NVP-CLR457

Cat. No.: HY-146260

CAS No.: 1453082-52-4

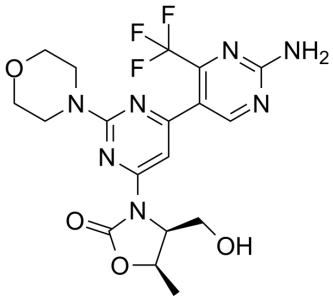
Molecular Formula: $C_{18}H_{20}F_3N_7O_4$

Molecular Weight: 455.39

Target: PI3K

Pathway: PI3K/Akt/mTOR

Storage: Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

NVP-CLR457 (compound 40) is an orally active, potent and balanced pan-class I PI3K inhibitor. NVP-CLR457 shows a clear dose-dependent PK/PD/efficacy relationship. NVP-CLR457 has antitumor activity[1].

IC_{50} & Target

PI3Kα	PI3Kβ	PI3Kδ	PI3Kγ
12 ± 1.5 nM (IC_{50})	8.3 ± 1.0 nM (IC_{50})	8.3 ± 2.0 nM (IC_{50})	230 ± 31 nM (IC_{50})

In Vitro

NVP-CLR457 (compound 40) shows the mTOR activity, with an IC_{50} of 2474 ± 722 nM, and inhibits RPS6 phosphorylation with an IC_{50} of 1633 ± 54 nM[1].

NVP-CLR457 has no impact on the DDR response at concentrations of 1 and 5 μM[1].

NVP-CLR457 has no effect on the rate of microtubule polymerization[1].

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

Western Blot Analysis

Cell Line:	U87MG cells[1]
Concentration:	0, 1. 4, 16, 63, 250, 1000 nM
Incubation Time:	24 h
Result:	Inhibited the readouts of class I PI3K activity in a dose-dependent manner, with IC_{50} and IC_{90} values of 100 and 507 nM determined for the inhibition of S473P-Akt, and had no significant change in the readouts of mTOR activity.

In Vivo

NVP-CLR457 (compound 40) (athymic nude mice bearing xenotransplanted Rat1-myr-p110α tumors, 3-20 mg/kg, PO, daily for 8 days) shows a dose-dependent inhibition of tumor growth[1].

NVP-CLR457 (Mice bearing xenograft HBRX2524 human primary breast tumor, 40 mg/kg, PO, daily for 15 days) inhibits the tumor growth throughout the study[1].

NVP-CLR457 (male Sprague-Dawley rats, 1.0 mg/kg, IV; 3.0 mg/kg, PO; once) shows high level of oral exposure and bioavailability[1].

Pharmacokinetic Parameters of NVP-CLR457 in male Sprague-Dawley rats[1].

compound	40

CL (mL/min/kg)	22 ± 6
Vss (L/kg)	4.4 ± 0.2
$t_{1/2}$ (h)	3.3 ± 0.2
AUC iv (nM*h)	1770 ± 443
oral F (%)	97 ± 20
HDM FA (%)	37

NVP-CLR457 (3 mg/kg (IV) and 10 mg/kg (PO) for female OF1 mice, 0.1 mg/kg (IV), 0.3 mg/kg (PO) for male beagle dogs, once) shows low clearance, moderate volume of distribution, and rapid absorption leading to moderate to long half-lives and high oral bioavailability[1].

Pharmacokinetic Parameters of NVP-CLR457 in female OF1 mice and male beagle dogs[1].

species	mouse	dog
PPB (%)	76	71
CL (mL/min/kg)	10	3 ± 0
Vss (L/kg)	2	1.5 ± 0.2
$t_{1/2}$ (h)	2	11 ± 3
AUC iv (nM*h)	3580	11213 ± 1169
AUC po (nM*h)	1738	11034 ± 1531
oral F (%)	49	98 ± 14
C_{max} (nM)	422	1121 ± 128
T_{max} (h)	0.5	1.3 ± 0.6

NVP-CLR457 (0.3-100 mg/kg, PO, once) leads to under-proportional increases in exposure (both AUC and Cmax) and much longer Tmax values[1].

Pharmacokinetic Parameters of NVP-CLR457 in male Sprague Dawley rats, male beagle dogs[1].

species	rat			dog	
dose (mg/kg)	3	30	100	0.3	3
AUC (nM*h)	1709 ± 362	913 ± 251	784 ± 342	12,970 ± 1828	11,213 ± 1169

C_{max} (nM)	213 ± 61	41 ± 6	22 ± 4	1121 ± 128	309 ± 40
T_{max} (h)	0.5-2	4–24	24	1-2	2-24

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

Animal Model:	Sprague Dawley rats (male)[1]
Dosage:	1 mg/kg (IV), 3 mg/kg (PO)
Administration:	IV or PO, once (Pharmacokinetic Analysis)
Result:	Showed high level of oral exposure and bioavailability.

Animal Model:	Female OF1 mice, male beagle dogs[1]
Dosage:	3 mg/kg (IV) and 10 mg/kg (PO) for mice, 0.1 mg/kg (IV), 0.3 mg/kg (PO) for dogs
Administration:	IV or PO, once (Pharmacokinetic Analysis)
Result:	Showed low clearance, moderate volume of distribution, and rapid absorption leading to moderate to long half-lives and high oral bioavailability.

Animal Model:	Male Sprague Dawley rats, male beagle dogs[1]
Dosage:	0.3, 3, 30, 100 mg/kg
Administration:	PO, once (Pharmacokinetic Analysis)
Result:	Led to under-proportional increases in exposure (both AUC and Cmax) and much longer Tmax values when it formulated as a suspension of the crystalline material.

Animal Model:	Female athymic nude mice (bearing xenotransplanted Rat1-myr-p110α tumors)[1]
Dosage:	3, 10, and 20 mg/kg
Administration:	PO, daily for 8 days
Result:	Observed dose-dependent exposure and PD responses, and showed a dose-dependent inhibition of tumor growth. The 3 mg/kg dose achieved 80% S473P-Akt inhibition only at the 1 h time point; the 10 mg/kg dose at the 1 and 4 h time points; and the 20 mg/kg at the 1, 4, and 10 h time points, with a high level of inhibition remaining at the 14 h time point (76%).

Animal Model:	Mice bearing xenograft HBRX2524 human primary breast tumor[1]Dosage: 40 mg/kg
Dosage:	40 mg/kg
Administration:	PO, daily for 15 days
Result:	Inhibited the tumor growth throughout the study, and showed a significant level of regression the end of the 15 day treatment period.

REFERENCES

[1]. Fairhurst RA, et al. Identification of NVP-CLR457 as an Orally Bioavailable Non-CNS-Penetrant pan-Class IA Phosphoinositol-3-Kinase Inhibitor. J Med Chem. 2022 May 2.

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