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Research Article

Steroid Sulfatase Inhibitors Based on Phosphate and Thiophosphate Flavone Analogs

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ABSTRACT A series of phosphate and thiophosphate flavone derivatives were synthesized and biologically evaluated in vitro for inhibition of steroid sulfatase (STS) activity. The described synthesis includes the straightforward preparation of 7-hydroxy-2-phenyl-4*H*-chromen-4-one 3a, 2-(4-fluorophenyl)-7-hydroxy-4*H*-chromen-4-one 3b, 7-hydroxy-2-(4-(trifluoromethyl)phenyl)-4*H*-chromen-4-one 3c, 7-hydroxy-2-(*p*-tolyl)-4*H*-chromen-4-one 3d modified with different phosphate or thiophosphate moieties. The inhibitory properties of the synthesized compounds were tested against human placenta STS. Some of the novel STS inhibitors had good activities against STS. In particular, the bis-(4-oxo-2-(*p*-tolyl)-4*H*-chromen-7-yl) hydrogenthiophosphate, 6i had the most potent inhibitory effect with an IC_{50} value of 3.25 μM as compared to an IC_{50} value of 8.50 μM for the 2-(4-trifluoromethylphenyl)-chromen-4-one-7-*O*-sulfamate used as a reference. Drug Dev Res 76 : 450–462, 2015.

Key words: steroid sulfatase; molecular modeling; STS inhibitors; breast cancer; flavones

INTRODUCTION

Flavones are a class of flavonoids based on the backbone of 2-phenylchromen-4-one. They are a large family of compounds that are present in fruit, vegetables, wine, tea, and cocoa mostly as glycosides and polymers [Harborne and Williams, 2000]. They accumulated in plant tissues and can participate in the photosynthetic process [Mukohata et al., 1978]. Flavonoids can bind to biological polymers, chelate transition metal ions like Fe^{2+}, Cu^{2+}, Zn^{2+}, and Mg^{2+}, catalyze electron transport and scavenge free radicals [Brandi et al., 1992]. Increased consumption of flavonoids is protective for circulatory system diseases [Rimm et al., 1996; Woodman and Chan, 2004] and diabetes [Jachak, 2002]. Flavonoids also have anti-inflammatory [Yao et al., 2004], antiallergic [Nakajima et al., 2001], anticancer [Lamson and Brignall, 1999; Middleton et al., 2000; Yang et al., 2001], antiaggregatory [Violi et al., 2002] and anti-atherosclerotic [Steffen et al., 2005] properties. The broad spectrum of activity of flavonoids make them attractive as potential therapeutics.

Natural flavonoid derivatives like quercetin, kaempferol or naringenin exhibit steroid sulfatase (STS) inhibitory activity [Huang et al., 1997] and enzyme responsible for the hydrolysis of steroid sulfates into their active forms that plays a crucial role in the

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