How to Cite:
Vats, N., Dahiya, L., Narang, R., Kumar, R., Sharma, D., & Rana, A. C. (2022). An overview of the synthesis, therapeutic potential and patents of thiazole derivatives. *International Journal of Health Sciences*, *6*(S8), 5272–5302. Retrieved from https://sciencescholar.us/journal/index.php/ijhs/article/view/13444

An overview of the synthesis, therapeutic potential and patents of thiazole derivatives

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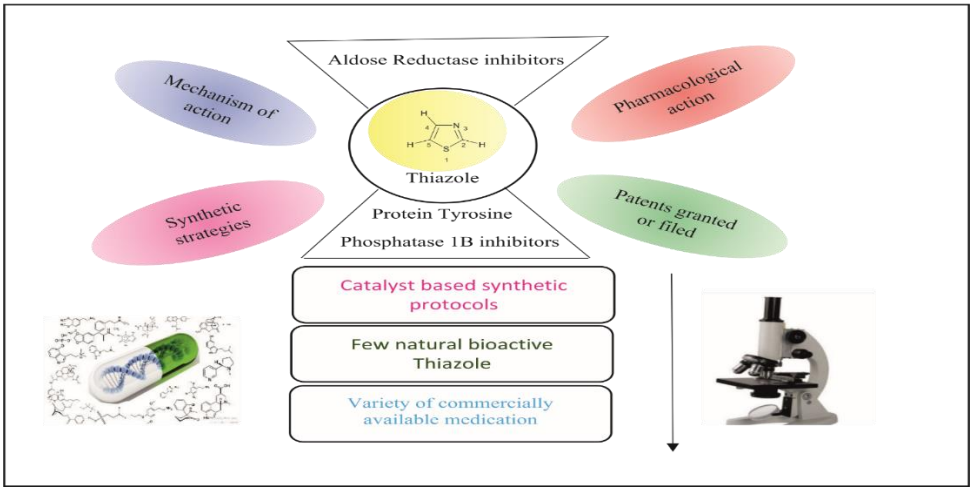
***Abstract*---**Thiazole is a nitrogen and sulphur containing heterocyclic five membered aromatic ring. Thiazole derivatives exhibited various medicinal applications in the treatment of cancer, diabetes, inflammation, microbial infections, psychosis etc. These are also naturally obtained from cyanobacteria, sea slugs, sea hare, red algae and higher plants. Thiazole derivatives can be synthesized by reaction of aldehyde and α-halo carbonyl coumarin. The present paper provides an overview of different methods used for synthesis of thiazole and various biological targets of thiazole derivatives. Further,

various patents related to pharmacological activities of thiazole derivatives published in last five years have been summarized. Hence, present review may provide reference for design and development of new thiazole derivatives with significant biological activities.

***Keywords*---**thiazole, heterocycles, synthesis, biological activities, anticancer, antiprotozoal, anti-inflammatory.

Graphical abstract



Introduction

Over the years, Heterocyclic ring containing nitrogen and sulphur such as thiazole and triazole, have been received a crucial attention due to their synthesis and biological applications [1]. Compounds having heterocyclic scaffold shows additional property of oral absorption, bioavailability and salt forming activity [2]. In the family of heterocyclic compounds, thiazole is a well-known heterocyclic moiety present in more than 18-FDA approved drugs as well in various investigated drugs [3]. In 1887, Hantzsch and Weber were the first to report this moiety [1]. Thiazole consist of 5-membered aromatic ring with a general formula of C_3H_3NS [4]. Thiazole represents one of the most important scaffolds in medicinal chemistry, exhibited extensive variety of biological activities such as anti-inflammatory, anti-oxidant, anti-gout, anti-helminthic, anti-bacterial, anti-fungal, analgesic, peptic ulcer inhibitor, anti-tubercular, anti-epileptics, antipsychotic and anti-Parkinson's [5-7].

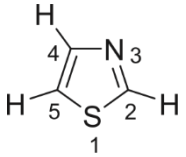


Fig. 1 Chemical Structure of thiazole

Thiazole (1,3-thiazole) belongs to the class of azoles, contains sulphur and nitrogen atom at position 1 and 3 (Fig. 1). The resonance structure of thiazole has been shown in Fig. 2. [4]. Thiazole have both an electron-accepting group (-C=N) as well as electron-donating group (-S-). Aromatic nature of ring owes to delocalization of a lone pair of electrons from the Sulphur atom [8]. The substitution of hydrogen atoms at position 2,4,5 with preferred moieties give rise to various derivatives of biological significance [9].

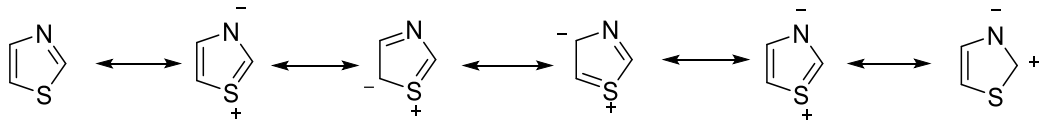


Fig. 2 Resonating structure of thiazole

From the literature, it was found that MEP played an important role in drug-target protein interaction. MEP surface of thiazole revealed that nitrogen is more negative charged atom than carbon and sulphur atom which are neutral [10] (Fig. 1). The medicinal effect of substituted thiazole derivatives may be influenced by the Huckel charge distribution on thiazole ring atoms, as well as substitutions at different places (Table 1) [11].

Table 1. Huckel charges on the thiazole ring

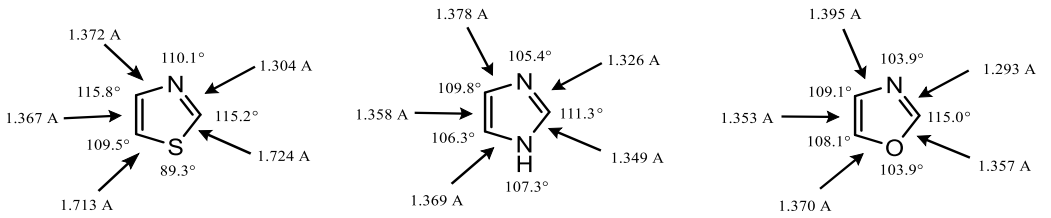
Atoms	Atom Type (MM2)	Charge (Huckel)[a]
S (1st)	Thiophene	0.833378
C (2nd)	Alkene	-0.0935773
N (3rd)	Imine	-0.406253
C (4th)	Alkene	-0.0876361
C (5th)	Alkene	-0.264457

[a] charge for Huckel were calculated using Chembio Office 2010

In thiazoles nucleus, small regions of low electron density on sulphur (σ holes) due to low-lying C-S σ^* orbitals, may play an important role in drug-target interactions [12]. Sulphur has a considerable impact on bond angles and the topology of the substituents attached with nucleus. Furthermore, thiazole ring system has clogP and clogD values close to 0.5, as well as pka and pK_{BHX} (the latter of which is connected to the H-bond interaction property) values of 2.53 and 1.37, respectively (Table 2) [13].

Table 2. Chemical and Physical characteristics of Thiazole, Imidazole and Oxazole Scaffolds.

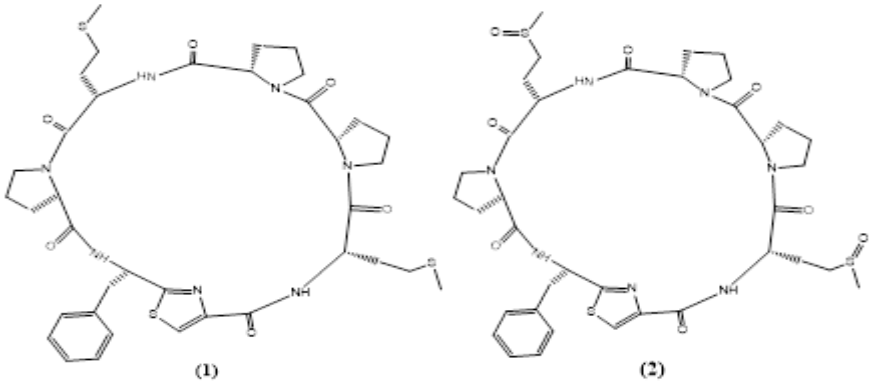
	Thiazole	Imidazole	Oxazole
Dipole moment (μ)	1.61	3.80	1.50
pKa	2.53	6.95	0.8
pK_{BHX}	1.37	2.42	1.30
cLog P	0.49	-0.03	-0.18
cLod $D_{7.0}$	0.44	-0.5	0.12



Thiazole nucleus present in many drugs showed diverse pharmacological actions due to its versatile chemical nature. Thiazole scaffold is present in vitamin B1 which help in the synthesis of acetylcholine and normal functioning of nervous system [8]. Thiazoles based chemical compounds have a profound use in treatment of cancer [14]. The thiazole class of compounds has previously been used as a powerful Central Nervous System (CNS) medication. Pramipexole has a cyclohexane ring bonded to a 2-amino-thiazole ring [15]. Riluzole, a novel neuroprotective medicine licensed for the use of amyotrophic lateral sclerosis, also contains the aminothiazole analogue [16]. Alanine *et al.* have developed a benzothiazole analogues with activity as adenosine receptor ligands [17]. In the quest for more effective adenosine A2AR antagonist, several additional thiazole analogues were created and patented. Analogues of amino thiazoles have also been found as possible dopamine receptor agonists. A2AR antagonist block immunosuppressive transcription by preventing the accumulation of highly intracellular cAMP, leading to suppression of activated tumor-reactive T cells and NK cells. Tetrahydro benzothiazoles represents a class of neuroprotective chemicals [18]. There has been a lot of research done on benzothiazoles [19] and phenolic thiazoles [20]. Apart from butyl thiazole analogues [21], ethynyl thiazole [22] analogues and pyrimidyl thiazole [23] offer the best glutamate receptor antagonist action for anxiety disorders. Anti-Alzheimer action was found in imidazole thiazole analogues [24], 2-aminothiazole analogues [25] and triazole linked thiazole derivatives [26], Riluzole derivatives [27], thiazolesemicarbazides [28], thiazolepyeidons [29] and thiazole carboxamide [30] derivatives.

Natural bioactive thiazole

Cyanobacteria ascidians are a natural source of thiazole-based peptide derivatives and other heterocyclic rings comprising cyclopolypeptides. Other potential sources of thiazole-based peptide derivatives were found in marine sponges and sea slugs, as well as actinomycetes, sea hare, red alga and higher plants. In the sponge derived cytotoxic hexapeptide heligramide A and B, the phenylalanyl thiazole (Phe-Tzl) moiety was found [31,32]. Waiakeamide's 2 bismethionine homologue had a Phe-Tzl moiety in addition to three proline units. In contrast to haligramide A [1], which only included methionine residues and waiakeamide [33], Haligramide B was a sponge-derived cyclohexapeptide with both methionine and methionine sulfoxide residues.

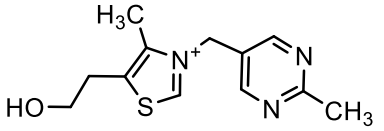
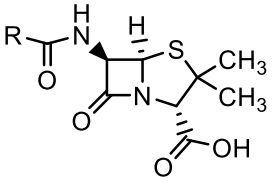
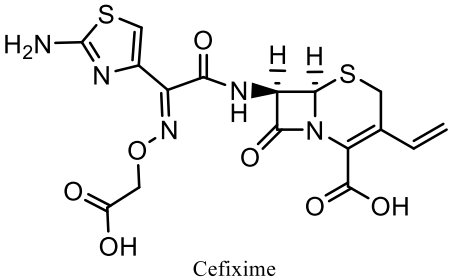


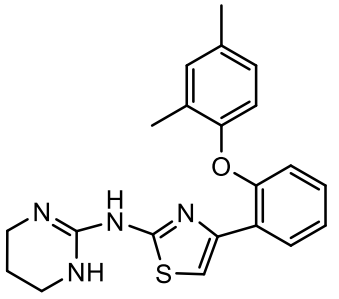
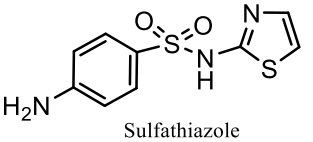
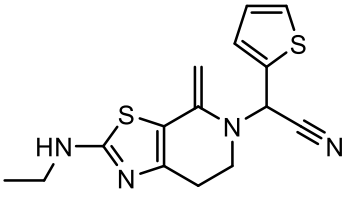
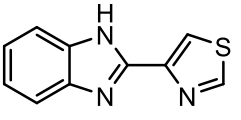
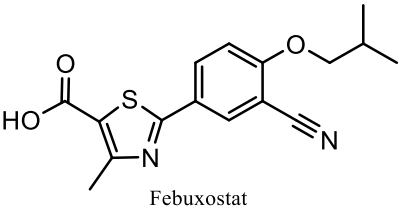
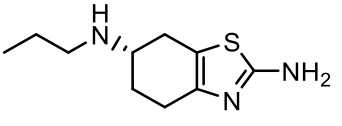
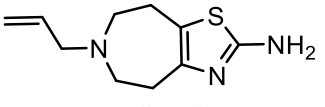
Structure of Haligramide A 1 and waiakeamide 2 with phenylalanylthiazole (Phen-Tzl) moieties

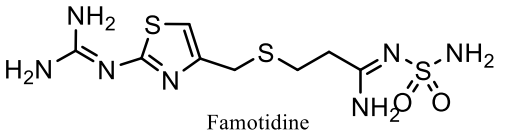
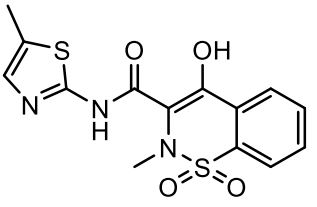
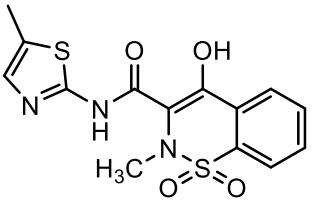
Marketed drugs

Compounds containing the thiazole moiety exhibited a broad spectrum of biological activities e.g. anti-inflammatory, anti-gout, anti-anthelmintic, anti-bacterial, anti-fungal, peptic ulcer inhibitor, anti-tubercular, anti-epileptics and anti-parkinson's [5-7]. Thiazole is found in a variety of commercially available medications (Table 3).

Table 3. Thiazole ring containing drugs and their uses

Drug structure and Name	Uses
 Thiamine (Vitamin B_1)	Treatment of thiamine deficiency (beriberi, optic neuropathy)
 Penicillin G	Penicillin antibiotic
 Cefixime	Cephalosporin antibiotic

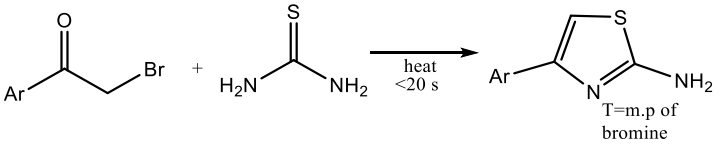
 Anafungin	Antifungal
 Sulfathiazole	Antimicrobial
 Ethaboxam	Anti-fungal
 Thiabendazole	Anthelmintic and Fungicide
 Febuxostat	Anti-Gout
 Pramipexol	Anti-Parkinson
 Talipexole	Anti-Parkinson

 Famotidine	Peptic Ulcer and Gastroesophageal reflux
 Meloxicam	NSAIDS
 Sudoxicam	NSAIDS

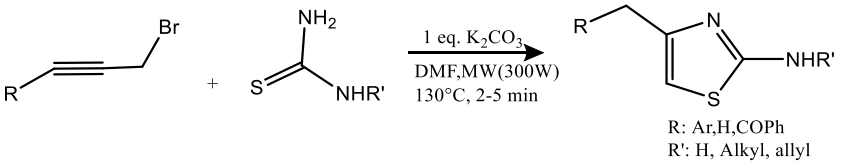
Synthesis of thiazole derivatives

Some methods for the preparation of Thiazole derivatives

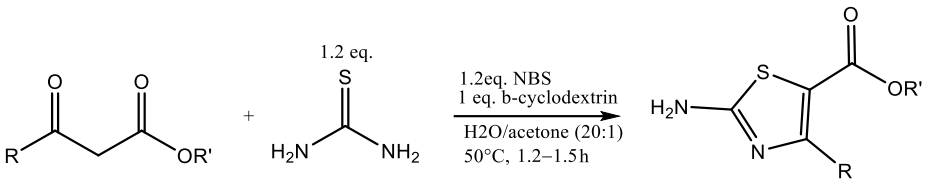
Scheme 1
Synthesis of 2-Aminothiazole
Facchinetti *et al.* described a method in which 2-bromoacetophenones were condensed with thiourea or selenourea to produce 2-aminothiazoles and 2-amino-1,3 selenazoles. This Hantzsch condensation does not use a catalyst, solvent and takes less time to produce excellent outcome [34].



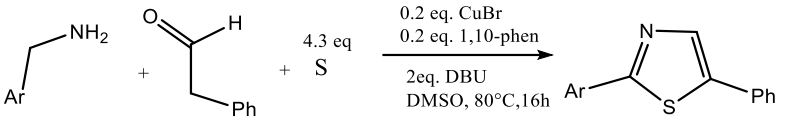
Scheme 2
Synthesis of polysubstituted 2-aminothiazoles.
Propargyl bromides undergo a domino alkylation-cyclization reaction with thioureas and thiopyrimidinones to produce 2-aminothiazoles under microwave irradiation [35].



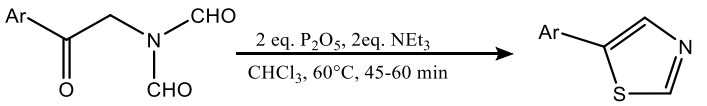
Scheme 3
Narender *et al.* described a method in which ***β***-keto esters were α-halogenated with N-Bromo succinimides and then cyclized using thioureate to give 2-amino-4-alkyl and 2-amino-4-arylthiazole5-carboxylates [36].



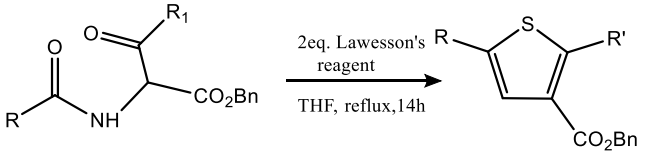
Scheme 4
Oxime, anhydride and KCN are used to make thiazoles
Wang *et al.* described a realistic Cu-catalyzed oxidative method, in which Multiple Csp^3-H a bond breaking technique was used to manufacture thiazole from simple aldehyde, amines and Sulphur in presence of a green oxidant (molecular O_2) [37].



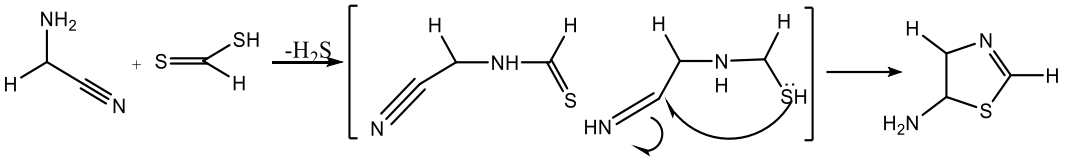
Scheme 5
In this method, 5-arylthiazoles can be synthesized by treating N, N-diformylaminomethyl aryl ketones with phosphorous pentasulfide in presence of chloroform and triethylamine. The reaction provides good yields of 5-arylthiazoles [38].



Scheme 6
Isocyanide cyclization with methyl and hetarenecarbodithioatesa are used to make thiazoles
Sanz-Cereva, created a small library of molecules with structural diversity and thiazole scaffolds at position 2 and 5. The intermediate α-amino-***β***-ketoesters are produced by twice acylation of a protected glycine, which react with Lawesson's reagent to yield 1,3-thiazoles [39].



Scheme 7
Cook-Heilborn's synthesis of thiazole
Cook-Heilborn developed a flexible substituted aminothiazole manufacturing technique. Under mild conditions, alpha-amino nitriles react with dithioacids or esters, carbon disulphide, carbonyl sulphide, and isothiocyanate to create 5-amino thiazoles [40].



Biological activities of thiazole derivatives

In the recent decades, thiazoles provide a valuable scaffold for the design and synthesis of new drugs in medicinal chemistry. It exhibited a variety of biological activities such as anti-oxidant, anti-inflammatory, anti-gout, anthelmintic, anti-bacterial, anti-fungal, analgesic, peptic ulcer inhibitor, anti-tubercular, anti-epileptics, antipsychotic and Parkinson's (Fig. 3).

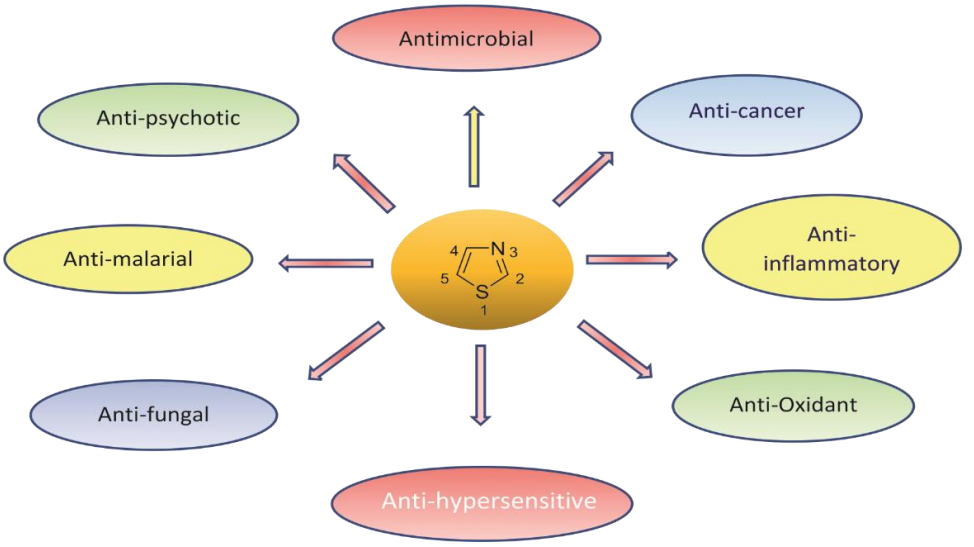


Fig. 3 Important therapeutical applications of thiazole derivatives.

Thiazole derivatives as anticancer agents

Due of the limits and adverse effects of current cancer treatments, the development of more safe and specialized anti-cancer drugs is a critical challenge for medical researchers. Special emphasis has been made to compounds containing sulphur heterocycles, such as thiophene, thione, benzothiophene and thiazine, in drug discovery efforts for various diseases. The thiazole ring is found in a variety of anti-cancer medications, bleomycin, sulfathiazole, thiazofurine and dasatinib (Fig. 4). Thiazole moiety have magnificent pharmacological properties,

creating this skeleton an appealing applicant for generating more powerful and guarded medications particularly in cancer [41].

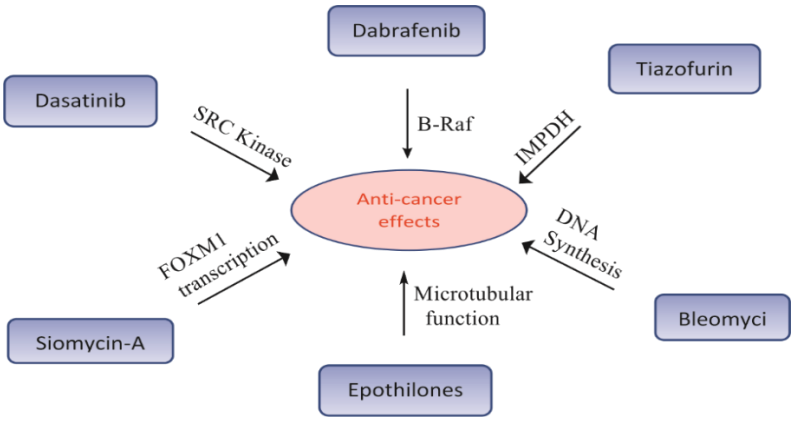
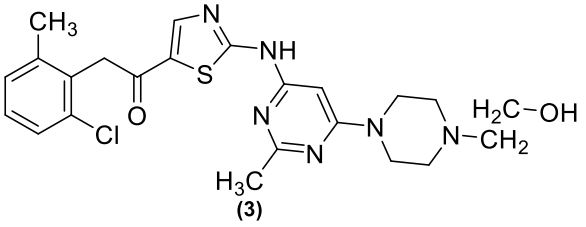


Fig. 4 Variety of Anti-Cancer medication

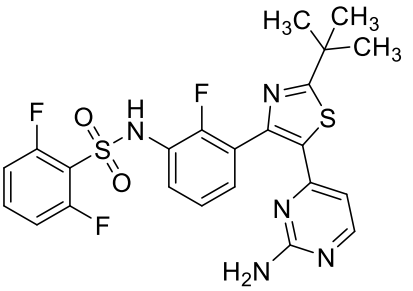
Dasatinib, formerly known as BMS-354825, is a thiazole-based anti-cancer medication marketed by Bristol-Myers Squibb (BMS). In terms of chemistry, it is 2-(2-chloro-6-methylphenyl)-1-(2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazol-5-yl)ethan-1-one Monohydrate of 5-thiazole carboxamide (3). Dasatinib is the most efficient tyrosine kinase inhibitor for people with Chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia with the Philadelphia chromosome (Ph+ALL), it's a first line orally active therapy. Patients with imatinib-resistant BCR-ABL+ leukemias are currently treated with the above medicine. Dasatinib is found to inhibit BCR/ABL (the Philadelphia chromosome), Src family kinases (SFK), c-Kit and various other tyrosine kinases. It decreases stage-dependent SFK activity and selectively inhibits FAK signaling in prostate cancer, resulting in cell adhesion, migration and invasion suppression. Dasatinib also suppresses c-KIT and EGFR in breast cancer cell lines(triple-negative), which lack estrogens, progesterone, and HER2 receptors. It inhibits the progression of the cell cycle from G1/G0 to S-phase and promotes apoptosis, limiting metastasis, invasion and migration in MDA-MB-468 cells. Other solid tumours that Dasatinib inhibits include Non-Small Cell Lung Cancer, colorectal and pancreatic malignancies, head and neck squamous cell carcinoma, melanoma, glioma, and advanced solid tumors such as osteoclast [42].



(3)

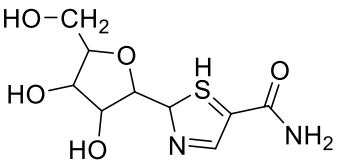
Dabrafenib N-(3-(5-(2-aminopyrimidin-4-yl)-2-(tert-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide (4), another thiazole-containing medication, is a strong anti-cancer medicine recently introduced by

GlaxoSmithKline. The medicine suppresses the human gene BRAF, a proto-oncogene that produces the protein serine/threonine protein kinase B-Raf, which is involved with the development of cells. With time, it was discovered that Dabrafenib had developed a resistance to it. As a result, the FDA has advised that the aforementioned medicine be used in conjunction with other medications, such as Trametinib, in relation to the use of BRAF V600E/K-mutant metastatic melanoma [43].



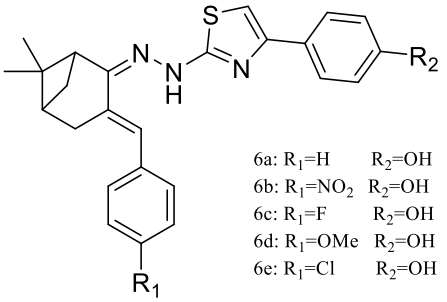
(4)

Tiazofurin (1R)-1- [4-(aminocarbonyl)-1,3-thiazol-2-yl] is an anti-neoplastic medication. -1,4-anhydroD-ribitols or 2-(3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2H-1l4-thiazole-5-carboxamide (5) is used to treat solid tumors. It also demonstrated high clinical response in patients with chronic myeloid leukemia's myeloid blast crisis, this thiazole derivative has an anti-proliferative impact by selectively blocking enhanced IMPDH activity in all cancer cells. It's also known as groove binders for several DNA intercalators in clinical terms [44-46].



(5)

Wang *et al.* synthesized novel thiazole-based triterpene derivatives [47] and evaluated anticancer activity against three cancer cell lines [48-52] using MTT assay. Etoposide was used as a reference medication. *β*-pinene based thiazole derivatives (6a, 6b, 6c, 6d, 6e) showed substantial cytotoxic effect. Biological evaluation revealed the presence of hydroxyl group in position 4 of the benzene ring as a thiazole ring (R_2) substituent for the improved activity. On the other hand, electron-withdrawing group (R_2=F) as well as R_1 substituents like OCH_3 and CH_3 had a deleterious effect, resulting in inactive chemicals or reducing anti-cancer activity, respectively.

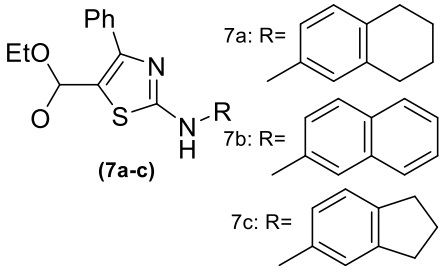


(6a - 6e)

Anti-inflammatory properties of thiazole derivatives

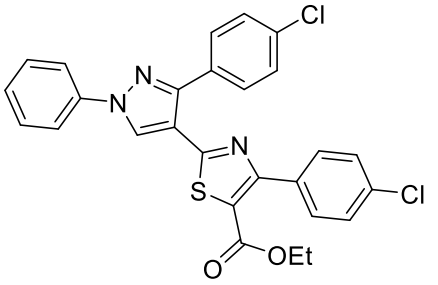
Inflammation is involved in many disorders that require long-term or repetitive therapy, Arthritis, asthma and psoriasis are only a few examples. The most extensively therapeutic agents used for the treatment of inflammatory illnesses are nonsteroidal anti-inflammatory medication (NSAIDs). They are used to treat inflammatory discomfort and fever, both acute and chronic. However, Long-term clinical application is linked to serious side effects such gastrointestinal (GI) issues [53,54], intestinal problems, severe cardiovascular events [55], kidney illness [56,57], hemorrhage and nephrotoxicity [54,58]. TNF neutralization, leukotriene receptor blockers, cytokine receptor blockers and components of the inflammatory response are among the therapeutic alternatives being researched for inflammation control.

Zhu *et al.* developed variety of thiazole derivatives and investigated them by hitting the human dihydroorotate dehydrogenase enzyme. Researchers found their effectiveness in the therapy of rheumatoid arthritis. The findings of the biological examination revealed that the compounds 7a (IC_{50}=18nm), 7b (IC_{50}=29nm), 7c (IC_{50}=26nm) having 5,6,7,8-tetrahydronaphthalene, naphthalene and 2,3-dihydro-1H-indene connected via amine group of thiazole ring, demonstrated optimum anti-inflammation action *in vivo* by inhibiting the bioactivity of the dihydroorotate dehydrogenase enzyme. Thiazole-scaffold are found to be potential therapeutic moieties for treating rheumatoid arthritis [59].

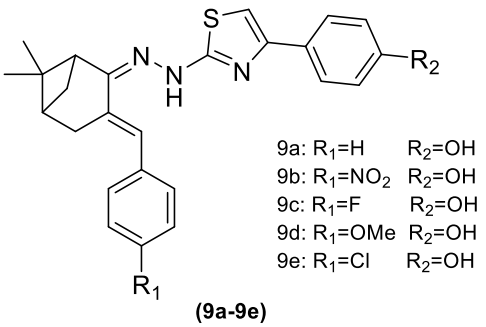


(7a-c)

Khloya *et al.* synthesized pyrazolylthiazolecarboxylates family and related acid derivatives. Carrageenan-induced rat paw edema was used to forge anti-inflammatory activity *in vivo*, From all derivatives 8, 9a, 9b were found to be the most active, with the inhibition ranges from 93.06 to 89.59 percent. The ester derivatives were found to be more potent than acid derivatives [60].



(8)



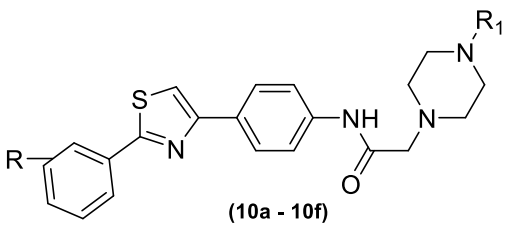
9a: R_1=H R_2=OH
9b: R_1=NO_2 R_2=OH
9c: R_1=F R_2=OH
9d: R_1=OMe R_2=OH
9e: R_1=Cl R_2=OH

(9a-9e)

Thiazole derivatives as antimicrobial agents

Due to the rise of multidrug-resistant strains including *Staphylococcus aureus*, *Enterococcus sp.*, *Acinetobacter boumannii* (*A. baumanni*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Enterobacter cloacae (E. cloacae*) [61] and *Candida sp.* with acquired fluconazole resistance [62], medicinal chemists are now focusing on the design and modification of antimicrobial drugs. For decades, the discovery of innovative antimicrobial medications remained sluggish, resulting in a scarcity of more effective drugs against Gram-negative bacteria. As a result, it's clear that new agents with various and quite innovative mechanisms of action are needed to target both susceptible and resistant strains [63].

Yurttas *et al.* developed sixteen 2-(4-arylpiperazine-1-yl)-N-[4-(2-(4-substituted phenyl) thiazol-4-yl)phenyl] acetamide derivatives. The derivatives were tested on gram-positive and gram-negative bacteria and fungus, using chloramphenicol and ketoconazole as reference compounds, respectively. The antibacterial activity of synthesized compounds was often weaker (MIC 100-400g/ml) than that of the standard medication (MIC=25-50g/ml). Among all compounds 10b and 10c, displayed significantly improved activity against Gram-positive *E. faecalis* [64].



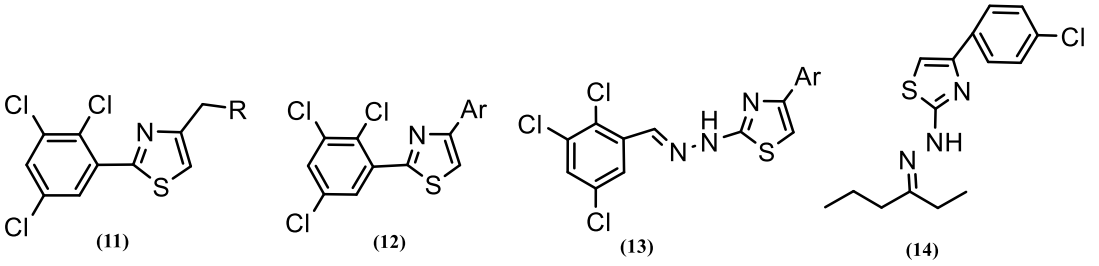
(10a - 10f)

10a: R=H, R_1=Ph-CH_3
10b: R=H, R_1=C_5H_5N
10c: R=H, R_1=pyrimidine
10d: R=4-OMe-Ph, R_1=C_5H_5N
10e: R=4-Cl-Ph, R_1=Ph-CH_2
10f : R=4-F-Ph, R_1=Ph-CH_2

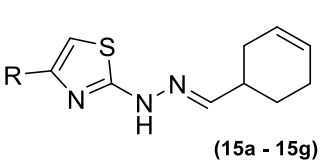
The chemicals are found to have their antifungal activity much stronger than their antibacterial activity. Compounds 10a, 10b, 10e, and 10f were found to be equally effective against *Candida albicans* (*C. albicans*) as ketoconazole (MIC 50µg/ml), compound 10d, on the other hand, was found to be effective in the fight against *Candida glabrata* (*C. glabrata*). Furthermore, when compared to the reference treatment, compounds 10a and 10b were equally effective against *Candida Krusei* (*C. krusei*) and *Candida parapsilosis* (*C. parapsilosis*).

Karegoudar *et al.* developed 4-substituted 2-(2,3,5-trichlorophenyl)-1,3-thiazoles compounds 11 and 12 and 4-substituted 2-(2,3,5-trichlorophenylidenehydrazino)-1,3-thiazoles compound 13 and tested the antimicrobial activity against bacterial strain, fungal strain more of antibacterial activity for the derivatives substituted with 4-(methylthio)phenyl, salicylamide, N-methyl piperazine, or 4,6 dimethyl-2-mercaptopyrimidine residues, whereas the antifungal activity was comparatively good for compounds substituted with 3-pyridyl,biphenyl, or 4-mrcaptopyrazolopyrimidine moieties [65].

Lino *et al.* created a newer class of hydrazone group containing thiazole compounds and evaluated *in vitro* against different fungal strains. As the intermediate molecule were devoid of antifungal activity therefore thiazole nucleus was found to be vital. Furthermore, the enhanced antifungal activity was due to the presence of aliphatic hydrophobic chain connected to the hydrazone functional group and benzene with chlorine atom at position 4. Compound 14 was found to be more effective than fluconazole against the *Candida* and *Cryptococcus* species [66].

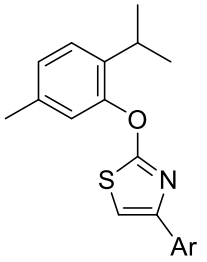


Biernasiuk *et al.* created fifteen new thiazoles with a cyclohexane moiety and investigated their antibacterial efficacy against seven Gram-positive, seven Gram-negative bacteria, four fungal Candida species. The compounds 15a, 15b, 15c, 15d had extremely good activity as per the study against *C. species*, with MICs ranging from 0.015 to 3.19µg/ml and were equal potent or more potent than the reference medication nystatin [67].



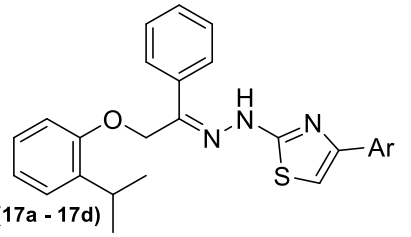
15a: R=4-F-C_6H_5
15b: R=4-Br-C_6H_5
15c: R=Cl-C_6H_5
15d: R=4-CF_3-C_6H_5
15e: R=4-OCH_3-C_6H_5
15f : R=CH_2COOEt
15g: R=CH_3

Pricopie *et al.* [68] synthesized a new antifungal medicine to satisfy the growing requirement for innovative antifungal drugs for Candida sp. infection resistance. Newer series of 1,3-thiazole derivatives 16, 17 with lipophilic C_4 substitutions were evaluated for antifungal activity against pathological Candida species. In human the evaluation revealed that the compounds from the second species were four times more powerful than fluconazole (MIC/MFC=15.62/32.24μM/ml) against *C. albicans* ATTCC10231, with MIC/MFC=3.9/7.8μM/ml.



(16a - 16d)

16,17a: Ar=4-OMe-C_6H_5
16,17b: Ar=4-Cl-C_6H_5
16,17c: Ar=4-Br-C_6H_5
16,17d: Ar=$C_{10}H_7$

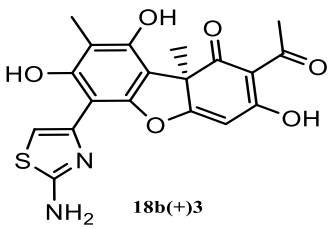


(17a - 17d)

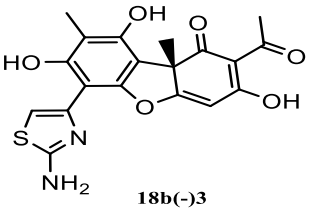
Thiazole derivatives as antimycobacterial agents

Tuberculosis (TB) is a contagious illness that kills millions of people worldwide each year [69]. Due to the rise of resistance *Mycobacterium TB* strains, it remains one of the most serious infectious diseases (*M. tuberculosis*). As per the World Health Organization, in 2019, 1million individuals died due to tuberculosis (TB), the greatest recorded number of infectious illness deaths. TB is one of the world's top ten causes of death [70]. Despite the fact that basic anti-tubercular drugs such as isoniazid, rifampicin, ethambutol and pyrazinamide may both prevent and treat this disease [71], TB cases decrease by just around approximately 2% per year. Furthermore, instances of multidrug-resistant tuberculosis (MDR-TB) are increasing year after year, going to represent major public health problems. As a result, there is an urgent need to develop new anti-tubercular agents.

Bekker *et al.* synthesized and evaluated *in vitro* new usnic acid derivatives on *Mycobacterium smegmatis* and *Mycobacterium TB* growth. The study revealed the importance of an amino group in the thiazole ring for inhibitory activity. The 18a (-) (-3) and 18b (+) (-3) isomers were tested for their kinase inhibitory action. Significant protein kinase activity was detected in the *S. lividans* APHVIII+ and *M. smegmatis* APHVIII+ test systems. The (-) isomer of usnic acid was shown to be more effective than the (+) isomer against the kanamycin-resistant *M. smegmatis* strain APHVIII+. *M. tuberculosis* H37Rv has substantial inhibitory action in both isomers, with a MIC_{99}=25μg/ml and MIC_{100}=50μg/ml, respectively [72].

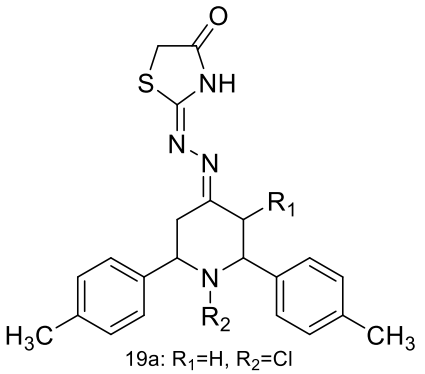


18b(+)3



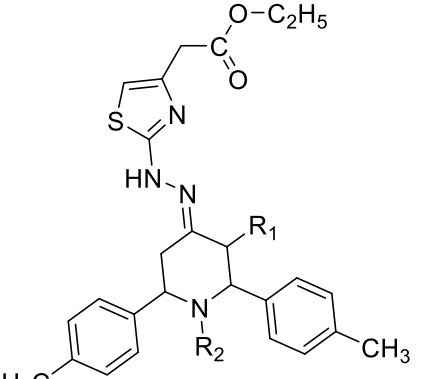
18b(-)3

Aridoss *et al.* used stereospecific synthesis to create thiazolidinedione and thiazole derivatives, which were subsequently investigated for antimycobacterial activity against *Mycobacterium tuberculosis*. The potency of the compounds 19a-c and 20a-c was twice as great (MIC=16g/ml) as that of the standard drug Rifampicin (MIC=32g/ml). The antimycobacterial activity of C-3 piperidone was shown to be completely diminished when the methyl group was substituted with ethyl in C-3 piperidone. The inclusion of the Schiff base, as well as the addition of halogens (Cl, Br, and F) and methoxy group to the nitrogen of the piperidine moiety resulting in improved antimycobacterial action [73].



19a: R_1=H, R_2=Cl
19b: R_1=H, R_2=Br
19c: R_1=CH_3, R_2=H

(19a-c)

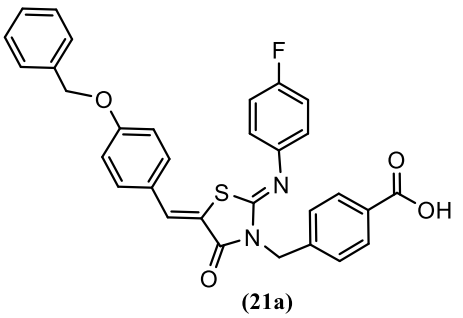


20a: R_1=H, R_2=F
20b: R_1=H, R_2=OCH_3
20c: R_1=CH_3, R_2=H

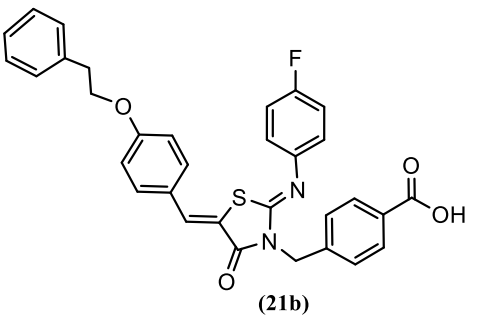
(20a-c)

Thiazole derivatives as antidiabetic agents

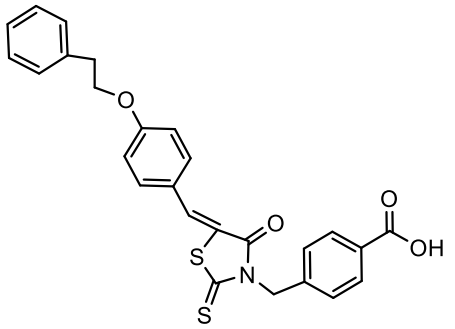
Inhibitors of Protein Tyrosine Phosphatase 1B (PTP1B) PTP1B (Protein Tyrosine Phosphatase 1B) is an important target in the treatment of type 2 diabetes. PTPs is a ubiquitously expressed enzyme that plays an essential role in the regulation of insulin signaling pathway by dephosphorylation insulin receptor substrate. Because of the various effects of PTP1B inhibitors, a considerable number of novel compounds have been synthesized in the last six years, emphasizing PTP1B's relevance in the treatment of type 2 diabetes. Based on prior work with PTP1B inhibitors Ottana *et al.* developed 4-(((Z)-5-((Z)-4-(benzyloxy)benzylidene)-2-((4-fluorophenyl)imino)-4-oxothiazolidin-3-yl)methyl)benzoic acid and 4-(((Z)-5-((Z)-4-(benzyloxy)benzylidene)-2-((4-fluorophenyl)imino)-4-oxothiazolidin-3-yl)methyl)benzoic acid derivatives [74-77]. The most active compounds (21a and 21c) had IC_{50} values of 1.6, 1.5 and 1.9μM respectively. The inclusion of an ethoxy chain between the two phenyl rings found to be beneficial for inhibitory action. Kinetic studies showed that Compounds have a mixed non-competitive behavior with compound 21b showing mixed type inhibition [78].



(21a)

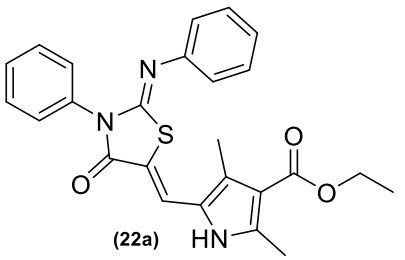


(21b)

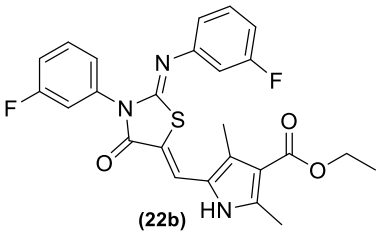


(21c)

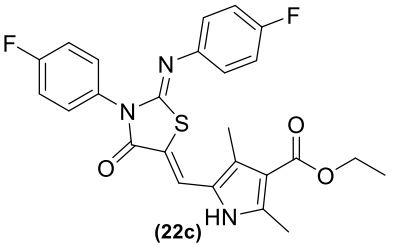
To develop novel PTP1B inhibitors, Meng *et al.* developed a series of 2-imino-3-substituted-5-heteroarylidene-1,3-thiazolidine-4-one derivatives. Replacement of pyridine groups with pyrrol groups at the 5-position of the 1,3-thiazolidine-4-one favored PTP1B inhibitory activity. Compounds 22a, 22b, 22c have shown potent anti-PTP1B activity, with compound 22c having the highest IC_{50}=6.37μM [79].



(22a)



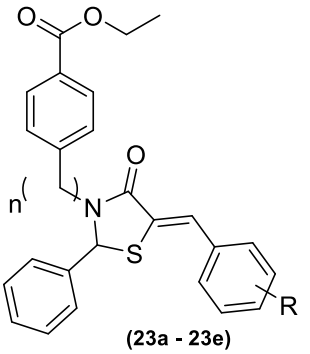
(22b)



(22c)

Liu *et al.* reported a series of 4-thiazolinone compounds (23a-e) with strong PTP1B inhibitory activity. Compound 23e was the most effective PTP1B inhibitor. Molecular docking investigations revealed that this compound formed hydrogen

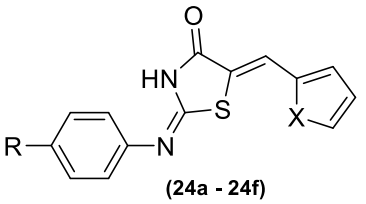
bonds with the catalytic residues Asp181, Cys215 and Gln 262 and attached to the PTP1B functional area via non-covalent contact [80].



(23a - 23e)

23a: R = 3-CH_3, n=0
23b: R = 3-OCH_2Ph, n=0
23c: R = 4-CH_3, n=0
23d: R = 3-Cl, n=1
23e: R = 4-CH_3, n=1

Patel *et al.* developed three series of thiazolidine-4-one compounds and examined their inhibitory potential. According to molecular docking experiments, these compounds can interact with the catalytic residues Cys215, Ser216 and Gln262 of PTP1B. SAR analyses demonstrated that the presence of a furan moiety and the presence of a nitrogen group in the preface of a benzene ring might increase the prohibitory action [81].



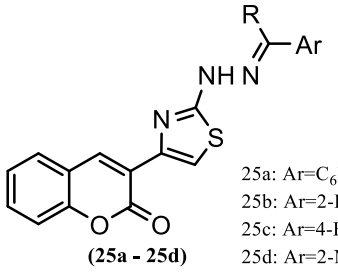
(24a - 24f)

24a: X=S, R = CH_3
24b: X-S, R = NO_2
24c: X=S, R = Cl
24d: X=O, R = CH_3
24e: X=S, R = NO_2
24f : X=NH, R = NO_2

Aldose Reductase (ALR) Inhibitors

Aldose reductase converts glucose to sorbitol in the presence of NADPH, which is then converted to fructose by sorbitol dehydrogenase [82]. People with type 2 diabetes mellitus (T2DM) who has poor sorbitol penetration and metabolism, accumulate too much sorbitol in their tissues, can lead to DM complications such as cataracts and glaucoma. Therefore, inhibition of aldose reductase enzyme may be a viable strategy for preventing and treating of diabetic complications.

Ibrar *et. al.* synthesized novel coumarin thiazole and oxazole derivatives and evaluated against ALR2 and ALR1. The coumarin-thiazole derivatives 25a, 25b and 25c had the highest activity against ALR2 with IC_{50} values of 0.12±0.05, 0.16±0.06, and 0.11±0.001 μM, respectively, outperforming the reference medication sulindac (EC_{50}=0.293 ± 0.08μM). however, Compound 25d was the most powerful ALR1 inhibitor, with an IC_{50} value of 0.459±0.001μM, which was more than 100 times stronger than valproic acid [83].



(25a - 25d)

25a: Ar=C_6H_5, R=CH_3
25b: Ar=2-Br_C_6H_4, R=CH_3
25c: Ar=4-Br-C_6H_4, R=CH_3
25d: Ar=2-NH_2-4-Cl-C_6H_3, R=CH_3

Mechanism of actions

Thiazole has a wide range of biological properties. Thiazole may inhibit DNA gyrase. Because of the molecular similarities of sequence homologies for targeting Src kinase enzyme, the development of thiazole medicines has recently got a lot of attention by the researchers. **Fig. 5** depicts various therapeutic targets for biological activities of thiazol

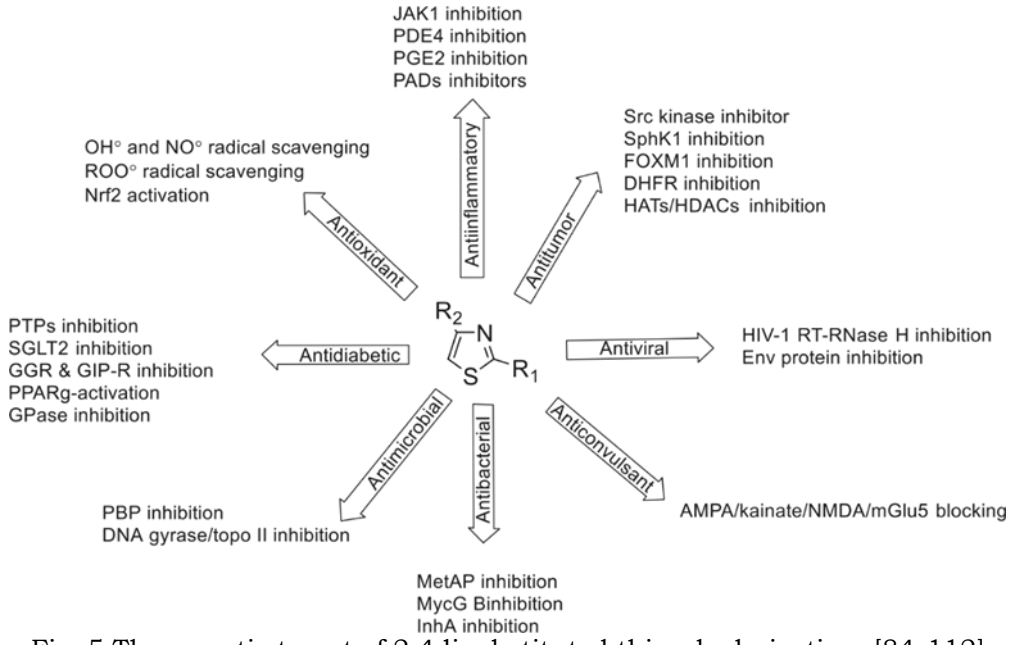


Fig. 5 Therapeutic target of 2,4disubstituted thiazole derivatives [84-112]

Recently issued patents on thiazole

Thiazole medicines have been used to treat microbes for years. Patents for the use of thiazole for antimicrobial activity have been awarded and submitted. Table 4 represents thiazole-based structures patented from 2017-2022.

Table 4 Patents mapping

S. No.	PATENT NUMBER	TITLE	DATE	REFERENCE
1.	US9745295B2	As spleen tyrosine kinase inhibitors Aminoheteroaryls substituted with thiazole	29-08-2017	(113)
2.	CN107207507A	The benzamide of the base of 1,3 thiazole 2-Substitution	26-09-2017	(114)
3.	CN108368040A	Diaryl monocycle beta-lactam compound and its method for treating bacterium Infection	03-08-2018	(115)
4.	CN104396970B	A kind of bactericidal composition and its Preparation and application containing zinc thiazole	30-10-2018	(116)
5.	CN105658631B	Antibacterial thiazole Carboxylic acid	18-06-2019	(117)
6.	CN106715430B	Inhibit transient receptor potential A1 Ion channel	17-09-2019	(118)
7.	CN105050575B	The combination of alkylamidoalkyl thiazole and preservative	01-10-2019	(119)
8.	CN106946867B	FXR receptor modulators and its Preparation method and application	12-11-2019	(120)
9.	EP3464284B1	Microbiocidal thiazole derivatives	21-10-2020	(121)
10.	JP6817962B2	Compounds and methods for targeted Androgen receptor degradation	20-01-2021	(122)
11.	JP2021020942A	Composition and methods of modulating Short-chain dehydrogenase activity	08-02-2021	(123)
12.	US10961200B2	lactate dehydrogenase inhibitors in small molecules and their applications	30-03-2021	(124)
13.	CN108430998B	Azabicyclo derivatives, their	09-07-2021	(125)

		manufacturing technique, and their use		
14.	JP6971999B2	Acid addition salt of piperazine derivatives	24-11-2021	(126)
15.	JP6987937B2	Thiazole carboxamide and pyridine Carboxamide substances that are effective PIM kinase inhibitors	05-01-2022	(127)

Conclusions

In this study, we carried out a review literature and emphasized recent advancement in biological activities of thiazole derivatives, which is continuously expanding. The natural as well as the synthetic derivatives of the thiazoles have been elaborated along with their potency. The compounds had great variety of medicinal properties more precisely anticancer, antigout, antimicrobial, anti-inflammatory etc. The references retrieved were reviewed and epitomized in the context of synthetic approaches and pharmacological actions of thiazole derivatives. Their great pharmacological potential laid the groundwork for a thorough investigation of these compound's roles in the manufacture and function of thiazole.

Abbreviations

MEP Molecular electronic potential
PGs Prostaglandins
PAN Pan Assay Interference chemicals
IC_{50} Half- maximal inhibitory concentration
Src Non receptor protein tyrosine kinase
MIC Minimum inhibitory concentration
BRAF Serine-threonine kinase
MFC Minimum fungicidal concentration
IMPDH Inosine-5'-monophosphate dehydrogenase
WHO World health organization
FOXM1 Forkhead box protein M1
SAR Structural-activity relationship
CML Chronic myelogenous leukemia
NADPH Nicotinamide Adenine dinucleotide
COX Cyclooxygenase
phosphate
MM2 Molecular mechanics force field
Pk_a acid dissociation constant
HER2 Human epidermal growth factor
PTPs Protein tyrosine phosphatase receptor 2
JAK1 Janus kinase inhibitor
FDA Food and Drug Administration
PDE4 Phosphodiesterase-4
DNA Deoxyribonucleic acid
PGE2 Prostaglandin E_2

NSAIDs Non-steroidal anti- inflammatory
PADs Protein arginine deiminases
Drugs
DHRF Dihydro folate reductase
TNF Tumor Necrosis factor
HATs histone acetyltransferases
HDACs histone deacetylase
MetAP Methionine aminopeptidase
SphK1 sphingosine kinase
MycG B Mycobacterial gyrase B
$PPAR_Y$ Peroxisome proliferator-activated receptors
InhA Enoyl-acyl carrier protein
gamma reductase encoded by InhA gene
NO• Nitric oxide radical
GCGR Glucagon receptor
ROO• Alkyl peroxy radical
GIP Gastric inhibitory polypeptide
Nrf2 Nuclear factor erythroid 2-related receptor 2

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