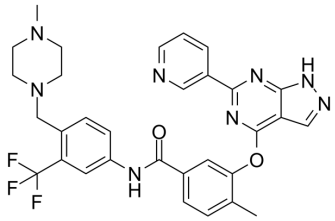
RET-IN-16

Cat. No.:	HY-146710
CAS No.:	2259657-48-0
Molecular Formula:	$C_{31}H_{29}F_3N_8O_2$
Molecular Weight:	602.61
Target:	RET
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	RET-IN-16 is a potent and selective RET inhibitor with IC_{50}s of 3.98 nM, 8.42 nM, 15.05 nM, 7.86 nM, 5.43 nM and 8.86 nM for RET(WT), RET(M918T), RET(V804L), RET(V804M), RET-CCDC6 and RET-KIF5B, respectively. RET-IN-16 has anticancer effects[1].
IC_{50} & Target	IC_{50}: 3.98 nM (RET(WT)), 8.42 nM (RET(M918T)), 15.05 nM (RET(V804L)), 7.86 nM (RET(V804M)), 5.43 nM (RET-CCDC6), 8.86 nM (RET-KIF5B)[1]

In Vitro

RET-IN-16 (compound 9x) (0.005-10 μM; 48 hours) exhibits potent activity against CCDC6-RET-Ba/F3 and KIF5B-RET-Ba/F3 with GI_{50} of 9 nM and 17 nM, respectively[1].

RET-IN-16 (1 μM; 48 hours) selectively suppresses the proliferation of CCDC6-RET fusion cells[1].

RET-IN-16 (50 and 100 μM; 4 hours) remarkably blocks the autophosphorylation of RET in KIF5B-RET and KIF5B-RET^{V804M} Ba/F3 cells, and the phosphorylation of the adapter protein SHC is also inhibited with a dose-dependent manner[1].

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

Cell Proliferation Assay

Cell Line:	LC-2/ad, A549, H3122, MDA-MB-231 and A375, SKGT4, HepG2, KYSE450 and BGC823 cells[1]
Concentration:	1 μM
Incubation Time:	48 hours
Result:	Potently suppressed the proliferation of LC-2/ad NSCLC cells harboring the CCDC6-RET fusion, but dramatically decreased potency against other RET-negative cancer cells.

Western Blot Analysis

Cell Line:	KIF5B-RET and KIF5B-RET^{V804M} Ba/F3 cells[1]
Concentration:	50 and 100 μM
Incubation Time:	4 hours
Result:	Remarkably blocked the autophosphorylation of RET, and the phosphorylation of the adapter protein SHC was also inhibited in a dose-dependent manner.

In Vivo

RET-IN-16 (1 mg/kg; IV; single) exhibits a good drug exposure (AUC_{0-t} = 6959 ± 762 ng·h/mL) and a moderate half-life ($T_{1/2}$ =

4.28 ± 0.43 h)[1].

RET-IN-16 (10 mg/kg; PO; single) exhibits a low maximum plasma concentration (C_{max} = 194 ± 47 ng·h/mL) and drug exposure (AUC_{0-t} = 2112 ± 117 ng·h/mL)[1].

RET-IN-16 (30 and 50 mg/kg; IV; daily; for 8 days) suppresses tumor growth in a dose-dependent manner, and significantly suppresses p-RET and p-SHC in both KIF5B-RET and KIF5B-RET^{V804M} in tumor tissues, as well as significantly induces apoptosis in vivo[1].

Pharmacokinetic Parameters of RET-IN-16 in male Sprague-Dawley rats[1].

	IV (1 mg/kg)	PO (10 mg/kg)
$T_{1/2}$ (h)	4.28 ± 0.43	7.59 ± 1.02
T_{max} (h)	0.083 ± 0	0.75 ± 0.43
C_{max} (ng/mL)	6097 ± 623	194 ± 47
AUC_{0-t} (ng/mL·h)	6959 ± 762	2112 ± 117
$AUC_{0-\infty}$ (ng/mL·h)	7014 ± 753	2343 ± 157
F (%)		3.0

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Animal Model:	Male Sprague-Dawley rats[1]
Dosage:	1 mg/kg for IV, 10 mg/kg for PO
Administration:	IV and PO; single (Pharmacokinetic Analysis)
Result:	Exhibited a good drug exposure (AUC_{0-t} = 6959 ± 762 ng·h/mL) and a moderate half-life ($T_{1/2}$ = 4.28 ± 0.43 h) at 1 mg/kg IV; observed a low maximum plasma concentration (C_{max} = 194 ± 47 ng·h/mL) and drug exposure (AUC_{0-t} = 2112 ± 117 ng·h/mL) at 10 mg/kg PO.

Animal Model:	Half male and female BALB/c-nu mice (6-8 weeks; injected with KIF5B-RET Ba/F3 and KIF5B-RETV804M Ba/F3)[1]
Dosage:	30 and 50 mg/kg
Administration:	IV; daily; for 8 days
Result:	Suppressed tumor growth in a dose-dependent manner, and significantly suppressed p-RET and p-SHC in both KIF5B-RET and KIF5B-RET^{V804M} in tumor tissues, as well as significantly induced apoptosis in vivo.

REFERENCES

[1]. Li X, Su J, Yang Y, et al. Discovery of 4-methyl-N-(4-((4-methylpiperazin- 1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-((6-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-oxy)benzamide as a potent inhibitor of RET and its gatekeeper mutant. Eur J Med Chem. 2020;207:112755.

Caution: Product has not been fully validated for medical applications. For research use only.

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