Research paper

Sulfonyl-containing phenyl-pyrrolyl pentane analogues: Novel non-secosteroidal vitamin D receptor modulators with favorable physicochemical properties, pharmacokinetic properties and anti-tumor activity

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Abstract

Modulating the vitamin D receptor (VDR) is an effective way to treat cancer. We previously reported a potent non-secosteroideal VDR modulator (sw-22) with modest anti-tumor activity, which could be due to its undesirable physicochemical and pharmacokinetic properties. In this study, we investigated the structure-activity and structure-property relationships around the 2'-hydroxyl group of sw-22 to improve the physicochemical properties, pharmacokinetic properties and anti-tumor activity. Compounds 15a and 27b, the potent non-secosteroideal VDR modulators, were identified as the most effective molecules in inhibiting the proliferation of three cancer cell lines, particularly breast cancer cells, with a low IC50 via the disruption of cell cycle and induction of apoptosis by stimulating the expression of p21, p27 and Bax. Further investigation revealed that 15a and 27b possessed favorable rat microsomal metabolic stability (2.22 and 2.3 times, respectively, more stable than sw-22), solubility (41.5 and 50.2 times, respectively, more soluble than sw-22) and in vivo pharmacokinetic properties. In addition, 15a and 27b showed excellent in vivo anti-tumor activity without cause hypercalcemia, which is the main side effect of marketed VDR modulators. In summary, the favorable physicochemical properties, pharmacokinetic properties and anti-tumor activity of 15a and 27b highlight their potential therapeutic applications in cancer treatment.

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1. Introduction

Vitamin D receptor (VDR), a member of the steroid–thyroid–retinoid receptor superfamily of ligand-activated transcription factors, which involve regulating calcium homeostasis and bone metabolism [1–3]. Recently, accumulating evidence suggests that VDR was involved in antineoplastic actions in various malignancies, such as breast, pancreatic and prostate cancer [4–8]. After being combined with its modulator, VDR dimerizes with the retinol X receptor (ROX) and binds to the vitamin D response elements (VDREs) to alter the rate of target gene transcription. With recruitment of co-modulators, the activated VDR can decrease tumor growth mainly by suppressing proliferation or promoting apoptosis of cancer cells [9,10]. In order to enable VDR play a more effective antineoplastic activity, large numbers of VDR modulators had been applied to anti-tumor researches [11–14]. The VDR modulators can be classified into "secosteroid" and "non-secosteroid" based on their structure specificity. Up to now, more than 3000 secosteroidal VDR modulators (SVDRMs) have been developed, such as calcipotriol (1), tacalcitol (2) and natural VDR modulator 1,25(OH)2D3 (3) [15]. However, secosteroidal-based chemical synthesis has proven to be difficult and costly [16]. What’s more, in clinical cancer treatment, the required doses of these SVDRMs induced serious hypercalcemia, the main side effect of VDR modulators which could induce abdominal pain, kidney stones and cardiac arrest [17]. In addition, clinical studies showed that 20 to 30 percent of cancer patients suffer from hypercalcemia at the...