Pharmaceutical Sciences, 2021, 27(3), 353-365
doi:10.34172/PS.2020.100
https://ps.tbzmed.ac.ir/

Research Article

Synthesis, Anti-Inflammatory Activity and Molecular Docking Studies of 1,4,5,6-Tetrahydropyrimidine-2-Carboxamides

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Article Info

Article History:
Received: 26 September 2020
Accepted: 18 December 2020
ePublished: 18 December 2020

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

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 vivo* 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.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the world.[1] 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.[2,3] COX-1[4,5] and COX-2[6] 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,[7] while COX-2 is an inducible enzyme, that is, it begins to function in certain situations.[7]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.[8] 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,[9] as well as synthetic derivatives of azepine,[10] benzimidazole,[11,12] triazole,[13-15] 1,3,4-oxadiazole,[16-20] xanthone,[21] coumarin,[22-24] quinazoline,[25,26] pyrrolidinone,[27,28] pyrrolisine,[29] pyrazole,[30-32] 1,3-thiazole,[33] pyridazine,[34] and other cyclic and acyclic systems.[35] Recently, pyrimidine derivatives have been of increasing interest as potential COX inhibitors.[36] Usually, they exhibit anti-inflammatory and analgesic activity *in vivo*,[37-46] and also give good results in *in silico* studies.[47,48] 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

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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,[49,50] exhibit antimicrobial[51,52] and anti-inflammatory properties.[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.

Materials and Methods

Materials

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 determinated 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.

Methods

The general procedure for the preperation of 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): δ = 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_6H_5), 7.34 (t, J = 7.9 Hz, 2H, C_6H_5), 7.62 (d, J = 7.7 Hz, 2H, C_6H_5), 10.50 – 10.82 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 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 $C_{12}H_{14}N_2O_2S$: 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): δ = 2.28 (s, 1H, 2H, CH_3), 3.67 (s, 4H, morpholine), 3.72 – 3.79 (m, 2H, morpholine), 4.08 – 4.15 (m, 2H, morpholine), 6.93 (d, J = 7.5 Hz, 1H, C_6H_4), 7.21 (t, J = 7.8 Hz, 1H, C_6H_4), 7.38 (d, J = 8.2 Hz, 1H, C_6H_4), 7.47 (s, 1H, C_6H_4), 10.55 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.14, 46.90, 52.06, 65.42, 65.94, 116.76, 120.02, 124.75, 128.67, 138.01, 138.11, 162.92, 191.05. LC-MS (ESI) [m/z]: $[M + H]^+$ = 265.0; $[M - H]^-$ = 263.0. Anal. Calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60. Found: C, 59.18; H, 6.01; N, 10.49.

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). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.26 (s, 3H, CH_3), 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, C_6H_4), 7.50 (d, J = 8.4 Hz, 2H, C_6H_4), 10.49 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60. Found: C, 59.01; H, 6.17; N, 10.51.

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). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.17 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 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, C_6H_3), 7.31 (dd, J = 8.1, 1.8 Hz, 1H, C_6H_3), 7.40 (s, 1H, C_6H_3), 10.46 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{14}H_{18}N_2O_2S$: 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). ^{1}H NMR (400 MHz, DMSO-d_6): 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, C_6H_4), 7.64 (dd, J = 9.1, 5.0 Hz, 2H, C_6H_4), 10.71 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{12}H_{13}FN_2O_2S$: 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-d_6): 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, C_6H_4), 7.37 (t, J = 8.1 Hz, 1H, C_6H_4), 7.50 (d, J = 8.2 Hz, 1H, C_6H_4), 7.80 (t, J = 2.0 Hz, 1H, C_6H_4), 10.78 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{12}H_{13}ClN_2O_2S$: C, 50.61; H, 4.60; N, 9.84. 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-d_6): 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, C_6H_4), 7.65 (d, J = 8.9 Hz, 2H, C_6H_4), 10.81 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{12}H_{13}ClN_2O_2S$: C, 50.61; H, 4.60; N, 9.84. 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-d_6): 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, C_6H_3), 7.61 (d, J = 8.8 Hz, 1H, C_6H_3), 7.99 (d, J = 2.3 Hz, 1H, C_6H_3), 10.97 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{12}H_{12}Cl_2N_2O_2S$: 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-d_6): 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, C_6H_4), 7.59 (d, J = 8.9 Hz, 2H, C_6H_4), 10.79 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{12}H_{13}BrN_2O_2S$: 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-d_6): δ = 3.64 – 3.69 (m, 2H, CH_2, morpholine), 3.69 – 3.74 (m, 2H, CH_2, morpholine), 3.74 – 3.78 (m, 2H, CH_2, morpholine), 4.10 – 4.15 (m, 2H, CH_2, morpholine), 7.72 (d, J = 8.8 Hz, 1H, C_6H_3), 7.87 (dd, J = 8.8, 2.4 Hz, 1H, C_6H_3), 8.21 (d, J = 2.5 Hz, 1H, C_6H_3), 11.14 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{13}H_{12}ClF_3N_2O_2S$: C, 44.26; H, 3.43; N, 7.94. Found: C, 44.33; H, 3.31; N 8.02.

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-d_6): δ = 3.69 (s, 4H, CH_2, morpholine). 3.73 – 3.79 (m, 2H, morpholine), 4.09 – 4.16 (m, 2H, morpholine), 7.74 (d, J = 8.7 Hz, 2H, C_6H_4), 7.93 (d, J = 8.7 Hz, 2H, C_6H_4), 10.98 (s, 1H, NH), 12.39 – 13.16 (br. s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): 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]: $[M+ H]^+$ = 295.0; $[M - H]^-$ = 293.0. Anal. Calcd. for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; N, 9.52. Found: C, 53.11; H, 4.70; N, 9.58.

N-[5-(4-Chlorobenzyl)-thiazol-2-yl]-2-morpholin-4-yl-2-thioxoacetamide (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-d_6): δ = 3.58 (s, 2H, morpholine), 3.64 (s, 2H, CH_2), 3.73 (s, 2H, morpholine), 4.07 (s, 2H, morpholine), 4.10 (s, 2H, $ArCH_2$), 7.26 – 7.34 (m, 3H, thiazole, C_6H_4), 7.36 (d, J = 8.2 Hz, 2H, C_6H_4), 12.65 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{16}H_{16}ClN_3O_2S_2$: C, 50.32; H, 4.22; N, 11.00. Found: 50.39; H, 4.13; N, 10.91.

N-[5-(4-Bromobenzyl)-thiazol-2-yl]-2-morpholin-4-yl-2-thioxoacetamide (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-d_6) 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, $ArCH_2$), 7.17 – 7.27 (d, J = 8.3 Hz, 2H, C_6H_4), 7.33 (s, 1H, thiazole), 7.46 – 7.57 (d, J = 8.4 Hz, 2H, C_6H_4), 12.52 – 12.78 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{16}H_{16}BrN_3O_2S_2$: 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 of 1,4,5,6-tetrahydropyrimidine-2-carboxamides 3a-k, 7a,b

Four mL of 1,3-diaminopropane were added to 0.0015 mol of the corresponding morpholin-4-yl-*N*-(het)aryl-2-thioxoacetamide **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). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.57 – 1.88 (m, 2H, CH_2), 3.32 (t, J = 5.6 Hz, 4H, CH_2), 7.08 (t, J = 7.4 Hz, 1H, C_6H_5), 7.32 (t, J = 7.9 Hz, 2H, C_6H_5), 7.76 (d, J = 8.3 Hz, 2H, C_6H_5). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{11}H_{13}N_3O$: 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). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.61 – 1.70 (m, 2H, CH_2), 2.50 (s, 3H, CH_3), 3.32 (t, J = 5.6 Hz, 4H, $2CH_2$), 6.90 (d, J = 7.4 Hz, 1H, C_6H_4), 7.19 (t, J = 7.8 Hz, 1H, C_6H_4), 7.53 (d, J= 8.2 Hz, 1H, C_6H_4), 7.59 (s, 1H, C_6H_4). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{12}H_{15}N_3O$: 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). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.59 – 1.70 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 3.31 (t, J = 5.6 Hz, 4H, 2 CH_2), 7.11 (d, J = 8.3 Hz, 2H, C_6H_4), 7.63 (d, J = 8.3 Hz, 2H, C_6H_4). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{12}H_{15}N_3O$: 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). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.48 – 1.83 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.31 (t, J = 5.6 Hz, 4H, $2CH_2$), 7.06 (d, J = 8.2 Hz, 1H, C_6H_3), 7.46 (d, J = 8.1 Hz, 1H, C_6H_3), 7.51 (s, 1H, C_6H_3). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{13}H_{17}N_3O$: 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). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.52 – 1.73 (m, 2H, CH_2), 3.32 (t, J = 5.6 Hz, 4H, CH_2), 7.15 (t, J = 8.9 Hz, 2H, C_6H_4), 7.79 (dd, J = 8.6, 5.2 Hz, 2H, C_6H_4), 8.69 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{11}H_{12}FN_3O$: 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). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.52 –1.85 (m, 2H, CH_2), 3.32 (t, J =5.6 Hz, 4H, $2CH_2$), 7.12 (d, J = 8.0 Hz, 1H, C_6H_4), 7.33 (t, J = 8.1 Hz, 1H, C_6H_4), 7.71 (d, J = 8.3 Hz, 1H, C_6H_4), 7.96 (s, 1H, C_6H_4), 8.84 (br.s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{11}H_{12}ClN_3O$: 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). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.58 – 1.78 (m, 2H, CH_2), 3.33 (t, J = 5.7 Hz, 4H, CH_2), 7.36 (d, J = 8.9 Hz, 2H, C_6H_4), 7.80 (d, J = 8.9 Hz, 2H, C_6H_4), 8.90 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{11}H_{12}ClN_3O$: C, 55.59; H, 5.09; N, 17.68. Found: C, 55.64; 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). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.52 – 1.85 (m, 2H, CH_2). 3.32 (t, J = 5.6 Hz, 4H, $2CH_2$), 7.12 (d, J = 8.0 Hz, 1H, C_6H_3), 7.33 (t, J = 8.1 Hz, 1H, C_6H_3), 7.71 (d, J = 8.3 Hz, 1H, C_6H_3), 7.96 (s, 1H, C_6H_3), 8.84 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{11}H_{11}Cl_2N_3O$: 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). ^{1}H NMR

(400 MHz, DMSO-d_6): δ = 1.52 – 1.77 (m, 2H, CH_2). 3.31 (t, J = 5.6 Hz, 4H, 2 CH_2), 7.49 (d, J = 8.8 Hz, 2H, C_6H_4), 7.76 (d, J = 8.8 Hz, 2H, C_6H_4), 8.80 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.67, 40.82, 115.35, 121.94, 131.37, 137.72, 148.08, 160.02. LC-MS (ESI) [m/z]: $[M + H]^+$ = 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}): 3286.54 (NH), 1684.74 (C=O), 1634.59 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 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_6H_3), 8.03 (dd, J = 8.8, 2.4 Hz, 1H, C_6H_3), 8.34 (d, J = 2.4 Hz, 1H, C_6H_3), 8.81 – 9.36 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 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 $C_{12}H_{11}ClF_3N_3O$: 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): δ = 1.93 (s, 2H, CH_2). 3.50 (s, 4H, 2CH_2), 7.36 (d, J = 7.6 Hz, 2H, C_6H_4), 7.80 (d, J = 7.6 Hz, 2H, C_6H_4), 11.45 – 11.52 (br.s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 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 $C_{12}H_{13}N_3O_3$: 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): δ = 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_6H_4), 7.34(d, J = 8.2 Hz, 2H, C_6H_4), 9.50 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 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 $C_{15}H_{15}ClN_4OS$: 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): δ = 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_6H_4), 7.48 (d, J = 8.4 Hz, 2H, C_6H_4), 9.45 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 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 $C_{15}H_{15}BrN_4OS$: C, 47.50; H, 3.99; N, 4.77. Found: C, 47.41; H, 4.04; N, 4.84.

Biological activity

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 Eq. 1.

$$\%Inhibition = \frac{V_{control} - V}{V_{control}} \times 100\% \qquad \textbf{Eq.(1)}$$

where $V_{control}$ 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 Protein Data Bank 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)-1*H*-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)-1*H*-pyrazol-1-yl) benzenesulfonamide (**S58**) (COX-2 enzyme), the code in cocrystallizate **2238 S58**.[66] 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[67] 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.[68]

Results and Discussion

The starting materials for the synthesis of the target 1,4,5,6-tetrahydropyrimidine-2-carboxamides (Table 1) were 2-morpholin-4-yl-*N*-(het)aryl-2-thioxoacetamides **2a-k**, which were obtained by the interaction of chloroacetanilides **1a-k** (Figure 1) with sulfur and morpholine by the method described in a previous work.[69] Their characteristics and ^{1}H NMR spectroscopy data are given in the experimental part.

The interaction of morpholin-4-yl-*N*-(het)aryl-2-thioxoacetamides **2a-k** (Figure 2) with 1,3-diaminopropane was studed. 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 ^{1}H NMR spectrum of the resulting product **3a-k** was in agreement with the given structure. In particular, the protons of the CH_2 group in the 5th position of the

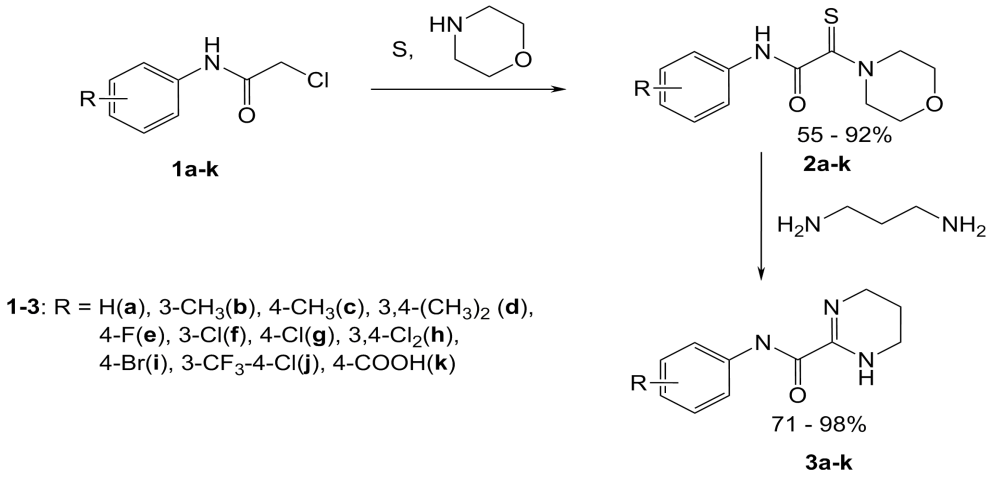


Figure 1. Synthesis of *N*-aryl-1,4,5,6-tetrahydropyrimidine-2-carboxamides **3a-k.**

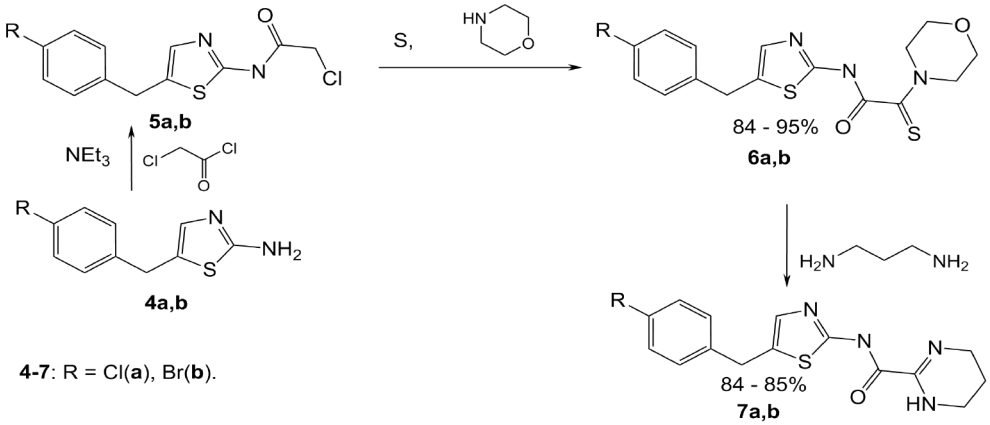


Figure 2. Synthesis of *N*-hetaryl-1,4,5,6-tetrahydropyrimidine-2-carboxamides **7a**,**b**.

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*-hetaryl-1,4,5,6-tetrahydropyrimidine-2-carboxamides **7a,b.**

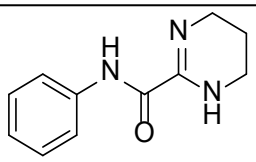
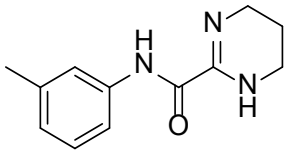
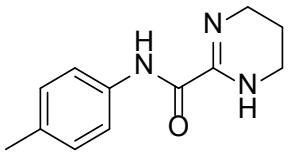
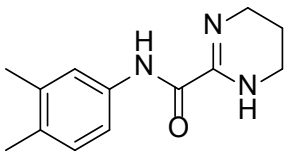
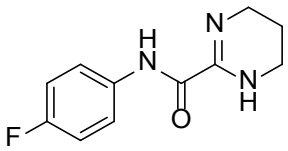
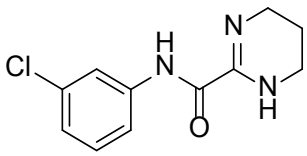
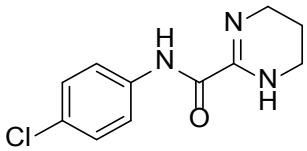
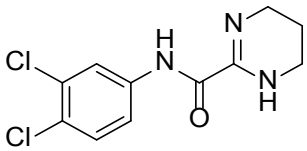
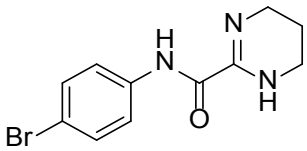
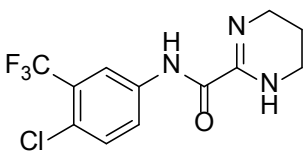
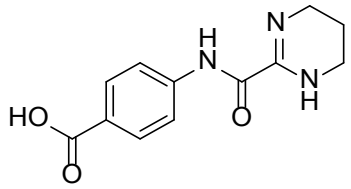
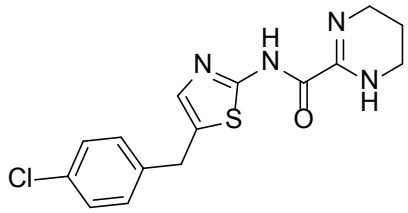
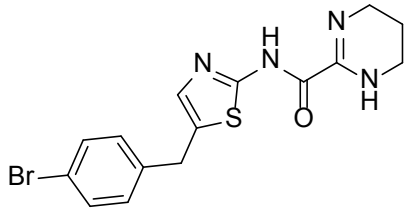
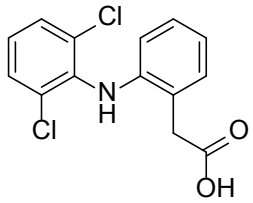
Comp.	Structure	Inhibition of the inflammatory response, %	ArgusLab 4.01 ΔG, kcal/mol	
			COX-1	COX-2
3a		12.9	-8.2	-9.0
3b		30.2	-10.1	-9.7
3c		15.9	-9.1	-9.2
3d		38.2	-10.8	-10.4
3e		26.4	-9.4	-9.5
3f		41.8	-11.0	-11.0
3g		46.7	-11.7	-11.2
3h		36.0	-9.8	-10.7
3i		8.6	-7.3	-9.2
3j		46.4	-11.6	-11.5

Table 1. Continued.

Comp.	Structure	Inhibition of the inflammatory response, %	ArgusLab 4.01 ΔG, kcal/mol	
			COX-1	COX-2
3k		25.2	-8.7	-9.4
7a		37.5	-10.7	-10.6
7b		29.3	-10.4	-11.0
Diclofenac		43.6	-10.8	-11.1

pyrimidine cycle appeared at 1.57-1.93 ppm, and the protons of the CH_2 groups in the 4th and 6th positions - at 3.32-3.50 ppm.

A method for the synthesis of *N*-[5-(4-R-benzyl)-1,3-thiazol-2-yl]-1,4,5,6-tetrahydropyrimidine-2-carboxamides **7a**, **b**. 5-(4-R-benzyl) thiazol-2-ylamines **4a**, **b**, were obtained by the described method in a previous study.[70] By acylation of **4a**, **b** with chloroacetyl chloride, the corresponding chloroacetamides **5a**, **b** were formed,[71] which upon interaction with sulfur and morpholine were converted to *N*-[5-(4-R-benzyl)thiazol-2-yl]-2-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-thiazol-2-yl]-1,4,5,6-tetrahydropyrimidine-2-carboxamides **7a**, **b** were synthesized.

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

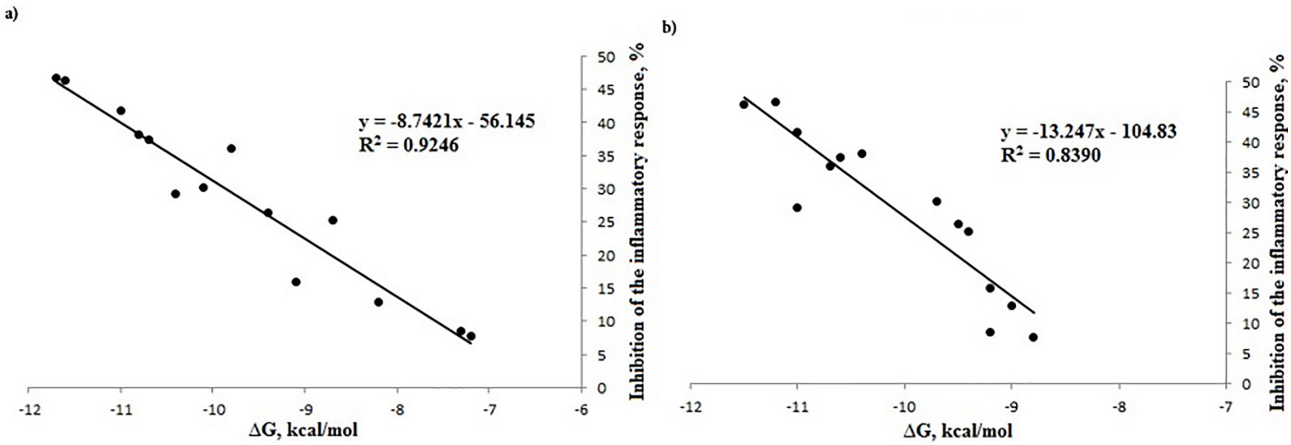


Figure 3. a) linear correlation between the binding energy (kcal/mol) with COX-1 and the rate of suppression of the inflammatory response (%); **b)** linear correlation between the binding energy (kcal/mol) of COX-2 and the rate of suppression of the inflammatory response (%).

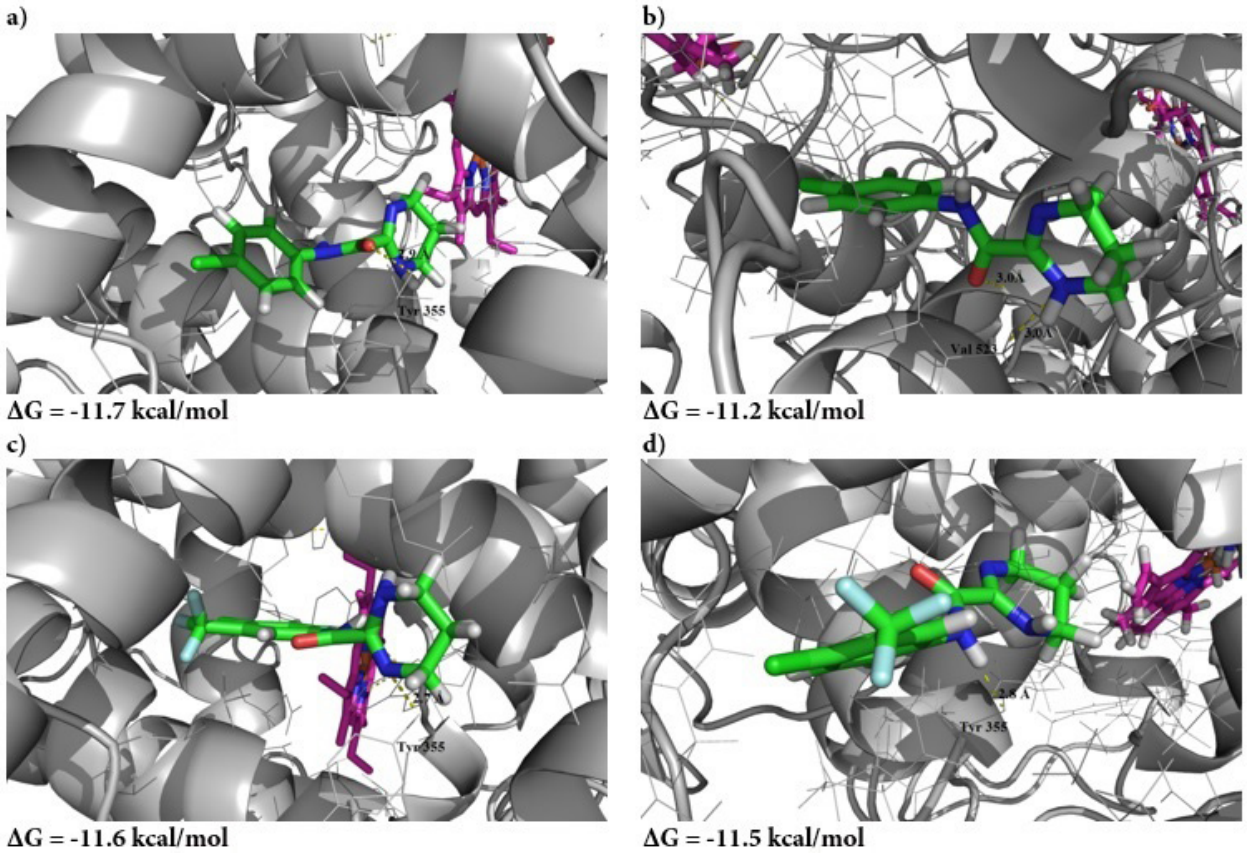


Figure 4. Position of molecules of hit compounds in the active sites of COX according to the results of the molecular docking: **a)** *N*-(4-chlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (**3g**) in the active site of the enzyme COX-1; **b)** *N*-(4-chlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (**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.

were in good agreement with the experimental data (Table 1, Figure 3), $R^2 > 0.92$ 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-chlorophenyl)-1,4,5,6-tetrahydropyrimidine-2-carboxamide (**3g**) and *N*-[4-chloro-3-(trifluoromethyl) phenyl]-1,4,5,6-tetrahydropyrimidine-2-carboxamide (**3j**) (Figure 4). 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 (Figure 4a). 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 (Figure 4b).

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 (Figure 4c), 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 (Figure 4d).

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-thioxoacetamides 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.

Ethical Issues

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.

Author Contributions

VYH: Planning and idea of work, organic synthesis, biological tests, discussion of the results, writing the initial version of the manuscript, writing the final version of the manuscript. PVZ: Molecular docking studies, discussion of the results, writing the initial version of the manuscript, writing the final version of the manuscript. IVH: Organic synthesis, biological tests. VSM: Work organization, experimental methods of analysis, interpretation of spectral data, discussion of the results, writing the initial version of the manuscript, writing the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The author declare there is no conflict of interest in this study.

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