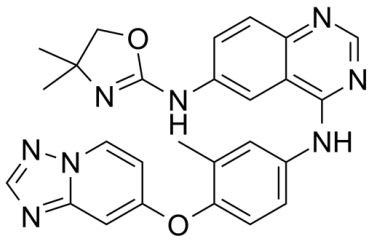
Data Sheet

Product Name:	Tucatinib
Cat. No.:	CS-3906
CAS No.:	937263-43-9
Molecular Formula:	C26H24N8O2
Molecular Weight:	480.52
Target:	EGFR
Pathway:	JAK/STAT Signaling; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : 50 mg/mL (104.05 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

Tucatinib (Irbinitinib; ARRY-380; ONT-380) is a potent and selective **HER2** inhibitor with an **IC_{50}** of 8 nM. IC50 & Target: IC50: 8 nM (HER2)[1] **In Vitro:** Tucatinib (ONT-380) is a potent, selective, ATP-competitive, orally administered small-molecule inhibitor of HER2. Tucatinib has nanomolar activity against purified HER2 enzyme and is approximately 500-fold selective for HER2 versus EGFR in cell-based assays. Tucatinib selectively inhibits the receptor tyrosine kinase HER2 relative to EGFR. In HER2 overexpressing cell lines, Tucatinib blocks proliferation and the phosphorylation of HER2 and its downstream effector, Akt. By contrast, in the EGFR overexpressing cell lines, it weakly inhibits phosphorylation and proliferation, demonstrating that Tucatinib may have potential to block HER2 signaling without causing the toxicities of EGFR inhibition[1]. **In Vivo:** In preclinical studies with intracranial tumor models, treatment of mice with Tucatinib (ONT-380) compared with GW572016 or neratinib shows a survival benefit when each drug is dosed at the maximum-tolerated dose[1]. In the Tucatinib (ARRY-380)-treated-group, 75% of the animals are alive on Day 43. Tucatinib and its active metabolite causes a significant reduction in brain pErbB2 (80%)[2]. Tucatinib (ARRY-380) demonstrates significant dose-related tumor growth inhibition (TGI; 50% at 50 mg/kg/d and 96% at 100 mg/kg/d) with numerous partial regressions (>50% reduction from baseline size) at the higher dose level in 9/12 animals. Tucatinib (50 mg/kg/d) in combination with trastuzumab shows a 98% TGI with complete regressions in 9/12 animals and two partial regressions. At dose of 100 mg/kg/d of Tucatinib in combination with trastuzumab, there is 100% TGI and all animals have complete responses[3].

PROTOCOL (Extracted from published papers and Only for reference)

Animal Administration: [3]Mice: For the SKOV-3 tumor studies, female nude mice are inoculated with cells subcutaneously in the flank. Animals received: doses of Tucatinib ranging up to 200 mg/kg/d, PO; and/or Trastuzumab at 20 mg/kg, IP, Q3D or QW; and/or RP-56976 at 10 mg/kg, IV, Q3D; and/or Bevacizumab at 10 mg/kg, IP, Q4D x3. Tumor size is measured at regular intervals and subsets of animals are monitored for up to 90 days to determine tumor-free survival[3].

References:

[1]. Moulder-Thompson S, et al. Phase 1 Study of ONT-380, a HER2 Inhibitor, in Patients with HER2$^+$ Advanced Solid Tumors, with an Expansion Cohort in HER2+ Metastatic Breast Cancer (MBC). Clin Cancer Res. 2017 Jan 4. pii: clincanres.1496.2016.

[2]. Abstract: In: Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research; 2012 Mar 31-Apr 4; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2012;72(8 Suppl):Abstract nr 852. doi:1538-7445.AM2012-852

[3]. P. Lee, et al. In Vivo Activity of ARRY-380, a Potent, Small Molecule Inhibitor of ErbB2 in Combination with RP-56976. Cancer Research

CAIndexNames:

4,6-Quinazolinediamine, N6-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-N4-[3-methyl-4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl]-

SMILES:

CC1=CC(NC2=C3C=C(NC4=NC(C)(C)CO4)C=CC3=NC=N2)=CC=C1OC5=CC6=NC=NN6C=C5

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