



Short Note

N-(Benzo[*d*]thiazol-2-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide

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Abstract: *N*-(Benzo[*d*]thiazol-2-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide was prepared by a reaction between benzo[*d*]thiazol-2-amine and flurbiprofen in high yield. The newly obtained flurbiprofen derivative was fully analyzed and characterized via ¹H, ¹³C, UV, IR, and mass spectral data.

Keywords: benzo[*d*]thiazol-2-amine; flurbiprofen; DCC; amide



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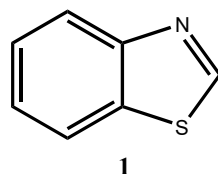


Figure 1. Structural formulas of benzo[*d*]thiazol.

2-Aminobenzothiazoles are highly reactive molecules and extensively employed as reactants or reaction intermediates for the synthesis of a variety of fused heterocyclic compounds [5]. The synthesis of C2-substituted benzothiazoles has received much attention. A number of drugs containing the benzothiazole core are commercially used to treat different pathologies. Riluzole 2 or 6-(trifluoromethoxy)benzo[*d*]thiazol-2-amine (Figure 2) owns a neuroprotective action useful in the treatment of amyotrophic lateral sclerosis [6].

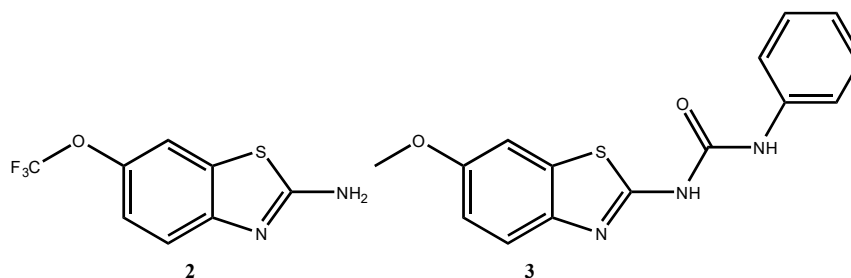


Figure 2. Structural formulas of Riluzole 2 and Frentizole 3.

Frentizole **3** or 1-(6-methoxybenzo[*d*]thiazol-2-yl)-3-phenylurea (Figure 2) is another example of a benzothiazole derivative possessing antiviral and immunosuppressant properties [7].

Flurbiprofen **4** (Figure 3) is a propionic acid derivative and is a non-steroidal anti-inflammatory drug (NSAID). It is known to have anti-inflammatory, analgesic, and antipyretic activities, and it is mainly used to treat osteoarthritis and similar diseases [8].

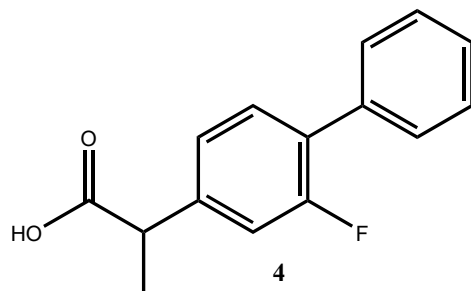


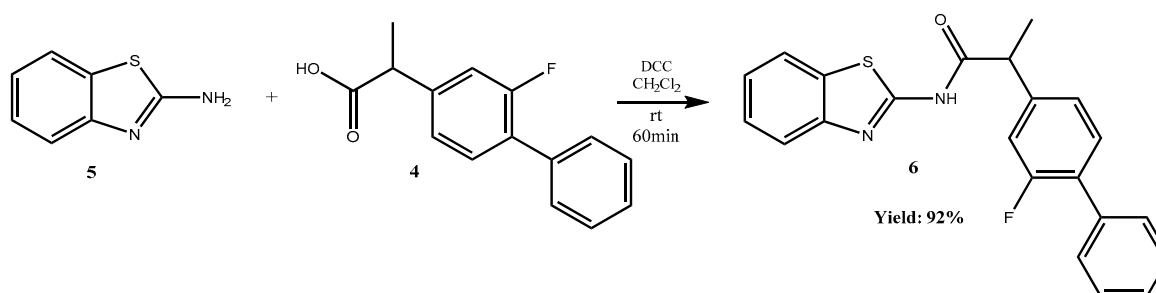
Figure 3. Structural formula of flurbiprofen.

The synthesis of amides is extremely important for the pharmaceutical industry, where it is estimated that amide preparation is the most common chemical reaction employed [9]. Approximately a quarter of all marketed drugs and two-thirds of all drug candidates contain a least one amide functional group [10]. A consideration of how amides interact with biological targets is also a key aspect of drug discovery [11].

Due to the importance of the amides in pharmaceutical synthesis, a coupling between flurbiprofen and benzo[*d*]thiazol-2-amine via amide bond formation was achieved in order to obtain *N*-(benzo[*d*]thiazol-2-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **6**.

2. Results

Herein, we report the successfully synthesized *N*-(benzo[*d*]thiazol-2-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **6**, as shown in Scheme 1.



Scheme 1. Synthesis of *N*-(benzo[*d*]thiazol-2-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **6**.

An easy and handy synthetic procedure for amide synthesis is through *N,N'*-dicyclohexylcarbodiimide (DCC) mediated coupling between amines and carboxylic acids. DCC is a dehydrating agent commonly used for the preparation of esters, anhydrides, and amides. The mechanism of DCC is to activate the carboxylic acid (flurbiprofen) to the nucleophilic amine. This reaction generally works in high yield.

The resultant compound is characterized by its melting point, ¹H-NMR and ¹³C-NMR, UV, IR, and HRMS spectra. The performed NMR analysis fully proves the structure of the obtained molecule. The observed signals of the ¹H-NMR spectrum comply with all protons from the molecule. The proton from the NH group is shifted at 12.65 ppm, and the signals for CH (quartet) and CH₃ (doublet) from the flurbiprofen part can be seen at 4.12 and 1.52 ppm, respectively. Looking at the ¹³C-NMR spectrum, a spin-spin interaction

with the ^{19}F atom was observed. In this regard, several doublets were present, which are described below in the experimental section. Analyzing the IR spectrum also gives us enough evidence for proving the structure of the analyzed molecule. The transmission of UV light through the amide **6** dissolved in methanol shows the presence of peaks at 255 and 307 nm. The molar absorptivity ϵ at the respective wavelength is also calculated. The HRMS analysis also unambiguously proves the authenticity of the structure.

The used method allows fast and easy synthesis of *N*-(benzo[*d*]thiazol-2-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **6** in high yield. Successfully obtained amide **6** is synthesized for the first time, and it is interesting because of its potential biological activity. The molecule contains on its structure proven pharmacophores, which are part of used in the medicinal practice medicines.

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). ^1H -NMR and ^{13}C -NMR spectra for compound **6** were taken in $\text{DMSO-}d_6$ at 600 MHz and at 150.9 MHz, respectively. Chemical shifts are given in relative ppm and were referenced to tetramethylsilane (TMS) ($\delta = 0.00$ 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).

Synthesis of *N*-(Benzo[*d*]thiazol-2-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **6** *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 benzo[*d*]thiazol-2-amine (1 mmol, 0.150 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.

N-(benzo[*d*]thiazol-2-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **6**: white solid (m.p. 119–121 °C), yield 92% (0.346 g), ^1H -NMR (600 MHz, $\text{DMSO-}d_6$) δ 12.65 (s, 1H), 7.99–7.95 (m, 1H), 7.74–7.72 (m, 1H), 7.54–7.49 (m, 3H), 7.48–7.44 (m, 2H), 7.42 (ddd, $J = 9.8, 5.4, 4.3$ Hz, 1H), 7.40–7.37 (m, 1H), 7.36–7.28 (m, 3H), 4.12 (q, $J = 7.0$ Hz, 1H), 1.52 (d, $J = 7.0$ Hz, 3H). ^{13}C -NMR (151 MHz, $\text{DMSO-}d_6$) δ 173.16 (C=O), 159.35 (d, $^1J_{\text{C-F}} = 246.4$ Hz), 158.35 (S(N=)C-NH), 148.93 (C, Ar), 142.80 (C, Ar), 135.25 (C, Ar), 131.88 (C, Ar), 131.38 (d, $^3J_{\text{C-F}} = 3.6$ Hz), 131.36 (C, Ar), 129.20 (C, Ar), 129.08 (C, Ar), 128.32 (C, Ar), 126.63 (C, Ar), 124.45 (C, Ar), 124.10 (C, Ar), 122.21 (C, Ar), 121.01 (C, Ar), 115.68 (d, $^2J_{\text{C-F}} = 23.6$ Hz), 44.93 (CH), 18.32 (CH_3). UV λ_{max} , MeOH: 255 ($\epsilon = 28,300$), 307 ($\epsilon = 14,400$) nm. HRMS Electrospray ionization (ESI) m/z calcd. for $\text{C}_{22}\text{H}_{18}\text{FN}_2\text{OS}^+ = 377.1124$, found 377.1128 (mass error $\Delta m = 1.06$ ppm). IR(KBr) ν_{max} , cm^{-1} : 3115, 3033 $\nu(\text{C}_{\text{sp}^2}\text{-H})$, 1701 $\nu(\text{C=O})$, secondary amide), 1622 $\delta(\text{N-H})$, 1600 $\nu(\text{C=C, Ph})$, 1539, $\delta(\text{N-H}) + \nu(\text{C-N})$, 1483 $\nu(\text{C=C, Ph})$, 1456 $\nu(\text{C=C, Ph})$, $\delta_{\text{as}}(\text{CH}_3)$, $\delta(\text{N-CH}_2)$, 1265, 1011 $\nu(\text{Ar-F})$, 768, 757, 730 $\gamma(\text{C}_{\text{sp}^2}\text{-H})$, 698, 673 $\nu(\text{C-S-C})$.

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: ^1H -NMR spectrum of compound **6**, Figure S2: ^{13}C -NMR spectrum of compound **6**, Figure S3: UV spectrum of compound **6**, Figure S4: ESI-HRMS of compound **6**, Figure S5: IR spectrum of compound **6**.

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

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