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Synthesis and steroid sulfatase inhibitory activities of *N*-alkanoyl tyramine phosphates and thiophosphates†

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A series of phosphate and thiophosphate analogs based on the frameworks of *N*-alkanoyl tyramines have been synthesized and biologically evaluated. Their binding modes have been modeled using docking techniques. The inhibitory effects of the synthesized compounds were tested on STS isolated from the human placenta as well as the MCF-7, MDA-MB-231 and SkBr3 cancer cell lines. Most of the new STS inhibitors possessed potent activity against STS. In the course of our investigation, 4-(2-dodecanoylamino-ethyl)-phenyl dimethyl phosphate **4a** demonstrated the greatest inhibitory effect, with IC_{50} values of 0.39 μM (IC_{50} value of 15.44 μM for the 4-(2-dodecanoylamino-ethyl)-phenyl sulfamate used as a reference). The compound **4a** exhibited the highest potency against the MCF-7, MDA-MB-231 and SkBr3 cancer cell lines, with a GI_{50} values of 8.80, 6.48 and 5.76 μM, respectively. The structure–activity relationships of the synthesized phosphate- and thiophosphate-based tyramine derivatives with the STS enzyme are discussed.

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Introduction

Approximately 1 in 9 women are affected by breast cancer during their lifetime, and this disease is a major cause of mortality of postmenopausal women. Estimates show that in the United States, more than 230 000 new cases of breast cancer were diagnosed and more than 40 000 deaths occurred from this disease in 2014 (according to National Cancer Institute data). Over the past decades, numerous reports have suggested the importance of biologically active hormone precursors in regulating the supply of estrogens to estrogen-dependent breast cancers. Sulfated steroids, including estrone sulfate (E1S) and dehydroepiandrosterone sulfate (DHEAS), play an important role in the process of human steroidogenesis and are considered to be the key endocrine factor involved in the initiation and promotion of breast cancer.[1] There are three enzyme pathways (including aromatase, 17β-hydroxysteroid dehydrogenase and steroid sulfatase STS) that are responsible for the formation of active estrogens in the breast tissue of postmenopausal women. Within these pathways, STS plays a major role in the formation of biologically active estrogens or androgens and acts by hydrolyzing aryl and alkyl steroid sulfates (including E1S and DHEAS).[2] It is worth noting that STS expression is detected in 90% of breast tumors, with much higher activity than the aromatase complex.[3] The detailed studies have shown that estrone (E1) and dehydroepiandrosterone (DHEA) (products of the hydrolysis of E1S and DHEAS) can act as precursors for the formation of the estrogenic steroids estradiol (E2) and androstenediol (Adiol) (Fig. 1). In addition, a variety of scientific research has shown that estradiol (E2) and androstenediol (Adiol) are responsible for the stimulation and proliferation of breast cancer cells *in vitro* and play a pivotal role in breast cancer tumorigenesis.

Because STS is strongly implicated in estrogenic stimulation of hormone-dependent breast cancer, research work on the design and synthesis of new and more effective agents that inhibit the activity of STS is of particular importance and is a major challenge for modern medicinal chemistry. Significant progress has been made in the past two decades in discovering and synthesizing STS inhibitors for clinical development. The achievements of steroid sulfatase inhibitors were presented in a series of review articles.[3–5] Among the first inhibitors reported to possess good inhibitory activity were danazol,[6] 2-phenylindole sulfates,[7] steroid sulfonyl halides,[8] steroid sulfates[9] and phosphates.[10] The breakthrough in the design of effective STS inhibitors was the discovery of estrone-3-*O*-sulfamate (EMATE), which exhibited very high activity in MCF-7 cells, with an IC_{50} value of 65 pM. Although possessing potent inhibitory activity, surprisingly, EMATE exhibits estrogenic activity, rendering it

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