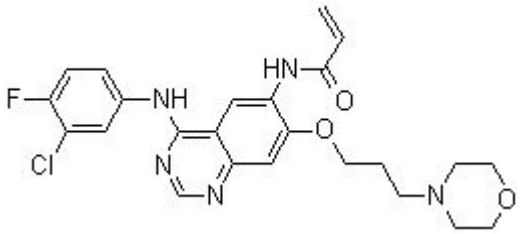
Product Introduction

Canertinib (CI-1033)

Canertinib (CI-1033) is a pan-**ErbB** inhibitor for **EGFR** and **ErbB2** with **IC50** of 1.5 nM and 9.0 nM, no activity to PDGFR, FGFR, InsR, PKC, or CDK1/2/4. Phase 3.

Technical Data:

Molecular Weight (MW):	485.94	
Formula:	$C_{24}H_{25}ClFN_5O_3$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 2 mg/mL	
	Water <1mg/mL	
	Ethanol 9 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	267243-28-7	

Biological Activity

CI-1033 shows excellent potency for irreversible inhibition of erbB2 autophosphorylation in MDA-MB 453 cells. CI-1033 also shows high permeability in Caco-2 cells and inhibits secretory transport of vinblastine, which indicates that CI-1033 is a likely inhibitor of the P-gp. [1] CI-1033 alone, significantly suppresses constitutively activated Akt and MAP kinase. In combination with gemcitabine, CI-1033 inhibits Akt and prevents increased levels of MAPK phosphorylation. CI-1033 stimulates p27 expression and p38 phosphorylation in MDA-MB-453 cells. [2] CI-1033 is highly specific to the erbB receptor family and not

sensitive to PGFR, FGFR or IR even at 50 μM. CI-1033 shows high levels of inhibition in A431 cells expressing EGFR with IC50 of 7.4 nM. CI-1033 suppresses heregulin-stimulated tyrosine phosphorylation of erbB2, erbB3 and erbB4 with IC50 of 5, 14 and 10 nM, respectively. CI-1033 also inhibits expression of $pp62^{c\text{-}fos}$ in response to heregulin. [3] CI-1033 is predicted to modify Cys773 covalently within the ATP binding site of the HER2 kinase and enhances destruction of both mature and immature ErbB-2 molecules. [4] CI-1033 induces a significant decrease in measurable phosphorylation of tyrosine residues 845 and 1068 of EGFR, which are responsible for Src and Ras/MAPK signaling respectively. The corresponding residues of Her-2, tyrosine residues 877 and 1248 are dephosphorylated significantly by CI-1033 at a concentration of 3 μM or higher. CI could block EGFR internalization and increase the rate of apoptosis in primary osteosarcoma cells in a titratable fashion. [5] In addition, CI-1033 inhibits the proliferation of TT, TE2, TE6 and TE10 cells significantly at 0.1 nM. [6]CI-1033 shows impressive activity against A431 xenografts in nude mice at 5 mg/kg of body weight. [1] CI-1033 (20 to 80 mg/kg/d) achieves a high degree of tumor regressions in H125 xenograft models. [3] Oral administration of CI-1033 causes a marked inhibition of growth in TT, TE6 and TE10 xenografts in nude mice, without animal death and <10% weight loss. [6]

First kinase inhibitor to show irreversible activity and to have entered clinical trials (serving as a template for further development).

References

[1] Smaill JB et al. J Med Chem. 2000; 43(7): 1380-1397.
[2] Nelson JM et al. J Biol Chem. 2001; 276(18): 14842-14827.
[3] Slichenmyer WJ et al. Semin Oncol. 2001; 28(5 Suppl 16): 80-85.
[4] Citri A et al. EMBO J. 2002; 21(10): 2407-2417.
[5] Hughes DP et al. Pediatr Blood Cancer. 2006; 46(5): 614-623.
[6] Ako E et al. Oncol Rep. 2007; 17(4): 887-893.
[7] Erlichman C, et al. Cancer Res, 2001, 61(2), 739-748.