A study of actoprotective activity of new 3-(thiophen-2-ylmethyl)-1H-1,2,4-triazole-5-thiol derivatives

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The issue of fatigue is quite topical for the modern humanity. In order to work harder and earn as much money as possible, a person takes various stimulants, which have a number of side effects. This problem is especially serious in Asian countries. To prevent such complications, scientists are trying to invent actoprotectors that would have minimal side effects. 1,2,4-triazole derivatives have proven themselves well as new substances with different spectrum of pharmacological activity.

The aim of this work is the investigation of actoprotective activity of new 3-(thiophen-2-ylmethyl)-1H-1,2,4-triazole-5-thiol derivatives.

Materials and methods. To study the actoprotective activity of new 3-(thiophen-2-ylmethyl)-1H-1,2,4-triazole-5-thiol derivatives, a group of 7 white nonlinear rats weighing 200–260 g was used. Pharmacological activity was studied with the method of forced swimming. The study compounds, as well as the reference standard – Riboxin® (manufactured by Kyiv Vitamin Plant) was administered orally 20 minutes prior to the immersion of animals at a dose of 100 mg/kg. For comparison, we also used a control group of animals that received saline 20 minutes prior to the immersion.

Gravimetric measurements were performed on laboratory electronic analytical scales model ESJ-200-4(US). Statistical results were calculated using Kolmogorov–Smirnov test and Shapiro–Wilk test.

Results. As a result, the actoprotective activity of 22 new compounds was investigated. Compounds Ia, IIb, IIh have been found to have an actoprotective effect. Compound Ia surpasses the comparison drug. The most active substance among the first synthesized salts is the potassium 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetate, which surpasses the comparison drug riboxin by 8.32 %.

Conclusions. Some conclusions are drawn regarding “structure – actoprotective effect” dependence: replacement of potassium cation by sodium cation leads to a decrease in biological activity; introduction of 4-chlorobenzylidene or 2,3-dimethoxybenzylidene substituent into the molecule of 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetohydrazide does not affect the actoprotective effect; introduction of benzylidene substituent, 3-nitrobenzylidene, 4-dimethylaminobenzylidene, 2,4-dimethylbenzylidene into the molecule of 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetohydrazide negatively affects the fatigue in rats.

Key words: triazoles, actoprotective activity, salts, heterocyclic compounds.
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Вопрос усталости достаточно остро стоит перед человечеством. Для того, чтобы больше работать и зарабатывать, люди начинают употреблять различные стимуляторы для борьбы с усталостью, но они имеют целый ряд побочных эффектов. Эта проблема актуальна в странах Азии. Для предотвращения таких осложнений ученые пытаются создать актопротекторы, которые имели бы минимальное количество побочных действий. Производные 1,2,4-триазола зарекомендовали себя в качестве новых веществ с различными спектрами фармакологической активности.

Цель работы – исследование актопротекторной активности среди новых производных 3-(тиофен-2-илметил)-1H-1,2,4-триазол-5-тиола.

Материалы и методы. Для изучения актопротекторной активности новых производных 3-(тиофен-2-илметил)-1H-1,2,4-триазол-5-тиола использовали группу из 7 белых нелинейных крыс весом 200–260 г. Фармакологическую активность изучали методом принудительного плавания. Исследуемое соединение, а также эталонный стандарт – Рибоксин® (производитель – Киевский витаминный завод) вводили перорально в дозе 100 мг/кг за 20 минут до погружения животных в воду. Для сравнения также использовали контрольную группу животных, получавших солевой раствор за 20 минут до погружения. Гравиметрические измерения проводили на лабораторных электронных аналитических весах модели ESJ-200-4 (США). Статистические результаты рассчитывали с помощью критериев Колмогорова–Смирнова и Шапиро–Уилка.

Результаты. Исследовали актопротекторную активность 22 новых соединений. Установили, что соединения Ia, IIb, IIh имеют актопротекторное действие. Вещество Ia превышает препарат сравнения. Самым активным веществом среди синтезированных соединений является красный 2-((3-(тиофен-2-илметил)-1H-1,2,4-триазол-5-ил)тио)ацетат, который превышает препарат сравнения рибоксин на 6,32 %.

Выводы. Некоторые выводы сделаны по зависимости «структура – актопротекторный эффект»: замена катиона калия на катион натрия приводит к снижению биологической активности; введение в молекулу 2-((3-(тиофен-2-илметил)-1H-1,2,4-триазол-5-ил)тио)ацетогидразы бензилиденового радикала, 3-нитробензилиденового, 4-диметиламино-бензилиденового негативно влияет на усталость крыс.

Ключевые слова: 1,2,4-триазол, актопротекторная активность, соли, гетероциклические соединения.

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Gravimetric measurements were performed on laboratory electronic analytical scales model ESJ-200-4(US).
Statistical results were calculated using Kolmogorov–Smirnov test and Shapiro–Wilk test.

**Results**
As a result, the actoprotective activity of 22 new compounds was investigated.
Compounds Ia, IIb, IIh, have been found to have an actoprotective effect. Compound Ia surpasses the comparison drug.
Some conclusions have been made regarding “structure – actoprotective activity” dependence.

**Discussion**
The most active substance among the initially synthesized salts is the compound Ia (potassium 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetate), which surpasses the comparison drug riboxin by 6.32 % (Table 1, 2).
Replacement of potassium cation by sodium cation in the molecule potassium 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetate leads to a decrease in biological activity (Fig. 1).
The introduction of morpholine as a cation to the molecule 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetate leads to a sharp decrease in the pharmacological effect.
Regarding the actoprotective activity of R-idene-2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetohydrazide, it should be noted that the compounds of this series both increase and reduce the actoprotective effect (Table 3, 4).
It should be noted that compounds IIb, IIh, IIj reduce the fatigue of the studied rats and have an actoprotective effect of 20.31 %, 24.27 % and 16.24 %, respectively. But despite the positive result, these compounds do not surpass the comparison drug riboxin (Fig. 2).
The introduction of 4-chlorobenzylidene substituent (compound IIc) or 2,3-dimethoxybenzylidene (compound IIo) into the molecule of 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetohydrazide does not affect the actoprotective effect.
Replacement of the above mentioned substituents with 2-chlorobenzylidene (IIc), 4-fluorobenzylidene (IId), 2-nitrobenzylidene (IIe), 3,4-dimethoxybenzylidene (IIo), 3,5-dimethoxybenzylidene (IIp) leads to a moderate actoprotective effect.

**Table 1.** "Structure–action" dependence of 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetates

| Compound | X             | Effect |
|----------|---------------|--------|
| Ia       | K             | ↑      |
| Ib       | Na            | ↓      |
| Ic       | morpholine    | ▼▼    |

**Table 2.** Actoprotective activity of 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetate salts

|        | mean    | std    | m   | Me (Q1:Q3) | M ± m   | % to mean control | % to Me control | ks-test   | Shapiro   |
|--------|---------|--------|-----|------------|---------|-------------------|----------------|-----------|-----------|
| Control| 241.71  | 40.58  | 3.38| 240        | 241.71 ± 3.38 | 0          | 0              | P < 0.001 | P > 0.05  |
| Riboxine| 304    | 60.76  | 5.06| 337        | 304.0 ± 5.06  | 25.77     | 40.42         | P < 0.001 | P < 0.05  |
| Ia     | 319.28  | 103.43 | 8.61| 369        | 319.29 ± 8.62 | 32.09     | 53.75         | P < 0.001 | P > 0.05  |
| Ib     | 212.28  | 72.99  | 6.08| 190        | 212.29 ± 6.08 | -12.17    | -20.83        | P < 0.001 | P > 0.05  |
| Ic     | 168.57  | 117.73 | 9.81| 100        | 168.57 ± 9.81 | -30.26    | -58.33        | P < 0.001 | P < 0.01  |
Table 3. “Structure–action” dependence of R-idene-2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetohydrazides

![Chemical structure](image)

| Compound | R | Effect |
|----------|---|--------|
| IIa | C\textsubscript{6}H\textsubscript{5} | ↓ |
| IIb | 2-Br-C\textsubscript{6}H\textsubscript{5} | ↑↑ |
| IIc | 2-Cl-C\textsubscript{6}H\textsubscript{5} | ↑ |
| IId | 4-Cl-C\textsubscript{6}H\textsubscript{5} | ↔ |
| IIe | 4-F-C\textsubscript{6}H\textsubscript{5} | ↑ |
| IIf | 2-NO\textsubscript{2}-C\textsubscript{6}H\textsubscript{4} | ↑ |
| IIg | 3-NO\textsubscript{2}-C\textsubscript{6}H\textsubscript{4} | ↓ |
| IIh | 2-OHC\textsubscript{6}H\textsubscript{4} | ↑↑ |
| IIi | 4-OHC\textsubscript{6}H\textsubscript{4} | ↑ |
| IIj | 3-OCH\textsubscript{3}-C\textsubscript{6}H\textsubscript{4} | ↑↑ |
| IIk | 4-N(CH\textsubscript{3})\textsubscript{2}-C\textsubscript{6}H\textsubscript{4} | ↓ |
| III | 3-Br-4-F-C\textsubscript{6}H\textsubscript{3} | ↑ |
| IIm | 2,3-(OCH\textsubscript{3})\textsubscript{2}-C\textsubscript{6}H\textsubscript{3} | ↔ |
| IIn | 2,4-(CH\textsubscript{3})\textsubscript{2}-C\textsubscript{6}H\textsubscript{3} | ↓ |
| IIo | 3,4-(OCH\textsubscript{3})\textsubscript{2}-C\textsubscript{6}H\textsubscript{3} | ↑ |
| IIp | 3,5-(OCH\textsubscript{3})\textsubscript{2}-C\textsubscript{6}H\textsubscript{3} | ↑ |
| IIq | 3-pyridin | ↓↓ |
| IIr | 5-nitrofuran | ↑ |
| IIIs | tiophen | ↓ |

Table 4. Actoprotective activity of R-idene-2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetohydrazides

| | mean | std | m | Me | (Q1:Q3) | M ± m | % to mean | % to Me | ks-test | Shapiro |
|---|---|---|---|---|---|---|---|---|---|---|
| Control | 245.42 | 33.69 | 2.80783 | 246 | (226.0:251.0) | 245.43 ± 2.81 | 0 | 0 | P < 0.001 | P > 0.05 |
| Riboxine | 315.28 | 66.70 | 5.58897 | 292 | (278.5:359.5) | 315.29 ± 5.56 | 28.46 | 18.7 | P < 0.001 | P > 0.05 |
| IIb | 295.28 | 100.97 | 8.41456 | 357 | (203.0:375.5) | 295.29 ± 8.41 | 20.31 | 45.12 | P < 0.001 | P > 0.05 |
| IIc | 271.28 | 102 | 8.49996 | 262 | (210.0:354.0) | 271.29 ± 8.5 | 10.54 | 06.5 | P < 0.001 | P > 0.05 |
| IIh | 305 | 104.48 | 8.70744 | 354 | (251.0:368.5) | 305.0 ± 8.71 | 24.27 | 43.9 | P < 0.001 | P > 0.05 |
| IIr | 221.85 | 108.62 | 9.05237 | 180 | (158.0:288.0) | 221.86 ± 9.05 | -9.6 | -26.83 | P < 0.001 | P > 0.05 |
| Control | 241.71 | 52.83 | 4.40276 | 253 | (228.0:266.5) | 241.71 ± 4.4 | 0 | 0 | P < 0.001 | P > 0.05 |
| Riboxine | 304 | 60.76 | 5.06349 | 337 | (240.0:353.0) | 304.0 ± 5.06 | 25.77 | 40.42 | P < 0.001 | P < 0.05 |
| IIIm | 237.42 | 91.71 | 7.64291 | 204 | (183.5:299.0) | 237.43 ± 7.64 | -1,77 | -15 | P < 0.001 | P > 0.05 |
| IIn | 224.42 | 59.67 | 8.70744 | 354 | (251.0:368.5) | 224.43 ± 8.71 | -17.13 | -27.67 | P < 0.001 | P > 0.05 |
| IIp | 260.85 | 46.82 | 3.90199 | 266 | (219.0:301.0) | 260.86 ± 3.9 | 7.92 | 10.83 | P < 0.001 | P > 0.05 |
| Control | 241 | 52.83 | 4.40276 | 253 | (228.0:266.5) | 241.0 ± 4.4 | 0 | 0 | P < 0.001 | P > 0.05 |
| Riboxine | 310.42 | 41.69 | 3.44 | 317 | (277.0:348.0) | 310.43 ± 3.47 | 28.81 | 25.3 | P < 0.001 | P > 0.05 |
| IId | 245.57 | 75.91 | 6.32618 | 260 | (197.5:299.5) | 245.57 ± 6.33 | 01.9 | 2.77 | P < 0.001 | P > 0.05 |
| IIg | 199.71 | 95.35 | 7.94956 | 183 | (121.5:265.5) | 199.71 ± 7.96 | -17.13 | -27.67 | P < 0.001 | P > 0.05 |
A study of actoprotective activity of new 3-(thiophen-2-ylmethyl)-1H-1,2,4-triazole-5-thiol derivatives

The introduction of benzylidene substituent (compound Ia), 3-nitrobenzylidene (compound Iig), 4-dimethylamino-benzylidene (IIk), 2,4-dimethylbenzylidene into the molecule 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetohydrazide negatively affects the fatigue of rats, and the introduction of pyridin-3-ylmethylene radicals greatly reduces the actoprotective effect.

Conclusions

As a result, the actoprotective activity of 22 new compounds was investigated.

Compounds Ia, IIb, IIh have been found to have an actoprotective effect. Compound Ia surpasses the comparison drug.

The most active substance among the initially synthesized salts is the potassium 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetate, which surpasses the comparison drug riboxin by 6.32 %. Some conclusions are drawn regarding “structure – actoprotective effect” dependence:

- replacement of potassium cation by sodium cation leads to a decrease in biological activity;
- introduction of 4-chlorobenzylidene substituent or 2,3-dimethoxybenzylidene into the molecule of 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetohydrazide does not affect the actoprotective effect;
- introduction of benzylidene substituent, 3-nitrobenzylidene, 4-dimethylaminobenzylidene, 2,4-dimethylbenzylidene into the molecule 2-((3-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-yl)thio)acetohydrazide negatively affects the fatigue of rats.

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