DEVELOPMENT OF A MYLTI-GRAM SYNTHESIS OF THE BRADYKININ RECEPTOR 2 AGONIST FR-190997 AND ANALOGUES THEREOF

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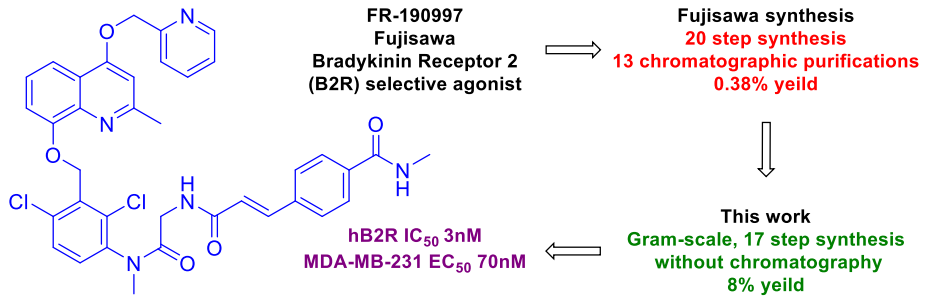
Using Fujisawa's B2R agonist FR-190997, we recently demonstrated for the first time that agonism at the bradykinin receptor type 2 (B2R) produces substantial antiproliferative effects[1]. FR-190997 elicited an EC50 of 80 nM in the triple-negative breast cancer (TNBC) cell line MDA-MB-231, a much superior performance to that exhibited by most approved breast cancer drugs. Consequently, we initiated a program aiming primarily at synthesising adequate quantities of FR-190997 to support further in vitro and in vivo studies towards its repurposing for various cancers and, in parallel, enable the generation of novel FR-190997 analogues for an SAR study. Prerequisite for this endeavour was to address the synthetic challenges associated with the FR-190997 scaffold, which the Fujisawa chemists had constructed in 20 steps, 13 of which required chromatographic purification. We succeeded in developing a 17-step synthesis amenable to late-stage diversification that eliminated all chromatography and enabled access to multigram quantities of FR-190997 and novel derivatives thereof, supporting further anticancer research based on B2R agonists.



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