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A new family of aminosteroid derivatives to treat refractory cancers

The development of cytotoxic agents that selectively promote the apoptosis of cancer cell while limiting the death of normal cells would represent a significant breakthrough in cancer therapy. The aminosteroid derivative RM-133 was recently developed in our research group as anticancer agents. 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 from androsterone using a sequence of six steps in an overall yield of 14%. It is a promising selective pro-apoptotic agent showing antiproliferative activity (IC50 ranging from 0.1 to 4.5 µM) on various human cancer cell lines (HL-60, PANC-1, LNCaP, LAPC-4, MCF-7, T-47D and 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 60-84% (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, steroid derivatives were synthesized and generated promising *in vivo* results against a series of cancer tumor models.

Biography

Professor Donald Poirier received his training in chemistry (B.Sc., 1977-1980) and organic chemistry (PhD, 1980-1985) at Université Laval (Québec City, Canada). He subsequently specialized in medicinal chemistry (Post-doctoral training at CHUL - Research Center, 1986-1990) and more recently in solid phase synthesis of small molecules of therapeutic interest. He is especially interested in the development of inhibitors of steroidogenic enzymes (17b-hydroxysteroid dehydrogenases (types 1, 2, 3, 7, 10 and 12) and steroid sulfatase) and antitumor agents for the treatment of different cancers (breast, prostate, ovary, leukemia). In addition to the synthesis of small molecules by classical chemistry, he succeeded by developing solid-phase synthesis of C18-steroid (estrane), C19-steroid (androstane) and C21-steroid (pregnane) derivatives that enabled the generation of model libraries of targeted therapeutic compounds. Thus, he developed a new sulfamate linker for solid-phase synthesis that produces two classes (phenol and sulfamate) of relevant steroidal or nonsteroidal compounds according to the conditions of cleavage. He also developed a diethylsilylacetylene linker to generate libraries of acetylenic tertiary alcohols, which are well known to be biologically more stable than their corresponding secondary alcohols.

He is also interested to additional aspects of organic chemistry (synthesis, new methodologies, NMR analysis, etc.) and medicinal chemistry (structure-activity relationships, molecular modelisation, biological assays, etc.). He is professor at the Department of Molecular Medicine (Faculty of Medicine, Université Laval, Québec City, Canada) since July 1991, researcher at CHU de Québec - Research Center (Québec City) since 1991 and director of the Organic Synthesis Service (CHU de Québec) since 2008. Professor Poirier is member of professional organizations such as ACS, CIC, OCQ, ACFAS and CRCQ. He published 202 papers and 8 patents. He was also author or co-authors of 414 presentations (invited speaker, oral and poster presentations).

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