Diuretic activity of some 4- and 3-thio-substituted 1,2,4-triazoles with fluorophenyl fragments

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Diuretics increase the volume of urine and sodium excretion, and therefore are often used to remove excess fluid from the body during various diseases, including hypertension, heart and kidney failure, nephrotic syndrome, cirrhosis, etc. Until now, a wide range of diuretics is known, but none of them is completely safe and has a number of side effects.

The aim of the work is to investigate the diuretic activity of 1,2,4-triazole derivatives containing fluorophenyl substituents at the fifth position of the 1,2,4-triazole fragment, as well as to establish the relationship between "chemical structure and diuretic action" among derivatives 1,2,4-triazole.

Materials and methods. To study the effect on kidney function, six groups of animals with seven rats each were used. When studying water diuresis, rats were kept on a constant diet with free access to water. Before water loading (5 % of body weight), rats were fasted for 2 hours without food and water. Since all tested compounds were insoluble in water, they were administered orally as an aqueous suspension stabilized with Tween-80. The compounds were administered at a dose of 1/10 LD_{50}.

Results. The diuretic activity of 28 new compounds of a number of substituted 1,2,4-triazole-3-thiols, which according to their chemical structure belong to different classes of compounds, was investigated.

Conclusions. Analysis of the results of diuretic activity indicates that there are a number of compounds whose activity is higher than hypothiazide, as well as a compound that exceeds the activity of furosemide.

Key words: diuretic effect, 1,2,4-triazole derivatives, "structure – action".

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Діуретична активність деяких 4- і 3-тіозаміщених 1,2,4-тріазолів із фторфенільними фрагментами

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Діуретики збільшують об'єм виділеної сечі та виведення натрію, їх часто використовують для зменшення надлишку рідини в організмі при різних захворюваннях: артеріальній гіпертензії, серцевій і нирковій недостатності, нефротичному синдромі, цирозі тощо. Нині на ринку доступний широкий вибір діуретиків, але немає жодного безпечного засобу – всі препарати спричиняють певні побічні ефекти.

Мета роботи – вивчення діуретичної активності похідних 1,2,4-тріазолу, що містять при в п'ятому положенні 1,2,4-тріазолового фрагмента фторофенільні замісники, а також встановлення взаємозв'язку «хімічна структура – сечогінна дія» серед похідних 1,2,4-тріазолу.

Матеріали та методи. Для вивчення впливу на функцію нирок здійснили дослідження на 6 групах по 7 щурів у кожній. Під час дослідження водного діурезу щурів утримували на постійній дієті з вільним доступом до води. Перед навантаженням водою (5 % від маси тіла) щурів витримували 2 години без їжі та води. Усі сполуки, які вивчали, нерозчинні в воді, тому їх вводили перорально як водну суспензію, стабілізовану твіном-80. Сполуки вводили в дозі 1/10 LD_{50}.

Результати. Дослідили діуретичну активність 28 нових сполук ряду заміщених 1,2,4-тріазол-3-тіолів, які за хімічною будовою належать до різних класів сполук.

Висновки. Аналіз результатів діуретичної активності показав: є ряд сполук, активність яких вища за гіпотіазид, а також є сполука, що перевищує активність фуросеміду.

Ключові слова: діуретична активність, похідні 1,2,4-тріазолу, «структура – дія».

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The achievements of Ukrainian scientists in the field of synthetic organic chemistry significantly contribute to the development of world science. Among the variety of known organic compounds, the heterocyclic system of 1,2,4-triazole deserves special attention, as it has been at the center of research for decades [1,2,5]. The 1,2,4-triazole cycle has unique properties, which make it a very attractive target for research [3,4].

Numerous publications by various scientific teams from around the world have demonstrated the high reactivity of 1,2,4-triazole derivatives, as well as their low toxicity [6,10], and a wide range of possibilities for their use as potential biologically active compounds [7–9]. Promising properties of some 1,2,4-triazole derivatives, which are used as effective plant growth regulators, have been described in [8,11]. It is worth emphasizing the possibility of using 1,2,4-triazole derivatives as veterinary drugs [9,10].

In particular, the drug "Trifuzol-Neo" is widely used in veterinary medicine, which has recently gained popularity due to its effectiveness. At the stage of registration is a new original antifungal veterinary drug in the form of liniment "VetMicoDerm". Therefore, the continuation of research related to the synthesis of new derivatives of 1,2,4-triazole, as well as the study of the pharmacological properties of new derivatives is an important scientifically attractive area, which undoubtedly offers promising opportunities in various aspects of human life.

In our opinion, the study of the diuretic activity of new 1,2,4-triazole derivatives deserves special attention. First, the creation of new diuretics is relevant today, and secondly, there is information that some 1,2,4-triazole derivatives have high diuretic activity [9]. Therefore, the aim of our work was to investigate the diuretic activity of new substituted 1,2,4-triazole-3-thiols.

Aim

The aim of the work is to study the diuretic activity of 1,2,4-triazole derivatives containing fluorophenyl substituents at the fifth position of the 1,2,4-triazole fragment, as well as to establish the relationship between "chemical structure and diuretic action" among derivatives 1,2,4-triazole.

Materials and methods

In our research, we used a series of new substituted 1,2,4-triazole-3-thiols (*Fig. 1*), which were first synthesized in the laboratory of organic synthesis of the Department of Natural Sciences for foreign students and toxicological chemistry of Zaporizhzhia State Medical and Pharmaceutical University. Physical-chemical constants of the synthesized compounds have been studied and described before, some of them are given in the literature [1,10].

Previously, we conducted a study to determine the dose of synthesized compounds, we also studied the general toxic effect and acute toxicity of these derivatives. The research was carried out according to the well-known express method of V. B. Prozorovsky, and the assessment of the degree of toxicity was determined by K. K. Sidorov. The animals were kept on a standard diet, under natural light regime "day and night" [12]. Further studies were performed taking into account the "Rules of preclinical safety assessment of pharmacological agents (GLP)" [13]. Acute toxicity studies of each compound were studied in a range of four doses, each of which was tested on 2 animals [14,16].

The follow-up period was 14 days, during which the nature and duration of symptoms of intoxication, the time of death, and the number of dead animals from each dose were taken into account [15,16]. The research was conducted in accordance with the national "General Ethical Principles of Animal Experiments" (Ukraine, 2001), which is consistent with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, France, 1985).

To study the effect on renal function, 6 groups of animals with 7 rats in each were used. In the study of aqueous diuresis, rats were kept on a constant diet with free access to water. Prior to water loading (5 % of body weight), rats were kept for 2 h without food and water. All compounds studied were water-insoluble, so they were administered orally as an aqueous suspension stabilized with tween-80. The compounds were administered at a dose of 1/10 of LD_{50}.

The amount of urine was measured every hour for 4 hours. The amount of urine excreted by the control group of animals (which did not receive test compounds) was taken as 100 %. The study and analysis of the obtained experimental data were performed in comparison with the reference diuretics: hypothiazide and furosemide.

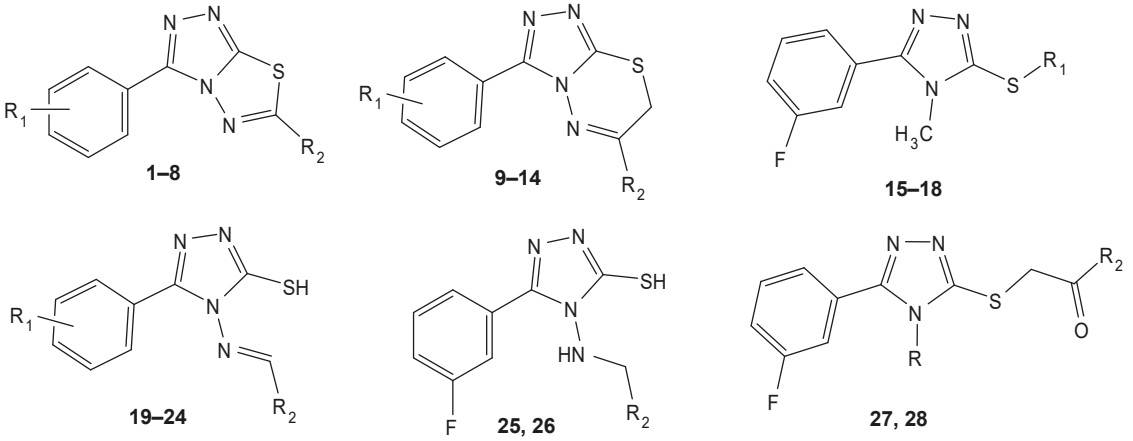
Results

Twenty-eight new compounds, including substituted 1,2,4-triazole-3-thiols belonging to different classes of compounds based on their chemical structure, were studied for their diuretic activity (*Fig. 1*).

Among the 3-(2-,3-fluorophenyl)-6-(aryl-,heteryl)-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazoles, four exceed the reference diuretic hypothiazide (2, 4, 5, 6, *Table 1*), and 3-(2-fluorophenyl)-6-(phenyl)-[1,2,4]triazole[3,4-*b*][1,3,4]thiadiazole (1), 3-(3-fluorophenyl)-6-(3-methoxyphenyl)-[1,2,4]triazole[3,4-*b*][1,3,4]thiadiazole (7) and 3-(3-fluorophenyl)-6-(2-bromo-4-fluorophenyl)-[1,2,4]triazole[3,4-*b*][1,3,4]thiadiazole (8) approximate by activity to furosemide. Regarding the activity of 3-(2-,3-fluorophenyl)-6-R_2-7*H*[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines (9–14, *Table 1*), high rates of diuretic action were not detected.

Discussion

Analysis of the results of the diuretic activity of 3-alkylthio-5-(3-fluorophenyl)-4-methyl-1,2,4-triazoles (15–18, *Table 1*) shows a fairly high activity against hypothiazide, especially for 3-propylthio-5-(3-fluorophenyl)-4-methyl-1,2,4-triazole (15) and 3-hexylthio-5-(3-fluorophenyl)-4-methyl-1,2,4-triazole (18).



1) R_1 = 2-F, R_2 = phenyl; 2) R_1 = 2-F, R_2 = 2-fluorophenyl; 3) R_1 = 2-F, R_2 = 4-fluorophenyl; 4) R_1 = 2-F, R_2 = 2-methoxyphenyl;
5) R_1 = 3-F, R_2 = phenyl; 6) R_1 = 3-F, R_2 = 2-methoxyphenyl; 7) R_1 = 3-F, R_2 = 3-methoxy-phenyl; 8) R_1 = 3-F, R_2 = 2-bromo-4-fluorophenyl;
9) R_1 = 2-F, R_2 = CH_3; 10) R_1 = 2-F, R_2 = 2-phenyl; 11) R_1 = 2-F, R_2 = 4-fluoro-phenyl; 12) R_1 = 2-F, R_2 =4-methoxyphenyl;
13) R_1 = 3-F, R_2 = CH_3; 14) R_1 = 3-F, R_2 =4-methoxyphenyl; 15) R_1 = C_3H_7; 16) R_1 = C_4H_9; 17) R_1 = C_5H_{11}; 18) R_1 = C_6H_{13};
19) R_1 = 2-F, R_2 = phenyl; 20) R_1 = 2-F, R_2 = 4-bromophenyl; 21) R_1 = 2-F, R_2 =3-fluorophenyl; 22) R_1 = 2-F, R_2 = 4-fluorophenyl;
23) R_1 = 3-F, R_2 = 4-fluorophenyl; 24) R_1 = 3-F, R_2 = 2-hydroxyphenyl; 25) R_2 = 4-fluorophenyl; 26) R_2 = 2-hydroxyphenyl;
27) R_1 = CH_3, R_2 = phenyl; 28) R_1 = NH_2, R_2 = phenyl

Fig. 1. Structure of some substituted 1,2,4-triazole-3-thiols.

Table 1. The results of the study of the diuretic activity of some substituted 1,2,4-triazole-3-thiols

No. connection	120 min, M ± m, ml	Δ % to control	240 min, M ± m, ml	Δ % to control
Control	1.330 ± 0.113	–	2.130 ± 0.117	–
Furosemide	4.0800 ± 0.0352*	186.07	6.050 ± 0.028*	188.77
Hypothiazide	2.710 ± 0.332*	83.12	3.610 ± 0.312*	77.18
1	3.660 ± 0.438*	96.08	6.110 ± 0.366*	137.18
2	2.770 ± 0.074*	72.54	5.590 ± 0.310*	94.33
3	2.090 ± 0.166	33.45	3.210 ± 0.208*	32.32
4	2.230 ± 0.484	54.17	4.870 ± 0.458*	96.28
Control	1.630 ± 0.159	–	2.740 ± 0.265	–
5	2.840 ± 0.088*	72.44	5.780 ± 0.209*	94.18
6	2.720 ± 0.187	73.22	5.750 ± 0.187	95.11
7	3.180 ± 0.344	96.09	6.170 ± 0.456	138.19
8	3.150 ± 0.445	96.12	6.130 ± 0.413	139.32
9	2.120 ± 0.222	17.17	3.280 ± 0.216	63.16
Control	1.330 ± 0.088	–	2.210 ± 0.249	–
10	2.130 ± 0.212*	43.77	4.210 ± 0.260*	73.13
11	1.540 ± 0.133*	3.35	3.110 ± 0.228	17.74
12	1.570 ± 0.214	15.54	2.420 ± 0.115	40.65
13	1.870 ± 0.175	33.54	3.300 ± 0.211*	31.55
14	3.240 ± 0.155	30.07	5.180 ± 0.319	69.21
15	4.110 ± 0.113	160.23	7.560 ± 0.221	162.16
Control	1.350 ± 0.172	–	2.520 ± 0.115	–
16	2.380 ± 0.609	53.85	4.750 ± 0.563	95.62

Cont. of table 1.

No. connection	120 min, M ± m, ml	Δ % to control	240 min, M ± m, ml	Δ % to control
17	1.870 ± 0.254	21.66	4.150 ± 0.432	98.28
18	2.690 ± 0.255	23.27	4.330 ± 0.417	100.15
19	2.220 ± 0.114	21.31	4.420 ± 0.113	96.41
20	1.450 ± 0.211	17.31	2.720 ± 0.477	12.63
21	2.120 ± 0.274*	47.87	4.720 ± 0.236*	124.11
22	2.620 ± 0.133*	46.46	4.380 ± 0.221	126.15
23	1.210 ± 0.019	11.18	3.230 ± 0.409	51.23
24	1.440 ± 0.113	12.19	3,770 ± 0.509	52.13
25	3.680 ± 0.0312*	182.02	5.470 ± 0.016*	186.25
26	2.630 ± 0.262	64.52	4.660 ± 0.233*	65.13
27	2.460 ± 0.218	62.11	4.520 ± 0.142	61.09
28	1.550 ± 0.172	7.63	3.050 ± 0.175	19.66

*: $p < 0.05$ in relation to control.

Molecules of 5-(2-,3-fluorophenyl)-4-(aryl-,heteryl) ylidene)amino-1,2,4-triazole-3-thiols (19–24, *Fig. 1*) consist of various functional substituents. Therefore, it is possible to assume with a certain probability that their activity depends on features of structure of substituents on amino group.

Thus, the introduction of a 3-fluorophenyl or 4-fluorophenyl substituent into the molecule leads to an increase in diuretic activity almost twice relative to hypothiazide (21, 22, *Table 1*). Of particular note is 5-(3-fluorophenyl)-4-(4-fluorophenylamino)-1,2,4-triazole-3-thiol (25, *Table 1*), whose diuretic activity is highest.

The obtained data were statistically processed using the standard software package Microsoft Office 2007 and Statistica for Windows 6.0. The significance of intergroup differences according to experimental data was established using Student's t-test. The level of statistical significance of differences in research results is $p < 0.01$. Analyzing the results of the experiment, it was found that some compounds that were studied in a number of new derivatives of 1,2,4-triazole-3-thiol, have a pronounced diuretic activity (*Table 1*).

Conclusions

1. The diuretic activity of a number of new 4- and 3-thio-substituted 1,2,4-triazoles with fluorophenyl fragments was studied for the first time.

2. A thorough analysis of the results of diuretic activity reveals several compounds with higher activity than hypothiazide, as well as a compound with greater activity than furosemide.

3. In some cases, certain patterns between the chemical structure of the molecules and their diuretic activity were observed.

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

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