Egypt. J. Chem. **Vol. 63**, No. 11 pp. 4387 - 4408 (2020)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

A Review on Synthesis, Therapeutic, and Computational Studies of Substituted 1, 3, 4 Thiadiazole Derivatives

Ahmed H. Shamroukh,[1] Mohamed I. Hegab[1*]

[1] *Photochemistry Department, National Research Centre, Dokki, 12622 Giza, Egypt*

pmihegab_2010@yahoo.com

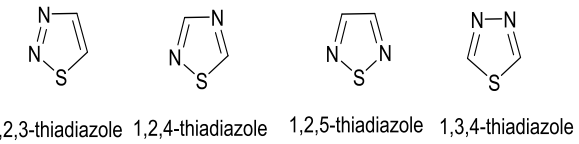
Abstract

Several studies have been reported on 1,3,4- thiadiazole and their derivatives because of their wide range of therapeutic activities. Many drugs containing thiadiazole derivatives are available in market such as acetazolamide, methazolamide, sulphamethazole, cefazoline. This review article highlights the recently synthesized 1,3,4-thiadiazole possessing important therapeutic activities and Computational Studies.

Keyword: 1,3,4-thiadiazole, therapeutic activities, computational Studies.

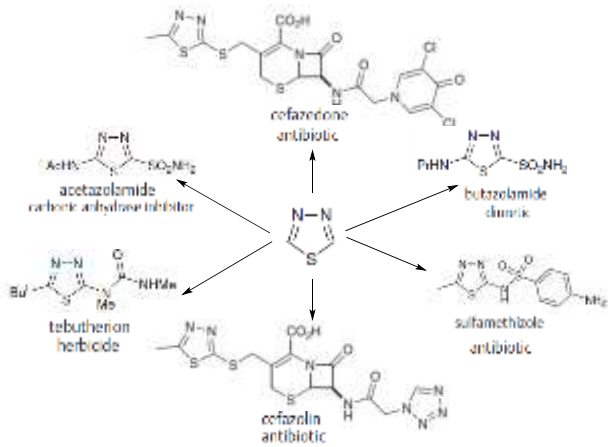
INTRODUCTION

Thiadiazole is one of the aromatic heterocyclic compounds with a five-membered ring possessing sulfur and nitrogen atom. There are four possible isomeric structures of the thiadiazole ring (Scheme 1): 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole and 1,3,4-thiadiazole.



Scheme 1: The four possible isomeric structures of the thiadiazole ring

It is not feasible to discuss the chemistry and applications of all these types in this report, since each type needs and deserves a separate treatment and presentation. So, the scope of the present work will be focused on the 1,3,4-thiadiazole derivatives due to their wide range of biological activities. Scheme 2 shows the structures of some of the more useful 1,3,4-thiadiazoles and their applications. Acetazolamide[1] is potent carbonic anhydrase inhibitors, and sulfamethizole[2] possess antimicrobial activity. Cefazolin[3] and cefazedone[4] belong to the first generation of the cephalosporin family. Many 1,3,4-thiadiazoles have now been synthesized and tested as antifungal,[5] anti-inflammatory,[6] antiparasitic,[7] antioxidant,[8] antidepressant,[9] anticonvulsivant,[10] and antitumor agents.[11] Furthermore other analogues have found use as dyestuffs,[12] lubricants,[13] and conducting polymers.[14]



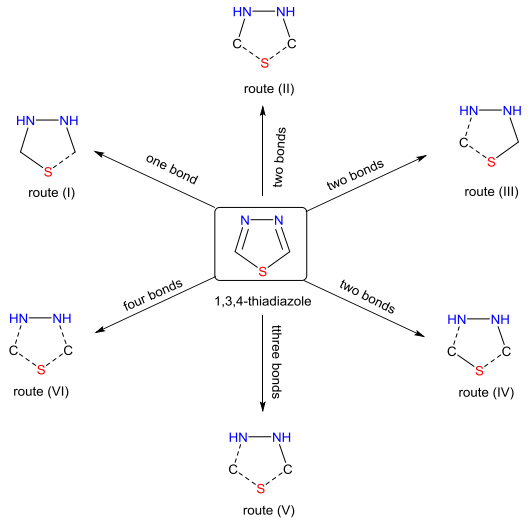
Scheme 2: Structures of some useful 1,3,4-thiadiazoles and their applications

*Corresponding author e-mail: Pmihegab_2010@yahoo.com.

EJCHEM use only: Receive Date: 07 March 2020, Revise Date: 10 April 2020, Accept Date: 12 April 2020
DOI: 10.21608/EJCHEM.2020.25343.2492

Methodologies for the Synthesis of 1,3,4-Thiadiazole

There are four general approaches for the cyclization of 1,3,4-thiadiazoles via a formation of one bond (route I), two bonds (route II, route III, route IV), three bonds (route V), or four bonds through one-pot reaction of three-component (route VI) (Scheme 3).



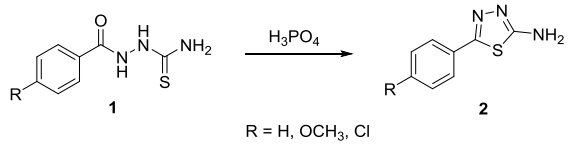
Scheme 3: Synthetic Routs of the formation of 1, 3, 4-thiadiazoles

Synthesis of 1,3,4-thiadiazole via formation of one bond

Rout (I) Synthesis:

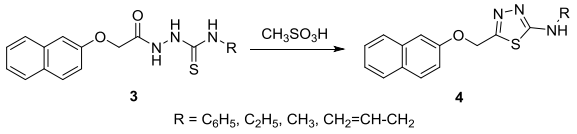
From monothiodiacylhydrazines

Monothiodiacylhydrazines were cyclized through dehydration with sulfuric, phosphorus oxytrichloride, phosphoric acid or methanesulfonic acids to give 1,3,4-thiadiazoles. Many syntheses of 1,3,4-thiadiazoles proceed from thiosemicarbazide cyclization, The procedure performed by Hoggarth (1949) involved the treatment of thiosemicarbazide derivatives **1** with phosphoric acid to form the thiadiazole derivatives **2** (Scheme 4).[15]



Scheme 4

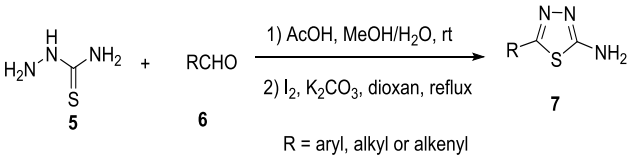
Palaska *et al*. reported the synthesis of 1,3,4-thiadiazole derivatives 4 from the treatment of Thiosemicarbazides **3** with methanesulfonic acid (Scheme 5).[16]



Scheme 5

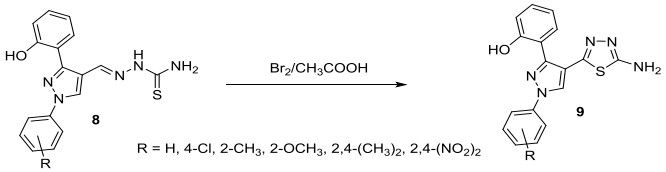
From thioacylhydrazone

Oxidative cyclization of thioacylhydrazone by common oxidants include bromine, ferric chloride, ammonium ferric sulfate, or potassium permanganate provided 1,3,4-thiadiazole derivatives. Niu *et al.* synthesized 2-aminosubstituted 1,3,4-thiadiazoles **7** via condensation of thiosemicarbazide 5 and the corresponding aldehydes **6**. After condensation, the reaction mixture was concentrated and then dissolved in 1,4-dioxane, followed by treatment with iodine and potassium carbonate to form the respective thiadiazole derivatives **7** (Scheme 6).[17]



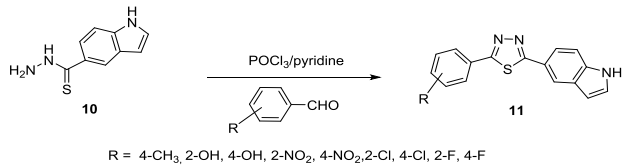
Scheme 6

Kariyappa *et al*., reported a synthesis of novel 1,3,4-thiadiazoles **9** that were obtained by the oxidative cyclization of thiosemicarbazones **8** using bromine dissolved in glacial acetic acid for 2-3 h at room temperature (Scheme 7).[18]



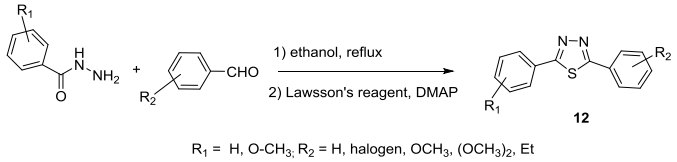
Scheme 7

A series indole bearing thiadiazoles were synthesized by treating thiohydrazide derivative **10** with various aryl aldehydes in pyridine/$POCl_3$ to form cyclized adducts **11** (Scheme 8).[19,20]



Scheme 8

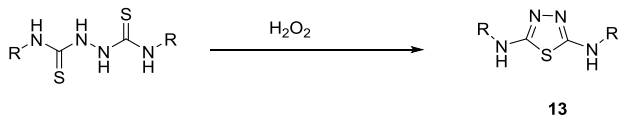
A one pot reaction of aryl hydrazides and aryl aldehydes using Lawesson's reagent is described, yielding 2,5-disubstituted-1,3,4-thiadiazoles **12** in moderate-to-high yields (Scheme 9).[21]



Scheme 9

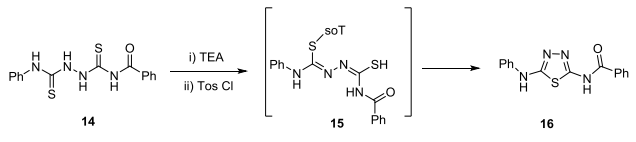
From acylbithioureas

Bisthioureas when treated with 3% hydrogen peroxide are converted to 2,5-diamino 1,3,4-thiadiazole derivatives **13** (Scheme 10).[22]



Scheme 10

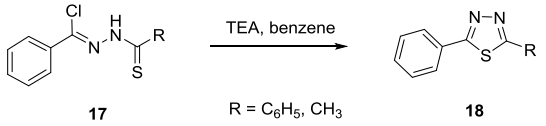
Also, the reaction of acylbithioureas **14** with *p*-tosyl chloride (*p*-TsCl) in presence of triethylamine (TEA) provided a 90% yield of the benzoylated thiadiazole **16**, presumably *via* the intermediate **15** (Scheme 11).[23]



Scheme 11

From thioacyl hydrazonoyl chloride

N-Thiobenzoyl and N-thioacetyl hydrazonoyl chlorides **17** gave 1,3,4-thiadiazole derivatives **18** upon treatment with TEA in benzene (Scheme 12).[24]



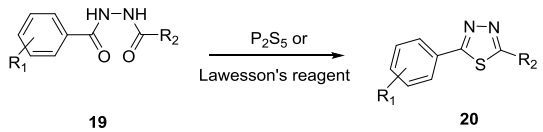
Scheme 12

Synthesis of 1,3,4-thiadiazole via formation of two bonds

Rout (II) Synthesis:

From Diacyl hydrazines with a sulfur source

1,3,4-Thiadiazoles **20** can be prepared from the reaction of diacylhydrazines **19** with a sulfur source. The reaction involves thionation of the carbonyl groups followed by cyclization with loss of H_2S. Phosphorus pentasulfide is commonly used for this cyclization but requires long reaction times and excess reagent, which often leads to low yields and side products. The alternative use of Lawesson's reagent gives higher yields and cleaner reactions (Scheme 13). [25-26]

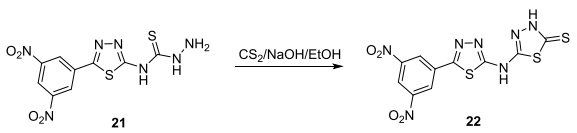


Scheme 13

Rout (III) Synthesis:

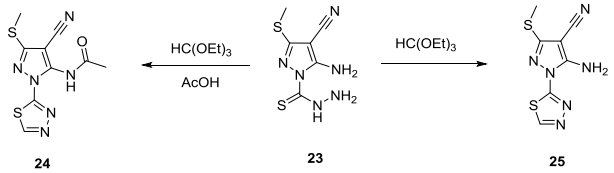
From Thiohydrazides with a carbon source:

Thiosemicarbazide **21** was used as a precursor to construct thiadiazole through the reaction with CS_2/NaOH to give 1,3,4-thiadiazole derivatives **22** in a good yield (Scheme 14).[27]



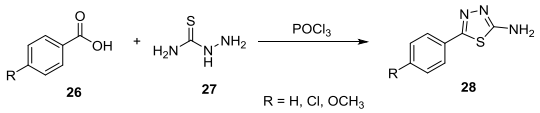
Scheme 14

Alkyl and aryl thiohydrazide derivatives react with orthoesters to afford 1,3,4-thiadiazoles *via* a thiosemicarbazone intermediate which cyclizes to eliminate alcohol or hydrogen. So, Treatment of the *N*-thiohydrazide pyrazole derivative **23** with triethyl orthoformate in acetic acid under reflux gave the 5-acetylamino-3-methylthio-1-(1,3,4-thiadiazol-2-yl)pyrazole-4-carbonitrile **24** and in the absence of acetic acid the 5-amino-3-methylthio-1-(1,3,4-thiadiazol-2-yl)pyrazole-4-carbonitrile **25** in good yield (Scheme 15).[28]



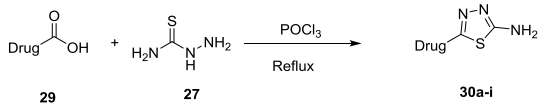
Scheme 15

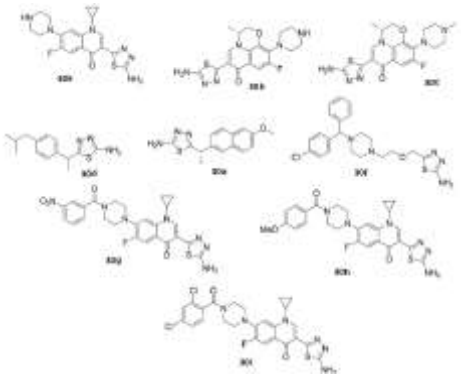
The 5-(4-substituted phenyl)-1,3,4-thiadiazole-2-amine **28** was obtained by the cyclization of aromatic carboxylic acids 26, treated with thiosemicarbazide **27** in the presence of phosphorus oxytrichloride (Scheme 16).[29]



Scheme 16

The carboxylic acid groups of the commercial drugs **29** were cyclized onto thiosemicarbazide in dry ethanol to afford the drug-1,3,4-thiazidazole hybrid compounds **30** in good yields (Scheme 17).[30]



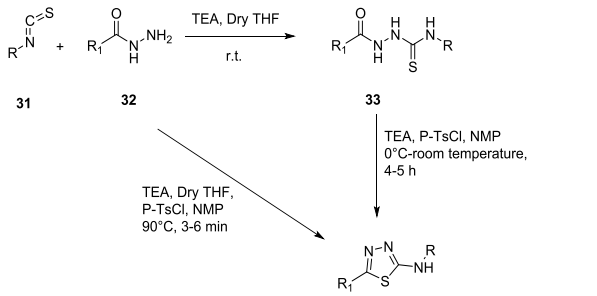


Scheme 17

Rout (IV) Synthesis:

From Hydrazides with C-S sources:

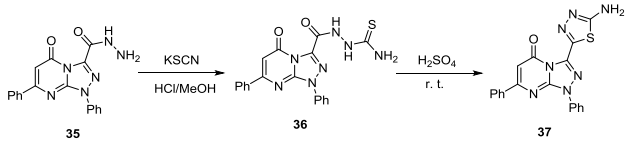
A series of 1,3,4-thiadiazole-2-amine derivatives **34** were synthesized starting from isocyanates and acid hydrazides, in the presence of triethyl amine (TEA) in dry tetrahydrofuran (THF) to obtain intermediate derivatives **33** which treated with TEA and *p*-tosyl chloride (*p*-TsCl) in N-methyl-2-pyrrolidone (NMP) under heating to obtain the 1,3,4-thiadiazole derivatives **34** as a conventional protocol. Also, the later compounds prepared via microwave-assisted protocol by a one-pot reaction of compound **31** with compound **32** in presence of TEA, Dry THF, *P*-TsCl, NMP with excellent yields (Scheme 18).[31]



(a) R = $PhCH_2$, R_1 = Ph;
(b) R = $PhCH_2$, R_1 = p-FC_6H_4;
(c) R = $PhCH_2$, R_1 = p-$NO_2C_6H_4$;
(d) R = Ph_CH_2, R_1 = p-ClC_6H_4;
(e) R = $PhCH_2$, R_1 = p-$MeOC_6H_4$;
(f) R = $PhCH_2$, R1 = p-MeC_6H_4Ph;
(g) R = p-$MeOC_6H_4$, R_1 = Ph;
(h) R = p-$CF_3C_6H_4$, R_1 = Ph;
(i) R = p-FC_6H_4, R_1 = Ph;
(j) R = p-$ClOC_6H_4$, R_1 = Ph;
(k) R = p-MeC_6H_4, R_1 = Ph;
(l) R = p-$NO_2C_6H_4$, R_1 = Ph;
(m)R =p-$MeOC_6H_4$, R_1 = Ph.

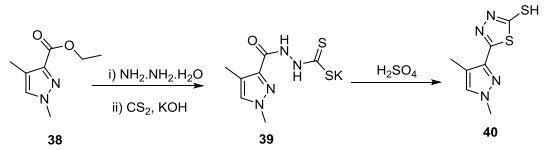
Scheme 18

Treatment of the acid hydrazide **35** with potassium thiocyanate in refluxing methanol, in the presence of hydrochloric acid, afforded the 1-(1,5-dihydro-5-oxo-1,7-diphenyl-1,2,4-triazolo[4,3-*a*]pyrimidine-3-carbonyl)thiosemicarbazide (**36**). Dehydrative cyclization of compound 36, in the presence of conc. sulfuric acid, led to the corresponding 1,7-diphenyl-3-(5-amino-1,3,4-thiadiazol-2-yl)-1,2,4-triazolo[4,3-*a*]pyrimidin-5-(1*H*)-one (**37**), which was separated as green solid soluble with difficulty in most organic solvents (Scheme 19).[32]



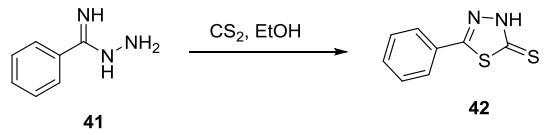
Scheme 19

Treatment of the pyrazole ester **38** with $NH_2NH_2.H_2O$ followed by CS_2 in presence of KOH afforded pyrazole salt **39** which stirring at room temperature in conc. H_2SO_4 to give the corresponding 1,3,4-thiadiazole derivative **40** with a low yield (Scheme 20).[33]



Scheme 20

Kubota *et. al*, described a reaction between benzamidrazone (**41**) and carbon disulfide to obtain the thiadiazole **42** (Scheme 21).[34]



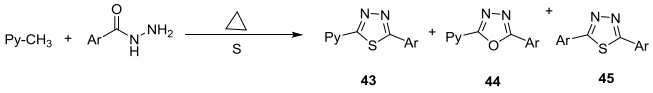
Scheme 21

Synthesis of 1,3,4-thiadiazole via formation of three bonds

Rout (V) Synthesis:

From Aroylhydrazines, sulfur with carbon source

Methyl pyridines and methyl quinolines were reacted with aroylhydrazines in the presence of sulfur to afford 5-aryl-1,3,4-thiadiazoles **43** in low yields. This method required high temperatures and long reaction times and gave a mixture of the desired products **43**, 1,3,4-oxadiazoles **44** and symmetrical diaryl-1,3,4-thiadiazoles **45** (Scheme 22).[35]



Py = Pyridyl, quinolyl

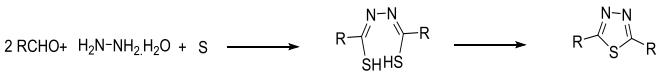
Scheme 22

Synthesis of 1,3,4-thiadiazole via formation of fourbonds

Rout (VI) Synthesis:

From Hydrazine, sulfur and Aldehydes:

Aldehydes were reacted with hydrazine hydrate and sulfur in one-pot synthesis to give 2,5-dialkyl- and 2,5-diaryl-1,3,4-thiadiazoles **46** in a high yield *via* a diazene intermediate (Scheme 23).[36.37]



R = CH_3, C_2H_5, n-C_3H_7, $CH(CH_3)_2$, n-C_4H_9, n-C_6H_{13}

Scheme 23

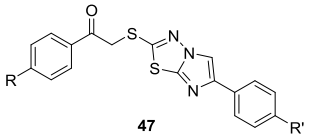
Therapeutic Studies

The 1,3,4-thiadiazole derivatives found to have diverse pharmacological activities such as, antibacterial,[38] anticonvulsant,[10] antidepressant,[38] antifungal,[38] antiglaucoma,[38] antihypertensive,[38] anti-inflammatory,[38] antiischemic,[38] antinociceptive,[39] antiparasitic,[38] antioxidant,[38] antiproliferative,[41] anti-Plant-Virus Potency,[40] antitubercular,[31] antitumor,[38] antiviral,[38] anxiolytic,[38] CNS depressant,[38] CNS stimulant,[38] herbicidal,[38] hypoglycemic,[38] insecticidal.[38]

1- **Antibacterial activity**

a novel series of phenyl substituted imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **47** were synthesized from the reaction of 2-amino-1,3,4-thiadiazole derivatives with 2-bromoacetophenone derivatives. The products **47** were characterized and explored for antibacterial activity against Gram-negative

Escherichia coli, Gram-positive Staphylococcus aureus and Bacillus subtilis and antifungal activity against Candida albicans. Most of the synthesized compounds exhibited remarkable antimicrobial activities, some of which being ten times more potent than positive controls. The most promising compound showed excellent activity with minimum inhibitory concentration (MIC) value of 0.03 mg/ml against both S. aureus and B. subtilis (MIC values of positive compound Chloramphenicol are 0.4 mg/ml and 0.85 mg/ml, respectively) (Scheme 24).[42]

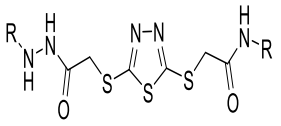


47

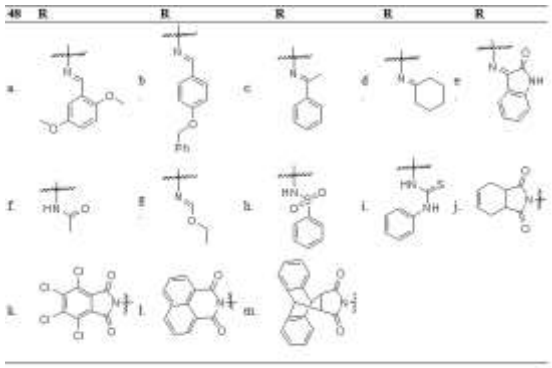
R = H, Cl, F; R' = H, Br, Cl, F, OCH_3, CN, Ph, NO_2

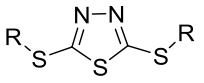
Scheme 24

A new series of 2,5-disubstituted-1,3,4-thiadiazoles **48a-m**, **49a-d, 50** (Scheme 25) were synthesized and screened against *E. coli* and *E. faecalis* strains, and the results are promising and showing that the fine-tuning of the structures **48e** and **50** can lead to some new antimicrobial reagents in treating microbial infections. The remaining tested compounds showed moderate inhibition effects. The higher activity of the mentioned compounds is mainly due to the presence of Schiff bases, thiol groups, pyrazole rings, triazole rings, and imide rings within the structure of 1,3,4-thiadiazole.[43]

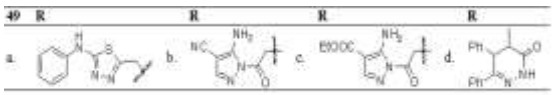


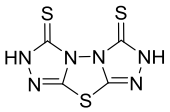
48





49

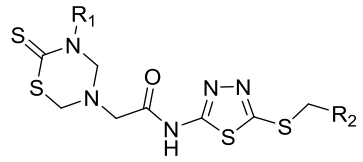




50

Scheme 25

A series of novel *N*-(5-(ethylthio)-1,3,4-thiadiazol-2-yl)-2-(5-methyl-6-thioxo-1,3,5-thiadiazinan-3-yl)acetamide derivatives **50a-p** (Scheme 26) were designed, synthesized and the antimicrobial activities of all the target compounds against *Xanthomonas oryzae pv. oryzicola*, *X. oryzae pv. oryzae*, *Rhizoctonia solani and Fusarium graminearum* were evaluated. The in vitro antimicrobial bioassays indicated that some title compounds exhibited noteworthy antimicrobial effects against the above strains. Notably, the compound *N*-(5-(ethylthio)-1,3,4-thiadiazol-2-yl)-2-(5-methyl-6-thioxo-1,3,5-thiadiazinan-3-yl)acetamide (**51m**) displayed obvious antibacterial effects against *X. oryzae pv. oryzicola and X. oryzae pv. oryzae* at 100 μg/mL with the inhibition rates of 30% and 56%, respectively, which was better than the commercial bactericide thiodiazolecopper. In addition, the anti-R. solani EC50 value of **51a** was 33.70 μg/mL, which was more effective than that of the commercial fungicide hymexazol (67.10 μg/mL).[44]

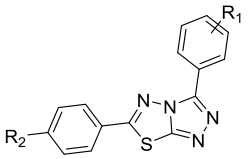


51

Compound	R_1	R_2	Compound	R_1	R_2
a.	Ph	Me	b.	Ph	Ph
c.	Ph	4-MePh	d.	Ph	4-ClPh
e.	Bn	Me	f.	Bn	Ph
g.	Bn	4-MePh	h.	Bn	4-ClPh
i.	4-FPh	Me	j.	4-FPh	Ph
k.	4-FPh	4-MePh	l.	4-FPh	4-ClPh
m.	Me	Me	n.	Me	Ph
o.	Me	4-MePh	p.	Me	4-ClPh

Scheme 26

Twelve novel triazolothiadiazole derivatives **52a-l** (Scheme 27) were synthesized from 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiols with various aromatic carboxylic acids by cyclization in the presence of phosphorous oxychloride. The antimicrobial activities of the title compounds were examined by disc diffusion method against Escherichia coli, Staphylococcus aureus, Pyricularia oryzae and Rhizoctnia solani. The bioassay indicated all synthesized triazolothiadiazole derivatives possessed moderate to good antibacterial and antifungal activities against the tested organisms. Especially, compounds **52e** and **52k** exhibited excellent antibacterial and antifungal activities among these triazolothiadiazole derivatives.[45]

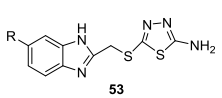


52

52	R_1	R_2	52	R_1	R_2
a.	2-Cl	H	b.	2-Cl	NO_2
c.	2-Cl	$C(CH_3)_3$	d.	2-F	H
e.	2-F	NO_2	f.	2-F	$C(CH_3)_3$
g.	4-Cl	H	h.	4-Cl	NO_2
i.	4-Cl	$C(CH_3)_3$	j.	4-F	H
k.	4-F	NO_2	l.	4-F	$C(CH_3)_3$

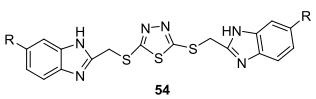
Scheme 27

A series of novel 5-amino-1,3,4-thiadiazole-2-thiol derivatives **53** and 1,3,4-thiadiazole-2,5-dithiol derivatives 54 of benzimidazole (Scheme 28) were synthesized through nucleophilic substitution reaction of 5-substituted-2-(chloromethyl)-1*H*-benzimidazole. All the target compounds were screened for their antibacterial activity toward gram-negative (*E. coli, P. aeruginosa*) and Gram-positive (*B. subtilis, S. aureus*) bacteria; most of the synthesized derivatives exhibited good to moderate activity toward both Gram-positive (*B. subtilis, S. aureus*) and Gram-negative (*E. coli, P. aeruginosa*) bacteria.[46]



53

a, R= H; b, R= CH_3; c, R= COOH; d, R= NO_2



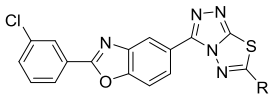
54

a, R= H; b, R= CH_3; c, R= COOH; d, R= NO_2

Scheme 28

2- Anticonvulsant activity

Novel 1,2,4-triazolo-1,3,4-thiadiazoles **55a-l** (Scheme 29) were successfully prepared and estimated for anticonvulsant activity by maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) tests. Entire compounds displayed moderate to good activity. Preliminary evaluation indicates the target compounds **55e**, **55g** and **55i** exhibited potent anticonvulsant activity at a lower dosage (30 mg/kg). The molecules like **55a, 55d, 55e, 55f, 55g, 55i** and **55l** exhibited activity at 0.5 and 4.0 h in contrast to seizures it may would-be worth as prototypic candidates. The anticonvulsant data shown that every compound showed distinctive decrease of hind limb tonic extensor stage. Moreover, anticonvulsant activities of the other tested compounds were found to be much less effective than standard drugs (phenytoin and carbamazepine). According to the results obtained it seems that presence of halo-substituted aryl at benzoxazole and hydroxyl and aldehyde substituted aryl at triazolo-thiadiazole moiety displayed the best anticonvulsant activity and favorable high protection. Compounds **55a, 55b, 55d, 55e, 55f, 55g, 55i** and **55l** supposedly were more lipophilic character having strong anticonvulsant activity. Compounds **55j** and **55k** were a lesser amount of lipophilicity and a reduced amount of activities in MES test. Subsequently, triazolo-thiadiazoles were found having anticonvulsant properties, and express to a favorable candidates with fascinating pharmacological values.[41]



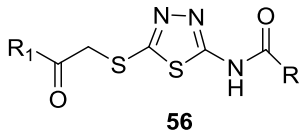
55

55	R	55	R
a.	4-$OCH_3C_6H_4$	b.	4-$C_6H_5C_6H_4$
c.	2-$C_6H_5C_6H_5CH_2$	d.	$C_6H_5OCH_2$
e.	4-$CHOC_6H_4OCH_2$	f.	$CHOC_6H_4$
g.	C_5H_4N	h.	$C_6H_5CH_2$
i.	3,4,6-OHC_6H_2	j.	$C_{10}H_7CH_2$
k.	2-OHC_6H_4	l.	2-$OCOCH_3C_6H_4$

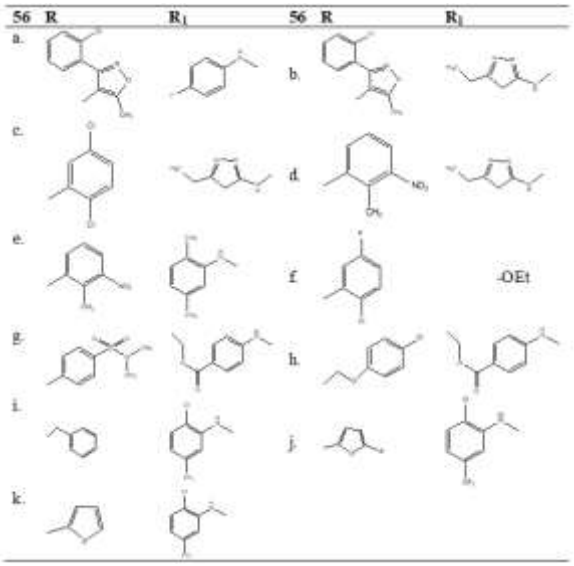
Scheme 29

New scaffold which represented by 2-amino-5-mercapto-1,3,4-thiadiazole basic structure bearing various substituents on both amino and mercapto groups has been proposed for perspective biologically active compounds. 5-R-Carbonylamino-1,3,4-thiadiazol-2-yl-sulfanylacetic acid derivatives **56a-k**

(Scheme 30) are proposed as promising anticonvulsant and anti-cancer agents.[47]



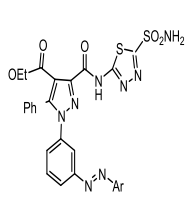
56



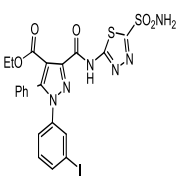
Scheme 30

3- Antiglaucoma activity

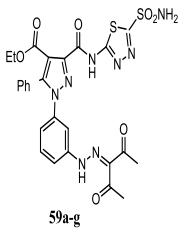
Pyrazole carboxylic acid derivatives of 5-amino-1,3,4-thiadiazole-2-sulfonamide (inhibitor 1) were synthesized from ethyl 3-(chlorocarbonyl)-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-4-carboxylate compound. The inhibitory effects of inhibitor 1, acetazolamide (AAZ) and of 11 synthesized amides (**57a-b, 58, 59a-g**, and **60**) (Scheme 31) on hydratase and esterase activities of carbonic anhydrase isoenzymes (hCA-I and hCA-II) have been studied in vitro. The comparison of newly synthesized amides to inhibitor 1 and to AAZ indicated that the new derivatives inhibit CA isoenzymes and they are more potent inhibitors than the parent inhibitor 1 and AAZ.[48]



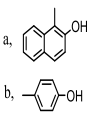
57a,b

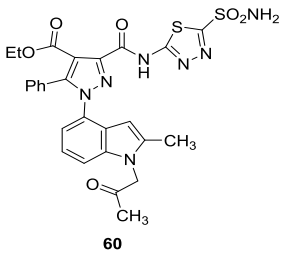


58



59a-g





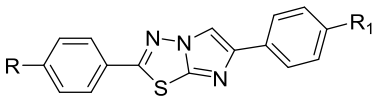
60

59	R_1	R_2
a.	CH_3	CH_3
b.	C_6H_5	CH_3
c.	C_6H_5	C_6H_5
d.	OEt	C_6H_5
e.	OEt	CH_3
f.	OEt	OEt
g.	CH_3	$OC(CH_3)_3$

Scheme 31

4- Anti-inflammatory activity

Non-steroidal anti-inflammatory drugs (NSAIDs) are an important pharmacological class of drugs used for the treatment of inflammatory diseases. They are also characterized by severe side effects, such as gastrointestinal damage, increased cardiovascular risk and renal function abnormalities. In order to synthesize new anti-inflammatory and analgesic compounds with a safer profile of side effects, a series of 2,6-diaryl-imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **61a–l** (Scheme 32) were synthesized and evaluated in vivo for their anti-inflammatory and analgesic activities in carrageenan-induced rat paw edema. Among all compounds, 61c showed better anti-inflammatory activity compared to diclofenac, the standard drug, and compounds **61g, 61i, 61j** presented a comparable antinociceptive activity to diclofenac. None of the compounds showed ulcerogenic activity. Molecular docking studies were carried out to investigate the theoretical bond interactions between the compounds and target, the cyclooxygenases (COX-1/COX-2). The compound 5c exhibited a higher inhibition of COX-2 compared to diclofenac.[29]

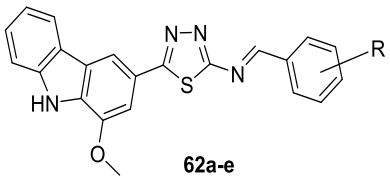


61a-l

61	R	R_1	61	R	R_1
a.	H	H	b.	H	Br
c.	H	CF_3	d.	H	OCH_3
e.	Cl	H	f.	Cl	Br
g.	Cl	CF_3	h.	Cl	OCH_3
i.	OCH_3	H	j.	OCH_3	Br
k.	OCH_3	CF_3	l.	OCH_3	OCH_3

Scheme 32

Murrayanine is the most highly explored molecule from Murraya koenigii L., known popularly as Indian curry plant (family Rutaceae) which demonstrates carminative, astringent, stomachic, purgative, febrifuge, anti-anemic, and anthelminthic. Thiadiazole is a scaffold of prime importance in medicinal chemistry. It has often been observed that thiadiazoles on hybridization with other heterocyclic scaffolds, demonstrates synergistic activity. Based on this fact, a hybrid of 1,3,4-thiadiazole was planned to fabricate with murrayanine and also to explore its synergistic potentials in a specific direction based on the available text information. Mahapatra et al.49 studied the synthesis of murrayanine-thiadiazole hybrids **62a-e** (Scheme 33) using a previously reported starting material (*E*)-2-((1-methoxy-9H-carbazol-3-yl)methylene)thiosemicarbazide and exploring the anti-inflammatory activity of the produced novel compounds. The compound **62c**, containing 3-OCH_3 and 4-OH substituents displayed the highest edema reducing activity after 3 hrs. The enhanced activity may be due to the interaction of the hydrophilic moiety, via oxygen moiety with the active site of the inflammation causing elements like Cyclooxygenase (COX) and Lipoxygenase (LOX). It was tried to establish a crystal clear structure-activity relationship, but due to mixed results, a true relationship cannot be predicted. Rather, an assumption was made based on the available interacting groups with the active sites of the chemical mediator.[49]

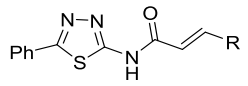


62a-e

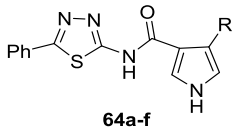
62	R
a.	H
b.	$CH(CH_3)_3$
c.	3-OCH_3; 4-OH
d.	3,4- OCH_3
e.	3,5- OCH_3; 4-OH

Scheme 33

Three new series of (*E*)-3-(4-substitutedphenyl)-*N*-(5-phenyl-1,3,4-thiadiazol-2-yl)acrylamide derivatives (**63a–f**), 4-(4-substitutedphenyl)-*N*-(5-phenyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazole-3-carboxamide derivatives (**64a–f**) and 4-(4- substitutedphenyl)-*N*-(5-phenyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrrole-3-carboxamide derivatives (**65a–f**) (Scheme 34) were synthesized and characterized by elemental analysis LCMS mass, FT-IR spectra ^{1}H and ^{13}C NMR. All the synthesized compounds were screened for their anti-inflammatory activity. Compounds **64c, 64d** and **65c** showed potent anti-inflammatory activities when compared with the standard drugs.[50]



63a-f



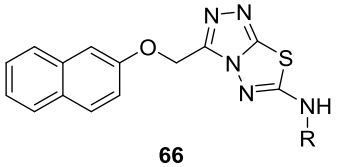
64a-f

65a-f

	R
a.	C_6H_5
b.	4-BrC_6H_4
c.	4-$NO_2C_6H_4$
d.	4-FC_6H_4
e.	4-IC_6H_4
f.	4-ClC_6H_4

Scheme 34

Amir *et al*., Synthesized 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives **66** from naphthoxy acetic acid and evaluated for anti-inflammatory activity (Scheme 35).[51]

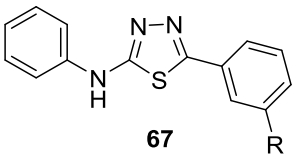


66

R = phenyl, methyl, propyl

Scheme 35

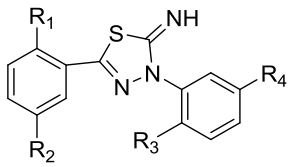
Kumari *et al*., synthesized 1,3,4-thiadiazole derivatives **67** and evaluated for its anti-inflammatory activities (Scheme 36).[52]



67

Scheme 36

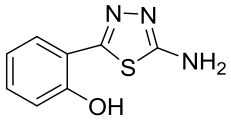
Asif *et al*., syntheszed 2,4-diphenyl-5-imino-1,3,4-thiadiazole derivatives **68** (Scheme 37) by cyclization of α-chlorobenzal phenylhydrazone derivatives using potassium thiocyanate. A-chlorobenzal phenylhydrazone derivatives were synthesized by chlorination of hydrazonyl derivatives using PCl_5 which in turn was synthesized from benzoyl chloride and phenyl hydrazine in pyridine. The thiadiazole derivatives synthesized were screened for in vivo anti-inflammatory activity by carageenan induced paw oedema and a few of them showed promising activity when compared to standard drug diclofenac sodium.[38]



68

Scheme 37

Gupta *et al*., synthesized disubstituted thiadiazole derivatives **69** (Scheme 38) by reaction between salicylic acid and thiosemicarbazide in presence of conc. H_2SO_4. In vivo anti-inflammatory activity was evaluated and compared with standard drug ibuprofen and all compounds showed moderate anti-inflammatory activity.[53]

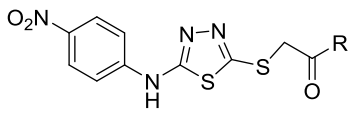


69

Scheme 38

5- Antinociceptive activity

New 1,3,4-thiadiazole derivatives (Scheme 39) were synthesized and investigated for their antinociceptive effects on nociceptive pathways of nervous system. The effects of these compounds against mechanical, thermal and chemical stimuli were evaluated by tail-clip, hot-plate and acetic acid-induced writhing tests, respectively. In addition, activity cage was performed to assess the locomotor activity of animals. The obtained data indicated that compounds **70b-e** and **70g-h** increased the reaction times of mice both in the hot-plate and tail-clip tests, indicating the centrally mediated antinociceptive activity of these compounds. Additionally, the number of writhing behavior was significantly decreased by the administration of compounds **70a, 70c, 70e** and **70f**, which pointed out the peripherally mediated antinociceptive activity induced by these four compounds. According to the activity cage tests, compounds **70a, 70c** and **70f** significantly decreased both horizontal and vertical locomotor activity of mice. Antinociceptive behavior of these three compounds may be non-specific and caused by possible sedative effect or motor impairments.[39]



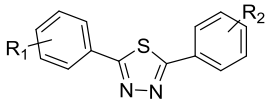
70a-h

70	R
a.	diethylamino
b.	(3-chlorophenyl)amino
c.	(4-chlorophenyl)amino
d.	(4-nitrophenyl)amino
e.	(1,3-benzodioxol-5yl-methyl)amino
f.	Morpholin-4-yl
g.	(Benzothiazol-2-yl)amino
h.	(6-Nitrobenzothiazol-2-yl)amino

Scheme 39

6- Antioxidant activity

Five-membered heterocyclic-ring systems, such as thiadiazoles, remain an important and prevalent scaffold in the development of novel leads in medicinal chemistry for a variety of therapeutic targets. A two-step, one-pot synthesis of 2,5-disubstituted-1,3,4-thiadiazole derivatives **71** (Scheme 40) from aryl hydrazides and aryl aldehydes using Lawesson's reagent is described, yielding 2,5-disubstituted-1,3,4-thiadiazoles in moderate-to-high yields. Based on preliminary biological experiments, some of the newly synthesized thiadiazoles show antioxidant activity.[21]



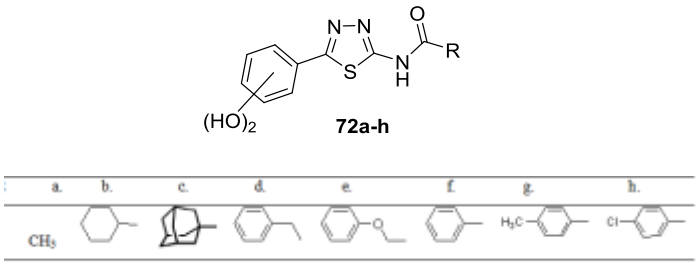
71

R_1 = H, OCH_3, R_2 = H, halogen, OCH_3, $(OCH_3)_2$, Et

Scheme 40

7- Antiproliferative activity

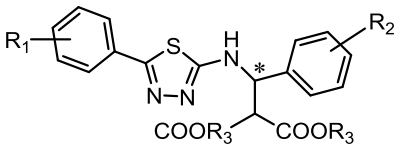
2-Amino-1,3,4-thiadiazoles (Scheme 41) containing phenolic hydroxyl groups were combined with different carboxylic acid chlorides giving amide derivatives with good antioxidant and antiproliferative potential. The compound **72c** with an adamantane ring displayed excellent DPPH radical scavenging activity and good cytotoxic activity against human acute promyelocytic leukemia HL-60 cells, while 1,3,4- thiadiazole **72h** with 4-chlorophenyl moiety was found to be the most effective in inhibition of survival of lung carcinoma A549 cells. All examined thiadiazoles except **72a** exerted higher cytotoxic activities on A549 and HL-60 cancer cells when compared with normal fibroblasts MRC-5, pointing to selectivity in their antiproliferative action. Some of the most active novel compound **72c**, induced significant increase in the percentage of HL-60 cells in the subG1 cell cycle phase in comparison with the control cells. The induction of cell death in HL-60 cells by this compound was at least partially dependent on activation of caspase-3 and caspase-8. The compound **72c** exerted strong antiangiogenic activity. Furthermore, compound **72c**, showed the ability to down-regulate the MMP2 and VEGFA expression levels in the treated HL-60 cells when compared with the control cell samples.[42]



Scheme 41

8- Anti-Plant-Virus Potency activity

A series of novel chiral 5-(substituted aryl)-1,3,4-thiadiazole derivatives **73a-h** (Scheme 42) were synthesized in an enantioselective three-component Mannich reaction using cinchona alkaloid squaramide catalyst with excellent enantioselectivities (up to >99% enantiomeric excess (ee)). The bioassay results showed that these derivatives possessed good to excellent activities against tobacco mosaic virus (TMV).[40]



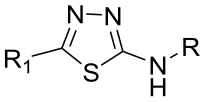
73a-h

73	a.	b.	c.	d.	e.	f.	g.	h.
R_1	H	2,4-di-Cl	3-F	2,4-di-Cl	2,4-di-Cl	4-Cl	4-Cl	3-F
R_2	H	3,4-di-Cl	3,4-di-Cl	2,3-di-Cl	2-F	2,3-di-Cl	2-F	3,4-di-Cl
R_3	Me	Me	Me	Et	Et	Et	Et	Et

Scheme 42

9- Antitubercular activity

A series of novel 5-phenyl-substituted 1,3,4-thiadiazole-2-amines **74a-m** (Scheme 43) were designed, synthesized, and screened for their antitumor and antitubercular activities. The target compounds were synthesized starting from isocyanates and acid hydrazides by conventional and microwave-assisted protocols. The structures of the products were confirmed by ^{1}H NMR, ^{13}C NMR, high-resolution mass spectrometry, and IR spectroscopy and elemental analysis. Some of the synthesized compounds showed significant in vitro antitumor activities against breast cancer and normal human cell lines. Among them, *N*-benzyl-5-(4-fluorophenyl)-, *N*-benzyl-5-(4- nitrophenyl)-, and 5-phenyl-*N*-(*p*-tolyl)-1,3,4-thiadiazole-2-amines demonstrated higher inhibitory activities against the MDA-MB-231 cell line than the cisplatin control (IC50 3.3 μM). *N*-Benzyl-5-(4-methoxyphenyl)-, 5-phenyl-*N*-{[4-(trifluoromethyl)phenyl]methyl}-, *N*-benzyl-5-(4-fluorophenyl)-, and *N*-benzyl-5-(4-nitrophenyl)-1,3,4-thiadiazole-2-amines exhibited high inhibitory activities against the HEK293T cell line (IC50 52.63, 42.67, 34.71, and 33.74 μM, respectively), which were higher compared to the cisplatin control. In antitubercular activity testing against mycobacterium smegmatis MC155, 5-phenyl-*N*-{[4-(trifluoromethyl)- phenyl]methyl}-1,3,4-thiadiazole-2-amine proved to be a more potent agent (MIC 26.46 μg/mL) compared to the Isoniazid control (12 μg/mL). Potential bioactivities of the synthesized compounds were computed using Molinspiration and Molsoft software tools.[31]



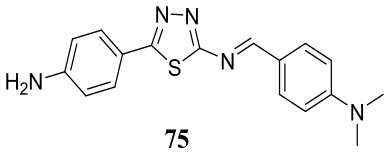
74a-m

74	R	R_1	74	R	R_1
a.	$PhCH_2$	Ph	b.	$PhCH_2$	p-FC_6H_4
c.	$PhCH_2$	p-$NO_2C_6H_4$	d.	$PhCH_2$	p-ClC_6H_4
e.	$PhCH_2$	p-$MeOC_6H_4$	f.	$PhCH_2$	p-MeC_6H_4Ph
g.	p-$MeOC_6H_4$	Ph	h.	p-$CF_3C_6H_4$	Ph
i.	p-FC_6H_4	Ph	j.	p-$ClOC_6H_4$	Ph
k.	p-MeC_6H_4	Ph	l.	p-$NO_2C_6H_4$	Ph
m.	p-$MeOC_6H_4$	Ph			

Scheme 43

10- Antitumor activity

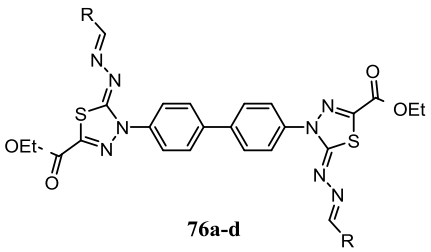
5-(4-aminophenyl)-2-amino-1,3,4-thiadiazole (Scheme 44) was prepared by reaction of Thiosemicarbazide with 4-amino benzoic acid under reflux condition for 7 hours. The compound which has been synthesized successfully was subjected to addition reaction with 4-(Dimethylamino) benzaldehyde under reflux condition for 6 hours to synthesize Schiff bases. These compounds were characterized by using FTIR and evaluated for their anticancer activity. The effect of (1,3,4-thiadiazole derivative) on the activity of malignant cells was studied by using different types of cell lines [Breast cancer, and human prostate cancer]. And was used the Electron microscope to show that the effect of the derivative on the cancer cells before and after 3 days of the injection time. It was found that the Schiff base of thiadiazole: 4-(((5-(4-aminophenyl)-1,3,4-thiadiazol-2-yl)imino)methyl)-*N*,*N*-dimethylaniline **75** was effective in reducing the size and density of malignant cells. That of 46.7 while in breast (145) DUprostate for growth inhibition produce of equal 85.9 µg/ml.[54]



75

Scheme 44

A novel series of bis(1,3,4-thiadiazole) derivatives **76** (Scheme 45) were synthesized in one step methodology with good yields by condensation reaction between bis-hydrazonoyl chloride and various reagents. The structures of the prepared compounds were confirmed by spectral data (IR, NMR, and MS), and elemental analysis. The anticancer activity against human breast carcinoma (MCF-7) cancer cell lines was evaluated in MTT assay. The results revealed that the bis-thiadiazole derivatives **76c,d** had higher antitumor activity than the standard drug Imatinib.[55]

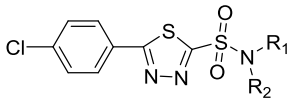


76a-d

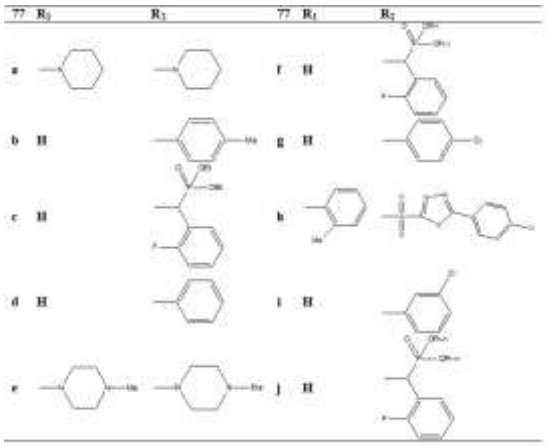
Scheme 45

11- Antiviral activity

Starting from 4-chlorobenzoic acid, new 5-(4-chlorophenyl)-*N*-substituted-*N*-1,3,4-thiadiazole-2-sulfonamide derivatives were synthesized in six-steps. Esterification of 4-chlorobenzoic acid with methanol and subsequent hydrazination, salt formation and cyclization afforded 5-(4-chlorophenyl)-1,3,4-thiadiazole-2-thiol. Conversion of this intermediate into sulfonyl chloride, followed by nucleophilic attack of the amines gave the title sulfonamides **77a-j** (Scheme 46) whose structures were confirmed by NMR, IR and elemental analysis. The bioassay tests showed that compounds **7b** and **7i** possessed certain antitobacco mosaic virus activity.[56]

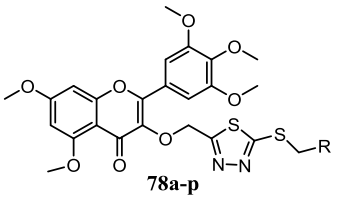


77a-j



Scheme 46

Bioassay results indicated that some target compounds (Scheme 47) exhibited potential antibacterial and antiviral activities. Among them, compounds **78a, 78b, 78d, 78f, 78i, 78m** and **78p** exhibited excellent antibacterial activities against Xanthomonas oryzae pv. Oryzae (Xoo), with EC50 values of 38.6, 20.8, 12.9, 22.7, 27.3, 18.3 and 29.4 μg/mL, respectively, which were better than that of thiadiazole-copper (94.9 μg/mL). Compounds **78b, 78d, 78e, 78f, 78i** and **78o** showed good antibacterial activities against Ralstonia solanacearum (Rs), with EC50 values of 37.9, 72.6, 43.6, 59.6, 60.6 and 39.6 μg/mL, respectively, which were superior to that of thiadiazole-copper (131.7 μg/mL). In addition, compounds **78d, 78f, 78i** and **3m** showed better curative activities against tobacco mosaic virus (TMV), with EC50 values of 152.8, 99.7, 127.1, and 167.3 μg/mL, respectively, which were better than that of ningnanmycin (211.1 μg/mL).[57]

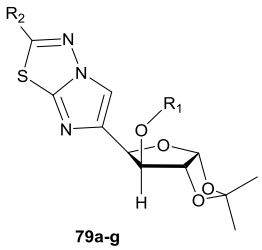


78a-p

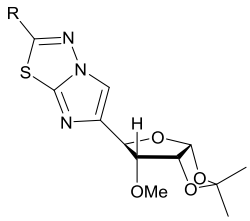
78	R	78	R
a.	H	b.	4-NO_2ph
c.	2-Meph	d.	4-Clph
e.	Me	f.	2-Clph
g.	2-Fph	h.	4-OMeph
i.	2,4-di-Clph	j.	3-NO_2ph
k.	4-Brph	l.	2-Brph
m.	2-Clph	n.	ph
o.	4-Meph	p.	Pyridin3-yl

Scheme 47

Fascio *et al*., describe the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **79a-h** and **80a-c** from carbohydrates with *D*-ribo and Dxylo configuration (Scheme 48). The antiviral activity of these compounds was tested against Junín virus (the etiological agent of Argentine hemorrhagic fever). The *p*-chlorophenyl derivatives showed antiviral activity in a range of micromolar concentration.[58]



79a-g



80a-c

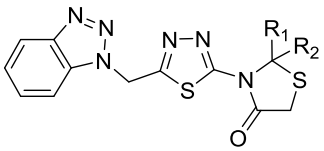
R = Et; p-Clph; p-NO_2ph

79	R_1	R_2	79	R_1	R_2
a.	Me	Et	b.	Me	*p*-Clph
c.	Me	3,4,5-tri-OMeph	d.	Me	p-NO_2ph
e.	*p*-OMeph	*p*-Clph	f.	*p*-OMeph	3,4,5-tri-OMeph
g.	*p*-OMeph	p-NO_2ph			

Scheme 48

12- Anxiolytic activity

5-[(*N*-benzotriazolomethyl)-1,3,4-thiadiazolyl]-4-thiazolidinone derivatives **81a-f** (Scheme 49) have been synthesized and evaluated for their anxiolytic activity. The antianxiety activities of the synthesized derivatives were evaluated using Equine Protozoal Myeloencephalitis (EPM) test and Bright and dark box test experimental models of anxiety. All results were expressed as mean± standard error means (SEM) and analysed by one-way ANOVA. Post-hoc comparisons were performed by applying Dunnet's test. P <0.05 was considered statistically significant.[59]



81a-f

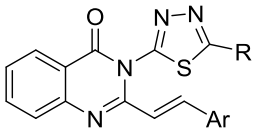
81	R_1	R_2	81	R_1	R_2
a.	H	C_6H_5	b.	C_6H_5	4Br- C_6H_5
c.	H	4Cl- C_6H_5	d.	CH_3	C_6H_5
e.	CH3	C_2H_5	f.	C_6H_5	C_6H_5

Scheme 49

13- CNS depressant activity

A series of novel 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones **82a-r** (Scheme 50) were synthesized and evaluated for anticonvulsant, sedative-hypnotic and CNS depressant activities. After i.p. injection to mice at

doses of 30, 100, and 300 mg/kg body weight. 2-styrylquinazolin-4(3*H*)-one derivatives were examined in the maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. The neurotoxicity was assessed using the rotorod method. Out of eighteen compounds only **82a, 82d, 82e, 82j** and **82k** showed anticonvulsant activity in one or more test models. All except **82e** and **82f** exhibited significant sedative-hypnotic activity via actophotometer screen. CNS depressant activity screened with the help of the forced swim pool method resulted into some potent compounds. From the experimental observation it can be concluded that synthesized compounds exhibited relatively better sedative-hypnotic and CNS depressant activities.[60]



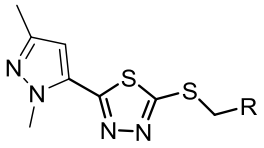
82a-r

82	Ar	R		Ar	R
a.	C_6H_5	C_6H_5	j.	p-$OCH_3C_6H_4$	p-ClC_6H_4
b.	C_6H_5	p-$OCH_3C_6H_4$	k.	p-$OCH_3C_6H_4$	m-ClC_6H_4
c.	C_6H_5	p-$CH_3C_6H_4$	l.	p-$OCH_3C_6H_4$	-CH=CHC_6H_4
d.	C_6H_5	p-ClC_6H_4	m.	p-$CH_3C_6H_4$	C_6H_5
e.	C_6H_5	m-ClC_6H_4	n.	p-$CH_3C_6H_4$	p-$OCH_3C_6H_4$
f.	C_6H_5	-CH=CHC_6H_4	o.	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$
g.	p-$OCH_3C_6H_4$	C_6H_5	p.	p-$CH_3C_6H_4$	p-ClC_6H_4
h.	p-$OCH_3C_6H_4$	p-$OCH_3C_6H_4$	q.	p-$CH_3C_6H_4$	m-ClC_6H_4
i.	p-$OCH_3C_6H_4$	p-$CH_3C_6H_4$	r.	p-$CH_3C_6H_4$	-CH=CHC_6H_4

Scheme 50

14- Herbicidal activity

A variety of pyrazole derivatives containing 1,3,4-thiadiazole moiety **83a-l** (Scheme 51) were synthesized under microwave irradiation, and their structures were confirmed by ^{1}H NMR and HRMS. They were evaluated for herbicidal and antifungal activities, and the results indicated that two compounds with a phenyl group **83a** and 4-*tert*-butylphenyl group **83l** possess good herbicidal activity for dicotyledon Brassica campestris and Raphanus sativus with the inhibition of 90% for root and 80%–90% for stalk at 100 ppm respectively. The structure-activity relationship of compounds **83a** and **83l** was also studied by density function theory method.[33]



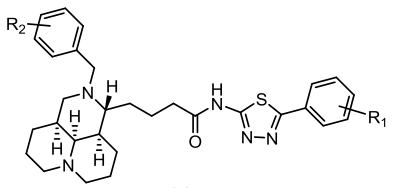
83a-n

78	R	78	R
a.	Ph	b.	2-ClPh
c.	2-ClPh	d.	4-CNPh
e.	2-FPh	f.	2,4-diClPh
g.	3ClPh	h.	3,4-diClPh
i.	4-BrPh	j.	t-BuPh
k.	CN	l.	CH = CH2

Scheme 51

15- Insecticidal activity

A series of matrinic amide derivatives containing 1,3,4-thiadiazole scaffold **84a-x** (Scheme 52) were prepared, and their insecticidal and acaricidal activities were evaluated against Mythimna separata and Tetranychus cinnabarinus. Some compounds exhibited potent insecticidal and acaricidal activities. It was suggested that R_1 as a nitro group and R_2 as a fluorine atom, were important for the insecticidal activity; R_1 as the electron-donating groups and R_2 as the methyl group, were necessary for the acaricidal activity.[61]

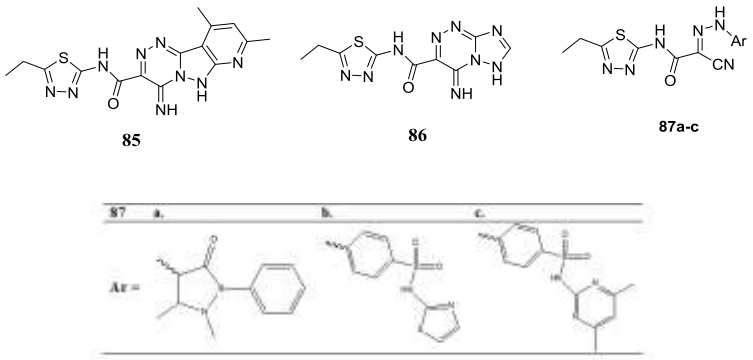


84a-x

84	R_1	R_2	84	R_1	R_2	84	R_1	R_2	84	R_1	R_2	84	R_1	R_2
a.	H	H	f.	3-Cl	H	k.	4-Me	4-Me	p.	2-Cl	4-Me	u.	3-NO_2	4-F
b.	4-Me	H	j.	2-Cl	H	l.	3-Me	4-Me	q.	4-Cl	4-Me	v.	3-Cl	4-F
c.	3-Me	H	h.	4-Cl	H	m.	4-OMe	4-Me	r.	4-Br	4-Me	w.	2-Cl	4-F
d.	4-OMe	H	i.	4-Br	H	n.	3-NO_2	4-Me	s.	H	4-F	x.	4-Br	4-F
e.	3-NO_2	H	j.	H	4-Me	o.	3-Cl	4-Me	t.	4-Me	4-F			

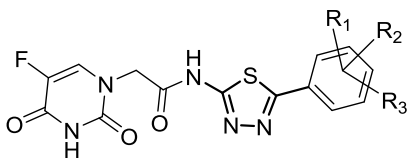
Scheme 52

2-Cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)acetamide was utilized as a versatile precursor for the synthesis of various heterocycles, such as pyrrole, pyridine, coumarin, thiazole, pyrido[2',3':3,4]pyrazolo[5,1-*c*]triazine, triazolo[5,1-*c*]triazine, aminopyrazole, thiophene, 1,3-dithiolane, triazolo[1,5-*a*]pyrimidine and benzo[d]imidazole derivatives. The newly synthesized compounds were identified by IR, MS, ^{1}H NMR, ^{13}C NMR, DEPT, H–H COSY, HMBC, and HSQC. Representative compounds of the synthesized products **85, 86** and **87a-c** (Scheme 53) were examined and estimated as insecticidal agents against the cotton leafworm, Spodoptera littoralis.[62]



Scheme 53

A series of novel 1,3,4-thiadiazole 5-fluorouracil acetamides derivatives **88a-p** (Scheme 54) were designed and synthesized .Their structures were confirmed by infrared, ^{1}H NMR spectroscopy, and elemental analysis .The insecticidal activities against Tetranychus cinnabarinus and Aphis craccivora of these new compounds were evaluated. The bioassay tests showed that most of these title compounds possessed a good combination of stomach toxicity as well as contact toxicity against Tetranychus cinnabarinus and Aphis craccivora. In particular, the insecticidal activity of the title compound 88e against Aphis craccivora was better than the commercialized thiacloprid and was also comparable to another commercialized product, imidacloprid. The introduction of fluorines to meta and para-position of the benzene ring was essential for high bioactivity.[63]

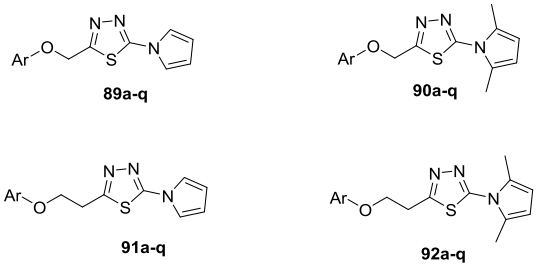


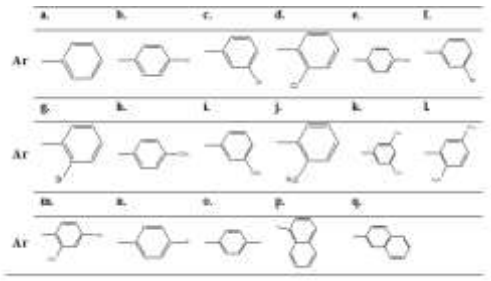
88	R^1	R^2	R^3
a.	3-OCH_3	H	H
b.	2-Cl	4-Cl	H
c.	3-CH_3	5-CH_3	H
d.	4-NO_2	H	H
e.	3-F	4-F	H
f.	4-(n-C_5H_{11})	H	H
g.	3-F	5-F	H
h.	2-NO_2	4-Br	H
i.	3-OCH_3	4-OCH_3	H
j.	2-F	6-F	H
k.	4-CH_3	H	H
l.	3-OCH_3	4-OCH_3	5-OCH_3
m.	4-OPh	H	H
n.	4-(n-$C_{12}H_{25}$)	H	H
o.	4-(n-C_8H_{17})	H	H
p.	H	H	H

Scheme 54

Computational Studies

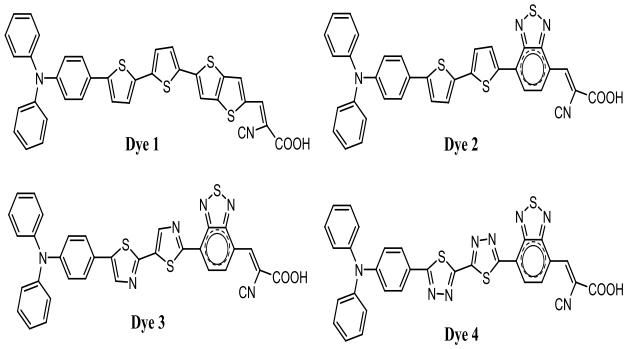
Enoyl acyl carrier protein reductase (ENR) is an essential type II fatty acid synthase (FAS-II) pathway enzyme that is an attractive target for designing novel antitubercular agents. It was reported sixty eight pyrrolyl substituted aryloxy-1,3,4-thiadiazoles **89-92** (Scheme 55) synthesized by three-step optimization processes. Three-dimensional quantitative structure–activity relationships (3D-QSAR) were established for pyrrolyl substituted aryloxy-1,3,4-thiadiazole series of InhA inhibitors using the comparative molecular field analysis (CoMFA). Docking analysis of the crystal structure of ENR performed by using Surflex-Dock in Sybyl-X 2.0 software indicates the occupation of pyrrolyl substituted aryloxy 1,3,4-thiadiazole into hydrophobic pocket of InhA enzyme. Based on docking and database alignment rules, two computational models were established to compare their statistical results. The analysis of 3D contour plots allowed us to investigate the effect of different substituent groups at different positions of the common scaffold. In vitro testing of ligands using biological assays substantiated the efficacy of ligands that were screened through in silico methods.[64]





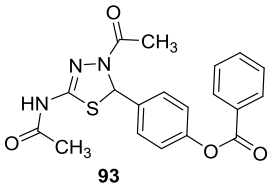
Scheme 55

Ramzan and Janjua have designed triphenylamine (TPA) dyes with D-A-II-A structure and their electro-optical and charge injection properties have been calculated. The computational techniques are used to study the effect of additional acceptor in π-conjugated systems on absorption spectra and electron injection of the dyes. All the dyes have shown absorbance in visible region. The effect of additional acceptor on the performance of sensitizers in dye sensitized solar cells has also been determined. In theoretical examination electron injection efficiency (Φinject.) and light harvesting efficiency (LHE) have been calculated. The results indicate that the combination and selection of appropriate conjugated bridge in dye sensitizer is an important way to design efficient dyes (Scheme 56).[65]



Scheme 56

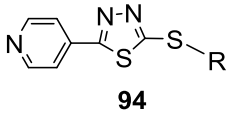
4[3-acetyl-5-(acetylamino)-2,3-dihydro-1,3,4-thiadiazole-2-yl]phenyl benzoate from the family of thiadiazole derivative **93** (Scheme 57) has been synthesized. It has good anticancer activity as well as antibacterial and less toxic in nature, its binding characteristics are therefore of huge interest for understanding pharmacokinetic mechanism of the drug. The binding of thiadiazole derivative to human serum albumin (HSA) has been investigated by studying its quenching mechanism, binding kinetics and the molecular distance, r between the donor (HSA) and acceptor (thiadiazole derivative) was estimated according to Forster's theory of non-radiative energy transfer. The Gibbs free energy (ΔG), enthalpy (ΔH) and entropy (ΔS) changes of temperature-dependent Kb was calculated, which explains that the reaction is spontaneous and exothermic. The microenvironment of HSA have also been studied using synchronous fluorescence spectroscopy, and the feature of thiadiazole derivative-induced structural changes of HSA have been carried using Fourier transform infrared spectroscopy and the Molecular modelling simulations explore the hydrophobic and hydrogen bonding interactions.[66]



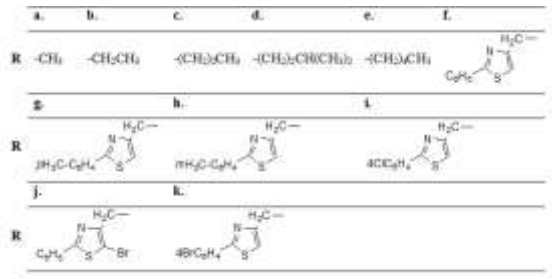
93

Scheme 57

The retention behavior for a series of polyheterocyclic compounds containing 1,3,4-thiadiazole rings **94** (Scheme 58) was investigated using reversed-phase thinlayer chromatography. Different approaches and computational methods were employed to evaluate their lipophilicity indices derived from chromatographic parameters. The obtained experimental results were correlated with various lipophilicity indices estimated via different computer software and internet websites. A strong correlation between experimental and computed results was observed. Furthermore, the lipophilicity parameters obtained by applying principal component analysis divided the investigated compounds into four groups according to their structural similarities.[67]



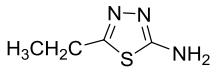
94



Scheme 58

Density functional theory (DFT) with two functionals, namely B3LYP and CAM-B3LYP with the 6-311++G(d,p)basis set was performed on six 2-amino-5-alkyl-1,3,4-thiadiazole derivatives (IC-2 to IC-13) used as corrosion inhibitors for steel in 1.0 M H_2SO_4 solution, along with the calculations on the parent compound 2-amino-1,3,4- thiadiazole (IC). The computations were carried out in non-protonated and protonated forms. The results obtained found a relationship between the molecular structures of the studied IC inhibitors and their experimental inhibition efficiencies. The order of the experimental inhibition efficiencies was matched with the order of a good number of the calculated global and local reactivity descriptors but with varying degrees of correlation. Supported by the Mulliken population analysis and natural population analysis, molecular electrostatic potential plots, and natural bond orbital analysis, the active sites in the inhibitors responsible for their adsorption on a steel surface have been predicted. Molecular dynamic simulationswere further carried out on the protonated forms of IC- 2 to IC-13 with an Fe (110) surface. Results obtained were in reasonable agreement with experimental data.[68]

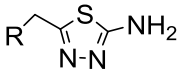
Raman (3500-5 cm^{-1}) and infrared (4000e300 cm^{-1}) spectra of 2-Amino-5-ethyl-1,3,4-thiadiazole 95 (AET; C4H7N3S) (Scheme 59) have been recorded in the solid phase. In addition, the ^1H and ^{13}C NMR spectra of AET were obtained in DMSO-d_6. As a result of internal rotations of either methyl and/or ethyl groups around the C-C bonds with NH_2 moiety being planar (sp^2) and/or non-planar (sp^3) eight structures are theoretically proposed (1-8). The conformational energies and vibrational frequencies have been calculated using Density Functional Theory (DFT) with the methods of B3LYP and B3PW91 utilizing 6-31G (d) and 6-311++G(d,p) basis sets. And then S-4 (the only conformer with real frequencies) was optimized, to yield S-9, however the Thiadiazole ring slightly twisted (tilt angle is 0.9˚). The ^1H and ^{13}C NMR chemical shifts were also predicted using a GIAO approximation at 6-311þþG(d,p) basis set utilizing B3LYP and B3PW91 methods with solvent effects using PCM method. The computational outcomes favor S-9; the methyl group being staggered to the lone pair of N4 and reside trans position to the S atom, whereas NH_2 is nonplanar in good agreement with the current study. Aided by the above mentioned DFT computations, a complete vibrational assignment of the observed infrared and Raman bands along with NMR chemical shifts has been proposed. The vibrational interpretations have been supported by normal coordinate analysis and potential energy distributions (PEDs). Finally, NH_2, CH_3 and C_2H_5 barriers to internal rotations were carried out using B3LYP/6-31G(d) optimized structural parameters (S-9). The results are reported herein and compared with X-ray structural parameters.[69]



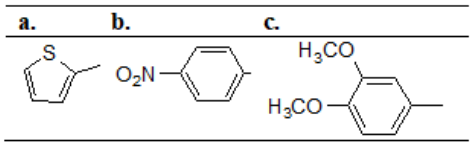
95

Scheme 59

Mustafa *et al*.,[70] studied synthesize and characterize compounds containing 2-amino-1,3,4-thiadiazole and compare experimental results to theoretical results. For this purpose, 2-amino-1,3,4-thiadiazole compounds **96a-c** (Scheme 60) were synthesized in relatively high yields (74-87%). The structures of **96b** ($C_9H_8N_4O_2S$) and **96c** ($C_{11}H_{13}N_3O_2S$) were elucidated by X-ray diffraction analysis. Lastly, IR spectrum, ^1H NMR and ^{13}C NMR chemical shift values, frontier molecular orbital (FMO) values of these molecules containing heteroatoms were examined using the Becke-3- Lee-Yang-Parr (B3LYP) method with the 6-31G(d) basis set. Two different molecular structures containing 2-amino-1,3,4-thiadiazole (**96b, 96c**) were used in that study to examine these properties. Also, compounds **96b** and **96c** form a stable complex with beta-Lactamase as can be understood from the binding affinity values and the results show that the compound might inhibit the beta-Lactamase enzyme. It was found that theoretical and experimental results obtained in the experiment were compatible with each other and with the values found in the literature.[70]

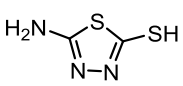


96a-c

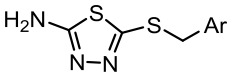


Scheme 60

5-Amino-1,3,4-thiadiazole-2-thiol **97** and 5-(benzylthio)-1,3,4-thiadiazol-2-amine derivatives **98a-d** (Scheme 61) were synthesized to investigate the reactions and the chemical species which take place in the investigated reactions computationally via density functional theory (DFT) calculations, to make a comparison between experimental and computationally obtained data, and to make a comparison between the computational methods to find out the best computational technique to simulate the investigated molecules and reactions. The study consists of two parts. In the first part, synthesis of 5-amino-1,3,4-thiadiazole-2-thiol and 5-(benzylthio)-1,3,4-thiadiazol-2-amine derivatives have been carried out. For both syntheses, it has been proposed that the reactions can be carried out effectively with the use of ultrasound. The results showed that ultrasound can increase the efficiency of the investigated reactions and can be a good alternative to conventional methods. In the second part of the study, some DFT calculations have been performed on the chemical species which take place in the investigated reactions. In computational studies, seven different basis sets have been used. In this second part, comparisons have been made between experimental and computationally obtained data, and between the computational techniques to reveal the best method for the investigated molecules.[71]



97

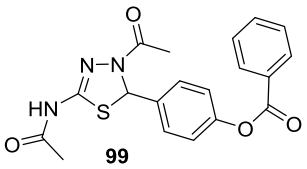


98a-d

	a	b	c	d
Ar	phenyl	2-chlorophenyl	4-chorophenyl	4-bromophenyl

Scheme 61

The interaction mechanism between newly synthesized 4-(3-acetyl-5-(acetylamino(-2-methyl-2,3-dihydro-1,3,4-thiadiazole-2-yl) phenyl benzoate (thiadiazole derivative) **99** anticancer active drug with calf thymus DNA was investigated by using various optical spectroscopy techniques along with computational technique (Scheme 62). The absorption spectrum shows a clear shift in the lower wavelength region, which may be due to strong hypochromic effect in the ctDNA and the drug. The results of steady state fluorescence spectroscopy show that there is static quenching occurring while increasing the thiadiazole drug concentration in the ethidium bromide- ctDNA system. Also the binding constant (K), thermo dynamical parameters of enthalpy change (ΔH°), entropy change (ΔS°) Gibbs free energy change (ΔG°) were calculated at different temperature (293 K, 298 K) and the results are in good agreement with theoretically calculated MMGBSA binding analysis. Time resolved emission spectroscopy analysis clearly explains the thiadiazole derivative competitive intercalation in the ethidium bromide-ctDNA system. Further, molecular docking studies was carried out to understand the hydrogen bonding and hydrophobic interaction between ctDNA and thiadiazole derivative molecule. In addition the docking and molecular dynamics charge distribution analysis was done to understand the internal stability of thiadiazole derivative drug binding sites of ctDNA. The global reactivity of thiadiazole derivative such as electronegativity, electrophilicity and chemical hardness has been calculated.[72]

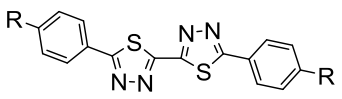


99

Scheme 62

A bi-thiadiazole derivative **100a,b** (Scheme 63) was revealed to exhibit an extremely stable thermotropic SmC phase and very interesting aggregation behavior in solutions. H- and J-aggregates could be formed simultaneously in chloroform solutions of 100b with moderate concentration (10-4 M), and the population of J-aggregates enlarges during further concentration increase. All monomers, H-aggregates and J-aggregates in solutions could be reserved in the drop-cast films, and both the presence of J-aggregates and the energy transfer path from H-aggregates to J-aggregates were considered to contribute to the

relative high solid state fluorescence quantum yield (33%). The 100a dimer potential energy surface (PES) was computed with M062x/6-31G** method, and the molecular packing pattern corresponding to the lowest minimum of the PES are in good agreement with the crystal structures. Exploring the effect of molecular packing on its electronic structure with the TD-M062x method revealed that J-aggregates could be formed by enlarging the intermolecular displacement along the molecular long axis by about 9.8 A°.[73]



100a,b

a: R = -OCH_3; b: R = -$OC_{14}H_{29}$

Scheme 63

List of abbreviations

Abbreviations	Name of reagent
DMAP	Dimethylaminopyridine
TEA	Triethylamine
THF	Tetrahydrofuran
NMP	N-methyl-2-pyrrolidone
p-TsCl	p-tosyl chloride
DPPH	2,2-diphenyl-1-picrylhydrazyl
ee	enantiomeric excess
Rs	Ralstonia solanacearum
ENR	Enoyl acyl carrier protein reductase
FAS-II	fatty acid synthase II
3D-QSAR	Three-dimensional quantitative structure–activity relationships
CoMFA	comparative molecular field analysis
LHE	light harvesting efficiency
MIC	Minimum inhibitory concentration
MES	Maximal electroshock seizure
scPTZ	Subcutaneous pentylenetetrazole
AAZ	Acetazolamide
CA-I	Carbonic anhydrase isoenzymes
NSAIDs	Non-steroidal anti-inflammatory drugs
TMV	Tobacco mosaic virus
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide
EPM	Equine Protozoal Myeloencephalitis
TPA	Triphenylamine
HSA	Human serum albumin
DFT	Density functional theory
B3LYP	Becke-3- Lee-Yang-Parr
PES	potential energy surface

References

[1] Miller W. H., A. M. Dessert, R. O. R. Jr, Heterocyclic Sulfonamides as Carbonic Anhydrase Inhibitors. *J. Am. Chem. Soc*., **72**, 4893 (1950).

[2] Hubner O., US 2 447 702, (1948); *Chem. Abstr*., 42, 41880 (1948).

[3] Kariyone K., H. Harada, M. Kurita, T. Takano, Cefazolin, a new semisynthetic cephalosporin antibiotic. I. Synthesis and chemical properties of cefazolin. *J. Antibiot*., **23**, 131 (1970).

[4] Russell A. D., D. T. Rogers, In vitro activity of cefazedone, a new cephalosporin antibiotic *J. Antimicrobial Chemotherapy*, **6**(2), 288–291 (1980).

[5] ChudzikI B., K. Bonio, W. DabrowskiI, D. PietrzakI, A. Niewiadomy, A. Olender, B. Pawlikowska-Pawlęga, M. Gagoś, Antifungal effects of a 1,3,4-thiadiazole derivative determined by cytochemical and vibrational spectroscopic studies, *PLoS ONE* **14**(9), 1-32 (2019).

[6] Chikkamath M. K., G. A. Hampannavar, M. B. Palkar, Design, synthesis, and biological evaluation of novel diclofenac analogs as promising anti-inflammatory agents, *Indian Journal of Health Sciences and Biomedical Research KLEU* **12**(1), 35-43 (2019).

[7] Serban G., Future Prospects in the Treatment of Parasitic Diseases: 2-Amino-1,3,4-Thiadiazoles in Leishmaniasis, *Molecules*, **24**(8), 1557 (2019).

[8] Taflan E. , H. Bayrak, M. Er , Ş.A. Karaoğlu , A. Bozdeveci, Novel imidazo[2,1-b][1,3,4]thiadiazole (ITD) hybrid compounds: Design, synthesis, efficient antibacterial activity and antioxidant effects, *Bioorganic Chemistry* **89**, 102998(2019).

[9] Altıntop M.D., Ö. D. Can, Ü. D. Özkay, Z. A. Kaplancıklı, Synthesis and Evaluation of New 1,3,4-Thiadiazole Derivatives as Antinociceptive Agents. *Molecules* **21**, 1004 (2016).

[10] Sarafroz M., Y. Khatoon, N. Ahmad, M. Amir, Salahuddin, F. H. Pottoo, Synthesis, Characterization and Anticonvulsant Activity of Novel Fused 1,2,4-Triazolo-1,3,4-Thiadiazoles. *Orient. J. Chem.*, **35**(1), 64-70 (2019).

[11] Hegab M. I., Morsy E. M. H., Abd El-Mageed A. E., Ali M. M., El-Senousy W.M, Tolan H. E. M., Gad F. A., and Abdel-Megeid F. M. E., Synthesis and characterization of new 3",5"-diaryl-3"H,4'H-dispiropyran/ thiopyran[4,2'-chroman-3',2"-[1,3,4-thiadiazol]-4'-one derivatives and related compounds as anticancer

and antiviral agents, *Phosphorus, Sulfur, Silicon and Related Elements* **190** (11), 1901-1911 (2015).

[12] Gür M., Synthesis, Characterization, and Antimicrobial Properties of New 1,3,4- Thiadiazoles Derived from Azo Dyes. *J. Heterocyclic Chem*., **56**, 980 (2019).

[13] Xue W., Ma W., Xu X., Li T., Zhou X., Wang P., Synthesis and properties of thiadiazole lubricant additives, *Industrial Lubrication and Tribology*, **69** (6) 891-896 (2017).

[14] Huang S., Ma C. , Li C., Min C., Du P., Xia Y., Yang C., Huang Q., Facile Synthesis, Characterization of Poly-2-mercapto-1,3,4-thiadiazole Nanoparticles for Rapid Removal of Mercury and Silver Ions from Aqueous Solutions. *Polymers*, **10**, 150 (2018).

[15] Hoggarth E., Compound related to thiosemicarbzide. Part II. 1-benzoylthiosemicarbzides. *J. Chem. Soc.*, 1163 (1949).

[16] Palaska E., Sahin G., Kelicen P., Durlu N. T., Altinok G., Synthesis and anti-inflammatory activity of 1-acylthiosemicarbazides, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazole-3-thiones. *IL Farmaco*, **57**, 101 (2002).

[17] Niu P., Kang J., Tian X., Song L., Liu H., Wu J., Yu W., Chang J., Synthesis of 2-amino-1,3,4-oxadiazoles and 2-amino-1,3,4-thiadiazoles via sequential condensation and I_2-mediated oxidative C−O/C−S bond formation. *J. Org. Chem.*, **80**, 1018 (2015).

[18] Kariyappa A. K., Gurunanjappa P., Design, synthesis and biological evaluation of 1,3,4-oxadiazoles/thiadiazoles bearing pyrazole scaffolds antimicrobial and antioxidant candidates. *Curr. Chem. Lett*., **5**, 109 (2016).

[19] Almandil N. B., Taha M., Gollapalli M., Rahim F., Ibrahim M., Mosaddik A., Anouar E., Indole bearing thiadiazole analogs: synthesis, β-glucuronidase inhibition and molecular docking study , *BMC Chem.* **13**, 14 (2019)

[20] Er M., Abounakhla A. Tahtaci M., H., Bawah A. H., Çınaroğlu S. S., Onaran A., Ece A., An integrated approach towards the development of novel antifungal agents containing thiadiazole: synthesis and a combined similarity search, homology modelling, molecular dynamics and molecular docking study , *Chem. Cent. J* ., **12**, 121 (2018).

[21] Ko I., Park S., Lee G., Kim H., An efficient one-pot synthesis of 2,5-disubstituted-1,3,4-thiadiazoles from aldehydes and hydrazides using Lawesson's reagent., *Arkivoc*, iii, 67-78 (2019).

[22] Papi D., Chakraborty A. T., De B., Saha A., Review on Chemistry and Therapeutic activity of the derivatives of Thiadiazole – the Sulphur containing Heterocycle, *Int. J. Pharm. Chem*., 0**9**(01), e5042 (2019).

[23] Kaur G., Singh R., Thiadiazole analogs as potential pharmacological agents: a brief review, *Int. J Pharm Pharm Sci*., **6**(8), 35-46 (2014).

[24] Shawali A. S., A review on bis-hydrazonoyl halides: Recent advances in their synthesis and their diverse synthetic applications leading to bis-heterocycles of biological interest, *Int. j. adv. res.*, **7**(6), 873-907 (2016).

[25] Kuo H. M., Li S. Y., Sheu H. S., Lai C. K., Symmetrical mesogenic 2,5-bis(6-naphthalen-2-yl)-1,3,4-thiadiazoles,*Tetrahedron* **68**, 7331-7337 (2012).

[26] Kaleta Z., Makowski B. T., Soós T., Dembinski R., Thionation Using Fluorous Lawesson's Reagent, *Org. Lett*., **8**(8), 1625-1628 (2006).

[27] El-Naggar M., Sallam H. A., Shaban S. S., Abdel-Wahab S. S., Amr A. E., Azab M. E., Nossier E. S., Al-Omar M. A., Design, Synthesis, and Molecular Docking Study of Novel Heterocycles Incorporating 1,3,4-Thiadiazole Moiety as Potential Antimicrobial and Anticancer Agents, *Molecules*, **24**, 1066 (2019).

[28] Hassan S. M., Emam H. A., Abdelall M. M., Heteroaromatization with ketene dithioacetals: Part I. Synthesis of some novel 5-amino-1-(1,3,4-thiadiazol-2- yl) and 1-(1,3,4-thiadiazin-2-yl)pyrazole-4-carbonitriles, *J. Chem. Research (S)*, 544–545 (2000).

[29] Cristina A., Leonte D., Vlase L., Bencze L. C., Imre S., Marc G., Apan B., Mogosan C., Zaharia V.; Synthesis, Characterization and Biological Evaluation of Imidazo[2,1-b][1,3,4]Thiadiazole Derivatives as Anti-Inflammatory Agents, *Molecules* **23**, 2425, (2018).

[30] Ujan R., Saeed A., Channar P. A., Larik F. A., Abbas Q., Alajmi M. F., El-Seedi H. R., Rind M. A., Hassan M., Raza H., Seo S.; Drug-1,3,4-Thiadiazole Conjugates as Novel Mixed-Type Inhibitors of Acetylcholinesterase: Synthesis, Molecular Docking, Pharmacokinetics, and ADMET Evaluation., *Molecules* **24**, 860 (2019).

[31] Sekhar D. C., Rao D. V. V., Rao A. T., Kumar U. L., Jha A.; Design and Synthesis of 1,3,4-Thiadiazole Derivatives as Novel Anticancer and Antitubercular Agents, *Russ. J. Gen. Chem*., **89**(4), 770–779 (2019).

[32] Ali A. A., Ragab E. A., Farghaly T. A., Abdalla M. M.; Synthesis of new functionalized 3-

subsitituted [1,2,4]triazolo[4,3-a]pyrimidine dreivatives: potential antihypertensive agents, *Acta Pol. Pharm.*, **68**(2), 237-247 (2011).

[33] Ding X., Zhai Z., Lv L., Sun Z., Liu X.; Design, synthesis, biological activity and density function theory study of pyrazole derivatives containing 1,3,4-thiadiazole moiety, *Front. Chem. Sci. Eng.*, **11**(3), 379–386 (2017).

[34] Kubota S., Koida Y., Kosaka T., Kirino O., Studies on the synthesis of 1,3,4-thiadiazoline-5-thiones from amidrazones and carbon disulfide. *Chem. Pharm. Bull*, **18**, 1696 (1970).

[35] Mazzone G., Puglisi G., Marchetta G., Corsaro A., 2- pyridyl- 5- alkyloxyphenyl- 1,3,4- thiadiaz oles by the action of sulfur on methylpyridines in the presence of alkyloxybenzoylhydrazines. *J. Heterocycl. Chem.*, **21**, 181 (1984).

[36] Hagen H., Kohler R., Fleig H., Synthese und Urnwandlungen neuer 1,3,4-Thiadiazole, Liebigs Ann. Chem., 1216 (1980).

[37] Mazzone G., Puglisi G., Bonina F., Corsaro A., A new synthesis of symmetrical 2,5- diaryl- 1,3,4- thiadiazoles. *J. Heterocycl. Chem.*, **20**, 1399 (1983).

[38] Asif M., Abida A., mini review on thiadiazole compounds and their pharmacological interest, *Int. J. Pharm. Chem. Anal.*, **5**(4), 156-164 (2018).

[39] Altıntop M. D., Can Ö. D., Özkay Ü. D., Kaplancıkl Z. A., Synthesis and Evaluation of New 1,3,4-Thiadiazole Derivatives as Antinociceptive Agents. *Molecules*, **21**, 1-10 (2016).

[40] Bai S., Zhu Y., Wu Q., Asymmetric Mannich Reaction: Synthesis of Novel Chiral 5-(substituted aryl)-1,3,4-Thiadiazole Derivatives with Anti-Plant-Virus Potency. *Heterocycl. Commun*. **25**, 47–51 (2019).

[41] Jakovljevic´K., Matic´I. Z., Stanojkovic´T., Krivokuc´A., Markovic´V., Joksovic´M. D., Mihailovic´N., Nic´iforovic´ M., Joksovic L.; Synthesis, antioxidant and antiproliferative activities of 1,3,4-thiadiazoles derived from phenolic acids. *Bioorg. Med. Chem. Lett*., **27**, 3709–3715 (2017).

[42] Tahtaci H., Karacık H., Ece A., Er M., Seker M G., Design, Synthesis, SAR and Molecular Modeling Studies of Novel Imidazo[2,1-b][1,3,4]Thiadiazole Derivatives as Highly Potent Antimicrobial Agents. *Mol. Inf.*, **37**, 1-14 (2018).

[43] Abo-Bakr A. M., Hashem H. E., New 1,3,4-Thiadiazole Derivatives: Synthesis, Characterization, and Antimicrobial Activity:; *J. Heterocyclic Chem*., **56**, 1038 (2019).

[44] Yan J., Si W., Hu H., Zhao X., Chen M., Wang X.; Design, synthesis and antimicrobial activities of novel 1,3,5-thiadiazine-2-thione derivatives containing 1,3,4-thiadiazole group. *Peer J*, 1-18 (2019).

[45] Lin L., Liu H., Wang D., Hu Y., Wei X., Synthesis and biological activities of 3,6-disubstituted-1,2,4- triazolo-1,3,4-thiadiazole derivatives : *Bull. Chem. Soc. Ethiop*., **31**(3), 481-489 (2017).

[46] Redayan M. A., Ali W. B., Mohammed A. M.; Synthesis, Characterization and Antibacterial Evaluation of some Novel Benzimidazole Derivatives Containing 1,3,4-thiadiazole moiety :*Orient. J. Chem*., Vol. **33**(6), 3138-3143 (2017).

[47] Sych I., Perekhoda L., Tsapko T.; Synthesis of 5-substituted 1,3,4-thiadiazol-2-ylsulfanylacetic acid derivatives. *Scr. Sci. Pharm.*, **2**(2) 53-59 (2015**)**.

[48] Kasımoğulları R., Bülbü M., Arslan B. S., Gökçe B; Synthesis, characterization and antiglaucoma activity of some novel pyrazole derivatives of 5-amino-1,3,4-thiadiazole-2-sulfonamide. *Eur. J. Med. Chem*. **45**, 4769e4773 (2010).

[49] Mahapatra D. K., Shivhare R. S., Haldar A. G. M.; Novel Schiff's Base Containing Murrayanine1,3,4-Thiadiazole Hybrids as Potential Anti-Inflammatory Agents: *Asian J. Chem. Pharm. Sci*., **2**(2), 27-32 (2017).

[50] Ahmed A. J., Pharmacological activity of 1,3,4-thiadiazole derivatives and its complexes; *Int. Res. J. Pharm*., **9**(10), 1-9 (2018).

[51] Amir M., Akhter M. W., Haq S. E.; Synthesis of some new condensed heterocyclic 6-substituted-1,2,4-triazol[3,4-b]-1,3,4-thiadiazole derivatives of 2-naphthoxyacetic acid as potent anti-inflammatory agents with reduced ulcerogenicity. *Indian J. Chem.* **56B**, 1177-1184 (2017).

[52] Kumari R., Sharma B. B., Dubey V.; Synthesis and biological activity of 1,3,4-thiadiazole derivatives. *World J Pharm Pharm Sci*., **6**(12), 1310-1317 (2017).

[53] Guptha S. K., Sharma P. K.; Synthesis and anti-inflammatory activity of disubstituted 1,3,4-thiadiazole. *Int J Drug Formulation Res*., **2**(2), 344-350 (2011).

[54] Hassan F., Hairunisa N., Mohammed S. A., Yousif E.; A Study on Antitumor Effect of 1,3,4-Thiadiazole Derivatives in Prostate and Breast Cancer Cell Lines (*In Vitro*), *Preprints*, 2017030053 (2017) (doi:10.20944/preprints201703.0053.v1).

[55] Gomha S. M., Kheder N. A., Abdelhamid A. O., Mabkhot Y. N.; One Pot Single Step Synthesis

and Biological Evaluation of Some Novel Bis(1,3,4-thiadiazole) Derivatives as Potential Cytotoxic Agents, *Molecules*, **21**, 1-8 (2016).

[56] Chen Z., Xu W., Liu K., Yang S., Fan H., Bhadury P. S., Hu D., Zhang Y.; Synthesis and Antiviral Activity of 5-(4-Chlorophenyl)-1,3,4-Thiadiazole Sulfonamides: *Molecules*, **15**, 9046-9056 (2010).

[57] Zhong X., Wang X., Chen L., Ruan X., Li Q., Zhang J., Chen Z., Xue W.; Synthesis and biological activity of myricetin derivatives containing 1,3,4-thiadiazole scaffold: *Chem. Cent. J.*, **106**, 1-9 (2017).

[58] Fascio M. L., Sepúlved C. S., E. Damonte B., D'Accorso N. B.; Synthesis and antiviral activity of some imidazo[1,2-b][1,3,4]thiadiazole carbohydrate derivatives, *Carbohydr. Res.*, **480**, 61–66 (2019).

[59] Singh V. K., Bharadwaj P., Rishishwar P., Synthesis and Anxiolytic Activity of 2-(Substituted)-5-[(N-Benzotriazolomethyl)-1,3‹4-Thiadiazolyl]-4-Thiazolidinone: *Drug Designing & Intellectual Properties International Journal*, 16-21 (2018).

[60] Jatav V., Mishra P., Kashaw S., Stables J. P., Synthesis and CNS depressant activity of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones, *Eur. J. Med. Chem.* **43**, 135-141 (2008).

[61] Lv M., Liu G., Ji M., Xu H., Synthesis of matrinic amide derivatives containing 1,3,4-thiadiazole scaffold as insecticidal/acaricidal agents, *Bioorg. Chem*., **81**, 88–92 (2018).

[62] Fadda A. A., Abd El Salam M., Tawfik E. H., Anwar E. M., Etman H. A., Synthesis and insecticidal assessment of some innovative heterocycles incorporating a thiadiazole moiety against the cotton leafworm, Spodoptera littorali, *RSC Adv.*, **7**, 39773–39785 (2017).

[63] Wan R., Zhang J., Han F., Wang P., Yu P., He Q., Synthesis and Insecticidal Activities of Novel 1,3,4-Thiadiazole 5-Fluorouracil Acetamides Derivatives: An RNA Interference Insecticide, *Nucleosides, Nucleotides and Nucleic Acids*, **30**, 280–292 (2011).

[64] Joshi S. D., More U. A, Koli D., Kulkarni MS, Nadagouda MN and Aminabhavi TM, Synthesis, evaluation and in silico molecular modeling of pyrroyl-1,3,4-thiadiazole inhibitors of InhA, *Bioorg. Chem.*, **59**, 151–167 (2015).

[65] Ramzan M., Janjua S. A., Quantum chemical designing of triphenylamine dyes with D-A-II-A configuration for dye sensitized solar cells: molecular engineering through first-principles calculations, *J. Chil. Chem. Soc*., **63**(1), 3850-3854 (2018).

[66] Karthikeyan S., Bharanidharan G., Mani K. A., Srinivasan N, Kesherwani M, Velmurugan D, Aruna P and Ganesan S, Determination on the binding of thiadiazole derivative to human serum albumin: a spectroscopy and computational approach, *J. Biomol. Struct. Dyn.*, **35**(4), 817–828 (2017).

[67] Toma A., Hapa D., Casoni D., Zaharia V., Heterocycles 33: Lipophilicity of a New Class of Thioethers Estimated by Reversed-Phase Thin-Layer Chromatography and Different Computational Methods, *J. Chromatogr. Sci.*, **52**, 1302–1307 (2014).

[68] Wazzan N. A., Obot I. B., Kaya S., Theoretical modeling and molecular level insights into the corrosion inhibition activity of 2-amino-1,3,4-thiadiazole and its 5-alkyl derivatives, *J. Mol. Liq*., **221**, 579–602 (2016).

[69] Shaaban I. A., Hassan A. E., Abuelela A. M., Zoghaieb W. M., Mohamed T. A., Infrared, Raman and NMR spectral analysis, vibrational assignments, normal coordinate analysis, and quantum mechanical calculations of 2-amino-5-ethyl-1,3,4-thiadiazole, *J. Mol. Struct*., 1103, 70-81 (2016).

[70] Er M., Isildak G., Tahtaci H., Karakurt T., Novel 2-amino-1,3,4-thiadiazoles and their acyl derivatives: Synthesis, structural characterization, molecular docking studies and comparison of experimental and computational results, *J. Mol. Struct*., **1110**, 102-113 (2016).

[71] Erdogan T., Ultrasound-assisted improved synthesis of 5-(benzylthio)-1,3,4-thiadiazol-2-amine derivatives: an experimental and computational study, *J. Iran. Chem. Soc*., **16**, 899–912 (2019).

[72] Karthikeyan S., Bharanidharan G., Mangaiyarkarasi R., Chinnathambi S., Sriram R., Gunasekaran K., Saravanan K., Gopikrishnan M., Aruna P., Ganesan S, A cytotoxicity, optical spectroscopy and computational binding analysis of 4- [3- acetyl- 5- (acetylamino)- 2- methyl- 2, 3- dihydro- 1,3,4-thiadiazole- 2- yl]phenyl benzoate in calf thymus DNA, *Luminescence*, **33**, 731–741 (2018).

[73] Wang H., Bai F., Liu H., Bai B., Ran X., Qu S., Shi J., Xie D., Li H., Li M., Zhang H., Experimental and theoretical study on molecular aggregation and its effect on the photo-physical properties of the mesogenic bi-1,3,4-thiadiazole derivative, *Phys. Chem. Chem. Phys*., **13**, 9697–9705 (2011).