ACTOPROTECTOR ACTIVITY OF 4-R-(IDENEAMINO)-5-R-4H-1,2,4-TRIAZOLE-3-THIOLS

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ABSTRACT

In this study, actoprotector activity of 1,2,4-triazole derivatives is described. The biological activity of synthetic 4-R-(ideneamino)-5-R-4H-1,2,4-triazole-3-thiols was analyzed. The forced swim test with a weight load of 10% of the test animal’s body weight was applied. According to the obtained results, compounds that contained NH4+ and CuSO4 substituents were among the most active, potency of which was close to that of the reference drug Riboxin. Introduction of propylamine, isopropylamine and piperazine groups into the molecule decreases the actoprotector activity. Compounds containing monoethanolamine, diethylamine, ethylamine, and magnesium sulfate moieties almost did not exhibit actoprotector activity.

KEYWORDS
actoprotector activity, 1,2,4-triazole derivatives, structure-activity.

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Fast pace of life people have nowadays often leads to mental and physical exhaustion. A great portion of people, especially those living in cities, have now regularly begun to experience chronic fatigue syndrome, which involves systemic decrease of adaptive defense mechanisms, work productivity, and immunity. This issue is pertinent to athletes who experience fatigue from physical exercises almost every day. The main reason behind the mentioned symptoms is continuous physical and mental loads of high and moderate intensity. In such cases, when rest cannot resolve these issues, physicians may prescribe actoprotectors.

The use of modern medications, which exhibit actoprotector properties, is a promising and effective solution for the enhancement of physical and mental productivity [1]. Various groups of medications are available to address fatigue, ranging from synthetic drugs (Mexidol, Mildronate, Bromantan, Chlodantal, etc.), vitamin products of plant and animal origin (Eleutherococcus, Echinacea purpurea and others), and pill dosage forms (Ecdisten, Immunal) [2]. However, the effect on physical performance becomes apparent only in several weeks after the beginning of the treatment, which creates inconveniences when fatigue must be overcome quickly.

In order to preclude this problem, an emerging class of low-toxic compounds may be used to stimulate productivity, which are actoprotectors [3,4]. Medicinal products of this class do not obstruct external respiratory and cardiovascular functions, stimulate physical productivity, and prevent fatigue. Heterocyclic systems pose great interest in this regard, and low-toxic 1,2,4-triazole derivatives hold a prominent place among them, particularly due to their antiviral, diuretic, anxiolytic, antitumor, and other biological effects [5-7].

Purpose.
Study the actoprotector activity of various 4-R-(ideneamino)-5-R-4H-1,2,4-triazole-3-thiols.
Materials and methods. The experiment was conducted on a group of outbred white rats with body weights within 135-319 g. The forced swim test (FST) with a weight load of 10% of the test animal’s body weight was applied [8]. Weight load was attached to the tailsets of the animals. Swimming was continued until exhaustion, which was recorded at 10 seconds after the animals were placed in the water. Each rat was placed into a separate water tank with water level of 60 cm. Water temperature was 24–27°C. The studied compounds and reference substance Riboxin were administered abdominally at the dose of 100 mg/kg in 20 minutes before FST [9]. The substances were administered at the dose of 1/10 of LD$_{50}$ [10]. Swim time was recorded in seconds. For reference, a control group of animals was used, which received normal saline in 20 min prior to the test.

Table 1.

| Compound no. | Kat$^+$ |
|--------------|---------|
| 1. | C$_4$H$_{10}$NO$^+$ |
| 2. | HO-CH$_2$CH$_2$-NH$_3^+$ |
| 3. | C$_4$H$_{12}$N |
| 4. | C$_2$H$_5$NH$_3^+$ |
| 5. | NH$_4^+$ |
| 6. | K$^+$ |
| 7. | Na$^+$ |
| 8. | 1/3Fe$^{3+}$ |
| 9. | 1/2Mg$^{2+}$ |
| 10. | 1/2Cu$^{2+}$ |
| 11. | C$_5$H$_{12}$N |
| 12. | CH$_3$NH$_3^+$ |
| 13. | C$_5$H$_{12}$NO |
| 14. | C$_{12}$H$_{15}$N$_3$O |
| 15. | C$_3$H$_{10}$N |
| 16. | 1/2Zn$^{2+}$ |
| 17. | C$_3$H$_{10}$N |
| 18. | (CH$_4$)$_2$NH$^+$ |
| 19. | C$_4$H$_{11}$N$_2$ |
Results and discussion.
Actoprotector activity of 19 new compounds was studied. It was established that 4-R-(ideneamino)-5-R-4H-1,2,4-triazole-3-thiols exhibit actoprotector effect in range between 34.28% and 12.86% as compared to the reference (Table 2).

Table 2.

| No. | Compound     | Forced swimming duration, s | Δ%   |
|-----|--------------|-------------------------------|------|
| I.  | Control (normal saline) | 235.43 ± 15.588              |      |
| II. | Riboxin      | 277.00 ± 11.745              | 17.66|
| III.| КП-56        | 253.00 ± 8.106               | 7.46 |
| IV. | КП-57        | 154.71 ± 6.335               | -34.28|
| V.  | КП-58        | 258.86 ± 12.512              | 9.95 |
| VI. | КП-59        | 209.29 ± 6.778               | -11.10|
| VII.| КП-60        | 265.71 ± 14.138              | 12.86|
| VIII.| КП-61       | 258.00 ± 8.861               | 9.59 |
| IX. | КП-62        | 261.14 ± 6.595               | 10.92|
| X.  | КП-63        | 260.14 ± 6.638               | 10.50|
| XI. | КП-64        | 155.57 ± 6.218               | -33.92|
| XII.| КП-65        | 265.57 ± 9.459               | 12.80|
| XIII.| КП-82      | 242.57 ± 11.633              | 3.03 |
| XIV.| КП-83        | 260.71 ± 12.440              | 10.74|
| XV. | КП-92        | 257.71 ± 6.046               | 9.47 |
| XVI.| КП-93        | 249.57 ± 14.328              | 6.01 |
| XVII.| КП-94      | 262.86 ± 9.349               | 11.65|
| XVIII.| КП-95     | 243.71 ± 11.718              | 3.52 |
| XIX.| КП-96        | 262.86 ± 7.022               | 11.65|
| XX. | КП-97        | 243.71 ± 11.718              | 3.52 |
| XXI.| КП-98        | 263.29 ± 6.736               | 11.83|
According to the obtained results, compounds containing NH₄⁺ and CuSO₄ substituents are among the most active, effect of which is close to that of the reference drug Riboxin. Introduction of propylamine, isopropylamine and piperazine groups into the molecule decreases the actoprotector activity.

Introduction of such radicals as NaHCO₃, FeCl₃, KHCO₃, and such substituents as methylamine and 4-methylmorpholine lowers the actoprotector activity of 2-(((3-mercapto-5-methyl-4H-1,2,4-triazol-4-yl)imino)methyl)benzoic acid.

Compounds (КП-56, КП-82, КП-93, КП-95, КП-97) have a slightly weaker actoprotector activity. At the same time, substances containing monoethanolamine, diethylamine, ethylamine, and MgSO₄ moieties almost do not exhibit actoprotector activity.

**Conclusions.**

Nineteen new synthetic 4-R-(idencamino)-5-R-4H-1,2,4-triazole-3-thiol derivatives were studied.

It was found that compounds that have NH₄⁺ and CuSO₄ in its structure are the most potent actoprotectors.

Compounds IV, V, VI, and XI do not exhibit any actoprotector activity.

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