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Synthesis and steroid sulfatase inhibitory activities of *N*-phosphorylated 3-(4-aminophenyl)-coumarin-7-*O*-sulfamates†‡

Mateusz Daśko,[a] Maciej Masłyk,[b] Konrad Kubiński,[b] Justyna Aszyk,[c] Janusz Rachon[a] and Sebastian Demkowicz*[a]

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In the present work, we report convenient methods for the synthesis and biological evaluation of *N*-phosphorylated derivatives of 3-(4-aminophenyl)-coumarin-7-*O*-sulfamate as potential steroid sulfatase (STS) inhibitors. Their binding modes were modeled using docking techniques. The inhibitory effects of the synthesized compounds were tested on STS isolated from human placenta. All of the newly synthesised coumarin derivatives were powerful inhibitors of STS with IC_{50} values ranging between 0.19 and 0.78 μM. In particular, we found that 3-[4-(diphenoxy-phosphorylamino)-phenyl]-coumarin-7-*O*-sulfamate **10e** and 3-[4-(dibenzyloxy-phosphorylamino)-phenyl]-coumarin-7-*O*-sulfamate **10f** produced the highest inhibitory effects, with IC_{50} values of 0.19 and 0.24 μM, respectively (IC_{50} values of 1.38 μM for coumarin-7-*O*-sulfamate **2** and 1.03 μM for coumate **3** used as reference). The structure–activity relationships of the synthesized coumarin derivatives toward the STS enzyme were discussed.

Introduction

Steroid sulfatase (STS) is a target enzyme of growing therapeutic importance. STS is responsible for the hydrolysis of steroid sulfates to their active forms (*e.g.*, estrone sulfate to estrone); therefore, the inhibition of this enzyme decreases the biosynthesis of the active hormones responsible for breast, endometrial or prostate cancer.[1] STS is widely distributed throughout the body, and its action is involved in physiological and pathological conditions.[2] Approaches for the development of effective and potent STS inhibitors include three different categories of compounds: alternative substrates (including competitive reversible inhibitors), reversible inhibitors, and irreversible inhibitors.[3] Most of the STS inhibitors that have been discovered to date act in an irreversible manner. EMATE **1**, one of the first irreversible inhibitors, exhibited a very potent activity in MCF-7 cells with an IC_{50} value of 65 pM.[4] Despite the exceptional potency of EMATE **1**, clinical trials for this compound have been discontinued due to its estrogenic properties.[5] The attempts to synthesize nonsteroidal agents (devoid of undesirable adverse endocrine effects *in vivo*) have promoted the generation of coumarin sulfamates. These compounds are also able to mimic the AB rings of the natural substrate and modulate several cancer-specific enzymes such as aromatase or steroid sulfatase.[6] The first potent inhibitors based on the coumarin scaffold were coumarin-7-*O*-sulfamate **2** and 4-methylcoumarin-7-*O*-sulfamate (coumate) **3**, which exhibited good activity when evaluated against placental microsomes.[7] Further modifications of their structures led to a wide range of tricyclic coumarin derivatives, which showed more potent inhibitory activities than coumate **3**. For example, 667-coumate **4** (the first of steroid sulfatase inhibitors to be entered into clinical trials for patients with hormone-dependent breast cancer) and 6610-coumate **5** have demonstrated a potent activity toward STS with IC_{50} values of 8 nM and 1 nM, respectively.[8]

Encouraged by our previous research,[9] we have decided to design and synthesize a series of *N*-phosphorylated derivatives of 3-(4-aminophenyl)-coumarin-7-*O*-sulfamate as compounds with potential STS inhibitory activity. We have found that the introduction of different phosphate or thiophosphate moieties into the structures of the coumarin scaffolds can significantly increase the inhibitory properties of the tested compounds (analog **6**, Fig.1). Furthermore, as is

[a] *Department of Organic Chemistry, Chemical Faculty, Gdansk University of Technology, Narutowicza 11/12, 80-233 Gdansk, Poland. E-mail: sebdemko@pg.gda.pl*
[b] *Department of Molecular Biology, Faculty of Biotechnology and Environment Sciences, The John Paul II Catholic University of Lublin, Konstantynów 1i, 20-708 Lublin, Poland*
[c] *Department of Analytical Chemistry, Chemical Faculty, Gdansk University of Technology, Narutowicza 11/12, 80-233 Gdansk, Poland*

† The authors declare no competing interests.

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