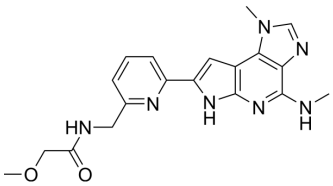
BMS-066

Cat. No.:	HY-18710
CAS No.:	914946-88-6
Molecular Formula:	$C_{19}H_{21}N_7O_2$
Molecular Weight:	379.42
Target:	IKK; JAK
Pathway:	NF-κB; Epigenetics; JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Stem Cell/Wnt
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	BMS-066 is an IKKβ/Tyk2 pseudokinase inhibitor, with IC_{50}s of 9 nM and 72 nM, respectively.	
IC_{50} & Target	IKKβ 9 nM (IC_{50})	Tyk2 72 nM (IC_{50})
In Vitro	BMS-066 is shown to inhibit IKKβ-catalyzed phosphorylation of IKKβ in vitro with an IC_{50} of 9 nM and is more than 500-fold selective for IKKβ over the closely related IKKα. To understand the selectivity on a more comprehensive scale, BMS-066 is assayed against 155 additional kinases at 10 μM, and only six of these kinases are inhibited more than 75%. This indicates that BMS-066 is more than 400-fold selective for IKKβ over more than 95% of the kinases tested. For the six kinases showing more than 75% inhibition at 10 μM, IC_{50} values are determined in dose-response assays and BMS-066 is shown to be more than 30-fold selective against even the next most potently inhibits kinase (Brk). BMS-066 inhibits LPS-stimulated cytokine production in human peripheral blood mononuclear cells, both at the protein and message level, with IC_{50} values of approximately 200 nM against these endpoints. BMS-066 inhibits the IKKβ-catalyzed phosphorylation of IkBα in LPS stimulated cells with a similar IC_{50} value[1]. BMS-066 shows IC_{50} values of 72 and 1020 nM against the Tyk2 pseudokinase domain probe displacement and IL-23-stimulated reporter assays, respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	
In Vivo	Once daily oral doses of 5 and 10 mg/kg starting at the time of adjuvant injection on day 1 significantly reduces paw swelling compared with vehicle-treated rats at the end of the study, with the high dose showing nearly complete suppression. The talocrural (ankle) joint space is narrowed. Inflammatory exudates containing neutrophils and cell debris are also evident within the joint space. The joints from animals receiving 10 mg/kg BMS-066 are normal or show minimal changes in both inflammation and bone resorption. Clear reduction of inflammation is also evident in the low dose of BMS-066 (5 mg/kg) and the bone resorption seems to be more focal and less severe compared with the control. Microcomputed tomography of the hind limbs also show that BMS-066 provides a dose-dependent protection against the pitting, loss of bone mass, woven porous bone, and fusion of the small bones evident in the rats. Bone density measurements also show a clear dose-dependent benefit of treatment with BMS-066. Serum drug level measurements in satellite animals on the first day of dosing show that a single dose provides coverage for approximately 3 h (6 h daily with twice daily dosing) of the mouse whole-blood IC_{50} value against LPS-induced TNF-α. It is also showed that IKKβ inhibitors suppress TNF-α and IL-1β production within these tissues in experimental arthritis model[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	

PROTOCOL

Cell Assay [1]	When measuring the inhibition by BMS-066 of the phosphorylation of IkBα in human PBMCs, cells at a density of 1×10^7 per mL in RPMI 1640 medium supplemented with 10% FBS are preincubated for 30 min BMS-066 at 37°C. Cells are then stimulated for 5 min with LPS (100 ng/mL) and pelleted by rapid centrifugation; the pellets are solubilized by use of ice-cold 10×cell lysis buffer. To measure effects on transcription, human PBMCs are plated on 24-well plates at a density of 3×10^6 cells/well in RPMI 1640 medium plus 10% FBS and HEPES with varying concentrations of BMS-066 (0-10 μM)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Rats, Mice[1] Male Lewis rats (225 g) are used. Vehicle (0.02 N HCl) or BMS-066 in vehicle is administered by oral gavage beginning on the day of adjuvant challenge. Eight animals are included in each treatment group. Male Lewis rats (250 g) are immunized intraperitoneally with 200 μg/rat of keyhole limpet hemocyanin diluted in phosphate-buffered saline. BMS-066 in 0.02 N HCl is administered by oral gavage once daily beginning on the day of immunization. Blood samples were collected on day 7 and on day 14 under isoflurane anesthesia. Male DBA/1 mice (20-25 g) are immunized with 200 μg/mouse of bovine type II collagen in 0.1 mL at the base of the tail on day 0 and on day 21. Vehicle (0.02 N HCl) or BMS-066 in vehicle is administered by oral gavage twice daily beginning on day 21. Mice were monitored after the second immunization for the development of paw inflammation. Each paw was individually scored as follows: 0, normal; 1, one or more swollen digits; 2, mild paw swelling; 3, moderate paw swelling; 4, fusion of joints/ankylosis[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Gillooly KM, et al. Periodic, partial inhibition of IkappaB Kinase beta-mediated signaling yields therapeutic benefit in preclinical models of rheumatoid arthritis. J Pharmacol Exp Ther. 2009 Nov;331(2):349-60.

[2]. Tokarski JS, et al. Tyrosine Kinase 2-mediated Signal Transduction in T Lymphocytes Is Blocked by Pharmacological Stabilization of Its Pseudokinase Domain. J Biol Chem. 2015 Apr 24;290(17):11061-74.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA