

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Significance of Thiazole-based Heterocycles for Bioactive Systems

Someshwar Pola

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/62077>

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^{60} may retain drug-like applications. The percentage of molecules prepared until today has been projected as one part in 10^{58} 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).

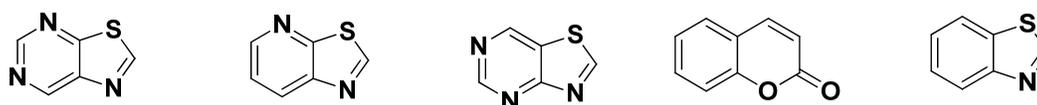


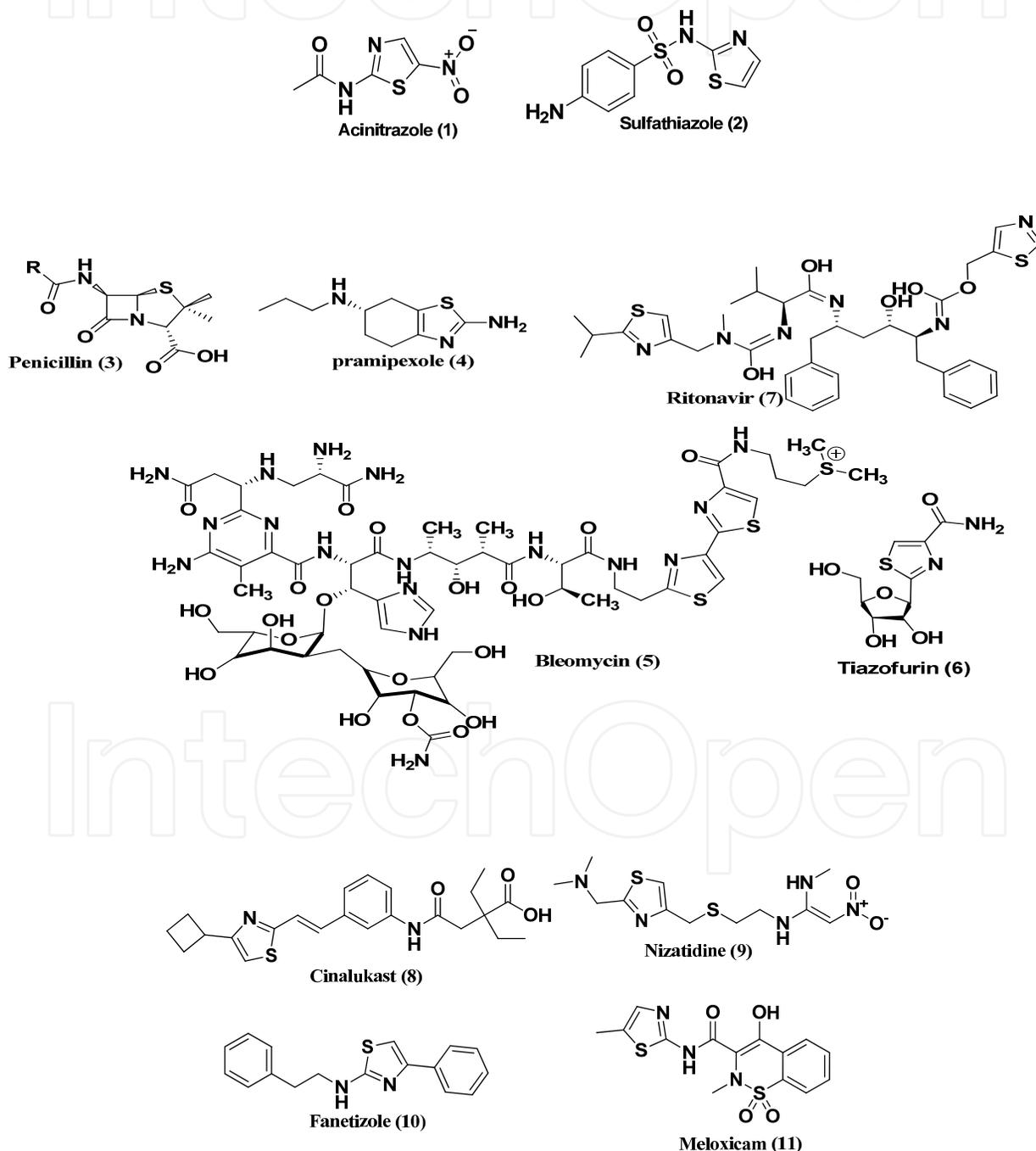
Figure 1. Examples of privileged structures

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].

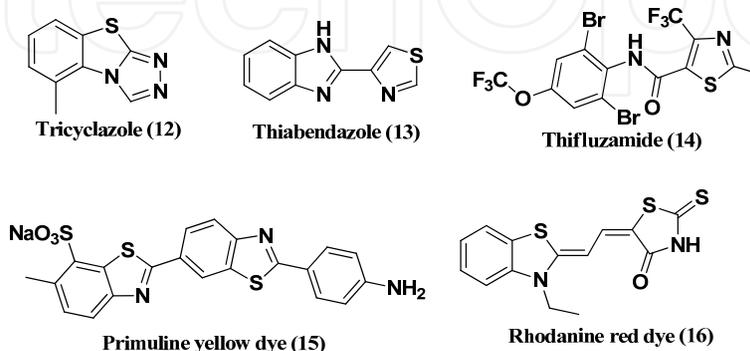
A thiazole ring system originates naturally in the crucial water soluble vitamin thiamin, also known as Vitamin B1, which supports the discharge of energy from carbohydrates through the course of metabolism. The occurrence of thiazole ring in vitamin B1 and its coenzyme play a significant role in the decarboxylation of α -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].



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.

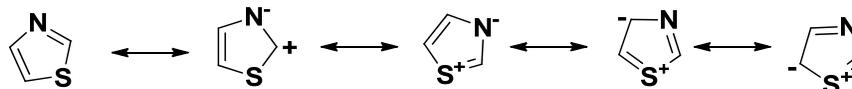


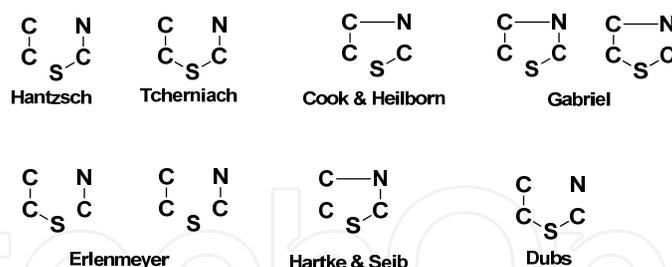
Figure 2. Resonating Structures of Thiazole

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 $H_2 \gg H_5 > H_4$.

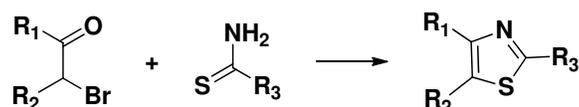
3. Synthesis of Thiazole

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].



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

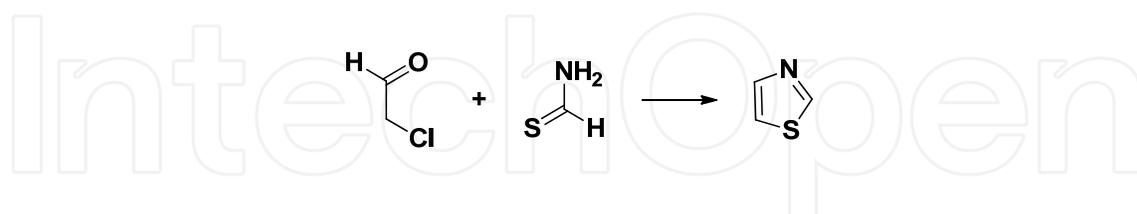
First designated in 1887 by Hantzsch, the cyclization of α -halo carbonyl compounds by a wide diversity of reactants attached to the N-C-S portion of the ring is the most extensively popular process for formation of thiazoles.



3.1.1. Reactions with Thioamides

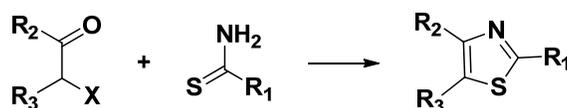
3.1.1.1. Chloroacetaldehyde and derivatives

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)

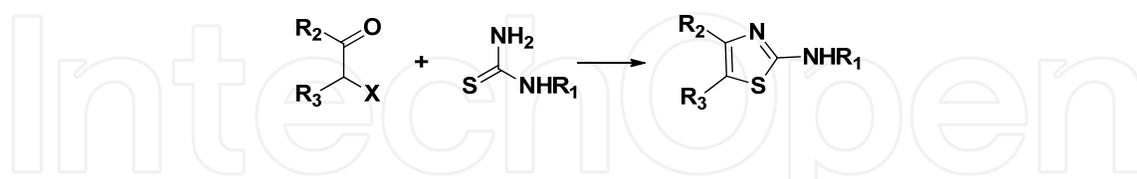
The reaction between thioamide and various α -halocarbonyl compounds has been utilized broadly, and numerous thiazoles with alkyl, aryl, arylalkyl or heteroaryl of several functional groups at 2-, 4- or 5-positions have been published.



3.1.2. Reactions with N-substituted Thiourea

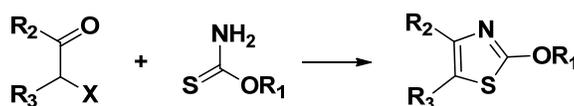
3.1.2.1. N-monosubstituted thioureas

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



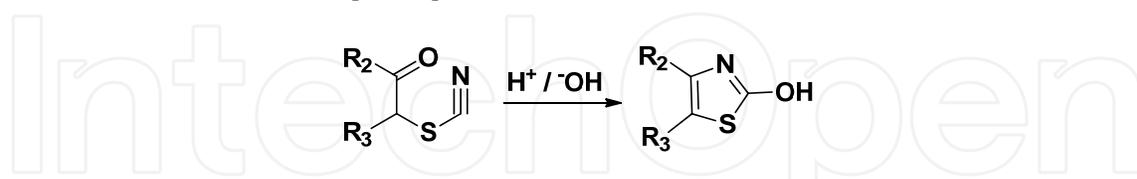
3.1.3. Reaction with salts and esters of thiocarbamic acid: 2-hydroxy thiazoles and derivatives

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.

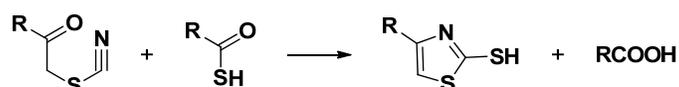


3.2. Thiazoles formation from reorganization of the α -thiocyanatoketones

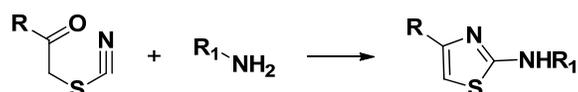
The simple cyclic reaction of α -thiocyanatoketones in aqueous acid concentrated sulfuric acid in acetic acid, and water or alkaline solution gives to 2-hydroxy thiazoles after dilution in water. These reactions can be conceded out for various hours at room temperature or by refluxing for 1 or 2 hrs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



α -Thiocyanatoacetophenone reacts thioacid to yield 2-mercapto-4-phenyl thiazole.



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

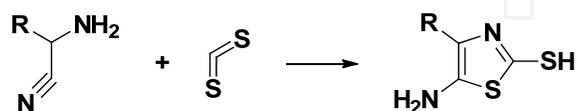


3.3. Thiazoles from α -aminonitriles (Cook-Heilbron's synthesis) (Type-II)

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.

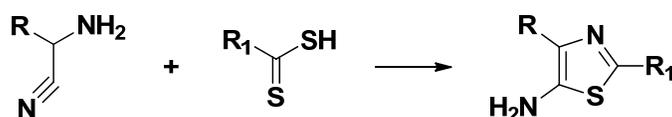
3.3.1. Carbon disulfide: 2-mercapto-5-aminothiazole derivatives

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



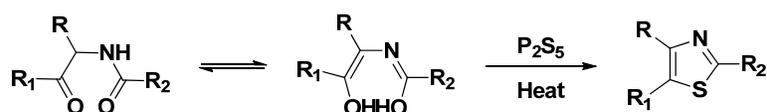
3.3.2. Esters and salts of dithioacids: 5-aminothiazole compounds and related condensations

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 (shown 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.

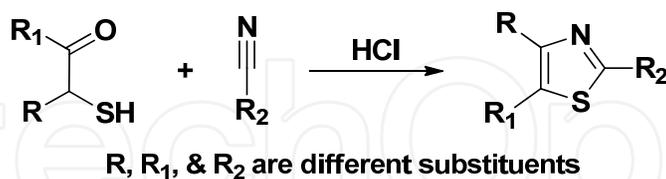


3.5. Thiazoles from nitriles and α -mercaptoketones: 2,4-disubstituted and 2,4,5-trisubstituted derivatives

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.

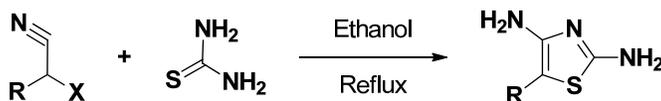
3.5.1. 2,4,5-Trisubstituted thiazoles from α -mercaptoketones and nitriles

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.



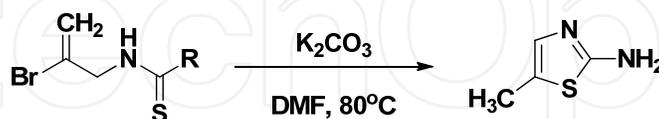
3.5.2. 2,4-Diaminothiazole derivatives from α -halonitriles and thiourea

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.



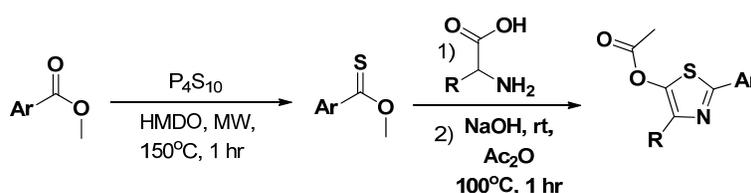
3.6. Thiazoles from Vinyl Bromide

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-bromoprop-2-enyl)thioamides [58]. This vinylic substitution technique would afford an exclusive synthetic method for a range of heterocycles.



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

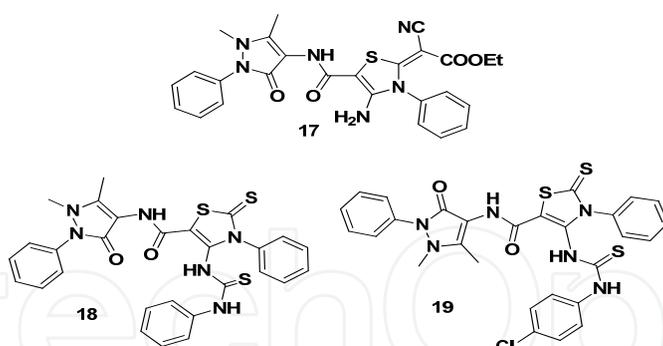
From the viable existing methyl benzoate derivatives and with racemic phenyl glycine, a range of 2,4- disubstituted-5-acetoxythiazoles obtained in worthy to reasonable yields exhausting the succeeding scheme [59]. Due to the excellent thermal stability of the thiazole nucleus, the polymers integrating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



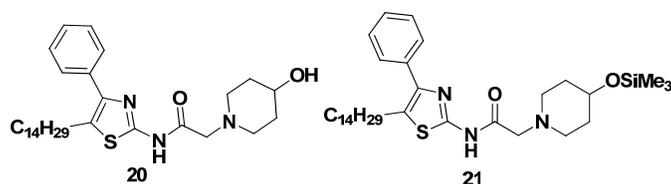
4. Biological importance of thiazoles

Thiazole moiety-containing compounds invention present an extensive range of applications in medicinal chemistry such as antibiotics, bacteriostatics, CNS regulants 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 *in vivo* progress of Xanthomonas, as a component of herbicides or as schistosomicidal and anthelmintic drugs [70].

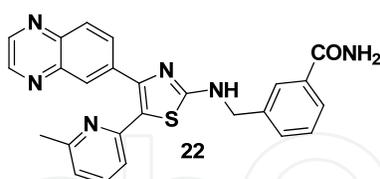
Sherif. et al. [71] syntheses of two series of compounds that is thiazolylantipyridines and thiadiazolylantipyridines, in which thiazolylantipyridine series exhibits better antibacterial potencies than the thiadiazolylantipyridine series of compounds. In thiazolylantipyridine series compounds **17** – **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.



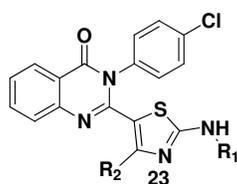
Zablotskaya A et al. [72] prepared trimethylsilyl ethers of different hydroxyl group bearing thiazole compounds. All the compounds examined possess antihypoxic properties and extend the life of mice under conditions of hypoxia by 20-78%. The silylated and unsilylated derivatives in the preponderance of circumstances show antihypoxic activity.



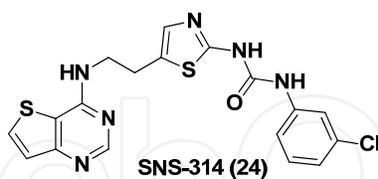
Dae-Kee K et al. [73] produced a set of 5-(pyridin-2-yl)thiazoles enclosing a *para* or *meta*-carboxamide or carbonitrile-substituted phenylmethylamino moiety at the 2-position of the thiazole ring and was estimated for activating receptor-like kinase 5 (ALK5) inhibitory activity in cell-based luciferase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



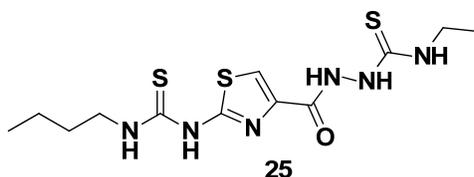
Rajan S G et al. [74] designed and synthesized a sequence of 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazolin-4-one **23** compounds. Synthesized molecules were estimated for their inhibitory activity in the course of record factors, nuclear factor-kB (NF-kB) and activating factor (AP-1) interceded transcriptional activation in a cell line based *in vitro* assay as well as for their anti-inflammatory activity *in vivo* model of severe inflammation.



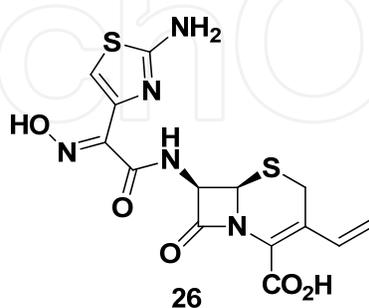
Johan et al. [75] synthesized a unique sequence for Aurora kinase inhibitors enclosing thiazole moiety (SNS-314, **24**). Also, key SAR as well as essential binding elements has been explained.



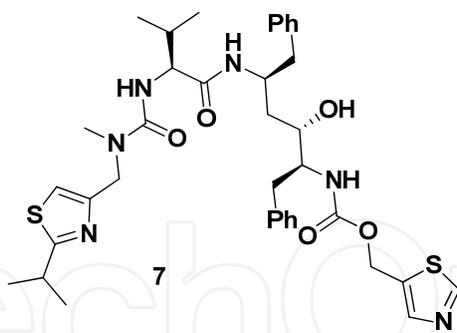
HI El-Subbagh et al. [76] synthesized a sequence of 2,4-disubstituted thiazole compounds containing *N*-n-butyl or *N*-cyclohexyl thioureido synthon at position-2 and *N*-substituted thiosemicarbazone moiety **25** at position-4 and verified for antitumor activity. All of the established derivatives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



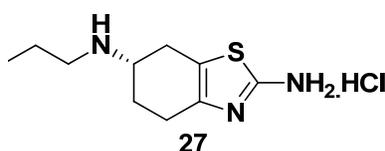
The unique model of a thiazole in the best 200 drugs citations is cefdinir **26** (Omnicef), a semi-synthetic third generation cephalosporin that is controlled orally and has a stretched antibacterial activity in contrast to both gram-positive and gram-negative bacteria. The key feature of cefdinir is 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].



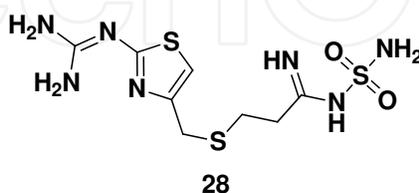
The HIV-1 protease inhibitor ritonavir [78] (Norvir 7) contains two different substituted thiazole rings, which are presented at the advanced steps in the synthesis of this peptidomimetic antiviral compound. Remarkably, ritonavir is a consequence of advanced enhancements on earlier candidates for the action of AIDS [80].



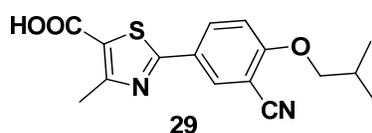
The dopamine D2-agonist pramipexole **27** (Mirapex) contains a fused bicyclic tetrahydrobenzothiazole design, which is also easy to obtain by a Hantzsch-type condensation reaction between a α -brominated protected form of 4-aminocyclohexanone and thiourea [81].



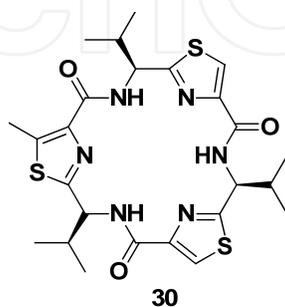
Famotidine (**28**, Pepcidine) is one of the top an H₂-receptor antagonists, which is equivalent to cimetidine that prevents various isoenzymes of the hepatic CYP450 system and the additional side effect (Swelling of the hands, feet or ankles) of enhancing the amount of gastric bacteria such as nitrate 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.



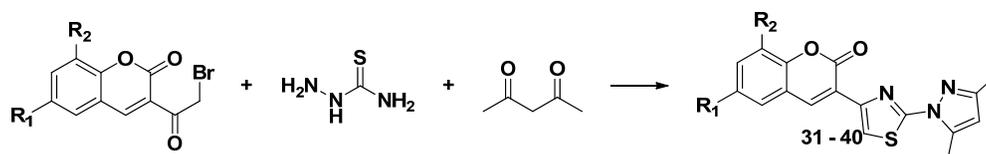
One more example of a thiazole ring enclosing drug is known in the unique xanthine oxidase inhibitor febuxostat **29** (Uloric) which was accepted by the FDA in 2009 [85]. This inhibitor works by hindering xanthine oxidase in a non-competitive manner. Subsequently, the quantity of the oxidation product uric acid is decreased. Thus, it is an extremely well-organized action for hyperuricemia in gout.



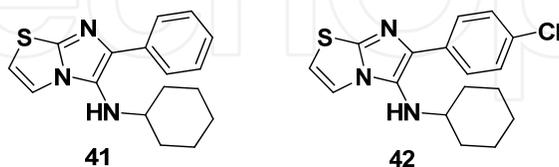
Takeuchi et al. described the total synthesis of the cyclic tripeptide bistratamide H **30** established in the procedure of an extremely fluororous amino protecting group and multistep purifying by F-LPE using FC-72 in which 15 out of the 17 steps were purified by F-LPE [86].



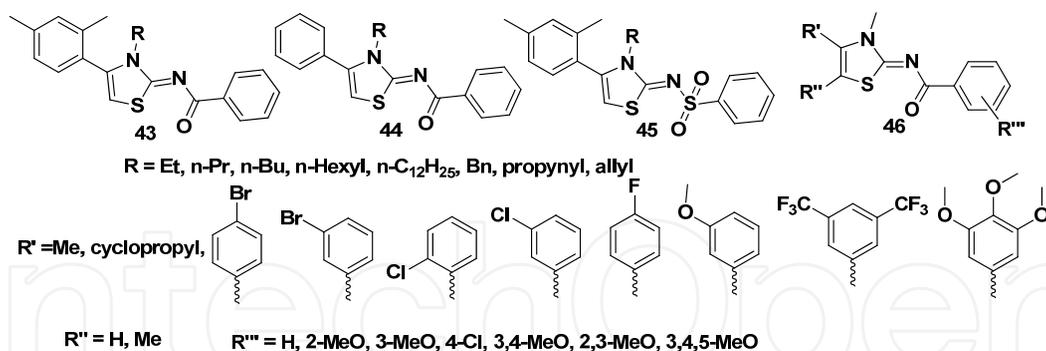
The construction of two heterocyclic rings in one synthetic step has been developed for the preparation of coumarin derivatives. In this process, the thiazole ring (**31 – 40**) is accomplished by Hantzsch reaction monitored by fabrication of pyrazole by reacting a 3-(2-bromoacetyl) coumarin with thiosemicarbazide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



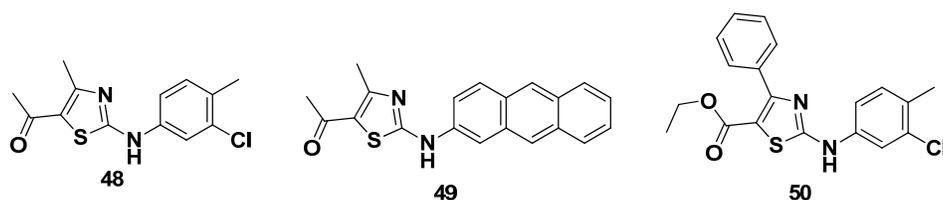
Adib et al. [88] described, in the latest work, a well-organized three component reaction that is significant to the formation of essential heterocycles titled by imidazo[1,2-*a*]thiazoles (**41 & 42**).



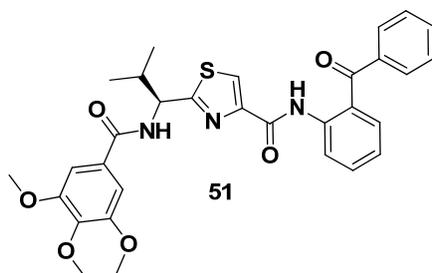
S. Zheng et. al. [89] synthesized five series of thiazole derivatives (**43 – 47**) for fascin therapeutic target as emerged from cancer cells is thoroughly related to tumor progression and metastasis. The entire compounds based on thiazole derivatives examined anti-migration and anti-invasion activities 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.



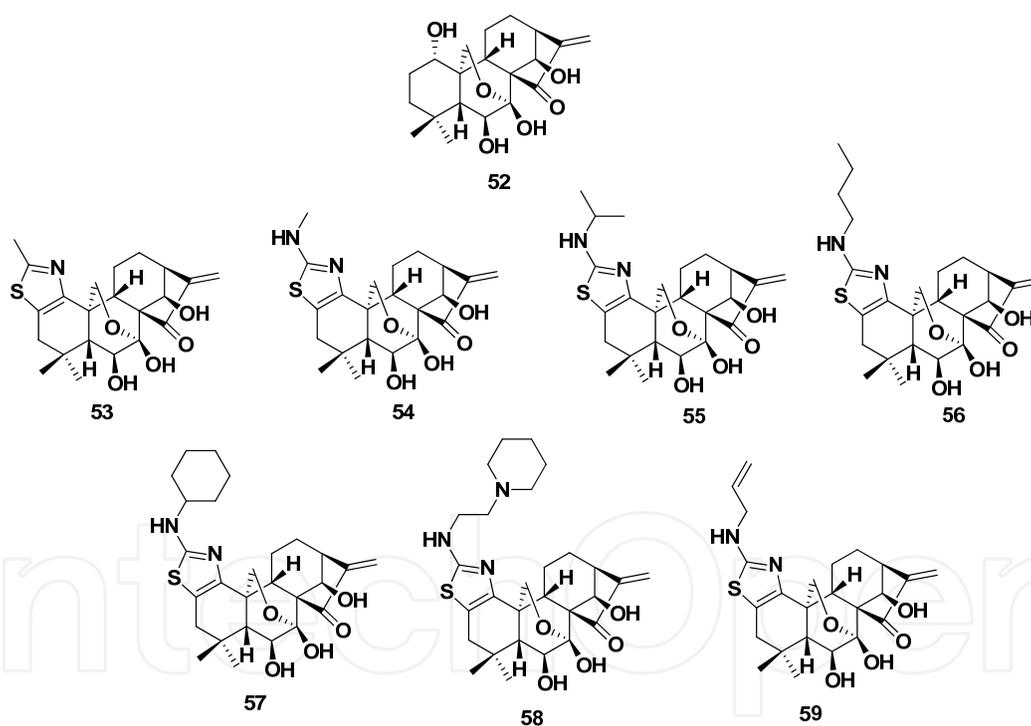
J. Zhu et al. [90] reported that Human dihydroorotate dehydrogenase (HsDHODH) is a flavin-dependent mitochondrial enzyme that has been specialized as a prospective therapeutic aim for the medication of rheumatoid arthritis and other autoimmune diseases. On the basis of the main compound **48**, which 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.



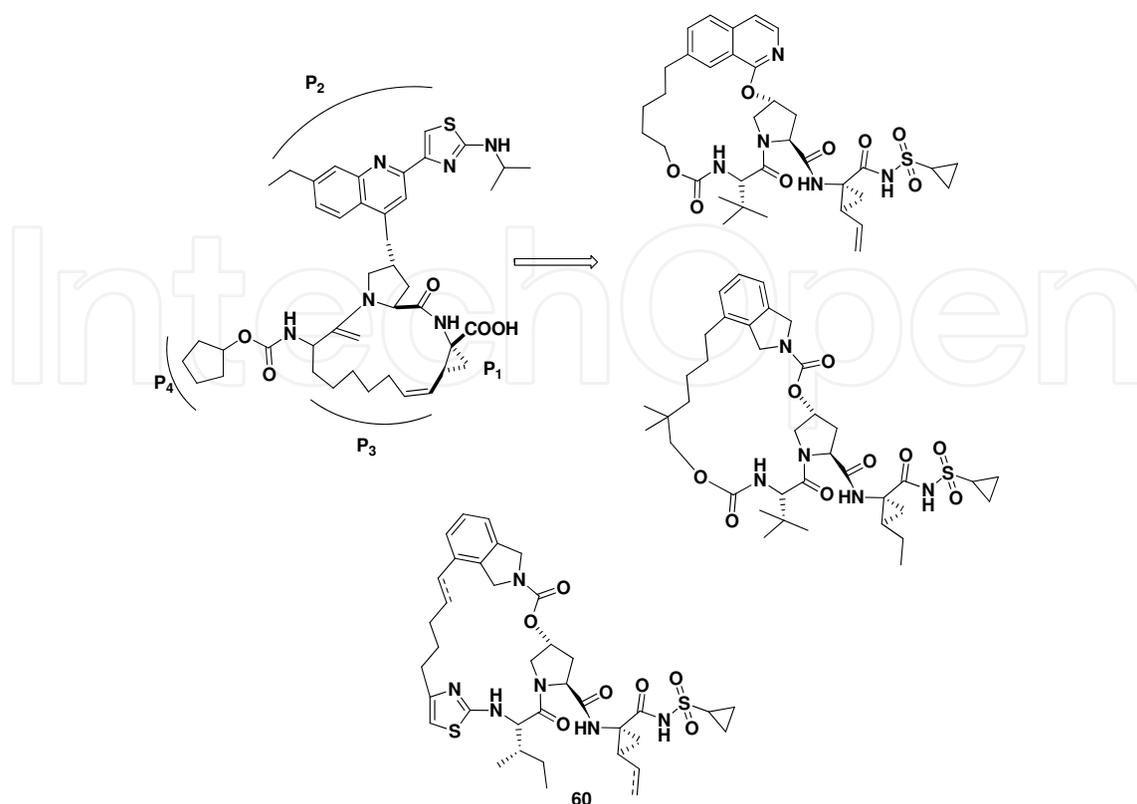
S. Singh et al. [91] P-glycoprotein (P-gp) works as a therapeutic target for the improvement of multidrug conflict reversal agents. In this study, we synthesized twenty-one novel derivatives by peptide coupling at equivalent carboxyl and amino termini of (S)-valinebased bis-thiazole and mono thiazole derivatives with different chemical scaffolds. Consuming calcein-AM efflux assay, we recognized compound **51** ($\text{IC}_{50} = 1.0 \mu\text{M}$) 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 $\text{IC}_{50} = 0.75 \mu\text{M}$ and motivated the basal ATP hydrolysis of P-gp in a concentration-dependent manner ($\text{EC}_{50} \text{ ATPase} = 0.027 \mu\text{M}$).



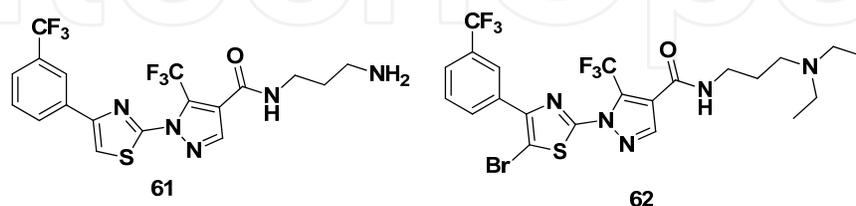
Oridonin **52**, a complex molecule *ent*-kaurane diterpenoid obtained from the traditional Chinese herb *Isodon rubescens*, has demonstrated great potential in the treatment of various human cancers due to its unique and safe anticancer pharmacological profile. However, with oridonin's poor solubility and poor bioavailability, hence C. Ding et. al.⁹² 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 IC₅₀ 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.



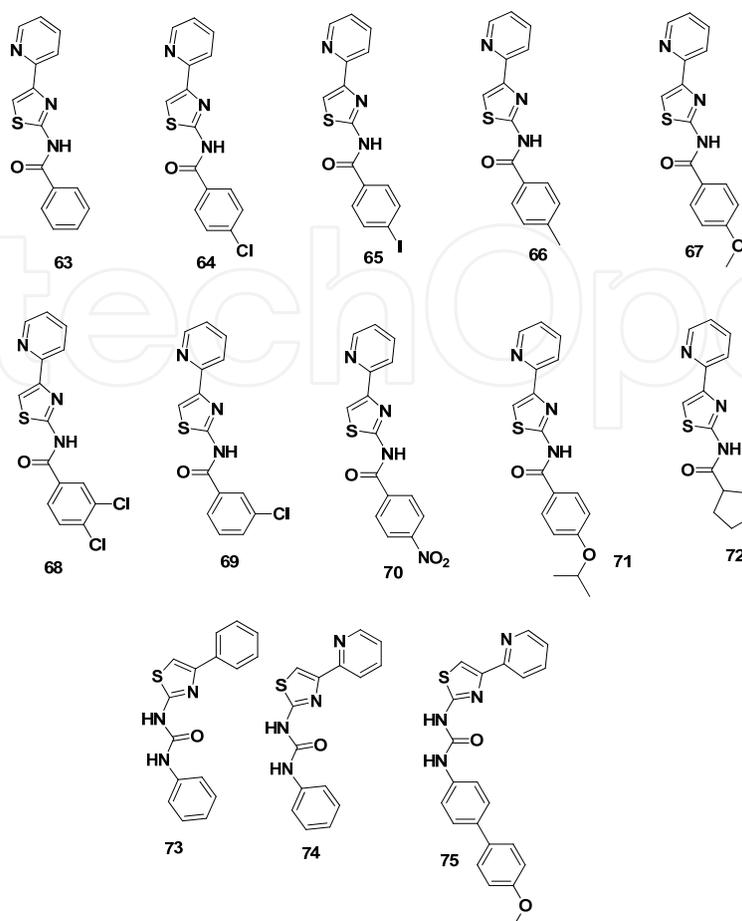
M. E. D. Francesco et. al. [93] reported a unique type of inhibitor, which designates the identification of a structurally various series of compounds including a 2-amino-1,3-thiazole as substitution of the carbamate in P4. Optimization studies motivated on structural variations in the P3, P2, and P1 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.



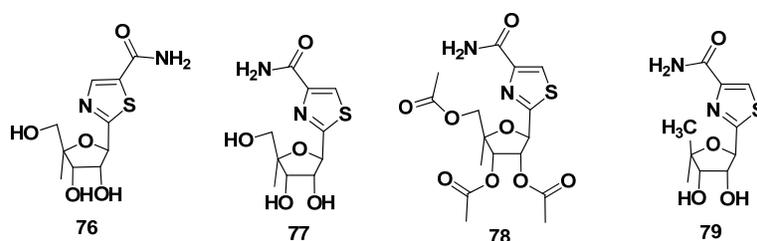
P. J. Sanfilippo et. al. [94] reported and described the synthesis and biological activity of a different kind of thiazole containing heterocycles as inhibitors of thrombin-induced human platelet aggregation. Additional estimation of selected compounds shows they inhibit platelet aggregation as motivated 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.



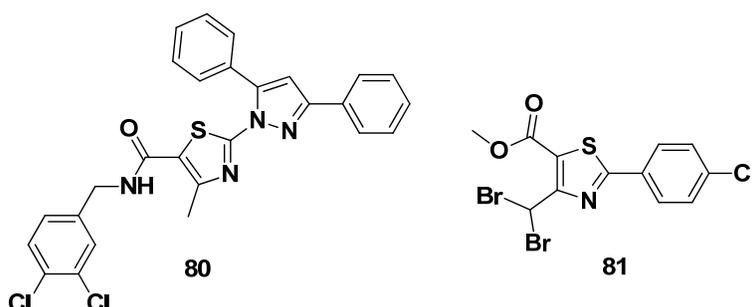
J. E. M. Koezen et. al. [95] prepared numerous *N*-[4-(2-pyridyl)thiazol-2-yl]benzamides, and these compounds exhibited adenosine affinities in the micromolar range. Most unexpected in the series of the *N*-[4-(2-pyridyl)thiazol-2-yl]amides were the retained adenosine affinities by the introduction of a cyclopentanamide instead of the benzamide.



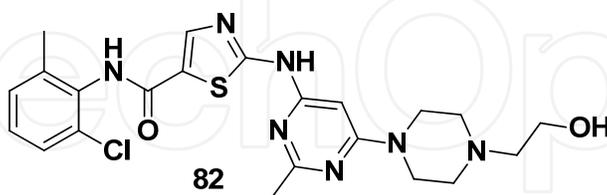
P. C. Srivastava et. al. [96] published a report in which they described the glycosylthiocarboxamides were used as the starting compounds for the synthesis of 2-D-ribofuranosylthiazole-4-carboxamide and 2-β-D-ribofuranosylthiazole-5-carboxamide (76). The structural variation of 2-β-D-ribofuranosylthiazole-4-carboxamide (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.

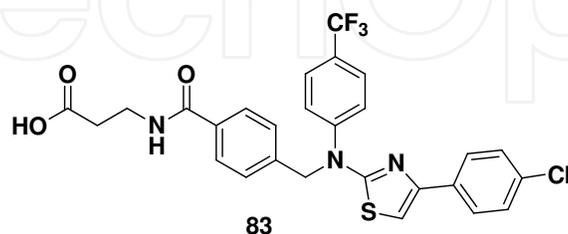


L. J. Lombardo et.al. [98] identified thiazole-based compounds as effective as Src/Abl kinase inhibitors with outstanding antiproliferative activity against hematological and solid tumor cell lines. Compound **82** was orally active in a K562 xenograft model of chronic myelogenous leukemia (CML), establishing 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.

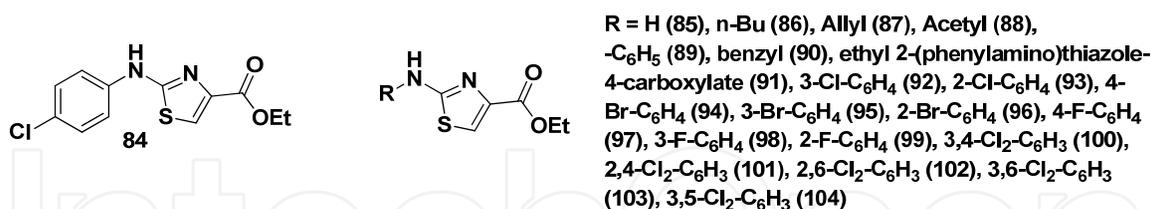


P. Madsen et. al. [99] explained the thiazole containing scaffold being potent human glucagon receptor antagonists with enhanced pharmacokinetic (PK) properties for expansion of pharmaceuticals for the medication of type-2 diabetes. The syntheses of compounds with cyclic moieties (5-aminothiazoles), 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

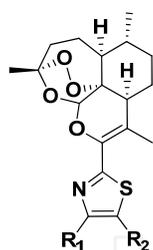
dogs with high oral bioavailabilities and constant high plasma coverages. The compounds exhibited species selectivity for glucagon receptor binding with very low affinities for the rat, mouse, rabbit, and pig receptors. However, dog and monkey glucagon receptor affinities seem to reflect the human situation. 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.

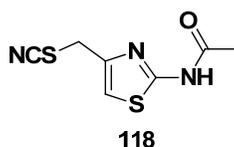


C. P. Hencken et. al. [101] synthesized 23 new dehydroartemisinin (DART) trioxane analogs in which 11 thiazoles moiety-containing compounds remaining are based on two oxadiazoles, and ten carboxamides and screened them for in vitro activity in the Toxoplasma lytic cycle. Fifteen (65%) of the analogs 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.

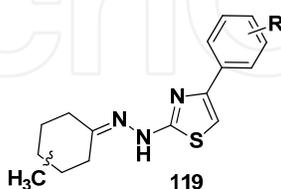


$R_1, R_2 = H$ (105); $R_1 = Me, R_2 = H$ (106); $R_1, R_2 = Me$ (107); $R_1 = Me, R_2 = H$ (108); $R_1 = Ph, R_2 = H$ (109); $R_1 = t-Bu, R_2 = H$ (110); $R_1 = Et, R_2 = H$ (111); $R_1 = C_6H_{11}, R_2 = H$ (112); $R_1 = p-CH_3C_6H_4, R_2 = H$ (113); $R_1 = p-CH_3OC_6H_4, R_2 = H$ (114); $R_1 = p-CH_3SC_6H_4, R_2 = H$ (115); $R_1 = p-CH_3S(O)_2Ph, R_2 = H$ (116).

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 $IC_{50} = 3.2$ NM. Mitotic blocking performs to be its key mechanism of cytotoxic activity. Compound 118 furthermore was the only compound that confirmed important in uiva antifiiarial activity against the adult worms of *Acanthocheilonema uiteae* in experimentally infected jirds.

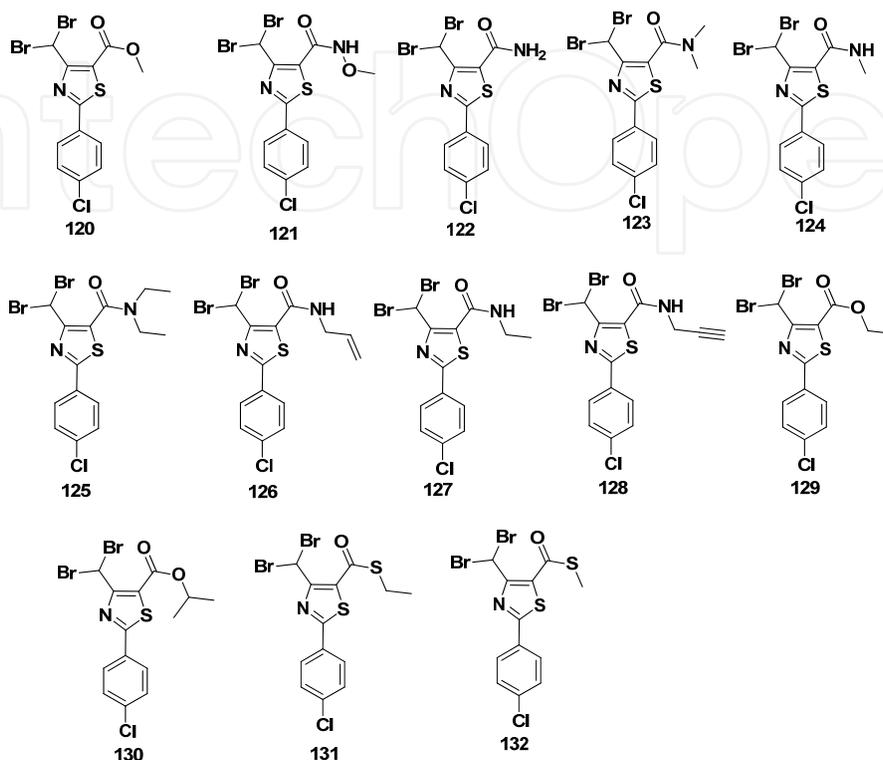


New thiazole based compounds [103] (1-(4-arylthiazol-2-yl)-2-(3-methylcyclohexylidene) - hydrazine) 119 are synthesized for the studied human B isoform of monoamine oxidase. These compounds were prepared as racemates and (R)-enantiomers by a stereoconservative synthetic arrangement in high yield and 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 IC_{50} ranging between 21.90 and 0.018 μ M.

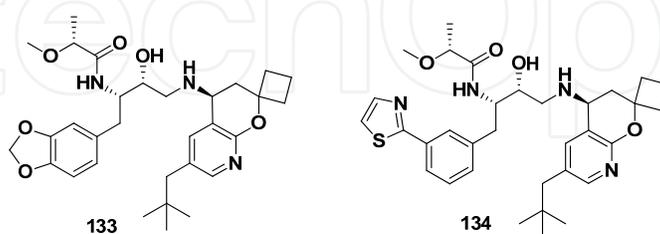


A. S. Mayhoub et.al. [104] synthesized a sequence of third-generation referents of methyl 4-(dibromomethyl)-2-(4-chlorophenyl)thiazole-5-carboxylate 120, which had the highly potent antiviral activity comparable to the first and second generation derivatives, have been synthesized and verified against 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**.

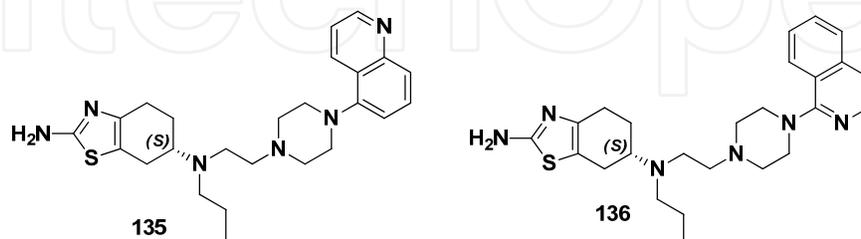


T. A. Dineen et.al. [105] reported the variation in structure **133** for the improved BACE1/CYP 3A4 inhibitors by a P1-phenyl ring of the hydroxyethylamine series to afford potent, which exhibit enhanced penetration into the CNS. Numerous compounds caused a robust decrease of A β levels in rat CSF and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

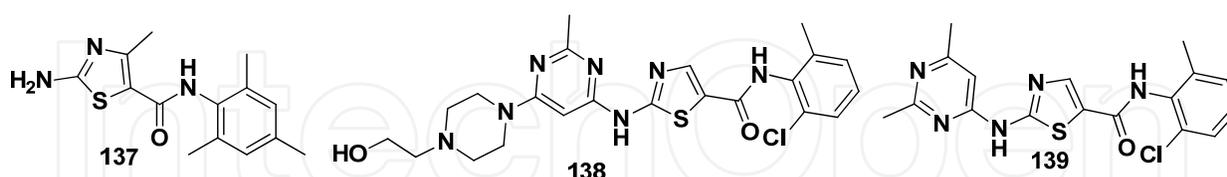


B. Ghosh et.al. [106] reported structure-activity relationship investigated on a unique hybrid sequence of derivatives where structural modification of aromatic hydrophobic moieties associated with the piperazine ring and bioisosteric exchange of the aromatic tetralin moieties were passed out. Binding assays were accepted with HEK-293 cells uttering either D2 or D3 receptors with tritiated spiperone to estimate inhibition constants (K_i). Functional activity of

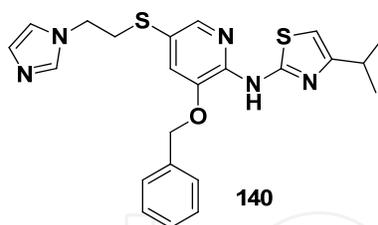
designated compounds in stimulating GTP γ S binding was evaluated with CHO cells uttering human D2 receptors and AtT-20 cells uttering human D3 receptors. SAR results recognized compound 136 as one of the lead molecules with better agonist activity for D3 receptor (EC_{50} (GTP γ S); D3= 0.52 nM; D2/D3 (EC_{50}): 223). Compounds 135 and 136 showed potent radical scavenging activity, the two lead compounds, 135 and 136, showed more *in vivo* activity in two Parkinson's disease (PD) animal models, reserpinized rat model and 6-OHDA brought unilaterally lesioned rat model.



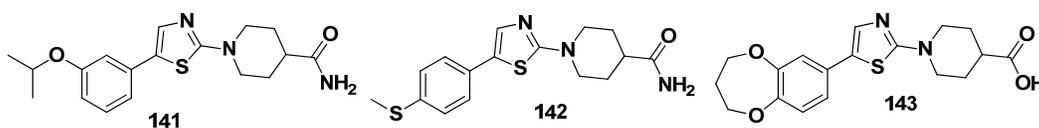
J. Das et.al. [107] explained that the 2-aminothiazole 137 was established as a unique Src family kinase inhibitor pattern through high calculated screening of their internal compound assembly. Optimization through consecutive structure-activity relationship iterations are recognized analogs 138 (Dasatinib, 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 *ex vivo* in mice (ED_{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.



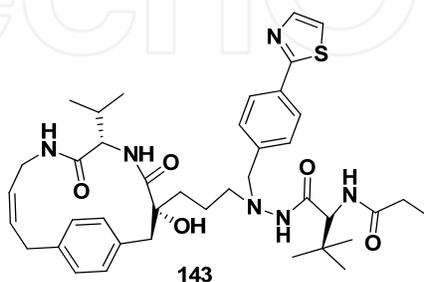
Major medicinal chemistry researcher focused on good docking small molecules inhibits the type 2 diabetes performances to have an insufficient or deficiency in one or both of these processes. Compounds that can activate glucokinase (GK) may serve as effective treatments for type 2 diabetes. In this process R. J. Hinklin et al. [108] reported that the recognition and preliminary optimization of a series of allosteric glucokinase activators (GKAs), revealed an early thiazolylamino pyridine-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 *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 spoiled 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 vivo* pharmacokinetics (PK) studies are necessary. J. Xiao et al. [109] reported SMA active theoretical 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.

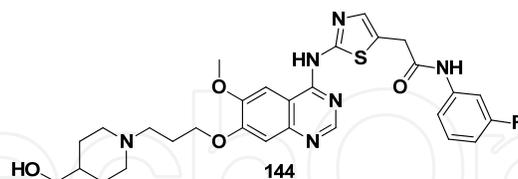


M. D, Rose, et al. [110] discussed the inhibition and antiviral activity consequence synthesis of 14- and 15-membered macrocycles for HIV-1 protease inhibitors (PIs) as obtained by ring-closing metathesis of the respective linear PIs. The macrocycles were very highly active than the linear precursors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

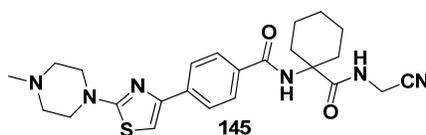


The preparation of a sequence of quinazolines inserted at C4 by aminothiazole ring is reported [111]. Their *in vitro* structure-activity relationships against Aurora A and B serine-threonine kinases are examined. The results reveal that quinazolines with a substituted aminothiazole

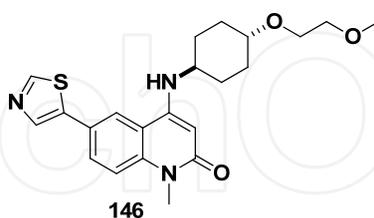
at C4 possess potent Aurora A and B inhibitory activity and outstanding selectivity against a panel of several serine-threonine and tyrosine kinases. Compound **144** also found that the location and nature of the substituent on the thiazole play vital roles in cellular potency.



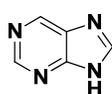
Approximately, the thiazole ring containing compound exhibits cathepsin K inhibitors [112]. The amalgamation of binding elements resulted at sub-250 pM, reversible, selective, and orally bioavailable cathepsin K inhibitors. In a series on of the compound exhibited single digit nanomolar inhibition *in 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.



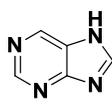
Haffner et. al. a series of thiazoloquinazolinones [113] were prepared and studied the inhibitory activity against CD38. Numerous compounds were also revealed to have good pharmacokinetic properties and established the capability to raise NAD levels in plasma, liver, and muscle tissue. Specifically, 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.



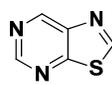
Thiazolo[5,4-d]pyrimidines and thiazolo[4,5-d]pyrimidines are structurally mimic with purines, in which a 1,3-thiazole ring system exchanges the imidazole moiety. While purine chemistry is broadly discussed in the literature, the number of medicinal chemistry publications that reported the synthesis 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.



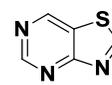
9H-purine
147



7H-purine
148

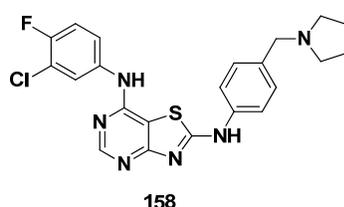
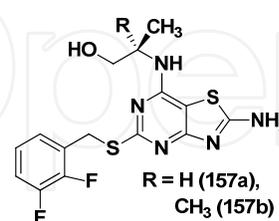
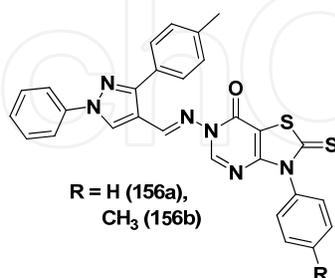
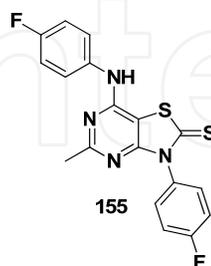
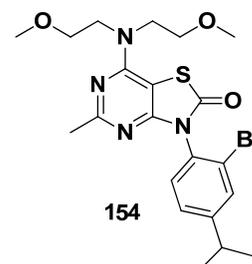
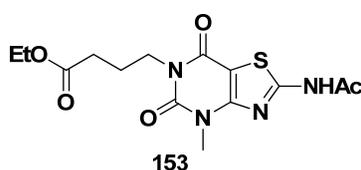
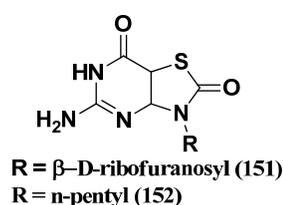


thiazolo[5,4-d]pyrimidine
149

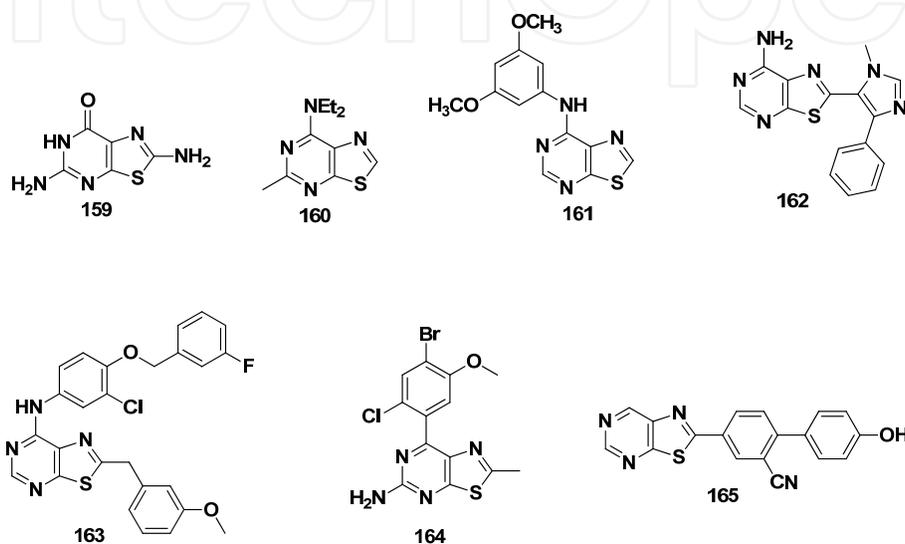


thiazolo[4,5-d]pyrimidine
150

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-arylthiazolo[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].

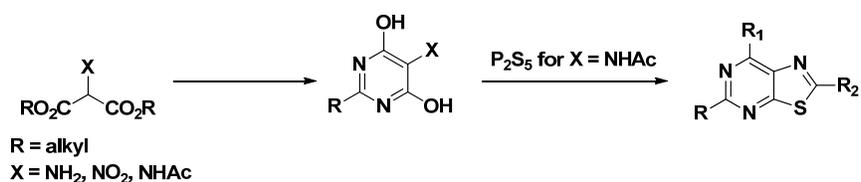


2,5-Diaminothiazolo[5,4-d]pyrimidin-7(6H)-one (Compound **159**), a thio-isostere of 8-amino-guanine, was established to be a poor inhibitor of purine nucleoside phosphorylase (PNP) [123]. 7-Diethylamino-5-methylthiazolo[5,4-d]pyrimidine **160** has vasodilating and hypotensive properties, inhibits platelet 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].

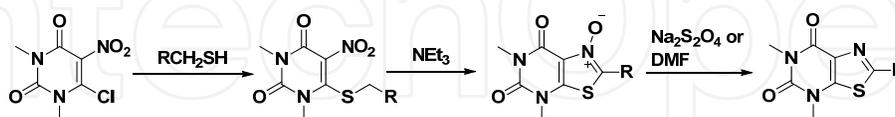


5. General Synthetic Routes to Thiazolo[5,4-d]pyrimidines

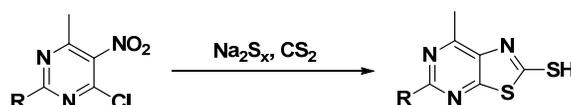
In wide-ranging, pyrimidines with a nitrogen-containing substituent at position 5 (such as an amino or nitro group) can work as precursors for the formation of thiazolo[5,4-d]pyrimidines by thiazole ring condensation. 5-Amino- or 5-nitropyrimidines can be organized from diethyl amino-, nitro-, or acetamino-malonate 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-dihydroxypyrimidine 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].



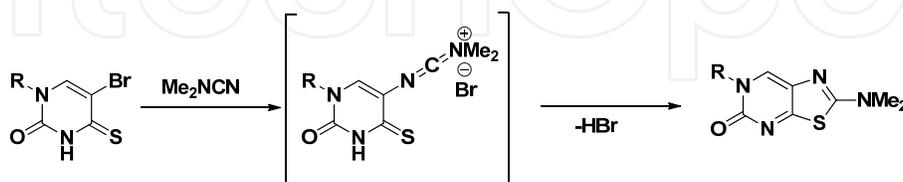
2-Mercaptothiazolo[5,4-d]pyrimidines easily obtained from 6-chloro-5-nitropyrimidines by the reaction with carbon disulfide and sodium sulfide [138].



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

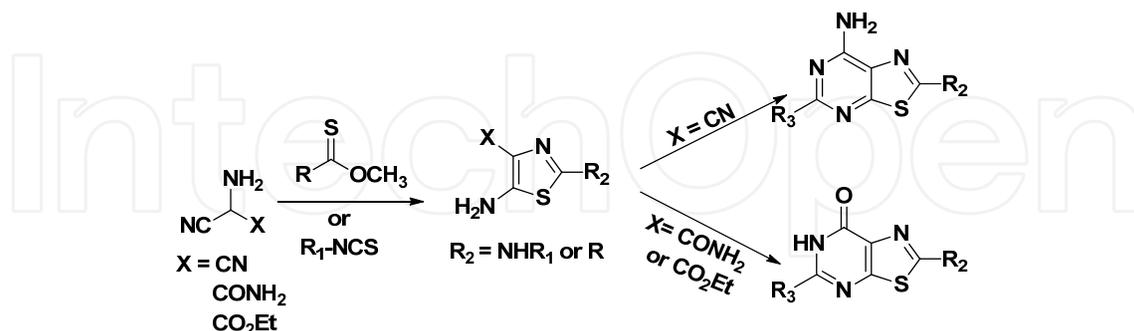


Ahmed et al. [140] reported the synthesis of thiazolo[5,4-d]pyrimidines from pyrimidines without 5-amino or 5-nitro substituents. The reaction between 5-bromo-4-thioxo-pyrimidinones and dimethylcyanamide affords carbodiimide intermediates, which is a very fast intramolecular cyclization to produce a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

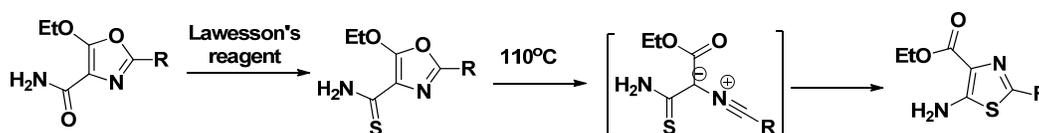


On the other hand, thiazolo[5,4-d]pyrimidines also obtained from 5-aminothiazole derivatives, are prepared from aminomalononitrile (or its derivatives) and isothiocyanates [141] or thioesters [142]. The next to 5-amino and 4-cyano (or conforming carboxamide or ester groups) on the thiazole ring are proper 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 to 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].

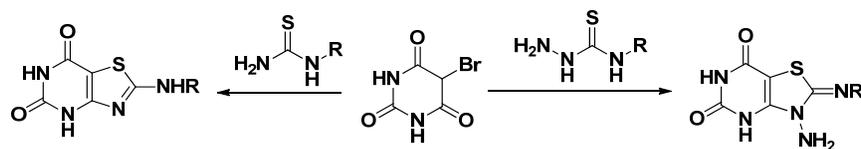


6. General Synthetic Routes to Thiazolo[4,5-d]pyrimidines

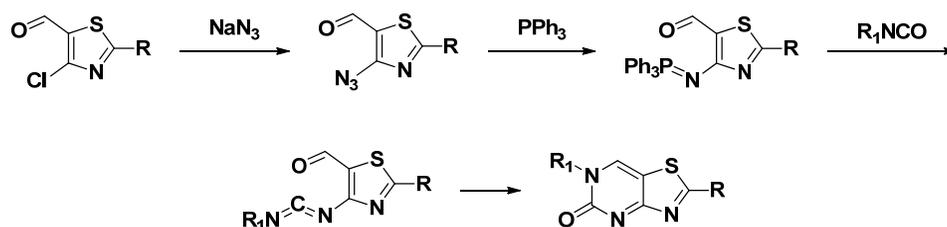
The preparation of thiazolo[4,5-d]pyrimidines from a properly substituted pyrimidine compound yields 2-aminothiazolo[4,5-d]pyrimidines. Thiocyanation of 6-aminopyrimidines reacts with potassium thiocyanate, bromine and pyridine, proceeded by cyclization yields the 2-aminothiazolo[4,5-d]pyrimidines [149].



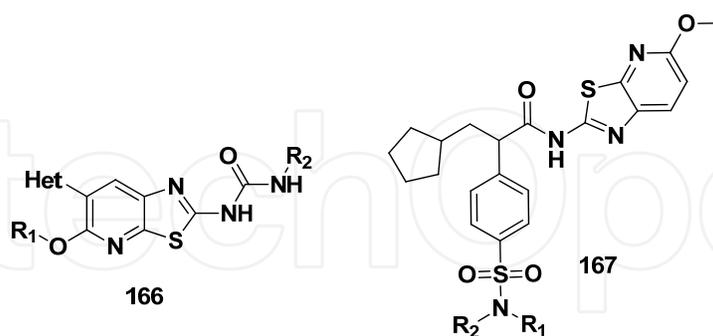
Condensation of 5-bromobarbituric acid with thiourea and/or its derivatives in the presence of an alkali yields thiazolo[4,5-d]pyrimidine derivatives [150].



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 Bebernitz and co-workers made use of the chlorosulfonic acid combined with thiazolopyridines scaffold [154] (compounds **166** and **167**)

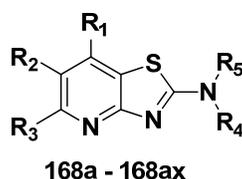


Bicyclic nitrogen, sulfur - containing heterocycles, such as Thiazolo[5,4-b]quinoline, thiazolopyridines, and thiazolopyrimidines are well-known pharmacophores in drug discovery [155-157]. Examples of promoted drugs with a bicyclic core structure include AMG-369 analogs performing as Lysophospholipid 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

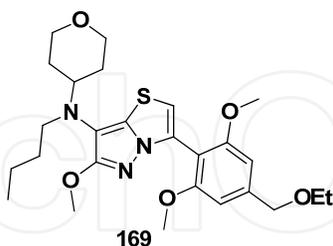
well as fused-pyridine analogs such as the thiopheno[2,3-b]pyridines [161] using the Friedlander reaction.

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 bioresponses. 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.

Acknowledgements

I acknowledge the Department of Chemistry, Nizam College, Osmania University. Moreover, grateful to Dr. Ravi Varala, Head, IIIT, Basara, India, for the valuable support to write this chapter.

Author details

Someshwar Pola*

Address all correspondence to: somesh.pola@gmail.com

Department of Chemistry, Nizam College, Osmania University, Hyderabad, Telangana, India

References

- [1] Drews J, Drug Discovery: A Historical Perspective, Science; 2000. P. 1960 - 1964. DOI: 10.1126/ science. 287.5460.1960

- [2] Wess G, Urmann M, Sickenberger B, *Medicinal Chemistry: Challenges and Opportunities*; *Angew. Chem. Int. Ed.*; 2001. p. 3341 - 3350. DOI: 10.1002/1521-3773(20010917)40:18<3341::AID-ANIE3341>3.0.CO;2-D
- [3] Lombardino J. G. Lowe J. A, *A guide to drug discovery: The role of the medicinal chemist in drug discovery – then and now*, *Nat. Rev. Drug Discov.*: 2004. p. 853 – 862. DOI: 10.1038/nrd1523
- [4] Kolb H.C, Finn M. G, Sharpless K. B, *Click Chemistry: Diverse Chemical Function from a Few Good Reactions*, *Angew. Chem. Int. Ed.*: 2001. p. 2004 - 2021. DOI: 10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5
- [5] Horton D. A, Bourne G. T, Smythe M. L, *The Combinatorial Synthesis of Bicyclic Privileged Structures or Privileged Substructures*, *Chem. Rev.*: 2003. p. 893 -930. DOI: 10.1021/cr020033s
- [6] Zoltewicz J. A, Deady L. W, "Quaternization of Heteroaromatic Compounds: Quantitative Aspects", *Advances in Heterocyclic Chemistry*, Elsevier: 1978. p. 71–121. DOI: 10.1016/S0065-2725(08)60103-8
- [7] Sammes P. G, *Comprehensive Organic Chemistry*” Heterocyclic compounds, Part 20-1, Ed., Pergamon Press, Oxford: Vol. 4, 1979. p. 976
- [8] Eledersfield R.C, “Heterocyclic compounds”, (Five membered Heterocycles containing two Hetero-atoms), Ed., John Wiley and Sons Inc., New York: 1961.
- [9] Breslow R, *On the Mechanism of Thiamine Action. IV.1 Evidence from Studies on Model Systems*, *J. Am. Chem. Soc.*: 1958. p. 3719 - 3726. DOI: 10.1021/ja01547a064
- [10] Borisenko V. E, Koll A, Kolmakov E. E, Rjasnyi A. G, *Hydrogen bonds of 2-aminothiazoles in intermolecular complexes (1:1 and 1:2) with proton acceptors in solutions*, *J. Mol. Struct.*: 2006. p. 101 – 115. DOI:10.1016/j.molstruc.2005.08.006
- [11] Bhargava P.N, Lakhan R, Tripathi K, *J. Ind. Chem. Soc.*, 1982, 59, 773; (b) Maulard T, Lagorce J. F, Thomos J. C, Raby C, *Biological Evaluation of Compounds with -NCS-Group or Derived from Thiazole and Imidazole. Activity on Prostaglandin Synthetase Complex*, *J. Pharm. Pharmacol.*: 1993. p. 731 - 735. DOI: 10.1111/j.2042-7158.1993.tb07098.x
- [12] Maj J, Rog Z, Skuza G, Kolodziejczyk K, *Antidepressant effects of pramipexole, a novel dopamine receptor agonist*, *J. Neural. Transm.*: 1997. p. 525 - 533.
- [13] Milne G. W. A, *Handbook of Antineoplastic Agents*, Gower; Ashgate, Ed., London, UK, 2000.
- [14] M. V. N. De Souza, M. V. De Almeida, *Drugs anti-HIV: past, present and future perspectives*, *Quim. Nova.*: 2003. p. 366 – 372. DOI.org/10.1590/S0100-40422003000300014

- [15] Markus B, Salome von G, Christoph B, Werner J P, Molecular Aspects of Drug Recognition by Specific T Cells, *Curr. Drug. Tar.:* 2004. p. 1 – 11. DOI: 10.2174/1389450033347082
- [16] Knadler M P, Bergstrom R. F, Callaghan J. T, Rubin A, Nizatidine, an H2-blocker. Its metabolism and disposition in man, *Drug Metab. Dispos.:* 1986. p. 175 - 182.
- [17] Lednicer D, Mitscher L. A, George G. I, *Organic Chemistry of Drug Synthesis*, Wiley, New York, Vol. 4, 1990, p. 95.
- [18] Rehman M. Z, Anwar C. J, Ahmad S, An Efficient Synthesis of 2-Alkyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxides, *Bull. Korean Chem. Soc.:* 2005. p. 1771 - 1775. DOI: <http://dx.doi.org/10.5012/bkcs.2005.26.11.1771>
- [19] Beuchet P, Varache-Lembege M, Neveu A, Leger J. M, Vercauteren J, Larrouture S, Deffieux G, Nuhrich A, New 2-sulfonamidothiazoles substituted at C-4: synthesis of polyoxygenated aryl derivatives and in vitro evaluation of antifungal activity, *Eur. J. Med. Chem.:* 1999. p. 773 - 779. DOI:10.1016/S0223-5234(99)00215-9
- [20] Fink B. E, Mortensen D. S, Stauffer S. R, Aron Z. D, Katzenellenbogen J. A. Novel structural templates for estrogen-receptor ligands and prospects for combinatorial synthesis of estrogens, *Chem. Biol.:* 1999. p. 205 - 219. DOI: 10.1016/S1074-5521(99)80037-4
- [21] van Muijlwijk-Koezen J. E, Timmerman H, Vollinga R. C, von DrabbeKunzel J. F, de Groote M, Visser S, IJzerman A. P. Thiazole and Thiadiazole Analogues as a Novel Class of Adenosine Receptor Antagonists, *J. Med. Chem.:* 2001. p. 749 - 762. DOI: 10.1021/jm0003945
- [22] Füßlein, Martin, Bretschneider, Thomas, Fischer, Reiner, Jeschke, Peter, Köhler, Adeline, Kluth, Joachim, Mühlthau, Friedrich August, Voerste, Arnd, Sato, Yoshitaka, United States Patent: 20110319428, 2011, December.
- [23] Wang Q, Li H, Li Y, Huang R. Synthesis and Herbicidal Activity of 2-Cyano-3-(2-chlorothiazol-5-yl)methylaminoacrylates, *J. Agric. Food Chem.:* 2004. p. 1918 - 1922. DOI: 10.1021/jf035312a
- [24] Tintcheva I, Maximova V, Deligeorgiev T, Zaneva D, Ivanov I. New asymmetric monomethine cyanine dyes for nucleic-acid labelling: absorption and fluorescence spectral characteristics, *J. Photochem. & Photobiol. A: Chem.:* 2000. p. 7 - 11. DOI: 10.1016/S1010-6030(99)00207-5
- [25] Rucker V. C, Foister S, Melander C, Dervan P. B. Sequence Specific Fluorescence Detection of Double Strand DNA, *J. Am. Chem. Soc.:* 2003. p. 1195 - 1202. DOI: 10.1021/ja021011q
- [26] Shibamoto T. Heterocyclic compounds found in cooked meats, *J. Agric. Food Chem.:* 1980. p. 237 - 243. DOI: 10.1021/jf60228a031

- [27] Buchanan J. L, Bohacek R. S, Luke G. P, Hatada M, Lu X, Dalgarno D.C, Narula S. S, Yuan R, Holt D. A. Structure-based design and synthesis of a novel class of Src SH2 inhibitors, *Bioorg. Med. Chem. Lett.*: 1999. p. 2353 - 2358. DOI: 10.1016/S0960-894X(99)00388-1
- [28] Hallinan E. A, Hagen T. J, Tsymbalov S, Stapelfeld A, Savage M. A. 2,4-Disubstituted oxazoles and thiazoles as latent pharmacophores for diacylhydrazine of SC-51089, a potent PGE2 antagonist, *Bioorg. Med. Chem.*: 2001. p. 1 - 6. DOI: 10.1016/S0968-0896(00)00229-7
- [29] Das B, Reddy S. V, Ramu R. A rapid and high-yielding synthesis of thiazoles and aminothiazoles using ammonium-12-molybdophosphate, *J. Mol. Catal. A: Chem.*: 2006. p. 235 - 237. DOI: 10.1016/j.molcata.2006.02.065
- [30] Narender M, Reddy S. M, Sridhar R, Nageswar Y, V. D, Rao R. K.. Aqueous phase synthesis of thiazoles and aminothiazoles in the presence of β -cyclodextrin, *Tetrahedron Lett.*: 2005. p. 5953 -5955. DOI: 10.1016/j.tetlet.2005.06.130
- [31] Siddiqui H. L, Iqbal A, Ahmed S, Weaver G. Synthesis and Spectroscopic Studies of New Schiff Bases, *Molecules*: 2006. p. 206 - 211. DOI: 10.3390/11020206
- [32] Karade H, Sathe M, Kaushik M.P., An efficient method for the synthesis of 2-aminothiazoles using silica chloride as a heterogeneous catalyst, *Catal. Commun.*: 2007. p. 741 - 746. DOI: 10.1016/j.catcom.2006.09.005
- [33] Egido E. G, Wong S. Y. F, Warrington B. H., A Hantzsch synthesis of 2-aminothiazoles performed in a heated microreactor system, *Lab Chip*, 2002. p.31 - 33. DOI: 10.1039/B109360F
- [34] George W. K, Arjun R. M. Microwave promoted synthesis of functionalized 2-aminothiazoles, *Tetrahedron Lett.*: 2006. p. 5171 - 5172. DOI: 10.1016/j.tetlet.2006.05.053
- [35] Metzger J. V. "Thiazole and its derivatives (Part I)", An Interscience Publication: 1979. p. 165 - 335. DOI: 10.1002/9780470187081
- [36] Willstatter R, Wirth T. Über Thioformamid, *Berichte*: 1909. p. 1908 - 1922. DOI: 10.1002/cber.19090420267
- [37] Otto H, Process for the production of Thiazoles, U. S. Patent No. 2160867: 1939.
- [38] George Y. S, Subhi A. A. Preparation and spectral characterization of substituted 2-aminothiazoles, *J. Chem. Eng. Data*: 1973. p. 99 - 102. DOI: 10.1021/je60056a029
- [39] G. Marchesini, *Gazz. Chim. Ital.*, 1893, 23, 437.
- [40] G. Marchesini, *Gazz. Chim. Ital.*, 1894, 24, 65.
- [41] Clarke H T, Gurin S, Studies of Crystalline Vitamin B1. XII. The Sulfur-Containing Moiety, *J. Am. Chem. Soc.*: 1935. p. 1876 - 1881. DOI: 10.1021/ja01313a035

- [42] Todd A R, Bergel F, Karimullah. Über Aneurin, II. Mitteil.: Über die Synthese von N-Arylthiazoliumsalsen; über Einzelheiten in der Konstitution des Aneurins und Thiochroms, *Berichte*: 1936. p. 217 - 223. DOI: 10.1002/cber.19360690139
- [43] Karimullah, Substituted phenyl- and benzyl-thiazolium salts, *J. Chem. Soc.*: 1937. p. 961 - 962. DOI: 10.1039/JR9370000961
- [44] Kiprianov A. I, Asnina F. I, Shako I. K.. *J. Gen. Chem., U.S.S.R.*, 1948, 18, 165.
- [45] E. D. Sych, E. K. Mikitenko, *Khim. Geterotsikl. Soedinenii*, 1971, 7, 857.
- [46] George W. W. Reactions in the thiazole series. ii. the reaction of 2-chlorobenzothiazole with thiourea in aqueous media, *J. Org. Chem.*: 1939. p. 436 - 441. DOI: 10.1021/jo01216a010
- [47] Ian H. S. Concerning amino-acids, peptides, and purines, *J. Chem. Soc.*: 1949. p. 2099 - 2107. DOI: 10.1039/JR9490002099
- [48] Cook A. H, Heilbron I, MacDonald S. F, Mahadevan A. P. Studies in the azole series. Part XII. Some thiazolopyrimidines, *J. Chem. Soc.*: 1949. p. 1064 - 1068. DOI: 10.1039/JR9490001064
- [49] Cook A. H, Heilbron I, Mahadevan A. P. Studies in the azole series. Part XI. The interaction of α -amino-nitriles, hydrogen sulphide, and ketones, *J. Chem. Soc.*: 1949. p. 1061 - 1064. DOI: 10.1039/JR9490001061
- [50] Cook A. H, Heilbron I. M, Levy A. L. Studies in the azole series. Part II. The interaction of α -amino-nitriles and carbon disulphide, *J. Chem. Soc.*: 1947. p. 1598 - 1609. DOI: 10.1039/JR9470001598
- [51] Cook A. H, Heilbron I. M, Stern E. Studies in the azole series. Part X. Some 5-amino-2-mercapto-4-alkylthiazoles and 2 : 4-dithio-5-alkylhydantions, *J. Chem. Soc.*: 1948. p. 2031 - 2033. DOI: 10.1039/JR9480002031
- [52] Hoggarth E. The rearrangement of 2-benzenesulphenamidothiazoles. Part II. Thiazole compounds substituted in position 4, *J. Chem. Soc.*: 1947. p.114 - 118. DOI: 10.1039/JR9470000114
- [53] Gabriel S. Synthese von Oxazolonen und Thiazolonen II, *Berichte*: 1910. p. 1283 - 1287. DOI: 10.1002/cber.19100430219
- [54] Asinger F, Thiel M, Pallas E. Über die gemeinsame Einwirkung von elementarem Schwefel und gasförmigem Ammoniak auf Ketone I. Die Gemeinsame Einwirkung von Schwefel und Ammoniak auf Diäthylketon, *Annalen*: 1957. p. 37 - 49. DOI: 10.1002/jlac.19576020104
- [55] Davies W, MacLaren J, Wilkinson L. The synthesis and properties of 2 : 4-diaminothiazoles *J. Chem. Soc.*: 1950. p. 3491 - 3494. DOI: 10.1039/JR9500003491

- [56] Chase B. H, Walker J. A novel reaction of thiourea, the structure of Jaffé's base, and related studies, *J. Chem. Soc.*: 1955. p. 4443 - 4450. DOI: 10.1039/JR9550004443
- [57] Alessandro D, Alberto M. Thiazole-Mediated Synthetic Methodology, *Chem. Rev.*: 2004. p. 2557-2599. DOI: 10.1021/cr0200791
- [58] Koichi N, Shen S. S, Mao-Yi L. Intramolecular nucleophilic substitution at an sp^2 carbon: synthesis of substituted thiazoles and imidazole-2-thiones, *Tetrahedron Lett.*: 2009. p. 3161 - 3163. DOI: 10.1016/j.tetlet.2008.12.118
- [59] Dominique R, Qiao Q, Goodnow Jr. R. 2,4-Disubstituted-5-acetoxythiazoles: useful intermediates for the synthesis of thiazolones and 2,4,5-trisubstituted thiazoles, *Tetrahedron Lett.*: 2008. p. 3682 - 3686. DOI: 10.1016/j.tetlet.2008.03.140
- [60] Sharma R N, Xavier F P, Vasu K K, Chaturvedi S C, Pancholi S S. Synthesis of 4-Benzyl-1,3-thiazole derivatives as potential anti-inflammatory agents: An Analogue-based Drug Design Approach, *J Enz Inhib Med Chem.*: 2009. p. 890 - 897. DOI: 10.1080/14756360802519558
- [61] Clark R F, Zhang T, Wang X, Wang R, Zhang X, Camp H S, Beutel B A, Sham H L, Gu Y J. Phenoxy thiazole derivatives as potent and selective acetyl Co-A carboxylase-2 inhibitors: Modulation of isozyme selectivity by incorporation of phenyl ring substituent, *Bioorg Med Chem Lett.*: 2007. p.1961-1965. DOI: 10.1016/j.bmcl.2007.01.022
- [62] Mahajan M. P, Sodnhi S. M, Ralhan N. K. Studies on Heterocyclics. V. Synthesis of Thiazolotriazepines, *Bull. Chem. Soc. Jpn.*: 1976. p. 2651 - 2652. DOI: 10.1246/bcsj.49.2651
- [63] Astrakhantseva N. I, Zhiryakov V. G, Abramenko P. I. Synthesis of 2-mercapto-substituted thieno[2,3-d]thiazoles and benzothieno[3,2-d] thiazoles, *Chem. Het. Compd.*: 1976. p. 1123 - 1124.
- [64] Beyer H, Lassing W, Ruhlig G. Über Thiazole, XV. Mitteil.: Über die Kondensation von Chloraceton mit Thiosemicarbazid und einige Umlagerungen in der Thiazolreihe, *Chem. Ber.*: 1953. p. 764 - 769. DOI: 10.1002/cber.19530860621
- [65] Haviv F, Ratajczyk J. D, DeNet R. W, Kerdesky F. A, Walters R. L, Schmidt S. P, Holms J. H, Young P. R, Carter G. W, 3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile derivatives: inhibitors of immune complex induced inflammation, *J. Med. Chem.*: 1988. p.1719 - 1728. DOI: 10.1021/jm00117a010
- [66] Patt W. C, Hamilton H. W, Taylor M. D, Ryan M. J, Jr. Taylor D. G, Connolly C. J. C, Structure-activity relationships of a series of 2-amino-4-thiazole-containing renin inhibitors, *J. Med. Chem.*: 1992. p. 2562 -2572. DOI: 10.1021/jm00092a006
- [67] Bell F. W, Cantrell A. S, Hoegberg M, Jaskunas S. R, Johansson N. G, Jordon C. L, Kinnick M. D, Lind P, Jr. Morin J. M, Noreen R, Oberg B, Palkowitz J. A, Parrish C. A. Phenethylthiazolethiourea (PETT) Compounds, a New Class of HIV-1 Reverse

- Transcriptase Inhibitors. 1. Synthesis and Basic Structure-Activity Relationship Studies of PETT Analogs, *J. Med. Chem.*: 1995. p. 4929 - 4936. DOI: 10.1021/jm00025a010
- [68] Fink B. A, Mortensen D. S, Stauffer S. R., Aron Z. D, Katzenellenbogen J. A. Novel structural templates for estrogen-receptor ligands and prospects for combinatorial synthesis of estrogens, *Chem. Biol.*: 1999. p. 205 -219. DOI: 10.1016/S1074-5521(99)80037-4
- [69] Van Muijlwijk-Koezen J. E, Timmerman H, Vollinga R. C, Von Drabbe Kunzel J. F, De Groote M, Visser S, Ijzerman A. P. Thiazole and Thiadiazole Analogues as a Novel Class of Adenosine Receptor Antagonists, *J. Med. Chem.*: 2001. p. 749 - 762. DOI: 10.1021/jm0003945
- [70] Metzger J. V. "Comprehensive Heterocyclic Chemistry Part-I", Pergamon: New York, 1984. p. 328.
- [71] Sherif A. F. R, Ibrahim M. El-A, Heba A. A. Design and synthesis of some thiazolyl and thiadiazolyl derivatives of antipyrine as potential non-acidic anti-inflammatory, analgesic and antimicrobial agents, *Bioorg. Med. Chem.*: 2009. p.882 – 895. DOI: 10.1016/j.bmc.2008.11.035
- [72] Zablotskaya A, Segal I, Germane S, Shestakova I, Domracheva I, Nesterova A, Geronikaki A, Lukevics E. Silyl Modification of Biologically Active Compounds. 8. Trimethylsilyl Ethers of Hydroxyl-containing Thiazole Derivatives, *Chem. Het. Comp.*: 2002. p. 859 – 866.
- [73] Dae-Kee K, Joon H. C, Young J. A. Synthesis and biological evaluation of 5-(pyridin-2-yl)thiazoles as transforming growth factor- β type1 receptor kinase inhibitors, *Bioorg. Med. Chem. Lett.*, 2008. p.2122 - 2127. DOI: 10.1016/j.bmcl.2008.01.084
- [74] Rajan S, Hardik G, Thaker M, Tony G, Kamala K. V. Design, synthesis and characterization of novel 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazoline-4-one derivatives as inhibitors of NF- κ B and AP-1 mediated transcription activation and as potential anti-inflammatory agents, *Eur. J. Med. Chem.*: 2009. p. 2184 - 2189. DOI: 10.1016/j.ejmech.2008.10.031
- [75] Johan D.O, et. al. Discovery of a potent and selective Aurora kinase inhibitor, *Bioorg. Med. Chem. Lett.*: 2008. p. 4880 - 4884. DOI: 10.1016/j.bmcl.2008.07.073
- [76] El-Subbagh H. I, Al-Obaid A. M. 2,4-Disubstituted thiazoles II. A novel class of anti-tumor agents, synthesis and biological evaluation, *Eur. J. Med. Chem.*: 1996. p.1017 - 1021. DOI: 10.1016/S0223-5234(97)86181-8
- [77] Guay D. R. P. Cefdinir: An advanced-generation, broad-spectrum oral cephalosporin, *Clin. Ther.*: 2002. p. 473 – 489. DOI: 10.1016/S0149-2918(02)85125-6; (b) Mooney M. T, Deguchi S, Tada T, Fujioka M, Okamoto Y, Yasuda T. Interaction of Cefdinir with Iron in Aqueous Solution, *Chem. Pharm. Bull.*: 1995. p. 374 – 377. DOI: org/10.1248/cpb.43.374; (c) González M, Rodríguez Z, Tolón B, Rodríguez J. C, Veléz H, Valdez B,

- Lopéz M. A, Fini A. An alternative procedure for preparation of cefdinir, *Farmaco*: 2003. p. 409 - 418. DOI: 10.1016/S0014-827X(03)00063-6
- [78] Kempf D. J, Marsh K. C, Denissen J. F, McDonald E, Vasavanonda S, Flentge C. A, Green B. E, Fino L, Park C. H, Kong X. P. ABT-538 is a potent inhibitor of human immunodeficiency virus protease and has high oral bioavailability in humans, *Proc. Natl. Acad. Sci. U. S. A.*: 1995. p. 2484 - 2488. DOI:10.1073/pnas.92.7.2484
- [79] Kerdesky F. A. J, Seif L. S. A Novel and Efficient Synthesis of 5-(Hydroxymethyl) Thiazole: An Important Synthone for Preparing Biologically Active Compounds, *Synth. Commun.*: 1995. p. 2639 - 2645. DOI: 10.1080/00397919508011810
- [80] Schneider C, Griss G, Hurnaus R, Kobinger W, Pichler L, Bauer R, Mierau J, Hinzen D, Schingnitz G, *Eur. Patent 186087B1*, 1986.
- [81] Juarez J. M, Silva Guisasola L. O. Method for the resolution of 2-amino-6-propylamino-4,5,6,7-tetrahydrobenzothiazol and intermediate compounds, *WO2006120268*: 2006.
- [82] Miodragović D. U, Bogdanović G. A, Miodragović Z. M, Radulović M. D, Novaković S. B, Kaluđerović G. N, Kozłowski H. Interesting coordination abilities of antiulcer drug famotidine and antimicrobial activity of drug and its cobalt(III) complex, *J. Inorg. Biochem.*: 2006. p. 1568 - 1574. DOI: 10.1016/j.jinorgbio.2006.05.009
- [83] Sprague J. M, Land A. H, Ziegler C, *Derivatives of 2-Amino-4-methylthiazole*, *J. Am. Chem. Soc.*: 1946. p. 2155 - 2159. DOI: 10.1021/ja01215a010
- [84] Hirata Y, Yanagisawa I, Ishii Y, Tsukamoto S, Ito N, Isamura Y, Takeda M, U.S.: *Patent 4283408*, 1981.
- [85] Hasegawa M. A Facile One-Pot Synthesis of 4-Alkoxy-1,3-benzenedicarbonitrile, *Heterocycles*: 1998. p. 857 - 864. DOI: 10.3987/COM-97-S(N)89
- [86] Nakamura Y, Takeuchi S, *Synthesis of Bistratamide H Using a New Fluorous Protecting Group*, *QSAR & Combinatorial Science*: 2006. p. 703 - 708. DOI: 10.1002/qsar.200640053; (b) Nakamura Y, Okumura K, Kojima M, Takeuchi S. An expeditious synthesis of bistratamide H using a new fluororous protecting group, *Tetrahedron Lett.*: 2006. p. 239 - 243. DOI: 10.1016/j.tetlet.2005.10.144
- [87] Rao V. R, Sumanth K. A facile one step synthesis of 3-[2-(3,5-dimethyl-1H-pyrazol-1-yl)-4-thiazolyl]-2H-1-benzopyran-2-ones under solvent free conditions, *J. Chem. Res.*: 2002. p. 420 - 421. DOI: org/10.3184/030823402103172725
- [88] Adib M, Mahdavi M, Noghani M. A, Mirzaei P. Catalyst-free three-component reaction between 2-aminopyridines (or 2-aminothiazoles), aldehydes, and isocyanides in water, *Tetrahedron Lett.*: 2007. p. 7263 - 7265. DOI: 10.1016/j.tetlet.2007.08.049
- [89] Zheng S, Zhong Q, Xi Y, Mottamal M, Zhang Q, Schroeder R. L, Sridhar J, He L, McFerrin H, Wang G, *Modification and Biological Evaluation of Thiazole Derivatives*

- as Novel Inhibitors of Metastatic Cancer Cell Migration and Invasion, *J. Med. Chem.*: 2014. p.6653 - 6667. DOI: 10.1021/jm500724x
- [90] Zhu J, Han L, Diao Y, Ren X, Xu M, Xu L, Li S, Li Q, Dong D, Huang J, Liu X, Zhao Z, Wang R, Zhu L, Xu Y, Qian X, Li H. Design, Synthesis, X-ray Crystallographic Analysis, and Biological Evaluation of Thiazole Derivatives as Potent and Selective Inhibitors of Human Dihydroorotate Dehydrogenase, *J. Med. Chem.*: 2015. p. 1123 - 1139. DOI: 10.1021/jm501127s
- [91] Singh S, Prasad N. R, Chufan E. E, Patel B. A, Wang Y. J, Chen Z. S, Ambudkar S. V, Talele T. T, Design and Synthesis of Human ABCB1 (P-Glycoprotein) Inhibitors by Peptide Coupling of Diverse Chemical Scaffolds on Carboxyl and Amino Termini of (S)-Valine-Derived Thiazole Amino Acid, *J. Med. Chem.*: 2014. p. 4058 – 4072. DOI: 10.1021/jm401966m; (b) Singh S, Prasad N. R, Kapoor K, Chufan E. E, Patel B. A, Ambudkar S. V. Talele T. T. Design, Synthesis, and Biological Evaluation of (S)-Valine Thiazole-Derived Cyclic and Noncyclic Peptidomimetic Oligomers as Modulators of Human P-Glycoprotein (ABCB1), *ChemBioChem*: 2014. p. 157 - 169. DOI: 10.1002/cbic.201300565
- [92] Ding C, Zhang Y, Chen H, Yang Z, Wild C, Chu L, Liu H, Shen Q, Zhou J. Novel Nitrogen-Enriched Oridonin Analogues with Thiazole-Fused A-Ring: Protecting Group-Free Synthesis, Enhanced Anticancer Profile, and Improved Aqueous Solubility, *J. Med. Chem.*: 2013. p. 5048 - 5058. DOI: 10.1021/jm400367n
- [93] Francesco M. E. D, Dessole G, Nizi E, Pace P, Koch U, Fiore F, Pesci S, Muzio J. D, Monteagudo E, Rowley M, Summa V. Novel Macrocyclic Inhibitors of Hepatitis C NS3/4A Protease Featuring a 2-Amino-1,3-thiazole as a P4 Carbamate Replacement, *J. Med. Chem.*: 2009. p. 7014 - 7028. DOI: 10.1021/jm900524b
- [94] Sanfilippo P. J, Urbanski M. J, Beers K. N, Eckardt A, Falotico R, Ginsberg M. H, Offord S, Press J. B, Tighe J, Tomko K, Gordon P. A. Novel Thiazole-Based Heterocycles as Selective Inhibitors of Fibrinogen-Mediated Platelet Aggregation, *J. Med. Chem.*: 1995. p. 34 – 41. DOI: 10.1021/jm00001a008
- [95] van Muijlwijk-Koezen J. E, Timmerman H, Vollinga R. C, Frijtag von Drabbe Kunzel J, de Groote M, Visser S, IJzerman A. P. Thiazole and Thiadiazole Analogues as a Novel Class of Adenosine Receptor Antagonists, *J. Med. Chem.*: 2001. p. 749 - 762. DOI:10.1021/jm0003945
- [96] Srivastava P. C, Pickering M. V, Allen L. B, Streeter D. G, Campbell M. T, Witkowski J. T, Sidwell R. W, Robins R. K. Synthesis and antiviral activity of certain thiazole C-nucleosides, *J. Med. Chem.*: 1977. p.256 - 262. DOI: 10.1021/jm00212a014
- [97] Li Z, Khaliq M, Zhou Z, Post C. B, Kuhn R. J. Cushman M. Design, Synthesis, and Biological Evaluation of Antiviral Agents Targeting Flavivirus Envelope Proteins, *J. Med. Chem.*: 2008. p. 4660 – 4671. DOI: 10.1021/jm800412d; (b) Suh J, Yum E. K, Cheon H. G, Cho Y. S. Synthesis and Biological Evaluation of N-aryl-4-aryl-1,3-Thia-

zole-2-Amine Derivatives as Direct 5-Lipoxygenase Inhibitors, *Chemical Biology & Drug Design*: 2012. p.89 - 98. DOI: 10.1111/j.1747-0285.2012.01371.x

- [98] Lombardo L. J, Lee F. Y, Chen P, Norris D, Barrish J. C, Behnia K, Castaneda S, Cornelius L. A. M, Das J, Doweyko A. M, Fairchild C, Hunt J. T, Inigo I, Johnston K, Kamath A, Kan D, Klei H, Marathe P, Pang S, Peterson R, Pitt S, Schieven G. L, Schmidt R. J, Tokarski J, Wen M. L, Wityak J, Borzilleri R. M. Discovery of N-(2-Chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a Dual Src/Abl Kinase Inhibitor with Potent Antitumor Activity in Preclinical Assays, *J. Med. Chem.*: 2004. p. 6658 – 6661. DOI: 10.1021/jm049486a; (b) Wityak J, Das J, Moquin R. V, Shen Z, Lin J, Chen P, Doweyko A. M, Pitt S, Pang S, Shen D. R, Fang Q, De Fex H. F, Schieven G. L, Kanner S. B, Barrish J. C. Discovery and initial SAR of 2-amino-5-carboxamidothiazoles as inhibitors of the Src-family kinase p56^{Lck}, *Bioorg. Med. Chem. Lett.*: 2003. p. 4007 - 4010. DOI: 10.1016/j.bmcl.2003.08.054
- [99] Madsen P, Kodra J. T, Behrens C, Nishimura E, Jeppesen C. B, Pridal L, Andersen B, Knudsen L. B, Aspegren C. V, Guldbrandt M, Christensen I. T, Jørgensen A. S, Yndal L, Brand C. L, Bagger M. A, Lau J. Human Glucagon Receptor Antagonists with Thiazole Cores. A Novel Series with Superior Pharmacokinetic Properties, *J. Med. Chem.*: 2009. p. 2989 – 3000. DOI: 10.1021/jm8016249; (b) Kearney P, Fernandez M, Flygare J. A. Solid-Phase Synthesis of 2-Aminothiazoles, *J. Org. Chem.*: 1998. p. 196 - 200. DOI: 10.1021/jo971542a
- [100] Cheng X, Yoshida H, Raoofi D, Saleh S, Alborzinia H, Wenke F, Goehring A, Reuter S, Mah N, Fuchs H, Navarro M. A. A, Adjaye J, Gul S, Utikal J, Mrowka R, Wolf S. Ethyl 2-((4-Chlorophenyl)amino)thiazole-4-carboxylate and Derivatives Are Potent Inducers of Oct3/4, *J. Med. Chem.*: 2015. p. 5742 - 5750. DOI: 10.1021/acs.jmedchem.5b00226
- [101] Hencken C. P, Brando L. J, Bordon C, Stohler R, Mott B. T, Yolken R, Posner G. H, Woodard L. E. Thiazole, Oxadiazole, and Carboxamide Derivatives of Artemisinin are Highly Selective and Potent Inhibitors of *Toxoplasma gondii*, *J. Med. Chem.*: 2010. p. 3594 -3601. DOI: 10.1021/jm901857d
- [102] Kumar Y, Green R, Borysko K. Z, Wise D. S, Wotring L. L, Townsend L. B. Synthesis of 2,4-disubstituted thiazoles and selenazoles as potential antitumor and antifilarial agents. 1. Methyl 4-(isothiocyanatomethyl)thiazole-2-carbamates, -selenazole-2-carbamates, and related derivatives, *J. Med. Chem.*: 1993. p. 3843 – 3848. DOI: 10.1021/jm00076a012
- [103] Chimenti F, Secci D, Bolasco A, Chimenti P, Granese A, Carradori S, Yanez M, Orallo F, Sanna M. L, Gallinella B, Cirilli R. Synthesis, Stereochemical Separation, and Biological Evaluation of Selective Inhibitors of Human MAO-B: 1-(4-Arylthiazol-2-yl)-2-(3-methylcyclohexylidene)hydrazines, *J. Med. Chem.*: 2010. p. 6516 - 6520. DOI: 10.1021/jm100120s

- [104] Mayhoub A. S, Khaliq M, Kuhn R. J, Cushman M. Design, Synthesis, and Biological Evaluation of Thiazoles Targeting Flavivirus Envelope Proteins, *J. Med. Chem.*: 2011. p. 1704 - 1714. DOI: 10.1021/jm1013538
- [105] Dineen T. A, Weiss M. M, Williamson T, Acton P, Khan S. B, Bartberger M. D, Brown J, Chen K, Cheng Y, Citron M, Croghan M. D, Dunn R. T, Esmay J, Graceffa R. F, Harried S. S, Hickman D, Hitchcock S. A, Horne D. B, Huang H, Ampiah R. I, Judd T, Kaller M. R, Kreiman C. R, La D. S, Li V, Lopez P, Louie S, Monenschein H, Nguyen T. T, Pennington L. D, San Miguel T, Sickmier E. A, Vargas H. M, Wahl R. C, Wen P. H, Whittington D. A, Wood S, Xue Q, Yang B. H, Patel V. F, Zhong W. Design and Synthesis of Potent, Orally Efficacious Hydroxyethylamine Derived β -Site Amyloid Precursor Protein Cleaving Enzyme (BACE1) Inhibitors. *J. Med. Chem.*: 2012. p. 9025 - 9044. DOI: 10.1021/jm300118s
- [106] Ghosh B, Antonio T, Zhen J, Kharkar P, Reith M. E. A, Dutta A. K.. Development of (S)-N6-(2-(4-(Isoquinolin-1-yl)piperazin-1-yl)ethyl)-N6-propyl-4,5,6,7-tetrahydrobenzo[d]-thiazole-2,6-diamine and Its Analogue as a D3 Receptor Preferring Agonist: Potent in Vivo Activity in Parkinson's Disease Animal Models, *J. Med. Chem.*: 2010. p. 1023 - 1037. DOI: 10.1021/jm901184n
- [107] Das J, Chen P, Norris D, Padmanabha R, Lin J, Moquin R. V, Shen Z, Cook L. S, Doweiko A. M, Pitt S, Pang S, Shen D. R, Fang Q, de Fex H. F, McIntyre K. W, Shuster D. J, Gillooly K. M, Behnia K, Schieven G. L, Wityak J, Barrish J. C. 2-Aminothiazole as a Novel Kinase Inhibitor Template. Structure-Activity Relationship Studies toward the Discovery of N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-1,3-thiazole-5-carboxamide (Dasatinib, BMS-354825) as a Potent pan-Src Kinase Inhibitor, *J. Med. Chem.*: 2006. p. 6819 - 6832. DOI: 10.1021/jm060727j
- [108] Hinklin R. J, Boyd S. A, Chicarelli M. J, Condroski K. R, DeWolf W. E, Lee P. A, Lee W, Singh A, Thomas L, Voegtli W. C, Williams L, Aicher T. D. Identification of a New Class of Glucokinase Activators through Structure-Based Design, *J. Med. Chem.*: 2013. p.7669 - 7678. DOI: 10.1021/jm401116k ; (b) Home P. D, Pacini G. Hepatic dysfunction and insulin insensitivity in type 2 diabetes mellitus: a critical target for insulin-sensitizing agents, *Diabetes Obes. Metab.*: 2008. p. 699 - 718. DOI: 10.1111/j.1463-1326.2007.00761.x; (c) Rizza R. A. Pathogenesis of Fasting and Postprandial Hyperglycemia in Type 2 Diabetes: Implications for Therapy, *Diabetes*: 2010. p. 2697 - 2707. DOI: 10.2337/db10-1032
- [109] Xiao J, Marugan J. J, Zheng W, Titus S, Southall N, Cherry J. J, Evans M, Androphy E. J, Austin C. P, Discovery, Synthesis, and Biological Evaluation of Novel SMN Protein Modulators, *J. Med. Chem.*: 2011. p. 6215 - 6233. DOI: 10.1021/jm200497t; (b) Wirth B, Riessland M, Hahnen E. Drug discovery for spinal muscular atrophy, *Expert Opin. Drug Discovery*: 2007. p. 437 - 451. DOI:10.1517/17460441.2.4.437; (c) Nicolaou K. C, He Y, Roschangar F, King N. P, Vourloumis D, Li T, Total Synthesis of Epothilone E and Analogues with Modified Side Chains through the Stille Coupling Reaction, An-

- gew. Chem. Int. Ed. Engl.: 1998. p. 84 - 87. DOI: 10.1002/(SI-CI)1521-3773(19980202)37:1/2<84::AID-ANIE84>3.0.CO;2-V
- [110] Rosa M. D, Unge J, Motwani H. V, Rosenquist Å, Vrang L, Wallberg H, Larhed M. Synthesis of P1 -Functionalized Macrocyclic Transition-State Mimicking HIV-1 Protease Inhibitors Encompassing a Tertiary Alcohol, *J. Med. Chem.*: 2014. p. 6444 – 6457. DOI: 10.1021/jm500434q
- [111] Jung F. H, Pasquet G, Brempt C. L, Lohmann J. M, Warin N, Renaud F, Germain H, De Savi C, Roberts N, Johnson T, Dousson C, Hill G. B, Mortlock A. A, Heron N, Wilkinson R. W, Wedge S. R, Heaton S. P, Odedra R, Keen N. J, Green S, Brown E, Thompson K, Brightwell S. Discovery of Novel and Potent Thiazoloquinazolines as Selective Aurora A and B Kinase Inhibitors, *J. Med. Chem.*: 2006. p. 955 – 970. DOI: 10.1021/jm050786h; (b) Andersen C. B, Wan Y, Chang J. W, Riggs B, Lee C, Liu Y, Sessa F, Villa F, Kwiatkowski N, Suzuki M, Nallan L, Heald R, Musacchio A, Gray N. S, Discovery of Selective Aminothiazole Aurora Kinase Inhibitors, *ACS, Chem. Biolog.*: 2008. p. 180 – 192. DOI: 10.1021/cb700200w; (c) Neaz M. M, Muddassar M, Pasha F, Cho S. J, Structural studies of B-type Aurora kinase inhibitors using computational methods, *Acta Pharmacologica Sinica*: 2010. p. 244 – 258. DOI: 10.1038/aps.2009.188; (d) Elrazaz E. Z, Serya R. A. T, Ismail N. S. M, Abou El Ella D. A, Abouzid K. A. M, Thieno[2,3-d]pyrimidine based derivatives as kinase inhibitors and anticancer agents, *Future J. Pharm. Sciences*. 2015. doi:10.1016/j.fjps.2015.09.001 (in press).
- [112] Palmer J. T, Bryant C, Wang D. X, Davis D. E, Setti E. L, Rydzewski R. M, Venkatraman S, Tian Z. Q, Burrill L. C, Mendonca R. V, Springman E, McCarter J, Chung T, Cheung H, Janc J. W, McGrath M, Somoza J. R, Enriquez P, Yu Z. W, Strickley R. M, Liu L, Venuti M. C, Percival M. D, Falguyret J. P, Prasit P, Oballa R, Riendeau D, Young R. N, Wesolowski G, Rodan S. B, Johnson C, Kimmel D. B, Rodan G. Design and Synthesis of Tri-Ring P3 Benzamide-Containing Aminonitriles as Potent, Selective, Orally Effective Inhibitors of Cathepsin K, *J. Med. Chem.*: 2005. p. 7520 - 7534. DOI: 10.1021/jm058198r
- [113] Haffner C. D, Becherer J. D, Boros E. E, Cadilla R, Carpenter T, Cowan D, Deaton D. N, Guo Y, Harrington W, Henke B. R, Jeune M. R, Kaldor I, Milliken N, Petrov K. G, Preugschat F, Schulte C, Shearer B. G, Shearer T, Smalley T. L, Stewart Jr. E. L, Stuart J. D, Ulrich J. C, Discovery, Synthesis, and Biological Evaluation of Thiazoloquin(az)olin(on)es as Potent CD38 Inhibitors, *J. Med. Chem.*: 2015. p. 3548 -3571. DOI: 10.1021/jm502009h
- [114] Kini G. D, Anderson J. D, Sanghvi Y. S, Lewis A. F, Smee D. F, Revankar G. R, Robins R. K, Cottam H. B, Synthesis and antiviral activity of certain guanosine analogs in the thiazolo[4,5-d]pyrimidine ring system, *J. Med. Chem.*: 1991. p. 3006 – 3010. DOI: 10.1021/jm00114a008; (b) Nagahara K, Anderson J. D, Kini G. D, Dalley N. K, Larson S. B, Smee D. F, Jin A, Sharma B. S, Jolley W. B, Robins R. K, Cottam H. B. Thiazolo[4,5-d]pyrimidine nucleosides. The synthesis of certain 3-β-D-ribofuranosylthiazolo[4,5-d]pyrimidines as potential immunotherapeutic agents, *J. Med. Chem.*:

1990. p. 407 – 415. DOI: 10.1021/jm00163a064 (c) Webber S. E, 3, 5-Disubstituted and 3,5,7-trisubstituted-3h-oxazolo and 3h-thiazolo [4,5-d]pyrimidin-2-one compounds and prodrugs, WO2006066080: 2006.
- [115] Robins R. K. Cottam H. B. Antiviral antitumor antimetastatic immune system enhancing nucleosides and nucleotides, WO198905649: 1987.
- [116] Lewis A. F, Revankar G. R, Fennanwald S. M, Huffman J. H, Rando R. F. Thiazolo[4,5-d]pyrimidines. Part I. synthesis and anti-human cytomegalovirus (HCMV) activity in vitro of certain alkyl derivatives, *J. Heterocyclic Chem.*: 1995. p. 547 - 556. DOI: 10.1002/jhet.5570320230
- [117] Carson D Thiazolopyrimidines useful as tnf α inhibitors, WO2000/69861: 2000.
- [118] Beck J. P, Curry M. A, Chorvat R. J, Fitzgerald L. W, Gilligan P. J, Zaczek R, Trainor G. L. Thiazolo[4,5-d]pyrimidine thiones and -ones as corticotropin-releasing hormone (CRH-R1) receptor antagonists, *Bioorg. Med. Chem. Lett.*: 1999. p. 1185 – 1188. DOI: 10.1016/S0960-894X(99)00159-6
- [119] Fahmy H. T. Y, Rostom S. A. F, Saudi M. N, Zjawiony J. K, Robins D. J. Synthesis and in vitro evaluation of the anticancer activity of novel fluorinated thiazolo[4, 5-d]pyrimidines, *Arch. Pharm. Pharm. Med. Chem.*: 2003. p. 216 - 225. DOI: 10.1002/ardp.200300734
- [120] Bekhit A. A, Fahmy H. T. Y, Rostom S. A. F, Baraka A. M, Design and synthesis of some substituted 1H-pyrazolyl-thiazolo[4,5-d]pyrimidines as anti-inflammatory–antimicrobial Agents, *Eur. J. Med. Chem.*: 2003. p. 27 - 36. DOI: 10.1016/S0223-5234(02)00009-0
- [121] Baxter A, Cooper A, Kinchin E, Moakes K, Unitt J, Wallace A. Hit-to-Lead studies: The discovery of potent, orally bioavailable thiazolopyrimidine CXCR2 receptor antagonists, *Bioorg. Med. Chem. Lett.*: 2006. p. 960 – 963. DOI: 10.1016/j.bmcl.2005.10.09
- [122] Binnun E. Substituted Thiazolo [4,5-d]pyrimidines as protein kinase inhibitors, US20070185139: 2007.
- [123] Sircar J. C, Suto M. J, Scott M. E, Dong M. K, Gilbertsen R. B. Inhibitors of human purine nucleoside phosphorylase. Synthesis, purine nucleoside phosphorylase inhibition, and T-cell cytotoxicity of 2,5-diaminothiazolo[5,4-d]pyrimidin-7(6H)-one and 2,5-diaminothiazolo[4,5-d]pyrimidin-7(6H)-one. Two thioisosteres of 8-aminoguanine, *J. Med. Chem.*: 1986. p. 1804 - 1806. DOI: 10.1021/jm00159a045
- [124] Ohnishi H. Thiazolopyrimidine derivative, JP82/00046 : 1982.
- [125] Xing S. X, Kemnitzer W. F, Sirisoma N. S, Zhang H. N-aryl-isoxazolopyrimidin-4-amines and related compounds as activators of caspases and inducers of apoptosis and the use, WO2008/057402 : 2008.
- [126] Walters I, Austin C, Austin R, Bonnert R, Cage P, Christie M, Ebden M, Gardiner S, Grahmes C, Hill S, Hunt F, Jewell R, Lewis S, Martin I, Nicholls D, Robinson D. SAR

- studies on thiazolo[4,5-d]pyrimidine based CXCR2 antagonists involving a novel tandem displacement reaction, *Bioorg. Med. Chem. Lett.*: 2007. p. 2731 - 2734. DOI: 10.1016/j.bmcl.2007.02.080
- [127] Sugihara Y. Thiazolopyrimidine derivative, EP1731523: 2006.
- [128] Kung P, Meng J. J. Fused 2-amino pyrimidine compounds and their use for the treatment of cancer, WO2008/059368: 2008.
- [129] Nishino T, Kobayashi T, Shinohara Y. Xanthine oxidase inhibitor, WO2007/004688: 2007.
- [130] Harnden M. R, Hurst D. T. The Chemistry of Pyrimidinethiols. III. The Synthesis of Some Substituted Pyrimidinethiols and Some Thiazolo[5,4-D]pyrimidines, *Aust. J. Chem.*: 1990. p. 55 - 62. DOI: 10.1071/CH9900055
- [131] Hurst D. T, Atcha S, Marshall K. L, The Synthesis of Some Thiazolo- and Oxazolo[5,4-d]pyrimidines and Pyrimidinylureas, *Aust. J. Chem.*: 1991. p. 129 - 134. DOI: 10.1071/CH9910129
- [132] Miller D. J, Ravikumar K, Shen H, Suh J, Kerwin S. M, Robertus J. D, Structure-Based Design and Characterization of Novel Platforms for Ricin and Shiga Toxin Inhibition, *J. Med. Chem.*: 2002. p. 90 - 98. DOI: 10.1021/jm010186s
- [133] Gomtsyan A, Didomenico S, Lee C, Matulenko M. A, Kim K, Kowaluk E. A, Wismer C. T, Mikusa J, Kohlhaas H. Y. K, Jarvis M. F, Bhagwat S. S. Design, Synthesis, and Structure-Activity Relationship of 6-Alkynylpyrimidines as Potent Adenosine Kinase Inhibitors, *J. Med. Chem.*: 2002. p. 3639 - 3648. DOI: 10.1021/jm020049a
- [134] Suzuki E, Sugiura S, Naito T, Inoue S, Studies on Pyrimidine Derivatives. X, *Chem. Pharm. Bull.*: 1968. p. 750 - 755. DOI: org/10.1248/cpb.16.750
- [135] Benedek-Vamos M, Promel R. Synthesis of pyrimidines and thiazolo[5,4-d]pyrimidines III. The N.M.R. Spectrum of thiazolo[5,4-d]pyrimidine, *Tetrahedron Lett.*: 1969. p. 1011 - 1014. DOI: 10.1016/S0040-4039(01)97724-X
- [136] Childress S. J, Mckee R. L. Thiazolopyrimidines, *J. Am. Chem. Soc.*: 1951. p. 3862 - 3864. DOI: 10.1021/ja01152a090
- [137] Senga K, Ichiba M, Kanazawa H, Nishigaki S, Synthesis and properties of thiazolo[5,4-d]pyrimidine 1-oxides, *J. Heterocycl. Chem.*: 1982. p. 77 - 80. DOI: 10.1002/jhet.5570190113
- [138] Yuan D. K, Li Z. M, Zhao W. G, Synthesis of Thiazolo[5,4-d]pyrimidine-2-thiol and Its Derivatives, *Chinese J. Org. Chem.*: 2003. p. 1155 - 1158. DOI: sioc-journal.cn/Jwk_yjhx/EN/Y2003/V23/I10/1155
- [139] Liu J, Patch R. J, Schubert C, Player M. R, Single-Step Syntheses of 2-Amino-7-chloro-thiazolo[5,4-d]pyrimidines: Intermediates for Bivalent Thiazolopyrimidines, *J. Org. Chem.*: 2005. p. 10194 - 10197. DOI: 10.1021/jo0517702

- [140] Ahmed A. F. S. Synthesis of Bicyclic Pyrimidine Nucleoside Derivatives, *J. Chem. Res. (S)*: 1998. p. 697 - 697. DOI: 10.1039/A805968C
- [141] Freeman F, Kim D. S. H. L. Reaction of aminopropanedinitrile 4-methylbenzenesulfonate (aminomalnonitrile p-toluenesulfonate (tosylate)) with isothiocyanates, *J. Org. Chem.*: 1991. p. 4645 - 4648. DOI: 10.1021/jo00015a015
- [142] Hennen W. J, Hinshaw B. C, Riley T. A, Wood S. G, Robins R. K. Synthesis of 4-substituted 5-amino-2-(.beta.-D-ribofuranosyl)thiazoles and 4-substituted 5-amino-2-(.beta.-D-ribofuranosyl)selenazoles, and their respective conversion into 2-(.beta.-D-ribofuranosyl)thiazolo[5,4-d]pyrimidines and 2-(.beta.-D-ribofuranosyl)selenazolo[5,4-d]pyrimidines. A new synthesis of tiazofurin and selenazofurin, *J. Org. Chem.*: 1985. p. 1741 - 1746. DOI: 10.1021/jo00210a033
- [143] Beck J. P. Thiazolo[4,5-d]pyrimidines and pyridines as corticotropin releasing factor (crf) antagonists, WO1999/51608: 1999.
- [144] Khaury A. M, Bayouki E, Basyouni W. M. New Thiazolo[5,4-d]pyrimidines with Molluscicidal Properties, *Bull. Chem. Soc. Jpn.*: 1988. p. 3794 - 3796. DOI: org/10.1246/bcsj.61.3794
- [145] Corrao S. L, Macielag M. J, Turchi I. J. Rearrangement of 4-(aminothiocarbonyl)oxazoles to 5-aminothiazoles. Synthetic and MINDO/3 MO studies, *J. Org. Chem.*: 1990. p. 4484 - 4487. DOI: 10.1021/jo00301a056
- [146] Senga K, Sato J, Nishigaki S. A New, Facile Synthesis of Oxazolo [5, 4-d] pyrimidines and Their Conversion into Thiazolo [5, 4-d] pyrimidines, *Chem. Pharm. Bull.*: 1978. p. 765 - 769. DOI: doi.org/10.1248/cpb.26.765
- [147] Baker J. A, Chatfield P. V. Synthesis of derivatives of thiazolo[4,5-d]pyrimidine, *J. Chem. Soc. (C)*: 1969. 603 - 606. DOI: 10.1039/J39690000603
- [148] Mi-Yeon Jang, Steven De Jonghe, Ling-Jie Gao, Bart Vanderhoydonck, Piet Herdewijn, Novel thiazolopyrimidines, British patent application GB09043530.
- [149] Bodeker J, Courault K, Kockritz A, Kockritz P. Reaktionen von Heteroarylaminotriphenylphosphoranen mit Heterokumulenen: Synthese und Cycloadditionen α -N-Heteroaryl-substituierter Carbodiimide, *J. Prakt. Chem.*: 1983. p. 463 - 474. DOI: 10.1002/prac.19833250316
- [150] Gewald K. Heterocyclen aus CH-aciden Nitrilen. VI. Reaktion von methylenaktiven Nitrilen mit Senfölen und Schwefel, *J. Prakt. Chem.*: 1966. p. 26 - 30. DOI: 10.1002/prac.19660320104
- [151] Stuckwisch C. G. Azomethine Ylids, Azomethine Imines, and Iminophosphoranen in Organic Syntheses, *Synthesis*: 1973. p. 469 - 483. DOI: 10.1055/s-1973-22235
- [152] Molina P, Arques A, Vinader M. V. Fused pyrimidines by a tandem aza-Wittig/electrocyclic ring closure strategy: synthesis of pyrazolo[3,4-d]pyrimidine, [1,2,3]triazolo-

- lo[4,5-d]pyrimidine, and thiazolo[4,5-d]pyrimidine derivatives, *J. Org. Chem.*: 1988. p. 4654 - 4663. DOI: 10.1021/jo00255a003
- [153] Kale M. G, Raichurkar A, Waterson S. H. P. D, McKinney D, Manjunatha M. R, Kranthi U, Koushik K, Jena L. K, Shinde V, Rudrapatna S, Barde S, Humnabadkar V, Madhavapeddi P, Basavarajappa H, Ghosh A, Ramya V. K, Guptha S, Sharma S, Vachaspati P, Kumar K. N. M, Giridhar J, Reddy J, Panduga V, Ganguly S, Ahuja V, Gaonkar S, Kumar C. N. N, Ogg D, Tucker J. A, Sjodin P. A. B, de Sousa S. M, Sambandamurthy V. K, Ghorpade S. R. Thiazolopyridine Ureas as Novel Antitubercular Agents Acting through Inhibition of DNA Gyrase B, *J. Med. Chem.*: 2013. p. 8834 - 8848. DOI: 10.1021/jm401268f
- [154] Bebernitz G. R, Beaulieu V, Dale B. A, Deacon R, Duttaroy A, Gao J, Grondine M. S, Gupta R. C, Kakmak M, Kavana M, Kirman L. C, Liang J, Maniara W. M, Munshi S, Nadkarni S. S, Schuster H. F, Stams T, Denny I. St, Taslimi P. M, Vash B, Caplan S. L. Investigation of Functionally Liver Selective Glucokinase Activators for the Treatment of Type 2 Diabetes, *J. Med. Chem.*: 2009. p. 6142 - 6152. DOI: 10.1021/jm900839k
- [155] Dolle R. E, Le Bourdonnec B, Goodman A. J, Morales G. A, Thomas C. J, Zhang W. J. Comprehensive Survey of Chemical Libraries for Drug Discovery and Chemical Biology: 2008, *Comb. Chem.*: 2009. p. 739 - 790. DOI: 10.1021/cc9000828
- [156] Lee J, Wu X, Pasca di Magliano M, Peters E. C, Wang Y, Hong J, Hebrok M, Ding S, Cho C. Y, Schultz P. G. A Small-Molecule Antagonist of the Hedgehog Signaling Pathway, *ChemBioChem*: 2007. p. 1916 - 1919. DOI: 10.1002/cbic.200700403
- [157] Milne J. C, Lambert P. D, Schenk S, Carney D. P, Smith J. J, Gange D. J, Jin L, Boss O, Perni R. B, Vu C. B, Bemis J. E, Xie R, Disch J. S, Ng P. Y, Nunes J. J, Lynch A. V, Yang H, Galonek H, Israelian K, Choy W, Iffland A, Lavu S, Medvedik O, Sinclair D. A, Olefsky J. M, Jirousek M. R, Elliott P. J, Westphal C. H. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes, *Nature*: 2007. p. 712 -716. DOI: 10.1038/nature06261 (b) Das J, Chen P, Norris D, Padmanabha R, Lin J, Moquin R. V, Shen Z, Cook L. S, Doweyko A. M, Pitt S, Pang S, Shen D. R, Fang Q, de Fex H. F, McIntyre K. W, Shuster D. J, Gillooly K. M, Behnia K, Schieven G. L, Wityak J, Barish J. C. 2-Aminothiazole as a Novel Kinase Inhibitor Template. Structure-Activity Relationship Studies toward the Discovery of N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-1,3-thiazole-5-carboxamide (Dasatinib, BMS-354825) as a Potent pan-Src Kinase Inhibitor, *J. Med. Chem.*: 2006. p. 6819 - 6832. DOI: 10.1021/jm060727j
- [158] Cee V.J, Frohn M, Lanman B. A, et al., Discovery of AMG 369, a Thiazolo[5,4-b]pyridine Agonist of S1P1 and S1P₅, *ACS Med. Chem. Lett.*: 2011. p. 107 - 112. DOI: 10.1021/ml100306h
- [159] Smethurst C. A, Borthwick J. A, Gaines S, Watson S, Green A, Schulz M. J, Burton G, Buson A. A, Arban R. The characterization of a novel V1b antagonist lead series, *Bioorg. Med. Chem. Lett.*: 2011. p. 92 - 96. DOI: 10.1016/j.bmcl.2010.11.061

- [160] Thomae D, Perspicace E, Hesse S, Kirsch G, Seck P. Synthesis of substituted [1,3]thiazolo[4,5-b]pyridines and [1,3]thiazolo[4,5-d, 1,2,3]triazines, *Tetrahedron*: 2008. p. 9309 - 9314. DOI: 10.1016/j.tet.2008.07.017
- [161] Thomae D, Kirsch G, Seck P. Synthesis of Thiophene Analogues of the Tacrine Series, *Synthesis*: 2007. p. 1027 - 1032. DOI: 10.1055/s-2007-965944
- [162] Komoriya S, Kobayashi S, Osanai K, Yoshino T, Nagata T, Haginoya N, Nakamoto Y, Mochizuki A, Nagahara T, Suzuki M, Shimada T, Watanabe K, Isobe Y, Furugoori T. Design, synthesis, and biological activity of novel factor Xa inhibitors: Improving metabolic stability by S1 and S4 ligand modification, *Bioorg. Med. Chem.*: 2006. p. 1309 - 1330. DOI: 10.1016/j.bmc.2005.09.056
- [163] Kulkarni S. S, Newman A. H, Discovery of heterobicyclic templates for novel metabotropic glutamate receptor subtype 5 antagonists, *Bioorg. Med. Chem. Lett.*: 2007. p. 2987 - 2991. DOI: 10.1016/j.bmcl.2007.03.066
- [164] Walczynski K, Zuiderveld O. P, Timmerman H. Non-imidazole histamine H3 ligands. Part III. New 4-n-propylpiperazines as non-imidazole histamine H3-antagonists, *Eur. J. Med. Chem.*: 2005. p. 15 - 23. DOI: 10.1016/j.ejmech.2004.09.010
- [165] Lin R, Johnson S. G, Connolly P. J, Wetter S. K, Binnun E, Hughes T. V, Murray W. V, Pandey N. B, Moreno-Mazza S. J, Adams M, Fuentes-Pesquera A. R, Middleton S. A. Synthesis and evaluation of 2,7-diamino-thiazolo[4,5-d] pyrimidine analogues as anti-tumor epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, *Bioorg. Med. Chem. Lett.*: 2009. p. 2333 - 2337. DOI: 10.1016/j.bmcl.2009.02.067
- [166] Singh B, Bacon E. R, Leshner G. Y, Robinson S, Pennock P. O, Bode D. C, Pagani E. D, Bentley R. G, Connell M. J, Hamel L. T, Silver P. J. Novel and Potent Adenosine 3',5'-Cyclic Phosphate Phosphodiesterase III Inhibitors: Thiazolo[4,5-b, 1,6]naphthyridin-2-ones, *J. Med. Chem.*: 1995. p. 2546 - 2550. DOI: 10.1021/jm00014a007
- [167] Lee T, Lee D, Lee Y, Gong Y. D. Solid-Phase Synthesis of Thiazolo[4,5-b]pyridine Derivatives Using Friedländer Reaction, *J. Comb. Chem.*: 2010. p. 95 - 99. DOI: 10.1021/cc900147y
- [168] Takahashi Y, Hashizume M, Shin K, Terauchi T, Takeda K, Hibi S, M.Tai K, Fujisawa M, Shikata K, Taguchi R, Ino M, Shibata H, Yonaga M. Design, Synthesis, and Structure-Activity Relationships of Novel Pyrazolo[5,1-b]thiazole Derivatives as Potent and Orally Active Corticotropin-Releasing Factor 1 Receptor Antagonists, *J. Med. Chem.*: 2012. p. 8450 - 8463. DOI: 10.1021/jm300864p

