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Actoprotective properties of 7’-((3-thio-4-methyl-4*H*-1,2,4-triazole-5-yl)methyl)theophylline derivatives

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Key words: *1,2,4-triazoles, Theophylline, Actoprotective Properties.*

The aim of this work was the study of actoprotective activity of compounds, which combine sintons of 1,2,4-triazole-3-thiol and theophylline.

Materials and methods. The first time synthesized 7’-((3-thio-4-phenyl-4*H*-1,2,4-triazole-5-yl)methyl)theophylline derivatives have been used for the research. The systemic toxicity and the acute toxicity of the studied compounds have been performed by the rapid method of Prozorovskiy to determine the optimal conditions for dispensing substances. Experiments have been conducted on a group of white nonlinear rats, 159–221 g weight. During the study of actoprotective activity the method of forced immersion in water with a load of 10% by weight of the rats has been used. The substances were administered at a dose 1/10 of LD_{50}, and the reference drug «Riboxin» at a dose of 100 mg/kg. The swim time was recorded in seconds. The control group of animals was used for comparison; these animals received saline solution intraperitoneally 20 minutes before immersion. The obtained results were statistically processed using the standard software package of Microsoft Office 2007 and «STATISTICA@ for Windows 6.0».

Results. According to the results of conducted researches it has been established that the most active compound among the studied was 7’-((5-(2-hydroxyethylthio)-4-phenyl-4*H*-1,2,4-triazole-3-yl)methyl)theophylline, which increased the duration of swimming by 14.31% comparing to control group, whereas the reference drug increased it by 20.57%. It has been established that 2-((5-((theophylline-7’-yl)methyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl)thio)-N’-(3,4-difluorobenzylidene)acetohydrazide also increases the duration of swimming.

Conclusion. The study of actoprotective activity of 13 first time synthesized compounds has been conducted. 7’-((5-(2-Hydroxyethylthio)-4-phenyl-4*H*-1,2,4-triazole-3-yl)methyl)theophylline has been detected as the most active compound among the studied ones.

Актопротективні властивості похідних 7’-((3-тіо-4-метил-4*H*-1,2,4-тріазол-5-іл)метил)теофіліну

А. С. Гоцуля

Мета роботи – дослідження актопротекторної дії сполук, що поєднують синтони 1,2,4-тріазол-3-тіолу та теофіліну.

Матеріали та методи. У дослідженнях використані вперше синтезовані похідні 7’-((3-тіо-4-метил-4*H*-1,2,4-тріазол-5-іл)метил) теофіліну. Для визначення оптимальних умов дозування речовин, що досліджені, попередньо визначили загальнотоксичну дію та гостру токсичність за експрес-методом Прозоровського. Досліди виконали на групі білих нелінійних щурів вагою 159–221 г. Під час вивчення актопротекторної активності використали метод примусового занурення у воду з навантаженням 10% від ваги щура. Речовини вводились у дозі 1/10 від LD_{50}, а референс препарат рибоксин – у дозі 100 мг/кг. Час запливу реєстрували в секундах. Для порівняння використовували також контрольну групу тварин, які внутрішньоочеревинно отримували фізіологічний розчин за 20 хвилин до занурення. Дані опрацьовано статистично за допомогою стандартного пакета програм Microsoft Office 2007 та «STATISTICA@ for Windows 6.0».

Результати. За результатами досліджень встановили, що найактивнішою сполукою серед досліджуваних виявився 7’-((5-(2-гідроксіетілтіо)-4-феніл-4*H*-1,2,4-тріазол-3-іл)метил)теофілін, який збільшував тривалість примусового плавання щурів із навантаженням порівняно з контрольною групою на 14,31%, тоді як референс препарат підвищував цей показник на 20,57%. Тривалість плавання щурів підвищував також 2-((5-((теофілін-7’-іл)метил)-4-феніл-4*H*-1,2,4-тріазол-3-іл)тіо)-N’-(3,4-дифлуоробензіліден)ацетогідразид.

Висновки. Досліджено актопротекторну активність 13 нових синтезованих сполук. Найбільш активним виявився 7’-((5-(2-гідроксіетилтіо)-4-феніл-4*H*-1,2,4-тріазол-3-іл)метил)теофілін.

Ключові слова: *1,2,4-тріазол, теофілін, актопротекторна активність.*

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Актопротекторные свойства производных 7’-((3-тио-4-метил-4*H*-1,2,4-триазол-5-ил)метил)теофиллина

А. С. Гоцуля

Цель работы – исследование актопротекторной активности соединений, сочетающих синтоны 1,2,4-триазол-3-тиола и теофиллина.

Материалы и методы. В исследованиях были использованы впервые синтезированые производные 7’-((3-тио-4-метил-4*H*-1,2,4-триазол-5-ил)метил)теофиллина. Для определения оптимальных условий дозирования веществ, которые были исследованы, предварительно установили общетоксическое действие и острую токсичность экспресс-методом Прозоровского. Опыты выполнены на группе белых нелинейных крыс весом 159–221 г. При изучении актопротекторной активности использован метод принудительного погружения в воду с нагрузкой 10% от веса крысы. Вещества вводились в дозе 1/10 от LD_{50}, а референс препарат рибоксин – в дозе 100 мг/кг. Время заплыва регистрировали в секундах. Для сравнения использовали также контрольную группу животных, которые внутрибрюшинно получали физиологический раствор за 20 минут до погружения. Полученные данные обработаны статистически с помощью стандартного пакета программ Microsoft Office 2007 и «STATISTICA@ for Windows 6.0».

Результаты. По результатам исследований было установлено, что наиболее активным среди исследуемых соединений оказался 7’-((5-(2-гидроксиэтилтио)-4-фенил-4*H*-1,2,4-триазол-3-ил)метил)теофиллин, который увеличивал продолжительность принудительного плавания крыс с нагрузкой по сравнению с контрольной группой на 14,31%, тогда как референс препарат повышал этот показатель на 20,57%. Продолжительность плавания крыс повышал также 2-((5-((теофиллин-7’-ил)метил)-4-фенил-4*H*-1,2,4-триазол-3-ил)тио)-N’-(3,4-ди-фторбензилиден)ацетогидразид. Переход от этилового к *н*-пропиловому и *н*-бутиловому эфирам 2-(5-(теофиллин-7’-ил) метил)-4-фенил-4*H*-1,2,4-триазол-3-илтио)ацетатной кислоты сопровождается появлением актопротекторной активности.

Выводы. Исследована актопротекторная активность 13 новых синтезированных соединений. Наиболее активным оказался 7’-((5-(2-гидроксиэтилтио)-4-фенил-4*H*-1,2,4-триазол-3-ил)метил)теофиллин.

Ключевые слова: *1,2,4-триазол, теофиллин, актопротекторная активность.*

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The activities of modern man in terms of many adverse externals factors and, often, in the absence of necessary rest, leads to acute and later chronic fatigue, that is characterized by decrease in systemic defense mechanism of adaptation, immunity and ability. Therefore, search for new drugs which increase physical performance is an actual problem of nowadays science.

The use of new drugs with actoprotective type of action is an effective and promising way to increase physical and mental performance [1,2].

Currently due to poor arsenal of actoprotective drugs only Bemithylum is used. This fact stimulates the search of new compounds, which are suitable for the creation of new drug with the specified activity on their basis. In this regard 1,2,4-triazoles and their derivatives represent great interest.

Today there are number of publications, which are addressed to the problem of actoprotective effect [1–3,6,8–10].

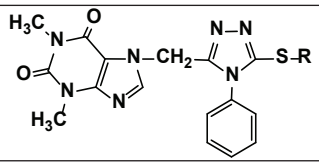
Purpose of research was to study actoprotective activity of 1,2,4-triazole derivatives, and to establish the relationship between chemical structure and pharmacological action of 1,2,4-triazole derivatives.

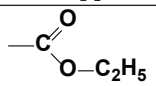
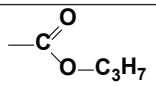
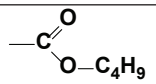
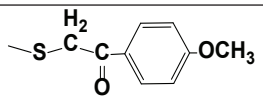
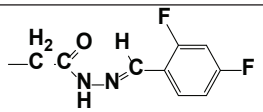
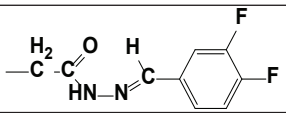
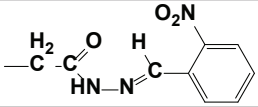
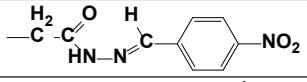
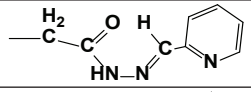
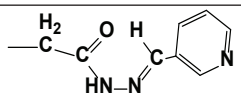
Materials and methods

The first time synthesized 7'-((3-thio-4-phenyl-4*H*-1,2,4-triazole-5-yl)methyl)theophylline derivatives have been used for the research (*Table 1*).

Table 1

Actoprotective properties of the synthesized compounds



№	Substance	The duration of forced swimming, s	Δ%
1	Control	230.57±10.598	100
2	Riboxin	278.00±4.990	20.57
	R	The duration of forced swimming, s	Δ%
3	-SH	236.71±11.224	2.66
4	$-CH_2COOH$	225.00±8.118	-2.42
5	$-S-(CH_2)_2-OH$	263.57±6.499	14.31
6		252.86±6.375	-2.04
7		249.43±5.883	8.18
8		248.29±7.309	7.68
9		255.43±8.451	10.78
10		242.43±6.546	5.14
11		258.57±6.672	12.14
12		247.86±6.840	7.50
13		250.71±6.893	8.74
14		252.57±8.038	9.54
15		233.86±5.926	1.43

The systemic toxicity and the acute toxicity of the studied compounds have been performed by the rapid method of Prozorovskiy [5] to determine the optimal conditions for dispensing substances.

Experiments have been conducted on a group of white nonlinear rats, 159–221 g weight. During the study of actoprotective activity the method of forced immersion in water with a load of 10% by weight of the rats has been used [4]. The load was recorded at the base of the tail of animals. Swimming was performed until exhaustion, which was fixed after 10 second immersion of laboratory animals under the water. Rats were immersed alone in a container with 60 cm level of water. Temperature of water was 24–27˚C. Test compounds and the standard of comparison «Riboxin» were injected intraperitoneally 20 minutes before the start of the animals dive. The substances were administered at a dose 1/10 of LD_{50}, and the reference drug «Riboxin» at a dose of 100 mg/kg (Solution for injection «RIBOXIN-DARNITSA» 20 mg/ml, 5 ml) [4]. The swim time was recorded in seconds. The control group of animals was used for comparison; these animals received saline solution intraperitoneally 20 minutes before immersion.

The obtained results were statistically processed using the standard software package of Microsoft Office 2007 and «STATISTICA@ for Windows 6.0». The reliability of intergroup differences according to the experimental data was ascertained using student's t-test. The level of statistical significance of differences of scientific results is ($p<0.05$) [4,5,7].

Results and conclusions

According to the results of conducted researches it has been established that the most active compound among the studied was 7'-((5-(2-hydroxyethylthio)-4-phenyl-4*H*-1,2,4-triazole-3-yl)methyl)theophylline, which increased the duration of swimming by 14.31% ($p<0.05$), comparing to control group, whereas the reference drug increased it by 20.57% ($p<0.05$). The duration of swimming rats was also increased by compound 11 ($p<0.05$). Substances 10 and 15 practically do not affect the performance of rats, as experimental animals swimming was at the level of the control values. Somewhat the duration of the swimming was reduced by compound 6 that may indicate its possible anxiolytic effect. It is also worth noting that the output of thion and its derivative 2-(5-(theophylline-7'-yl)methyl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate acid do not show actoprotective properties in their application.

After analyzing the data of experimental studies some regularity between the chemical structure and the pharmacological action of the test substances has been established. So, the transition of 2-(5-(theophylline-7'-yl)methyl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetic acid from ethyl to *n*-propyl and *n*-butyl esters is accompanied by the appearance of actoprotective activity.

Conclusions

The study of actoprotective activity of 13 first time synthesized compounds has been conducted. 7'-((5-(2-Hydroxyethylthio)-4-phenyl-4*H*-1,2,4-triazole-3-yl)methyl)theophylline has been detected as the most active compound among the studied ones, as it increased the duration of the forced swimming of rats by 14.31% comparing to the control group. Increasing of the length of carbon chain's residue fragment of complex ester is accompanied by the appearance of actoprotective activity.

Conflicts of Interest: authors have no conflict of interest to declare.

References

1. Bobkov, Yu. G., Vinogradov, V. I., Katkov, V. F., Losev, S. S., & Smirnov, A. V. (1984). *Farmakologicheskaya korrekciya utomleniya. [Pharmacological correction of fatigue]*. Moscow: Meditsin. [in Russian].
2. Garev, A. I., Marysheva, V. V., & Shabanov, P. D. (2010) Aktoprotektornoe dejstvie antigipoksantov tiazoloindol'nogo ryada [The actoprotective action of thiazoloindole antihypoxic agents]. *E'ksperimental'naya i klinicheskaya farmakologiya*, 73(2), 25–30. [in Russian].
3. Lapach, S. N, Chubenko, A. V., Babich, P. N. (2001*). Statisticheskiye metody v mediko-biologicheskikh issledovaniyakh s vnedreniyem Excel* [Statistical methods in biomedical research with the introduction of *Excel*]. Kiev: Morion, 408. [in Ukrainian].
4. Stefanov, A. V. (Eds) (2001). *Metodychní vkazívki po do klínichnomu vyvchenniu líkars'kykh zasobív*. *[Guidelines for the clinical study of drugs]*. Kyiv. [in Ukrainian].
5. Prozorovskii, V. B. (2007). Statisticheskaya obrabotka rezul'tatov farmakologicheskikh issledovanij. [Statistic processing of data of pharmacological investigations]. *Psikhofarmakologiya i biologicheskaya narkologiya*, 7(3–4), 2090–2120. [in Russian].
6. Andronati, S. A., Soboleva, S. G., Zamkovaya, A. V., Karaseva, T. L., Rakipov, I. M., & Cimbal D. I. (2016). Proizvodnye [(N-aril) piperazinil]butilpirimidinov, obladayushchie nejrotropnymi i aktoprotektornymi svojstvami. [[(N-aryl)piperazinil] buthylpyrimidine derivatives with neurotropic and actoprotective properties]. *Zhurnal orhanichnoii ta farmatsevtychnoii khimii*, 1(53), 53–60. [in Ukrainian].
7. Rebrova, O. Yu. (2002). *Statisticheskij analiz medicinskikh dannykh. Primeneniye paketa prikladnykh programm STATISTICA [Statistical analysis of medical data. The use of STATISTICA software package]*. Moscow: MediaSfera. [in Russian].
8. Ruda, N. V., Stepanyuk, H. Y., & Drachuk, O. P. (2013). Aktoprotektornoe deystvie kalievoy soli 2-glitsino-3-hlor-1,4-naftohinona v usloviyakh e'ksperimentalnoj gipokinezii [Actprotective activity of potassium salt of 2-glicino-3-chlor-1,4-naphthoquinone in experimental hypokinetic conditions]. *Curierul medical*, 1(56), 26–29. [in Moldova].
9. Soboleva, S. G., Andronati, S. A., Karaseva, T. I., Kostenko, E. A. (2013). Sintez i aktoprotektornye svojstva proizvodnykh 2-(β-morfolino)e'tilmerkapto-1,6-digidropirimidina [Synthesis and actoprotective properties of 2-(β-morpholino)-ethylmercapto-1,6-dihydropirimidine derivatives]. *Dopovidi Natsionalnoi akademii nauk*, 2, 119–124. [in Ukrainian].
10. Stepaniuk, H. I., Pochelova, O. V., Chornoívan, N. H., Denysiuk, O. M. (2012). Kharakterystyka aktoprotektornoii dii pokhidnykh (3-R-okso-2N-[1,2,4]-triazyno-[2,2-s]-khinazolin-6-il) karbonovykh kyslot za riznykh temperaturnykh rezhymiv [Characteristics of actoprotective actions of (3-R-oxo-2*H*-[1,2,4]-triazino-[2,2-c]-quinazolin-6-yl) carboxylic acid derivatives at different temperature conditions]. *Farmakolohiia ta likarska toksykolohiia*, 19, 132–134. [in Ukrainian].

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