Chapter

Role of Click Chemistry in Organic Synthesis

Ayushi Sethiya, Nusrat Sahiba and Shikha Agarwal

Abstract

Click chemistry involves highly efficient organic reactions of two or more highly functionalized chemical entities under eco-benign conditions for the synthesis of different heterocycles. Several organic reactions such as nucleophilic ring-opening reactions, cyclo-additions, nucleophilic addition reactions, thiol-ene reactions, Diels Alder reactions, etc. are included in click reactions. These reactions have very important features *i.e.* high functional group tolerance, formation of a single product, high atom economy, high yielding, no need for column purification, etc. It also possesses several applications in drug discovery, supramolecular chemistry, material science, nanotechnology, etc. Being highly significant and valuable, we have elaborated on several aspects of click reactions in organic synthesis in this chapter. Recent advancements in the field of organic synthesis using click chemistry approach have been deliberated by citing last five years articles.

Keywords: click chemistry, organic synthesis, eco-benign synthesis, selectivity, atom economy, cyclo-addition

1. Introduction

Presently, researchers are paying considerable attention to devise eco-friendly approaches for organic transformations. There has been a significant hike in interest among the scientists for more environmentally acceptable processes in the chemical industries. Synthetic chemistry has led us to the development of more potent structural analogs of natural products. The high therapeutic efficiency, bioavailability, and pharmacological characteristics of synthetic molecules have increased their use in medicinal chemistry as compared to natural products. Pharmaceutical chemistry encompasses the design, synthesis, and evaluation of compounds. In designing drugs, there is an upsurge demand for eco-benign pathways to accomplish the green aspects of chemistry. Novel green pathways play a vital role in the synthetic chemistry field by eradication of harmful solvents and chemicals or suitable handling of waste materials. The quest for new and proficient approaches for the synthesis of numerous biologically active scaffolds has made click chemistry a promising approach in chemistry. Click chemistry is a fruitful approach for the fabrication of molecules.

Huisgen and co-workers demonstrated a click reaction, Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC). The advanced use of this reaction and click chemistry was introduced by K. Barry Sharpless in 2001. The term click chemistry not only refers to the reaction which occurs fast but also to those that involve twelve principles of green chemistry *i.e.* selective, easier product isolation, mild reaction condition, high yield, good atom economy, avoid toxic catalyst and solvent, and so on. They encompass reactions that are high yielding, fast, modular, and wide in scope. They are practical and tolerant for a variety of functional groups. Finally, the product isolation is expected to be effortless due to lack of by-products. These vast characteristics make click chemistry a powerful tool that paves a path in several fields of research *viz.* designing of drugs and lead structures [1–4]. Therefore the synergy between these disciplines has given rise to an area of intense research activity. The click chemistry has been such an engrossing topic of research that a lot of review articles have been published so far which explained its applicability in various fields of chemistry like manufacturing and alteration of metal–organic frameworks [5], making devices in bio-sensing system for responsive copper identification [6], designing bio-adhesives for hastening wound closure [7], in virus-related research [8], generation of biosensors [9], proteomics analysis [10], in strategy for indirect ^{18}F-labeling [11], *in vivo* bio-imaging [12], to identify the interaction of curcumin with protein [13], synthesis of polymers and material science [14], for surface modification [15], and so on. In this chapter, the state-of-art modernization with a particular focus on click chemistry assisted synthesis and their uses in various fields of science have been discussed. An attempt has been done to prepare an outline of the importance of click chemistry and its foremost requirement in the research area. It is predicted that this methodical study will pave the way for future opportunities in this direction and design of safer, economical, and eco-friendly pathways.

2. Green aspects of click reactions

According to Sir John Cornforth, a Noble Prize laureate in chemistry in 1975, ideal reaction has been defined as "The ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bath-tub and collecting the pure product from the drain hole" [16]. Click reactions are designed in such a way that it involves all the twelve principles of green chemistry. Click chemistry includes synthetic methods that are designed to maximize the inclusion of all resources used in the process into the final product. Due to involvement of addition and rearrangement reactions, they have high atom economy. The products are designed with maximum efficacy and minimum cytotoxicity [17]. The green aspects have been depicted in **Figure 1**.

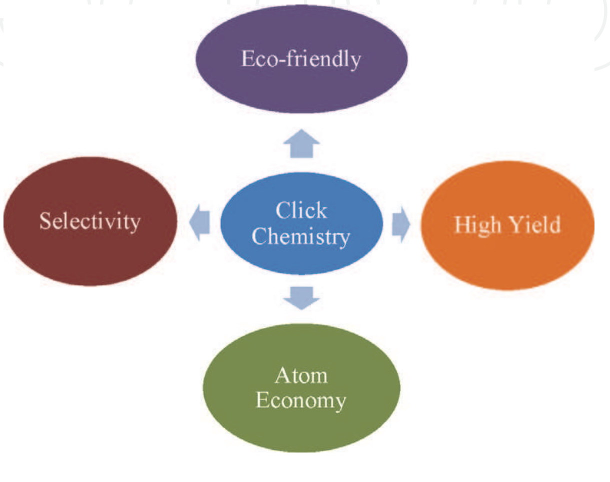


Figure 1.
Green aspects of click chemistry.

3. Role of click reactions in synthetic chemistry

Click chemistry includes a cluster of powerful linking chemical reactions that are easy to perform, have high yields, require no or minimal purification, and are flexible in the unification of different structures without the prerequisite of protection steps. Molecular diversity, modularity, and efficiency are essential in synthetic organic chemistry and expected to be involved in the preparation of several complexes and multi-purpose compounds. In general "Click Chemistry" is a class of biocompatible reactions, to link desired substrates with particular biomolecules. Natural products are produced by joining tiny modular units *via* biosynthesis as well as photosynthesis [18]. Click chemistry provides a route for the synthesis of several heterocyclic scaffolds, amino acids, triazole-fused heterocycles, peptides, and chromophores [19, 20].

3.1 Classification of click reaction

There is no specific classification of click reactions. The chief requisite for "Click Chemistry" is well met by reactions that take place in nature and their mimic in the laboratory is the closest and most desirable to the mind and spirit of most synthetic organic chemists. Usually, four main classifications of click reactions have been identified [21, 22].

- **Cycloadditions**: These refers to 1,3-dipolar cycloadditions reactions and hetero-Diels-Alder cycloadditions.

- **Nucleophilic ring-opening reactions**: This classification belongs to the opening of strained heterocyclic electrophiles, such as epoxides, aziridines, aziridinium ions, cyclic sulfates episulfonium ions, etc.

- **Nucleophilic addition reaction:** It includes the reaction of carbonyl groups like formation of hydrazones, urease, thiourease, oxime ethers, aromatic heterocycles, amides, etc.

- **Additions to carbon–carbon multiple bonds:** It involves epoxidation, dihydroxylation, aziridination, nitrosyl halide addition, sulfenyl halide addition, and certain Michael additions.

Presently, click chemistry inspired synthesis has become the most fascinating approach. Several multi-component reactions have been designed in an eco-friendly manner like aldol condensation followed by Michael addition, Ugi reaction/aldol reaction, Ugi reaction/Huisgen reaction, Ugi Reaction/Diels-Alder reaction, Ugi reaction/Heck reactions, Michael addition/Mannich reaction, etc. [23]

The most famous click reaction is the classical reaction between an azide and an alkyne. Both the substrates do not react under physiological conditions and go through a cycloaddition reaction only at a particular temperature. The uncatalyzed reaction is usually slow and not regio-selective. On the other hand, it was found that the use of electron-deficient terminal alkynes can cause 1,4-regioselectivity to a great extent. These factors limit the use of uncatalyzed Huisgen cycloaddition as an efficient conjugation pathway [24].

3.2 Metal-catalyzed approach for the click synthesis

3.2.1 Synthesis of triazole derivatives

Metals have been used to catalyze several click reactions. The mechanism of metal catalyzed azide alkyne click reaction involves formation of π-alkynyl complex with metal followed by complexation of azide by metal of the π-coordinated triple bond. After cyclization, metallacycle is formed followed by the reductive elimination to afford the relevant 1,2,3-triazole. Several metal like Cu, Ru, Ag, Au, etc. have been employed to accomplish click reactions [25–28]. This section has been divided in two subsections:

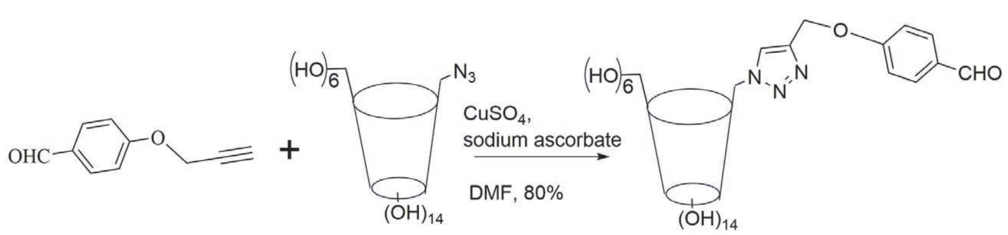
3.2.1.1 Metal-catalyzed synthesis of triazole derivatives

Transition metals have been used to catalyze several organic reactions as they provide large surface area and they have vacant d-orbitals due to which they can show variable oxidation state that help in generation of intermediate for organic synthesis [29, 30]. The common process for the click reaction is the transition metal catalyzed synthesis of 1,2,3-triazoles. 1,3-dipolar cyclo-addition of an azide and an alkyne catalyzed by Cu is the most extensively used click-chemistry pathway due to its high selectivity and simplicity [31]. In 2014, Guo and co-workers synthesized β-cyclodextrin derivatives (1) using mono-6-azidocyclodextrin and aromatic aldehydes by Cu^{I}-catalyzed azide–alkyne cyclo-addition. The mono, di, and tri derivatives were synthesized upto 75% yield under mild reaction conditions [32] **(Figure 2).**

Later on, Kumar *et al.* [33] designed a library of new nucleosides **(2 and 3)** having 1,2,3-triazole scaffold at the 2″-position of the sugar nucleus. It was synthesized by 2″-azidouridine using the copper (I)-catalyzed Huisgen–Sharpless–Meldal 1,3-dipolar cyclo-addition reaction **(Figure 3).** The reaction gave 52–82% yield and 1,4-disubstituted 1,2,3-triazoles were obtained.

Tale and co-workers also synthesized 1,2,3-triazoles in excellent yields using (1-(4-methoxybenzyl)-1-*H*-1,2,3-triazol-4-yl)methanol (MBHTM) ligand (1.1 mol%) and $CuSO_4$ (1 mol%) as a catalyst and sodium ascorbate (5 mol%) in DMSO:H_2O(1:3) as a solvent [34]. Shamla and co-workers synthesized coumarin substituted triazole derivatives (4) in good yields using 4-bromomethylcoumarins, terminal alkynes, and sodium azide in the presence of triethylamine and CuI as a catalyst [35] (**Figure 4**).

Yarlagadda *et al*. synthesized N-((l-benzyl-sl*H*-l,2,3-triazol-5-yl) methyl)-4-(6-methoxy benzo[d]thiazol-2-yl)-2-nitrobenzamide derivatives (5) and examined their anti-microbial activity. Among these compounds, compounds **5a, 5 h, 5i** possessed promising activity in comparison to standard drug ciprofloxacin and miconazole (**Figure 5**) [36].



(1)

Figure 2.
Synthesis of β-cyclodextrin derivatives using click chemistry approach.

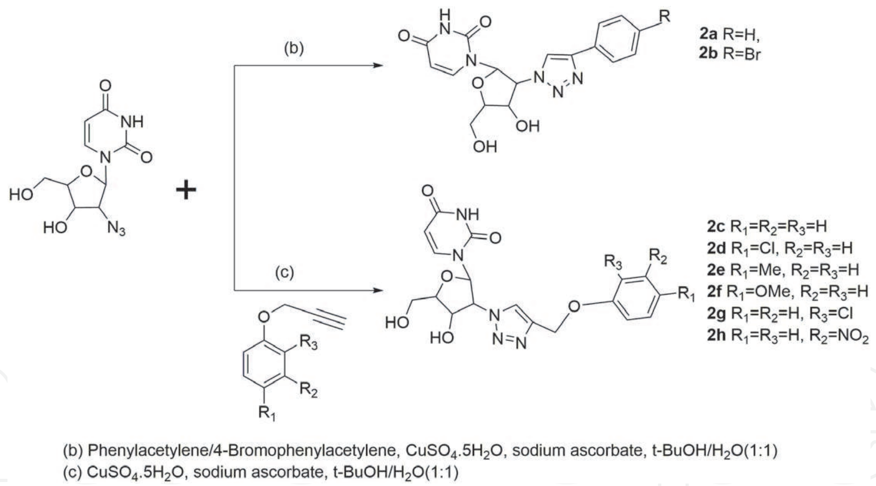


Figure 3.
Synthesis of library of traizole substituted nucleosides.

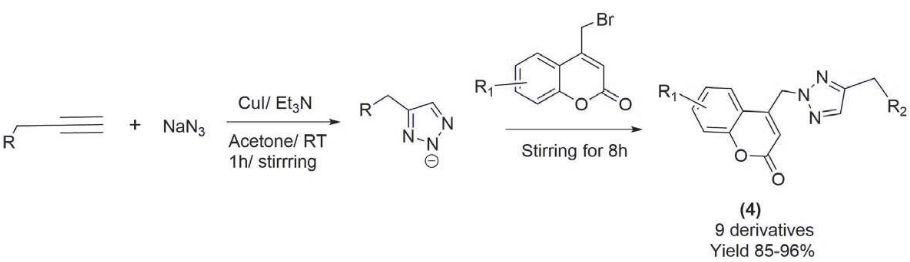


Figure 4.
Synthesis of coumarin substituted triazole derivatives.

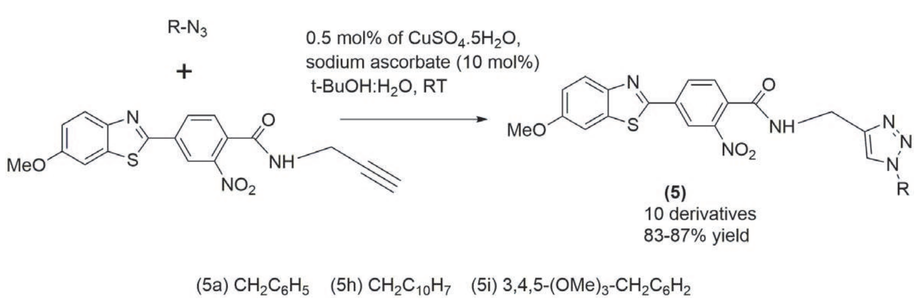
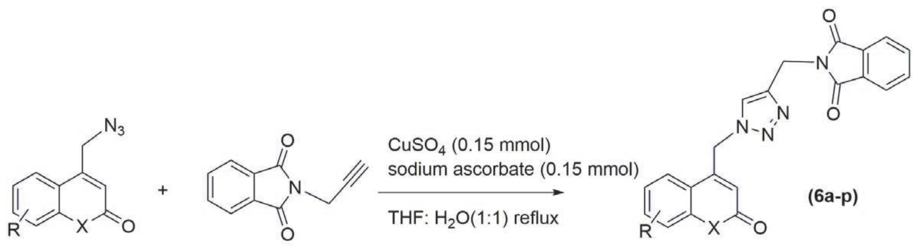


Figure 5.
Synthesis of N-((l-benzyl-lH-l,2,3-triazol-5-yl) methyl)-4-(6-methoxy benzo[d]thiazol-2-yl)-2-nitrobenzamide derivatives.

Anand *et al*. designed Cu(I) catalyzed regio-selective synthesis of iso-indoline-1,3-dione linked 1,4 coumarinyl 1,2,3-triazoles (6) and Ru (II) catalyzed pathway of 1,5 coumarinyl 1,2,3-triazoles in high yields with no need for further purification (**Figure 6**) [37].

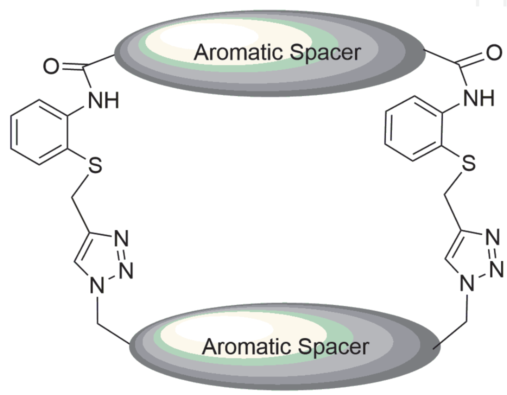
Anandhan *et al*. prepared a series of triazole-based macrocyclic amides (7) *via* click chemistry using $CuSO_4$ (5 mol%), sodium ascorbate (10 mol %) in the presence of H_2O/THF (1:1), RT. The synthesized compounds showed good anti-inflammatory activity although at low concentration (50 μg/mL) in comparison to the reference drug prednisolone (**Figure 7**) [38].

Li and co-workers designed triazole derivatives (8 and 9) by click chemistry using $CuSO_4$•$5H_2O$ (0.1 g) and ascorbic acid (0.1 g) in tBuOH/H_2O as a solvent and investigated their applications to synthesize self-assembled membrane against copper corrosion. As per the investigation results, it was found that 2-(1-tosyl-1*H*-1,2,3-triazol-4-yl)-ethanol (TTE) (8) and 2-(1-tosyl-1*H*-1,2,3-triazol-4-yl)-propan-2-ol (TTP) (9) coating on film can sturdily decrease the corrosion caused by copper in



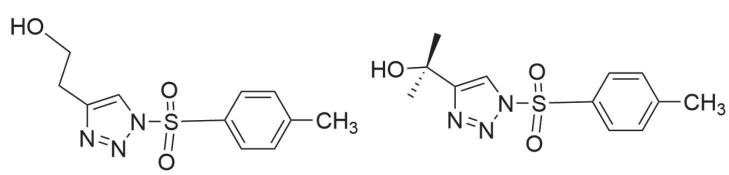
X=O, R=6-Me, 7-Me, benzo[f], benzo[h], 5,7-(Me)2, 7,8-(Me)$_2$, 6-OMe, 7-OMe, 7-Cl, 6-Cl, 6-Br, 7-OH
X= NH, R=H, 8-Me, 6-Cl, 7-Cl

Figure 6.
Synthesis of iso-indoline-1,3-dione linked 1,4 coumarinyl 1,2,3-triazoles derivatives.



(7)

Figure 7.
Triazole based macrocyclic amides.



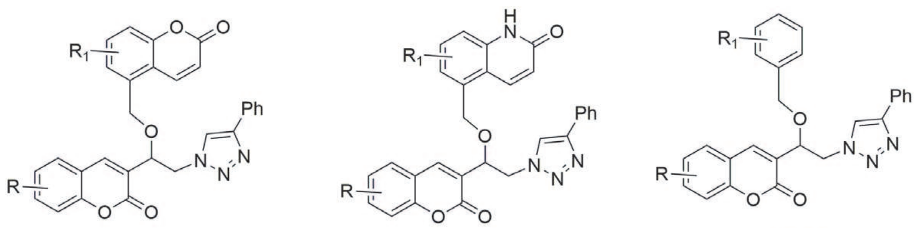
(8) (9)

Figure 8.
Derivatives of triazole.

3 wt.% NaCl solution and the inhibition effectiveness of TTP and TTE were 93.1% and 89.4%, respectively (**Figure 8**) [39].

Savanur and co-workers developed facile click chemistry inspired synthesis of triazole ring fused coumarin and quinolinone derivatives using $CuSO_4$ (10 mol%), sodium ascorbate (10 mol%), H_2O:PEG, RT followed by K2CO_3/DMF at 50–60 °C and examined their anti-microbial activity. Among the synthesized compounds, compounds **10j, 11 g** and **12f** displayed good anti-bacterial activities. Derivatives **10e** and **10j** were found highly active against yeast strains. Compound **11f** was highly active against filamentous strain *A. niger* and yeast fungi [40] (**Figure 9**).

Yarovaya *et al.* [41] fabricated a conjugate of cytisine with camphor having triazole ring using click chemistry pathway by employing $CuSO_4$•5H_2O, sodium ascorbate, t-BuOH/H_2O. The designed molecules were examined for *in vitro* antiviral activity against A/PuertoRico/8/34 influenza virus (H1N1). The compound (13) has highest inhibition activity with IC_{50} = 8 ± 1 μmol (**Figure 10**).

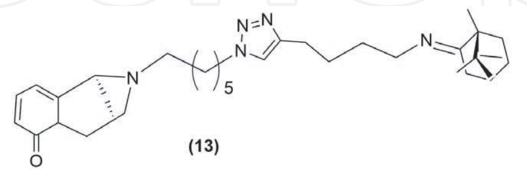


(10a-k)
(10e) R_1=6-OMe, R=H
(10j) R_1=6-OMe, R=6-Cl

(11a-g)
(11g) R=R_1=6=-Cl
(11f) R=6-Cl, R_1=7-Me

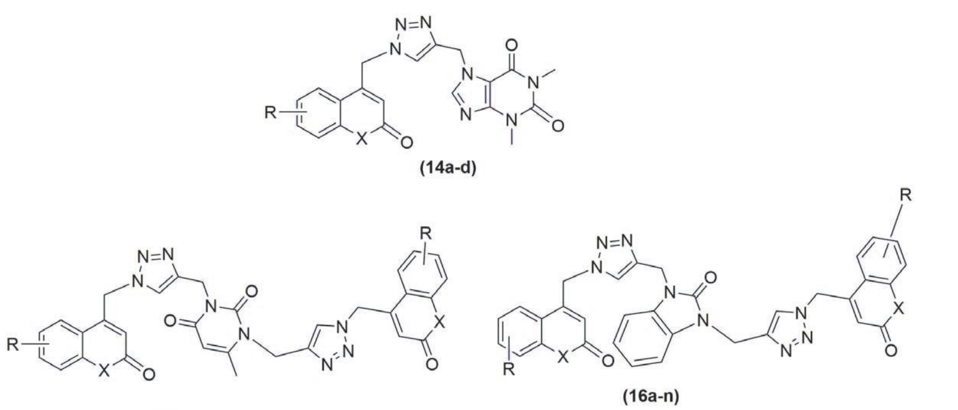
(12a-f)
(12f) R=6-Cl, R_1=3-Cl

Figure 9.
Triazole ring fused coumarin and quinolinone derivatives.



(13)

Figure 10.
Cytisine conjugated triazole derivative.



(14a-d)

(15a-e)

(16a-n)

Figure 11.
Methyluracil and theophylline mono-triazole compounds and Bis-triazole compounds.

Khanapurmath *et al*. synthesized various derivatives of triazole by click chemistry approach using $CuSO_4$ and ascorbic acid in H_2O:DMF solvent and assessed them against *Mycobacterium tuberculosis H37Rv*. 6-Methyluracil and theophylline mono-triazole compounds **14(a-d)** and bis-triazole compounds, **15(a-e)** showed reasonable inhibition of *M. tuberculosis H37Rv*, with MIC values in the range of 55.62–115.62 μM. Benzimidazolone bis-triazole derivatives **16(a-n)** inhibited *M. tuberculosis H37Rv* with MIC 2.35–18.34 μM (**Figure 11**) [42].

3.2.1.2 Metal Nano-particle based triazole synthesis

Green synthesis is the fundamental requirement of present synthetic protocol and use of nanoparticles (Nps) is one of the key tackle for organic transformations. NPs are microscopic particles with dimension between 1–100 nm. These are used as catalysts because they provide large surface area, high catalytic activity, nontoxic, heterogeneous nature, etc. In lieu of this, Chetia *et al*. designed copper Nps (nano particles) supported over hydrotalcite and used these Nps (15 mg) to catalyze 1,3 dipolar cycloaddition reaction to form 1,4 disubstituted-1,2,3-triazoles (17)

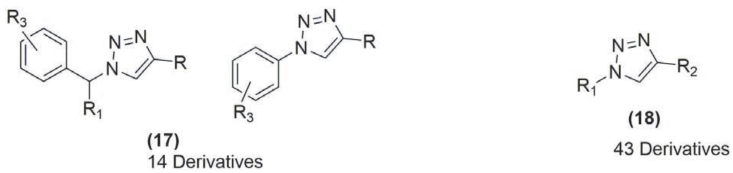


Figure 12.
Triazole derivatives.

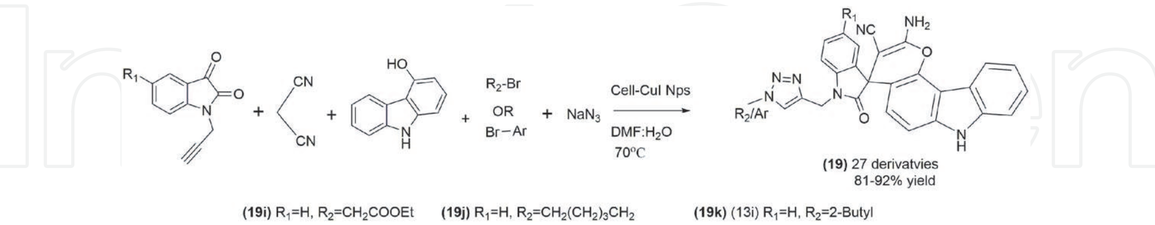


Figure 13.
Spirochromenocarbazole tethered 1,2,3-triazole derivatives.

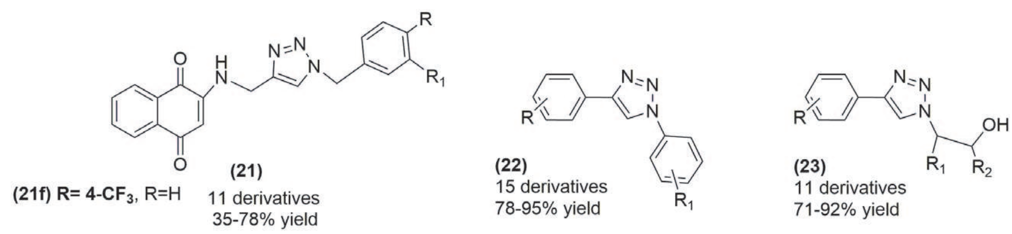


Figure 14.
Structures of different triazole derivatives.

(**Figure 12**) at room temperature using ethylene glycol as a solvent. The catalyst is heterogeneous, easily recyclable, and further reusable [43]. In this context, Poshala and co-workers developed copper Nps (0.1 mmol) using rongalite as a reducing agent and examined their catalytic efficiency in synthesizing triazole (18) derivatives in the presence of β-cyclodextrin (0.02 mmol) [44].

Chavan *et al*. [45] designed a click chemistry assisted MCR strategy for the synthesis of spirochromenocarbazole tethered 1,2,3-triazoles (19) using CuINps supported over cellulose (7 mol%) as a catalyst in the presence of DMF:Water (1:2) (**Figure 13**). The synthesized compounds were screened for anti-cancer activity against MCF-7, HeLa, MDA-MB-231, A-549, PANC-1 and THP-1. Compounds **19i** and **19j** were observed to be the most potent against MCF-7 with IC_{50} = 2.13 μM and 4.80 μM respectively. Compound **19 k** was the most potent one against MDA-MB-231 with (IC_{50} = 3.78 μM). All the products were found to be safe against the human umbilical vein endothelial cells (HUVECs).

Elavarasan *et al*. prepared nano rod shaped triazine functional hierarchical mesoporous organic polymers (HMOP) containing Cu metal. This catalyst was used to synthesize triazole derivatives (20) *via* stirring at 80 °C in the presence of water as a solvent [46]. In the same year 2019, Gholampour *et al*. synthesized a library of 1,4-naphthoquinone-1,2,3-triazole hybrids (21) using $CuSO_4$ (0.15 mmol) and sodium ascorbate (.05 mmol) catalyzed click chemistry approach from 2-(prop-2-ynylamino)naphthalene-1,4-dione and different azidomethyl-benzene analogs. The anti-cancer activity of synthesized compounds was anticipated against three cancer cell lines (MCF-7, HT-29 and MOLT-4) by MTT assay. The compound **21f** possessed the highest activity [47]. In continuation to this, magnetic CuFe2O4/g-C3N4 hybrids were synthesized and their catalytic activity was examined in the synthesis

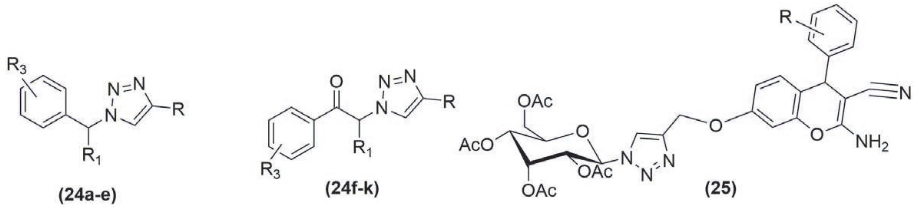


Figure 15.
Triazole derivatives.

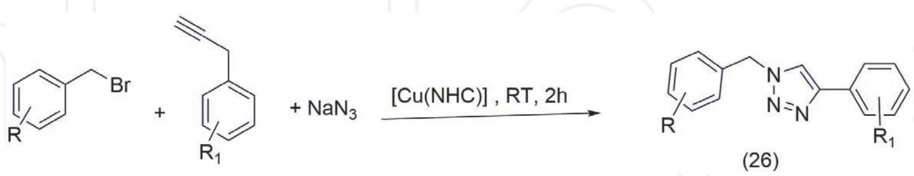


Figure 16.
Synthesis of triazole derivatives.

of triazole derivatives (22 and 23) using terminal alkyne, azide, epoxide or haloarene (**Figure 14**) [48].

Pourmohammad *et al*. synthesized (CuI@[PMMA-CO-MI]) (0.02 g) nano catalyst and employed them in the synthesis of triazole derivatives using terminal alkynes, α-haloketones or alkyl halides and sodium azide in H_2O at RT to give 1,4-disubstitued 1,2,3-triazoles (24) (**Figure 15**). The catalyst being heterogenous and regioselective gave high yields in short reaction times [49].

Thanh *et al*. [50] designed a hybrid structure of chromene and triazole by applying click chemistry approach for the synthesis of 1H-1,2,3-triazole-tethered 4H-chromene-D-glucose analogs (25) using Cu@MOF-5 (2 mol%) as a catalyst to afford 80–97.8% yields. The copper supported over metal organic frame work was found better catalyst in comparison to conventional catalysts *viz*. $CuSO_4.5H_2O$-sodium ascorbate, CuI, Cu Nps, $CuIM_2$(IM is imidazole) as it afforded high yields of desired products in less reaction time and in the presence of ethanol whereas other required long reaction time and non green solvent. All the derivatives were assessed for *in vitro* anti-microbial activity with MIC values in the range of 1.56–6.25 μM (**Figure 15**).

3.2.2 Synthesis of other organic molecules

Click chemistry has been used to synthesize biologically active hybrids of several synthetic organic molecules. In lieu of this, Sharova *et al*. [51] demonstrated click chemistry inspired phosphorylation of anabasine, camphor, and cytisine using Cu assisted 1,3-diploar cycloaddition reaction. Later on, Touj *et al.* [52] synthesized copper N-heterocyclic carbene (Cu-NHC) complexes using benzimidazolium salt as a catalyst. These complexes were further used for the synthesis of triazole derivatives (26) **(Figure 16**).

The reaction involved mild reaction conditions, water as a green solvent with low catalyst loading, no need of further purification which made the protocol eco-friendly. Bernard *et al*. [53] investigated a cost effective, and convenient click chemistry inspired synthesis of cyclooctyne (27) and trans-cyclooctene (28) using inexpensive Cu powder as a catalyst **(Figure 17**).

Qui *et al.* [54] synthesized parthenolide–thiazolidinedione (29) hybrids using click chemistry-mediated coupling. The compounds were screened for anti-proliferative activity against prostate (PC3), breast (MDA-MB-231), and human

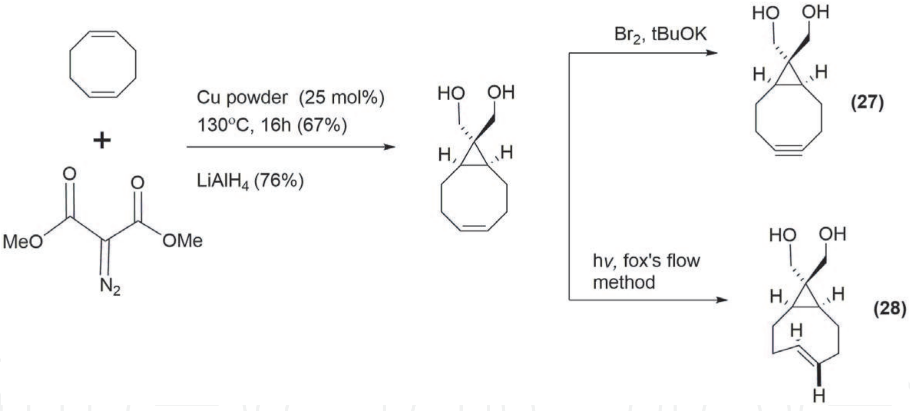


Figure 17.
Synthesis of cyclooctyne and trans-cyclooctene.

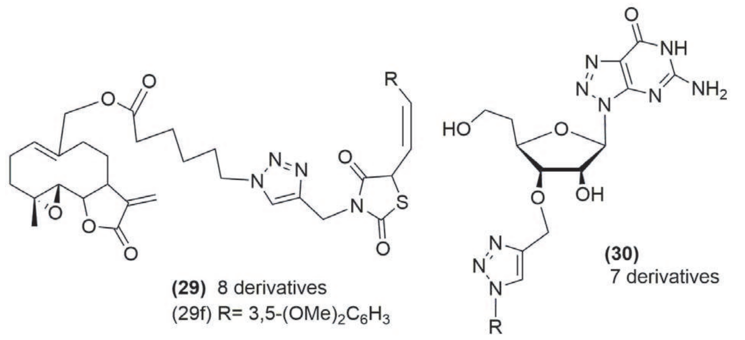


Figure 18.
Synthesis of parthenolide–thiazolidinedione and 3'-O-1,2,3-triazolyl-guanosine-5′-o-monophosphate derivatives.

erythroleukemia cell line (HEL) by MTT assay. The compound (29f) having 3,5-dimethoxyphenyl group exhibited the highest inhibitory effect against HEL (IC_{50} = 2.99 ± 0.22 μM), MDAMB-231 (IC_{50} = 2.07 ± 0.19 μM), and PC3 (IC_{50} = 3.09 ± 0.20 μM) (**Figure 18**).

Senthilvelan *et al.* [55] designed synthesis of 3'-O-1,2,3-triazolyl-guanosine-5′-*o*-monophosphate (30) from in situ generation of azide from the resultant bromide followed by copper and β-cyclodextrin catalyzed cyclo-addition with 3′-O-propargyl guanosine monophosphate in aqueous media. The designed pathway has high regioselectivity and gave good yield of products (**Figure 18**).

3.3 Metal-free approach for click reaction

Several new metal-free click chemistry assisted syntheses of heterocyclic scaffolds have been designed up to date. These pathways involve a variety of functional group tolerance in the substrate of cyclo-addition reaction. These synthetic pathways can be achieved under mild conditions and give high yields of desired products using organo-catalyst [56, 57]. In 2010, Fokin and co-authors developed the first transition metal-free synthesis of 1,5-diaryl-1,2,3-triazoles (31) employing azide-alkyne cyclo-addition [58] (**Figure 19 Method 1**). In this reaction, tetraalkylammonium hydroxide was used as the catalyst that provided moderate to high yield of products. Later on, in 2013, Ramachary and co-workers [59] achieved a region-selective synthesis of N-arylbenzotriazoles at room temperature using a cyclic enone and an arylazide under pyrrolidine catalysis at room temperature. Additional aromatization by DDQ gave fused heterocyclic scaffolds (32) (**Figure 19 Method 2).** In the subsequent year, a one-pot tandem,

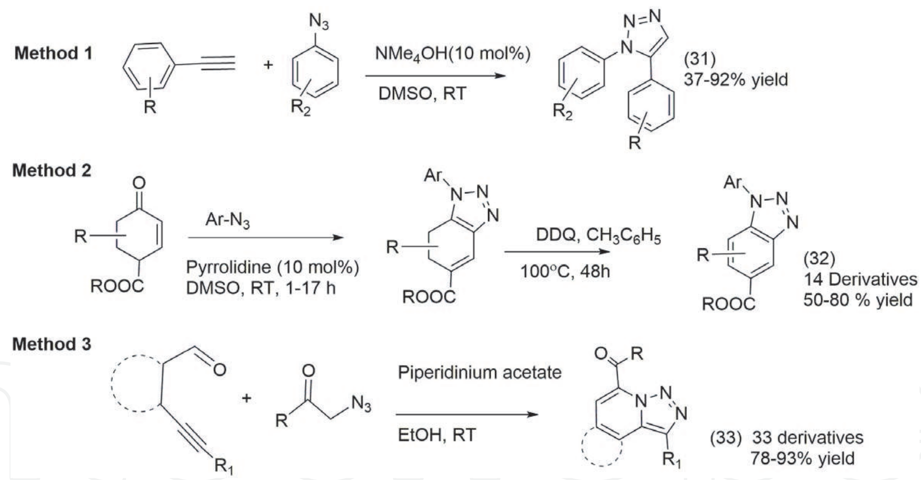
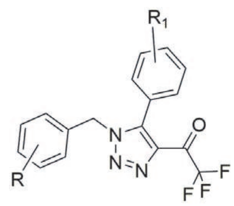


Figure 19.
Metal-free synthetic route of triazole based heterocycles.



(34)
12 derivatives
(32b) R=4-CH_3, R_1=H

Figure 20.
4-Trifluroacetyl 1,2,3-triazole derivatives.

Knoevenagel/azide-alkyne cycloaddition reaction between indole, aromatic aldehydes or pyrazole and phenylazide was fruitfully accomplished in the presence of piperidinium acetate in methanol to furnish the desired triazole derivatives (33) (**Figure 19 Method 3**) [60].

In 2018, Han *et al*. [61] developed a metal-free and solvent-free approach for the synthesis of 4-trifluroacetyl 1,2,3-triazoles in good yields with great selectivity. The synthesized compounds were examined for the anti-cancer activity and compound **34b** possessed superior activity as compared to others against HePG2 (0.0267 μmol/mL) (**Figure 20**).

In the same year, Tan *et al*. [62] used thiol-ene click chemistry for the controlled functionalization of poly vinylidene fluoride in the presence of a base. The mechanism of the reaction suggests that it involves addition reaction followed by both Markonikov and anti-Markonikov mechanism and furnishes the same product. Later on in 2019, Moore and co-workers [63] designed a novel methodology for the synthesis of ionic liquids which were based on fluoroalkynyl imidazolium using thio-ene/yne click chemistry. The pathway has high conversion efficiency and high yields with no need for further purification.

3.4 Visible light assisted click chemistry

Visible-light-assisted organic transformations have received a huge response in chemical synthesis in order to design environmentally friendly approaches. The synthesis using economical, easily available visible-light sources have become vanguard in the synthetic chemistry as a prevailing approach for the activation of small molecules to furnish the desired products [64–66].

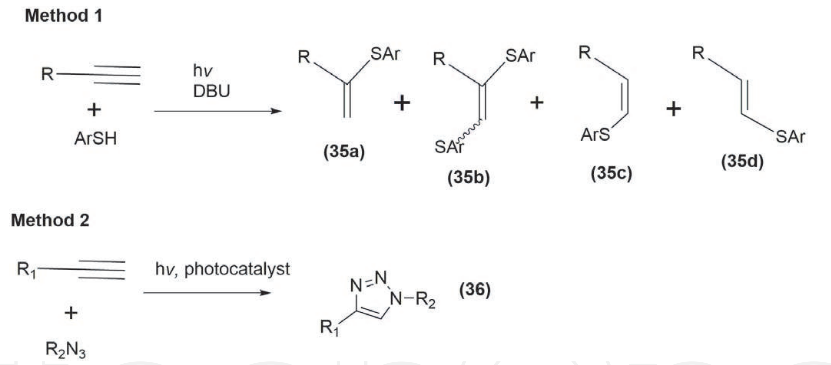


Figure 21.
Visible light assisted synthesis of vinyl sulphide.

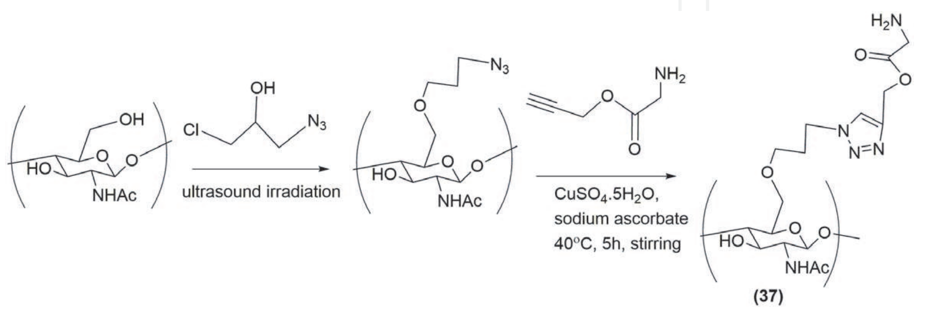


Figure 22.
Synthesis of ultrasound assisted 1-azido-3-chloropropan-2-ol azido chitin derivatives.

Burykina *et al*. [67] synthesized different kinds of vinyl sulphides **(35)** in high yields with good selectivity using thiol-yne click reaction using visible light. The designed pathway is transition-metal-free and gave Markonvikov-type product through a radical photo-redox pathway (**Figure 21 Method 1**).

Recently, Wu *et al*. [68] synthesized triazole analogs **(36)** through photo-redox electron-transfer mechanism. The authors inspected the reaction of benzyl azide with phenylacetylene using diverse photo-catalysts under ambient reaction conditions like room temperature (RT), air, and visible light irradiation. The catalyst $(piq)_2Ir(acac)$ or TPPT-Cl catalyzed the formation of triazole derivatives. The designed pathway is high region-selective, high yielding, having a high atom economy, and using solar catalysis **(Figure 21 Method 2).**

3.5 Ultrasound assisted click chemistry

Ultrasound assisted reactions are milder and faster. The mechanism of ultrasound is based on an acoustic cavitation phenomenon. This technology hastens the reaction in both heterogeneous and homogeneous media, due to amplified energy intake. It shortens the reaction time and augments the competence of the system by triggering the catalyst surface area and removing deposited impurities [69, 70]. A decades ago, Cintas *et al*. [71] depicted the synthesis of 1,4- disubstituted 1,2,3-triazole analogs using Cu under ultrasound irradiation exclusive of a ligand. Later on, a heterogeneous catalytic system, Cu(II) doped clay was used at RT with ultrasonic irradiations [72]. The use of heterogeneous catalyst evaded needless complexity due to copper (I) salt redox protocol that involved the presence of ligands and protecting agents. The reaction is eco-friendly, easy to prepare, and recoverable. One-pot synthesis of 1,4-disubstituted-1,2,3-triazoles was successfully achieved using a benzyl or alkyl halide, sodium azide, and a terminal alkyne under these conditions [73]. The formation of triazole starting from a TMS protected alkynylglycoside was also demonstrated under ultrasound conditions with *in situ* deprotection of TMS group [74]. In 2020, Kritchenkov *et al*. synthesized triazole chitin derivatives and used them in the synthesis of Pd(II) complexes. Initially, ultrasound-assisted interaction of chitin with 1-azido-3-chloropropan-2-ol gave azido chitin and was further converted to triazole derivatives **(37)** that were used as ligands for the complex formation (**Figure 22**) [75].

3.6 Microwave-assisted click chemistry

The use of microwave irradiation in cyclo-addition reactions for click chemistry has also been comprehensively deliberated. It allows efficient internal heat transfer and therefore decreases the reaction time as well as enhances the reaction rate with high yield [76, 77]. The increased temperature can be used over short periods thus avoiding decomposition or polymerization. Ashok and co-workers demonstrated the synthesis of 1,2,3-triazole analogs using microwave irradiations in 8–10 min and examined their antimicrobial activity [78] (**Figure 23 Method 1**). This method has also been applied in the preparation of 1,2,3-triazole analogs of nucleosides [79] (**Figure 23 Method 2**). In general, those reactions which require prolonged conventional heating are accomplished in just 10–15 min using microwave irradiation. A chronological one pot Ru catalyzed cycloaddition was also designed from primary aryl or aliphatic bromides (**Figure 23 Method 3**) [80].

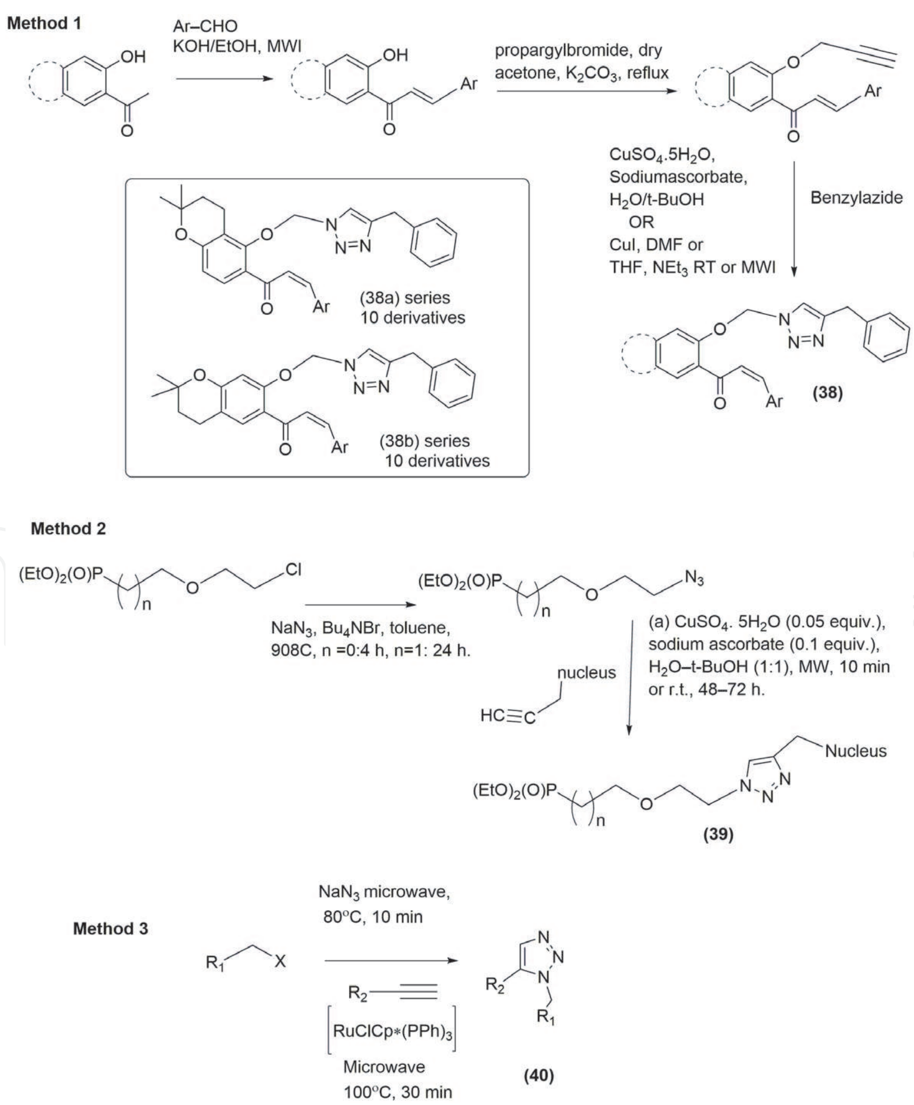


Figure 23.
Microwave assisted synthesis of triazole based scaffolds.

4. Click chemistry in polymer synthesis

In the past two decades, various polymers have been introduced through ionene synthesis, click chemistry, and Michael addition *via* polycondensation and polyaddition process. Click chemistry reactions are known as reliable, powerful, high-yielding, and selective for the synthesis of novel and combinatorial compounds *via* Diels Alder cyclo-additions, copper-catalyzed azide-alkyne cycloadditions (CuAAC), and azide nitrile cycloadditions process [81, 82]. In 2013, Pasini reviewed the utility of click reaction for the efficient synthesis of macrocyclic structures like polymers, bio-conjugates, and dendrimers in different contexts [83]. Recently, Arslan and Tasdelen systematically reviewed the applications of click chemistry in polymer design and synthesis, and studies based on their architecture like block, cyclic, star, hyperbranched, and graftbrush comb polymers [84].

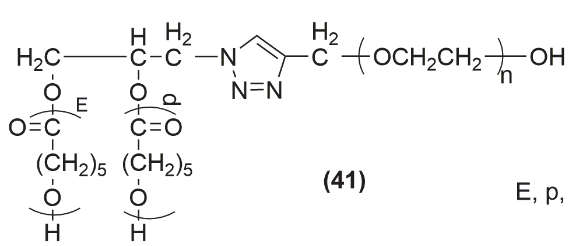
In 2018, Acik and co-authors demonstrated a simple copper (I)-catalyzed azide-alkyne cyclo-addition "click" reaction for the synthesis of polypropylene-graft-poly (L-lactide) copolymers (PP-g-PLAs) using different feeding ratio of alkyne end-functionalized poly(L-lactide) azide and side-chain functionalized polypropylene in the presence of CuBr/PMDETA and CuAAC [85]. This polymer exhibited special characteristics like good thermal property, wettability and biodegradability.

Öztürk and companions introduced efficient click chemistry inspired synthesis of an amphiphilic copolymer **(41)** from the reaction of propargyl-PEG and terminally azidepoly(ε-caprolactone) in $CHCl_3$ at ambient temperature **(Figure 24)** [86]. This method displayed a synergistic arrangement of hydrophilic PEG and crystalline PCL to furnish novel materials with good applicability.

Yang *et al*. synthesized poly(3-hexylthiophene)-multiwalled carbon nanotube (P3HT-MWCNT) hybrid materials from in-situ click chemistry using Cu(I) / DBU catalytic system [87]. This novel hybrid also termed as organic–inorganic donor-acceptor material displayed special characteristics such as better thermal stability, higher melting point of 243.2 °C, good solubility, and optical properties.

Wang *et al*. reported a novel and efficient method for the synthesis of amphiphilic star-like rod-coil block copolymer poly(acrylic acid)-*block*poly(3-hexylthiophene) through the combined effect of atom transfer radical polymerization, quasi-living Grignard metathesis method, and thiol–ene click reaction to furnish narrow molecular weight distribution and well-defined molecular structures [88].

Agrihari *et al.* introduced CuAAC catalyzed synthesis of *p-tert*-butylcalix[4] arene linked benzotriazolyl dendrimers using $CuSO_4.5H_2O$ and NaN_3 to prepare N-1, N-2 type 6 fold compounds in good yields [89]. The synthesized compounds were evaluated for *in vitro* and *in vivo* anti-bacterial studies against a range of microbes and demonstrated good biological potential. Chen and his companions devised superhydrophobic cotton fabric from mercaptan and vinyl trimethoxysilane using ultraviolet irradiation *via* thiol-ene click chemistry [90]. This fabric possesses special characteristics like economic, highly resistant towards acids, acetone, UV light, water, and other liquids.



(41)

Figure 24.
Poly(CL-co-EG)star-type amphiphilic coploymer.

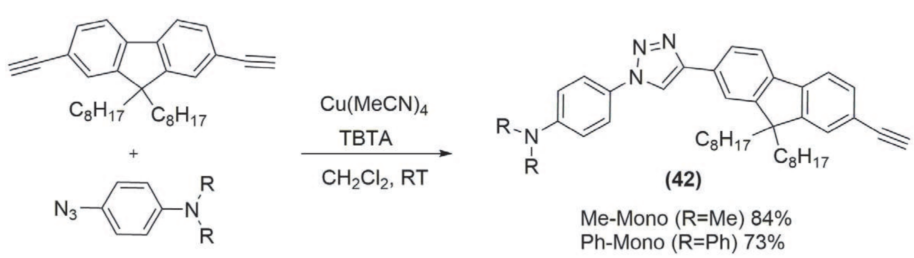


Figure 25.
Synthesis of triazole-based photo-initiators.

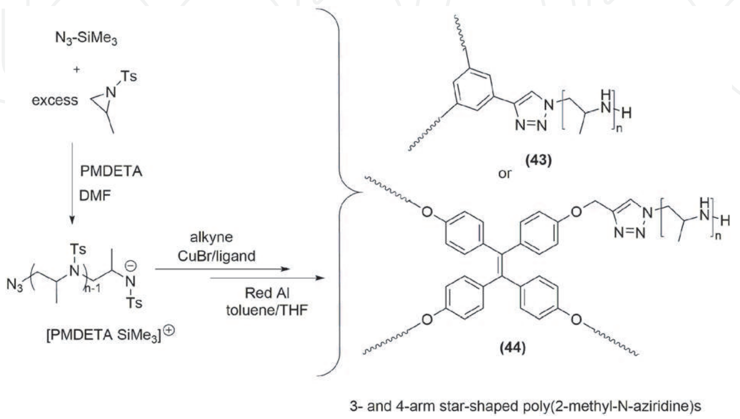


Figure 26.
3-and 4-arm star-shaped poly(2-methyl-N-aziridine)s.

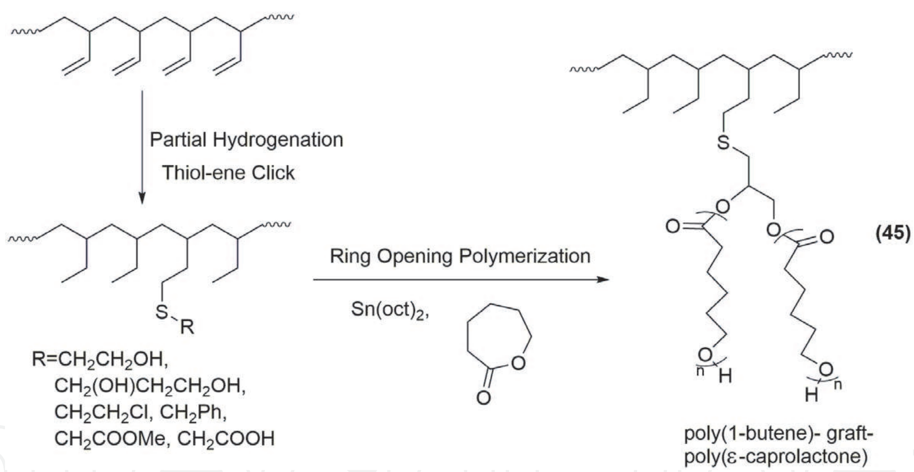


Figure 27.
Functionalized poly(1-butene) synthesis.

Henning *et al*. utilized copper-catalyzed azide/alkyne cycloaddition reaction for the efficient synthesis of triazole-based photo-initiators **(42)** for the two-photon polymerization process **(Figure 25)** [91]. Here Me-Mono and Ph-Mono initiators displayed higher tolerability and sensitivity in microfabrication areas.

A novel, facile and efficient synthesis of 3- and 4-arm star-shaped poly (2-methyl-N-aziridine)s **(43, 44)** from ring opening reaction of N-sulfonyl aziridines in the presence of trimethylsilylazide and PMDETA (N,N,N′,N″,N″-pentamethyldiethylenetriamine) through click reaction with CuBr and alkyne was demonstrated by Luo *et al*. **(Figure 26)** [92].

Cai *et al.* presented a one-step click chemistry process for the synthesis of high performance graphene oxide/ styrene-butadiene rubber (GO/SBR) composites using pentaerythritoltetra(3-mercapto propionate) [93]. Experiments and molecular simulation results concluded that these composites displayed upgraded gas permeability, thermal conductivity, dynamic, and static mechanical performances.

Tian and companions demonstrated the synthesis of the functionalized poly(1-butene)**(45)** *via* sequential thiol-ene click reaction and ring-opening polymerization using poly(1,3-butadiene) as a substrate **(Figure 27)** [94]. Here C=C bond was further functionalized from thiol-ene reaction using hydroxyl-containing thiol compounds.

Zhang *et al*. devised synthesis of thiol-maleimide 'click' chemistry based β-cyclodextrin polymers in an aqueous medium without generating by-products [95]. The structure of products was affected by temperature range *i.e.* higher temperature gave higher molecular weighted and compact structures. The obtained polymers showed better dissolution performance and drug complex-forming capacity as compared to the parental structure.

Gao *et al*. reported thiol-ene click reactions in polysulfide oligomers and acrylate monomers to prepare processable and self-healable thermosets and elastomers **(46)** *via* different pathways like photo-initiator, redox-initiator system and base mediated catalytic approaches **(Figure 28)** [96]. Reprocessable and self-healable properties depend upon polymer structure and their synthetic methodology, therefore, DBU based catalytic synthesis displayed better activity as compared to other processes, due to their catalytic efficiency for disulfide bond exchanges.

Zhu *et al*. introduced facile click chemistry assisted poly(2,2,6,6-tetramethyl-piperidin-1-oxyl-4-yl methacrylate) graphene oxide composite (PTMA-GO) **(47)** assisted reaction in ambient conditions and utilized them as cathode materials **(Figure 29)** [97]. After completing 300 charge–discharge cycles,the specific capacity was found to be 2.3 times higher for this composite as compared to the PTMA electrode.

Shen *et al.* devised synthesis of superhydrophilic and superoleophobic PEGylated PAN membrane **(48)** from poly (ethylene glycol) methyl ether methacrylate (PEGMA) monomers *via* thiol-ene click chemistry **(Figure 30)** [98]. After this fabrication, pore size of the membrane was reduced and displayed low flux. The

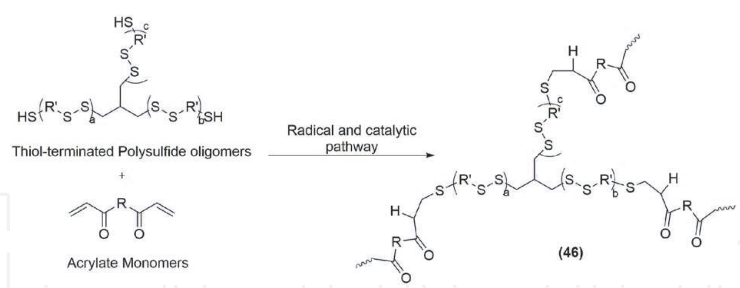


Figure 28.
Process able and self-healable polymer synthesis.

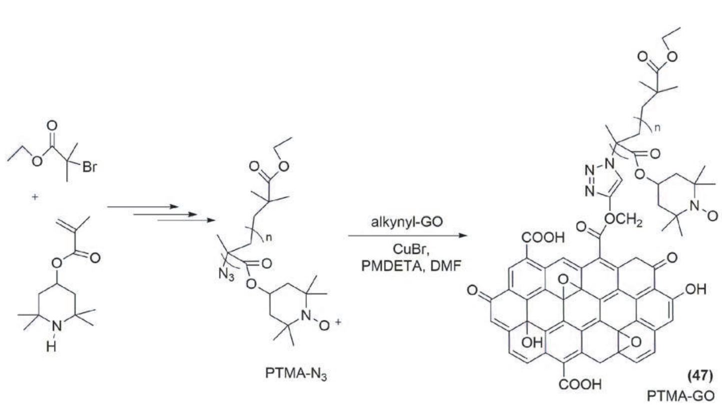
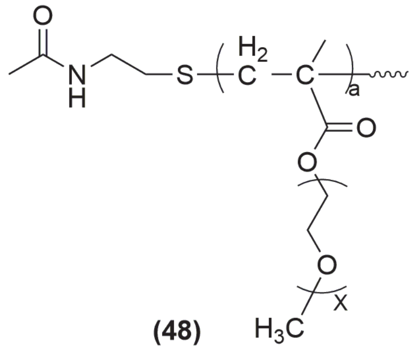


Figure 29.
PTMA-GO polymer synthesis.



(48)

PEGylated PAN membranes

Figure 30.
PEGylated PAN membranes.

fabricated membrane exhibited excellent separation (99%) of various oil–water emulsion and fouling-resistant ability.

5. Conclusion

Synthetic organic chemistry includes the synthesis of biologically active molecules and designing of potent scaffolds. Click chemistry is one of the toolboxes for chemistry, biology, nano, and material sciences. It has vivid applications in the synthesis of organic molecules, polymers, nanoparticles, biosensors, and many more. The concept of click chemistry fulfills the green aspects of a reaction. In this chapter, we have deliberated an incredible flurry of activities in the field of click chemistry inspired synthesis. This study highlights the current advancements in the synthesis of heterocyclic and other cyclic structures using click reactions. The insertion of a triazole ring with the help of click reaction increases the biological activity of the synthesized compounds. Different pathways with metal or metal-free conditions using conventional or non-conventional reaction methods have also been demonstrated in this chapter.

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Conflict of interest

The authors declare no conflict of interest.

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