# 产品名称：Abbvie Mcl-1 Inhibitor
# 产品别名：A-1210477

## 生物活性：

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| **Description** | A-1210477 is a potent and selective inhibitor of MCL-1 with a $K_i$ of 0.45 nM. |

| **$IC_{50}$ & Target** | Mcl-1 | Bcl-2 | Bfl-1 | Bcl-W |
|---|---|---|---|---|
| | 0.45 nM (Ki) | 132 nM (Ki) | 660 nM (Ki) | 2280 nM (Ki) |

**In Vitro**

A-1210477 (10 μM) reduces the amount of BIM co-immunoprecipitated with MCL-1 antibody, and triggers MCL-1 elevation in a variety of cancer cell lines, including the breast cancer cell line HCC-1806. A-1210477 inhibits MCL-1-NOXA interactions with an IC50 of approximately 1 μM, while having no effect on BCL-2-BIM or BCL-XL-BCL-XS interactions. The NSCLC cell lines H2110 and H23 are sensitive to A-1210477 with cell viability IC50<10 μM, confirming that A-1210477 can kill MCL-1-dependent cell lines[1]. A-1210477 induces extensive concentration-dependent apoptosis in H929 cells following a brief (4 h) exposure. A-1210477 interacts with MCL-1 with Kd of appr 740 nM. A-1210477 (10 μM) induces extensive mitochondrial fragmentation in a DRP-1-dependent manner[2]. A-1210477 upregulates MCL-1 expression in BRAF-mutant CRC cells and in the melanoma cell line A375 in a dose-dependent manner. A-1210477 releases BAK from MCL-1 and cobimetinib induces BIM that is required for BAX activation[3]. A-1210477 (0, 5, 10 and 15 μM) has minimal effect on cell viability but substantially sensitizes resistant BCL2High NHL cell lines to navitoclax[4].

**Solvent&Solubility**

***In Vitro:***

**DMSO : 10 mg/mL (11.76 mM;** Need ultrasonic)

**$H_2O$ : < 0.1 mg/mL** (insoluble)

| **Preparing Stock Solutions** | Solvent / Mass / Concentration | **1 mg** | **5 mg** | **10 mg** |
|---|---|---|---|---|
| | 1 mM | 1.1764 mL | 5.8821 mL | 11.7642 mL |
| | 5 mM | 0.2353 mL | 1.1764 mL | 2.3528 mL |
| | 10 mM | 0.1176 mL | 0.5882 mL | 1.1764 mL |

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

***In Vivo:***

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 1 mg/mL (1.18 mM); Clear solution

此方案可获得 ≥ 1 mg/mL (1.18 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 10.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

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| | 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline)<br>Solubility: 1 mg/mL (1.18 mM); Suspended solution; Need ultrasonic<br>此方案可获得 1 mg/mL (1.18 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。<br>以 1 mL 工作液为例，取 100 μL 10.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。<br><br>3.请依序添加每种溶剂： 10% DMSO →90% corn oil<br>Solubility: ≥ 1 mg/mL (1.18 mM); Clear solution<br>此方案可获得 ≥ 1 mg/mL (1.18 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。<br>以 1 mL 工作液为例，取 100 μL 10.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。 |
| **References** | [1]. Leverson JD, et al. Potent and selective small-molecule MCL-1 inhibitors demonstrate on-target cancer cell killing activity as single agents and in combination with ABT-263 (navitoclax). Cell Death Dis. 2015 Jan 15;6:e1590.<br>[2]. Milani M, et al. DRP-1 is required for BH3 mimetic-mediated mitochondrial fragmentation and apoptosis. Cell Death Dis. 2017 Jan 12;8(1):e2552<br>[3]. Kawakami H, et al. Mutant BRAF Upregulates MCL-1 to Confer Apoptosis Resistance that Is Reversed by MCL-1 Antagonism and Cobimetinib in Colorectal Cancer. Mol Cancer Ther. 2016 Dec;15(12):3015-3027<br>[4]. Phillips DC, et al. Loss in MCL-1 function sensitizes non-Hodgkin's lymphoma cell lines to the BCL-2-selective inhibitor venetoclax (ABT-199). Blood Cancer J. 2015 Nov 13;5:e368 |

**实验参考：**

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| **Cell Assay** | Adherent cell lines are seeded at 50 000 cells per well in 96-well plates and treated for 48 h with compounds diluted in half-log steps starting at 30 μM and ending at 0.001 μM. Multiple myeloma cell lines are seeded at 15 000-20 000 cells per well and treated similarly. Effects on proliferation and viability are determined using CellTiter-Glo reagent from Promega according to the manufacturer's instructions. $IC_{50}$ values are determined by non-linear regression analysis of the concentration response data. [1] |
| **Kinase Assay** | TR-FRET-binding affinity assays are performed for BCL-2, BCL-XL, and MCL-1 in 4.52 mM monobasic potassium phosphate, 15.48 mM dibasic potassium phosphate, 1 mM sodium EDTA, 0.05% Pluronic F-68 detergent, 50 mM sodium chloride, and 1 mM DTT (pH 7.5) for BCL-XL.6 For MCL-1 assays, GST-tagged MCL-1 (1 nM) is mixed with 100 nM f-Bak, 1 nM Tb-labeled anti-GST antibody, and compound at room temperature (RT) for 60 min. Fluorescence is measured on an Envision plate reader using a 340/35 nm excitation filter and 520/525 (f-Bak) and 495/510 nm (Tb-labeled anti-GST antibody) emission filters. [1] |
| **References** | [1]. Leverson JD, et al. Potent and selective small-molecule MCL-1 inhibitors demonstrate on-target cancer cell killing activity as single agents and in combination with ABT-263 (navitoclax). Cell Death Dis. 2015 Jan 15;6:e1590.<br>[2]. Milani M, et al. DRP-1 is required for BH3 mimetic-mediated mitochondrial fragmentation and apoptosis. Cell Death Dis. 2017 Jan 12;8(1):e2552<br>[3]. Kawakami H, et al. Mutant BRAF Upregulates MCL-1 to Confer Apoptosis Resistance that Is Reversed by MCL-1 Antagonism and Cobimetinib in Colorectal Cancer. Mol Cancer Ther. 2016 |

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