ANTICANCER EFFECT OF 1,2,3-TRIAZOLE-CONTAINING COMPOUNDS.

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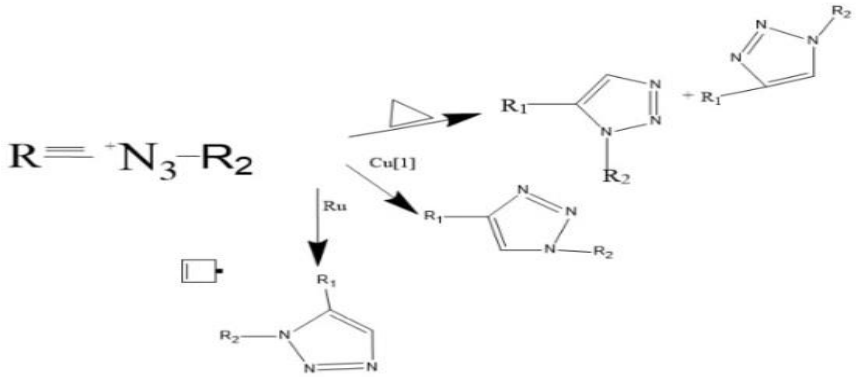
Abstract. Natural compounds and derivatives of natural compounds containing 1,2,3-Triazole are widely used in cancer treatment in combination therapy. Although the 1,2,3-triazole moiety does not occur in nature, the production of "1,2,3-triazole-natural compound" hybrids has become active in medicinal chemistry and has attracted interest as an anticancer candidate.

Key words: melampomagnolide B-triazole, apoptosis, transwell assay, 1,2,3-triazoles, epithelial proteins, snail, zonula occludens-1 (ZO-1), E-cadherin.

INTRODUCTION. In the last fifteen years, the chemistry and biology of azole derivatives have been studied as very popular topics. Uzbek scientist Kh. Bozorov, together with Chinese scientists, examined various published reports from the Scopus database (2018) and found that among azoles (using the keywords “imidazole”, “pyrazole”, “triazole”, “tetrazole” and “pentazole”), triazole motifs are the most studied, which are derivatives of 1,2,3-triazole compounds[1]. One of the most widely used reactions is the 1,3-dipolar cycloaddition reaction between azides and alkynes catalyzed by copper(I) salts to form the 1,2,3-triazole moiety[2]. The triazole moiety is often found as a candidate in clinical drugs or medical preparations due to its high degree of reliability, complete specificity and biocompatibility. Although the 1,2,3-triazole moiety does not exist in nature, it has attracted interest as an anticancer candidate.

LITERATURE ANALYSIS. Huysgen, who studied the synthesis of 1,2,3-triazoles in depth, introduced the 1,3-dipolar cycloaddition of 1,2,3-triazoles [4], which gave 1,4- and 1,5-substituted triazole regioisomers upon the reaction of an alkyne with an azide. Although the thermally induced Huysgen [3+2]-cycloalkylation reaction of alkynes with azides to form 1,2,3-triazoles has been known for over a century, these compounds have only become popular in the last two decades due to the remarkable copper-catalyzed regioselective synthesis reaction developed by the groups of Meldal and Sharpless (Scheme 1) [3.]



Scheme 1. 1,3-dipolar cycloaddition between azides and alkynes.

Recently, 1,2,3-triazole derivatives have become important compounds with unique chemical and physical properties and are widely used as drugs in medicine. In recent years, more and more attention has been paid to anti-cancer treatment in medicine and new drug products have been created. In particular, heterocyclic azoles, including 1,2,3-triazole derivatives, are one of the most effective anti-cancer agents and have been widely used in medicine against various cancer cells. In particular, Chinese scientists Ding Y, Guo H, Ge W, et al. reported in their article “Synthesis of

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melampomagnolide B-triazole conjugates based on copper (I) oxide nanoparticles catalyzed click chemistry and their anti-cancer activity" on the chemically catalyzed synthesis of a series of MMB-triazole conjugates on copper (I) oxide nanoparticles and their evaluation of their anti-cancer activity. Another article by Ke Y, Liang J-J, Hou R-J et al., "Synthesis and Biological Evaluation of New Jiyuan Oridonin A-1,2,3-triazole-azole Derivatives as Antiproliferative Agents" (2018), reported that Jiyuan Oridonin A-1,2,3-triazole-azole derivatives can be used as good anticancer agents.

RESEARCH METHODOLOGY. The article discusses the evaluation of the anticancer activity of 1,2,3-triazole derivatives, as reported in the scientific literature. The most active 1,2,3-triazole derivatives are characterized by their significant efficacy in inducing apoptosis, inhibiting the proliferation and migration of cancer cells. It was studied and analyzed that triazole derivatives containing 1,2,3-triazole are useful heterocyclic moieties that affect cytotoxicity.

TAHLILLAR VA NATIJALAR. Derivatives of natural compounds containing 1,2,3-triazole are widely used in combination therapy for cancer treatment. Although the 1,2,3-triazole moiety does not occur in nature, the production of "1,2,3-triazole-natural compound" derivatives has been actively pursued in the pharmaceutical industry and has attracted interest as anticancer candidates.[1.] This trend was further strengthened when Ding et al. reported the Cu2O nanoparticle-catalyzed "click" reaction involved in the synthesis of melampomagnolide B-triazole conjugates and their high anticancer activity.[5.]. The most potent derivative (HCT116, IC50 = 0.43 μM), which was almost 11.5 times more potent than melampomagnolide B (HCT116, IC50 = 4.93 μM), 1 (Figure 1) had no effect on normal cells (FHC, HPDE6-C).), and significantly induced apoptosis [Apoptosis is a process of programmed cell death (self-destruction). According to it, each cell, after completing its life cycle, must die and be replaced by a new one.], as well as inhibited [slowed down] the proliferation and migration of cancer cells

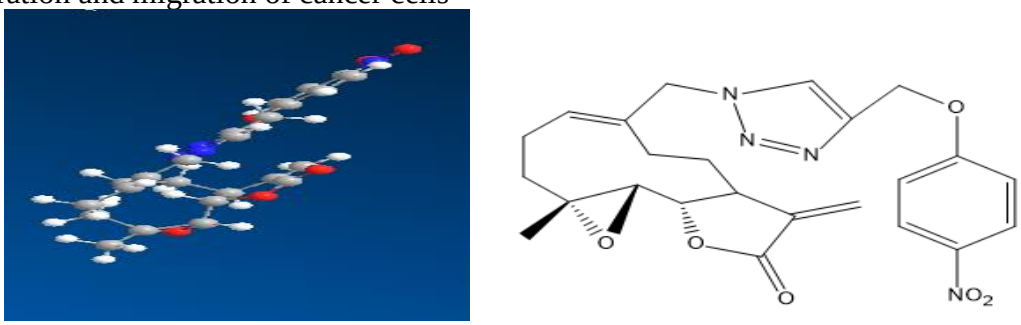

Figure 1. (HCT116, IC_{50} = 0,43 mkM)

The effect of HCT116 on cell migration was measured using a Transwell assay, and the number of migrated cells was significantly reduced after 48 hours of exposure to melampomagnolide B-triazole 1. In addition, the expression of epithelial proteins such as snail, zonula occludens-1 (ZO-1), and E-cadherin, as well as mesenchymal marker proteins such as vimentin, zinc finger E-box binding homeobox 1 (ZEB1), and N-cadherin 1, was effectively reduced after treatment with its derivatives, confirming that the triazole compound 1 inhibited and could affect the migration of HCT116 cells.[1]

Another melampomagnolide B-triazole conjugate, compound 2 (Figure 2), is a leukemia (GI_{50} = 0,10-0,23 mkM), colon (GI_{50} = 0,14-1,17 mkM), melanoma (GI50 = 0,15-1.47). μM), kidney (GI_{50} = 0,02–0,70 μM), ovary (GI_{50} = 0,15–1,86 μM), prostate (GI_{50} = 0,72–0,83 μM) and chest (GI_{50} = 0,17–1,03 mkM) It is an effective and potent drug against several cancer cell lines, including basal cell carcinoma.[6.] Further studies have shown that the triazole compound 2 is a potent inhibitor of nuclear factor (NF)-κB and cell proliferation of the TMD-231 (MDA-MB-231) cell line. In addition, treatment of TMD-231 cells with the 2 derivative reduced DNA binding activity, increased basal

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IκBα levels by inhibiting NF-κB kinase (IKK)-β inhibitor-mediated phosphorylation of NF-κB, and significantly increased NF-κBα activation and IκBα turnover.

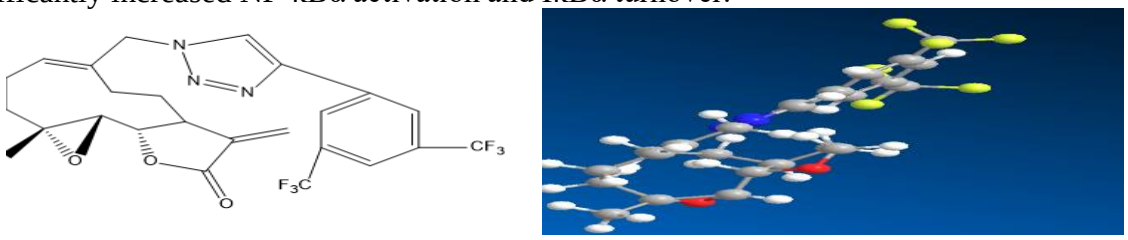

Figure 2.RXF 383(GI_{50}=0,02 mkM)

Yu et al. [7.] synthesized a series of 1,2,3-triazolo-dihydroartemisinin coumarin hybrids and tested their anticancer potential in two types of cancer cells. These hybrids showed moderate cytotoxicity against HT-29 and MDA-MB-231 cell lines, especially under hypoxic conditions. However, the hybrid was more active in HT-29 cells than in MDA-MB-231 cells (normoxic IC_{50} = 1.5 μM and hypoxic IC_{50} = 0.01 μM, respectively) (Figure 3). Furthermore, this hybrid trapped HT-29 cells in the G0/G1 phase, slowed tumor cell migration, and significantly reduced mitochondrial membrane potential, which led to apoptosis of HT-29 cells.

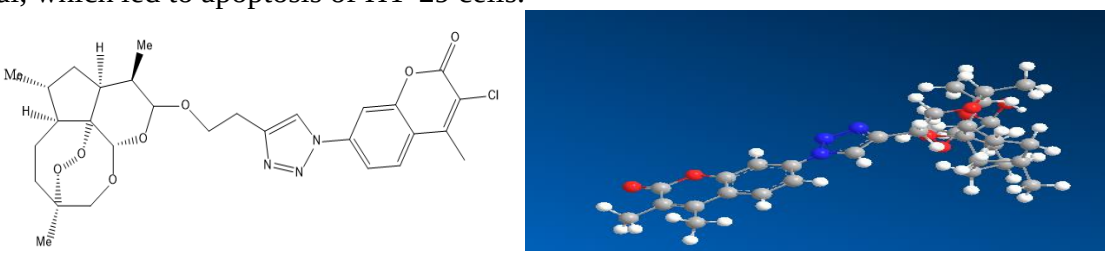

Figure-3. HT-29 (normoxic IC_{50} = 1,5 mkM and hypoxic IC_{50} = 0,01 mkM)

The 1,2,3-triazole-containing diterpenoid moiety of Jiyuan Oridonin A was tested for its antiproliferative properties.[8.] The triazole ring-containing derivative 4 (Figure 4) also showed good antiproliferative [cell growth inhibitory] activity against other tested cell lines with IC_{50} values of 2.7 μM against the Eca109 cell line and 1.5 μM against the MCF-7 breast cancer cell line. In addition, the IC_{50} value of 4 was also tested in MGC-803 (0.6 μM) and PC-3 (0.6 μM) cancer cells. Cellular mechanism studies showed that compound 4 arrested the cell cycle in G1 phase and induced potent apoptosis of the SMMC-7721 cell line; it also inhibited colony migration and formation in these cells via the Wnt signaling pathway.

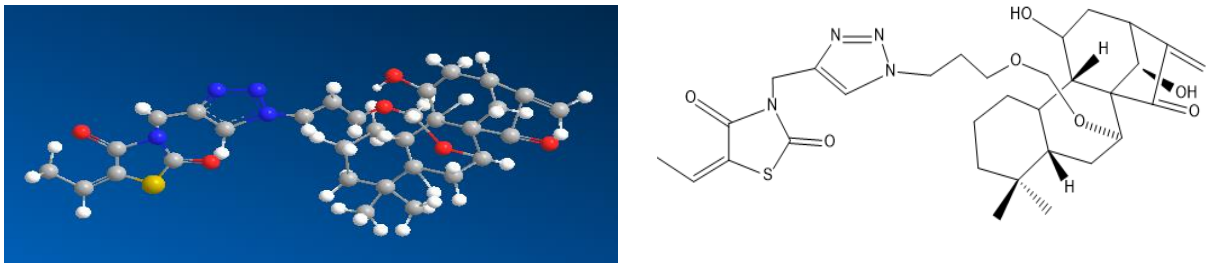

Figure 4.MCF-7 ,IC_{50} 1,5= mkM

Two more ent-kaurene diterpenoid derivatives were tested for their antiproliferative properties in four cancer cell lines (Eca109, EC9706, SMMC7721 and MCF-7 cells). Compound 5 (Figure 5) showed high anticancer potential in all tested cell lines (IC50 values of 2.70, 5.04, 4.44 and 4.76 μM against Eca109, EC9706, SMMC7721 and MCF-7, respectively). [9.]The positive control of oridonin confirmed that triazole derivatives containing 1,2,3-triazole are useful heterocyclic moieties that exert cytotoxicity.

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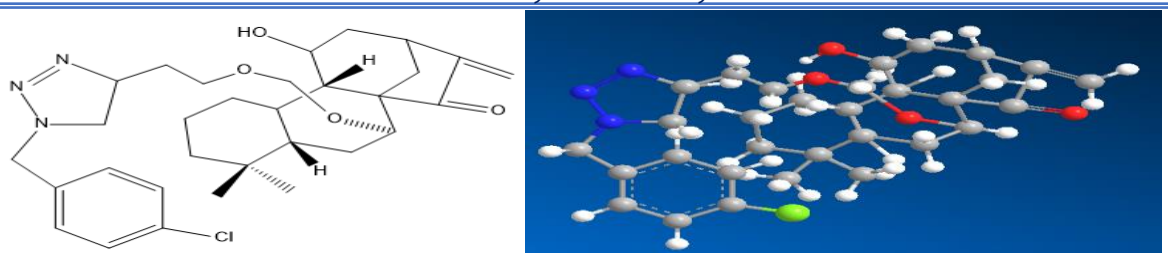

Figure 5. Eca109, EC 9706, SMMC 7721 and MCF-7 cells (IC_{50}= 2.70, 5.04, 4,44 and 4.76 mkM)

Anticancer mechanism studies showed that reactive oxygen species (ROS) 5 increased in cancer cell lines, leading to a decrease in mitochondrial membrane potential and the release of cytochrome C into the cytoplasm. Furthermore, this effect was further enhanced and activated by caspase-9 to induce apoptosis.

Wei et al. synthesized a series of 1,2,3-triazole-containing albiziabioside A derivatives and evaluated their anticancer potential in vitro and in vivo. [10.] Targeted lead 6 (Figure 6) showed significant activity in HCT116 cells (IC50 = 5.19 μM). Furthermore, this triterpene saponin triazole derivative showed favorable selectivity and was effective in multidrug-resistant (MDR) cancer cells, where it induced ferroptosis [Ferroptosis is a type of programmed oxidative necrotic cell death, the hallmark of which is iron-dependent lipid peroxidation.] and apoptosis as a p53 activator via the mitochondrial pathway.

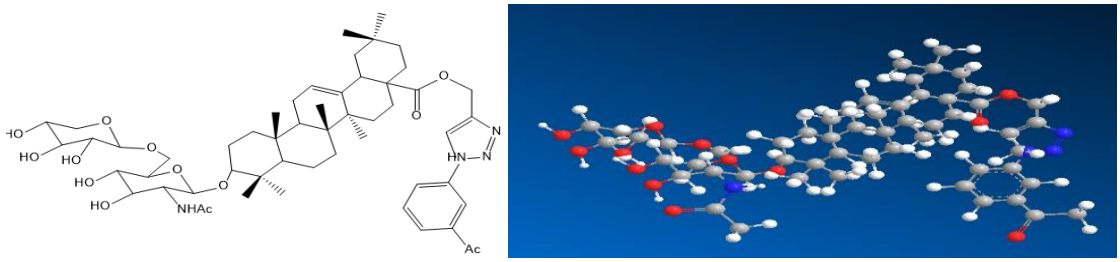

Figure 6. HCT116. (IC_{50} = 5,19 mkM).

In vivo studies showed that the introduction of a triazole fragment into the triterpene skeleton significantly slowed tumor formation without causing toxicity to normal cells.

CONCLUSION. In conclusion, we believe that the examples presented in this review play an important role in pharmaceutical chemistry within the framework of click chemistry. Although this review is not exhaustive, only selected examples have been described for the anticancer applications of 1,2,3-triazole derivatives in medicinal chemistry. The collection of compounds that have been synthesized but not discussed in this work is still very large.

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