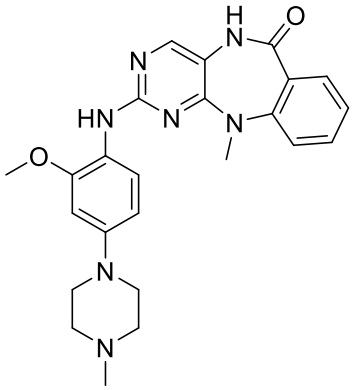
XMD8-87



XMD8-87

Chemical Formula: $C_{24}H_{27}N_7O_2$

Molecular Weight: 445.5270

Category	Parameter	Description
Compound	Name	XMD-8-87
	Citation	*Cancer Res.* **2016**, *76*, 127-138. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 126948 *Chem. Biol.* **2011**, *18*, 868-879.
	Chemical descriptors	O=C1C2=C(C=CC=C2)N(C)C3=NC(NC4=C(OC)C=C(N5CCN(C)CC5)C=C4)=NC=C3N1
	Chemical name	2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-11-methyl-5,11-dihydro-6H-benzo[e]pyrimido[5,4-b][1,4]diazepin-6-one
	Entries in chemical databases	PubChem CID 53322923
	Availability	https://www.medchemexpress.com/XMD8-87.html
	Additional comments	Identified as TNK2 inhibitor in *Cancer Res*. paper; SAR evaluation in *BMCL* paper. TNK2 is also known as ACK1.
In vitro profiling	Target (potency)	TNK2: 44 nM (LanthaScreen)
	Target (potency)	Potential off-targets from KinomeScan: BRK, CSF1R, DCAMKL1, ERK5, FRK. **BRK** (37 nM K_d in Ambit binding assay, 47 nM IC_{50} in Invitrogen kinase assay) **CSF1R** (330 nM K_d in Ambit binding assay, 428 nM IC_{50} in Invitrogen kinase assay) **DCAMKL1** (280 nM K_d in Ambit binding assay) **DCAMKL2** (690 nM K_d in Ambit binding assay, 3200 nM IC_{50} in Invitrogen kinase assay) **FRK** (96 nM K_d in Ambit binding assay, 264 nM IC_{50} in Invitrogen kinase assay) **GAK** (270 nM K_d in Ambit binding assay) **TNK1** (110 nM K_d in Ambit binding assay)
	Selectivity	Excellent kinome selectivity. S(35) = 0.08, S(10) = 0.03, S(1) = 0.02 in the DiscoverX KinomeScan at 10 μM screening concentration.
	Potential reactivity	Chemically stable; 1,4-diaminophenyl is a metabolic liability.
	SAR	Described in the paper; secondary amide is key for potency.
	Mechanism of inhibition	ATP-competitive, reversible.
	Structure of target-probe complex	Docking only
	Additional comments	Several more-potent compounds were identified in BMCL paper, but did not improve PK properties, and were not evaluated for kinome selectivity.

Cellular profiling	Validation of cellular target	Antiproliferation in Ba/F3 TNK2 D163E cells (EC_{50} = 0.19 μM)
	Validation of cellular specificity	Comparison to parental Ba/F3 cells (EC_{50} >10 μM)
Pharmacodynamics	PPB (mouse)	92%
Pharmacokinetics	Microsome stability	$T_{1/2}$ 27.9 min (mouse); $T_{1/2}$ 60.8 min (human)
	IV dosing 3 mg/kg in CD1 mice (n=3)	IV Cl 150 mL/min/kg IV $T_{1/2}$ 0.7 hr
	PO dosing 10 mg/kg in CD1 mice (n=3)	AUC_{inf} 56 ng*hr/mL F% = 5
Synthetic scheme