Review Article

A REVIEW ON METHODS OF SYNTHESIS OF 1,2,4-TRIAZOLE DERIVATIVES

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ABSTRACT

In the last few decades, heterocyclic compounds have been studied extensively owing to their interesting biological activities. One of them is triazole nucleus which exist in two isomeric forms: 1,2,3-triazole & 1,2,4-triazole. Out of which 1,2,4-triazole nucleus possess broad spectrum of pharmacological activities. This diversity in the pharmacological activity has attracted the attention of many researchers to explore the skeleton for its wide potential. This review summarizes the literature dealing with the conventional and green synthesis of 1,2,4-triazole nucleus.

Keywords: 1,2,4-triazole, Green Synthesis, Heterocyclic Chemistry, Microwave Synthesis, Ultrasound Synthesis.

INTRODUCTION

Heterocyclic chemistry

The history of hetero-cycles began its journey in the early nineteenth century when Luigi Brugnatelli first isolated the heterocyclic compound alloxan (2,4,5,6-pyrimidinetrone) in 1818¹. It is a very important branch of organic chemistry accounting for nearly one-third of modern publications. In fact two thirds of organic compounds are heterocyclic compounds. A cyclic organic compound having all carbon atoms in ring formation is referred to as carbocyclic compound. If at least one atom other than carbon forms a part of the ring system then it is designated as a heterocyclic compound. Nitrogen, Oxygen and Sulfur are the common heteroatoms but heterocyclic rings containing other hetero atoms are also widely known².

There is significant and continuous concern in the chemistry of five-membered N-heterocyclic compounds, mainly tetrazole, triazoles, and their substituted derivatives. Five-membered N-heterocyclic compounds are important structural fragments and considered as biologically active compounds. In 1885, Bladin was the first scientist who gave the name triazole to the carbon nitrogen ring system³.

Triazole

Triazole, also known as pyrroldiazole, is one of the classes of organic heterocyclic compounds containing a five membered di-unsaturated ring structure composed of three nitrogen atoms and two carbon atoms at non-adjacent positions. Two isomers of triazole are:

Tautomers of 1,2,4-triazoles

1,2,4-triazoles exists in two tautomeric forms. 1H and 4H-1,2,4-triazole is considered to be pharmacologically important nucleus⁴.

Methods of synthesis

Pellizzari Reaction

The synthesis of 1,2,4-triazole derivatives by the mixture of amide and acyl hydrazide is generally referred to as the Pellizzari Reaction. It has been reported that heating the mixture of formamide and hydrazine hydrochloride with KOH yield of 1,2,4-triazole. For example benzamide and benzoyl hydrazide gave 3,5-diphenyl-1,2,4-triazole^{5,6}.

Einhorn- Brunner Reaction

The synthesis of 1,2,4-triazoles by condensation between hydrazines or mono substituted hydrazine and diacylamines in the presence of weak acid is known as the Einhorn–Brunner reaction. For example: *N*-formyl benzamide and phenyl hydrazine gave 1,5-diphenyl-1,2,4-triazole ^{5,6}.

Pharmacological activities of 1,2,4- triazole derivatives

1,2,4-Triazole and its derivatives possess widely differing activities e.g. antibacterial⁷⁻¹⁴, antifungal ^{15,16}, anticancer¹⁷⁻²⁵, anti-tubercular²⁶⁻²⁸, anti-inflammatory^{29,30}, analgesic³¹, antiviral^{32,33}, anti-nociceptive³⁴⁻³⁶, anti-convulsant³⁷⁻⁴⁰, anti-corrosive⁴¹, anti-helminthic⁴², antioxidant⁴³⁻⁴⁷, urease & lipase inhibitors⁴⁸, hypoglycaemic⁴⁹, anti-migraine, anti-proliferative, sedative, diuretic, muscle relaxant and anti- HIV ⁵⁰.

Clinically used 1,2,4-triazole containing drugs

S. No.	Drug	Chemical Structure	Pharmacological activity
1.	Ribavirin		Antiviral
2.	Rizatriptan		Anti-migraine
3.	Estazolam		Anxiolytic

4.	Alprazolam		Anxiolytic
5.	Letrozole		Breast cancer
6.	Anastrozole		Breast cancer
7.	Itraconazole		Anti-fungal
8.	Fluconazole		Anti-fungal
9..	Vorozole		Aromatase inhibitor

10.	Posaconazole		Anti-fungal
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Synthesis of 1,2,4-triazole derivatives

Synthesis of 4-alkyl-5-(3-chlorophenyl)-1,2,4-triazole-3H-1,2,4-triazole-3-thione

A mixture of 3-chlorobenzhydrazide (0.01mol, 1.70g) and equimolar amount of the alkyl isothiocyanate heated in an oil bath

at 120°C for 1min to obtain 4-alkyl-1-(3-chlorobenzoyl)thiosemicarbazides (11) which was dissolved in 2% NaOH and the resulting solution was refluxed for 2h & after cooling neutralized with 3M HCl the precipitates of compound 12 formed⁵¹.

Synthesis of 4-((1H-benzo[d]imidazol-2-yl)methyl)-5-(pyridin-4-yl)-2H-1,2,4-triazole-3(4H)-thione

The compound 13 (5.0g, 11mmol) dissolved in 20mL water under heating, conc. HCl (20mL) added with glycine (3.45g, 8.0mmol) & then refluxed for 50–55 min at 70–73°C. Then, cooled & neutralized with ammonia solution to precipitate the product 15. A suspension of 15 (4.5g, 10.0mmol) dissolved in pyridine (2.69mL, 7.5mmol) and iodine (2.62g, 7.0mmol) at 0–5°C & allowed to stir for 20 min and then carbon disulfide (2.58mL, 5.5mmol) added at 0–5°C & stirred for 4h at 0–5°C and

excess CS₂ and pyridine removed by vacuum distillation to obtain crude product 16. A mixture of 16 (3.8g, 7.5 mmol) dissolved in water, Isoniazid 17 (1.6g, 7.0 mmol) added into it and refluxed with 40 mL ethanol for 3.5h & then cooled at 0–5°C and was distilled off to remove ethanol from it and extracted with ethyl acetate & distilled off to get compound 18. Compound 18 (2g, 12.5mmol) dissolved in 2M NaOH (30 mL) and refluxed at 75–78°C for 6.0h, cooled and acidified with HCl and extracted with ethyl acetate to get crude product 19⁵².

Synthesis of 2-[4-(substitutedbenzylideneamino)-5-(substitutedphenoxy)methyl]-4H-1,2,4-triazol-3-ylthio]acetic acid derivatives

An intimate mixture of thiocarbohydrazide 20 (1.06g, 0.01mol) and substituted phenoxy acetic acid 21 (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 23. A mixture of compound 22 (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 24. Equi-molar proportions of 24 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 25 separated out⁵³.

Synthesis of (5-mercapto-4H-triazol-3-yl)-8-(trifluoromethyl)quinolin-4-ol

A suspension of 26 (5g, 31mmol) and diethyl ethoxymethylene malonate 8g (37.2mmol) heated to 110 °C for 4h, then cooled to RT, the formed solid taken in pet ether and stirred for 15 min and filtered to get compound 27. Compound 27 (9g, 27mmol) heated at 250°C for 4h & cooled to RT and added hexane and stirred for 15 min, the solid thus precipitated as compound 28. A mixture of 28(10g, 35mmol) and hydrazine hydrate 60% (5.2g, 105mmol) in 50mL of ethanol refluxed for 2.5h to form hydrazide (29). A

suspension of 29 (1mmol), isothiocyanate (1.5mmol) and a catalytic amount of pyridine (0.2mmol) in ethanol (10mL) refluxed on oil bath for 3h, concentrated and the solid thus obtained was taken in minimum quantity of ethanol, stirred for 10 min and filtered as compound 30. A suspension of 30 (1mmol) in 50mL of aqueous KOH (4mmol) heated to 105°C for 2h, cooled to RT, added 10mL of water and aqueous layer was extracted with diethyl ether. Then the aqueous layer was cooled to 0°C, acidified to pH-4, the precipitates of 31 obtained⁵⁴.

Synthesis of 5-((6-methyl-2-p-tolyl-1H-imidazo[1,2-a]pyridine-3-yl)methyl-4-phenyl-4H-1,2,4-triazole-3-thiols

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-phenylthiosemicarbazides (34). Compound 34 (0.005mol) & 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 compound 35⁵⁵.

Synthesis of 3-(4-isopropylthiazol-2-yl)-5-methyl-4-phenyl-4H-1,2,4-triazole

A mixture of compound 37 (10mmol) which was formed by refluxing hydrazide derivative with carbon disulphide 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 38. 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 39 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 compound 40⁵⁶.

R- $\text{C}_6\text{H}_4\text{Br}(4-)$, $\text{C}_6\text{H}_4\text{OH}(2-)$, $\text{C}_6\text{H}_4\text{Cl}(2-)$, $\text{C}_6\text{H}_4\text{OCH}_3(4-)$, $\text{C}_6\text{H}_4(\text{OCH}_3)_2(2,4-)$, $\text{C}_6\text{H}_4(p\text{-N,N-diCH}_3)$ p-methylphenyl

Synthesis of 4-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

The key intermediate 6-(4-bromophenyl)imidazo[2,1-b]thiazole-3-aceticacid hydrazide (44) was prepared from compound 43 and

hydrazine hydrate. 4-alkyl/aryl-1-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)-3-thiosemicarbazides (45) were obtained by the reactions of alkyl/aryl isothiocyanates with compound 44. Alkaline cyclisation of the compound 45 using sodium hydroxide afforded 46⁵⁷.

R- CH₃, C₂H₅, C₄H₉, C₆H₅, C₆H₄Br(4-), C₆H₄Cl(4-)

Synthesis of 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

4-amino-5-(1H-indol-3-yl)-4H-[1,2,4]triazole-3-thiol 54 (0.1mmol), 1,2-dibromoethane 55 (0.1mmol), the 2-mercapto-5-

substituted-1,3,4-oxadiazoles 51 (0.1mmol), K₂CO₃ (0.2 mmol), and acetonitrile (10mL) were mixed & sonicated (25kHz, constant frequency) at 30°C for 15–35 min, washed with 5mL of acetonitrile and concentrated *in vacuo* to get the crude solid product 56⁵⁸.

Synthesis of some 4-amino-5-(substituted-phenyl)-4H-[1,2,4]triazole-3-thiol derivatives

Hydrazine hydrate (1.0mol) & 0.2mol of carbon disulfide (15.2g, 12.1mL) was added drop-wise while maintaining the temperature below 15°C and then raised gradually to 85°C for 1.5h, cooled to 10°C to get precipitates of thiocarbonylhydrazide (59). A mixture of substituted benzoic acid (0.01mol) and compound 59 (0.015mol) were taken & melted, the product 4-Amino-5-(substituted-

phenyl)-4H-[1,2,4]-triazole-3-thiol (60) obtained on cooling. To a suspension of compound 60 (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 (61). 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 62⁵⁹.

Synthesis of 4-(substitutedphenyl)-3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl pyrimidin-2(1H)-one

An equi-molar mixture of compound 63 (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 (64) separated. Compound 64 (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 compound 65⁶⁰.

Synthesis of 1-[(3H-indol-2-ylamino)methyl]-4-substitutedphenyl-4,5-dihydro-1H-1,2,4-triazole-3-thiol

1,3-benzothiazol-2-amine (2.0mol) in acetone and ethylchloroacetate (2.0mol) was added drop-wise in presence of potassium carbonate (8g) in the mixture with stirring & refluxed for 20h to yield acetate (67). A mixture of compound 67, hydrazine hydrate and ethanol placed in microwave oven and irradiated for 6 min to get compound 68. Salt form of compound

68 (1mol) prepared by refluxing it in the presence of alcohol and KOH for 1h on water bath & then solution of carbon disulphide in alcohol added drop wise & refluxed till evolution of hydrogen sulphide ceases to get 4-[(1,3-benzothiazol-2-ylamino)methyl]-4,5-dihydro-1,3,4-oxadiazole-2-thiol (69). The mixture of compound 69 & substituted aniline mixed in ethanol & refluxed for 8h to obtain compound 70⁶¹.

Synthesis of 3-(2,4-dichloro-5-fluorophenyl)-6-(substitutedphenyl)-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazines

A mixture of 2,4-dichloro-5-fluorobenzoic acid 71 (0.01mol) and thiocarbohydrazide (0.015mol) were melted & product 4-Amino-

3-(2,4-dichloro-5-fluorophenyl)-5 mercapto-1,2,4-triazole (73) was obtained on cooling. A mixture of compound 73 (10mmol) and substituted phenacyl bromide (10mmol) in ethanol (25mL) refluxed on a water-bath for 6h to yield compound 75⁶².

Synthesis of 2-*t*-Butyl-4-chloro-5[(3-(substituted phenyl)-1*H*-1,2,4-triazol-5-yl)thio]pyridazin-3(2*H*)-one
 5-phenyl-2*H*-1,2,4-triazole-3-thiol 79 (2mmol) and NaH (2mmol) dissolved in DMSO (10mL) & stirred for 1h at RT.

Then, 2-*t*-butyl-4,5-dichloro-pyridazinone (2mmol) was added into the mixture and continued stirring for about 10h & then poured into water (20mL), extracted by chloroform (30mL) to get compound 84⁶³.

Synthesis of 6-(4-arylfuryl)-3-[4-(methylthio)benzyl][1,2,4]triazolo[3,4*b*][1,3,4]thiadiazoles

A mixture of (4-methylthiophenyl)acetonitrile 85 (16.3g, 0.1mol) and a solution of potassium hydroxide (11.2g, 0.2mol) in water (25mL) refluxed for 8h, cooled to 20°C and acidified with dilute HCl to obtain (4-methylthiophenyl) acetic acid (86). An equimolar mixture of compound 86 and thiocarbonylhydrazide heated on

an oil bath till the contents melted & then cooled to form the product 4-amino-5-mercapto-3-[4-methylthio benzyl]-4*H*-1,2,4-triazole (87) & treated with dilute sodium bicarbonate. Further the mixture of triazole (0.01mol), substituted aryl furoic acids (0.01mol) and phosphorus oxychloric acid (10mL) heated for 8h to obtain the compound 88⁶⁴.

Synthesis of 2-(4-Amino-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4-(2,3-dichlorophenyl)-phthalazin-1-(2H)-one

The compound 90 prepared by refluxing the mixture of *o*-aroyl benzoic acid (0.02mol) in dry pyridine (20mL) and hydroxylamine hydrochloride (0.02mol) for 3h, cooled, then poured over ice-cold dil. HCl. To a solution of compound 89 (0.02mol) in absolute ethanol (20mL), a mixture of ethyl glycinate and sodium acetate (0.02mol) added, refluxed for 2h and cooled to obtain acetate (91). To a solution of the ester 91

(0.02mol) in absolute ethanol (20mL), hydrazine hydrate (0.02mol) added & refluxed for 5h & the product separated as acetohydrazide (92). A mixture of compound 92 (0.02 mol) and ethyl chloroformate (0.02mol) in *n*-butanol (20mL) refluxed with stirring for 20h, then cooled to form 4-(2,3-Dichlorophenyl)-2-[5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl] phthalazin-1-(2H)one (93). A mixture of oxadiazole 93 (0.02mol) and hydrazine hydrate (0.02mol) in *n*-butanol (20mL) refluxed with stirring for 15h, then cooled to separate the product 94⁶⁵.

Synthesis of 5-Methyl-4-(2-morpholine-4-yl-ethyl)-2-[(substitutedphenyl)sulfonyl]-2,4-di-hydro-3H-1,2,4-triazole-3-one

A mixture of compound 95 (10mmol) and 2-morpholinoethanamine (10mmol) heated at 110-120°C in an oil-bath for 2h & then *n*-butyl acetate-diethyl ether (1:2) added and kept overnight in cold conditions to yield compound 96. The Compound 96 (10mmol) & 1eq. of sodium in absolute ethanol refluxed for 2h, ethylbromoacetate (10mmol) added, refluxed for an 8h to obtain acetate (97). A solution of compound 97 (10mmol)

in ethanol refluxed in the presence of hydrazine hydrate (25mmol) for 5-8h & cooled to RT, acetone added, kept overnight in cold conditions to acetohydrazide (98). A solution of compound 97 (10mmol) in dichloromethane refluxed in the presence of metallic sodium (10mmol) until the metallic sodium disappeared completely (about 7-8 h) & then a suitable aryl sulfonylchloride added, followed by refluxing for an additional 8h, water added and the organic phase separated to compound 99 obtained⁶⁶.

Synthesis of 1-[4-(5-amino[1,3,4]thiadiazol-2-yl)quinazolin-2-yl]ibuprofen

A solution of acid chloride (5mmol) & substituted acid in dry pyridine (30mL), refluxed for 3h, cooled and poured into cold diluted HCl, the solid 103 separated. A mixture of oxazine 103 (6mmol) and ammonium acetate (6mmol) fused in an oil-bath for 2h, then poured into water & separated as compound 105. A mixture of compound 105 (5mmol) and phosphorus pentasulfide

(5mmol) in dry xylene (50mL) refluxed for 1h, the product 106 obtained. A mixture of compound 106 (5mmol) and thiosemicarbazide (5mmol) and phosphorus oxychloride (5mmol) warmed at 60°C for 1h and the temperature raised to 90°C for additional 2h, the contents poured onto crushed ice, cooled to 10°C, pH adjusted to 8 - 10 with NaOH and the resulting solid separated as compound 107⁶⁷.

Synthesis of 4-aryl-5-[(2-methyl-1H-benzimidazol-1-yl)methyl]-4H-1,2,4-triazole-3-thiols

The key intermediate acetohydrazide (110) was prepared by the reaction of 2-methyl-1H-benzimidazole (108) 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 110 (0.001mol) in

ethanol (30mL), substituted phenyl isothiocyanate (0.001mol) added and refluxed for 1h, concentrated and cooled to separate solid 111. A solution of compound 111 (0.001mol) in 2M NaOH (20mL) refluxed for 4h, cooled, poured into ice cold water (50 mL) and neutralized with acetic acid, the precipitates of compound 112 filtered⁶⁸.

Synthesis of 6-aryl-7,8-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-3-thiones

Equimolar amounts of thiocarbonylhydrazide 114 and appropriate carboxylic acid 113 (10mmol of each) mixed and heated at 165-

170°C for 30 min. Boiling water (20mL) added to the solid 115 and the mixture kept at RT for 24h & the precipitates of targeted compound 116 filtered⁶⁹.

Synthesis of 3-(3,4-substituted-phenyl)-4-(4-fluoro-phenyl)-5-methyl-4H-1,2,4-triazoles

Potassium carbonate (18.5g) followed by methyl iodide (8.7mL) added to a solution of 4-fluoroaniline (8.3g) in acetonitrile (200mL) & stirred at 50°C for 2h to yield ester (118). To this

solution of compound 118 (6g) in DMF (100mL), 4-bromobenzoic acid hydrazide 119 (4.2g) and sodium carbonate (100mg) added & refluxed at 110°C for 24h, cooled & extracted with ethyl acetate. The ethyl acetate layer washed with water, brine solution, the solvent removed to get crude product 120⁷⁰.

Synthesis of 4-amino-3-alkyl-5-mercapto-1,2,4-triazole Derivatives

The reaction conducted by taking the reactants thiocarbohydrazide 121 & aliphatic acid in the ratio of 1:1.5,

irradiated in microwave at 400W for 4-8 min & the desired triazole derivatives 123 generated in good yield ⁷¹.

R- H, CH₃, C₂H₅

Synthesis of 4-alkyl-5-(3-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione derivatives

A mixture of 0.01mol (1.70g) of 3-chlorobenzhydrazide 124 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 125 which was dissolved in 2% NaOH and refluxed for 2h, cooled, neutralized with 3M HCl & the precipitates of targeted compound 126 formed ⁷².

R- C₂H₅, C₄H, C₅H₁₁, C₆H₁₃

Synthesis of 6-methyl-4-aryl-5-(5-phenyl-4H-1,2,4-triazole-3-yl)-3,4-dihydropyrimidin-2(1H)-one/thione

A mixture of substituted aldehyde 127 (0.01mol), ethylacetoacetate (0.015mol), urea /Thiourea (0.01mol) & concentrated sulphuric acid (1-5 drops) in ethanol (10mL) taken & zapped inside the microwave oven for a period of 3-4 min at 160W, then allowed to stand at RT and poured on ice to get

compound 129. The mixture of compound 129 (0.01mol) in ethanol & hydrazine hydrate (0.99%, 0.015mol) zapped with liquid NH₃ solution and then cooled & poured on ice to obtain carbohydrazide (130) which (0.003mol) dissolved in acetic acid (10mL), a pinch of Ammonium acetate followed by the addition of different aromatic aldehyde (0.003mol) & then mixture stirred for 24h at RT, then neutralized to get the compound 131 ⁷³.

X- O, S; R- OH(2-), OH(4-), Cl(4-), OCH₃(4-)

Synthesis of N⁴-amino-1,2,4-triazoles

N⁴-amino 1,2,4-triazoles (133) were obtained directly in excellent yields from the reaction of substituted aryl hydrazides 132

(0.010mol) with excess of hydrazine hydrate (0.08mol) in absence of organic solvents under microwave irradiation (800W, 250°C) for 4-12 minutes ⁷⁴.

Solid phase synthesis of 3,4,5-trisubstituted-1,2,4-triazoles derivatives from the resin-bound acylhydrazines

To the mixture of the acylhydrazide resin 134 (0.5g, loading= 1.59 mmol/g, based on N microanalysis) in orthoester (5mL), alum $KAl(SO_4)_2 \cdot 12H_2O$ (0.38g, 0.8mmol) was 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 136. 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 137. The resin 137 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 was combined to afford the crude product 138 by evaporation⁷⁵.

Synthesis of 5-(4-(substituted benzylideneamino)-5-(phenylamino)-4H-1,2,4-triazol-3-yl)benzene-1,2,3-triol

Propyl Gallate 139 (0.01moles) and hydrazine hydrate (0.01moles) refluxed for 6h and then cooled & poured into ice cold water to obtain 3,4,5-trihydroxybenzohydrazide 140 (Galloyl hydrazide). A mixture of compound 140 (0.01mol) and phenyl isothiocyanate (0.001mol) in ethanol (25ml) refluxed on a

water-bath for 2h, the solvent was concentrated and the precipitated product 141 was filtered. Compound 141 (0.002mol) and hydrazine hydrate (0.025mol) refluxed in methanol for 2h at a temperature between 50-60°C, cooled and poured over crushed ice which yield compound 142. To a solution of compound 142 (0.01mol) in absolute ethanol (30mL), the aromatic aldehydes (0.012mol) added & refluxed for 4h to yield compound 143⁷⁶.

Synthesis of 5-amino-3-(het)aryl-1,2,4-triazoles

(Het)aroylaminoguanidines 145 were prepared from hydrazides of appropriate acid, methyl isothiourea sulfate and sodium

hydroxide in water. Compound 145 (0.02mole) heated under reflux in 15mL of water for 3-5h, cooled, the precipitated triazoles 146 filtered, washed with ice-cold water and dried⁷⁷.

Synthesis of 3-methyl-1,5-diphenyl-1H-1,2,4-triazoles

Amide derivatives (1.0mmol), acid anhydrides (3.0mmol) 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 (2-10mL), and the combined organic layer was washed with 5% aq. NaHCO_3 (2-10mL), and brine (20mL), dried over anhydrous

MgSO_4 , and evaporated to provide the crude material *N*-acylated amide 149. The mixture of compound 149 (1.0mmol), hydrazine hydrochloride (2.0mmol), 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. The solvent was evaporated to the crude product 150⁷⁸.

Synthesis of 6-substitutedthiazolo[3,2-b]-1,2,4-triazole-5(6H)-ones

The equi-molar amounts of compound 155), aldehyde, chloroacetic acid and sodium acetate added to 6mL of acetic acid and 8mL of acetic anhydride. After completion of the reaction,

poured on ice, and precipitates filtered and dissolved in dichloromethane and washed with a sodium bicarbonate and saturated sodium chloride solution. The organic layer evaporated to dryness and the crude product 156 obtained⁷⁹.

Ar- naphthyl, biphenyl

Synthesis of 4-amino-3,5-dialkyl-1,2,4-triazoles

To the solution of corresponding imino ester hydrochloride in absolute ethanol (10mmol) was added the solution of corresponding acyl hydrazine (10mmol) in absolute ethanol and the mixture was stirred at $0-5^\circ\text{C}$ for 6h. Then, the precipitated ammonium chloride was filtered off. After evaporating the

solvent at $35-40^\circ\text{C}$, a white solid of ethyl carboxylate acyl hydrazones (158) and the part that did not dissolve in petroleum ether was recrystallized from ethanol; thus, 2,5-dialkyl 1,3,4-oxadiazole (159) obtained. The corresponding compound 158 (10mmol) refluxed with hydrazine hydrate (25mmol) in propanol for 24h & then, cooled to RT to obtain the compound 160⁸⁰.

R- $\text{C}_6\text{H}_4\text{CH}_3$ (4-), CH_3 ; R¹- $\text{C}_5\text{H}_4\text{N}$, $\text{C}_6\text{H}_4\text{OH}$ (4-), $\text{C}_6\text{H}_4\text{Cl}$ (4-), CH_3

Synthesis of 1,2-Bis[o-(N-methylidenamino-3,5-substitutedphenyl-4H-1,2,4-triazole-4-yl)-phen oxy]alkane

Salicylaldehyde (0.01mol) dissolved in hot ethanolic KOH and the solvent removed *in vacuo*. The residue dissolved in DMF (25mL) and dihalide (0.005mol) added & refluxed for 5 min, during which KCl separated out. The solvent then removed *in vacuo* and the remaining material was bis aldehydes (165). A solution of hydrazide (0.01mol) in ethanol (25mL) added to a solution of iminoester hydrochloride (0.01mol) in ethanol (25mL)

& stirred for 6h at $0-5^\circ\text{C}$ and subsequently for 2h at RT. The reaction mixture then poured into a beaker containing cold water (40mL) and ice (10g) & precipitates of hydrazones formed. Compound 161 (0.005mol) added to a solution of hydrazine hydrate (0.01mol) and 1-propanol (50mL) and refluxed for 24h, cooled to precipitates of compound 162. The compound 165 (0.01mol) added to a solution of compound 162(0.005mol) in glacial acetic acid (20mL) and refluxed for 16h, then cooled to get compound 166⁸¹.

Synthesis of 1-piperidinomethyl-3-[3-(o-fluorobenzyl)-5-oxo-4,5-dihydro-1,2,4-triazol-1-yl]-iminoisatin

The ethyl imidate hydrochlorides 168 (0.01mol) dissolved in absolute ethanol (50mL) with ice-bath cooling and ethyl carbazate (0.01mol) dissolved in ethanol (50mL) was then added, stirred for 6h at 0-5°C, the precipitate filtered to remove the ammonium chloride & the filtrate evaporated at 30-35°C to yield compounds ethoxycarbonyl hydrazones 169. Compound 169 (0.01mol) added to a solution of hydrazine hydrate (0.01mol) in water (50mL) and refluxed for 5h, cooled to precipitate of 3-

substituted benzyl-4-Amino-4,5-dihydro-1H-1,2,4-triazole-5-one (170). Equi-molar quantities (0.01mol) of isatin or 5-chloroisatin and compound 170 dissolved in warm ethanol (50mL) containing glacial acetic acid (0.5mL) & refluxed for 4h and then kept at RT overnight to get solid iminoisatin (171). The compound 171 (0.002mol) dissolved in absolute ethanol (100mL), then formaldehyde (37%, 0.5mL) and piperidine (0.002mol) added drop-wise with vigorous stirring & then stirred at RT for 12h to get the solid product 172⁸².

Synthesis of 2-[4-(substituted benzylideneamino)-5-(substitutedphenoxy)methyl]-4H-1,2,4-triazol-3-yl-thio]acetic acid derivatives

An intimate mixture of thiocarbohydrazide 173 (1.06g, 0.01mol) and substituted phenoxy acetic acid (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 175. A mixture of compound 175 (0.01mol) and the corresponding various aromatic aldehydes (0.01mol) in ethanol (25mL) was treated with concentrated HCl (0.5mL) and refluxed for 2h & cooled to RT to obtain compound 176. Equimolar proportions of compound 176 and chloroacetic acid were dissolved in ethanol containing 3-4 drops of pyridine and refluxed for 2-3h, cold to get solid of compound 177⁸³.

Synthesis of {4-[(9H-fluoren-3-yl)methylidene]amino}-3-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}acetic acid

Compounds 179 (0.01mol) and 9H-fluorene-2-carbaldehyde (0.01mol) in dry ethanol (10mL) irradiated in a microwave oven at 125°C for 10 min, then cooled to RT to get substituted 1,2,4-triazol-3-one (180). Dry K₂CO₃ (0.025mol) added to a solution of compound 180 (0.01mol) in acetone (10mL) & irradiated in a microwave oven at 90°C for 5 min. Then, cooled to RT and ethyl

bromoacetate (0.012mol) added. Again, irradiated in microwave at 90°C for 10 min at 300W & cooled to RT, transferred to a beaker and the product 181 precipitated by addition of water. The mixture of compound 181 (0.01mol) and NaOH (0.1mol) in ethanol taken and exposed to microwave irradiation at 110°C for 15 min. & then cooled to RT, poured into cold water and acidified to pH 5 with conc. HCl to get the compound 182⁸⁴.

Synthesis of 2-(5-amino-2-oxo-1,2-dihydrospiro(indole-3,3-(1,2,4)triazol)-4(2H)-yl)substituted aliphatic acid.

An equi-molar mixture of substituted aromatic aldehyde (0.01mol), 4-chloro-2-nitro aniline (0.01mol), and methylphenyl thiosemicarbazide in water (15mL containing 1-2mL of ethanol) in the presence of lemon juice (2 mL) mixed in RBF and refluxed to form 3,4,5- trisubstituted triazole 185. An equimolar mixture

of substituted 1H-indole-2,3-dione 187 (0.012mol), substituted amino acids 186 (0.012mol) and thiosemi-carbazide in water (15mL containing 1-2mL of ethanol) mixed in RBF and refluxed. The initial syrupy reaction mixture solidifies within 2-3 h. After completion, cooled to RT and the solid mass of compound 188 was obtained⁸⁵.

Synthesis of 3-(substitutedthio)-5-((4-chlorophenoxy)methyl)-4-phenyl-4H-1,2,4-triazole

4-Chlorophenol (0.1mol), acetone(40mL), ethyl-2-chloroacetate (0.12mol), K_2CO_3 (16.56g, 0.12mol) and catalytic amount of KI added to a 100mL three-necked flask, then refluxed to form compound 190. A mixture of compound 190 (1.4 g, 10mmol) and 85% hydrazine hydrate (2mL, 35mmol) refluxed for 6h, then cooled to RT to give acetohydrazide (191). A mixture of compound 191 (10mmol) with isothiocyanato benzene (10mmol) refluxed for 5h in ethanol, cooled to RT, the product

carbothioamide (192) obtained. A mixture of compound 192 (10mmol) in NaOH solution (5mL, 2N) refluxed for 4h & cooled to RT, HCl (4N) added to afford precipitate of compound 193. A CEM designed 10mL pressure rated vial charged with DMF (5 mL), 193(1mmol), RCH_2Cl (1.1mmol) and NaOH (1.2mmol) & irradiated in a CEM Discover Focused Synthesizer (150W, 90°C, 200psi, 15min) & cooled to RT by passing compressed air through the microwave cavity for 2 min & then poured into ice (40mL) and precipitates of compound 194 filtered with thioether ^{86,87}.

Synthesis of 5-benzyl-N-(heterocyclicnucleus-2-yl)methyl)-1-(pyridin-3-yl)-1H-1,2,4-triazole-3-carboxamide

3-aminopyridine (25g, 0.265mol) dissolved in 250mL of 6N HCl (250mL), sodium nitrite (18.2g, 0.265mol) in water (50mL) added drop-wise to it and stirred for 30 min. Later, ethyl-2-chloroacetate (43g, 0.265mol) in ethanol (100mL) added drop-wise for 1h at 0°C. After 30 min, sodium acetate (65g, 0.795mol) in water (200mL) added dropwise and stirred for 12h & the precipitated solid compound (196) obtained. Ammonia gas bubbled through it (10g, 0.044mol) at -30°C for 30 min and stirred at RT for 2h. The solvent removed under vacuum; the

residue dissolved in 50mL of dry chloroform and filtered to remove NH_4Cl . The filtrate evaporated and triturated with diethylether (25mL) to afford acetate (197). Phenylacetyl chloride (4.4g, 0.0288mol) added drop wise to a stirred solution of 197 (5g, 0.024mol) in toluene (25 mL) at 0°C & warmed to RT and refluxed for 12h, solvent evaporated, the residue dissolved in CH_2Cl_2 (120mL) and washed with 1N HCl, 10 % $NaHCO_3$ and brine to give the desired product 198. To a solution of the amine (1.1eq) in dry toluene (5mL) added 198 (1eq) followed by heating to 130°C under microwave conditions for 30 min to form 1,2,4-triazole-3-carboxamides 199 ⁸⁸.

One-pot synthesis of 3,4,5-trisubstituted-1,2,4-triazoles via the addition of hydrazides to activated secondary amides

A general approach has been developed for the one-pot synthesis of 3,4,5-trisubstituted 1,2,4-triazoles from secondary amides and hydrazides via triflic anhydride activation followed by

microwave-induced cyclodehydration. Compound 200 (1.0mmol), solvent (0.3M), 2-fluoropyridine as base (1.1eq), Tf_2O (1.1eq) at 0°C for 10 min, then 201 (1.1eq) and cyclodehydration performed at 140°C for 2h ⁸⁹.

Synthesis of 3,5-disubstituted 4-amino-1,2,4-triazoles

Recently, a one-step synthesis of compound 205 by direct reaction of hydrazine derivatives on nitriles bearing a variety of substituted aromatic rings or heteroaromatic has been reported. The initial product, in each synthesis of amino triazoles, is the orange-coloured, dihydro-1,2,4,5-tetrazine (204) which

rearranges on treatment under acidic conditions into the compound 205 refluxing at 130°C for 45 min to an hour or by irradiating in MW for 5-10 min. Addition of hydrazine dihydrochloride or sulfate was used to generate protons promoted the rearrangement of 204 into the compound 205⁹⁰.

Synthesis of optically pure 3,4,5-trisubstituted 1,2,4-triazoles using silver benzoate

Up to 18mmol of thioamide 206 treated with 1.2 equivalents of hydrazides 207 dissolved in AcOH & stirred for 6h at RT in presence of silver benzoate (2eq) to get the compound 208⁹¹.

Rapid synthesis of 1,3,5-substituted 1,2,4-triazoles from carboxylic acids, amidines, and hydrazines

Substituted benzoic acid (1.0eq) and benzamidine (1.5eq) reacted for the formation of the acylamidine 211 through a screen of standard peptide coupling reagents HATU (2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl uranium hexafluorophosphate) was selected for further evaluation based

on availability and ease of removal of coupling byproducts using diisopropylethylamine (DIPEA, 3-4eq) as a base and DMF as the reaction solvent. After addition of isopropylhydrazine 214 (1.5equiv) and acetic acid (10 equiv) to the crude solution of compound 213, cyclization completed after 3h at 80°C to give triazole 215⁹².

Synthesis of 1,3-diphenyl-5-(substitutedphenyl/ alkyl)-1H-1,2,4-triazole

Bisarylhydrazone 216 (0.3mmol) and 4-methylbenzylamine 217 (0.9mmol) in the presence of 20mol% I₂ and TBHP(0.9mmol) in CH₃CN (1mL) refluxed under air at 90°C for 4h to get the desired cyclized product 218⁹³.

An aqueous medium synthesis of 3(5)-amino-5(3)-het(aryl)-1,2,4-triazoles

(Het)arylamidoguanidines 219 (1mmol) irradiated in 3mL of water using a CEM 'Discover' microwave apparatus at 100W for 150s. After cooling, the precipitated product 220 filtered, washed with ice-cold water and dried⁹⁴.

Synthesis of 4,5-diphenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione

N-arylidenearylthiosemicarbazide 221 (0.5mmol), CuBr₂ (0.15mmol), in DMSO (2mL) refluxed at 80° C for 2h to form the compound 222⁹⁵.

Synthesis of 3,6-diphenyl-(NH)-1,2,4-triazole from 3,6-diaryl-1,2,4,5-tetrazines

3,6-Diphenyl-1,2,4,5-tetrazine 223 (1.00g, 4.2mmol) added to a solution of benzyl cyanide 224 (0.50g, 4.2mmol) in dry THF (15mL). Upon the addition of DBU (1mL), the mixture was heated to reflux for 3h. The resulting solution was evaporated

under reduced pressure, and was extracted using CH₂Cl₂ (3-50mL). The organic layer was washed with water (3-50mL) and with dilute HCl (5N, 3-50mL). The organic layer was dried over anhydrous Na₂SO₄ and was evaporated *in vacuo* to compound 225⁹⁶.

Synthesis of 1,2,4-triazoles from amidines via copper-catalyzed oxidative c(sp³)-h functionalization

A mixture of arylamidines 226(0.25mmol), copper chloride ((1eq), K₃PO₄ (1eq) in DMF (0.25M) refluxed at 100 °C for 14h to yield the compound 227⁹⁷.

Traceless liquid-phase synthesis of 3-alkylamino-4,5-disubstituted-1,2,4 triazoles on poly ethylene glycol (PEG)

PEG-supported 230 (1mmol) added into the mixture of AcOH (two drops) and CH₃CN (20mL) and amine (5mmol) added and subsequently treated with 1.06g (5mmol) of sodium triacetoxy borohydride, then stirred for 8h at RT. Et₂O added to it to precipitate the PEG-supported 231. A solution of isothiocyanate (4mmol) in CH₂Cl₂ (20mL) added to compound 231 (1mmol) and

stirred at RT for 6h. Et₂O added to offer the compound 232. A mixture of compound 232 (1mmol) and arylacyl hydrazide (4mmol) in CH₃CN (30mL) treated with (4mmol) of Hg(OAc)₂ for 36h at RT, and then filtered. The filtrate concentrated and Et₂O added to precipitate the PEG supported triazoles 233. The compound 233 cleaved with 10% TFA/CH₂Cl₂ at RT for 2h. CH₂Cl₂ removed, and water added to give the desired compound 234⁹⁸.

Synthesis of 1,5-disubstituted 3-Amino-1H-1,2,4-triazoles from 1,3,4-oxadiazolium hexa fluorophosphate

N-substituted Hydrazide 235(0.50g, 1.77mmol), HX (1.1eq), and Ac₂O (2.5mL) taken and stirred at RT, then MTBE (6.0mL) added to facilitate precipitation and the mixture was stirred at R.T. for 18h to afford the desired salt of 1,3,4-oxadiazolium

hexafluoro phosphate (236). To a 20mL vial was added the salt 236 (1.0mmol), *i*-PrOH (2.0mL), solid cyanamide (127mg, 3.0mmol, 3.0eq), and Et₃N (0.42mL, 3.0equiv). The mixture was heated at 80°C for 2h. Upon completion, the mixture diluted with CH₂Cl₂ (20mL), washed with H₂O (3 × 10mL) and the organic layer concentrated to compound 237⁹⁹.

Synthesis of new 5-aza-isosteres of guanine containing aryl and hetaryl substituents on the 1,2,4-triazole ring

Benzylidene derivative 239 obtained by the reaction of 4-amino-substituted-6-hydrazinyl -1,3,5-triazin-2-ones (238) with the corresponding benzaldehyde in ethanol at RT to 75°C for 5- 10h. 5-Nitrofurylidene 240 obtained by refluxing hydrazinyl-1,3,5-triazines with 5-nitrofurfural diacetate in ethanol, and the

reactions required longer times (upto 42h) at 75°C. The desired 2-aryl(hetaryl)-5-amino-1,2,4-triazolo[1,5-a]-1,3,5-triazin-7-ones (243) obtained via oxidative cyclization of the corresponding arylidene (hetarylmethylidene)hydrazinyl-1,3,5-triazinones (239, 240) with lead(IV)tetraacetate in acetic acid by refluxing at 80-85°C for 10-15h¹⁰⁰.

Synthesis of 3,5-disubstituted 1,2,4-triazoles from nitriles and hydrazides

A mixture of nitrile (3mmol), hydrazide (1mmol), and K₂CO₃ (0.5mmol) in n-BuOH (2mL) in a microwave synthesizer tube placed under microwave irradiation 150°C for 1-3h, then evaporated, diluted with MeOH to yield the compound 246¹⁰¹.

Synthesis of highly substituted 3-*N,N*-Dialkylamino-1,2,4-triazoles

Thus di-2-pyridyl-thiocarbonate 248 was treated sequentially with the primary amine 247 bearing the R₃ residue followed by the secondary amine corresponding to the desired *N,N*-dialkylamino side-chain 250. The thioureas converted into the *S*-

methylisothioureas 251 by treatment with potassium *tert*-butoxide and methyl tosylate. To a stirred solution of compound 251 (1g, 2.5mmol) in THF: AcOH (10:1, 11 mL) was added acyl hydrazine (1g, 5.2mmol) and the whole was heated at 60°C for 4h, then cooled and solvent was removed to give triazole 252 as foam ¹⁰².

R₁ R₂ R₃- heterocyclic substituents

Synthesis of [1,2,4]triazolo[4,3-*a*]pyridines and [1,2,4]triazolo[4,3-*a*]pyrazines via ceric ammonium nitrate catalyzed oxidative cyclization of amidrazones

A mixture of amidrazone 256 (1.00g, 0.0047mol), benzaldehyde 253 (0.50g, 0.0047mol), PEG-300 (5mL) and CAN (5mol%) heated at 80°C for 1h, cooled to RT and extracted with Et₂O (3 × 20mL). The combined organic layers washed with H₂O (2 ×

30mL) and aq. NaHCO₃ solution (2 × 30mL), dried over anhydrous Na₂SO₄ and concentrated to afford pure 4-(substituted aryl)-3,5-diphenyl-4*H*-1,2,4-triazole. A mixture of *N*-phenyl benzamidrazone 254, benzaldehyde 253 and ceric ammonium nitrate in PEG stirred at 80°C for one hour. After the completion of the reaction, the mixture extracted with diethyl ether (3 × 20mL) to obtain product 255 ¹⁰³.

R₁- C₆H₅, C₆H₄Br(4-), C₆H₄CH₃(4-), C₆H₄Cl(4-), C₆H₄Cl(3-)
 R₂- C₆H₅, C₆H₄Br(4-), C₆H₄NO₂(4-), *n*-propyl, 3-pyridyl

Copper-Catalyzed Synthesis of 2-phenyl-1,2,4-triazolopyridine

When the compound 258 and 259 were reacted in the presence of 5mol% CuBr and 1,10 phenanthroline (1,10-Phen) & 10mol % ZnI₂ in 1,2-dichlorobenzene (DCB) at 130°C under an air atmosphere, 2-phenyl-1,2,4-triazolopyridine (260) was obtained ¹⁰⁴.

Ar- C₆H₄Br(4-), C₆H₄OCH₃(4-), C₆H₄Cl(4-), C₆H₄CF₃(3-)

Synthesis of Substituted aryl (1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-1-oxopropan-2-yl)carbamate

A mixture of dimethyl cyano dithioiminocarbonate 261 (0.44g, 3mmol) and primary or secondary amine (3mmol) in Et₂O (5mL) or EtOH (5mL) subjected to microwave irradiation for 5-30 min at 130-198°C, compound 262 precipitated. A reaction mixture of the isothiourea 262(2mmol) and 72% hydrazine hydrate (0.2 g, 4mmol) in EtOH (5mL) subjected to microwave irradiation

(80°C, 100W, 5-10 min), then solvent removed to get N-aryl-1*H*-1,2,4-triazol-5-amine (263). A mixture of the respective *N*-(protected α-aminoacyl)benzotriazole (1mmol) and compound 263(1mmol) in dry THF (3mL) subjected to microwave irradiation (70°C, 100W, 30 min). The product 264 isolated and purified with water (2mL) and extracted with EtOAc (3x10mL) ¹⁰⁵.

R₁ R₂ - (CH₂)₂O(CH₂)₂-, Ph, H; **R₃**- H; CH₃; C₆H₄CH₂-

Synthesis of 1-aryl 1,2,4-triazole from anilines

A mixture of Tosylate (1.2eq), EtSO₃H (2eq, 10-100 mol %) taken in THF & aniline added slowly to it. The mixture refluxed at 60°C for 4h, then cooled to RT to form the compound 266 ¹⁰⁶.

Catalyst free synthesis of 1-substituted phenyl-1*H*-1,2,4-triazole

To a dried microwave tube was added phenylhydrazine 267 (108mg, 1mmol) and formamide 268 (0.82mL, 20mmol). The tube was sealed with a plastic microwave septum and then placed into the microwave cavity and irradiated at 160°C, 250psi, and

230W for 10 min. After completion of reaction (TLC), cooled to R.T, distilled H₂O (10mL) was added, and the mixture extracted with EtOAc (3x10mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get compound 269 ¹⁰⁷.

R- *t*-butyl, C₆H₁₀, C₆H₅, C₆H₄Br(4-), C₆H₄OCH₃(3-), C₆H₄Cl(4-), C₆H₄F(3-)

I₂ mediated one-pot synthesis of 3,5- diphenyl-1*H*-1,2,4-triazole

The compound 271 obtained by stirring the compound 270(1mmol), base (2mmol) and iodine (1mmol) in solvent (3.0mL) for 16h at RT to 130 °C ¹⁰⁸.

Base- CS₂CO₃, NaHCO₃, K₂CO₃, NaOMe, DBU
Solvent- Toluene, DMSO, DMF, o-DCB

Synthesis of 5-substituted 3-mercapto-1,2,4-triazoles via Suzuki–Miyaura reaction

Building blocks N,S-diprotected mercaptotriazole (275) obtained from formyl hydrazine (272) and benzyliothiocyanate (3). Intermediate acyl thiosemicarbazide (273) subjected to base-promoted cyclization to give triazole 274. Benzylolation of compound 274 provided compound 275, which was halogenated

at position 5 with NBS or NIS yielding mercapto triazole derivatives 276 which were subjected to Suzuki–Miyaura cross-coupling with $\text{Pd}(\text{PPh}_3)_4$ as the catalyst and K_2CO_3 as the base in degassed THF/ H_2O and dehalogenated to N,S-dibenzyl-mercaptotriazole. Finally the deprotection could be achieved successfully using AlCl_3 in toluene at 80°C ¹⁰⁹.

Synthesis of fused [5,5]-, [5,6]-, and [5,7]-3-[(E)-2-(arylvinyl)]-1,2,4-triazoles

Diethoxyphosphinyl acetic acid hydrazide (1.05g, 5.0mmol) added to a toluene (15mL) solution of 2,3,4,5-tetrahydro-6-methoxypyridine 279 (0.57g, 5.0mmol) under N_2 to afford a cloudy suspension. After stirring overnight treated with NaOEt

solution (21wt% in EtOH, 2.05mL, 5.5mmol) followed by benzaldehyde (0.51mL, 5.0mmol), refluxed for 2h and then concentrated to a yellow solid residue. Water (30mL) was added to this residue and the resulting yellow slurry was stirred for 20 min. The slurry was filtered and the solid product was washed with water and dried to afford the compound 282 ¹¹⁰.

Synthesis of 5-aryl-[1,2,4]triazolidine-3-thiones

Aldehyde 283 (1mmol), hydrazine hydrate (1mmol) mixed & stirred for 5 min. Then, TMSNCS 284 (1mmol) added to the mixture along with catalyst (20mol %) in ethanol (5mL, 95%). The mixture was refluxed for 48-72h to yield the compound 285 ¹¹¹.

Synthesis of 5-(2,4-dichloro-benzyl)-1-(4-fluoro-benzyl)-1H-[1,2,4]triazol-3-yl-amine

A 3mL microwave tube was charged with benzyl [(1Z)-{[(2,4-dichlorophenyl) acetyl]amino} (methylthio) methylene]carbamate 288 (123mg, 0.3mmol). (4-fluorobenzyl)

hydrazine hydrochloride (318mg, 1.8mmol) and triethylamine (0.25mL, 1.8mmol) were added sequentially. The resulting mixture heated in a microwave oven at 160°C for 30 min to afford compound 290 as a white solid ¹¹².

Alumina-Promoted Synthesis of *N*-aryl-1,2,4-triazoles

A mixture of hydrazine 291(0.2mmol) & imide 292 (0.1mmol) in refluxed at 60°C for 12h, then filtered through Al_2O_3 (1g) to yield the compound 293 ¹¹³.

Synthesis of 3-[1-*p*-(chlorophenyl)-5-methyl-1,2,3-triazol-4-yl]-4*H*-1,2,4-triazole-5-thioacetic acid

1-(*p*-chlorophenyl)-5-1,2,3-triazol-4-carbohydrazide 294 (0.01mol) and benzoylthioisocyanate (0.01mol) in anhydrous acetonitrile (40mL) refluxed for 4h and cooled to get 4-benzoyl-1-[1-(*p*-chlorophenyl)-5-methyl-1,2,3-triazol-4-carbonyl]thiosemicarbazide (295). The compound 295

(0.001mol) taken in 2N NaOH (15mL) refluxed for 8h, cooled, filtered & acidified with dil. HCl to obtain 3-[1-*p*-(chlorophenyl)-5-methyl-1,2,3-triazol-4-yl]-4*H*-1,2,4-triazole-5(4*H*)-thione (297). A Mixture of obtained product (0.005mol), chloroacetic acid (0.005mol), 10% aqueous NaOH (6mL), ethanol (15 mL) refluxed for 3h and got the targeted compound 298 ¹¹⁴.

Synthesis of sodium 1-[4-(1,3-dioxo-1,3-dihydroisindol-2-yl)-5-mercapto-4*H*-[1,2,4]triazol-3-yl]heptadecane-1-sulfonate

Sodium salt of α -sulphonate of stearic acid hydrazide 299 (0.01mol) added to alcohol (50mL) containing KOH (1.6g) at RT, CS_2 added (2.3g, 0.013 mole) and the mixture stirred at RT for 10h, then diluted with ether (30mL) and stirred for further 1h. The obtained potassium salt was used for the next stage without further purification. Hydrazine hydrate (99%, 0.02 mol) added to

above potassium salt (0.01mol) dissolved in water (20mL) with stirring and refluxed gently for 3h, cooled to 5°C, acidified with conc. HCl to pH 1.00, a yellow solid of Sodium-1-(4-amino-5-mercapto-4*H*-[1,2,4] triazol-3-yl)heptadecane-1-sulfonate (300). A mixture of compound 300 (0.01mol) and phthalic anhydride (0.01mol) in butanol (20mL) refluxed for 4h, then concentrated and the solid obtained as compound 301 ¹¹⁵.

Synthesis of 9-aryl-6-(3-fluorophenyl)-1,2,4-triazole[4,3-a][1,8]naphthyridines

2-aminonicotinaldehyde (0.01mol), 3-fluorophenyl acetonitrile (0.01mol) & 10% KOH (5 drops) exposed to microwave irradiation at 200W for 2.5 min, then cooled to the solid 304. To a cold solution of compound 304 (0.01mol) in 2M HCl (25mL) added $NaNO_2$ solution (0.01mol in 25mL water) & stirred at RT for 0.5h, precipitates of 305 obtained. A mixture of compound 305 (0.01mol) & $POCl_3$ (10mL) subjected to microwave irradiation at 200W for 1.5 min, then cooled to RT and poured

into mixture of crushed ice and $NaHCO_3$ to form compound 306 which (0.01mol) and hydrazine hydrate (0.015mol) in ethanol (20mL) refluxed on water bath for 3.5h, cooled to obtain compound 307. A mixture of compound 307 (0.01mol), aromatic aldehyde (0.01mol) & DMF (5 drops) subjected to microwave irradiation at 200W, cooled & digested with cold water to get precipitates of compound 308. Hydrazones (0.01mol) & $FeCl_3 \cdot 6H_2O$ (0.01mol) exposed to microwave irradiation at 200W & then cooled to get the targeted product 309¹¹⁶.

Synthesis of 2-(((4-substitutedphenyl)amino)methyl)-5-(3-methoxyphenyl)-1-phenyl-1H-1,2,4-triazole-3(2H)thione

A mixture of 5g 3-methoxybenzoic acid (310) & 7.5mL thionyl chloride in 250 mL RBF refluxed for 8h, after completion, excess of thionyl chloride distilled & solution allowed to stand at RT to get solid product of 3-methoxybenzoylchloride (311) of which (0.01 mol) taken in dry acetone (50mL), ammonium thiocyanate

(0.01mol) added & stirred for an hour, the formed precipitates of ammonium chloride filtered, the filtrate contained compound 312, phenyl hydrazine (0.01mol) added to it & refluxed for 5h, to get compound 313. A mixture of compound 313 (0.01 mol), formaldehyde and derivative of aniline (0.01mol) in 1,4-dioxane stirred for 22h, neutralized with liquid ammonia and extracted with ethyl acetate to get triazole derivatives 314¹¹⁷.

Synthesis of ω -(5-aryl-1,2,4-triazole-3-thio)- ω -(1H-1,2,4-triazole-1-yl)acetophenone

A solution of 5-aryl-1,2,4-triazole-3-thiols 317 (2mmol) in 20mL ethanol, added drop-wise to a solution of ω -bromo- ω -(1H-1,2,4-triazole-1-yl)acetophenones 320 (2mmol) in 20mL ethanol and stirred at R.T for 5h and solvent was evaporated to get the product 321¹¹⁸⁻¹¹⁹.

Synthesis of 1,4-bis-[4-amino-5-mercapto-1,2,4-triazol-3-ylmethoxy]phenylenes

A mixture of bis-phenoxyacetic acids 323 (0.01 mol) and thiocarbohydrazide (0.02 mol) heated in an oil bath until the contents melted. The mixture was maintained at this temperature for 15–20 min, the product 324 obtained on cooling was heated with dilute Na₂CO₃ solution to remove the unreacted bis-phenoxyacetic acid¹²⁰.

Synthesis of ethyl 3-(benzo[d][1,3]dioxol-5-yl)-1-methyl-1H-1,2,4-triazole-5-carboxylate

The compound 326 formed by stirring at RT for 20h with methylhydrazine sulfate in the presence of K₂CO₃ which further stirred with substituted acid in the presence of T3P (50% w/w in EtOAc), 3eq DIPEA, 1,4-dioxane at RT for 1h then concentrated and dissolved in AcOH/ 1,4-dioxane (1:1) at 100°C for 1h to get the compound 328¹²¹.

Synthesis of triazole derivatives via highly efficient cyanoimide of aldehydes

Reactions were carried out with molar ratio aldehyde/H₂NCN/base (t-BuONa) 1:1.2:1.5 at RT for 30 min, and

then oxidant (NBS, 1.5 equiv. of aldehyde) was added at 50°C for 12h to yield the compound 336 which then further refluxed for 4h with phenyl hydrazine in CH₃OH with a substrate/PhNHNH₂ ratio of 1:1.2 to get the compound 337¹²².

Synthesis of 3-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)-1-(1H-benzo[d]imidazol-2-yl)propan-1-one

A solution of o-phenylenediamine (0.01mol), □-ketoglutaric acid (0.01mol) in methanol/water mixture (1:1) and HCl (4N, 5mL) refluxed for 6h and cooled, 10% NaOH solution added to neutralize, a solid mass 331 precipitated out. A solution of compound 331 (0.01mol) in ethanol (25mL) refluxed for 10h in presence of conc. H₂SO₄ (0.1mL) to obtain oxobutanoate 332 &

formed hydrazide by reacting with hydrazine hydrate which (0.01mol) then refluxed with CS₂/KOH (0.01mol) in ethanol/water (1:1) refluxed for 6h, cooled and acidified to precipitate compound 334. To a solution of compounds 334(0.01mol) in n-butanol (40mL), hydrazine hydrate (0.03mol) was added & refluxed for 5 h and after completion, KOH (0.015mol) was added to precipitate the compound 335¹²³.

Synthesis of 1,5-disubstituted triazole derivatives from amidine and hydrazine

To a slurry of 340 (X= N or O; 1.15 g, 5.52mmol) in 5 volumes of EtOAc (6mL) was added 1eq of *N,N*-dimethyl formamide diethyl acetal (1.00 mL, 5.52mmol). The mixture was heated at 50°C for 4h and then heptane (20mL) was added. After that

mixture was cooled to RT to obtain compound 341. To the mixture of amidine 341 (0.21g, 0.80mmol) and hydrazine (0.11g, 0.75mmol) was added 5 volumes of AcOH (0.6mL) & stirred for 2.5h and then cooled in an ice bath and EtOAc was added followed by sat. NaHCO₃ solution & then concentrated to give 342 as a light yellow solid¹²⁴.

Synthesis of 1-(substitutedphenyl)-3,5-diacetyl-4-alkoxycarbonylamino-4,5-dihydro-1H-1,2,4-triazole
Triethylamine (5g, 5mmol) was added to the stirred mixture of pyruvaldehyde hydrazones 343(7.5-10mmol) and the appropriate

hydrazonoyl halides 343 (5mmol) in dioxane (50mL) at RT and stirring was continued for 12-16h or refluxed for 2-4h. The precipitated salt was filtered off as compound 346¹²⁵.

Ar- C₆H₅, C₆H₄F(4-), C₆H₄OCH₃(4-), C₆H₄Cl(4-); R- CH₃, C₆H₅, C₆H₅NH, 2-C₄H₃O

Synthesis of 1,4-bis-[2-mercapto-1,3,4-triazolo[5,1b]-1,3,4-oxadiazole-5-yl]phenyl

Compound 348 (0.27g, 0.001mole) with hydrazine hydrate (1mL) in abs. ethanol (15mL) refluxed for 20h, solvent evaporated, cooled to get precipitates of 1,4-bis-[1,3,4-oxadiazole-2-

hydrazine-5-yl]phenyl(349). To a stirred solution of compound 349 (0.27g, 0.001mole) in pyridine (2.6mL) was added slowly CS₂ (1mL) & refluxed for 24h, then allowed to cool & the solid compound 350 obtained¹²⁶.

Synthesis of 2,4-dinitramino-5-nitro-1,2,4-triazol-3-one (DTNT)

Semicarbazide hydrochloride (6.6g) & formic acid (6.9mL) stirred until solution formed. Then excess of formic acid removed & 10mL of water added, distillation continued to dryness and residue was collected as 2,4-dihydro-3H-1,2,4-triazol-3-one (TO, 351). TO (1g) added to nitric acid (10mL) at 0°C & heated to

70°C for 16h with constant stirring & 5-nitro-2,4-dihydro-3H-1,2,4-triazol-3-one (NTO, 352). Acetic anhydride (1.56g) added slowly to the mixture of fuming nitric acid (0.580g) & HCl (0.124g), stirred for half an hour at 0°C, NTO (0.500g) added in small portions & stirred overnight at RT and 1-2h at 35-40°C, then cooled to compound 353¹²⁷.

Synthesis of 5-(3-chloro-1-benzothien -2-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol

To a solution of compound 335(0.001mol) in dry chloroform (5mL), hydrazine hydrate (0.0018mol) was added & refluxed for one hour, solvent removed *in vacuo* and the product collected 3-chlorobenzo[b]thiophene-2-carboxylic acid hydrazide (356). A

mixture of compound 356 (0.01mol) and phenyl isothiocyanate (0.01mol) in dry C₆H₆ refluxed for 6h, cooled to give compound 357. A stirring mixture of compound 357 (1 mmol) and sodium hydroxide (40mg, 1mmol) refluxed for 4h, cooled & acidified to get precipitates of compound 358¹²⁸.

Synthesis of 3-alkyl/aryl-6-(1-chloro-3,4-dihydronaphth-2-yl)-5,6-dihydro-s-triazolo[3,4-b][1,3,4]thiadiazoles

A mixture of alkyl/aryl-4-amino-3-mercapto-1,2,4-triazole (0.005mol), 1-chloro-2-formyl-3,5-dihydronaphthalene (0.960g,

0.005mol), *p*-TsOH (50mg) and DMF (1mL) irradiated in a domestic microwave oven at 300W for 2-3 min. & then cooled to get the compound 362¹²⁹.

R- CH₃, C₂H₅, C₃H₇, C₆H₅, C₆H₅CH₂-

Synthesis of 3-(α -L-arabinopyranosylthio)-6-phenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole

To a solution of compound 363 (500mg, 3.4mmol) in *N,N*-dimethyl formamide (3.0mL) and triethyl amine (1mL, 7.2mmol) was added 2,3,4-tri-O-acetyl-b-L-arabinopyranosyl bromide (364) (900mg, 2.6mmol) and stirred overnight, diluted with ice water to get the precipitates of compound 365. A mixture of

compound 365 (406mg, 1.0mmol) and carboxylic acid (1mmol) or acyl chloride (1mmol) in phosphoryl chloride (2mL) refluxed in an oil bath for 8h. The excess of phosphoryl chloride removed to yield the compound 366. Dry gaseous ammonia was passed through a solution of compound 366 (1mmol) in dry methanol (10mL) for about 1h with cooling and stirring then concentrated at reduced pressure to afford a solid compound 367¹³⁰.

R- C₆H₅, C₆H₄NH₂(4-), C₆H₄Cl(4-), C₆H₄NO₂(4-)

Synthesis of some 4-amino-5-substituted aryl-3-mercapto-(4H)-1,2,4-triazoles & triazolo thiadiazole derivatives

Substituted carboxylic acids converted into ester by reacting with methanol. Ester (0.12mol) reacted with hydrazine hydrate (0.12mol) to yield hydrazides which (0.01mol) further stirred at RT for 8h with carbon disulfide (0.05mol) in the presence of KOH (0.03mol) & methanol (15ml) to obtain potassium

dithiocarbazates. The suspension of potassium salt (0.02mol) in water further used without purification & refluxed with hydrazine hydrate (0.04mol) again to form mercapto triazole. Amino mercapto triazole (0.01mol) when refluxed with substituted aromatic acid (0.01mol) in the presence of POCl₃ (10mL), the precipitates of triazolothiadiazoles obtained¹³¹⁻¹⁴⁰.

R_1 , R_2 , Ar - different substituted aromatics according to the mentioned references

Synthesis of 5-methyl-2-[(6-methyl[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-3-yl)methyl]-4-[4-(6-methyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

A solution of compound 374 (1.25 g, 0.002 mol) in water (3 ml) was added to a solution of carboxylic acid (0.004mol) and PPA

(5mL) in EtOH (10mL) in a microwave vial. The mixture was irradiated with microwaves at 140°C for 45 min. After the completion of the reaction (TLC, MeOH), the solution was poured into cold water (100mL). The precipitated solid was filtered off as compound 375¹⁴¹.

ABBREVIATIONS

s- second
min- minute
RT- Room Temperature
DMF- Di Methyl Formamide
DMSO- Di Methyl Sulph Oxide
THF- Tetra Hydro Furan
PEG- Poly Ethylene Glycol
DBU- 1,8-Diaza Bicyclo[5.4.0] Undec-7-ene
TFA- Tri Fluoro Acetic acid
MTBE- Methyl Tertiary Butyl Ether
CAN- Ceric Ammonium Nitrate
NBS- *N*- Bromo Succinimide
NIS- *N*- Iodo Succinimide
TMSNCS- Tri Methyl Silyl Iso Thio Cyanate
T3P- Propylphosphonic Anhydride
DIPEA- *N,N*- Di Iso Propyl Ethyl Amine
PPA- Poly Phosphoric Acid
DCC- *N,N'*-Di Cyclohexyl Carbodiimide
TBHP- Tertiary Butyl Hydro Peroxide

CONCLUSION

Triazoles have attracted considerable attention in the field of medicine due to their unique structures and properties. Triazoles derivatives possess a great importance in medicinal chemistry & acts as a promising medicinal agent for the scientists working over this field. The various synthetic methods discussed here may helpful to develop various newer compounds possessing triazoles moiety that could be better in terms of efficacy and lesser toxicity, evaluate more activities of triazole for many diseases whose

treatment are challenging in the field of medical sciences. So it can be seen from the literature review that 1,2,4-triazole ring containing heterocyclic system has wide medicinal applications. Thus by studying all the derivatives showing variety of activities can say that 1,2,4-triazole ring have been explored in past years and is still used for future development of new drugs against many more pathological conditions.

REFERENCES

1. Guzeldemirci NU and Kucukbasmaci O: Synthesis and antimicrobial activity evaluation of new 1,2,4- triazoles and 1,3,4-thiadiazoles bearing imidazo[2,1-b]thiazole moiety. Eur J Med Chem, 2010; 4:63-68.
2. Alaraji YH, Shneine JK and Ahmed ANAA: Synthesis, characterization, and antibacterial activity of new schiff's bases with 1,2,4-triazole moiety. Journal of Science 2015; 5(5):293-299.
3. Abdulrasool MM and Jawad AH: Synthesis, characterization and evaluation of biological activity of new heterocyclic compounds containing 1,2,4-triazole and 1,3,4-thiadiazole rings. Int. J. App. Sci. Tech 2012; 2(10):155-164.
4. Jassim WK, Fayad AA and Jassim IK: Synthesis and characterization of some substituted heterocyclic compounds and evaluation of biological activity. Kerbala J. Pharm. Sci. 2011; 2: 228-240.
5. Al-Khuzai MGA and Al-Majidi SMH: Synthesis, characterization and evaluation antimicrobial activity of some new substituted 2-mercapto-3-phenyl-4(3h)-quinazolinone. Iraqi J. Sci 2014; 55(2B):582-593.

6. Hanif M, Saleem M, Hussain MT, Rama NH, Zaib S, Aslam MAM, Jones PG and Iqbal J: Synthesis, urease inhibition, antioxidant and antibacterial studies of some 4-amino-5-aryl-3*H*-1,2,4-triazole-3-thiones and their 3,6-disubstituted 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole derivatives. *J. Braz. Chem. Soc.* 2012; 23(5):854-860.
7. Wang XL, Wan K and Zhou CH: Synthesis of novel sulfanilamide derived 1,2,3-triazoles and their evaluation for antibacterial and antifungal activities. *Eur J Med Chem* 2010; 45:4631-4639.
8. Prasad D, Aggarwal N, Kumar R and Nath M: Synthesis of novel heteroarenes based [1,2,3]-triazoles via click chemistry and their evaluation for antibacterial activity. *Indian J Chem* 2012; 51(5):731-738.
9. Xiang L, Xue Q, He-M, Xue X and Zhi H: Synthesis and evaluation of antitumor activities of novel chiral 1,2,4-triazole Schiff bases bearing γ -butenolide moiety. *Org. & Med. Chem. Lett.* 2012; 2:26.
10. Yan S, Liu Y, Chen Y, Liu L, Lin J, An efficient one-pot synthesis of heterocycle-fused 1,2,3-triazole derivatives as anti-cancer agents. *Bioorg & Med Chem Lett* 2010; 20:5225-5228.
11. Yu J, Wua Q, Zhang Q, Liu Y, Li Y, Zhou Z, Synthesis and antitumor activity of novel 20, 30-dideoxy-20,30-diethane thionucleosides bearing 1,2,3-triazole residues. *Bioorg & Med Chem Lett* 2010; 20:240-243.
12. Kurumurthy C, Rao PS, Swamy BV, Kumar GS, Rao PS, Narsaiah B, Velatooru LR, Pamanji R and Rao JV: Synthesis of novel alkyltriazole tagged pyrido[2,3-*d*]pyrimidine derivatives and their anticancer activity. *Eur J Med Chem* 2011; 46:3462-3468.
13. Amin KM and El-Zahar MI: Synthesis and anticancer activity of novel tetralin-6-ylpyridine and tetralin-6-ylpyrimidine derivatives. *Acta. Polo. Pharm. Drug Res.* 2009; 66(3):279-291.
14. Arul K and Smith KK: In-Silico design, synthesis and in vitro anticancer evaluation of some novel 1,2,4-triazole derivatives. *The Experiment* 2014; 21(1):1439-1452.
15. Baviskara BA and Khadabadi SS. Synthesis of clubbed triazolylindeno[1,2-*c*]isoquinolines as an novel anticancer agent. *Pel. Res. Lib. Pharm. Sin* 2012; 3(1):24-30.
16. Hou K and Juan Sun: Synthesis and antitumor activity of 1,2,4-triazoles having 1,4-benzodioxan fragment as a novel class of potent methionine aminopeptidase type inhibitors. *Bio. Med. Chem* 2011; 19:5948-5954.
17. Bekircan O and Kahveci B: Synthesis and anticancer evaluation of some new unsymmetrical 3,5-diaryl-4*H*-1,2,4-triazole derivatives. *Turk J Chem* 2006; 30:29-40.
18. Mandal SK, Saha D, Jain VK and Jain B: Synthesis and antitubercular activity of some triazole derivatives of propyl gallate. *Inter J Pharma Sci and Res* 2010; 1:465-473.
19. Mali RK, Somani RR, Toraskar MP, Mali KK, Naik PP and Shirodkar PY: Synthesis of some antifungal and anti-tubercular 1,2,4-triazole analogues. *Inter J Chem Tech Res* 2009; 1(2):168-173.
20. Meenaxi MM and Ainapure R: Triazolone and their derivatives for anti -tubercular activities. *Asian J. Res. Chem* 2011; 4(7):1050-1054.
21. Singh RG and Singh DJ: Novel synthetic approach to some new 1,2,4-triazolothiadiazines and 1,2,4-triazolothiadiazinones and their anti-inflammatory activities. *Int. J. Chem. Tech. Res* 2009; 1(4): 1239-1243.
22. Akhter MW, Hassan MZ and Amir M: Synthesis and pharmacological evaluation of 3-diphenyl methyl-6-substituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles: a condensed bridgehead nitrogen heterocyclic system. *Arabian J. Chem* 2014; 4:1-9.
23. Shenone S, Bruno O, Ranise A, Bondavalli W, Falcone G, Giordano L and Vitelli M: 3-arylsulphonyl-5-arylamino-1,3,4-thiadiazol-2(3*H*)ones as anti-inflammatory and Analgesic agents. *Bioorg Med Chem* 2001; 9:2149-2153.
24. Ilango K and Valentina P: Synthesis and biological activities of novel 1,2,4-triazolo-[3, 4-*b*]-1,3,4-thiadiazoles. *Der Pharma Chemica* 2010; 2(2):16-22.
25. Streeter DG, Witkowski JT and Khare GP: Mechanism of action of 1- β -d-ribofuranosyl-1,2,4-triazole-3-carboxamide (virazole). a new broad-spectra antiviral agent. *Proc. Nat. Acad. Sci. USA* 1973; 70(4):1174-1178.
26. Bay HA, Quaddouri B, Guaadaoui A, Touzani R, Benchat N, Hamal A, Taleb M, Bellaoui M and Kadiri SE: Synthesis and Biological Activity of New Triazole Compounds. *Drug Design & Discov* 2010; 7:41-45.
27. Hanane A, Bouchra Q, Abdelkarim A, Rachid T, Nour-eddin B, Abdellah H, Mustafa T, Mohammed B and Sghirel K: Synthesis and biological activity of new triazole compounds. *Lett Drug Design & Discov* 2010; 7:41-45.
28. Patel NB, Khan IH and Rajani SD: Pharmacological evaluation and characterizations of newly synthesized 1,2,4-triazoles. *Euro J Med Chem* 2010; 45: 4293-4299.
29. Guan LP, Sui X, Deng XQ, Quan YC and Quan ZS: Synthesis and anticonvulsant activity of a new 6-alkoxy-[1,2,4]triazolopyridazine. *Eur J Med Chem* 2010; 45:1746-1752.
30. Siddiqui N and Ahsan W: Triazole incorporated thiazoles as a new class of anticonvulsants: Design, synthesis and *in vivo* screening. *Eur J Med Chem* 2010; 45:1536-1543.
31. Husain A, Naseer MA and Sarafroz M: Synthesis and anticonvulsant activity of some novel fused heterocyclic 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole derivatives. *Acta. Polo. Pharm. Drug Res* 2009; 66(2):135-140.
32. Alswah M and Ghiaty A: Synthesis and biological evaluation of some [1,2,4]triazolo[4,3-*a*]quinoxaline derivatives as novel anticonvulsant agents. *ISRN Org. Chem* 2013; 1:1-7.
33. Sripriya S, Subha C and Selvaraj A: The inhibition chemistry of 2-amino, 5-phenyl 1, 3, 4-triazole for aluminium in hydrochloric acid solution. *IOSR-JAC* 2013; 6(2):25-29.
34. Kharb R, Sharma PC, Bhandari A and Shaharyar M: Synthesis, spectral characterization and anthelmintic evaluation of some novel imidazole bearing triazole derivatives. *Der Pharm Lett.* 2012; 4:652-657.
35. Vishnumurthy KA, Satyendra RV, Vagdevi HM, Rajesh KP, Manjunatha H and Shruthi A: Synthesis, in vitro antioxidant, anthelmintic and molecular docking studies of novel dichloro substituted benzoxazoletriazolothione derivatives. *Eur J Med Chem* 2011; 46: 3078-3084.
36. Padmaja A, Rajasekhar C, Muralikrishna A and Padmavathi V: Synthesis and antioxidant activity of disubstituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles. *J Chem & Pharm Res* 2012; 4(1):294-302.
37. Kemal S, Yasemin U, Dilek U, Esra D, Gulcan K, Fatih C and Emrah B: Synthesis, Characterization, and antioxidant activities of new trisubstituted triazoles. *Turk J Chem* 2012; 36:457-466.
38. Abdul Hameed A and Hassan F: Synthesis, Characterization and Antioxidant Activity of Some 4-Amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol Derivatives. *Int. J. App. Sci. Tech* 2012; 4(2); 202-211.
39. Sancak K, Unver Y, Unluer D, Dugdu E, Kor G, Celik F and Birinci E: Synthesis, characterization, and

- antioxidant activities of new trisubstituted triazoles. *Turk. J. Chem* 2012; 36:457-466.
40. Bekircan O, Menteşe E and Ulker S: Synthesis of some new 1,2,4-triazole derivatives starting from 3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4H-1,2,4-triazol with anti-lipase and anti-urease activities. *Arch. Pharm. Chem. Life Sci.* 2014; 347:387-397.
41. Mhasalkar MY, Shah MH, Pilankar PD, Nikam ST, Anantanarayanan KG and Deliwala CV: Synthesis and hypoglycaemic activity of 3-aryl(or pyridyl)-5-alkyl amino-1,3,4, thiadiazole and some sulfonyl urease derivatives of 4H-1,2,4 triazoles. *J Med Chem* 1971;14(10):1000-3.
42. Sharma V , Shrivastava B, Bhatial R, Bachwani M, Khandelwal R and Ameta J: Exploring potential of 1,2,4-triazole: A brief review. *Pharmacologyonline* 2011; 1:1192-1222.
43. Plech T, Luszczki JJ, Wujec M, Flieger J and Pizo M: Synthesis, characterization and preliminary anticonvulsant evaluation of some 4-alkyl-1,2,4-triazoles. *European Journal of Medicinal Chemistry* 2013; 60:208-215.
44. Barot KP, Manna KS and Ghathe MD: Design, synthesis and antimicrobial activities of some novel 1,3,4-thiadiazole, 1,2,4-triazole-5-thione and 1,3-thiazolan-4-one derivatives of benzimidazole. *Journal of Saudi Chemical Society* 2013.
45. Hunashal RD, Ronad PM, Maddi VS, Satyanarayana D and Kamadod MA: Synthesis, anti-inflammatory and analgesic activity of 2-[4-(substituted benzylideneamino)-5- (substituted phenoxyethyl)-4H-1,2,4-triazol-3-yl thio] acetic acid derivatives. *Arabian Journal of Chemistry* 2014; 7:1070-1078.
46. Eswaran S, Adhikari AV and Shetty NS: Synthesis and antimicrobial activities of novel quinoline derivatives carrying 1,2,4-triazole moiety. *European Journal of Medicinal Chemistry* 2009;44:4637-4647.
47. Salunkhe NG: Green synthesis, characterization and biological evaluation of some triazole and thiadiazole. *Journal of Current Chemical and Pharmaceutical Sciences* 2012; 2 (2):100-106.
48. Kumar GVS, Rajendraprasad V, Mallikarjuna BP, Chandrashekar SM and Kistayya C: .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* 2010; 45:2063-2074.
49. Guzeldemirci NU and Kucukbasmac O: Synthesis and antimicrobial activity evaluation of new 1,2,4-triazoles and 1,3,4-thiadiazoles bearing imidazo[2,1-b]thiazole moiety. *European Journal of Medicinal Chemistry* 2010; 4:63-68.
50. Shi Z, Zhao Z, Huang M and Fu X: Ultrasound-assisted, one-pot, three-component synthesis and antibacterial activities of novel indole derivatives containing 1,3,4-oxadiazole and 1,2,4-triazole moieties. *Comptes Rendus Chimie* 2015.
51. Gupta AK, Prachand S, Patel A and Jain S: Synthesis of some 4-amino-5-(substituted-phenyl)-4H-[1,2,4]triazole-3-thiol derivatives and antifungal activity. *International journal of pharmacy & life sciences* 2012; 3:1848-1857.
52. B Andrews and Ahmed M: Synthesis and Characterization of Pyrimidine bearing 1,2,4- triazole derivatives and their potential antifungal action. *International Journal of ChemTech Research* 2014; 6:1013-1021.
53. Asrondkar A, Patil V, Pande S, Bobade AS and Chowdhary AS: Synthesis of substituted 1, 2, 4-triazole derivatives by microwave irradiation . *IOSR Journal of Applied Chemistry* 2013; 6:16-19.
54. Bhat KS, Poojary B, Prasad DJ, Naik P and Holla B: Synthesis and antitumor activity studies of some new fused 1,2,4-triazole derivatives carrying 2,4-dichloro-5-fluorophenyl moiety. *European Journal of Medicinal Chemistry* 2009; 44:5066-5070.
55. Chai B, Qian X, Cao S, Liu H and Song G: Synthesis and insecticidal activity of 1,2,4-triazole derivatives. *Arkivoc* 2003; 2:141-145.
56. Prasad DJ, Ashok M, Karegoudar P, Poojary B, Holla BS and Kumari NS: Synthesis and antimicrobial activities of some new triazolothiadiazoles bearing 4-methylthiobenzyl moiety. *European Journal of Medicinal Chemistry* 2009; 44:551-557.
57. Yassin FA and Seleim AF: Synthesis and reactions of oxadiazolo, thiadiazolo and triazolo phthalazin-1(2H)-one derivatives. *Der Pharma Chemica* 2012; 4 (3):860-866.
58. Sahin D, Bayrak H, Demirbas A, Demirbas N and Karaoglu SA: Design and synthesis of new 1,2,4-triazole derivatives containing morpholine moiety as antimicrobial agents. *Turk J Chem* 2012; 36:411-426.
59. Abdulla IQ: Synthesis and antimicrobial activity of ibuprofen derivatives. *Natural Science* 2014; 6(2):47-53.
60. Ansari KF, Lal C and Khitoliya RK: Synthesis and biological activity of some triazole-bearing benzimidazole derivatives. *Journal of Serbian Chemical Society* 2011; 76(3):341-352.
61. Tehrani KHME, Mashayekhi M, AzerangP, Minaei S, Sardari S and Kobarfard F: Synthesis and antimycobacterial activity of some triazole derivatives- new route to functionalized triazolopyridazines. *Iranian Journal of Pharmaceutical Research* 2015; 14:59-68.
62. Desabattina VNK, Aluru RGP, Narasimha SY, Dharmapuri RR, Rao RL and Rao K: Synthesis, characterization and antimicrobial studies of certain 1,2,4-triazole derivatives. *Journal of Applied Pharmacy* 2014; 6(1):01-07.
63. Dandia A, Gupta SL, Sudheer and Quraishi MA: Microwave assisted economic synthesis of 4-amino-3-alkyl-5-mercapto-1, 2, 4-triazole derivatives as green corrosion inhibitors for copper in hydrochloric acid. *Journal of Material & Environmental Science* 2012; 3(5):993-1000.
64. Plech T, Luszczki JJ, Wujec M, Flieger J and Pizon M: Synthesis, characterization and preliminary anticonvulsant evaluation of some 4-alkyl-1,2,4-triazoles. *European Journal of Medicinal Chemistry* 2013; 60:208-215.
65. Piste PB and Waghmare SP: Green synthesis of triazole derivatives with pyrimidine moiety. *International Journal of Pharmaceutical Sciences Review and Research* 2013; 22(2):46-49.
66. Raghav N and Singh M: Acyl hydrazides and triazoles as novel inhibitors of mammalian cathepsin B and cathepsin H. *European Journal of Medicinal Chemistry* 2014; 77:231-242.
67. Xie R, Liu X, Mai C and Liu Z: Solid phase synthesis of 3,4,5-trisubstituted-1,2,4-triazoles derivatives from the resin-bound acyl hydrazines. *International Journal of Organic Chemistry* 2013; 3:35-40.
68. Mandal S, Saha D, Jain VK and Jain B: Synthesis, characterization and evaluation of antibacterial and antifungal activity of triazole derivatives of gallic acid. *International Journal of Applied Biology and Pharmaceutical Technology* 2010; 3(1):1300-1311.

69. Dolzhenko AV, Chia HS and Chui WK: Synthesis of 5-amino-3-(het)aryl-1*H*-1,2,4-triazoles via cyclization of (het)aroylaminoguanidines in aqueous medium. 9th electronic conference on synthetic organic chemistry 2005; 1-30.
70. Lee J, Hong M, Jung Y, Cho EJ and Rhee H: Synthesis of 1,3,5-trisubstituted-1,2,4-triazoles by microwave-assisted N-acylation of amide derivatives and the consecutive reaction with hydrazine hydrochlorides. *Tetrahedron Letters* 2012; 68: 2045-2051.
71. Baran AU, Tel BC, Sangol D, Ozturk EI, Kazkayasi I, Okay G, Ertan M and Tozkoparan B: Thiazolo[3,2-*b*]-1,2,4-triazole-5(6*H*)-one substituted with ibuprofen: Novel non-steroidal anti-inflammatory agents with favorable gastrointestinal tolerance. *European Journal of Medicinal Chemistry* 2012; 1-9.
72. Gumrukcuoglu N, Serdar M, Celik E, Sevim A and Demirbas N. Synthesis and antimicrobial activities of some new 1,2,4-triazole derivatives. *Turk J Chem* 2007; 31:335-348.
73. Bekircan O and Bektas H: Synthesis of new bis-1,2,4-triazole derivatives. *Molecules* 2006; 11:469-477.
74. Bekircan O and Bektas H: Synthesis of schiff and mannich bases of isatin derivatives with 4-amino-4,5-dihydro-1*H*-1,2,4-triazole-5-ones. *Molecules* 2008; 13:2126-2135.
75. Hunashal RD, Ronad PM, Maddi VS, Satyanarayana D and Kamadod MA: Synthesis, anti-inflammatory and analgesic activity of 2-[4-(substituted benzylideneamino)-5-(substituted phenoxymethyl)-4*H*-1,2,4-triazol-3-ylthio] acetic acid derivatives. *Arabian Journal of Chemistry* 2014; 7:1070-1078.
76. Karaali N, Mentesea E, Imaz F, Usta A and Kahveci B: Microwave-assisted synthesis of some 1*H*-1,2,4-triazol-3-one derivatives. *South African Journal of Chemistry* 2013; 66:72-76.
77. Sachdeva H, Saroj R, Khaturia S and Dwivedi D: Environ-economic synthesis and characterization of some new 1,2,4-triazole derivatives as organic fluorescent materials and potent fungicidal agents. *Organic Chemistry International* 2013; 19.
78. MinLJ, Shi YX, Wu HK, Sun ZH, Liu XH, Li BJ and Zhang YJ: Microwave-assisted synthesis and antifungal activity of some novel thioethers containing 1,2,4-triazole moiety. *Applied Sciences* 2015; 5:1211-1220.
79. Rao DVN, Prasad ARG, Spoorth YN, Rao DR and Ravindranath LK: Synthesis, characterization and pharmacological studies of sulphur containing 1,2,4-triazole derivatives. *Journal of Taibah University Medical Sciences* 2014; 9(4): 293-300.
80. Jaisankar KR, Kumaran K, Kamil SRM and Srinivasan T: Microwave-assisted synthesis of 1,2,4-triazole-3-carboxamides from esters and amines under neutral conditions.
81. Bechara WS, Khazhieva IS, Rodriguez E and Charette AB: One-pot synthesis of 3,4,5-trisubstituted 1,2,4-triazoles via the addition of hydrazides to activated secondary amides. *Organic Letters* 2015; 17:1184-1187.
82. Bentiss F, Lagrene M and Barbry D: Accelerated synthesis of 3,5-disubstituted 4-amino 1,2,4-triazoles under microwave irradiation. *Tetrahedron Letters* 2000; 41:1539-1541.
83. Bibian M, Blayo AL, Moulin A, Martinez J and Fehrentz JA: Multi-gram scale mercury-free synthesis of optically pure 3,4,5-trisubstituted 1,2,4-triazoles using silver benzoate. *Tetrahedron Letters* 2010; 51:2660-2663.
84. Castanedo GM, Seng PS, Blaquiére N, Trapp S and Staben ST: Rapid synthesis of 1,3,5-substituted 1,2,4-triazoles from carboxylic acids, amidines, and hydrazines. *Journal of Organic Chemistry* 2011; 76:1177-1179.
85. Chen Z, Li H, Dong W, Miao M and Ren H: I₂ catalyzed oxidative coupling reactions of hydrazones and amines and the application in the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles. *Organic Letters*.
86. Dolzhenko AV, Pastorin G, Dolzhenko AV and Chui WK: An aqueous medium synthesis and tautomerism study of 3(5)-amino-1,2,4-triazoles. *Tetrahedron Letters* 2009; 50: 2124-2128.
87. Gogoi A, Guin S, Rajamanickam S, Rout SK and Patel BK: Synthesis of 1,2,4-triazoles via oxidative heterocyclization: selective C-N bond over C-S bond formation. *The Journal of Organic Chemistry* 2015; 1-37.
88. Haddadin MJ and Zadeh EHG: A novel method for the synthesis of 3,5-disubstituted-(NH)-1,2,4-triazoles from 3,6-diaryl-1,2,4,5-tetrazines. *Tetrahedron Letters* 2010; 51:1654-1656.
89. Huang H, Guo W, Wu W, Li CJ, Jiang H. Copper-catalyzed oxidative c(sp³)-h functionalization for facile synthesis of 1,2,4-triazoles and 1,3,5-triazines from amidines. *Organic letters*.
90. Zong YX, Wang JK, Yue GR, Feng L, Song ZE, Song H and Han YQ: Traceless liquid-phase synthesis of 3-alkylamino-4,5-disubstituted-1,2,4-triazoles on polyethylene glycol (PEG). *Tetrahedron Letters* 2005; 46:5139-5141.
1. Wong B, Stumpf A, Carrera D, Gu C and Zhang H: A Safe Synthesis of 1,5-di substituted-3-amino-1*H*-1,2,4-triazoles from 1,3,4-oxadiazolium hexafluorophosphates. *Synthesis* 2013; 45:1083-1093.
2. Zavodskaya AV, Bakharev VV, Parfenov VE, Gidaspov AA, Slepukhin PA, Isenov ML and Eltsov OS: Synthesis of new 5-aza-isosteres of guanine containing aryl and hetaryl substituents on the 1,2,4-triazole ring. *Tetrahedron Letters* 2015.
3. Yeung KS, Farkas ME, Kadow JF and Meanwell NA: A base-catalyzed, direct synthesis of 3,5-disubstituted 1,2,4-triazoles from nitriles and hydrazides. *Tetrahedron Letters* 2005; 46:3429-3432.
4. Batchelor DV, Beal DM, Brown TB, Ellis D, Gordon DW, Johnson PS, Mason HJ, Ralph MJ, Underwood TJ and Wheeler S: A convenient synthesis of highly substituted 3-*N,N*-dialkylamino-1,2,4-triazoles. *Synlett* 2008; 16:2421-2424.
5. Nakka M, Tadikonda R, Rayavarapu S, Sarakula P and Vidavalur S: A simple and efficient synthesis of 3,4,5-trisubstituted/n-fused 1,2,4-triazoles via ceric ammonium nitrate catalyzed oxidative cyclization of amidrazones with aldehydes using polyethylene. *Synthesis* 2015; 47:517-525.
6. Ueda S and Nagasawa H: Facile synthesis of 1,2,4-triazoles via a copper-catalyzed tandem addition-oxidative cyclization. *Journal of American Chemical Society* 2009; 131:15080-15081.
7. Hansen FK, Beagle LK, Todadze E and Katritzky AR: Efficient microwave-assisted synthesis of 1,2,4-triazole-based peptidomimetics using benzotriazole methodology. *Heterocycles* 2012; 84.
8. Tam A, Armstrong IS and Cruz TEL: Multicomponent synthesis of 1-aryl 1,2,4-triazoles. *Organic. Letters* 2013.
9. Shelkea GM, Rao VK, Jha M, Cameron TS and Kumar A: Microwave-assisted catalyst-free synthesis of substituted 1,2,4-triazoles. *New York-Synlett* 2015; 26: 404-407.

10. Inturi SB, Kalita B and Ahamed AJ: I₂ mediated one-pot synthesis of 1,2,4-triazoles from amidines and imidates. *Tetrahedron Letters* Accepted Manuscript.
11. Katkevica S, Salun P and Jirgensons A: Synthesis of 5-substituted 3-mercapto-1,2,4-triazoles via Suzuki–Miyaura reaction. *Tetrahedron Letters* 2013; 54:4524-4525.
12. Liu F, Palmer DC and Sorgi KL: Diethoxyphosphinyl acetic acid hydrazide: a uniquely versatile reagent for the preparation of fused [5,5]-, [5,6]-, and [5,7]-3-[(*E*)-2-(arylviny)]-1,2,4-triazoles. *Tetrahedron Letters* 2004; 45:1877-1880.
13. Mane MM and Pore DM: A novel one pot multi-component strategy for facile synthesis of 5-aryl-[1,2,4]triazolidine-3-thiones. *Tetrahedron Letters* Accepted Manuscript.
14. Meng J and Kung PP: Rapid, microwave-assisted synthesis of *N*¹-substituted 3-amino-1,2,4-triazoles. *Tetrahedron Letters* 2009; 50:1667-1670.
15. Neuhaus WC and Moura-Letts G: Alumina-promoted synthesis of *N*-aryl-1,2,4-triazoles from substituted hydrazines and imides. *Tetrahedron Letters* Accepted Manuscript.
16. Sun XW, Hui XP, Chu CH and Zhang ZY: Synthesis of 1,3,4-thiadiazole, 1,2,4-triazole, 1,3,4-oxadiazole containing 1-(*p*-chlorophenyl)-5-methyl-1,2,3-triazol-4-yl moiety. *Indian journal of chemistry* 2001; 40B:15-19.
17. Sayed RE: Synthesis, antibacterial and surface activity of 1,2,4-triazole derivatives. *Indian Journal of Chemistry* 2006; 45B:738-746.
18. Mogilaiah K, Prasad RS and Swamy JK: Microwave-assisted synthesis of 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines using FeCl₃·6H₂O under solvent free conditions. *Indian journal of chemistry* 2010; 49B:335-339.
19. Godhani DR, Jogel AA, Sanghani AM and Mehta JP: Synthesis & biological screening of 1,2,4-triazole derivatives. *Indian journal of chemistry* 2015; 54B:556-564.
20. Chu CH, Zhang Y, Zhang ZY, Li ZC and Liao RA: Synthesis & anti-fungal activities of ω-(5-aryl-1,2,4-triazol-3-thio)-ω-(1*H*-1,2,4-triazol-1-yl)acetophenones. *Indian Journal of Chemistry* 2000; 39B:791-793.
21. Narwade SK, Halnor VB, Dalvi NR, Gill CH and Karale BK: Conventional & ultrasound mediated synthesis of some thiadiazoles, triazoles & oxadiazoles. *Indian journal of chemistry* 2006; 45B: 2776-2780.
22. Holla BS, Poojary KN, Rao BS and Shivananda MK: New bis-aminomercaptotriazoles and bis-triazolothiadiazoles as possible anticancer agents. *European Journal of Medicinal Chemistry* 2002; 37:511–517.
23. Degorce S, Delouvrie B, Davey PRJ, Didelot M, Germain H, Harris CS, Brempt CL, Lebraud H and Ouvry G: Facile, diversity-orientated one-pot synthesis of ethyl 1,5-disubstituted-1*H*-1,2,4-triazole-3-carboxylates. *Tetrahedron Letters* 2012; 53: 6078–6082.
24. Husain A, Rashid M, Shaharyar M, Siddiqui AA and Mishra R: Benzimidazole clubbed with triazolo-thiadiazoles and triazolo-thiadiazines: New anticancer agents. *European Journal of Medicinal Chemistry* 2012; 1-14.
25. Yin P, Ma WB, Chen Y, Huang WC, Deng Y and He L: Highly Efficient Cyanoimidation of Aldehydes. *Organic Letters* 2009; 11(23): 5482-5485.
26. Xu Y, McLaughlin M, Bolton EN and Reamer RA: Practical Synthesis of Functionalized 1,5-Disubstituted 1,2,4-Triazole Derivatives. *Journal of Organic Chemistry* 2010; 75: 8666–8669.
27. Dalloul HM: Synthesis of new 1,2,4-triazole derivatives via 1,3-dipolar cycloaddition reaction of nitrilimines with hydrazones. *Canadian Chemical Transactions* 2015; 3(1): 108-117.
28. Al-Daeif YA: Synthesis of bis-heterocyclic phenyl containing 4-oxo-1,3-thiazolidine, 2,3-dihydrothiazole, 1,2,4-triazolo[3,4*b*]-1,3,4-thiadiazine and pyrazol derivatives. *Journal of Al-Nahrain University* 2011; 14 (2):67-74.
29. Jadhav HS, Talawar MB, Dhavale DD, Asthana SN and Krishnamurthy VN: Synthesis, characterization and thermolysis of 2,4-dihydro-2,4,5-trinitro-3*H*-1,2,4-triazole-3-one (DTNTO): A new derivative of 3-nitro-1,2,4-triazole-5-one (NTO). *Indian Journal of Engineering and Material sciences* 2005; 12:467-471.
30. Sharba HK, Al-Bayati RH, Aouad M and Rezki N: Synthesis of oxadiazoles, thiadiazoles and triazoles derived from benzo[*b*]thiophene. *Molecules* 2005; 10:1161-1168.
31. Kamotra P, Gupta AK, Gupta R, Somal P and Singh S: Microwave-assisted synthesis and biological activity of 3-alkyl/aryl-6-(1-chloro-3,4-dihydronaphth-2-yl)-5,6-dihydro-s-triazolo [3,4-*b*][1,3,4]thiadiazoles. *Indian Journal of Chemistry* 2007; 46B:980-984.
32. Khalil NSAM: N and S-α-L-arabinopyranosyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole: First synthesis and biological evaluation. *European Journal of Medicinal Chemistry* 2007; 42:1193-1199.
33. Sahu JK, Ganguly S and Kaushik A: Synthesis of some novel heterocyclic 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives as possible antimicrobial agents. *Journal of Applied Pharmaceutical Science* 2014; 4(2):81-86.
34. Hameed AA and Hassan F: Synthesis, characterization and antioxidant activity of some 4-amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol derivatives. *International Journal of Applied Science and Technology* 2014; 4(2):202-211.
35. Lakshman B and Gupta RL: Microwave assisted synthesis of some 4-amino-5-substituted aryl-3-mercapto-(4*H*)-1,2,4-triazoles. *Asian Journal of Chemistry* 2009; 21(1):86-92.
36. Joshi SS and Karnik AV: Rapid and efficient microwave-assisted synthesis of 4-amino-3-mercapto-5-substituted-1,2,4-triazoles. *Indian Journal of Chemistry* 2006; 45B:1057-1059.
37. Kamel MM and Abdo NYM: Synthesis of novel 1,2,4-triazoles, triazolothiadiazines and triazolothiadiazoles as potential anticancer agents. *European Journal of Medicinal Chemistry* 2014; 86:75-80.
38. Upmanyu N, Kumar S, Kharya MD, Shah K and Mishra P: Synthesis and anti-microbial evaluation of some novel 1,2,4-triazole derivatives. *Acta Poloniae Pharmaceutica n Drug Research* 2011; 68(2):213-221.
39. Karegoudar P, Prasad DJ, Ashok M, Mahalinga M, Poojary B and Holla BS: Synthesis, antimicrobial and anti-inflammatory activities of some 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles and 1,2,4-triazolo [3,4-*b*][1,3,4]thiadiazines bearing trichlorophenyl moiety. *European Journal of Medicinal Chemistry* 2008; 43:808-815.
40. Chidananda N, Poojary B, Sumangala V, Kumari NS, Shetty P and Arulmoli T: Facile synthesis, characterization and pharmacological activities of 3,6-disubstituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles and 5,6-dihydro-3,6-disubstituted-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles. *European Journal of Medicinal Chemistry* 2012; 51:124-136.

41. Husain A and Naseer MA: Studies on fused heterocyclic 3,6-disubstituted-1,2,4-triazolo-1,3,4-thia-diazoles: synthesis and biological evaluation. *Med Chem Res* 2011; 20:47–54.
42. Invidiata FP, Furno G, LampRonti I and Simoni D: 1,2,4-triazoles. Improved synthesis of 5-substituted-4-amino-3-mercapto-(4*H*)-1,2,4-triazoles and a facile route to 3,6-disubstituted-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles. *Journal of Heterocyclic Chemistry* 1997; 34:1255-1258.
43. Ozil1M, Bodur O, Ulker S and Kahveci B: Microwave-promoted synthesis and biological activity of some 2-hetarylmethyl-4-(4-hetarylphenyl)-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one derivatives. *Chemistry of Heterocyclic Compounds* 2015; 51(1):88-96.

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