# Data Sheet

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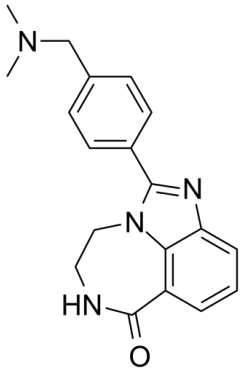
| **Product Name:** | AG14361 |
| **Cat. No.:** | CS-0175 |
| **CAS No.:** | 328543-09-5 |
| **Molecular Formula:** | C19H20N4O |
| **Molecular Weight:** | 320.39 |
| **Target:** | PARP |
| **Pathway:** | Cell Cycle/DNA Damage; Epigenetics |
| **Solubility:** | DMSO : 25 mg/mL (78.03 mM; Need ultrasonic) |




## BIOLOGICAL ACTIVITY:

AG14361 is a potent **PARP-1** inhibitor, with a **$K_i$** of < 5 nM, and in permeabilized SW620 and intact SW620 cells, the **$IC_{50}$**s are 29 nM and 14 nM, respectively. IC50 & Target: Ki: < 5 nM (PARP-1)[1]

IC50: 29 nM (PARP-1, in permeabilized SW620 cells), 14 nM (PARP-1, in intact SW620 cells)[1] **In Vitro:** AG14361 is a potent PARP-1 inhibitor, with a $K_i$ of < 5 nM, and in permeabilized SW620 and intact SW620 cells, the $IC_{50}$s are 29 nM and 14 nM, respectively. AG14361 inhibits the proliferation of human cancer cells, such as A549, LoVo, and SW620 cells, with $GI_{50}$s of 14 μM, 11.2 μM and 20 μM, respectively. Furthermore, AG14361 in combination with NSC 362856 markedly reduces the $GI_{50}$ value of NSC 362856 in LoVo and A549 cells, but does not exert such an effect in SW620 cells[1]. AG14361 suppresses breast cancer cells with $IC_{50}$s of 17 μM and 25 μM for 92 J-wt-BRCA1 and 92 J-sh-BRCA1 cells, respectively. AG14361 induces caspase 3/7 activation and cell cycle abnormalities, and also inhibits NF-κB signaling[2]. AG14361 (0.4 μM) enhances the growth-inhibitory and cytotoxic effects of topoisomerase I poisons, with no obvious effect on the formation and reversal of cleavable complexes, and increases the persistence of camptothecin-induced DNA single-strand breaks[3]. **In Vivo:** AG14361 (5 and 15 mg/kg, i.p.) has no toxicity and does not inhibit the growth of tumor. However, AG14361 markedly enhances NSC 362856 activity against LoVo xenografts and delays tumor growth when combined with NSC 362856. AG14361 (15 mg/kg, i.p.) treatment before irradiation dramaticly increases the sensitivity to radiation therapy of mice bearing LoVo xenografts[1]. AG14361 (30 mg/kg) synergizes lestaurtinib activity on inhibiting breast cancer tumors in allografts[2].

## PROTOCOL (Extracted from published papers and Only for reference)

**Kinase Assay:** [1]The activity of **full-length recombinant human PARP-1** is measured in a reaction mixture containing 20 nM PARP-1, 500 μM $NAD^+$ plus [$^{32}$P]$NAD^+$ (0.1-0.3 μCi per reaction mixture), and activated calf thymus DNA (10 μg/mL) at 25°C; the reaction is terminated after 4 minutes by adding ice-cold 10% (wt/vol) trichloroacetic acid. The reaction product [$^{32}$P]ADP-ribose incorporated into acid-insoluble material is deposited onto Whatman GF/C glass fiber filters with a microfiltration apparatus and quantified with a PhosphorImager. Inhibition of PARP-1 activity by **AG14361 at 0-600 nM** is measured, and the $K_i$ for AG14361 is calculated by nonlinear regression analysis[1]. **Cell Assay:** AG14361 is dissolved in DMSO and then added to 10% fetal bovine serum-containing DMEM.[2]Cell viability assay is performed using a luciferase-coupled ATP quantization assay of metabolically active cells in a 96-well plate and **MTT**. For MTT, **1 to 2 × $10^4$ cells** are plated per one well of a 24-well plate. Target drugs **(AG14361) at various concentrations are dissolved in DMSO and then added to the cells in 10% fetal bovine serum-containing Dulbecco's modified Eagle's medium (DMEM)**, $IC_{50}$ concentration of AG14361 are also added to each well. The final DMSO concentration is kept at 0.1% after the addition to medium. After 48 hr medium is removed and 0.3 mL of 0.1% MTT in phosphate-buffered saline (PBS) is added in each well. After incubation for 30 min in a 37°C $CO_2$ incubator, MTT solution is removed and 0.8 mL of 2-propanol is added. After shaking for 30 min, OD560 is measured using a plate reader. Plating for each time point is done in triplicate[2]. **Animal Administration:** AG14361 is formulated in normal saline.[1]**CD-1 nude mice** bearing palpable, subcutaneous **SW620 or LoVo xenografts** are treated intraperitoneally with **normal saline** (control animals) or **AG14361 (at 5 or 15 mg/kg)** alone daily for 5 days (five mice per group). For

drug combinations, **AG14361 is administered intraperitoneally** daily for 5 days immediately before administering the cytotoxic drug (NSC 362856 at 68 mg/kg orally or CPT-11 at 2.5 mg/kg intraperitoneally) or 30 minutes before applying 2 Gy of x-irradiation locally to the tumor daily for 5 days. Tumor volumes, determined from two-dimensional caliper measurements and the equation $a^2 \times b/2$ (where a is the width and b is the length of the tumor), are presented as median relative tumor volume (RTV). That is, RTV1 is the tumor volume on the initial day of treatment (day 0), and RTV4 is the tumor volume 4 times that on the initial day of treatment. Tumor growth delay is defined as the time to RTV4 in drug-treated or irradiated mice compared with the time to RTV4 in control (vehicle alone) mice[1].

## References:


[1]. Calabrese CR, et al. Anticancer chemosensitization and radiosensitization by the novel poly(ADP-ribose) polymerase-1 inhibitor AG14361. J Natl Cancer Inst. 2004 Jan 7;96(1):56-67.

[2]. Vazquez-Ortiz G, et al. Drug repurposing screen identifies lestaurtinib amplifies the ability of the poly (ADP-ribose) polymerase 1 inhibitor AG14361 to kill breast cancer associated gene-1 mutant and wild type breast cancer cells. Breast Cancer Res. 2014 Jun 24;16(3):R67.

[3]. Smith LM, et al. The novel poly(ADP-Ribose) polymerase inhibitor, AG14361, sensitizes cells to topoisomerase I poisons by increasing the persistence of DNA strand breaks. Clin Cancer Res. 2005 Dec 1;11(23):8449-57.


## CAIndexNames:

Imidazo[4,5,1-jk][1,4]benzodiazepin-7(4H)-one, 2-[4-[(dimethylamino)methyl]phenyl]-5,6-dihydro-

## SMILES:

O=C1NCCN2C3=C1C=CC=C3N=C2C4=CC=C(C=C4)CN(C)C

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