al.\(^9\) inserted thiazole ring. The shortest way of synthesis of a series of novel nitrogen contained oridonin derivatives inserted thiazole-fused A-ring system through an active protecting group-free synthetic approach is the best of them, including compounds, 53–59 exhibited effective anti-proliferative effects against breast, pancreatic, and prostate cancer cells with low micromolar to submicromolar IC\(_{50}\) values as well as significantly improved aqueous solubility. These new derivatives achieved by realistically transforming the natural product have been established not only to induce considerably the apoptosis and inhibits the growth of triple-negative MDA-MB-231 breast cancer both in vitro and in vivo but also active against drug-resistant ER-positive MCF-7 clones.

M. E. D. Francesco et al. \(^[93]\) reported a unique type of inhibitor, which designates the identification of a structurally various series of compounds including a 2-amino-1,3-thiazole as substitution of the carbamate in P4. Optimization studies motivated on structural variations in the P3, P2, and P1 regions of the macrocycle as well as on the linked chain caused the discovery of numerous analogs characterized by outstanding levels of enzyme and cellular activity. Among these, compound 60 exhibited the best pharmacokinetic profile in preclinical species and revealed constant liver levels subsequent oral administration in rats.
P. J. Sanfilippo et al. [94] reported and described the synthesis and biological activity of a different kind of thiazole containing heterocycles as inhibitors of thrombin-induced human platelet aggregation. Additional estimation of selected compounds shows they inhibit platelet aggregation as motivated by a range of agonists. The highly active compounds also were established to inhibit fibrinogen binding to platelets. To further explain the mechanism of the action of these compounds, direct binding studies with the cleaned glycoprotein (GP) IIb/IIIa receptor were conducted. Flow cytometry analyzes of 61 and 62 designate that these compounds block the activation process of the GPIIb/IIIa receptor without denaturing the integrin receptor. On the basis of results, 62 showed the best profile as a novel non-peptide inhibitor of fibrinogen-mediated platelet aggregation.

J. E. M. Koezen et al. [95] prepared numerous N-[4-(2-pyridyl)thiazol-2-yl]benzamides, and these compounds exhibited adenosine affinities in the micromolar range. Most unexpected in the series of the N-[4-(2-pyridyl)thiazol-2-yl]amides were the retained adenosine affinities by the introduction of a cyclopentanamide instead of the benzamide.
P. C. Srivastava et al. [96] published a report in which they described the glycosylthiocarboxamides were used as the starting compounds for the synthesis of 2-D-ribofuranosylthiazole-4-carboxamide and 2-β-D-ribofuranosylthiazole-5-carboxamide (76). The structural variation of 2-β-D-ribofuranosylthiazole-4-carboxamide (77) into 2-(2,3,5-tri-O-acetyl- β-D-ribofuranosyl)thiazole-4-carboxamide (78), 2-β-D-ribofuranosylthiazole-4-thiocarboxamide, and 2-(5-deoxy- β-D-ribofuranosyl)thiazole-4-carboxamide (79) is also designated. These thiazole nucleosides were verified for in vitro activity against type-1 herpes virus, type-3 parainfluenza virus, and type-13 rhinovirus and an in vivo test was run against parainfluenza virus. They were also analyzed as potential inhibitors of purine nucleotide biosynthesis. It was revealed that the compounds (77 and 79) which influenced the most noteworthy antiviral activity were also active inhibitors (40-70%) of guanine nucleotide biosynthesis.
Z. Li et al. [97] described the virtual screening data for flavivirus envelope proteins (E proteins) having been exposed to play a vital role in virus assembly, morphogenesis, and infection of host cells. Inhibition of flavivirus infection of a host cell by utilizing the small molecule envelope protein antagonist is an interesting approach to the development of antiviral agents. The virtual screening of the NCI Chemical database utilizing the dengue virus envelope protein structure showed numerous theoretical hit compounds. Bioassay consequences recognized a class of thiazole compounds with antiviral potency in cell-based analyzes. Variation of these lead compounds directed to a series of derivatives with enhanced antiviral activity and reduced cytotoxicity. The maximum activity exhibit compounds 80 and 81 were potent in the low micromolar concentration range in a cellular evaluate method.

![Chemical structures](image)

L. J. Lombardo et al. [98] identified thiazole-based compounds as effective as Src/Abl kinase inhibitors with outstanding antiproliferative activity against hematological and solid tumor cell lines. Compound 82 was orally active in a K562 xenograft model of chronic myelogenous leukemia (CML), establishing complete tumor regressions and very low toxicity at multiple dose levels. On the basis of its powerful *in vivo* activity and promising pharmacokinetic profile, 82 was designated for supplementary characterization for oncology manifestations.

![Chemical structure](image)

P. Madsen et al. [99] explained the thiazole containing scaffold being potent human glucagon receptor antagonists with enhanced pharmacokinetic (PK) properties for expansion of pharmaceuticals for the medication of type-2 diabetes. The syntheses of compounds with cyclic moieties (5-aminothiazoles), their binding affinities for the human glucagon and GIP receptors, as well as affinities for mouse, pig, rat, dog, and monkey glucagon receptors. Normally, the compounds had less glucagon receptor affinity corresponding to compounds of the earlier series slightly, but this was rewarded for by much developed PK summaries in both rats and
dogs with high oral bioavailabilities and constant high plasma coverages. The compounds exhibited species selectivity for glucagon receptor binding with very low affinities for the rat, mouse, rabbit, and pig receptors. However, dog and monkey glucagon receptor affinities seem to reflect the human situation. One of the compound sequence, 83, was tested intravenously in an anesthetized glucagon-challenged monkey model of hyperglucagonaemia and hyperglycaemia and was revealed dose-dependently to reduce glycaemia.

X. Cheng et al. [100] reported a cell-based high throughput screening (HTS) operation for the search for potential candidates for octamer-binding transcription factor 4 (Oct3/4). In that process, they recognized numerous efficient small molecules for inducers of Oct3/4 expression. From HTS, optimized compounds are based on thiazole ring containing scaffold such as ethyl 2-((4-chlorophenyl) amino)-thiazole-4-carboxylate, 84, exhibiting high activity in implementing Oct3/4 expression. On the source of chemical expansion, once again screened the recognized derivatives requiring improved activities in the direction of Oct3/4 induction. Therefore, 84 and its analogs had afforded better potential small molecules proper for an iPSC generation.

C. P. Hencken et al. [101] synthesized 23 new dehydroartemisinin (DART) trioxane analogs in which 11 thiazoles moiety-containing compounds remaining are based on two oxadiazoles, and ten carboxamides and screened them for in vitro activity in the Toxoplasma lytic cycle. Fifteen (65%) of the analogs were noncytotoxic to host cells (TD₅₀ ≥ 320 μM). Eight thiazole compounds exhibited effective inhibition of Toxoplasma growth (IC₅₀ = 0.25-0.42 μM), similar in potency to artemether (IC₅₀ = 0.31 μM) and >100 times stronger inhibitory than the presently working front-line drug trimethoprim (IC₅₀ = 46 μM). The thiazoles as a ring were more efficient than other analogs at the inhibiting progress of extracellular as well as intracellular parasites. Surprisingly, two thiazole trioxanes (109 and 110) were parasiticidal; both inhibited parasite replication permanently after parasite contact to 10 μM of the drug for 24 h. However, the standard trioxane drugs artemisinin and artemether were not parasiticidal.
Y. Kumar et al. [102] reported that Methyl-4-(isothiocyanatomethyl)thiazole-2-carbamate have been obtained via chemical conversion containing 2-amino-4-(chloromethyl)thiazole (117) as precursor. The homoanalog, methyl 4-(2-isothiocyanatoethyl)thiazole-2-carbamate was synthesized via (2-aminothiazol-4-yl)acetic acid. All thiazole compounds synthesized were estimated for their capability to inhibit leukemia L1210 cell proliferation. Methyl 4-(isothiocyanatomethyl) thiazole-2-carbamate (118) was the active compound in this screen, inhibiting the growth of L1210 leukemic cells with an IC50 = 3.2 NM. Mitotic blocking performs to be its key mechanism of cytotoxic activity. Compound 118 furthermore was the only compound that confirmed important in uiua antifiliarial activity against the adult worms of Acanthocheilonema uitea in experimentally infected jirds.

New thiazole based compounds [103] (1-(4-arylthiazol-2-yl)-2-(3-methylcyclohexyldiene) - hydrazine) 119 are synthesized for the studied human B isoform of monoamine oxidase. These compounds were prepared as racemates and (R)-enantiomers by a stereoconservative synthetic arrangement in high yield and enantiomeric excess. The (S)-enantiomers of the highly active analogs have been separated by enantioselective HPLC. All compounds showed selective activity against hMAO-B with IC50 ranging between 21.90 and 0.018 μM.

A. S. Mayhoub et al. [104] synthesized a sequence of third-generation referents of methyl 4-(dibromomethyl)-2-(4-chlorophenyl)thiazole-5-carboxylate 120, which had the highly potent antiviral activity comparable to the first and second generation derivatives, have been synthesized and verified against yellow fever virus consuming a cell-based assay. The compounds were aimed at the objectives of enlightening metabolic stability, therapeutic index, and antiviral potency. The biological effects of C4 and C5 substitution were studied. The
methylthio ester and the dihydroxypropylamide analogs had the effective antiviral potencies and enhanced therapeutic indices and metabolic stabilities comparative to the parent compound 120.

T. A. Dineen et al. [105] reported the variation in structure 133 for the improved BACE1/CYP 3A4 inhibitors by a P1-phenyl ring of the hydroxyethylamine series to afford potent, which exhibit enhanced penetration into the CNS. Numerous compounds caused a robust decrease of Aβ levels in rat CSF and brain subsequently oral dosing, and compound 134 showed a better cardiovascular safety profile comparative to 133.

B. Ghosh et al. [106] reported structure-activity relationship investigated on a unique hybrid sequence of derivatives where structural modification of aromatic hydrophobic moieties associated with the piperazine ring and biosisosteric exchange of the aromatic tetralin moieties were passed out. Binding assays were accepted with HEK-293 cells uttering either D2 or D3 receptors with tritiated spiperone to estimate inhibition constants (Ki). Functional activity of
designated compounds in stimulating GTPγS binding was evaluated with CHO cells uttering human D2 receptors and AtT-20 cells uttering human D3 receptors. SAR results recognized compound 136 as one of the lead molecules with better agonist activity for D3 receptor (EC\textsubscript{50} (GTPγS); D3= 0.52 nM; D2/D3 (EC\textsubscript{50}): 223). Compounds 135 and 136 showed potent radical scavenging activity, the two lead compounds, 135 and 136, showed more \textit{in vivo} activity in two Parkinson's disease (PD) animal models, reserpinized rat model and 6-OHDA brought unilaterally lesioned rat model.

J. Das et al. [107] explained that the 2-aminothiazole 137 was established as a unique Src family kinase inhibitor pattern through high calculated screening of their internal compound assembly. Optimization through consecutive structure-activity relationship iterations are recognized analogs 138 (Dasatinib, BMS-354825) and 139 as pan-Src inhibitors with nanomolar to subnanomolar strengths in cellular and biochemical assays. Molecular modeling techniques are utilized to conceptualize a recognized binding model for Lck inhibition by this type of compounds. The oral efficiency of this type of inhibitors was established with 139 in inhibiting the proinflammatory cytokine IL-2 \textit{ex vivo} in mice (ED\textsubscript{50} - 5 mg/kg) and in decreasing TNF levels in a serious murine model of inflammation. The oral efficiency of 139 was further verified in a chronic model of adjuvant arthritis in rats with recognized disease when ordered orally at 0.3 and 3 mg/kg two times daily.

Major medicinal chemistry researcher focused on good docking small molecules inhibits the type 2 diabetes performances to have an insufficient or deficiency in one or both of these processes. Compounds that can activate glucokinase (GK) may serve as effective treatments for type 2 diabetes. In this process R. J. Hinklin et al. [108] reported that the recognition and preliminary optimization of a series of allosteric glucokinase activators (GKAs), revealed an early thiazoylaminopyridine-based hit that was elevated using a structure-based design approach and recognized 140 as an early lead. Compound 140 validated a good steadiness of \textit{in vitro} effectiveness and enzyme kinetic limits and confirmed blood glucose decreases in oral glucose patience tests in both C57BL/6j mice and high-fat fed Zucker diabetic fatty rats.
Spinal muscular atrophy (SMA), an inherited autosomal neurodegenerative disease, is the foremost genetic disorder disturbing infant mortality. Clinically, there are four kinds of SMA (types I, II, III, and IV). In fact, SMA is the top one genetic origin of death in children below the age of two, and several children life have been spoil due to confined to wheelchairs. There is presently no medication or effective treatment for SMA. Structure-activity relationships including microsomal stability, cell permeability, and in vitro pharmacokinetics (PK) studies are necessary. J. Xiao et al. [109] reported SMA active theoretically lead candidate selected from a sequence may work for as a valuable analysis for exploring the therapeutic aids of SMN protein up-regulation in SMA animal models and an initial point for clinical improvement. With regard to all the features including ADME properties, analogs 141 and 142 possessed the greatest combination of effectiveness, efficiency, mouse liver microsomal steadiness, and cell permeability of all the analogs that showed good activity.

M. D, Rose, et al. [110] discussed the inhibition and antiviral activity consequence synthesis of 14- and 15-membered macrocycles for HIV-1 protease inhibitors (PIs) as obtained by ring-closing metathesis of the respective linear PIs. The macrocycles were very highly active than the linear precursors and compound 143, with a 2-thiazolyl ring was the best potent PI of this new series (K, 2.2 nM, EC_{50} = 0.2 μM).

The preparation of a sequence of quinazolines inserted at C4 by aminothiazole ring is reported [111]. Their in vitro structure-activity relationships against Aurora A and B serine-threonine kinases are examined. The results reveal that quinazolines with a substituted aminothiazole
at C4 possess potent Aurora A and B inhibitory activity and outstanding selectivity against a panel of several serine-threonine and tyrosine kinases. Compound 144 also found that the location and nature of the substituent on the thiazole play vital roles in cellular potency.

Approximately, the thiazole ring containing compound exhibits cathepsin K inhibitors [112]. The amalgamation of binding elements resulted at sub-250 pM, reversible, selective, and orally bioavailable cathepsin K inhibitors. In a series on of the compound exhibited single digit nanomolar inhibition in vitro (of rabbit osteoclast-mediated degradation of bovine bone). The effective compound in this series, 145 (CRA-013783/L-006235), was orally bioavailable in rats, with a terminal half-life of over 3 h, 145 was medicated orally in ovariectomized rhesus monkeys once per day for 7 days.

Haffner et. al. a series of thiazoloquinazolinones [113] were prepared and studied the inhibitory activity against CD38. Numerous compounds were also revealed to have good pharmacokinetic properties and established the capability to raise NAD levels in plasma, liver, and muscle tissue. Specifically, compound 146 was agreed to diet induced obese (DIO) C57Bl6 mice, enriching NAD > 5-fold in liver and >1.2-fold in muscle against control animals at a 2 h time point.

Thiazolo[5,4-d]pyrimidines and thiazolo[4,5-d]pyrimidines are structurally mimic with purines, in which a 1,3-thiazole ring system exchanges the imidazole moiety. While purine chemistry is broadly discussed in the literature, the number of medicinal chemistry publications that reported the synthesis and biological studies of thiazolopyrimidines is narrow comparable with purines. Seemingly, the thiazolopyrimidine scaffold is not very often used in drug discovery platforms. However, biological activities of unequivocal thiazolo[4,5-d]pyrimidines and thiazolo[5,4-d]pyrimidines have been described. A summary of available compounds with their biological significance is presented in Figures 147, 148, 149 and 150.
Thiazolo[4,5-d]pyrimidine derivative 151 revealed *in vivo* activity towards a broad range of RNA and DNA viruses [114] and also had antitumor and antimetastatic activity [115]. The guanine analogs 152 exhibited potent in vitro activity against human cytomegalovirus (HCMV) [116]. Thiazolo[4,5-d]pyrimidine-5,7-dione analogs (compound 153) have been described as having potential anti-inflammatory activities, because of TNF inhibition [117]. 4-2-Oxo-3-arylthiazolo[4,5-d]pyrimidine analogs (compound 154) have been produced as antagonists of the corticotrophin-releasing hormone (CRH) R1 receptor [118]. 2-Thio-3-aryl-thiazolo[4,5-d]pyrimidine and its derivatives have been reported as having anticancer (compound 155) [119], antimicrobial and anti-inflammatory activity (compound 156a & 156b) [120]. 2-Aminothiazolo[4,5-d]pyrimidines (compound 157a & 157b) which performance as CXCR2 receptor antagonists are also recognized [121]. Lately, 2,7-substituted-thiazolo[4,5-d]pyrimidines (compound 158) have been explained as ATP-competitive inhibitors of protein kinase [122].
2,5-Diaminothiazolo[5,4-d]pyrimidin-7(6H)-one (Compound 159), a thio-isostere of 8-amino-guanine, was established to be a poor inhibitor of purine nucleoside phosphorylase (PNP) [123].

7-Diethylamino-5-methylthiazolo[5,4-d]pyrimidine 160 has vasodilating and hypotensive properties, inhibits platelet aggregation, and decreasing cholesterol levels [124]. Thiazolo[5,4-d]pyrimidines were enclosed by numerous patent properties such as activators of caspases and inducers of apoptosis (compound 161) [125], anti-angiogenic agents (compound 162) [126], growth factor receptor inhibitors (compound 163) [127], heat shock protein 90 (HSP-90) inhibitors (compound 164) [128], and xanthine oxidase inhibitors (compound 165) [129].

5. General Synthetic Routes to Thiazolo[5,4-d]pyrimidines

In wide-ranging, pyrimidines with a nitrogen-containing substituent at position 5 (such as an amino or nitro group) can work as precursors for the formation of thiazolo[5,4-d]pyrimidines by thiazole ring condensation. 5-Amino- or 5-nitropyrimidines can be organized from diethyl amino-, nitro-, or acetylamino-malonate by reacts with coupling reagents such as thiourea [130], urea [131], guanidine [132] and amidines [133] in alkali conditions. By reaction of the 4,6-dihydropyrimidine analog with a thionation reagent (Lawesson’s reagent or phosphorus pentasulfide) in pyridine, alteration of oxygen into sulfur and thiazole ring closure is accomplished. Interaction of 5-amino-6-mercaptopyrimidines with reagents such as phosgene [134], formic acid [135], and acid anhydride [136] also gives thiazolo[5,4-d]pyrimidines.
Thiazolo[5,4-d]pyrimidine-1-N-oxides, ready to obtain from 6-chloro-1,3-dimethyl-5-nitropyrimidinone by reaction with mercapto compounds, monitored by base catalyzed dehydrative cyclization, can be simply deoxygenated to produce thiazolopyrimidines. Reductive deoxygenation by treatment of the thiazolopyrimidine oxides with sodium dithionite or oxidative deoxygenation with dimethylformamide at reflux temperature can produce the anticipated thiazolopyrimidines [137].

2-Mercaptothiazolo[5,4-d]pyrimidines easily obtained from 6-chloro-5-nitropyrimidines by the reaction with carbon disulfide and sodium sulfide [138].

2-Amino-7-chlorothiazolo[5,4-d]pyrimidines are prepared from 5-amino-4,6-dichloropyrimidine and isothiocyanate in presence base [139].

Ahmed et al. [140] reported the synthesis of thiazolo[5,4-d]pyrimidines from pyrimidines without 5-amino or 5-nitro substituents. The reaction between 5-bromo-4-thiopyrimidinones and dimethylcyanamide affords carbodiimide intermediates, which is a very fast intramolecular cyclization to produce a thiazole ring.

On the other hand, thiazolo[5,4-d]pyrimidines also obtained from 5-aminothiazole derivatives, are prepared from aminomalononitrile (or its derivatives) and isothiocyanates [141] or thioesters [142]. The next to 5-amino and 4-cyano (or conforming carboxamide or ester groups) on the thiazole ring are proper functionalities to concept a fused pyrimidine ring system. 7-Aminothiazolo[5,4-d]pyrimidines can be prepared from 5-amino-4-cyanothiazoles by reaction
with reagents such as orthoesters and amidines [143,144]. The reaction between 5-amino-4-carboxamide (or carboxylate) thiazoles and orthoesters [145], formamide [146], and ethyl chloroformate/DMF [147] gives thiazolo[5,4-d]pyrimidin-7(6H)ones.

Additionally, Thiazolo[5,4-d]pyrimidinones readily obtained from the corresponding oxazolopyrimidines. In fact, that 1,3-oxazole ring system is quickly converted into a 1,3-thiazole by a thermal rearrangement. The thioamide replaced oxazole derivative is prepared from the corresponding amide by reacts with Lawesson’s reagent. Heating generates the nitrile ylide by electrocyclic ring opening, followed by a 1,5-dipolar electrocyclization affording the thiazole [148].

6. General Synthetic Routes to Thiazolo[4,5-d]pyrimidines

The preparation of thiazolo[4,5-d]pyrimidines from a properly substituted pyrimidine compound yields 2-aminothiazolo[4,5-d]pyrimidines. Thiocyanation of 6-amino pyrimidines reacts with potassium thiocyanate, bromine and pyridine, proceeded by cyclization yields the 2-aminothiazolo[4,5-d]pyrimidines [149].

Condensation of 5-bromobarbituric acid with thiourea and/or its derivatives in the presence of an alkali yields thiazolo[4,5-d]pyrimidine derivatives [150].
Another significant technique for the preparation of thiazolo[4,5-d]pyrimidines from thiazoles is via the aza-Wittig reaction [151]. The iminophosphorane intermediates are found from 4-chloro-5-formylthiazoles which reacts with sodium azide and triphenylphosphine (Staudinger reaction). In Addition, reaction with isocyanates affords the corresponding carbodiimides, followed by heating, and undergo an electrocyclic ring closing, which upon a Dimroth-type rearrangement obtained thiazolo[4,5-d]pyrimidines [152].

It is needed to expand the hit ratio in HTS campaigns; fortunate molecular scaffold systems offer a perfect basis of main compounds. A particular library created on preferable bioisosteres groups are inserted into the main scaffold and can generate the bioactive compounds in a broad range of biological tests. Numerous researchers have developed these structures in such a fashion. For example, Ghorpade and co-workers built a library based on the thiazolopyridines privileged scaffold [153] whereas Bebermitz and co-workers made use of the chlorosulfonic acid combined with thiazolopyridines scaffold [154] (compounds 166 and 167).

Bicyclic nitrogen, sulfur-containing heterocycles, such as Thiazolo[5,4-b]quinoline, thiazolopyridines, and thiazolopyrimidines are well-known pharmacophores in drug discovery [155-157]. Examples of promoted drugs with a bicyclic core structure include AMG-369 analogs performing as Lysophospholipid edg1 (S1P1) and Receptor Agonists Lysophospholipid edg8 (S1P5) Receptor Agonists [158]. Thiazole sulfonamides based scaffold, used as antidepressants and for the treatment of Vasopressin (AVP) V1b Antagonists [159]. Kirsch and co-workers described a solution-phase synthesis of 7-amino-thiazolo[4,5-b]pyridine derivatives [160] as
well as fused-pyridine analogs such as the thiopheno[2,3-b]pyridines [161] using the Friedlander reaction.

Thiazolo[4,5-b]pyridine derivatives reveal a broad range of biological properties. For example, thiazolo[4,5-b]pyridines have confirmed actions as serine protease factor Xa (fXa) inhibitors for thrombosis [162], as metabotropic glutamate receptor 5 (mGluR5) antagonists for several CNS syndromes [163], as histamine H3-receptor antagonists for epilepsy and Alzheimer’s disease [164], as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors [165], and as cAMP phosphodiesterase (PDE) III inhibitors for congestive heart catastrophe [166].

T. Lee et. al. [167] reported a series of 2,5,6,7-tetrasubstituted thiazolo[4,5-b]pyridine derivatives (168) from solid-phase synthesis. Thorpe-Ziegler type cyclization of solid supported cyanocarbonimidodithioate with α-halo ketones gave thiazole resin, which were transformed to the preferred thiazolopyridine resin by the Friedlander procedure under microwave irradiation conditions. After oxidation of sulfides to sulfones, nucleophilic desulfonative substitution with amines yielded the target thiazolo[4,5-b]pyridine derivatives.

Y. Takahashi et. al [168] described the synthesis and structure-activity relationships of a unique series of 7-dialkylamino-3-phenyl-6-methoxy pyrazolo[5,1-b]thiazole derivatives to utilize as selective antagonists of the corticotropin-releasing factor 1 (CRF1) receptor. The best favorable compound, N-butyl-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-N-(tetrahydro-2H-pyran-4-yl)pyrazolo-[5,1-b, 1,3]thiazole-7-amine (169), exhibited very high affinity (IC$_{50}$ = 70 nM) and functional antagonism (IC$_{50}$ = 7.1 nM) for the human CRF1 receptor.

7. Summary

This chapter discusses the high synthetic perspective of several methods for synthesis of thiazoles and its derivatives that have been published in the last three decades. Many pharmaceutically active heterocycles have been obtained based on the reaction of acid hydrazides particularly concerning Hantzsch reaction, Dimroth type rearrangement, Tchernich reaction,
CooK–Heilbron reaction, Gabriel reaction, Erlenmeyer reaction, Hartke–Seib reaction and Dubs reaction. Fundamentally α-halo carbonyl compounds and substituted thiourea or thiosemicarbazide are potential precursors for the creation of wide range of thiazole analogous as main synthon constituents for generation of several diverse heterocycles. The aza-Wittig product such as iminophosphorane intermediates obtained from 4-chloro-5-formylthiazoles by treatment with sodium azide and triphenylphosphine (Staudinger reaction) with most other various reagents like isocyanate, isothiocyanate and carbondisulfide for bicyclic generation system containing thiazole moiety under basic, acidic or neutral reaction conditions. Most of these reagents are available from simply or commercially accessible, inexpensive precursors. This chapter has also verified the noticeable feature to the advancement of an eco-friendly experimental technique for the synthesis of heterocyclic compounds. The synthetic approaches showed in this chapter can be comprehensive to the synthesis of natural macrocyclic thiazole ring containing heterocycles and also suggest that α-halo carbonyl compounds can be a favorable building block in combinatorial synthesis of functionalized heterocyclic derivatives used for the design of unique very active pharmaceutical drugs with a broad spectrum of bioreponses. In certain cases, reports on the less yield of bioactive heterocycles in this chapter could be overwhelmed by forthcoming synthetic chemists with this sustained research and new methods for extensive approach and explained experimental procedures could be explored for its development for generation of a library of such multi-functional heterocycles to afford a useful encouragement to medicinal chemistry.

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Significance of Thiazole-based Heterocycles for Bioactive Systems


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