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SYNTHESIS AND EVALUATION OF IBUPROFEN AMIDE DERIVATIVES IDENTIFYING A PROMISING LEAD WITH ENHANCED ANTIINFLAMMATORY AND ANTIOXIDANT ACTIVITY

B. Karuna. Devi[1,✉], K. Madhavi[2], and G. Rajitha[2]
[1]Department of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad-500900, Telangana, India
[2]Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Technology, Sri Padmavati Mahila Vishvavidyalayam (Women's University), Tirupati, Chittoor-517502, Andhra Pradesh, India
✉Corresponding author: karuna.barla@gmail.com

ABSTRACT
Ibuprofen, a 2-arylpropionic acid NSAID, is widely used to treat pain, fever, and inflammation but may cause gastrointestinal ulcers, liver injury, and renal impairment on prolonged use. Ulcerogenicity is mainly due to the interaction of its carboxylic acid group with the COX-1 enzyme, though this group is essential for activity. In this study, the carboxylic acid of Ibuprofen was modified into amide derivatives using 4-aminobenzoic acid, aminophenolic acids, and their esters. The designed molecules were synthesized and characterized by physical parameters and relevant spectral data. The synthesized derivatives were evaluated for their *in vitro* antioxidant properties by DPPH scavenging and nitric oxide free radical scavenging assays, and *in vitro* antiinflammatory activity by erythrocyte membrane stabilization and protein denaturation methods. The antioxidant studies (DPPH and nitric oxide scavenging) showed good radical scavenging activity for compounds 14, 17 and 18. *In vitro* antiinflammatory assays revealed that several derivatives, particularly 15, 18, and 19, exhibited significant membrane stabilization and protein denaturation inhibition comparable to Ibuprofen. Additionally, computational analysis was performed using Molinspiration, PASS analysis, and Osiris Property Explorer to assess drug-likeness, antiinflammatory potential, and toxicity properties respectively, for the synthesized compounds (9-20). *In silico* ADMET and toxicity predictions confirmed favorable drug likeness, good oral absorption, and low toxicity profiles. Overall, compound 18 emerged as the most promising lead, showing consistent performance across the biological assays. This study contributes to the development of safer NSAID derivatives. The findings provide a promising framework for designing gastroprotective anti-inflammatory agents and support further optimization and *in vivo* evaluation.
Keywords: Ibuprofen, Amide, Ester, Antiinflammatory, Antioxidant, *In silico* Studies
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INTRODUCTION

Inflammation underlies a vast spectrum of diseases, accounting for a significant proportion of global morbidity, yet its effective management remains a persistent challenge due to drug-induced adverse effects. While nonsteroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen are widely prescribed for pain and inflammation, their prolonged use is frequently associated with gastrointestinal, hepatic, and renal toxicities, with gastric ulceration being the most prevalent concern.[1-9] This limitation highlights a critical need for safer anti-inflammatory agents that retain therapeutic efficacy while minimizing side effects. In this context, the present study aims to address the challenge of NSAID-induced ulcerogenicity by modifying the carboxylic acid group of Ibuprofen into amide derivatives through conjugation with 4-aminobenzoic acid, 4- and 5-aminosalicylic acids, and their esters. This structural modification is intended to reduce gastrointestinal irritation by masking the free carboxyl group, which is known to interact with key amino acid residues in the cyclooxygenase (COX) active site[10], while potentially improving selectivity toward COX-2. Such an approach also leverages the prodrug concept, where enzymatic hydrolysis by intestinal amidases regenerates the active form, thereby enhancing safety and

therapeutic performance.[11-13] Furthermore, this research aligns with the United Nations Sustainable Development Goals, particularly SDG 3 (Good Health and Well-being), by contributing to the development of safer and more effective therapeutic agents. Studies have also highlighted the diverse pharmacological potential of Ibuprofen amide derivatives, including anti-inflammatory, analgesic, antimicrobial, anticancer, and neuroprotective activities[14-24], reinforcing their significance in modern drug design. Accordingly, the designed compounds (**9–20**) were synthesised and characterised using physical and spectral methods, followed by evaluation of their in vitro antioxidant and anti-inflammatory activities. Additionally, *in silico* analyses were conducted to assess drug-likeness, anti-inflammatory potential, and toxicity profiles, providing a comprehensive understanding of their therapeutic promise.

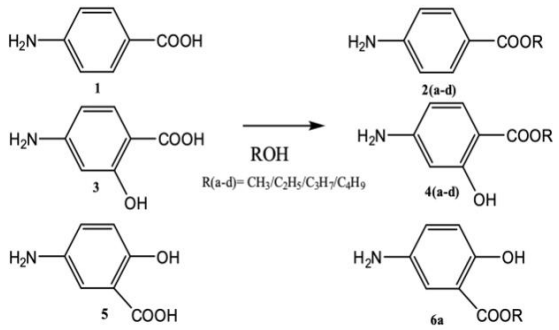
EXPERIMENTAL

Material and Methods

Ibuprofen, 4-aminobenzoic acid (PABA), 4-aminosalicylic acid (4-ASA), and 5-aminosalicylic acid (5-ASA) were procured from BDL Pharma, and all other chemicals were of AR grade. Melting points were recorded by using a melting point apparatus (Bio-Technics, India) and were reported uncorrected. Precoated aluminium plates with silica gel were used to perform thin layer chromatography (TLC) using silica gel 60 F_{254} plates (Merck, Germany) with a solvent system of hexane: ethylacetate (4:1) ratio and spots were detected in an Ultraviolet (UV) chamber (Bio-Technics, India). Using Bruker OPUS_7.5.18, infrared (IR) spectra were recorded, and the absorption bands were expressed in cm^{-1} using the potassium bromide (KBr) pellet method. ^{1}H and ^{13}C NMR spectra were obtained on an Agilent 400 MHz spectrometer and a 100 MHz spectrometer, respectively, using tetramethylsilane (TMS) as internal standard. Chemical shifts were reported as parts per million (δ ppm) and dimethylsulfoxide (DMSO) as a solvent. Mass spectra were measured on an Agilent with ESI and a Shimadzu LCMS/ ESI-APCI.

Synthesis of Esters 2 (a-d), 4 (a-d) and 6a by Simple Esterification

The esters were prepared by the addition of 15 mL of a (methanol), b (ethanol), c (propanol) and d (butanol) to 0.01 M of (1.37 g) 4-amino benzoic acid (1) and (1.53 g) 4-aminosalicylic acid (4-ASA) (3), respectively. Compound 6a was obtained by treating 15 mL of a (methanol) to 0.01 M of (1.53 g) 5-aminosalicylic acid (5-ASA) (5). Further, 2 mL of concentrated sulphuric acid was added and refluxed for 3 hrs.[25] After reflux, the contents were cooled, and sodium bicarbonate was added until precipitation of the respective esters occurred. Esters 2(a-d), 4(a-d) and 6a were recrystallized from rectified spirit. The esters (Scheme-1) obtained were used in the subsequent reactions.



Scheme-1: Synthesis of Esters by Simple Estrification

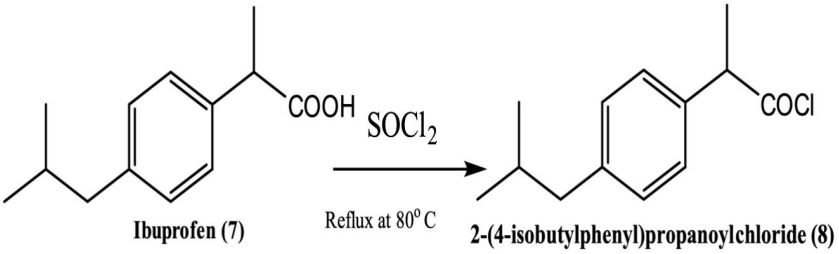
Synthesis of 2-(4-isobutylphenyl)propanoyl chloride 8

Ibuprofen (**7**) (0.01mole, 2.06 g) was added to dry toluene (25 mL), and then thionyl chloride (2 mL) was added in small portions with constant stirring. For about 2 hrs, the contents were heated at 80 °C on a water bath and excess thionyl chloride was removed under vacuum.[11] The slightly yellow-coloured acid chloride (Scheme-2) obtained was used immediately in the next step.

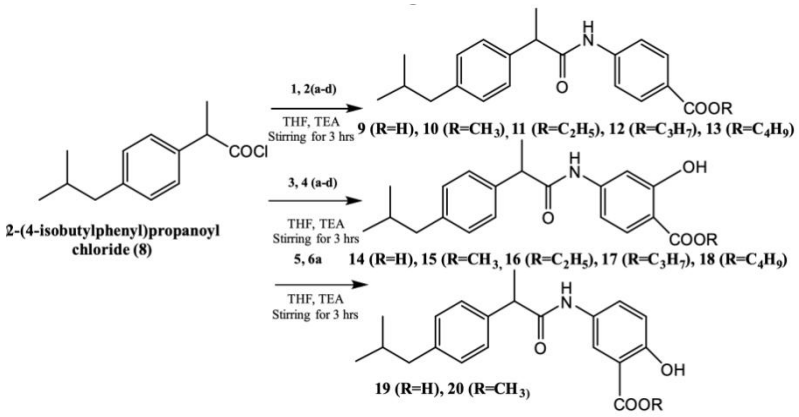
Synthesis of Ibuprofen Amide Derivatives 9-20

The titled compounds (9-20) (Scheme-3) were synthesized by stirring at room temperature (RT) 0.01 M of 1, 2a, 2b, 2c, 2d, 3, 4a, 4b, 4c, 4d, 5 and 6a with compound 8 (0.01 M, 2.26 g) in tetrahydrofuran (THF)

(50 mL) with few drops of triethylamine (TEA) for 3 hrs.[13] The completion of the reaction was observed by performing TLC. Vacuum evaporation was employed to remove the solvent, and 40 mL of distilled water was added to the round-bottomed flask (RBF). After filtration, the crude product was purified through recrystallisation with absolute ethanol.



Scheme-2: Synthesis of 2-(4-isobutylphenyl)propanoyl Chloride



Scheme-3: Ibuprofen Amide Derivatives (9 to 20)

Biological Activity

***In vitro* Antioxidant Activity**

Evaluation of *in vitro* antioxidant properties using DPPH radical and nitric oxide (NO) radical scavenging assays.

DPPH Radical Scavenging Assay

Test solutions of 100 µM concentration were prepared by using absolute ethanol and were added to 100 µM DPPH in absolute alcohol. All the test tubes were kept at RT for about 20 min in a dark place, and the absorbance of the samples was determined using a UV-visible absorbance spectrophotometer at 517 nm.[26] A control experiment was performed without a test compound. Ascorbic acid and Ibuprofen were used as a standard reference.

$$\% \text{ Reduction of DPPH} = \frac{A_{control-A_{test}}}{A_{control}} \times 100 \qquad [1]$$

Nitric Oxide Free Radical Scavenging Assay

To the phosphate buffer saline, pH 7.4, was added sodium nitroprusside (5 mM) and was incubated for 150 min at 25 °C with test compounds of 100 µM concentration prepared in absolute ethanol. From the incubated solution, 2 mL was withdrawn and mixed with 2 mL of Griess reagent, then allowed to stand for 30 min.[27] The control experiment was performed without a test compound. Ascorbic acid and Ibuprofen were used as standard reference.

$$\% \text{ Nitric oxide free radical scavenging activity} = \frac{A_{control-A_{test}}}{A_{control}} \times 100 \qquad [2]$$

***In vitro* Antiinflammatory Activity**

Erythrocyte membrane stabilization and protein denaturation methods were followed to assess *in vitro* anti-inflammatory activity.

Erythrocyte Membrane Stabilization Method

The erythrocyte suspension was obtained as described by Anosike *et al*.[28.] Test samples were prepared by taking 0.5 mL (100 µM) test solution, 1 mL phosphate buffer (pH 7.4, 0.15 M) and 2mL of hyposaline (0.36 %) and 0.5 mL of erythrocyte suspension (10 % v/v). Control was prepared by omitting the test solution. Ibuprofen was used as a standard reference. At 37 ºC, all the assay mixtures were allowed to incubate for 30 min and at 3000 rpm, they were centrifuged. For hemoglobin content, the supernatant liquid was estimated using a UV spectrophotometric method at 560 nm.[29]

$$\% \text{ Protection} = 100 - \frac{\text{Optical density}_{\text{test}}}{\text{Opical density}_{\text{control}}} \times 100 \qquad [3]$$

Protein Denaturation Method

Egg albumin solution (5% w/v) 0.2 mL, phosphate buffer saline (pH 6.4) 2.8 mL and test solution (100 µM) 2 mL were taken. A control experiment was carried out with distilled water in place of the test compound. Ibuprofen was taken as the reference standard. Test samples, control and standard were left aside for 15 min. Heat the samples to 70 ºC for 5 min, and after cooling under tap water, the absorbance values were noted at 660 nm.[30]

$$\% \text{ Inhibition of protein denaturation} = \frac{A_{\text{control}-A_{\text{test}}}}{A_{\text{control}}} \times 100 \qquad [4]$$

***In-silico* Analysis**

Molinspiration

By using the Molinspiration chemical structures of compounds (**9–20),** were generated and molecular properties were calculated.[31] Percentage absorption was computed by using the formula 109-(0.345*TPSA). These parameters were used to predict the compounds' absorption, distribution, metabolism, and elimination (ADME) characteristics.[32]

PASS analysis

PASS is a software tool designed for evaluating the biological potential of a drug-like molecule. Based on the chemical structure, PASS predicts the probable biological activities the drug-like molecule possesses before the chemical synthesis.[33,34]

OSIRIS Property Explorer

OSIRIS is a freely available online tool used for the prediction of toxicity-related parameters of drug-like compounds, such as mutagenicity, tumorigenicity, irritancy, and reproductive effects. The predicted results are visually interpreted through colour coding: green signifies favorable, drug-like properties, while red highlights potential risks, such as poor intestinal absorption or toxic effects like mutagenicity.[35,36]

RESULTS AND DISCUSSION

Spectral Data

4-(2-(4-Isobutylphenyl)propanamido)benzoic acid (9)

M.F: $C_{20}H_{23}NO_3$, Colour: White, Yield: 85%, M.P: 177-178°C; IR ν_{max} cm^{-1}: 3449.52 (O-H, acid and N-H, amide), 2954.14 (C-H, alkyl), 1668.06 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.80-0.88 (d, 6H, $(CH_3)_2$), 1.33-1.41 (d, 3H, CH_3), 1.76-1.84 (m, 1H, CH-$(CH_3)_2$), 2.39-2.40 (d, 2H, CH_2), 3.80-3.85 (q, 1H, CH-CH_3), 7.08-7.12 (d, 2H, Ar), 7.17-7.30 (d, 2H, Ar), 7.69-7.71 (d, 2H, Ar), 7.85-7.87 (d, 2H, Ar), 10.32 (s, 1H, NH), 12.65 (bs, 1H, COOH) ppm; ^{13}C-NMR (100 MHz, DMSO): 18.58, 22.15 (2C), 29.57, 44.19, 45.66, 118.36 (2C), 126.95 (2C), 127.07, 128.95 (2C), 130.30 (2C), 138.81, 139.58, 143.19, 169.20, 172.86 ppm; MASS (m/z): 326.07 $(M+1)^+$.

Methyl 4-(2-(4-isobutylphenyl)propanamido)benzoate (10)

M.F: $C_{21}H_{25}NO_3$, Colour: White, Yield: 84%, M.P: 90-94 °C; IR ν_{max} cm^{-1}: 3449.59 (N-H, amide), 2954.83 (C-H, alkyl), 1715.06 (C=O, ester), 1665.59 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.83-0.84 (d, 6H, $(CH_3)_2$), 1.39-1.41 (d, 3H, CH_3), 1.77-1.80 (m, 1H, CH-$(CH_3)_2$), 2.38-2.40 (d, 2H, CH_2), 3.80 (q, 1H, CH-CH_3), 3.83 (s, 3H, CH_3), 7.10-7.12 (d, 2H, Ar), 7.27-7.29 (d, 2H, Ar), 7.72-7.74 (d, 2H, Ar),

7.88-7.90 (d, 2H, Ar), 10.37 (s, 1H, NH) ppm; ^{13}C- NMR (100 MHz, DMSO): 18.59, 22.11 (2C), 29.58, 44.22, 45.73, 51.77, 118.49 (2C), 123.83, 126.98 (2C), 128.95 (2C), 130.22 (2C), 138.78, 139.59, 143.67, 165.76, 172.95 ppm; MASS (m/z): 340.20 $(M+1)^+$.

Ethyl 4-(2-(4-isobutylphenyl)propanamido)benzoate (11)
M.F: $C_{22}H_{27}NO_3$, Colour: White, Yield: 80%, M.P: 108-110°C; IR ν_{max} cm^{-1}: 3329.37 (N-H, amide), 2954.17 (C-H, alkyl), 1713.29 (C=O, ester), 1660.62 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.83-0.85 (d, 6H, $(CH_3)_2$), 1.28-1.31 (t, 3H, CH_3), 1.39-1.41 (d, 3H, CH_3), 1.76-1.82 (m, 1H, CH-$(CH_3)_2$), 2.39-2.40 (d, 2H, CH_2), 3.80-3.85 (q, 1H, CH-CH_3), 4.24-4.29 (q, 2H, CH_2), 7.10-7.12 (d, 2H, Ar), 7.27-7.29 (d, 2H, Ar), 7.72-7.74 (d, 2H, Ar), 7.87-7.90 (d, 2H, Ar), 10.36 (s, 1H, NH) ppm; ^{13}C- NMR (100 MHz, DMSO): 14.15, 18.57, 22.12 (2C), 29.55, 44.19, 45.69, 60.36, 118.47 (2C), 124.10, 126.95 (2C), 128.94 (2C), 130.14 (2C), 138.76, 139.58, 143.56, 165.25, 172.92 ppm; MASS (m/z): 354.3 $(M+1)^+$.

Propyl 4-(2-(4-isobutylphenyl)propanamido)benzoate (12)
M.F: $C_{23}H_{29}NO_3$, Colour: Light brown, Yield: 60%, M.P: 60-63°C; IR ν_{max} cm^{-1}: 3456.01 (N-H, amide), 2959.13 (C-H, alkyl), 1713.97 (C=O, ester), 1665.04 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.83-0.92 (d, 6H, $(CH_3)_2$), 0.93-0.97 (t, 3H, CH_3), 1.40-1.41 (d, 3H, CH_3), 1.65-1.76 (m, 2H, CH_2), 1.77-1.82 (m, 1H, CH-$(CH_3)_2$), 2.39-2.40 (d, 2H, CH_2), 3.80-3.85 (q, 1H, CH-CH_3), 4.18-4.20 (t, 2H, CH_2), 7.09-7.12 (d, 2H, Ar), 7.28-7.30 (d, 2H, Ar), 7.73-7.75 (d, 2H, Ar), 7.88-7.90 (d, 2H, Ar),10.37 (s, 1H, NH) ppm; ^{13}C- NMR (100 MHz, DMSO): 10.36, 18.60, 21.63, 22.16 (2C), 29.61, 44.22, 45.70, 65.81, 118.51 (2C), 124.09, 126.99 (2C), 128.98 (2C), 130.19 (2C), 138.79, 139.62, 143.61, 165.33, 172.97 ppm; MASS (m/z): 368.15 $(M+1)^+$.

Butyl 4-(2-(4-isobutylphenyl)propanamido)benzoate (13)
M.F: $C_{24}H_{31}NO_3$, Colour: Slight yellow, Yield: 76 %, M.P: 54-56 °C; IR ν_{max} cm^{-1}: 3331.46 (N-H, amide), 2954.27 (C-H, alkyl), 1710.28 (C=O, ester), 1668.59 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.83-0.84 (d, 6H, $(CH_3)_2$), 0.90-0.94 (t, 3H, CH_3), 1.35-1.45 (m, 5H, CH_3, CH_2), 1.63-1.70 (m, 2H, CH_2), 1.75-1.82 (m, 1H, CH-$(CH_3)_2$), 2.38-2.40 (d, 2H, CH_2), 3.80-3.85 (q, 1H, CH-CH_3), 4.21-4.24 (t, 2H, CH_2), 7.10-7.12 (d, 2H, Ar), 7.28-7.29 (d, 2H, Ar), 7.72-7.74 (d, 2H, Ar), 7.87-7.90 (d, 2H, Ar),10.39 (s, 1H, NH) ppm; ^{13}C- NMR (100 MHz, DMSO): 13.61, 18.61, 18.76, 22.16 (2C), 29.62, 30.28, 44.22, 45.70, 64.07, 118.50 (2C), 124.09, 127.00 (2C), 128.98 (2C), 130.19 (2C), 138.81, 139.62, 143.63, 165.32, 172.97 ppm; MASS (m/z): 382.40 $(M+1)^+$.

2-Hydroxy-4-(2-(4-isobutylphenyl)propanamido)benzoic acid (14)
M.F: $C_{20}H_{23}NO_4$, Colour: Slight brown, Yield: 75 %, M.P: 138-140°C; IR ν_{max} cm^{-1}: 3452.62 (O-H, acid and N-H, amide), 2958.00 (C-H, alkyl), 1620.07 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.83-0.88 (d, 6H, $(CH_3)_2$), 1.36-1.40 (d, 3H, CH_3), 1.76-1.82 (m, 1H, CH-$(CH_3)_2$), 2.39-2.41 (d, 2H, CH_2), 3.77-3.81 (q, 1H, CH-CH_3), 7.02-7.03 (dd, 1H, Ar), 7.05 (d, 2H, Ar), 7.26-7.28 (d, 2H, Ar), 7.33-7.34 (s, 1H, Ar), 7.66-7.69 (d, 1H, Ar), 10.25 (s, 1H, NH) ppm; ^{13}C- NMR (100 MHz, DMSO): 18.60, 22.19 (2C), 29.62, 44.22, 45.76, 105.89, 107.76, 110.12, 126.99 (2C), 129.01 (2C), 130.96, 138.73, 139.65, 145.48, 162.12, 171.57, 173.09 ppm; MASS (m/z): 342.43 $(M+1)^+$.

Methyl 2-hydroxy-4-(2-(4-isobutylphenyl)propanamido)benzoate (15)
M.F: $C_{21}H_{25}NO_4$, Colour: Off white, Yield: 79 %, M.P: 62-64°C; IR ν_{max} cm^{-1}: 3450.77 (N-H, amide), 2948.62 (C-H, alkyl), 1672.85 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.83-0.88 (d, 6H, $(CH_3)_2$), 1.38-1.40 (d, 3H, CH_3), 1.75-1.82 (m, 1H, CH-$(CH_3)_2$), 2.38-2.40 (d, 2H, CH_2), 3.78-3.85 (m, 4H, CH-CH_3 and CH_3), 7.07-7.10 (m, 3H, Ar), 7.12-7.28 (d, 2H, Ar), 7.40 (s, 1H, Ar), 7.69-7.71 (d, 1H, Ar), 10.31 (s, 1H, NH), 10.60 (s, 1H, OH) ppm; ^{13}C- NMR (100 MHz, DMSO): 18.57, 22.16 (2C), 29.60, 44.22, 45.78, 52.19, 106.12, 107.31, 110.47, 126.99 (2C), 128.80 (2C), 130.73, 138.68, 139.66, 145.68, 161.22, 169.01, 173.17 ppm; MASS (m/z): 356.10 $(M+1)^+$.

Ethyl 2-hydroxy-4-(2-(4-isobutylphenyl)propanamido)benzoate (16)
M.F: $C_{22}H_{27}NO_4$, Colour: White, Yield: 79 %, M.P: 56-58 °C; IR ν_{max} cm^{-1}: 3441.14 (N-H, amide), 2954.00 (C-H, of alkyl), 1673.68 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.83-0.85 (d, 6H, $(CH_3)_2$), 1.29-1.33 (t, 3H, CH_3), 1.38-1.40 (d, 3H, CH_3), 1.75-1.82 (m, 1H, CH-$(CH_3)_2$), 2.39-2.40 (d, 2H,

CH_2), 3.77-3.82 (q, 1H, CH-CH_3), 4.29-4.34 (q, 2H, CH_2), 7.06-7.12 (m, 3H, Ar), 7.26-7.28 (d, 2H, Ar), 7.40 (s, 1H, Ar), 7.70-7.72 (d, 1H, Ar), 10.32 (s, 1H, NH), 10.68 (s, 1H, OH) ppm; ^{13}C- NMR (100 MHz, DMSO): 14.01, 18.57, 22.15 (2C), 29.57, 44.19, 45.76, 61.03, 106.07, 107.32, 110.41, 126.97 (2C), 128.98 (2C), 130.63, 138.65, 139.64, 145.63, 161.35, 168.71, 173.14 ppm; MASS (m/z): 370.12 $(M+1)^+$.

Propyl 2-hydroxy-4-(2-(4-isobutylphenyl)propanamido)benzoate (17)
M.F: $C_{23}H_{29}NO_4$, Colour: Brown, Yield: 73 %, M.P: 58-60°C; IR ν_{max} cm^{-1}: 3436.86 (N-H, amide), 2963.00 (C-H, alkyl), 1670.17 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.83-0.85 (d, 6H, $(CH_3)_2$), 0.92-0.97 (t, 3H, CH_3), 1.38-1.40 (d, 3H, CH_3), 1.75-1.84 (m, 3H, CH-$(CH_3)_2$ and CH_2), 2.39-2.40 (d, 2H, CH_2), 3.77-3.83 (q, 1H, CH-CH_3), 4.21-4.25 (t, 2H, CH_2), 7.05-7.08 (m, 3H, Ar), 7.17-7.19 (d, 2H, Ar), 7.41 (s, 1H, Ar), 7.71-7.73 (d, 1H, Ar), 10.32 (s, 1H, NH), 10.68 (s, 1H, OH) ppm; ^{13}C- NMR (100 MHz, DMSO): 10.26, 18.57, 21.45, 22.15 (2C), 29.57, 44.19, 45.75, 66.32, 106.09, 107.32, 110.45, 126.97 (2C), 128.98 (2C), 130.61, 138.66, 139.64, 145.65, 161.36, 168.75, 173.15 ppm; MASS (m/z): 384.12 $(M+1)^+$.

Butyl 2-hydroxy-4-(2-(4-isobutylphenyl)propanamido)benzoate (18)
M.F: $C_{24}H_{31}NO_4$, Colour: Slight brown, Yield: 75%, M.P: 50-52°C; IR ν_{max} cm^{-1}: 3449.10 (N-H, amide), 2956.85 (C-H, alkyl), 1670.00 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.83-0.85 (d, 6H, $(CH_3)_2$), 0.90-0.94 (t, 3H, CH_3), 1.38-1.43 (m, 5H, CH_2, and CH_3), 1.66-1.68 (m, 2H, CH_2), 1.70-1.84 (m, 1H, CH-$(CH_3)_2$), 2.39-2.40 (d, 2H, CH_2), 3.79-3.81 (q, 1H, CH-CH_3), 4.26-4.29 (t, 2H, CH_2), 7.05-7.08 (dd, 1H, Ar), 7.09-7.12 (d, 2H, Ar), 7.26-7.28 (d, 2H, Ar), 7.40-7.41 (s, 1H, Ar), 7.69-7.71 (d, 1H, Ar), 10.30 (s, 1H, NH), 10.67 (s, 1H, OH) ppm; ^{13}C- NMR (100 MHz, DMSO): 13.55, 18.57, 18.66, 22.16 (2C), 29.57, 30.05, 44.19, 45.75, 64.61, 106.08, 107.32, 110.46, 126.97 (2C), 128.99 (2C), 130.61, 138.66, 139.64, 145.64, 161.35, 168.75, 173.15 ppm; MASS (m/z): 398.67 $(M+1)^+$.

2-Hydroxy-5-(2-(4-isobutylphenyl)propanamido)benzoic acid (19)
M.F: $C_{20}H_{23}NO_4$, Colour: Brown, Yield: 70%, M.P: 154-156°C; IR ν_{max} cm^{-1}: 3449.38 (O-H, acid and N-H, amide), 2908.87 (C-H, alkyl), 1668.06 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.83-0.85 (d, 6H, $(CH_3)_2$), 1.39-1.40 (d, 3H, CH_3), 1.78-1.81 (m, 1H, CH-$(CH_3)_2$), 2.39-2.41 (d, 2H, CH_2), 3.78-3.83 (q, 1H, CH-CH_3), 7.04-7.12 (2d, 3H, Ar), 7.27-7.29 (d, 2H, Ar), 7.35 (s, 1H, Ar), 7.68-7.70 (d, 1H, Ar), 10.28 (s, 1H, NH) ppm; ^{13}C- NMR (100 MHz, DMSO): 19.08, 22.66 (2C), 30.09, 44.70, 46.25, 106.39, 108.31, 110.60, 127.47 (2C), 129.48 (2C), 131.43, 139.20, 140.13, 145.93, 162.59, 172.04, 173.59 ppm; MASS (m/z): 342.00 $(M+H)^+$.

Methyl 2-hydroxy-5-(2-(4-isobutylphenyl)propanamido)benzoate (20)
M.F: $C_{21}H_{25}NO_4$, Colour: Slight brown, Yield: 75%, M.P: 120-122°C;IR ν_{max} cm^{-1}: 3451.04 (N-H, amide), 2962.96 (C-H, alkyl), 1651.68 (C=O, amide); ^{1}H NMR (400 MHz, DMSO) δ: 0.83-0.85 (d, 6H, $(CH_3)_2$), 1.38-1.40 (d, 3H, CH_3), 1.77-1.81 (m, 1H, CH-$(CH_3)_2$), 2.39-2.40 (d, 2H, CH_2), 3.72-3.74 (q, 1H, CH-CH_3), 3.88 (s, 3H, CH_3), 6.91-6.93 (d, 1H, Ar), 7.09-7.11 (d, 2H, Ar), 7.27-7.29 (d, 2H, Ar), 7.63-7.66 (dd, 1H, Ar), 8.15 (d, 1H, Ar), 10.04 (s, 1H, NH), 10.24 (s, 1H, OH) ppm; ^{13}C- NMR (100 MHz, DMSO): 18.57, 22.14 (2C), 29.59, 44.22, 45.52, 52.43, 112.31, 117.49, 119.99, 126.94 (2C), 127.25, 128.90 (2C), 131.23, 139.08, 139.48, 155.90, 169.03, 172.13 ppm; MASS (m/z): 356.20 $(M+1)^+$

Chemistry
The esters 2(a-d) and 4(a-d) were prepared by simple esterification by treating 4-aminobenzoic acid (1) and 4-ASA (3) with 4 different alcohols, such as methanol (a), ethanol (b), propanol (c) and butanol (d), respectively. Ester 6a was prepared by treating 5-ASA (5) with methanol. All the esters 2(a-d), 4(a-d) and 6a obtained were recrystallized with rectified spirit. Ibuprofen acid chloride (8) was prepared by heating Ibuprofen (7) in toluene in the presence of thionyl chloride. The Ibuprofen amide derivatives (9-20) were synthesized by stirring compound 1, 2(a-d), 3, 4(a-d), 5 and 6a with compound (8) in THF with a few drops of TEA for 3 hrs. All the Ibuprofen amide derivatives were recrystallized from absolute ethanol and were characterised by their physical parameters and relevant spectral data. All the compounds (9-20) in the IR spectra were characterized by the presence of -NH str, for amides in the range of 3329.37-3456.01 cm^{-1}. In ^{1}H-NMR spectra, a singlet was observed in the range of δ 10.04 to 10.68 for the -NH proton, confirming the formation of an amide bond between Ibuprofen acid chloride and the amine group of acids

and esters for all the synthesized compounds. The ^{1}H NMR spectra of the Ibuprofen amide derivatives containing aliphatic ester protons (10-13, 15-18, 20) displayed characteristic signals in the range of δ 0.90 to 4.34 ppm, confirming the presence of an aliphatic proton environment. In ^{13}C-NMR, the appearance of new carbon signals in the aliphatic region was observed in the range of δ 13–52 corresponding to the alkyl groups of the esters of compounds 10, 11, 12, 13, 15, 16, 17, 18, and 20, whereas such signals are absent for compounds 9, 14 and 19 that are acids. Prominent $(M+1)^{+}$ peaks were observed in the mass spectra for all synthesized compounds (9–20), consistent with their calculated molecular weights and supporting their successful synthesis.

Table-1: *In-vitro* Antioxidant Activity and *In-vitro* Anti-Inflammatory Activities of Ibuprofen Amide Derivatives 9-20

S. No.	Compound	*In vitro* anti-oxidant activity		*In vitro* antiinflammatory activity	
		% Inhibition by DPPH method* (100 µM)	% Inhibition by Nitric Oxide radical scavenging method* (100 µM)	% Protection by erythrocyte membrane stabilisation method* (100 µM)	%Inhibition by Protein denaturation method* (100 µM)
1	9	62.82	66.92	58.69	59.07
2	10	56.17	61.79	62.69	66.07
3	11	58.06	64.19	64.23	64.65
4	12	61.83	65.74	66.63	68.64
5	13	65.60	68.66	61.84	64.93
6	14	68.43	69.24	63.44	70.29
7	15	71.07	65.65	62.64	70.56
8	16	72.67	67.86	64.14	67.49
9	17	74.08	66.26	63.19	67.49
10	18	74.65	70.40	71.23	71.89
11	19	63.09	60.66	68.56	64.01
12	20	68.90	64.89	63.59	67.40
13	Ibuprofen	76.81	75.06	76.62	74.77
14	Ascorbic acid	82.47	82.12	-	-

*Average of triplicate measurements

In-vitro Antioxidant Activity

The *in vitro* antioxidant activity of the compounds (9-20) was demonstrated using the DPPH radical scavenging assay, and the results are summarised in Table-1. Among the synthesised derivatives, compound 20 (74.65%) exhibited the highest DPPH scavenging activity, followed by compound 18 (74.65%), compound 17 (74.08%), compound 16 (72.67%), and compound 15 (71.07%). Ascorbic acid was used as the standard with the highest DPPH scavenging activity of 82.47%, followed by Ibuprofen with 76.81%. Compounds 20 and 14 showed moderate activity (68.9% and 68.43%, respectively). The compounds 9, 10, 11, 12, and 13 exhibited DPPH scavenging activity in the range of 56.17 % to 65.60 %. All the above results suggest that the presence of a phenolic hydroxyl group in compounds (14-20), particularly with electron-donating groups (e.g., methyl, ethyl, or butyl), showed significantly improved antioxidant activity compared to 4-amino benzoic acid conjugates of Ibuprofen.[37] Compounds 17 and 18 exhibited DPPH scavenging activity closer to that of Ibuprofen, indicating the presence of a phenolic hydroxyl group on the aromatic ring in enhancing radical scavenging potential. Compounds (9-13) showed relatively lower antioxidant activity; this may be due to the absence of phenolic OH groups or less efficient electron donation capacity compared to the 4-ASA and 5-ASA-based derivatives. The NO activity of the synthesised compounds (9–20) was evaluated, and the results are summarised in Table-1 The % inhibition values ranged from 60.66% to 70.40%, indicating that most compounds exhibited moderate to good NO radical scavenging activity. Among the tested derivatives, compound 18 showed the highest NO scavenging activity (70.40%), followed closely by compound 14 (69.24%), compound 13 (68.66%), and compound 16 (67.86%). Compounds 9, 12, 11, 17, and 15 also demonstrated inhibition values in the range of 64–67%, suggesting comparable efficiency within the series. In contrast, compound

18 exhibited the inhibitory activity of 60.66%, indicating relatively weaker NO. The ascorbic acid and Ibuprofen standards exhibited 82.12% and 75.06% NO scavenging activity.

***In-vitro* Antiinflammatory Activity**

The % protection values at 100 µM ranged from 58.69% to 74.23%, indicating that most compounds exhibited moderate to good membrane-stabilising activity. Compound 18 exhibited the highest activity with 71.23%, followed by compound 19 with 68.56%, and compound 12 with 66.63%. Compounds 9, 13, 15, 16, 17, and 20 exhibited moderate activity in the range of 58.69 %–64.14 %, suggesting a reasonable protective effect. These results indicate that the phenolic hydroxyl group-containing acid exhibited better activity than the esterified compounds.

Table-2: Predicted Physicochemical Properties of Ibuprofen Amide Derivatives (9–20) by Molinspiration Cheminformatics

S. No.	Compound	milogP	TPSA	N atom	MW	HBA	HBD	n violation	N rot	Volume	% ABS
1	9	4.93	66.40	24	325.41	4	2	0	6	313.98	86.09
2	10	5.19	55.40	25	339.44	4	1	1	7	331.51	89.89
3	11	5.57	55.40	26	353.46	4	1	1	8	348.31	89.89
4	12	6.07	55.40	27	367.49	4	1	1	9	365.11	89.89
5	13	6.63	55.40	28	381.52	4	1	1	10	381.91	89.89
6	14	4.93	86.62	25	341.41	5	3	0	6	322.00	79.12
7	15	5.19	75.63	26	355.43	5	2	1	7	339.52	82.91
8	16	5.57	75.63	27	369.46	5	2	1	8	356.33	82.91
9	17	6.07	75.63	28	383.49	5	2	1	9	373.13	82.91
10	18	6.63	75.63	29	397.5	5	2	1	10	389.93	82.91
11	19	4.93	86.62	25	341.41	5	3	0	6	322.00	79.12
12	20	5.19	75.63	26	355.43	5	2	1	7	339.52	82.91

Partition coefficient (milogP); Topological polar surface area (TPSA); No: of total atoms (N atom); Molecular weight (MW); Hydrogen bond acceptor (HBA); Hydrogen bond donor (HBD); No: of violations (n violations); No: of rotatable bonds (N rot), Percentage of absorption (% ABS= 109-(0.345*TPSA))

The % inhibition by protein denaturation ranged from 59.07% to 71.89% at 100 µM and was summarised in Table-1. Compound 18 showed the highest inhibition (71.23%), surpassing all other test compounds. Compounds 14 and 15 exhibited comparable activity (70.29% and 70.56%, respectively). Compounds 10, 11, 12, 16, 17 and 20 demonstrated inhibition values between 64–68%, indicating good anti-denaturation potential. The reference drug Ibuprofen showed 76.62% membrane stabilisation and 74.77% inhibition of protein denaturation. The present study supports the goals of sustainable healthcare by contributing to the development of safer anti-inflammatory agents with reduced adverse effects. This aligns with the United Nations Sustainable Development Goals (SDG 3: Good Health and Well-being), emphasising improved therapeutic safety and efficacy. The identification of promising Ibuprofen derivatives highlights their potential to address drug-induced toxicity challenges in clinical practice.

***In-silico* ADMET Prediction**

Molinspiration Cheminformatics

Compounds having 0 or 1 violation are said to obey the Lipinski rule. Physicochemical properties such as logP (3.46–5.08), molecular weight (283.28–373.36 Da) and TPSA (86.62–132.45 Å²) showed moderate variation, suggesting drug-likeness of these molecules. From the predicted values, it was observed that no compound has more than one violation; hence, they are considered to have good oral bioavailability. The physical properties calculated are represented in Table-2.

PASS Analysis

The PASS analysis provided Pa values ranging from 0.505 to 0.621 for the synthesised Compounds, indicating their probability of exhibiting good anti-inflammatory activity and the data is represented in Table-3. The highest Pa values were observed for compounds 14 (0.621), 19 (0.619), 18 (0.611), and 17

(0.610). Compounds 15, 16, and 20 also showed good predicted activity with Pa values above 0.60. The remaining compounds (9–13) showed moderate predicted antiinflammatory potential (Pa = 0.505–0.520). A Pa value greater than 0.5 indicates a reasonably good likelihood of biological activity, suggesting that all compounds possess promising anti-inflammatory potential, consistent with the experimental erythrocyte membrane stabilisation and protein denaturation results. The strong PASS predictions for 4-ASA and 5-ASA conjugates of Ibuprofen (14–20) correlate well with their observed *in vitro* activity, supporting the importance of aminosalicylic scaffolds and their esterified derivatives in enhancing antiinflammatory effects.

Table-3: Predicted Anti-Inflammatory Activity (PASS analysis) and Toxicity Profiles (Osiris property explorer) of Ibuprofen Amide Derivatives (9–20)

S. No.	Compound	PASS Analysis	Toxicity Prediction			
		Pa value; antiinflammatory activity	Mutagenicity	Teratogenicity	Immunotoxicity	Reproductive toxicity
1	9	0.515	G	G	G	G
2	10	0.505	G	G	G	G
3	11	0.506	G	G	G	G
4	12	0.516	G	G	G	G
5	13	0.520	G	G	R	G
6	14	0.621	G	G	G	G
7	15	0.608	G	G	G	G
8	16	0.606	G	G	G	G
9	17	0.610	G	G	G	G
10	18	0.611	G	G	G	G
11	19	0.619	G	G	G	G
12	20	0.606	G	G	G	G
G = Low Risk R = Risk						

OSIRIS Property Explorer

From the OSIRIS property explorer, it was observed that all the compounds were free from all the toxicities except compound 13 (butyl ester of PABA conjugate), which showed immunotoxicity.

CONCLUSION

In the present study, the Ibuprofen amide derivatives were synthesized by conjugating Ibuprofen acid chloride (8) with 4-aminobenzoic acid, its esters, 4- and 5-aminosalicylic acids and their esters. All the compounds (9-20) were evaluated for their *in vitro* antioxidant properties and *in vitro* anti-inflammatory activity. Compounds (9-20) exhibited good to moderate *in vitro* antioxidant and *in vitro* anti-inflammatory activities. Ibuprofen amide derivatives obtained from 4-ASA and 5-ASA consistently demonstrated superior activity, confirming the crucial role of the phenolic hydroxyl (OH) group[36]. Compound 18 (butyl ester of 4-ASA conjugate) and Compound 17 (propyl ester of 4-ASA conjugate) showed the highest DPPH scavenging activity, approaching Ibuprofen's efficacy. The free acids, compound 18 and compound 14, were most effective for NO scavenging and exhibited superior antiinflammatory potential. Compound 18 demonstrated protein denaturation inhibition comparable to Ibuprofen. Thus, the presence of the phenolic OH group and alkyl side chains proves essential, marking compounds 14, 17, 18 and 19 as promising drug leads for further *in vivo* analysis. *In silico* drug-likeness analysis by Molinspiration Cheminformatics, anti-inflammatory potential by PASS analysis and toxicity prediction by Osiris Property Explorer were performed. All the compounds complied with the Lipinski rule of five, indicating good oral absorption. PASS analysis predicted that all the compounds showed Pa values greater than 0.5, indicating good anti-inflammatory activity. Compounds 13 (butyl ester of 4-aminobenzoic acid conjugate) exhibited Immunotoxicity as predicted by OSIRIS property explorer, and all other compounds were safe and free from toxicities. The outcomes of this study contribute to the United Nations Sustainable Development Goals (SDG 3: Good Health and Well-being) by advancing the development of safer anti-inflammatory agents with improved therapeutic profiles. These findings

highlight the potential of Ibuprofen amide derivatives to minimize NSAID-induced toxicity while maintaining efficacy, supporting future drug development efforts. Further *in vivo* studies are required to validate the safety and efficacy of the most promising compounds.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest, financial or otherwise.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

Barla Karuna Devi https://orcd.org/0000-0002-5746-4346
Kuchana Madhavi https://orcd.org/0000-0002-9564-8920.
Galla Rajitha https://orcd.org/0000-0001-6178-0715

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