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Review on Anti-Cancer Potential of Novel Imidazothiazoles and their Synthetic Methods

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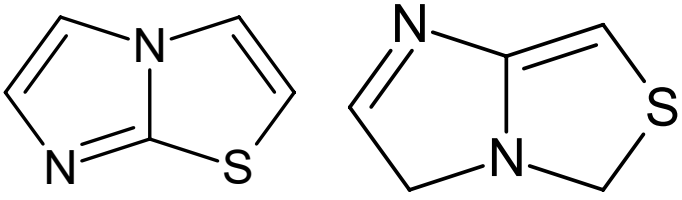
Abstract

In recent studies on cancer treatment, researchers find out that several enzymatic mutations lead to the development of cancerous cells. Such as Indoleamine 2,3-dioxygenase 1 (IDO1), B-Raf kinase, and ErB4 (HER4) kinase inhibitors. Imidazothiazole-based derivatives are gained more attention among scientists due to their wide variety of pharmacological activities, such as anti-fungal, anti-bacterial, anthelmintic, and anti-cancer activities as well as ease of synthesis of these compounds. During the search for compounds that can act as anti-neoplastic agents through inhibition of these enzymatic receptors, researchers found that imidazothiazole-based compounds and their derivatives show more potent anticancer activity. In this review, we focus on some traditional synthetic methods proposed by researchers to prepare imidazothiazole derivatives and their anticancer potential along with docking studies and cell line studies. Which will help researchers to develop their studies through imidazothiazole derivatives.

Keywords: IDO1 • B-Raf kinase • Imidazothiazole • HER4

Introduction

The significance of heterocyclic compounds has increased in medical chemistry over the past few decades, particularly those with bridgehead nitrogen atoms. Due to the variety of their biological actions, chemical compositions, and pharmacological characteristics. A group of chemical compounds known as imidazothiazole derivatives is made up of a bicyclic heterocyclic ring structure in which an imidazole ring and a thiazole ring have been united. It is well known that imidazothiazoles, including imidazo [2,1-b] thiazoles and imidazo [1,2-c] thiazoles, and their derivatives, have biological activity. They can therefore be used to treat a variety of illnesses. (Figure 1) depicts the structure of the imidazothiazole core. Imidazothiazole is the lead component of the well-known and widely used medication levamisole. It is currently used as an anthelmintic agent in animals. In addition to its anthelmintic effects, this compound also demonstrates biological response-modifying action, immuno-stimulating, and immune-modulating properties. It is used as an adjuvant in cancer therapy in conjunction with 5-fluorouracil, particularly following surgical resection of stage TNM 3 or Duke's C colon cancer [1]. Numerous researchers have studied imidazothiazoles and their derivatives as a result of the variety of pharmacological effects of levamisole.



Imidazo[2,1-b] thiazole Imidazo[1,2-c] thiazole

Figure 1. Imidazothiazoles.

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The synthesis of medicines with anticancer [2-5], anti-inflammatory [6,7], anthelminthic [8-10], antiphrastic [11], anti-oxidant [12,13], fungicidal [14,15], antimicrobial [16,17] and antiviral [18,19] activity may be accomplished using different imidazothiazole scaffolds, according to study. Numerous investigations have shown that a wide range of synthetic techniques may be used to create therapeutic medicines that include imidazothiazole. An efficient way to make imidazothiazole and its derivatives is using the Vilsmeier-Haack-and-Knoevenagel condensation process [20]. One-pot synthesis, catalyst-free microwave synthesis and other methods can also be used for synthesis. In this review, we concentrated on a few novel effective synthetic techniques to synthesize imidazothiazole derivatives and also their significant biological functions.

Imidazothiazole

Traditional synthetic strategies and some related derivatives: One of the traditional methodologies to synthesize imidazothiazole is the reaction involving α-substituted ketones with sulfur heterocycles (Figure 2).

Some research reports also suggest that these sulfur heterocyclic systems can react with acyl chlorides, esters, or carboxylic acids substituted with a halogen atom on α-position to obtain imidazo [1,2-b] thiazoles. Treatment of thiourea with phenacyl bromide derivatives (1a-c), gives 2-amino-4-arylthiazoles(2a-c). These sulfur heterocycles react with chloroacetic acid led to obtaining 3-arylimidazo [2,1-b] thiazol-6(5H)-one (3a-c) at a yield of 72-82%. So many researchers synthesized imidazothiazole derivatives by using the above-mentioned methodologies and these compounds show a broad spectrum of pharmacological activities (Figure 3). Synthesized polyphenol groups substituted imidazothiazole derivatives and reported their anticancer activity, in their research they found that compounds 4 and 5 (Fgure 2) showed inhibition of the transcription factor NF$\kappa\beta$ (nuclear factor kappa beta, involved in the cancer development and progression) with (IC_{50} 3.8 ± 1.1 µM and 0.53 ± µM) respectively, using tosyl phenyl alanyl chloromethyl ketone (IC_{50} 3.8 ± 1.1 µM) and BAY-11 (IC_{50} ± 0.54 µM) as positive controls.

Imidazothiazoles bearing a pyrazole ring were also possessing antitumoral activity, synthesized a series of imidazothiazole pyrazole derivatives by refluxing different 3-aryl-6-hydrazinylimidazo [2,1-b] thiazoles with diethyl malonate, ethyl acetoacetate or acetylacetone in glacial acetic acid. They find out that compounds bearing pyrazolidine-3,5-dione (6a-c), 3¬methyl-1-H-pyrazole-5 (4H)-one 7(a-c), and 3,5-dimethyl-1-H-pyrazoles (8a-c) showed to be promising leads for further

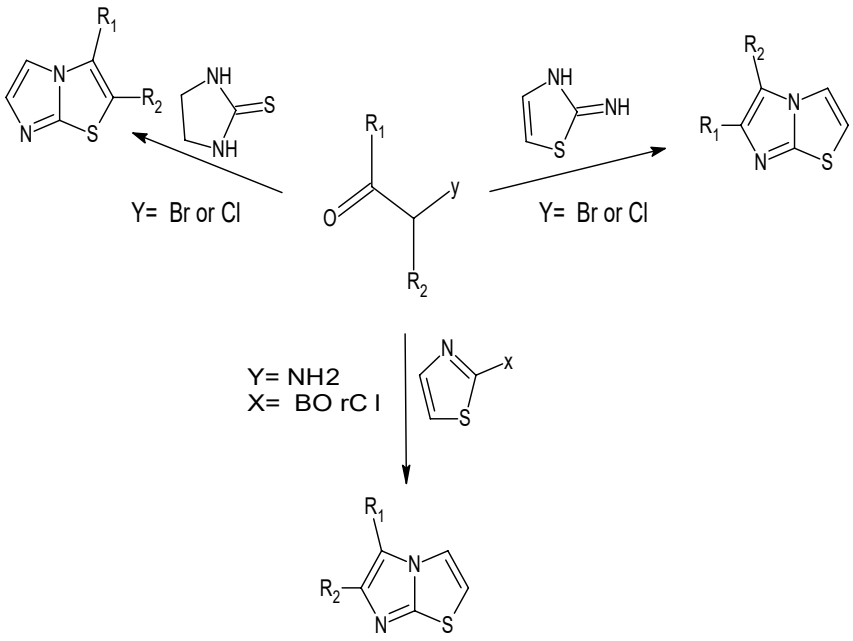
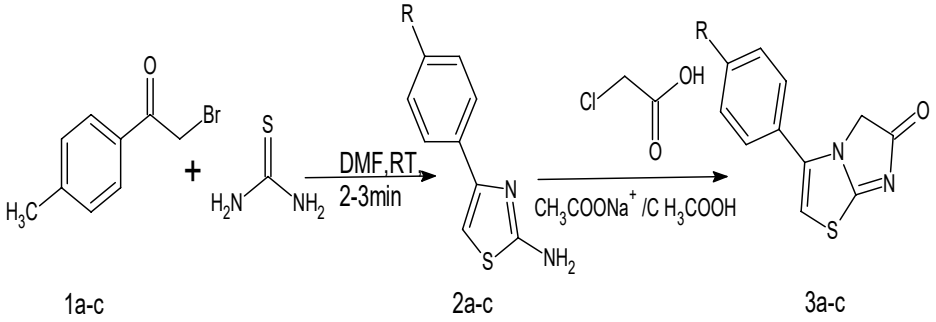


Figure 2. Methodologies to obtain imidazothiazoles from sulfur heterocycles.



a: R=H, b: R=Cl, c: R=CH_3

Figure 3. Synthesis of 3-arylimidazo [2,1-b] thiazol-6(5H)-one.

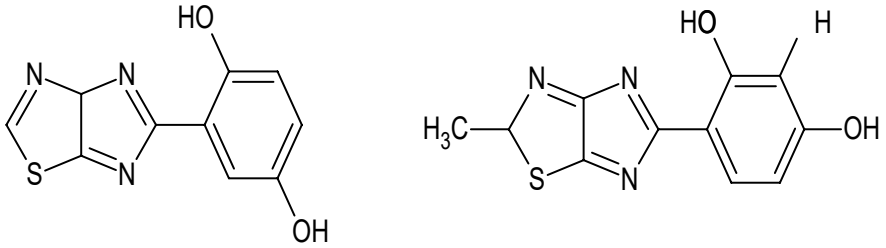
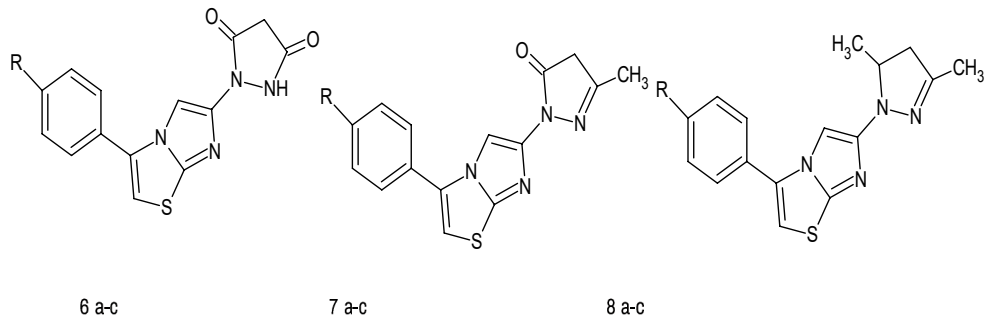


Figure 4. Imidazothiazoles endowed with polyphenolic structures.



a) R=H, b) R=Cl, c) R=CH_3

Figure 5. Imidazothiazole pyrazole derivatives.

development of anticancer drugs (Figure 4).

Imidazothiazole derivatives as IDO1 inhibitors: Indoleamine 2,3-dioxygenase 1 (IDO1) is considered a promising target for treating several diseases including neurological disorders and cancer. IDO1 is a home containing protein it catalyzes kynurenine pathway of tryptophan catabolism by promoting the oxidative cleavage of C_2-C_3 double bond of indole in tryptophan to provide N-formyl-kynurenine, thus generated N-formyl-kynurenine further metabolized into bioactive metabolites such as kynurenine, kynurenic acid, 3-hydroxy-kynurenine, and quinolinic acid, that are involved in a number of neurological disorders, such as Alzheimer's, Parkinson's disease and cerebral ischemia. Also, in tumor cells overexpression of IOD 1 has been reported, and IOD 1 is considered as a key factor in cancer immunosuppression. Several studies pointed out that 4-phenyl imidazole (PI) analogs and thiazolotriazole analogs have IDO1 inhibitory action. Designed para-tolyl imidazothiazole (compound 8) by combining PI and thiazolotriazole, as a novel scaffold with more potent IDO1 inhibitory activity.

They synthesized imidazothiazole derivatives by taking 4-bromothiazole-2-amine 10 with N, N-dimethylformamide dimethyl acetal to get amidine compound 11. It is then treated with ethyl bromoacetate to form salt, it is then converted into imidazothiazole derivatives by using DBU. They synthesized ethyl ester derivatives 12a-h. 12i, and 12j are bromine and benzyl derivatives respectively by Suzuki coupling reaction with a boronic acid or pinacol boronate, also they prepared amide derivatives by hydrolysis of 12a to carboxylic acid 13 and subsequently converted it in to amide compounds 14a-c with $R^2CH_2CH_2NH_2$ and WSC·HCl. They reduced ethyl ester 12i with DIBAL-H to afford alcohol 15. The alcohol group of 15 is converted with DPPA and DBU to azide compound 16 which is then reduced under Staudinger condition to provide amine compound 17 thus they treated this amine derivative with isocyanate to produce urea compound 18a-g.

Reagents and conditions: (a) N,N-dimethylformamide dimethyl acetal, DMF, 80°C; (b) ethyl bromoacetate, 80°C; (c) DBU,DMF, 60°C; (d) $R1B(OH)_2$ or R1BPin, $Pd(pph_3)_4$, K_2CO_3, 1,4-dioxane-H_2O (3:1), 100°C; (e) 1 N NaOH, MeOH-THF (99%); (f) $R^2CH_2CH_2NH_2$, WSC·HCl, HOBt, i-Pr_2NEt, DMF; (g) DIBAL-H, THF, 0°C (94%); (h) DPPA, DBU, DMF,60°C (75%); (i) PPh_3, H_2O, THF, 45°C (90%); (j) R^3NCO, i-Pr_2Net, THF. To improve IDO1 Inhibitory activity they use ethyl ester derivatives to optimize pocket-A of IDO1 in Figure 5, it is shown in Table 1, among these derivatives they found that para-tolyl compound 12a was preferable to the meta-tolyl compound 12b or the ortho-tolyl compound 12c, while the non-substituted phenyl compound 12d and the 1-cyclohexene compound 12e not effective. IDO1 inhibitory activity of the ethyl compound 12f and methoxy compound 12g is less than that of 12a.

They also attempted to optimize pocket-B shown in Figure 6 by using amide derivatives 14a-c within these derivatives 14b generates an induced fit and is located adjacent to Phe226, but not to Arg231. So, they tried to introduce a more rigid structure to pocket B to allow it to interact with both Phe226 and Arg231. Hence Shingo Tojo and co-workers introduced a urea group into the linker moiety (Table 2). These urea groups improved IDO1 inhibitory activity in compounds 18a-g. They found that 18a was more active than 18b and 18c, also the meta or para-substituted compounds (17d-g) particularly nitrile compound 18g were more effective than 18a which was unsubstituted.

Table 1. IDO1 inhibitory activity of the ethyl ester derivatives 12a-j.

Compd	R1	IDO1 IC50 (μM) a
12a	4-tolyl	18 ± 3.7
12b	3-tolyl	>100
12c	2-tolyl	>100
12d	Phenyl	>100
12e	1-cyclohexenyl	>100
12f	4-Et-C_6H_4	24 ± 4.0
12g	4-MeO-C_6H_4	56 ± 2.0
12h	4-Cl-C_6H_4	8.1 ± 1.7
12i	4-Br-C_6H_4	5.5 ± 2.2
12j	benzyl	>100

aIC50 values are the mean of at least two independent assays.

Imidazothiazole derivatives as promising B-Raf kinase enzyme inhibitor: B-Raf kinase enzyme is considered as an important element in the MAPK cascade-based signaling pathway which controls cell growth and proliferation, mutation of B-Raf leads to uncontrolled cell proliferation and melanoma. Nowadays B-Raf inhibitors such as vemurafenib and dabrafenib got approval from FDA. Based on this Ammar UM, et al. synthesized imidazothiazole derivatives with B-Raf inhibitory activity.

They synthesized derivatives 28a-p as shown in Figure 7. The side chain 21a-p incorporated by them was prepared by reaction of appropriate diamines 19a, b with different substituted benzene sulfonyl chloride 20a-h through nucleophilic substitution mechanism. Compound 22 was condensed with 2-aminothiazole 23 to obtain compound 24. Cross-coupling of 24 with aryl halide 25 is accomplished through Heck reaction to get compound 26. Then they treated compound 26 with oxone to oxidize SMe moiety to obtain key intermediate 27. This intermediate thus obtained is treated with amine-based side chain 20a-h in the presence of base followed by reduction of NO_2 group in presence of Od/C under H_2 atmosphere to obtain imidazothiazole derivatives 28a-p. As shown in Figure 8.

Reagents and conditions. a, TEA, DCM, 0°C-rt, 8 h; b, EtOH, reflux, 18 h; c, $Pd(OAc)_2$, Ph3P, K_2CO_3, DMF, 80°C, 8 h; d, Oxone, MeOH/H_2O, rt, 9 h; e, DIPEA, DMSO, 90°C, 8 h; f, H_2, Pd/C, MeOH, rt, 9h.

For all synthesized derivatives they conducted *in vitro* inhibitory activity study on the B-Raf kinase enzyme (V600E B-Raf), the mean percent inhibition was summarized in Table 3. They find out that compounds 28k, 28l, 28n, and 28o exhibit more potent activity than other derivatives.

The most active compounds, 28l, and 28n (IC_{50} = 1.20 and 4.31Nm, respectively), showed additional H-bond interaction between the new substitution (NH_2 group) and Cys 532 amino acid residue of V600E B-Raf kinase active site (Figure 6). From the molecular docking study, they found that tested derivatives conserved binding interactions of dabrafenib.

In their study, Ammar and his coworkers found that NH_2-based imidazothiazole derivatives possess V600E B-Raf kinase enzyme inhibitory activity, among these compounds 28l, 28n, and 28o were more potent derivatives.

Imidazothiazole as potent ErbB4 (HER4) Kinase inhibitor: Epidermal growth factor receptor (EGFR) plays a pivotal role in carcinogenesis, it has four

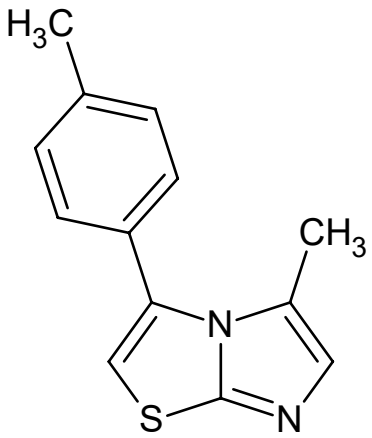


Figure 6. Para-tolyl-imidazothiazole.

Table 2. IDO1 inhibitory activity of the urea derivatives 18a-g.

Compd	R3	IDO1 IC50 (μM) α
18a	Phenyl	0.22 ± 0.03
18b	Benzyl	0.75 ± 0.01
18c	Cyclohexanyl	1.8 ± 0.40
18d	3,4-methylenedioxyphenyl	0.12 ± 0.04
18e	3-MeO-C_6H_4	0.16 ± 0.03
18f	4-MeO-C_6H_4	0.19 ± 0.05
18g	4-CN-C_6H_4	0.077 ± 0.015

αIC50 values are the mean of at least two independent assays.

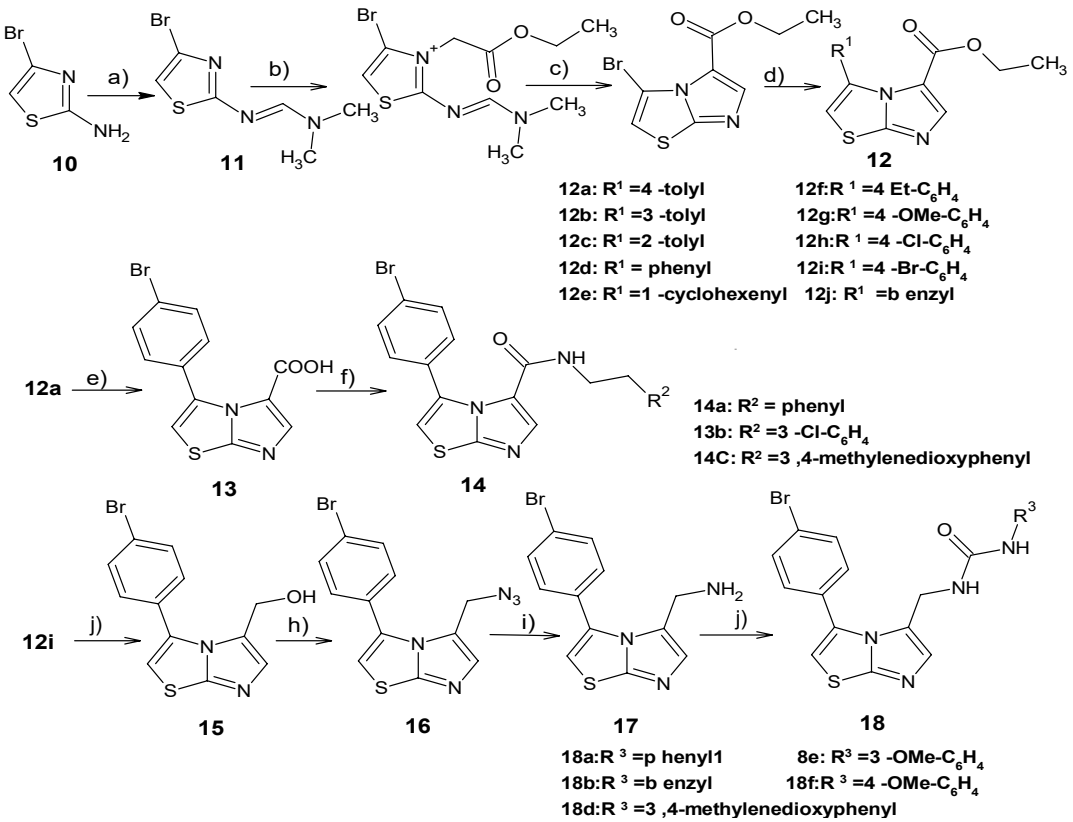


Figure 7. Synthesis of the Imidazothiazole compounds.

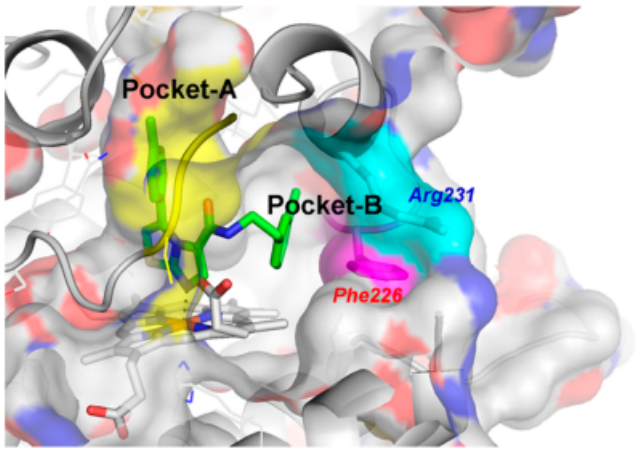


Figure 8. Crystal structure of IDO1/13b complex (green) (PDB: 4PK6). Main chain Ala260-Ser263 (yellow), Phe226 (pink), and Arg231 (cyan) are shown.

Table 3. They find out that compounds 28k, 28l, 28n, and 28o exhibit more potent activity than other derivatives.

Compound	n	Ar	V600e B-Raf IC50α
28a	1	3-Fph	28.3
28b	1	4-Meph	59.1
28c	1	4-CF_3Ph	141
28d	1	4-OMePh	23.4
28e	1	4-ClPh	16.7
28f	1	4-BrPh	73.7
28g	1	4-FPh	12.7
28h	1	1-Naph	152
28i	2	3-FPh	13.5
28j	2	4-MePh	NDb
28k	2	4-CF_3Ph	11.4
28l	2	4-OMePh	1.2
28m	2	4-ClPh	20.4

28n	2	4-BrPh	4.31
28o	2	4-FPh	6.21
28p	2	1-Naph	24.5
Vemurafenib	-	-	31
Dabrafenib	-	-	0.5

b=Not determined, α=nM.

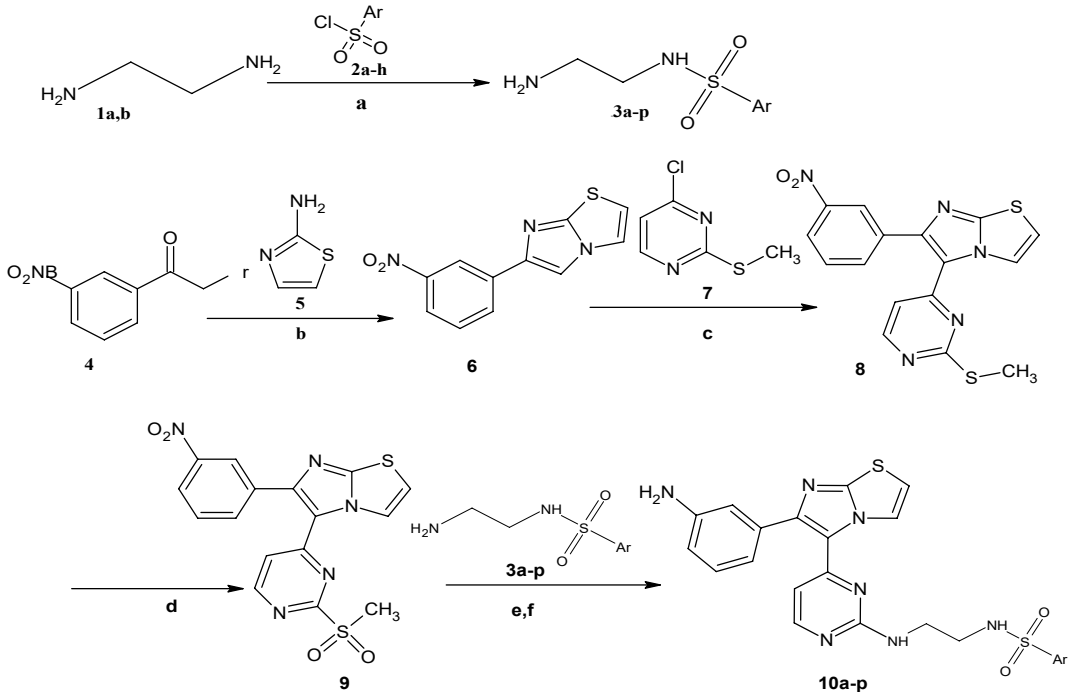


Figure 9. Imidazothiazole derivatives.

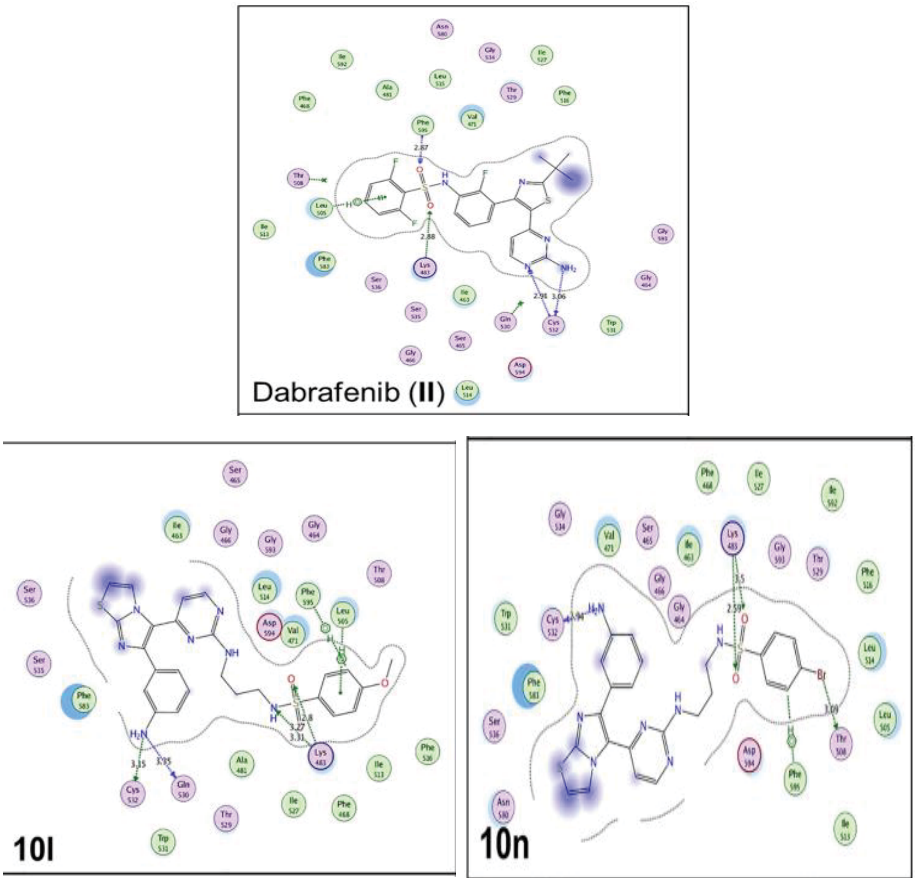


Figure 10. 2D ligand interaction of dabrafenib (II) and tested compounds (10l and 10n) with V600E B-Raf kinase domain.

subtypes of kinases HER1, HER2, HER3, and HER4 (ErbB4). The first three kinases are studied thoroughly by researchers HER4 is yet to be studied deeply, despite that it has correlation with the initiation and progression of breast cancer. Novel studies have shown that it has a correlation with other cancers such as prostate cancer, colorectal cancer, ovarian cancer, lung cancer, melanoma, and brain tumor. Different molecules shown ErbB4 inhibitory activity mainly quinazoline derivatives (allitinib, poziotinib, dacomitinb), quinoline derivatives (neratinib and pyrotinib), pyrazolopyrimidine derivative (ibrutinib), and pyrrolotriazine derivative

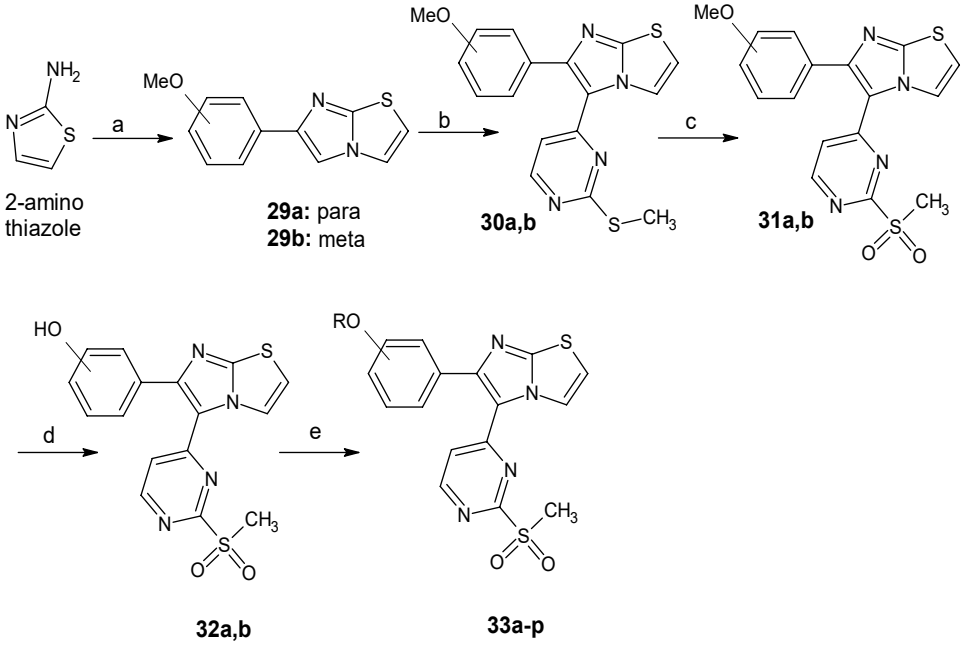


Figure 11. Reagents and reaction conditions: a) a-Bromo-3(4)-methoxyacetophenone, EtOH, reflux, 16 h, 80e85%; b) 4-Iodo-2-(methylthio)pyrimidine, $Pd(OAc)_2$, Cs_2CO_3, PPh3, DMF, 80 C, 12 h, 30e34%; c) Oxone, MeOH, H_2O, rt, 16 h, 80e85%; d) BBr_3, CH_2Cl_2, -78 C, 1 h; rt, overnight, 55e60%; e) Appropriate substituted alkyl halide reagent or sulfamoyl chloride, K_2CO_3 (with alkyl halide) or NaH (with sulfamoyl chloride), anhydrous DMF, 0 C then rt, 1e2 h, 20e60%.

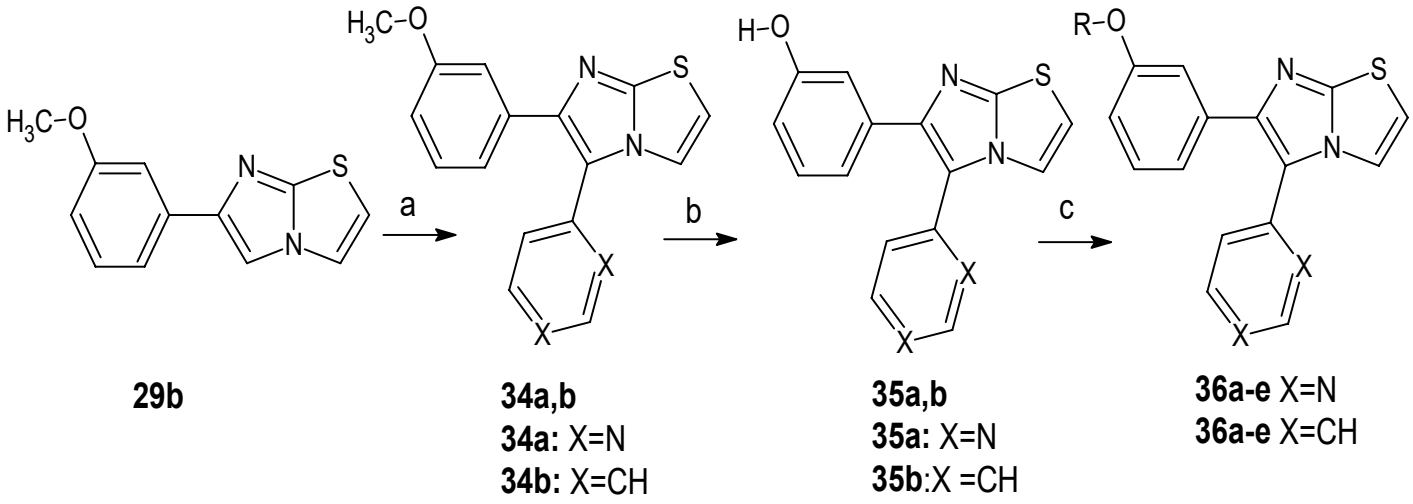


Figure 12. Reagents and reaction conditions: a) 4-Iodopyrimidine or iodobenzene, $Pd(OAc)_2$, Cs_2CO_3, PPh_3, DMF, 80^{0}C, 12 h, 25-30%; b) BBr_3, CH_2Cl_2, -78^{0}C, 1 h; rt, overnight, 35-40%; c) Appropriate aralkyl halide reagent, K_2CO_3, anhydrous DMF, 0^{0}C then rt, 1e2 h, 30-55%.

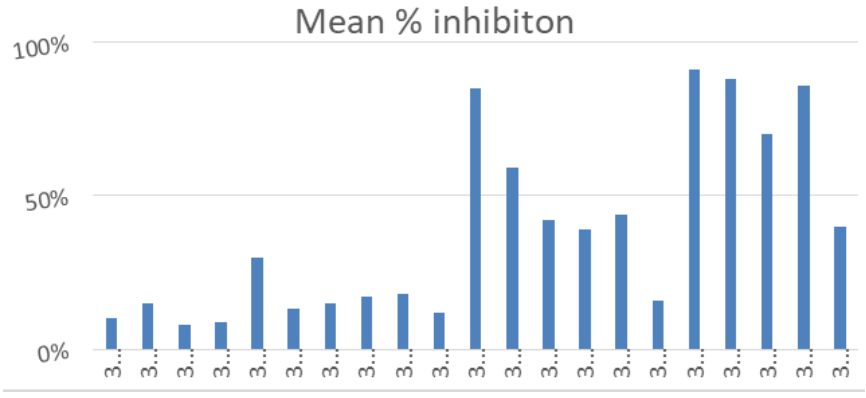


Figure 13. Mean inhibition percentage values of all the target compounds against ErbB4 at 1μM concentration.

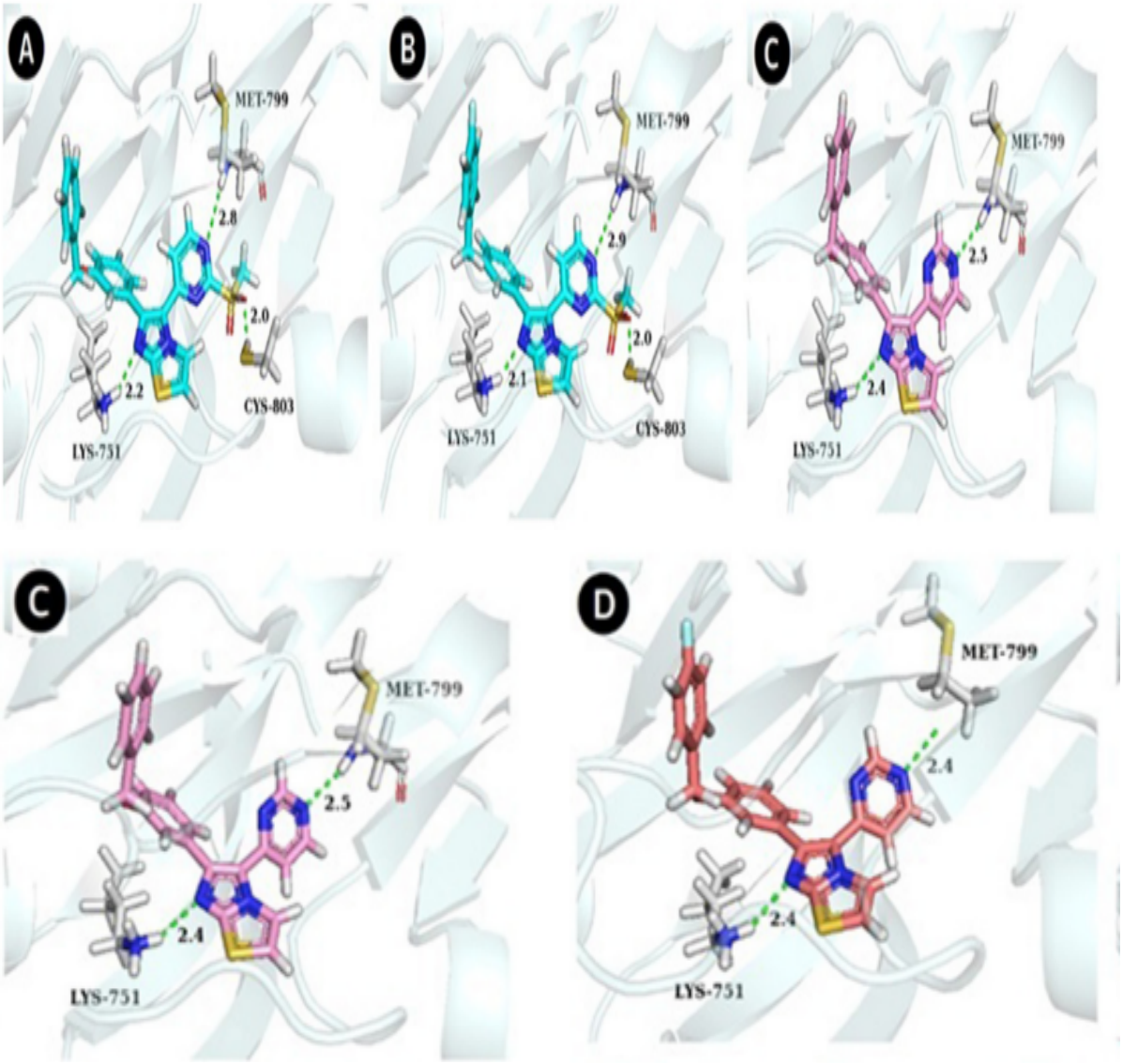


Figure 14. Best-docked poses and interactions of compounds 33k, 33l, 36a, and 36b, (respectively a-d) within the ErbB4 active site (PDB ID: 2R4B). The enzyme is represented in ribbon style. Green dashed lines represent hydrogen bond interactions while important amino acid residues are in sticks rendering.

(AC-480). These molecules show's good ErbB4 potency (Figure 9).

Recent studies indicate that imidazothiazole derivatives show selective inhibition of the ErbB4 (HER4) kinase enzyme. Synthesized novel imidazothiazole derivatives that show anti-cancer activity *via* inhibition of HER4 kinase.

They prepared imidazothiazole derivatives as shown in Figure 10. The intermediate 29a,b was prepared by cyclization of α-bromo-3(4)-methoxy-acetophenone and 2-amino-thiazole by refluxing with ethanol. Then the intermediates obtained coupled with 4-iodo-2-(methyl-thio) pyrimidine in the presence of palladium(II) acetate, triphenylphosphine as a ligand, and cesium carbonate to obtain 30a,b. then it undergoes oxidation with oxone to get 31a,b it is then demethylated with the aid of boron tribromide to form hydroxyl analogues 32a,b and it is treated with an appropriately substituted alkyl halide or sodium hydride to yield 33a-p.

They also prepared derivatives 36a-e in a similar manner as compounds 33a-p synthesized. But using either 4-iodopyramidine or iodobenzene in the first step instead of 4-iodo-2-methylthiopyramidine as shown in Figure 11.

They tested synthesized compounds against ErbB4 kinase inhibitory activity at 1μM concentration. The percentage inhibition is founded as shown in Figure 12. They figured out that among the synthesized compounds 33k and 36a are more potent than others, and the substitution of benzyl with p-fluoro (compounds 33l and 36b) led to a significant reduction in kinase inhibitory activity.

The biological report they obtained is strengthened by molecular docking and dynamic simulation studies as shown in Figure 13 and Figure 14. Among these derivatives, 33k possesses high selectivity against cancer cells than normal cells. The most potent ErbB4 inhibitors among the series are 33k and 36a.

Conclusion

This review summarizes the synthetic strategies to obtain novel imidazothiazole derivatives and their relative anticancer activities along with their docking studies to strengthen the anticancer potential of imidazothiazole scaffolds. Para-tolyl imidazothiazole derivatives show potent IDO1 inhibitory activity, also B-Raf kinase inhibitory activity showed by NH_2-based imidazothiazole scaffolds as well as ErbB4 kinase inhibitory action is shown by methyl-sulfonyl based imidazothiazole derivatives. All these studies point towards the anti-neoplastic potential of imidazothiazole derivatives.

All these findings will lead to further research on imidazothiazole moiety to develop potent anti-neoplastic derivatives.

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