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Review

Synthesis of sex hormone-derived modified steroids possessing antiproliferative activity

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ABSTRACT

During recent years intensive research has been focused on the synthesis of structurally modified steroid hormones in order to obtain compounds with beneficial biological activity such as cell-growth inhibition. Experimental results have revealed that some steroidal derivatives possess direct cytostatic effect on cancer cells in a hormone receptor-independent manner. After a brief account on the most important biological function and characteristics of the naturally occurring sex hormones in physiological and pathological conditions, structural modifications of estrane and androstane scaffolds are discussed in detail. The review covers literature publications (from 2002 to 2012) relating to the synthesis and antiproliferative activity of semisynthetic sex hormone-derived molecules containing simple or heterocyclic substituents. The compounds reviewed are divided into three main categories according to their sterane framework and the nature of substitution.

This article is part of a Special Issue entitled 'Synthesis of steroids'.

Contents

1. Introduction

Natural sex hormones, *i.e.* androgens, estrogens and progestogens, which are produced primarily by the gonads and in smaller amounts by the adrenal glands and other tissues, exert a wide range of biological effects on the body, affecting the growth and function of the reproductive organs and the development of secondary sexual characteristics. Androgens are also the original anabolic steroids and the precursors of all estrogens, which (together with progesterone) play a major role in the regulation of the menstrual cycle and pregnancy. Thanks to their nonpolar and hydrophobic sterane framework, steroid hormones can easily penetrate through the cell membranes and interact with their specific intracellular receptors, either in the cytosol or in the nucleus of the target cells. Through this slow genomic mechanism, the ligand–receptor complex acts as a transcription factor in the nucleus, augmenting or suppressing particular transcription genes by its action on DNA [1]. Recent studies suggest, however, that the effects of steroid hormones can also be mediated by fast nongenomic mechanisms through membrane-associated receptors and signaling cascades [2]. As a result of extensive structure–activity relationship (SAR) studies, a considerable amount of information is available concerning the structural features of the intracellular receptors, the pharmacophore moiety of the ligands and hormone–receptor binding [3–5]. Besides hydrophobic interactions, hydrogen-bonding in some regions of the steroid binding pocket is also involved in the

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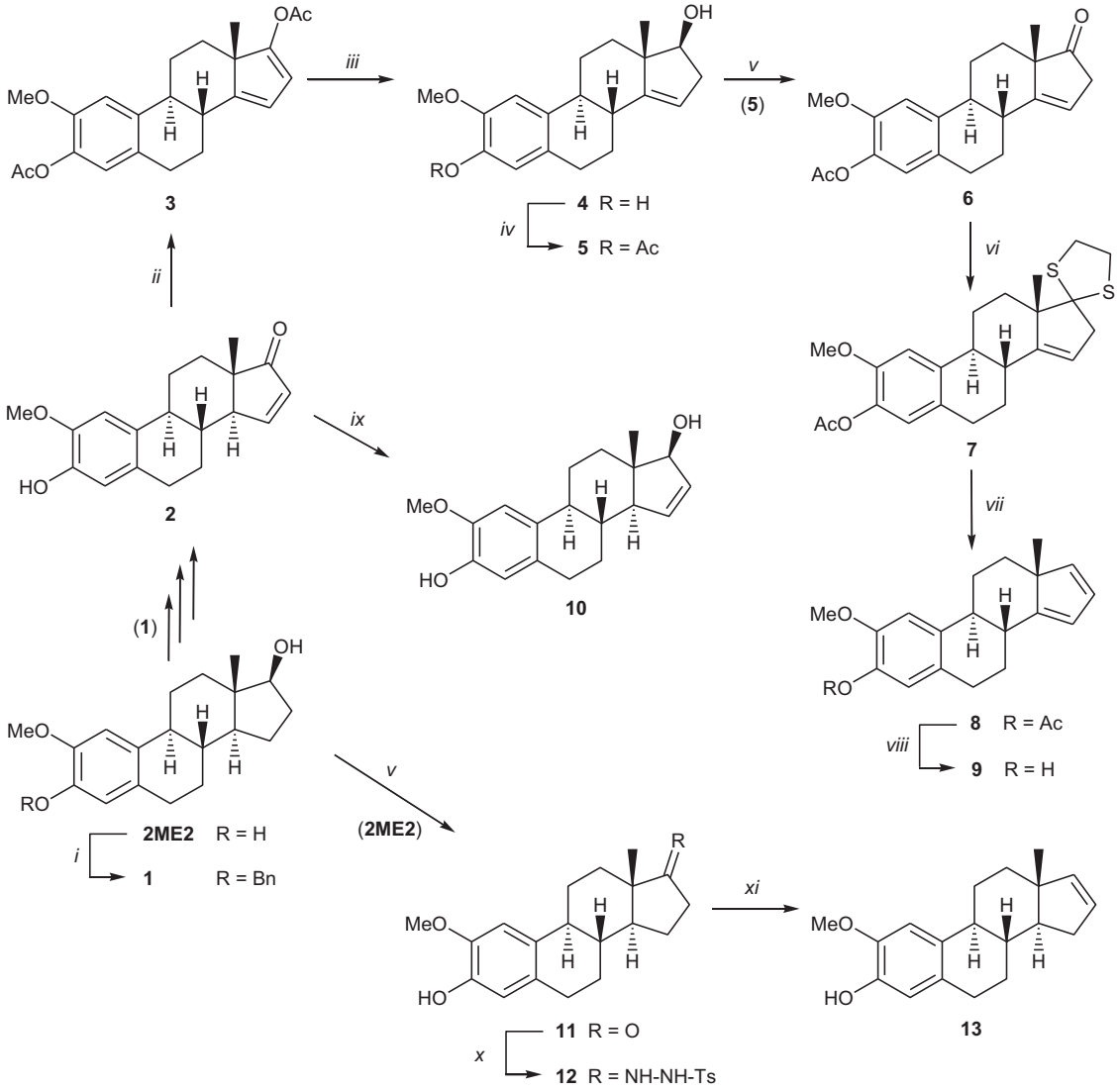

Scheme 1. Synthesis of D-ring-unsaturated analogs of **2ME2**. *Reagents and conditions*: (*i*) BnBr, K_2CO_3, DMF; (*ii*) isopropenyl acetate, Ac_2O, TsOH; (*iii*) $NaBH_4$, MeOH, THF, H_2O; (*iv*) Ac_2O, NaOH, *i*PrOH, H_2O; (*v*) Jones reagent, acetone; (*vi*) $HS(CH_2)_2SH$, $BF_3{\cdot}OEt_2$, AcOH; (*vii*) Raney Ni, acetone; (*viii*) K_2CO_3, MeOH, H_2O; (*ix*) $LiAlH_4$, Et_2O; (*x*) $TsNHNH_2$, MeOH; (*xi*) *n*BuLi, THF.

binding mechanism. All semisynthetic modifications involving the apolar sterane skeleton or the polar functional groups at C-3 and C-17 in the natural hormones may exert a significant influence on the binding affinity of the molecule.

In consequence of the important functions of steroid hormones, they and their modified analogs have been applied exogenously to humans in order to attain certain benefits in health or even to improve physical and growth performance. Estrogens and progestogens are administered as components of oral contraceptives and in hormone replacement therapy, while androgens are used to correct natural hormone deficiencies and to reduce "male menopause" symptoms such as the lack of sex drive, anxiety and depression. Furthermore, extensive effort has been devoted to the synthesis of potentially therapeutic derivatives providing enhanced anabolic potency with reduced androgenic effects, though with only modest success [4].

In addition to the modulation of normal development and maintenance of the reproductive tract, sex steroids play a crucial role in the malignant growth of these organs [6]. As steroid hormones are powerful drivers of the gene expression in hormone-dependent cancer cells, changes in the levels or activities of certain hormones can cause these cancers to cease growing, or even undergo cell death. Hormonal therapy is therefore one of the major possibilities for the medical treatment of cancer, involving manipulation of the endocrine system through the exogenous administration of steroid hormones, or drugs which inhibit the production or activity of the endogenous ligand. Thus, a number of modified steroid molecules have been described as potent inhibitors of specific enzymes involved in the biosynthesis of sex hormones, allowing their potential use in the medication of hormone-dependent diseases. Steroidal *exo*-heterocycles, for example, such as the therapeutically used abiraterone, can block androgen synthesis at an early stage by inhibiting 17α-hydroxylase/$C_{17,20}$-lyase ($P450_{17\alpha}$) and can therefore be effective in the treatment of prostate cancer [7–11]. Moreover, some drugs exert their biological activity as aromatase inhibitors by reducing estrogen production and can thus be applied in the treatment of estrogen receptor-positive (ER+) breast cancer [12,13]. Another approach in cancer therapy is the application of antagonists which bind to the receptor of a given hormone, thereby preventing its activation. However, the effectiveness of these drugs is limited by their partial agonist properties, which can cause undesirable side-effects [14]. Experimental

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