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Extended Abstract

Steroid Sulfatase Inhibition: From Concept to Clinic and Beyond †

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Many tumours are hormone-dependent, and estrogens (E1/E2) play a key role in development. Despite aromatase inhibitor (AI) therapy, patients relapse and acquire resistance. Evidence is growing that steroid sulfatase (STS) inhibition will attenuate estrogenic stimulation in hormone-dependent breast cancer (HDBC). E1-3-*O*-sulfamate was the first potent oral, irreversible STS inhibitor, reaching phase II clinical trials. E2-3-*O*-sulfamate is in trials for endometriosis. Superior non-steroidal, non-estrogenic sulfamate-based drugs lead to clinical STX64/Irosustat that is highly orally bioavailable in vivo. Phase I/II clinical trials against locally advanced/metastatic breast cancer showed evidence of stable disease. Trials showed clinical benefit in endometrial cancer and first efficacy both in early breast cancer and in AI combination. A prostate cancer trial has been performed, with further potential elsewhere. Highly potent aryl sulfamate-based STS inhibitors will be discussed around various templates. We investigated inhibition using a soluble bacterial STS, and mechanistic aspects will be reviewed. Dual inhibition of aromatase and STS may address acquired resistance, and high potency inhibitors in vitro and in vivo on both targets will be discussed.

To exploit the aryl sulfamate pharmacophore in hormone-independent settings, we developed STX140**,** based around endogenous 2-methoxyestradiol. STX140 has potent STS inhibitory activity and a multi-targeted mechanism with striking in vivo anticancer results and in autoimmune inflammatory disease and activity against the hypoxic tumour carbonic anhydrase CAIX. SAR Translation led to non-steroidal systems with a similar activity profile and wide applicability, and steroidal and non-steroidal sulfamates have been co-crystallized with a CAIX mimic. Three agents were co-crystallised with $\alpha\beta$-tubulin, demonstrating the first colchicine site binding of a sulfamate–based ligand and uncovering mechanistic aspects. STS is a promising form of anti-endocrine and attractive clinical target in oncology and the aryl sulfamate pharmacophore a powerful motif for drug design.



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