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Short Note

N-(2-(1*H*-Indol-3-yl)ethyl)-2-(6-methoxynaphthalen-2-yl)propanamide

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Abstract: The title compound was obtained in high yield in the reaction between tryptamine and naproxen. The newly synthesized naproxen derivative was fully analyzed and characterized via ^{1}H, ^{13}C-NMR, UV, IR, and mass spectral data.

Keywords: amide; naproxen; SARS-CoV-2; tryptamine

1. Introduction

Naproxen **1** (Figure 1) is a nonsteroidal anti-inflammatory drug (NSAID) used to treat pain, menstrual cramps, inflammatory diseases such as rheumatoid arthritis, and fever initially introduced in 1976. The mechanism of action of naproxen involves blocking arachidonate binding to competitively inhibit both cyclooxygenase (COX) isoenzymes, COX-1, and COX-2, resulting in analgesic and anti-inflammatory effects. COX-1 and COX-2 are catalysts of arachidonic acid conversion to prostaglandin G, the first step of synthesis of prostaglandins and thromboxanes that are involved in rapid physiological responses [1].

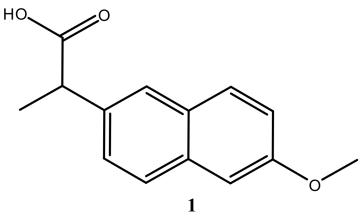

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Figure 1. Structural formula of naproxen.

A combination of three drugs, including naproxen, has been successfully used to treat patients hospitalized for influenza A (H3N2) infection [2] and reduces the mortality of the patients. Ongoing trials suggest that naproxen could combine broad-spectrum antiviral activity with its well-known anti-inflammatory action that could help to reduce severe respiratory mortality associated with COVID-19 [3]. Tryptamine is a biogenic amine, naturally occurring in plants, animals, and microorganisms [4], and is a metabolite of tryptophan [5]. Its structure is a shared feature of neuromodulators and psychedelic derivatives such as melatonin, serotonin, bufotenine, psilocybin, psilocin, et al. [6,7]. Tryptamine derivatives play a fundamental role in the human body. 5-Hydroxytryptamine or serotonin is one of the most important signaling hormones [8] in the body. Tryptamine natural derivatives are involved in the regulation and modulation of multiple processes within the central nervous system, such as sleep, cognition, memory, temperature regulation, and behavior [9]. Due to the diverse pharmacological properties of tryptamine **3** and the proven anti-inflammatory properties of naproxen, it is of great interest to synthesize a hybrid molecule that combines tryptamine and naproxen together in order to combine their properties. Rose and co-authors report the synthesis of serotonin derivatives containing

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NSAIDs in their structures [10]. Figure 2 presents the structural formula of the serotonin derivative of naproxen **2**.

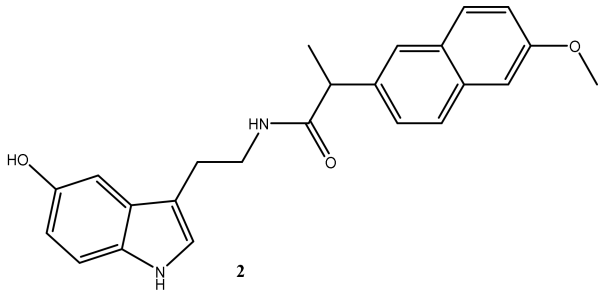


Figure 2. Structural formula of *N*-(2-(5-hydroxy-1*H*-indol-3-yl)ethyl)-2-(6-methoxynaphthalen-2-yl)propanamide **2**.

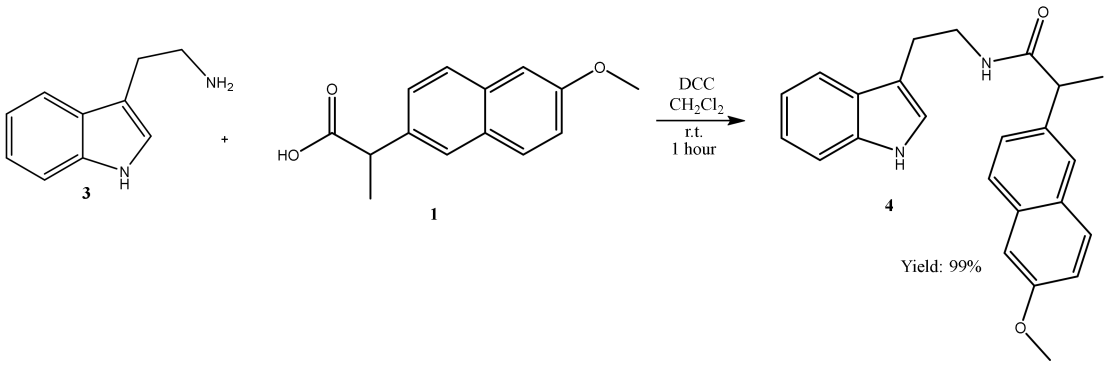
Due to the importance of the amides in the pharmaceutical synthesis [11,12], a coupling between naproxen **1** and tryptamine **3** via amide bond formation was achieved in order to obtain *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(6-methoxynaphthalen-2-yl)propanamide **4**. Compound **4** and its *S*-enantiomer are registered at the Chemical Abstract Service (CAS) under the numbers 1017153-76-2 and 1212098-73-1, respectively. A 6-methyl derivative is also registered (CAS: 1288027-94-0) but has not been as fully characterized as the others. These compounds are commercially available to buy from some suppliers (Aurora Fine Chemicals LLC, 7929 Silverton Avenue, Suite 609, San Diego, CA, 42126, USA; Enamine, SIA Chemspace, Ilukstes iela 38-5, Riga, LV-1082, Latvia), but the synthesis and characterization are not reported.

2. Results

We report the synthesis of *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(6-methoxynaphthalen-2-yl)propanamide **4**, as shown in Scheme 1.

An easy synthetic procedure for amide synthesis is the DCC-mediated (*N*,*N*′-dicyclohexylcarbodiimide) coupling between carboxylic acids and amines. DCC is commonly used for the preparation of esters, amides or anhydrides. DCC reacts with the carboxyl group of naproxen to produce an activated acylating agent that reacts with the amino group of amines to form an amide bond. The naproxen used in the reaction is a racemic mixture of *R*- and *S*- enantiomers so the obtained product is a racemate.

The resultant compound was characterized by its melting point, ^{1}H and ^{13}C-NMR, UV, IR, and HRMS spectra.



Scheme 1. Synthesis of *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(6-methoxynaphthalen-2-yl)propanamide **4**.

3. Materials and Methods

All reagents and chemicals were purchased from commercial sources (Sigma-Aldrich S.A. and Riedel-de Haën, Sofia, Bulgaria) and used as received. Melting points were determined on a Boetius hot stage apparatus and are uncorrected. The NMR spectral data were recorded on a Bruker Avance II+600 spectrometer (BAS-IOCCP—Sofia, Bruker, Billerica, MA, USA). ^{1}H-NMR and ^{13}C-NMR spectra for compound **4** were taken in DMSO-d_6 at 600 MHz and at 150.9 MHz, respectively. Chemical shifts are given in relative ppm and were referenced to tetramethylsilane (TMS) (δ = 0.00 ppm) as an internal standard; the coupling constants are indicated in Hz. The NMR spectra were recorded at room temperature (ca. 295 K). Mass analyses were carried out on a Q Exactive Plus mass spectrometer equipped with a heated electrospray ionization (HESI-II) probe (Thermo Fisher Scientific, Waltham, MA, USA). IR spectra were measured on VERTEX 70 FT-IR spectrometer (Bruker Optics, Ettlingen, Germany). TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates (Merck KGaA, Darmstadt, Germany), using diethyl ether/*n*-hexane = 1/1 as a chromatographic system.

Synthesis of N-(2-(1H-indol-3-yl)ethyl)-2-(6-methoxynaphthalen-2-yl)propanamide **4**

N,*N*′-Dicyclohexylcarbodiimide (1 mmol, 0.206 g) was added to a solution of naproxen (1 mmol, 0.230 g) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 10 min. After the addition of tryptamine (1 mmol, 0.160 g), the reaction mixture was stirred for 50 min, during which time white crystalline dicyclohexylurea precipitated. The urea was separated by filtration over a sintered glass filter. The filtrate was washed with dilute hydrochloric acid (HCl:H_2O = 1:4 (*v*/*v*)), a saturated solution of Na_2CO_3, and brine. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The compound was purified by filtration through a short column chromatography (silica gel 60, 70–230 mesh, Merck; diethyl ether).

N-(2-(1*H*-Indol-3-yl)ethyl)-2-(6-methoxynaphthalen-2-yl)propanamide (**4**): white solid (m.p. 114–115 °C), yield 99% (0.369g), ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.53 (s, 1H), 7.76–7.71 (m, 3H), 7.70 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.44 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.34–7.32 (m, 1H), 7.26 (d, *J* = 2.6 Hz, 1H), 7.14 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.07–7.05 (m, 1H), 7.04 (s, 1H), 6.95 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H), 3.88 (s, 3H), 3.73 (q, *J* = 7.1 Hz, 1H), 3.40–3.35 (m, 2H), 2.84–2.81 (m, 2H), 1.44 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.77 (C=O), 157.63 ((Ar)$\underline{C}OCH_3$), 138.13 (C, Ar), 136.92 (C, Ar), 133.67 (C, Ar), 129.50 (C, Ar), 129.05 (C, Ar), 127.86 (C, Ar), 126.99 (C, Ar), 126.95 (C, Ar), 125.77 (C, Ar), 122.97 (CH), 121.29 (C, Ar), 118.79 (C, Ar), 118.67 (C, Ar), 118.64 (C, Ar), 112.52 (C, Ar), 111.77 (C, Ar), 106.70 (C, Ar), 55.74 (O$\underline{C}H_3$), 48.16 (CH_3), 45.85 (CH_2), 24.85 (CH_2), 19.05 (CH_3). UV λ_{max}, MeOH: 236 (ε = 69000), 281 (ε = 6987) nm. HRMS Electrospray ionization (ESI) *m*/*z* calcd for $C_{24}H_{25}N_2O_2^+$ = 373.1911, found 373.1910 (mass error Δm = −0.27 ppm). IR(KBr) ν_{max}, cm^{-1}: 3399 ν(N-H), 3326 ν(N-H), 3258 ν(N-H), 3056 ν($C_{sp}{}^2$-H), 2930 ν_{as}($C_{sp}{}^3$-H, >CH_2), 2851 ν_s($C_{sp}{}^3$-H, > CH_2), 2666, 1664 $_\nu$(C=O), 1628 ν(C=C), 1605, 1573 ν(C=C, Ph), δ(N-H), 1539 δ(N-H) + ν(C-N), 1505 ν(C=C, Ph), 1487 δ_s(>CH_2) and ν(C=C, Ph), 1456 ν(C=C, Ph), δ_{as}(CH_3), δ(N-CH_2), 1450, 1436, 1419, 1391, 1374 δ_s(CH_3), 1347, 1340 δ_s(-CH<), 1311 ν(C-N), 1299, 1268 ν(Ph-NH), 1244, 1230 ν(HN-C=O), 1214, 1195, 1173, 1159 ν(C-N), 1119, 1092, 1069, 1045, 1030, 926, 893, 855 γ($C_{sp}{}^2$-H), 815 γ($C_{sp}{}^2$-H), 739 γ($C_{sp}{}^2$-H), 700, 681, 660, 641, 581, 493, 476, 421 δ(C-N-C).

Copies of all spectra and ESI-HRMS (Figures S1–S5) are provided in the Supplementary Materials file.

Supplementary Materials: Figure S1: ^{1}H-NMR spectrum of compound **4**, Figure S2: ^{13}C-NMR spectrum of compound **4**, Figure S3: UV spectrum of compound **4**, Figure S4: ESI-HRMS of compound **4**, Figure S5: IR spectrum of compound **4**.

Author Contributions: S.M. and I.I. are responsible for the synthesis, writing, revising, NMR, IR analysis and final English check of the manuscript. D.B. is responsible for the UV and ESI-HRMS analysis. All authors have read and agreed to the published version of the manuscript.

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

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