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Diverse Applications of Click Chemistry-A Review

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Abstract: *In simple Language the term "Click" means joining molecular entities as easily as clicking together the two pieces of a seat belt buckle. Click Chemistry" was first described by K. B. Sharpless in 2001, he describes reactions that gives products with high yields. In general, the definition of click chemistry is explained as follows:*

- *Give very high chemical yields of desired products.*
- *Combination of readily available simple building blocks.*
- *Generate almost no byproducts.*
- *Simple product isolation by non-chromatographic methods.*
- *Reaction proceeds in water, as well as in organic solvents.*

Several Organic Chemical reactions such as nucleophilic ring-opening reactions, cyclo-additions, nucleophilic addition reactions, Diels Alder reactions, etc. are included in click reactions. Click Chemistry refers to a group of reactions that are fast, simple to use, easy to purify, versatile, regiospecific, and give high product yields. It also possesses several applications in drug discovery, supramolecular chemistry, material science, nanotechnology, etc.

Keywords: Click Chemistry, Principle of click Chemistry, Applications of Click Chemistry, Chemical reactions Using Click Chemistry

I. INTRODUCTION

Click chemistry, as first articulated by Sharpless and colleagues in 2001[1], was born of a desire to harness the power of molecular assembly for the widest possible range of applications. The logic behind click chemistry is simple:
New molecular properties are needed everywhere;

- Such properties can emerge from the joining of small molecular building blocks;
- Scientists and engineers not trained in synthetic chemistry often lack the skills and equipment needed to perform such connecting operations reliably.
- Chemical methods exist, and more can be developed, that make molecular connections easily.

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-hetero atom (C−X−C) linkages in joining modular building blocks [2-5]

Principle of Click Chemistry

Click reactions are characterized by their high yields, simple reaction conditions, and tolerance to diverse functional groups. The most widely used click reactions include the Huisgen 1, 3-dipolar cycloaddition, copper-catalyzed azide-alkyne cycloaddition (CuAAC), and strain-promoted azide-alkyne cycloaddition (SPAAC). These reactions proceed rapidly and selectively, making them ideal for diverse applications.

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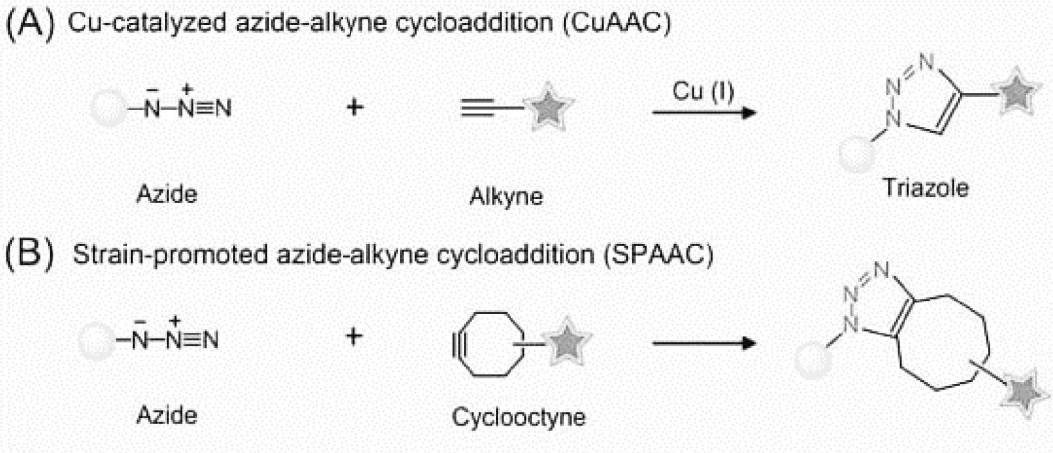
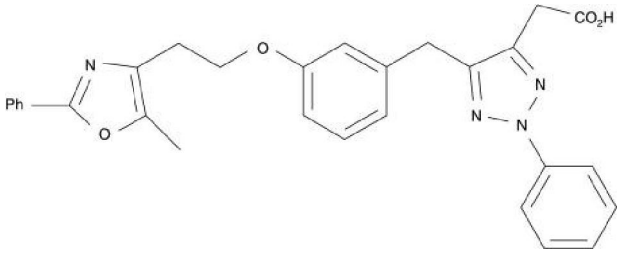


Applications of Click Chemistry

1. ***Drug Discovery:***

Drug discovery based on natural products can be hampered by slow, complex synthesis. Click Chemistry, on the other hand, simplifies and optimizes synthesis, providing faster, efficient reactions. Click Chemistry was employed by Zhang et al. to produce the peroxisome proliferator-activated receptor γ (PPAR-γ) agonists for the treatment of type II diabetes[6]. The 1, 2, 3-triazole click reaction product displays biologic activities, such as anti-HIV activity and antimicrobial activity against Gram- positive bacteria[7, 8].



2. Bio conjugation:

Click chemistry has become a burgeoning strategy of bio conjugation in the development of bifunctional molecules. Bio conjugation involves the 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. Although bio conjugation is applicable to the *in vivo* labeling of biomolecules, only a handful of reactions are actually useful[2, 4].

3. Biological Sensors:

Hydrogels are elastic soft materials that are suitable for wearable applications and as electronic skins and biosensors in medicine[9]. In the past, silicon nanomaterials were often used, but they had shortcomings such as opacity, poor stretchability, and low temperature responsiveness[10]. Now hydrogel materials have overcome these shortcomings, and the widespread use of "click" chemistry has allowed the field to be rapidly developed. Wang and co-workers layer-by-layer synthesized a hydrogel via an in situ Schiff base reaction composed of oxidized dextran (PO-Dex), chitosan, and glucose oxidase (GOD).11 Touching the hydrogel film to glucose caused a pH change, as the pH-responsiveness of the "click" reaction caused the film to swell. This changed the optical properties of the film, thereby monitoring the glucose concentration. The sensor's response to the glucose concentration was reversible within a certain range, and it could continuously monitor the glucose concentration. The hydrogel film was very thin, so information was transmitted quickly, allowing it to monitor the blood glucose concentration in real-time. Ahmad et.al., designed a hydrogel film for collagenase monitoring using the thiol–ene reaction[12].

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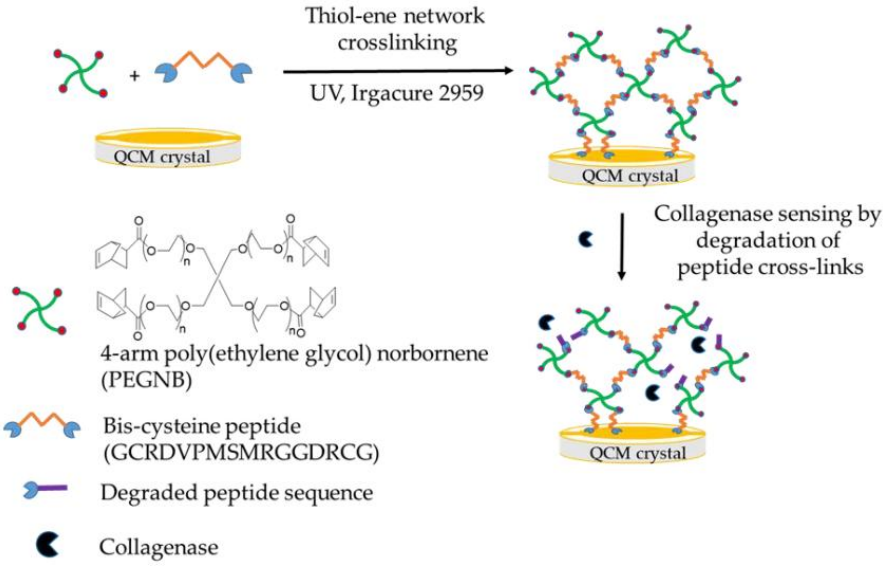

4. Targeted Delivery of Drugs:

Drug delivery is an important medical method in modern medicine, and it is necessary to ensure a high efficiency, specificity, and bio orthogonality of the processes used to transport drugs to designated locations. These points cater to the characteristics of "click" chemistry. Combined with metabolic engineering, functional groups can be introduced at specific sites, and "click" reactions occur with special groups introduced on drugs. It's extremely high specific recognition and reaction efficiency provides an efficient drug delivery method. In 2012, Koo's team injected intra tumoral injections of tetra acetylated N-azido acetyl-d-mannosamine (Ac4ManNAz), an unnatural substance with an azide group. Then alkynyl-modified liposomes were injected to perform a "click" reaction in mice, and it was found that many liposomes were bound to the surface of the cancer cells at a very fast rate[13].

5. ***Click Chemistry in Chemical Biology:***

Click chemistry has emerged as a powerful tool in chemical biology, facilitating the synthesis of bioactive small molecules, probes, and molecular imaging agents. These molecules enable the study of biological processes with high spatiotemporal resolution.

6. ***Sustainable Synthesis:***

Click chemistry enables the development of sustainable synthesis methods by minimizing waste generation and reducing the use of hazardous reagents. Click reactions can be conducted under mild conditions, eliminating the need for harsh solvents or high temperatures, thereby reducing energy consumption and environmental impact.[14]

7. ***Bioorthogonal Labeling:***

Click chemistry facilitates the attachment of specific molecules to biomolecules in living systems without interfering with native biological processes. Glycans are label on cell surfaces with fluorescent probes for imaging studies without affecting cellular functions.[15]

8. ***Surface Functionalization:***

Click chemistry is utilized for precise and selective modification of surfaces with desired functional groups or molecules. Glass surfaces are coated with click-reactive molecules for subsequent attachment of biomolecules or nanoparticles.[15]

9. ***Polymer Synthesis:***

Click chemistry enables the synthesis of polymers with precise control over their structure and properties. This is

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essential for designing advanced materials with tailored functionalities, such as drug delivery systems, coatings, and sensors.[16]

10. Drug Synthesis

Click Chemistry has a high reaction yield, almost no byproducts, and a fast reaction rate. These advantages are undoubtedly the dream of drug preparation. Therefore, "click" chemistry has attracted much attention in the field of drug synthesis17 because the original "click" reaction relies on copper ions that are toxic to organisms, it has not been frequently used in the field of medicine. However, with the development of "click" chemistry and the introduction of various copper-free "click" chemistry reactions, "click" chemistry has become very popular in the field of biomedicine, as well as for drug synthesis. "Click" chemistry provides an easy method to synthesize 1, 2, 3-triazoles, which have good pharmacological effects and have been developed and applied to the synthesis of various antiviral agents, antibacterial agents, and anticancer agents.18

II. CONCLUSION

It is concluded that Click Chemistry is found to have numerous applications across a wide variety of disciplines, including materials research, polymer chemistry, and the pharmaceutical sciences. It has still a developing and powerful method in the biomedical field, which has a wide range of applications from combinatorial Chemistry to target-oriented in vitro Chemistry and plays an important role in identifying active compounds that will benefit drug design and converting them into more active and clinically useful entities.

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