IRAQI Academic Scientific Journals

Samarra Journal of Pure and Applied Science

SJPAS

www.sjpas.com

p ISSN: 2663-7405
e ISSN: 2789-6838

Review Article:
Evaluation and application of click reaction

Zainab Faiyq Saeed
Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Mosul, Iraq

https://doi.org/10.54153/sjpas.2023.v5i2.451

Article Information

Received: 24/01/2023
Revised: 20/04/2023
Accepted: 24/05/2023
Published:30/12/2023

Keywords:

Click reaction, Antibacterial, Anticancer, Drugs discovery

Corresponding Author

E-mail:
zainabfa1q@uomosul.edu.iq

Abstract

Click chemistry has been frequently used in the past to speed up lead finding and optimization. In 2001, the term "click chemistry" was coined to describe chemistry designed to swiftly and consistently join tiny molecules to form compounds. Click chemistry, which involves reliably incorporating two highly reactive compounds in a reliable manner without any by-products, is a valuable tool in many fields. One of the most common click reactions, CuAAC, is the azide-alkyne-catalyzed cyclic addition reaction commonly used by chemical biologists, materials science professionals, and polymer chemists. The reaction of CuAAC combines an azide with an alkene to produce a triazole that binds two different molecular entities. The uses of click chemistry in drug discovery have been the subject of this review.

Introduction

Sharpless invented the term "Click Chemistry" in 2001 to describe a method of synthesis that emphasizes the utilization of a few key chemical events to synthesize molecules containing certain chemical groups by linking tiny units together. Because the reactions are directed by a strong driving force, the original components react constantly, immediately, efficiently, and without generating any undesirable byproducts [1]. Nature also joins compounds by linking small modular elements, which inspired this. It is true, that complex procedures have been investigated less frequently recently than in the previous century, and have gradually been displaced by easier tools. These techniques required sophisticated equipment, challenging experimental settings, and extensive purification processes [2]. In this framework, simple click responses have grown in popularity in both academic and industry research, as indicated by a nearly exponential increase in the number of relevant publications.

Guida estimated the pool of approved drugs to be 1063 drugs in 1996, built on the hypothesis that a candidate composed of less than 30 atoms of non-hydrogen content, and less than 500 Daltons, is comprised of hydrogen, nitrogen, carbon, phosphorus, oxygen, chloride, sulfur, and bromide atoms, and is stable at room temperature and towards water and oxygen [3]. High-throughput screening, which uses click chemistry in conjunction with

combinatorial chemistry, accelerates the discovery of novel drugs by enabling every reaction in a multi-step synthesis rapid, effective, and predictable [4].

A click reaction meets numerous characteristics, including the ability to be modularly and broadly applicable, to create high chemical yields, to generate smallest byproducts that can be eliminated using chromatographic techniques, and to be stereospecific (although not necessarily enantioselective) when appropriate [5]. Furthermore, it has uncomplicated reaction conditions, uses commonly accessible initial materials, reagents, and a solvent (ideally water), and allows for facile product separation by crystallization or evaporation. Click reactions have high negative free energies and so entail carbon-heteroatom bond formation. As a result, unlike numerous traditional synthetic reactions, the value of click chemistry rests in its easiness and convenience of usage [6].

Although achieving the prerequisites of a click response is a difficult order, four primary reaction classes have been found that rise to the mark (Figure 1), and these four classes can be explained as follow [7]:

- **Cycloadditions:** primarily refers to 1, 3-dipolar cycloadditions, as well as hetero-Diels-Alder cycloadditions.

- **Nucleophilic ring openings:** are composed of strained heterocyclic electrophile openings such as aziridines, cyclic sulfates, epoxides, aziridinium ions, episulfonium ions, and so on.

- **Non-aldol carbonyl chemistry:** involve the synthesis of ureas, hydrazones, thioureas, aromatic heterocycles, oxime ethers, amides, and so on. Aldol carbonyl reactions have modest thermodynamic driving forces, resulting in extended reaction durations and the production of side products, and so can't be termed click reactions.

- **Carbon-carbon multiple bonds:** including Epoxidations, aziridinations, dihydroxylations, sulfonyl halide add, nitrosyl halide additions, plus some Michael additions.

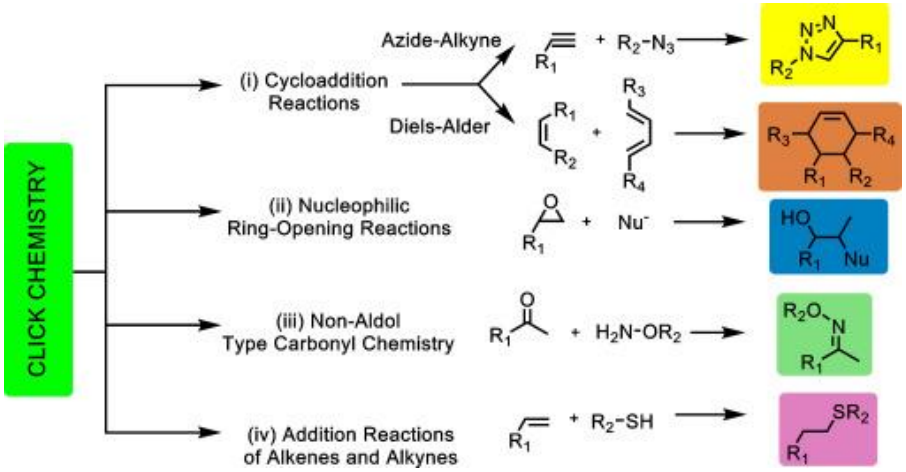

Fig. 1 Main click chemistry reaction groups. R1, R2, R3, R4 are the reaction groups [7].

Mechanism of CuAAC

The copper (I) catalyzed variation 8, 9 of the Huisgen 1, 3-dipolar cycloaddition (CuAAC) 10-12 definitely has been the choice of click reactions, to the point that it is now

unquestionably the leading example of the click chemical reaction [8]. Arthur Michael originally described the production of 1,2,3-triazoles via 1,3-dipolar cycloaddition of azides and alkynes near the end of the nineteenth century, and Rolf Huisgen considerably developed it in the 1960s [9].

Generally, cycloadditions take place via an associated process. Experimental kinetic data and molecular modelling of the Huisgen 1, 3-dipolar cycloaddition process, on the other hand, appear to suggest a stepwise reaction route [10]. According to experimental data and the fact that the copper-catalyzed process is expected to occur in a stepwise fashion, beginning with the formation of copper (I) acetylide (5) (Figure 2).

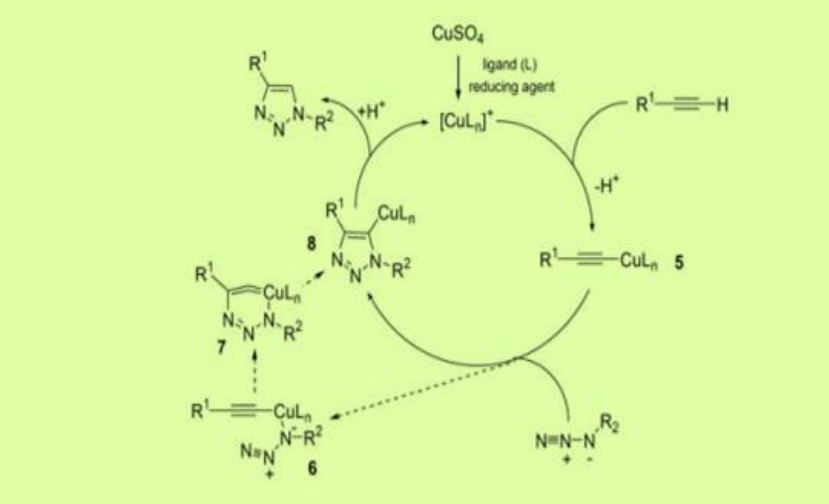

Fig. 2 Proposed catalytic cycle for the CuI [10].

Depending on the reaction circumstances, numerous distinct types of Cu-acetylide complexes can be generated; compound 5 is only one of them [11]. The π CuI complexation reduces the pKa of the terminal alkyne by up to 9.8 pH units, permitting deprotonation to take place without the addition of a base in an aqueous solution [12].

Applications of Click Chemistry

Since its introduction in 2001, click chemistry has sparked an explosion in the number of articles outlining a broad variety of applications for this practical and reasonable chemical method. Initially developed, to meet the challenges of drug discovery, click chemistry is now being used in many facets of drug discovery, from lead generation to DNA and proteomics studies [13].

Remarkably, the philosophy of click chemistry has lately supplied a potent tool in material sciences, resulting in an abundance of innovative, tailor-made biomacromolecules with amazing structural traits and capabilities [14]. Using alkyne–azide click cycloadditions, several alternative synthetic techniques have been described to produce the connection of polymers with proteins, peptides, nucleic acids, sugars, or even organisms and viruses [15]. Furthermore, biological uses of click chemistry, particularly in bioconjugation concepts, are developing as a click-field of significant concern. A possible explanation is because bioconjugation is important in many fields of study, including Nanomedicine. The unexpected validity of the Cu-catalyzed azide–acetylene association, the inertness of the reaction under biological circumstances, and the mild environments under which the biologicals and other

delicate structures exist will not lose their functions advantage *in vivo* and *in vitro* bioconjugation applications [16]. The three most relevant types of major fields where click chemistry has had considerable influence are; i) drug discovery, (ii) materials science, and (iii) bio conjugation.

Employment of click chemistry in drug discovery

Click chemistry is rapidly being employed in pharmaceutics, from drug innovation and optimization to detection in biological systems such as nucleotides, proteins, and entire organisms [17]. In latest years, combinatorial chemistry has assisted the hard process of lead identification and optimization, which is reliant on the fidelity of specific reactions utilized to form a novel arrangement of chemical connections [18]. By making it simple to synthesize building blocks for novel chemical entities, click chemistry has considerably aided the entire drug development process (NMEs) [19]. By aiding with lead detection and optimization, it has enhanced and broadened conventional drug discovery methods, while it has not entirely replaced them.

The application of click chemistry promotes "structure-based design" and enhances "combinatorial chemistry" approaches, and via the selection of the proper "building blocks", it can produce derivatives or recreate known pharmacophores, biological compounds, and medicines. [21]. Triazole linkage is characterized as a strong pharmacophore due to the significant dipole motion and binds firmly to numerous proteins in a variety of ways [22]. Massarotti and Aprile investigated triazole ring's pharmacophoric relevance, the "X-ray crystal structure" of 1, 2, and 3-triazoles complexes with DNA or proteins (protein-triazole). Additionally, the function of triazole was examined to comprehend its capacity to inactivate hepatic cytochromes, catabolic/anabolic constancy, and general water dissolvability of the materials [23]. Triazole pharmacophores could serve as intercalating agents through π-π "stacking interactions, act as H-bond donors with N2 and N3 atoms, and engage in C-H hydrogen-bonding interactions", be metabolically inactive "(1,4-triazoles) or active (1,5-triazoles)", reduce water solubility, replace an amide without varying the binding posture, and have modest inhibitory effects on CYP enzymes, which might behave as reactive intermediates [23].

There are three forms of click chemistry-based drug discovery: i) "high-throughput screening" (HTS); (ii) "fragment-based drug discovery" (FBDD); plus (iii) "dynamic template-assisted techniques in FBDD" [24].

High-throughput screening (HTS)

HTS is a well-established approach for leading drug development in the pharmaceutical business and academia. Computers, miniature assays, and massive data processing are used to screen vast chemical libraries for action towards biological targets [25]. Numerous biochemical targets identified in contemporary drug invention attempts belong to enzyme families such as proteases, kinases, phosphatases, phosphodiesterase, oxidoreductases and transferases [26]. In light of the increasing number of genes and proteins, the insufficient number of molecular targets for which pharmaceuticals have been approved (324 targets) reveals that some targets are still problematic to control by "low-molecular-weight chemicals" (i.e., tiny biomolecules), while others are still inaccessible to current methods and, as a result,

not only represent a significant challenge but also promise limitless potential for pharmaceuticals development [27, 28].

Combining click chemistry with HT enzyme assay methods including microarrays has modernized lead generation and optimization in drug development. Click chemistry's small-molecule libraries have been effectively employed in the development of novel inhibitors and activity-led fingerprinting of key enzymes might influence the identification and classification of novel enzyme subsets [29].

Fragment-based drug discovery (FBDD)

According to FBDD, the free binding energy of a protein-ligand is governed by its molecular components. For improved binding affinity, the first pieces that cling to the protein scaffold are altered after the discovery of a small-molecule fragment that sticks to the protein scaffold of interest, and the lead structure is optimized [30]. Even though numerous enzymes have several binding pockets, most inhibitor discovery concentrates on the active region. Secondary or allosteric binding sites, on the other hand, often feature selectivity as well as potency [31]. Because of its incredibly flexible and competent reactive nature, click chemistry is one of the best plausible techniques for the creation of “fragment-based inhibitors” in this situation. Because of the click reaction's efficiency and water compatibility, the formed compounds may be evaluated for inhibition instantly without the need for purification [32].

Dynamic template-assisted approaches in FBDD

Scholars have proposed dynamic template-assisted approaches to tackle the difficulty of detecting low-affinity regions and physiologically beneficial active connections associated with FBDD. In all of these procedures, a chemical-reaction, whether “reversible or irreversible/enzymatic or non-enzymatic”, is used to find the optimal fragment pattern [33]. Click reactions add azide and alkyne groups into segments that engage well with the enzyme and are chosen to engage partly with the enzymatic attachment domain. Therefore, the fragments are joined together via cycloaddition between azide and alkyne to create the final inhibitor [34]. As a consequence, a present combination of two or more bioorthogonal segmented prodrugs is formed, which may be provided concurrently or consecutively for *in vivo* drug self-assembly through a target-driven mechanism, and it is incorporated in the gene/protein-specific pharmaceutical design [35].

As a consequence, small biomolecules in medicines with much desired pharmacological characteristics may be developed, and issues associated with “plasma level biodistribution” can be reduced for clinical use [36]. Therefore, using click chemistry, Pharmaceutical formulations containing essentially identical but “fragmented prodrugs” can be created to interrelate directly with biological foci, whether proteomic or genomic foci, resulting in custom-made biosimilars [37].

Use of click chemistry in the production of enzyme inhibitors

Enzymes are therapeutic goals for numerous ailments, including tumours, diabetes, neurodegenerative diseases, tuberculosis, and numerous other serious illnesses, and therefore may exhibit a vital role in treating such disorders [38]. With a rising figure of patients suffering from such terminal ailments, click chemistry is influencing chemical synthesis and development in a more quickly and effectively way, giving fresh techniques for

compounds library screening. Through fragment-based enzyme inhibitor synthesis, synthetic chemists have been able to produce libraries of various kinds of molecules. Each enzyme inhibitor's typical structure is shown in Figure 3 thanks to click chemistry's exceptionally modular and effective reaction properties [39].

"Protein kinases" (PKs) are enzymes that act by phosphorylating the hydroxyl groups of threonine and serine amino acid residues to regulate the activity of other proteins. Abnormalities in a kinase or its expression level are associated with several illnesses, including cancer and diabetes. Because of their importance in various biological stimuli transmission pathways, new drug identification and isolation are concentrated on PKs as the main therapeutic targets [40,41]. CuAAC-coupled azidos b-D-glucoside, b-D-mannoside, and b-D-galactoside were combined with alkynyl lipids of rising sequence distance to generate triazolyl glycolipids, which rendered drug-resistant bacteria more susceptible to b-lactam antibiotics (Figure 3) [40,42]. The clicking derivatives show the capacity to deactivate methicillin-resistant Staph. aureus (MRSA) synergistically with currently available b-lactam antibiotics. Despite the increasing use of CuAAC for biological chemical synthesis, the combination of copper with reducing chemicals remain a source of contention due to reports of Cu radicals damaging or demolishing protein and/or peptide complexes through conventional reactions of CuAAC [43].

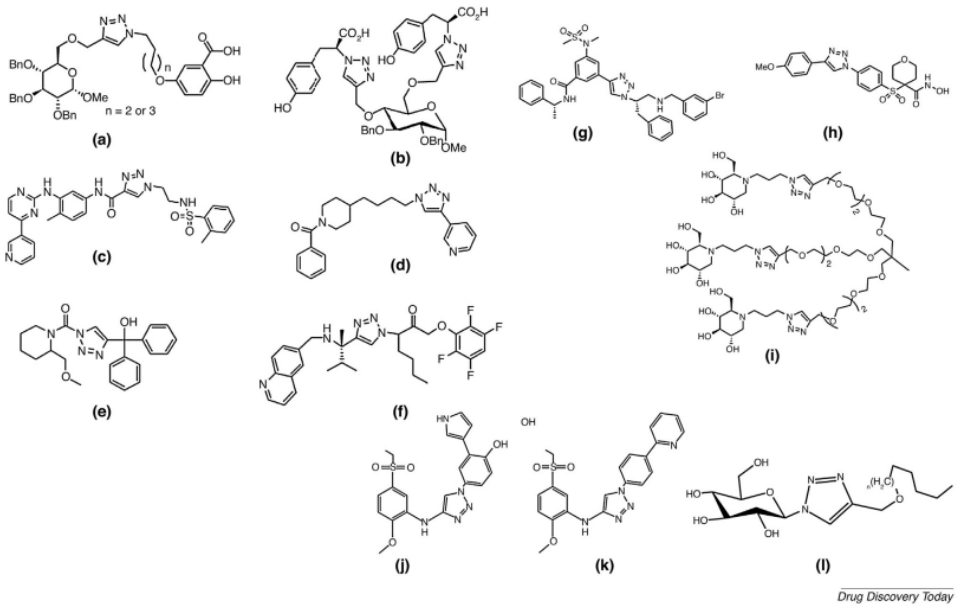

Fig. 3 The following are some illustrations of the chemical configurations of many inhibitors produced by click chemistry: (a,b) protein TPP inhibitors; (c) PK inhibitors; (d) transferase inhibitors; (e) SH inhibitors; (f) cysteine protease inhibitors; (g) aspartic protease inhibitors; (h) MMP inhibitors; I (PBP2a inhibitors) [40].

Using whichever hydrophilic ligands like "bis-(L-histidine) or improved Cu (I) ligands" that give modest Cu (I) packing via a catalytic procedure, has improved CuAAC cell compatibility [44]. Moreover, copper chains have been proven to catalyze a process in the absence of a ligand or reductant [45].

In situ click chemistry

Throughout the last few years, innovative techniques for discovering lead compounds depending on click chemistry have been studied, in which the target molecule energetically participates in the creation of its specific blocking chemical. [46]. These “fragment-based” techniques, also known as “target guided synthesis (TGS)”, are a subclass of the standard combinatorial strategy in which the biological receiver is used to direct the synthesis (either DNA or protein) and plays an active role in the selection of ligands built from a pool of minor segments (Figure 4).

In the use of this reaction to TGS, the delayed interaction among inactivated alkynes and azides is critical. Sharpness and Finn employed the “alkyne-azide click reaction (AAC)” to produce a “template-directed enzyme inhibitor”, with the enzyme acting as the cucurbituril host. The application of AAC reactions in TGS is referred to as "click chemistry *in situ*"[48]. This irreversible reaction has the following properties that make it suitable for finding leads: It has bio-orthogonality, which means that azides and alkynes are inactive *in vivo* and can persist in biological settings. It also has the following advantages: I it is exceptionally thermodynamically favourable; (ii) it involves no third parties, such as catalysts or other elements; and (iii) it is free of third-party participants [49].

The cholinergic enzyme acetylcholinesterase (AChE) was chosen as the original aim for *in situ* click chemistry because it is a crucial aspect of neurobiological role, especially in neurological diseases, and because of the assembly of its determinant loci. Sharpless *et al.* chemically introduced 98 variants of AChE inhibitors from 16 AChE building blocks using the *in situ* click approach [50].

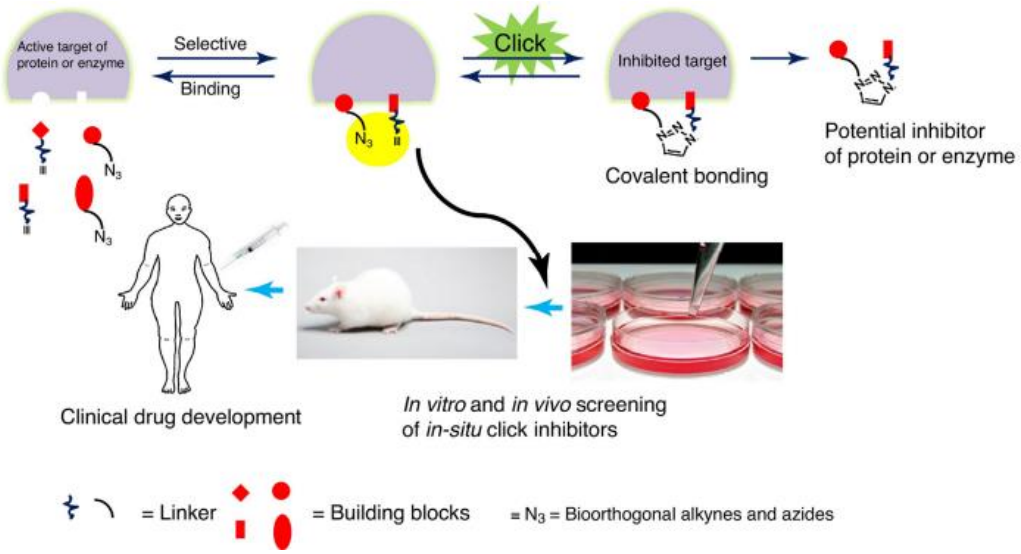

Fig. 4 In situ click chemistry employed to generate protein or enzyme inhibitors and drugs is depicted schematically [47].

Conclusions

The utilization of click chemistry has resulted in the clinical transformation of medicine in order to produce medications for people with unmet medical requirements. Despite its shortcomings, click chemistry remains one of the most adaptable chemical techniques for a wide range of pharmaceutical applications. Its endurance to typical biological circumstances

as well as the most diversified functional groups, as well as the covalent connections produced among the click groups' high aqueous solubility.

References

1. Hassan, E.M., Mustafa, Y.F. and Merkhan, M.M. (2022). Computation in Chemistry: Representative Software and Resources. International Journal of Analysis of Basic and Applied Science, 6(4).
2. Gehringer, M. and Laufer, S.A. (2017). Click chemistry: Novel applications in cell biology and drug discovery. *Angewandte Chemie International Edition*, *56*(49), pp.15504-15505. https://doi.org/10.1002/anie.201710195
3. Peplow, M. (2019). Click chemistry targets antibody-drug conjugates for the clinic. *Nature Biotechnology*, *37*(8), pp.835-838. https://link.gale.com/apps/doc/A625734765/HRCA
4. Ma, N., Wang, Y., Zhao, B.X., Ye, W.C. and Jiang, S. (2015). The application of click chemistry in the synthesis of agents with anticancer activity. *Drug design, development and therapy*, *9*, p.1585. 10.2147/DDDT.S56038
5. Takayama, Y., Kusamori, K. and Nishikawa, M. (2019). Click chemistry as a tool for cell engineering and drug delivery. *Molecules*, *24*(1), p.172. https://doi.org/10.3390/molecules24010172
6. Mashayekh, K. and Shiri, P. (2019). An overview of recent advances in the applications of click chemistry in the synthesis of bioconjugates with anticancer activities. *ChemistrySelect*, *4*(46), pp.13459-13478. https://doi.org/10.1002/slct.201902362
7. Khattab, R.R., Alshamari, A.K., Hassan, A.A., Elganzory, H.H., El-Sayed, W.A., Awad, H.M., Nossier, E.S. and Hassan, N.A. (2021). Click chemistry based synthesis, cytotoxic activity and molecular docking of novel triazole-thienopyrimidine hybrid glycosides targeting EGFR. *Journal of enzyme inhibition and medicinal chemistry*, *36*(1), pp.504-516. https://doi.org/10.1080/14756366.2020.1871335
8. Vishnuvardhan, M.V.P.S., Chandrasekhar, K., Nayak, V.L., Sayeed, I.B., Alarifi, A. and Kamal, A. (2017). Click chemistry-assisted synthesis of triazolo linked podophyllotoxin conjugates as tubulin polymerization inhibitors. *Medchemcomm*, *8*(9), pp.1817-1823. https://doi.org/10.1039/C7MD00273D
9. Kaur, J., Saxena, M. and Rishi, N. (2021). An overview of recent advances in biomedical applications of click chemistry. *Bioconjugate Chemistry*, *32*(8), pp.1455-1471. https://doi.org/10.1021/acs.bioconjchem.1c00247
10. Döhler, D., Michael, P. and Binder, W.H. (2017). CuAAC-based click chemistry in self-healing polymers. *Accounts of chemical research*, *50*(10), pp.2610-2620. https://doi.org/10.1021/acs.accounts.7b00371
11. Meldal, M. and Diness, F. (2020). Recent fascinating aspects of the CuAAC click reaction. *Trends in Chemistry*, *2*(6), pp.569-584. https://doi.org/10.1016/j.trechm.2020.03.007
12. Agrahari, A.K., Bose, P., Jaiswal, M.K., Rajkhowa, S., Singh, A.S., Hotha, S., Mishra, N. and Tiwari, V.K. (2021). Cu (I)-catalyzed click chemistry in glycoscience and their diverse applications. *Chemical Reviews*, *121*(13), pp.7638-7956. https://doi.org/10.1021/acs.chemrev.0c00920
13. Arslan, M., Acik, G. and Tasdelen, M.A. (2019). The emerging applications of click chemistry reactions in the modification of industrial polymers. *Polymer Chemistry*, *10*(28), pp.3806-3821. https://doi.org/10.1039/C9PY00510B

14. Altinkok, C., Karabulut, H.F., Tasdelen, M.A. and Acik, G. (2020). Bile acid bearing poly (vinyl chloride) nanofibers by combination of CuAAC click chemistry and electrospinning process. *Materials Today Communications*, *25*, p.101425. https://doi.org/10.1016/j.mtcomm.2020.101425
15. Kim, E. and Koo, H. (2019). Biomedical applications of copper-free click chemistry: in vitro, in vivo, and ex vivo. *Chemical science*, *10*(34), pp.7835-7851. https://doi.org/10.1039/C9SC03368H
16. Yi, G., Son, J., Yoo, J., Park, C. and Koo, H., 2018. Application of click chemistry in nanoparticle modification and its targeted delivery. *Biomaterials Research*, *22*(1), pp.1-8. https://doi.org/10.1186/s40824-018-0123-0
17. Rondon, A. and Degoul, F. (2019). Antibody pretargeting based on bioorthogonal click chemistry for cancer imaging and targeted radionuclide therapy. *Bioconjugate Chemistry*, *31*(2), pp.159-173. https://doi.org/10.1021/acs.bioconjchem.9b00761
18. Wu, L., Xianyu, Y., Wang, Z., Dong, Y., Hu, X. and Chen, Y. (2019). Amplified magnetic resonance sensing via enzyme-mediated click chemistry and magnetic separation. *Analytical chemistry*, *91*(24), pp.15555-15562. https://doi.org/10.1021/acs.analchem.9b03550
19. Gao, H., Gonçalves, C., Maze, D., Pichon, C. and Midoux, P. (2021). CEBA: A new heterobifunctional reagent for plasmid DNA functionalization by click chemistry. *International Journal of Pharmaceutics*, *601*, p.120566. https://doi.org/10.1016/j.ijpharm.2021.120566
20. Meghani, N.M., Amin, H.H. and Lee, B.J. (2017). Mechanistic applications of click chemistry for pharmaceutical drug discovery and drug delivery. *Drug Discovery Today*, *22*(11), pp.1604-1619. http://dx.doi.org/10.1016/j.drudis.2017.07.007
21. Pokorski, Jonathan K. and Laurie E. Smith. ""Click" Chemistry for Medicine and Biology." *Mol. Pharmaceutics15, (8)* (2018): 2891-2906. https://doi.org/10.1021/acs.molpharmaceut.8b00743
22. Wang, H., Zhang, Y., Chen, Y., Pan, H., Ren, X. and Chen, Z. (2020). Living Supramolecular Polymerization of an Aza-BODIPY Dye Controlled by a Hydrogen-Bond-Accepting Triazole Unit Introduced by Click Chemistry. *Angewandte Chemie International Edition*, *59*(13), pp.5185-5192. https://doi.org/10.1002/ange.201914966
23. Massarotti, A., Aprile, S., Mercalli, V., Del Grosso, E., Grosa, G., Sorba, G. and Tron, G.C. (2014). Are 1, 4-and 1, 5-Disubstituted 1, 2, 3-Triazoles Good Pharmacophoric Groups?. *ChemMedChem*, *9*(11), pp.2497-2508. https://doi.org/10.1002/cmdc.201402233
24. Saha, P., Panda, D. and Dash, J. (2019). The application of click chemistry for targeting quadruplex nucleic acids. *Chemical Communications*, *55*(6), pp.731-750.. https://doi.org/10.1039/C8CC07107A
25. Seo, J., Shin, J.Y., Leijten, J., Jeon, O., Camci-Unal, G., Dikina, A.D., Brinegar, K., Ghaemmaghami, A.M., Alsberg, E. and Khademhosseini, A. (2018). High-throughput approaches for screening and analysis of cell behaviors. *Biomaterials*, *153*, pp.85-101. https://doi.org/10.1016/j.biomaterials.2017.06.022
26. [Ganesan, L., Shieh, P., Bertozzi, C.R. and Levental, I. (2017). Click-chemistry based high throughput screening platform for modulators of Ras palmitoylation. *Scientific reports*, *7*(1), pp.1-9. https://doi.org/10.1038/srep41147
27. Wong, I.L., Zhu, X., Chan, K.F., Law, M.C., Lo, A.M., Hu, X., Chow, L.M. and Chan, T.H. (2018). Discovery of Novel Flavonoid Dimers To Reverse Multidrug Resistance Protein 1 (MRP1,

ABCC1) mediated drug resistance in cancers using a high throughput platform with “Click Chemistry”. *Journal of Medicinal Chemistry*, *61*(22), pp.9931-9951. https://doi.org/10.1021/acs.jmedchem.8b00834

28. Song, J.M., Menon, A., Mitchell, D.C., Johnson, O.T. and Garner, A.L. (2017). High-Throughput Chemical Probing of Full-Length Protein–Protein Interactions. *ACS combinatorial science*, *19*(12), pp.763-769. https://doi.org/10.1021/acscombsci.7b00128
29. Thanzeel, F.Y., Balaraman, K. and Wolf, C. (2018). Click chemistry enables quantitative chiroptical sensing of chiral compounds in protic media and complex mixtures. *Nature communications*, *9*(1), pp.1-8. https://doi.org/10.1038/s41467-018-07695-9
30. Saur, M., Hartshorn, M.J., Dong, J., Reeks, J., Bunkoczi, G., Jhoti, H. and Williams, P.A. (2020). Fragment-based drug discovery using cryo-EM. *Drug Discovery Today*, *25*(3), pp.485-490. https://doi.org/10.1016/j.drudis.2019.12.006
31. Kirsch, P., Hartman, A.M., Hirsch, A.K. and Empting, M. (2019). Concepts and core principles of fragment-based drug design. *Molecules*, *24*(23), p.4309. https://doi.org/10.3390/molecules24234309
32. Bancet, A., Raingeval, C., Lomberget, T., Le Borgne, M., Guichou, J.F. and Krimm, I. (2020). Fragment linking strategies for structure-based drug design. *Journal of Medicinal Chemistry*, *63*(20), pp.11420-11435. https://doi.org/10.1021/acs.jmedchem.0c00242
33. Tassinari, M., Lena, A., Butovskaya, E., Pirota, V., Nadai, M., Freccero, M., Doria, F. and Richter, S.N. (2018). A fragment-based approach for the development of G-quadruplex ligands: role of the amidoxime moiety. *Molecules*, *23*(8), p.1874. https://doi.org/10.3390/molecules23081874
34. Hegedüs, Z., Hóbor, F., Shoemark, D.K., Celis, S., Lian, L.Y., Trinh, C.H., Sessions, R.B., Edwards, T.A. and Wilson, A.J. (2021). Identification of β-strand mediated protein–protein interaction inhibitors using ligand-directed fragment ligation. *Chemical science*, *12*(6), pp.2286-2293. https://doi.org/10.1039/D0SC05694D
35. Hagler, L.D., Krueger, S.B., Luu, L.M., Lanzendorf, A.N., Mitchell, N.L., Vergara, J.I., Curet, L.D. and Zimmerman, S.C. (2021). Versatile Target-Guided Screen for Discovering Bidirectional Transcription Inhibitors of a Trinucleotide Repeat Disease. *ACS Medicinal Chemistry Letters*, *12*(6), pp.935-940. https://doi.org/10.1021/acsmedchemlett.1c00064
36. Kopka, K., Benešová, M., Bařinka, C., Haberkorn, U. and Babich, J. (2017). Glu-ureido–based inhibitors of prostate-specific membrane antigen: lessons learned during the development of a novel class of low-molecular-weight theranostic radiotracers. *Journal of Nuclear Medicine*, *58*(Supplement 2), pp.17S-26S. https://doi.org/10.2967/jnumed.116.186775
37. Hong, T., Liu, W., Li, M. and Chen, C. (2019). Click chemistry at the microscale. *Analyst*, *144*(5), pp.1492-1512. https://doi.org/10.1039/C8AN01497C
38. Cañeque, T., Müller, S. and Rodriguez, R. (2018). Visualizing biologically active small molecules in cells using click chemistry. *Nature Reviews Chemistry*, *2*(9), pp.202-215.. https://doi.org/10.1038/s41570-018-0030-x
39. Brandao, G.C., Missias, F.C.R., Arantes, L.M., Soares, L.F., Roy, K.K., Doerksen, R.J., de Oliveira, A.B. and Pereira, G.R. (2018). Antimalarial naphthoquinones. Synthesis via click chemistry, in vitro activity, docking to PfDHODH and SAR of lapachol-based compounds. *European journal of medicinal chemistry*, *145*, pp.191-205. https://doi.org/10.1016/j.ejmech.2017.12.051

40. Bhardwaj, A., Kaur, J., Wuest, M. and Wuest, F. (2017). In situ click chemistry generation of cyclooxygenase-2 inhibitors. *Nature communications*, *8*(1), pp.1-14. https://doi.org/10.1038/s41467-016-0009-6
41. Lauwaet, T., Miyamoto, Y., Ihara, S., Le, C., Kalisiak, J., Korthals, K.A., Ghassemian, M., Smith, D.K., Sharpless, K.B., Fokin, V.V. and Eckmann, L. (2020). Click chemistry-facilitated comprehensive identification of proteins adducted by antimicrobial 5-nitroimidazoles for discovery of alternative drug targets against giardiasis. *PLoS Neglected Tropical Diseases*, *14*(4), p.e0008224. https://doi.org/10.1371/journal.pntd.0008224
42. Leophairatana, P., De Silva, C.C. and Koberstein, J.T. (2018). How good is CuAAC "click" chemistry for polymer coupling reactions?. *Journal of Polymer Science Part A: Polymer Chemistry*, *56*(1), pp.75-84. https://doi.org/10.1002/pola.28872
43. Xu, L. and Dong, J. (2020). Click chemistry: evolving on the fringe. *Chinese Journal of Chemistry*, *38*(4), pp.414-419. https://doi.org/10.1002/cjoc.201900421
44. Farrer, N.J. and Griffith, D.M. (2020). Exploiting azide–alkyne click chemistry in the synthesis, tracking and targeting of platinum anticancer complexes. *Current Opinion in Chemical Biology*, *55*, pp.59-68. https://doi.org/10.1016/j.cbpa.2019.12.001
45. Bao, C., Yin, Y. and Zhang, Q. (2018). Synthesis and assembly of laccase-polymer giant amphiphiles by self-catalyzed CuAAC click chemistry. *Biomacromolecules*, *19*(5), pp.1539-1551. https://doi.org/10.1021/acs.biomac.8b00087
46. Wang, Y., Zhu, J. and Zhang, L. (2017). Discovery of cell-permeable O-GlcNAc transferase inhibitors via tethering in situ click chemistry. *Journal of medicinal chemistry*, *60*(1), pp.263-272. https://doi.org/10.1021/acs.jmedchem.6b01237
47. Yang, Z., Yu, J., Fu, K. and Tang, F. (2018). Facile preparation of asymmetric phthalocyanine/multi-walled carbon nanotube hybrid material by in situ click chemistry. *Journal of Materials Science: Materials in Electronics*, *29*(24), pp.21078-21087. https://doi.org/10.1007/s10854-018-0255-y
48. Izquierdo, E. and Delgado, A. (2018). Click chemistry in sphingolipid research. *Chemistry and physics of lipids*, *215*, pp.71-83.https://doi.org/10.1016/j.chemphyslip.2018.07.004
49. Parker, C.G. and Pratt, M.R. (2020). Click chemistry in proteomic investigations. *Cell*, *180*(4), pp.605-632. https://doi.org/10.1016/j.cell.2020.01.025
50. Tiwari, S.V. and Ibrahim, M.Z. (2021). Role of Click Chemistry in development of Biomedicines. https://doi.org/10.31024/apj.2021.6.2.2.

IRAQI Academic Scientific Journals
Samarra Journal of Pure and Applied Science
SJPAS
مجلة سامراء للعلوم البحتة والتطبيقية
www.sjpas.com
p ISSN: 2663-7405
e ISSN: 2789-6838

تقييم وتطبيق كيمياء النقر: مراجعة

زينب فايق سعيد
كلية الطب البيطري، جامعة الموصل، العراق

معلومات البحث:
تأريخ الاستلام: 2023/01/24
تاريخ التعديل : 2023/04/20
تأريخ القبـــول: 2023/05/24
تاريخ الـنشر: 2023/12/30
الكلمات المفتاحية:
تفاعلات النقر، مضادات البكتيريا، مضادات السرطان، اكتشاف الادوية

معلومات المؤلف
الايميل:
zainabfa1q@uomosul.edu.iq

الخلاصة:
استخدمت كيمياء النقر بشكل متكرر في الماضي لتسريع العثور على العملاء المحتملين وتحسينهم. في عام 2001، تمت صياغة مصطلح "كيمياء النقر" لوصف الكيمياء المصممة للانضمام بسرعة وثبات إلى جزيئات صغيرة لتشكيل مركبات. تعد كيمياء النقر، التي تتضمن دمج مركبين شديدي التفاعل بطريقة موثوقة دون أي منتجات ثانوية، أداة قيمة في العديد من المجالات. أحد أكثر تفاعلات النقر شيوعا، النحاس ثنائي القطب، هو تفاعل الإضافة الدورية المحفزة بالألكاين والأزيد التي يشيع استخدامها من علماء الأحياء الكيميائية والمتخصصين في علوم المواد وكيميائيي البوليمرات. يجمع تفاعل النحاس ثنائي القطب بين أزيد وألكين لإنتاج تريازول يربط كيانين جزيئيين مختلفين. كانت استخدامات كيمياء النقر في اكتشاف الأدوية موضوع هذه المراجعة.