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REVIEW ARTICLE

Recent progress in the development of steroid sulphatase inhibitors – examples of the novel and most promising compounds from the last decade

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ABSTRACT

The purpose of this review article is to provide an overview of recent achievements in the synthesis of novel steroid sulphatase (STS) inhibitors. STS is a crucial enzyme in the biosynthesis of active hormones (including oestrogens and androgens) and, therefore, represents an extremely attractive molecular target for the development of hormone-dependent cancer therapies. The inhibition of STS may effectively reduce the availability of active hormones for cancer cells, causing a positive therapeutic effect. Herein, we report examples of novel STS inhibitors based on steroidal and nonsteroidal cores that contain various functional groups (e.g. sulphamate and phosphorus moieties) and halogen atoms, which may potentially be used in therapies for hormone-dependent cancers. The presented work also includes examples of multitargeting agents with STS inhibitory activities. Furthermore, the fundamental discoveries in the development of the most promising drug candidates exhibiting STS inhibitory activities are highlighted.

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1. Introduction

Cancer is among the leading causes of death. According to the *International Agency for Research on Cancer* estimates in 2018, there were more than 18 million new cases and 9.5 million tumour-related deaths worldwide[1]. Additionally, the *National Cancer Institute* (NCI) expects that the number of new cancer cases will have risen to approximately 23.6 million per year by 2030. The NCI warns that this disease will be diagnosed in approximately 38.4% of men and women during their lifetimes. The most common types are breast, lung, and bronchus, prostate and colorectal tumours, and they account for almost 50% of all new cancer cases. Moreover, lung and bronchus, colorectal, pancreatic, and breast cancers are responsible for nearly 50% of all deaths. The estimates for 2019 indicate that almost 270,000 and 175,000 patients will be diagnosed with breast and prostate tumours, respectively, and more than 41,000 (breast) and 31,000 (prostate) deaths will occur from these diseases in the United States[2]. It is known that most cancers show a hormone-dependent nature in their early stages (e.g. more than 90% of breast cancer cases are initially hormone-dependent)[3]. Therefore, the *World Health Organisation* (WHO) describes biologically active hormones (androgens and oestrogens) as the main cancer growth stimulants. Considering the aforementioned facts, the application of drugs that can effectively reduce concentrations of active hormones should be the basis of modern therapies[4].

The hormone signalling pathway is a well-established target for the development of hormone-dependent cancer drugs (e.g. breast cancer)[5]. For example, the clinically used drug *Tamoxifen* **1** (Figure 1) acts as a selective oestrogen receptor modulator (SERM). In contrast, chemotherapeutics, which may influence the hormone formation process, are also of high therapeutic importance. The biosynthesis of active steroids (e.g. oestradiol [E2] and androstenediol [Adiol]) in cancer tissues mainly depends on the following three enzymatic pathways: aromatase (AROM), 17β-hydroxysteroid dehydrogenase (17β-HSD), and steroid sulphatase (STS) (Scheme 1)[6]. For example, currently used *Letrozole* **2** and *Anastrozole* **3** (Figure 1) block the conversion of androgens to oestrogens *via* inhibition of the AROM complex. However, therapies using the described above drugs often turn out to be unsatisfactory and result in the development of resistance, leading to relapses in tumour progression[7–10]. In light of recent research indicating that sulphation/desuphfation process disorders may be responsible for numerous pathologies[11], another enzyme implicated in the steroidogenesis process, STS, is becoming a new interesting molecular target in the development of novel and effective hormone-dependent cancer treatment methods. In contrast to aromatase, STS activity is present in most cancer cases (e.g. STS expression is detected in 90% of breast tumours)[12]. Furthermore, it has been noticed that STS mRNA levels in malignant tissues have been higher than in normal breast tissues in 87% of tested patients[13].

STS belongs to a group of 15 human sulphatases[6]. This protein consists of 587 amino acid residues and is encoded by the *STS* gene. STS is found ubiquitously throughout the body, what is

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