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Research Article

Derivatives of 3-(alkylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amines as Anti-fatigue Substances

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ABSTRACT

In today's society, especially in eastern countries such as China, Japan etc., the problem of fatigue and even death at work is acute. One of the solution to this problem is complex therapy with increasing efficiency drugs. Derivatives of 1,2,4-triazole have already proven themselves as potential compounds for pharmacological correction of fatigue. Compounds were synthesized at the Department of toxicological and inorganic chemistry ZSMU. Using method of forced swimming on a group of white nonlinear rats activity of anti-fatigue of the compounds were analyzed. Having analyzed the data of pharmacological correction of fatigue for 3-(alkylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amines, it should be noted that this series of compound do not show anti-fatigue effect. Introduction in molecule 3-(nonylthio)-5-(thiophen-2-ylmethyl)-4H- 1, 2, 4-triazol-4-amine 4-fluorbenzylidene, 4-(dimethylamino) benzylidene, 4-methoxybenzylidene, 2-chloro-6-fluorobenzylidene radicals lead to increase actoprotective effect. The most active compound is N-(2-chloro-6-fluorobenzylidene)-3-(nonylthio)-5-(thiophen- 2-ylmethyl)- 4H- 1, 2, 4- triazol- 4-amine which exceeds the standard (riboxin).

Key words: 1, 2, 4-triazole, pharmacological correction of fatigue, method of forced swimming.

INTRODUCTION

The rapid development of modern society leads to global fatigue of people. The stresses, the lottime stressful work, the insufficiently treated illnesses lead to even more fatigue. Therefore, the interest of chemists in the creation of new synthetic actoprotectivesubstances is huge. Actoprotectors improve memory, endurance, adaptation to lack of oxygen, increase resistance to cold and heat. They are compounds of economizing action, contributing to a certain amount of work with minimal cost. Also actoprotectors are used by athletes as stimulators of physical working capacity, affecting many organs and systems of the body and preventing the development of fatigue. Actoprotectors prevent the development of negative effects of hypoxia, which increases with intense physical exertion, as well as inadequate oxygen content in the inspired air and adaptation to new environmental conditions, for example, under climate-belt adaptation (Balkhayev *et al.*, 2014). There is a small number of actoprotectors at the moment. An inexhaustible source for the creation of new BAS with different types of activity is derivatives of 1,2,4-triazole(Aksonova *et al.*, 2014, Cervantes-Elizarrarás *et al.*, 2017, Chen *et al.*, 2017). Derivatives of 1,2,4-triazole have a wide range of effects and can exhibit diverse activity. (Danilchenko *et al.*, 2015, Kumar *et al.*, 2013, Parchenko, 2012, Patel *et al.*, 2013, Pattan *et al.*, 2012). The actoprotective activity of some derivatives of 1,2,4-triazole has already been investigated (Salionov *et al.*, 2013). The compounds have a rather high actoprotective effect.

Thus, after analyzing literary sources, it can be concluded that the derivatives of 1,2,4-triasole are a very promising class for the study of biological activity (Shcherbyna *et al.*, 2014, Tkachenko *et al.*, 2010, Varynskyi *et al.*, 2015), namely actoprotective activity. The derivatives of 3-(alkilthio)-5-(thiophen-2-ylmethyl)-4H-

1,2,4-triazol-4-amines is insufficiently studied. The aim of work was to study actoprotective effect of derivatives 3-(alkylthio)- 5- (thiophen-2-ylmethyl)- 4H-1,2,4-triazol-4-amines.

MATERIAL AND METHODS

Synthesys of compounds

Compounds were synthesized at the Department of toxicological and inorganic chemistry ZSMU. Synthesys and analisys of compounds were described in previous work (Safonov, 2016).

Animals

In 105 white nonlinear rats of both sexes weighing 220-260 g were used. Rats were obtained from the kennel of the Institute of Pharmacology and Toxicology of the AMS Ukraine. Animals were kept on a standard diet, with the natural light mode "day and night" (room temperature kept 24-28ºC).

The studies were conducted using the "Rules of preclinical safety assessment of pharmacological agents (GLP)".

Induction procedure

The compounds were injected intraperitoneally to laboratory animals in the form of a solution at a dose of 100mg/kg, with compliance with the rules of asepsis and antiseptics. The solution was prepared in distilled water (1mL of solution per 100g of animal) for water-soluble. Hard-soluble or insoluble substances injected in the form of a fine aqueous suspension, which was stabilized Twin-80 (0.2mL of Twin-80per 50mg of substance). It was used a control group of animals that also received an intraperitoneal physiological solution as a comparison.

Research procedure

Investigation of actoprotectiveof substances was performed on a group of white nonlinear rats weighing 200-260g. It used method of forced swimming. A load of 10% of the rat's weight was fixed at the base of the animal's tail. Swimming was performed prior to exhaustion, which was recorded after 10s of immersion of laboratory animals underwater. Rats were immersed alone in a large dishes. The value of the water layer was more than 60cm. The water temperature was 30-35ºC. Time was recorded in seconds (Stefanova, 2001).

RESULT AND DISCUSSION

Statistical analysis of the results was performed using parametric statistical methods (t-Student's t test). It used "Riboxine" Darnitsya® as comparing drug (Table I, Table II).

Having analyzed the data of 3-(alkylthio)-5-(thiophen-2-ylmethyl)- 4H- 1, 2, 4- triazol- 4-amines' anti-fatigue, it should be noted that this series of compound do not show actoprotective effect (Ie) or suppresses actoprotective activity (Ia-Id, If).

Compound Ia has anti-actoprotective effect and reduces average value forced swimming of rats to 111.29±14.708s, which corresponds to -51.70% relative to control. Approximately similar activity is shown by the compound Ib (-47.61%). An increase in the carbon chain leads to a slight increase in the actoprotective effect, but compounds Ic, Id, If still increase fatigue.

Among these compounds, the Ie compound should be isolated, which practically does not change the data on the actoprotective effect.

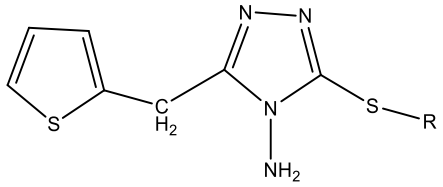
N-R-idene-3-(nonylthio)-5- (thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amines show average anti-fatigue effect. It should be noted that blocking a free amino group in mostcases results increase the actoprotective effect. Exceptions are compounds IIa and IId.

Introduction in molecule 3-(nonylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol- 4-amine 4-fluorbenzylidene (IIc), 4-(dimethylamino) benzylidene (IIb), 4-methoxybenzylidene (IIf), 2-chloro-6-fluorobenzylidene (IIe) radicals leads to increase actoprotective effect.

It should be noted that compounds IIb (31.80%), IIe (39.37%), IIf (33.35%) exhibit an anti-fatigue effect and exceed the riboxin comparison drug.

Replace 2-chloro-6-fluorobenzylidene at 3-nitrobenzylidene in molecule N-(2-chloro-6-fluorobenzylidene)- 3- (nonylthio)- 5(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine leads to decrease farmacological activity.

Table I. Structure-activity for 3-(alkylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amines



Substance №	R	Average value forced swimming of rats, sec, M±m	Actoprotectiveeffect, Δ%	Effect
Control	-	230.43±7.840	-	
Riboxine	-	281.29±21.450	22.07	
Ia	H-C_4H_9	111.29±14.708*	-51.70	↓
Ib	H-C_5H_{11}	120.71±7.377*	-47.61	↓
Ic	H-C_6H_{13}	194.43±11.487*	-15.62	↓
Id	H-C_7H_{15}	189.29±16.614*	-17.85	↓
Ie	H-C_9H_{19}	225.86±9.364	-1.98	↔
If	H-$C_{10}H_{21}$	190.71±13.298*	-17.23	↓

Note. * – p <0,05 in relation to control
↓ - decrease actoprotective effect
↔ - non actoprotective effect

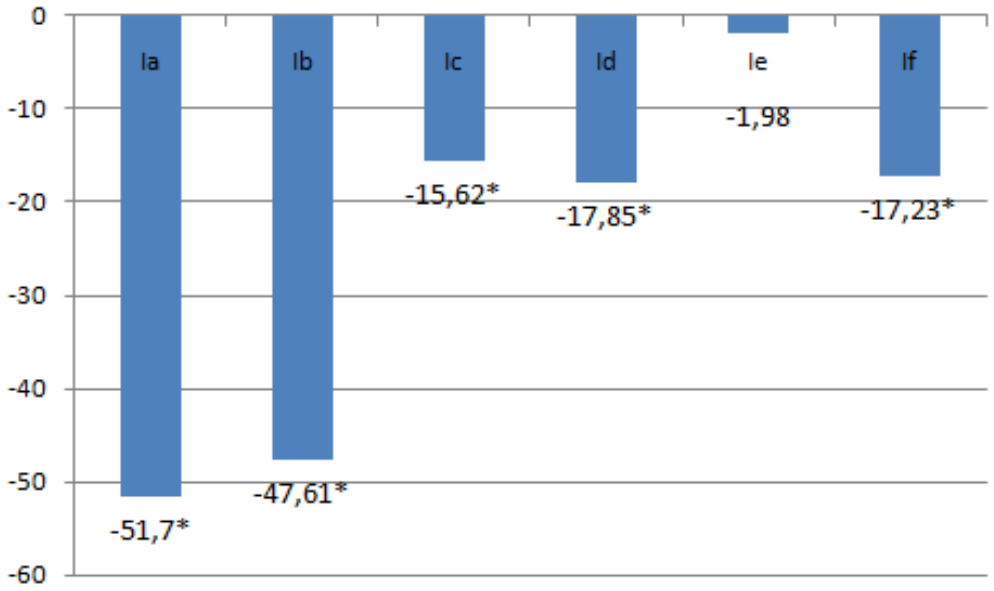
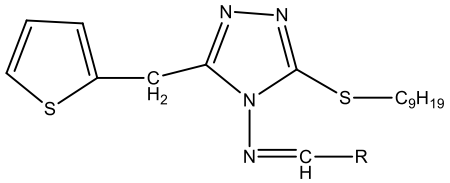


Figure 1. Diagram of 3-(alkylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amines' anti-fatigue effect

Compound IIa has anti-actoprotective effect and reduces average value forced swimming of rats to 206.14±20.080s, which corresponds to -10.54% relative to control. Compound IId shows similar effect (-28.15%).

The most active compound is N-(2-chloro- 6- fluorobenzylidene)- 3- (nonylthio)- 5 (thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amine which exceeds the standard (riboxin). It actoprotective effect is 39.37%.

Table II. Structure-activity for N-R-idene-3-(nonylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amines



Substance №	R	Average value forced swimming of rats, sec, M±m	Actoprotective effects, Δ%	Effect
Control	-	230.43±7.840	-	
Riboxine	-	281.29±21.450	22.07	
IIa	-NO_2-C_6H_4	206.14±20.080	-10.54	↓
IIb	4-N-$(CH_3)_2$-C_6H_4	303.71±11.271*	31.80	↑
IIc	4-F-C_6H_4	282.71±22.319*	22.69	↑
IId	iiophen-2-yl	165.57±14.374*	-28.15	↓
IIe	2-Cl-6-F-C_6H_3	321.14±6.120*	39.37	↑
IIf	4-OCH_3-C_6H_4	307.29±10.851*	33.35	↑
IIg	C_6H_5	241.43±11.311	4.77	↔

Note. * – p <0,05 in relation to control

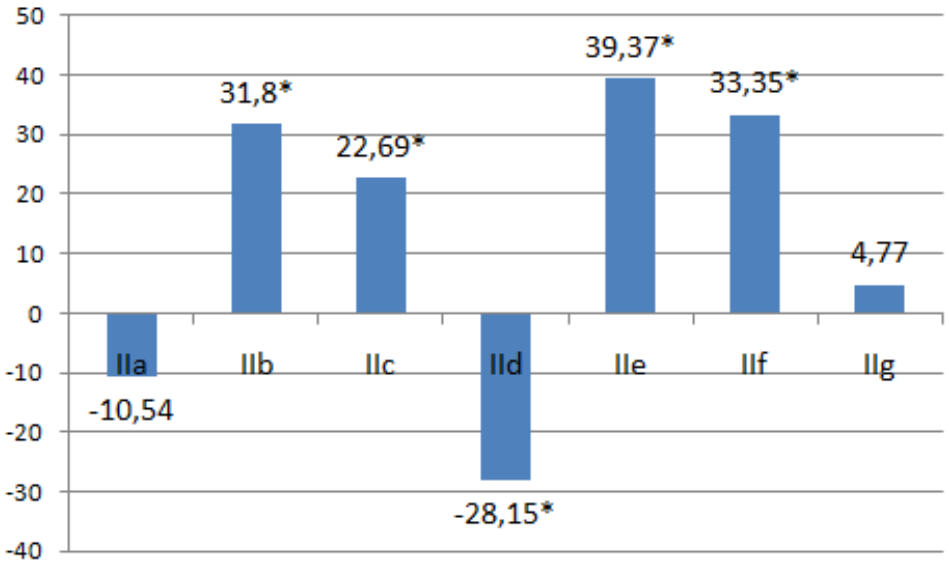


Figure 2. Diagram of N-R-idene-3-(nonylthio)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-4-amines' anti-fatigue effect

CONCLUSION

The pharmacological correction of fatigue was studied 13 new compounds of 3-(alkylthio)- 5- (thiophen- 2- ylmethyl)- 4H-1,2,4-triazol-4-amines' derivatives.

The synthesized compounds show moderate actoprotective effects. Found patterns "structure-activity".

The most active compound is N-(2-chloro-6- fluorobenzylidene)- 3- (nonylthio)- 5-(thiophen- 2- ylmethyl)- 4H-1, 2, 4- triazol- 4-amine.

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