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Review

Steroid derivatives as inhibitors of steroid sulfatase

Yaser A. Mostafa, Scott D. Taylor*

Department of Chemistry, University of Waterloo, 200 University Ave. West, Waterloo, ON, Canada

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ABSTRACT

Sulfated steroids function as a storage reservoir of biologically active steroid hormones. The sulfated steroids themselves are biologically inactive and only become active in vivo when they are converted into their desulfated (unconjugated) form by the enzyme steroid sulfatase (STS). Inhibitors of STS are considered to be potential therapeutics for the treatment of steroid-dependent cancers such as breast, prostate and endometrial cancer. The present review summarizes steroid derivatives as inhibitors of STS covering the literature from the early years of STS inhibitor development to October of 2012. A brief discussion of the function, structure and mechanism of STS and its role in estrogen receptor-positive (ER+) hormone-dependent breast cancer is also presented.

This article is part of a Special Issue entitled "Synthesis and biological testing of steroid derivatives as inhibitors".

Contents

1. Introduction

Inhibitors of enzymes involved in the biosynthesis and storage of steroids have been pursued as drugs for treating steroid-dependent (i.e. breast, prostate, endometrial) cancers for many years. The aromatase inhibitors that are currently used for treating hormone-dependent breast cancer are perhaps the best known examples of drugs that function in this manner [1]. Although some success has been achieved with aromatase inhibitors, inhibition of aromatase does not prevent production of androgens such as 5-androstenediol (Adiol) and studies have indicated that Adiol is able to bind to the estrogen receptor (ER) and stimulate the growth of breast cancer cells [2–4]. Moreover, aromatase inhibitors would not be expected to be effective against androgen-dependent cancers such as prostate cancer. Hence, the pursuit of new cancer drugs that function by inhibiting other enzymes involved in the biosynthesis and storage of steroids has continued unabated.

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* Corresponding author at: Department of Chemistry, University of Waterloo, 200 University Ave. West, Waterloo, ON, Canada N2L 3G1. Tel.: +1 519 888 4567; fax: +1 519 746 0435.
E-mail addresses: s5taylor@sciborg.uwaterloo.ca, s5taylor@uwaterloo.ca (S.D. Taylor).

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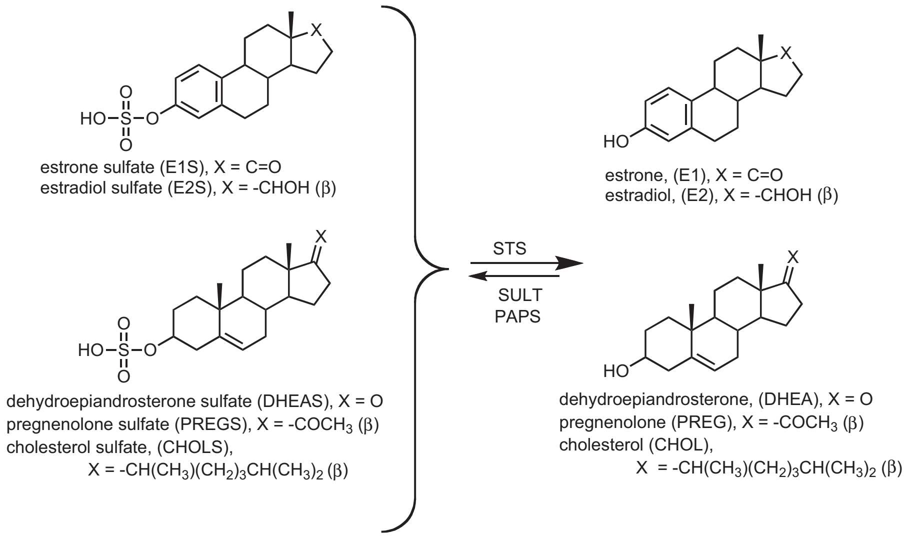

Fig. 1. The reaction catalyzed by STS. The best characterized steroidal STS substrates are shown.

This review focuses upon inhibitors of steroid sulfatase (STS) an enzyme that catalyzes the desulfation of steroidal sulfates to give unconjugated steroids (Fig. 1). It has been a target for the treatment of steroid-dependent cancers for over 20 years, however; only relatively recently have these efforts begun to bear fruit in that a compound has been evaluated in early stage clinical trials and more compounds are expected to do so in the near future. This review outlines the advances that have been made in the development of steroid derivatives as inhibitors of STS.

1.1. STS – substrates and function

STS is one of a family of sulfatases known as aryl sulfatases (ARSs) and is sometimes referred to as aryl sulfatase C (ARSC). The best characterized steroidal substrates of STS are the sulfates of estrone (E1), estradiol (E2), dehydroepiandrosterone (DHEA), pregnenolone (PREG) and cholesterol (CHOL) (Fig. 1). Like all ARSs, STS can also act upon simple aryl sulfates such as *p*-nitrophenyl sulfate (NPS) and 4-methylumbelliferyl sulfate (MUS) though the K_m's for these substrates are more than 100 times higher than the K_m's of the natural steroidal substrates (0.6–2 μM) (Fig. 2). Nevertheless, NPS and MUS have found use as chromogenic or fluorescent substrates for assaying STS and screening inhibitors. ARS-catalyzed reactions are not reversible. Another family of enzymes known as sulfotransferases (SULT), which use 3′-phosphoadenosine-5′-phosphosulfate (PAPS) as a cofactor, are responsible for sulfation.

Sulfated steroids are unable to bind to steroid hormone receptors and are biologically inactive until removal of the sulfate group by STS. It has been proposed that the role of sulfated steroids is as a storage reservoir that acts as a source of biologically active steroid hormones when activated by STS. This is supported by the finding that circulating plasma concentrations of the sulfated steroids, estrone sulfate (E1S), and dehydroepiandrosterone sulfate (DHEAS), are significantly higher than those of their non-sulfated counterparts, E1 and DHEA, a precursor to Adiol [5–7]. In addition, the half-life of E1S and DHEAS in plasma is about 10–12 h, which is considerably longer than the 30–40 min half-life of E1 and DHEA [8].

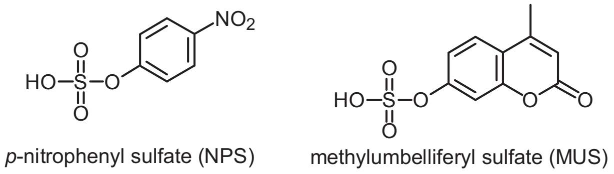

Fig. 2. Common non-steroidal STS substrates.

1.2. STS and breast cancer

The vast majority of research on STS inhibitors has been directed toward the development of drugs for treating estrogen receptor-positive (ER+) hormone-dependent breast cancer. This type of breast cancer occurs most frequently in post-menopausal women which is paradoxical as ovarian production of estrogen, which is the main, though not only source of estrogens, has stopped. Instead of local production of estrogens in tumors, it has been hypothesized that tumor growth is stimulated in part by estrogens derived from their sulfated precursors which are produced in peripheral tissues. These soluble sulfated precursors are transported into the cancer cells by specific membrane transporters where they are then desulfated by STS [9].

Several lines of evidence suggest that STS plays an important role in the progression of steroid-dependent breast cancer. The production of E1 from estrone sulfate (E1S) in breast cancer tissue is approximately 10 times greater than from androstenedione, which is converted to E1 by aromatase (Fig. 3) [10]. 90% of Adiol in post-menopausal women originates from DHEAS via desulfation of DHEAS by STS to give DHEA which is converted into Adiol by a dehydrogenase [11]. There is approximately 50–200 times greater STS activity than aromatase activity in malignant breast tissues [7,12,13]. Sulfatase activity in breast cancer cells is higher than that of normal breast cells [14]. Finally, STS expression in breast tissue is significantly higher than in normal tissue and STS expression is now used as a prognostic factor in human breast carcinoma [15–17].

1.3. STS localization, structure and mechanism

STS is found in all mammalian tissues, but localized primarily in skin, fallopian tubes, testis, ovary, adrenal glands, brain, fetal lung, endometrium, aorta, kidney, bone, placenta, and breast [18]. The placenta is particularly rich in STS. It is expressed as a 63–73 kDa