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Review

"Click Chemistry": An Emerging Tool for Developing a New Class of Structural Motifs against Various Neurodegenerative Disorders

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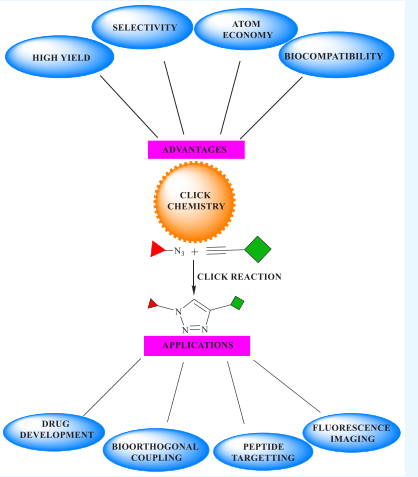
ABSTRACT: Click chemistry is a set of easy, atom-economical reactions that are often utilized to combine two desired chemical entities. Click chemistry accelerates lead identification and optimization, reduces the complexity of chemical synthesis, and delivers extremely high yields without undesirable byproducts. The most well-known click chemistry reaction is the 1,3-dipolar cycloaddition of azides and alkynes to form 1,2,3-triazoles. The resulting 1,2,3-triazoles can serve as both bioisosteres and linkers, leading to an increase in their use in the field of drug discovery. The current Review focuses on the use of click chemistry to identify new molecules for treating neurodegenerative diseases and in other areas such as peptide targeting and the quantification of biomolecules.



1. INTRODUCTION

1.1. Click Reactions. Click chemistry (CC) refers to a collection of potent, incredibly dependable, and specific reactions that can produce molecules instantly by fusing together small units through heteroatom connections.[1] CC was devised by Sharpless in 2001,[2] and for his tremendous contributions to the field, the 2022 Nobel Prize was jointly awarded to Sharpless, along with Meldal and Bertozzi.[3] CC encompasses almost all branches of chemistry, including organic chemistry,[4] drug discovery,[5] polymers,[6,7] bioconjugation,[8] and radiochemistry,[9] with a broad spectrum of applications and advantages.[10] "CC" originated as a way to describe reactions that produce products with high yields by the generation of carbon−heteroatom bonds. The term "click" described the simple combining of molecular building blocks, similar to how a seatbelt buckles two pieces that click together.[11] CC reactions are quick, extremely specific, easy to carry out, and insensitive to oxygen and water.[12−14] They can also produce a wide range of structures in large quantities. Additionally, these reactions require barely any chromatographic purification during their workup, which makes it very simple.[14] These reactions are commonly referred to as spring-loaded reactions, i.e., thermodynamically driven reactions that are rapid and nonreversible to produce the reaction product with high reaction selectivity.[15] The byproduct of the process could be readily eliminated without needing any chromatography techniques.[16] The needed attributes of the reaction comprise facile reaction conditions, easily accessible starting components and reagents, and the utilization of no solvents or a solvent like water or one that is quickly removed, along with easy product isolation.[17] Based on all of the criteria, click reactions were categorized into 4 types: (i) cycloaddition reaction, including specifically hetero-Diels−Alder reactions, and the Huisgen 1,3-cycloaddition reaction; (ii) nucleophilic ring-opening reactions (epoxides, aziridines); (iii) reactions in carbonyl chemistry ranging from the formation of oxime ethers, hydrazones, and aromatic heterocycles; and (iv) addition reactions to C−C multiple bonds including the epoxidation and dihydroxylation, as well as Staudinger ligation, a type of azide−phosphine coupling reaction[10,18−21] (Figure

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