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STUDIES IN THE FIELD OF CHEMISTRY OF NITRO COMPOUNDS (TO 100TH BIRTHDAY ANNIVERSARY OF S. S. NOVIKOV)

Quantum-Chemical Parameters of 2-Substituted 5-Nitrofuran Derivatives

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Abstract—Quantum-chemical parameters of molecules of 2-substituted 5-nitrofuran derivatives were calculated using the GAMESS software package and their correlation with the antibacterial activity of the compounds was analyzed. Regression analysis technique was employed to find linear relationships between the logarithm of the average inhibiting concentration of 5-nitrofuran derivatives and the quantum-chemical parameters. The largest correlation coefficient (0.932) was found for the dependence of the antibacterial activity on the amount of charge on the nitrogen atom of the nitro group. The results obtained are in agreement with modern concepts about the nature of the antibacterial activity of 2-substituted 5-nitrofuran derivatives.

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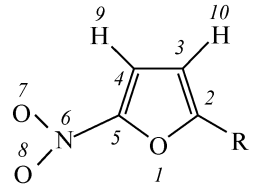
The comparatively fast habituation of microorganisms to chemotherapeutic preparations stimulates a permanent search for new effective antibacterial means. The still used total screening practice requires a large expenditure of resources and loss of time and is characterized by a low probability of success. For prognosticating new effective medicinal preparations, it seems promising to reveal a relationship between the structure and biological activity in local series of biologically active compounds having the common basic chemical structure. In this context, particular attention is being given to analysis of 5-nitrofuran derivatives containing substituents in position *2* of the heteroring. Some derivatives of this series possess a broad spectrum of antibacterial activity and are effective against antibiotic-resistant infectious agents.

As a rule, 5-nitrofuran derivatives containing substituents in position *3* have no antibacterial properties. It has also been noted that the antibacterial activity of 5-nitrofuran derivatives grows as the electron-acceptor capacity of a substituent in position 2 increases [2, 3].

A rough correlation has been revealed between the antibacterial activity of 2-substituted 5-nitrofuran derivatives and the potential of polarographic reduction of the nitro group and the energy of the lowest unoccupied orbital, calculated by the LCAO-MO method [4].

To find a more precise correlation between the antibacterial activity of 5-nitrofuran derivatives containing a substituent in position *2* and the electronic structure, we analyzed the relationship between the antibacterial activity, on the one hand, and the HOMO and LUMO energies, partial charges on atoms of the furan ring, hydrophilic–lipophilic balance, and interatomic distances calculated using the GAMESS software package, on the other.

We used the following numbering of atoms in 5-nitrofuran derivatives:



The following parameters were calculated for 5-nitrofuran derivatives: Q1, Q2, Q3, Q4, Q5, Q6, Q7, Q8, Q9, and Q10 are the partial charges on atoms 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, respectively; R 5–6, R 7–8, and R 7–9, interatomic distances between atoms 5 and 6, 6 and 7, and 7 and 9, respectively; log *P*, hydrophilic–lipophilic

Table 1. Quantum-chemical parameters of 2-substituted 5-nitrofuran derivatives

Comp. no.	R	c, μg ml^{-1} (*E. coli* 645)	Quantum-chemical parameters of a molecule									
			Q2	Q3	Q4	Q6	Q7	Q9	R 5-6	log *P*	Hydr. En.	Polar
1	NO_2	1.5	–0.354	–0.147	–0.147	1.366	–0.587	0.267	1.496	–6.20	–14.08	11.28
2	COOH	50.0	–0.050	–0.0221	–0.125	1.371	–0.598	0.259	1.486	–3.74	–13.11	11.99
3	$COOC_2H_5$	50.0	–0.048	–0.231	–0.125	1.372	–0.601	0.258	1.486	–3.36	–8.46	15.66
4	$CH(OCOCH_3)_2$	6.5	–0.052	–0.237	–0.108	1.375	–0.601	0.255	1.481	–3.82	–9.16	20.06
5	$CH=N–NHCONH_2$	12.5	0.023	–0.282	–0.107	1.375	–0.600	0.255	1.482	–3.04	–17.04	16.83
6	CH=NOH	6.5	0.049	–0.295	–0.101	1.376	–0.604	0.252	1.479	–3.49	–20.45	12.84
7	Br	2.5	–0.102	–0.275	–0.096	1.377	–0.607	0.254	1.480	–4.19	–8.15	12.10
8	H	25.0	–0.074	–0.321	–0.092	1.378	–0.605	0.251	1.478	–3.21	–9.88	9.43
9	I	12.5	–0.146	–0.285	–0.092	1.378	–0.607	0.251	1.478	–4.19	–8.28	14.45
10	CH_3	12.5	0.033	–0.322	–0.086	1.379	–0.610	0.250	1.476	–3.04	–8.02	11.27
11	$NHCOOC_2H_5$	200.0	0.052	–0.379	–0.049	1.387	–0.614	0.248	1.472	–2.12	–9.16	17.01

balance of the compounds; Hydr.En, hydration energy of molecules of the compounds; and Polar, polarizability of a compound.

The data on the antibacterial activity of 5-nitrofuran derivatives, listed in Table 1, were taken from [2]. Because the activities of the 5-nitrofuran derivatives toward various bacteria are rather well correlated, the dependence of the antibacterial activity on quantum-chemical parameters was only considered for the example of *E. coli* 645 bacteria.

We used as the antibacterial characteristic of 5-nitrofuran derivatives the average values of the concentration c inhibiting the bacterial growth. The approximated dependence was expressed as a linear equation

$$\log c = A - BX \quad (1)$$

where log c is the logarithm of the average inhibiting concentration of 5-nitrofuran derivatives, and X, quantum-chemical characteristic of molecules of the derivatives.

Table 2. Constants A and B in the correlation equations log c = $A + BX$ of the relationship between the logarithm of the average inhibiting concentration, log c, of 5-nitrofuran derivatives against bacteria of *E. coli* 645 species and quantum-chemical parameters X of molecules

X	A	B	Linear correlation coefficient K for log c as a function of X
Q3	–1.2	–8.009	0.895
Q4	3.106	20.943	0.930
Q6	–134.864	98.728	0.932
Q7	–35.787	–60.943	0.815
Q9	21.785	–81.620	0.784
R 5–6	106.508	71.236	0.820
log *P*	2.659	0.431	0.855

Our analysis revealed the existence of a comparatively good correlation between the antibacterial activity of 5-nitrofuran derivatives and the following quantum-chemical parameters: Q3, Q4, Q6, Q7, Q9, Q10, R 5–6, and log *P*.

The largest correlation coefficient is observed in the dependence of log c on the charge Q6 on the nitrogen atom of the nitro group (Table 2).

The antibacterial activity of 5-nitrofuran derivatives substituted in position *2* can be prognosticated using the regression equation log c = –160 + 117Q6, derived upon a correlation analysis of the antibacterial activity of 5-nitrofuran derivatives against nine species of bacteria (*E. coli* 645, *B. typhi abd., B. paratyphi B., B. Clysenth*

fexner 1294, *Protens vulgaris, Kl. pneumoniac, Staph aurens Zhaov, Strept. haemoliticus*).

Among the 5-nitrofuran derivatives considered, a significant deviation from the correlation dependence is observed for 5-nitrofuran-2-carboxylic acid and its ethyl ester, which can be attributed to full dissociation of the acid and to rapid hydrolysis of the ester within microorganism cells.

The data obtained are in agreement with modern concepts, according to which the antibacterial activity of 5-nitrofuran derivatives is due to their intracellular reduction [3].

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