The 7th International Electronic Conference on Medicinal Chemistry (ECMC 2021)
01–30 NOVEMBER 2021 | ONLINE

Analgesic activity of new 1,4-dihydropyridine-2-thiols containing a benzocaine fragment

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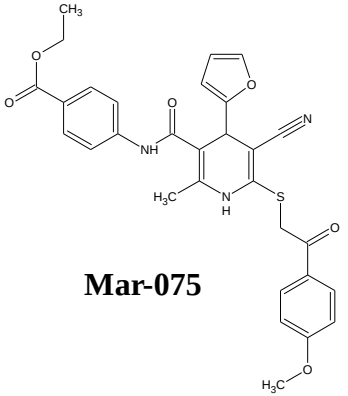
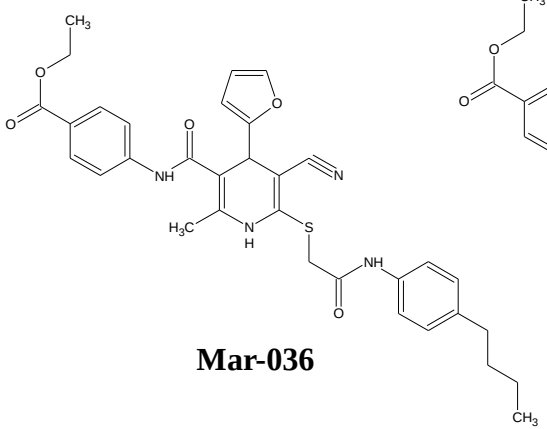
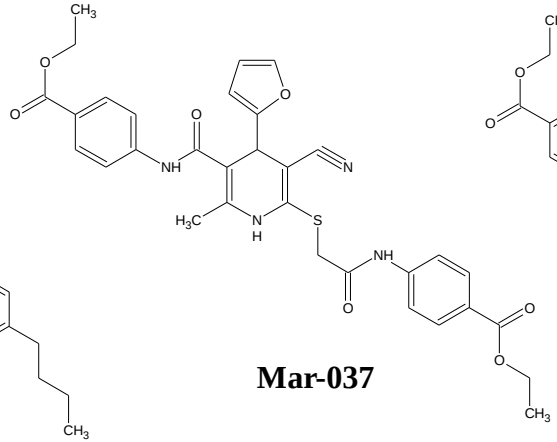


Mar-075



Mar-036



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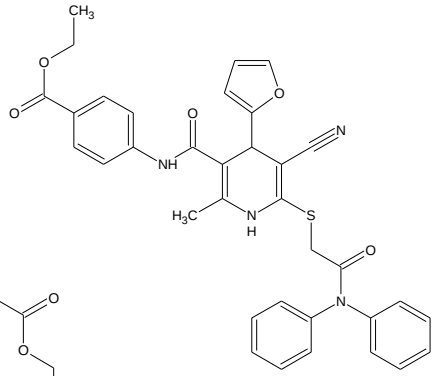

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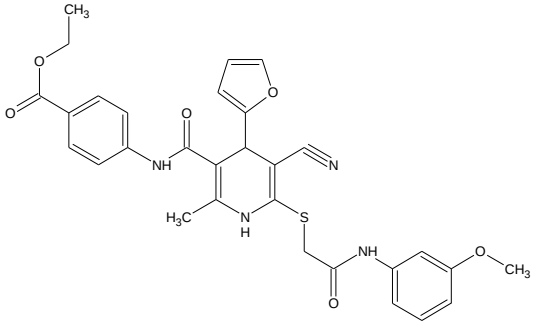
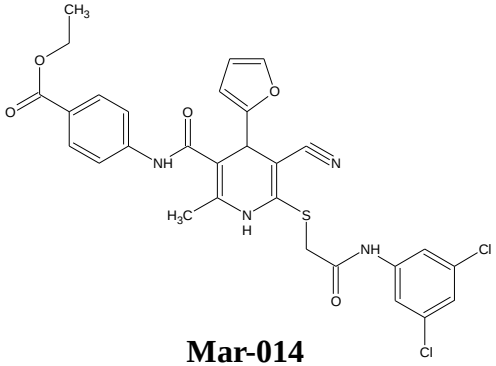
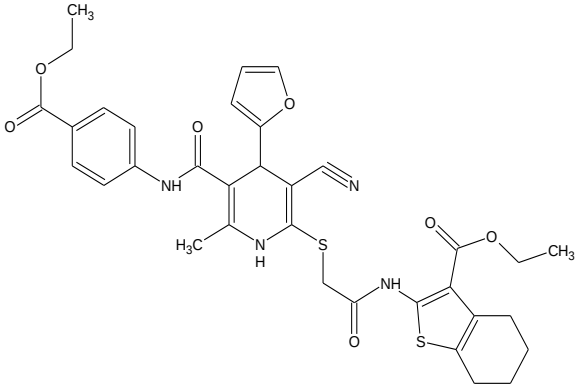


Mar-035



Mar-014



Mar-033

Abstract

Experiment was run on ninety white mongrel male rats weighing 220-250 g. Rats were divided into control group (with orofacial trigeminal pain modelling by subcutaneous injection of 0.1 ml 5% formaldehyde solution in the vibrissae area), reference group (which received metamizole sodium at a dose of 7 mg/kg) and seven test groups (received 1,4-dihydropyridine-2-thiols at a dose of 5 mg/kg intragastrically 1.5 hours prior to administration of algogenic substance) of ten animals each. Quantitative description is the number of orofacial scratching movements (NSM) per minute. Measurements were made 10, 15, 20 minutes after the algogenic substance administration.

In control group average NSMs were 90.2, 65.2, 35.2 after 10, 15, 20 minutes respectively. Animals were restless, scratching skin to scrapes. Metamizole sodium administration reduced NSM to 60, 37.6, 19.7 respectively. Mar-033 sample gave similar results; mar-035, mar-037 in the 10th and 15th minutes gave activity similar to metamizole sodium, in the 20th minute NSMs were 7.6 and 7.5 respectively; mar-040 after 10, 15, 20 minutes reduced NSMs to 36.2, 13.4, 5.3 respectively; mar-014 to 26.4, 6.6, 2; mar-075, mar-036 drastically reduced NSMs to 8.6 and 7.3 at the beginning of observation, to 6.6 and 3.3 respectively after 15 minutes and to 1 and less after 20 minutes.

Research showed that three substances had the maximum analgesic activity: mar-036 (ethyl 4-{[6-({2-[(4-butylphenyl)amino]-2-oxoethyl}thio)-5-cyano-4-(2-furyl)-2-methyl-1,4-dihydropyridin-3-yl)carbonyl}amino}benzoate), mar-075 (ethyl-4-{[(5-cyano-4-(2-furyl)-6-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-2-methyl-1,4-dihydropyridin-3-yl)carbonyl]amino}benzoate) were 19.7 times; mar-014 (ethyl-4-{[5-cyano-6-({2-[(3,5-dichlorophenyl)amino]-2-oxoethyl}thio)-4-(2-furyl)-2-methyl-1,4-dihydropyridin-3-yl)carbonyl]amino}benzoate) was 9.8 times more efficient than metamizole sodium.

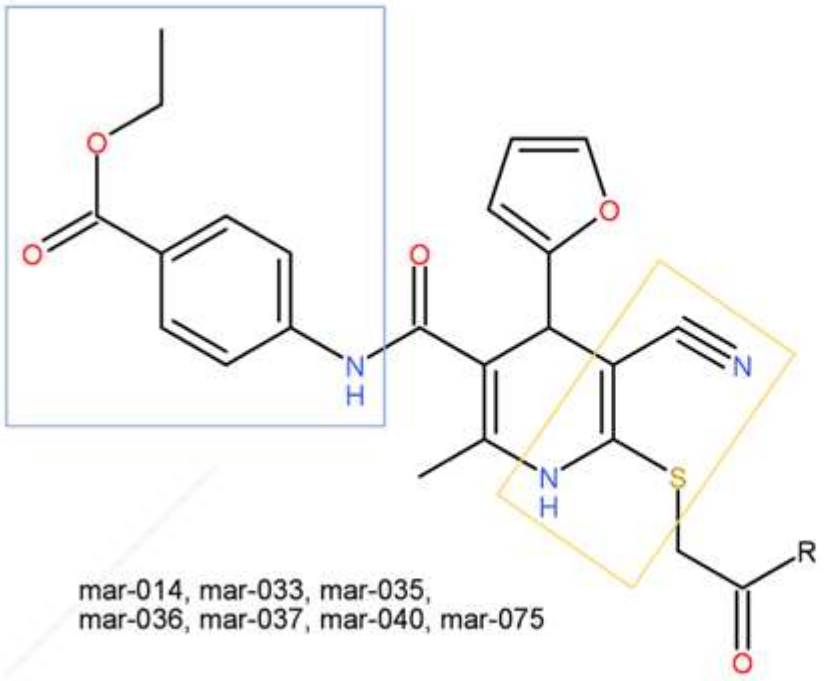
Keywords

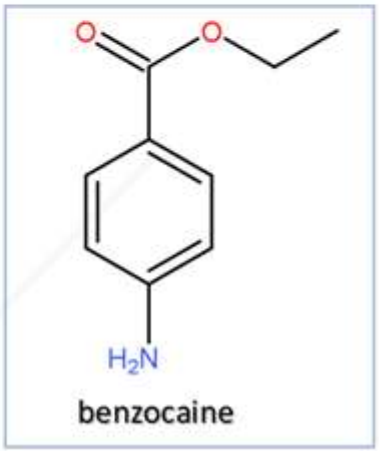
1,4-dihydrothiopyridines; analgesic activity; number of scratching movements; metamizole sodium; benzocaine; cyanothioacetamide derivatives

Introduction

Currently one of the most common syndromes in oncological, traumatological, dental, cambustiological, anesthesiological, surgical and rheumatological clinical practice is pain syndrome. Especially intensive chronic pain caused by metastases of malignant neoplasms, traumatic damage to the integrity of tissues, autoimmune inflammatory processes and many others. Therefore, the relevance of the search for highly effective and safe medicines for the relief of pain syndrome is extremely high.

Of particular interest at present are cyanothioacetamide derivatives, which have high activity against tick-borne encephalitis virus and Powassan virus, pronounced anti-inflammatory and analeptic effects, adaptogenic effect, moderate anti-HIV activity. These compounds can be used as an autotaxin inhibitor and an inhibitor of beta-amyloid peptide formation.

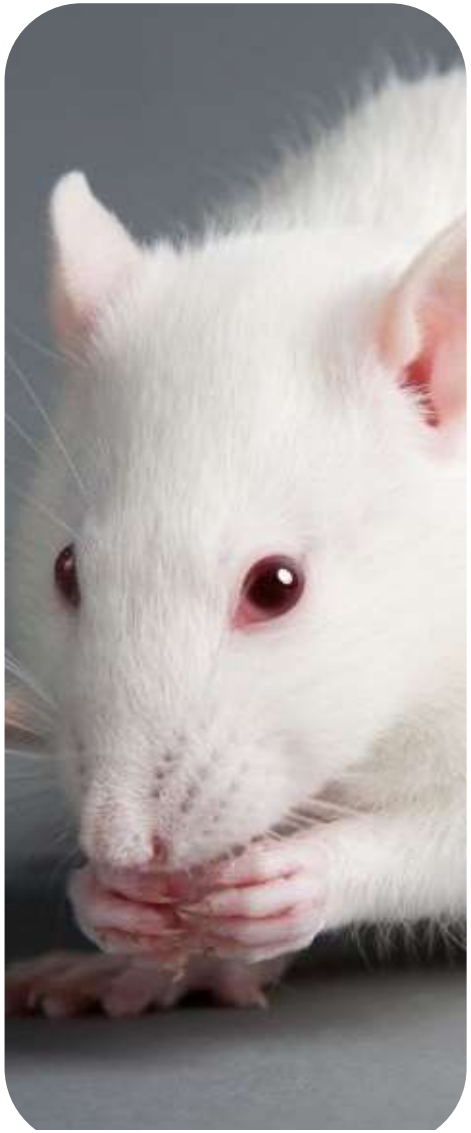




The 170 new derivatives of di- and tetrahydropyridines synthesized by us were subjected to virtual screening using the Swiss Target Prediction software package developed by scientists from the Swiss Institute of Bioinformatics, [http://swisstargetprediction.ch/index.php], on-line resources: Online SMILES Translator and Structure File Generator from U.S. National Cancer Institute [https://cactus.nci.nih.gov/translate/], OPSIN: Open Parser for Systematic IUPAC nomenclature from University of Cambridge, Centre for Molecular Informatics [https://opsin.ch.cam.ac.uk/].

Seven samples of 1,4-dihydrothiopyridines selected using virtual bioscreening software with laboratory ciphers Mar-014, Mar-033, Mar-035, Mar-036, Mar-037, Mar-040, Mar-075 are recommended for further preclinical studies in experiments on laboratory animals in various tests to study analgesic activity.

Results and discussion



The experiment was carried out on white mongrel male rats weighing 220-250 g, obtained from the vivarium of Lugansk State Medical University in the autumn-winter period in the laboratory of the Department of Fundamental and Clinical Pharmacology under the following conditions:

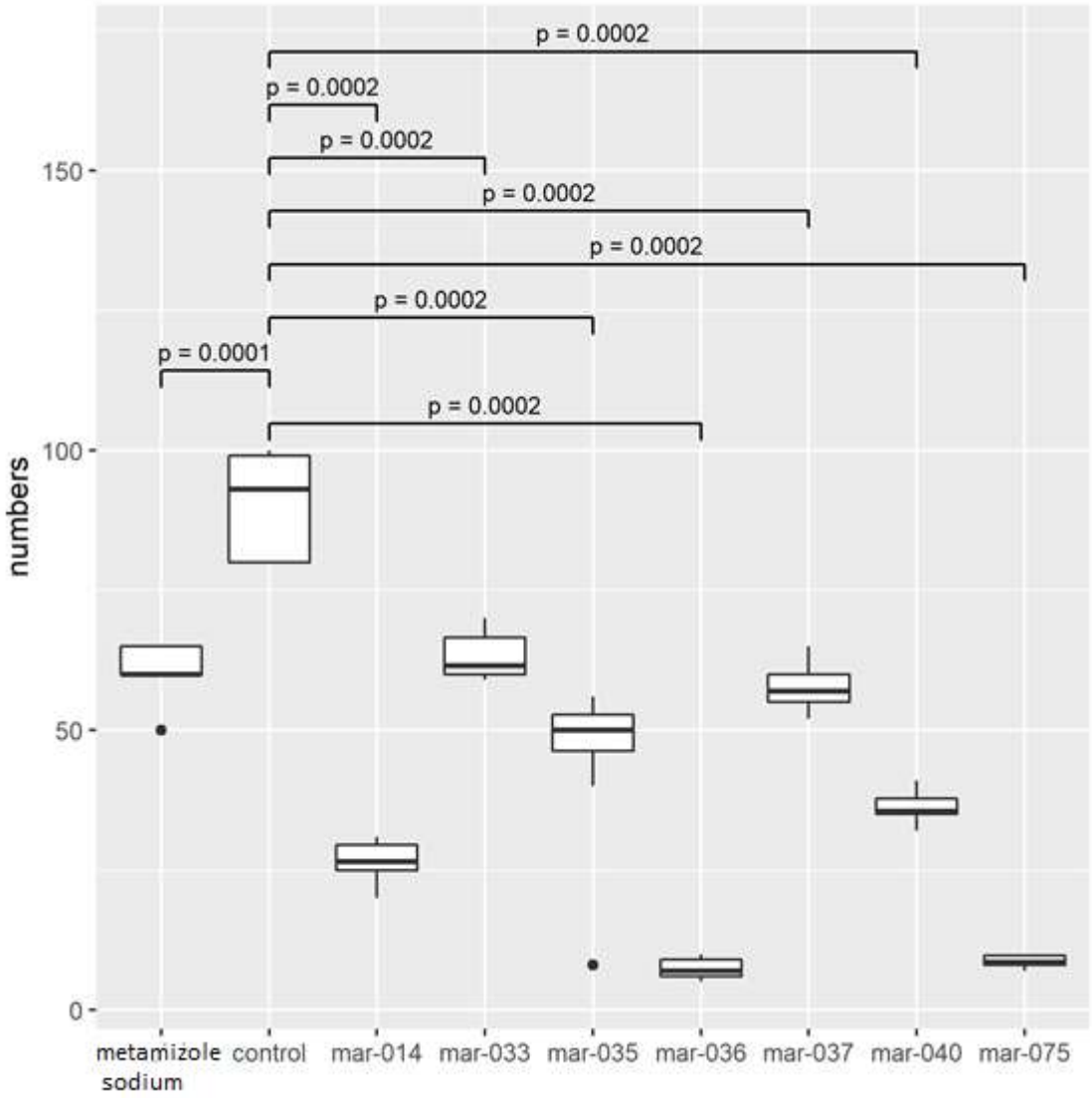
- lighting mode: natural;
- ambient temperature: 22-24°C;
- relative humidity: 40-50%.

The sample size is 90 individuals, according to the calculations of the online calculator (https://medstatistic.ru/calculators/calcsize.html) and recommendations. The studies were conducted in accordance with the rules of high-quality laboratory practice in conducting preclinical studies in the Russian Federation (Order of the Ministry of Health and Social Development of the Russian Federation dated August 23, 2010, N. 708n), as well as the rules and International Recommendations of the European Convention for the Protection of Vertebrates Used in Experimental Studies (1997).

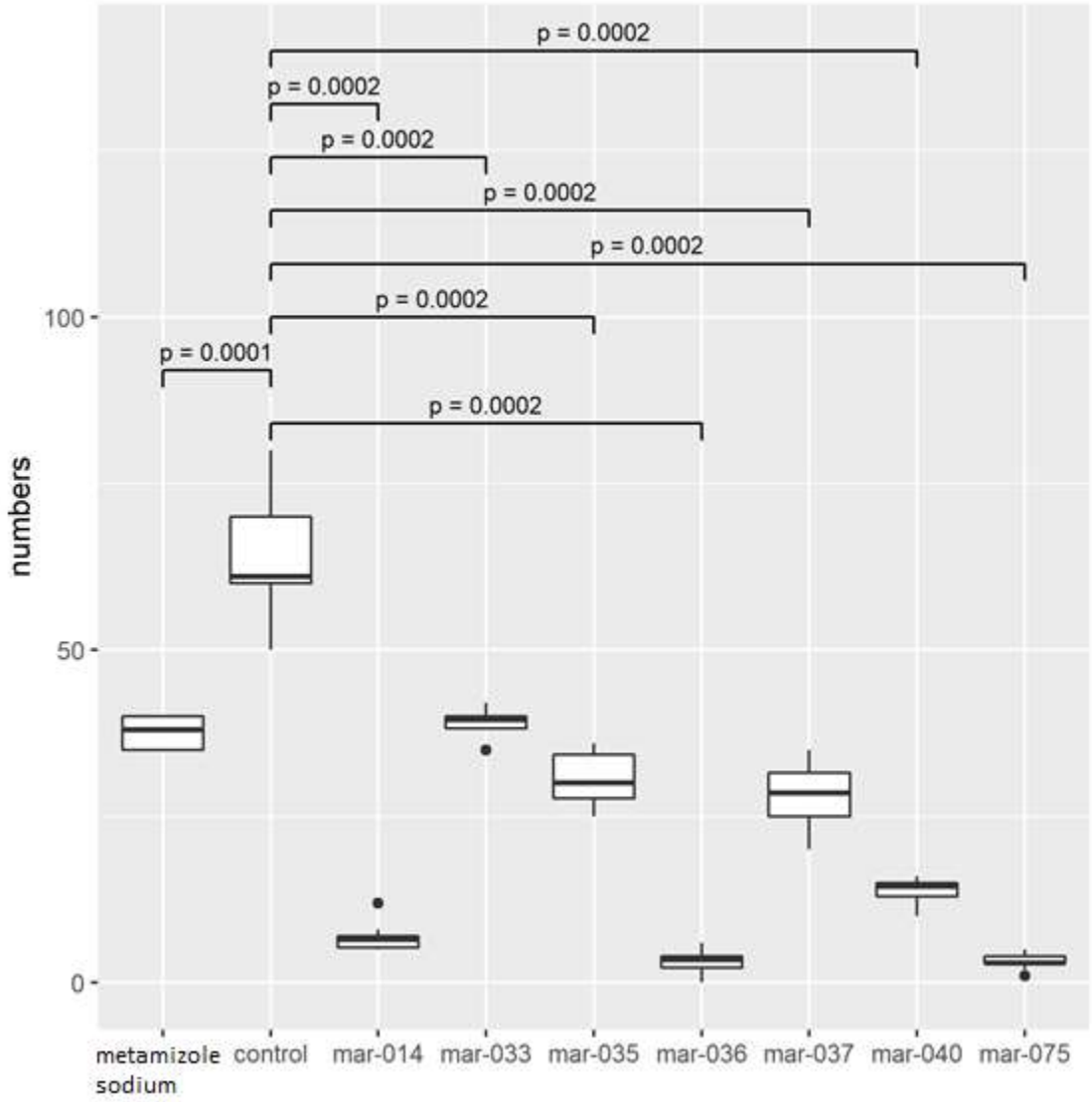
Experimental groups were formed by random selection. Before the start of the experiment, all laboratory animals were carefully examined, their weight, age, motor activity and the condition of the hair were taken into account. The rats were divided into a control group (with simulated orofacial trigeminal pain), a reference group and seven experimental groups according to the number of studied original newly synthesized sulfur-containing 1,4-dihydropyridines. The experiment used groups consisting of 10 animals. Determination of analgesic activity was carried out in a test of orofacial trigeminal pain, which was modeled by subcutaneous injection of 0.1 ml of 5% formaldehyde solution into the vibrissus area in laboratory rats. Metamizole sodium at a dose of 7 mg/kg was used as a reference drug for the reference group of rats. Samples of 1,4-dihydropyridine-2-thiols were administered intragastrically at a dose of 5 mg/ kg 1.5 hours before the administration of the algogenic substance used (5% formaldehyde solution). The quantitative experimental characteristic in the work is the number of scratching movements with the front paws of the orofacial area per minute, which was calculated after 10, 15 and 20 minute intervals after the introduction of the algogenic substance.

Dispersion analysis of indicators of analgesic activity (temporal activity by the number of scratching movements) of 1,4-dihydropyridine-2-thiols in the dynamics of the direction of efficiency improvement

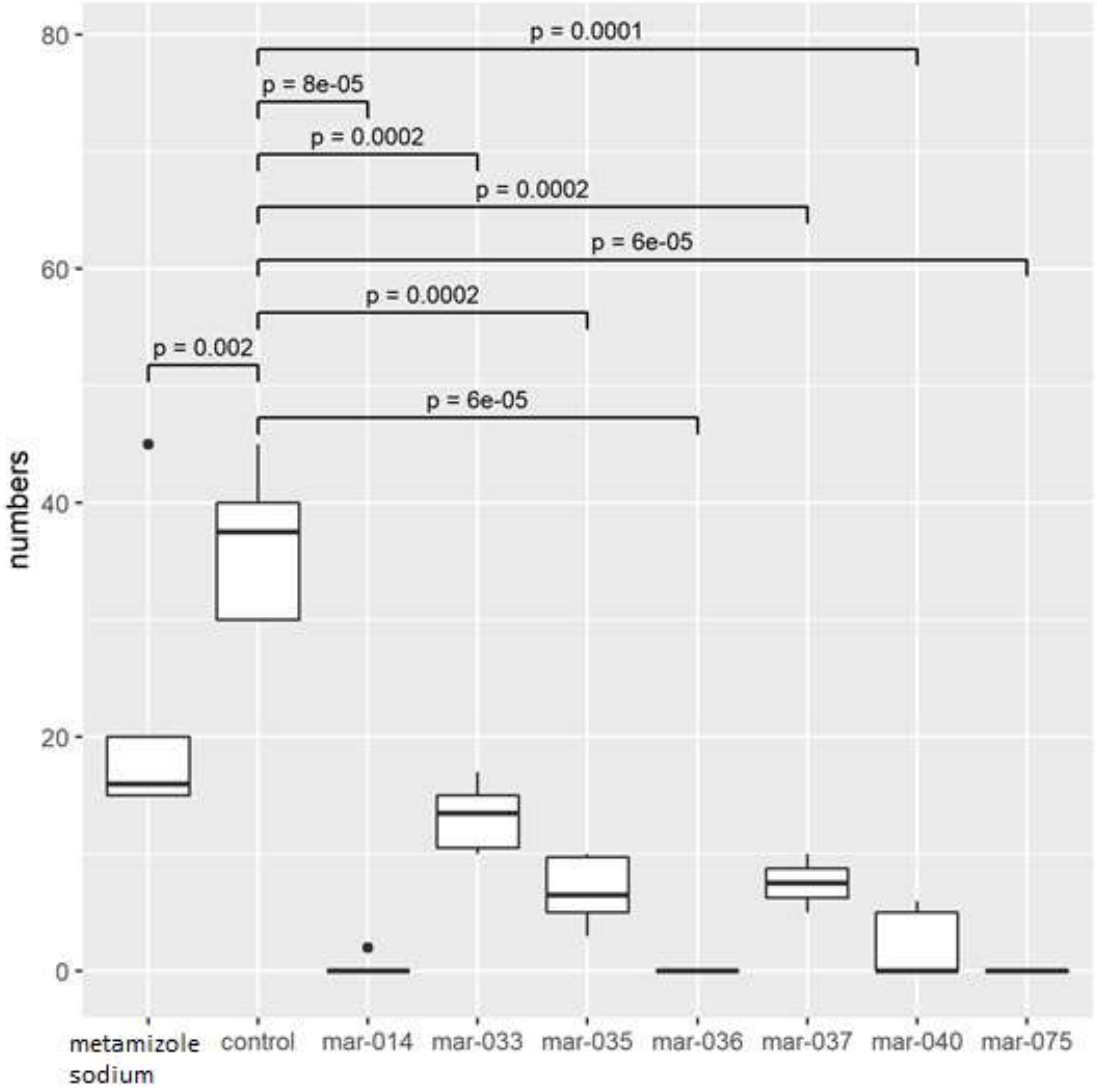
Group ofanimals	After 10 minutes Arithmetic mean (*a*), dispersion σ^2, mean-square deviation (σ), coefficient of variation (*V*)	After 15 minutes Arithmetic mean (*a*), dispersion σ^2, mean-square deviation (σ), coefficient of variation (*V*)	After 20 minutes Arithmetic mean (*a*), dispersion σ^2, mean-square deviation (σ), coefficient of variation (*V*)
1. Control group (injection of 0.1 ml of 5% formaldehyde solution into the vibrissus area)	a = 90,2; σ^2 = 96,4; σ = 9,8; V = 10,9	a = 65,2; σ^2 = 92,6; σ = 9,62; V = 14,8	a = 35,2; σ^2 = 36,0; σ = 6,0; V = 17,0
2. Comparison group (metamizole sodium, 7 mg/ kg)	a = 60,0; σ^2 = 33,3; σ = 5,8; V = 9,6	a = 37,6; σ^2 = 6,5; σ = 2,5; V = 6,8	a = 19,7; σ^2 = 84,0; σ = 9,2; V = 46,5
3. **mar-033** (5 mg/ kg)	a = 63,2; σ^2 = 16,2; σ = 4,0; V = 6,4	a = 39,0; σ^2 = 6,0; σ = 2,4; V = 6,3	a = 13,2; σ^2 = 7,3; σ = 2,7; V = 20,5
4. **mar-035** (5 mg/ kg)	a = 50,3; σ^2 = 22,5; σ = 4,7; V = 9,4	a = 30,6; σ^2 = 15,2; σ = 3,9; V = 12,7	a = 7,6; σ^2 = 7,1; σ = 2,7; V = 38,1
5. **mar-037** (5 mg/ kg)	a = 57,5; σ^2 = 16,9; σ = 4,1; V = 7,2	a = 27,6; σ^2 = 26,0; σ = 5,1; V = 18,5	a = 7,5; σ^2 = 3,4; σ = 1,8; V = 24,6
6. **mar-040** (5 mg/ kg)	a = 36,2; σ^2 = 8,2; σ = 2,9; V = 7,9	a = 13,4; σ^2 = 3,8; σ = 2,0; V = 14,6	a = 5,3; σ^2 = 0,3; σ = 0,6; V = 10,8
7. **mar-014** (5 mg/ kg)	a = 26,4; σ^2 = 12,7; σ = 3,6; V = 13,5	a = 6,6; σ^2 = 2,5; σ = 1,6; V = 23,9	a = 2,0; σ^2 = -; σ = -; V = -
8. **mar-075** (5 mg/ kg)	a = 8,6; σ^2 = 1,4; σ = 1,2; V = 13,7	a = 3,3; σ^2 = 1,6; σ = 1,3; V = 37,9	a = NaN; σ^2 = 0; σ = 0; V = NaN%
9. **mar-036** (5 mg/ kg)	a = 7,3; σ^2 = 3,6; σ = 1,9; V = 25,9	a = 3,9; σ^2 = 1,6; σ = 1,2; V = 32,2	a = NaN; σ^2 = 0; σ = 0; V = NaN%



The impact of 1,4-dihydropyridine-2-thiols derivatives on the number of scratching movements 10 minutes after the introduction of the algogenic substance into the orofacial area



The impact of 1,4-dihydropyridine-2-thiols derivatives on the number of scratching movements 15 minutes after the introduction of the algogenic substance into the orofacial area



The impact of 1,4-dihydropyridine-2-thiols derivatives on the number of scratching movements 20 minutes after the introduction of the algogenic substance into the orofacial area

Conclusions

1. Screening studies conducted in vivo to seven new 1,4-dihydropyridine-2-thiols showed maximum analgesic activity at a dose of 5 mg/kg three ports:

- mar-036 (ethyl 4-({[6-({2-[(4-butylphenyl)amino]-2-oxoethyl}thio)-5-cyano-4-(2-furyl)-2-methyl-1,4-dihydropyridin-3-yl]carbonyl}amino) (19.7 times more effective than metamizole sodium in the later stages of observation);
- mar-075 (ethyl 4-{[(5-cyano-4-(2-furyl)-6-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-2-methyl-1,4-dihydropyridin-3-yl)carbonyl]amino}benzoate) (19.7 times more effective than metamizole sodium in the later stages of observation);
- mar-014 (ethyl 4-({[5-cyano-6-({2-[(3,5-dichlorophenyl)amino]-2-oxoethyl}thio)-4-(2-furyl)-2-methyl-1,4-dihydropyridin-3-yl]carbonyl}amino) (9.8 times more effective than metamizole sodium in the later stages of observation).

2. High analgesic activity exceeding the effect of the use of the reference drug (metamizole sodium) was shown by samples with the codes mar-037 (ethyl 4-[({[3-cyano-5-({[4-(ethoxycarbonyl)phenyl]amino}carbonyl)-4-(2-furyl)-6-methyl-1,4-dihydropyridin-2-yl]thio}acetyl)amino]benzoate) and mar-040 (ethyl 4-({[5-cyano-6-{[2-(diphenylamino)-2-oxoethyl]thio}-4-(2-furyl)-2-methyl-1,4-dihydropyridin-3-yl]carbonyl}amino)benzoate).

The prospects of our further research are to confirm their analgesic activity in other classical tests, to identify antiexudative effects in these compounds, as well as to study their acute and chronic oral toxicity.