STRUCTURE—ACTIVITY. ASSOCIATION OF THE ELECTRONIC PARAMETERS OF SUBSTITUTED BENZO-2,1,3-THIA- AND SELENADIAZOLES WITH THEIR ANTIFUNGAL ACTIVITY AND TOXICITY

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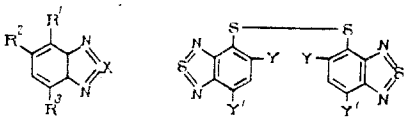
UDC 615.282.84:547.794.3].012.1

The antifungal activity of benzo-2,1,3-thiadiazoles [5, 8, 9, 20], which was shown on different test objects, is known. However, there is no single method for the primary investigations of the antifungal agents [7, 20]. This hinders the establishment of a quantitative association between the structure of the compounds and their biological action. The present work investigated the antifungal activity and toxicity of a large series of benzo-2,1,3-thia- and selenadiazoles under the same conditions and established an association between the structure of the compounds and their biological action – the antifungal activity and toxicity; this allowed the isolation of the significant parameters (descriptors) of the compounds with statistical reliability for the prediction of new structures with the proposed biological action among the indicted heterocycles. The results of the investigations carried out are reported below.

The compounds (I)-(LXIX) (see Table 1) were obtained by the methods described in [1-6, 8, 10, 12, 18, 20]. Regarding 4- and 5-hydroxybenzo-2,1,3-selenadiazoles (LXXI), we improved the methods of their isolation, present in [18], having increased their yield from 15 and 38% correspondingly to 60-80%, studied the chlorination and bromination of the compounds indicated using sulfuryl chloride and bromine in acetic acid, and synthesized the 4-hydroxy-5,7-dichloro-, 4-chloro-5-hydroxy-, and 4-bromo-5-hydroxybenzo-2,1,3-selenadiazones (LXXII)-(LXXIV).



I-LII, LXX-LXXIV LIII-LIX

The structure of the hydroxy derivatives (LXX)-(LXXIV) was shown in the following way. The 4- and 5-hydroxy, 4-chloro-5-hydroxy-, 4-bromo-5-hydroxy-, and 4-hydroxy-5,7-dichlorobenzo-2,1,3-thiadiazoles, (XXIX), (XXX), (XXXIII), (LXXV), and (XXVI) of known structure [10] were subjected to reductive desulfurization with iron in 10% HCl. The resulting intermediate products – 2,3-diamino-, 3,4-diamino-, 2-chloro-3,4-diamino-, 2-bromo-3,4-diamino-, and 4,6-dichloro-2,3-diaminophenols (LXXVII)-(LXXXI) – were condensed with selenious acid prior to the isolation of the compounds (LXX)-(LXXIV).

EXPERIMENTAL

The monitoring of the course of the reactions and the evaluation of the discreteness of the substances were performed using TLC on plates of Silufol UV-254 in the 2:1:2 system of acetone—chloroform—hexane (system A) and the 100:50:1 system of benzene—acetone—acetic acid (system B). The compounds were developed in UV light using the "Kromatoskop-M" instrument. The IR spectra were taken on the "Specord 75 IR" spectrophotometer using the solution in abs. chloroform.

Hydroxybenzo-2,1,3-selenadiazoles (LXX) and (LXXI). To the mixture of 5 g (33 mmole) of the compound (XXIX) or (XXX) in 100 ml of a 10% solution of hydrochloric acid are added 10 g (178.55 mmole) of iron with the avoidance of vigorous frothing; the mixture is boiled for 20 min and filtered in the hot form. The residue on the filter is washed with 500 ml of

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 25, No. 12, pp. 49-53, December, 1991. Original article submitted May 17, 1990.

 0091-150X/91/2512-0900$12.50

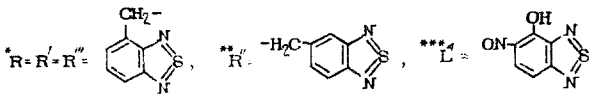
TABLE 1. Electronic Parameters, Antifungal Activity, and Toxicity of Derivatives of Benzo-2,1,3-thia- and -selenadiazoles

Compound	R¹	R²	R³	Suppress. of dev. of phytophthoro-sis (P), % (conc. subs. 0.1%)	Suppress. of growth of fungal mycelium, % (conc. subs. 0.003%)			log LD_{50}	Number of atoms in the molecule, n	Number of electrons in the molecule, e	e^{*} (number of eleectrons on the atom) $e^{*} = e/n$
					Venturia inaqualis (V)	Aspergillus niger (A)	Fusarium moniforme (F)				
I	NO_2	Cl	H	100	100	100	86	1,8	15	108	7,20
II	NO_2	Br	H	83	100	100	100	1,69	15	126	8,40
III	NO_2	Cl	Cl	100	100	100	87	1,45	15	124	8,26
IV	Cl	H	NO_2	100	52	76	42	1,81	15	108	7,20
V	NO_2	Cl	Cl	99	84	87	52	—	15	142	9,46
VI	Cl	NO_2	NO_2	98	25	6	33	—	17	130	7,65
VII	Br	NO_2	NO_2	98	79	40	46	1,71	17	148	8,70
VIII	NO_2	Cl	H	97	100	76	54	—	15	126	8,40
IX	H	NO_2	H	83	21	31	19	2,6	15	92	6,13
X	NO_2	Br	H	100	37	49	12	1,45	15	144	9,60
XI	NO_2	CH_3	H	75	12	55	56	—	18	100	5,55
XII	OH	NO_2	NO_2	75	31	21	33	2,4	18	122	6,77
XIII	NO_2	H	H	72	100	100	65	1,71	15	110	7,33
XIV	NO_2	OH	H	72	42	48	33	—	16	100	6,25
XV	NO_2	H	H	46	47	21	42	2,61	15	92	6,13
XVI	OH	NO_2	H	36	11	15	22	—	16	100	6,25
XVII	Cl	CH_3	NO_2	0	46	0	47	—	18	116	6,44
XVIII	OC_2H_5	NO_2	NO_2	0	31	21	19	2,25	24	138	5,75
XIX	OC_4H_9	NO_2	NO_2	0	31	31	33	2,30	30	154	5,13
XX	CH_2NH_2	H	H	76	12	10	0	2,78	18	86	4,78
XXI	COOH	H	H	0	18	5	20	2,78	16	92	5,75
XXII	OH	H	$COCH_3$	0	21	32	13	2,56	19	100	5,26
XXIII	$COCH_3$	OH	H	—	0	9	15	—	19	100	5,26
XXIV	H	OC_2H_5	H	—	28	48	50	2,70	20	94	4,70
XXV	NH_2	NH_2	H	68	12	6	3	2,78	17	86	5,06
XXVI	NH_2	CH_3	H	96	12	12	16	2,48	18	86	4,78
XXVII	NH_2	H	H	0	5	5	7	2,30	15	78	5,20
XXVIII	H	NH_2	H	0	11	35	0	2,30	15	78	5,20
XXIX	OH	H	H	0	23	11	7	1,88	14	78	5,57
XXX	H	OH	H	37	11	11	0	2,36	14	78	5,57
XXXI	CH_2Cl	OCH_3	H	0	11	17	3	—	20	110	5,50
XXXII	OH	Cl	OH	—	50	100	43	—	13	86	6,62
XXXIII	Cl	OH	H	0	31	25	36	—	14	94	6,71
XXXIV	OCH_3	H	CH_2Cl	75	6	6	6	—	20	110	5,50
XXXV	OH	CH_3	H	82	12	6	12	2,52	17	86	5,06
XXXVI	Cl	$OCH_2COOC_2H_5$	H	71	18	6	13	2,78	26	140	5,38
XXXVII	OH	Br	Br	73	37	25	40	—	14	146	10,43
XXXVIII	OCH_2COOH	Br	Br	64	11	17	7	—	20	176	8,80
XXXIX	H	$OCH_2COOC_2H_5$	H	46	11	11	7	—	26	124	4,77
XL	NO	OH	H	—	11	15	12	—	15	92	6,13
XLI	CH_2COOH	H	Cl	75	22	29	8	—	19	116	6,10
XLII	Br	CH_3	Br	91	36	21	19	—	16	146	9,12
XLIII	SH	H	H	—	5	5	0	3,0	14	86	6,14
XLIV	SH	CH_3	H	0	23	21	12	—	17	94	5,53
XLV	SH	H	Br	0	17	15	0	—	14	120	8,57
XLVI	SO_2H	H	H	61	38	9	32	2,70	16	102	6,37
XLVII	SO_2H	CH_3	H	46	27	4	10	—	19	110	5,79
XLVIII	SO_2H	H	Br	51	7	0	0	—	16	136	8,50
XLIX	SO_2H	Cl	Cl	63	38	0	24	—	16	134	8,37
L	$CH_2SPO(ONa)_2$	H	H	58	0	0	0	3,0	22	154	7,00
LI	H	$CH_2NH(CH_2)_2SPO(ONa)_2$	H	0	12	26	27	2,78	30	178	5,93
LII	$CH_2NH(CH_2)_2S_2O_3Na$	H	H	67	16	16	0	2,30	29	168	5,79
LIII	—	—	—	6	27	18	10	—	26	170	6,54
LIV	—	—	—	53	28	40	90	—	32	186	5,81
LV	—	—	—	—	6	35	40	—	26	238	9,15
LVI	—	—	—	67	6	45	50	—	26	200	7,69
LVII	$(*RS-)_2$			0	12	5	25	—	32	186	5,81
LVIII	$(*R'NHCH_2CH_2S)_2$			76	12	0	0	2,30	48	234	4,87
LIX	$(**R''-NHCH_2CH_3S-)_2$			0	12	10	12	2,30	48	234	4,87
LX	$(*R'''-NHCH_2CH_2S-)_2=C=S$			0	5	0	3	2,95	50	256	5,12
LXI	L^1CuCl_2 (L^1- comp. XXIX)			81	7	0	0	—	16	140	8,75
LXII	L^2_2Co			0	0	0	0	—	27	181	6,70
LXIII	L^2CuCl_2 (L^2- comp. XXXV)			0	0	0	23	—	19	148	7,79
LXIV	L^3_2Co (L^3- comp. XXVI)			71	0	0	0	—	31	227	7,32
LXV	$***L^4_2Co$			0	0	0	0	—	43	300	6,97
LXVI	L^5_2Co (L^5- comp. XL)			0	7	0	0	—	43	300	6,97
LXVII	L^6CoCl_2 (L^6- comp. XLIII)			90	0	4	17	—	16	146	9,12
LXVIII	L^7CoCl_2 (L^7- comp. XLIV)			60	6	3	25	—	19	154	8,10
LXIX	L_8CoCl_2 (L^8- comp. XLV)			0	18	0	11	—	16	180	11,25
LXX	OH	H	H	0	5	26	48	—	14	96	6,86

TABLE 1 (continued)

Compound	R'	R''	R'''	Suppres. of dev. of phytophthorosis (P), % (conc. subs. 0.1%)	Suppress. of growth of fungal mycelium, % (conc. subs. 0.003%)			log LD_{50}	Number of atoms in the molecule, n	Number of electrons in the molecule, e	e^{*} (number of electrons on the atom) $e^{*} = e/n$
					Venturia inaqualis (V)	Aspergillus niger (A)	Fusarium moniliforme (F)				
LXXI	H	OH	H	0	12	34	11	—	14	96	6,86
LXXII	OH	Cl	Cl	0	29	0	60	—	14	130	9,28
LXXIII	Cl	OH	H	72	50	36	40	—	14	112	8,00
LXXIV	Br	OH	H	72	42	48	33	—	14	128	9,14

Note.



X=S (I—IV, VI, VII, IX, XI, XII, XIV—LII), Se (V, VIII, X, XIII, LXX—LXXIV);
Y=H (LIII, LV), CH_3 (LIV), Cl (LVI); Y'=H (LIII, LIV), Br (LV), Cl (LVI).

hot water. The filtrate obtained is mixed with the solution of 7 g (54.5 mmole) of selenious acid in 50 ml of water. The precipitate is filtered off, washed with water until a neutral reaction is obtained, and dried. The compounds (LXX) or (LXXI) are obtained.

The yield of the compound LXX is 82%; it has mp 203-205°C (from toluene) and does not give a depression of the melting temperature with the compound (LXX) obtained according to [18]. Their IR spectra agree; the R_f is 0.65 (system A).

4-Hydroxy-5,7-dichloro- and 4-Chloro-5-hydroxybenzo-2,1,3-selenadiazoles (LXXII) and (LXXIII). A. The mixture of 1 g (5.03 mmole) of the compound (LXX) or (LXXI) in 10 ml (174.83 mmole) of acetic acid are added, in the first case, 1.2 ml (14.82 mmole) and, in the second case, 0.6 ml (7.41 mmole) of sulfuryl chloride. The reaction mass is maintained for 20 min at 60-65°C, cooled, and poured into water. The residue is filtered off, washed with water, and dried. The compounds (LXXII) or (LXXIII) are obtained. The yield of the compound (LXXII) is 92%; it has mp 205-207°C (from toluene). The IR spectrum is characterized at 3511 cm^{-1} (C—OH). The R_f is 0.7 (B). $C_6H_2Cl_2N_2OSe$.

B. To the mixture of 1 g (4.52 mmole) of the compound (LXXVI) or 1 g (5.36 mmole) of the compound (XXVIII) in 20 ml of 10% hydrochloric acid are added 2 g (35.71 mmole) of iron with the avoidance of vigorous frothing. The subsequent process, as well as the isolation of the compounds (LXXII) and (LXXIII), is conducted by analogy with the isolation of the compounds (LXX) and (LXXI).

The yield of the compound (LXXII) is 12%; it has mp 205-207°C (from toluene), and does not give a depression of the melting temperature with the compound (LXXII) obtained by the method A. The R_f is 0.7 (B).

The yield of the compound (LXXIII) is 45%; it has mp 254-256°C (from toluene), and does not give a depression of the melting temperature with the compound (LXXIII) obtained by the method A. The R_f is 0.61 (B).

4-Bromo-5-hydroxybenzo-2,1,3-selenadiazole (LXXIV). A. The compound (LXXI) (5 g, 25.15 mmole), 50 ml (874.15 mmole) of acetic acid, and 0.75 ml (29.1 mmole) of bromine are mixed. The mixture is boiled for 20 min, cooled to room temperature, and poured into 250 ml of water. The residue is filtered off, washed with water, and dried. The compound (LXXIV) is obtained with the yield of 74%; it has mp 213-215°C (from toluene). The IR spectrum is characterized at 3492 cm^{-1} (C—OH). The R_f is 0.61 (B). $C_6H_3BrN_2OSe$.

B. The compound (LXXIV) is obtained by analogy with the compound (LXXII) or (LXXIII) (the method B) from 1 g (4.33 mmole) of the compound (LXXV). The yield of the compound (LXXIV) is 25%; it has the mp 213-215°C (from toluene), and does not give a depression of the melting temperature with the compound (LXXIV) obtained by the method A. The R_f is 0.61 (B).

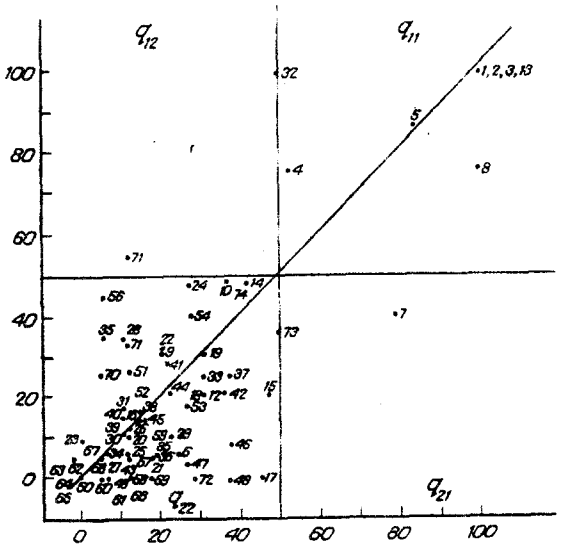


Fig. 1

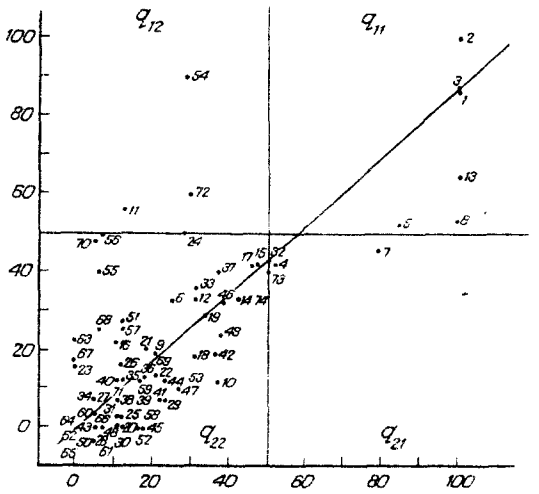


Fig. 2

Fig. 1. Association between the activities of Venturia inaqualis and Aspergillus niger. The X-axis shows the suppression of the growth of the mycelium of the fungus Venturia inaqualis, % (V, %); the Y-axis shows the suppression of the growth of the mycelium of the fungus Aspergillus niger, % (A, %). Here, and in the Figs. 2 and 3, Arabic numerals designate the corresponding compounds coded in the text with Roman numerals.

Fig. 2. Association between the activities of Venturia inaqualis and Fusarium moniliforme. The X-axis shows the suppression of the growth of the mycelium of the fungus Venturia inaqualis, % (V, %); the Y-axis shows the suppression of the growth of the mycelium of the fungus Fusarium moniliforme, % (F, %).

The antifungal activity was studied by the methods of [7, 8]. The toxicity was studied according to the method described in [14]. The results of the investigation are presented in Table 1. The values of the electronic descriptors, obtained as a result of the analysis of the association of the structure of the compound with the biological activity, are presented there.

It should be noted that the analysis is based on the assumption that each molecular structure, consisting of charged entities (nuclei and electrons), produces an electrostatic field around itself [19] which affects mechanisms regulating the processes of activity thereby determining the biological activity of the compound.

Since the potential (ϕ) is an energy characteristic of the electrostatic field, it could be proposed that there exists an association between the biological activity of the compounds and the potentials of the electrostatic fields formed by them.

A similar proposition occurs in agreement with literature data. An example can be presented in the works [13, 17], where the association between different types of biological activity of the compounds and their polarographic potentials is described.

Since the utilization of the complete molecular potential, including the Coulomb interaction of the nuclei and the electrons and the interelectronic repulsion determined by the Pauli Exclusion principle, is mathematically complex and unwieldy, we considered it possible to choose a more simple electronic parameter to establish the association with the biological activity of the compounds.

It follows from the analytical expressions for the potential ϕ, presented in [19], that the potential is associated with the charge q [19], and the parameter q depends on the atomic radius and the number of the electrons in the atom [16]. Since no difficulties are presented by calculating the number of electrons in one atom in the molecule, the number of electrons in the atom e* was taken as the descriptor characterizing the molecule in the present work.

We will introduce the threshold value $\bar{e}^* = 7.0$, which is equal to the mean value for the whole selection of compounds. We will assume that some compound will be active ($A \geq 50\%$) if $e^* \geq \bar{e}^*$, and that such a compound will be inactive or of low activity ($A < 50\%$) if $e^* < \bar{e}^*$. The values of e^* calculated for the series of compounds investigated are presented in Table 1.

We will perform the quantitative verification of this proposition, for which we will employ the statistical method for the comparison of qualitative characteristics possessing alternative variation [15]. For this purpose, we will separate all the compounds into four groups:

1. q_{11} – the number of compounds for which $e^* \geq \bar{e}^*$, $A \geq 50\%$;
2. q_{12} – the number of compounds for which $e^* < \bar{e}^*$, $A > 50\%$;
3. q_{21} – the number of compounds for which $e^* > \bar{e}^*$, $A < 50\%$;
4. q_{22} – the number of compounds for which $e^* \leq \bar{e}^*$, $A \leq 50\%$.

In accord with the data of Table 1, we have for the phytophthorosis: $q_{11} = 23$, $q_{12} = 15$, $q_{21} = 3$, and $q_{22} = 26$. We will determine the Yule coefficient of association ϕ_1 according to [15] for the phytophtorosis activity of the compounds and the value of e^*

$$\varphi_1 = \frac{q_{11}q_{22} - q_{12}q_{21}}{q_{11}q_{22} + q_{12}q_{21}} = 0.86, \quad n = 67.$$

For the level of significance $\alpha = 0.05$ with one degree of freedom between the variables, the verification of the coefficient ϕ_1 by the χ^2-criterion taking into account the corrections of Iest, according to [15], gives $\chi_1^2 = 15.39 > \chi^2_{0.05,1} = 3.84$. The significant excess of the critical value of χ^2 confirms the lack of chance and the interdependence of the chosen method for the classification of the compounds by the activity in accordance with the values of the dichotomous descriptor e^*, as well as the high significance of the coefficient ϕ_1.

The analogous method for the analysis of the association of the structure of a compound with the antifungal activity was applied to the study of quantitative features for Venturia inaqualis, Aspergillus niger, and Fusarium moniliforme.

Using the method for the comparison of qualitative characteristics, we find:

for Vent. inaq, $q_{11} = 9$, $q_{12} = 1$, $q_{21} = 18$, $q_{22} = 46$, $\phi_2 = 0.92$, $n = 74$, $\chi_2^2 = 11$, and $74 > \chi^2_{0.05,1} = 3.84$;

for Asperg. niger, $q_{11} = 9$, $q_{12} = 2$, $q_{21} = 17$, $q_{22} = 46$, $\phi_3 = 0.85$, $n = 74$, $\chi_3^2 = 10.07 > \chi^2_{0.05,1} = 3.84$;

for Fusar. monil., $q_{11} = 8$, $q_{12} = 3$, $q_{21} = 18$, $q_{22} = 45$, $\phi_4 = 0.74$, $n = 74$, $\chi_4^2 = 6.19 > \chi^2_{0.05,1} = 3.84$. The established dependence of the different activities with the single parameter permit the proposition of an association between the activities themselves. The Figs. 1-3 show the dependences between the activities of Aspergillus niger and Venturia inaqualis, Fusarium moniliforme and Venturia inaqualis, and Aspergillus niger and Fusarium moniliforme, whereby q_{11} represents compounds possessing activities $\geq 50\%$ by two tests, q_{12} and q_{21} represent compounds possessing the activity $> 50\%$ by one of the two tests (see Figs. 1-3), and q_{22} represents compounds which are inactive or have low activity ($A \leq 50\%$) by the two tests.

In the first case, the method of the comparison of the qualitative characteristics gives $\phi_5 = 0.99$ ($q_{11} = 8$, $q_{12} = 1$, $q_{21} = 1$, $q_{22} = 64$). In the second case, ϕ_6 0.97 ($q_{11} = 6$, $q_{12} = 3$, $q_{12} = 2$, $q_{22} = 63$). In the third case, $\phi_7 = 0.98$ ($q_{11} = 7$, $q_{12} = 2$, $q_{21} = 2$, $q_{22} = 63$). This confirms the existence of a reliable statistical association between the activities under consideration.

As a result of the analysis, the descriptor utilized in the present work proved to be highly informative. It can be utilized to describe the toxicity (LD_{50}) of the compounds

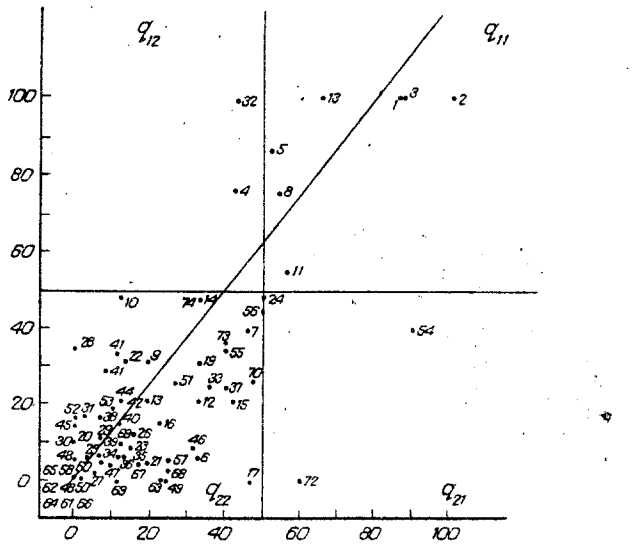


Fig. 3. Association between the activities of Fusarium moniliforme and Aspergillus niger. The X-axis shows the suppression of the growth of the mycelium of the fungus Fusarium moniliforme, % (F, %); the Y-axis shows the suppression of the growth of the mycelium of the fungus Aspergillus niger, % (A, %).

quantitatively. However, in this case, the dependence of the activity on e* bears not a threshold but a linear character, and can be described by the following expression

$$\log LD_{50} = \frac{e^*}{X_1 + X_2 e^*} = \frac{e^*}{2.36 + 0.0125 e^*},$$

where X_1 and X_2 are regression coefficients found by the method of least squares according to [11].

Since the correlation coefficient,

$$r = \frac{\log \overline{LD}_{50\ exp}}{\log \overline{LD}_{50\ calc}}, \quad n = 32,$$

where $\log \overline{LD}_{50\ calc}$ and $\log \overline{LD}_{50\ exp}$ are the arithmetic means of 32 values of the $\log LD_{50}$ calculated by formula or obtained experimentally (see Table 1), is high (r = 0.91), there can be an indication of a substantial reliable statistical association between the logarithm of the toxicity and the number of the electrons on the atom, whereby the following principle is realized in the given case: the higher the value of the descriptor e*, the more toxic is the preparation.

The threshold processes are characterized by another principle: while some critical value of the descriptor has not been achieved, the probable action of the compound is insignificant. At the same time, the action of the preparation is close to the maximal in the region where the critical parameter is exceeded.

Therefore, a statistically reliable dependence between the structure and biological activity can be established where there are inadequate experimental physicochemical data on an investigated substance. In our opinion, such an approach is promising and allows the possible prediction of new structures with a proposed biological action in the series of benzo-2,1,3-thia- and selenadiazole. However, the broadening of the criteria obtained to include new classes of compounds has insufficient basis at the present time.

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