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Thiadiazole—a Promising Structure in Medicinal Chemistry

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Many compounds containing a five-membered heterocyclic ring display exceptional chemical properties and versatile biological activities. In this Minireview, thiadiazoles are summarized according to their therapeutic potential, highlighting the versatility of this scaffold in medicinal chemistry. The unique properties of thiadiazoles are also discussed in relation to their potential effect on activity. Thiadiazole is a bioisostere of pyrimidine and oxadiazole, and given the prevalence of pyrimidine in nature it is unsurprising that thiadiazoles exhibit significant therapeutic potential. The sulfur atom of the thiadiazole imparts improved liposolubility, and the mesoionic nature of thiadiazoles makes these compounds better able to cross cellular membranes. By summarizing the thiadiazole-containing compounds reported in recent decades, we aim to give a brief introduction to their synthesis and diverse biological activities, such as anti-inflammatory, anticancer, antibacterial, antifungal, antiviral, antiparasitic, anticonvulsant, anticoagulant, antidiabetic, and to show the significant utility of the thiadiazole scaffolds in medicinal chemistry.

1.0 Introduction

Heterocyclic compounds are attractive to medicinal chemists because of their unique chemical properties and wide-ranging biological activities. Despite significant research progress on heterocyclic ring systems, efforts are ongoing to identify novel heterocyclic compounds with potent bioactivities. Five-membered heterocycles, such as imidazole, oxazole, thiazole, oxadiazole and thiadiazole, are common and typically possess biological activities. The thiadiazole ring has been used to link compounds such as antiparasitic and antimicrobial agents in the past, and some of the resultant drugs are still in clinical use.[1] In recent decades, research has indicated that the thiadiazole ring is an important framework with broad-spectrum biological activity.

There are four types of thiadiazole: 1,3,4-, 1,2,4-, 1,2,5- and 1,2,3-thiadiazole (Figure 1 a), the most fully investigated of these being the 1,2,4- and 1,3,4-thiadiazoles. It has been widely reported that compounds bearing thiadiazole rings exhibit anticancer, anti-inflammatory, antibacterial, antifungal, antiviral, anticonvulsant and antiparasitic activities.[1]

A number of thiadiazole-containing drugs are currently on the market: acetazolamide (**1**) and methazolamide (**2**) are diuretics, acting through inhibition of carbonic anhydrase; their derivatives display additional activities, including anticonvulsant and selective cerebral vasodilation, as well as the anticipated inhibition of carbonic anhydrase.[2a] Other thiadiazole-containing drugs include, cefazolin sodium (CFZL; **3**) and cefazedone (CFZD; **4**)—first-generation cephalosporins; timolol (**5**)—a nonselective β-adrenergic receptor blocker used for the treatment of hypertension, angina, tachycardia and glaucoma; xanomeline (**6**)—a selective agonist of muscarinic acetylcholine receptor subtypes M1 and M4; and megazol (**7**)—an antiparasitic drug.

Based on the similar chemical properties of benzene and thiophene, Burger proposed the theory of ring equivalents, aiming to describe the effects of –CH=CH– and –S– exchange.[2b] According to this theory, 1,2,4-thiadiazole is the bioisostere of pyrimidine (Figure 1 b)

The pyrimidine ring is a scaffold for nucleobases, components of nucleic acids (Figure 2). Compounds containing a thiadiazole ring, which acts as a bioisostere of pyrimidine, can interfere with the normal metabolism of nucleic acids.[2c] Thiadiazoles are also bioisosteres of oxadiazole, oxazole and benzene, and substitution of these heterocycles with a thiadiazole typically leads to analogues with improved activities because the sulfur atom imparts improved liposolubility.[2d]

1,3,4-Thiadiazoles are mesoionic—a poly-heteroatomic system containing a five-membered heterocyclic ring associated with conjugated p and π electrons and distinct regions of positive and negative charges (Scheme 1).[3] Mesoionic systems are dense and highly polarizable, with a net neutral electron

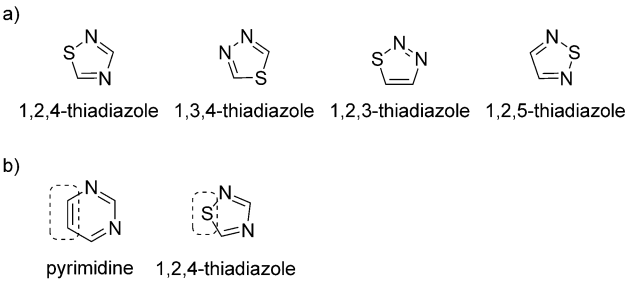
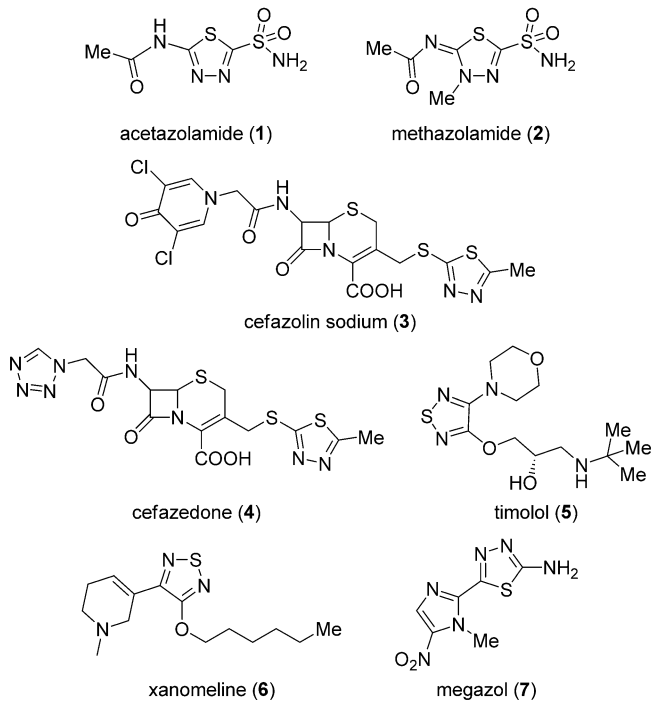


Figure 1. a) Core structures of thiadiazoles discussed in this Minireview. b) A side by side comparison of the basic structures of the pyrimidine and 1,2,4-thiadiazole scaffold.

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charge; these characteristics allow mesoionic compounds to cross cellular membranes and interact with biological targets with distinct affinities.

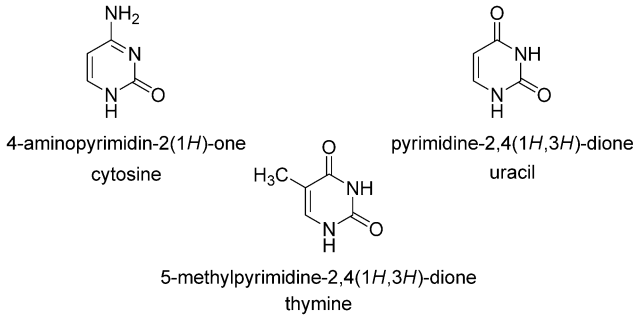


Figure 2. Pyrimidine bases are found in nucleic acids, namely RNA and DNA.

Fused systems containing the thiadiazole ring also give rise to compounds with varied bioactivities, such as anticancer,[4] anticonvulsant,[5] antimicrobial,[6] antitubercular[7] and antiviral[8] properties. Although thiadiazoles have advantages over other commonly found therapeutic scaffolds, their toxicity should not be underestimated.

Through discussing this scaffold according to the associated biological activity and therapeutic application, this Minireview aims to demonstrate the potential of thiadiazole rings in medicinal chemistry.



Scheme 1. The mesoionic system formed by 1,3,4-thiadiazole.

2.0 Biological Activities

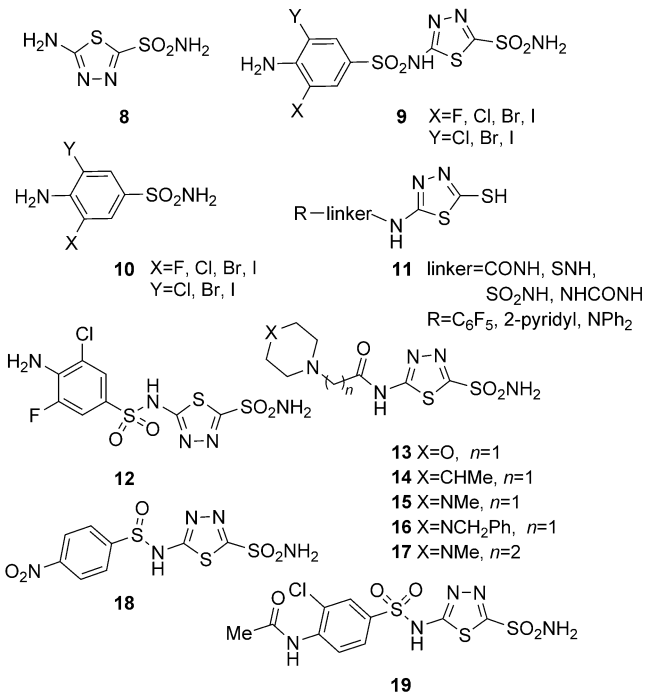
Different types of thiadiazole-containing compounds have been designed and synthesized, and many of them exhibit broad-spectrum biological activities.

2.1 Carbonic anhydrase inhibitors

Carbonic anhydrases (CAs), ubiquitously expressed metalloenzymes, are pivotal regulators in catalyzing the reversible hydration of CO_2 to HCO_3^- and H^+, and participate in numerous other biological pathways. Many CA isozymes are confirmed therapeutic targets in the treatment of a range of disorders such as edema, glaucoma, obesity, cancer, epilepsy and osteoporosis.

The sulfamide group of sulfonamides is similar to the carbonate ion and can competitively inhibit CAs. Compounds containing a thiadiazole, a benzene bioisostere, should also possess high inhibitory activity when bonded with a sulfamide group. From lead compound **8**, some of the most widely used CA inhibitors were obtained, among which acetazolamide (**1**) is the most potent inhibitor.[9] Ilies et al. synthesized and evaluated several sulfonamides as inhibitors of CA.[10] The affinity of compound **9** for CA increases significantly when substituted with sulfonamides **10** connected with 1,3,4-thiadiazole derivative **8**.[10] These results indicate that the thiadiazole ring has advantages over benzene in the context of CA inhibition.

Compared with other heterocycles, the thiadiazole ring has unparalleled advantages. For example, Almajan et al. designed two series of thiols **11** containing thiadiazole or thiazole as CA inhibitors. They found that thiadiazoles display generally higher activity than thiazoles against all of the CA isozymes investigated.[11]



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The X-ray crystal structures of compound **8** in complex with human (h) CA II, reported in 2006 by Menchise et al., indicated that the thiadiazole ring interacts with hCA II through hydrogen bonding and van der Waals forces. The amino group connected to the thiadiazole forms a hydrogen bond with a structural water molecule. The sulfamide group forms crucial hydrogen bonds and binds with the pivotal Zn^{2+} in hCA II.[12] Further study showed that introducing an acyl or sulfonyl group into the 5-amino position of compound **8** could enhance the interaction because the oxygen atoms of the acyl and sulfonyl groups form additional hydrogen bonds with hCA II.[9,13] Aryl-substituted 5-amino derivatives have a large aromatic system that is able to form π–π stacking interactions with hCA II.[14] The fluorine of the $-CF_2-$ group introduced between the thiadiazole ring and the sulfamide could potentially interact with hCA II through a fluorine hydrogen bond (Figure 3).[15]

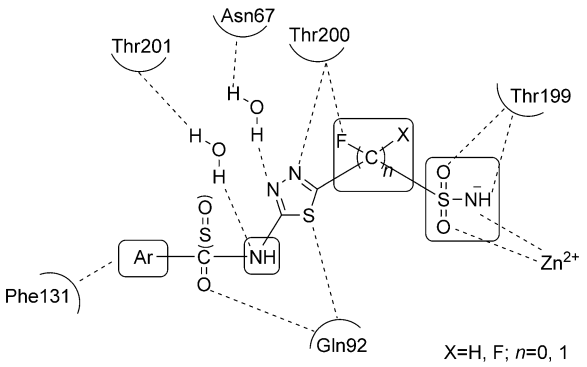
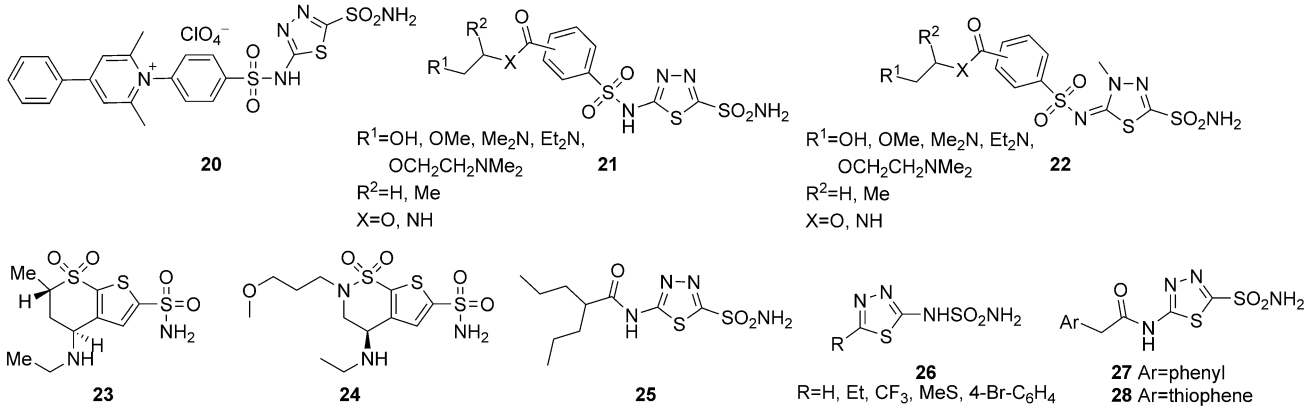


Figure 3. A function model of CA inhibitors.[15]

Many compounds containing a thiadiazole ring possess CA inhibitory activity. Compound **12** is a very potent inhibitor of hCA I, with an inhibition constant (K_i) of 1.4 nM, which is 178-fold higher than acetazolamide (**1**).[9] Moreover, compound **12** also shows potent inhibitory activity against the physiologically dominant isoform of CA, hCA II; the corresponding K_i value was found to be 0.3 nM.[9] Acetazolamide derivatives **13**–**17** also exhibited excellent inhibitory activities against hCA II, with K_i values in the range of 0.9–3.8 nM, suggesting that these compounds are much better inhibitors than clinically used compounds, such as acetazolamide (**1**).[16] In 2005, it was reported that some aromatic and heteroaromatic sulfonamides demonstrated anticancer activity.[17] Compound **18** was discovered, which shows the highest affinity for hCA I, hCA II and hCA XII, with K_i values of 3 nM, 1 nM and 1.9 nM, respectively.[17] Supuran et al. also conducted research on the CA-mediated lipogenetic processes and found that compounds synthesized showed excellent inhibitory activities against hCA I, hCA II, bovine (b) CA IV and murine (m) CA V; the corresponding K_i values for the most potent compound (**19**) were 5, 1, 4 and 5 nM, respectively.[18]

A series of positively charged sulfonamides bearing 1,3,4-thiadiazole systems were synthesized and evaluated against several CA isoforms by Casey et al.[19] All of the compounds were found to have much higher affinities for CAs than the known drugs, acetazolamide (**1**) and methazolamide (**2**). Compound **20** exhibited the highest affinity for CA isoforms, with K_i values of 3, 0.2, 2 and 6 nM against hCA I, hCA II, bCA V and hCA IX, respectively.[19] Compounds **21** and **22** were also identified as having antiglaucoma activity, and most of the compounds in the series exhibited improved potency over the standard drugs in 2003, namely dorzolamide (**23**) and brinzolamide (**24**).[20] Compound **25** exhibited very strong anticonvulsant properties, inhibiting hCA I and hCA II with K_i values of 50 nM and 6 nM, respectively, and protecting 100% of mice at a dose of 30 mg kg^{-1} (i.p.) when evaluated in vivo using a MES test three hours after dosing.[2]

Some thiadiazoles designed as CA inhibitors are selective for specific isoforms. The first selective CA VA/VB inhibitors with 1,3,4-thiadiazole-5-sulfamide were reported by Smaine et al. Compound **26** displays much higher inhibitory activity against hCA VA and hCA VB than hCA I, hCA II and hCA IV, making it more selective than some known drugs (e.g., acetazolamide (**1**), zonisamide and topiramate).[21] Compounds **27** and **28** show moderate inhibition of hCA I and hCA II, and good inhibitory activity against hCA VA and hCA VB. The K_i values of compound **28** (Ar = thiophene) against hCA I, hCA II, hCA VA and hCA VB were found to be 72, 51, 7.6 and 7.4 nM, respectively; the K_i values of compound **27** (Ar = phenyl) against the same CA isoforms were 63, 51, 8.4 and 5.1 nM, respectively.[22] Some copper(II) complexes revealed selectivity for tumor-associated



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isoforms hCA IX and XII, and those compounds containing thiadiazole were found to exhibit higher affinity for hCA XII than others without the thiadiazole ring.[23]

2.2 Anti-inflammatory and analgesic activity

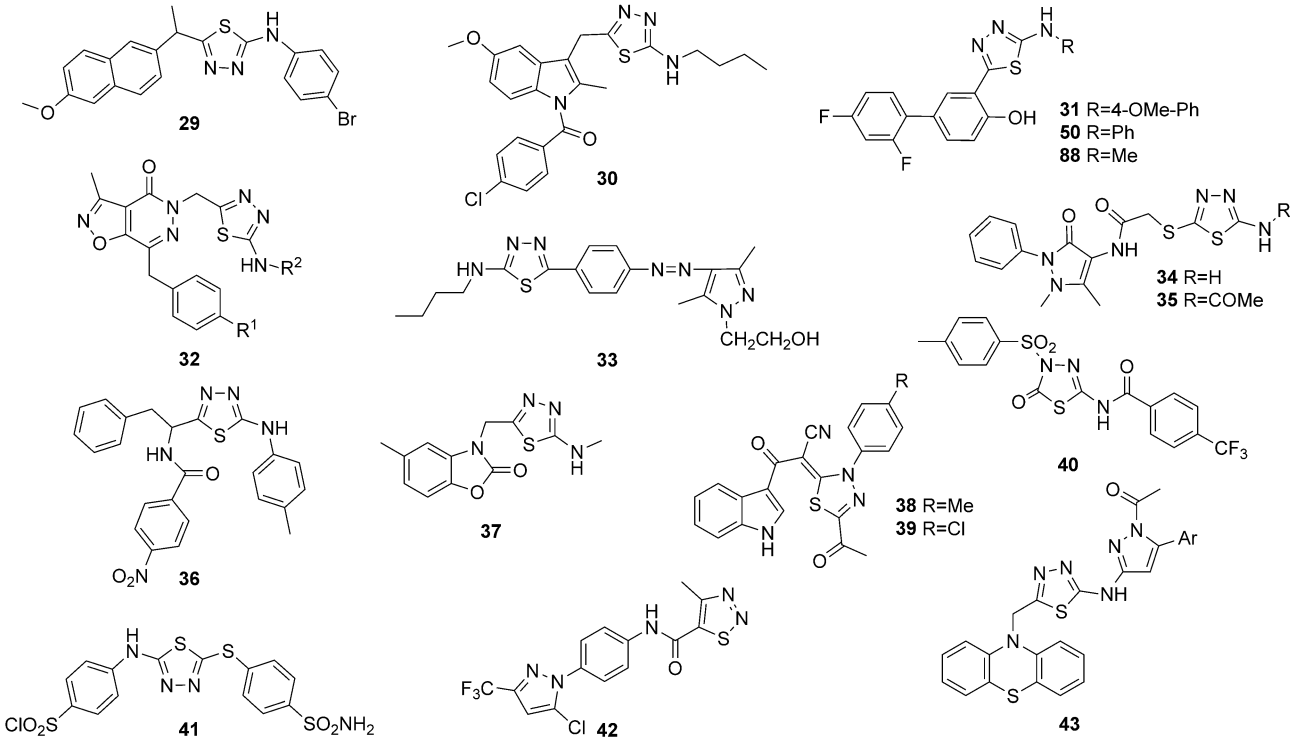
Nonsteroidal anti-inflammatory drugs (NSAIDs), including multifarious drugs with diverse structures, exhibit a broad spectrum of anti-inflammatory, analgesic and antipyretic effects. It is reported that a carboxylic acid (COOH) group is essential for anti-inflammatory activity; however, some compounds still display anti-inflammatory activity when the COOH group is replaced by a thiadiazole ring.[24, 25] This could be because thiadiazoles show weaker basicity than other azoles on account of the inductive effect of the additional heteroatom.

Replacement of the carboxyl group in naproxen, a standard drug, with *N*-(4-bromophenyl)-1,3,4-thiadiazol-2-amine to generate compound **29** had little effect on the anti-inflammatory activity, as determined by the percent inhibition in the carrageenan-induced rat paw edema test where compound **29** and naproxen exhibited values of 75% and 74%, respectively.[24] Amir also designed a series of indomethacin derivatives with various types of heterocycles in an attempt to design out the undesired gastric toxicity associated with these derivatives. Of the potent compounds, compound **30**, generated by replacement of the COOH group in indomethacin with substituted amino-1,3,4-thiadiazol, showed a distinct advantage in anti-inflammatory and analgesic activity.[25] These cases indicate that 1,3,4-thiadiazole is an effective moiety in the design of anti-inflammatory and analgesic agents.

Kucukguzel reported that thiadiazol derivatives of salicylic acid showed significant anti-infective activity and excellent anti-inflammatory activity.[26] Compound **31**, obtained by replacing the carboxyl in diflunisal with *N*-(*p*-tolyl)-1,3,4-thiadiazol-2-amine, showed improved anti-inflammatory activity over the parent compound diflunisal, a marketed NSAID in clinical use, with percent inhibition values of 55% and 24% for compound **31** and diflunisal, respectively, in the carrageenan-induced rat paw edema test. Compound **31** was also evaluated in vivo for analgesic activity (paw withdrawal latency in seconds $\pm$SEM), exhibiting a value of 19.2$\pm$0.91, while that of diflunisal was 19.1$\pm$1.18.[26]

Compared with other heterocycles, thiadiazoles have advantages as analgesics. Özadalı et al. synthesized two series of compounds containing 1,3,4-thiadiazole or 1,2,4-triazole; in vitro, thiadiazoles **32** showed better inhibition of 5-lipoxygenase (5-LOX) than the corresponding triazoles.[27] Similarly, Oruc et al. synthesized a series of compounds containing 1,3,4-thiadiazole or 1,2,4-triazole as analgesics, in which thiadiazole-containing compound **33** exhibited good analgesic activity.[28]

Rostom et al. reported the anti-inflammatory effects, as well as the antimicrobial activities, of a series of compounds including **34** and **35**.[29] These derivatives were evaluated using the formalin-induced paw edema and the turpentine oil-induced granuloma pouch bioassays, with diclofenac sodium as a reference NSAID drug. Taking the anti-inflammatory activity after three hours as a criterion for the formalin-induced paw edema bioassay (acute inflammatory model), compounds **34** and **35** proved to be more effective (49% and 46%, respectively) than the reference drug (44%).[29] In another study by Moise et al., all compounds with anti-inflammatory activity synthesized showed low toxicity than the corresponding compounds without thiadiazole ring, with compound **36** exhibiting the lowest.[30]



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Most compounds reported by Salgin-Goksen and co-workers exhibited potent anti-inflammatory and analgesic activity. In the acetic-acid-induced abdominal writhing test, the most potent compound (**37**) displayed 74% inhibition, compared with 66% for aspirin. In the hot plate test, compound **37** displayed 54% inhibition; in the same assay, morphine exhibited 51% inhibition.[31]

In a study by Radwan et al., compound **38** was identified as the most potent anti-inflammatory of the compounds tested, inhibiting carrageenan-induced edema of the hind paw in mice (33%).[32] Compared with the NSAID indomethacin, compound **39** exhibited enhanced analgesic activity in a hot-plate test in mice, with a 3.1-fold improvement relative to indomethacin.[32]

All of the compounds designed by Schenone et al. acted as good analgesics in the acetic acid-induced writhing test, and some compounds in this series also showed similar anti-inflammatory activity in the carrageenan rat paw edema test. The best compound was compound **40**, with an inhibition value of 48.8% at a dose of 12.5 mg kg^{-1}.[33]

Thiadiazoles possess good anti-inflammatory and analgesic activities, and some also exhibit high selective index for cyclooxygenase (COX), which can decrease the side effects associated with long-term clinical administration of traditional NSAIDs. Using the colorimetric COX inhibitor screening assay, all compounds obtained by Sharma et al. were evaluated for COX-1 and COX-2 inhibition. Compared with indomethacin and tramadol hydrochloride, compound **41** showed the most potent COX-2 inhibition (42%) and significant anti-inflammatory and analgesic activity (inhibition of paw edema after 3 h 56 mg kg^{-1}: 53.48 ± 0.02%).[34]

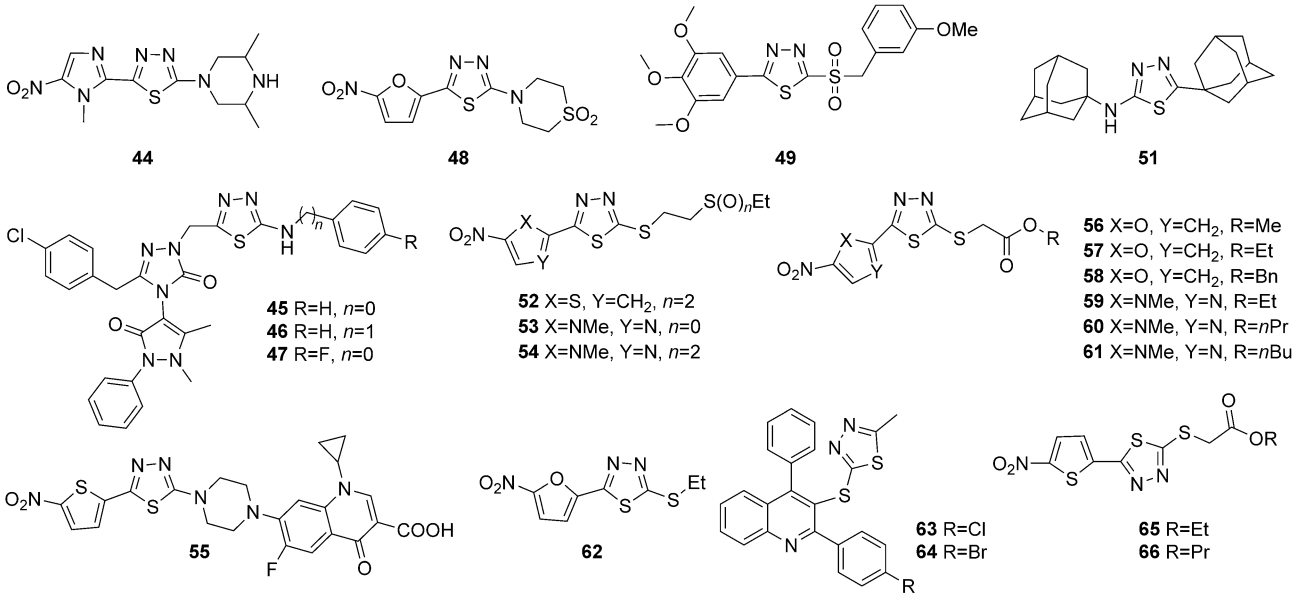
In addition to COX-2 and 5-LOX, inhibiting ion channels or other enzymes can also give rise to an anti-inflammatory effect. Yonetoku et al. designed several Ca^{2+} release–activated Ca^{2+} (CRAC) channel inhibitors as anti-inflammatory and immunosuppressive agents. Among these compounds, compound **42** displayed the most potent anti-inflammatory activity in the thiadiazole series (IC_{50} = 82 nM against CRAC)[35]

Multiple factors are involved in the etiology and progression a disease; targeting these processes is the mission of medicinal chemists, and there can never be too many scaffolds for the development of potential therapeutic agents. Combining two or more pharmacophores can produce a hybrid molecule, which might display novel bioactivities or improved potency over the individual components, as they might act on different targets. Furthermore, this approach also has the potential to eliminate or decrease unwanted side effects.[36] In a series of compounds designed by Pluta et al., 10*H*-phenothiazine was linked with varied heterocycles to obtain compounds possessing diverse biological activities.[37] Compared with phenylbutazone, an NSAID drug presently used in veterinary care but originally designed for use in humans, compound **43**, with a 1,3,4-thiadiazole ring substituted in position 10, showed significant in vivo anti-inflammatory activity and fewer ulcerogenic side effects.[37]

Another successful case of combined scaffolds is the series of piperazinyl quinolone derivatives reported by Foroumadi et al.[38] They connected a thiadiazole ring to quinolones, generating compounds with improved antimicrobial activity (see below).[38]

2.3 Antibacterial and antifungal activity

There are numerous compounds bearing the thiadiazole ring possessing excellent antimicrobial activities. Several 1,3,4-thiadiazoles synthesized by Moshafi et al. were evaluated for antibacterial activity against *Helicobacter pylori* in a disc diffusion test at 0.5 μg/disc. At this dose, compound **44** gave a zone of inhibition of 30.9 mm in diameter, five times greater than that observed for the positive control metronidazole (6 mm).[39] Some antipyrine derivatives reported by Bayrak et al., namely compounds **45**–**47**, displayed excellent antimicrobial activity at



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5 μg mL^{-1} (Table 1).[36g] In the study conducted by Mirzaei et al., only a small difference was observed between the anti-*H. pylori* activities of their compounds and the antibiotic metronidazole at doses of 4 and 2 mg/disc, with all compounds giving zones of inhibition of approximately 20 mm at these doses.[40] However, at the higher dose of 8 mg/disc, compound **48** was identified as the most potent derivative, exhibiting very strong activity with a zone of inhibition of 40 mm in diameter against both metronidazole-sensitive and -resistant strains.[40]

Table 1. Results of the disc diffusion test for antipyrine derivatives reported by Bayrak et al.[36g]

Bacterial strain	Zone diameter [mm]		
	45	**46**	**47**
Escherichia coli (ATCC 25922)	25	25	20
Enterobacter aeroginosa (ATCC 13048)	25	25	25
Yersinia pseudotuberculosis (ATCC 911)	25	25	25
Pseudomonas aeruginosa (ATCC 43288)	35	30	20
Mycobacterium smegmatis (ATCC 607)	25	25	25

Among the series of sulfones designed by Chen et al., compound **49** showed good activity against *Gibberella zea*e, *Botrytis cinerea*, and *Sclerotinia sclerotiorum*, with inhibitory values (%) of 43.2 ± 6.6, 53.4 ± 7.0 and 74.5 ± 3.1, respectively, at a concentration of 50 μg mL^{-1}.[41]

The diflunisal hydrazide derivatives synthesized by Kucukguzel et al. were tested against numerous microbes to ascertain their antimicrobial and antiviral effects.[26] Through structural variation, all of these derivatives exhibited improved antibacterial activities over known broad-spectrum antibiotic cefepime. Compound **50** showed the highest activity against *E. coli* A1 and *Streptococcus pyogenes* ATCC 176 at a concentration of 31.25 mg mL^{-1}.[26]

Thiadiazole derivatives of amantadine exhibited moderate antibacterial activities, particularly against Gram-positive bacteria *Bacillus subtilis*.[42] However, compound **51** displayed outstanding antifungal activity when evaluated in a in a disc diffusion assay against *Candida albicans*, exhibiting a zone of inhibition of 18 mm in diameter.[42]

The antibacterial activity against *H. pylori* of a series of 5-(nitroaryl)-1,3,4-thiadiazoles was evaluated by Foroumadi et al.[43] The results of a disc diffusion assay indicated that compound **52** was the most potent compound against clinical isolates of *H. pylori*, with an average zone of inhibition of 18.2 mm in diameter at a concentration of 0.5 μg/disc. However, closer evaluation suggested that compounds **53** and **54** have greater therapeutic potential because of their considerable anti-*H. pylori* activity (IC_{50} = 61.5 ± 7.7 and 100 ± 7 μg mL^{-1}, respectively, against *H. pylori*) and decreased cytotoxic effects.[43] The in vitro antibacterial data reported by Foroumadi et al. showed that thiadiazole analogues of ciprofloxacin, norfloxacin and enoxacin had better activity against the Gram-positive bacteria than the corresponding oxacins.[38] However, all of the compounds evaluated were almost inactive against Gram-negative bacteria. Ciprofloxacin analogue **55** was the most active against Gram-positive bacteria, with a minimum inhibitory concentration (MIC) value ranging from 0.008 to 0.015 μg mL^{-1}.[38]

Foroumadi et al. later synthesized further thiadiazoles derivatives and evaluated their activity against *M. tuberculosis*.[44] Among the nitrofuran derivatives reported, compounds **56**–**58** showed good antitubercular activity, with MIC values ranging from 0.78 μg mL^{-1} to 3.13 μg mL^{-1}. In the nitroimidazole series, compounds **59**–**61** displayed significant activity against *M. tuberculosis*, with MIC values ranging from 0.78 μg mL^{-1} to 1.56 μg mL^{-1}. The cytotoxicity of the compounds active against *M. tuberculosis* was evaluated by serial dilution in Vero cells, and IC_{50} values varied from 2.3 μg mL^{-1} to more than 10 μg mL^{-1}.[44] Among the compounds reported by Foroumadi et al. in 2002, compound **62** showed the most potent antitubercular activity (IC_{50} = 0.7 μg mL^{-1}, MIC = 0.78 μg mL^{-1}) and the lowest toxicity to Vero cells.[45]

Chitra et al. synthesized a series of 3-heteroarylthioquinoline derivatives and screened them in vitro against *M. tuberculosis* $H_{37}Rv$.[46] Compounds **63** and **64** were found to be the most potent compounds in these series, with MIC values of 3.2 and 3.5 μM, respectively. Evaluation of the cytotoxicity of these two compounds in vitro indicated that they are nontoxic to normal cells, with IC_{50} values of 1263 μM and 2050 μM, respectively, against murine NIH 3T3 fibroblasts.[46]

Mahdiuni et al. investigated antitubercular compounds **65** and **66** for their effect on OmpF channels.[47] Compound **65** (MIC = 6.75 μg mL^{-1}) showed no effect, while compound **66** (MIC = 0.39 μg mL^{-1}) decreased channel conductance considerably and changed the gating pattern of the channel. The authors postulated that there are two modes of action for these compounds that result in different OmpF channel gating behavior. One model supposes direct binding of the compound to the channel leading to obstruction of the conducting path, and the other model involves an indirect effect of the compound through interfering with the channel's surrounding membrane microenvironment.[47]

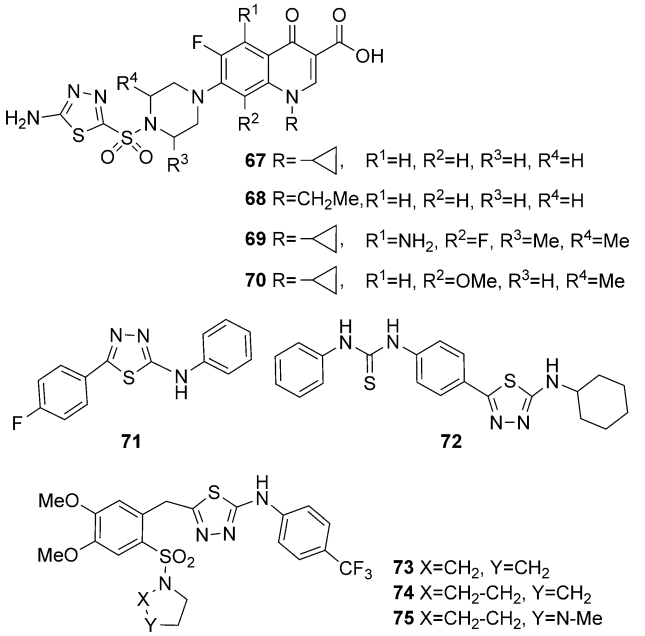
Talath et al. described a series of quinolone derivatives containing a substituted thiadiazole ring (**67**–**70**).[48] Compared with a number of known drugs (ciprofloxacin, norfloxacin, sparfloxacin and gatifloxacin), compounds **67**–**70** exhibited improved activity against Gram-positive bacteria, such as *Staphylococcus aureus*, *Enterococcus faecelis*, and *Bacillus* sp., with MIC values in the range of 1–5 μg mL^{-1}. Compared with isoniazid, a clinically used antitubercular drug, when evaluated in vitro for antitubercular activity against *M. tuberculosis* strain $H_{37}Rv$, compounds **67** and **68** were both only moderately active (MIC = 10 μg mL^{-1}).[48] In unrelated studies, compounds **71** and **72** also showed activity in vitro against the *M. tuberculosis* $H_{37}Rv$ strain, with inhibitory values of 69% and 67%, respectively.[49]

Some thiadiazoles show significant antibacterial activity as well as antifungal activity, such as those reported by Camoutsis et al.[50] Compared with the commercial fungicide bifonazole, the compounds evaluated in this study showed potent antifungal activity against all species tested. Compound **73** possessed the best antibacterial activities against a panel of mi-

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crobes including *E. coli*, *S. aureus*, and *P. aeruginosa*, with MIC values in the range of $0.95–1.8\times10^{-2}$ μmol mL^{-1}. Compounds **74** and **75** showed the best activity against the panel of fungi used.[50] Compound **75** not only exhibited the best antifungal potential with minimal fungicidal concentration (MFC) values of $1.79–3.58\times10^{-2}$ μmol mL^{-1}, but it also possessed good antibacterial activity with MIC values of $0.89–1.79\times10^{-2}$ μmol mL^{-1}.[50]

Taken together, the literature reports summarized above indicate that thiadiazole-containing compounds display excellent antimicrobial activity. As previously mentioned, the thiadiazole ring is a bioisostere of pyrimidine, and as such, it might interact with microbial DNA more readily than other moieties. Furthermore, thiadiazoles are heteroatom-rich, providing multiple points through which the ring can interact with the biological target, potentially leading to improved affinity, potency and selectivity.

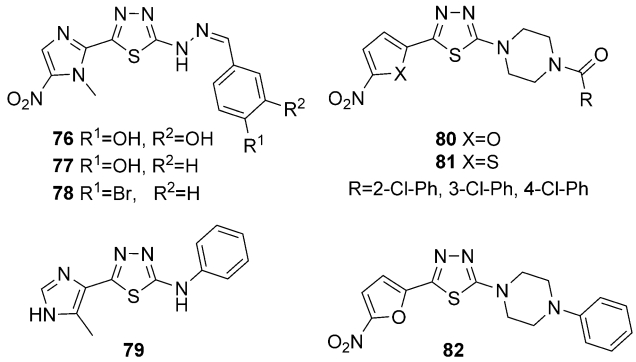
2.4 Antiparasitic activity

Parasitic infection can cause dysfunction of host physiological processes leading to illness and eventual death of the host. Some parasitic diseases are epidemic in certain regions of the world largely due socioeconomic reasons but also because of resistance and a lack of effective treatment options. The antiparasitic properties of 1,3,4-thiadiazoles have been well documented. Furthermore, introducing other heterocycles onto the thiadiazole scaffold can improve the antiparasitic effects, depending on the type and position of the substituents introduced.[51] These compounds (**76**–**82**) share the same backbone with substituents on the 1,3,4-thiadiazole ring varying in two positions: 1) a substituted five-membered aromatic ring at position 2; 2) a nonaromatic six-membered ring containing at least one nitrogen atom at position 5.[52] It was reported that the C-5 substituent is the most adaptable site for structural modification, and this fragment determines the potency and physicochemical properties of 2-(nitroaryl)-1,3,4-thiadiazoles.[52]

Compound **76** was twofold more potent in vitro against trypomastigotes than the clinically used trypanocidal agent megazol (**7**), however, it had no effect in vivo.[53] In contrast, compounds **77** and **78** decreased parasitemia and mortality of infected mice at a dose of 200 mg kg^{-1}. Specifically, compound **77** led to a 50% decrease of the parasitemia peak, with all animals surviving at 40 day post-infection, and compound **78** led to a 60% decrease of the parasitemia peak and 7/8 animals surviving at the same time point.[53]

Liesen et al. synthesized a series of compounds and tested their antimicrobial and antiparasitic activities. Compared with hydroxyurea and sulfadiazine, most of the tested compounds showed improved activity against the parasite *Toxoplasma gondii* and outperformed the reference agents against intracellular tachyzoites. Of the compounds studied, **79** was the most potent against intracellular parasites with low toxicity against healthy cells ($LD_{50} > 10$ mM).[54]

The majority of compounds in series **80** and **81** reported by Behrouzi-Fardmoghadam et al. exhibited potent inhibitory activity at non-cytotoxic concentrations against *Leishmania major*, the trypanosomatid protozoan parasite that causes leishmaniasis.[55] Among the 2-(5-nitro-2-furyl) and 2-(5-nitro-2-thienyl)-5-substituted-1,3,4-thiadiazoles evaluated, compound **82** displayed the highest potency against *Leishmania major* promastigotes with an IC_{50} value of 0.1 μM.[56]



2.5 Antiviral activity

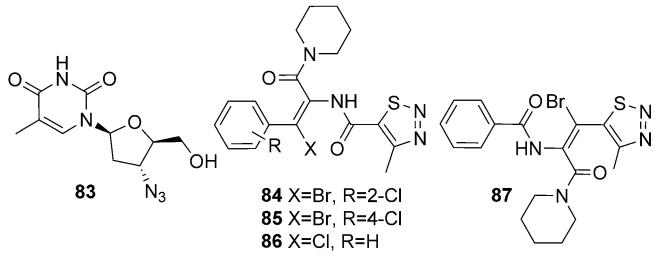
It is noteworthy that 50% of the incidence of human disease are caused by viruses, such as influenza, acquired immune deficiency syndrome (AIDS), hepatitis B, measles, to name just a few. Given that zidovudine (**83**), an antiviral identified in 1987 against human immunodeficiency virus (HIV), the virus that causes AIDS, is a nucleoside analogue, and as discussed before, the thiadiazole ring is a bioisostere of pyrimidine, a nucleobase scaffold found in nucleosides, it follows that thiadiazole derivatives should also possess antiviral activities. This is in fact the case, with some thiadiazoles displaying excellent antiviral activities.

Among the compounds synthesized by Dong et al., compounds **84**–**86** exhibited potent inhibition of the replication of

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hepatitis B virus (HBV) DNA, with IC_{50} values lower than the known HBV drug lamivudine (IC_{50} ($\mu g\,mL^{-1}$) = 10.4 for **84**; 3.59 for **85**; 9.00 for **86**; 14.8 for lamivudine). Moreover, compound **87** significantly inhibited secretion of the HBV extracellular antigen HBeAg (IC_{50} = 12.26 $\mu g\,mL^{-1}$).[57]

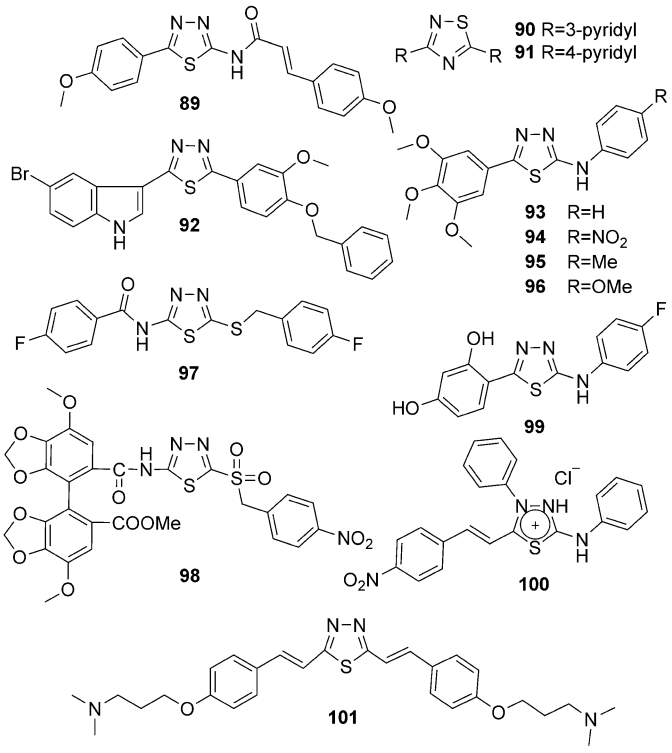
Antiviral thiadiazole derivatives have also been identified against less common viral diseases. For example, compounds reported by Küçükgüzel et al. in 2007 showed antiviral activity, and compound **88** displayed the most potent activity against the *Sindbis* virus, the causative agent of Sinbus fever, at 9.6 $mg\,mL^{-1}$.[26]

2.6 Anticancer activity

Tumor malignancy is a serious threat to human health. Compounds containing the thiadiazole ring are known to possess excellent anticancer activities in vitro.[58] Compounds containing thiadiazole with high potency have been reported in the literature, and some of them displayed excellent activities against a range of tumor cells. The ability of thiadiazoles to target DNA could explain their potential anticancer activity as uncontrolled DNA replication/cell division is a hallmark of neoplastic diseases. Furthermore, the heteroatoms of the thiadiazole are able to form interactions, such as hydrogen bonds, with biological targets which include key kinases that participate in tumorigenesis, such as CA IX and XII.

Yang et al.[59] synthesized and evaluated a series of compounds, identifying 1,3,4-thiadiazole **89** as a potent inhibitor of breast (MCF-7) and lung (A549) adenocarcinoma epithelial cell lines in vitro, with IC_{50} values of 0.28 $\mu g\,mL^{-1}$ and 0.52 $\mu g\,mL^{-1}$, respectively. Closer evaluation identified compound **89** as a potent inhibitor of tubulin polymerization, a key step in cell division, with an IC_{50} value of 1.16 $\mu g\,mL^{-1}$.[59]

Mayhoub et al. designed a series of 1,2,4-thiadiazole-based analogues of the natural product resveratrol believed to have chemoprotective activity. Compared with resveratrol, compounds **90** and **91** revealed much higher inhibitory activity against aromatase, a chemopreventative target, and greater target selectivity.[60] 1,3,4-Thiadiazole-based compounds were also described by Kumar et al.[1] In this study, compound **92** displayed good anticancer effects against a range of tumor cell lines, with IC_{50} values of 8.9 μM, 3.6 μM and 7.5 μM against prostate cancer cell lines LnCaP, DU145 and PC3, respectively, 8.3 μM and 6.2 μM against breast cancer cell lines MCF-7 and MDA-MB-231, respectively, and 1.5 μM against the pancreatic cancer cell line PaCa2.[1] Recently, additional 1,3,4-thiadiazole-based compounds (**93**–**96**) from Kumar et al. were reported to



possess significant anticancer potency against several cancer cell lines, with IC_{50} values ranging from 4.3 to 9.2 μM, and high selectivity for the cell lines tested, such as LnCap, DU145, PC3, MCF-7, MDA-MB-231 and PaCa2.[61]

Radi et al. described a series of 1,3,4-thiadiazole derivatives as potent ATP-competitive inhibitors of the oncogenic tyrosine kinase Bcr-Abl.[62] Of the compounds synthesized, **97** was the most active with inhibitory activities against tyrosine kinases c-Src and Abl of 0.354 μM and 0.044 μM, respectively.[62] However, compound **97** was considered to be too lipophilic which would likely lead to poor pharmacokinetic properties. Therefore, they designed less lipophilic thiadiazoles by replacing the phenyl with a pyridine moiety.[63]

Dimethyl [1,1′-biphenyl]-2,2′-dicarboxylate (a-DBD), derived from the natural product schisandrin C, has a dialkoxybiphenyl skeleton which appears to be essential for anticancer activity.[64] To improve the activity of these derivatives, Kong et al. designed a class of compounds containing both the alkoxybiphenyl skeleton and a 1,3,4-thiadiazole moiety, exemplified here by compound **98** which exhibited potent activities against multiple cancer cell lines, including hepatic carcinoma HepG2 cells (IC_{50} = 6.6 ± 2.2 μM), KB carcinoma cells (IC_{50} = 18.9 ± 0.4 μM), non-small-cell lung cancer A549 cells (IC_{50} = 9.9 ± 0.5 μM), K562 erythromyeloblastoid leukemia cells (IC_{50} = 6.4 ± 1.5 μM) and MCF-7 breast cancer cells (IC_{50} = 11.8 ± 0.6 μM).[58]

Matysiak and co-workers designed, synthesized and evaluated 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives, such as **99** in vitro as potential antiproliferative agents.[65] Compound **99** exhibited potent antiproliferative activities against both peripheral cancers, with IC_{50} values of 6.2 ± 1.4,

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3.6 ± 1.1 and $4.2 \pm 1.2\ \mu g\,mL^{-1}$ against HCV29T (bladder), SW707 (rectal), and T47D (breast) cell lines, respectively,[65] and those of the central nervous system (CNS), such as medulloblastoma/rhabdosarcoma, neuroblastoma, and glioma.[66] Furthermore, this compound was found to be nontoxic to normal cells.[66]

In 1997, Grynberg et al. synthesized the mesoionic compound 4-phenyl-5-(4-nitrocinnamoyl)-1,3,4-thiadiazolium-2-phenylamine chloride (MI-D; **100**) and evaluated it in mouse models of carcinoma and sarcoma.[3a] MD-I (**100**) exhibited potent inhibition of tumor growth and enhanced survival rates, with no significant concomitant alterations in the hematological parameters of test animals.[3a] Senff-Ribeiro et al. studied the in vitro effects of MD-I (**100**) on some established human melanoma cell lines.[3b] At a test concentration of 50 μM, 48 hours after administration, MD-1 caused complete cell death (100%) in MEL-85 and A2058 cells, near complete cell death in MEWO cells, and 90% cell death in SK-MEL.[3b] When evaluated against B16-F10 murine melanoma, MD-I exhibited inhibitory activity both in vitro and in vivo.[67] These results suggest that MD-I (**100**) is a potentially useful tool compound for the investigation of human melanoma.[3b,67]

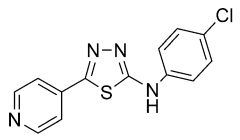
Compounds synthesized by Chou et al. were tested for cytotoxic effects on human lung cancer cells (A549) using an MTT assay.[68] Compound **101** was the most effective in the series described, with IC_{50} values against A549 (lung), PC3 (prostate) and HA22T (liver) cancer cell lines were 6.8 ± 1.0, 6.3 ± 0.6 and 9.7 ± 0.9 μM, respectively. Moreover, **101** induced apoptosis in A549 cells in the early-phase via Bcl-XL downregulation, and in the late-phase through upregulation of Bax expression as well as inhibition of Akt/PKB activation.[68]

2.7 Activity in the CNS

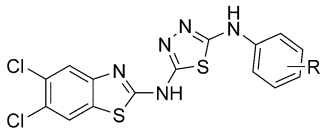
Despite the progress made in the treatment of epilepsy and the recent development of several new anticonvulsants, patients still suffer from various side effects, such as neurotoxicity, depression and other CNS-related conditions. Therefore, the design of novel anticonvulsant drugs with increase specificity and decreased off-target activity is needed. A number of literature reports indicate that thiadiazoles are suitable scaffolds for the design on novel anticonvulsant agents.

Yar et al. synthesized and evaluated a series of thiadiazoles, exemplified here by **102**, for their anticonvulsant activity using a maximal electroshock seizure (MES) test. At a dose of $25\ mg\,kg^{-1}$, compound **102** displayed 100% protection against shock-induced seizures, in contrast to the reference antiepileptic drug phenytoin sodium.[69] Among the synthesized compounds, those with electron-withdrawing substituents exhibited excellent anticonvulsant activities, and those with unsubstituted phenyl rings also showed good activities. The results indicated that additional modifications could potentially give rise to compounds with further improved activity and less toxic effects.[69]

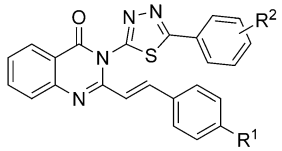
Several aryl-substituted benzothiazole semicarbazones were reported to possess significant anticonvulsant activity.[70] In a follow-up study, incorporation of a 1,3,4-thiadiazole moiety into position 2 of the benzothiazole ring reportedly led to compounds (e.g., **103** and **104**) with increased anticonvulsant activity.[71] These compounds were shown to be equally as effective as phenytoin sodium in a MES test. After i.p. injection ($30\ mg\,kg^{-1}$), both **103** and **104** displayed 100% protection against seizures, as did phenytoin sodium.[71] In the MES and subcutaneous pentylenetetrazole (ScPTZ) tests conducted by Jatav et al., compounds **105**–**109** showed anticonvulsant activity in at least one test model; these compounds also exhibited potent sedative–hypnotic activity in an actophotometer screen.[72] 1,3,4-Thiadiazoles reported by Dawood et al. were screened for anticonvulsant activity using a MES test and subcutaneous metrazole (ScMet) assay in mice. These compounds were found to possess anticonvulsant and anti-inflammatory activities by selectively inhibiting COX-2. Compound **110** was the most effective at minimizing inflammation (45% after 2 h), and compound **111** exhibited comparable activity to the reference compound phenytoin in the MES test.[73]



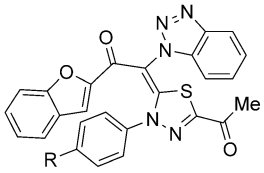
102



103 R=3-Cl
104 R=4-Br



105 R^1=H, R^2=H
106 R^1=H, R^2=4-Cl
107 R^1=H, R^2=3-Cl
108 R^1=OMe, R^2=H
109 R^1=OMe, R^2=3-Cl



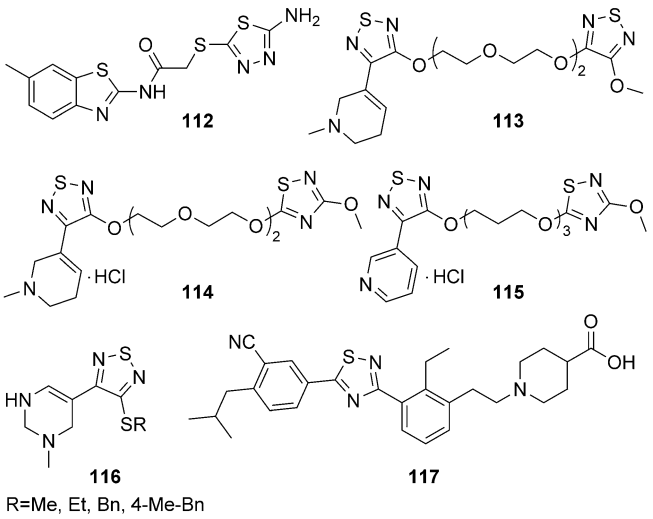
110 R=H
111 R=Cl

Acetylcholine plays an important role in learning, memory, stimulation of smooth muscle contraction, and the promotion of exocrine gland secretion. Acetylcholine released into the synaptic gap is rapidly hydrolyzed by acetylcholinesterase (AchE), and dysregulation of this process can lead to a range of diseases. There are both cholinergic and anticholinergic drugs currently in clinical use. Altintop et al. designed several AchE inhibitors containing a 1,3,4-thiadiazole moiety, among which compound **112** was the most active, with cytotoxicity lower than the effective dose ($66 \pm 0.71\ \mu g\,mL^{-1}$), a highly desirable quality in AchE inhibitors to avoid neuronal cell death.[74]

Muscarinic receptors are a class of acetylcholine receptors, which are classified into five subtypes, namely M_1–M_5. They mediate a variety of physiological responses to the neurotransmitter in the central and peripheral nervous systems. Muscarinic agonists were reported to be useful in the treatment of neurological disorders, such as schizophrenia, Alzheimer's disease, chronic pain and drug abuse.[75] Some muscarinic receptor agonists contain a 1,2,5-thiadiazole ring, such as xanomeline (**6**);

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related derivatives might be useful for the development of improved muscarinic receptor agonists. Recently, bivalent ligands were developed that exhibited potent agonist activity towards the M_1 and M_4 receptors but very low activity towards the M_3 and M_5 receptors. Among these ligands, compound **113** displayed potent agonist activity towards M_1 receptors.[75]

Compound **114** showed significantly higher binding affinities for M_2 and M_4 receptors, with pIC_{50} values of 6.6 ± 0.0 and 5.9 ± 0.3, respectively.[76] It also exhibited significant functional selectivity for M_1 over M_5 receptors, with pEC_{50} values of 6.6 ± 0.1 and 6.2 ± 0.1, respectively.[76] Compound **115** exhibited relatively high efficacy against the M_4 receptor and decreased potency towards the M_1 receptor.[76] Compared with known muscarinic acetylcholine receptor partial agonists arecoline and milameline, compound **116** was identified as an M_1-selective muscarinic receptor agonist, with a higher binding affinity for the human (h) M_1 receptor over the other subtypes, but the affinity of **116** for the M_1 receptor was still much lower than that of xanomeline (**6**).[77] Comparison of the experimental results lead to the conclusion that the binding affinity for the h-M_1 receptor is dependent on the length of the alkyl substituent, with longer alkyl substituents typically giving rise to compounds with higher affinity.[77]

Finally, sphingosine 1-phosphate receptor subtype 1 ($S1P_1$), a G-protein-coupled receptor (GPCR), plays important roles in autoimmune diseases. Ren et al. reported a series of thiadiazole derivatives as $S1P_1$ agonists, among which compound **117** was identified to be the most potent compound ($pEC_{50} = 9.1$ nM).[78]

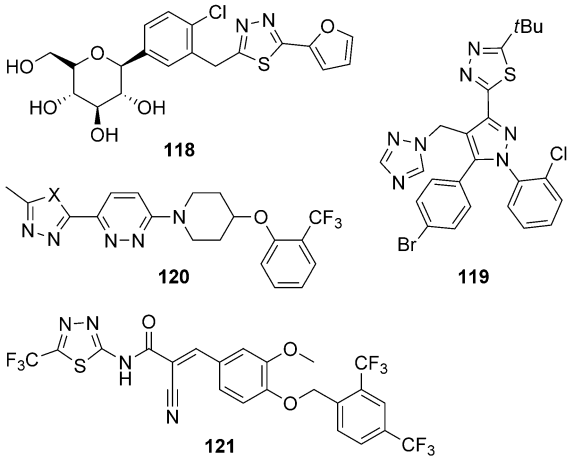
2.8 Activity against diseases of the endocrine system

According to the World Health Organization, more than 5% of the world's population (347 million people) suffer from diabetes.[79a] It is a chronic metabolic disorder resulting from the body's inability to generate insulin or to respond adequately to circulating insulin. Sodium-dependent glucose cotransporters (SGLTs) are potent regulators of glucose metabolism and couple the transportation of glucose against a concentration gradient with the simultaneous transportation of sodium ions down the concentration gradient.[79b] It was reported that SGLT2 plays an important role in renal glucose reabsorption, being responsible for a high proportion of glucose taken up via this route.[80] Therefore, the inhibition of SGLT2 is a feasible method for the treatment of diabetes.

Lee et al. designed and synthesized 1,3,4-thiadiazole-containing C-aryl glucoside as potential SGLT2 inhibitors. Among the compounds tested, **118** exhibited in vitro activity against SGLT2 ($IC_{50} = 7.03$ nM) as well as in vivo potency.[81] In the same year, they reported a series of thiadiazole derivatives as cannabinoid receptor 1 (CB1) inhibitors. CB1 belongs to the superfamily of GPCRs and is widely expressed in mammalian cells. It shows higher levels of expression in the hypothalamus and the limbic system, which are important structures in the brain that control a variety of processes including food intake. Inhibition of CB1 could be effective in decreasing food intake and increasing energy consumption. Among the compounds reported by Lee et al., thiadiazole **119** showed the highest binding affinity for rat CB1 ($IC_{50} = 0.681$ nM) and was selected as a preclinical candidate for the treatment of obesity.[82]

Stearoyl-CoA desaturase (SCD) catalyzes the desaturation of the saturated fatty acyl-CoAΔ9-*cis*, generates monounsaturated fatty acids, and is an important enzyme in fat metabolism. SCD1 plays an important role in diabetes, obesity, atherosclerosis and other related metabolic disorders.[83] Léger et al. synthesized a series of compounds containing thiadiazole and oxadiazole moieties as SCD1 inhibitors, the most promising compound (**120**) was a thiadiazole, exhibiting an IC_{50} value of 2.3 nM against SCD1 in vitro.[84]

The estrogen-related receptor α (ERRα) belongs to the nuclear receptor superfamily and is principally expressed in tissues involved in fatty acid metabolism; ERRα targeting genes include genes participating in energy metabolism.[85] While its exact physiological function is not yet know, its expression profile suggests that it could be a potential target for the treatment of metabolic disorders. Busch et al. identified a potent and selective ligand for ERRα from a series of compounds, establishing the biological and physiological relevance of this re-



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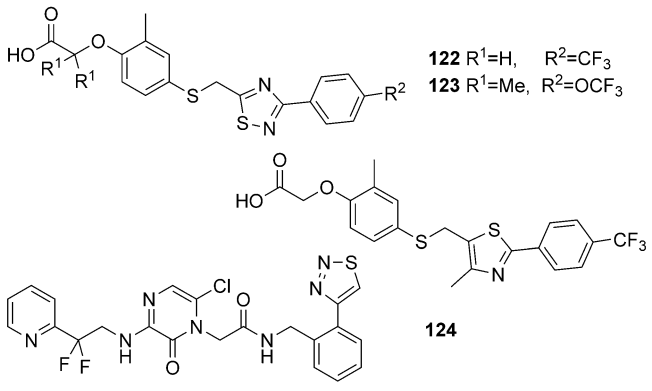
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ceptor via reverse endocrinology. Compound **121** displayed the highest potency (109% inhibition at 10 μM) and inverse agonist activity ($IC_{50}=0.37$ μM) in the cell-based GAL4-ERRa transfection assay.[86] Using compound **121**, they demonstrated that ERRα inverse agonists altered the ERRα/PGC-1 signaling pathways, which validated ERRα as a target for the regulation of energy metabolism and type II diabetes.[86,87]

2.9 Activity in the circulatory system

Cardiovascular diseases, including hyperlipaemia and hypertension, are the most common cause of death worldwide.[88] Disorders of fatty acid metabolism can result in hyperlipaemia, and several studies have provided evidence that peroxisome proliferator-activated receptors (PPARs) are key regulators of fat metabolism.[88] Shen et al. designed several compounds as potent and orally active PPARα/δ dual agonists.[89] Compounds **122** and **123** were generated by the replacement of the methylthiazole of GW501516 (**124**), a PPARδ modulator evaluated in phase II clinical trials in 2007,[89] with a 1,2,4-thiadiazole ring. Compound **122** exhibited partial agonist activity in the sub-micromolar range against PPARα ($EC_{50}=468$ nM, 42%) and was also highly potency against PPARδ ($EC_{50}=10$ nM, 79%).[89] The good in vivo efficacy of compound **123** observed in the mouse model was consistent with the more than twofold higher potency against PPARα ($EC_{50}=33$ nM, 44%) and twofold higher potency against PPARδ ($EC_{50}=3$ nM, 73%).[89]

Finally, thrombin inhibitors can be used to treat circulatory issues caused by blood clotting and thickening. Young et al. reported several 1,2,3-thiadiazole-containing compounds as thrombin inhibitors, among which compound **125** showed moderate activity against purified protein ($K_i=0.84$ nM).[90]



2.10 Other activities

In addition to the biological activities mentioned above, thiadiazole-containing compounds display other diverse bioactivities, such as regulation of plant growth, inhibition of urease, and antioxidant effects. Certainly, numerous other novel effects have yet to be discovered. In some cases, compounds containing a thiadiazole ring show higher activity and less toxicity than the corresponding thiazole derivative. Reiter et al. discovered that the idiosyncratic toxicity of some thrombopoietin receptor agonists (**126**) was eliminated by replacing the thiazole in with a thiadiazole moiety to give **127**.[91]

Maw et al. synthesized some glutarimide analogues as neutral endopeptidase inhibitors. Of the compounds tested, 1,3,4-thiadiazole-containing **128** exhibited much higher potency than derivatives lacking the thiadiazole ring. Compound **129** was obtained by optimization of compound **128**, and the IC_{50} value exhibited by this compound was 30 nM.[92]

Wang et al. synthesized two series of *N*-*tert*-butyl-*N*,*N*′-diacylhydrazines as insecticides and discovered that introduction of a 4-methyl-1,2,3-thiadiazole had no negative effect on insecticidal activity and in some cases improved potency. When evaluated with leaf film feeding method at 1 μg mL^{-1}, compounds **130**–**132** and the reference pesticide tebufenozide were equipotent, all causing 100% insect death.[93a]

It has been reported that upregulation of c-Jun N-terminal kinase (JNK) expression is related to cancer, inflammation, type II diabetes, stroke and obesity.[93b] De et al. synthesized thiadiazoles as JNK inhibitors, among which compound **133** was identified as the most potent ($IC_{50}=0.7$ μM).[94]

Rosenbaum et al. reported that a 1,2,5-thiadiazole containing a carbamate moiety, such as compound **134**, is necessary for the inhibition of lysosomal acid lipase (LAL), with **134** exhibiting an IC_{50} value of 68 nM against LAL.[95]

In 2007, Teng et al. reported heterocyclic compounds **135** as necroptosis inhibitors.[96] When the heterocycle was 1,2,3-thiadiazole, the EC_{50} value of this compound was 1.0 μM. In contrast, when the heterocycle was thiazole, thiophene and furan, the EC_{50} values were 20, 7.0 and 13 μM, respectively. Furthermore, use of 2-methyl-thiazole, 2-(4-chlorophenyl)-thiazole, oxazole or pyridazine as the heterocycle lead to essentially inactive compounds ($EC_{50}>100$ μM).[96] These results clearly indicate the advantages of the thiadiazole ring over other heterocycles against this biological target.

Khan et al. synthesized a series of thiadiazoles and evaluated them for their antioxidant activity. Some of the compounds tested were found to possess excellent antioxidant activity, and compound **136** ($IC_{50}=94.84\pm0.34$ μM) was found to be more potent than *n*-propyl gallate, a reference antioxidant agent.[97]

In the study by Amtul et al., several 1,3,4-thiadiazoles were found to be active urease inhibitors, with the most active compound (**137**) exhibiting a K_m value of 5.0 ± 0.12 μM (pH 8.2).[98]

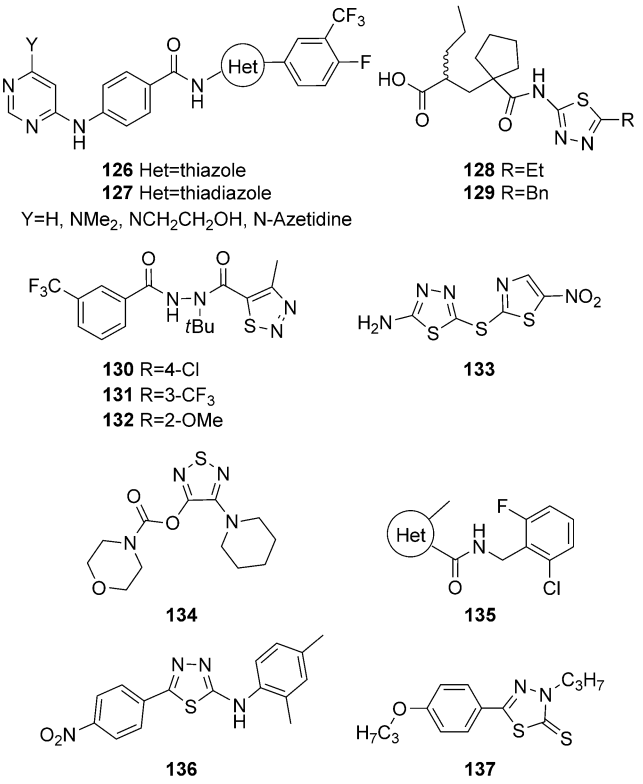
3.0 Synthesis

Different synthetic methods can be employed for the preparation of thiadiazole rings (Scheme 2). Generally, 1,2,4-thiadiazoles can be synthesized from carboxylic acid and reagents containing *N*′-mercaptoformimidamide through condensation and dehydrative cyclization. 1,2,4-Thiadiazoles with the same groups in the 3- and 5-positions can be obtained by oxidation of the corresponding thioamide.[99a] 3-Chloro-1,2,4-thiadiazole, an important intermediate, can be synthesized by the appro-

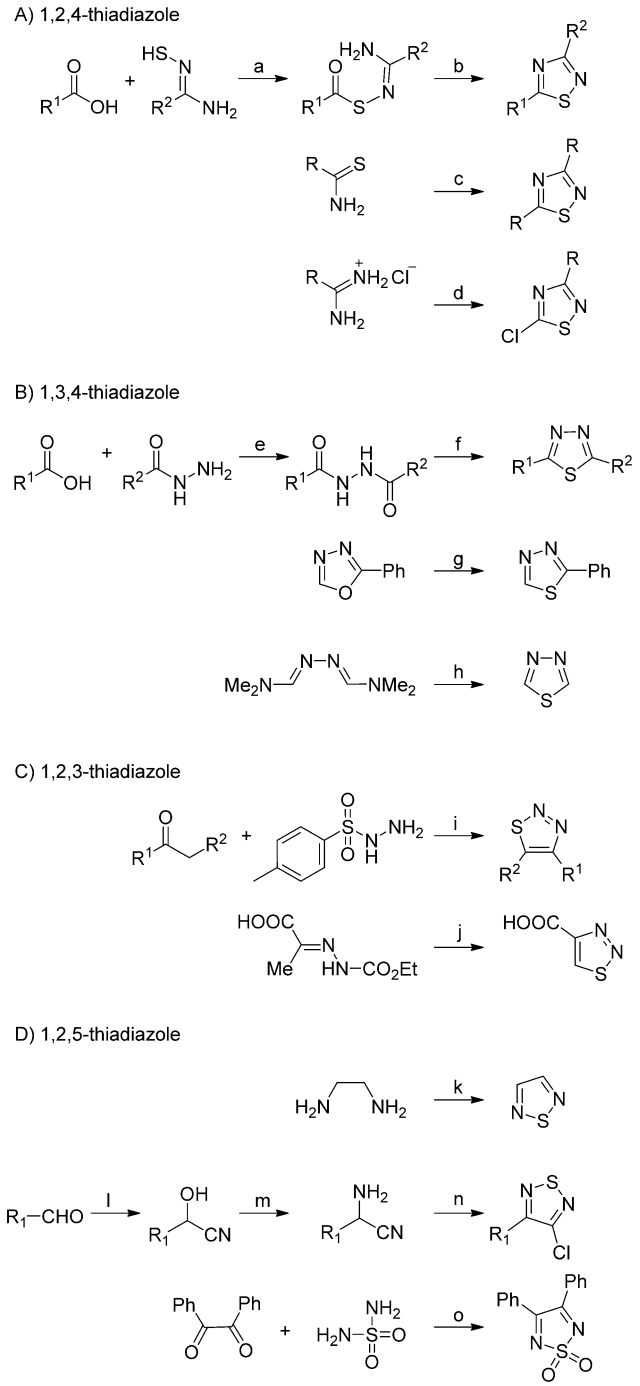
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priate amidine and trichloromethyl hypochlorothioite (Scheme 2a).[99b] 1,3,4-Thiadiazoles can be prepared using Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-dithione) after the condensation of a carboxylic acid and hydrazide (Scheme 2b).[1] They also can be obtained by the reaction of 1,3,4-oxadiazoles and phosphorus pentasulfide.[99c] The 1,3,4-thiadiazole ring can be generated by the cyclization of *N*′-((dimethylamino)methylene)-*N*,*N*-dimethylformohydrazonamide and hydrogen sulfide.[99d] 1,2,3-Thiadiazoles can be made by reaction of 1,2-substituted-ethanone and 4-methylbenzenesulfonohydrazide.[99e] 4-Carboxyl-1,2,3-thiadiazole can be prepared from (*E*)-2-(2-(ethoxycarbonyl)hydrazono)propanoic acid and thionyl chioride (Scheme 2c).[100a] Finally, the 1,2,5-thiadiazole ring can be synthesized by the oxidative cyclization of ethane-1,2-diamine.[100b] 3-Chloro-4-substituted-1,2,5-thiadiazole can be obtained by the cyclization of disulfur dichloride and 2-amino-2-substituted-acetonitrile, which can be made from aldehydes.[75] The condensation reaction of 1,2-diketones and $SO_2(NH_2)_2$ produces 1,2,5-thiadiazole-1,1-dioxides (Scheme 2d).[100c]



Scheme 2. Synthesis of A) 1,2,4-thiadiazole: a) Carbonyldiimidazole (CDI), DMF; b) CDI, DMF, Δ; c) I_2, EtOH; d) CCl_3SCl, NaOH, CH_2Cl_2. 8 °C; B) 1,3,4-thiadiazole: e) 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), hydroxybenzotriazole (HOBt), THF, RT; f) Lawesson's reagent, THF, reflux; g) P_4S_{10}, xylene, Δ; h) H_2S, MeOH, RT; C) 1,2,3-thiadiazole: i) 1. EtOH, reflux, 3 h; 2 $SOCl_2$, $CHCl_3$, 0–5 °C, 4 h; j) $SOCl_2$, 60 °C; D) 1,2,5-thiadiazole: k) S_2Cl_2, DMF, 80 °C; l) $KCN/H_2O/HOAc$; m) NH_4Cl/NH_3 (aq); n) S_2Cl_2/DMF; o) HCl, EtOH, RT.

4.0 Outlook

1,3,4-, 1,2,4-, 1,2,5- and 1,2,3-Thiadiazoles were shown to be present in compounds with diverse activities, such as anti-inflammatory, anticancer, antibacterial, antifungal, antiviral, antiparasitic, anticonvulsant, anticoagulant, antidiabetic and so on. Based on the activities of the thiadiazole-containing compounds summarized here, we can conclude that the thiadiazole scaffolds have significant utility in the development of therapeutically relevant and biologically active compounds.

The thiadiazole ring possesses similar chemical properties to the pyrimidine ring, and can be considered a bioisostere.

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Given that the pyrimidine structure is found in nucleobases, components of nucleotides, the building blocks of DNA and RNA, it seems likely that thiadiazole could readily interact with DNA and RNA, potentially explaining the broad and often potent activity. Furthermore, this activity against DNA suggests that thiadiazoles derivatives could potentially be used for chemical intervention at the gene level.

Thiadiazoles are mesoionic system, a poly-heteroatomic system containing a five-membered heterocycle associated with a conjugation of p and π electrons and distinct regions of positive and negative charges leading to highly polarizable derivatives. This distinctive characteristic allows mesoionic compounds to effectively cross cellular membranes and interact with biological molecules in unique ways, further explaining the high potential of this scaffold in medicinal chemistry.

The good liposolubility of the sulfur atom in the heterocycle might also have a positive effect on the biological activity and pharmacokinetic properties of thiadiazole-containing compounds.

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Keywords: bioisosteres · biological activities · heterocycles · thiadiazoles · therapeutic agents

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