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Synthesis and biological evaluation of thiophosphate tricyclic coumarin derivatives as steroid sulfatase inhibitors

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Steroid sulfatase (STS) enzyme inhibition is an important approach to the management of hormone-dependent breast cancer. In this paper, we report convenient methods for the synthesis and biological evaluation of thiophosphate tricyclic coumarin analogs exhibiting STS activity. The described methods are based on the straightforward preparation of 7-hydroxy-2,3-dihydro-1H-cyclopenta[c]chromen-2-one, 3-hydroxy-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one, and 3-hydroxy-8,9,10,11-tetrahydro-7H-cyclohepta[c]chromen-6-one and their further modification by the introduction of various thiophosphate moieties. The inhibition properties of the synthesized compounds were tested toward STS isolated from human placenta. Most of the new STS inhibitors possessed good to moderate activity toward STS. During the course of our investigation, the largest inhibitory effects in the STS enzyme assays were observed for the two compounds **3f** and **4r**, with IC_{50} values of 13.3 and 30.3 μM, respectively (the IC_{50} value of 1 μM for the 665-COUMATE was used as a reference). The structure–activity relationships of the synthesized coumarin derivatives toward STS enzymes are discussed.

Keywords: breast cancer; coumarin; thiophosphate; steroid sulfatase inhibitors

1. Introduction

Coumarins are an important class of naturally occurring compounds (found in a variety of plant sources) that are widely used in the agrochemical, cosmetic, or pharmaceutical industries. They occur as secondary metabolites in the seeds, roots, and leaves of many plant species or in the tonka bean. Their function is unclear, but it is suspected that they play an important role in plant growth regulation, fungistasis, or bacteriostasis [1]. Substituted coumarin derivatives have been reported to exhibit a variety of biological activities. They have been recognized to possess antioxidant, antiallergic, anti-inflammatory, hepatoprotective, antithrombotic, antiviral, or anticancer activities [2]. Of particular interest in the treatment of breast cancer, some coumarins and their derivatives have exhibited sulfatase and aromatase inhibition as well as selective estrogen receptor modulators activities [3,4]. Among the female population of the industrialized countries, breast cancer is one of the most frequently diagnosed diseases. Estimates for 2014 (according to National Cancer Institute data) showed that more than 230,000 new cases of breast cancer have been diagnosed and more than 40,000 deaths from this disease in the USA have been reported. The World Health Organization lists estrogens as one of the most important factors favoring the

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