SYNTHESIS AND *IN SILICO* STUDY OF NEW KETOPROFEN DERIVATIVES

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Abstract

Ketoprofen is a widespread non-steroidal anti-inflammatory agent used in treatment of acute pain and chronic arthritis. On the other hand, isoquinoline alkaloids are very well known with their wide range of biological activities. From this point of view it is of interest to us to obtain new isoquinolines containing a ketoprofen residue in their structure as new substances with potential biological activity. To estimate general efficacy and safety of the newly obtained compounds, their biological potential has been evaluated.

Keywords: *Ketoprofen, NSAIDs, 1,2,3,4-tetrahydroisoquinoline, In silico, α-amidoalkylation reaction, TfOH/SiO_2, Heterogeneous catalysis*

INTRODUCTION

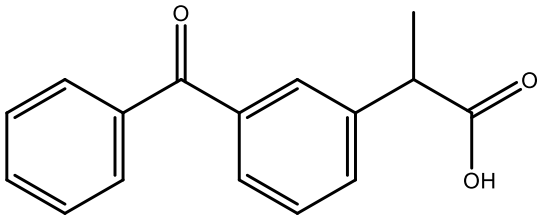
The medicinal chemistry is one of the fastest growing areas and connects many other scientific disciplines, including organic chemistry, physico-chemistry, pharmacology, microbiology, biochemistry and computational chemistry. The main and basic task of medical chemistry is the discovery, design, synthesis and interaction of pharmaceutical products (drugs) with the body. The object of the study are mainly small organic molecules, which can be both natural and synthetically derived [1].

Inflammation is a process by which the body's white blood cells and substances they produce protect us from infection with foreign organisms, such as bacteria and viruses. Inflammation can be described as the series of changes that occur in living tissues following injury. The injury may be caused by various factors, which in turn initiate protective response in the host cell. The signs of inflammation are redness, swelling, heat, pain and loss of functional activities [2].

The non-steroidal anti-inflammatory drugs are drug substances with different chemical composition having peripheral analgesic, antipyretic and anti-inflammatory action. What distinguishes between them and steroid anti-inflammatory drugs is the steroid structure. The most commonly used non-steroidal anti-inflammatory drugs are aspirin, ibuprofen, ketoprofen and naproxen. The mechanism by which these NSAIDs elicit the therapeutic effects as antipyretic, analgesic, and anti-inflammatory is inhibition of prostaglandin synthesis. The NSAIDs competitively inhibit COXs, the enzymes catalyzing the synthesis of cyclic endoperoxides from arachidonic acid to form prostaglandins [3].

Depending on their chemical structure, non-steroidal anti-inflammatory agents can be divided into several groups: acetic acid derivatives and related substances, propionic acid derivatives, oxicams, coxibs, butylpyrazolidines, fenamates and others [4].

Ketoprofen or 2-[3-benzoylphenyl] propionic acid **1** is a non-steroidal anti-inflammatory drug. It's part of the propionic acid derivatives series. It has been synthesized in 1967 at the Rhône-Poulenc Research Center in Paris [5]. As early as 1973, ketoprofen was introduced in France and the United Kingdom. The efficacy of ketoprofen it has been demonstrated from the beginning of treatment of ankylosing spondylitis [6], rheumatoid arthritis [7], and osteoarthritis of the hip and knee [8,9]. In now a days ketoprofen is still one of the most popular non-steroidal anti-inflammatory agents.



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Figure 1. Structural formula of ketoprofen.

During the years vast array of ketoprofen derivatives have been synthesized and analyzed for its biological activities. Have been reported [10] successfully obtaining of 2-(3-benzoyl phenyl) propanohydroxamic acid and 2-{3-[(hydroxyimino) (phenyl) methyl] phenyl} propionic acid and were screened for their anti-inflammatory activity in rat paw edema and in vitro antitumor activity against 60 human tumor cell lines. The authors have reported that 2-{3-[(hydroxyimino) (phenyl) methyl] phenyl} propionic acid is more potent than ketoprofen in rat paw edema model. Also, both new obtained ketoprofen derivatives showed moderate anticancer activity ranging from 1 to 23% inhibition of growth in 38 cell lines of 8 tumor subpanels at 10μM concentration in a single dose experiment.

Another synthesis, characterization and examination of physicochemical properties of several different prodrugs of ketoprofen were reported by the same scientist group [11]. The results confirm all the ester prodrugs have been synthesized are chemically stable, possess increased lipophilicity compared to their parent compounds and converted to the active drugs in vivo. All the compounds exhibit anti-inflammatory activity ranging from 91.8% to 113.3% in comparison with the parent ketoprofen. A compound obtained from ketoprofen and salicylic acid has been noted to potentiate the activity making it most active molecule of the series.

Research team from Yemen [12] have tried to improve the specificity of the NSAIDS for COX-2. They have successfully synthesized ibuprofen and ketoprofen derivatives with 2-amino-5-methyl -1,3,4-thiadiazole and 2-amino-5-(methylthio)-1,3,4-thiadiazole and have evaluated their pharmacological activity which indicates that some of the compounds showed maximal anti-inflammatory activity with less ulcerogenic effect, while other compounds showed least ulcer indexes these effects may be refer to the presence of certain structural features of heterocyclic ring.

Rehman and co-workers [13] have reported the synthesis of Schiff base between isoniazid and ketoprofen. The authors pointed the potential use of the newly obtained compound to treat tuberculosis as well as fever and fatigue related to tuberculosis. Razić and co-workers [14] have published an article describing the synthesis of a series of novel ketoprofen derivatives containing amide as well as carbamate functional groups. The authors' antioxidative screenings revealed that some of the compounds possess excellent lipid peroxidation inhibition at 0.1mM concentration. Few of the compounds also show high soybean lipoxygenase inhibition activity. The amidocarbamate derivatives show weak reducing activity against 1,1-diphenyl-2-picrylhydrazyl radicals. The cytostatic activity of the most compounds is reported as a moderate (IC50: 10-25μM). Two new glucopyranoside ketoprofen derivatives have been synthesized from Sahu and co-workers [15] the compounds have been evaluated for their anti-inflammatory, analgesic and gastrointestinal activity. The obtained results show that the newly obtained derivatives have improved the anti-inflammatory and analgesic activity over the parent drug (ketoprofen).

On other hand the isoquinoline alkaloids are known for owning a wide range of biological activities [16-21].

Because of the side effects as well as the incompatibility of ketoprofen with other drugs, it is of interest to produce new ketoprofen analogues to study their biological activity and seek a correlation between their structure and activity.

RESULTS AND DISCUSSION

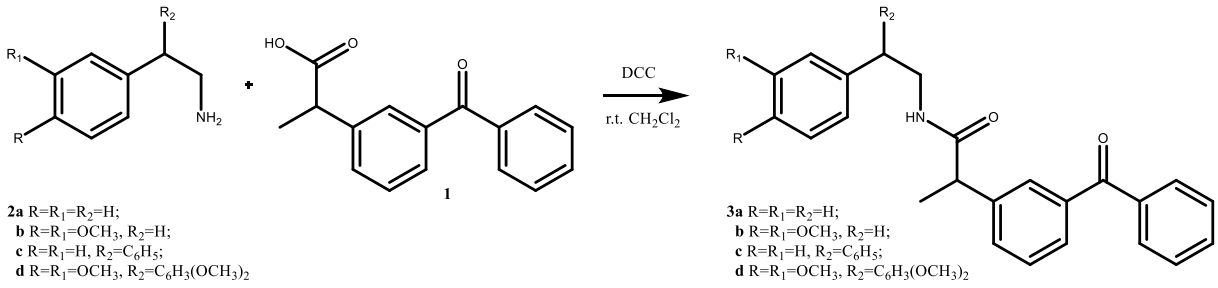
In the Department of Organic Chemistry at the University of Plovdiv "Paisii Hilendarski" for the last few decades successfully have been applied the *α*-amidoalkylating reaction for the synthesis of a number of new isoquinoline derivatives [22-36]. Two different versions of the *α*-amidoalkylation reaction- intermolecular and intramolecular have been developed.

The concept of the green chemistry has played an important role in recent years in meeting the fundamental challenges of protecting our environment. One of the areas in which work can be done is to study alternative conditions for chemical transformation with the formation of a small amount of by-products and waste materials as well as minimal use of volatile and toxic organic solvents. That's why it is of paramount importance to seek simpler and more effective methods for the various organic transformations, which is set in the green chemistry.

A silica gel supported acids has achieved appreciable interest in organic synthesis because of its unique properties such as high efficiency –related with the surface area, more thermal stability and reusability, low toxicity, greater selectivity, ease of handling and high selectivity. The catalyst immobilization contributes easy separation of the products from the catalysts without tedious experimental workup, and enables the efficient recovery of the catalysts, and potentially allows the adaptation of the immobilized catalysts to continuous flow-type processes.

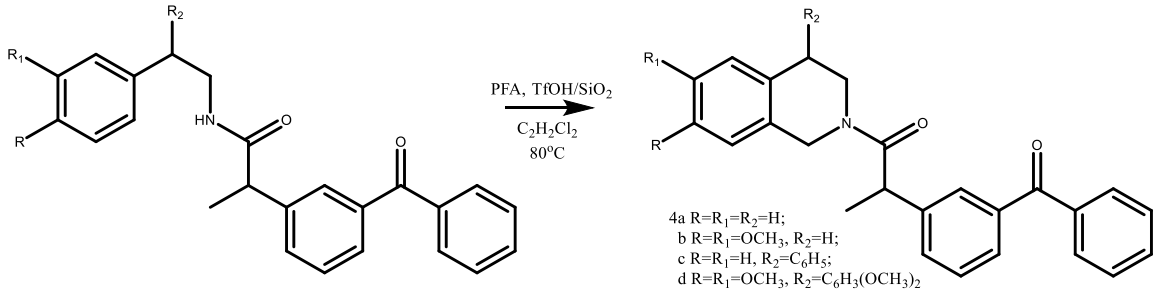
In our previous experiments we have successfully reported [37-39] the application of heterogeneous acid catalysts for obtaining of different heterocyclic compounds. To apply heterogeneous catalysts in reaction of *α*-amidoalkylation for obtaining a series of isoquinoline derivatives of ketoprofen firstly we had to obtain the starting ketoprofen amides.

As ketoprofen is carboxylic acid one possible way for the synthesis of the starting amides **3** is by using *N*, *N*-dicyclohexylcarbodiimide (DCC). DCC is a dehydrating agent commonly used for the preparation of esters, amides or anhydrides. It is commercially available as a crystalline waxy substance with a low melting point of 34-35° C. DCC reacts with the carboxyl group of ketoprofen to provide an activated acylation agent that reacts with the amino group of the other molecule to form an amide bond. The course of the reaction was monitored by thin-layer chromatography and, after complete depletion of the starting materials, the target compounds were easily isolated. The obtained four amides **3** are new compounds (Reaxys) interesting because of their potential biological activities. The yields of compounds **3** are shown in table 1 below.



Scheme 1. Synthesis of ketoprofen amides **3**.

The next step in our work was cyclisation of the newly obtained amides **3**. For this purpose method which involves the application of "heterogeneous catalyst" ($TfOH/SiO_2$) in the reaction of intramolecular *α*-amidoalkylation have been applied. To begin with - paraformaldehyde and $TfOH/SiO_2$ were added into the obtained amides **3** dissolved in dichloroethane. The reaction mixture is stirred with an electromagnetic stirrer at 80°C, observing that for 60 minutes (**4b** and **4d**) and 120minutes (**4a** and **4c**) under these reaction conditions the reaction is complete. The course of the reaction is monitored by thin layer chromatography. The separation of the final products is quick and easy without obtaining of any waste products.



Scheme 2. Synthesis of compounds **4**.

In Table 1 are shown the yields of the obtained ketoprofen derivatives.

	R	**R_1**	**R_2**	**Yield,%**
3a	H	H	H	98
b	OCH_3	OCH_3	H	97
c	H	H	C_6H_5	95
d	OCH_3	OCH_3	$C_6H_3(OCH_3)_2$	97
4a	H	H	H	89
b	OCH_3	OCH_3	H	91
c	H	H	C_6H_5	84
d	OCH_3	OCH_3	$C_6H_3(OCH_3)_2$	92

Table 1. Yields of the obtained compounds **3** and **4**.

The application of computer simulation of the biological effect of compounds, based on the relationship "structure-activity" (SAR), allows determining the potential of their application and reducing the cost of the biological screening tests which need to be conducted. Most of biologically active compounds have both pharmacotherapeutic and side/toxic actions. To estimate general efficacy and safety of the newly synthesized compounds **3** and **4**, their biological potential has been calculated.

A computerized prediction of biological activity for the compounds studied was performed using available online services. Possible therapeutic effects were predicted using the PASS Online program [40, 41], and the acute toxicity values for LD_{50} rats were determined by the GUSAR Online platform [42]. Also the lipophilicity as a fundamental property of the matter was evaluated by calculating Log*P* of the obtained compounds *via* ACD/ChemSketch/LogP Predictor v.14.08. The results are presented in Table 2 below.

Compound	Therapeutic effects Predicted (top 5)	Predicted LD_{50} values in mg/kg, type of administration*, toxicity class	Calculated Log*P*
3a	**1.**Calcium channel (voltage-sensitive) activator **2.**Fibrinolytic **3.**Antihypoxic **4.**Antineurotic **5.**Insulin promoter	458.9, IP, class 4 41.360, IV, class 4 1245, PO, class 4 841.2, SC, class 4	4.02 ±0.51
3b	**1.**Calcium channel (voltage-sensitive) activator **2.**Fibrinolytic **3.**Antineurotic **4.**Antieczematic **5.**Mucositis treatment	697.4, IP, class 5 74.290, IV, class 4 1459, PO, class 4 1320, SC, class 5	3.76 ±0.54
3c	**1.**Fibronolytic **2.**Mucomembranous protector **3.**Oxidoreductase inhibitor **4.**Calcium channel (voltage-sensitive) activator **5.**Spasmolytic, urinary	540.6, IP, class 5 55.340, IV, class 4 2102, PO, class 5 1452, SC, class 5	5.62 ±0.54
3d	**1.**Fibrinolytic **2.**Calcium channel (voltage-sensitive) activator **3.**Spasmolytic, urinary **4.**Oxidoreductase inhibitor **5.**Mucomembranous protector	1372, IP, Non Toxic 75.540, IV, class 4 1455, PO, class 4 2549, SC, Non Toxic	5.09 ±0.59
4a	**1.**Fibrinolytic **2.**Antineurotic **3.**Analgesic **4.**Anti-inflammatory **5.**Antihypoxic	398.5, IP, class 4 27.170, IV, class 3 602.3, PO, class 4 310.4, SC, class 4	4.65 ±0.55
4b	**1.**Fibrinolytic **2.**Antineurotic **3.**MAP kinase stimulant **4.**Anti-inflammatory **5.**General pump inhibitor	478.0, IP, class 4 30.750, IV, class 3 968.5, PO, class 4 516.6, SC, class 4	4.39 ±0.58
4c	**1.** Antineurotic **2.** Fibrinolytic **3.**Analgesic **4.**Phobic disorders treatment **5.**Anti-inflammatory	832.2, IP, class 5 48.150, IV, class 4 1673.0, PO, class 4 499.6, SC, class 4	6.10 ±0.56

4d	**1.**Antineurotic **2.**Fibrinolytic **3.**Gluconate (acceptor) inhibitor **4.**Anti-inflammatory **5.**General pump inhibitor	2-dehydrogenase	906.8, IP, class 5 31.560, IV, class 3 945.4, PO, class 4 790.4, SC, class 4	5.57 ±0.61

*IP - Intraperitoneal route of administration; IV- Intravenous route of administration; PO- oral route of administration; SC- subcutaneous route of administration;

Table 2. Results of prediction of therapeutic effects, LD_{50} values of acute toxicity of rats and LogP of the new obtained compounds **3** and **4**.

Using the PASS online service we have obtained output information as a list of predicted types of activity with the estimated probability for each type of activity "to be active" Pa and "to be inactive" Pi, which vary from zero to one. The probabilities Pa and Pi also indicate the estimated probabilities of first- and second-kind errors, respectively [41].

As the obtained compounds **3** and **4** are ketoprofen derivatives they all have shown promising values of anti-inflammatory activity as can be seen in table 3. All the cyclic compounds **4** have greater values (in top 5) than the corresponding starting amide **3**. Only for comparison the calculated ketoprofen Pa value is 0.933.

	Pa		**Pa**	
3a	0.489	<	0.604	**4a**
3b	0.469	<	0.585	**4b**
3c	0.450	<	0.553	**4c**
3d	0.439	<	0.532	**4d**

Table 3. Comparison of the anti-inflammatory Pa values of compounds **3** and **4**.

Considering the obtained results can also be seen that the amides **3** as well as 1,2,3,4-tetrahydroisoquinolines **4** have high probability to own fibrinolytic properties. Fibrinolytic drugs are also called thrombolytic drugs, and they are capable of stimulating the dissolution of a blood clot (thrombus). The mechanism of their work is explained with activating the so-called fibrinolytic pathway. Here we have obtained higher values for compounds **3c**, **3d**, **4a** and **4b**. For comparison only the fibrinolytic Pa value we have obtained for ketoprofen is 0.950.

	Pa		**Pa**	
3a	0.692	<	0.762	**4a**
3b	0.705	<	0.788	**4b**
3c	0.724	>	0.684	**4c**
3d	0.736	>	0.709	**4d**

Table 4. Comparison of the fibrinolytic Pa values of compounds **3** and **4**.

Other predicted activity which can be seen in most top 5 values is antineurotic activity (see **Table 1**). The predicted antineurotic Pa value for the starting ketoprofen is 0.615. We have obtained higher numbers for the cyclic compounds **4** (see **Table 5**). From this point of view can be concluded that 1,2,3,4-tetrahydroisoquinoline connected *via* amide bond to ketoprofen will potentially increase the antineurotic activity of the starting NSAID **1**, as the calculated Pa value for 1,2,3,4-tetrahydroisoquinoline is 0.845.

	Pa		Pa	
3a	0.678	<	0.706	**4a**
3b	0.698	<	0.742	**4b**
3c	0.420	<	0.800	**4c**
3d	0.446	<	0.832	**4d**

Table 5. Comparison of the antineurotic Pa values of compounds **3** and **4**.

All starting amides **3** have obtained relatively large Pa values for calcium channel (voltage-sensitive) activator in comparison with the cyclic compounds **4**. Having high Pa value compounds **3** (see **Table 6**) could play a major role both in the normal functioning and also in various pathological processes that occur in neuronal, neurosecretory and muscle cells, as calcium channel activators do. The calculated calcium channel (voltage-sensitive) activator Pa values for ketoprofen and 1,2,3,4-tetrahydroisoquinolin are respectively 0.568 and 0.596.

	Pa		Pa	
3a	0.681	>	0.451	**4a**
3b	0.694	>	0.469	**4b**
3c	0.633	>	0.354	**4c**
3d	0.647	>	0.373	**4d**

Table 6. Comparison of the calcium channel (voltage-sensitive) activator Pa values of compounds **3** and **4**.

Other predicted activities of the obtained compounds are antihypoxic, insulin promoter, antieczematic, mucomembranous protector, oxidoreductase inhibitor, urinary spasmolytic, MAP kinase stimulant, general pump inhibitor, phobic disorders treatment, gluconate 2-dehydrogenase (acceptor) inhibitor etc., and the probability for possible real activity here is smaller.

The *In Silico* studies for acute toxicity carried out shows that more of the compounds are non-toxic or less toxic (Class 5 and 4 of acute toxicity). Some of the compounds show moderate toxicity (Class 3).

Log*P* is used in the pharmaceutical industries for understanding the behavior of drug molecules in the human body [43]. As the lipophilicity is a major determining factor in a compound's absorption, distribution in the body, penetration across vital membranes and biological barriers, metabolism and excretion. According to "Lipinski's Rule of 5" the log*P* of a compound intended for oral administration should be less than 5(log*P*<5). According the results, we have obtained (see **Table 2**) compounds **3a**, **3b**, **4a** and **4b** theoretically are suitable for oral administration as their log *P* values are below 5. More lipophilic compounds may not be ideal for penetration through certain barriers. A log*P* value around 2 should have a drug targeting the central nervous system. For oral and intestinal absorption, the best values are between the interval 1.35 - 1.8, while a drug intended for sub-lingual

absorption may have a log*P* value higher than 5 (log*P*>5) as compounds **3c**, **3d**, **4c** and **4d**. The difference between the two groups' compounds (**3a**, **3b**, **4a**, **4b** and **3c**, **3d**, **4c**, **4d**) is the presence of an extra phenyl group which is responsible for the higher lipophilicity. For comparison the obtained log*P* value for ketoprofen **1** is 2.81±0.33.

EXPERIMENTAL SECTION

All the reagents and chemicals were purchased from commercial sources (Sigma-Aldrich, S.A., Sofia, Bulgaria) and used as received. Melting points were determined on a Boetius hot stage apparatus and are non-corrected. The spectral data were recorded on a Bruker Avance II + 600 spectrometer (BAS-IOCCP—Sofia, Sofia, Bulgaria). The ^{1}H-NMR and ^{13}C-NMR spectra were taken in $CDCl_3$ or DMSO at 600 MHz and 150.9 MHz, respectively. Chemical shifts are given in ppm relative and were referenced to TMS (δ = 0.00 ppm) as an internal standard with the coupling constants indicated in Hz. The NMR spectra were taken at room temperature (ac. 295 K). TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates.

Synthesis of ketoprofen amides 3

To the solution of ketoprofen **1** (1mmol) in 25ml CH_2Cl_2, *N*, *N*-dicyclohexylcarbodiimide (1mmol) has been added. For 10 min the reaction mixture was stirred at room temperature. After the addition of the corresponding amine **2** (1mmol) the reaction mixture was stirred for another 50 minutes and formation of white crystals was observed. The side product of dicyclohexylurea (white crystals) was separated *via* sintered glass filter. The filtrate was washed with diluted hydrochloric acid, saturated solution of Na_2CO_3 and brine. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure.

3a: 2-(3-benzoylphenyl)-N-phenethylpropanamide

^{1}H NMR (600 MHz, DMSO) δ 7.75 – 7.64 (m, 4H), 7.53 (m, 6H), 7.16 (m, 4H), 5.44 (s, 1H), 3.29 (ddd, J = 20.0, 13.4, 6.6 Hz, 1H), 2.69 (t, J = 7.1 Hz, 2H), 2.50 (t, J = 7.1 Hz, 2H), 1.37 (d, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 196.14, 173.27, 157.25, 143.30, 139.92, 137.65, 132.88, 131.94, 129.87, 128.97, 128.90, 128.87, 128.81, 128.58, 128.20, 126.35, 48.15, 45.61, 33.77, 24.84, 18.92.

3b: 2-(3-benzoylphenyl)-N-(3, 4-dimethoxyphenethyl) propanamide

^{1}H NMR (600 MHz, DMSO) δ 8.10 (t, J = 5.6 Hz, 1H), 7.75 – 7.70 (m, 3H), 7.61 – 7.54 (m, 5H), 7.49 (t, J = 7.7 Hz, 1H), 6.74 (dd, J = 10.1, 5.1 Hz, 2H), 6.56 (dd, J = 8.1, 2.0 Hz, 1H), 3.67 (d, J = 3.1 Hz, 6H), 3.24 – 3.20 (m, 1H), 2.59 (dd, J = 10.5, 4.7 Hz, 2H), 2.50 (dt, J = 3.6, 1.8 Hz, 2H), 1.34 (d, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 196.20, 173.19, 148.98, 147.58, 143.23, 137.50, 137.28, 133.16, 132.26, 132.08, 130.13, 130.09, 129.04, 128.98, 128.96, 128.54, 120.90, 112.84, 112.12, 55.71, 45.28, 34.99, 19.00, 15.63.

3c: 2-(3-benzoylphenyl)-N-(2,2-diphenylethyl) propanamide

^{1}H NMR (600 MHz, DMSO) δ 7.73 – 7.61 (m, 5H), 7.58 – 7.53 (m, 3H), 7.50 – 7.45 (m, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.23 – 7.20 (m, 5H), 7.18 – 7.11 (m, 4H), 5.44 (t, J = 6.9 Hz, 1H), 4.18 (t, J = 7.8 Hz, 1H), 3.76 – 3.65 (m, 2H), 3.63 (q, J = 7.0 Hz, 1H), 1.29 (d, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 196.10, 173.38, 143.08, 137.87, 137.58, 132.88, 131.88, 129.88, 128.90, 128.84, 128.71, 128.68, 128.35, 128.30, 128.16, 126.64, 50.52, 45.42, 43.94, 18.82.

3d: 2-(3-benzoylphenyl)-N-(2, 2-bis (3,4-dimethoxyphenyl) ethyl) propanamide

^{1}H NMR (600 MHz, DMSO) δ 7.72 (s, 1H), 7.71 (d, J = 1.3 Hz, 1H), 7.65 (dd, J = 8.5, 6.8 Hz, 3H), 7.55 (dd, J = 10.7, 4.6 Hz, 3H), 7.47 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 6.81 – 6.79 (m, 4H), 6.70 (ddd, J = 26.7, 8.3, 2.0 Hz, 2H), 4.04 (t, J = 7.8 Hz, 1H), 3.71 (s, 6H), 3.70 (d, J = 4.1 Hz, 6H), 3.67 – 3.64 (m, 2H), 2.50 (dt, J = 3.7, 1.8 Hz, 1H), 1.30 (d, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 196.09, 173.34, 149.52, 148.25, 143.12, 137.88, 137.52, 136.33, 132.84, 131.87, 129.86, 128.88, 128.82, 128.65, 128.18, 120.63, 113.32, 56.39, 49.70, 45.41, 44.13, 18.88.

Synthesis of compounds 4

To the corresponding 2-phenylethylamides (3 mmol) and paraformaldehyde (5 mmol) dissolved in a $C_2H_4Cl_2$ (10 mL) 0.06 g of catalyst ($TfOH/SiO_2$, 0.5 mmol/g) have been added. The reaction mixture was stirred at 80°C for 1(2) hour(s). After the completion of the reaction the reaction mixture was cooled down and the catalyst was separated by simple filtration. The catalyst TfOH/SiO2 was prepared using the procedure detailed by Liu [44].

4a: 2-(3-benzoylphenyl)-1-(3,4-dihydroisoquinolin-2(1H)-yl)propan-1-one

^{1}H NMR (600 MHz, CDCl3) δ 7.71 – 7.69 (m, 1H), 7.63 – 7.60 (m, 1H), 7.55 – 7.51 (m, 1H), 7.46 – 7.34 (m, 5H), 7.16 – 7.08 (m, 3H), 6.96 – 6.93 (m, 2H), 4.65 (s, 2H), 3.48 (q, J = 7.2 Hz, 1H), 3.46 – 3.38 (m, 1H), 3.34 (td, J = 13.1, 6.9 Hz, 1H), 2.70 – 2.61 (m, 2H), 1.45 (d, J = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, CDCl3) δ 196.53, 173.46, 141.74, 138.67, 138.00, 137.39, 132.63, 131.59, 130.07, 129.15, 129.14, 128.80, 128.71, 128.59, 128.37, 126.48, 77.28, 77.07, 76.85, 49.08, 47.01, 40.77, 25.63, 18.50.

4b: 2-(3-benzoylphenyl)-1-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-one

^{1}H NMR (600 MHz, CDCl3) δ 7.73 – 7.69 (m, 2H), 7.65 (tt, J = 6.8, 3.4 Hz, 2H), 7.60 – 7.58 (m, 1H), 7.54 – 7.48 (m, 3H), 7.42 – 7.40 (m, 1H), 7.37 – 7.34 (m, 2H), 4.65 (s, 2H), 4.07 – 3.96 (m, 1H), 3.78 (t, J=1.9, 2H), 3.74 (t, J = 3.9 Hz, 6H), 3.70 (s, 1H), 3.54 (t, J = 5.9 Hz, 1H), 1.44 (d, J = 1.9 Hz, 3H). ^{13}C NMR (151 MHz, CDCl3) δ 196.57, 171.99, 147.81, 147.63, 138.13, 137.43, 132.59, 131.51, 131.26, 130.06, 129.12, 129.07, 129.01, 128.80, 128.75, 128.38, 128.35, 128.32, 125.17, 120.61, 111.66, 111.17, 111.09, 109.31, 55.98, 52.56, 47.06, 43.31, 28.67, 18.83**.**

4c: 2-(3-benzoylphenyl)-1-(4-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-one

^{1}H NMR (600 MHz, DMSO) δ 7.74 – 7.65 (m, 1H), 7.64 – 7.51 (m, 2H), 7.49 – 7.43 (m, 1H), 7.32 – 7.24 (m, 1H), 7.22 – 7.19 (m, 2H), 7.16 – 7.09 (m, 1H), 5.76 (s, 1H), 4.12 (t, J = 7.9 Hz, 1H), 3.69 (ddd, J = 10.6, 7.7, 5.8 Hz, 1H), 3.62 (dd, J = 9.4, 6.3 Hz, 1H), 2.50 (dt, J = 3.6, 1.8 Hz, 1H), 1.26 (d, J = 7.0 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 196.19, 173.39, 143.24, 143.12, 142.98, 137.52, 137.22, 133.15, 132.02, 130.10, 129.04, 128.96, 128.84, 128.77, 128.75, 128.47, 128.33, 128.28, 126.71, 55.38, 50.35, 45.04, 18.80.

4d: 2-(3-benzoylphenyl)-1-(4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-one

^{1}H NMR (600 MHz, DMSO) δ 7.76 – 7.59 (m, 4H), 7.57 – 7.42 (m, 4H), 7.39 – 7.09 (m, 1H), 6.89 – 6.80 (m, 1H), 6.75 – 6.53 (m, 2H), 6.44 – 6.27 (m, 2H), 3.90 (s, 2H), 3.75 (d, J = 5.3 Hz, 2H), 3.70 (t, J = 10.6 Hz, 1H), 3.36 (s, 12H), 2.50 (dt, J = 3.5, 1.7 Hz, 1H), 1.08 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 195.98, 172.51, 149.20, 148.98, 148.91, 148.24, 148.16, 147.93, 147.79, 143.23, 142.71, 142.66, 142.54, 137.81, 137.70, 137.59, 137.53, 137.49, 137.38, 137.31, 137.13, 135.41, 133.23, 133.17, 133.03, 132.27, 130.07, 130.00, 128.99, 128.69, 128.61, 128.57, 128.42, 128.37, 126.18, 125.93, 120.95, 120.85, 120.70, 112.54, 112.36, 74.66, 65.40, 55.93, 55.84, 52.38, 45.57, 15.63.

CONCLUSIONS

In conclusion, we have successfully synthesized 4 amides and 4 1,2,3,4-tetrahydroisoquinoline derivatives containing ketoprofen fragment in its structure. Possible therapeutic effects, acute toxicity values for LD_{50} rats and lipophilicity of the newly obtained compounds were calculated. The obtained compounds **3** and **4** are promising for further biological examinations.

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