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A BRIEF REVIEW ON THE THIAZOLE DERIVATIVES: SYNTHESIS METHODS AND BIOLOGICAL ACTIVITIES

(Ulasan Ringkas Terbitan Tiazol: Kaedah Sintesis dan Aktiviti Biologi)

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Abstract

Thiazole is one of the leading heterocyclic five-membered ring compounds that contain sulphur atoms at position 1 and nitrogen atoms at position 3. Many of its natural and synthetic derivatives possess diverse biological activities. In drug research development, the substituent at thiazole ring was modified to generate new molecules with potent biological activities. This review describes the chemistry of thiazole, the synthetic pathway of thiazole, and their biological activities that could benefit other researchers to design new molecules of thiazole derivatives with more potent biological activities.

Keywords: thiazole, chemistry, synthetic pathway, biological activities

Abstrak

Tiazol merupakan sebatian heterosiklik bergelang lima yang mempunyai atom sulfur dan nitrogen pada kedudukan masing-masing 1 dan 3 pada gelang tersebut. Sebatian ini, samada semulajadi atau sintetik banyak diaplikasikan dalam pelbagai bidang biologi. Di dalam kajian penghasilan ubatan baru, banyak terbitan baru sebatian tiazol dapat dicipta dengan menukarkan pelbagai penukarganti yang sesuai terhadap gelang tiazol tersebut supaya mempunyai potensi dalam aktiviti biologi. Di dalam kajian ini, kimia sebatian tiazol, laluan sintetik tiazol dan aplikasi sebagai bahan antibiologi dibincangkan. Diharap, ulasan ini dapat memberi manfaat kepada penyelidik yang ingin mengkaji dengan lebih mendalam potensi sebatian tiazol sebagai agen biologi.

Kata kunci: tiazol, kimia, laluan sintetik, aktiviti biologi

Introduction

The exploration of new compounds with multifunctional biological behaviour is an interest research area due to its cruciality and significance. Several inorganic [1], polymer [2], and organic compounds [3] were synthesised and the isolation of natural products [4] have been proved to possess biological activities. Among these compounds, the organic compound appears to be the most favourable in the biological field due to its facile synthesis methods [5] and a high percentage yield [6]. One of the main research areas that focuses on organic chemistry to develop an antimicrobial drug is the synthesis of heterocyclic compounds. Heterocyclic compound is a cyclic

compound with at least two different atoms as the members in the ring and has been extensively applied in medicinal and biological applications. For example, benzimidazole, pyrimidine and oxazole were claimed to possess antimicrobial [7], antifungal [8], anti-inflammatory as well as antitumor [9] properties.

Over the years, research on a small molecule of heterocyclic ring integrated with nitrogen and sulphur such as thiazole [10, 11] and triazole [12,13] have been extensively studied based due to their synthetic and biological applications. Thiazole is the most commonly reported compound in the literature. Thiazole is a 5-membered ring moiety containing nitrogen and sulphur at position 1 and 3, respectively. The structural pattern of thiazole derivatives as active compounds is predominantly focused on the substitution of hydrogen atoms with desired moieties at position 2, 4, 5 [14,15]. The derivatives were reported to demonstrate anti-inflammatory [14], antifungal [17], anticancer [14, 20], antibacterial [14, 16], anticonvulsant [19], antiviral [17], and antitumor [14, 20] activities. This has generated an urge to extend the study by synthesising new thiazole derivatives as potential candidates for drug discovery prospect.

Methods

The search for literature related to thiazole derivatives and their application in biological activities were retrieved from PUBMED, Science Direct, Scopus, Springer, and Google Scholar databases. The articles chosen for this study were articles published from 2009 to 2018 covering thiazole and its derivatives, synthesis, and applications.

Chemistry of thiazole

Thiazole employs both an electron-donating group (-S-) and an electron accepting group (C=N) and these create a stable heterocyclic compound [21]. Thiazole and its analogue such as oxazole are considered as an important group of heterocycles possessing several biological properties [22]. Thiazole compound is isomeric with an azole compound such as isothiazole that comprises similar atoms compound (nitrogen and sulphur) but at a different position. Thiazole is a clear pale-yellow liquid with a boiling point of 116 -118 ºC [17], soluble in alcohol and ether but moderately soluble in water [23]. The heterocyclic ring of thiazole contains a delocalisation of 6 π electrons corresponding to Huckel's rule from the lone pair electrons, which is the sulphur atom [24]. Figure 1 shows the resonance forms of thiazole **(1)**. Thiazole derivatives are desirable model compounds for chemistry study due to its planar and aromatic structure that exhibits larger π-electron delocalisation compared to oxazole [23].

The aromatic behaviour of the thiazole ring was verified using ^{1}H NMR spectroscopy whereby the chemical shift of the protons is spotted between 7.27 and 8.77 ppm [21]. The reactivity of the thiazole derivatives ring was strained due to the addition of different substituents at C-2, C-4, and C-5 positions, which could lead to further structural consideration [25]. For example, the effect of the methyl group (electron donating group) substituent was recognised when it was located at any position of the thiazole ring, leading to an increase in its basicity and nucleophilicity properties. However, the basicity and nucleophilicity reductions occur when a strong electron withdrawing group such as a nitro group was incorporated into the molecule [26, 27].

The molecular frame of thiazole is unique due to its versatile building blocks as bioactive compounds [28]. Several studies have reported that the thiazole ring is present in most natural and synthetic products with an extensive range of biological properties [29, 30]. One of the examples is vitamin B1 or known as thiamine involving thiazole moiety where it naturally supports the nervous system by connecting its role in acetylcholine synthesis [31]. Moreover, thiazole derivatives **(3)** that are shown in Figure 2 possessed amphiphilic character due to having both hydrophobic (lipophilic) and hydrophilic (lipophobic) parts. This property increases its potential to diffuse facilely into the cell membrane of bacteria for inhibition activity [32]. Compound with both hydrophilic and lipophilic sections is beneficial against both Gram-negative and Gram-positive bacteria [33] by breaking through the cell membrane of bacteria for an inhibition process. This penetration leads to cytoplasmic materials leakage, cell physiology disturbance, and apoptosis [34].

Synthetic approach of thiazole derivatives

The explorations of thiazole derivatives have emerged as an important topic throughout the years due to its various applications. The most appealing characteristic is the derivatives can be synthesised with a good yield from the starting material by a simple synthesis method [35]. The unique structure and significance of thiazole compounds have led to the expansion of methods by applying various conditions, catalysts, and approaches.

Hantzsch synthesis

The most notable method to synthesise thiazole is the Hantzsch thiazole synthesis [36, 37], which was invented in 1887 by a German chemist named Hantzsch. This method utilises the condensation reaction of α-haloketone with nucleophilic reagents such as thioamide, thiourea, ammonia thiocarbamate or dithiocarbamate derivatives [38,39]. Moreover, Hantzsch thiazole synthesis was suggested to be the most productive method for the synthesis of thiazole derivatives [40]. In this method, four thiazole derivatives were prepared by employing the Hantzsch reaction of thionicotinamide (**3**) with four types of α-haloketone namely chloroacetone (**5**), 3-chloroacetylacetone (**6**), 3-bromoacetylcoumarin (**7**), and p-chloroacetylacetanilide (**8**) in the presence of catalytic triethylamine (**4**). The reaction produced 2-(3-pyridyl) thiazole derivatives (**9**-**12**) as shown in Scheme 1.

Several studies reported that this method has major drawbacks such as low percentage yields, harsh reaction condition, prolonged reaction time, and employs expensive catalysts [5, 41, 42, 43]. In contrast, it was reported by another researcher that this method gives high yields *via* dehalogenation of the haloketone during the reaction [44]. The nature of halide as a good leaving group has promoted the vacant site for a nucleophilic attack to furnish the reaction. The Hantzsch cyclisation method was proposed by synthesising thiazole derivatives, in which the tetrafluroethoxy moiety was directly attached to the carbon atom of the heterocyclic ring [45]. In their research, α-bromo-α-tetrafluoroethoxyacetophenone (**13**) was heated with thiobenzamide (**14**) at 60 °C in dioxine that led to the formation of 2,4-diphenyl-5-(1,1,2,2-tetrafluorethoxy)-thiazole (**15**) (Scheme 2). However, the percentage of yield is low (18-20%) due to the unstable thiobenzamide in an acidic medium.

Cook-Heilbron synthesis

In addition, thiazole ring can also be synthesised from α-aminonitriles or α-aminoamides and carbon disulfide as the reactants, known as Cook-Heilbron synthesis that is discovered by Cook and Heilbron [26]. The Cook-Heilbron method produced 5-aminothiazoles in which substitution occurred at position 2 by the reaction of aminonitrile with salt and esters of thioacids, carbon disulfide or isothiocyanates under mild conditions [46]. Scheme 3 depicts the reaction of α-aminonitriles (**16**) with carbon disulfide (**17**) to form 5-amino-2-mercapto-thiazole (**18**).

Gabriel synthesis

Another alternative of a synthetic approach to synthesise thiazole derivatives is Gabriel synthesis. This method focuses on the closure of the thiazole ring by reacting acylamino-ketone with phosphorus pentasulfide producing 2,5- disubstituted thiazole derivatives [47]. This study was promoted by Kotadiya [48] whereby the synthesis of the desired compound involved heating of acylamino compounds namely *N*-(2-oxopropyl) acetamide (**19**) with phosphorus pentasulfide (**20**) to produce 2,5-dimethylthiazole (**21**) as shown in Scheme 4.

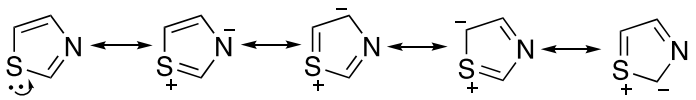

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Figure 1. Resonance forms of thiazole compound

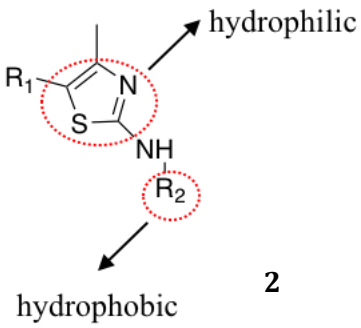
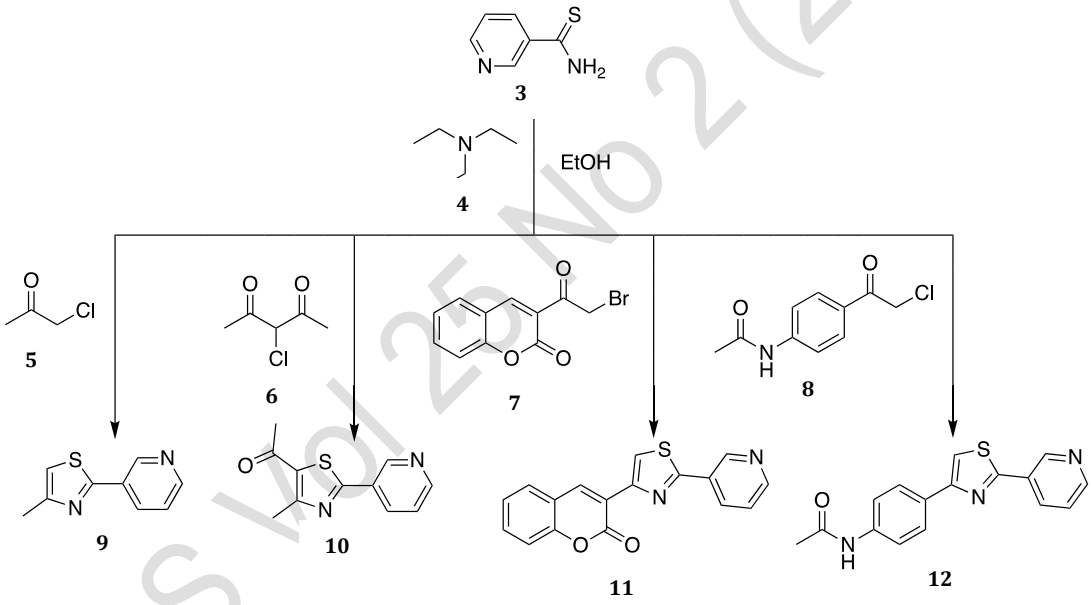
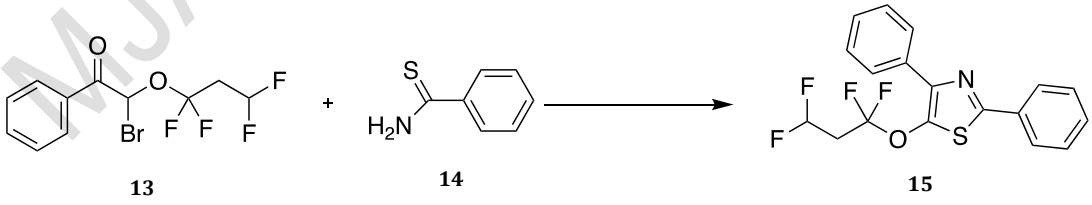


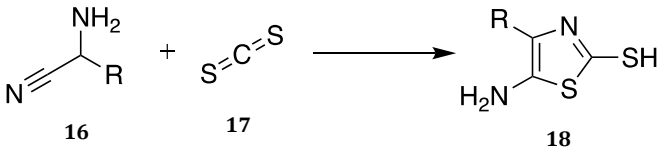
Figure 2. Structure of thiazole derivatives



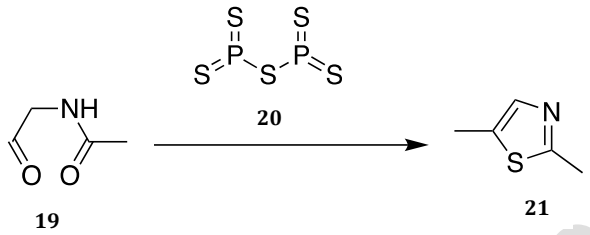
Scheme 1. Reaction synthesis of 2-(3-pyridyl) thiazole derivatives [40]



Scheme 2. Hantzsch type synthesis of 2,4-diphenyl-5-(1,1,2,2-tetrafluorethoxy)-thiazole



Scheme 3. The Cook-Heilbron thiazole synthesis [26]



Scheme 4. Synthesis of thiazole compound *via* Gabriel reaction [48]

However, Hantzsch cyclisation, Cook-Heilbron, and Gabriel synthesis methods have major drawbacks in terms of time consuming and unsatisfactory percentage yields. Hence, several studies have improved the method. For example, the synthesis of thiazole derivatives by occupying the chemoenzymatic organic reactions or known as an enzymatic synthesis of heterocyclic compounds were designed [49]. In the study, a medium condition of chemoenzymatic was applied in a one-pot multicomponent reaction. The reaction of the starting materials such as secondary amine (**22**), benzoyl isothiocyanate (**23**), and dimethyl acetylenedicarboxylate (**24**) was catalysed by α-amylase derived from *Aspergillus oryzae* in ethanol (Scheme 5).

Furthermore, the synthetic pathway improvement of thiazole synthesis coping with environmental-friendly and practical methods has been also investigated. The designation of *N*-substituted 2-aminothiazole analogue namely *N*-(4-phenyl-1,3-thiazol-2-yl)-benzamide (**30**) comprises two stages of reaction synthesis was developed [50] whereby phenylthiazole was reacted with benzoyl chloride with continuous stirring at room temperature. Scheme 6 displays the synthetic routes to synthesise the thiazole compound in ethanol with continuous heating and stirring for 8 hours.

A simple but potent synthetic route of thiazole derivatives is still under investigation and improvement. The prominent method should exert low energy consumption, less waste generated, high percentage yield, and involve a one-pot reaction.

Biological application of thiazole derivatives

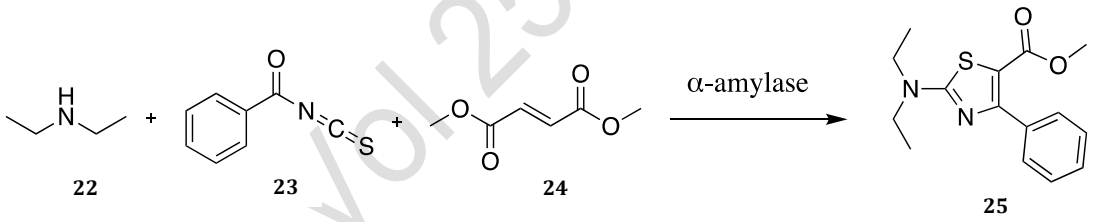
Thiazole derivatives have been comprehensively applied in the field of biology as well as pharmacology with a well-established ability in pharmaceutical drugs. They were reported to exhibit antimicrobial [51,53], antioxidant [52], anticancer [53], and antitubercular [53] behaviour. Thiazole compound namely bis-(4-phenylthiazol-2-yl) amine **(31)** and 1-(4-methyl-2-(2-(1-phenylethylidene) hydrazineyl)-4,5-dihydrothiazol-5-yl) ethenone **(32)** as shown in Figure 3 possess anti-inflammatory due to the presence of nitrogen and sulphur atoms in the molecules [53].

Besides that, a compound with thiazole as the core structure demonstrated an antioxidant agent [54]. The antioxidant properties of the synthesised thiazole derivatives (**33**, **34** and **35**) were evaluated using DPPH (1,1-diphenyl-2-picyrylhydrazyl) scavenging capacity test. The results showed that the DPPH radical inhibition for compound **33** and **34** were 18.73% and 15.62%, respectively. No antioxidant activity was seen from compound **35**, which could be due to the lack of several active atoms leading to a decrease in possible resonance in the structure. The chemical structures of compound **33**, **34,** and **35** are shown in Figure 4.

In another application, thiazole compounds have also been explored as a drug candidate for an antibacterial agent. The appearance of antibiotic (drug) resistance against bacterial strains has captivated outstanding concern in the discovery and development of a new suited antimicrobial drug. Since thiazole moiety is widely known in biological activity, investigations on thiazole derivatives as an antimicrobial agent have been vigorously conducted. Introduction of various substituents in the main molecular framework of thiazole showed optimistic result towards the tested bacterial strains [10]. A number of studies have been extensively performed to improve the chemical structures of thiazole derivatives for antimicrobial applications. In particular, trichlorophenyl thiazole compound exhibited considerable inhibitory effect against numerous Gram-positive and Gram-negative strains such as *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Pseudomonas fluorescens* [26].

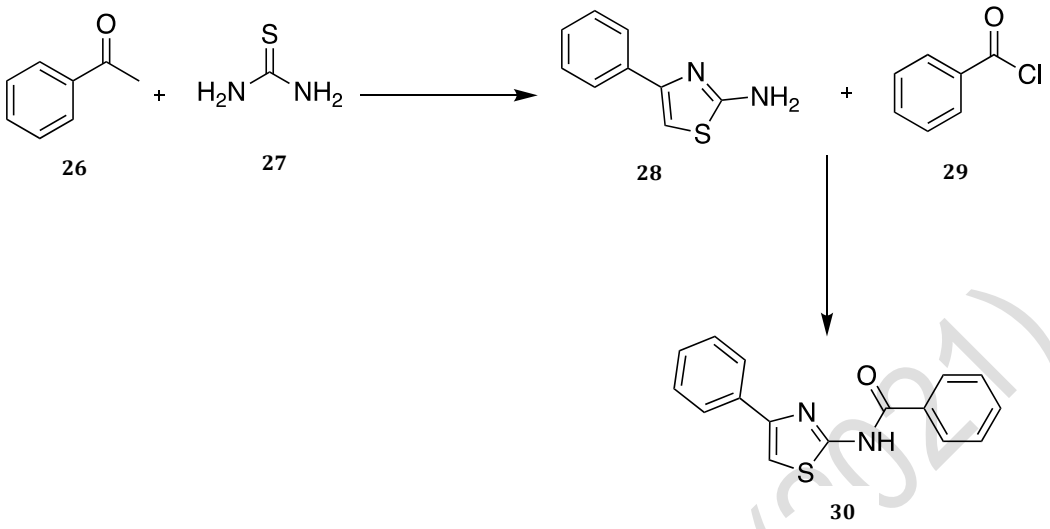
Prolongation synthesis of active antimicrobial agents resulted in a series of 2,4-disubstituted-1,3-thiazole derivatives (Figure 5) designation with identifiable *in-vitro* antimicrobial activities [55]. The synthesised analogues of **36** and **37** comprising nitro group at phenyl substituents exhibited active results towards *B. subtilis*, *S. aureus* and *E. coli* with MIC values of 3.92-4.01, 3.39-4.11 and 3.59-4.23 µM/mL, respectively compared to compound **38** with values of 4.51, 4.60 and 4.32 µM/mL, respectively. This is a result of the existence of nitro moiety at the para position, which makes a strong hydrogen bonding with the amino acid residue in the tested microorganisms. Therefore, it can be concluded that the thiazole ring with nitro at position 4 played crucial roles to inhibit microorganism activities as well as the optimisation of the substituent at the ring [26].

In another study, the -C=N spacer in the thiazole was reported to be the advantageous factor for the antifungal behaviour of the compounds [56]. The synthesised compounds of **39** and **40** (Figure 6) demonstrated high antifungal activity against *U. tritici* and *P. striiformis.*



22 **23** **24** **25**

Scheme 5. One-pot multicomponent synthesis of thiazole derivatives using derived enzyme [49]



Scheme 6. Synthesis of thiazole derivatives in two stages of reaction

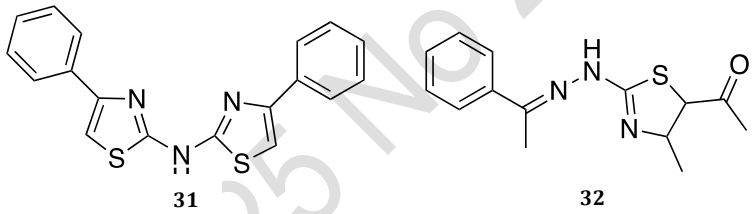


Figure 3. Chemical structures of 2-aminothiazole derivatives as an anti-inflammatory agent

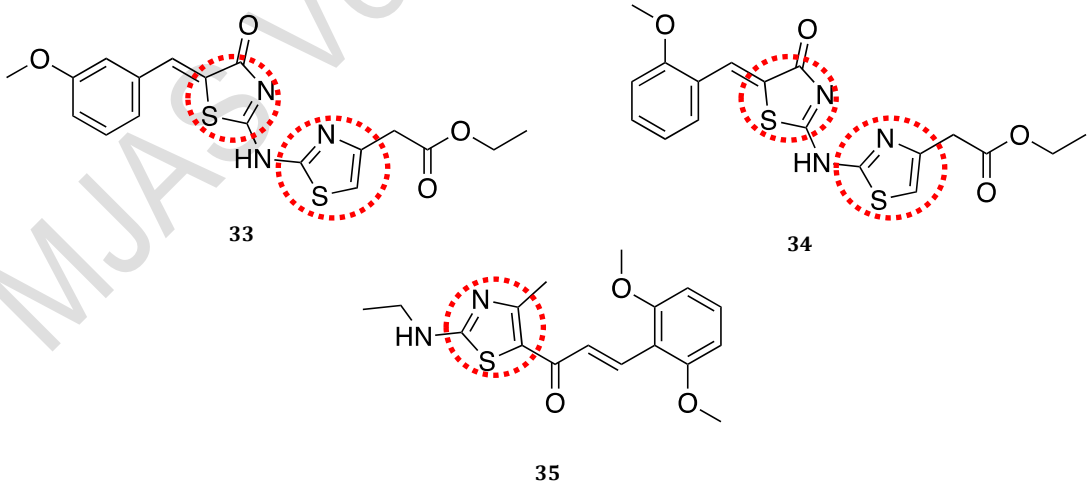
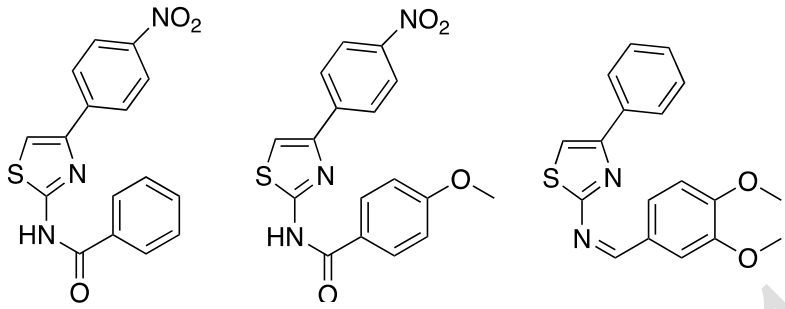
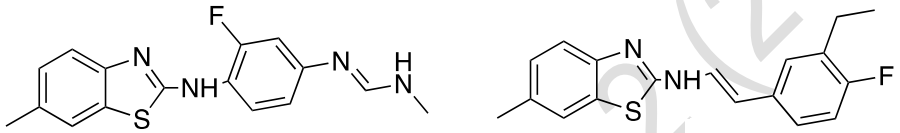


Figure 4. Chemical structures of thiazole derivatives possess antioxidant activities



36 **37** **38**

Figure 5. Series of 2,4-disubstituted thiazole derivatives as antimicrobial agents



39 **40**

Figure 6. Chemical structures of fluorinated benzothiazole-2-yl-1,2,4-triazoles derivatives

Conclusion

In summary, there were numerous methods reported on the synthetic pathway of thiazole derivatives. A new practical method can be designed to synthesise thiazole derivatives with a high yield. In biological application, several new structures were designed and synthesised by modifying the substituent at thiazole ring with suitable substituent groups in order to improve the biological activities. Therefore, research on thiazole derivatives can be the focal point for future exploration due to its special attributes and potential.

Acknowledgement

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