Synthesisand Bioactivityof 1,2,4-Triazoles

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Abstract:

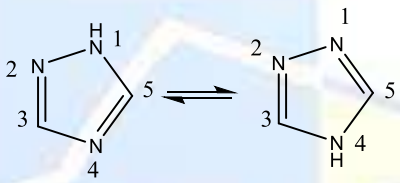
This review highlightsresearch works of many researchers on 1,2,4-triazoles and their derivatives.The chemistry of triazoles and their derivatives has gotten a lot of attention in recent years because of their synthetic and biological relevance. Triazoles can be synthesized using various different methods. Triazole derivatives are showing very promising and excellent therapeutic effectiveness. The simplest 1,2,4-triazole nucleus is present in compounds involved in research to get new products. The major activities exhibited by these compounds includes insecticial, antifungal, antiviral, antibacterial, sedative,hypnotic, anticonvulsant and anti-inflammatory.

Keywords: Pyrrodiazole,Therapeutic Effectiveness, Triazoles Moiety,Hydrazine Hydrate.

Introduction:

1,2,4-Triazoleshavefive-memberheterocyclic ring of two carbon atom and three nitrogen atomand referred as isomeric compounds of molecular formula $C_2H_3N_3$.During, the last three decadesa considerable attention has been devoted to synthesis of triazoles and their derivatives because of their important structural fragments and wide biological activities such as anticonvulsant[1], antidepressant[2], antibacterial[3], antifungal[4], anti-inflammatory[5], analgesic[6], anticancer[7] and anti-viralactivities[8-9].

The history of triazoles began its journey in the early 19^{nth} century when Luigi Brugnatelli, first isolated the heterocyclic compound in 1818. The chemistry of 1,2,4-triazoles described briefly in the literature[10]. The first 1,2,4-triazole derivatives have been synthesized by Bladin in 1885. 1,2,4-triazole derivatives are also useful as analytical reagents[11], photographic chemicals[12] and in polymer synthesis[13].1,2,4-triazole, also known as pyrrodiazole which exists in two tautomeric forms. 1H and 4H-1,2,4-triazole is considered to be pharmacologically important nucleus.

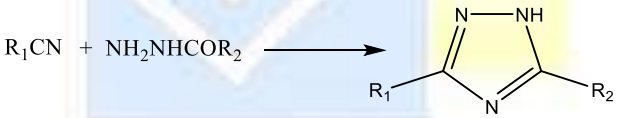


In view of the above findings, it was thought worthwhile to reviewthe compounds having features of 1,2,4-triazole moiety with different substituents and studied their pharmacology.

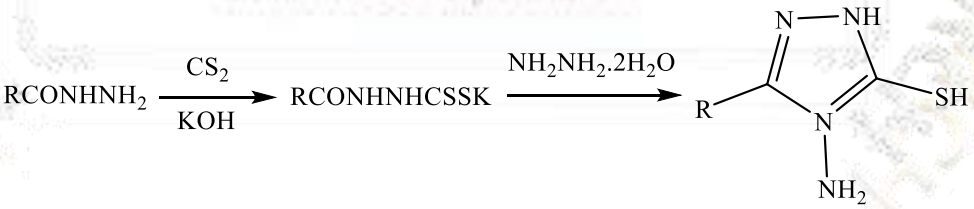
Methods of synthesis of 1,2,4-triazole:

Various 1,2,4-triazole derivatives are known but their practical applications have been hitherto very little. 1,2,4-triazoles are easily prepared with good stability and yieldbut the starting materials are quite expensive or sensitive intermediates appear which depressed industrial synthesis and its applications.Many methods are reported to synthesize 1,2,4-triazole and its derivatives, out of which some are as discussedbelow:-

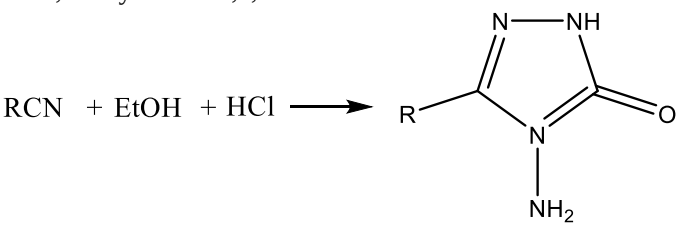
An one step, base-catalyzed synthesis of 3,5-disubstituted-1,2,4-triazoles by the condensation of a nitrile and a hydrazide is reported[14].



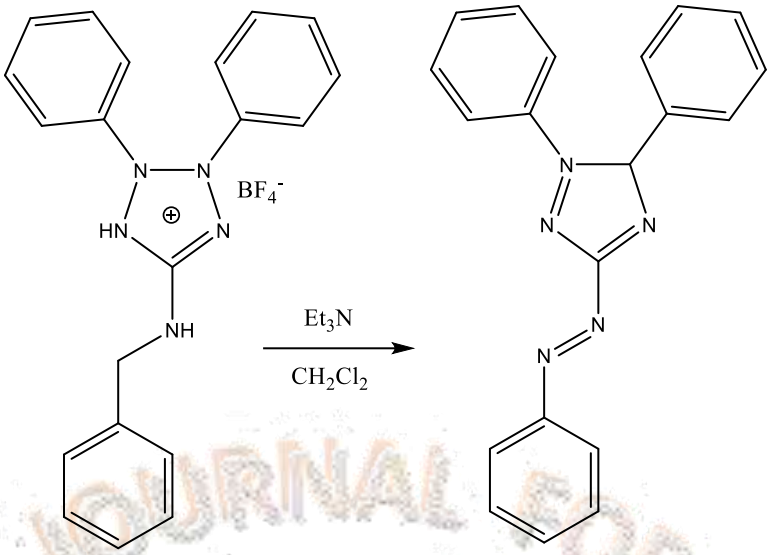
Reid and Heindel have reported the reaction of aryl acid hydrazide with CS_2, KOH and hydrazine hydrate furnished triazoles[15].



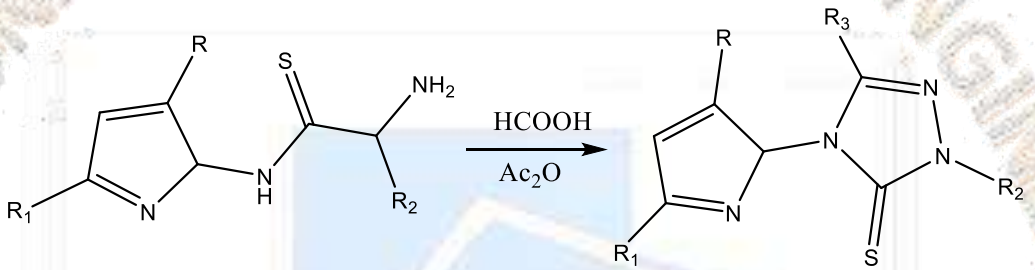
B. Kahvecihave reported that the iminoester hydrochlorides are converted into ester ethoxycarbonyl hydrazones, which turn into a new series of substituted 4-amino-4,5-dihydro-1H-1,2,4-triazole-5-ones[16].



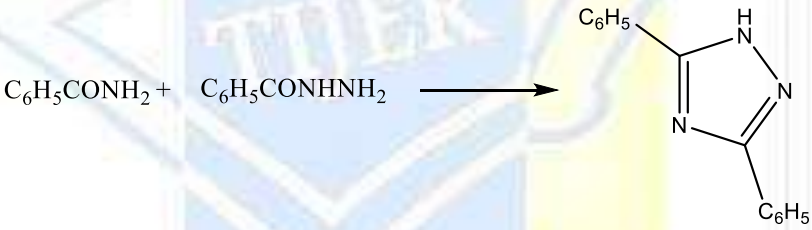
Khosrow Zamani *et al.*,have prepared triazole derivatives from substituted carboxylic acid hydrazides and 4-methylphenylisothiocyanate[17].Li-Li Liu and Guang Yanghave described a facile method to prepare 1,2,4-triazole by the reaction of isonicotinonitrile with excess amount of hydrazine[18].Shuki Araki *et al.*,havereported the synthesis of 1,2,4-triazoles from 2,3-diphenyltetrazolium salt using triethylamine[19].



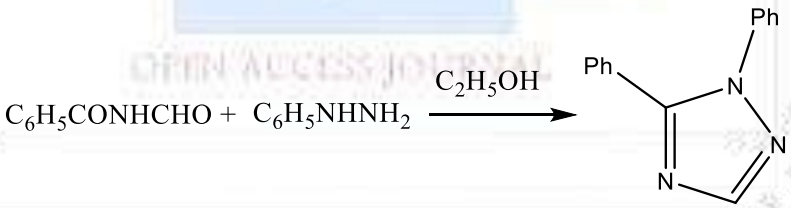
The synthesis of 1,2,4-triazoles is described by E. Diez-Barra *et al.*,using different approaches[20].Kee-Jung lee *et al.*,have reported 1,2,4-triazole from the electrocyclic reaction of conjugated heterocumulenes[21].Chande *et al.*, have reported 4-anilino-5-mercapto-5-triazoles from *β*-acyldithiocarbazinate and phenyl hydrazine[22].Shin-ichi Nagaihave alsoreported the synthesis using thiosemicarbazidesand formic acid in the presence of acetic anhydride[23].



Yan Shiquainghave reported the synthesis of triazole by the treatment of ferrocenecarboxylic acid hydrazide with aryl isothiocyanate and cyclization of the product gave 3,4-disubstituted 4H-1,2,4-triazole-5-thiol[24].B. J. Rai and co-workers have synthesized 3-amino-5-aryl-2-phenyl-2H-1,2,4-triazole by reaction of aroylcyanide with phenylhydrazine[25].It has also been reported that reaction of formamide and hydrazine hydrochloride in presence of KOH yields 1,2,4-triazole derivativesand referred as the Pellizzari Reaction. For example, benzamide and benzoyl hydrazide yields 3,5-diphenyl-1,2,4-triazole[26].

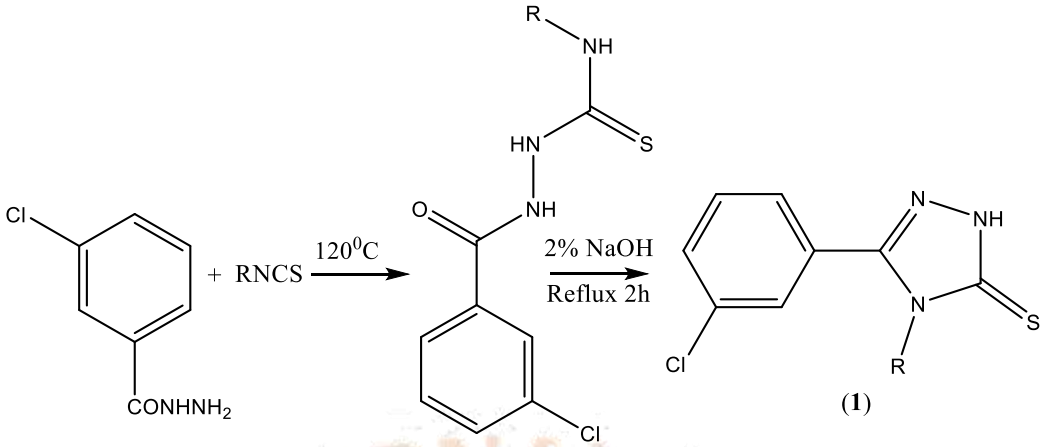


The synthesis of 1,2,4-triazoles by hydrazines or substituted hydrazine and diacylamines condensation in the presence of weak acid is called as the Einhorn-Brunner reaction. For example, N-formyl benzamide and phenyl hydrazine yields 1,5-diphenyl-1,2,4-triazole[27].



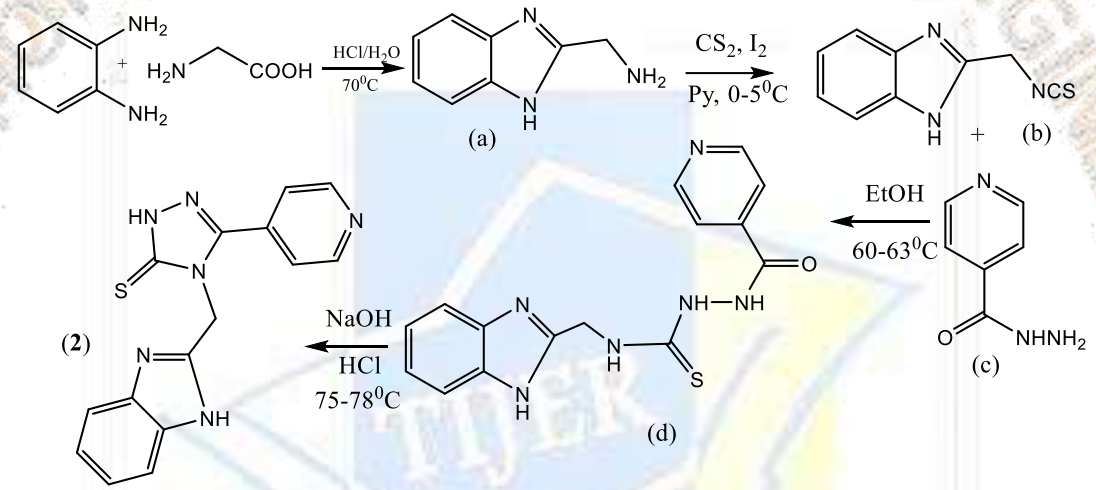
Methods of synthesis of 1,2,4-triazole derivatives:

A mixture of 3-chlorobenzhydrazide (0.01mol, 1.70g) and equimolar amount of the alkyl isothiocyanate heated in an oil bath at 120°C to obtain 4-alkyl-1-(3-chlorobenzoyl)-thiosemicarbazideswhich was dissolved in 2% NaOH and the resulting solution was refluxed for 2h and after neutralized with 3M HCl the precipitates of 4-alkyl-5-(3-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (1**)** formed[28].

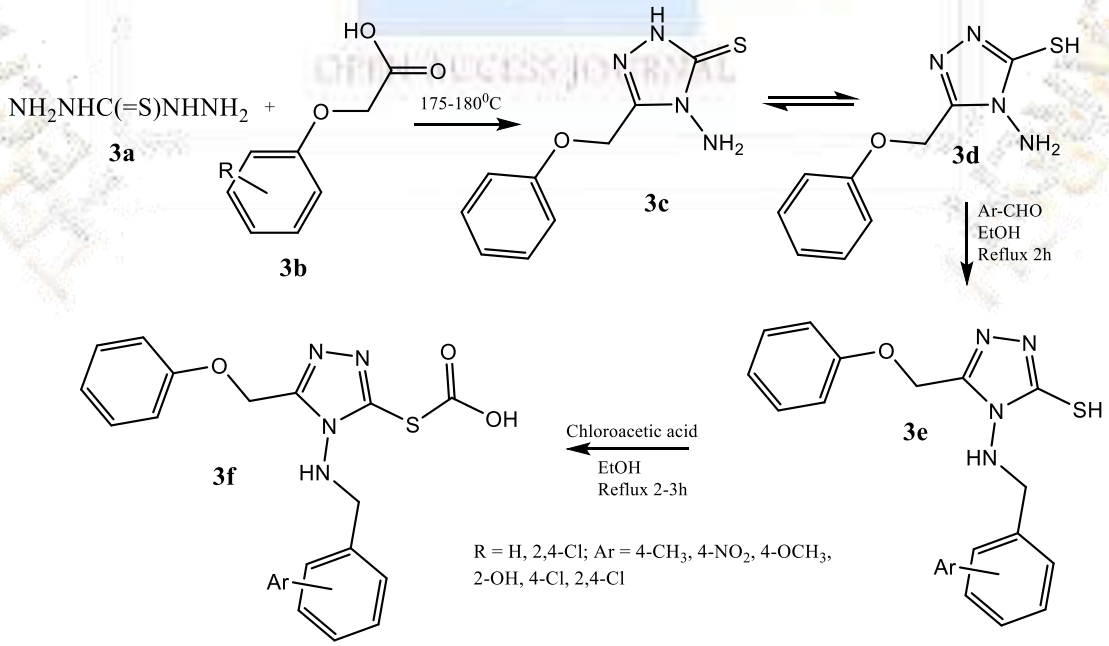


R = C_2H_5, C_4H_9,C_5H_{11},C_6H_{13},C_7H_{15}, C_9H_{19}

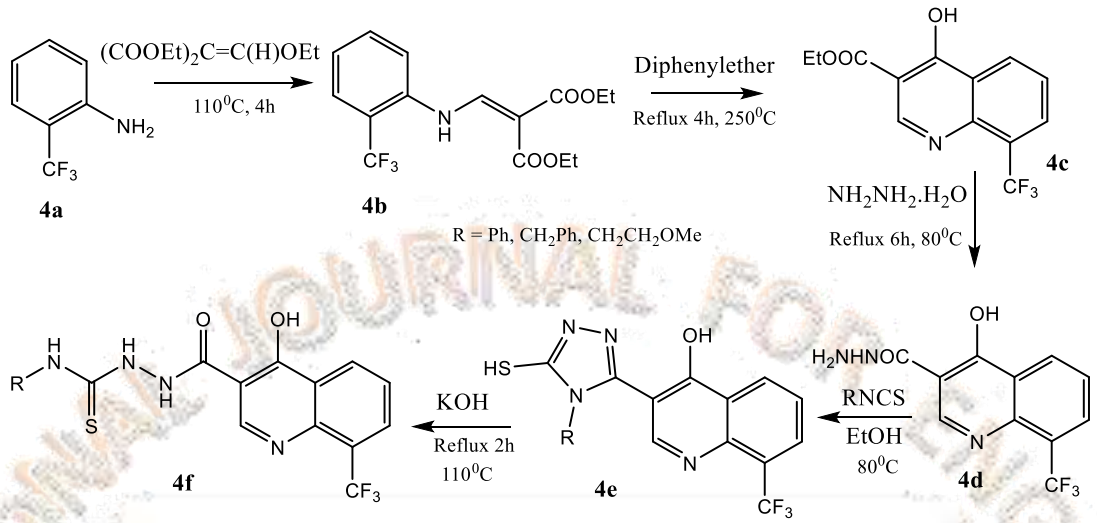
o-Phenylenediamine (5.0g, 11mmol) dissolved in hot water, acidified with conc. HCl, added glycine (3.45g, 8.0mmol) and refluxed for 50-55 min at ~70°C. The precipitate (a)obtained after neutralization with ammonia solution. A pyridine solution of (a)(4.5g, 10mmol) and iodine (2.62g, 7mmol) allowed to stir for 20 min and then treated with carbon disulfide (2.58mL, 5.5mmol)resulting (b)was obtained.Anaqueous solution of compound (b) (3.8g, 7.5 mmol) and Isoniazid (c) (1.6g, 7.0 mmol)) were refluxed in EtOH for 3.5h and cooled at 0-5°C to get compound (d). Compound(d) (2g, 12.5mmol) dissolved in 2M NaOH (30 mL) and refluxed, cooled and acidified with HCl gives4-((1*H-benzo*[d]imidazol-2-yl)methyl)-5-(pyridin-4-yl)-2H-1,2,4-triazole-3(4H)-thione(2)[29].



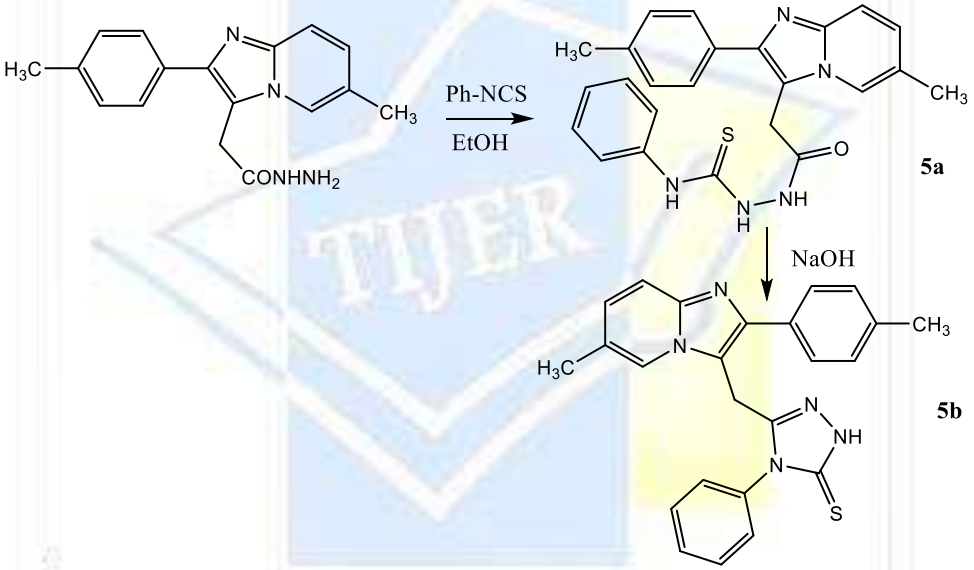
A mixture of thiocarbohydrazide (3a) (1.06g, 0.01mol) and substituted phenoxy acetic acid (3b) (0.01mol) heated in an oil bath at 175-180°C for 2h, the fused mass was triturated with hot water, filtered and washed with sodium bicarbonate to form compound (3d). A mixture of compound 3c (0.01mol) and aromatic aldehydes (0.01mol) in ethanol (25mL) treated with concentrated HCl (0.5mL) and refluxed for 2h, reaction mixture was cooled to room temperature to obtain compound (3e). Equi-molar proportions of (3e) and chloroacetic acid dissolved in ethanol containing 3-4 drops of pyridine and refluxed for 2-3h, on pouring the reaction mixture into cold water a solid 2-[4-(substitutedbenzylideneamino)-5-(substitutedphenoxymethyl)-4H-1,2,4-triazol-3-ylthio] acetic acid derivatives(3f) separated out[30].



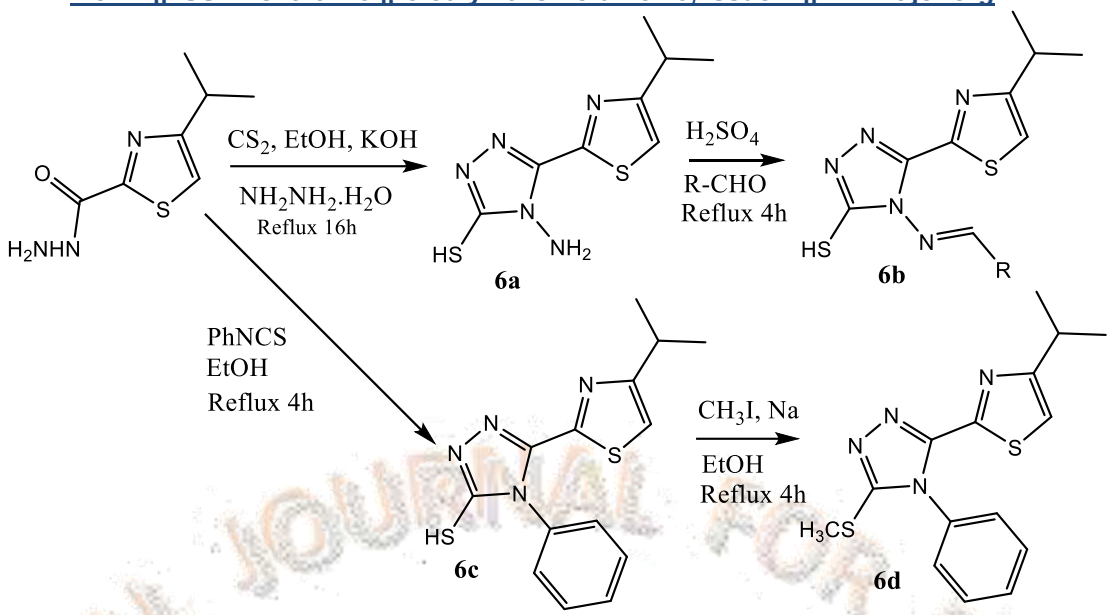
A solution of (4a)with diethyl ethoxymethylene malonate heated to110°C for 4h,cooled, the obtained solid was taken in ether and stirred for 15 min and filtered to get compound (4b). Compound (4b)againheated at 250°C for 4h, cooled and dissolved in hexane and stirred for 15 min, the solid precipitated as compound (4c). A mixture of (4c)and hydrazine hydrate in ethanol refluxed for 2.5h to form compound(4d). Analcoholic solution of (4d), isothiocyanate and a small amount of pyridine (0.2mmol) refluxed on oil bath for 3h. The solution was concentrated by evaporation and the solid thus obtained was filtered as compound (4e).The above compound was heated at 105°C for 2h with aqueous KOH, cooled, added water and aqueous layer was extracted with diethyl ether resulting good yield of (5-mercapto-4H-triazol-3-yl)-8-(trifluoromethyl)quinolin-4-ol(4f) obtained[31].



Acid hydrazide (0.01mol) and aryl isothiocyanates (0.01mol) taken in 15mL of ethanol and heated under reflux for 60 min to obtain 1-(2-(6-methyl-2-p-tolyl-1H-imidazo[1,2-a]pyridin-3-yl)-acetyl-4-phenylthiosemi- carbazides (5a). Compound (5a) (0.005mol) and 10mL of 2N NaOH solution was irradiated inside a microwave oven for 1-2.5 min at 300W power, with short interruption of 15s which yielded 5-((6-methyl-2-*p*-toly-l*H*-imidazo[1,2-a]pyridine-3-yl)methyl-4-phenyl-4H-1,2,4-triazole-3-thiols(5b)[32].

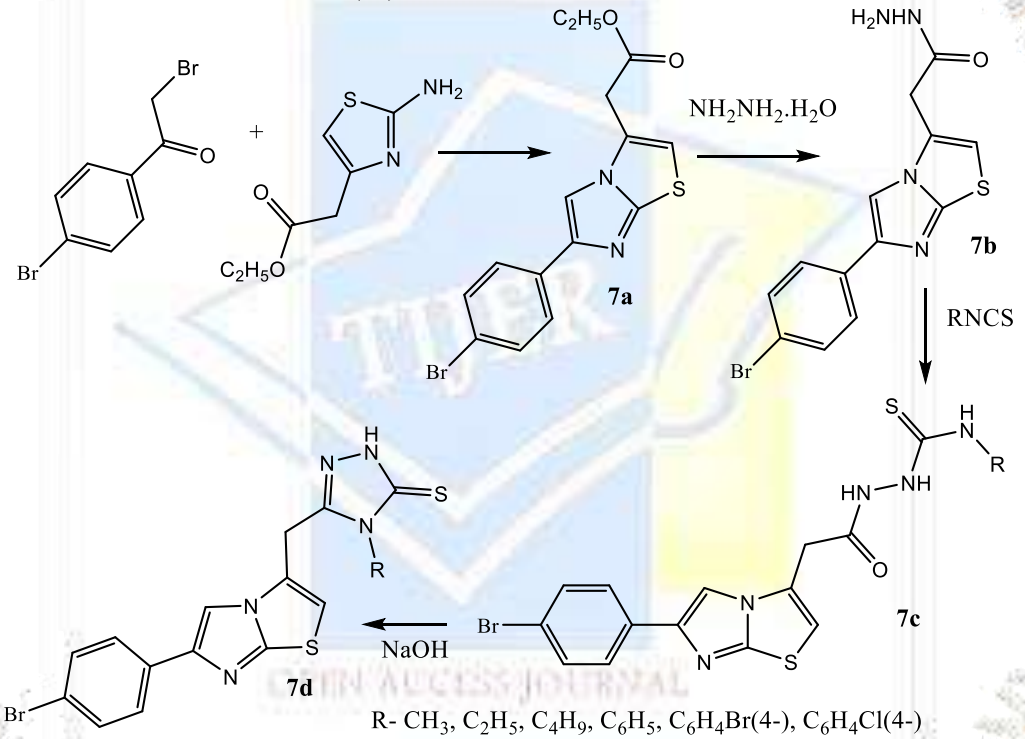


A mixture of compound (6a)(10mmol) which was formed by refluxing hydrazide derivative with carbondisulphide and hydrazine hydrate, substituted benzaldehydes (10mmol) and 4-5 drops of conc. H_2SO_4 in ethanol refluxed for 4h to get the precipitated solid (6b). A mixture of hydrazide (10mmol) and phenylisothiocyanate (15mmol) refluxed in ethanol for 4h to give a white solid which was dissolved in 2N NaOH and refluxed for 3h, then cooled and acidified to pH 3-4 with 37% HCl to give a white solid (6c)which (10mmol) dissolved in ethanol, 1eq of sodium added & stirred at RT for 30 min, then methyl iodide (20mmol) added and refluxed for 4h to get solid 3-(4-isopropylthiazol-2-yl)-5-methyl-4-phenyl4H-1,2,4-triazole (6d)[33].



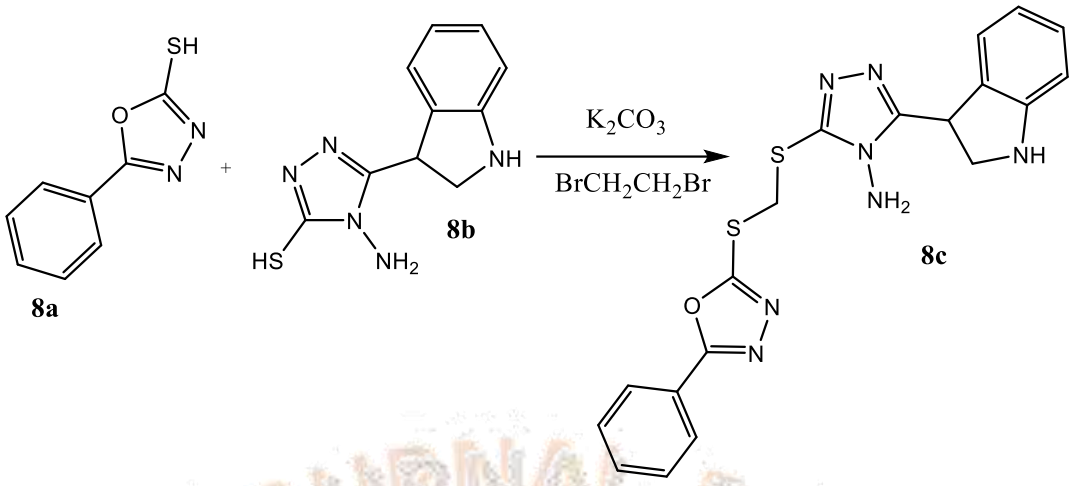
R = $C_6H_4Br(4-)$,$C_6H_4OH(2-)$,$C_6H_4Cl(2-)$, $C_6H_4OCH_3(4-)$, $C_6H_4(OCH_3)_2(2,4-)$

The key intermediate 6-(4-bromophenyl)imidazo[2,1-b]thiazole3-aceticacid hydrazide (7b) was prepared from compound (7a) and hydrazine hydrate. 4-alkyl/aryl-1-((6-(4-bromophenyl) imidazo[2,1-b]thiazol-3-yl)acetyl)-3-thiosemicarbazides(7c)were obtained by the reactions of alkyl/arylisothiocyanates with compound (7b). Alkaline cyclisation of the compound (7c)using sodium hydroxide afforded4-alkyl/aryl-2,4-dihydro-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-3H-1,2,4- triazole-3-thiones derivatives (7d)[34].

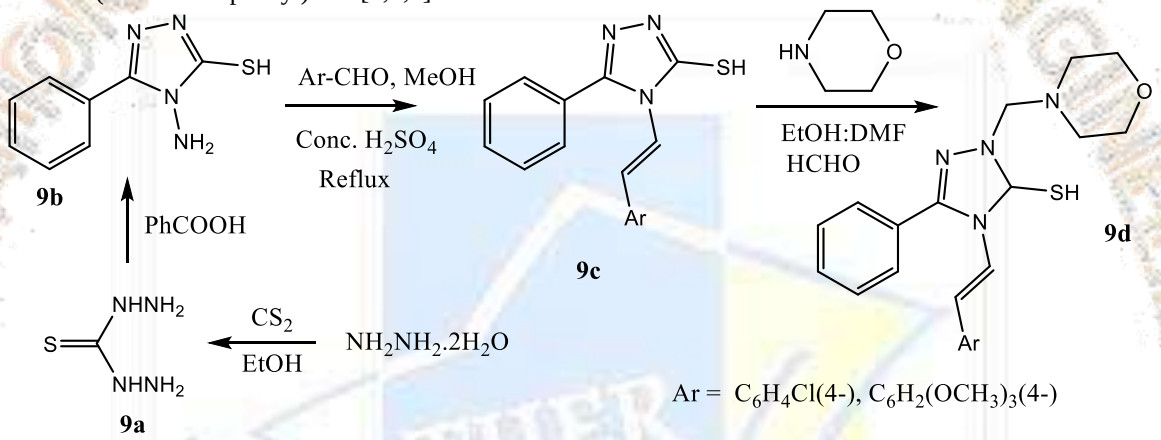


R- CH_3, C_2H_5, C_4H_9, C_6H_5, $C_6H_4Br(4-)$, $C_6H_4Cl(4-)$

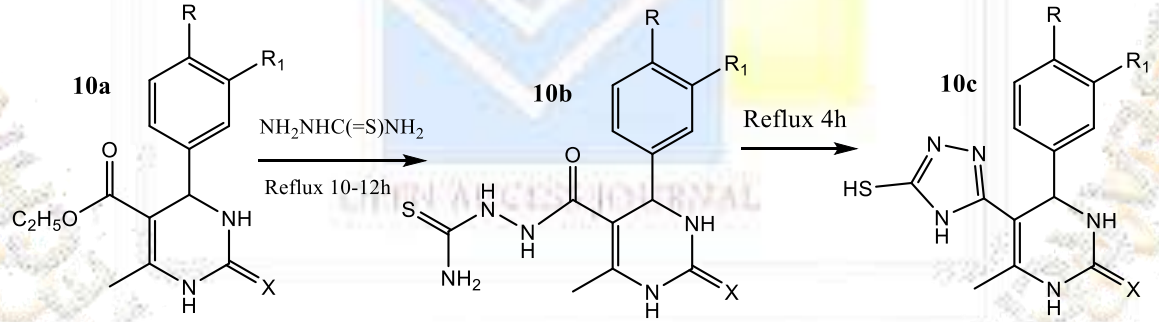
4-Amino-5-(1H-indol-3-yl)-4H-[1,2,4]triazole-3-thiol(8b) (0.1mmol), 1,2-dibromoethane (0.1mmol), the 2-mercapto-5-substituted-1,3,4-oxadiazoles (8a)(0.1mmol), K_2CO_3 (0.2 mmol), and acetonitrile (10mL) were mixed at 30°C for 15-35 min, washed with 5mL of acetonitrile and concentrated in vacuo to get the crude solid(8c)3-(1H-indol-3-yl)-5-[[2-[[5-(2-substitutedphenyl)-1,3,4-oxadiazol-2-yl]thio]ethyl]thio]-4H-1,2,4-triazol-4-amine[35].



Hydrazine hydrate and carbon disulfide was added drop-wise below 15°C and then raised gradually to 85°C for 1.5h, cooled at 10°C to get precipitates of thiocarbohydrazide (9a). A mixture of substituted benzoic acid (0.01mol) and compound (9a**)** (0.015mol) were taken & melted, the product 4-amino-5-(phenyl)-4H-[1,2,4]-triazole-3-thiol (9b) obtained. To a suspension of compound (9b)(0.2mol) in methanol, substituted benzaldehyde (0.2mol) with 3-4 drops of sulphuric acid added & refluxed for 2-3h at 80-90°C to get Schiff base (9c). The mixture of Schiff base (0.01mol) in a mixture of ethanol and DMF & formaldehyde (40%, 1.5mL) and primary/secondary amine (0.01mol) stirred for 2-3 hand kept overnight at RT for obtaining the Mannich bases(9d)4-amino-5-(substituted-phenyl)-4H-[1,2,4]triazole-3-thiol derivatives[36].

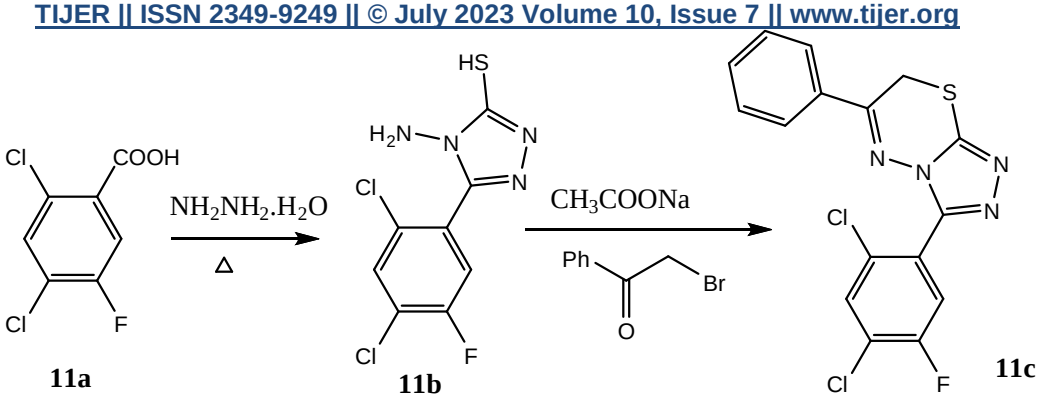


An equimolar mixture of compound (10a) (0.01mol) and thiosemicarbazide (0.01mol) in acetone was refluxed for 10-12h and allowed to cool and yellow solid of 5-(Carbothioamide)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one (10b) separated. Compound(10b) (0.01mol) was added into 8% NaOH & heated under reflux for 4h. The reaction mixture was cooled to RT and acidified with dilute acetic acid to obtain shiny crystals of 4-(substitutedphenyl)-3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methylpyrimidin-2(1H)-one(10c)[37].

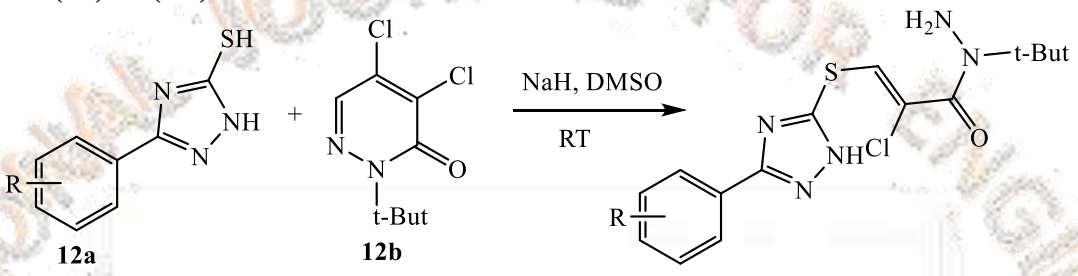


R- H, Cl, OH, $N(CH_3)_2$, R_1- H, NO_2

A mixture of 2,4-dichloro-5-fluorobenzoic acid(11a) (0.01mol) and thiocarbohydrazide (0.015mol) were melted and product 4-Amino3-(2,4-dichloro-5-fluorophenyl)-5-mercapto-1,2,4-triazole (11b) was obtained on cooling. A mixture of compound (11b) (10mmol) and phenacyl bromide (10mmol) in ethanol (25mL) refluxed on a water-bath for 6h to yield 3-(2,4-dichloro-5-fluorophenyl)-6-(phenyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines(11c)[38].

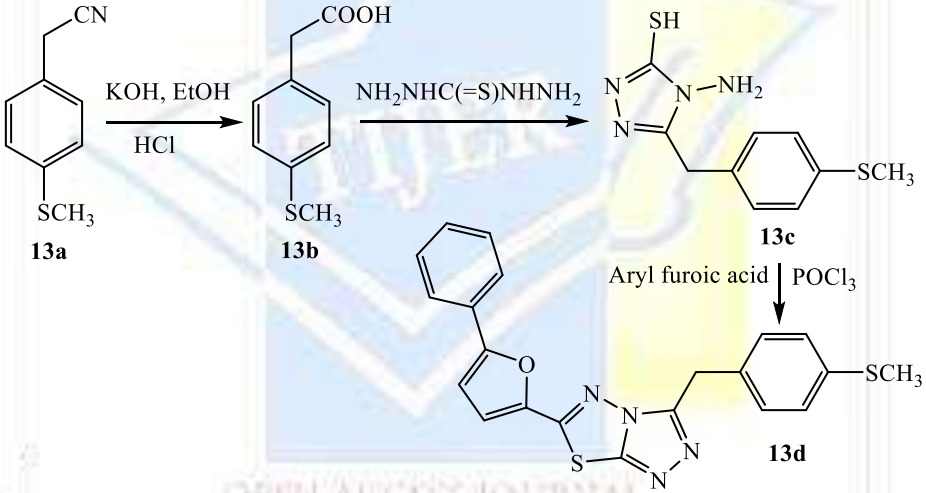


5-Phenyl-2H-1,2,4-triazole-3-thiol(12a) (2mmol) and NaH (2mmol) dissolved in DMSO (10mL) and stirred for 1h at RT. Then, 2-t-butyl-4,5-dichloro-pyridazinone(12b)(2mmol) was added into the mixture and continued stirring for about 10h & then poured into water (20mL), extracted by chloroform (30mL) to get 2-t-butyl-4-chloro-5[(3-(substituted phenyl)-1H1,2,4-triazol-5-yl)thio]pyridazin-3(2H)-one(12c)[39].

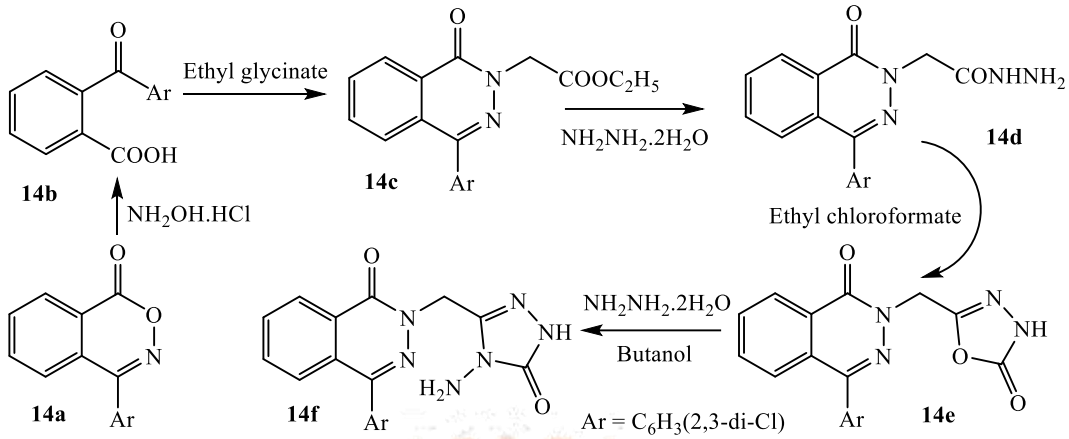


R = H, 4-NO_2, 2-OCH_3, 3-NO_2, 2-CH_3, 4-F

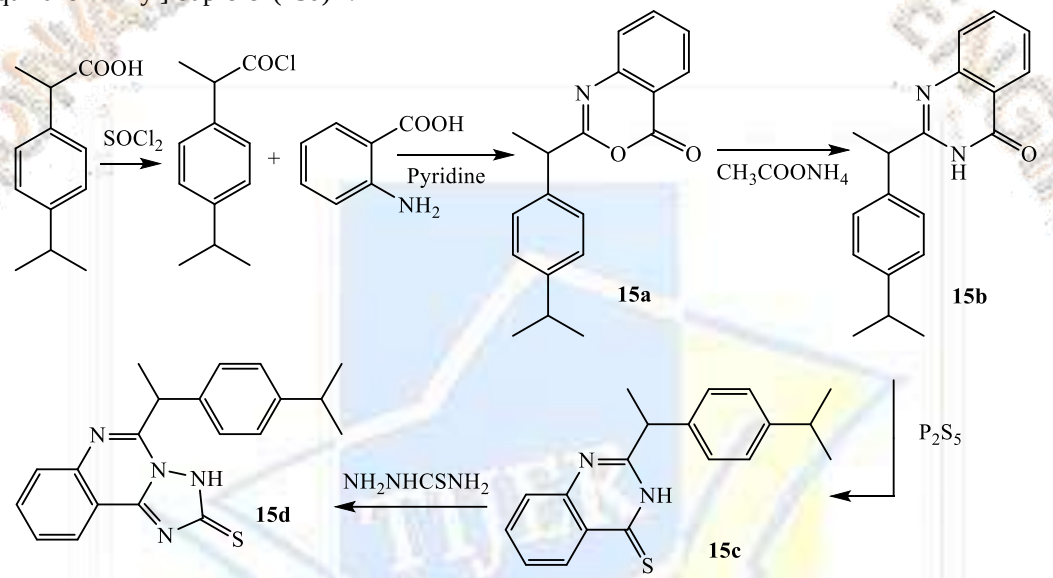
4-methylthiophenylacetonitrile(13a)and aq. solution of potassium hydroxide was refluxed for 8h, cooled at 20°C and acidified with dil. HCl to obtained 4-methylthiophenylacetic acid (13b).The obtained compound was heated on an oil bath with thiocarbohydrazide upto molten state and cooled the 4-amino-5-mercapto-3-[4-methylthio benzyl]-4H-1,2,4-triazole (13c)and treated with sodium bicarbonate. Further the mixture of triazole, substituted aryl furoic acids and phosphorus oxychloric acid heated for 8h to obtained as6-(4-arylfuryl)-3-[4-(methylthio)benzyl][1,2,4]triazolo[3,4b][1,3,4]thiadiazoles(13d)[40].



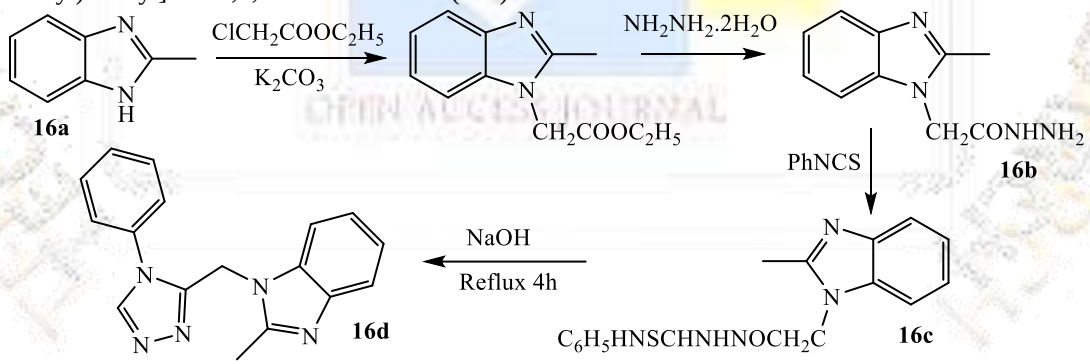
The compound (14b)was prepared by refluxing the mixture of *o*-aroyl benzoic acid in pyridine and hydroxylamine hydrochloride for 3h, cooled and then poured over ice-cold dil. HCl. To an alcoholic solution of compound (14a)(0.02mol) a mixture of ethyl glycinate and sodium acetate were refluxed for 2h and cooled to obtain compound(14c). To analcoholic solution of (14c)(0.02mol) hydrazine hydrate (0.02mol) refluxed for 5h as compound acetohydrazide (14d). A mixture of compound (14d) (0.02 mol) and ethyl chloroformate (0.02mol) in n-butanol (20mL) refluxed with stirring for 20h,then cooled to obtained 4-(2,3-Dichlorophenyl)-2-[5-oxo4,5-dihydro1,3,4-oxadiazol-2-yl)methyl] phthalazin-1-(2H)one (14e). A mixture of oxadiazole (14e) (0.02mol) and hydrazine hydrate (0.02mol) in n-butanol (20mL) refluxed with stirring for 15h resulting 2-(4-amino-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)4-(2,3dichlorophenyl)-phthalazin-1-(2H)-onewas obtained(14f)[41].



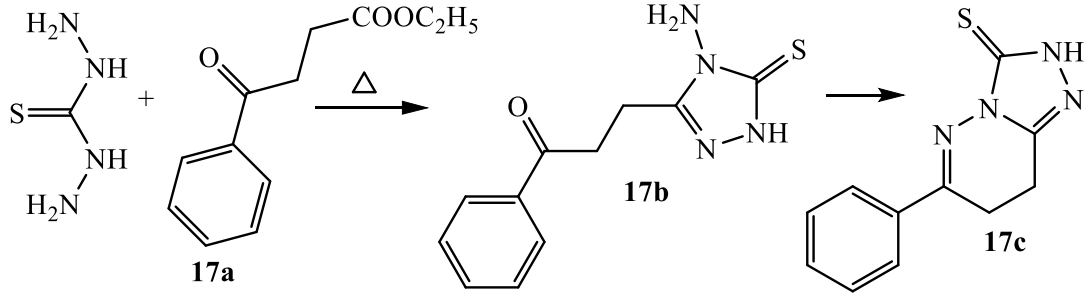
Acid chloride and substituted acid were refluxedin pyridine, cooled and poured into cold dil. HCl, the solidseparated asoxazine(15a). The mixture of oxazine and ammonium acetate fused in an oil-bath for 2h and poured in water andseparated as (15b) which was further refluxed with phosphorus pentasulfide (5mmol) in xylene for 1h, gave the product(15c). Thiosemicarbazide (5mmol) and phosphorus oxychloride (5mmol) warmed at 60˚C for 1h with obtained product and the temperature raised to 90˚C for additional 2h, cooled at 10˚C, pH adjusted to 8-10 with NaOH yields1-[4-(5-amino[1,3,4]-thiadiazol-2-yl)quinazolin-2-yl]ibuprofen(15d)[42].



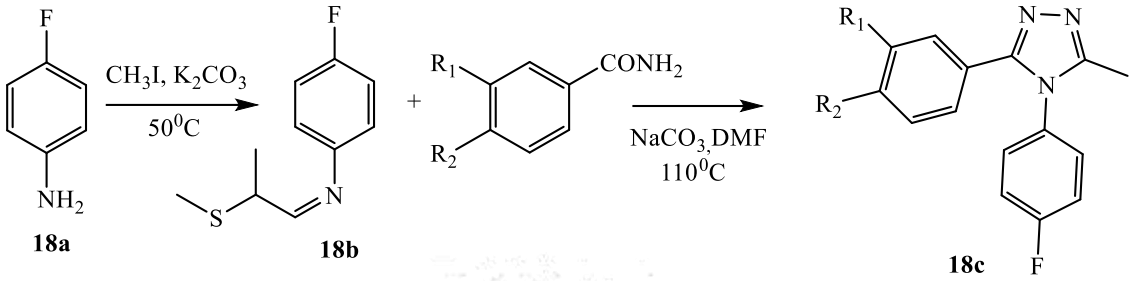
The intermediate acetohydrazide (16b) was prepared by the reaction of 2-methyl-1H-benzimidazole (16a) with ethylchloroacetate in the presence of anhydrous potassium carbonate as a base, followed by the reaction with hydrazine hydrate. To a boiling solution of compound (16b)(0.001mol) in ethanol (30mL), substituted phenyl isothiocyanate (0.001mol) added and refluxed for 1h, concentrated and cooled to separate solid (16c). A solution of compound (16c) (0.001mol) in 2M NaOH (20mL) refluxed for 4h, cooled, poured into ice cold water (50 mL) and neutralized with acetic acid, the precipitates 4-aryl-5-[(2-methyl-1H-benzimidazol-1-yl)methyl]-4H-1,2,4-triazole-3-thiols(16d)filtered[43].



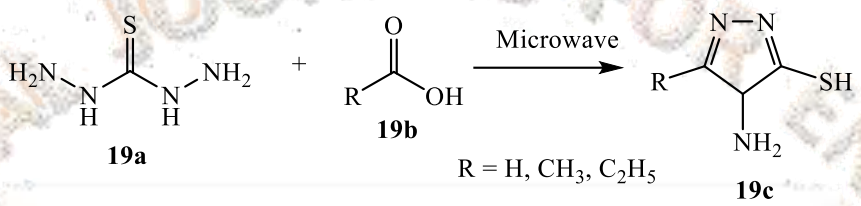
Equimolar amounts of thiocarbohydrazide and appropriate carboxylic acid (17a) mixed and heated at 165-170°C for 30 min. Boiling water (20mL) added to compound (17b) and the mixture kept at RT for 24h and the precipitates of 6-aryl-7,8-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-3-thiones(17c) filtered[44].



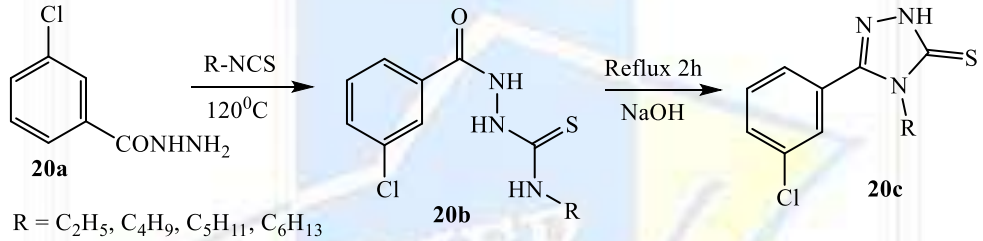
Potassium carbonate (18.5g) followed by methyl iodide (8.7mL) added to a solution of 4-fluoroaniline (8.3g) in acetonitrile (200mL) and stirred at 50°C for 2h to yield ester (18a). To the solution of this compound (6g) in DMF (100mL), 4-bromobenzoice acid hydrazide (18b) (4.2g) and sodium carbonate (100mg) added and refluxed at 110°C for 24h, cooled and extracted with ethyl acetate. The ethyl acetate layer washed with water, brine solution, the solvent removed to get 3-(3,4-substituted-phenyl)-4-(4-fluoro-phenyl)-5-methyl-4H-1,2,4-triazoles(18c)[45].



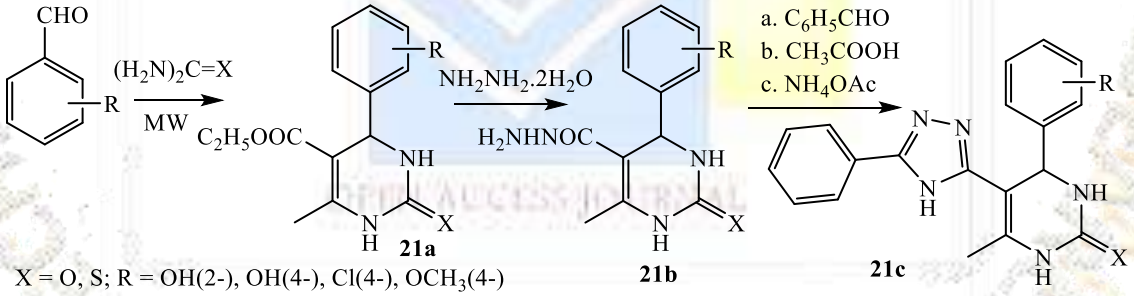
The reaction conducted by taking the reactants thiocarbohydrazide (19a)and aliphatic acid(19b) in the ratio of 1:1.5, irradiated in microwave at 400W for 4-8 min and the desired 4-amino-3-alkyl-5-mercapto-1,2,4-triazole derivatives(19c)obtained in good yield[46].



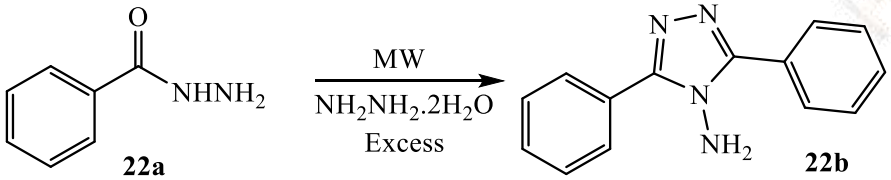
A mixture of 0.01mol (1.70g) of 3-chlorobenzhydrazide (20a) and equimolar amount of alkyl isothiocyanate heated in an oil-bath at 120°C for 1 min, cooled, the product precipitated as 4-alkyl-1-(3-chlorobenzoyl)thiosemicarbazide (20b) which was dissolved in 2% NaOH and refluxed for 2h,cooled, neutralized with 3M HCl and the precipitates of 4-alkyl-5-(3-chlorophenyl)-2,4-[dihydro-],2,4-triazole-3-thione derivatives(20c) formed[47].



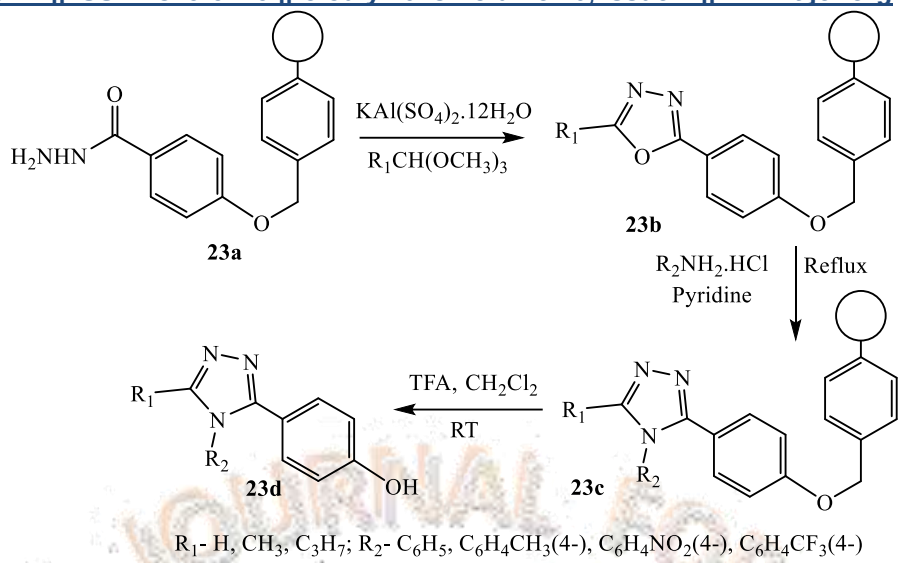
A substituted aldehyde (0.01mol), ethylacetoacetate (0.015mol), urea /thiourea (0.01mol) andconc.H_2SO_4 in EtOH were taken and zapped inside the oven for a period of 3-4 min at 160W, then the content was poured on ice to get compound (21a). The alcoholic solution of compound (21a) (0.01mol) and hydrazine hydrate zapped with liquid NH_3 solution, cooled and poured on ice to obtain carbohydrazide which dissolved in acetic acid, a pinch of ammonium acetate followed by the addition of different aromatic aldehydesand then mixture stirred for 24h, and neutralized to get 6-methyl-4-aryl-5-(5-phenyl-4H-1,2,4-triazole-3-yl)-3,4,dihydropyrim-idin-2(1H)-one/thione(21c)[48].



N[4]-amino-1,2,4-triazole(22b) was obtained directly in excellent yields from the reaction of substituted aryl hydrazides(22a) (0.010mol) with excess of hydrazine hydrate (0.08mol) in absence of organic solvents under microwave irradiation (800W, 250°C) for 4-12 minutes[49].

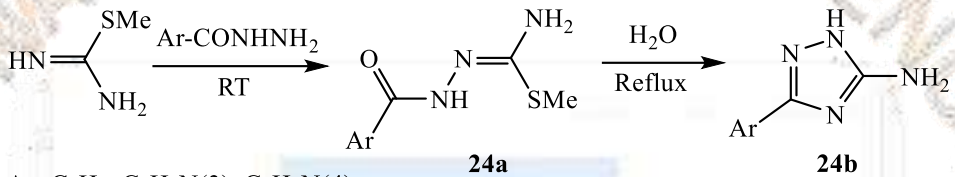


To the mixture of the acylhydrazide resin (23a)**(**0.5g, loading= 1.59 mmol/g, based on N microanalysis) in orthoester (5mL), and $KAl(SO_4)_2.12H_2O$ (0.38g, 0.8mmol) were added, then the mixture stirred and heated at 100°C for 10h. The resin filtered, washed with H_2O, EtOH and CH_2Cl_2 to remove contaminated species and then dried to afford the resin (23b). A mixture of resin 136, aniline hydrochloride (1.03g, 8mmol), and pyridine (5mL) refluxed for 12h, then filtered and washed with 10% HCl, H_2O, EtOH and CH_2Cl_2 and dried to afford the resin (23c). This resin was well swollen in 3 mL CH_2Cl_2, then 0.5mL TFA was added & the mixture was stirred at RT for 1h and then filtered. The resin washed completely with EtOH and acetone and the filtrate were combined to afford 3,4,5-trisubstituted-1,2,4-triazoles derivatives from the resin-bound acylhydrazines(23d)by evaporation[50].



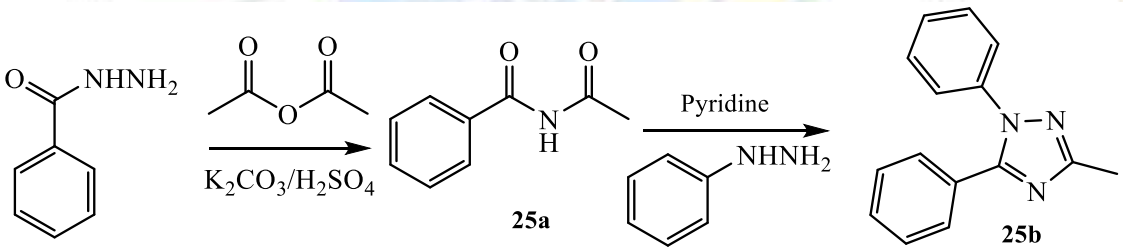
R_1- H, CH_3, C_3H_7; R_2- C_6H_5, $C_6H_4CH_3$(4-), $C_6H_4NO_2$(4-), $C_6H_4CF_3$(4-)

Aroylaminoguanidines(24a) were prepared from hydrazides of appropriate acid, methyl isothiourea sulfate and sodium hydroxide in water. Compound (24a) (0.02mol) refluxed in 15mL of water for 3-5h, cooled, the precipitated 5-amino-3-(het)aryl-1,2,4-triazoles(24b)filtered, washed with ice-cold water and dried[51].



Ar- C_6H_5, C_5H_4N(3), C_5H_4N(4)

Amide derivatives (1mmol), acid anhydrides (3mmol) and 2 drops of conc. H_2SO_4 placed in a 50mL RBF equipped with a reflux condenser. The reaction flask was microwave irradiated (50W, 100°C) for 3 min, then extracted with ethyl acetate (10mL), and the combined organic layer was washed with 5% aq. $NaHCO_3$ (10mL), and brine (20mL), dried over anhydrous $MgSO_4$, and evaporated to provide the crude material N-acylated amide(25a). The mixture of compound (25a)(1mmol), hydrazine hydrochloride (2mmol), and pyridine (1mL) microwave irradiated (300W, 200°C) for 1min with stirring then ethyl acetate (20mL) added to precipitate residual hydrazine hydrochloride, and then filtered as 3-methyl-1,5-diphenyl-1H-1,2,4-triazoles(25b)[52].



Biological activities of 1,2,4- triazole derivative:

1,2,4-Triazole attracts the attention of researchers due to its broad spectrum of biological activities such as:-

Tariq *et al.* reported a novel class of N-[3-(substituted-4H-1,2,4-triazol-4-yl)]benzo-(d)] thiazol-2-amine derivatives and evaluated for their in *vivo* anti-inflammatory[53] and Diuretic activity[54].Ju *et al.* reported a new class of 1,2,3-triazole oseltamivir analogues and screened their antiviral activity against three different strains (H5N1, H5N2, H5N6) in both enzymatic assay and cellular assay. Jordao *et al*. synthesized a novel series of N-amino-1,2,3-triazole compounds and screened their anti-viral activity against Cantagalo virus. Kucukguzel*et al*. investigated a new series of novel thiourea containing triazole derivatives and tested their anti-HIV activity[55].

Okazaki *et al.* afforded the synthesis of alkyl-substituted pyrazolo[1,5-b][1,2,4]triazole derivatives and screened for their angiotensin II receptor antagonistic activity. Some compounds inhibited the angiotensin II-induced pressor response in rats after oral administration in the in *vivo* tests. These compounds also produced a dose-dependent decrease in blood pressure when administered orally to conscious furosemide-treated dogs, having a longer duration of action as compared to DuP753 suggesting them to be useful agents for the treatment of angiotensin II-dependent disease, such as hypertensionactivity[56].

Khar*bet al.* investigated fifteen novel imidazolecontaining triazole derivatives and screened their anthelmintic activity towards Pheretimaposthuma as compared with the albendazole as positive control. Gupta *et al.* reported five derivatives and evaluated for their anthelmintic activity against P. posthuma. Satyendra *et al.* synthesized novel di-chloro substituted benzoxazole-triazolo-thione derivatives, and their anthelmintic activities were evaluated[57] and also reported bactericidal activities[58].Verma *et al.* reported a series of novel 4,5-disubstituted-2,4-dihydro-3H-1,2,4-triazole-3-thione derivatives for anticonvulsant activity. Anticonvulsant activity of compound wastes by maximal electroshock (MES), subcutaneous pentylenetetrazol (scPTZ) test in mice and rat and neurotoxicity screened at 30, 100, and 300 mg/kg dose and was suspended in 30% PEG 400 by an oral route to the mice. Wang *et al.* reported a novel series of triazolecontaining 7-phenyl-4,5,6,7-tetrahydrothieno[3,2-b]-pyridine derivatives and screened their anticonvulsant activity[59], herbicidal[60], insecticidal andacaricidal activities[61].

Collin *et al.*have reported the antifungal activity using following yeast strains*i.e.,* C. albicans, C. tropicalis and Saccharomyces cerevisiae. They also interpreted the overall electron density of aromatic and heterocyclic rings and found responsible for the antifungal activity[62].

Fabrice *et al.* synthesized a series of 1,2,4-triazole and reported their antifungal activity.The compound (2-(2,4-dichlorophenyl)-3-(1H-indol-1-yl)-1-(1,2,4-1H-triazol-1-yl)propan-2-ol exhibited the excellent activity against Candida, particularly against low fluconazole susceptible species. Result showed that this compound exhibited high activity as compared with fluconazole and similar to voriconazole against C. glabrata, C. krusei, and C. albicans. Wujec *et al.* synthesized the ten compounds which contain the manic base1,2,4-triazole. The broth microdilution technique was used against Gram-positive and Gram-negative bacteria to evaluate anti-microbial activity of these compounds and showed the potent activity with MIC value 30 µg/mL against M. luteus and 60 µg/mL against three different bacterial strains (B. subtilis, S. aureus, and S. epidermidis)[63].

Mahanti *et al.* reported a series of fused acridine containing 1,2,4-triazole derivatives and screened their anti-proliferative activity towards several human cell lines including, MCF7 (Breast), A549 (Lung), A375 (Melanoma), and HT-29 (Colon). The IC50 value of target compound in range between 0.11 ± 0.02 and 13.8 ± 0.99 µM as compared with the standard range 0.11 ± 0.02 to 0.93 ± 0.056 µM. Result revealed these compounds exhibited the excellent anticancer activity. SAR investigations of this series revealed that introduction of 4-chloro, 3,4,5-(CH3O)3, and 4- CF3CH3 groups at para-position of the phenylring displayed the significant anticancer activity. Al-Wahaibi*et al.* reported a novel series of 1,2, 4-Triazolyl coumarin derivatives and evaluated their anti-proliferative activity towards human colon cancer cell line (HCT116). Result showed that antiproliferative activity with IC50 values 4.363 µM. Ma *et al.*have also been reported a series of 1,2,3-triazolepyrimidine-urea derivatives and their antiproliferative activity[64].

Zhang *et al.*reported sprouting of wheat and radish seeds. They have treatedthe solutions of 100 µg/mL and 10 µg/mL of triazoles for 7 days, the germination percentages determined and plant growth regulating activities have also been calculated[65].Antileishmanial[66], antitumor[67]antidepressant and anxiolytic activities have also been reported[68].

Rossi Carla havereported 1,2,4-triazoles having antigestative immunosuppressant and antitumor activity[69]. Michael *et al.* have reported triazoles as potential antibacterial agents[70]. H. Mikali *et al.* have documented triazoles as antimicrobial agents[71]. Substituted 1,2,4-triazole have been reported for their pharmacological activity[72]by Bahittin Kahveci *et al.* and antifungal activity[73]. Liu. Chanjian*et al.* have investigated triazoles as IMPDH inhibitors[74].

A series of 4-amino-5-(substituted phenyl) [1,2,4]triazoles[75]were synthesized by Loredana Salerno *et al.* with the aim of to obtaining new selective 5-HT1A ligands. All New compounds were tested in radioligand binding experiments, from many of them showed a preferential affinity for the 5 - HT1A receptor.

Mari Makoto *et al.* have prepared water soluble triazoles as fungicides[76]. Laddawahetty*et al.*have synthesized triazole as selective human GABA receptor for the treatment of anxiety[77] and enhancing cognition. Eight novel compounds were synthesized and their insecticidal activities[78] were tested by Bing Chai and co-workers. The newly designed substituted triazole derivatives were synthesized by Maria Grazia Mamolo*et al.* and tested for their in vitro antifungal and anti-mycobacterial activity[79].

New1,2,4-triazole compounds containing a D, L-methionine moiety were synthesized by Otilia Pintilie *et al.* and exhibited promising antimicrobial activities[80]. A series of 4-amino-3-(2-furyl)-5-mercapto1,2,4-triazole were prepared by Jingde Wu and coworker. All the synthesized substituted triazole derivatives were reported as an anti-HIV-1 agents by examined their inhibition activity of HIV-1-induced cytopathogenicity in MT-4 cells and by determined their inhibitory effect on HIV-1 reverse transcriptase[81].

A variety of fluconazole derivatives were synthesized by Ruchita Ohlan and coworkers. The synthesized compounds were evaluated for their in vitro antifungal activity[82] against C.albicans and A. Niger. Jian-yuJin and coworkers have discovered new 1,2,4-triazole derivatives, which may possess significant biological activities, Plant growth-regulating activity tests of all compounds showed remarkable effects on the growth of radish and wheat[83].

John W. Hull Jr. *et al.* have investigated a new family of functionalized 2,6-dihaloaryl 1,2,4 triazole insecticides[84]. Ibtehal A. Al-Juwaiser*et al.* have synthesized anhydronucleosides of 1,2,4-triazole derivatives[85]**.**Mevlut Serdar and co-worker have synthesized a new series of triazoleand screened their antimicrobial and antifungal activities[86].Thirteen new triazoles containing 1,3-dioxolane rings were synthesized by Liang-Zhong Xu *et al.* and their results of preliminary biological tests show that all of these compounds possess some fungicidal and plant growth regulant activities[87].

Giorgia pastorin*et al.* have documented 1,2,4-triazoles as adenosine receptor antagonist and also as human A3 and A2B adenosine receptor[88].B.Shivarama Holla *et al.* have screened 1,2,4-triazoles for anticancer property[89]. Uesaka *et al.* documented triazoles as adrenergic a2C receptor antagonists[90].Aoki Satosh*et al.* have investigated triazoles as potent cyclooxygenase inhibitor[91].

In spite of all these activities, triazoles are also active as antihypertensive agentand neuroprotective agents. Triazole nucleus was found to possess significant atypical behaviour and good potency to block 5-HT receptors and good ability of selective antagonists towards the human vasopressin V1A receptor[92].

Conclusion:

This review article highlightedthe research works of many researchers on 1,2,4-triazoles and their derivatives. The chemistry of triazoles and their derivatives has gotten a lot of attention in recent years because of their synthetic and biological relevance.Triazoles have attracted considerable attention in the field of medicine due to their unique structures and properties. 1,2,4-triazoles has unique moiety or template that is responsible for various biological activities. More investigations must be carried out to investigatemany more activities for many diseases which treatment are dilemmas in the fields of medical sciences. The various synthetic methods discussed above are may helpful to developnewer compounds of triazoles.

Acknowledgement: The authoris thankful to Post Graduate College, Ghazipur, for the support of laboratory and others facilities required in review writing.

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