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A comprehensive review on triazoles as anticancer agents

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ABSTRACT: Despite the advancements in anticancer drug design, new pharmacological compounds that are safer, more effective, and able to stop the emergence of resistance to themselves are still desperately needed. Triazoles have a broad range of biological activities, including anticancer, antiviral, and antibacterial activities. Also, they can interact with diverse enzyme systems via hydrogen bonds, electrostatic interactions, and other mechanisms. Due to these advantages, triazoles have become one of the most popular scaffolds in medicinal chemistry and have attracted researchers' attention. In this review, a comprehensive overview of recent advances in anticancer triazoles, focusing on developments within the last five years, their classification based on their mode of action and synthesis methodology, and a summary of historical progress in synthesis techniques are provided to offer researchers a broad perspective.

KEYWORDS: triazole; anticancer; synthesis; activity; molecular modelling

1. INTRODUCTION

Cancer is a major public health problem, being one of the deadliest and most frightening diseases in the world [1, 2]. According to the World Health Organization (WHO), it is a broad category of illnesses that can begin in any organ or tissue in the body due to the unchecked growth of aberrant cells, and they can spread to other bodily areas through a process known as metastasis. Metastasis is the major cause of cancer-related death worldwide after cardiovascular diseases [3]. According to reports, the United States recorded 1.958.310 new cases of cancer in 2023 and 609.820 fatalities from cancer-related causes [4]. In line with global demographic data, it is estimated that the incidence of cancer will increase in 2025 and affect approximately 20 million people annually [2]. According to Global Burden of Disease (GBD) 2015 data, the most frequent malignancies are prostate, lung, and colorectal cancer in men, while breast, colorectal, and lung cancer are the most common in women. Regarding cancer-related deaths, it is reported that lung, liver, and gastric cancer are the most prevalent causes of death in men, whereas breast, lung, and colorectal cancer are the leading causes of death in women [5]. Avoiding carcinogenic infections and lifestyle changes are extremely important to reduce the incidence of the mentioned cancers. While infection-related cancers such as HCV, HBV, and HPV are predominant in low-income countries, the incidence of lifestyle-related cancers such as smoking, alcohol use, and obesity is higher in high-income countries [3]. Although progress is being made every day in the avoiding and curing cases of cancer, finding a good course of treatment is still difficult [6]. To date, there are more than 100 drug molecules approved for the treatment of various types of cancer [7]. However, the rapidly developing drug resistance, the acute side effects caused by these drugs, and the lack of selectivity towards cancer cells are the challenging aspects of an effective chemotherapy [7-9]. Consequently, there is an urgent requirement to design new anticancer drugs that exhibit fewer side effects, efficacy at low doses, selectivity towards tumor cells, and the ability to prevent the development of resistance.

Triazoles' diverse variety of biological actions has drawn researchers' attention for years [6, 10]. There are two isomeric forms of triazoles, which are also referred to as pyrodiazoles: 1,2,3-triazoles and 1,2,4-triazoles [10]. Among these isomeric forms, 1,2,3-triazoles are extremely resistant to hydrolysis under different ambient conditions [11]. 1,2,3- and 1,2,4-triazoles are aromatic compounds in which all atoms are sp2 hybridized and have a total of 6π electrons [12]. Owing to the stability provided by this aromatic structure, they are also quite stable under reductive and oxidative conditions[11]. In addition, 1,2,3-triazoles

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are frequently used as amide bioisosteres due to their high stability. Notably, one of the E/Z forms of amides, the E-isomer, is very similar to 1,2,3-triazoles in terms of electronic and surface properties [13].

Triazoles have the potential to display a great variety of biological activities by acting on many different target enzyme and protein systems, thanks to their ability to make non-covalent interactions such as hydrophobic interactions, hydrogen bonds, van der Waals forces, and dipole-dipole interactions [7]. Thus, compounds bearing triazole core have appeared in literature with several biological activities such as anticancer [14-18], antiproliferative [19], anticonvulsant [20], antifungal [21, 22], antibacterial [23, 24], immune stimulant [25], antidiabetic [26], antiallergic [27], anti-inflammatory [28], antitubercular [29, 30], antimalarial [31] and antiviral activities [32-34]. Furthermore, approved drug molecules containing triazoles that are used to treat various diseases include the β-lactamase inhibitor tazobactam, the cephalosporin antibiotic cefatrizine, the 14-α-demethylase inhibitors fluconazole, voriconazole, and posaconazole, the antidepressants nefazodone and trazodone, the antiviral ribavirin, and the antiepileptic rufinamide [11, 35]. Among the diverse range of biological activities of triazoles, their anticancer activities are particularly noteworthy. Interactions of triazoles with diverse enzyme systems like carbonic anhydrase [36, 37], thymidylate synthase [38], aromatase [39, 40], vascular endothelial growth factor receptor (VEGFR) [41] and epidermal growth factor receptor (EGFR) mediate their anticancer properties [42]. In this review, triazole derivative compounds and triazole synthesis methods will be explained according to their anticancer effect mechanisms, thus providing convenience to researchers in the design and synthesis of more effective anticancer agents.

2. TRIAZOLE SYNTHESIS METHODS

2.1 1,2,3-Triazole Synthesis

There are many approaches in the literature for the synthesis of 1,2,3-triazole. These methods are classified under 4 main groups:

I. Huisgen 1,3-dipolar cycloaddition
II. Metal-catalysed 1,3-dipolar cycloaddition
III. Strain-promoted azide-alkyne cycloaddition
IV. Metal-free synthesis [43, 44].

Among these methods, the synthesis of 1,2,3-triazoles via the Huisgen 1,3-dipolar cycloaddition is the most well-known and easiest method. [45]. Under heating circumstances, this cycloaddition reaction between azides and alkynes always yields regioisomeric mixes of 1,4- and 1,5-disubstituted 1,2,3-triazoles [44]. Since this situation caused the desired product to be obtained in low yield, copper-catalyzed alkyne-azide cycloaddition reactions were subsequently developed. These copper-catalyzed reactions are called "click chemistry" [44, 46].

As an example of “click chemistry”, Rostovtsev et al. developed a new approach for copper-catalyzed regioselective 1,4-disubstituted 1,2,3-triazole synthesis. Accordingly, 1,4-disubstituted 1,2,3-triazoles are produced in high yields between 6-36 hours at room temperature via Cu (I) catalysts obtained from the reduction of Cu (II) salts (such as $CuSO_4.5H_2O$) using sodium ascorbate as a reductive agent. It is also stated that water and many organic solvents give very successful results in this method [47]. Using a solid-phase reaction between azides and alkynes, Tornoe et al. produced 1,4-disubstituted-1,2,3-triazoles with yields as high as 95% in the same year (Figure 1) [48].

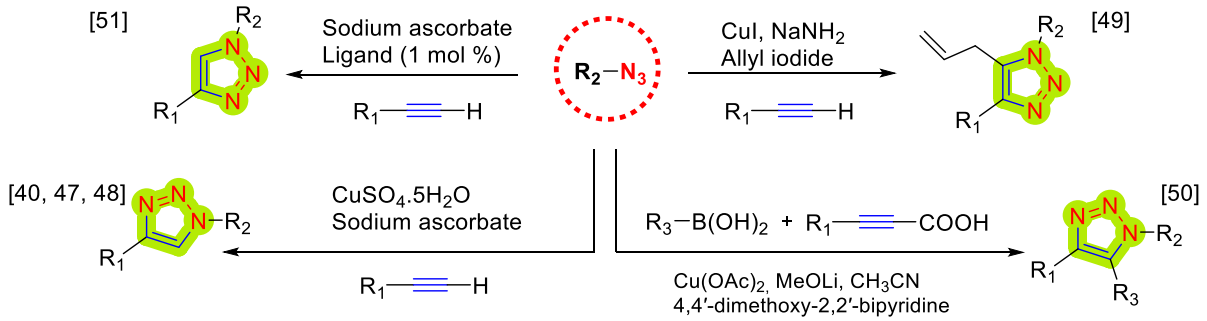

Figure 1. 1,2,3-Triazole synthesis via Cu catalyst

Song et al. carried out the synthesis of 5-allyl-1,2,3-triazoles using copper (I) iodide. The reaction of alkynes and benzyl azides with allyl iodide gave the desired product with high yield and selectivity when carried out in toluene at room temperature (Figure 1) [49].

Wang et al. carried out the copper-catalyzed reaction of aryl propiolic acids with benzyl azides and arylboronic acids for the synthesis of fully substituted 1,2,3-triazoles. Cu (II) acetate was used as a copper catalyst in this reaction (Figure 1) [50].

In 2021, a pyrazole-based tridentate ligand containing Cu (II) was designed for the synthesis of 1,2,3-triazole. This ligand is transformed into Cu (I) by the reductive effect of sodium ascorbate in the reaction environment, thus the reaction of aryl/sulphonylazides with alkynes is catalyzed by the Cu (I) provided by this ligand, resulting in the synthesis of 1,2,3-triazoles. As a result of the reactions carried out at 80°C in an environment containing *tert*-butanol-water, the synthesis of triazoles was completed with a yield of 79-98% (Figure 1) [51].

In 2023, Maghraby et al. used the Cu (II) catalyzed "click chemistry" approach to design and synthesize 1,2,3-/1,2,4-triazole hybrids. This two-step process produced 1,2,3-triazole. First, ethyl 2-chloroacetate was reacted with sodium azide to yield ethyl azidoacetate. Next, the ethyl azidoacetate was reacted with phenylacetylene in tetrahydrofuran (THF) - water (1:1) with $CuSO_4.5H_2O$ and sodium ascorbate catalyst. The 1,2,3-triazoles were obtained with %96 yield after 24 h reaction time at room temperature (Figure 1) [40].

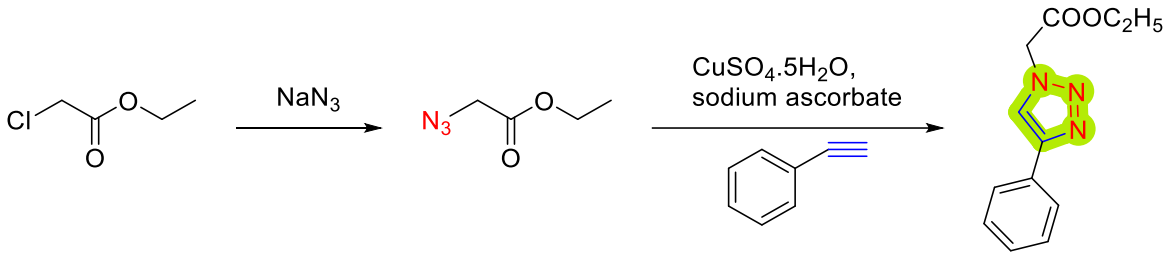

Figure 2. 1,2,3-Triazole synthesis via cycloaddition reaction

Although "click chemistry" methods have attracted the attention of researchers by being successful in triazole synthesis, the metal catalysts used here are extremely harmful to the biological environment. Consequently, attempts have been made to enhance methods for the synthesis of 1,2,3-triazoles using more environmentally friendly methods [44]. In this direction, methods called strain-promoted alkyne-azide cycloaddition reactions have been developed. In strain-promoted methods, the synthesis of 1,2,3-triazoles is accomplished through cyclooctynes without using copper catalysts (Figure 2) [52, 53]. This synthesis method first emerged in 1961, when Wittig and Krebs obtained the triazole derivative compound as a result of the strain-promoted reaction of cyclooctyne and azidobenzene. Then, in 2004, Bertozzi and colleagues discovered the first cyclooctyne compound, OCT, and unearthed the development of strain-promoted azide-alkyne cycloaddition (SPAAC) methods. Examples of cyclooctyne developed in this direction are difluorinated cyclooctyne (DIFO), dibenzocyclooctyne (DIBO), azadibenzocyclooctyne (DIBAC), biarylazacyclooctynone (BARAC), etc (Figure 3) [54].

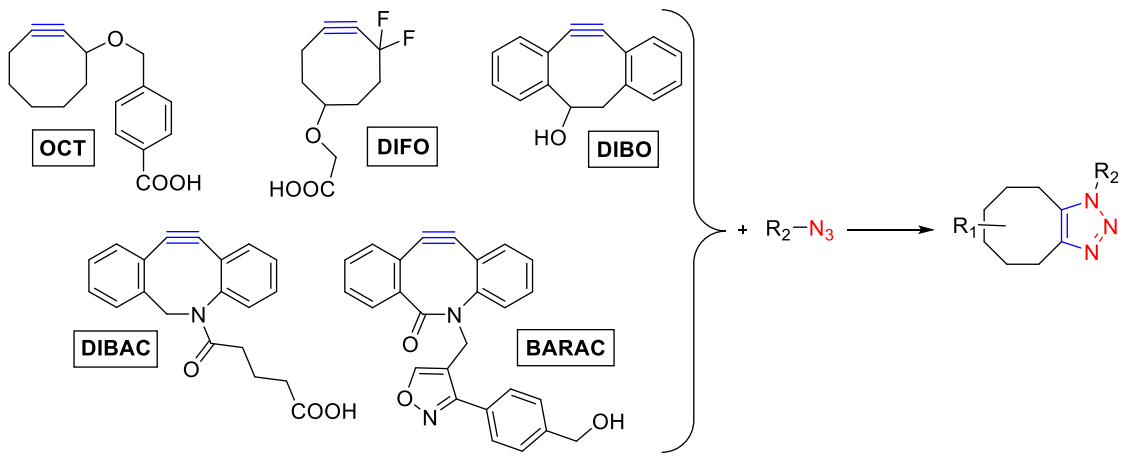

Figure 3. 1,2,3-Triazole synthesis via SPAAC methods

The first example of metal-free synthesis was proposed by Rossi and his colleagues in 1986. Accordingly, the researchers synthesized 1,2,3-triazoles via the reaction of aromatic azides with enediamines in toluene under reflux (Figure 4) [44].

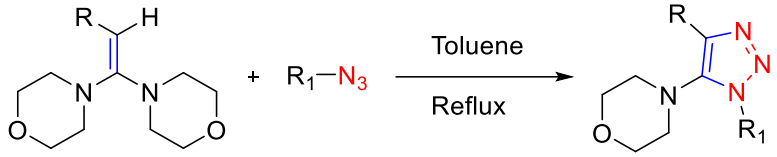

Figure 4. Metal-free 1,2,3-triazole synthesis by Rossi et al.

In 2010, heterocycle-fused 1,2,3-triazole rings were synthesized as a result of the reaction of heterocyclic ketene aminal or N,O-acetals with sodium azide and polyhalo isophytalonitrile compounds. In this one-pot reaction with no catalyst, toluene, dichloromethane, THF, acetonitrile, *N*,*N*-dimethylformamide (DMF) and dioxane were tried as solvents; although DMF was determined as the best solvent, toluene was determined as the worst solvent. In this method 1,2,3-triazoles can be synthesized with yields up to 90% at room temperature (Figure 5) [55].

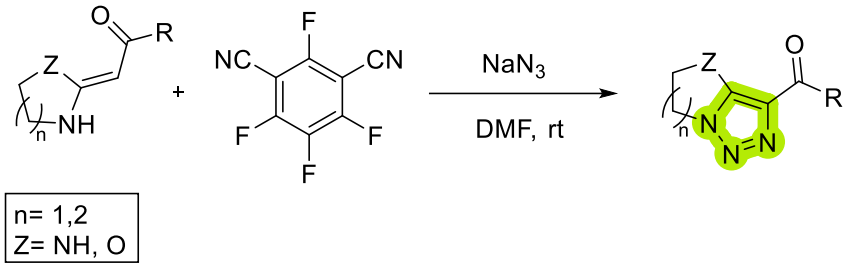

Figure 5. Synthesis method of heterocycle containing 1,2,3-triazole rings

Thomas et al. used enolizable ketones as starting materials for the synthesis of 1,5-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles. As a result of heating alkylamines, ketones and azides at high temperatures in the presence of molecular sieves with acetic acid in toluene, the synthesis of the corresponding triazoles was achieved with yields of 56-93% (Figure 6) [56].

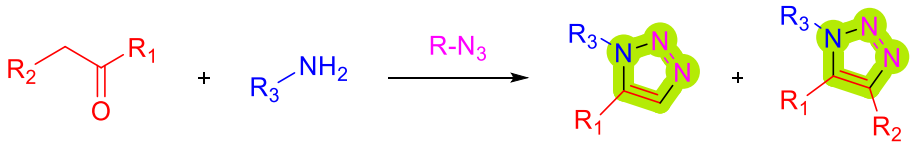

Figure 6. 1,2,3-Triazole synthesis reported by Thomas et al.

As another example of 1,2,3-triazole synthesis without using transition metal, Siliveri et al. synthesized 1,2,3-triazole benzene sulphonamides derivatives including isoxazoline and pyrazoline. For this, first azido benzene sulfonamide and acetylacetone were added to a methanolic solution of CH_3ONa and refluxed overnight. The pure compound was obtained with a 95% yield after recrystallization from ethanol (Figure 7) [57].

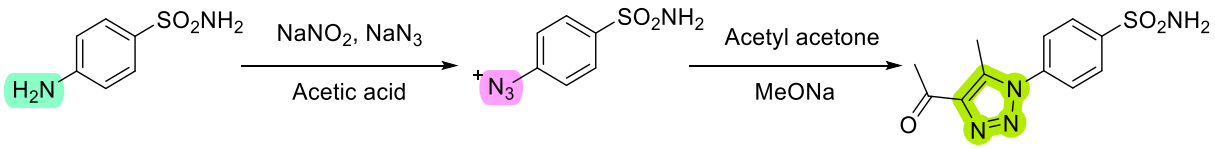

Figure 7. 1,2,3-Triazole synthesis reported by Siliveri et al.

Silaichev et al. presented two different approaches to synthesize 1,2,3-triazoles via base catalyst without transition metals. In the first approach, the reaction of amide and azides in 1,4-dioxane is carried out in mild conditions with 1,8-diazabicyclo (5.4.0)undec-7-ene (DBU) as the non-nucleophilic base catalyst. In the second approach, the reaction is carried out in an ethanolic solution with sodium hydroxide (NaOH) as

the base catalyst. Reaction yields for both methods were recorded in the range of 83-98%. However, when the reactions were carried out with NaOH at 0°C, higher yield was obtained (Figure 8) [58].

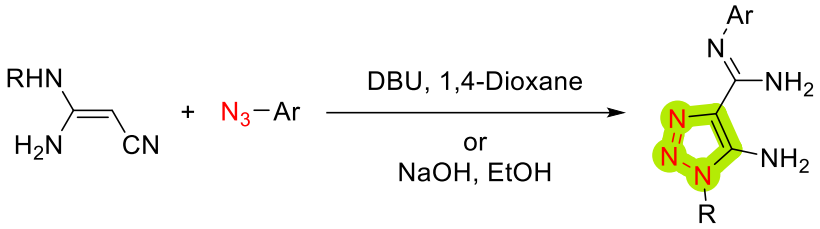

Figure 8. Fully conjugated 1,2,3-triazole synthesis by Silaichev et al.

2.2. 1,2,4-Triazol Synthesis

The methods proposed for the synthesis of 1,2,4-triazoles, which attract attention with their wide range of biological activities, mostly include ring-closing reactions using hydrazide, hydrazone, amidine, imidate, amidrazone, aryldiazonium, and thiosemicarbazone compounds. The non-substituted 1*H*-1,2,4-triazole ring is obtained as a result of the hydrolysis reaction of the 1,2-di(butane-2-ylidene)hydrazine compound in the presence of formamide at high temperatures [12, 59].

The Einhorn-Brunner synthesis, one of the first 1,2,4-triazole synthesis methods, was developed in 1905 and provides the production of 1-alkyl substituted 5-methyl-1,2,4-triazoles as a result of the acid-catalyzed reaction of formylacetamide with alkylhydrazine. Similarly, the Pellizzari synthesis, developed by the researcher of the same name in 1911, provides the synthesis of 1,2,4-triazoles by ring closure via the acyl amidrazone intermediate as a result of the reaction of amides with hydrazides [12].

In the synthesis of bis-1,2,4-triazoles, Arafa and Ibrahim employed a method involving the addition of formylhydrazine and a K_2CO_3 solution in water to a solution of bis-thiourea compounds in ethanol. The resulting mixture was subjected to sonication at room temperature before iodide (I_2) was gradually introduced. Further sonication was performed for an additional 10 minutes. The desired 1,2,4-triazole derivatives were successfully formed with yields of up to 96%. However, the researchers discovered that this synthesis method resulted in the formation of a combination of regioisomeric compounds (Figure 9) [60].

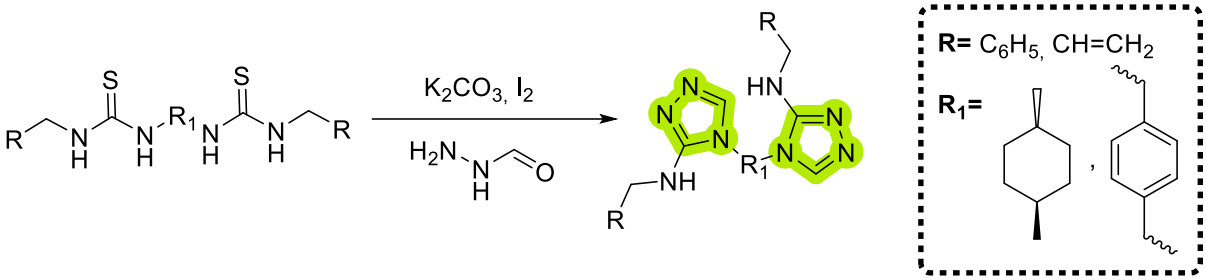

Figure 9. Synthesis of bis-1,2,4-triazoles by Arafa and Ibrahim

In 2019, Xia et al. carried out the 1,2,4-triazole ring closure reaction as a result of the reaction between nitriles, amines, and amidines using a copper catalyst. In this synthesis method, the researchers used 1,10-phenanthroline-functionalized MCM-41-supported copper(I) complex [Phen-MCM-41-CuBr] as a copper catalyst. 2-Aminopyridine and amidine compounds formed the 1,2,4-triazole ring with high yield when heated at 120-130 °C with the relevant catalyst in DMSO or 1,2-dichlorobenzene as solvent. This catalyst is significant as it can be easily obtained by a two-step synthesis, cost-effectiveness, favorable catalytic activity, and reuse capability, enabling the synthesis of various types of 1,2,4-triazoles in high yield (Figure 10) [61].

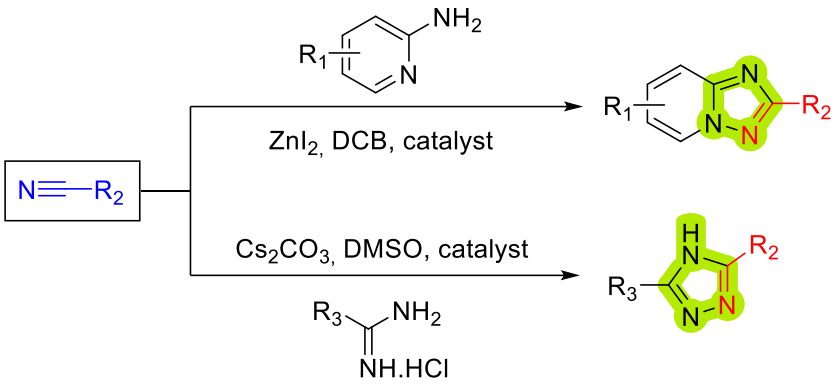

Figure 10. 1,2,4-Triazole synthesis via Phen-MCM-41-CuBr catalyst

In 2020, Balewski et al. synthesized imidazo[2,1-c][1,2,4]triazole derivatives without the use of any catalyst. In this synthesis, excess 2-chloroimidazoles reacted with 1-arylhydrazinecarbonitriles in dichloromethane, resulting in the desired compound with yields of 48-64% (Figure 11) [62].

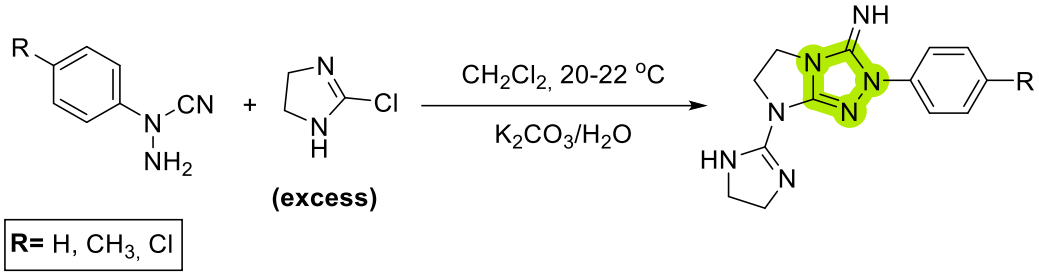

Figure 11. Synthesis method of imidazo[2,1-c][1,2,4]triazoles

Channa Basappa and colleagues obtained dithiocarbazinate salts with CS_2 in an alkaline environment through hydrazides. Then they synthesized 1,2,4-triazoles by heating these intermediate products with hydrazine hydrate under reflux conditions, leading to the evolution of H_2S. Despite the reaction time of 18-20 hours, it was found advantageous that the desired products could be obtained with yields of 56-62% through recrystallization with ethanol [63]. In 2023, researchers managed to obtain 5-amino-1,2,4-triazole-5-thions with a 91% yield using Channa Basappa's method [40]. In the same study, for the synthesis of 4-alkyl substituted 1,2,4-triazole-5-thiones, the researchers carried out ring-closing reactions with 84-86% yields by heating the carbodithioate intermediate product with alkylisothiocyanates under reflux conditions in n-butanol (Figure 12) [40].

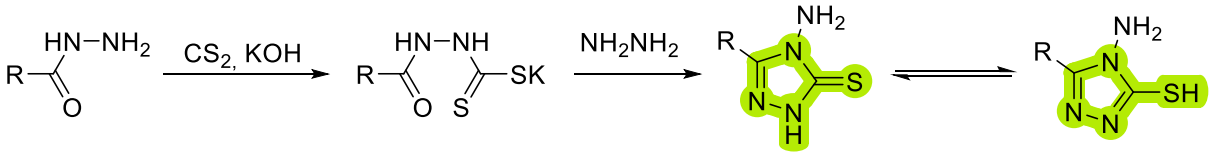

Figure 12. 1,2,4-Triazole synthesis with dithiocarbazinates and hydrazine hydrate

For the synthesis of 1,2,4-triazole-3-amines, Jahani et al. first obtained trichloroacetamide derivatives as a result of the reaction of various anilines with trichloroacetonitrile, and then carried out the reaction of these compounds with hydrazinoyl chlorides, catalyzed by triethylamine and CuI, and synthesized the desired products. They achieved 59-70% yields from the reactions they carried out at room temperature (Figure 13) [64].

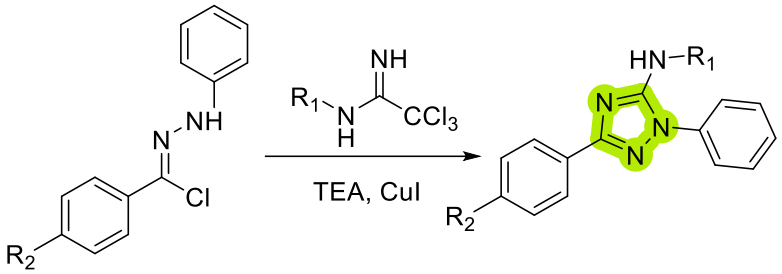

Figure 13. 1,2,4-Triazole synthesis reported by Jahani et al.

In 2021, Guo et al. synthesized 1,2,4-triazoles using the [2+1+2] cycloaddition method. The formation of fully substituted 1*H*-1,2,4-triazole-3-amines in toluene was achieved under mild reaction conditions without an extra catalyst, ligand, or metal via desulphurization and deamination condensation between amidines, isothiocyanates, and hydrazines using a base catalyst (Figure 14) [65].

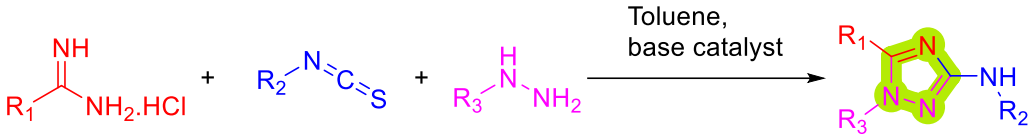

Figure 14. 1,2,4-triazole synthesis by the [2+1+2] cycloaddition

Zhang et al. synthesized 4-substituted-1,2,4-triazol-3-one derivatives based on aryldiazonium salts. For this purpose, they carried out the reaction of aryldiazonium compounds with ethyl 2-chloroacetoacetate and sodium acetate, followed by an amination reaction and subsequent reaction of the obtained compounds with *p*-nitrophenyl chloroformate. The synthesis of fully-substituted 1,2,4-triazoles was completed with this last step reaction, which initially proceeded at room temperature and then under reflux conditions (Figure 15) [66].

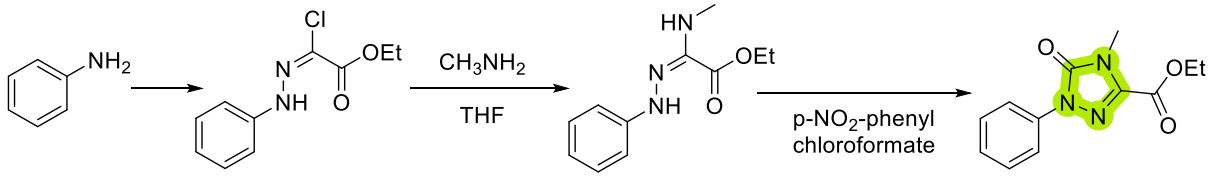

Figure 15. Fully substituted 1,2,4-triazole synthesis by Zhang et al.

In 2022, Semenets et al. obtained thiosemicarbazide structures by reacting hydrazides with various isothiocyanates for the synthesis of 4-substituted-1*H*-1,2,4-triazole-5-thione structures. Then, by heating the thiosemicarbazides in the presence of NaOH, ring closure occurred, leading to the synthesis of the desired products within 3 hours. Additionally, with this synthesis method, it was possible to synthesize 1,2,4-triazoles with yields up to 71-78% (Figure 16) [67].

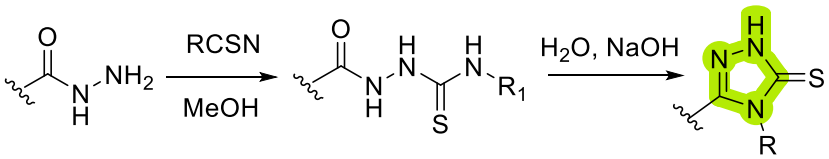

Figure 16. Synthesis of 4-substituted-1H-1,2,4-triazole-5-thion structures by Semenets et al.

Liu et al. synthesized 1,2,4-triazolo[4,3-c]pyrimidine derivatives based on arylhydrazines. According to this method, CS_2 was added to the anhydrous ethanolic solution of the relevant arylhydrazine and triethylamine as a catalyst and heated under reflux conditions until the reaction was completed, resulting in the formation of the 1,2,4-triazole ring with 53.4% efficiency (Figure 17) [68].

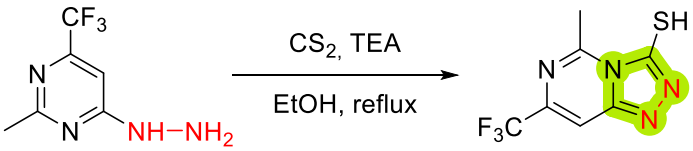

Figure 17. Triazole synthesis with hydrazines

In another study in 2022, trifluoromethyl-1,2,4-triazoles were synthesized. Consequently the [3+2] cycloaddition reaction of trifluoroacetohydrazonoyl chlorides with substituted imidate compounds. In this method, thirty-six compounds were synthesized with 61-99% yields using K_2CO_3 as the catalyst and dichloroethane as the solvent at 80°C. High regioselectivity, compatibility with many substituents, and moderate conditions were presented as the advantages of the method (Figure 18) [69].

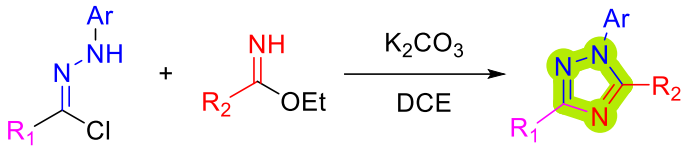

Figure 18. Cycloaddition reaction of imidates with hydrazonoyl chlorides

3. LITERATURE REVIEW OF TRIAZOLE-CONTAINING MOLECULES

1,2,3/1,2,4-Triazoles show anticancer effects by inhibiting a wide range of enzymes with their high interaction ability. In this review, the anticancer activity of triazoles will be explained in detail by classifying them according to the enzyme systems they inhibit.

3.1. Carbonic Anhydrase Inhibitors

Carbonic anhydrase (CA) enzyme contains zinc metal and plays a role in various important physiological and pathophysiological functions in the body [70]. There are six different types called α, β, γ, δ, ζ, and η, which are evolutionarily distinct from each other [71]. It is the α subtype found in mammals, and 16 different α-CAs have been isolated [72]. Notably, hCA IX and hCA XII isoenzymes have emerged as important targets for improving biomarkers and treatments used for various types of cancer [73]. Molecules that selectively inhibit the tumor-associated hCA IX and hCA XII enzymes, which are (over)expressed in tumor cells. The role of these enzymes is important in the treatment of cancer types that are insensitive to traditional cancer treatment methods [74-76].

In 2019, Vats et al. produced sulfonamide-derived 1,2,3-triazoles to examine their inhibitory activity on several hCA isoforms. In this study, the 1,2,3-triazole ring was used as the linking group, while 1,2,4-triazoles were used as the tail group. The 22 molecules they synthesized exhibited inhibitory activity on the cancer-related hCA IX isoform in the range of *Ki* =51 nM – 3.198 µM (Figure 19) [77].

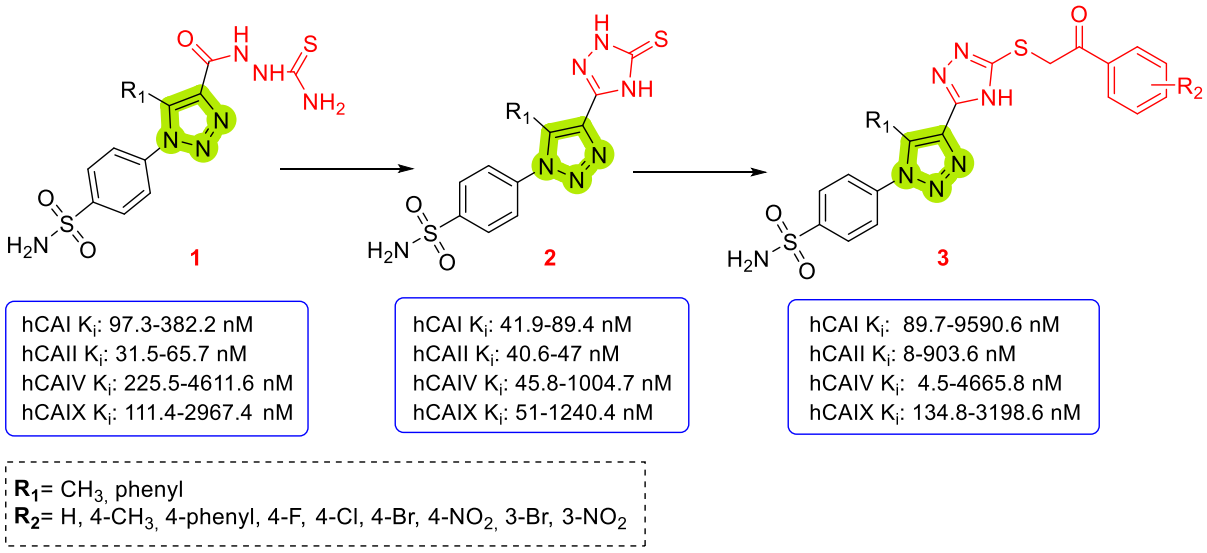

Figure 19. Sulfonamide-derived 1,2,3-triazoles by Vats et al.

1,2,3-triazole is known to be an effective binder, which is useful in the development of CA inhibitors. Based on this, in 2020, Chinchili et al. synthesized 1,2,3-triazole-benzenesulfonamide derivatives triazino[5,6-b]indoles as anticancer compounds. Here, 1,2,3 triazole acts as the linking group, while [1,2,4]triazino[5,6-b]indole acts as the tail group. The synthesized 15 molecules were examined for their inhibitory activity

against different hCA isoforms. According to the obtained results, four out of these compounds (**4**, **5**, **6**, **7**) were determined as the best CA IX inhibitors with *Ki* <values ranging from 34.9 nM to 41.3 nM values. Among these four combinations, the compound with the best activity is **7**, which carries fluorine at the 8-position and isopropyl residue at the 5-position of the [1,2,4]triazino[5,6-b]indole ring with a *Ki* = 34.9 nM (Table) [78].

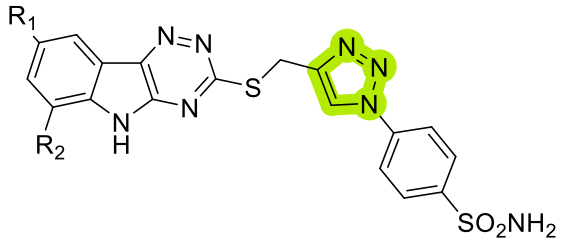

Table. The hCA inhibition data of compounds **4**, **5**, **6,** and **7**

	R_1	R_2	*hCA I (Ki, nM)*	*hCA II (Ki, nM)*	*hCA IX (Ki, nM)*	*hCA XIII (Ki, nM)*
4	H	Isopropyl	314.7	20.09	37.8	65.8
5	H	Allyl	535.8	41.7	41.1	626.7
6	F	Methyl	766.2	59.6	41.3	834.8
7	F	Isopropyl	379.2	7.7	34.9	736.2

In 2020, Hao et al. designed and synthesized 18 carbohydrate-based sulfonamides using the sugar tail approach. In this approach, the 1,2,3-triazole ring acts as a covalent link between the aromatic sulfonamide group, which acts as a pharmacophore group in binding to carbonic anhydrase, and the hydrophilic sugar tail part. The inhibitory activity of these compounds against three isoenzymes of carbonic anhydrase (hCA I, hCA II, and hCA IX) was examined *in vitro* to determine the structure-activity relationship (SAR). The obtained compounds were observed to have inhibitory effects against all three CA isoforms, especially hCA IX, which is associated with tumors. According to the findings of this study, all compounds exhibited a reasonable level of antiproliferative activity against two cancer cell lines (HT-29 and MDA-MB-231) with compound **8** exhibiting the strongest antitumor activity. Notably, compound **8**, with its hCA IX inhibitory effect with an IC_{50} value of 7 nM, is four times more effective than acetazolamide (AAZ) (IC_{50}= 30 nM), which was used as a clinical reference (Figure 20) [79].

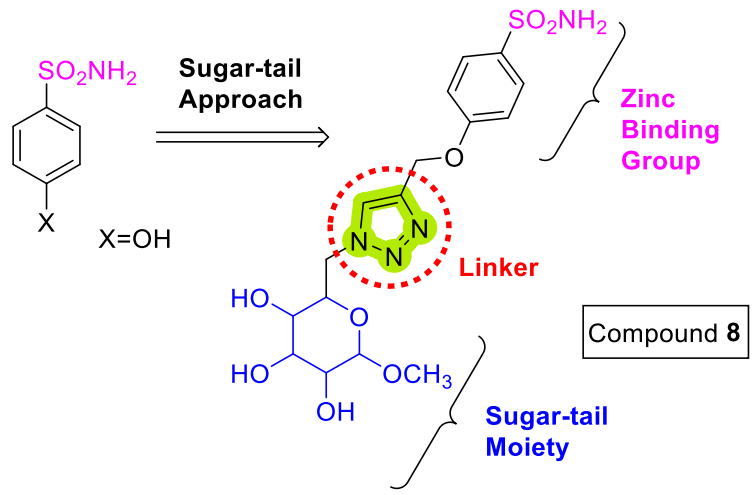

Figure 20. Carbohydrate-based sulfonamides with sugar tail approach

Kumar Amit et al. (2022) have synthesized sulfonamide derivatives with a tail approach, as well as arylthiazolylhydrazono-1,2,3-triazole compounds with a methylamide derivative. The study aimed to investigate the inhibitory effects of these compounds on hCA isoforms I, II, IV, and IX. The 1,2,3-triazole group was used as the linking group in these compounds. The results showed that among the 22 compounds synthesized, the sulfonamide derivatives (**9a-k**) exhibited greater efficacy in inhibiting cytosolic hCA I and II isoforms compared to the methylamide derivatives (**10a-k**). Compounds containing methanylamide

conjugates (**10a-k**) exhibited better hCA IV and tumor-associated transmembrane hCA IX inhibitory activities. Among the synthesized compounds, **9b** developed the most potent cytosolic hCA I inhibitor (*Ki* = 40.6 nM), surpassing the activity of acetazolamide (*Ki* = 250 nM). Importantly, compound **10e** was highlighted as the only analog in the complete series that potentially inhibits the tested hCA I, II, IV, and IX isoforms (**Figure 21**) [80].

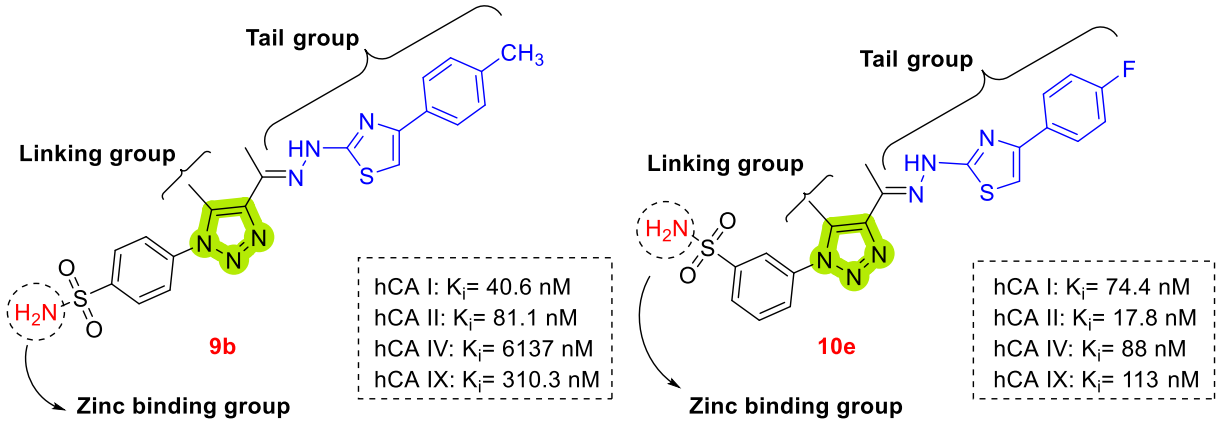

Figure 21. Tail-approached based arylthiazolylhydrazono-1,2,3-triazole compounds

3.2. Aromatase Inhibitors

In the human body, androgens are converted to estrogens by the aromatase enzyme. Inhibitors of the aromatase enzymes are of great importance in the treatment of endometrial and breast cancers. [81]. Anastrozole and letrozole, classified as third-generation aromatase inhibitors, contain a 1,2,4-triazole ring. In 2009, to ensure more effective use of aromatase inhibitors in the clinic, Takahashi-Shiga et al examined the anti-proliferative action of these molecules on endometrial carcinoma (Ishikawa and RL95-2) and breast carcinoma (MCF-7) cell lines. The study revealed that anastrozole inhibited cell proliferation in Ishikawa and RL95-2 co-cultures.[82].

Kang et al. produced 20 new molecules by adding 1,2,4-triazole or imidazole substituents to the 3-position of the 2-phenyl indole as a linker to increase their binding ability to aromatase. Among these compounds, the combination 3-((1*H*-1,2,4-triazol-1-yl)methyl)-6-fluoro-2-(4-methoxyphenyl)-1*H*-indole (**11**) exhibited the maximum inhibitory activity for aromatase (It has been experimentally confirmed to have IC_{50}/aromatase= 14.1 nM). Letrazol, used as a reference, exhibited inhibitory activity at IC_{50}/aromatase= 49.5 nM. In further cell activity tests, compound **11** was found to have low cytotoxicity (IC_{50}/MCF-7= 3.25 µM), exhibiting superior properties than the standard compound letrozole (IC_{50}/MCF-7= 4.73 µM). The information gathered turned out to be a useful starting point for the creation of novel aromatase inhibitors. The compound **11**-enzyme complex exhibited a greater binding relationship to aromatase than the letrozole-enzyme complex, as clarified by molecular modeling experiments carried out to predict the binding modes (Figure 22) [83].

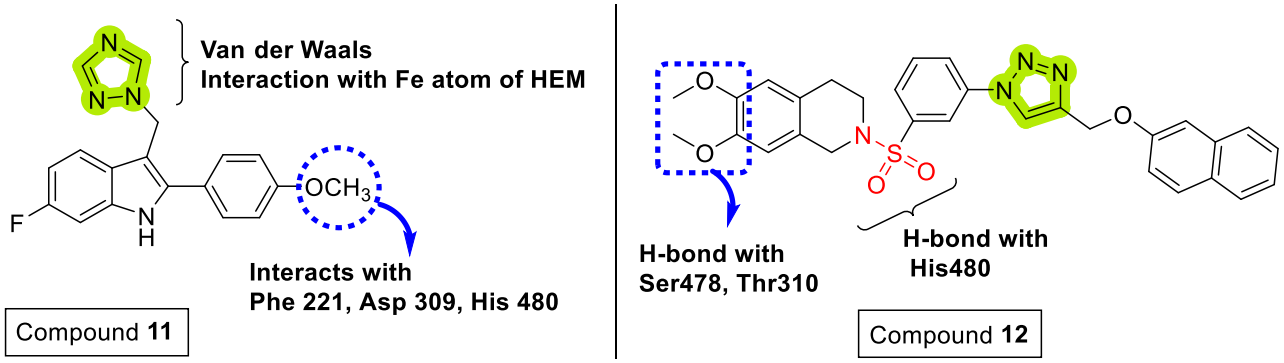

Figure 22. 1,2,4-triazole with 2-phenyl indole compound

In 2019, Chamduang et al. synthesized 13 triazole-tetrahydroisoquinoline (isoquinoline-sulfonamide-triazole) derivative molecules to examine aromatase inhibitor activities. In this study, the aim was to discover more effective compounds based on the molecules that were synthesized in 2015. The most effective compound was selected as the hit compound. Since it is known that the sulfonamide group in these molecules creates strong aromatase inhibitory activity by forming an H-bond with His480, they preserved this group in their newly designed molecules. 7 out of 13 new compounds obtained showed aromatase inhibitory activity in the range of IC_{50}= 0.07-1.9 µM. Consequently, the most effective molecule was compound **12**, which carries the naphthalenyloxymethyl substituent at the 4-position of the triazole link, with inhibitory efficiency with an IC_{50} value of 70 nM. The H-bond interaction with the Thr310 amino acid of compound **12**, which does not show any significant cytotoxicity in normal cells, has a significant contribution to the inhibition (Figure 22)[84].

In 2020, Mohamed El-Naggar et al. created pyrazole-substituted 1,2,3-triazoles and examined them for their 5α-reductase and aromatase inhibitory activities with the aim of determining their use in anti-hormone-dependent cancers. In this study, the aromatase activities were evaluated *in vivo* using letrozole compound as the standard molecule. Among the 15 molecules examined, nine of them were found to be more effective than the standard. The most effective molecule, compound **13**, exhibited IC_{50} values of 0.00024 µM, while the IC_{50} rate of the reference molecule letrozole was found to be 0.00280 µM (Figure 23)[85].

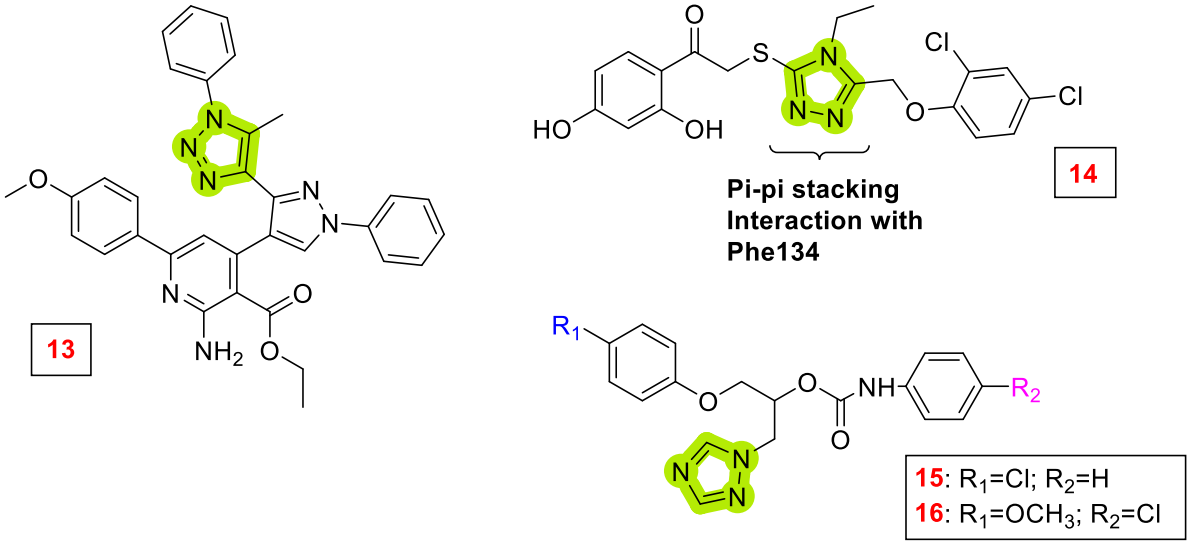

Figure 23. Pyrazole-substituted 1,2,3-triazoles

In 2021, Osmaniye et al. produced eight diaryl substituted triazoles based on the triazole-containing aromatase inhibitors, letrozole and anastrozole. The anticancer effectiveness of these molecules was studied in MCF7 (Michigan cancer foundation-7) breast cancer cell lines, and IC_{50} values were determined in NIH3T3 (mouse embryonic fibroblast cells) healthy cell lines to determine their selectivity. According to the information obtained from MCF7 cell lines, the synthesized molecules exhibited IC_{50} values between 7.50 µM-39.39 µM. The most effective molecule was compound **14**, which, unlike the others, carries a 2,4-dihydroxy phenyl residue as an aryl ring attached to the triazole compound. This compound showed superiority over the standard doxorubicin (IC_{50}= 16.38 µM) with an IC_{50}= 7.50 µM. In addition, letrozole, used as a standard in aromatase enzyme inhibition experiments, exhibited an IC_{50}= 0.00280 µM value, while compound **14** exhibited an IC_{50}= 0.00240 µM value. Molecular modeling works show that the triazole link of molecule **14** established pi-pi stacking interaction with the Phe134 amino acid in the aromatase enzyme (PDB ID: 3EQM)[86].

Ammazzalorso et al. created imidazole and 1,2,3-triazole derivative carbamates. The aromatase inhibitory activity of these molecules in comparison with letrozole and the cytotoxic activity of the molecules was examined on MCF7 breast cancer cell lines. While only two of the triazole derivative carbamates (**15**= 46%, **16**= 49%) exhibited moderate inhibitory effects, imidazole derivatives were found to be more effective [87].

In 2023, Maghraby et al. synthesized 11 new 1,2,3-triazole and 1,2,4-triazole hybrids (**17a,b** and **18a-i,** respectively) and examined their antiproliferative activity. Erlotinib was used as the reference compound in

the evaluation of anticancer activity. The most effective of the synthesized compounds are compounds **18a** (GI_{50}= 40 nM) and **18b** (GI_{50}= 35 nM), which carry 4-methoxybenzylideneamino and 3,4,5-trimethoxybenzylideneamino residues in the 1,2,4-triazole ring's 4-position, respectively. In experiments where aromatase enzyme inhibition was determined, compounds **18a** (IC_{50}= 0.12 ± 0.01) and **18b** (IC_{50}= 0.09±0.01) were determined to be the strongest aromatase inhibitors, similar to their antiproliferative effect. When it came to inhibiting aromatase, these substances were less successful than letrozole (IC_{50}= 0.002 ± 0.0002) but much stronger than the standard ketoconazole (IC_{50}= 2.6 ±0.20). In molecular modeling studies, the molecule with the best binding energy was determined as **18a** (−9.64 kcal/mol), and the compound **18b**, which exhibited the best activity in *in vitro* experiments, was determined to have a binding affinity of −9.94 kcal/mol. In compound **18a**, the 1,2,3-triazole ring showed pi-pi interaction with the amino acid Val370, while in compound **18b**, this ring showed H-bond coaction with amino acid Thr310. It has also been determined that the 1,2,3-triazole ring interacts with amino acids such as Arg115 and Cys437 in other molecules (Figure 24) [40].

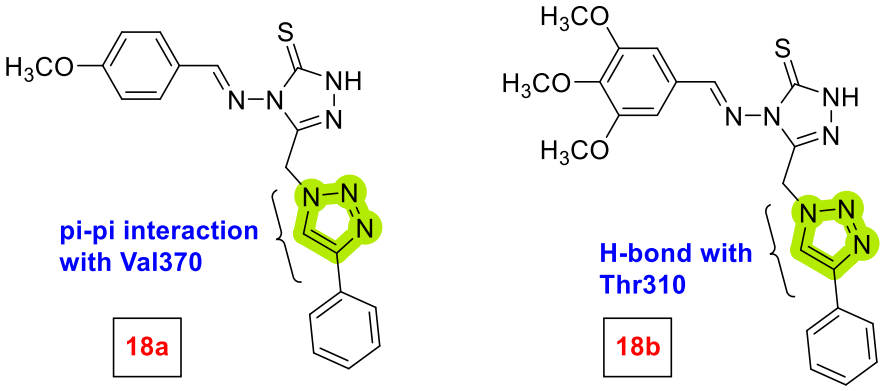

Figure 24. 1,2,3-Triazole containing compounds synthesized by Maghraby et al.

3.3. Tubulin Polymerisation Inhibitors

Tubulin protein is significant in splitting, forming the cytoskeleton and trying to hold intracellular organs together. Tubulins are formed as a result of the assembly and polymerization of microtubules. Tubulin polymerization inhibitors prevent carcinoma from undergoing mitosis, causing them to remain in cell's G2/M phase, division, and undergo apoptosis. There are many tubulin inhibitor compounds in drug development targeting different carcinomas by inhibiting tubulin polymerization [88-92].

Fu et al. synthesized 15 new trimethoxyphenyl-1,2,3-triazole derivatives and evaluated their antiproliferative activities against three carcinomas (PC3, MGC803, and HepG2). Among the synthesized compounds, *N*-(4-methoxybenzyl)-2-(4-(((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(3,4,5-trimethoxyphenyl)acetamide (**19**) exhibited the most antiproliferative activity results (GI_{50}=0.34, 0.13 and 1.74 µM). Molecular modeling studies determined that the Val353 residues formed hydrogen bonding with the triazole ring (Figure 25) [93].

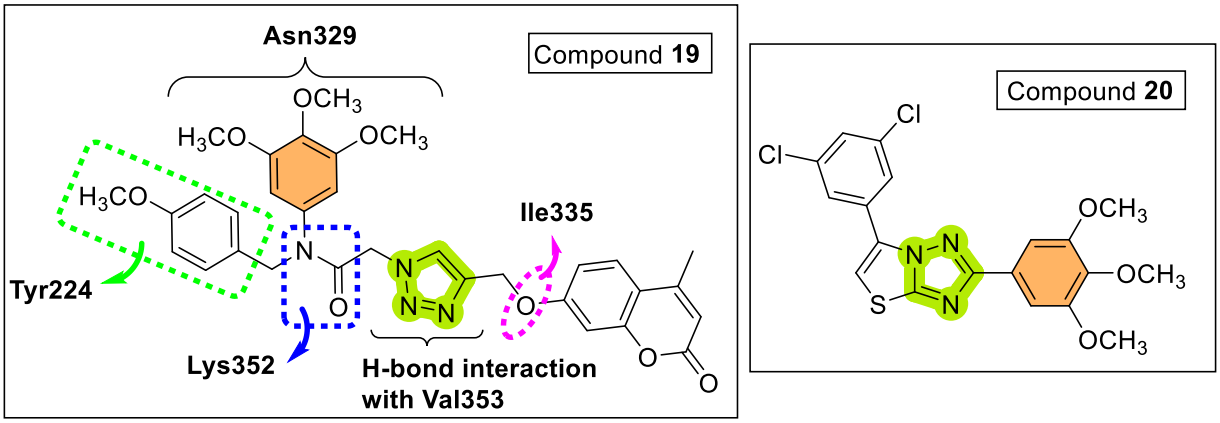

Figure 25. 3,4,5-Trimethoxyphenyl-triazole hybrids

In 2022, Mohammed et al. created 1,2,3-triazole hybrids, which act like a bridge, providing an extra binding site between ciprofloxacin and chalcone compounds. It has been reported that these molecules also inhibit topoisomerase I and II enzymes making them valuable in the fight against colorectal cancer as multi-target anticancer compounds (Figure 26) [94].

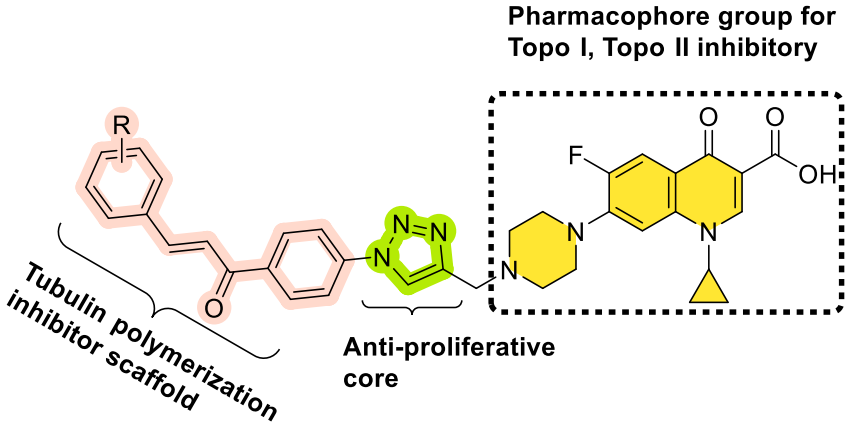

Figure 26. Hybrid molecules containing 1,2,3-triazoles

Li et al. produced tubulin polymerization inhibitors, 6-aryl-2-(3,4,5-trimethoxyphenyl)thiazole[3,2-b][1,2,4]triazole derivatives, aiming to attach to the colchicine-binding site of tubulin. Research conducted with colchicine as a reference drug demonstrated that compound **20** has an inhibition action similar to that of colchicine. Compound **20**'s activity against SGC-7901 is (IC_{50}= 0.21 µM), while the activity of colchicine is (IC_{50}= 0.11 µM). Furthermore, compound **20**'s cytotoxicity to HUVEC less whence colchicine and also displayed *in vivo* antitumor action to 4T1. Complex **20** was observed to effectively reduce tumor weight by 84.0%, without significant toxicity in *in vivo* experiments. In the *in silico* studies, **20** conformationally bind tightly to the P1 and P3 domains of the colchicine binding domain (Figure 25) [95].

3.4. Thymidylate Synthase Inhibitors

Thymidylate synthase (TS) is the enzyme that creates deoxythymidine monophosphate (dTMP). Then, dTMP is phosphorylated to the deoxythymidine triphosphate (dTTP) form and plays a role as a precursor in DNA polymerization. Inhibition of this enzyme inhibits thymidylate synthesis, causing cell expansion and proliferation to cease. Investigations have shown that TS has attracted attention in the development of drug molecules used in cancer treatment, based on its prominent roles in DNA synthesis. [96-98].

Lu et al. designed and synthesized the uracilsulfonamide-containing 1,2,3-triazole compounds as TS inhibitors with potential anticancer properties. These hybrid compounds were evaluated for their antiproliferative activities against A549, OVCAR-3, SGC-7901, and HepG2 cell lines. PTX (Pemetrexed) was used as the reference drug and exhibited IC_{50}= 3.29 µM against the A549 cancer cell line and an IC_{50} of 2.04 µM for TS enzyme inhibition experiment. Among the compounds synthesized by the researchers, compound **21**, which contains Cl in the phenyl group's ortho position attached to the triazole, exhibited an IC_{50} of 1.18 µM against A549 cancer cell line, and an IC_{50} of 0.13 µM in the inhibit TS enzyme experiment. Furthermore, when comparing the selectivity index (SI) for both molecules, it can be said that compound **21** (SI= 17.29) shows a higher selectivity than PTX (SI = 7.71) (Figure 27) [99].

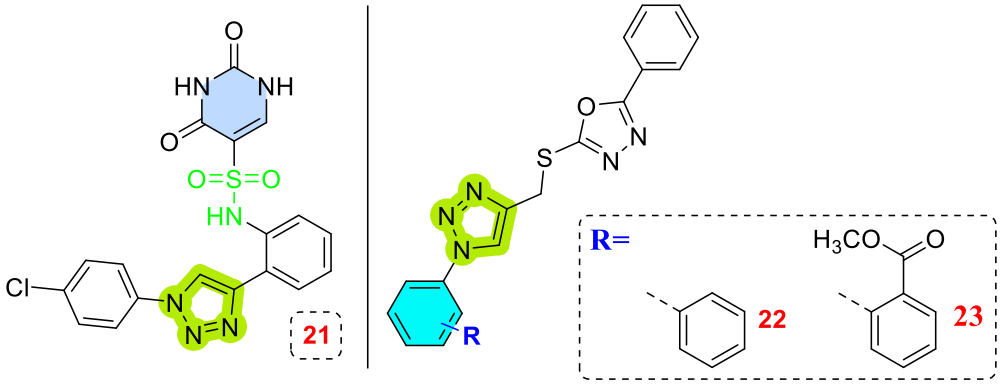

Figure 27. 1,2,3-Triazole hybrids as thymidylate synthase inhibitor

In 2020, Alam et al., designed and synthesized thymidylate synthase inhibitor 1,2,3-triazole-1,3,4-oxadiazole hybrids. These molecules were evaluated for their anticancer activities against three various types of cancer (MCF7, HCT-116, HepG2). As a result, compound **22** with phenyl substitution and compound **23** with *o*-methoxycarbonylphenyl substitution showed prominent inhibitory action against MCF-7 and HCT-116 cells. For the MCF-7 cell line, compound **22** exhibited activity with an IC_{50} value of 5.8 µM and compound **23** showed activity with an IC_{50} rate of 1.26 µM. These results are five times active more than the standard tamoxifen (IC_{50}= 5.12 µM) and 24 times more than 5-fluorouracil (5-FU) (IC_{50}= 24.74 µM). For HCT-116, compound **22** exhibited activities with an IC_{50} value of 14.8 µM and compound **13** with an IC_{50} rate of 17.3 µM, showing preferable anticancer properties compared to the reference compounds. In the molecular modeling study against the TS enzyme (PDB ID: 6QXG), a comparison was made with the TS inhibitor 5-FU, which showed various binding interactions with the enzyme's active site. Similar to 5-FU, compounds **22** and **23** interacted with the amino acid ASN226 and showed comparable docking results (Figure 27) [100].

1,2,3-Triazole hybrids based on thymol were synthesized by Alam et al., and their anticancer potential was assessed against the cancer cell lines MCF-7 and MDA-MB-231. Among these combinations, 4-((2-isopropyl-5-methylphenoxy)methyl)-1-*o*-tolyl-1*H*-1,2,3-triazole (**24**) was found to be the most effective in terms of cytotoxicity with an IC_{50} value of 6.17 µM against MCF-7, making it maximum effective compound. Against MDA-MB-231 cancer cells, compound **24** exhibited superior activities over tamoxifen and 5-FU, which were used as references, with an IC_{50} value of 10.52 µM. When compared to PTX (IC_{50}= 5.39 µM), which is used as the standard in TS inhibition, complex **24** (IC_{50}= 2.21 µM) and complex **25** (IC_{50}= 4.27 µM) showed better activity than the reference, suggesting that the how effective these molecules are via TS inhibition. Furthermore, molecular modeling studies carried out with the TS enzyme (PDB ID: 6QXG), revealed that these compounds exhibited very good binding affinities by establishing H-bond and π-π interaction in the binding region of the enzyme (Figure 28) [101].

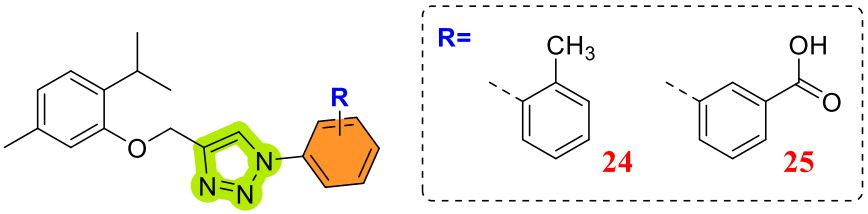

Figure 28. Thymol- based 1,2,3-triazoles

3.5.VEGFR Inhibitors

The vascular endothelial growth factor receptor (VEGFR) is essential for angiogenesis, which is involved in a large variety of functions. Recent works have revealed that angiogenesis is also related to cancer pathophysiology, prompting the adoption of new approaches targeting angiogenesis in current anticancer treatment [102].

Wang and his colleagues designed and synthesized 2-indolinone/1,2,3-triazole hybrids and conducted VEGFR-2 inhibition studies of these compounds. The results were particularly promising for compounds **26** (IC_{50}= 26.38 nM) and **27** (IC_{50}= 36.9 nM), while several other compounds had lower IC_{50}

values compared to the reference Sunitinib (IC_{50}= 83.20 nM). Additionally, compound **26** was found to be less toxic to HUVEC. Molecular modeling studies have shown that this compound is effective in the active site by establishing hydrogen bond interactions with VEGFR-2 (Figure 29) [103].

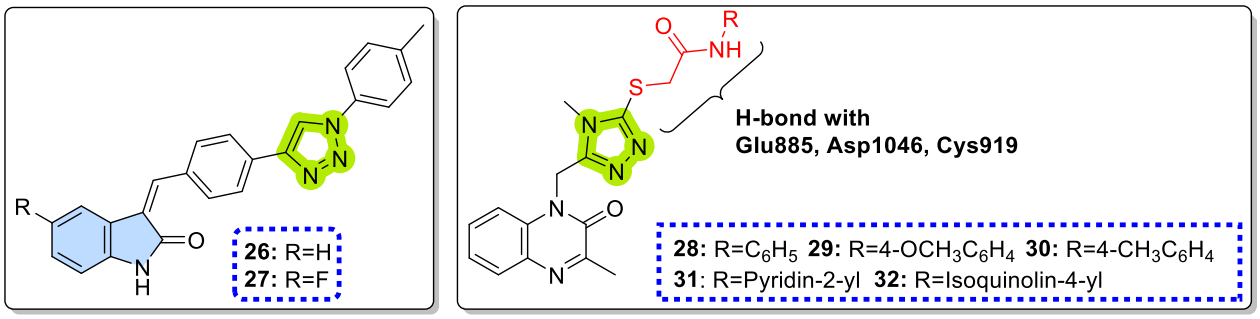

Figure 29. VEGFR-2 inhibitor 1,2,3 and 1,2,4-triazole hybrids

Zengin et al. designed and produced 2-oxoquinoxalinyl-1,2,4-triazoles as VEGFR-2 inhibitor antitumor agents. Out of twelve in this series, eight compounds displayed increased activity against MCF-7 with GI_{50} 1.6 and 8.06 µM, surpassing staurosporine (GI_{50}= 8.39 µM) and sorafenib (GI_{50}= 11.20 µM) as standards. Furthermore, the majority of the compounds displayed IC_{50} values in the nanomolar range, according to the outcomes of *in vitro* VEGFR-2 inhibition studies. Notably, compounds **28** (3-fluorophenyl), **29** (4-methylphenyl), **30** (pyridine), and **31** (isoquinoline) are potent compounds with comparable activity (IC_{50}= 0.047, 0.06, 0.07, and 0.094 µM, respectively). Compound **32** bearing the 4-methoxyphenyl substituent, is the most effective (IC_{50}= 0.037 µM) among these derivatives. Additionally, molecular modeling studies (PDB ID= 4ASD) indicated that compound **32** formed H-bonds with Asp1046 and Glu885, akin to sorafenib, as well as an additional hydrogen bond interaction with Cys919 residues (Figure 29) [104].

In 2023, Zawal and colleagues designed and synthesized seventeen new 1,2,4-triazole-based hybrid molecules as VEGFR-2 inhibitors that could be utilized as antimycobacterial and anticancer agents. The inhibition studies were conducted for all the synthesized molecules against VEGFR-2 using Sorafenib (GI_{50}= 0.12 µM) as a reference. Compounds **33a**, **33b**, **33c**, **33d**, **33e**, **33f**, **34a**, **34b** and **34c** showed encouraging inhibition on VEGFR-2 (IC_{50}= 0.15 – 0.39 µM). The two most successful compounds were **33c** (GI_{50}= 0.15 µM), which carried 4-anisyl at the 5-position of the 1,2,4-triazole ring, and **34a** (GI_{50}= 0.21 µM), which had modest cytotoxicity against normal cells and substantial antiproliferative activity against malignant cells. High binding affinities of these compounds to the target enzymes (VEGFR-2 and Mtb InhA) were found by molecular modeling studies, which led to the development of 1,2,4-triazole analogues as effective antimycobacterial and antitumor medicines (Figure 30) [105].

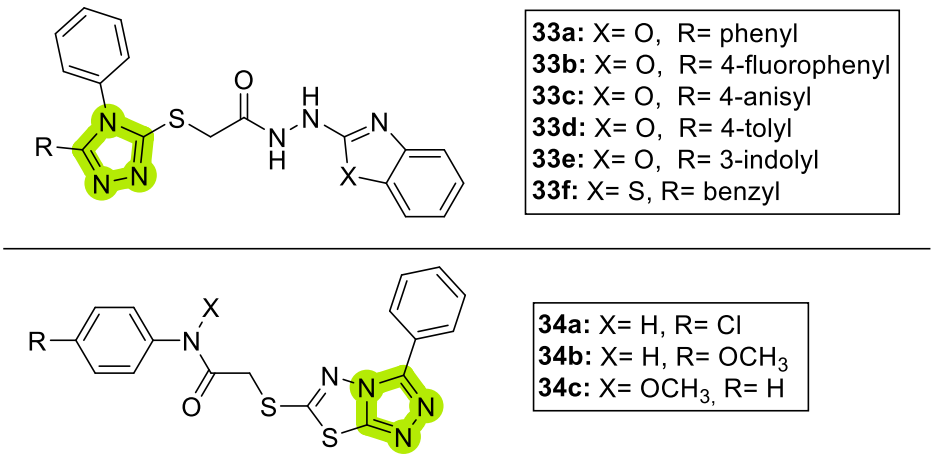

Figure 30.VEGFR-2 inhibitory anticancer compounds

In 2023, Othman et al. synthesized EGFR, VEGFR-2 and Topo II inhibitory anticancer compounds based on 1,2,3 triazole-benzimidazole. In this study, Gefitinib (IC_{50}= 0.052 mM) was used as reference for EGFR inhibition, Sorafenib (IC_{50}= 0.0482 mM) for VEGFR-2, and Doxorubicin (IC_{50}= 3.62 mM) for Topo II. HepG-2, HCT-116, MCF-7, and HeLa cancer cells were used to test the activity of the compounds. The **35a-h**

series, which has the carbothio(oxo)amide part as a longer connector and contains a 5-membered linking group, exhibited superior activity compared to the benzylidene derivatives **36a-g** containing a 4-membered linking group. The compound with the best activity is a carbothioamide derivative **35a**, which carries a 4-chlorophenyl residue and exhibited IC_{50} values of 0.086 µM for EGFR inhibition, 0.107 µM for VEGFR-2 inhibition and 2.52 µM for Topo II inhibition. In the **36a-g** series, compound **36g** stood out with inhibitory activities at the level of IC_{50}= 0.131 µM for EGFR, IC_{50}= 0.229 µM for VEGFR-2 and IC_{50}= 8.37 µM for Topo II. They also conducted molecular modeling and physicochemical studies to highlight the binding modes of active compounds (Figure 31) [106].

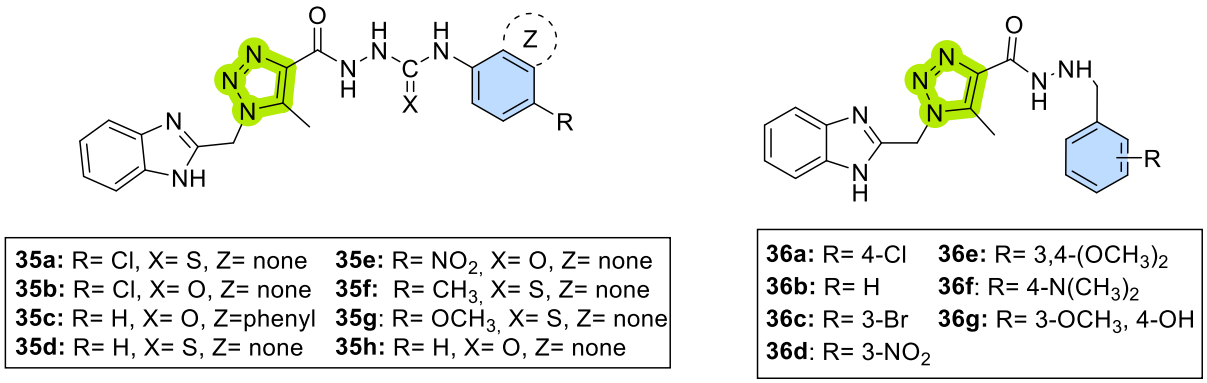

Figure 31. 1,2,3-Triazole-benzimidazole hybrids as antitumor compounds

3.6. EGFR Inhibitors

The epidermal growth factor receptor (EGFR) family is one of the most deeply assessed receptor tyrosine kinases due to its involvement in both normal human physiology and malignancies. [107]. The overexpression of EGFR is well-documented in solid tumors, making it a target for the successful treatment of many cancers such as head and neck cancer, lung cancer, breast cancer, and their metastasized types [108].

Mao and colleagues created 1,2,3-triazole-icotinib hybrids with the goal of treating non-small cell lung cancer (NSCLC) by targeting both wild-type and mutant EGFR types. The researchers tested the anticancer properties of these compounds on H460, H1975, H1299, A549 and PC-9 cell lines. They found that when compared to icotinib, which was the standard in cell lines other than the PC-9 cell line, many of the compounds showed superior activity (Figure 32) [109].

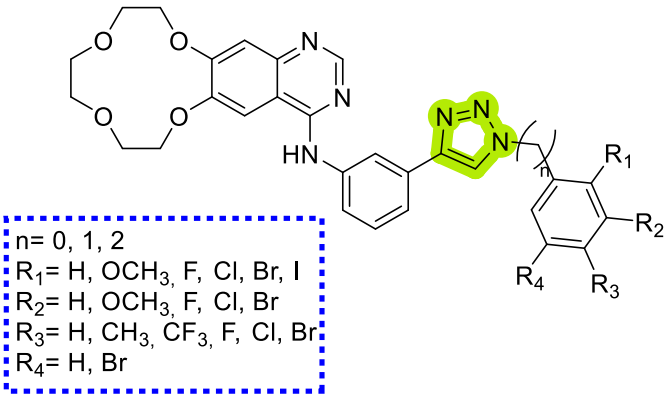

Figure 32. Hybrid compounds containing 1,2,3-triazole and icotinib

In 2020, Rezki et al. created 10 novel molecules by hybridizing 1,2,3-triazoles bearing benzenesulfonamide residues with isatin and benzothiazole rings. The anticancer activities of these compounds were studied in MCF7 (a breast cancer cell line), HCT116 (a human colorectal carcinoma cell lines) and HepG2 (a human liver carcinoma cell lines) cell lines. The inhibition of wild-type EGFR by these compounds was also evaluated and most of them showed superior inhibitory action in comparison with the standard erlotinib. Benzothiazole derivatives were found to be more effective than isatin derivatives. The most effective molecules were compounds **37a** and **37b** with IC_{50} rates of 103 and 104 nM (Figure 33) [23].

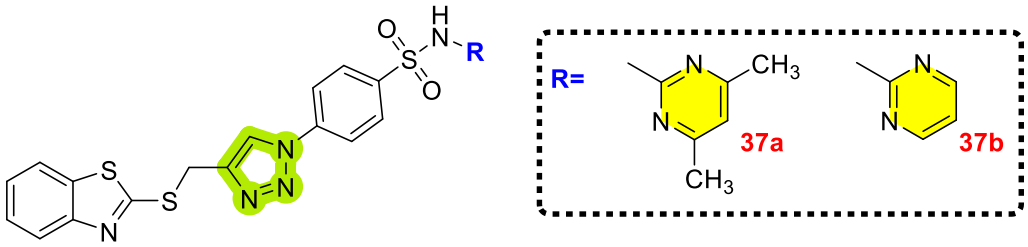

Figure 33. 1,2,3-Triazoles with isatin and benzothiazole rings

Ihmaid et al. examined the anticancer activities of the compounds obtained by substituting the 1,2,3 triazole and terminal lipophilic groups into the phthalimide active core against MCF7, HCT116 and HepG2 cell lines. Among all synthesized compounds, compound **38** stood out with its anticancer activities, with an IC_{50} of 0.12±1.22 µM in the HepG2 cell line. Compounds **39** and **40** also show good activity, with IC_{50} values of 0.22 ± 0.26 µM and 0.56±1.25 µM in the MCF7 cell line, respectively. In addition, the EGFR inhibitory activities of these compounds were compared with the reference erlotinib, and compound **39** showed superior inhibitory activity, compound **38** showed similar levels and compound **40** showed weaker inhibitory activity. Through detailed structure-activity relationships, it was determined that compound **39** has very good metabolic stability and a long duration of action (Figure 34) [110].

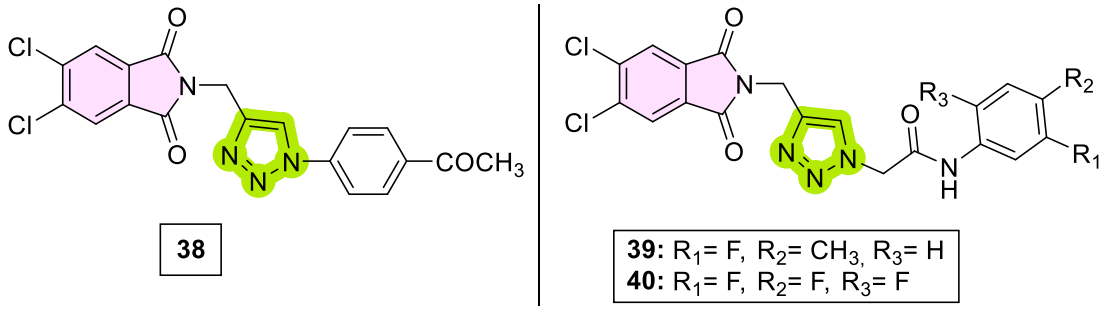

Figure 34. 1,2,3-Triazoles as EGFR inhibitor

3.7. c-Met Inhibitors

Hepatocyte growth factor receptor, also known as mesenchymal-epithelial transition factor (c-MET), a member of the receptor tyrosine kinase family, plays an essential role in diverse cellular processes through autophosphorylation of multiple tyrosine residues [111]. Overexpression of c-MET and/or its natural ligand hepatocyte growth factor (HGF) due to mutations is associated with the development of certain tumors, such as neck, breast, pancreas, bladder, kidney, ovary, prostate, and other cancer types [111-113]. c-Met inhibitors are categorized into two classes based on their binding modes to the receptor and structural characteristics: class I and class II. Class I inhibitors selectively bind to the ATP-binding pocket at the entry of the kinase domain of c-Met, while class II inhibitors can reach deep hydrophobic regions of the receptor [112, 113].

Structure-activity relationship studies of c-Met kinases have shown that class II inhibitors consist of four units: 1) a fused heterocycle, 2) phenyl derivatives, 3) five-atom linker or H-bond provider groups containing nitrogen atoms, and 4) phenyl derivatives. 1,2,3-Triazoles act as both five-atom linkers and H-bond providers. Damghani et al. designed and synthesized imidazo[1,2-α]pyridine hydrazones carrying 1,2,3-triazole targeting c-Met kinase. Among the synthesized compounds, compound **41** bearing a dichlorophenyl group on the triazole ring showed the best inhibitory effect with 51.3% at 25 µM concentration in the homogeneous time-resolved fluorescence (HTRF) assay. Also, compound **42,** containing a *tert*-butyl group on the triazole ring, showed 53.0% inhibition potency against c-Met kinase and demonstrated anticancer effects with IC_{50} values ranging from 3.0-15.1 µM against lung (EBC-1) and pancreatic cancer cells (AsPc-1, Suit-2 and Mia-PaCa-2) (Figure 35) [111].

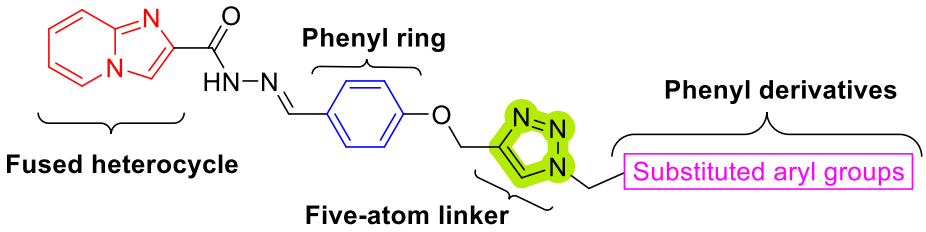

Figure 35. 1,2,3-triazole substitued imidazo[1,2-α]pyridine hydrazones

Liu et al. created and produced 4-phenoxypyridine derivatives as class II c-Met kinase inhibitors and examined their inhibitory activity. Imidazole-4-carboxamide and 4-methyl-5-oxo-4,5-dihydro-1,2,4-triazole-3-carboxamide groups were used as five-atom linkers. Eleven out of total twenty-six compounds were found to be effective below 1 µM concentration. Among of all compounds, compound **43** showed the best promising result to IC_{50} of 0.012 µM. The structure-activity relationship of this series has emphasized importance of five-atom linker group. They found that imidazole-4-carboxamides have better inhibitor activity than 1,2,4-triazole-3-carboxamides (Figure 36) [112].

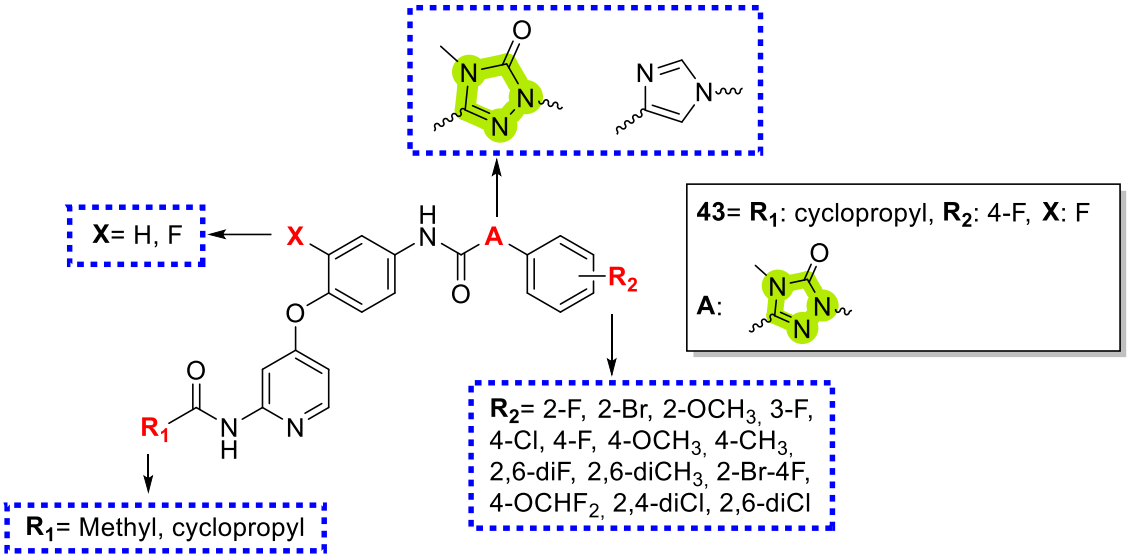

Figure 36. Phenoxypyridine derivatives containing 1,2,4-triazol rings

In recent years, 4-phenoxyquinoline and 4-aminoquinazoline cores are known to be kinase inhibitors. Cabozantinib carrying 4-phenoxyquinoline structure is a multi-kinase inhibitor and has been approved for use in metastatic medullary thyroid cancer, renal cell carcinoma and hepatocellular carcinoma. Based on this, Mortazavi et al. designed 4-(arylidenehydrazino)-quinazoline as c-Met kinase inhibitors. Aryl-substituted 1,2,3-triazole groups were used as five-atom linker with the ability to form H-bond interaction with the target enzyme. The novel compounds were evaluated for their c-Met kinase inhibitor activity with enzyme-based and cell-based assays and anticancer activity against AsPC-1, EBC-1 and MKN-45 cells as c-Met dependent cancer lines and also Mia-Paca-2, HT-29 and K562 cells. Additionally, molecular modeling was conducted to determine the binding modes of the complexes. Among this series, compound **44** and **45**, which have 4-methyl and 4-*tert*-butylphenyl groups respectively, were more hopeful compounds with the lowest IC_{50} rates against c-Met-dependent tumors. Molecular modeling studies found that two N atoms of the 1,2,3-triazole groups of compound **44** and **45** made H-bond interaction with Met1160 residues of c-Met kinase (PDB ID: 3LQ8). Also, their affinity energies were determined as − 10.88 and -10.89 kcal/mol for compound **44** and **45**, respectively (Figure 37) [114].

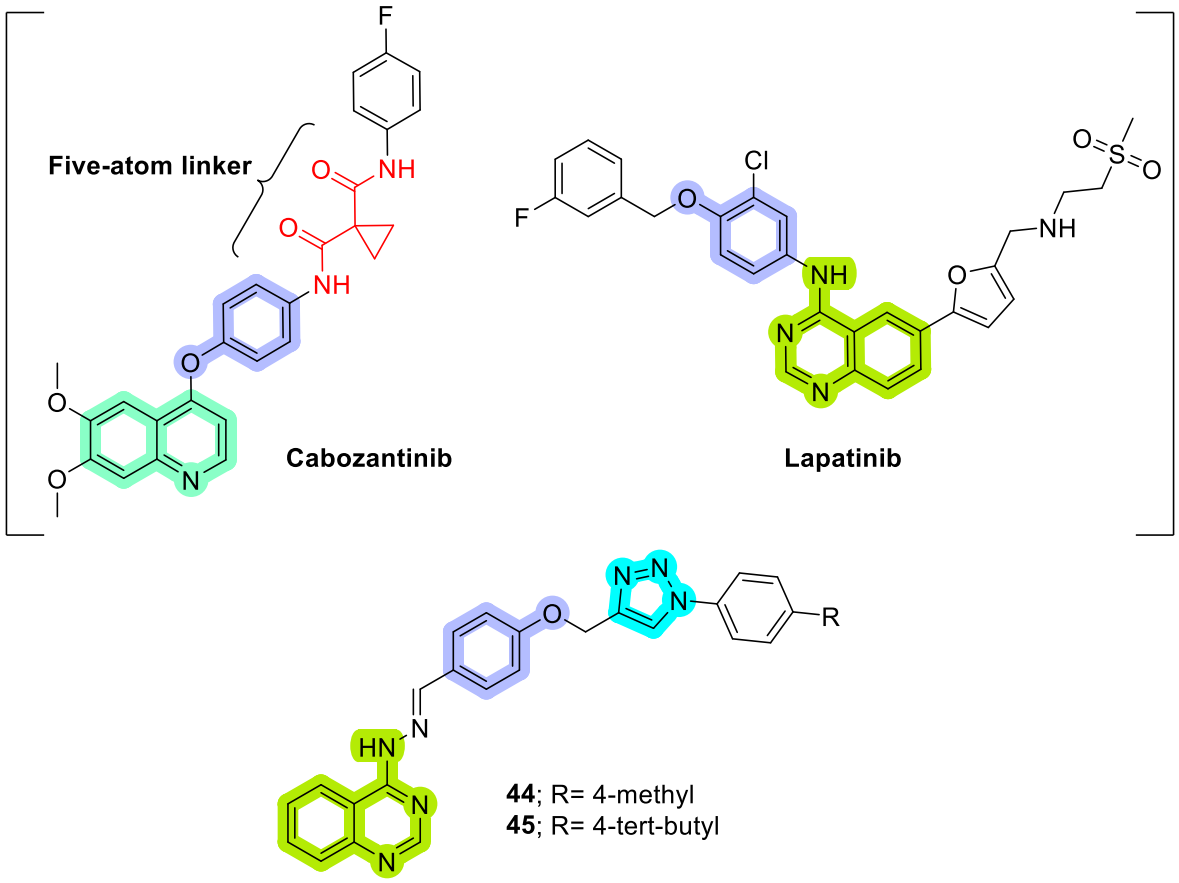

Figure 37. c-Met kinase inhibitor molecules

3.8. PARP Inhibitors

PARP (poly[ADP-ribose] polymerase) consists of 17 enzymes classified under the ART (ADP-ribosyl transferase) protein group. ART enzymes organize the transfer of ADP-ribose molecules from β-NAD+ (beta nicotinamide adenine dinucleotide) to form PAR (poly-ADP-ribose) units and covalently attach them to acceptor proteins via specific amino acid regions, called "PARylation". It was several cellular mechanisms, chromatin metabolism and apoptosis. PARP-1 is the most common and well-characterized type of this group and has a major role in the discovery of targeted antitumor drugs [115-117].

Li and colleagues synthesized hemoerythrina alkaloids with 1,2,3 triazole rings in 2020 as PARP-1 inhibitors. According to the results obtained from the antiproliferative activity of these compounds, they were evaluated against 4 cancer cell lines (A549, OVCAR-3, HCT-116, and MCF-7). The results showed that compounds bearing electron-withdrawing groups in the triazole-bonded phenyl ring displayed better antiproliferative effects than those with the electron-donating group. Among them, compound **46** containing the *o*-fluorophenyl substituent had optimum antiproliferative activity against A549 cells (IC_{50}= 1.89±0.23 µM) (Figure 38) [118].

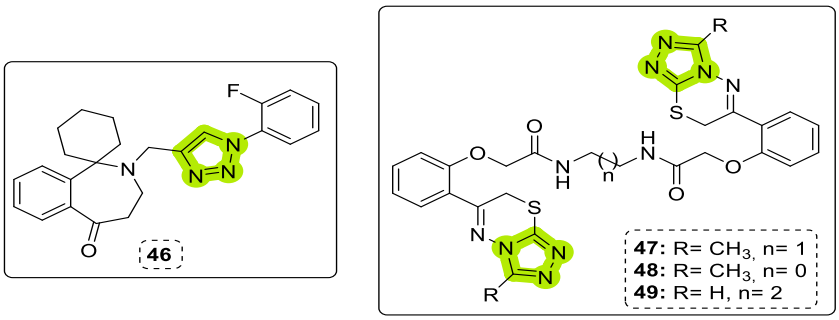

Figure 38. PARP-1 inhibitor 1,2,3 and 1,2,4-triazoles

In 2022, Thabet et al. synthesized bis(1,2,4-triazolo[3,4-b][1,3,4]thiadiazine) derivatives and evaluated their cytotoxicity and PARP-1 inhibitor activity. Among these compounds, compound **47**, **48**, and **49** exhibited IC_{50}= 0.41, 0.12, and 0.86 µM activity against the MDA-MB-231 cell line, and IC_{50}= 2.14, 1.31, and 5.31 µM activity in the MFC-7 cell line, respectively. Compound **48** showing the best activity was selected for PARP-1 inhibition and compared with Olaparib as the benchmark. According to the results obtained, compound **48** exhibited IC_{50}= 1.37 nM activity for PARP-1, while Olaparib showed activity with an IC_{50} of 1.49 nM. Additionally, molecular modeling studies was conducted to determine that compound **48** binds to the active site of PARP-1. Therefore, compound **48** can be considered as an effective anti-breast cancer agent (Figure 38) [119].

Othman et al. synthesized 1,2,3-triazole-chalcone hybrids for the treatment of leukemia. All produced combinations were tested for their cytotoxicity effects to 60 cancer cells using staurosporin as reference. Four out of all compounds (**50**, **51**, **52**, and **53**) exhibited significant anticancer properties against RPMI-8226 cells at low micromolar concentrations. Compound **51**, which contains a nitro group in the ortho position, stood out with an IC_{50}= 3.17 µM value. In molecular modeling studies conducted on the PARP-1 enzyme (PDB code: 4BJC), it was determined that these four compounds bind to the enzyme by establishing H-bonding and π-π stacking interactions (Figure 39) [120].

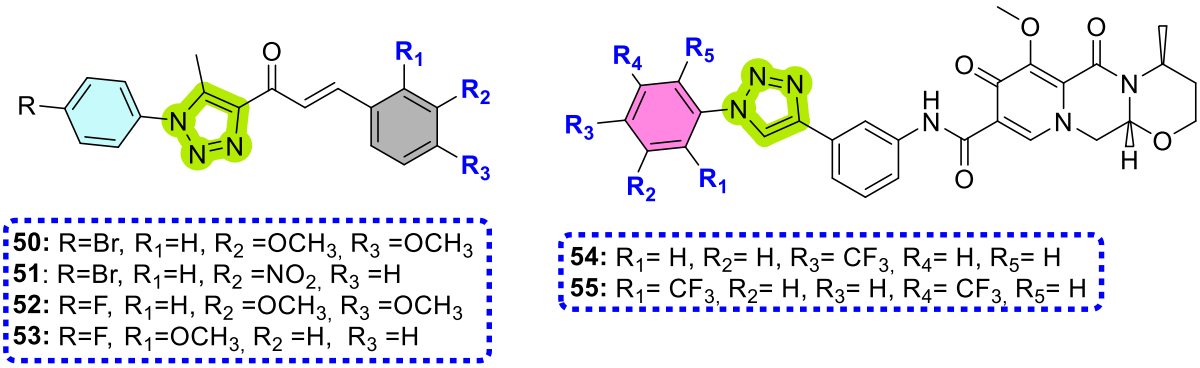

Figure 39. 1,2,3-Triazole hybrids as PARP inhibitors

In 2023, Zhou et al. developed the PARP inhibitor mavitegravir-1,2,3-triazole hybrids for the treatment of prostate cancer. DNA damage detection and molecular docking were conducted to understand the mechanisms of action of compounds showing anticancer activity in PC3 and DU145 prostate cancer cells. It was determined that these compounds exhibited anticancer activity by causing DNA damage through binding to the PARP enzyme. The most effective compounds **54** and **55** showed IC_{50} values of 8.08 and 5.32 µM, against PC3, respectively, and IC_{50} values of 5.08 µM and 5.519 µM against DU145, respectively, (Figure 39) [121].

3.9. IDO and TDO Inhibitors

More than 95% of tryptophan in the body is converted to kynurenine metabolites such as *N*-formylkynurenine (NFK). Enzymes such as indoleamine-2,3-dioxygenase 1 (IDO1), indoleamine-2,3-dioxygenase 2 (IDO2) and tryptophan 2,3-dioxygenase (TDO) play a role in this transformation [122]. In recent year, studies show that IDO and TDO enzymes are overexpressed in the tumor microenvironment. For this reason, agents that inhibit this enzyme appear as a new approach in anticancer treatment that attracts the attention of researchers. [123, 124].

In 2020, 1-phenyl-1*H*-naphtho[2,3-d][1,2,3]triazole-4,9-dione derivatives were designed and synthesized as both IDO and TDO inhibitors. According to the structure-activity relationships obtained from enzyme inhibition experiments, it was determined that the most effective compound was compound **56**, which contains fluorine atom in 6-position of naphtho[2,3-d][1,2,3]triazole ring. The activity of the compound, which was also examined in the *in vivo* LL2 and Hepa 1-6 allotransplant models, was determined to have less inhibition than expected in in vivo experiments due to the solubility problem of the compound with inhibitory effect at nanomolar level (Figure 40) [125].

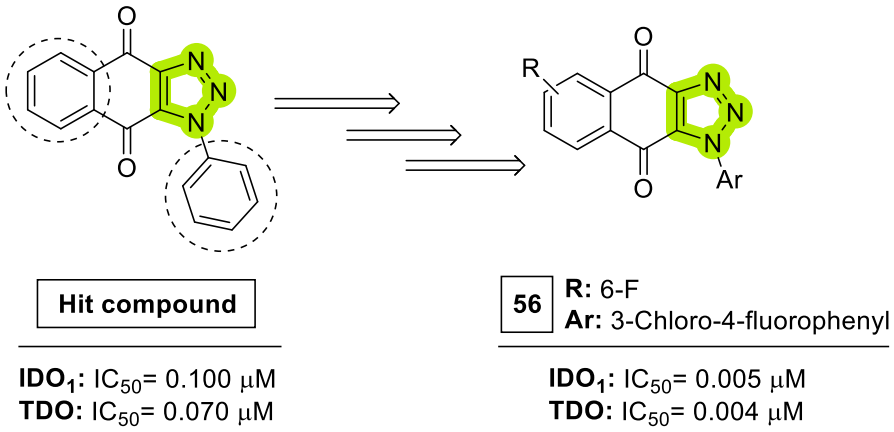

Figure 40. IDO-TDO inhibitors 1,2,3-triazoles by Pan et al.

Mao et al. created icotinib-1,2,3-triazole hybrids with IDO1 inhibitor effect. They conducted the IDO1 inhibition studies of the twenty-two molecules they synthesized. It has been determined that most of these molecules show improved inhibitory activity according to the reference icotinib. In structure-activity studies, it has been stated that derivatives bearing a benzyl residue in the triazole ring are more effective than phenyl derivatives. Molecular modeling studies of the compounds **57** and **58**, which showed the best inhibitory activity, revealed that the triazole ring is located on the upper part of the HEM in the enzyme and tends to generate a coordination bond between the nitrogen atom of triazoles and the Fe atom of the HEM, as well as π-π stacking with Phe163 (Figure 41) [124].

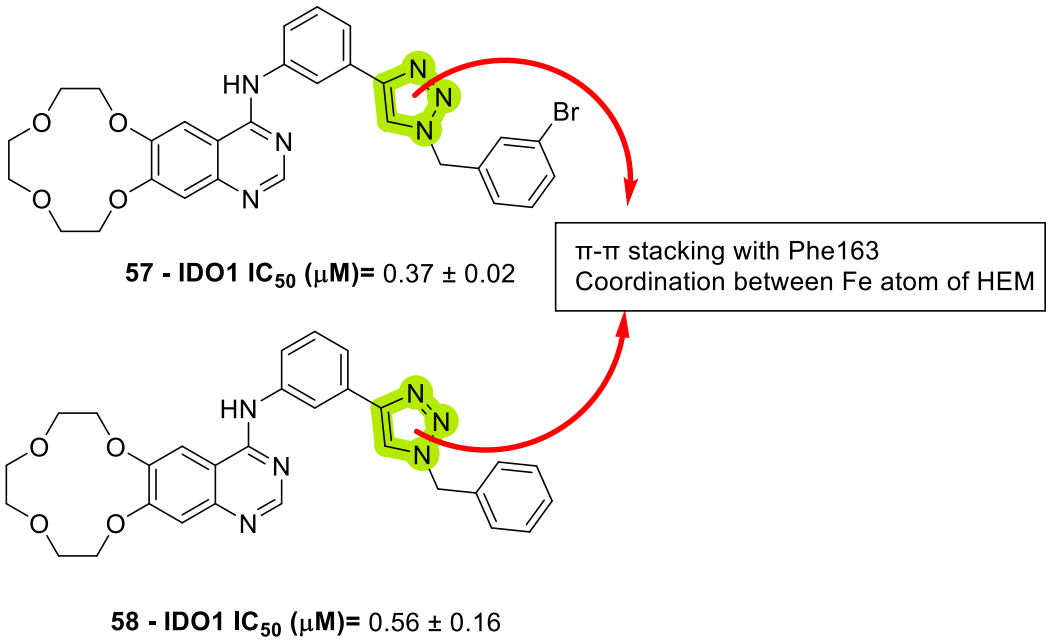

Figure 41. Icotinib-1,2,3-triazole hybrids with IDO1 inhibitor effect

Based on erlotinib, Hou et al. developed a number of IDO1 inhibitor anticancer molecules. In this study, the ethinyl group of erlotinib was converted into substituted 1,2,3-triazoles and the IDO1 inhibition studies of the molecules were conducted by *in vitro* experiments. Accordingly, the most active compound was compound **59**, which carries a 3,5-dibromobenzyl residue in the triazole ring. This molecule's IC_{50} value was found to be 0.59 µM, whereas the reference epacadostat has an IC_{50} value of 0.097 µM. Additionally, the effectiveness of compound **59** was examined *in vivo* in the IDO1-overexpressing murine 4T1 breast model, and as a result, significant inhibitory activity was obtained, comparable to erlotinib and epacadostat (Figure 42) [126].

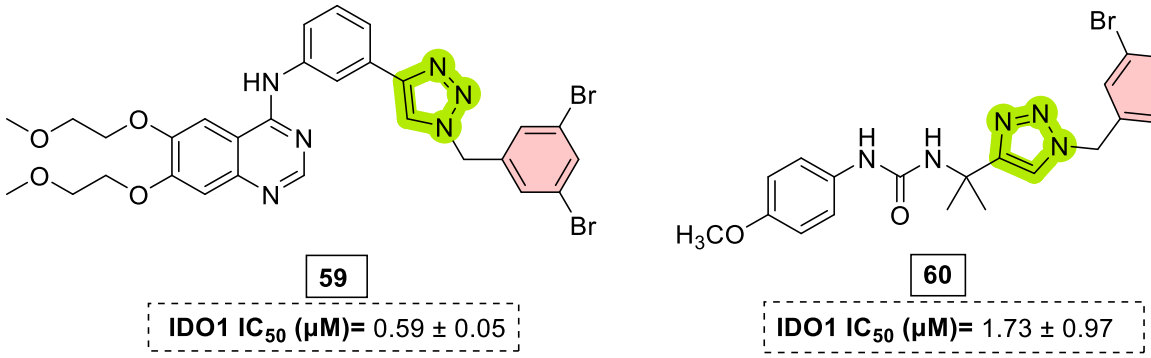

Figure 42. IDO1 inhibitor anticancer compounds

In 2023, Hou et al. designed 1,2,3-triazoles bearing *N*,*N*-disubstituted ureas to inhibit selectively only IDO1 enzyme. Among the ten new compounds they synthesized, the most effective inhibitor in IDO1 inhibition experiments was compound **60** (1-(2-(1-(3-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)-3-(4-methoxyphenyl)urea. In docking studies, it was determined that this compound bound to the enzyme with a docking score of -6.876 kcal/mol, and since the triazole ring of the compound **60** was adjacent to HEM in the structure of the enzyme, it was more prone to coordination with the Fe atom in the center of HEM (Figure 42) [123].

4. CONCLUSION

Cancer, the world's second leading cause of mortality after cardiovascular disease, is an age-related disease with a complex treatment process. In recent years, the development of targeted smart therapies has emerged as a promising approach. These therapies selectively induce a cytotoxic effect on tumor cells by inhibiting specific enzymes found in cancer cells and subsequently leading to a reduction in toxicity for healthy cells. Molecules bearing the 1,2,3 and 1,2,4-triazole ring, an important heterocyclic ring, exhibit a wide range of pharmacological activities, including anti-HIV, anti-cancer and antimicrobial effects. This review presents previously designed and synthesized examples of compounds consisting of hybrids of 1,2,3 and 1,2,4 triazole rings with other anticancer pharmacophore groups. These derivatives have exhibited anticancer activities through the inhibition of enzymes such as hCA, EGFR, VEGFR, PARP, thymidylate synthase, tubulin and aromatase. The review also compiles potential anticancer compounds that have shown the best activity and lowest toxicity based on *in vitro* and *in vivo* tests conducted within the last five years. This information will be beneficial in the design and synthesis of new drugs with anticancer activity in the future.

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