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Short Note

(±)-2-(4-Isobutylphenyl)-*N*-(naphthalen-1-yl)propanamide

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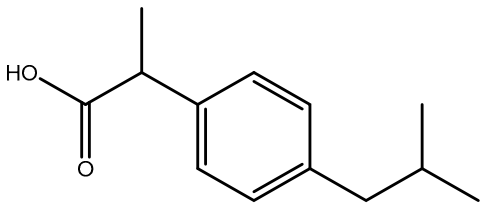
Abstract

We describe the synthesis of (±)-2-(4-isobutylphenyl)-*N*-(naphthalen-1-yl)propanamide, followed by comprehensive structural characterization. The compound was analyzed through melting point determination, ^{1}H and ^{13}C NMR spectroscopy, infrared spectroscopy, and mass spectrometry. The concordant results from these techniques provide clear evidence for the successful preparation and structural confirmation of the target molecule.

Keywords: hybrid molecule; amide; ibuprofen; naphthalen-1-amine; DCC

1. Introduction

Ibuprofen **1** or ±-2-(4-isobutylphenyl)propionic acid (Figure 1) is among the most extensively used nonsteroidal anti-inflammatory drugs (NSAIDs), valued for its analgesic, antipyretic, and anti-inflammatory properties. In clinical use, ibuprofen operates primarily by inhibiting cyclooxygenase (COX-1 and COX-2) enzymes, thereby reducing prostaglandin synthesis, which underlies its efficacy in alleviating pain, fever, and inflammation. However, despite its widespread over-the-counter availability, there remain challenges and concerns regarding its safety at high doses, its environmental persistence, and opportunities for improving its therapeutic index [1].



1

Figure 1. Structural formula of ibuprofen.

Meanwhile, efforts in medicinal chemistry have focused on modifying the ibuprofen molecule or generating novel derivatives to reduce gastrointestinal and other adverse effects while retaining or enhancing efficacy [2–4].

There has also been increasing attention to ibuprofen as an environmental contaminant: its incomplete degradation and accumulation in water systems lead to cytotoxic, genotoxic, and ecological effects, motivating studies into its biodegradation and remediation [5].

Numerous biologically active natural products are known to feature a naphthalene or naphthoquinone core as a central structural motif [6]. Representative compounds containing prominent naphthalene motifs include biaryl naphthylisoquinoline alkaloids

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illustrated in Figure 2, such as korupensamines (e.g., korupensamine A **2**) [7,8] and their dimeric counterparts, michellamines (e.g., michellamine B **3**) [9–11]. Korupensamines are recognized for their antimalarial properties, whereas michellamines display potent anti-HIV activity.

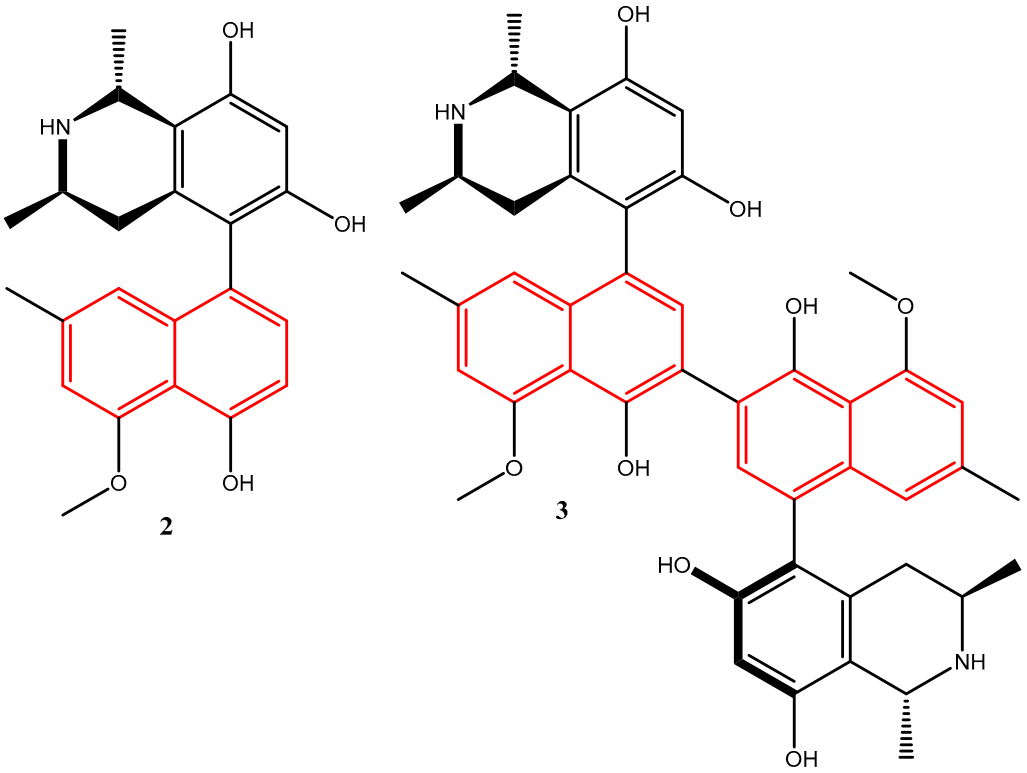


Figure 2. Structural formulas of the naphthalene containing alkaloids korupensamine A **2** and michellamine B **3**.

The reported compound has been used previously by Lehrhofer et al. together with a series of other ibuprofen derivatives but has not been characterized. The authors employed high-performance liquid chromatography with cellulose-based chiral stationary phases to achieve enantioseparation, making use of covalently immobilized selectors prepared via Cu(I)-catalyzed click chemistry, which provided enhanced solvent compatibility and robust separation performance [12].

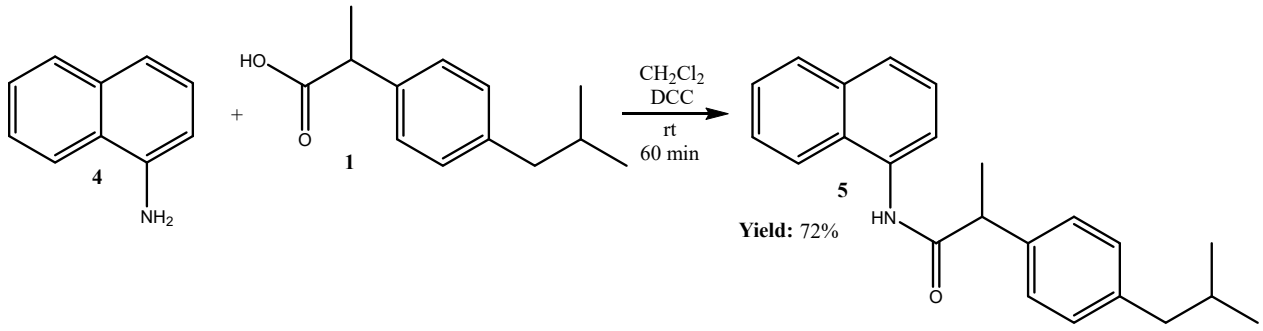
Naphthalene-containing natural products exhibit significant biological activities, including antimalarial and anti-HIV effects, highlighting the pharmacological relevance of this structural motif. Connecting naphthalene with ibuprofen via an amide bond represents a promising strategy to combine the therapeutic properties of both scaffolds while potentially modulating pharmacokinetics and biological activity.

2. Results

Synthesis

Herein, we report the successful synthesis of (±)-2-(4-isobutylphenyl)-*N*-(naphthalen-1-yl)propanamide **5**, as depicted in Scheme 1.

A convenient and efficient method for amide formation involves *N*,*N*′-dicyclohexyl -carbodiimide (DCC)-mediated coupling between carboxylic acids and amines. DCC, a widely used dehydrating agent, facilitates the synthesis of esters, anhydrides, and amides. In this process, DCC activates the carboxylic acid (e.g., ibuprofen), rendering it more susceptible to nucleophilic attack by the amine group of naphthalen-1-amine, thereby promoting amide bond formation. For the purpose of this synthesis we used racemic ibuprofen.



Scheme 1. Synthesis of 2-(4-isobutylphenyl)-*N*-(naphthalen-1-yl)propanamide **5**.

The resulting compound was characterized using melting point determination, ^{1}H and ^{13}C NMR, and IR spectroscopy, as well as high-resolution mass spectrometry (HRMS).

The ^{1}H NMR spectrum confirms the presence of all 25 expected protons (Supplementary Materials, Figure S1). The two methyl groups of the ibuprofen isobutyl substituent appear as a strong doublet at 0.87 ppm (integrating for six protons). A further doublet, corresponding to the remaining methyl group (three protons), is also observed. A multiplet at 1.83 ppm is attributable to the methine proton adjacent to both the $(CH_3)_2$ group and the methylene unit. The methylene protons are observed as a doublet at 2.45 ppm. The signal corresponding to the methine proton attached to the chiral carbon appears as a quartet at 3.80 ppm. A broad singlet at 7.41 ppm is assigned to the NH proton. Finally, the aromatic protons resonate within the range of 7.07–7.93 ppm. The ^{13}C NMR spectrum further corroborates the presence and expected count of carbon atoms in the structure (Figure S2).

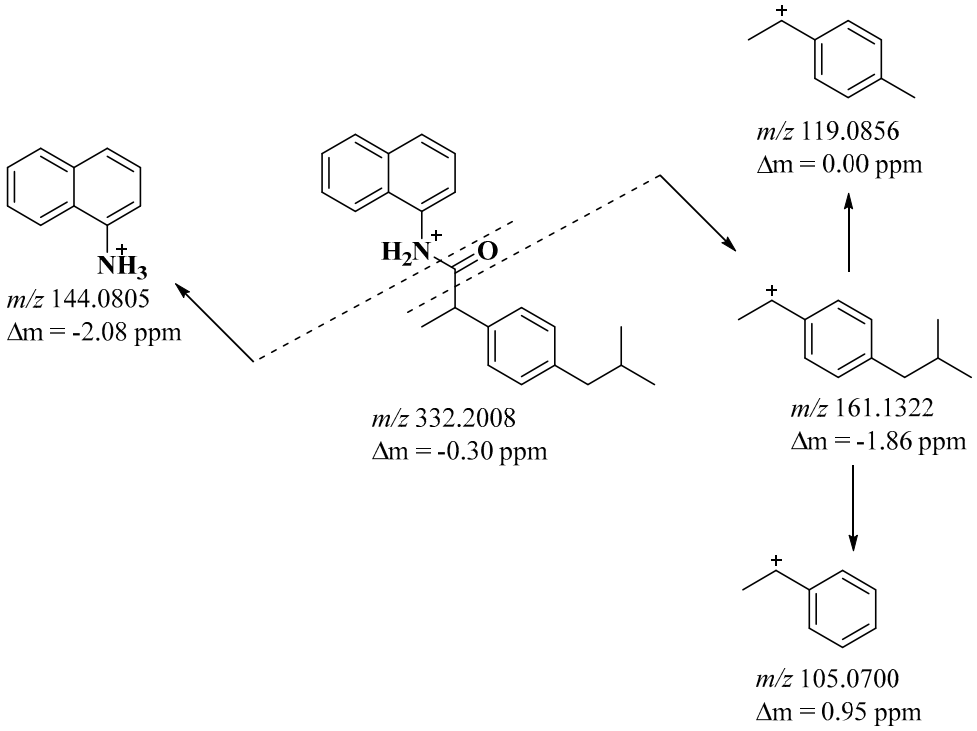
The IR spectrum (Figure S3) clearly reveals the characteristic absorption bands associated with the principal functional groups of the compound. In the solid and liquid phases, secondary amides typically display a strong absorption band at approximately 3284 cm^{-1}.

Mass spectrometric analysis of the investigated compound reveals two characteristic fragmentation pathways, as illustrated in Figure S5 and Scheme 2. The molecular ion at *m/z* 332 undergoes two principal cleavages involving the amide bond, leading to the formation of resonance-stabilized cations.

The first pathway involves cleavage of the N–C(=O) bond, yielding a characteristic fragment at *m/z* 144, whose stabilization arises from conjugation within the aromatic system. The second major fragmentation pathway, involving C(=O)–C bond cleavage, produces an ion at m/z 161, which is likewise stabilized through delocalization of the positive charge within the aromatic ring.

The fragment at *m/z* 161 undergoes further dissociation via two parallel mechanisms, generating daughter ions at m/z 119 and m/z 105. In both cases, the process favors the formation of smaller and more stable aromatic cations, thereby underscoring the crucial role of aromatic stabilization and electronic delocalization in the fragmentation mechanism (Figure S5 and Scheme 2).

The structure of the synthesized compound was comprehensively confirmed through melting point determination, ^{1}H- and ^{13}C- NMR, IR spectroscopy, and HRMS analysis. The spectroscopic data unequivocally verified the presence of all expected protons and carbons, while the IR spectrum revealed characteristic absorptions. Mass spectrometric studies further elucidated the fragmentation pathways, highlighting the stabilizing role of aromatic conjugation and charge delocalization. These results confirm both the successful synthesis and the structural integrity of the target amide.



Scheme 2. Proposed fragmentation of compound **5**.

3. Materials and Methods

All reagents and chemicals were purchased from commercial suppliers (Sigma-Aldrich S.A. and Riedel-de Haën, Sofia, Bulgaria) and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance Neo 400 spectrometer (BAS-IOCCP, Sofia; Bruker, Billerica, MA, USA) operating at 400 MHz and 101 MHz, respectively, in $CDCl_3$, with chemical shifts (δ) referenced to tetramethylsilane (TMS, δ = 0.00 ppm) and coupling constants (*J*) reported in Hz at ambient temperature (~295 K). Melting points were determined on a Boetius hot-stage apparatus (Plovdiv University; Boetius, Germany) and are reported uncorrected. IR spectra were recorded on a Bruker Alpha II FT-IR spectrometer (Plovdiv University; Bruker, Billerica, MA, USA). High-resolution mass spectrometry (HRMS) analyses were performed using a Q Exactive Plus spectrometer (Thermo Fisher Scientific, Bremen, Germany) with a heated electrospray ionization (HESI-II) source, coupled to a Dionex Ultimate 3000 RSLC UHPLC system (Waltham, MA, USA). Thin-layer chromatography (TLC) was carried out on 0.2 mm silica gel 60 plates (Fluka, Merck KGaA, Darmstadt, Germany).

3.1. Synthesis of 2-(4-Isobutylphenyl)-N-(naphthalen-1-yl)propanamide **5**

N,*N*′-dicyclohexylcarbodiimide (1 mmol, 0.206 g) was added to a solution of ibuprofen **1** (1 mmol, 0.206 g) in CH_2Cl_2 (40 mL). The reaction mixture was stirred at room temperature for 10 min. After the addition of naphthalen-1-amine **4** (1 mmol, 0.143 g), the reaction mixture was stirred for 50 min and the formation of white crystalline dicyclohexylurea was observed and then separated by filtration over a sintered glass filter. The filtrate was washed with a diluted hydrochloric acid (HCl:H_2O = 1:4, *v/v*) (15 mL), a saturated solution of Na_2CO_3 (15 mL), and brine (15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The compound was purified by filtration through short-column chromatography on silicagel with eluent Diethyl ether/Petrol/Methanol = 1:3:0.068.

3.2. 2-(4-Isobutylphenyl)-N-(naphthalen-1-yl)propanamide **5**

Pale pink solid (m.p. 123–124 °C), yield 72 % (0.2392 g), R_f = 0.44 (Diethyl ether/Petroleum = 1/2, *v*/*v*), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.41 (s, 1H, NH), 7.33 (dt, *J* = 14.9, 7.8 Hz, 4H), 7.23 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.19–7.13 (m, 2H), 7.07 (d, *J* = 8.5 Hz, 1H), 3.80 (q, *J* = 7.2 Hz, 1H), 2.45 (d, *J* = 7.2 Hz, 2H), 1.83 (m, 1H), 1.62 (d, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.05 (C=O), 141.49 (Ar), 138.21 (Ar), 133.99 (Ar), 132.23 (Ar), 130.16 (Ar), 128.75 (Ar), 127.81 (Ar), 126.57 (Ar), 126.11 (Ar), 125.79 (Ar), 125.28 (Ar), 119.82 (Ar), 119.65 (Ar), 47.83 ($(CH_3)_2CHCH_2$), 45.05 (CH_3CH), 30.28 ($(CH_3)_2CH$), 22.40 ($(CH_3)_2CH$), 18.02 (CH_3CH). IR (KBr) νmax., cm^{-1}: 3284 ν(N-H), 1654 ν(C=O), 1537 δ(N-H) + δ(C-N). HRMS Electrospray ionization (ESI) *m*/*z* calcd for $[M + H]^+$ $C_{23}H_{26}NO^+$ = 332.2009, found 332.2008 (mass error Δm = −0.30 ppm); for $[M + Na]^+$ $C_{23}H_{25}NONa^+$ = 354.1829, found 354.1825 (mass error Δm = −1.13 ppm).

Supplementary Materials: The following supporting information can be downloaded, Figure S1: ^{1}H-NMR spectrum of compound **5**; Figure S2: ^{13}C-NMR spectrum of compound **5**; Figure S3: IR spectrum of compound **5**; Figure S4: ESI-HRMS of compound **5**; Figure S5: ESI-MS/MS spectrum of compound **5**.

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Data Availability Statement: The data presented in this study are available in this article and supporting supplementary material.

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Conflicts of Interest: The authors declare no conflicts of interest.

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