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Synthesis, Analgesic And Anti-Inflammatory Activities Of 4-Oxo-4-(4-(Pyrimidin-2-Yl) Piperazin-1-Yl)Butanoic Acid Derivatives

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ABSTRACT

A series of 4-oxo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)butanoic acid derivatives were synthesized and tested for their analgesic and anti-inflammatory activities, cyclooxygenase inhibition as well as for their ulcerogenic potential.

KEYWORDS

Analgesic;
Anti-inflammatory;
COX inhibitors;
Pyrimidines;
Piperazines;
Butanoic acid amides.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all therapeutic agents of diverse chemical classes. Among the many reported classes of anti-inflammatory agents, aryl and heteroaryl (alkyl) carboxylic acids possessed wide clinical applications but with incidence of gastrointestinal damage and ulceration[1]. Furthermore, conversion of these acids to amides resulted in more potent derivatives[2,3] and some of them showed reduced ulcerogenic effects[4].

Heteroaryl piperazine scaffolds were already incorporated in a variety of alkanoic acid anti-inflammatory agents[5,6] and in the recent generation of pain-killers named vanilloid receptor antagonists (Figure 1)[7-9].

On the basis of the above data and continuing our research program aimed at obtaining new anti-inflammatory agents, characterized by low ulcero genicity[10]. The present investigation deals with the synthesis of compounds having in their structure the pyrimidinyl piperazine scaffold bearing butanoic acid derivatives in order to investigate the effect of such molecular variation not only on the analgesic, anti-inflammatory and COX inhibition activities but also on their ulcerogenicity as well.

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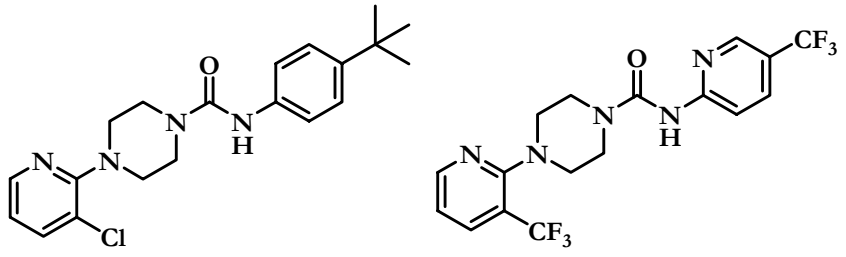


Figure1: Examples of the analgesic heteroaryl piperazine derivatives designed as vanilloid receptors antagonists.

EXPERIMENTAL

Chemistry

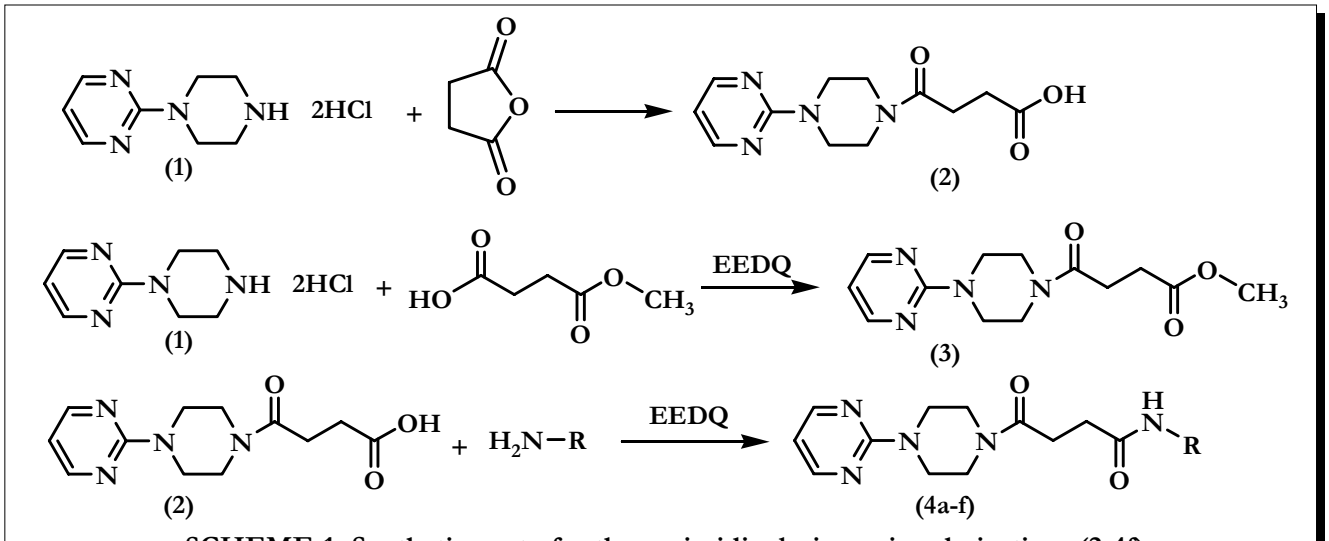
Melting points were determined on Electrothermal Melting Point Apparatus and are uncorrected. Elemental microanalyses were performed on Perkin-Elmer, 240 Elemental Analyzer, at the central laboratory, Assiut University. TLC was carried out using silica gel 60 F_{254} precoated sheets (E. Merck, Germany) and was visualized using UV lamp at 254 nm. IR spectra were recorded as KBr disks on a 470-Shimadzu Spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-AL 300 FT NMR system. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS) as internal standard. DMSO-d_6 was used as solvent unless otherwise specified. ^{13}C-NMR spectra were recorded on JEOL-JNM-EX 300, 75.45 MHz. Mass spectra were recorded on JEOL, JMS-600H (EI, 70 ev) (JEOL, Tokyo, Japan).

Synthesis of 4-oxo-4-(4-(pyrimidin-2-yl) piperazin-1-yl) butanoic acid (2)

A solution of 1-(2-pyrimidinyl)piperazine 2HCl (20 mmol), triethylamine (40 mmol) and succinic anhydride (20 mmol) was refluxed in $CHCl_3$ (20 ml) for 10 minutes, cooled and left overnight at room temperature. A white precipitate was obtained, filtered off and dried in desiccator. Recrystallization from EtOH/Et_2O to give the titled compound m.p. 158-160°C (reported 168-170°C)[11], IR (KBr) ν cm^{-1}: 3470-3200, 1726, 1618. Anal. Calcd. for $C_{12}H_{16}N_4O_3$: C, 54.54; H, 6.10; N; 21.20; Found C, 53.99, H; 6.09; N, 21.17

General coupling procedure (SCHEME 1)

To a solution of the appropriate carboxylic acid (20 mmol) in $CHCl_3$ (20 ml), the appropriate amine



SCHEME 1: Synthetic route for the pyrimidinyl piperazine derivatives (2-4f)

(20 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (20 mmol) were added during stirring at 0°C. The reaction mixture was stirred for 1 h at 0°C then overnight at room temperature. The mixture was washed with 5% $NaHCO_3$, and brine then dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated under reduced pressure. The crude product was crystallized from $CHCl_3$-Et_2O and dried under vacuum in desiccator.

Methyl-4-oxo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)butanoate (3)

Prepared from 1-(2-pyrimidinyl)piperazine 2HCl and 3-(methoxycarbonyl)propanoic acid as described by the general coupling procedure and crystallized from ethylacetate:n-hexane. IR (KBr) ν cm^{-1}: 3550, 3410, 3230, 1738, 1636, 1221 ; ^{1}H-NMR (DMSO-d_6) δ ppm: 2.7 (s, 4H, $2CH_2$), 3.56-3.73 (m, 8H, Pip), 3.83-3.90 (m, 3H, OCH_3), 6.52-6.56 (t, 1H, Pyrim), 8.32-8.33 (d, 2H, Pyrim) ; ^{13}C-NMR (DMSO-d_6): (δ ppm) 27.94, 29.58, 41.49, 42.44, 43.56, 45.01, 51.52, 110.37, 157.40, 161.35, 169.83, 173.49. EI-MS: m/z 278 (43.4 %) $[M]^+$, 279 (45.4 %) $[M+1]^+$, 280 (6.6 %) $[M+2]^+$, 247 (35.8 %) $[M-OCH_3]^+$. Anal. Calcd. for $C_{13}H_{18}N_4O_3.0.5\,H_2O$: C, 54.34; H, 6.67; N, 19.50; Found C, 54.74, H; 6.14; N, 19.38

N-Furan-2-ylmethyl-4-oxo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)-butanamide (4a)

Prepared from 4-Oxo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)butanoic acid and furfurylamine as described by the general coupling procedure. IR (KBr) ν cm^{-1}: 3545, 3410, 3235, 1669, 1633; ^{1}H-NMR (DMSO-d_6) δ ppm: 2.36-2.40 (t, 2H, CH_2), 2.56-2.61 (t, 2H, CH_2), 3.32-3.33 (m, 2H, Pip), 3.50-3.52 (m, 2H, Pip), 3.68-3.75 (m, 4H, Pip), 4.22-4.24 (d, 2H, $NHCH_2$), 6.23 (d, 1H, Furan), 6.36 (t, 1H, Pyrim), 6.62-6.66 (t, 1H, NH), 7.54 (d, 1H, Furan), 8.29 (t, 1H, Furan), 8.36-8.37 (d, 2H, Pyrim);^{13}C-NMR (DMSO-d_6): (δ, ppm) 27.75, 30.20, 35.44, 40.28, 40.40, 43.02, 43.32, 44.37, 106.59, 110.34, 141.88, 152.40, 157.89, 161.05, 170.03, 171.24. Anal. Calcd. for $C_{17}H_{21}N_5O_3$: C, 59.46; H, 6.16; N; 20.40; Found C, 59.10, H; 6.25; N, 20.44

4-Oxo-N-pyridin-2-ylmethyl-4-(4-(pyrimidin-2-yl)piperazin-1-yl)-butanamide (4b)

Prepared from 4-Oxo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)butanoic acid and 2-aminomethylpyridine as described by the general coupling procedure. IR (KBr) ν cm^{-1}: 3550, 3410, 3260, 1637, 1620; ^{1}H-NMR (DMSO-d_6) δ, ppm: 2.67-2.69 (t, 2H, CH_2), 2.75-2.79 (t, 2H, CH_2), 3.56-3.58 (t, 2H, Pip), 3.60-3.68 (t, 2H, Pip), 3.79-3.86 (m, 4H, Pip), 4.56-4.58 (d, 2H, $NHCH_2$), 6.52-6.55 (t, 1H, Pyrim), 7.02 (s, 1H, NH), 7.16-7.28 (m, 2H, Pyrid), 7.62-7.68 (m, 1H, Pyrid), 8.30-8.33 (m, 2H, Pyrim), 8.52-8.53 (m, 1H, Pyrid). Anal. Calcd. for $C_{18}H_{22}N_6O_2$: C, 61.00; H, 6.26; N; 23.71; Found C, 61.00, H; 6.40; N, 24.13

4-Oxo-N-pyridin-3-ylmethyl-4-(4-(pyrimidin-2-yl)piperazin-1-yl)-butanamide (4c)

Prepared from 4-Oxo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)butanoic acid and 3-aminomethylpyridine as described by the general coupling procedure. IR (KBr) ν cm^{-1}: 3550, 3410, 3295, 1636, 1620 ; ^{1}H-NMR (DMSO-d_6) δ ppm: 2.59-2.63 (t, 2H, CH_2), 2.73-2.77 (t, 2H, CH_2), 3.54-3.55 (t, 2H, Pip), 3.60-3.65 (t, 2H, Pip), 3.78-3.86 (m, 4H, Pip), 4.44-4.46 (d, 2H, $NHCH_2$), 6.53-6.56 (m, 1H, Pyrim), 6.83 (s, 1H, NH), 7.22-7.27 (m, 2H, Pyrid), 7.62-7.64 (d, 1H, Pyrid), 8.30-8.33 (m, 2H, Pyrim), 8.48-8.52 (m, 1H, Pyrid). Anal. Calcd. for $C_{18}H_{22}N_6O_2$: C, 61.00; H, 6.26; N; 23.71; Found C, 60.7, H; 6.25; N, 23.83

N-Morpholin-4-yl-4-oxo-4-(4-(pyrimidin-2-yl)-piperazin-1-yl)-butanamide (4d)

Prepared from 4-Oxo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)butanoic acid and morpholine as described by the general coupling procedure. IR (KBr) ν cm^{-1}: 3545, 3410, 3235, 1652, 1627; ^{1}H-NMR (DMSO-d_6) δ ppm: 2.67-2.78 (m, 4H, $2CH_2$), 3.54-3.72 (m, 12H, Pip & Morph. CH_2NCH_2), 3.81-3.90 (m, 4H, CH_2OCH_2), 6.52-6.55 (t, 1H, Pyrim), 8.31-8.33 (d, 2H, Pyrim). Anal. Calcd. for $C_{16}H_{23}N_5O_3$: C, 57.64; H, 6.95; N; 21.01; Found C, 57.43, H; 6.98; N, 21.18

4-Oxo-N-phenyl-4-(4-(pyrimidin-2-yl)piperazin-

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1-yl)-butanamide (4e)

Prepared from 4-Oxo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)butanoic acid and aniline as described by the general coupling procedure. IR (KBr) ν cm^{-1}: 3550, 3410, 3235, 1676, 1634 ; ^{1}H-NMR (DMSO-d_6) δ ppm: 2.76-2.82 (m, 4H, $2CH_2$), 3.56-3.60 (m, 2H, Pip), 3.70-3.73 (m, 2H, Pip), 3.81-3.90 (m, 4H, Pip), 6.53-6.56 (t, 1H, Pyrim), 7.04-7.09 (t, 1H, Phenyl), 7.26-7.32 (m, 2H, Phenyl), 7.51-7.54 (d, 2H, Phenyl), 8.32-8.33 (d, 2H, Pyrim), 8.44 (s, 1H, NH). Anal. Calcd. for $C_{18}H_{21}N_5O_2$: C, 63.70; H, 6.24; N; 20.64; Found C, 62.97, H; 6.23; N, 20.55

N-((Benzo[d][1,3]dioxol-6-yl)methyl)-4-oxo-4-(4-(pyrimidin-2-yl)piperazin-1-yl) butanamide (4f)

Prepared from 4-Oxo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)butanoic acid and piperonylamine as described by the general coupling procedure. IR (KBr) ν cm^{-1}: 3545, 3410, 3270, 1634, 1620; ^{1}H-NMR (DMSO-d_6) δ ppm: 1.97-2.61 (t, 2H, CH_2), 2.72-2.76 (t, 2H, CH_2), 3.56-3.58 (m, 2H, Pip), 3.67-3.69 (m, 2H, Pip), 3.78-3.86 (m, 4H, Pip), 4.32-4.34 (d, 2H, $NHCH_2$), 5.91 (s, 2H, OCH_2O), 6.52-6.55 (t, 1H, Pyrim), 6.73-6.76 (m, 3H, Ar-H), 7.26 (s, 1H, NH), 8.32-8.33 (d, 2H, Pyrim). Anal.Calcd. for $C_{20}H_{23}N_5O_4$: C, 60.44; H, 5.83; N; 17.62; Found C, 59.85, H; 5.78; N, 17.61

Biology

Animals

Local breed male albino mice weighing 23 ± 2 g were used for all experiments. The animals were housed in colony cages (6 mice each), maintained on standard pellet diet and water and left for two days adaptation before the experimental sessions. The food was withdrawn on the day before the experiment, but free access to water was allowed. All experiments were carried out according to the suggested ethical guidelines for care of laboratory animals.

Preparation of samples for biological assay

The synthesized compounds were given orally to test animals after suspending in 0.5% solution of sodium carboxymethylcellulose (CMC) in water. The control animals received the same experimental handling as those of the test groups except that the drug treatment was replaced with appropriate volumes of dosing vehicle. Either indomethacin (10 mg/kg) or aspirin (100 mg/kg) in 0.5% CMC was used as reference drug.

p-Benzoquinone-induced writhing test

The synthesized compounds were administered orally (100 mg/kg) in 0.5% carboxymethylcellulose solution 1 hour prior to the intra-peritoneal injection with 0.1 ml /10 g body weight of 2.5 % (v/v) p-benzoquinone (Merck) solution in distilled water. Aspirin was used as the reference. The control group received an appropriate volume of dosing vehicle 1 h before p-benzoquinone injection. The mice were placed in cages after p-benzoquinone injection and the numbers of the abdominal contractions (writhing movement) per animal were recorded during the following 15 minutes, starting on the 5th minute after the p-benzoquinone injection. The data represent the average of the total number of writhing movement observed. Percent analgesic activity was calculated as follows:

Percent antinociceptive activity = (n-n' /n) x 100
n: Average number of writhing of control group
n': Average number of writhing of test group

Anti-inflammatory activity

Carrageenan-induced hind paw edema was employed for testing anti-inflammatory activity. Six mice per group were used. Sixty minutes after the oral administration of the test compound (100 mg/kg) or dosing vehicle, each mouse was injected subcutaneously with a freshly prepared (0.5 mg/25 μl) carrageenan suspension in physiological saline into the plantar surface of the right hind paw and 25 μl of saline solution into that of the left as a secondary control. The difference in footpad thickness between the right and left foot was measured in 90-minutes interval with a pair of dial thickness gauge calipers. The mean values of the treated groups were compared with those of the control group treated with indomethacin and analyzed using statistical method.

Gastric side effects

Eight hours after the analgesic activity experiment mice were killed under deep ether anesthesia and their stomachs was removed. Then the stomach of each mouse was opened through great curvature and examined under a dissecting microscope for lesions or bleedings.

Acute toxicity

The animals used in the carrageenan-induced paw edema experiment were observed for the next 24 hours and mortality was recorded for each group at the end of the observation period.

Effect of compounds on human whole blood COX-1 and COX-2 activities[5]

The *in vitro* inhibitory activity of compounds **(4b,4f)** on COX-1 and COX-2 was assayed by the use of the COX inhibitor screening assay kit. Fresh human blood, obtained from non-fasted donors of either sex who had not taken aspirin or any NSAID during the prior 14 days, was collected in sodium heparin and distributed in 1 ml aliquots per well of 24-well tissue culture plate. The plates were placed on a gently rotating platform shaker in a 5% CO_2 incubator at 37 °C for 15 min. Test compounds (**4b**, **4f** and Celecoxib) were dissolved and diluted in DMSO, and 1 mL of each dilution of the test compound was added per well in duplicate wells. To induce COX-2, lipopolysaccharide from *E. coli* (Sigma Chemical Co.) was added at 10 mg/ml to appropriate wells 15 min after the addition of the test compounds.

To activate COX-1, the calcium ionophore A23187 (Sigma Chemical Co.) was added to a final concentration of 25 mM to separate wells 4.75 hours after the addition of the test compounds. At 30 minutes after ionophore addition or 5 hours after lipopoly saccharide addition, all incubations were terminated. COX-1 activity is determined by the production of thromboxane B_2, while COX-2 activity is determined by the production of prostaglandin E_2 (PGE_2).

RESULTS AND DISCUSSION

Synthesis and spectral data

All the new compounds were synthesized according to SCHEME 1. Reaction of the commercially available pyrimidinyl piperazine hydrochloride **(1)** with succinic anhydride afforded the 4-oxo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)butanoic acid **(2)** that consequently give the amides **(4a-f)** when coupled with amines using 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ). Likewise, coupling **(1)** with succinic acid mono methyl ester gave the corresponding ester **(3)**. The identities of the compounds obtained were confirmed by elemental analyses, IR, ^{1}HNMR, ^{13}CNMR and mass spectral data. Some physical data of the synthesized compounds are shown in TABLE 1.

Analgesic activity

The potential analgesic activity of all the synthesized compounds was evaluated in mice using the p-benzoquinone-induced writhing test.[5] The analgesic activity of the compound was assessed by measuring the inhibition of writhing in treated animals relative to the writhing in untreated group. Aspirin was used as a positive control. As shown in TABLE 2, all the tested compounds significantly (at least $P< 0.01$) possessed analgesic activity. The N-pyridin-2-ylmethyl amide **(4b)** showed superior (67.38%) analgesic profile compared to aspirin (58.28%). On the other hand, the N-phenyl amide **(4e)** and the N-piperonyl amide **(4f)** showed comparable activity (57.63% and 51.97%, respectively) with reference drug, aspirin, which showed 58.28%.

Anti-inflammatory activity

The anti-inflammatory activity of all the synthesized compounds was tested by their ability to inhibit the carrageenan-induced paw edema at 100 mg kg^{-1} orally dosing using indomethacin as positive control[5].

As shown in TABLE 3, all the tested compounds significantly (at least $P< 0.05$) possessed anti-inflammatory activity by comparing the percentage of edema inhibition of the tested compounds relative to the control at different time intervals. Compounds **(4b)** and **(4f)** possessed anti-inflammatory activity comparable to that of indomethacin at all the time intervals (% edema inhibition of **(4b)** and **(4f)** is 51.78 % and 49.58 %, respectively, compared to in-

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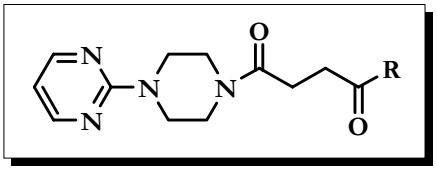
TABLE 1: Physical data of the pyrimidinyl piperazine derivatives (2-4f)



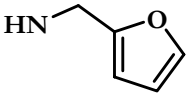
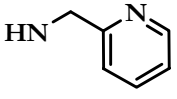
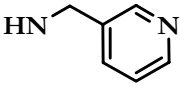
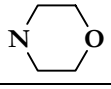
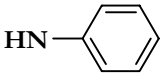
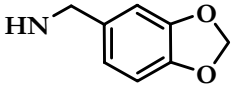
Compound	R	m.p.°C	Yield (%)	Mol. Formula (Mol. Wt)
2	OH	158-160	85	$C_{12}H_{16}N_4O_3$ (264.28)
3	OCH_3	68-70	72	$C_{13}H_{18}N_4O_3$ (278.31)
4a		155-157	65	$C_{17}H_{21}N_5O_3$ (343.38)
4b		144-145	63	$C_{18}H_{22}N_6O_2$ (354.41)
4c		160-162	55	$C_{18}H_{22}N_6O_2$ (354.41)
4d		138-140	60	$C_{16}H_{23}N_5O_3$ (333.39)
4e		168-170	75	$C_{18}H_{21}N_5O_2$ (339.39)
4f		183-185	68	$C_{20}H_{23}N_5O_4$ (397.43)

TABLE 2: Antinociceptive activity of tested compounds (2-4f)

Compound No.	Average number of writhing ± SEM	Antinociceptive activity (%)[a],*	Incidence of gastric lesions
Control	32.5 ± 3.31	-	0 / 6
2	26.92 ± 2.11	17.17	2 / 6
3	25.7 ± 2.01	20.92	1 / 6
4a	21.5 ± 1.21	33.85	0 / 6
4b	10.6 ± 1.17	67.38	0 / 6
4c	20.31 ± 1.43	37.51	0 / 6
4d	23.53 ± 1.15	27.60	0 / 6
4e	13.77 ± 1.28	57.63	0 / 6
4f	15.61 ± 1.11	51.97	0 / 6
Aspirin	13.56 ± 1.06	58.28	2 / 6

[a] Antinociceptive activities of the compounds and aspirin were tested at 100 mg/kg dose as described in the experimental part. *At least $P < 0.01$ for all tested compounds in comparison with control group.

TABLE 3: Anti-inflammatory activity of tested compounds (2-4f)

Compound No.	Anti-inflammatory activity (Percentage of edema inhibition)[a],*			
	90 min	180 min	270 min	360 min
Control	0	0	0	0
2	18.12	17.76	29.29	31.75
3	15.94	15.01	24.77	25.64
4a	16.16	17.34	25.5	23.6
4b	46.51	47.36	52.44	51.78
4c	26.42	27.7	37.79	37.35
4d	8.08	7.19	18.99	20.03
4e	13.76	15.01	23.33	22.58
4f	38.65	39.32	47.38	49.58
Indomethacin	40.17	43.97	50.99	50.59

[a] Anti-inflammatory activities of the synthesized compounds and indomethacin were tested at 100 mg/kg dose and 10 mg/kg dose, respectively as detailed in experimental part. * At least $P < 0.05$ for all tested compounds in comparison with control group.

TABLE 4: *In vitro* human whole blood COX-1 and COX-2 inhibition by selected compounds (4b, 4f and Celecoxib).

Compound	COX-1 Inhibition, (%) 100 μM	COX-2 Inhibition, (%) 10 μM
4b	41	69
4f	25	82
Celecoxib	76	100

domethacin which showed 50.59 % inhibition of the edema.

COX inhibitory activity

The most *in vivo* active compounds **(4b** and **4f)** were tested for their ability to inhibit COX-1 and COX-2 isozymes in human whole blood. For this initial *in vitro* screening, the compounds were assayed against COX-1 at 100 μM and COX-2 at 10 μM (TABLE 4).

The results reported in TABLE 4 show that compound **(4f)** showed selective COX-2 inhibition (COX-2 inhibition: 82 % at 10 μM; COX-1 inhibition: 25% at 100 μM). On the other hand, compound **(4b)** enhanced the COX-1 inhibitory activity slightly (COX-1 inhibition by **(4b)**: 41% at 100 μM) while leaving COX-2 activity slightly decreased (COX-2 inhibition by **(4b)**: 69 % at 10 μM). These results confirmed the conclusion that **(4f)** is a highly potent and selective COX-2 inhibitor (TABLE 4).

Ulcerogenic effects

The incidence of gastric lesions after the oral administration was used as a measure for ulcerogenicity of the tested compounds. As shown in TABLE 2, the acid **(2)** and the ester **(3)** showed ulcerogenic effect while all the amide derivatives **(4a-f)** possessed no ulcerogenic effects.

In conclusion, one can safely conclude that the amide derivatives **(4b)** and **(4f)** seemed to have a good analgesic and anti-inflammatory activities. The anti-inflammatory activity of compound **(4f)** is seemed to be through selective inhibition of COX-2 enzyme. Furthermore, it has no ulcerogenic effect so can be considered as good candidate for further biological evaluation.

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