Pomalidomide

Cat. No.: HY-10984

CAS No.: 19171-19-8

Molecular Formula: $C_{13}H_{11}N_3O_4$

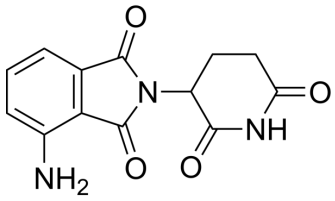
Molecular Weight: 273.24

Target: Ligands for E3 Ligase; Apoptosis; Molecular Glues

Pathway: PROTAC; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (182.99 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.6598 mL	18.2989 mL	36.5979 mL
	5 mM	0.7320 mL	3.6598 mL	7.3196 mL
	10 mM	0.3660 mL	1.8299 mL	3.6598 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 0.5% CMC-Na >> 0.5% Tween-80
   Solubility: 10 mg/mL (36.60 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (9.15 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (9.15 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Pomalidomide, the third-generation immunomodulatory agent, acts as molecular glue. Pomalidomide interacts with the E3 ligase cereblon and induces degradation of essential Ikaros transcription factors.

IC_{50} & Target

Cereblon

In Vitro

Pomalidomide also inhibits Whole Blood TNF-α with IC_{50} of 25 nM[1]. Exposure of lymphoma cells to Pomalidomide (CC-4047) leads to 40% decrease in cell proliferation when compared with vehicle-treated controls. Pomalidomide inhibits by

40% the DNA synthesis of Raji cells (P=0.036)[2]. In both $CD4^+$ and $CD8^+$ cells, Pomalidomide (CC-4047) is the most potent IL-2-elevator, followed by CC-6032 and CC-5013. Pomalidomide is significantly more potent than CC-5013 at elevating IL-2, IL-5, and IL-10, and slightly more potent than CC-5013 at elevating IFN-γ[3].

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

In Vivo

The administration of Pomalidomide (CC-4047) for two consecutive days before mAb therapy enhances the antitumor activity of Rituximab and doubled the median survival of lymphoma-bearing mice. Statistically, significant differences are observed between animals treated with Rituximab versus Pomalidomide+Rituximab. The median survival time of animals treated with Pomalidomide and Rituximab is longer (median survival, 74 days; 95% CI, 70-78) than those treated with Rituximab monotherapy (median survival, 38 days; 95% CI, 26-50; log-rank test, P=0.002). The administration of CC-5013 or Pomalidomide for two consecutive days leads to a significant increase in the number of circulating NK cells as shown by flow cytometry analysis, in lymphoma-bearing SCID mice[2]. Following a 50 mg/kg PO administration of Pomalidomide (POM) to rats, unbound concentrations in blood reach a C_{max} value of 1100±82 ng/mL at 4.6±2.4 hours, with a concomitant $AUC_{(0-10)}$ value of 6800±2000 ng?hr/mL. Unbound POM in the brain, however, has a C_{max} value of 430±63 ng/mL at 4.1±1.5 hours and an $AUC_{(0-10)}$ value of 2700±740 ng?hr/mL, giving an unbound AUC_{brain} to AUC_{blood} ratio of 0.39±0.03. These values are consistent with excellent blood-brain-barrier penetration. The results obtained in this study are consistent with those seen in a concurrent study looking at whole brain POM content following its oral administration to mice[4].

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PROTOCOL

Cell Assay [2]

Lymphoma cell lines are placed in 96-well plates (1×10^5 cells per well) and exposed to escalating concentrations of CC-5013, Pomalidomide (2.5, 5, 10, 20, and 40 μg/mL), or vehicle control single agents or in combination with Rituximab or Trastuzumab (isotype), at a final antibody concentration of 10 μg/mL. The final concentration is adjusted to 200 μL with 10% RPMI. The cell lines are incubated at 37°C and 5% CO_2 for 24 and 48 hours. Following 24 or 48 hours, 1 μCi per well of [^{3}H]-thymidine is added and cells are incubated for 18 hours more. Cells are then harvested using the Harvest system into the 96-well glass filters and [^{3}H]-thymidine uptake is measured using an automated scintillation counter. Each experiment is done in triplicate at three different times; results are presented as the mean of counts per minute (cpm) at 24 and 48 hours±SD[2].

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Animal Administration [2][4]

Mice[2]

Six- to 8-week-old SCID mice are used for this purpose. On day 0, all the animals receive 1×10^6 Raji cells via tail vein injection. After 72 hours of tumor engraftment, the animals are divided into seven cohorts. The first cohort (group A) serve as control and receive no treatment. Groups B and C consist of animals treated with either CC-5013 (0.5 mg/kg) or Pomalidomide (0.5 mg/kg) given i.p. on days +3, +4, +8, +9, +13, +14, +18, and +19. Groups D and E are treated with Rituximab or Trastuzumab (isotype control) monotherapy given via tail vein injection at 10 mg/kg on days +5, +10, +15, and +20. Finally, groups F and G consist of animals treated with Rituximab in combination with CC-5013 (group E) or Pomalidomide (group G). IMiDs are given i.p. for two consecutive days before each dose of Rituximab. After completion of therapy, animals are observed for a period of 90 days. The end point of the study is survival defined as the time for the development of limb paralysis. Animals that reach the end point or survived after 3 months of observation are sacrificed by cervical dislocation. Pathologic examination of all organs (liver, lung, and brain) is done to detect any residual disease. The experiments are repeated in three separate occasions.

Rats[4]

A total of 3 male CD-IGS rats are used. Pomalidomide is administered as a single PO administration via the stomach cannula, at 50 mg/kg (5 mL/kg) in a 0.5% carboxymethylcellulose/0.25% Tween 80 suspension formulation. Microdialysate is collected in a cooling fraction collector, set at 4°C at intervals of 25 minutes for 10 hours after dosing. To calculate AUC, the corrected concentration of each sample is multiplied by the interval over which the sample is collected; in this case 25 minutes, and divided by 60 minutes per hour. The sum of these values represented the total AUC value over the specified time range. To generate graphs, the concentration at each time point is plotted at the mid-point of each collection interval. Microdialysates are collected at the specified time points and analyzed for Pomalidomide concentration using a LC-MS/MS assay, within 12 hours.

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CUSTOMER VALIDATION

- Cell. 2021 Oct 14;184(21):5375-5390.e16.
- Cancer Cell. 2022 Aug 26;S1535-6108(22)00372-5.
- Nat Cancer. 2022 May;3(5):595-613.
- Nat Commun. 2022 Sep 10;13(1):5324.
- Nat Commun. 2017 May 22;8:15398.

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REFERENCES

[1]. Zhu YX, et al. Molecular mechanism of action of the immune-modulatory drugs, thalidomide, lenalidomide and pomalidomide in multiple myeloma. Leuk Lymphoma. 2013 Apr;54(4):683-7.

[2]. Hernandez-Ilizaliturri FJ1, et al. Immunomodulatory drug CC-5013 or CC-4047 and rituximab enhance antitumor activity in a severe combined immunodeficient mouse lymphoma model. Clin Cancer Res. 2005 Aug 15;11(16):5984-92.

[3]. Schafer PH, et al. Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs. J Pharmacol Exp Ther. 2003 Jun;305(3):1222-32.

[4]. Li Z, et al. Pomalidomide shows significant therapeutic activity against CNS lymphoma with a major impact on the tumor microenvironment in murine models. PLoS One. 2013 Aug 5;8(8):e71754.

[5]. Lu J, et al. Hijacking the E3 Ubiquitin Ligase Cereblon to Efficiently Target BRD4. Chem Biol. 2015 Jun 18;22(6):755-63.

[6]. Liu D, et al. Tumour necrosis factor-α inhibits hepatic lipid deposition through GSK-3β/β-catenin signaling in juvenile turbot (Scophthalmus maximus L.). Gen Comp Endocrinol. 2016 Mar 1;228:1-8.

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