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Short Note

2-(2-(Fluorosulfonyloxy)phenyl)benzoxazole

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Abstract: The fluorosulfate derivatives of benzoxazole attract attention since benzoxazole-based compounds have a wide range of biological activities, and the ability of the $-SO_2F$ group to react with various functional groups makes it possible to synthesize various new derivatives. The new 2-(2-(fluorosulfonyloxy)phenyl)benzoxazole (**2**) has been synthesized by the SuFEx click reaction in a two-chamber reactor. Compound **2** is the first example of a benzoxazole derivative with a fluorosulfate-containing substituent at position *two* of the benzoxazole heterocycle. The anti-cancer potency of **2** was evaluated in silico using molecular docking. The docking results suggest that title compound **2** is of great interest for further studies as a possible anaplastic lymphoma kinase inhibitor.

Keywords: benzoxazole; SuFEx; molecular docking

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1. Introduction

Benzoxazole is one of the most important heterocyclic scaffolds which has been found in many biologically active compounds. Benzoxazole derivatives have a wide range of biological activity, such as antitumor, antimicrobial, antiviral, antihistamine, antioxidant, anti-ulcer, anticonvulsant, antihelmintic, antidepressant, and analgesic effects [1]. Some important natural products, such as calcimycin, nakijinol, and boxazomycin A (Figure 1), contain benzoxazole moiety in their structure [2]. Numerous benzoxazole derivatives are described as agonists or antagonists of important receptors [3,4]. Among synthetic and naturally occurring benzoxazole derivatives, there are compounds showing anti-cancer activity against several human cancer cell lines [5]. Moreover, benzoxazoles possess fluorescent properties and can be used as fluorescent labels or materials for sensor technologies [6].

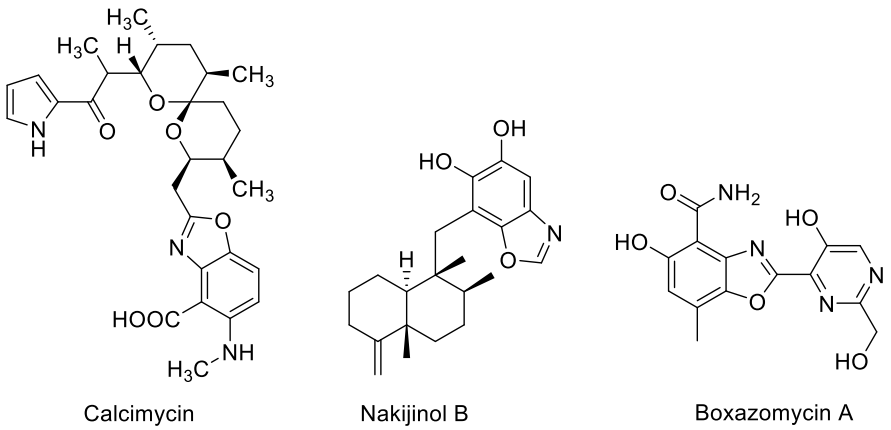


Figure 1. Structures of some biological active benzoxazole derivatives.

Click reactions of sulfur (VI) fluoride exchange (SuFEx) have been successfully used for the synthesis of small molecules in chemical biology for labeling proteins and in material

science for obtaining polymeric materials and surface modification [7,8]. The general method for the SuFEx-based synthesis of fluorosulfates is shown in Figure 2.

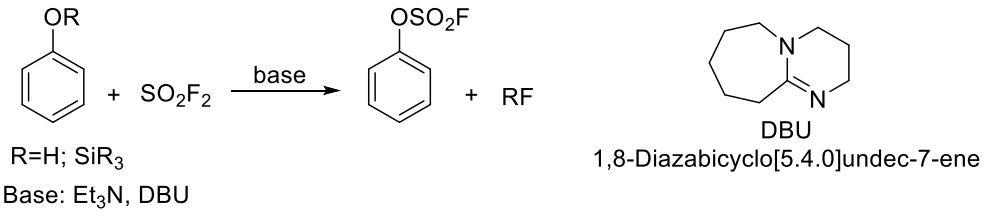


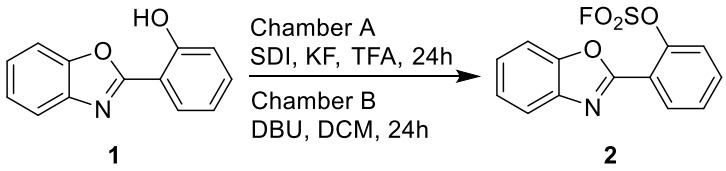
Figure 2. A general scheme for SuFEx-based synthesis of fluorosulfates.

Despite this, the SuFEx reactions have not been widely used for the preparation of benzoxazole derivatives. The aim of the present work was to obtain a new fluorosulfate derivative of benzoxazole and make an in silico evaluation of its interaction with anaplastic lymphoma kinase R1275Q.

2. Results and Discussion

The preparation of new sulfur-containing compounds using the SuFEx reaction is of scientific and practical interest, since the key starting reagent SO_2F_2 is readily available, and the reaction itself is operationally simple, proceeds with high yields and high rates. Despite a fairly wide range of known benzoxazole derivatives, little is known about the effect of the additional –SO_2F group on biological activity.

Using the SuFEx reaction between compound **1** and SO_2F_2 in the presence of DBU, we obtained 2-(2-(fluorosulfonyloxy)phenyl)benzoxazole (**2**) (Scheme 1). The process was carried out in a two-chamber reactor (Figure S1), where in chamber A gaseous SO_2F_2 was formed, and a click reaction proceeded in chamber B. To our knowledge, compound **2** is the first example of a benzoxazole derivative with a fluorosulfate-containing substituent at position *two* of the benzoxazole heterocycle.



Scheme 1. Synthesis of title compound **2**.

During the reaction, the formation of large amounts of a by-product, *bis*(2-(benzoxazol-2-yl)phenyl)sulfate (Figure 3), was observed, due to a further interaction of the target product (**2**) with the starting 2-(2-hydroxyphenyl)benzoxazole (**1**). In this regard, we investigated the effect of an increased excess of gaseous SO_2F_2 on the yield of the target compound and the by-product of the reaction. The results are shown in Table 1.

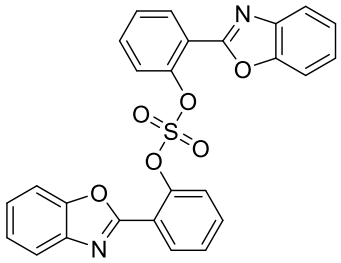


Figure 3. Structure of by-product *bis*(2-(benzoxazol-2-yl)phenyl)sulfate.

Table 1. Influence of excess SO_2F_2 on the yields of the target compound and by-product of the SuFEx reaction.

No. *	Chamber A			Target Product Yield, g (%) **	By-Product Yield, g (%) **
	SDI, mmol	KF, mmol	TFA, mL		
1	1.5	4	1	0.0498 (34)	0.0695 (57)
2	2.5	6.5	1.6	0.1095 (75)	0.0285 (24)

* In both variants, the loading in chamber B was the same: 0.5 mmol of 2-(2-hydroxyphenyl)benzoxazole, 3 mL of DCM, 2 mmol of DBU.
** The presented yields were obtained after chromatographic column purification.

Considering that the volume of the two-chamber reactor was 10 mL, we estimated the SO_2F_2 pressure under the condition of complete SDI conversion in experiments one and two (Table 1) as 1.5 and 2.25 atm, respectively.

From the results presented in Table 1, it can be concluded that with an increase in the gaseous SO_2F_2 excess by 1.5 times, the yield of the target product increased almost 2-fold, while the by-product yield decreased by 1.5 times.

The main characteristics of the target product: colorless crystals, M.p. 74–75 °C, soluble in ethyl acetate and chloroform.

Molecular Docking

For a number of biotargets, inhibition by 2-substituted benzoxazole derivatives had already been studied, and with great success [9,10]. From the Protein Data Bank (PDB), we selected a biotarget important from a practical point of view: anaplastic lymphoma kinase (ALK) mutation R1275Q represented by the PDB structure 4FNY. ALK is a tyrosine kinase enzyme that, when genetically altered by mutation, amplification, chromosomal translocation or inversion, plays an oncogenic role in some types of cancer. One of the most common mutations is R1275Q [10]. The docking poses found by us for compounds **1** and **2** are shown in Figure 4.

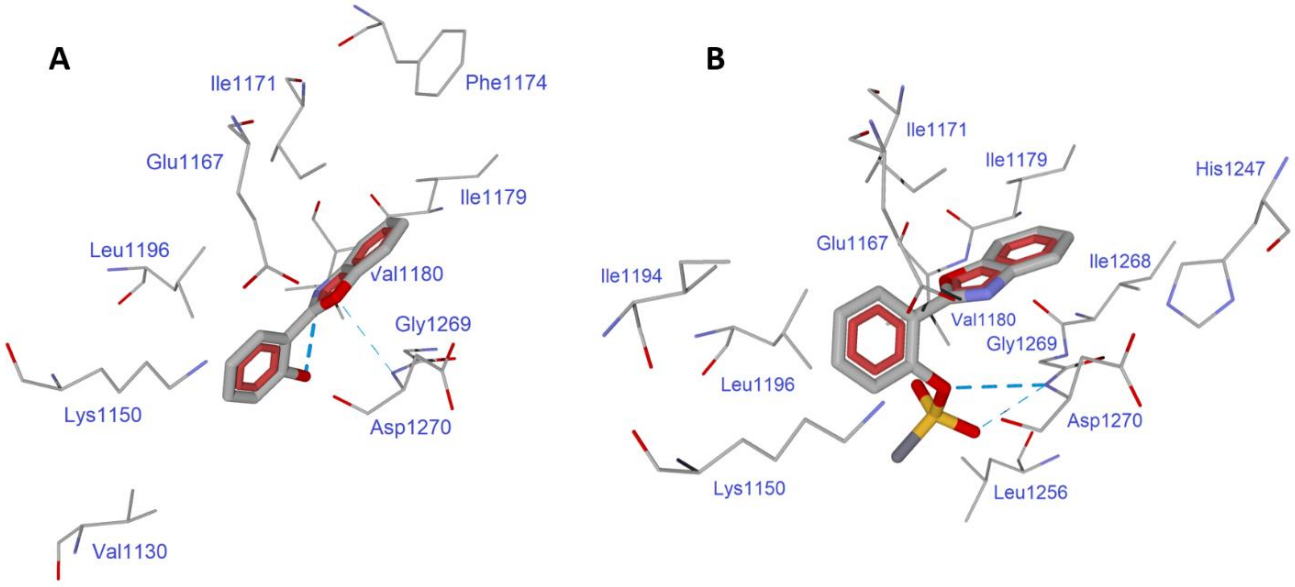


Figure 4. Docking poses of compounds **1** and **2** (Panels (**A**,**B**), respectively) in the binding site of R1275Q (PDB code 4FNY). Residues within 3 Å from each pose are visible. Hydrogen bonds are shown in blue dashed lines. The OH group of compound **1** forms an intramolecular H-bond with the benzoxazole nitrogen atom (Panel (**A**)).

3. Materials and Methods

3.1. General Information and Compound **2** *Synthesis*

Gas chromatography–mass spectrometry (GC/MS) analysis was performed using a GC-MS system consisting of an Agilent 5975C mass detector and an Agilent 7890A gas

chromatograph. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE III HD instrument (operating frequency ^{1}H—400 MHz; ^{13}C—100 MHz). The ^{19}F NMR spectra were recorded on a Bruker Advance 500, operating frequency 470.592 MHz. Melting points of the obtained compounds were measured using a Melting Point Apparatus SMP30, heating rate 2.5 °C/min. The reaction mixture was monitored by a thin layer chromatography (TLC) on Silufol UV-254 and Merck plates, silica gel 60, F254.

2-(2-(Fluorosulfonyloxy)phenyl)benzoxazole (**2**). Chamber A of a flame-dried small two-chamber reactor (Figure S1) was filled with 1,1′-sulfonyldiimidazole (SDI, 495 mg, 2.5 mmol) and potassium fluoride (378 mg, 6.5 mmol). Next, chamber B was charged with compound **1** (106 mg, 0.5 mmol), DBU (300 µL, 2.0 mmol) and dichloromethane (DCM, 3 mL). Finally, 1.6 mL trifluoroacetic acid (TFA) was added by injection through the septum in chamber A and instant gas formation was observed.

After 18 h stirring at room temperature, one of the caps was carefully removed to release the residual pressure. The reaction was stirred for another 15 min to ensure that all sulfuryl fluoride was extracted out of the fume hood. Next, the content of chamber B was transferred to a 100 mL round-bottomed flask. Chamber B was rinsed two times with 2 mL of dichloromethane and these fractions were added to the same flask. Then the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane–chloroform, 1:1). The title compound was obtained as colorless crystals (0.1095 g, 75%).

M.p. 74–75 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.41 (m, 2H, CH_{Ar}), 7.59 (m, 4H, CH_{Ar}), 7.85 (dd, H, CH_{Ar}, *J* 6.4 Hz, ^{4}J 3.2 Hz), 8.42 (dd, H, CH_{Ar}, *J* 7.6 Hz, ^{4}J 1.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ 109.84, 119.70, 119.86, 121.69, 123.98, 125.08, 128.17, 130.37, 131.84, 140.39, 146.27, 149.47, 157.27. ^{19}F NMR (470.592 MHz, $CDCl_3$) 42.09.

GC-MS *m*/*z* 293.1 (63.32%, $(M)^{+\bullet}$).

The NMR spectra and GC-MS data are shown in Figures S2–S5.

3.2. Molecular Docking

The 3D structures of ligands **1** and **2** were built using the ChemOffice 2016 software, pre-optimized with the MM2 force field, and saved in the Tripos MOL2 format. The ligand structures were further imported in the Molegro Virtual Docker 6.0 (MVD) program (CLC Bio, Copenhagen, Denmark). A structure of anaplastic lymphoma kinase R1275Q was also imported in MVD from PDB (4FNY entry) with co-crystallized water molecules removed. The search area for docking was chosen as a sphere of 10 Å in radius positioned at the geometric center of gravity of the co-crystallized N-(4-chlorophenyl)-5-((6,7-dimethoxyquinolin-4-yl)oxy)-1,3-benzoxazol-2-amine ligand [10]. The "Detect Cavities" tool of the MVD was used with default options in order to locate cavities in the protein. The largest found cavity was 113 Å^3 in volume and fully included the co-crystallized ligand. Docking of compounds **1** and **2** was performed with MolDock scoring function [11] using the defined search area with the option "Constrain Poses to Cavity" enabled. The receptor was considered rigid, while a full conformational flexibility of the ligands was allowed. Ligand evaluation included internal H-bonds and sp^2–sp^2 torsions. The post-processing options "Energy minimization" and "Optimize H-Bonds" of the MVD were switched on. For each of the compounds, 500 docking runs were performed. The lowest-energy docking poses were saved and analyzed.

4. Conclusions

In this work, we presented an efficient synthesis of the new benzoxazole fluorosulfate derivative **2**. The compound structure was confirmed by NMR spectrometry and GC-MS. The in silico study using molecular docking predicted anticancer potency of compound **2** through ALK R1275Q inhibition. Thus, the title compound is of great interest for further studies as a possible anaplastic lymphoma kinase inhibitor.

Supplementary Materials: The following are available online at. Figures S1–S5: NMR spectra and GC-MS data for compound **2**.

Author Contributions: Conceptualization was conducted by N.V.D. and A.I.K.; methodology and experimental works were conducted by N.V.D. and V.I.S.; data analysis, writing, and editing of the paper were conducted by N.V.D. and A.I.K.; project administration and supervision was conducted by A.I.K. 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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