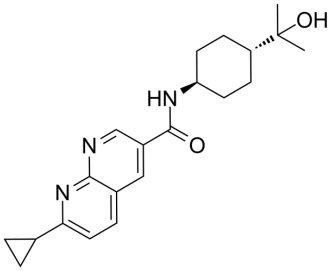
HPGDS inhibitor 3

Cat. No.:	HY-146662
CAS No.:	2255311-93-2
Molecular Formula:	$C_{21}H_{27}N_3O_2$
Molecular Weight:	353.46
Target:	PGE synthase
Pathway:	Immunology/Inflammation
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

HPGDS inhibitor 3 is an orally active and highly potent peripherally restricted hematopoietic prostaglandin D synthase (H-PGDS) inhibitor with IC_{50} value of 9.4 nM and EC_{50} of 42 nM, respectively. HPGDS inhibitor 3 exhibits good selectivity, good pharmacokinetic parameters in mouse, rat, and dog, and no CNS toxicity. HPGDS inhibitor 3 has anti-inflammatory activity [1].

IC_{50} & Target

IC_{50}: 9.4 nM (H-PGDS)[1]
EC_{50}: 42 nM (H-PGDS)[1]

In Vivo

HPGDS inhibitor 3 (compound 1y) (1-3 mg/kg; PO and IV; single) has a lower IV clearance, similar steady state volume of distribution, longer terminal half-life, and high oral bioavailability, as well as very low brain exposures in mouse, rat and dog [1].

HPGDS inhibitor 3 (0.003-1 mg/kg; PO; single) attenuates PGD_2 release to baseline levels in a dose-dependent manner; also inhibits LPS-induced PGD_2 increase in plasma and skeletal muscle in a dose-dependent manner[1].

HPGDS inhibitor 3 (0.003-1 mg/kg; PO; single) [1].

HPGDS inhibitor 3 (1, 3, and 10 mg/kg; PO; q.d., for 16 days) significantly enhances functional recovery of injured limbs, and hastens the time to full functional recovery of injured limb muscles[1].

HPGDS inhibitor 3 (10, 30 and 100 mg/kg; PO; once daily, for 7 days or 4 days) exhibits well tolerated at 30 mg/kg/day in rat but not tolerated at 100 mg/kg/day; shows well tolerated at 30 mg/kg/day in dogs but not tolerated at 75 mg/kg/day[1].

Pharmacokinetic Parameters of HPGDS inhibitor 3 in mice, rats and dogs[1].

	Mouse IV, 1 mg/kg PO, 3 mg/kg	Rat IV, 0.4 mg/kg PO, 2.4 mg/kg	Dog IV, 0.5 mg/kg PO, 1 mg/kg
$T_{1/2}$ (h)	2.9	5.1	6.2
CL (mL/min/kg)	9.0	4.5	1.9
V_{ss} (L/kg)	1.6	1.6	1.0

F (%)	71	100	92
Brain:blood ratio	0.06		

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Male C57BL/6J mice (murine mast cell degranulation model of inflammation)[1]
Dosage:	0.003, 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg
Administration:	PO; single (anesthetized 1 hour later, intraperitoneally injected with 0.2 mL PBS or 48/80 (0.75 mg/mL))
Result:	Attenuated PGD_2 release to baseline levels in a dose-dependent manner with an ED_{50} of 0.009 mg/kg (blood EC_{50} = 3.4 nM) in this acute inflammation model.

Animal Model:	Male C57BL6/N mice (12 weeks, n=6)[1]
Dosage:	0.003, 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg
Administration:	PO; single (intraperitoneally injection of PBS or 20 ng/kg LPS 1 hour later)
Result:	Inhibited LPS-induced PGD2 increase in plasma and skeletal muscle in a dose-dependent manner.

Animal Model:	Male C57Bl/6 mice (10-12 weeks, n=7-8; chronic eccentric contraction-induced muscle injury models)[1]
Dosage:	1, 3, and 10 mg/kg
Administration:	PO; q.d., for 16 days
Result:	Significantly enhanced functional recovery of injured limbs, and significantly hastened the time to full functional recovery of injured limb muscles, with maximal efficacy observed at ≥ 10 mg/kg q.d..

Animal Model:	Mdx mouse (6-8 mouths, duchenne muscular dystrophy model)[1]
Dosage:	0.1, 0.3, 1, 3, and 10 mg/kg
Administration:	PO; q.d., for 43 days
Result:	Significantly improved functional recovery (~90% to 100% restoration), following eccentric contraction-induced muscle injury in mdx mice.

Animal Model:	Male Wistar Han rat and dog[1]
Dosage:	10, 30 and 100 mg/kg for rat; 10, 30, and 75 mg/kg for dog
Administration:	PO; once daily; for 7 days (rat) or for 4 days (dog)
Result:	In rat, the AUC values at 10, 30, and 100 mg/kg/day were 120, 410, and 820 μg•hr/mL,

	respectively; respective C_{max} values were 8.7, 24, and 57 μg/mL. In dog, it showed well tolerated at dose levels up to 30 mg/kg/day with no abnormal microscopic findings; but exhibited discoloration in the small intestine and esophagus (female) at 75 mg/kg/day.

Animal Model:	Mice, rats, dongs[1]
Dosage:	1 mg/kg IV and 3 mg/kg p.o in mice, 0.4 mg/kg IV and 2.4 mg/kg PO in rat, 0.5 mg/kg IV and 1 mg/kg PO in dog
Administration:	IV and PO; single (Pharmacokinetics Analysis)
Result:	Had a lower IV clearance, similar steady state volume of distribution, longer terminal half-life, and high oral bioavailability, as well as very low brain exposures in mouse, rat and dog.

REFERENCES

[1]. Cadilla R, Deaton DN, Do Y, et al. The exploration of aza-quinolines as hematopoietic prostaglandin D synthase (H-PGDS) inhibitors with low brain exposure. Bioorg Med Chem. 2020;28(23):115791.

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