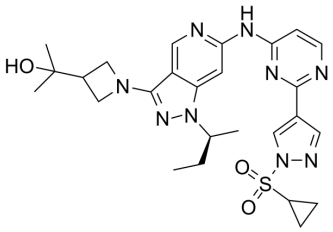
EGFR-IN-2

Cat. No.:	HY-100520
CAS No.:	1643497-70-4
Molecular Formula:	$C_{26}H_{33}N_9O_3S$
Molecular Weight:	551.66
Target:	EGFR
Pathway:	JAK/STAT Signaling; Protein Tyrosine Kinase/RTK
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	EGFR-IN-2 is a a noncovalent, irreversible, mutant-selective second generation EGFR inhibitor.
IC_{50} & Target	EGFR[1]
In Vitro	EGFR-IN-2 (Compound 21) inhibits EGFR autophosphorylation with IC_{50}s of 0.027 μM, 0.009 μM ,0.033 μM , and 0.218 μM in double mutant TMLR cell line H1975, double mutant TMdel cell line PC9-ER, activating mutant del cell line PC9, and wild type cell line H292. In addition, EGFR-IN-2 demonstrats strong antiproliferative effect on the T790M mutant carrying H1975 cell line (IC_{50}=0.361 μM) and the single activating mutant PC9 cell line (IC_{50}=0.151 μM). Furthermore, EGFR-IN-2 also shows good selectivity against other kinases when evaluated in a 225-kinase panel (12/225 kinases inhibited at >70% when tested at 0.1 μM, 61-fold over the TMLR K_i and 63-fold over the TMdel K_i)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	To examine its inhibitory effect on pEGFR levels in vivo, EGFR-IN-2 (Compound 21) is studied in a mouse H1975 (TMLR) xenograft model. After a single oral dose of 21 at 50 mg/kg, free plasma concentrations of EGFR-IN-2 at or exceeding the in vitro p-EGFR IC_{50} of 0.027 μM are sustained over 8 h. When administered at 100 mg/kg, the coverage of p-EGFR IC_{50} is extended to the last measured time point of 16 h postdose. Corresponding knockdown of p-EGFR and the downstream effectors pERK1/2 and AKT levels are observed at those time points, suggesting target engagement in vivo. In mouse, after intravenous and oral administration, the plasma clearance of EGFR-IN-2 is determined to be 104 mL/kg per min with a bioavailability of 19%. In dogs, the plasma clearance is 13 mL/kg per min with an oral bioavailability of 30%[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Mice[1] Eight week old female SCID beige mice are inoculated subcutaneously with 5×10^6 NCI-H1975 cells. When tumors reach a mean volume of 300 to 500 mm^3, mice with similarly sized tumors are randomized into treatment groups. EGFR-IN-2 at 50 mg/kg or 100 mg/kg is administered orally as a single dose. Tumor and plasma samples are collected at 2, 8 or 16 h post dose[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Chan BK, et al. Discovery of a Noncovalent, Mutant-Selective Epidermal Growth Factor Receptor Inhibitor. J Med Chem. 2016 Oct 13;59(19):9080-9093.

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