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Research paper

Synthesis and biological evaluation of fluorinated *N*-benzoyl and *N*-phenylacetoyl derivatives of 3-(4-aminophenyl)-coumarin-7-*O*-sulfamate as steroid sulfatase inhibitors

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ABSTRACT

In the present work, we report convenient methods for the synthesis of 3-(4-aminophenyl)-coumarin-7-*O*-sulfamate derivatives *N*-acylated with fluorinated analogues of benzoic or phenylacetic acid as steroid sulfatase (STS) inhibitors. The design of these potential STS inhibitors was supported by molecular modeling techniques. Additionally, computational docking methods were used to determine the binding modes of the synthesized inhibitors and to identify potential interactions between inhibitors and amino acid residues located in the active site of STS. The inhibitory effects of the synthesized compounds were tested on STS isolated from human placenta and against estrogen receptor-(ER)-positive MCF-7 and T47D cells, as well as ER-negative MDA-MB-231 and SkBr3 cancer cell lines. In the course of our investigation, compounds **6c** and **6j** demonstrated the highest inhibitory effect in enzymatic STS assays, both with IC_{50} values of 0.18 μM (the IC_{50} value of coumarin-7-*O*-sulfamate is 1.38 μM, used as a reference). Compound **6j** exhibited the highest potency against the MCF-7 and T47D cell lines (15.9 μM and 8.7 μM, respectively). The GI_{50} values of tamoxifen (used as a reference) were 6.8; 10.6; 15.1; 12.5 μM against MCF-7, T47D, MDA-MB-231 and SkBr3 cancer cell lines, respectively. Despite the slightly lower activity of compounds **1** and **2** (both in enzymatic and cell-based experiments) compared to **6g** and **6j**, analogues **1** and **2** proved to selectively inhibit the growth of ER- and PR-positive cell lines.

1. Introduction

The World Health Organization (WHO) lists biologically active hormones, including estrogens, as one of the most important factors inducing the development of breast cancer. Novel treatment strategies for breast cancer involve inhibitors, which prevent the synthesis of estrogens in peripheral tissues [1]. Steroid sulfatase (STS) is one enzyme responsible for the formation of active estrogens in the breast tissue of postmenopausal women. STS hydrolyses estrone sulfate (E1S) and dehydroepiandrosterone sulfate (DHEAS) into estrone (E1) and dehydroepiandrosterone (DHEA), which can be converted into steroids that exhibit estrogenic properties (estradiol and androstenediol) [2].

The design and synthesis of compounds that regulate hormone levels in tissues through inhibition of STS activity is a major challenge for modern medicinal chemistry. Most known STS inhibitors act irreversibly. To date, various research groups have synthesized steroidal and non-steroidal irreversible inhibitors of STS substituted with various functional groups including phosphates, thiophosphates or sulfamates [3–10]. Because the sulfamate moiety of STS inhibitors such as EMATE was designed to mimic sulfate moiety of natural substrates, it is assumed that the inhibition mechanism of these compounds involves an FGly75 residue located inside the active site of STS. The FGly75 residue coordinates to a calcium ion and plays a crucial role in the enzymatic hydrolysis of

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