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New 4-(2-furyl)-1,4-dihydropyridine-2-thiols as potential agents with anti-inflammatory activity

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New 4-(2-furyl)-1,4-dihydropyridine-2-thiols as potential agents with anti-inflammatory activity

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Abstract :

We synthesized new 4-(2-furyl)-1,4-dihydropyridine-2-thiols.

Based on the results of virtual bioscreening, seven samples with laboratory codes ***mar-014, mar-033, mar-035, mar-036, mar-037, mar-040, mar-075*** were selected as the most promising compounds, taking into account the assumed biological targets of pharmacocorrection of the inflammatory process in preclinical studies.

The experiment was implemented in white male rats. Evaluation of the anti-inflammatory activity of the synthesized compounds was carried out on the model of acute "formalin edema", simulated by subplantar injection of formalin solution into the right hind limb . The substances were administered intragastrically, two hours before the induction of edema.

Animals of the control group received an equivalent amount of sodium chloride solution. Diclofenac sodium, indomethacin, meloxicam, and metamizole sodium intragastrically were used as comparison drugs .

The anti-inflammatory effect was assessed oncometrically, one and two days after the induction of inflammation, by changing the size of the limb.

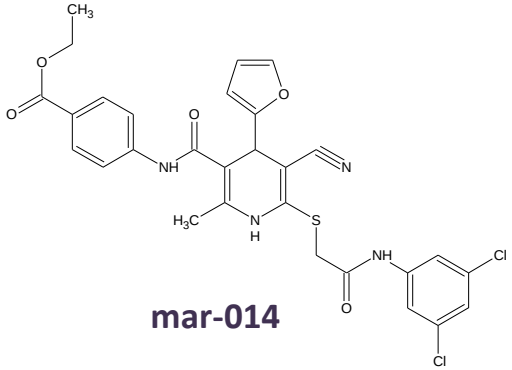
The most pronounced anti-inflammatory activity at a dose of 5 mg / kg is possessed by: *mar -040* 33-fold superior to indomethacin, 26-fold to diclofenac sodium, 25-fold to meloxicam, and 30-fold to analgin; *mar -037* was 17-23-fold superior to reference drugs; *mar -014* and *mar -033* were 2.7-fold more efficient than the comparison drug.

Compounds *mar-035* and *mar-036* exhibited an anti-inflammatory activity similar to meloxicam, diclofenac and metamizol sodium.

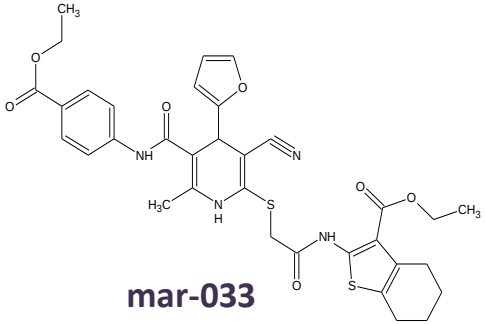
Keywords : Anti-inflammatory activity; 1,4-dihydrothiopyridines; formalin edema.

On the basis of the Chimex laboratory (Lugansk, LPR), we have synthesized new derivatives of dihydropyridines containing a 2-furyl substituent in the fourth position.

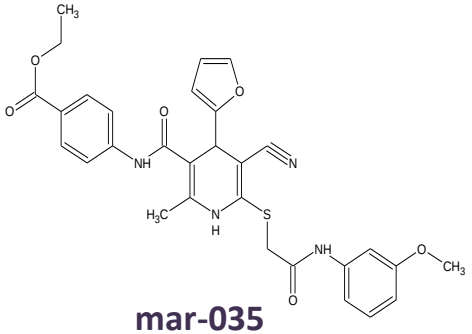
Based on the results of virtual bioscreening, seven samples of 1,4-dihydrothiopyridines with laboratory codes **mar-014, mar-033, mar-035, mar-036, mar-037, mar-040, mar-075** were selected, as the most promising with taking into account the alleged biological targets of the pharmacological correction of the inflammatory process in preclinical studies.



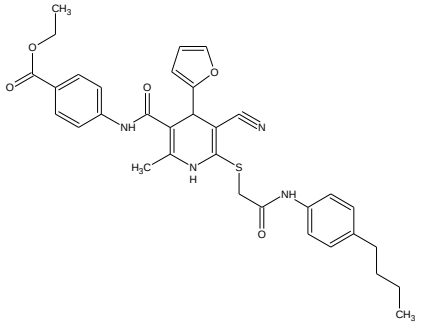
mar-014



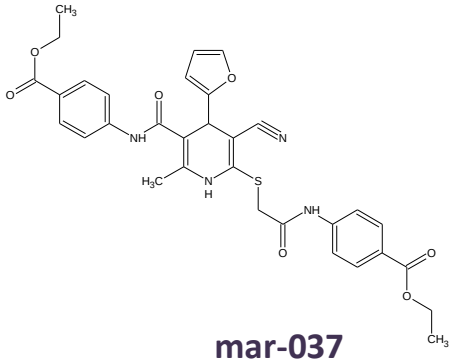
mar-033



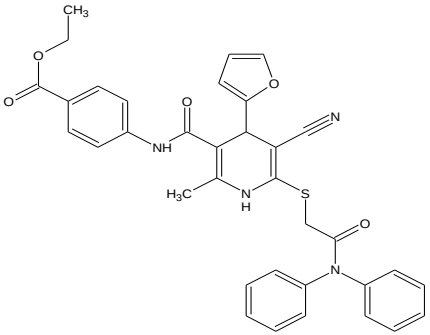
mar-035



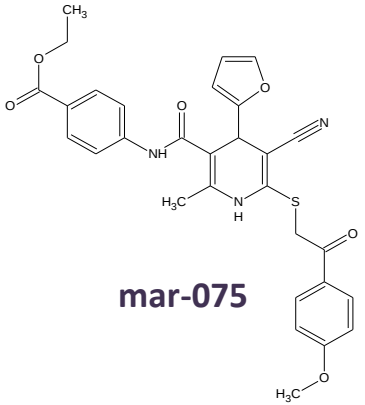
mar-036



mar-037



mar-040



mar-075

The chemical structure of samples with laboratory codes

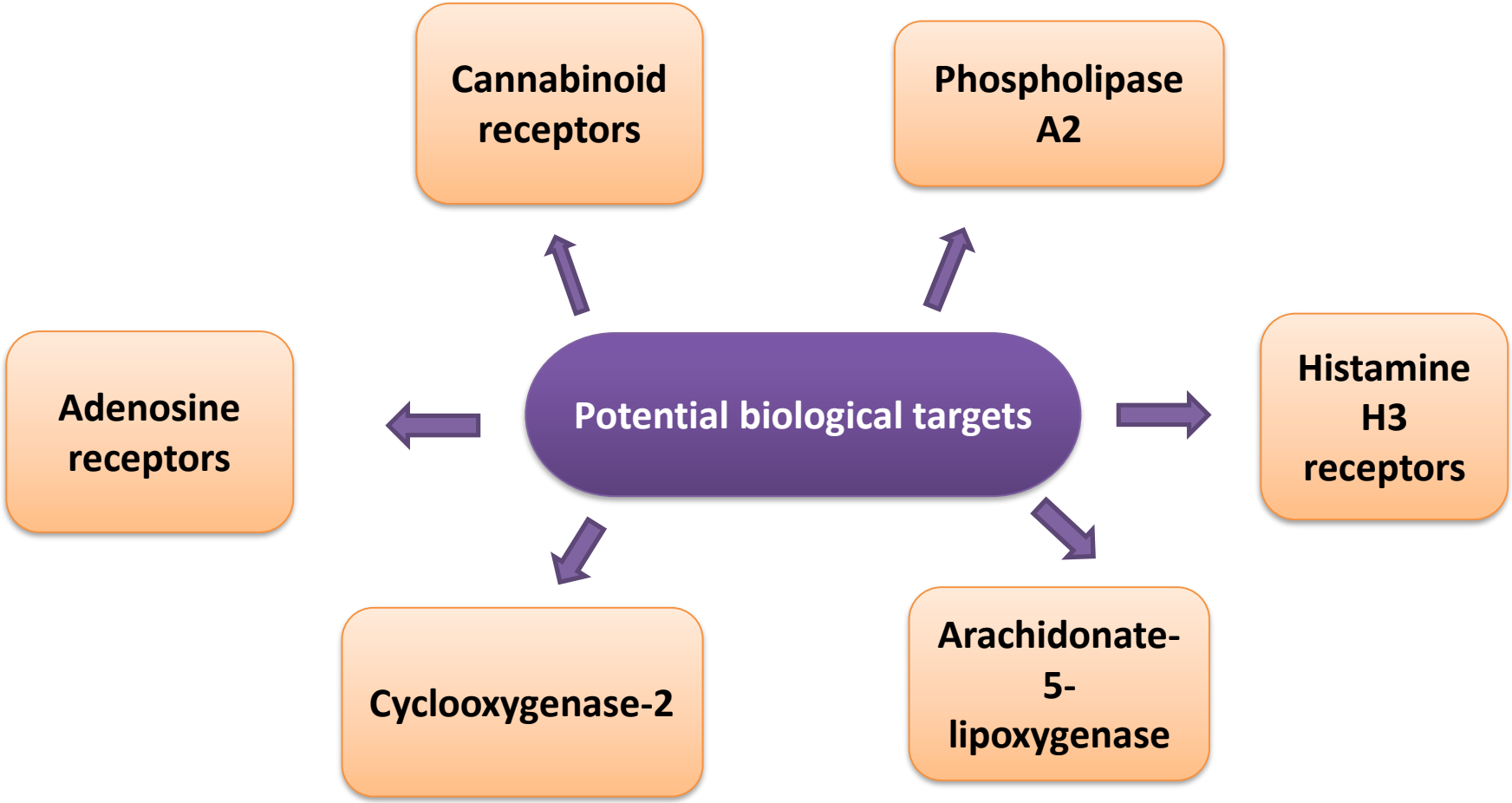
mar-014, mar-037, mar-040, mar-075

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);

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);

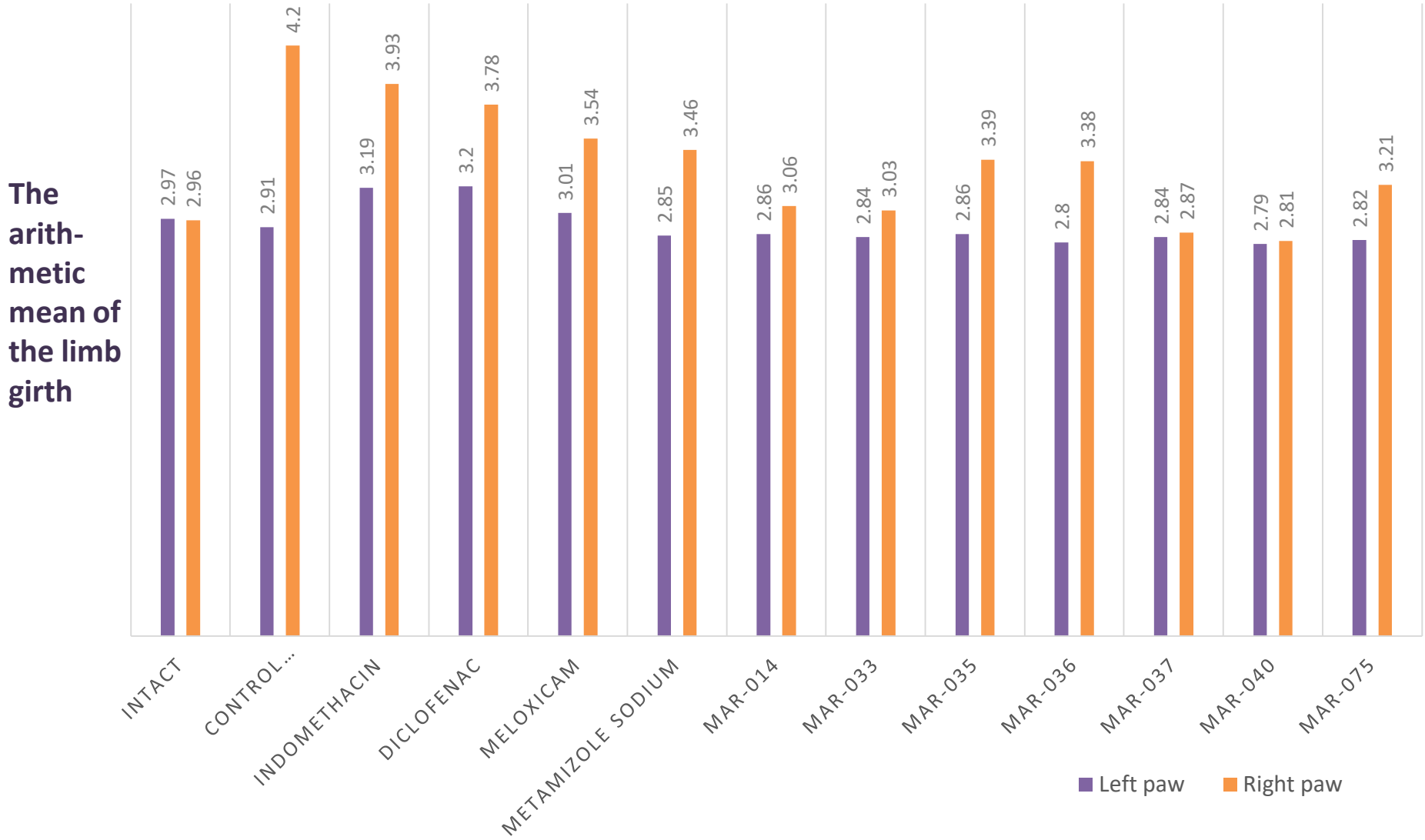
Mar-040 (ethyl 4-({[5-cyano-6-{[2-(diphenylamino)-2-oxoethyl]thio}-4-(2-furyl)-2-methyl-1,4-dihydropyridin-3-yl]carbonyl}amino)benzoate) ;

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).

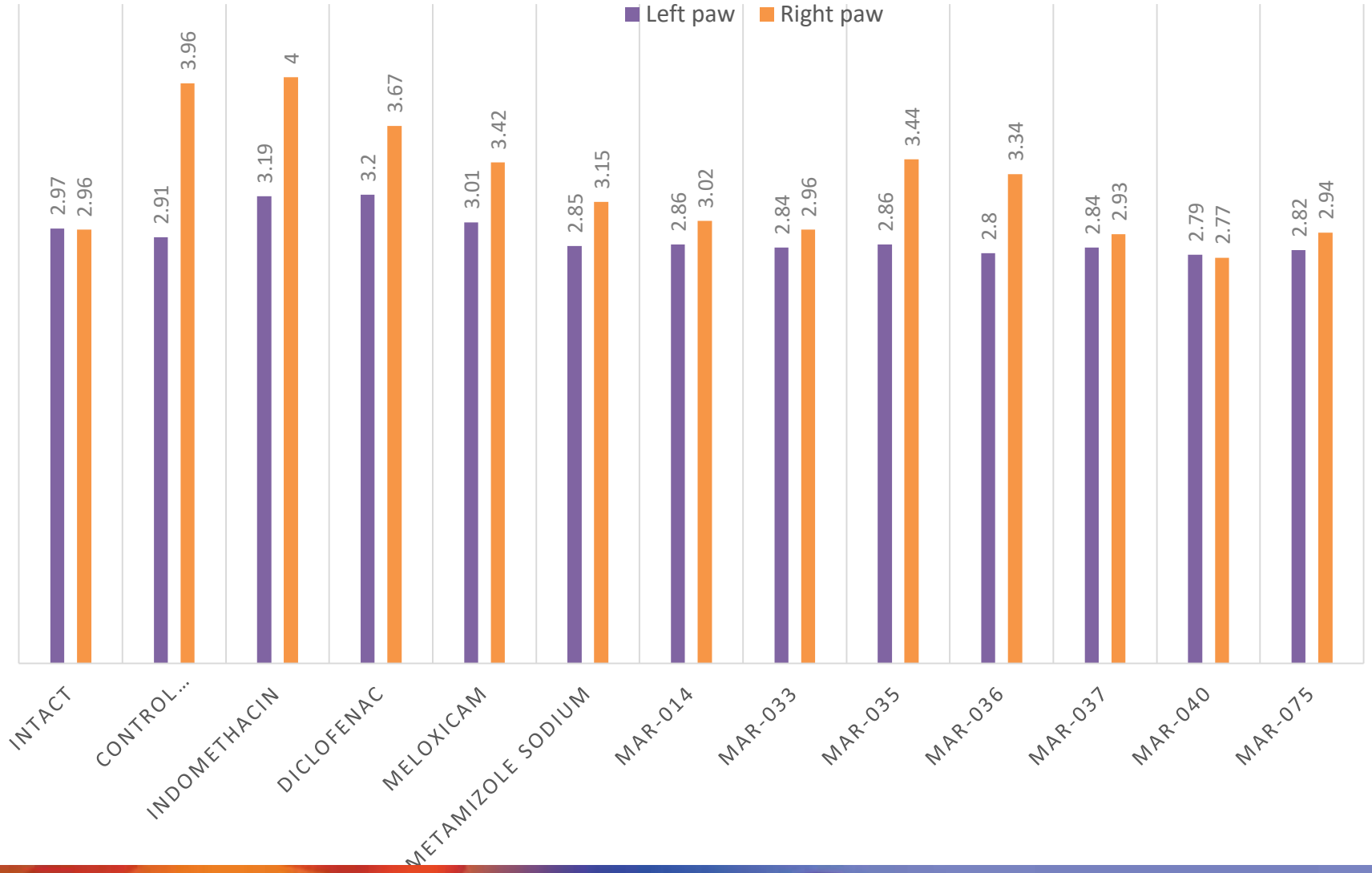

Cannabinoid receptors
Phospholipase A2
Adenosine receptors
Potential biological targets
Histamine H3 receptors
Cyclooxygenase-2
Arachidonate-5-lipoxygenase

- The experiment was carried out on 130 white male rats. Evaluation of the anti-inflammatory activity of the synthesized compounds was carried out on the model of acute "formalin edema", simulated by subplantar injection into the right hind limb of 0.1 ml of 2% formalin solution.
- **Mar-014, mar-033, mar-035, mar-036, mar-037, mar-040, mar-075** were administered intragastrically, at a dose of 5 mg / kg 1.5 hours before the induction of edema.
- Animals of the control group received an equivalent amount of 0.9% sodium chloride solution.
- Diclofenac sodium, indomethacin, meloxicam and metamizole sodium intragastrically were used as reference drugs, at doses of 10 mg / kg, 10 mg / kg, 10 mg / kg and 7 mg / kg, respectively.
- The anti-inflammatory effect was assessed oncometrically, 24 and 48 hours after the induction of inflammation, by changing the size of the limb.

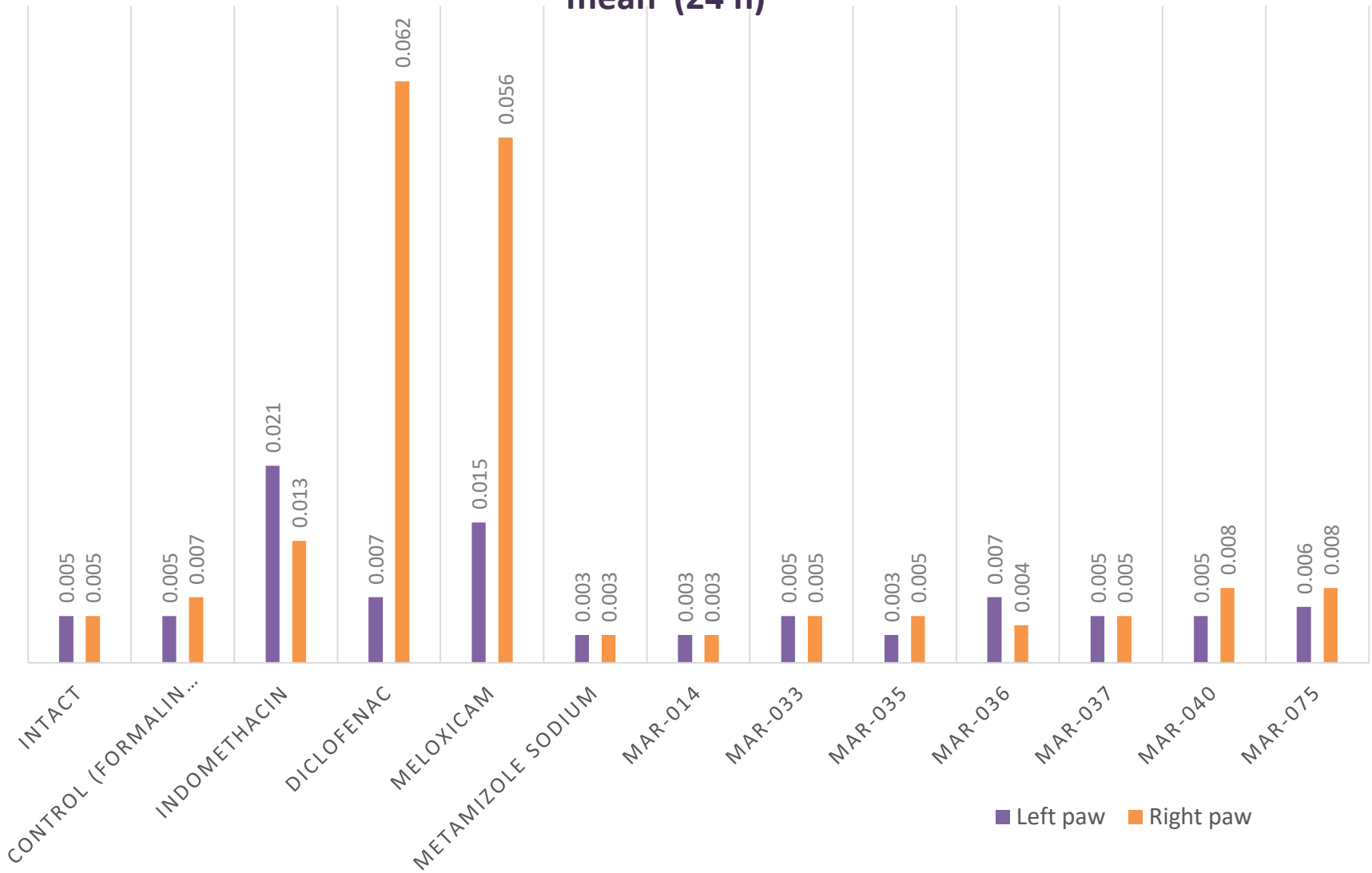
Changes in the girth of the limbs of rats after the formation of formalin edema **24 hours** after the induction of inflammation



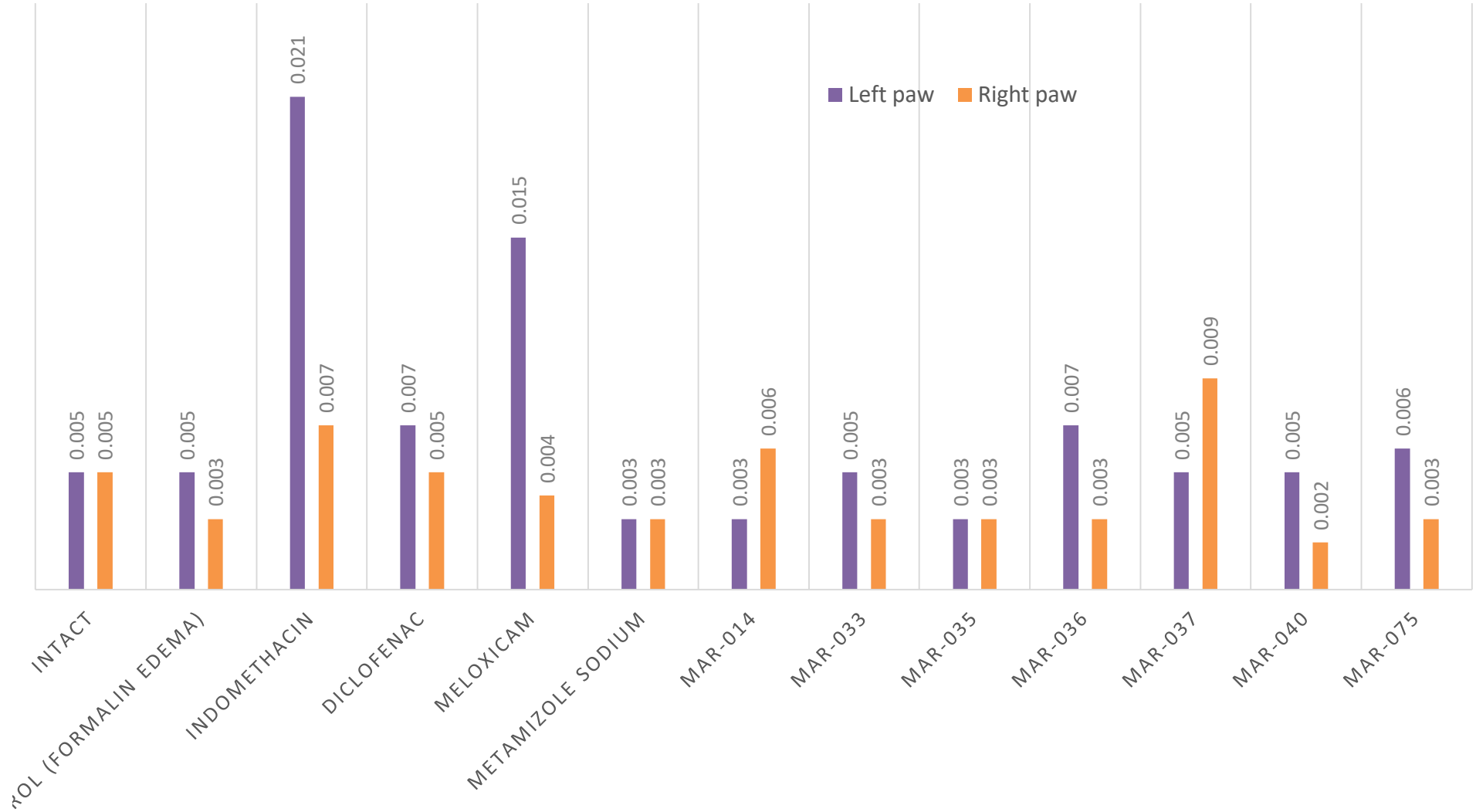
The arithmetic mean of the limb girth *(48* h)



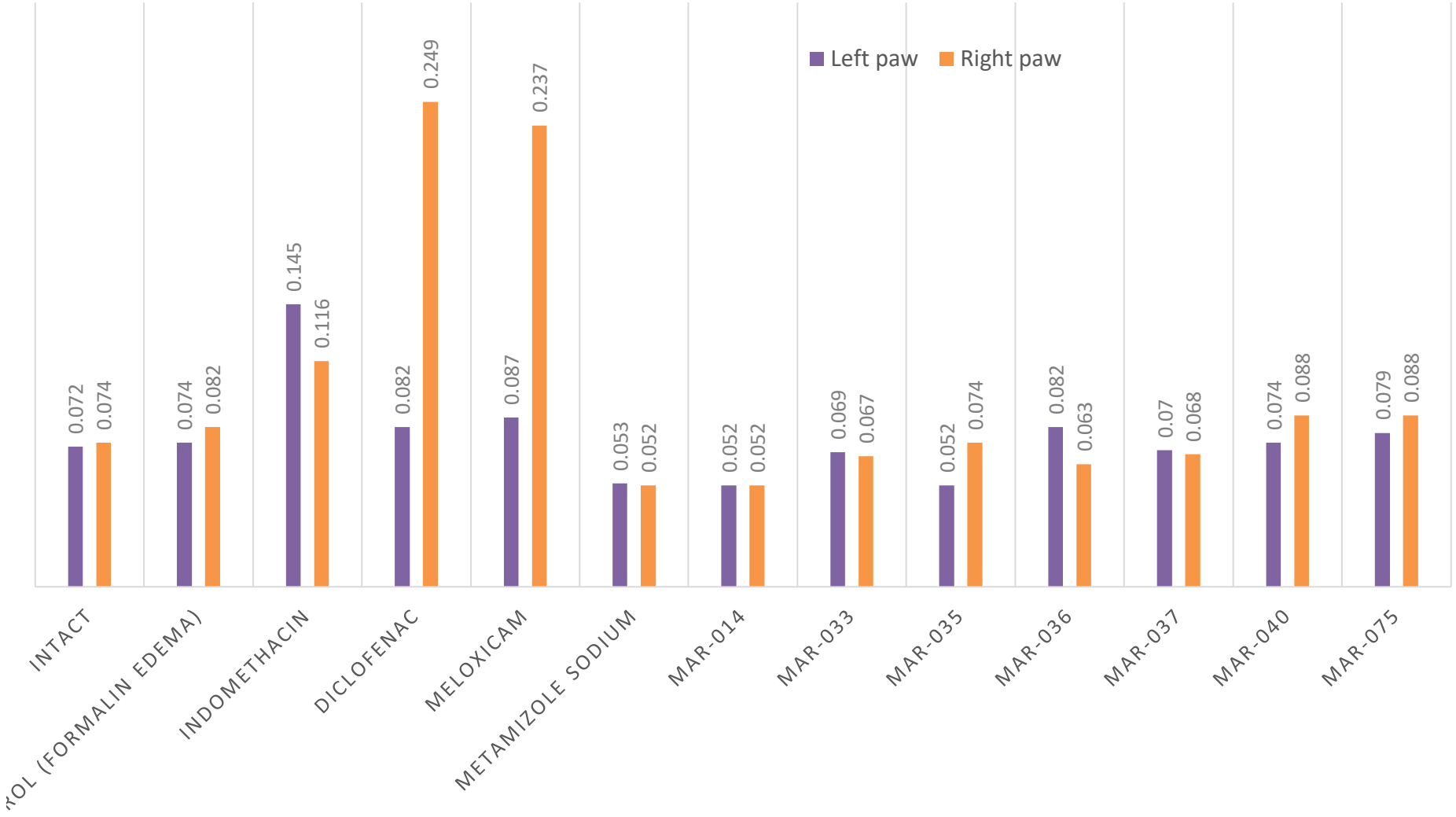
Variance of values around the arithmetic mean (24 h)



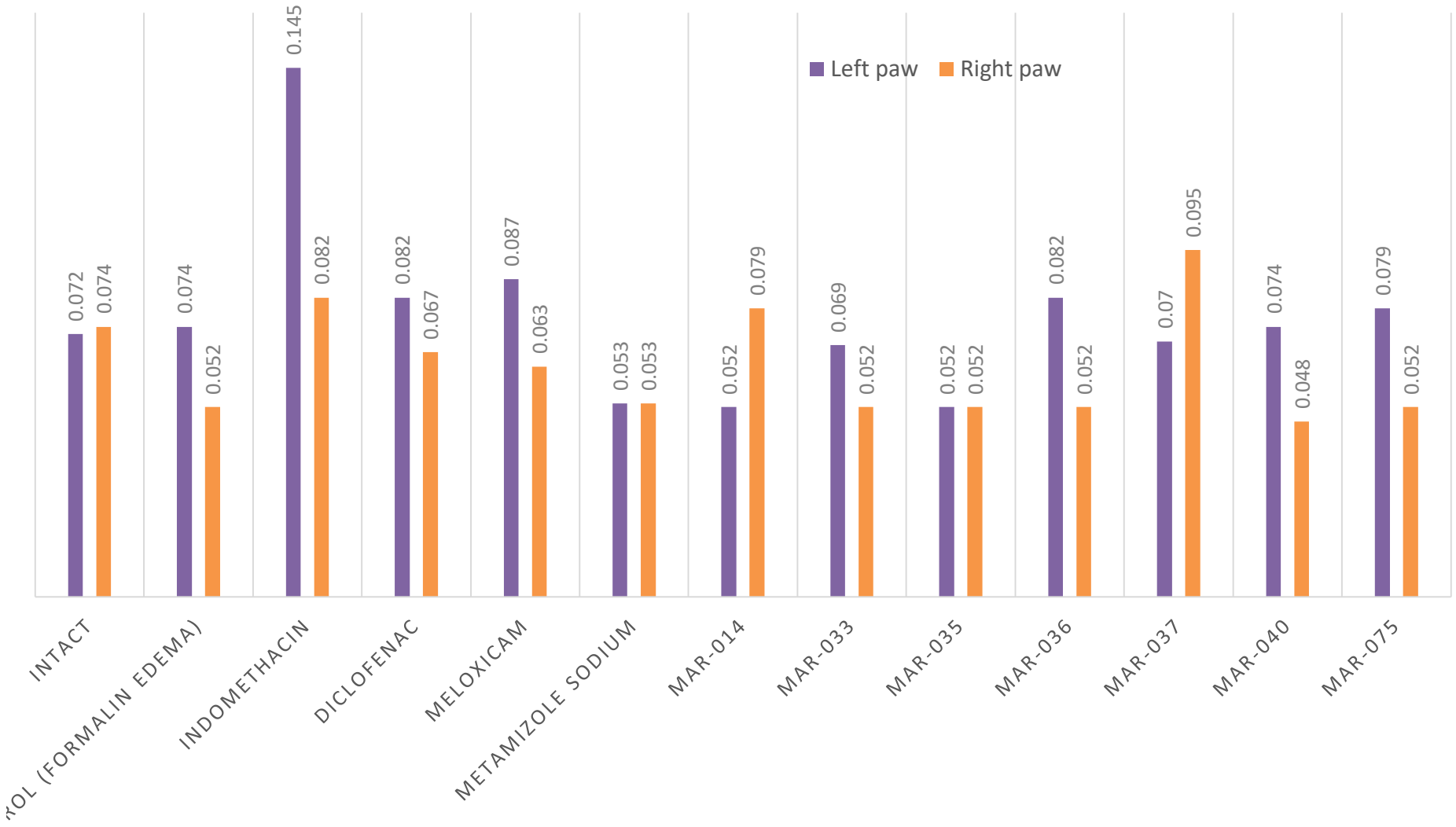
Variance of values around the arithmetic mean (48 h)



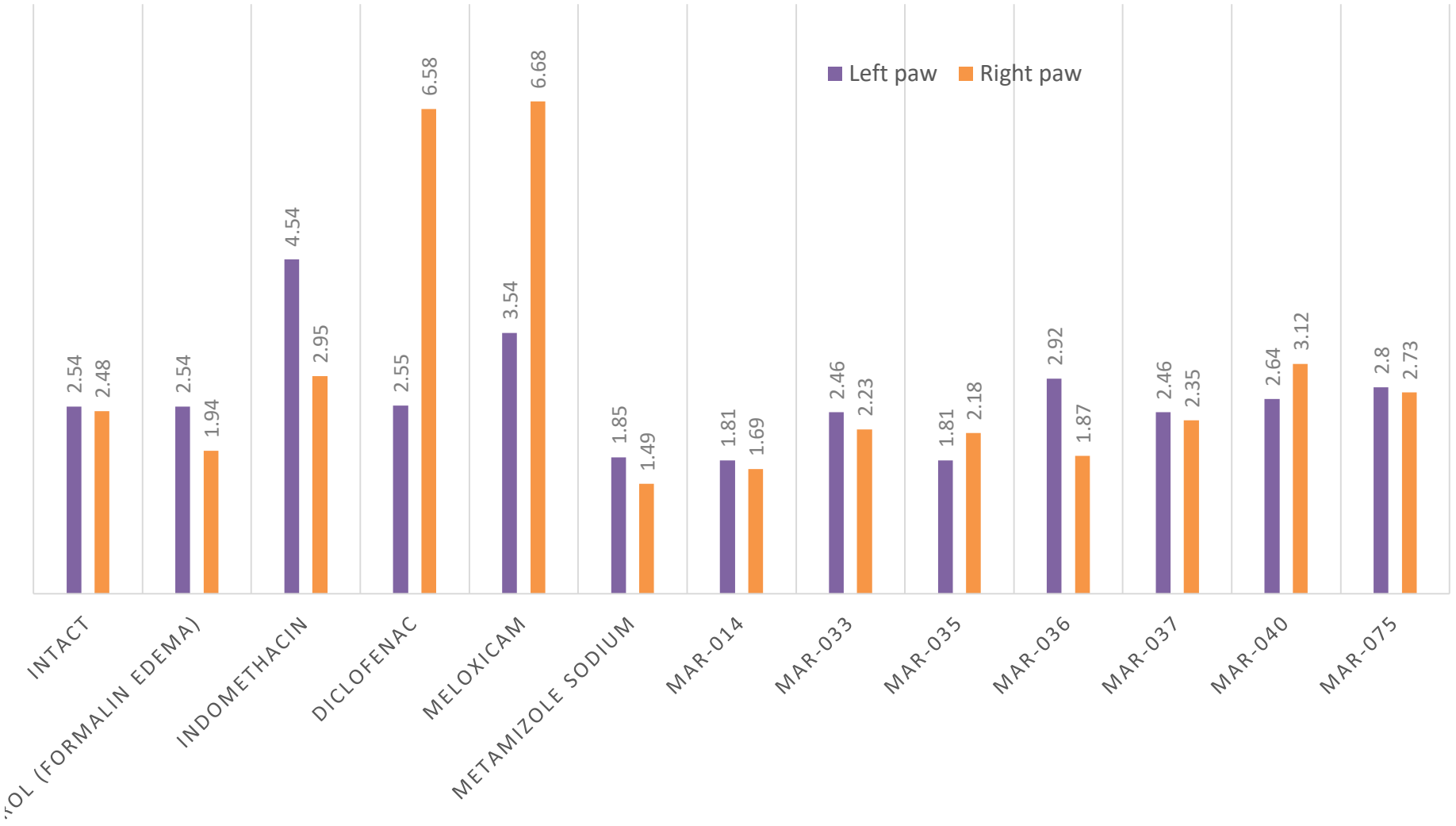
Standard deviation (24 h)



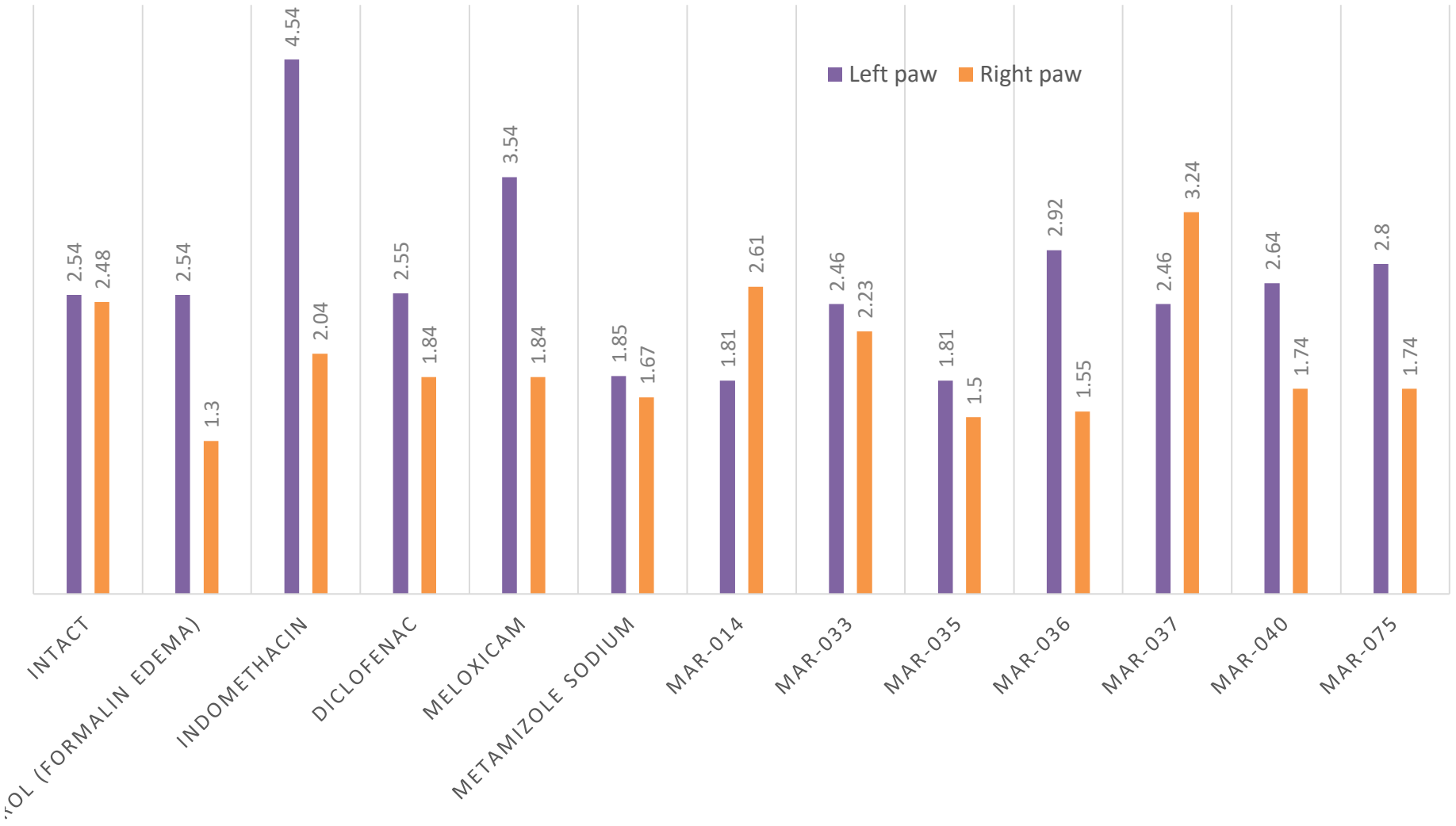
Standard deviation (48 h)



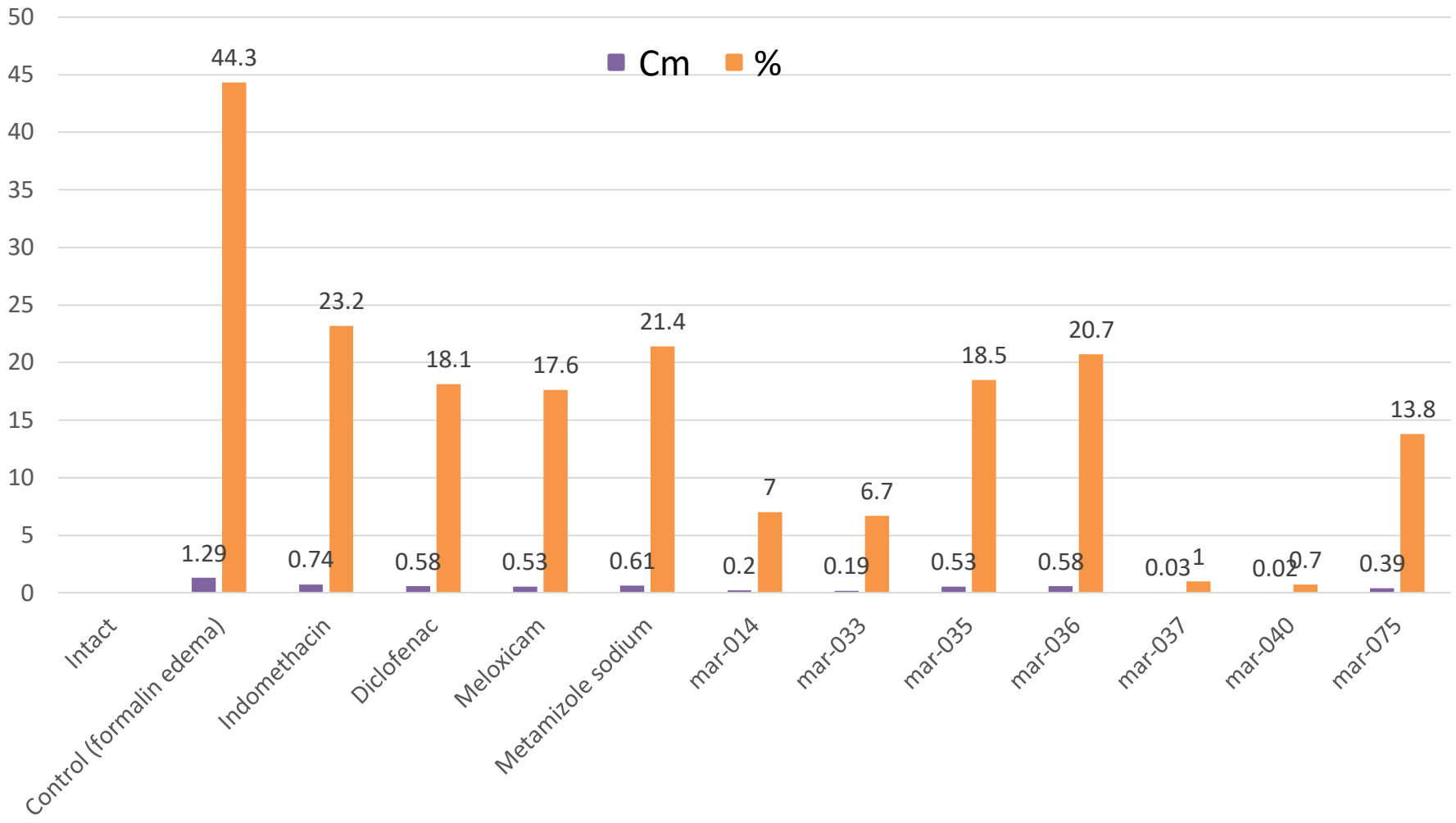
Coefficient of variation *(24* h)

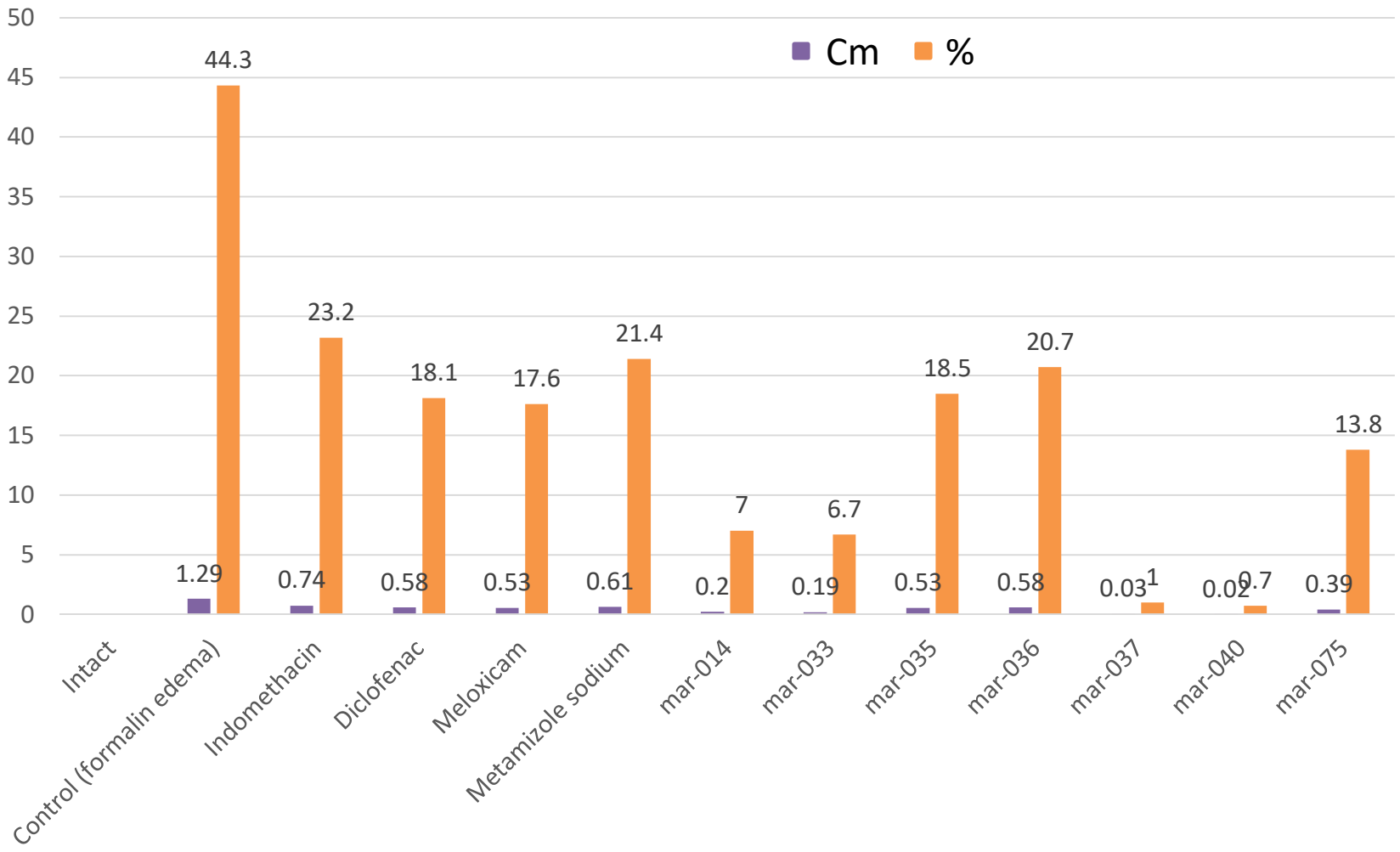


Coefficient of variation (48 h)



Difference (24 h)




Difference (48 h)
Cm
%
50
45
40
35
30
25
20
15
10
5
0
44.3
23.2
18.1
17.6
21.4
7
6.7
18.5
20.7
13.8
1.29
0.74
0.58
0.53
0.61
0.2
0.19
0.53
0.58
0.03
1
0.02
0.7
0.39
Intact
Control (formalin edema)
Indomethacin
Diclofenac
Meloxicam
Metamizole sodium
mar-014
mar-033
mar-035
mar-036
mar-037
mar-040
mar-075

Conclusions :

The most pronounced anti-inflammatory activity at a dose of 5 mg / kg is possessed by:

mar-040 superior to indomethacin 33 times, diclofenac sodium 26 times, meloxicam 25 times and metamizol sodium 30 times;

mar-037 17-23 times superior to reference drugs;

mar-014 and ***mar-033*** , which is 2.7 times more efficient than the comparison drug.

Connections (***mar-035*** and ***mar-036***) in terms of anti-inflammatory activity similar meloxicam amu , diclofenac and metamizol sodium.

THANK YOU FOR YOUR ATTENTION!

We are open for cooperation!