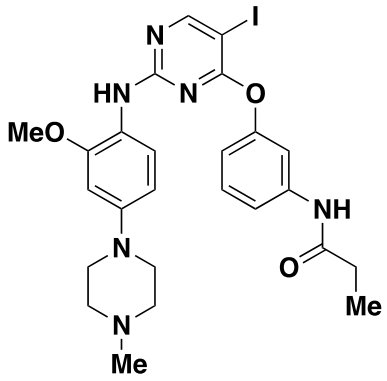
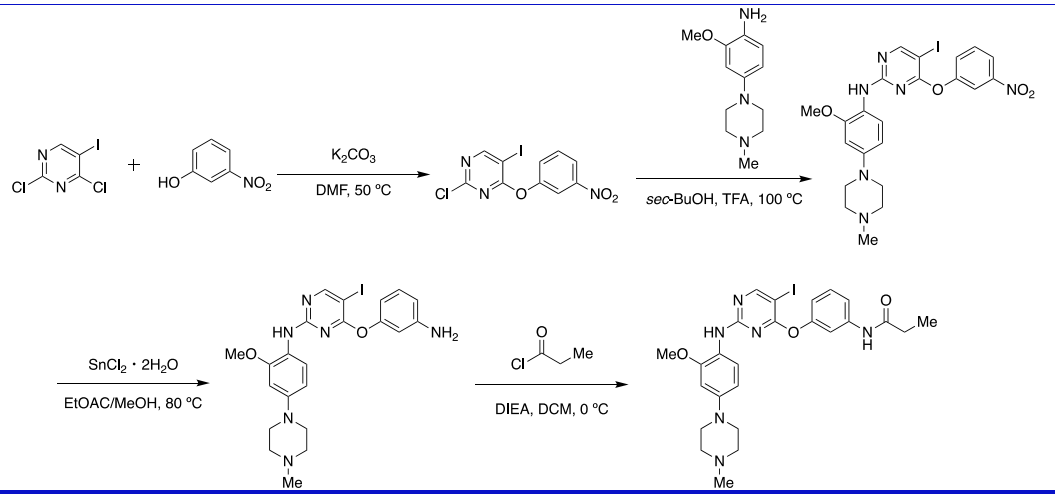
HTH-02-006



Chemical Formula: $C_{25}H_{29}IN_6O_3$
Molecular Weight: 588.45

Category	Parameter	Description
Compound	Name	HTH-02-006
	Citation	Yuan WC, et al. Nat Commun. 2018 Nov 16;9(1):4834. doi: 10.1038/s41467-018-07394-5. PubMed PMID: 30446657. https://www.nature.com/articles/s41467-018-07394-5
	Chemical descriptors	IC1=CN=C(NC2=C(OC)C=C(N3CCN(C)CC3)C=C2)N=C1OC4=CC=CC(NC(CC)=O)=C4
	Chemical name	*N*-(3-((5-iodo-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)propionamide
	Entries in chemical databases	
	Availability	
In vitro profiling	Target (potency)	NUAK1 (IC_{50} = 8 nM in a radioactive (^{33}P-ATP) filter-binding assay)[a] (IC_{50} = 69.1 nM in Adapta® Kinase Assay)
	Target (potency)	NUAK2 (IC_{50} = 126 nM in a radioactive (^{33}P-ATP) filter-binding assay)[a] (IC_{50} = 179 nM in LanthaScreen® Binding Assay)
	Selectivity	**KINOME*scan*® at 1 μM (468 kinases in the panel)** List of top wild-type kinase hits in order: FAK (0.1); **NUAK1 (0.7)**; FLT3 (0.95); ULK2 (1.6); STK33 (2.4); PHKG2 (2.7); CLK4 (3.4); GCN2-KD2 (3.6); ULK1 (6); **NUAK2 (6.6)**; DAPK3 (6.9); TTK (8.8)
	SAR	Derived from WZ4003
	Mechanism of inhibition	Reversible small-molecule inhibitor
	Structure of target-probe complex	N.A.
Cellular profiling	Validation of cellular target	HTH-02-006 reduces MYPT1(S445) phosphorylation in HuCCT-1 cells, suggesting NUAK1/2 inhibition.
	Validation of cellular specificity	N.A.
Pharmacodynamics		HTH-02-006 ameliorates YAP(S127A)-induced hepatomegaly, and reduces MYPT1(S445) phosphorylation in the same tissues. HTH-02-006 delays the outgrowth of YAP-induced HuCCT-1 xenograft tumors in nude mice, supposedly through NUAK2 inhibition.
Pharmacokinetics		Half-life in 1 mg/ml of mouse hepatic microsomes: 11.4 minutes Single intravenous (Dose: 1 mg/kg) and oral (Dose: 10 mg/kg) administration in male Swiss Albino mice: $T_{1/2}$ = 2.04 hours; CL = 18.32 (mL/min/kg); V_{ss} = 2.01 (L/kg); F = 37%

Synthetic scheme



[a] http://www.kinase-screen.mrc.ac.uk/kinase-assay