Chapter

Synthesis and Biological Evaluation of Thiazole Derivatives

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Abstract

Thiazoles belong to the group of azole heterocycles. They are aromatic five-membered heterocycles containing one sulfur and one nitrogen atom. In recent years thiazoles, their derivatives, and isomers have gained considerable attention because of their broad applications in different fields, such as agrochemicals, industrial, and photographic sensitizers. Also, they have pharmaceutical and biological activities that include antimicrobial (sulfazole), antiretroviral (ritonavir), antifungal (abafungin), anticancer (tiazofurin), antidiabetic, anti-inflammatory, anti-Alzheimer, antihypertensive, antioxidant, and hepatoprotective activities. The compounds containing thiazole moieties are a prominent structural feature in a variety of natural products, such as vitamin B and penicillin. Thus, in this chapter several types of thiazole-based heterocyclic scaffolds such as monocyclic or bicyclic systems synthesis and their biological activities studies are presented. Furthermore modification of thiazole-based compounds at different positions to generate new molecules with potent antitumor, antioxidant, and antimicrobial activities is described.

Keywords: azole heterocycles, thiazoles, biological activities, antioxidants, antimicrobial, anticancer, anti-Alzheimer, antihypertensive

1. Introduction

Thiazoles are five-membered heterocyclic compounds containing nitrogen and sulfur atoms with isothiazole isomer. Thiazoles are a basic scaffold found in many natural compounds as vitamin B1-thiamine, alkaloids, anabolic steroids, flavones [1].

The interest in the synthesis of compounds containing the thiazole moiety has been increasing steadily in view of their utility in the field of photosensitizers, rubber vulcanization [2], liquid crystals [3, 4], sensors [5], sunscreens [6], catalysts [7], dyes [8], pigments [1], and chromophores [9, 10]. Moreover, thiazoles occupy a prominent place in current medicinal chemistry due to their wide range of applications in the field of drug design and discovery [11]. They appear in the bacitracin, penicillin antibiotics [12], and various synthetic drugs as short-acting sulfa drug sulfathiazole [1]. Also, they are used as an antidepressant drug (pramipexole) [13], antiulcer agent (nizatidine) [14], anti-inflammatory drug (meloxicam) [15], HIV/AIDS drug (ritonavir) [16], and cancer treatment drug (tiazofurin) [17]. In fact, thiazole is a more common component of FDA-approved pharmaceuticals than related five-membered heterocycles such as isothiazole, thiophene, furan,
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isoxazole, and oxazole. On the other hand, the metal complexes of thiazole are widely used in photocatalysis [18]. 1,3-Thiazoles undergo different types of reactions to yield various biologically active fused heterocyclic moieties as thiazolopyrimidine, imidazothiazoles, thiazolopyridine, etc. [19–21].

2. Synthesis strategies of 1,3-thiazole derivatives

Thiazole ring system were easily synthesized by well-known methods of Hantzsch [22], Cook-Heilbron [23], and Gabriel [24]. A number of compounds may serve as nucleophilic reagent in this reaction, such as thioamides, thiourea, ammonium thiocarbamate or dithiocarbamate, and their derivatives. Hantzsch synthesized the simple thiazole nucleus in 1887 [25]. This synthesis approach involves cyclization and condensation of haloketones with thioamide, and it is considered the most widely popular process for the synthesis of thiazole moiety. In contrast, Gabriel synthesized thiazoles by treating α-acylaminoketones with stoichiometric amounts of P2S5 or Lawesson’s reagent [26]. Also, Cook-Heilbron used versatile methods for the synthesis of substituted aminothiazoles involving the reaction of α-aminonitriles with dithioacids or esters, carbon disulfide, carbonyl sulfide, and isothiocyanates under mild conditions [27].

Lately, thiazole derivatives were synthesized in the presence of various catalysts [28–31] and with the use of a microwave irradiation technique [32].

2.1 Synthesis from α-halocarbonyl compounds (Hantzsch’s synthesis) (type I)

2.1.1 Reactions with thioamides

Thioamides and various α-halocarbonyl compounds were reacted to give numerous thiazoles with alkyl, aryl, arylalkyl, or heteroaryl of several functional groups at position 2, 4, or 5 (2.1.1) [33, 34] (Figure 1).

2.1.2 Reactions with N-substituted thiourea

2-Monosubstituted or disubstituted aminothiazoles (2.1.2) were obtained by the reaction of halocarbonyl compounds with N-substituted thiourea compounds [35] (Figure 2).

2.1.3 Reaction with esters of thiocarbamic acid

The condensation of α-halocarbonyl compounds with thiocarbamates gave 2-hydroxythiazole derivatives (2.1.3) [36, 37] (Figure 3).

Figure 1.
Synthesis of 2-, 4-, 5-trisubstituted thiazole.
2.2 Synthesis from α-aminonitrile compounds (Cook-Heilbron’s synthesis) (Type II)

This class of synthesis gives 5-aminothiazole with different substituted in position 2 by interacting aminonitrile with salts and esters of dithioacids carbon oxysulfide, carbon disulfide, and isothiocyanates significantly [38–40].

2.2.1 Reaction with carbon disulfide

The condensation of carbon disulfide with α-aminonitriles gave 2-mercapto-5-amino thiazoles, which can be converted to 5-amino thiazoles substituted in position 2 (2.2.1) [41, 42] (Figure 4).

2.3 Reaction with esters and salts of dithioacids

The salts or the esters of both dithioformic and dithiophenacetic acids were reacted with α-aminonitriles to give 5-aminothiazoles (2.3) in good yields [43] (Figure 5).

2.4 Reaction with acylaminocarbonyl compounds and phosphorus pentasulfide and related condensation (Gabriel’s synthesis) (Type III)

This reaction was originally designated by Gabriel in 1910. The reaction of phosphorus pentasulfide with acylaminoketone gave 2-phenyl-5-alkyl-thiazole in good yield (2.4) [44] (Figure 6).

2.5 Synthesis with eco-friendly methods

2.5.1 Using microwave-assisted synthesis (MAOS)

The synthesis of thiazole derivatives involves vigorous reaction conditions and wastage of solvents and catalysts. To overcome these shortcomings, eco-friendly methods as microwave irradiation technique are commonly used for synthesis of
thiazole derivatives [45]. Rapid and elegant synthesis of a series of thiazoles (2.5.1) uses microwave heating under solvent-free conditions [32, 46, 47] (Figure 7).

2.5.2 One-pot multicomponent reaction in aqueous medium

Water is economically viable, nontoxic, and the most friendly reaction medium available, making it an environmentally acceptable solvent for the design and development of green chemistry technique. A three-component reaction of phenyl acetylene, N-bromosuccinimide, and thiourea in aqueous medium gave substituted thiazole derivatives (2.5.2) in good yield [48] (Figure 8).

2.5.3 Using silica-supported tungstosilisic acid

An efficient and green method has been developed for the synthesis of new substituted Hantzsch thiazole derivatives (2.5.3) by one-pot multicomponent procedure. 3-(Bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one was reacted with
thiourea and substituted benzaldehydes in the presence of silica-supported tungs-
tosilic acid as a catalyst under conventional heating or under ultrasonic irradiation
technique [46, 49] (Figure 9).

2.6 Miscellaneous methods

Hantzsch construction of thiazole derivatives (2.6) was established by the
reaction of α-chloroglycinate esters with thioamides or thioureas. Targeted
compounds are obtained from readily available and inexpensive building
blocks through an environmentally benign process and without catalysts [50]
(Figure 10).

The C – H substitution reaction of thiazole by the catalysis of the palladium/
copper system is carried out in the presence of tetrabutylammonium fluoride under
mild conditions. Various 2,5-diarylthiazole derivatives (2.6.1) were synthesized in
good yields [51] (Figure 11).
2.7 Using oxidizing agents and thiourea

The mixtures of thiourea and acetophenone were treated with various oxidizing agents as sulfuryl chloride, chlorosulfonic acid, thionyl chloride, sulfur monochloride, sulfur trioxide, sulfuric acid, nitric acid, and sulfur. In each case a large amount of 2-amino-4-phenylthiazole (2.7) was obtained [52] (Figure 12).

3. Biological importance of thiazoles

Thiazole and its derivatives are among the most active classes of compounds that are known for their broad spectrum of activity, e.g., antibacterial [53], antifungal [54], antimalarial [55], antitubercular [56], antiviral [57], anti-inflammatory [58], antidiabetic [59], anthelmintic [60], anticancer [61], antioxidant [62], anticancer [63], and cardiovascular activities [64], and known as new inhibitors of bacterial DNA gyrase B [65]. Some drugs that already are on the market including the recent entry dasatinib possess thiazoles nucleus [66].

3.1 Antitumor activity

Compounds containing thiazole have marked their presence in a number of clinically available anticancer drugs such as tiazofurin [67], dasatinib [68], dabrafenib [69], patellamide A [70], ixabepilone [71], and epothilone [72].

Ramla et al. synthesized a variety of 4-amino-3-methyl-5-(2-methyl-1H-benzo[d]imidazol-1-yl)thiazol-2(3H)-one (3.1.1) and evaluated them for antitumor activity [73] (Figure 13).

Popsavin et al. reported a set of 2-(2,3-anhydrofuranosyl) thiazole-4-carboxamide (2',3'-anhydrotiazofurin) derivatives (3.1.2) and screened them for their antitumor activity [74] (Figure 14).

A series of 5-arylidene derivatives were synthesized and evaluated for their antitumor activity. Compound 2-{2-[3-(benzothiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidenemethyl]-4-chlorophenoxy}-N-(4-methoxyphenyl)-acetamide (3.1.3) was found to be the most active among the tested compounds [75] (Figure 15).

In another approach towards triple-negative breast cancer, Zhou et al. synthesized and optimized a series of hybrids of 2,4-diaminopyrimidine and thiazole derivatives (3.1.4). These compounds showed anti-proliferative properties against two breast cancer cell lines, MCF-7 and MDA-MB-231. Several of these compounds also exhibited potent activities against tumor cell colony [76] (Figure 16).

A series of 2-(4-benzoyl-phenoxy)-N-(4-phenyl-thiazol-2-yl)-acetamides were synthesized by Prashanth et al. The authors suggest that the effect of compound (3.1.5) could be due to methyl, fluoro, and methoxy groups which are attached to phenoxy, benzoyl, and the phenyl ring of thiazole, respectively [77] (Figure 17).

Dae-Kee K et al. produced a set of 5-(pyridin-2-yl)thiazoles enclosing a p- and/or m-carboxamide or carbonitrile-substituted phenylmethylamino moiety at position 2 of the thiazole ring (3.1.6). This series is evaluated for its ALK5 inhibitory activity [78, 79] (Figure 18).
A series of 2,4-disubstituted thiazole compounds containing $N$-n-butyl or $N$-cyclohexyl thioureido synthon at position 2 and $N$-substituted thiosemicarbazone moiety (3.1.7) at position 4 were synthesized by HI El-Subbagh et al. and verified for their antitumor activity. All of the established derivatives revealed antineoplastic activity [80] (Figure 19).

Santos et al. synthesized 6,7-bis(hydroxymethyl)-1H,3H-pyrrolo[1,2-c]thiazole (3.1.8) which showed activity for the triple-negative breast cancer, the most challenging tumor in clinical practice [81] (Figure 20).

El-Borai et al. synthesized a series of 2 6-substituted-3-(pyridin-3-yl) imidazo[2,1-b]thiazole (3.1.9) which are tested for anticancer activity against human cancer cell lines HEPG2 (liver cancer) and MCF7 using sulforhodamine B

![Structure of compound 3.1.1.](image1)

![Structure of compound 3.1.2.](image2)

![Structure of compound 3.1.3.](image3)
(SRB) assay. All the synthesized compounds displayed more anticancer activity towards the selected cell line cancer, suggesting that it might be a potential alternative agent for human hepatic cancer therapy [82] (Figure 21).

3.2 Antimicrobial activity

Fungal and bacterial resistance to antimicrobial drugs is increasing rapidly due to nonselective antimicrobial activities and a limited number of drugs. To overcome this situation, several molecules containing thiazole are synthesized to treat bacterial and fungal infections [83, 84].
El-Borai et al. work on an ongoing program in the field of synthesis and evaluated antimicrobial activity of medicinally important new compounds, taking the fused thiazole compounds as thiazolopyrimidines (3.2.1), imidazothiazoles (3.2.2), and their derivatives as new examples in this domain [82] (Figure 22).

Vicini et al. synthesized a new set of 2-thiazolylimino-5-arylidene-4-thiazolidinones which were assayed in vitro for their antimicrobial activity against Gram-positive and Gram-negative bacteria and yeast. Compound (3.2.3) exhibited activity against Gram-positive bacteria [85] (Figure 23).

A series of thiazolyl thiazolidine-2,4-dione derivatives were synthesized by Dundar et al. These compounds were screened for their antibacterial and antifungal activities against methicillin-resistant *S. aureus*, *E. coli*, and *C. albicans*. All the compounds particularly (3.2.4) were found to be moderately potent against screened microorganisms [86] (Figure 24).

Abdel-Wahab et al. synthesized 3- (benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles (3.2.5). The synthesized compounds were screened for their antibacterial and antifungal activities and showed a significant activity against *E. coli* higher than that of the control drug, whereas antifungal activity against *Aspergillus niger* was also exhibited and equal to that of the reference drug [87] (Figure 25).

Bera et al. Synthesized pyridinyl thiazole ligand having hydrazone moiety and its cobalt complex. Both ligand and its complex were tested for antibacterial properties towards Gram-positive and Gram-negative bacteria. The results revealed that the ligand (3.2.6) exhibited excellent antibacterial activity. The presence of pyridinium ion in the ligand showed increased solubility of the ligand which enhances the cell penetrating ability and cell binding activity of the ligand. Hydrolysis of ligand decreases the pH of the medium which facilitates easy penetration of ligand into the cell [88] (Figure 26).
Figure 22.  
Structure of compounds 3.2.1 and 3.2.2.

Figure 23.  
Structure of compound 3.2.3.

Figure 24.  
Structure of compound 3.2.4.

Figure 25.  
Structure of compound 3.2.5.
3.3 Antifungal activity

Narayana et al. synthesized a series of 5-(2-substituted–1,3-thiazol-5-yl)-2-alkoxybenzamides and 5-(2-N-(substituted aryl)-1,3-thiazol-5-yl)-2-alkoxy benzamides. The synthesized compounds were screened for their antifungal activity. The derivatives of compound (3.3.1) exhibited significant activity [89] (Figure 27).

Chimenti et al. reported the synthesis of a novel series of 2-thiazolylhydrazone derivatives and the influence of the substituents on the thiazole ring and on antifungal activity. Some of the tested compounds were found to possess significant antifungal activity when compared to clotrimazole, in particular compound (3.3.2) which exhibited higher potency against most of the Candida [90] (Figure 28).

3.4 Antioxidant activity

Antioxidants are of great interest due to their participation in important biological and industrial processes. They are generated in the human body and may cause damage to lipids, proteins, and DNA and thus may lead to various diseases such as cancer, atherosclerosis, diabetes, cirrhosis, and Alzheimer’s and inflammatory diseases [91]. Thiazole and derivatives are the core structure in a variety of pharmaceuticals with a wide range of biological activity [92–94].

Figure 26. Structure of compound 3.2.6.

Figure 27. Structure of compound 3.3.1.

Figure 28. Structure of compound 3.3.2.
The antioxidant potential compounds (3.4.1) was evaluated by spectrophotometric method, using DPPH radical or Fe (TPTZ)$^{3+}$ complex, and EPR spectroscopy and revealed that the synthesized compounds were showing potent antioxidant activity [95] (Figure 29).

Bozdag-Dundar et al. synthesized a series of 2, 4-dichlorothiazolyl thiazolidine-2,4-dione and 4-chloro-2-benzylsulfanylthiazolyl-thiazolidine-2,4-dione derivatives, and they were tested for their antioxidant properties. Compound (3.4.2) showed the best superoxide anion scavenging activity [96] (Figure 30).

Gouda et al. synthesized 2-amino thiazole derivatives and evaluated their antioxidant activity. They reported that the three compounds (3.4.3) showed potent antioxidant activity after postulating the structure–activity relationship (SAR) [97] (Figure 31).

A series of N2-[2-chloro-4(3,4,5-trimethoxy phenyl) azetidin-1-yl]-N4-(substituted aryl)-1,3-thioazol-2,4-diamine (3.4.4) were synthesized and screened for their in vitro antioxidant properties. The IC50 values revealed that some of the synthesized compounds were showing potent antioxidant activity [98] (Figure 32).

![Figure 29. Structure of compound 3.4.1.](image1)

![Figure 30. Structure of compound 3.4.2.](image2)

![Figure 31. Structure of compound 3.4.3.](image3)
4. Conclusion

Thiazole moieties have occupied a pivotal position in the modern organic and medicinal chemistry due to its broad-spectrum pharmacological and medicinal activities such as antimicrobial, anticancer, and antioxidant. The presence of thiazole ring in many drugs such as penicillin, pramipexole, tiazofurin, meloxicam, and nizatidine motivates the chemists to design new thiazole scaffolds. Thiazole nucleus exhibited an important role in finding new leads and drugs for various diseases. This chapter has illustrated the commonly used approaches to synthesize subsisted thiazole derivatives, described their key electronic properties, and highlighted their most important chemical reactivity. A particular focus has been on the use of thiazole in dyes and their metal complexes and miscellaneous applications of thiazole dyes. Also we have focused our attention on the biological application of thiazole derivatives.

List of abbreviations

| Abbreviation | Definition                                      |
|--------------|-------------------------------------------------|
| FDA          | Food and Drug Administration (USA)              |
| SAR          | structure–activity relationships                |
| MAOS         | microwave-assisted synthesis                    |
| HTIB         | [hydroxy-(tosyloxy)-iodo] benzene               |
| TBAF         | tetrabutylammonium fluoride                     |

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References

[1] Borisenko VE, Koll A, Kolmakov EE, Rjasniy AG. Hydrogen bonds of 2-aminothiazoles in intermolecular complexes (1,1 and 1,2) with proton acceptors in solutions. Journal of Molecular Structure. 2006;783(1):101-115

[2] Milne GWA. Handbook of Antineoplastic Agents. London, UK: Gower/Ashgate; 2000

[3] Kiryanov AA, Sampson P, Seed AJ. Synthesis of 2-alkoxysubstituted thiophenes, 1,3-thiazoles, and related S-heterocycles via Lawesson’s reagent-mediated cyclization under microwave irradiation: Applications for liquid crystal synthesis. The Journal of Organic Chemistry. 2001;66:7925

[4] Mori A, Sekiguchi A, Masui K, Shimada T, Horie M, Osakada K, et al. Facile synthesis of 2,5-diaryltiazoles via palladium-catalyzed tandem C–H substitutions. Design of tunable light emission and liquid crystalline characteristics. Journal of the American Chemical Society. 2003;125:1700

[5] Kim BY, Kim HS, Helal A. A fluorescent chemosensor for sequential recognition of gallium and hydrogen sulfate ions based on a new phenylthiazole derivative. Sens. Actuators B-Chem. 2015;206:430

[6] Bach T, Heuser S. Synthesis of 2-(o-hydroxyaryl)-4-aryltiazoles by regioselective Pd(0)-catalyzed cross-coupling. Tetrahedron Letters. 2000;41:1707

[7] Dondoni A. Heterocycles in organic synthesis: Thiazoles and triazoles as exemplar cases of synthetic auxiliaries. Organic & Biomolecular Chemistry. 2010;8:3366

[8] Metwally MA, Abdel-Latif E, Amer FA, Kaupp G. Synthesis of new 5-thiazolyl azo-disperse dyes for dyeing polyester fabrics. Dyes and Pigments. 2004;609(3):249-264

[9] Guo XG, Quinn J, Chen ZH, Usta H, Zheng Y, Xia Y, et al. Dialkoxybithiazole: A new building block for head-to-head polymer semiconductors. Journal of the American Chemical Society. 2013;135:1986-1996

[10] Maj J, Rog Z, Skuza G, Kolodziejezyk K. Antidepressant effects of pramipexole, a novel dopamine receptor agonist. Journal of Neural Transmission. 1997;104(4-5):525-533

[11] Vishnuji R, Arun S, Mahendra N, Ramendra P. The Chemistry of Heterocycles: Nomenclature and Chemistry of Three-to-Five Membered Heterocycles2019. pp. 149-478

[12] Maulard T, Lagorce JF, Thomos JC, Raby C. Biological evaluation of compounds with –NCS group or derived from thiazole and imidazole. activity on prostaglandin synthetase complex. The Journal of Pharmacy and Pharmacology. 1993;54(8):731-735

[13] Markus B, Salome VG, Christoph B, Werner JP. Molecular aspects of drug recognition by specific T cells. Curr. Drug Tar. 2004:1-11

[14] Knadler MP, Bergstrom RF, Callaghan JT, Rubin A. Nizatidine, an H2-blocker. Its metabolism and disposition in man. Drug Metabolism and Disposition. 1986;14(2):175-182

[15] Rehman MZ, Anwar CJ, Ahmad S. An Efficient synthesis of 2-alkyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxides. Bulletin of the Korean Chemical Society. 2005;26(11):1771-1775

[16] De Souza MVN, De Almeida MV. Drugs anti-HIV: Past, present and future perspectives. Quimica Nova. 2003:366-372
[17] Popsavin M, Torović L, Svircev M. and antiproliferative activity of two new tiazofurin analogues with 2'-amido functionalities. Bioorganic & Medicinal Chemistry Letters. 2006;16(10):2773-2776

[18] Huo J, Zeng H. A novel triphenylamine functionalized bithiazole– metal complex with C60 for photocatalytic hydrogen production under visible light irradiation. Journal of Materials Chemistry. 2015;3:6258

[19] Koppireddi S, Chilaka DRK, Avula S, Komssani JR, Kotamraju S, Yadla R. Synthesis and anticancer evaluation of 3-aryl-6-phenylimidazo [2,1-b]thiazoles. Bioorganic & Medicinal Chemistry Letters. 2014;24:5428-5431

[20] Chaniyara R, Tala S, Chen C-W, Lee PC, Kakadiya R, Dong H, et al. Synthesis and antitumor evaluation of novel benzo[d]pyrrolo[2,1-b]thiazole derivatives. European Journal of Medicinal Chemistry. 2012;53:28-40

[21] Lee T, Lee D, Lee IY, Gong YD. Solid–phase synthesis of thiazolo[4,5-b]pyridine derivatives using friedländer reaction. Journal of Combinatorial Chemistry. 2010;12:95-99

[22] Serpil E, Emine TC, Onder İ, Ersin İ, Zehra K, Misira E, et al. Derivatives of pyridine and thiazole hybrid: Synthesis, DFT, biological evaluation via antimalarial and DNA cleavage activity. Bioorganic & Medicinal Chemistry. 2020;95:103476

[23] Sammes PG. Comprehensive Organic Chemistry Heterocyclic Compounds, Part 20-1. Vol. 4. Oxford: Pergamon Press; 1979. p. 976

[24] Elederfield RC. Heterocyclic Compounds (Five Membered Heterocycles Containing Two Hetero-Atoms). New York: John Wiley and Sons Inc; 1961

[25] ZoltewichJA, Deady LW. Quaternization of heteroaromatic compounds: Quantitative Aspects. Advances in Heterocyclic Chemistry. 1978:71-121

[26] Gabriel S. Synthese von oxazolen und thiazolen II. European Journal of Inorganic Chemistry. 1910;43:1283-1287

[27] Rajappa S, Nair MD, Advani BG, Sreenivasan R, Desai JAA. General synthesis of thiazoles. Part 3. Comparative evaluation of different functionalised thioureas as precursors. Journal of the Chemical Society, Perkin Transactions. I. 1979:1762-1764

[28] Das B, Reddy SV, Ramu R. A rapid and high-yielding synthesis of thiazoles and aminothiazoles using ammonium-12-molybodophosphate. Journal of Molecular Catalysis A: Chemical. 2006:235-237

[29] Narender M, Reddy SM, Sridhar R, Nageswar YVD, Rao RK. Aqueous phase synthesis of thiazoles and aminothiazoles in the presence of β-cyclodextrin. Tetrahedron Letters. 2005:5953-5955

[30] Karade H, Sathe M, Kaushik MP. An efficient method for the synthesis of 2-aminothiazoles using silica chloride as a heterogeneous catalyst. Catalysis Communications. 2007;8:741-746

[31] Egido EG, Wong SYF, Warrington BH. A Hantzsch synthesis of 2-aminothiazoles performed in a heated microreactor system. Lab on a Chip. 2002;2(1):31-33

[32] George WK, Arjun RM. Microwave promoted synthesis of functionalized 2-aminothiazoles. Tetrahedron Letters. 2006;47:5171-5172

[33] Willstatter R, Wirth T. Über Thioformamid. Berichte: IntechOpen; 1909. pp. 1908-1922. DOI: 10.1002/9780470187081

[34] Otto H. Process for the Production of Thiazoles. U. S. Patent No. 2160867. ExLi4EvA; 1939
[35] George YS, Subhi AA. Preparation and spectral characterization of substituted 2-aminothiazoles. Journal of Chemical & Engineering Data. 1973;18(1):99-102

[36] Ayman WE, Sherif MS, Hatem MG. The chemistry of α-haloketones and their utility in heterocyclic synthesis. Molecules. 2003;8(1):793-865

[37] Someshwar P. Significance of Thiazole-Based Heterocycles for Bioactive Systems. IntechOpen; 2016. DOI: 10.5772/62077

[38] Cook AH, Heilbron I, MacDonald SF, Mahadevan AP. Studies in theazole series. Part XII. Some thiazolopyrimidines. The Royal Society of Chemistry's Journals, Books and Databases. 1949:1064-1068. DOI: 10.1039/JR9490001064

[39] Cook AH, Heilbron I, Mahadevan AP. Studies in the azole series. Part XI. The interaction of α-amino-nitriles, hydrogen sulphide, and ketones. Journal of the Chemical Society. 1949;225:1061-1064

[40] Mara T, Gabriele L, Pamela P, Federico VR, Samuele L, Gianluca B, et al. Catalyst-Free Synthesis of polysubstituted 5-acylamino-1,3-thiazoles via hantzsch cyclization of α-chloroglycinates. Molecules. 2019;24:3846

[41] Cook AH, Heilbron IM, Levy AL. Studies in the azole series. Part II. The interaction of α-amino-nitriles and carbon disulphide. Journal of the Chemical Society. 1947:1598-1609

[42] Cook AH, Heilbron IM, Stern E. Studies in the azole series. Part X. Some 5-amino-2-mercaptop-4-alkylthiazoles and 2:4-dithio-5-alkylhydantions. Journal of the Chemical Society. 1948:2031-2033

[43] Hoggarth E. The rearrangement of 2-benzenesulphenamidothiazoles. Part II. Thiazole compounds substituted in position 4. Journal of the Chemical Society. 1947:114-118

[44] Jacques VM. General synthetic methods for thiazole and thiazolium salts. The chemistry of heterocyclic compounds. In: Thiazole and Its Derivatives, Chapter II. Vol. 34. 1979

[45] Sukanta K, Kimberly M, Edward RB. Microwave-assisted Hantzsch thiazole synthesis of N-phenyl-4-(6-phenylimidazo[2,1-b] thiazol-5-yl)thiazol-2-amines from the reaction of 2-chloro-1-(6-phenylimidazo[2,1-b]thiazol-5-yl) ethanones and thioureas. Tetrahedron Letters. 2012;53:4921-4924

[46] Nayak S, Gaonkar SL. A Review on recent synthetic strategies and pharmacological importance of 1,3-thiazole derivatives. Mini-Reviews in Medicinal Chemistry. 2019;19(3):215-238

[47] Cáceres-Castillo D, Carballo RM, Tzec-Interián JA, Mena-Rejón GJ. Solvent-free synthesis of 2-amino-4-arylthiazoles under microwave irradiation. Tetrahedron Letters. 2012;53(30):3934-3936

[48] Madhav B, Murthy SN, Anil Kumar BSP, Ramesh K, Nageswar YVD. A tandem one-pot aqueous phase synthesis of thiazoles/selenazoles. Tetrahedron let. 2012;53:3835-3838

[49] Bouherrou H, Saidoun A, Abderrahmani A, Abdellaziz L, Rachedi Y, Dumas F, et al. Synthesis and biological evaluation of new substituted hantzsch thiazole derivatives from environmentally benign one-pot synthesis Using silica supported tungstosilisic acid as reusable catalyst. Molecules. 2017;22(5):E757

[50] Tomassetti M, Lupidi G, Piermattei P, Rossi FV, Lillini S, Bianchini G, et al.
Catalyst-free synthesis of polysubstituted 5-acylamino-1,3-thiazoles via hantzsch cyclization of α-chloroglycinates. Molecules. 2019;24(21):3846

[51] Mori A, Sekiguchi A, Masui K, Shimada T, Horie M, Osakada K, et al. Facile synthesis of 2,5-diarylthiazoles via palladium-catalyzed tandem C-H substitutions. Design of tunable light emission and liquid crystalline characteristics. Journal of the American Chemical Society. 2003;125(7):1700-1701

[52] Dodson RM, King LC. The reaction of acetophenone with thiourea and oxidizing agents. Journal of the American Chemical Society. 1946;68(5):871-871

[53] Waad DA, Mahmoud EH, Shahenda MM, Abdulmalik A, Hussein S, El-Sayed EH. Antibacterial, antifungal, and molecular modeling study of some antitumor thiazole based chalcones as a new class of DHFR inhibitors. Microbial Pathogenesis. 2019;136:103674

[54] Khahnadideh S, Rezaei Z, Pakshir K, Zomorodian K, Ghafari N. Synthesis and antifungal activity of benzimidazole, benztrotiazole and aminothiazole derivatives. Research in Pharmaceutical Sciences. 2012;7(2):65-72

[55] Bueno JM, Carda M, Crespo B, Cunat AC, de Cozar C, Leon ML, et al. Design, synthesis and antimalarial evaluation of novel thiazole derivatives. Bioorganic & Medicinal Chemistry Letters. 2016;26(16):3938-3944

[56] Andreani A, Granaiola M, Leoni A, Locatelli A, Morigi R, Rambaldi M. Synthesis and antitubercular activity of imidazo[2,1-b]thiazoles. European Journal of Medicinal Chemistry. 2001;36(9):743-746

[57] Dawood KW, Eldebss TM, El-Zahabi HS, Yousef MH. Synthesis and antiviral activity of some new bis-1,3-thiazole derivatives. European Journal of Medicinal Chemistry. 2015;18(102):266-276

[58] Sharma RN, Xavier FP, Vasu KK, Chaturvedi SC, Pancholi SS. Synthesis of 4-benzyl-1,3-thiazole derivatives as potential anti-inflammatory agents: An analogue-based drug design approach. Journal of Enzyme Inhibition and Medicinal Chemistry. 2009;24(3):890-897

[59] Bozdag-Dundar O, Ceylan-Unlusoy M, Verspohl EJ, Ertan R. Synthesis and antidiabetic activity of novel 2,4-thiazolidinedione derivatives containing a thiazole ring. Arzneimittel-Forschung/Drug Research. 2006;56(9):621-625

[60] Weikert RJ, Bingham S Jr, Emanuel MA, Fraser-Smith EB, Loughhead DG, Nelson PH, et al. Synthesis and anthelmintic activity of 3′-benzoyleurea derivatives of 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole. Journal of Medicinal Chemistry. 1991;34(5):1630-1633

[61] Ucar H, Van Derpoorten K, Cacciaguerra S, Spampinato S, Stables JP, Depovere P, et al. Synthesis and anticonvulsant activity of 2(3H)-benzoxazolone and 2(3H)-benzothiazolone derivatives. Journal of Medicinal Chemistry. 1998;41(7):1138-1145

[62] Kurt BZ, Gazioglu I, Sonmez F, Kucukislamoglu M. Synthesis, antioxidant and anticholinesterase activities of novel coumarylthiazole derivatives. Bioorganic Chemistry. 2015;59:80-90

[63] Thoraya AF, Ghada SM, Zeinab AM, Marwa FH. Discovery of thiazole-based-chalcones and 4-hetarylthiazoles as potent anticancer agents: Synthesis, docking study and anticancer activity. Bioorganic Chemistry. 2020;98:103761

[64] Omar AM, Eshba NH. Synthesis and biological evaluation of new
2,3-dihydrothiazole derivatives for antimicrobial, antihypertensive, and anticonvulsant activities. Journal of Pharmaceutical Sciences. 1984;73(8):1166-1168

[65] Xu R, Tian Y, Huang S, Yu J, Deng Y, Zhan M, et al. Synthesis and evaluation of novel thiazole-based derivatives as selective inhibitors of DNA-binding domain of the androgen receptor. Chemical Biology & Drug Design. 2018;91(1):172-180

[66] Das D, Sikdar P, Bairagi M. Recent developments of 2-aminothiazoles in medicinal chemistry. European Journal of Medicinal Chemistry. 2015;109:89-98. DOI: 10.1016/j.ejmech.2015.12.022

[67] Franchetti P, Cappellacci L, Grifantini M, Barzi A, Nocentini G, Yang H, et al. Furanfurin and thiophenfurin: Two novel tiazofurin analogues. Synthesis, structure, antitumour activity, and interactions with inosine monophosphate dehydrogenase. Journal of Medicinal Chemistry. 1995;38(19):3829-3837

[68] Li X, He Y, Ruiz CH, Koenig M, Cameron MD. Characterization of dasatinib and its structural analogs as CYP3A4 mechanism-based inactivators and the proposed bioactivation pathways. Drug Metabolism and Disposition. 2009;37(6):1242-1250

[69] Hu-Lieskovan S, Mok S, Homet Moreno B, Tsoi J, Robert L, Goedert L, et al. An Improved antitumour activity of immunotherapy with B-RAF and MEK inhibitors in BRAF(V600E) melanoma. Science Translational Medicine. 2015;18(7):279, 279-41

[70] Rashid MA, Gustafson KR, Cardellina JH, Boyd MR, Patellamide F. A new cytotoxic cyclic peptide from the colonial ascidian Lissoclinum patella. Journal of Natural Products. 1995;58(4):594-597

[71] Yao Y, Chen S, Zhou X, Xie L, Chen A. 5-FU and ixabepilone modify the microRNA expression profiles in MDA-MB-453 triple-negative breast cancer cells. Oncology Letters. 2014;7:541-547

[72] Altmann KH. Epothilone B and its analogs—A new family of anticancer agents. Mini Reviews in Medicinal Chemistry. 2003;3(2):149-158

[73] Ramla MM, Omar MA, El-Khamry AMM, El-Diwan HI. Synthesis and antitumor activity of 1-substituted-2-methyl-5-nitrobenzimidazoles. Bioorganic & Medicinal Chemistry. 2006;14:7324

[74] Popsavin M, Spaic S, Svircev M, Kojic V, Bogdanovic G, Popsavin V. Synthesis and antitumor activity of new tiazofurin analogues bearing a 2,3-anhydro functionality in the furano ring. Bioorganic & Medicinal Chemistry Letters. 2007;17:4123

[75] Helal CJ, Sanner MA, Cooper CB, Gant T, Adam M, Lucas JC, et al. Discovery and SAR of 2-aminothiazole inhibitors of cyclin-dependent kinase 5/p25 as a potential treatment for Alzheimer's disease. Bioorganic & Medicinal Chemistry. 2004;14:5521

[76] Mohammadi-Farani A, Foroumadi A, Rezvani Kashani M, Aliabadi A. N-Phenyl-2-p-tolylthiazole-4-carboxamide derivatives: Synthesis and cytotoxicity evaluation as anticancer agents. Iranian Journal of Basic Medical Sciences. 2014;17:502-508

[77] Zhou W, Huang A, Zhang Y, Lin Q, Guo W, You Z, et al. Design and optimization of hybrid of 2,4-diaminopyrimidine and arylthiazole scaffold as anticancer cell proliferation and migration agents. European Journal of Medicinal Chemistry. 2015;96:269-280

[78] Gross S, Lengauer C, Hoeflich KP, Gross S, Rahal R, Stransky N, et al.
Targeting cancer with kinase inhibitors. Journal of Clinical Investigation. 2015;125:1780-1789

[79] Kim D, Choi JH, An J, Soon H. Synthesis and biological evaluation of 5-(pyridin-2-yl) thiazoles as transforming growth factor-b type1 receptor kinase inhibitors. Bioorganic & Medicinal Chemistry Letters. 2008;18:2122-2212

[80] Kojic V, Svrč M, Bogdanovic G. Synthesis and in vitro antitumour screening of 2-(B-D-xylofuranosyl) thiazole-4-carboxamide and two novel tiazofurin analogues with substituted tetrahydrofurodioxol moiety as a sugar mimic. Bioorganic & Medicinal Chemistry Letters. 2012;226700-226704

[81] Virginia S, Alessandro A, Stella C, Anna C, Alessandra M, Paola B, et al. Synthesis and antitumor activity of new thiazole nortopsentin analogs. Marine Drugs. 2016;14(12):226

[82] dos Santos TAR, da Silva AC, Silva EB, de Moraes Gomes PAT, Espíndola JWP, de Oliveira Cadoso MV, et al. Antitumor and immunomodulatory activities of thiosemicarbazones and 1,3-thiazoles in Jurkat and HT-29 cells. Biomed, Pharma. 2016;82:555-556

[83] Lin R, Johnson SG, Connolly PJ, Wetter SK, Binnun E, Hughes TV, et al. Analogues as antitumor epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. Bioorganic & Medicinal Chemistry Letters. 2009;19:2333-2337

[84] Liu W, Zhang X, Zhao J, Li Cui J, Mao Z. Inhibition of cervical cancer cell metastasis by benzo[b]thiazole through up-regulation of E-cadherin expression. Microbial Pathogenesis. 2017;111:182-186

[85] Weidner-Wells MA, Werblood HM, Goldschmidt R. Synthesis and Antibacterial Activity of novel oxazolidinone analogs containing substituted thiazole/ fused bicyclic Gr. Chemical Research in Chinese Universities. 2006;22(4):459-464

[86] Vicini P, Geronikaki A, Anastasia K, Incerti M, Zani F. Synthesis and antimicrobial activity of novel 2-thiazolyllimino-5-arylidine-4-thiazolid. Bioorganic & Medicinal Chemistry. 2006;14:3859

[87] Abdel-Wahab BF, Abdel-Aziz HA, Ahmed EM. Synthesis and antimicrobial evaluation of 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles. European Journal of Medicinal Chemistry. 2009;44:2632

[88] Mohd AS, Kanugala S, Ibrahim BS, Irfan K, Thripparu G, Syed A, et al. Synthesis of new triazole fused imidazo[2,1-b]thiazole hybrids with emphasis on Staphylococcus aureus virulence factors. Bioorganic & Medicinal Chemistry Letters. 2019;29:126621

[89] Bharti SK, Nath G, Tilak R, Singh SK. Synthesis, antibacterial and anti-fungal activities of some novel Schiff bases containing 2,4-disubstituted thiazole ring. European Journal of Medicinal Chemistry. 2010;45:651-660

[90] Chimenti F, Bizzarri B, Maccioni E, Secci D, Bolasco A, Fioravanti R, et al. Synthesis and in vitro activity of 2-thiazolylhydrazone derivatives compared with the activity of clotrimazole against clinical isolates of Candida spp. Bioorg,Med.Chem. Lett. 2007;17:4635

[91] Geronikaki AA, Pitta EP, Liaras KS. Thiazoles and thiazolidinones as antioxidants. Current Medicinal Chemistry. 2013;20(36):4460-4480
[92] Karegoudar P, Karthikeyan MS, Prasad DJ, Mahalinga MB, Holla S, Kumari NS. Synthesis of some novel 2,4-disubstituted thiazoles as possible antimicrobial agents. European Journal of Medicinal Chemistry. 2008;43(2):261-267

[93] Hassan FA. Synthesis, characterization, anti-inflammatory, and antioxidant activities of some new thiazole derivatives. Current Journal of Applied Science. Technol. 2012;2(7):180-187

[94] Siddiqui N, Ahsan MW, Alam MS. Thiazoles: A valuable insight into the recent advances and biological activities. International Journal of Pharmacy and Pharmaceutical Sciences. 2009;1(3):136-143

[95] Estevão MS, Carvalho LC, Ribeiro D, Couto D, Freitas M, Gomes A, et al. Antioxidant activity of unexplored indole derivatives: Synthesis and screening. European Journal of Medicinal Chemistry. 2010;45:4869-4878

[96] Bozdag-Dundar O, Coban T, Ceylan-Unlusoy M, Ertan R. Radical scavenging capacities of some thiazoylthiazolidine-2,4-dione derivatives. Medicinal Chemistry Research. 2009;18:1

[97] Gouda MA, Berghot MA, Baz EA, Hamama WS. Synthesis and antioxidant evaluation of some new sulphadimidine incorporating thiophene moiety. European Journal of Chemistry. 2014;5(4):595-600

[98] Jaishree V, Ramdas N, Sachin J, Ramesh B. In vitro antioxidant properties of new thiazole derivatives. Journal of Saudi Chemical Society. 2012;16:371-376