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Review

Estrogen *O*-sulfamates and their analogues: Clinical steroid sulfatase inhibitors with broad potential

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ABSTRACT

Estrogen sulfamate derivatives were the first irreversible active-site-directed inhibitors of steroid sulfatase (STS), an emerging drug target for endocrine therapy of hormone dependent diseases that catalyzes *inter alia* the hydrolysis of estrone sulfate to estrone. In recent years this has stimulated clinical investigation of the estradiol derivative both as an oral prodrug and its currently ongoing exploration in endometriosis. 2-Substituted steroid sulfamate derivatives show considerable potential as multi-targeting agents for hormone-independent disease, but are also potent STS inhibitors. The steroidal template has spawned nonsteroidal STS inhibitors one of which, Irosustat, has been evaluated clinically in breast cancer, endometrial cancer and prostate cancer and there is potential for innovative dual-targeting approaches. This review surveys the role of estrogen sulfamates, their analogues and current status.

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1. Introduction

The majority of sufferers of female breast cancer are post-menopausal and about three-quarters of such cancers are hormone-dependent [1]. Many other cancers are hormone-dependent and respond to endocrine therapy, with tumour growth being stimulated by estrogens and/or androgens. The estrogens (estrone E1, estradiol E2 and estriol E3) have an aromatic A ring, while the non-aromatic androgen androstenediol also has estrogenic effects but is about 100-fold weaker than estradiol, though in a post-menopausal setting it is produced in relatively large amounts [2]. One well-established approach to preventing the action of estrogens is to block the estrogen receptor with a selective estrogen receptor modulator (SERM) [3]. Another approach is to inhibit the biosynthetic enzymes involved in estrogen production.

Estrogens (with an aromatic A ring) are synthesized from non-aromatic androgens in a reaction catalysed by cytochrome P450

Abbreviations: 17β-HSD*n*, 17β-hydroxysteroid dehydrogenase (where *n* is a number denoting the subtype of this enzyme); AR, aromatase; CAII, carbonic anhydrase II; DASI, dual aromatase-sulfatase inhibitor; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; E1, estrone; E1S, estrone sulfate; E2, estradiol; E3, estriol; ER, estrogen receptor; SERM, selective estrogen receptor modulator; STS, steroid sulfatase.

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aromatase (Fig. 1), and several clinically useful aromatase inhibitors are on the market: in post-menopausal women they have been found to reduce systemic estrogen levels by as much as 98%. However, there is a large circulatory reservoir of the conjugate estrone sulfate (E1S) and, after entering cells through organic anion transporters and through the subsequent action of steroid sulfatase (STS), E1S can be converted to free estrone *in situ* in tumour cells and can then be reduced to estradiol by 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) [4,5] thus producing E1 in an intracrine fashion. Levels of STS and 17β-HSD1 are reported to be higher in breast cancer tissue than in other tissues so this may be the main route of local estrogen production [6–9]. Also, androstenediol is formed from androstenediol sulfate, itself derived from dehydroepiandrosterone sulfate (DHEAS) and both of these are substrates for STS. STS was found to hydrolyze readily both DHEAS and estrone sulphate, thus indicating that only one sulfatase exists for both estrogen and androgen pathways [10]. Thus, inhibition of STS should not only affect the *in situ* generation of estrone and estradiol, as above, but also should block the other pathway of estrogenic stimulation *via* androstenediol, both pathways importantly being independent of aromatase inhibition. The importance of intracrinology as a concept has been recently reviewed [11] and its key role in breast cancer in particular [12]. STS inhibitors, therefore, as emerging endocrine modulators, might be particularly beneficial for tumours expressing high levels of STS, something that might also facilitate complementary patient stratification.

The structural biology and enzymology of the enzymes of estrogen metabolism have been recently reviewed [13] and there are multiple reviews that cover various aspects of the biology and chemistry of STS and STS inhibitors [14–19], as well as the intellectual property status of the STS field [20]. This mini-review focuses on the role of estrogen sulfamates and their analogues as STS inhibitors and, now that several clinical studies up to phase II have been performed, it is timely to review the potential of this approach and future directions.

2. Estrone 3-*O*-sulfamate (EMATE)

Estrone 3-*O*-sulfamate, known as EMATE, was the first estrogen sulfamate to be tested against cancer cells and was identified after a thorough search of structural surrogates for the

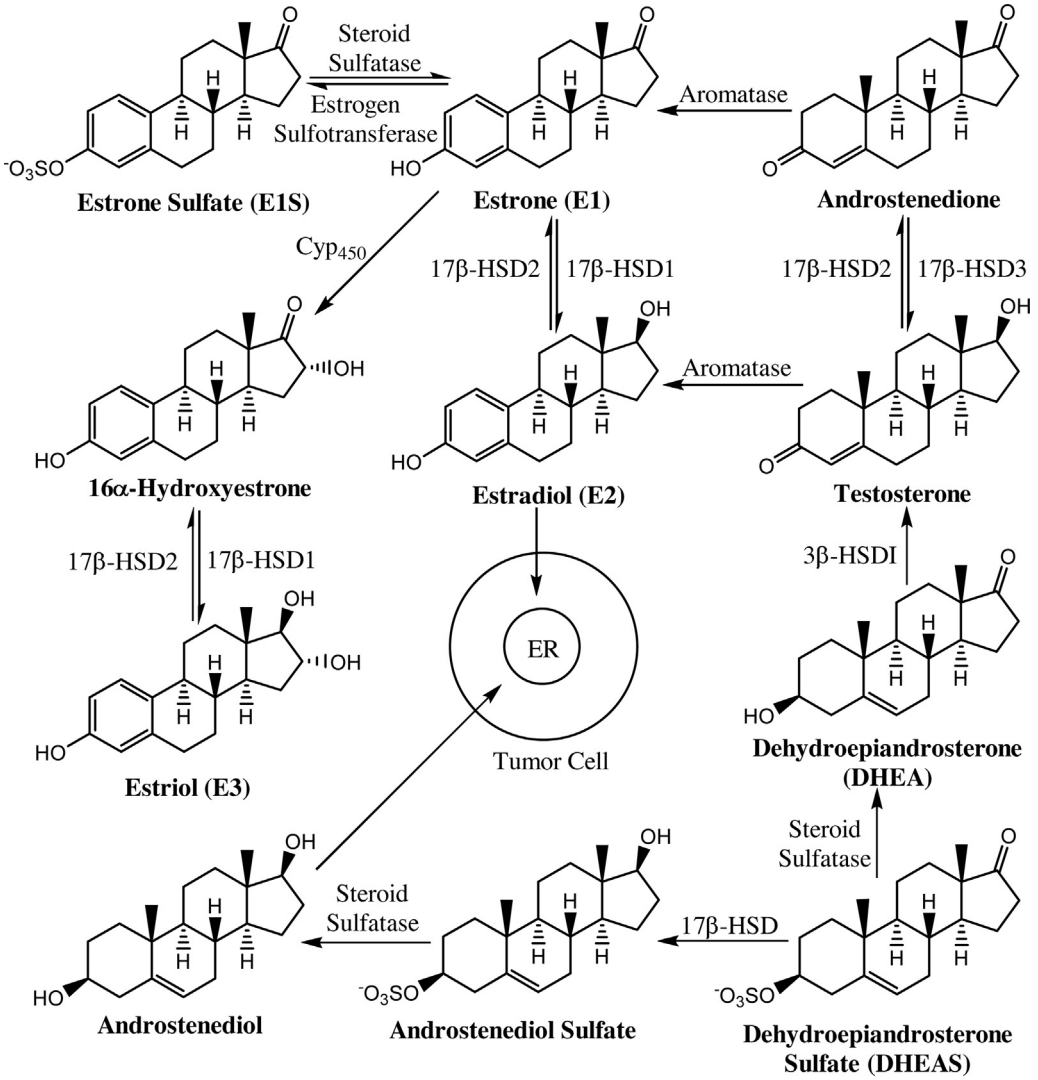

Fig. 1. The origin of estrogenic steroids in post-menopausal women with hormone-dependent breast cancer. Cyp_{450}–cytochrome P_{450}. ER–estrogen receptor. 3β-HSDI–3β-hydroxysteroid dehydrogenase C5,C4-isomerase. 17β-HSD–17β-hydroxysteroid dehydrogenase–the numeral after the HSD denotes the subtype of this enzyme.