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RESEARCH ARTICLE

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# Novel steroid sulfatase inhibitors based on *N*-thiophosphorylated 3-(4-aminophenyl)-coumarin-7-*O*-sulfamates

Mateusz Daśko[1] | Sebastian Demkowicz[2] | Karol Biernacki[2] | Amira Harrous[2] | Janusz Rachon[2] | Witold Kozak[3] | Aleksandra Martyna[4] | Maciej Masłyk[4] | Konrad Kubiński[4] | Anna Boguszewska-Czubara[5]

[1]Department of Inorganic Chemistry, Faculty of Chemistry, Gdansk University of Technology, Gdansk, Poland

[2]Department of Organic Chemistry, Faculty of Chemistry, Gdansk University of Technology, Gdansk, Poland

[3]Department of Physical Chemistry, Faculty of Chemistry, University of Gdansk, Gdansk, Poland

[4]Department of Molecular Biology, Faculty of Biotechnology and Environment Sciences, The John Paul II Catholic University of Lublin, Lublin, Poland

[5]Department of Medical Chemistry, Medical University of Lublin, Lublin, Poland

**Correspondence**
Mateusz Daśko, Department of Inorganic Chemistry, Faculty of Chemistry, Gdansk University of Technology, Narutowicza 11/12, 80-233 Gdansk, Poland.
Email: mateusz.dasko@pg.edu.pl

Sebastian Demkowicz, Department of Organic Chemistry, Faculty of Chemistry, Gdansk University of Technology, Narutowicza 11/12, 80-233 Gdansk, Poland.
Email: sebdemko@pg.gda.pl

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## Abstract

In the present work, we described convenient methods for the synthesis of *N*-thiophosphorylated 3-(4-aminophenyl)-coumarin-7-*O*-sulfamates as steroid sulfatase (STS) inhibitors. To design the structures of the potential STS inhibitors, molecular modeling techniques were used. A computational docking method was used to determine the binding modes of the synthesized inhibitors as well as to identify potential interactions between specified functional groups on the inhibitors and the amino acid residues present in the active site of the enzyme. The inhibitory activities of the synthesized compounds were tested in an enzymatic assay with STS isolated from a human placenta. Within the set of newly synthesized compounds, **9e** demonstrated the highest inhibitory activity in the enzymatic assay with an $IC_{50}$ value of 0.201 μM (the $IC_{50}$ value of **667-COUMATE** in the same test was 0.062 μM). Furthermore, we tried to verify if the obtained STS inhibitors are able to pass through the cellular membrane effectively in cell line experiments. In the course of our study, we determined the STS activity in the MCF-7 cell line after incubation in the presence of the inhibitors (at 100 nM concentration). For this evaluation, we included newly synthesized compounds **9a-g** and their *N*-phosphorylated analogs **6a-h**, whose synthesis has been previously described. We found that the lowest STS activities were measured in the presence of *N*-phosphorylated derivatives **6e** (0.1% of STS activity) and **6f** (0.2% of STS activity). The measured STS activity in the presence of **667-COUMATE** (used as a reference) was 0.1%. Moreover, at concentrations up to 1 μM, the most active compounds (**6e**, **6f**, **9b**, and **9e**) did not exert any toxic effects on zebrafish embryos.

KEYWORDS

breast cancer, coumarin sulfamates, steroid sulfatase, STS inhibitors

## 1 | INTRODUCTION

The STS enzyme plays a crucial role in the hydrolysis of biologically inactive steroid sulfates of into their unsulfated derivatives with biological activity. The activity of STS is responsible for the production of steroidal hormones, which induce the proliferation of cancer cells in a number of hormone-dependent cancers (Shah, Singh, Singh, Singh Jaggi, & Singh, 2016). Inhibition of the STS enzyme may be important

  