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REVIEW ARTICLE

Click chemistry: A fascinating, Nobel-winning method for the improvement of biological activity

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ABSTRACT

Click chemistry is totally an approach consisting of efficient and reliable reactions that bind two molecular building blocks and require no complex purification techniques. The aspire of achieving molecules with the desired characteristics and behaviour is the key to the click chemistry concept. In this concept, in order to obtain 1,2,3-triazole products as diversely functionalized molecules, copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has been widely used for years in the field of materials science, organic synthesis and the biochemistry. This review focusses on the importance of click chemistry for obtaining biologically active triazole molecules and therefore the applications of such 1,2,3-triazole derivatives in medicinal chemistry field are highlighted.

Keywords: Click Chemistry; Triazole; CuAAC; Cycloaddition; Drug Discovery; Biological Activity

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1. Introduction

In order to create novel properties and functions, chemistry has a unique ability of achieving larger structures from small building blocks. Researchers in the field of materials, polymers, and even biotechnology are in an ongoing pace of research on binding strategies that can be effectively used in the presence of a wide range of different functional groups encountered. To develop successful binding strategies, basic requirements such as high selectivity, tolerance against other functional groups, compatibility for water and other protic solvents, and most importantly, good quantitative yield must be provided[1–3]. Materials scientists and those working in the field of biotechnology have tended to advanced synthetic organic concepts day by day in order to progress in this direction and reach the goal. As a result of these efforts, the efficiency level and satisfactory/further developable results achieved in molecules with biological activity have encouraged scientists to search better processes.

In this context, the most popular and maybe the most striking topic, click chemistry consisting of several distinct chemical reactions (cycloadditions, additions to carbon-carbon multiple bonds, nucleophilic substitutions and carbonyl chemistry of non-aldol typed transformations) has been a significant totally approach for molecular design and synthesis emphasizing the construction of carbon-heteroatom (C–X–C) linkages in joining modular building blocks[4–7]. Comprising carbon-heteroatom

bond formation rather than C–C bond reveals great potential of simplifying drug synthesis methods and so accelerating the drug discovery processes[8,9]. Moreover, the reaction processes have characteristics such as simple operation, mild reaction conditions (not sensitive to oxygen and water), high selectivity and so high reaction yield along with non-difficult purification/product isolation technique. Within this scope, among the mentioned multicomponent reactions that offer many opportunities for a great number of post-condensation cyclizations, cycloaddition between azides and alkynes (Huisgen reaction) has gained much more and ever-increasing attention in consequence of yielding potentially biological active 1,2,3-triazole compounds[10–12].

Briefly, click reactions and of course 1,2,3-triazole scaffold have a wide range of applications in a biological sense, and in recent years, some excellent reviews have summarized the successful applications in that field[13–16]. However, this review does not focus on only one topic, but also aims to present up-to-date approaches about the biological applications of 1,2,3-triazole-appended hybrids in the recent year by examining the structure-activity relationship with the support of theoretical synthesis knowledge. We hope this review will be of an insight to researchers for the rational design of novel compounds with higher efficacy biological applications.

2. Design, synthesis, properties and applications of 1,2,3-triazoles

Click chemistry is still developing as a powerful method in the biomedical field, which has a wide range of applications from combinatorial chemistry to target-oriented *in vitro* chemistry and plays a role in identifying active compounds that will benefit drug design and converting them into more active and clinically appropriate drugs with various modifications[17–19]. When the reason of such importance and increasing popularity of the related reaction are questioned, the pharmacological importance of 1,2,3-triazole compounds emerges as an answer.

As a heterocyclic group, the 1,2,3-triazole ring system has been continuing to be the subject of extensive research due to its pharmacological properties and usefulness in synthetic organic chemistry. In addition to their application (corrosion inhibitors, photographic photoreceptors, photostabilizers of polymers, dyestuff, fluorescent whiteners, optical brighteners) in many fields in the industry[20], 1,2,3-triazoles also steer with many successful applications in the field of pharmaceuticals and agrochemicals due to their wide biological activity capacity[21,22]. Moreover, thanks to their tolerance for typical biological conditions and almost all functional groups along with hydrogen bonding capacity based high solubility in aqueous solutions, 1,2,3-triazole compounds are targeted in the synthesis of various polymeric carrier systems and dendrimers, crosslinking of micelles and the syntheses on modifying the surfaces of various nanoparticle carrier systems[23–27]. The stability of those compounds makes the reaction in which they are synthesized extremely ideal for bioconjugation, and so as a result, the binding of oligonucleotides, proteins, polysaccharides, viruses and bacteria such as E. coli to various substrates is successfully accomplished using this approach[28–33].

After click chemistry approach has been first introduced by Karl Barry Sharpless in 1999, Cu-catalyzed azide-alkyne cycloaddition (CuAAC) version of Huisgen 1,3-dipolar cycloaddition reaction was separately reported by Sharpless and Meldal groups. In fact, the 1,3-dipolar cyclization of Huisgen which occurs with the absence of a catalyst, cannot be basically classified in click chemistry since it is a non-selective reaction that progresses slowly and has a mechanism in which 1,4- and 1,5-disubstituted products are formed in equal proportions (**Figure 1**). When the heat-assisted reaction occurred, the probability of attack of the azide group that triggers the reaction to both sides of the alkyne group increases, resulting in the formation of these 1,4- and 1,5-products (in a ratio 1:1) and reducing the yield[34,35].

In the study that the foundations of click chemistry were laid by Sharpless and co-workers in 2001, the breakthrough of the related reaction into the click concept classification was made possible as a result of accelerating the process with various metal catalysts such as Cu(I), Ru, Ni, Pd and Pt and improving its yield significantly by increasing its regioselectivity. In the related work, it was reported that only 1,4-

disubstituted product was formed when the Huisgen process was carried out with copper catalysis, and there was a significant increase in reaction rate, selectivity and yield, and so such reactions were defined as “copper-catalyzed azide-alkyne cycloaddition reaction” (CuAAC) (**Figure 1**). Along with the most common catalysts used for this purpose being as Cu(I) salts (CuI, CuBr), the relevant catalytic medium can also be provided by the conversion of Cu(II) salts ($CuSO_4.5H_2O$, $Cu(OAc)_2$) to Cu(I) with a reducing agent such as sodium ascorbate or metallic copper[36–38].

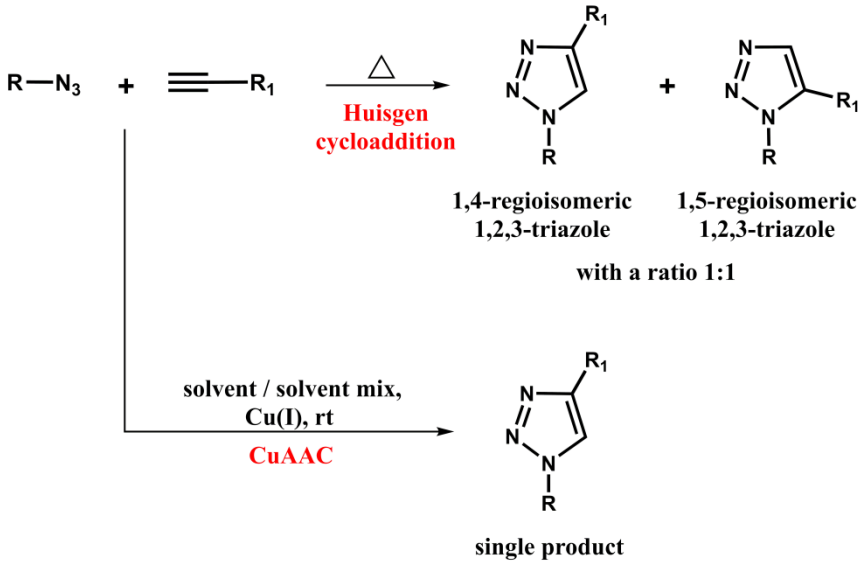

Figure 1. Synthetic routes for 1,2,3-triazoles.

In addition to those, various mixtures of solvents such as *t*-BuOH, H_2O and THF are used together with related catalysts, and in that case, there is no need for using a base for the formation of the copper-acetylene complex. However, in cases where aqueous solutions cannot be used, catalysts such as CuI, $Cu(CH_3CN)_4PF_6$, $CuBr(PPh_3)_4$, $CuIP(OEt)_3$ and $CuOTf.C_6H_6$ in stoichiometric ratio, and an excessive amount of tertiary base (TEA, DIPEA, 2,6-lutidine) in the presence of organic solvents (THF, toluene, CH_2Cl_2, acetonitrile) could be used[39,40].

Although synthetically derived those compounds containing 1,2,3-triazole group have various biological activities such as anticancer[41–44], antibacterial[45,46], antifungal[47,48], anti-HIV[49,50], antituberculosis[51,52], antioxidant[53,54], antiproliferative[55,56] and enzyme inhibitory[57,58], these compounds are not found in nature. Therefore, the importance of these compounds in medicinal chemistry field has become undeniable, and so 1,2,3-triazole groups have been described as a “pharmacophore group” with the meaning of the main functional group responsible for the effect of a drug compound and the synthesis of the related compound has been carried out by many scientists after that time[59].

Another term used in the scientific community especially in pharmaceutical sciences to indicate the importance of 1,2,3-triazole groups is the concept of “bioisostere”. The use of this concept is based on the term “isosterism” which was defined by Langmuir in 1919 to denote molecules or ions containing the same number of atoms and valence electrons[60]. Bioisosterism means the formation of compounds with the same biological characteristics as a result of the replacement of atoms or molecular groups constituting a compound with other atoms or groups having similar physical/chemical properties. And the term “bioisostere” is defined as substituents or groups with the same physical or chemical properties that bring in substantially similar biological activity to a compound. When evaluated in terms of 1,2,3-triazole compounds, those compounds are likened to peptide bonds that connect amino acids in the structure of proteins, and for this reason, the two groups have been described as bioisosteres of each other by being similar to amide compounds from the point of electronic and bonding properties[61,62].

As seen in **Figure 2**, the triazole ring is

structurally similar to the amide group, depending on the substitution status of the "R" groups on it, and by considering these substitution orientations, it comes out that the 1,4-disubstituted triazole compound structurally mimics the *trans*-amide bond. While the unpaired electron on the highly polar carbonyl oxygen is imitated by the unshared pair on the nitrogen in the triazole structure, the donor feature of the N-H bond in the amide structure coincides with the donor feature of the acetylene proton in the triazole ring[63,64].

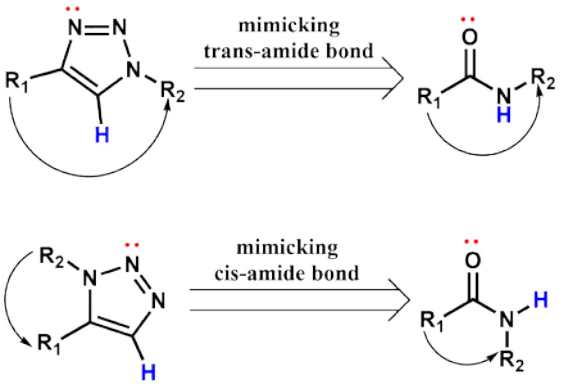

Figure 2. Isosteric similarity of 1,4- and 1,5-disubstituted 1,2,3-triazole with the amide functional group, showing cis/trans arrangements and H-bond donating/accepting sides.

Besides, another important feature is that the amide carbonyl carbon is imitated by the quaternary acetylene carbon in the triazole scaffold, along with a small difference on the distance between the substituents (two atoms in the amide, and three atoms in the triazole structure). As can be seen in the same figure, the 1,5-disubstituted triazole ring mimics the cis-amide bond. In the 1,5-disubstituted structure, while acceptor/donor parts with the H-bonding capacity are similar, the presence of a negatively charged nitrogen atom instead of the more important electrophilic carbonyl carbon can make the 1,5-disubstituted structure less active than the 1,4-disubstituted one[65,66]. Therefore, for the literature survey, it can be said that the 1,5-disubstituted structure is less reported compared with the 1,4-disubstituted triazole scaffold.

As is well known, until today, among the most known triazole compounds in terms of their activities and uses, Ticagrelor, Rufinamide, Cefatrizine, Tazobactam, Carboxyamidotriazole (CAI), tert-Butyldimethylsilylspiroaminooxathioledioxide (TSAO), Volitinib, Redezolid and Solithromycin have taken part as approved drugs or clinical trials/drug candidates[67–70]. In order to synthesize the examples given and other many 1,2,3-triazole compounds in the literature, copper catalyzed azide-alkine cycloaddition (CuAAC) reactions under Huisgen's temperature catalyzed azide-alkyne 1,3-dipolar [3+2] cycloaddition and so click chemistry classification have been continuing their popularity from past to present. Considering that the field in question is classified under the title of multidisciplinary chemistry as a result of synthesis-biological activity correlation, it is understood that this click reaction offers a unique approach for the synthesis of molecules containing 1,2,3-triazole group, and, has shown a motivating and guiding feature for many scientists and has directed various syntheses with the attractiveness of their remarkable activity potentials.

Bioorthogonal click chemistry which was briefly introduced to the scientific community by Bertozzi and her group in the early 2000s as the version of click chemistry performed in a biological media, refers to the chemical strategies that can occur both *in vitro* and *in vivo* environments without any disorders on inherent biochemical processes, metabolism and viability[71]. In this context, Tei and Baskin[72] discussed phosphatidic acid (PA) molecule that functions as both a key intermediate for phospholipid synthesis and controls such processes as vesicle trafficking, actin dynamics, cell growth, and migration with its potent signalling feature (**Figure 3**). In order to determine PA production, they visualized phospholipase D enzyme (PLD) that plays an active role in its synthesis. In this sense, as a result of attaching alkyne group containing OH functionality to the PLD enzyme and then performing click reaction with various azide structures, the activity of PA activity in living cells was determined by monitoring PLD-mediated PA signals through the fluorescently labelled PLD enzyme via bioorthogonal click chemistry tagging technique. This developed technique called imaging phospholipase D activity with clickable alcohols via transphosphatidylation (IMPACT) was reported as promising many new insights into lipid signalling pathways.

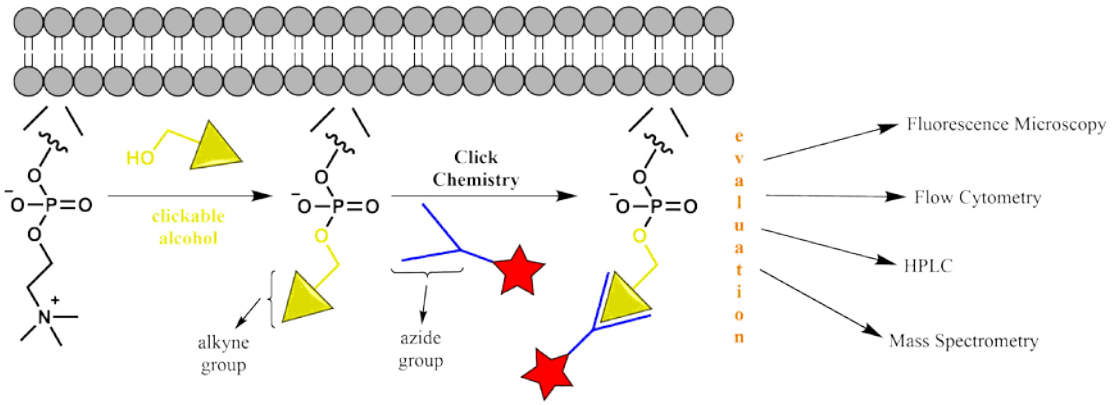

Figure 3. General overview of the bioorthogonal click chemistry approach for visualization of PLD-mediated PA signaling.

Kuczynska *et al.*[73] reported twelve 1,2,3-triazoles derived from a triterpenoid namely betulin showing a broad range of biological activities including antimalarial, anti-inflammatory, antiviral and cytotoxic (**Figure 4**). Newly synthesized azide derivatives of betulin skeleton were coupled with various phenylalkynes having different substituents via copper-catalyzed 1,3-dipolar cycloaddition (CuAAC) reaction affording the target 1,2,3-triazole scaffolds. These compounds were tested for their cytotoxic activities in cancer cell lines (CEM, MCF-7, HeLa, G-361) along with human skin BJ healthy fibroblasts. It was reported that, a few of twelve compounds showed good activity and selectivity against cancer cell line and that further manipulation of functional groups within the lupane scaffold appeared to be necessary.

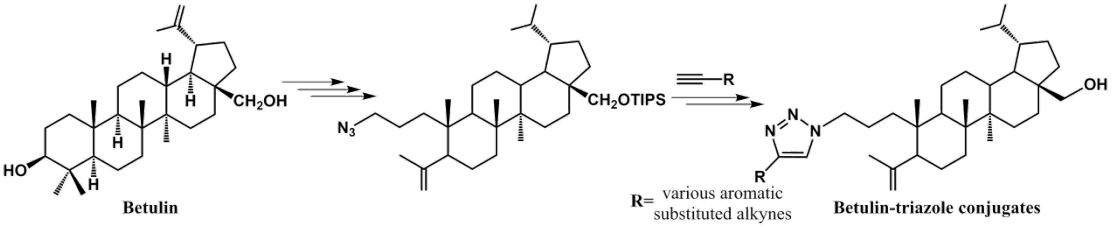

Figure 4. Synthesis of new cytotoxic derivatives of already biologically active compound betulin *via* CuAAC reaction.

In order to develop new drug classes, especially novel antibacterials, Daher and his group[74] have worked with an approved drug, solithromycin (SOL). In accordance with the structure-activity relationship studies, they presented design and synthesis of sixteen SOL analogs by the side chain and amino sugar modifications via click chemistry (**Figure 5**). Then, in order to make comparative evaluation of the *in vitro* potential and scope of SOL and its triazole analogs, they were all tested against various bacterial strains including Staphylococcus aureus and Escherichia coli. The results of the minimum inhibition concentration (MIC) assays revealed that four analogs were equipotent with SOL while two analogs displayed enhanced antibacterial activity against strains in comparison to SOL.

In another work, Antoszczak and his group[75] chose to use Salinomycin (Sal), a biologically active natural product, as a starting material and then synthesized its derivative namely Ironomycin containing a terminal alkyne group (**Figure 6**). As the related alkyne derivatized compound showed more potent against breast cancer stem cells than Sal, eight 1,2,3-triazole derivatives of Ironomycin were obtained using various organic azides through click chemistry. As a result of their antiproliferative activity for the breast cancer stem cells, four triazole products exhibited much more potent activity than promising starting material Ironomycin.

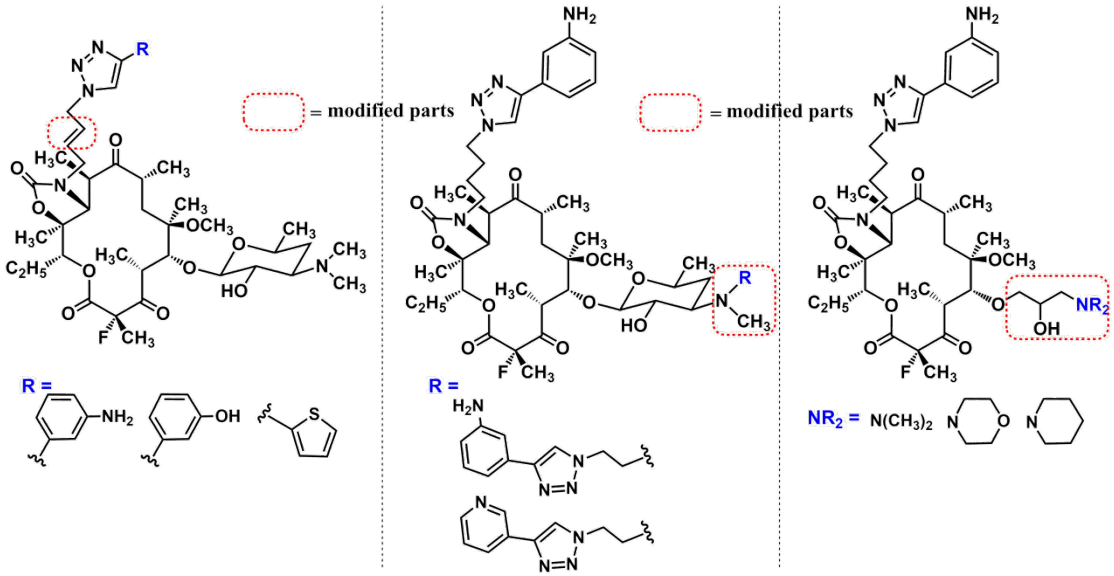

Figure 5. Design and synthesis of a novel series of a drug under clinical development, namely solithromycin, in order to explore structure-activity relationship.

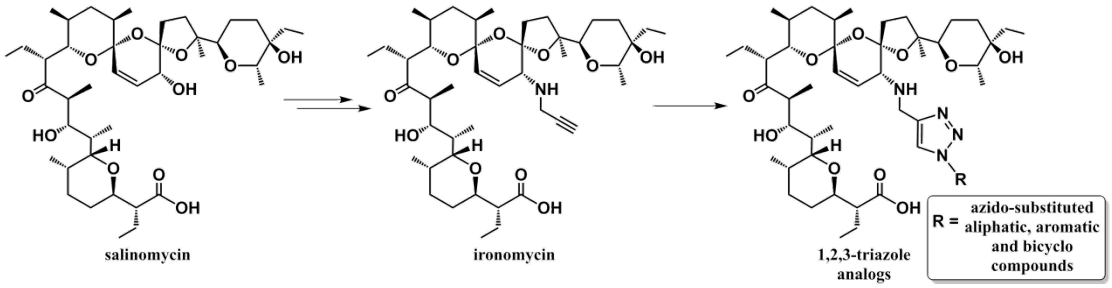

Figure 6. Synthetic access to Salinomycin-triazole analogues through the click chemistry concept for developing more potent active compounds towards cancer stem cells.

By following a similar approach, Carvalho *et al.*[76] tried to get higher biological activity by modifying Lavendustin A, a natural product that presents strong tyrosine kinase inhibitory feature along with anticancer activity (**Figure 7**). Also, inspired by the antiproliferative and anti-infective activities of its synthetic derivatives, they searched for the antiprotozoal activity of ten triazole bioisosteric analogs of Lavendustin A. In cell culture conditions, IC_{50} data against Trypanosoma cruzi protozoa exhibited significant antiprotozoal/antiparasitic activity for four triazole analogs with the values between 7.6 and 14.1 μM.

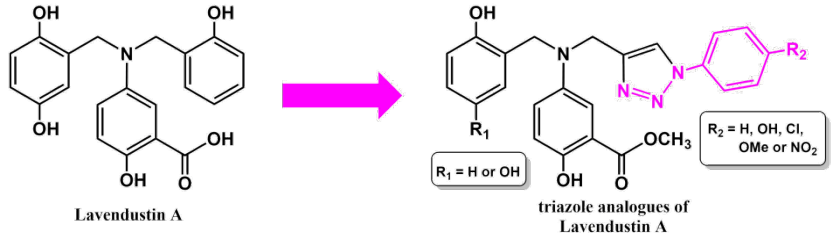

Figure 7. Schematic representation of Lavendustin A-triazole analogues synthesis employing CuAAC reaction in order to achieve more potent antitrypanosomal activity.

In order to find a way out for the coronavirus disease (COVID-19) that has caused very trouble time for humanity, Traube *et al.*[77] followed the small interfering RNA (siRNA) based strategy against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral agent (**Figure 8**). In the related work, they synthesized chemically modified siRNAs containing alkyne groups, and followingly, by performing the Cu(I)-catalysed click reaction with azido-modified peptide, the peptide-siRNA conjugate

was obtained. Within the context of nucleic acid-based therapeutics, the researchers reported that viral loads and virus induced cytotoxicity were reduced by five-fold by their siRNA in cell lines challenged with SARS-CoV-2.

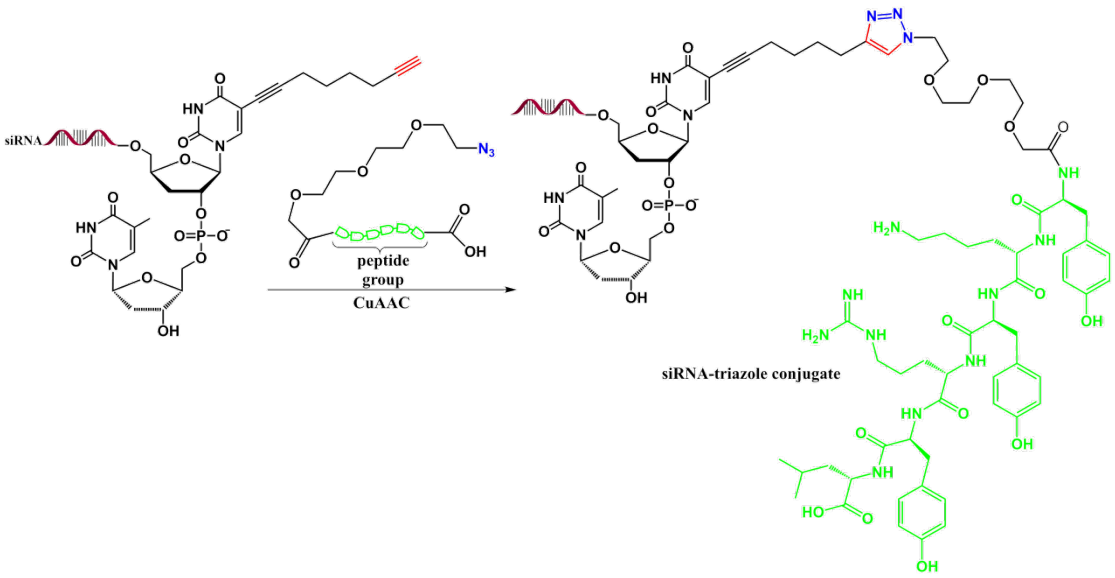

Figure 8. Click chemistry modified siRNA for an antiviral defence strategy against SARS-CoV-2 virus.

Table 1. Summary of the survey for 1,2,3-triazole based scaffolds with biological application

Type of the 1,2,3-triazole based-compound	Method of preparation	Biological activity/application	Reference
Enzyme labelling through alkynols and fluorescently active azides	Bioorthogonal (copper free) click reaction (SPAAC)	Visualization of Phospholipase D enzyme	[72]
Analogs of Betulin	CuAAC	Anticancer activity	[73]
Analogs of Solithromycin	CuAAC	Antibacterial activity	[74]
Analogs of Salinomycin	CuAAC	Antiproliferative activity against cancer stem cells	[75]
Analogs of Lavendustin A	CuAAC	Antiprotozoal/antiparasitic activity	[76]
siRNA-peptide conjugate through alkyne containing RNA and azido-peptide	CuAAC	Anti-SARS-CoV-2 activity	[77]
Derived from enolizable carbonyl compounds, primary amines and 4-nitrophenyl azide	Temperature catalyzed azide-alkyne [3+2] cycloaddition	Anti-SARS-CoV-2 activity	[78]
Derived from arylsulfanes and benzylacetates	CuAAC	Antimalarial/antibacterial/antifungal activity	[79]
Phenanthridinyl piperazine analogs coupled with aryl and aryl sulfonyl groups	CuAAC	Antiproliferative activity against cancer cells	[80]
Acridinone analogs coupled with aromatic azides	CuAAC	Anticancer activity	[81]
Indole-acrylamide analogs coupled with aromatic azides	CuAAC	Enzyme (α-glucosidase) inhibitory activity	[82]
Thiosemicarbazone analogs coupled with aromatic azides	CuAAC	Antibacterial activity	[83]
Analogs of (R)-carvone coupled with internal alkyne	Temperature catalyzed azide-alkyne [3+2] cycloaddition	Antiproliferative activity against cancer cells	[84]
Sulfonamide analogs coupled with aromatic azides	CuAAC	Antibacterial activity	[85]

Because a complete survey of 1,2,3-triazole based biologically beneficial compounds is too much difficult with the meaning of describing all publications in this paper, readers/colleagues who have been interested in looking for more frameworks could consult several publications given in **Table 1** along with the criticized works given above.

3. Conclusions

In this review, we have highlighted the importance of the click chemistry concept and especially the use of 1,4-disubstituted 1,2,3-triazole compounds as bioisosteres of Z-amide bond of amide functional groups. In the majority of the conveyed studies about drug discovery/development, in order to enhance the stability of the parent molecule while retaining/improving its biological activity, the amide bond is substituted with 1,4-disubstituted 1,2,3-triazole scaffold. In other words, that type of triazole compounds possess wide range of promising biological activity, so conjugation/hybridization of 1,2,3-triazole and other pharmacophores has been a pretty reasonable strategy to discover new biological active candidates. Not surprisingly, all the assertive studies cited were published in the past couple of years, demonstrating that the click chemistry concept along with 1,2,3-triazole scaffold has been still continuing to develop for the design biologically active compounds.

Conflict of interest

The authors declare that they have no conflict of interest.

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