EXPLORING THE APPLICATIONS OF "CLICK CHEMISTRY"

Dr. Thasnim. P

PG Department of Chemistry, KAHM Unity Women's College, Manjeri,

Narukara (PO), Malappuram (Dt), Kerala, Pin: 676122

E-mail: thasnim6390@gmail.com

Abstract

Mimicking natural biochemical processes, click chemistry is a modular approach to organic synthesis, joining together small chemical units quickly, efficiently and predictably. In contrast to complex traditional synthesis, click reactions offer high selectivity and yields, near-perfect reliability and exceptional tolerance towards a wide range of functional groups and reaction conditions. These 'spring loaded' reactions are achieved by using a high thermodynamic driving force, and are attracting tremendous attention throughout the chemical community. Originally introduced with the focus on drug discovery, the concept has been successfully applied to materials science, polymer chemistry and biotechnology.

Introduction

The term "Click Chemistry" was introduced bySharpless*etal*. in 2001 to describe chemistry tailored to generate substances quickly and reliably by selectively joining ("click") small units together similar to the modular strategies adopted by Nature.[1]These authors suggested a set of requirements to be fulfilled by a reaction toclassifyitasa 'Click' reaction.[1]The main goal was to encourage synthetic chemists to focus more on the production of arrays of simple molecules with the same properties available in complex natural molecules by making use of carbon-carbon and caron-hetero atom bond formations in a much simplar way similar to Nature's synthetic strategy.[1]Click reactions are modular reactions with wide scope, high product selectivity and high thermodynamic driving force, usually greater than 20 $kcalmol^{-1}$. Such "spring-loaded" reactions proceed rapidly to completion and also tend to be highly selective towardsthe formation of a single product. Generally, Click reactions are room temperature reactions based on readily available starting

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materials and benign solvents, yielding near quantitative amount of products via simple and non-chromatographic separation methods.

Among the various reactions that are fulfilling the Click criteria, the [3+2]azide-alkyne cycloaddition (Huisgen cycloaddition) is now emerged as an established tool in modern medicinal chemistry.[2]Azide and alkyne functionalities can be readily introduced and have a high tolerance for various other functional groups and have enough kinetic stability.[3] Since the work presented in the upcoming chapters are on the use of Copper (I) catalyzed the [3+2]azide-alkyne cycloaddition for the development of multipurpose small molecules for medicinal and materials applications, the focus of this review has been restricted to 1,3-dipolar click cycloadditions.

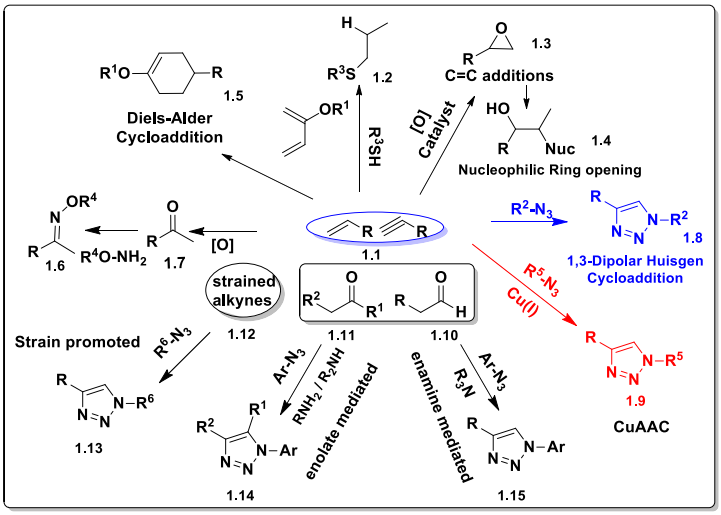

Figure 1: Classification of Click reactions

1,3 -Dipolar Cycloadditions and CuAAC

The 1,3-dipolar cycloaddition is a chemical reaction between a 1,3-dipole and a dipolarophile to form a five-membered ring. In 1960s, recognized this type of reaction for its generality, scope and mechanism by Huisgen, and he coined the term 1,3-dipolar cycloaddition.[4]Hence, the reaction is sometimes referred to as the Huisgencycloaddition.Unfortunately, the thermal Huisgen 1,3-Dipolar cycloaddition of alkynes to azides requires high temperatures and often produces mixtures of the 1,4- and 1,5-disubstituted 1,2,3-triazoles when using asymmetric alkynes.[5]A copper-catalyzed variation of Huisgen'sazide–alkyne cycloaddition (CuAAC reaction) was reported by the groups of Meldal and Sharpless independently in 2002.[6]This reaction fits the "click chemistry" concept

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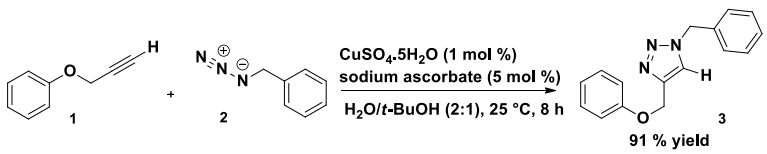
well because a close examination of the azide-alkyne cycloaddition shows that it fulfills many of the prerequisites of click concept.



Scheme1. Example for CuAAC reaction of benzyl azide with (prop-2-yn-1-yloxy)benzene

This reaction is applicable to a wide variety of substrates with various functional groups and the catalytic process is insensitive towards the presence of air and pH changes in a solvent mixture of water and *t*-BuOH. This strictly regioselective stepwise process selectively produce 1,4-disubstituted 1,2,3-triazole only and accelerates the reaction by a factor of up to 10^7 in comparison to Huisgen'sthermal procedure.[7]In addition to this, since large number of monosubstituted alkynes and organic azides are commercially available and many others can easily be synthesized with a wide range of functional groups, it is easy to make large library of 1,2,3-triazoles derivatives for screening purpose.

Applications of Click Chemistry (CUAAC)

The popularity of the CuAAC is largely a result of the unique properties of both azides and the resulting triazoles.[8]The combination of the robustness of the triazole bond, the resemblance to an amide bond, and the potential biological properties it could endow make the triazole linkage not merely a benign, easily synthesized linker, but an integral part of the success of click chemistry. In addition to this, the simplicity, reliability and the bioorthogonality of the starting materials has made the CuAAC reaction an asset to a hugely varied range of scientific applications. The wide scope of CuAAC is firmly demonstratedby the use in different areas of life and material sciences such asdrug discovery,[9] bioconjugation,[10] polymer and materialsscience,[11]including supramolecularchemistry.[12] DNA labeling[13]and oligonucleotide synthesis,[14] assembly of glycoclusters[15]and glycodendrimers,[16] preparation ofstationary phases for HPLC column,[17] development of microcontact printing,[18] conjugation of molecular cargos to the headgroup of phospholipids,[19] and construction of bolaamphiphilicstructures[20]are a further examples of the use of CuAAC. It would be impossible to give a complete overview of the numerous applications of the CuAAC. For our purposes, the applications of 'click' chemistry have been summarized with

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illustrative examples in various categories; applications in materials science, for radiolabelling, for bioconjugation, and in drug discovery.

a) Material Science

The value of click chemistry for materials synthesis possibly becomes most apparent in the area of material chemistry. Several recent reviews have described the use of CuAAC for the synthesis of macromolecular structures like dendritic, branched, linear and cyclic co-polymers.[21] Triazole-based dendrons can be divergently synthesized via CuAAC reaction. These dendrons were then anchored to avariety of polyacetylene cores to generate dendrimers. Since then, the CuAAC reaction has been widely employed to synthesize or modify various dendrimers.[22]A click chemistry based dendrimer **4** is shown in Figure 2.

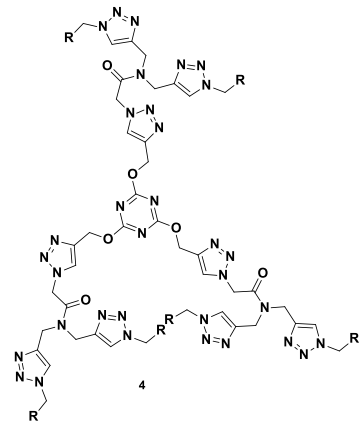

Figure 2.‘Click’ chemistry based dendrimers

b) Bioconjugation

Bioconjugation is the process by which synthetic molecules are attached to biological targets or by which biomolecules are linked together. It involves attachment of synthetic labels to biomolecular building blocks, such as fusing two or more proteins together or linking a carbohydrate with a peptide, and covers a wide range of science between molecular biology and chemistry. The possibility of applying click chemistry in bioconjugation was first demonstrated by Meldal*et al* for the preparation of peptidotriazoles*via* solid state synthesis.[6a] Their goal was to develop new and more efficient synthetic methods to prepare various [1,2,3]-triazole pharmacophores for potential biological targets. This initial report made

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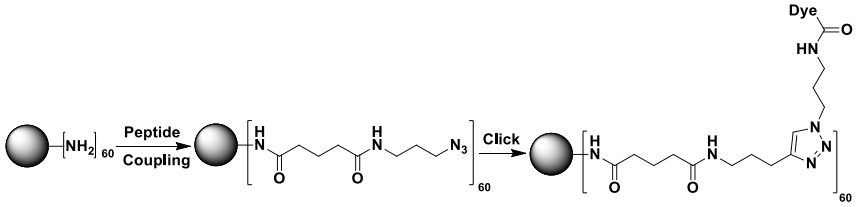
possible the introduction of various novel functional and reporter groups into biomolecules such as peptides and proteins,[23] for DNA labeling and modification,[24] and for cell surface labeling.[25]

Finn and co-workers successfully labeled Cowpea mosaic virus particles (CPMV) with fluorescein with >95% yield.[26] Similarly, Tirrell and Link were able to modify *Eschericia coli* with an azide-bearing outer membrane protein C(OmpC). Schultz *et al* developed a method to genetically-encode proteins of *Saccharomyces cerevisiae* with azide- or acetylene-based synthetic amino acids.[27]The genetic modification was done by reacting an alkyne or an azide bearing protein with the counterpart unnatural amino acid. Click chemistry continues to attract attention for labeling of proteins and live organisms.



Scheme 2. Labelling of virus capsids by CuAAC

c) Radiochemistry

The CuAAC is an ideal ligation reaction for radiolabeling sensitive biomolecules. Alkyne or azide derivatives of radioisotope containing compounds could be used for labeling biomolecules such as folic acid, peptides, proteins, and glycopeptides. For example, an ^{11}C isotope label was introduced via converting [^{11}C]-CH_3I into [^{11}C]-CH_3N_3 by nucleophilic substitution and subsequently reacting the azide with an alkyne-modified peptide. ^{18}F labeling for PET imaging was achieved by clickingazidomethyl-4-[^{18}F]-fluorobenzene to a modified peptide.[28]CuAAC ligations have a significant impact on the synthesis and development of radiopharmaceuticals and it has vast application in the preparation of imaging agents for SPECT and PET, including small molecules, peptides, and proteins labeled with radionuclides such as ^{18}F, ^{64}Cu, and ^{111}In.[29] Various researchers have shown that CuAAC is a great approach for the construction of radiotracers also.

d) Drug Discovery

In history and even now a days, lead discovery and optimization had aided by combinatorial methods and high throughput screening to generate library of test compounds

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for screening. However, due to unreliability and new discoveries revealed click chemistry as a modular for the synthesis of drug-like molecules that can accelerate the drug discovery process by utilizing a few practical and reliable reactions. It is a new type of chemistry that able to synthesize complex molecule in an efficient manner.[1]It makes use of few chemical reactions for the synthesis and designing of new building blocks.Drug discovery based on Natures secondary metabolites is very slow and complex synthesis and thereby, click chemistry provides faster lead discovery and optimization.[1]

Thiscommendably straightforward chemistry, which can be conducted in aqueous media, has been widely applied as a powerful tool for theselective modifications of enzymes[30] viruses[31]and cells.[32] Among the best-known examples of triazole-containing structures is, a β-lactamase inhibitor which is marketed in combination with the broad spectrum antibiotic piperacillin. Indeed, when first described, tazobactam and related triazole-containing compounds (**5**, Figure 3) turned out to be potent β-lactamase inhibitors with higher potency than clavulanic acid and sulbactam, and the triazole ring appears to play a pivotal role for its potency.[33] In the antibiotics field, triazoles have been also used to improve pharmacokinetic properties of the desired drug. For example, cephalosporins endowed with good oral availability were obtained linking the triazoles moiety to the cephalosporin core (**6**, Figure 3).[34]Indeed; it is not just antibiotics which benefit from the triazole ring.

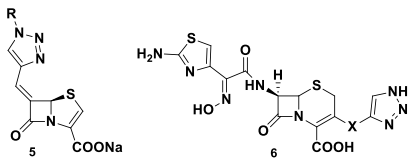

Figure 3. Example of β-lactamase inhibitors incorporating the 1,2,3-triazole moiety

Click chemistry, due to its highly modular and efficientreaction nature, has been identified as one of the most practicalmethods toward fragment-based enzyme inhibitor development. Using fragment pro-inhibitor library screening and click chemistry reaction, researchers developed a large class library of efficient enzyme inhibitors of various enzymes such as Protein Tyrosine Phosphatase Inhibitors, Protein Kinase Inhibitors, Transferase Inhibitors, Glycogen Phosphorylase Inhibitors, Serine Hydrolase Inhibitors, Metalloproteinase Inhibitors, Aspartic Protease Inhibitors, Oxidoreductase Inhibitorsand Glycosidase Inhibitors etc.[35]

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Click Derived Cancer Growth Inhibitors

Chemotherapy is considered as the most effective method among many other methods prevalent to treat cancer. Several nucleoside drugs have been developed ascancer treatment agents: cladribine, clofarabine, capecitabine, cytarabine,fludarabine, gemcitabine, decitabine, and floxuridine.[36]The development of new therapeuticapproach to breast cancer remains one of the mostchallenging areas in cancer research. Inhibitors of cyclin-dependent kinases (CDKs) are an emerging class of drugs for the treatment of breast cancers. Experimental evidence suggests that CDK inhibitors inhibit the cyclin D–dependent kinase activity and thus prevent tumor growth and/or at least partially revert the transformed phenotype. Several compounds are currently in clinical trials including flavopiridol (**7**), R-roscovitine (CYC202) (**8**), BMS-387032 (**9**), and UCN-01 (7-hydroxystaurosporine) (**10**).[37] CDK inhibitors are currently under evaluation in clinical trials as single agents and as sensitizers in combination with radiation therapy and chemotherapies.

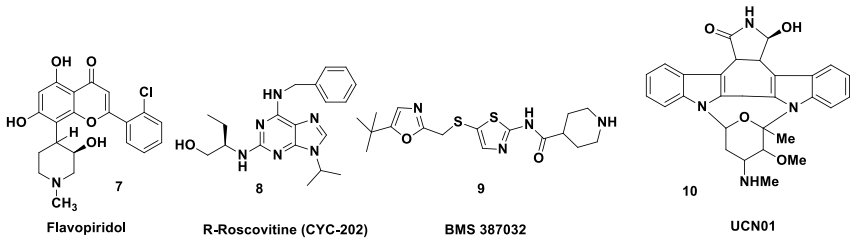

Figure 6. CDK inhibitors under clinical trials

Conclusions

In conclusion, this review summarizes the growing application of ‘‘click’’ chemistry in diverse areas such as bioconjugation, drug discovery, materials science, and radiochemistry. Click chemistry has found increasing applications in all aspects of drug discovery in medicinal chemistry, such as for generating lead compounds through combinatorial methods. Bioconjugation via click chemistry is rigorously employed in proteomics and nucleic research. In radiochemistry, selective radiolabeling of biomolecules in cells and living organisms for imaging and therapy has been realized by this technology.

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Click chemistry has proven itself to be superior in satisfying many criteria, thus, one can expect it will consequently become a more routine strategy in the near future for a wide range of applications since it links various types of chemistry with biology and can tailor various useful syntheses in future.

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