A COMPREHENSIVE OVERVIEW OF THE SYNTHETIC METHODS OF OXADIAZOLE, THIADIAZOLE AND TRIAZOLE.

*[1]Shruti Suryawanshi, [2]Sheetal Parse, [3]Pooja Wagh, [4]Nagasawjanya Dongari, [5]Trupti Chitre, [6]Kalyani Asgaonkar

Student [1, 2, 3, 4], Associate Professor[5] Assistant professor[6]

[1]Department of Pharmaceutical Chemistry,
[1]All India Shri Shivaji Memorial Society's College of Pharmacy, Kennedy Road, Near R.T.O., Pune-411001, M.S., India.

Abstract **-** Many drugs are producing resistance to the various diseases. So, there is an urgent need to synthesize the new chemical entities with potent biological activity. This review may help the medicinal chemist to develop the new chemical entities with Oxadiazole, Thiadiazole and Triazole as the heterocyclic nucleus with higher efficiency and less side effects. This review gives the information about the synthetic routes of the Oxadiazole, Thiadiazole and triazole.

Index Terms **- Oxadiazole, Thiadiazole, Triazole, Synthesis.**

I. INTRODUCTION

It is observed that the five membered heterocyclic rings such as Oxadiazole, Thiadiazole and Triazole give variety of biological activities. [1] [2].

Oxadiazoles are 5-membered heterocyclic fragment compounds consisting of 1 oxygen atom, 2 nitrogen atoms and 2 carbon atoms.[3] Depending on the position of the nitrogen with inside the ring, numerous isomers exist together with 1,2,4-; 1,2,5-; 1,2,3; and 1,3,4-oxadiazole (Figure 1) [4] Various pharmacological activities such as Antibacterial [5], Anti-Fungal [6], Anticonvulsant [7], Anticancer [8], Antitubercular [9], Antimicrobial [10] as well as Analgesic [11] have been reported for this scaffold.

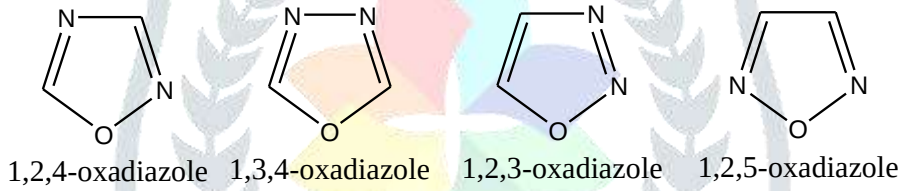


Fig 1 – Isomers of Oxadiazole

Thiadiazole is a five membered ring system containing two nitrogen atoms, one sulphur, two carbon atoms in ring system. [12, 13] Thiadiazole is found in four forms 1,2,4thiadiazole,1,2,3 thiadiazole,1,2,5 thiadiazole and 1,3,4 thiadiazole. (Figure 2) [14] Various pharmacological activities such a [15]. Anti-diabetic [16], antimicrobial [17], anticancer [18], antitumor [19], anti-inflammatory [20], antitubercular [21]as well as antiviral [22] have been reported for this scaffold.

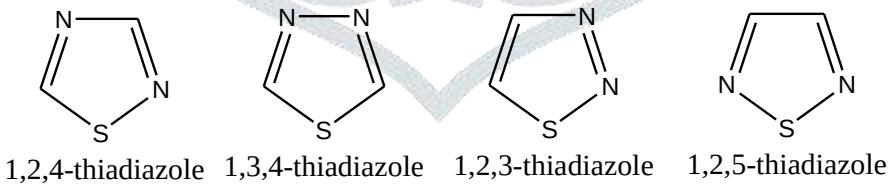


Fig. 2 – Isomers of Thiadiazole.

Triazole is one of the classes of organic heterocyclic compounds containing a five membered structure composed of three nitrogen atoms and two carbon atoms. Two isomers of Triazole are present these are as follows (figure 3):

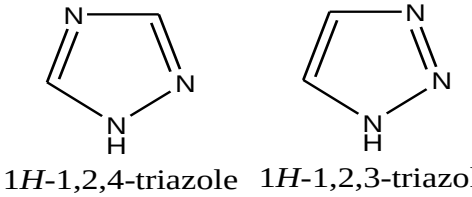


Fig. 3 – Isomers of Triazole.

Various pharmacological activities such as antibacterial[23][24][25][26][27], anticancer[28][29][30], anti-proliferative [31] antitubercular , anti-inflammatory[32], antiviral[33],antifungal [34][35], urease & lipase inhibitors[36] ,anti-tumour activity [37] antioxidant [38][39] anti-corrosive[40] hypoglycaemic [41] anti-tyrosinase [42] anti-nociceptive, anti-convulsant, anthelmintic , anti-migraine, sedative, diuretic, muscle relaxant as well as anti- HIV [43][44][45] have been reported for this scaffold.

The research upon these three heterocycles is going on to get the new chemical entities. The synthesis of these three heterocycles is a very important task now a days. So, to make the work easy for new researchers we have made the review on the synthesis schemes of these three heterocycles. The various schemes were studied from various research papers and are combined in this review paper.

.

II. Synthetic schemes

2.1 Oxadiazole derivatives

1) Mansouri E. et.al. reported the synthesis of 1,3,4- oxadiazole homonucleosides and their double-headed analogs as antitumor agents. In the first step N- alkylation of theophylline (0.25 mol) is carried out using ethyl bromoacetate (0.50 mol) in presence of excess of dimethylformamide (DMF) and potassium carbonate (K_2CO_3) to give ethyl 2-(1,3-dimethyl-1,2,6-dioxo-1,2,3,6-tetrahydropurin-7-yl) acetate. The intermediate formed is further reacted with Phosphoryl chloride (POCl3) to get the product. [47,48] (Figure 4).

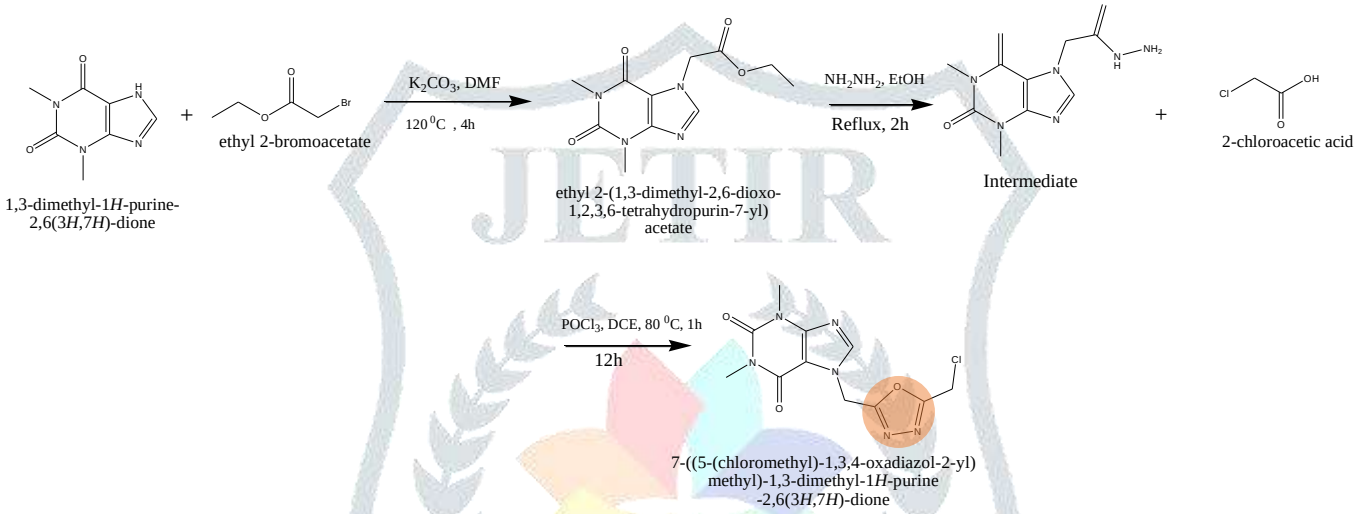


Fig. 4 – Synthesis scheme for 7-((5-(chloromethyl)-1,3,4-oxadiazole-2-yl) methyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione.

2) Following synthesis was performed by Zhanga Y. et.al. Benzoic acid (1.5 mol) and N- dihydroxy-1H-indol-5-carboxamidine (2.0 mol) were reacted in presence of 1-Ethyl-3- (3-dimethylaminopropyl) carbodiimide (EDCl), Hydroxy benzotriazole (HOBT), N, N-Diisopropylethylamine (DIEA), Dimethylformamide (DMF) to obtain the oxadiazole derivative. The reaction conditions involved heating in microwave at 180 0C for 20 minutes.[49] (Figure 5).

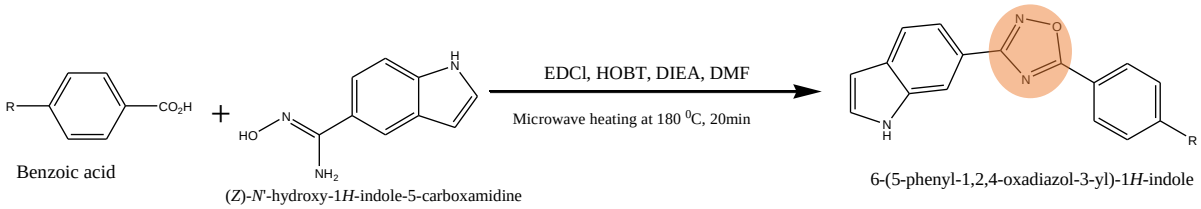


Fig. 5 – Synthesis scheme for 6-(5-phenyl-1,2,4-oxadiazole-3-yl)-1H-indole.

3) Caneschi W. et.al. reported synthesis of 5-phenyl-1,3,4-oxadiazole-2-thiol. First step involved refluxing of benzoic acid (0.1 mol) with concentrated sulphuric acid (H_2SO_4), Ethanol (EtOH), Hydrazine (NH_2NH_2) (2.0 mol) for 20 hours to form benzo hydrazide. This in the second step when heated at 55^0c for 48 hours with potassium hydroxide (KOH), Ethanol and Carbon disulphide (CS_2) (4.0 mol) formed the title compounds.[50] (Figure 6).

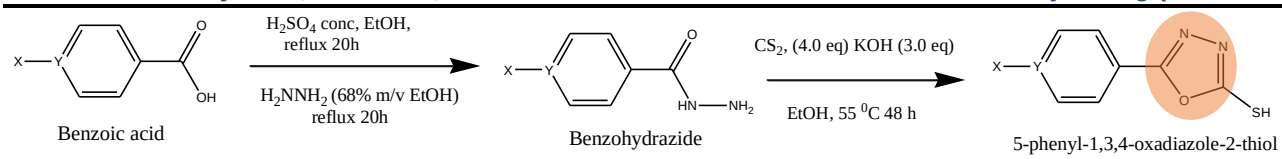


Fig. 6 – Synthesis scheme of 5-phenyl-1,3,4-oxadiazole-2-thiol.

4) This synthesis was reported by Bhati S. et.al. Ethyl 2-(4-methylpiperazine-1-yl) acetate (0.01 mol) is reacted with dry acetone (0.02 mol) and Potassium carbonate (K_2CO_3) (2 g) and ethylchloracetate ($ClCH_2COOC_2H_5$) to get 2-(4-methylpiperazine-1-yl) acetohydrazide. 2-(4-methylpiperazine-1-yl) acetohydrazide is reacted with Hydrazine (NH_2NH_2), H_2O and Ethanol (C_2H_5OH) to get 1-methyl-4-((5-methyl-1,3,4-oxadiazole-2-yl) methyl) piperazine.[51]. (figure 7).

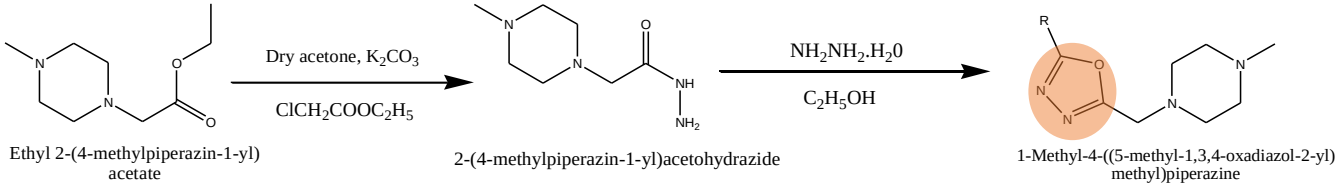


Fig. 7 – Synthesis scheme of 1-methyl-4-((5-methyl-1,3,4-oxadiazol-2-yl) methyl) piperazine.

5) Taha M. et.al. reported the synthesis of phenyl linked oxadiazole- phenylhydrazone hybrids. By refluxing methyl-2-methoxybenzoate (0.3 mol) with Hydrazine (0.1 mol) for 6 hours 2-methoxybenzohydrazide was synthesized. The resulting 2-methoxybenzohydrazide was reacted with different aromatic aldehydes to yield hydrazone. Hydrazone upon oxidative cyclization with phenyliododiacetate (PhI (OAc_2)) in dry chloroform forms oxadiazole ring. Further it was converted into the phenyl linked oxadiazole-hydrazide hybrid by reacting with hydrazine hydrate. [52] (figure 8).

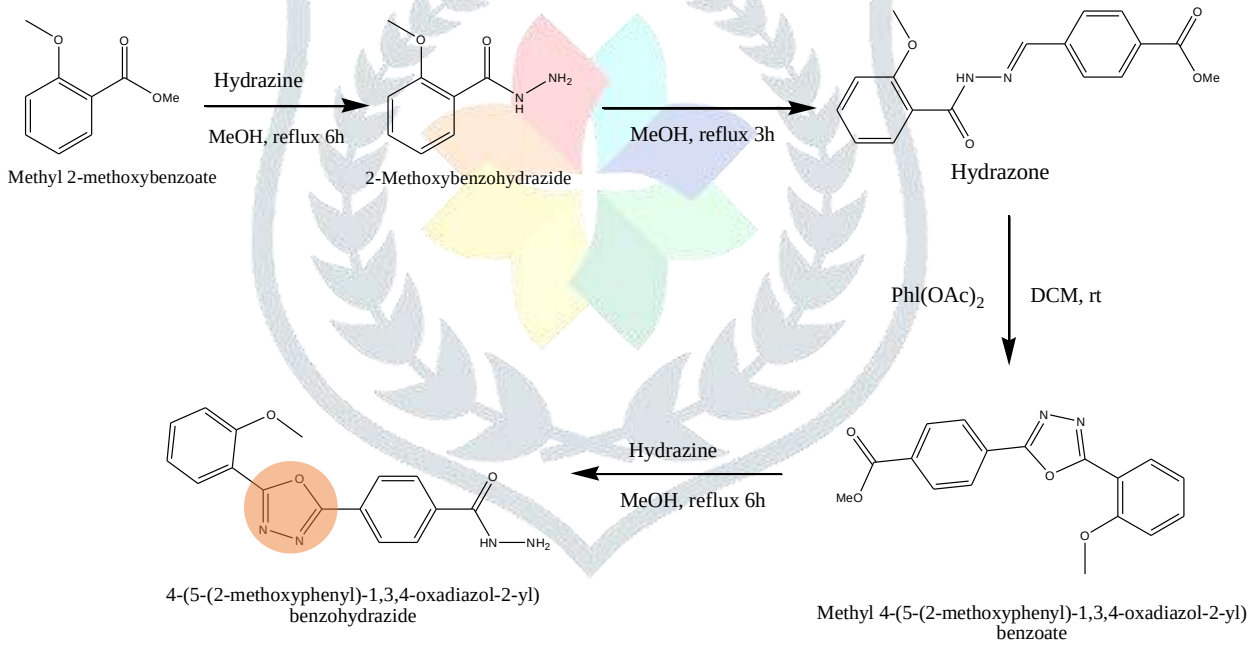


Fig. 8 – Synthesis scheme for methyl-4-(5-(2-methoxyphenyl)-1,3,4-oxadiazole-2-yl) benzoate.

6) Following synthesis was performed by Yadava N. et.al. The 4-(tert-butyl) benzo hydrazide (0.01 mol) was reacted with carbon disulphide (2 ml) in presence with ethanol and potassium hydroxide (0.01 mol) 0 degrees for 20 minutes and then refluxed for 4 hours until the Hydrogen Sulfide (H_2S) is evolved. The formed intermediate 5-(4-tert-butylphenyl)-1,3,4-oxadiazole-2(3H)-thione was purified by column chromatography and further reacted with different amines in the presence of formaldehyde in anhydrous ethanol at room temperature to yield 1,3,4-oxadiazole thions.[53]. (figure 9).

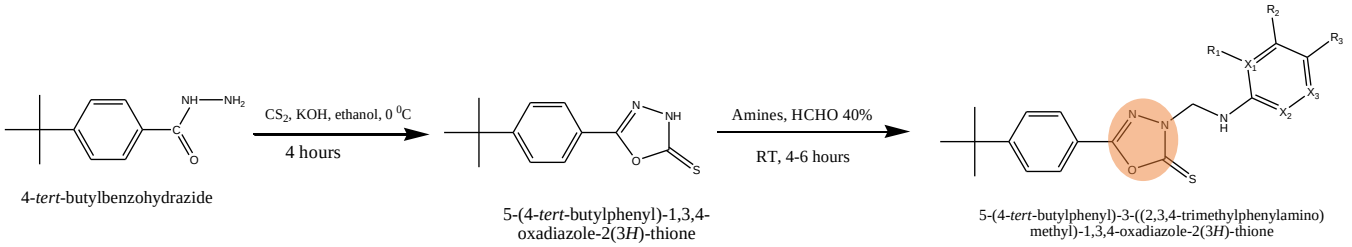


Fig. 9 – Synthesis scheme for 5-(4-tert-butylphenyl)-3-((2,3,4-trimethylphenylamino) methyl)-1,3,4-oxadiazole-2(3H)-thione

7) Kumaraswamy B. et.al. reported the synthesis of derivatives of phenyl-oxadiazole hybrids. 4-fluorophenol (0.2 mol) is heated at 40-45 ^{0}C with acetyl chloride (0.01 mol) to get 4 fluorophenyl acetate. The prepared 4-fluorophenyl acetate is treated with Aluminium Chloride ($AlCl_3$) and methanol at 140-145 ^{0}C to get 1-(5-fluoro-hydroxyphenyl) ethenone. The reaction takes place by one pot Friedel Craft acetylation followed by Fries rearrangement. The 1-(5-fluoro-hydroxyphenyl) ethenone is reacted with diethyl oxalate and methanol in presence of Sodium methoxide (NaOMe) at 65-70 ^{0}C gives ethyl 4-(5-fluoro-2-hydroxyphenyl)-2,4-dioxobutanoate. Ethyl 4-(5-fluoro-2-hydroxyphenyl)-2,4-dioxobutanoate is treated with hydrochloric acid at 85–90 ^{0}C. acid catalysed cyclisation is the mechanism of reaction. The formed product is then treated with acetic acid at 75-80 ^{0}C to get 6-fluoro-3,4-dihydro-2H-chromene-2-carboxylic acid. 6-fluoro-3,4-dihydro-2H-chromene-2-carboxylic acid is refluxed with methanol and sulphuric acid the 6-fluoro-3,4-dihydro-2H-chromene-carboxylate. This product is obtained by hydrogenation. By hydrazinolysis of ester hydrazides was obtained. The hydrazide is a key product for synthesis of 2, 5 disubstituted 1, 3, 4 oxadiazole by refluxing in Phosphoryl chloride (POCl3) with substituted aromatic carboxylic acid derivatives to afford final products. [54,55] (figure 10).

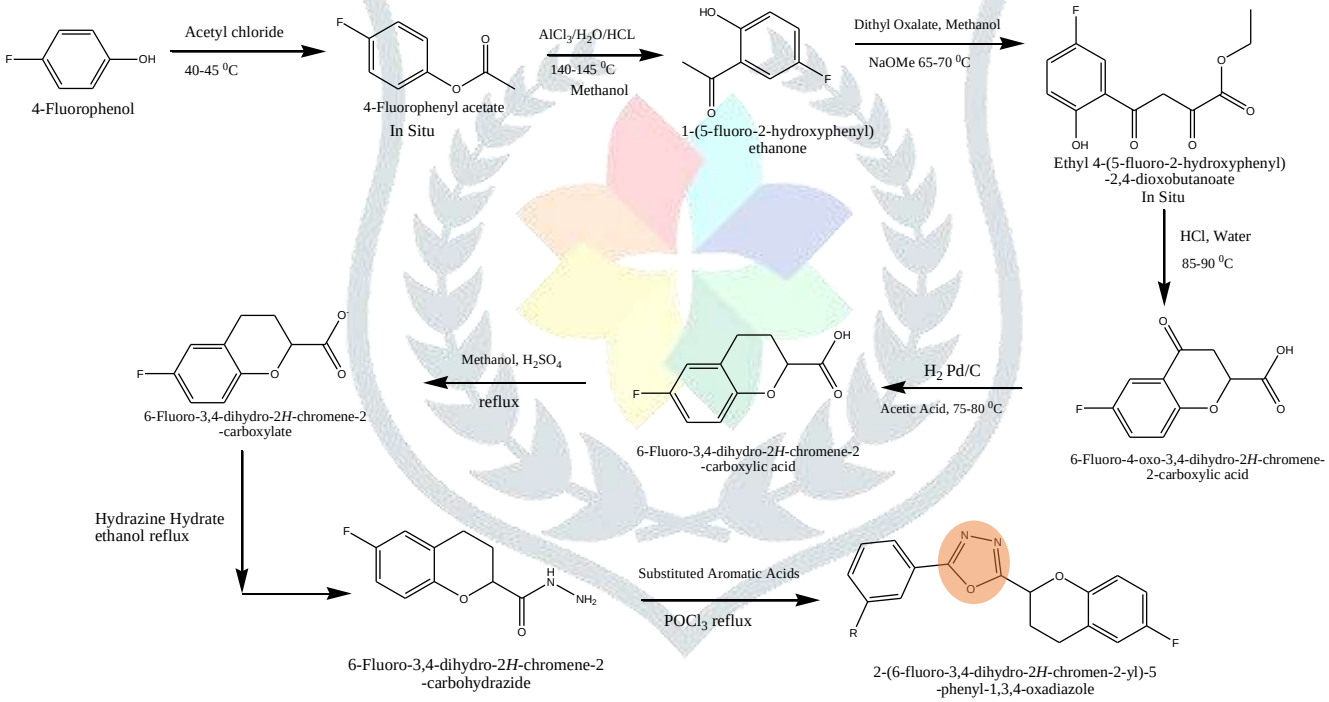


Fig. 10 – Synthetic scheme for 2-(6-fluoro-3,4-dihydro-2H-chromen-2-yl)-5-phenyl-1,3,4-oxadizole

8) Ningegowda R. et.al. synthesized the series of 12 derivatives for their anti-tubercular activity against Mycobacterium tuberculosis. The 2,3-dichlorobenzoic acid (131.60 mmol) is refluxed with Methanol (MeOH) (200 ml) and sulphuric acid (H_2SO_4, 2 drops) to get methyl2,3-dichlorobenzoate. Then this prepared benzoate is refluxed with Hydrazine hydrate (NH_2-NH_2.H_2O) and Ethanol (EtOH)to get 2,3-dichlorobenzohydrazide. This 2,3-dichlorobenzohydrazide is reacted with any acid and Phosphoryl chloride ($POCl_3$) a cyclization agent at room temperature and the final product with oxadiazole ring is prepared i.e., 2-(2,3-dichlorophenyl)-1,3,4-oxadiazole.[56] (figure 11)

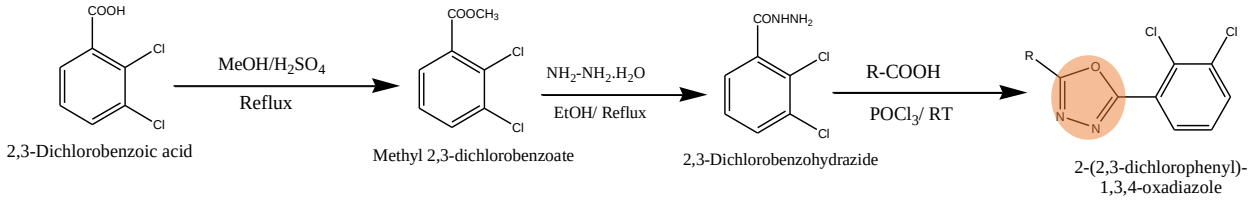


Fig. 11 – Synthetic scheme for 2-(2,3-dichlorophenyl)-1,3,4-oxadiazole

9) This synthesis procedure was performed by Khanfara M. et.al. 1-Isothiocynato-4-methylbenzene was heated at 65-80 ^{0}C for 1 hour with Hydrazine (N_2H_4) and Methanol (MeOH) to get 4-phenylthiosemicarbazide. That formed 4-phenylthiosemicarbazide (1.0 mol) is treated with acetic acid (1.0 mol) in presence of 1-Ethyl-3- (3-dimethylaminopropyl) carbodiimide (EDCl) and Dichloromethane (CH_2Cl_2) to get the desired product 5-methyl-N-m-tolyl-1,3,4-oxadiazole-2-amine. The thiosemicarbazides were readily prepared by reacting the corresponding iso thiocyanate with hydrazine under reflux in Methanol (MeOH).[57] (figure 12).

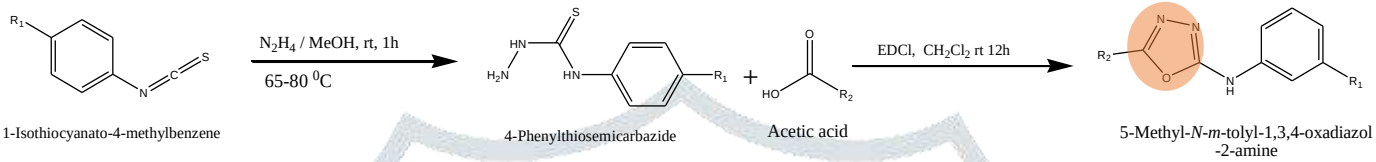


Fig. 12 – Synthesis scheme for 5-methyl-N-m-tolyl-1,3,4-oxadiazol-2-amine

10) Chortani S. et.al. performed the synthesis of the quinazoline and oxadiazole hybrid derivatives. 2-Aminobenzamide (5 mmol) and Benzaldehyde (5 mmol) was heated together under reflux for 24 hours in the presence of dry Acetonitrile (50 ml) and Iodine to form the intermediates. The formed intermediates 2-p-tolylquinazolin-4(3H)-one, 2-(4-oxo-2-p-tolylquinazolin-3-(4H)-yl) acetohydrazide and n-ethylidene-2-(-4-oxo-2-p-tolylquninazolin-3(4H)-yl) acetohydrazide are treated with Hydrazine (NH_2-NH_2), Ethanol (EtOH), Monochloroacetic acid (Cl-CH_2COOEt). The resulted product 2-(4-oxo-2-p-tolylquinazolin-3(4H)-yl) acetohydrazide was reacted with Ethanol (EtOH) to produce N-ethylidene-2-(4-oxo-2-p-tolylquinazolin-3(4H)-yl) acetohydrazide. The prepared product was reacted with the Potassium carbonate (K_2CO_3) and excess of Iodine in presence of Dimethyl Sulfoxide (DMSO) to get the product with the Oxadiazole ring. [58] (figure 13)

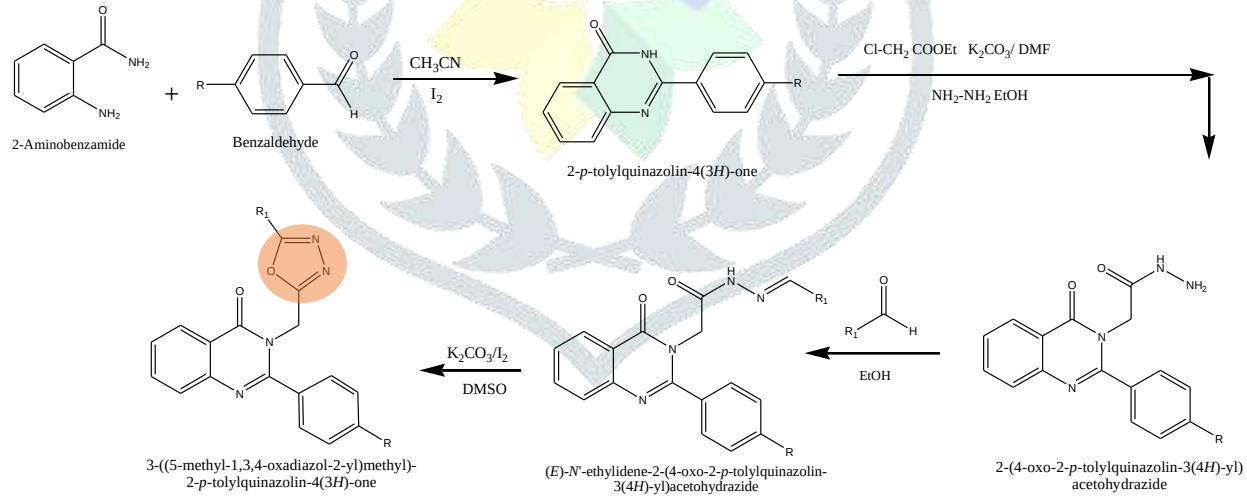


Fig. 13 – Synthesis scheme for 3-((5-methyl-1,3,4-oxadiazol-2-yl) methyl)-2-p-tolylquinazolin-4(3H)-one

2.2 Thiadiazole derivatives

1) Charitos G. et.al. synthesized 3,4 disubstituted 1,2,4 triazolo [3,4 - b] 1,2,4 thiadiazole derivative. In first step ethyl -2-(N, N- sulphomoyl)- 4-5dimethoxy-phenylacetate (0.01 mol) [59] treated with hydrazine hydrate (0.01 mol) in xylol allowed to react with carbon sulphoxide (0.015 mol) in mixture of potassium hydroxide (0.015 mol) in ethanol (150 ml) stirred for 20 hours to obtained 2-(N, N dimethyl sulfamoyl)-4-5 dimethoxy- phenyl acetyl hydrazine. After that this leads to ring closure with hydrazine hydrate (0.01 mol) and prepared 5[2-(N, N dimethyl sulfamoyl)-4-5 dimethoxybenzyl]-3-mercapto 4 amino-1,2,4 triazole. Resulted solution treated with further aromatic acid (0.01 mol) refluxed for 2 hours solid product filtered was 3,4 disubstituted 1,2,4 triazolo [3,4 – b] 1,2,4 thiadiazole. [60] (figure14).

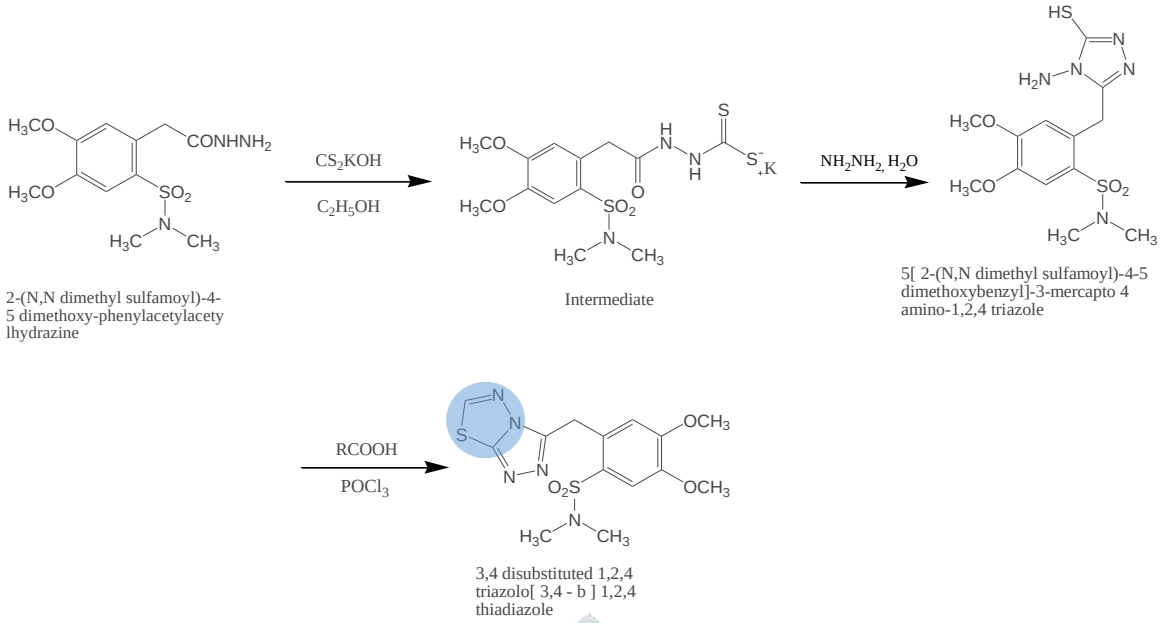


Fig. 14 – Synthesis scheme for 3,4 disubstituted 1,2,4 triazolo [3,4 - b] 1,2,4 thiadiazole

2) Khan S. A. et.al. reported synthesis of biphenyl-4yl thiadiazole derivative. First step involved biphenyl-4ylacetic acid (0.026mol) refluxed with Ethanol (100ml) and sulphuric acid (2.7ml) for 18-20 hours in water bath prepared ethylbiphenyl-4yl acetate. ethylbiphenyl-4yl acetate(0.1mol) reacted with hydrazine hydrate(0.5mol) in ethanol refluxed for12-15 hours prepared biphenyl-4yl hydrazide and then mixture of hydrazide (0.002 mol) and 2-methylthiocynate (0.002 mol) in ethanol refluxed on water bath and thiosemicarbazides. Thiosemicarbazides (0.004 mol) added in small portion to 30 ml of 2 % sodium hydroxide refluxed for12 hours concentrated under vacuum filtered the solid Biphenyl-4yl thiadiazole derivative was prepared. [61] (figure 15).

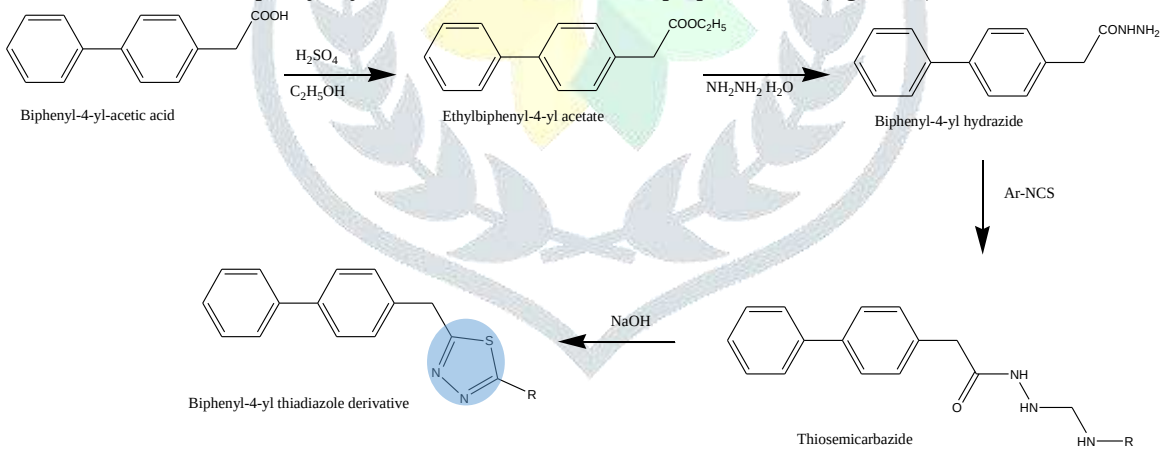


Fig. 15 – Synthesis scheme for Biphenyl-4yl thiadiazole derivative

3) X. Lv et.al. prepared Quinazoline-4(3H)-one;1,2,4-Triazolo[3,4-b] [1,3,4] thiadiazole derivative. In first step Methyl 2 – amino benzoate (2 mol) refluxed with formamide (10 ml) for 12-14 hours to obtained quinazolin-4-one. In second step it treated with bromo acetate with continuous stirring to prepare ester (3 mol). In third step ester treated with ethanol (50ml) and refluxed for 12 hours to prepared hydrazide. Then hydrazide dissolved with ethanol (60ml) and potassium hydroxide (20.0mol) forms intermediate, then in last step intermediate (1.0mmol) reacts with ethanol (40 ml) and hydrazine hydrate (131.7 mol) then refluxed for 5 hours with Phosphoric chloride to obtained Quinazoline-4(3H)-one;1,2,4-Triazolo[3,4-b] [1,3,4] thiadiazole. [62] (figure 16).

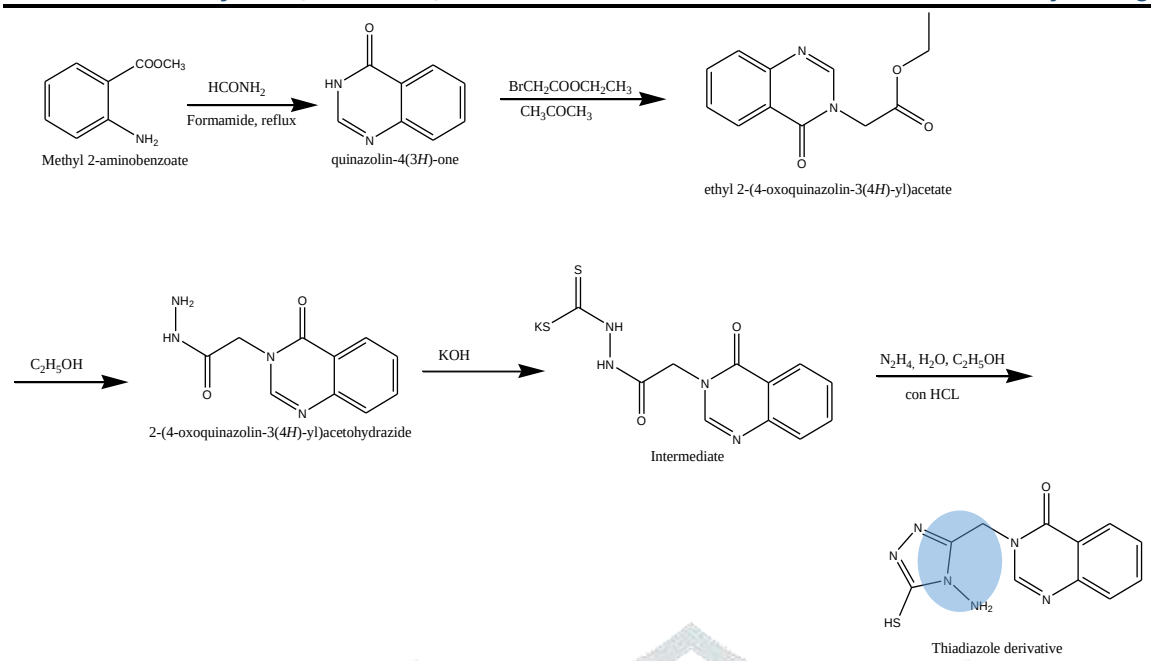


Fig.no 16– Synthesis scheme for Quinazoline-4(3H)-one; 1,2,4-Triazolo[3,4-b] [1,3,4] thiadiazole

4) M. Soleiman-Beigi et.al. synthesised phenylamino-5-alkylthio-1, 3, 4-thiadiazole. In first step Phenylthiosemicarbazide (0.1 mmol) and carbon disulphide (0.3mmol) in dimethylformamide (2.0 ml) stirred for 15 min at RT. Then in step second resulting solution heated at 70 0C for 7 hr. In final step alkyl halide (1.2 mmol) and Et3N added to hot solution of second step and obtained 2-phenylamino-5-alkylthio-1, 3, 4-thiadiazole monitored by TLC. [63] (figure 17).

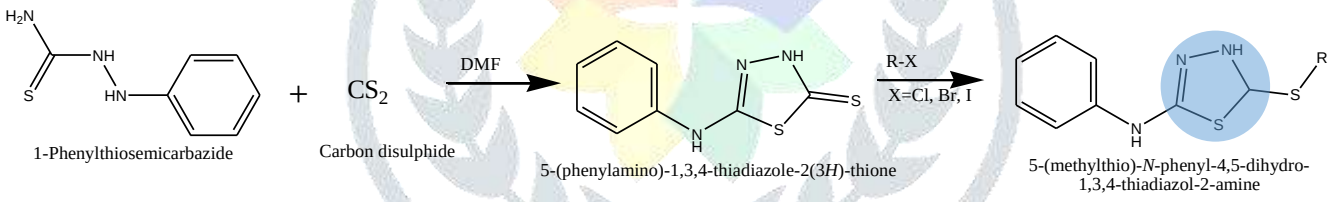


Fig. no.17 – Synthesis scheme for 2-phenylamino-5-alkylthio-1, 3, 4-thiadiazole

5) Dilek M. et.al. reported synthesis of 4-nitrophenyl thiadiazole derivative. 4-nitrophenyl isothiocyanate (0.1 mol) and hydrazine hydrate (0.2mol) mixed to prepared 4-(4-nitrophenyl) thiosemicarbazides [64]. Via ring closure reaction of 4-(4-nitrophenyl) thiosemicarbazides (1) synthesized 5-(4-nitrophenylamino-1,3,4-thiadiazole-2(3h)-thione [65]. then finally reaction of 5-(4-nitrophenylamino-1,3,4-thiadiazole-2(3h)-thione with N-(alkyl/aryl)2chlroacetamide was stirred with acetone and potassium carbonate at room temperature for 8 hours filtered the solution and residue was thiadiazole derivative. [66] (figure 18).

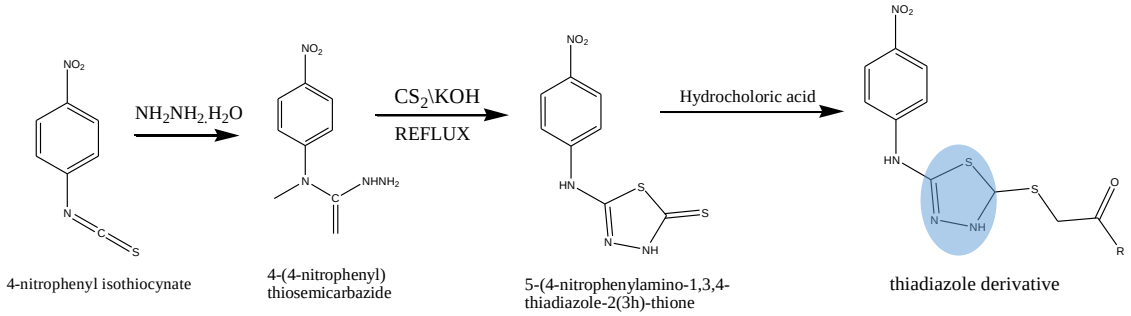


Fig.no.18 – Synthesis scheme for 5-(4-nitrophenylamino-1,3,4-thiadiazole-2(3h)-thione

6) Dilek M. et.al. synthesized a series of 4-(trifluoromethyl) phenyl thiadiazole derivative. In that 4-(trifluoromethyl) phenyl isothiocyanate (0.01mol) is reacted with ethanol (30ml) and hydrazine hydrate(0.02mol) stirred at room temperature for 4 hours to prepared 4-(trifluoromethyl) phenyl thiosemicarbazides [67]. The above mixture (0.01mol) was dissolved with carbon sulphide (0.1 mol) and potassium hydroxide (0.1 mol) in ethanol (30 ml) and refluxed for 10 hours prepared thiadiazole thions. [68] (figure 19).

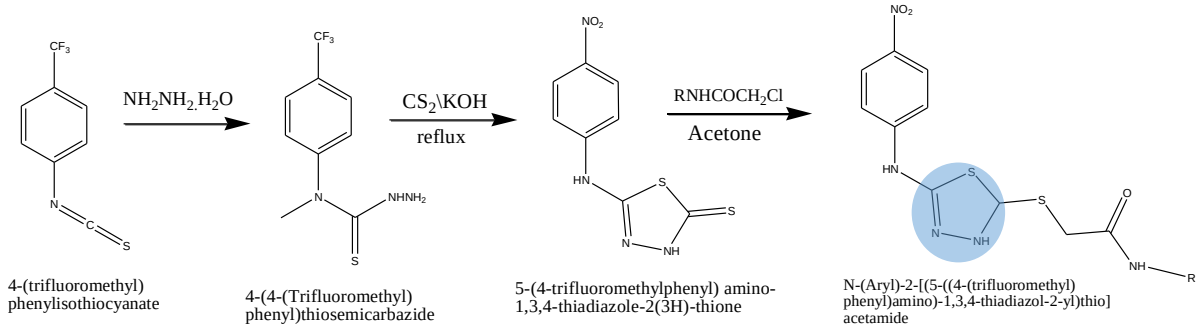


Fig. 19 – Synthesis scheme for N-(Aryl)-2-[(5-((4-(trifluoromethyl) phenyl) amino)-1,3,4-thiadiazol-2-yl) thione] acetamide

7) Ahmet C. et.al. reported synthesis of 2-((5-((4-Chlorophenyl) amino)-1,3,4-thiadiazol-2-yl) thione)-1-phenyl derivative. In first step hydrazine hydrate (0.1mol) was mixed with 4-Chloro phenyl isothiocyanate (0.22 mol) in ethanol (40ml) for 2 hours stirred in ice bath to obtained 4- (Chlorophenyl) hydrazine carbothioamide. In second step mixture of above compound (0.02 mol) carbon disulphide (0.024mol) added ethanol (40ml) with sodium hydroxide (0.024mol) refluxed for 4 hours. In last step 4 (Chlorophenyl)amino1,3,4, thiadiazole-2-thiol (0.83 mmol) was reacting with 2-bromoacetophenone (0.83 mmol) and potassium carbonate (0.83 mmol) were stirred in acetone (10 ml) to obtained 2-((5-((4-Chlorophenyl) amino)-1,3,4-thiadiazol-2-yl) thione)-1-phenyl derivative. [69] (figure 20).

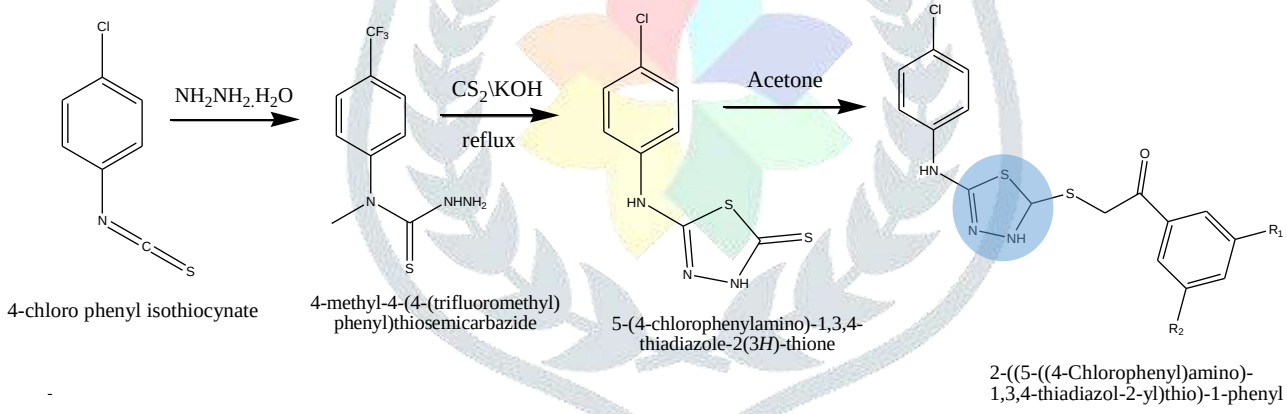


Fig. no. 20 – Synthesis scheme for 2-((5-((4-Chlorophenyl) amino)-1,3,4-thiadiazol-2-yl) thione)-1-phenyl

8) Following synthesis performed by Halit M. et.al. to prepared N- aryl thiadiazole derivative. Thiophene- 3-carboxylic acid (0.2 mol) chilled in refrigerator with N- Aryl Semi thiocarbazide (0.2 mol) reacted with phosphorus oxychloride (0.02 mol) drop wise stirred 4 hours at 90oC residue was filtered and washed synthesised thiadiazole derivative. [70] (figure 21).

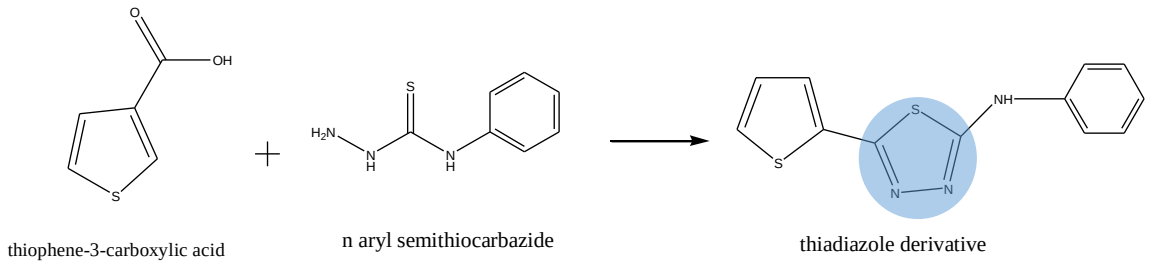


Fig.no.21 – Synthesis scheme for N- aryl thiadiazole derivative

9) Zongjie G. et.al. synthesized a series of 2-((5-((4-Chlorophenyl) amino)-1,3,4-thiadiazol-2-yl) thione)-1-phenylderivative. It involved reaction of benzothiohydrazide (0.2 mol) and N, N-dimethyl acetamide (0.2 mol) with (0.01 mol) KHSO4 which shows cyclization thiohydrazines acts as transamination or dehydrating agent which shows thiadiazole ring formation and obtained target compound. [71], (figure 22).

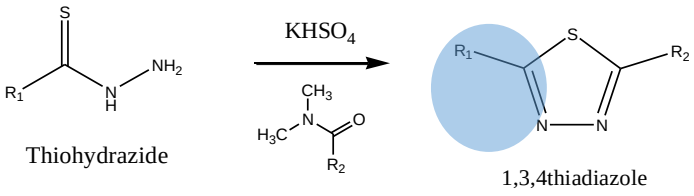


Fig. no.22 – Synthesis scheme for 2-((5-((4-Chlorophenyl) amino)-1,3,4-thiadiazol-2-yl) thione)-1-phenyl

10) M.T. Javid et.al. reported synthesis of 2-amino 1,3,4 thiadiazole derivative. First step involved thiosemicarbazides (1 mol) and Benz aldehyde (1 mol) was refluxed with hydrochloric acid (2-3 ml) were refluxed with ethanol (10 ml) for 3-4 hours. In final step cyclization was done by iodine (0.1mol) and potassium carbonate (0.1mol) with 1, 4 dioxane refluxed for 4 hours at 80 0C above mixture was cooled at room temperature and solid particle was collected. [72] (figure 23).

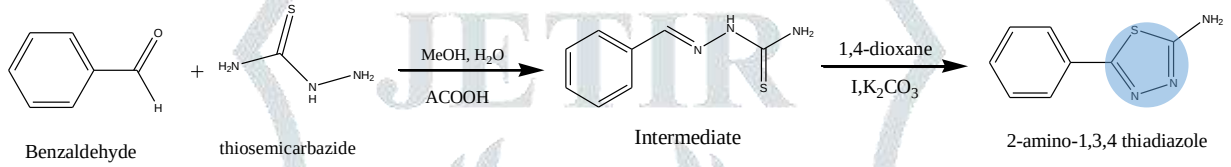


Fig.no.23 – Synthesis of 2-amino-1,3,4 thiadiazole

2.3 Triazole derivatives

1) Grytsaia O. et.al. reported the Synthesis of N,3-diphenyl-1H-1,2,4-triazol-5-amines is done by reaction of benzoyl chloride (1 mol) with substituted anilines(1mol) and aryl carbonyl isothiocyanate (1.1 mol) refluxed for 12 h to give N-(phenylcarbamothioyl) nicotinamides (1 mol) then it reacted with hydrazine hydrate (3 mol) and 1,4 –dioxane (10 ml/1mmol) at 0 °C The reaction was stirred for 24–30 h at room temperature to get the product [73] (figure 24).

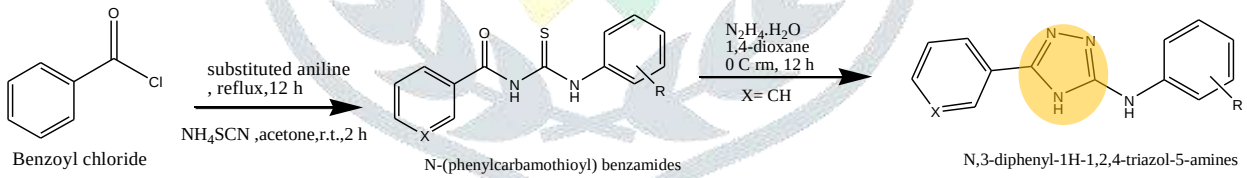


Fig. 24 – synthesis scheme for N-3-diphenyl-1H-1,2,4-triazol-5-amines.

2) Following synthesis was performed by Lin S. et.al. hydrazonoyl chlorides (5.0 mmol, 1.0 mol) react with bubbled ammonia (NH_3) in presence of dioxane solution (2.9 ml) at 0 ◦C for 24 h to formed hydrazo amides which reacted with 2.0 mol of 2-chloroacetyl chloride and NEt3 (5.0 mol) in toluene solution at refluxed for 5 h to yield methyl 5-(halomethyl)-1-aryl-1H-1,2,4-triazole-3-carboxylate derivatives [74] (figure 25).

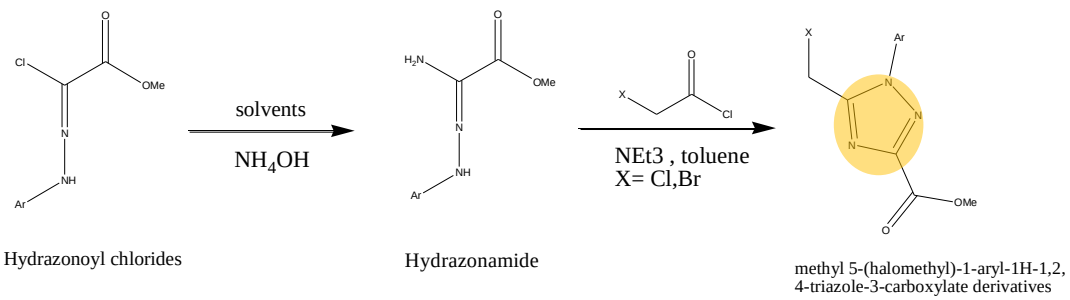


Fig. 25 – synthesis scheme for methyl 5-(halomethyl)-1-aryl-1H-1,2,4-triazole-3-carboxylate.

3) Zhang l. et.al. reported the synthesis of 5-(2-flurophenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol In the first step 2-flurobenzoic acid in presence of thionyl chloride , ethanol refluxed for 3 h to formed ethyl 2-flurobenzoate then it reacted with hydrazine hydrate and ethanol to give 2-flurobenzohydrazine then it react with phenyl isothiocyanate and ethanol refluxed for 3 h to form 1-(2-flurobenzoyl)-4-phenylthiosemicarbazide [75][76] the intermediate formed is further reacted with sodium hydroxide and hydrochloric acid refluxed for 4 h. then the solution of 5-(2-fluorophenyl)-4-phenyl-4H- 1,2,4-trizole-3-thiol (1 mmol) and anhydrous ethanol (10 ml), 4-substituted piperazine (1 mmol) and 37% formaldehyde (3 mmol) is prepared , then the solution was stirred at r.t. for 1–2 h to get the product [77] (figure 26).

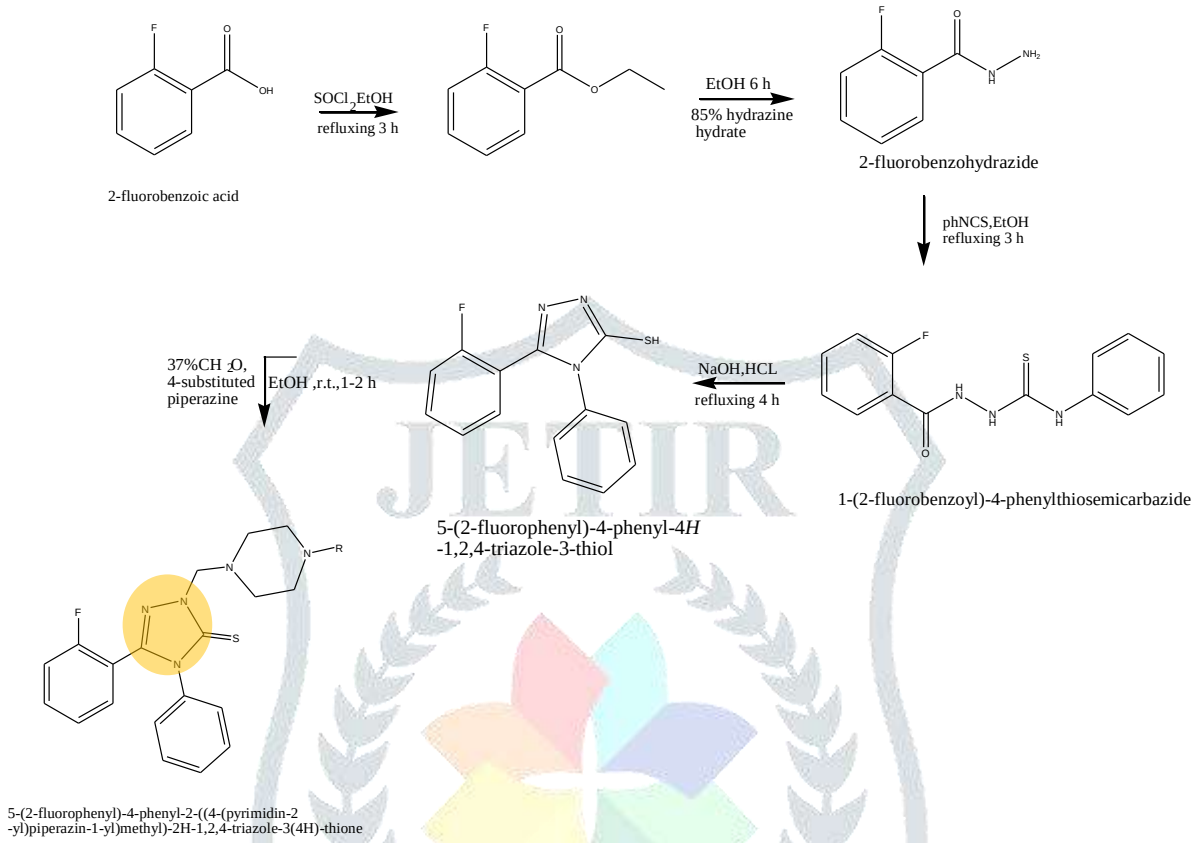


Fig. 26 – synthesis scheme for 5-(2-flurophenyl)-4-phenyl-2-(4-(pyrimidin-2-yl) piperazine-1-yl) methyl)-2H-1,2,4-triazole-3(4H)-thione.

4) Following synthesis was performed by Dewangan D. et.al. Potassium hydroxide solution at 0.15M, absolute ethanol (200ml), and pyridyl-2-carbohydrazide 0.10M were mixed and then reacted with carbon disulphide at 0.15M then 150ml of ethanol was added to the mixture, after dilution, agitation was applied for 12–16h. After16h, 200 ml of dry ether was added to the resulting solution, to form 5-(pyridine-3-yl)-4H-1,2,4-triazole-thiol [78] (figure 27).

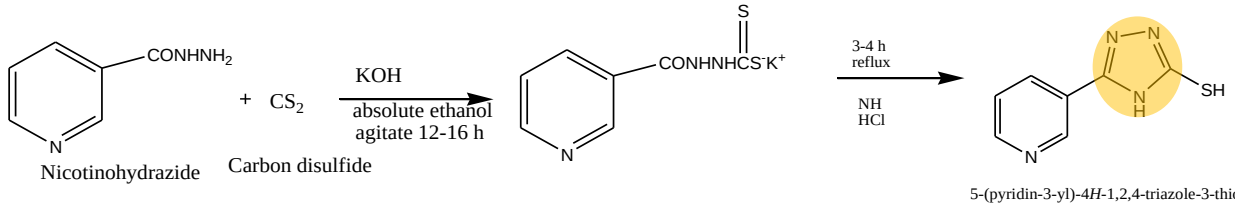


Fig .27 – synthesis scheme for 5-pyridin-3-yl-4H-1,2,4-triazole-3-thiol.

5) Beyzaei H. et.al. reported the Synthesis of 1,2,4-Triazole-3-thiones the reaction of aryl hydrazides (1mmol) and 4-nitrophenyl isothiocyanates (1mmol) in presence of Gly/potassium carbonate as a solvent to get carbothioamides. Condensation of intermediate carbothioamides to yield 1,2,4-triazole-3-thione derivatives occurred at a minimum temperature of 100 °C [79] (figure 28).

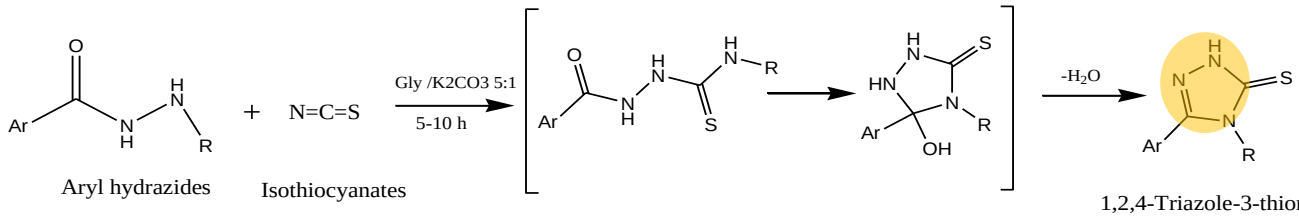


Fig. 28 – synthesis scheme for 1,2,4-triazole-3-thiones.

6) Following reaction was performed by Guillon C. et.al. Reaction of Thiocabonohydrazide with substituted acids to give 4-amino-3-mercapto-5-(R1)-4H-1,2,4-triazole [80] (0.50 mmol) the intermediate formed is further reacted with aldehyde, trans-cinnamaldehyde (1.16 mmol) solubilized in 4 ml of absolute ethanol or THF. The mixture was stirred and refluxed usually for 6 hours, and a solid precipitate was obtained. The flask was cooled down to r. temp., then put in the freezer (-20°C) overnight. The precipitate was filtered and rinsed with cold ethanol (0.323 mmol, 64 %) or tetrahydrofuran to give the expected 4- (R2-imino)-3-mercapto-5-(R1)-4H-1,2,4-triazole [81] (figure 29).

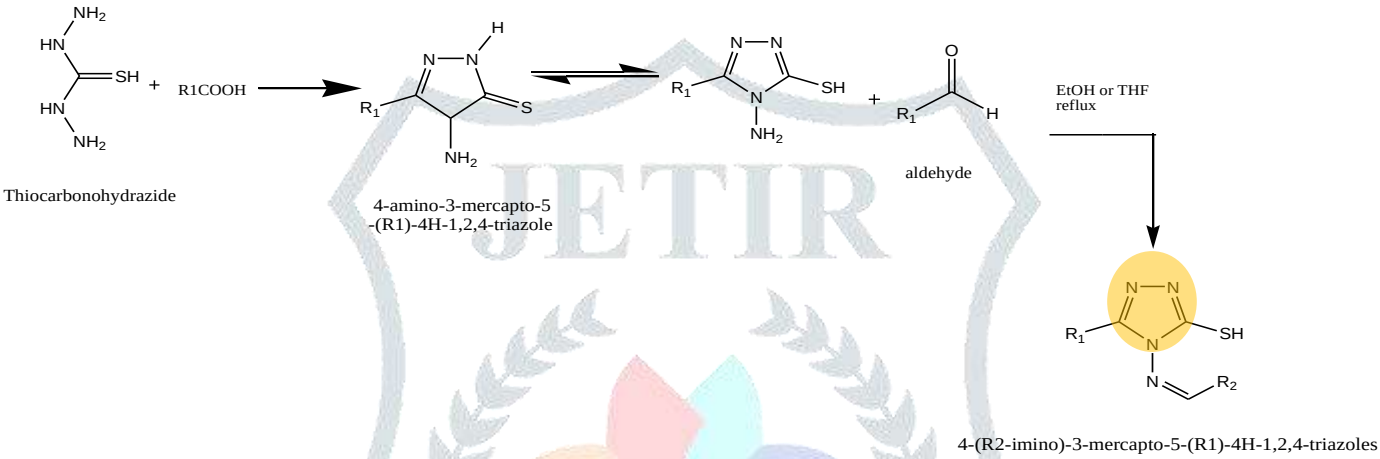
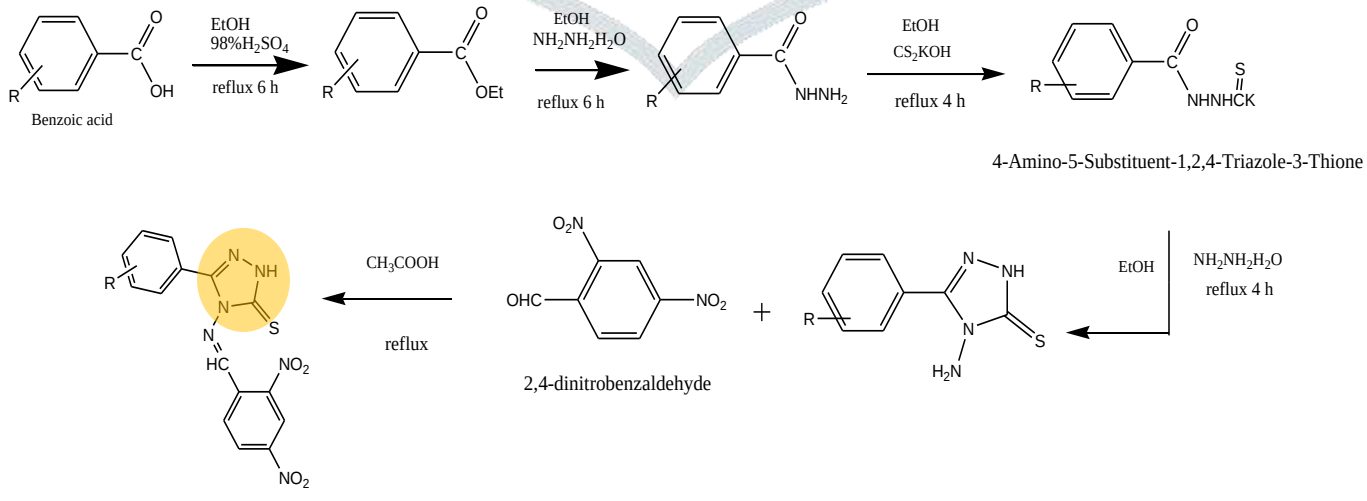


Fig. 29 - synthesis scheme for 4-R2-imino-3-mercapto-5-R1-4H-1,2,4-triazole.

7) Zhang W. et.al. reported the synthesis of 4-(2,4-dinitrobenzylideneamino)-5-m-tolyl-2H-1,2,4-triazole-3(4H)-thione reaction of benzoic acid with different substituted esters, which includes esterification, hydrazidation, salt formation, and cyclization. To obtained 4-Amino-5-Substituent-1,2,4-Triazole-3-Thione [82][83][84] (5mmol) was added to the solution of 2,4-dinitrobenzaldehyde (5 mmol) in glacial acetic acid (10 ml), the mixture was refluxed for about 4 h. The reaction mixture was left standing overnight and then filtrated to collect product [85] (figure 30).



4-(2,4-dinitrobenzylideneamino)-5-m-tolyl-2H-1,2,4-triazole-3(4H)-thione

Fig 30 – synthesis scheme for 4-(2,4-dinitronenzylideneamino)-5-m-tolyl-2H-1,2,4-triazole-3(4H)- thione.

8) Following reaction was performed by Osmanov V. et.al. solution of 1-isoselenocyanato-3-methoxybenzene (20 mmol) in anhydrous ethanol (20 ml) was added to the boiling solution of 2-(2-thienyl) acetohydrazide (20 mmol) and anhydrous ethanol (50 ml). The reaction mixture was refluxed for 4 h and cooled to 20°C. A precipitate of N-(3-methoxyphenyl)-2-(2 thienyl acetyl) -hydrazinecarboselenoamide was formed and filtered off, washed with ethanol (50 mL) and then with diethyl ether (50 mL). then N-(3-methoxyphenyl)-2-(2 thienyl acetyl)- hydrazinecarboselenoamide (10 mmol) was added to the aqueous solution of potassium hydroxide (100ml, 10%) and heated to a boil for 5 h. After cooling to r.t., the reaction mixture was filtered from dissolved particles and a 10% solution of undissolved was added to pH=3. Precipitate of 4-(3-methoxyphenyl)-5-(2-thienylmethyl)-2,4-dihydro-3H-1,2,4-triazole-3- selone [86] was washed with water. (figure 31).

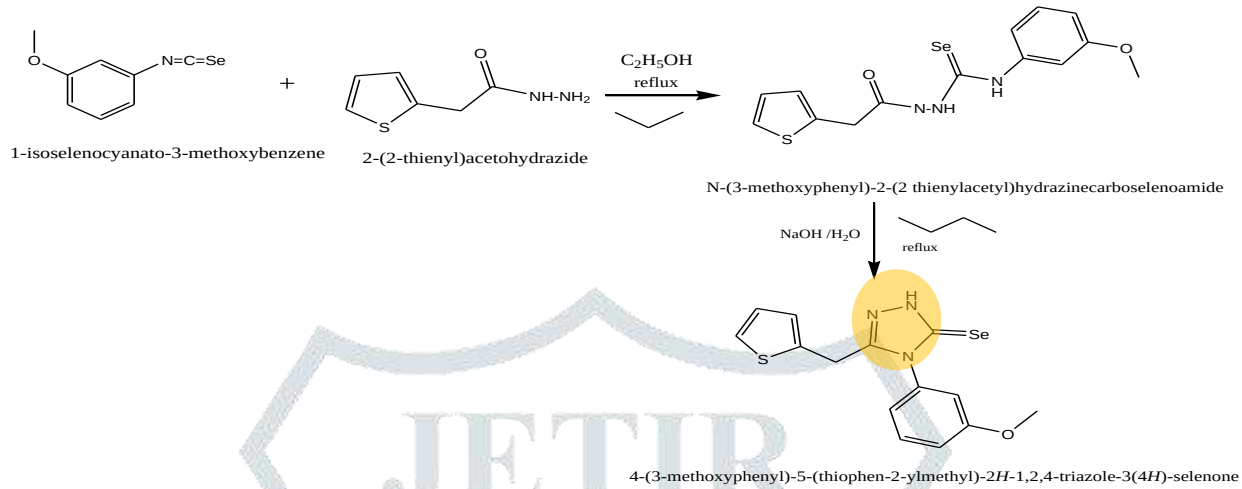
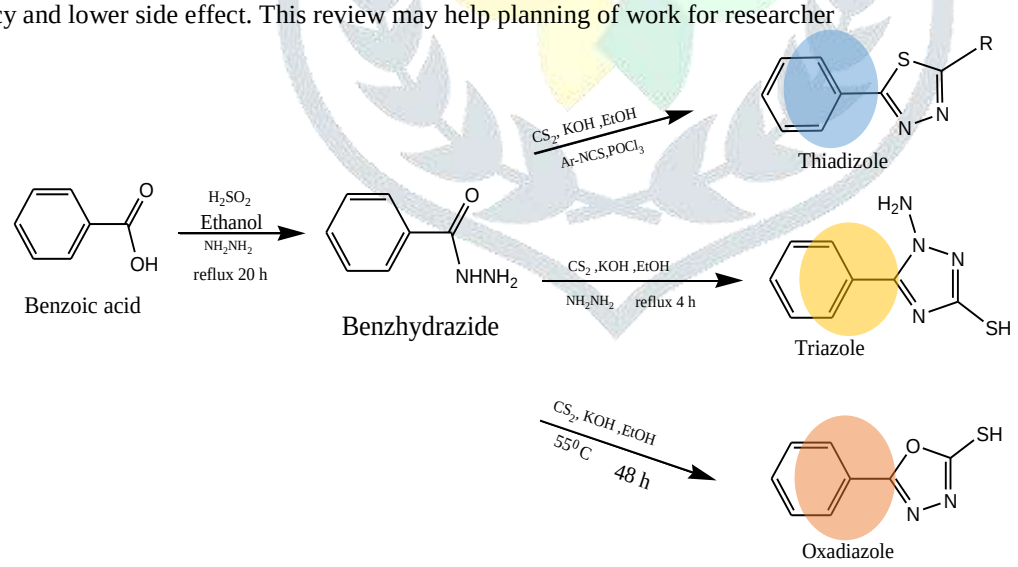


Fig 31 – synthesis scheme for 4-(-3-methoxyphenyl)-5-(thiophen-2-ylmethyl)-2H-1,2,4-triazole-3(4H)-selenone.

III Conclusion

Thiadiazole, oxadiazole, Triazole, Tetrazole have attracted considerable attention in the field of medicine due to their structure and properties. Due to possessing a great activity and importance in medicinal chemistry, this is quite important for synthesis and work on all derivatives it takes an interest. By the various method of synthesizing of these heterocycles in this review, it may help in preparing newer compound and evaluate the activity for heterocycle which may use in almost type of disease with high efficacy and lower side effect. This review may help planning of work for researcher



Acknowledgment

The authors are thankful to Dr. Ashwini R. Madgulkar, Principal AISSMS College of Pharmacy for her continuous motivation, support, and providing the necessary infrastructure to carry out this work.

REFERENCES

[1] Haidar S., Alam M., Hamid H. 2014. 1,3,4-Thiadiazoles: A Potent Multi Targeted Pharmacological Scaffold. European Journal of Medicinal Chemistry, 12(92): 1-49.

[2] Karabelyov V., Burdina M., Angelova V. 2020. Synthetic approaches to unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles and their MAO-B inhibitory activity. A Review, Bioorganic & Medicinal Chemistry, 10(29): 1-37.

[3] Fraser W. 2008. 1,2,3-Oxadizoles, Reference Module in Chemistry. Molecular Science and Chemical Engineering, 5(10): 211-241.

[4] Hill J. 1984. 1,3,4-Oxadiazzoles. Comprehensive Heterocyclic Chemistry, 4: 427-446.

[5] Wang J., Ansari M., Zhou C. 2021. Unique Para-aminobenzensulfonyl Oxadiazole as Novel Structural Potential Membrane Actve Antibacterial Agents Towards Drug-Resistance Methicillin resistance *Staphylococcus aureus*. Bioorganic and Medicinal Chemistry Letters, 53(7): 995.

[6] Shi J., Luo N., Ding M., Bao X. 2020. Synthesis in vitro Antibacterial and Antifungal Evaluation of Novel 1,3,4-Oxadiazole Thioether Derivatives Bearing the fluoroquinazolinylpiperidinyl moiety. Chinese Chemical Letters, 31(2): 434-438.

[7] Khanaposhtani M., Ahangar N., Sobhani S., Masihi P., Shakiba A., Saeedi M. 2019. Design Synthesis in vivo and in silico evaluation of new coumarin-1,2,4-Oxadiazole hybrids as anticonvulsant agents. Bioorganic Chemistry, 89(10): 989.

[8] Balaraju V., Kalyani S., Sridhar G., Laxminarayana E. 2021. Design, Synthesis and Biological Assessment of 1,3,4-Oxadiazole Incorporated Oxazole-Triazole Derivatives as anticancer agents. Chemical Data Collections, 33: 695.

[9] Ambhore A., Kamble S., Kadam M., Kamble R., Hebade M., Gaikwad M., Dawane B. 2019. Design, Synthesis and in silico Study of Pyridine based 1,3,4-Oxadiazole embedded hydrazinececarbothioamide derivatives as potent anti-tubercular agent. Computational Biology and Chemistry, 80: 54-65.

[10] Ansari K., Lal C. 2009. Synthesis, Physicochemical Properties and Antimicrobial activity of some new benzimidazole derivatives. European Journal of Medicinal Chemistry, 33(6): 4028-4033.

[11] Zabiulla A., Gulnaz R., Mohammed H., Khanum S. 2019. Design, Synthesis and Molecular Docking of Benzophenone Conjugates with Oxadiazole Sulphur Bridge Pyrazole Pharmacophores as Anti-Inflammatory and Analgesic agents. Bioorganic Chemistry, 200: 220-240.

[12] Katritzky A. R., Ramsden C. A., Joule J. A., Zhdankin V. V. 2010. Handbook of Heterocyclic Chemistry. 3 rd. ed; Elsevier: Oxford, UK. 1759-1761.

[13] Gupta R. R., Kumar M., Gupta V. 2005. Five membered heterocycles with more than two heteroatoms in heterocyclic Chemistry II. Springer, 120(15): 491-494.

[14] Jain A., Sharma S., Vaidya A., Ravichandran V., Agrawal R. 2013. 1,3,4-thiadiazole and its derivative: A Review on Recent Progress in biological activites. john wiley and sons, 135: 655-659.

[15] Haider S., Alam M. S., Hamid H. 2014. 1,3,4-thiadiazole: A Potent Medicinal Scaffold. European Journal of Medicinal chemistry, 92: 156-177.

[16] Taha M., Javid M., Imran S., Selvaraj M., Chigurupati S., Ullah H., Khan F., Rahim F., Mohammed J., khan K. 2017. Synthesis and Study of Alpha Amylase Inhibitory Potential of Thiadiazole Quinoline Derivative. Bioinorganic & Medicinal Chemistry, 74: 179 – 186.

[17] Chandrakantha B., Isloor A., sheety P., Kun fun H., Hegde G. 2013. Synthesis and Biological Evaluation of Novel Substituted 1,3,4-thiadiazole and 2,6-aryl substituted imidazol [2,1-b] [1,3,4]- thiadiazole derivative. European Journal of Medicinal chemistry, 10: 56-68.

[18] Ahadi H., Shokrzadeh M., Khan Z., Barghi N., Ghasemian M., Emadi E., Zargari M., Razzaghi-Asl N., Emami S. 2020. Synthesis and Biological assessment of Ciprofloxacin- derivative 1,3,4 – thiadiazole as an Anticancer agent. Bioorganic Chemistry, 10: 174-189.

[19] Zhang J., Wang X., Yang J., Guo L., Wang X., Song B., Dong W., Wang W. 2019. Novel diogenin derivatives containing 1,3,4-oxadiazole/thiadiazole moieties as potential antitumor agent: Design, synthesis and cytotoxic evaluation. European Journal of Medicinal chemistry, 44(7): 1688-1697.

[20] Kadi A., El-Brollosy N., Al-Deeb O., Habib E., Ibrahim T., El-Emam. 2007. A synthesis, Antimicrobial and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted -1,3,4-oxadiazoles and 2-(1-adamantylamino)-5-substituted 1,3,4, -thiadiazole. European Journal of Medicinal chemistry, 42: 235-242.

[21] Talath S., Gadad A. 2006. Synthesis, antibacterial and antitubercular activities of some 7-[4-5-amino-[thiadiazol-2-sulfonyl)- piperazin -1-yl] fluoroquinolone derivative. European Journal of Medicinal chemistry, 41(25): 918-924.

[22] Chen Z., Xu W., Liu K., Yang S., Fan H., Bhandury P., Hu D., Zang Y. 2010. Synthesis and Antiviral study of-5(4 – Chlorophenyl)- 1,3,4 – thiadiazole sulphonamides. Molecules, 15(2): 9046-9056.

[23] Sureshkumar G.V., Rajendraprasad Y., Mallikarjuna B.P., Chandrashekar S.M., Kistayya C. 2010. Synthesis of some novel 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as potential antimicrobial and antitubercular agents. European Journal of Medicinal Chemistry, 33(50): 2063–2074.

[24] Agisho H., Esatu H., Hairat S. 2020. TBHP/TBAI–Mediated simple and efficient synthesis of 3,5-disubstituted and 1,3,5-trisubstituted 1H-1,2,4-triazoles via oxidative decarbonylation of aro- matic aldehydes and testing for antibacterial activities. Tetrahedron Letters, 120(30): 1-20

[25] Joshi D.S., Vagdevi M.H., Vaidya P.V., Gadaginamath S.G. 2008. Synthesis of new 4-pyrrol-1-yl benzoic acid hydrazide analogs and some derived oxadiazole, triazole and pyrrole ring systems: A novel class of potential antibacterial and antitubercular agents. European Journal of Medicinal Chemistry, 99(10): 1989-1996.

[26] Sseelam N., Gupta S. 2012. Synthesis and in vitro study of some fused 1,2,4-triazole derivatives as antimycobacterial agents, Journal of Saudi Chemical Society, 25(9): 1-8.

[27] Gao F., Wang T., Xiao J., Huang G. 2019. Antibacterial activity study of 1,2,4-triazole derivatives. European Journal of Medicinal Chemistry, 45(32): 1-21.

[28] Aouad M., Al-Mohammadi H., Al-blewi F., Ihmaid S. 2019. Introducing of Acyclonucleoside analogues tethered 1,2,4-triazole as Anticancer agents with Dual Epidermal Growth Factor Receptor Kinase. Microtubule Inhibitors, Bioorganic Chemistry, 159: 1-17.

[29] El-Sherief A.H., Youssif G.B., Bukhari N.S., Abdel-Aziz M. 2017. Novel 1,2,4-triazole derivatives as potential anticanceragents: Design, synthesis, molecular docking and mechanistic studies. Bioorganic Chemistry, 104: 1-18.

[30] Kamel M., Megally Abdo N. 2014. Synthesis of novel 1,2,4-triazoles, triazolothiadiazines and triazolothiadiazoles as potential anticancer agents. European Journal of Medicinal Chemistry, 47(8): 75-80.

[31] Mohassab M.A., Hassan A.H., Abdelhamid D., Gouda M.A. 2020. Design and Synthesis of Novel quinoline/chalcone/1,2,4-triazole hybrids as potent antiproliferative agent targeting EGFR and BRAFV600E kinases. Bioorganic Chemistry, 106: 1-25.

[32] Tozkoparan B., Kupeli E. 2007. Preparation of 5-aryl-3-alkylthio-l,2,4-triazoles and corresponding sulfones with antiinflammatory–analgesic activity. Bioorganic & Medicinal Chemistry, 15(4): 1808–1814.

[33] Al-Soud Y., Al-Dweri M. 2004. Synthesis, antitumor and antiviral properties of some 1,2,4-triazole derivatives. FARMACO, 59: 775–783.

[34] Mahmoudi Y., Badali H., Hashemi S., Ansari M. 2019. New Potent Antifungal Triazole Alcohols Containing N-benzylpiperazine Carbodithioate Moiety: Synthesis, in Vitro Evaluation and In Silico Study. Bioorganic Cemistry, 105: 27-45.

[35] Xie F., Ding Z. 2020. Bioorganic Chemistry, Design Synthesis and In Vitro Evaluation of Novel Triazole Analogues Featuring Isoxazole Moieties as Antifungal Agents. Bioorganic Chemistry, 1-27.

[36] Aaltone N., Savinainen R.J., Ribas C. 2013. Piperazine and Piperidine Triazole Ureas as Ultrapotent and Highly Selective Inhibitors of Monoacylglycerol Lipase. Chemistry & Biology, 39(11): 379–390.

[37] Al-Soud Y., Al-Masoudi N. 2004. Synthesis, antitumor activity and DNA affinity of bis-N, N′-trisubstituted 1,2,4-triazolo-piperazines. farmaco,229: 41–46.

[38] Beyzaei H., Kudeyani M. 2020. Synthesis, antimicrobial and antioxidant evaluation, and molecular docking study of 4,5-disubstituted 1,2,4-triazole-3-thiones. Journal of Molecular Structure, 55(20): 31-39.

[39] El Sayed H., El Ashry E., EL-Rafey., Rezki N. 2011. Evaluation of some functionalized imidazoles and 1,2,4-triazoles as antioxidant additives for industrial lubricating oils and correlating the results with the structures of additives using empirical AM1 calculations. Journal of Saudi Chemical Society, 199: 1-7.

[40] El Aoufir Y. 2020.The effect of the alkyl chain length on corrosion inhibition performances of 1,2,4-triazole-based compounds for mild steel in 1.0 M HCl: Insights from experimental and theoretical studies. Journal of Molecular Liquids, 87(22): 334-345.

[41] Iqbal K.A., Khan A. 2012. Synthesis, hypoglycemic and hypolipidemic activities of novel thiazolidinedione derivatives containing thiazole/triazole/oxadiazole ring. European Journal of Medicinal Chemistry, 45(7): 308-315.

[42] Penga Z., Wangb G., Zeng Q. 2016. Synthesis, antioxidant and anti-tyrosinase activity of 1,2,4-triazole hydrazones as antibrowning agents. Food Chemistry, 66: 55-64.

[43] Shneine J., Alaraji Y. 2016. Chemistry of 1, 2, 4-Triazole. International Journal of Science and Research, 185(44): 2319-7064.

[44] Kaur P., Kaur R., Goswami M. 2018. A review on methods of synthesis of 1,2,4-triazole derivatives. International research journal of pharmacy, 155: 1-35.

[45] Zhang J., Wang S., B Y., Xu Z. 2019. 1,2,4-Triazole-quinoline/quinolone hybrids as potential anti-bacterial agents. European Journal of Medicinal Chemistry, 149(39): 67-75.

[46] Mani K., Sharma S. 2020. Promising Antifungal Agents: a minireview. Bioorganic and medicinal Chemistry, 28(7): 1-46.

[47] Baddi L., Ouzebla D., Mansouri E., Smietana M., Vasseur J., Lazrek B. 2020. Efficient one-pot, three-component procedure to prepare new α-aminophosphonate and phosphonic acid acyclic nucleosides. Nucleosides, Nucleotides & Nucleic Acids, 64(21): 1-25.

[48] Mansouri E., Oubella A., Mehdi A., AitItto M. Y., Zahouily M., Morjani H., Hassan B. L. 2020. Design, synthesis, biological evaluation and molecular docking of new 1,3,4- oxadiazole homonucleosides and their double-headed analogs as antitumor agents. Bioorganic Chemistry, 68(30): 1- 40.

[49] Zhanga Y., Zhanga Q., Zhanga J., Songa J., Lia C., Hanb K., Huangc J., Jianga C., Zhanga H. 2020. Synthesis and evaluation of 1,2,4-oxadiazole derivatives as potential anti-inflammatory agents by inhibiting NF-κB signalling pathway in LPSstimulated RAW 264.7 cells. Bioorganic & Medicinal Chemistry Letters, 30: 1-6.

[50] Caneschi W., Enes K., Mendonça C., Fernandes F., Miguel B., Martins S., Hyaric M., Pinho R., Duarte M., Oliveira M., Santos H., Lopes T., Dittz D., Silva H., Costa C. 2019. Synthesis and anticancer evaluation of new lipophilic 1,2,4 and 1,3,4-oxadiazoles. European Journal of Medicinal Chemistry, 165(1): 18-30.

[51] Bhati S., Kumar V., Singh S., Singh J. 2019. Synthesis, Biological Activities and Docking Studies of Piperazine Incorporated 1, 3, 4-Oxadiazole Derivatives. Journal of Molecular Structure,11(91): 197-208.

[52] Taha M., Ismail H., Imran S., Anouar H., Selvaraj M., Jamil W., Muhammad A., Muhammad K., Fazal R., Khan M., Adenan M. 2016. Synthesis and Molecular Modelling Studies of Phenyl Linked Oxadiazole phenylhydrazone Hybrids as Potent Antileis. European Journal of Medicinal Chemistry, 16(31): 1-33.

[53] Yadava N., Kumarb P., Chhikarab A., Chopra M. 2017. Development of 1,3,4-Oxadiazole Thione Based Novel Anticancer Agents: Design, Synthesis and In-Vitro Studies. Biomedicine & Pharmacotherapy, 95(8): 721-730.

[54] Kumaraswamy B., Sirassu N., Reddy N., Rao M. S. 2017. Synthesis and Antimicrobial Evaluation of Some Novel Thiomorphalin Derived 1,4-Disubstituted 1,2,3-Triazole. Journal of Serbian Chemical Soc., 33(5): 1–12.

[55] Kashida B., Salunkhea P., Dongarea B., Morec K., Khedkard V., Ghanwat A. 2020. Synthesis of Novel of 2, 5-Disubstituted 1, 3, 4-Oxadiazole Derivatives and Their In-Vitro Anti-Inflammatory, Anti-Oxidant Evaluation and Molecular Docking Study. Bioorganic & Medicinal Chemistry Letters, 30: 1-7.

[56] Ningegowda R., Chandrashekharappa S., Singhc V., Mohanlall V., Venugopala K. N. 2020. Design, Synthesis and Characterization of Novel 2-(2, 3-dichlorophenyl)-5-aryl-1,3,4-oxadiazole Derivatives for their Anti-Tubercular Activity Against *Mycobacterium tuberculosis*. Chemical Data Collections, 28(6): 1-8.

[57] Khanfara M., Reinera D., Hagenowa S., Stark H. 2018. Design, Synthesis and Biological Evaluation of Novel Oxadiazole and Thiazole Based Histamine H_3R ligands. Bioorganic & Medicinal Chemistry,26: 4034-4046.

[58] Chortani S., Edziri H., Manachou M., Al-Ghamdi Y., Almalki S. G., Alqurashi Y., Jannet H., Romdhane A. 2020. Novel 1,3,4-Oxadiazole Linked Benzopyrimidinones Conjugates: Synthesis, DFT Study and Antimicrobial Evaluation. Journal of Molecular Structure, 1217(135): 1-9.

[59] Ezabadi I., Camoutsis C., Zoumpoulakis P., Geronikaki A., Sokovic M., Glamocilija J., Ciric A. 2008. Sulphonamide-1,2,4-triazole derivative as antifungal and antibacterial agent: Synthesis, biological evaluation, lipophilicity and conformational studies bioorganic medicinal chemistry, 16: 1150-116.

[60] Charitos G., Trafalis D.T., Dalezis P., Potamitis C., Sarli V., Zoumpoulakis P., Camoutsis C. 2019.Synthesis and anticancer activity of novel 3,6-disubstituted 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole derivatives. Arabian Journal of chemistry, 12: 4784-4794.

[61] Khan S A, Imam S, Ahmad A, Bhasha S H, Husain A. 2018. Synthesis, molecular docking with cox I&II enzyme, ADMET screening and in vivo anti-inflammatory activity of oxadiazole, thiadiazole and triazole analogs of felbinac. Journal of Saudi chemical society, 22: 469-484.

[62] Xinyang L V., Lan Y., Fan Z., Bao X. 2018. synthesis and antimicrobial activity of novel quinazolin-4 (3H)-one derivative containing a 1,2,4-trizolo[3,4-b] [1,3.4] thiadiazole moiety. journal of Saudi chemical society, 79(22): 101-109.

[63] Beigi M., Alikarami M.,Kohzadi H. 2019. Chemoselective one pot synthesis of 2- phenylamino-5-alkylthio-1,3,4-thiadiazole derivative from phenylthiosemicarbazide and CS_2. Arabian Journal of chemistry, 166(12): 1501-1506.

[64] Ermut G., Karali N., Cetin I.,Topcul M., Birteksoz S. 2017. Synthesise of chemotherapeutic activities of 5-chloro-1H-indole-2,3-dione-thiosemicarbazone. Marmara Pharm journal, 13: 346-367.

[65] Tomkinson A., Chen X., Dziegieleaska B., Mackerell A., Zhong S.,Wilson G. 2010. Compound that inhibits Human DNA Ligases and Methods of treating Cancer US20100099683A1, 136: 1768-1770.

[66] Altintop M D., Can O D., Ozkay U D.,Kaplancikli Z A. 2016. synthesis and evaluation of new 1,3,4-thiadiazole Derivative as Anti-nocieptive Agents. Molecules, 34: 1004-1020.

[67] Kaplancikli Z., Altintop M.,Sere B., Canturk Z.,Özdemir A .2016. Synthesis and in vitro evaluation of new Thiosemicarbazone Derivative as potential Antimicrobial Agent. journal of chemistry, 18(90): 1540-1563.

[68] Altintop M D., Ibrahim H., Radwan M O., Sever B., Kaplancikli Z A., Ali T., Kaga R., Fujta M., Otsuka M., Ozdemir A. 2018. Design, synthesis and biological Evaluation of novel 1,3,4 -thiadiazole Derivative as Potential Antitumor Agents against Chronic Myelogenous Leukemia: Striking Effect of Nitrothiazole Moiety. Molecules, 23(59): 1-17.

[69] Karaburun A C., Cevik U A., Osmaniye D., Sagilik B N., Çavus B K., Levent S., Özkay Y., Ali S., .Behcet M., Kaplancikli Z A. 2018. Synthesis and Evaluation of New 1,3,4-thiadiazole derivative as potent Antifungal Agents. Molecule, 24(67): 3123-3139.

[70] Muglu H., Yakan H., Shouaib H A. 2019. New 1,3,4-thiadiazole based on Thiophene -2-Carboxylic acid: Synthesis. Characterization and antimicrobial activities Journal of Molecule ,93: 136-148.

[71] Gan Z., Tian B., Yuan J., Ran D., Zhang L., Dong G., Pan T., Zeng Y., Zeng Y., Yu Y. 2020. A KHSO4 promoted tandem synthesis of 1,3,4 thiadiazole from Thiohydrazines and DMF derivative, Tetrahedron Letters, 12(68): 490-499.

[72] Javid M., Rahim F., Taha M., Rehman H., Nawz M., Wadood A., Imran S., Uddin M., Alomari M., Rahim F., Mosaddik A., Khan K. 2018. Synthesis in vitro glucosidase inhibitory potential and molecular docking study of thiadiazole analog. Bioinorganic Chemistry, 34(78): 201 – 209.

[73] Grytsaia O., Valiashko O., 2020. Synthesis and biological evaluation of 3-amino-1,2,4-triazole derivatives as potential anticancer compounds. Bioorganic Chemistry, 96(20): 1-20.

[74] Lin S., Tsai S., Chiang C., Chung C., 2020. New methyl 5-(halomethyl)-1-aryl-1H-1,2,4-triazole-3-carboxylates as selective COX-2 inhibitors and anti-inflammatory agents: Design, synthesis, biological evaluation, and docking study. Bioorganic Chemistry, 125: 1-28

[75] Tong J., Shi Y., Liu X., Sun N., B.J. Li, 2012. Synthesis and fungicidal activity of 1,2,4-triazole derivatives containing 2-fluorophenyl moiety. Chin. J. Org. Chem., 67(8): 2373–2377.

[76] Liu C., Zhao Q., Li J., 2001. Synthesis study of new Schiff base containing thiocaba mide group derivatives of 3-argl-4-amino-5-mercapto-1,2,4-triazoles. Chem.Reag., 90(6): 344–345.

[77] Zhan Y.,2015. Synthesis and biological activities of some fluorine- and 4 piperazine-containing 1,2,4-triazole thione derivatives. Chinese Chemical Letters, 155: 345-355.

[78] Dewangan D. yaishnav Y., Mishra A. 2021. Synthesis, Molecular Docking, and Biological Evaluation of Schiff Base Hybrids of 1,2,4-Triazole-Pyridine as Dihydrofolate Reductase Inhibitors. current research in pharmacology and drug discovery, 33(10): 1-12.

[79] Beyzaei H., Kudeyani M., Delaram H., Aryan R. 2020. Synthesis, antimicrobial and antioxidant evaluation, and molecular docking study of 4,5-disubstituted 1,2,4-triazole-3-thiones. Journal of Molecular Structure, 49(9): 1-26.

[80] Reid J., Heindel N. 1976. Improved syntheses of 5-substituted-4-amino-3-mercapto-(4H)- 1,2,4-triazoles. J. Heterocycl. Chem., 55: 925–926.

[81] Guillon C., Vetrano A.,Saxena J., Hunte A.,Verderone G. 2020. Derivatives of 1,2,4- triazole imines acting as dual iNOS and tumor cell growth inhibitors. Bioorganic Chemistry, 22(5): 1-20.

[82] Jin R., Zeng C., Liang X., Sun X., Liu Y., Wang Y., S. Zhou. 2018. Design, Synthesis and biological activities and DFT Calculation of novel 1,3,4-triazole. Bioorg. Chem., 80(4): 253-260.

[83] Wang, Z. J. Sun Z., Liu X. 2016. Synthesis and biological evaluation of novel 1,2,4-triazol as antimicrobial agents. Chin. J. Struct. Chem., 77: 212-218.

[84] Bayrak H., Demirbas A., Karaoglu S., Demirbas N. 2009. Synthesis of new 1,2,4-triazole their mannich and Schiff bases and evaluation of their antimicrobial activities. Eur. J. Med. Chem., 12(5): 1057-1066.

[85] Wu S., Zhang W., Qi L., Ren Y., Ma H.,2019, Investigation on 4-amino-5 substituent-1,2,4-triazole-3-thione Schiff bases an antifungal drug by characterization (spectroscopic, XRD), biological activities, molecular docking studies and electrostatic potential (ESP). Journal of Molecular Structure, 66: 445-455.

[86] Osmanov V., Askerov R., Chipinsky E., Borisova G. 2020. 4-(3-Methoxyphenyl)-5-(2-thienylmethyl2,4-dihydro-3H-1,2,4-triazole-3-selone: synthesis, structural characteristics and reactions. Journal of Molecular Structure, 55(13): 1-21.