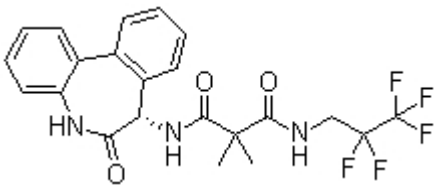
Product Introduction

RO4929097

RO4929097 is a **γ secretase** inhibitor with **IC50** of 4 nM, inhibiting cellular processing of Aβ40 and Notch with **EC50** of 14 nM and 5 nM, respectively. Phase 2.

Technical Data:

Molecular Weight (MW):	469.4	
Formula:	C22H20F5N3O3	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 94 mg/mL	
	Water <1 mg/mL	
	Ethanol 16 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	847925-91-1	

Biological Activity

RO4929097 decreases the amount of Aβ peptides secreted into the culture medium in HEK293 cells with EC50 of 14 nM. RO4929097 strongly inhibits Notch processing with EC50 of 5 nM in the Notch cell-based reporter assay. The potency of RO4929097 in cell-free and cellular assays is in the low nanomolar range with >100-fold selectivity observed with respect to 75 other proteins of various types including receptors, ion channels, and enzymes (CEREP panel). After 5 days of treatment, RO4929097 reduces the production of ICN in the human NSCLC A549 cells inducing a flattened and less transformed tumor cell phenotype in

tissue culture. [1] RO4929097 blocks Notch processing in human non-small cell lung carcinoma cells and decreases expression of the Notch transcriptional target gene Hes1. Treatment with RO4929097 reveals a two- to threefold decrease in the expression of direct Notch target genes, Hes1, Hey1, and Heyl in SUM149 and a 3.5- to eightfold decrease in expression in SUM190 cells. RO4929097 modestly inhibits the growth of SUM149 cells in a dose-dependent manner. At a concentration of 1 μM of RO4929097, growth inhibition is 20 % for SUM149 and 10 % for SUM190 cells, relative to vehicle-treated controls. RO4929097 decreases the production of inflammatory cytokines by T-cells. Furthermore, with RO4929097 treatment, there is a shift in favor of TH2 over TH1 cytokines. In addition, T-cell activation induced IL-6 production would be increased with RO4929097. [2] Upon RO4929097 treatment, the selected melanoma cell lines reveals downregulation of NOTCH downstream effector HES1. A decrease in the amount of melanospheres formed upon RO4929097 treatment in primary melanoma cell lines is detected. [3]

Oral injection of 3 to 60 mg/kg RO4929097 once daily or twice daily to nude mice bearing A549 NSCLC xenografts for either 7, 14, or 21 days of a 21-day schedule results in significant tumor growth inhibition compared with vehicle-treated animals. The tumor growth inhibition values ranges from 66% to 91%. When mice are treated with 60 mg/kg RO4929097 twice daily with the 7+/14- schedule, treatment initially arouses regression of established A549 tumors. At the end of the 21-day cycle (day 47), tumor growth prevention is still 91% compared with vehicle control mice. Inhibition of tumor growth remains prolonged and sustained up to 34 days post-treatment (day 67). On day 67, these mice are retreated with the same dose of RO4929097 for a second cycle (7 days) until day 74. Importantly, the antitumor effects are sustained after dosing is completed. [1] RO4929097 leads to reduced expression of genes associated with angiogenesis in A549 xenograft model. In contrast, the RO4929097-resistant H460a xenograft displays little change in expression of these genes, underscoring the in vivo anti-angiogenesis mechanism of action of RO4929097.[2] For IL6 and IL8 overexpressing tumors, RO4929097 no longer impacts angiogenesis or the infiltration of tumor associated fibroblasts. [4]

References

[1] Luistro L, et al. Cancer Res. 2009, 69(19), 7672-7680.
[2] Debeb BG, et al. Breast Cancer Res Treat. 2012.
[3] Huynh C, et al. PLoS One. 2011, 6(9), e25264.
[4] He W, et al. Mol Oncol. 2011, 5(3), 292-301.
[5] Li YM, et al. Proc Natl Acad Sci U S A. 2000, 97(11), 6138-6143.

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