Review Article

A Review of Synthesis and Biological Activity of Aminothiazole and Its Derivatives

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ABSTRACT

Aminothiazole derivatives' varied pharmacological activity and therapeutic potential have attracted a lot of interest in medicinal chemistry. Recent developments in the synthesis and characterisation of amino thiazole derivatives are thoroughly examined in this study. We examine several synthetic approaches, such as condensation techniques and cyclisation procedures, emphasizing how distinct substituents affect these molecules' biological activity. We also give a summary of their bioactivity profiles, which include antioxidant, antibacterial, anticancer, and anti-inflammatory qualities. This study attempts to serve as a useful resource for researchers working in the fields of medicinal chemistry and drug development by providing an overview of recent findings and potential future paths.

Keywords: Synthesis, Characterization, Aminothiazole derivatives, Biological application.

INTRODUCTION

Two heteroatoms (S and N) are positioned at positions one and three in a heterocyclic ring to form the five-member ring structure known as thiazole. According to reports, thiazoles have a wide range of biological activity and are helpful structural units in the field of medicinal chemistry[1]. The thiazole nucleus is commonly found in the structures of a wide range of naturally occurring products and physiologically active substances, such as thiamine (vitamin B), along with some antibiotic medications like penicillin and micrococcin8, as well as numerous metabolic products of fungus and primitive marine animals. Numerous compounds of thiazoles exhibit good biological and pharmacological properties, such as algicidol, antibacterial and antifungal, anti-inflammatory, analgesic, antitubercular, central nervous system (CNS) stimulant, and anti-HIV.[2] The N=C=S thiazole molecule has been utilised as an antimalarial and antipsychotic. Derivatives of 2-aminothiazoles have been thoroughly investigated as effective therapeutic drugs, and certain thiazole derivatives have demonstrated suppression of the herpes simplex virus. There are numerous thiazole compounds with diverse biological activities. A few 2-aminothiazole derivatives with an arylazo moiety at 5-position have demonstrated strong cytostatic properties. The synthesis and biological assessment of 2-amino-thiazoles are the topics of this research. [3, 4]

Drug Containing 2-aminothiazole Moiety: Pramipexole (1) is used to treat restless legs syndrome, Parkinson's disease, and occasionally cluster headaches. Although Pramipexol's exact mode of action is uncertain, it is thought to function as a dopamine receptor agonist. A third-generation broad spectrum cephalosporin antibiotic, **cefdinir (2)** is used to treat bacterial infections, including tonsillitis, sinusitis, pharyngitis, pneumonia, chronic bronchitis, and various skin infections. It works on penicillin binding proteins (PBPs) to prevent the formation of cell walls. [5,6] One sulpha medication used as an antibacterial is **sulfathiazole (3).**

It works by preventing prokaryotes from synthesising folic acid. These days, it is used to treat vaginal infections in conjunction with sulfabenzamide and sulfacetamide. A nonsteroidal anti-inflammatory medicine (NSAID) called **meloxicam (4)** is used to treat fever, dysmenorrhea, and arthritis. It prevents prostaglandin formation by inhibiting the cyclooxygenase (COX) enzyme. As a nonsteroidal anti-inflammatory medicine (NSAID), **sudoxicam (5)** inhibits the cyclooxygenase (COX) enzyme, which in turn reduces the production of prostaglandins.

An H_2-receptor antagonist called **famotidine (6)** is used to treat gastro-oesophageal reflux disease and peptic ulcer disease. It works by preventing the generation of stomach acid. It doesn't affect the cytochrome P450 enzyme system like other H_2 antagonists do. It binds to H2-receptors competitively to prevent the effects of histamine. [7, 8] One medication used as an anticonvulsant is **riluzole (7)**. Although Riluzole's exact mode of action is yet uncertain, it is thought to work by indirectly blocking glutamate receptor activity. A dopamine agonist called **talipexole (8)** is used to treat Parkinson's disease. An antibacterial drug called **abafungin (9)** is used to treat dermatomycoses. By blocking the cytochrome P450 enzyme 14α-demethylase, it stops lanosterol from being converted to ergosterol. It also affects the fungal cell membrane. [9, 10]

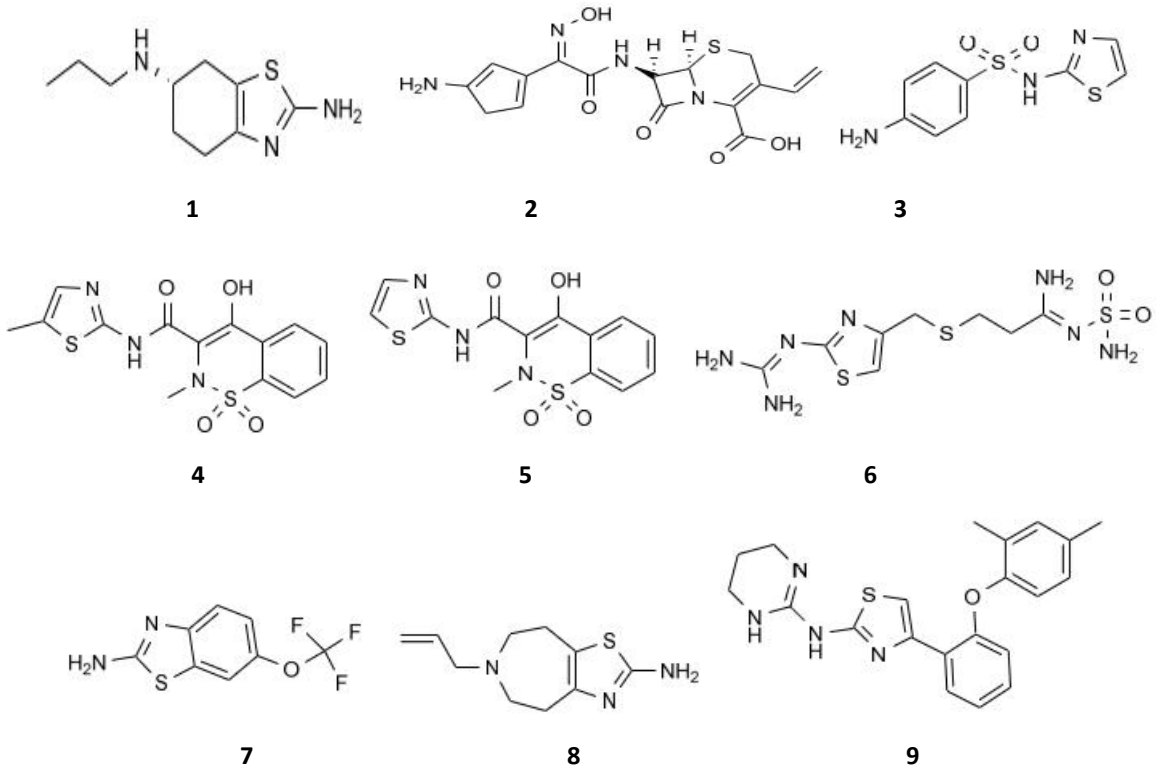


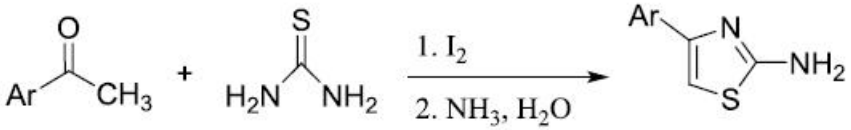
Figure 1: Drug containing 2-aminothiazole moiety

2. SYNTHESIS APPROACH OF AMINOTHIAZOLE

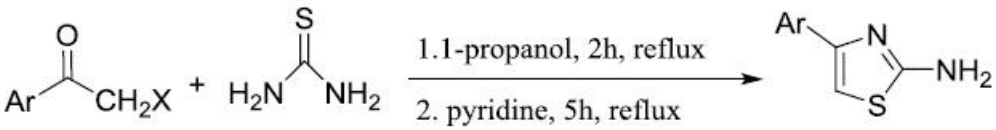
1. Liu and colleagues used two distinct techniques to create a variety of 2-aminothiazole derivatives[11]. I_2 and Thiourea were triturated in the first manner with acetophenone present. For eight hours, the mixed reaction was heated on a water bath while being stirred. Diethyl ether was used to triturate the solid product in order to eliminate any unreacted $C_6H_5C(O)CH_3$, and surplus I_2 was then removed using aqueous sodium thiosulphate. In the second technique, 1-propanol was added to a solution of thiourea and 2-chloro-1-(2,4-dichlorophenyl) ethanone. For two hours, the mixed reaction was refluxed. Pyridine was then added to the mixed reaction, and the reflux was maintained for five hours. [12, 13]

2. A novel 2-aminothiazole synthesis process was reported by Ujwaldev et al. Thiourea, ketone, PEG-400, iodine, and $FeCl_3.6H_2O$ were combined in this synthesis. For a full day at 110°C, the mixture was swirled in an oil bath. Ethyl acetate was then used three times to extract the mixture. Fe(III)/iodine served as the catalyst, whereas PEG-400 served as the solvent.[14]

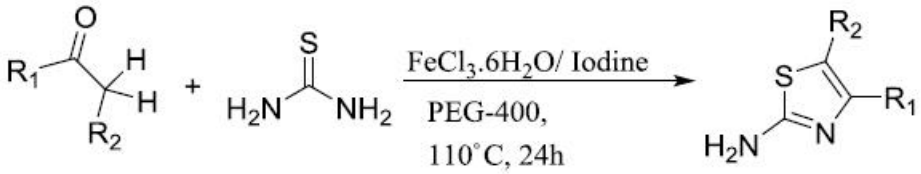
3. Some of the novel compounds of 2-aminothiazoles were developed by Ma et al., combined tween-80 and olefin at room temperature with DBH and water. It was then allowed to cool to room temperature. After that, thiourea was added to the mixture while EtOH was present, and it was agitated for two hours at 80°C. Following these steps, the derivatives of 2-aminothiazoles were produced.[15]



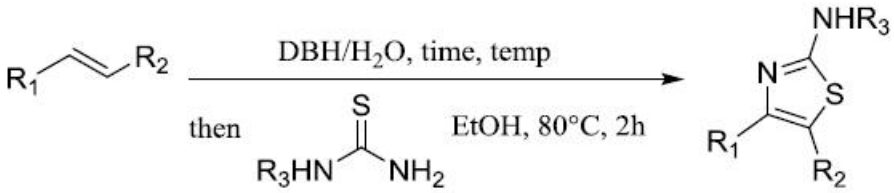
Scheme 1a:



Scheme 1b:

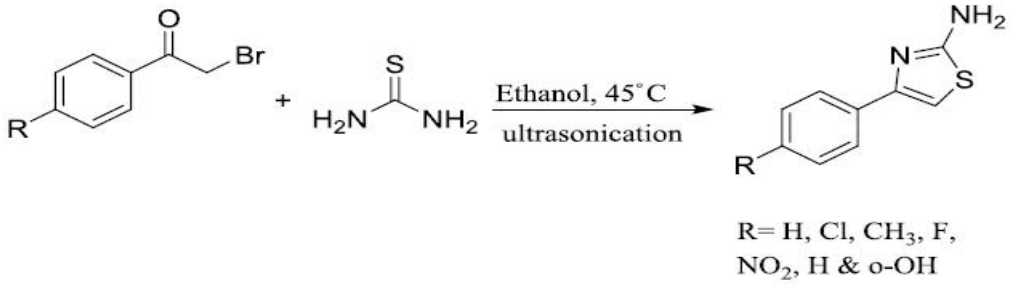


Scheme 2:



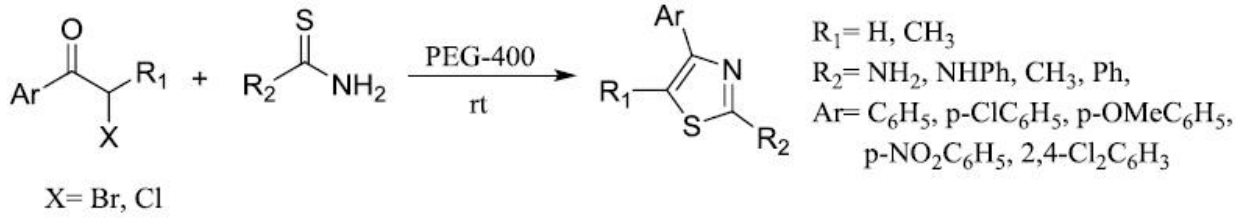
Scheme 3:

4. Novel 2-Amino-4-aryl thiazole compounds were synthesised by Sinha et al., combined phenacyl bromide and thiourea with ethanol, then ultrasonically sonicated in an ultrasonic bath at 45°C.[16]



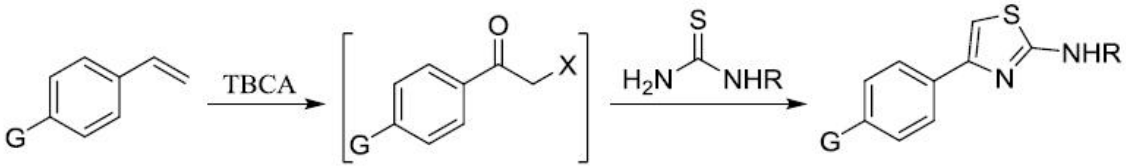
Scheme 4:

5. Tri and disubstituted thiazoles were synthesised by Zhu et al., without the use of a catalyst. This procedure involved mixing PEG-400 with α-haloketone and thiourea/thioamide, then stirring the mixture at room temperature until the specified time had passed.[17]



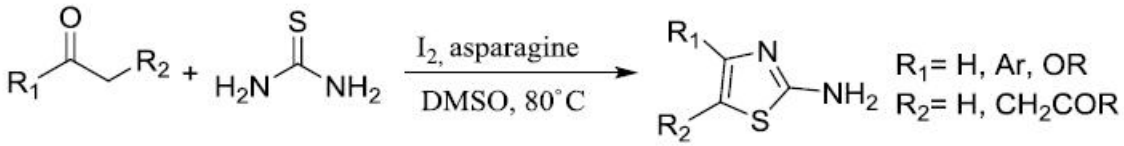
Scheme 5:

6. A new class of compounds of 4-aryl-2-aminothiazoles was reported by de Andrade et al. The first step involved preparing phenacyl bromide by mixing styrene and TBCA in aqueous acetone at 70°C for two hours. They were then allowed to sit at room temperature for fifteen minutes while thiourea and phenacyl bromide were combined in the presence of acetonitrile/water (1:1). It was simple to synthesise the product (4-aryl-2-aminothiazoles).[18]



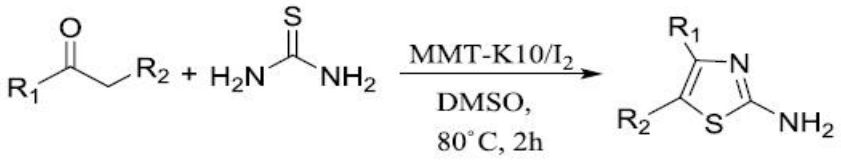
Scheme 6:

7. Using the novel technique, Safari et al., synthesised a few 2-aminothiazole derivatives. Using a one-pot technique, I_2, methylcarbonyl, thiourea, and asparagine were combined with DMSO. At 80°C, the reaction mixture was agitated for a predetermined amount of time. Asparagine served as a green organocatalyst in this reaction, and this was its new aspect.[19]



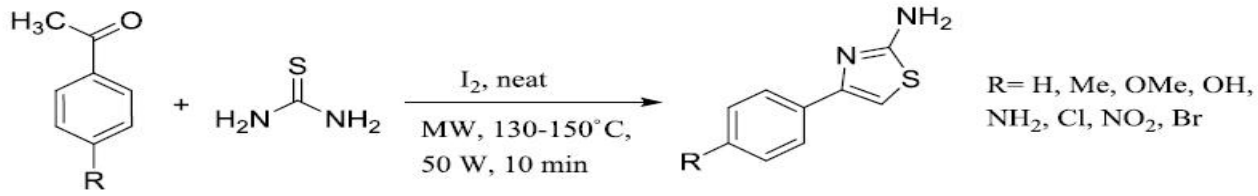
Scheme 7:

8. Safari and associates, in a different investigation, MMT-K10, iodine, thiourea, and methylcarbonyl were combined with DMSO and then agitated for two hours at 80°C.[20]

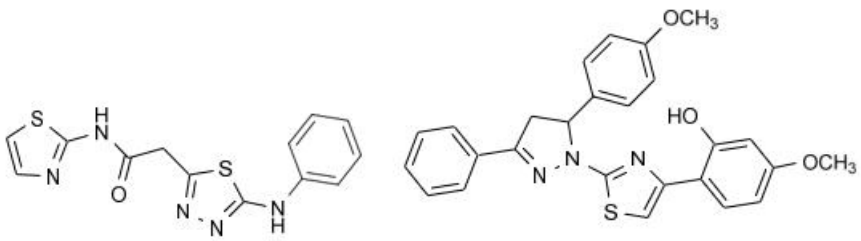


Scheme 8:

9. Novel thiazole compounds were synthesised without the use of solvents, according to Fayed et al. Thiourea, p-substituted acetophenones, and I2 were combined in this reaction, and the result was produced by microwave irradiation at 130–150°C for ten minutes.[21]



Scheme 9



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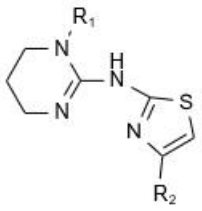
3. BIOLOGICAL ACTIVITY

We focused on reported biological activities of 2-aminothiazoles with their brief profile of a number of biological activities as well as drug molecules containing 2-aminothiazole moiety.

1) Antihypertensive Activity: Triazole derivatives, tetrachloro-isoindolylimide, and thiazolylmalonamide were synthesised by Abdel-Wahab et al. and their antihypertensive properties were assessed. Many of the synthesised compounds had better activity than the usual medication, minoxidil. Acute toxicity research was also conducted on these substances. **Compound (10)** had good efficacy and low toxicity[22] within these series. A few 1-(4-arylthiazol-2-yl)-3,5-diaryl-2-pyrazoline derivatives were described by Turan-Zitouni G et al., who also assessed their hypotensive potential. Every synthetic molecule outperformed the traditional medication (clonidine) in terms of activity. The general structure of the compound series is shown by **compound (11)**.[23]

2) Antitubercular Agents: 2-Aminothiazole derivatives (12) have been described as antitubercular drugs in U.S. patents. Tetrahydropyrimidinylthiourea reacts with ω-hydroxy-3-substitutedmethylacetophenones[24] to produce these chemicals. According to Karuvalam RP et al., a number of (2-aminothiazol-4-yl)methylester derivatives were prepared and tested against Mycobacterium smegmatis (ATCC 19420), Mycobacterium fortuitum (ATCC 19542), and *M. tuberculosis* (H37Rv strain). **Compound (13)** has demonstrated superior antitubercular action compared to the conventional medications (Rifampicin and Isoniazid) among the synthesised compounds[25]. New thiazolidinone and thiazole compounds were synthesised

by Aridoss G et al., who then assessed their antimycobacterial efficacy. **Compound (14)** outperformed the standard medication (rifampicin) in terms of activity among the series of compounds[26]. The production and antitubercular assessment of a series of **N-{4-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-1,3-thiazol-2-yl}-2-substitutedamide derivatives (15)** were described by Shiradkar MR et al. Some compounds showed comparable activity with standard drug (Rifampin)[27].



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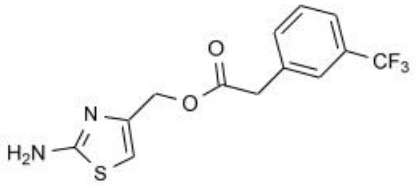

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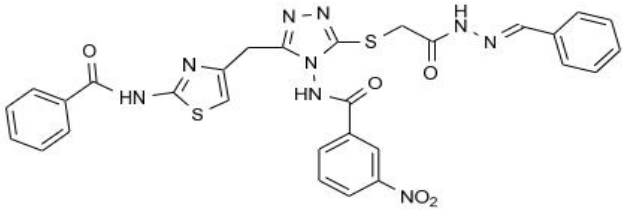

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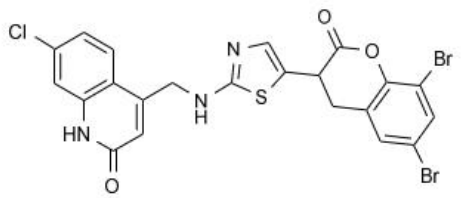
3) Anti-Inflammatory Agents: The synthesis of tricyclic thiazoles and an assessment of their anti-inflammatory properties utilising a formalin-induced paw oedema model were reported by Kalkhambkar et al. Comparable action was demonstrated by **compound (16)** and the conventional medication (phenyl butazone)[28]. Arylaminothiazoles were synthesised by Holla BS et al. and tested for anti-inflammatory properties. The activity of **compounds (17)** and **(18)** was similar to that of the common medication, ibuprofen[29]. Using a rat paw oedema model caused by carrageenan, Giri S et al., reported a variety of 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazoline-4-one derivatives and assessed their anti-inflammatory properties. The most active chemical in this series, **compound (19),** was discovered to be more active than the typical medication, ibuprofen[30]. Singh N et al. reported synthesising thiazolylformazanylindoles and investigating their anti-inflammatory effects using a carrageenan-induced oedema model. **Compound (20)** was the most powerful and least poisonous of the synthesised compounds[31]. A 2-amino thiazole derivative with various structural characteristics was synthesised by Franklin PX et al., and its anti-inflammatory properties were assessed. Rat paw oedema models and chronic formalin-induced rat paw oedema models were used to test anti-inflammatory activity. **Compound (21)** and **(22)** and the usual medication (Dexamathasone)[32] exhibited similar levels of action. The synthesis of adamantane derivatives of thiazolyl-N-substituted amides and their assessment as anti-inflammatory drugs were reported by Kouatly O et al. The carrageenin-induced rat paw oedema model was used to test the anti-inflammatory activity. Among the series, **compound (23)** found to be most potent active compound[33]. The synthesis of the 3-[40-(p-chlorophenyl)-thiazol-20-yl] series was reported by Kumar A et al. 2-[(thiazolidinone/substitutedazetidinone)-aminomethyl]4-ones of 6-bromoquinazolin. Rat paw oedema was used to test these substances' anti-inflammatory properties. The most active component in this series was discovered to be **compound (24)**, whose activity was on par with that of the common medication phenyl-butazone[34]. Using a carrageenan-induced paw oedema model, Sondhi et al. synthesised acridinyl-thiazolino derivatives and tested their anti-inflammatory properties. **Compounds (25)** and **(26)** exhibit activity that is comparable to that of the common medication, ibuprofen[35].



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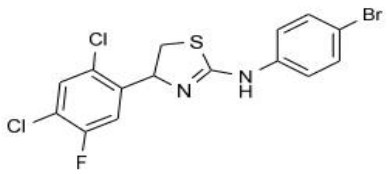

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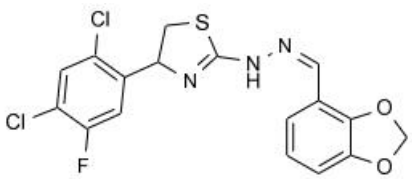

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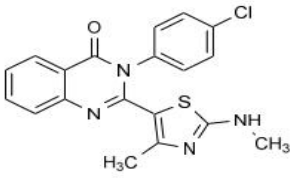

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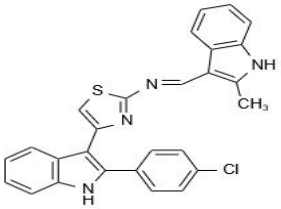

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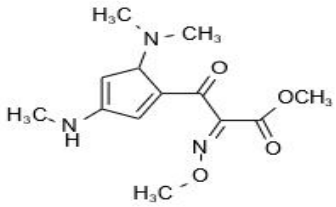

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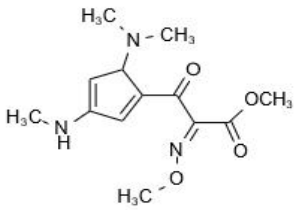

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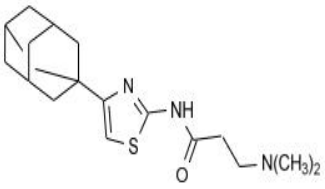

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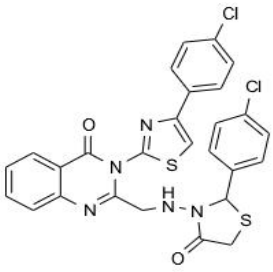

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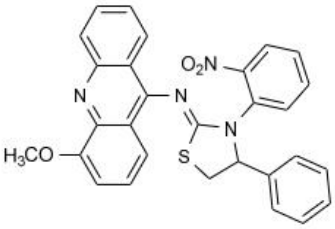

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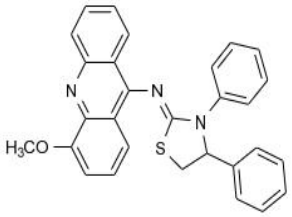

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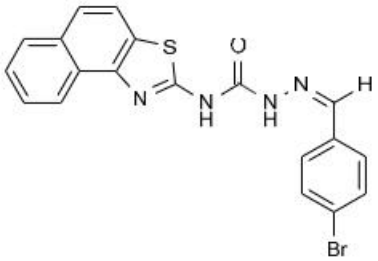
4) Anticonvulsant Activity: Azam F et al. synthesised a variety of N4-(naphtha[1,2-d]thiazol-2-yl)semicarbazides and used the maximum electroshock (MES) and pentylenetetrazole (PTZ)-induced seizure test to assess their anticonvulsant activity. The majority of the compounds were found to exhibit broad spectrum action. The general structure of the series[36] is represented by **structure (27)**. Certain thiazole-substituted coumarine compounds were described by Amin KA et al. as anticonvulsant drugs. The PTZ-induced seizures test was used to gauge the anticonvulsant activity. The highest active molecule in the synthesised series was **compound (28)**[37].

5) Neuroprotective and Antioxidant Activity: Coumarine-incorporated thiazole compounds were reported by He H et al. as antioxidants. The antioxidant activity of **compounds (29, 30, and 31)** was comparable to that of normal ascorbic acid (Ascorbic acid)[38]. The synthesis of sydnonyl substituted thiazolidinone and thiazoline derivatives, as well as an assessment of their antioxidant properties, were reported by Shih MH et al. The DPPH test was used to assess the antioxidant activity. **Compound (32)** had stronger antioxidant activity than the typical compound (Vitamin E) among these series[39].

6) Antiprotozoal agents: The antihelmintic activity of N-methylated thiazolylamino acids and peptide was examined by Himaja MN et al. Comparing **compound (33)** to the usual medication (mebendazole)[40], compound (33) had the strongest activity among the synthesised compounds. **Nitazoxanide (34)** has been described as an antiprotozoal agent by Muluk MB et al. In vitro in microplates, this substance and its metabolite tizoxanide were tested against six axenic isolates of Giardia intestinalis in comparison to metronidazole. When it came to metronidazole-susceptible isolates, tizoxanide was eight times more effective than the drug, and when it came to resistant isolates, it was twice as effective[41].



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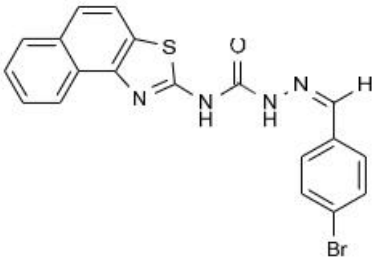

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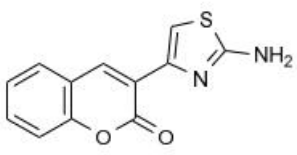

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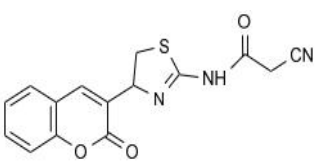

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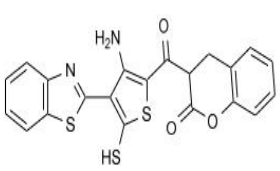

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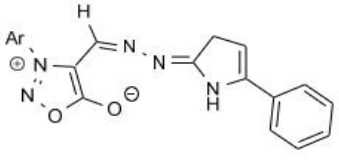

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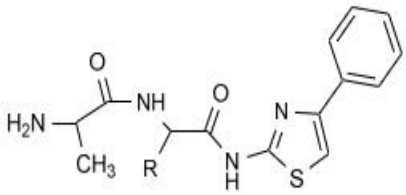

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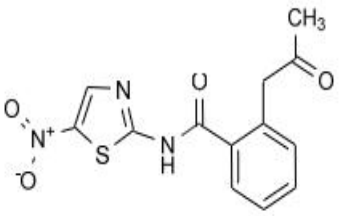

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7) Anti-HIV Agents: 2-aryl-3-heteroaryl-1,3-thiazolidin-4-one derivatives were synthesised by Rawal RK et al. and their anti-HIV efficacy was assessed using an in vitro assay. Among the synthesised compounds, **compound (35)** was determined to be the most active analogue. In comparison to the usual medication (thiazobenzimidazole), it demonstrated a low toxicity and a good EC50 value[42]. Aromatic and heterocyclic **thiazolylthioureas (36)** have been identified as anti-HIV drugs by Venkatachalam TK et al. Some of these derivatives and compounds were mildly hazardous to human peripheral blood mononuclear cells and demonstrated sub-nanomolar IC_{50} values for the suppression of HIV replication[43]. 3,4-diaryl-3Hthiazol-2-ylidene)pyrimidin-2-yl amine derivatives were synthesised and their anti-HIV efficacy assessed by Turan-Zitouni et al. **Compound (37)** exhibited strong activity[44] in this series. Phenylthiazolylthioureas (38) have been reported by Bell WF et al. as anti-HIV drugs. HIV-1 is inhibited by N-(2-phenethyl)-N'-(2-thiazolyl)thiaourea, the series' main chemical.[45]

8) Antibacterial Agents: Schiff bases and N-Mannich bases were created by Pandeya et al. through the reaction of isatin derivatives with N-[4-(49-chlorophenyl)thiazol-2-yl]thiosemicarbazide. The agar dilution method was used to test the synthetic compounds' antibacterial effectiveness against 28 harmful microorganisms. In the synthesised series[46], **compound (39)** was discovered to be the highest active compound. The bactericidal qualities of 2-amino-4-arylthiazoles have been described and investigated by Dighe SN et al. **Compounds (40)** and **(41)** outperformed the typical medication (nitrofurantoin) 47 in terms of activity among the synthesised compounds. A number of 1-(4-(4'-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1H-imidazol-5yl) series were synthesised by Dawane BS et al. Analogues of 2-pyrazoline and assessed for antimicrobial efficacy. **Compound (42)** outperformed the usual medication (tetracycline) in its ability to combat four different bacterial types[48]. A set of 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl] were assessed by Abdel-Wahab et al. 1H-pyrazoles for their antibacterial properties. **Compounds (43 and 44)** in these series shown greater action against S. aureus and E. coli, respectively, than the common medication (Amoxicillin)[22]. In order to test for bactericidal activity, Joshi et al. synthesised flourine that contained **2-(N-arylamino)-2 / 2-methyl-4-arylthiazoles 3 (45 and 46).** [49] The antibacterial activity of a stereospecific series of thiazolidinones and thiazole derivatives was assessed by Aridoss et al. **Compounds (47, 48, and 49)** had similar efficacy to the reference medication, Ciprofloxacin.[26]

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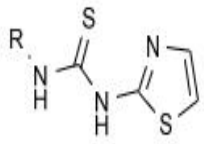

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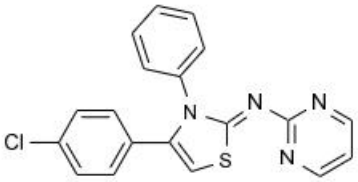

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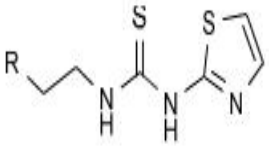

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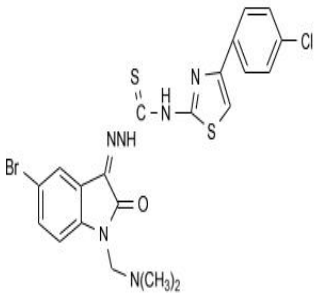

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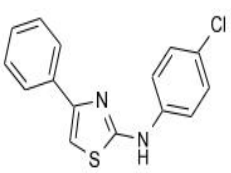

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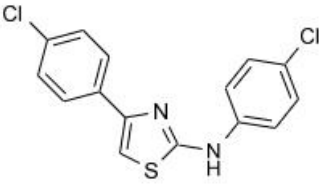

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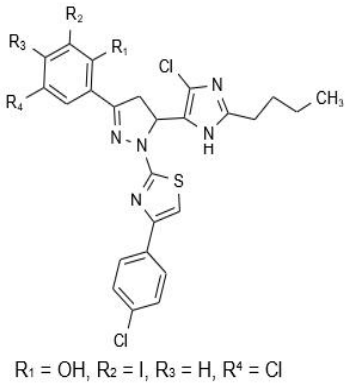

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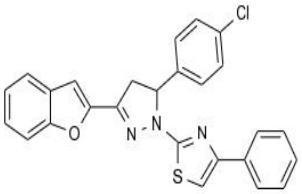

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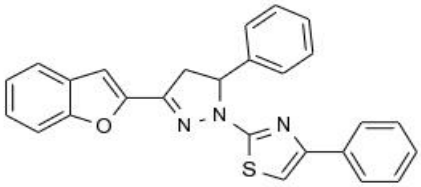

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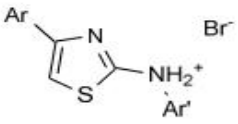

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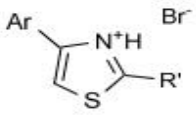

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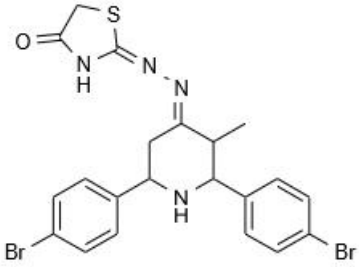

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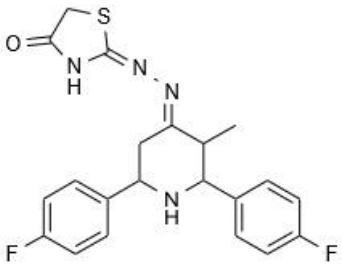

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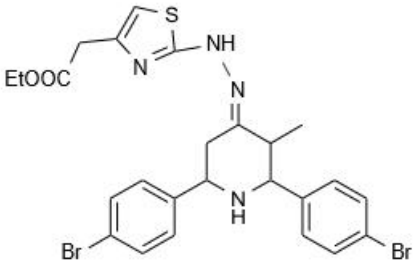

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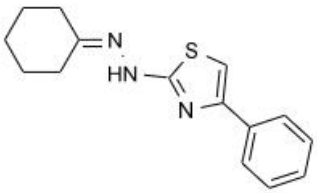

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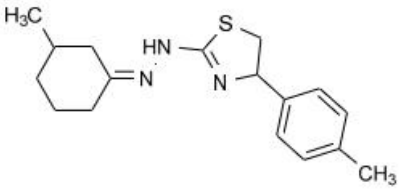

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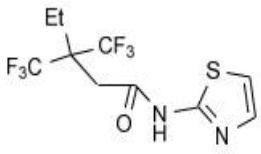

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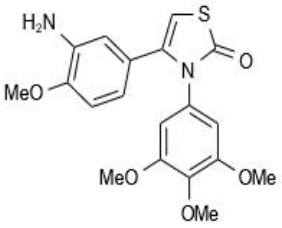

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9) Antifungal Agents: Logu AD *et al.,*have investigated in vitro antifungal activity **cyclohexylidenehydrazo-4-phenylthiazole (50)** against isolates of candida spp. including fluconazole-resistant candida albicans[50]. Chimenti F et al., reported the synthesis of some new 2-sulfonamidothiazoles derivatives and evaluated for antifungal activity against candida species. In this series, **compound (51)** showed good activity against variety of candida species[51].

10) Anticancer Activity: Some N-bis(trifluoromethyl)alkyl-N'-thiazolylureas derivatives were synthesised by Luzina EL et al. and their anticancer potential against human cancer cell lines was assessed. **Compound (52)** demonstrated good efficacy against PC-3 cancer cells (prostate cancer, log GI50 −7.10)[52] among the synthesised compounds. Liu and colleagues synthesised three derivatives of 3,4-diarylthiazol-2(3H)-imines and 3,4-diarylthiazol-2(3H)-ones and assessed their cytotoxicity against cancer cell lines. **Compounds (53)** (IC_{50} = 0.12 µM) and 68 (IC_{50} = 0.24 µM) were discovered to exhibit strong activity against human CEM cells..[11]

CONCLUSION

Finally, we highlighted the synthesis of 2-aminothiazole derivatives in this review. The optimal approach for the synthesis of these scaffolds is being used with considerably greater effort by researchers in this field. These scaffolds produced structures with outstanding biological activity. We anticipate that both synthetic methodologists and researchers working in 2-aminothiazole chemistry will find this review to be highly interesting. 2-Aminothiazole is quite interesting from a biological and medical standpoint. This heterocyclic moiety was also present in a few of the marketed medications. Antibacterial, antifungal, antitubercular, anti-HIV, antiprotozoal, anticancer, anti-inflammatory, dopaminergic, PARP-1 inhibitor, antioxidant, anticonvulsant, antidiabetic, and antihypertensive properties are among the biological actions that have been documented. It is evident from all of these activities that medicinal chemistry is very interested in the 2-aminothiazoles moiety.

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