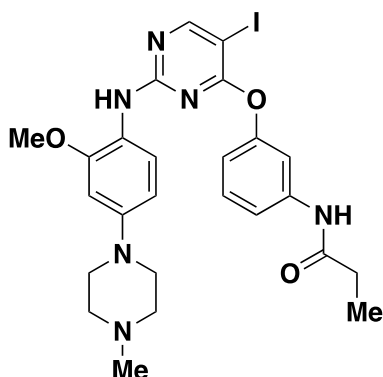
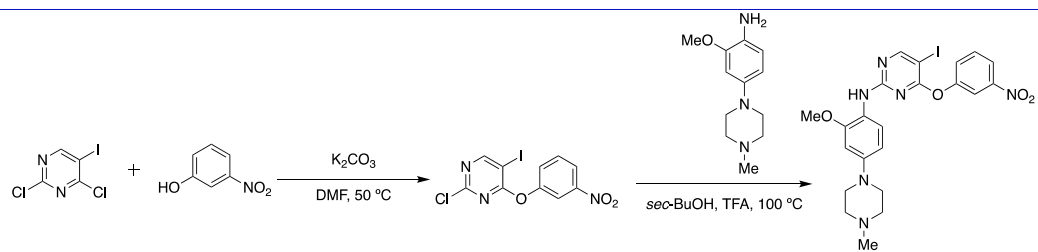


HTH-02-006

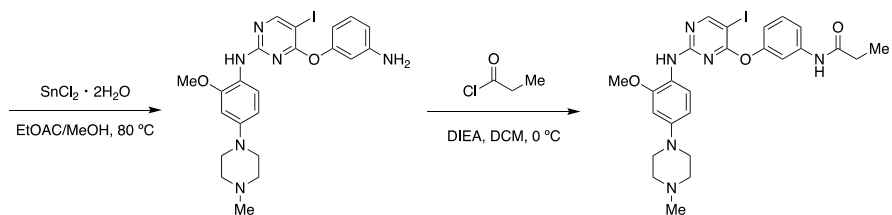


Chemical Formula:  $C_{25}H_{29}IN_6O_3$   
Molecular Weight: 588.45

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. <a href="https://www.nature.com/articles/s41467-018-07394-5">https://www.nature.com/articles/s41467-018-07394-5</a>
	Chemical descriptors	IC1=CN=C(NC2=C(OC)C=C(N3CCN(C)CC3)C=C2)N=C1OC4=CC=CC(NC(C)C=O)=C4
	Chemical name	<i>N</i> -(3-((5-iodo-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)propionamide
	Entries in chemical databases	
	Availability	
<i>In vitro</i> profiling	Target (potency)	NUAK1 (IC <sub>50</sub> = 8 nM in a radioactive ( <sup>33</sup> P-ATP) filter-binding assay) <sup>a</sup> (IC <sub>50</sub> = 69.1 nM in Adapta® Kinase Assay)
	Target (potency)	NUAK2 (IC <sub>50</sub> = 126 nM in a radioactive ( <sup>33</sup> P-ATP) filter-binding assay) <sup>a</sup> (IC <sub>50</sub> = 179 nM in LanthaScreen® Binding Assay)
	Selectivity	<b>KINOMEscan® at 1 μM (468 kinases in the panel)</b> List of top wild-type kinase hits in order: FAK (0.1); <b>NUAK1 (0.7)</b> ; FLT3 (0.95); ULK2 (1.6); STK33 (2.4); PHKG2 (2.7); CLK4 (3.4); GCN2-KD2 (3.6); ULK1 (6); <b>NUAK2 (6.6)</b> ; 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. Half-life in 1 mg/ml of mouse hepatic microsomes: 11.4 minutes
Pharmacokinetics		Single intravenous (Dose: 1 mg/kg) and oral (Dose: 10 mg/kg) administration in male Swiss Albino mice: T <sub>1/2</sub> = 2.04 hours; CL = 18.32 (mL/min/kg); V <sub>ss</sub> = 2.01 (L/kg); F = 37%



Synthetic scheme



<sup>a</sup> <http://www.kinase-screen.mrc.ac.uk/kinase-assay>