Recent advances in the synthesis of triazole derivatives

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Avances recientes en la síntesis de los derivados de triazol

Avanços recents en la síntesi dels derivats de triazol

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RESUMEN

El sistema anular del triazol ha tenido y tiene un creciente interés para los químicos orgánicos y para aquellos que trabajan con compuestos medicinales ya que dispone de un potencial versátil en la interacción con los sistemas biológicos. Los compuestos de triazol poseen una gama amplia de actividades biológicas y se centran especialmente en la función antifúngica. En este artículo hemos resumido los desarrollos recientes en las metodologías sintéticas de este sistema anular. Principalmente se trata de metodologías que se ocupan de síntesis fáciles y apropiadas

Palabras clave: 1,2,3-triazol; 1,2,4-triazol; reacciones de acoplamiento azidas-alquinos; hidrazidas.

SUMMARY

Triazole ring system has attracted a continuously growing interest of synthetic organic chemists and those dealing with the medicinal compounds due to its versatile potential to interact with biological systems. The triazole compounds possess a wide range of biological activities and are especially focused for antifungal behavior. In this review article, we have summarized the recent developments in the synthetic methodologies of this ring system. The main focus was on the methodologies which deal with the facile and convenient synthesis.

Key Words; 1,2,3-triazole; 1,2,4-triazole; azide-alkyne coupling reactions; hydrazides

RESUM

El sistema anular del triazol continua tenint un interès creixent per els químics orgànics i per tots aquells que treballen amb compostos medicinals degut al seu potencial versàtil en la interacció amb els sistemes biològics. Els compostos de triazol tenen una varietat amplia d'activitats biològiques i es concentren especialment en la funció antifúngica. En aquest article hem fet un resum dels recents desenvolupaments en metodologies sintètiques d'aquest sistema anular. Es tracta principalment de metodologies que s'ocupen de síntesis fàcils y convenients.

Paraules clau: 1,2,3-triazol; 1,2,4-triazol; reaccions d'acoblament azides-alquins; hidrazides.

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1.1 INTRODUCTION

Triazole ring system has got considerable fame due to the versatile biological activities of a huge number of its derivatives. Many of such compounds are important as agrochemicals [1-3]. There is a continuous need for the development of new drugs as the currently available drugs are becoming ineffective due to the drug resistance developed by pathogens. Moreover, life threatening infections caused by pathogenic fungi are increasingly becoming very common [4-6]. Triazole compounds have shown a great efficacy against antifungal infections. In 1944, Woolly discovered excellent antifungal properties of azole derivatives which led to the invention of fluconazole, variconazole, albaconazole and itraconazole [7-10]. Further structural modifications of this ring system are expected to result in potential candidates for antifungal agents. These modifications are carried out by using different functionalities, aliphatic chains, aromatic rings and heterocyclic ring systems *etc.* [11-14].

The mechanism of inhibition of fungal growth is well established and it is found that azoles perform their antifungal action in two steps: inhibition of ergosterol synthesis, a major component of fungal membrane and second step involves the blocking of P450-dependent enzyme *i.e.,* lanodterol 14-α- demethylase (CYP 51). [15] The 3D model of CYP 51 obtained on the basis MTCYP51 (*M.Tuberclosis 14-α-demethylase*) showed that triazole ring coordinated to the heme iron of CYP51,a key step in antifungal activity of triazole. [16] Lack of ergosterol and accumulation of 14-α-demethylase disfunctionalize the fluidity of several enzyme located in membrane which result in inhibition of fungal growth and replication of its DNA.

1.2 Synthetic routes of triazole ring system

Triazole ring system is currently being prepared by various synthetic methodologies. It exists in two isomeric forms; 1,2,3-triazole and 1,2,4-triazole.

1.2.1 Synthetic methodologies for 1,2,3-triazoles

1.2.1.1. 1,3-Dipolar cycloaddition reactions of azides

Classic Huisgen reaction which involved thermal 1,3-dipolar cycloaddition of alkynes to azides [17]. This cycloaddition reaction usually affords mixtures of 1,4- and 1,5-disubstituted 1,2,3-triazoles [18,19]. This method has been widely used for the incorporation of 1,2,3-triazole ring in a broad range of molecules. The molecule must contain a terminal alkyne, which on treatment with an azide undergo cycloaddition reaction. Recent reports using this methodology are summarized below: In this respect, the classic 1,3-dipolar cycloaddition fails as a true click reaction.

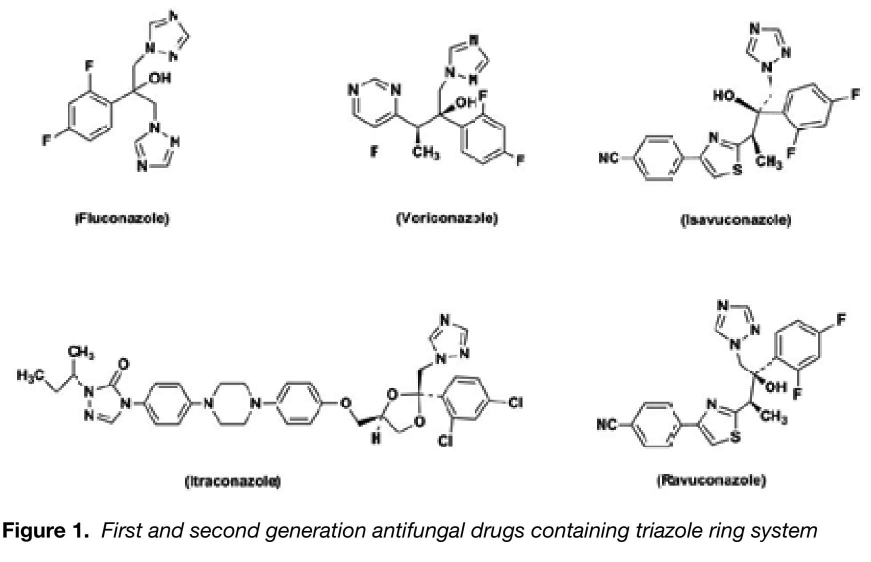
1.2.1.1.1 1,3 Dipolar cycloaddition reactions of azides catalyzed by copper salts

Sharpless [20] and Meldal [21] reported, that 1,4-disubstituted 1,2,3-triazoles with high regioselectivity, are specifically prepared from azides and terminal alkynes under copper (I) catalysis which follows a different mechanism can be conducted under aqueous conditions, even at room temperature. In the mechanism proposed by Sharpless for this reaction, the copper (I) ion is inserted into the terminal alkyne, forming the copper (I) acetylide; this compound reacts with an organic azide and a subsequent rearrangement forms the 1,2,3-triazole product. Because of the existence of copper (I) acetylide , the reaction was regiospecific and only the 1,4-disubstituted 1,2,3-triazole was formed. A copper catalyzed Huisgen reaction complies fully with the definition of click chemistry and is a widespread tool in click chemistry.

The regioisomeric 1,5-disubstituted triazoles are available from azides and terminal alkynes by the use of either magnesium acetylides or ruthenium catalysts. There are a huge number of triazole compounds reported by using this method.

A novel disubstituted [1,2,3]-triazoles were synthesiszed by Wu *et al*. Effectiveness of 1,3-dipolar cycloaddition reaction was enhanced by treating the fluoro-alkylated azides **1** with terminal alkynes **2** (**Figure 2**). Completions of the reaction only lead to the regioselective formation of fluoroalkylated 1,4-disubstituted [1,2,3]-triazoles **3** in the presence of Cu(I) salt as catalyst. [22,23]

Triazole containing monomer *i.e.,* 2-(1-naphthalen-1-yl-methyl-1*H*-[1,2,3]triazol-4-yl)-ethyl methacrylate (NTEMA) **7** was prepared by Jin and his coworkers by using click chemistry and was further subjected to polymerization (**Figure 3**) [24].



(Fluconazole) (Voriconazole) (Isavuconazole)

(Itraconazole) (Ravuconazole)

Figure 1. *First and second generation antifungal drugs containing triazole ring system*

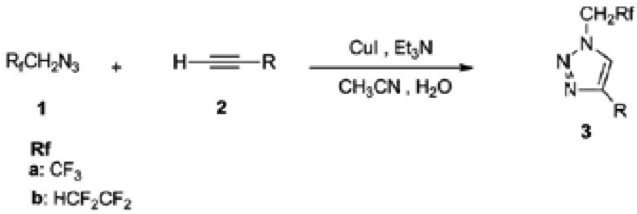


Figure 2. *Synthetic layout for disubstituted [1,2,3]-triazoles by reaction of fluoro-alkylated azides 1 with terminal alkynes* ***2***

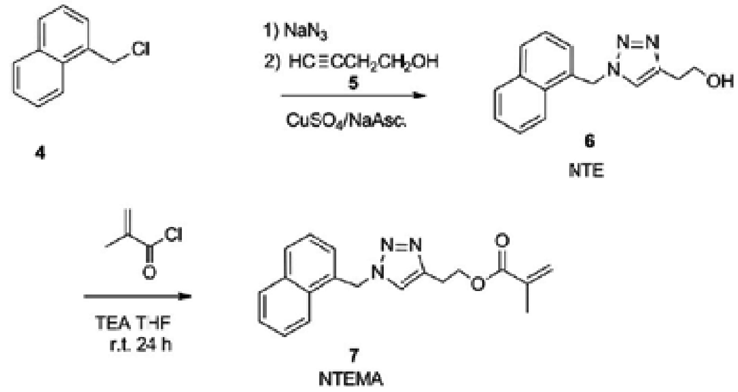


Figure 3. *Click chemistry synthetic route of 2-(1-naphthalen-1-ylmethyl-1H-[1,2,3]triazol-4-yl)-ethyl methacrylate* **(NTEMA) 7**

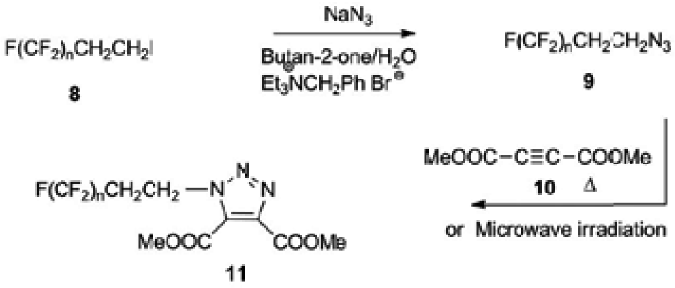


Figure 4*. Synthetic route for fluoroalkylated 1,2,3-triazoles* ***11***

Mayto *et al* reported the synthesis of novel series of fluoroalkylated 1,2,3-triazoles **11** starting from the commercial available 2-perfluoroalkyl-1-iodoethanes **8** and sodium azides to get the 2-perfluoroalkyl-ethylazides **9** followed by its 1,3-dipolar cycloaddition with acetylenic esters **10** or acids. Microwave irradiation (750 W) under solvent free conditions is also very effective. Acetylenic diacids react in refluxing acetone affording the desired compounds (**Figure 4**). Physicochemical study of synthesized compounds showed surfactant behavior [25].

Potewar *et al* obtained 1,2,3-triazole-sucrose derivatives **13** by cycloaddition reaction of sucrose azides and terminal alkynes (**Figure 5**) [26].

Similar approach was used by Odlo *et al.,*[27]; Piotrowska *et al.,*[28]; Pospieszny *et al.*, [29]; Ciocoiu *et al.*, [30,31]; Wilkinson *et al*., [32]; Sreedhar *et al.,* [33]; Li *et al*., [34,35]; Castro *et al*., [36]; Bokor *et al*., [37] in the syntheses of **12**, **13**, **14**, **15**, **16**, **17**, **18**, **19** (**Figure 6**).

1.2.1.1.2 Modifications in the alkyne-azide cycloaddition reaction

(a)Using tap water as solvent

By using magnetically separable and reusable copper ferrite nano particles in a one pot reaction and tap water as the reaction medium, kumar and his coworkers obtained aryl substituted 1,4-disubstituted 1,2,3-triazoles **24** (**Figure 7**). On completion of the reaction, the catalyst was magnetically separated from the reaction mixture, using an external magnet [38].

(b) Using quaternary ammonium salt

Jervis *et al* reported benzotriazole-containing analogue **27** using [3+2] dipolar cycloaddition of 6'-azido-6'-deoxy-$\alpha\beta\beta$-galactosyl ceramide **25** with in situ-generated benzyne intermediate instead of alkynes. Reaction was carried out by mixing azide and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate in the presence of TBAF (**Figure 8**) [39].

(c) Synthesis of 1,2,3-triazole-derived naphthalimides.

Click chemistry led to the synthesis of 1,2,3 triazole bearing counter part of napthalamides as reported by Lv *et al*. Key intermediate diprop-2-ynylamino-naphthalimide **30** synthesized from 4-bromo-1,8-naphthalic anhydride was treated with corresponding halogen-substituted aryl azides in the presence of copper to yield 1,2,3-triazole-derived naphthalimides **31**(**Figure 9**) [40].

(d)Synthesis of triazole analogues of chalcones

Mesenzani *et al* reported that olefinic bond in chalcons can be substitued by stable hetrocyclic compounds like

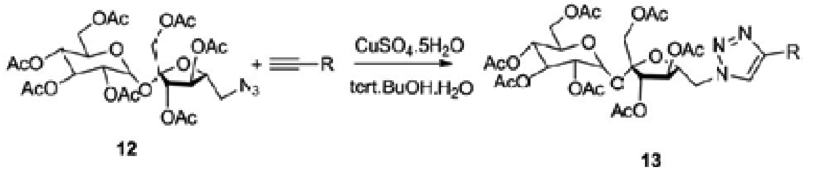


Figure 5. *Cycloaddition synthetic route for 1,2,3-triazole-sucrose derivatives*

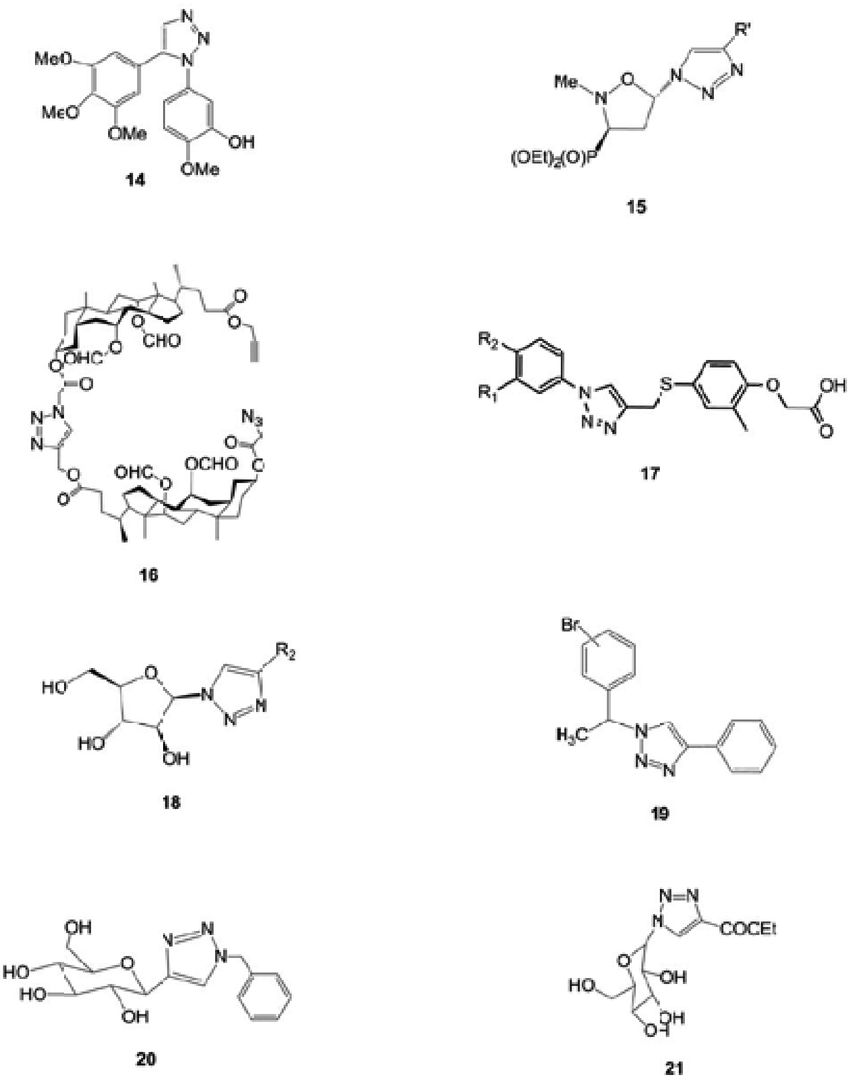


***Figure 6**. Structures of novel 1,2,3-triazole derivatives by 1,3-cycloaddition reactions*

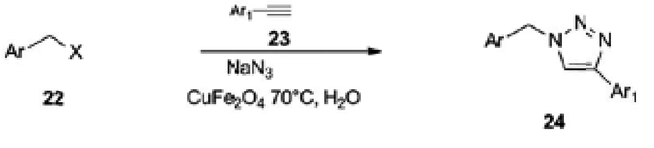


Figure 7. *One pot synthesis of 1,4-disubstituted 1,2,3-triazoles* **24** *using tap water as solvent*

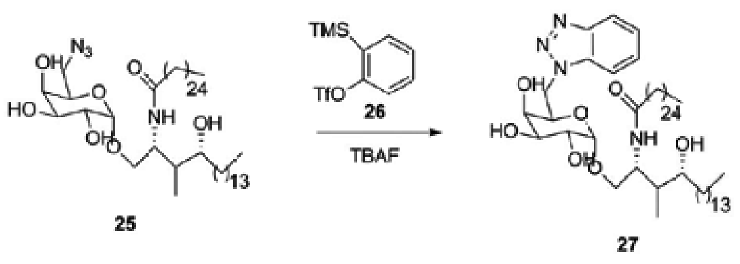


Figure 8. *Cycloaddition synthetic route for benzotriazole-containing analogue* **27** *by using quaternary ammonium salt*

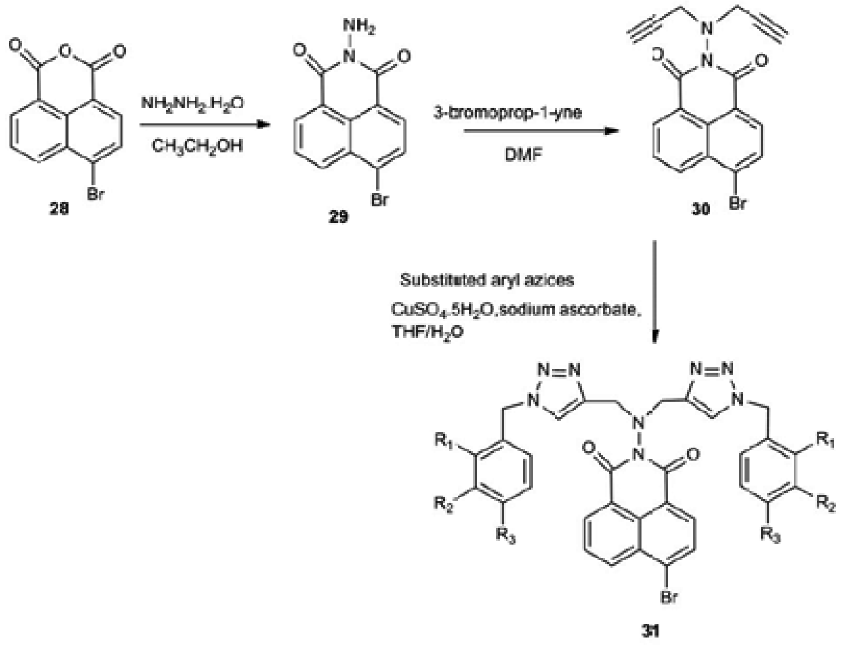


Figure 9. *Click chemistry synthetic route for 1,2,3 triazole-derived naphthalimides*

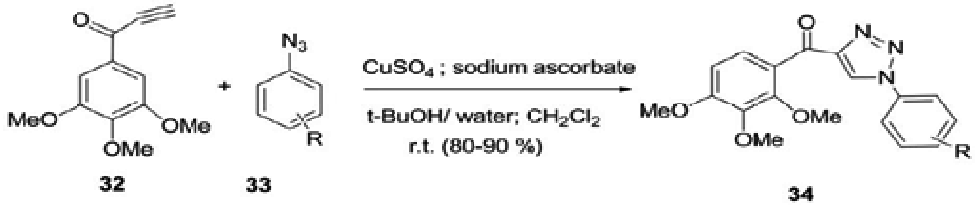


Figure 10. *Synthetic route for triazole analogues of chalcones*

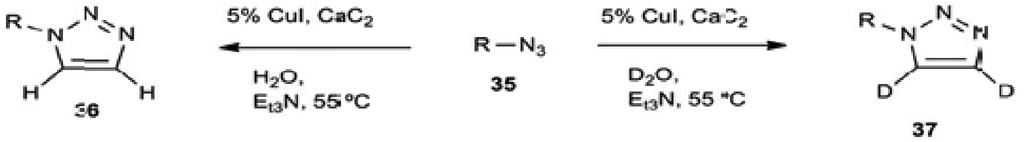


Figure 11. *Synthetic layout for fully deuterated analogs 1-monosubstituted 1,2,3-triazoles via copper-catalyzed azide-alkyne cycloaddition*

triazole and tetrazole. Cycloaddition reaction proposed by sharpless and folkins [41] between ynone **32** and aryl azides **33**
was used to prepare the target compounds (**Figure 10**) [42].

(e) Synthesis of deuterated analogues of triazoles
Copper-catalyzed azide-alkyne cycloaddition (CuAAC) for tiazole synthesis undergo several improvements due to its high efficiency. Based upon this frame work, Gonda *et al* exclusively developed wide variety of fully deuterated analogs 1-monosubstituted 1,2,3-triazoles **36** and **37** via copper catalyzed reaction. Secondary azides **35** were allowed to react with acetylene generated in situ from CaC$_2$ in the presence of H$_2$O or D$_2$O (**Figure 11**) [43].

(f) By Coupling azide and acetyl acetone
Kamalraj *et al* reported the synthesis of regioisomers of 1-aryl-4-acetyl-5-methyl-1,2,3-triazole **41** by 1,3 dipolar cycloaddition of benzyl azide **39** with acetyl acetone **40** under basic condition in ethanol (**Figure 12**). All the synthesized compounds showed fluorescent behavior [44].

Similarly arylazide **42** were cyclized with ß-ketoesters **43** under basic condition to yield conformationally restricted 1,5-diaryl-1,2,3- triazole-4-carboxylates **44** (**Figure 13**) [45].

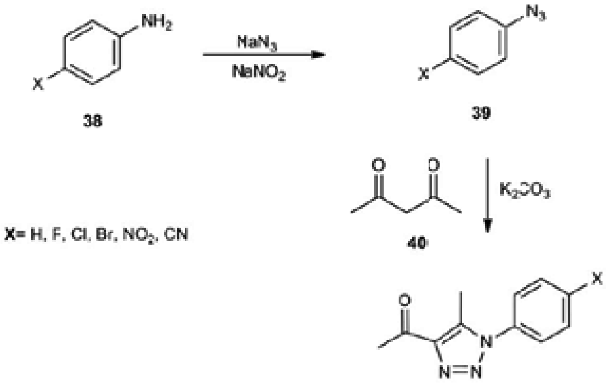


Figure 12. *Synthetic route for regioisomers of 1-aryl-4-acetyl-5-methyl-1,2,3-triazole* **41**

(g)Synthesis of 1,2,3- triazole containing coumarin derivatives

Zhang *et al* utilized click chemistry to report the coumarin derivatives containing 1,2,3-triazole **47** by following 1,3 dipolar cycloadditon reaction of 4-azido-coumarin **45** and alkynes **46** using copper sulphate as catalyst (**Figure 14**). The fact of high reactivity and yield (60-80%) of coumarin derivatives may be attributed to the additional hydrogen boding with active site of receptor due to additional carbonyl group of coumarine ring system [46].

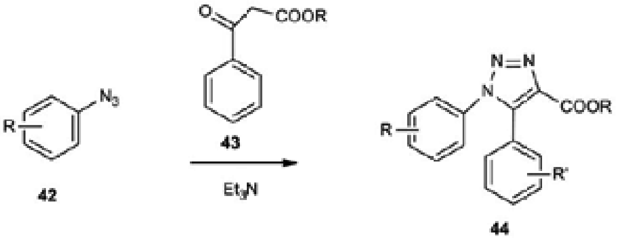


Figure 13. *Synthesis of 1,5-diaryl-1,2,3- triazole-4-carboxylates* **44**

(h) Synthesis of 1,2,3-Triazole Containing Glycosides

Chen *et al* reported the stereo selective methodology for 1-glucosyl-4-heterocyclyl-5-(*p*-substituted-phenyl)-1,2,3-triazoles **51** by reaction of 2-Aroylmethylene-hexahydro- pyrimidines **48** with 2,3,4,6-tetra-*O*-acetyl-b-D-glucopyranosyl azide **49** (**Figure 15**). Diazepine also reacted with azide to produce the same linkage. *N*-glucosylic compound were found to possess antitumour and antiviral activities [47].

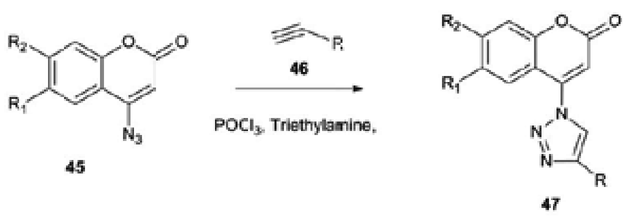


Figure 14. *Synthesis of novel 1,2,3- triazole containing coumarin derivatives*

(i) Synthesis of 1,2,3-triazoles derived from heterocyclic ketene aminals (HKAs)

Yan and his coworkers reported catalyst free one-pot synthesis of novel 1,3-diazoheterocycle fused 1,2,3-triazole derivatives **54** as antitumor agents via 1,3-dipolar cycloaddition of heterocyclic ketene aminals (HKAs) **52** or *N*,*O*-acetals with sodium azide and polyhalo isophthalonitriles **53** at room temperature (**Figure 16**) [48].

(j) Synthesis of dihydropyrrolo 1,2,3-triazoles

Durust *et al* reported the synthetic layout for a series of novel oxadiazolyl pyrrolo triazole diones by 1,3-dipolar cycloaddition reaction of 5-azidomethyl 3-aryl substituted-1,2,4-oxadiazoles **58** and *N*-phenyl maleimide results in the formation of 1,6-α-dihydropyrrolo[1,2,3]triazole-(3,5)-diones **59** (**Figure 17**) [49].

(k) Synthesis of *N*-substituted-phenyl-4-difluoromethyl-1,2,3-triazoles

Costa *et al* reported novel *N*-substituted-phenyl-1,2,3-triazole-4-carbaldehydes **62**. Cycloaddition reactions between diazomalonaldehyde **60** and aniline hydrochlorides **61** in water were effectively used to prepare the *N*-substituted-phenyl-1,2,3-triazole-4-carbaldehydes (**Figure 18**). The privileged activity of the targeted compounds against

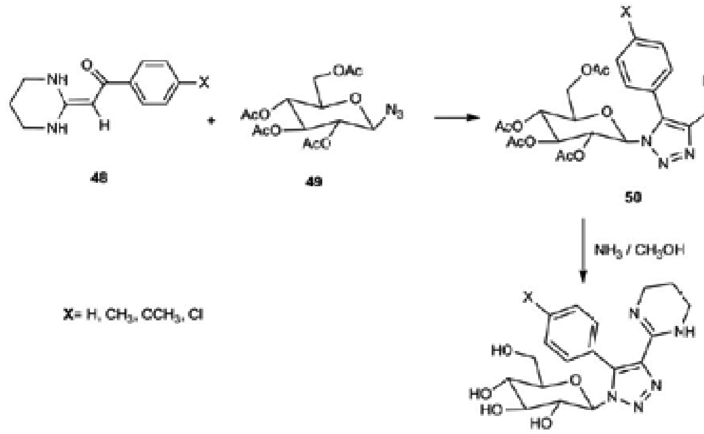
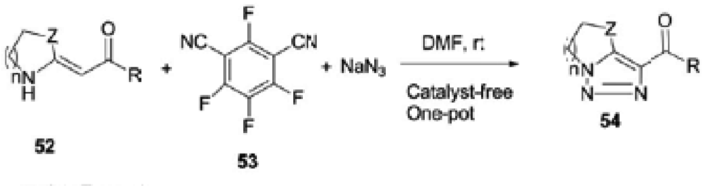


Figure 15. *Stereoselective synthesis of 1-glucosyl-4-heterocyclyl-5-(p-substituted-phenyl)-1,2,3-triazoles* **(51)**



n=1,2; Z=NH,O
R=Me; p-MeOPh, p-MePh, Ph, p-ClPh

Figure 16. *Catalyst free one-pot synthesis of novel 1,3-diazoheterocycle fused 1,2,3-triazole derivatives* **54**

M. avium and *M. maomoense* is very promising, considering the high pathogenicity of these strains [50].

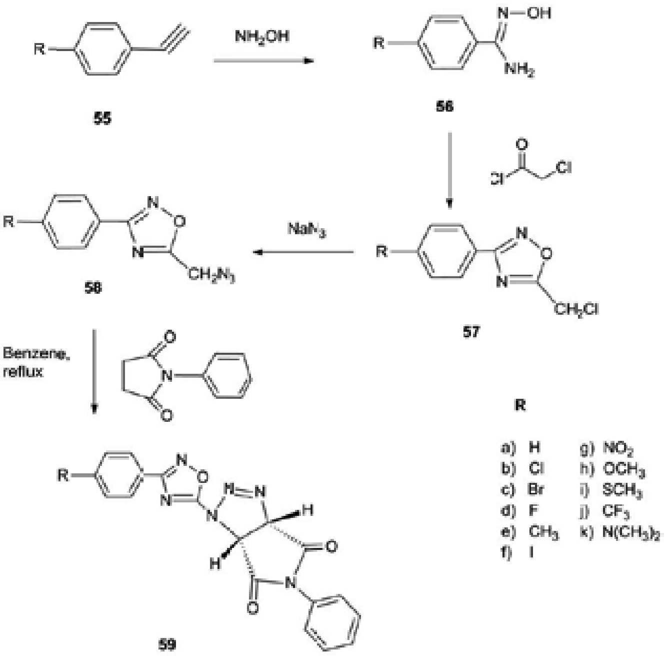


Figure 17. *Synthetic layout for a series of novel oxadiazolyl pyrrolo triazole diones*

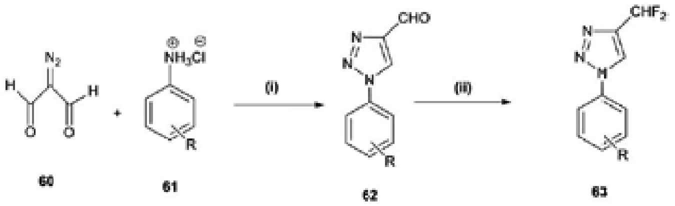


Figure 18. *Cycloaddition synthetic layout for novel N-substituted-phenyl-1,2,3-triazole-4-carbaldehydes* **62**

1.2.1.2. Synthesis of 1,2,3-triazoles from α-diazoimines
Jordao *et al* prepared new series of arysubstituted-1*H*-1,2,3-triazole derivatives **68** and evaluated their ability to inhibit the in vitro replication of HSV-1. Intermolecular 1,5-electrocyclization of β-substituted α-diazocarbonyl compounds is also a most convenient rout to synthesize triazole moiety. This methodology involves two pathways: (i) starting from β -amino-α,β-unsaturated ketones or esters followed by a diazo transfer reaction (pathway I) and (ii) starting from α-diazocarbonyl compounds followed by α-diazoimino formation (pathway II) (**Figure 19**) [51].

(l) Synthesis of 1*H*-1,2,3-triazole from α-diazo-1,3-dicarbonyl compounds
Condensation reaction of amine with α-diazo-1,3-dicarbonyl compounds gives 1*H*-1,2,3-triazole is often superior to cycloaddition reaction of acetylene and azide due to its simplicity and regiospecificity. Dabak *et al* condensed the α-diazo-1,3-dicarbonyl compound **69** with different amines **70** to yield 4-acyl-1*H*-1,2,3-triazole derivatives **71**(**Figure 20**) [52].

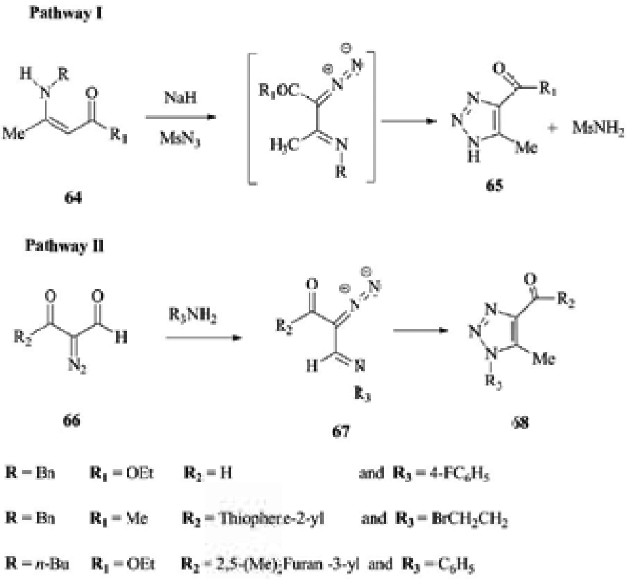


Figure 19. *Two synthetic pathways for 1,2,3-triazoles from α-diazoimines*

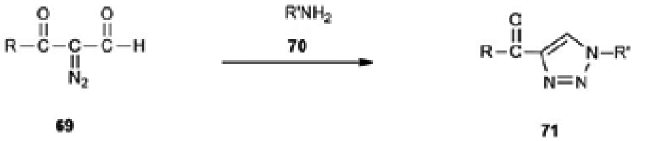


Figure 20. *Synthesis of 1H-1,2,3-triazole from α-diazo-1,3-dicarbonyl compounds*

(m) Synthesis of 1,4,5-trisubstituted-1,2,3-triazoles
Diazotization of diaminomaleonitrile (DAMN) **74** with 4-Nitrophenyl diazonium salt **75** provided an efficient approach for synthesis of 1,4,5-trisubstituted-1,2,3-triazoles **76** under mild conditions(**Figure 21**). Isolated product was utilized as precursor for the variety of transformations [53].

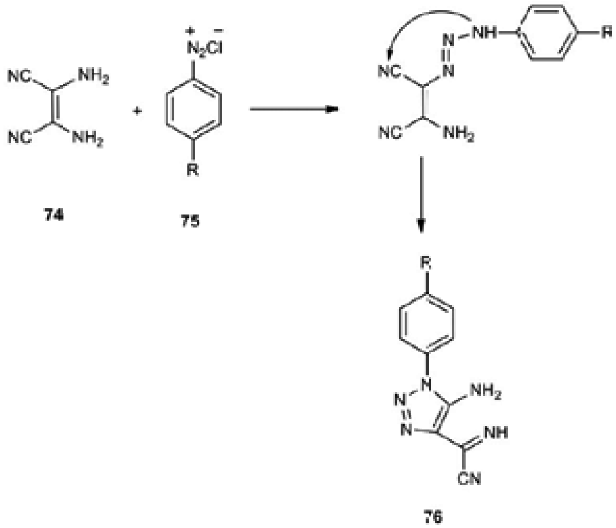
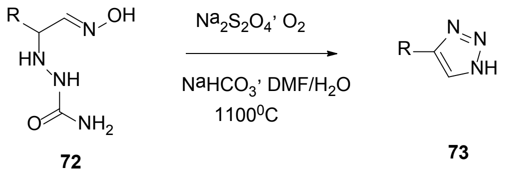


Figure 21. *Diazotization synthetic approach for of 1,4,5-trisubstituted-1,2,3-triazoles* **76**

1.2.1.3. From arylglyoxaldoxime
Recently, He *et al* reported a novel approach for the one pot synthesis of 4-aryl-1*H*-1,2,3-triazoles without azides

and metal catalization. The efficient procedure involves deprotection of arylglyoxaldoxime by using sodium dithionite under basic conditions. The best yields of triazole was obtained in DMF/H$_2$O as reaction medium (**Figure 22**) [54].



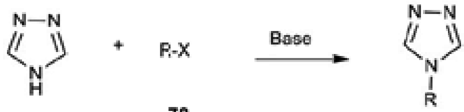
72 73

Figure 22. *One pot synthesis of 4-aryl-1H-1,2,3-triazoles*

1.2.2 Synthetic methods for 1,2,4-triazole compounds

1.2.2.1. By *N*-Alkylation of 1,2,4-triazole compound

This methodology deals with the incorporation of 1,2,4-triazole ring system to the molecules being active functionality of a nucleophilically replaceable leaving group (**Figure 23**).



77 78 79

Figure 23. *Synthesis of N-Alkylated derivatives of 1,2,4-triazole*

Many scientists utilized this technique for the synthesis of bioactive molecules, like Qin *et al* synthesized plant growth regulators (**80 & 81**), [55-57] Wang and his coworkers synthesized **82 & 83** (**Figure 24**) [58].

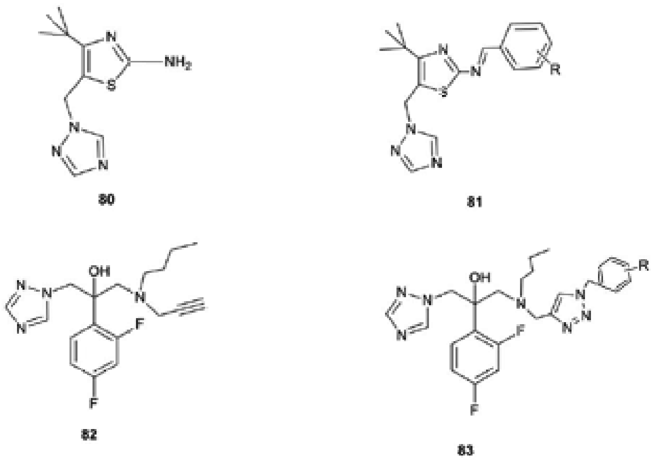


Figure 24. *Structures of N-Alkylated derivatives of 1,2,4-triazole as plant growth regulators*

1.2.2.2. Through thiosemicarbazide intermediate

A convenient route for the synthesis of 1,2,4-triazole derivatives is through the synthesis of thiosemicarbazide intermediate **86** (**Figure 25**).

The route has resulted in enormous compounds having wide variety of applications especially in the biological active synthesis.

Plech *et al* synthesized these compounds **89 & 90** as antimicrobial agents, [59] Siddiqui *et al* synthesized **91** as antihypertensive agents, [60] Zong *et al* prepared **92**, [61] Senthilvelan *et al* [62] synthesized 1,2,4-triaozle based benzothiazines **93**,**94** obtained through photocyclization/photodesulfurisation. Koparir *et al* reported the **95** [63], Patel and Park also reported **96** (**Figure 26**) [64].

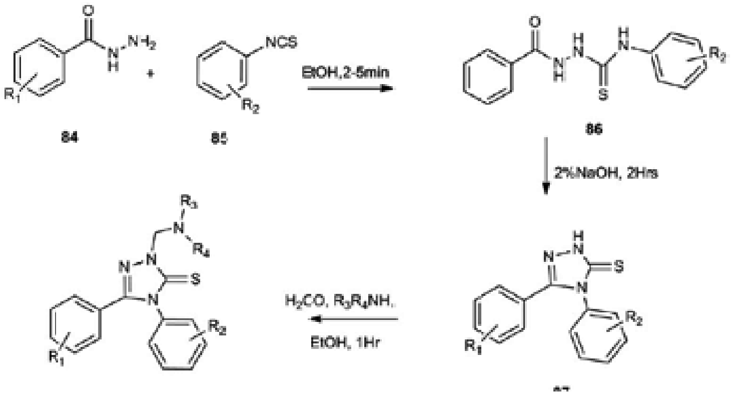


Figure 25. *Synthetic methods for 1,2,4-triazole derivatives via thiosemicarbazide intermediate* **(86)**

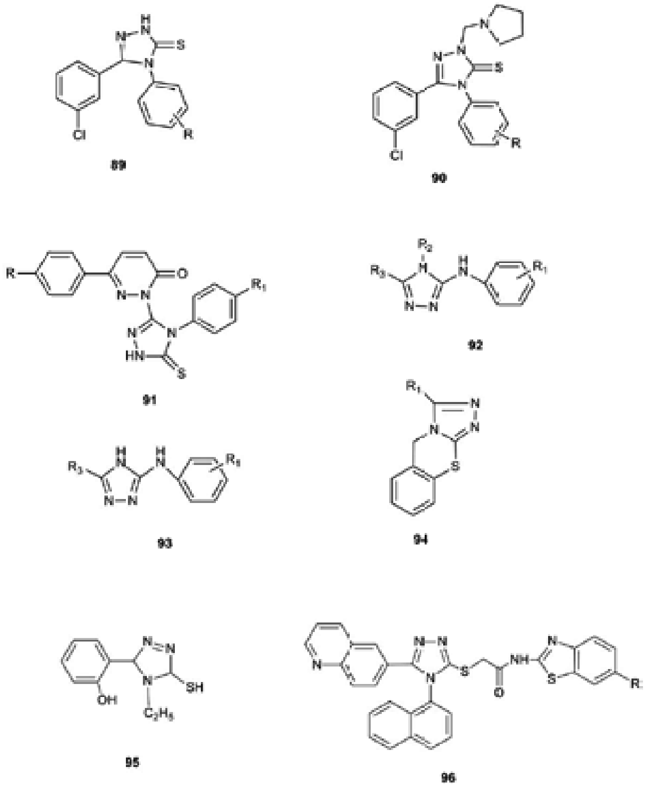


Figure 26. *Structures of biological synthesized 1, 2, 4-triazole derivatives*

1.2.2.3. Through potassium salt of hydrazinecarbodithioates

Another efficient method for the formation of triazole ring system is through carbohydrazide **99** intermediate which when treated with carbon disulfide results in the formation of potassium salt of hydrazinecarbodithioates. It is cyclized with hydrazine hydrate to form 1,2,4-triazole ring with active functionalities of amino and SH (**Figure 27**). These compounds are the precursors for thousands of Schiff bases potent for antifungal drugs.

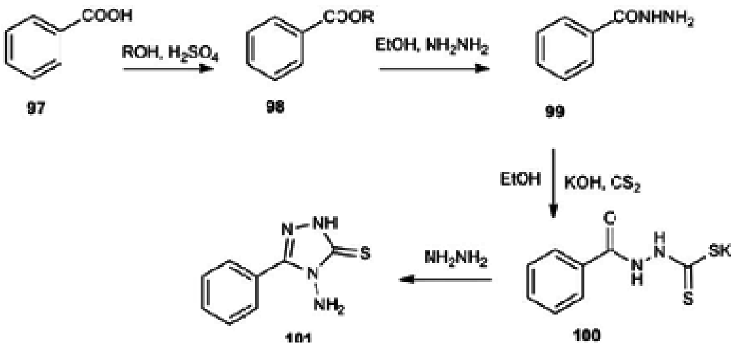


Figure 27. *Synthesis of 1,2,4-triazole derivatives through potassium salt of hydrazinecarbodithioates*

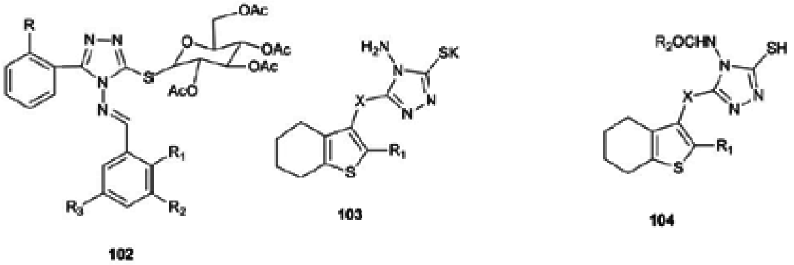


Figure 28. *Structures of biological active 1,2,4-triazole derivatives having S-β-D-glucosides and cyclohexyl thiophenes moieties*

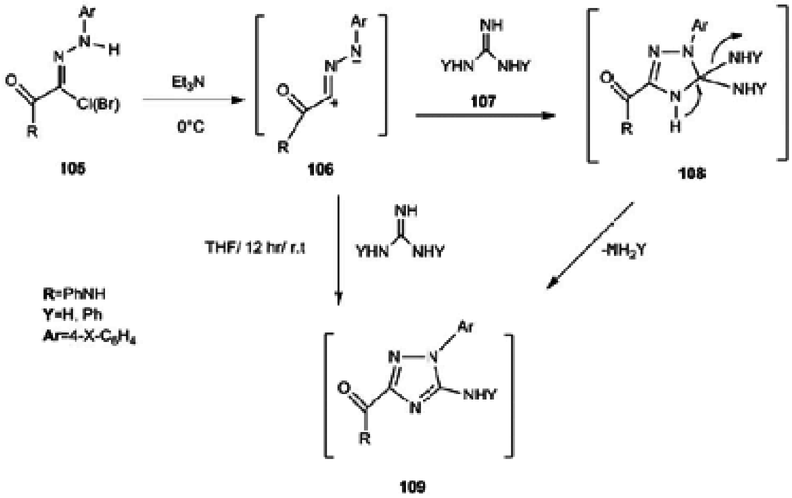


Figure 29. *Synthetic layout of novel 1,3,5-trisubstituted-1,2,4-triazoles* **109**

Figure 30. *Synthesis of 4-(pyrid-4-yl)-1,2,4-triazole (pytz)*

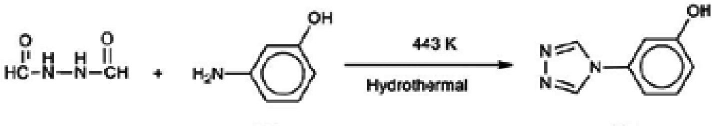


Figure 31. *Synthesis of (m-phenol)-1,2,4-triazole (ptr) 115*

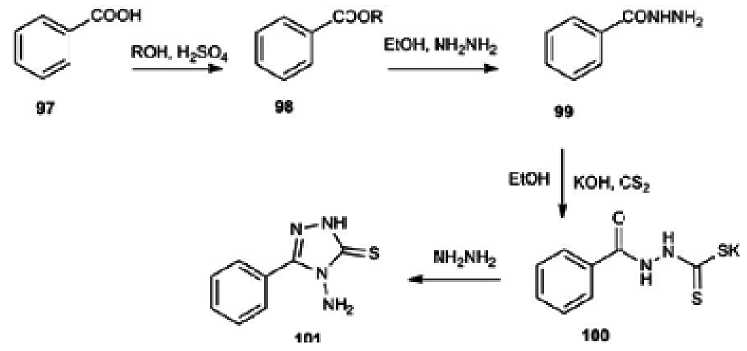


Figure 27. *Synthesis of 1,2,4-triazole derivatives through potassium salt of hydrazinecarbodithioates*

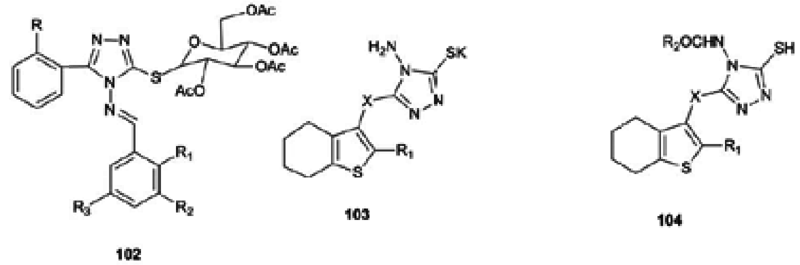


Figure 28. *Structures of biological active 1,2,4-triazole derivatives having S-β-D-glucosides and cyclohexyl thiophenes moieties*

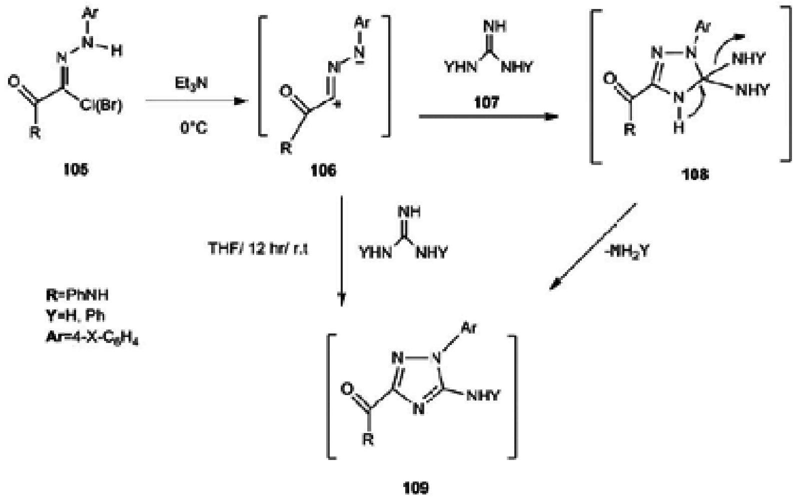


Figure 29. *Synthetic layout of novel 1,3,5-trisubstituted-1,2,4-triazoles* **109**

Figure 30. *Synthesis of 4-(pyrid-4-yl)-1,2,4-triazole (pytz)*

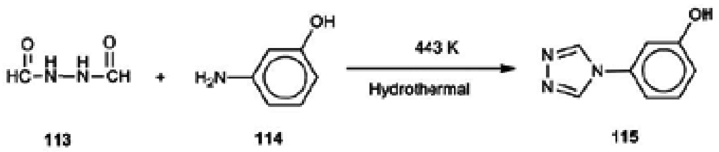


Figure 31. *Synthesis of (m-phenol)-1,2,4-triazole (ptr) 115*

Using this methodology, Ji *et al* reported an efficient synthesis of S-β-D-glucosides of 5-aryl-1,2,4-triazole-3-thiones derivatives **102** with significant biological activities [65]. Shiradkar *et al* obtained methyl linked cyclohexyl thiophenes with triazole **103 & 104** as possible candidate for the treatments of Alzheimer's disease (**Figure 28**) [66].

1.2.2.4. Synthesis of 1,3,5-trisubstituted-1,2,4-triazoles

Dalloul reported the synthetic layout of novel 1,3,5-trisubstituted-1,2,4-triazoles **109** by 1,3-dipolar cycloaddition reaction of *C*-phenyl amino-carbonyl-*N*-arylnitrilimines with guanidine derivatives via 5,5-diamino-1,2,4-triazoles **108** as an intermediate through nucleophilic addition of electron pair of the imino group of guanidine followed by the cyclization at the imine carbon, or by cycloaddition onto C,N of the guanidine moiety (**Figure 29**). Final compound exhibited antimicrobial activities [67].

1.2.2.5. Synthesis of 4-(pyrid-4-yl)-1,2,4-triazole (pytz)

Tahli *et al* synthesized the triazole lignds based complexes using dimethyl acetamide or dimethyl-formamide as a solvent. The potentially tritopic bridging ligand 4-(pyrid-4-yl)-1,2,4-triazole (pytz) **112** further reacts with cadmium (II) nitrate tetrahydrate, $Cd(NO_3)_2.4H_2O$ and sodium dicyanamide (Na-dca) to form the molecular complex $[Cd(dca)_2(kNpy\text{-}pytz)_2(H_2O)]_2$. The pytz ligand coordinates through the nitrogen of pyridine to the metal atom (**Figure 30**) [68].

1.2.2.6. By treating diformylhydrazine with anilines

Liu *et al* reported the synthesis of triazole based coordination polymers and four triazole-bridging coordination complexes. Diformyl- hydrazine **113** and *m*-aminophenol **114** were used to prepare (*m*-phenol)-1,2,4-triazole (*ptr*) **115**. Cu and Zn metal possessed antiferromagnetic interaction with triazole-bridging coordination complexes (**Figure 31**) [69].

1.2.2.7. Synthesis of 1,2,4-triazoles by oxidative intramolecular cyclization of heterocyclic hydrazones

Ciesielski *et al* explored the synthesis of novel series of 1,2,4-triazoles by oxidative intramolecular cyclization of heterocyclic hydrazones with copper dichloride. General applicability of this simple transformation was confirmed by the synthesis of moderate to high yields of 1,2,4-triazolo[4,3-*a*]pyridines and 1,2,4-triazolo [4,3-*a*] pyrimidines. A 1,2,4-triazolo[4,3-e]purine-6,8 (7*H*)-dione was obtained in a lower yield. Hydrazones of aromatic and aliphatic aldehydes with both electron-withdrawing and electron-donating substituents were oxidized to give the corresponding fused 1,2,4-triazoles (**Figure 32**) [70].

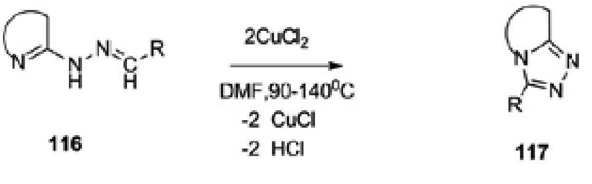


Figure 32. *Oxidative intramolecular cyclization of heterocyclic hydrazones as a synthetic approach for fused 1,2,4-triazoles derivatives*

1.2.2.8. From 1,3-disubstituted thioureas

Guin *et al* reported a regioselective approach, mediated by iodine for tandem synthesis of 1,2,4-triazoles. Synthesis was achieved by 1,3- disubstituted thioureas **118** using molecular iodine. In this one-pot strategy, the intermediate carbodiimide generated in situ from thiourea upon reaction with $HCONHNH_2$ gave diaryl/alkylhydrazine-carboximidamide or acylureidrazone, which then undergoes an intramolecular cyclodehydration to afford the corresponding 3-amino-[1,2,4]-triazole **119** (**Figure 33**) [71].

Figure 33. *Regioselective synthetic approach for 3-amino-[1,2,4]-triazole* **(119)**

1.2.2.9. From 2,2,2-trichloroethylImidate

Mangarao *et al* employed 2,2,2-TrichloroethylImidate for the synthesis of 1,2,4-triazole ring system under environmental friendly conditions *i.e.,* ethylene glycol as a solvent (**Figure 34**). PTSA served as a catalyst for this conversion [72].

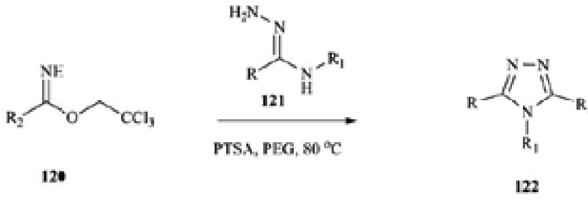


Figure 34. *Environmental friendly synthetic approach for 1,2,4-triazole ring system*

1.2.2.10 Synthesis of D-glucopyranosyl-1,2,4-triazole-3-thione.

Li *et al* reported a series of D-glucopyranosyl-1,2,4-triazole-3-thione. Schiff base of 1,2,4- triazole, obtained through multistep synthesis using benzohydrazide as starting material were mixed with 2,3,4,6-tetra-*O*-acetyl-s-D-glucopyranosyl bromide in ethanol to obtained biologically active derivatives in 50 % yield (**Figure 35**) [73].

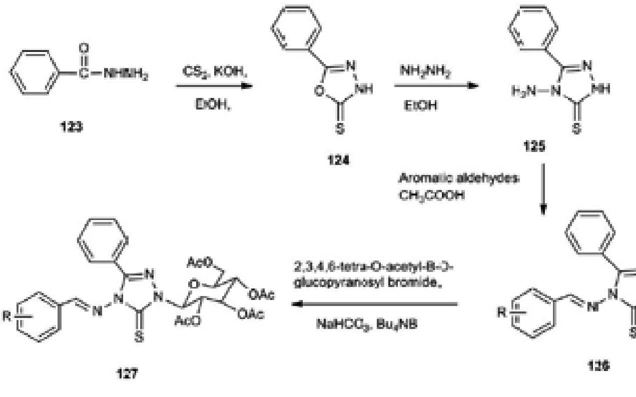


Figure 35. *Synthetic route for novel D-glucopyranosyl-1,2,4-triazole-3-thione*

1.2.3. CONCLUSION

In this review article, we have summed up the recent work in the synthesis of triazole ring system. This effort would be useful for common researchers working in the relevant area. Moreover, the research opens a huge scope for exploitation of this ring system as a template for novel useful biologically active compounds. The major focus was to highlight the procedures which were easy to carry out and result in good to excellent yields. It is evident from the above discussion that click chemistry route has been utilized by a vast majority of researchers for the introduction of 1,2,3-triazole ring system. On the other hand, use of thiosemicarbazide and thiocarbamate intermediates were among the most highlighted methodologies for incorporation of 1,2,4-triazole ring system. In addition, the advancements in the click chemistry synthesis and the methods dealing with environmental friendly procedures were also discussed.

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