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## Two families of steroid derivatives to treat hormone-dependent and hormone-independent cancers

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PBRM and RM-133 are two steroid derivatives recently developed in our research group as anticancer agents. PBRM, or 3-{[(16β, 17β)-3-(2-bromoethyl)-17-hydroxyestra-1(10,2,4-trien-16-yl]methyl} benzamide, was synthesized in solution from estrone (E1) using a sequence of eight steps in an overall yield of 11%. PBRM inactivated the transformation of E1 into estradiol (E2), the most potent estrogen, by the action of steroidogenic enzyme 17β-hydroxysteroid dehydrogenase (17β-HSD) type 1, which is thought to play a pivotal role in the progression of estrogen-sensitive breast cancer. In fact, PBRM inhibited the 17β-HSD1 in T-47D cells ($IC_{50}$ = 83 nM), the pure enzyme ($K_i$ = 381 nM, $k_{inact}$ = 0.084 $min^{-1}$) and did not inhibit other key enzymes such as 17β-HSD2, 17β-HSD7, 17β-HSD12, CYP3A4 and CYP-2D6, suggesting a good selective action. Interestingly, in the estrogen-sensitive breast cancer cell line T-47D and in ovariectomized mice (uterine and vagina weight), PBRM showed no estrogenic activity. When tested on the T-47D xenograft tumor model in female ovariectomized nude mice, PBRM (250 µg/mouse/day) fully blocked (100%) the tumor growth induced with exogenous E1 (0.1 µg/mouse/day). RM-133, or {4-[(2β,3α,5α,17α)-3,17-dihydroxypregn-20-yn-2-yl]piperazin-1-yl}[(2S)-1-(quinolin-2-ylcarbonyl)pyrrolidin-2-yl] methanone, was synthesized in solution from androsterone using a sequence of six steps in an overall yield of 14%. RM-133 is a promising pro-apoptotic agent showing antiproliferative activity ($IC_{50}$ ranging from 0.1 to 4.5 µM) on various human cancer cell lines (HL-60, PANC-1, LNCaP, LAPC-4, MCF-7, T-47Dand OVCAR-3). For *in vivo* assessment on animal models (xenografts), nude mice were inoculated in both flanks with human cancer cells (HL-60, MCF-7, PANC-1 or OVCAR-3) and tumors obtained after two-three weeks were treated or not with RM-133 using a mixture of ethanol (EtOH) and propylene glycol (PG) or dimethyl sulfoxide (DMSO) and 0.4% aqueous methylcellulose (MC) as vehicle for subcutaneous (*sc*) injection. The tumor size was measured twice weekly and the result expressed as percentage of the initial tumor. In a first series of experiments, RM-133 reduced the tumor growth of all four tested xenografts: HL-60 cells (leukemia) by 58% (60 mg/kg/day, *sc*, EtOH:PG/8:92), MCF-7 cells (breast cancer) by 60% (60 mg/kg/day, *sc*, EtOH:PG/8:92), PANC-1 cells (pancreas cancer) by 63% (240 mg/kg/2 days, sc, EtOH:MC/8:92), OVCAR-3 cells (ovary cancer) by 50% (60 mg/kg/day, sc, EtOH:MC/8:92). When tested at higher dose on the OVCAR-3 xenograft tumor model, RM-133 (2 x 240 mg/kg/2 days, sc, EtOH:MC/8:92) fully blocked (100%) the tumor growth. RM-133 was also well tolerated by mice and no weight loss was recorded. These interesting results, especially those obtained for two refractory cancers (pancreas and ovary), encourage us to pursue the optimization and mechanistic studies. In summary, both PBRM and RM-133 steroid derivatives were synthesized and generated promising *in vivo* results against a series of cancer tumor models.

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