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New biaryl-chalcone derivatives of pregnenolone *via* Suzuki–Miyaura cross-coupling reaction. Synthesis, CYP17 hydroxylase inhibition activity, QSAR, and molecular docking study

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ABSTRACT

A new class of steroids is being synthesized for its ability to prevent intratumoral androgen production b inhibiting the activity of CYP17 hydroxylase enzyme. The scheme involved the synthesis of chalcon derivative of pregnenolone **5** which was further modified to the corresponding biaryl-chalcone pre nenolone analogs **16–25** using Suzuki–Miyaura cross-coupling reaction. The synthesized compoun were tested for activity using human CYP17α hydroxylase expressed in *Escherichia coli*. Compounds was the most active inhibitor in this series, with IC_{50} values of 0.61 μM and selectivity profile of 88. inhibition of hydroxylase enzyme. Molecular docking study of **21** was performed and showed the hydr gen bonds and hydrophobic interaction with the amino acid residues of the active site of CYP17.

1. Introduction

A number of steroids and their derivatives possess divers pharmacological activities as drugs for the treatment of a large number of diseases including cardiovascular [1], autoimmune diseases [2], brain tumors, breast cancer, prostate cancer, osteoarthritis, etc. [3]. Recently, a large number of steroidal derivatives containing five- or six-membered 17β-*exo*-heterocycles (preferably nitrogen containing), such as steroidal azoles [4,5] have been found to cause the inhibition of 17α-hydroxylase/C17-20-lyase (P45017α) which can block adrenal androgen synthesis at an early stage and may therefore be useful in the treatment of prostatic carcinoma [6–11]. In 1996, Njar et al. [12] reported the first steroidal inhibitors of CYP17 bearing a heterocyclic moiety bound to C17 by a nitrogen atom, among which the imidazolyl derivative **1** was found to be the most promising [12–15]. Later, in 2005, the same group reported the synthesis of galeterone **2** and its Δ^4-3-keto derivative [15–17], where **2** is currently undergoing phase I/II clinical trials for the treatment of chemotherapy naive CRPC [18,19]. However, patients suffering from castration-resistant prostate canc (CRPC) can clearly benefit from the newly approved drug a raterone acetate (Zytiga) **3** [20,21]. Hartmann and co-work [22–24] have reported the synthesis of several CYP17 inhibit as a new strategy for the treatment of prostate carcinoma. 2014, we have synthesized novel 17-pregnenolone-imine deriv tives as well as the 3-*O*-sulfonate and ester analogs at C designed as new CYP17A1 inhibitors [25]. Banday et al. ha reported recently some D-ring substituted steroidal chalcon [26] and isoxazolines and oxazolines [27] derivatives with rema able activity against breast cancer and potential antiproliferat agents against LNCaP, PC-3 and DU-145 cells, respectively.

CYP17 catalyzes two reactions, the 17R-hydroxylation of pre nenolone and progesterone to the corresponding 17R alcoh and the subsequent 17,20-lyase reaction cleaving the C_{17}—C bond. This yields the 17-keto androgens androstenedione a dehydroepiandrosterone, precursors of all other androgens, inclu ing testosterone.

In continuation of our program on the synthesis of D-ring steroidal inhibitors, we investigated the synthesis of biaryl-ch cone pregnenolone derivatives *via* Suzuki cross-coupling reacti together with the CYP17 hydroxylase enzyme inhibition activi QSAR and the molecular modeling study.

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