The following manuscript was accepted for publication in Pharmaceutical Sciences. It is assigned to an issue after technical editing, formatting for publication and author proofing. Citation: Horishny VY, Zadorozhnii PV, Horishnia IV, Matiychuk VS. Synthesis, anti-inflammatory activity and molecular docking studies of 1,4,5,6-tetrahydropyrimidine-2-carboxamides, Pharm. Sci. 2020, doi: 10.34172/PS.2020.100

Synthesis, anti-inflammatory activity and molecular docking studies of 1,4,5,6-tetrahydropyrimidine-2-carboxamides.

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Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the world. The widespread use of NSAIDs is associated with a number of serious side effects and complications observed for both selective and non-selective COX inhibitors. Therefore, the search for new COX inhibitors, which along with their effectiveness will have minimal side effects, is a very important and urgent task.

Methods: This work studied the synthesis of new 1,4,5,6-tetrahydropyrimidine-2-carboxamides based on the reaction of 2-morpholin-4-yl-N-(het)aryl-2-thioxoacetamides with 1,3-diaminopropane. All obtained compounds were tested for anti-inflammatory activity in vitro and in silico conditions. All synthesized 1,4,5,6-tetrahydropyrimidine-2-carboxamides were tested for influence on the course of the exudative phase of the inflammatory process based on the carrageenan model of paw edema of laboratory nonlinear heterosexual white rats weighing 220-250 g, using Diclofenac as a reference. Optimization of the geometry of the studied structures and molecular docking was carried out using the ArgusLab 4.0.1 software package.
Results: The target products were obtained with yields of 71-98% and easily isolated from the reaction mixture. The best anti-inflammatory activity was found in N-(4-chlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide and in N-[4-chloro-3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydropyrimidine-2-carboxamide, suppression of the inflammatory response was 46.7 and 46.4%, respectively. The results of molecular docking with COX-1 and COX-2 enzymes were in good agreement with the experimental data, $R^2 > 0.92$ and $R^2 > 0.83$, respectively.

Conclusion: The compounds under study were shown to be promising as potential anti-inflammatory agents.

Keywords: Tetrahydropyrimidine, COX-1, COX-2, Antiinflammatory activity, SAR analysis, Molecular docking

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the world. Their anti-ability to alleviate the symptoms of inflammation and pain is usually due to the inhibition of cyclooxygenases (COX) - enzymes involved in the synthesis of prostanoids. COX-1 and COX-2 isoforms of the enzyme form the greatest interest as biological targets for NSAIDs. COX-1 is a constitutive enzyme, that is, it works almost constantly and performs physiologically important functions, while COX-2 is an inducible enzyme, that is, it begins to function in certain situations.

The widespread use of NSAIDs is associated with a number of serious side effects and complications observed for both selective and non-selective COX inhibitors. Therefore, the search for new COX inhibitors, which along with their effectiveness will have minimal side effects, is a very important and urgent task. Work is underway to find potential NSAIDs among substances of natural origin, as well as synthetic derivatives of azepine, benzimidazole, triazole, 1,3,4-oxadiazole, xanthone, coumarin, quinazoline, pyrrolidinone, pyrrolidine, pyrazole, 1,3-thiazole, pyridazine, and other cyclic and acyclic systems.

Recently, pyrimidine derivatives have been of increasing interest as potential COX inhibitors. Usually, they exhibit anti-inflammatory and analgesic activity in vivo, and also give good results in in silico studies.

This work is devoted to the synthesis and study of the anti-inflammatory properties of 1,4,5,6-tetrahydropyrimidine-2-carboxamides. It should be noted that this class of amides is practically unexplored, methods for their preparation have not been developed and nothing is known about their biological activity either. At the same time, derivatives of 6-oxo-1,4,5,6-tetrahydropyrimidine-2-
carboxylic acid and compounds obtained by transformation of the 6-oxo group in their structure as well as condensed analogues based on them are well studied. In particular, they are inhibitors of various enzymes,\textsuperscript{49,50} exhibit antimicrobial\textsuperscript{51,52} and anti-inflammatory properties.\textsuperscript{53} These facts indicate a high pharmacological potential of the compounds of 1,4,5,6-tetrahydropyrimidine series, and therefore, further research in this direction is an urgent and promising task.

Material and Methods

Chemistry

All starting materials were purchased from Merck and used without purification. NMR spectra were determined with «Varian Mercury VX-400 », (400 MHz and 100 MHz) spectrometer, in DMSO-$d_6$. Melting points were determined in open capillary tubes and are uncorrected. MS (ESI) spectra were recorded on an LC-MS system - HPLC Agilent 1100 (Agilent Technologies Inc., Santa, Clara, CA USA) equipped with a diode array detector Agilent LC/MSD SL. Parameters of analysis: Zorbax SB - C18 column (1.8 μm, 4.6-15 mm, PN 821975-932), solvent water – acetonitrile mixture (95:5), 0.1% of aqueous trifluoroacetic acid; eluent flow 3 mL/min; injection volume 1 μL. IR spectra were recorded on a Vertex 70 Bruker” (Bruker, Karlsruhe, Germany) spectrometer in KBr pellets.

The general procedure for the preparation 2-morpholin-4-yl-N-(het)aryl-2-thioxoacetamides 2a-k, 6a,b

A suspension of 0.009 mol of crushed sulfur in 9 mL of morpholine was stirred for 5 minutes. A solution of 0.003 mol of the corresponding chloroacetamide 1a-k or 5a, b in 3 mL of DMF was added in portions to the formed cherry-brown solution. The reaction mixture was continued to stir for 60 minutes, and then it was poured into 100 mL of water and left for 1 day. The precipitate formed was filtered off, washed with water, dried and recrystallized from alcohol.

2-Morpholin-4-yl-N-phenyl-2-thioxoacetamide (2a). White crystals; yield 0.41g (55%); mp 168-170°C; IR (cm$^{-1}$): 3313.55 (NH), 1655.81 (C=O), 1599.88 (C=S). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 3.69$ (s, 4H, morpholine), 3.74 – 3.79 (m, 2H, morpholine), 4.07 – 4.17 (m, 2H, morpholine), 7.11 (t, $J = 7.4$ Hz, 1H, C$_6$H$_5$), 7.34 (t, $J = 7.9$ Hz, 2H, C$_6$H$_5$), 7.62 (d, $J = 7.7$ Hz, 2H, C$_6$H$_5$), 10.50 – 10.82 (br.s, 1H, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 46.94$, 52.07, 65.42, 65.96, 119.55, 124.06, 128.83, 138.10, 162.93, 191.06. LC-MS (ESI) [m/z]: [M + H]$^+$ = 251.0; [M – H]$^-$ = 249.2. Anal. Calcd. for C$_{12}$H$_{14}$N$_2$O$_2$S: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.34; H, 5.79; N, 11.24.

N-(3-Methylphenyl)-2-morpholin-4-yl-2-thioxoacetamide (2b). White crystals; yield 0.69g (87%); mp 111-112°C; IR (cm$^{-1}$): 3327.05 (NH), 1666.42 (C=O), 1615.31 (C=S). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 2.28$ (s, 1H, 2H, CH$_3$), 3.67 (s, 4H, morpholine), 3.72 – 3.79 (m, 2H,
N-(4-Methylphenyl)-2-morpholin-4-yl-2-thioxoacetamide (2c). White crystals; yield 0.63g (79%); mp 180-182°C; IR (cm⁻¹): 3274.01 (NH), 1647.13 (C=O), 1597.95 (C=S). ¹H NMR (400 MHz, DMSO-d₆): δ = 2.26 (s, 3H, CH₃), 2.48 – 2.52 (m, 4H, morpholine), 3.73 – 3.78 (m, 2H, morpholine), 4.09 – 4.15 (m, 2H, morpholine), 7.14 (d, J = 8.4 Hz, 2H, C₆H₄), 7.50 (d, J = 8.4 Hz, 2H, C₆H₄), 10.49 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ = 20.46, 46.91, 52.06, 65.43, 65.96, 119.51, 133.09, 135.59, 162.78 191.14. LC-MS (ESI) [m/z]: [M + H]⁺ = 265.0; [M – H]⁻ = 263.0. Anal. Calcd. for C₁₃H₁₆N₂O₂S: C, 59.07; H, 6.10; N, 10.60. Found: C, 59.18; H, 6.01; N, 10.49.

N-(3,4-Dimethylphenyl)-2-morpholin-4-yl-2-thioxoacetamide (2d). White crystals; yield 0.65g (78%); mp 140-142°C; IR (cm⁻¹): 3311.62 (NH), 1667.38 (C=O), 1618.2 (C=S). ¹H NMR (400 MHz, DMSO-d₆): δ = 2.17 (s, 3H, CH₃), 2.19 (s, 3H, CH₃), 3.67 (s, 4H, morpholine), 3.71 – 3.77 (m, 2H, morpholine), 4.07 – 4.14 (m, 2H, morpholine), 7.08 (d, J = 8.2 Hz, 1H, C₆H₅), 7.31 (dd, J = 8.1, 1.8 Hz, 1H, C₆H₅), 7.40 (s, 1H, C₆H₅), 10.46 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ = 18.80, 19.57, 46.90, 52.03, 65.42, 65.93, 117.09, 120.69, 129.62, 131.90, 135.78, 136.50, 162.77, 191.22. LC-MS (ESI) [m/z]: [M + H]⁺ = 279.2; [M – H]⁻ = 277.2. Anal. Calcd. for C₁₄H₁₈N₂O₂S: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.53; H, 6.43; N, 10.12.

N-(4-Fluorophenyl)-2-morpholin-4-yl-2-thioxoacetamide (2e). Yellow crystals; yield 0.52g (64%); mp 168-170°C; IR (cm⁻¹): 3254.72 (NH), 1649.06 (C=O), 1614.34 (C=S). ¹H NMR (400 MHz, DMSO-d₆): δ = 3.68 (s, 4H, morpholine), 3.71 – 3.77 (m, 2H, morpholine), 4.09 – 4.15 (m, 2H, morpholine), 7.19 (t, J = 8.9 Hz, 1H, C₆H₅), 7.64 (dd, J = 9.1, 5.0 Hz, 2H, C₆H₄), 10.71 (s, 1H). ¹³C NMR (100 MHz, DMSO-d₆): δ = 46.93, 52.08, 65.43, 65.99, 115.48 (d, J = 22.4 Hz), 121.36 (d, J = 8.0 Hz), 134.46 (d, J = 2.5 Hz), 158.44 (d, J = 240.8 Hz), 162.83, 190.82. LC-MS (ESI) [m/z]: [M + H]⁺ = 269.2; [M – H]⁻ = 267.2. Anal. Calcd. for C₁₂H₁₂FN₂O₂S: C, 53.72; H, 4.88; N, 10.44. Found: C, 53.84; H, 4.96; N, 10.31.

N-(3-Chlorophenyl)-2-morpholin-4-yl-2-thioxoacetamide (2f). White crystals; yield 0.74g (87%); mp 135-137°C; IR (cm⁻¹): 3323.19 (NH), 1670.2 (C=O), 1596.98 (C=S). ¹H NMR (400 MHz, DMSO-d₆): δ = 3.69 (s, 4H, morpholine), 3.76 (t, J = 4.9 Hz, 2H, morpholine), 4.09 – 4.15 (m, morpholine), 7.17 (dd, J = 7.8, 1.8 Hz, 1H, C₆H₄), 7.37 (t, J = 8.1 Hz, 1H, C₆H₄), 7.50 (d, J = 8.2 Hz,
1H, C₆H₅), 7.80 (t, J = 2.0 Hz, 1H, C₆H₅), 10.78 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ = 46.93, 52.11, 65.43, 66.01, 118.02, 119.03, 123.82, 130.59, 133.13, 139.52, 163.06, 190.37. LC-MS (ESI) [m/z]: [M + H]⁺ = 285.0; [M − H]⁻ = 283.0. Anal. Calcd. for C₁₂H₁₂ClN₂O₂: C, 50.61; H, 4.60; N, 8.84. Found: C, 50.70; H, 4.55; N, 9.88.

_N-(4-Chlorophenyl)-2-morpholin-4-yl-2-thioxoacetamide (2g)._ White crystals; yield 0.63g (74%); mp 184-186°C; IR (cm⁻¹): 3298.12 (NH), 1651.95 (C=O), 1604.7 (C=S). ¹H NMR (400 MHz, DMSO-d₆): δ = 3.68 (s, 4H, morpholine), 3.72 – 3.80 (m, 2H, morpholine), 4.08 – 4.15 (m, 2H, morpholine), 7.41 (d, J = 8.9 Hz, 2H, C₆H₅), 7.65 (d, J = 8.9 Hz, 2H, C₆H₅), 10.81 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ = 46.96, 52.09, 65.42, 65.98, 121.14, 127.75, 128.75, 162.93, 190.68. LC-MS (ESI) [m/z]: [M + H]⁺ = 285.0; [M − H]⁻ = 283.0. Anal. Calcd. for C₁₂H₁₂ClN₂O₂: C, 50.61; H, 4.60; N, 8.84. Found: C, 50.55; H, 4.67; N 9.79.

_N-(3,4-Dichlorophenyl)-2-morpholin-4-yl-2-thioxoacetamide (2h)._ Light yellow crystals; yield 0.88g (92%); mp 188-190°C; IR (cm⁻¹): 3331.87 (NH), 1678.95 (C=O), 1589.27 (C=S). ¹H NMR (400 MHz, DMSO-d₆): δ = 3.68 (s, 4H, morpholine), 3.72 – 3.79 (m, 2H, morpholine), 4.09 – 4.14 (m, 2H, morpholine), 7.53 (dd, J = 8.8, 2.4 Hz, 1H, C₆H₅), 7.61 (d, J = 8.8 Hz, 1H, C₆H₅), 7.99 (d, J = 2.3 Hz, 1H, C₆H₅), 10.97 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ = 46.95, 52.13, 65.43, 66.03, 119.66, 120.80, 125.66, 130.80, 131.09, 138.16, 163.03. LC-MS (ESI) [m/z]: [M + H]⁺ = 319.0. Anal. Calcd. for C₁₂H₁₂Cl₂N₂O₂S: C, 45.15; H, 3.79; N, 8.78. Found: C, 45.02; H, 3.84; N, 8.69.

_N-(4-Bromophenyl)-2-morpholin-4-yl-2-thioxoacetamide (2i)._ White crystals; yield 0.84g (85%); mp 190-192°C; IR (cm⁻¹): 3298.12 (NH), 1652.92 (C=O), 1601.8 (C=S). ¹H NMR (400 MHz, DMSO-d₆): δ = 3.67 (s, 4H, morpholine), 3.73 – 3.77 (m, 2H, morpholine), 4.08 – 4.14 (m, 2H, morpholine), 7.53 (d, J = 8.9 Hz, 2H, C₆H₅), 7.59 (d, J = 8.9 Hz, 2H, C₆H₅), 10.79 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ = 46.92, 52.10, 65.43, 65.98, 115.81, 121.45, 131.68, 137.49, 162.92, 190.55. LC-MS (ESI) [m/z]: [M + H]⁺ = 329.0. Anal. Calcd. for C₁₂H₁₂BrN₂O₂S: C, 43.78; H, 3.98; N, 8.51. Found: C, 43.72; H, 4.03; N, 8.56.

_N-[3-Chloro-4-(trifluoromethyl)phenyl]-2-morpholin-4-yl-2-thioxoacetamide (2j)._ Light yellow crystals; yield 0.96g (91%); mp 178-180°C; IR (cm⁻¹): 3325.12 (NH), 1677.99 (C=O), 1612.41 (C=S). ¹H NMR (400 MHz, DMSO-d₆): δ = 3.64 – 3.69 (m, 2H, CH₂, morpholine), 3.69 – 3.74 (m, 2H, CH₂, morpholine), 3.74 – 3.78 (m, 2H, CH₂, morpholine), 4.10 – 4.15 (m, 2H, CH₂, morpholine), 7.72 (d, J = 8.8 Hz, 1H, C₆H₅), 7.87 (dd, J = 8.8, 2.4 Hz, 1H, C₆H₅), 8.21 (d, J = 2.5 Hz, 1H, C₆H₅), 11.14 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ = 47.00, 52.15, 65.43, 66.05.
118.32 (q, J = 5.7 Hz), 122.61 (q, J = 273.1 Hz), 124.41, 124.91 (q, J = 1.7 Hz), 126.80 (q, J = 30.8 Hz), 132.24, 137.61, 163.10, 190.01. LC-MS (ESI) [m/z]: [M + H]^+ = 353.2; [M − H]^− = 351.0. Anal. Calcd. for C_{13}H_{12}ClF_{3}N_{2}O_{2}S: C, 52.19, 65.27, 65.79, 128.48, 130.21, 131.84, 134.69, 139.23, 156.50, 162.57, 189.06. LC-MS (ESI) [m/z]: [M+ H]^+ = 295.0; [M − H]^− = 293.0. Anal. Calcd. for C_{13}H_{14}N_{2}O_{4}S: C, 53.05; H, 4.79; N, 9.52. Found: C, 53.11; H, 4.70; N, 9.58.

4-[[Morpholin-4-yl(thioxo)acetyl]amino]benzoic acid (2k). White crystals; yield 0.71g (80%); mp 237-238°C; IR (cm⁻¹): 3226.75 (NH), 1720.42 (C=O), 1645.2 (C=O), 1597.95 (C=S). 1H NMR (400 MHz, DMSO-d₆): δ = 3.69 (s, 4H, CH₂, morpholine), 3.73 – 3.79 (m, 2H, morpholine), 4.09 – 4.16 (m, 2H, morpholine), 7.74 (d, J = 8.7 Hz, 2H, C₆H₄), 7.93 (d, J = 8.7 Hz, 2H, C₆H₄), 10.98 (s, 1H, NH), 12.39 – 13.16 (br. s, 1H, COOH). 13C NMR (100 MHz, DMSO-d₆): δ = 46.91, 52.13, 65.41, 65.96, 118.91, 125.94, 130.42, 142.13, 163.10, 166.76, 190.36. LC-MS (ESI) [m/z]: [M+ H]^+ = 380.0. Anal. Calcd. for C_{16}H_{16}ClN_{3}O_{4}S: C, 53.02; H, 4.22; N, 11.00. Found: 50.39; H, 4.13; N, 10.91.

N-[[4-Chlorobenzyl]-thiazol-2-y]l-2-morpholin-4-yl-2-thiooxacetamide (6a). White crystals; yield 0.96g (84%); mp 238-240°C; IR (cm⁻¹): 3173.71 (NH), 1669.31 (C=O), 1574.8 (C=S). 1H NMR (400 MHz, DMSO-d₆): δ = 3.58 (s, 2H, morpholine), 3.64 (s, 2H, CH₂), 3.73 (s, 2H, morpholine), 4.07 (s, 2H, morpholine), 4.10 (s, 2H, ArCH₂), 7.26 – 7.34 (m, 3H, thiazole, C₆H₄), 7.36 (d, J = 8.2 Hz, 2H, C₆H₄), 12.65 (s, 1H, NH). 13C NMR (100 MHz, DMSO-d₆): δ = 30.87, 46.91, 52.19, 65.27, 65.79, 128.48, 130.21, 131.84, 134.69, 139.23, 156.50, 162.57, 189.06. LC-MS (ESI) [m/z]: [M+ H]^+ = 382.0; [M − H]^− = 380.0. Anal. Calcd. for C_{16}H_{16}ClN_{3}O_{2}S_{2}: C, 50.32; H, 4.22; N, 11.00. Found: 50.39; H, 4.13; N, 10.91.

N-[[4-Bromobenzyl]-thiazol-2-y]l-2-morpholin-4-yl-2-thiooxacetamide (6b). White crystals; yield 1.22g (95%); mp 231-233°C; IR (cm⁻¹): 3171.79 (NH), 1670.27 (C=O), 1573.84 (C=S). 1H NMR (400 MHz, DMSO-d₆): δ = 3.57 (c, 2H, morpholine), 3.64 (d, J = 3.2 Hz, 2H, morpholine), 3.73 (s, 2H, morpholine), 4.08 (s, 2H, morpholine), 4.09 (s, 2H, ArCH₂), 7.17 – 7.27 (d, J = 8.3 Hz, 2H, C₆H₄), 7.33 (s, 1H, thiazole), 7.46 – 7.57 (d, J = 8.4 Hz, 2H, C₆H₄), 12.52 – 12.78 (br.s, 1H, NH). 13C NMR (100 MHz, DMSO-d₆): δ = 31.20, 46.91, 52.19, 65.27, 65.79, 119.56, 130.60, 131.41, 131.76, 139.62, 189.06. LC-MS (ESI) [m/z]: [M+ H]^+ = 426.0; [M − H]^− = 424.0. Anal. Calcd. for C_{16}H_{16}BrN_{3}O_{2}S_{2}: C, 45.07; H, 3.78; N, 9.86. Found: C, 45.18; H, 3.84; N, 9.78.

The general procedure for the preperation 1,4,5,6-tetrahydropyrimidine-2-carboxamides 3a-k, 7a,b

4 mL of 1,3-diaminopropane were added to 0.0015 mol of the corresponding morpholin-4-yl-N-(het)aryl-2-thiooxacetamide 2a-k or 6a, b and stirred for 5 minutes at room temperature. The resulting solution was heated to 50°C and continued stirring for 40-50 minutes at that temperature.
Then, it was cooled, poured into 30 mL of water and left for 1 day. The precipitate was filtered off, washed with water, dried and recrystallized from alcohol (3k, 7a, b) or diluted alcohol (3a-j).

**N-Phenyl-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3a).** White crystals; yield 0.27g (89%); mp 131-133°C; IR (cm⁻¹): 3266.29 (NH), 1673.17 (C=O), 1629.77 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ = 1.57 – 1.88 (m, 2H, CH₂), 3.32 (t, J = 5.6 Hz, 4H, CH₂), 7.08 (t, J = 7.4 Hz, 1H, C₆H₅), 7.32 (t, J = 7.9 Hz, 2H, C₆H₅), 7.76 (d, J = 8.3 Hz, 2H, C₆H₅). ¹³C NMR (100 MHz, DMSO-d₆): δ = 19.76, 40.91, 119.74, 123.70, 128.63, 137.92, 147.98, 159.91. LC-MS (ESI) [m/z]: [M + H]⁺ = 204.2. Anal. Calcd. for C₁₂H₁₃N₃O: C, 65.01; H, 6.45; N, 20.67. Found: C, 65.12; H, 6.49; N, 20.74.

**N-(3-Methylphenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3b).** White crystals; yield 0.23g (71%); mp 115-117°C; IR (cm⁻¹): 3374.3 (NH), 1671.24 (C=O), 1631.7 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ = 1.61 – 1.70 (m, 2H, CH₂), 2.50 (s, 3H, CH₃), 3.32 (t, J = 5.6 Hz, 4H, 2CH₂), 6.90 (d, J = 7.4 Hz, 1H, C₆H₅), 7.19 (t, J = 7.8 Hz, 1H, C₆H₅), 7.53 (d, J= 8.2 Hz, 1H, C₆H₅), 7.59 (s, 1H, C₆H₅). ¹³C NMR (100 MHz, DMSO-d₆): δ = 19.74, 21.15, 40.92, 116.84, 120.14, 124.42, 128.50, 137.77, 137.88, 147.94, 159.78. LC-MS (ESI) [m/z]: [M + H]⁺ = 218.2. Anal. Calcd. for C₁₂H₁₅N₃O: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.44; H, 7.05; N, 19.27.

**N-(4-Methylphenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3c).** White crystals; yield 0.31g (95%); mp 137-139°C; IR (cm⁻¹): 3357.91 (NH), 1689.56 (C=O), 1636.52 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ = 1.59 – 1.70 (m, 2H, CH₂), 2.25 (s, 3H, CH₃), 3.31 (t, J = 5.6 Hz, 4H, 2CH₂), 7.11 (d, J = 8.3 Hz, 2H, C₆H₅), 7.63 (d, J = 8.3 Hz, 2H, C₆H₅). ¹³C NMR (100 MHz, DMSO-d₆): δ = 19.76, 20.43, 40.86, 119.66, 129.03, 132.69, 135.40, 147.98, 159.72. LC-MS (ESI) [m/z]: [M + H]⁺ = 218.2. Anal. Calcd. for C₁₂H₁₅N₃O: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.25; H, 7.01; N, 19.42.

**N-(3,4-dimethylphenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3d).** White crystals; yield 0.33g (94%); mp 129-131°C; IR (cm⁻¹): 3279.79 (NH), 1673.17 (C=O), 1632.66 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ = 1.48 – 1.83 (m, 2H, CH₂), 2.16 (s, 3H, CH₃), 2.18 (s, 3H, CH₃), 3.31 (t, J = 5.6 Hz, 4H, 2CH₂), 7.06 (d, J = 8.2 Hz, 1H, C₆H₅), 7.46 (d, J = 8.1 Hz, 1H, C₆H₅), 7.51 (s, 1H, C₆H₅). ¹³C NMR (100 MHz, DMSO-d₆): δ = 18.73, 19.54, 19.75, 40.87, 117.06, 120.76, 129.52, 131.57, 135.50, 136.32, 148.00, 159.56. LC-MS (ESI) [m/z]: [M + H]⁺ = 232.2. Anal. Calcd. for C₁₃H₁₇N₃O: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.63; H, 7.32; N, 18.29.

**N-(4-fluorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3e).** White crystals; yield 0.29g (88%); mp 116-117°C; IR (cm⁻¹): 3252.79 (NH), 1677.99 (C=O), 1632.66 (C=N). ¹H

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NMR (400 MHz, DMSO-d₆): δ = 1.52 – 1.73 (m, 2H, CH₂), 3.32 (t, J = 5.6 Hz, 4H, CH₂), 7.15 (t, J = 8.9 Hz, 2H, C₆H₄), 7.79 (dd, J = 8.6, 5.2 Hz, 2H, C₆H₄), 8.69 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ = 19.74, 40.88, 115.14 (d, J = 22.2 Hz), 121.69 (d, J = 7.8 Hz), 134.55 (d, J = 2.5 Hz), 147.99, 158.25 (d, J = 240.4 Hz), 159.92. LC-MS (ESI) [m/z]: [M + H]⁺ = 222.2. Anal. Calcd. for C₁₁H₁₂FN₃O: C, 59.72; H, 5.47; N, 18.99. Found: C, 59.85; H, 5.41; N, 19.12.

N-(3-Chlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3f). White crystals; yield 0.34g (96%); mp 118-119°C; IR (cm⁻¹): 3375.27 (NH), 1675.1 (C=O), 1635.56 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ = 1.52 – 1.85 (m, 2H, CH₂), 3.32 (t, J = 5.6 Hz, 4H, CH₂), 7.12 (d, J = 8.0 Hz, 1H, C₆H₄), 7.33 (t, J = 8.1 Hz, 1H, C₆H₄), 7.71 (d, J = 8.3 Hz, 1H, C₆H₄), 7.96 (s, 1H, C₆H₄), 8.84 (br.s, 1H). ¹³C NMR (100 MHz, DMSO-d₆): δ = 19.64, 40.48, 118.59, 119.52, 123.23, 130.19, 132.91, 140.09, 148.20, 160.05. LC-MS (ESI) [m/z]: [M + H]⁺ = 238.0. Anal. Calcd. for C₁₁H₁₂ClN₃O: C, 55.59; H, 5.09; N, 17.68. Found: C, 55.54; H, 5.03; N, 17.73.

N-(4-Chlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3g). White crystals; yield 0.35g (98%); mp 158-159°C; IR (cm⁻¹): 3358.87 (NH), 1690.53 (C=O), 1637.49 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ = 1.58 – 1.78 (m, 2H, CH₂), 3.33 (t, J = 5.7 Hz, 4H, CH₂), 7.36 (d, J = 8.9 Hz, 2H, C₆H₄), 7.80 (d, J = 8.9 Hz, 2H, C₆H₄), 8.90 (br.s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ = 19.68, 40.84, 121.54, 127.26, 128.46, 137.27, 148.04, 160.02. LC-MS (ESI) [m/z]: [M + H]⁺ = 238.0. Anal. Calcd. for C₁₁H₁₂ClN₃O: C, 55.59; H, 5.09; N, 17.68. Found: C, 55.54; H, 5.11; N, 17.63.

N-(3,4-Dichlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3h). White crystals; yield 0.39g (96%); mp 161-163°C; IR (cm⁻¹): 3370.44 (NH), 1698.24 (C=O), 1643.27 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ = 1.52 – 1.85 (m, 2H, CH₂), 3.32 (t, J = 5.6 Hz, 4H, CH₂), 7.12 (d, J = 8.0 Hz, 1H, C₆H₄), 7.33 (t, J = 8.1 Hz, 1H, C₆H₄), 7.71 (d, J = 8.3 Hz, 1H, C₆H₄), 7.96 (s, 1H, C₆H₄), 8.84 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ = 19.30, 40.39, 120.79, 121.78, 124.59, 130.31, 130.68, 140.21, 149.20, 159.45. LC-MS (ESI) [m/z]: [M + H]⁺ = 272.0. Anal. Calcd. for C₁₁H₁₁Cl₂N₃O: C, 48.55; H, 4.07; N, 15.44. Found: C, 48.64; H, 3.97; N, 15.30.

N-(4-Bromophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3i). White crystals; yield 0.35g (83%); mp 157-158°C; IR (cm⁻¹): 3357.91 (NH), 1692.45 (C=O), 1636.52 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ = 1.52 – 1.77 (m, 2H, CH₂), 3.31 (t, J = 5.6 Hz, 4H, 2 CH₂), 7.49 (d, J = 8.8 Hz, 2H, C₆H₄), 7.76 (d, J = 8.8 Hz, 2H, C₆H₄), 8.80 (br.s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ = 19.67, 40.82, 115.35, 121.94, 131.37, 137.72, 148.08, 160.02. LC-MS (ESI) [m/z]:

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[M + H]^+ = 284.0. Anal. Calcd. for C_{11}H_{12}BrN_3O: C, 46.83; H, 4.29; N, 14.89. Found: C, 46.89; H, 4.33; N, 14.94.

**N-[4-chloro-3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydropyrimidine-2-carboxamide** (3j). White crystals; yield 0.40g (88%); mp 141-143°C; IR (cm\(^{-1}\)) 3286.34 (NH), 1684.74 (C=O), 1634.59 (C=N). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta = 1.65 - 1.81\) (m, 2H, CH\(_2\)), 3.34 (t, J = 5.7 Hz, 4H, CH\(_2\)), 7.61 (d, J = 8.8 Hz, 1H, C\(_6\)H\(_5\)), 8.03 (dd, J = 8.8, 2.4 Hz, 1H, C\(_6\)H\(_5\)), 8.34 (d, J = 2.4 Hz, 1H, C\(_6\)H\(_5\)), 8.81 – 9.36 (br.s, 1H, NH). \(^13\)C NMR (100 MHz, DMSO-d\(_6\)): \(\delta = 19.25, 40.26, 119.74\) (q, J = 5.6 Hz), 122.82 (q, J = 273.0 Hz), 123.41 (q, J = 1.8 Hz), 125.71, 126.43 (q, J = 30.7 Hz), 131.62, 140.52, 149.71, 159.38. LC-MS (ESI) [m/z]: [M + H]^+ = 306.0. Anal. Calcd. for C\(_{12}\)H\(_{11}\)ClF\(_3\)N\(_3\)O: C, 47.15; H, 3.63; N, 13.75. Found: C, 47.24; H, 3.56; N, 13.64.

**4-[(1,4,5,6-Tetrahydropyrimidin-2-ylcarbonyl)amino]benzoic acid** (3k). White crystals; yield 0.36g (96%); mp > 260°C; IR (cm\(^{-1}\)) 3410.95 (OH), 3303.9 (NH), 1708.85 (C=O), 1666.42 (C=O), 1608.56 (C=N). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta = 1.93\) (s, 2H, CH\(_2\)), 3.50 (s, 4H, 2CH\(_2\)), 7.36 (d, J = 7.6 Hz, 2H, C\(_6\)H\(_4\)), 7.80 (d, J = 7.6 Hz, 2H, C\(_6\)H\(_4\)), 11.45 – 11.52 (br.s, 1H, COOH). \(^13\)C NMR (100 MHz, DMSO-d\(_6\)): \(\delta = 16.87, 38.36, 119.91, 127.22, 130.34, 141.02, 152.02, 154.55, 166.63. LC-MS (ESI) [m/z]: [M + H]^+ = 248.2; [M − H]− = 246.0. Anal. Calcd. for C\(_{12}\)H\(_{13}\)N\(_3\)O: C, 58.29, H 5.30, N 16.99; Found C 58.36, H 5.27, N 16.91.

**N-[5-(4-Chlorobenzyl)-1,3-thiazol-2-yl]-1,4,5,6-tetrahydropyrimidine-2-carboxamide** (7a). Light yellow crystals; yield 0.42g (84%); mp 252-254°C; IR (cm\(^{-1}\)) 3161.18 (NH), 1667.38 (C=O), 1567.09 (C=N). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta = 1.83\) (s, 2H, CH\(_2\)), 3.35 (s, 4H, 2CH\(_2\)), 4.01 (s, 2H, ArCH\(_2\)), 7.12 (s, 1H, thiazole), 7.26 (d, J = 8.2 Hz, 2H, C\(_6\)H\(_4\)), 7.34(d, J = 8.2 Hz, 2H, C\(_6\)H\(_4\)), 9.50 (s, 1H, NH). \(^13\)C NMR (100 MHz, DMSO-d\(_6\)): \(\delta = 17.64, 32.21, 38.15, 128.24, 128.90, 130.16, 130.64, 135.27, 140.03, 155.27, 156.25, 167.88. LC-MS (ESI) [m/z]: [M + H]^+ = 335.0. Anal. Calcd. for C\(_{15}\)H\(_{13}\)ClN\(_2\)OS: C, 53.81; H, 4.52; N, 16.73. Found: C, 53.93; H, 4.46; N, 16.79.

**N-[5-(4-Bromobenzyl)-1,3-thiazol-2-yl]-1,4,5,6-tetrahydropyrimidine-2-carboxamide** (7b). Light yellow crystals; yield 0.48g (85%); mp 243-245°C; IR (cm\(^{-1}\)) 3162.14 (NH), 1667.38 (C=O), 1567.09 (C=N). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta = 1.83\) (s, 2H, CH\(_2\)), 3.35 (s, 4H, 2CH\(_2\)), 4.00 (s, 1H), 7.11(s, 1H, thiazole), 7.20 (d, J = 8.4 Hz, 2H, C\(_6\)H\(_4\)), 7.48 (d, J = 8.4 Hz, 2H, C\(_6\)H\(_4\)), 9.45 (s, 1H, NH). \(^13\)C NMR (100 MHz, DMSO-d\(_6\)): \(\delta = 17.64, 32.27, 38.15, 119.09, 128.81, 130.56, 131.16, 135.33, 140.47, 155.27, 156.25, 167.89. LC-MS (ESI) [m/z]: [M + H]^+ = 379.0. Anal. Calcd. for C\(_{15}\)H\(_{13}\)BrN\(_4\)OS: C, 47.50; H, 3.99; N, 4.77. Found: C, 47.41; H, 4.04; N, 4.84.

**Biological activity**

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The effect of the synthesized substances on the course of the exudative phase of the inflammatory process was studied on the basis of the carrageenan model of the paw edema of non-linear heterosexual white rats weighing 220-250 g, against the background of the reference anti-inflammatory drug Diclofenac. The animals were divided into 14 groups, five rats each. One group was kept as a control, and the remaining 13 (test groups) were used to determine the anti-inflammatory activity exhibited by Diclofenac and another 12 test substances. Before the experiment, the rats were kept in an animal shelter under standard lighting and temperature conditions, on a standard diet. The reference anti-inflammatory drug Diclofenac, at a therapeutic dose of 10 mg/kg, and the test substances, at a dose of 50 mg/kg body weight, were administered intraperitoneally to the animals of only test groups in the form of a suspension with tween 80. Thirty minutes later, all animals were caused edema by introducing 0.1 mL of a 2% solution of carrageenin in saline solution into aseptic conditions under the aponeurosis of the sole of the right hind limb of the rats. The presence of an inflammatory reaction among the animals of the control and test groups was established by measuring the volume of their limbs by the oncometric method at the beginning of the experiment and 4 hours after the administration of the phlogogenic agent. The inhibition of the inflammatory reaction was determined by the degree of reduction of limb edema among the animals of the test groups in comparison with the control one. It was calculated according to equation (1.1).

\[
\% \text{ Inhibition} = \frac{V_{\text{control}} - V}{V_{\text{control}}} \times 100\% \quad (1.1)
\]

where \(V_{\text{control}}\) is the increase in paw volume in the control group animals; \(V\) is the increase in paw volume in animals injected with the test substances.

**Molecular Docking Studies**

**Ligand preparation:**

Prior to molecular docking, the structures of all test compounds 1-14 were optimized in the semi-empirical PM3 method\(^{54}\) using the ArgusLab 4.0.1 software package.\(^{55-64}\)

**Protein preparation:**

We used a number of different crystal structures of the COX-1 and COX-2 enzymes from LC-MS for molecular docking studies. The best correlation between biological test results and calculated values was observed for structures 1EQG\(^{65}\) and 1CX2.\(^{66}\) Three-dimensional crystal structures of COX-1 enzyme cocrystallization and Ibuprofen (PDB ID: 1EQG), as well as COX-2 enzyme cocrystallization and inhibitor (S58) 4-(5-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-
1-yl) benzenesulfonamide (PDB ID: 1CX2), were downloaded in PDB format from the protein molecule database (http://www.rcsb.org). Before docking, the molecules of all non-protein components, except for these inhibitors and hemes, were removed. Water molecules were also removed from the binding site.

**Molecular docking procedure:**

Ligand groups with the name Ligand_X-ray were created based on Ibuprofen molecule (COX-1 enzyme), the code in the cocrystallizate 701 IBP, and the molecule of 4-(5-(4-bromophenyl)-3-( trifluoromethyl)-1H-pyrazol-1-yl) benzenesulfonamide (S58) (COX-2 enzyme), the code in cocrystallizate 2238 S58. Based on these groups, three-dimensional models of binding sites were created, the dimensions of which were calculated automatically and were for the enzyme COX-1 along the X axis - 17.098000, the Y axis - 14.533000 and the Z axis - 18.345000 Å and for the enzyme COX-2 along the X axis - 23.613000, the Y axis - 19.421000 and the Z axis - 23.120000 Å, respectively. The docking was performed with a flexible ligand. The semi-empirical AScore function (based on the XScore function was used to calculate the scores. The lattice pitch was set at 0.250 Å. Type of calculation - Dock; Docking Engine - ArgusLab. Visualization of the results was performed using the program PyMOL 0.99rc6.

**Results and Discussion**

The starting materials for the synthesis of the target 1,4,5,6-tetrahydropyrimidine-2-carboxamides were 2-morpholin-4-yl-N-(het)aryl-2-thioxoacetamides 2a-k, which were obtained by the interaction of chloroacetanilides 1a-k with sulfur and morpholine by the method described in. Their characteristics and 1H NMR spectroscopy data are given in the experimental part.

We studied the interaction of morpholin-4-yl-N-(het)aryl-2-thioxoacetamides 2a-k with 1,3-diaminopropane. It was found that heating at a temperature of 50-70°C for 40-50 minutes in 1,3-diaminopropane medium was required for the successful interaction. N-aryl-1,4,5,6-tetrahydropyrimidine-2-carboxamides 3a-k were isolated as a result of the reaction with yields of 71-98%.

The 1H NMR spectrum of the resulting product 3a-k was in agreement with the given structure. In particular, the protons of the CH₂ group in the 5th position of the pyrimidine cycle appeared at 1.57-1.93 ppm, and the protons of the CH₂ groups in the 4th and 6th positions - at 3.32-3.50 ppm.
We also developed a method for the synthesis of \( N-[5-(4-R-benzyl)-1,3\text{-thiazol-2-yl}]-1,4,5,6\text{-tetrahydropyrimidine-2-carboxamides} \ 7a, b. \) 5-(4-R-benzyl) thiazol-2-ylamines \( 4a, b \), which were obtained by the method described in.\textsuperscript{70} were used as starting reagents in this transformation. By acylation of \( 4a, b \) with chloroacetyl chloride, the corresponding chloroacetamides \( 5a, b \) were formed,\textsuperscript{71} which upon interaction with sulfur and morpholine were converted to \( N-[5-(4-R-benzyl)\text{-thiazol-2-yl}]-2\text{-morpholin-4-yl-2-thioxoacetamides} \ 6a, b. \) By the reaction \( 6a, b \) with 1,3-diaminopropane according to the above procedure, \( N-[5-(4-R-benzyl)-1,3\text{-thiazol-2-yl}]-1,4,5,6\text{-tetrahydropyrimidine-2-carboxamides} \ 7a, b \) were obtained.

The effect of synthesized substances on the course of the exudative phase of the inflammatory process was studied on the basis of the carrageenan model of the paw edema of non-linear heterosexual white rats.

The results of the study of anti-inflammatory activity are shown in Table 1. It was found that the test substances showed different levels of activity. The most active compounds were \( 3g \) and \( 3j \). Their effect was superior to the reference drug Diclofenac. An effect commensurate with this drug was observed in compounds \( 3d, 3f, 3h, 7a \). At the same time, the antiexudative activity of the remaining compounds was somewhat lower than the standard. An analysis of the data allowed us to draw some conclusions regarding the patterns of “the structure – action” relationship in a series of synthesized compounds. The introduction of substituents, both electron-donating and electron-withdrawing, in the aromatic nucleus always led to an increase in antiexudative activity, in comparison with basic phenylamide \( 3a \). Comparative characterization of the effect of electron-donating methyl substituents in aromatics (compounds \( 3b-d \)) was in favor of disubstituted \( 3d \) relative to monosubstituted analogues \( 3b, c \). The transition from electron-donating to electron-withdrawing substituents (halogen atoms), with rare exceptions (bromine derivative \( 3i \)), was accompanied by an increase in activity. This was especially pronounced in the case of chlorine-substituted \( 3f, g \) and the asymmetric dihalogen derivative \( 3j \). It should also be noted that in general, chloro derivatives \( (3f-h) \) were preferable to fluoro and especially bromo derivatives \( (3e, i) \).

The ability of substances to show anti-inflammatory activity is usually associated with the inhibition of COX-1 and COX-2 enzymes, with which we conducted molecular docking studies. The results of the molecular docking were in good agreement with the experimental data (Table 1, Fig. 1), \( R^2 > 0.92 \) and 0.83 for COX-1 and COX-2, respectively. Most likely, compounds \( 3a-k \) and \( 7a, b \) inhibited the activity of both enzymes. According to the results of the molecular docking, the most stable complexes with active sites of both enzymes formed compounds \( N-(4\text{-chlorophenyl})-1,4,5,6-\)tetrahydropyrimidine-2-carboxamides.
tetrahydropyrimidine-2-carboxamide (3g) and N-[4-chloro-3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3j) (Fig. 2). Compounds 3g and 3j were superior to the reference drug Diclofenac in the strength of complexes formed with COX-1 and COX-2 (see Table 1).

\[ N-(4-Chlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide \] (3g) was further fixed in the active site of the enzyme COX-1 due to the formation of an intermolecular hydrogen bond between the oxygen atom of the amide group and the hydroxyl group of the amino acid Tyr 355, the bond length -NHC=O...HO (Tyr 355) was 2.9 Å (Fig. 2a). In turn, in the active site of COX-2, this compound was additionally fixed due to the formation of two hydrogen bonds with a length of about 3.0 Å, which were formed between the amide group and the peptide bonds of amino acids Val 523 and Ala 527 (Fig. 2b).

\[ N-[4-Chloro-3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydropyrimidine-2-carboxamide \] (3j) was additionally fixed in the active sites of the enzymes COX-1 and COX-2 due to the formation of hydrogen bonds with the hydroxyl group of the amino acid Tyr 355. In the case of COX-1, the hydrogen bond formed a Nitrogen atom of the pyrimidine ring, the bond length N...HO (Tyr 355) was 2.7 Å (Fig. 2c), and in the case of COX-2 — a Nitrogen atom of the amide group, the bond length of NH...HO (Tyr 355) was 2.8 Å (Fig. 2d).

It is noteworthy that for \( N-(3-chlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide \) (3f), the energies of complexes with the enzymes COX-1 and COX-2 were practically equal and amounted to about 11.0 kcal/mol. Most likely, this compound could equally inhibit both enzymes.

**Conclusion**

This work studied the synthesis of new 1,4,5,6-tetrahydropyrimidine-2-carboxamides based on the reaction of 2-morpholin-4-yl-N-(het)aryl-2-thioacacetamides with 1,3-diaminopropane. The target products were obtained with yields of 71-98% and easily isolated from the reaction mixture. All synthesized 1,4,5,6-tetrahydropyrimidine-2-carboxamides were tested for effects on the exudative phase of the inflammatory process based on the carrageenan model of paw edema of laboratory nonlinear heterosexual white rats weighing 220-250 g, using Diclofenac as a reference. The best anti-inflammatory activity was found in \( N-(4-chlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide \) and \( N-[4-chloro-3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydropyrimidine-2-carboxamide \), suppression of the inflammatory response was 46.7 and 46.4%, respectively. The ability of the synthesized compounds to exhibit anti-inflammatory activity was most likely related to the inhibition of COX-1 and COX-2 enzymes with which molecular docking studies had been performed. The
results of the molecular docking are in good agreement with the experimental data, $R^2 > 0.92$ and 0.83 for COX-1 and COX-2, respectively.

**Compliance with ethical standards.**

**Ethical approval.** All animal experiments were conducted in keeping with European Convention on Protection of Vertebrate Animals (Strasbourg 1986) and the corresponding Law of Ukraine (N944, 14.12.2009). Structure of this study and experimental procedures were approved by the Ethics Committee of Lviv National Medical University (N2, 16.02.2015).

This article does not contain any studies with human participants performed by any of the authors.

**Conflict of interest.**
The authors declare that they have no conflict of interest.

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Scheme 1. Synthesis of \(N\)-aryl-1,4,5,6-tetrahydropyrimidine-2-carboxamides 3a-k

1-3: \(R = H(a), 3-\text{CH}_3(b), 4-\text{CH}_3(c), 3,4-(\text{CH}_3)_2(d), 4-\text{F(e)}, 3-\text{Cl(f)}, 4-\text{Cl(g)}, 3,4-\text{Cl}_2(h), 4-\text{Br(i)}, 3-\text{CF}_3-4-\text{Cl(j)}, 4-\text{COOH(k)}\)
Scheme 2. Synthesis of N-het-1,4,5,6-tetrahydropyrimidine-2-carboxamides 7a,b

4-7: R = Cl(a), Br(b).
Fig. 1. a) linear correlation between the binding energy (kcal/mol) with COX-1 and the rate of suppression of the inflammatory response (%); b) linear correlation between the binding energy (kcal/mol) of COX-2 and the rate of suppression of the inflammatory response (%).
**Fig. 2.** Position of molecules of hit compounds in the active sites of COX according to the results of the molecular docking: a) N-(4-chlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3g) in the active site of the enzyme COX-1; b) N-(4-chlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3g) in the active site of the enzyme COX-2; c) N-[4-chloro-3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3j) in the active site of the enzyme COX-1; d) N-[4-chloro-3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydropyrimidine-2-carboxamide (3j) in the active site of the enzyme COX-2. Heme is shown in pink.

**Table 1** Results of anti-inflammatory activity and molecular docking study of N-aryl-1,4,5,6-tetrahydropyrimidine-2-carboxamides 3a-k and N-het-1,4,5,6-tetrahydropyrimidine-2-carboxamides 7a,b

| Comp. | Structure | Inhibition of the inflammatory response, % | ArgusLab 4.01 ∆G, kcal/mol |
|-------|-----------|------------------------------------------|-----------------------------|
|       |           |                                          | COX-1 | COX-2 |
| 3a    | ![Structure](as.png) | 12.9                                     | -8.2  | -9.0   |
| Comp. | Structure | Inhibition of the inflammatory response, % | ArgusLab 4.01 \( \Delta G \), kcal/mol |
|-------|-----------|----------------------------------------|----------------------------------------|
|       |           |                                        | COX-1                  | COX-2                  |
| 3b    | ![Structure](image) | 30.2                                    | -10.1                   | -9.7                   |
| 3c    | ![Structure](image) | 15.9                                    | -9.1                    | -9.2                   |
| 3d    | ![Structure](image) | 38.2                                    | -10.8                   | -10.4                  |
| 3e    | ![Structure](image) | 26.4                                    | -9.4                    | -9.5                   |
| 3f    | ![Structure](image) | 41.8                                    | -11.0                   | -11.0                  |
| 3g    | ![Structure](image) | 46.7                                    | -11.7                   | -11.2                  |
| 3h    | ![Structure](image) | 36.0                                    | -9.8                    | -10.7                  |
| 3i    | ![Structure](image) | 8.6                                     | -7.3                    | -9.2                   |
| 3j    | ![Structure](image) | 46.4                                    | -11.6                   | -11.5                  |
| 3k    | ![Structure](image) | 25.2                                    | -8.7                    | -9.4                   |
| Comp. | Structure | Inhibition of the inflammatory response, % | ArgusLab 4.01 $\Delta G$, kcal/mol |
|-------|-----------|------------------------------------------|-----------------------------------|
|       |           |                                          | COX-1 | COX-2 |
| 7a    | ![Structure 7a](image) | 37.5 | -10.7 | -10.6 |
| 7b    | ![Structure 7b](image) | 29.3 | -10.4 | -11.0 |
| Diclofenac | ![Structure Diclofenac](image) | 43.6 | -10.8 | -11.1 |
Graphical abstract

The carrageenan model of the paw edema white rats

Molecular docking with COX-1 and COX-2

hit compounds