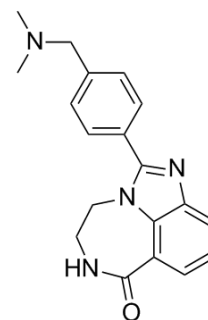


## AG14361

Cat. No.:	HY-12032		
CAS No.:	328543-09-5		
Molecular Formula:	C <sub>19</sub> H <sub>20</sub> N <sub>4</sub> O		
Molecular Weight:	320.39		
Target:	PARP		
Pathway:	Cell Cycle/DNA Damage; Epigenetics		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



### SOLVENT & SOLUBILITY

In Vitro	DMSO : 25 mg/mL (78.03 mM; Need ultrasonic)					
		Solvent Concentration	Mass	1 mg	5 mg	10 mg
	Preparing Stock Solutions	1 mM		3.1212 mL	15.6060 mL	31.2120 mL
		5 mM		0.6242 mL	3.1212 mL	6.2424 mL
10 mM			0.3121 mL	1.5606 mL	3.1212 mL	
Please refer to the solubility information to select the appropriate solvent.						
In Vivo	1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline Solubility: ≥ 2.5 mg/mL (7.80 mM); Clear solution					
	2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (7.80 mM); Clear solution					
	3. Add each solvent one by one: 10% DMSO >> 90% corn oil Solubility: ≥ 2.5 mg/mL (7.80 mM); Clear solution					

### BIOLOGICAL ACTIVITY

Description	AG14361 is a potent PARP-1 inhibitor, with a K <sub>i</sub> of < 5 nM, and in permeabilized SW620 and intact SW620 cells, the IC <sub>50</sub> s are 29 nM and 14 nM, respectively.
IC <sub>50</sub> & Target	PARP-1 0.5 nM (K <sub>i</sub> )
In Vitro	AG14361 is a potent PARP-1 inhibitor, with a K <sub>i</sub> of < 5 nM, and in permeabilized SW620 and intact SW620 cells, the IC <sub>50</sub> 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  $\mu$ M, 11.2  $\mu$ M and 20  $\mu$ M, 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<sup>[1]</sup>. AG14361 suppresses breast cancer cells with  $IC_{50}$ s of 17  $\mu$ M and 25  $\mu$ M 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- $\kappa$ B signaling<sup>[2]</sup>. AG14361 (0.4  $\mu$ M) 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<sup>[3]</sup>. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

#### 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 dramatically increases the sensitivity to radiation therapy of mice bearing LoVo xenografts<sup>[1]</sup>. AG14361 (30 mg/kg) synergizes lestaurtinib activity on inhibiting breast cancer tumors in allografts<sup>[2]</sup>. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

## PROTOCOL

#### Kinase Assay <sup>[1]</sup>

The activity of full-length recombinant human PARP-1 is measured in a reaction mixture containing 20 nM PARP-1, 500  $\mu$ M NAD<sup>+</sup> plus [<sup>32</sup>P]NAD<sup>+</sup> (0.1-0.3  $\mu$ Ci per reaction mixture), and activated calf thymus DNA (10  $\mu$ g/mL) at 25°C; the reaction is terminated after 4 minutes by adding ice-cold 10% (wt/vol) trichloroacetic acid. The reaction product [<sup>32</sup>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<sup>[1]</sup>.

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

#### Cell Assay <sup>[2]</sup>

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  $\times 10^4$  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<sub>2</sub> 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<sup>[2]</sup>.

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#### Animal Administration <sup>[1]</sup>

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<sup>[1]</sup>.

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

## CUSTOMER VALIDATION

- J Mol Med (Berl). 2019 Aug;97(8):1183-1193.

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## REFERENCES

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- [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.
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**Caution: Product has not been fully validated for medical applications. For research use only.**

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