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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 for cancer. We previously reported a potent non-secosteroidal 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 **19a** and **27b**, the potent non-secosteroidal 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 IC_{50} via the distribution of cell cycle and induction of apoptosis by stimulating the expression of p21, p27 and Bax. Further investigation revealed that **19a** and **27b** possessed favorable rat microsomal metabolic stability (2.22 and 2.3 times, respectively, more stable than **sw-22**), solubility (43.9 and 50.2 times, respectively, more soluble than **sw-22**) and *in vivo* pharmacokinetic properties. In addition, **19a** 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 **19a** and **27b** highlight their potential therapeutic applications in cancer treatment.

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 retinoid X receptor (RXR) 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-secosteroidal” 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 $1,25(OH)_2D_3$ (**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

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