Product Data Sheet

Chemical Properties

Product Name: Tivantinib (ARQ 197)
Cas No.: 905854-02-6
M.Wt: 369.42
Formula: C23H19N3O2
Synonyms: ARQ-197; ARQ197

Chemical Name: (3S,4R)-3-(5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(1H-indol-3-yl)pyrrolidine-2,5-dione

Canonical SMILES: O=C([C@H](C(C1=CC=C2)=CN3C1=C2CCC3)[C@@H]4C5=CNC6=CC=CC=C56)NC4=O

Solubility: ≥18.471mg/mL in DMSO
Storage: Store at -20°C

General tips: For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shopping Condition: Evaluation sample solution: ship with blue ice
All other available size: ship with RT, or blue ice upon request

Biological Activity

Targets: Tyrosine Kinase
Pathways: c-MET

Description:
Tivantinib (ARQ 197) is an oral, non–adenosine triphosphate-competitive, selective, small-molecule met proto-oncogene (c-MET) inhibitor. The calculated inhibitory constant (Ki) for tivantinib to inhibit recombinant human c-MET was approximately 355 nmol/L. c-MET, a type of receptor tyrosine kinase, is a high-affinity receptor of the hepatocyte growth factor (HGF). Dysregulated HGF/c-MET-signaling pathway frequently occurs in human cancer [1].
Tivantinib had weak inhibitory effects on VEGF receptor-3 (Flt4), p21-activated kinase 3, calmodulin-dependent kinase II delta, and Pim-1 [1]. Tivantinib displayed cytotoxic activity against a wide panel of human tumor cell lines with an EC50 ranging from 300-600 nmol/L [4]. Remarkably, A549, H3122, PC9 (Del E746_A750), PC9 GR4 (Del E746_A750/T790M), HCC827, HCC827 GR6, H1993 and EBC-1 cell lines showed some degree of sensitivity to tivantinib, with IC50s ranging between 0.36 and 0.8 μM [5]. In tumor cell lines, GTL-16, MKN-45, Hs746T, SNU-5, EBC-1, H1993, NCI-H441, A549, HCT-116, U87-MG, A2780, and TOV-112D, tivantinib indiscriminately inhibited cell proliferation independently of c-MET gene amplification and MET protein expression with an EC50 ranging from 60 to 600 nmol/L. Further research showed that tivantinib promotes mitotic arrest, prevents cells from re-entering G1, and drives them to apoptosis, and induces programmed cell death regardless of the presence or absence of a functional MET kinase [4].

Tivantinib has demonstrated antitumor activity in a wide range of human tumor cell lines and in xenograft models of human lung, colon, prostate, pancreas, and breast cancer [1] [2] [3]. Female 4-week-old athymic nude (nu/nu) mice were used as experimental animals. Tivantinib at a dose of 120 mg/kg significantly inhibited tumor burden in the bone of treated animals compared with the controls, starting from 14 to 21 days after cell injection. Increasing doses of tivantinib decreased the number and the extent of osteolytic lesions [6].

Reference:

Protocol

Cell experiment:

Cell lines EBC1, MKN45, SNU638, A549, H460 and HCC827 cells

Preparation method The solubility of this compound in DMSO is >10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for
10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20 °C for several months.

<table>
<thead>
<tr>
<th>Reacting conditions</th>
<th>0 ~ 4 nM; 72 hrs</th>
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**Applications**

Compared with A549, H460 and HCC827 cells, Tyr1234/Tyr1235-phosphorylated and total c-MET were highly expressed in the EBC1, MKN45 and SNU638 cells. In addition, the EGFR-addicted HCC827 cell line showed high expression of c-MET as well, which, however, was driven by EGFR signaling and thus resistant to c-MET inhibitors.

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**Animal experiment [3]:**

**Animal models**

Nude mice bearing 1833/TGL cell xenografts

**Dosage form**

30, 60 and 120 mg/kg, p.o.; q.d.

**Applications**

The appearance of cancer cells in the leg bones showed differences since 11 to 14 days after cell implant, and increased over time, both in control and Tivantinib-treated groups. Of note, the signal from the hindlimbs of Tivantinib-treated (30 mg/kg) mice was very similar to that of control mice as well. At the doses of 60 and 120 mg/kg, Tivantinib induced a dose-dependent delay and a reduction of bone metastatic growth.

**Other notes**

Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

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**Reference:**

