Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 14, Issue 4, 2024, 46
https://doi.org/10.33263/BRIAC142.046

Review on Synthetic Strategies for 1,3,4-Thiadiazines and its Biological Activity

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Received: 6.04.2023; Accepted: 2.07.2023; Published: 4.02.2024

Abstract: Heterocycles containing nitrogen and sulfur, known as thiazine, play a vital role in pharmaceutical chemistry and agriculture chemistry. The thiadiazines compound contains one sulfur and two nitrogen atoms at varied positions in six-membered rings. Thiadiazines possess an N-C-S linkage that is believed to be very useful in medicinal and pharmaceutical chemistry. Sulfur-containing drugs are known as sulpha drugs, like sulfadiazine's silver, used to treat burn infection, sulfacetamide for eye infection, and dapsone for leprosy. This review aims to summarize recent synthetic strategies and biological properties of 1,3,4-thiadiazines derivatives.

Keywords: thiadiazines; anti-inflammatory; anti-biotic; antimicrobial; anti-tuberculosis; anticancer.

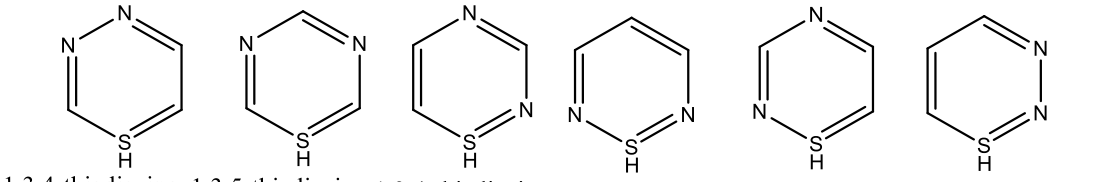
1. Introduction

Organic synthesis involves one of the biggest and most diverse families of aromatic heterocycles. [1] Among them, aromatic heterocyclic compounds are found in many bioactive natural, synthetic compounds, pharmaceutical, medicinal, agrochemical, etc. [2, 3] and are extensively used in the manufacturing of polymeric materials and dyes.

Recently, in the organic synthetic field, there has been a high demand for a novel synthetic methodology for the synthesis of several known as well as unknown aromatic heterocyclic compounds due to their advantages like one step reactions, easily handle, less expensive, low save time, save energy, green solvent, [4, 5] recyclable catalyst, [6, 7] ultrasonic technique [8-11] and greenery approaches [12]. Aromatic heterocyclic compounds have high demand in pharmaceutical and medicinal fields due to their applications: anticancer [13], antibacterial [14], antifungal [15], and anti-inflammatory [16].

Thiadiazines are heteroatomic aromatic compounds, and they contain heterocycles of one sulfur and two nitrogen atoms at varied positions in six-membered rings. Wide variaty of thiadiazines are synthesized such as1,2,3-thiadiazine, 1,2,4-thiadiazines, 1,2,5- thiadiazines 1,3,4-Thiadiazines, 1,2,6-thiadiazines and 1,3,5-thiadiazine. From that 1,3,4-Thiadiazines, 1,2,6-thiadiazines, and 1,3,5-thiadiazine derivatives are highly biologically activity. 1,2,3-thiadiazine, 1,2,4-thiadiazines, 1,2,5- thiadiazines derivatives are least known. This is in part due to their ease of formation and their stability, 1,3,4-Thiadiazines are widely studied for

biologically active compounds and show excellent cardiotonic and hypertensive activities; some of their fused derivatives exhibit antibacterial, anti-inflammatory, fungicidal, anticancer, anti-tuberculosis, antiepileptic, antimalarial, antioxidant, and trypanocide activities. Such examples have been proved by authors in their relevant literature as follows.

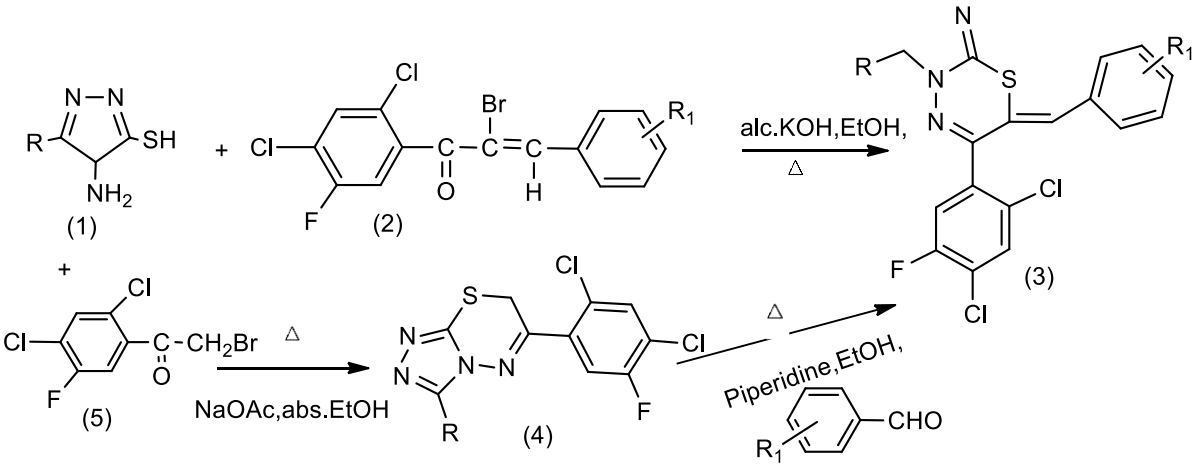


Scheme 1. General structures of thiadiazines.

During the last decades, several thiadiazine derivatives have been developed and have found wide pharmaceutical and clinical applications. Herein, we are focusing on the synthesis of thiadiazine derivatives with their pharmaceutical activities that are now in development.

2. Synthetic Strategy

Holla *et al.* [17] synthesized a series of 7-arylidene-6-(2,4-dichloro-5-fluorophenyl)-3-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines **(3)** by the condensation of 4-amino-5-mercapto-3-substituted-1,2,4-triazoles **(1)** with 3-aryl-1-(2,4-dichloro-5-fluorophenyl)-2-bromo-2- propen-1-one **(2).** They also synthesized the product **(3)** from an alternative method, in which amino mercaptotriazoles **(1)** condensed with 2,4-dichloro-5-fluorophenacyl bromide to yield 7H-3-substituted-6 - (2,4 - dichloro - 5 - fluorophenyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines **(4)** which on condensation with the suitable aromatic aldehydes in the presence of piperidine gives **(3)** Scheme 2 [17].



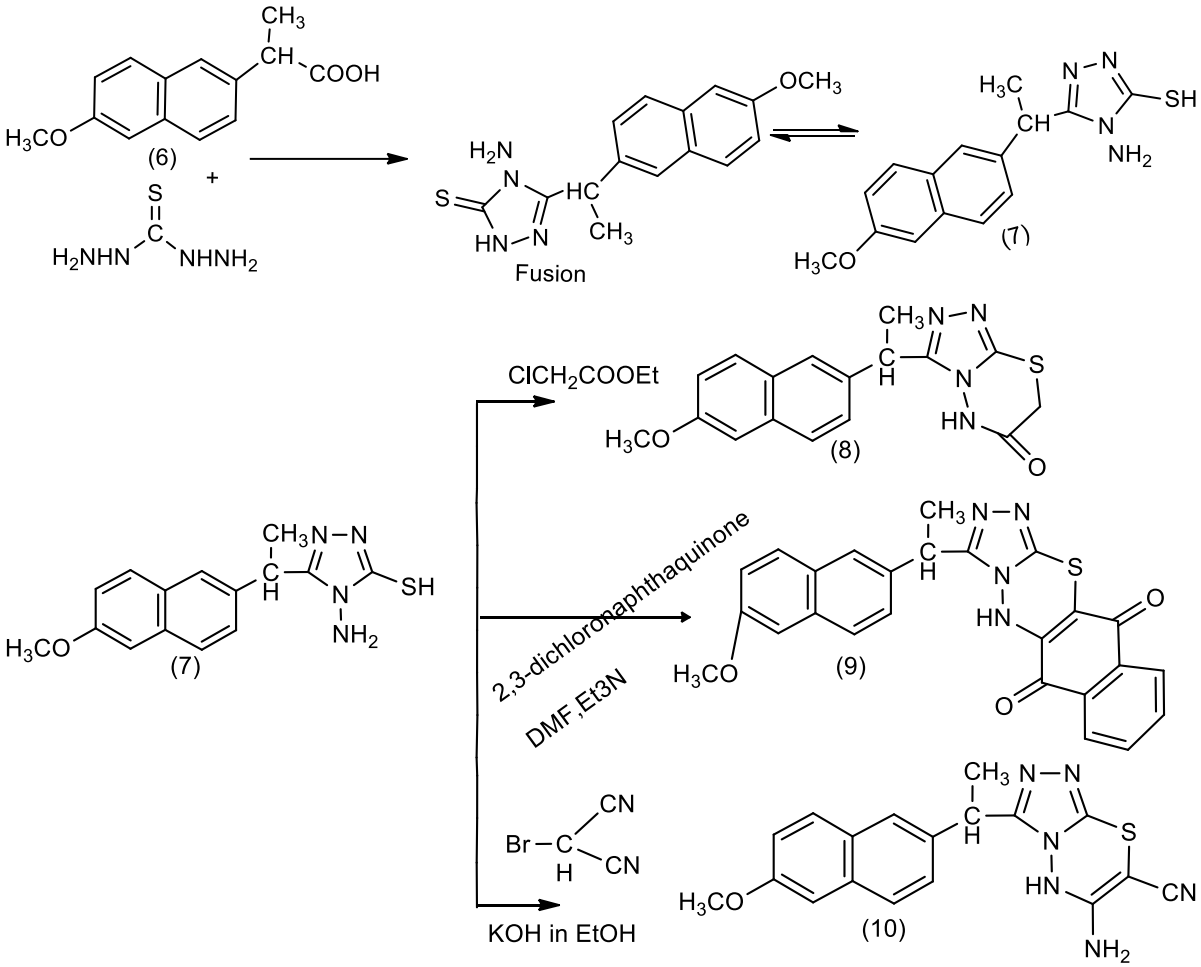
Scheme 2. 7-arylidene-6-(2,4-dichloro-5-fluorophenyl)-3-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines.

Newly synthesized triazolothiadiazines **(3)** were screened by the author for their antibacterial activities against *S. aureus*, *P. aeruginosa*, *E. coli*, and *B. subtilis* by the serial dilution method. The compound showed the highest antibacterial activity against *S. aureus, P. aeruginosa,* and *E. coli*. Some newly synthesized compounds were screened for their anticancer activities at NIH, Bethesda, MD. It was found to be active in the preliminary screening studies. The three cell lines used here are NCI-H 460 (lung), MCF 7 (breast), and SF 268 (CNS).

Y. A. Ammer *et al.*[18] synthesized several s-triazolo[3,4-b] [1,3,4] thiadiazines from 2-(6-methoxy-2-naphthyl) propanoic acid **(6)** (Naproxen).

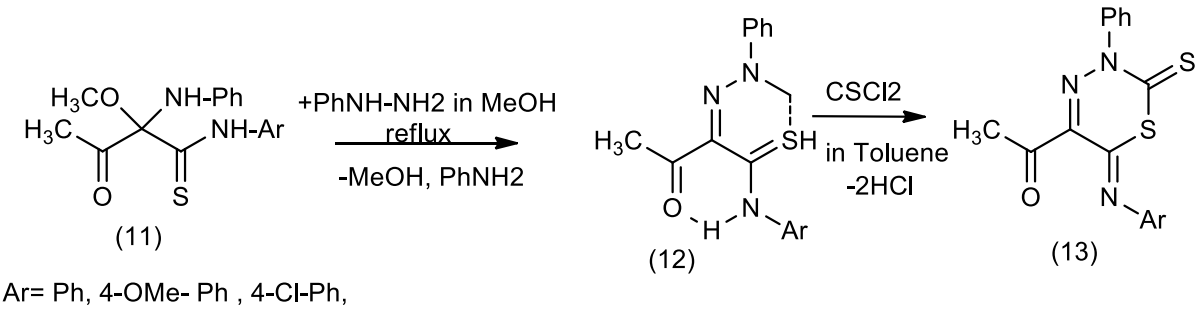
The starting material, 1-(6-methoxy-2-naphthyl)-1- (5-amino-4-mercapto-s-triazol-3-yl) ethane **(7)** was prepared by fusion of 2-(6-methoxy- 2-naphthyl) propanoic acid (Naproxen) **(6)** with thiocarbohydrazide. The reaction of **(7)** with ethyl chloroacetate gives the triazolo 1,3,4-thiadiazine derivative **(8),** while the reaction of **(7)** with 2,3-dichloronaphaqinone in DMF and triethyl amine gives 1-[(6-Methoxy-2-naphthyl)-1-(60,110-dioxo (naphtho[5,6:2,3][1,3,4]thiadiazino-[2,3-c]-striazol-3-yl)]ethane **(9).**When compound 7 refluxed with a mixture of bromomalononitrile and KOH in ethanol 1-[(6-Methoxy-2-naphthyl)-1-(6'-amino-7'-cyano-5H-s-triazolo[3,4-b][1,3,4]-thiadiazin-3-yl)] ethane **(10)** Scheme 3 [18].

The author studied triazolothiadiazine **(10)** bearing amino and cyano groups and found them to be the most active compounds against all the fungi under investigation, namely *Aspergillus ochraceus* Wilhelm (AUCC-230), *Aspergillus flavus* Link (AUCC-164); *Penicillium chrysogenum* Thom (AUCC-530), and *Candida albicans* (Robin) Berkho (AUCC-1720).



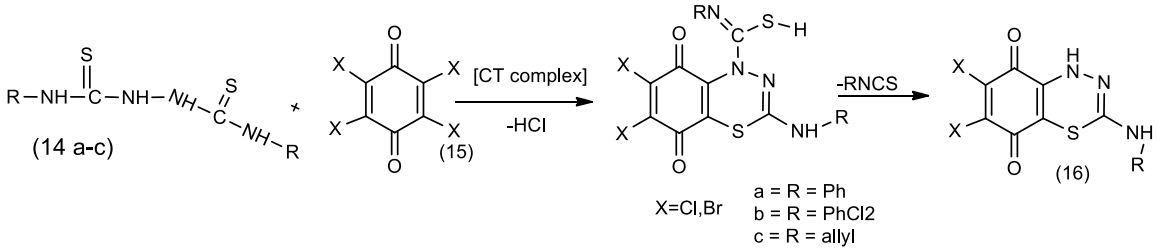
Scheme 3. Triazolo[3,4-b] [1,3,4] thiadiazines from 2-(6-methoxy-2-naphthyl) propanoic acid [18].

Zaleska *et al.* find a novel route to synthesize 1,3,4-thiadiazine derivatives **(13)** from 1,2-diamine **(11)** on treatment with phenyl hydrazine converted into phenyl hydrazone **(12),** which on further treatment with toluene in carbon disulfide gives 2-Thioxo-3,6-dihydro-2H-1,3,4-thiadiazine Derivatives **(13)** Scheme 4 [19].



Scheme 4. 2-Thioxo-3,6-dihydro-2H-1,3,4-thiadiazine derivatives [19].

Alaa A. Hassan *et al.* synthesized 6,7-dichloro-3-substituted amino-1H-benzo[1,3,4]-thiadiazine-5,8-diones **(16)** from reaction with N,N`-disubstituted hydrazine carbothioamides **(14 a-c)** with 2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil, 12a) or 2,3,5,6-tetrabromo-1,4-benzoquinone (bromanil, 15 b) Scheme 5 [20].



Scheme 5. 6,7-dichloro-3-substituted amino-1H-benzo[1,3,4]-thiadiazine-5,8-diones.

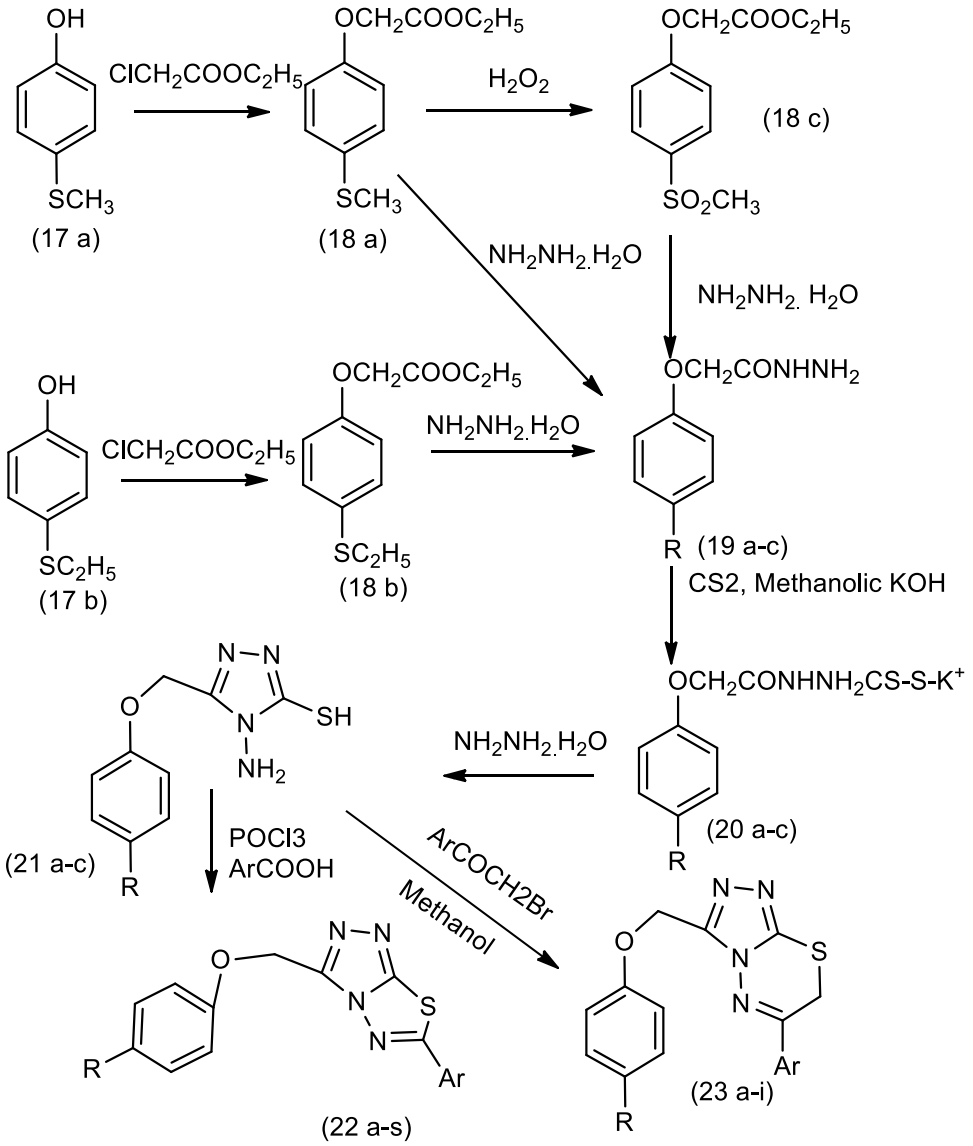
T.Karbansanagouda *et al.* synthesized new 6-aryl-3-{(4-substituted phenoxy) methyl}-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles **(22a-s)** and 6-aryl-3-{(4-substituted phenoxy methyl}-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines **(23a-l)** from 4-thioalkyl phenols **(17a-b)** through a multistep reaction sequence Scheme 6 [21].

The antimicrobial activity study revealed that all the compounds tested by the author showed moderate to good antibacterial and antifungal activities against pathogenic strains.

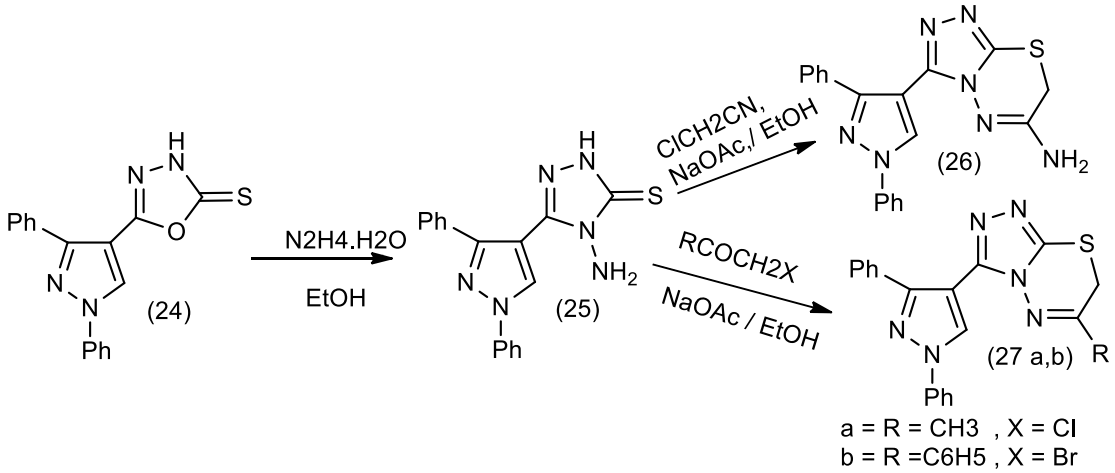
Abdel-Rahman Farghaly *et al.* [22] synthesized 1,3,4-thiadiazine derivatives from 4-amino-3-(1,3-diphenyl-1H-pyrazol-4-yl)-4,5-dihydro-[1,2,4] triazole-5(1H)- thione **(25)**.

The starting (**25)** was prepared by reacting the oxadiazole thione (**24)** with hydrazine hydrate. Which on refluxing in ethanol with chloro acetonitrile and sodium acetate form corresponding 6-amino-3-(1,3- diphenyl-1*H*-pyrazol-4-yl)-7*H* [1,2,4] triazolo[3,4-*b*][1,3,4] thiadiazine **(26)** in 90 % yield. The reaction of (**25)** with chloroacetone and α–bromoacetophenone in boiling ethanol form the corresponding 3-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-6-methyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine (**27a,b)** Scheme 7 [22].

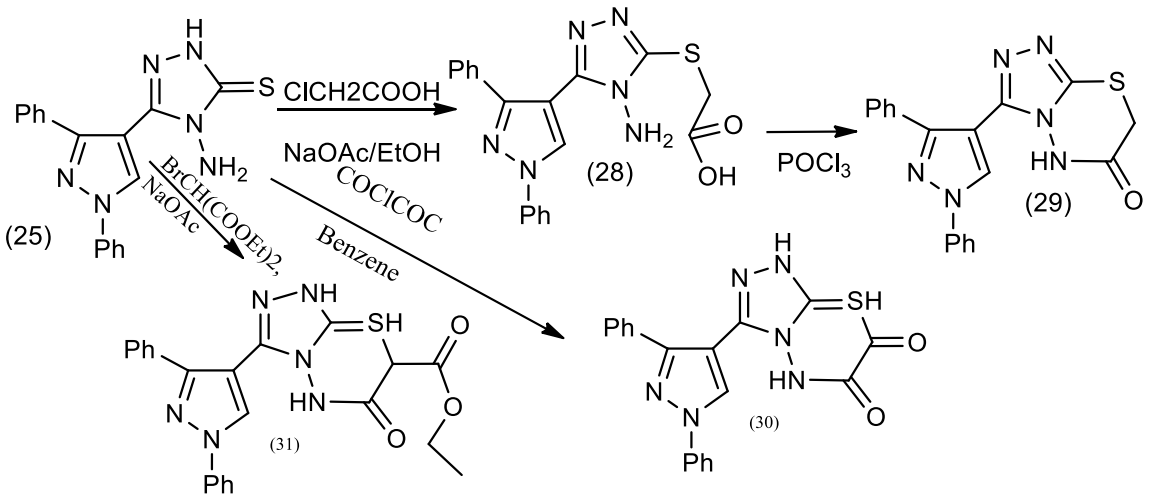
Treatment of the amino thione (**25)** with chloroacetic acid gives product **(28)** which on cyclization on boiling with POCl3 gives 3-(1,3-Diphenyl-1H-pyrazol-4-yl)-5,7-dihydro [1,2,4] triazolo[3,4-b][1,3,4] thiadiazin-6-one **(29)**. Amino thione **(25)** on treatment with oxalyl chloride form 3-(1,3-Diphenyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6,7-dione (**30)**. Where as a reaction of **(25)** with bromodiethyl malonate led to the formation of Ethyl 3-(1,3-diphenyl-1H-pyrazol-4-yl)-6-oxo-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b] [1,3,4] thiadiazine-7-carboxylate (**31).** Compound (31) shows antiviral activity and cytotoxicity in various viral test systems, Scheme 8 [22].



Scheme 6. 6-aryl-3-{(4-substituted phenoxy) methyl}-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles.

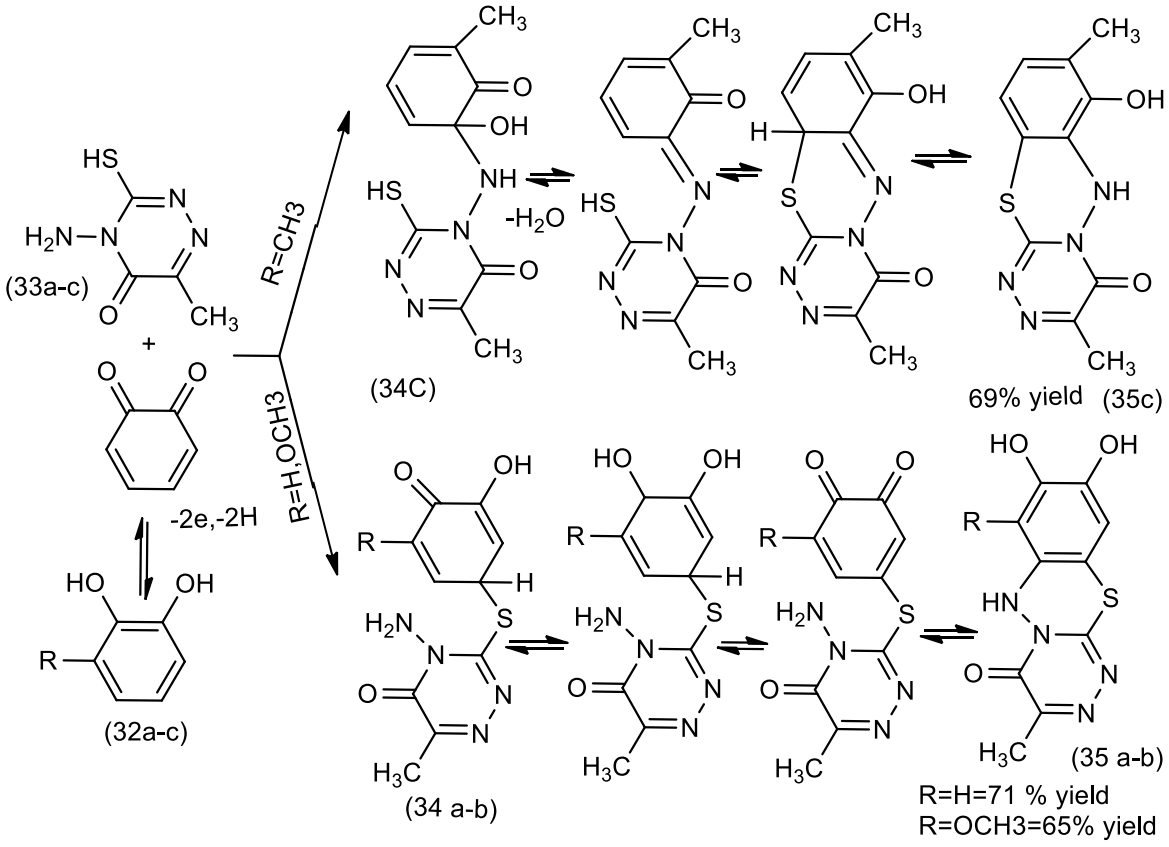


Scheme 7. 1,3,4-thiadiazine derivatives from 4-amino-3-(1,3-diphenyl-1H-pyrazol-4-yl)-4,5-dihydro-[1,2,4] triazole-5(1H)- thione.



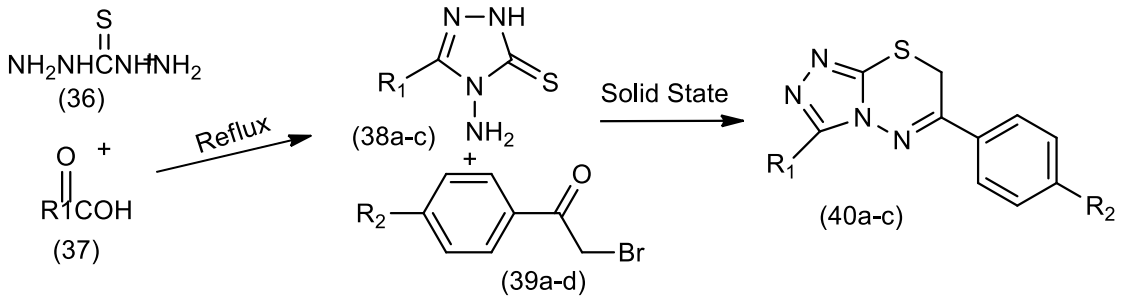
Scheme 8. 3-(1,3-Diphenyl-1H-pyrazol-4-yl)-5,7-dihydro [1,2,4] triazolo[3,4-b][1,3,4] thiadiazin-6-one, 3-(1,3-Diphenyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6,7-dione and Ethyl 3-(1,3-diphenyl-1H-pyrazol-4-yl)-6-oxo-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b] [1,3,4] thiadiazine-7-carboxylate.

L. Fotouhi *et al.* on electrosynthesis, i.e., electrochemical oxidation of catechol (32a-c) in the presence of 4-amino-6-methyl-1,2,4-triazine-3-thion-5-one (**33a-c).** Synthesize of 1,2,4-triazino[3,4-b]-1,3,4-thiadiazines **(35 a,b,c)** Scheme 9 [23].



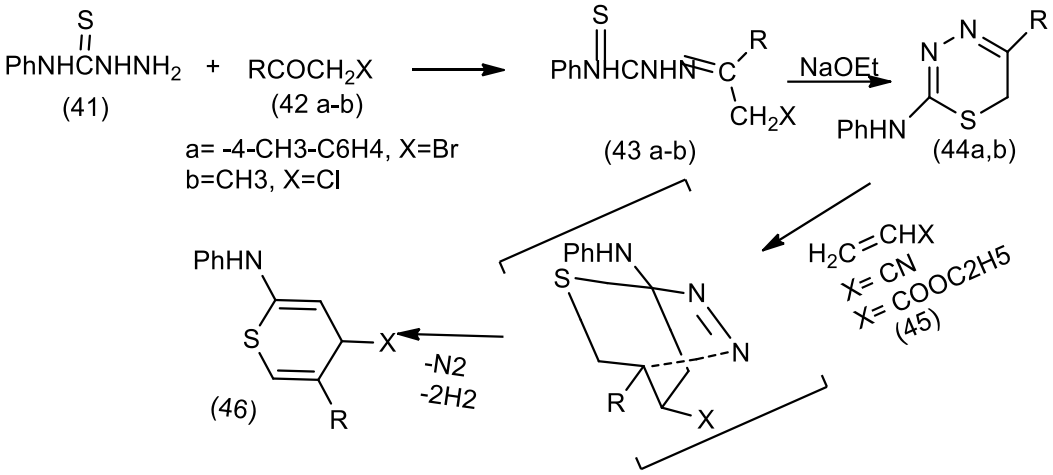
Scheme 9. 1,2,4-triazino[3,4-b]-1,3,4-thiadiazines.

Hui *et al.* reported the solid-state synthesis of s- triazolo [3,4-b]- 1,3,4-thiadiazine derivatives **(40 a-c)** by condensation reaction of 3-alkyl-4-amino-5-mercapto-1,2,4-triazole **(38)**with 2-bromo-4'-substituted acetophenone**(39)**. The compound **(38)** is formed by reaction of thiaosemicarbazide **(36)** with carboxylic acid **(37**) Scheme 10 [24].



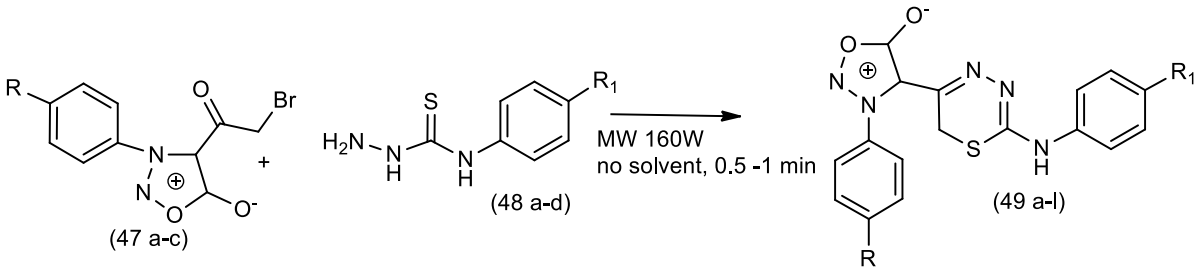
Scheme 10. s- triazolo [3,4-b]- 1,3,4-thiadiazine derivatives.

Wardakhan *et al.* synthesized 1,3,4-thiadiazine derivatives from 4-Phenyl-3-thiosemicarbazide **(41)** on reaction with the α-halo carbonyl compounds (**42a, b)** to give the thiosemicarbazone derivatives (**43 a, b)** which on cyclization gives the product 1,3,4-thiadizine derivative **(44).** The product (44) used as a precursor on [2+4] cycloaddition reaction gives different pyran derivatives **(46) (**Scheme 11) [25].



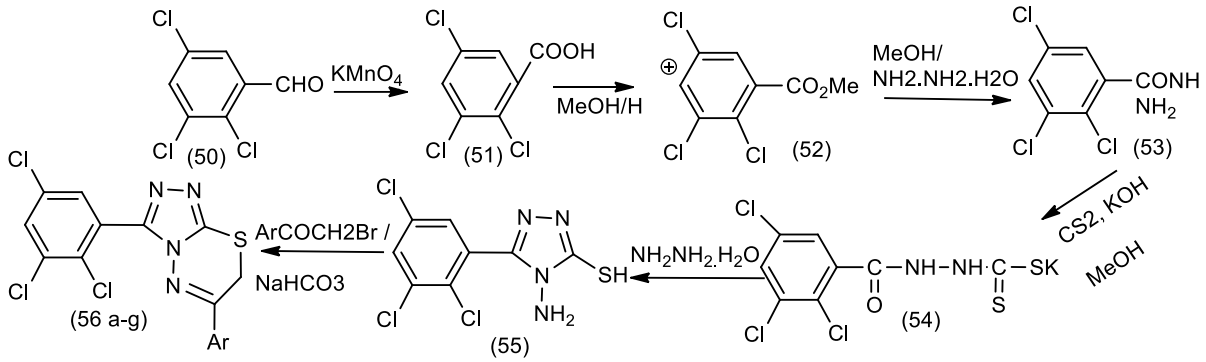
Scheme 11. 1,3,4-thiadizine derivative.

Hedge *et al.* synthesized 2-arylamino-5-(3′-arylsydnone-4-yl)-1,3,4-thiadiazines **(49a-l)** by the interaction of 3-substituted-4-bromoacetyl sydnones **(47 a-c)** with substituted thiosemicarbazides **(48 a-d)** under MW irradiation and solvent-free condition (Scheme 12) [26].



Scheme 12. Synthesized 2-arylamino-5-(3′-arylsydnone-4-yl)-1,3,4-thiadiazines.

Karegoudar *et al.* synthesized 6-(substituted aryl)-3-(2,3,5-trichlorophenyl)-7H-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazines **(56)** by the condensation of 3-(2,3,5-trichlorophenyl)-4-amino-1,2,4-triazole-5-thione **(55)** with aromatic carboxylic acid in presence of phenacyl bromide. The compound **(55)** is formed by treating 2,3,5-trichlorobenzoic acid hydrazide **(53)** with carbon disulfide and potassium hydroxide, followed by a reaction with hydrazine Hydrate (Scheme 13) [27].



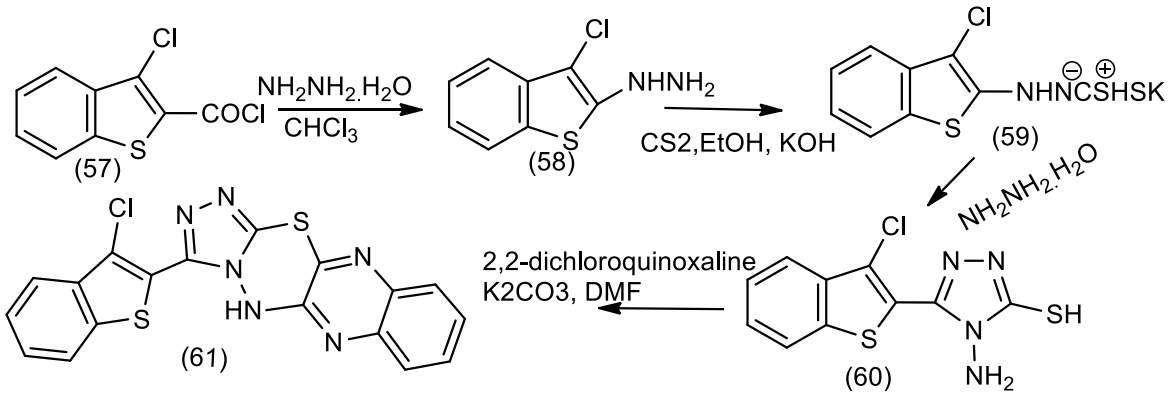
Scheme 13. Synthesized 6-(substituted aryl)-3-(2,3,5-trichlorophenyl)-7H-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazines.

The antimicrobial activity study conducted by the author revealed that all the compounds (38 a-g) tested showed moderate to good antibacterial and antifungal activities against pathogenic strains.

E.S.H.El Ashray *et al.* synthesized 3-(3- chlorobenzo[b]thien-2-yl)-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazino[5,6-b]quinoxaline **(61)** by reaction of 4-amino-5-(3-chlorobenzo[b]thien-2-yl)-3-mercapto-1,2,4-triazole **(60)** with 2,3-dichloroquinoxaline.

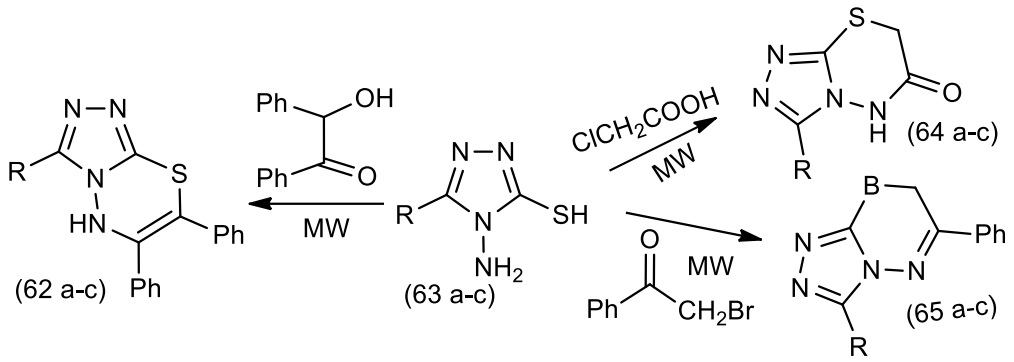
Conventional heating and microwave (MW) irradiation of 3-chloro-2-chlorocarbonylbenzo [b]thiophene **(57)** with hydrazine hydrate form 3-chloro-2-hydrazinocarbonylbenzo [*b*] thiophene (**58**). Potassium dithiocarbazate **(59)** on cyclisation with hydrazine form **(60).**

The reaction of **(60)** with 2,3-dichloroquinoxaline in the presence of K_2CO_3 and DMF form under conventional heating for 2 Hrs gives 82 % yield of **(61)** whereas under MW irradiation for 1.5 min gives **(61)** with 94% yield (Scheme 14) [28].



Scheme 14. Synthesized 3-(3- chlorobenzo[b]thien-2-yl)-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazino[5,6-b]quinoxaline.

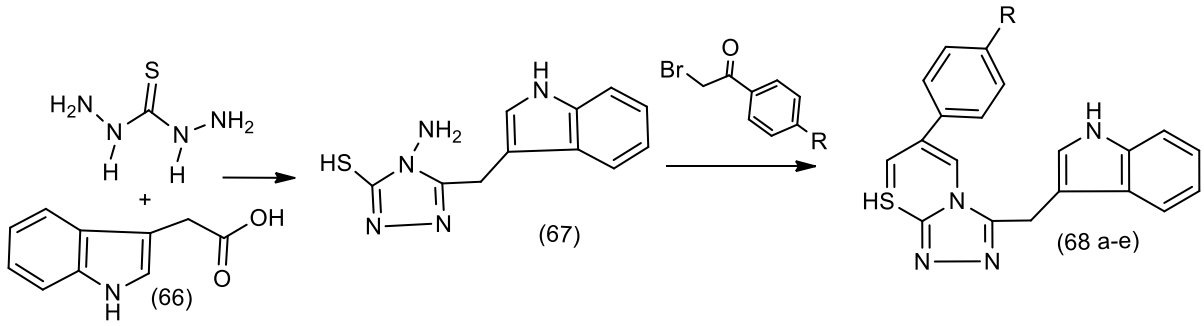
Kidwai and Mothsra *et al.* synthesized s-triazo[3,4-b]-1,3,4-thiadiazine from 4-amino-5-mercapto-3-substituted-s-triazoles **(62 a-c**) by using microwave-assisted heat reaction technology. The author observed that compound **(62a-c)** on treatment with benzoin under microwave irradiation formed 6,7-Diphenyl-5H-3-substituted-1,2,4-s-triazolo[3,4-b] [1,3,4] thiadiazines **(63 a–c).** Compound **(62 a-c)** on reaction with chloroacetic acid under microwave irradiation formed (7H)-3-substituted-1,2,4-striazolo[3,4-b][1,3,4]thiadiazine-6(5H)-ones (**64 a–c).** while **(62 a-c)** on microwave irradiation with phenacyl bromide afforded 7H-3-substituted-striazolo [3,4-b] [1,3,4]thiadiazines **(65a–c**) (Scheme 15). [29]



Scheme 15. Synthesized s-triazo[3,4-b]-1,3,4-thiadiazine from 4-amino-5-mercapto-3-substituted-s-triazoles.

Kaplancikli *et al.* [30] synthesized 3- [(1H-indol-3-yl)methyl]-6-aryl-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines **(68 a-e)** by condensing 4-amino-3-mercapto-5-[(1H-indol-3-yl)methyl]-4H-1,2,4-triazole **(67)** with phenacyl bromides in absolute ethanol. 1H-indol-3-acetic acid **(66)** on heating with thiocarbohydrazide formed compound **(67).**

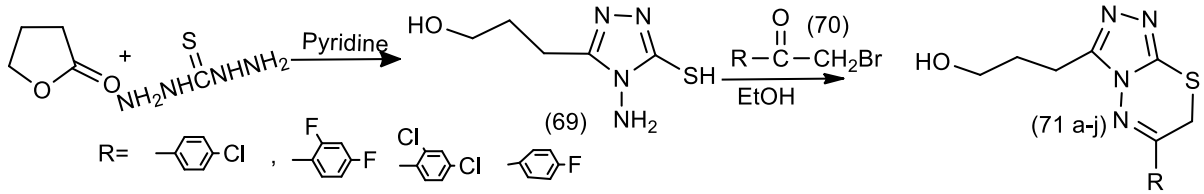
Author found that all the compound (68 a-e) shows higher antimicrobial activity when studied with *Micrococcus luteus* (NRLL B-4375), *Bacillus cereus* (NRRL B-3711), *Proteus vulgaris* (NRRL B-123), *Salmonella typhimurium* (NRRL B-4420), *Staphylococcus aureus* (NRRL B-767), *Escherichia coli* (NRRL B-3704), *Candida albicans, Candida glabrata* than triazole derivatives (Scheme 16). [30]



R = H,Cl,CH_3,NO_2,$N(CH_3)_2$

Scheme 16. Synthesized 3- [(1H-indol-3-yl)methyl]-6-aryl-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines.

Jin *et al.* synthesized 6-aryl-3-(3-hydroxypropyl)-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazines **(71 a-j)** by the reaction of 4-amino-3-(3-hydroxypropyl)-5-mercapto-1,2,4-triazole (**69**) with substituted *ω*-halo acetophenones**(70)** (Scheme 17) [31].

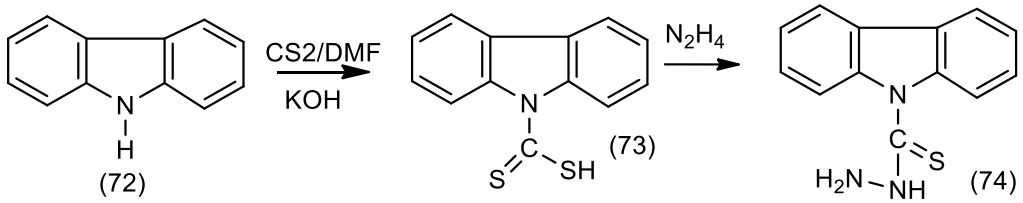


Scheme 17. Synthesized 6-aryl-3-(3-hydroxypropyl)-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazines.

The author observed that the newly synthesized compounds **71a~j** show a more pronounced inhibiting effect than 4-amino-3-(3-hydroxypropyl)-5-mercapto-1,2,4-triazole (**69**) on the growth of wheat and radish**.**

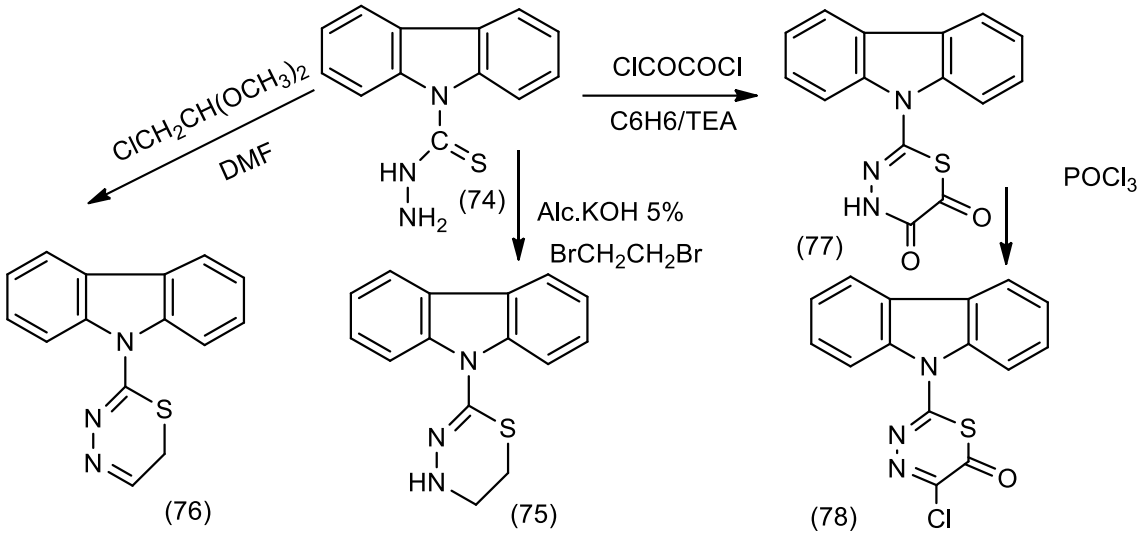
T. M. Abdel-Rahman *et al.* [32] synthesized Some 1,3,4-Thiadiazine Derivatives of Carbazole by a novel synthesis method. Carbazole-9-thiocarbohydrazide **(74)** was obtained by treatment of carbazole **(72)** with carbon disulfide in a DMF-potassium hydroxide mixture to

give carbazole-9-carbodithioic acid **(73)** followed by a reaction with hydrazine hydrate (Scheme 18) [32].

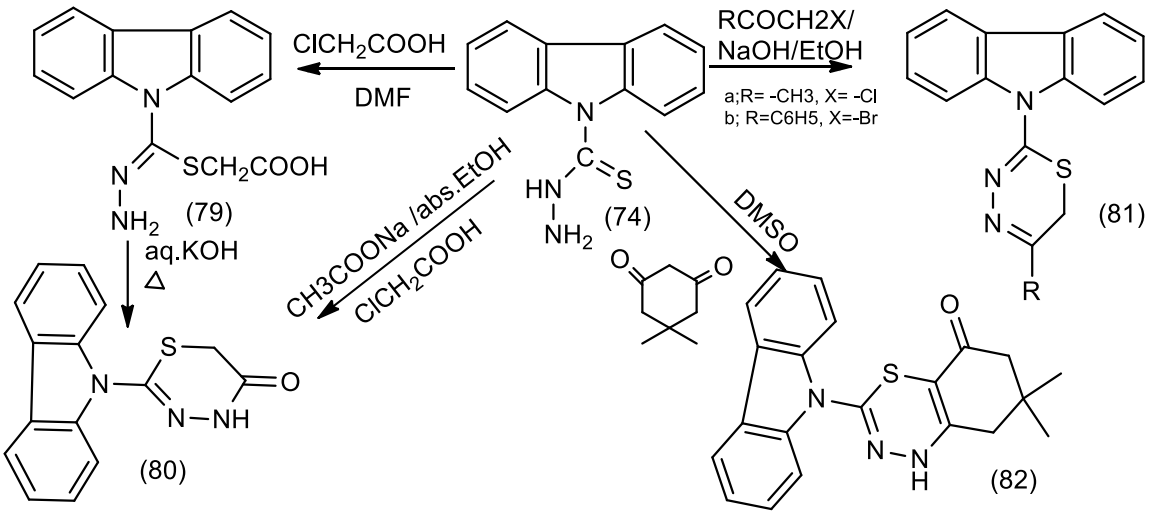


Scheme 18. Synthesis of carbazole-9-thiocarbohydrazide.

Furthermore, the alkylation of compound (**74)** with 1,2-dibromoethane in alcoholic potassium hydroxide led to the formation of 2-(carbazol-9-yl)-5,6-dihydro-4H-1,3,4-thiadiazine **(75)**. However, the alkylation of **(74)** with chloroacetaldehyde dimethyl acetal in DMF yielded 2-(carbazol-9-yl)-6H-1,3,4-thiadiazine **(76)**. Moreover, the treatment of **(74)** with oxalyl dichloride gives 2-(carbazol-9-yl)-4H-1,3,4-thiadiazine-5,6-dione **(77).** Chlorination of the thiadiazine (**77)** using phosphoryl chloride gave 2-(carbazol-9-yl)-5-chloro-4,5-dihydro-1,3,4-thiadiazin-6-one **(78),** (Scheme 19) [32].



Scheme 19. Syntheis of series of thiadiazines.

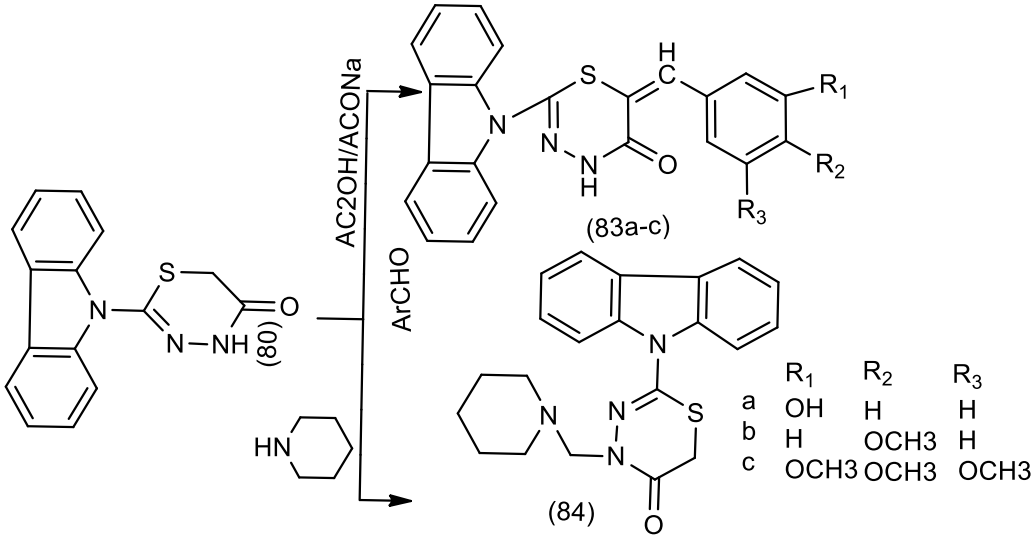


Scheme 20. Synthesis of series of thiadiazines products 80, 81, and 82.

The reaction of compound **(74)** with monochloroacetic acid in DMF resulted in the formation of compound **(79)**, which, upon refluxing with potassium hydroxide, yielded 2-

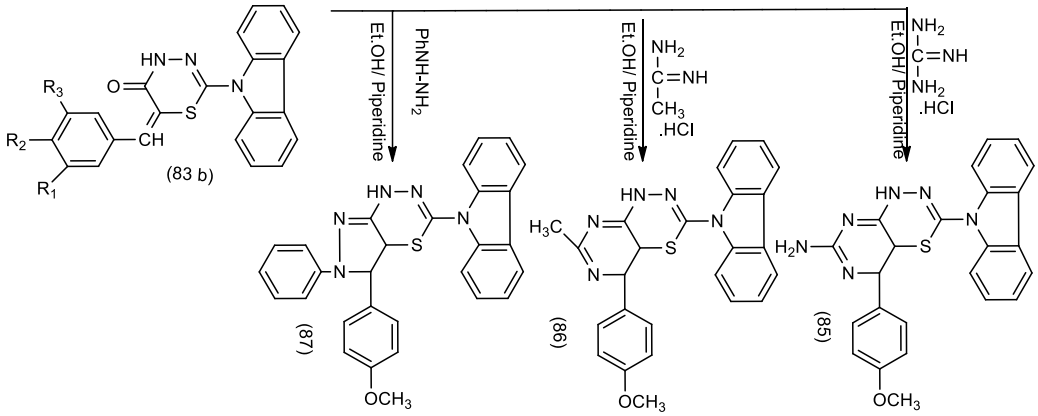
(carbazol-9-yl)-1,3,4-thiadiazin- 5(4H,6H)-one **(80)**. Product **(80)** was also obtained from the reaction of compound **(74)** with monochloroacetic acid and sodium acetate. The hetero cyclization of **(74)** with *α*-halo ketones, such as chloroacetone and/or phenacyl bromide in basic media, afforded 2-(carbazol-9-yl)-5-(methyl or/phenyl)-6H-1,3,4-thiadiazine **(81a,b)**, respectively. The cyclocondensation of **(74)** with dimedone in DMSO led to the direct formation of 2-(carbazol-9-yl)-4H-6,6-dimethyl-5,7-dihydro-8-oxobenzo[e]-1,3,4-thiadiazine **(82)** in Scheme 20 [32].

The presence of an active methylene group in compound **(80)** was deduced from its condensation with m-hydroxybenzaldehyde, p-methoxy benzaldehyde, and 3,4,5-trimethoxybenzaldehyde in boiling acetic acid to give 2-(carbazol-9-yl)-6-arylidene-1,3,4-thiadiazin-5(4H)- one **(83a–c)**, respectively (Scheme 21) [32].



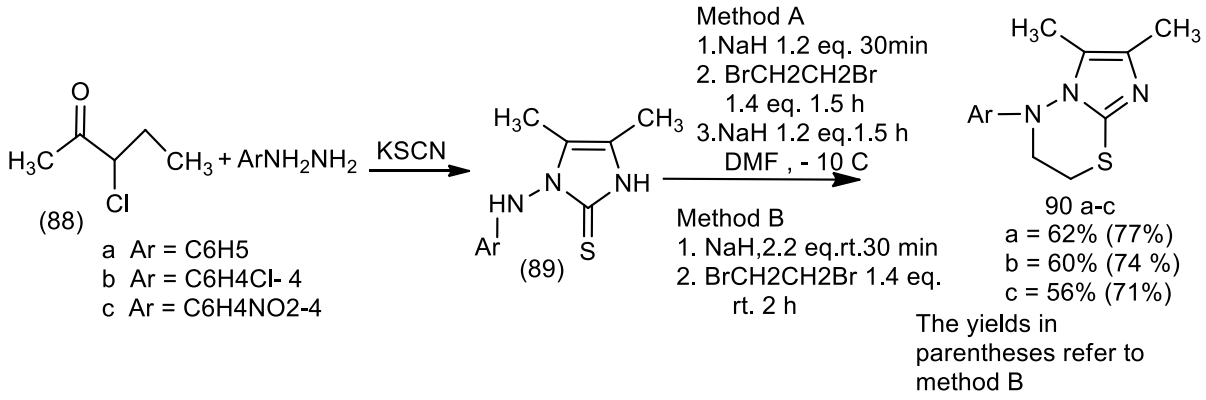
Scheme 21. Syntheis of series of thiadiazin**es** product 83a-c, 84.

Compound **83 b** on nucleophilic attack of nitrogen compounds, such as guanidine hydrochloride, acetamidine hydrochloride, and phenyl hydrazine hydrochloride, affording 2-(carbazol-9-yl)-4H-8H-6-amino-8-(4_-methoxyphenyl)-pyrimidino[4,5-e]1,3,4-thiadiazine **(85)**,2-(carbazol-9-yl)-4H-8H-6-methyl-8-(4-methoxyphenyl)-pyrimidino[4,5-e][1,3,4] thiadiazine **(86)**, and 2-(carbazol-9-yl)-4H,6H,7H-6-phenyl-7-(4_-methoxyphenyl)- pyrazolo [3,4-e] [1,3,4]-thiadiazine **(87),** respectively, (Scheme 22) [32]. The author evaluated new compounds obtained for *in vitro* antitumor activity against brain tumor cell line (U251) and Hela (Cervix carcinoma cell line) at a drug concentration between 1.00–10.00 μg/mL. Using the sulforhodamine **B (SRB)** protein assay. 26 The IC50 percent control of infected and uninfected response values as calculated.



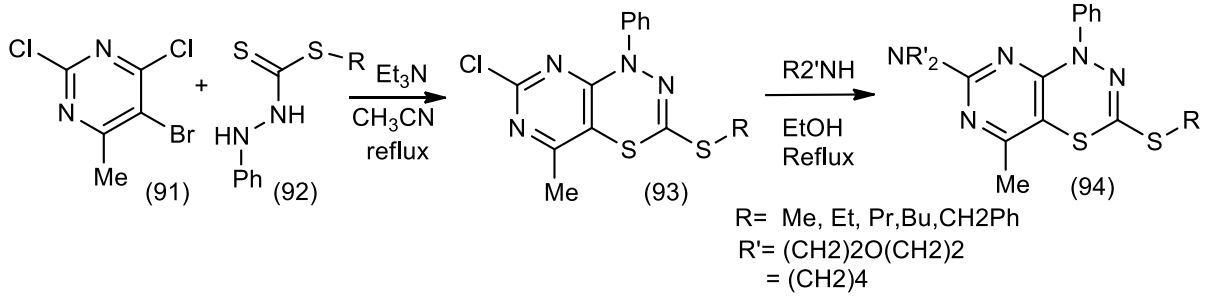
Scheme 22. Synthesis of series of thiadiazines product 85, 86,87.

Constantinos Neochoritis *et al.* synthesized imidazo[2,1-b] [1,3,4] thiadiazines **(90 a-c)** from 1-Arylamino- 4,5-dimethylimidazole-2-thiones **(89).** Compound **(89)** is prepared by reacting 3-chloro-2-butanone **(88)** with potassium thiocyanate and arylhydrazines. Compound (89) on treatment with 1,2-dibromoethane and sodium hydrazide form **(90 a-c)** with 56-62% yield (method 1). The author found that the yield of the product **(90 a-c)** considerably increased when 2.2 equi. Sodium hydrazide is added after 30 minutes by dropwise addition of 1,2-dibromoethane (method 2) (Scheme 23) [33].



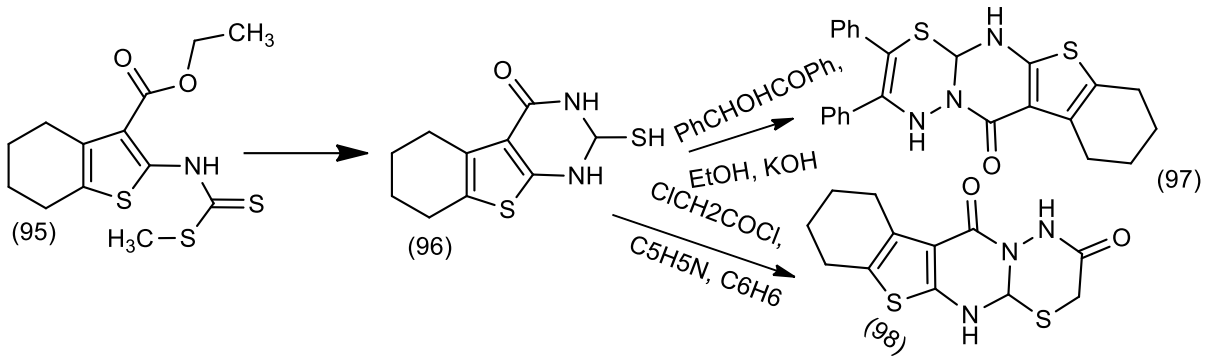
Scheme 23. Synthesis of series of thiadiazines product 90.

Mohsen Nikpour, *et al.* synthesized pyrimido derivatives of 1,3,4-thiadiazine, i.e**.,** New 3-alkylsulfanyl-7-chloro-5-methyl-1-phenyl-1*H*-pyrimido[4,5-*e*] [1,3,4] thiadiazines **(45)** *via* the cyclocondensation of alkyl-2-phenyl hydrazine carbodithioates (**44)** with 5-bromo-2,4-dichloro-6-methylpyrimidine **(43)** in basic acetonitrile, [Scheme 24) [34].



Scheme 24. Synthesized pyrimido derivatives of 1,3,4-thiadiazine.

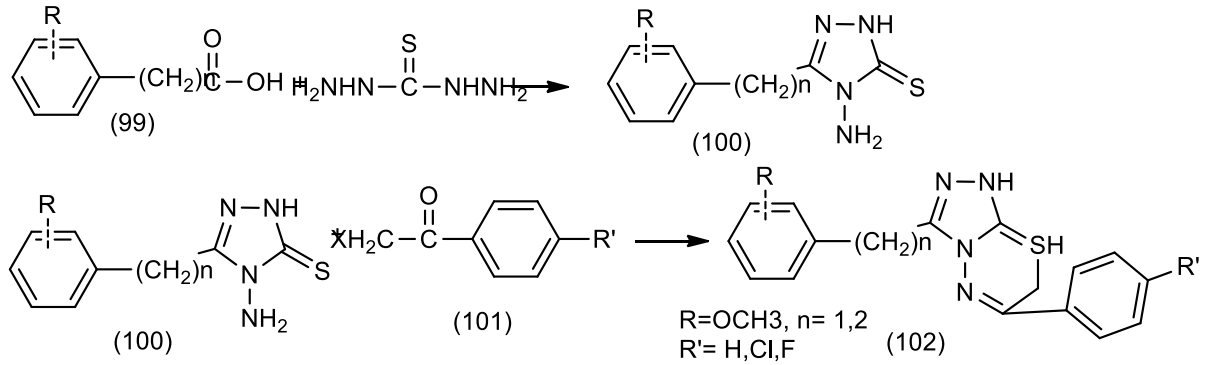
Vishagaperumal *et al.* synthesized some derivatives of 1, 3, 4-thiadiazoles and 1, 3, 4-thiadiazines **(97, 98**) from 3-amino-2-mercapto-5, 6, 7, 8 tetrahydrobenzothieno-(2, 4-d) pyrimidine-43H)-one-2 **(96)**. Compound **(96)** is formed by refluxing **(95**) with hydrazine hydrate in isopropyl alcohol for 6 hrs. (**96)** on heating with benzoin in ethanol for 30min in presence of KOH gives 2, 3-Diphenyl-4a, 5, 7, 8, 9, 10-hexahydro-1H, 11H-thieno [2', 3':4, 5]pyrimido[2, 1-b] [1, 3, 4] thiadiazin-9-one **(97). (96)** on refluxing with benzene, chloroacetyl chloride and a few drops of pyridine for 6 hrs form 1H, 4aH-7, 8, 9, 10-Tetrahydro benzothieno[2', 3':4, 5]pyrimido[2, 1-b] [1, 3, 4]thiadiazine-2, 11 (3H,5H) –dione **(98) (**Scheme 25) [35].



Scheme 25. Synthesized thiadiazine products 97 and 98.

These compounds **(97)** and **(98)** were screened by the author for antibacterial activity against gram-positive organisms like *S. aureus*; *B. subtilis* and gram-negative organisms like *E. coli*; *P. aureginosa* and antifungal activity against *C. albicans* and *A. niger*. They show mild to good activity.

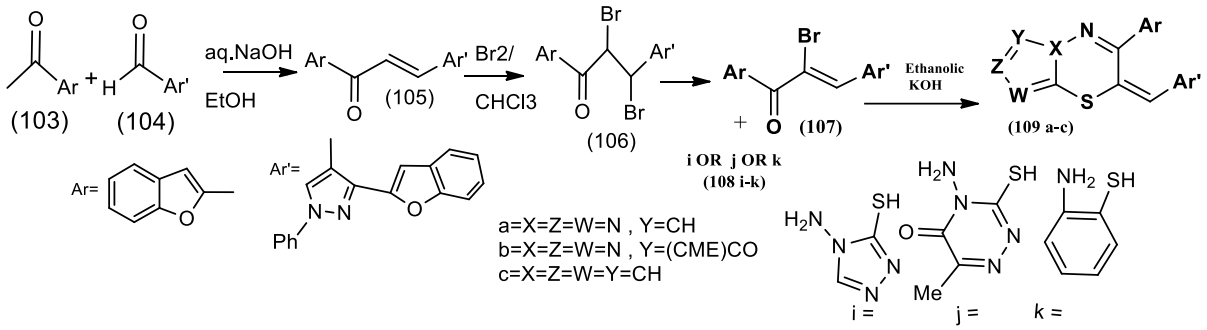
Birsen Tozkoparan, *et al.* synthesized a new series of 3,6-disubstituted-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine (102) compounds by the reaction of 4-amino-3-substituted-1,2,4-triazole-5-thiones (100) with phenacyl bromides (or chlorides) in anhydrous ethanol under reflux (101). The required starting compounds (100) were obtained by the reaction of corresponding acetic or propionic acids (99) with thiocarbohidrazide (Scheme 26) [36].



Scheme 26. Synthesized a new series of 3,6-disubstituted-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine.

The author observed that compound 102 exhibited both a significant and consistent analgesic /anti-inflammatory effect in mice without inducing gastric lesions and minimal lipid peroxidation and deserves further attention to develop new leads.

Shehry *et al.* synthesized benzofuran derivatives of 1,3,4-thiadiazine **(109 a-c).** 2-Acetylbenzofuran **(103)** and 3-(benzofuran-2-yl)-1-phenyl-1Hpyrazole-4-carbaldehyde **(104)** [12] reacted in the presence of aqueous sodium hydroxide yielded the 1,3-disubstituted prop-2- en-1-one derivative **(105)**. Bromination of **(105)** with bromine in chloroform yielded 2,3-dibromo-1,3-disubstituted propan-1-one (**106)** in good yield. Compound **(106)** undergoes dehydrobromination by using triethylamine in dry benzene yielded 2-bromo-1,3-disubstituted prop-2-en-1-one (107), (Scheme 27) [37].



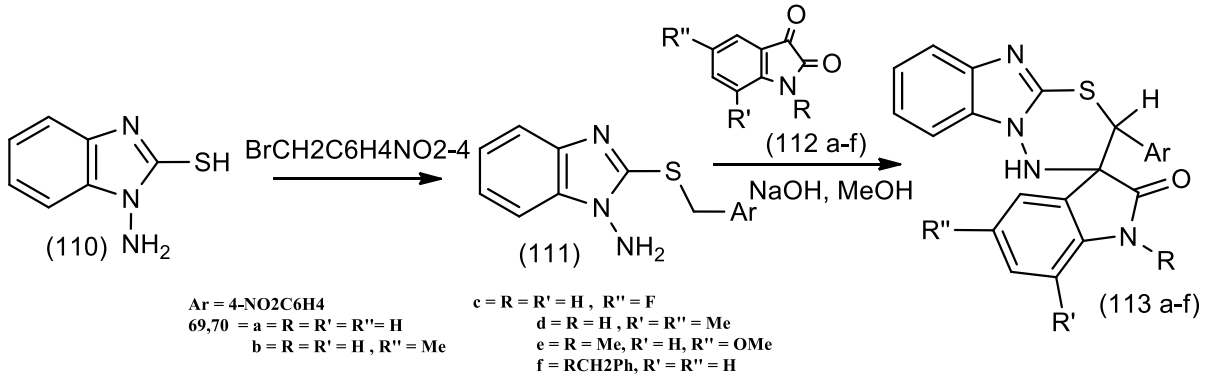
Scheme 27. 6-(Benzofuran-2-yl)-7-((3-(benzofuran-2-yl)-1-phenyl-1Hpyrazol-4-yl)methylene)-7H [1,2,4] triazolo [3,4-b][1,3,4] Thiadiazine.

6-(Benzofuran-2-yl)-7-((3-(benzofuran-2-yl)-1-phenyl-1Hpyrazol-4-yl)methylene)-7H [1,2,4] triazolo [3,4-b][1,3,4] Thiadiazine **(109 a**), 3-(Benzofuran-2-yl) -2-((3-(benzofuran-2-yl)-1-phenyl-1Hpyrazol- 4-yl) methylene) -7-methylpyrimido[2,1-b][1,3,4]thiadiazin-8(2H)-one **(109 b)** and 3-(Benzofuran-2-yl)-2-((3-(benzofuran-2-yl)-1-phenyl-1Hpyrazol-4-yl) methylene) -2H-benzo[b][1,4] thiazine **(109 c)** thiadizine derivatives formed on treatment of a-bromopropenone derivative **(107)** with 4-amino-4H-1,2,4-triazole-3-thiol **(108 i)** or 1-amino-2- mercapto-5-methylpyrimidin-4(1H)-one **(108 j)** or with 2-aminothiophenol **(108k)** in ethanolic potassium hydroxide solution.

The author studied that **109a**, showed potent molluscicidal activities while compounds **109b** and **109c** showed a moderate effect compared to the standard molluscicidal agent (Bayluscide).

Gaponenko *et al.* synthesized spiro[indole-3,3´-[1,3,4]thiadiazino [3,2_a] benzimidazoles (113) and spiro[indole-3,6´-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines].

Compound **(110)** on reaction with 4-nitrobenzyl bromide yielded 1-amino-2-[(4-nitro-benzyl) thio]-1H-benzimidazole **(111**), which on further base-catalyzed cyclization with isatin **112(a-f)** formed corresponding spirocyclic [1,3,4]thiadiazino [3,2-a]benzimidazoles **(113a-f**), (Scheme 28) [38].

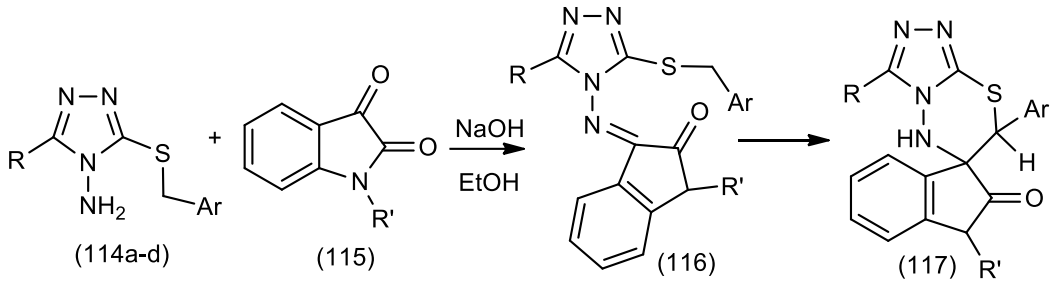


Scheme 28. Spirocyclic [1,3,4]thiadiazino [3,2-a]benzimidazoles.

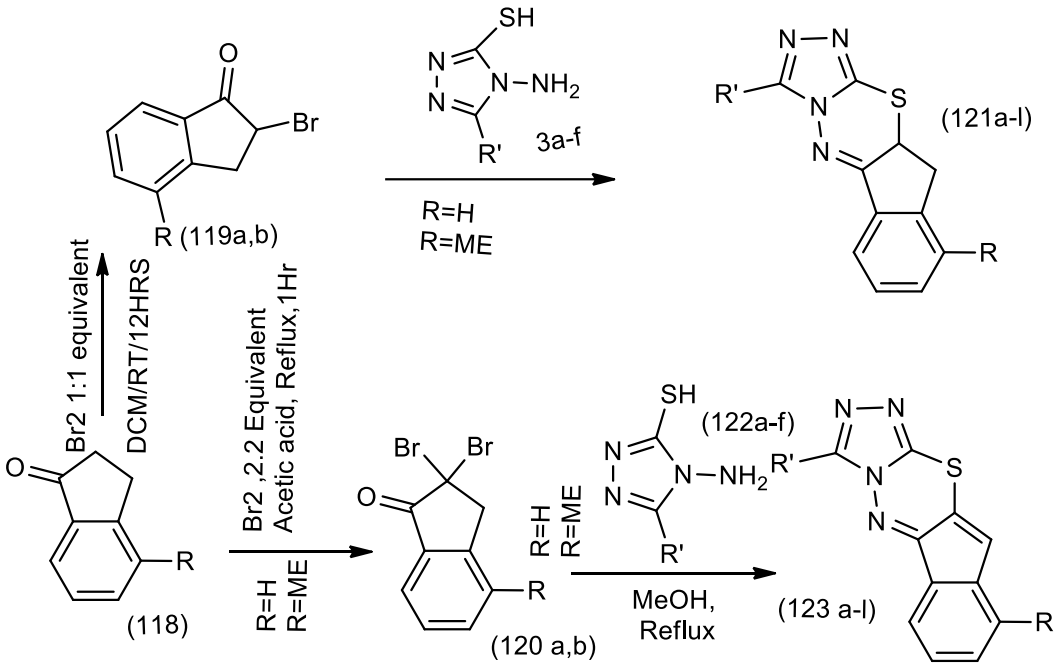
The base-catalyzed condensation of 4-amino-3-[(4-nitrobenzyl) thio]-4H-1,2,4-triazoles **(114 a-d)** with alkyl satins **(115**) formed corresponding acyclic N-benzylthiotri-azolyl imine **(116)** which on further cyclization produced spirocyclic triazolo[3,4-b] [1,3,4]thiadiazines **(117a-h)** (Scheme 29) [38].

Om Prakash *et al.* synthesized two series of compounds, namely, dihydro indeno and indeno [1,2-e] [1,2,4] triazolo [3,4-b] [1,3,4] thiadizines (**121a-l & 123a-l**) by cyclocondensation between a-bromo indanones **(119a-b)** or/ and a,a-dibromo indanones **(120a-b)** and various 3-alkyl/aryl-4-amino-5-mercapto-1,2,4-s-triazoles (3aef) in methanol. They also

studied their effect on the *in vitro* growth of microorganisms causing microbial infection (Scheme 30) [39].



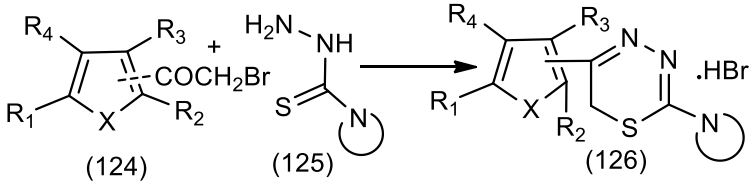
Scheme 29. Spirocyclic triazolo[3,4-b] [1,3,4]thiadiazines.



Scheme 30. Dihydro indeno and indeno [1,2-e] [1,2,4] triazolo [3,4-b] [1,3,4] thiadizines (**121a-l & 123a-l**).

The author reported that all the twenty-four compounds (**121a-l**) and (**123a-l**) were screened for their *in vitro* antibacterial activity against two Gram-positive bacteria, namely *Staphylococcus aureus* (MTCC 96), Bacillus subtilis (MTCC 121) and two Gram-negative bacteria namely *Escherichia coli* (MTCC 1652), *Pseudomonas aeruginosa* (MTCC 741) by agar well diffusion method and all the tested compounds possessed moderate to excellent antibacterial activity against both Gram-positive (*S. aureus, B. subtilis*) and Gram-negative bacteria(*E. coli, P. aeruginosa*).

Chupakin *et al.* synthesized A series of new 5-(thienyl-2)-, 5-(furyl-2)-, and 5-(thienyl-3)-1,3,4-thiadiazine derivatives **(126)** based on the cyclocondensation of bromoacetylthiophenes or _-bromo-2-acetylfurans **(124)** with 4-substituted thiosemicarbazides **(125)** (Scheme 31) [40].

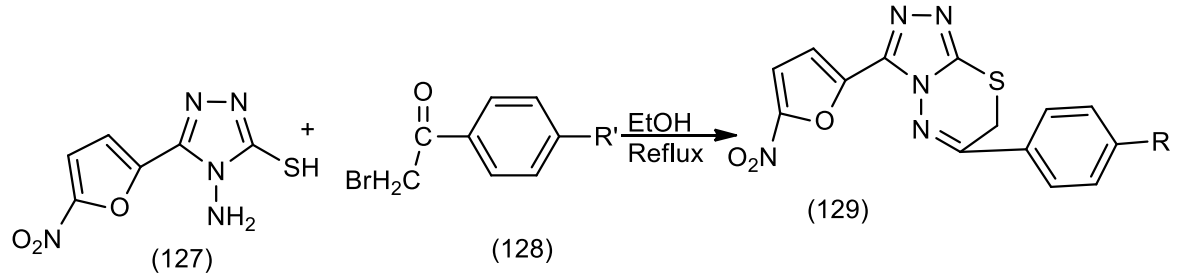


X=O,S;R1=H,CH3,Br,Cl, ;R2= H,Cl;R3=R4=H

Scheme 31. Synthesized A series of new 5-(thienyl-2)-, 5-(furyl-2)-, and 5-(thienyl-3)-1,3,4-thiadiazine derivatives (**126**).

The author observed that these compounds 126 have good potential as emergency drugs for the treatment and prophylaxis of infarction and stroke.

Badr, *et al.* synthesized 6-(4-substituted phenyl)-3-(5-nitrofuran-2-yl)-7H-[1,2,4]-triazolo[3,4-b] [1,3,4] thiadiazines **(129)** by the reaction of 4-amino-5-(5-nitrofuran-2-yl)-4H-1,2,4-triazole-3-thiol **(127)** with 4-substituted phenacyl bromides, **(128**) (Scheme 32) [41].

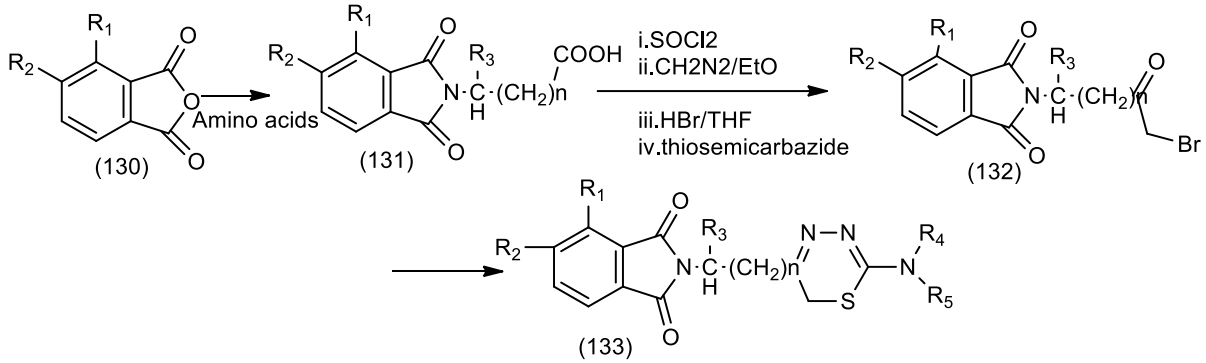


R=H.Br,Cl,NO2,OCH3

Scheme 32. Synthesized 6-(4-substituted phenyl)-3-(5-nitrofuran-2-yl)-7H-[1,2,4]-triazolo[3,4-b] [1,3,4] thiadiazines **(129).**

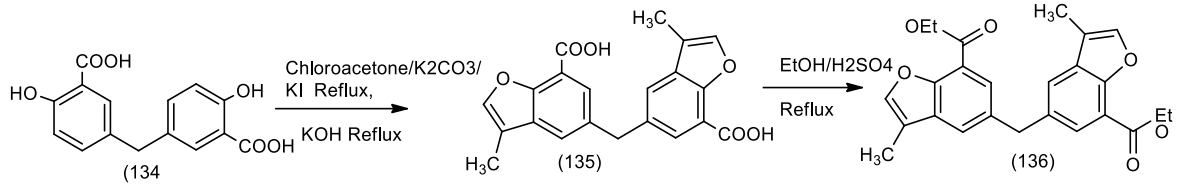
A new series of thiadiazine derivatives 129 have been evaluated by the author for their antibacterial activity against *S. aureus*. and evaluated for their *in vitro* cytotoxic activity against Hep-G2 and HCT-116 cell lines,

Yang *et al.* synthesized a series of novel 1,3,4-thiadiazine derivatives **(133)** from (3-phthalimido-2-oxo-n-butyraldehyde bisthiosemicarbazone,) **(132)** refluxing in EtOH followed by cyclization. Compound (**132)** synthesized from c**on**densation of phthalandiones **(130)** with amino acid followed by bromination with 4-substituted thiosemicarbazides **(131**) (Scheme 33) [42].



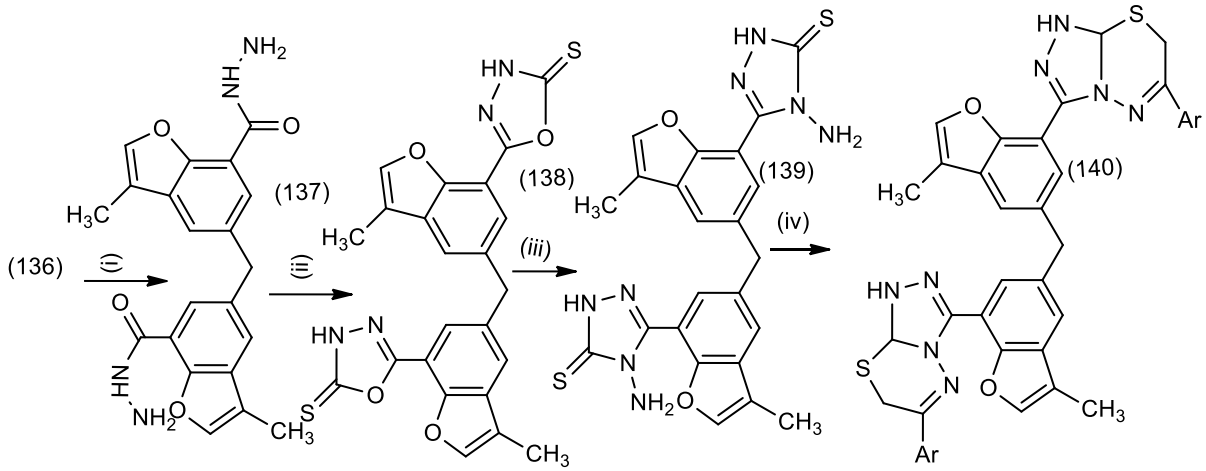
Scheme 33. Synthesized a series of novel 1,3,4-thiadiazine derivatives **(133).**

Reddy *et al.* synthesized series of novel bis[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazines **140 a**–**j** has been synthesized by the reaction of [5,5'-methylenebis(3-methylbenzofuran-7,5-diyl)]bis[(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methanone] (**135**) with a variety of phenacyl bromides in ethanol under reflux. The 5,5'-methylenebis (2-hydroxybenzoic acid)**(134**) on condensation with chloroacetone in the presence of K2CO3 and a catalytic amount of KI at reflux for 12 h followed by cyclization in alc. KOH at reflux for 18 h, in 72% yield form 5,5'-methylenebis(3-methylbenzofuran-7-carboxylic acid) **(135),** which on reaction with absolute ethanol in the presence of a catalytic amount of conc. H2SO4 at reflux for 3 h gave the diethyl 5,5'-methylenebis(3-methylbenzofuran-7-carboxylate)**(136)** in 74% yield (Scheme 34) [43].



Scheme 34. Diethyl 5,5'-methylenebis(3-methylbenzofuran-7-carboxylate)**(136).**

The Compound **(136)** on refluxing with hydrazine hydrate in ethanol form intermediate, 5,5'-methylenebis (3-methylbenzofuran-7-carbohydrazide) **(137)** which on reaction with carbon disulfide in the presence of potassium hydroxide in ethanol afforded the [5,5'-methylenebis(3 methylbenzofuran-7,5-diyl)]bis[(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) methanone] **(138)** in 71% yield. Compound **(138),** when reacted with hydrazine hydrate in ethanol at reflux for 6 h, resulting in the [5,5'-methylenebis(3-methylbenzofuran-7,5-diyl)] bis[(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl) methanone] **(139)** which on given reaction condition form (**140a–j)** (Scheme 35) [43].



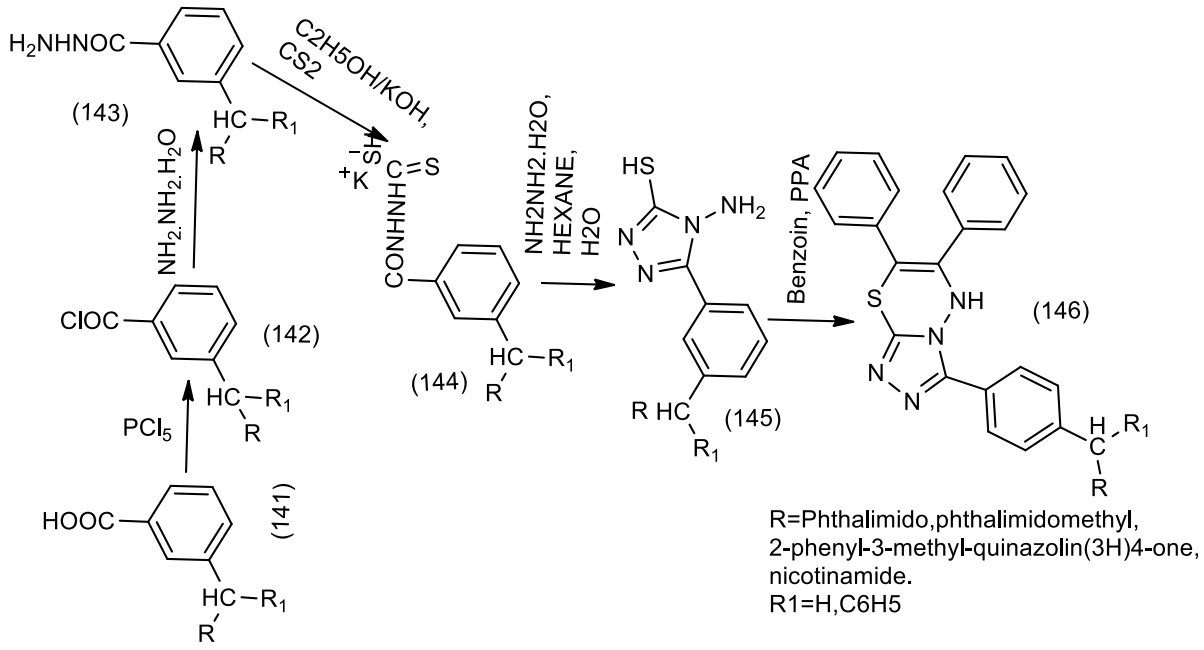
(i)= NH2-NH2 · H2O/EtOH, reflux 4 h, 70%; (ii) CS2/KOH/EtOH, reflux, 12 h, 71%;
(iii) NH2-NH2 · H2O/EtOH, reflux 6 h, 68%; (iv) Ar-COCH2Br/EtOH, reflux 6 h, 62–72%.

Scheme 35. Synthesized novel bis[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines (**140**).

A series of novel bis[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines (140) shows antimicrobial activity against various bacterial and fungal strains. Some of these compounds exhibit excellent antibacterial and antifungal activity and can be classified as antimicrobial agents.

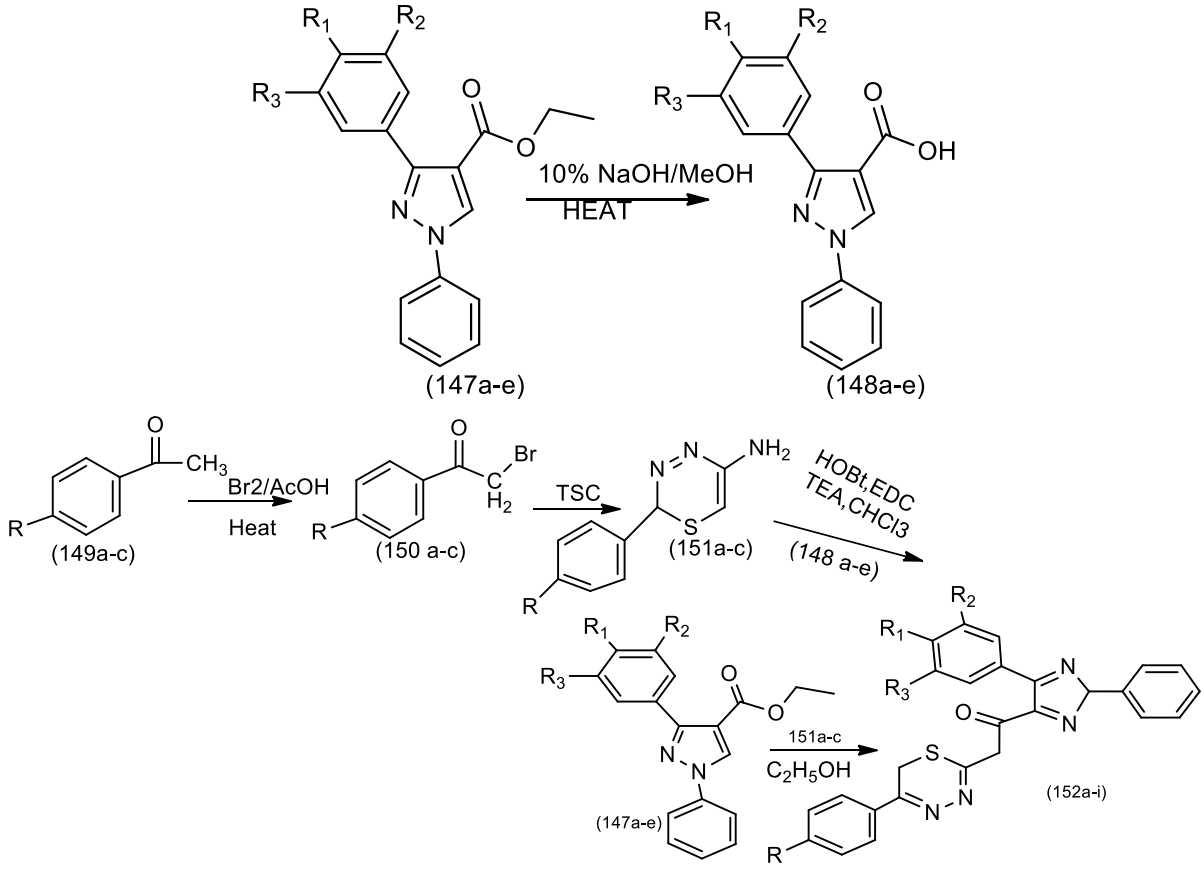
Pandey *et al.* synthesized a series of novel 4-amino-5-mercapto-3-[(3-aralkyl amido/imidoalkyl) phenyl]-1,2,4-triazoles **(145 a-d)** were obtained by treating m-(aralkyl amido/imidoalkyl) benzoic acid hydrazides **(143 a-d)** with carbon disulfide in alcoholic KOH and hydrazine hydrate, respectively. Condensation of these triazole derivatives **(145)** with benzoin in the presence of polyphosphoric formed 5-[(3-aralkyl amido/imidoalkyl) phenyl]-1,2,4- triazolo[3,4-b]-1,3,4-thiadiazines **(146 a-d)** (Scheme 36) [44].

The newly synthesized compounds were evaluated for their antiviral activity against two animal viruses, namely, Japanese encephalitis virus (JEV) strain P20778 and herpes simplex virus-1 (HSV-1) strain 753166, and showed moderate antiviral activity**.**



Scheme 36. 5-[(3-aralkyl amido/imidoalkyl) phenyl]-1,2,4- triazolo[3,4-b]-1,3,4-thiadiazines.

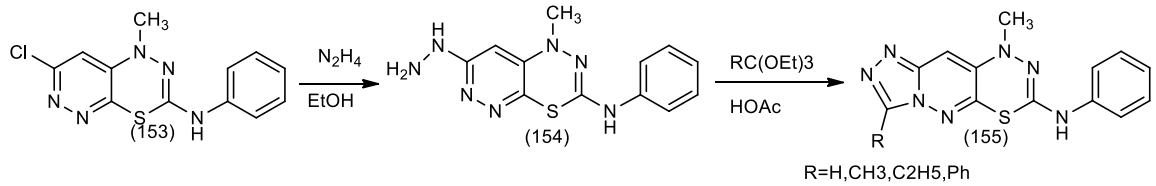
Shubhakar *et al.* synthesized 5-methyl-1,3-diphenyl-1H-pyrazole-4-carboxylic acid-(5-phenyl-6H-[1,3,4]-thiadiazin-2-yl)-amide **(152a-i)** in 30% yield by condensing 2-Amino-5-phenyl-6H-[1,3,4]-thiadiazine **(151 a-c)** with pyrazole-4-carboxylate **(147a-e)** using alcohol as a solvent. The same product is obtained from pyrazole-4-acid **(148a-e)** (Scheme 37) [45] in the presence of HOBt (1 -hydroxy benzotriazole) and EDC (N-ethyl-N'-(3-dimethyl-aminopropyl)-carbodiimide hydrochloride) in triethyl amine using $CHCl_3$ as a solvent, in 75-85% yields [45].



Scheme 37. Synthesized 5-methyl-1,3-diphenyl-1H-pyrazole-4-carboxylic acid-(5-phenyl-6H-[1,3,4]-thiadiazin-2-yl)-amide **(152a-i).**

The author found that all synthesized pyrazole-1,3,4-thiadiazine **(152a-i**) derivatives were found to exhibit antimicrobial activities against the human pathogenic bacterial strain *Bacillus cereus* (B. cereus), *Escherichia coli* (*E. coli*), *Klebsiella pneumonia* (K. pneumonia) and Shigella flexneri (S. flexneri) by the disc diffusion method.

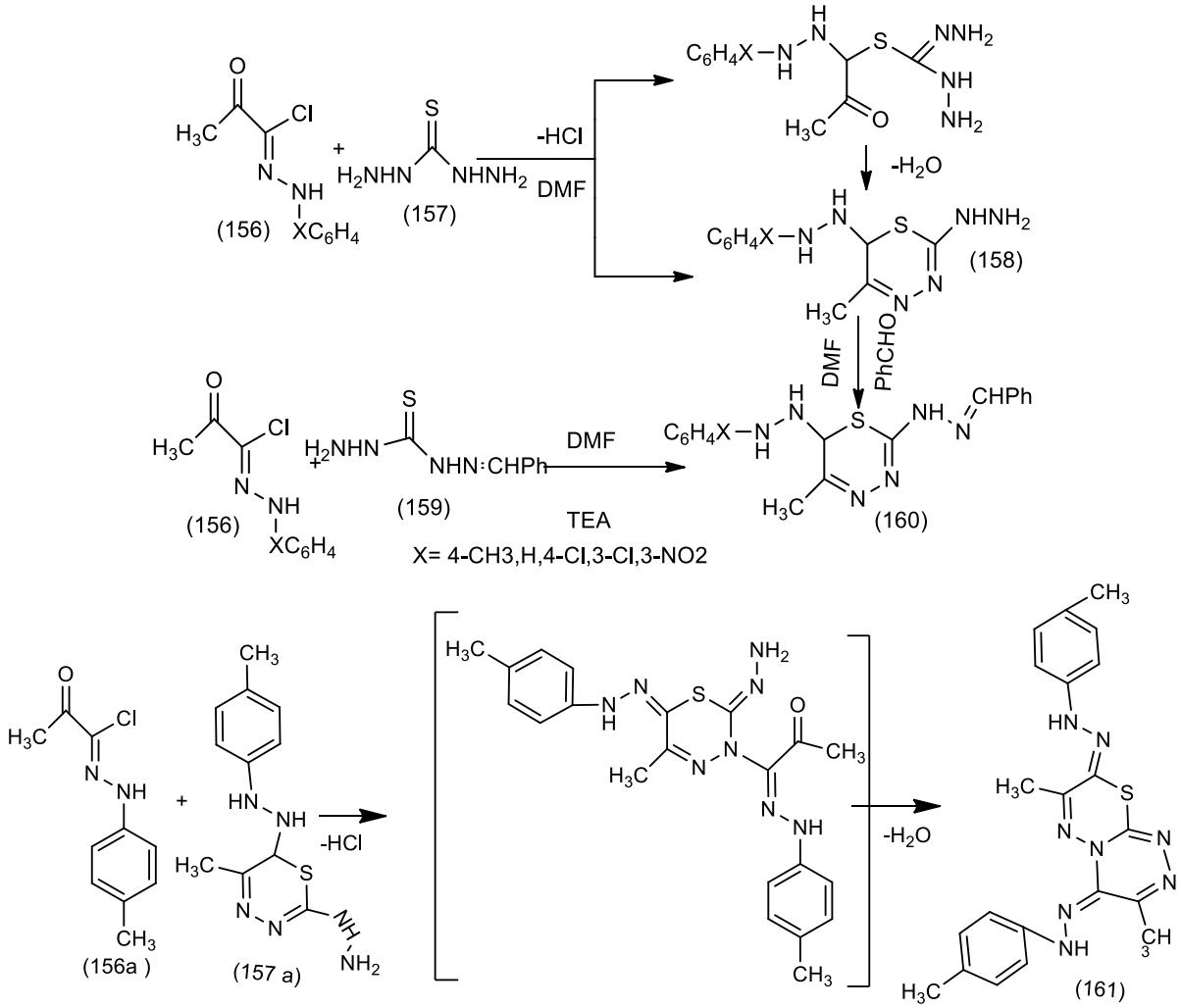
Rahimizadeh *et al.* synthesized a series of 1,2,4-triazolo [3 ′,4 ′ :6,1] pyridazino [4,3-e] [1,3,4] thiadiazines **(155)** by the reaction of 3-anilino- 7-chloro-1-methyl-1 H -pyridazino [4,3- e][1,3,4] thiadiazine **(153)** with hydrazine hydrate in refluxing ethanol form 3-anilino-7-hydrazino-1-methyl- 1 H -pyridazino[4,3- e][1,3,4]thiadiazine**(154)** which on cyclo condensation with triethyl ortho esters in acetic acid gives a final product **(155)** (Scheme 38) [46].



Scheme 38. synthesized a series of 1,2,4-triazolo [3 ′,4 ′ :6,1] pyridazino [4,3- e] [1,3,4] thiadiazines **(155).**

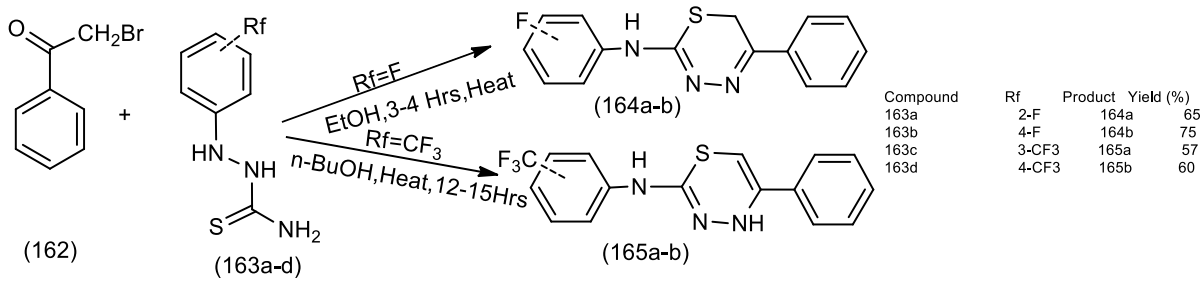
The author concluded that compounds **155a–d** are highly active against Bacillus subtilis and *Staphylococcus aureus* and less active against *Pseudomonas aeruginosa* and *Escherichia coli* Gram-negative bacteria.

Sayed *et al.* synthesized [1,3,4]thiadiazine **(160)** and [1,2,4]triazino[3,4-b][1,3,4] thiadiazine **(161)**, from the reaction of α-halo keto hydrazonoyl halides **(156)** with carbonothioic dihydrazide **(157)** (Scheme 39) and their analog respectively [47].



Scheme 39. Synthesized [1,3,4]thiadiazine **(160)** and [1,2,4]triazino[3,4-b][1,3,4] thiadiazine **(161).**

Shchegol' kov *et al.* synthesized Fluorinated 2-amino-5-phenyl-1,3,4-thiadiazines by refluxing α-bromoacetophenone **(162)** and (fluorophenyl)-thiosemicarbazides **(163a-d)** in ethanol. The synthesis of a product **(164 a-b)** containing more electron withdrawing group in phenyl ring required more drastic conditions like solvent t-BuOH having a higher boiling point than product **(165 a-b),** (Scheme 40) [48].

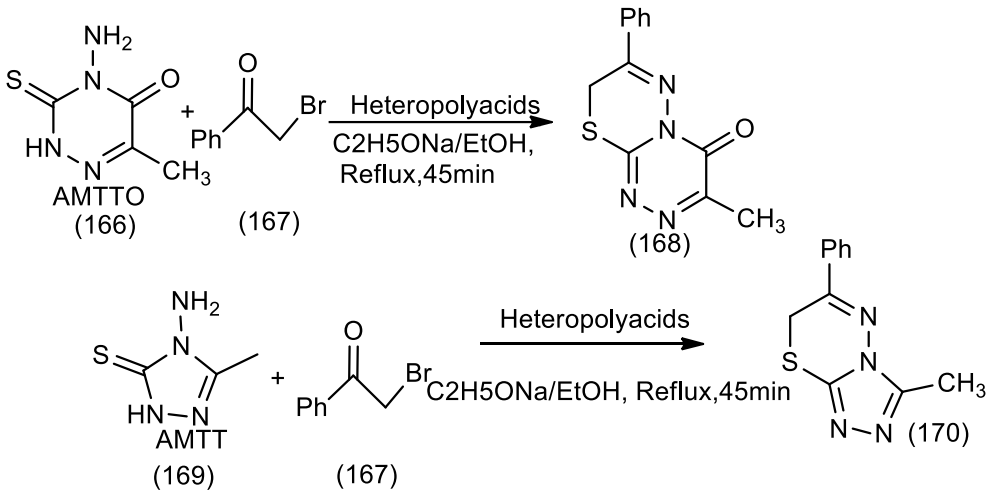


Compound	Rf	Product	Yield (%)
163a	2-F	164a	65
163b	4-F	164b	75
163c	3-CF3	165a	57
163d	4-CF3	165b	60

Scheme 40. Synthesized Fluorinated 2-amino-5-phenyl-1,3,4-thiadiazines.

: The author found that the electron-withdrawing F atoms change substances' reactivity and biological activity. In connection with this, fluorinated 2-amino,1,3,4-thiadiazines could be expected to be physiologically more active and/or have a broader spectrum of action.

Hakimi *et al.* Synthesized [3,4-b][1,3,4]thiadiazines **(168, 170**) from the condensation of 4-amino-6-methyl-3-thioxo- 1,2,4-triazine-5(2H)-one (AMTTO)**(166)** or 4-amino-1,4-dihydro-5-methyle-1,2,4-triazole-5-thione (AMTT)**(168)** with phenacyl bromide**(167)** in the presence of a catalytic amount of various hetero-poly acids (HPAs) under refluxing condition as a green and reusable catalyst (Scheme 41)[49]. Heteropoly anions exhibited interesting catalytic properties as green and eco-friendly catalysts and d a higher yield of 60-95% [49].

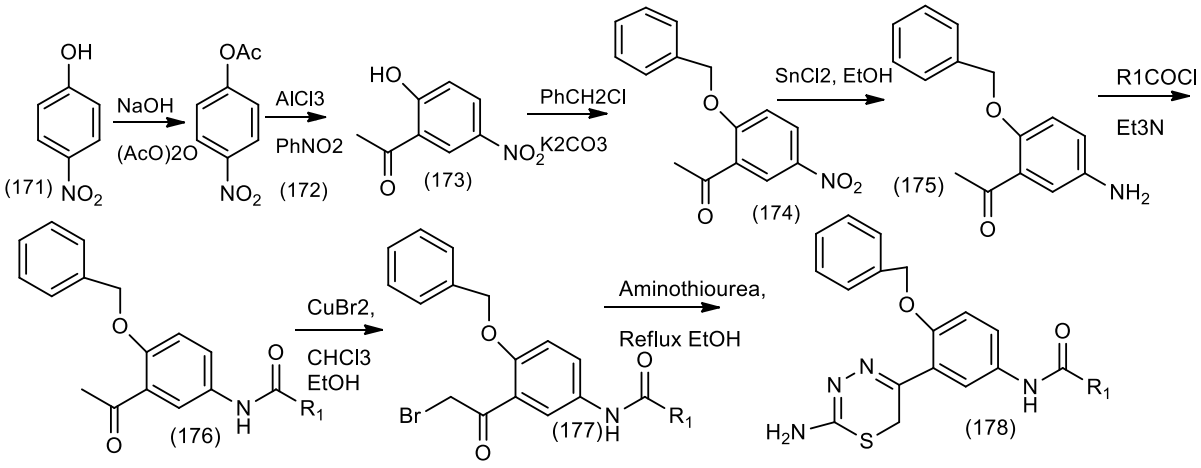


Scheme 41. Synthesized [3,4-b][1,3,4]thiadiazines **(168, 170**).

Shangguan *et al.* synthesized 2-amino-6H-1,3,4-thiadizines derivatives (178) and evaluated them as β-secretase (BACE-1) inhibitors from nitro phenol. 4-nitrophenol **(171)** on treatment with acetic anhydride in aqueous NaOH solution furnished 4-nitrophenyl acetate (**172**), which was converted to 2'-hydroxy-5'-nitro-acetophenone **(173)** through a Fries rearrangement catalyzed by AlCl3 in nitrobenzene. Alkylation of **(173)** with benzyl chloride in the presence of potassium carbonate in ethanol provided 2'-benzyloxy-5'-nitro-acetophenone **(174),** which was reduced using stannous chloride to yield 2'-benzyloxy-5'-amino-acetophenone **(175).** Then, **(175)** was condensed with different aromatic acyl chlorides to afford amides **(176),** which were brominated with CuBr2 in chloroform to give the α-

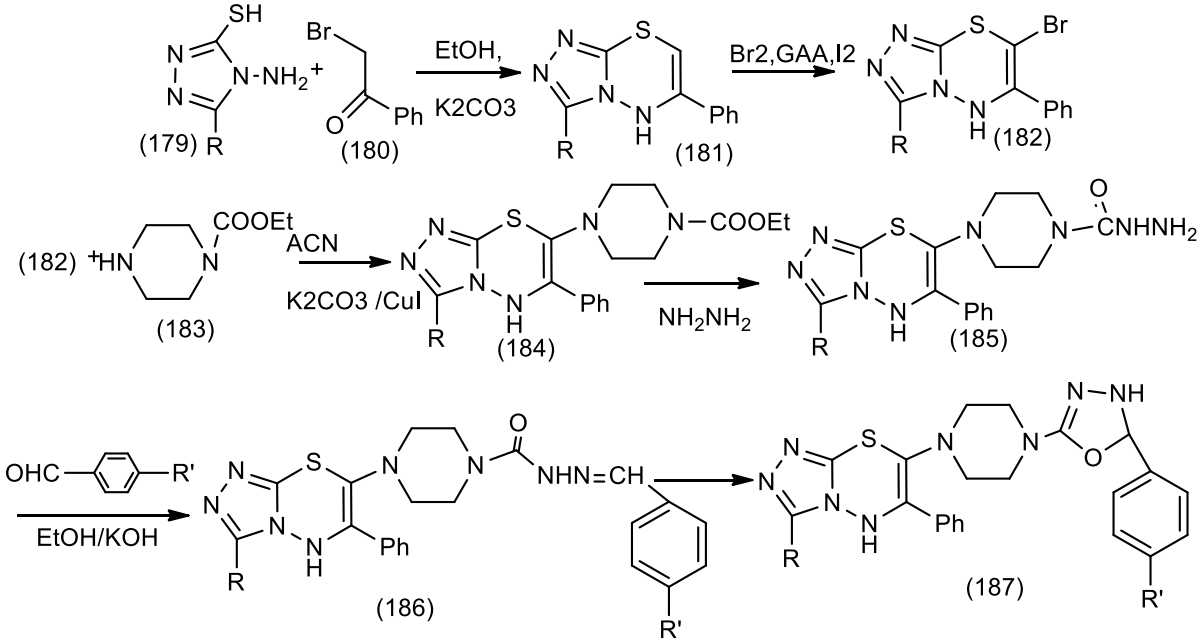
bromoacetophenone derivatives **(177)**. Finally, **(177)** were condensed with amino thiourea in ethanol or DMF and formed target compounds **(178)** (Scheme 42) [50].

The author found that the results show compounds (178) demonstrated promising BACE-1 inhibitory activities, and a preliminary SAR study revealed that a 2-amino-6*H*-1,3,4-thiadizine moiety and α-naphthyl group were favorable for BACE-1 inhibition.



Scheme 42. Synthesized 2-amino-6H-1,3,4-thiadizines derivatives (**178**).

Dabholkar *et al.* synthesised a new series of 7-{4-[5-(4-Methoxy-phenyl)-4,5-dihydro-[1,3,4] oxadiazol -2-yl]-piperazin-1-yl}-3-methyl-6-phenyl-5H-[1,2,4] triazolo[3,4-b][1,3,4]Thiadiazine **(187)** from -substituted-4-amino-5-mercapto-1,2,4-triazoles **(179)** by reaction with phenacyl bromide **(180)** (Scheme 43) [51].

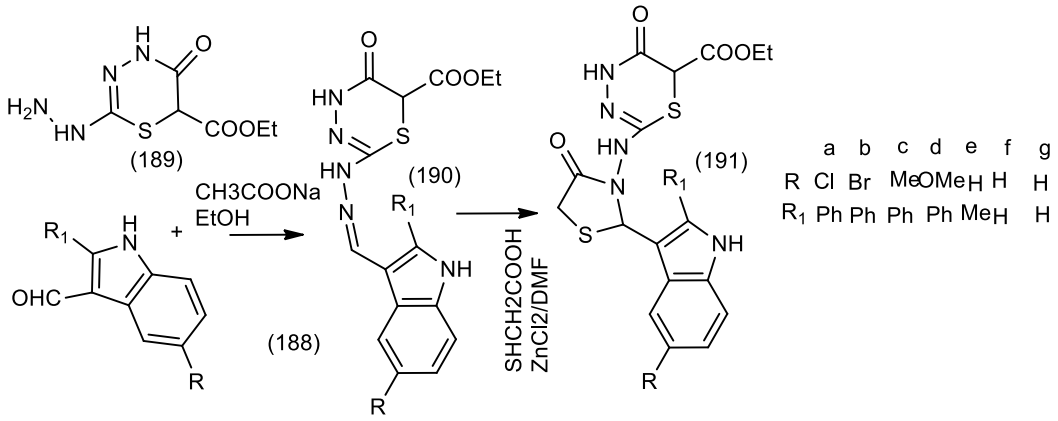


Scheme 43. synthesised new series of 7-{4-[5-(4-Methoxy-phenyl)-4,5-dihydro- [1,3,4] oxadiazol -2-yl]-piperazin-1-yl}-3-methyl-6-phenyl-5H-[1,2,4] triazolo[3,4-b][1,3,4]Thiadiazine **(187).**

The author observed that the compound (187) *in vitro* shows antimicrobial activity against gram-positive and gram-negative microorganisms.

Anekal and Biradar *et al.* synthesized A series of Ethyl 2-[2-(2,5-disubstituted-1H-indol-3-yl)-4-oxothiazolid-3-ylamino]-5,6-dihydro-5-oxo-4H-1,3,4 thiadiazine- 6-carboxylates (**191a–g**) from cyclocondensation of Ethyl 2 {(2E)-2-[(2,5-disubstituted-1H-indol-3-yl) methyleno] hydrazine}-5-oxo-5,6-dihydro- 4H-1,3,4-thiadiazine-6-carboxylates **(190a–g)** with thioglycolic acid in the presence of the catalytic amount of zinc chloride. The

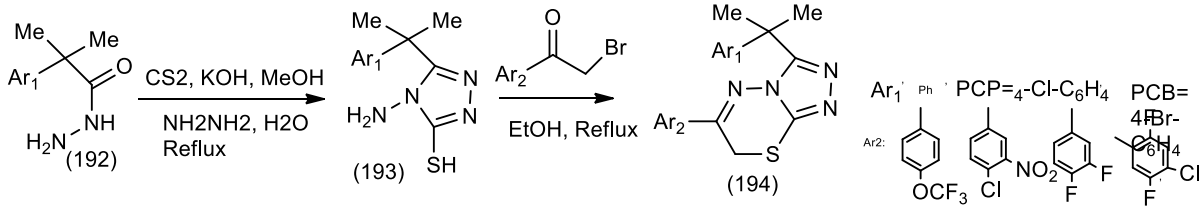
compounds **(190a–g)** were obtained from the reaction of Ethyl 2-hydrazinyl-5,6-dihydro-5-oxo-4H-1,3,4-thiadiazine-6-carboxylate **(189)** with various substituted indole-3-carboxaldehydes (**188a–g)** (Scheme 44) [52].



Scheme 44. Synthesized A series of Ethyl 2-[2-(2,5-disubstituted-1H-indol-3-yl)-4-oxothiazolid-3-ylamino]-5,6-dihydro-5-oxo-4H-1,3,4 thiadiazine- 6-carboxylates (**191a**–**g**).

Among the title compounds, 191c, 191d, and 191f have shown analgesic properties, and 191a-f has displayed significant anti-inflammatory properties.

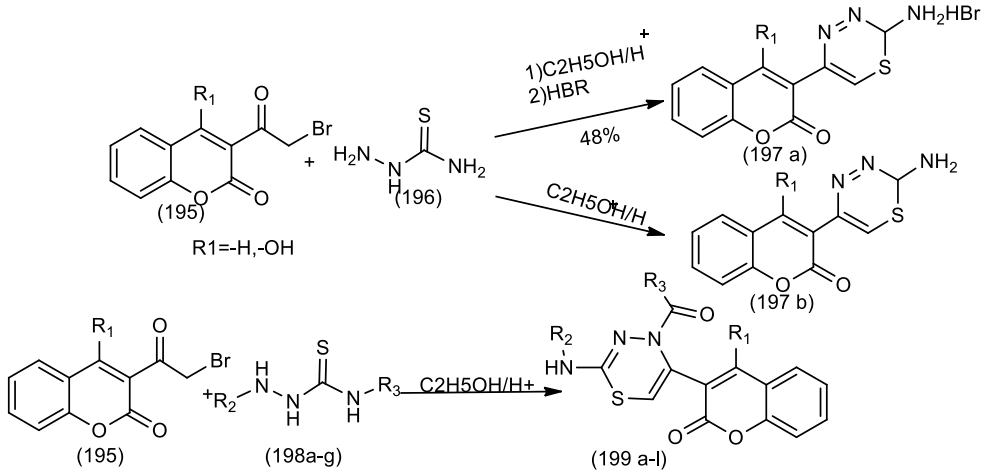
Puthiyapurayil *et al.* synthesized a Novel Series of 6-Arylsubstituted-3-[2-(4-substituted phenyl) propan-2-yl]-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines **(194),** (Scheme 45) [53].



Scheme 45. Synthesized synthesized a Novel Series of 6-Arylsubstituted-3-[2-(4-substituted phenyl) propan-2-yl]-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines **(194)**.

Cacic *et al.* synthesized coumarin derivatives of 1,3,4-thiadiazines i.e. 5-(2-oxo-2H-chromen-3-yl)-6H-1,3,4-thiadizin-2-aminium bromide **(197 a)** and 3-(2-amino-6H-1,3,4-thiadiazin-5-yl)-4-hydroxy-2H-chromen-2-one **(197 b).** from 3,α- bromoacetylcoumarin **(195)** and thiosemicarbazide **(196)** [54].

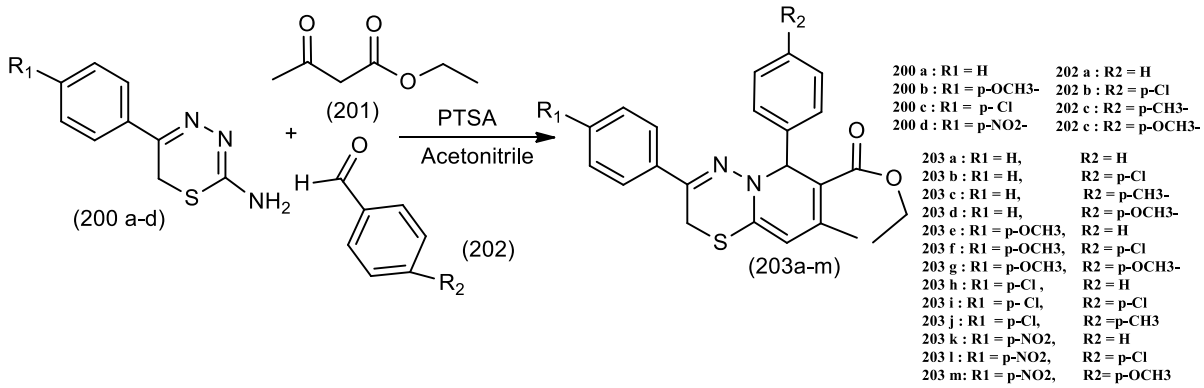
Compound **(195)** on treatment with **(198 a-g)** in the presence of ethanol gives 4H-1,3,4-thiadiazines derivatives**(199a–l)** (Scheme 46) [54].



Scheme 46. 4H-1,3,4-thiadiazines derivatives (**199a–l**).

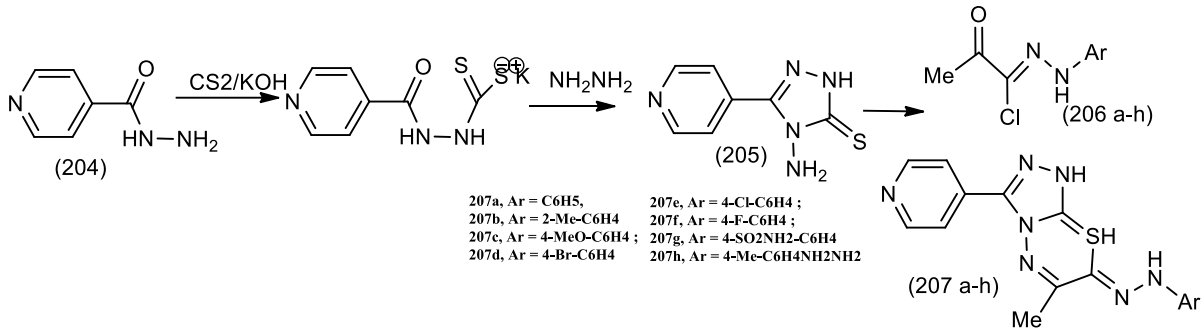
The author observed that coumarin derivatives of 1,3,4-thiadiazine were subjected to antioxidant (DPPH scavenging, iron chelating and reducing power) and antifungal investigation on four mycotoxicogenic fungi, *A. flavus*, *A. ochraceus*, *F. graminearum* and *F. verticillioides* namely. The new thiadiazine derivatives were proven to possess excellent antioxidant activity, comparable to ascorbic acid, while not showing reducing power activity simultaneously.

Shubakara *et al.* synthesized a series of ethyl 8-methyl-3,6-diphenyl-2,6-dihydropyrimido [2,1-b][1,3,4] thiadiazine-7-carboxylate derivatives **(203 a-m)** in excellent yield by the cyclocondensation reaction of 2-amino-6H-1,3,4- thiadiazines **(200a-d)** with ethyl acetoacetate **(201)** and various substituted aldehydes **(202a-d)** in the presence of the catalytic amount of PTSA in acetonitrile using multi-component reaction in one pot process, Scheme 47) [55].



Scheme 47. Ethyl 8-methyl-3,6-diphenyl-2,6-dihydropyrimido [2,1-b][1,3,4] thiadiazine-7-carboxylate derivatives (**203 a-m**).

The newly synthesized compounds 203 (a-m) were screened by Umesha *et al.* for *in vitro* antibacterial activity against *Bacillus cereus* (MTCC 8372), *Staphylococcus aureus* (MTCC 96) (gram-positive bacteria) *Escherichia coli* (MTCC 724) and *Klebsiella pneumonia*, (gram-negative bacteria) using the agar disc diffusion method and shows good antimicrobial activity Bhat *et al.* synthesized a series of derivatives of [hydrazinylidene] -6-methyl-3-(pyridin-4-yl)-7H-[1,2,4] triazolo[3,4-b][1, 3, 4]thiadiazine**(207)** from the reaction of 4-amino-3-(4-pyridyl)-5-mercapto-4H-1,2,4-triazole **(205)** with substituted aryl hydrazonoyl chlorides **(206).** Compound **(205)** is formed by dissolving isonicotinic acid hydrazide **(204)** ethanol containing KOH, which on further treatment with CS2 followed by reaction with hydrazine at specific reaction conditions gives compound (**205)** [56].

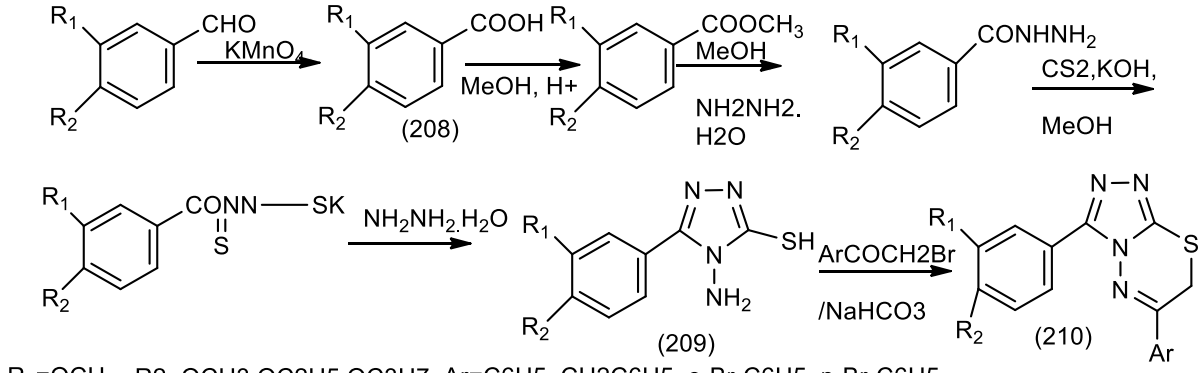


Scheme 48. Synthesized a series of derivatives of [hydrazinylidene] -6-methyl-3-(pyridin-4-yl)-7H-[1,2,4] triazolo[3,4-b][1, 3, 4]thiadiazine**(207).**

The author tested all the derivatives *in vitro* against eleven candida species, showing good anticandidal activity and potential cytotoxicity on non-cancer cell lines**.** Among these

compounds, the compounds bearing p-chlorophenyl **207e,** p-methoxyphenyl **207c**, phenyl **207a**, and p-sulphonamidophenyl **207g** substituents on triazolothiadiazine system were found to be the most effective derivatives against *Candida* species.

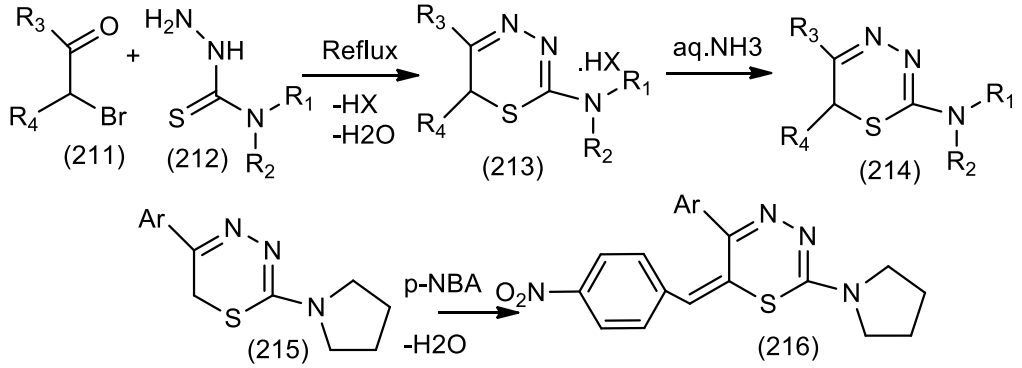
Sahu, *et al.* synthesized a series of 6-aryl-3- (3,4 -dialkoxyphenyl)-7H -[1,2,4]triazolo [3,4-b][1,3,4] thiadiazine **(210a-k)** was synthesized by condensing 4-amino-5-(3,4-dialkoxyphenyl)-4H-[1,2,4]-triazole-3-thiol **(209)** with various aromatic carboxylic acids**(208)** in the presence of phenacyl bromides through one-pot reaction (Scheme 49) [57].



Scheme 49. Synthesized 6-aryl-3- (3,4 -dialkoxyphenyl)-7H -[1,2,4]triazolo [3,4-b][1,3,4] thiadiazine.

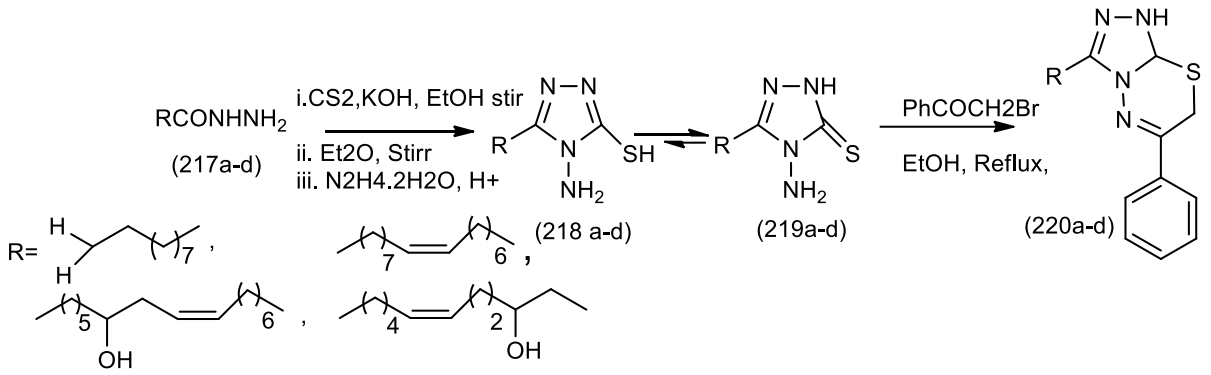
The antibacterial activity of the newly synthesized compounds **210 a-k** was reported as minimum inhibitory concentration (MIC) at the concentration range 1.56-100 μg/ml against *S. aureus*, B. cereus (gram-positive bacteria) and *E. coli*, *P. aeruginosa* (gram-negative bacteria) using Gentamycin as standard. *S. aureus*, B. cereus (gram-positive bacteria) and *E. coli*.

Knak, *et al.* synthesized a variety of 2-pyrrolidino-, 2-N-methylpiperazino-, 2-piperidino, and 2-morpholino-1,3,4-thiadiazines **(214)** were prepared by cyclocondensation of phenacyl halides **(212)** with thiosemicarbazides **(213)**. 2-pyrrolidino-5-aryl-(4-nitrophenylbenzylidene)- 1,3,4-thiadiazines prepared **(216)** (Scheme 50) in the presence of p.NBA [58].



Scheme 50. Synthesized 2-pyrrolidino-5-aryl-(4-nitrophenylbenzylidene)- 1,3,4-thiadiazines.

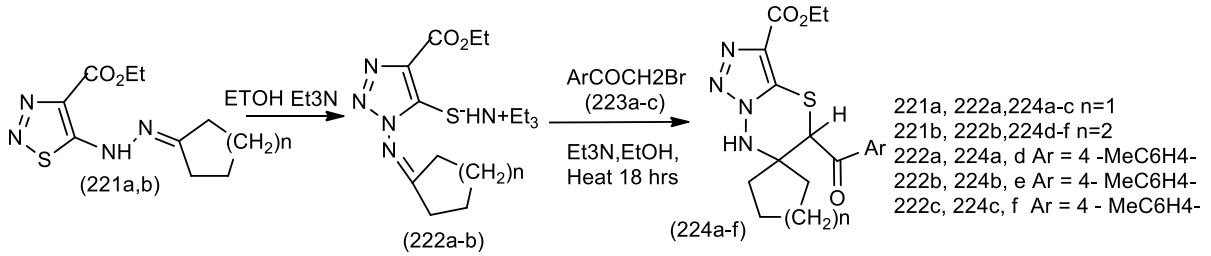
A. Ahmad *et al.* synthesized alkenyl/hydroxyalkenyl-6-phenyl-(7H)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines(220) using long chain alkenyl /hydroxy alkenyl hydrazides (217) Scheme 51) [59].



Scheme 51. Sinthesized alkenyl/hydroxyalkenyl-6-phenyl-(7H)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines(**220**).

The author observed that thione derivatives dominate, and all compounds show anticancer activity *in vitro* against PBMCs and three different human cancer cell lines. Based on the result author concluded that the potency of drugs depends on the nature of FA chain and the electrocyclic ring system.

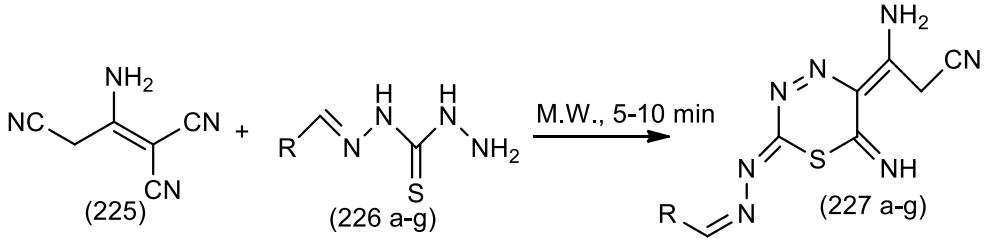
Kalinina *et al.* synthesized spirocyclic 6,7-dihydro-5H-[1,2,3]triazolo[5,1-b][1,3,4]thiadiazines **(224 a-f)** from 3-Cyclopentylidene(cyclohexylidene)amino-3H-1,2,3-triazole-4-thiolates,**(222a-b)** via Dimroth rearrangement of 1,2,3-thiadiazolylhydrazones of cyclopentanone and cyclohexanone **(221a,b)** in the presence of triethylamine, reacted in situ with α-bromoacetophenones **(223a-c)** (Scheme 52) [60].



Scheme 52. Synthesized spirocyclic 6,7-dihydro-5H-[1,2,3]triazolo[5,1-b][1,3,4]thiadiazines **(224).**

Compounds **(224a, b)** stimulate the growth of human embryonic kidney cells HEK-293 and rhabdomyosarcoma tumor cells RD while inhibiting the growth of normal human fibroblasts. Compound **(224d)** shows cytotoxic effects against all cell types except tumor culture RD. Compounds **(224c,e,f)** exhibit stimulating activity in regards to the normal fibroblasts while having cytotoxic effects on tumors and transformed cell lines.

Elkanzi *et al.* Synthesized 6-Imino-1,3,4-thiadiazines **(227 a–g)** from the reaction of malononitrile dimer **(225)** with thiocarbohydrazones **(226a–g)** (Scheme 53) under MW for 5-10 minutes using green synthesis [61].

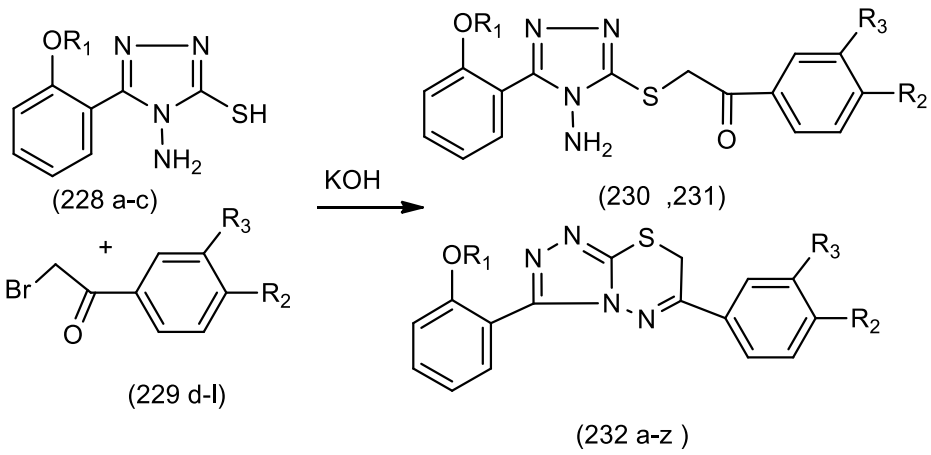


R=a=C6H5(72%), b=4-Me-C6H4(80%), c=4-NO2-C6H4(60%), d= OH-C6H4(65%),e= 4-NH2-C6H4, f=naphthyl(75%, g =2-(5-methylfuryl(65%)

Scheme 53. Synthesized 6-Imino-1,3,4-thiadiazines (**227 a–g**).

Iradyan *et al.* synthesized 3,6-diaryl-7H-[1,2,4] triazolo[3,4-b]- [1,3,4]thiadiazines **(232 a-z)**from 4-amino-5-(2-alkoxyphenyl)-4H-[1,2,4]triazole-3-thiols **(228 a-c)** on treatment

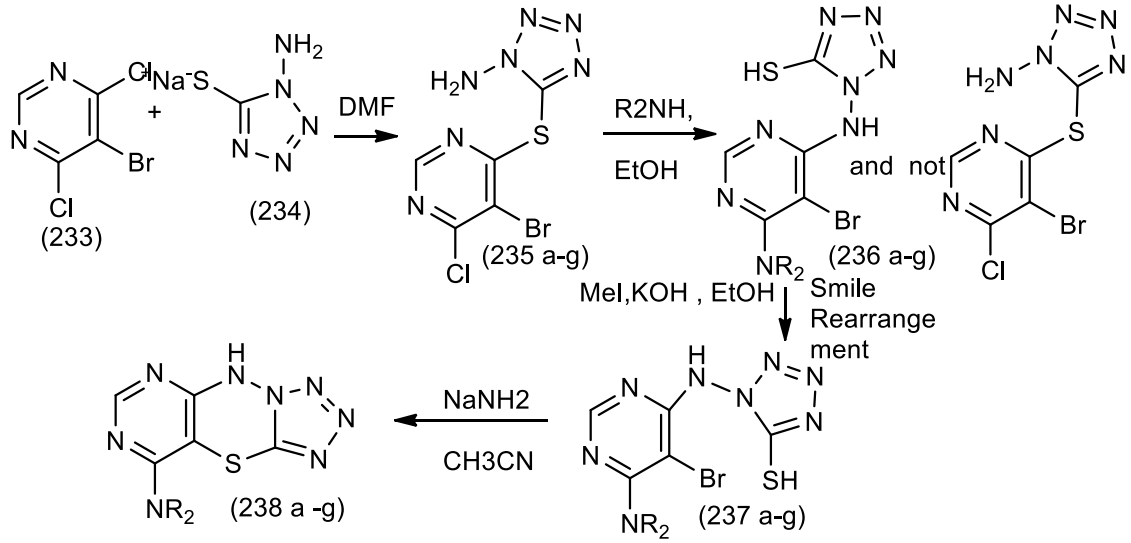
with substituted phenacyl bromides **(229 d-l)** in presence equimolar amount of potassium hydroxide, the HBr evolved during reaction catalyzed intra-molecular cyclization. In some cases, the reaction involves forming intermediate non-cyclized products **(230,231**) (Scheme 54) [62].



Scheme 54. Synthesized 3,6-diaryl-7H-[1,2,4] triazolo[3,4-b]- [1,3,4]thiadiazines **(232).**

All the derivatives formed show antimicrobial activity against Gram-positive *Staphylococci* and Gram-negative rods.

Igei *et al.* synthesized new pyrimido[4,5-e] tetrazolo[5,1-b] [1,3,4] thiadiazine derivatives(**238a-g)** via an S–N type Smiles rearrangement using 5-bromo-4,6-dichloropyrimidin **(233)** as starting material on reaction with sodium 1-amino-1H-tetrazole-5-thiolate **(234)** form **(235a-g)** which on further reaction with amine form intermediate **(236)** This on smile rearrangement form compound **(237a**-g), the compound (**237)**on refluxation on with NaNH2 in dry acetonitrile form final product **(238 a-g.)** (Scheme 55) [63].



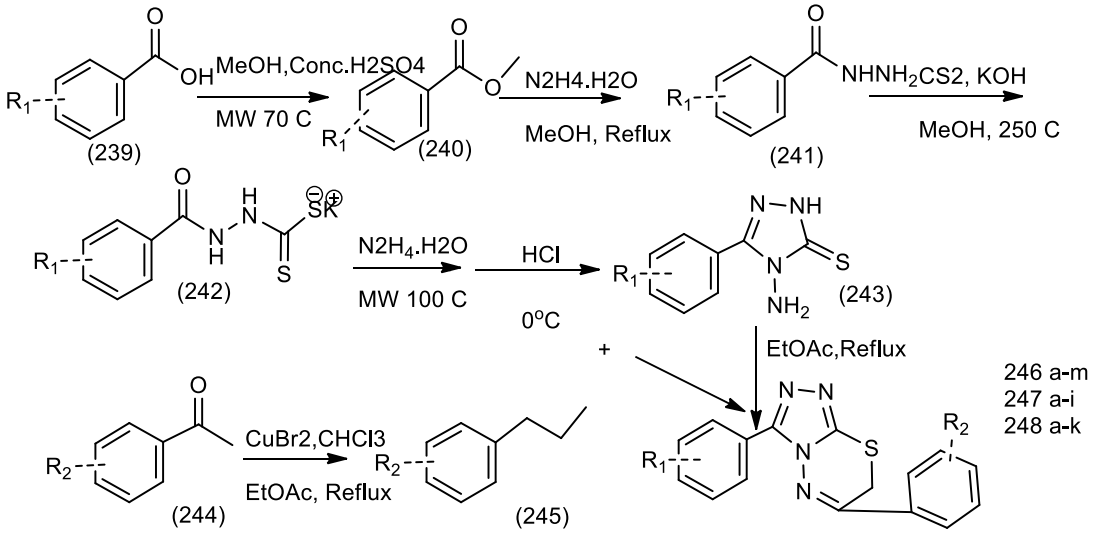
NR2=a= Pyrrolidin-1-yl, b=Piperidin-1-yl, c=4-Me-piperidin-1-yl, d=morpholin-1-yl, e=4-Me-piperazine-1-yl , f=4-Et--piperazine-1-yl , g=4-Ph–piperazine-1-yl

Scheme 55. New pyrimido[4,5-e] tetrazolo[5,1-b] [1,3,4] thiadiazine derivatives (**238a-g).**

The newly synthesized 238 a-g compounds exhibit minimal antibacterial activity against *Proteus mirabilis* (PTCC 1776); B: *Bacillus subtilis* subsp. spizizenii (PTCC 1023); C: *Proteus vulgaris* (PTCC 1079); D: Salmonella typhi (PTCC 1609); E: *Streptococcus pneumoniae* (PTCC 1240); F: *Staphylococcus aureus* (PTCC 1189); G: Rhodococcus equi (PTCC 1633); H: *Bacillus thuringiensis*.

Xu *et al.* [64] synthesized a series of 3,6-diaryl-7 H-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazine as novel tubulin inhibitors. The substituted benzoic acids (239) on treatment with excess methanol with concentrated sulfuric acid as catalyst form corresponding esters (240), which on further reaction with 80% hydrazine monohydrate in methanol to give hydrazides(241) under microwave (250 W, 70 ^{o}C) irradiation. The hydrazides **(241)** reacted with carbon disulfide and potassium hydroxide in methanol to give corresponding dithiocarbazinates **(242),** and then dithiocarbazinates **(242)** further reacted with excess 80% hydrazine monohydrate to form the key intermediate aryl triazoles **(243).**

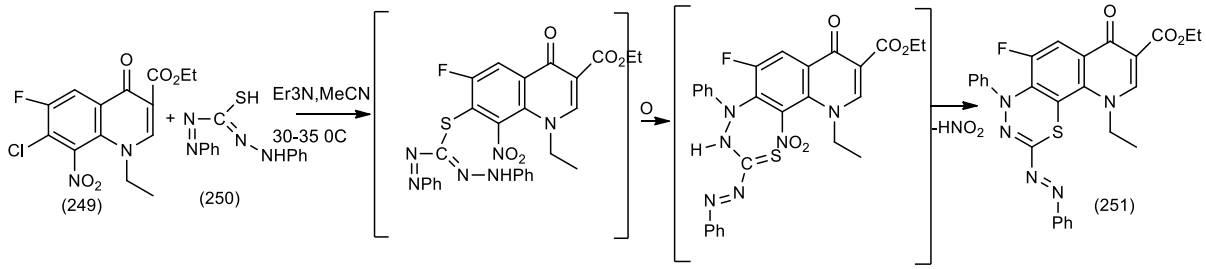
Commercially available starting acetophenones **(244)** were subjected to α-bromination with copper bromide in refluxing chloroform/ethyl acetate to get α-bromoacetophenones **(245)** shown in scheme 56 **[64].** Finally, α-bromoacetophenones **(245),** in reaction with aryl triazoles **(243),** form final compounds in ethanol within 5 min under microwave (250 W, 80 °C) irradiation in the absence of catalysts.



Scheme 56. Synthesis of thiadiazine (**246**, **247** and **248**).

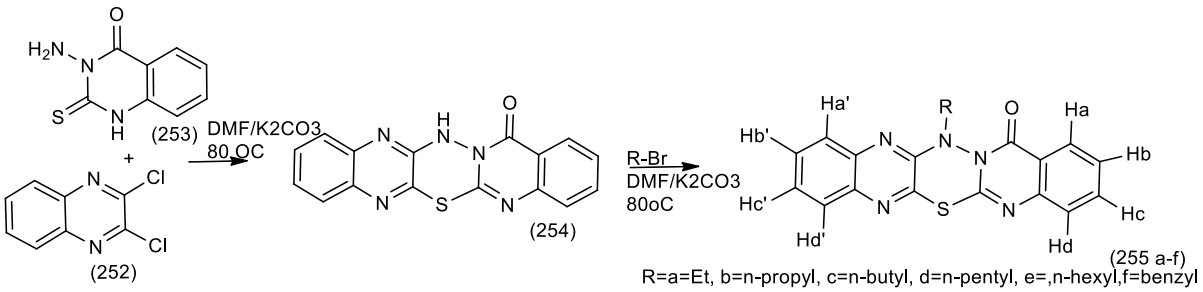
El-Abadelah *et al.* synthesized 5-fluoro-7-oxodihydo[1,3,4]thiadiazino [5,6-h]quinoline-8-carboxylic acid and ester **(251)** from 7-chloro-8-nitro-4-oxoquinoline derivatives **(249)** on reaction with 1-fluoro-2,4-dinitrobenzene with dithizone **(250).**

Compound **(251)** in scheme 57, exhibited moderate activity against *S. aureus* (MIC = 25 μg mL−1) but was inactive against *E. coli***.** [65].



Scheme 57. Synthesized 5-fluoro-7-oxodihydo[1,3,4]thiadiazino [5,6-h]quinoline-8-carboxylic acid and ester **(251).**

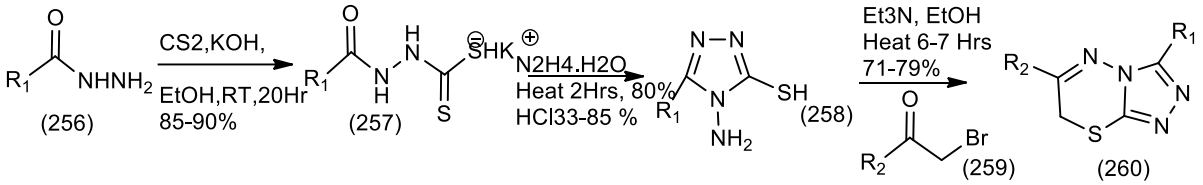
Mousavi *et al.* synthesized Quinoxalino[2',3':5,6][1,3,4]thiadiazino[2,3-b]quinazolin-15-one(255) in scheme 58, a novel fused heterocyclic system, from a one-pot condensation reaction of 2,3-dichloroquinoxaline(252) and 3-amino-2-thioxo-2,3-dihydroquinazolin-4(1H)-one(253) under mild condition [66].



Scheme 58. Synthesized Quinoxalino[2',3':5,6][1,3,4]thiadiazino[2,3-b]quinazolin-15-one(**255**).

Kulikov *et al.* synthesized 7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazinesbased on a condensation reaction between aryl(hetaryl) α-bromo ketones and commercially available thiocarbohydrazide, followed by treatment of the obtained 2-hydrazinyl-6H-1,3,4-thiadiazine hydrobromides with ortho esters in the presence of trifluoroacetic acid under mild conditions [67].

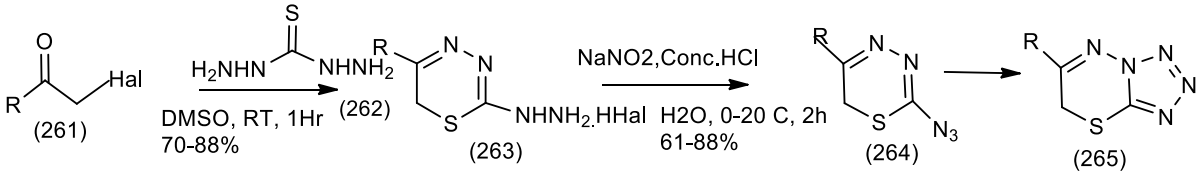
The compounds **(260)** formed from the synthesis of 5-substituted 1,2,4-triazoles **(258)** that contain reactive vicinal amino and mercapto groups, followed by annulation of thiadiazine ring by reacting triazoles (**258**) with α-halo ketones R1 synthesis of the starting 1,2,4-triazoles **(258)** and their subsequent transformations are performed with toxic reagents (CS2, N2H4·H2O) and at elevated temperatures (Scheme 59) [67].



R1= i-Pr, 4-Py, R2= Ar

Scheme 59. 7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines.

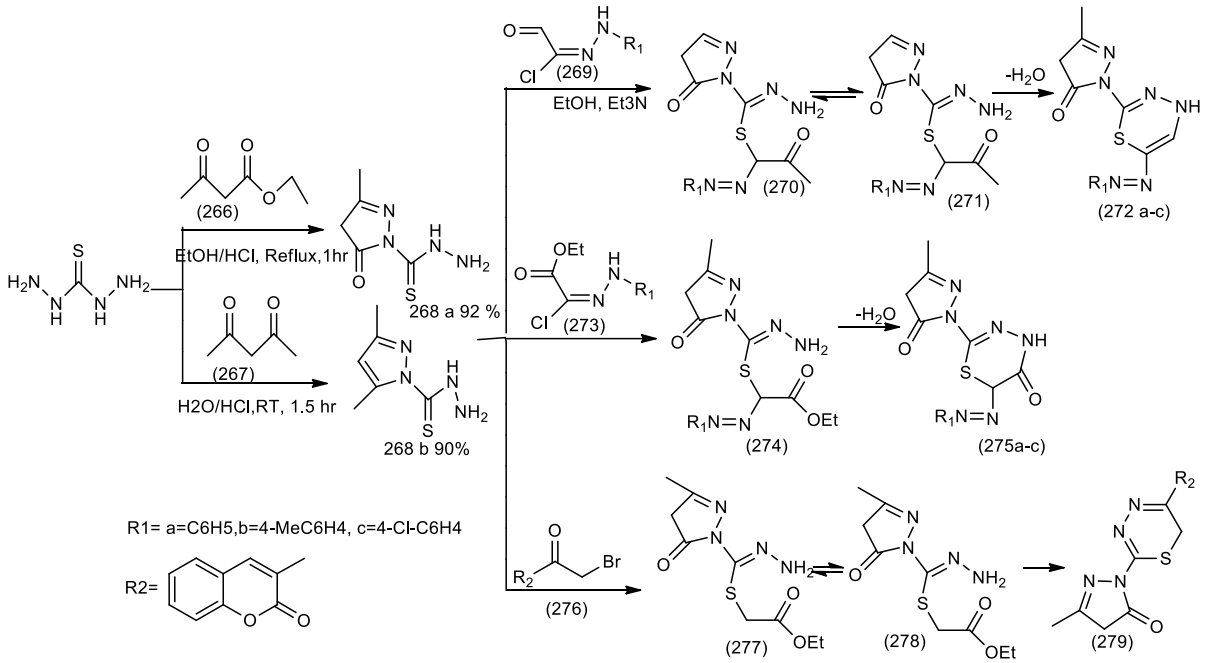
In contrast to that, Alexander S.Kulikov *et al.* recently developed a method for the synthesis of 7H-tetrazolo[5,1-b][1,3,4]thiadiazines **(265).** The method includes condensation of α-bromo ketones **(261)** with the commercially available thiocarbohydrazide **(262)** at room temperature in DMSO and nitrosation of the formed 2-hydrazinyl-1,3,4- thiadiazine hydrobromide **(263)** by treatment with NaNO2 in hydrochloric acid. The nitrosation product – azido derivative (264) undergoes azide-tetrazole tautomerism, the equilibrium of which is completely shifted toward the tetrazole form. (Scheme 60) [67].



Scheme 60. Synthesis of 7H-tetrazolo[5,1-b][1,3,4]thiadiazines **(265).**

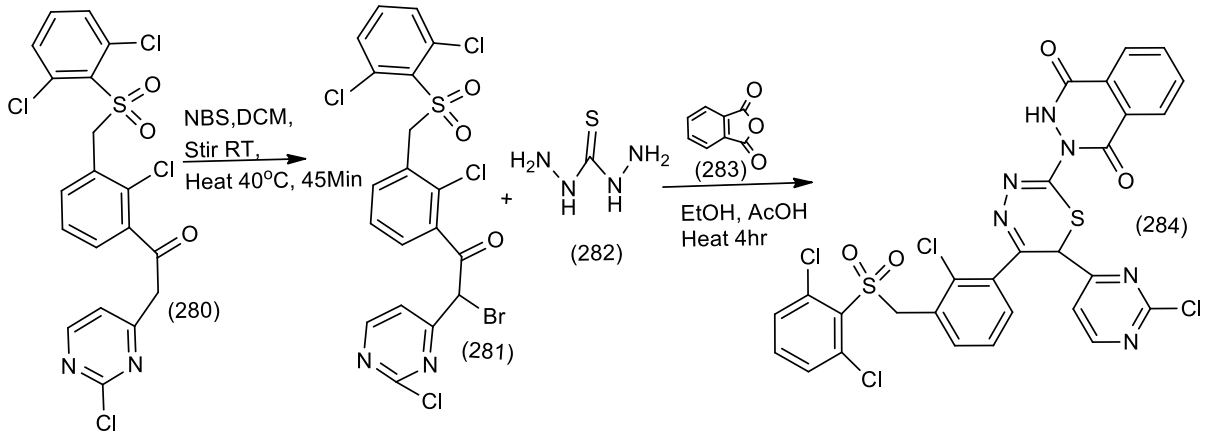
Radini *et al.* synthesized a novel series of pyrazolyl 1,3,4-thiadiazines **272a**–**c**, **275a**–**c**, **279**, from the reaction of pyrazole-1-carbothiohydrazide (**268 a)**, with 2-oxo-N'-arylpropane hydrazonoyl chloride **(269)** , 2-chloro-2-(2-arylhydrazono)acetate**(273**) and 3-bromoacetyl coumarin**(276)** in scheme 61, respectively [68].

The author observed that the presence of free carbothiohydrazide moiety increases antimicrobial activity.



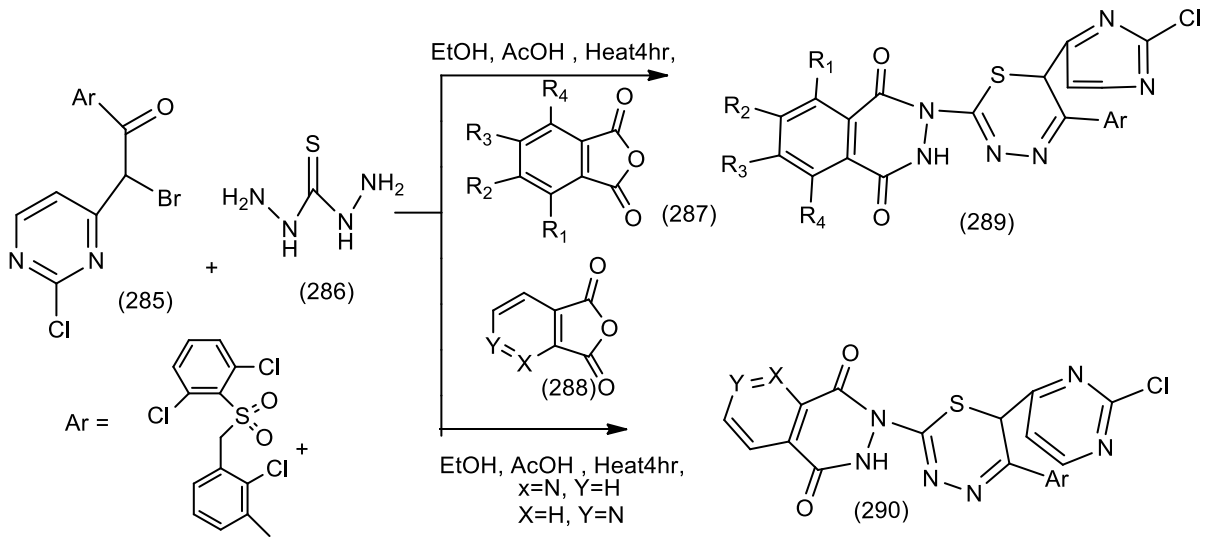
Scheme 61. Synthesized a novel series of pyrazolyl 1,3,4-thiadiazines **272a–c**, **275a–c**, **279.**

Gudala *et al.* [69] Synthesized series of novel, multifunctional 2,6-dichloro-N-(2-chloro-3-(6-(2-chloro pyrimidin-4-yl)-2-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-6H-1,3,4-thiadiazin-5-yl) phenyl) benzene sulfonamide **(284)** bearing phthalazines, by the reaction of (3-(2-bromo-2-[2-chloropyrimidin-4-yl] acetyl)-2-chlorophenyl)-2,6-dichloro benzene-sulfonamide **(281)** with thiocarbohydrazide **(282)** and various anhydrides **(283)** in Scheme 62 [69].



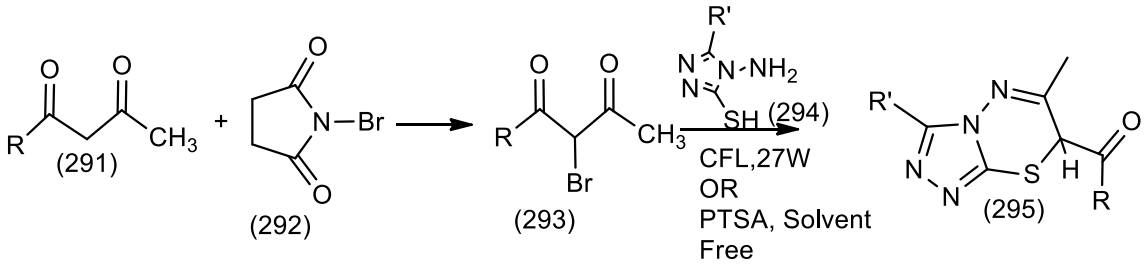
Scheme 62. Synthesized 2,6-dichloro-N-(2-chloro-3-(6-(2-chloro pyrimidin-4-yl)-2-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-6H-1,3,4-thiadiazin-5-yl) phenyl) benzene sulfonamide **(284).**

Gudala *et al.* [69] also Synthesized series of novel 1,3,4-thiadiazine derivatives **(289, 290**) bearing phthalazines, pyridazines and pyrido pyridazines by the reaction of (3-(2-bromo-2-[2-chloropyrimidin-4-yl] acetyl)-2-chlorophenyl)-2,6-dichloro benzene-sulfonamide**(285)** with thiocarbohydrazide **(286)** and various anhydrides **(287, 288)** in scheme 63.



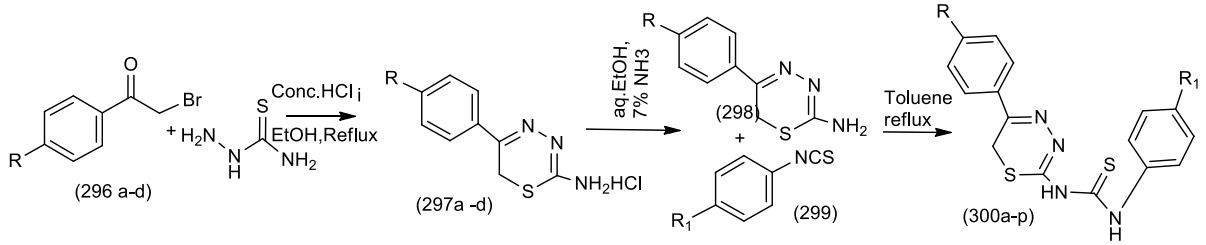
Scheme 63. Synthesized series of novel 1,3,4-thiadiazine derivatives **(289, 290)**.

Aggarwal *et al.* synthesized novel [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines (295) by the reaction of α-bromodiketones (293), generated in situ by the bromination of a diverse array of β-diketones(291) with N-bromosuccinimide (192), with 4-amino-[1,2,4]triazole-3-thiols (294) in scheme 64 [70].



Scheme 64. Synthesized novel [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines (**295**).

Ragab *et al.* synthesized a series of thiourea derivatives of 1,3,4-thiadiazines (300a-p) by a cyclocondensation reaction through the stirring of phenacyl bromide derivatives (296a-d) with thiosemicarbazide in ethanol, Catalytic amount of hydrochloric acid was added followed by neutralization of (297a-d) by the addition of a 7% solution of NH_4OH form the thiadiazine derivatives (298a-d). The thiourea derivatives (300a-p were synthesized by refluxing (298a-d) with various phenyl isothiocyanates (299a-d) (scheme 65) in toluene [71].



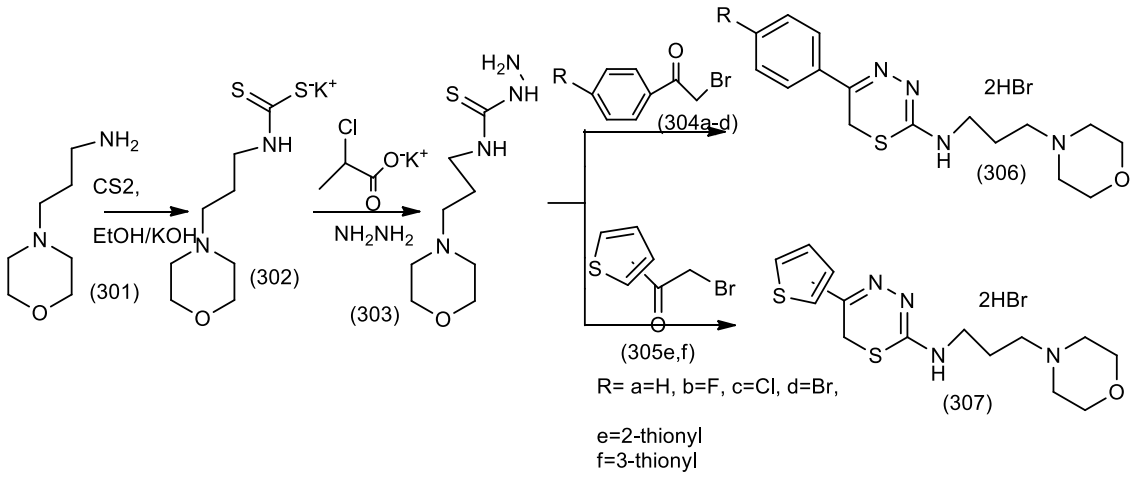
Scheme 65. Synthesized series of thiourea derivatives of 1,3,4-thiadiazines (**300a-p**).

The newly synthesized compounds 300a-p were screened for their cytotoxic activity against A549 cell line using MTT assay. The cytotoxic activity was measured as the concentration that reduces the growth of the cancer cells by 50%, represented as IC50 μM.

Tseitler *et al.* synthesized group of novel 2-propylmorpholino-5-aryl- and 5-thienyl-6H-1,3,4-thiadiazine dihydrobromides **(306, 307)** by cyclocondensation of 4-[3-(4-

morpholino) propyl]-3-thiosemicarbazide **(303**) with _-haloacetoarenones **(304)** or α-haloacetyl thiophenones **(305**) (Scheme 66) [72].

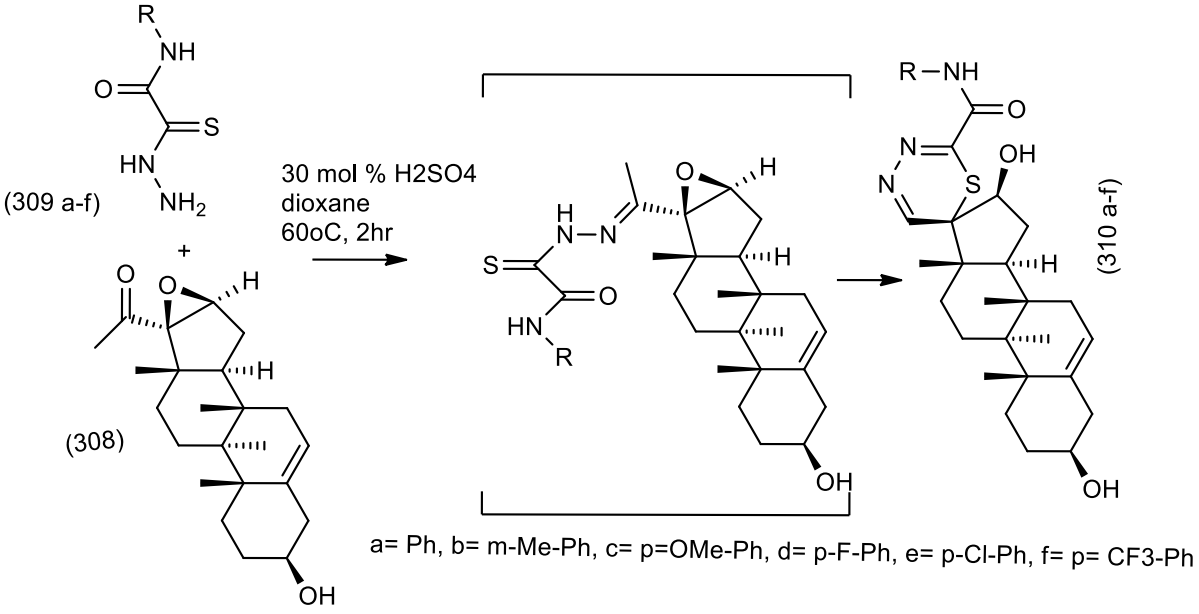
Two compounds of this group were found to produce effective inhibition of non-enzymatic protein glycation in an *in vitro* model system.



Scheme 66. Synthesized synthesized group of novel 2-propylmorpholino-5-aryl- and 5-thienyl-6H-1,3,4-thiadiazine dihydrobromides **(306, 307).**

Komendantova *et al.* synthesized (N-Aryl carbamoyl) spiroandrostene-17,6′ [1,3,4] thiadiazines and (N-aryl carbamoyl)17-[1′,3′,4′]thiadiazine-substituted androstanes, novel types of heterosteroids, were from 16β,17β-epoxypregnenolone and 21-bromopregna-5,16-dien-20-one in good to high yields by the treatment with oxamic acid thiohydrazides [73].

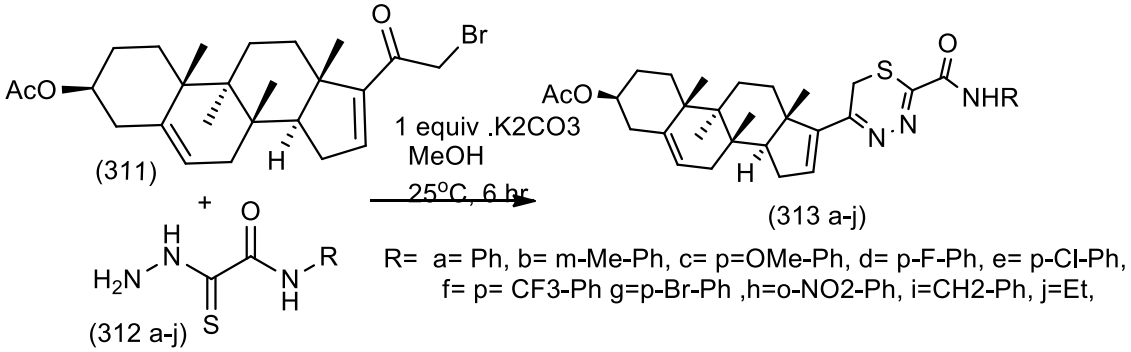
Synthesized 16β-hydroxyspiro-androsteno-17,6′[1,3,4]thiadiazines **(310 a-f)** by the reaction of thiohydrazides **(309 a-f)** containing both electron-donating and withdrawing substituents on the aryl group with 16β, 17β-epoxypregnenolone **(308)**. The reaction of thiohydrazides **(309)** with oxirane **(308)** in 1,4-dioxane in the presence of a catalytic amount of H2SO4 at 60 °C after 2 h, form the corresponding spiro(androstane thiadiazines) **(310 a-f)** in good yield, (scheme 67) [73].



Scheme 67. Synthesized (N-Aryl carbamoyl) spiroandrostene-17,6′ [1,3,4] thiadiazines.

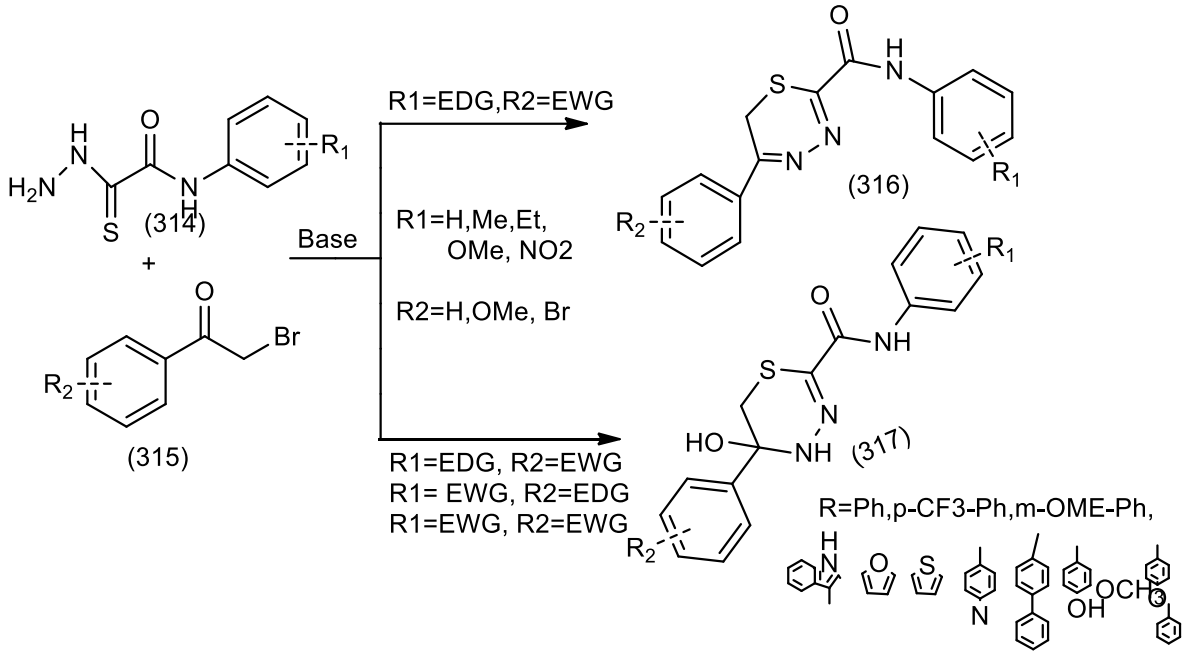
Komendantova *et al.* [73] also synthesized thiadiazines and (N-aryl carbamoyl)17-[1′,3′,4′]thiadiazine-substituted androstanes**.**

Also synthesized -(6′H-1′,3′,4′-thiadiazine-2′-carboxamide) androst-5,17-dienes (313 a-j) by treating 21-bromopregna-5,16-dien-20-one (311) with oxamic acid thiohydrazides (312 a-j) under mild basic conditions (Scheme 68) [73].



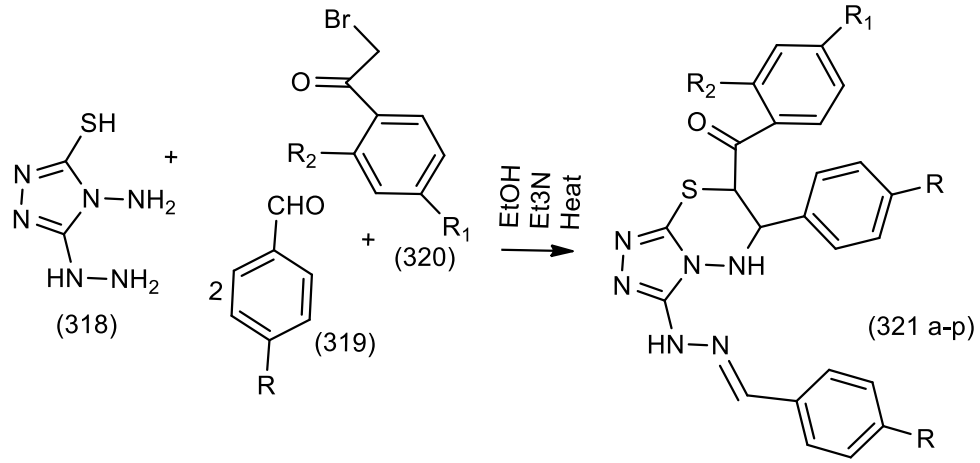
Scheme 68. Synthesized 17-(6′H-1′,3′,4′-thiadiazine-2′-carboxamide) androst-5,17-dienes (**313 a-j**).

The author observed that steroidal 1,3,4-thiadiazines 310 and 313 are lead compounds for developing novel and highly effective anticancer drugs for the treatment of prostate cancer. Komendantova *et al.* synthesized Novel 2-carboxamide-substituted 1,3,4-thiadiazines **(316)** and 5,6-dihydro-4H-1,3,4-thiadiazin-5-ols **(317)** by the reaction of an equimolar mixture of thiohydrazide **(314)** and α-bromoacetophenones (**315**) (Scheme 69) in methanol under basic conditions [74].



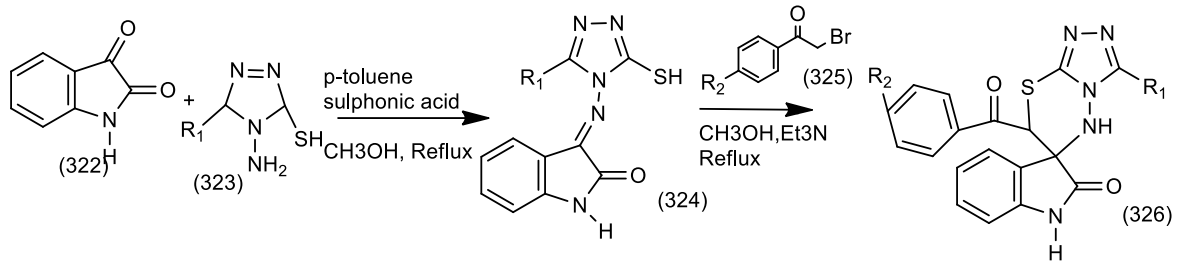
Scheme 69. Synthesized Novel 2-carboxamide-substituted 1,3,4-thiadiazines **(316)** and 5,6-dihydro-4H-1,3,4-thiadiazin-5-ols **(317).**

Sujatha and Vedula synthesized a series of novel triazolo thiadiazines (321 a-p) by a simple, highly efficient, one-pot pseudo-four-component approach involving the condensation of 4-amino-5-hydrazinyl-4H-1,2,4-triazole-3-thiol **(318**), aromatic aldehydes **(319),** and various phenacyl bromides **(320)** (Scheme 70) with good yields [75].

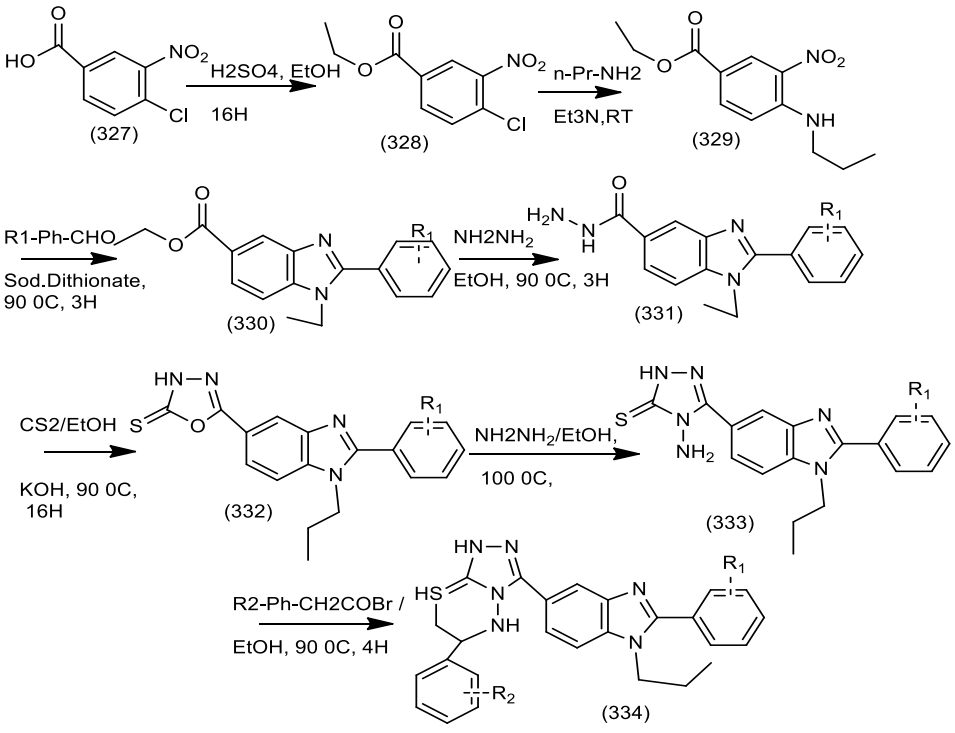


Scheme 70. Synthesized a series of novel triazolo thiadiazines (**321 a-p**).

Ji *et al.* synthesized Spiro oxindoles derivatives of [1,2,4] triazolo[3,4-b] [1,3,4] thiadiazine **(326).** 3-substituted-4-amino-1,2,4-triazol-5-thiol **(323)** on refluxation with indoline-2,3-dione **(322)** in presence of p-toluene sulphonic acid gives intermediate **(324)** which on alkylation of the mercapto group with substituted-2-bromo-1-phenylethanones **(325)** gives spiro oxindoles derivatives of [1,2,4] triazolo[3,4-b] [1,3,4] thiadiazine **(326)** in Scheme 71 [76].



Scheme 71. Synthesized spiro oxindoles derivatives of [1,2,4] triazolo[3,4-b] [1,3,4] thiadiazine (**326**).

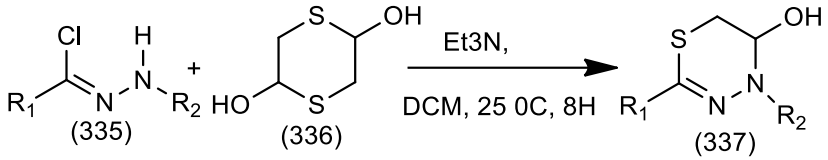


Scheme 72. Synthesized Fourteen novel [1,2,4] triazolo[3,4-b] [1,3,4] thiadiazine derivatives bearing benzimidazole moiety **(334).**

Novel spiro oxindole molecules containing [1,2,4] triazolo[3,4-b][1,3,4]thiadiazine moiety and evaluated there *in vitro* antitumor activities against DU145, EC109, MGC803, and MCF-7 human tumor cell lines by MTT assay. Several compounds inhibited the proliferation better than positive control 5-Fluorouracil. Novel derivatives show Antitumour activity.

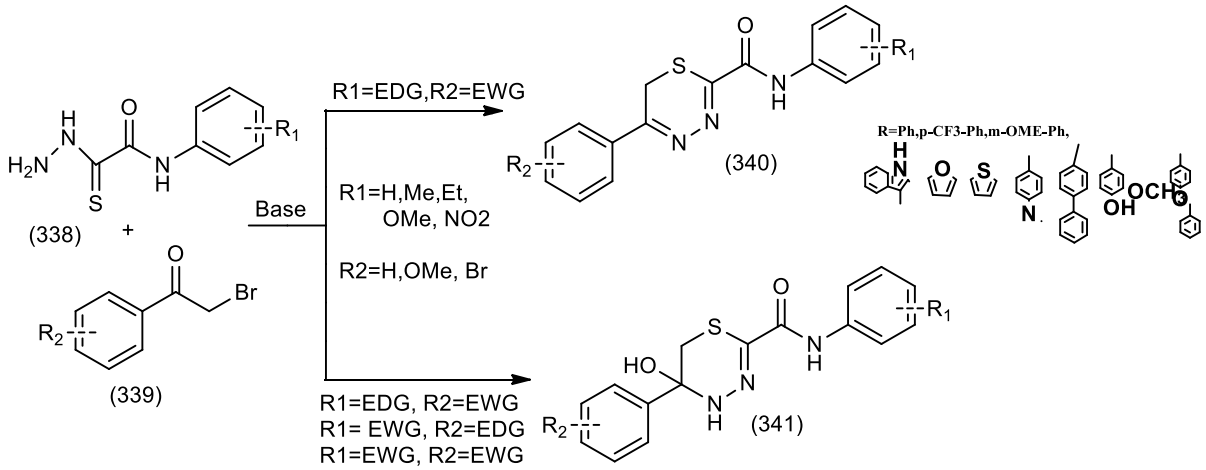
Sathyanarayana *et al.* synthesized Fourteen novels [1,2,4] triazolo[3,4-b] [1,3,4] thiadiazine derivatives bearing benzimidazole moiety **(334)** using the one-pot nitro reductive cyclization method from ethyl-4-chloro-3-nitrobenzoic acid **(327)** (Scheme 72) as starting material [77].

Cao *et al.* synthesized 13 novel derivatives of 1,3,4-thiadiazine derivatives by new methods using 2,5-dihydroxy-1,4-dithiane and α-chloroindole containing different substituents (Scheme 73) [78].



Scheme 73. Synthesized novel 13 derivatives of 1,3,4-thiadiazine derivatives.

Ismail *et al.* synthesized Novel 7H-[1,2,4]Triazolo[3,4-b] [1,3,4] thiadiazine Inhibitors as Antitumor Agents in a stepwise process (Scheme 74) [79].

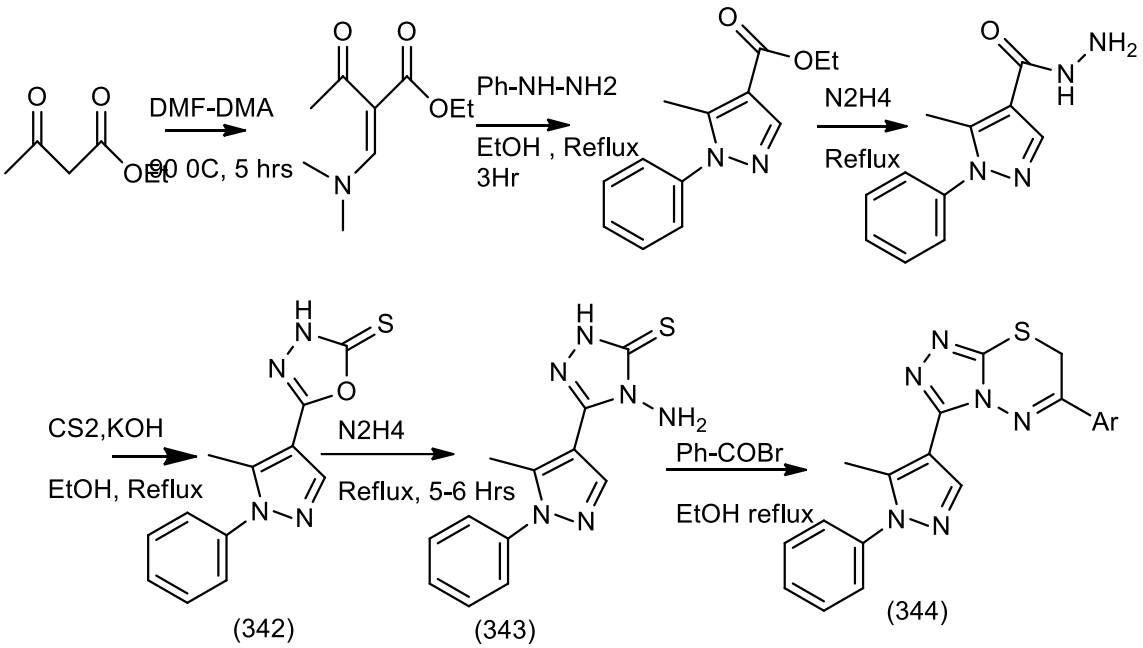


Scheme 74. Synthesized Novel 7H-[1,2,4]Triazolo[3,4-b] [1,3,4] thiadiazine.

The author observed that the synthesized compounds were screened for their cytotoxic activity against 60 cell lines by the National Cancer Institute (NCI), NIH, Bethesda, Maryland, USA, under the Developmental Therapeutics Program (DTP) for NCI-60 human tumor cell lines screen. The operation of this screen utilizes 60 different human tumor cell lines, representing leukemia, NSCLC, colon, CNS, ovarian, renal, prostate, breast cancers, and melanoma.

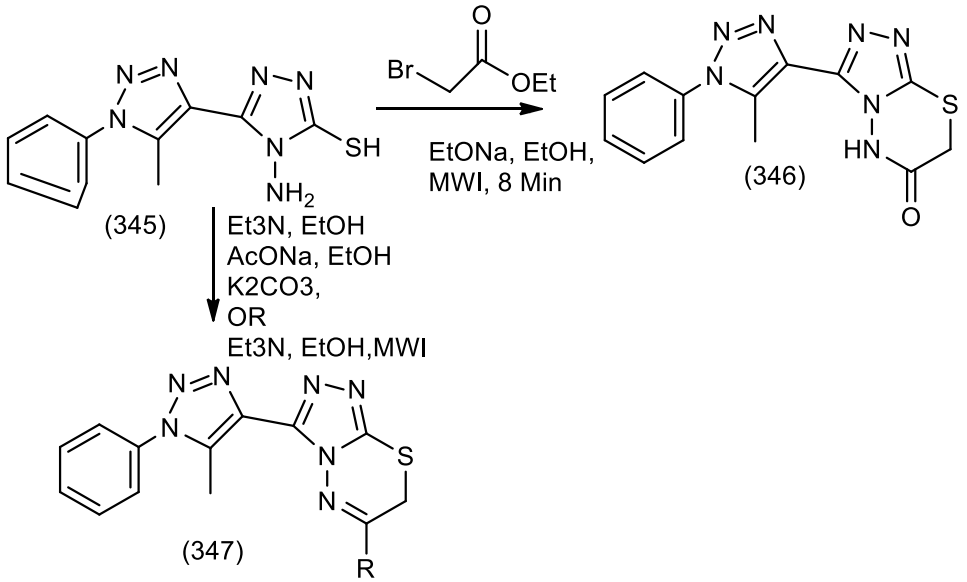
Nayak and Poojari *et al.* synthesized derivatives of 6-(substituted-phenyl)-3-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H- [1,2,4] triazolo[3,4-b] [1,3,4] thiadiazine (344) from 5-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-1,3,4-oxadiazole-2(3H) -thione **(342).** Intermediate **(342)** reflux with hydrazine hydrate for 5-6 hrs with ethanol to form **(343),** which on further treatment with phenacyl bromide in ethanol for 5 hrs form final product **(344**) in Scheme 75 [80].

The author observed that compound **(344)** shows antibacterial activity against four bacterial strains i.e., *Staphylococcus aureus* and *Enterococcus faecalis* (gram-positive bacterial strains), and *Escherichia coli* and *Pseudomonas aeruginosa* (gram-negative bacterial strains**)** [80].



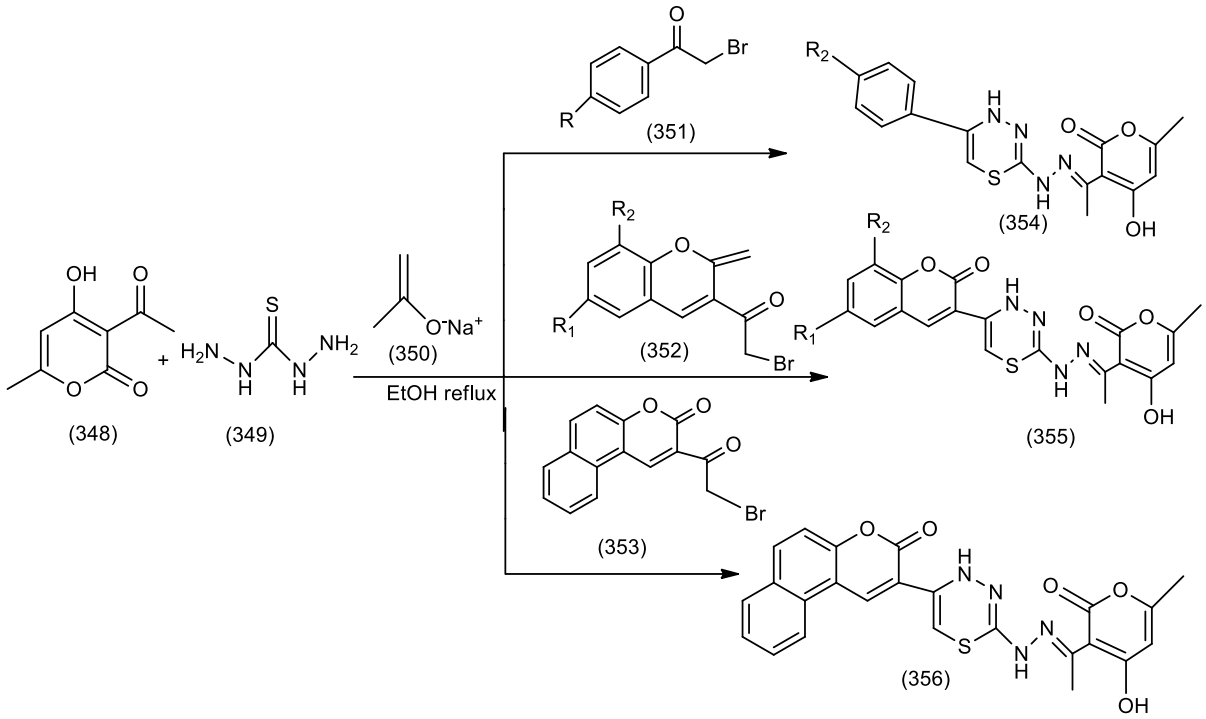
Scheme 75. Synthesized derivatives of 6-(substituted-phenyl)-3-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4] triazolo[3,4-b] [1,3,4] thiadiazine (**344**).

El-Sayed *et al.* synthesized N-bridged triazolo[3,4-b] [1,3,4]thiadiazine **(347)** by both conventional and microwave methods. Initially, compound **(345)** on refluxing with a-halo ester, acid chloride, or/ketones by conventional method form compound **(346), (347)** (Scheme 76), respectively. The same product is formed by microwave irradiation with a short time and high yield. The microwave radiation green synthesis method reduces reaction time from 6-7 hrs to 10-15 minutes [81].



Scheme 76. Synthesized N-bridged triazolo[3,4-b] [1,3,4]thiadiazine **(347).**

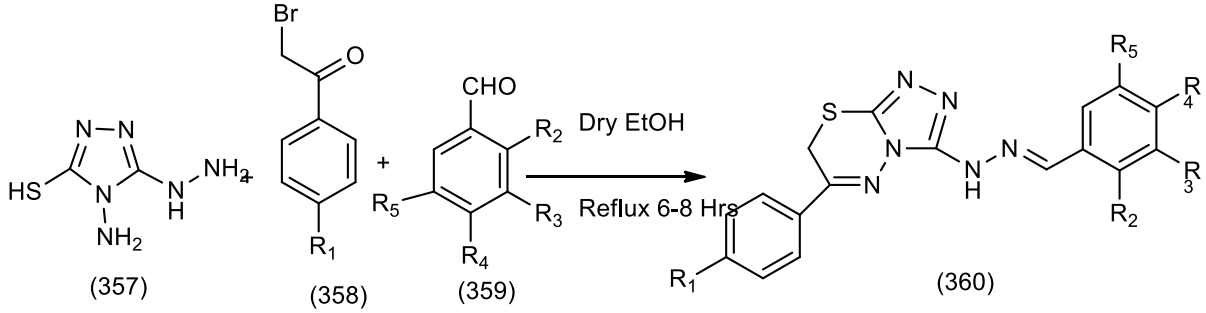
Mamidala *et al.* synthesized 1,3,4-thiadizine derivatives **(354, 355, 356)** by a one-pot three-component system by the conventional method. dehydroacetic acid **(348),** thiocarbohydrazide **(349),** and substituted phenacyl bromides **(350)** or substituted 3-(2-bromoacetyl) coumarins **(351, 352, 353)** (Scheme 77) in one pot method on reflux with various solvent and observed that the yield is more in EtOH as compare to other solvents like DMF, DMSO and evaluate their anticancer activity of compound [82].



Scheme 77. Synthesized 1,3,4-thiadizine derivatives **(354, 355, 356).**

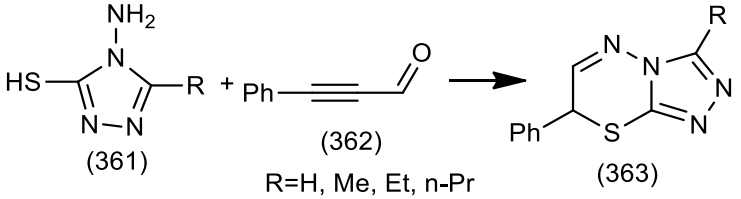
The author observed that compound (355) has great anticancer activity, which is due to the presence of coumarin moiety in the compound (355).

Jilloju *et al.* synthesized 3-(2-benzylidenehydrazinyl) −6-phenyl-7 H -1,2,4] triazolo [3,4- b] [1,3,4] thiadiazines **(360)** by one-pot multi-component reaction from 4-amino-5-hydrazinyl-4 H -1,2,4- triazole-3-thiol (Purpald) **(357),** substituted phenacyl bromides **(358)** and various aromatic aldehydes **(359)** (Scheme 78) in presence of ethanol under reflux condition. The product is studied for molecular docking [83].



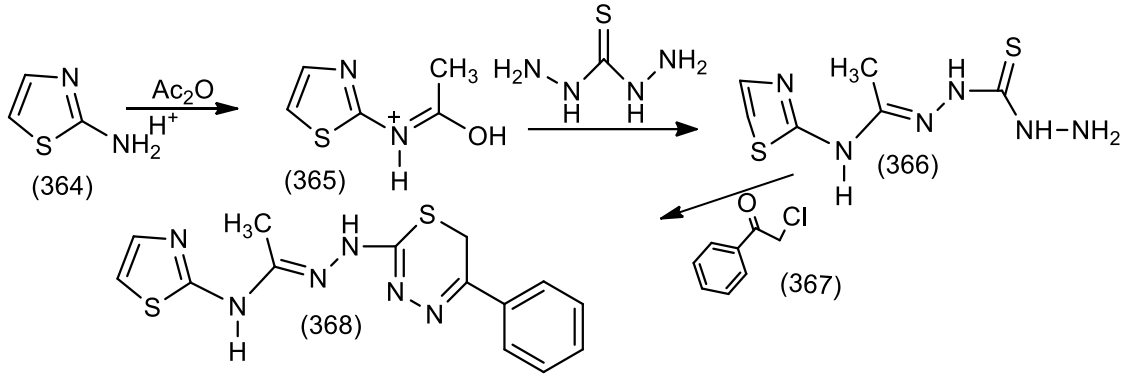
Scheme 78. Synthesized 3-(2-benzylidenehydrazinyl) −6-phenyl-7 H -1,2,4] triazolo [3,4- b] [1,3,4] thiadiazines **(360).**

Khramchikhin *et al.* synthesized 7-benzylidene-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **(363)** from 3-substituted 4-amino-4H-1,2,4- triazole-5-thiols **(361)**and 3-phenyl-2-propynal **(362)** in scheme 79 [84].



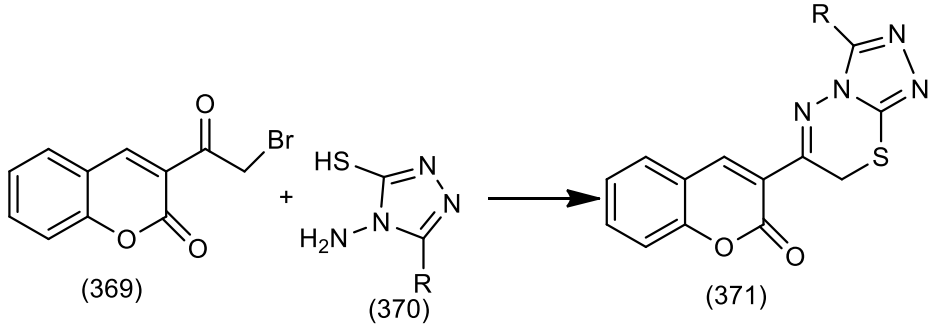
Scheme 79. Synthesized 7-benzylidene-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **(363).**

Shabaan *et al.* synthesized 1,3,4-thiadiazine derivatives **(368)** using ultrasound as green synthesis. They treat 2-aminothiazole **(364)** with acetic anhydride for acetylation by irradiation for 20 min at 70°C under ultrasound irradiation to form N-(thiazol-2-yl) acetamide **(365),** which on further ultrasonic irradiation for 20 min at 70°C with thiocarbohydrazide form bis-hydrazone **(366).** The compound **(366),** in reaction with phenacyl bromide on ultrasonic irradiation for 20 minutes at 70°C formed final 1,3,4-thiadizine derivatives **(368)** in scheme 80 [85].



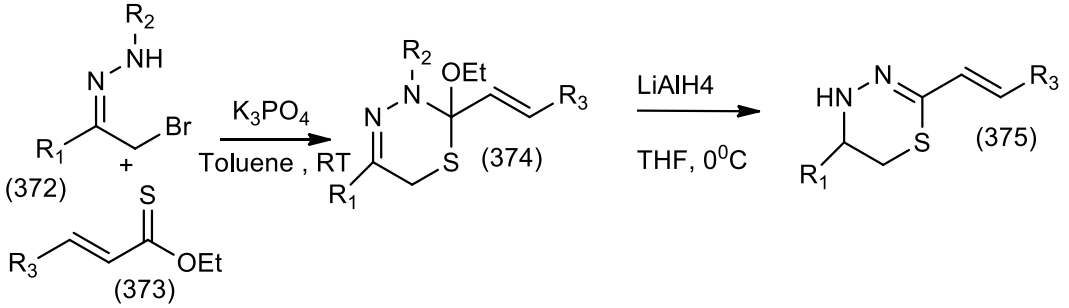
Scheme 80. Synthesized 1,3,4-thiadizine derivatives **(368).**

Mohammed *et al.* synthesized coumarin derivatives of 1,3,4 thiadiazine **(371)** from 3-(2-bromoacetyl)-2H-chromen-2-one **(369)** in scheme 81 and studied their anticancer activity. He found that it shows anticancer activity toward Leukaemia K-562, Renal Cancer UO-31and Breast Cancer T-47D cancer cell lines with a growth inhibition percentage of 27.00% [86].



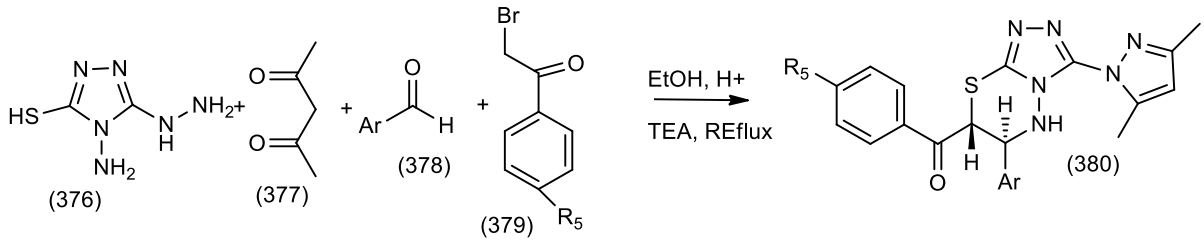
Scheme 81. synthesized coumarin derivatives of 1,3,4 thiadiazine **(371).**

Shen *et al.* synthesized 5,6-dihydro-4H-1,3,4-thiadiazines **(375)** through Diels-Alder reaction. They treat 1,2-diaza-1,3-dienes **(372)** with α,β-unsaturated thioesters **(373)** as dienophiles in the presence of K3PO4 and toluene as solvent to form derivatives of 3,6-dihydro-2H-1,3,4-thiadiazine**(374).** This product, on reduction with Lithium aluminum hydride, is converted to 5,6-dihydro-5H-1,3,4-thiadiazine **(375)** in scheme 82 [87].



Scheme 82. Synthesized 5,6-dihydro-4H-1,3,4-thiadiazines **(375).**

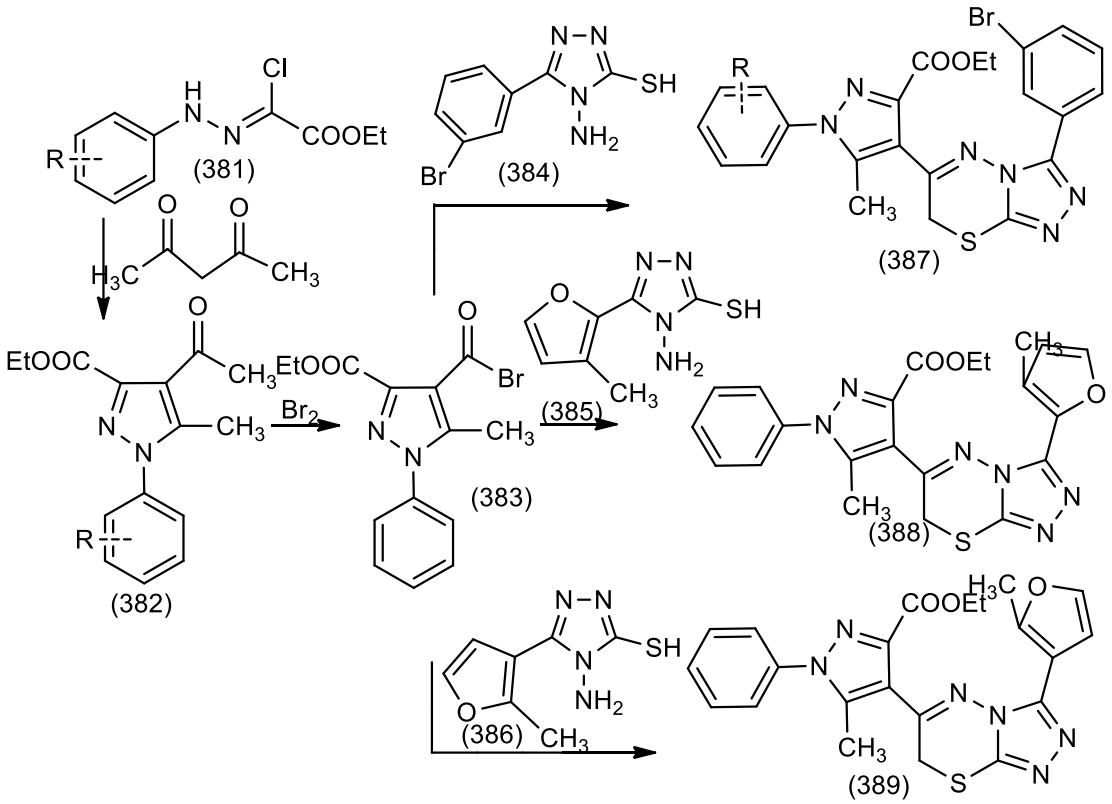
Jilloju *et al.* synthesized (±)-3-(1 H -pyrazol-1-yl)-6,7-dihydro-5 H -[1,2,4]triazolo[3,4- b][1,3,4] thiadiazine derivatives **(380)** and evaluated its biological activity. They found these compounds have good anti-coronavirus and anti-tumoural activity.The compound **(380)** is formed by refluxing with EtOH in one pot reaction with 4-amino-5-hydrazinyl-4H-1,2,4-triazole-3-thiol **(376)**, phenacyl bromide **(377)**, aromatic aldehyde **(378)** or acetyl acetone **(379)** in scheme 83, refluxing with EtOH [88].



Scheme 83. Synthesized (±)-3-(1 H -pyrazol-1-yl)-6,7-dihydro-5 H -[1,2,4]triazolo[3,4- b][1,3,4] thiadiazine derivatives **(380).**

The authors observed that compound 380 derivatives show anti-coronavirus and antitumoral activity.

Myrko *et al.* synthesized pyrazole-substituted 7H-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazines **(387-389)** from ethyl (2Z)-chloro(phenylhydrazone) acetates **(381)** by reaction of diketone followed by bromination formed bromoketone**(383)**. The bromoketone formed on further reaction with 4-amino-5-aryl(getaryl)-2,4-dihydro-3H-1,2,4-triazole-3-thiones compound **(384-386)** afford corresponding 1,3,4-thiadizine derivatives **(387-389)** in Scheme 84 [89].



Scheme 84. Synthesized pyrazole-substituted 7H-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazines **(387-389)**.

3. Conclusions

Thiadiazine is a unique ring associated with several medicinal and pharmaceutical potentials due to its versatile biological active properties such as anticancer, antidiabetic, and anti-corona virus. It is one of the best platforms for research in the organic heterocyclic synthesis community. This review plays the vital role of a mirror of isoxazole derivatives to get the innovative idea about synthesizing thiadiazine derivatives through various researchers.

We concluded that this review will play an important role in synthesizing Thiadiazine derivatives.

Funding

This research received no external funding.

Acknowledgments

The authors are grateful to the Head of the Department of Chemistry, Dr. Babasaheb Ambedkar College, Mahad, Maharashtra, India, for providing the necessary facilities.

Conflicts of Interest

The authors declare no conflict of interest.

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