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Review

Diverse Biological Activities of 1,3,4-Thiadiazole Scaffold

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Abstract: The chemistry of 1,3,4-thiadiazole is one of the most interesting scaffolds for synthesizing new drug molecules due to their numerous pharmacological activities. Several modifications in the thiadiazole ring have been made, proving it to be more potent and highly effective with a less toxic scaffold for various biological activities. There are several marketed drugs containing 1,3,4-thiadiazole ring in their structure. In this review article, we have tried to compile the newly synthesized 1,3,4-thiadiazole derivatives possessing important pharmaceutical significance since 2014.

Keywords: 1,3,4-thiadiazole; scaffolds; pharmacological activities; marketed drugs; synthesized derivatives

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1. Introduction

Drug resistibility is one of the major problems occurring worldwide and to deal with this, the need of synthesizing new compounds has become one of the most interesting research areas. Thiadiazole nucleus is a well-known and one of the most important heterocyclic nuclei, exhibiting various biological activities, such as anti-microbial [1–5], anti-convulsant [6–8], anti-cancer [4,9,10], anti-viral [11,12], anti-tuberculosis [12,13], anti-inflammatory and analgesic [14–16], diuretic [17], anti-diabetic [18,19], anti-depressant [20,21], anti-ulcer [16,22], anti-malarial, anti-leishmanicidal [23,24], anti-influenza [25,26], anti-hypolipidemic, anti-hyperlipidemia [27,28], anti-hypertensive [29], etc. Thiadiazole is a five-membered heterocyclic ring containing a sulfur atom, two nitrogen atoms, and hydrogen binding domain. It was discovered by Emil Fischer in 1882 and its properties were described by two chemists named Kuh and Freund. It is generally known as 3,4-dioxythiophene, 4-azathiazole and is available in four isomeric forms, i.e. 1,2,4-thiadiazole **1**, 1,2,3-thiadiazole **2**, 1,3,4-thiadiazole **3** and 1,2,5-thiadiazole 4 (Figure 1). The researchers are working more on the 1,3, 4-thiadiazole isomer than the other three isomers of thiadiazole altogether. "The biological activities of 1,3,4-thiadiazole derivatives are based on assumptions like: the presence of =N-C-S- moiety and the strong aromaticity of the ring, which is responsible for providing low toxicity and great in vivo stability". The 1, 3,4-thiadiazole ring possesses high aromaticity, becoming stable in acid but forming a ring cleavage with base. This scaffold is electron deficient, relatively inert towards electrophilic substitution, and displays nucleophilic substitution at 2nd and 5th positions due to which it is highly activated and reacts easily. Because of these properties of 1, 3,4-thiadiazole, it is widely used in research by chemists and scientists [30,31].

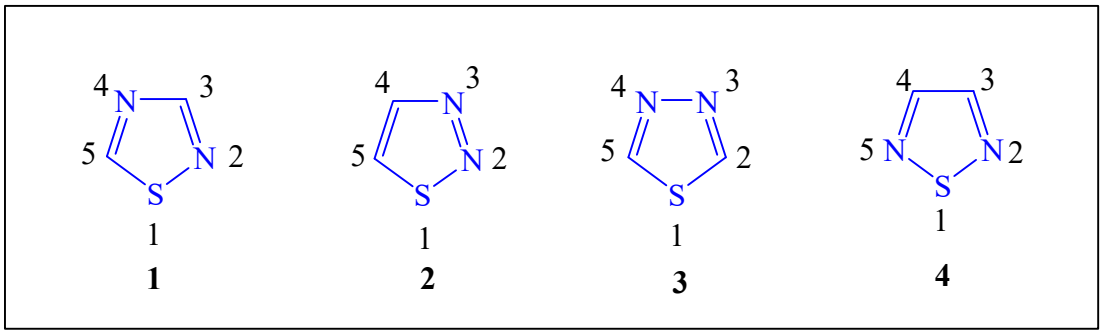

Figure 1. Isomers of thiadiazole.

2. Pharmacological Activities

2.1. Anti-Convulsant Agents

Epilepsy is a neurological disorder which is commonly characterized by convulsions (repeated seizures) over time. It is a term given collectively to a group of syndromes that involve abnormal, intermittent, and impulsive electrical activity in the brain. In last 20 years, some new anti-epileptic drugs have been introduced to the market having fewer side effects and potent anti-convulsant activity [32]. To this, recently Dinesh R. et al. also contributed by synthesizing new thiadiazole derivatives by two methods (microwave and conventional). They confirmed the structure using analytical spectroscopy and further screened the compounds for in-vitro anti-convulsant activity on Swiss albino mice. Compounds 5 and 6 were found to be highly potent, while compound 7 displayed moderate anti-convulsant activity [33]. Aliyu A et al. (2021) also designed and synthesized a new thiadiazole derivative by condensation reaction and evaluated it for in-vitro anti-convulsant activity on mice by PTZ and MES method and found 8 to be a potent compound with no toxicity [34] (Figure 2).

2.2. Anti-Alzheimer Agents

Alzheimer's is a neurological disorder characterized by dementia and other cognitive symptoms. In recent years, scientists have made great progress in understanding the pathophysiology of Alzheimer's disease and synthesizing drugs for its cure, but to date there is no cure for the disease. However, recently, some drugs have become available on the market, which helps to decrease the rate of Alzheimer's by inhibiting cholinesterase enzyme [35]. Considering this information, chemists are taking keen interest in developing new drug to cure this disease with fewer side effects. In this context, new analogues of 1,3,4-thiadiazole using thiosemicarbazide and propanoic acid as precursor was synthesized by Aggarwal N et al. The structure was confirmed by NMR (^{13}C and ^{1}H), MS, and IR, and the compounds were evaluated for in-vitro Alzheimer's activity by inhibiting acetylcholinesterase (AChE) enzyme using Ellman's method. It was concluded that compound 9 and 10 displayed highest AChE inhibition in comparison with donepezil and can be used as a lead molecule for anti-Alzheimer's activity [36]. In 2022, Karcz D et al. designed and synthesized a novel series of coumarin–thiadiazole derivatives and identified their structure using elemental analysis. Further the compounds were tested for Alzheimer's activity. Moderate inhibition of cholinesterase enzyme (AChE and BuChE) was observed by compound 11 compared to standard (tacrine). It was concluded that the rigid structure of the compound was responsible for preventing them to adopt the necessary conformation for docking in enzyme binding site [37]. In 2021, a similar research group reported new analogues 12 of coumarin–thiadiazole and their corresponding Zn(II) and Cu(II) complexes and evaluated them for in-vitro Alzheimer's activity, concluding that substituting with amide group increases the inhibition of cholinesterase enzyme [38] (Figure 2).

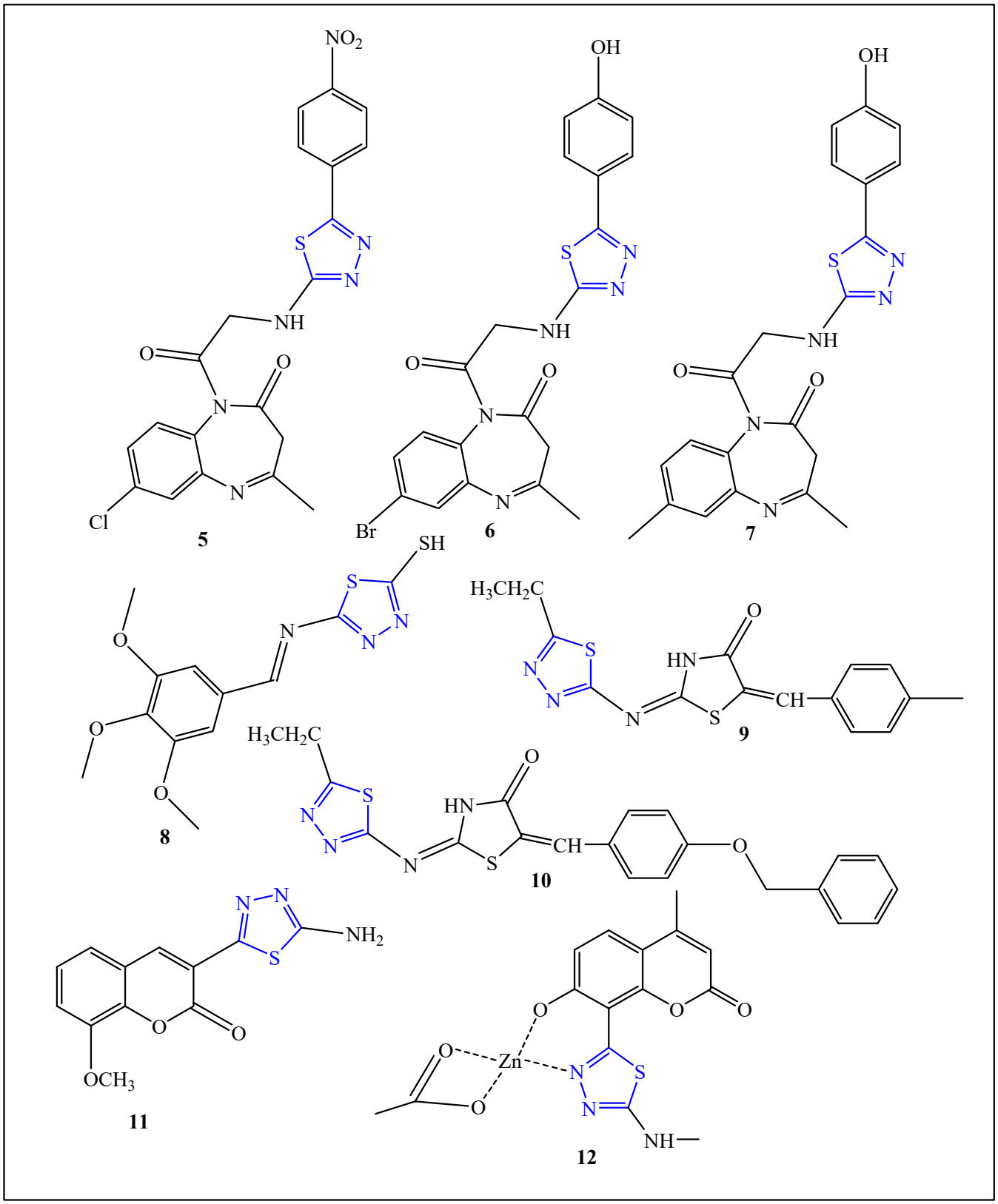

Figure 2. 1,3,4-thiadiazole derivatives **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12** as anti-convulsant agents and anti-alzheimer agents.

2.3. Anti-Cancer and Anti-Tumor Agents

Cancer is the second largest cause of death throughout the world. Furthermore, the treatments, such as radical surgery or chemotherapy, eventually fail to control the disease. Generally metastatic diseases develop even after the treatment and can cause death. Cancer chemoprevention has been an active research area for several years. Various efforts were made by different scientists in this felid to find a permanent cure for cancer [39]. An attempt was made by Anastassova et al. to synthesize new thiadiazole hybrids and evaluate them as anti-cancer agent against breast cancer and lung adenocarcinoma cell lines by the MTT method. It was concluded that compound 13 can be considered as potent anti-cancer agent [40]. Kandemir L et al. also reported new 1,3,4-thiadiazole derivatives and evaluated them for anticancer activity by the MTT method and concluded that the synthesized compounds **14, 15** showed moderate inhibition in the cell line [41]. A series of twenty-eight new 1,3,4-thiadiazole analogues were synthesized by Liu Y et al., who further evaluated the synthesized compounds for in vitro anti-proliferative activities by cell counting kit-8 (CCK-8) method. Three compounds, **16**, **17**, and **18**, showed the highest anti-proliferation effect on SMMC-7721, A549, and Hela cell line, and can be considered as less toxic more effective anti-tumor agents [42] Chen C et al. reported new derivatives of 2,5-diphenyl-1,3,4-thiadiazole hydroxamate and tested them for in-vitro anti-tumor activity. It was concluded that compound **19** exhibited the most potent inhibitory activity against HDAC1 cell line with the IC50 of 15 nM and can be considered as a promising lead compound for further investigation [43] (Figure 3).

2.4. Anti-Diabetic Agents

Metabolic disorder occurred due to insulin deficiency or inadequate insulin secretion resulting in hyperglycemia is known as diabetes. Diabetes is an endocrine disorder affecting 5–7% of the population globally. At present, the drugs available in the market do not cure it completely, but slow down and manage the symptoms to some extent [19]. Recently, twenty-five new derivatives of triazinoindole containing thiadiazole ring were reported by Khan et al. Further, the compounds were evaluated for in-vivo anti-diabetic assay. It was observed that all the synthesized compounds were found to be potent, but compounds **20** and **21** showed high anti-diabetic activity by inhibiting α-glucosidase enzyme in comparison with the standard. Further, they conducted a molecular docking study of all the compounds against α-glucosidase protein, finding that the synthesized compounds can be potent anti-diabetic agents in future use [44]. Deswal Y et al. also synthesized some new Schiff base derivatives of thiadiazole and their metal complexes. Furthermore, they performed a comparative in-vitro anti-diabetic assay and molecular docking study of all synthesized compounds and observed that the Schiff base metal complex derivatives **22** and **23** showed high inhibition against α-amylase and α-glucosidase enzymes in comparison to Schiff base derivative [45] Radha P.V et al. synthesized four Schiff base metal complex thiadiazole derivatives after studying their geometrical parameters, thermal stability, energy gap, and confirming the structure of the synthesized compounds. They further evaluated them for in-vitro anti-diabetic assay and found that **24** inhibited α-amylase enzyme more than standard and could be a potent anti-diabetic agent [46] (Figure 4).

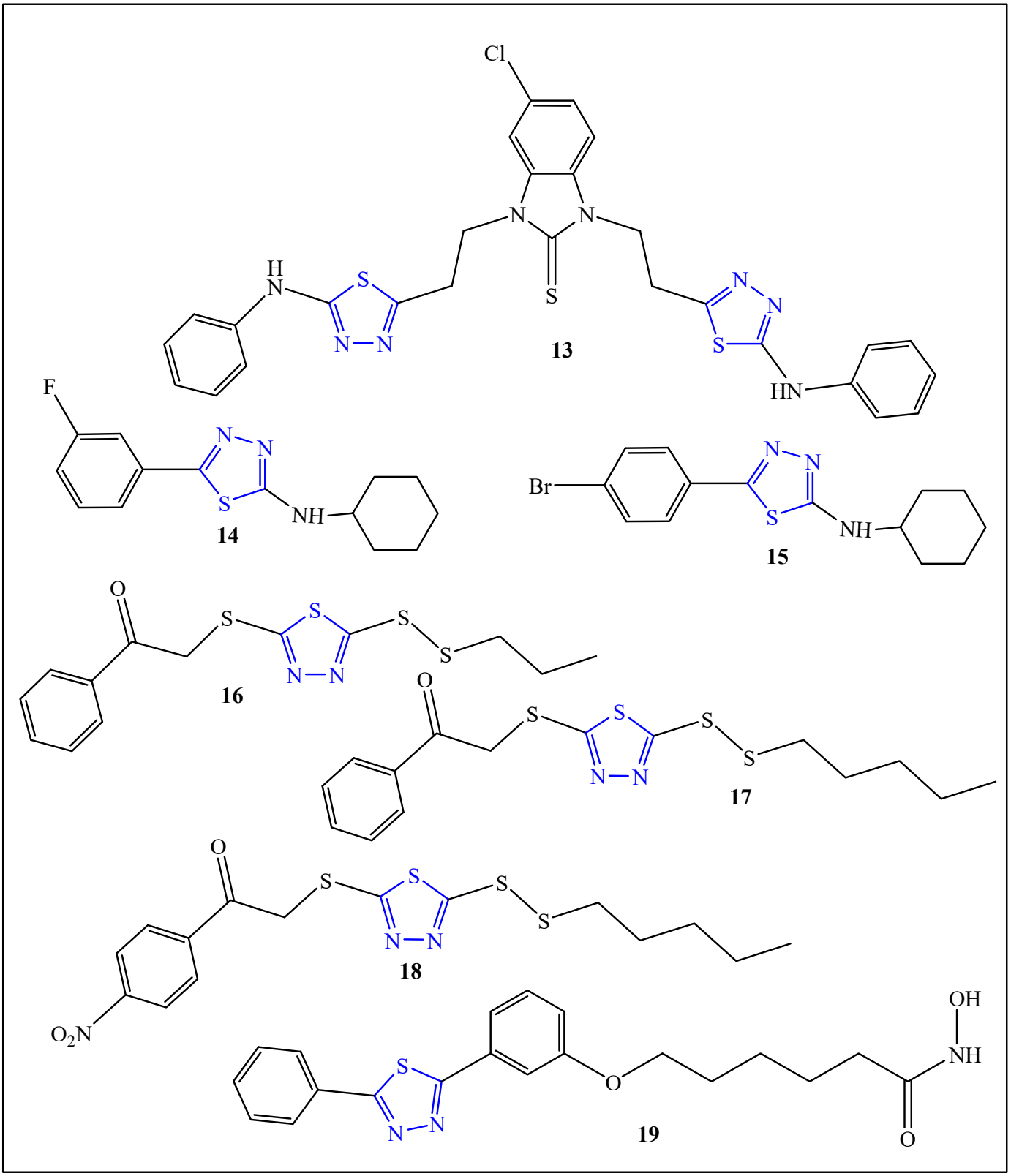

Figure 3. 1,3,4-thiadiazole derivatives **13**, **14**, **15**, **16**, **17** **18**, **19** as anti-cancer and anti-tumor agents.

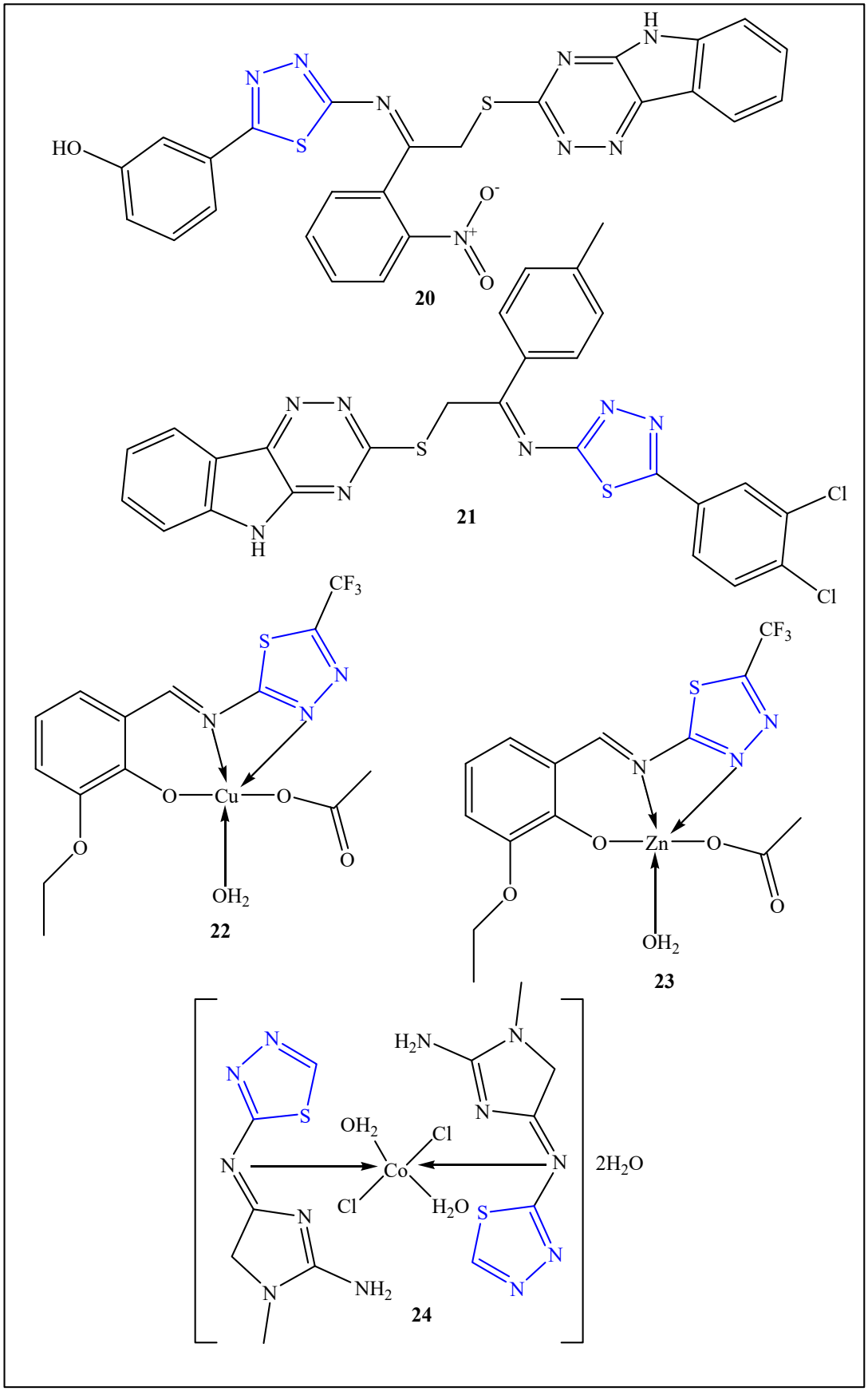

Figure 4. 1,3,4-thiadiazole derivatives **20**, **21**, **22**, **23**, **24** as anti-diabetic agents.

2.5. Anti-Viral Agents

2.5.1. Treatment of SARS-CoV-2 Virus

In late December 2019, a new infectious disease named COVID-19, spread by SARS-CoV-2 virus, emerged in China (Wuhan), then spread quickly in different countries. COVID-19 resulted in serious psychological and physical damage to human health and in March 2020 WHO declared it as a pandemic. Therefore, investigation of medicine to treat COVID-19 became an urgent demand in medical science and recently attracted more interest among chemists as a particular drug for the treatment of COVID-19 is not available on the market [47,48].

Since the emergence of COVID-19, physicians and scientists all over the world have been trying their best to understand the epidemiology, devise possible treatment, and develop vaccines or new effective therapeutic agents of this new emergent disease. To this Rashdana, M.R.H and Abdelmonsef, A.H. also contributed in 2022 by synthesizing novel derivatives of thiadiazole and confirmed their structures using analytical spectroscopy. Further, they performed the in-silico studies on four SARS-CoV-2 target enzymes, namely papain-like protease (PLpro), main protease (Mpro), receptor-binding domain (RBD) of the spike protein, and RNA-dependent RNA polymerase (RdRp), and tested their likeness properties. Out of seven synthesized compounds, **25** displayed promising binding affinities and excellent likeness properties inside the body. Hence, it could be considered a potential therapeutic agent against COVID-19 [49]. In 2020, the same research group synthesized eight new derivatives of 1,3,4-thiadiazole and checked their potency by performing in silico studies, targeting TMPRSS2 enzyme and using PyRx software. Further ADMET studies were also performed using free software. Out of the eight synthesized compounds, compound **26** had highest binding affinity (−9.1 kcal/mol) toward the target enzyme, and could thus be a potential therapeutic agent for coronavirus [50].

2.5.2. Treatment of Hepatitis B Virus (HBV) and Human Immunodeficiency Virus (HIV)

Approximately 3.5 million people suffer with HIV and HBV infection worldwide. At present, there is no definitive treatment available on the market for curing of these infectious diseases. Therefore, some drugs are available on the market which help to decrease the rate of these infectious diseases [51,52]. Considering this information, researchers and chemists are taking keen interest in developing new drugs for the treatment of these diseases with fewer side effects. In this context, Liu Y et al. reported new series of thiadiazole derivatives **27, 28** and evaluated them for in vitro anti-HBV assay. They concluded that substitution of methyl group at 5th position and replacement of sulfide group with sulfinyl group increase the inhibition of DNA (HBV) [53]. In 2018, a novel chiral 1,3,4-thiadiazole based bis-arylsulfonamides was synthesized and evaluated for the treatment of HIV-1 and HIV-2 by Shafique M et al. They found that compound **29** could be considered a new lead for the treatment of HIV as it displayed significant inhibitory activity against HIV-1 [54] (Figure 5).

2.6. Anti-Platelet Agents

The agents containing hydrazone group in their structure are found to be potent anti-platelet agents. Considering this property of hydrazone Tehrani E.M.H.K et al., designed and synthesized new 2-hydrazinyl-1,3,4-thiadiazole derivatives and after confirming the structure of the synthesized compounds they were further screened for in-vitro anti-platelet aggregation assay using turbidimetric method and concluded that **30**, **31**, **32** compounds showed highest inhibition of COX enzyme and hence can be a potent anti-platelet aggregation agent [55]. Ruel R et al. synthesized some novel derivatives of 1,3,4-thiadiazole and screened them for in-vivo anti-platelet activity, concluding that compound **33** was highly potent and could be a lead as a new anti-platelet agent [56] (Figure 6).

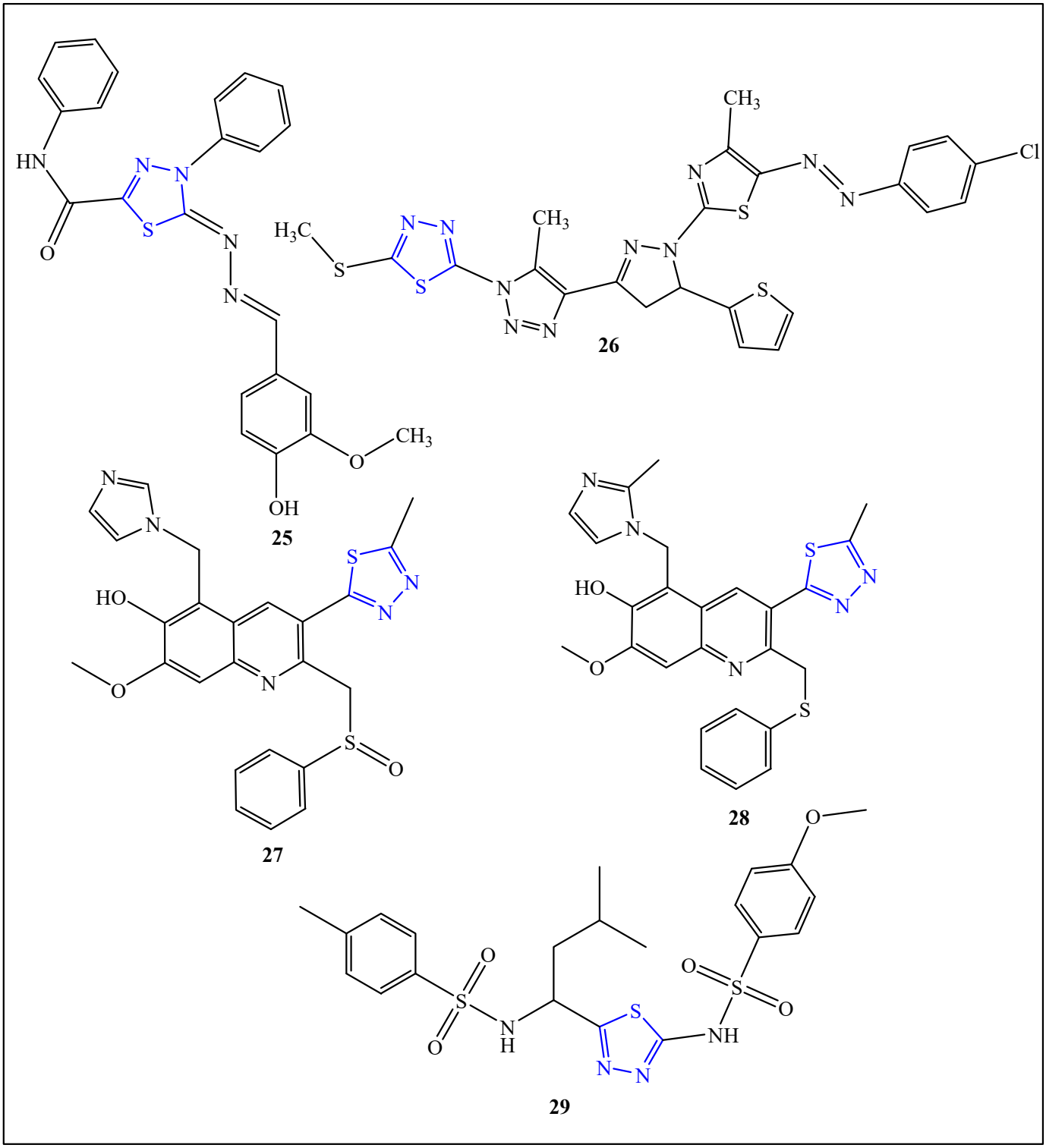

Figure 5. 1,3,4-thiadiazole derivatives **25**, **26**, **27**, **28**, **29** as anti-viral agents.

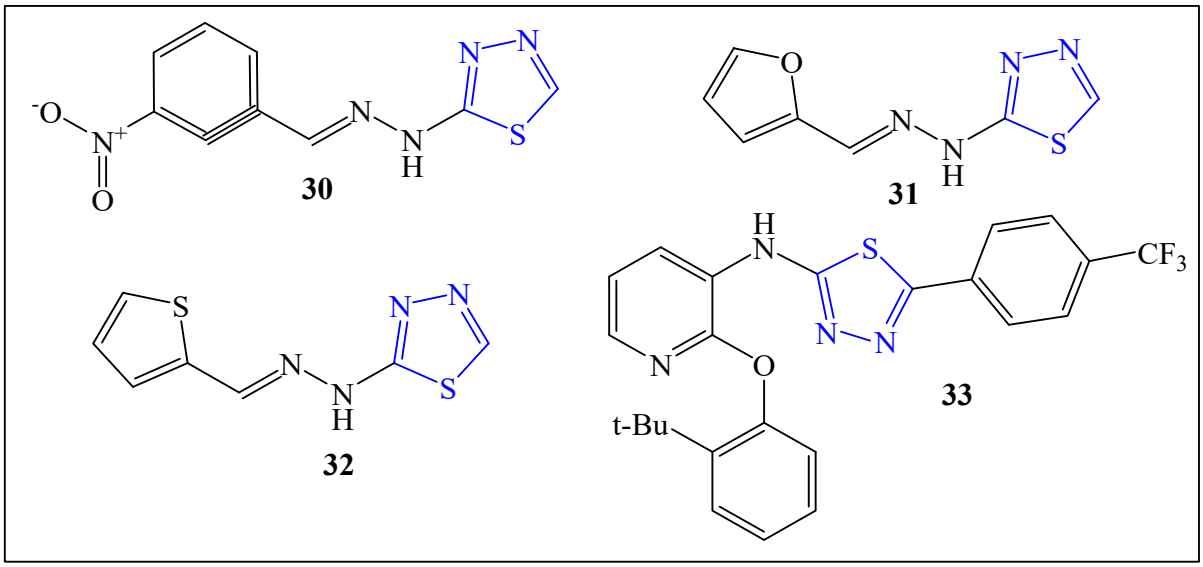

Figure 6. 1,3,4-thiadiazole derivatives, **30**, **31**, **32**, **33** as anti-platelet agents.

2.7. Anti-Tuberculosis Agents

Tuberculosis is a disease caused by *Mycobacterium tuberculosis*, which affects the lungs. Several chemists and scientists are working to solve the drug resistant *Mycobacterium tuberculosis* issue. Patel H et al. also contributed by designing, synthesizing, and characterizing new 1,3,4-thiadiazole derivatives, screening them for in-vitro anti-tuberculosis activity. It was observed that compound **34** displayed significant inhibition against MDR-TB and H37Rv strains in comparison to standard [57]. Some new 2-hydrazinyl-1,3,4-thiadiazole derivatives were synthesized by Tehrani E.M.H.K et al., who evaluated the synthesized compounds for in-vitro anti-mycobacterial and concluded that **35** and **36** compounds were highly potent [55] (Figure 7).

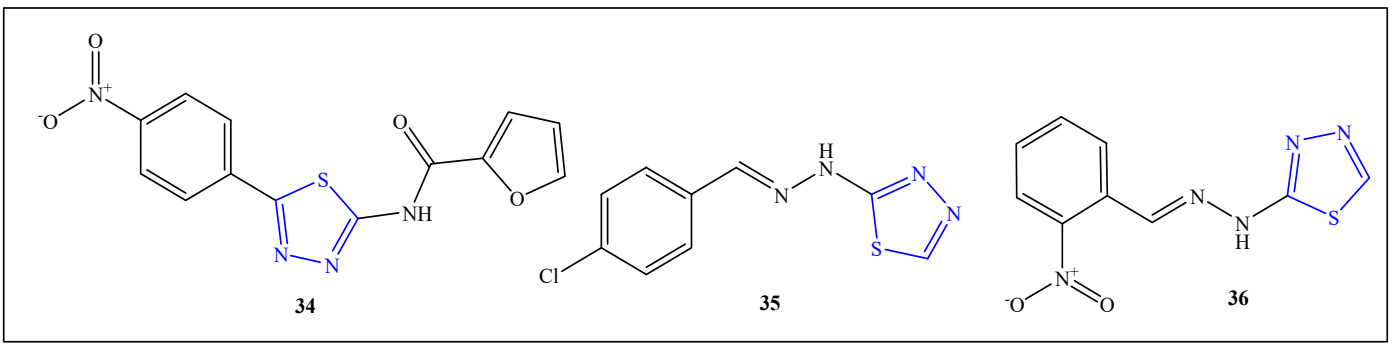

Figure 7. 1,3,4-thiadiazole derivatives **34**, **35**, **36** as anti-tuberculosis agents.

2.8. Anti-Microbial Agents

N, N-disubstituted piperazine derivatives containing 1, 3,4-thiadiazole ring was synthesized and evaluated for antifungal and antibacterial activity by Omar Z.A et al. Further, they confirmed the activity by performing molecular docking studies and concluded that compound **37** was highly potent as it inhibited bacterial and fungal stains more than the standard and in docking studies the compound displayed proper interaction with good binding score and hence can be considered as a potent candidate for anti-microbial activity [58]. Rashdan M.R.H et al. synthesized six novel 1,3,4-thiadiazole derivatives and tested them against a few strains of Gram-negative bacteria, Gram-positive bacteria, and black fungus using the micro-dilution method. Further, to confirm the anti-fungal and anti-bacterial activity more clearly on the basis of receptor binding ability, molecular docking

was also performed. Result of this research suggested that **38** compound can be considered as promising compound against pathogenic bacteria and fungus (especially black fungus) [59]. Kamel G.M et al. reported seventeen new 1, 3,4-thiadiazole analogues and screened them for anti-microbial activity. They concluded that compound **39** was highly potent in inhibiting *B. mycoides*, *C. albicans*, and *E. coli* strains in comparison to the streptomycin (standard) [60]. Karcz D et al. synthesized novel coumarin–thiadiazole derivatives, and tested the synthesized compounds for in-vitro anti-fungal and anti-bacterial activity. It was observed that only one compound **40** inhibited bacterial growth moderately, when compared to standard [37]. Pan N et al. designed and synthesized twenty new pyrimidine analogues containing 1,3,4-thiadiazole ring. The synthesized compounds were screened against a few strains of fungus using the mycelial growth rate method. Compound **41** was observed to be potent in comparison with the standard (pyrimethanil) [61] (Figure 8).

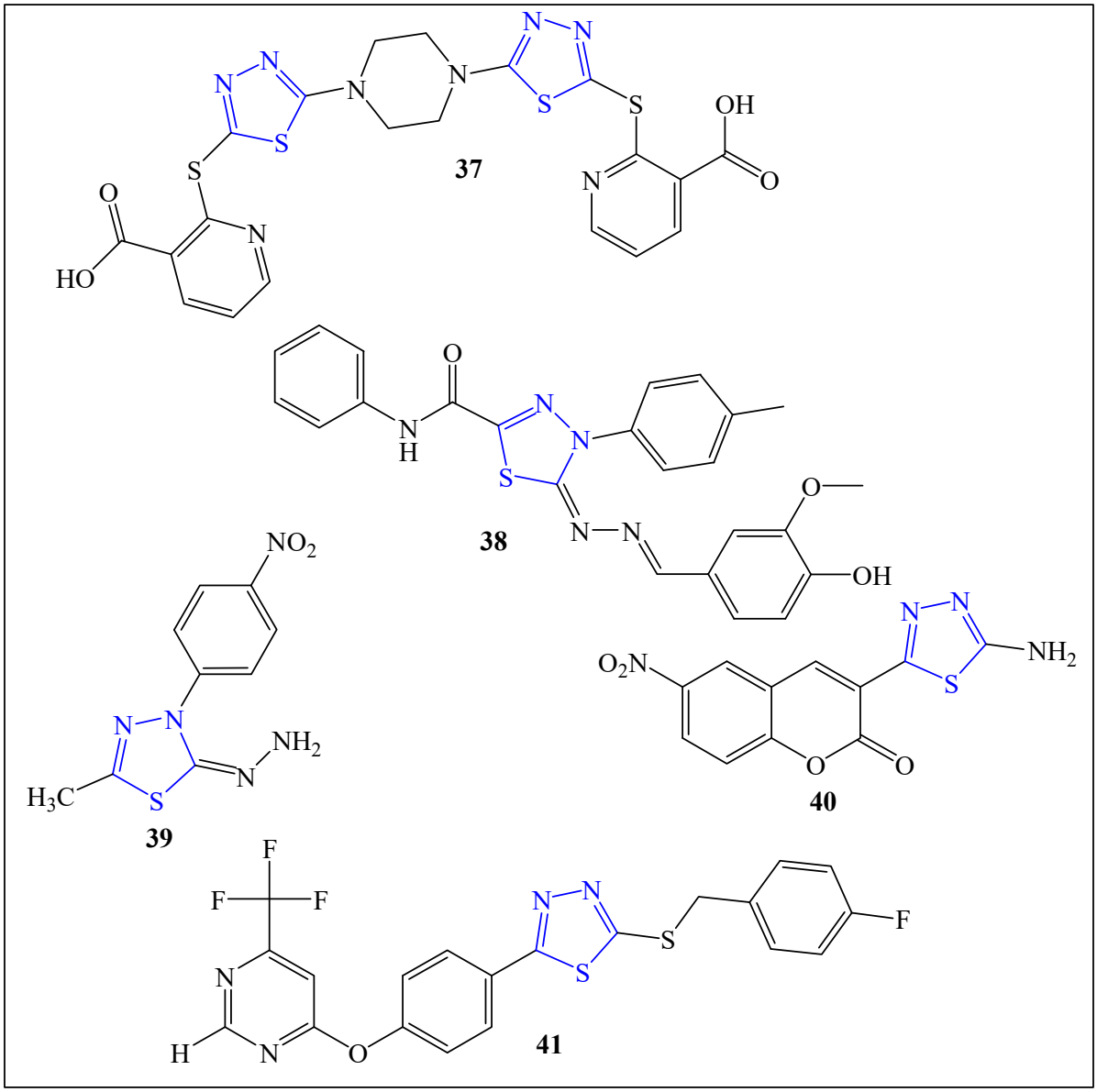

Figure 8. 1,3,4-thiadiazole derivatives **37**, **38**, **39**, **40**, **41** as anti-microbial agents.

3. Others Uses

3.1. Carbonic Anhydrase Inhibitor Agents

Kumar R et al. synthesized a series of benzene sulfonamides containing thioureido-linked amino-thiadiazole derivatives as novel carbonic anhydrase inhibitors. Further, in-silico studies of all the synthesized compounds were performed using human carbonic anhydrase (hCA) enzyme. It was concluded that compounds (**42** and **43**) were highly potent in inhibiting cytosolic isoform hCA (I and II), while moderate inhibition was observed in isoforms hCA (IX and XII) in comparison to standard. Hence, **42** and **43** can be considered potent compounds in curing various diseases, e.g., altitude sickness, glaucoma, epilepsy, etc. [62]. Swain B et al. synthesized new imidazothiadiazole analogues and confirmed their structure by analytical spectroscopy. The synthesized compounds were further evaluated for inhibitory activity in human carbonic anhydrase (hCA (I, II, VA, IX)) by stopped-flow CO_2 hydrase assay, and molecular docking studies was also performed using Schrodinger suite software. It was observed that the compounds inhibited hCA II and I more than hCA IX and VA. Furthermore, among the two isoforms, hCA II was more effectively inhibited as compared with hCA I. Although all the synthesized derivatives displayed inhibition properties to some extent, two compounds, **44** and **45,** displayed the highest inhibition in both I and II isoforms of hCA and can be considered as a potent hCA inhibitors [63] (Figure 9).

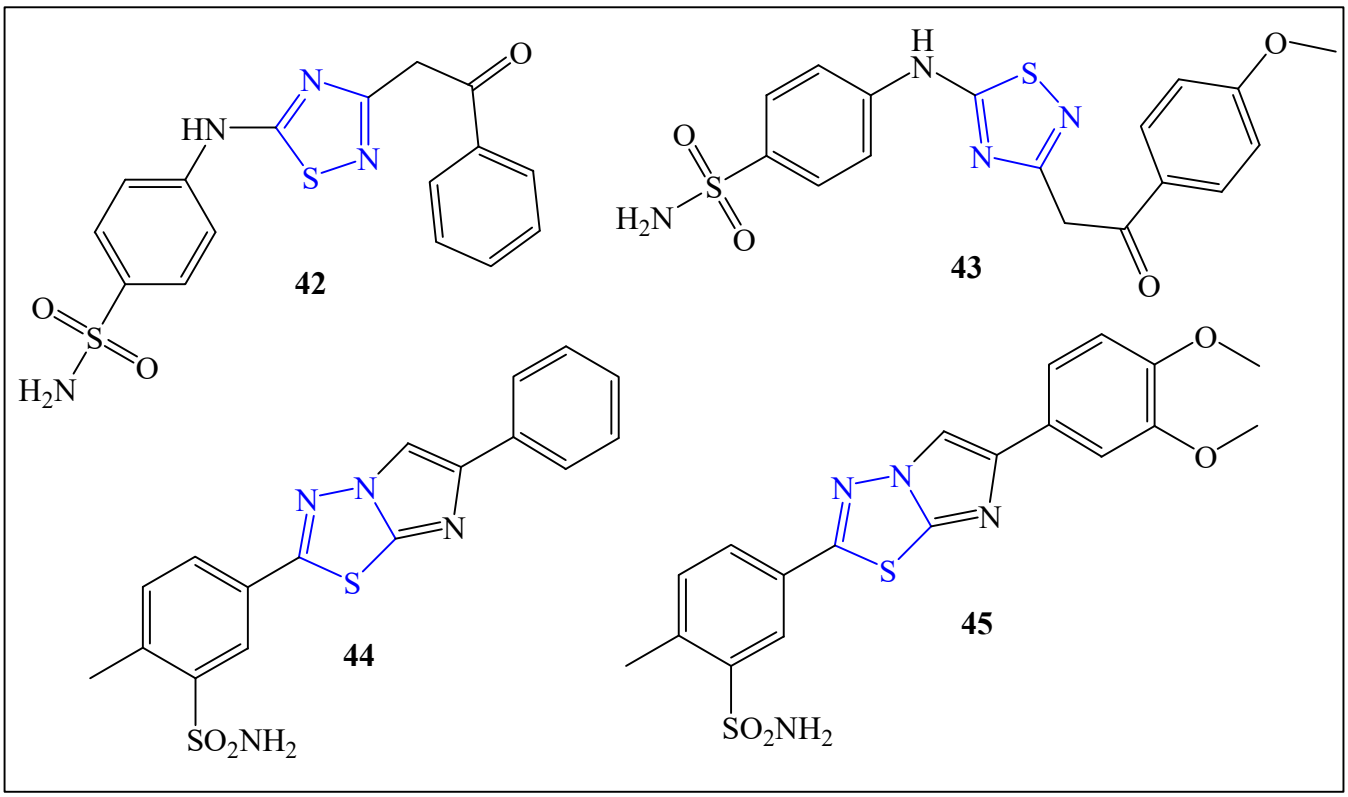

Figure 9. 1,3,4-thiadiazole derivatives **42**, **43**, **44**, **45** as carbonic anhydrase inhibitor agents.

3.2. Diuretic Agents

Seven new 2- and 5-thioate derivatives containing 1,3,4-thiadiazole ring were reported using K_2CO_3 and $(CH_3)_2CO$ by Ergena A et al. After structural characterization of the synthesized compounds, they were further evaluated for in-vivo diuretic activity on mice. It was observed that compounds **46** and **47,** which were substituted with methyl group at 5th position, displayed high diuretic activity as compared to compounds substituted with amino group at 5th position [64]. Sixteen new 5-amino-1,3,4-thiadiazole-2-thiol derivatives were synthesized, characterized, and screened for their in-vivo diuretic activity in rats by

Drapak V.I et al. It was observed that compounds containing amine groups **48**, **49,** and **50** were found to be highly potent and can be considered as potent diuretic agents [65] (Figure 10).

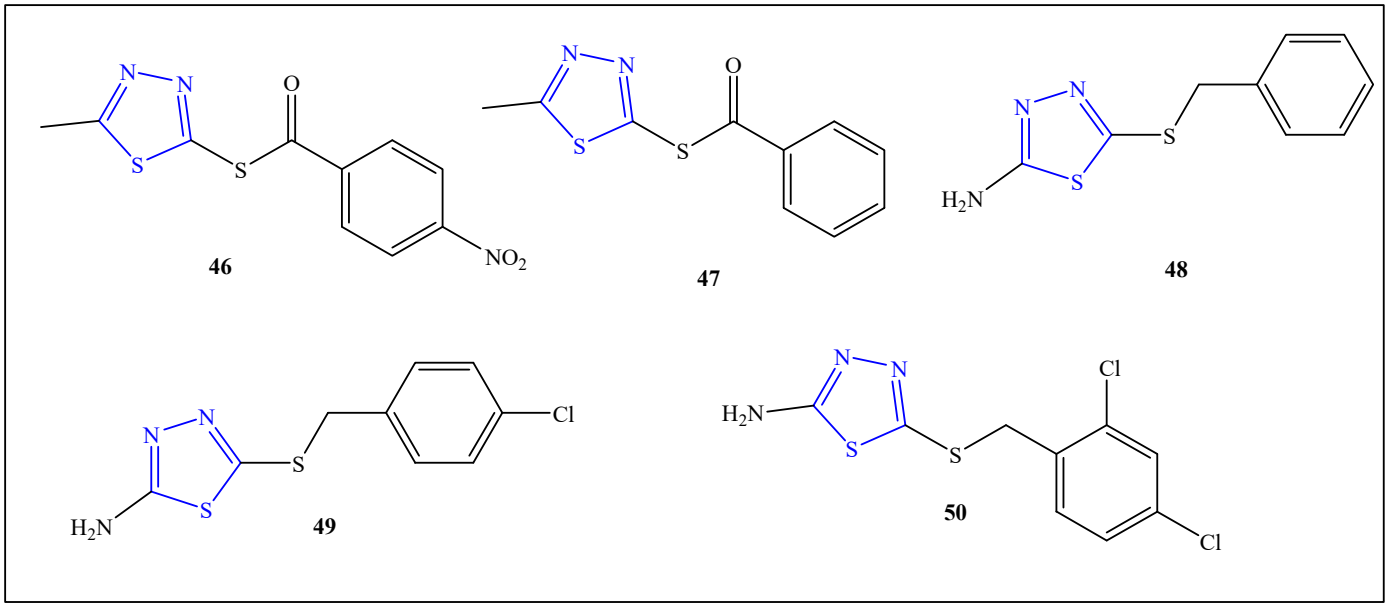

Figure 10. 1,3,4-thiadiazole derivatives **46**, **47**, **48**, **49**, **50** as diuretic agents.

3.3. In the Treatment of Obesity

Cannabinoid receptor 1 (CB1) antagonist is a new target for treating obesity. Considering this new mechanism, Seo J.H et al. designed and synthesized some biarylpyrazole-1,3,4-thiadiazole derivatives and performed in-vitro and in-silico studies in rats. They concluded that two compounds (**51** and **52**) displayed high inhibition of cannabinoid receptor 1. Hence, they can be considered as a lead for the treatment of obesity [66] (Figure 11).

3.4. Insectiside and Acaraside Agents

Mohamed M.M.A et al. used the solvent free method to synthesize new 1,3,4-thiadiazolo [3,2-a]pyrimidine and 1,3,4-thiadiazole analogues using different electrophilic reagents and confirmed the structure by different spectroscopic methods. Insecticidal activity of the synthesized compound was checked against *S. littoralis*. It was observed that both the derivatives displayed good activity but the compound **53** containing pyrimidine ring in the structure displayed high insecticidal activity (100% toxicity) in comparison to the compounds not containing the ring [67]. In 2020, a similar research group designed and synthesized several new 1,3,4-thidiazole derivatives. After confirming their structure, they further screened for insecticidal activity using the leaf dip method and concluded that one compound **54** was highly potent as it displayed 100% toxicity (LC_{50} = 328.34 ppm). Hence, it can be considered a highly effective insecticide [68]. Lv M et al. synthesized some new matrinic derivatives containing amide 1,3,4-thiadiazole and studied their acaricidal and insecticidal activities against *T. cinnabarinus* and *M. separata* by the leaf-dipping and slide-dipping methods. They concluded that compound **55** containing a nitrogen group and fluorine atom in their structure was a highly potent insecticide, while compound **56** containing methyl and electron donating groups was found to be highly potent for acaricidal activity [69]. In 2017, Fadda A.A et al., reported 1,3,4-thiadiazole analogue and confirmed its structure by elemental analysis. The synthesized compounds were further tested for in-vitro insecticidal activity against larvae of *Spodoptera littoralis* (cotton leaf worm) using the leaf dip method. Out of the entire synthesized compounds, three compounds displayed effective insecticidal activity. One compound, **57,** showed the highest activity and toxicity (100%) and can be considered a good insecticide [70] (Figure 12).

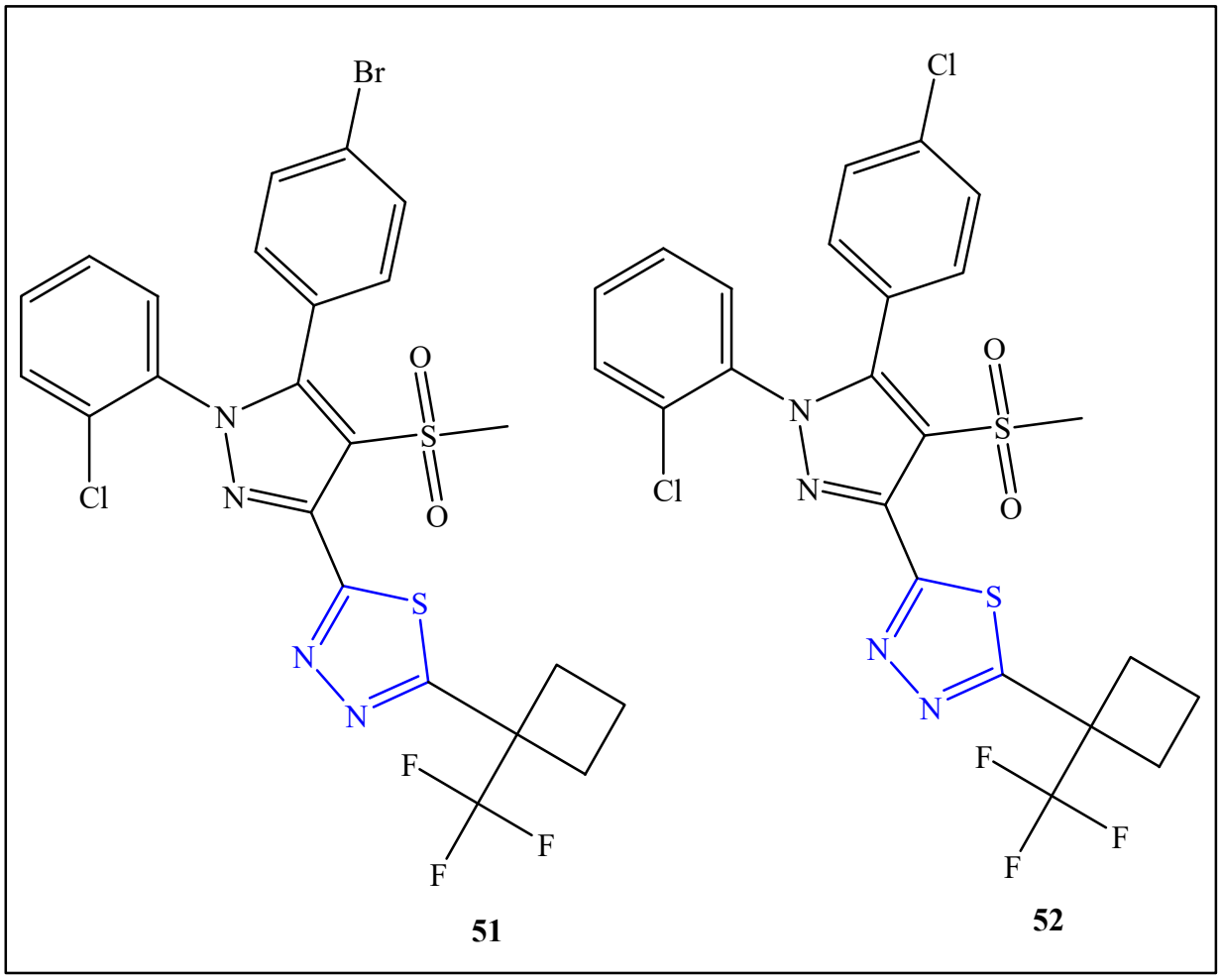

Figure 11. 1,3,4-thiadiazole derivatives **51**, **52** in treatment of obesity.

3.5. Rodenticide Agents

Any chemical substance or its mixture which is deliberately used to kill, destroy, repel, prevent, or mitigate any rodents (rat, mice, woodchucks, squirrels etc.) is known as a rodenticide. Though rodent's species contribute an important role in nature, they can cause great damage to the food crops, transmit disease to human or other animals, cause ecological damage, etc. Thus, rodents need to be controlled. There are several chemical, physical, and biological methods by which rodents can be controlled, but rodenticide (chemical) application is the most commonly used method. There are several chemicals available on the market, such as warfarin, bromadiolone, difethialone, etc., which work according to an anti-coagulant mechanism [71,72]. However, resistivity to the already present rodenticides on the market increases the demand for new rodenticides with different mechanisms of action.

In 19th century, two therapeutic compounds, benzocaine (anesthetic) and para-aminopr opiophenone (PAPP) (vertebrate pesticide), were introduced to the market. The major drawback of these compounds was that they induce methemoglobinemia, due to which the blood oxygen level in brain decreases and finally causes death. Seeing this property of benzocaine, in 2014, Conole D et al. decided to use it as a new approach for controlling and maintaining rodents. The research group reported novel benzocaine 1,3,4-thiadiazole derivative and, after confirming the structure by elemental analysis, they tested it as a rodenticide by performing in-vivo studies in male and female rats. They found that the synthesized compound **58** was moderately effective as a rodenticide [73] (Figure 13).

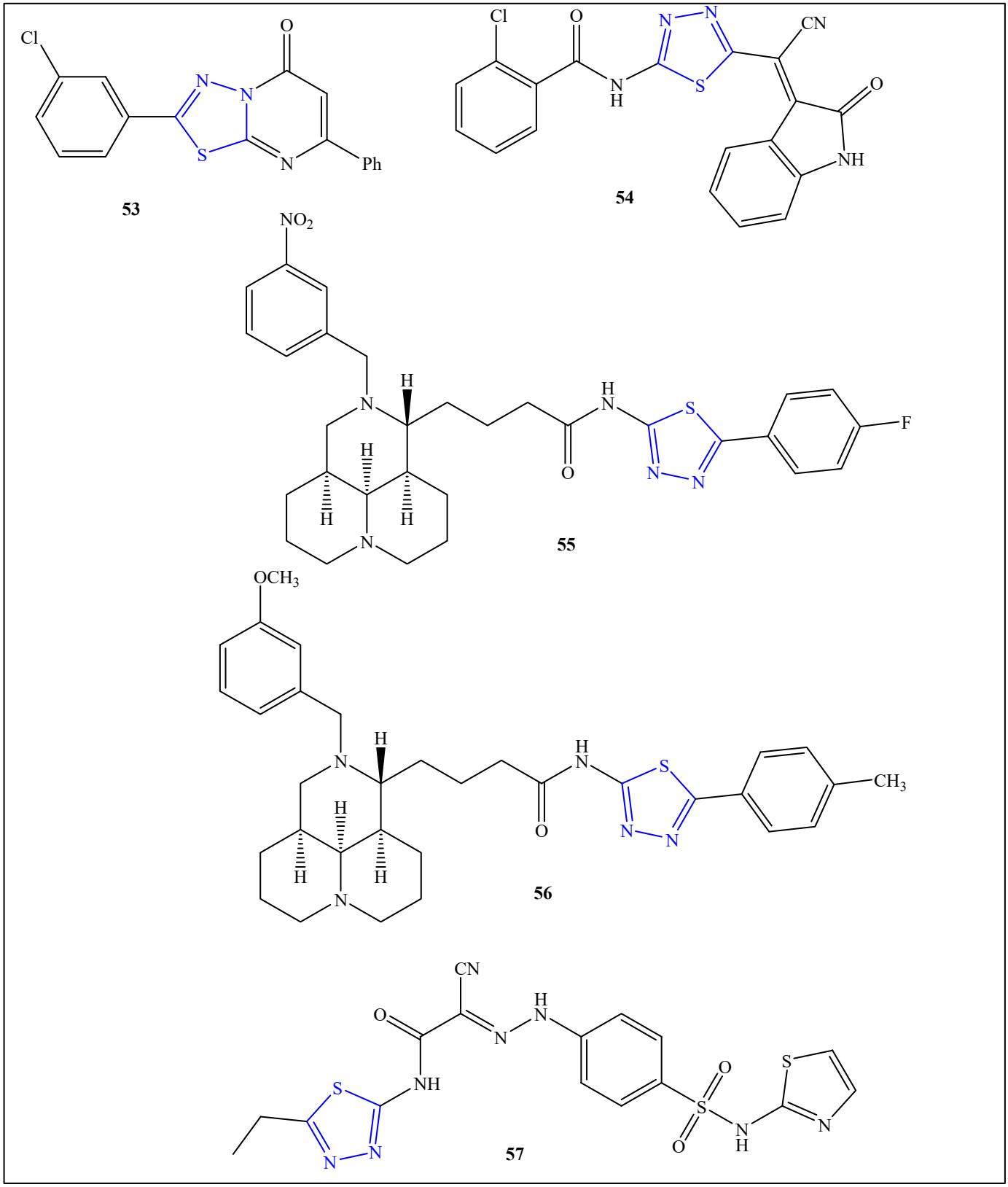

Figure 12. 1,3,4-thiadiazole derivatives **53**, **54**, **55**, **56**, **57** as insecticide and acaraside agents.

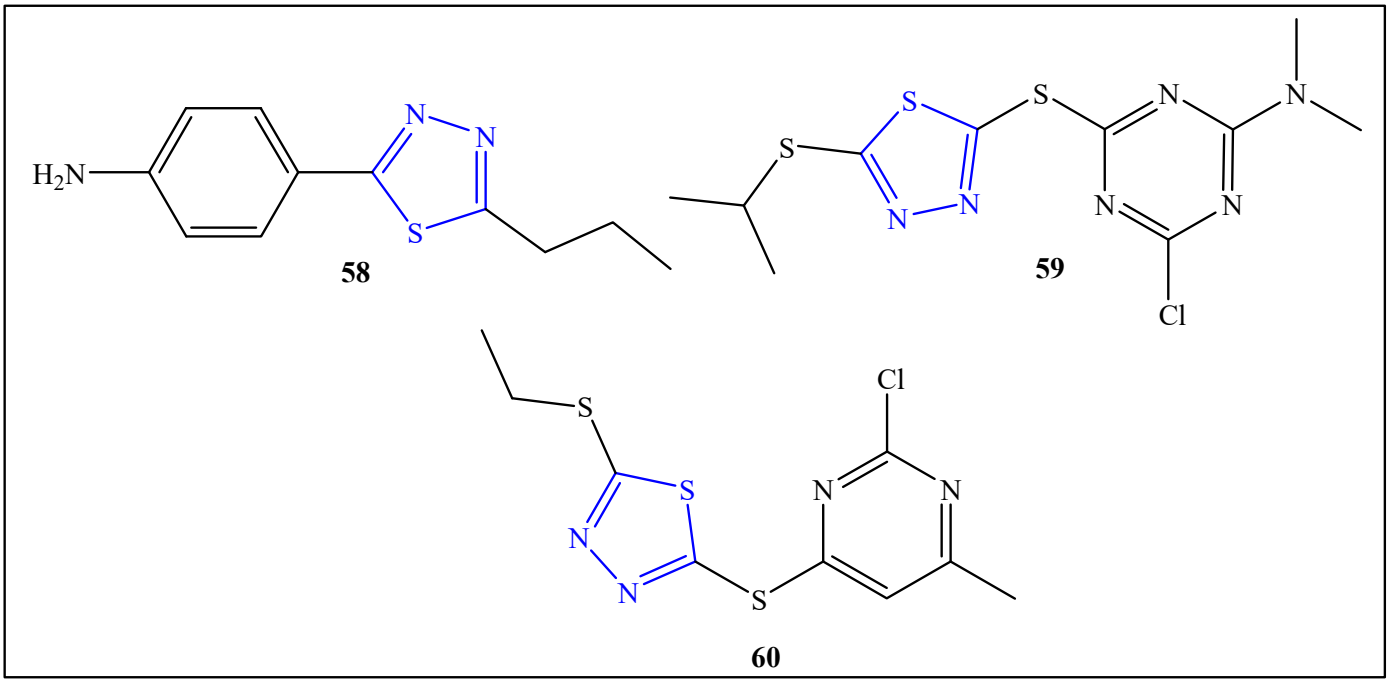

Figure 13. 1,3,4-thiadiazole derivatives **58**, **59**, **60** as rodenticide and plant growth stimulator agents.

3.6. Plant Growth Stimulator Agents

Hambardzumyan N.E et al. synthesized several thiadiazole derivatives by different schemes and confirmed their structure by IR and NMR. They further evaluated the synthesized compounds for plant growth stimulator using bean seeds and concluded that out of the synthesized compounds, five compounds **59** displayed a 75% increase in plant growth while compound **60** displayed 100% stimulation in growth in comparison with heteroauxin and hence can be considered as a new compound for field research as a plant growth stimulator [74] (Figure 13).

4. Conclusions

The 1,3,4-thiadiazole is a heterocyclic moiety that is responsible for various pharmacological activities, such as anti-cancer, anti-inflammatory, anti-microbial, anti-viral, antidepressant, anti-parasitic, anti-obesity, anti-influenza, anti-HIV, anti-convulsant, herbicidal, etc. It can also be a lead molecule in treating new diseases, e.g., COVID-19 and black fungus. Thus, the 1,3,4-thiadiazole ring remains as therapeutic target for the development of new molecules in modern research. The chemical, physical, and pharmacokinetic properties of 1,3,4-thiadiazole still maintain the importance of this moiety despite the rising levels of drug resistance in today's era.

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