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Advances In The Application Of Click Chemistry In The Research Of Targeted Therapeutic Drugs

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Abstract. Click chemistry has become an important tool in the research of targeted therapeutic drugs due to its high efficiency, specificity and mild reaction conditions. Cancer, as one of the major diseases that endanger human health, urgently needs more accurate and efficient treatment methods. Traditional targeted therapeutic methods have the problems of poor selectivity and easy to cause serious side effects, while click chemistry significantly improves the specificity and effect of treatment by efficiently connecting drugs with targeting ligands (such as antibodies, peptides, small molecules, etc.). Especially in the development of antibody-drug conjugates (ADCs) and nanodrug delivery systems, click chemistry not only optimizes the synthesis process, but also improves the stable release of drugs at the tumor site and reduces systemic toxicity. In addition, nanocarriers constructed based on click chemistry can further improve the targeting and bioavailability of drugs and achieve more effective treatment. Although the application of click chemistry in vivo still faces challenges such as reaction conditions, biocompatibility and safety, with the development of bioorthogonal reaction systems and the continuous emergence of new reactions, the application potential of click chemistry in the targeted therapy field will continue to expand. In the future, click chemistry is expected to be combined with cutting-edge technologies such as nanomedicine, immunotherapy, and artificial intelligence-assisted drug design to promote personalized and precision medicine to a higher level.

Keywords: Click chemistry; cancer; biomedical applications.

1. Introduction

Nevertheless, the classical targeted therapy lacks selectivity and easily brings extreme side effects. The click chemistry is a chemical synthesis concept which can construct complicated molecular structures effectively through click reactions. Its high efficacy and selectivity make it a perfect method for designing and synthesizing drug carriers and targeted therapeutics.Click chemistry reactions, e.g. coppercatalyzed azide-alkyne cycloaddition (CuAAC) which could efficiently conjugate drugs with targeting ligands, hence enhancing the precision and efficiency of targeted therapy [1].

Click chemistry has been applied extensively on the development of targeted therapies in the stage of cancer exploration. Click chemistry provides an efficient way to covalently conjugate therapeutic agents to targeting agents (such as antibodies, peptides and small molecules) to enhance specific actions toward cancer cells. The delivery of the strategy can be used for a small molecule drug, nanoscale drugs, ADCs and even immunotherapies [2]. As an example, ADCs that attach cytotoxic drugs to monoclonal antibodies with stable chemical linkers, have demonstrated outstanding potential to deliver high potent drugs selectively to tumour cells, with reduced systemic toxicity [1]. Click chemistry was instrumental in refining their synthesis and in ensuring their controlled release at the tumour site [3].

Furthermore, click chemistry has been widely adopted in the development of drug delivery systems, for example nanocarriers, which enable targeted delivery of a therapeutic agent. Targeting ligands/cell penetrating peptides conjugated to a nanoparticle with the use of click chemistry has allowed researchers to improve targeted specificity and bioavailability of the drug for a more effective therapy [4].

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2. Click Chemistry

Click chemistry is a method of chemical synthesis that rapidly connects small chemical units to achieve high yields and obtain target products. This concept was first proposed by Barry Sharpless in 2001 and has attracted significant attention in the field of chemical synthesis. The main features of click chemistry include high yield, no or harmless by-products, readily available reaction materials, simple conditions, strong selectivity, and the need for high thermodynamic driving force [5]. After more than 20 years of development, it has achieved certain accomplishments in the synthesis of medical biomaterials and drug development. The basic reactions of click chemistry are all classic reactions in the history of organic synthesis, such as conjugate addition, tension ring opening, acylation/sulfonation, α-effect nucleophile capture of aldehydes, and cycloaddition reactions.

2.1. Principle of Click Chemistry

Click reactions are sometimes defined as chemical reactions that meet the criteria of click chemistry. These reactions involve the formation of an intermolecular link between two chemicals; azides, alkynes, or cyclooctynes are frequently involved.

It can be distinguished in three distinct generations: In its first generation, Click Chemistry employed a Cu(I) catalyst to speed up the reaction between an azide and a terminal alkyne. Even in the presence of an effective coupling reaction, the addition of a Cu(I) catalyst may harm the biomolecule. In its second generation, Click Chemistry uses a strain-promoted azide-alkyne mechanism to facilitate the reaction between cyclooctyne and an azide. This reaction, which is free of copper, is made possible by the molecule under stress with high activation energy. Reagents including DBCO, OCT, and BCN are typically used in this copper-free click chemistry. BCN and other reagents are used to prevent the creation of regioselective combinations. The ligation reaction between a tetrazine and trans-Cyclooctene (TCO) without the need of a Cu(I) catalyst is the subject of the third generation of Click Chemistry [6].

2.2. The Reaction Types of Click Chemistry

The Click reactions can be categorized into four main types: cycloaddition reactions, particularly 1,3-dipolar cycloaddition reactions, as well as heterocyclic Diels-Alder reactions; nucleophilic ring-opening reactions, especially those involving electrophiles of strained heterocycles; and ring-opening processes; carbonyl chemistry other than aldehydes and ketones; addition reactions of multiple carbon-carbon bonds. This essay mainly introduces Dipolar Cycloaddition Reaction and Nucleophilic Ring-Opening Reaction.

2.2.1. Dipolar Cycloaddition Reaction

The 1,3-dipolar cycloaddition reaction between terminal alkynes and azides is often regarded as the "cream of the crop" among click reactions. Although the cycloaddition of azides and alkynes was first reported in the early 20th century, it yielded a mixture of both 1,4- and 1,5-disubstituted triazoles. Later, the use of Cu(I) catalysts enabled the selective formation of 1,4-triazoles with yields up to 91% and reduced the reaction time from 18 hours to 8 hours [7]. The mechanism of the Cu(I)-catalyzed reaction is shown in Figure 1 [8].

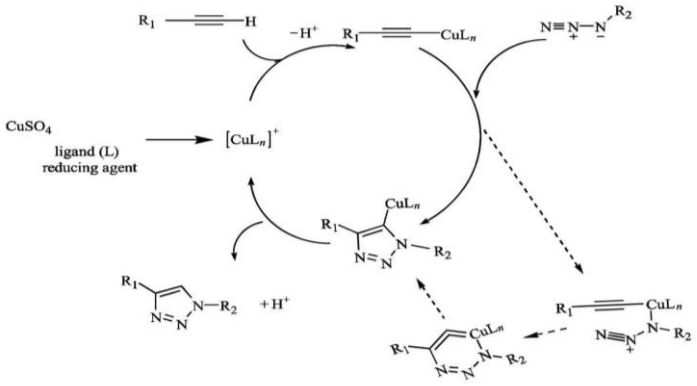

Fig. 1 The reaction mechanism of terminal alkynes and azides [9].

2.2.2. Nucleophilic Ring-Opening Reaction

Nucleophilic ring-opening reactions primarily involve the nucleophilic opening of strained three-membered heteroatom rings, which release their inherent strain energy. This category includes epoxide derivatives, aziridines, cyclic sulfates, cyclic sulfoxamides, aziridinium ions, and cyclic sulfoxonium ions. Among these three-membered heterocyclic compounds, epoxides and aziridinium ions are the most frequently utilized substrates in click reactions; their ring-opening processes can yield a variety of highly regioselective products. Such reactions may be conducted in alcohol-water mixed solvents or even without any solvent. For instance, in the reaction between ethylene oxide and benzylamine (Figure 2), the presence of the protic solvent methanol results in a 90% yield of 1,4-diol; conversely, when performed without a solvent, a 94% yield of 1,3-diol is achieved [10].

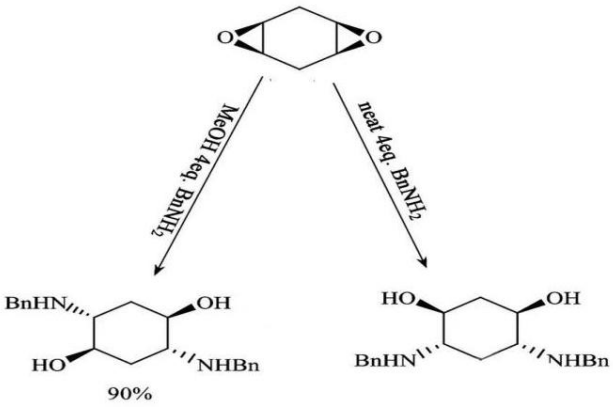

Fig. 2 The regioselectivity of the ring-opening of ethylene oxide [9].

3. The Current Research and Application Situation of Targeted Therapeutic Drugs

3.1. Transmembrane Receptor Tyrosine Kinase (MET)

MET is an oncogene which located on chromosome 7q21-q31, encoding a transmembrane receptor tyrosine kinase expressed in epithelial cells, and its natural ligand is hepatocyte growth factor (HGF) [11]. The MET receptor tyrosine kinase (RTK) and its ligand, hepatocyte growth factor (HGF), have emerged as significant targets for the treatment of lung cancer. In lung cancer, MET can be activated through various mechanisms, including binding to HGF, overexpression, amplification, or mutation. These activation pathways present potential therapeutic targets. Notably, in non-small cell lung cancer (NSCLC), the overexpression of both MET and HGF is associated with a poor prognosis [12].

Crizotinib, recognized for its inhibitory effects on ALK, ROS1, and MET, has been assessed for its efficacy and safety in patients with advanced NSCLC exhibiting MET amplification. The findings indicated that crizotinib was effective in this patient population with MET-amplified NSCLC while adverse events were manageable. Importantly, the objective response rate (ORR) correlated positively with the level of MET amplification.

On February 3, 2021, tepotinib received approval from the FDA for treating metastatic NSCLC characterized by MET exon 14 skipping mutations. In the VISION trial involving 152 patients with advanced or metastatic NSCLC harboring these mutations who received daily oral tepotinib treatment, partial responses were observed in approximately half of the participants [13]. Furthermore, camitinib was approved by the FDA in 2022 for treating metastatic NSCLC featuring detectable MET exon 14 skipping mutations via FDA-approved tests. This approval stemmed from results obtained in the GEOMETRY mono-1 trial which evaluated camitinib's efficacy among patients with either MET exon 14 mutations or MET amplification within an NSCLC context. Camitinib demonstrated notable antitumor activity particularly among patients carrying higher gene copy numbers of those with advanced NSCLC exhibiting MEF exon 14 skipping mutations [14].

Abnormal activation of the MET gene (including overexpression, amplification, mutation, etc.) in NSCLC provides an important target for tumor treatment and is usually associated with poor prognosis. Targeted therapeutic drugs targeting the MET pathway have made progress in clinical applications. Crizotinib, as a multi-target inhibitor (ALK, ROS1, MET), has shown good efficacy in NSCLC patients with MET amplification, and adverse reactions are controllable. Subsequently, targeted drugs specifically targeting MET exon 14 jumping mutations, such as Tepotinib and Capmatinib, have been approved by the FDA. These drugs have shown a high partial remission rate in their respective clinical trials (VISION and GEOMETRY mono-1), and the treatment effect is positively correlated with the MET amplification level or gene copy number. Overall, abnormalities in the MET pathway are not only one of the important pathogenic mechanisms of NSCLC, but also an important breakthrough in targeted therapy, suggesting that in the future, based on precise molecular typing, individualized treatment for MET abnormalities will further improve patient prognosis.

3.2. Applications of Click Chemistry

Francesco Colombo and other reseachers utilized the Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition reaction to synthesize a novel compound（CF-120）, which can inhibit the diffusion of MDCK (epithelial cells) induced by HGF, as well as the in vitro tumor formation of H1437 (non-small cell lung cancer) and GTL-16 (human gastric cancer) [14]. Consistent with the biochemical and biological results, the docking study conducted within the ATP binding site of Met indicated that the binding mode of the newly synthesized compound was similar to that of the previously reported active compound Triflorcas.

CF120 features 1,2,3-triazole as a linker between the imidazo [2,1-b] benzothiazole-2-ylphenyl and phenyl-N-phenethylacetamide moieties. The synthesis is based on Cu(I)-catalyzed 1,3-dipolar cycloaddition 9 as a major step [14]. The cell scattering experiment can be effectively used to screen compounds and/or biologically verify the inhibitory characteristics of compounds on the biological responses triggered by Met.

Although CF-120 has shown good MET inhibitory activity in in vitro experiments, current research still has certain limitations. First, the existing results are mainly based on in vitro cell experiments (MDCK, H1437, GTL-16), and there is still a lack of pharmacodynamic verification in animal models. Pharmacokinetic properties such as bioavailability, metabolic stability and in vivo safety have not been systematically evaluated. Secondly, although molecular docking analysis shows that CF-120 can effectively bind to the ATP binding site of MET, its specificity for other tyrosine kinases is still unclear, and potential off-target effects and toxicity problems caused by this need further verification. In addition, due to the redundancy and compensation mechanisms of the MET signaling pathway

(such as EGFR and AXL pathway activation), single inhibition of MET may be difficult to control tumor progression for a long time, and drug resistance issues need to be paid attention to [15].

In view of the above limitations, future research can be carried out from the following aspects. First, the in vivo antitumor activity, safety and pharmacokinetic properties of CF-120 should be systematically evaluated in animal models to provide data support for subsequent clinical development. Secondly, it is necessary to verify its target selectivity through a more comprehensive kinase spectrum screening, and reduce potential off-target effects through structural optimization. At the same time, considering the mechanism of drug resistance, the combined use of CF-120 with other signaling pathway inhibitors such as EGFR and AXL can be explored to enhance the therapeutic effect and delay the occurrence of drug resistance. In addition, its drug properties can be improved by modifying the linker or hydrophobic region, such as improving oral bioavailability or enhancing blood-brain barrier permeability to meet more clinical treatment needs. Overall, CF-120 has shown good application potential as a new MET inhibitor, but further systematic research is still needed to promote its clinical transformation.

4. Conclusion

Click chemistry, with its high efficiency, specific and mild reaction characteristics, has become an important tool in the research of targeted therapeutic drugs. Whether in the precise construction of drug molecules or in the development of drug delivery systems and ADCs, click chemistry has demonstrated significant advantages. Particularly in the precise treatment of major diseases such as cancer, click chemistry provides an effective means to improve therapeutic selectivity and reduce toxic side effects.

Although there are still challenges such as reaction condition limitations, biocompatibility and safety in the application of this technology in living organisms at present, with the development of bioorthogonal click reactions and the continuous emergence of new reaction systems, the application potential of click chemistry in targeted therapy will be further released. In the future, click chemistry is expected to be combined with other cutting-edge technologies such as nanomedicine, immunotherapy and artificial intelligence-assisted drug design, promoting personalized and precision medicine to a higher level.

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