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Synthesis, anti-inflammatory activity and molecular docking of 2-methyl-3-furamides

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ABSTRACT

In an effort to develop novel anti-inflammatory agents, a series of novel 2-methyl-3-furamides were synthesized and modified.The structures of the obtained compounds 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. Researched substances impact effect on the inflammation exudative phase course was studied on the basis of white rats paws inflammatory edema carrageenan model. Anti-inflammatory activity researches have shown that synthesized compounds have possessed expressed anti-inflammatory properties, and some of them, in terms of activity, approach or exceed the comparison drug Ibuprofen.

Keywords: *organic synthesis; 2-methyl-3-furamides; molecular docking; anti-inflammatory activity.*

1. INTRODUCTION

The problem of pharmacological regulation of inflammation is relevant for modern medicine. There are a significant number of drugs that are used to treat inflammation [1]. Current approaches to overcome inflammation include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), immune selective anti-inflammatory derivatives, selective glucocorticoid receptor agonists, resolvins/protectins and TNF inhibitors [2]. Non-steroidal anti-inflammatory drugs, which combine a whole range of properties displaying anti-inflammatory, analgesic, antipyretic activity are in special demand [3]. However, they all have ulcerogenic properties to varying degrees [3]. In order to overcome these restrictions worldwide, the development of new effective and safe anti-inflammatory drugs is continuing.

Modern computer molecular techniques simulation is an integral part of basic research [4]. The integration of these *in silico* techniques makes it possible to search for new anti-inflammatory drugs. In this article which is the part of our researching biologically active heterocycles [5-20] we described synthesis, molecular docking and anti-inflammatories properties of some novel 2-methyl-3-furamides.

It should be noticed that 2-methyl-3-furamides display antifungal [21, 22], antileishmanial [23] and anticancer [24] activities. They are inhibitors of Carboxylesterase [25], Tyrosyl-DNA phosphodiesterase 2 (TDP2) [26], succinate dehydrogenase [27], HIV-1 reverse transcriptase [28], selective *V1A* receptor antagonists [29, 30] and allosteric glucokinase activators [31].

Such furancarboxamide as Fenfuram, Furancarbanil and Methfuroxam are commercially available fungicides [32]. Thus, the development of novel anti-inflammatory agents, among 2-methyl-3-furamides should be continued.

2. MATERIALS AND METHODS

2.1. Materials.

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

2.2. Chemistry.

All melting points were determined in an open capillary. The elemental analysis experimental data on contents of Carbon, Hydrogen and Nitrogen were within ±0.3% of the theoretical values. ^{1}H NMR spectra of synthesized compounds in dimethyl sulfoxide (DMSO)-d6 solutions were recorded on a spectrometer Varian Mercury VX-400 [Agilent Technologies, San Francisco, USA] (400 MHz) at 298 K. Chemical shifts are reported as δ (ppm) relative to tetramethylsilane (TMS) as an internal standard. The coupling constant *J* is expressed in Hz.

General procedure for synthesis of 5-aryl-2-methyl-3-furoic acids (1b, c): To a solution of 0.2 mol of the corresponding acid (**2**) and 2 g of $CuCl_2$ x $2H_2O$ in 80 ml of acetone with stirring was added dropwise a solution of areenediazonium chloride (**3g, h)** obtained by diazotation (HCl, $NaNO_2$) of 0.21 mol of the corresponding aromatic amine. The temperature was maintained in the range of 20-30 °C. The reaction was carried out until the evolution of Nitrogen ceased. 200 ml of water was added, the reaction product was filtered off and recrystallized in a mixture of alcohol DMF.

5-(2,4-Dichlorophenyl)-2-methyl-3-furoic acid (1b). Yield 68%, mp 257-258 °C. ^{1}H NMR (400 MHz, DMSO): δ =12.51 (s, 1H, COOH), 7.81 (d, J = 8.4 Hz, 1H, C_6H_3), 7.81 (d, J = 8.4 Hz, 1H, C_6H_3), 7.56 (s, 1H, C_6H_3), 7.43 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, C_6H_3), 7.24 (s, 1H, furane), 2.63 (s, 3H, CH_3). Anal. Calcd. for $C_{12}H_8Cl_2O_3$: C, 53.17; H, 2.97. Found: C, 53.25; H, 2.94.

5-(2,5-dichlorophenyl)-2-methyl-3-furoic acid (1c). Yield 51%, mp 283-284 °C. ^{1}H NMR (400 MHz, DMSO): δ =12,83 (s, 1H, COOH), 7,83 (s, 1H, C_6H_3), 7,44 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, C_6H_3), 7.31 (s, 1H, furane), 2.62 (s, 3H, CH_3). Anal. Calcd. for $C_{12}H_8Cl_2O_3$: C, 53.17; H, 2.97. Found: C, 53.44; H, 3.01.

General procedure for synthesis of 5-R-2-methylfuran-3-carboxamides (9a-c, 10a-d and 11a-f). To a solution of 0.01 mol of corresponding amine (**4a-f**, **7a-c**, **8a,b**) and 1 ml of triethylamine in 30 ml of anhydrous dioxane we added under stirring 1.59 g (0.01 mol) of 2,5-dimethyl-3-furoyl chloride (**6**). The mixture was left to stand for 0.5 h and diluted with water, and the precipitate was filtered off, washed with water.

2,5-Dimethyl-N-[3-(trifluoromethyl)phenyl]-3-furamide (9a). Yield 85%, mp 105-106 °C. ^{1}H NMR (400 MHz, DMSO): δ = 9.69 (s, 1H, NH), 8.16 (s, 1H, C_6H_4), 7.96 (d, *J* = 8.0 Hz, 1H, C_6H_4), 7.47 (t, *J* = 8.0 Hz, 1H, C_6H_4), 7.30 (d, *J* = 7.6 Hz, 1H, C_6H_4), 6.61 (s, 1H, furane), 2.52 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). Anal. Calcd. for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27; N, 4.94. Found: C, 59.38; H, 4.24; N, 4.85.

Ethyl 4-[(2,5-dimethyl-3-furoyl)amino]benzoate (9b). Yield 87%, mp 143-144 °C. ^{1}H NMR (400 MHz, DMSO): δ = 9.69 (s, 1H, NH), 7.90 (d, *J* = 8.8 Hz, 2H, C_6H_4), 7.86 (d, *J* = 9.0 Hz, 2H, C_6H_4), 6.64 (s, 1H, furane), 4.30 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 2.53 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 1.37 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.22; H, 6.03; N, 4.80.

4-[(2,5-Dimethyl-3-furoyl)amino]phenyl thiocyanate (9c). Yield 84%, mp 177-178 °C. ^{1}H NMR (400 MHz, DMSO): δ = 9.69 (s, 1H, NH), 7.91 (d, *J* = 8.7 Hz, 2H, C_6H_4), 7.54 (d, *J* = 8.7 Hz, 2H, C_6H_4), 6.62 (s, 1H, furane), 2.53 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.54; H, 4.28; N, 10.35.

2,5-Dimethyl-N-1,3-thiazol-2-yl-3-furamide (10a). Yield 90%, mp 180-181 °C. ^{1}H NMR (400 MHz, DMSO): δ = 11.88 (s, 1H, NH), 7.41 (d, *J* = 3.5 Hz, 1H, thiazole), 7.02 (d, *J* = 3.5 Hz, 1H, thiazole), 6.81 (s, 1H, furane), 2.55 (s, 3H, CH_3), 2.26 (s, 3H, CH_3). Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 53.88; H, 4.45; N, 12.41.

N-(5-Ethyl-1,3,4-thiadiazol-2-yl)-2,5-dimethyl-3-furamide (10b). Yield 85%, mp 196-197 °C. ^{1}H NMR (400 MHz, DMSO): δ = 12.19 (s, 1H, NH), 6.84 (s, 1H, furane), 3.01 (q, *J* = 7.6 Hz, 2H, $\underline{CH_2}CH_3$), 2.56 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 1.37 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72. Found: C, 52.49; H, 5.14; N, 16.80.

5-(2,4-Dichlorophenyl)-N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-methyl-3-furamide (10c). Yield 76%, mp 240-241 °C. ^{1}H NMR (400 MHz, DMSO): δ = 12.62 (s, 1H, NH), 8.10 (s, 1H, C_6H_3), 7.84 (d, *J* = 8.6 Hz, 1H, C_6H_3), 7.57 (d, *J* = 1.9 Hz, 1H, C_6H_3), 7.47 – 7.42 (m, 1H, C_6H_3), 3.03 (q, *J* = 7.5 Hz, 2H, $\underline{CH_2}CH_3$), 2.72 (s, 3H, CH_3), 1.39 (t, *J* = 7.6 Hz, 3H, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{16}H_{13}Cl_2N_3O_2S$: C, 50.27; H, 3.43; N, 10.99. Found: C, 50.36; H, 3.48; N, 11.11.

5-(2,5-dichlorophenyl)-2-methyl-N-1,3-thiazol-2-yl-3-furamide (10d). Yield 71%, mp 247-248 °C. ^{1}H NMR (400 MHz, DMSO): δ = 12.37 (s, 1H, NH), 8.16 (s, 1H, C_6H_3), 7.82 (d, *J* = 2.1 Hz, 1H, thiazole), 7.52 (d, *J* = 8.6 Hz, 1H, C_6H_3), 7.47 (d, *J* = 3.5 Hz, 1H, thiazole), 7.32 (dd, *J* = 8.5, 2.0 Hz, 1H, C_6H_3), 7.10 (d, *J* = 3.4 Hz, 1H, C_6H_3), 2.75 (s, 3H, CH_3). Anal. Calcd. for $C_{15}H_{10}Cl_2N_2O_2S$: C, 51.01; H, 2.85; N, 7.93. Found: C, 51.08; H, 2.79; N, 7.85.

***N-(5-benzyl-1,3-thiazol-2-yl)-2,5-dimethylfuran-3-carboxamide* (*11a*).** Yield 80%, mp 157-158 °C. ^{1}H NMR (400 MHz, DMSO): δ = 11.90 (s, 1H, NH), 7.38 – 7.25 (m, 5H, C_6H_4, thiazole), 7.22 (t, *J* = 7.0 Hz, 1H, C_6H_4), 6.81 (s, 1H, furane), 4.08 (s, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.22 (s, 3H, CH_3). Anal. Calcd. for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.22; H, 5.09; N, 8.88.

2,5-Dimethyl-N-[5-(3-methylbenzyl)-1,3-thiazol-2-yl]furan-3-carboxamide (11b). Yield 76%, mp 116-117°C. ^{1}H NMR (400 MHz, DMSO): δ = 11.90 (s, 1H, NH), 7.27 (s, 1H, thiazole), 7.19 (t, *J* = 7.4 Hz, 1H, C_6H_4), 7.12 – 6.99 (m, 3H, C_6H_4), 6.81 (s, 1H, furane), 4.03 (s, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.22 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.06; H, 5.49; N, 8.41.

2,5-Dimethyl-N-[5-(4-methylbenzyl)-1,3-thiazol-2-yl]furan-3-carboxamide (11c). Yield 84%, mp 155-156 °C. ^{1}H NMR (400 MHz, DMSO): δ = 11.89 (s, 1H, NH), 7.25 (s, 1H, thiazole), 7.15 (d, *J* = 7.9 Hz, 2H, C_6H_4), 7.11 (d, *J* = 7.9 Hz, 2H, C_6H_4), 6.80 (s, 1H, furane), 4.02 (s, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.22 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.11; H, 5.48; N, 8.47.

N-[5-(4-fluorobenzyl)-1,3-thiazol-2-yl]-2,5-dimethylfuran-3-carboxamide (11d). Yield 91%, mp 146-147°C. ^{1}H NMR (400 MHz, DMSO): δ = 11.91 (s, 1H, NH), 7.31 (dd, J_{HH} = 8.1, J_{HF} =5.7 Hz, 2H, C_6H_4), 7.27 (s, 1H, thiazole), 7.13 (t, *J* = 8.8 Hz, 2H, C_6H_4), 6.81 (s, 1H, furane), 4.08 (s, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.22 (s, 3H, CH_3). Anal. Calcd. for $C_{17}H_{15}FN_2O_2S$: C, 61.80; H, 4.58; N, 8.48. Found: C, 61.63; H, 4.51; N, 8.37.

N-[5-(4-Chlorobenzyl)-1,3-thiazol-2-yl]-2,5-dimethylfuran-3-carboxamide (11e). Yield 93%, mp 140-141°C. ^{1}H NMR (400 MHz, DMSO): δ = 11.90 (s, 1H, NH), 7.35 д (2H, *J* = 8.3 Hz, ClC_6H_4), 7.30-7.25 м (3H, ClC_6H_4 + thiazole), 6.81 (s, 1H, furane), 4.94 с (2H, CH_2), 2.49 (s, 3H, CH_3), 2.22 (s, 3H, CH_3). Anal. Calcd. for $C_{17}H_{15}FN_2O_2S$: C, 61.73; H, 4.57; N, 8.47. Found: C, 61.60; H, 4.53; N, 8.35.

N-[5-(4-methoxybenzyl)-1,3-thiazol-2-yl]-2,5-dimethylfuran-3-carboxamide (11f): Yield 88%, m.p. 155-156 °C. ^{1}H NMR (400 MHz, DMSO): δ = 11.88 (s, 1H, NH), 7.24 (s, 1H, thiazole), 7.18 (d, *J* = 8.5 Hz, 2H, C_6H_4), 6.87 (d, *J* = 8.6 Hz, 2H, C_6H_4), 6.80 (s, 1H, furane), 4.00 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 2.49 (s, 3H, CH_3), 2.22 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 63.01; H, 5.22; N, 8.19.

2.3. Molecular docking. Molecular docking was conducted with the OpenEye Scientific Software program [Software, Santa Fe, New Mexico, USA] as a computer based approach to the search of molecules with affinity to certain biotargets. Other software used included MakeReceptor, Vida, Omega 2 and Hybrid programs [Software, Santa Fe, New Mexico, USA].

2.4. Pharmacology.

Anti-inflammatory activity 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 European requirements of the convention for the protection of vertebrate animals used for experimental and other scientific purposes. The experimental protocol was approved by the Danylo Halytsky Lviv National Medical University ethics committee, constituted by the Ministry of Health of Ukraine.

Animals were divided into 14 groups comprising five rats per group. One group was kept as the control and the remaining 13 groups (test groups) were used to determine the anti-inflammatory activity elicited by Ibuprofen and the 12 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 body weight) and the test compounds (50 mg/kg body weight) were dissolved in DMSO and administered through an intraperitoneal route. DMSO was injected into the control group. At 30 minutes 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 [Orchid Scientific, Mumbai, India] and a 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. Inhibition of the inflammatory response was expressed as a percentage reduction in paw volume and was calculated by the following formula:

$$\%\,\text{Inhibition} = \frac{V_{\text{control}} - V}{V_{\text{control}}} \cdot 100\,\%$$

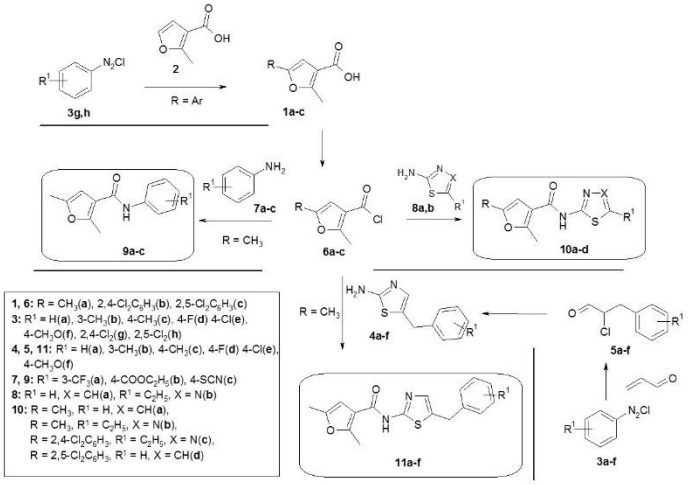
where V_{control} is the increase in paw volume in control group animals;

V is the increase in paw volume in animals injected with the test substances.

3. RESULTS

3.1. Synthesis of some 2-methyl-3-furamides.

As started reagents for synthesis of target amides 2,5-dimethyl-3-furoic **1a** and 5-aryl-2-methyl-3-furoic **1b,c** acids were used. 5-Aryl-2-methyl-3-furoic acids **1b,c** were prepared by arylation of 2-methyl-3-furoic acid **2** by diazonium salts **3g,h** in Meerwein condition reaction [33] as described in [34, 35]. 5-R-benzyl-1,3-thiazol-2-amine **4a-f** were also synthesized using diazonium salts **3a-f** as a started material. Diazonium salts **3a-f** react with acroleine to form 3-aryl-2-chloropropanales **5a-f** [36]. These aldehydes were converted with high yields into 5-R-benzyl-thiazol-2-ylamines **4a-f** according to the previously reported synthetic protocols [36-38]. To prepare target amides **9**–**11** 2,5-dimethyl-3-furoic and 5-aryl-2-methyl-3-furoic acids were converted into acyl chlorides **6a-c** that were used for acylation of amines **4a-f**, **7a-c** and **8a,b**.



Scheme 1. Synthesis of some 2-methyl-3-furamides.

The structure of synthesized compounds was confirmed by ^{1}H NMR spectroscopy and by microanalyses. All these new compounds gave spectroscopic data in accordance with the proposed structures.

In ^{1}H NMR spectra signals for the protons of all the structural units were observed in their characteristic ranges. In compounds **11a-f** the protons of thiazole and furan rings were recorded as singlets at δ 7.24–7.38 ppm and 6.80–6.81 ppm appropriately, methylene groups at 4.00–4.94 ppm. H–N amide protons in these compounds appeared as a singlet at δ 11.88–11.91 ppm and two other singlets in compounds **9a-c** and **11a-f** at δ 2.22–2.29 and 2.49–2.56 ppm indicated methyl groups of furan rings.

3.2. Molecular docking.

Chrystallographic models of COX-1 and COX-2 (1PGG and 4PH9 correspondingly) were obtained from Protein Data Bank (www.rcsb.org). As research objects: 2-methyl-3-furamides derivatives, common NSAIDs (aspirin, mefenamic acid, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac, 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. Next up is the Hybrid program, which uses ligand design elements to increase productivity. Typically, the structure of a protein is determined by X-ray crystallography in the presence of a known binding ligand (or bound ligand). Eo increase the efficiency of docking, this program uses information that is present both in the structure of the protein and the bound ligand.The 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 Diclofenac and 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 **11a** in comparison with inhibitors of COX-1 (Flurbiprofen) and COX-2 (Ibuprofen) are shown in Figure 1. 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 **11a** based on the *in vitro* screening results was also predicted to be the most active in the docking studies.

3.3. Evaluation of the anti-inflammatory activity *in vivo*.

The one of the most widely used methods used to investigate anti-inflammatory activity is carrageenan-induced edema paws of rats. The influence of the synthesized substances on the inflammation exudative phase course study was performed on the basis of white rats legs inflammatory edema carrageenan model [39]. The NSAID

drug Ibuprofen in its effective therapeutic dose was tested simultaneously as an activity reference. The protection against inflammation percentage was calculated as % inhibition by comparison between DMSO injected control group and drug-tested groups. The results of the anti-inflammatory activity Ibuprofen and of the novel compounds are given in table 2The synthesized compounds possess anti-inflammatory activity variety - from its almost complete absence to a distinct anti-inflammatory effect. The compared with the control group for some compounds (**9a-c**, **10b-d**, **11f**) showed no significant decrease in carrageenan-induced rat paw edema as their inhibition rates were only 16.5-33.7%.. The anti-inflammatory effect for compounds **11a-c** is approximately equivalent to that of the reference drug. However, some substances **(11e, d**) activity exceeds Ibuprofen. The anti-inflammatory effect for these compounds resulted in inhibition rates of 43.4-45.9%, which gives reason to consider this scaffold as a promising molecular framework for the design of potential anti-inflammatory agents.

Table 1. Values of the Chemgauss 4 score of 2-methyl-3-furamides derivatives and reference compounds.

Compound ID or reference compound	Chemgauss 4 score 1PGG (COX-1)	Chemgauss 4 score 4PH9 (COX-2)	Compound ID or reference compound	Chemgauss 4 score 1PGG (COX-1)	Chemgauss 4 score 4PH9 (COX-2)
9a	-7.524521	-10.729573	Aspirin	-8.055377	-8.950326
9b	-10.206500	-10.960499	Diclofenac	-8.471702	-10.132541
9c	-8.606261	-11.746645	Etoricoxib	0.866820	-7.237532
10b	-8.093850	-12.120781	Flurbiprofen	-11.647477	-13.220425
10c	-7.721201	-11.946198	Ibuprofen	-12.359507	-10.210879
10d	-9.970696	-12.011646	Indomethacin	-9.386655	-11.982500
11a	-10.788911	-12.260530	Isoxicam	-8.652688	-11.823118
11b	-6.586852	-10.738570	Ketoprofen	-12.274237	-12.527678
11c	-6.418277	-11.572229	Ketorolac	-12.641514	-12.760300
11d	-8.486995	-11.564221	Lumiracoxib	-9.720785	-12.322708
11e	-10.106500	-10.960499	Meloxicam	-8.498905	-12.353498
11f	-10.662773	-12.548939	Parecoxib	-8.727989	-10.550035

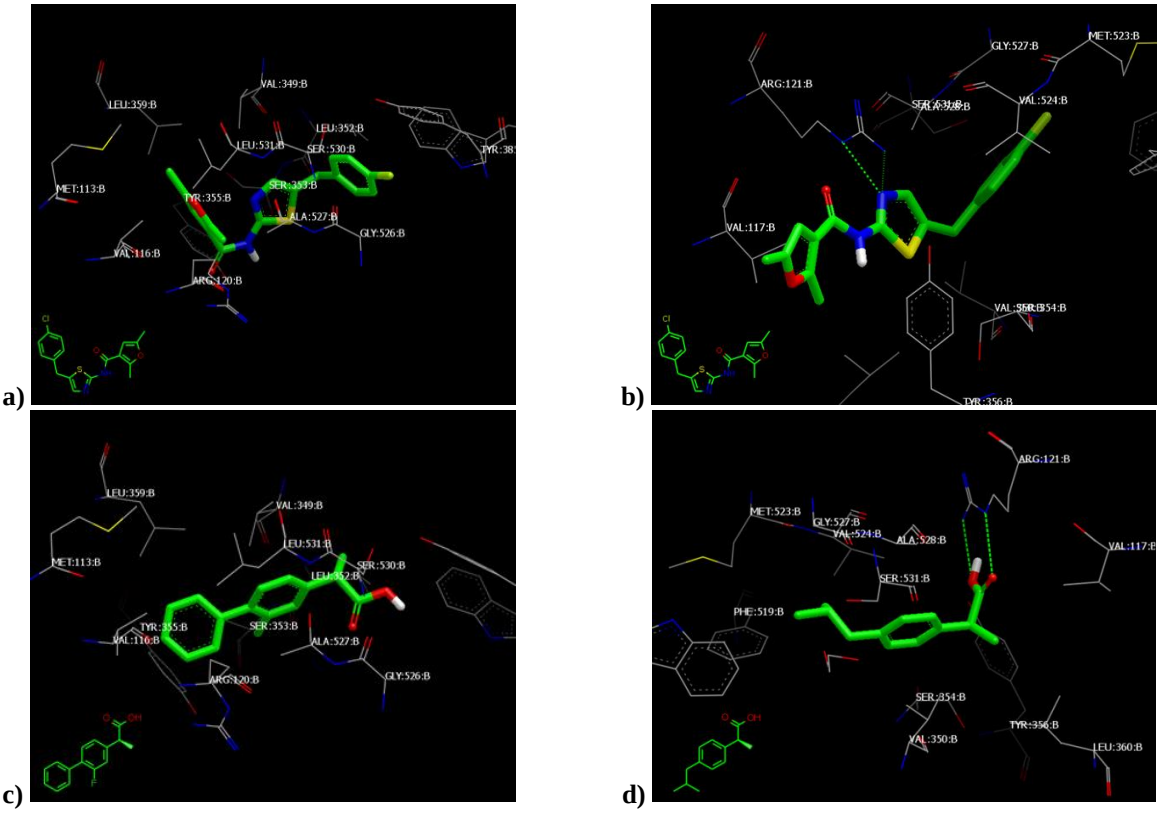


Figure 1. Compound **11a** docked in the active site of COX-1 (**a**) and COX-2 (**b**) in comparison with inhibitors Flurbiprofen (**c**) and Ibuprofen (**d**) docked in the active site of COX-1 and COX-2 correspondingly.

Table 2. Anti-inflammatory effect of 2-methyl-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	-	
9a	1.62± 0.040	**26.6**	*66.2*
9b	1.70 ± 0.045	**22.9**	*57.0*
9c	1.84 ± 0.045	**16.5**	*41.1*
10b	1.79 ± 0.045	**18.5**	*46.0*

Synthesis, molecular docking and anti-inflammatory activity of 2-methyl-3-furamides			
Compound ID	**Paw edema volume (mL) ± SEM***	**% Inhibition**	**Activity relative to Ibuprofen, %**
10c	1.60 ± 0.040	**27.4**	*68.2*
10d	1.71± 0.045	**22.5**	*55.6*
11a	1.41± 0.035	**36.2**	*90.1*
11b	1.33± 0.035	**39.5**	*98.3*
11c	1.40± 0.035	**36.5**	*90.8*
11d	1.25± 0.020	**43.4**	*108.0*
11e	1.19 ± 0.020	**45.9**	*114.2*
11f	1.46 ± 0.035	**33.7**	*83.8*
Ibuprofen	1.32 ± 0.035	**40.2**	*100*

***SEM denotes standard error of mean.

4. CONCLUSIONS

In our present work, we presented an efficient synthesis, molecular docking and anti-inflammatory activity evaluation of some 2-methyl-3-furamides. We have shown that the proposed approaches provide the possibility to design furamides diversity with a considerable chemical novelty. The synthesized compounds were preselected *via* molecular docking to be tested for their anti-inflammatory activity *in vitro*. Evaluation of novel compounds over the carageenin induced rat paw edema revealed strong anti-inflammatory action of some compounds even exceeding the standard – Ibuprofen.

5. REFERENCES

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