INHIBITION OF STEROID SULFATASE: A NEW APPROACH TO TREAT ESTROGEN- AND ANDROGEN-DEPENDENT DISEASES

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Steroid sulfatase (STS) catalyses the hydrolysis of the sulfate esters of 3-hydroxy steroids. Among the substrates are dehydroepiandrosterone sulfate and estrone sulfate, which are inactive transport or precursor forms of androgens and estrogens. STS regulates the local production of these hormones within target tissues. Thus, blockade of STS with pharmacological inhibitors could be a means to modulate local hormone levels only, without influencing systemic levels.

Preclinical development of STS inhibitors is most advanced for the indication of breast cancer, and there is increasing evidence that the steroid sulfatase pathway is the major source of estrogens in breast and endometrial tumours. Inhibitors of STS are thus considered potential new therapeutic agents for the treatment of estrogen-dependent cancers, but additional potential indications include androgen-dependent diseases such as prostate cancer, androgenetic alopecia, and acne [1].

In this review, we give a comprehensive summary of the current knowledge and problems in the field of medicinal chemistry of STS inhibitors. The various types of inhibitors are presented and structure-activity relationships are discussed. Until recently the field has been dominated by irreversible, arylsulfamate-based inhibitors, all derived from the lead estrone sulfamate (EMATE), the amido analogue of the natural substrate estrone sulfate. There are two major issues associated with STS inhibitors: potential estrogenicity and chemical stability. With the design of several potent, non-estrogenic inhibitors, the estrogenicity issue appears to be solved. The second issue is the inherent limited chemical stability of arylsulfamates in solution, even though they are stable in bulk. Stable, potent reversible inhibitors should be less problematic for development. However, the design was apparently hampered by the lack of the 3D structure of STS until recently, and the discovery of novel inhibitor types has been limited to (high-throughput) screening. We were successful with HTS to identify an interesting lead structure for further optimisation. Initial SAR of this novel STS inhibitor class will be presented. Besides increasing cellular and in vivo potency, one of the next challenges will be to identify the structural commonalities among the available, structurally diverse inhibitors. The recent publication of the 3D structure of STS is expected to help here and, in general, to further stimulate research in the area of STS inhibitors.

[1] P. Nussbaumer, A. Billich: Med. Res. Rev. **2004**, *24* (4), 529-576.