ANTICANCER PROPERTIES OF 1,2,4-TRIAZOLES

Onur AKYILDIRIM
Kafkas University

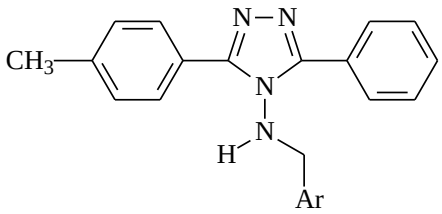
Murat BEYTUR
Kafkas University

Anticancer Properties of 1,2,4-Triazoles

Cancer, one of the most serious diseases threatening human life, is characterized by the uncontrolled division of cells. There are many different types of cancer. There are claims that oxidative stress plays a crucial role in tissue damage related to various diseases such as cancer (Harmankaya et al., 2020, 2021; Harmankaya & Harmankaya, 2022). Scientists are doing various studies on this disease intensively.

Compounds bearing 1,2,4-triazole ring generally show many biological activities. In this section, the anticancer properties of various types of compounds with 1,2,4-triazole ring are discussed.

In a study by Bekircan et al., the anticancer activities of four compounds containing 1,2,4-triazole ring were investigated. Compound of 2,6-$Cl_2C_6H_3$ derivatived was found to exhibit higher anticancer activity in preliminary tests with breast cancer, non-small cell lung cancer and CNS cancer cancer cell lines. This compound has been reported to exhibit significant anticancer potential in screening tests with 60 human cancer cell lines (Bekircan et al., 2006).



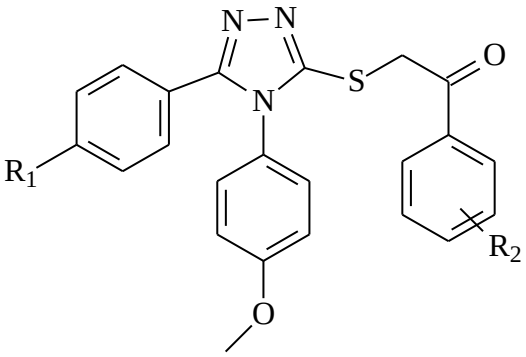
Ar= 2-OHC_6H_4, 2,4-$Cl_2C_6H_3$, 2,6-$Cl_2C_6H_3$, 3,4,5-$(OCH_3)_3C_6H_2$

Figure 1 Structure of the compounds (Bekircan et al., 2006).

In a 2011 study, a series of indolyl-1,2,4-triazoles were synthesized as anticancer agents and the cytotoxic effects of these compounds were investigated in six human cancer cell lines using 3-(4,5-dimethyldiazol-2-yl)-2,5-diphenyltetrazolium-bromide. The synthesized indolyl-1,2,4-triazole compounds have been reported to be investigated against prostate, breast and pancreatic cancer cell lines. Compounds 3-(3′,4′,5′-trimethoxyphenyl)-5-(*N*-methyl-3′-indolyl)-1,2,4-triazole and 3-(4′-piperidinyl-5-(*N*-methyl-3′-indolyl)-1,2,4-triazole carrying 3,4,5-trimethoxyphenyl and 4-piperidinyl substituents were found to have significant inhibitory effects against the cancer cell lines studied (Kumar et al., 2011).

The effect of some 1,2,4-triazole derivatives on human colon cancer appears to have been studied *in vitro* and *in vivo* in rats. According to this study, it was determined that 1,2,4-triazole derivatives have antitumor activity (Parlak et al., 2019).

A very recent study was conducted on the antiproliferative effects of 3-alkylsulfanyl-1,2,4-triazole derivatives on three human cancer cell lines, including breast cancer, lung cancer and ovarian cancer. These studied compounds were found to show moderate to promising antiproliferative activities against different cancer cell lines (Ghanaat et al., 2020).



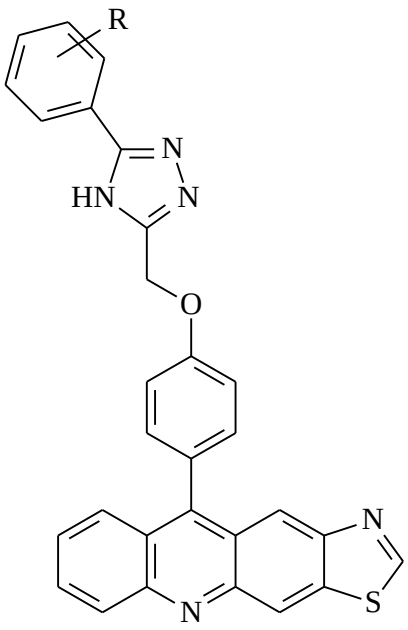
R_1= H, 3,4,5-$(OMe)_3$
R_2= H, 3,4,5-$(OMe)_3$, 4-Cl

Figure 2. 3-Alkylsulfanyl-1,2,4-triazole derivatives (Ghanaat et al., 2020).

A recent study investigated the anticancer activity of a series of novel (S)-Naproxen derivatives carrying a thiosemicarbazide/1,2,4-triazole moiety against human breast cancer cell lines (Han et al., 2022).

The antitumoral activity of 1,2,4-triazole D-ribose derivatives against T cell lymphoma cell line was investigated. Structures containing 1,2,4-triazolic ring attached to the carbohydrate moiety by sulfur have been reported in the literature to exhibit moderate anti-proliferative activity (Avanzo et al., 2012).

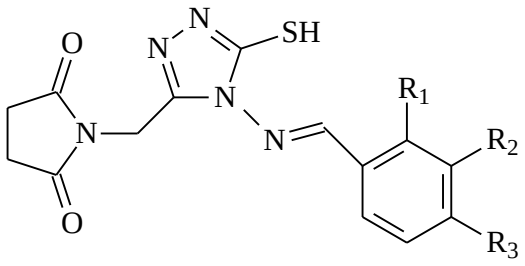
A study appears to have been made on a new series of fused acridines containing 1,2,4-triazole derivatives. All these derivatives were studied for their anticancer activities against four human cancer cell lines, including lung, breast, melanoma and colon cancers. Among these compounds, compounds bearing 3,4,5-trimethoxy, 4-chloro and 4-trifluoromethyl groups in the para position of the phenyl ring were found to exhibit the strongest anticancer activity against these four cancer cell lines (Mahanti et al., 2019).



R= H, 4-methyl, 4-methoxy, 3,4,5-trimethoxy, 4-bromo, 4-chloro, 4-fluoro, 4-trifluoromethyl, 4-nitro, 4-cyano

Figure 3. Series of fused acridine containing 1,2,4-triazole derivatives (Mahanti et al., 2019).

In a study conducted in 2017, 1,2,4-triazole-derived Schiff base and their complexes were investigated for their anticancer activities in breast cancer cell lines (Deodware et al., 2017).
It has been reported that 1,2,4-triazole derived compounds have been studied for anticancer activity against human breast cancer cell line and human cervical cancer cell line. These compounds were found to exhibit cytotoxicity to all cell lines studied (Mahar et al., 2020).



R_1= H, OH, Cl
R_2= H, OCH_3, NO_2
R_3= H, $N(CH_3)_2$, $N(C_2H_5)_2$, OCH_3, NO_2, Cl

Figure 4. *(E)*-1-((4-(arylideneamino)-5-mercapto-*4H*-1,2,4-triazol-3-yl)methyl)pyrrolidine-2,5-diones (Mahar et al., 2020).

The anticancer activity of compounds containing 4,5-diphenyloxazol-1,2,4-triazole derivatives against prostate lung cancer cell lines was investigated. Some of these have been reported to be considered promising precursor molecules for cancer therapy (Maddali et al., 2021).

In a study conducted by Parlak in 2018, the anticancer activity of [(4-substituted-5-pyridin-4yl-4*H*-1,2,4-triazol-3-yl)thio] acetic acid derivatives was investigated. These compounds have been investigated *in vitro* on human breast cancer and murine leukemia cells. It has been reported that the compounds tested in the study may have anticancer activity in different cancer series under *in vitro* conditions (Parlak, 2018).

In a study by Luo et al., 4-(3-(naphthalen-1-yl)-1-phenyl-1*H*-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-diene-3,8-dione compound has been reported that has significant *in vitro* cytotoxic activity. It has also been found that this compound suppresses breast cancer tumor growth *in vivo*. These results indicate 4-(3-(naphthalen-1-yl)-1-phenyl-1*H*-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-diene-3,8-dione compound could be a potential anticancer agent (Luo et al., 2021).

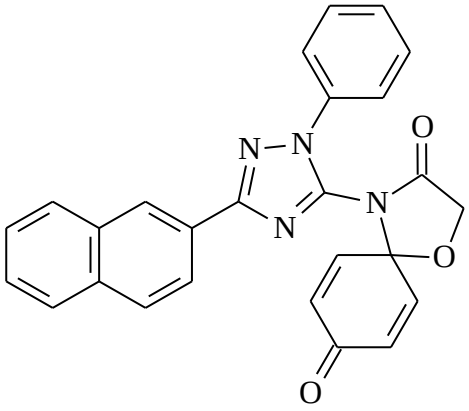
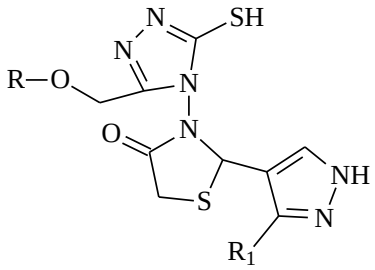


Figure 5. 4-(3-(Naphthalen-1-yl)-1-phenyl-1*H*-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-diene-3,8-dione compound (Luo et al., 2021).

Compounds composed of ligands Zn^{2+}, Cd^{2+} and UO_2^{2+} with a 1,2,4-triazol ring were investigated in vitro against human hepato Carcinoma (Gaber et al., 2018).

8-substituted-[(1,2,4-triazol-3-yl)methoxy]quinoline derivatives have been found to exhibit antitumor activity. The presence of dihydro-1,2,4-triazolyl moiety in the structure shows that it positively affects the interaction of molecules with biological targets (Rashad et al., 2010).

Some of 2-(3-substituted-1*H*-pyrazol-4-yl)-3-(3-substituted-5-sulfanyl-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-ones have been reported to show anticancer activity in human breast cancer cells in a dose-dependent manner. 2-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)-3-(3-mercapto-5-(o-tolyloxymethyl)-4*H*-1,2,4-triazol-4-yl)thiazolidin-4-one compound has been determined that the presence of chlorine in the ortho position and a methyl group in the significantly increases the anticancer activity of this compound (Isloor et al., 2013).

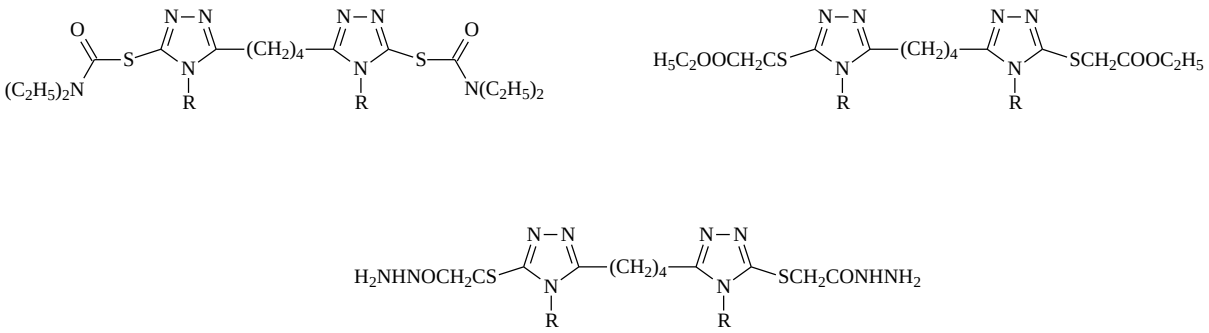


R= Phenyl, 2-methylphenyl, 4-methylphenyl, 1-naphthyl, 2-naphthyl

R_1= 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl

Figure 6. 2-(3-substituted-1*H*-pyrazol-4-yl)-3-(3-substituted-5-sulfanyl-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-ones (Isloor et al., 2013).

The *in vitro* cytotoxicity of 1,4-bis(4-substituted-5-mercapto-1,2,4-triazol-3-yl)butane derivatives was investigated. These compounds were studied for their *in vitro* cytotoxicity against three human cell lines of lung carcinoma, colon adenocarcinoma and breast cancer. As a result, it was determined that the compounds carrying *p*-tolyl and *p*-ethoxy phenyl groups as substituted groups showed more activity than other compounds (Purohit & Mayur, 2012).



R= Phenyl, *p*-tolyl, *m*-tolyl, *p*-ethoxy phenyl, cyclohexyl, *n*-butyl

Figure 7. 1,4-bis(4-substituted-5-mercapto-1,2,4-triazol-3-yl)butane derivatives (Purohit & Mayur, 2012).

Antitumor activities of *N*-substituted amides of 3-(3-ethylthio-1,2,4-triazol-5-yl)propenoic acid compounds were investigated. It was evaluated for their anticancer activities against two cancer cell lines, the human lung cancer cell line and the human breast carcinoma cell line (Pachuta-Stec et al., 2009).

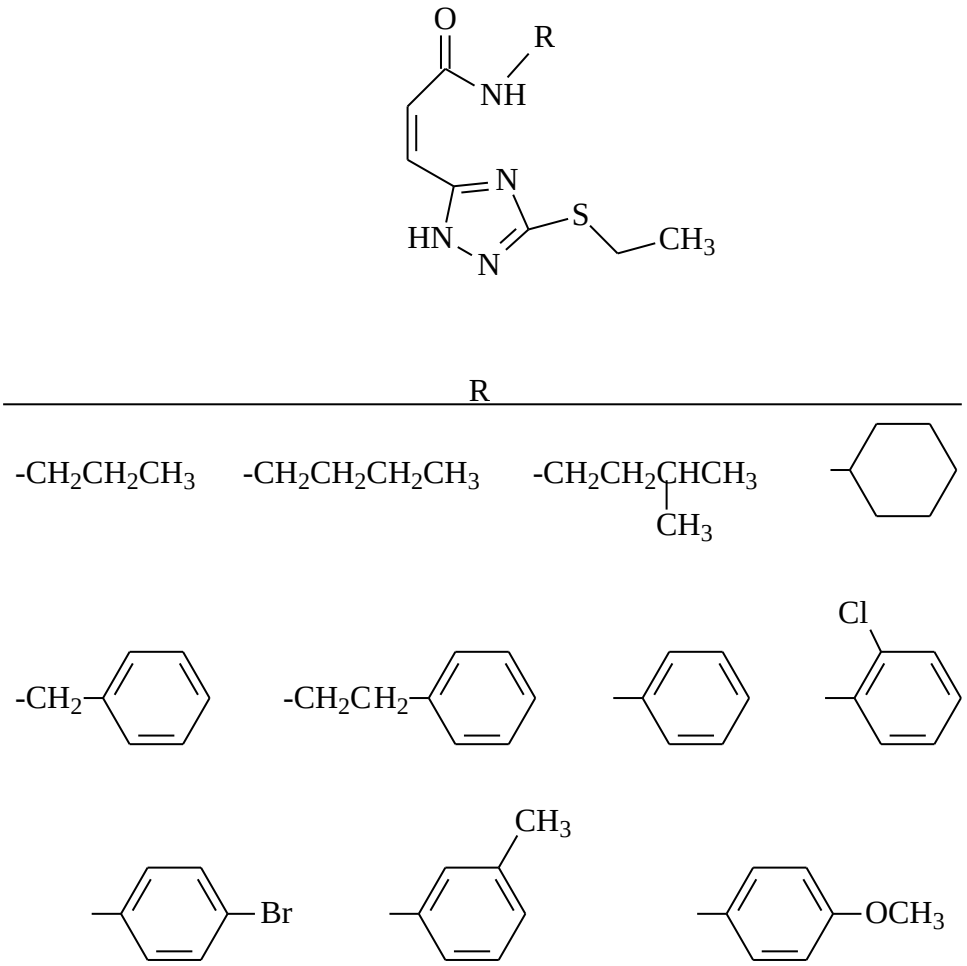


Figure 8. *N*-substituted amides of 3-(3-ethylthio-1,2,4-triazol-5-yl)propenoic acid compounds (Pachuta-Stec et al., 2009).

It is thought that some of the derivatives of phenylcarbamoylazinane-1,2,4-triazole amides may lead to the synthesis of effective drug-like molecules that can be used in the treatment of colon cancer (Saeed et al., 2022).

In a very recent study, 4-(((4-ethyl-5-(thiophen-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-6,8-dimethyl-coumarin compound synthesis was performed and cytotoxic effects of this compound on different cell lines were investigated. Research has been reported on human breast adenocarcinoma cell line, human umbilical vein endothelial cell line, and human gastric cancer cell line (Koparir et al., 2022).

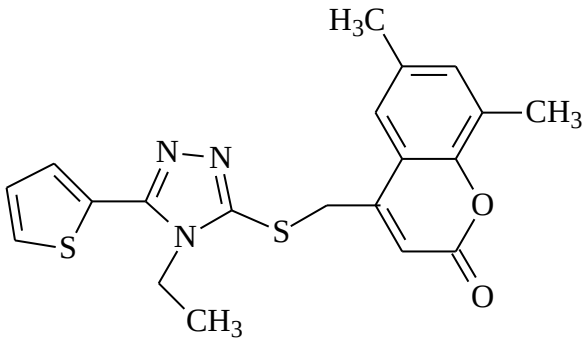
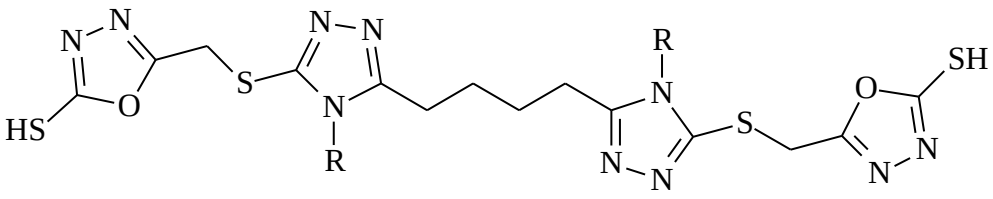


Figure 9. 4-(((4-ethyl-5-(thiophen-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-6,8-dimethyl-coumarin compound (Koparir et al., 2022).

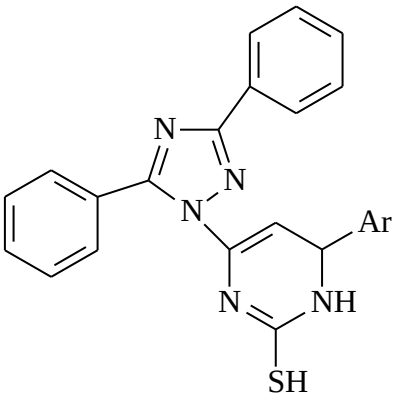
1,4-bis[5-(5-mercapto-1,3,4-oxadiazol-2-yl-methyl)-thio-4-substituted-1,2,4-triazol-3-yl]-butane series, evaluated for *in vitro* cytotoxicity potential using the standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) test. It has been tested against three human cancer cell lines: lung cancer, colon cancer, and breast cancer (Purohit et al., 2011).



R= Phenyl/*p*-tolyl/*m*-tolyl/*p*-ethoxy phenyl/cyclohexyl/*n*-butyl

Figure 10. 1,4-bis[5-(5-mercapto-1,3,4-oxadiazol-2-yl-methyl)-thio-4-substituted-1,2,4-triazol-3-yl]-butane series (Purohit et al., 2011).

The anticancer activity of 6-(substituted aryl)-4-(3,5-diphenyl-1*H*-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol compounds against 60 cell lines of different human tumors was investigated. Compounds with 4-chlorophenyl and 4-methoxyphenyl substituents were found to be active on non-small cell lung cancer (Khanage et al., 2012).

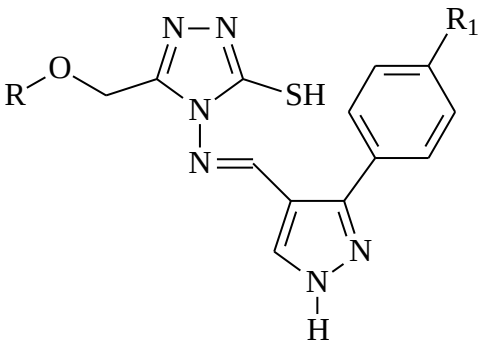


Ar= 4-chlorophenyl/2-chlorophenyl/3-nitrophenyl/4-methoxyphenyl/4-dimethyl aminophenyl phenyl/2-furyl/4-bromophenyl/4-hydroxyphenyl/2,4-dimethoxyphenyl

Figure 11. 6-(substituted aryl)-4-(3,5-diphenyl-1*H*-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol compounds (Khanage et al., 2012).

The cytotoxicity of compounds containing 1,2,4-triazole ring containing adamantane and monoterpenoid moieties has been reported in the literature using cervical cancer and colon cancer cell lines (Munkuev et al., 2021).

In one study, the antitumor activities of Schiff base with three 1,2,4-triazole rings against Ehrlich ascites carcinoma (EAC) in Swiss albino mice were investigated. 4-({[3-(4-fluorophenyl)-1*H*-pyrazol-4-yl]methylene}amino)-5-[(2-methylphenoxy)methyl]-1,2,4-triazole-3-thiol compound has been reported to increase the survival time of infected mice (Sunil et al., 2013).



R= 4-methyl benzene, 2-methyl benzene
R_1= Cl, F

Figure 12. Structure of Schiff bases with 1,2,4-triazole ring (Sunil et al., 2013).

Azo dye ligand containing 1,2,4-triazole ring was synthesized and its *in vitro* cytotoxicity was investigated against human liver carcinoma cell line. Azo dye ligand has been found to have strong antitumor activity. It has been reported to be a promising result in terms of acceptability as an anticancer drug (El-Ghamry et al., 2018).

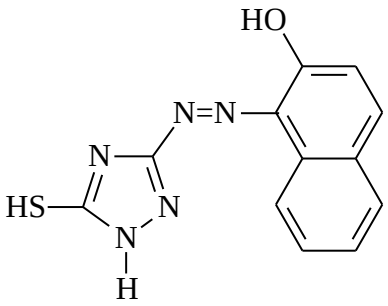


Figure 13. Structure of azo ligand (El-Ghamry et al., 2018).

Cu(II) and Ag(I) complexes of Schiff bases with 1,2,4-triazole ring were synthesized. Their cytotoxic activities against human breast cancer cell line were studied. As a result of cytotoxic activity examination, it has been reported that Cu(II) complex may be a potential anticancer agent (Abdelghany et al., 2021).

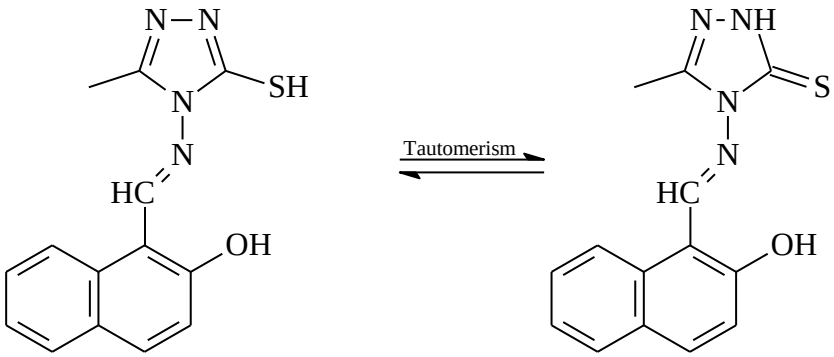
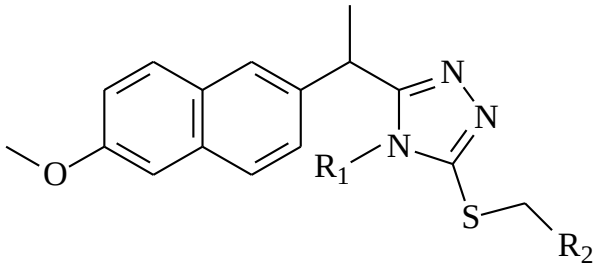


Figure 14. The proposed structure of Schiff base (Abdelghany et al., 2021).

In a study conducted in 2020, the synthesis of 4-substituted-5-(1-(6-methoxynaphtalen-2-yl)ethyl)-3-((substitutedbenzyl)thio)-4*H*-1,2,4-triazole compounds was made. These compounds have been studied against prostate cancer. (S)-3-((2,4,6-trimethylphenyl)thio)-4-(4-fluorophenyl)-5-(1-(6-methoxynaphtalen-2-yl)ethyl)-4*H*-1,2,4-triazole compound has been reported to be a potential candidate for *in vivo* prostate cancer therapy (Birgul et al., 2020).



R_1= 3-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl
R_2= phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dichlorophenyl, 2,4,6-trimethylphenyl.

Figure 15. 4-substituted-5-(1-(6-methoxynaphtalen-2-yl)ethyl)-3-((substitutedbenzyl)thio)-4*H*-1,2,4-triazoles (Birgul et al., 2020).

The cytotoxic and apoptotic activities of heterocyclic compounds with 1,2,4-triazole ring containing indole were investigated against breast cancer. The compounds have been reported to exhibit cytotoxic activity against breast cancer cells (Nafie & Boraei, 2022).

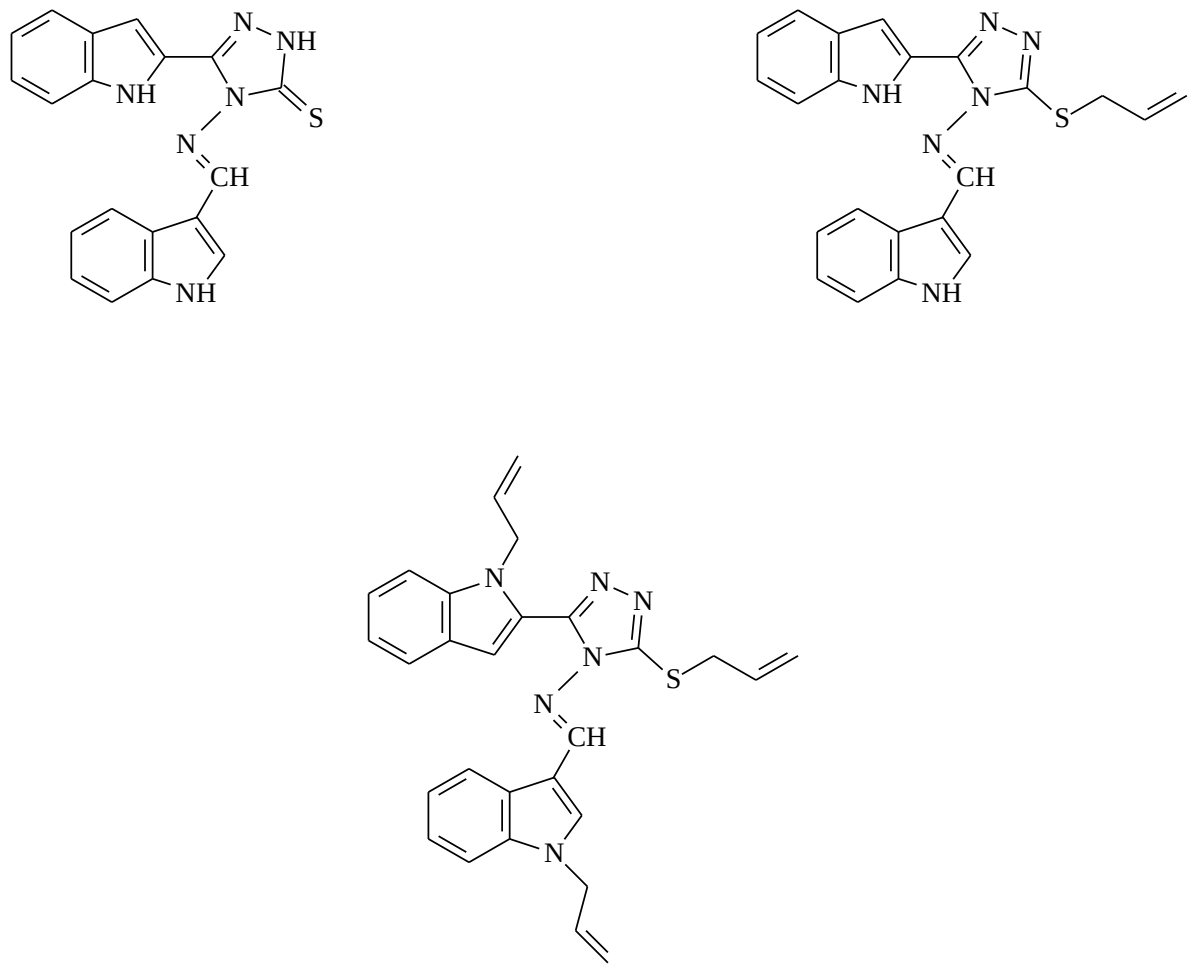


Figure 16. Structures of the compounds (Nafie & Boraei, 2022).

Three versatile half-sandwich ruthenium(II) *p*-cymene complexes carrying triazole ligands were investigated against lung adenocarcinoma and breast adenocarcinoma cells. It has been reported to show cancer cell growth inhibitory activity. These complexes have been reported to show good efficacy to kill cancer cells (Muley et al., 2021).

In a 2011 study, 3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-5-(2-fluorobenzylthio)-4-phenyl-4*H*-1,2,4-triazole has been reported that the compound may be a potential antitumor agent against liver cancer cells according to the results of apoptosis assay and Western-blot (Hou et al., 2011).

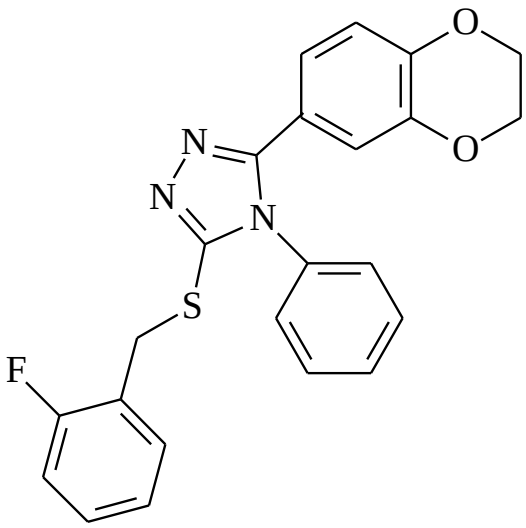


Figure 17. Structure of 3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-5-(2-fluorobenzylthio)-4-phenyl-4*H*-1,2,4-triazole (Hou et al., 2011).

4-(((4,5-Diphenyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)-1-hexadecyl-1*H*-1,2,3-triazole, 1-(4-bromophenyl)-4-(((4,5-diphenyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)-1*H*-1,2,3-triazole, and 1-(4-bromophenyl)-4-(((5-methyl-4-phenyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)-1*H*-1,2,3-triazole compounds were investigated in human colon carcinoma, human cervical carcinoma, and human breast adenocarcinoma. 4-(((4,5-Diphenyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)-1-hexadecyl-1*H*-1,2,3-triazole compound were reported to be the most potent compounds tested against the human breast adenocarcinoma cell line. The other two compounds were reported to have good anticancer activity against the human breast adenocarcinoma cell line (Al Sheikh Ali et al., 2020).

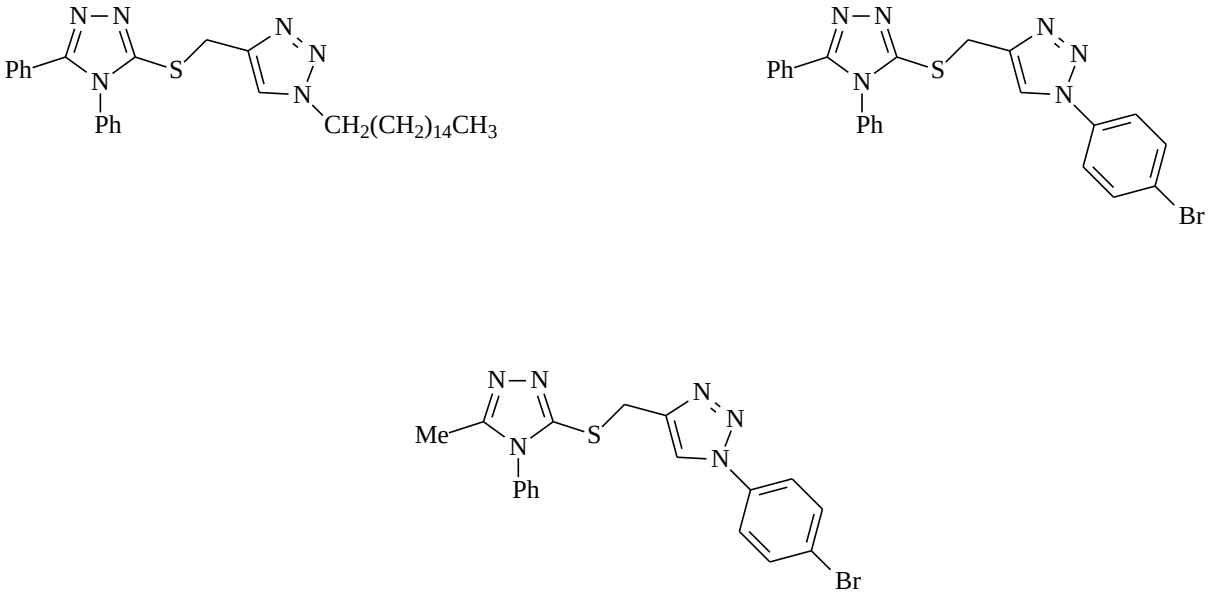


Figure 18. Structure of the compounds (Al Sheikh Ali et al., 2020).

The *in vitro* anticancer activity of compounds with a 1,2,4-triazole ring against human breast cancer cell line was investigated. The compounds have been reported to have significant anticancer activity (Desai et al., 2021).

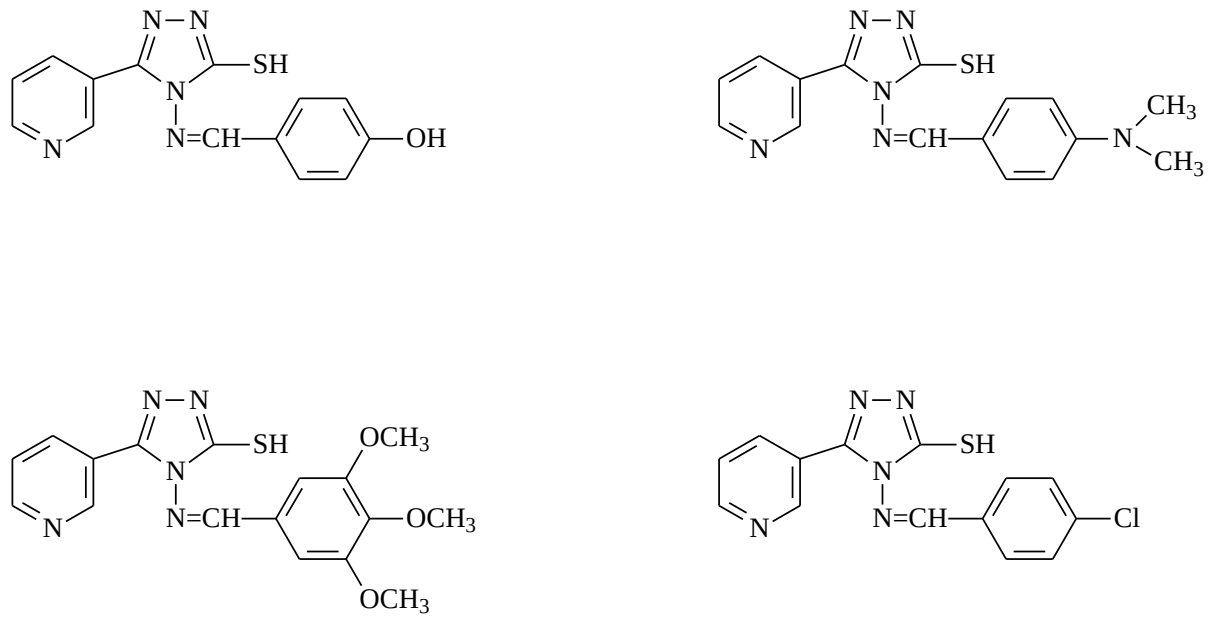
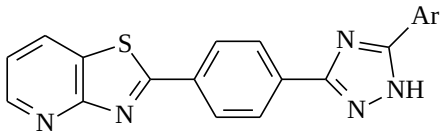


Figure 19. Structure of compounds **1**, **2**, **3** and **4** (Desai et al., 2021).

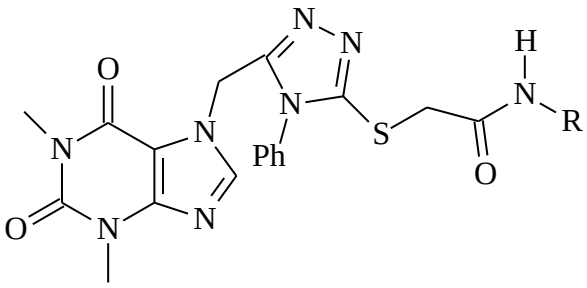
Anticancer activities of thiazolepyridine compounds combined with 1,2,4-triazole derivatives against human cancer lines including prostate cancer, lung cancer and breast cancer were investigated. Some of these compounds have been reported to exhibit significant activity (Sumalatha et al., 2020).



Ar= Pyridine-4-yl hydrochloride, 4-nitrophenyl, 3,5-dinitrophenyl, 3,4,5-trimethoxyphenyl, 3,5-dimethoxyphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-bromophenyl, 4-cyanophenyl, 4-methylphenyl.

Figure 20. Structure of 1,2,4-triazolearyl incorporated thiazolepyridine derivatives (Sumalatha et al., 2020).

Some Mannich bases with 1,2,4-triazole ring have been reported to have antiproliferative activity on prostate, liver and breast human cancer cells (Ceylan et al., 2020).
Compounds containing 1,2,4-triazole ring with *N*-phenyl acetamide moieties were tested against lung and breast cancer cell lines for their *in vitro* potential (Shahzadi et al., 2021).



R= C_6H_5, 2,4-Cl_2-C_6H_3, 2,4-Me_2-C_6H_3, 3,4-Cl_2-C_6H_3, 4-F-C_6H_4, 2-Cl-C_6H_4, 4-Me-C_6H_4, 3,4-Me_2-C_6H_3, 4-Cl-C_6H_4, 2-F-C_6H_4

Figure 21. Structure of Thio *N*-(substituted-phenyl)acetamide derivatives of theophylline-7-acetic acid (Acefylline) (Shahzadi et al., 2021).

REFERENCES

Abdelghany, M. M., Ahmed, I. S., Dessouki, H. A., & Abdelrahman, E. A. (2021). Facile Synthesis of CuO and Ag Nanoparticles by Thermal Decomposition of Novel Schiff Base Complexes. *Journal of Inorganic and Organometallic Polymers and Materials*, *31*(11), 4281–4299. https://doi.org/10.1007/s10904-021-02032-y

Al Sheikh Ali, A., Khan, D., Naqvi, A., Al-Blewi, F. F., Rezki, N., Aouad, M. R., & Hagar, M. (2020). Design, synthesis, molecular modeling, anticancer studies, and density functional theory calculations of 4-(1, 2, 4-triazol-3-ylsulfanylmethyl)-1, 2, 3-triazole derivatives. *ACS Omega*, *6*(1), 301–316.

Avanzo, R. E., Anesini, C., Fascio, M. L., Errea, M. I., & D'Accorso, N. B. (2012). 1,2,4-Triazole D-ribose derivatives: Design, synthesis and antitumoral evaluation. *European Journal of Medicinal Chemistry*, *47*, 104–110. https://doi.org/10.1016/j.ejmech.2011.10.028

Bekircan, O., Kahveci, B., & Kucuk, M. (2006). Synthesis and anticancer evaluation of some new unsymmetrical 3,5-diaryl-4H-1,2,4-triazole derivatives. *Turkish Journal of Chemistry*, *30*(1), 29–40.

Birgul, K., Yildirim, Y., Karasulu, H. Y., Karasulu, E., Uba, A. I., Yelekci, K., Bekci, H., Cumaoglu, A., Kabasakal, L., Yilmaz, O., & Kucukguzel, S. G. (2020). Synthesis, molecular modeling, in vivo study and anticancer activity against prostate cancer of (thorn) (S)-naproxen derivatives. *European Journal of Medicinal Chemistry*, *208*, 112841. https://doi.org/10.1016/j.ejmech.2020.112841

Ceylan, Ş., Cebeci, Y. U., Demirbaş, N., Batur, Ö. Ö., & Özakpınar, Ö. B. (2020). Antimicrobial, Antioxidant and Antiproliferative Activities of Novel Quinolones. *ChemistrySelect*, *5*(36), 11340–11346.

Deodware, S. A., Sathe, D. J., Choudhari, P. B., Lokhande, T. N., & Gaikwad, S. H. (2017). Development and molecular modeling of Co(II), Ni(II) and Cu(II) complexes as high acting anti breast cancer agents. *Arabian Journal of Chemistry*, *10*(2), 262–272. https://doi.org/10.1016/j.arabjc.2016.09.024

Desai, S. P., Momin, Y. H., Taralekar, S. T., Dange, Y. D., Jagtap, S. R., & Khade, H. P. (2021). Evaluation of potential in vitro anticancer and antimicrobial activities of synthesized 5-mercapto-4-substituted 1, 2, 4 triazole derivatives. *Ann Phytomedicine Int J*, *10*, 273–279.

El-Ghamry, H. A., Fathalla, S. K., & Gaber, M. (2018). Synthesis, structural characterization and molecular modelling of bidentate azo dye metal complexes: DNA interaction to antimicrobial and anticancer activities. *Applied Organometallic Chemistry*, *32*(3), e4136. https://doi.org/10.1002/aoc.4136

Gaber, M., El-Ghamry, H. A., Fathalla, S. K., & Mansour, M. A. (2018). Synthesis, spectroscopic, thermal and molecular modeling studies of Zn-2(+),Cd2+ and UO22+ complexes of Schiff bases containing triazole moiety. Antimicrobial, anticancer, antioxidant and DNA binding studies. *Materials Science & Engineering C-Materials for Biological Applications*, *83*, 78–89. https://doi.org/10.1016/j.msec.2017.11.004

Ghanaat, J., Khalilzadeh, M. A., Zareyee, D., Shokouhimehr, M., & Varma, R. S. (2020). Cell cycle inhibition, apoptosis, and molecular docking studies of the novel anticancer

bioactive 1,2,4-triazole derivatives. *Structural Chemistry*, *31*(2), 691–699. https://doi.org/10.1007/s11224-019-01453-3

Han, M. I., Tunc, C. U., Atalay, P., Erdogan, O., Unal, G., Bozkurt, M., Aydin, O., Cevik, O., & Kucukguzel, S. G. (2022). Design, synthesis, and in vitro and in vivo anticancer activity studies of new (S)-Naproxen thiosemicarbazide/1,2,4-triazole derivatives. *New Journal of Chemistry*, *46*(13), 6046–6059. https://doi.org/10.1039/d1nj05899a

Harmankaya, A., & Harmankaya, S. (2022). Use of Herbs And Spıces as Natural Antıoxıdants in Foods. In *Functional Foods and Nutraceuticals: Bioactive Compounds* (pp. 49–67).

Harmankaya, A., Özcan, A., Dalginli, K., Erdağ, D., Aydin Dursun, Y., & Güngör, B. (2021). The Effect of Trolox on Oxidative Stress Index and Nitric Oxide Levels. *Journal of the Institute of Science and Technology*, 3262–3268. https://doi.org/10.21597/jist.951122

Harmankaya, A., Özcan, A., Kaya, R., Özbey, Ç., AtakiSi, O., & Dalginli, K. (2020). Effect of ACE Plus Selenium on Total Antioxidant/Oxidant Capacity and Nitric Oxide Levels in Rabbits. *Caucasian Journal of Science*. https://doi.org/10.48138/cjo.830176

Hou, Y.-P., Sun, J., Pang, Z.-H., Lv, P.-C., Li, D.-D., Yan, L., Zhang, H.-J., Zheng, E. X., Zhao, J., & Zhu, H.-L. (2011). Synthesis and antitumor activity of 1, 2, 4-triazoles having 1, 4-benzodioxan fragment as a novel class of potent methionine aminopeptidase type II inhibitors. *Bioorganic & Medicinal Chemistry*, *19*(20), 5948–5954.

Isloor, A. M., Sunil, D., Shetty, P., Malladi, S., Pai, K. S. R., & Maliyakkl, N. (2013). Synthesis, characterization, anticancer, and antioxidant activity of some new thiazolidin-4-ones in MCF-7 cells. *Medicinal Chemistry Research*, *22*(2), 758–767. https://doi.org/10.1007/s00044-012-0071-5

Khanage, S. G., Raju, S. A., Mohite, P. B., & Pandhare, R. B. (2012). Synthesis and Pharmacological Evaluation of Some New Pyrimidine Derivatives Containing 1,2,4-Triazole. *Advanced Pharmaceutical Bulletin*, *2*(2), 213–222. https://doi.org/10.5681/apb.2012.033

Koparir, P., Sarac, K., & Omar, R. A. (2022). Synthesis, Molecular Characterization, Biological and Computational Studies of New Molecule Contain 1,2,4-Triazole, and Coumarin Bearing 6,8-Dimethyl. *Biointerface Research in Applied Chemistry*, *12*(1), 809–823. https://doi.org/10.33263/BRIAC121.809823

Kumar, D., Narayanam, M. K., Chang, K.-H., & Shah, K. (2011). Synthesis of Novel Indolyl-1,2,4-triazoles as Potent and Selective Anticancer Agents. *Chemical Biology & Drug Design*, *77*(3), 182–188. https://doi.org/10.1111/j.1747-0285.2010.01051.x

Luo, L., Jia, J. J., Zhong, Q., Zhong, X., Zheng, S., Wang, G., & He, L. (2021). Synthesis and anticancer activity evaluation of naphthalene-substituted triazole spirodienones. *European Journal of Medicinal Chemistry*, *213*, 113039. https://doi.org/10.1016/j.ejmech.2020.113039

Maddali, N. K., Ivaturi, V. K. V., Murthy Yellajyosula, L. N., Malkhed, V., Brahman, P. K., Pindiprolu, S. K. S. S., Kondaparthi, V., & Nethinti, S. R. (2021). New 1,2,4-Triazole Scaffolds as Anticancer Agents: Synthesis, Biological Evaluation and Docking Studies. *Chemistryselect*, *6*(26), 6788–6796. https://doi.org/10.1002/slct.202101387

Mahanti, S., Sunkara, S., & Bhavani, R. (2019). Synthesis, biological evaluation and computational studies of fused acridine containing 1,2,4-triazole derivatives as

anticancer agents. *Synthetic Communications*, *49*(13), 1729–1740. https://doi.org/10.1080/00397911.2019.1608450

Mahar, J., Saeed, A., Chaudhry, G.-S., Irfan, M., Channar, P. A., Faisal, M., & Larik, F. A. (2020). Synthesis, characterization and cytotoxic studies of novel 1,2,4-triazole-azomethine conjugates. *Journal of the Iranian Chemical Society*, *17*(4), 943–951. https://doi.org/10.1007/s13738-019-01826-9

Muley, A., Karumban, K. S., Gupta, P., Kumbhakar, S., Giri, B., Raut, R., Misra, A., & Maji, S. (2021). Synthesis, structure, spectral, redox properties and anti-cancer activity of Ruthenium(II) Arene complexes with substituted Triazole Ligands. *Journal of Organometallic Chemistry*, *954–955*, 122074. https://doi.org/10.1016/j.jorganchem.2021.122074

Munkuev, A. A., Mozhaitsev, E. S., Chepanova, A. A., Suslov, E., Korchagina, D., Zakharova, O. D., Ilina, E. S., Dyrkheeva, N. S., Zakharenko, A. L., Reynisson, J., Volcho, K. P., Salakhutdinov, N. F., & Lavrik, O. (2021). Novel Tdp1 Inhibitors Based on Adamantane Connected with Monoterpene Moieties via Heterocyclic Fragments. *Molecules*, *26*(11), 3128. https://doi.org/10.3390/molecules26113128

Nafie, M. S., & Boraei, A. T. A. (2022). Exploration of novel VEGFR2 tyrosine kinase inhibitors via design and synthesis of new alkylated indolyl-triazole Schiff bases for targeting breast cancer. *Bioorganic Chemistry*, *122*, 105708. https://doi.org/10.1016/j.bioorg.2022.105708

Pachuta-Stec, A., Rzymowska, J., Mazur, L., Mendyk, E., Pitucha, M., & Rzaczynska, Z. (2009). Synthesis, structure elucidation and antitumour activity of N-substituted amides of 3-(3-ethylthio-1,2,4-triazol-5-yl)propenoic acid. *European Journal of Medicinal Chemistry*, *44*(9), 3788–3793. https://doi.org/10.1016/j.ejmech.2009.04.034

Parlak, A. E. (2018). Investigation of Anticancer Effect of Acetic Acid Derivatives Containing 1,2,4-Triazole Moiety Against Two Different Cancer Cell Lines. *Fresenius Environmental Bulletin*, *27*(12B), 9894–9901.

Parlak, A. E., Tekin, S., Karatepe, A., Koparir, P., Telceken, H., Ceribasi, A. O., & Karatepe, M. (2019). In vitro and histological investigation of antitumor effect of some triazole compounds in colon cancer cell line. *Journal of Cellular Biochemistry*, *120*(7), 11809–11819. https://doi.org/10.1002/jcb.28460

Purohit, M., & Mayur, Y. C. (2012). Synthesis, in vitro cytotoxicity, and anti-microbial studies of 1,4-bis(4-substituted-5-mercapto-1,2,4-triazol-3-yl)butanes. *Medicinal Chemistry Research*, *21*(2), 174–184. https://doi.org/10.1007/s00044-010-9517-9

Purohit, M., Prasad, V. V. S. R., & Mayur, Y. C. (2011). Synthesis and Cytotoxicity of Bis-1,3,4-oxadiazoles and Bis-pyrazoles Derived from 1,4-Bis[5-thio-4-substituted-1,2,4-triazol-3-Yl]-butane and Their DNA Binding Studies. *Archiv Der Pharmazie*, *344*(4), 248–254. https://doi.org/10.1002/ardp.201000177

Rashad, A. E., El-Sayed, W. A., Mohamed, A. M., & Ali, M. M. (2010). Synthesis of New Quinoline Derivatives as Inhibitors of Human Tumor Cells Growth. *Archiv Der Pharmazie*, *343*(8), 440–448. https://doi.org/10.1002/ardp.201000002

Saeed, A., Ejaz, S. A., Sarfraz, M., Tamam, N., Siddique, F., Riaz, N., Abul Qais, F., Chtita, S., & Iqbal, J. (2022). Discovery of Phenylcarbamoylazinane-1,2,4-Triazole Amides

Derivatives as the Potential Inhibitors of Aldo-Keto Reductases (AKR1B1 & AKRB10): Potential Lead Molecules for Treatment of Colon Cancer. *Molecules*, *27*(13), 3981. https://doi.org/10.3390/molecules27133981

Shahzadi, I., Zahoor, A. F., Rasul, A., Mansha, A., Ahmad, S., & Raza, Z. (2021). Synthesis, Hemolytic Studies, and In Silico Modeling of Novel Acefylline–1, 2, 4-Triazole Hybrids as Potential Anti-cancer Agents against MCF-7 and A549. *ACS Omega*, *6*(18), 11943–11953.

Sumalatha, S., Namrata, V., Lakshmi, M., & Sridhar, G. (2020). Synthesis and Anticancer Activity of Different 1, 2, 4-Triazolearyl Incorporated Thiazolepyridine Derivatives. *Russian Journal of General Chemistry*, *90*(12), 2381–2385.

Sunil, D., Isloor, A. M., Shetty, P., Nayak, P. G., & Pai, K. S. R. (2013). In vivo anticancer and histopathology studies of Schiff bases on Ehrlich ascitic carcinoma cells. *Arabian Journal of Chemistry*, *6*(1), 25–33. https://doi.org/10.1016/j.arabjc.2010.12.016

About The Authors

Onur AKYILDIRIM completed his MSc and PhD degrees at Faculty of Science and Letters, Kafkas University, Kars, Turkey. He is working as an Associate Prof. Dr. in Department of Chemical Engineering, Faculty of Engineering and Architecture at Kafkas University in Turkey. His research interests include organic chemistry, biosensor/ nanosensor and applications.

E-mail: onurakyildirim@gmail.com, ORCID: 0000-0003-1090-695X

Murat BEYTUR completed his MSc and PhD degrees at Faculty of Science and Letters, Kafkas University, Kars, Turkey. He is working as an Associate Prof. Dr. in Department of Chemistry, Faculty of Science and Letters at Kafkas University in Turkey. His research interests include organic chemistry, biochemistry (antioxidant and antimicrobial properties), theoretical chemistry, biosensor/nanosensor and applications.

E-mail: muratbeytur83@gmail.com, ORCID: 0000-0002-7098-5592

To Cite This Chapter

Akyıldırım, O. & Beytur, M. (2022). Anticancer Properties of 1,2,4-Triazoles. In H. Yüksek & M. Beytur (Eds.), *Chemistry of 1,2,4-Triazoles in Current Science*, (63-81). ISRES Publishing