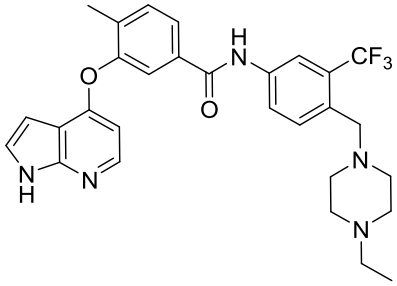
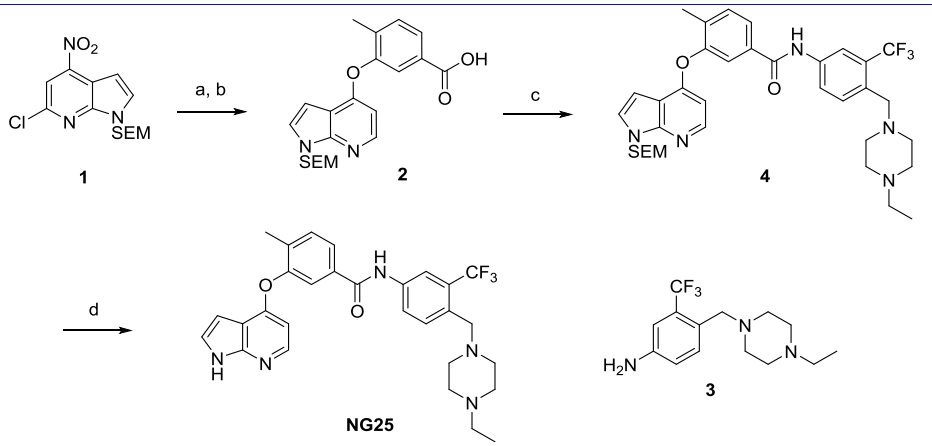
TAK1/MAP4K2 dual inhibitor (NG25)



Chemical Formula: $C_{29}H_{30}F_3N_5O_2$
Molecular Weight: 537.59

Category	Parameter	Description
Compound	Name	TAK1/MAP4K2 dual inhibitor (NG25)
	Citation	*J Med Chem.* **2014** jm500480k.
	Chemical descriptors	CC1=CC=C(C=C1OC2=CC=NC3=C2C=CN3)C(NC4=CC=C(C(C(F)(F)F)=C4)CN5CCN(CC5)CC)=O
	Chemical name	3-((1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)oxy)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide
	Availability	
In vitro profiling	Target (potency)	**TAK1** (149 nM IC50 in LanthaScreen binding assay, 97% inhibition at 1.0 µM IC_{50} in ActivX KiNativ assay), **MAP4K2** (22 nM IC50 in Z'-Lyte assay, >99% inhibition at 1.0 µM IC_{50} in ActivX KiNativ assay)
	Additional Target (potency)	**p38α** (102 nM IC50 in Z'-Lyte assay) **ABL1** (75 nM IC50 in Z'-Lyte assay)
	Selectivity	
	Potential reactivity	None to our knowledge
	SAR	
	Mechanism of inhibition	ATP-competitive
	Structure of target-probe complex	
Cellular profiling	Validation of cellular target	NG25 dose-dependently inhibited TAK1 downstream signaling induced by TNFα, IL-1 and other cytokines in various cells with IC50 between 0.1 and 0.3 µM. NG25 dose-dependently inhibited MAP4K2 downstream signaling induced by TGFβ in TAK1-null MEF cells with IC50 of 0.1 µM. Compound phenotypes were compared to literature. The cellular effects were correlated with *in vitro* biochemical activities.
	Validation of cellular specificity	
Pharmacodynamics		
Pharmacokinetics		$T_{1/2}$ = 2.0 hours, CL = 80.8 (mL/min/Kg), Vss = 11.9 (L/Kg), F = 70%

Synthetic scheme



Reagents and conditions: (a) 3-hydroxy-4-methylbenzoic acid, K2CO3, DMSO, 100 oC; (b) Pd/C, MeOH; (c) 3, HATU, DMAP, DIEA, CH2Cl2; (d) i) TFA, CH2Cl2, ii) LiOH, H2O/THF.