New Materials, Compounds and Applications
Vol.8, No.1, 2024, pp.5-12
https://doi.org/10.62476/nmca8105

MOLECULAR DOCKING OF 4-AZIDO-2-(4-SUBSTITUTED-PHENYL)-5-(2-NITROPHENYL)-2H-1,2,3-TRIAZOLES

Afaq A. Abdullayeva, Nigar E. Ahmadova*, Gulnar T. Atakishiyeva, Nazrin R. Zeynalli, Irada M. Shikhaliyeva, Shafiga A. Ibrahimova, Irada J. Ahmadova, Namiq Q. Shikhaliyev, Abel A. Maharramov

Department of Organic Chemistry, Baku State University, Baku, Azerbaijan

Abstract. Molecular docking of 4-azido-2-(4-substituted-phenyl)-5-(2-nitrophenyl)-2H-1,2,3-triazoles was fulfilled by means of SwissADME prediction software and carried out analysis on P-glycoprotein and Cytochrome P450 isoenzymes as well as calculations of the pharmacokinetic properties of the compounds.
4-azido-2-(4-substituted-phenyl)-5-(2-nitrophenyl)-2H-1,2,3-triazole were considered as molecules which meet the requirements for the synthesis of medicinal substances. At the same time, by means of Swiss Targeted Prediction software were made calculations using the Brain or Intestine permeability method (BOILED-Egg) and obtained positive results.

Keywords: *Triazoles, molecular docking, SwissADME prediction software.*

Corresponding Author: *Nigar E. Ahmedova, Department of Organic Chemistry, Baku State University, Baku, Azerbaijan, e-mail: nigarahmadova91@gmail.com*

Received: *8 January 2023;* ***Accepted:*** *7 March 2024;* ***Published:*** *15 April 2024.*

1. Introduction

For many years, researchers have been engaged in the synthesis of new drugs that are effective, can have a long lasting effect, are less harmful, have minimal side effects and more positive properties. In the synthesis of the new medicinal substances, were used the available modern research methods of each era. In the meanwhile, as science and technology growing up, the requirements for the synthesis of medicines change (Paolo *et al.*, 2000; Billo, 1998; Paglietti *et al.*, 1994).

The synthesis of functionally substituted synthetic organic compounds with an unknown mechanism of antimicrobial effect against bacterial resistance will has great potential as an antibacterial agent in the close future. Recently, functionally substituted compounds have been extensively used in view of increasing the resistance of bacteria to medicinal substances (Giuseppe *et al.*, 1999; Ya-Bin *et al.*, 2008).

In general, it should be noted that after the synthesis of a one medicinal substance, it requires several decades and some 100 million dollars of funds for its clinical experiments. However, the prediction of the biological activity of molecules ahead of time through the Swiss ADME (Switzerland) software has opened broad opportunities

How to cite (APA):
Abdullayeva, A.A., Ahmadova, N.E., Atakishiyeva, G.T., Zeynalli, N.R., Shikhaliyeva, I.M., İbrahimova, S.A., Shikhaliyev, N.Q. & Maharramov, A.A. (2024). Molecular docking of 4-azido-2-(4-substituted-phenyl)-5-(2-nitrophenyl)-2h-1,2,3-triazoles. *New Materials, Compounds and Applications*, *8*(1), 5-12 https://doi.org/10.62476/nmca8105

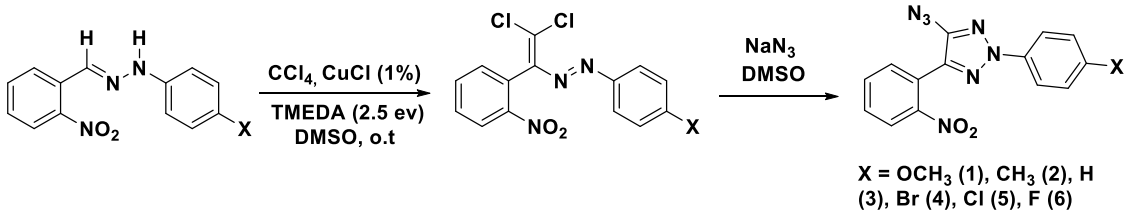
for the synthesis of new drugs in a shorter period of time. This system gives opportunity precedently selecting compounds with appropriate structures and rejecting compounds with low activity. Through this software, it is theoretically possible to predict which possibilities the molecule has. In this case, no fund is needed. By use of the Swiss ADME software, it is estimated how well the molecule meet the requirements set as a medicinal substance (Yasushi *et al.*, 2012, Oludotun *et al.*, 2009, Şahin *et. al.*, 2023).

Also, through the utility of Swiss ADME software are performed such as pharmocokinetic, physico-chemical, bio-chemical calculations, membrane permeability calculations and studied properties such as lipophilicity, volume, polarity, insolubility, unsaturation and elasticity.

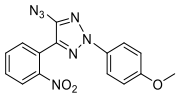
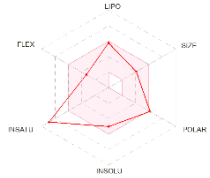
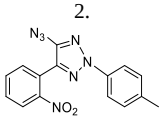
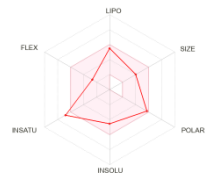
2. Result and discussion

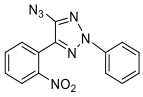
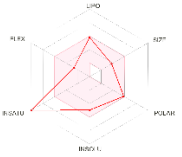
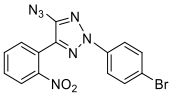
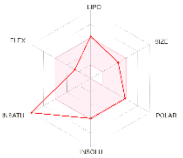
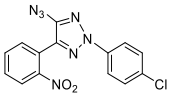
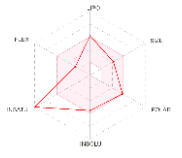
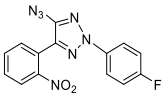
In previous studies, was carried out the synthesis of 1-(4-substituted phenyl)-2-(2,2-dichloro-1-(2-nitrophenyl)vinyl)diazenes (Shikhaliyev *et al.*, 2018; 2019; Maharramov *et al*, 2018; Nenajdenko *et al.*, 2022; Atakishiyeva *et al.*, 2023) by conversion of 2-substituted-1,2,3-triazoles. During the reaction, discontinuous bis-azides are formed as a result of the addition of the azide anion to the carbon atom in the C=C double bond.

Later, 4-azido-2H-1,2,3-triazoles were obtained by discarding of nitrogen (Häring *et al.*, 2015; Nenajdenko *et al.*, 2017; Shastin *et al.*, 2018; Tsyrenova *et al.*, 2020; Maharramov *et al.*, 2023).



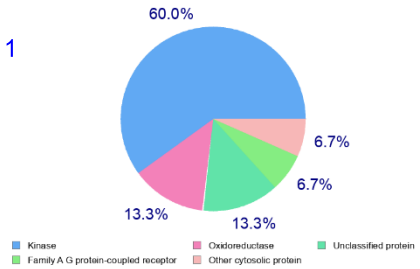
The Swiss ADME software (Şahin *et. al.*, 2023), for molecular docking and prediction of biological activities of azido triazoles synthesized by our research group is freely available at http://www.swissadme.ch. In the following table listed the biological activity of the compounds.

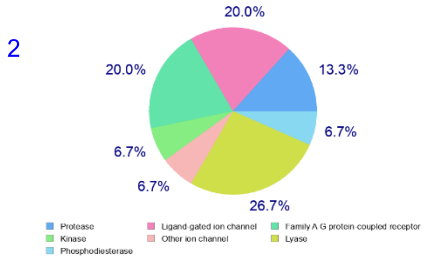
Formula of the substance	Bioavailability	Liphophilicity	Volume	Polarity	Insolubility	Insaturation	Elasticity
1 		Located in the pink zone	Located in the pink zone	Located in the pink zone	Located in the pink zone	Located out of the pink zone	Located in the pink zone
2. 		Located in the pink zone	Located in the pink zone	Located in the pink zone	Located in the pink zone	Located out of the pink zone	Located in the pink zone

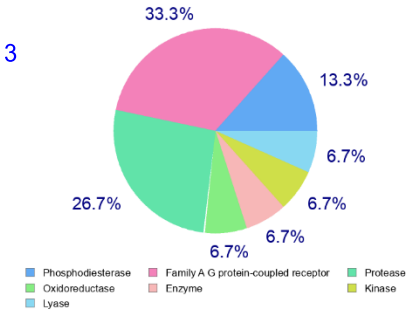
3. 		Located in the pink zone	Located in the pink zone	Located in the pink zone	Located in the pink zone	Located out of the pink zone	Located in the pink zone
4. 		Located in the pink zone	Located in the pink zone	Located in the pink zone	Located in the pink zone	Located out of the pink zone	Located in the pink zone
5. 		Located in the pink zone	Located in the pink zone	Located in the pink zone	Located in the pink zone	Located out of the pink zone	Located in the pink zone
6. 		Located in the pink zone	Located in the pink zone	Located in the pink zone	Located in the pink zone	Located out of the pink zone	Located in the pink zone

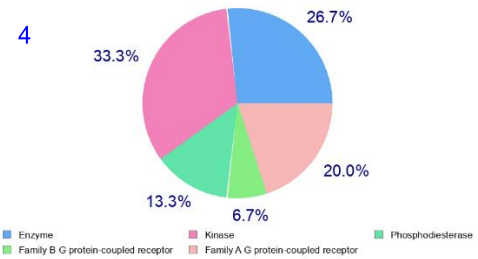
By means of the software it was determined from the obtained results that the insaturation property of the 6 synthesized compounds was located outside the pink zone. Thus, the mentioned property is weak in synthesized compounds. All other properties of the synthesized compounds are located in the pink zone, which let us to foresee previously about their high demonstration of biological activity.

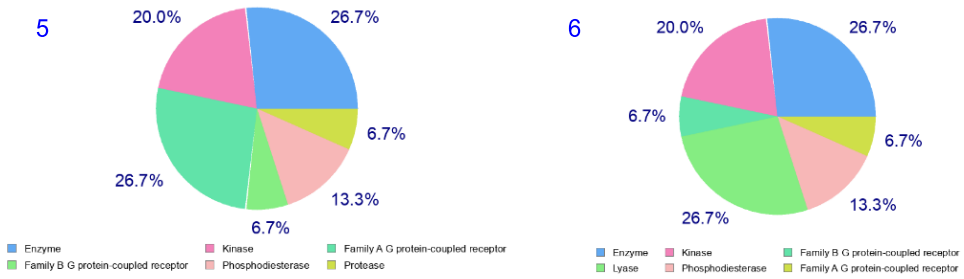
Alikeness of synthesized compounds to some proteins and enzymes was given by means of Swiss Target Prediction software.









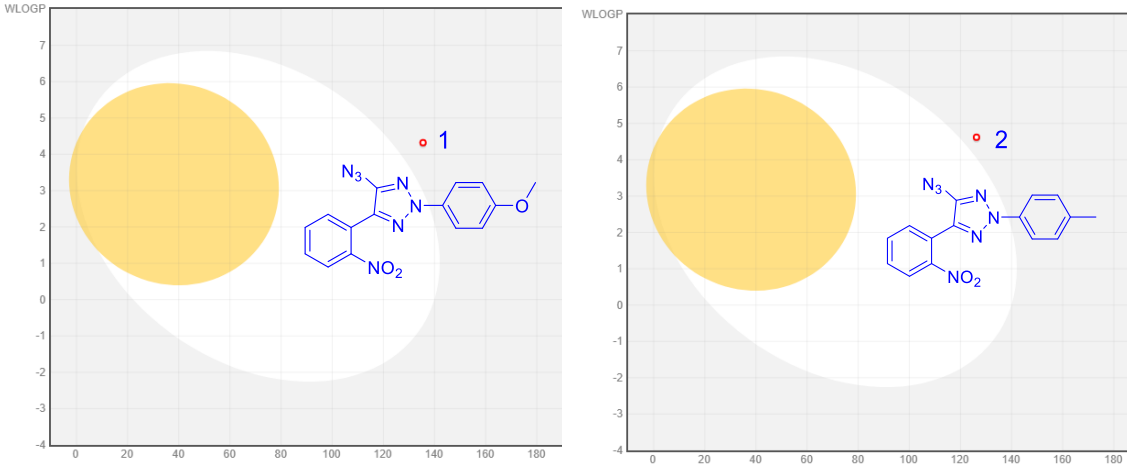


For determining the relevant molecules of the synthesized dichlorodiazadienes among 3068 proteins for one or more experimentally recognized active compounds were performed Screenings (both 2D and 3D)

The similarity of 4-azido-2-(4-methoxyphenyl)-5-(2-nitrophenyl)-2H-1,2,3-triazole (1) and 4-azido-2-(4-bromophenyl)-5-(2- nitrophenyl)-2H-1,2,3-triazole (4) molecules to kinase enzyme, 4-azido-5-(2-nitrophenyl)-2-(p-tolyl)-2H-1,2,3-triazole (2) to Lyase, 4-azido-5-(2-nitrophenyl)-2-phenyl-2H-1,2,3-triazole (3) to A.G. Family protein-coupled receptor enzyme is predominates.

The similarity of 4-azido-2-(4-chlorophenyl)-5-(2-nitrophenyl)-2H-1,2,3-triazole (5) A.G. Family protein-coupled compound to enzyme, 4-azido-2-(4-fluorophenyl)-5-(2-nitrophenyl)-2H-1,2,3-triazole (6) to enzyme and Lyase compared with others are similar in properties more than 26.7%.

Through Swiss ADME prediction software was used the Brain or Gut permeability method (BOILED-Egg).



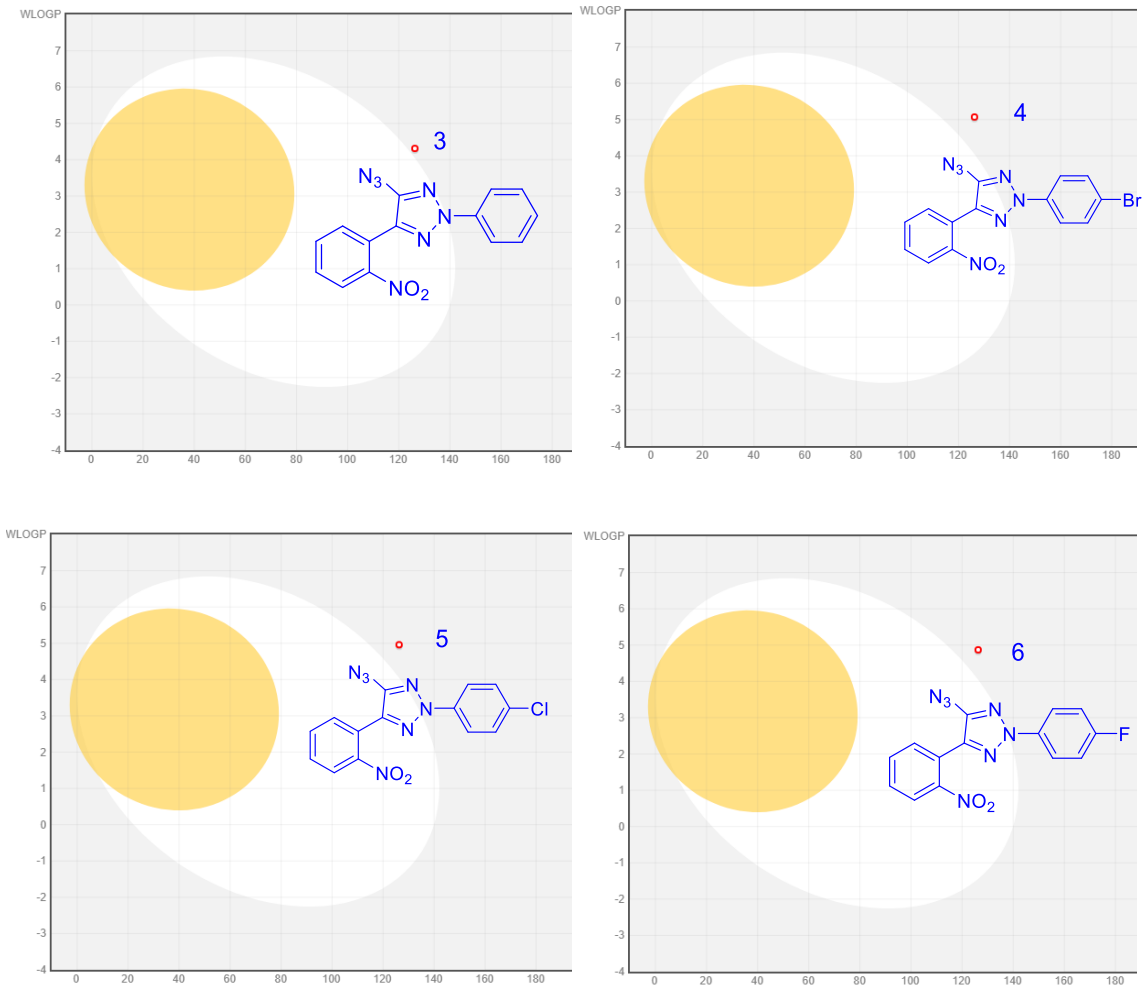


Table 1. Pharmacokinetic properties of the compound

Substance	GI absorption	BBBermeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation) cm/s
1	Low	-	-	+	+	+	-	-	--5.07
2	Low	-	-	+	+	+	-	-	-4.69
3	Low	-	-	+	+	+	-	-	-4.87
4	Low	-	-	+	+	+	-	-	-4.86
5	Low	-	-	+	+	+	-	-	-4.63
6	Low	-	-	+	+	+	-	-	-4.90

Table 2. Calculation of physical and chemical properties of biotransformation products

Given data	1	2	3	4	5	6
Formula	C15H11N7O3	C15H11N7O2	C14H9N7O2	C14H8BrN7O2	C14H8ClN7O2	C14H8FN7O2
Molecular weight	337.29 g/mol	321.29 g/mol	307.27 g/mol	386.16 g/mol	341.71 g/mol	325.26 g/mol
Num. heavy atoms	25	24	23	24	24	24
Num. arom. heavy atoms	17	17	17	17	17	17
Fraction Csp3	0.07	0.07	0.00	0.00	0.00	0.00
Num. rotatable bonds	5	4	4	4	4	4
Num. H-bond acceptors	8	7	7	7	7	8
Num. H-bond donors	0	0	0	0	0	0
Molar Refractivity	87.65	86.12	81.16	88.85	86.16	81.11
TPSA	135.51 Å²	126.28 Å²	126.28 Å²	126.28 Å²	126.28 Å²	126.28 Å²

It should be noted that all compounds are located neither in egg whites nor in yolks.

So, since compounds 1-6 are not absorbed through the blood-brain barrier, the molecules are located in the gray area (outside the Egg model). Also, the mentioned molecules are detected in the form red dots. So, this indicates that compounds 1-6 are not evaluated by the central nervous system through P-glucoprotein.

At the same time, were performed the pharmokinetic calculations of P-glucoprotein and cytochrome P450 proteins. The synthesized compound was also analyzed by Swiss ADME software over P-glucoprotein and Cytochrome P 450 isozymes. During the investigation of the compounds, it was revealed that this compound is not a substrate for P-glucoprotein. But as an inhibitor for cytochrome P450 was obtained positive result (Table 1).

3. Conclusion

If we consider the results of visual calculations of the synthesized (**1-6)** 4-azido-2H-1,2,3-triazoles using the Swiss ADME software, we will see that:

1. The requirements (lipophilicity, volume, polarity, saturation, elasticity) for the properties of medicinal substances are met.

This let us to assume that the synthesized compounds will be appropriate for use as a applicable drug substances in the future.

2. While studying the Brain or Intestinal Permeability (BOILED-Egg) of the synthesized **1-6** compounds, the location of the compounds in the gray area (in the edge of the Egg model) let us to assume that they are not absorbed through the blood brain barrier.

3. At the same moment, the observation of compounds in the form of red dots indicates that they are not evaluated by the central nervous system through P-glucoprotein. Skrining of the similarity of structures and properties of synthesized dichlordiazadienes among one or more proteins were carried out:

- molecules of **1** and **4** to the kinase enzyme,
- molecules of **2** and **6** to Lyase,
- molecules of **3** and **5** Family A.G protein-coupled receptor enzyme,
- molecules of **5** and **6** to enzyme,

Property similarity is prioritized by percentage.

References

Atakishiyeva, G.T., Qajar, A.M., Babayeva, G.V., Mukhtarova, S.H., Zeynalli, N.R., Ahmedova, N.E. & Shikhaliyev, N.Q. (2023). Biological new targets prediction & adme profiling of 1, 1-dichlordiazodienes on the basis of o-nitrobenzoic aldehyde. *New Materials, Compounds and Applications, 7*(2), 84-92.

Billo, N.E. (1998). Global aspects of tuberculosis. In *Mycobacteria: II Chemotherapy*, 1-14. Boston, MA: Springer US.

Caliendo, G., Fiorino, F., Grieco, P., Perissutti, E., Santagada, V., Meli, R. & De Nucci, G. (1999). Preparation and local anaesthetic activity of benzotriazinone and benzoyltriazole derivatives. *European Journal of Medicinal Chemistry*, *34*(12), 1043-1051.

Häring, A.P., Kirsch, S.F. (2015). Synthesis and chemistry of organic geminal di-and triazides. *Molecules*, *20*(11), 20042-20062.

Maharramov, A.M., Shikhaliyev, N.Q., Suleymanova, G.T., Gurbanov, A.V., Babayeva, G.V., Mammadova, G.Z. & Pombeiro, A.J. (2018). Pnicogen, halogen and hydrogen bonds in (E)-1-(2, 2-dichloro-1-(2-nitrophenyl) vinyl)-2-(para-substituted phenyl)-diazenes. *Dyes and Pigments*, 159, 135-141.

Maharramov, A., Shikhaliyev, N.Q., Abdullayeva, A., Atakishiyeva, G.T., Niyazova, A., Khrustalev, V.N. & Bhattarai, A. (2023). Crystal structure and Hirshfeld surface analysis of 4-azido-2-(3, 5-dimethylphenyl)-5-(4-nitrophenyl)-2H-1, 2, 3-triazole. *Acta Crystallographica Section E: Crystallographic Communications*, *79*(10).

Nenajdenko, V.G., Shastin, A.V., Gorbachev, V.M., Shorunov, S.V., Muzalevskiy, V.M., Lukianova, A.I. & Khrustalev, V.N. (2017). Copper-catalyzed transformation of hydrazones into halogenated azabutadienes, versatile building blocks for organic synthesis. *ACS Catalysis*, *7*(1), 205-209.

Nenajdenko, V.G., Shikhaliyev, N.G., Maharramov, A.M., Atakishiyeva, G.T., Niyazova, A.A., Mammadova, N.A. & Tskhovrebov, A.G. (2022). Structural organization of dibromodiazadienes in the crystal and identification of Br⋯ O halogen bonding involving the nitro group. *Molecules*, *27*(16), 5110.

Paglietti, G., Sanna, P., Carta, A., Sparatore, F., Vazzana, I., Peana, A. & Satta, M. (1994). Choleretic activity of 3-[ring substituted benzotriazol-1 (2)-yl] alkanoic and alkenoic acids. *Farmaco (Societa Chimica Italiana: 1989)*, *40*(11), 693-702.

Phillips, O.A., Udo, E.E., Abdel-Hamid, M.E. & Varghese, R. (2009). Synthesis and antibacterial activity of novel 5-(4-methyl-1H-1, 2, 3-triazole) methyl oxazolidinones. *European Journal of Medicinal Chemistry*, *44*(8), 3217-3227.

Şahin, İ., Çeşme, M., Özgeriş, F.B., Güngör, Ö. & Tümer, F. (2022). Design and synthesis of 1, 4-disubstituted 1, 2, 3-triazoles: Biological evaluation, in silico molecular docking and ADME screening. *Journal of Molecular Structure*, 1247, 131344.

Şahin, İ., Çeşme, M., Yüce, N. & Tümer, F. (2023). Discovery of new 1, 4-disubstituted 1, 2, 3-triazoles: in silico ADME profiling, molecular docking and biological evaluation studies. *Journal of Biomolecular Structure and Dynamics*, *41*(5), 1988-2001.

Sanna, P., Carta, A. & Nikookar, M.E.R. (2000). Synthesis and antitubercular activity of 3-aryl substituted-2-(1H (2H) benzotriazol-1 (2)-yl) acrylonitriles. *European Journal of Medicinal Chemistry*, *35*(5), 535-543.

Shastin, A.V., Tsyrenova, B.D., Sergeev, P.G., Roznyatovsky, V.A., Smolyar, I.V., Khrustalev, V.N. & Nenajdenko, V.G. (2018). Synthesis of a new family of 1, 1-diazidoethenes: One-pot construction of 4-azido-1, 2, 3-triazoles via nitrene cyclization. *Organic Letters*, *20*(24), 7803-7806.

Shikhaliyev, N.Q., Ahmadova, N.E., Gurbanov, A.V., Maharramov, A.M., Mammadova, G.Z., Nenajdenko, V.G. & Pombeiro, A.J. (2018). Tetrel, halogen and hydrogen bonds in bis (4-((E)-(2, 2-dichloro-1-(4-substitutedphenyl) vinyl) diazenyl) phenyl) methane dyes. *Dyes and Pigments*, 150, 377-381.

Shikhaliyev, N.Q., Kuznetsov, M.L., Maharramov, A.M., Gurbanov, A.V., Ahmadova, N.E., Nenajdenko, V.G. & Pombeiro, A.J. (2019). Noncovalent interactions in the design of bis-azo dyes. *CrystEngComm*, *21*(34), 5032-5038.

Tsyrenova, B., Khrustalev, V. & Nenajdenko, V. (2020). 2 H-Bis-1, 2, 3-triazolo-isoquinoline: design, synthesis and photophysical study. *The Journal of Organic Chemistry*, *85*(11), 7024-7035.

Yoshida, Y., Takizawa, S. & Sasai, H. (2011). Synthesis of spiro bis (1, 2, 3-triazolium) salts as chiral ionic liquids. *Tetrahedron Letters*, *52*(51), 6877-6879.

Yoshida, Y., Takizawa, S. & Sasai, H. (2012). Design and synthesis of spiro bis (1, 2, 3-triazolium) salts as chiral ionic liquids. *Tetrahedron: Asymmetry*, *23*(11-12), 843-851.

Zhao, Y.B., Zhang, L.W., Wu, L.Y., Zhong, X., Li, R. & Ma, J.T. (2008). Silica-supported pyrrolidine–triazole, an insoluble, recyclable organocatalyst for the enantioselective Michael addition of ketones to nitroalkenes. *Tetrahedron: Asymmetry*, *19*(11), 1352-1355.