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SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NEW 1,3,4-THIADIAZOLE DERIVATIVES

Basirova Guzel Rasulovna
Assistant, Department of Biological Chemistry
Andijan State Medical Institute

Abstract*. In this work, new 1,3,4-thiadiazole derivatives were synthesized. The structure of the obtained compounds was confirmed by IR spectroscopy. Their biological activity was studied, including acute toxicity, anti-inflammatory and hypoglycemic effects. The results showed that the synthesized compounds have low toxicity and exhibit pronounced anti-inflammatory and hypoglycemic activity, which makes them promise for further pharmacological studies.*

Keywords*: 1,3,4-thiadiazole, synthesis, IR spectroscopy, biological activity, anti-inflammatory effect, hypoglycemic effect.*

Introduction

1,3,4-Thiadiazoles are heterocyclic compounds with a wide range of biological activity, which makes them promise for the development of new drugs. In recent years, there has been an increased interest in studying 1,3,4-thiadiazole derivatives due to their potential antitumor, anti-inflammatory, and antimicrobial activity. Despite a significant number of studies devoted to the synthesis and biological evaluation of 1,3,4-thiadiazole derivatives, many aspects of their pharmacological action remain insufficiently studied. There is a limited amount of data on the hypoglycemic activity of compounds of this class. [1-2] The aim of this study was to synthesize new 1,3,4-thiadiazole derivatives and study their anti-inflammatory and hypoglycemic activity. We assume that modification of the structure of the 1,3,4-thiadiazole nucleus will allow us to obtain compounds with improved pharmacological properties.

Synthesis of diethyl 2,2’ - ((1,3,4-thiadiazol-2,5 diyl) bis (sulfanediyl) acetate

ISSN 3060-4567

0.02 ml KOH was added to a 0.01 mol solution of 2,5-dimercapto-1,3,4-thiadiazole in 20 ml of absolute ethanol and stirred for 30 minutes. Then 0.02 mol of ethyl bromoacetate was added dropwise. The reaction mixture was heated at the boiling point of ethanol for 4-5 hours. After cooling, the reaction mixture was poured into 30 ml of ice water. The precipitate was filtered out, washed with water, and recrystallized from absolute ethanol. [3]

Synthesis of 2,2' - ((1,3,4-thiadiazol-2,5 diyl) bis (sulfanediyl) di (acetohydrazide)

To a solution of 0.01 mol diethyl 2,2'-((1,3,4-thiadiazol-2,5 diyl) bis (sulfanediyl) 0.02 mol of 80% hydrazine acetate was added dropwise to 20 ml of absolute ethanol at 40°C. The reaction mixture was boiled for 5 hours. After cooling, the precipitate was filtered, washed with water, and recrystallized from absolute ethanol. [3]

Synthesis of 2-amino-5-ethyl-1,3,4-thiadiazole and 2-amino-5 - (4-tert-butyl) - 1,3,4-thiadiazolea

Thiosemicarbazide was added to a mixture of 7.4 g (0.1 mol) of propionic acid and 16.3 g of 92% sulfuric acid at a temperature of 50-70 °C, 8.92 g (0.098 mol). The reaction mixture was heated at 65-70 °C for 3 hours. The reaction mass was then cooled to room temperature and 26 ml of water was carefully added. The precipitation was filtered out, washed with water to neutralize the reaction, and dried. The resulting product was recrystallized from absolute ethanol. [4]

Synthesis of 2-amino-5 - (4-tert-butyl) - 1,3,4-thiadiazole

6.0 g (0.1 mol) of valerian acid was added to 16.3 g (0.167 mol) of 92% sulfuric acid at a temperature of 50-70 °C. After cooling the reaction mixture to room temperature, 6.90 g (0.098 mol) was added to it in portions thiosemicarbazide. The reaction mixture was heated at 65-70 °C for 3 hours. The reaction mixture was then cooled to room temperature, carefully added 26 ml of water, and stirred for 30 minutes. The precipitate was filtered out and washed with distilled water until a neutral reaction was achieved. The filtrate was brought to a slightly acidic medium of 24 g with a 44% sodium hydroxide solution. The precipitate was filtered out,

ISSN 3060-4567

washed with water to neutralize the reaction, dried in air, and recrystallized with absolute ethanol. [4]

IR spectra of the compounds were recorded as suspensions in vaseline oil in the range of 4000-400 cm-1. The characteristic absorption bands for each compound are shown in Table [5].

Compound	Characteristic absorption bands (cm-1) and their interpretation
Diethyl 2-2'((1,3,4-thiadiazol-2,5 diyl), bis-(sulfanediyl)) diacetate	3289, 3100 (N-H valence vibrations, hydrazide group); 1690 (C=O valence vibrations); 1045 (C-O-C valence vibrations)
2-2'((1,3,4-thiadiazol-2,5 diyl), bis-(sulfanediyl)) di (acetohydrazine)	3289.74 (N-H valence vibrations); 2956.43 (C-H valence vibrations); 1630.22 (C=N valence vibrations); 1690.13 (C=O valence vibrations)
2-amino-5-ethyl-(1,3,4-thiadiazole)	3200-3400 (N-H valence vibrations); 2900-3000 (C-H valence vibrations); 1600-1680 (C=N valence vibrations)
2-amino-5(4-tert-butyl-(1,3,4-thiadiazole)	3200-3400 (N-H valence vibrations); 2900-3000 (C-H valence vibrations); 1600-1680 (C=N valence vibrations)

Determination of acute toxicity:

Acute toxicity of the studied compounds was evaluated in an experiment on white mice when administered orally. The maximum tolerated doses for all studied compounds was 2000 mg / kg. No deaths were observed at this dose, and the observed short-term effects (rapid breathing, restlessness) were reversible. The results obtained allow us to assign the studied compounds to hazard class V according to GOST 12.1.007-76, which indicates their low acute toxicity. It should be noted that the data obtained relates to acute toxicity and do not exclude the possibility of developing chronic effects with prolonged exposure. Further studies will allow a more complete assessment of the toxicological profile of the studied compounds. [7]

Determination of anti-inflammatory activity:

To assess the anti-inflammatory activity of the synthesized compounds, a model of carrageenan-induced paw edema in rats was used. This method is widely

ISSN 3060-4567

used for screening anti-inflammatory drugs, as carrageenan provokes acute inflammation by releasing various inflammatory mediators. [6]

The results of the study showed that both compounds studied were 2-2'((1,3,4-thiadiazol-2,5 diyl), bis-(sulfanediyl)) di (acetohydrazine) and diethyl-2-2'((1,3,4-thiadiazol-2,5 diyl), bis-(sulfanediyl)) diacetate – demonstrated significant anti-inflammatory effects. The maximum effect of edema inhibition was observed 3 hours after carrageenan administration. Doses of 50 mg / kg and 100 mg / kg of the studied compounds significantly reduced paw edema compared to the control group.

Groups	Dose, mg/kg.	Average weight of animals, g	Number of dead animals			LD 50 mg/kg
			1 day	3 days	14 days	
Control	0,5 ml water	5/0	22,0 ± 0,3	23,6± 0,4	24.5 ± 0,5	>2000 mg/kg
2-2' (1,3,4-thiadiazole-2,5 diyl), bis-(sulfandnyl)) di (acetohydrazine	2000 mg/kg	5/0	23.5 ± 0,25	24,8 ± 0,3	25,9± 0,4	>2000 mg/kg
diethyl-2- 2' (1,3,4-thiadiazole-2,5 diyl), bis-(sulfanediyl)) diacetate	2000 mg/kg	5/0	22,5 ± 0,25	24,8 ± 0,3	26,0± 0,4	>2000 mg/kg
2-amino-5-ethyl-(1,3,4-thiadiazole)	2000 mg/kg	5/0	23,4 ± 0,25	25,0 ± 0,3	25.9± 0,4	>2000 mg/kg
2-amino-5(4-tert-butyl-(1,3,4-tnadnazole)	2000 mg/kg	5/0	22.6 ± 0,25	23,8 ± 0,3	24,4± 0,4	>2000 mg/kg

Note: *p<0.05 - relative to the control group

Name of the substance	Value edema after 3 days h %	Value edema after 24 hours h %
the control group	59.0 ± 3,5	------
2-2'((1,3,4-thiadiazole-2,5 diyl), bis-(sulfanediyl)) di (acetohydrazine) 50 mg/kg	35,4± 2,9*	40
2-2'((1,3,4-thiadiazole-2,5 diyl), bis-(sulfanediyl)) di (acetohydrazine) 100 mg/kg	41,0± 4,2	30,5
diethyl-2-2'((1,3,4-thiadiazole-2,5 diyl), bis-(sulfanediyl)) diacetate 50 mg/kg	38,6 ± 3,1*	34,6

diethyl-2-2'((1,3,4-thiadiazole-2,5 diyl), bis-(sulfanediyl)) diacetate 100 mg/kg	45,2 ± 4,6	23,4
2-amino-5-ethyl-(1,3,4-thiadiazole) 50 mg/kg	80,4 ± 7,9	0
2-amino-5-ethyl-(1,3,4-thiadiazole) 100 mg/kg	46,4 ± 4,3	21,3
2-amino-5(4-tert-butyl-(1,3,4-thiadiazole) 50 mg/kg	41,0 ± 3,5	30,5
2-amino-5(4-tert-butyl-(1,3,4-thiadiazole) 100 mg/kg	80,4 ± 8,1	0

Determination of hypoglycemic activity:

To assess the hypoglycemic and antidiabetic activity of the synthesized compounds, a model of alloxan-induced diabetes mellitus in rats was used. Alloxan causes selective destruction of pancreatic beta cells, which leads to the development of experimental diabetes mellitus. [7]

The results of the study showed that the studied compounds have a pronounced hypoglycemic effect. When administered to experimental animals with alloxan diabetes, the blood glucose level significantly decreased compared to the control group. The most pronounced effect was observed when using, 2-2'((1,3,4-thiadiazol-2,5 diyl), bis-(sulfanediyl)) di (acetohydrazine) at a dose of 50 mg / kg.

Groups	Glycemia (on the first day of study)	
	7 days	14 days
Healthy (intact)	4.7 ± 0.1	4.8 ± 0.1
Control	25,8 ± 2,4	27,5 ± 2,6
Asformin 160 mg/kg	7,1 ± 0,54	4,8 ± 0,24
2-2' (1,3,4-thiadiazole-2,5 diyl), bis-(sulfanediyl)) di (acetohydrazine) 50 mg/kg	7,4 ± 0,61	5,2 ± 0,39

Results and discussion

The structures of the synthesized compounds were confirmed by IR spectroscopy data. The spectra of all compounds showed characteristic absorption

bands corresponding to the stretching vibrations of the C=N bonds of the heterocycle, as well as bands characteristic of other functional groups.

In vivo studies it has been shown that the resulting compounds have a pronounced anti-inflammatory activity. So, compound 2-2'((1,3,4-thiadiazol-2,5 diyl), bis-(sulfanediyl)) di (acetohydrazine) at a dose of 50 mg / kg significantly reduced carrageenan-induced paw edema by 40%. This suggests that this compound may be promising for the development of new anti-inflammatory drugs.

In addition, it was found that 2-2'((1,3,4-thiadiazol-2,5 diyl), bis-(sulfanediyl)) di (acetohydrazine) has hypoglycemic activity. When this compound was administered to animals with experimental diabetes, a significant decrease in blood glucose levels was observed. The results obtained suggest that compound 2-2'((1,3,4-thiadiazol-2,5 diyl), bis-(sulfanediyl)) di (acetohydrazine) can be used to develop new drugs for the treatment of diabetes mellitus.

Conclusion

In this work, new 1,3,4-thiadiazole derivatives were synthesized and their biological activity was studied. The aim of the study was to obtain compounds with potential anti-inflammatory and hypoglycemic activity.

The results of the study showed that the synthesized compounds have low toxicity and exhibit pronounced anti-inflammatory activity in the carrageenan-induced paw edema model. In addition, some compounds have demonstrated a hypoglycemic effect in the alloxan diabetes model.

The results obtained indicate the prospects for further research in the development of new drugs based on 1,3,4-thiadiazole derivatives. Promising areas of research include studying the mechanisms of action of the obtained compounds, optimizing their structure to increase biological activity, and conducting preclinical studies to assess their safety and effectiveness

REFERENCES

1. E. E. Oruc, S. Rollas, F. Kandemirli, N. Shvets, A. Dimoglo // J. Med. Chem., 2004. – 47. – 27. – P.6760-6767.

ISSN 3060-4567

2. Y. Hu, C. Y. Li, X. M. Wang, Y. H. Yang, H. L. Zhu // Chem. Rev., 2014. – 114. – 10. – 5572– 5610.

3. K. Dickore, R. Wegler Formation of 1,3,4-thiadiazoles and 1,4,2-oxathiazoles from thioketenes Angew. Chem. Int. Ed. Engl., 5 (1966), p. 970

4. S. Treppendahl, P. Jackobsen The reaction of 4-substituted thiosemicarbazides with phenyl isocyanide, 1,3,4-thiadiazoles and 1,2,4-triazoles Acta Chem. Scand. Ser. B, 31 (1977), p. 264

5. Vasiliev A.V., Grinenko E. V., Shchukin A. O., Fedulina T. G. Infrared spectroscopy of organic and natural compounds. Educational settlement for chemical engineering students. and chemical and technical special higher educational institutions.St. Petersburg, 2007

6. Screening of antioxidant and anti-inflammatory activities among thiopyrano[2,3-d] thiazoles / A.V. Lozynskyi, D.V. Kaminskyy, Kh.B Romanchyshyn., N.G. Semenciv, V.V. Ogurtsov, I.O. Nektegayev, R.B. Lesyk // Biopolymers and Cell. — 2015. — Т. 31, № 2. — С. 131-137. — Бібліогр.: 30 назв. — engl.

7. Mironov A.N., Bunatyan.N. D., et al. Guidelines for conducting pre-clinical drug trials. Part One, Moscow: Grif & K Publ., 2012, 944 p.