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Biological Applications of Imidazothiazole Scaffolds: A Current Review

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ABSTRACT

Due to the broad-spectrum biological activities, fused heterocyclic compounds are one of the most important systems in medicinal chemistry. Among them, the imidazothiazole which contains a bridgehead nitrogen atom has a vital role because of various applications such as anticancer, antimalarial, antiviral, etc. Designing various imidazothiazole scaffolds has become more important because of their several biological applications. The present review paper discusses the numerous biological applications of imidazothiazole scaffolds in the field of medicine. The review would be useful in future drug design for the development of more promising drug-like scaffolds.

1. Introduction

Heterocyclic compounds are organic molecules with at least one carbon atom and at least one additional heteroatom, such as N, O, or S, that play an important part in the metabolism of living cells. It may be either nonaromatic or aromatic. Most of them are five or six membered and some of the rings contain higher than that of three, four, seven or larger rings. Fused heterocyclic compounds, which generally have five or six members, have sparked a lot of interest in medicinal chemistry because of their wide range of pharmacological and therapeutic implications [1,2].

Among the various fused heterocyclic compounds, Imidazothiazole contains a bridgehead nitrogen atom and a sulphur atom which are biologically active and plays a prominent role in medicinal chemistry [3] (Fig. 1). Imidazothiazoles and their derivatives are one of the important scaffolds in pharmaceuticals due to their broad applications and therapeutic properties [4]. It is made up of a five-membered heterocyclic ring thiazole fused to an imidazole ring. The imidazole ring is widely present in natural and synthetic origin and it readily allows binding with receptors and enzymes [5].

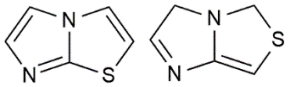

Fig. 1 Structures of imidazothiazoles

In order to attain the synergistic biological activity, the pharmacophore hybridization enables to design hybrids bearing two scaffolds [6]. Imidazo[2,1-b] thiazole is a fused heterocycle that has piqued the interest of medicinal chemists due to its broad range of biological activity [6,7]. The compounds containing this scaffold were initially employed as a core unit in anthelmintics and immune modulators i.e., Levamisole [7]. In recent years, these scaffolds have been used against various diseases and disorders such as apoptosis-inducing agents [6], anticancer [7], antiviral [8], antitubercular [9,10], antimicrobial [9,11], antioxidant [12], anti-inflammatory [13], etc. These scaffolds also act as the inhibitors of RSK2 Kinase [14], B-Raf 4600E [15], Selective ErbB$_4$ Kinase [16], carbonic anhydrase [17], IDO1 inhibitors [18], Selective COX-2 inhibitors [19], Novel SIRT1 activators [20], etc.

Different compounds of imidazothiazole, such as benzo[d]imidazo[2,1-b]thiazole conjugates, act as tubulin polymerization inhibitors [15]. Benzothiazole is a benzoheterocycle that plays a role in medicinal chemistry. Many pharmacologically significant chemicals contain the nitrogen bridgehead fused heterocycles and benzothiazole structural moiety. Tubulin polymerization inhibitory action was found in the substances 2- aryl benzo[d]imidazo[2,1-b]thiazoles and 3- substituted 2-phenylbenzo[d]imidazo[2,1-b]thiazoles to induce apoptosis [5,7]. Its derivative imidazo[2,1-b]thiazole – guanylhydrazone, which was considered as a potential lead and p90 Ribosomal S6 Kinase 2 inhibitors with antiproliferative efficacy against a number of cell lines [21].

Levamisole and tetramisole are the main drugs for imidazo[2,1-b]thiazole which has anthelmintic and immune modulatory activities [4,7]. Nocodazole is also an imidazothiazole containing a drug which acts as tubulin polymerization inhibitor and also inhibits cell proliferation [21]. Levamisole, also known as 2,3,5,6 – tetrahydro – 6 – phenylimidazo[2,1-b]thiazole, is one of the most fully explored imidazothiazole derivatives in medicinal chemistry. It was first used to treat parasitic infections. [22]. It has also acted as the compound with antitumor, immunostimulant activities in cancer [22,23], cocaine adulterant, curious contaminant, anthelmintic, etc. [24]. Tertamisole, the first member of aminothiazole derivative which is the racemic mixture and the L-isomer is more potent whereby D-isomer has no anthelmintic activity and levamisole is purely L-isomer [25] (Fig. 2).

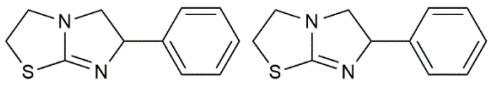

Fig. 2 Structures of levamisole and tetramisole

The imidazo[2,1-b]thiazoles and their derivatives can be synthesized using different methods like one – pot synthesis [26], one – pot three component reaction [27,28], one – pot four component reaction [29,30], microwave assisted green synthesis [9], catalyst – free microwave synthesis [31], visible light-triggered catalyst-free approach [32], $FeCl_3/ZnCl_2$ catalyzed aerobic oxidation cyclization [33], copper-catalyzed A^3 coupling [34], A^3 coupling using CNT_S embraced Nickel-Ferrite magnetic nanoparticles assisted multicomponent reaction [35], Oxone mediated direct aryl selenation [36], etc.

In this review, only those literatures indexed in ScienceDirect, PubMed, Google Scholar, PlosOne, Europe PMC, EMBASE, ResearchGate, ACS and RSC databases between 2010 and 2021 were surveyed. The keywords for this survey include imidazothiazole, benzo imidazothiazoles, antimicrobial, antiviral, anti-inflammatory, analgesic, antimalarial and anticancer, biological activities, both individually and in combination were

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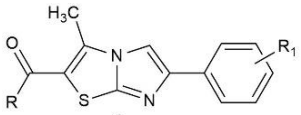
applied and shortlisted according to the purpose of this study. Here, this work summarized the various novel and efficient imidazothiazole scaffolds having various biological applications.

2. Biological Activities of Imidazothiazole Scaffolds

2.1 Antimicrobial Activity

Vekariya et al. [9] prepared novel imidazothiazole derivatives (**1**) using microwave assisted green synthesis as well as under thermal heating at 90 °C. The efficacy of the synthesized compounds was tested using the agar dilution method against Gram-positive (*Staphylococcus aureus, Streptococcus pyogenes*) and Gram-negative (*Escherichia coli, Pseudomonas aeruginosa*) bacterial strains, as well as three fungal strains (*Aspergillus clavatus, Candida albicans* and *Aspergillus niger*) and ampicillin, ciprofloxacin, and chloramphenicol were used as standard controls for antibacterial activity, whereas nystatin and griseofulvin were used as standard controls for antifungal activity. Compounds 1a and 1b were found to be the most active against Gram-positive *S. aureus* growth with MIC values of 50 µg/mL and 62.5 µg/mL, respectively which were lower than ampicillin (250 µg/mL). Compound 1a had greater activity against *S. pyogenes* with a MIC of 62.5 µg/mL and was more powerful than ampicillin (100 µg/mL). Furthermore, compounds 1c and 1d showed potential to be equally effective as ampicillin, but 50 percent less effective than chloramphenicol or ciprofloxacin.



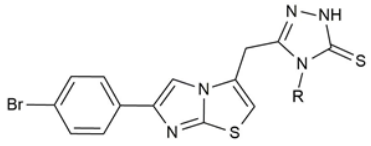
1

1a R=Me, R_1=2-Cl-C_6H_4
1b R=OEt, R_1=4-OMe-C_6H_4
1c R=OEt, R_1=2-OMe-C_6H_4
1d R=OEt, R_1=4-F-C_6H_4
1e R=OEt, R_1=4-NO_2-C_6H_4

Fig. 3 Structures of 1-(3-methyl-6-phenylimidazo[2,1-b]thiazol-2-yl)ethanone

Compound 1e showed excellent efficacy against gram-negative strain *E. coli*, with a MIC of 62.5 µg/mL and against another gram-negative strain *P. aeruginosa*, with a MIC of 62.5 µg/mL. However, when it came to antifungal action, some of these compounds showed sensitivity to the *C. albicans* strain while being insensitive to the other two strains.

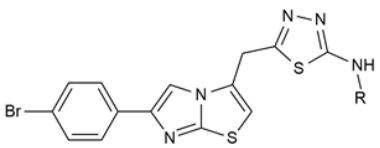
A series of 4-alkyl/aryl-2,4-dihydro-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-3H-1,2,4-triazole-3-thiones (**2**) and 2-alkyl/arylamino-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-1,3,4-thiadiazoles (**3**) were developed and evaluated for their antimicrobial activity by Guzeldemirci et al. [11]. The synthesized compounds were tested against bacterial strains *S. aureus, P. aeruginosa, E. coli* and the strains *C. albicans, Candida parapsilosis, Candida krusei, Trichophytan mentagrophytes* var. erinaceid, *Microsporum gypseum* and *Trichophyton tonsurans* were used for antifungal activity using the micro broth dilution method.



2

2a R=C_2H_5
2b R=C_3H_7

Fig. 4 Structures of 4-alkyl/aryl-2,4-dihydro-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-3H-1,2,4-triazole-3-thiones



3

3a R=CH_3
3b R=C_2H_5

Fig. 5 Structures of 2-alkyl/arylamino-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-1,3,4-thiadiazoles

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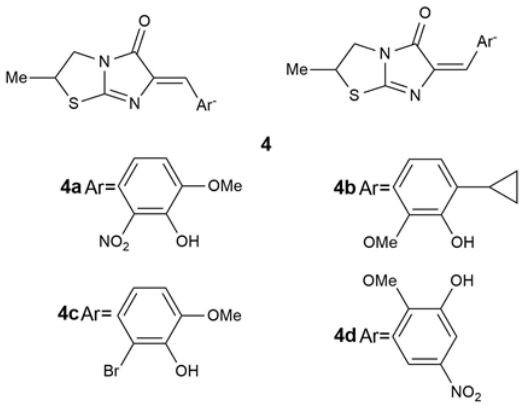
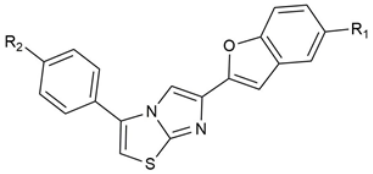
The compounds 2a and 3b with the MIC value of 32 µg/cm³ showed better antibacterial activity against *S.aureus* and *E.coli* respectively. For antifungal activity, compounds 2a, 2b, 3a and 3b showed more activity against *T. tonsurans* with the MIC value of 8 µg/cm³ and compound 2a had the same MIC value against *T. mentagrophytes* ver. Erinaceid strain. 6-arylidenimidazothiazolothiazolone (**4**) was synthesized and tested its antibacterial efficacy against bacterial and fungal species. *S. aureus, E. coli, P. aeruginosa, Enterococcus faecalis* were utilized as bacterial strains, while *C. albicans* and *A. niger* were employed as fungus strains. The compounds 4a, 4b, 4c, and 4d were found to be active against *A. niger*, with compound 4a having the highest MIC value of 15.61 µg/mL against *C. albicans* [13].



4

Fig. 6 Structures of arylidenimidazothiazolothiazolone

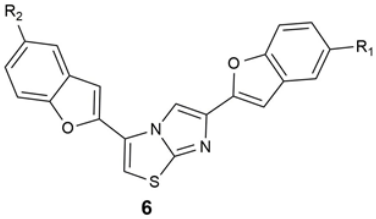
Shankerrao et al. [37] synthesized a series of imidazothiazole derivatives of benzofuran i.e. (6-(1-benzofuran-2-yl)3-phenylimidazo[2,1-b][1,3]thiazole (**5**) and 3,6-bis(1-benzofuran-2-yl)imidazo[2,1-b][1,3]thiazole (**6**) derivatives. Bacterial and fungal strains were used to test the compound's antimicrobial efficacy by agar-well diffusion method. The strains used were *S. aureus, P. aeruginosa, Enterococcus feltis, Klbesilla pneumona* and *E. coli* as the bacterial strains and *A. niger* and *Trichioderma virdae* as fungal strains. Among the synthesized compounds, the different compounds were effective against different strains, such that the compounds 5a and 6a were very effective against *S. aureus, P. aeruginosa* and *E. feltis* with the highest zone of inhibition and the compounds 5b and c against *S. aureus* and *E. coli* showed the excellent activity. On focusing towards the antifungal activity, the compounds 5a, 5d and 6b against the two human pathogen fungal species showed the excellent antifungal effect with a higher zone of inhibition than the other compounds and nearly equivalent to that of standard drug fluconazole.



5

5a R_1=Br, R_2=H
5b R_1=H, R_2=F
5c R_1=Br, R_2=F
5d R_1=Br, R_2=CH_3

Fig. 7 Structures of (6-(1-benzofuran-2-yl)3-phenylimidazo[2,1-b][1,3]thiazole



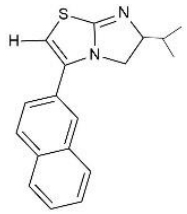
6

6a R_1=H, R_2=Br
6b R_1=Br, R_2=Br

Fig. 8 Structures of 3,6-bis(1-benzofuran-2-yl)imidazo[2,1-b][1,3]thiazole

Li et al. [38] developed a novel antimicrobial agent and tested their efficiency against methicillin-resistant *S. aureus* (MRSA). By using standard microdilution broth method, the efficiency of the 5,5-dihydroimidazo[2,1-b]thiazoles (**7**) against microbes were screened by

using three gram positive bacterial strains such as *S. aureus* ATCC BAA-44, *S. aureus* ATCC 33591 (MRSA) and *S. aureus* Mu50 ATCC 700699. The tests were carried out using Muller-Hinton broth that had not been diluted.



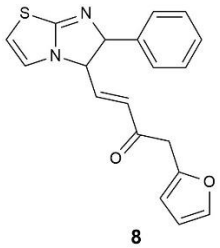
7

Fig. 9 Structure of 5,5-dihydroimidazo[2,1-b]thiazoles

In vitro antibacterial growth inhibitory assay was performed for the set of eight compounds and exhibited greater than 80% growth inhibition against *S. aureus* (MRSA). Their efficiency was tested against MRSA ATCC 33591 and multidrug-resistant BAA-44. The majority of the drugs had MIC_{90} values of 8-64 µg/mL against MRSA strains. The S-enantiomers have a 2-fold inhibitory effect against the BAA-44 strain when compared to ATCC 33591 strains.

Li et al. [38] synthesized R-enantiomer analogs to identify the compounds having higher activity. In this, three different *S. aureus* strains were used namely, MRSA ATCC 33591, multidrug-resistant BAA-44 and vancomycin-intermediate *S. aureus* strains VISA ATCC 700699. On comparison with BAA-44 and ATCC 33591 strains, on the basis of MIC_{90} values, the VISA strains thickened the cell walls and may decrease the antimicrobial activity. When compared to S-enantiomer, R-enantiomer was about half the value of that and the imidazothiazole with R-enantiomer had increased antimicrobial activity. By this study, the R6h was identified as a hit compound [38].

The series of imidazothiazole derivatives **(8)** were synthesized by Koudad et al. [39] via Claisen-Schmidt condensation. The antibacterial study was performed for the imidazothiazole derivatives by agar diffusion medium against the bacterial strains *P. aeruginosa, E. coli* and *S. aureus*. It showed strong inhibitory effect against *P. aeruginosa* and *E. coli* with MIC ≤ 0.2 mg/mL and MIC ≤ 0.5 mg/mL for *S. aureus*.



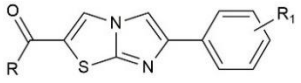
8

Fig. 10 Structure of (3*E*)-1-(furan-2-yl)-4-(6-phenyl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazol-5-yl)but-3-en-2-one

The antifungal activity was performed for the imidazothiazole compounds against the *Fusarium oxysporum* strain and the mycelial growth inhibition of the compounds was screened. All the compounds showed better inhibition with an IC_{50} value not exceeding 0.07 mg/mL. The docking reliability of the active compound 8 into the active site of thymidylate kinase protein was confirmed by redocking co-crystallized ligand (ODF) into the binding site of *P. aeruginosa* Thymidylate kinase. The docking score and RMSD values were found to be -7.81 kcal/mol and 0.242 Å, respectively.

2.2 Anti-Tubercular Activity

Vekariya et al. [9] used green synthesis strategy to make novel imidazo[2,1-b]thiazole **(9)** derivatives that could be used as antitubercular drugs. Lowestein-Jensen (L.J) agar (MIC) method was used to test the *in vitro* potency of the synthesized compounds against *Mycobacterium tuberculosis* $H_{37}R_V$. Isoniazid and rifampicin were used as standards. According to preliminary screening, compounds 9a and 9b had the best activity against MTB $H_{37}R_V$ strain, with a MIC of 50 g/mL.

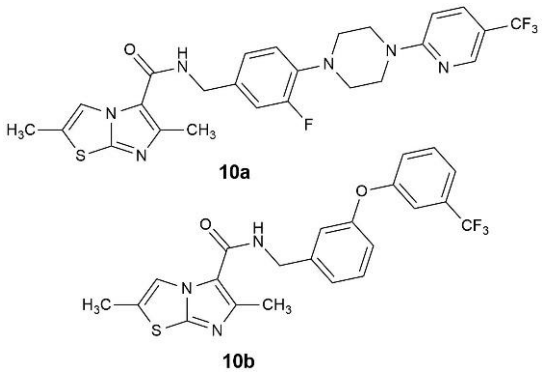


9

9a R=Me, R_1=4-OMe-C_6H_4
9b R=Me, R_1=4-NO_2-C_6H_4

Fig. 11 Structures of 1-(3-methyl-6-phenylimidazo[2,1-b]thiazol-2-yl)ethanone

Moraski et al. [10] developed imidazo[2,1-b]thiazole-5-carboxamides (ITAs) (**10**), which show potential as antitubercular agents and QcrB targeting agents. MTB replicating and non-replicating tests were conducted on the *M. tuberculosis* $H_{37}R_V$ strain. Low oxygen recovery assay was used in the MTB non-replicating investigation. The efficiency of the synthesized imidazo[2,1-b]thiazole-5-carboxamides against both replicating and non-replicating MTB $H_{37}R_V$ was tested. Among the ITA compounds, compound 16a (clogP=5.4) showed the potent activity, as well as compound 10b (clogP=6.6) also showed the activity as similar to 10a. To determine the ability of the compound to inhibit *M. tuberculosis ex vivo*, an intracellular model of *M. tuberculosis* along with positive controls was performed using a macrophage assay. The compounds 10a and 10b exhibited lower MIC values of 0.0625 and 0.25 µM respectively. From the screening against drug-resistant strains, compound 10a highlighted the low nanomolar potency against rifampicin and isoniazid.



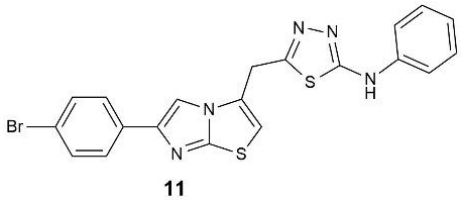
10a

10b

Fig. 12 Structures of imidazo[2,1-b]thiazole-5-carboxamides

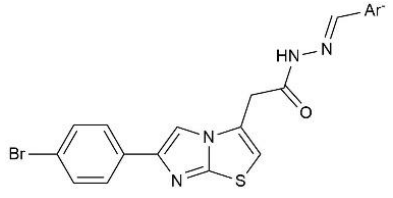
From the *in vivo* tolerability, no acute toxicity was observed (MTD = >500 mg/kg) and the compound was found to be slowly absorbed in presence of *CYP*-Inhibitor which was observed by the *in vivo* single-dose pharmacokinetic study. The *in vivo* chronic murine model of TB was performed for compound 10a and observed that compound 10a was active in the chronic murine model as that of other QcrB inhibitors and the compound 10a was found to be the potent compound among the imidazo[2,1-b]thiazole-5-carboxamide class [10].

The series of 2-alkyl/arylamino-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-1,3,4-thiadiazole (**11**) was designed and screened for their activity against *M. tuberculosis* $H_{37}R_V$ strain using the MABA method by Guzeldemirci et al. [11]. Against the particular strain, the compound 11 was found to be most active compound with 16% inhibition and the MIC value of >6.25 µg/mL.



11

Fig. 13 Structure of 2-alkyl/arylamino-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-1,3,4-thiadiazole



12

12a Ar=C_6H_5Cl
12b Ar=$C_6H_5NO_2$
12c Ar=$C_6H_4(NO_2)_2$
12d Ar=$C_4H_3ONO_2$

Fig. 14 Structures of N'-(arylidene)-2-(6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetohydrazides

Guzeldemirci and Gursoy et al. [40] developed a novel N'-(arylidene)-2-(6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetohydrazides (**12**) and tested their antimycobacterial action *in vitro*. A broth microdilution experiment was used to test the compounds' antimycobacterial activity

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against *M. tuberculosis* $H_{37}R_V$ in BACTEC 12B medium. The true MIC values were determined using the microplate alamar blue susceptibility assay. The BACTEC 460 radiometric device is used to test substances that display fluorescence. Among these compounds, the compounds 12a, 12b, 12c and 12d exhibited greater than 90% of inhibition with the MIC value of 6.25 µg/mL against *M. tuberculosis* $H_{37}R_V$. The most active compound was found to be compound 12c from the level I (preliminary) and II (MIC) assay. The most active compound was tested against VERO cells and found to have an IC_{50} value of >10 g/mL and a selectivity index of >1.6 (SI=IC50/MIC), indicating that the active compound 12e had greater antimycobacterial activity.

Moraski et al. [41] discovered Imidazo[2,1-b]thiazole-5-carboxamides (**13**), which act as new QcrB targeting agents. These compounds were tested *in vitro* against the replicating MTB laboratory strain $H_{37}R_V$, the microplate alamar blue assay (MABA), non-replicating MTB in the low oxygen recovery assay (LORA), drug resistant MTB, and toxicity against African Green Monkey kidney epithelial (VERO) cells. To establish the efficacy of blocking the target, the selectivity against gram-positive and gram-negative strains, as well as against QcrB mutants, was tested. Among the 13 compounds tested, compounds 13a, 13b, 13c, and 13d were more effective than rifampicin at replicating MTB $H_{37}R_V$. The potency of compound 13a with a MIC of 0.006-0.061 µM was similar to that of compound 13c with a MIC of 0.0009-0.007 µM. On these four compounds, only compound 13c was found to be somewhat active against non-replicating MTB, with a MIC value of 1 µM. Thus, the imidazo[2,1-b]thiazole-5-carboxamides were found to be the most active against reproducing MTB and to target oxygen-dependent respiration through the QcrB-bc1 complex.

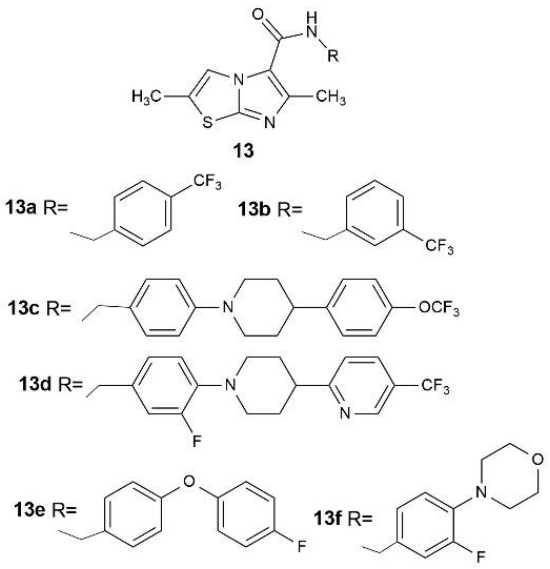


Fig. 15 Structures of imidazo[2,1-b]thiazole-5-carboxamides

The synthesized compounds were potent against *M. vaccae* only. To determine the effect of QcrB targeting, the compounds 13a, 13c, 13e, 13d and 13f were screened against a panel of six QcrB mutants. Finally, the two drugs (13c and 13d) were tested in J774A in an *ex vivo* setting, macrophages infected with MTB strain Erdman. Both of the compounds exhibited modest inhibition of growth than the standard drug rifampicin and showed low toxicity to VERO cells with excellent antimycobacterial activity [41].

Imidazo[2,1-b]thiazole and benzo[d]imidazo[2,1-b]thiazole derivatives (**14-16**) were developed by Samala et al. [42] and screened their potency against the inhibition of *M. tuberculosis pantothenate synthetase*. Thirty compounds were synthesized and their potency against *M. tuberculosis* was tested using MTB screening. *In vitro* MTB screening and the *in vivo* efficiency were tested using the *M. marinum* induced adult zebrafish model. The *in vitro* MTB screening was performed against *M. tuberculosis* $H_{37}R_V$ by the microplate alamar blue assay (MABA) method. MTB inhibition investigation was used to test all thirty substances against the *pantothenate synthetase* enzyme. All of the compounds had good IC_{50} values that ranged from 0.520.24 to 5.830.24 µM. In these compounds, only eight compounds (14a, 14b, 15a, 15b, 16a, 16b, 16c and 16d) inhibited MTS with nanomolar concentration. Among these compounds, the most active compounds were identified as 16c and 14b with IC_{50} values of 0.52±0.24 and 0.53±0.13 µM respectively. The *in vivo* screening against *M. marinum* infected adult zebrafish model also showed that compound 14b has the potent and most promising activity with only 10.4% cytotoxicity.

https://doi.org/10.30799/jacs.244.22080101

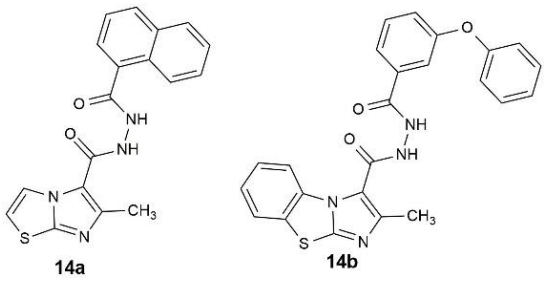


Fig. 16 Structures of imidazo[2,1-b]thiazole and Imidazo[2.1-b]benzothiazole carboxyhydrazide derivatives

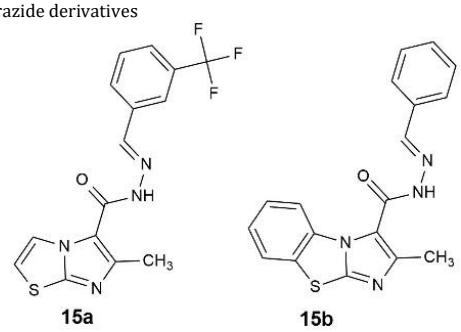
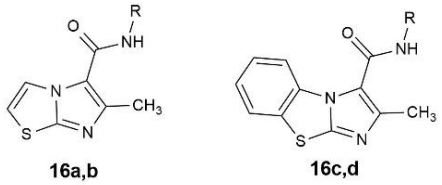


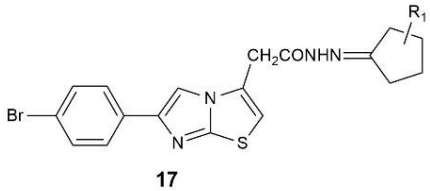
Fig. 17 Structures of imidazo[2,1-b]thiazole and Imidazo[2.1-b]benzothiazole 5-carboxyhydrazide derivatives



16a R=4-bromophenyl
16b R=Phenyl
16c R=4-bromophenyl
16d R=Phenyl

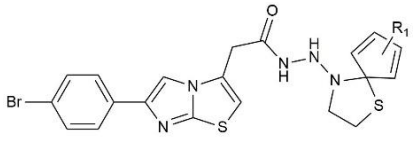
Fig. 18 Structures of methylimidazo[2,1-b]thiazole and methyimidazo[2,1-b]benzothiazole-5-carboxamide derivatives

Gursoy et al. [43] synthesized a variety of new acyl-hydrazone (**17**) and spirothiazolidinone (**18**) imidazo[2,1-b]thiazole derivatives and tested their efficacy against *M. tuberculosis* $H_{37}R_V$ in BACTEC 12B medium using the Microplate alamar blue assay. The preliminary screening was conducted against *M. tuberculosis* $H_{37}R_V$ in BACTEC 12B medium and those compounds having at least 90% inhibition in primary screening were re-screened to determine the MIC using MABA. The compounds 18a-c was evaluated against *M. tuberculosis* H37RV utilizing MABA and was found to be active compounds based on *in vitro* primary screening. The acyl-hydrazone moiety imidazo[2,1-b]thiazole derivatives 17a-c exhibited no or poor activity in these derivatives, and the conversion of these derivatives to spirothiazolidinone derivatives of imidazo[2,1-b]thiazole (compounds 18a-c) showed promising activity by the ring closure.



17a R_1=H, n=1
17b R_1=H, n=2
17c R_1=C_6H_5, n=2

Fig. 19 Structures of acyl-hydrazone imidazo[2,1-b]thiazoles

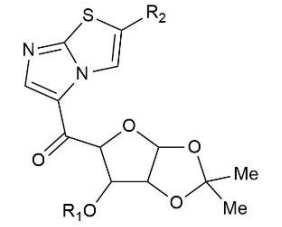


18a R_1=H, n=1
18b R_1=H, n=2
18c R_1=C_6H_5, n=2

Fig. 20 Structures of spirothiazolidinone imidazo[2,1-b]thiazoles

2.3 Anti- Viral Activity

Barrados et al. [8] synthesized 3,5-disubstituted imidazo[2,1-b]thiazole (**19**) derivatives and evaluated their antiviral activity. Virus yield inhibition assay was performed against Vero and A548 virus infected cells (JUNV Strain IV4454) using rifampicin as a standard drug and the extracellular virus yield was determined using plaque assay which was carried out for cells infected with JUNV at MOI of 0.1 in the absence of compound against Vero cells. All the compounds showed inhibitory activity against JUNV replication, but compounds 19a and 19b showed the highest inhibitory activity than rifampicin with an EC_{50} value around 1 μM and SI was found to be 268.2 and 463.7 respectively. But the compound 19a exerted the effect only during the intracellular multiplication of JUNV. Further, compound 19a was evaluated for the inhibition of human hemorrhagic fever and found to be effective against JUNV replication in A549 human cells with the CC_{50} (MTT) and EC_{50} (JUNV inhibition assay) values of 274 μM and 2.8±0.5 μM, respectively. Thus, compound 19a was found to be most active in human cells and provided the potential against hemorrhagic fever viruses.

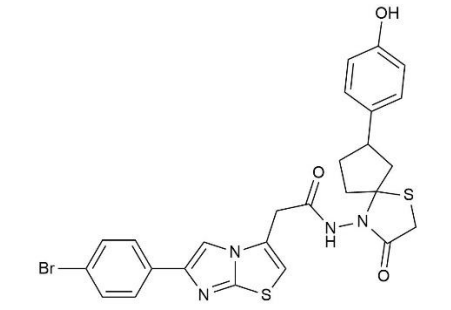


19

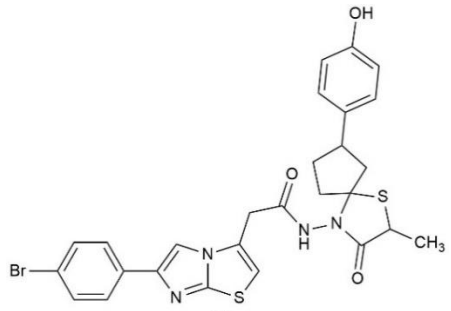
19a R_1=CH_3, R_2=COC_6H_4Cl-p
19b R_1=CH_3, R_2=COC_6H_4F-p

Fig. 21 Structures of 3,5-disubstituted imidazo[2,1-b]thiazole

Gursoy et al. [43] created a series of novel imidazo[2,1-b]thiazole-spirothiazolidione (**20, 21**) derivatives. The produced compounds were tested for antiviral activity against both RNA and DNA viruses. The Feline corona virus or Feline herpes virus infected Crandell Rees Feline kidney cells, Herpes simplex virus-1 or 2 infected human embryonic lung (HEL) fibroblast cells, vesicular stomatitis virus-infected Human cervix carcinoma HeLa cells, Parainfluenza-3-virus, Sindbis virus, Coxsackie B4 virus-infected African green monkey kidney Vero cells, influenza A/H1N1, A/H3N2 or B virus Mardin-Draby canine kidney cells and HIV-1 or 2 infected human T-lymphoblast MT-4 cells were used in this study to determine the efficiency of the synthesized compounds.



20

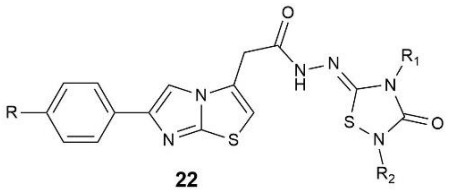


21

Fig. 22 Structures of Imidazo[2,1-b]thiazole-spirothiazolidiones

Among the eight compounds, compound 20a showed better activity against the Feline coronavirus in CRFK cells with an EC_{50} and SI value of 4.8 μg/mL and higher than 20 respectively. Similarly, this compound against Feline Herpes virus showed activity, but four-fold less active than Feline coronavirus and compound 21a was found to be another active compound against Coxsackie B4 virus with an EC_{50} and SI values of 10 μg/mL and greater than or equal to 2. These compounds only possessed promising activity against only two cells (RNA viruses) because these spirothiazolidione derivatives of imidazo[2,1-b]thiazole did not show activity against DNA viruses. In comparison to *Urtica dioica* agglutinin lectin (UDA) and Ganciclovir references, cytotoxicity against Feline corona and Feline herpes viruses was tested in CRFK cell cultures, and the compound 20a was found to be extremely effective. Thus, the spirothiazolidionone derivatives 20a and 21a were found to be more potent antiviral compounds.

Guzeldemirci et al. [44] synthesized a series of novel 3-alkyl/aryl-2-(((6-(phenyl(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono)-5-nonsubstituted/methyl-4-thiazolidinones (**22**) and evaluated their potency against different diverse RNA and DNA viruses. The Feline corona virus or Feline herpes virus infected Crandell Rees Feline kidney cells, Herpes simplex virus-1 or 2 infected human embryonic lung (HEL) fibroblast cells, vesicular stomatitis virus-infected Human cervix carcinoma HeLa cells, Parainfluenza-3-virus, Sindbis virus, Coxsackie B4 virus-infected African green monkey kidney Vero cells, influenza A/H1N1, A/H3N2 or B virus Mardin-Draby canine kidney cells and HIV-1 or 2 infected human T-lymphoblast MT-4 cells were used in this study to determine the efficiency of the synthesized compounds.



22

22a R=H, R_1=CH_2=CH.CH_2, R_2=CH_3
22b R=Cl, R_1=CH_3, R_2=CH_3
22c R=Cl, R_1=C_6H_5, R_2=CH_3
22d R=Cl, R_1=C_3H_7, R_2=CH_3

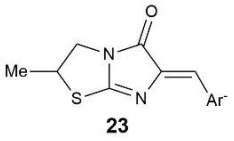
Fig. 23 Structures of 3-alkyl/aryl-2-(((6-(phenyl(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono)-5-nonsubstituted/methyl-4-thiazolidinones

From the cytopathic effect reduction assay, compounds 22a and 22b exhibited activity against vesicular stomatitis virus with EC50 values of 9 μM and 2 μM, respectively. These compounds had SI values of 11 and 10, respectively. The anti-RSV activity was displayed by the compound 22b and the compound 22c with five-fold lower than 22k but had the same SI value of 10. The methyl substituent is present at the R2 position in these three molecules.

Only one of the compounds, 22d, showed equal activity in the CPE or MTS assays and was determined to be active against the influenza A virus and its subtypes (H1N1 and H3N2). None of the compounds were shown to be active against HIV-1 or 2 when compared to other viral cell cultures, however, they did show activity against a variety of RNA viruses.

2.4 Anti-Inflammatory Activity

Saliyeva et al. [13] designed 6-arylidenimidazothiazolones (**23**) and the anti-inflammatory or anti-exudative activity of the synthesized compounds was determined against carrageenan-induced paw edema. The decrease of paw edema against the synthesized compounds was performed using male albino rats. The standard drug was diclofenac, at a dose of 8 mg/kg.



23

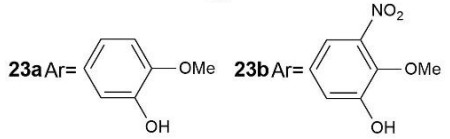


Fig. 24 Structures of 6-arylidenimidazothiazolones

All the synthesized novel 6-arylidene-2-methyl-2,3-dihydroimidazo[2,1-b][1,3]thiazole-5(6H)-ones were studied for their anti-inflammatory activity. Among the 14 compounds, the compounds 23a and 23b displayed better activity than others with the percentage inhibition of 40.3 and 38.8% respectively. Diclofenac, a common medication, has a percentage inhibition of 48.2 %. As a result, when compared to the standard, compound 23a was found to have

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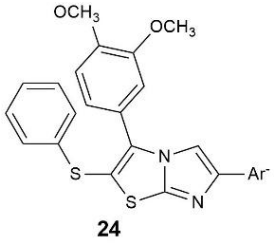
approximately or nearly the same impact as the standard, demonstrating its anti-exudative activity through the suppression of carrageenan-induced inflammation.

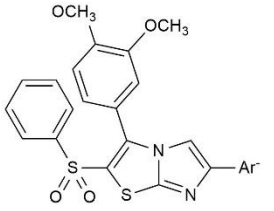
Shetty et al. [45] tested a series of novel 6-aryl-3-(3,4-dimethoxy-phenyl)-2-phenylsulfonyl-imidazo[2,1-b]thiazole (**24**) and 6-aryl-2-benzenesulfonyl-3-(3,4-dimethoxy-phenyl)imidazo[2,1-b]thiazole (**25**) *in vivo* for anti-inflammatory efficacy against carrageenan-induced hind paw edema. Among the 6 compounds, compound 25a exhibited the higher activity with the percentage inhibition of 40% at 2h and 48% at 3h. The derivatives 25a-c showed the better activity when compared to 24a-c with a higher rate of percentage inhibition and the compound 25a has the activity (% inhibition) nearly to that of standard (60% at 2h and 65% at 3h) and provides the promising anti-inflammatory activity.



24

24a Ar=p-BrPh
24b Ar=p-ClPh
24c Ar=NO_2Ph

Fig. 25 Structures of 6-aryl-3-(3,4-dimethoxy-phenyl)-2-phenylsulfonyl-imidazo[2,1-b]thiazole



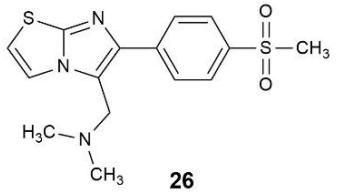
25

25a Ar=p-BrPh
25b Ar=p-ClPh
25c Ar=NO_2Ph

Fig. 26 Structures of 6-aryl-2-benzenesulfonyl-3-(3,4-dimethoxy-phenyl)imidazo[2,1-b]thiazole

2.5 COX-2 Inhibitory Activity

A series of imidazo[2,1-b]thiazole (**26**) derivatives having the methyl sulfonyl COX-2 pharmacophore were developed by Sharasbi et al. [19] and the COX-2 inhibitory activity of all the generated compounds was tested. To determine the *in vitro cyclooxygenase* inhibitory activity, enzyme chemiluminescent kit was used and the efficiency of COX inhibitors was screened using Cayman chemical chemiluminescent COX inhibitor screening assay. All of the compounds were found to be selective inhibitors of COX-2 isoenzyme *in vitro* with IC_{50} values ranging from 0.08 to 0.16 μM. When the IC_{50} values were compared, the compound 26 (N, N-dimethyl-1-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b]thiazol-5-yl)methanamine) was found to be a more potent and selective COX-2 inhibitor. The docking studies also showed that the compound 26 and SC558 were superimposed tightly in COX active site and found to be more selective and potent inhibitor of COX-2.

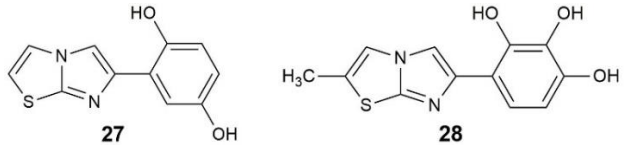


26

Fig. 27 Structure of 1-{6-[4-(methanesulfonyl)phenyl]imidazo[2,1-*b*][1,3]thiazol-5-yl}-*N*,*N*-dimethylmethanamine

2.6 Anti-Oxidant Activity

Andreani et al. [12] synthesized 6-substituted imidazo[2,1-b]thiazoles (imidazothiazoles bearing phenolic groups) (**27,28**) and evaluated their antioxidant activity using Briggs-Rauscher method (BR method), DPPH test and Trolox Equivalent Antioxidant activity (TEAC) assay. The compounds against BR oscillating reaction method under acidic conditions, the compound 27 (1.032±0.002 μM) was found to be having similar activity to that of standard resorcinol (1.00 μM) and the compound 28 (0.14±0.03 μM) was found to be equipotent to the standard. Further, these compounds under TAEC assay at pH 7.4, compound 27 was found to be possessing relatively higher activity and compound 28 (3.06±0.05 mM) which contains methyl group at 2-position also showed the same activity as that of standard quercetin (3.1 mM). In DPPH assay also, these compounds 27 and 28 exhibited similar potency i.e., 0.71±0.02 and 1.38±0.05 mM, respectively.



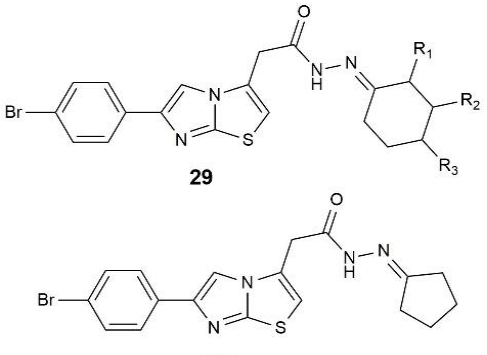
27 **28**

Fig. 28 Structures of imidazothiazoles bearing phenolic groups

A series of novel oxo-hydrazone and spiro condensed-thiazolidine derivatives of imidazo[2,1-b]thiazole (**29-31**) was produced by Dincel et al. [46] and evaluated their antioxidant property by inhibition of $FeCl_3$/ascorbate system-induced lipid peroxidation of lecithin liposome (anti-LPO) scavenging activity against ABTS radical and Ferric Reducing Antioxidant Power (FRAP) activity.

The inhibitory effects of imidazo[2,1-b]thiazole derivatives on iron (III) and ascorbic acid-induced lipid peroxidation were investigated and the compounds 29a-j, 30a, 30b, 31a, 31b and 31c were found to be having a dose-dependent inhibitory action on TBARS formulation. Based on the EC_{50} values, the compound 28a (0.565±0.051) and 29b (0.708±0.074) were found to be having the best inhibitory activity. Among these two compounds, compound 30a had the maximum activity due to the non-substitution at R4.

For the compounds having dose-dependent inhibitory activity, the ABTS radical scavenging activity was performed and the compound 29d which is the member of oxo-hydrazone derivatives was found to possess the better activity than others with an EC_{50} value of 2.289±0.491. From the FRAP activity, the compound having a high FRAP value indicates the higher reducing power and based on this, the compounds 29i and 29a with reducing power of 2.11±0.077 and 2.046±0.033 respectively were found to be the most active compounds. At the 10mM concentration, on the comparison with the reference α-tocopherol, the derivatives were found to be possessing close FRAP values (p>0.05) and found to be having the ability to remove lipid peroxide radicals and inhibition of lipid peroxidation.

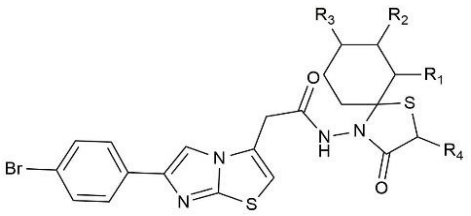


29

29d

29a R_1=CH_3, R_2=H, R_3=H
29b R_1=H, R_2=H, R_3= CH_3CH_2
29c R_1=H, R_2=H, R_3=H

Fig. 29 Structures of oxo-hydrazone derivatives of imidazo[2,1-b]thiazole



30a, 31a,b

30a R_1=H, R_2=H, R_3=C_6H_4OH, R_4=H
31a R_1=CH_3, R_2=H, R_3=H, R_3=CH_3
31b R_1=H, R_2=H, R_3=C_6H_4OH, R_4=CH_3

Fig. 30 Structures of oxo-hydrazone - spiro condensed-thiazolidine derivatives of imidazo[2,1-b]thiazole

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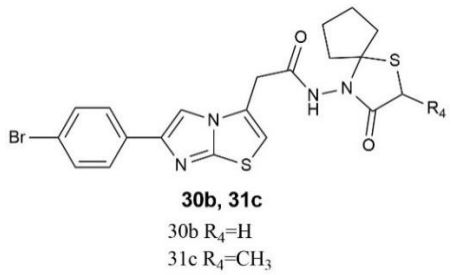


Fig. 31 Structures of oxo-hydrazone - spiro condensed-thiazolidine derivatives of imidazo[2,1-b]thiazole

Sonawane et al. [47] used Claisen-Schmidt condensation to obtain a series of condensed imidazo[2,1-b]thiazole chalcones (**32, 33**), which were then tested for *in vitro* antioxidant activity. The DPPH assay was performed and the compounds 31a, 31b, 33a and 33b were exhibited the moderate activity. The compound 32a was found to be the most potent compound with the strongest percentage of inhibition (53.42%) and found to be more potent than the standard ascorbic acid (44.18%). The SOD assay also showed the activity of 32a (42.85%) with moderate activity as that of standard (74.07%).

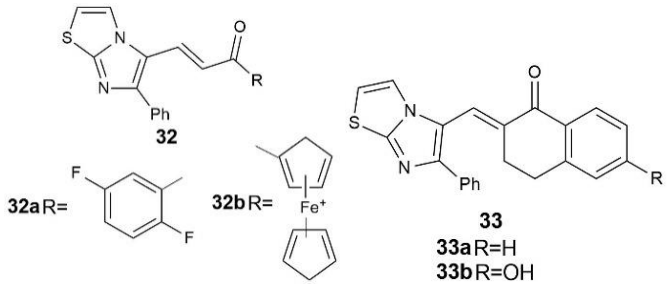


Fig. 32 Structures of imidazo[2,1-b]thiazole chalcones

2.7 Antimalarial Activity

Vekariya et al. [9] synthesized some imidazo[2,1-b]thiazole(**34**) derivatives using microwave assisted green synthesis and evaluated them against *Plasmodium falciparum* 3D7 chloroquine-sensitive strain to determine the *in vitro* antimalarial activity using quinine and chloroquine as the reference standards. All of the produced compounds were tested against the selected strain and the compounds 34a and 34b were discovered to have high activity against *P. falciparum* with IC_{50} values of 0.2 µg/mL and 0.22 µg/mL, respectively. Both of these compounds feature two electron-deactivating groups at the 2 and 4 positions of the phenyl ring and their activity was found to be equivalent to that of the conventional medicine quinine (IC_{50} = 0.268).

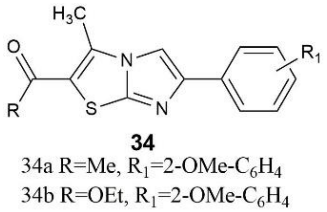


Fig. 33 Structures of 1-(3-methyl-6-phenylimidazo[2,1-b]thiazol-2-yl)ethanone

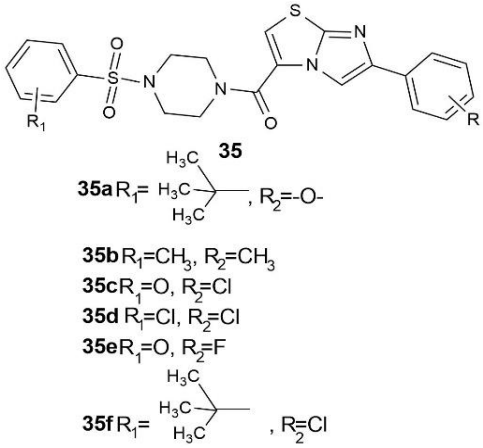


Fig. 34 Structures of imidazo[2,1-b]thiazole-sulfonyl piperazine

2.8 Carbonic Anhydrase Inhibitory Activity

A variety of new imidazo[2,1-b]thiazole-sulfonyl piperazine compounds (**35**) were developed by Manasa et al. [17] and tested their effectiveness against inhibition of *carbonic anhydrase* utilizing four isoforms: cytosolic isoenzyme hCA I, II, and transmembrane tumor-assisted isoforms hCA IX and hCAXII. The acetazolamide was used as a reference. By the stopped-flow CO_2 hydrase assay, all the synthesized compounds were screened against four isoforms and the compounds 35a, 35b, 35c, 35d, 35e, 35f and 35g exhibited the inhibitory activity against hCA II, while others were found to be ineffective. hCA I, hCA IX, and hCA XII were shown to be unaffected by any of the compounds. Based on the Ki values, the compound 35a (Ki = 57.7 µM) was found to be the most potent and promising *carbonic anhydrase* inhibitor.

2.9 15-Lipoxygenase Inhibitory Activity

Terani et al. [48] tested a variety of 3,6-diphenylimidazo[2,1-b]thiazol-5-amine (**36**) derivatives to determine their efficacy against *15-lipoxygenase* inhibition. A spectrophotometric experiment was used to test the produced compound's LOX inhibitory activity. The compound 36a was shown to be the most powerful chemical against soybean 15-LOX enzyme, having an IC_{50} value of 11.5 µM. When compared to the standard drug quercetin, the compound 36a has two times more potent activity and the compound is also found to be potent as that of quercetin. When compared to the cyclohexyl substituted compounds, the compounds with tert-butyl substituents showed better inhibitory activity. For the most active compound 36a, the neuroprotective activity against oxidative stress-induced cell death in differentiated PCl_2 cells was performed within the range of 1-10 µM because the active compound did not show toxicity in the range of 1-10 µM. The H_2O_2-treated group had a 49% reduction in cell viability, while compound 36a protected $PC1_2$ neurons against H_2O_2-induced cell death (p0.001). The docking studies were done using Autodock Vina (ver.1.1.1) and it showed that the most active compound 36a had the proper interaction with 15-LOX by hydrophobic interaction and proved its potential as 15-LOX inhibitors.

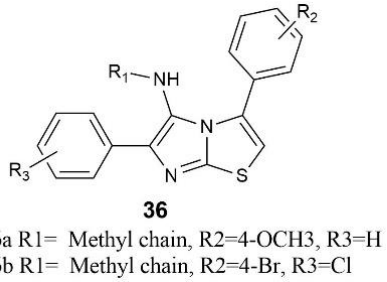


Fig. 35 Structure of 3,6-diphenylimidazo[2,1-b]thiazol-5-amine

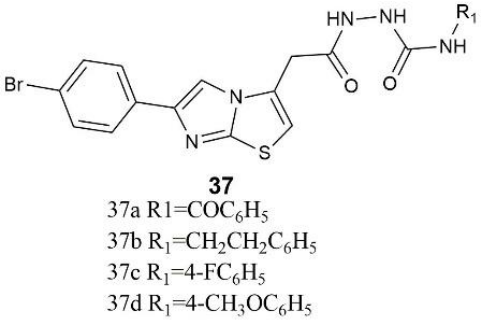


Fig. 36 Structures of 2-((6-(4-bromophenyl)imidazo[2,1-b]thaizol-3-yl)acetyl)-N-alkyl/arylhydrazine carbothioamide

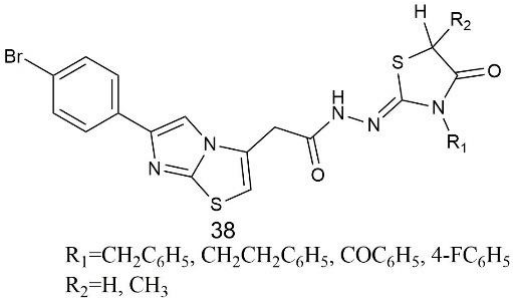


Fig. 37 Structures of 3-alkyl/aryl-2-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)hydrazono)-5-nonsubstituted/methyl-4-thiadiazolidinone

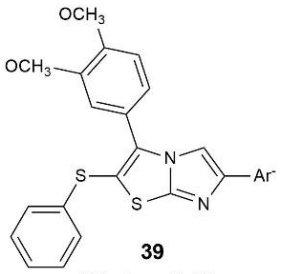
https://doi.org/10.30799/jacs.244.22080101

2.10 Aldose Reductase Inhibitory Activity

The novel 2-((6-(4-bromophenyl)imidazo[2,1-b]thaizol-3-yl)acetyl)-N-alkyl/arylhydrazine carbothioamide (**37**) and 3-alkyl/aryl-2-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)hydrazono)-5-nonsubstituited/methyl-4-thiadiazolidinone (**38**) derivatives were evaluated to determine their effect as *aldose reductase* inhibitors by Guzeldemirci et al. [49]. The activity of *aldose reductase* was measured in the kidneys of Wrister albino rats. The *aldose reductase* enzyme was isolated, and the ability of substances to inhibit *aldose reductase* was determined using a UV-1700 visible spectrophotometer to measure the drop in NADPH concentration at 340nm. Among the screened compounds, compound 37a exhibited the best *aldose reductase* inhibitory activity at the rate of 25.41% and the other compounds 37b, 37c and 37d also showed activity with the inhibition rate of 14.03%, 21.31% and 13.73%, respectively. But the compound 38 and its derivatives showed very less inhibition. Thus, the hydrazine carbothioamide compound 37a-d were found to be effective and the compound 37a as most active *aldose reductase* inhibitor.

2.11 Anthelmintic Activity

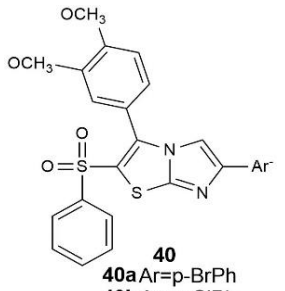
Shetty et al. [45] synthesized a series of 6-aryl-3-(3,4-dimethoxyphenyl)-2-phenylsulfonyl-imidazo[2,1-b]thiazole (**39**) and 6-aryl-2-benzenesulfonyl-3-(3,4-dimethoxyphenyl)imidazo[2,1-b]thiazole (**40**) and their efficiency against *Pheritima postuma* earthworms were evaluated using piperazine citrate as reference. By the paralysis of earthworms, both the compounds 39 and 40 exhibited the anthelmintic activity but the 2-arene-sulfonyl derivatives (40) displayed better activity than aryl thiol derivatives (39). Among the three compounds (40a-c), the compound 40a showed better anthelmintic activity with the dead time of 58 and 65 minutes at 2.5 and 1.0% W/V concentration respectively. This revealed that the compound 40a was more potent than the standard drug piperazine citrate and provides promising anthelmintic activity.



39

39a Ar=p-BrPh
39b Ar=p-ClPh
39c Ar=NO_2Ph

Fig. 38 Structures of 6-aryl-3-(3,4-dimethoxyphenyl)-2-phenylsulfonyl-imidazo[2,1-b]thiazole



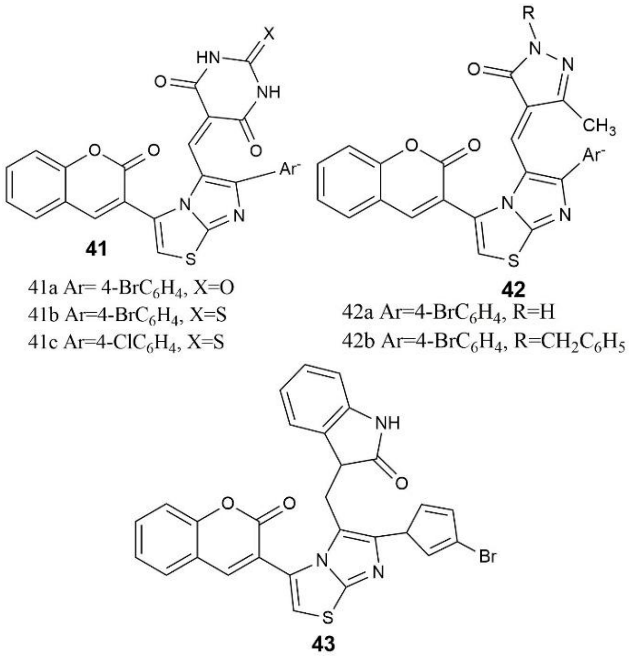
40

40a Ar=p-BrPh
40b Ar=p-ClPh
40c Ar=NO_2Ph

Fig. 39 Structures of 6-aryl-2-benzenesulfonyl-3-(3,4-dimethoxyphenyl)imidazo[2,1-b]thiazole

2.12 Anticancer Activity

Gali et al. [4] tested a series of novel coumarinylimidazo[2,1-b]thiazoles (**41-43**) for cytotoxicity using the MTT assay against MCF-7 (breast), HepG2, (liver), HeLa (cervical) and NCI-H460 (lung) cancer cell lines. With IC_{50} values of 10.99±0.7, 13.92±0.2 and 50.18±0.0 μM, respectively, compound 41c showed higher activity against MCF-7, HepG2 and HeLa cell lines with IC_{50} values of 10.83±0.5 and 6.77±0.2 M, compound 43 was found to be active against MCF-7 and HeLa cell lines, respectively. Furthermore, the compounds 41a, 41b and 42a were discovered to be active against HeLa cell lines with IC_{50} values of 7.13±0.14, 14.21±0.6 and 17.87±0.5 μM, respectively, and the compound 42b was discovered to be significantly active against NCI-H460 with an IC_{50} value of 16.27±0.5 μM. As a result, the compounds 41a, 41b, 42a, 42b, 42c and 43 were discovered to have higher cytotoxic activity.



41

41a Ar= 4-BrC_6H_4, X=O
41b Ar=4-BrC_6H_4, X=S
41c Ar=4-ClC_6H_4, X=S

42

42a Ar=4-BrC_6H_4, R=H
42b Ar=4-BrC_6H_4, R=$CH_2C_6H_5$

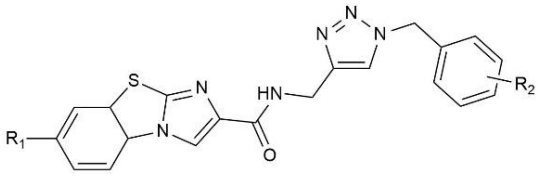
43

Fig. 40 Structures of coumarinylimidazo[2,1-b]thiazoles

Using the MTT method, novel 1,2,3-triazolo linked benzo[d]imidazo[2,1-b]thiazole conjugates (**44**) were investigated by Shaik et al. [5] to evaluate their cytotoxic activity against prostate (DU-145), cervical (HeLa), breast (MCF-7), liver (HepG2) and lung (A549) cell lines. The compounds 44a and 44b were shown to be the most active among the produced compounds with IC_{50} values of 0.607 and 0.781 μM, respectively against the MCF-7 cell line.

The activity of the active compounds 44a and 44b against tubulin polymerization inhibition was investigated further. The cell cycle analysis by flow cytometry showed that the compounds slowly arrested the G_2/M cell cycle with 33.9 and 32.6% of cell accumulation. The cyclin B1 protein level investigation demonstrated that the compounds 47a and 47b induce a mitotic arrest and the Cdk_1 and Aurora B kinases levels were analyzed.

Because the compounds above were successful at arresting the G2/M cell cycle, tubulin polymerization inhibition was screened and found to have 49.9% and 52.3 % inhibition, with IC_{50} values of 1.23 and 1.65 μM, respectively. The potential of the powerful compounds 44a and 44b to induce apoptosis was studied using an Annexin V FITC/PI dual staining assay and found to be more potent than etoposide with only 13.7 and 8.7% of cells alive at 5 μM, respectively. The molecular docking studies revealed that the active compounds 44a and 44b had better binding and interaction with colchicine binding site of tubulin (between the α and β subunits).



44

44a R_1=H, R_2=4-F
44b R_1=Me, R_2=4-F

Fig. 41 Structures of 1,2,3-triazolo linked benzo[d]imidazo[2,1-b]thiazole

Shareef et al. [6] tested a series of imidazo[2,1-b]thiazole-based aryl hydrazones (**45**) against a panel of human cancer cell lines. All the synthesized compounds were tested against DU145 (prostate), MDA-MB-231 (breast), HeLa (cervical), A549 (lung) and HEK-293 (kidney) cell lines by MTT assay. The compounds 45a, 45b and 45c showed the best cytotoxicity, with IC_{50} values ranging from 1.12 to 5.2 μM. With IC_{50} values of 1.65 and 1.12 μM, respectively, the compounds 45b and 45c demonstrated promising action against the MDA-MB-231 cell line. These potential compounds on flow cytometry analysis showed the arresting of the G_0/G_1 phase cell cycle with 72 and 75.8% of accumulation and found to be equipotent to that of doxorubicin (81%).

The Annexin-V-FITC and Propidium iodide staining assay revealed that the compounds 45b and 45c had a higher percentage of early apoptotic cells than the control and that these compounds increased intracellular ROS generation using a *peroxidase* sensitive fluorescent dye, demonstrating ROS accumulation potential and promoting apoptosis.

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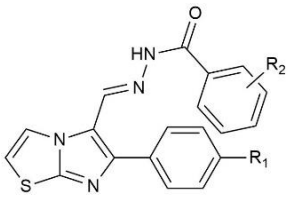
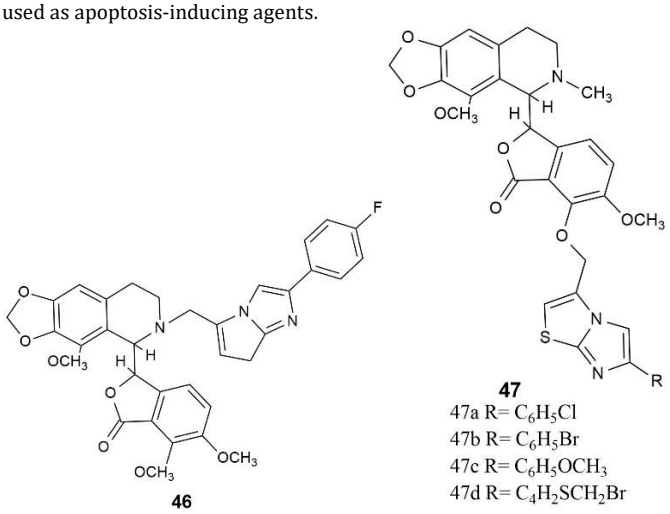


45

45a R_1=H, R_2=3,4,5-trimethoxyphenyl
45b R_1=4-OCH3, R_2=3-hydroxyphenyl
45c R_1=4-F, R_2=3,4,5-trimethoxyphenyl

Fig. 42 Structures of imidazo[2,1-b]thiazole-based aryl hydrazones

A series of imidazothiazole coupled noscapinoids (**46, 47**) were evaluated by Nagireddy et al. [7] to determine their efficiency as anticancer agents against HeLa (cervical), MIA PaCa-2 (epithelial), SK-N-SH (neuroblastoma) and DU145 (prostate) cancer cell lines using SRB assay. To determine the potency of the synthesized compounds, the five-dose screening for all the 31 compounds were performed and the compounds 46, 47a, 47b, 47c and 47d were found to be active against NCI-60 panel cell lines. The IC_{50} values of the above said compounds were found to be 54±0.16, 21.8±1.4, 20.5±1.7, 18.7±0.5 and 17.1±1.1 against DU145 cell line, 55.8±2.4, 37.5±1.4, 32.2±2.1, 33.8±1.8 and 35.4±2.3 against MCF-7 cell line, 66.8±3.3, 33.2±3.4, 50.5±2.2, 48.3±2.3 and 47.2±3.1 against SK-N-SH cell line and 56.8±2.1, 3.9±0.6, 4.2±1.4, 6.9±1.4 and 3.6±1.3 against MIA PaCa-2 cell line, respectively. Among the derivatives, compounds 46 with p-fluoro substitution and O-derived 49d were found to be more potent compounds. The cell survival experiment was used to evaluate the active substances. The compound 47d was found to be inhibiting the formation of colonies in pancreatic cells and the compounds 47b and 47c also displayed equal activity. These compounds arrested the G2/M cell cycle and showed tubulin polymerization inhibitory efficacy. By flow cytometry, it was found to be the most effective compound for G_2/M phase cell cycle arresting with 76.94% of accumulation via apoptosis induction, caspase-3 inhibition and increasing levels of cyclin-B1 and CDK-1. Thus, the imidazo[2,1-b]thiazole coupled noscapine derivatives possessed potent anticancer activity and were also used as apoptosis-inducing agents.

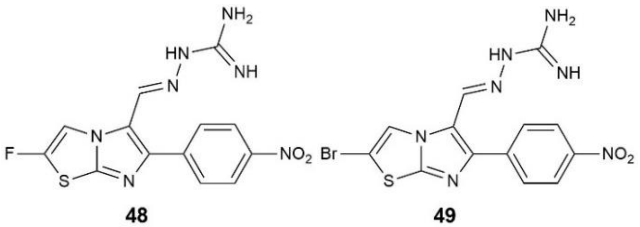


46 47

47a R= C_6H_5Cl
47b R= C_6H_5Br
47c R= $C_6H_5OCH_3$
47d R= $C_4H_2SCH_2Br$

Fig. 43 Structures of imidazothiazole coupled noscapinoids

A variety of imidazo[2,1-b]thiazoleguanylhydrazoles(**48, 49**) were produced by Andreani et al. [14] and tested their efficacy as RSK2 inhibitors in p90 ribosomal s6 kinase 2. To determine their efficacy, cell-based screening was conducted first, followed by high-throughput kinase (enzyme) inhibition screening against RSK1, RSK2, CHK1 and CHK2. MCF-7 (breast), MCF-10A (normal human breast cell line), T47D (hypotriploid human cancer cell line), and HEK-293 (embryonic cell line) cell lines were used to test the antiproliferative activity of the synthesized compounds.



48 49

Fig. 44 Structures of Imidazo[2,1-b]thiazoleguanylhydrazoles

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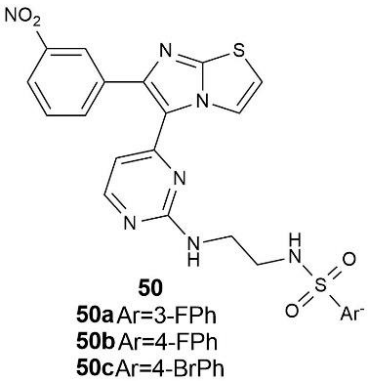
The compounds 48 and 49 were reported to be active against RSK2 with IC_{50} values of 1.23 and 2.15 μM, respectively, when tested against kinase enzymes. The antiproliferative cell-based experiments were done against MCF-7 (human breast cancer cell line) and MCF-10A, and these compounds were revealed to have more potent kinase inhibitory activity as well as tumor growth suppression (normal human breast cell line). Both compounds stopped cancer cells from growing, while compound 49 stopped cancer cells from growing in both cell lines. Thus, compounds 48 and 49 possessed the selective inhibition of cancer cells, as well as GSK3 biomarker inhibition which showed that the compounds affected RSK2.

Ammar et al. [15] designed novel imidazo[2,1-b]thiazole (**50**) derivatives and evaluated its cytotoxicity against NCI panel cell lines and checked their activity against mutated B-Raf kinase inhibition. All the synthesized compounds were tested against mutated B-Raf kinase and compound 46a completely inhibited the B-Raf V600E at 10 μM. The compounds 50a, 50b, and 50c were found to have stronger inhibitory activity than standard vemurafenib with IC_{50} values of 0.021, 0.035 and 0.020 μM, respectively. To estimate the *in vitro* cytotoxicity, a one-dose assay against NCI-60 cell lines was performed and the compounds 50a and 50b were found to be potent compounds that exhibited 160% inhibition against melanoma cell lines and 90% inhibition against leukemia and prostate cancer. Compounds against BT-549 (aneuploid), MCF-7 (breast), MDA-MB-468(breast) and T47D (hypotriploid) cell lines, 100% inhibition was obtained. The added NO_2 group in the terminal phenyl ring had effective binding with B-Raf V600E kinase and was found to be effective B-Raf V600E kinase inhibitors through H-bond interactions with amino acid residues, according to molecular docking studies.

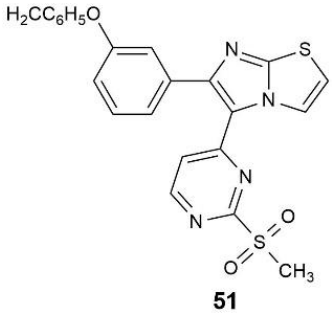


50

50a Ar=3-FPh
50b Ar=4-FPh
50c Ar=4-BrPh

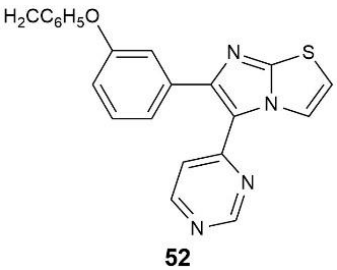
Fig. 45 Structures of N-(2-((4-(6-(3-nitrophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)methanesulfonamide

Zaraei et al. [16] screened novel imidazothiazole derivatives (**51, 52**) to determine its potency against $ErbR_4$ (HER4) inhibitors. The antiproliferative activity of all produced compounds was tested against the NCI-60 panel.



51

Fig. 46 Structure of 6-(3-(benzyloxy)phenyl)-5-(2-(methylsulfonyl)pyrimidin-4-yl)imidazo[2,1-b]thiazole



52

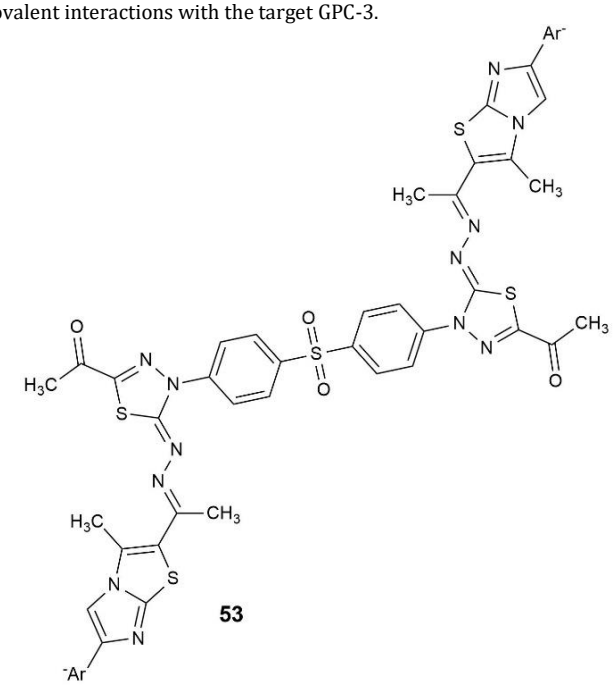
Fig. 47 Structure of 6-(3-(benzyloxy)phenyl)-5-(pyrimidin-4-yl)imidazo[2,1-b]thiazole

The compounds 51 and 52 exhibited enhanced antiproliferative activity and were subjected to 5-dose testing using sorafenib, which is a multi-kinase inhibitory anticancer drug and ibrutinib, which is a pan-HER inhibitory anticancer drug as reference standards. Compound 51 was found to be more effective against seven cell lines than sorafenib, whereas compound 52 was found to be active against six cell lines. When compared to normal ibrutinib, compound 51 was more effective against six cell lines, particularly SK-MEL-5 (hyperpentaploid) with an IC_{50} of 0.51 μM and compound 52 was effective against five cell lines.

The kinase inhibition of the selected compounds 51 and 52 was screened and found to be active against $ErbB_4$ kinase with the percentage inhibition of 96.10% and 60.21%, respectively. Further, compound 51 was tested against 54 kinases and found to be active against EGFR, $ErbB_4$, JAK_3 and V600E-BRAF. Based on the 10-dose assay, the compound was found to be an $ErbB_4$ kinase inhibitor with an IC_{50} value of 15.24 μM. The second most potent kinase inhibitor 52 also showed more than 60% of inhibition against 12 kinases including $ErbB_4$.

In order to determine the inhibition of $ErbB_4$ kinase inside the cells by crossing the membrane, the most active compound 51a was tested against T47D (hypotriploid) cell line using lapatinib as standard. The compound 52k was found to be inhibiting the ErbB4 kinase intracellularly with an IC_{50} value of 3.30±0.05 μM, but based on the NCI panel, it was 4.08 μM. Thus, the compound 52k against the T47D cell line was found to be having more antiproliferative activity with partial $ErbB_4$ inhibition. By molecular docking and dynamic stimulation, the compound 51a was found to be having higher selectivity against cancer cells, weak inhibition against HERG ion channels and weak potency against *CYP3AA* and *2D6* isoenzymes inhibition. Thus, the active compounds were found to be selective $ErbB_4$ kinase inhibitors [16].

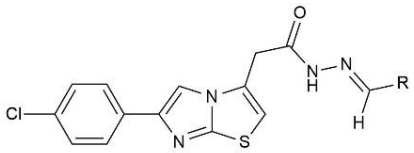
Rashdan et al. [21] investigated the effectiveness of imidazo[2,1-b]thiazole scaffolds coupled thiadiazole derivatives (**53**) against HepG2 (liver) cancer cell lines. This compound 53 has higher antiproliferative activity against HepG2 and normal cell lines, with IC_{50} values of 12.731.36 and 8.341.81 μg/mL, respectively compared to 3.560.46 and 3.210.32 μg/mL for the reference drug doxorubicin. The *in silico* molecular docking for compound 53 was performed against GPC protein using the PyRx tool and the binding affinity was found to be -10.30 kcal/mol. The compound 53 forms two pi-cation interactions with the ARG197 at distances of 6.42 and 6.49Å. As a result, it had a high binding affinity and had superior non-covalent interactions with the target GPC-3.



53

Fig. 48 Structure of imidazo[2,1-b]thiazole scaffolds coupled thiadiazole

Varieties of arylidene hydrazide (54) derivatives were tested on a panel of human cancer cell lines by Karaman et al. [22]. All the synthesized compounds were tested against NCI panel of cell lines and the compounds 54a and 54b were found to be active compounds. 54a, an R-2-hydroxyphenyl substituted compound, showed the most promising antiproliferative and inhibitory impact against malignant cell lines when compared to 54b. When compared to standard drugs cisplatin and sorafenib, the active chemical 54a was found to be selectively active against ovarian cancer cell line (OVACAR-3). This also stopped ACHN, RXF-393, and UIO-31 from growing *in vitro*, with $\log_{10}GI_{50}$ values of -5.75, -6.11, -5.57 and -6.30, respectively.



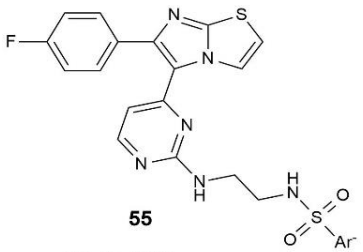
54

54a R=C_6H_5OH

54b R=$C_6H_4(OCH_3)_2$

Fig. 49 Structures of arylidene hydrazide imidazothiazole

Abdel-Maksoud et al. [50] synthesized a number of 5,6-diarylimidazo[2,1-b]thiazole (**55**) derivatives and tested them *in vitro* against NCI panel cell lines. Based on one-dose *in vitro* antiproliferative testing, the ethylene linked derivatives 55a, 55b, 55c and 55d showed more activity than their propylene derivatives and the compounds 55e and 55f with propylene derivatives exhibited more activity than their ethylene derivatives.



55

55a Ar=C_6H_5

55b Ar=$C_6H_5CH_3$

55c Ar=$C_6H_4(OCH_3)_2$

55d Ar=C_6H_5OH

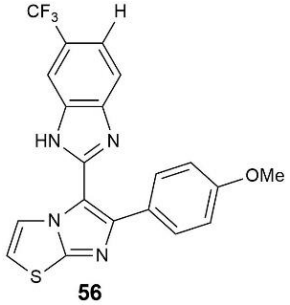
55e Ar=$C_6H_5CF_3$

55f Ar=Naphthalene

Fig. 50 Structures of 5,6-diarylimidazo[2,1-b]thiazole

The compound 55d with ethylene spacer and para-hydroxyphenyl terminal ring exhibited better antiproliferative activity against COLO205 colon cancer cell line and MCF-7 breast cancer cell line with IC_{50} values of 0.845 and 0.476 nM, respectively and was also found to be more potent than sorafenib based on the five-dose screening. In order to determine the inhibition of kinase, the potent antiproliferative compound 55d was tested at a single-dose concentration (10 μM) against wild type B-RAF, V600E-B-RAF and C-RAF kinases. The compound 55d was reported to have a greater inhibitory effect on V600E-B-RAF kinase than sorafenib with an IC_{50} value of 39.9 nM and had stronger potency against over-expressed V600E-B-RAF in cell lines such as COLO205, HT29 colon cancer, and SK-MEL-5 melanoma cancer cell lines. The compound 55d was then tested against MEK/ERK containing A375 cell lysate using a Western blot assay and found to strongly reduce MEK1/2 and ERK1/2 phosphorylation. Thus, the compound 55d was found to be a more potent antiproliferative compound with ERK pathway and kinase inhibition.

Using nocodazole as a reference standard, a variety of imidazo[2,1-b]thiazole-benzimidazole (**56**) compounds were developed by Biag et al. [51] and tested their effectiveness against HeLa (cervical), A549 (lung), MCF-7 (breast), and DU145 (prostate) cancer cell lines. The compound 56 was reported to have significant activity against the A549 cell line with IC_{50} values of 1.08 and 1.13 μM and to be arresting the G2/M cell cycle at 1 and 2 μM doses with topoisomerase inhibition capabilities. The compound 56 was also tested for its capacity to inhibit tubulin polymerization and it was discovered to have a strong tubulin polymerization inhibition with an IC_{50} value of 1.68 μM similar to the preceding compounds. The active molecule has greater binding and interaction with the tubulin's colchicine site, according to molecular docking studies.



56

Fig. 51 Structure of imidazo[2,1-b]thiazole-benzimidazole

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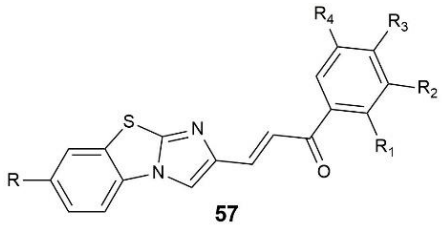
Sulatana et al. [52] synthesised a series of benzo[d]imidazo[2,1-b]thiazole-chalcone (**57**) derivatives and used the MTT assay to assess their cytotoxic activity against the human cancer cell lines A549 (lung), MDA-MB-231 (breast), DU145 (prostate) and HT29 (colorectal). The compounds 57a and 57b against MDA-MB-231 with IC_{50} values of 1.3 and 1.2 μM, respectively were found as having higher cytotoxicity among the 27 compounds.



57

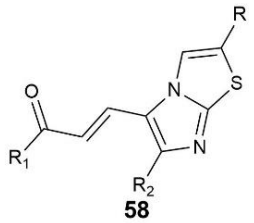
57a R=OMe, R_1=H, R_2=OH, R_3=OMe, R_4=H
57b R=H, R_1=H, R_2=H, R_3=OMe, R_4=H

Fig. 52 Structures of benzo[d]imidazo[2,1-b]thiazole-chalcone

The active compounds 57a and 57b were further investigated to determine their ability on cell cycle arresting, inhibition of tubulin polymerization, binding affinity and apoptosis detection. By flow cytometry on the MDA-MB-231 cell line, the compounds 57a and 57b at 1 and 2μM concentrations, 57a showed 14.8% and 21.1% arresting in S phase, whereas 57b with 21.81% and 23.14% G_2/M phase arresting and nocodazole was used as the reference standard. The compounds 57a and 57b suppressed tubulin polymerization by 59.16 and 61.38 percent, respectively in a study on tubulin polymerization inhibition. The IC_{50} values were found to be 1.93 and 1.88 μM, respectively and were found to be equipotent to that of standard drug nocodazole (1.97 μM).

The active compounds had improved contact and binding towards the colchicine site of tubulin in the colchicine binding assay and molecular dynamics investigations further verified the binding of compounds at the colchicine binding pocket of tubulin. The compounds 57a and 57b triggered apoptosis with 17.79 and 24.27 percent at 1 M; 23.61 and 33.67 percent at 2 μM, respectively according to flow cytometry analyses [52].

Kamal et al. [53] developed varieties of imidazothiazole-chalcone (58) compounds and studied their ability to induce apoptosis in cells. The cytotoxic activity of the synthesized compounds against NCI-60 panel cell lines were investigated and the compound 58a was found to be exhibiting excellent cytotoxicity against leukemia, colon, prostate and breast cancer cell lines with an IC_{50} values of 0.26-4.74 μM. The compound 58b was found to be active against SR and HC7-116 cell lines. The cell viability of compounds 58a-d against MCF-7 at 4 μM concentration, exhibited higher cytotoxicity at the range of 0.873±0.005 to 0.862±0.006. Thus, compound 58c was found to be having cytotoxicity nearly to that of doxorubicin (0.623±0.025). The compound 58c arrested G_0/G_1phase cell cycle with 91% inhibition and was found to be potent as that of standard doxorubicin (93%). It also resulted in a reduction in BrdU incorporation into cellular DNA.



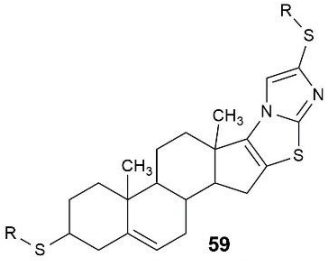
58

58a R=H, R_1=3,4,5-trimethoxyphenyl, R_2=2-thienyl
58b R=H, R_1=3,4,5-trimethoxyphenyl, R_2=trifluoromethyl
58c R=h, R_1=3,4,5-trimethoxyphenyl, R_2=3,4-dimethoxyphenyl
58d R=Me, R_1=3,4,5-trimethoxyphenyl, R_2=4-fluoromethyl

Fig. 53 Structure of imidazothiazole-chalcone

G1 phase cell cycle arrest was triggered via down-regulation of phosphor-b and subsequent up-regulation of G1/S-checkpoint associated tumor suppressor proteins by the active chemicals. As a result, compound 58b was discovered to be the most active and appropriate compound for treating breast cancer [53].

A series of steroidal[17,16-d]thiazolo[2,1-b]imidazole (**59**) derivatives were tested by Zhang et al. [54] to access their antiproliferative activity against EC109 (Human esophageal carcinoma), EC9706 (Human esophageal carcinoma) and MGC-803 (Human gastric carcinoma) using the MTT assay with 5-fluorouracil as the standard. Both compounds had higher antiproliferative activity and compounds 59a and 59b were found to be effective against MGC-803 cell lines. These compounds showed better activity and provided the relationship between structure and activity for the design of novel antiproliferative agents.

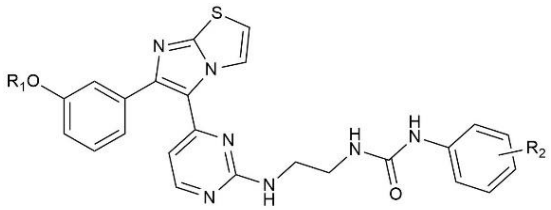


59

59a R= $C_6H_5CH_3$
59b R=$C_6H_5NH_2$

Fig. 54 Structures of steroidal[17,16-d]thiazolo[2,1-b]imidazole

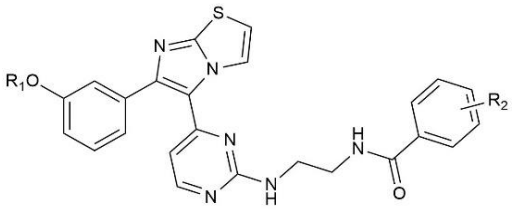
A variety of imidazo[2,1-b]thiazole(**60, 61**) derivatives were synthesized by Park et al. [55] and assessed their antiproliferative activities *in vitro* against the A375P human melanoma cell line and the NCI panel using sorafenib as a control. Among the 18 compounds, the compounds 60a, 60b, 60c, 61a, 61b, 61c, 61d and 61e were found to be active against the A375P cell line and found to be potent as that of sorafenib. The active compounds 61b and 61d have a higher potency than the others with IC_{50} values of 0.5 and 2.1 μM, respectively. The antiproliferative activity against NCI-60 panel cell lines was investigated and the compounds 60a, 60c, 61b and 61c exhibited the highest activity at initial dose screening. Then the active compounds were further tested in five-dose testing mode and the compounds 60a and 60c showed better activity against all types of cancer cell lines. With selectivity ratios of 4.25 and 4.14, the compounds 61c and 61d showed good selectivity against melanoma. The *in silico* studies also demonstrated that the compounds 61c and 61d were potent and selective compounds against melanoma.



60

60a R_1=CH_3, R_2=3-CF_3
60b R_1=CH_3, R_2=3,5-bis(CF_3)
60c R_1=H, R_2=3-CF_3

Fig. 55 Structures of 1-phenyl-3-(2-((4-(6-phenylimidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)urea



61

61a R_1=CH_3, R_2=3-CF_3
61b R_1=H, R_2=H
61c R_1=H, R_2=2-OH
61d R_1=H, R_2=3-CF_3
61e R_1=H, R_2=3-CF_3,5-morpholine

Fig. 56 Structures of N-(2-((4-(6-phenylimidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)benzamide

Mohmoud et al. [56] prepared a series of thiazolylimidazothiazole (**62-65**) derivatives and all of the produced compounds were screened using the MTT assay with doxorubicin as a reference against HCT-116 (colorectal) and MCF-7 (breast) cancer cell lines. All the compounds were found to be effective against the MCF-7 cell line, whereas the compounds 62, 63, 64a, 64b, 64c, 65a, 65b, 65c, 65d and 65e had exhibited better cytotoxicity against the HCT-116 cell line with IC50 values of 1.1, 5.6, 1.8, 1.1, 7.3, 8.0, 8.5, 8.9 and 6.2 μM, respectively. The potency of these compounds was higher than that of doxorubicin (IC_{50}=9.4 μM). The higher efficiency of compound 65 was due to the binding of DNA of tumor and amino and carbonyl groups.

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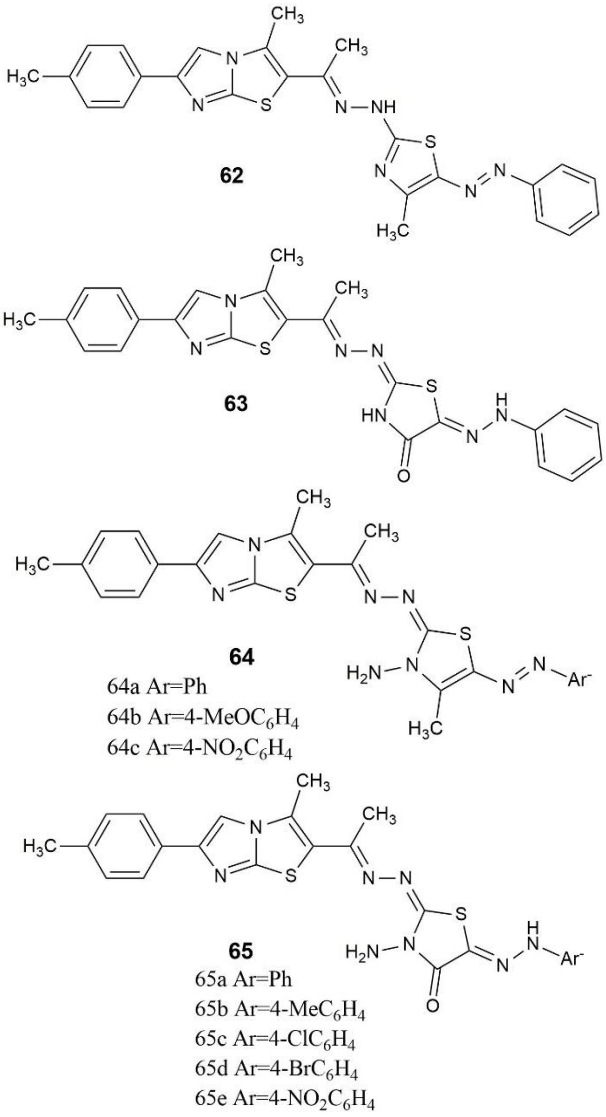

Fig. 57 Structures of thiazolylimidazothiazoles

Shaik et al. [57] tested a range of imidazo[2,1-b]thiazole linked triazole compounds (**66**) and their antiproliferative efficacy *in vitro* using the MTT assay against HeLa (cervical), DU145 (prostate), A549 (lung), MCF-7 (breast) and HepG2 (liver) cell lines. All of the produced compounds demonstrated action against the cancer cell lines A549 and MCF-7. The compounds 66a and 66b were discovered to have superior cytotoxic activity against A549 cell lines with IC_{50} values of 0.924 and 0.778 μM, respectively and against MCF-7 cell lines with IC_{50} values of 1.737 and 1.013 μM, respectively. Further, these active compounds on cell cycle analysis, showed that they arrested the G_2/M phase cell cycle with 20.4 and 21.7% of accumulation at 0.5 μM concentration and 26.2 and 28.5% of accumulation at 1 μM concentration.

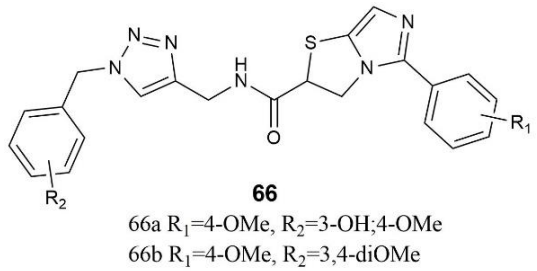

Fig. 58 Structures of imidazo[2,1-b]thiazole linked triazoles

Then, their efficiency on the inhibition of tubulin polymerization was analyzed and found to be having significant inhibition of tubulin polymerization with 70.2 and 74.3% inhibition and IC_{50} values of 1.62 and 1.43 μM, respectively. Thus, it was found to be having potent inhibition as that of standard nocodazole (71.0% inhibition). The percentage increase of apoptosis was revealed by Hoechst staining, Western plot analysis and the mitochondrial membrane potential of A549 cell lines was significantly reduced. 9.34 and 22.4% apoptosis were observed for compounds 66a and 66b at 0.5 μM concentration whereas 30.64 and 31.88% at 1 μM concentration which was observed by Annexin-V-FITC analysis. The efficient binding and interaction of 66a and 66b at the colchicine site of tubulin was discovered using molecular docking experiments [57].

The potency of a variety of benzo[d]imidazo[2,1-b]thiazole(**67**) derivatives against human cancer cell lines was studied by Deng et al. [58]. The MTT test was used to determine the inhibitory impact of all synthesized compounds against HeLa (cervical), HepG2 (liver), HL7702 (liver) and HUVEC (umbilical vein). The compounds 67a, 67b, 67c, 67d and 67e were shown to be active against HeLa cell lines with IC_{50} values of 0.42, 2.49, 14.05, 32.06 and 43.70 μM, respectively and the compound 67a was found to have potent action with equal potency to gefitinib.

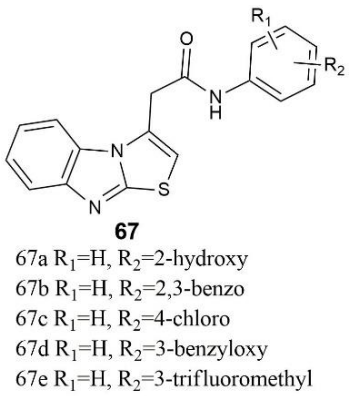

Fig. 59 Structures of benzo[d]imidazo[2,1-b]thiazole derivatives

From the *in vitro* EGFR inhibition study, the compounds 67a, 67b and 67c were found to be active against EGFR kinase with IC_{50} values of 55.0, 88.3 and 100 mmol/l, respectively and comparatively less potent than standard gefitinib (1.9) and Osimertinib (3.1). As a result, benzo[4,5]imidazo[2,1-b]thiazole derivatives have been identified as possible antiproliferative agents and new EGFR inhibitors [58].

Using the MTT assay, Koppireddi et al. [59] assessed a variety of new 3,6-diphenylimidazo[2,1-b]thiazole (**68**) derivatives and their efficacy against HeLa (cervical), MDA-MB-231 (breast), A549 (lung) and THP1 (leukemia) cell lines. Four cancer cell lines were used to screen all of the synthesized structures and the compounds 68a and 68b were found to be the most active compounds against the tested four types of cancer cells. The compound 68b was found to be a potent antiproliferative compound at the concentration range of 6-17.5 μM and arrested G_0/G_1 phase cell cycle with 54.78% of accumulation at 10 μM, 51.54% at 6.5 μM, respectively. This potent compound 68b also increased the apoptosis in HeLa cells and significantly increased caspase-3 and caspase-8 activities.

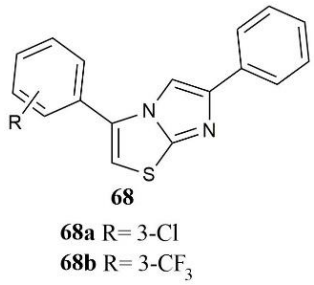

Fig. 60 Structures of 3,6-diphenylimidazo[2,1-b]thiazoles

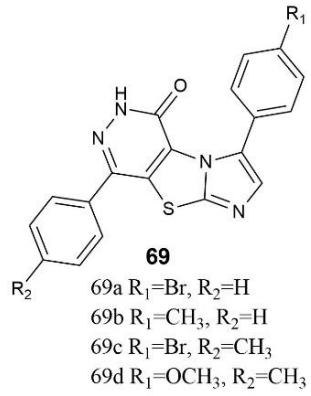

Fig. 61 Structures of imidazo[2',1':2,3]thiazolo[4,5-d]pyridazine

https://doi.org/10.30799/jacs.244.22080101

A series of imidazo[2',1':2,3]thiazolo[4,5-d]pyridazine analogues (**69**) were synthesized by Ewida et al. [60] and tested their efficiency as DHFR inhibitors. Anticancer investigations on ovarian and MDA-MB-435 melanoma cell lines *in vitro*. The compound 69a was determined to be the most effective inhibitor with an IC_{50} of 0.06 M, while the other compounds 69b, 69c, and 69d were the active inhibitors with IC_{50} values of 0.09, 0.11 and 0.15 μM, respectively.

The *in vitro* anticancer activity against NCI-60 panel cell lines, compounds 69a exhibited potent activity with 87.4% against HL-60, 83.9% against K-562, 87.6% against HT29 (colon), 86.3% against MCF-7 (breast), MDA-MB-468 (breast) cancer cell lines, respectively and found to be most active against OVCAR-3 (ovarian) cancer and MDA-MB-435 (melanoma) cell line. With IC_{50} values of 0.32 and 0.465 μM, this compound was shown to be more cytotoxic. Flow cytometry revealed typical DNA apoptosis during the G0/G1, S and G2/M phases of the cell cycle. The molecular docking study using Discovery studio 2.5 software was performed and compound 69a favored the binding mode and fixed orientation [60].

3. Conclusion

The numerous biological actions of imidazo[2,1-b]thiazole derivatives are summarized in this review. Being an important class of compounds in heterocyclic chemistry, the imidazo[2,1-b]thiazole moiety and its derivatives had antimicrobial, antiviral, anti-inflammatory, antimalarial, anticancer, antitubercular, antioxidant, analgesic, and other biological effects. In the case of anticancer, it particularly inhibited protein kinases, induced apoptosis and acts as tubulin targeting and polymerizing agent. These scaffolds exhibited better activities against various diseases with better IC_{50} values and inhibition rates. To enlarge and enrich the chemistry and biological activities of this scaffold, beyond synthetic chemistry, it can be performed under the reactions of green chemistry principles. The development of new imidazo[2,1-b]thiazole derivatives are continuously increasing with additional therapeutic applications remains interesting in the field of medicinal chemistry.

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