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A new family of steroidal 17 beta-HSD type 1 inhibitors to treat hormone-dependent breast cancers

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PBRM is steroid derivative 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 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 type 1 (17β-HSD 1), which is thought to play a pivotal role in the progression of estrogen-dependent breast cancer. In fact, PBRM inhibited the 17β-HSD1 in T-47D cells (IC_{50} = 83 nM), in 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 selectivity of action. In the presence of microsomes, PBRM was gradually transformed into an oxidized form of PBRM (100% after 12h). This PBRM metabolite has proven almost as active as PBRM for the transformation of E1 to E2 by 17β-HSD1 (49 and 87% vs. 87 and 95% of inhibition at 0.1 and 1 µM, respectively). When injected subcutaneously (*sc*) in mouse, PBRM is the major product (660 ng/mL at 5h) found in blood and oxidized PBRM is present in small quantities (8.5 ng/mL at 5h). Most tissues reach their maximum level of PBRM 6h after *sc* injection. PBRM was observed mostly in digestive tract over the first 6h, but did not accumulate in any other organ. It was recuperated in feces (93%) and in urine (7%), with 68% of the elimination occurring in the first 24h. 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). In summary, PBRM represent a new generation of 17β-HSD1 inhibitors that generated promising *in vitro* and *in vivo* results against breast cancer cells and tumor model.

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-author of 414 presentations (invited speaker, oral and poster presentations).

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