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Investigation Of The Analgesic And Anti-Inflammatory Activity Of A Newly Synthesized 1,2,3-Triazole Derivative

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Abstract

In our research, we investigated the analgesic and anti-inflammatory activity of 4-(4-((4-formylphenoxy)methyl)-1H-1,2,3-trizol-1-yl)benzoic acid, a newly synthesized derivative of 1,4-substituted 1H-1,2,3-triazole. The studied substance demonstrated analgesic activity of 70.7% in the “Hot plate” test at a dose of 100 mg/kg, 81% in the “Acetic acid writhing” test at a dose of 50 mg/kg, and 79% in the “Acetylcholine writhing” test at a dose of 50 mg/kg. The anti-inflammatory activity of the substance under study - 4-(4-((4-formylphenoxy)methyl)-1H-1,2,3-trizol-1-yl) benzoic acid - was studied in the "formalin paw edema" model, showed 49.1% activity at a dose of 100 mg/kg. When we studied the profile of inflammatory and anti-inflammatory cytokines in serum, it was found that 4-(4-((4-formylphenoxy)methyl)-1H-1,2,3-trizol-1-yl) benzoic acid at a dose of 100.0 mg/kg increased the level of the anti-inflammatory cytokine IL-4 by 1.5 times compared to the control group, and decreased the levels of the inflammatory cytokines IL-6 and α-FNO by 1.5 and 2.4 times, respectively.

Keywords: 4-(4-((4-formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl) benzoic acid, "hot

plate", "acetic acid writhing", "acetylcholine-induced writhing", cytokines

Introduction.

According to modern theories, the source of any pain is an inflammatory process (Sota Omoigui at.al. 2007)[17]. The International association for the study of pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"(Graven-Nielsen et.al. 2022., Neelakanth M Jeedi et al. 2023)[4,12]. Pain arises in damaged tissues under the influence of mediators such as bradykinin, histamine, serotonin, and prostaglandins (Priya M et.al.2013)[14]. A key aspect of pain syndrome treatment is the reduction of inflammatory mediator production and their inhibition, as well as the suppression of their effects on the afferent and efferent neuronal systems (Matei Daniela et.al. 2022)[10].

Nonsteroidal anti-inflammatory drugs (NSAIDs), included in the WHO list of essential medicines, are the most commonly used agents for reducing pain and inflammation (Samik Bindua et.al. 2020)[16]. NSAIDs are competitive inhibitors of the enzyme cyclooxygenase (COX), which is involved in the bioconversion of arachidonic acid into inflammatory prostaglandins (PG)(Jahnavi K et.al.2019)[6].

Most orally administered NSAIDs have a toxic effect even at low doses. According to the World Toxicology Center, the number of NSAID poisoning cases, both prescription and over-the-counter, increases significantly each year (Imothy J Wiegand et al. 2023)[5]. One of the main side effects of NSAIDs on the body is their impact on the gastrointestinal tract, which manifests as nausea, vomiting, heartburn, and erosive changes in the gastric mucosa (Laine L et al. 202)[9]. The second most common side effect caused by NSAID use is kidney damage. Under the action of NSAIDs, prostaglandin levels decrease, leading to a reduction in renal blood flow and, consequently, a decrease in glomerular filtration rate. This results in the retention of salt, water, and potassium in the body (Riley DJ et.al.1994)[15].

We have reviewed above the side effects of the most widely used group of drugs. Considering this, one of the strategies set before modern pharmacology remains the creation of "ideal drugs" with minimal side effects on the body, which act as antagonists of the synthesis of inflammatory mediators (bradykinin, histamine, serotonin) and prevent their activating effect on the nociceptive system (Gonçalves E.C.D et.al 2021)[3].

The aim of this study is to investigate the analgesic and anti-inflammatory activity of 4-(4-((4-formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl) benzoic acid.

Materials and methods

The research object was 4-(4-((4-formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl) benzoic acid, synthesized at the Department of Organic Synthesis of the Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan.

Experimental pharmacological part

The experiments were conducted on white outbred mice weighing 18–20 g and rats weighing 200–220 g, kept under standard vivarium conditions with controlled temperature and humidity, as well as free access to food and water.

The animal experiments were conducted in accordance with the ETS No. 123 (1986)

Convention (European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, ETS №123, Strasbourg 1986)[1] for the protection of vertebrate animals used for experimental and other scientific purposes. The experimental groups were formed using random selection. Prior to the start of the experiment, all test animals underwent a 14-day adaptation period. The test animals were divided into the following groups: the control group, the comparison group (ketoprofen), and the experimental group. A solution of the new test substance at concentrations of 1%, 1.5%, and 2% was administered to the animals in the experimental group at doses of 25.0 mg/kg, 50.0 mg/kg, 100.0 mg/kg, 150.0 mg/kg, and 200.0 mg/kg. Ketoprofen was used as the reference drug and was studied at doses of 1.0 mg/kg, 5.0 mg/kg and 10.0 mg/kg.

The analgesic effect of this substance was studied in mice using the "hot plate," "acetic acid writhing," and "acetylcholine-induced writhing" tests (Mironov A.N. 2012)[11]. The primary model for studying the potential analgesic effect of the tested substances on thermal stimuli is the "hot plate" test (Krilova S.G et.al 2014)[8]. The study of analgesic activity in the "hot plate" test is based on the occurrence of responses mediated by supraspinal structures in reaction to pain stimuli. For this purpose, a glass plate wrapped in a cylinder and heated to 57°C was used. A constant temperature was maintained using a WATER BATH: 2000-III model water bath. In the experiment, the time was recorded from the moment the animal was placed on the hot surface to the appearance of a behavioral response to nociceptive stimulation, including licking of the hind paw, withdrawal of the hind paw, or jumping reactions.

Acute and deep somatic pain were studied using the "acetic acid writhing" and "acetylcholine writhing" tests. A characteristic sign of the pain response is "writhing" (movements involving contraction and relaxation of the abdominal muscles, stretching of the hind limbs, and arching of the back), induced by intraperitoneal administration of a 2.5% aqueous solution of acetic acid at a dose of 250.0 mg/kg or a 0.1% aqueous solution of acetylcholine at a dose of 3.2 mg/kg to the test animals. The analgesic effect of the tested substance was evaluated based on its ability to reduce the number of "writhing" episodes (within 20 minutes after injection) and to increase the latency period before the onset of the pain response. The efficacy criterion was determined by a 50% reduction in the pain response compared to the control group. An acute inflammatory response was induced by subplantar injection (under the plantar aponeurosis) of 0.1 ml of a 2.5% aqueous formalin solution into the right hind paw of the rat. Subplantar injection of formalin induces proliferative inflammation in the rat's paw, leading to cell damage at the injection site and the release of endogenous inflammatory mediators such as histamine, serotonin, prostaglandins, and bradykinin. Such tissue damage to the rat's paw caused by formalin leads to the development of chronic and localized inflammation. The maximum development of edema after formalin injection is observed 180 minutes after the administration of the phlogogenic substance to the animals (Kong Xong Xan et al. 2015)[7].

The test substance was administered intragastrically at doses of 25.0 mg/kg, 50.0 mg/kg, 100.0 mg/kg, 150.0 mg/kg, and 200.0 mg/kg 60 minutes prior to the introduction of the inflammatory agent.

The comparative drugs were administered at the following doses: ketoprofen — 1.0, 5.0, and 10.0 mg/kg; diclofenac — 8.0 and 10.0 mg/kg.

The edema size was measured using the oncometric method by assessing changes in the limb volume of experimental animals (Fereidoni M et.al.2000., Novikov V.E et.al. 2015)[2,13]. The limb volume of the animals was measured before the administration of the inflammatory agent and 180 minutes after its administration. The criteria for evaluating the anti-inflammatory effect of the tested substances include the absence of paw volume increase and the inhibition of the inflammatory process.

Results and discussion

In the control group animals, the latency period of the pain response to thermal stimulation was 18.8 seconds.

The comparative drug ketoprofen, at a dose of 10.0 mg/kg, doubled the latency period of the pain response and demonstrated analgesic activity at 106.2% relative to the baseline value.

4-(4-((4-Formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl) benzoic acid at a dose of 100.0 mg/kg increased the latency period of the pain response by 1.7 times compared to the baseline and demonstrated analgesic activity at 70.7% (Table 1).

(Table 1)

Analgesic effect of tested substances on mice in response to thermal pain stimulation (hot plate method), M±m, n=6

№	Compound	Dose (mg/kg)	Latency period of pain response (sec)		
			Before administration	After administration at 150 minutes, %	
1	Intact physiological saline	0.2 ml	12.6±1.4	18.8±2.2	-
2	Ketoprofen (peros)	1.0	12.4±1.1	19.7±2.5	58.8
		5.0	12.5±1.6	24.3±2.7	94.4
		10.0	12.8±1.5	26.4±2.3	**106.2***
3	4-(4-((4-Formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl) benzoic acid	25.0	13.2±1.5	16.0±2.2	31.2
		50.0	12.6±1.8	15.8±2.5	45.3
		100.0	12.3±1.6	21.0±3.1	**70.7***
		150.0	11.9±1.4	19.4±2.9	63.0

		200.0	12.7±1.5	20.5±3.2	61.4

*Note: *P=0.05 compared to the baseline time*

In the "acetic acid writhing" test, 4-(4-((4-formylphenoxymethyl)-1H-1,2,3-triazol-1-yl) benzoic acid exhibited the greatest analgesic effect at a dose of 50.0 mg/kg, reducing the number of "writhing" episodes by 81.0%. Ketoprofen, at a dose of 5.0 mg/kg, reduced the number of "writhing" episodes by 71.6% (Table 2).

Table 2

Analgesic activity of tested substances in chemical irritation (acetic acid writhing test) in mice following oral administration (M±m, n=6)

№	Compound	Dose (mg/kg)	Number of writhes	Effect (%)
1	Intact Acetic Acid 2.5% 250.0 mg/kg i./p.	0.2	37.0±3.6	-
2	Ketoprofen	1.0	11.7±2.4	68.3
		5.0	10.5±2.7	**71.6***
		10.0	14.2±2.3	61.6
3	4-(4-((4-Formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl) benzoic acid	25.0	8.3±2.1	77.5
		50.0	7.0±2.4	**81.0***
		100.0	9.0±2.6	76.5
		150.0	18.3±2.9	62.5
		200.0	20.5±3.1	48.5

*Note: *P=0.05 compared to the intact group*

In the "acetylcholine writhing" test, the tested compound demonstrated a significantly stronger analgesic effect compared to the reference drug: 4-(4-((4-formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl) benzoic acid at a dose of 50.0 mg/kg showed 79.0% efficacy, while ketoprofen at a dose of 5.0 mg/kg achieved 57.3% efficacy (Table 3).

Table 3

Analgesic activity of tested substances and the reference drug ketoprofen in mice under chemical irritation (acetylcholine test) (M±m, n=6)

Compound (n=6)	Weight	Dose (mg/kg)	Number of writhes in 10 minutes	Efficacy (%)
Intact + Acetylcholine 3.2 mg/kg i./p.	20	0.2 мл	7.6±1,2	-

Ketoprofen	21	1.0	6.0±0.5	51.6
	10	5.0	5.3±0.8	**57.3***
	20	10.0	6.4±0.6	48.4
4-(4-((4-Formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl) benzoic acid	19	25.0	2.4±0.7	68.5
	20	50.0	1.6±0.3	**79.0***
	21	100.0	2.0±0.4	73.7
	20	150.0	2.9±0.5	61.9
	18	200.0	3.2±0.6	57.9

*Note: *P=0.05 compared to the intact group*

At 180 minutes after subplantar injection of formalin, rats exhibited the development of acute inflammatory paw edema. In the control group animals, the paw volume was 1.43 ± 0.05 cm³, which represents a 74.3% increase compared to the baseline volume.

Among all administered doses of the novel compound 4-(4-((4-formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl) benzoic acid, the most effective dose was 50.0 mg/kg. In experimental animals receiving this dose, the paw edema volume induced by acute inflammation increased by only 37.8% compared to the baseline volume.

The experiments established that this result was significantly lower than the edema level observed in the control group.

The maximum level of inflammation inhibition achieved by the tested compound, 4-(4-((4-formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl) benzoic acid, was 49.1%. In comparison, ketoprofen at a dose of 10.0 mg/kg reduced the inflammatory process by 73.4% (Table 4).

Table 4

Effect of 4-((1-phenyl-1h-1,2,3-triazol-4-yl) methoxy) benzaldehyde and NSAIDs on rat limb volume 3 hours after formalin injection

Animal Groups, (n=6)	**Dose (mg/kg)**	**Paw Volume, cm³, (M±m)**		**Volume Increase, %**	**Inflammation inhibition, %**
		Before administration	**After Administration**		
Control Group: Formalin 2.5%, 0.1 ml	0,2 мл физ.рас	0.82±0.03	1.43 ±0.05	74.3	
Ketoprofen	1.0	0.85±0.04	1.29±0.01	51.7	30.4
	5.0	0.92±0.05	1.21±0.03	31.5	57.6

	10.0	0.96±0.01	1.15±0.05	19.7*	**73.4***
Diclofenac	8.0	0.84±0.02	1.06±0.06	26.1	64.8
	10.0	0.92±0.04	1.15±0.02	25.0	66.3
4-(4-((4-Formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl) benzoic acid	25.0	0.92±0.06	1.31±0.07	42.3	43.6
	50.0	0.85±0.01	1.18±0.03	38.8	47.7
	100.0	0.82±0.03	1.13±0.04	37.8	**49.1***
	150.0	0.86±0.06	1.19±0.01	38.3	48.4
	200.0	0.91±0.02	1.28±0.06	40.6	45.3

Note: P=0.05 compared to the control group

The occurrence of an acute inflammatory reaction following formalin injection into the rat paw is associated with the migration of leukocytes to the injection site. As is well known, inflammatory and anti-inflammatory cytokines play a crucial role in the development of edema and the migration of neutrophils after formalin administration into the rat paw [15]. In the study of cytokine profiles in blood serum, it was found that administration of 4-(4-((4-formylphenoxymethyl)-1H-1,2,3-triazol-1-yl) benzoic acid at a dose of 100.0 mg/kg increased the level of the anti-inflammatory cytokine IL-4 by 1.5 times compared to the control group. Meanwhile, the levels of the pro-inflammatory cytokines IL-6 and TNF-α decreased by 1.5 and 2.4 times, respectively.

In conclusion, 4-(4-((4-formylphenoxymethyl)-1H-1,2,3-triazol-1-yl) benzoic acid demonstrated high central and peripheral analgesic activity at low doses compared to the reference drugs, as well as comparable effects on the inflammatory process, as confirmed experimentally. Further research into the pharmacological and toxicological properties and mechanisms of action of this compound on a broader scale will contribute to expanding the range of new nonsteroidal analgesic and anti-inflammatory drugs in medical practice.

REFERENCES:

1. European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, ETS №123, Strasbourg 1986.
2. Fereidoni M., Ahmadiani A., Semnanian S., Javan M. An accurate and simple method for measurement of paw edema // Pharm. Toxicol. Methods J. — 2000. — Vol. 43. — P. 11–14

3. Gonçalves E.C.D., Vieira G., Gonçalves T.R., Simões R.R., Brusco I., Oliveira S.M. et al. Bradykinin receptors play a critical role in the chronic postischaemia pain model. Cell Mol. Neurobiol. 2021;41(1):63–78. DOI: 10.1007/s10571-020- 00832-3.
4. Graven-Nielsen, Thomas, 2022. Mechanisms and manifestations in musculoskeletal pain: from experimental to clinical pain settings. Pain. 163(S1), Pages - S29-S45. Doi: 10.1097/j.pain.00 00000000002690.
5. Imothy J Wiegand, MD; Chief Editor: Gil Z Shlamovitz, MD. Nonsteroidal Anti-inflammatory Drug (NSAID) Toxicity Sep 15, 2023
6. Jahnavi K, Pavani Reddy P, Vasudha B, Narender B, Non-steroidal anti-inflammatory drugs: an overview, Journal of Drug Delivery and Therapeutics. 2019; 9(1-s):442-448http://dx.doi.org/10.22270/jddt.v9i1-s.2287
7. Kong Hong Han, Khaziakhmetova VN, Ziganshina LE Modeling of inflammatory edema: are the models interchangeable? Experimental and Clinical Pharmacology. 2015. Vol. 78. No. 7. pp. 24-31
8. Krylova S.G., Zorikov P.S., Zueva E.P., Razina T.G., Amosova E.N., Rybalkina O.Yu. Experimental study of analgesic activity of Kuznetsov aconite extract. Pacific Medical Journal, 2014, No. 2, pp. 38-40
9. Laine L. Gastrointestinal safety of coxibs and outcomes studies: what's the verdict?. *J Pain Symptom Manage*. 2002 Apr. 23(4 Suppl):S5-10; discussion S11-4. [QxMD MEDLINE Link].
10. Matei Daniela, Luca Catalina , Onu Ilie , Matei Paula , Iordan Daniel-Andrei and Buculei Ioana. Effects of Exercise Training on the Autonomic Nervous System with a Focus on Anti-Inflammatory and Antioxidants Effects. Antioxidants 2022, 11, 350. https://doi.org/10.3390/antiox11020350
11. Mironov A.N. Guidelines for conducting preclinical studies of drugs. Part one. M: Grif i K, 2012.-944 p.
12. Neelakanth M Jeedi, Sandeep Bajji, Pradeepkumar M Ronad, Shrishail K Nimbal, Santosh B Patil, 2023. Analgesic and anti-inflammatory investigation of 1,2,4- triazole derivatives in rats . Journal of medical pharmaceutical and allied sciences, V 12 - I 3, Pages - 5850 – 5858. Doi: https://doi.org/10.55522/jmpas.V12I3.4666
13. Novikov V.E., Pozhilova E.V., Ilyukhin S.A. Effect of antihypoxants on the development of acute formalin edema. Reviews of clinical pharmacology and drug therapy. Vol. 13/2015/1. pp. 41-44
14. Priya M, Sathya NV, Satyajit M, et al, 2013. Screening of cetirizine for analgesic activity in mice. International Journal of Basic & Clinical Pharmacology. 2(2), Pages - 187-192. Doi: 10.5455/2319-2003.ijbcp20130313.
15. Riley DJ, Weir M, Bakris GL. Renal adaptation to the failing heart. Avoiding a 'therapeutic misadventure'. *Postgrad Med*. 1994 Jun. 95(8):153-6. [QxMD MEDLINE Link].
16. Samik Bindua , Somnath Mazumderb,1 , Uday Bandyopadhyay. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochemical Pharmacology 180 (2020) 114
17. Sota Omoigui, MD. The Biochemical Origin of Pain: The origin of all Pain is Inflammation and the Inflammatory Response. PART 2 of 3 – Inflammatory Profile of Pain Syndromes. Med Hypotheses. 2007 ; 69(6): 1169–1178. doi:10.1016/j.mehy.2007.06.033.