The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)
01–30 NOVEMBER 2022 | ONLINE

Modeling of new VHR inhibitors based on 4*H*-1,3,5-oxadiazine derivatives.

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

pharmaceuticals MDPI

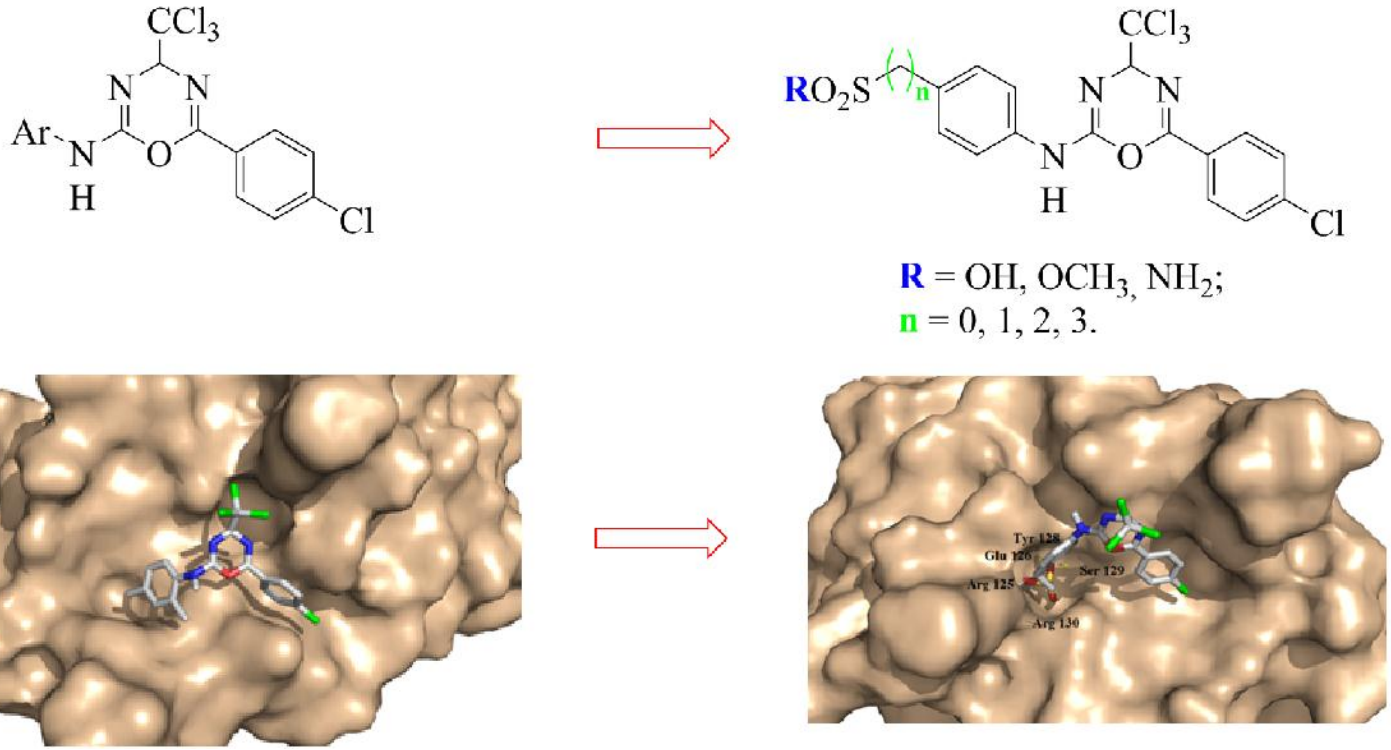
Elizaveta R. Lominoga, Pavlo V. Zadorozhnii *, Olha O. Hrek, Vadym V. Kiselev and Aleksandr V. Kharchenko

Department of Pharmacy and Technology of Organic Substances, Ukrainian State University of Chemical Technology, Gagarin Ave 8, 49005 Dnipro, Ukraine.

* Corresponding author: torfp@i.ua

Modeling of new VHR inhibitors based on 4*H*-1,3,5-oxadiazine derivatives.

Graphical Abstract



Abstract: Vaccinia H1-related phosphatase (VHR) is a dual-specific phosphatase that is a promising potential target for the treatment of many human diseases. In this work, we have proposed a series of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines as potential VHR inhibitors. The SuperPred online server predicts VHR inhibition for the studied compounds with a probability of 88.88-98.51%. To establish the efficiency of binding of 4*H*-1,3,5-oxadiazine derivatives to the active site of VHR (PDB ID: 3F81) in the AutoDock Vina program, we have carried out molecular docking studies. According to its results, the studied compounds effectively interact with the hydrophobic region of the VHR active site due to aromatic rings and the trichloromethyl group, but the polar catalytic cavity is not involved, and therefore inhibition cannot be effective. In this regard, we have built a number of model compounds containing a sulfate group and its derivatives (methyl ester and amide) in the *para*-position of the arylamine fragment. According to the results of molecular docking, these compounds effectively bind to the polar catalytic cavity of the enzyme due to hydrogen bonds, but due to the relative rigidity of their molecules, hydrophobic interactions are not fully realized. Therefore, in these model compounds between the arylamine fragment and the sulfo group, we introduced a spacer with a length of one to three methylene groups. Hit compounds have been selected - 2-(4-((6-(4-chlorophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-yl)amino)phenyl)ethane-1-sulfonic acid and its amide.

Keywords: 4*H*-1,3,5-oxadiazine; molecular docking; VHR; cancer; inhibitor

Introduction

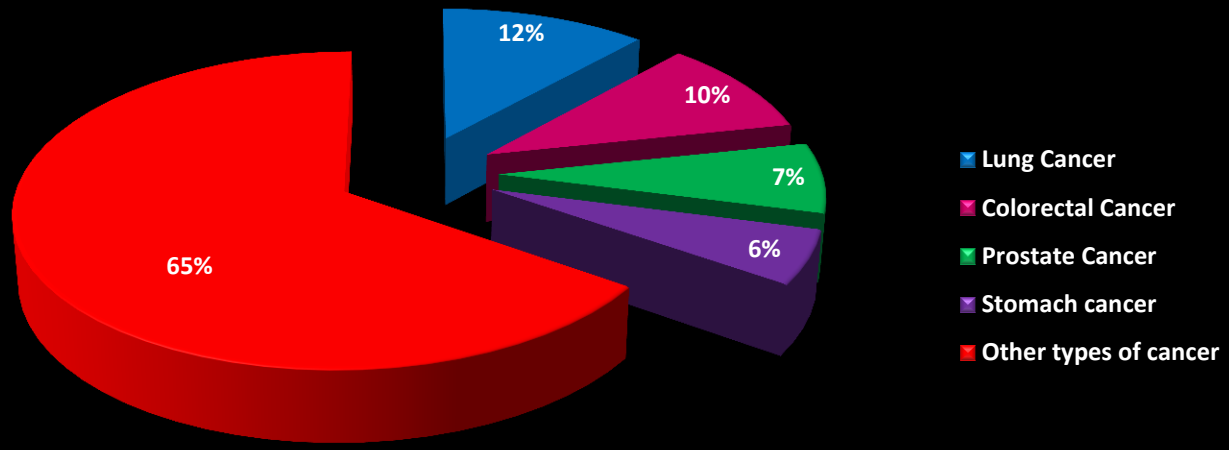


Figure 1. Ratio of some newly diagnosed cancers in 2020.

Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209-249. https://doi.org/10.3322/caac.21660

Introduction

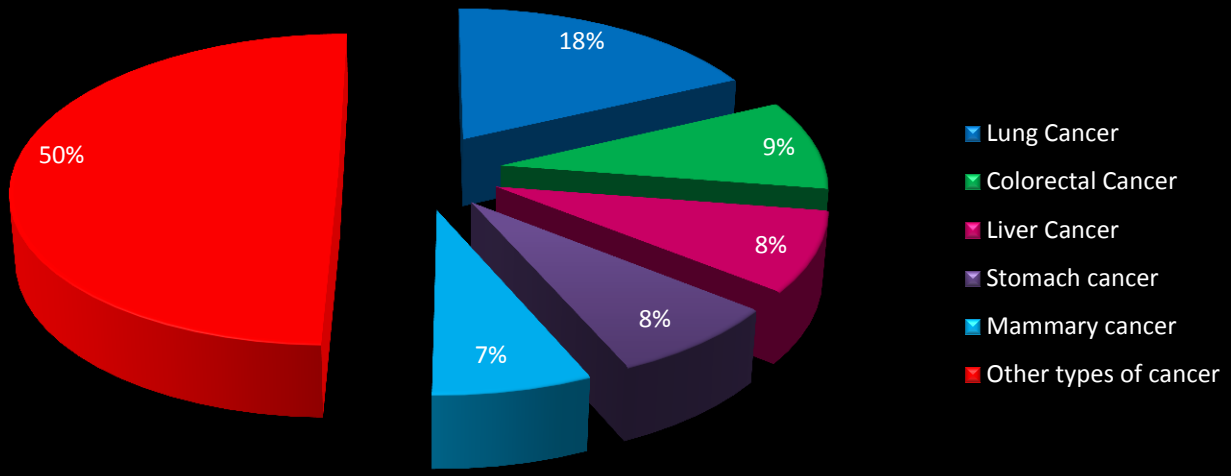
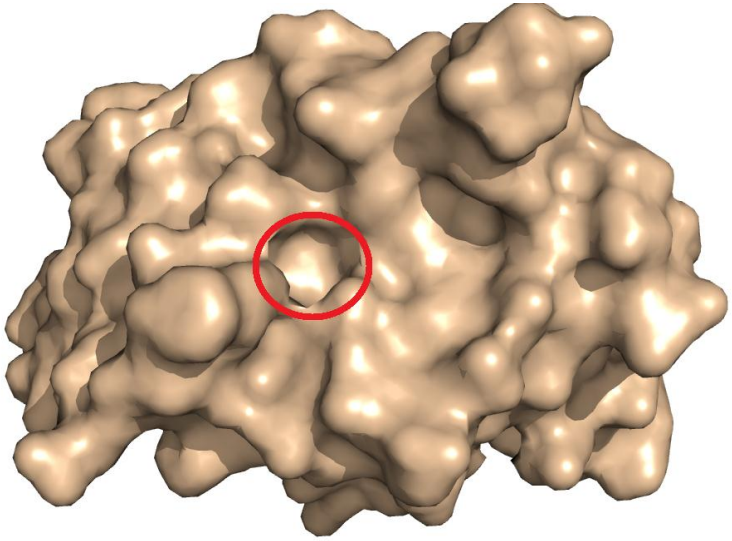


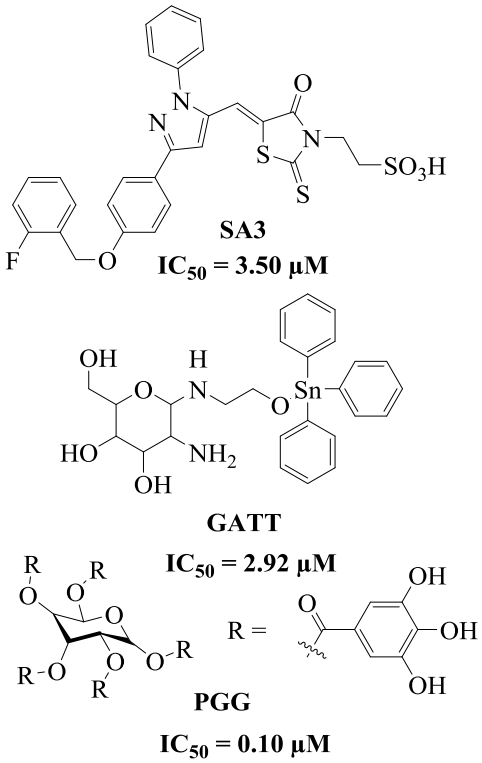
Figure 2. The ratio of deaths from certain types of cancer as of 2020.

Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209-249. https://doi.org/10.3322/caac.21660

Introduction



(a)



(b)

Figure 3. Structure of VHR **(a)** and some of its inhibitors **(b)**.

Wu, S.; Vossius, S.; Rahmouni, S.; Miletic, A.V.; Vang, T.; Vazquez-Rodriguez, J.; Cerignoli, F.; Arimura, Y.; Williams, S.; Hayes, T.; Moutschen, M.; Vasile, S.; Pellecchia, M.; Mustelin, T.; Tautz, L. Multidentate small-molecule inhibitors of vaccinia H1-related (VHR) phosphatase decrease proliferation of cervix cancer cells. *J. Med. Chem.* **2009**, *52*, 6716-6723. https://doi.org/10.1021/jm901016k

Shi, Z.; Tabassum, S.; Jiang, W.; Zhang, J.; Mathur, S.; Wu, J.; Shi, Y. Identification of a potent inhibitor of human dual-specific phosphatase, VHR, from computer-aided and NMR-based screening to cellular effects. *ChemBioChem* **2007**, *8*, 2092-2099. https://doi.org/10.1002/cbic.200700397

Yoon, S.Y.; Kim, D.H.; Min Roh, K.; Ahn, D.; Jin Kang, H.; Chung, S.J. Identification of Vaccinia-H1 Related Phosphatase as an Anticancer Target for 1,2,3,4,6-O-Pentagalloylglucose. *Chem. Biodivers.* **2020**, *17*, e1900414. https://doi.org/10.1002/cbdv.201900414

Introduction

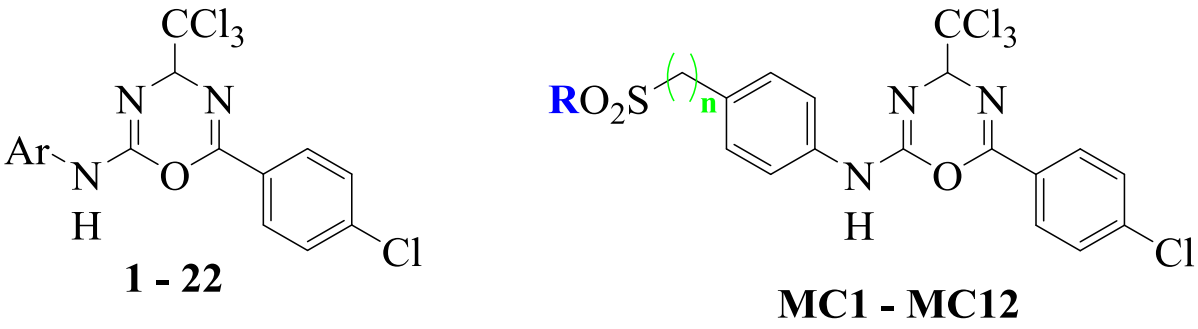


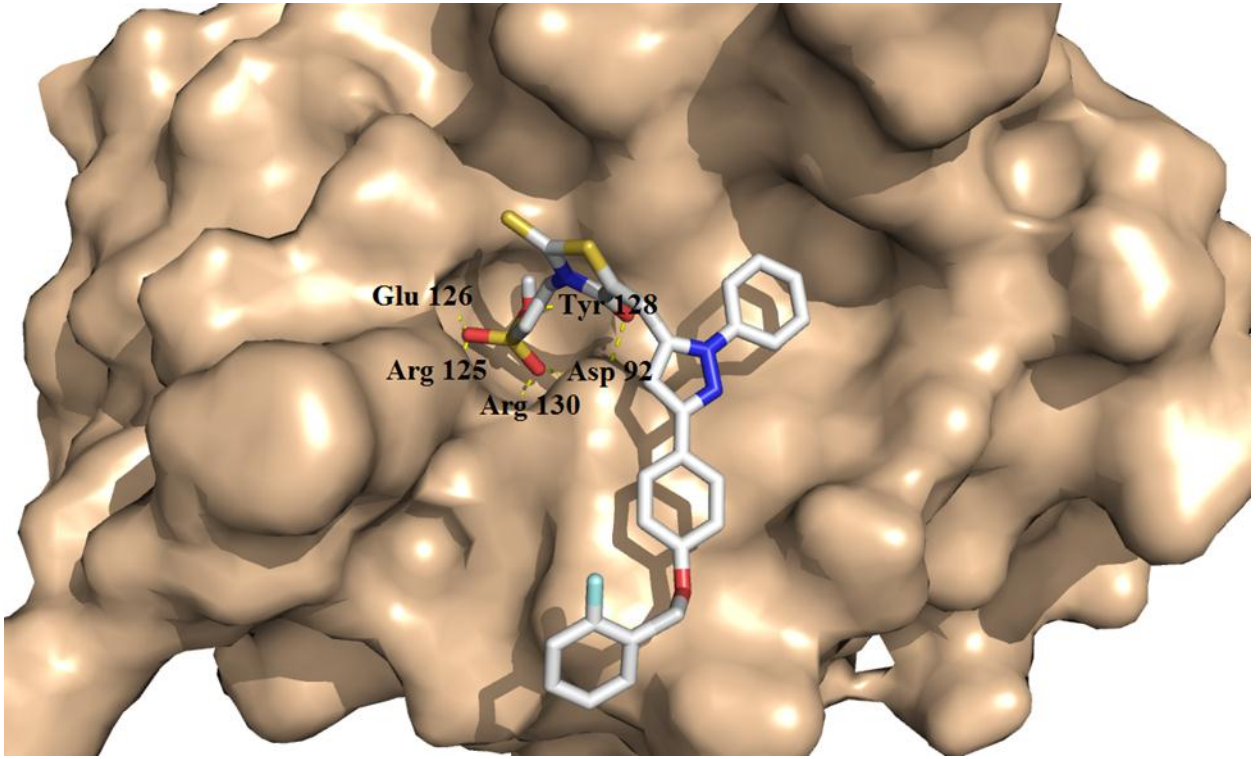
Figure 4. Structures of the studied compounds as potential VHR inhibitors.

Zadorozhnii, P.V.; Kiselev, V.V.; Pokotylo, I.O.; Kharchenko, A.V. A new method for the synthesis of 4*H*-1,3,5-oxadiazine derivatives. *Heterocycl. Commun.* **2017**, *23*, 369-374. https://doi.org/10.1515/hc-2017-0083

Zadorozhnii, P.V.; Kiselev, V.V.; Pokotylo, I.O.; Okhtina, O.V.; Kharchenko, A.V. 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*, 273-278. https://doi.org/10.1515/hc-2018-0082

Zadorozhnii, P.V.; Pokotylo, I.O.; Kiselev, V.V.; Kharchenko, A.V.; Okhtina, O.V. Synthesis and Spectral Characteristics of Some New 4*H*-1,3,5-Oxadiazine Derivatives. *Res. J. Pharm., Biol. Chem. Sci.* **2019**, *10*, 1508-1515.

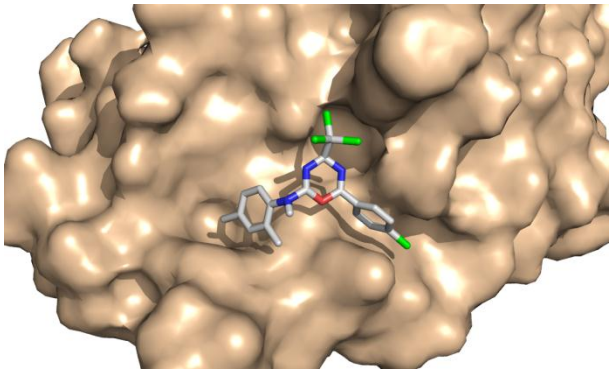
Results and discussion



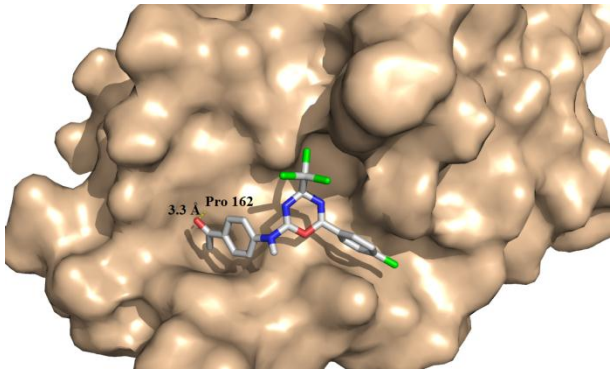
Hydrogen bonds	
Amino acid	**Length, Å**
Asp 92	3.0
Arg 125	3.4
Glu 126	3.0
Tyr 128	3.1
Ser 129	2.9
Arg 130	3.0, 3.2, 3.3

Figure 5. The position of the **SA3** molecule in the active site of the VHR according to the results of molecular docking studies.

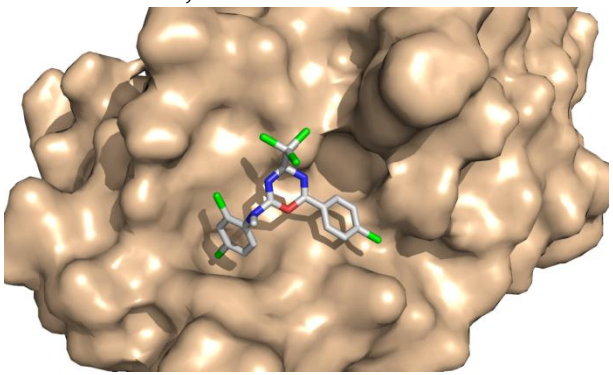
Results and discussion



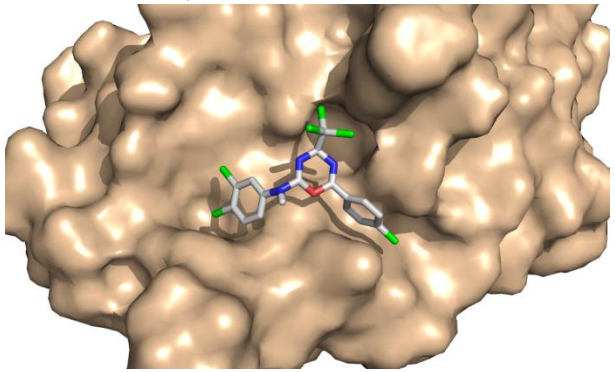
3, ΔG = -7.4 kcal/mol



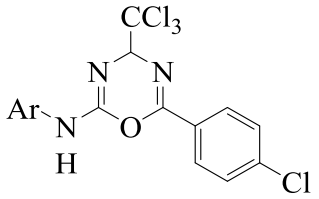
8, ΔG = -7.2 kcal/mol



17, ΔG = -7.1 kcal/mol



19, ΔG = -7.1 kcal/mol



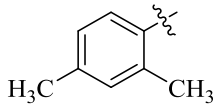
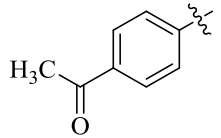
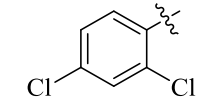
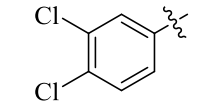
Comp.	Ar
3	
8	
17	
19	

Figure 6. Position of molecules **3**, **8**, **17**, and **19** in the VHR active site from molecular docking studies.

Results and discussion

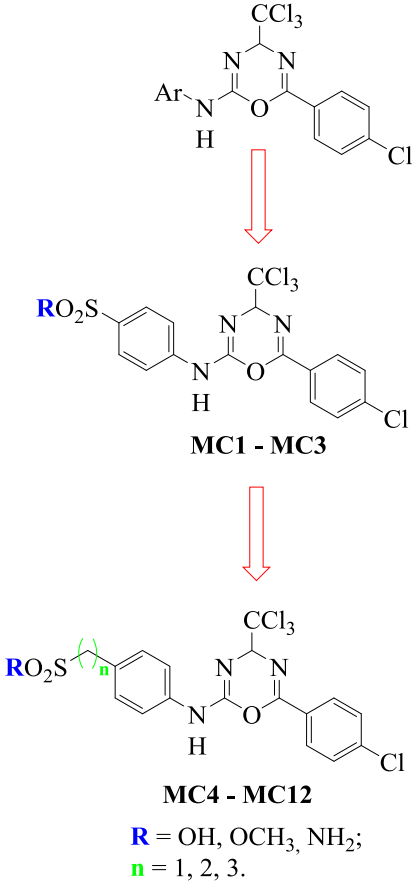
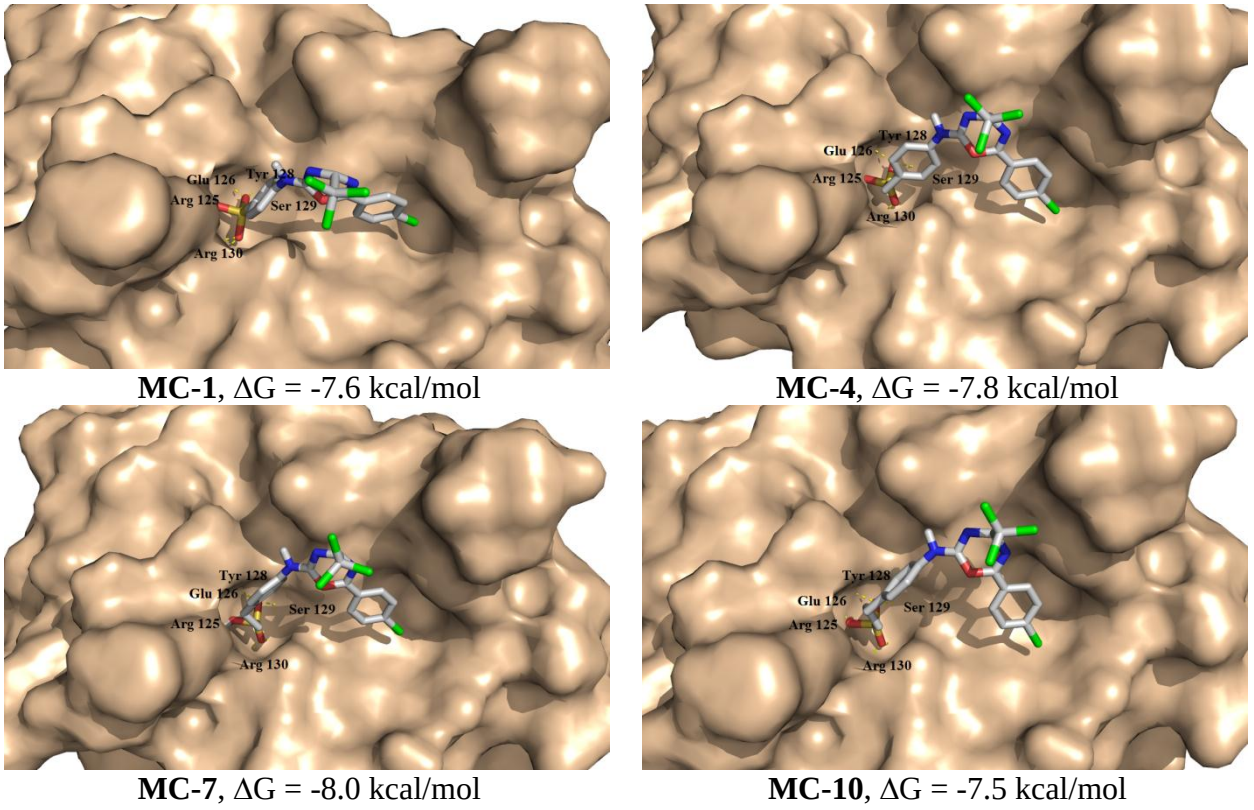


Figure 7. Algorithm for creating model connections **MC1**-**MC12**.



MC-1, ΔG = -7.6 kcal/mol

MC-4, ΔG = -7.8 kcal/mol

MC-7, ΔG = -8.0 kcal/mol

MC-10, ΔG = -7.5 kcal/mol

Figure 8. Differences in the position of the molecules of the model compounds in the VHR active site depending on the length of the spacer between the sulfo group and the aromatic ring.

Conclusions

In this work, using the methods of SAR prediction and molecular docking, we have tested 22 derivatives of 1,3,5-oxadiazine for the potential ability to inhibit VHR. It has been shown that the studied compounds effectively interact with the hydrophobic region of the VHR active site due to aromatic rings and the trichloromethyl group, but interaction with the polar catalytic cavity requires the additional introduction of a highly polar group into the aromatic substituent. In this regard, based on the principles of rational design, we have constructed a series of model compounds containing, directly or through a spacer, a sulfate group and its derivatives (methyl ester and amide) in the *para*- position of the arylamine fragment. According to the results of molecular docking, the most stable complexes with VHR are formed by model compounds containing sulfate or sulfamide groups and a spacer of two methylene groups. Hit compounds have been selected - 2-(4-((6-(4-chlorophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-yl)amino)phenyl)ethane-1-sulfonic acid and its amide, which are superior to the known SA3 inhibitor in terms of binding strength to VHR.

Thank you for your attention!