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RESEARCH LETTER

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Synthesis and biological evaluation of *N*-acylated tyramine sulfamates containing C–F bonds as steroid sulfatase inhibitors

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Steroid sulfatase (STS) is responsible for the hydrolysis of biologically inactive sulfated steroids into their active un-sulfated forms and promotes the growth of various hormone-dependent cancers (e.g., breast cancer). Therefore, the STS enzyme is a promising therapeutic target for the treatment of steroid-sensitive cancers. Herein, we report the synthesis and biological evaluation of sulfamate analogs as potential STS inhibitors based on *N*-acylated tyramines that contain C–F bonds. The inhibitory effects of the analogs were tested using STS isolated from human placenta. Of the analogs tested, 4-(2-perfluoroundecanoylaminoethyl)-phenyl sulfamate, **5r**, demonstrated the greatest inhibitory effect, with an IC_{50} value of 2.18 μM (IC_{50} value of 2.13 μM for coumarin-7-*O*-sulfamate was used as a reference). These findings were supported by the results our computational analyses performed using molecular docking techniques.

KEYWORDS
breast cancer, steroid sulfatase, STS inhibitors, sulfamates, tyramine

1 | INTRODUCTION

Different enzymes are involved in the conversion of androgens and estrogens during steroidogenesis. One such enzyme that regulates the level of steroids is steroid sulfatase (STS), one of the fifteen known human sulfatases. STS catalyzes the desulfation of sulfated steroids, exemplified by the conversion of estrone sulfate (E1S) into estrone (E1) that regulates the function of many physiological molecules.[1] The solubility and half-life of E1S is several fold higher than that of its un-sulfated form E1. This allows E1S to act as a steroid reservoir, with its local concentrations reaching up to ten times that of E1 in tissues, efficiently stimulating tumor growth.[2,3] Sulfatases have been implicated in the development of numerous pathophysiological conditions, including hormone-dependent cancers, lysosomal storage disorders, developmental abnormalities, and bacterial pathogenesis.[4] In patients with hormone-dependent cancers, the reduction in estrogen and androgen concentrations is crucial. Therefore, because STS is involved in biosynthesis of active steroids, it is a promising therapeutic target for the treatment of steroid-sensitive cancers. In addition to their utility in breast cancer treatment, STS inhibitors may be effective in the treatment of endometrial and prostate cancers as well as other hormone-dependent cancers.[5]

Various approaches have been used in the design of effective STS inhibitors. Extensive research efforts in the recent years have focused on finding novel steroidal and non-steroidal inhibitors of STS containing different functional groups, for example, the sulfamate moiety.[6] One of the most promising compounds was steroidal EMATE (Figure 1), which exhibited a very high activity in MCF-7 cells, with an IC_{50} value of 65 pM. Despite its high inhibitory activity, EMATE was withdrawn from clinical trials due to its estrogenicity.[7] To avoid such adverse side-effects, several research groups attempted the synthesis of new compounds based on non-steroidal structures. Coumarin derivatives are another important class of potent STS inhibitors. An earlier study reported that coumarin-7-*O*-sulfamate and its derivatives, such as COUMATE (IC_{50} value of 380 nM in an assay with placental microsomes), showed no significant estrogenicity.[8]

