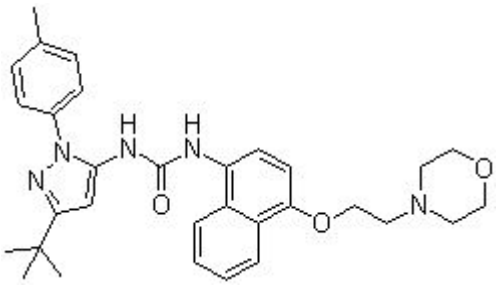
Product Introduction

BIRB 796 (Doramapimod)

BIRB 796 (Doramapimod) is a highly selective **p38α MAPK** inhibitor with K_d of 0.1 nM, 330-fold greater selectivity versus JNK2, weak inhibition for c-RAF, Fyn and Lck, insignificant inhibition of ERK-1, SYK, IKK2, ZAP-70, EGFR, HER2, PKA, PKC, PKCα/β/γ.

Technical Data:

Molecular Weight (MW):	527.66	
Formula:	$C_{31}H_{37}N_5O_3$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 106 mg/mL	
	Water <1 mg/mL	
	Ethanol 106 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	285983-48-4	

Biological Activity

BIRB 796 shows no significant inhibition to ERK-1, SYK, IKK2β, ZAP-70, EGF receptor kinase, HER2, protein kinase A (PKA), PKC, PKC-α, PKC-β (I and II) and PKC-γ. BIRB 796 greatly improves binding affinity by forming a hydrogen bond between the morpholine oxygen and the ATP-binding domain of p38α. BIRB 796 represents one of the most potent and slowest dissociating inhibitors against human p38 MAP

kinase now known. [1] BIRB 796 potently inhibits c-Raf-1 and Jnk2α2 with IC50 of 1.4 and 0.1 nM, respectively. [2] BIRB796 also inhibits the activity and the activation of SAPK3/p38γ at a higher concentration than it does in p38α. BIRB796 blocks the stress-induced phosphorylation of the scaffold protein SAP97, which is a physiological substrate of SAPK3/p38γ. BIRB796 blocks JNK1/2 activation and activity in HEK293 cells, while not inhibits the activation and activity of ERK1/ERK2 in Hela cells. Moreover, the binding of BIRB796 to the p38 MAPKs or JNK1/2 is impairing their phosphorylation by the upstream kinase MKK6 or MKK4 rather than enhancing their dephosphorylation. [3] BIRB 796 blocks baseline and bortezomib-triggered upregulation of p38 MAPK and Hsp27 phosphorylation, thereby enhancing cytotoxicity and caspase activation. BIRB 796 downregulates IL-6 and VEGF secretion in BMSCs triggered by TNF-α and TGF-β1. [4] BIRB-796 has a pyrazole scaffold that places a lipophilic t-butyl group into the lower selectivity site and a tolyl ring into the upper selectivity site. BIRB-796 also inhibits B-Raf and Abl with IC50 of 83 nM and 14.6 μM, respectively. [5]

BIRB 796 (30 mg/kg) inhibits 84% of TNF-α in LPS-stimulated mice and demonstrates efficacy in a mouse model of established collagen-induced arthritis. [1] BIRB 796 has good pharmacokinetic performance even after oral administration in mice. [2]

The first p38 MAPK inhibitor to be tested in a phase III clinical trial.

References

[1] Pargellis C, et al. Nat Struct Biol, 2002, 9(4), 268-272.

[2] Regan J, et al. J Med Chem, 2002, 45(14), 2994-3008.

[3] Kuma Y, et al. J Biol Chem, 2005, 280(20), 19472-19479.

[4] Yasui H, et al. Br J Haematol, 2007, 136(3), 414-423.

[5] Dietrich J, et al. Bioorg Med Chem. 2010, 18(15), 5738-5748.

[6] Regan J, et al. J Med Chem, 2003, 46(22), 4676-4686.

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