

## Study of the Activity of Newly Synthesized 1,2,3-Triazole Derivatives in Various Inflammation Models

Aytmuratova Urkhiya Kallibekovna<sup>1\*</sup>, Azamatov Azizbek Azamat o'g'li<sup>1</sup>, Tursunkhodzhaeva Furuza Muratovna<sup>1</sup>, Ashurmetov Rustam Isayevich<sup>1</sup> and Ortikov Ilhomjon Sobirovich<sup>2</sup>

<sup>1</sup>Department of Pharmacology and Toxicology of the Institute Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan.

<sup>2</sup>Department of Pharmacology and Chemistry, Alfraganus University, Tashkent, Uzbekistan.

\*Corresponding Author E-mail: urxiyaaytmuratova@mail.ru

<https://dx.doi.org/10.13005/bpj/3205>

(Received: 06 April 2025; accepted: 20 May 2025)

Inflammation is a universal protective mechanism of the body that occurs in response to pathological changes caused by phlogogenic agents. The progression of the inflammatory process depends on the balance between pro-inflammatory and anti-inflammatory cytokines, primarily on the level of anti-inflammatory cytokine synthesis. The anti-inflammatory effect of triazole derivatives is based on the inhibition of the cyclooxygenase-2 enzyme, which enhances the synthesis of inflammatory mediators such as prostaglandins, bradykinin, and serotonin from arachidonic acid. In the study of the anti-inflammatory effects of 13 newly synthesized derivatives of 1,4-disubstituted 1H-1,2,3-triazole on the models of «formalin-induced paw edema», «carrageenan-induced paw edema» and «serotonin-induced aseptic arthritis» compound 5 at a dose of 100.0 mg/kg demonstrated the highest anti-inflammatory activity - 78%, 77.4%, and 79.8%, respectively. The study of the effect of this compound on the cytokine dynamics in blood serum revealed that, compared to the control group animals, it increased the level of IL-4 by 3.25 times, decreased the level of IL-6 by 5.16 times and reduced the level of TNF- $\alpha$  by 3.48 times.

**Keywords:** Carrageenan-induced paw edema; Cytokines; Formalin-induced paw edema; Inflammation; Serotonin-induced aseptic arthritis; 1,4-disubstituted 1H-1,2,3-triazole derivatives.

---

Inflammation is a universal protective mechanism of the body that occurs in response to sequential changes triggered by various damaging factors in the microcirculatory bloodstream, blood system, and connective tissue, involving immune and reparative mechanisms.<sup>1</sup> Factors that trigger an inflammatory response are called phlogogens.<sup>2</sup> Phlogogens can be of exogenous or endogenous origin and are classified as biological (bacteria,

viruses, fungi), physical (radiation, high and low temperatures, vibration), immunological (immune complexes, antigens, autoantibodies), chemical (acids, alkalis, pharmaceuticals), and metabolic (metabolic byproducts such as uric acid crystal deposits or gallstone formation).<sup>3</sup> The primary markers of the inflammatory process include inflammatory mediators (bradykinin, histamine, serotonin, prostaglandins) and cytokines.<sup>4</sup>

Cytokines are polypeptide molecules synthesized by various tissue cells of the body, with the most active producers being immune system cells.<sup>5</sup> Cytokines regulate a number of normal physiological functions, protective responses against various pathogens, as well as the development of many pathological processes, including carcinogenesis, cardiovascular diseases, autoimmune disorders, allergic reactions, and others.<sup>6-7</sup> The regulation of the inflammatory process involves pro-inflammatory (IL-1B, IL-6, IL-8, IL-17, TNF- $\alpha$ ) and anti-inflammatory (IL-4, IL-10) cytokines.<sup>8-9</sup> The development of the inflammatory process depends on the balance of these cytokines, primarily on the level of anti-inflammatory cytokine synthesis. Insufficient production of anti-inflammatory cytokines can lead to uncontrolled inflammation, while their synthesis in high concentrations can result in immunosuppression.<sup>10-11</sup>

#### **Objective of the study**

To investigate the anti-inflammatory activity of 1,4-disubstituted 1H-1,2,3-triazole derivatives.

### **MATERIALS AND METHODS**

#### **Materials**

Thirteen 1,4-disubstituted 1H-1,2,3-triazole derivatives, synthesized in the Department of Organic Synthesis at the Institute of Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, were selected as the study subjects. Experiments to assess the anti-inflammatory activity of the substances were conducted on male rats weighing 200-220 g, kept under standard vivarium conditions (controlled temperature and humidity, free access to food and water). Phlogogenic agents are substances that, after being introduced into the body, induce proliferative inflammation by enhancing the release of endogenous inflammatory mediators such as histamine, serotonin, prostaglandins, and bradykinin.

#### **Methods**

In our experiments, the acute inflammatory response was induced by subplantar injection of phlogogenic agents into the right hind paw of the test animals: 0.1 ml of 2% formalin solution (Sigma Aldrich, Sent-Luis, Missouri, USA), 0.1 ml

of 0.1% carrageenan solution (Sigma Aldrich, Sent-Luis, Missouri, USA), and 0.1 ml of 1% serotonin solution (Sigma Aldrich, Sent-Luis, Missouri, USA). The maximum swelling of the paw was observed 180 minutes after the injection of the phlogogenic agent.<sup>11-14</sup>

Before the start of the experiment, all the test animals underwent a 14-day adaptation period and were randomly divided into groups. The test animals were divided into the following groups: control group, comparison group, and experimental group. Six animals were selected for each group. The test substances were administered intragastrically in doses of 25.0, 50.0, 100.0, 150.0, and 200.0 mg/kg 60 minutes before the administration of the phlogogenic agent.

In the conducted experiments, an aqueous solution of Tween-80 (Sigma Aldrich, Sent-Luis, Missouri, USA) was used as a solvent for the test substances. The comparison drugs, Ketoprofen (Velpharm, Russia), were administered orally in doses of 1.0-5.0-10.0 mg/kg, and Sodium Diclofenac (Hemopharm, Russia) was administered in doses of 8.0-10.0 mg/kg. The degree of swelling was measured using the oncometric method, based on changes in the volume of the paws of the experimental animals.<sup>15</sup> The volume of the animal's paws was measured before the administration of the inflammatory agent and 180 minutes after its administration.

To study the dynamics of pro-inflammatory and anti-inflammatory cytokines in the blood, an acute inflammatory reaction was induced in male rats weighing 200–220 g by subcutaneous injection of 0.1 ml of a 2% formalin solution into the thigh area.

The experimental animals were divided into three groups: group I control group: after the development of acute inflammation, the animals were orally administered 0.2 ml of sodium chloride physiological solution for 7 days; group II comparison group: the animals were orally administered Ketoprofen at doses of 1.0, 5.0, and 10.0 mg/kg and Diclofenac sodium at doses of 8.0 and 10.0 mg/kg for 7 days; group III experimental group: the animals were orally administered the test substances at doses of 25.0, 50.0, 100.0, 150.0, and 200.0 mg/kg for 7 days.

After the development of an acute inflammatory process in the experimental animals,

**Table 1.** Anti-inflammatory activity of 1,4-disubstituted 1H-1,2,3-triazoles and comparison drugs Ketoprofen and sodium Diclofenac (n=6)

Compound	Dose, mg/kg	Formalin-induced paw edema model	Carrageenan-induced paw edema model	Serotonin-induced aseptic arthritis model
		Percentage (%) increase in paw volume relative to baseline	Percentage (%) increase in paw volume relative to baseline	Percentage (%) increase in paw volume relative to baseline
		Effect %	Effect %	Effect %
1	Control	74.3±0.63	71.4±0.54	86.3±0.78
		-	-	-
	Phys. solution			
	0,2 ml			
2	Ketoprofen	51.7±0.41	49.6±0.31	58.3±0.62
	1.0	30.4	30.5	32.5
	5.0	31.5±0.38	31.7±0.26	35.0±0.46
	10.0	73.4	75.0	75.8
3	Sodium Diclofenac	26.1±0.25	29.7±0.34	25.3±0.34
	8.0	64.8	58.5	66.3
4	1	25.0±0.49	23.1±0.39	29.1±0.38
	10.0	66.3	67.7	70.7
	25.0	55.5±0.43	48.8±0.25	60.5±0.47
	50.0	47.6±0.56	46.9±0.32	52.5±0.31
	100.0	45.7±0.42	41.1±0.37	51.2±0.43
	150.0	42.0±0.51	37.7±0.26	49.3±0.27
	200.0	39.5±0.37	34.9±0.34	50.6±0.45
5	2	45.2±0.55	45.3±0.28	49.3±0.34
	25.0	39.1	36.5	42.8
	50.0	42.5±0.60	38.2±0.33	47.8±0.31
	100.0	35.8±0.39	36.5±0.37	44.3±0.36
	150.0	41.1±0.36	42.3±0.24	50.0±0.43
	200.0	43.8±0.34	47.6±0.39	42.0
6	3	50.6±0.42	45.4±0.28	59.4±0.54
	25.0	31.8	36.4	31.1
	50.0	41.8±0.52	39.5±0.35	47.2±0.47
	100.0	39.2±0.37	32.5±0.32	38.9±0.38
	150.0	40.4±0.46	38.8±0.41	46.4±0.51
	200.0	43.0±0.38	41.4±0.36	52.6±0.43
7	4	46.5±0.51	48.8±0.31	58.7±0.37
	25.0	37.4	31.6	31.9
	50.0	44.7±0.46	44.0±0.34	51.8±0.46
	100.0	40.9±0.34	41.3±0.28	50.0±0.39
	150.0	37.0±0.49	38.5±0.30	46.0±0.36
	200.0	40.2±0.33	40.4±0.36	51.3±0.42
8	5	32.9±0.45	31.8±0.39	29.7±0.28
	25.0	55.7	55.5	65.6
	50.0	18.1±0.28	19.1±0.34	24.3±0.34
	100.0	16.3±0.32	16.2±0.32	17.5±0.24
	150.0	19.1±0.19	17.5±0.27	21.0±0.37
		74.3	75.5	75.7

9	6	200.0	19.3±0.24	74.0	18.0±0.25	74.8	20.2±0.29	76.6
		25.0	47.1±0.46	36.6	50.0±0.40	29.9	62.1±0.45	28.0
		50.0	44.0±0.38	40.7	47.6±0.36	33.3	56.4±0.41	34.6
		100.0	41.8±0.51	43.7	44.5±0.28	37.6	50.6±0.36	41.3
		150.0	40.0±0.44	46.1	41.5±0.34	41.8	48.6±0.32	43.6
		200.0	45.6±0.56	38.6	43.4±0.37	39.2	52.6±0.43	39.0
10	7	25.0	47.1±0.47	36.6	46.5±0.24	34.8	53.5±0.47	38.0
		50.0	41.3±0.32	44.4	43.2±0.36	39.4	46.7±0.35	45.8
		100.0	40.4±0.41	45.6	38.3±0.27	46.3	41.9±0.39	51.4
		150.0	42.5±0.53	42.7	40.9±0.23	42.7	47.2±0.31	45.3
		200.0	48.1±0.39	35.2	44.8±0.34	37.2	53.9±0.42	37.5
11	8	25.0	46.6±0.48	37.2	50.0±0.38	29.9	59.4±0.47	31.1
		50.0	45.1±0.32	39.3	42.8±0.26	40.0	51.8±0.40	39.9
		100.0	40.6±0.46	45.3	39.5±0.24	44.6	48.0±0.36	44.3
		150.0	36.9±0.51	50.3	37.2±0.37	47.8	44.4±0.31	48.5
		200.0	41.5±0.48	44.1	38.8±0.31	45.6	48.7±0.47	43.5
12	9	25.0	47.1±0.35	36.6	48.8±0.25	31.6	57.5±0.41	33.3
		50.0	40.9±0.54	44.9	38.5±0.36	46.0	54.9±0.53	36.3
		100.0	42.3±0.57	43.0	40.9±0.32	42.7	49.3±0.35	42.8
		150.0	45.0±0.43	39.4	41.9±0.28	41.3	46.9±0.31	45.6
		200.0	46.5±0.40	37.4	45.8±0.35	35.8	52.6±0.46	39.0
13	10	25.0	47.6±0.36	35.9	49.4±0.37	30.8	60.2±0.54	30.2
		50.0	45.1±0.32	39.3	46.3±0.34	35.1	58.9±0.43	31.7
		100.0	43.3±0.41	41.7	43.9±0.29	38.5	56.3±0.47	34.7
		150.0	42.0±0.46	43.4	43.6±0.35	38.9	53.7±0.41	37.7
		200.0	47.6±0.52	35.9	47.5±0.28	33.4	56.1±0.35	34.9
14	11	25.0	50.6±0.49	31.8	51.1±0.33	28.4	56.0±0.46	35.1
		50.0	44.1±0.37	40.6	47.5±0.36	33.4	53.9±0.40	37.5
		100.0	42.8±0.51	42.3	45.9±0.27	35.7	52.0±0.36	39.7
		150.0	41.5±0.42	44.1	41.7±0.34	41.5	47.4±0.52	45.0
		200.0	40.0±0.35	46.1	39.2±0.38	45.0	59.1±0.47	31.5
15	12	25.0	44.8±0.29	39.7	50.0±0.31	30.0	53.6±0.43	37.8
		50.0	43.4±0.46	41.5	46.9±0.29	34.3	50.6±0.49	41.3
		100.0	40.4±0.41	45.6	36.7±0.24	48.5	48.6±0.36	43.6
		150.0	44.1±0.48	40.6	39.3±0.32	44.9	46.5±0.41	46.1
		200.0	45.1±0.37	39.3	44.0±0.37	38.3	49.3±0.38	42.8
16	13	25.0	43.8±0.52	41.0	47.6±0.34	33.3	56.1±0.31	34.9
		50.0	41.6±0.34	44.0	41.4±0.25	42.0	47.5±0.47	44.9
		100.0	37.9±0.29	48.9	37.7±0.38	47.1	46.0±0.54	46.6
		150.0	43.9±0.46	40.9	42.1±0.32	41.0	51.3±0.35	40.5
		200.0	46.5±0.53	37.4	47.0±0.36	34.1	56.9±0.48	34.0

Note: P=0.05 compared to the control group

**Table 2.** Cytokine profile (interleukin-4, interleukin-6, and TNF- $\alpha$ ) of rat serum during acute inflammation

	Drug	Dose, mg/kg	IL-4		IL-6	TNF- $\alpha$
			Phys. solution 0,2 ml	Phys. solution 0,2 ml		
1	Intact		0.16(0.145-0.175)		0.31(0.29-0.33)	0.65(0.32-0.68)
2	Control		2.0(1.84-2.16)		2.4(1.37-3.43)	1.275(1.03-2.26)
3	Ketoprofen	1.0	0.35(0.31 $\pm$ 0.39)		0.13(0.11 $\pm$ 0.15)	1.13(1.11 $\pm$ 1.15)
		5.0	0.39(0.34 $\pm$ 0.43)		0.12(0.11 $\pm$ 0.15)	1.09(1.05 $\pm$ 1.18)
		10.0	0.45(0.42 $\pm$ 0.49)		0.09(0.07 $\pm$ 0.11)	0.98(0.93 $\pm$ 1.03)
4	Sodium Diclofenac	8.0	0.37(0.33 $\pm$ 0.41)		0.11(0.14 $\pm$ 0.17)	1.07(1.12 $\pm$ 1.19)
		10.0	0.42(0.39 $\pm$ 0.44)		0.08(0.04 $\pm$ 0.12)	0.98(0.85 $\pm$ 1.12)
		25.0	0.22(0.20 $\pm$ 0.24)		0.26(0.23 $\pm$ 0.29)	1.32(1.30 $\pm$ 1.34)
5	1	50.0	0.24(0.21 $\pm$ 0.27)		0.25(0.21 $\pm$ 0.29)	1.29(1.25 $\pm$ 1.33)
		100.0	0.25(0.22 $\pm$ 0.28)		0.23(0.21 $\pm$ 0.25)	1.27(1.24 $\pm$ 1.30)
		150.0	0.27(0.24 $\pm$ 0.30)		0.21(0.19 $\pm$ 0.23)	1.26(1.23 $\pm$ 1.29)
6	2	200.0	0.29(0.27 $\pm$ 0.31)		0.20(0.18 $\pm$ 0.22)	1.25(1.22 $\pm$ 1.28)
		25.0	0.25(0.22 $\pm$ 0.28)		0.25(0.22 $\pm$ 0.28)	1.27(1.24 $\pm$ 1.30)
		50.0	0.28(0.25 $\pm$ 0.31)		0.22(0.20 $\pm$ 0.24)	1.24(1.21 $\pm$ 1.27)
7	3	100.0	0.32(0.30 $\pm$ 0.34)		0.19(0.17 $\pm$ 0.21)	1.20(1.18 $\pm$ 1.22)
		150.0	0.30(0.27 $\pm$ 0.33)		0.21(0.19 $\pm$ 0.23)	1.22(1.20 $\pm$ 1.24)
		200.0	0.27(0.24 $\pm$ 0.30)		0.24(0.22 $\pm$ 0.26)	1.25(1.22 $\pm$ 1.28)
8	4	25.0	0.22(0.20 $\pm$ 0.24)		0.26(0.24 $\pm$ 0.28)	1.28(1.25 $\pm$ 1.31)
		50.0	0.26(0.23 $\pm$ 0.29)		0.23(0.20 $\pm$ 0.26)	1.26(1.23 $\pm$ 1.29)
		100.0	0.29(0.27 $\pm$ 0.31)		0.20(0.17 $\pm$ 0.23)	1.23(1.20 $\pm$ 1.26)
9	5	150.0	0.27(0.24 $\pm$ 0.30)		0.22(0.20 $\pm$ 0.24)	1.25(1.23 $\pm$ 1.27)
		200.0	0.24(0.21 $\pm$ 0.27)		0.25(0.23 $\pm$ 0.27)	1.27(1.24 $\pm$ 1.30)
		25.0	0.24(0.20 $\pm$ 0.28)		0.23(0.20 $\pm$ 0.26)	1.28(1.25 $\pm$ 1.31)
10	6	50.0	0.25(0.23 $\pm$ 0.27)		0.21(0.18 $\pm$ 0.24)	1.25(1.23 $\pm$ 1.27)
		100.0	0.27(0.24 $\pm$ 0.30)		0.20(0.17 $\pm$ 0.23)	1.23(1.20 $\pm$ 1.26)
		150.0	0.31(0.29 $\pm$ 0.33)		0.17(0.14 $\pm$ 0.20)	1.20(1.18 $\pm$ 1.22)
10	6	200.0	0.29(0.26 $\pm$ 0.32)		0.19(0.17 $\pm$ 0.21)	1.22(1.20 $\pm$ 1.24)
		25.0	0.38(0.30 $\pm$ 0.43)		0.12(0.08 $\pm$ 0.15)	1.03(0.97 $\pm$ 1.08)
		50.0	0.42(0.37 $\pm$ 0.45)		0.08(0.04 $\pm$ 0.12)	0.98(0.92 $\pm$ 1.05)
10	6	100.0	0.52(0.49 $\pm$ 0.55)		0.06(0.02 $\pm$ 0.09)	0.89(0.86 $\pm$ 0.92)
		150.0	0.49(0.45 $\pm$ 0.52)		0.07(0.05 $\pm$ 0.12)	0.94(0.94 $\pm$ 1.05)
		200.0	0.44(0.41 $\pm$ 0.48)		0.07(0.04 $\pm$ 0.10)	0.92(0.89 $\pm$ 0.95)
10	6	25.0	0.19(0.17 $\pm$ 0.21)		0.26(0.23 $\pm$ 0.29)	1.30(1.27 $\pm$ 1.33)
		50.0	0.21(0.19 $\pm$ 0.23)		0.24(0.21 $\pm$ 0.27)	1.27(1.23 $\pm$ 1.31)
		100.0	0.22(0.20 $\pm$ 0.24)		0.22(0.20 $\pm$ 0.24)	1.25(1.23 $\pm$ 1.27)

11	7	150.0 200.0 25.0 50.0 100.0 150.0 200.0	0.24(0.21±0.27) 0.20(0.18±0.22) 0.22(0.20±0.24) 0.24(0.21±0.27) 0.26(0.23±0.29) 0.23(0.20±0.26) 0.20(0.18±0.22)	0.21(0.19±0.23) 0.23(0.20±0.26) 0.24(0.21±0.27) 0.21(0.19±0.23) 0.20(0.16±0.24) 0.23(0.20±0.26) 0.22(0.19±0.25)	1.23(1.20±1.26) 1.26(1.24±1.28) 1.26(1.22±1.30) 1.23(1.20±1.26) 1.21(1.19±1.23) 1.24(1.21±1.27) 1.27(1.24±1.30)
12	8	25.0 50.0 100.0 150.0 200.0	0.25(0.22±0.28) 0.27(0.25±0.29) 0.30(0.27±0.33) 0.32(0.29±0.35) 0.29(0.27±0.31)	0.22(0.20±0.24) 0.20(0.17±0.23) 0.18(0.15±0.21) 0.16(0.13±0.19) 0.19(0.17±0.21)	1.25(1.22±1.28) 1.23(1.20±1.26) 1.20(1.18±1.22) 1.19(1.17±1.21) 1.22(1.19±1.25)
13	9	25.0 50.0 100.0 150.0 200.0	0.21(0.19±0.23) 0.28(0.25±0.31) 0.26(0.23±0.29) 0.25(0.22±0.28) 0.23(0.20±0.26)	0.24(0.20±0.28) 0.18(0.15±0.21) 0.20(0.17±0.23) 0.23(0.20±0.26) 0.25(0.22±0.28)	1.25(1.21±1.29) 1.20(1.18±1.22) 1.23(1.20±1.26) 1.24(1.21±1.27) 1.26(1.23±1.29)
14	10	25.0 50.0 100.0 150.0 200.0	0.16(0.14±0.18) 0.18(0.15±0.21) 0.20(0.17±0.23) 0.21(0.19±0.23) 0.17(0.14±0.20)	0.27(0.24±0.30) 0.24(0.21±0.27) 0.23(0.20±0.26) 0.21(0.19±0.23) 0.25(0.23±0.27)	1.30(1.27±1.33) 1.27(1.24±1.30) 1.25(1.23±1.27) 1.24(1.21±1.27) 1.29(1.25±1.33)
15	11	25.0 50.0 100.0 150.0 200.0	0.20(0.18±0.22) 0.22(0.19±0.25) 0.25(0.22±0.28) 0.27(0.24±0.30) 0.29(0.25±0.33)	0.23(0.21±0.25) 0.21(0.19±0.23) 0.19(0.16±0.21) 0.18(0.15±0.21) 0.16(0.13±0.19)	1.30(1.27±1.33) 1.28(1.26±1.30) 1.26(1.23±1.29) 1.25(1.22±1.28) 1.22(1.20±1.24)
16	12	25.0 50.0 100.0 150.0 200.0	0.21(0.19±0.23) 0.25(0.22±0.28) 0.27(0.24±0.30) 0.26(0.23±0.29) 0.23(0.20±0.26)	0.24(0.21±0.27) 0.19(0.17±0.21) 0.18(0.16±0.20) 0.20(0.17±0.23) 0.22(0.20±0.24)	1.31(1.28±1.34) 1.28(1.26±1.30) 1.26(1.23±1.29) 1.27(1.24±1.30) 1.29(1.27±1.31)
17	13	25.0 50.0 100.0 150.0 200.0	0.21(0.19±0.23) 0.28(0.26±0.31) 0.30(0.27±0.33) 0.25(0.23±0.27) 0.22(0.20±0.24)	0.19(0.15±0.23) 0.15(0.13±0.17) 0.20(0.17±0.23) 0.22(0.20±0.24)	1.23(1.20±1.26) 1.21(1.19±1.23) 1.19(1.17±1.21) 1.22(1.19±1.25) 1.25(1.21±1.29)

Note: P=0.05 compared to the control group

divided into groups, blood samples were collected before the start of the experiment and 7 days after its initiation to study the production levels of key cytokines.

The animal study was conducted in accordance with the International Convention for the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes (Strasbourg, 1986),<sup>16</sup> and the protocol was approved by the Scientific Council of the Institute of Chemistry of Plant Substances based on the annual work plan of the Department of Pharmacology and Toxicology (Protocol No.1, January 17, 2024). The concentration of key cytokines in the serum of rats, namely: interleukin-4, interleukin-6, and TNF- $\alpha$ , was determined by enzyme-linked immunosorbent assay (ELISA) using the Mindray MR-96a immunoassay analyzer (China) with reagent kits manufactured by LLC «Vector-Best» (Russia), following the manufacturer's instructions. The data are presented as the mean  $\pm$  standard deviation for different groups. Statistical analysis was performed using the OriginPro 9.0 software (MicroCal Software, Northampton, MA). A difference was considered statistically significant at  $p < 0.05$ .

## RESULTS

The results obtained when the anti-inflammatory activity of 1,4-disubstituted 1H-1,2,3-triazole derivatives was studied in the «formalin edema», «carragenin edema» and «serotonin aseptic arthritis» models are listed in Tables 1 and 2.

## DISCUSSION

When studying the anti-inflammatory activity of 1,4-disubstituted 1H-1,2,3-triazole derivatives on the «formalin-induced paw edema», «carrageenan-induced paw edema» and «serotonin-induced aseptic arthritis» models, the reference drugs demonstrated the following anti-inflammatory activity compared to the control group: Ketoprofen at a dose of 10.0 mg/kg - 73.4%, 75%, and 75.8%, respectively, and Diclofenac sodium - 66.3%, 67.7%, and 70.3%, respectively. Among the tested compounds, substance 5 at a dose of 100.0 mg/kg showed anti-inflammatory activity of 78%, 77.4%, and 79.8%, respectively (Table 1).

Based on the results of the study of cytokine dynamics in the serum of experimental animals during the acute inflammatory process, among the tested substances, compound 5 showed a more pronounced effect on the dynamics of cytokines (IL-4, IL-6, TNF- $\alpha$ ) compared to the reference drugs. Relative to the control group, Ketoprofen at a dose of 10.0 mg/kg increased the IL-4 level by 2.81 times, Diclofenac sodium at a dose of 8.0 mg/kg increased it by 2.62 times, and compound 5 at a dose of 100.0 mg/kg increased it by 3.25 times. The IL-6 level decreased by 3.44 times with Ketoprofen at a dose of 10.0 mg/kg, by 3.87 times with Diclofenac sodium at a dose of 8.0 mg/kg, and by 5.16 times with compound 5 at a dose of 100.0 mg/kg. The TNF- $\alpha$  level decreased by 3.16 times with Ketoprofen at a dose of 10.0 mg/kg, by 3.16 times with Diclofenac sodium at a dose of 8.0 mg/kg, and by 3.48 times with compound 5 at a dose of 100.0 mg/kg. (Table 2)

## CONCLUSION

1. The results of the conducted experiments showed that in the study of the anti-inflammatory activity of 13 new 1,4-disubstituted 1H-1,2,3-triazole derivatives on the «formalin-induced paw edema», «carrageenan-induced paw edema» and «serotonin-induced aseptic arthritis» models, compound 5 at a dose of 100.0 mg/kg demonstrated the highest anti-inflammatory activity - 78%, 77.4% and 79.8%, respectively.
2. The results of the study on the effect of this compound on cytokine dynamics in the serum showed that compared to the control group, it increased the IL-4 level by 3.25 times, decreased the IL-6 level by 5.16 times and decreased the TNF- $\alpha$  level by 3.48 times. Further in-depth pharmacological and toxicological studies of this compound with pronounced anti-inflammatory activity will provide a basis for expanding the range of non-steroidal, low-toxicity drugs with analgesic and anti-inflammatory effects in medical practice.

## ACKNOWLEDGEMENT

The author would like to thank Institute Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan for granting the Ph.D. research work. The Department

of Pharmacology and toxicology of the Institute Chemistry of Plant Substances, is highly appreciated for allowing the laboratory work. This work was carried out using budgetary funds of ICPS the Academy of Sciences of the Republic of Uzbekistan.

#### Funding source

The author(s) received no financial support for the research, authorship, and/or publication of this article.

#### Conflict of interest

The author(s) do not have any conflict of interest.

#### Data availability

This statement does not apply to this article.

#### Ethics statement

The animal study was conducted in accordance the protocol was approved by the Scientific Council of the Institute of Chemistry of Plant Substances based on the annual work plan of the Department of Pharmacology and Toxicology (Protocol No.1, January 17, 2024).

#### Informed consent statement

This study did not involve human participants, and therefore, informed consent was not required.

#### Clinical trial registration

This trial is registered at [study of the activity of newly synthesized 1,2,3-triazole derivatives in various inflammation models] with the registration number [BPJ/8095].

#### Permission to reproduce material from other sources

Not Applicable.

#### Authors' contribution

Aytmuratova U.K: Conceptualization, Methodology, Writing – Original Draft; Azamatov A.A: Conceptualization, Methodology, Project Administration; Tursunkhodzhaeva F.M: Data Collection, Analysis, Writing – Review & Editing; Ashurmetov R.I: Visualization, Supervision; Ortikov I.S: Visualization, Supervision, Resources.

## REFERENCES

- Gusev E, Zhuravleva Y. Inflammation: a new look at an old problem. *Int J Mol Sci.* 2022;23(9):4596. doi:10.3390/ijms23094596
- Serebrennikova S, Seminskiy I, Guzovskaya E, et al. Inflammation is a fundamental pathological process: lecture 1 (alteration, vascular reactions). *Baikal Med J.* 2023;2(2):53-64.
- Novitsky V V, Urazova O I, eds. *Pathophysiology.* Vol 1. Moscow: GEOTAR-Media; 2020:640.
- Petrova SY, Khlgtian SV, Berzhets VM, et al. Modern ideas about mechanisms of allergen-specific immunotherapy. *Russ J Allergy.* 2020;17(4):38-45.
- Kashtalyan O, Ushakova L. Cytokines as universal regulation system. *Med Novosti.* 2017;(9):3-7.
- Simbirtsev A, Totolyan A. Cytokines in laboratory diagnostics. *Infect Dis News Opin Educ.* 2015;(2):82-98.
- Amin M, Siddiqui S, Ibrahim M, et al. Inflammatory cytokines in the pathogenesis of cardiovascular disease and cancer. *SAGE Open Med.* 2020;8:2050312120965752. doi:10.1177/2050312120965752
- Wong CK, Ho CY, Ko FWS, et al. Proinflammatory cytokines (IL-17, IL-6, IL-18 and IL-12) and Th cytokines (IFN- $\alpha$ , IL-4, IL-10 and IL-13) in patients with allergic asthma. *Clin Exp Immunol.* 2001;125(2):177-183.
- Troshina E. The role of cytokines in the processes of adaptive integration of immune and neuroendocrine reactions of the human body. *Probl Endocrinol.* 2021;67(2):4-9.
- Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. *Crit Rev Immunol.* 2012;32(1):23-63.
- Vanderwall AG, Milligan ED. Cytokines in pain: harnessing endogenous anti-inflammatory signaling for improved pain management. *Front Immunol.* 2019;10:3009. doi:10.3389/fimmu.2019.03009
- Mironov AN. *Guidelines for Conducting Preclinical Studies of Drugs.* Grifi K; 2012:750.
- Aytmuratova UK, Azamatov AA, Ortikov IS, et al. Investigation of the analgesic and anti-inflammatory activity of a newly synthesized 1,2,3-triazole derivative. *Front Health Inform.* 2024;13(6):686-693.
- Aytmuratova UK, Azamatov AA, Ortikov IS, et al. Invention patent No. IAP 7858. Derivatives of 1H-1,2,3-triazole with analgesic and anti-inflammatory effects. 2024.
- Novikov V, Pozhilova E, Ilyukhin S. Effect of antihypoxants on the development of acute formalin edema. *Rev Clin Pharmacol Drug Ther.* 2015;13(1):41-44.
- Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. *Off J Eur Union.* 2010.