# Product Data Sheet

Product Name: ARRY-380
Cat. No.: GC12478

## Chemical Properties

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|---|---|---|---|
| Cas. No. | 937265-83-3 | | |
| Chemical Name | 6-[5-[(2-methylsulfonylethylamino)methyl]furan-2-yl]-N-[3-methyl-4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl]quinazolin-4-amine | | |
| SMILES | CC1=C(C=CC(=C1)NC2=NC=NC3=C2C=C(C=C3)C4=CC=C(O4)CNCCS(=O)(=O)C)OC5=CC6=NC=NN6C=C5 | | |
| Formula | $C_{29}H_{27}N_7O_4S$ | M.Wt | 569.63 |
| Solubility | ≥ 28.5mg/mL in DMSO | Storage | Store at -20°C |
| General tips | For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months. | | |
| Shipping Condition | Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request. | | |
| Structure | ARRY-380 | | |

## Protocol

### Cell experiment [1]:

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| Cell lines | BT474 cells, NIH-3T3 cells |
| Preparation method | Soluble in DMSO >28.5mg/mL. General tips for obtaining a higher concentration: Please warm the tube at 37℃ for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20℃ for several months. |


***Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com***
***Address: 10292 Central Ave. #205, Montclair, CA, USA***

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| Reacting condition | N/A |
| Applications | ARRY-380 is an orally active, selective, small molecule inhibitor of ErbB2(human epidermal growth factor receptor-2). Its activity (IC50) against ErbB2 enzyme is 14 nM and it inhibits the phosphorylation of ErbB2 in BT474 cells in culture with an IC 50 of 21 nM. ARRY-380 also potently inhibits phosphorylation of AKT(protein kinase B), induces apoptosis and inhibits growth of BT474 cells in vitro. Marked tumor growth inhibition has been demonstrated in NIH-3T3 cells stably transfected with constitutively active ErbB2 kinase (3T3-rErbB2). |

**Clinical experiment [2]:**

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| Disease models | Patients with HER2-positive cancers (including HER2+MBC(Metastatic Breast Cancer)) |
| Dosage form | Dose-escalation cohorts(HER2+ cancer): A starting dose of 25 mg BID(twice-daily)was utilized with additional cohorts at planned dose levels of 50, 100, 200, 300, 500, 650 and 800 mg dosing in a fed state in continuous 28-day cycles (600mg BID was the MTD(maximum tolerated dose)) in Cycle 1.expansion cohort(HER2+MBC): 600mg BID in continuous 28-day cycles in Cycle 2. |


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| Application | ARRY-380 had a lower incidence and severity of diarrhea and rash than that typically associated with current dual HER2/EGFR (Epidermal Growth Factor Receptor) inhibitors and showed notable anti-tumor activity in heavily pretreated HER2+MBC patients, supporting its continued development. |
| 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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References:

[1]. Pheneger, T., et al., In vitro and in vivo activity of ARRY-380: A potent, small molecule inhibitor of ErbB2. Presented at the American Association of Cancer Research 100th Annual Meeting Apr 18-22, 2009; Cancer Res 69 (abstr 1795).

[2]. Moulder SL1, Borges VF2, et al, Phase I 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 Jul 15;23(14):3529-3536. doi: 10.1158/1078-0432.CCR-16-1496. Epub 2017 Jan 4.

## Background

IC50: 8 nM (HER2)

HER2 is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family. Amplification or overexpression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of breast cancer. ARRY-380 is an orally bioavailable inhibitor of the human epidermal growth factor receptor tyrosine kinase ErbB-2 (also called HER2) with potential antineoplastic activity.

In vitro: ARRY-380 is reported to be a reversible, ATP-competitive inhibitor with nanomolar activity against HER2 enzyme. In cell-based assays, ARRY-380 is ~500-fold

selective for HER2 vs. EGFR and is equipotent against truncated p95-HER2 [1].

In vivo: ARRY-380 treatment significantly enhances survival in two ErbB2 driven intracranial tumor xenograft models, with superior activity compared to other ErbB2 agents in these studies. Additionally, ARRY-380 has demonstrated durable clinical activity in heavily pre-treated patients with ErbB2+ MBC. These preclinical and clinical data suggest that ARRY-380 may provide benefit to patients with ErbB2+ MBC with brain metastases. These preclinical and clinical data suggest that ARRY-380 may provide benefit to patients with ErbB2+ MBC with brain metastases and warrants further study [2].

Clinical trial: In a phase 1 clinical trial, 15 patients have been treated in 5 dosing cohorts at doses of 25 to 300 mg BID. No DLTs have been observed and drug-related adverse events have included Grade 1 nausea, rash and fatigue and Grade 2 fatigue in 2 patients at the 200 mg BID dose level. Preliminary PK analyses indicate a trend for increasing Cmax and AUC with increasing dose, a median Tmax of 2 hours and a mean t1/2 of 4.6 hours across all cohorts. Two patients with HER2+ breast cancer have had stable disease for ≥ 4 months with no significant toxicity. One of these two patients had a notable reduction in liver metastases (28%) after 2 cycles of ARRY-380 and is currently on study.These findings indicate ARRY-380 has demonstrated an acceptable safety and PK profile and preliminary signs of clinical benefit. Dose escalation continues to determine the MTD [3].

References:
[1] S.  L. Moulder, V. Borges, S. K. L. Chia, T. Baetz, E. Barrett, J. Garrus, K. Guthrie, C. Kass, E. Laird, J. Lyssikatos, F. Marmsater, E. Wallace. ARRY-380, a Selective HER2 Inhibitor: From Drug Design to Clinical Evaluation. Poster of AACR-NCI-EORTC, Nov 12-16, 2011, San Francisco, CA.
[2] Victoria Dinkel, Deborah Anderson, Shannon Winski, Jim Winkler, Kevin Koch and Patrice Lee.  ARRY-380, a potent, small molecule inhibitor of ErbB2, increases survival in intracranial ErbB2+ xenograft models in mice. Poster available at www.arraybiopharma.com
[3] S.  Chia, T. Baetz, S. D'Aloisio, G. Fernetich, B. Freeman, E. Barrett, C. Kass, J. Kang, B. Sajan, S. Moulder, and J. Garrus. A Phase 1 Study To Assess the Safety, Tolerability and Pharmacokinetics of ARRY-380 – An Oral Inhibitor of HER2. Cancer Res 2009;69(24 Suppl):Abstract nr 5111.

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