Application of Click Chemistry in Drug Discovery and Development

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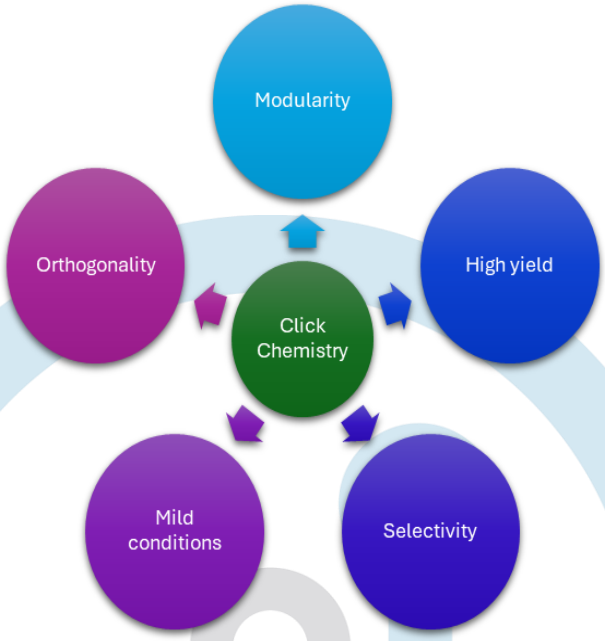
Abstract:
The concept Click chemistry was introduced by K. Barry Sharpless in 2001 and honored with the 2022 Nobel Prize in Chemistry, comprises a class of highly efficient, selective, and bioorthogonal reactions that facilitate the rapid construction of complex molecular architectures under mild conditions. This review examines the role of click chemistry throughout the drug discovery and development pipeline, ranging from fragment-based lead identification and combinatorial library generation to targeted drug delivery, fabrication of antibody–drug conjugates (ADCs), prodrug activation, chemical proteomics, and radiopharmaceutical applications. The mechanistic aspects of key click reactions—including copper-catalysed azide–alkyne cycloaddition (CuAAC), strain-promoted azide–alkyne cycloaddition (SPAAC), tetrazine ligation, and thiol–ene reactions—are discussed, along with a critical assessment of their benefits, limitations, and progress toward clinical translation. Additionally, emerging areas such as DNA-encoded chemical libraries, covalent drug discovery, and in vivo bioorthogonal chemistry are highlighted.

Keywords*:* Click chemistry, bioorthogonal chemistry, azide-alkyne cycloaddition, antibody-drug conjugates, drug delivery, chemical proteomics, fragment-based drug discovery

INTRODUCTION:
Organic chemistry plays a fundamental role in drug discovery and development because most of pharmaceutical compounds are organic in nature. The design, synthesis, and optimization of drug molecules depend on the principles of organic reactions and molecular transformations. But organic synthetic method involves multistep procedures, low yields, and the generation of unwanted byproducts, which can limit efficiency and increase cost. Hence, there is a growing need for chemical strategies for synthesis and design of drug molecules. Addressing these challenges the click chemistry has emerged as a powerful approach for synthesis and design of drug molecules. The chemical reaction should be efficient, reproducible and capable of proceeding under mild condition, the most likely requirement of synthesis of drug molecules and all these requirements are effectively fulfilled by Click Chemistry. The concept of click chemistry focuses on simplifying chemical synthesis through the use of modular, high-yielding, and reliable reactions that proceed with remarkable specificity and minimal side reactions. In click chemistry complex molecular architectures are constructed using a limited set of highly efficient and selective reactions a natural synthetic strategy. Click chemistry has revolutionized drug discovery by enabling the rapid synthesis of diverse molecules and facilitating high-throughput screening. Its high selectivity and efficiency allow easy modification of drug structures, which is essential for structure–activity relationship (SAR) studies and lead optimization. Overall, it accelerates the identification and development of effective drug candidates.

OBJECTIVES:
To understand the fundamental principles of click chemistry.
To study types of click reactions used in drug discovery and development.
To analyse the role of click chemistry in the synthesis of pharmaceutical compounds
To evaluate its applications in drug discovery and development
To explore recent advancements and future prospects in this field

PRINCIPLES OF CLICK CHEMISTRY:
1.High Efficiency and Yield: The chemical reactions proceed rapidly with high product yield and high efficiency.
2.Selectivity: High regioselectivity and stereospecificity ensure formation of a single desired product.
3.Modularity: Simple building blocks can be easily combined to form complex molecules.
4. Mild Reaction Conditions: Reactions occur under gentle conditions (room temperature, aqueous media), making them suitable for biological systems.
5.Orthogonality: Reactions occur without interfering with other functional groups present in the system.
6. Minimal By-products: Generates little to no unwanted side products, simplifying purification.



CLICK CHEMISTRY IN DRUG DISCOVERY AND DEVELOPMENT

1.Fragment-Based Drug Discovery (FBDD)

Fragment-Based Drug Discovery (FBDD) is an important technique in medicinal chemistry that involves the recognition of small, low-molecular-weight fragments that bind weakly to a biological target. These fragments are very important starting points for the evaluation of drugs molecules. They have simple structures and low affinity. By using a technique such as NMR spectroscopy, the fragments are first screened against a target protein. After recognition of binding fragments their binding affinity and specificity was enhanced. This is done either growing (adding functional groups), linking (joining two fragments), or merging them.

Click chemistry plays a significant role in FBDD by allowing the rapid and efficient linking of fragments through highly selective and high-yielding reactions, such as azide–alkyne cycloaddition. This allows the quick formation of more complex and potent drug molecules. Drugs molecules developed with FBDD-click approaches include potent PARP inhibitors and beta-secretase (BACE1) inhibitors.

2. Antibody–Drug Conjugates (ADCs)

Antibody–Drug Conjugates (ADCs) are an advanced class of targeted therapy in which specific monoclonal antibodies linked with cytotoxic drugs. They are designed in a such wdy that active drugs should be selectively deliver to only diseased cell not normal cells, hence healthy cells are not damaged. Click chemistry allow precise and stable conjugation between the antibody and drug molecules, hence play an important role in ADC development. Reactions such as azide–alkyne cycloaddition allow site-specific attachment, improving the stability, efficacy, and safety of ADCs. Controlled drug release at the target site is achieved through this approach, thereby enhancing therapeutic efficiency and reducing systemic toxicity. As a result, ADCs have become a promising strategy in targeted drug delivery systems.

Feature	**Explanation**
Target Specificity	Delivers drug directly to diseased cells
Reduced Toxicity	Minimizes damage to healthy tissues
High Efficiency	Combines targeting ability with potent drugs
Controlled Release	Drug is released at the desired site

3. Prodrug Design and Targeted Activation

Prodrug design is the strategic approach in which the chemical or enzymatic process inactive or less active compound (prodrug) is converted into active form within the body. This approach is used to modify properties such as solubility, stability, bioavailability, and targeted delivery of drugs. The prodrug is converted into its active form at targeted site such as infected cells, hence there is no side effect on healthy cells.

The role of click chemistry in prodrug design lies in its ability to introduce bioorthogonal functional groups that are inactive under physiological conditions but undergo selective reactions at the target site. These reactions allow precise activation of the drug in response to specific stimuli, such as enzymes, pH changes, or external triggers.

Overall, prodrug design combined with targeted activation enhances therapeutic efficiency, improves drug safety, and represents a promising strategy in modern drug development.

4. DNA-Encoded Chemical Libraries (DELs)

DNA-Encoded Chemical Libraries (DELs) are a powerful technology in drug design and discovery that allow the fast screening of millions to billions of small molecules simultaneously. In this approach, each small molecule is labelled with a unique DNA sequence

that acts as a molecular barcode, encoding its identity and synthetic history. During the screening process, the whole library is exposed to a biological target (such as a protein). Those molecules that bind to the target are isolated, and their attached DNA tags are ordered to identify the active compounds. Efficient identification of potential drug candidates with high specificity is achieved through this approach.

Click chemistry plays a important role in the building of DELs by facilitating the efficient and selective attachment of chemical building blocks to DNA tags. Due to its high yield, specificity, and mild reaction conditions, compatibility with sensitive DNA molecules is maintained, preventing degradation during synthesis. Overall, this approach enables the efficient identification of novel bioactive compounds while minimizing time, cost, and resource requirements in drug discovery.

5. Chemical Proteomics and Target Identification

Chemical proteomics is a important approach used to study protein function, interactions, and drug–target correlation within complex biological systems. It plays a important role in drug discovery by allowing the selection of molecular targets and comprehension the mechanism of action of drug molecules.

Activity-Based Protein Profiling (ABPP) is a key technique in chemical proteomics that utilizes reactive chemical probes to selectively target the catalytic sites of enzymes. These probes are typically designed with small clickable moieties, such as azides or alkynes, which do not disrupt protein binding. Click chemistry plays a crucial role in this process by enabling the conjugation of reporter tags, such as fluorophores or biotin, after the probe has interacted with the target protein. This two-step approach facilitates sensitive detection, visualization, and isolation of labelled proteins through fluorescence imaging or affinity-based purification techniques. An advanced technique, competitive ABPP (cABPP), evaluates probe labelling in both the presence and absence of a drug candidate, enabling the identification of specific targets and binding sites without prior information.

Overall, the integration of chemical proteomics and click chemistry offers a highly efficient platform for target identification, off-target evaluation, and elucidation of drug mechanisms, thereby accelerating the development of safer and more effective therapeutics.

LIMITATIONS AND FUTURE PROSPECTS OF CLICK CHEMISTRY

Category	Aspect	Description
Limitations	Copper Toxicity	Copper catalysts (CuAAC) may be toxic in biological systems, due to which limiting in vivo use
	Limited Substrate Scope	All functional groups are not compatible with click reactions
	Cost of Reagents	Catalysts and reagents can be expensive
	Scalability Issues	Challenges in large-scale industrial applications
	Reaction Conditions	Some reactions require careful optimization for biological environments
Future Prospects	Copper-Free Reactions	Development of safer reactions like SPAAC for biological applications
	Bioorthogonal Chemistry	Improved targeted drug delivery and in vivo reactions
	Nanotechnology Integration	Enhanced drug delivery systems
	Personalized Medicine	Development of patient-specific therapies
	AI Integration	Faster drug design and optimization
	Chemical Biology Expansion	Better understanding of biological systems and disease mechanisms

CONCLUSION:

In modern drug discovery and development, the click chemistry has important transformative approach as it offering highly efficient, selective, and reliable methods for the synthesis and modification of complex molecules. It have remarkable development in area such as fragment-based drug discovery, targeted drug delivery, and chemical proteomics due to its modular nature and compatibility with biological systems.

The incorporation of click chemistry into modern techniques, including DNA-encoded libraries and activity-based protein profiling, has strengthened target identification and mechanistic understanding. Furthermore, its use in antibody–drug conjugates and prodrug design has enhanced therapeutic selectivity while minimizing systemic toxicity.

Meanwhile there are certain limitations, such as catalyst toxicity and large-scale challenges, hence it needs to development of copper-free and bioorthogonal reactions.

Overall, click chemistry plays a vital role in speeding up drug discovery processes and shows significant potential for the development of safer, more effective, and targeted therapeutic agents in the future.

REFERENCES:

1.Akhtar, M.S. et al. (2013). Biogenic synthesis of iron oxide nanoparticles via green route. Colloids and Surfaces B: Biointerfaces.
2.Shameer M. Kondengadan, Shubham Bansal, Ce Yang, Dongning Liu, Zach Fultz; Click chemistry and drug delivery: A bird's-eye view Author links open overlay panel.
3. Click Chemistry and Its Applications in Medicinal Chemical Synthesis November 3, 2022
4. Khemchand R. Surana1; A Recent Concept of Importance: Click Chemistry, Progress in Chemical and Biochemical Research 2024, 7(4), 394-411.
5. Piyush Chaturvedi*1, Nupur Chaturvedi; CLICK CHEMISTRY: A NEW APPROACH FOR DRUG DISCOVERY by International Journal of Pharmaceutical Sciences Review and Research Volume 10, Issue 2, September – October 2011; Article-022.
6. Jiang Hong Cai; Recent updates in click and computational chemistry for drug discovery and development February 2023.