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Research paper

Synthesis of bicoumarin thiophosphate derivatives as steroid sulfatase inhibitors

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ABSTRACT

Based on the frameworks of 7-hydroxy-2,3-dihydro-*1H*-cyclopenta[c]chromen-4-one, 3-hydroxy-7,8,9,10-tetrahydro-*6H*-benzo[c]chromen-6-one and 3-hydroxy-8,9,10,11-tetrahydro-*7H*-cyclohepta[c]chromen-6-one, a series of bicoumarin thiophosphate analogs have been synthesized and biologically evaluated. Additionally, their binding modes have been modeled using docking techniques. The inhibitory properties of the synthesized compounds were tested against the STS isolated from human placenta. Most of the new STS inhibitors possessed good activities against STS. In particular, we found that the bis-(6-oxo-7,8,9,10-tetrahydro-*6H*-benzo[c]chromen-3-yl) hydrogenthiophosphate (**10b**) produced the largest inhibitory effect, with an IC_{50} value of 860 nM (an IC_{50} value of 1 μM for the 665-COUMATE used as a reference). The structure-activity relationships of the synthesized bicoumarin thiophosphate derivatives toward the STS enzyme have been discussed previously.

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1. Introduction

Biologically active hormones, including androgens and estrogens, play an important role in the development of many diseases, such as hormone-dependent breast cancer (HDBC). One approach for the treatment of HDBC is based on the inhibitors of the steroid sulfatase (STS) [1]. The STS is responsible for the hydrolysis of steroid sulfates into their active forms and thus plays a crucial role in the formation of biologically active steroids. The STS hydrolyses, among others, estrone sulfate (E1S) and dehydroepiandrosterone sulfate (DHEAS) into estrone (E1) and dehydroepiandrosterone (DHEA), respectively, which can be converted into steroids that exhibit estrogenic properties (estradiol or androstenediol) [2]. The wide distribution of the STS enzyme throughout the body is an indication of its involvement in numerous physiological and pathological conditions [3]. Although the crystal structure of the STS has been determined [4], relatively little is known about the regulation of its expression and activity.

Because of the close relationship between the steroid sulfatase and the arylsulfatases A and B, the topology of the active site of all three enzymes is similar. A characteristic feature of all sulfatases is the exposure of a posttranslational modification that involves the conversion of the cysteine residue in the active site of the enzyme into a formylglycine (FGly) residue [5]. In the resting state, the active site of the human STS consists of a sulfated FGly residue in its gem-diol form, which is coordinated to a Ca^{2+} cation. The catalytic region of the STS is also formed by nine other catalytically important amino acid residues: Asp35, Asp36, Arg79, Lys134, His136, His290, Asp342, Gln343, and Lys368. Furthermore, when the natural substrate, e.g., E1S, is located in the active site of the STS, the Leu74, Arg98, Thr99, Val101, Leu103, Leu167, Val177, Phe178, Thr180, Gly181, Thr484, and Phe488 amino acid residues surround and interact with the steroidal core of the substrate *via* an hydrophobic interaction [3].

Taking into account that the unsulfated FGly residue in its gem-diol form plays a crucial role in the hydrolysis of the sulfate substrates by the arylsulfatase A and B [6], the putative mechanism of action of the STS is shown the in Fig. 1. First, the formation of the unsulfated FGly residue (gem-diol) from the structure containing the sulfate moiety (FGlyS) occurs. This step can be performed *via* the desulfation of the FGlyS, which is catalyzed by the nonesterified hydroxyl group, followed by the nucleophilic attack of the water

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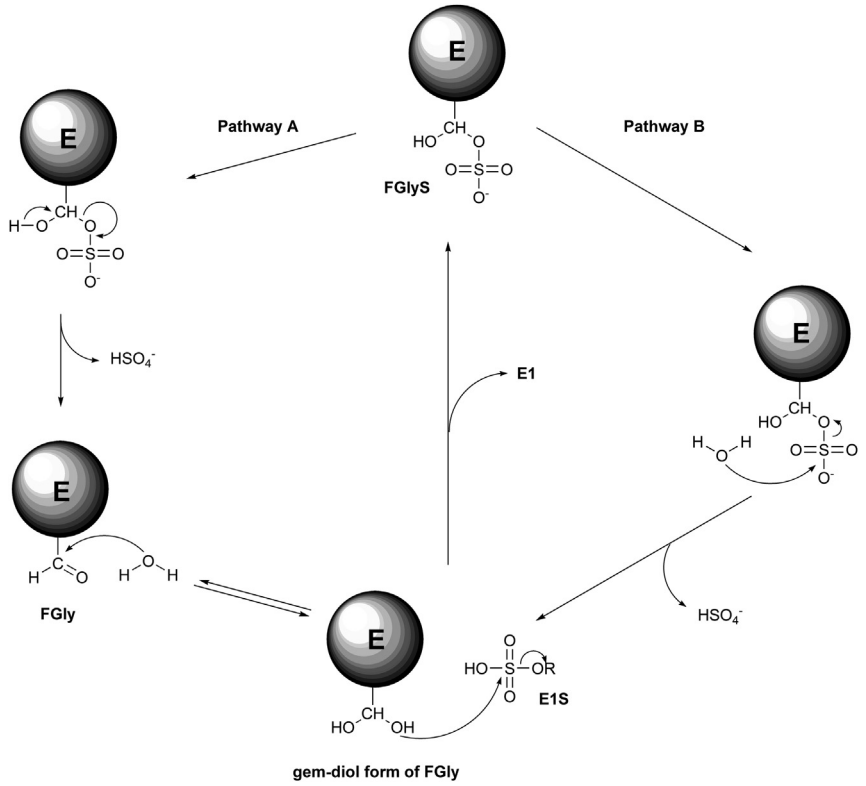

Fig. 1. Putative mechanism of action of the STS (E – enzyme).

molecules on the carbon atom of the FGly intermediate (pathway A). The pathway B assumes a direct nucleophilic substitution reaction on the sulfur atom of the FGlyS. Finally, an S_N2 attack of the hydroxyl group of the FGly (gem-diol) on the sulfur atom of the substrate (e.g., E1S), hydrolyzes the conjugate alcohol and creates a sulfated FGly (FGlyS) [3].

The design and synthesis of new and more effective agents that inhibit the activity of the STS is a major challenge for modern medicinal chemistry. Most of the STS inhibitors discovered to date act in an irreversible way. One of the first irreversible inhibitors was the EMATE (**1**), which exhibits a very high activity in MCF-7 cells and has an IC_{50} value of 65 pM [7] (Fig. 2).

Despite the exceptional potency of the EMATE, it is not used to treat hormone-dependent breast cancer because of its estrogenic properties [8]. It has been known for a long time that the non-steroidal agents and their metabolites, which were designed for potential therapeutic use, induce fewer undesirable endocrine effects *in vivo* than do their steroidal analogues. The attempts to synthesize non-estrogenic compounds have promoted the generation of the tricyclic coumarin sulfamates. Among them, the compound 667 COUMATE (**2**) (currently in clinical trials) was shown to be a potent STS inhibitor, with an IC_{50} value of 8 nM in placental

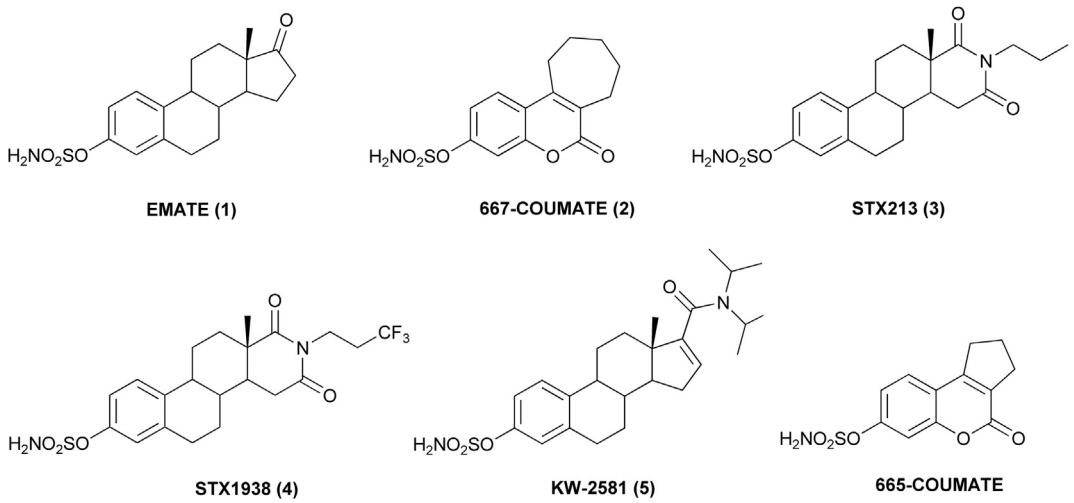

Fig. 2. Chemical structure of the STS inhibitors.

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