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Short Note

N-(2-(1*H*-indol-3-yl)ethyl)-2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanamide

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Abstract: *N*-(2-(1*H*-Indol-3-yl)ethyl)-2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanamide was prepared by a reaction between tryptamine and flurbiprofen, applying *N*,*N*′-dicyclohexylcarbodiimide, as a coupling agent. The obtained new amide has a fragment similar to *Brequinar*, a compound used in SARS-CoV-2 treatment trials. The newly synthesized compound was fully analyzed and characterized via ^{1}H, ^{13}C-NMR, UV, IR, and mass spectral data.

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

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1. Introduction

One of the most potent currently known 2-arylpropionic acids is flurbiprofen, which has anti-inflammatory, analgesic, and antipyretic effects [1]. Flurbiprofen is widely used as an anti-inflammatory drug, both orally and topically, for the symptomatic treatment of chronic inflammatory diseases such as rheumatoid arthritis and osteoarthritis. Flurbiprofen is generally used as a racemate of (*R*)- and (*S*)-enantiomers. For the inhibition of cyclooxygenase activity, (*S*)-flurbiprofen is responsible. Along with the positives, the use of flurbiprofen can cause many side effects, such as abdominal cramps and pain, diarrhea, dyspepsia, edema, headache, and nausea [2]. Biphenyl substituent is very well known for owing biological activity. Flurbiprofen has the same biphenyl nucleus as *Brequinar*, differing only in the position of the fluorine atom (Figure 1). From the literature, it is known that *N*-contained six-membered cycles with biphenyl substituent are inhibitors of dihydroorotate dehydrogenase (DHODH) [3]. The inhibitors of DHODH have immunosuppressant, antiproliferative, and antimalarial activities, e.g., DSM265 [4]. *Brequinar* is a well known inhibitor of human DHODH, which is used in some pathologies in clinical trials including newly emerged coronavirus SARS-CoV-2 [5–7].

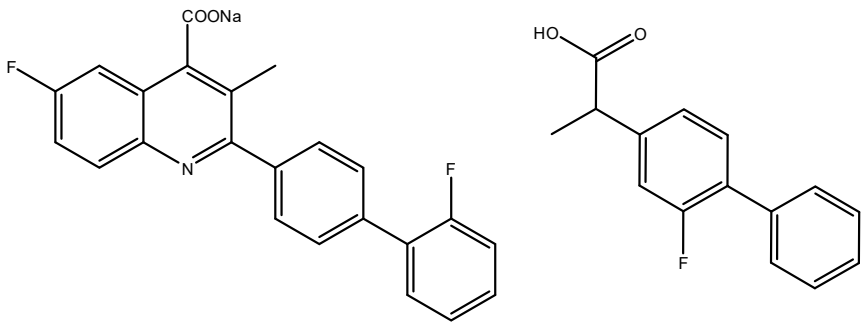


Figure 1. Structural formulas of *Brequinar* (left) and *Flurbiprofen* (right).

The fluorine substitution of biologically active molecules exercises an influence on their properties and activities. Fluorine substitution in a drug molecule can influence not

only pharmacokinetic properties, such as absorption, tissue distribution, excretion, and the route and rate of biotransformation, but also its pharmacodynamics and toxicology [8].

Tryptamine is a biogenic amine, naturally occurring in plants, animals, and microorganisms [9]. It also belongs to the so-called "trace amine" group, compounds present in all vertebrate and invertebrate species, typically in the central nervous system [10]. Due to the diverse pharmacological properties of tryptamine and the proven anti-inflammatory properties of flurbiprofen, it is of great interest to create a molecule that combines the two molecules together and improves their properties. Rose and co-authors reported the synthesis of serotonin derivatives containing NSAIDs (Nonsteroidal anti-inflammatory drugs) in their structures [11]. In Figure 2 is presented the structural formula of the serotonin derivative of flurbiprofen.

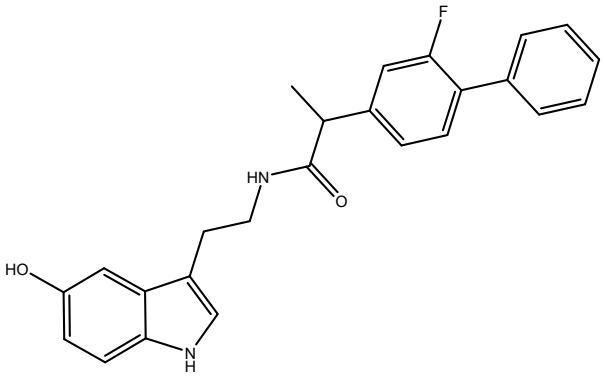
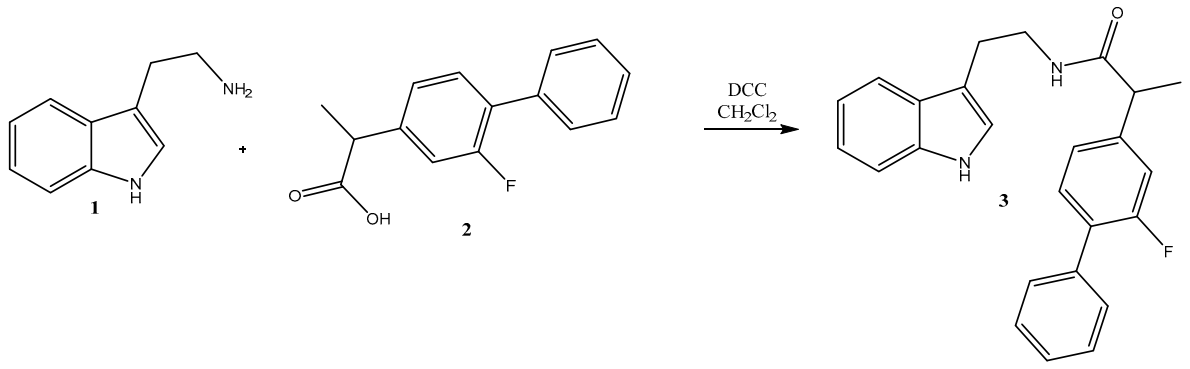


Figure 2. Structural formula of 2-(2-fluoro-[1,1′-biphenyl]-4-yl)-*N*-(2-(5-hydroxy-1*H*-indol-3-yl)ethyl)propanamide.

Due to the importance of the amides in pharmaceutical synthesis [12,13], a coupling between flurbiprofen and tryptamine via amide bond formation was achieved in order to obtain *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanamide **3**.

2. Results

Herein, we report the successfully synthesized *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanamide **3**, as shown in Scheme 1.



Scheme 1. Synthesis of *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanamide **3**.

An easy synthetic procedure 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. DCC reacts with the carboxyl group of flurbiprofen 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 M Hz and at 150.9 M Hz, 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-(2-fluoro-[1,1′-biphenyl]-4-yl)propanamide **3**

N,N′-dicyclohexylcarbodiimide (1 mmol, 0.206 g) was added to a solution of flurbiprofen (1 mmol, 0.244 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 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-(2-fluoro-[1,1′-biphenyl]-4-yl)propanamide (**3**): white solid (m.p. 122–124 °C), yield 98% (0.379g), ^{1}H NMR (600 M Hz, DMSO) δ 10.57 (s, 1H), 7.82 (s, 1H), 7.53 (ddd, *J* = 7.5, 3.5, 2.4 Hz, 3H), 7.48–7.45 (m, 2H), 7.44–7.41 (m, 1H), 7.40–7.37 (m, 1H), 7.35–7.33 (m, 1H), 7.23 (s, 1H), 7.21 (s, 1H), 7.08–7.04 (m, 2H), 6.97 (ddd, *J* =7.9, 7.0, 1.0 Hz, 1H), 3.68 (q, *J* = 7.0 Hz, 1H), 3.42–3.36 (m, 2H), 2.86 (t, *J* = 7.3 Hz, 2H), 1.40 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 M Hz, DMSO) δ 173.11 (C=O), 159.42 (d, $^{1}J_{C\text{-}F}$ = 245.5 Hz), 136.94 (C, Ar), 135.67 (C, Ar), 130.77 (d, $^{3}J_{C\text{-}F}$ = 3.6 Hz), 129.12 (C, Ar), 129.10 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 128.93 (C, Ar), 128.04 (C, Ar), 127.88 (C, Ar), 126.78 (C, Ar), 124.24 (C, Ar), 124.22 (C, Ar), 123.02 (CH), 121.31 (C, Ar), 118.67 (C, Ar), 118.65 (C, Ar), 115.31 (d, $^{2}J_{C\text{-}F}$ = 23.5 Hz), 112.48 (C, Ar), 111.78 (C, Ar), 48.17 (CH), 45.36 (CH_2), 33.78 (CH_2), 24.85 (CH_3). UV λ_{max}, MeOH: 230 (ε = 15600), 254 (ε = 14800) nm. HRMS electrospray ionization (ESI) *m*/*z* calcd for $C_{25}H_{24}FN_2O^+$ = 387.1867, found 387.1865 (mass error Δm = 0.52 ppm). IR(KBr) ν_{max}, cm^{-1}: 3390 ν(N-H), 3327 ν(-CON-H), 3259 ν(N-H), 3092 ν($C_{sp}{}^{2}$-H), 2929 ν_{as}($C_{sp}{}^{3}$-H), 2851 ν_{s}($C_{sp}{}^{3}$-H), 2666, 1699, 1654 ν(C=O), 1634 ν(C=C), 1573 ν(C=C), δ(N-H), 1536 δ(N-H), ν(C-N), 1484 δ_{s}(CH_2), ν(C=C), 1457 ν(C=C), δ_{as}(-CH_3), δ(N-CH_2), 1450, 1436, 1412, 1383, 1374 δ_{s}(-CH_3), 1359, 1337 δ_{s}(-CH<), 1310 ν(C-N), 1298, 1272 ν(Ph-NH), 1239, 1222 ν(HN-C=O), 1187, 1158 ν(C-N), 1132 ν(C-F), 1093, 1079, 1068, 1040, 1011, 928, 893, 877 γ(Csp^2-H), 834, 813, 765, 746 γ(Csp^2-H), 723, 699 γ($C_{sp}{}^{2}$-H), 641, 626, 582, 571, 538, 527, 481, 429 δ(C-N-C).

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

Supplementary Materials: The following are available online, 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: The first two authors S.M. and I.I. are responsible for the synthesis, writing, revising, NMR, IR analysis and final English check of the manuscript. The third author 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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Data Availability Statement: The data presented in this study are available in this article and supporting supplementary material.

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

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