URA
УКРАЇНСЬКА
НАУКОВО-ДОСЛІДНИЦЬКА
АСОЦІАЦІЯ

ЗАПИСКИ
УКРАЇНСЬКОЇ НАУКОВО-ДОСЛІДНИЦЬКОЇ АСОЦІАЦІЇ

Тези доповідей
Всеукраїнської конференції наукових дослідників
Львів, 19-25 вересня 2021 року

ЛЬВІВ
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УКРАЇНСЬКА НАУКОВО-ДОСЛІДНИЦЬКА АСОЦІАЦІЯ

ЛЬВІВСЬКИЙ НАЦІОНАЛЬНИЙ УНІВЕРСИТЕТ ІМЕНІ ІВАНА ФРАНКА

ЗАПИСКИ УКРАЇНСЬКОЇ НАУКОВО-ДОСЛІДНИЦЬКОЇ АСОЦІАЦІЇ

ТЕЗИ ДОПОВІДЕЙ

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19-25 вересня

2021 року

Львів

2021 рік

IN VITRO AND IN SILICO ESTIMATION OF PYRAZOLO[1,5-a][1,3,5]TRIAZINES

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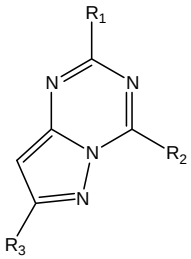
Advancements in drugs design on the basis of the purine cycle inspired parallel development in the chemistry and biology of a structurally related heterocyclic systems for the discovery of novel therapeutic agents that target selectively purine dependent enzymes and receptors, exhibiting antiviral and anticancer activity. Early has been shown that biphenyl substituted pyrazolo[1,5-a][1,3,5]triazine **1** exhibits anticancer and antiviral activity. The next step was to modify compound **1** to the corresponding isomers **2** and **3**:



Compd	R_1	R_2	R_3
1	$-CHCl_2$	$-C_6H_4$	$-C_6H_4$
2	$-C_6H_4$	$-CHCl_2$	$4\text{-Me-}C_6H_4$
3	$4\text{-Me-}C_6H_4$	$-CHCl_2$	$-C_6H_4$

The FBDD strategy was used to screen test (including molecular docking and fragment-to fragment approach) compounds **1-3** for vascular endothelial growth factor (VEGF) because a large number of cancers were dependent on angiogenesis and responded well to antiangiogenic therapy. It turned out that compounds **1-3** are inhibitors of VEGFR2 and interact with ATP binding sites. The *in silico* results show a similar binding mode of compounds 1-3 in the active site VEGFR2 with the formation of stable protein-ligand complexes (Table 1).

Compd / Pro-perties	Molecular docking results, Δ*G*, kcal/mol	"Fragment-to-fragment" approach, Δ*E*, kcal/mol	The Anticancer activity of the compounds **1-3** (the concentrations GI_{50}, TGI and LC_{50}, mol/L, given as lg)*			Topological index φ_0	Barriers of rotation of the residues, Δ*E*, kcal/mol		
			***lg GI_{50}**	***lg TGI**	***lg LC_{50}**		**R_1**	**R_2**	**R_3**
1	-9.4	-10.5	-6.16	-5.60	-5.10	0.374	-	-7.08	-4.17
2	-8.6	-9.1	-6.17	-5.74	-5.34	0.393	-7.57	-	-4.62
3	-8.2	-8.6	-6.32	-5.90	-5.44	0.402	-7.86	-	-4.83
*was obtained as the mean of the values Five Doses Full NCI 60 Cell Panel Assay of the compounds **1-3**									

A joint quantum chemical and experimental study of π-conjugated phenyl substituted isomers of pyrazolo[1,5-a][1,3,5]triazines **1-3** showed that the reduction of barriers to the rotation leads to an increase the anticancer activity, which is in a good agreement with the change in the parameter of biological affinity $\varphi_{ю}$.