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A comprehensive review of 1,2,3 & 1,2,4 triazoleanalogs for their versatile biological activities

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Abstract
Triazoles, nitrogen-containing heterocyclic molecules, have demonstrated effectiveness in various pharmaceutical applications. Structurally, five-membered triazoles are categorized into two types: 1,2,3-triazoles and 1,2,4-triazoles. These triazoles can undergo electrophilic and nucleophilic substitutions around their basic structures, enabling the synthesis of new bioactive compounds. Triazoles and their analogues exhibit diverse biological properties, including antibacterial, anticancer, anti-infective, anti-Alzheimer's, antibiofilm, and more. They also play essential roles in organocatalysis, agriculture, and the textile industry. However, to achieve greater efficacy with fewer side effects, the azole family has undergone careful revision due to adverse events such as hepatotoxicity and hormonal issues. Triazoles have indeed been the foundation for numerous effective medications, including fluconazole and ketoconazole, which are widely used to treat fungal infections. The synthesis of triazole scaffolds has attracted considerable interest due to their importance in medicinal chemistry. This review focuses on several key aspects, including the medicinal uses of triazoles, their synthesis methods, the development of versatile hybrid molecules, and their structural

characteristics.Understanding these facets can provide valuable insights into the diverse pharmacological applications and synthetic strategies involving triazoles and related compounds.
Keywords:Antibacterial, anticancer, anti-biofilm, anti-Alzheimer, Anti-infective, structure-activity relationship.

1. Introduction

Nitrogen-containing heterocycles have indeed shown remarkable application value across various fields, particularly in medicinal chemistry. These molecules possess unique structures that enable them to exhibit a wide range of biological activities, including but not limited to antifungal, anti-human immunodeficiency virus (HIV), antimicrobial, insecticidal, and herbicidal properties. Their diverse pharmacological effects make them valuable candidates for drug discovery and development, as well as in other applications such as agriculture and pest control.[1,2]

The synthesis of triazoles has indeed received significant attention due to its importance in organic chemistry and pharmaceuticals. One of the most common methods for synthesizing the 1,2,3-triazole moiety is through the 1,3-dipolar cycloaddition reaction between an azide and a terminal alkyne. However, this method has limitations such as weak regioselectivity, low product yield, and high reaction temperatures, which initially restricted its use for synthesizing 1,2,3-triazoles[3].

Although this reaction was known since the early 20th century, it wasn't until later that its precise mechanism was elucidated. To overcome the limitations of traditional methods, the Click Chemistry approach, particularly the Copper-catalyzed azide–alkyne cycloaddition reaction (CuAAC), was proposed. Click Chemistry, including CuAAC, has had a profound impact on organic synthesis due to its high efficiency, selectivity, and versatility. It has become a widely-used tool in both industrial and research settings, enabling the synthesis of diverse molecular architectures, including 1,2,3-triazoles, in large quantities.[4,5].

Antibiotic resistance poses a significant threat to global public health, leading to increased mortality, healthcare costs, and economic burden. If left uncontrolled, drug-resistant infections could result in devastating consequences, including millions of deaths and substantial economic losses. In fact, projections suggest that the world economy could lose trillions of dollars by 2050 if antibiotic resistance is not effectively addressed.[6]

To combat this urgent public health crisis, it is essential for all nations to have a comprehensive understanding of the current status of antibiotic resistance. This includes monitoring the prevalence of resistant bacteria, tracking patterns of resistance emergence and spread, and identifying factors contributing to the development of resistance.

By implementing robust surveillance systems, promoting judicious antibiotic use, investing in research and development of new antimicrobial agents, and implementing effective infection prevention and control measures, countries can work together to mitigate the threat of antibiotic resistance and safeguard public health globally.

The triazole heterocycle, found in many biologically active molecules and currently marketed drugs, is considered a privileged scaffold in medicinal chemistry. Ongoing interest in triazoles, including 1,2,3 and 1,2,4-triazole scaffolds and their derivatives[7], stems from their versatility and wide range of biological activities.

Functionalized heterocycles with positional substitutions exhibit diverse biological actions, making them promising candidates for drug development. These actions include anti-viral, antihypertensive, anti-TB (anti-tuberculosis), antineoplastic (anti-cancer), antiulcer, and enzyme

inhibitor characteristics. Additionally, triazoles possess drug-like properties that are favorable for pharmacological applications.

The ability to modify triazole derivatives with various functional groups allows for the optimization of their pharmacokinetic and pharmacodynamic properties, enhancing their therapeutic potential. As a result, triazole-containing compounds continue to be investigated and developed for various medical applications, contributing to advancements in drug discovery and development.

2. Chemistry of Triazoles

Triazoles are notable for their versatile chemistry and have become a prominent structural motif due to their extensive applications across various scientific fields. Comprising a 5-membered heterocyclic ring with the molecular formula C2H3N3, triazoles consist of two carbon and three nitrogen atoms.

The development of two important isomers arises from the possible positional configurations of nitrogen atoms within the 5-membered ring: 1,2,3-triazole (v-triazole) and 1,2,4-triazole (s-triazole). Each of these isomers can exist in two tautomeric forms, depending on the arrangement of hydrogen atoms attached to the ring nitrogen atoms.

In the structure of 4H-1,2,3-triazole, it's true that it's non-aromatic. However, both 1,2,3-triazole and 1,2,4-triazole can exhibit aromaticity. Each atom in both types of triazoles adopts a planar configuration and undergoes sp2 hybridization. Both forms possess six π (pi) electrons distributed around the ring, conferring them with an aromatic character. This aromaticity is essential for their

stability and reactivity. Triazoles are considered energy-rich heterocycles due to the presence of three nitrogen atoms[8] which contribute to their diverse biological activities and synthetic utility.In the solid state, monocyclic 1,2,3-triazoles exist as an equimolar mixture of 1H- and 2H-1,2,3-triazoles, although in solution and gas phases, they often exhibit an equilibrium between these tautomeric forms. In aqueous solutions, the 2H-1,2,3-triazole form is predominant compared to the 1H-1,2,3-triazole form, with a ratio of approximately 2:1. The parent 1H-1,2,3-triazole has a calculated topological polar surface area of 41.6 square angstroms, making it soluble in water. It is a clear liquid with a boiling point of 203 degrees Celsius

Most 1,2,3-triazoles are synthesized from azides. The presence of both pyrrole-type and pyridine-type nitrogen atoms contributes to the stability of the 1,2,3-triazole ring system, making quaternization difficult. Additionally, the ring system can be easily electrophilically substituted by either nitrogen or carbon atoms, which further contributes to its synthetic versatility.

The parent compound of 1,2,4-triazoles is a white powder solid known as 1H-1,2,4-triazole, with a melting point of 120-121 degrees Celsius and a boiling point of 260 degrees Celsius. Similar to 1H-1,2,3-triazole, it is highly soluble in water and miscible in organic solvents. The two tautomeric forms of 1,2,4-triazole, 1H- and 4H-, rapidly equilibrate.

According to Potts (1961)[9], the 1H-1,2,4-triazole tautomer is more stable than the 4H-1,2,4-triazole tautomer. Chemically, 1H-1,2,4-triazole undergoes both electrophilic and nucleophilic substitution reactions. Due to their high electron density, only nitrogen atoms undergo electrophilic substitution. Nucleophilic substitution, on the other hand, occurs at both ring carbon atoms under mild reaction conditions. This is because both carbon atoms in the ring become π-deficient and are bound to two electronegative nitrogen atoms, rendering them sensitive to nucleophiles.

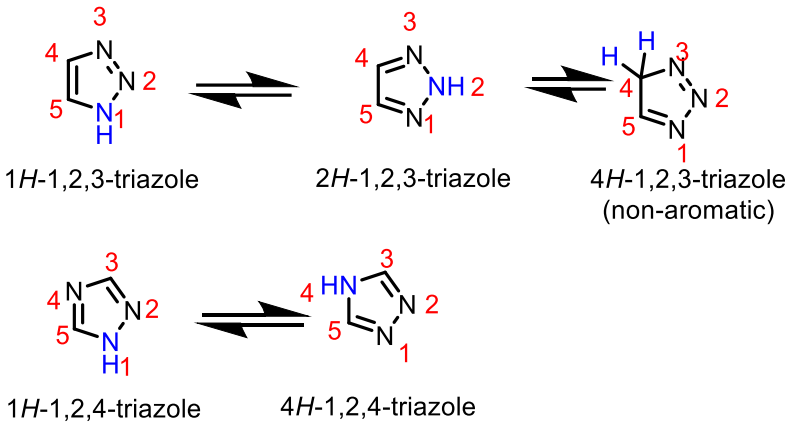


Figure 1. Structures of isomeric triazoles

The incorporation of the 1,2,4-triazole scaffold into diverse heterocycles can significantly influence various molecular properties such as hydrophobicity, polarity, lipophilicity, and hydrogen bonding capacity. This can lead to improvements in pharmacological, pharmacokinetic, physicochemical, and toxicological properties of the molecules. Hybrid molecules, which combine multiple structural domains with distinct biological properties and functions, have emerged as promising candidates in drug discovery. These hybrids have the potential to alter pharmacokinetic profiles, reduce toxicity, and overcome drug resistance.

The market availability of numerous analogues highlights their efficacy in treating a wide range of illnesses. In recent years, there has been a trend towards modifying triazole scaffolds with other pharmacophores to synthesize novel candidates with enhanced activity against both drug-sensitive and drug-resistant pathogens. This approach has shown promise in addressing the challenges posed by antimicrobial resistance and in developing more effective therapeutics.[10,11,12]

3. 1,2,4-Triazole-quinolone hybrids as antibacterial agents

The most widely used antibiotics in the quinolone class include norfloxacin, ciprofloxacin, and moxifloxacin, which are crucial in treating several bacterial infections. Numerous 1,2,4-triazole hybrids with (fluoro)quinolone medications have been explored as promising therapeutic candidates . Aggarwal et al. (2011) synthesized a series of 1,2,4-triazole-3-thione derivatives (Figure 2), which were screened for their antibacterial activity against Gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis) and Gram-negative bacteria (Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa).

The azomethine derivatives demonstrated significant antibacterial activity, with a minimum inhibitory concentration (MIC) of 16 µg/mL against P. aeruginosa, indicating a high level of activity. Among the synthesized compounds, the most potent was a triazolothiadiazole derivative (compound 2), which featured a chloro-substituent at the 2-position on the phenyl ring. This compound exhibited MICs of 16 µg/mL against all tested microorganisms, showing comparable efficacy to the standard antibiotic streptomycin (MIC: 2–15 µg/mL).

These findings suggest that the incorporation of 1,2,4-triazole moieties into quinolone-based structures can enhance their antibacterial properties, making them potent candidates for further development in the fight against bacterial infections.

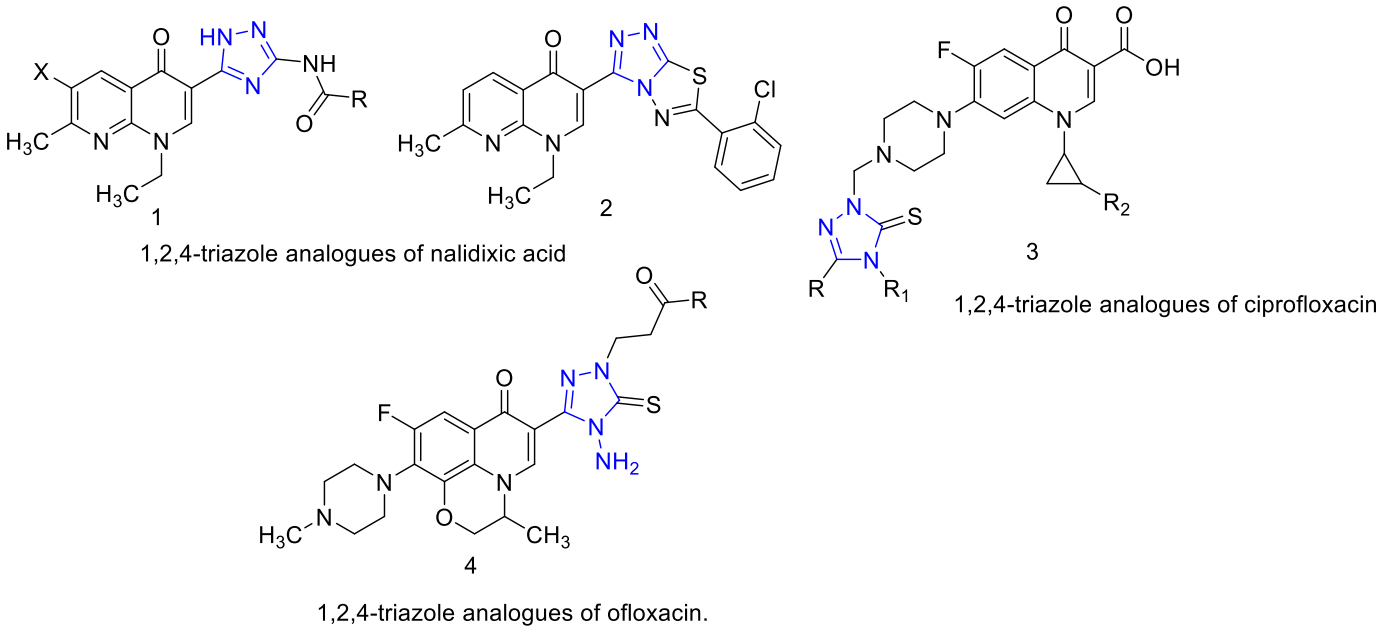


Figure 2. Chemical structures of 1,2,4-triazole-quinolone hybrids

In 2012, an Indian research team synthesized novel ofloxacin analogues (Figure 2) incorporating 1,2,4-triazole moieties as antimicrobial agents. These ofloxacin derivatives demonstrated significant antibacterial properties, with minimum inhibitory concentration (MIC) values ranging from 0.25 to 1 µg/mL. These compounds were effective against one Gram-negative pathogen (Escherichia coli) and all tested Gram-positive pathogens (Staphylococcus aureus, Staphylococcus epidermidis, and Bacillus subtilis). The MIC values of these novel derivatives were comparable to those of ofloxacin, which ranges from 0.25 to 2 µg/mL, indicating their potent antibacterial qualities.

3. 1,2,4-quinolone hybrids

The most widely used antibiotics are quinolones, which include norfloxacin, ciprofloxacin, and moxifloxacin. They play a crucial role in the treatment of several bacterial infections. Numerous 1,2,4-triazole hybrids with (fluoro)quinolone medications have been included as promising therapeutic candidates.[13]

Aggarwal et al. (2011) synthesized 1,2,4-triazole-3-thione derivatives 1-2 (Figure 2),[14]which were then screened against Gram-positive bacteria (S. aureus, B. subtilis) and Gram-negative bacteria (E. coli, K. pneumoniae, P. aeruginosa). The azomethine derivatives demonstrated a minimum inhibitory concentration (MIC) of 16 µg/mL, indicating a high level of activity against P. aeruginosa. The most potent triazolothiadiazole against all tested microorganisms had MICs of 16 µg/mL, particularly compound 2 with a chloro-substituent at the 2-position on the phenyl ring, compared to the typical medication, streptomycin (MIC: 2–15 µg/mL).

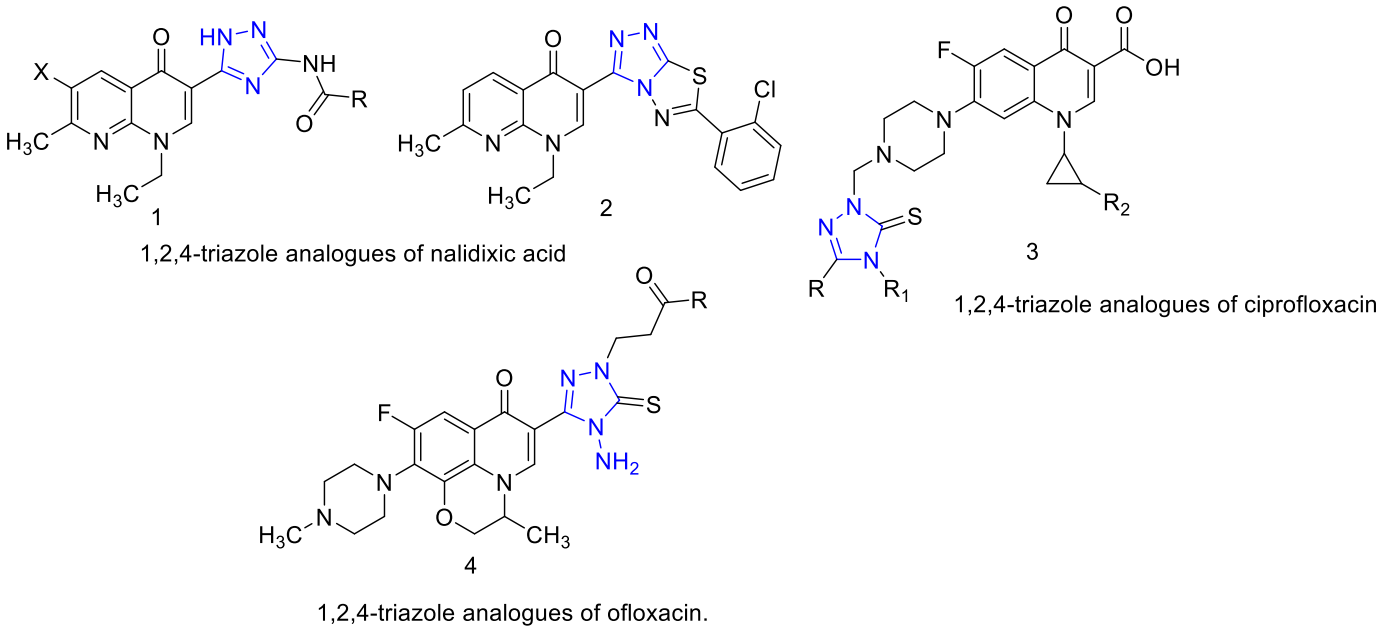


Figure 3. Chemical structures of 1,2,4-Triazole-quinolone hybrids

Novel ofloxacin analogues 4 (Figure 3) were synthesized by an Indian research team in 2012 as antimicrobial agents. These ofloxacin derivatives, containing 1,2,4-triazole moieties, exhibited MIC values ranging from 0.25 to 1 µg/mL. They demonstrated significant antibacterial activity against one Gram-negative pathogen (E. coli) and all tested Gram-positive pathogens (S. aureus, S. epidermidis, and B. subtilis). The MICs of these derivatives were comparable to those of ofloxacin (0.25-2 µg/mL).[15]

4. 4-amino-1,2,4-triazole-hybrids antibacterial agents

In 2010, Indian scientists synthesized 4-amino-5-aryl-4H-1,2,4-triazole derivatives and evaluated their in vitro antibacterial activity against E. coli, B. subtilis, P. aeruginosa, and P. fluorescens (recultured). The compound bearing the 4-trichloromethyl group attached to the phenyl ring at the 3-position of the triazole exhibited the highest antibacterial activity, with a MIC of 5 µg/mL and a zone of inhibition ranging from 14 to 22 mm. Compounds with 4-chloro and 4-bromo substituents demonstrated good activity comparable to ceftriaxone. However, acetylation of the NH2 group at the 4-position and the presence of a free SH group at the 3-position reduced the antibacterial activity of the triazoles against most bacterial strains.

In 2013, Gadegoni et al. presented the synthesis and antimicrobial properties of 3-[4-amino-3-(1H-indol-3-yl-methyl)-5-oxo(5-thioxo)-4,5-dihydro-1,2,4-triazol-1-yl]-propionitriles and their 1,3,4-oxadiazole analogues. In vitro antimicrobial testing against E. coli, B. subtilis, S. aureus, M. luteus, P. vulgaris, and S. typhimurium was conducted for each compound. The compounds with thione-substituted triazole rings showed equipotent activity with the standard drug ampicillin against B. subtilis, S. aureus, and P. vulgaris (MICs: 1.56, 1.56, and 6.25 µg/mL, respectively), while its 5-oxo analogue exhibited the strongest action against E. coli (MIC = 3.12 µg/mL). Triazoles were found to be more potent than oxadiazole analogues. Additionally, all examined compounds displayed strong anti-inflammatory properties.[16,17]

In 2015, researchers from China synthesized novel indole derivatives of 4-amino-4H-1,2,4-triazole-3-thiol using an ultrasonic-assisted method. They evaluated the in vitro[17] antibacterial activity of these derivatives against four pathogenic strains: E. coli, B. subtilis, S. aureus, and P.

aeruginosa. The amino-containing derivative exhibited a strong inhibitory effect against S. aureus and E. coli, with MICs of 2 and 8 µg/mL, respectively. These values were 2- and 8-fold more potent than amoxicillin, according to the preliminary results of the antibacterial assay.

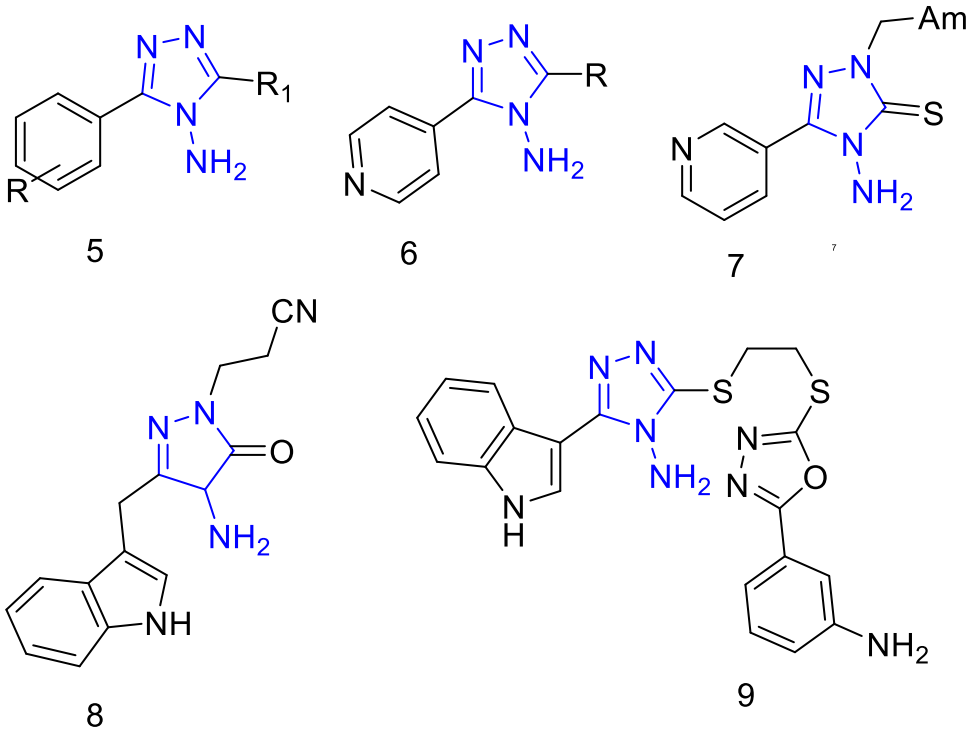


Figure 4. Chemical structures of 4-amino-1,2,4-Triazole derivatives antibacterial agents

5. Schiff bases 4-amino-1,2,4-Triazole Hybrids

In 2010, Al-Omar et al. evaluated the antibacterial activity of Schiff and Mannich bases derived from 5-(1-adamantyl)-4-amino-2,4-dihydro-3H-1,2,4-triazol-3-thione against Gram-positive (S. aureus, B. subtilis, and M. luteus) and Gram-negative bacteria. The compounds showing antibacterial activity were determined by measuring the diameter of growth inhibition zones and then subjected to minimum inhibitory concentration (MIC) analysis. Among them, 5-[(4-hydroxybenzylidene)amino]-4-(1-adamantyl)-Mannich bases containing two 4-ethoxycarbonyl-1-piperidyl and -3-mercapto-1,2,4-triazole exhibited the most potent inhibitory action against Staphylococcus aureus and Bacillus subtilis, with MICs ranging from 1 to 2 µg/mL, comparable to gentamycin and ampicillin.

Similarly, Çalişir et al. (2010) synthesized Schiff bases derived from 4-amino-5-(1-phenylethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione as antibacterial agents against six human pathogenic bacteria (S. aureus, S. epidermidis, E. coli, K. pneumoniae, P. aeruginosa, and P. mirabilis). The results showed that Schiff base with a 4-nitrophenyl substituent exhibited antibacterial efficacy against S. epidermidis at a minimum inhibitory concentration (MIC) of 9 µg/mL, equivalent to that of cefuroxime, a commonly used medication.[18]

In 2012, Murthy et al. evaluated Schiff and Mannich bases derived from 4-amino-5-benzyl-2,4-dihydro-3H-1,2,4-triazole-3-thione. Their study aimed to assess the antibacterial properties of these compounds.

Additionally, Mange et al. conducted a study in 2013 on the antibacterial properties of Schiff bases derived from N-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-4-substituted benzamides. They evaluated the antimicrobial activity of these compounds against both Gram-

negative (E. coli and P. aeruginosa) and Gram-positive (S. aureus and B. subtilis) bacteria. The newly synthesized compounds exhibited moderate activity against the tested bacteria, with comparable effectiveness against Staphylococcus aureus to that of the standard medication, ceftriaxone.[19,20]

In 2013, Chinese scientists investigated the antibacterial activity of Schiff bases derived from symmetric disulfides linked to 4-amino-3-(1-benzyl-1H-indol-3-yl)-5-thiomethyl-1,2,4-triazole against E. coli, S. aureus, and P. aeruginosa. They found that a compound with a 3-bromophenyl substituent exhibited potent activity against all three bacteria, comparable to the standard drug sparfloxacin. However, compounds containing an unsubstituted phenyl ring or 2-furyl showed low effectiveness against the bacterial strains.

In a separate study in 2014, the same researchers synthesized 3-[1-(4-fluorobenzyl)-1H-indol-3-yl]-5-(4-fluorobenzylthio)-4H-1,2,4-triazol-4-amine. They observed that the presence of halogen and nitro groups significantly increased the inhibitory activity against all tested bacteria. These findings underscored the importance of the aromatic substituent at the 4-position of the triazole ring in determining antibacterial activity.[21,22]

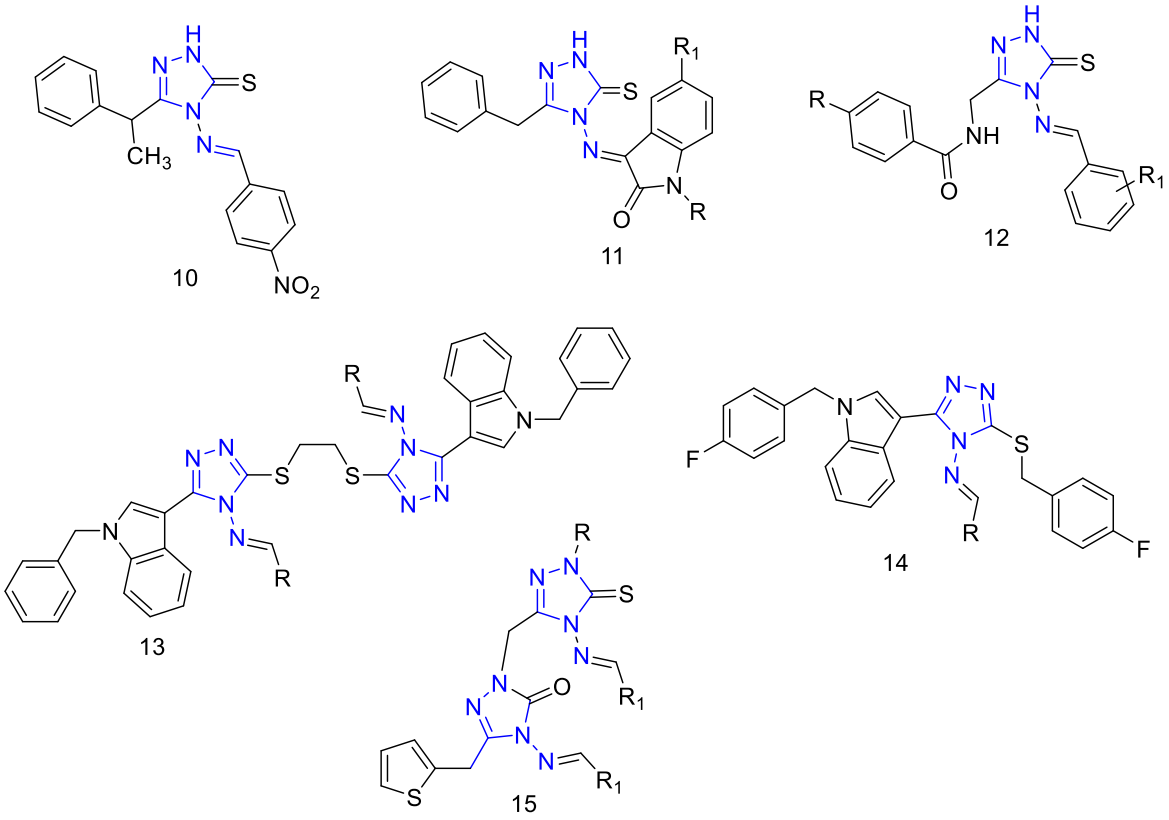


Figure 5. Chemical structures of Schiff bases 4-amino-1,2,4-Triazole hybrids as antibacterial.

Ünver et al. (2016) evaluated the antibacterial activity of hybrid 1,2,4-triazole molecules against a panel of bacteria including E. coli, Y. pseudotuberculosis, P. aeruginosa, E. faecalis, S. aureus, B. cereus, and Mycobacterium smegmatis.On the other hand, Rajasekaran et al. (2017) designed Schiff bases of 1,2,4-triazole with various substituted aromatic groups at the C-3 and N-4 positions, as well as oxygen or sulfur at the 5-position of the triazole ring. Each synthetic compound was tested for antibacterial activity against three Gram-negative bacteria (E. coli, P. aeruginosa, and K. pneumoniae) and three Gram-positive bacteria (M. luteus, S. albus, and S. aureus).[23,24]

6. 1,2,4- Triazole-Beta-Lactum Hybrids

The primary building block of beta-lactam antibiotics is 2-azetidinone. Therefore, coupling 1,2,4-triazole with a beta-lactam fragment might enhance its antibacterial activity. Among the 1,2,4-triazole-beta-lactam hybrids studied, a compound with a MIC range of 0.125-0.5 mg/mL was identified as the most potent inhibitor. This compound showed positive activity against a series of isogenic strains of Escherichia coli harboring individual beta-lactamases. Additionally, one hybrid, 16a, exhibited strong activity against 88 Enterobacteriaceae strains with a MIC of 2 mg/mL, surpassing the references meropenem (MIC: >64 mg/mL) and aztreonam (MIC: 32 mg/mL). While hybrids 17 and 18 displayed some activity against certain bacteria, further modification was deemed necessary to enhance their biological functions.[25,26,27]

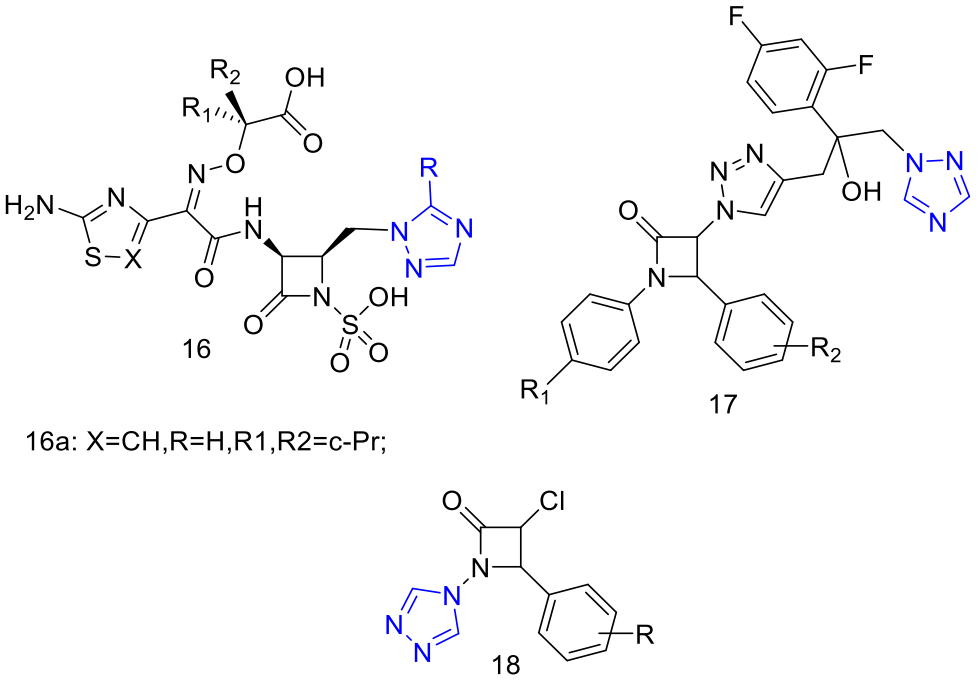


Figure 6. Chemical structure of 1,2,4-Triazole-beta-lactum hybrids

7. 1,2,4-Triazole thioether and thiazolo[3,2-b]-1,2,4-triazole hybrids bearing the 6-Fluoroquinazolinyl moiety

Lesinurad, an antigout medication containing a 1,2,4-triazole thioether moiety, is a selective inhibitor of uric acid reabsorption. Thioether linkers, such as the one present in lesinurad, are known to enhance the drug-likeness of bioactive molecules by reducing their lipophilicity and providing an additional acceptor for hydrogen bonds.[28,29]Thiazolo[3,2-b]-1,2,4-triazole derivatives, derived from the 1,2,4-triazole thio-ethanone precursor, have demonstrated various bioactivities, including antibacterial, fungicidal, antiproliferative, and anti-inflammatory properties.[30] These derivatives feature a 1,2,4-triazole fused with a 1,3-thiazole ring.

On the other hand, derivatives of 6-fluoroquinazolinyl are extensively used as antibacterial, antifungal, anticancer, anti-inflammatory, and anti-tobacco mosaic virus (anti-TMV) agents. The presence of a fluoro substituent in a molecule is generally expected to enhance its metabolic stability, bioavailability, and lipophilicity.

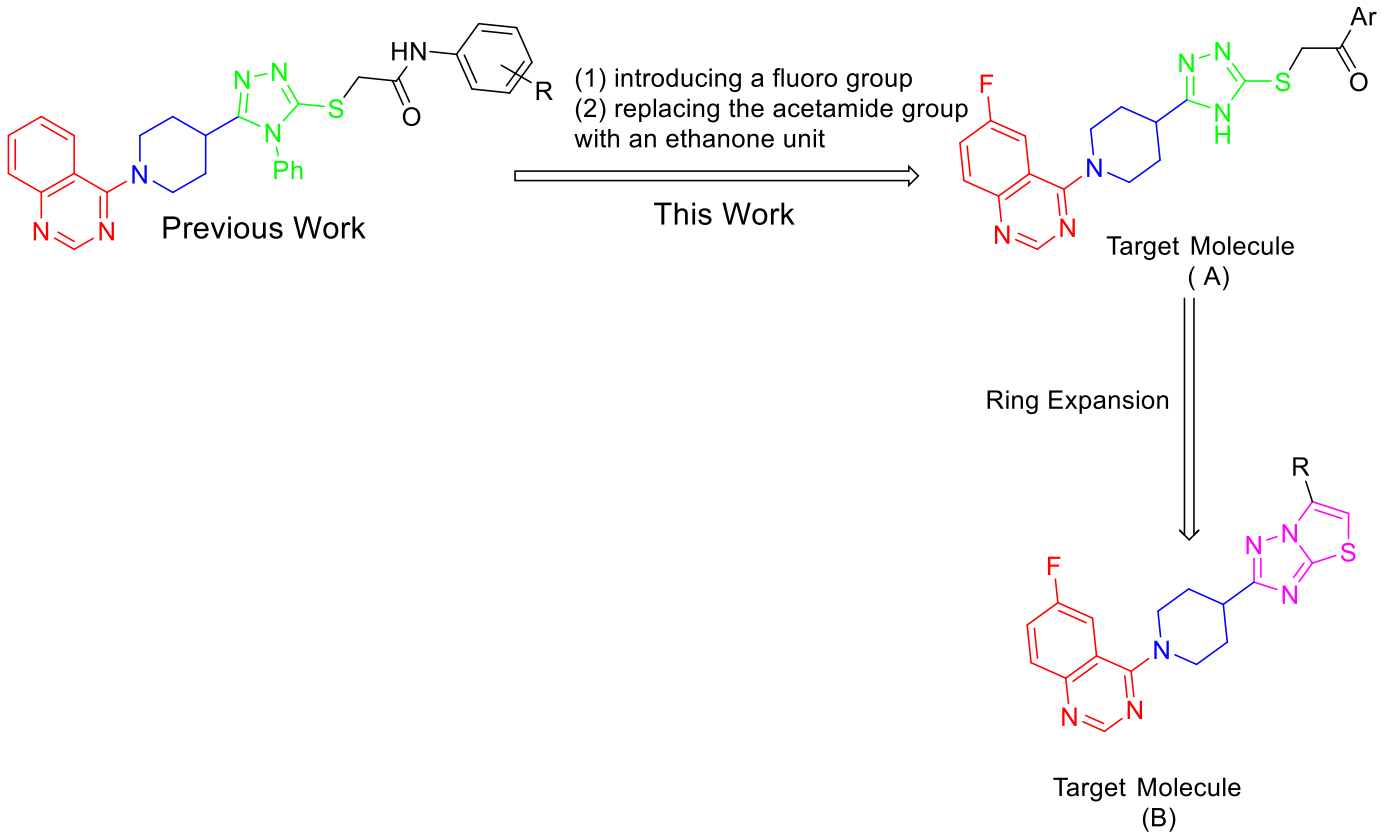


Figure 7. Design strategy of target molecules in this work

8.1,2,3-Triazole hybridizes with anticancer pharmacophore

The distinction between aromatic and nonaromatic forms is crucial in understanding the behavior of triazoles. While the 4H-1,2,3-triazole is nonaromatic, both the 1H- and 2H-1,2,3-triazoles exhibit aromatic characteristics and are in equilibrium in both gaseous and fluid phases. The 1H-1,2,3-triazole, in particular, serves as a prominent scaffold found in numerous pharmaceutical products. Its prevalence is increasing due to its extensive applications in pharmaceutical chemistry, agrochemicals, and material science.[31]

9. 1,2,3-Triazole-artemisinin hybrids

The combination of artemisinin analogs, renowned for their efficacy in malaria treatment, with 1,2,3-triazole presents an intriguing prospect for anticancer therapy. Artemisinin and its analogs possess sesquiterpene lactone frameworks containing peroxide, which contribute to their potent antimalarial properties. Interestingly, these analogs have also demonstrated a remarkable affinity for cancer cells and exhibit diverse anticancer actions, particularly against drug-resistant tumors. This efficacy against cancer cells is attributed to their ability to generate carcinogenic Reactive Oxygen Species, causing damage to cancerous cells.[32,33,34]

Integrating 1,2,3-triazole with the artemisinin domain could lead to the development of promising anticancer candidates with enhanced efficacy and specificity against a wide range of carcinomas. This hybrid approach capitalizes on the unique properties of both artemisinin analogs and triazoles, potentially offering novel therapeutic options for cancer treatment.

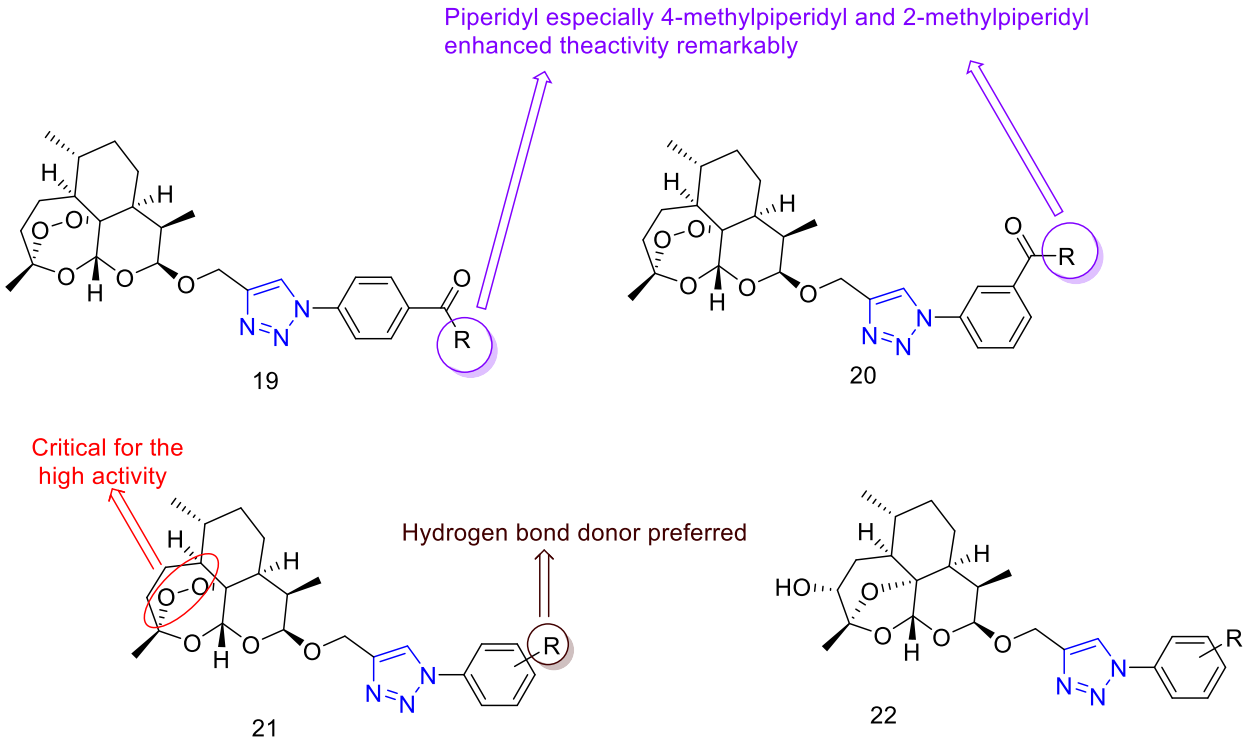
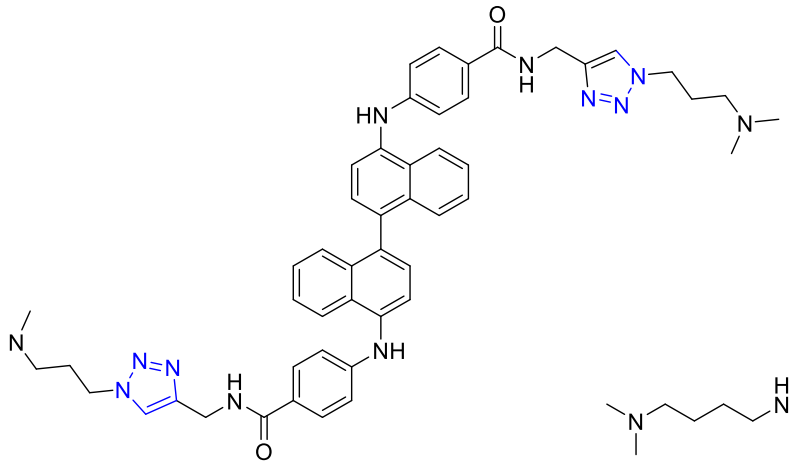


Figure 9. Chemical structures of 1,2,3-Triazole-artemisinin hybrids

The 1,2,3-triazole-artemisinin compounds 19 (IC50: 2.5-175.9 mM, 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide assay) and their regio-isomers 20 (IC50: 5.7e108.1 mM) show wide-ranging in vitro anticancer properties across 4 tumor cell lines: MCF-7, LU-1, HL-60, and P388 cellular structures. A significant fraction of them exceeded the standard Dihydroartemisinin (IC50: 39.9-84.3 mM).[35] The 1,2,3-triazole-artemisinin hybrids 21 and their analogs 22 showed potential activity towards tumor cell lines K562, PC-3, A431, MDAMB-231, COLO-205, and A449 (IC50: 4.06-89.85 mM,) .The three hybrids demonstrated superior anticancer activity relative to their derivative 22, indicating that the endoperoxide structure was essential for the enhanced activity.[36,37]

10. 1,2,3-Triazole-triazole hybrids

Enhancing the pharmacological, pharmacokinetic, and physicochemical properties of molecules can be achieved using triazole, a bioisostere of ester and amide, which exists as 1,2,3-triazole and 1,2,4-triazole.[38] Consequently, 1,2,3-triazole-triazole hybrids could be considered as prototypes for new anticancer drug development. When evaluated against HeLa and A549 cancer cell lines, the binaphthylamino-linked 1,2,3-triazole dimer 23a (IC50: 5.53 and 9.13 mM, MTT assay) exhibited promising activity." "When tested on normal mouse myoblast C2C12 cells, it exhibited no toxicity (IC50: ~40 mM)[39]. Dimer 23a showed higher anticancer activity compared to its analog 23b (IC50: 7.24 and 15.13 mM), suggesting that the 1,2,3-triazole unit may boost anticancer efficacy. This dimer displayed a strong affinity for binding the c-MYC G-quadruplex, effectively suppressing both the transcriptional and translational levels of c-MYC production.



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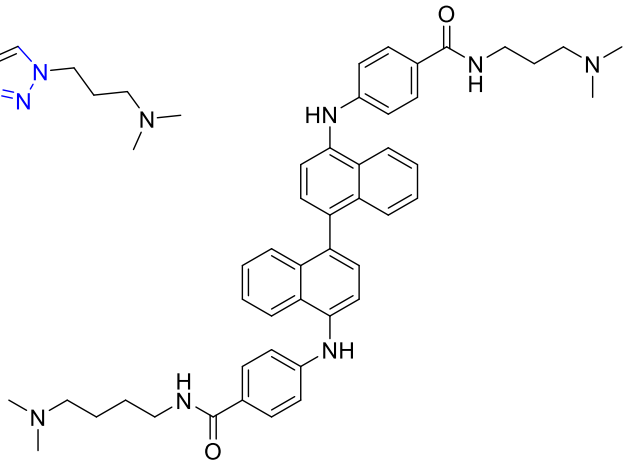

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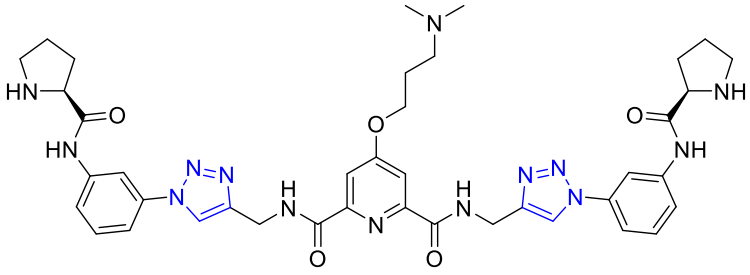

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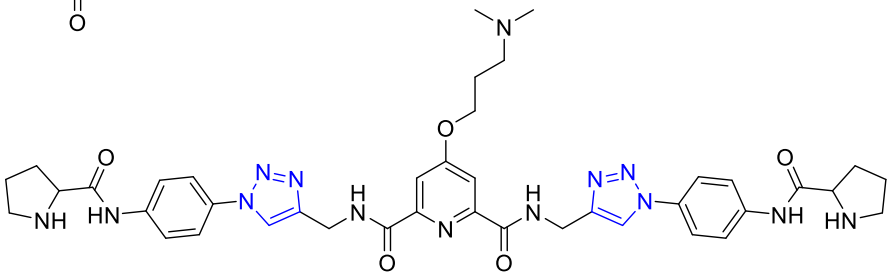

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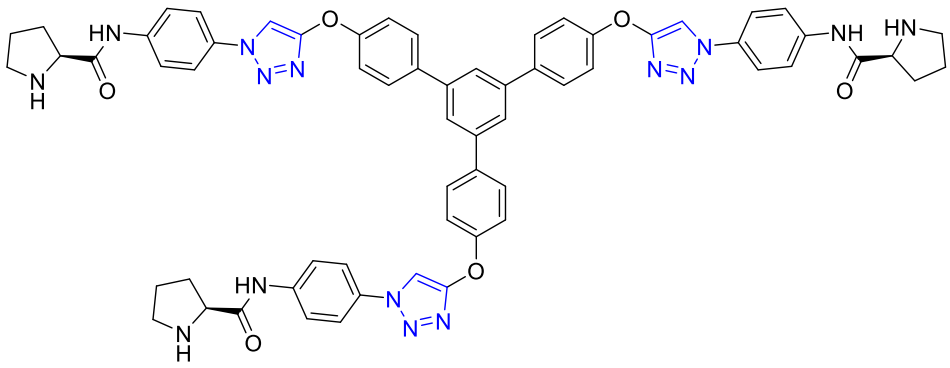

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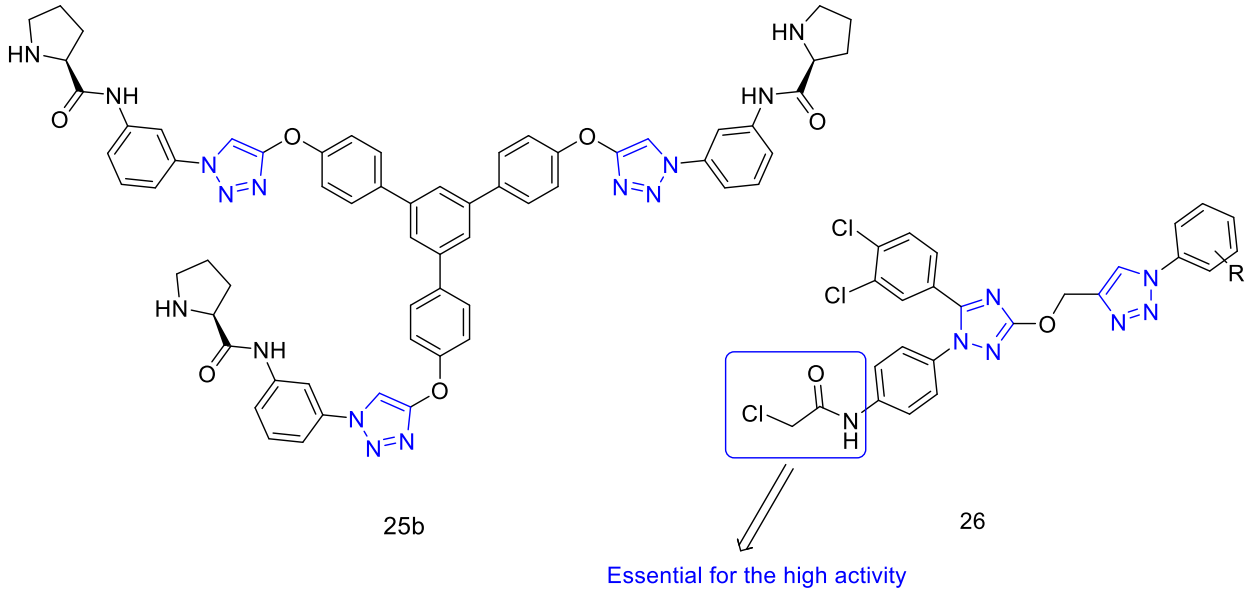


Figure 10. Chemical structures of 1,2,3-Triazole-triazole hybrids anticancer agents

Furthermore, dimer 23a inhibited cancer cell proliferation by inducing apoptosis and causing cell cycle arrest in the Sub G1 phase. Compounds 23a and 24a were more potent than their regio-isomers 24b and 25b, indicating that the 1,2,3-triazole and amide groups at the meta-position of the phenyl ring were more effective than those at the para-position. The pyridine-linked 1,2,3-triazole dimer a (IC50: 1.7 and 1.3 mM, MTT assay) and its regioisomer 24b (IC50: 14.4 and 15.1 mM), along with the 1,2,3-triazole trimers 25a,b (IC50: 7.1–13.4 mM, MTT assay), also exhibited significant activity against the MCF-7 and HCT-116 cancer cell lines. All four compounds demonstrated a positive safety profile, exhibiting no toxicity towards C2C12 cells (IC50: >40 mM). Cellular studies revealed that dimer 24a upregulated BCL-2 gene expression in cancer cells, while dimer 24b downregulated it. In the HCT116 and HepG2 cancer cell lines, pyrazoline-containing dimers 26 (IC50: >100 μg/mL, MTT assay) without an amide group showed no activity. However, these dimers were comparable to 5-Fluorouracil (IC50: 30.00μg/mL) against MCF-7 cells.In addition to the previously discussed 1,2,3-triazole-triazole hybrids, the 1,2,3-triazole-1,2,4-triazole hybrids and benzotriazole-1,2,3-triazole hybrids also demonstrated potential anticancer activity.[40] The 1,2,3-triazole-1,2,4-triazole hybrids 26 (IC50: 0.31–0.60 μM, CCK-8 assay) showed significant activity against the ABC-DLBCL cell line. Surface plasmon resonance (SPR) analysis indicated that the 2-chloroacetylamide group was crucial for this high activity.[41]

11. 1,2,3-Triazole-imidazole hybrids anticancer agents

1,2,3-Triazole-imidazole hybrids present a promising avenue for discovering novel anticancer candidates effective against both drug-sensitive and drug-resistant cancers. This potential is supported by the high potency of imidazole derivatives, such as Pretomanid (PA-824) and Delamanid, against multidrug-resistant organisms.[42]

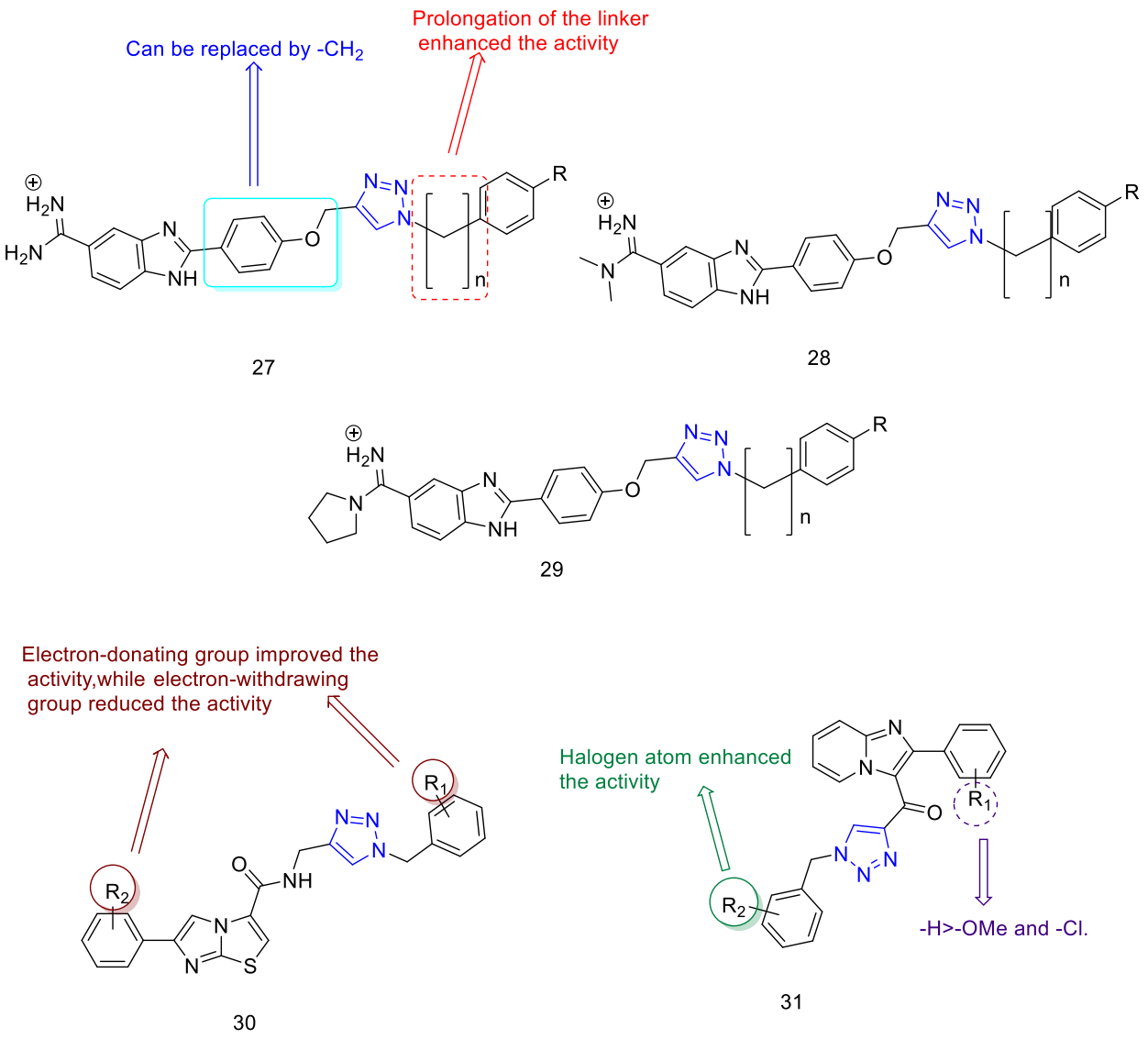


Figure 11. Chemical structures of 1,2,3-Triazole imidazole hybrids

The majority of 1,2,3-triazole-benzimidazole hybrids 27-31 (IC50: 0.05–62.14 μM, MTT assay) exhibited significant activity against A549, HeLa, CFPAC-1 (ductal pancreatic adenocarcinoma), and SW620 (metastatic colorectal adenocarcinoma) cells, potentially inducing apoptosis and primary necrosis.[43] In the case of hybrids 30 (IC50: 0.788–63.09 μM, MTT assay) tested against a panel of four human cancer cell lines—HeLa, DU-145, MCF-7, and HepG2—it was observed that the presence of an electron-donating group at R1 and R2 positions was advantageous, whereas an electron-withdrawing group was found to be detrimental to the activity.[44]The conjugates 31 (IC50: 0.51–47.64 μM, MTT assay) primarily exhibited inhibition against cancer cell lines A549, DU-145, HCT-116, and MDAMB 231.[45] Comparing them with the unsubstituted analogs, the Structure-Activity Relationship (SAR) analysis revealed that adding electron-donating methoxy or electron-withdrawing chloro at the R1 position decreased activity, while adding a halogen atom at the R2 position increased activity. Additionally, the 1,2,3-triazole-oxazole hybrids (IC50: 3.1–88 μM, MTT assay) demonstrated anticancer SAR against various human solid cancer cell lines, including A549, HBL-100 (breast), HeLa, SW1573 (non-small cell

lung), T-47D (breast), and WiDr (colon)." The findings indicated that the presence of the oxazole moiety was crucial for achieving high activity, and replacing oxazole with thiazole resulted in a decrease in activity.[46] The 1,2,3-triazole-benzoxazole hybrid demonstrated potential against HeLa, SKBr3, and HepG2 cancer cells, with IC50 values of 6.8, 7.1, and 11.2 mg/mL, respectively, as determined by the MTT assay.[47]

12. 1,2,3-Triazole-Chalcone Hybrids

Chalcone, a naturally occurring substance, is abundant in nature and its derivatives exhibit various biological properties, including the regulation of over 400 genes associated with inflammation, angiogenesis, invasion, cell survival, and metastasis. These properties extend to anticancer activity.[48] Combining chalcone with 1,2,3-triazole through hybridization could present a valuable therapeutic approach in cancer management. Compared to 1,2,3-triazole-chalcone hybrids 32 (GI50: 1.3–186.2 μM, SRB assay), trimethoxy chalcone (GI50: 0.06–0.08 μM) demonstrated superior inhibitory activity against A549, HeLa, DU145, and HepG2 cancer cell lines.[49]The Structure-Activity Relationship (SAR) analysis indicated that replacing the α,β-unsaturated ketone fragment with the pyrazoline moiety resulted in a loss of activity. Preferred substituents at the para-position included fluoro, amino, and methoxy, which could enhance activity. While one conjugate of 33 (IC50: 17.11–69.90 μM, MTT assay) displayed activity against all tested cancer cells, performing comparably to or better than doxorubicin (IC50: 17.69–69.33 μM) against IMR-32, DU-145, and A549 cells, most hybrids 33 showed no activity against human cancer cell lines .[50]Significant inhibitory activity was observed with 1,2,3-triazole-chalcone hybrids 34 against various cancer cell lines, including MCF-7, MIA-Pa-Ca-2, A549, and HepG2, with growth inhibition ranging from 6% to 70% at 10 μM, as determined by the MTT assay. Notably, these cell lines included IMR32 (neuroblastoma), HepG2, MCF-7, DU-145, and A549. The Structure-Activity Relationship (SAR) analysis revealed that substituents at the R1 and R2 positions significantly influenced the activity.

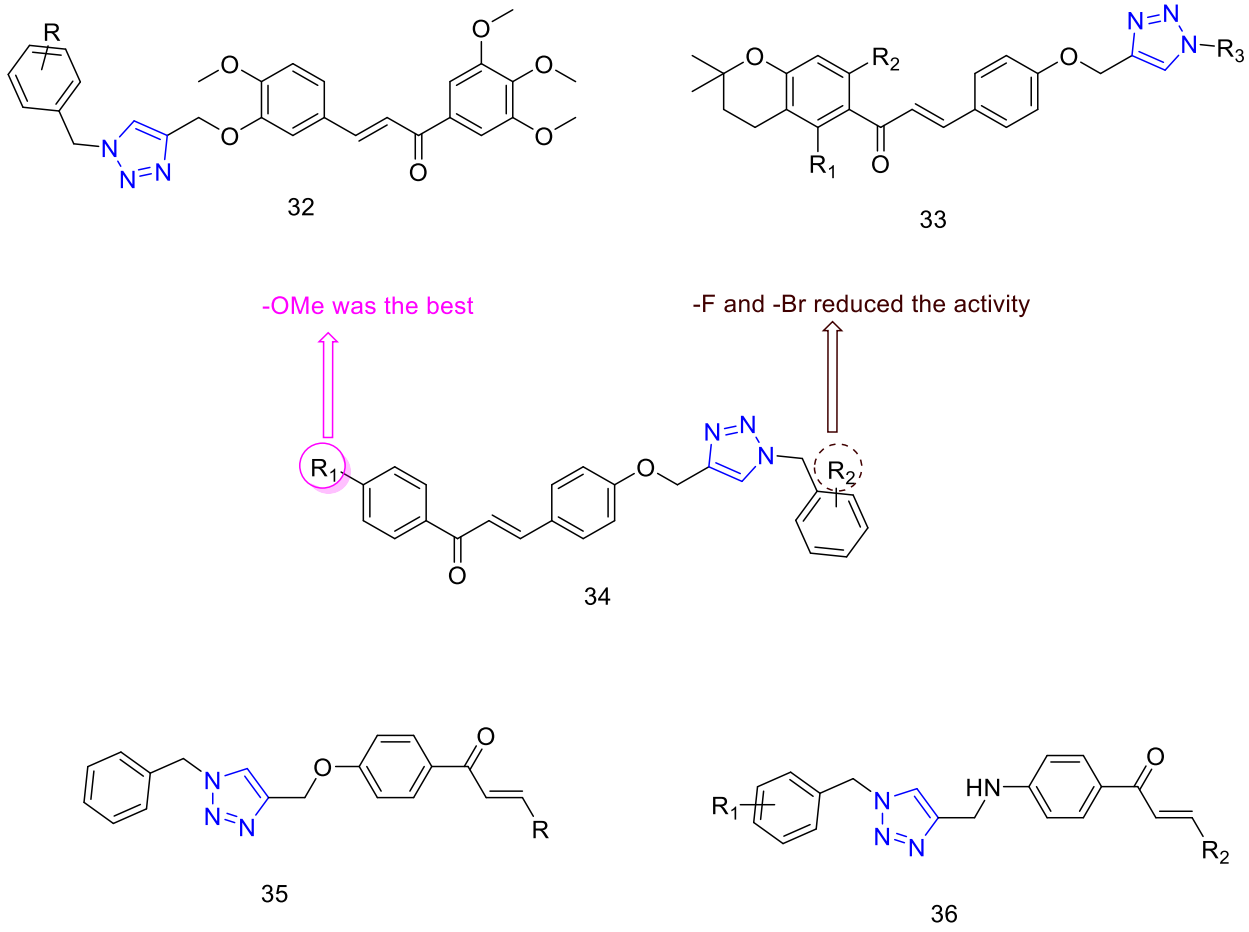


Figure 12. Chemical structures of 1,2,3-Triazole-chalcone hybrids anticancer agents

The presence of methoxy at the R1 position enhanced activity, while the incorporation of fluoro and bromo at the R2 position reduced it. Generally, amine-linked hybrids exhibited greater potency compared to their ether-tethered counterparts. The majority of ether and amine-tethered 1,2,3-triazole-chalcone hybrids 35 (IC50: 6.44–50.57 µM, MTT assay) and 36 (IC50: 1.53–42.38 µM, MTT assay) demonstrated activity against MGC-803 (gastric), SK-N-SH (neuroendocrine), and HepG2 cancer cell lines.[51,52]

13. 1,2,3-Triazole-coumarin hybrids

Coumarin and flavone, prominent natural products, boast a diverse array of pharmacological attributes. Their derivatives have demonstrated inhibition of numerous cancer cell lines, including those resistant to drugs, as well as kinase inhibition, monocarboxylate, and aromatase activity.[53]

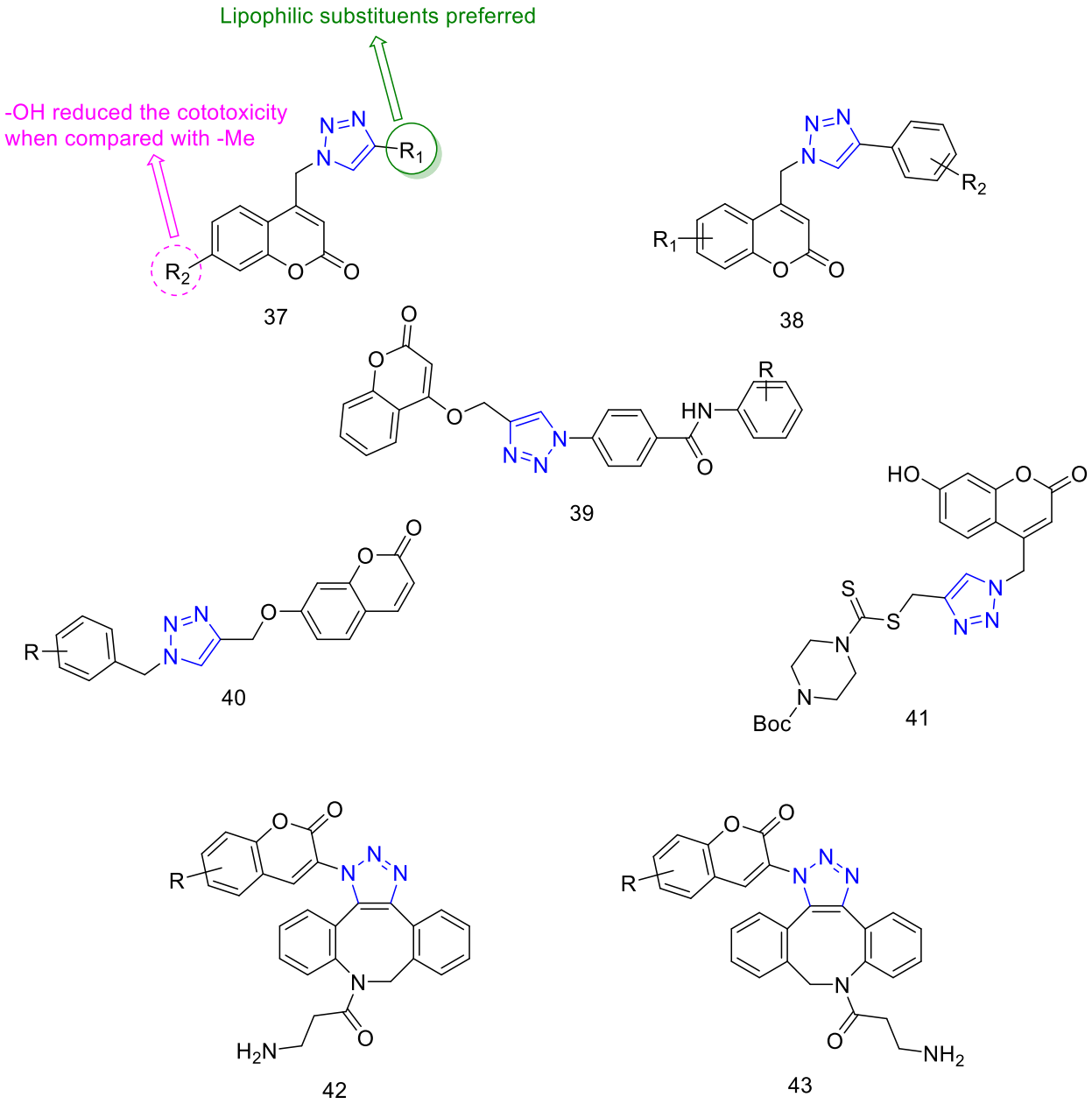


Figure 13. Chemical structures of 1,2,3-Triazole-coumarin hybrids

The potential of coumarin and flavone derivatives in discovering anticancer agents is exemplified by ongoing clinical trials of compounds such as Irosustat and Luteolin for treating diverse cancers.[54] 1,2,3-Triazole-coumarin hybrids 37 exhibited weak to moderate activity (IC50: 0.90->100 mM, MTT assay) against A549, HepG2, CFPAC-1, HeLa, and SW620 cancer cell lines, with some displaying notable potency against drug-resistant bacteria.

Introducing lipophilic substituents at the R1 position was found to enhance activity, with a strong correlation observed between the lipophilicity of hybrids and their anticancer potency. In contrast to hybrids containing methyl at the R2 position, the corresponding hydroxyl analogs exhibited minimal toxicity towards WI38 and 3T3 normal fibroblast cells. The Structure-Activity Relationship (SAR) of ether-tethered 1,2,3-triazole-coumarin hybrids 39 (IC50: 0.03–91.61 μM, MTT assay) against MDA-MB-231 cells revealed that hybrids with 3,4-disubstituents displayed

the highest activity, and attachment of substituents at the para-position of the phenyl ring could further enhance activity. Other derivatives of Compound 40 (PC50: 8.5–29 μM) demonstrated activity against PANC-1, MIA PaCa-2, and Capan-1 cancer cell lines, while the majority of hybrids 40 (PC50: >100 μM, EB/AO assay) were ineffective against PANC-1 cells.[55,56,57]The position of the trifluoromethyl group significantly influenced activity, with its relocation from meta- to para-position resulting in decreased activity. Hybrid 41 (IC50: 4.96–36.84 μM, MTT assay) exhibited activity against MGC-803, MCF-7, and PC-3 cancer cell lines that was either higher or comparable to that of 5-Fluorouracil (IC50: 7.01–27.07 μM), suggesting it as a promising lead for developing drugs targeting different cancer types.[58] The activity of 1,2,3-triazole-coumarin hybrids 42 and their regio-isomers 43 (IC50: 9.83–26.21 μM, MTT assay) against MCF-7 and HeLa cancer cell lines was comparable to that of cisplatin (IC50: 18 and 10 μM), but lower than that of doxorubicin (IC50: 5.2 and 3.83 μM).In the case of hybrids 50 (IC50: 7.5->100 μM, MTT assay) tested against AGS cancer cells, the Structure-Activity Relationship (SAR) revealed that phenyl ring hybrids were more effective than their corresponding benzyl analogs.[59,60]

14. 1,2,3-Triazole-steroid hybrids

Steroids are naturally occurring compounds found in plants, animals, and fungi. They serve as signaling molecules and essential components of cell membranes, influencing membrane fluidity.[61] The development of anticancer agents like Aromasin, Galeterone, and Fulvestrant based on steroidal pharmacophores has sparked considerable interest in utilizing steroids as pharmacologically relevant scaffolds in current years. The 1,2,3-triazole-diosgenin hybrids demonstrated broad-spectrum activity against HBL-100, A-549, HT-29, and HCT-116 cancer cell lines (IC50: 5.16–31.00 μM, MTT assay), with some exhibiting greater potency than the parent Diosgenin (IC50: 10.80–13.30 μM). Surface Area Reaction (SAR) analysis revealed that the addition of electron-withdrawing groups such as nitro and cyano at the ortho-position of the phenyl ring enhanced activity compared to the unsubstituted analog. In contrast to their corresponding diastereoisomers 45, 1,2,3-triazole-estradiol 44 displayed lower anticancer activity against various cancer cell lines including HeLa, MCF-7, A431, A2780, T47D (expressing estrogen, progesterone, and androgen receptors), MDA-MB-231 (expressing HER2 and estrogen receptor), and triple-negative MDA-MB-361.[62]

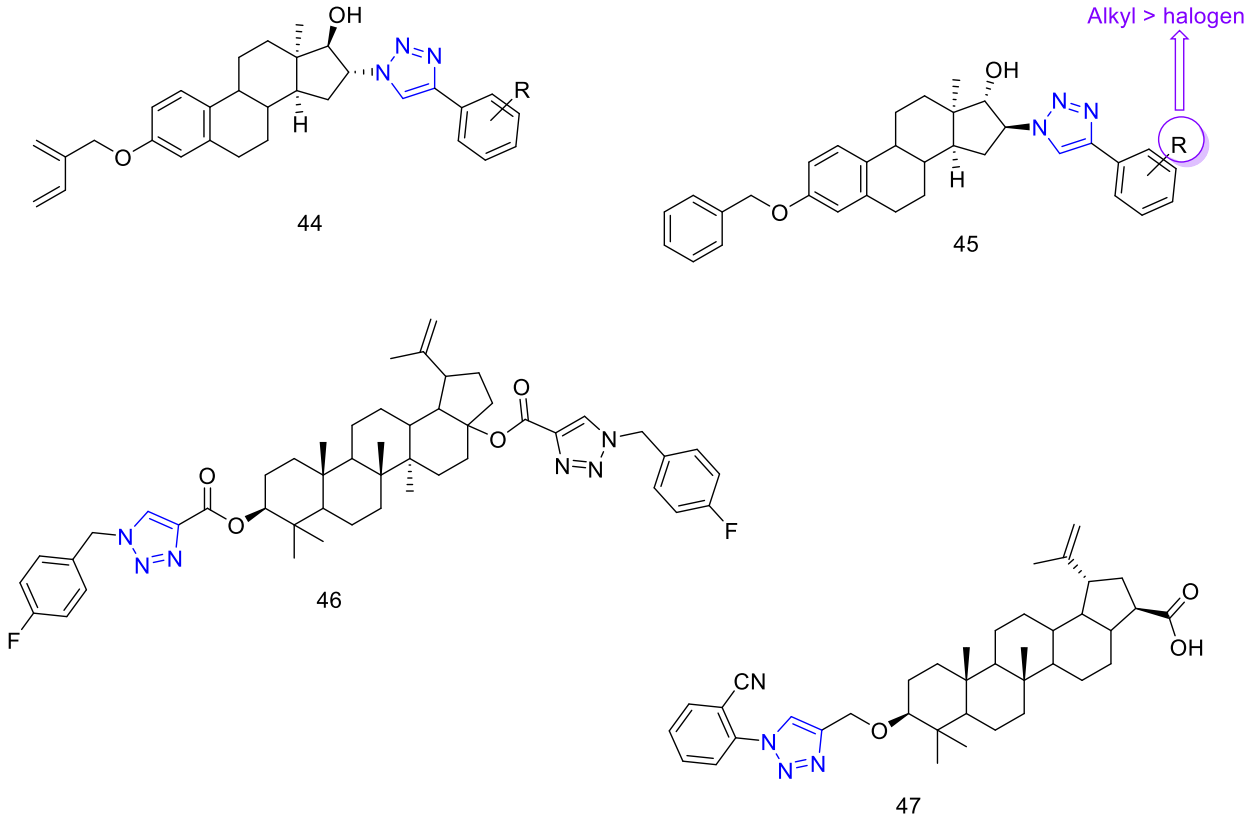


Figure 14. Chemical structures of 1,2,3-Triazole-steroid hybrids

Regarding hybrids 45, it was observed that halogen-containing hybrids were less effective compared to their alkyl-substituted counterparts.[63]Betulin and betulinic acid are typically non-toxic to normal cells but selectively toxic to various cancer cell lines.[64] 1,2,3-Triazole-betulin/betulinic acid hybrids display broad-spectrum anticancer activity, with some showing exceptional potency.

15. 1,2,3-Triazole- sugar hybrids

Sugars are vital for cellular viability and contribute to fundamental molecular and cellular processes in cancer.[65] To enhance the anticancer activity of compounds and facilitate their delivery to cancer cells, the hybridization of 1,2,3-triazole with sugar offers potential advantages.[66]

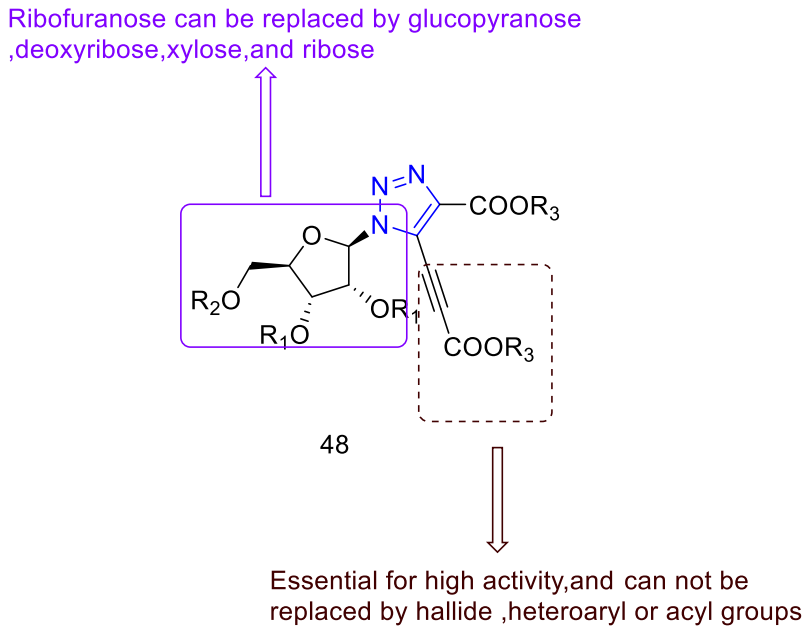


Figure 15. Chemical structures of 1,2,3-Triazole-sugar hybrids

Preliminary data suggests that 1,2,3-triazole-ribofuranose hybrids 48 (IC50: 0.15–2.50 mM, XTT assay) were significantly more potent against K562 CML cancer cells compared to the parent drug, alesine (IC50: 800 mM), with activity ranging from 320 to 5000 times greater.[67] The SAR analysis indicated that substituents at the C-5 position of the 1,2,3-triazole motif, such as halide, heteroaryl, or acyl groups, did not contribute to antiproliferative efficiency. Conversely, alkynyl substituents terminated by an ester function were associated with high activity. The ribofuranose moiety in 1,2,3-triazole-sugar hybrids can be substituted by glucopyranose, deoxyribose, xylose, and ribose. Most of these hybrids (IC50: 0.18–54.89 mM, MTT assay) exhibited greater potency than 5-Fluorouracil (IC50: 8.45–69.07 mM) and showed moderate to high inhibitory activity against PC3, HT29, HepG2, A549, HL60, and U937 cancer cell lines.[68] According to the Structure-Activity Relationship (SAR), hybrids with (substituted) phenyl groups on the 1,2,3-triazole moiety were more active than the pyridine-3-yl analog. Activity could be enhanced by adding electron-donating or electron-withdrawing groups to the phenyl ring, with para- > meta- > ortho- position having a significant influence. While some other analogs displayed weaker anticancer activities ranging from moderate to weak compared to references,[69] the SAR was nevertheless improved.

16. Natural Product-based 1,2,3-triazole analogues as anti-biofilm agents

Biofilms are intricate, hydrated structures comprising multicellular communities enveloped in a protective extracellular matrix, which they produce themselves. These formations adhere to various surfaces, both living and non-living. Bacteria within biofilms exhibit remarkable resistance to conventional antibiotics, often rendering them ineffective. They also display resilience against external stresses and the host's immune response. Biofilm-associated diseases pose significant health risks, including food-borne illnesses, periodontitis, prostatitis, cystic fibrosis pneumonia, and recurrent urinary tract infections. Additionally, biofilms contribute to issues like clogged filtration membranes, corroded pipes, and fouled marine surfaces, serving as reservoirs for water and foodborne pathogens. While numerous strategies are being explored to develop antimicrobials capable of preventing biofilm formation, modifying naturally occurring products has emerged as a promising approach.[70,71,72]

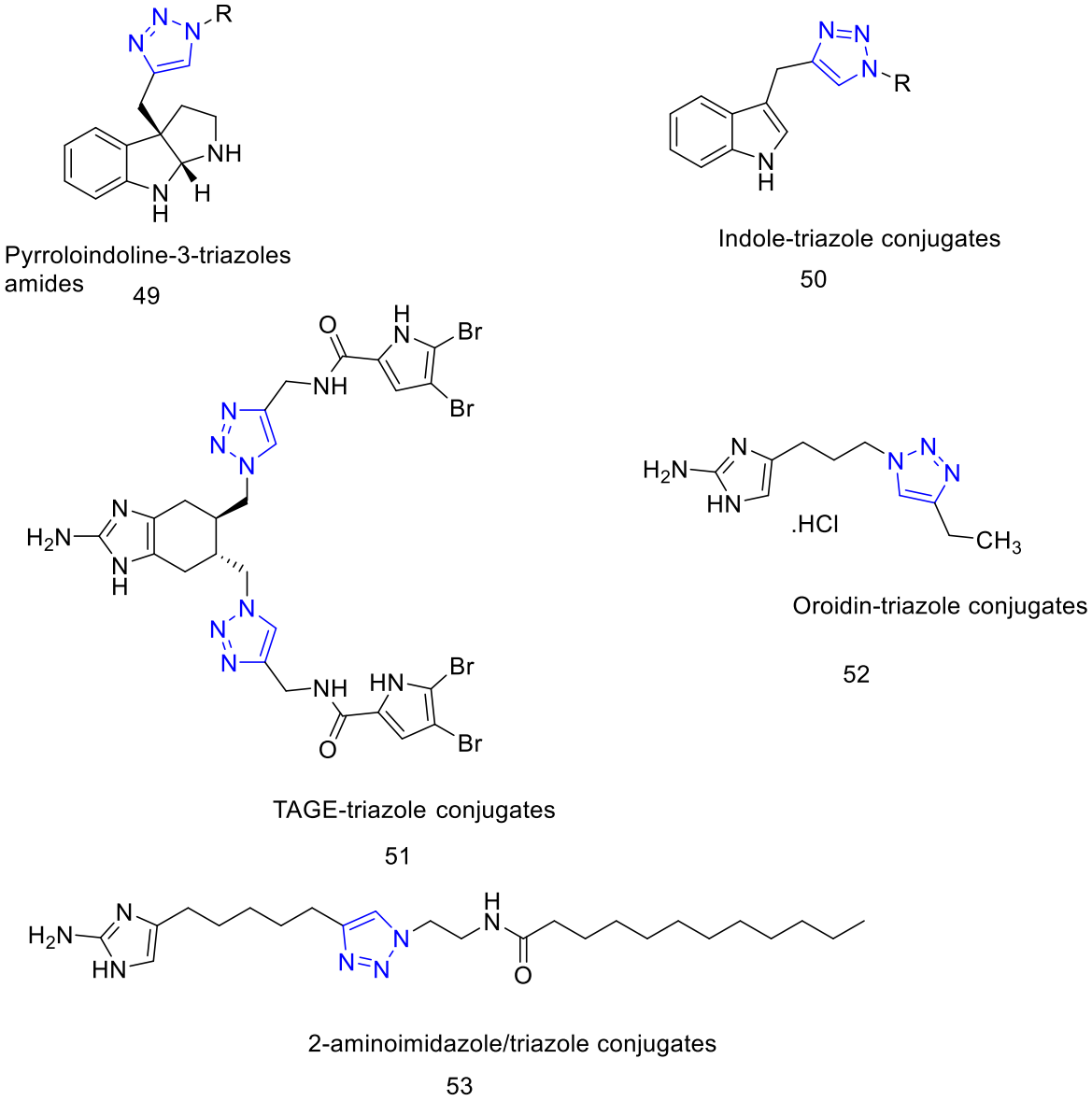


Figure 16. Natural product-based 1,2,3-triazole analogues as anti-biofilm agents

The inhibition of biofilm formation is a critical aspect in combating bacterial infections, particularly those caused by antibiotic-resistant strains. Numerous natural products and their derivatives have been found to possess significant biofilm-inhibiting properties. By incorporating triazole moieties into these natural compounds, researchers have developed potent analogues with enhanced antimicrobial activities.[73,74]

Here are some notable examples:

Pyrroloindoline-3-triazole amides inspired by flustramine C: These compounds draw structural inspiration from flustramine C, a natural product known for its antimicrobial properties. The addition of the triazole ring has enhanced their effectiveness against various bacterial strains.

Conjugates of indole-triazole amide: Indole-based compounds are well-known for their biological activities. By attaching triazole moieties to indole amides, researchers have

synthesized compounds with improved antibacterial properties and biofilm inhibition capabilities.

Oroidin-triazole conjugates: Oroidin is a natural marine compound with notable antimicrobial activity. Its conjugation with triazole units has resulted in derivatives that exhibit potent biofilm-inhibiting properties against both Gram-positive and Gram-negative bacteria.

2-Aminoimidazole-triazole conjugates: 2-Aminoimidazole derivatives are known for their ability to disrupt bacterial communication systems involved in biofilm formation. Incorporating triazole rings into these molecules has enhanced their biofilm inhibition and antimicrobial efficacy.

Aminoimidazole-triazole conjugates: Similar to the 2-aminoimidazole variants, these conjugates also target bacterial communication pathways, offering robust activity against biofilm-forming bacteria.

Triazole-TAGE conjugates: These compounds combine triazole rings with TAGE (trans-activator of gene expression) structures, resulting in hybrids with significant antimicrobial properties, particularly in biofilm prevention.

Conjugates of pyrazolo-[3,4-b]pyridine-triazole: These hybrids are another example of triazole derivatives showing enhanced antimicrobial and biofilm inhibition activities due to the synergistic effects of the combined structures.

Triazoles with isonaamine and naamine A: Isonaamine and naamine A are naturally occurring compounds with inherent antimicrobial properties. The incorporation of triazole rings into their structures has led to the creation of derivatives with superior biofilm inhibition capabilities.

Moreover, triazole derivatives of geraniol and farnesol, two natural compounds known for their antimicrobial effects, have shown significant potential in inhibiting biofilm formation. These triazole derivatives mimic the action of the natural compounds but with enhanced efficacy.

The continuous search for potent antimicrobial agents is driven by the need to combat biofilm-associated infections, which are often resistant to conventional antibiotics. The incorporation of 1,2,3-triazole functionality into natural scaffolds has proven to be a successful strategy, leading to the development of novel compounds with strong antimicrobial and biofilm inhibition properties. This approach holds promise for creating new therapeutics to address the challenges posed by bacterial biofilms and resistant infections.[75]

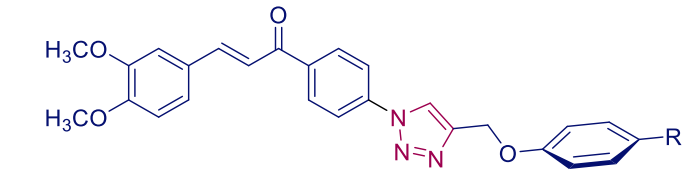
17. 1,2,3-triazole-genipin analogues and their anti-alzheimer's activity

Gardenia Jasminoides Ellis, a flowering plant from the gardenia genus of the Rubiaceae family, is esteemed for its medicinal properties. Its fruits are utilized for their high biological activity in treating inflammation, jaundice, and hepatic diseases.[76] Commonly employed in herbal medications and functional food supplements, this plant offers therapeutic benefits for central nervous system (CNS) illnesses such as dementia and cerebral stroke, as well as antioxidant properties, without any negative or toxic side effects.[77]Geniposide, the major component of the fruit, is an iridoid glycoside that can be converted into genipin 1 by intestinal bacteria following ingestion.

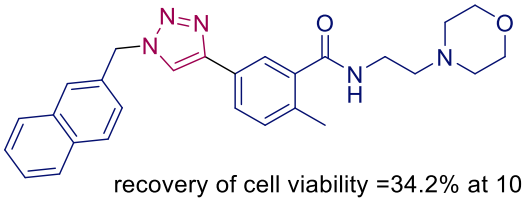
Genipin, the principal active compound, exhibits promising bioactivities as a potent neuroprotective agent. It functions by inhibiting high levels of lactate dehydrogenase (LDH) in the blood, thereby mitigating amyloid-β (Aβ) peptide toxicity in cultured neurons. Studies by Huang et al. have demonstrated that piperazine-genipin compounds can effectively reduce both acetylcholinesterase (AChE) activity and Aβ1-42 aggregation, leading to a significant 22.3% reduction in neuronal cell damage caused by Aβ peptide toxicity. These compelling findings

have sparked interest in modifying genipin's structure to explore the potential of its derivatives as treatments for Alzheimer's disease.[78,79]

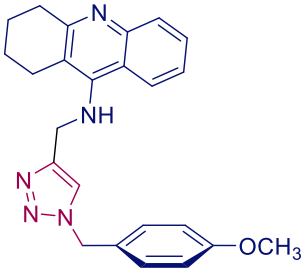
A novel series of 1,2,3-triazole-genipin analogs was synthesized and evaluated for their inhibitory activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), as well as their neuroprotective properties. In vitro assessments demonstrated potent neuroprotective effects against H2O2 toxicity, along with significant inhibitory activity against BuChE. Particularly noteworthy were the pinacanalogues containing phenol hydroxy and diphenyl hydroxy triazoles, which exhibited IC50 values of 31.77 µM and 54.33 µM, respectively, compared to 34.05 µM for galantamine.



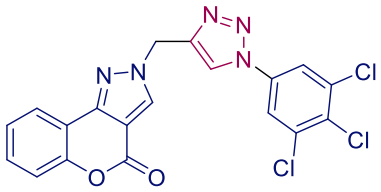
R = H; recovery of cell viability =20.8% at 1.0 µM
R = CHO; recovery of cell viability =14.3% at 1.0 µM
Neuroprotective
Sooknual P.et.al (2020)
(a)



recovery of cell viability =34.2% at 10.0 µM
Neuroprotective
Li JC.et.al.(2016)
(b)



Anti-BChE
Najafi Z.et.al (2017)
(c)



Anti-BChE
Chekir S.et.al (2018)
(d)

Figure 17. Examples of 1,2,3-triazole used as inhibitors of butyrylcholinesterase (BuChE) and neuroprotective agents

The molecular docking studies of these genipin analogs revealed robust binding energies and favorable interactions with the critical amino acids of BuChE, involving hydrogen bonding and hydrophobic interactions. Triazole-genipins thus emerge as promising lead compounds for the development of medications targeting Alzheimer's disease.[80]

Triazole compounds have been identified as powerful and highly selective inhibitors of butyrylcholinesterase(BuChE), an enzyme implicated in the pathology of neurodegenerative diseases such as Alzheimer's. Additionally, these compounds often exhibit neuroprotective properties, making them promising candidates for the treatment of neurodegenerative conditions.Below is a description of such triazole compounds and their significance:

Triazole Compounds as BuChE Inhibitors and Neuroprotectants

BuChE Inhibition and Neuroprotection: BuChE inhibitors are critical in the management of neurodegenerative diseases because they help maintain acetylcholine levels in the brain, thereby improving cholinergic transmission and cognitive function. Selective inhibition of BuChE, over

acetylcholinesterase (AChE), is particularly beneficial in the later stages of Alzheimer's disease, where BuChE activity increases while AChE activity decreases.

Key Structural Features: Triazole compounds designed as BuChE inhibitors often incorporate various functional groups that enhance their binding affinity and selectivity for BuChE. These modifications can include:

Aromatic Rings: These provide hydrophobic interactions with the enzyme's active site.

Substituents on the Triazole Ring: Functional groups such as alkyl, aryl, or heteroaryl substituents can improve the compound's pharmacokinetic properties and selectivity.

Linker Units: Flexible linkers between the triazole core and other pharmacophoric groups can enhance the overall binding efficiency and selectivity.

Mechanism of Action: Triazole compounds inhibit BuChE by binding to the active site of the enzyme, preventing the hydrolysis of acetylcholine. This inhibition helps maintain higher levels of acetylcholine in the brain, which is crucial for cognitive functions. The neuroprotective properties of these compounds are often attributed to their ability to reduce oxidative stress and inhibit apoptosis in neuronal cells.

Therapeutic Potential: The development of triazole-based BuChE inhibitors holds significant promise for the treatment of Alzheimer's disease and other neurodegenerative disorders. Their high selectivity and potency, combined with neuroprotective effects, make them attractive candidates for further development and clinical testing.

In conclusion, triazole compounds represent a promising class of BuChE inhibitors with potential neuroprotective benefits. Their unique chemical structures and mechanisms of action make them valuable tools in the ongoing effort to develop effective treatments for neurodegenerative diseases.

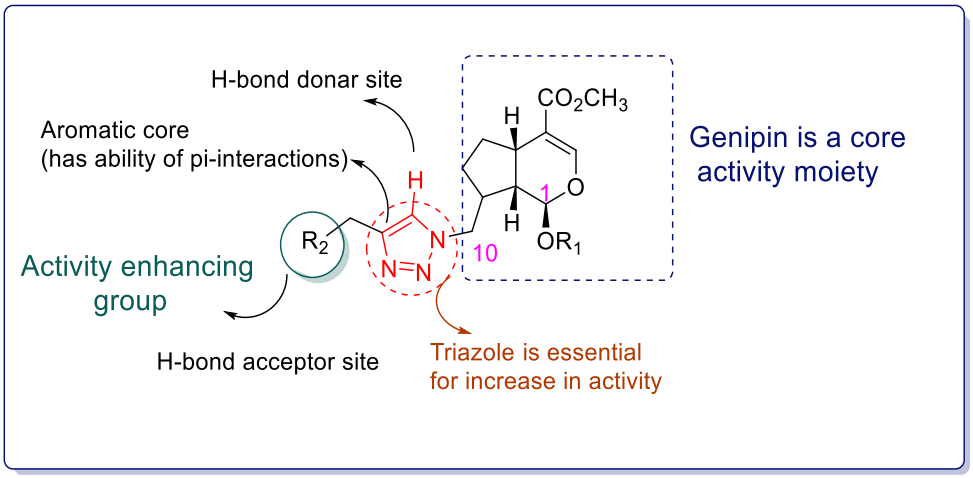


Figure 18. Design of novel 1,2,3-triazole-genipin analogues

The connection of genipin and 1,2,3-triazole units holds the promise of generating hybrids with enhanced neuroprotective potential compared to the parent genipin. In this study, a novel series of 1,2,3-triazole-genipin compounds was synthesized with the aim of evaluating their biological activity as selective BuChE inhibitors with neuroprotective properties. Additionally, molecular docking experiments were conducted to provide insights into enzyme inhibition (Figure 18).

18. Thiazolotriazoles as Anti-infectives

The rational design of new thiazolo [2,3-c][1,2,4]triazole derivatives was undertaken, drawing from the previously reported antitubercular hit molecule H127. This effort aimed to identify effective compounds with antibacterial activity.[81]

N-heterocycles play a pivotal role in medicinal chemistry due to nitrogen's dual nature, allowing for effective ligand-receptor interactions.[82] In 2019, the FDA approved 48 new medications, with 27 of them being small compounds containing N-heterocycles, underscoring their significance in drug development. Thiazole and triazole are preferred scaffolds indrug development programs due to their wide-ranging pharmacological activities. Moreover, thiazole or triazole conjugates with various heterocycles have been investigated for their efficacy against diverse illnesses.[83,84,85]

Thiazolotriazole, a condensed heterocycle derived from thiazole and triazole, exists in three isomeric forms: thiazolo[2,3-c][1,2,4]triazole, thiazolo[3,2-b][1,2,4]triazole, and isothiazolo[3,2-c][1,2,4]triazole. These compounds demonstrate diverse pharmacological activities, including anticancer, antimicrobial, anti-inflammatory, analgesic, antidiuretic, and COX2 inhibition. While research has predominantly focused on antimicrobial drug design, the [3,2-b] ring system has been more extensively studied compared to the [2,3-c] ring system.

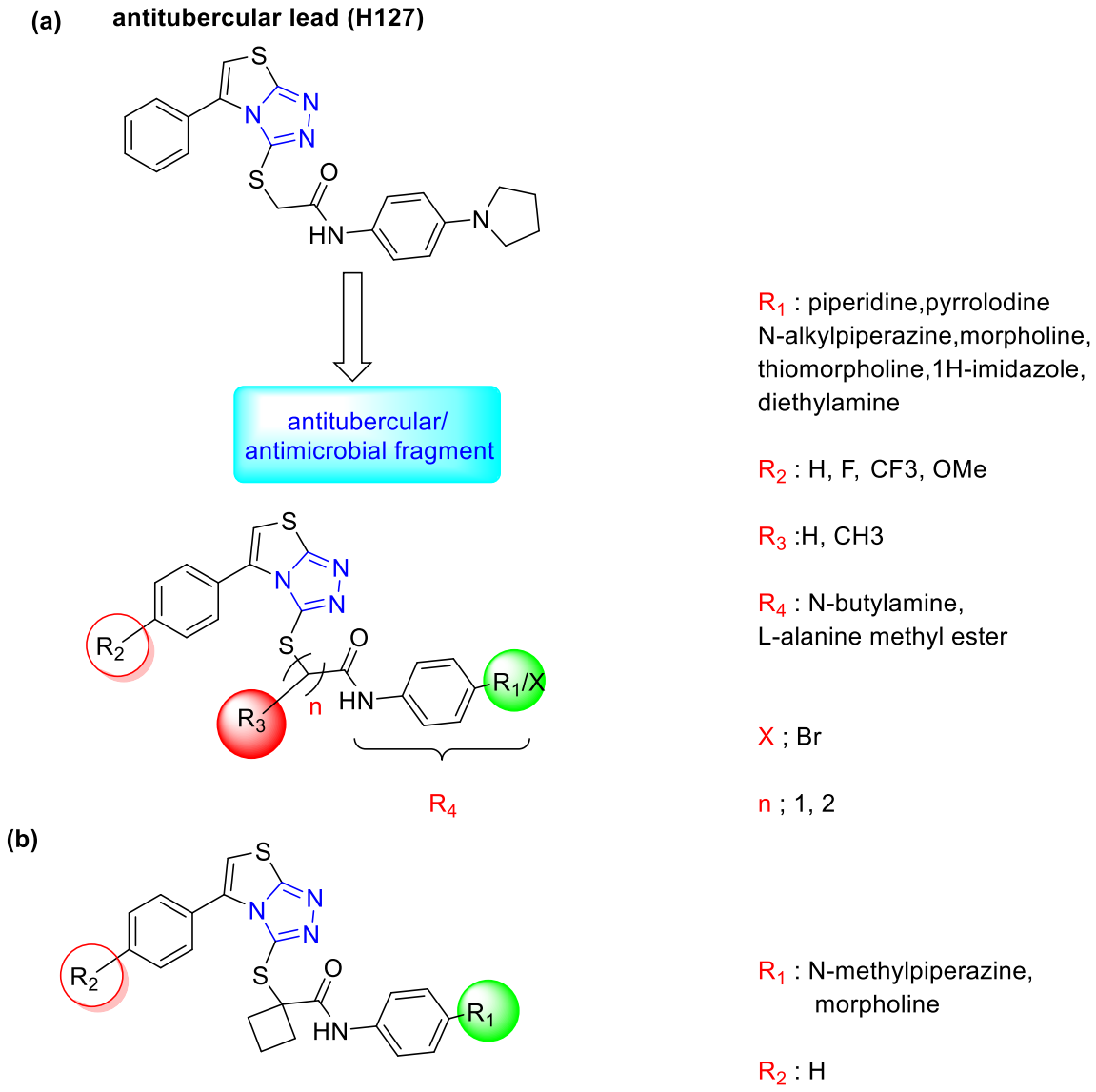


Figure 19. (a,b) Design of H127 Analogues

19. Miscellaneous triazole hybrids

Pyridine serves as a crucial pharmacophore in the development of new drugs, given its frequent occurrence as a substructure in medications such as isoniazid.[86]

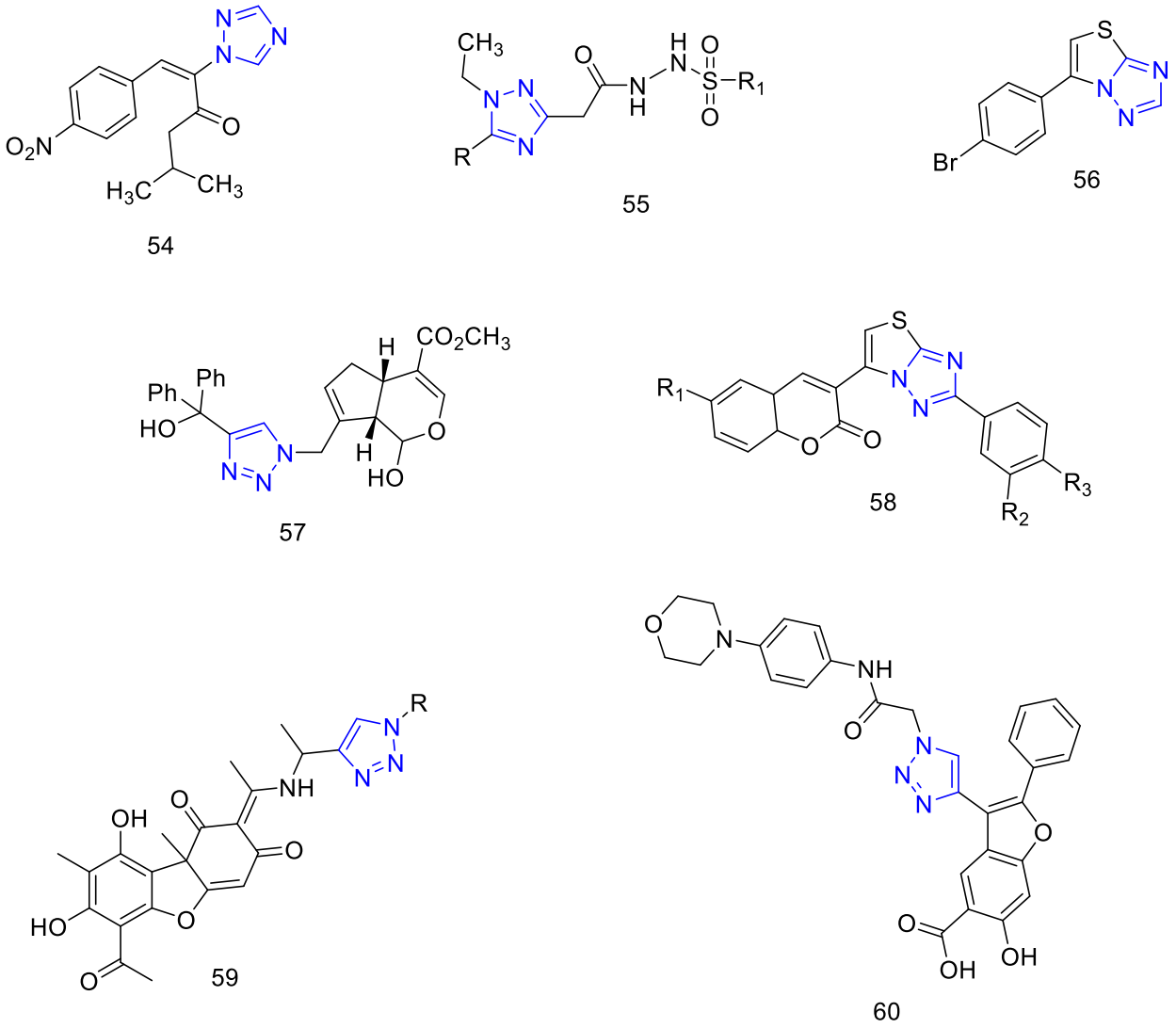


Figure 20. Chemical structures of 1,2,3 and 1,2,4-Triazolehybrids

Thomas et al. (2019) investigated various 1,2,4-triazoles as antibacterial derivatives. They evaluated the minimum inhibitory concentration (MIC) values of these compounds against clinical isolates carrying different resistance mechanisms (including MRSA, VRE, extended-spectrum β-lactamase-producing Escherichia coli, and Pseudomonas aeruginosa resistant to efflux pump), as well as against reference strains (S. aureus, E. faecalis, E. coli, and P. aeruginosa). The most potent compound, featuring a decyl moiety, exhibited 2-, 4-, and 8-fold higher potency against sensitive and resistant strains of S. aureus, E. faecalis, and P. aeruginosa, respectively, compared to the reference compound, chlorhexidine. Overall, all the prepared bis-1,2,4-triazoliums displayed robust activity against the majority of tested strains. Unfortunately, there was significant toxicity associated with the compounds.[87]Stingaci et al. (2020) synthesized derivatives of vinyl-1,2,4-triazole as antimicrobial agents. Compound X demonstrated exceptional activity against all bacterial species tested, including B. subtilis, P. fluoresces, E. amylovora, E. carotovora, and X. campestris, with MIC and MBC values ranging from 0.0002 to 0.0033 mM, similar to those of ampicillin and chloramphenicol.[88]

Conclusion

The review emphasizes that triazole derivatives in combination with various agents such as quinolone, beta-lactam, artemisinin, sugar, steroids, thiazolotriazoles, chalcone, and other fused derivatives exhibit potential activity. It also highlights how modifying the core triazole ring structures with higher aromatic stabilization energy enhances their solubility and selectivity, particularly through interaction with distinct pharmacophores. This modification allows them to function effectively as enzyme inhibitors and participate in a variety of biological processes. The review underscores the significance of triazole derivatives in diverse biological processes, including fragment-based drug design and docking studies. Beyond existing triazole medications, researchers are exploring novel scaffolds based on triazole cores, which hold promise in biomedical and biotechnology applications. The study highlights the structural characteristics of triazoles, recent synthetic advancements, and potential biological uses to promote deeper understanding and ongoing research and development of these compounds. The review findings on the activities of 1,2,3-triazole, 1,2,4-triazole, and their hybrids with various pharmacophores further support their diverse potential applications.

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