Actoprotective activity research of 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetates

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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

Severe fatigue can occur due to overwork, lack of exercise, depression, insomnia, etc. It should be understood that fatigue, weakness, both emotional and physical, is not a disease. Often, actoprotective substances are used to reduce fatigue. To search for new substances with a different spectrum of pharmacological activity, 1,2,4-triazole derivatives have proven themselves well.

The aim of work was to investigate actoprotective activity among previously synthesized 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetates.

Materials and methods. The compounds used to study pharmacological activity were synthesized at the Department of Natural Sciences for International Students and Toxicological Chemistry ZSMU. White nonlinear rats weighing 200–260 g of 7 animals per group were used to study the actoprotective activity of 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetates. As a method for the study of pharmacological activity was used the method of forced swimming with a load of 10 % by weight of the rat. Statistical results were calculated using Kolmogorov–Smirnov test and Shapiro-Wilk test.

Results. Compounds Ia, Ib, IIb, IIk, IIj had been found to have a moderate actoprotective effect. But none compound had exceeded the comparison drug. Some conclusions were drawn regarding the dependence of "structure – actoprotective effect": the most active compound was 2-aminoethanol 2-((5-(2-bromophenyl)-4-ethyl-4*H*-1,2,4-triazole-3-yl)thio)acetate (IIj); conversion to 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetate salts and selection as sodium, potassium, or 2-aminoethanol cations was resulted in to increase the actoprotective effect.

Conclusions. As a result, the actoprotective activity of 18 new 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetates was investigated. Some conclusions were drawn regarding the dependence of "structure – actoprotective effect".

Дослідження актопротекторної активності 2-((5-(2-бромфеніл)-4-заміщених-4*H*-1,2,4-тріазол-3-іл)тіо)ацетатів

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Сильна втома може виникнути через постійну перевтому, недостатню фізичну активність, депресію, безсоння тощо. Слід розуміти, що втома, слабкість (і емоційна, і фізична) – це не хвороба. Часто для зменшення стомлюваності використовують активозахисні речовини. Для пошуку нових речовин із різним спектром фармакологічної активності зарекомендували себе похідні 1,2,4-тріазолу.

Мета роботи – дослідження актопротекторної активності серед синтезованих раніше 2-((5-(2-бромфеніл)-4-заміщених-4*H*-1,2,4-тріазол-3-іл)тіо)ацетатів.

Матеріали та методи. Сполуки, що використали для вивчення фармакологічної активності, синтезовані на кафедрі природничих дисциплін для іноземних студентів та токсикологічної хімії Запорізького державного медичного університету. Для дослідження актопротекторної активності 2-((5-(2-бромфеніл)-4-заміщених-4*H*-1,2,4-тріазол-3-іл)тіо)ацетатів використовували білих нелінійних щурів вагою 200–260 г, 7 тварин на групу. Для дослідження фармакологічної активності використали метод примусового плавання з навантаженням 10 % від маси щура. Статистичні результати розраховували за допомогою тесту Колмогорова–Смирнова та тесту Шапіро–Уїлка.

Результати. Виявили, що сполуки Ia, Ib, IIb, IIk, IIj мають помірний актопротекторний ефект, але жодна сполука не перевершує препарат порівняння. Зробили кілька висновків щодо залежності «структура – актопротекторна дія»: найактивніша сполука – 2-етаноламоній 2-((5-(2-бромфеніл)-4-етил-4*H*-1,2,4-тріазол-3-іл)тіо)ацетат (IIj); перехід у 2-((5-(2-бромфеніл)-4-заміщені-4*H*-1,2,4-тріазол-3-іл)тіо)ацетатні солі та вибір катіону – натрій, калій або 2-етаноламоній – призводить до посилення актопротекторного ефекту.

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Key words: actoprotective activity, 1,2,4-triazole, acids, salts, heterocyclic compounds.

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Висновки. В результаті роботи дослідили актопротекторну активність 18 нових 2-((5-(2-бромфеніл)-4-заміщених-4*H*-1,2,4-тріазол-3-іл)тіо)ацетатів. Зробили висновки щодо залежності «структура – актопротекторний ефект».

Ключові слова: 1,2,4-тріазол, актопротекторна активність, кислоти, солі, гетероциклічні сполуки.

Актуальні питання фармацевтичної і медичної науки та практики. 2020. Т. 13, № 2(33). С. 260–264

Исследование актопротекторной активности 2-((5-(2-бромфенил)-4-замещенных-4*H*-1,2,4-триазол-3-ил)тио)ацетатов

А. А. Сафонов, А. В. Невмывака

Сильная усталость может возникнуть из-за переутомления, недостатка физических упражнений, депрессии, бессонницы и т. д. Следует понимать, что усталость, слабость (и эмоциональная, и физическая) не являются болезнью. Часто актопротекторные вещества используют для уменьшения усталости. Производные 1,2,4-триазола зарекомендовали себя для поиска новых веществ с широким спектром фармакологической активности.

Цель работы – исследование актопротекторной активности среди ранее синтезированных 2-((5-(2-бромфенил)-4-замещенных-4*H*-1,2,4-триазол-3-ил)тио)ацетатов.

Материалы и методы. Соединения, использованные для изучения фармакологической активности, синтезированы на кафедре естественных дисциплин для иностранных студентов и токсикологической химии Запорожского государственного медицинского университета. Для изучения актопротекторной активности 2-((5-(2-бромфенил)-4-замещенных-4*H*-1,2,4-триазол-3-ил)тио)ацетатов использовали белых нелинейных крыс весом 200–260 г, 7 животных на группу. Для исследования фармакологической активности использовали метод принудительного плавания с нагрузкой 10 % от веса крысы. Статистические результаты рассчитаны с использованием теста Колмогорова–Смирнова и теста Шапиро–Уилка.

Результаты. Установлено, что соединения Ia, Ib, IIb, IIk, IIj имеют умеренный актопротекторный эффект, но ни одно соединение не превышает препарат сравнения. Сделано несколько выводов о зависимости «структура – актопротекторное действие»: самое активное соединение – 2-этаноламмоний 2-((5-(2-бромфенил)-4-этил-4*H*-1,2,4-триазол-3-ил)тио)ацетат (IIj); переход в 2-((5-(2-бромфенил)-4-замещенные-4*H*-1,2,4-триазол-3-ил)тио)ацетатные соли и выбор катиона (натрий, калий или 2-этаноламмоний) приводит к усилению актопротекторного эффекта.

Выводы. В результате работы исследована актопротекторная активность 18 новых 2-((5-(2-бромофенил)-4-замещенных-4*H*-1,2,4-триазол-3-ил)тио)ацетатов. Сделаны выводы о зависимости «структура – актопротекторный эффект».

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

Актуальные вопросы фармацевтической и медицинской науки и практики. 2020. Т. 13, № 2(33). С. 260–264

There are many factors that "depress" our body: bad habits, constant stress, lack of sleep, hormonal failure, and even anemia.It should be understood that fatigue, weakness, both emotional and physical, is not a disease. Severe fatigue can occur due to overwork, lack of exercise, depression, insomnia, etc. Often, actoprotective substances are used to reduce fatigue. To search for new substances with a different spectrum of pharmacological activity, 1,2,4-triazole derivatives have proven themselves well [1–4]. New 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetates was studied not sufficiently [5–12].

Aim

That's why the aim of this work was to investigate actoprotective activity among previously synthesized 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetates.

Materials and methods

The compounds used to study pharmacological activity were synthesized at the Department of Natural Sciences for International Students and Toxicological Chemistry, ZSMU [13].

White nonlinear rats weighing 200–260 g of 7 animals per group were used to study the actoprotective activity of 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl) thio)acetates.

As a method for the study of pharmacological activity was used the method of forced swimming [14] with a load of 10 % by weight of the rat.

Loads were fixed at the base of the tail of the animals. After immersing the animals underwater for 10 seconds, the laboratory rats' swimming time was measured until depletion in seconds. The rats were immersed individually in a large container with a water layer in excess of 60 cm. The water temperature was maintained at 24–27 °C. The tested compounds, as well as the standard of comparison – Riboxin® (manufactured by Kyiv Vitamin Plant) were injected intraperitoneally 20 minutes before the start of immersion of animals at a dose of 100 mg/kg. For comparison, we also used a control group of animals with intraperitoneal injection of saline 20 minutes before 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 18 new compounds was investigated. Compounds Ia, Ib, IIb, IIk, IIj had been found to have an actoprotective effect. But none compound exceeded the comparison drug. Some conclusions have been made regarding the dependence "structure – actoprotective activity".

Discussion

It should be noted that the most active compound was 2-((5-(2-bromophenyl)-4-methyl-4*H*-1,2,4-triazole-3-yl)thio) acetate acid among 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazole-3-yl)thio)acetate acids (*Table 1*).

It increase actoprotective activity to 8.27 % compared to control (*Table 2*).

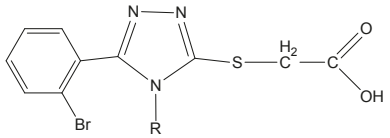
The replacement of the methyl radical with ethyl or phenyl by the fourth position of the 1,2,4-triazole in the 2-((5-(2-bromophenyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetate acid molecule resulted in the disappearance and reduction of the actoprotective effect (*Fig. 1*).

Considering the actoprotective activity of 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetate salts, the compounds IIb, IIk, IIj exhibited actoprotective effect 20.45 %, 13.48 %, 22.88 %, respectively. The most active compound was 2-aminoethanol 2-((5-(2-bromophenyl)-4-ethyl-4*H*-1,2,4-triazole-3-yl)thio)acetate (IIj) (*Table 3*).

The introduction of the phenyl radical in the fourth position of the 1,2,4-triazole of 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetate salts led to a decrease in the actoprotective effect.

The most active salt among 2-((5-(2-bromophenyl)-4-phenyl-4*H*-1,2,4-triazole-3-yl)thio)acetates was potassium salt. The change cation led to a decrease in actoprotective activity (*Table 4*).

Table 1. "Structure – activity" dependence between 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetate acids



Substance	R	Effect
Ia	CH_3	↑
Ib	C_2H_5	↔
Ic	C_6H_5	↔

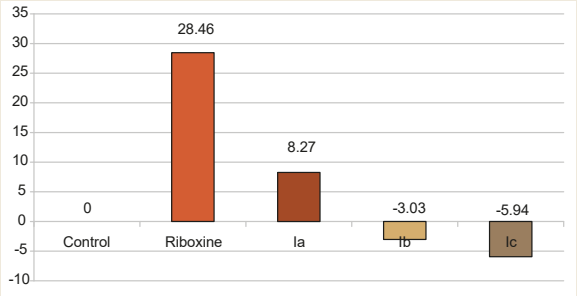


Fig. 1. The actoprotective activity of 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetate acids.

Table 2. The actoprotective activity of 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetate acids

	mean	std	Me	(Q1:Q3)	M ± m	% to mean control	% to Me control	KS-test	Shapiro
Control	245.43	33.69	246	(226.0:251.0)	245.43 ± 2.81	0	0	P < 0.001	P > 0.05
Riboxine	315.28	66.70	292	(278.5:359.5)	315.29 ± 5.56	28.46	18.7	P < 0.001	P > 0.05
Ia	265.71	109.70	254	(204.0:360.5)	265.71 ± 9.14	8.27	3.25	P < 0.001	P > 0.05
Ib	238	80.44	231	(187.5:283.5)	238.0 ± 6.7	-3.03	-6.1	P < 0.001	P > 0.05
Ic	230.85	74.10	221	(182.5:273.5)	230.86 ± 6.18	-5.94	-10.16	P < 0.001	P > 0.05

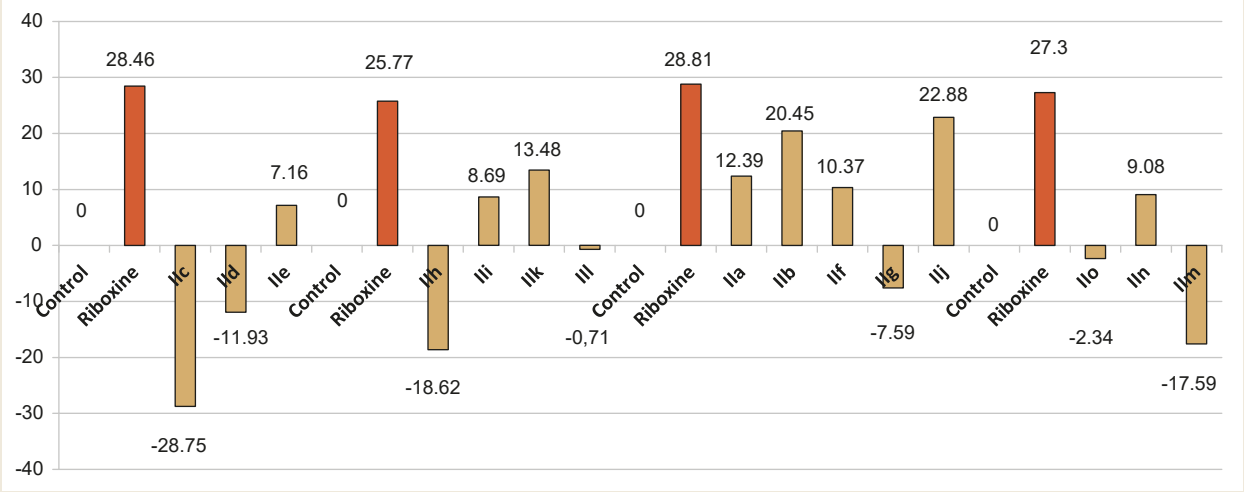
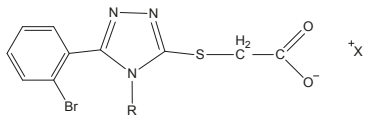


Fig. 2. Actoprotective activity of 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetate salts.

Table 3. "Structure – activity" dependence between 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetate salts



Substance	R	X	Effect
IIa	CH_3	K	↑
IIb	CH_3	Na	↑↑
IIc	CH_3	$(CH_3)_2NH$	↓
IId	CH_3	morpholine	↓
IIe	CH_3	2-aminoethanol	↑
IIf	C_2H_5	K	↑
IIg	C_2H_5	Na	↔
IIh	C_2H_5	$(CH_3)_2NH$	↓
IIi	C_2H_5	morpholine	↔
IIj	C_2H_5	2-aminoethanol	↑↑
IIk	C_6H_5	K	↑
III	C_6H_5	Na	↔
IIm	C_6H_5	$(CH_3)_2NH$	↓
IIn	C_6H_5	morpholine	↑
IIo	C_6H_5	2-aminoethanol	↔

Among 2-((5-(2-bromophenyl)-4-methyl-4*H*-1,2,4-triazole-3-yl)thio)acetates, the most active was compound IIb, which contained sodium cation.

The substitution of sodium cation with potassium cation or 2-aminoethanol resulted in a nearly 2-fold reduction in the actoprotective effect.

The introduction of a cation of morpholine or dimethylammonium into 2-((5-(2-bromophenyl)-4-methyl-4*H*-1,2,4-triazole-3-yl)thio)acetates molecule resulted in an anti-actoprotective effect (*Fig. 2*).

As a result of the research, the conversion to 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetate salts and the selection as cations of sodium, potassium or 2-aminoethanol led to an increase in the actoprotective effect.

Conclusions

As a result, the actoprotective activity of 18 new 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetates was investigated.

Compounds Ia, Ib, IIb, IIk, IIj had been found to have a moderate actoprotective effect. But none compound exceeded the comparison drug.

Some conclusions were drawn regarding the dependence of "structure – actoprotective effect":

Table 4. The actoprotective activity of 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetate salts

	mean	std	Me	(Q1:Q3)	M ± m	% to mean control	% to Me control	KS-test	Shapiro
Control	245.43	33.69	246	(226.0:251.0)	245.43 ± 2.81	0	0	P < 0.001	P > 0.05
Riboxine	315.28	66.70	292	(278.5:359.5)	315.29 ± 5.56	28.46	18.7	P < 0.001	P > 0.05
IIc	174.85	104.42	150	(123.0:168.0)	174.86 ± 8.7	-28.75	-39.02	P < 0.001	P < 0.01
IId	216.14	105.51	174	(131.5:314.0)	216.14 ± 8.79	-11.93	-29.27	P < 0.001	P > 0.05
IIe	263	136.91	251	(153.5:393.5)	263.0 ± 11.41	7.16	2.03	P < 0.001	P > 0.05
Control	241.71	40.58	240	(218.5:264.0)	241.71 ± 3.38	0	0	P < 0.001	P > 0.05
Riboxine	304	60.76	337	(240.0:353.0)	304.0 ± 5.06	25.77	40.42	P < 0.001	P < 0.05
IIh	196.71	91.31	209	(114.5:271.5)	196.71 ± 7.61	-18.62	-12.92	P < 0.001	P > 0.05
IIi	262.71	89.47	319	(183.5:322.5)	262.71 ± 7.46	8.69	32.92	P < 0.001	P > 0.05
IIk	274.28	78.83	295	(214.5:325.5)	274.29 ± 6.57	13.48	22.92	P < 0.001	P > 0.05
III	240	81.65	208	(181.5:305.0)	240.0 ± 6.8	-0.71	-13.33	P < 0.001	P > 0.05
Control	241	52.83	253	(228.0:266.5)	241.0 ± 4.4	0	0	P < 0.001	P > 0.05
Riboxine	310.42	41.69	317	(277.0:348.0)	310.43 ± 3.47	28.81	25.3	P < 0.001	P > 0.05
IIa	270.85	113.67	310	(185.5:356.5)	270.86 ± 9.47	12.39	22.53	P < 0.001	P > 0.05
IIb	290.28	125.50	302	(216.5:398.5)	290.29 ± 10.46	20.45	19.37	P < 0.001	P > 0.05
IIf	266	76.04	303	(243.5:313.0)	266.0 ± 6.34	10.37	19.76	P < 0.001	P > 0.05
IIg	222.71	89.54	202	(165.5:257.0)	222.71 ± 7.46	-7.59	-20.16	P < 0.001	P > 0.05
IIj	296.14	106.07	340	(228.0:367.0)	296.14 ± 8.84	22.88	34.39	P < 0.001	P > 0.05
Control	250.14	33.78	252	(233.0:258.5)	250.14 ± 2.82	0	0	P < 0.001	P > 0.05
Riboxine	318.42	60.19	312	(283.0:354.0)	318.43 ± 5.02	27.3	23.81	P < 0.001	P > 0.05
IIo	244.28	77.03	222	(179.0:309.5)	244.29 ± 6.42	-2.34	-11.9	P < 0.001	P > 0.05
IIn	272.85	82.63	275	(245.0:322.5)	272.86 ± 6.89	9.08	9.13	P < 0.001	P > 0.05
IIm	206.14	62.37	227	(173.5:241.5)	206.14 ± 5.2	-17.59	-9.92	P < 0.001	P > 0.05

– the most active compound was 2-aminoethanol 2-((5-(2-bromophenyl)-4-ethyl-4*H*-1,2,4-triazole-3-yl)thio) acetate (IIj)

– conversion to 2-((5-(2-bromophenyl)-4-substituted-4*H*-1,2,4-triazole-3-yl)thio)acetate salts and selection as sodium, potassium, or 2-aminoethanol cations was resulted in to increase the actoprotective effect.

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