IIIM-985

[Target: Cdk-4]

It is a non-toxic and non-planar analog of fascaplysin. It does not possess DNA intercalation liability (no EtBr displacement up to 100 μM), which was associated with the parent natural product (EtBr displacement at 1 μM). It is a selective inhibitor of Cdk4/D1 (83-fold selectivity versus Cdk2/A) and it also inhibits tubulin polymerization. It displayed promising in-vitro cytotoxicity in lung cancer cell line A549 ((IC_{50} = 0.92 μM), Calu-1 (2.8 μM), NCI-H460 (0.6 μM), NCI-H1299 (0.9 μM), NCI-H358 (0.68 μM). It does not possess efflux pump liability (caco-2 permeability, efflux ratio = 1.1). It does not inhibit other kinases: EGFR, GSK-3β, MAPK1, MEK1, PDGFR, Plk3, PKA, PKC-α, IGF-1R (no inhibition up to 10 μM). MTD is 1000 mg/kg (Swiss albino rats). Excellent in-vivo efficacy in NCI-H460 xenograft model: 100 mg/kg i/p = 85% TGI (mortality = 0/7) and HCT-116 xenograft model: 100 mg/kg i/p = 80% TGI (mortality = 0/7). Presently, the new formulation is being developed for this lead to improve its oral PK exposure.