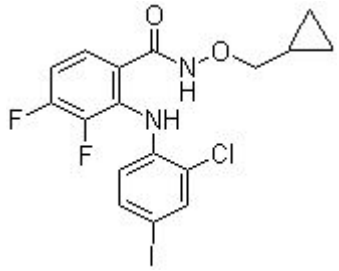
Product Introduction

PD184352 (CI-1040)

CI-1040 (PD 184352) is an ATP non-competitive MEK1/2 inhibitor with IC50 of 17 nM, 100-fold more selective for MEK1/2 than MEK5. Phase 2.

Technical Data:

Molecular Weight (MW):	478.67	
Formula:	$C_{17}H_{14}ClF_2IN_2O_2$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 96 mg/mL	
	Water <1 mg/mL	
	Ethanol 14 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃ Powder	
	6 months-80℃ in DMSO	
CAS No.:	212631-79-3	

Biological Activity

CI-1040 treatment produces a reduction of pMAPK levels in multiple tumor cells including Colon 26, BX-PC3 pancreatic, A431 cervical, HT-29 colon, ZR-25-1 breast and SKOV-3 ovarian carcinomas. CI-1040 treatment doesn't inhibit the phosphorylation of Jun kinase, p38 kinase or Akt, indicating CI-1040 specifically targets MEK. Inhibition of MAPK activation by CI-1040 prevents cell cycle progression and induces a G1 block. [1] The IC50 for inhibition of MEK1 by CI-1040 is 0.3 μM, 15-fold higher than the concentration required to inhibit the EGF-induced activation of ERK2 in Swiss 3T3 cells. These results indicate CI-1040 exerts its effects on cells by suppressing the activation of MKK1, and not by blocking its activity. 2 nM PD184352 inhibits the activation of MKK1 in Swiss 3T3 cells by 50%, while over 100-fold concentration of CI-1040 inhibits MEK1 in vitro. PD184352 also inhibits the Raf-catalysed phosphorylation

of MEK1 without any effect on the Raf-catalysed phosphorylation of myelin basic protein. [2] CI-1040 inhibits 86% of papillary thyroid carcinoma (PTC) cell growth with the RET/PTC1 rearrangement at 10μM compared with cells treated with DMSO only. CI-1040 shows potent inhibition to PTC cells (BRAF mutation) with GI50 of 52 nM, but low activity to RET/PTC1 rearrangement type with GI50 of 1.1 μM. [3]A recent research indicates CI-1040 increases the apoptotic effect of BMS-214662 in a CML blast crisis cell line, K562, and in primary chronic phase CD34+ CML cells. [4]

Oral dosing of CI-1040 impairs the growth of colon tumor xenografts of mouse and human with a wide dose range of 48-200 mg/kg per dose, but not of P388 leukemia. [1] CI-1040 inhibits the tumor xenografts from PTC cells carrying a BRAF mutation with 31.3% reduction, carrying the RET/PTC1 rearrangement with 47.5% reduction than in untreated (vehicle) mice after 3 weeks of oral administration (300 mg/kg/d). No toxic effects are observed in any mice when they are treated with CI-1040. [2] Transient exposure of mammary tumors to CI-1040 and UCN-01 causes tumor cell death in vivo and prolonged suppression of tumor regrowth. Combined treatment with CI-1040 (25 mg/kg) and UCN-01 (0.1-0.2 mg/kg) significantly reduces MDA-MB-231, and largely abolishs MCF7 tumor growth in implanted athymic mice, while either single treatment has no significant activity. The drug combination leads to profound tumor cell death which correlates with a reduction in the phosphorylation of ERK1/2 and the immuno-reactivity of Ki67 and of CD31. [5]

First MEK inhibitor to begin clinical development.

References

[1] Sebolt-Leopold JS, et al. Nat Med, 1999, 5(7), 810-816.

[2] Davies SP, et al. Biochem J, 2000, 135(1), 95-105.

[3] Henderson YC, et al. Arch Otolaryngol Head Neck Surg, 2009, 135(4), 347-354

[4] Pellicano F, et al. Leukemia, 2011, 25(7), 1159-1167.

[5] Hawkins W, et al. Cancer Biol Ther, 2005, 4(11), 1275-1284.

[6] Legrier ME, et al, Cancer Res, 2007, 67(23), 11300-11308.

[7] Ou DL, et al, Clin Cancer Res, 2009, 15(18), 5820-5828.

[8] Jimeno A, et al, Mol Cancer Ther, 2007, 6(3), 1079-1088.

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