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,

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**).

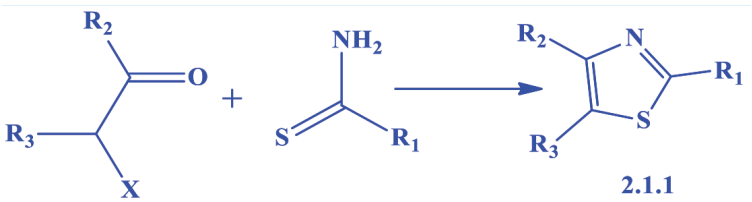

Figure 1.
Synthesis of 2-, 4-, 5-trisubstituted thiazole.

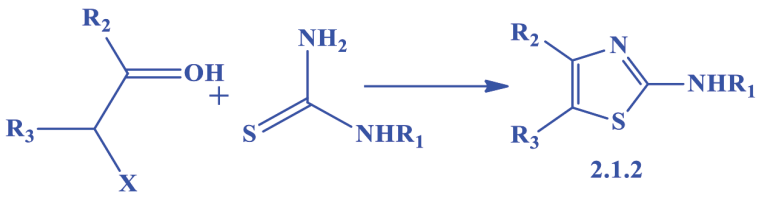

Figure 2.
Synthesis of substituted aminothiazoles.

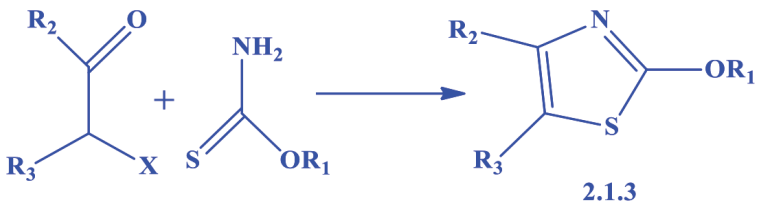

Figure 3.
Synthesis of 2-hydroxythiazole derivatives.

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

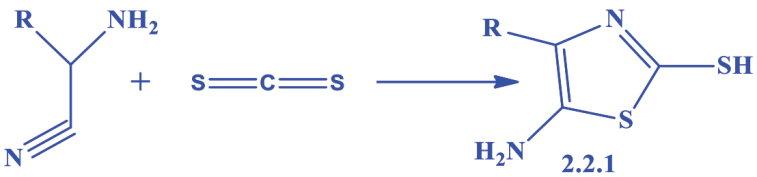

Figure 4.
Synthesis of 5-aminothiazole derivatives.

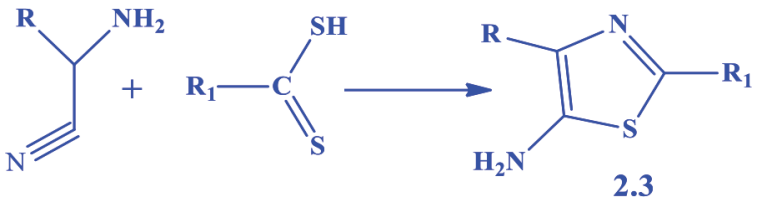

Figure 5.
Synthesis of 5-aminothiazoles derivatives.

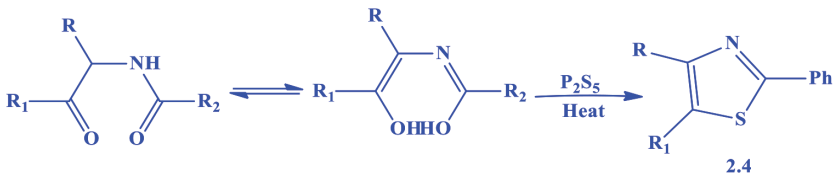

Figure 6.
Synthesis of 2-phenyl-5-alkyl-thiazole derivatives.

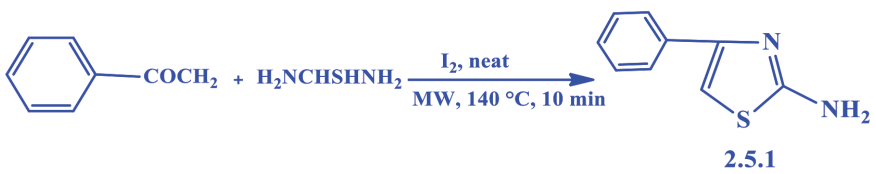

Figure 7.
Synthesis of thiazoles under microwave irradiation.

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-2*H*-pyran-2-one was reacted with

thiourea and substituted benzaldehydes in the presence of silica-supported tungstosilisic 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**).

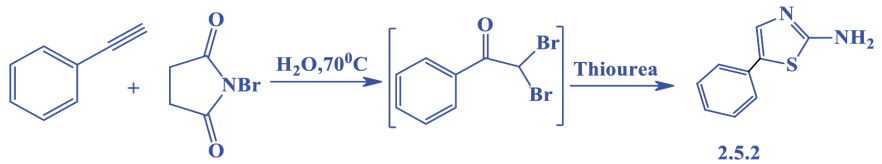

Figure 8.
Synthesis of 2-aminothiazole in aqueous medium.

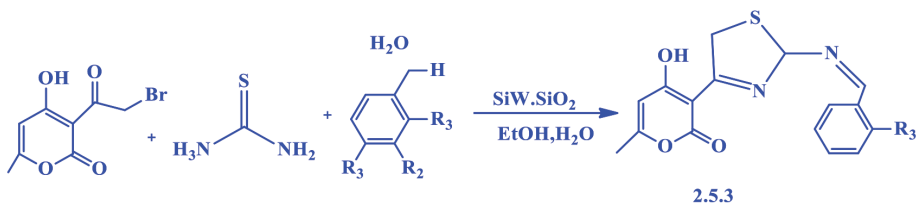

Figure 9.
Synthesis of thiazole derivatives using silica.

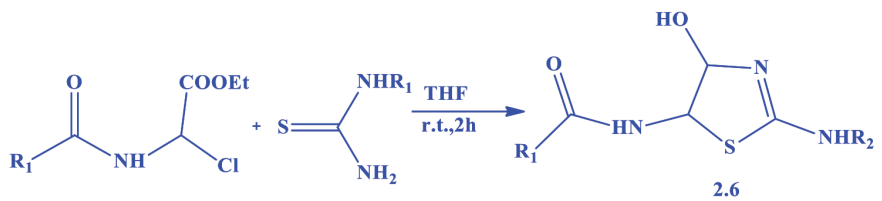

Figure 10.
Synthesis of thiazole derivatives.

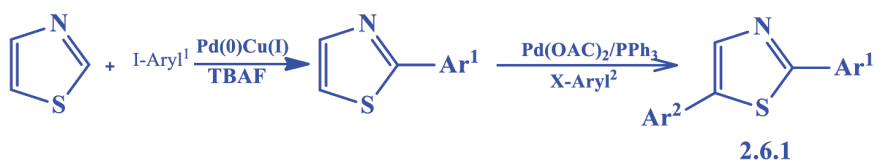

Figure 11.
Synthesis of thiazole derivatives using palladium/copper.

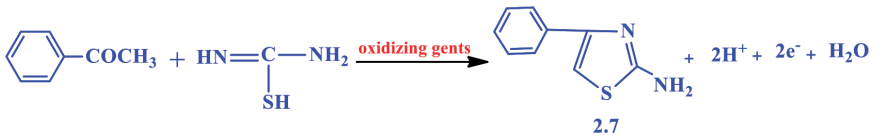

Figure 12.
Synthesis of thiazole derivatives using oxidizing agents.

2.7 Using oxidizing agents and thiourea

The mixtures of thiourea and acetophenone were treated with various oxidizing gents 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], anticonvulsant [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-1*H*-benzo[*d*]imidazol-1-yl)thiazol-2(3*H*)-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

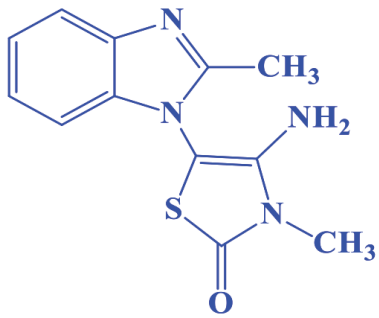

Figure 13.
*Structure of compound **3.1.1**.*

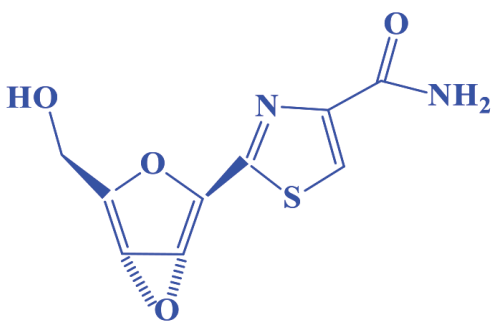

Figure 14.
*Structure of compound **3.1.2**.*

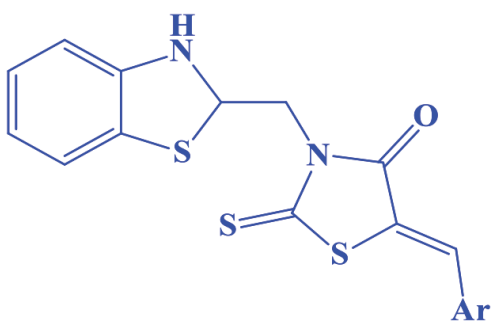

Figure 15.
*Structure of compound **3.1.3**.*

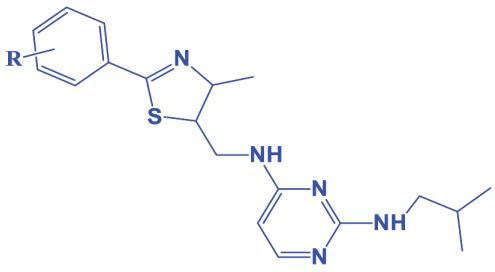

Figure 16.
*Structure of compound **3.1.4**.*

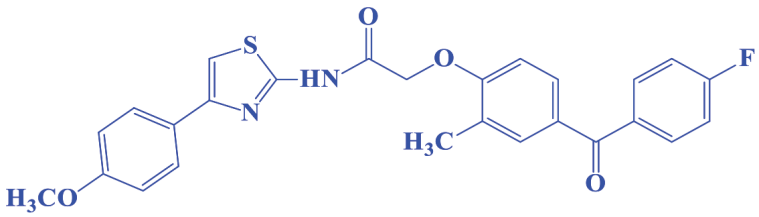

Figure 17.
*Structure of compound **3.1.5**.*

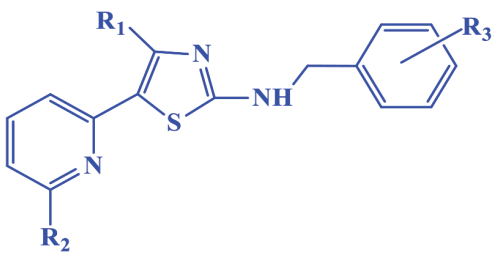

Figure 18.
*Structure of compound **3.1.6**.*

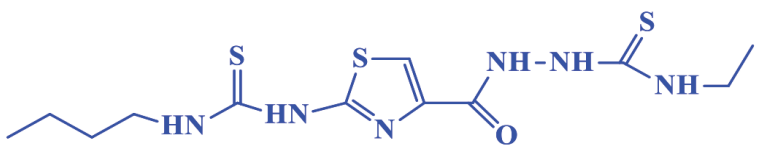

Figure 19.
*Structure of compound **3.1.7**.*

(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].

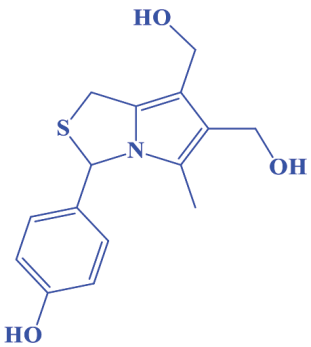

Figure 20.
*Structure of compound **3.1.8**.*

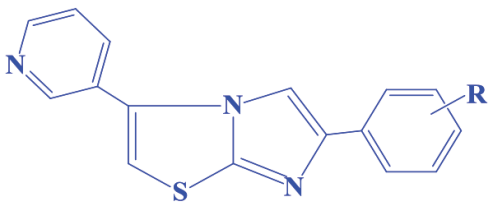

Figure 21.
*Structure of compound **3.1.9**.*

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**), imidazolothiazoles (**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]-1*H*-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**).

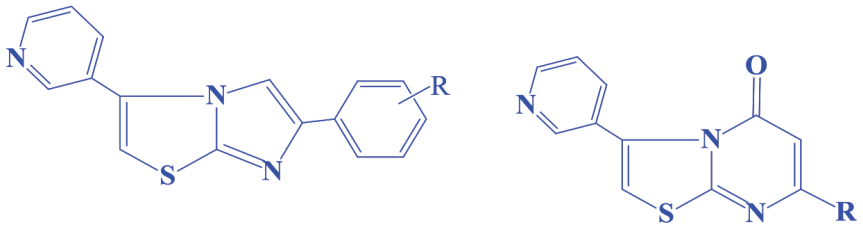

Figure 22.
*Structure of compounds **3.2.1** and **3.2.2**.*

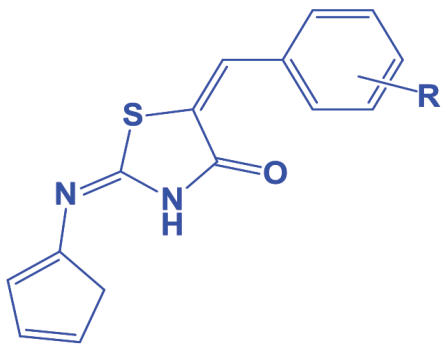

Figure 23.
*Structure of compound **3.2.3**.*

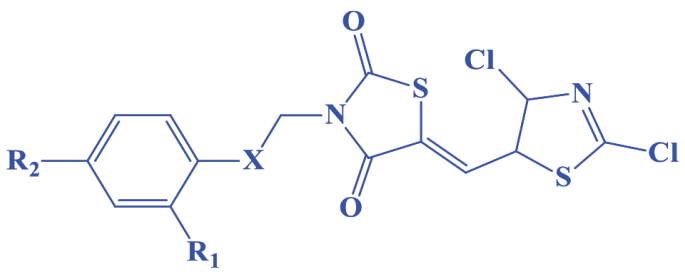

Figure 24.
*Structure of compound **3.2.4**.*

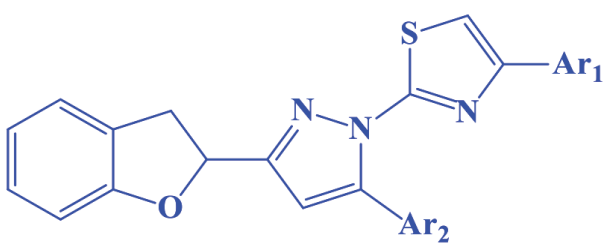

Figure 25.
*Structure of compound **3.2.5**.*

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].

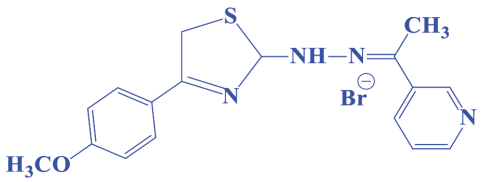

Figure 26.
*Structure of compound **3.2.6**.*

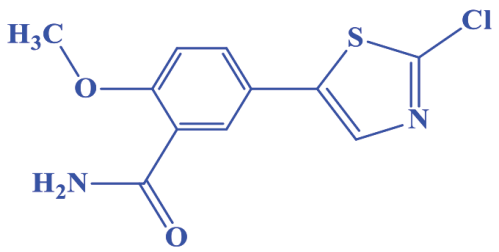

Figure 27.
*Structure of compound **3.3.1**.*

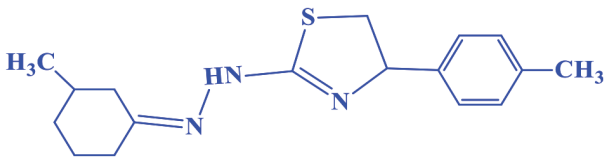

Figure 28.
*Structure of compound **3.3.2**.*

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**).

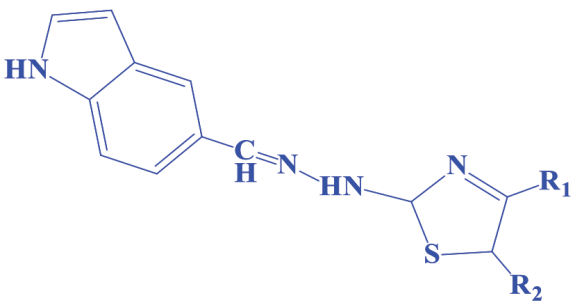

Figure 29.
*Structure of compound **3.4.1**.*

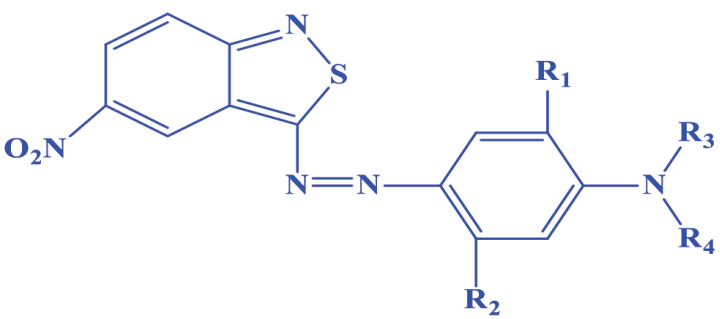

Figure 30.
*Structure of compound **3.4.2**.*

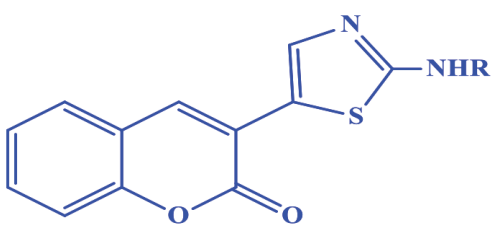

Figure 31.
*Structure of compound **3.4.3**.*

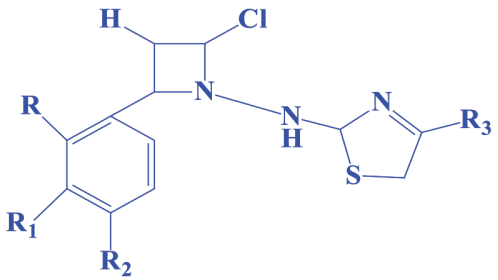

Figure 32.
Structure of compound ***3.4.4****.*

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

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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