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ANTIVIRAL ACTIVITY OF ADAMANTANE-CONTAINING NITROGEN HETEROCYCLES AND RESULTS OF QUANTUM CHEMICAL CALCULATIONS

Annotation. The antiviral activity of 17 adamantane containing nitrogenous heterocyclic compounds against the vaccinia virus in Vero cell culture was studied and the data obtained were compared with the results of ab initio quantum chemical calculations using the DFT method (density functional theory). By analyzing the calculated descriptors of the studied molecules, namely, the energy differences of the frontier molecular orbitals and dipole moments, as well as their antiviral activity data, a convenient method for pre-screening the least active compounds has been developed, which allows for the optimization of the search process for new biologically active substanses.

Keywords: antiviral activity, adamantane-containing nitrogen heterocycles, quantum chemical calculations, density functional theory, frontier molecular orbitals, Fukui method, selectivity index

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ПРОТИВОВИРУСНАЯ АКТИВНОСТЬ СОДЕРЖАЩИХ АДАМАНТАН АЗОТИСТЫХ ГЕТЕРОЦИКЛОВ И РЕЗУЛЬТАТЫ КВАНТОВО-ХИМИЧЕСКИХ РАСЧЕТОВ

Аннотация. Изучена противовирусная активность 17 содержащих адамантан азотистых гетероциклических соединений в отношении вируса осповакцины в культуре клеток *Vero* и проведено сопоставление полученных данных с результатами квантово-химических расчетов *ab initio* методом DFT (теории функционала плотности, англ. *density functional theory*). Методом анализа расчетных дескрипторов исследованных молекул, а именно разности энергий граничных орбиталей и дипольных моментов, а также данных их противовирусной активности разработан удобный способ предварительной выбраковки наименее активных соединений, что позволяет оптимизировать процесс поиска новых биологически активных веществ.

Ключевые слова: противовирусная активность, азотистые содержащие адамантан гетероциклы, квантово-химические расчеты, теория функционала плотности, граничные молекулярные орбитали, метод Фукуи, индекс селективности

Для цитирования. Дикусар, Е. А. Противовирусная активность содержащих адамантан азотистых гетероциклов и результаты квантово-химических расчетов / Е. А. Дикусар, Е. Н. Маргун, В. И. Поткин // Весці Нацыянальнай акадэміі навук Беларусі. Серыя хімічных навук. – 2026. – Т. 62, № 3. – С. 215–221. https://doi.org/10.29235/1561-8331-2026-62-3-215-221

Introduction. An important task in pharmaceutical chemistry is the improvement and development of new, effective antiviral drugs, due to the ability of viruses to undergo structural changes resulting from various mutations, leading to the development of resistance to the drugs used. One of the most common ways to search for new drugs is the chemical modification of compounds with known biological activity, namely the study of ways to "reanimate" the activity of compounds that have lost their antiviral properties [1–5]. Adamantane fragments, when introduced into the structure of known pharmacophores, improve the pharmacokinetic properties of modified compounds, often enhancing their biological acti-

vity [6, 7]. In work [5], a synthesis of a number of aromatic amides based on 1- and 2-aminoadamanatanes was carried out, most of which showed significant activity against the cowpox virus in combination with much lower toxicity. The tetrazole derivatives of adamantane obtained in [7] showed high activity against the influenza virus A/*Puerto-Rico/8/34* sensitive to rimantadine. In our previous work, we described the condensation of rimantadine with various substituted hydroxybenzaldehydes, esters and ethers based on them, as well as 1,2-azole-3-carbaldehydes, the production of azomethines based on them, whose subsequent reduction yielded various adamantane derivatives; further acylation of these derivatives containing active amino and hydroxyl groups yielded compounds containing two 1,2-azole fragments in one molecule [8].

Main part. The aim of this work is to search for correlation dependencies between experimentally obtained data on the antiviral activity of a series of adamantane-containing nitrogen heterocyclic compounds **1–17**, described in work [8], and some molecular parameters (descriptors) of these compounds, calculated using quantum chemical methods. The use of this type of correlation dependence allows for the selection and elimination of the least promising compounds even at the stage of quantum chemical modeling, which should lead to significant savings in laboratory materials and culture media and reduce the labor costs of medical and biological personnel. The determination of the antiviral activity of the studied compounds **1–17** was carried out at the Federal Budgetary Institution of Science "State Research Center of Virology and Biotechnology "Vector" of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing" (Koltsovo village, Novosibirsk region, Russia) and the obtained data were published in work [9] (Table 1). Quantum-chemical modeling of adamantane-containing nitrogen heterocyclic compounds **1–17** by *the ab initio* DFT method was carried out using the B3LYP1/MIDI level of theory, the GAMESS software package [10] and the MIDI basis set [11] (Table 2).

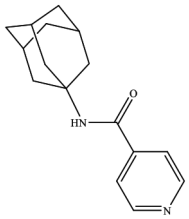
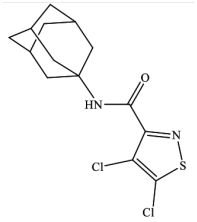
By analyzing the difference in energies of the HOMO and LUMO using the method developed by K. Fukui [12, 13] (formula 1), the values (ΔF, eV) were calculated (Table 2):

$$\Delta F = | E_{\text{HOMO}} - E_{\text{LUMO}} |. \quad (1)$$

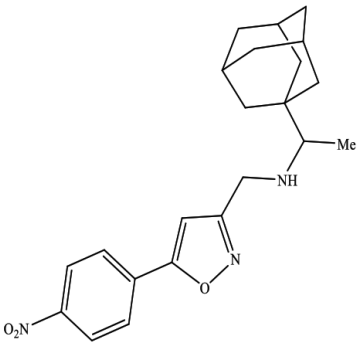
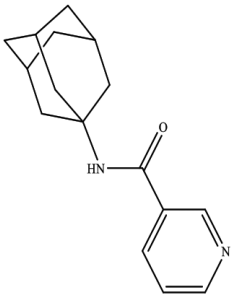
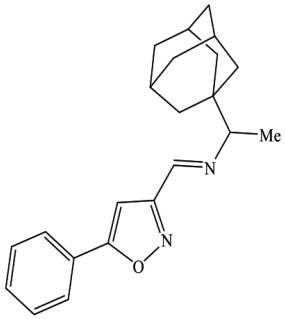
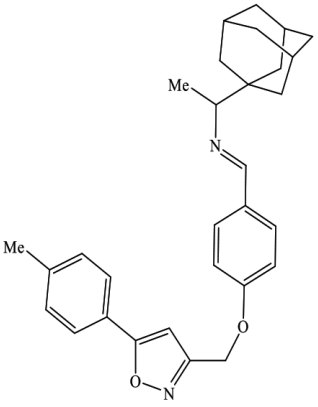
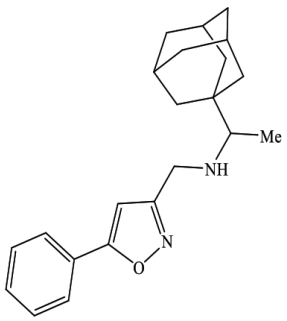
The value (ΔF) shows that the smaller its value, the less energy is required for the transition of one electron from the HOMO to the LUMO, and, consequently, the transition of the molecule to an excited state. The value (ΔF) in a number of cases agrees well with experimental data obtained for a series of compounds with similar chemical structures [14, 15]. At the same time, the higher the value of the dipole moment (D), the more biologically active the given compound is [14, 15]. To illustrate the relationship between the experimentally obtained data on the antiviral activity of adamantane-containing nitrogen heterocyclic compounds **1–17** (Table 1) and some calculated parameters of the molecules, the index (I) was used, calculated using formula 2:

$$\text{I} = \Delta F/\text{D}. \quad (2)$$

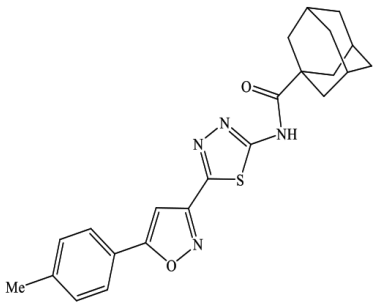
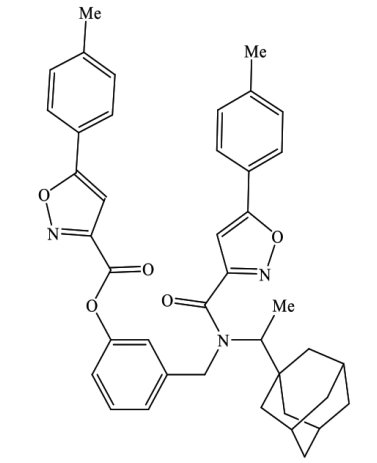
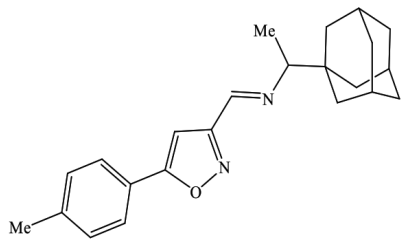
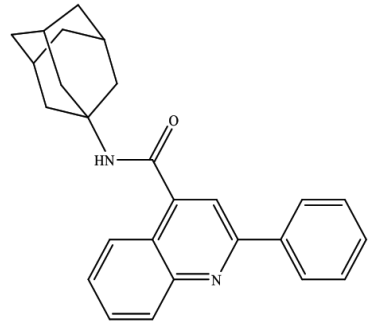
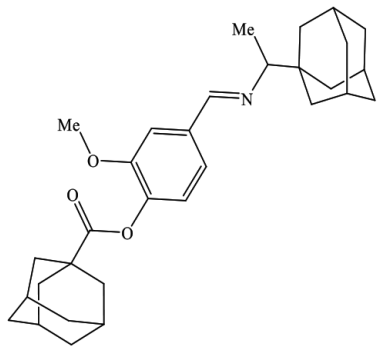
T a b l e 1. **Toxicity (CC_{50}), activity (IC_{50}), selectivity index (SI) and index (I) of nitrogenous heterocyclic compounds 1–17**

№	Structure and name	CTD_{50}, mg/ml (μM)		EC_{50}, mg/ml (μM)	SI
1		*N*-(*3s*,*5s*,*7s*)-Adamantane-1-ilisonico-tinamide	> 100 (> 390)	0.891 (3.476)	> 112.23
2		*N*-(*3s*,*5s*,*7s*)-Adamantan-1-yl-4,5-dichloroisothiazole-3-carboxamide	25.905 (78.201)	0.991 (2.992)	25.22

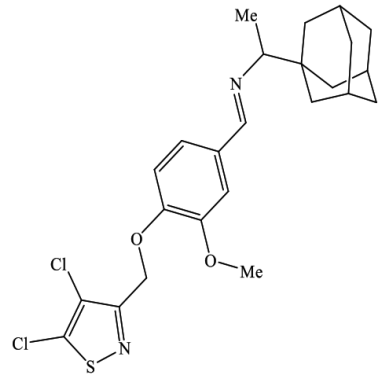
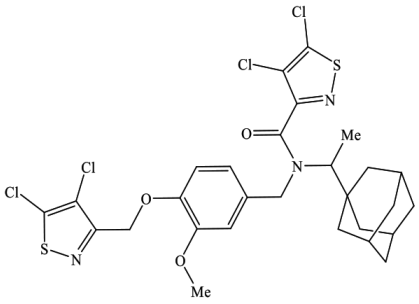
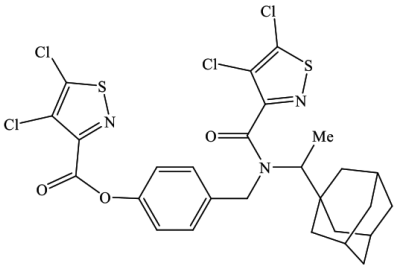
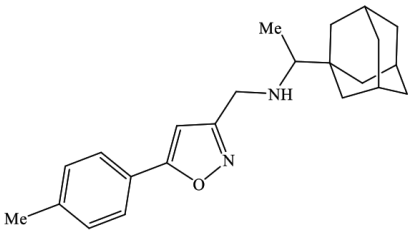
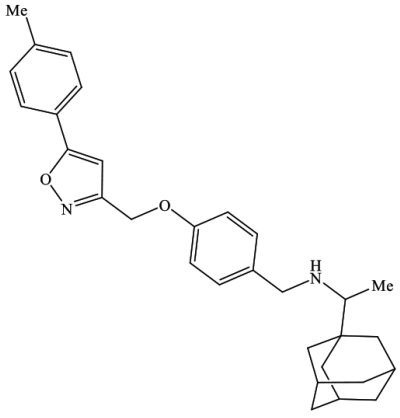
Continuation of table 1

№	Structure and name	CTD_{50}, mg/ml (μM)		EC_{50}, mg/ml (μM)	SI
3		1-(*1s*,*3s*)-Adamantan-1-yl-*N*-[5-(4-nitrophenyl)isoxazol-3-l] methylethan-1-amine	78 (204.467)	3.665 (9.607)	21.28
4		*N*-(*3s*,*5s*,*7s*)-Adamantan-1-ylnicotin-amide	25.823 (100.733)	4.396 (17.148)	5.87
5		(E)-*N*-1-(*1s*,*3s*)-Adamantan-1-ylethyl-1-(5-phenylisoxazol-3-yl)methanimine	100 (28.989)	25.714 (76.882)	3.89
6		E)-*N*-1-(*1s*,*3s*)- Adamantan-1-ylethyl -1-{4-[5-(*p*-Tolyl) isoxazol-3-yl]-methoxy} phenylmethanimine	30.848 (67.856)	19.083 (41.977)	1.62
7		1-(*1s*,*3s*)-Adamantan-1-yl-*N*-[(5-phenylisoxazol-3-yl)methyl]ethan-1-amine	5.206 (15.472)	4.724 (14.039)	1.1

Continuation of table 1

№	Structure and name	CTD_{50}, mg/ml (μM)		EC_{50}, mg/ml (μM)	SI
8		(*3r*,*5r*,*7r*)-*N*-{5-[5-(*p*-Tolyl) isoxazol-3-yl]-1,3,4-thiadiazol-2-yl}adamantane-1-carboxamide	> 100 (237.795)	Inactively	–
9		3-[*N*-1-(*1s*,*3s*)-Adamantan-1-ylethyl-5-(p-tolyl)isoxazole-3-carboxamido]-methylphenyl 5-(*p*-tolyl)isoxazole-3-carboxylate	> 100 (152.486)	Inactively	–
10		(E)-*N*-[1-(*3r*,5r,*7r*)-Adamantan-1-yl]-ethyl-1-[5-(*p*-tolyl)isoxaz-ol-3-yl]-methanimine	> 100 (286.952)	Inactively	–
11		*N*-(*3s*,*5s*,*7s*)-Adamantan-1-yl-2-phenylquinoline-4-carboxamide	> 100 (261.431)	Inactively	–
12		4-(E)-[1-(*3r*,*5r*,*7r*)-Adamantan-1-yl]-ethyliminomethyl-2-methoxyphenyl (*3r*,*5r*,*7r*)-adamantane-1-carboxylate	> 100 (210.230)	Inactively	–

End of table 1

№	Structure and name	CTD_{50}, mg/ml (μM)		EC_{50}, mg/ml (μM)	SI
13		4-(E)-[1-(*3r*,*5r*,*7r*)-Adamantan-1-yl]-ethyl-1-[4-(4,5-dichloroisothiazol-3-ylmethoxy-3-methoxyphenyl]-methanimine	27.537 (57.433)	Inactively	–
14		*N*-1-(*1s*,*3s*)-Adamantan-1-ylethyl-4,5-dichloro-*N*-[4-(4,5-dichloroisothiazol-3-yl)-3-methoxybenzyl] isothiazole-3-carboxamide	14.092 (21.304)	Inactively	–
15		4-[*N*-1-(*1s*,*3s*)-Adamantan-1-ylethyl]-4,5-dichloroisothiazol-3-carboxami-domethylphenyl 4,5-dichloroiso-thiazol-3-carboxylate	5.625 (8.715)	Inactively	–
16		1-(*3r*,*5r*,*7r*)-Adamantan-1-yl- *N*-[5-(*p*-tolyl)isoxazol-3-yl]methylethan-1-amine	5.341 (15,238)	Inactively	–
17		1-(*3r*,*5r*,*7r*)-Adamantan-1-yl-*N*-{4-[5-(*p*-tolyl)isoxazol-3yl]methoxy} benzyl ethan-1-amine	4.967 (10.878)	Inactively	–

The regression model describing the mathematical relationship between the biological parameters (CTD_{50}, EC_{50} and SI, Table 1) and the calculated quantum-chemical descriptors (E_{HOMO}, E_{LUMO}, ΔF, D, I, Table 2) [the determination coefficient (R^2), Table 3] demonstrates an extremely low degree of relationship between these parameters (from 0 to 0.0289). This does not allow these descriptors to be used for direct prediction of antiviral activity. Therefore, an empirical method was developed that allows for the preliminary rejection of obviously inactive samples by comparing a pre-calculated index (I) for a series of similar compounds. The index (I) value was found to be in the range of 0.54–1.65 for compounds exhibiting a high (compound **1**) or moderate (compound **2**, **3**) selectivity index (SI, Table 1).

Table 2. **Data from quantum chemical calculations of compounds 1–17**

№	E_f, **a.** u.	E_{HOMO}, eV	E_{LUMO}, eV	ΔF, eV	D, D	M	N	I
1	–801.78547	–6.6070	–0.4898	6.1172	3.71	256.35	39	1.65
2	–2035.81853	–7.0179	–2.2504	4.7675	3.49	331.26	36	1.37
3	–1237.08822	–6.1090	–2.9008	3.2082	5.89	381.48	55	0.54
4	–801.78662	–6.4900	–0.7265	5.7635	1.59	256.35	39	***3.62***
5	–1032.61084	–6.4464	–0.2204	6.2260	2.44	334.46	51	***2.55***
6	–1415.22853	–6.2070	1.7252	7.9322	3.23	454.61	68	***2.46***
7	–1033.80361	–5.4233	–1.3905	4.0328	3.77	336.48	53	1.07
8	–1649.14191	–6.4764	–1.3987	5.0777	8.92	420.53	54	0.57
9	–2114.92825	–6.3784	–1.5946	4.7838	3.99	655.80	90	1.20
10	–1071.69287	–6.3675	–1.8014	4.5661	4.64	348.49	54	0.98
11	–1184.24616	–6.1770	–0.9306	5.2464	3.33	382.51	55	1.58
12	–1477.76254	–5.9403	–1.1402	4.8001	2.81	475.67	76	***1.71***
13	–2496.56203	–6.0274	–0.1252	5.9022	3.10	479.46	59	***1.90***
14	–2497.77083	–5.4668	–2.2722	3.1946	3.38	661.48	69	0.95
15	–4049.85947	–6.9825	–1.3334	5.6491	4.72	645.44	64	1.20
16	–1072.89709	–5.6219	–1.3742	4.2477	3.66	350.51	56	1.16
17	–1416.44196	–5.4124	–1.3497	4.0627	2.88	456.63	70	1.41

Notes: total energies of the system (E_f, Hartree atomic units), energies of the highest occupied molecular orbitals (HOMO, eV) and lowest unoccupied molecular orbitals (LUMO, eV), energy differences between HOMO and LUMO (ΔF, eV), dipole moments (D, D), index (I), molecular weight (M, dalton), and the total number of atoms (N). The values (I) for low-activity compounds are shown in bold and italics.

Table 3. **Determination coefficients (R^2) of (CTD_{50}, EC_{50} and SI) in relation to the calculated descriptors (E_{HOMO}, E_{LUMO}, ΔF, D, I)**

	E_{HUMO}	E_{LUMO}	ΔF	D	I
CTD_{50}	0.0289	0	0.0035	0.0002	0.0002
EC_{50}	0.000407	0	0.000026	0.000079	0
SI	0.01001	0	0.0008	0	0

Notes: calculations were carried out using the program Microsoft Excel 2010.

Compounds with high index (I) values of 1.71–3.62 (compounds **4–6**, **12** and **13**) showed either very weak activity (**4–6**) or were inactive. In the remaining cases (compounds **7–11** and **14–17**), no correlation was found. However, the use of the index (I) allows for the early rejection of such unpromising compounds as (**4−6**, **12**, **13**), the number of which in the sample of 17 compounds presented in this article was 29.4 %.

Conclusions. Using this technique allows for a nearly 30 % reduction in labor costs associated with the synthesis, purification, and biological testing of unpromising, low-activity chemical compounds.

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