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Olena Klenina, Iryna Drapak, Taras Chaban, Volodymyr Ogurtsov, Igor Chaban and Iryna Golos

QSAR STUDIES OF SOME THIAZOLO[4,5-*b*]PYRIDINES AS NOVEL ANTIOXIDANT AGENTS: ENHANCEMENT OF ACTIVITY BY SOME MOLECULAR STRUCTURE PARAMETERS

Danylo Halytsky Lviv National Medical University,
69, Pekarska str., 79010 Lviv, Ukraine; olena_klenina@yahoo.com

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Abstract. The antioxidant activity of novel N^3 and C^6 substituted 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one derivatives was evaluated *in vitro* by the method of scavenging effect on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. The correlation analysis between the antioxidant activity and different subsets molecular descriptors was carried out for 19 compounds. The regression models derived with QSAR-analysis display the significant influence of topological structure, atom and bond type counts, physicochemical properties, and quantum-chemical structure parameters on the free radical scavenging effect of the compounds.

Keywords: thiazolo[4,5-b]pyridines, antioxidant activity, QSAR-analysis, molecular descriptors.

1. Introduction

Antioxidant capacity is related with compounds capable of protecting a biological system against the potentially harmful effect of processes or reactions involving reactive oxygen and nitrogen species (ROS and RNS) [1, 2]. These protective effects of antioxidants have received the increasing attention within biological, medical, nutritional, and agrochemical fields and resulted in the requirement of simple, convenient and reliable antioxidant capacity determination methods.

Many methods which differ from each other in terms of reaction mechanisms, oxidant and target/probe species, reaction conditions, and expression of results have been developed and tested. The use of spectroscopy technique provides an easy, rapid, and convenient method to evaluate the antioxidants and radical scavengers.

The 4-thiazolidone core was recognized as a biophoric structural pattern. Consequently, the combination of 4-thiazolidone template with pyridine moiety can be considered as a promising approach in drug-like molecules design with 4-thiazolidone as a precursor for the synthesis of some polyfunctionally substituted fused derivatives for which we might expect a wide spectrum of bioresponses.

Thiazolo[4,5-*b*]pyridines being considered as a privileged scaffold known to be associated with several biological activities are also of considerable importance as purine isosteres. In particular, the substances possessing fungicidal action [3], antagonists of H3-histamine receptors [4], antagonists of metabotropic glutamate receptors 5 (mGluR5) [5] of high inhibitor activity with respect to the receptors of the epidermal growth factor [6] and a number of other enzymes [7] were found among this type compounds. Fused thiazolidone based heterocycles are also the integral part of new drug discovery with improved free radicals scavenging action.

Quantitative structure-activity (QSAR) analysis is one of the techniques used to investigate the correlation between biological activity and molecular and physicochemical properties of a set of molecules. QSAR models derived provide remarkable information on the structural feature of the drug-like molecules and give guidance for the novel drug design.

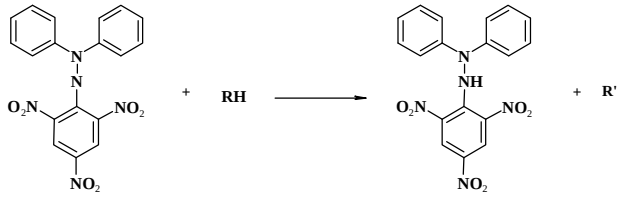
The objectives of the present work is the QSAR studies of some thiazolo[4,5-*b*]pyridine derivatives as novel antioxidant agents. We are reporting on the free radicals scavenging evaluation of N^3 and C^6 substituted 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridines as the response for further QSAR analysis we thought it being essential to perceive the importance of the molecular properties, which are critical in accentuating the biological activity.

2. Experimental

Previously we reported on the development of synthetic approach to the construction of substituted thiazolo[4,5-*b*]pyridines based on 4-iminothiazolidine-2 as an initial compound capable of [3+3] cyclocondensation with acetylacetone and α-phenylazoacetylacetone on account of its N,C-binucleophylic properties [8-10]. Some biological actions of the novel fused heterocycles like antitumor and antioxidant ones have been also evaluated.

In the current report the wider range of N^3 and C^6 substituted 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridines has been evaluated as free radicals scavenging agents. Analysis conditions, substrate and antioxidant concentration simulated real biological systems as much as possible when selecting the antioxidant activity evaluation method. Spectrophotometric DPPH assay was used for free radicals scavenging potency (hydrogen donating ability) of the synthesized thiazolo [4,5-*b*]pyridine derivatives evaluation.

The stable 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) is a kind of nitrogen-centered radical. Because of its odd electron, DPPH in its ethyl alcohol solution gives strong adsorption maxima at 517 nm (purple color) by visible spectroscopy. As the odd electron of the radical becomes paired off in the presence of a hydrogen donor, i.e., a free radical scavenging antioxidant, the adsorption intensity is decreased, and the resulting decolouration is stoichiometric with respect to the number of the electrons captured. The mechanism of free radicals scavenging with DPPH is depicted in Scheme 1.



Scheme 1. DPPH free radical scavenging reaction mechanism

The effect of the studied compounds on DPPH radicals was estimated according to the method of Blois [11, 12] with minor modifications. The free-radical-scavenging activities of each compound were assayed using a stable DPPH and were quantified by decolorization the solution being mixed with DHHP at a wavelength of 540 nm. The absorbance of DPPH solution in ethanol (150 μmol/l) was measured as 0.770. Ascorbic acid was used as a positive standard.

The QSAR studies workflow included a few stages. Firstly the input geometries of novel thiazolo [4,5-*b*]pyridine derivatives were minimized with molecular dynamics simulation followed by semi-empirical quantum chemical AM1 method implemented into HyperChem software [13]. On the next stage > 1600 molecular descriptors were generated with DRAGON E-version software [14, 15] for the whole structures set. Stepwise variables selection procedure for the statistically significant QSAR models development as multiple linear regression equations was performed with BuildQSAR software [16] application. The predictive ability of the deriver models was also estimated.

3. Results and Discussion

3.1. Free Radical Scavenging Screening Results

A series of novel 5,7-dimethyl-3*H*-thiazolo [4,5-*b*]pyridines has been evaluated as free radicals scavenging agents with DPPH assay. The selected structures of N^3 and C^6 substituted 5,7-dimethyl-3*H*-thiazolo[4,5-b]pyridine derivatives are depicted in Fig. 1, while the substituents R and R^1 structures and percentage of free-radical-scavenging activity expressed *via* percent inhibition are listed in Table 1. Each experiment was performed in triplicate and average values were recorded.

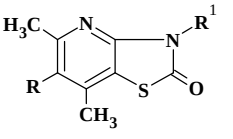


Fig. 1. Thiazolo[4,5-*b*]pyridines scaffold structure

The pharmacology screening allowed identifying five leading compounds so free radical scavenging activities exceed those of ascorbic acid. Their structures are depicted in Fig. 2.

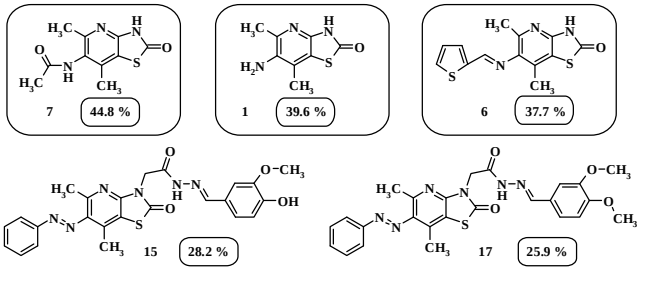
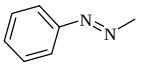
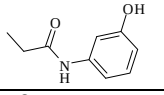
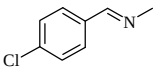
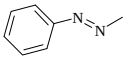
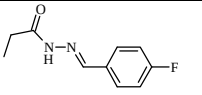
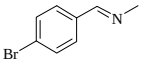
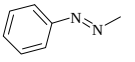
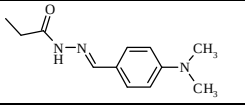
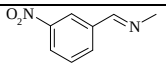
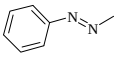
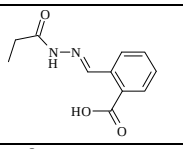
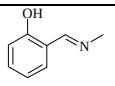
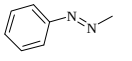
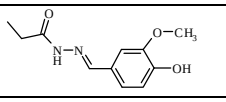
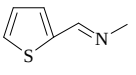
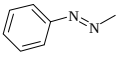
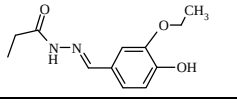
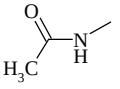
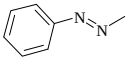
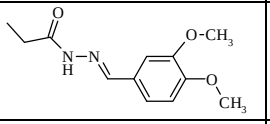
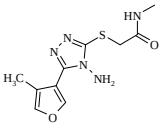
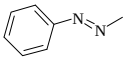
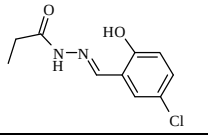
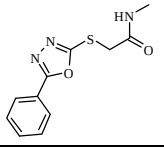
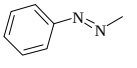
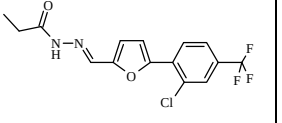
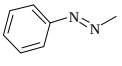
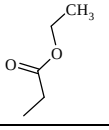


Fig. 2. Leading structures of novel thiazolo[4,5-*b*]pyridines as free radical scavengers. The rest of the compounds possess low or moderate antioxidant activity

Table 1

N^3 and C^6 substituents structures and free radical scavenging activity evaluation for 5,7-dimethyl-3*H*-thiazolo[4,5-b]pyridine derivatives

Compo-und ID	R	R^1	% Inhibition	Compound ID	*R*	R^1	% Inhibition
1	NH_2	H	39.6	**11**			9.0
2		H	10.4	**12**			10.5
3		H	11.0	**13**			10.6
4		H	20.0	**14**			11.0
5		H	10.4	**15**			28.2
6		H	37.7	**16**			17.0
7		H	44.8	**17**			25.9
8		H	9.0	**18**			21.8
9		H	9.3	**19**			9.9
10			13.9	**Ascorbic acid**			24.7

3.2. Quantitative Structure-Activity Relationship Studies (QSAR)

3.2.1. Data sets preparation and molecular descriptors calculation

2*D* structures of all molecules were drawn and converted to 3*D* structures using Hyper-Chem 7.5 software. The model built and the molecular mechanics energy minimized of all compounds were carried out by using the MM+ force field, and repeated minimization was performed using the semi-empirical AM1 quantum-chemical method until the root-mean-square (rms) deviation of 0.001 kcal/mol was achieved. Conformations of compounds were optimized through a semiempirical AM1 method with the global minimum selection among all energy-minimal conformers. SD file prepared with 3*D* globally minimized structures was used as inputs for E-DRAGON software.

The software was used for calculating 20 subsets of molecular descriptors which have been further grouped according to their dimensionality as: 0*D*, 1*D*, 2*D*, and 3*D* as

Table 2

Some constitutional 0*D* descriptors for thiazolo[4,5-*b*]pyridine-2-ones

Compound ID	*Sv*	*Se*	*nAT*	*nSK*	*nBT*	*ARR*	*RBF*
1	14.37	22.36	22	13	23	0.429	0
2	23.27	33.45	33	21	35	0.522	0.057
3	23.66	33.36	33	21	35	0.522	0.057
4	20.79	30.23	29	21	31	0.522	0.097
5	23.08	34.45	34	21	36	0.522	0.056
6	21.06	30.32	30	19	32	0.524	0.063
7	17.48	27.57	27	16	28	0.353	0.036
8	30.66	47.27	46	29	49	0.5	0.102
9	29.67	44.06	43	28	46	0.548	0.109
10	28.78	44.65	44	26	46	0.429	0.13
11	33.78	50.75	50	31	53	0.529	0.094
12	35.37	53.04	52	33	55	0.5	0.109
13	39.45	60.4	60	35	63	0.474	0.111
14	37.28	56.18	55	35	58	0.474	0.121
15	37.88	58.07	57	35	60	0.474	0.117
16	39.48	60.95	60	36	63	0.462	0.127
17	39.48	60.95	60	36	63	0.462	0.127
18	36.47	54.18	53	34	56	0.486	0.107
19	43	64.48	62	42	66	0.5	0.106

Table 3

Constitutional descriptors identification

Descriptor	Explanation
nAT	Number of atoms
Se	Sum of atomic Sanderson electronegativities (scaled on Carbon atom)
nBT	Number of bonds
ARR	Aromaticity ratio
Sv	Sum of atomic van der Waals volumes (scaled on Carbon atom)
nSK	Number of non-H atoms
nAB	Number of aromatic bonds
RBF	Rotatable bond fraction

well as "Others" group descriptors. Each group of descriptors was subjected to stepwise multiply linear regression analysis for the most significant variables being able to explain as much of the activity diversity as possible. Some 0*D*, 2*D*, "Molecular properties" subset and quantum-chemical descriptors were recognized to reflect the structural diversity of the compounds with the respect of their antioxidant activity variance explanation.

Constitutional descriptors being 0*D* subset ones are independent from molecular connectivity and conformations and refer to atom and bond type counts. Some Constitutional DRAGON generated descriptors are listed in Table 2 while their identification is described in Table 3.

2*D* descriptors, called graph invariants or topologic descriptors, are derived from molecular graph, and are conformationally independent. "Molecular properties" subgroup descriptors define some physicochemical properties of substances while quantum chemical descriptors generated with HyperChem software referred to descriptors derived from quantum-chemical molecular system description taking into account the electronic density distribution between the atoms in a molecule and atoms partial charges. Some of these groups descriptors for the synthesized thiazolo [4,5-*b*]pyridine derivatives and their identifications are listed in Tables 4 and 5, respectively.

3.2.2. Descriptors selection strategy and predictive QSAR models generation

The QSAR models including different dimensionality subsets descriptors were generated by Multiple Linear Regression (MLR) method with BuiltQSAR

software [16] using. Multivariate regressions derived in this way relate the dependent variable as a free radical scavenging inhibition percent to a number of independent variables (molecular descriptor) by using linear equations. This method of regression estimates the values of the regression coefficients by applying the least square curve fitting method. MLR is the traditional and standard approach for multivariate data analysis of multidimensional data metrices by using statistical evaluation techniques. For getting reliable results, parameters were set so that the regression equation might generate a number of independent variables (*M*) 5 times less than that of compounds (N): $N/M \geq 5$. The program computes the best model on the basis of correlation coefficient *R*, standard deviation *s*, Fischer's value which represents *F*-ratio between the variance of calculated and observed activity, while the models predictive ability was validated by using leave-one-out cross validation coefficient (Q^2_{LOO}), prediction errors sum of squares standard deviation S_{PRESS}, and prediction error standard deviation S_{DEP}. The larger *F* index and the small confidence interval *p* value indicate the high level of statistical significance of the model.

The best bivariate linear regressions obtained with constitutional descriptors are listed in Table 6 while their statistical parameters are listed in Table 7. Combination of 0*D* descriptors yielded in seven top statistically significant QSAR models construction suggesting the correlation coefficients ranging as $R = 0.817–0.836$. These models are able to describe about 55 % of the LOO cross-validation variance. At the multivariate linear regression models generation the compound **6** was recognized as an outlier and it was expelled from the general compounds set.The next stage of QSAR studies workflow included the regressions development with the groups of 2*D*, "Molecular properties" subset and quantum-chemical descriptors. The QSAR models derived in this way of the best statistics fitting and the highest predictive ability are listed in Table 8 while their statistical parameters are listed in Table 9.

It may be observed that the resulted QSAR models displayed a high level of accuracy and predictivity the last one achieves the highest value in regressions **9**, **16**, and **19**.

3.2.3. Outcome of the QSAR studies

All regression coefficients negative sign for the Models **1-7** obtained with Constitutional descriptor show their negative contribution to the antioxidant action. By interpretation these QSAR models it is possible to predict that an improvement in biological activity could be achieved by decreasing the total number of atoms as well as the number of non-H atoms which would result in the number of bonds and rotatable bonds decreasing. The number of aromatic rings and aromaticity ratio decreasing would also result in free radicals scavenging

Table 4

Some 2*D*, "Molecular properties" subset and quantum-chemical descriptors generated for thiazolo[4,5-*b*]pyridine-2-one derivatives

Compound ID	*JGI*9	*BELm*2	*BELv*2	*BELe*1	*BEHp*1	*BELp*2	*BELe*2	*X*1*A*	*GATS*3*p*	*MATS*3*e*	*MLOGP*	E_{HOMO}, eV	log*P*
1	0.000	1.47	1.444	1.831	3.875	1.438	1.187	0.435	0.982	-0.193	0.672	-8.2387	1.22
2	0.008	1.86	1.878	1.88	3.902	1.869	1.795	0.437	1.034	-0.162	3.116	-8.7690	4.3
3	0.008	1.856	1.875	1.881	3.904	1.866	1.796	0.437	0.901	-0.156	3.239	-8.8846	4.57
4	0.008	1.803	1.883	1.887	3.87	1.891	1.756	0.44	0.986	-0.245	2.126	-9.3272	-5.14
5	0.011	1.867	1.892	1.882	3.901	1.888	1.797	0.437	1.065	-0.198	2.079	-8.6172	3.49
6	0.007	1.602	1.591	1.846	3.922	1.580	1.481	0.436	1.000	-0.127	2.157	-8.7010	1.24
7	0.000	1.555	1.584	1.84	3.881	1.583	1.320	0.440	0.916	-0.122	0.825	-8.5901	0.85
8	0.008	1.738	1.794	1.841	3.889	1.804	1.647	0.433	1.320	-0.154	2.401	-9.2223	0.96
9	0.008	1.893	1.933	1.846	3.888	1.926	1.84	0.436	1.302	-0.172	3.222	-8.8898	4.05
10	0.007	1.874	1.891	1.862	3.899	1.886	1.798	0.447	1.029	-0.058	2.559	-8.8457	4.47
11	0.009	1.925	1.940	1.863	3.903	1.938	1.832	0.439	1.114	-0.138	2.356	-8.7146	4.87
12	0.007	1.931	1.935	1.862	3.902	1.932	1.842	0.442	1.065	-0.091	3.419	-8.7850	5.91
13	0.008	1.942	1.967	1.871	3.904	1.964	1.862	0.443	1.084	-0.019	2.993	-8.4844	6.04
14	0.008	1.942	1.958	1.875	3.904	1.955	1.862	0.443	1.036	-0.096	2.797	-9.0269	-0.09
15	0.006	1.927	1.954	1.862	3.903	1.953	1.851	0.444	1.036	-0.004	2.054	-8.7798	5.24
16	0.007	1.929	1.956	1.862	3.903	1.956	1.852	0.445	1.042	0.003	2.262	-8.7279	5.58
17	0.007	1.93	1.959	1.863	3.903	1.958	1.854	0.446	1.024	0.009	2.262	-8.7167	5.27
18	0.008	1.904	1.933	1.862	3.903	1.929	1.843	0.441	1.065	-0.141	2.785	-8.8265	6.01
19	0.007	1.931	1.943	1.882	3.932	1.937	1.862	0.435	0.897	-0.105	3.943	-8.8004	5.66

Table 5

2*D*, "Molecular properties"subset and quantum-chemical descriptors identification

Descriptor	Subset	Explanation
MLOGP	Molecular properties	Moriguchi octanol-water partition coefficient (log*P*)
E_{HOMO}	Quantum chemical	Energy of the highest occupied molecular orbital, eV
log*P*	Molecular properties	Octanol-water partition coefficient (HyperChem)
*JGI*9	Topological charge indices	Mean topological charge index of order 9, Galvez topological charge index
*BELm*2	Burden eigenvalues	Smallest eigenvalue n. 2 of Burden matrix weighted by mass
*BELv*2	Burden eigenvalues	Smallest eigenvalue n. 2 of Burden matrix weighted by van der Waals volume
*BELe*1	Burden eigenvalues	Smallest eigenvalue n. 1 of Burden matrix weighted by electronegativity
*BELp*2	Burden eigenvalues	Smallest eigenvalue n. 2 of Burden matrix weighted by polarizability
*BELe*2	Burden eigenvalues	Smallest eigenvalue n. 2 of Burden matrix weighted by electronegativity
*BEHp*1	Burden eigenvalues	Largest eigenvalue n. 1 of Burden matrix weighted by polarizability
*MATS*3*e*	2*D* autocorrelations	Moran autocorrelation of lag 3 weighted by Sanderson electronegativity
*GATS*3*p*	2*D* autocorrelations	Geary autocorrelation of lag 3 weighted by polarizability
*X*1*A*	Connectivity indices	Average connectivity index of order 1

Table 6

Bivariate QSAR models: % = $a^{x}X_1 + b^{x}X_2 + c$ obtained with Constitutional 0*D* descriptor

Model ID	*a*	X_1	*b*	X_2	*c*
1	- 0.238	*nAT*	- 172.542	*ARR*	111.667
2	- 0.231	*Se*	- 172.285	*ARR*	111.418
3	- 0.226	*nBT*	- 171.182	*ARR*	111.035
4	- 164.706	*ARR*	- 96.1078	*RBF*	105.910
5	- 0.361	*Sv*	- 168.131	*ARR*	109.783
6	- 0.364	*nSK*	- 167.165	*ARR*	108.595
7	- 150.438	*ARR*	- 0.686	*nAB*	100.493

Table 7

Statistical parameters of 0*D* QSAR regressions

Model ID	*n*	*R*	*s*	*F*	Q^2_{LOO}	S_{PRESS}	*p*	S_{DEP}
1	18	0.826	6.526	16.070	0.563	7.644	0.0002	7.180
2	18	0.825	6.544	15.939	0.561	7.665	0.0002	7.200
3	18	0.826	6.529	16.051	0.563	7.646	0.0002	7.183
4	18	0.836	6.341	17.470	0.584	7.460	0.0001	7.008
5	18	0.825	6.543	15.947	0.562	7.660	0.0002	7.196
6	18	0.820	6.627	15.357	0.550	7.760	0.0002	7.289
7	18	0.817	6.676	15.020	0.542	7.832	0.0003	7.357

Table 8

Monovariate, bivariate, and trivariate QSAR models % = $a^{x}X_1 + b^{x}X_2 + c^{x}X_3 + d$ obtained with 2*D*, "Molecular properties" subgroup and quantum-chemical descriptors

Model ID	*a*	X_1	*b*	X_2	*c*	X_3	*d*
8	- 3457.812	*JGI*9	–	–	–	–	41.363
9	- 10.819	*MLOGP*	–	–	–	–	44.464
10	- 79.469	*BELp*2	1809.200	*X*1*A*	–	–	- 628.957
11	- 80.457	*BELm*2	66.767	*MATS*3*e*	–	–	174.554
12	- 29.328	*GATS*3*p*	- 10.274	*MLOGP*	–	–	73.890
13	- 80.888	*BELm*2	1407.312	*X*1*A*	–	–	- 452.011
14	- 75.463	*BELv*2	1355.532	*X*1*A*	–	–	- 437.486
15	- 582.174	*BELe*1	- 73.078	*GATS*3*p*	–	–	1179.574
16	- 56.175	*BELe*2	1188.178	*X*1*A*	–	–	- 406.332
17	- 94.525	*BELm*2	167.725	*BEHp*1	1978.877	*X*1*A*	- 1331.529
18	- 567.803	*BELe*1	- 71.105	*GATS*3*p*	- 0.874	logP	1153.700
19	- 77.182	*BELm*2	1337.527	*X*1*A*	5.053	E_{HOMO}	383.722

Table 9

Statistical parameters of 2*D*, "Molecular properties" subset and quantum-chemical QSAR regressions

Model ID	*n*	*R*	*s*	*F*	Q^2_{LOO}	S_{PRESS}	*p*	S_{DEP}
8	18	0.869	5.534	49.569	0.699	6.142	< 0.0001	5.958
9	18	0.822	6.376	33.393	0.570	7.348	< 0.0001	7.129
10	18	0.917	5.026	39.586	0.765	6.103	< 0.0001	5.733
11	18	0.905	5.275	33.939	0.730	6.438	< 0.0001	6.048
12	18	0.876	5.584	24.700	0.664	6.703	< 0.0001	6.296
13	19	0.879	5.845	27.125	0.659	7.148	< 0.0001	6.739
14	19	0.874	5.947	25.929	0.643	7.319	< 0.0001	6.900
15	19	0.873	5.972	25.651	0.677	6.963	< 0.0001	6.565
16	19	0.871	6.012	25.199	0.642	7.323	< 0.0001	6.905
17	18	0.937	4.538	33.838	0.818	5.558	< 0.0001	5.043
18	19	0.900	5.522	21.236	0.679	7.168	< 0.0001	6.544
19	19	0.884	5.910	17.908	0.634	7.655	< 0.0001	6.988

activity improving. The presence of strong electro-negative atoms or bulky substituents in a molecular structure will influence negatively the antioxidant activity as it is depicted with the correlation coefficients negative signs for sum of atomic Sanderson electronegativities and sum of atomic van der Waals volumes (scaled on carbon atom) descriptors. Thus, it is obvious that just small aromatic molecules containing no substituents and bulk atoms with high electronegativity would possess the strongest antioxidant effect.

The regressions **8-19** obtained with 2*D*, "molecular properties" subset and quantum-chemical descriptors display the most significant influence of some molecular properties of the compounds particularly lipophilicity, the highest occupied molecular orbital energy quantum-chemical descriptor and Burden matrix eigenvalues, Topological charges indices, 2*D* autocorrelations and connectivity indices 2*D* blocks descriptors towards the free radical scavenging activity. Compound **6** was recognized as an outlier and was expelled from the compounds set while models **8-12** and **17** were constructed.

According to the free-radical-scavenging activity QSAR models **9**, **12**, and **18** Moriguchi octanol-water partition coefficient *MLOGP* [17] and HyperChem generated octanol-water partition coefficient log*P* make negative contribution to potency of inhibition, so the decrease of lipophilicity enhances the antioxidant activity of the synthesized compounds.

The absolute value decreasing of the highest occupied molecular orbital energy E_{HOMO} contributes positively to the free radical scavenging enhancing as it is suggested with **19** QSAR regression. Thus the percent inhibition of radical reactive species with thiazolo[4,5-b]pyridines would become stronger with their reduction ability increasing.

QSAR models **10**, **11**, **13-16**, and **18-19** were derived with Burden matrix eigenvalues descriptors: lowest eigenvalues no. 2, weighted with atomic mass (*BELm*2), by van der Waals volume (*BELv*2), Sanderson electronegativity (*BELe*2), and polarizability (*BELp*2), and also the lowest eigenvalues no. 1 of Burden matrix, weighted with polarizability (*BEHp*1). Highest eigenvalues no. 2 of Burden matrix, weighted with polarizability (*BEHp*1) are included into model **17**. These variables have different contributions to the antioxidant activity according to the regression coefficients: negative signs of the regression coefficients for all lowest eigenvalues of Burden matrix and the considerable positive regression coefficient for the highest Burden matrix eigenvalue suggests that the scavenging activity would increase with all listed lowest Burden matrix eigenvalues decreasing and the indicated highest Burden matrix eigenvalue increasing.

Burden matrix eigenvalues molecular descriptors are generated from the modified connectivity matrix (based on the H-depleted molecular graph) where the diagonal elements are atomic numbers and the off-diagonal elements are associated with the connectivity between the pair of atoms and equal $p^* \cdot 10^{-1}$ where p^* corresponds to the relative bond order being defined as 0.1, 0.2, 0.3 and 0.15 for single, double, triple and aromatic bonds, respectively. But now the whole matrix diagonal elements correspond to atomic masses, atomic van der Waals volumes, Sanderson electronegativities and atomic polarizabilities. The lowest eigenvalues represent the topology of the whole molecule. The highest eigenvalues represent the information about the electronic surroundings of atoms and thus relates the eigenvalues of the electronic distribution of the entire molecule.

So the models which contain Burden matrix eigenvalues may be interpreted as follows: the free radical scavenging activity enhancing would be observed in the case of molecules composed by small atoms with low atomic masses, electronegativities and polarizabilities. Moreover the double or aromatic bonds formation between the atoms with high polarizabilities would be preferable.

The presence of lag 3 2*D* autocorrelations in QSAR regressions **4**, **5**, **8**, and **11** may be reviewed as the association of activity information content with structural fragments of such size. It should be noted that

electronegativity weighted Moran autocorrelation coefficient *MATS*3*e* makes a positive contribution to the free radical scavenging activity while the polarizability weighted Geary graph spatial auto-correlation coefficient *GATS*3*p* makes a negative contribution. In another words, the presence of structural fragments of lag 3, in which the terminal atoms have high electronegativity and low polarizability would be preferable for the antioxidant activity enhancing.

The model **8** was derived by using Galvez mean topological charge index of order 9 (*JGI*9) which influences negatively the compounds antioxidant action possessing. In general Galvez topological charges indices describe the molecular topology and the charge transfer through the molecule. The highest values of *JGI*9 descriptor for compounds **5** and **11** show mainly the relative position of hydroxyl group electronic density that is altered around the phenyl ring this group is attached to and possess the most probable electro-topological conformation of the molecules. The model interpretation indicates this descriptor negative contribution into the antioxidant activity which corresponds to the minimal electron density transferring throughout the molecule.

QSAR models **10**, **13**, **14**, **16**, and **18** contain the average connectivity index of order 1 (*X*1*A*) which makes the significant positive contribution to the activity enhancing. Randic connectivity indices descriptors may be interpreted as a contribution of one molecule into the bimolecular interaction which may occur as a result of two identical molecules intersection. Thus, the interpretation of these models may propose the increase in antioxidant activity of the compounds in case of the minimal vertices degrees for each two adjacent vertices of the molecular graph that is when all bonds can participate in the intersection within the intermolecular interactions. This interpretation excludes the presence of branched substituents in the molecules of antioxidant potential.

Conclusions

QSAR studies for the series of novel 3*H*-thiazolo[4,5-b]pyridine-2-one derivatives were developed as their computation involves integration of the structural fragments, quantum-chemical molecular parameters, physicochemical molecular information, atom and bond types counts making it possible to traverse backward from a large amount of structural features into a single number of a structural interpretation.

The interpretation of the QSAR models derived with multiply linear regression technique reveals the antioxidant action enhancing with the increase of the synthesized compounds hydrophilic properties and reduction ability. Moreover small aromatic molecules without bulky and branched substituent or atoms with high electronegativity are supposed to possess a stronger free radical scavenging activity.

It has been demonstrated statistically that achieved models could be used for identifying novel free radical scavengers based on the same congeneric series.

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QSAR АНАЛІЗ ДЕЯКИХ ТІАЗОЛО[4,5-*b*] ПІРИДИНІВ ЯК НОВИХ АНТИОКСИДАНТНИХ АГЕНТІВ: ВПЛИВ ДЕЯКИХ ПАРАМЕТРІВ МОЛЕКУЛЯРНОЇ БУДОВИ СПОЛУК НА ЗРОСТАННЯ ЇХ АКТИВНОСТІ

Анотація. *Визначено антиоксидантну активність синтезованих похідних 5,7-диметил-тіазоло[4,5-b]піридин-2-ону, що містять замісники різної природи у 3-му та 6-му положеннях базового гетероциклу. Антиоксидантну активність сполук досліджували in vitro, визначаючи зменшення концентрації вільного радикалу 2,2-дифеніл-1-пікрилгідразилу. Для виборки з 19 похідних було проведено кореляційний аналіз залежності їх антиоксидантної активності від різних типів молекулярних дескрипторів. Аналіз рівнянь регресії, одержаних на основі проведеного QSAR аналізу, свідчить про суттєвий вплив топологічної будови молекул, кількостей атомів та зв'язків різних типів, фізико-хімічних властивостей речовин та квантово-хімічних параметрів їх структури на величини радикалпоглинаючої активності досліджуваних сполук.*

Ключові слова: *похідні тіазоло[4,5-b]піридину, антиоксидантна активність, QSAR аналіз, молекулярні дескриптори.*