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1,2,3-TRIAZOLIUM SALTS DERIVATIVES AS ANTICANCER REAGENTS

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Abstract:
A group of organic compounds known as 1,2,3-triazolium salts include the triazolium cation, a five-membered ring made up of three nitrogen and two carbon atoms. Due to their wide spectrum of characteristics and prospective uses in chemistry, materials science, and medicine, these compounds have attracted a lot of attention in recent years. The triazolium ring's substituents can be changed to create derivatives of 1,2,3-triazolium salts. The type and location of these substituents have a significant impact on the compound's characteristics and reactivity. Some 1,2,3-triazolium salt compounds have demonstrated strong biological activity, including antibacterial, antifungal, and anticancer activities. This makes them potential candidates for the development of new drugs and therapies. 1,2,3-Triazolium salts derivatives have shown potential as anticancer reagents due to their ability to selectively target cancer cells and inhibit their growth. These derivatives exhibit cytotoxicity towards cancer cells while demonstrating minimal toxicity towards normal healthy cells. This review provides a comprehensive overview of synthetic strategies for the preparation of 1,2,3-triazolium salts and highlights the structures of various derivatives that exhibit biological activities (anti-cancer). It is important to note that the development of 1,2,3-triazolium salts derivatives as anticancer reagents is an active area of research, and specific compounds and mechanisms may vary. Further studies are required to optimize their efficacy, selectivity, and safety profiles before their clinical application.

Keywords: Synthesis; 1,2,3-Triazolium Salts; Triazole Ring; Anticancer; Biological Activity

INTRODUCTION

In the realms of insecticides and medications, 1,2,3-triazoles are a class of chemicals with broad-spectrum bioactive capabilities [1]. However, the widespread use of triazole medications has increased the issue of drug resistance, highlighting the requirement for the creation of new pharmacophores [2]. Due to its strong bioactivities, the 1,2,3-triazolium unit is a prominent bioactive group that has received a lot of attention recently. 3-12]. Numerous biological activity, including antibacterial, antifungal, anticancer, and antileishmanial characteristics, have been demonstrated for molecules with 1,2,3-triazolium units [13–19]. Salts of 1,2,3-triazolium have unusual chemical features, including excellent stability, controllable reactivity, and distinctive electronic properties [20,21]. They have been used to create new catalysts, antibacterial substances, fluorescent dyes, and bioactive compounds and are useful building blocks in chemical synthesis [22,23]. Three active sites—N- in position one, N- in position three, and C- in position four of triazole ring of the 1,2,3-triazolium salts can be coupled with various functional groups in a region-selective way to control their cytotoxicity and biological activity [3]. Therefore, a summary of the structure-bioactivity relationship (SAR) and chemical structure of triazolium salt derivatives with varied biological activities throughout the previous 25 years is required. The two primary components of this review are the creation of 1,2,3-triazolium salts and their anticancer properties. This review aims to serve as an inspiration for future 1,2,3-triazolium salt structure design and synthesis for anti-cancer applications.

Synthesis of 1,2,3-Triazolium Salts

The Sharpless group made an important contribution to triazole chemistry in the early twenty-first century when they popularized the idea of "click" chemistry [24]. Using this method, which is a potent synthetic strategy,

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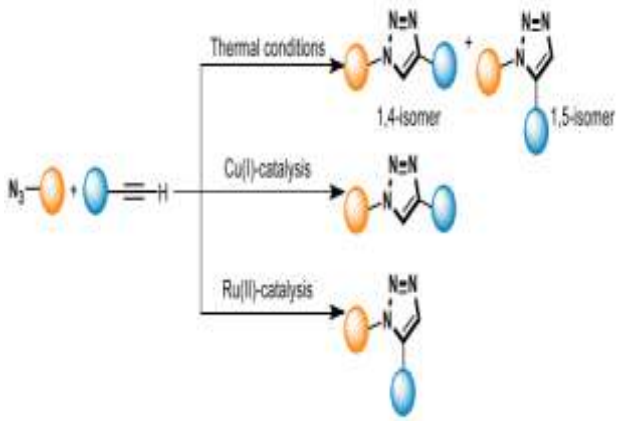
it is possible to build chemical bonds efficiently and with great precision while maintaining favorable reaction conditions [23-25]. The synthesis of 1,2,3-triazolium salts is one of the most adaptable uses of click chemistry [26]. Azide and alkyne are used as the starting ingredients for the three processes that make up the click chemistry method for making 1,2,3-triazolium salts: 1,2,3-triazole cycloaddition reaction, N-alkylation, and salt metathesis. This process is quick, easy to use, simple to purify, adaptable, region-specific, and produces large amounts of product. Overall, click chemistry has developed into a potent tool for the quick and effective synthesis of biomedical hydrogels, functional macromolecules, and other molecular entities in the pharmaceutical sciences [20,21].

Non-Selective Huisgen Reaction

There have been significant improvements in 1,2,3-triazole use and manufacture in recent years. [26] These substances have existed since Huisgen identified a high-temperature cycloaddition reaction including azide derivatives and alkyne compounds in the 1960s (Scheme 1). Triazoles are produced as a result of this reaction [27]. However, this approach has drawbacks because it necessitates extensive heating and involves the purification of the resultant triazoles from a combination of 1,4- and 1,5-regioisomers [26,28].



Scheme 1. Synthesis of 1,2,3-triazole: Thermal reaction and catalytic cycloaddition reaction

Selective Huisgen Reaction Mediated by Metal Catalysis

In order to create 1,2,3-triazoles, an azide and an alkyne undergo a cyclization reaction. Huisgen and his team found in 1974 that copper(I) cations might serve as catalysts for this process [4]. They proved that the 1,4-disubstituted isomer could be produced solely by the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction when catalytic conditions were present [4]. The key step in the Huisgen synthesis is the creation of a copper(I) acetylide intermediate from an alkyne and a copper catalyst [28-30]. A highly stable 1,2,3-triazole product is produced after this intermediate reacts with the azide. The reaction exhibits strong regioselectivity under favorable conditions, favoring the generation of the primary isomer, the 1,4-disubstituted triazole (Scheme 1) [29]. Compared to conventional methods of triazole synthesis, the selective Huisgen synthesis has a number of benefits [28]. It proceeds swiftly, typically completing the conversion in a few minutes to several hours, and it tolerates a wide range of functional groups, allowing the incorporation of a number of different chemical elements into the triazole structure. The reaction can be carried out in water or under bio-orthogonal conditions, making it suitable for usage in biological systems [28]. In 2008, Fokin's team used ruthenium(II) as a catalyst to quicken the reaction between organic azides and terminal alkynes with various functional groups. At high temperatures, this catalytic system produced 1,2,3-triazole compounds that were 1,5-disubstituted (Scheme 1) [31]. Ruthenium(II) catalysts are preferred to copper catalysts for cycloaddition processes involving internal alkynes, aryl azides, and other thermally labile reactants at ambient temperatures [31] due to their ease of manufacturing and air stability. However, excellent activity, chemo- and regio-selectivity are displayed by both catalyst systems. The unique ruthenium-catalyzed azide-alkyne cycloaddition reaction (RuAAC) procedure, in addition to the catalyst CuAAC reaction, makes it simpler to access all of the 1H-1,2,3-triazole's regioisomers [30,31].

N-Alkylation reaction and Salt Metathesis

It is very easy to access 1,4-disubstituted 1,2,3-triazoles thanks to the Cu(I)-catalyzed azide-alkyne "click" cycloaddition reaction (CuAAC), which is why they are frequently utilized as scaffolds in synthetic chemistry [30]. Using alkyl halides, tosylate, trifluoromethane sulfonate, or trialkyloxoniums, it is simple to create complex 1,2,3-triazolium salts with intricate structures from the corresponding 1,2,3-triazoles (Scheme 2) [22, 23]. The 1,2,3-triazole is normally deprotonated using a base before being reactive with the alkylating agent in the alkylation process. This transformation typically demonstrates region-selectivity favoring the N-3 position and is generally tolerant of different functional groups at the N-1 and C-4 locations of the triazole ring [22, 23].

Scheme 2. N-alkylation reaction of 1,2,3-triazolium salts

Through protonation or other appropriate transformations, the resulting alkylated molecules can be transformed into various kinds of 1,2,3-triazolium salts [4,23]. For instance, utilizing an exchange resin

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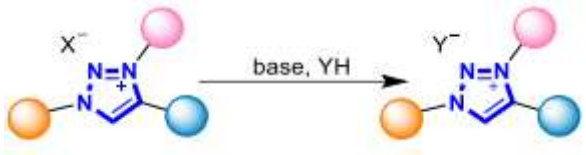
[17] or washing with excessive inorganic salt can easily replace the anionic counter ion (X^-) of the triazolium salt (Scheme 3).



Scheme 3. Salt metathesis of 1,2,3- triazolium

Anticancer Activities of 1,2,3-Triazolium Salts

Cancer remains a leading cause of death in developed countries, despite decades of research and significant funding dedicated to its study [32]. The complexity and genetic instability of cancer, characterized by the involvement of multiple genes related to cell signaling, growth suppression, cell death evasion, replicative immortality, angiogenesis, invasion, and genomic diversity, make it a challenging disease to treat effectively [33]. Targeted therapies that focus on specific molecular pathways have shown promise but are limited to specific tumor types. Therefore, there is a need to synthesize and screen new compounds with potential anticancer properties to enhance treatment efficacy [34]. For the quick synthesis of compound scaffolds, contemporary synthetic chemistry provides effective techniques. One instance of such chemistry is the catalyzed azide-alkyne cycloaddition reaction, which results in 1,2,3-triazoles (also known as "click" triazoles). Additionally, this chemistry permits the creation of a number of derivatives, such as 1,3,4-trisubstituted 1,2,3-triazolium salts, sometimes known as "click" triazolium salts. Numerous biological activities, including those that are antiviral, anti-inflammatory, antibacterial, analgesic, antifungal, anticonvulsant, antidiabetic, antihistaminic, antiparasitic, antiobesity, antihypertensive, anti-neuropathic, and anticancer, are demonstrated by 1,2,3-triazoles and their derivatives. These compounds also have drug-like properties. These substances therefore show promise as potential cancer treatments [35–37]. When it comes to the anticancer activity of 1,2,3-triazolium salts fused with 1,4-naphthoquinone, only one study has been made to date. This is in contrast to the many publications on the cytotoxic activities of compounds containing a triazole moiety. 1,3,4-trisubstituted 1,2,3-triazolium salts have not been shown to have cytotoxic properties. It is necessary to assess these compounds' anticancer activity and learn more about the underlying mechanism causing their antiproliferative effects given their distinctive features, such as their charge and hydrogen bonding capacity [38-40].

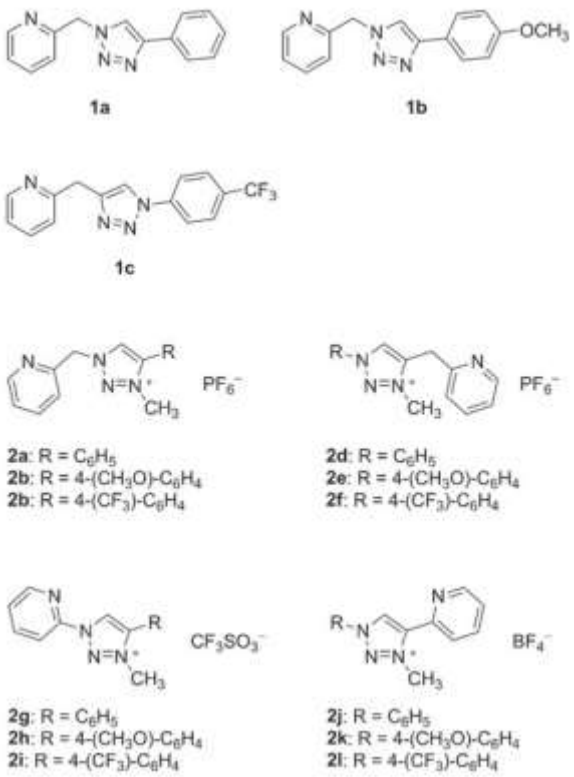


Figure 1. The chemical structures of 1,2,3-triazoles and 1,2,3-triazolium salts.

Numerous compounds with anticancer properties have been created by combining fatty chains with triazolium cationic units [10,41,42]. Numerous studies have shown that 1,3,4-trisubstituted 1,2,3-triazolium compounds can serve as useful building blocks for the creation of brand-new cancer therapies [10,11,41,43]. A number of novel triazole compounds and salts of the 1,2,3-triazolium family, including 1-(2-pyridyl), 4-(2-pyridyl), 1-(2-pyridyl), and 4-(2-pyridyl)-3-methyl-1,2,3-triazolium, were successfully synthesized in 2016 by Osmak et al. In several tumor cell lines, the triazolium salt compounds showed greater anticancer activity to the triazole compounds. Notably, compound 27 had a therapeutic index of 7.69 for lung cancer cell H460, indicating that it was much more toxic to tumor cells than to normal cells (Figure 2). Compound 27's mechanism of action involves stopping cell mitosis during the G1 phase of the cell cycle. Instead of binding to double-stranded DNA (dsDNA), it causes treated cells to produce reactive oxygen species (ROS), which ultimately causes cell death [10].

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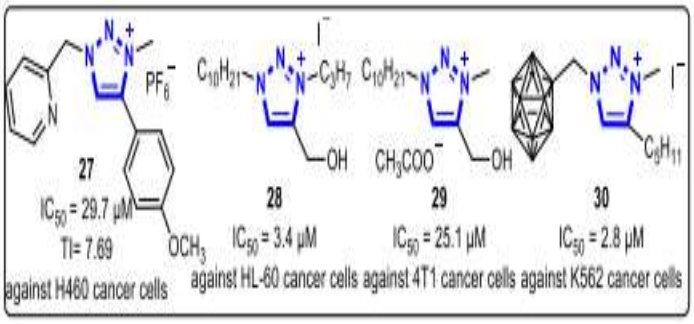

Figure 2. Structures of 1,2,3-triazolium salt derivatives with anticancer activities

In later studies, Silva et al. synthesized different 1,2,3-triazolium salt compounds with different substituents and examined how well these compounds inhibited the growth of several cancer cell lines, including osteomyeloid leukemia HL-60, lymphoid leukemia JURKAT, breast cancer MCF-7, and colon cancer MCT-116. With an IC50 value of 3.4 M, compound 28 (Figure 12) from this group of compounds demonstrated significant anticancer activity, particularly against HL-60 cell lines [36]. Additionally, 1,2,3-triazolium salt 29 outperformed miltefosine in its ability to eradicate MDAMB-231, 4T1, and HEK-293 cancer cell lines with IC50 values of 60.1 M, 25.1 M, and 49.6 M, respectively. In summary, several studies have investigated the anticancer activities of different 1,2,3-triazolium salts and their derivatives, comparing them to known anticancer drugs. Miltefosine, a commercial anticancer drug, displayed IC50 values of 191.4 μM, 105.9 μM, and 96.9 μM against specific cancer cell lines. Compound 29, along with miltefosine, exhibited potent anticancer effects on the breast cancer cell line HEK-293, with an IC50 value below 4.2 μM. Compound 29 demonstrated the highest water solubility among its derivative counterparts and showed minimal toxicity to human peripheral blood mononuclear cells (PBMCs) [42].

Additionally, in 2019, Antonenko et al. synthesized a carborane-thiazolium cationic salt (compound 30), which displayed significant anticancer activity against K562 cancer cell lines, with an IC50 value of 2.8 μM. Notably, this boron-containing polyhedral triazolium cationic compound exhibited the ability to transport protons across biological membranes, suggesting its potential importance in the development of anticancer treatments [11]. Furthermore, a study conducted by Chang et al. in 2013 demonstrated that the cationic anthraquinone analog compound 31 exhibited promising anticancer activities against various cancer types, including melanoma, colon cancer, non-small cell lung cancer, and central nervous system (CNS) cancers. Compound 31 displayed GI50 values ranging from 0.15 to 1.68 μM. These findings highlight the potential of 1,2,3-triazolium salts and their derivatives as effective anticancer agents, showcasing their comparable or superior activities compared to existing anticancer drugs. Further research is warranted to explore their mechanisms of action, optimize their structures, and evaluate their efficacy in preclinical and clinical settings [43].

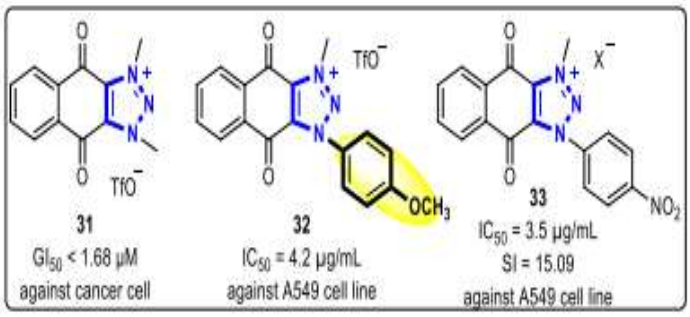

Figure 3. Structures of anthraquinone triazolium compounds with anticancer activities.

Additionally, the anticancer potential of substances 32 [44] and 33 [20] was investigated, and it was found to have a substantial effect on A549 cancer cell lines. Figure 3 shows that compound 32 had an IC50 value of 4.2 g/mL and compound 33 had an IC50 value of 3.5 g/mL. With a selectivity index (SI) of 15.09, compound 33, which was significant, showed extraordinary selectivity towards A549 cancer cells as compared to normal human lung cells [20]. Dehaen and colleagues studied a number of allobetulin derivatives with 1,2,3-triazolium moieties in 2020. These derivatives showed better anticancer activity in comparison to the original molecule allobetulin and the widely used anticancer medication gefitinib. Compound 34a, one of these derivatives, had an IC50 value of 1.12 M and significantly inhibited SGC-7901 cancer cells. With IC50 values of 1.52 M and 1.04 M, respectively, against the HepG2 and Eca-109 cell lines, compound 34b demonstrated broad-spectrum anticancer activity.

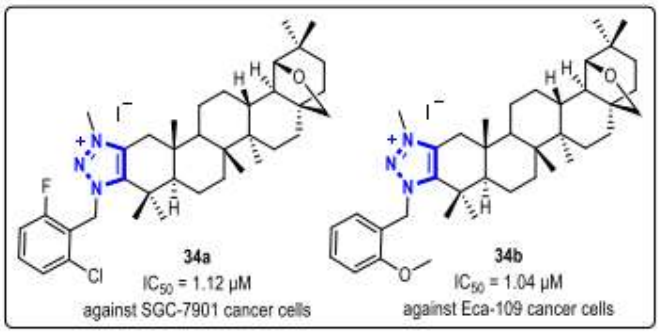

Figure 4. Structures of anticancer allobetulin 1,2,3-triazolium derivatives.

In a 2013 study, Riela and coworkers modified the exterior of halloysite with triazolium salts to produce a positively charged halloysite nanotube functionalized with triazolium salt 35 (Figure 5). This nanotube was used as a drug-loading device and exhibited remarkable benefits like great efficacy in drug encapsulation and

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capacities for controlled, sustained release. The water solubility of two anticancer medicines, curcumin and cardanol, was improved by using this drug-loading technique, overcoming their limits for clinical applications. Additionally, the two anticancer medicines and the drug delivery method had synergistic effects, which boosted anticancer activity [45,46].

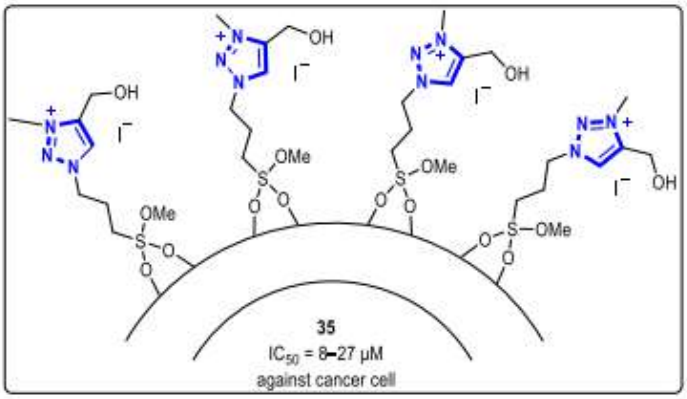

Figure 5. Structures of the anti-cancer 1,2,3-triazolium complex.

Analysis of the Structure-Activity Relationship of the Anticancer Drug 1,2,3-Triazolium Aryl substitutes are essential for controlling how hazardous 1,2,3-triazolium salts are to tumor cells. In comparison to compounds containing electron-neutral groups (such as phenyl) or electron-withdrawing groups (such as 4-(trifluoromethyl)phenyl), compound 27—which has an electron-donating group (4-methoxyphenyl)—displays more anticancer activity [10]. The N-1 positions of compounds 28 and 29, which contain decyl substituents, exhibit potent cytotoxicity against cancer cells. It's interesting to note that the same triazolium salts' various anionic forms have little effect on their anticancer activity [41,42]. A successful moiety for targeting mitochondria is the 1,2,3-triazolium group [11,42]. According to studies, 1,2,3-triazolium salts cause cell cycle arrest and mitochondrial death in cancer cells [11]. This result could be explained by the fact that cancer cells have a larger mitochondrial electrical effect than normal cells. Additionally, a variety of stereoelectronic phenomena [42] have an impact on the structure-activity connection of 1,2,3-triazolium salt compounds in complex living cell systems (Figure 6).

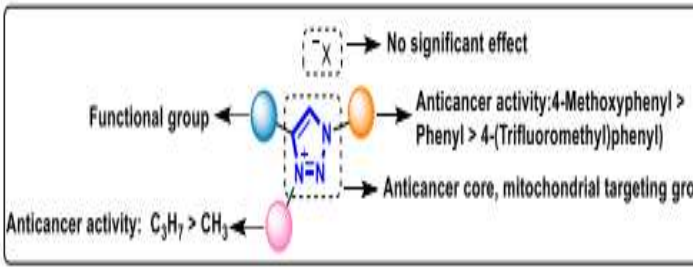

Figure 6. The 1,2,3-triazolium anticancer 1,2,3-triazolium structure-activity connection in brief.

CONCLUSION

In conclusion, 1,2,3-triazolium salts and their derivatives have emerged as promising anticancer reagents. Through extensive research and investigation, these compounds have demonstrated significant cytotoxicity against various cancer cell lines. The introduction of aryl substituents has been found to regulate their anticancer activity, with electron-donating groups showing enhanced efficacy compared to electron-neutral or electron-withdrawing groups. Additionally, the presence of decyl substituents at the N-1 positions has shown strong cytotoxic effects on cancer cells. Furthermore, the 1,2,3-triazolium group exhibits effective mitochondrial targeting, making it a valuable component for designing targeted anticancer drugs. Studies have revealed that the mechanism of action of 1,2,3-triazolium salts involves inducing apoptosis through mitochondrial pathways and cell cycle arrest. The selective mitochondrial electronic effect observed in cancer cells further enhances their potential as anticancer agents. Importantly, the structure-activity relationship of 1,2,3-triazolium salts in complex living cell systems is influenced by a combination of stereoelectronic effects, highlighting the intricate nature of their interactions with cellular components. Overall, the research on 1,2,3-triazolium salts and their derivatives as anticancer reagents has shown promising results, indicating their potential as a new class of compounds for developing effective cancer treatments. Further studies and investigations are warranted to explore their therapeutic applications, optimize their structures, and improve their selectivity and efficacy, ultimately bringing us closer to developing innovative and targeted anticancer therapies.

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