

Phosphate and Thiophosphate Biphenyl Analogs as Steroid Sulfatase Inhibitors

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ABSTRACT In the present work, we report convenient methods for the synthesis and biological evaluation of phosphate and thiophosphate biphenyl derivatives exhibiting steroid sulfatase (STS) activity. The described synthesis is based on straightforward preparation of biphenyl-4-ol and 4'-hydroxybiphenyl-4-carboxylic acid ethyl ester modified with various phosphate or thiophosphate moieties. The inhibitory effects of these compounds were tested on STS isolated from human placenta and led to two compounds of interest, **5a** and **5d** with IC₅₀ values of 28.0 and 22.1 μM, respectively and that had interesting new binding modes in the STS active site. Drug Dev Res 76 : 94–104, 2015. © 2015 Wiley Periodicals, Inc.

Key words: steroid sulfatase; STS inhibitors; breast cancer; biphenyls

INTRODUCTION

Biphenyl, an aromatic hydrocarbon occurs naturally in coal tar, crude oil, and natural gas. It forms an incomplete combustion of mineral oil and coal. Historically, some biphenyls were widely used as intermediates in chemical syntheses that resulted in a wide range of pesticides including the polychlorinated biphenyls (PCBs). Emerging trends in synthetic chemistry have led a number of substituted biphenyl derivatives prepared by various coupling reactions that therapeutic potential [Jain et al., 2013]. These derivatives have angiotensin receptor (Losartan, Telmisartan) [Zhu et al., 2004], antihypertensive (biphenyl carboxylic benzimidazole derivatives) [Kumar et al., 2006], diuretic (N-((substituted)1,3-benzothiazol-2-yl)-1,1-biphenyl-4-carboxamides) [Yar and Ansari, 2009], anti-inflammatory (biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amides) [Deep

et al., 2010], antipsychotic and anxiolytic (biphenylindanone A) [Ruggero et al., 2006] and antimicrobial (biphenyl hydrazide-hydrazone) [Deep et al., 2010] activities. Of particular interest is the use of biphenyl scaffolds in designing new steroid sulfatase (STS) inhibitors based on phosphate and thiophosphate derivatives that may be potential new therapeutics for the treatment of estrogen- and androgen-dependent

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