

Triazole-based click chemistry as strategic for novel therapeutics treatments of cancer: A bibliometric analysis 2007–2024

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ARTICLE HISTORY

Received on: 24/10/2024
Accepted on: 13/01/2025
Available Online: 05/04/2025

Key words

Click chemistry, triazole, hybrids, anticancer activity, bibliometric analysis.

ABSTRACT

Click chemistry is nowadays a versatile strategy for obtaining new bioactive compounds for different diseases, including cancer. Click strategy-based synthetic approaches offer effective routes for the rapid and mild production of bioactive compounds. Triazole ring is known to have significant pharmaceutical value because its derivatives have been shown to have a variety of pharmacological actions, including cancer. There are numerous techniques for triazole ring construction, but click chemistry offers a quick, selective, and dependable approach. The reaction of an azide with a terminal alkyne based on the CuI-catalyzed Huisgen 1,3-dipolar cycloaddition to create 1,2,3-triazoles is the most frequent reaction in click chemistry. The resulting triazole ring is essential in the composition of some clinically approved drugs and other compounds with strong anticancer effects since this fragment may help to improve selectivity, optimize pharmacokinetic features, and overcome resistance. This work shows a bibliometric analysis of published studies on click chemistry and their application in the synthesis of hybrid and conjugate molecules with anticancer activity. Also, we revealed that molecular docking showed the possible mechanism of action of some compounds. Furthermore, bibliometric analysis is shown, providing a holistic overview of the areas in which click chemistry investigations have been focused. Chemistry, materials science, chemical engineering, pharmacology, toxicology and pharmaceuticals, and biochemistry, genetics, and molecular biology were the primary fields of study in the field. Finally, the findings show that there has been a notable increase in study on click chemistry, its hybrids, and conjugates, with molecular docking simulations emerging as a new field.

INTRODUCTION

Cancer is one of the main public health problems in the world causing around 10 million deaths in 2022 [1,2]. Cancer is defined as a heterogeneous group of malignant diseases characterized by unregulated proliferation and invasion of abnormal cells into different tissues and organs of the body. This uncontrolled division process originates from genetic alterations that modify the control mechanisms of the cell cycle, apoptosis, and genomic stability [3]. Among the main causal factors of cancer are genetic mutations that can be inherited or acquired throughout life. In addition, lifestyle factors, such as

tobacco use, alcohol, poor diet, and lack of physical activity, also contribute significantly to the risk of developing certain types of cancer. The most common cancers are breast, lung, colon and rectum, and prostate cancer. About 10 million deaths, or one in six deaths, were caused by cancer in 2020, making it the second most common cause of death worldwide, according to the WHO [2].

Surgery, radiation therapy, chemotherapy, and other treatments are available for this illness. Despite serious side effects and a high rate of treatment failures brought on by drug resistance, chemotherapy is still the most often utilized form of treatment. Surgery, radiation therapy, chemotherapy, and other treatments are available for this illness. Chemotherapy is the most widely utilized treatment modality, despite its severe side effects and high rate of drug resistance-related treatment failures [4]. For these reasons, in order to combat resistance and increase the efficacy of chemotherapy, it is imperative to create new medications with lower toxicity and higher selectivity [5].

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Heterocycles are continuously being exploited to find novel lead compounds. Heterocycles make up most natural products, such as carbohydrates, alkaloids (such as morphine, atropine, and reserpine), proteins, amino acids, nucleic acids, hemoglobin, hormones, enzyme cofactors, vitamins, and proteins. Furthermore, due to its intriguing pharmacological properties, and adaptability, and that these compounds may be effective against a variety of metabolic pathways and cellular processes involved in cancer pathogenesis, the heterocyclic nucleus is present in many therapeutically approved drugs, including anticancer medications such as methotrexate, vinblastine, vincristine, daunorubicin, 5-fluorouracil (5-FU), and doxorubicin [6–10].

Nowadays, molecular hybridization is used for rationally designing new therapeutic alternatives [11,12]. This method creates novel hybrid compounds that may be more effective than their original pharmacophores by covalently combining the pharmacophoric moieties of several bioactive substances [13–17]. Another approximation used in drug discovery is molecular conjugation. It consists of the structural modification of compounds that are biologically active.

One of the methodologies used to carry out the molecular hybridization and conjugation is the so-called click reaction, which is the name given to a class of reactions that are quick, easy to employ, adaptable, regiospecific, and yield large amounts of product. An illustration of this reaction is the CuI-catalyzed Huisgen 1,3-dipolar cycloaddition of azides with terminal alkynes to produce 1,2,3-triazoles (Fig. 1) [18,19].

Morten Meldal and Barry Sharpless were granted the 2022 Nobel Prize in Chemistry for establishing the principles of click chemistry and advancing chemistry into the functionalism time. Carolyn Bertozzi, who started mapping cells with click chemistry and expanded its use, shares the award with them. Currently, her bioorthogonal protocols are helping to develop more focused cancer therapies [20].

Click reaction can be carried out with readily available reagents, starting ingredients, and environmentally friendly solvents such as water. Furthermore, this reaction can be carried out with straightforward workup and purification techniques for product separation under ambient reaction conditions. The production of 1,4-disubstituted-1,2,3-triazoles in a regiospecific manner with extremely high yields can be easily accessed with this synthetic technique. The resulting triazole has advantageous physicochemical characteristics (such as a propensity to form hydrogen bonds, stacking and dipole–dipole interactions, and familiarity with amide bonds in terms of planarity and distance), which enhances target binding and cell permeability and is highly resistant to biotransformation [11].

A method that helps in providing a macroscopic perspective of substantial volumes of scientific literature is bibliometric analysis. This information can be used to assess the research patterns during a defined timespan. In click reaction, there are several reviews available, including advances in triazole and their pharmacological application [21–24,19], constructing liquid separation membranes for water treatment, combination for analysis of food hazard factors, and preparation of biomedical hydrogels, among others [25].

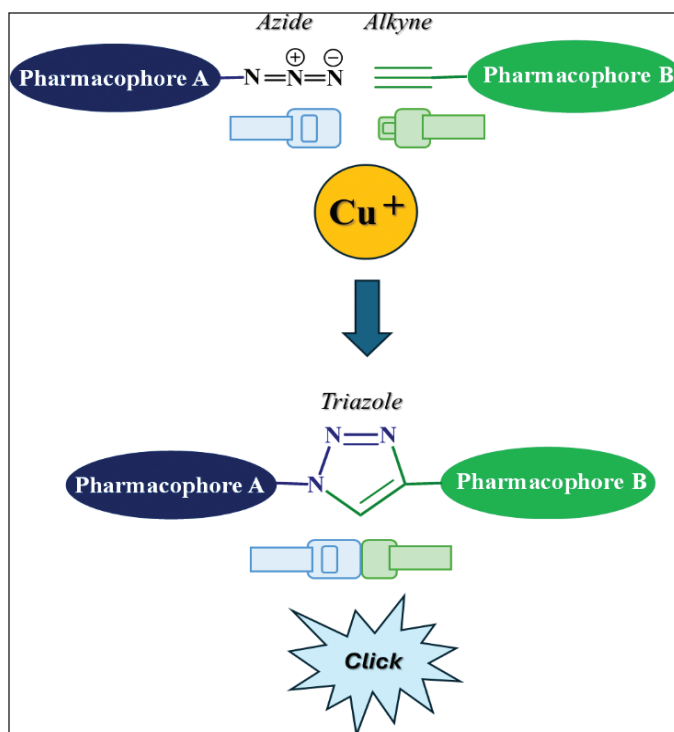


Figure 1. General representation of the click reaction for obtaining hybrid molecules.

In the case of cancer, 1,2,3-triazole-containing hybrids and conjugates are a useful scaffold for the development of novel drug candidates because they could exert dual or multiple anticancer mechanisms of action [18,26,27].

The current study summarizes the new 1,2,3-triazole-incorporating hybrids and conjugates reported in the last years. In addition, a bibliometric study of these compounds in cancer was carried out.

METHODS

Database selection

This study relied exclusively on the Scopus database to conduct a bibliometric analysis of triazole-based click chemistry for anticancer applications. Scopus was selected due to its extensive coverage across disciplines, including chemistry and biomedical sciences, as well as its rigorous indexing criteria, which support reliable bibliometric insights. Expanding the search to include additional databases, such as Web of Science or PubMed, could provide further insights but would likely involve considerable overlaps with the Scopus-indexed studies.

Search strategy

The bibliographic data retrieved include the most relevant works related to “click reaction” and “hybrid.” The search query was designed using the terms “Click reaction” and “hybrid,” connected with the Boolean operator “AND.” The final query was as follows:

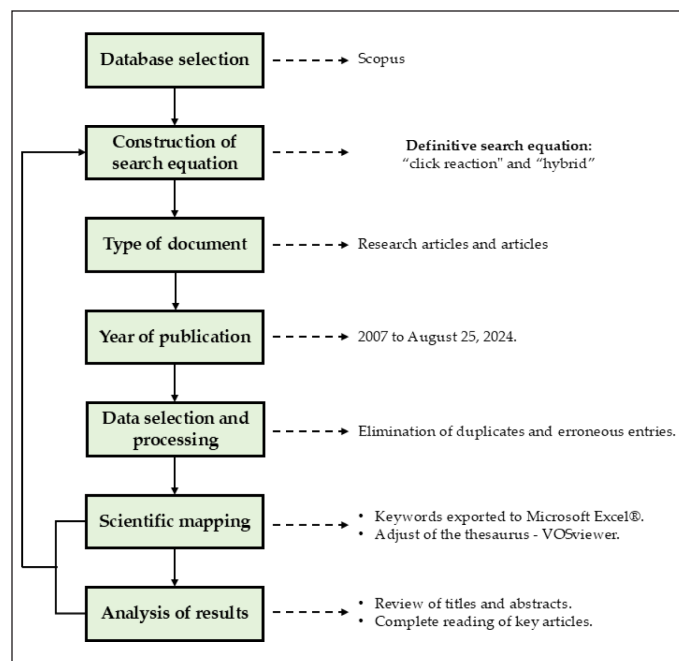


Figure 2. Research methodology for bibliometric analysis.

First query: (TITLE-ABS-KEY ("click reaction") AND TITLE-ABS-KEY (hybrid)) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re"))

Timespan: 2007 to August 25, 2024.

Second query: (TITLE-ABS-KEY ("click reaction") AND TITLE-ABS-KEY ("1,2,3-triazoles") AND TITLE-ABS-KEY (hybrid)) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re"))

Timespan: 2008 to November 21, 2024.

Keywords, abstract, and article title were used to conduct the search, which was then further refined to only include articles and reviews. Duplicate records were removed using the Mendeley Reference Manager to minimize limitations or potential biases in the bibliometric analysis. A schematic of the methods employed in this investigation is shown in Figure 2.

Bibliometric data export

Citation and bibliographical information, abstracts, and keywords were among the bibliographic data that were obtained for research publications and reviews. CSV files of the data were retrieved from Scopus and exported to Excel®. Afterward, data analysis and visualization were conducted using VOSviewer 1.6.19 [28].

Bibliometric indicators

Furthermore, bibliometric indicators were assessed, including the number and growth of published articles and reviews, subject areas, co-occurrence keyword overlay and network visualizations, top journals and institutions, and international collaboration networks.

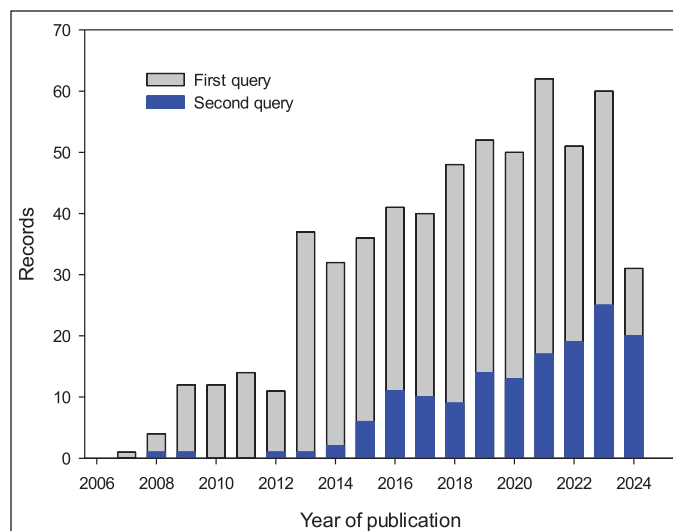


Figure 3. Development of published research on hybrids produced by click reactions based on triazoles.

RESULTS

Evolution of published papers, journals, and institutions related to triazole-based click reactions

For the first query, a total of 594 articles were retrieved from Scopus. The increase in published research on click reactions and hybrids between 2007 and August 25, 2024, is depicted in Figure 3. During this period, a notable increase in the number of articles was observed, starting from 2012. The primary areas of focus in these studies were: (i) chemistry, (ii) materials science, and (iii) chemical engineering, representing, respectively, 35.7%, 20.4%, and 11.8% of the records. Furthermore, China, India, and the United States ranked first, second, and third, respectively, followed by Iran and Germany as the countries with the most published articles and reviews in this field.

Likewise, Osmania University, the Chinese Academy of Sciences, and the People's Republic of China's Ministry of Education were found to be the top three universities in this discipline. These prestigious universities are located in the previously mentioned top-ranked nations (China and India), as was to be expected.

Similarly, 152 records were obtained for the second query, and the evolution of the number of published studies showed a similar pattern. Nevertheless, 44.7%, 17.6%, and 16.5% of the records were related to: (i) chemistry, (ii) toxicology pharmacology and pharmaceuticals, and (iii) genetics, biochemistry, and molecular biology.

Bibliometric networks of hybrids obtained via triazole-based click chemistry

The co-occurrence network of the authors' keywords for the first query has 33 nodes and 7 clusters (Fig. 4a). Notably, 1,2,3-triazoles, molecular docking, hybrids, and drug delivery (green light, and green and blue clusters) stand out as key topics. In addition, Figure 4b highlights the research topics that were

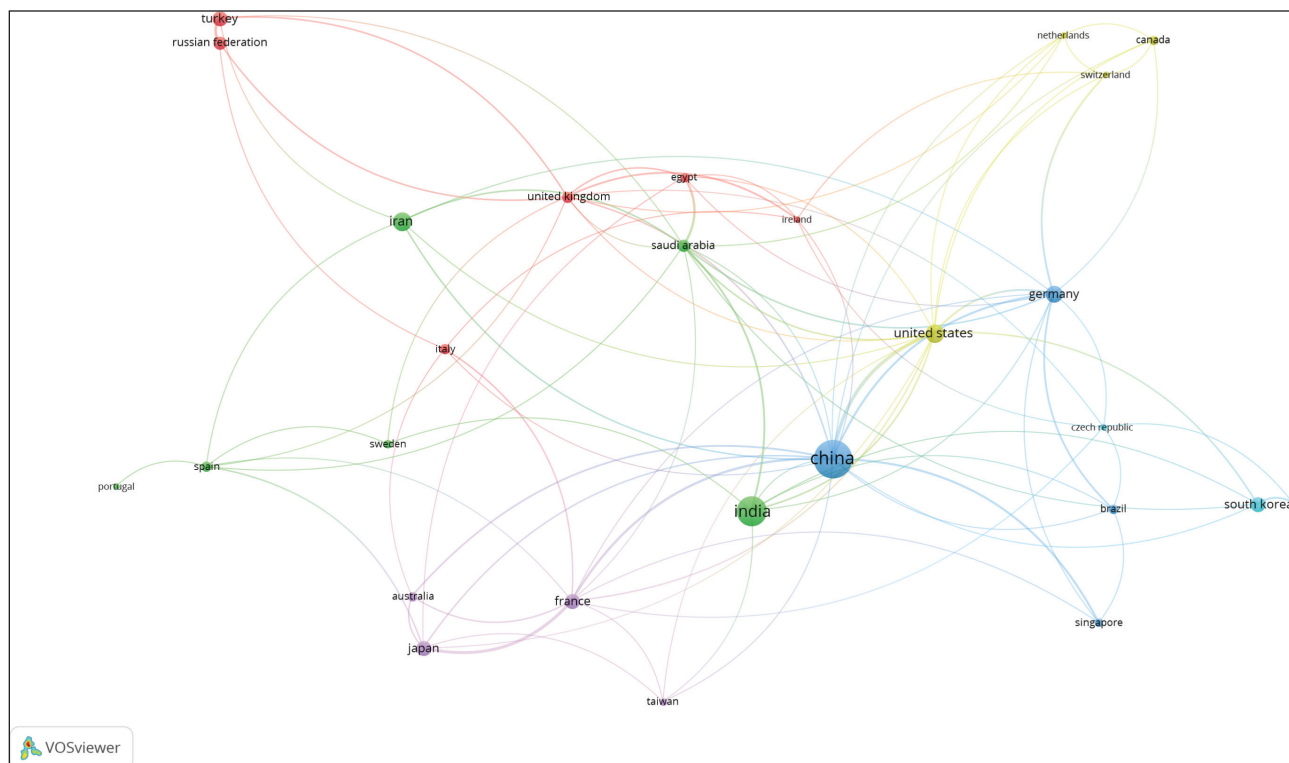


Figure 5. Bibliometric map of international cooperation network between nations studying hybrids, acquired by click chemistry between 2007 and August 25, 2024.

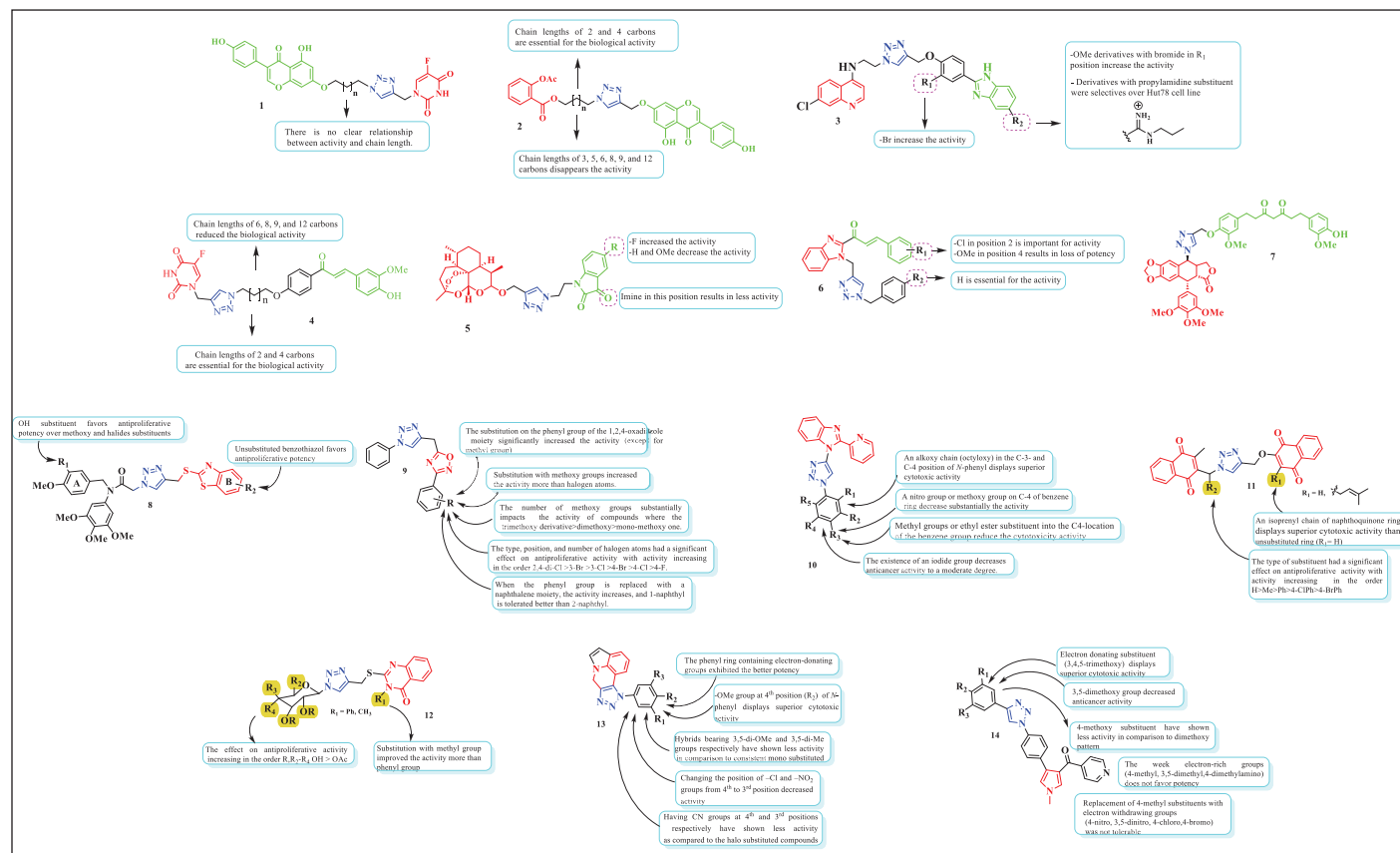


Figure 6. Chemical structure of hybrids obtained via click chemistry.

lymphoma 2) protein system and cyclooxygenase-2 with Vina scores between -10.1 and -9.3 kcal/mol [31]. The quinoline–benzimidazole hybrid **3** ($R_1 = \text{H}$ and $R_2 = \text{propylamidine}$) exhibited potent and selective antiproliferative response over lymphoma cell line growth, HuT78 cells, with an $\text{IC}_{50} = 10.86$ μM and $\text{SI} = 9.2$. In comparison to untreated cells, this hybrid reduced the number of cells in the G1 and G2/M phases by 68%, $p < 0.05$, increasing the fraction of subG0/G1 phase cells. The alterations in other cell cycle phases were not statistically significant. The docking analysis on the TAO2 kinase domain (PDB: 2GCD) showed that compound **3** had high binding energy (-140.44 kcal/mol), which is due to the hydrophobic surface of the ATP-binding cleft of TAO2, along with a large number of hydrogen bonds and van der Waals interactions [32].

Hybrids 5-FU-curcumin **4a** ($n = 0$) and **4b** ($n = 3$) displayed good activity against 5-FU-resistant colon cancer cells (SW-480) with inhibitory concentrations at around 17.37 and 2.43 μM , respectively). Furthermore, compound **4b** was active over the SW620 cell line ($\text{IC}_{50} = 7.51 \pm 1.47$ μM). These hybrids were more cytotoxic and selective than curcumin alone, 5-FU, the reference drug, and the equimolar mixture of curcumin and 5-FU. Determining the importance of the length of the aliphatic chain that connects the triazole, which binds to 5-FU, the chalcone analog of curcumin was one of the objectives of the biological evaluation in connection to the SAR. The results of the IC_{50} value analysis showed that the hybrid compounds' biological activity improved when the linker's chain length increased to five carbons. The data therefore demonstrated that the hybrids with chain lengths of 6, 8, 9, and 12 carbons reduced the biological potency. In addition, compounds **4b** in SW620 and hybrids **4a** and **4b** in SW480 produced a significant increase in the population in the sub-G0/G1 phase in both cell lines, and compound **4b** in SW620 caused S-phase cell cycle arrest [13]. Dihydroartemisinin-isatin hybrids **5a** ($R = \text{H}$) and **5b** ($R = \text{F}$) were investigated for their antiproliferative effectiveness against A549, doxorubicin-resistant A549 (A549/DOX), and cisplatin-resistant A549 (A549/DDP). The result showed that these compounds exhibited good activity over all cell lines (**5a**: 8.32, 12.1, and 10.7 μM ; **5b**: 7.54, 9.89, and 8.77). From this study, the substituents at positions C-3 and C-5 of the isatin moiety significantly affected the activity, according to the structure–activity connections, while the activity was decreased by the imine at position C-3 and increased by the fluoro group at position C-5 [33].

Triazole–benzimidazole–chalcone hybrid **6** ($R_1 = 2\text{-Cl}$ and $R_2 = \text{H}$) exhibited IC_{50} values of 6.23, 5.89, and 10.7 μM against T47-D, MDA-MB-231, and PC3 cancer cells, as well as the prostate PC3 cancer cell line [34]. This study demonstrated that the benzyl group attached to the 1,2,3-triazole moiety and the chloro substituents at the chalcone ring of the triazole–benzimidazole–chalcone skeleton enhanced the cytotoxic effects in both breast and prostate cancer cell lines. Podophyllotoxin–tetrahydrocurcumin hybrid **7** was evaluated over HCT 116 and HeLa human cancer cell lines. The result showed that this compound exhibited IC_{50} values of 18 and 83 μM [35].

Recently, Wu *et al.* [36] reported that triazole hybrids containing benzothiazole **8** possess potent anti-proliferative activities against esophageal cancer cells Kyse30 and EC-109.

The SAR for this series revealed that alkoxy and halide groups do not favor activity on A-ring, while the 2-hydroxysubstitution on A-ring and unsubstituted benzothiazole (B-ring) was essential for the major antiproliferative activity (IC_{50} of 0.042 and 0.038 μM , respectively) [36].

On the other hand, the apoptotic antiproliferative action of 1,2,3-triazole bearing a 1,2,4-oxadiazole framework **9** was reported in 2024 by Mahmoud. Comparing these hybrids to Erlotinib ($\text{GI}_{50} = 33$ nM), most of them demonstrated strong antiproliferative efficacy with GI_{50} values ranging from 28 to 104 nM. The SAR analysis showed that the activity was considerably enhanced by substitution on the 1,2,4-oxadiazole moiety's phenyl group, indicating that methoxy group substitution increased the activity more than halogen atom substitution. Besides, the activity of hybrids is greatly impacted by the number of methoxy groups in the order trimethoxy derivative > dimethoxy > mono-methoxy one. The antiproliferative activity of compounds was significantly influenced by the type, position, and number of halogen atoms; activity increased in the order 2,4-di-Cl > 3-Br > 3-Cl > 4-Br > 4-Cl > 4-F. The activity increases when a naphthalene moiety is added in place of the phenyl group, and 1-naphthyl is more tolerable than 2-naphthyl [37].

On another side, the hybrid of 1,2,3-triazole containing the 2-(2-pyridinyl)-1H-benzo[d]imidazole ring **10** was recently prepared and their anticancer ability was investigated. An SAR analysis revealed that the *in vitro* anticancer activity was strongly correlated with the type of substituents attached to the *N*-phenyl group. Thereby, 1) *N*-phenyl exhibits greater cytotoxic action when an alkoxy chain (octyloxy) is present in its C-3 and C-4 positions; 2) a nitro group or methoxy group on C-4 of benzene ring decrease substantially the activity; 3) the cytotoxicity action is decreased when methyl or ethyl ester substituents are added to the benzene at C4 position; and 4) the presence of an iodide group moderately reduces anticancer activity [38]. In 2024, de Souza *et al.* [39] reported a new series of naphthoquinone-1H-1,2,3-triazole hybrids **11** exhibiting strong antiproliferative effects in a cell line of breast cancer (MCF-7) at lower concentrations, around 6 μM . An inspection of the structure–activity correlation revealed that an isoprenyl chain of naphthoquinone ring displays superior cytotoxic activity than an unsubstituted ring ($R_1 = \text{H}$), as well as the type of substituent in R_2 had a notable impact on antiproliferative activity, with potency increasing as follows: $\text{H} > \text{Me} > \text{Ph} > 4\text{-ClPh} > 4\text{-BrPh}$ [39]. Abdel-Rahman *et al.* [40] examined a number of 1,2,3-triazole substituted/quinazolin hybrids **12** for their capacity to induce cytotoxicity to human cancer cell lines, which revealed excellent potency (IC_{50} range = 5.70–8.10 μM). A close view of the SAR determined that 1) replacement of acetylated glycosides with hydroxylated glycosides increases the effect on antiproliferative activity and 2) the substitution with methyl group on quinazoline ring improved the activity more than the phenyl group [40]. On another side, several quinoline-fused/1,2,3-triazole hybrid molecules **13** were recently reported and their anti-breast cancer activity against MCF-7, MDA-MB-468, and MDA-MB-231 cell lines was investigated. The IC_{50} values for most potent compounds were found in the range of 2.8–9.4 μM . The authors of the study used the SAR to determine that 1) the phenyl ring with electron-donating

groups was the most potent of all the hybrids; 2) the methoxy group at position 4 (R₂) of N-phenyl is the most cytotoxic; 3) hybrids with 3,5-di-OMe and 3,5-di-Me groups were less active than consistent mono substituted compounds; 4) moving the -Cl and -NO₂ groups from position 4 to the third position reduced activity; and 5) having CN groups at the fourth and third positions, respectively, has demonstrated less activity than the halo substituted compounds [41]. Aravind and collaborators investigated recently the anticancer profile of 1,2,3-triazole incorporated pyrrole derivatives **14** against four types of human cancer cell lines such as human breast cancer (MCF-7), lung cancer (A549), colon cancer (Colo-205), and ovarian cancer (A2780). These compounds exhibited inhibitory concentration in the range of 0.02–11.8 μ M. Further SAR studies indicated that electron-donating substituent (3,4,5-trimethoxy) displays the superior cytotoxic activity, 3,5-dimethoxy group decreased anticancer activity, and 4-methoxy substituent decreased activity in comparison to the dimethoxy pattern. The weak electron-rich groups (4-methyl, 3,5-dimethyl, 4-dimethylamino) do not favor cytotoxic potency. In addition, the replacement of 4-methyl substituents with electron-withdrawing groups (4-nitro, 3,5-dinitro, 4-chloro, and 4-bromo) resulted in compounds with very poor activities [42].

Anticancer activity of conjugates obtained via click chemistry

Figure 7 shows several conjugates obtained via click chemistry that have been active over various cancer lines. These conjugates are discussed as follows.

Rufinamide is a sodium channel blocker that is being developed as an adjunctive treatment for patients with partial seizures. It differs structurally from antiepileptic medications currently on the market and works better for generalized seizures in kids with Lennox-Gastaut syndrome, a severe kind of infantile epilepsy. This drug is marketed as BANZEL® [43].

In vitro tests of the anticancer properties of 1,2,3-triazole levonorgestrel conjugates **15a** (R₁ = R₄ = OMe, R₃ = NO₂, and R₂ = H) and **15b** (R₂ = R₄ = -CO₂-(CH₂CH₂O)₄Me, R₁ = R₃ = H) were conducted on four human cancer cell lines: colon cancer (HCT116), hepatoblastoma (HePG2), prostate cancer (PC3), and breast adenocarcinoma (MCF-7). These compounds displayed activity comparable to the standard drug doxorubicin. Conjugate **15a** showed IC₅₀ values of 9.70, 16.18, 12.11, and 26.89 μ M, while compound **15b** exhibited IC₅₀ values of 8.14, 10.69, 17.47, and 7.48 μ M. The conjugates showed moderate toxicity over normal cell line WI38 (**15a**: IC₅₀ = 68.36 μ M and **15b**: IC₅₀ = 49.74 μ M). The molecular docking showed that the activity could be attributed to the presence of nitro and methoxy groups in **15a**. In addition to their hydrophobic interactions with the cytochrome P450 17A1 residue, the two tetraglyme groups connected to the aromatic ring in **15b** facilitate the creation of hydrogen bonds [44].

The anticancer properties of 1,2,3-triazole-based glycosides containing 1,3,4-Thiadiazolyl, Indolyl, and Arylacetamide scaffolds were reported by Elganzory *et al.* Conjugates **16a**, **16b**, and **16c** (R₁ = Me and R₂ = R₃ = H) exhibited the best activity against MCF-7 human breast cancer cells among these compounds (IC₅₀ = 0.5, 4.2, and 0.6 μ M, respectively). These conjugates were further tested in human colorectal cancer cells (HCT-116), yielding IC₅₀ values of 15.5,

4.6, and 11.4 μ M. Furthermore, in contrast to the untreated MCF-7 cells, conjugates **16a** and **16c** caused a notable cell cycle arrest at the sub-G1 and S phases. In addition, with IC₅₀ ranges of 0.21–0.38, 1.50–1.95, and 2.18–2.77 μ M, respectively, compounds **16a**, **16b**, and **16c** demonstrated strong potential inhibitory effects against the EGFRWT, EGFR T790M, and HER-2 enzymes. Finally, docking experiments have shown that the natural ligands erlotinib, gefitinib, and TAK-285 are easily integrated into the binding pockets of EGFRWT, EGFR T790M, and HER-2 by similar H-bonding with the essential amino acids Met769, Met793, and Met801, respectively [45].

Conjugate **17** (R₂ and R₄ = esters with tetraethylene glycol chains) was examined against three cancer cell lines and one nontumoral cell line: breast cancer (MCF-7), colorectal carcinoma/colon cancer (HCT-116), hepatocellular carcinoma (HepG2), and human lung fibroblasts (WI38, control cell line). In each tumor cell line tested, this derivative showed high activity (IC₅₀ = 13.67, 9.92, and 7.92). According to molecular docking, this compound established various amounts of hydrogen bonds that improve its complex stability within the TGF- β R1 pocket and, in turn, inhibit downstream pathways implicated in the growth and proliferation of cancer cells [46].

Conjugate **18** (R = -NH₂) exhibited cytotoxic activity over HepG-2, HCT-116, and MCF-7 cells, with IC₅₀ = 12.22, 14.16, and 14.64 μ M, respectively. According to the SAR analysis, utilizing electron-releasing substituents (-NH₂ group) instead of an electron-withdrawing group (-COOH or -NO₂) in the phenyl ring had a greater cytotoxic effect on the three cell lines. According to molecular docking studies, this molecule had a score of -17.01 kcal/mol and bound to the EGFR active site in a similar manner as lapatinib, forming three H bonds with Thr854 (via H₂O), Met793, and Cys797 by binding OCH₂ to the triazole (at N-2) and amino group [47].

On the one hand, compound **19** (R₃ = NO₂ and R₄ = Me) exhibited IC₅₀ = 19.13, 28.87, and 16.57 μ M against PC3, Panc1, and MDA-MB-231, respectively [48]. On the other hand, derivative **20** (R₁ = OCF₃ and R₂ = H) was active with an IC₅₀ against lung cancer = 6.06 μ M and also induced apoptosis and triggered ROS generation [49]. With IC₅₀ values of 1.2 $\pm$ 0.2 μ M and 1.4 $\pm$ 0.2 μ M, conjugate **21** (R₁ = R₃ = H and R₂ = R₄ = OMe) demonstrated activity against the MCF-7 and Panc-1 cell lines. In addition, tests of Caspase-3/8/9, Cytochrome C, BAX, and Bcl-2 validated the compound's cell cycle arrest at the G2/M phase [50]. Maleimide-1,2,3-triazole conjugate **22** (R₁ = Me and R₂ = Br) showed an IC₅₀ = 1.32, 0.80, and >10.6 mM over HCT-116, T47D, and VERO, respectively [51]. Purine-triazole conjugates **23a** (R = Cl) and **23b** (R = Br) exhibited an IC₅₀ = 22.3 μ M and 22.9 μ M for MCF-7, respectively. In addition, these compounds showed IC₅₀ = 9.3 μ M and 16.7 μ M for MDA-MB-231 [52]. Pyrrolobenzodiazepine embrace 1,2,3-triazole **24** (R₁ = Cl and R₂ = H) showed cytotoxic activity on SNB-75 with a percent inhibition of 43.45% [53].

A recent publication described a new library of 1,2,3-triazole-incorporated 1,3,4-oxadiazole-triazine derivatives **25**. Compounds in this study show exceptional *in vitro* anticancer activity against the cancer cell lines PC3 and DU-145 (prostate cancer), A549 (lung cancer), and MCF-7 (breast cancer). The SAR studies of these derivatives determined that when electron-donating groups as methoxy were attached to the

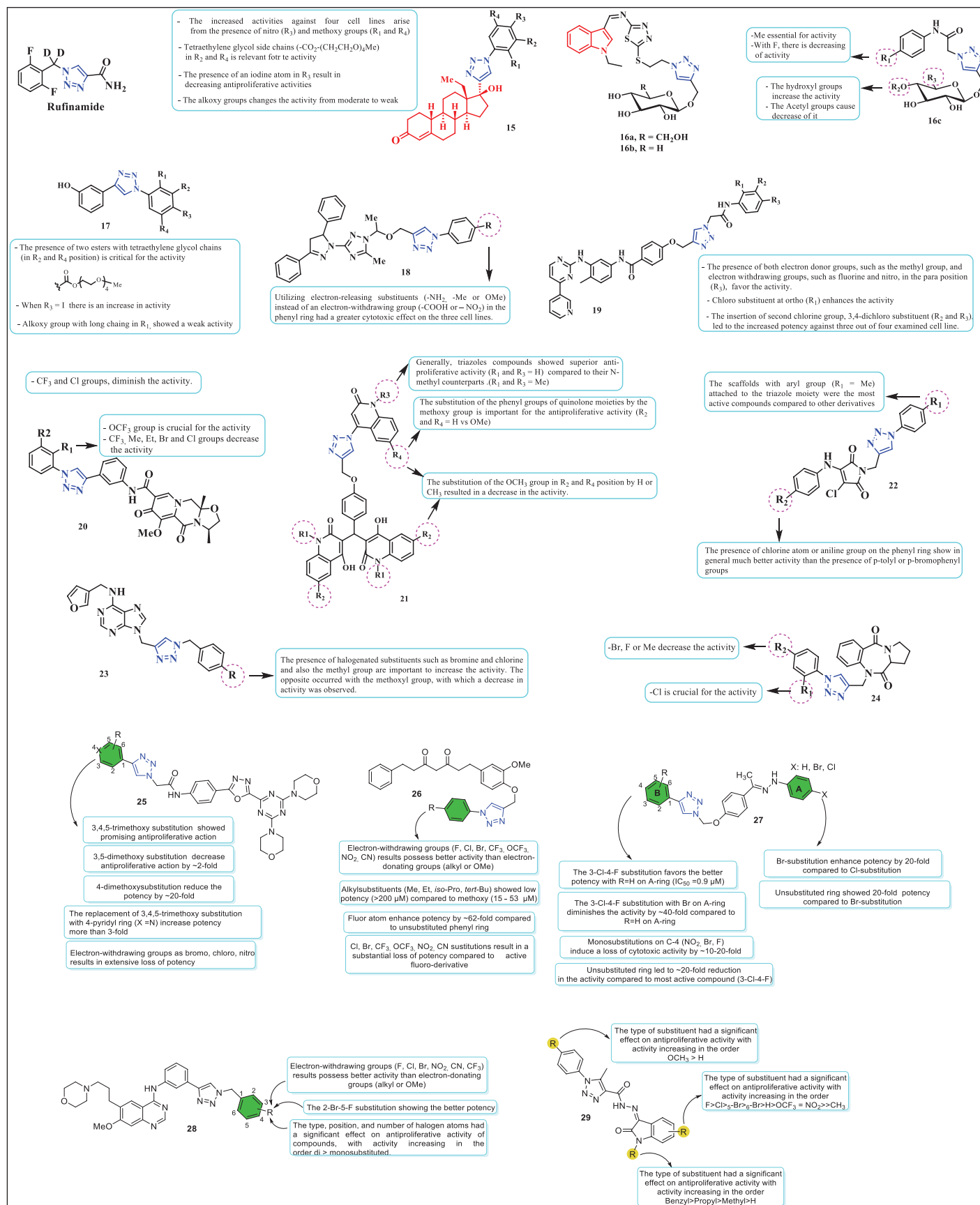


Figure 7. Chemical structure of conjugates obtained via click chemistry.

phenyl moiety (in green) favored, exceptionally the potency in comparison to electron-withdrawing group (Cl, Br, and NO₂). The 3,4,5-trimethoxy-substitution showed favorable activity than those 3,5-dimethoxy, 4-methoxysubstituted derivatives. Interestingly, the most effective molecule in this series, the 4-pyridyl moiety (X = N), demonstrated more potency than the 3,4,5-trimethoxy-substitution against PC3, A549, MCF-7, and DU-145 cell lines, with IC₅₀ values of 0.17 ± 0.063 μM, 0.19 ± 0.075 μM, 0.51 ± 0.083 μM, and 0.16 ± 0.083 μM, respectively [54]. The anticancer activity of a set of 1,2,3-triazole linked tetrahydrocurcumin derivatives **26** was examined by Duan *et al.* [35] against four cancer cell lines, including human cervical carcinoma (HeLa), human lung adenocarcinoma (A549), human hepatoma carcinoma (HepG2), and human colon carcinoma (HCT117). The SAR examination of these compounds determined that electron-withdrawing group (F, Cl, Br, CF₃, OCF₃, NO₂, and CN) favors activity than electron-donating groups (alkyl or OMe). Alkylsubstituents (Me, Et, *iso*-Pro, and *tert*-Bu) showed no significant potency (>200 μM) compared to methoxysubstituent (15–53 μM). Furthermore, attached Cl, Br, CF₃, OCF₃, NO₂, and CN groups to the phenyl ring result in a substantial loss of potency compared to fluoro-substitution (IC₅₀ = 1.09 ± 0.17 μM), which displayed superior anticancer activity [55]. More recently, Das and colleagues reported the cytotoxicity activity against MCF-7 (breast cancer cell line) of a series of 1,2,3-triazole-containing hydrazones **27** with inhibitory concentrations between 0.9 to 42 μM. A general SAR analysis revealed that when Br is attached to C-4 on A-ring the activity is higher than Cl substitution by 3–10-fold. In particular, the 2,4,5-Cl-substitution (on B-ring) and unsubstituted A-ring (R =H) were essential for the potent cytotoxic activity (IC₅₀ ~0.9 μM), whereas a 2,4,5-Cl-substitution (on B-ring) with bromo on A-ring diminished notably the cytotoxic potency by ~40-fold. When the B-ring was monosubstituted on C-4 (NO₂, Br, and F), a loss of cytotoxic activity by ~10–20-fold was observed. Finally, unsubstituted B-ring led to ~20-fold reduction in the activity compared to most potent compound (3-Cl-4-F) [56]. In addition, a set of 20 new gefitinib derivatives that contain the 1,2,3-triazole moiety **28** were recently reported, and potential anticancer responses to human lung adenocarcinoma cells (NCI-H1437) and EGFR wild-type human nonsmall cell lung cancer cells (NCI-H1299, A549) were examined. A comparative structure–activity analysis of the anticancer response determined that in general, electron-withdrawing groups (F, Cl, Br, NO₂, and CN) results possess better activity than electron-donating groups (alkyl or OMe). The antiproliferative activity of compounds was significantly influenced by the type, location, and quantity of halogen atoms, with activity increasing in the order di > monosubstituted, being the 2-Br-5-F, the most active substitution pattern showing the higher cytotoxic concentrations (IC₅₀ ~1.83–3.94 μM) [57]. The antiproliferative effects of isatin-grafted phenyl-1,2,3-triazole derivatives **29** against PC3 (prostate cancer) and PANC1 (pancreatic cancer) cells were recently studied by Elsebaie *et al.* [58] The IC₅₀ values ranged from 0.13 to 2.34 μM and from 0.10 to 1.56 μM. The SAR studies of these derivatives determined that 1) the antiproliferative activity of the N-aryltriazole ring was significantly influenced by the type of substituent, with

potency enhancing in the sequence OCH₃ > H; 2) for the isatin-fused phenyl ring, the antiproliferative activity increasing in the order F>Cl>5-Br>6-Br>H>OCF₃ = NO₂>>CH₃; and 3) for the N-substitution on isatin, the antiproliferative response increased in the order Benzyl>Propyl>Methyl>H [58].

CONCLUSION

An increasing amount of attention has been given to the development of innovative chemopreventive pharmaceutical medications because of the high incidence and mortality rates of cancer as well as the adverse side effects of conventional chemotherapy therapies. Triazole-based chemistry has attracted great interest in drug discovery through the synthesis of anticancer agents, including hybrid molecules and conjugates. This is mainly due to its versatility and the use of environmentally friendly solvents such as water for its synthesis. In this review, we showed the hybrids and conjugates, which exhibited anticancer activity based on different *in vitro* and *in vivo* studies. Here, we also showed that molecular docking revealed the possible mechanism of action of some compounds described in this study. Finally, it is important to continue exploring the great potential of triazole-based chemistry to develop new therapeutic alternatives against cancer. Furthermore, a substantial amount of reviews and articles have been published throughout the past 20 years, with increasing since 2012. Furthermore, bibliometric network analysis revealed molecular docking studies as an emerging topic.

ACKNOWLEDGMENTS

The authors acknowledge the University of Antioquia and the Ministry of Science, Technology and Innovation (Minciencias), through the Program 92332 “Progress in the development of preventive and therapeutic alternatives based on nanobioconjugates for the treatment of colorectal cancer in Colombia”. NanoBioCancer 2.0 GAT 2.0. Code: 121092092332, Contract: 621-2022. Projects: Nanovehicles 92355 and Preclinical 92391.

AUTHOR CONTRIBUTIONS

Each author accepted responsibility for all parts of the work, consented to have the work submitted to the journal in publication, and made substantial contributions to the conception and design, data collection, analysis, and interpretation. They were also involved in the authoring or critical review of the article for significant intellectual substance.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

PUBLISHER'S NOTE

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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How to cite this article:

Cardona-Galeano W, Yepes AF, Ramírez-Malule H. Triazole-based click chemistry as strategic for novel therapeutics treatments of cancer: A bibliometric analysis 2007–2024. *J Appl Pharm Sci.* 2025;15(05):064–074. DOI: 10.7324/JAPS.2025.221899