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Short Note

4-(Benzoxazol-2-yl)phenyl 3-((3-Chloro-1,4-Naphthoquinon-2-yl)amino)phenyl Sulfate

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Abstract: New 4-(benzoxazol-2-yl)phenyl 3-((3-chloro-1,4-naphthoquinon-2-yl)amino)phenyl sulfate was synthesized via the SuFEx click reaction between fluorosulfate-containing 1,4-naphthoquinone and 2-(4-hydroxyphenyl)benzoxazole. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used as an organic base, while triethylamine was inactive in this reaction.

Keywords: benzoxazole; 1,4-naphthoquinone; SuFEx

1. Introduction

A quinone molecular scaffold (Figure 1) is found in many synthetic and natural organic compounds with various biological activities [1,2]. One of such effects is antitumor activity, which stipulates obtaining new 1,4-naphthoquinone derivatives as prospective anticancer agents [3].

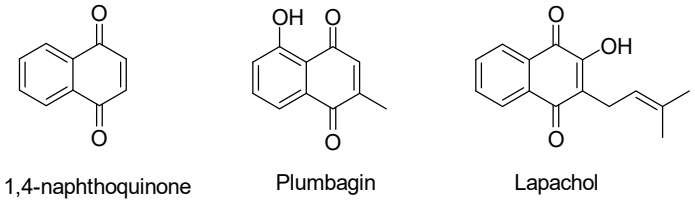

Figure 1. Structures of some biologically active 1,4-naphthoquinone derivatives.

On the other hand, benzoxazole molecular scaffold (Figure 2) is one of the important heterocyclic moieties present in a range of biologically active compounds which possess antihistamine, anticonvulsant, antimicrobial, antiviral, antioxidant, anti-ulcer, antidepressant, antitumor, or analgesic effects [4,5]. Some examples of known therapeutics containing the benzoxazole pharmacophore are shown in Figure 2 [6]. Moreover, numerous benzoxazoles possess fluorescent properties and can be used as fluorescent labels [7].

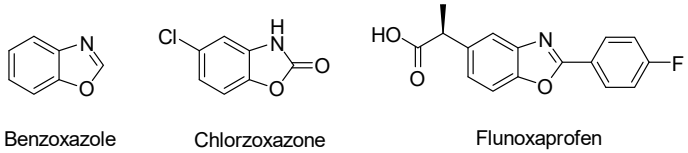

Figure 2. Structures of some biologically active benzoxazole derivatives.

In this work, we synthesized the novel compound 4-(benzoxazol-2-yl)phenyl 3-((3-chloro-1,4-naphthoquinon-2-yl)amino)phenyl sulfate, which includes both naphthoquinone and benzoxazole scaffolds. A product of this combination may exhibit beneficial properties from both moieties or demonstrate novel characteristics.

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Joining molecular fragments via the sulfate linker can be achieved using the sulfur(VI) fluoride exchange (SuFEx) click reaction, which has been successfully used for the synthesis of small molecules [8,9] (Figure 3).

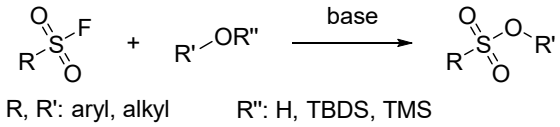
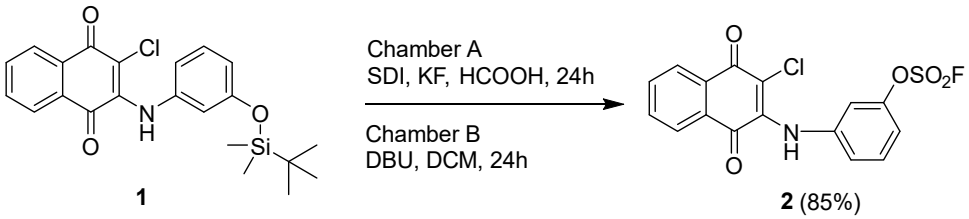


Figure 3. The general scheme of SuFEx reaction for oxygen-containing substrates.

The SuFEx reaction can exploit the unique properties of the -SO_2F group and was used in this work for the synthesis of the title compound.

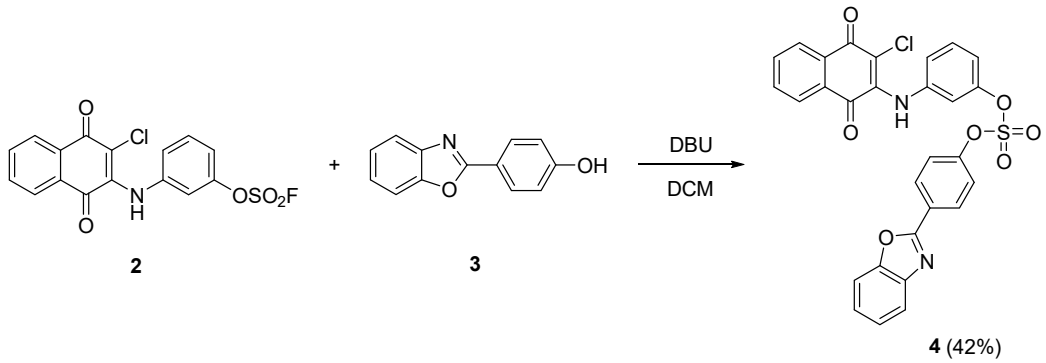
2. Results

Previously, we utilized the SuFEx reaction to obtain fluorosulfate-containing 1,4-naphthoquinones [10] and synthesized 3-((3-chloro-1,4-naphthoquinon-2-yl)amino)phenyl fluorosulfate (**2**) (Scheme 1) via the interaction between silyl ether **1** and SO_2F_2 in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). For this synthesis, we used a two-chamber reactor where gaseous SO_2F_2 was generated in the first chamber through the reaction between 1,1′-sulfonyldiimidazole (SDI), potassium fluoride, and formic acid. The click reaction proceeded simultaneously in the second chamber.



Scheme 1. Synthesis of the fluorosulfate derivative of 1,4-naphthoquinone.

Further, we carried out the reaction between the naphthoquinone-based fluorosulfate **2** and 2-(4-hydroxyphenyl)benzoxazole in the presence of an organic base. For this study, we tried to use two bases—triethylamine and DBU. The reaction with triethylamine did not lead to a significant conversion of the starting materials. The synthesis in the presence of DBU was successful and led to 4-(benzoxazol-2-yl)phenyl 3-((3-chloro-1,4-naphthoquinon-2-yl)amino)phenyl sulfate (**4**) (Scheme 2).



Scheme 2. Synthesis of the title compound.

The reaction was completed in 24 h and afforded the target product in 42% yield. Compound **4** is one of the first examples of molecules combining naphthoquinone and benzoxazole molecular scaffolds.

3. Materials and Methods

General Information and Compounds Synthesis

The LC/MS analysis utilized an Agilent Infinity chromatograph (Santa Clara, CA, USA) coupled with an Accurate Mass QTOF 6530 mass detector (Santa Clara, CA, USA). Liquid chromatography was performed using a Zorbax Eclipse Plus C18 column (1.8 µm particle size, 2.1 × 50 mm dimensions) with a mobile phase of water and acetonitrile (15:85% *v*/*v*) at a flow rate of 0.2 mL/min. The mass spectrometric detection employed electrospray ionization (ESI) operating in positive mode. The NMR spectra were obtained using a Bruker AVANCE III HD spectrometer (Billerica, MA, USA) operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei. Fourier-transform infrared (FTIR) spectroscopic analysis was conducted on an Agilent Cary 630 FTIR spectrometer (Santa Clara, CA, USA). The UV–Vis spectrum was recorded on a SF-2000 UV–Vis spectrophotometer (OKB SPECTR LLC, Saint-Petersburg, Russia). The melting point determination was performed using a Cole-Parmer SMP30 Melting Point Apparatus (Staffordshire, UK) with a heating rate of 3 °C/min. Reaction progress was monitored using thin-layer chromatography (TLC) performed on silica gel 60 F254 plates which were manufactured by Merck (Rahway, NJ, USA). Elemental analysis was performed with a Carlo Erba instrument (Waltham, MA, USA).

Compounds **2** [10] and **3** [11,12] were prepared according to the literature methods.

4-(Benzoxazol-2-yl)phenyl 3-((3-chloro-1,4-naphthoquinon-2-yl)amino)phenyl sulfate (**4**). Compounds **2** (0.25 mmol) and **3** (0.25 mmol) were placed in a round-bottom flask and dissolved in dichloromethane (DCM, 3 mL). DBU (0.3 mmol) was added, and the resulting mixture was stirred for 24 h at room temperature (TLC monitoring, eluent: hexane–ethyl acetate, 8:2). Product **4** was purified using column chromatography on silica gel. Red-orange crystals; yield 42%; M.p. 177.5–179.5 °C; ^{1}H NMR ($CDCl_3$), δ, ppm: 8.35 (2H, d, *J* = 9 Hz, H-10, H-11), 8.15 (1H, d, *J* = 8 Hz, H-1), 8.11 (1H, d, *J* = 8 Hz, H-4), 7.79–7.81 (1H, m, H-16), 7.75 (1H, t, *J* = 8 Hz, H-3), 7.69 (1H, t, *J* = 7 Hz, H-2), 7.64 (1H, s, NH), 7.59–7.62 (1H, m, H-13), 7.50 (2H, d, *J* = 9 Hz, H-9, H-12), 7.38–7.45 (3H, m, H-7, H-14, H-15), 7.18 (1H, d, *J* = 8 Hz, H-6), 7.07 (1H, d, *J* = 8 Hz, H-8), 7.01 (1H, s, H-5). The atom numbering used for the ^{1}H NMR signal assignment is shown in Figure 4. ^{13}C NMR ($CDCl_3$), δ, ppm: 180.3, 177.5, 161.6, 152.6, 150.9, 150.2, 141.1, 139.4, 136.1, 135.29, 135.26, 133.4, 132.4, 129.9, 129.8, 129.7, 127.4, 127.3, 125.9, 125.2, 123.2, 121.9, 120.3, 117.8, 117.0, 116.7, 111.0. Found, %: C 60.56, H 2.83, N 4.92. $C_{29}H_{17}ClN_2O_7S$. Calculated, %: C 60.79, H 2.99, N 4.89. IR spectrum, cm^{-1}: 681 (C-Cl), 1338 (S=O), 1647 (arom.); 3277 (N-H). UV–Vis spectrum (acetonitrile), λ_{max}, nm (log ε): 276 (4.58), 458 (3.50). LC/MS (ESI$^+$); m/z: 573.0519 $[M + H]^+$ experimental ($[C_{29}H_{17}ClN_2O_7S + H]^+$ = 573.0518 theor.), 595.0337 $[M + Na]^+$ experimental ($[C_{29}H_{17}ClN_2O_7S + Na]^+$ = 595.0337 theor.).

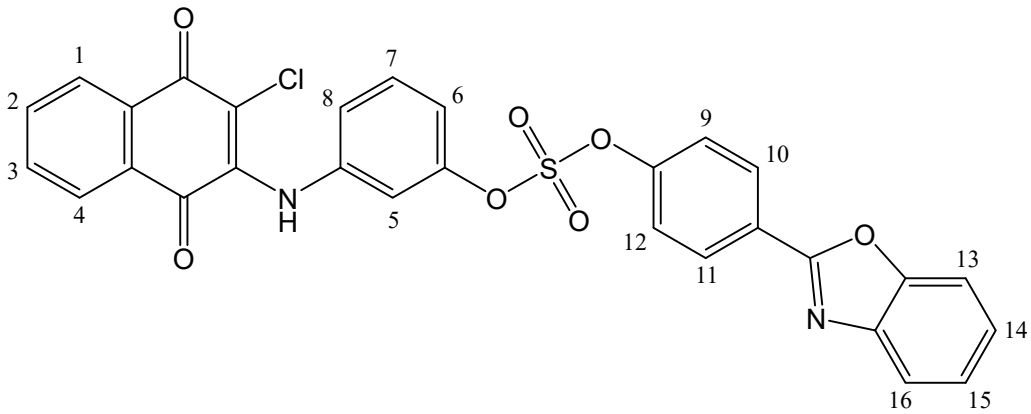


Figure 4. Atom numbering in molecule **4** used for the ^{1}H NMR signal assignment.

The NMR, HRMS, IR, and UV–Vis spectra of compound **4** are shown in Figures S1–S5.

4. Conclusions

In this work, we presented the synthesis and characterization of new compound **4** containing the benzoxazole and 1,4-naphthoquinone moieties. The title compound is of great interest for further studies as a possible anticancer agent.

Supplementary Materials: Figures S1–S5: NMR, HRMS, IR, and UV–Vis spectra of compound **4**.

Author Contributions: Conceptualization was conducted by N.V.D. and A.I.K.; methodology and experimental works were conducted by N.V.D. and M.O.L.; data analysis, writing, and editing of the paper were conducted by N.V.D. and A.I.K.; project administration and supervision were conducted by A.I.K. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data used in this study are available in this article.

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

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