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Ibuprofen amino acid derivatives: synthesis, docking and biological studies

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Abstract

This work aimed to synthesize new Ibuprofen amino acid derivatives as safe non-steroidal anti-inflammatory drugs (NSAIDs). The structures of the synthesized compounds have been determined using various spectral data. For tested compounds, molecular docking was performed into the cyclooxygnase-2 (COX-2) active site. The lowest root-mean-square deviation of atomic positions (RMSD) pose has been chosen for the binding affinity discussion. Docking protocol revealed that the binding interaction increased by the presence of hydrazide fragment in the tested compounds. Passed compounds through docking profile were examined for their anti -inflammatory and analgesic activities. Using a carrageenan-induced mouse model of hind paw edoema, we investigated the potential anti-inflammatory efficacy of the synthetic compounds in comparison to their parent molecule, ibuprofen. In addition to assessing the antinociceptive and ulcerogenic properties of the synthesized compounds

Keywords NSAIDs; Peptide candidates; Anti-inflammatory and Analgesic agents; docking

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) and their derivatives are widely used as analgesics and anti-inflammatory drugs. Their effect is thought to be due to inhibition of cyclooxygnase (COX), which results in a decrease in the concentration of prostaglandin (PG) in various tissues and fluids[1, 2]. Due to the presence of a free carboxylic group in their molecules. NSAIDs have been linked to gastrointestinal problems[3]. As a result, blocking this acidic group could be a viable way to reduce or eliminate gastrointestinal toxicity [4-6]. Synthesis of ester prodrugs of NSAIDs have reported an improved therapeutic index for oral delivery of NSAIDs [7]. In addition, Naproxyl amino acid methyl esters show similar anti-inflammatory activity[8]. Furthermore, NSAIDs glycol amide nitrate were reported to have less stomach harm when taken orally[9]. m-aminobenzoic acid analogues of NSAIDs have also been reported to be the most efficacious anti-inflammatory drugs with less ulcerogenic properties[10]. Furthermore, compared to the parent NSAIDs, the amide prodrug of NSAIDs derivatives demonstrated strong anti-inflammatory action [11]. Furthermore, propane-amide derivatives of NSAIDs were found to have antibacterial activity against Gram-positive bacteria such as Staphylococcus aureus and Bacillus subtilis, as well as Gram-negative bacteria such as Escherichia coli and Pseudomonas aeruginosa, which was comparable to standard antibiotics ampicillin for Gram-positive bacteria and ciprofloxacin for Gram-negative bacteria[12]. In addition, when tumor-bearing rates were treated with NSAIDs, the rate of tumour growth was lowered by 58 percent [13]. Furthermore, the hydroxamic acid derivatives of NSAIDs inhibited histone deacetylase (HDAC) effectively[14]. Furthermore, propanamide and urea NSAID derivatives were discovered to have a potential inhibitory impact against the colon cancer cell line HCT-116[15]. Furthermore, NSAIDs are expected to be promising leaders for novel compounds with antiviral activities against influenza A virus [16]. Furthermore, γ-tocopherol NSAIDs ester (e.g. γ-tocopherol acetylsalicylic acid ester) exhibit good antioxidant activity [17-21]. Several peptide candidates exhibit antibacterial effects against a variety of drug resistances and have a low proclivity

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for resistance enhancement [22-24]. Peptides as (LupronTM), (SandostatinTM), and (ZoladexTM) are employed as therapeutic agents [25, 26]. Peptides are powerful therapies because of their inherent ability to interact with biological systems [27-29]. The aim of research in our laboratory was study the effect of combination of *p*-ABA with glycine amino acid derivatives and evaluate their pharmacological activity.

Results and Discussion

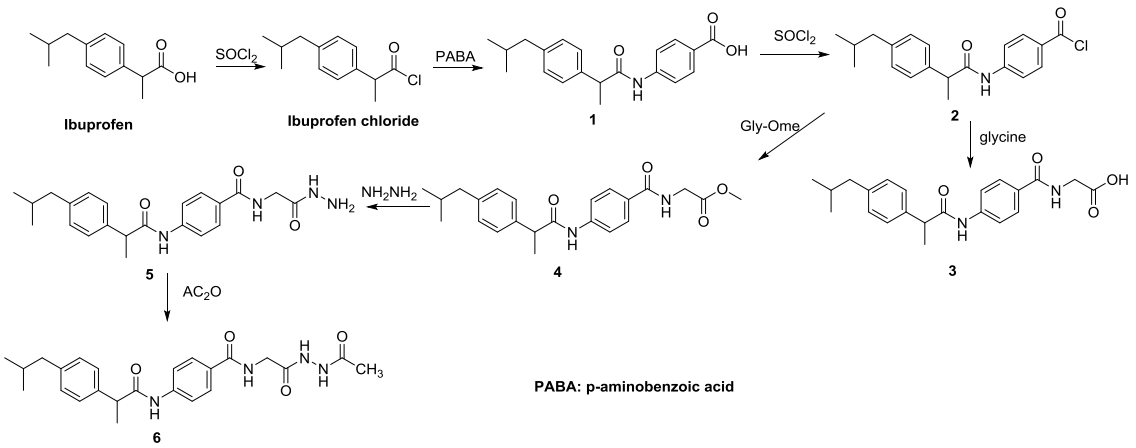
Chemistry

In our previous studies of peptide candidates, we found that they have good antimicrobial properties [18-20] and anticancer activities [30]. Thus, this study aims to synthesize new Ibuprofen amino acid derivatives hoping to possess various anti - inflammatory and analgesic activities.

The synthesis of the new compounds **3-17** was based on the acid chloride **2** which is produced after three steps starting from Ibuprofen (Schemes 1-3).

First , Ibuprofen was reacted with thionyl chloride to produce its chloride derivative, then reacted with *p*-aminobenzoic acid (PABA) to give compound **1** which in turn reacted with thionyl chloride to afford compound **2** (Scheme1)

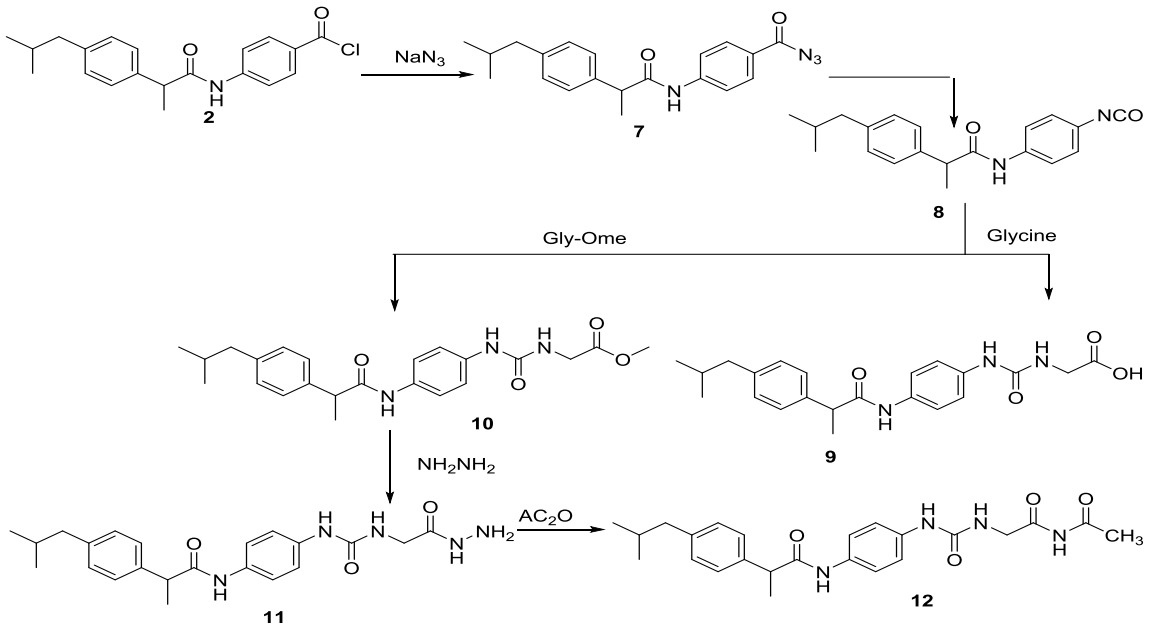
Compound **2** was reacted with glycine to give peptide derivate **3**, and with glycine methyl esterhydrochloride to afford compound **4**. Compound **4** underwent hydrazinolysis to produce hydrazide compound **5** that reacted with acetic anhydride to give compound **6** (Scheme 1). IR spectrum of compound **1** showed absorption bands at 3363 and 3460 cm^{-1} due to OH and NH groups, in addition to the presence of two absorption bands of carbonyl groups at 1720 cm^{-1} , and at cm^{-1}. 1H-NMR of **1** showed the characteristic signal of OH for carboxylic group of the amino acid moiety in the range δ =12.21 ppm NH for glycine were appeared in ^{1}H-NMR spectra at rang 3.44-8.05 and for compounds **3-6**.



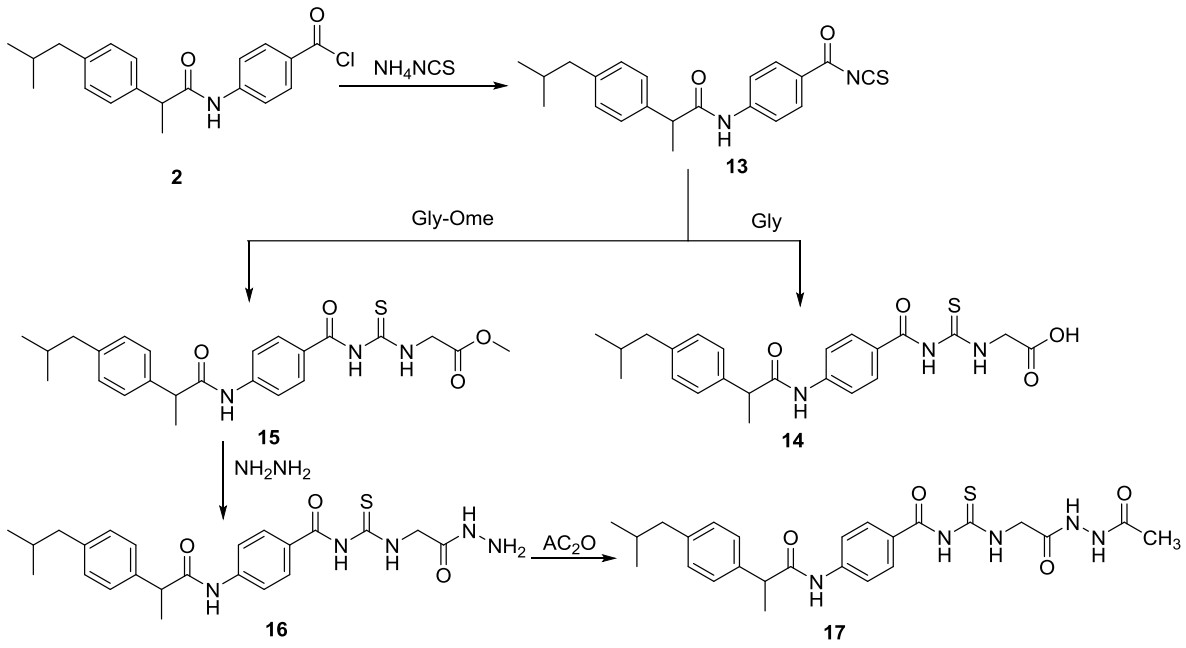
Scheme 1: Synthetic route for compounds **1**-**6**.

On the other hand, compound **2** was reacted with sodium azide to give 4-(2-(4-isobutylphenyl)propanamido)benzoyl azide (**7**) , which converted to 2-(4-isobutylphenyl)-N-(4-isocyanatophenyl)propenamide(**8**) by refluxing in dioxan. Then reaction of compound **8** with glycine to give ((4-(2-(4-isobutylphenyl)propanamido) phenyl) carbamoyl)glycine **(9)**, also reaction of compound **8** with glycin methyl ester afforded the methyl derivative **10**. Compound **10** reacted with hydrazine hydrate solution to give hydrazide derivative **11**, which was acylated by acetic anhydride to give methyl ((4-(2-(4- isobutylphenyl)propanamido)phenyl) carbamoyl) glycinate **12** (Scheme 2).

Compound **2** was reacted with NH_4NCS to give the isothiocyanate derivative **13** which reacted with glycine to give ((4-(2-(4-isobutylphenyl)-propanamido)benzoyl)carbamothioyl)glycine **14** and with glycine methyl ester hydrochloride to afford the methyl ester derivative **15**. Compound **15** in turn reacted with hydrazine hydrate solution to give N-((2-hydrazineyl-2-oxoethyl)carbamothioyl)-4-(2-(4-isobutylphenyl)propanamido)benzamide (**16**) which was acylated to N-((2-hydrazineyl-2-oxoethyl) carbamothioyl)-4-(2-(4-isobutylphenyl) propanamido)benzamide (**17**) upon reaction with acetic anhydride (Scheme 3).



Scheme 2: Synthetic routes for compounds **7-12**



Scheme 3: Synthetic routes for compounds **13-17**

Molecular Docking studies.

In trying to identify a suitable anti-inflammatory agent from the synthesized compounds, docking studies were performed for compounds **3-17**.The molecular docking was carried out as a pre-investigation for biological data with a structural foundation. The X-ray crystal structure of COX-2 (ID: 1PXX; [35]) complexed with the reference inhibitor was employed [32].

Tyr-385 and Ser-530 (Tyrosine-385) (Serotonin-530) have a critical functional structural for chelating arachidonic acid , and produce a tetrahedral intermediate that has been stabilized in the binding pocket by the negative charge[33- 36]

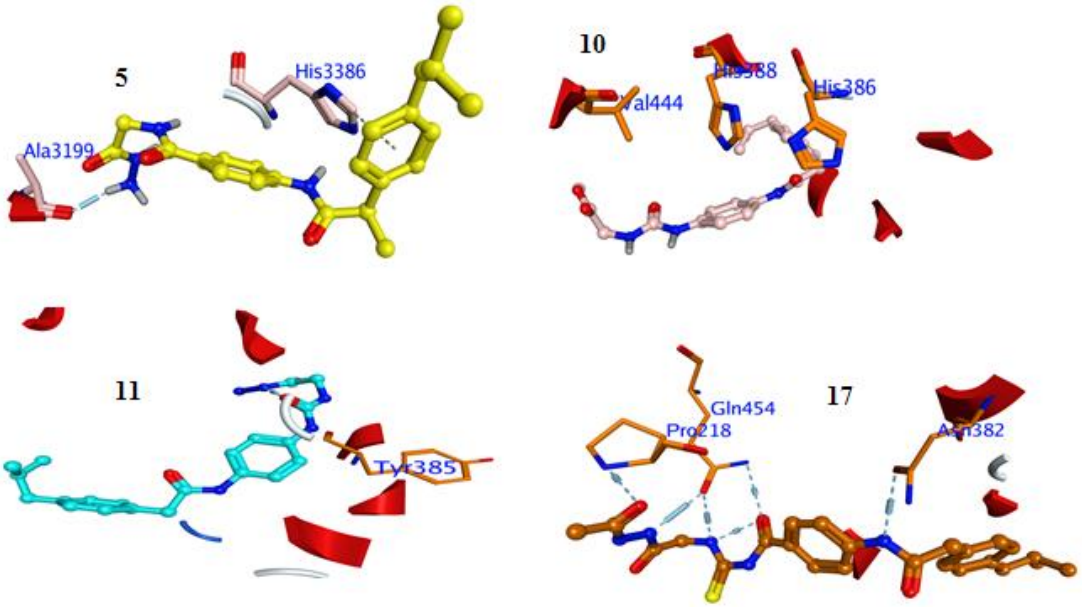


Fig.1 : The binding mode of most binding efficacy complexes (**5,10,11** and **17**) into the active site of COX-2, H-bond represented as blue dashed color

After the reference inhibitor was removed, compounds **5-20** re-docked into the COX-2 active site. The scoring score was used to examine the docking outcome. For the discussion of the binding affinity of (inhibitor-COX-2.) complex, the docking procedure with the lowest root-mean square deviation (RMSD) was used [35], MOE observed the (Ligand-COX-2) complexes with an RMSD root-mean-square deviation of atomic positions range of (1.119587A°-1.991136) for compounds **5-20**. The results of (table 1) show that all compounds had accurate binding energies (RMSD< 1 °A), with the exception of acetyl derivatives (3-17), which had significant RMSD (RMSD > 1°A) for binding energies (table 1).

Table 1: Docking scores of the synthesized compounds (3-17)

mseq	ΔE	rmsd	H.B	Int.	E_ele
3	-8.52508	1.119587	-8.79369	-20.3446	-8.64951
4	-8.43701	1.594102	35.37805	-18.3768	-7.15118
5	-9.3427	1.925192	47.23379	-15.7115	-7.93689
6	-8.27006	1.573833	-21.0949	-20.6559	-10.3292
7	-9.58089	1.483404	2.702431	-16.5787	-7.73023
9	-7.65405	1.797409	-10.0161	-19.5561	-8.123
10	-8.8903	1.991136	-115.573	-20.3042	-9.22536
11	-7.91111	1.332329	-59.8735	-14.7914	-9.40391
12	-9.018	1.261335	-85.5715	-21.8855	-7.98091
14	-8.90229	1.209473	-183.478	-5.83972	-9.15836
15	-9.19619	1.8981	-167.335	-16.7943	-8.36216
16	-8.8584	1.579354	-91.1952	-14.5985	-9.1499
17	-8.89857	1.666318	-53.8858	-16.4631	-7.9975

ΔE: Free binding energy of the ligand, Int.: Affinity binding energy of hydrogen bond interaction with receptor, H.B.: Hydrogen bonding energy between protein and ligand. Eele: Electrostatic interaction with the receptor.

The binding-interaction has improved by adding hydrazide moiety to the orginal compound. compounds **5, 10, 11** and **17** form important H-bond interactions with active binding pocket. These compounds trapped into the amino acid backbone of the binding pocket, through adjusting phenyl rings in perpendicular mode with Tyr-385 (Fig. 1). Furthermore, these compounds stabilize with itself to caped binding pocket, through arranged isobutyl phenyl rings in orthogonal position with amino acid's fragments (Fig.1). The results showed that the amino acid residues near the reference molecules are largely the same as those found in the tested compounds. The high binding score and process for the investigated

drugs suggested that they may be effective COX-2 inhibitors. All compounds possess Non-carcinogenic effect (~0.6-0.9 mg/kg body wt/day), without any acute oral toxicity (~0.47-0.63 mg/kg). tested compounds exhibit a low Rat acute level with lethal dose values (LD50 = ~2.43-2.66 , mol/kg). All compounds haven't act as both inhibitors and substrates against P-glycoprotein. Thus, we can able to safe retention of these compounds without any effect [37]. All compounds (3-17) were displayed positivity acceptance for blood brain barrier. Permeability of compounds through blood brain barrier (BBB) indicated that these compounds may be effective in treating inflammation. The compounds have displayed a weak inhibition action against Human Ether-a-gogo-Related Gene (hERG). These features can conduct to long QT syndrome[38-39]. Thus, we have concluded that, the synthesized compounds are a good oral bioavailability without observed any marked health effects via rodent toxicity profiles.

Pharmacological activities

Paw edema experiment:

The carrageenin induced paw edema technique was used to assess the anti-inflammatory efficacy of the produced compounds **5,10,11**, and **17**. [40]. The compounds were examined at a 35 mg kg^{-1} body mass oral dosage and compared to the conventional medication ibuprofen at the same dose. The anti-inflammatory activity of the substances studied ranged from 45 to 55 percent (Table 2, figure 2), with the conventional medication ibuprofen inhibiting inflammation by 49 percent after 4 hours. After 4 hours, compound **11** had the highest inhibitory percentage (55 percent). Compound **5** resulted in the lowest percent inhibition (45%) measured.

Table 2: Percent inhibition of inflammatory response post-carrageenan injection.

Drug/time	% inhibition after 1 hr	% inhibition after 2 hrs	% inhibition after 3 hrs	% inhibition after 4 hrs
BRU	18.81±2.4	34.37±5.9	38.11±3.7	48.65±1.2
5	55.78±6.6	55.10±7.6	43.73±6.3	45.77±2
10	65.20±3.7	45.77±5.8	58.14±7.9	54.365±3.6
11	69.73±7.4	53.48±1.7	45.42±1.5	54.88±2.9
17	61.21±14.2	56.27±3.9	57.81±5.7	50.68±2.2

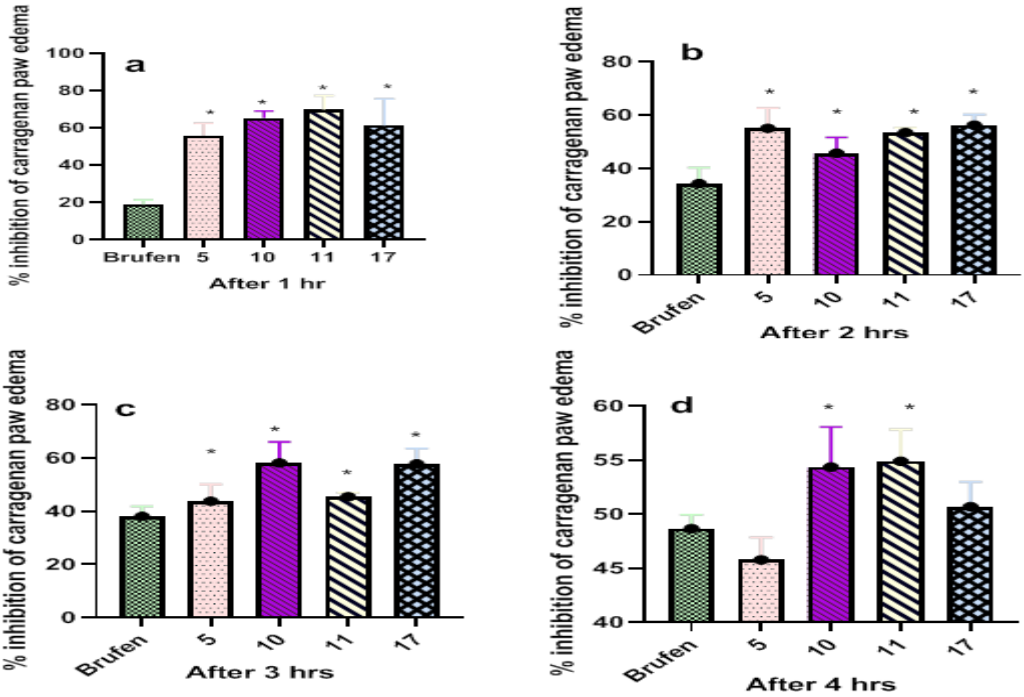


Fig.2: Percent inhibition of inflammatory response post-carrageenan injection. Compounds were administered orally at the dose of 35 mg/kg after the administration of 1% carrageenan solution. (*) means significant difference at P <0.05 compared to ibuprofen (BRU). Data are presented as means ± SD, n=6

Tail flick test:

The antinociceptive effect after injection of in tail-flick test was illustrated in Fig. 3. In The latency time-response bar chart of different groups (Fig. 3a), When compared to ibuprofen, there was a substantial difference in variance between groups. And the time response curve differed depending on the medication administered; the synthetic compounds **5** and **10** had the longest delay time and had a 100% MPE (Fig 3b), compared to just 22% in rats treated with the positive control (ibuprofen). [41] .

The antinociceptive effect after injection of in tail-flick test was illustrated in Fig. 3. In The latency time-response bar chart of different groups (Fig. 3a), it was seen that variation was significantly different among groups compared to ibuprofen. The time response curve was different based on drug injected, the synthetic compounds **26** showed significantly the highest latency time moreover, it showed a 81% MPE(Fig 3b), compared to only 22% in rats treated with the positive control (ibuprofen).

Acute ulcerogenesis:

Acute ulcerogenesis test was done according to Cioli [42] The tested compounds didn't show any ulceration or redness except **5** compound which displayed some erythema. Otherwise, the therapeutic dose of either ibuprofen or compounds **10**,**11** and **17** didn't show any acute ulcerogenic potential (Table 4).

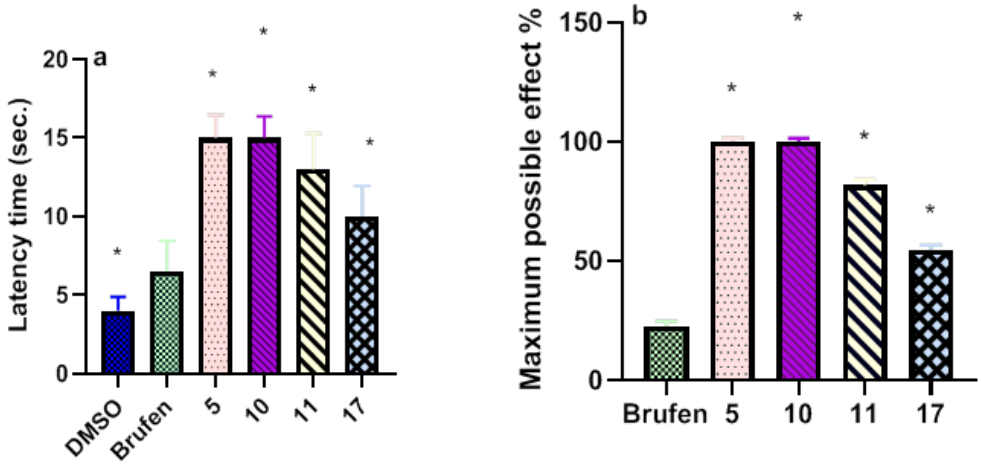


Fig 3.: The antinociceptive effect of ibuprofen and synthetic compounds **5**, **10**, **11** and **17** in tail flick test. animals received DMSO (vehicle), synthetic drugs in the dose of 35 mg/kg. (a) The time course of latency times of drugs. (b) Maximum Possible Effect percent (%MPE) of groups. Data were compared using one way ANOVA. * means significant difference at P <0.05 compared to ibuprofen. Data are presented as means ± SD, n=6

Table3: latency time and %MPE of tail flick test in response to the administration of DMSO (vehicle), Ibuprofen (BRU) and synthetic compounds **5**,**10**,**11** and **17**.

Drug	*Latency time (sec.)*	*MPE%*
DMSO	*4±0.89*	___
Bru	*6.5±1.96*	*22.7±1.96*
5	*15±1.47*	*100±1.47*
10	*15±1.37*	*100±1.37*
11	*13±2.28*	*81.81±2.28*
17	*10±1.96*	*54.54±1.96*

Table 4: Severity index of ibuprofen and synthetic compounds **5, 10,11** and **17**

Drug	***Severity index***
ru	***0***
5	***0.03±0.02***
10	***0***
11	***0***
17	***0***

Materials and Methods

Animals

Mature Wistar rats weighing 130-150 grams were purchased from the animal unit at the National Research Centre. Standard conditions 12:12 light-dark cycle and well ventilated rooms have been established for housing of the animals. Animals were kept in hygienic cages and given free access to clean standard pellet diet food and water. One week before conducting experiments, all the animals were shifted to be adapted to the laboratory environment.

This study was done according to standards of the ethics committee of the National Research Centre which is in accordance with the National Regulations on Animal Welfare and Institutional Animal Ethical Committee (IAEC).

Experimental

Chemistry

The solvents, chemicals, and thin layer chromatography employed in this study were provided from E. Merck (Hohenbrunn, Germany). Carrageenan was provided from Sigma Aldrich, Germany. The melting points were determined using the Digital Electro thermal melting point apparatus in opened international chemical companies: Sigma (Ronkonkoma, NY, USA), Fluka (Buchs, Switzerland), and glass capillary tubes and are uncorrected. Elemental micro-analyses for carbon, nitrogen, and hydrogen (Micro-Analytical Unit, Cairo University, Cairo, Egypt) were obtained within good limits of the theoretical values. Infrared (IR) spectra were listed as KBr disks using the Fourier transform infrared spectrophotometer (Shimadzu; Model: IRAffinity-1S) at the Micro-Analytical Unit at Cairo University in Egypt. The measurements of mass spectra occurred on a gas chromatograph–mass spectrometer (Shimadzu, Kyoto, Japan; Model: QP2010 ultra) at the Micro-analytical Unit at Cairo University in Egypt. The ^{1}H-NMR spectra were run on JEOL, JöEL500 MHz instruments (Tokyo, Japan) in DMSO-d6

Synthesis of 4-(2-(4-isobutylphenyl)propanamido)benzoic acid (1)

Ibuprofen A refluxed with pure thionyl chloride in Dioxane for 5 hrs to give product B. Then stirring product (B) with para amino benzoic acid in dioxin (20 ml) for 3hrs. The solvent was removed under vacuum to get product 1.

Product **1** was separated as colorless crystals, yield 95 %. mp 177-178 ^{o}C. IR (KBr, cm^{-1}): 3460 (NH), 3363 (OH), 3043 (CH aromatic), 2954 (CH aliphatic), 1720 (C=O), 1670 (C=O), 1624 (C=C), 1508 (C-N), 1323 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 12.21 (s, 1H, OH), 7.71 (d, *J* = 5 Hz, 2H, CH_{arom}), 7.28 (d, *J* = 5 Hz, 2H, CH_{arom}), 7.21 (d, *J* = 10 Hz, 2H, CH_{arom}), 6.65 (d, 2H, *J* = 10 Hz, CH_{arom}), 5.97 (s, 1H, NH), 3.73 (m, *J* = 5, 10 Hz, 1H, *CH*-Me), 2.52 (d, *J* = 10.0 Hz, 2H, CH_2), 1.90 (m, *J* = 10 Hz, 1H, CH), 1.45 (d, *J* = 10 Hz, 3H, CH_3), 0.95 (m, 6H, *J* = 10Hz, 2CH_3). MS (*m/z*): M^+ 325 (25%). Analysis for $C_{20}H_{23}NO_3$ (325.17). Calced.: % C, 73.82; H, 7.12; N, 4.30. Found: % C, 73.79; H, 7.20; N, 4.15.

(4-(2-(4-isobutylphenyl)propanamido)benzoyl)glycine (3)

The titled compound was synthesized by stirring of Glycine with compound (2) in THF (50 ml) and few drops of pyridine for 5 hrs at room temperature. The solvent was removed under vacuum to get product 3

Product **3** was separated as colorless crystals (ethanol), yield 85 %. mp 189-190^{o}C. IR (KBr, cm^{-1}): 3363 (NH), 3043 (CH aromatic), 2954 (CH aliphatic), 1720, 1666, 1624 (3 C=O), 1600 (C=C), 1508 (C-N), 1323 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 12.37 (br. s, 1H, OH), 8.15 (s, 1H, NH), 7.58 (d, *J* = 5 Hz, 2H, CH_{arom}), 7.14 (d, *J* = 5 Hz, 2H, CH_{arom}), 7.06 (d, *J* = 5 Hz, 2H, CH_{arom}), 6.50 (d, *J* = 5 Hz, 2H, CH_{arom}), 5.85 (s, 1H, NH), 3.96 (s, 2H, CH_2), 2.38 (d, *J* = 10.0 Hz, 2H, CH_2), 1.81 (m, *J* = 10 Hz, 1H, CH), 1.31 (d, *J* = 10 Hz, 3H, CH_3), 0.82 (m, 6H, *J* = 10Hz, 2CH_3). MS (*m/z*): M^+ 382 (20%). Analysis for $C_{22}H_{26}N_2O_4$ (382.19). Calced.: % C, 69.09; H, 6.85; N, 7.32. Found: % C, 69.25; H, 6.72; N, 7.25.

Methyl (4-(2-(4-isobutylphenyl)propanamido)benzoyl)glycinate (4)

The titled compounds were synthesized by stirring of Glycine methyl ester hydrochloride with compound (2) in THF (50 ml) and few drops of triethyl amine (TEA) for 3hrs. The solvent was removed under vacuum to get product 4.

Product **4** was separated as colorless crystals (ethanol), yield 78 %. mp 167-168 ^{o}C. IR (KBr, cm^{-1}): 3460 (NH), 3352 (NH), 3089 (CH aromatic), 2954 (CH aliphatic), 1716 (C=O), 1662 (C=O), 1600 (C=C), 1504 (C-N), 1354 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 7.58 (d, *J* = 10 Hz, 2H, CH_{arom}), 7.15 (d, *J* = 5 Hz, 2H, CH_{arom}), 7.07 (d, *J* = 5 Hz, 2H, CH_{arom}), 6.51 (d, *J* = 5, 10 Hz, 2H, CH_{arom}), 5.85 (s, 1H, NH), 3.61 (m, 3H, *CH*-Me, CH_2), 3.34 (br. s, 1H, NH), 2.99 (s, 3H, CH_3), 2.38 (d, *J* = 10.0 Hz, 2H, CH_2), 1.79 (m, *J* = 10 Hz, 1H, CH), 1.30 (d, *J* = 10 Hz, 3H, CH_3), 0.82 (m, 6H, *J* = 10Hz, 2CH_3). MS (*m/z*): M^{+2} 394 (25%). Analysis for $C_{23}H_{28}N_2O_4$ (396.20). Calced.: % C, 69.68; H, 7.12; N, 7.07. Found: % C, 69.76; H, 7.05; N, 7.19.

***N*-(2-hydrazineyl-2-oxoethyl)-4-(2-(4-isobutylphenyl)propanamido)benzamide (5)**

The titled compound was synthesized by heating compound (4) with ethanolic hydrazine hydrate solution (40 ml) for 1/2hr. The solvent was removed under vacuum

Product **5** was separated as colorless crystals, yield 65 %. mp 201-202 ^{o}C. IR (KBr, cm^{-1}): 3460 (NH),

3352 (NH), 3082 (NH), 3047 (CH aromatic), 2954 (CH aliphatic), 1720 (C=O), 1662 (C=O), 1604 (C=C), 1554 (C-N), 1323 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 7.83 (s, 1H, NH), 7.58 (d, *J* = 7.7 Hz, 2H, CH_{arom}), 7.15 (d, 2H, CH_{arom}), 7.05 (d, *J* = 6.6 Hz, 2H, CH_{arom}), 6.50 (d, 2H, *J* = 7.7 Hz, CH_{arom}), 6.17 (br s, 3H, NH, NH_2), 3.55 (t, *J* = 5.2 Hz, 1H, *CH*-Me), 2.38 (d, *J* = 10.0 Hz, 2H, CH_2), 1.79 (m, *J* = 10 Hz, 1H, CH), 1.30 (d, *J* = 10 Hz, 3H, CH_3), 0.82 (m, 6H, *J* = 10Hz, $2CH_3$). MS (*m/z*): M^+ 395 (30%). Analysis for $C_{22}H_{28}N_4O_3$ (396.22). Calced.: % C, 66.65; H, 7.12; N, 14.13. Found: % C, 66.85; H, 7.20; N, 14.25.

***N*-(2-(2-acetylhydrazineyl)-2-oxoethyl)-4-(2-(4-isobutylphenyl)propanamido) benzamide (6)**

The titled compound was synthesized by refluxing of compound **5** in acetic anhydride (50 ml) for 8 hrs. The solvent was removed under vacuum

Product **6** was separated as colorless crystals(ethanol), yield 75 %. mp 210-212 °C. IR (KBr, cm^{-1}): 3460 (NH), 3352 (NH), 3305 (NH), 3228 (NH), 3045 (CH aromatic), 2954 (CH aliphatic), 1716 (C=O), 1670 (C=O), 1660 (C=O), 1650 (C=O), 1604 (C=C), 1519 (C-N), 1354 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 8.03, 7.82, 7.64 (3s, 1H, 3NH), 7.58 (d, *J* = 5, 2H, CH_{arom}), 7.14 (d, *J* = 8.2, 5.7 Hz, 2H, CH_{arom}), 7.05 (d, 2H, CH_{arom}), 6.51 (d, *J* = 8.3, 5.8 Hz, 2H, CH_{arom}), 2.36 (d, *J* = 10.0 Hz, 2H, CH_2), 2.05 (s, 3H, Me),1.87 (m, *J* = 10 Hz, 1H, CH), 1.80 (s, 3H, CH_3), 1.29 (d, *J* = 10 Hz, 3H, CH_3), 0.82 (m, 6H, *J* = 10Hz, $2CH_3$). MS (*m/z*): M^+ 437 (20%). Analysis for $C_{24}H_{30}N_4O_4$ (438.23). Calced.: % C, 65.73; H, 6.90; N, 12.78. Found: % C, 65.95; H, 6.75; N, 12.60.

4-(2-(4-isobutylphenyl)propanamido)benzoyl azide (7)

The titled compound was prepared by the reaction of compound **2** with NaN_3 in acetone by stirring for 5 hrs .The solvent was removed under vacuum to get product **7**

Product **7** was separated as colorless crystals, yield 78 %. mp 181-182 °C. IR (KBr, cm^{-1}): 3363 (NH), 3045 (CH aromatic), 2993 (CH aliphatic), 2137 (N_3), 1705 (C=O), 1650 (C=O), 1608 (C=C), 1508 (C-N), 1400 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 7.96 (d, *J* = 8.2, 2H, CH_{arom}), 7.72 (d, *J* = 8.2, 5.7 Hz, 2H, CH_{arom}), 7.45 (d, 2H, CH_{arom}), 6.24 (d, *J* = 8.3, 5.8 Hz, 2H, CH_{arom}), 6.61 (s, 1H, NH), 3.55 (q, *J* = 5.2 Hz, 1H, *CH*-Me), 2.14 (m, 2H, CH_2), 1.97 (t, *J* = 6.1 Hz, 1H, CH), 1.61 (d, 3H, CH_3), 1.06 (d, *J* = 6.3 Hz, 6H, 3 CH_3). MS (*m/z*): M^+ 350 (15%). Analysis for $C_{20}H_{22}N_4O_2$ (350.42). Calced.: % C, 68.55; H, 6.33; N, 15.99. Found: % C, 68.85; H, 6.46; N, 15.63.

2-(4-isobutylphenyl)-N-(4-isocyanatophenyl)propanamide (8)

The titled compound was prepared by refluxing compound (7) in dioxane for 5 hrs . The solvent was removed under vacuum

Product **8** was separated as colorless crystals(ethanol), yield 74 %. mp 155-156 °C. IR (KBr, cm^{-1}): 3360 (NH), 3093 (CH aromatic), 2954 (CH aliphatic), 2048 (NCO), 1660 (C=O), 1608 (C=C), 1504 (C-N), 1323 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 8.20 (d, *J* = 8.2, 2H, CH_{arom}), 7.76 (d, *J* = 8.2, 5.7 Hz, 2H, CH_{arom}), 7.32 (d, 2H, CH_{arom}), 7.11 (d, *J* = 8.3, 5.8 Hz, 2H, CH_{arom}), 6.67 (s, 1H, NH), 3.54 (q, *J* = 5.2 Hz, 1H, *CH*-Me), 2.40 (m, 2H, CH_2), 2.13 (t, *J* = 6.1 Hz, 1H, CH), 1.69 (d, 3H, CH_3), 1.14 (d, *J* = 6.3 Hz, 6H, 3 CH_3). MS (*m/z*): M^{+1} 320 (5%). Analysis for $C_{20}H_{22}N_2O_2$ (322.41). Calced.: % C, 74.51; H, 6.88; N, 8.69.Found: % C, 74.25; H, 6.63; N, 8.84.

((4-(2-(4-isobutylphenyl)propanamido)phenyl)carbamoyl)glycine (9)

The titled compound was synthesized by stirring Glycine with the compound (8) in THF (35 ml) and few drops of pyridine for 5 hrs at room temperature. the reaction monitored via TLC. The reaction mixture poured into water and acidified with 1N HCl afforded the crude materials which purified by recrystallization from ethanol, yield product **9**.The solvent was removed under vacuum

Product **9** was separated as colorless crystals(ethanol), yield 69 %. mp 220-223°C. IR (KBr, cm^{-1}): 3460 (OH), 3360 (NH), 3093 (CH aromatic), 2954 (CH aliphatic), 1716, 1666 (2 C=O), 1612 (C=C), 1507 (C-N), 1323 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 12.14 (br. S, 2H, OH, NH), 8.18 (s, 1H, NH), 7.62 (d, *J* = 10 Hz, 2H, CH_{arom}), 7.18 (d, *J* = 10 Hz, 2H, CH_{arom}), 7.08 (d, *J* = 10 Hz, 2H, CH_{arom}), 6.55 (d, *J* = 10 Hz, 2H, CH_{arom}), 5.89 (s, 1H, NH), 3.72 (br. s, 2H, 2 NH), 2.72 (d, *J* = 10.0 Hz, 2H, CH_2), 2.41 (s, 3H, Me),1.84 (m, *J* = 10 Hz, 1H, CH), 1.80 (s, 3H, CH_3), 1.34 (d, *J* = 10 Hz, 3H, CH_3), 0.88 (m, 6H, *J* = 10Hz, $2CH_3$). MS (*m/z*): M^+ 395 (15%). Analysis for $C_{22}H_{27}N_3O_4$ (397.48). Calced.: % C, 66.48; H, 6.85; N, 10.57. Found: % C, 66.65; H, 6.62; N, 10.23.

Methyl ((4-(2-(4-isobutylphenyl)propanamido)phenyl)carbamoyl)glycinate (10)

The titled compound was synthesized by stirring of glycine methyl ester hydrochloride with compound (9) in THF (40 ml) and few drops of tri ethyl amine (TEA) for 3hrs. The solvent was removed under vacuum

Product **10** was separated as colorless crystals, yield 65 %. mp 267-268 °C. IR (KBr, cm^{-1}): 3460 (NH), 3362 (NH), 3232 (NH), 3089 (CH aromatic), 2954 (CH aliphatic), 1720 (C=O), 1660 (C=O), 1630 (C=O), 1600 (C=C), 1554 (C-N), 1323 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 7.60 (d, *J* = 10 Hz, 2H, CH_{arom}), 7.17 (d, *J* = 10 Hz, 2H, CH_{arom}), 7.08 (d, *J* = 10 Hz, 2H, CH_{arom}), 6.51 (d, *J* = 8.2 Hz, 2H, CH_{arom}), 5.86 (s, 1H, NH), 3.30 (s, 3H, Me), 3.59 (d, *J* = 5.7 Hz, 1H, *CH*-Me), 3.57 (s, 1H, NH), 3.00 (s, 1H, NH), 2.39 (s, 2H, CH_2), 1.80 (d, 2H, CH_2), 1.32 (d, *J* = 6.9 Hz, 3H, CH_3), 0.85 (2 d, *J* = 6.4 Hz, 6H, 2 CH_3). MS (*m/z*): M^+ 410 (5%). Analysis for $C_{23}H_{29}N_3O_4$ (411.50).

Calced.: % C, 67.13; H, 7.10; N, 10.21. Found: % C, 67.43; H, 7.31; N, 10.34.

N-(4-(3-(2-hydrazineyl-2-oxoethyl)ureido)phenyl)-2-(4-isobutylphenyl)propanamide (11)

The titled compound was synthesized by heating compound (10) with ethanolic hydrazine hydrate solution (40 ml) for 1/2hr. The solvent was removed under vacuum

Product **11** was separated as colorless crystals (ethanol), yield 65 %. mp 255-256. ºC. IR (KBr, cm^{-1}): 3460 (NH), 3352 (NH), 3232 (NH), 3047 (CH aromatic), 2943 (CH aliphatic), 1716 (C=O), 1666 (C=O), 1597 (C=C), 1519 (C-N), 1350 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 12.36 (br.s, 1H, NH), 8.17 (s, 1H, NH), 7.64 (d, *J* = 7.7 Hz, 2H, CH_{arom}), 7.21 (d, 2H, CH_{arom}), 7.12 (d, *J* = 6.6 Hz, 2H, CH_{arom}), 6.57 (d, 2H, *J* = 7.7 Hz, CH_{arom}), 5.85 (br s, 1H, NH), 3.75 (t, *J* = 5.2 Hz, 1H, *CH*-Me), 3.38 (br s, 2H, NH_2), 2.43 (d, 2H, CH_2), 1.90 (d, *J* = 5.9 Hz, 2H, CH_2), 1.87 (m, 1H, CH), 1.35 (d, *J* = 6.1 Hz, 3H, CH_3), 0.87 (t, *J* = 5.8 Hz, 6H, 2 CH_3). MS (*m/z*): M^+ 409 (5%). Analysis for $C_{22}H_{29}N_5O_3$ (411.51). Calced.: % C, 64.21; H, 7.10; N, 17.02. Found: % C, 63.50; H, 6.39; N, 17.18.

N-(4-(3-(2-acetamido-2-oxoethyl)ureido)phenyl)-2-(4-isobutylphenyl)propanamide (12)

The titled compound was synthesized by refluxing of compound (**11**) in acetic anhydride (50 ml) for 8 hrs. The solvent was removed under vacuum

Product **12** was separated as colorless crystals(ethanol), yield 58 %. mp 299-301 ºC. IR (KBr, cm^{-1}): 3460 (NH), 3352 (NH), 3359 (NH), 3232 (NH), 3066 (CH aromatic), 2954 (CH aliphatic), 1720 (C=O), 1670 (C=O), 1660 (C=O), 1597 (C=O), 1604 (C=C), 1519 (C-N), 1354 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 12.50 (s, 1H, NH), 9.80 (s, 1H, NH), 8.27 (s, 1H, NH), 7.71 (d, *J* = 8.2, 2H, CH_{arom}), 7.28 (d, *J* = 8.2, 5.7 Hz, 2H, CH_{arom}), 6.63 (d, *J* = 8.3, 5.8 Hz, 2H, CH_{arom}), 5.12 (s, 1H, NH), 3.94 (s, 3H, Me), 3.80 (t, *J* = 5.2 Hz, 1H, *CH*-Me), 2.37 (d, *J* = 6.4 Hz, 2H, CH_2), 2.05 (s, 2H, CH_2), 1.92 (t, *J* = 6.1 Hz, 1H, CH), 1.41 (t, *J* = 6.1 Hz, 1H, CH_3), 0.93 (2t, *J* = 6.3 Hz, 6H, CH_3). MS (*m/z*): M^+ 437 (10%). Analysis for $C_{24}H_{30}N_4O_4$ (438.23). Calced.: % C, 65.73; H, 6.90; N, 12.78. Found: % C, 65.95; H, 6.75; N, 12.60.

4-(2-(4-isobutylphenyl)propanamido)benzoyl isothiocyanate (13)

The titled compound was prepared by the reaction of compound (2) with NH4NCS in acetone (35 ml.) by refluxing for 5 hrs, After removing NH_4CL residue, the solvent was removed in vacuo and

Product **13** was separated as colorless crystals(ethanol), yield 74 %. mp 191-192 ºC. IR (KBr, cm^{-1}): 3452 (NH), 3093 (CH aromatic), 2954 (CH aliphatic), 2048, 2002 (NCO), 1716 (C=O), 1681 (C=O), 1604 (C=C), 1539 (C-N), 1323 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 7.56 (d, *J* = 10Hz, 2H, CH_{arom}), 7.12 (d, *J* = 10 Hz, 2H, CH_{arom}), 7.04 (d, 2H, CH_{arom}), 6.50 (d, *J* = 10 Hz, 2H, CH_{arom}), 5.81 (s, 1H, NH), 3.55 (q, *J* = 5.2 Hz, 1H, *CH*-Me), 2.35 (m, 2H, CH_2), 2.22 (t, *J* = 6.1 Hz, 1H, CH), 1.27 (d, 3H, CH_3), 0.79 (d, *J* = 6.3 Hz, 6H, 3 CH_3). MS (*m/z*): M^+ 366 (5%), 308 (20%, M^+-NCS). Analysis for $C_{21}H_{22}N_2O_2S$ (366.48). Calced.: % C, 68.83; H, 6.05; N, 7.64; S, 8.75.Found: % 68.55; H, 6.35; N, 7.49.

((4-(2-(4-isobutylphenyl)propanamido)benzoyl)carbamothioyl)glycine (14)

The titled compound was synthesized by stirring Glycine amino acid with the compound (13) in THF (35 ml) and few drops of pyridine for 5 hrs at room temperature. The solvent was removed under vacuum

Product **14** was separated as colorless crystals, yield 60 %. mp 270-271ºC. IR (KBr, cm^{-1}): 3441 (OH), 3360 (NH), 3093 (CH aromatic), 2954 (CH aliphatic), 1716, 1666 (2 C=O), 1650 (C=S), 1612 (C=C), 1507 (C-N), 1327 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 7.56 (d, *J* = 10 Hz, 2H, CH_{arom}), 7.13 (d, *J* = 10 Hz, 2H, CH_{arom}), 7.05 (d, *J* = 10 Hz, 2H, CH_{arom}), 6.50 (d, *J* = 10 Hz, 2H, CH_{arom}), 5.78 (s, 1H, OH), 5.00 (s, 1H, NH), 3.57 (q, *J* = 5.2 Hz, 1H, *CH*-Me), 3.37 (br. s, 2H, 2 NH), 3.05 (d, *J* = 12.1 Hz, 2H, CH_2), 2.35 (m, *J* = 7.9 Hz, 1H, CH), 1.28 (d, *J* = 10 Hz, 2H, CH_2), 0.79 (d, *J* = 10 Hz, 6H, 2 CH_3). MS (*m/z*): M^+ 440 (15%). Analysis for $C_{23}H_{27}N_3O_4S$ (441.55). Calced.: % C, 62.56; H, 6.16; N, 9.52; S, 7.26. Found: % C, 62.75; H, 6.25; N, 9.44.

Methyl ((4-(2-(4-isobutylphenyl)propanamido)benzoyl)carbamothioyl)glycinate (15)

The titled compound was synthesized by stirring of glycine methyl ester hydrochlorides with compound (13) in THF (40 ml) and few drops of tri ethyl amine (TEA) for 3hrs. The solvent was removed under vacuum

Product **15** was separated as colorless crystals (ethanol), yield 65 %. mp 235-236 ºC. IR (KBr, cm^{-1}): 3460 (NH), 3356 (NH), 3232 (NH), 3047 (CH aromatic), 2952 (CH aliphatic), 1720, 1666 (2 C=O), 1624 (C=S), 1604 (C=C), 1550 (C-N), 1323 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 8.08 (br.s, 1H, NH), 7.57 (d, *J* = 10 Hz, 2H, CH_{arom}), 7.13 (d, *J* = 10 Hz, 2H, CH_{arom}), 7.05 (d, *J* = 10 Hz, 2H, CH_{arom}), 6.51 (d, *J* = 8.2 Hz, 2H, CH_{arom}), 5.82 (s, 1H, NH), 3.66 (s, 3H, Me), 3.57 (d, *J* = 5.7 Hz, 1H, *CH*-Me), 3.34 (br. s, 1H, NH), 3.08 (s, 2H, CH_2), 2.47 (d, *J* = 10.0 Hz, 2H, CH_2), 1.80 (s, 3H, CH_3), 1.74 (m, *J* = 10 Hz, 1H, CH), 1.30 (d, *J* = 10 Hz, 3H, CH_3), 0.80 (m, 6H, *J* = 10Hz, 2CH_3). MS (*m/z*): M^+ 454 (15%). Analysis for $C_{24}H_{29}N_3O_4S$ (455.57). Calced.: % C, 63.28; H, 6.42; N, 9.22; S, 7.04. Found: % C, 63.55; H, 6.63; N, 9.41.

N-((2-hydrazineyl-2-oxoethyl)carbamothioyl)-4-(2-(4-isobutylphenyl)propanamido) benzamide (16)

The titled compound was synthesized by heating compound (**15**) with ethanolic hydrazine hydrate

solution (40 ml) for 1/2hr. The solvent was removed under vacuum

Product **16** was separated as colorless crystals (ethanol), yield 50 %. mp 200-201 ºC. IR (KBr, cm^{-1}): 3441 (NH), 3360 (NH), 3317 (NH), 3093 (CH aromatic), 2954 (CH aliphatic), 1720 (C=O), 1660 (C=S), 1624 (C=C), 1516 (C-N), 1327 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 7.56 (d, *J* = 7.7 Hz, 2H, CH_{arom}), 7.39 (br.s, 1H, NH), 7.14 (d, 2H, CH_{arom}), 6.97 (d, *J* = 6.6 Hz, 2H, CH_{arom}), 6.45 (d, 2H, *J* = 7.7 Hz, CH_{arom}), 5.48 (s, 1H, NH), 4.44 (br s, 1H, NH, NH_2), 3.35 (t, *J* = 5.2 Hz, 1H, *CH*-Me), 3.02 (s, 1H, NH), 2.35 (d, 2H, CH_2), 1.88 (d, *J* = 5.9 Hz, 2H, CH_2), 1.78 (m, 1H, CH), 1.24 (d, *J* = 6.1 Hz, 1H, CH_3), 0.80 (t, *J* = 5.8 Hz, 6H, 2 CH_3). MS (*m/z*): M^+ 454 (15%). Analysis for $C_{23}H_{29}N_5O_3S$ (455.58). Calced.: % C, 60.64; H, 6.42; N, 15.37; S, 7.04. Found: % C, 60.40; H, 6.66; N, 15.15.

N-((2-(2-acetylhydrazineyl)-2-oxoethyl)carbamothioyl)-4-(2-(4-isobutylphenyl) propanamido)benzamide (17)

The titled compound was synthesized by refluxing of compound (16) in acetic anhydride (50 ml) for 8 hrs. The solvent was removed under vacuum

Product **17** was separated as colorless crystals (ethanol), yield 45 %. mp 246-247 ºC. IR (KBr, cm^{-1}): 3541 (NH), 3498 (NH), 3305 (NH), 3271 (NH), 3066 (CH aromatic), 2943 (CH aliphatic), 1720 (C=O), 1670 (C=S), 1660 (C=O), 1650 (C=O), 1620 (C=C), 1504 (C-N), 1392 (CH_3). ^{1}H NMR (500 MHz, DMSO-D6) δ 7.56 (d, *J* = 8.2, 2H, CH_{arom}), 7.52 (s, 1H, NH), 7.10 (d, *J* = 8.2, 5.7 Hz, 2H, CH_{arom}), 6.98 (d, *J* = 8.3, 5.8 Hz, 2H, CH_{arom}), 6.48 (d, *J* = 8.3, 5.8 Hz, 2H, CH_{arom}), 5.21 (br.s, 1H, 4 NH), 3.40 (s, 3H, Me), 3.05 (t, *J* = 5.2 Hz, 1H, *CH*-Me), 2.35 (d, *J* = 6.4 Hz, 2H, CH_2), 2.05 (s, 2H, CH_2), 1.78 (t, *J* = 6.1 Hz, 1H, CH), 1.25 (t, *J* = 6.1 Hz, 1H, CH_3), 0.80 (2t, *J* = 6.3 Hz, 6H, CH_3). MS (*m/z*): M^+ 496 (5%). Analysis for $C_{25}H_{31}N_5O_4S$ (497.61). Calced.: % C, 60.34; H, 6.28; N, 14.07; S, 6.44. Found: % C, 60.66; H, 6.41; N, 14.23.

Computational Model:

Docking study :

Docking study was carried out for the target compounds into EGFR using MOE 2015 [43,44]. The crystal structures of the (COX-2) complexes with diclofenac (ID: 1PXX[33]) was obtained prepared using MOE 2015. Water and inhibitors molecule were removed, and hydrogen atoms were added. The parameters and charges were assigned with MMFF94x force field. We defined active site based on the original ligand in the crystal using the site finder module of MOE. The optimized 3D structures of molecules were subjected to generate different poses of ligands using triangular matcher placement method, which generating poses by aligning ligand triplets of atoms on triplets of alpha spheres represented in the receptor site points, a random triplet of alpha sphere centers were used to determine the pose during each iteration. The pose generated was rescored using London dG scoring function. The poses generated were refined with MMFF94x forcefield, also, the solvation effects were treated. The Born solvation model (GB/VI) was used to calculate the final energy, and the finally assigned poses were assigned a score based on the free energy in kcal/mol. The results have analyzed by Discovery Studio 2017 software [45]

Pharmacological activities

The pharmacological activities for the new synthesized compounds were estimated in rats (130-150 g). In a preliminary test to choose the dose for biological testing, animals in groups of six rats for each group, received (0.2 mMol/100 g, orally) in DMSO for the tested compounds and (0.1 mMol/100 g, orally) in DMSO for ibuprofen. Animals were observed for 24 h for signs of toxicity and number of deaths. No deaths were recorded, and no observed signs of distress, dyspnea, impaired movement, seizures or any other abnormal clinical signs.

Anti-inflammatory activity

The activity was tested according to winter et al method, in which edema was induced by injecting a freshly prepared suspension of carrageenin (1.0% m/v, 0.1 mL) was injected in the plantar region of the right hind paw of each rat. Rats were divided into 6 groups of 6 rats each. The 1st group was kept as control, and was given the respective volume of the solvent (1% DMSO orally).

The other groups were pretreated orally with the tested compounds in a dose of 35 mg/kg body weight (dissolved in 1% DMSO), 1 hour before carrageenan injection. Results were expressed as % inhibition. The edema rate and inhibition rate of each group were calculated as follows:

Percentage change of Edema rate (E) % = ((Vt-Vo) \Vo)*100

Inhibition rate (I) % = ((Ec-Et)\Et) *100

Where:

Vo is the volume before carrageenan injection (ml).

Vt is the volume at t hour after carrageenan injection (ml).

Ec is the edema rate of control group

Et is the edema rate of treated group.

Analgesic activity

The analgesic validation of the tested compounds was evaluated using tail-flick test method [41]. The latency for the tail withdrawal reflex was measured. Rats were gently held with the tail put on the tail-flick apparatus (Ugo Basile, Italy) and the tail flick response was elicited by applying a radiant heat stimulus to the ventral surface of the rat-tail about 3-4 cm from the tip of the tail. The time in seconds, from initial heat source activation until tail withdrawal was recorded. The mean of two measures was used for each experimental animal as the tail withdrawal latency. In order to avoid excessive suffering of animals, a cut-off was set at 30.

Acute ulcerogenesis

This study was carried out on healthy Albino rats [42]. The animals were divided into different groups of six each, the 1st group served as control and received vehicle only, the 2nd group received pure naproxen (0.1 mMol/100 g, orally) in DMSO and the other 16 groups received (0.2 mMol/100 g, orally) in DMSO of the tested compounds. Food but not water was removed 24 h prior administration of the tested compounds. Rats were fed with normal diet for 17 h after the drug treatment and then sacrificed. The stomach was removed and opened along the greater curvature, washed with distilled water and cleaned gently by dipping in saline. The mucosal damage was examined by means of a magnifying glass. For each stomach, the mucosal damage was assessed macroscopic examination

Statistical analysis

Results were compared to untreated and standard groups and analyzed using one way ANOVA followed by Dunnett's multiple comparisons using SPSS statistics 17.0 (Chicago, USA), and expressed as means ± standard error

Conclusion

Ibuprofen glycine derivatives were synthesized with the objective of developing better anti-inflammatory molecules with minimal ulcerogenic activity . compounds were characterized by different spectral data. Chemical reactivity analysis was performed, which introduced a possible explanation for reactivity of ligands against receptors. The molecular docking has performed into the COX-2 active site for tested compounds 3-17. Compounds (**5,10,11 and 17**) passed through docking and ADMET profiles were examined as anti-inflammatory and analgesic agents. Compounds 10,11 and 17 showed higher anti-inflammatory potency than reference drug and tested compounds after 4 hours. All tested compounds exhibited the highest analgesic potency compared to other tested compounds. Compounds (**10,11 and 17**) showed negligible ulcerogenic effect , and may be considered safer drugs than Ibuprofen for treating inflammatory conditions

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