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Short Note

N-(2-(1*H*-indol-3-yl)ethyl)-2-(6-chloro-9*H*-carbazol-2-yl)propanamide

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Abstract: The titular compound was prepared by a reaction between tryptamine and carprofen, applying, as a "dehydrating" reagent, *N*,*N*′-dicyclohexylcarbodiimide. The newly synthesized compound was fully analyzed and characterized via ^{1}H, ^{13}C-NMR, UV, IR, and mass spectral data.

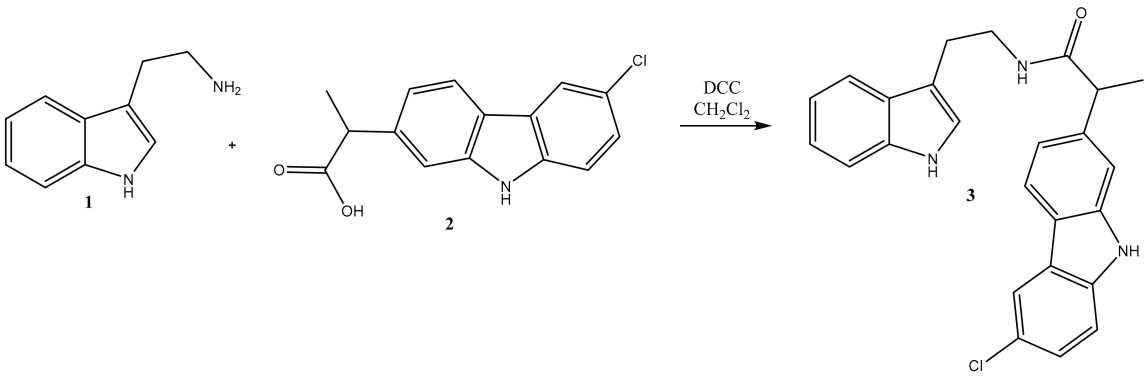
Keywords: amide; carprofen; tryptamine

1. Introduction

2-Arylpropanoic acids are an important class of non-steroidal anti-inflammatory drugs (NSAIDs) [1]. Used by veterinarians, carprofen is a non-narcotic NSAID applied to relieve the pain and inflammation associated with osteoarthritis and to control the post-operative pain associated with soft tissue and orthopedic surgeries in dogs, horses, and cattle [2]. Moreover, carprofen has a weak and competitive inhibitory effect on the activity of the prostaglandin synthetase enzyme complex. It inhibited the formation of prostaglandins E2 and F2 α and was found to be a weak inhibitor of the arachidonate lipoxygenase activity of human platelets [3]. Tryptamine **1** is also known for its vast array of biological activities [4]. A similar molecule was synthesized and studied earlier via UVA irradiation [5]. Due to the diverse pharmacological properties of tryptamine and the proven anti-inflammatory properties of carprofen, it is of great interest to create a molecule that combines the two molecules together and improves their properties. Because of the importance of amides for the pharmaceutical industry, a coupling between carprofen and tryptamine via amide bond formation was achieved in order to obtain *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(6-chloro-9*H*-carbazol-2-yl)propanamide **3**.

2. Results

Herein, we report the successfully synthesized *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(6-chloro-9*H*-carbazol-2-yl)propanamide **3**, as shown in Scheme 1.



Scheme 1. Synthesis of *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(6-chloro-9*H*-carbazol-2-yl)propanamide **3**.

A handy method for amide synthesis is the *N*,*N*′-dicyclohexylcarbodiimide (DCC)-mediated coupling between carboxylic acids and amines. DCC is commonly used for the preparation of esters, amides, or anhydrides. It is available commercially as a white crystalline substance with a low melting point of 34–35 °C. DCC reacts with the carboxyl group of carprofen to produce an activated acylating agent that reacts with the amino group of the other molecule to form an amide bond.

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

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 **3** 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 (ac. 295 K). Mass analyses were carried out on a Q Exactive Plus mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). 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-chloro-9H-carbazol-2-yl)propanamide **3***

N,*N*′-dicyclohexylcarbodiimide (1 mmol) was added to a solution of carprofen (1mmol) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 10 min. After the addition of tryptamine (1 mmol), 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, 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 short column chromatography (silica gel 60, 70–230 mesh, Merck; diethyl ether).

N-(2-(1*H*-indol-3-yl)ethyl)-2-(6-chloro-9*H*-carbazol-2-yl)propanamide (**3**): white solid (m.p. 186–189 °C), yield 96%, ^{1}H-NMR (600 MHz, DMSO) δ 11.01 (s, 1H), 10.44 (s, 1H), 8.02 (d, *J* = 1.9 Hz, 1H), 7.95–7.92 (m, 1H), 7.62 (s, 1H), 7.44–7.37 (m, 3H), 7.25 (dd, *J* = 13.3, 4.9 Hz, 2H), 7.05 (dd, *J* = 16.8, 8.2 Hz, 1H), 6.98–6.93 (m, 2H), 6.86 (t, *J* = 7.4 Hz, 1H), 3.68 (q, *J* = 7.1 Hz, 1H), 3.31–3.27 (m, 2H), 2.79–2.70 (m, 2H), 1.36 (d, *J* = 7.0 Hz, 3H). ^{13}C-NMR (151 MHz, DMSO) δ 173.86 (C=O), 141.62 (C, Ar), 141.26 (C, Ar), 138.99 (C, Ar), 136.91 (C, Ar), 127.86 (C, Ar), 125.32 (C, Ar), 124.37 (C, Ar), 123.42 (CH), 122.96 (C, Ar), 121.29 (C, Ar), 120.80 (C, Ar), 120.61 (C, Ar), 119.86 (C, Ar), 119.44 (C, Ar), 118.67 (C,

Ar), 118.64 (C, Ar), 112.69 (C), 112.53 (C, Ar), 111.76 (C, Ar), 110.19 (C, Ar), 48.17 (CH), 46.39 (CH_2), 33.78 (CH_2), 24.85 (CH_3). λ_{max}, MeOH: 224 (ε = 35 000), 241 (ε = 30 000), 265 (ε = 15 000), 303 (ε = 13 000) nm. HRMS Electrospray ionization (ESI) *m*/*z* calcd for $C_{25}H_{23}ClN_3O^+$ = 416.1524, found 416.1526 (mass error Δm = −0.48 ppm). IR(KBr) ν_{max}, cm^{-1}: 506 ν, δ (C=C-Cl), 1106 (*p*-Cl-C=C Ar), 1233, 1266 δ_{as} ((-(C=O)-N(R)-H), 1657 ν (C=O), 3101, 3366 ν(-(C=O)-N(R)-H).

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 **3**, Figure S2: ^{13}C-NMR spectrum of compound **3**, Figure S3: UV spectrum of compound **3**, Figure S4: ESI-HRMS of compound **3**, Figure S5: IR spectrum of compound **3**.

Author Contributions: S.M., 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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