Synthesis and applications of bi- and bis-triazole systems

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Abstract

The current review article represents the synthetic routes to all possible classes of bi- and bis-triazole systems along with their research and biological applications. The classification is based on the connection between the two triazole rings.

Keywords: Bi-triazoles, bis-triazoles, synthesis, applications, heterocycles
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1. Introduction

1,2,3- and 1,2,4-Triazoles are important heterocyclic scaffolds of interesting chemical and biological applications. Several therapeutically active compounds containing 1,2,3-triazole moiety have been reported as antimicrobials, anti-HIV agents and kinase inhibitors.\(^1\)-\(^4\) Some 1,2,4-triazole derivatives have antibacterial\(^5\)-\(^7\) and antifungal\(^8\),\(^9\) properties. Triazole units were incorporated in the core structure of some commercial drugs in the market. For example, Cefatrizine is using as antibiotic, Tazobactum as anti-bacterial agent\(^10\),\(^11\) and Suvorexant for the treatment of insomnia, was approved by the US-FDA\(^12\) in 2014 (Figure 1). 1,2,3- and 1,2,4-triazoles were also employed as efficient corrosion inhibitors in an acid aqueous medium.\(^13\),\(^14\) Considerable interest is also focused on the synthesis of bi-heterocycles, due to their wide range of applications. For example, 3,3′-bi-1,2,4-triazoles have proved to possess bactericidal, fungicidal, and anthelmintic activities.\(^15\) Some bis-triazole-based commercial drugs are also available in the market, for example Fluconazole, Itraconazole and Posaconazole were used as antifungal drugs and Vorozole as antineoplastic drug (Figure 1).

Fluconazole was the first-line bis-triazole-antifungal drug recommended by World Health Organization (WHO).\(^16\)-\(^19\) Nonsymmetric 1,3′-Bitriazole derivatives were reported to have antiviral activity against tobacco mosaic virus and exhibited powerful antiproliferative effects on different cancer cell lines.\(^20\) The application of bitriazoles as chelating N-heterocyclic carbene ligands for ruthenium(II), palladium(II), and rhodium and their applications in catalytic organic synthesis have also been reported.\(^21\),\(^22\) The coordination chemistry of the π-electron excessive bi-1,2,4-triazole ligands was also intensively explored for synthesis of coordination polymers with unique properties.\(^23\)-\(^27\) In the view of the above results and in connection with our previous review articles about biologically active heterocyclic systems,\(^28\)-\(^33\) we prepared this review to disclose the intensive survey on the synthetic routes to symmetrical and nonsymmetrical bi- and bis-triazole systems (Figure 2) and their applications reported in the literature until the end of 2017.
2. Synthesis and Application of Bitriazole Systems

2.1. 1,1′-Bi-triazoles
Treatment of 3,4-phthaloylisatoic anhydride 1 with oxamide-dihydrazone 2 in nitrobenzene and pyridine at 150 °C, followed by treatment with polyphosphoric acid at 130 °C, then 175 °C afforded the 5,5′-bis(1-amino-2-anthraquinonyl)-1,1′-bi-1,2,3-triazole derivative 3 (Scheme 1)."
2.2. 1,3'-Bi-triazoles

The 1,3'-bitriazole compounds 6 were synthesized in good to excellent yields via the copper(I)-catalyzed Huisgen reaction of the azidotriazole 4 with alkynes 5. Treatment of 6 with NH$_3$/MeOH at room temperature resulted in the formation of the 1,3'-bitriazole derivatives 7 (Scheme 2). The bitriazole compounds 6 showed high antiviral activity against tobacco mosaic virus.

Scheme 2

The 1,3'-bi-triazoles 10 and 12 were prepared by a nucleophilic substitution reaction of the sodium salt of 1,2,4-triazole 8 with the halotriazole derivatives 9 and 11, respectively (Scheme 3).
2.3. 1,5'-Bi-triazoles

Treatment the sodium salt of 1,2,4-triazole 8 with the halotriazole derivatives 9 yielded the 1,5'-bitriazole 13 in high yield (Scheme 4).\(^{37}\)

The nucleophilic aromatic substitution reaction of 1,3-dinitro-1,2,4-triazole 14 with sodium salt of 3-nitro-1,2,4-triazoles 15 in methanol and sodium carbonate at room temperature furnished the 1,5'-bi-1,2,4-triazole derivatives 16 (Scheme 5).\(^{38}\) The bi-triazoles 16 exhibited various energetic properties with high thermal stability and low sensitivity.

The synthesis of the 1,5'-bitriazole derivatives 18 was conducted under mild conditions, where the azidotriazole derivative 17 was readily engaged in a copper(I)-catalyzed Huisgen reaction with various terminal acetylenes 5. Treatment the bi-triazolyl compounds 18 with NH\(_3\)/MeOH led to the formation of the corresponding amides 19 (Scheme 6).\(^{39,40}\) The 1,5'-bitriazole derivatives 18 and 19 constituted interesting leads for the development of new antiviral candidates where they were more potent antiviral than the commercial products, DHT and ribavirin.
Scheme 6

1,5'-Bi-1,2,4-triazoles 21 were obtained in 20–70% yields by the reaction of 1-nitro-1,2,4-triazoles 20 with aqueous alkali hydroxides and reducing agents (KI, Fe\(^{2+}\), H\(_2\)PO\(_2\)\(^-\)) or with triethylamine in acetonitrile (Scheme 7).\(^{41}\)

Scheme 7

2.4. 3,3'-Bi-triazoles

Reaction of the oxalodihyrazonyl dihalide derivatives 22 with sodium azide in aqueous dimethylformamide at room temperature afforded the corresponding N,N'-diaryl oxalodihyrazonyl diazides 23 in 80-85% yields. Reduction of 23 with lithium aluminum hydride in ether yielded the diaminadrazine derivatives 24 in 65-72% yields. Reactions of 24 with acyl chlorides 25 in refluxing benzene gave the 3,3'-bi-1,2,4-triazole derivatives 26 in 43-60% yields (Scheme 8).\(^{42}\)

Scheme 8
3,3′-Bi-1,2,4-triazolo[3,4-α]isoquinolines 28 were prepared in good yields via 1,3-dipolar cycloaddition reaction of dihydrazonoyl halides 22 with 3,4-dihydroisoquinolines 27 (Scheme 9).43

\[
\begin{align*}
\text{R}=\text{Me, Et; } R^1=\text{H, Me; } \text{Ar}=\text{Ph, 4-MeC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{NOC}_6\text{H}_4, 2,4-\text{Cl}_2\text{C}_6\text{H}_3 ; \text{X} = \text{Br, Cl}
\end{align*}
\]

**Scheme 9**

The bi-1,2,4-triazolo[a,c]quinoxaline derivatives 32 were prepared via reaction of 2,3-dichloroquinoxaline 29 with the acid hydrazide derivatives 30, followed by thermal cyclization via refluxing the resulting quinoxaline derivatives 31 with phosphorus oxychloride in an oil bath at 140 °C (Scheme 10).

\[
\begin{align*}
\text{R} = \text{Me, Ph, 2-ClC}_6\text{H}_4, 2-\text{OHC}_6\text{H}_4, 4-\text{NH}_2\text{C}_6\text{H}_4, 2-\text{OH}-4-\text{SO}_3\text{H}_2\text{C}_6\text{H}_3
\end{align*}
\]

**Scheme 10**

Reaction of oxalic acid dihydrazide 33 with isothiocyanates yielded the respective thiosemicarbazide derivatives 34. Cyclization of 34 in alkaline medium afforded the corresponding 4,4'-substituted-5,5'-mercapto-3,3'-bi-1,2,4-triazole 35 (Scheme 11).

\[
\begin{align*}
\text{O} & \quad \text{H} & \quad \text{N} & \quad \text{NH}_2 \\
\text{N} & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{S} & \quad \text{HN} & \quad \text{ArNCS} & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{N}
\end{align*}
\]

**Scheme 11**

Reaction of oxalo-bis-hydrazide 33 with carbon disulfide followed with hydrazines afforded the 3,3'-bi-1,2,4-triazoles 37. Also reaction of the oxalo-bishydrazide 33 with carboxylic acids gave the bioxadiazoles 38 which on treatment with hydrazines or amines yielded the 3,3'-bi-1,2,4-triazole derivatives 39 (Scheme 12).15
The 3,3′-bi-1,2,4-triazole derivative 41 was prepared in moderate yield by reaction of \(N,N′\)-diphenyloxalohydrazonoyl dichloride 22 with 2-(methylthio(phenylamino)methylene)-malononitrile 40 in refluxing ethanol and triethylamine (Scheme 13).\(^{46}\)

4,4′,5,5′-Tetraamino-3,3′-bi-1,2,4-triazole 43 was synthesized from heating 1,3-diaminoguanidine monohydrochloride 42 with oxalic acid in the presence of polyphosphoric acid (PPA). Heating of 43 in the presence of acetic anhydride, yielded the corresponding tetracetamido-3,3′-bi-1,2,4-triazole derivative 44 in 98% (Scheme 14).\(^{47-49}\)
2.5. 3,4′-Bi-triazoles

Heating of the 1,2,3-triazolylhydrazides 45 with ammonium acetate and aromatic aldehydes in ethanol catalyzed by 20 mol% ZrOCl$_2$.8H$_2$O, afforded the corresponding 3,4′-bitriazole derivatives 46 in 80-85% yields (Scheme 15).$^{50}$

\[
\begin{align*}
\text{R} &= \text{Boc, SO$_2$Me, COCH$_3$}, \quad \text{R'} = \text{Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$}
\end{align*}
\]

Scheme 15

Heating diformylhydrazine 47 and 3-amino-1H-1,2,4-triazole 48 in a Teflon-lined stainless steel autoclave in a furnace at 170°C for 3 days yielded the 3,4′-bitriazole derivative 49 in 80% yield (Scheme 16).$^{51}$

Scheme 16

2.6. 4,4′-Bi-triazoles

The 4,4′-bi(1,2,3-triazole) derivatives 52 were prepared in high yields directly from 1,4-bis(trimethylsilyl)butadiyne 50 by reaction with two equivalents of the azides 51 in H$_2$O/t-BuOH in the presence of K$_2$CO$_3$ and a catalytic amount of CuSO$_4$. The reaction proceeded via tandem deprotection/click transformations and the presence of K$_2$CO$_3$ allowed the in situ removal of the TMS group of the alkyne reactants (Scheme 17). The 4,4′-bi(1,2,3-triazole) derivatives 52 were reported as bidentate chelators by forming stable Ru(II) complexes 53 which are coordinatively symmetrical, largely optically transparent and nonfluorescent. Compound 52 (R = Et) formed Re(I) complex 54 by its reaction with Rhenium(I) pentacarbonyl chloride Re(CO)$_5$Cl, which was useful for homogeneous- and electro-catalysis fields (Scheme 17).$^{52-56}$
An alternative synthesis of 1,1’-diphenyl-4,4’-bi(1,2,3-triazole) 52 (R = Ph) was reported in two steps; firstly reaction of anilines with tert-butyl nitrite then trimethylsilyl azide to obtain aryl azide. Afterward, 1,4-bis(trimethylsilyl)buta-1,3-diyn 50, pyridine, potassium carbonate, CuSO4·5H2O and sodium ascorbate in H2O were added to give 55 in 51-85% yield (Scheme 18).57

Using the click copper-catalyzed azide alkyne cycloaddition (CuAAC) condition, the reaction of 1,4-bis(trimethylsilyl)butadiyne 50 with two equivalents of epi-azido quinine 55 led to the formation of the 4,4’-bi(1,2,3-triazole) derivative 56 in excellent yield (Scheme 19). The bitriazole 56 was applied as ligand in several copper-catalyzed asymmetric Michael-type addition reactions.58
Dipolar cycloaddition of perfluorohexa-2,4-diyne 57 with azides 51 in hexane afforded the 4,4'-bi-1,2,3-bitriazole derivatives 58 in good yields. In addition, the 4,4'-bi-1H-1,2,3-triazole derivatives 59 were synthesized by the CuI-catalyzed click reaction between buta-1,3-diyne and the aryl azides 51 (Scheme 20).59,60

![Scheme 20](image)

Fiandanese et al. reported the synthesis of the unsymmetrically substituted 4,4'-bi-1,2,3-triazole derivatives 62 from the reaction of 1-trimethylsilyl-1,3-butadiyne 60 with the azide derivatives 51. Reaction of the azides 51 with compound 60 in the presence of Cu(OAc)₂, as a catalyst, in water provided 51–92% yields of the corresponding 1,4-triazole adducts 61. Treatment of compounds 61 with the azides 51 in THF, at room temperature employing Cul catalyst and TBAF, in the presence of 1,1,4,7,7-pentamethyl-diethylenetriamine, led to the formation of the 4,4'-bitriazole derivatives 62 in 52-86% yields (Scheme 21).61

![Scheme 21](image)

The 4,4'-bi-1,2,3-triazole derivatives 64 were obtained smoothly and in high yields by cycloaddition reactions of compound 63 with alkyl azides 51 (Scheme 22).62
Scheme 22

4,4'-Bi-1,2,3-triazole 67 was synthesized in two steps from 1,4-dichloro-2-butyne 65 with sodium azide to give 4-ethynyl-1H-1,2,3-triazole 66 as an intermediate via an azabutatriene type rearrangement. Compound 67 was obtained from 66 via “click chemistry” with trimethylsilyl azide (Scheme 23).63 The 4,4'-1H-1H-bi-1,2,3-triazole 67 was reported as capable of mimicking the hydrogen bonding of water in the solid state and was able to conduct protons in the presence of poly(ethylene oxides) under anhydrous conditions. The bitriazole 67 was found to have sufficient thermal and electrochemical stability for fuel cell applications.63

Scheme 23

4,4'-Bi-1,2,4-triazole derivatives 69 were prepared by Raney nickel catalyzed desulfurization reaction of the bis-s-triazolothiadiazines 68 (Scheme 24).37

Scheme 24

α-1,2,4-Triazolylcarbonyl arylhydrazines 71 were synthesized via nucleophilic substitution reaction of the corresponding α-(chloroformyl)arylhydrazine hydrochlorides 70 with 1H-1,2,4-triazole. Cycloaddition of 71 with 1,2,4-triazole at 60 °C and in the absence of base gave the 2,2'-diaryl-4,4'-bi-1,2,4-triazole derivatives 72 in low yields (13-18%) (Scheme 25).64
Scheme 25

Heating of N,N-dimethylformamide azine dihydrochloride 73 with 4-amino-1,2,4-triazole 74 in benzene gave 4,4'-bi-1,2,4-triazole 75 in significant yield (73%) via direct transamination. Treatment of 75 with iodine monochloride in water at r.t., resulted in the formation of tetraiodo-4,4'-bi-1,2,4-triazole 76 in 85% yield (Scheme 26). N-Quaternization of the bi-1,2,4-triazole 75 with methyl iodide gave the corresponding iodide salt 77 in high yield. The application of the 1,1'-dimethyl-4,4'-bi-1,2,4-triazolium bitriazolium diiodide as chelating N-heterocyclic carbene ligand for ruthenium(II), palladium(II), and rhodium(II) to form the corresponding complexes 78-80 was reported.

Scheme 26
When an equimolar mixture of appropriate hydrazonoyl halide 81 and 1,4-diphenyl-2,3-diaza-1,3-butadiene 82a was refluxed in dry benzene in the presence of triethylamine, it afforded the cycloadduct 4-(phenylmethylene)amino-1,2,4-triazole derivatives 83. Treatment of the cycloadducts 83 with the hydrazonoyl halides 81 afforded the corresponding 5,5′-diphenyl-1,1′,3,3′-tetrasubstituted 4,4′-bi-1H-1,2,4-triazole derivatives 84 in good yields (Scheme 27).69

\[
\begin{align*}
\text{R} = \text{X} & \quad \text{Ph} - \text{C} = \text{N} - \text{N} = \text{C} = \text{Ph} \quad \text{benzene} / \text{Et}_3\text{N} \\
\rightarrow & \quad \text{Ph} - \text{C} = \text{N} - \text{N} = \text{C} = \text{Ph} \\
\rightarrow & \quad \text{Ph} - \text{C} = \text{N} - \text{N} = \text{C} = \text{Ph} \\
\rightarrow & \quad \text{Ph} - \text{C} = \text{N} - \text{N} = \text{C} = \text{Ph} \\
\rightarrow & \quad \text{Ph} - \text{C} = \text{N} - \text{N} = \text{C} = \text{Ph} \\
\rightarrow & \quad \text{Ph} - \text{C} = \text{N} - \text{N} = \text{C} = \text{Ph}
\end{align*}
\]

a: R = CO\text{Ph}, Ar = Ph
b: R = CO\text{2Et}, Ar = 4-MeC_6\text{H}_4
X = (a) Br, (b) Cl

**Scheme 27**

The reaction between 4-amino-3,5-dimethyl-4H-1,2,4-triazole 85 and bis(α-chlorobenzylidene)hydrazine 86 in refluxing xylene yielded 3,3′-dimethyl-5,5′-diphenyl-4,4′-bi-4H-1,2,4-triazole 87. Initial nucleophilic displacement of chlorine in 86 by the amino group followed by an intramolecular ring closure and subsequent elimination of diazoethane to give 89 was disclosed. Repeating this reaction at the second imidoyl chloride centre yielded the 4,4′-bi-1,2,4-triazole derivative 90 (Scheme 28).70

\[
\begin{align*}
\text{Me} - \text{N} - \text{N} - \text{Me} & \quad + \quad \text{Ph} - \text{C} = \text{N} - \text{N} = \text{C} = \text{Ph} \\
\rightarrow & \quad \text{Me} - \text{N} = \text{N} - \text{N} = \text{C} = \text{Ph} \\
\rightarrow & \quad \text{Me} - \text{N} = \text{N} - \text{N} = \text{C} = \text{Ph} \\
\rightarrow & \quad \text{Me} - \text{N} = \text{N} - \text{N} = \text{C} = \text{Ph} \\
\rightarrow & \quad \text{Me} - \text{N} = \text{N} - \text{N} = \text{C} = \text{Ph}
\end{align*}
\]

**Scheme 28**

Heating the three component reaction of 3-aryl-5-methyl-1,3,4-oxadiazol-2(3H)-ones 91 with thiocarbazide 92 and aliphatic carboxylic acids, resulted in the formation of the 4,4′-bi-1,2,4-triazole derivatives 95 via the intermediates 93 and 94 as shown in Scheme 29.71
Scheme 29

Condensation of dinitromethane with glyoxal afforded 1,1,4,4-tetranitro-1,3-butadiene 96. Reaction of the latter compound with sodium azide led to formation of 4,4'-bi-1,2,3-triazole derivative 98 via 1,1,4,4-tetranitro-2,3-butanediol intermediate 97 (Scheme 30).72

Scheme 30

Thermal rearrangement of 3-acylisoxazole arylhydrazones 100, prepared by heating of 1-(5-methylisoxazol-3-yl)ethanone 99 with phenylhydrazine in ethanol, allowed facile preparation of 1-(1,2,3-triazol-4-yl)propan-2-ones 101. Reaction of the 1,2,3-triazolylpropanone derivatives 101 with isoamyl nitrite then arylhydrazine produced α-hydroxyiminohydrazones 102. Reaction of 102 with phosphorus pentachloride afforded 4,4'-bi-1,2,3-triazoles 103 (Scheme 31).73
**Scheme 31**

Copper(I)-catalyzed alkyne–azide ‘click’ [2+3] cycloaddition reactions (CuAAC) method was applied in the synthesis of nonsymmetrical-substituted 4,4'-bis(1,2,3-triazolium) salts 105 by reaction of 3-alkyl-4-ethynyl-1,2,3-triazolium salts 104 with alkyl and aryl azides (Scheme 32).\(^\text{74}\)

**Scheme 32**

2.7. 4,5'-Bi-triazoles

The 4,5'-bitriazoly acyclonucleosides 107 were synthesized in good yields via a one-step Huisgen cycloaddition reaction using sodium azide and the 5-alkynylytriazole acyclonucleosides 106 in DMF at 90°C (Scheme 33). The synthesized bitriazolyl compounds exhibited potent antiviral activity against tobacco mosaic virus and were devoid of any notable toxicity.\(^\text{75}\)
The 4,5'-bitriazolyl acyclonucleosides 109 were synthesized in excellent yields via the copper catalyzed cycloaddition reaction of aryl azides and the 5-acetynyltri(azole acyclonucleoside 108 in THF-water followed by ammonolysis with NH₃/MeOH mixture (Scheme 34). The synthesized compounds exhibited powerful antiproliferative effects on numerous cancer cell lines.⁷⁶
Cycloaddition of phenylacetylene 5 and benzyl azide using catalytic amount of copper(I) iodide in the presence of NaOH yielded the 5,5'-bi-1,2,3-triazole derivative 111 via the intermediates 112-114 according to the reaction mechanism depicted in Scheme 36.77

![Reaction Mechanism Diagram](image_url)

**Scheme 36**

The oxidative dimerization was extrapolated in the copper-mediated Huisgen reaction of the terminal alkynes 5 with azides 51 to yield the 5,5'-bi-1,2,3-triazole derivatives 115 under basic reaction conditions (Scheme 37).78

![Cycloaddition and Oxidative Dimerization Diagram](image_url)

**Scheme 37**

Trimethylsilylacetylene 116 and 2-(3-thienyl)ethyltrimethylsilane 118 were also reported as effective substrates for the cycloaddition with benzyl azide and oxidative dimerization to give the corresponding 5,5'-bitriazole derivatives 117 and 119 in 25 and 38% yields, respectively (Scheme 38).78
Scheme 38

Heating the oxalo-bis-hydrazide derivative 120 in water in the presence of bases, (alkali metal carbonates, or guanidinium or aminoguanidinium carbonates) at a molar ratio of 1:2 and subsequent acidification of the mixture resulted in the formation of the corresponding 5,5'-bi(3-nitroamino-1,2,4-triazole) salts 121 in excellent yields (Scheme 39). 79-81

Scheme 39

3,3'-Diamino-5,5'-bi-1,2,4-triazole 123 (DABT) was synthesized from the reaction of oxalic acid and aminoguanidinium bicarbonate 122 in concentrated hydrochloric acid and subsequent cyclization in basic media. Oxidation of DABT 123 by Sandmeyer reaction via diazotization in sulfuric acid and subsequent reaction with sodium nitrite yielded 3,3'-dinitro-5,5'-bi-1,2,4-triazole (DNBT) 124 (Scheme 40). Oxidation of 3,3'-dinitro-5,5'-bi-1,2,4-triazole 124 in an buffered aqueous solution of oxone at 40 °C led to the selective oxidation to 3,3'-dinitro-5,5'-bi-1,2,4-triazole-1,1'-diamine 127 (Scheme 41). The DNBT, as nitrogen-rich ligand, was employed in the development of energetic metal-organic frameworks (MOFs) of high density and thermal stability. 82-87

Synthesis of 3,3'-dinitro-5,5'-bi-1,2,4-triazole-1,1'-diamine 127, as new explosive and energetic material, was reported employing amination conditions using either O-tosylhydroxylamine or O-mesitylenesulfonyl hydroxylamine reagents of the in situ ammonium salts of the 3,3'-dinitro-5,5'-bi-1,2,4-triazole 126 as outlined in Scheme 41. 88-90
NH₂
122

HCO₃⁻ + O₂
1. HCl
2. NaOH

H₂N
123
70%

H₂N
124
82%

N
O₂N

NH₂
125
81%

Scheme 40

O₂N
126
N
N
N
N
N
N
N
N
N
N
N
OH
OH

(a) Et₄NOH/H₂O then O-mesitylenesulfonyl hydroxylamine/MeCN, yield 80%

(b) NH₃/H₂O then O-tosylhydroxylamine/DMF/CHCl₃, yield 45%

(c) DBU/CH₃CN then O-tosylhydroxylamine /CH₂Cl₂, yield 56%

Scheme 41

3. Synthesis and Application of Bistriazole Systems

3.1. Bis-(1,2,3-triazoles)

Copper promoted click chemistry was reported to be useful tool for the facile formation of bis(1,2,3-triazoles). Copper catalyzed cycloaddition reaction between the alkyl azides 129, prepared by heating of bromide 128 with sodium azide in DMF at 100 °C, and 4-bromo-1-butene 130 in H₂O at room temperature in the presence of Cu(OAc)₂.H₂O, led regioselectively to 4-(2-bromoethyl)-1,2,3-triazoles 131 in excellent yields (Scheme 42).
Scheme 42

Photo irradiation of dibenzo[a,e]cyclooctadiyne (DIBOD) 132 with 350 or 420 nm fluorescent lamps in the presence of the appropriate azide resulted in the efficient formation of the bis-triazole derivatives 134 via the intermediate 133 (Scheme 43). 93,94

Scheme 43

1,8-Diiodonaphthalene 136, prepared from naphthalene-1,8-diamine 135, reacted with 4-aryl-1,2,3-triazoles 137 in dry DMSO in the presence of CuI and K2CO3 under N2 atmosphere to give the naphthalene-bridged bis-triazole derivatives 138 in 42-66% yields (Scheme 44). 95 The naphthalene-bridged bis-triazole derivatives 138 were reported to be potential fluorophores for chemical and biological applications and showed high fluorescence efficiency and large Stokes shifts.

Scheme 44

The bis(1,2,3-triazole) 140, was synthesized in 83% from N-propargyl-5-phenyltriazole 139 with tosyl azide in the presence of copper(II) thiophene-2-carboxylate (CuTc) catalyst in dry toluene under N2 atmosphere. Treatment of 140 with Rh(II) catalyst led to selective decomposition of the 1,4-disubstituted...
1,2,3-triazole core, leading to a 3,4-fused dihydroindole 141 in 76% via intramolecular [3+2]-annulation reaction. Further treatment of 141 with MnO₂ at 80 °C afforded fused indole of bis(1,2,3-triazole) 142 in good yield (Scheme 45).²⁶

**Scheme 45**

Synthesis of the bis-1,2,3-triazole derivatives 144 was conducted starting from a azido-glycoside derivative 143 using Cul-catalyst under microwave irradiation condition. The azide 143 was treated with different terminal alkynes 5 using PMDETA (N,N,N,N,N-pentamethyldiethylenetriamine) as the base in THF (Scheme 46).²⁷

**Scheme 46**

Symmetrically substituted bis(1,2,3-triazoles) 146 having butyl or phenyl spacer groups were synthesized in high yields from reaction of the corresponding dialkynes 145 and benzyl azide using copper(I) oxide nanoparticles (Cu₂ONP) in glycerol (Scheme 47).²⁸
The copper-catalyzed coupling bis-alkynes 147 with various organic azides 51 afforded the corresponding bis(1,2,3-triazole) derivatives 149 through 148 using the polymer-supported catalyst Amberlyst A-21•CuI in DCM at room temperature (Scheme 48). Some of the bis-triazole products 149 showed noteworthy activity against B16 melanoma included in the range 1-20 μM.

![Scheme 48](image)

One-pot three-component coupling reactions of 150 consisted by double [3+2] reactions followed by substitutions with allylamine, as nucleophile, successfully afforded the bis(1,2,3-triazole) derivative 151 in moderate yield (Scheme 49).

![Scheme 49](image)

Thermally driven [3+2] cycloadditions of internal bis-ynamides 152-154 with benzyl azide led to the formation of the bis(1,2,3-triazole) derivatives 155-157 in moderate yields (Scheme 50).

The bis-1,2,3-triazolyl benzothiadiazole derivative 160 was synthesized by ruthenium-catalyzed azide-alkyne cycloaddition between the benzothiadiazole bis-alkyne 158 and azido alanine 159 in 52% yield as shown in Scheme 51. Photophysical studies demonstrated the crucial role of the prepared bistriazole 160 in the design of new fluorescent chemosensors.

The reaction of 1,4-bis(azidomethyl)benzene 161 with 2 equiv. of ethyl 4-anilino-4-oxo-2-butynoate 162 in toluene under microwave irradiation furnished the mixed regioisomeric bis(1,2,3-triazole) derivatives 163 in 65% yield (Scheme 52).
**Scheme 50**

\[
\text{158} \quad \begin{array}{c}
\text{TMS} \quad \begin{array}{c}
\text{MeO}_2C
\end{array}
\end{array}
\quad +
\begin{array}{c}
\text{159} \quad \begin{array}{c}
\text{NHBOc}
\end{array}
\end{array}
\quad \xrightarrow{1) \text{K}_2\text{CO}_3 / \text{MeOH}}
\begin{array}{c}
\text{160} \quad \begin{array}{c}
\text{MeO}_2C
\end{array}
\end{array}
\quad \xrightarrow{2) \text{Cp}^*\text{RuCl(COD)}, \text{THF}, \text{Ar}}
\begin{array}{c}
\text{BocHN}
\end{array}
\end{array}
\quad \text{52%}
\]

**Scheme 51**

\[
\text{161} \quad \begin{array}{c}
\text{Cl}\quad \text{N}\quad \text{N}_3
\end{array}
\quad +
\begin{array}{c}
\text{162} \quad \begin{array}{c}
\text{EtO}_2C
\end{array}
\end{array}
\quad \xrightarrow{\text{PhMe, MW}}
\begin{array}{c}
\text{163} \quad \begin{array}{c}
\text{R} = \text{Ph}, 4-\text{MeC}_6\text{H}_4
\end{array}
\end{array}
\quad \text{120 W, 75 °C}
\]

**Scheme 52**
Reaction of 1,2-, 1,3- and 1,4-bis(azidomethyl)benzenes 164 with acetylenedicarboxylate esters 165 afforded the corresponding bis(1,2,3-triazole) derivatives 166 (Scheme 53).104

Scheme 53

Click reaction of the sugar azides 51 with chalcogeno bis-propargylated catechols and resorcinol derivatives 170 and 174, [prepared by reaction of 167 or 172, with propargyl bromide to afford 168 or 173 which then reacted with methyl ketones 169] using tetrahydrofuran and water as solvent resulted in the formation of the sugar-chalcone based bis-triazole derivatives 171 and 175 in high yields (Scheme 54).105

Scheme 54
Synthesis of bis-1,2,3-triazoles 177 via Cu(I)-catalyzed click reaction of aryl azides and 1,3-bis(prop-2-yn-1-yl)oxy)benzene 176. The latter were synthesized from the reaction of resorcinol with propargyl bromide in the presence of potassium carbonate (Scheme 55).

Copper(I)-catalyzed click reaction of the bis-alkyne derivatives of catechol 178 or 6,7-dihydroxycoumarin 181 with the azide esters 179 yielded the corresponding bis-1,2,3-triazole derivatives 180 and 182 respectively in high yields (Scheme 56).

1,2,5,6-Di-O-isopropylidene-D-mannitol 183 reacted with propargyl bromide in NaOH and DMF solvent to give the bis-alkyne 184. The Cu(I)-catalyzed 1,3-dipolar cycloaddition of the bis-alkyne 185 with alkyl azides 51 in DMSO at 50 °C gave the corresponding bis-triazoles 186 in quantitative yields (Scheme 57).
The “click” reaction of diazeniumdiolate prodrugs having terminal alkyne groups 188 with the bis-azide 187 was performed using CuSO₄/Na-ascorbate in THF/water. The reaction proceeded quickly (15-45 min) and gave a mixture of two products. The major product was in each case the bis-triazole derivative 189 and the minor product was 5,5′-triazolo-triazole 190. The use of CuI and diisopropylethylamine (DIPEA) as base predominantly gave the cycloaddition/oxidative coupling products; 5,5′-triazolo-triazole 189 as major products (Scheme 58). The products were reported to have potential biological applications as NO-donors.

Synthesis of the bis-triazolyl ethisterone glycoconjugates 195 was reported using CuAAC reaction condition. At first, the sugar based triazolyl azido-alcohols 195 were synthesized via one pot click reaction of glycosyl alkynes 193 with epichlorohydrin 192 in aqueous medium. Treatment of the triazolyl azido-alcohols 193 with the naturally occurring steroid alkyne (ethisterone) 194 yielded the bis-triazolyl ethisterone.
glycoconjugates 195 regioselectively in good yields (Scheme 59). The products 195 were of potential application in androgen receptor pharmacology and chemical biology.110

Scheme 59

3.2. Bis-(1,2,4-triazoles)
Reaction of arylamino sulfonylacetic acid hydrazide 196 with sulfonyldiacetic acid 197 in the presence of POCl₃ resulted in the formation of bis(1,3,4-oxadiazole) derivatives 198. Treatment of the latter compounds with hydrazine hydrate in n-butanol gave the bis(1,3,4-triazole) derivatives 199 (Scheme 60).111 Compounds 199 exhibited good antioxidant activity using DPPH, nitric oxide (NO), and hydrogen peroxide (H₂O₂) methods at 50, 75, and 100 μM concentration.

Scheme 60

The bis(1,2,4-triazole) derivative 202 was synthesized in 42% yield from the reaction of 2-cyano-3-methylthio-3-phenylaminoacrylonitrile 201 with the bis-hydrazonoyl halide 200 in refluxing DMF/EtOH in the presence of triethylamine (Scheme 61).112
The reaction of 4-amino-1,2,4-triazole 74 with sodium dichloroisocyanurate (SDCI) afforded the bis(1,2,4-triazole) derivative 203 in 90% yield. Increasing the molar ratio of SDCI to 4-amino-1,2,4-triazole, the chlorinated bis(1,2,4-triazole) 204 was formed in 45% yield (Scheme 62).\(^\text{113}\)

![Scheme 61](image1)

**Scheme 61**

Reaction of the amine bis-bromide compounds 205 reacted with 1H-1,2,4-triazole in the presence of potassium carbonate in acetonitrile at 40-70 °C to give the corresponding amine bis(1,2,4-triazole) derivatives 206 in 67-75% yields (Scheme 63).\(^\text{114}\) The obtained bis-triazoles 206 exhibited more potent antifungal activity than the clinically prevalent antifungal drug Fluconazole against C. albicans with MIC value of 0.25 mg/mL.

![Scheme 62](image2)

**Scheme 62**

Reaction of terephthalic acid bis-hydrazide 207 with aryl iso(thio)cyanate in DMF in the presence of sodium hydride followed by treatment with concentrated HCl afforded the corresponding (thio)semicarbazide 208. The bis-(thio)semicarbazides on treatment with sodium hydroxide led to the formation of the bis(1,2,4-triazole) derivatives 209 in 64-69% yields (Scheme 64).\(^\text{115}\)

![Scheme 63](image3)

**Scheme 63**
Fusion of 1,4-bis-phenoxyacetic acids 211, prepared by heating of 210 with chloroacetic acid and sodium hydroxide in water, with thiocarbazide 92 afforded 1,4-bis-(1,2,4-triazol-3-ylmethoxy)phenylenes 212 in a one pot reaction in good yields (Scheme 65).116

Scheme 65

References

   https://doi.org/10.1021/jm901265h

   https://doi.org/10.1021/jm0509750

   https://doi.org/10.1021/jm800149m

   https://doi.org/10.1021/jm0400810


https://doi.org/10.1007/s11178

https://doi.org/10.1002/jhet.5570370221

https://doi.org/10.1055/s-0030-1260061

https://doi.org/10.1016/j.jbcl.2010.10.141

https://doi.org/10.1021/jm300534u

https://doi.org/10.1016/j.tetlet.2011.05.002

https://doi.org/10.1002/anie.200700399

https://doi.org/10.1007/s11178-005-0184-0

https://doi.org/10.1007/s11178-005-0091-4

https://doi.org/10.1007/s11178-005-0033-1

https://doi.org/10.1002/chem.201202483

https://doi.org/10.1002/ejic.201200221

https://doi.org/10.1021/acscgd.5b00336


https://doi.org/10.1021/acs.inorgchem.6b02383

https://doi.org/10.3390/molecules22071068

https://doi.org/10.1002/anie.201506744

https://doi.org/10.1002/anie.201507456


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