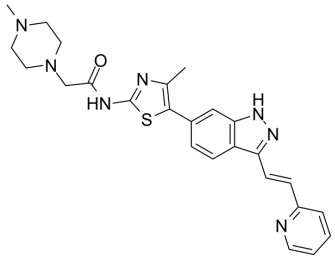
# IHMT-TRK-284

| | |
|---|---|
| **Cat. No.:** | HY-146697 |
| **CAS No.:** | 2416844-79-4 |
| **Molecular Formula:** | $C_{25}H_{27}N_7OS$ |
| **Molecular Weight:** | 473.59 |
| **Target:** | Trk Receptor; c-Fms; PDGFR; Bcr-Abl; c-Kit; Apoptosis |
| **Pathway:** | Neuronal Signaling; Protein Tyrosine Kinase/RTK; Apoptosis |
| **Storage:** | Please store the product under the recommended conditions in the Certificate of Analysis. |



## BIOLOGICAL ACTIVITY

**Description** IHMT-TRK-284 (Compound 34) is a potent, orally active type II TRK kinase inhibitor with $IC_{50}$ values of 10.5, 0.7, and 2.6 nM to TRKA, B, and C respec great selectivity profile in the kinome and good in vivo antitumor efficacies[1].

| $IC_{50}$ & Target | | | | |
|---|---|---|---|---|
| | TrkB<br>0.7 nM ($IC_{50}$) | TrkC<br>2.6 nM ($IC_{50}$) | TrkA<br>10.5 nM ($IC_{50}$) | CSF1R<br>1.2 nM ($IC_5$ |
| | PDGFRα<br>24.2 nM ($IC_{50}$) | PDGFRβ<br>95.7 nM ($IC_{50}$) | Abl1<br>83.6 nM ($IC_{50}$) | KIT<br>2167 nM (I |

**In Vitro**

IHMT-TRK-284 (Compound 34) (0-10 μM, 72 h) shows antiproliferative effects against BaF3 cells, a panel of kinase transformed BaF3 cells, and KM-1
IHMT-TRK-284 (0-10 μM, 24 h) induces apoptosis and arrests the cell cycle into G0/G1 phase in KM-12-LUC cells[1].
IHMT-TRK-284 exerts its inhibitory effect to the colon cancer cells through on-target inhibition of TRK[1].
IHMT-TRK-284 could overcome drug resistant mutants including V573M and F589L in the ATP binding pocket as well as G667C/S in the DFG region[1
IHMT-TRK-284 shows selectivity over VEGFR2 kinase[1].

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

Cell Proliferation Assay[1]

| | |
|---|---|
| Cell Line: | BaF3 cells, a panel of kinase transformed BaF3 cells, and KM-12-LUC cells |
| Concentration: | 0-10 μM |
| Incubation Time: | 72 h |
| Result: | Showed antiproliferative effects against BaF3 cells, a panel of kinase transformed BaF3 cells, and KM-12 LUC cells was 0.002 μM.<br>Antiproliferative effects of IHMT-TRK-284 against a panel of kinase transformed BaF3 cells[1]. |

| Target | BaF3-TEL-ABL | BaF3-TEL-CSF1R | BaF3-TEL-KIT | BaF3-TEL-PDGFRα | BaF3-TEL-PDGFRβ | BaF3-TEL-TRKA |
|---|---|---|---|---|---|---|
| $GI_{50}$ (nM) | 411.1 | 4 | 923.2 | 1.7 | 1.4 | 8.5 |

| | |
|---|---|
| | Antiproliferative effects of IHMT-TRK-284 against a panel of TRKs wt/mutants transformed BaF3 cells (n<br>Showed antiproliferative effects with $GI_{50}$s of 1.4 ± 0.011, 0.007 ± 0.001, 0.003 ± 0.001, 0.004 ± 0.001, 0.19<br>0.002 ± 0.001 μM against BaF3, BaF3-LMNA-TRKA, BaF3-LMNA-TRKA-V573M, BaF3-LMNA-TRKA-F589L, Ba<br>BaF3-LMNA-TRKA-G667C, BaF3-LMNA-TRKA-G667S cells, respectively. |

Western Blot Analysis[1]

| | |
|---|---|
| Cell Line: | BaF3-TEL-TRKA, BaF3-TEL-TRKB, BaF3-TEL-TRKC, BaF3-LMNATRKA-V573M, BaF3-LMNA-TRKA-F589L, BaF3-L<br>LMNA-TRKA-G667C/S, and KM-12-LUC cells |
| Concentration: | 0, 0.01, 0,03, 0.1, 0.3, 1, 3, and 10 μM |
| Incubation Time: | 2 h |
| Result: | In transformed BaF3 cells: Inhibited the phosphorylation of TRKA Y490 ($EC_{50}$ = 0.026 μM) and corresponding<br>Y515 ($EC_{50}$ = 0.069 μM) and TRKC Y516 ($EC_{50}$ = 0.029 μM); potently inhibited the phosphorylation of Y490 in V<br>mutants with $EC_{50}$s of 0.013 μM, 0.021 μM, 0.067 μM, and 0.074 μM respectively. In KM-12-LUC cells: Blocked<br>TRKA Y490 at the concentration of 0.01 μM; remarkably inhibited the phosphorylation of downstream signal<br>T308/S473 and ERK1/2 (T202/Y204) ($EC_{50}$ less than 0.03 μM). |

Apoptosis Analysis[1]

| | |
|---|---|
| Cell Line: | KM-12-LUC cells |
| Concentration: | 0, 0.01, 0,03, 0.1, 0.3, 1, 3, and 10 μM |
| Incubation Time: | 24 h |
| Result: | Induced dose-dependent cell apoptotic death. |

Cell Cycle Analysis[1]

| | |
|---|---|
| Cell Line: | KM-12-LUC cells |
| Concentration: | 0, 0.01, 0,03, 0.1, 0.3, 1, 3, and 10 μM |
| Incubation Time: | 24 h |
| Result: | Arrested the cell cycle into G0/G1 phase. |

**In Vivo**

IHMT-TRK-284 (Compound 34) (40 and 80 mg/kg; p.o.; daily, 10 days) shows good in vivo PK and antitumor efficacy properties[1].

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

| | |
|---|---|
| Animal Model: | Four-week old female nu/nu mice, one million BaF3-TELTRKA, BaF3-TEL-TRKB, BaF3-TEL-TRKC, BaF3-LMNA-<br>TRKA-G667S, and five million KM-12-LUC cells in DMEM medium were formulated as a 1:1 mixture with matri<br>subcutaneous space on the right flank of nu/nu mice[1] |
| Dosage: | 40 mg/kg and 80 mg/kg |
| Administration: | Daily oral gavage, 10 days |
| Result: | Dose-dependently inhibited the BaF3-TEL-TRKA, BaF3-TEL-TRKB, and BaF3-TEL-TRKC tumor progression wi<br>inhibition) of 68%, 93%, and 58%. Dose-dependently inhibited the tumor progression and exhibited the TGI<br>and 95% at 80 mg/kg/day in KM-12-LUC cells inoculated xenograft mouse model. Potently inhibited the tum<br>of 88% and 89% respectively at 80 mg/kg dosage in BaF3- LMNA-TRKA-F589L and BaF3-LMNA-TRKA-G667S c |

| | |
|---|---|
| Animal Model: | Mice, sprague dawley rats, and beagle dogs[1] |
| Dosage: | 1 mg/kg and 10 mg/kg |
| Administration: | Intravenous injection and oral administration (Pharmacokinetic Analysis) |
| Result: | Pharmacokinetic study of IHMT-TRK-284 in mice, sprague dawley rats, and beagle dogs[a][1] |

| Parameter | Mice i.v. (1 mg/kg) | Mice p.o. (10 mg/kg) | Rats i.v. (1 mg/kg) | Rats p.o. (10 mg/kg) | Beagle Dogs i.v. (1 mg/kg) | Beagle Dogs p.o. (10 mg/kg) |
|---|---|---|---|---|---|---|
| AUC(0-t) (ng/mL*h) | 748 | 1431 | 393 | 952 | 323 | 464 |
| Tmax (h) | 0.033 | 1.5 | 0.03 | 4.7 | 0.08 | 4.3 |
| $T_{1/2}$ (h) | 2.6 | 3.4 | 2.7 | 2.5 | 0.03 | 11.8 |
| Vz (mL/kg) | 4934 | 31567 | 9682 | | | |

## REFERENCES

[1]. Beilei Wang, et al. Discovery of (E)-N-(4-methyl-5-(3-(2-(pyridin-2-yl)vinyl)-1H-indazol-6-yl)thiazol-2-yl)-2-(4-methylpiperazin-1-yl)acetamide orally available type II TRK kinase inhibitor capable of overcoming multiple resistant mutants. Eur J Med Chem. 2020 Dec 1;207:112744.

McePdfHeight



Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA