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•Commentary•

Click chemistry and natural products

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The 2022 Nobel Prize in Chemistry was awarded to American scientists Carolyn Bertozzi, K. Barry Sharpless, and Danish scientist Morten P. Merdahl for their contributions to the development of click chemistry and bioorthogonal chemistry.

The conceptual foundation of click chemistry is attributed to Sharpless' analytical examination of biosynthetic pathways in natural products. Typically, the formation of carbon-carbon (C−C) bonds is impeded by substantial energy barriers, leading to the generation of numerous non-target byproducts [1]. However, nature adeptly synthesizes intricate biomolecules *via* carbon-hetero (C−X) bond formation utilizing a limited set of 20 amino acids and 10 primary metabolites. Sharpless then introduced an innovative synthetic strategy, leveraging C−X bonds as "bridges" to incorporate small modular units into "carbon skeletons". This approach, now recognized as click chemistry, embodies several distinctive characteristics: 1) modularity; 2) resilience against solvent variations and insensitivity to oxygen and water; 3) high chemical yields and atom economy; 4) regiospecificity and stereospecificity; 5) operational simplicity [2].

The advent of click chemistry heralds a new era in natural product-based pharmaceutical research, enhancing methodologies in structural modification and target identification.

Click Chemistry-based Structural Modification for Natural Products

Natural products, characterized by intricate structures and multiple stereocenters, present substantial challenges in structural modification or in developing derivative libraries, such as complicated synthesis strategies, prolonged synthesis durations, low yields, and a restricted variety of derivatives [3]. Click chemistry has emerged as an effective way to overcome these challenges. The Cu(I)-catalyzed huisgen 1,3-dipolar cycloaddition between alkynes and azides (CuAAC) has been particularly noteworthy in this regard. Additionally, other click chemistry methods, such as strain-promoted azide-alkyne cycloaddition (SPAAC), inverse electron-demanded Diels-Alder (IEED-DA), and sulfur (VI) fluoride exchange (SuFEx) chemistry, have also been well-established [4].

The CuAAC click reaction, in particular, facilitates the efficient linkage of two natural products or the conjugation of one natural product with another pharmacophore *via* a 1,2,3-triazole moiety. This process manifests primarily in two contexts (Fig. 1) [5]: 1) The triazole moiety acts as a linker, uniting two distinct natural products with different activities, which could enhance the synergistic effect and expand the molecular mechanism of action. For example, chalcone-1,2,3-triazole-azazerumbone hybrids, synthesized by linking chalcone with azazerumbone *via* a triazole linker, exhibited broad-spectrum activity against LU, A549, HepG2, MCF-7, P338, SW480, and Bel-7402 cancer cell lines. Importantly, these hybrids demonstrated superior potency to azazerumbon, zerumbone, and matrine [6]. 2) The 1,2,3-triazole itself serves as

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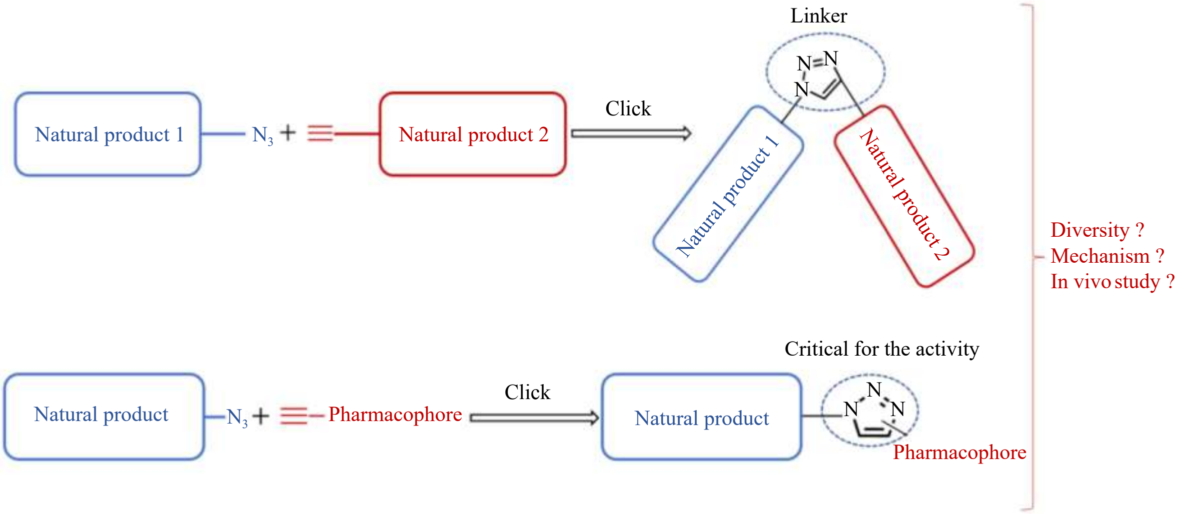

Fig. 1 Application of click chemistry in modifying natural products.

a pivotal pharmacophore, displaying antibacterial, antimalarial, antifungal, antiviral, anti-tuberculosis, and anticancer activities. This is attributed to the triazole's ability to form various non-covalent interactions, including hydrophobic interactions, hydrogen bonding, van der Waals forces, and dipole-dipole interactions, with diverse biological targets. For example, artemisinin derivatives synthesized through click chemistry, effective in targeting cancer cells, owe their broad-spectrum anticancer effects to their ability to generate cytotoxic reactive oxygen species (ROS). Structure-activity relationship studies have indicated the partial necessity of the triazole moiety for these activities [7].

While click chemistry offers significant advantages in natural product-based drug discovery, there remain areas that require further exploration and development:

1) The variety and commercial availability of click blocks are currently limited, constraining the diversity of natural product-click chemical derivatives synthesized and evaluated for functionality. Future efforts should aim to increase the diversity of click blocks and enhance the compilation of natural product-click chemistry libraries.

2) The molecular targets of most natural product-triazole derivatives, primarily identified through phenotypic screening, are yet to be elucidated. Investigating the targets and mechanisms of these compounds represents a crucial research direction.

3) The *in vivo* metabolism, pharmacodynamics, and toxicity profiles of natural product derivatives, predominantly tested *in vitro*, warrant comprehensive study for a complete evaluation of their therapeutic potential (Fig. 1).

Click Chemistry-based Target Identification for Natural Products

The structural uniqueness, biocompatibility, and functional diversity of natural product drugs offer significant therapeutic benefits. However, these compounds frequently encounter challenges such as unclear mechanisms of action and difficulty in the identification of targets [8]. Identifying the protein targets of natural products is a critical step in elucidating their mechanisms and in guiding structure-activity relationship studies, integral to the advancement of natural product-based drug discovery.

Traditional methods for target identification of natural products, including affinity chromatography, protein microarrays, mass spectrometry, and computational approaches, present various limitations. Affinity chromatography and protein microarrays require extensive quantities of purified proteins, which are often expensive and laborious to produce. Although mass spectrometry and computational approaches are less dependent on protein availability, they necessitate substantial computational power and specialized analytical expertise.

In this context, click chemistry-based target identification has emerged as a robust and innovative approach for identifying the targets of natural products [9]. The inherent advantages of click chemistry—speed, mild reaction conditions, and non-toxicity—facilitate the use of probe and reporter molecules for swift and efficient *in situ* detection of drug targets [10]. The introduction of relatively small bioorthogonal groups, such as alkynes, into bioactive natural product molecules generally maintains or only slightly alters their pharmacological properties [11].

The process of the target identification of natural products *via* click chemistry usually includes three steps: 1) The design and synthesis of probes based on natural products; 2) The attachment of these probes to target proteins through click chemical reactions with reporter groups; 3) The subsequent purification, enrichment, and characterization of the targets (Fig. 2).

This method has led to the successful identification of targets for various bioactive natural products, including andrographolide [12], glycyrrhetinic acid, and geraniol by the CuAAC reaction, fumaric acid by the IEED-DA reaction [13], and artemisinin by the SPAAC reaction [14].

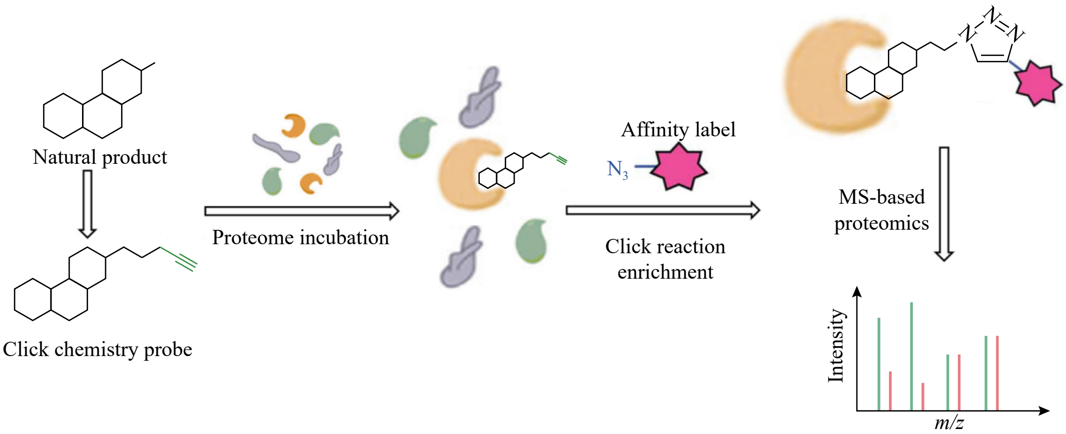

Fig. 2 Target identification of natural products using click chemistry.

Despite its numerous benefits, click chemistry in target identification is not without its limitations. The reaction itself may interfere with the binding or activity of the natural product, potentially leading to inaccurate or non-specific target identification. Moreover, the application of click chemistry-based techniques often requires specialized equipment and expertise, which may be inaccessible to a broad range of researchers [15].

Conclusion

The integration of click chemistry and natural product research marks a pivotal shift in the landscape of natural product-based drug discovery. This integrative approach harnesses the respective merits of both fields, setting the stage for groundbreaking advancements. Currently, this approach primarily emphasizes the exploration of structural modifications and target identification of natural product-based drugs, a critical effort aimed at addressing the prevailing challenges in these areas. Persistent and innovative research in this field is poised to significantly expedite the development of natural product-based drugs. These drugs, characterized by their safety and efficacy, are anticipated to make substantial contributions to the treatment of a wide range of human diseases.

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