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# 1,3,4-Thiadiazoles: Aryl, Heteroaryl and Glycosyl Hybrids Synthesis and Related Bioactivities

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***Abstract***

Developing novel therapeutics in different medicinal fields is ongoing need for control of various threats and disease. 1,3,4-Thiadiazole nucleus is a versatile scaffold in medicinal chemistry which could be located as separate ring, fused ring or newly emerged glycoside. Here, a look on some different preparation routes, biological activities of thiadiazole containing compounds and insights on the ring role from structure activity relationship view. Also, a view on newly emerged thiadiazole glycosides as strategy for enhancement activity of aglycan part of the target compound.

***Key Words:***

1,3,4-Thiadiazole, synthesis, hybrids, glycosides, bioactivity, inhibition, interaction modes.

## 1. Introduction

Heterocyclic compounds exhibit a wide range of biological activity, among them thiadiazoles are extensively studied due to, ability for hydrogen bonding via electron donor atoms, producing mesoionic salts, and play as bioisostere of vital natural compounds as pyrimidine and pyridazine [1-3].

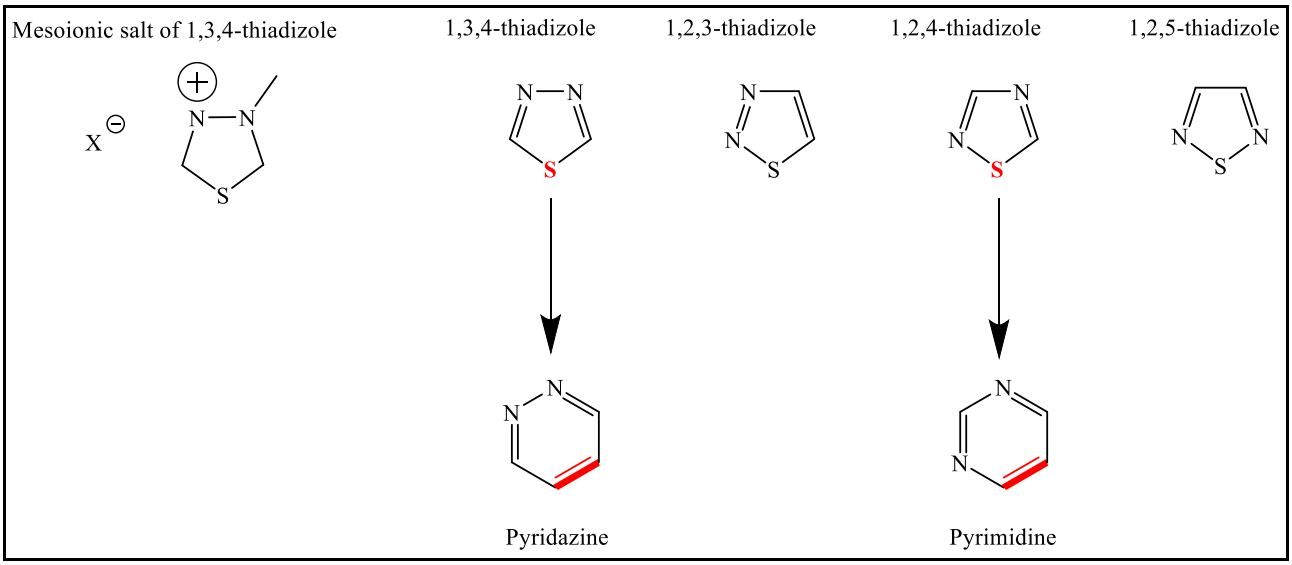



***Figure 1, Thiadiazole isomers***

- Different isomers of thiadiazole ring.
- Bioisostere of pyrimidine and pyridazine with corresponding thiadiazole ring by substitution of bold double bond carbon with sulfur atom.

1,3,4-Thiadiazoles showed intensive interest due to their wide spectrum of bioactivities as reported in recent literature, antimicrobial [1], antiviral [4], anti-tuberculosis [5], anti-inflammatory [6], hypnotic [7], DNA binding [8], structure modification [9] and antitumor [10].

1,3,4-Thiadiazole based drugs like acetazolamide, methazolamide are Carbonic anhydrase inhibitors and used as diuretics, also as anti-glaucoma drugs [11]. Other drugs like Sulfamethizole and Cefazolin used as antibiotics where Megazol used in the treatment of human African

trypanosomiasis [5]. One the other hand, Imidazothiadiazole used as anticancer drug [12], Desaglybuzole anti-diabetic [8] and thiazfluron, Tebuthiuron as herbicides.

In the following, a review of some newly reported 1,3,4-thiadiazole synthesis methods, bioactivity of non-glycoside 1,3,4-thiadiazole hybrid compounds and their interaction mode via thiadiazole ring with target active site as showed by docking studies. In addition, another view on glycosides of 1,3,4-thiadiazole hybrid compounds as new emerged strategy in enhancement of bioactivity.

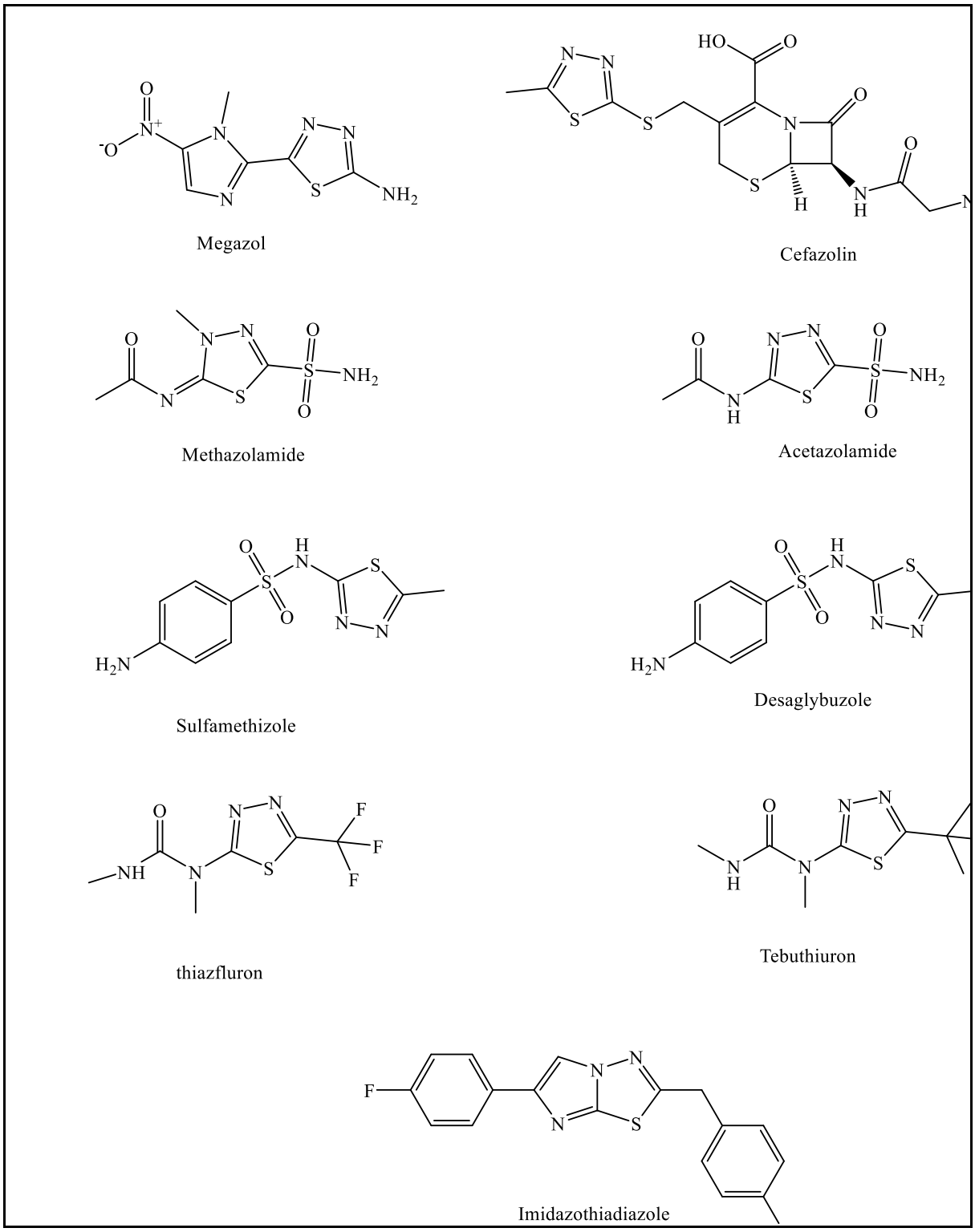



***Figure 2, Some 1,3,4-Thiadiazoles used derivatives***

## 2. Synthesis of 1,3,4-Thiadiazole

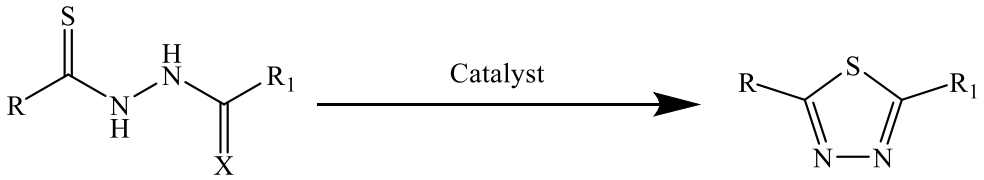
1,3,4-Thiadiazoles can be prepared by common two routes, cyclization of open chain precursors or transformation from other ring like 1,3,4-oxadiazole or 1,2,4-triazole.

Herein, a summarized strategies of 1,3,4-thiadiazole preparation as outlined [13] and other recent strategies.

### 2.1.1. Synthesis from acyclic components

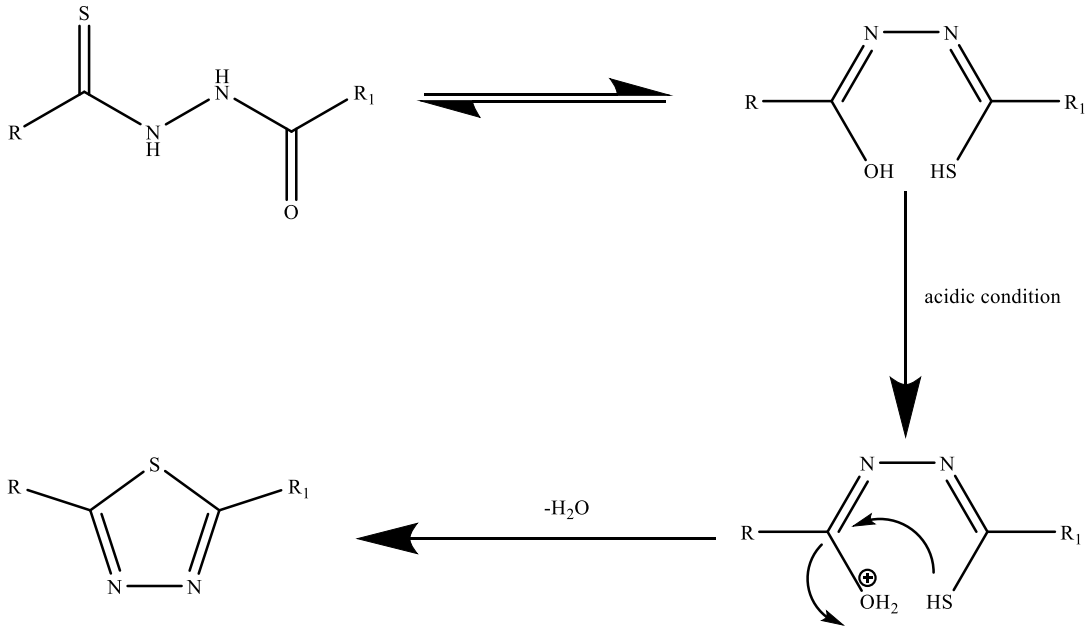
#### 2.1.1.1. Formation of one bond

S-C-N-N-C fragments can be prepared by various routes and induced to cyclization to 1,3,4-thiadiazoles upon application of appropriate catalyst.



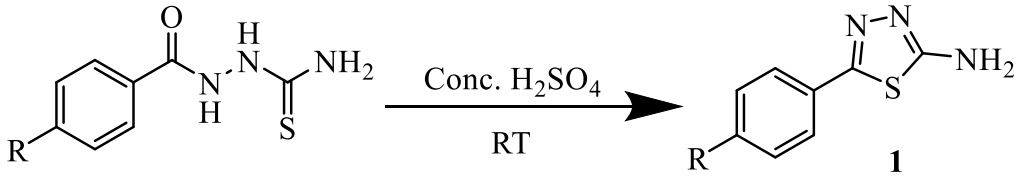

X= O, S, or N

For example, catalysis by acidic condition lead to cyclization of ring by dehydration via the following proposed mechanism.

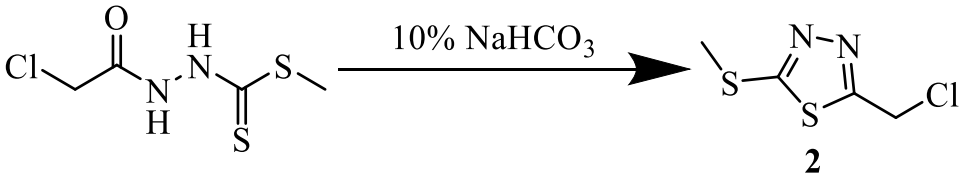



**Monothiodiacylhydrazine** (X=O) can be cyclized under induction of acidic or basic condition, it can be synthesized then isolated and treated with catalyst as reported in the following routes,

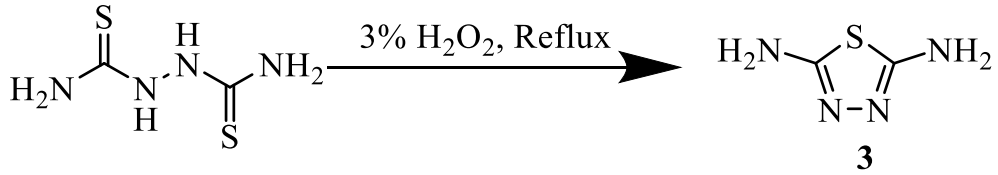
1. Acylation of thiosemicarbazide followed by treatment with concentrated acid give compound **1** as reported [5]




2. Aside from using above catalytic acid condition [14] used basic condition as catalyst for cyclization of S-C-N-N-C fragment to give compound **2**.

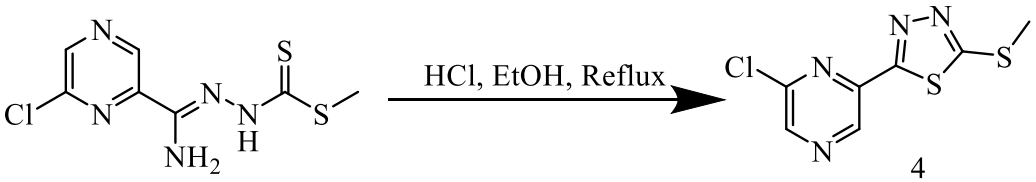


- **Dithiodiacylhydrazine** (X=S) can be prepared by reaction of hydrazine or thiosemicarbazide derivatives with isothiocyanates, which induced to cyclization by oxidation as reported [15] that give symmetrical substituted ring **3**.



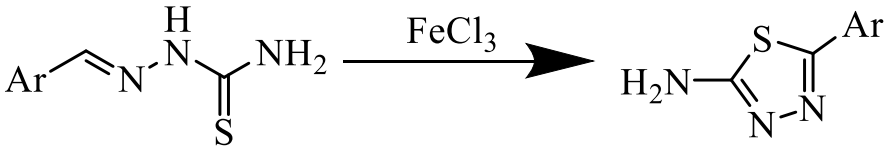

**3**

- **Thioacylhydrazone** (X=N, **Amidrazone**) resulted from reaction of thiohydrazides with nitrile, and can be cyclized either under oxidation condition by bromine [16], or cyclization induced in acidic condition as mentioned [17] to give derivative **4**.




4

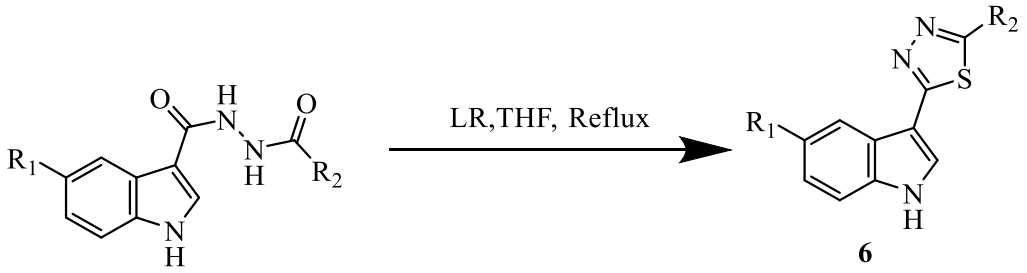
Another approach of thioacylhydrazone via schiff base intermediate resulted from reaction of thiohydrazides and aldehyde, Metal oxidant as ferric chloride used as catalyst for cyclization as reported [7] that give compound **5**.




5

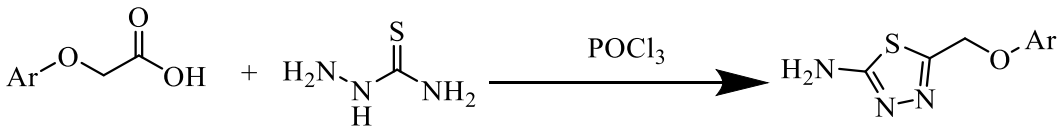
### 2.1.1.2. Formation of two bonds

- **Diacylhydrazines,** C-N-N-C fragment react with a sulfur source give rise to thionation of carbonyl, then loss of $H_2S$ [18]. Lawesson's reagent used as sulfur source [16,19] lead to 1,3,4-thiadiazoles **6** via oxidative cyclization in dry THF.



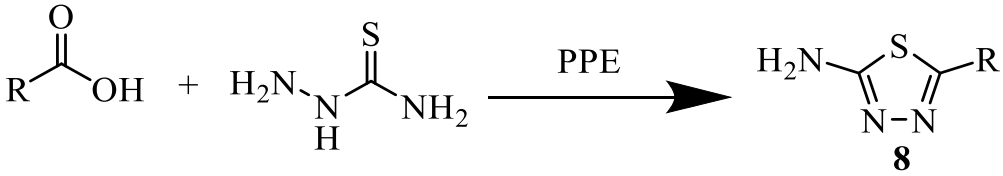

**6**

- **Thiohydrazides**, S-C-N-N fragment reacts with carboxylic acid or their derivatives as carbon source in the presence of dehydrating agent [20] used $POCl_3$ for condensation of thiosemicarbazide with derivatives of acetic acid to give amino substituted ring **7**.



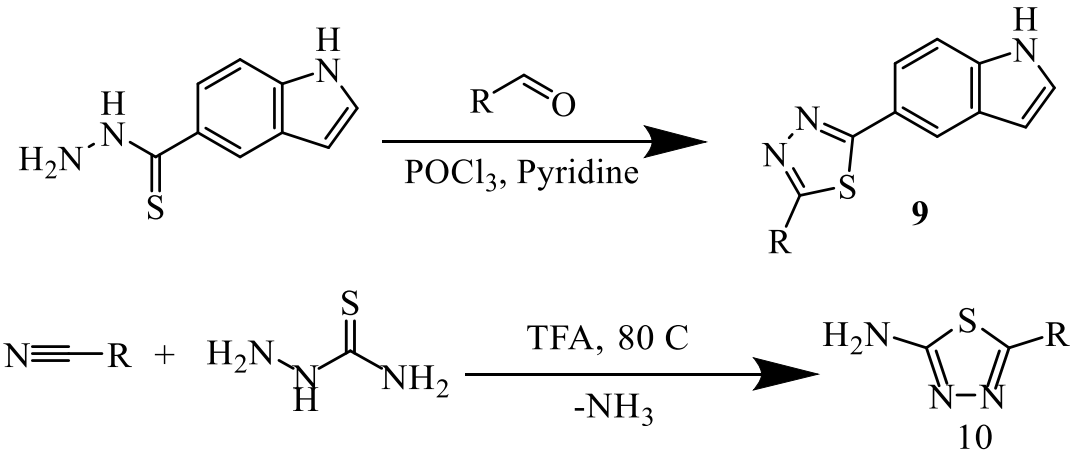

**7**

Further improvement in coupling of carboxylic acid with thiosemicarbazide was reported [21] who use polyphosphate ester (PPE) as dehydrating agent which is less toxic than $POCl_3$ to give product **8**.

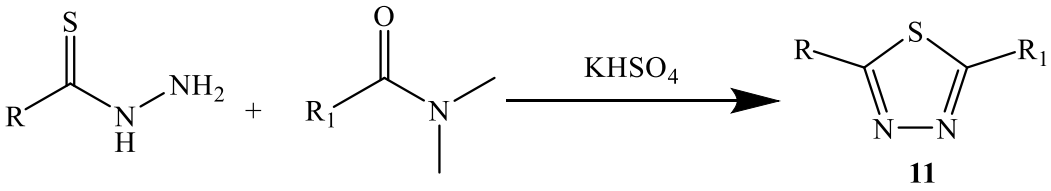



**8**

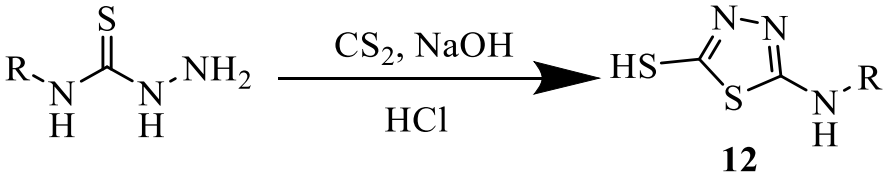
Other carboxylic acid derivatives as aldehyde was used [22] to give product **9**, while nitrile used [23] to give compound **10**.




Using a different catalytic approach, [24] used $KHSO_4$ as both transamidation and dehydrating agent for cyclization of thiohydrazides and (DMF) derivatives to give product **11** using S-C-N-N-C fragment as proposed intermediate.




Thiohydrazides react with $CS_2$ under basic condition and reflux to induce cyclization as reported [25] to give peripheral SH **12**.

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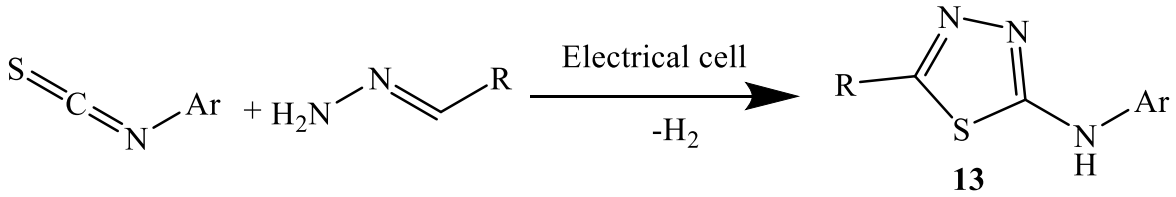
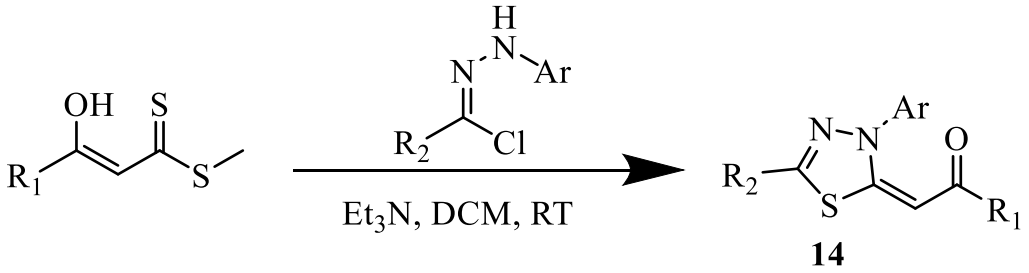
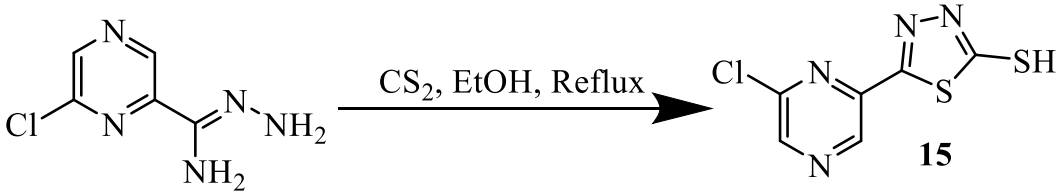
- **Hydrazone,** Hydrazone (N-N-C) react with isothiocyanates (S-C) under mild oxidizing environment lead to electrochemical synthesis of product **13** as reported [26].




Condensation of α-enolic dithioesters as sulfur-containing block with active 1,3-dipole imine generated access to 1,3,4-thiadiazoles **14** under mild conditions [27].

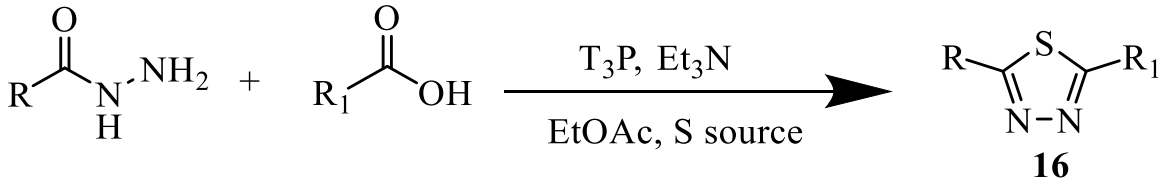



- 
- **Amidrazone,** Amidrazone (N-N-C) reacts with $CS_2$ (S-C) to give intermediate that can be induced to cyclization to give **15** as reported [17,18].
- 




### 2.1.1.3. Formation of three bonds

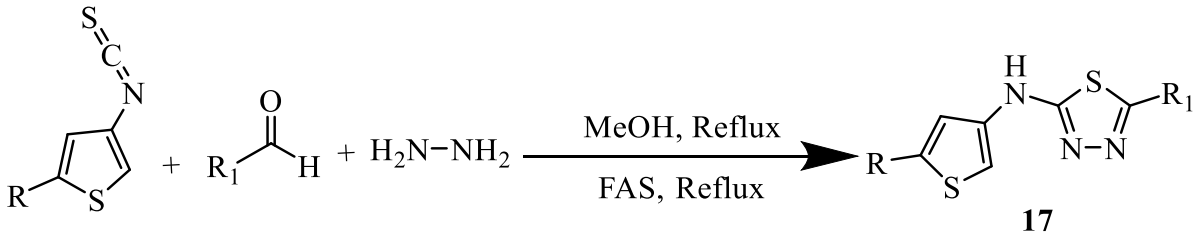
Hydrazide (C-N-N) reacts with carboxylic acid as carbon source and a source of sulfur using $T_3P$ - propylphosphonic anhydride- as dehydration and coupling agent, which lead to 1,3,4-thiadiazole **16** [28].




**16**

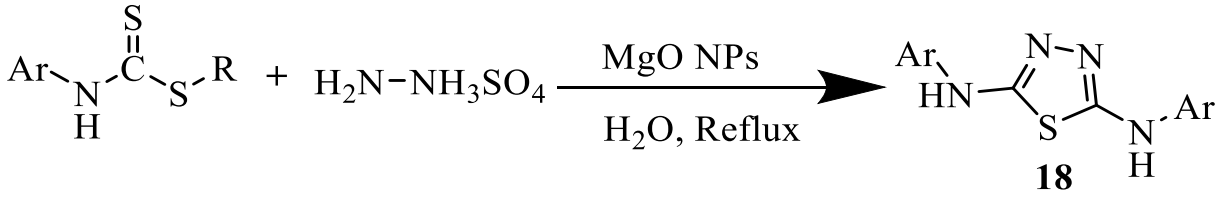
Hydrazine hydrate (N-N) reacts with (C-S) in aromatic isothiocyanates and aromatic aldehydes C to give 1,3,4 Thiadiazole. The reaction is proceed by using ionic liquid BF4 (1-butyl-3-methylimidazolium tetrafluoroborate), as both solvent and Brønsted acid catalyst [29].

Another catalysis approach [30,31] avoiding use of ionic liquid and using ferric ammonium sulfate (FAS) in methanol for getting expected thiadiazole ring **17**.




**17**

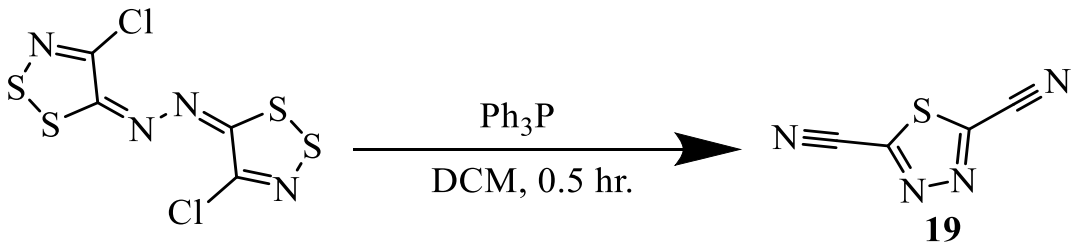
A green route for the synthesis of symmetrical 1,3,4-thiadiazoles derivatives **18** introduced [32] via reaction of 2 moles of dithiocarbamate (C-S) and hydrazine sulfate (N-N) in presence of magnesium oxide nanoparticles as basic catalysts.




**18**

### 2.1.2. Synthesis of Thiadiazoles by Transformation

Ring transformation from is another synthetic routes for preparation of thiadiazoles, analogues as 1,3,4-Oxadiazoles can be transformed to 1,3,4-thiadiazoles after treatment with sulfur source as $PS_5$ or thiourea. Other analogues as bis-1,2,3-dithiazoles when treatment with triphenylphosphine bounded polymer give product **19** [33].



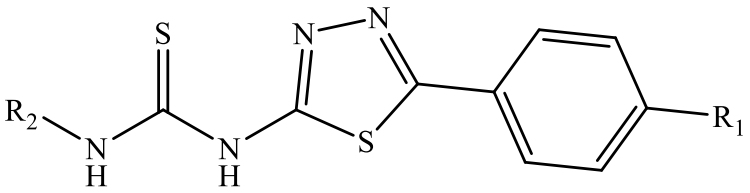

**19**

## 3. Biological Activity of 1,3,4-Thiadiazole

### 3.1.1. Non-Glycoside Based Compounds

#### 3.1.1.1. Antimicrobial

Design and synthesis of novel compounds that contain thiourea beside 1,3,4-thiadiazole were reported [5], three of them give a good activity against *Mycobacterium tuberculosis*. Derivatives **20, 21** and **22** showed the highest activity with MIC value 10.96, 17.81 and 11.48 $\mu$M respectively. Docking studies give good docking scores with (InhA) protein reductase, Only compound **21** showed interaction with Tyr158 via H bond with 3$^{rd}$ N atom of 1,3,4-thiadiazole.



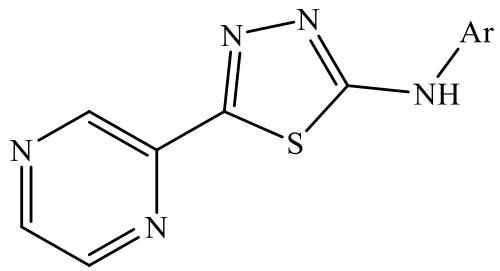

**20;** $R_1$ = Cl $R_2$ = 4-Fluorophenyl

**21;** $R_1$ = Cl $R_2$ = 4-Cl-3-(trifluoromethyl) phenyl

**22;** $R_1$ = F $R_2$ = 4-Fluorophenyl

New 1,3,4-thiadiazole-Pyrazine derivatives were prepared [34], their antimicrobial activity were tested against *Candida albicans*, *Staphylococcus aureus*, and *Escherichia coli*. Compounds showed activity against *Staphylococcus aureus* and *Candida albicans*, but not active against *Escherichia coli*.

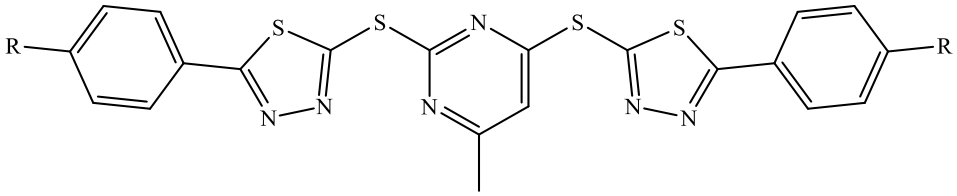
Compound **23** has highest activity against *Candida albicans*, where compound **24** exhibited the highest activity against *Staphylococcus aureus*.




**23;** Ar = benzyl

**24;** Ar = 2- methylphenyl

A new class of 1,3,4-thiadiazoles pyrimidine derivatives were prepared [35] using conventional and ultrasound irradiation methods. Key compounds were tested as antibacterial candidates, compounds **25** and **26** showed promising activity against *P. aeruginosa* with MIC 6.25 µg/well.

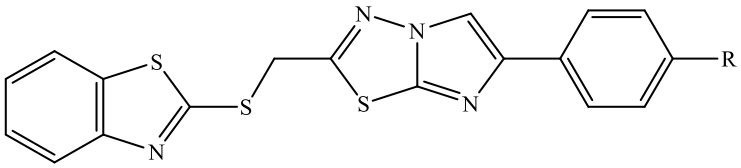



**25;** R = Cl

**26;** R = $NO_2$

Anti-leishmanial and antibacterial activity of the compounds studied [36] were reported. Compound **27** was highly effective against *Escherichia coli* with MIC 625 µg/mL, where compound **28** showed the highest anti-leishmanial activity with MIC 10 000 µg/mL.

Docking results showed that compound **27** could be a potential inhibitor for *Escherichia coli* 2eg7 protein, the compound mainly interact via weak non-covalent interactions as H bond and alkyl interactions.



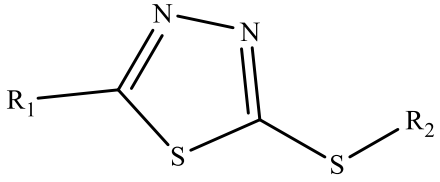
**27;** R = Cl

**28;** R = Br

A series of sulfanyl-1,3,4-thiadiazole derivatives were prepared [37]. Derivatives were evaluated against two pathogenic *Rhizoctonia bataticola* and *Rhizoctonia solani* and results revealed their fungicidal potency.

Compound **29** was the most potent against tested fungi with $ED_{50}$ values 3.9 and 4.2 µg/mL respectively.

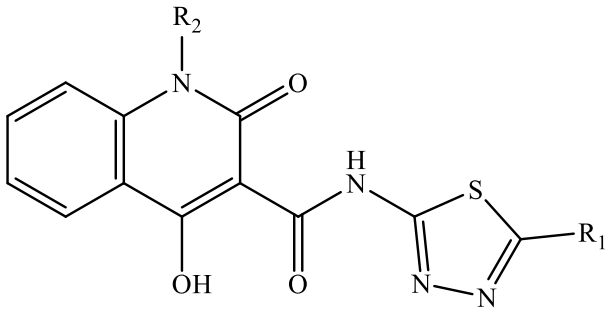
Potency of compound **29** improved after being nano-sized and fungicidal activity of nano-forms were $ED_{50}$ values 2.27 and 3.83 µg/mL respectively compared with previous conventional sized.



**29;** R = $NH_2$, $R_2$ = n-$C_6H_{13}$

A series of N-thiadiazole-quinolone derivatives synthesized [23], then evaluated against *S. aureus* including MRSA. Compound **30** showed potent inhibition against target strains with MIC range 0.25-1 µg/mL compared with vancomycin 1-64 µg/mL as reference drug.

*S. aureus* DNA gyrase B identified as potential target by molecular docking which revealed that thiadiazole might interact with 3 amino acid residues via conserved water molecule Also, it forms both hydrophobic and electrostatic interaction with Ile86 and Glu58 respectively.



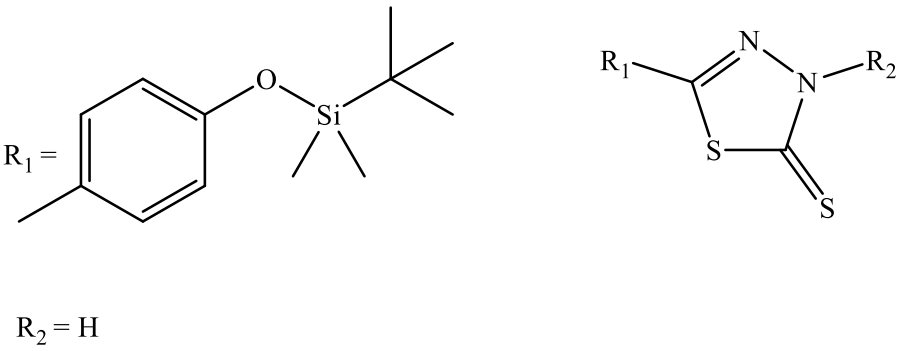

**30;** $R_1$ = thiazol-2-yl, $R_2$ = ethyl

### 3.1.1.2. Enzyme Inhibitors

Inhibition activities of new series of 1,3,4-thiadiazole-2-thiones were studied [38] against both snake and human NPP1 enzyme.

Compound **31** was the most active compound with $IC_{50}$ = 66.47 µM against the snake enzyme and inhibition was of pure non-competitive type.

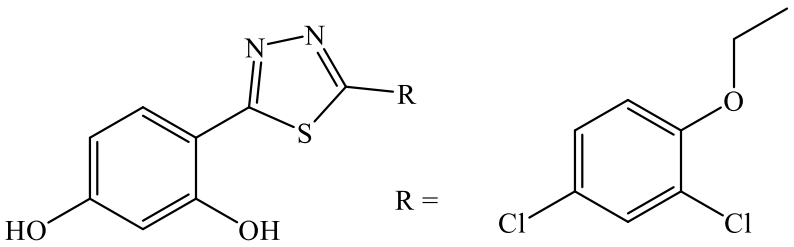
SAR study found that S in the ring play important role activity compared with compound **31** analogue (oxadiazole ring) has $IC_{50}$ =383 µM.




$R_2$ = H

**31**

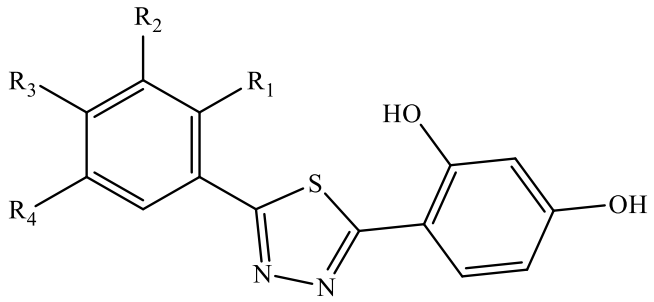
The synthesis of novel 1,3,4-thiadiazole-Resorcinol based derivatives were reported [39], anticholinesterases activity have been investigated and most of them showed (AChE) and (BuChE) inhibition. The most potent compound **32** with $IC_{50}$ = 0.053 µM was also selective toward AChE versus BuChE.




**32**

A new derivatives of 1,3,4-thiadiazole containing Resorcinol has been designed, synthesized [39], their potential inhibition of AChE and BuChE was investigated. Compounds **33** and **34** are the most potent against AChE with $IC_{50}$ 0.06 and 0.09 µM respectively.

Docking study showed mainly bounding with the AChE catalytic active site that create many interactions as π-π tacking interactions.

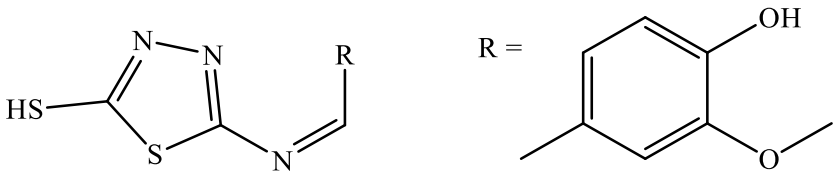



**33;** $R_1$ = Br, $R_2$ = $R_3$ = $R_4$ = H

**34;** $R_1$ = $R_2$ = $R_4$ = H, $R_3$ = $CF_3$

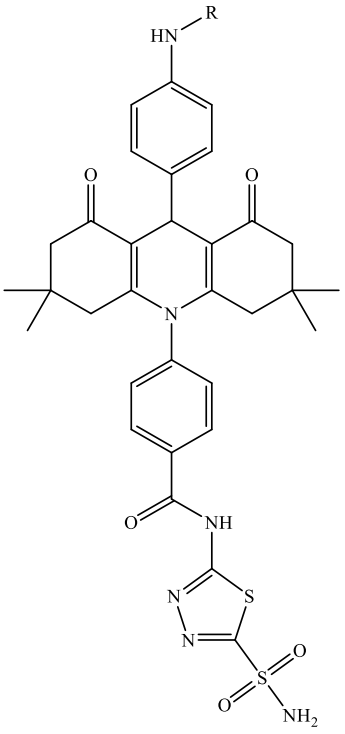
New derivatives of 1,3,4-Thiadiazole linked to Schiff base were designed, synthesized [40], and further evaluated as tyrosinase inhibitors.

Compound **35** exhibited superior inhibitory effect among derivatives with $IC_{50}$ 0.036 µM, compound **35** docking studies declared its strong affinity to bind with mushroom tyrosinase, also formation of pi-Lone pair interaction between GLY281 residue and thiadiazole ring.

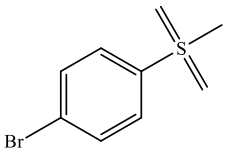



**35**

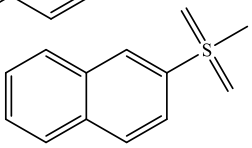
Synthesis of new compounds contain acridine, sulfonamide and thiadiazole moieties were report [41], in vitro evaluation of compounds against hCA I, II, IV and VII showed that some derivatives are a potent inhibitors. Compound **36** was the most active against hCAVII with a $K_i$ of 2.5 nM and compound **37** had highest potency against hCA II with a $K_i$ of 7.9 nM.




**36; R =**

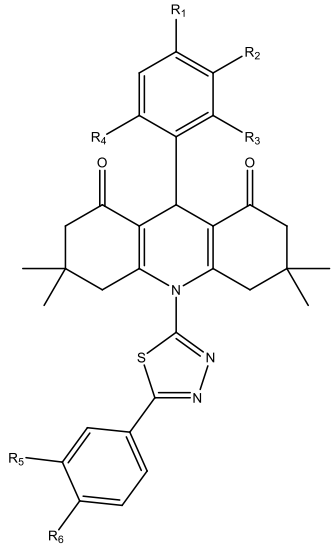



**37; R =**




Synthesis of novel acridine-thiadiazole derivatives were reported [42], anticholinesterase (AChE & BuChE) evaluation of derivatives showed their inhibiting of both enzymes with higher selectivity towards AChE.

Compounds **38** and **39** with $IC_{50}$ 0.006 and 0.002 μM respectively have potent inhibition against AChE compared with tacrine as reference compound ($IC_{50}$ = 0.016 μM).

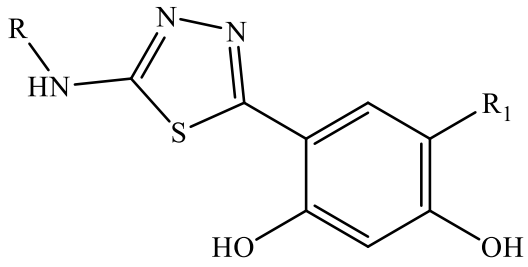



**38;** $R_1 = R_4 = R_6 = Cl$, $R_2 = R_3 = R_5 = H$

**39;** $R_1 = R_6 = NO_2$, $R_2 = R_3 = R_4 = R_5 = H$

A novel 1,3,4-thiadiazole-resorcinol based derivatives were prepared [43] and tested as cholinesterase inhibitors. Derivatives **40** and **41** showed highest anti-AChE activity with $IC_{50}$ 0.031 & 0.029 μM respectively.

SAR relieved that thiadiazole ring linked with –NH– is more potent than analogues without it, docking studies showed a great affinity for enzyme and thiadiazole ring involved in π-π stacking interactions with Phe330 residue.



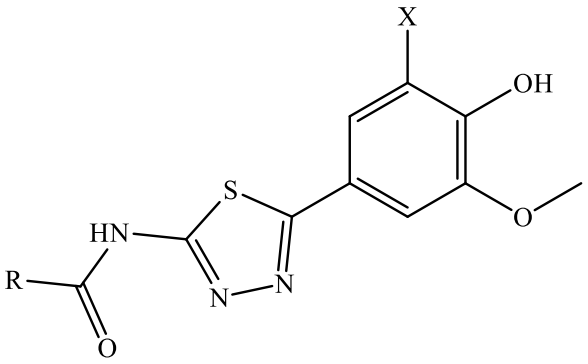

**40;** R = 2-Cl-$C_6H_4$-, $R_1$ = Et

**41;** R = $C_4H_9$-, $R_1$ = H

### 3.1.1.3. Anti-inflammatory

1,3,4-Thiadiazole ring was incorporated [44] as a method to get capsaicin analogues through the synthesis of new thiadiazole alkyl amide derivatives, then evaluated on HEK-293T cells that express (TRPV1) receptor.

Compounds **42** and **43** were the most potent against capsaicin receptor with values 0.18 & 0.15 nM respectively. Structural studies showed that potency of derivatives might be related to conformation and polarity resulting from thiadiazole incorporation in region B of capsaicin analogues.

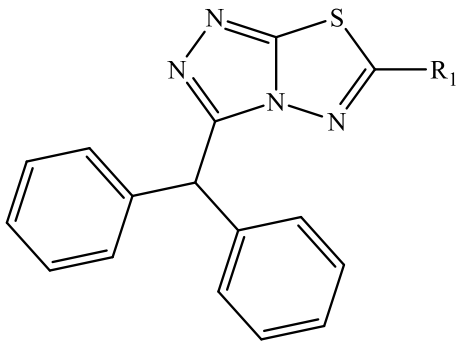



**42;** R = - $(CH_2)_7$-$CH_3$, X = H

**43;** R = - $(CH_2)_6$-$CH_3$, X = H

A series of thiadiazole fused triazol derivatives were synthesized [45]. Anti-inflammatory and other activities as analgesic, ulcerogenic and lipid peroxidation were assigned in vivo for these derivatives.

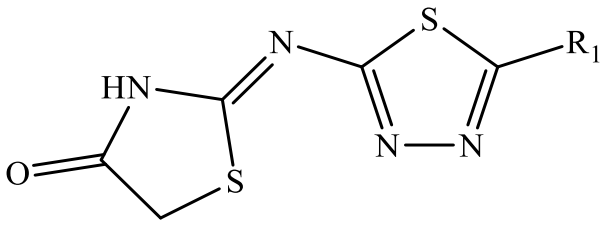
Compounds **44** and **45** were the most active compounds with minimum toxicity.




**44;** $R_1$ = 4-Cl-$C_6H_4$

**45;** $R_1$ = 2,4-$(Cl)_2$-$C_6H_3$

Biological evaluation of new thiazolidin-thiadiazole based derivatives were reported [6] the as dual inhibitors of 15-LOX/COX. Compound **46, 47** has the higher activity among derivatives against 15- LOX with $IC_{50}$ 2.74 & 2.54 μM and against COX-1 with $IC_{50}$ 3.87 & 3.98 μM respectively, while compound **48** showed the highest activity against COX-2 with $IC_{50}$ 0.19 μM.



**46;** $R_1 = CH_3$

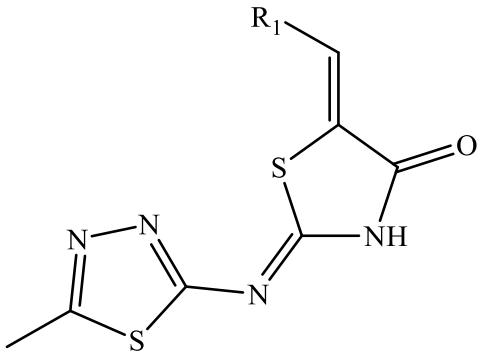
**47;** $R_1 = C_6H_5$

**48;** $R_1 = 3,4,5\text{-}(CH_3O)_3\text{-}C_6H_2$

The results showed the sensitivity of $R_1$ group for binding as 15-LOX enzyme favor small ones, while COXs enzymes favor bulk groups.

Further optimization of compounds **46** give other derivatives by various substitutions on 5$^{th}$ position of thiazolidin ring, from which derivatives **49** inhibits activity of 15-LOX at 3.11 μM, compound **50** inhibit activity of COX-1 at 4.52 μM, and **51** against COX-2 at 0.1 μM.

Docking study explores both pi-hydrogen and hydrogen bond ability of thiadiazole ring as mode of interaction with COX-2.



**49;** $R_1 = 4\text{-}CH_3\text{-}C_6H_5$

**50;** $R_1 = C_6H_{11}$ cyclohexyl

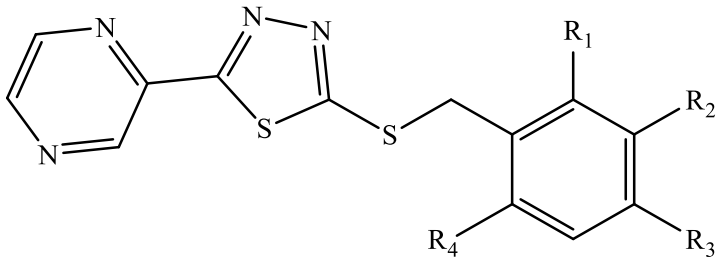
**51;** $R_1 = F_5\text{-}C_6H_0$ pena fluro

### 3.1.1.4. Anti-proliferative

A number of products were designed and synthesized [46] as a series of novel thiadiazole-pyrazine based derivatives. All compounds evaluated as anti-proliferative against HEPG-2, SW-1116, HeLa and BGC823; also as potential telomerase inhibitors.

Compound **52** was the most potent derivative against HEPG2 and SW1116 cells with $IC_{50}$ 0.78 & 1.47 µM respectively, also it demonstrated the highest inhibition activity against telomerase even better than positive control with $IC_{50}$ = 1.24 µM.

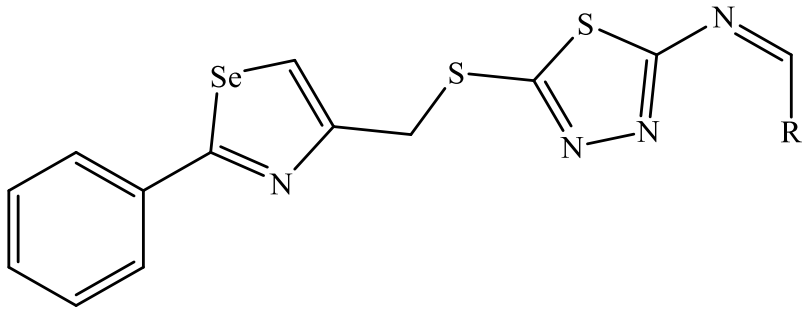
Docking studies of the compound into the telomerase structure active site showed four interactions two of which related to thiadiazole ring as Arg 194 residue simultaneously forms two H bonds with thiadiazole two N atoms.




**52;** $R_1 = R_2 = R_4 = H$, $R_3 = Br$

1,3-Selenazole moiety was incorporated [47] with 1,3,4-thiadiazole ring resulting in a novel hybrid derivatives with Schiff base moieties. Derivatives evaluated for their antiproliferative activity against MCF-7 and L1210, activity against MCF-7 cell was better than reference compound.

Compound **53** was the most potent with $IC_{50}$ 4.02 µM compared with 16.56 µM for control positive. SAR studies declared the important role of phenyl ring substituted to thiadiazole Schiff base in the potency compound as electron-withdrawing group (Cl) enhanced antitumor activity.




**53;** R = 4-Cl-Ph

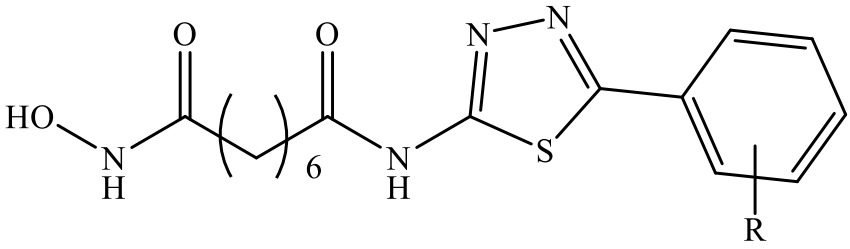
A series of thiadiazole- hydroxamic acid based derivatives were synthesized [48] and evaluated as SAHA analogues, which was the first inhibitor for histone deacetylase, a target enzyme in T-cell lymphoma treatment.

Cytotoxicity activity of compounds was evaluated against five types of cancer cell, NCI-H460, PC-3, SW-620, MCF-7 and AsPC-1 compared to SAHA as reference drug.

Among compounds, derivative **54** showed highest activity against three studied cell lines with $IC_{50}$ 0.34, 0.42 and 0.11 µM against SW620, PC-3 and NCI-H460 respectively.

Other two cell lines, derivative **55** gave a potent activity against MCF-7 and **56** against AsPC-1 with $IC_{50}$ 0.73 and 0.08 µM respectively.

It was concluded that presence of a thiadiazole ring between amide and phenyl moieties enhance cytotoxicity compared to reference SAHA, further Docking studies agreed with that as **54** gave a better affinity toward HDAC8 enzyme than SAHA.

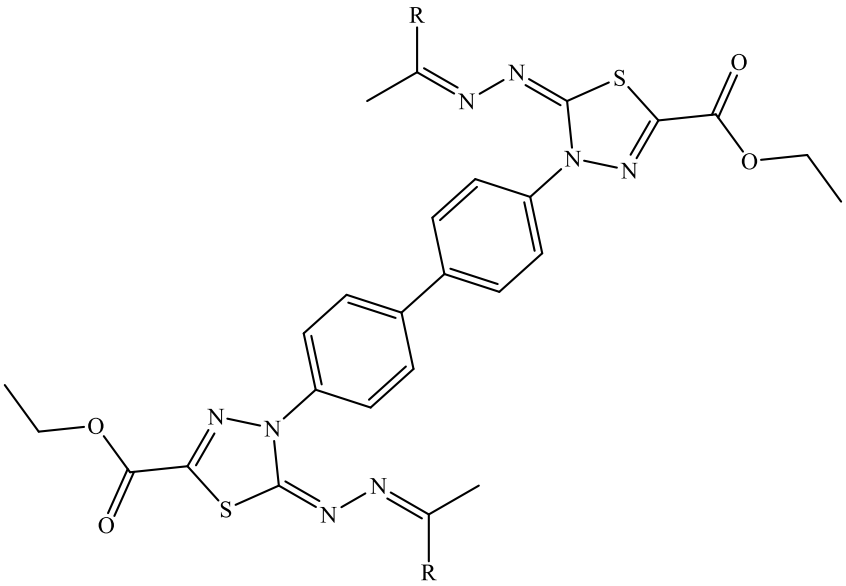



**54;** R = 2-Cl

**55;** R = 4-Cl

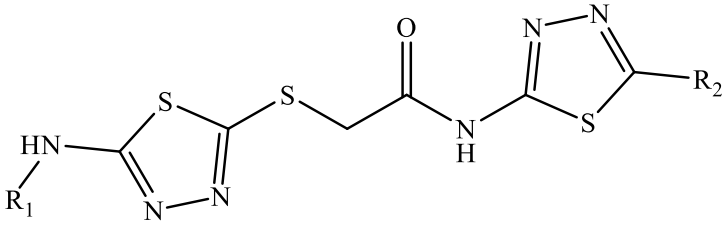
**56;** R = 4-Br

Derivatives of *bis*-thiadiazole were synthesized [49] via condensation of *bis*-hydrazonoyl chloride with various reagents. Anticancer evaluation against MCF-7 cell lines revealed that derivative **57** showed higher activity than Imatinib as standard drug.



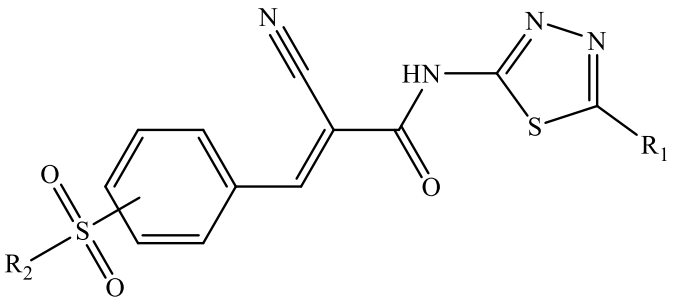
**57;** R = pyridine-3-yl

New thiadiazole derivatives containing two ring linked through acetamide group were synthesized [25]. Among evaluated compounds, derivative **58** exhibited a promising activity against MCF-7 and A549 cancer cell with an $IC_{50}$ 0.084 and 0.034 mM respectively. Furthermore, compound **39** showed promising inhibition activity against aromatase in MCF-7 cell line with $IC_{50}$ of 0.062 mM. SAR studies revealed that presence of aromatic ring linked with amine end of thiadiazole increase activity.



**58;** $R_1$ = 4-Methylphenyl, $R_2$ = Ethyl

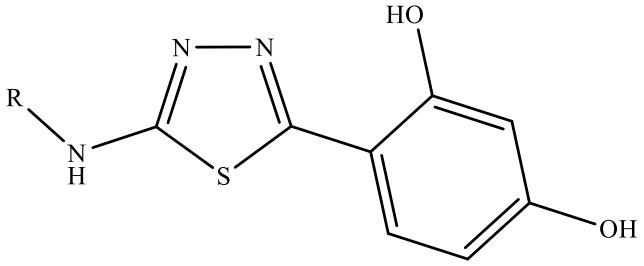
Thiadiazole-acrylamide based derivatives were synthesized [50] and tested or their cytotoxic activity. The highest active derivative was **59** with $IC_{50}$ 0.84 and 3.12 μM against acute leukemia tumor RS4-11 and HL-60, while on normal cells HEK-293T, $IC_{50}$ > 50 μM which indicate no obvious cytotoxicity.




**59;** $R_1$ = 4-OMe-Bn, $R_2$ = 4-OMe-Ph, Ortho

New compounds based on both thiadiazole and resorcinol rings were synthesized [51], then evaluated for their antiproliferative activity against SW-707, HCV29T, A549, and T-47D cancer cell lines.

Compound **60** showed the highest activity against SW-707 and T-47D with $ID_{50}$ 2.8 ± 2.6 and 1.5 ± 1.3 μg/ml respectively, also compounds **61**, **62** showed remarked activity against SW707 with $ID_{50}$ 3.6 ± 1.1 and 3.7 ± 1.1 μg/ml respectively.

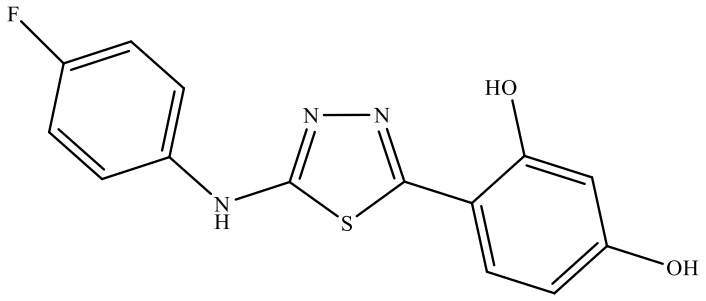



**60;** R = 2,4-Cl-$C_6H_3$-

**61;** R = 4-F-$C_6H_4$-

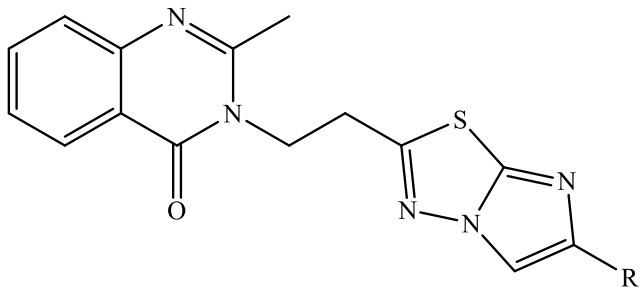
**62;** R = 3-Cl-$C_6H_4$-

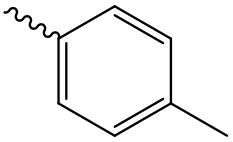
Compounds **61** and **62** further modified [52] via –Cl or $–CH_2CH_3$ substitution at $C_5$ of resorcinol ring that resulted in 4 derivatives, then all derivatives evaluated as anti- glioblastoma (GBM).
All six compounds showed a remarked cytotoxicity against GBM with 15–110 times more than reference drug. Compound **61** was the most promising with $IC_{50}$ 45: 68 μM for target GBM and >100 μM for non-target normal astrocytes.

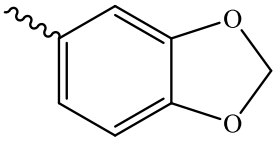


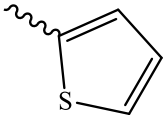

**61**

A novel fused thiadiazole derivatives based on Quinazolinone were synthesized [12], then evaluated as anti-proliferative against A549, HeLa, and MDA-MB-231 cancer cell lines.
Compound **63** showed inhibition against A549 with $GI_{50}$ 0.25 μM, while **64** was promising against MDA-MB-231 with $GI_{50}$ 0.23 μM, whereas **65** have the highest activity against HeLa with $GI_{50}$ 0.36 μM.
Docking studies showed the ability of compounds for binding to β-tubulin active site and compound **65** has the highest docking score among derivatives.



**63**; R = 

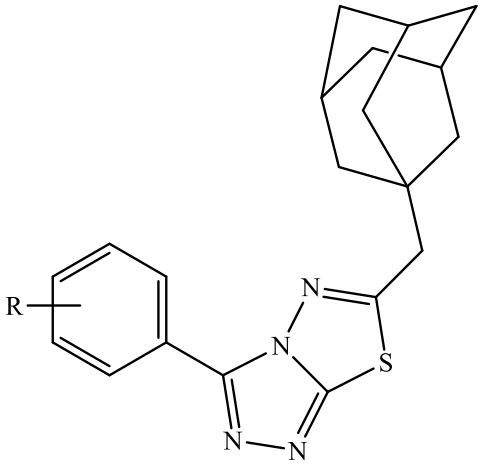
**64**; R = 

**65**; R = 

### 3.1.1.5. Anti-viral

Novel triazolo-thiadiazoles fused compounds containing adamantyl moiety were synthesized [53] with the aim to develop novel HIV inhibitors, anti-HIV activity evaluation declared that compound **66** had the highest activity in the series.

Docking of its analogue **67** with HIV-RT enzyme showed some SAR points, one of them favorable position of thiadiazole nitrogen and sulfur atom for H bonding with residues Lys101 and Lys100.

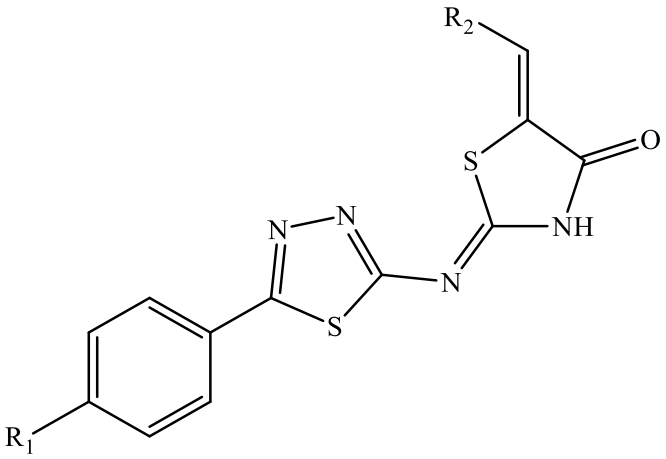


**66;** R = 3-Me

**67;** R = 2-Cl

Novel HCV NS5B RdRp inhibitors designed and synthesized [54]. Some compounds exhibit inhibition activity against HCV NS5B and Compound **68** was the most promising with $IC_{50}$ 5.6 µM.

Analysis of binding mode to NS5B via docking revealed that thiadiazole ring participate in aromatic-aromatic interaction with Tyr477, also two nitrogen atoms located within hydrogen bonding distances.

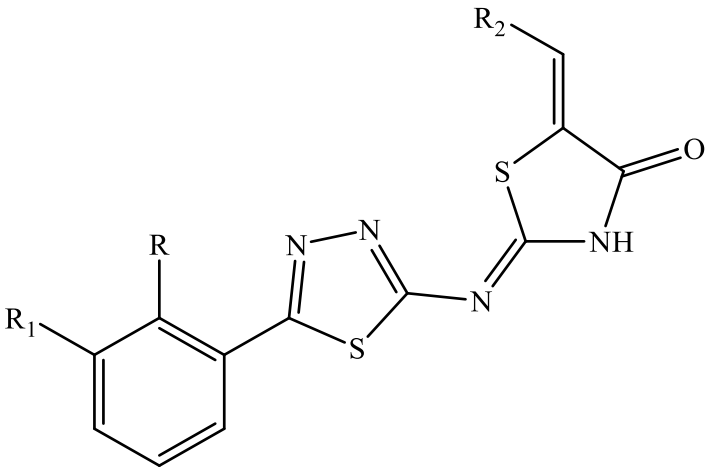



**68;** $R_1$ = Cl, $R_2$ = 2,6-dichlorophenyl

Further optimization of previous thiazolidinone-thiadiazole scaffold conducted [55] through modification of new derivatives and evaluated as DENV-2 NS5 RdRp inhibitors, the replicating enzyme in Dengue virus.

Compounds **69** and **70** showed Promising results with $IC_{50}$ 2.3 and 2.1 µM respectively among 39 derivatives, SAR analysis of these derivatives declared 3-fluorobenzylidene as optimized substituent on $C_5$ of thiazolidinone ring, where substituents 2-Cl-phenyl or 3-F-phenyl are optimized on $C_5$ of thiadiazole ring.

Docking studies revealed that two N atoms of thiadiazole ring contribute in H bonding with Trp833 in binding site of DENV NS5.



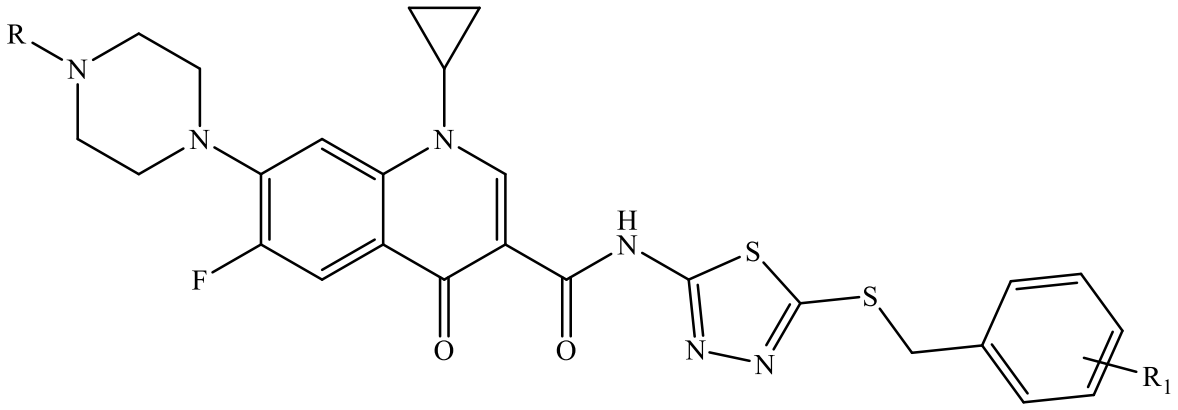
**69;** R = H, $R_1$ = F, $R_2$ = $C_6H_4F$ (3)

**70;** R = Cl, $R_1$ = H, $R_2$ = $C_6H_4F$ (3)

### 3.1.1.6. Structure Modification

Modified ciprofloxacin derivatives containing 1,3,4-thiadiazol was prepared as potential anticancer candidates [9], Compounds were evaluated against MCF-7, A549 and SKOV-3 cancer cells. Compounds **71** and **72** gave the highest activity against MCF-7 and SKOV-3 cells with $IC_{50}$ 3.26 and 3.58 μM respectively, while compound **73** was the most potent against A549 with the $IC_{50}$ 2.79 μM.

Analysis of cell cycle showed that compound **71** could increase sub-G1 phase leading to apoptosis and DNA fragmentation. This modification of ciprofloxacin could be a new entry for anticancer agents' development by shift activity from antibacterial to anticancer.



**71;** R = H, $R_1$ = 3,4-$Cl_2$

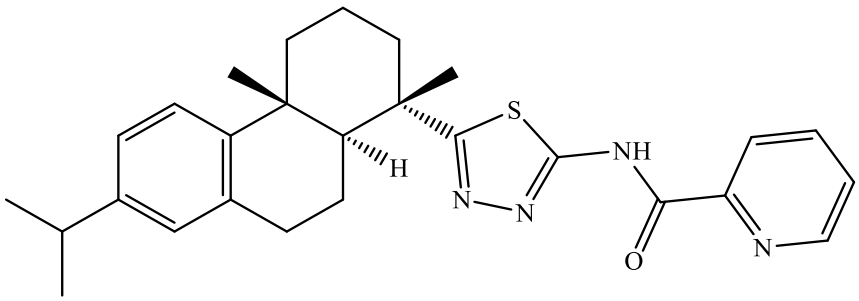
**72;** R = H, $R_1$ = 4-F

**73;** R = Et, $R_1$ = 4-F

Two dehydroabietic acid derivatives designed and synthesized [56] to get anticancer compounds derived from natural rosin. Starting from active carboxyl group, three moieties of thiadiazole, pyridine and amide were incorporated in base structure.

Both compounds showed selective cytotoxicity with better anti-proliferative activity for derivative **74**, also it exhibited better results against A431 cell line compared to reference cisplatin and oxaliplatin with $IC_{50}$ 8.75, 10.50, 15.75 μM respectively.

Result showed that antiproliferative activity could be related to their binding ability with calf thymus DNA (CT DNA).

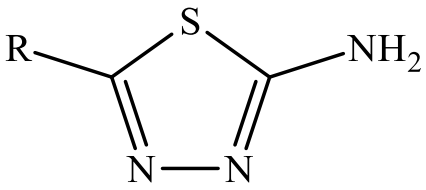


**74**

### 3.1.1.7. DNA Binding Affinity

Five derivatives of 2-amino-5-phenyl thiadiazole have been prepared [8] and DNA binding affinity was studied and the binding affinity of compounds are in the order of 4>3>2>1.

The ethidium bromide quenching results indicates that Thiadiazoles quenched CT-DNA by static quenching mechanism; also, DNA cleavage studies revealed that cleavage might be oxidative type.



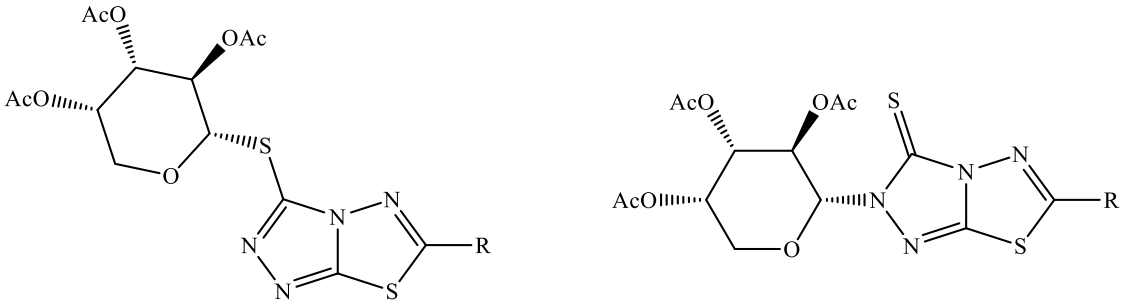
**75;** R = 1) Phenylethenyl, 2) Phenyl, 3) 4-methylphenyl, 4) 4-methoxyphenyl, 5) 4-ethylphenyl

## 3.1.2. Glycoside 1,3,4-Thiadiazole Based Compounds

### 3.1.2.1. Antimicrobial

The synthesis of N & S arabinosides of triazolo-thiadiazole fused system was reported [57], then antimicrobial activity of two selected compounds was studied.

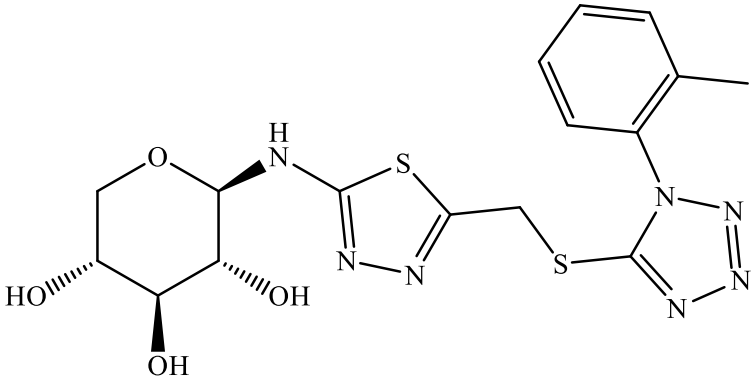
S isomer **76** showed higher inhibition activity than its N isomer **77** when studied against *A. fumigatus, P. italicum, S. racemosum* fungal strains and *S. aureus, P. aeruginosa, B. subtilis and E. coli* bacterial strains with MIC range 12.5-1600 µg/mL.



**76, 77;** R = 4-Cl-$C_6H_4$

A series of xylopyranosyl-thiadiazole derivatives were prepared [58]; Compounds were evaluated against *Staphylococcus aureus*, *Colibacillus* and *Candida albicans*; also tested for PTP1B inhibition.

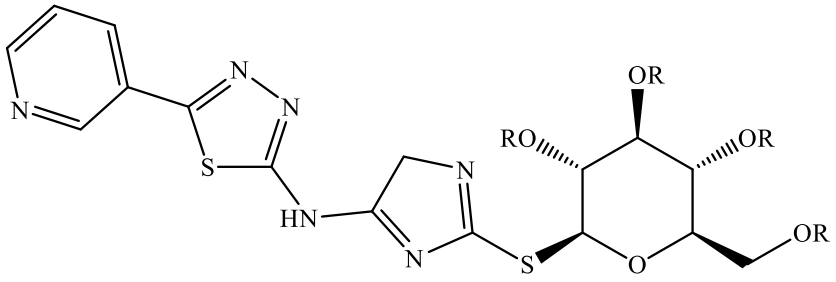
Some of synthesized compounds as **78** displayed PTP1B inhibition with $IC_{50}$ 94.46 µM and inhibition activity against *Staphylococcus aureus*, and better than its acetylated precursor.




**78**

Substituted pyridine-thiadiazoles based derivatives with corresponding C or S glycoside were synthesized [59], compounds antimicrobial activity were assayed and results showed moderate to high activity.

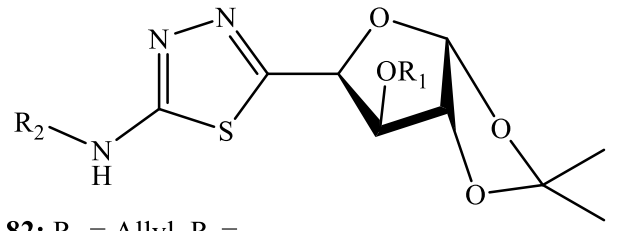
Compound **79** one of the derivatives exhibit highest antibacterial activity, while de-acetylated form **80** showed remarked antifungal and antibacterial activity, which indicate relative higher activity of free hydroxyl glucoside derivative than corresponding acetylated derivative.



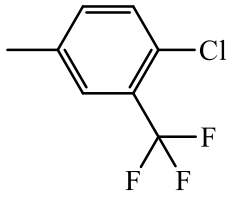

**79;** R = Ac

**80;** R = H

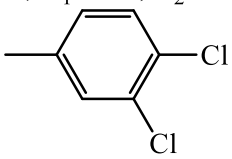
Novel glycosylthiadiazole derivatives were designed and synthesized [60], compounds were evaluated as fungicidal against six fungal species. Derivatives **81** and **82** exhibited highest activities against *Sclerotinia sclerotiorum* and *Pyricularia oryzae* as fungicidal. SAR revealed that sugar full OH protection displayed the most promising results.



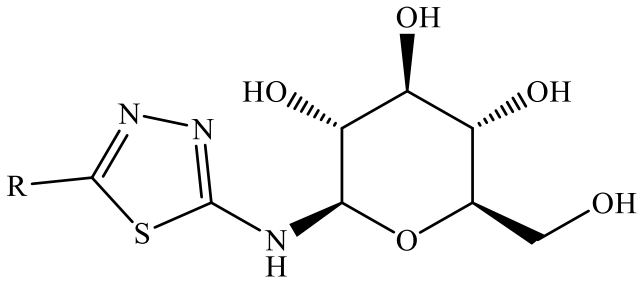
**82;** $R_1$ = Allyl, $R_2$=



**81;** $R_1$ = Ac, $R_2$=



Six azole rings were synthesized from n-hexanoic acid [61] and three N-glycosides were prepared from them. Surface activity properties as surface tension, cloud point and critical micelle concentration were tested for water-soluble derivatives also antibacterial activities were assessed. Only four derivatives that affect all tested gram positive and negative bacteria among them thiadiazole based derivative **83** exhibited promising activity in comparison to reference antibiotics.

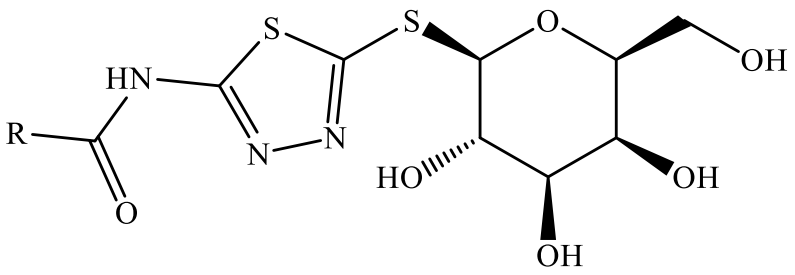


**83;** R = - $(CH_2)_4CH_3$

Thioglycosides of 5-fatty-acylamido-thiadiazole based derivatives were synthesized [62], antimicrobial activity of compounds **84** and **85** exhibited good and moderate activity against both *Klebsiella pneumonia* and *Bacillus subtilis* respectively.

Other investigation against four cancer cell line, compounds **84** and **86** gave promising cytotoxicity against HeLa without any toxicity towards normal CHO-K1 cells, contrary to their acetylated analogs that exhibit toxic activity to normal cells.

Results proved that hybrid molecules of thiadiazole and thioglycoside exhibit both inhibition of cancer cells and antimicrobial activity, beside activity of free OH group preceded activity of acetylated one.

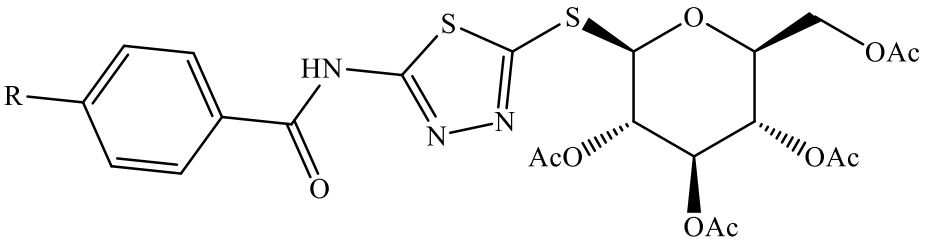



**84;** R = lauric

**85;** R = Myristic

**86;** R = Oleic

Novel glucosides derivatives of thiadiazole derivatives were synthesized [63]. Bioactivity results showed that compounds **87**, **88** exhibit higher antifungal activities against *Phytophthora infestans* with $EC_{50}$ 3.43 and 5.02 μg/ml respectively.



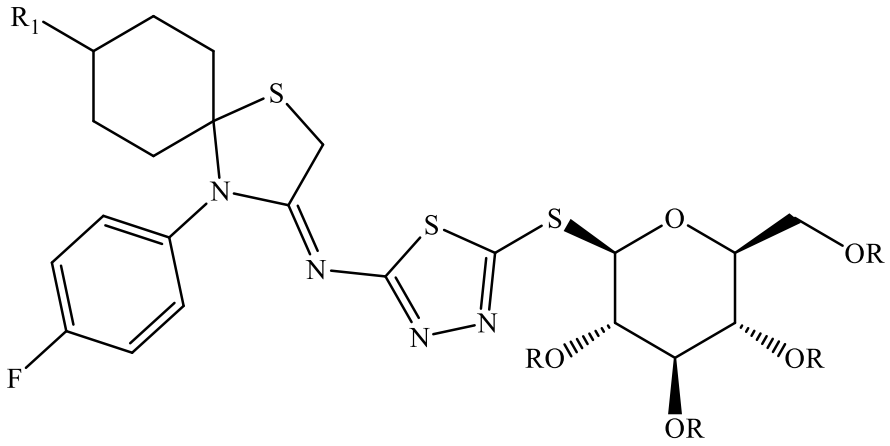

**87;** R = F

**88;** R = $NO_2$

### 3.1.2.2. Anti-proliferative

thia-azaspiro derivatives of thiadiazole and their thioglycoside were synthesized [64], also their anticancer activity was studied against three cancer cell lines. Compounds **89** and **90** expressed the highest activity against HCT-116 and PC-3 respectively, while both compounds were less active against HepG-2.

Results indicate the importance of glycosyl moieties linked to the 1,3,4-thiadiazolyl - thiazolidinone systems to enhance activity of compounds.



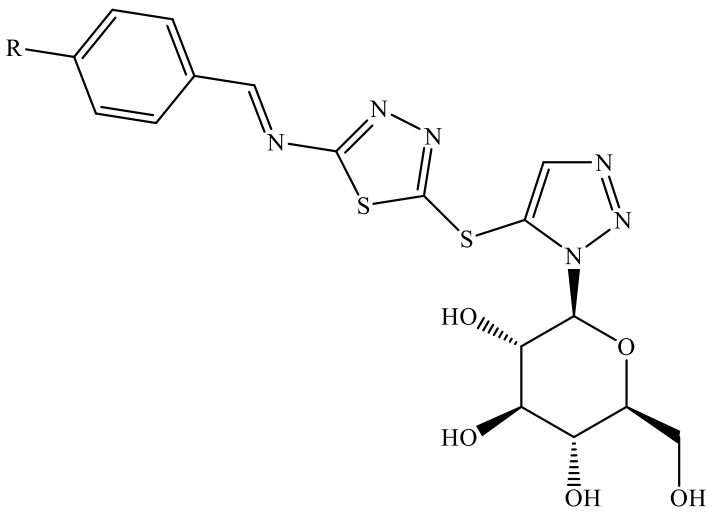

**89;** R = Ac, $R_1$ = H

**90;** R = H, $R_1$ = $CH_3$

New 1,3,4-thiadiazole thioglycosides and their analogs N- glycosides via triazol linker were synthesized [65], then compounds were biologically evaluated against two cell lines HCT-116 and MCF-7.

Compound **91** was more potent against MCF-7 cells than reference drug with $IC_{50}$ =17.3 & 20.5µM respectively, where its activity nearly equal reference drug activity against HCT-116 cell lines with $IC_{50}$ =12.1 & 12.3 µM respectively.

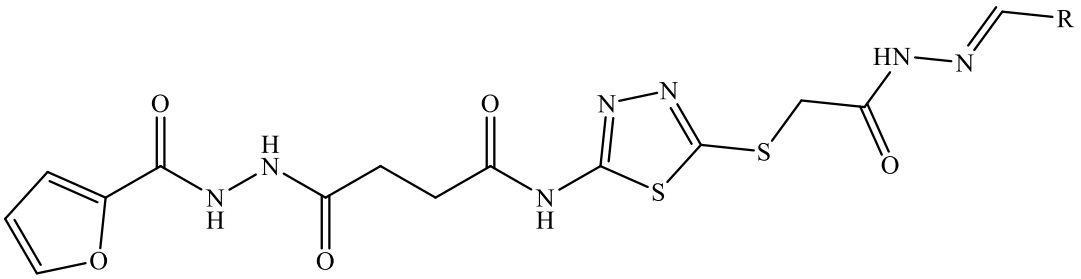
Results indicated that the free hydroxyl groups in N-glycosides showed higher cytotoxicity than its acetylated precursors, where incorporation of 1,2,3-triazole linker to 1,3,4-thiadiazole aglycan part in the desired glycoside enhance activity against HCT-116 as $IC_{50}$ changed from =15.6 to 12.1 µM.




**91;** R = -N-$(CH_3)_2$

New sugar hydrazones with furan-thiadiazole system were prepared [66], anticancer activity was studied against HepG-2 carcinoma cell and normal RPE-1 cells. Among derivatives, Compound **92** exhibited high cytotoxic activity with $IC_{50}$ value 4.2 µM and near to reference drug with $IC_{50}$ value 3.4 µM.

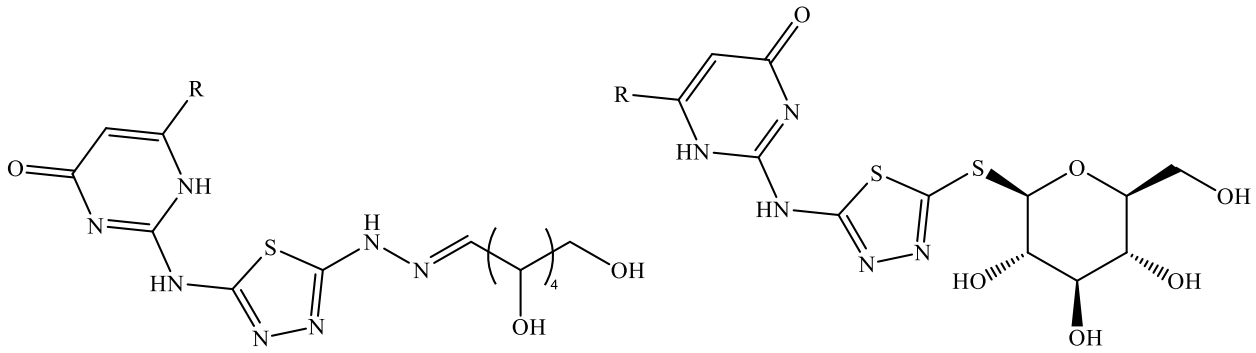
Attachment of sugar moiety to aglycan precursor of compound **92** greatly enhance activity with $IC_{50}$ change from 53.7 to 4.2 µM but increase cytotoxicity to normal cell by nearly two folds which need more optimization of sugar moiety.



**92;** R = D-mannose

New thiadiazole S glycosides linked to pyrimidine derivatives were synthesized [67] and studied for their cytotoxic activity against HepG-2 and MCF-7 cell lines. Compound **93** showed the highest cytotoxic activity among other derivatives with $IC_{50}$ equal 58.2 and 66.6 µM against tested cell lines respectively.

Results indicated better activity of glycosides than activity of their aglycan part alone, also linear sugar form showed better behavior than pyranose form as compound **94** has cytotoxic activity with $IC_{50}$ equal 92.3 and 81.7 µM respectively.

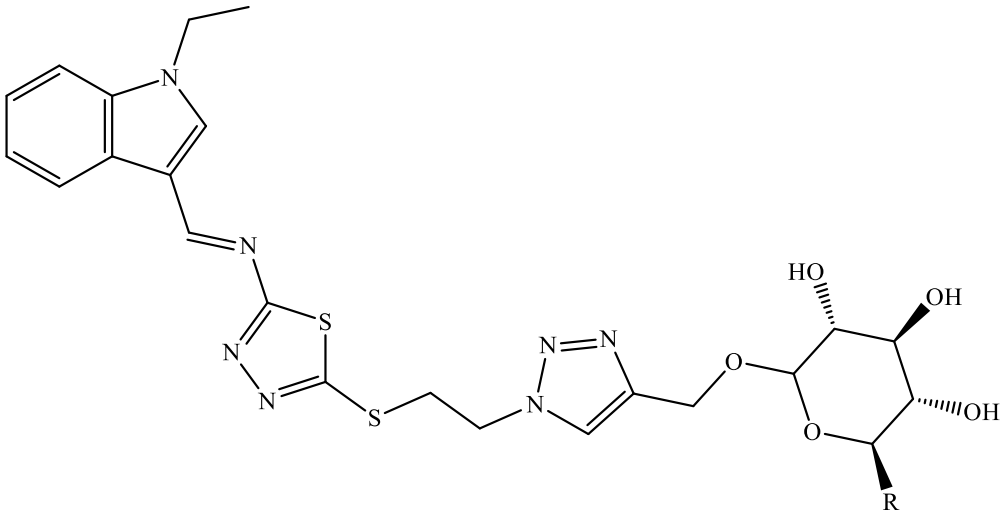


**93, 94;** R = n-Pr

New 1,3,4-thiadiazole-1,2,3-triazole hybrid glycosides were synthesized [68] via click reaction. The compound's cytotoxic activities were studied against HCT-116 and MCF-7 cell lines using the MTT assay. Compound **95** was the highest activity against MCF-7 with $IC_{50}$ 0.5 µM, while **96** showed best activity against HCT-116 with $IC_{50}$ 4.6 µM.

In addition, Enzyme inhibition assay were conducted for **EGFR** receptor, and the results were matched with previous potency of **95** and **96**.

Docking studies showed H-bonds between glycoside scaffold OH and amino acids in $EGFR^{WT}$ binding pocket. Moreover, thiadiazole fragments were observed to play a vital role in π-π interaction.




**95;** R = $CH_2OH$

**96;** R = H

## 4. Conclusion

Thiadiazole moiety showed a role in enhancement activity of various compounds by different interaction modes with target active sites, either via single type of interaction or presence of more types.

Interaction modes were reported as, π-π interactions, hydrogen bonding, pi-hydrogen, pi-Lone pair, conserved water molecule, hydrophobic and electrostatic interaction was reported. Moreover, SAR studies declared the correlation of activity with nature of moieties linked to thiadiazole nucleus as amide and schiff bases.

Enhancement activity of aglycan part by glycosides were declared either in acetylated form or in free form. Relatively little literature in glycosyl derivatives could be a leading strategy for further design of novel compounds with expected bioactivity.

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