Synthesis and CYP17α hydroxylase inhibition activity of new 3α- and 3β-ester derivatives of pregnenolone and related ether analogues

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Abstract A new class of 3α-ester derivatives of pregnenolone, using Mitsunobu reaction conditions, is described. The scheme involved the conversion of pregnenolone (**4**) into 20-(2-hydroxyethyl)imino-pregn-5-en-3β-ol (**8**), followed by tritylation to give the analogue **9**. Treatment of **9** with various aryl carboxylic acids afforded the tritylated 3α-ester pregnenolone analogues **18–23**. Detritylation with AcOH furnished the 3α-substituted aryl ester derivatives **24–29**. Analogously, the 3β-ester analogues **31** and **32** were synthesized from pregnenolone (**4**) and its analogue **30**, using Steglich coupling method, by treatment with rhodamine B in the presence of DCC/DMAP. These derivatives were screened for their CYP17α hydroxylase inhibition activity expressed in *Escherichia coli*. Compound **27** was the most active inhibitor among both series, with IC_{50} value of 1.12 μM and selectivity profile of 88.56 % inhibition of CYP17α hydroxylase enzyme.

Keywords CYP17α hydroxylase · Mitsunobu reaction · Pregnenolone · Prostate cancer · Steglich coupling method

Introduction

Pregnenolone is a known neuroactive steroid (Marx *et al.*, 2011; Ritnner *et al.*, 2014; Marx *et al.*, 2014) and may represent a promising and mechanistically novel agent for cognitive and negative symptoms in schizophrenia and for the treatment of acute or chronic lesions of the nervous system, especially certain neurodegenerative diseases (Flood *et al.*, 1992). Pregnenolone and its sulfated derivative enhance learning and memory in animal models at concentrations that are physiologically relevant and known to be present in human brain (Akwa *et al.*, 2001; Darnaudéry *et al.*, 1998; Vallee *et al.*, 2001; Wong *et al.*, 2015). Further, pregnenolone sulfate (**1**) is known to have antidepressant, anxiogenic, and proconsultant effects (Reddy, 2010). Recently, Baulieu *et al.*, (2011), Bianchi and Baulieu (2012) reported that 3β-methoxypregnenolone (MAP4343) (**2**) is an innovative therapeutic approach for depressive disorders, which associated with neuronal abnoramalties in brain microtubule function, including changes in α-tubulin isoforms.

The presence of different functional groups located around the rigid tetracyclic core of pregnenolone and analogues leads to diversity in the biological actions as these serve as substrates for different targets. Abiraterone acetate (Zytiga) (**3**) (de Bono *et al.*, 2011; Bryce and Ryan, 2012), galeterone and its Δ^4-3-keto derivative (Handratta *et al.*, 2004, 2005; Brodie and Njar, 2006), both

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