Chapter 7
Synthesis and Biological Evaluation of Some Fused Pyrrolothiazoles, Pyrazolothiazoles, and Imidazothiazoles

Pankaj Teli, Hemant Kumar Rundla, Lokesh Kumar Agarwal, Dinesh Kumar Jangid, and Shikha Agarwal

7.1 Introduction

Heterocyclic compounds play significant part in the cellular metabolism of whole living organisms, with a majority of fused heterocyclic compounds comprising five-membered rings exhibiting significant biological activity. Thiazole-fused heterocycles hold paramount importance in drug discovery due to their varied pharmacological profile and structural versatility. These compounds, which incorporate the thiazole ring as a core moiety, demonstrated a far-reaching range of medicinal activities, viz. antimicrobial, anticancer, anti-inflammatory, and antiviral effects [1, 2]. Thiazole-fused heterocycles also play a fundamental role in the development of pharmaceutical agents, serving as key structural motifs in many drugs [2–4]. Moreover, their unique structural features enable scientists to design and synthesize novel compounds with improved pharmacokinetic and pharmacodynamic profiles [5, 6]. By exploring the synthetic pathways and pharmacological activities of thiazole-fused heterocycles, researchers aim to discover new therapeutic agents to combat various diseases and address unmet medical needs [7]. Therefore, the study and development of thiazole-fused heterocycles represent a significant area of research in modern pharmaceutical sciences, offering promising avenues for the advancement of medicine and healthcare.

In this lieu, several moieties were fused with thiazole scaffold such as pyrrolothiazole, imidazothiazole, benzothiazole, pyrazolothiazole, and pyridazinothiazole, etc. (Fig. 7.1). These compounds exhibit diverse pharmacological activities and are

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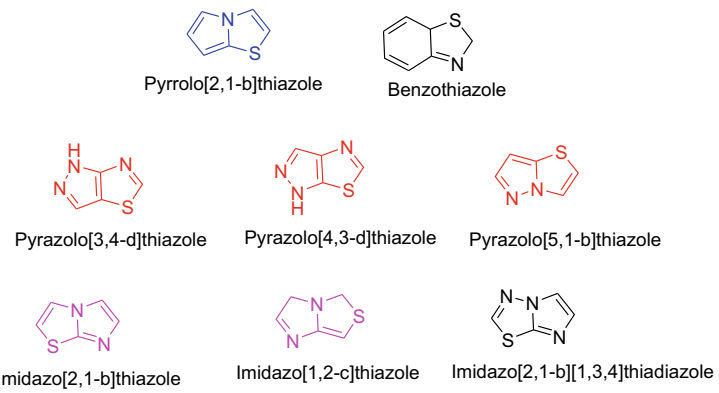


Fig. 7.1 Several thiazole-fused molecules

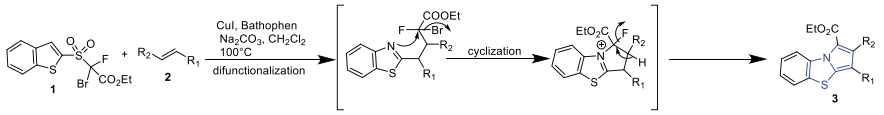
utilized in medicinal chemistry for drug development. Thiazole-fused rings are found in various natural and synthetic compounds, serving as key structural motifs in drug molecules.

This chapter discusses different synthetic aspects that have been employed for pyrrolo[2, 1-b]thiazole, imidazo[2, 1-b]thiazole, and pyrazolo[3, 4-d]thiazole molecules.

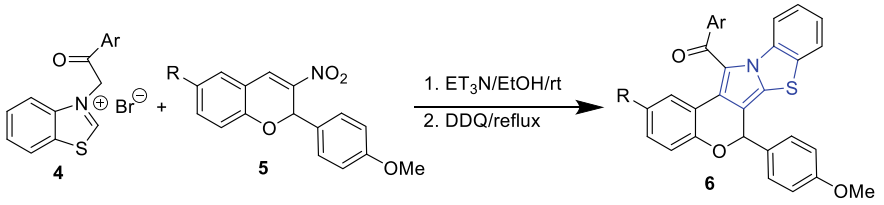
7.2 Synthesis of Pyrrolothiazole

The compounds bearing pyrrolothiazole were found to exhibit excellent pharmacological activities such as anticonvulsant [8], hepatoprotective [9], antitumor [10], anti-inflammatory, antipsychotic, antidiabetic [11], and so on [12]. So, there is an urgent need for advancement of effective synthetic protocols for the synthesis of this molecule. These compounds are commonly synthesized by either creating the bicyclic structure from existing pyrrole or thiazole rings using alkylation and dipolar cycloaddition reactions or by synthesizing them from acyclic precursors.

Numerous pyrrolo[2, 1-b]thiazoles **(3)** have been developed using a reaction of different kinds of alkenes **(2)** with a heterocyclizing reagent using CuI as a catalyst with bathophen as a ligand and Na_2CO_3 as a base in DCM solvent at 100 °C. The reaction involved radical-mediated heteroaryl migration, initiated by single electron transfer (SET) between Cu(I) and the C–Br bond of compound **1**, forming an intermediate and driving the conversion forward. Following the addition of reactant **1** to the alkene, a series of steps including ipso-heteroaryl shift and SO_2 removal occur, resulting in the formation of a radical species. This radical may subsequently abstract a chlorine (Cl) or bromine (Br) atom, further influencing the reaction pathway [13] (Scheme 7.1).



Scheme 7.1 Synthesis of diverse pyrrolo[2, 1-b]thiazoles using CuI as a catalyst



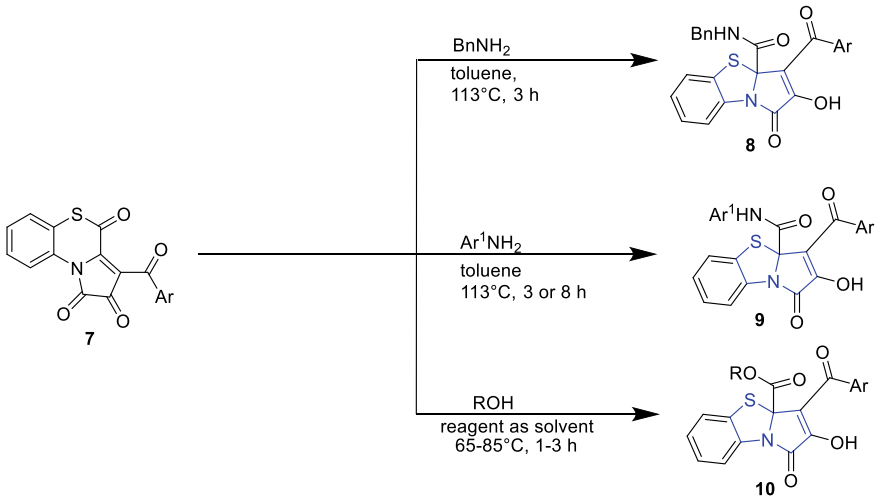
Scheme 7.2 Synthesis of benzo[d]chromeno[3′,4′:3,4]pyrrolo[2, 1-b]thiazoles

A novel two-step pathway has been introduced for the synthesis of benzo[d]chromeno[3′,4′:3,4]pyrrolo[2, 1-b]thiazoles **(6)** using triethylamine-assisted 1,3-dipolar cycloaddition reaction of 3-nitrochromenes **(5)** with 2-phenacyl- or 2-alkoxycarbonylmethylbenzothiazolium bromides **(4)** in ethanol (EtOH) medium at room temperature (RT) followed by sequential oxidation with DDQ at reflux. The reaction was advanced through endo-[3 + 2] cycloaddition of the cyclic dipolarophiles to the in situ generated anti-form ylides [14] (Scheme 7.2).

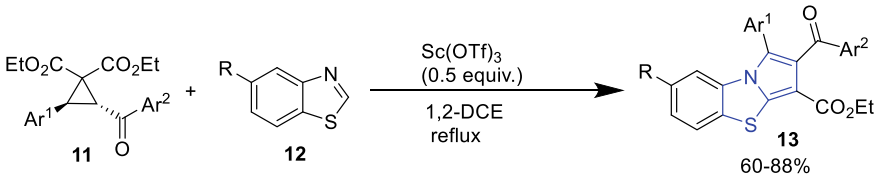
A new approach has been explored for the synthesis of pyrrolo[2, 1-b][1, 3]benzothiazoles **(8, 9 and 10)** through the nucleophile-caused ring contraction of 1,4-benzothiazine. The reaction involved the mixing of several nucleophiles such as arylamine, benzylamines, and alkanols, with 3-aroylpyrrolo[2, 1-c][1, 4]benzothiazine-1,2,4-triones **(7)** and the reaction progressed through cleavage of C-S bond of **7** in the influence of nucleophile to obtain 1-(2-thiophenyl)pyrrole analogs that underwent intramolecular cyclization to furnish the final molecule [15] (Scheme 7.3).

The synthesis of benzo[d]pyrrolo[2, 1-b]thiazoles **(13)** involved a (3 + 2) annulation process in which benzothiazoles **(12)** were reacted with donor − acceptor cyclopropanes substituted with aroyl **(11)**, facilitated by catalytic amount of $Sc(OTf)_3$ in 1,2-dichloroethene (1,2-DCE) at reflux condition. The annulation process resulted in the generation of dearomatized (3 + 2) adducts. Following this, there was an unforeseen occurrence of dehydrogenative and decarbethoxylative rearomatization, leading to the formation of complete aromatized products. This distinct reactivity is ascribed to the existence of an additional aroyl group within the donor − acceptor cyclopropanes [16] (Scheme 7.4).

A two-stage procedure was used to create the pyrrolo[2, 1-b][1, 3]benzothiazoles **(18)**. The first step produced a 92% product yield by employing microwave (MW) irradiation for 10 min at 40 °C to synthesize 2-cyano-methyl-1,3-benzothiazole **(16)**. The compound **16** was then subjected to MW irradiation with several aldehydes at



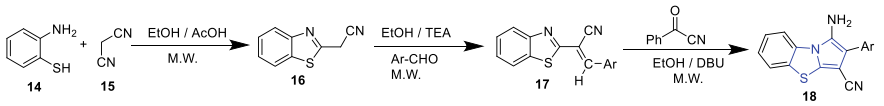
Scheme 7.3 Synthesis of pyrrolo[2, 1-b][1, 3]benzothiazoles through the nucleophile-caused ring contraction



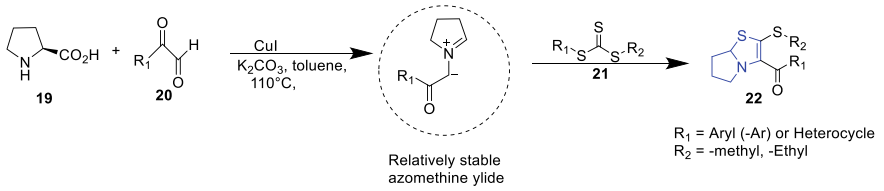
Scheme 7.4 Synthesis of benzo[d]pyrrolo[2, 1-b]thiazoles via (3 + 2) annulation

60 °C in the second phase. This process produced the target compounds **(18)** with higher yields than traditional heating techniques. The two steps of the synthesis were a base-catalyzed Knoevenagel condensation among aldehydes and 2-cyanomethyl-1,3-benzothiazole, which produced 2-arylidenecyanomethyl 1,3-benzothiazoles **(17)** as first step and [4 + 1] cycloaddition of **17** to benzoyl cyanide as the second step [17] (Scheme 7.5).

A different technique produced 5,6,7,8a-tetrahydropyrrolo[2, 1-b]thiazoles **(22)** by decarboxylating proline **(19)** and its analogues to form azomethine ylide in the presence of K_2CO_3 and phenyl glyoxal **(20)**. This was followed by an oxidative [3



Scheme 7.5 Synthesis of the pyrrolo[2, 1-b][1, 3]benzothiazole derivatives via [4 + 1] cycloaddition

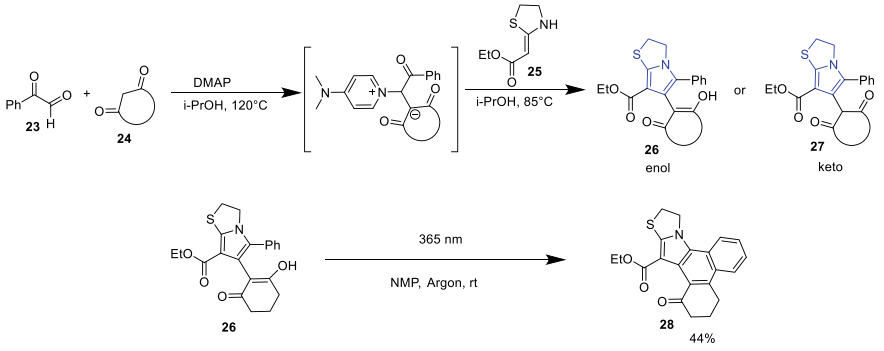


Scheme 7.6 Synthesis of 5,6,7,8a-tetrahydropyrrolo[2, 1-b]thiazoles via azomethine ylide intermediate

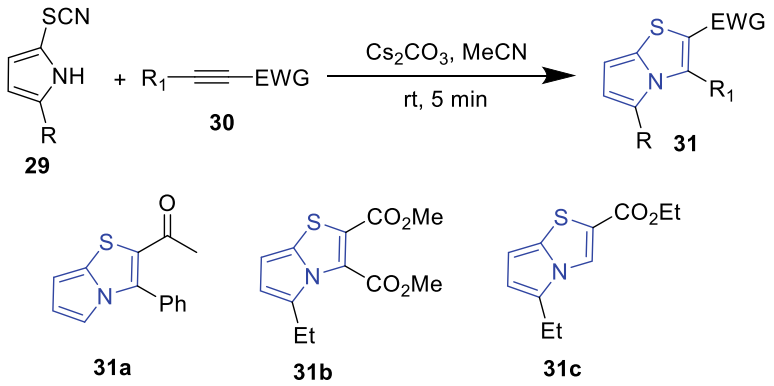
+ 2] cycloaddition reaction with dialkyl trithiocarbonate **(21)**. CuI catalyst acted as the catalyst for this reaction, which had high regiospecificity. This was probably because Cu(I) catalyst was involved in a delayed, symmetry-controlled transition state. Additionally, the reaction demonstrated exceptional tolerance to several proline substitutions, including pipecolinic acid, thiazolidine-4-carboxylic acid, and 4-hydroxyproline, yielding outstanding product yields [18] (Scheme 7.6).

In a two-step, one-pot approach supported by DMAP, 2,3-dihydropyrrolo[2, 1-b]thiazoles were synthesized using ethyl 2-(thiazolidin-2-ylidene)acetate **(25)** as a substrate. This substrate was mixed with several cyclic 1,3-dicarbonyl molecules **(24)**, and phenyl glyoxal **(23)** to produce pyrrolo[2, 1-b]thiazole derivatives, in moderate to excellent yield. Interestingly, pyrrolo[2, 1-b]thiazole **(26)** showed a conjugated benzene diene molecule in its enol form. Moreover, an attempt has been made to create a polyheteroaromatic core using photochemical cyclization. This endeavor led to the formation of the anticipated polyheterocycle **(28)**, achieving a 44% yield when exposed to ultraviolet (UV) irradiation at 365 nm [19] (Scheme 7.7).

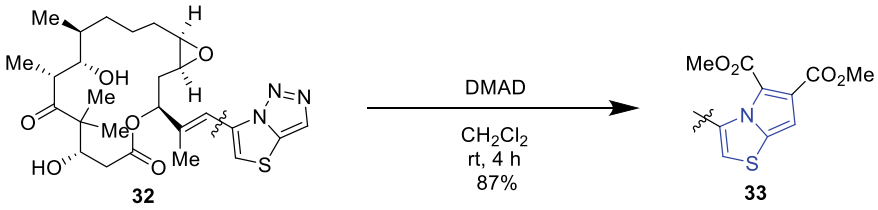
The synthesis of pyrrolothiazoles entailed the interaction between amphiphilic dithioloimines **(29)** and arynes or alkynes **(30)** featuring electron-withdrawing groups. Under standard conditions, the reaction employed Cs_2CO_3 in acetonitrile at RT, resulting in favorable yields of the targeted pyrrolothiazoles **(31)**



Scheme 7.7 Synthesis of 2,3-dihydropyrrolo[2, 1-b]thiazoles using ethyl 2-(thiazolidin-2-ylidene)acetate



Scheme 7.8 Synthesis of pyrrolothiazoles using dithioloimines



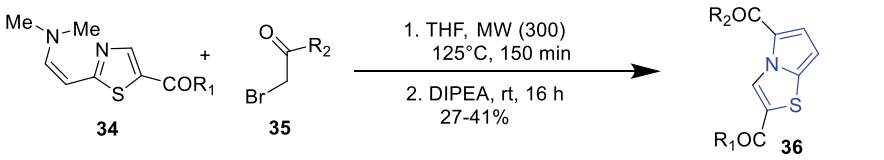
Scheme 7.9 Synthesis of pyrrolo[2, 1-b]thiazole-5,6-dicarboxylate

[20] (Scheme 7.8). In different method, synthesis of pyrrolo[2, 1-b]thiazole-5,6-dicarboxylate **(33)** was achieved through the reaction of triazoloepothilone **(32)** with dimethyl acetylenedicarboxylate (DMAD) in DCM at RT with 87% yield [21] (Scheme 7.9).

By using an innovative synthesis approach, pyrrolo[2, 1-b]thiazoles attached with a protected carbohydrate moiety have been obtained in which MW irradiation helped with the N-alkylation step. A two-step method has been developed to synthesize pyrrolo[2, 1-b]thiazoles substituted with a protected carbohydrate moiety using substituted thiazoles as a starting material. To generate target compounds **(36)**, DIPEA was added after MW irradiation in THF initially mediated the N-alkylation phase [22] (Scheme 7.10).

7.3 Synthesis of Pyrazolothiazoles

Pyrazolothiazoles comprise molecules with a fused structure of pyrazole and thiazole rings. Currently, three systems within this category have been explored in scientific literature, depicted as pyrazolo[4, 3-d]thiazoles, pyrazolo[3, 4-d]thiazoles and pyrazolo[5, 1-b]thiazoles (Fig. 7.2). Research indicates that pyrazolothiazoles



Scheme 7.10 Synthesis of pyrrolo[2, 1-b]thiazoles substituted with a protected carbohydrate moiety

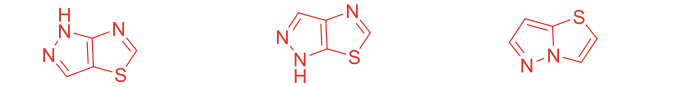


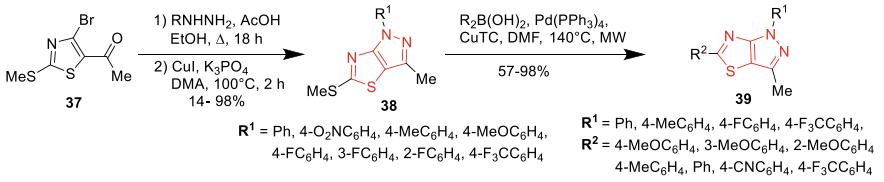
Fig. 7.2 Different kinds of pyrazolothiazoles

possess varied biological functionalities, including their role as an antagonist of the corticotropin-releasing factor 1 [CRF(1)] receptor [23], anti-tubercular activities [24], antimicrobial [25] and protein kinase modulators for cancer [26], and other medical conditions.

Generally, two methods have been employed for synthesizing these types of molecules. One approach involves annulating the pyrazole ring around an existing thiazole molecule, while the other entails annulating the thiazole ring around an existing pyrazole ring. It's noteworthy that the formation of the pyrazole ring around the thiazole ring is more commonly utilized in synthesis [27]. This section describes various procedures that have been developed for the synthesis of pyrazolothiazole moiety in recent times.

*7.3.1 Synthesis of Pyrazolo[3,4-*d*]thiazoles*

The reaction of hydrazines with 1,3-difunctional electrophilic precursors is recognized to be the primary method for producing functionalized and fused pyrazoles. By using this approach, pyrazolo[3, 4-d]-thiazoles **(38)** were created by condensation of 5-acyl-4-bromo-2-(methylsulfanyl)thiazole **(37)** with arylhydrazine or hydrazine to form the pyrazole ring, which was then followed by an intramolecular cyclization catalyzed by copper [28].Then the synthesized compounds were functionalized by reacting with several monosubstituted aromatic boronic acids via Liebeskind–Srogl cross-coupling reaction, using palladium complex as a catalyst under MW irradiation [29] (Scheme 7.11).



Scheme 7.11 Synthesis of pyrazolo[3, 4-d]-thiazoles and their post-functionalization

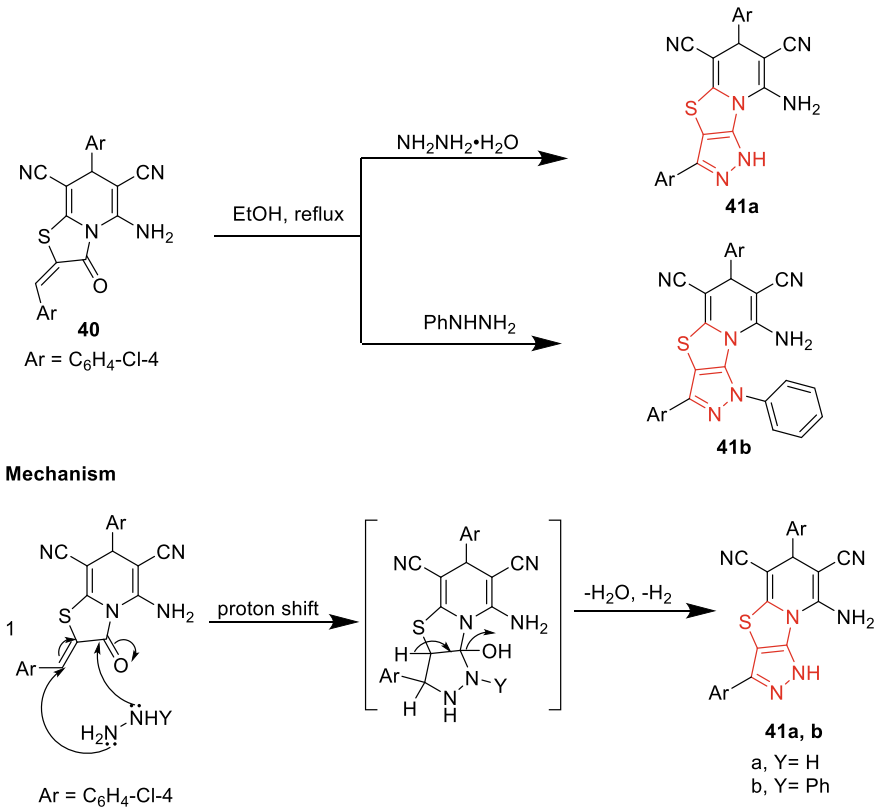
A 5-aminothiazolo[3, 2-a]pyridine derivative **(40)** was effectively converted into pyrazolo[3,4:4,5]thiazolo[3, 2-a]pyridine **(41a, b)** by reacting with hydrazine or aryl-hydrazine in EtOH solvent at reflux condition via intramolecular cyclocondensation followed by the oxidation of cycloadduct [30] (Scheme 7.12). In other study, the pyrazole ring was annulated on thiazolo[3, 2-a]pyrimidine ring structure through reacting phenyl hydrazine with arylidine compounds **43a-e** in EtOH solution under reflux condition using piperidine as a catalyst [31] (Scheme 7.13).

In another approach, two pyrazolo[3, 4-d]-thiazoles **(46a and b)** were synthesized by reacting chalcone **45** with phenyl hydrazine ($PhNHNH_2$) and hydrazine hydrate (NH_2NH_2) using EtOH as a solvent and hydrochloric acid as a catalyst [32] (Scheme 7.14). In a study, first thiazole ring derivatives **(52)** were synthesized by reacting various aldehydes with 4-(1*H*-benzo[d]imidazol-2-yl)thiazol-2-amine **(51)** using EtOH as a solvent and glacial acetic acid (AcOH) as a catalyst afforded compound **(52)** which again reacted with thioglycolic acid and several aldehydes in the presence of zinc chloride in 1,4-dioxane solvent under reflux. Then, the pyrazole ring was annulated on thiazole ring by the condensation of **53** with hydrazine hydrate using glacial AcOH and anhydrous sodium acetate at reflux. In this reaction, **51** was synthesized by condensation of **47** and **48** followed by oxidation of synthesized compound **49** into compound **50** that further reacted with thiourea and yielded **51** [33] (Scheme 7.15).

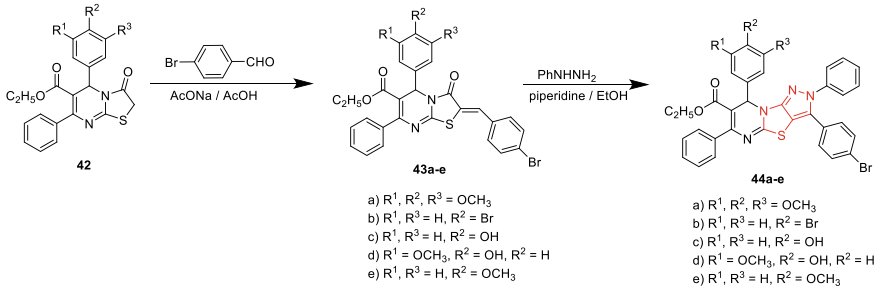
The pyrazolo[3, 4,d]thiazoles **(59)** were synthesized using the condensation of thiazol-2-yl possessing 2-imino-thiazolidin-4-ones **(57)** with various aldehydes in EtOH and sodium acetate that further cyclized with NH_2NH_2 in AcOH [34] (Scheme 7.16). The pyrazolo[3, 4,d]thiazoles **(61a-c)** were synthesized through the reaction of 4-((5-((dimethylamino)methylene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) benzene sulfonamide **(60)** with either $PhNHNH_2$, hydrazinecarbothioamide or NH_2NH_2 in EtOH medium in the presence of Et_3N under reflux condition followed by cyclization and aromatization [35] (Scheme 7.17).

Hantzsch reaction was used for the synthesis of pyrazolo[3, 4-d]thiazole-5-thione analogs **(63)** through annulation of thiazole ring by reaction of 3-methyl-1-tosyl-1*H*-pyrazol-5(4*H*)-one **(62)** and methyl/phenylisothiocyanate with elemental sulfur in the solvent system of dimethylformamide (DMF)/EtOH using influence of Et_3N as a catalyst at reflux conditions [36] (Scheme 7.18).

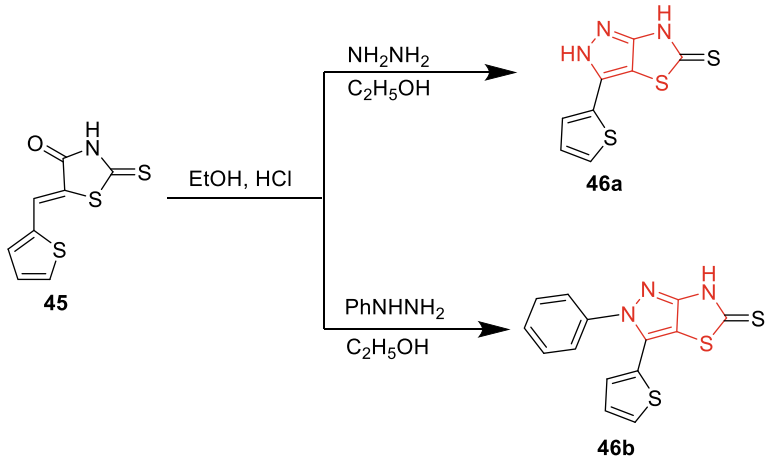
The annulation of thiazole moiety for the synthesis of 3-(pyridin-3-yl)-1-*p*-tolyl-1*H*-pyrazolo [3, 4-d]thiazol-5-amine **(65)** was achieved through reacting KSCN with 3-(pyridin-3-yl)-1-*p*-tolyl-1*H*- pyrazol-5-amine **(64)** in the influence of glacial AcOH



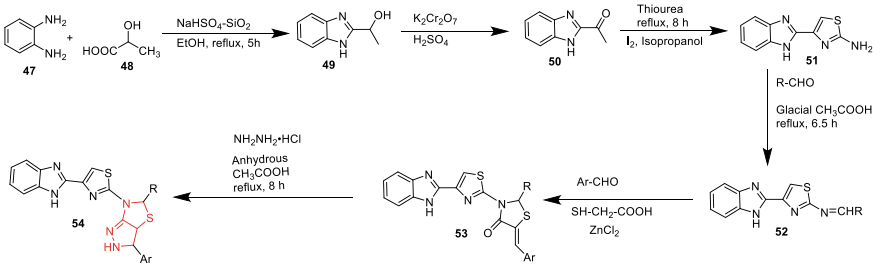
Scheme 7.12 Synthesis and plausible mechanism of synthesis of pyrazolo[3,4:4,5]thiazolo[3, 2-a]pyridine



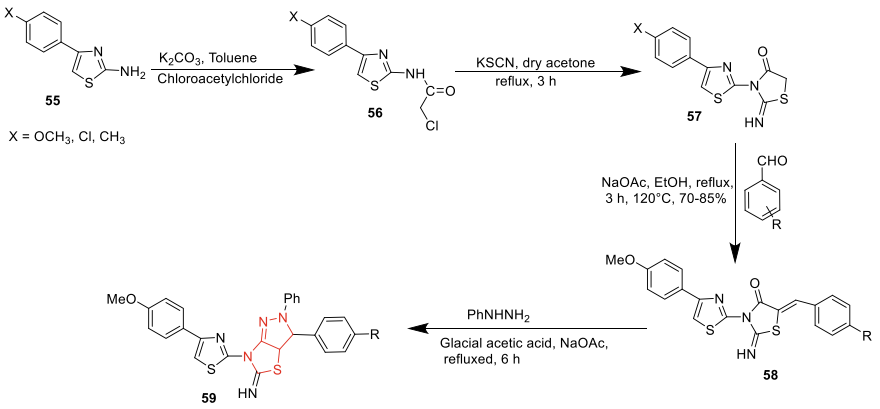
Scheme 7.13 Synthesis of pyrazolo[3, 4-d]-thiazoles via pyrazole ring annulation



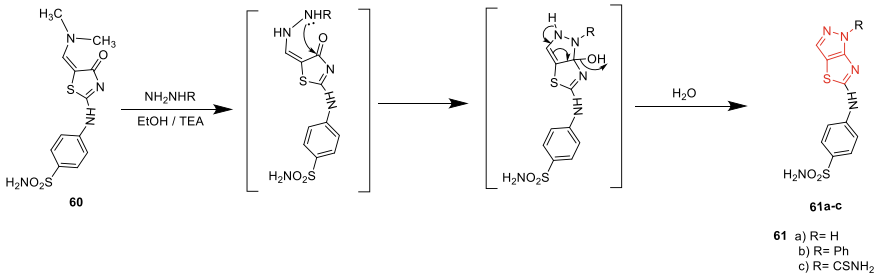
Scheme 7.14 Synthesis of chalcone-substituted pyrazolo[3, 4-d]-thiazoles



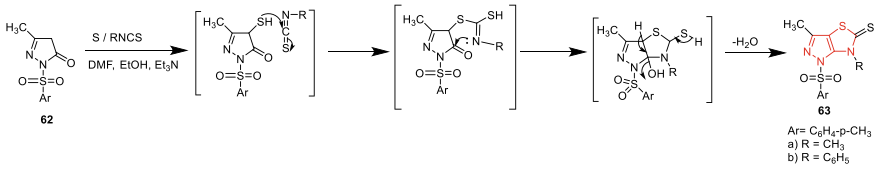
Scheme 7.15 Schematic synthesis of pyrazolo[3, 4-d]-thiazoles using 4-(1*H*-benzo[d]imidazol-2-yl)thiazol-2-amine



Scheme 7.16 Synthesis of pyrazolo[3, 4,d]thiazoles by condensation of thiazol-2-yl-substituted 2-imino-thiazolidin-4-ones



Scheme 7.17 Synthesis of pyrazolo[3, 4,d]thiazoles by condensation of 4-((5-((dimethylamino)methylene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) benzene sulfonamide



Scheme 7.18 Synthesis of pyrazolo[3, 4-d]thiazole-5-thione derivatives

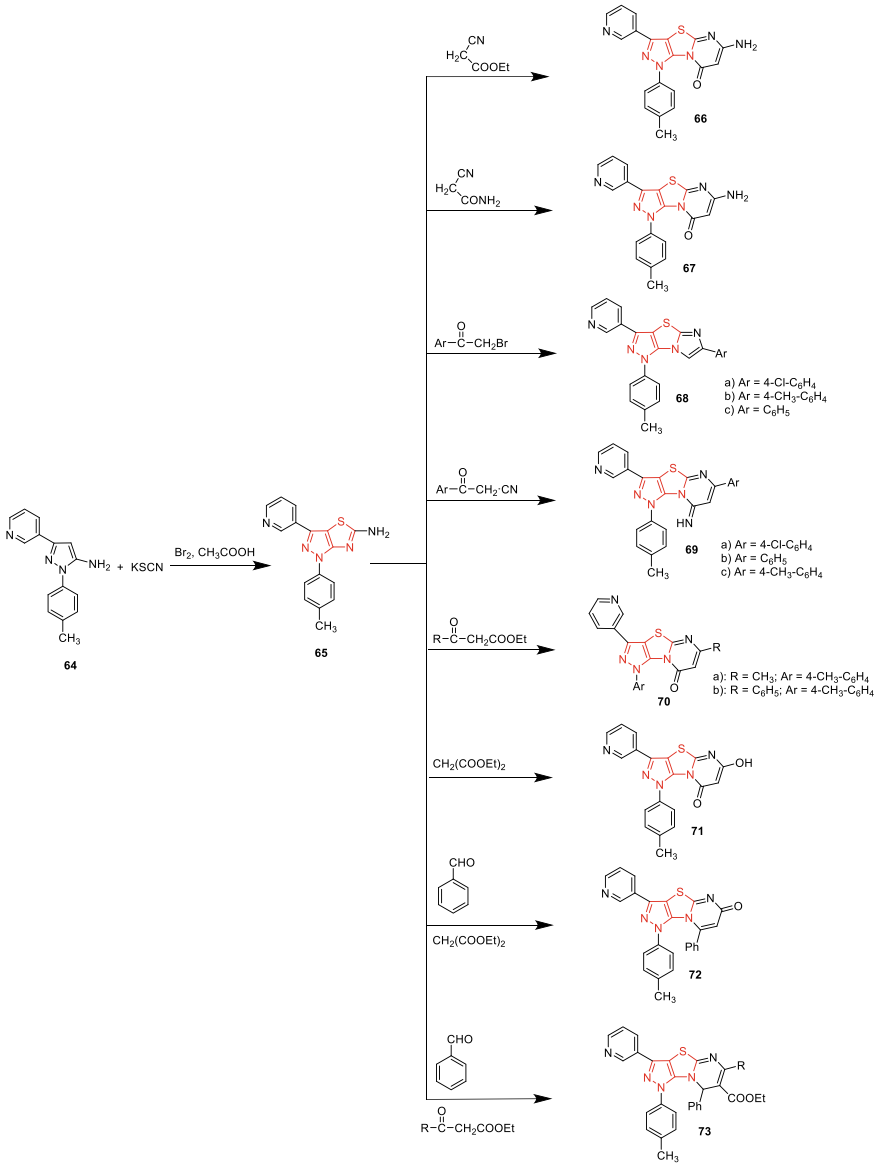
and bromine. Then, 3-(pyridin-3-yl)-1-*p*-tolyl-1*H*-pyrazolo[3, 4-d]thiazol-5-amine **(65)** was employed as versatile precursor for the synthesis of novel fused heterocyclic moieties containing imidazoles or pyrimidines **(66–73)** [37] (Scheme 7.19).

*7.3.2 Synthesis of Pyrazolo[4,3-*d*]thiazoles*

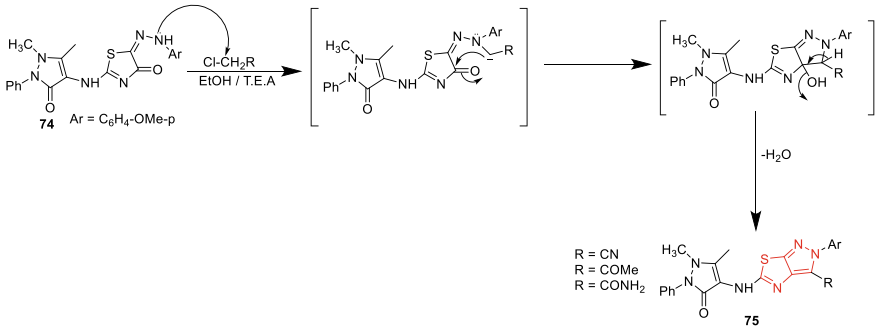
Pyrazolo[4, 3-d]thiazole derivatives **(75)** were synthesized by the condensation of hydrazone derivative **(74)** with different halo compounds such as chloroacetone, chloroacetamide, or chloroacetonitrile using EtOH as a solvent and triethylamine as a catalyst under reflux condition followed by cyclization and tautomerism to form pyrazole ring [38] (Scheme 7.20).

*7.3.3 Synthesis of Pyrazolo[5,1-*d*]thiazoles*

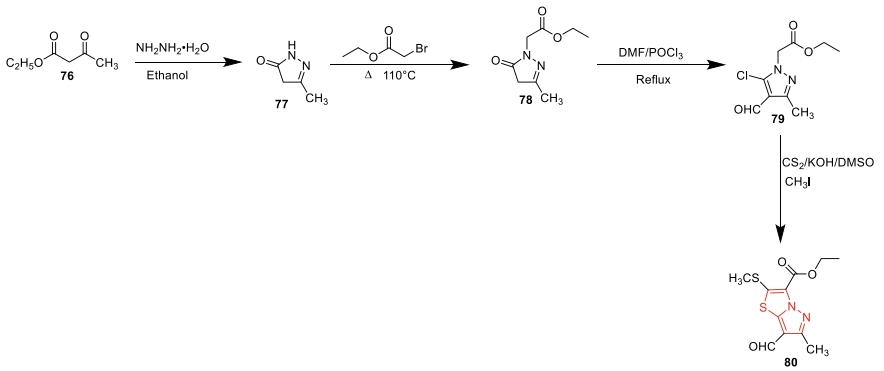
Fused pyrazolo[5, 1-b]thiazole aldehyde **(80)** were synthesized by multiple step reactions that include synthesis of 3-methylpyrazolone **(77)** from the condensation of ethyl acetoacetate with hydrazine hydrate in EtOH that again reacted at 110 °C with ethyl bromoacetate and obtained pyrazolone-acetate **(78)**. Further, pyrazolone-acetate underwent formylation via Vilsmeier–Haack reaction using DMF and phosphorus oxychloride and afforded pyrazolone-acetate-substituted aldehyde **(79)**. At



Scheme 7.19 Synthesis of 3-(pyridin-3-yl)-1-*p*-tolyl-1*H*-pyrazolo [3, 4-d]thiazol-5-amine and their post-functionalization



Scheme 7.20 Synthesis of pyrazolo[4, 3-d]thiazole derivatives



Scheme 7.21 Synthesis of fused pyrazolo[5, 1-b]thiazole aldehyde

last, prepared aldehyde was reacted with potassium hydroxide and CS_2 in DMSO solvent in the presence of iodomethane furnished the fused pyrazolo[5, 1-b]thiazole aldehyde **(80)** [39] (Scheme 7.21).

7.3.4 Synthesis of Imidazothiazole

The imidazothiazole core demonstrates versatile therapeutic applications, including antihelminthic [40, 41], antitumor [42–45], anti-inflammatory [46], cardiotonic [47], antiviral [48], antiparasitic [49], anti-hypertensive [50], fungicidal [51–53], antibacterial [54–56], and antioxidant properties [57]. Notably, Levamisole, a crucial imidazothiazole derivative, is extensively utilized in cancer therapy (Fig. 7.3). Additionally, imidazothiazoles serve as potent IDO1 inhibitors, aiding in cancer treatment [57]. Furthermore, derivatives of imidazothiazoles (imidazo[2, 1-b]thiazole and

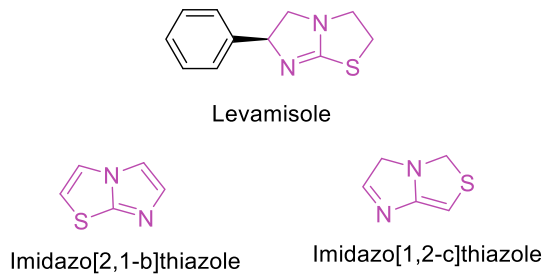


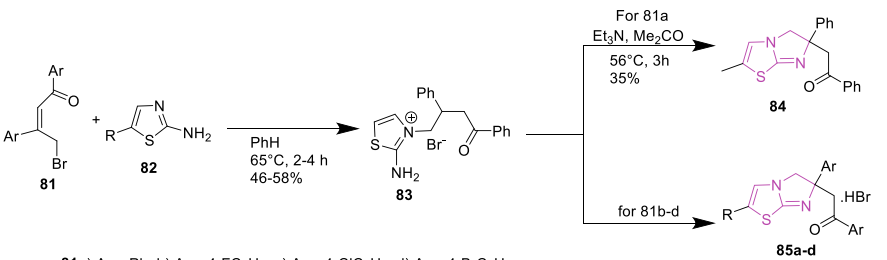
Fig. 7.3 Different kinds of imidazothiazole and biologically active compounds

imodazo[1, 2-c]thiazole (Fig. 7.3) exhibit potential as HIV-1 RT inhibitors, emphasizing their significance in medicinal chemistry [59]. These diverse pharmacological roles underscore the usefulness of imidazothiazole moieties in drug discovery. Consequently, the synthesis of these moiety holds predominant importance in organic chemistry. This section presents several approaches that have been incorporated for the development of imidazothiazole analogs.

An effective approach has been explored for the synthesis of imidazo[2, 1-b][1, 3]thiazole compounds **(84 and 85)** by condensation of (2Z)-1,3-diaryl-4-bromobut-2-en-1-one analogs **(81)** with 2-aminothiazoles **(82)** in the presence of base. The reaction underwent through Michael addition via cyclization using base as a catalyst [60] (Scheme 7.22).

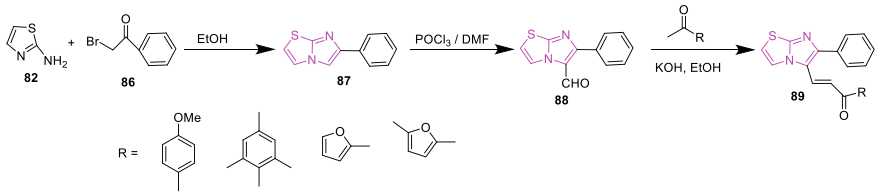
In a different work, aldehyde with various methyl ketone was subjected to Claisen–Schmidt condensation to create derivatives of imidazothiazoles replaced with chalcone. Through cyclocondensation of 2-aminothiazole **(82)** and an α-halogenated carbonyl molecule **(86)** in the presence of EtOH, imidazo[2, 1-b]thiazole **(87)** was produced. Imidazo[2, 1-b]thiazole carbaldehyde **(88)** was produced using the Vilsmeier–Haack reaction with the resultant product **87** in phosphoryl chloride ($POCl_3$) and DMF. Further, the chalcone derivatives **(89)** were synthesized by the reaction of aromatic aldehyde **88** and different methyl ketones in the presence of KOH and EtOH [61] (Scheme 7.23).

In order to synthesize imidazothiazole derivatives, α-bromo-3(4)-methoxyacetophenone **(90)** was cyclized with 2-amino-thiazole **(82)** in EtOH

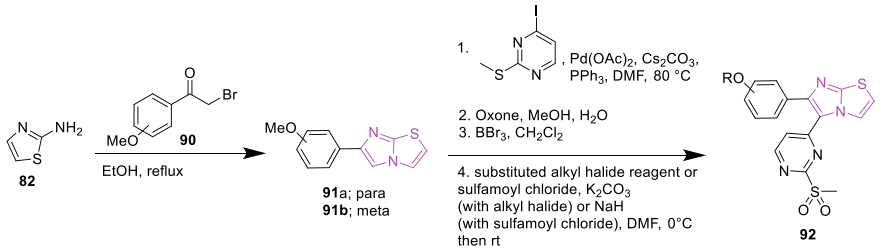


81a) Ar = Ph, b) Ar = 4-FC_6H_4, c) Ar = 4-ClC_6H_4, d) Ar = 4-BrC_6H_4;
85a) Ar = 4-FC_6H_4, R = H; b) Ar = 4-FC_6H_4, R = Me; c) Ar = 4-ClC_6H_4, d) Ar = 4-BrC_6H_4, R = H

Scheme 7.22 Synthesis of imidazo[2, 1-b] [1, 3] thiazoles



Scheme 7.23 Synthesis of imidazo[2, 1-b]thiazole by cyclocondensation between 2-aminothiazole and an α-halogenated carbonyl compound



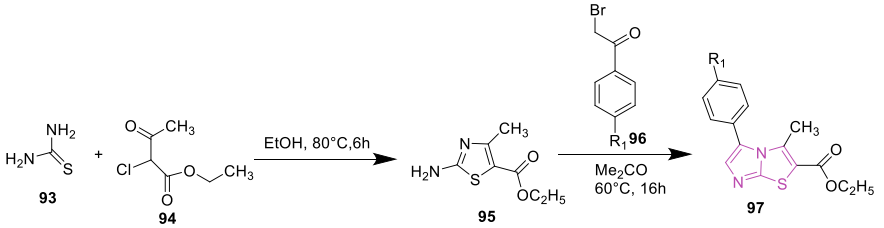
Scheme 7.24 Synthesis of imidazo[2, 1-b]thiazole by cyclization of α-bromo-3(4)-methoxyacetophenone with 2-amino-thiazole

at reflux to produce intermediates **(91)**. These intermediates were then reacted with 4-iodo-2-(methylthio)pyrimidine in the influence of caesium carbonate, triphenylphosphine as a ligand, and palladium (II) acetate as a catalyst to form compounds. Oxone was used to produce the methylsulfide's subsequent oxidation to sulfone. The next step was to use boron tribromide to remove the methoxy group from molecules, which produced the equivalent hydroxyl counterparts. The required target derivatives **(92)** were obtained in the last stage by adding alkyl halide or sulfamoyl chloride using potassium carbonate or sodium hydride, respectively [62] (Scheme 7.24).

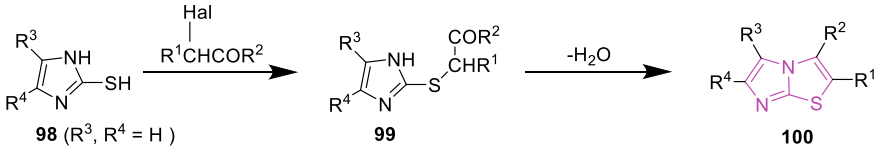
3-Methyl-imidazo[2, 1-b]thiazole-based analogs **(97)** were prepared in two steps, initially precursor 2-amino-4-methylthiazole-5-carboxylate **(95)** was synthesized by the reaction of thiourea **(93)** with 2-chloroacetoacetate **(94)** in EtOH medium at reflux, then it was reacted with different 2-bromo-1-(4-substituted phenyl)ethanone analogs **(96)** at 60 °C in acetone solvent and yielded the target compounds **(97)** [63] (Scheme 7.25).

When 2-mercaptoimidazole **(98)** underwent reaction with aliphatic alpha-halogenoketones in EtOH or butanol in the absence of alkali, it led to a cyclization reaction, resulting in the production of imidazo[2, 1-b]thiazoles **(100)** [64] (Scheme 7.26).

For the synthesis of triazole-substituted imidazothiazole analogs **(106)**, a multi-step reaction strategy was employed. The process initiated with the treatment



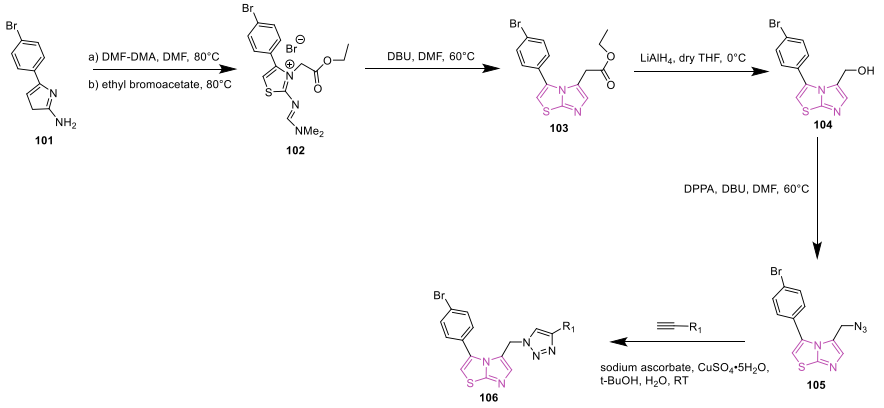
Scheme 7.25 Synthesis of 3-methyl-imidazo[2, 1-b]thiazole-based analogs



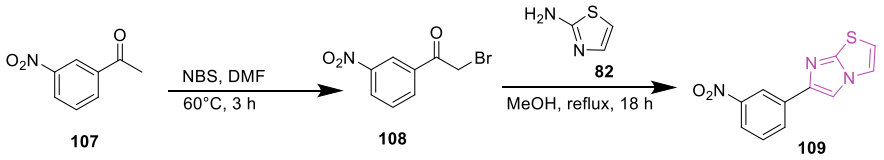
R^1 = H, Ac: R^2 = Alk, Ar: R^3 = H, Ar: R^4 = H, Ar

Scheme 7.26 Synthesis of imidazo[2, 1-b]thiazoles using 2-mercaptoimidazole

of 4-(4-bromophenyl)thiazol-2-amine **(101)** using ethyl bromoacetate and DMF-dimethylacetamide (DMA), leading to the formation of intermediate **102**. Subsequently, intermediate **102** underwent an intramolecular cyclization, followed by reduction, resulting in the formation of compound **103**. This compound, in turn, reacted with DPPA to yield azide **105**. Expanding the scope, alkynes were carefully selected, and target compounds **(106)** were synthesized through the utilization of click chemistry reactions under classical conditions. The comprehensive approach provides insights into the systematic and controlled synthesis of these specialized imidazothiazoles [58] (Scheme 7.27).



Scheme 7.27 Synthesis of triazole-substituted imidazothiazoles



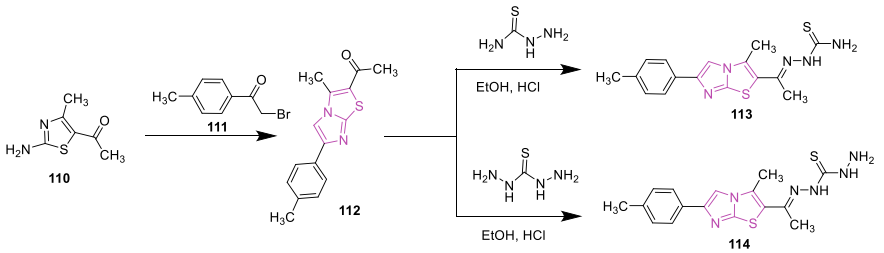
Scheme 7.28 Synthesis of imidazothiazole derivatives using 3′-nitroacetophenone

When 3′-nitroacetophenone **(107)** reacts with N-bromosuccinamide in DMF, α-bromination takes place, yielding compound **107.** Subsequently, compound **108** underwent reflux with 2-aminothiazole **(82)** in MeOH, resulting in the formation of compound **109**. This synthetic pathway outlines the stepwise conversion of 3′-nitroacetophenone into the targeted compound **109** through controlled chemical reactions [65] (Scheme 7.28).

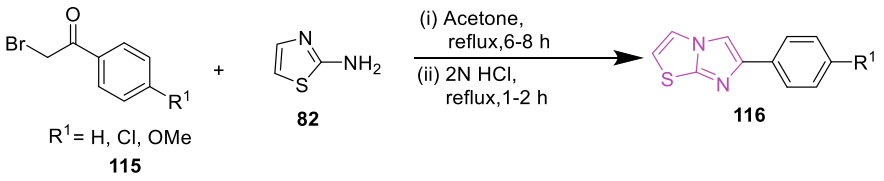
2-Acetyl-(3-methyl-6-(substituted)-imidazo[2, 1-b]thiazoles **(113 and 114)** were synthesized by the cyclization of phenacylbromide derivative **(111)** with 5-acetyl-2-amino-4-methylthiazole **(110)**, which further underwent condensation with thiosemicarbazide and thiocarbohydrazide in refluxing EtOH/HCl, respectively [66] (Scheme 7.29).

In a different approach, imidazo[2, 1-b]thiazoles **(116)** were synthesized through reacting 2-aminothiazole **(82)** with 2-bromoacetophenone **(115)** in acetone under reflux followed by addition of HCl [67] (Scheme 7.30).

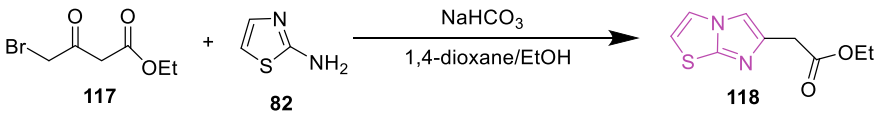
In another study, 2-aminothiazole **(82)** reacted with ethyl 4-bromoacetoacetate **(117)** in the influence of sodium bicarbonate as a catalyst and mixture of 1,4-dioxane



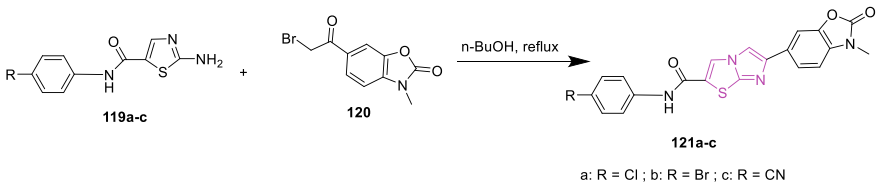
Scheme 7.29 Synthesis of 2-acetyl-(3-methyl-6-(substituted)-imidazo[2, 1-b]thiazole



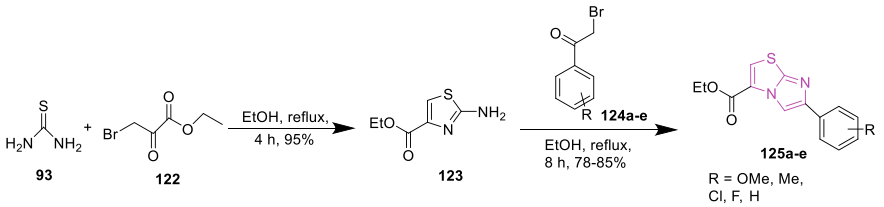
Scheme 7.30 Synthesis of imidazo[2, 1-b]thiazoles



Scheme 7.31 Synthesis of ethyl imidazo[2, 1-b] thiazole-6-yl acetate



Scheme 7.32 Synthesis of benzoxazole-substituted imidazo[2, 1-b][1, 3]thiazole-2-carboxamides



Scheme 7.33 Synthesis of imidazothiazole derivatives via two-step approach

and EtOH as solvent system afforded the ethyl imidazo[2, 1-b] thiazole-6-yl acetate **(118)** in significant yield [68] (Scheme 7.31).

A series of benzoxazole-substituted imidazo[2, 1-b][1, 3]thiazole-2-carboxamide derivatives **(121a-c)** were synthesized by the condensation of 1,3-thiazole-5-carboxamides **119a-c** with benzoxazole **120** in n-butanol at reflux condition followed by cyclization [69] (Scheme 7.32).

Imidazothiazole derivatives were synthesized in two-step reaction in which initially thiourea **(93)** was condensed with ethyl bromopyruvate **(122)** in EtOH under reflux which afforded ethyl-2-aminothiazole-4-carboxylate **(123)** as an intermediate, which further reacted with several phenacyl bromides **(124a-e)** in EtOH medium and underwent cyclization reaction to obtain the desired compounds **(125a-e)** [70] (Scheme 7.33).

7.3.5 Conclusion

The synthesis of fused pyrollothiazole, pyrazolothiazole, and imidazothiazole compounds represents a significant advancement in heterocyclic chemistry with profound implications for drug discovery and development. Through innovative

synthetic methodologies, researchers have successfully accessed these complex heterocyclic scaffolds, paving the way for the exploration of their diverse pharmacological properties.

The biological significance of these compounds is underscored by their therapeutic potential across various diseases, including cancer, infectious diseases, inflammation, and neurological disorders. Leveraging the synthetic versatility of these frameworks, medicinal chemists can tailor molecular structures to optimize drug-like properties and enhance biological activity, thereby accelerating the development of novel therapeutics.

Moreover, computational modeling and mechanistic studies have provided invaluable insights into reaction pathways and structure–activity relationships, facilitating rational design strategies for the synthesis of next-generation analogs with improved pharmacokinetic profiles and target selectivity.

In conclusion, the synthesis of fused pyrollothiazole, pyrazolothiazole, and imidazothiazole derivatives represents a dynamic field at the intersection of organic synthesis and medicinal chemistry, offering exciting opportunities for the discovery of therapeutically relevant compounds with enhanced efficacy and safety profiles.

References

1. Chhabria MT, Patel S, Modi P, Brahmkshatriya PS (2016) Thiazole: a review on chemistry, synthesis and therapeutic importance of its derivatives. Curr Top Med Chem 16:2841–2862
2. Ayati A, Emami S, Asadipour A, Shafiee A, Foroumadi A (2015) Recent applications of 1,3-thiazole core structure in the identification of new lead compounds and drug discovery. Eur J Med Chem 97:699–717
3. Arshad MF, Alam A, Alshammari AA, Alhazza MB, Alzimam IM, Alam MA, Mustafa G, Ansari MS, Alotaibi AM, Alotaibi AA, Kumar S, Asdaq SMB, Imran M, Deb PK, Venugopala KN, Jomah S (2022) Thiazole: a versatile standalone moiety contributing to the development of various drugs and biologically active agents. Molecules 27
4. Gümüş M, Yakan M, Koca İ (2019) Recent advances of thiazole hybrids in biological applications. Future Med Chem 11:1979–1997
5. Abdu-Rahem LR, Ahmad AK, Abachi FT (2021) Synthesis and medicinal attributes of thiazole derivatives: a review. Sys Rev Pharm 12:290–295
6. Kashyap SJ, Garg VK, Sharma PK, Kumar N, Dudhe R, Gupta JK (2012) Thiazoles: having diverse biological activities. Med Chem Res 21:2123–2132
7. Ali SH, Sayed AR (2021) Review of the synthesis and biological activity of thiazoles. Synth Commun 51:670–700
8. Trapani G, Franco M, Latrofa A, Carotti A, Cellamare S, Serra M, Ghiani CA, Tuligi G, Biggio G, Liso G (2011) Synthesis and anticonvulsant activity of some 1,2,3,3a-tetrahydropyrrolo[2,1-b]-benzothiazol-, -thiazol-or -oxazol−1−ones in Rodents. J Pharm Pharmacol 48:834–840
9. Hasegawa M, Nakayama A, Yokohama S, Hosokami T, Kurebayashi Y, Ikeda T, Shimoto Y, Ide S, Honda Y, Suzuki N (1995) Synthesis and pharmacological activities of novel bicyclic thiazoline derivatives as hepatoprotective agents. II. (7-alkoxycarbonyl-2, 3, 5, 6-tetrahydropyrrolo[2,1-b]thiazol-3-ylidene)acetamide derivatives. Chem Pharm Bull 43:1125–1131
10. Soares MIL, Brito AF, Laranjo M, Paixão JA, Botelho MF, Pinho e Melo TMVD (2013) Chiral 6,7-bis(hydroxymethyl)-1*H*,3*H*-pyrrolo[1,2-c]thiazoles with anti-breast cancer properties. Eur J Med Chem 60:254–262

11. Aicher TD, Balkan B, Bell PA, Brand LJ, Cheon SH, Deems RO, Fell JB, Fillers WS, Fraser JD, Gao J, Knorr DC, Kahle GG, Leone CL, Nadelson J, Simpson R, Smith HC (1998) Substituted tetrahydropyrrolo[2,1-b]oxazol-5(6*H*)-ones and tetrahydropyrrolo[2,1-b]thiazol-5(6*H*)-ones as hypoglycemic agents. J Med Chem 41:4556–4566
12. Fascio ML, Errea MI, D'Accorso NB (2015) Imidazothiazole and related heterocyclic systems. Synthesis, chemical and biological properties. Eur J Med Chem 90:666–683
13. Zhang H, Wang M, Wu X, Zhu C (2021) Heterocyclization reagents for rapid assembly of N-fused heteroarenes from alkenes. Angew Chem 60:3714–3719
14. Jiang W, Sun J, Yan C-G (2017) Diastereoselective synthesis of benzo[d]chromeno[3′,4′:3,4]pyrrolo[2,1-b]thiazoles via cycloaddition reaction of benzothiazolium salts with 3-nitrochromenes. RSC Adv 7:42387–42392
15. Lystsova EA, Dmitriev MV, Maslivets AN, Khramtsova EE (2023) Nucleophile-induced ring contraction in pyrrolo[2,1-c][1,4]benzothiazines: access to pyrrolo[2,1-b][1,3]benzothiazoles. Beilstein J Org Chem 19:646–657
16. Thangamalar S, Srinivasan K (2023) Tandem dearomative/rearomative (3+2) annulation of aroyl-substituted donor–acceptor cyclopropanes with benzothiazoles. J Org Chem 88:3903–3907
17. Al-Mutairi AA, Hafez HN, El-Gazzar A-RBA, Mohamed MYA (2022) Synthesis and antimicrobial, anticancer and anti-oxidant activities of novel 2,3-dihydropyrido[2,3-d]pyrimidine-4-one and pyrrolo[2,1-b][1,3]benzothiazole derivatives via microwave-assisted synthesis. Molecules 27:1246
18. Molla SA, Ghosh D, Basak A, Khamarui S, Maiti DK (2023) Cu(I)-catalysed cross-coupling reaction of in situ generated azomethine ylides towards easy construction of fused N-heterocycles. Chem Commun 59:4664–4667
19. Peshkov AA, Gapanenok D, Puzyk A, Amire N, Novikov AS, Martynova SD, Kalinin S, Dar'in D, Peshkov VA, Krasavin M (2023) Substrate-controlled three-component synthesis of diverse fused heterocycles. J Org Chem 88:10508–10524
20. Pawliczek M, Garve LKB, Werz DB (2015) Exploiting amphiphilicity: facile metal free access to thianthrenes and related sulphur heterocycles. Chem Commun 51:9165–9167
21. Ranade AR, Higgins L, Markowski TW, Glaser N, Kashin D, Bai R, Hong KH, Hamel E, Höfle G, Georg GI (2016) Characterizing the epothilone binding site on β-tubulin by photoaffinity labeling: identification of β-tubulin peptides TARGSQQY and TSRGSQQY as targets of an epothilone photoprobe for polymerized tubulin. J Med Chem 59:3499–3514
22. Barradas JS, Errea MI, Sepúlveda C, Damonte EB, D'Accorso NB (2014) Microwave-assisted synthesis of pyrrolo[2,1-b]thiazoles linked to a carbohydrate moiety. J Heterocycl Chem 51:96–100
23. Takahashi Y, Hashizume M, Shin K, Terauchi T, Takeda K, Hibi S, Murata-Tai K, Fujisawa M, Shikata K, Taguchi R, Ino M, Shibata H, Yonaga M (2012) 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 55:8450–8463
24. Lu X, Tang J, Liu Z, Li M, Zhang T, Zhang X, Ding K (2016) Discovery of new chemical entities as potential leads against *Mycobacterium tuberculosis.* Bioorg Med Chem Lett 26:5916–5919
25. Alsayari A, Muhsinah AB, Asiri YI, Al-Aizari FA, Kheder NA, Almarhoon ZM, Ghabbour HA, Mabkhot YN (2021) Synthesis, characterization, and biological evaluation of some novel pyrazolo[5,1-b]thiazole derivatives as potential antimicrobial and anticancer agents. Molecules 26
26. Abdel-Wahab BF, Mohamed HA (2013) Pyrazolothiazoles: synthesis and applications. Phosphorus, Sulfur Relat Elem 188:1680–1693
27. Khodykina ES, Kolodina AA (2023) Recent methods for the synthesis of fused pyrazolo[3,4(4,3)-d]thiazoles and pyrazolo[3,4(4,3)-d][1,4]thiazines. Chem Heterocycl Compd 59:643–645
28. Ostache N-C, Hiebel M-A, Fînaru A-L, Guillaumet G, Suzenet F (2019) Copper-assisted synthesis of novel pyrazolo[3,4-d]thiazoles. ChemCatChem 11:3530–3533

29. Ostache N-C, Paris A, Hiebel M-A, Fînaru A-L, Daniellou R, Suzenet F, Guillaumet G (2022) Cytotoxic evaluation of original pyrazolo[3,4-d]thiazoles and pyrazolo[3,4-c]pyrazoles. Farmacia 70:258–265
30. Mahmoud NFH, Balamon MG (2020) Synthesis of various fused heterocyclic rings from thiazolopyridine and their pharmacological and antimicrobial evaluations. J Heterocycl Chem 57:3056–3070
31. Nemr MTM, Sonousi A, Marzouk AA (2020) Design, synthesis and antiproliferative evaluation of new tricyclic fused thiazolopyrimidines targeting topoisomerase II: molecular docking and apoptosis inducing activity. Bioorg Chem 105:104446
32. El-Sattar N, Badawy EHK, AbdEl-Hady WH, Abo-Alkasem MI, Mandour AA, Ismail NSM (2021) Design and synthesis of new CDK2 inhibitors containing thiazolone and thiazolthione scafold with apoptotic activity. Chem Pharm Bull 69:106–117
33. Gullapelli K, Maroju R, Merugu R (2021) An efficient synthesis, in-vitro and in-silco evaluation of new pyrazole and isoxazole derivatives as anti-inflammatory agents. Indian J Chem Technol 28:343–350
34. Kasralikar HM, Jadhavar SC, Goswami SV, Kaminwar NS, Bhusare SR (2019) Design, synthesis and molecular docking of pyrazolo-[3,4d]-thiazole hybrids as potential anti-HIV-1 NNRT inhibitors. Bioorg Chem 86:437–444
35. Othman IMM, Gad-Elkareem MAM, Radwan HA, Badraoui R, Aouadi K, Snoussi M, Kadri A (2021) Synthesis, structure-activity relationship and in silico studies of novel pyrazolothiazole and thiazolopyridine derivatives as prospective antimicrobial and anticancer agents. ChemistrySelect 6:7860–7872
36. Alamshany ZM, Algamdi EM, Othman IMM, Anwar MM, Nossier ES (2023) New pyrazolopyridine and pyrazolothiazole-based compounds as anti-proliferative agents targeting c-Met kinase inhibition: design, synthesis, biological evaluation, and computational studies. RSC Adv 13:12889–12905
37. Rizk HF, El-Borai MA, Ragab A, Ibrahim SA (2020) Design, synthesis, biological evaluation and molecular docking study based on novel fused pyrazolothiazole scaffold. J Iran Chem Soc 17:2493–2505
38. Alamshany ZM (2024) Design, synthesis, and antimicrobial evaluation of new antipyrine derivatives bearing thiazolopyridazine and pyrazolothiazole scaffolds. Synth Commun 54:22–40
39. Berry S, Bari SS, Yadav P, Garg A, Khullar S, Mandal SK, Bhalla A (2020) Stereoselective synthesis of trans-3-functionalized-4-pyrazolo[5,1-b]thiazole-3-carboxylate substituted β-lactams: potential synthons for diverse biologically active agents. Synth Commun 50:2969–2980
40. Amarouch H, Loiseau PR, Bacha C, Caujolle R, Payard M, Loiseau PM, Bories C, Gayral P (1987) Imidazo[2,1-b]thiazoles: analogues du lévamisole. Eur J Med Chem 22:463–466
41. Robert JF, Boukraa S, Panouse JJ, Loppinet V, Chaumont JP (1990) Derivatives of the imidazo[2,1-b]thiazoles X. Fungistatic properties of 2-aminothiazoles and 6-arylimidazo[2,1-b]-thiazoles respectively substituted in 4 and in 3 by arylethyl, aroylmethyl, β-hydroxy β-arylethyl and ethoxycarbonylmethyl groups. Eur J Med Chem 25:731–736
42. Andreani A, Rambaldi M, Locatelli A, Bossa R, Fraccari A, Galatulas I (1993) Potential antitumor agents. XXII. Synthesis and cytotoxic activity of imidazo[2,1-b]thiazole adamantylthioureas. J Pharm Belg 48:378–382
43. Gürsoy E, Güzeldemirci NU (2007) Synthesis and primary cytotoxicity evaluation of new imidazo[2,1-b]thiazole derivatives. Eur J Med Chem 42:320–326
44. Park J-H, El-Gamal MI, Lee YS, Oh C-H (2011) New imidazo[2,1-b]thiazole derivatives: synthesis, in vitro anticancer evaluation, and in silico studies. Eur J Med Chem 46:5769–5777
45. Andreani A, Burnelli S, Granaiola M, Leoni A, Locatelli A, Morigi R, Rambaldi M, Varoli L, Calonghi N, Cappadone C, Farruggia G, Zini M, Stefanelli C, Masotti L, Radin NS, Shoemaker RH (2008) New antitumor imidazo[2,1-b]thiazole guanylhydrazones and analogues. J Med Chem 51:809–816

46. Jadhav VB, Kulkarni MV, Rasal VP, Biradar SS, Vinay MD (2008) Synthesis and anti-inflammatory evaluation of methylene bridged benzofuranyl imidazo[2,1-b][1,3,4]thiadiazoles. Eur J Med Chem 43:1721–1729
47. Andreani A, Rambaldi M, Locatelli A, Bossa R, Galatulas I, Ninci M (1992) Synthesis and cardiotonic activity of 2, 5-dimethoxyphenylimidazo[2, 1-b]thiazoles. Eur J Med Chem 27:431–433
48. Barradas JS, Errea MI, D'Accorso NB, Sepúlveda CS, Damonte EB (2011) Imidazo[2,1-b]thiazole carbohydrate derivatives: synthesis and antiviral activity against Junin virus, agent of Argentine hemorrhagic fever. Eur J Med Chem 46:259–264
49. Scribner A, Meitz S, Fisher M, Wyvratt M, Leavitt P, Liberator P, Gurnett A, Brown C, Mathew J, Thompson D, Schmatz D, Biftu T (2008) Synthesis and biological activity of anticoccidial agents: 5,6-Diarylimidazo[2,1-b][1,3]thiazoles. Bioorg Med Chem Lett 18:5263–5267
50. Budriesi R, Ioan P, Locatelli A, Cosconati S, Leoni A, Ugenti MP, Andreani A, Di Toro R, Bedini A, Spampinato S, Marinelli L, Novellino E, Chiarini A (2008) Imidazo[2,1-b]thiazole system: a scaffold endowing dihydropyridines with selective cardiodepressant activity. J Med Chem 51:1592–1600
51. Gupta GD, Jain KK, Gupta RP, Pujari HK (1983) Heterocyclic-systems containing bridgehead nitrogen atom.46. Reaction of 4,5-disubstituted 2-mercapto imidazoles with alpha-halogenoketones and 1,2-dibromoethane. Indian J Chem B 22:268–269
52. Dangi RR, Hussain N, Talesara GL (2011) Synthesis characterization and biological evaluation of some alkoxyphthalimide derivatives of 3-(4-substituted phenyl)-6,6-diphenyl-3,3a-dihydro-2*H*-imidazo[2,1-b]pyrazolo[3,4-d][1,3]thiazol-7(6*H*)-one. Med Chem Res 20:1490–1497
53. Juspin T, Laget M, Terme T, Azas N, Vanelle P (2010) TDAE-assisted synthesis of new imidazo[2,1-b]thiazole derivatives as anti-infectious agents. Eur J Med Chem 45:840–845
54. Güzeldemirci NU, Küçükbasmacı Ö (2010) Synthesis and antimicrobial activity evaluation of new 1,2,4-triazoles and 1,3,4-thiadiazoles bearing imidazo[2,1-b]thiazole moiety. Eur J Med Chem 45:63–67
55. Shetty NS, Koti RS, Lamani RS, Badiger NP, Khazi IAM (2008) Synthesis and antimicrobial activities of some ethyl 2-arylthio-6-arylimidazo[2,1-b]thiazole-3-carboxylates and their sulfones. J Sulfur Chem 29:539–547
56. Lamani RS, Shetty NS, Kamble RR, Khazi IAM (2009) Synthesis and antimicrobial studies of novel methylene bridged benzisoxazolyl imidazo[2,1-b][1,3,4]thiadiazole derivatives. Eur J Med Chem 44:2828–2833
57. Andreani A, Leoni A, Locatelli A, Morigi R, Rambaldi M, Cervellati R, Greco E, Kondratyuk TP, Park E-J, Huang K, van Breemen RB, Pezzuto JM (2013) Chemopreventive and antioxidant activity of 6-substituted imidazo[2,1-b]thiazoles. Eur J Med Chem 68:412–421
58. Serafini M, Torre E, Aprile S, Massarotti A, Fallarini S, Pirali T (2019) Synthesis, docking and biological evaluation of a novel class of imidazothiazoles as IDO1 inhibitors. Molecules 24:1874
59. Peng X, Qin F, Xu M, Zhu S, Pan Y, Tang H, Meng X, Wang H (2019) Synthesis of imidazo[1,2-c]thiazoles through Pd-catalyzed bicyclization of tert-butyl isonitrile with thioamides. Org Biomol Chem 17:8403–8407
60. Potikha LM, Brovarets VS (2020) Synthesis of imidazo[2,1-b][1,3]thiazoles—potential anticancer agents derived from γ-bromodipnones. Chem Heterocycl Compd 56:1073–1077
61. Koudad M, El Hamouti C, Elaatiaoui A, Dadou S, Oussaid A, Abrigach F, Pilet G, Benchat N, Allali M (2020) Synthesis, crystal structure, antimicrobial activity and docking studies of new imidazothiazole derivatives. J Iran Chem Soc 17:297–306
62. Zaraei S-O, Sbenati RM, Alach NN, Anbar HS, El-Gamal R, Tarazi H, Shehata MK, Abdel-Maksoud MS, Oh C-H, El-Gamal MI (2021) Discovery of first-in-class imidazothiazole-based potent and selective ErbB4 (HER4) kinase inhibitors. Eur J Med Chem 224:113674
63. Ewida MA, Ewida HA, Ahmed MS, Allam HA, ElBagary RI, George RF, Georgey HH, El-Subbagh HI (2021) 3-Methyl-imidazo[2,1-b]thiazole derivatives as a new class of antifolates: synthesis, in vitro/in vivo bio-evaluation and molecular modeling simulations. Bioorg Chem 115:105205

64. Shashiprabha NK, Thomas SP, Nayak SP, Rao KS, Shridhara K, Row TNG (2020) A novel reaction of 2-phenacyl mercaptoimidazole with acetic anhydride: formation of an imidazothiazole with loss of a phenyl group. J Chem Sci 132:120
65. Ammar UM, Abdel-Maksoud MS, Ali EMH, Mersal KI, Ho Yoo K, Oh C-H (2020) Structural optimization of imidazothiazole derivatives affords a new promising series as B-Raf V600E inhibitors; Synthesis, in vitro assay and in silico screening. Bioorg Chem 100:103967
66. Mahmoud HK, Gomha SM, Farghaly TA, Awad HM (2021) Synthesis of thiazole linked imidazo[2,1-b]thiazoles as anticancer agents. Polycycl Aromat Compd 41:1608–1622
67. Shareef MA, Sirisha K, Sayeed IB, Khan I, Ganapathi T, Akbar S, Ganesh Kumar C, Kamal A, Nagendra Babu B (2019) Synthesis of new triazole fused imidazo[2,1-b]thiazole hybrids with emphasis on *Staphylococcus aureus* virulence factors. Bioorg Med Chem Lett 29:126621
68. Dylong A, Goldeman W, Sowa M, Ślepokura K, Drożdżewski P, Matczak-Jon E (2016) Synthesis, crystal structures and spectral characterization of imidazo [1, 2-a] pyrimidin-2-yl-acetic acid and related analog with imidazo [2, 1-b] thiazole ring. J Mol Struct 1117:153–163
69. Soyer Can O, Ünlü S, Ocak H, Çöldür EÇ, Sipahi H, Bilgin Eran B (2022) Synthesis of new imidazothiazole derivatives and investigation of their anti-inflammatory and analgesic activities. J Iran Chem Soc 19:579–587
70. Manasa KL, Pujitha S, Sethi A, Arifuddin M, Alvala M, Angeli A, Supuran CT (2020) Synthesis and biological evaluation of imidazo[2,1-b]thiazole based sulfonyl piperazines as novel carbonic anhydrase II inhibitors. Metabolites 10:136