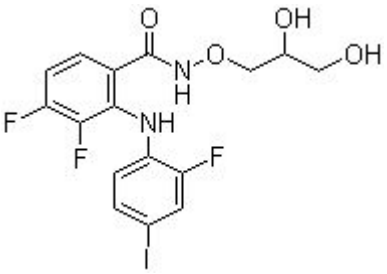
Product Introduction

PD0325901

PD0325901 (PD325901) is selective and non ATP-competitive **MEK** inhibitor with **IC50** of 0.33 nM, roughly 500-fold more potent than CI-1040 on phosphorylation of ERK1 and ERK2. Phase 1/2.

Technical Data:

Molecular Weight (MW):	482.19	
Formula:	C16H14F3IN2O4	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 96 mg/mL	
	Water <1 mg/mL	
	Ethanol 40 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	391210-10-9	

Biological Activity

PF0325901 shows higher permeability than CI-1040, another MEK inhibitor. PD0325901 should be able to achieve higher systemic exposures than CI-1040. [1] PD0325901 is exquisitely specific and highly potent against purified MEK, revealing a Kiapp of 1 nM against activated MEK1 and MEK2. [2] PD0325901 is roughly 500-fold more potent than CI-1040 with respect to its cellular effects on phosphorylation of ERK1 and ERK2, displaying subnanomolar activity. [2] PD0325901 prevents the growth of melanoma cell lines. PD0325901 inhibits the growth of TPC-1 cells and K2 cells with GI50 of 11 nM and 6.3 nM, respectively. [3]

PD0325901 significantly prevents the the growth of PTC cells harboring a BRAF mutation at very low concentration (10 nM) and only moderately increases the growth of the PTC cells carrying the RET/PTC1 rearrangement at the same concentration. PD0325901 effectively inhibits the phosphorylation of ERK1/2 in multiple PTC cell lines. [3]

The improved potency of PD0325901 relative to CI-1040 is evident. A single oral dose of PD0325901 (25 mg/kg) inhibits phosphorylation of ERK by more than 50% at 24 hours post-dosing. In contrast, CI-1040 at a much higher dose (150 mg/kg) only inhibit pERK levels for roughly 8 hours, returning to control levels by 24 hours after treatment. [2] Therefore, the dose required to produce a 70% incidence of complete tumor responses (C26 model) is 25 mg/kg/day versus 900 mg/kg/day for PD0325901 and CI-1040, respectively. Anticancer activity of PD 0325901 has been demonstrated for a broad spectrum of human tumor xenografts. [2] After 1 week of oral administration of PD0325901 (20–25 mg/kg/day) in mice, no tumor growth is detected in mice inoculated with PTC cells bearing a BRAF mutation. [3] For PTC with the RET/PTC1 rearrangement, the average tumor volume of the orthotopic tumor is decreased by 58% as compared with controls. In conclusion, PTC cells carrying a BRAF mutation are more sensitive to PD0325901 than are PTC cells carrying the RET/PTC1 rearrangement. [3]

References

[1] Barrett SD, et al. Bioorg Med Chem Lett, 2008, 18(24), 6501-6504.
[2] Judith SS, et al. Proc Amer Assoc Cancer Res.2004,45, Abstract #4003
[3] Henderson YC, et al. Mol Cancer Ther, 2010, 9(7), 1968-1976.
[4] Paterson A, et al. Blood, 2012, 119(7), 1726-1736.
[5] Ricciardi MR, et al. J Mol Med (Berl), 2012, 90(10), 1133-1144.
[6] Pratilas CA, et al. Cancer Res, 2008, 68(22), 9375-9383.
[7] Legrier ME, et al. Cancer Res, 2007, 67(23), 11300-11308.
[8] Barrett SD, et al. Bioorg Med Chem Lett, 2008, 18(24), 6501-6504.

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