PHARMACEUTICAL SCIENCES

ANALGESIC ACTIVITY OF 4-R-5-PYRIDINE-1,2,4-TRIAZOLE-3-THIOL DERIVATIVES IN THE EXPERIMENT

Yevhenii Mykhailiuk[1]
Ivan Bilai[2]

DOI: https://doi.org/10.30525/978-9934-26-204-3-17

Modern pharmaceutical science creates medicines that directly affect the causes of disease. However, the etiology of many diseases accompanied by pain has not yet been established, which does not allow to write off the drugs of symptomatic therapy, which have a depressant effect on the manifestations and symptoms of the pathological process [1, p. 1579]. The modern pharmaceutical market contains a wide range of drugs with anti-inflammatory and analgesic activity, primarily non-steroidal anti-inflammatory drugs that have a lot of side effects, including ulcerogenic action.

It is worth noting the prospects for the use of azaheterocycle derivatives as a promising class of safe drugs with different types of pharmacological properties. Among them were found compounds that exhibit high analgesic, anti-inflammatory, antimicrobial, antifungal, diuretic and other biological effects. Pyridine derivatives of 1,2,4-triazoles, which are well known for their biological activity and low toxicity, are no less attractive in their action [2, p. 104].

The aim is investigation of analgesic activity of 4-R-5-pyridine-1,2,4-triazole-3-thiol derivatives in experimental with rats.

[1] Zaporizhzhya State Medical University, Ukraine
[2] Zaporizhzhya State Medical University, Ukraine

We choose 9 new organic compounds among 4-R, 5-pyridine-1,2,4-triazole-3-thiol derivatives for the study. These substances were synthesized in the laboratory of organic synthesis of the Department of Physical Chemistry of Zaporizhzhya State Medical University. The synthesis of substituted 3-R, 4-pyridine-1,2,4-triazole-3-thiols was carried out under the direction of Dr. of pharmacy, Professor Kaplaushenko A.H.

The structure of the synthesized compounds was confirmed by the methods of elemental analysis, IR and UV spectroscopy, PMR spectrometry, and the individuality of the synthesized compounds was confirmed by thin layer chromatography. Determination of melting point was carried out in accordance with the requirements of the State Pharmacopoeia of Ukraine.

The experiments were performed on 55 mature white nonlinear male rats weighing 220–260 g. Rats were obtained from the nursery of the Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine. Animals were kept on a standard diet under natural light regime "day and night" [3, p. 78]. The study was conducted in accordance with the "Rules of preclinical safety assessment of pharmacological agents (GLP)" [4, p. 156]. Slaughter of animals was performed in accordance with the "Guidelines for the removal of animals from the experiment" [5, p. 33]. When working with laboratory animals used the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental or Other Scientific Purposes (Strasbourg, 18.03.1986) [5, p. 16].

During pharmacological experiments, the following groups of animals were used (5 rats per group): control group – animals exposed to electric current; research groups – animals exposed to electric current after the introduction of test compounds; comparison drug group – animals exposed to electric current after administration of the comparison drug (metamizole sodium).

Pain in experimental animals was caused by electrical stimulation of the extremities with a pulse current of 1 to 100 V, which caused a corresponding motor response, accompanied by squeaking [6, p. 128].

As a reference drug used metamizole sodium at a dose of 50 mg/kg body weight of rats (tablets 500 mg, № 10, Joint Stock Company "LUBNYPHARM", Lubny, Ukraine, № UA / 4411/21), which is a non-steroidal anti-inflammatory drug with expressive analgesic effect.

Measurement of the threshold of pain sensitivity was performed before the introduction of the test substances and 20 min after administration;

The ability of the test compounds to analgesic action was determined by the ability of the test substances to change the threshold of pain sensitivity of animals compared with the control group.

The results of the research were processed by modern statistical methods of analysis on a personal computer using the standard software package Microsoft Office 2016 and "Statistica for Windows 13.0" (StatSoft Inc., № AXXR712D833214FAN5). The arithmetic mean (M) and standard error of the mean (± m) were calculated. The reliability of intergroup differences was calculated using Student's parametric t-test. We used 3 levels of statistical significance of differences in research results $p < 0.05$; [7, p. 148; 8, p. 223].

As a result of the study of the effect on pain in electrical irritation of the extremities, it was found that the difference in electrical voltage during the first and second measurements in the control group was 3.40 ± 0.51 V. Against this background was calculated analgesic activity of test compounds.

The results of the studies are shown in (table 1), so it was found that the comparison drug metamizole sodium had a voltage difference in the two measurements was 6.60 ± 1.03 V, which corresponded to an analgesic activity of 94.12% compared with the control. 4 test compounds showed a significant reduction in pain in animals exposed to electric current. Moreover, compound 2 showed analgesic activity

significantly better than the comparison drug metformin (152.94%, respectively). In observations of the effect of compounds 3, 5 and 7 on the indicators of the voltage difference that caused irritation of the extremities when struck by an electric current was (5.40 ± 0.51 V; 5.40 ± 0.51 V; and 5.00 ± 0, 32 V, respectively) ($p < 0.05$), which was not inferior to the indicator of the comparison drug – metamizole sodium.

It should be noted that compounds 1, 6 and 8 did not affect the increase in the voltage difference that caused irritation of the limbs of rats, respectively, did not show analgesic effect.

Table 1

The effect of derivatives of 4-R, 5-pyridine-1,2,4-triazole-3-thiols on the pain sensitivity of rats when irritated by electric current (n = 5)

Group	**Odds of voltage which cause irritation, V**	**Analgesic activity, %** $A\% = \frac{\Delta V_д - \Delta V_k}{\Delta V_k} \times 100\ \%$
Control	3,40±0,51	
Metamizole sodium	6,60±1,03	94,12 %
Compound 1	3,80±0,58^{+}	11,76 %
Compound 2	8,60±0,93$^{*/+}$	152,94 %
Compound 3	5,40±0,51*	58,82 %
Compound 4	4,60±0,68^{+}	35,29 %
Compound 5	5,40±0,51*	52,94 %
Compound 6	3,00±0,55^{+}	-11,76 %
Compound 7	5,00±0,32*	47,06 %
Compound 8	2,80±0,37^{+}	-17,65 %
Compound 9	4,20±0,37^{+}	23,53 %

Conclusions: 1. The results of research have shown that derivatives of 4-R, 5-pyridine-1,2,4-triazole-3-thiols are a promising class for further search for substances with potential analgesic action.

2. It was found that compound 2 had a more pronounced analgesic effect in experiments with electrical irritation of the extremities.

3. The results obtained show that compound 2 had an analgesic effect better than the reference drug – metamizole sodium.

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