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IN SILICO ANALYSIS OF 6-(4-CHLOROPHENYL)-*N*-ARYL-4-(TRICHLOROMETHYL)-4*H*-1,3,5-OXADIAZIN-2-AMINES AS POTENTIAL ANTAGONISTS OF VEGFR-1

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Abstract:

In this study, the antagonistic activity of 6-(4-chlorophenyl)-N-aryl-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amines against the vascular endothelial growth factor receptor (VEGFR-1) was analyzed using the PASS system. It was shown that the probability of antagonism of the analyzed compounds towards VEGFR-1 formed 24.7-59.9%. N,6-bis(4-chlorophenyl)-4-(trichloromethyl)-4H-1,3,5-oxadiazin-2-amine showed the best results, for which P_a was almost 60%. It was established that the introduction of ether and ester groups into the aromatic substituent of the studied compound significantly reduced the probability of antagonism towards VEGFR-1. It was shown that the introduction of any substituent in the para- position of the aromatic ring increased the probability of manifestation of this type of biological activity compared with ortho- and meta- isomers. For the studied 4H-1,3,5-oxadiazine derivatives, acute toxicity for rats was calculated by the intravenous and oral routes of administration. All compounds were tested for compliance with Lipinski criteria.

Keywords: *In silico, PASS, VEGF, VEGFR-1, 1,3,5-oxadiazine, GUSAR*

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INTRODUCTION:

Angiogenesis is the process of formation of new blood vessels in organs and tissues. It plays an important role in normal tissue growth, wound healing, the reproductive cycle in women and the development of the organism as a whole [1]. The main stimulator of angiogenesis in health and disease is the vascular endothelial growth factor (VEGF), which was discovered in 1983 [2]. The VEGF family includes seven members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, placenta growth factor (PlGF), and a group of viral homologs called VEGF-E and VEGF-F [3].

There are three types of VEGF receptors - VEGFR-1, VEGFR-2 and VEGFR-3, belonging to the family of tyrosine kinase receptors, capable of transforming and phosphorylating the "target" proteins. VEGF receptors are localized predominantly in endothelial cells and are involved in the regulation of angiogenesis, stabilization of newly formed vessels, changes in their permeability, and dilatation of vessels [4].

A number of pathological conditions of the body are characterized by impaired growth of blood vessels. Excessive angiogenesis is typical for cancer [5,6], diabetic retinopathy [7], rheumatoid arthritis [8,9], atherosclerosis [10], psoriasis [11], endometriosis [12], arterial hypertension [13] and other diseases [14]. Since VEGF is the main stimulator of angiogenesis, much attention is paid to the study of its formation and functioning in these diseases. Of particular interest is focused on the growth of tumors. It is the formation of the new blood supply system that allows the tumor to grow. This process, described as tumor angiogenesis, is also an integral part of the spread of tumor cells and the growth of metastases [6,15,16].

Therefore, VEGF receptors are of great interest as molecular targets for cancer therapy, and the search for new substances with antagonistic activity to them is a very important and urgent task. In this work, using the PASS system [17], we have analyzed the antagonistic activity of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines [18-20] in relation to VEGFR-1.

MATERIALS AND METHODS:

The computer system PASS (Prediction of Activity Spectra for Substances) [21] is based on the concept of the spectrum of biological activity, which is considered as the entire complex of biological effects that a substance can cause under certain conditions of interaction with biological objects, without taking into account the features of specific experiments. The PASS program predicts the spectrum of biological activity of organic compounds based on their structural formulas, i.e. the biological activity of a substance is considered its intrinsic property, which depends only on its structure.

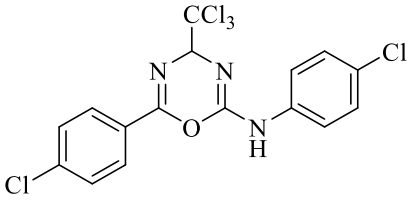
The PASS system evaluates the analyzed compounds according to the criteria of "similarity" or "difference" in relation to the known biologically active substances. The results of the forecast are presented in the form of a list of possible types of activity with estimated evaluation of presence (P_a) and absence (P_i) of activity, which have a value from 0 to 1. The greater the value for a particular activity (P_a) and the smaller the value (P_i), the greater the probability of detecting this activity in experimental conditions.

For forecasting, the structures were introduced on the official website (http://www.pharmaexpert.ru) using the graphical editor Marvin Sketch. After that, these structures were sent to the server in the form of MNA descriptors (*Multilevel Neighborhoods of Atoms*) [17,21]. The results of the prediction of the biological activity spectrum were visualized on the display and saved by "copy-paste".
The forecast of acute toxicity for rats was performed using the GUSAR program [22]. An algorithm similar to that used to predict biological activity in the PASS system was used.

RESULTS AND DISCUSSION:

The probability of antagonism of the analyzed compounds towards VEGFR-1 was 24.7-59.9% (see Table 1).

Table 1: The results of the prediction of antagonism towards VEGFR-1 and acute toxicity of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines



Comp.	Ar	Antagonism of VEGFR-1		Toxic LD_{50} (mg/kg)		Ref.
		P_a	P_i	IV	Oral.	
1	C_6H_5	0.581	0.004	80.190	1735.000	[18]
2	2-Me-C_6H_4	0.435	0.004	63.680	1305.000	[20]
3	2,4-diMe-C_6H_3	0.420	0.004	78.360	1643.000	[18]
4	2-MeO-C_6H_4	0.539	0.004	62.940	588.000	[18]
5	4-EtO-C_6H_4	0.394	0.004	67.650	1475.000	[20]
6	2,5-diMeO-C_6H_3	0.551	0.004	101.400	977.200	[18]
7	2-NO_2-4-MeO-C_6H_3	0.281	0.005	63.330	781.400	[18]
8	4-MeC(O)C_6H_4	0.327	0.005	61.730	2029.000	[20]
9	2-MeOC(O)C_6H_4	0.371	0.005	51.170	1066.000	[20]
10	4-*n*-BuOC(O)C_6H_4	0.247	0.007	116.900	1680.000	[18]
11	2-Br-C_6H_4	0.431	0.004	76.430	519.300	[19]
12	3-Br-C_6H_4	0.515	0.004	74.230	568.700	[18]
13	4-Br-C_6H_4	0.525	0.004	84.360	393.300	[19]
14	2,4-diBr-6-Me-C_6H_2	0.379	0.004	92.590	467,000	[20]
15	2-Cl-C_6H_4	0.498	0.004	71.340	1416.000	[19]
16	4-Cl-C_6H_4	0.599	0.003	84.460	1660.000	[19]
17	2,4-diCl-C_6H_3	0.494	0.004	78.950	1937.000	[19]
18	2,5-diCl-C_6H_3	0.512	0.004	82.520	1336.000	[18]
19	3,4-diCl-C_6H_3	0.583	0.004	104.900	1771.000	[19]
20	2-I-C_6H_4	0.391	0.004	103.600	911.000	[20]
21	4-I-C_6H_4	0.489	0.004	121.300	190.900	[20]
22	4-F-C_6H_4	0.510	0.004	95.120	1087.000	[20]

* IV - The estimated LD_{50} value in intravenous administration.
** Oral - The estimated LD_{50} value in oral administration.

As can be seen from Table 1, the introduction of ester and ester groups into the aromatic substituent of the studied compound significantly reduced the likelihood of antagonism towards VEGFR-1. However, the introduction of any substituent in the *para*- position of the aromatic ring increased the probability of this type of biological activity compared with *ortho*- and *meta*-isomers. The following dependence of the P_a value on the position of the substituent was observed: *para*- > *meta*- > *ortho*-. At the same time, *N*,6-*bis*(4-chlorophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine **16** showed the best results, for which P_a was almost 60%. It should be noted that this compound had relatively low toxicity, its calculated LD_{50} value for oral administration was 1660 mg/kg.

Using the Molinspiration web resource (http://www.molinspiration.com/cgi-bin/properties), the compounds studied were tested for compliance with Lipinski criteria [23]. All compounds meet the

criteria with the exception of **10, 14, 20**, **21**, which had a molecular weight of more than 500 and a lipophilicity coefficient of more than 5 (Table 2).

Table 2: Verification of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines for compliance with Lipinsky criteria

Comp.	Ar	Mr	logP	$Rot._{Bond}$	H_{donor}	$H_{acceptor}$
1	C_6H_5	403.10	5.57	4	1	4
2	2-Me-C_6H_4	417.12	5.97	4	1	4
3	2,4-diMe-C_6H_3	431.15	6.40	4	1	4
4	2-MeO-C_6H_4	433.12	5.58	5	1	5
5	4-EtO-C_6H_4	447.15	6.00	6	1	5
6	2,5-diMeO-C_6H_3	463.15	5.61	6	1	6
7	2-NO_2-4-MeO-C_6H_3	478.12	5.51	6	1	8
8	4-MeC(O)C_6H_4	445.13	5.47	5	1	5
9	2-MeOC(O)C_6H_4	461.13	5.87	6	1	6
10	4-*n*-BuOC(O)C_6H_4	503.21	7.31	9	1	6
11	2-Br-C_6H_4	481.99	6.33	4	1	4
12	3-Br-C_6H_4	481.99	6.36	4	1	4
13	4-Br-C_6H_4	481.99	6.38	4	1	4
14	2,4-diBr-6-Me-C_6H_2	574.91	7.49	4	1	4
15	2-Cl-C_6H_4	437.54	6.20	4	1	4
16	4-Cl-C_6H_4	437.54	6.25	4	1	4
17	2,4-diCl-C_6H_3	471.99	6.86	4	1	4
18	2,5-diCl-C_6H_3	471.99	6.86	4	1	4
19	3,4-diCl-C_6H_3	471.99	6.86	4	1	4
20	2-I-C_6H_4	528.99	6.61	4	1	4
21	4-I-C_6H_4	528.99	6.65	4	1	4
22	4-F-C_6H_4	421.09	5.74	4	1	4

CONCLUSION:

In this study, using the PASS system, we have analyzed the antagonistic activity of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines towards the first type vascular endothelial growth factor receptor (VEGFR-1). It is shown that the probability of antagonism of the analyzed compounds towards VEGFR-1 is 24.7-59.9%. *N*,6-*bis*(4-chlorophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine has shown the best results, for which P_a is almost 60%. It has been established that the introduction of ether and ester groups into an aromatic substituent of the studied compound significantly reduces the likelihood of antagonism towards VEGFR-1. It is shown that the introduction of any substituent in the *para*- position of the aromatic ring increases the probability of manifestation of this type of biological activity compared with *ortho*- and *meta*- isomers. For the studied 4*H*-1,3,5-oxadiazine derivatives, acute toxicity for rats has been calculated by the intravenous and oral routes of administration. All compounds have been tested for compliance with Lipinski criteria.

REFERENCES:

1. Tahergorabi Z, Khazaei M. A Review on Angiogenesis and Its Assays. Iran J Basic Med Sci, 2012; 15 (6): 1110-1126.
2. Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science, 1983; 219 (4587): 983-985. doi: 10.1126/science.6823562
3. Hoeben A, Landuyt B, Highley MS, Wildiers H, Van Oosterom AT, De Bruijn EA. Vascular endothelial growth factor and angiogenesis. Pharmacol Rev, 2004; 56 (4): 549-580. doi: 10.1124/pr.56.4.3
4. Stuttfeld E, Ballmer-Hofer K. Structure and function of VEGF receptors. IUBMB Life. 2009; 61 (9): 915-922. doi: 10.1002/iub.234

5. Kerbel RS. Tumor Angiogenesis. N Engl J Med, 2008; 358 (19): 2039-2049. doi: 10.1056/NEJMra0706596
6. Nishida N, Yano H, Nishida T, Kamura T, Kojiro M. Angiogenesis in cancer. Vasc Health Risk Manag, 2006; 2 (3): 213-219.
7. Gupta N, Mansoor S, Sharma A, Sapkal A, Sheth J, Falatoonzadeh P, Kuppermann BD, Kenney MC. Diabetic Retinopathy and VEGF. Open Ophthalmol J, 2013; 7: 4-10. doi: 10.2174/1874364101307010004
8. Koch AE. The role of angiogenesis in rheumatoid arthritis: recent developments. Ann Rheum Dis, 2000; 59 (suppl 1): i65-i71. doi: 10.1136/ard.59.suppl_1.i65
9. Kim H-R, Kim K-W, Kim B-M, Cho M-L, Lee S-H. The Effect of Vascular Endothelial Growth Factor on Osteoclastogenesis in Rheumatoid Arthritis. PLoS One, 2015; 10 (4): e0124909. doi: 10.1371/journal.pone.0124909
10. Camaré C, Pucelle M, Nègre-Salvayre A, Salvayre R. Angiogenesis in the atherosclerotic plaque. Redox Biol, 2017; 12: 18-34. doi: 10.1016/j.redox.2017.01.007
11. Marina ME, Roman II, Constantin A-M, Mihu C M, Tătaru AD. VEGF involvement in psoriasis. Clujul Med, 2015; 88 (3): 247-252. doi: 10.15386/cjmed-494
12. Rocha ALL, Reis FM, Taylor RN. Angiogenesis and Endometriosis. Obstet Gynecol Int, 2013; ID 859619, 8 pages. doi: 10.1155/2013/859619
13. Mangiliova TA. Vascular endothelial growth factor system and arterial hypertension. Sertse i Sudyny, 2012; 4: 107-115.
14. Shibuya M. VEGF-VEGFR Signals in Health and Disease. Biomol Ther (Seoul), 2014; 22 (1): 1-9. doi: 10.4062/biomolther.2013.113
15. Rajabi M, Mousa ShA. The Role of Angiogenesis in Cancer Treatment. Biomedicines, 2017; 5 (2): 34. doi: 10.3390/biomedicines5020034
16. Goel HL, Mercurio AM. VEGF targets the tumour cell. Nat Rev Cancer, 2013; 13 (12): 871-882. doi: 10.1038/nrc3627
17. Filimonov DA, Lagunin AA, Gloriozova TA, Rudik AV, Druzhilovskii DS, Pogodin PV, Poroikov VV. Prediction of the biological activity spectra of organic compounds using the PASS online web resource, Chem Heterocycl Comp, 2014; 50 (3): 444-457. doi: 10.1007/s10593-014-1496-1
18. Zadorozhnii PV, Kiselev VV, Pokotylo IO, Kharchenko AV. A new method for the synthesis of 4*H*-1,3,5-oxadiazine derivatives. Heterocycl Commun, 2017; 23 (5): 369-374. doi: 10.1515/hc-2017-0083
19. Zadorozhnii PV, Kiselev VV, Pokotylo IO, Okhtina OV, Kharchenko AV. Synthesis and mass spectrometric fragmentation pattern of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines. Heterocycl Commun, 2018; 24 (5): 273-278. doi: 10.1515/hc-2018-0082
20. Zadorozhnii PV, Pokotylo IO, Kiselev VV, Kharchenko AV, Okhtina OV. Synthesis and Spectral Characteristics of Some New 4*H*-1,3,5-Oxadiazine Derivatives. Res J Pharm, Biol Chem Sci, 2019; 10 (1): 1508-1515.
21. Sadym AV, Lagunin AA, Filimonov DA, Poroikov VV. Internet System Predicting the Spectrum of Biological Activity of Chemical Compounds. Pharm Chem J, 2002; 36 (10): 538-543. doi: 10.1023/A:1022402425883
22. Lagunin A, Zakharov A, Filimonov D, Poroikov V. QSAR modelling of rat acute toxicity on the basis of PASS prediction. Mol Inf, 2011; 30 (2-3): 241-250. doi: 10.1002/minf.201000151
23. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Delivery Rev, 1997; 23 (1-3): 3-25. doi: 10.1016/S0169-409X(00)00129-0