

# Effect of 5-R-Thio-Tetrazolo[1,5-C] Quinazoline Derivatives on the Physical Performance in Different Types of Physical Exercise

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## Abstract

**Aim:** To study the effect of 5-R-thio-tetrazolo[1,5-c]quinazoline derivatives on the physical performance in different types of physical exercise. **Materials and Methods:** The experiments were performed on Wistar white male rats weighing 190-210 g. The investigated substances and a comparator, 2-ethylthiobenzimidazol hydrobromide, were injected intraperitoneally to animals OD during 5 days in ED<sub>50</sub> doses. Physical performance of rats was assessed by treadmill running tests at a speed of 42 m/min with a 10° slope angle and holding rats at a 15 rpm rotarod test. The study was performed on the day 5 of the experiment, 40 min after the past injection. **Results and Discussion:** We revealed that a 5-day course administration of 5-R-thio-tetrazolo[1,5-c]quinazoline derivatives at an ED<sub>50</sub> dose contributed to growing the length of a rat treadmill running. The results of the test presented that physical endurance of animals grew with compounds KB-10, KB-28, KB-51, and KB-55 by 47.1, 60.7, 32.3, and 46.0 %, respectively. The duration of holding rats on rotarods with a pharmacological correction was 41.2-71.4 % higher than in the control group. The dynamics of physical endurance against treadmill running and rotarod tests results in the group of animals administered the reference medicine, 2-ethylthiobenzimidazol hydrobromide, made up 50.7 and 59.4% compared to the control, respectively. **Conclusion:** KB-28 (sodium 2-(tetrazolo[1,5-c]quinazoline-5-ylthio)acetate) demonstrated the greatest effect on physical endurance of study participants among all 5-R-thio-tetrazolo[1,5-c]quinazoline derivatives. This substance was not only similar with the reference medicine in efficacy but also had ED<sub>50</sub> 19 times lower than reference actoprotector.

**Key words:** Physical endurance, 5-R-thio-tetrazolo[1,5-c]quinazoline, 2-ethylthiobenzimidazol hydrobromide derivatives, rotarod test, treadmill running

## INTRODUCTION

The professional activities of contemporary humans are accompanied by adverse physical, chemical, and informational factors. These include hypoxia of different genesis, hypokinesia, radiation, physical, and mental overload, and stress.<sup>[1]</sup> Their impact depletes energy potential and the defenses of the human body, manifesting in rapid onset of fatigue, and reduced efficiency. As a result, one may experience different psychosomatic diseases, a typical manifestation of which is chronic fatigue syndrome, accompanied by a significant decrease in efficiency of human organism.<sup>[2,3]</sup> Therefore, the actual problem of modern pharmacology is searching for new highly efficient substances, able to increase

physical endurance in normal and extreme conditions and to ensure full recovery after the physical load.

For this purpose, people use low-toxic biologically active medicines that provide targeted impact on the processes of the human body restoration by way of rational use and quick

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replenishment of energy and plastic resources and economize a number of physiological processes in the body. Widely used are herbal, vitamin, mineral, and amino acid complexes.<sup>[4,5]</sup> Especially, effective are considered synthetic medicines of metabolic inexhaustible type of action, which prevent the development of fatigue, promote physical performance, and efficiency of physical work without increasing oxygen consumption and heat production. An important place among these substances belongs to actoprotectors. One of the important features of actoprotector effect is their high activity in extreme situations (impact of high or low temperatures, vibration, hypoxia, etc.).<sup>[6]</sup> The scope of use of these substances covers sports, military, and emergency medicine applications.

Given the fact that the class of these substances is quite small in numbers, and the medicines available have low activity, and significant side effects, one of the urgent tasks of experimental pharmacology is searching for new highly efficient substances, able to improve physical endurance. The promising ones in this respect are derivatives of quinazoline.<sup>[7-10]</sup> According to the results of previous studies, among 15 new 5-R-thio-tetrazolo[1,5-c]quinazoline derivatives we chose four compounds that most increased duration of swimming test under conditions of normo-, hyper- and hypo-thermia.<sup>[11-13]</sup> The above substances were synthesized at the department of organic chemistry of Zaporizkyi State Medical University under the leadership of professor Antypenko *et al.*<sup>[8]</sup> To find a leading compound, it was reasonably to investigate the effect of the most active compounds on the physical endurance of rats.

## Aims

The objective of the study was to investigate the effect of 5-R-thio-tetrazolo[1,5-c]quinazoline derivatives on endurance of organism in different types of physical exercises.

## Settings and design

The experiments were performed on white male Wistar rats weighing 190-210 g, obtained from the vivarium of the National Pyrogov Memorial Medical University, Vinnytsya. The duration of quarantine was 2 weeks. The animals were kept on a standard diet with free access to water and feed with a natural day and night regimen. Individually marked animals, selected after quarantine, were divided into groups of six animals each with homogenous body weight ( $\pm 15\%$ ). All interventions were carried out in compliance with the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (Strasbourg, 1986), as evidenced by the opinion of the bioethics commission of the Pyrohov Memorial Vinnytsia National Medical University (Minutes No. 7 dated 24 April 2014).

The rats were divided into six groups: I - rats, administered intraperitoneally the equivolumic dose of 0.9 % sodium

chloride solution (control); I-V groups, consisting of animals treated with KB-10 (4.8 mg/kg), KB-28 (1.7 mg/kg), KB-51 (5.5 mg/kg), and KB-55 (5.2 mg/kg) compounds; and VI – rats administered 2-ethylthiobenzimidazol hydrobromide at a dose of 32.0 mg/kg. The substances with laboratory designators KB-51 and KB-55 were diluted in isotonic sodium chloride solution, previously suspended with tween-80. Compounds KB-10, KB-28, and comparator substance were diluted directly in 0.9% sodium chloride solution. The investigational and referent compounds were administered to animals OD during 5 days.

## MATERIALS AND METHODS

The effect of 5-R-thio-tetrazolo [1,5-c]quinazoline derivatives on physical endurance of rats was assessed by treadmill running and rotarod tests. As a reference compound, we used chemical substance of reference actoprotector 2-ethylthiobenzimidazol hydrobromide (2-ethylthiobenzimidazol hydrobromide).<sup>[6]</sup> The investigational substance and reference compound were used at ED<sub>50</sub> doses under swimming test, calculated graphically by Litchfield-Wilcoxon method.<sup>[14]</sup>

Physical performance of rats was assessed against the results of treadmill running test at a speed of 42 m/min and with a 10° slope angle.<sup>[15]</sup> We recorded duration of the rat run (min) until failure as evidenced by the lack of response to stimulation with electrical charges (40V) on the starting line of the treadmill. The animals were previously adapted to a specific type of load by a 5 min running at the speed of the treadmill 25 m/min with a 10° slope angle on days 1 and 3 of the experiment. In the second series of the experiment, we determined a rotarod holding time in rats at a rate of 15 rpm.<sup>[16]</sup> The animals were adapted for this type of load by training on days 2 and 4 at a 10 rpm rate of the rod rotation. The study was performed on the day 5 of the experiment, 40 min after the last injection of medicines. The physical endurance was evaluated against the dynamics (%) compared to control.

## Statistical analysis used

We processed the digital data of the study using the method of variation statistics and IBM SPSS Statistic 22 software, calculated a mean value  $M$ , the arithmetic mean error  $m$ , t-Student criterion for normal distribution, non-parametric criterion  $W$  - for abnormal distribution, and Wilcoxon signed-ranked test  $\check{T}$  - to determine changes in the dynamics within the group. Statistically significant were considered the changes in parameters at  $P < 0.05$ .<sup>[14]</sup>

## RESULTS

The results of the study of animal physical endurance using the treadmill running test are shown in Table 1 we established,

that the average duration of treadmill running in the control group of rats was 5.35 min.

Physical endurance of animals, administered investigational substances, and reference compound during 5 days, increased statistically significantly compared to control. This manifested in an increase of the length of rat treadmill running. Thus, when administered compound with laboratory name KB-10 at a dose of 4.8 mg/kg, the dynamic endurance of rats increased statistically significant by 47.1% compared to control animals. The duration of animal running in the experimental conditions with KB-28 (1.7 mg/kg) was 8.6 min, which corresponded to a 60.7% growth of physical endurance relative to control. Administration of medium-effective course doses of KB-51 and KB-55 compounds contributed to growing the dynamic index of physical performance compared to the control group by 32.3% and 46.0%, respectively. Daily intraperitoneal administration of 2-ethylthiobenzimidazol hydrobromide at a dose of 32.0 mg/kg also contributed to growing endurance of animals: The duration of running increased by 50.7%.

The positive effect of 5-R-thio-tetrazolo[1,5-c]quinazoline derivatives on physical performance was also noted during the second series of experiments; see the results in Table 2.

Thus, in the course of administration of 5-R-thio-tetrazolo[1,5-c]quinazoline derivatives, time of holding animals on the rotarod statistically significantly increased compared to the control group ( $P < 0.05$ ). The compounds with laboratory names KB-10, KB-51, and KB-55 demonstrated the growth within 41.2-49.5%. The physical endurance

of rats administered compound KB-28 in the rotarod test increased by 71.4%. The dynamics in the group of animals treated with the reference medicine 2-ethylthiobenzimidazol hydrobromide was registered at the level of 59.4% compared to control.

The investigational medicines were similar to 2-ethylthiobenzimidazol hydrobromide in the rate of physical endurance in the first series of experiment (running on a treadmill). In the second series of the experiment (rotarod), KB-10 and KB-28 were similar to the reference substance, and KB-51 and KB-55 were inferior to the latter ( $P < 0.05$ ).

The results indicate the ability of the investigated substances to increase physical endurance. It should also be noted that 5-R-thio-tetrazolo[1,5-c]quinazoline derivatives were more active agents than reference actoprotector 2-ethylthiobenzimidazol hydrobromide as they had the same efficacy being used at much smaller doses. The results of compound KB-28 (1.7 mg/kg) presented the greatest activity. Under this indicator, ( $ED_{50}$ ), sodium 2-(tetrazolo[1,5-c]quinazoline-5-ylthio)acetate (compound KB-28) was 18.8 times more active than reference drug.

## CONCLUSIONS

Using the results of a 5-day course administration of compounds KB-10, KB-28, KB-51, and KB-55 at  $ED_{50}$  doses, we determined the statistically significant increase of the duration of animal treadmill running and rotarod holding.

**Table 1:** Effect of 5-R-thio-tetrazolo[1,5-c]quinazoline derivatives and 2-ethylthiobenzimidazol hydrobromide on the duration of rat treadmill running, ( $M \pm m$ ,  $n=6$ )

Animal group	$ED_{50}$ , mg/kg	Running duration, min	Trend relative to control, %
0.9% NaCl, trained control	-	5.35±0.18	-
KB-10	4.8	7.87±0.30*	47.1
KB-28	1.7	8.60±0.21*	60.7
KB-51	5.5	7.08±0.14*°	32.3
KB-55	5.2	7.81±0.31*	46.0
2-ethylthiobenzimidazol hydrobromide	32.0	8.06±0.36*	50.7

\* $P < 0.05$  - statistically significant relatively to control; ° $P < 0.05$  - statistically significant relatively to 2-ethylthiobenzimidazol hydrobromide;

° $P < 0.05$  - statistically significant relatively to KB-28; n - number of animals in the group

**Table 2:** Effect of 5-R-thio-tetrazolo[1,5-c]quinazoline derivatives and 2-ethylthiobenzimidazol hydrobromide on rat rotarod test results ( $M \pm m$ ,  $n=6$ )

Animal group	$ED_{50}$ , mg/kg	Rotarod hold duration, sec	Trend relative to control, %
0.9% NaCl, trained control	-	87.83±2.29	-
KB-10	4.8	131.33±2.30*°	49.5
KB-28	1.7	150.50±3.33*	71.4
KB-51	5.5	124.00±3.73*#	41.2
KB-55	5.2	126.33±2.81*#	43.8
2-ethylthiobenzimidazol hydrobromide	32.0	140.00±3.69*	59.4

The leading compound was found sodium 2-(tetrazolo[1,5-c]quinazoline-5-ylthio)acetate (KB-28, 1.7 mg/kg, intraperitoneally), as being administered, it resulted in growing the dynamic endurance of rats and the rotarod holding time by 60.7% and 71.4%, accordingly.

The compound KB-28 was not only similar to 2-ethylthiobenzimidazol hydrobromide in efficacy, but had ED<sub>50</sub> 19 times lower than reference actoprotector.

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