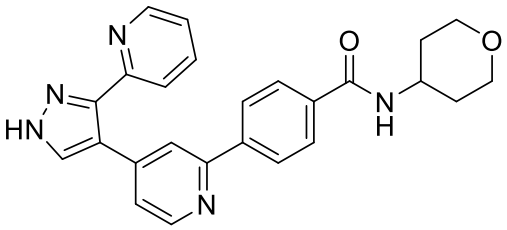
Product data sheet

MedKoo Cat#: 401488 Name: GW788388 CAS#: 452342-67-5 Chemical Formula: $C_{25}H_{23}N_5O_2$ Exact Mass: 425.18518 Molecular Weight: 425.48	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
GW788388 is a new TGF-beta type I receptor inhibitor with a much improved pharmacokinetic profile compared with SB431542. We studied its effect in vitro and found that it inhibited both the TGF-beta type I and type II receptor kinase activities, but not that of the related bone morphogenic protein type II receptor. Further, it blocked TGF-beta-induced Smad activation and target gene expression, while decreasing epithelial-mesenchymal transitions and fibrogenesis.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	48	112.81

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.35 mL	11.75 mL	23.50 mL
5 mM	0.47 mL	2.35 mL	4.70 mL
10 mM	0.24 mL	1.18 mL	2.35 mL
50 mM	0.05 mL	0.24 mL	0.47 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Petersen M, Thorikay M, Deckers M, van Dinther M, Grygielko ET, Gellibert F, de Gouville AC, Huet S, ten Dijke P, Laping NJ. Oral administration of GW788388, an inhibitor of TGF-beta type I and II receptor kinases, decreases renal fibrosis. Kidney Int. 2008 Mar;73(6):705-15. doi: 10.1038/sj.ki.5002717. Epub 2007 Dec 12. PMID: 18075500.

In vivo study

1. Petersen M, Thorikay M, Deckers M, van Dinther M, Grygielko ET, Gellibert F, de Gouville AC, Huet S, ten Dijke P, Laping NJ. Oral administration of GW788388, an inhibitor of TGF-beta type I and II receptor kinases, decreases renal fibrosis. Kidney Int. 2008 Mar;73(6):705-15. doi: 10.1038/sj.ki.5002717. Epub 2007 Dec 12. PMID: 18075500.

2. Tan SM, Zhang Y, Connelly KA, Gilbert RE, Kelly DJ. Targeted inhibition of activin receptor-like kinase 5 signaling attenuates cardiac dysfunction following myocardial infarction. Am J Physiol Heart Circ Physiol. 2010 May;298(5):H1415-25. doi: 10.1152/ajpheart.01048.2009. Epub 2010 Feb 12. PMID: 20154262.

7. Bioactivity
Biological target:

Product data sheet

GW788388 is a potent and selective inhibitor of ALK5 with IC50 of 18 nM in a cell-free assay.

In vitro activity

To test the specificity of GW788388, an in vitro kinase assay was performed on full-length constitutively actively signalling receptors. Human embryonic kidney 293T cells were transiently transfected with expression plasmids encoding constitutively active ALK (caALK)5, TβRII, BMPRII, or activin type II receptor (ActRII). Receptors were immunoprecipitated and challenged with γ-32P-labelled ATP and 10 μM of compounds. GW788388 potently inhibited autophosphorylation of ALK5, TβRII, and to some extent ActRII (Figure 1b). The compound had no effect on the BMP type II receptor kinase activity. To address if GW788388 was cytotoxic, cells were treated with a dilution range of the compound and measured cell viability after 72 h. GW788388 showed no toxicity in Namru murine mammary gland (NMuMG) (Figure 1c), MDA-MB-231, renal cell carcinoma (RCC)4, and U2OS cells (data not shown) when treated with dilutions from 4 nM to 15 μM. Similar results were obtained with the SB431542 inhibitor (Figure 1c).

Reference: Kidney Int. 2008 Mar;73(6):705-15. https://linkinghub.elsevier.com/retrieve/pii/S0085-2538(15)53061-5

In vivo activity

The db/db mouse model of spontaneous diabetic nephropathy was chosen for further in vivo characterisation of GW788388. Six-month-old mice were used, with advanced-stage renal disease, significant glomerular changes, and elevated albuminuria. Mice were treated with oral administration of 2 mg kg−1 day−1 of GW788388 for 5 weeks. No adverse side effects were observed with the treatment. Figure 7a shows diabetic mouse kidneys stained with Masson's Trichrome stain. Collagen deposits are observed in blue. Robust collagen deposits were seen in glomeruli and minimal to mild glomeropathy was evident in most diabetic animals (left panel). Treatment with GW788388 at 2 mg kg−1 day−1 resulted in a reduced collagen staining (Figure 7a, right panel). Glomerulopathy was assessed independently in picric acid stain-stained sections, scored blinded. Diabetic mice had significant glomerulopathy marked by mesangial matrix expansion, mesangial hypertrophy, proliferation, and glomerular basement membrane thickening. This was significantly reduced when treated with GW788388 (Figure 7b). Urinary albumin excretion was additionally measured and corrected for creatinine concentrations. In diabetic mice, urinary albumin levels were significantly elevated (Figure 7c). GW788388 appeared to decrease urinary albumin concentrations, although not statistically significant, suggesting that the underlying glomerular dysfunction persisted in the treated animals. To confirm that the observed changes, in glomerulopathy and the trend for reduced albuminuria, correlated with inhibition of TGF-β target genes in vivo, RNA was extracted from whole kidneys and the levels of matrix mRNAs examined. FN, COL-I, PAI-1, and COL-III expression levels were significantly increased in diabetic mice as compared with their lean littermates (Figure 7d). Treatment with 2 mg kg−1 day−1 of GW788388 significantly reduced the mRNA levels of PAI-1, COL-I, and COL-III to nearly the same levels as seen in the non-diabetic lean littermates. Taken together, these results indicate that GW788388 attenuates TGF-β signalling in vivo and effectively reduces hallmarks of fibrogenesis in mice suffering from late-stage diabetic nephropathy.

Reference: Kidney Int. 2008 Mar;73(6):705-15. https://linkinghub.elsevier.com/retrieve/pii/S0085-2538(15)53061-5