SYNTHESIS, MOLECULAR DOCKING AND ANTI-INFLAMMATORY ACTIVITY 2,4-DIMETHYL-*N*-(2-ARYL)-3-FURAMIDES

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2,4-Dimethyl-*N*-aryl-3-furamides were synthesized by the reaction of 2,4-dimethyl-furan-3-carbonyl chloride with aromatic amines in dry dioxane in the presence of triethylamine. The structures of the obtained substances were confirmed by ^{1}H NMR spectroscopy and elemental analysis. The synthesized compounds were preselected via molecular docking to be tested for their anti-inflammatory activity. The anti-inflammatory effect of the prepared compounds was investigated applying the carrageenan-induced paw edema model. The results have shown that the some novel furamides demonstrated considerable anti-inflammatory effect.

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INTRODUCTION

Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing. This process may vary from a localized to a generalized response characterized by the accumulation of fluids and leukocytes leading to edema and pain.[1] The non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most common therapeutic groups of agents used worldwide for the treatment of inflammation. However, NSAIDs have high incidence of serious side effects.[2] Although drug treatment has been improved to some extent yet, it is still a challenge for the pharmaceutical chemists to explore the more effective and potent therapeutic agents to treat inflammation and reduce the signs and symptoms of acute inflammation and chronic inflammatory diseases.[3]

Furan derivatives are an important class of heterocyclic compounds that possess important biological properties. During last few decades a considerable amount of attention has been focussed on synthesis of furan derivatives and screening them for different pharmacological activities. Amides of furan-3-carboxic acids are also promising compounds with a broad spectrum of biological activity. Fenfuram, furcarbanil and methfuroxam are used as agrochemical fungicides. About of the activity of analogues of these drugs was reported in the works.[4] Furan-3-carboxamides exhibit antiproliferative[5] activities also. They are inhibitors of carboxylesterase,[6] glycosidase,[7] β-galactosidase[7] and HCV NS5B Polymerase.[8]

In a previous work[9] we have described the synthesis and anti-inflammatory activities of some 2,5-dimethyl-3-furan-3-carboxamides and 5-aryl-2-methyl-3-furan-3-carboxamides. In this article which is the part of our project on of biologically active heterocycles[10-23] we describe synthesis, molecular docking and anti-inflammatory activities of 2,4-dimethyl-*N*-(2-aryl)-3-furamides.

EXPERIMENTAL

All chemicals were of analytical grade and commercially available. All reagents and solvents were used without further purification and drying. Ibuprofen was purchased from a medical store.

All the melting points were determined in an open capillary and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 400 (400 MHz for ^{1}H) instrument with TMS or deuterated solvent as an internal reference. Satisfactory elemental analyses were obtained for new compounds (C±0.17, H±0.21, N±0.19).

Syntheses

Ethyl 2,4-dimethyl-3-furoate (3)

To a solution of 6.5 g (0.05 mol) of ethyl acetoacetate (**1**), in 100 mL of 0.5 M alcoholic solution of sodium ethoxide, was added a solution of 9.05 g (0.05 mol) of dimethyl-2-propynylsulfonium bromide in 100 mL of ethanol. The mixture was refluxed for 6-7 h and the ethanol was distilled off in a water bath. To the residue was added 200 mL of ether and the suspension was filtered. The ether was distilled off from the filtrate under atmospheric pressure. The residue was distilled at 130–132 ºC/20 Torr.

2,4-Dimethyl-3-furoic acid (4)

To a solution of 8.5 g (0.05 mol) of **3** in 30 mL of alcohol was added a solution of 4.5 g (0.08 mol) of potassium hydroxide in 20 mL of alcohol. The mixture was refluxed for 30 min, then dissolved in an equal amount of water and

acidified with diluted (1:1) hydrochloric acid. The precipitate was filtered off, washed with water and recrystallized. Yield 82 %, m.p. 119–120 °C (m.p. [d1] 118–119 °C).[24]

2,4-Dimethyl-3-furoyl chloride(5)

A mixture of 2.8 g (0.02 mol) of **4** and 3 mL of thionyl chloride in 50 mL of dry benzene was refluxed until complete dissolution of the acid. After cooling, the benzene was distilled off and the residue was distilled in vacuum at 115–118 ºC /20 Torr.

General procedure for preparation of 2,4-dimethyl-N-(2-aryl)-3-furamides (7a-n)

To a mixture of 0.01 mol of corresponding amine **6a-n** and 0.12 mL of triethylamine in 10 mL of dry dioxane a solution of 1.58 g (0.01 mol) of **5** in 10 mL of dry dioxane was added with stirring. The reaction mixture was left overnight and then was poured into water. The formed precipitate was filtered and recrystallized from alcohol.

2,4-Dimethyl-N-(2-methylphenyl)-3-furamide (7a)

Yield 83 %, m.p. 131–132 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.02 (s, 1H, NH), 7.45 (d, *J* = 8.1 Hz, 1H, C_6H_4), 7.26 – 7.04 (m, 4H, C_6H_4 + 5-H_{furane}), 2.46 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.12 (s, 3H, CH_3). Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.45; H, 6.64; N, 6.02.

2,4-Dimethyl-N-(3-methylphenyl)-3-furamide (7b)

Yield 84 %, m.p. 104–105 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.56 (s, 1H, NH), 7.50 (s, 1H, C_6H_4), 7.43 (d, *J* = 8.1 Hz, 1H, C_6H_4), 7.19 (s, 1H, 5-H_{furane}), 7.13 (t, *J* = 7.8 Hz, 1H, C_6H_4), 6.83 (d, *J* = 7.7 Hz, 1H, C_6H_4), 2.40 (s, 3H, CH_3), 2.32 (s, 1H, CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.21; H, 6.60; N, 6.22.

2,4-Dimethyl-N-(4-methylphenyl)-3-furamide (7c)

Yield 90 %, m.p. 115–116 °C.^{1}H NMR (400 MHz, DMSO) δ = 9.55 (s, 1H, NH), 7.53 (d, *J* = 8.0 Hz, 2H, C_6H_4), 7.19 (s, 1H, 5-H_{furane}), 7.06 (d, *J* = 8.4 Hz, 1H, C_6H_4), 2.40 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.43; H, 6.51; N, 6.03.

N-(4-isopropylphenyl)-2,4-dimethyl-3-furamide (7d)

Yield 89 %, m.p. 192–194 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.56 (s, 1H, NH), 7.55 (d, *J* = 8.5 Hz, 2H, C_6H_4), 7.19 (s, 1H, 5-H_{furane}), 7.10 (d, *J* = 8.4 Hz, 2H, C_6H_4), 2.91 – 2.80 (m, 1H, CH), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.22 (d, *J* = 6.9 Hz, 6H, 2 CH_3). Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.78; H, 7.36; N, 5.56.

***N*-(3,4-dimethylphenyl)-2,4-dimethyl-3-furamide (7e)**

Yield 82 %, m.p. 119–120 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.46 (s, 1H, NH), 7.42 (s, 1H, C_6H_3), 7.35 (d, *J* = 8.2 Hz, 1H, C_6H_3), 7.18 (s, 1H, 5-H_{furane}), 6.99 (d, *J* = 8.1 Hz, 1H, C_6H_3), 2.40 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.91; H, 7.12; N, 5.85.

N-(3,5-dimethylphenyl)-2,4-dimethyl-3-furamide (7f)

Yield92 %, m.p. 164–165 °C.^{1}H NMR (400 MHz, DMSO) δ = 9.46 (s, 1H, NH), 7.27 (s, 2H, C_6H_3), 7.19 (s, 1H, 5-H_{furane}), 6.65 (s, 1H, C_6H_3), 2.39 (s, 3H, CH_3), 2.27 (s, 6H, 2*CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.94; H, 7.02; N, 5.68.

N-(3-chlorophenyl)-2,4-dimethyl-3-furamide (7g)

Yield 91 %, m.p. 77–78 °C.^{1}H NMR (400 MHz, DMSO) δ 9.54 (s, 1H, NH), 7.89 (t, *J* = 2.0 Hz, 1H, C_6H_4), 7.64 – 7.58 (m, 1H, C_6H_4), 7.25 (t, *J* = 8.1 Hz, 1H, C_6H_4), 7.03 – 6.98 (m, 1H, C_6H_4), 6.59 (s, 1H, 5-H_{furane}), 2.51 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.65; H, 4.73; N, 5.75

N-(4-chlorophenyl)-2,4-dimethyl-3-furamide (7h)

Yield 87 %, m.p. 152–153 °C.^{1}H NMR (400 MHz, DMSO) δ = 9.80 (s, 1H, NH), 7.69 (d, *J* = 8.9 Hz, 2H, C_6H_4), 7.26 (d, *J* = 8.8 Hz, 2H, C_6H_4), 7.21 (s, 1H, 5-H_{furane}), 2.49 (s, 3H, CH_3), 2.40 (s, 3H, CH_3). Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.65; H, 4.91; N, 5.54.

N-(3,4-dichlorophenyl)-2,4-dimethyl-3-furamide (7i)

Yield 85 %, m.p. 151–152 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.93 (s, 1H, NH), 8.02 (d, *J* = 2.4 Hz, 1H, C_6H_3), 7.59 (dd, *J* = 8.8, 2.4 Hz, 1H, C_6H_3), 7.42 (d, *J* = 8.8 Hz, 1H, C_6H_3), 7.22 (s, 1H, 5-H_{furane}), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{13}H_{11}Cl_2NO_2$: C, 54.95; H, 3.90; N, 4.93. Found: C, 55.06; H, 3.81; N, 5.04.

N-(4-bromophenyl)-2,4-dimethyl-3-furamide (7j)

Yield 89%, m.p. 158–159°C. ^{1}H NMR (400 MHz, DMSO) δ = 9.80 (s, 1H, NH), 7.64 (d, *J* = 8.8 Hz, 2H, C_6H_4), 7.39 (d, *J* = 7.3 Hz, 1H, C_6H_4), 7.21 (s, 1H, 5-H_{furane}), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{13}H_{12}BrNO_2$: C, 53.08; H, 4.11; N, 4.76. Found: C, 53.19; H, 4.02; N, 4.84.

N-(4-methoxyphenyl)-2,4-dimethyl-3-furamide (7k)

Yield 95 %, m.p. 123–124 °C °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.50 (s, 1H, NH), 7.56 (d, *J* = 8.7 Hz, 2H, C_6H_4), 7.18 (s, 1H, 5-H_{furane}), 6.81 (d, *J* = 8.3 Hz, 2H, C_6H_4), 3.74 (s, 3H, CH_3O), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.65; H, 6.08; N, 5.83.

N-(4-ethoxyphenyl)-2,4-dimethyl-3-furamide (7l)

Yield 90 %, m.p. 159–160 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.45 (s, 1H, NH), 7.54 (d, *J* = 8.9 Hz, 2H, C_6H_4), 7.18 (s, 1H, 5-H_{furane}), 6.79 (d, *J* = 8.8 Hz, 2H, C_6H_4), 3.99 (q, *J* = 6.9 Hz, 2H $\underline{CH_2}CH_3$), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.36 (t, *J* = 6.9 Hz, 3H, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.57; H, 6.52; N, 5.56.

N-[4-(acetylamino)phenyl]-2,4-dimethyl-3-furamide (7m)

Yield 84 %, m.p. 191–192 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.71 (s, 1H, NH), 9.58 (s, 1H, NH), 7.55 (d, *J* = 8.9 Hz, 2H, C_6H_4), 7.46 (d, *J* = 8.8 Hz, 2H, C_6H_4), 7.19 (s, 1H, 5-H_{furane}), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.01 (s, 3H, CH_3). Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.27; H, 6.01; N, 10.18.

Methyl 2-[(2,4-dimethyl-3-furoyl)amino]-4,5-dimethoxybenzoate (7n)

Yield 87 %, m.p. 146–147 °C. ^{1}H NMR (400 MHz, DMSO) δ = 11.11 (s, 1H, NH), 8.44 (s, 1H, C_6H_2), 7.41 (s, 1H. C_6H_2), 7.24 (s, 1H, 5-H_{furane}), 3.90 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 3.79 (d, J s, 3H, CH_3O), 2.51 (s, 3H, CH_3), 2.18 (s, 3H, CH_3). Anal. Calcd. for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.34; H, 5.69; N, 4.31.

Molecular docking

Molecular docking was conducted with the OpenEye Scientific Software program as a computer based approach to the search of molecules with affinity to certain biotargets. Other software used included Fred Receptor, Vida, Omega 2 and Hybrid programs.

Pharmacology

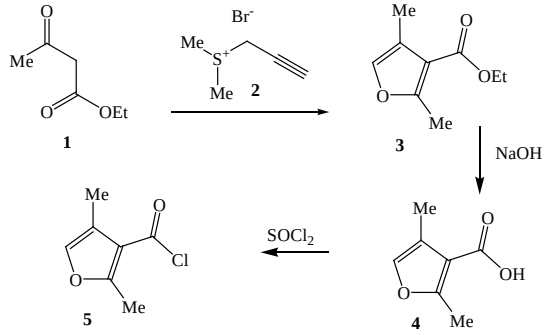
Anti-inflammatory activity[25] was evaluated using the carrageenan-induced rat paw edema method in Wistar rats (weight 180–220 g). The experiments were carried out in accordance with the requirements of the European convention for the protection of vertebrate animals used for experimental and other scientific purposes. The experimental protocol was approved by the DanyloHalytskyLviv National Medical University ethics committee, constituted by the Ministry of Health of Ukraine. Animals were divided into 16 groups comprising five rats per group. One group was kept as the control and the remaining 15 groups (test groups) were used to determine the anti-inflammatory activity elicited by Ibuprofen and the 14 compounds. Rats were kept in the animal house under standard conditions of light and temperature on a standard diet prior to the experiment. The standard drug, Ibuprofen (50 mg kg^{-1} body weight) and the test compounds (50 mg kg^{-1} body weight) were dissolved in DMSO and administered through an intraperitoneal route. DMSO was injected into the control group. At 30 min later, 0.1 mL of a 2 % carrageenan solution in saline was injected in the sub-plantar region of the right hind paw of each rat. At 4 h after the carrageenan injection, the volume of paw edema (in mL) was measured using a water plethysmometer and decrease in paw edema was compared between the control group and the test groups. Results of decreased paw edema were expressed as the mean ± standard deviation and compared statistically with the control group using Student's t-test. A level of $p<0.05$ was considered to be significant. The inflammatory reaction inhibition was expressed as a percent reduction of paw volume and was calculated using Eqn. (1),

$$\%\,(\text{inhibition}) = \frac{V_{\text{control}} - V}{V_{\text{control}}} \times 100 \qquad (1)$$

where $V_{control}$ is the increase in paw volume in control group; *V* is the increase in paw volume in animals injected with the test substances

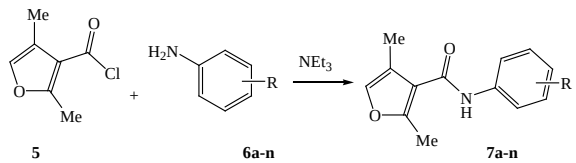
RESULTS AND DISCUSSION

The starting material, **5**, was prepared according scheme 1. In the first stage, **2** was reacted with an acetoacetic ester **1** to form ethyl 2,4-dimethyl-3-furoate **3** which was hydrolyzed with an aqueous solution of sodium hydroxide. Next 2,4-dimethyl-3-furoyl chloride **5** was prepared by the reaction of acid **4** with thionyl chloride.



Scheme 1. Synthesis 2,4-dimethyl-3-furoyl chloride.

The target 2,4-dimethyl-*N*-aryl-3-furamides **7a-n** were synthesized by the reaction of 2,4-dimethyl-furan-3-carbonyl chloride **5** with aromatic amines **6a-n** in dry dioxane in the presence of triethylamine (Scheme 2). Yields of the reaction products were 84–92 %.

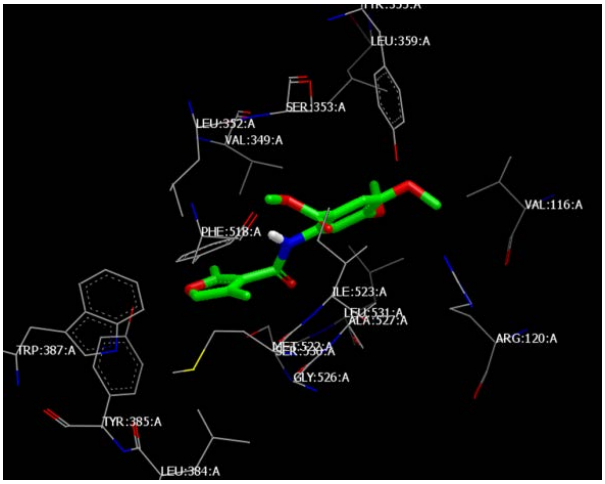


6, **7**: R = 2-CH_3(**a**), 3-CH_3(**b**), 4-CH_3(**c**), 4-$CH(CH_3)_2$(**d**), 3,4-$(CH_3)_2$(**e**), 3,5-$(CH_3)_2$(**f**), 3-Cl(**g**), 4-Cl(**h**), 3,4-Cl_2(**i**), 4-Br(**j**), 4-CH_3O(**k**), 4-C_2H_5O(**l**), 4-$CH_3C(O)NH$(**m**), 2-CO_2CH_3-4,5-$(CH_3O)_2$(**n**)

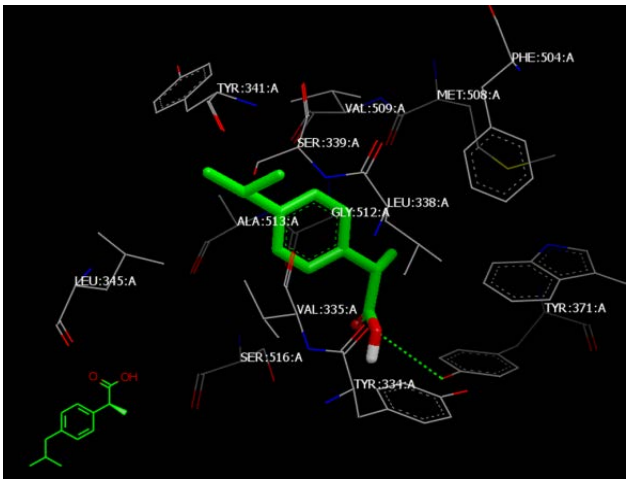
Scheme 2. Synthesis 2,4-dimethyl-*N*-aryl-3-furamides.

Table 1. Values of the Chemgauss 4 score of 2,4-dimethyl-N-(2-aryl)-3-furamides derivatives and reference compounds.

Compound ID or reference compound	Chemgauss 4 score		Compound ID or reference compound	Chemgauss 4 score	
	1HT5 (COX-1)	3MQE (COX-2)		1HT5 (COX-1)	3MQE(COX-2)
7a	-9.003030	-10.270514	Aspirin	-7.977182	-8.933105
7b	-8.843842	-10.332836	Diclofenac	-8.298965	-10.573636
7c	-8.943698	-10.325527	Etoricoxib	0.489733	-9.833312
7d	-9.316087	-10.865539	Flurbiprofen	-12.727644	-12.073698
7e	-7.995869	-11.244852	Ibuprofen	-12.126113	-10.477378
7f	-7.564784	-10.768264	Indomethacin	-8.843241	-11.326180
7g	-7.970945	-10.427266	Isoxicam	-7.356161	-9.013797
7h	-9.477314	-10.019304	Ketoprofen	-10.003001	-11.834192
7i	-7.862546	-10.936769	Ketorolac	-9.982499	-12.177383
7j	-9.574938	-10.233967	Lumiracoxib	-10.311695	-12.314234
7k	-8.871384	-10.072598	Meloxicam	-6.610479	-9.254274
7l	-8.582786	-10.723902	Parecoxib	-8.273745	-11.163197
7m	-7.314748	-9.674338			
7n	-9.126192	-11.325491			



(a)



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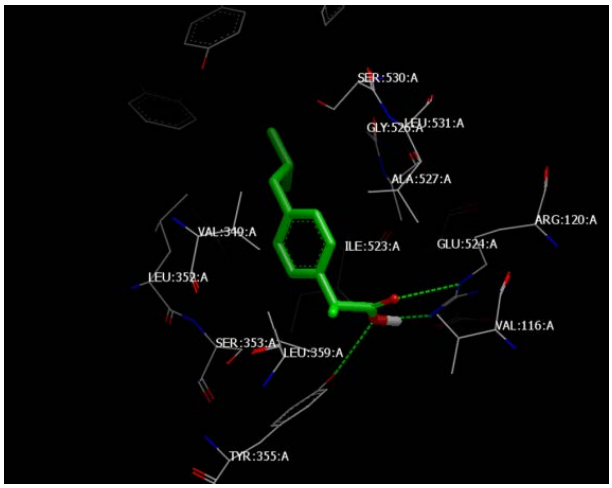

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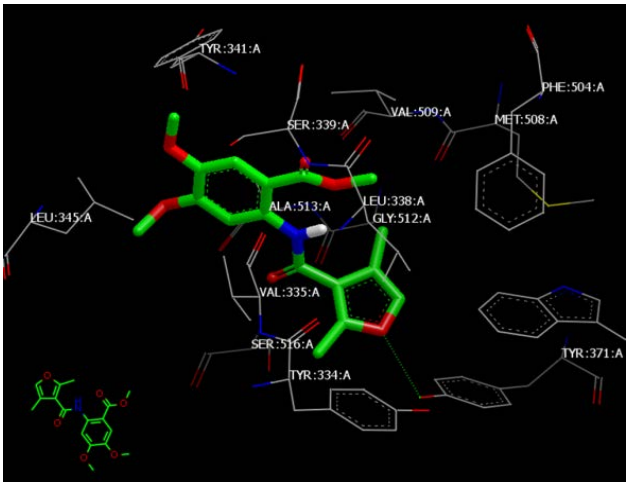

(d)

Figure. Compound **7n** docked in the active site of COX-1 (**a**) and COX-2 (**b**) in comparison with inhibitor Ibuprofen (**c** and **d**) docked in the active site of COX-1 and COX-2 correspondingly.

The structures of the obtained compounds were confirmed by ^{1}H NMR spectroscopy and elemental analysis. All these new compounds gave spectroscopic data in accordance with the proposed structures.

Molecular docking

Chrystallographic models of COX-1 and COX-2 (1HT5 and 3MQE correspondingly) were obtained from Protein Data Bank (www.rcsb.org). As research objects: 2,4-dimethyl-N-(2-aryl)-3-furamides derivatives, common NSAIDs (aspirin, mefenamic acid, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac and others) and well-known selective COX-2 inhibitors, such as parecoxib, lumiracoxib, etoricoxib and others, were chosen. To estimate *in silico* COX-2-compound and COX-1-compound binding scoring function values were calculated. Chemgauss 4 scoring function ranking allowed us to select compounds, which could prospectively be selective COX-2 inhibitors. Make Receptor program allows to extract the active sites (biotarget) of COX-2 and COX-1 from crystallographic models for molecular docking.

Molecular docking studies included generation of R-, S- and cys-trans isomers of ligands and them conformers using program were generated via Omega 2 with Flipper parameter. Further program Hybrid that uses elements of ligand based design to enhance performance. Typically, the protein structure is determined with X-ray crystallography in the presence of a known binding ligand (or bound ligand). The Hybrid program uses the information present in both the structure of the protein and the bound ligand to enhance docking performance.

Values of the scoring function (Chemgauss 4) were obtained as a result. Ranking property of the scoring function allowed to analyze the results easily (table 1).

Ranking and analysis of the molecular docking results were obtained using the selected compounds and crystallographic model of COX-2 and COX-1 with scoring function (Chemgauss 4). Results allowed us to select compounds, which could prospectively be COX inhibitors at the level of Ibuprofen for future (in-depth) pharmacological studies for further evaluation of in vitro anti-inflammatory activity. The interactions between COX-1 and COX-2 active site and the most active compound **7n** in comparison with Ibuprofen (non-selective inhibitor of COX-1&2) is shown in Figure. Moreover, it should be noted that results predicted via docking correlate quite well with that obtained in the in vitro assay. The selected "lead" compound **7n** based on the *in vitro* screening results was also predicted to be the most active in the docking studies.

Pharmacology

Carrageenan-induced paw edema is a well-known animal model of acute inflammation, and is the most widely used in the search for new anti-inflammatory drugs. In vivo studies of novel 2,4-dimethyl-*N*-aryl-3-furamides were performed for anti-inflammatory activity. The results of the anti-inflammatory activity of the synthesized compounds and Ibuprofen are shown in Table 2.

The synthesized compounds induce various anti-inflammatory activity – from almost complete absence to a pronounced anti-inflammatory effect. Evaluation indicated that 11 compounds (**7a**, **7b**, **7c**, **7d**, **7e**, **7f**, **7g**, **7j**, **7k**, **7l**, **7m**) showed no significant decrease in carrageenan-induced rat paw edema, as their inhibition rates were only 7.2-35.6%, as compared to the control group. The anti-inflammatory effect for compounds **7h** and **7i** is approximately equivalent to that of the reference drug. However, the anti-inflammatory activity of the for compound **7n** gave the result at the level of 45.4 % inhibition indicating the methyl 2-[(2,4-dimethyl-3-furoyl)amino]-4,5-dimethoxybenzoate were more potent than Ibuprofen.

Table 2. Anti-inflammatoryeffect of 2,4-dimethyl-*N*-aryl-3-furamides on carrageenan-induced rat paw edema (mL) in vivo evaluation, % protection from inflammation.

Compound ID	Paw edema volume (mL)±SEM*	% Inhibition	Activity relative to Ibuprofen, %
Control	2.20 ± 0.050	-	-
7a	1.71± 0.040	22.3	55.5
7b	1.93± 0.045	12.1	30.1
7c	1.84± 0.045	16.2	40.3
7d	2.04 ± 0.050	7.2	17.9
7e	1.58 ± 0.040	28.3	70.4
7f	1.90 ± 0.045	13.5	33.6
7g	1.42± 0.035	35.6	88.6
7h	1.31± 0.035	40.5	100.8
7i	1.29± 0.035	41.2	102.5
7j	1.51± 0.035	31.2	77.6
7k	1.86± 0.045	15.6	38.8
7l	1.65 ± 0.040	25.1	62.4
7m	1.71 ± 0.040	22.3	55.5
7n	1.20 ± 0.030	45.4	112.9
Ibuprofen	1.32 ± 0.035	40.2	100

CONCLUSION

In summary, we have presented an efficient approach of the synthesis of 2,4-dimethyl-*N*-(2-aryl)-3-furamides.The synthesized compounds were preselected via molecular docking for further testing of their anti-inflammatory activity in vitro. During the study of synthesized substances anti-inflammatory effect in the carrageenan model of inflammatory oedema of white rats paws, we found three highly active compounds with a pronounced anti-inflammatory effect. Further optimization of the structure to improve biological activity is currently in progress.

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