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Research Article

QSAR-analysis of 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholine-4-yl]propyl)-2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one's derivatives as potential antioxidants

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Abstract

Aim. The aim of study was to determine of the parameters of the molecular structure of new 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholine-4-yl]propyl)-2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one derivatives and QSAR-analysis. The latter can be considered as the theoretical basis for de novo design of new potential antioxidants.

Materials and methods. 14 new derivatives of 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholine-4-yl] propyl)-2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one were involved in the study and their antioxidant activities were evaluated. Hyper-Chem 7.59 and Build-QSAR software were used for calculation of molecular descriptors and building the QSAR-models.

Results. The calculation of number of molecular descriptors (electronic, steric, geometric, energy) was carried out for the tested compounds: 14 derivatives of 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholine-4-yl] propyl) -2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one. For QSAR analysis, the compounds studied were divided into a training and test sample. The correlations between the antioxidant activity level and abovementioned molecular descriptors were shown in multivariate linear QSAR-model: Activity = $\Sigma x_i a_i + b_i$, where x_i – molecular descriptor. Based on the analysis of the obtained QSAR-models, it was found that antioxidant activity increases with decreasing of the area, molecular volume, lipophilicity, polarisation and increasing the magnitude of the dipole moment. The increase in the energy of the bonds, the energy of inter-nuclear interactions, the energy of the lower vacant molecular orbit and the reduction of the energy of hydration and energy of the higher vacant molecular orbitals also results in an increase in the antioxidant activity. The greatest effect of effective charges on atoms on the antioxidant activity was detected: the increase in the charge value on the morpholine cycle Oxygen and the decrease in the charge size on the Sulphur atom of the thiazole ring and the Oxygen atom of the acetyl group. QSAR models with better statistics were selected. QSAR models obtained are characterised by high predictive ability, determined both by internal and external validation and can be used for virtual screening of the antioxidant activity of substances of this class of compounds.

Conclusions. 1). The study of the structure–activity relationships for 1-[2-(R-phenylimino)-4-methyl-3-(3- [morpholine-4-yl]propyl)-2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one derivatives were carried out. 2). QSAR analysis revealed the following: polarisation, dipole moment, lipophilicity, energy parameters as well as the size of the molecule and its branching possessed the most significant effect on antioxidant activity; the antioxidant activities of the compounds were increased with the increase in their hydrophilic and reductive properties; the molecules with small volume and surface area showed the higher level of antioxidant activity. 3). Obtained QSAR models are proposed for antioxidant activity prediction within the above-mentioned row of compounds and can be considered as a theoretical basis for *de novo* design of new potential antioxidants.

Keywords

antioxidant activity, molecular descriptors, 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholine-4-yl]propyl)-2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one derivatives, QSAR analysis

Introduction

In silico study and theoretical research including QSAR (Quantitative Structure-Activity Relationship) analysis are of special interest and a basis for design and directed synthesis of new drug-like molecules. QSAR-analysis consists of the identification and quantitative description of structural parameters or physico-chemical properties (descriptors) of a molecule in order to reveal the effect of each of them on the biological activity of a substance. Obtained QSAR models provide the information on the structural features of the molecules and outline the main directions for further design and optimisation of active compounds (Lionta et al. 2014; Lavecchia and Di Giovanni 2013).

Currently, the role of free radicals, damage of biologically important molecules and oxidative stress are discussed. Such pathological conditions and diseases, such as cancer, atherosclerosis, Parkinson's disease, staining processes, various types of ischaemia, cataract, neurodegenerative, cardiovascular diseases and aging processes are mainly associated with free radical oxidation and are considered as oxidative-stress related diseases and processes. Thus, the search for new efficient antioxidant/antiradicals entities is important for the prevention and therapy of the above-mentioned oxidative-stress related diseases (Kumar et al. 2015).

Thiazole derivatives are promising in the search for biologically active compounds, since the thiazole frame is a powerful biophore fragment for the rational design of drug-like molecules. Thiazole derivatives possess various types of biological activity: anticonvulsant (Satoh et al. 2009), anti-inflammatory (Giri et al. 2009), antihypertensive (Abdel-Wahab et al. 2008), antiviral (El-Sabbagh et al. 2009) and antioxidant Andreani et al. 2013).

The **aim** of the study was to determine the molecular structure parameters of the new 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholin-4-yl]propyl)-2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one derivatives and building the QSAR models as a theoretical basis for *de novo* design of new thiazole-based antioxidants.

Materials and methods

Fourteen new derivatives of 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholin-4-yl]propyl)-2,3-dihydro-1,3-thiazole-5-yl]ethane-1-one, with established antioxidant activity, were used. Target thiazole-based compounds **II** (Fig.1) were synthesised by the Hantzsch method, starting from asymmetric thiourea and 3-chloropentane-2,4-dione (Taha et al. 2015; Yeromina et al. 2016); additionally 3-[3-(morpholin-4-yl)propyl]-1-phenylthiourea **I** (starting compound) was involved in the study.

Calculation of molecular descriptors was carried out using Hyper-Chem 7.5 software (HyperCube, Inc.) (licence for HyperChem 7.5 software is available for Danylo Halytsky Lviv National Medical University): BuildQSAR softaware was used for QSAR-model building (De Olivera and Gaudio 2000).

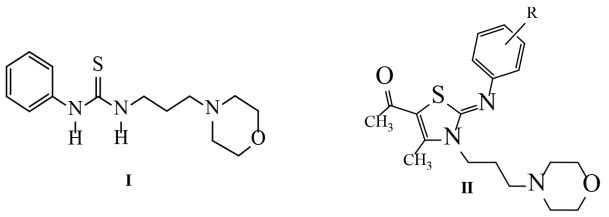

Figure 1. Structure of investigated compounds. R= **a**) H, **b**) 2-CH_3, **c**) 2,3-$(CH_3)_2$, **d**) 2,4-$(CH_3)_2$, **e**) 2,6-$(CH_3)_2$, **f**) 3,4-$(CH_3)_2$, **g**) 3,5-$(CH_3)_2$, **h**) 2-OCH_3, **i**) 3-OCH_3, **j**) 4-OCH_3, **k**) 2-Cl, **l**) 3-Cl, **m**) 4-Cl.

The antioxidant activity (AOA) of the tested compounds was evaluated *in vitro* at the initiation of free radical processes by modelling the artificial oxidative stress, using the emulsion with yolk lipoprotein as a substrate for oxidation. Butylated hydroxytoluene (BHT) and quercetin (q) were taken as reference substances. The experiment was carried out under simulated conditions; the experiment variants included a control substance (DMSO solvent), solutions of reference substances (BHT, quercetin) and tested substances with a concentration in an incubation medium 0.3 kg/

m^3. Levels of compound activities were presented as a percentage of inhibition of the TBARs formation (tiobarbituric reactive substances) compared to BHT and quercetin activities: AOA_{BHT} (percentage of inhibition under BHT action) and AOA_Q (percentage of inhibition under quercetin action) (Perekhoda et al. 2017) (Table 1).

Table 1. Antioxidant activity of 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholin-4-yl]propyl)-2,3-dihydro-1,3-thiazol-5-yl] ethane-1-one derivatives (as inhibition % of the TBA-active products formation).

№	AOA_{BHT}	AOA_Q
I	45.78	58.25
II a	42.66	54.26
II b	41.09	52.28
II c	36.96	47.03
II d	5.81	7.39
II e	15.07	27.79
II f	16.08	20.26
II g	20.34	25.87
II h	32.06	40.79
II i	31.75	40.40
II j	31.65	40.26
II k	44.88	57.10
II l	44.72	56.90
II m	23.61	30.03

Results and discussion

The preliminary optimisation of the molecular structure of the investigated compounds was carried out using the molecular mechanics method MM+ (HyperChem software package) to achieve the RMS gradient value less than 0.1 kcal/(mol · Å). The final minimisation of the energies of the investigated structures was carried out using AM1 semi-empirical quantum chemical method to achieve a RMS gradient value less than 0.01 kcal/(mol · Å). The use of the AM1 method was due to the fact that it allowed the most accurate calculation of the electron-spatial structure of heterocyclic compounds containing Oxygen and Nitrogen atoms (Lipkowitz and Boyd 1990; Szabo and Ostlund 1989). This allowed the calculation of a number of molecular descriptors: electronic, steric, geometric, energy etc., which assessed the charges on individual atoms of the investigated compounds: Sulphur atoms of the thiazole cycle (Ch_S), Oxygen (Ch_O), Nitrogen and Oxygen atoms of the morpholine cycle (Ch_N(m), Ch_O(m)); the lipophilicity parameter (logP); the dipole moment (D); the volume of the molecule (V), the surface area of the molecule (S), the refractivity (R), the polarisability (P), the total energy of the molecule (TE), the binding energy (BE), the electronic energy (EE), the energy of isolated atomic energy (IAE), core-core interaction (CCI), heat of formation (HF), hydration energy (EH); parameters characterising the molecular orbitals: energies of the highest occupied molecular orbital and lowest unoccupied molecular orbital (HOMO and LUMO). Calculated molecular descriptors of the investigated compounds are presented in Tables 2 and 3.

Based on the obtained results of charge values, the following conclusions can be made. Effective charges on Sulphur atoms of the thiazole cycle have additional values: least value of 0.458 (compound **IId**) and largest value of 0.700 (compound **IIh**), the charge on the Sulphur atom in the unsubstituted thiourea has an electronegative value of (-)0.291. The effective charges on the Oxygen atom for the test compounds take values from (-) 0.270 (**IId**) to (-) 0.370 (**IIh**). Thus, amongst the studied compounds, the most electronegative is the Oxygen atom and the most positive charge is on the Sulphur atom in the **IIh** compound, which contains the methoxy group in position 2 of the phenyl fragment. The compound **IId,** with methyl substituents in the phenyl fragment at positions 2,6, is characterised by the lowest value of the charge on the Sulphur atom and the lowest value on the Oxygen atom. The effective charges on the Oxygen and Nitrogen atoms of the morpholine cycle for the studied compounds are characterised by almost identical values of (-) 0.26 (Ch_O (m)), (-) 0.25 Ch_N (m).

Comparing the values of refractivity and polarisability, which are known to characterise the mobility of the mole-

Table 2. Molecular descriptors of 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholin-4-yl]propyl)-2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one derivatives.

№	Ch_S	Ch_O(m)	Ch_N(m)	Ch_O	logP	R	P	D	S	V
I	-0.291	-0.269	-0.256	0	0.82	87.77	32.28	3.693	519.38	861.48
II a	0.467	-0.266	-0.250	-0.274	0.68	110.2	39.91	5.052	584.10	1025.57
II b	0.461	-0.261	-0.250	-0.272	0.83	114.49	41.74	4.874	604.44	1068.10
II c	0.461	-0.261	-0.251	-0.274	0.99	118.77	43.58	5.036	628.34	1113.10
II d	0.458	-0.267	-0.250	-0.270	0.99	118.77	43.58	4.930	632.07	1121.94
II e	0.514	-0.268	-0.258	-0.284	0.99	118.77	43.58	2.245	611.81	1084.38
II f	0.467	-0.267	-0.248	-0.278	0.99	118.77	43.58	5.412	631.99	1121.20
II g	0.461	-0.261	-0.250	-0.271	0.99	118.77	43.58	4.966	642.83	1130.90
II h	0.700	-0.265	-0.262	-0.380	-0.31	116.58	42.38	12.871	607.52	1081.99
II i	0.464	-0.267	-0.250	-0.269	-0.31	116.58	42.38	5.422	628.10	1105.53
II j	0.466	-0.268	-0.259	-0.279	-0.31	116.58	42.38	5.662	627.92	1103.68
II k	0.482	-0.268	-0.261	-0.280	0.46	114.92	41.84	5.429	602.54	1062.59
II l	0.478	-0.268	-0.259	-0.278	0.46	114.92	41.84	5.018	608.96	1070.60
II m	0.476	-0.266	-0.251	-0.274	0.46	114.92	41.84	4.812	606.84	1068.49

Table 3. Energy parameters of 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholin-4-yl]propyl)-2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one derivatives.

№	TE	BE	IAE	EE	CCI	HF	HOMO	LUMO	EH
I	-74183	-3944	-70239.1	-495470	421286	7.538	-8.270	-0.149	-7.78
II a	-97589	-5078	-92510.6	-774500	676911	-4.85	-8.111	-0.192	-3.57
II b	-101183	-5361	-95822.3	-831881	730698	-11.88	-8.070	-0.170	-2.57
II c	-104776	-5642	-99134.1	-885438	780661	-17.87	-8.050	-0.172	-1.65
II d	-104778	-5643	-99134.1	-881757	776978	-19.49	-8.039	-0.128	-1.49
II e	-104732	-5597	-99134.1	-910580	805848	26.48	-6.894	-0.848	-1.70
II f	-104777	-5643	-99134.1	-876830	772052	-19.12	-8.058	-0.182	-1.53
II g	-104778	-5644	-99134.1	-876880	772102	-19.93	-8.084	-0.116	-1.45
II h	-108497	-5384	-103112	-885766	777269	23.99	-7.034	-1.457	-2.85
II i	-108563	-5451	-103112	-878934	770370	-42.60	-8.110	-0.116	-4.94
II j	-108563	-5450	-103112	-877278	768714	-42.07	-8.054	-0.247	-5.23
II k	-105893	-5061	-100831	-833546	727653	-10.88	-8.173	-0.343	-3.15
II l	-105893	-5062	-100831	-827008	721114	-11.48	-8.232	-0.364	-3.22
II m	-105894	-5062	-100831	-824380	718485	-12.07	-8.215	-0.319	-3.25

cule electron shell (Todeschini and Consonni 2000, 2009), it was established that the least value of these parameters had compound **I**. Compounds with methyl substituents in the phenyl fragment at 2-, 2,3-, 2,4-, 2,6-, 3,4- and 3,5-positions (**II b-g**), compounds with methoxy group in the phenyl fragment at 2-, 3- and 4- positions (**II h-j**) and compounds containing the Chlorine atom in the phenyl fragment at 2, 3 and 4 positions (**IIk-m**) had similar values of refractivity and polarisability.

The reactivity of a substance depends on the hydrophilic-hydrophobic balance of the molecule, the quantitative criterion of which is the value of the dipole moment. The value of the dipole moment of the investigated compounds has very different values from 2.245 **(IIe**) to 12.871 (**IIh**).

An important characteristic of substances is lipophilicity (logP). It is known that an increase of lipophilicity leads to an increase in the penetration of biologically active substances through cell membranes, but a reduction in the water solubility and elimination from the body (Todeschini and Consonni 2009). For the studied compounds, the logP value has a similar value for the compounds, depending on the presence of methyl-, methoxy- and chlorine-substituents in the phenylimine fragment of the molecule: -0.31 (**IIh-j**), 0.99 (**IIc-g**), 0.46 (**IIk-m**).

The surface area of the molecule and the volume of the molecule were the smallest for compound **I** and the largest value of these parameters were for compound **IIg**.

Based on the energy parameters, it can be concluded that compound **I** has the minimum values for total energy of the molecule, binding energies, energy of isolated atoms, electronic energy and energy of internuclear interactions. The energies of the frontier orbitals are responsible for the donor-acceptor properties of the molecules: the minimum HOMO value is in compound **I** (-8.270) and the largest value in compound **IIe** (-6.894); the least LUMO value is in **IIh** compound (-1.457), the largest value in **IIg** and **IIi** compounds (-0.116). The calculated energy gap (the energy difference between the lower occupied and the upper vacant molecular orbitals) value of the molecules for the studied compounds is within the range of 7.8–7.9, with the exception **I** compound having the value of 8.121, **IIe** compound –(6.046 value) and **IIh** compound - (5.577 value).

The structure-activity relationships were studied using the calculated descriptors and antioxidant activity values for the studied compounds. For this purpose, the construction of mathematical QSAR models was carried out using the BuildQSAR programme and the GA-MLRA method, which had allowed the generation of one- or multi-parameter models with a maximum value of the correlation coefficient (r) and the minimum value of standard deviation (s). Obtained QSAR models were analysed by the Fisher coefficient (F) value and "leave-one-out" method under confirmation of the predictive model capability, which had been verified by the value of the cross-validation coefficient (Q^2), calculated using the sum of squares of prediction error (SRRESS) (Yeromina et al. 2016). The predictive power of QSAR models is calculated by internal and external validate-using the methods of leave-one-out (LOO) and leave-group-out (LGO) cross-validation. QSAR model is predictive, if the following conditions are satisfied (Golbraikh and Tropsha 2002): $Q^2 > 0.5$, which can be calculated by the formula:

$$Q^2 = 1 - \frac{\Sigma\left(a_{obs} - a_{pred}\right)^2}{\sum\left(a_{obs} - a_{mean}\right)^2},$$

where a_{obs} is the observed or experimental activity, a_{pred} is the activity predicted by a certain model, a_{mean} is the average activity.

The QSAR models were presented in the next formula:

$$\% = a + b \cdot X1 + c \cdot X2 + d \cdot X3,$$

where the activity parameter % is AOA_{BHT} or AOA_Q and X1, X2, X3 are molecular descriptors.

The mathematical dependence between the inhibition of BHT and quercetin was described by the equation: $\mathbf{AOA_{BHT}}$ = +0.784 **AOA_Q** +0.0598. Therefore, the parameter of activity AOA_{BHT} was used in QSAR-analysis.

The total sample of compounds was divided into three groups according to the values of their antioxidant ac-

tivity: **1** group - active compounds (AOA_{BHT} more than 40%): **I**, **IIa, IIb, IIk, IIl**; **2** group - average activity AOA_{BHT} 25–40%: **IIc, IIh, IIi, IIj** and group **3** - compounds with a low activity AOA_{BHT} of less than 25%: **IId, IIe, IIf, IIg, IIm**. For QSAR analysis, the compounds studied were divided into a training and test sample. The test sample includes compounds **IIb**, **IIe**, **IIh**, **IIl**. The remaining compounds were a training sample. Thus, the ratio of compounds in the training and test sample was 78.57% and 21.43%. Compound **I** was also in the training and in the test sample.

When one-parameter QSAR-models were built in the training sample, the largest correlation coefficient r = 0.717 was observed with the use of the descriptor – the area of the molecule. The anti-oxidant activity increases with the decrease of the area of the molecule:

1. $\mathbf{AOA_{BHT}}$ = -0.224 (±0.174) **S** +153.343(±96.297)
   (n=010; r=0.717; s=9.857; F=8.446; Q^2=0.126; SPRESS=13.212)

The QSAR model is characterised by low prognostic ability.

From the two-parameter QSAR models in the training sample of compounds, model **2** was selected, which was characterised by a higher correlation coefficient (r) and predictive power (Q^2):

2. $\mathbf{AOA_{BHT}}$ = -0.367(±0.213) **S** + 15.431(±16.563) **D** + 154.458(±81.478)
   (n = 010; r = 0.841; s = 8.180; F = 8.440; Q^2 = 0.514; SPRESS = 10.538)

When three-parameter QSAR-models were obtained in the training sample, the correlation coefficients had high values of 0.959–0.841.

3. $\mathbf{AOA_{BHT}}$ = -0.357(±0.106)**V** + 35.910(±13.811)**D** + 3546.238(±1827.550) **Ch_O(m)** + 1175.132(±526.812)
   (n = 010; r = 0.959; s = 4.621; F = 22.950; Q^2 = 0.809; SPRESS = 7.126)
4. $\mathbf{AOA_{BHT}}$ = -0.509(±0.189) **S** + 22.475(±13.016) **D** + 2498.261(±2004.255) **Ch_O(m)** + 861.58139 (±570.222154)
   (n = 010; r = 0.938; s = 5.647; F = 14.705; Q^2 = 0.240; SPRESS = 14.229)
5. $\mathbf{AOA_{BHT}}$ = + 0.051(±0.020) **BE** + 30.985(±17.148) **D** + 3696.943(±2519.472**) Ch_O(m)** + 1124.146(±699.651)
   (n = 010; r = 0.926; s = 6.143; F = 12.117; Q^2 = 0.517; SPRESS = 11.800)
6. $\mathbf{AOA_{BHT}}$ = -0.835(±0.494)**V**-0.00048(±0.00032) **EE** + 1911.515(±2428.216)**Ch_O(m)** + 1040.745 (±803.539)
   (n = 010; r = 0.898; s = 7.176; F = 8.343; Q^2 = 0.410; SPRESS = 19.381)
7. $\mathbf{AOA_{BHT}}$ = -0.880(±0.535)**V** + 0.00056(±0.00039) **CCI** + 1737.653(±2426.985)**Ch_O(m)** + 1035.634(±814.382)
   (n = 010; r = 0.895; s = 7.275; F = 8.065; Q^2 = 0.271; SPRESS = 18.401)
8. $\mathbf{AOA_{BHT}}$ = -7.938(±4.034)**P** + 33.855(±22.349) **D** + 3349.00072(±2943.253)**Ch_O(m)** + 1079.513(±836.794)
   (n = 010; r = 0.893; s = 7.331; F = 7.912; Q^2 = 0.227; SPRESS = 14.349)
9. $\mathbf{AOA_{BHT}}$ = -14.07748(±14.38322)**logP**-0.311(±0.177)**S** + 2497.805(±2977.171)**Ch_O(m)** + 873.634(±853.328)
   (n = 010; r = 0.872; s = 7.979; F = 6.367; Q^2 = 0.422; SPRESS = 12.412)
10. $\mathbf{AOA_{BHT}}$ = -0.632(±0.731)**V** + 0.00036(±0.00062)**CCI** + 8.011(±29.439)**D** + 407.662(±439.413)
    (n = 010; r = 0.852; s = 8.553; F = 5.281; Q^2 = 0.042; SPRESS = 16.661)
11. $\mathbf{AOA_{BHT}}$ = -0.903(±0.814)**V** + 0.00066(±0.00079) **CCI**-32.793(±119.469)**Ch_S** + 536.002(±371.253)
    (n = 010; r = 0.852; s = 8.549; F = 5.289; Q^2 = 0.452; SPRESS = 11.454)
12. **12.** $\mathbf{AOA_{BHT}}$ = -0.713(±0.650)**V** -0.826(±5.486)**EH** + 0.00047(±0.00046)**CCI** + 456.532(±392.891)
    (n = 010; r = 0.844; s = 8.752; F = 4.955; Q^2 = 0.011; SPRESS = 16.230)
13. $\mathbf{AOA_{BHT}}$ = -0.814(±0.761)**V** + 0.00053(±0.00056)**CCI** + 14.946(±106.470)**LUMO** + 525.610(±430.731)
    (n = 010; r = 0.844; s = 8.764; F = 4.936; Q^2 = 0.047; SPRESS = 16.701)
14. $\mathbf{AOA_{BHT}}$ = -0.384(±0.275)**S** + 11.623(±102.755) **LUMO** + 16.777(±21.778)**D** + 158.873(±97.849)
    (n = 010; r = 0.843; s = 8.783; F = 4.904; Q^2 = 0.466; SPRESS = 11.921)
15. $\mathbf{AOA_{BHT}}$ = -1.499 (±17.015) **logP** -0.357(±0.262)**S** + 14.219(±22.873)**D** + 155.841(±91.292)
    (n = 010; r = 0.842; s = 8.804; F = 4.872; Q^2 = 0.478; SPRESS = 12.206)
16. $\mathbf{AOA_{BHT}}$ = -0.357(±0.299)**S**-8.698(±151.229)**HOMO** + 15.674(±18.799)**D** + 76.83871(±1352.516)
    (n = 010; r = 0.841; s = 8.822; F = 4.844; Q^2 = 0.350; SPRESS = 13.153)
17. $\mathbf{AOA_{BHT}}$ = -6.567(±15.048)**logP** -0.329(±0.298)**S** -61.493(±148.169)**Ch_O** + 199.959(±135.929)
    (n = 010; r = 0.812; s = 9.531; F = 3.863; Q^2 = 0.448; SPRESS = 16.069)

Based on the analysis of the obtained QSAR-models, it was found that antioxidant activity increases with decreasing of the area, molecular volume, lipophilicity, polarisation and increasing the magnitude of the dipole moment. The increase in the energy of the bonds, the energy of inter-nuclear interactions, the energy of the lower vacant molecular orbit and the reduction of the energy of hydration and energy of the higher vacant molecular orbitals also result in an increase in the antioxidant activity. The greatest effect of effective charges on atoms on the anti-oxidant activity was detected: the increase in the charge value on the morpholine cycle Oxygen and the decrease in the charge size on the Sulphur atom of the thiazole ring and the Oxygen atom of the acetyl group.

From the received QSAR models, models with the highest correlation coefficient and predictive power of **2, 3, 5, 15** were selected. To estimate the accuracy of the predictive ability of the received QSAR models, the prediction error values for compounds of the training sample were calculated (Table 4).

Figures 2 and 3 depict the dependence of the observed and predicted anti-oxidant activities for QSAR-model **2**, **3**, **5** and **15**.

QSAR-model **3** is characterised by the best statistical indicators. Since in QSAR-models **2** and **15** for compounds **IIc** and **IId**, there was a large discrepancy between the observed and predicted anti-oxidant activities and these compounds were removed from the training sample for these models. The obtained QSAR models **2-1** and **15-1** were characterised by better statistical indicators.

2-1. $\mathbf{AOA_{BHT}}$ = -0.337(±0.169)**S** +13.190 (±12.625)**D** +148.870(±58.968)
(n=008; r=0.920; s=5.354; F=13.709; Q^2=0.495; SPRESS=16.668)

15-1. $\mathbf{AOA_{BHT}}$ = -6.725(±7.142)**logP**-0.475 (±0.122)**S** +19.148(±9.752)**D** +194.955(±40.710)
(n=008; r=0.985; s=3.241; F=44.855; Q^2=0.638; SPRESS=24.412)

Using the obtained QSAR models with the best statistical parameters, the activity of the compounds from the test sample was predicted. Table 5 shows experimental antioxidant activity data and predicted using QSAR models.

The predictive ability of the constructed models, tested with the use of compounds from the test sample, was quantified by the value of the cross-validation LGO coefficient Q^2, which were for QSAR models **2-1**, **3, 5, 15-1** – 0.530,

Table 4. Observed and predicted antioxidant activities and residual for QSAR- model **2**, **3, 5, 15** for compounds of the training sample.

№	QSAR- model 2			QSAR- model 3		
	Observed antioxidant activity	Predicted antioxidant activity	Residual	Observed antioxidant activity	Predicted antioxidant activity	Residual
I	45.780	45.283	0.497	45.780	45.926	-0.146
II a	42.660	45.078	-2.418	42.660	46.722	-4.062
II c	36.960	23.732	13.228	36.960	32.596	4.364
II d	5.810	17.796	-11.986	5.810	4.353	1.457
II f	16.080	23.517	-7.437	16.080	21.997	-5.917
II g	20.340	13.628	6.712	20.340	23.712	-3.381
II i	31.750	27.513	4.219	31.750	27.885	3.865
II j	31.650	33.054	-1.040	31.650	33.619	-1.969
II k	44.880	42.228	2.852	44.880	39.937	4.943
II m	23.610	27.675	-4.065	23.610	22.764	0.846
№	**QSAR- model 5**			**QSAR- model 15**		
I	45.780	43.970	1.810	45.780	45.552	0.228
II a	42.660	39.588	3.072	42.660	44.496	-1.836
II c	36.960	28.999	7.961	36.960	23.287	13.673
II d	5.810	3.450	2.360	5.810	17.598	-11.788
II f	16.080	18.w404	-2.324	16.080	22.783	-6.703
II g	20.340	26.725	-6.385	20.340	13.517	6.823
II i	31.750	28.459	3.291	31.750	28.628	3.122
II j	31.650	32.225	-0.575	31.650	33.810	-2.160
II k	44.880	44.742	0.138	44.880	41.758	3.122
II m	23.610	30.958	-7.328	23.610	28.092	-4.482

Table 5. Values of experimental antioxidant activity and activity predicted by QSAR models **2-1**, **3**, **5**, and **15-1** for compounds from test sample.

№	Experimental antioxidant activity	Predicted antioxidant activity for QSAR- models and residuals							
		2-1	Residual	3	Residual	5	Residual	15-1	Residual
I	45.78	45.28	0.49	45.93	-0.15	43.97	1.81	45.55	0.23
IIb	41.09	33.95	7.14	42.16	-1.07	38.27	2.82	33.56	7.53
IIe	15.07	15.90	-0.83	18.97	-3.9	9.61	6.09	16.87	-1.17
IIh	32.06	34.23	-2.17	34.87	-2.81	34.72	-2.66	33.23	-1.17
III	44.72	33.63	11.09	38.36	6.36	35.07	9.65	33.72	11

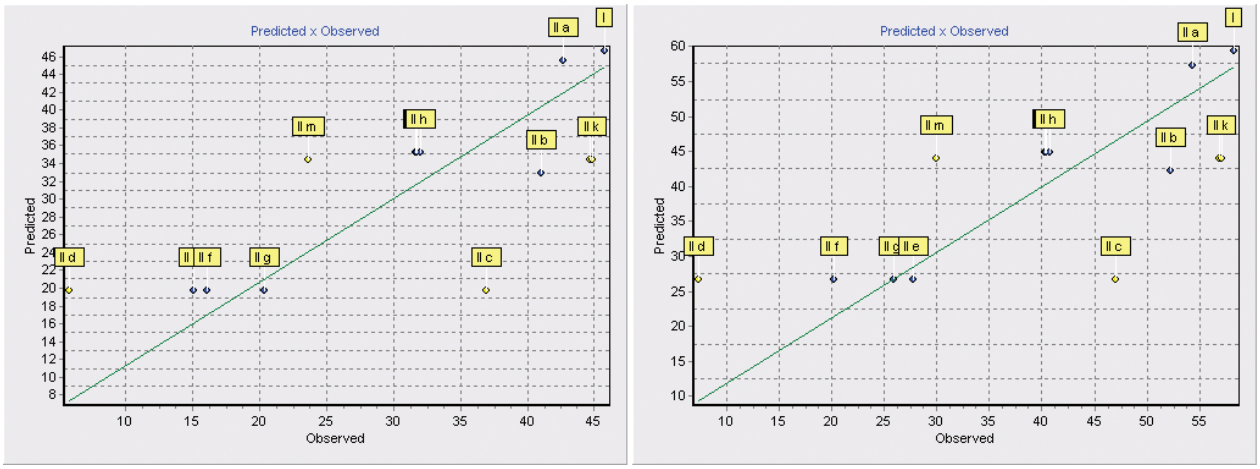

Figure 2. The dependence of observed and predicted antioxidant activities for QSAR-models **2**(a) and **3**(b) for compounds of the training sample.

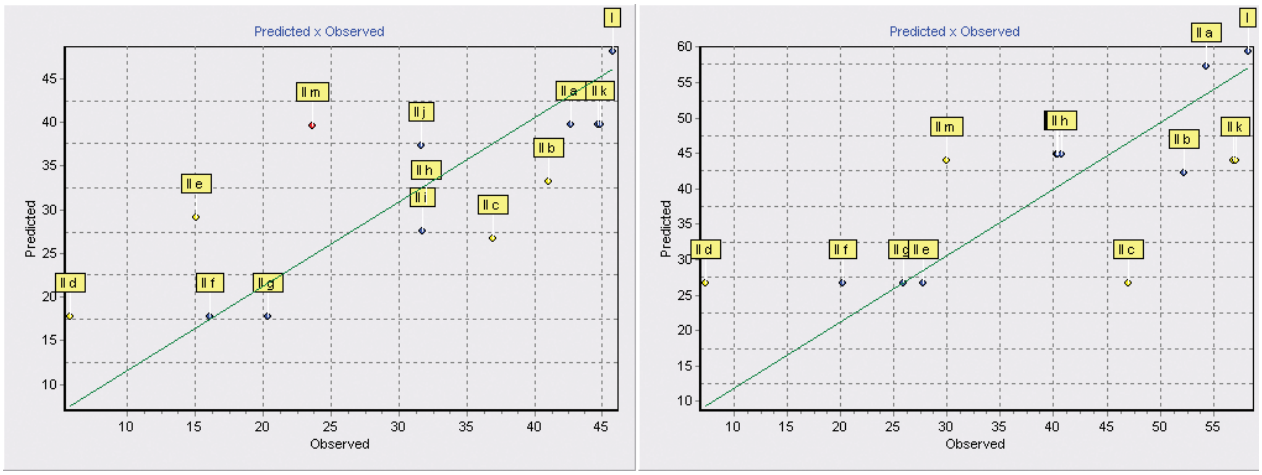

Figure 3. The dependence of the observed and predicted antioxidant activity for QSAR-models **5**(a) and **15**(b) for compounds of the training sample.

0.769, 0.608, 0.665, respectively. Thus, it can be assumed that the QSAR models obtained are characterised by high predictive ability, determined both by internal and external validation and can be used for virtual screening of the antioxidant activity of substances of this class of compounds.

Conclusions

1. The study of the structure–activity relationships for 1-[2-(R-phenylimino)-4-methyl-3-(3- [morpholine-4-yl]propyl)-2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one derivatives was carried out.
2. QSAR analysis revealed the following: polarisation, dipole moment, lipophilicity, energy parameters, as well as the size of the molecule and its branching, possessed the most significant effect on antioxidant activity; the antioxidant activity of the compounds was increased with the increasing of their hydrophilic and reductive properties; the molecules with small volume and surface area showed the higher level of antioxidant activity.
3. Obtained QSAR-models are proposed for antioxidant activity prediction within the above-mentioned row of compounds and can be considered as a theoretical basis for *de novo* design of new potential antioxidants.

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