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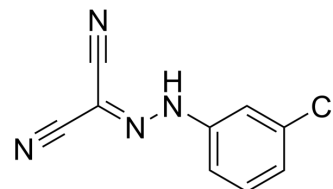
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## CCCP

|                    |  |
|--------------------|--|
| Cat. No.:          | HY-100941  |
| CAS No.:           | 555-60-2   |
| Molecular Formula: | C <sub>9</sub> H <sub>5</sub> ClN <sub>4</sub>   |
| Molecular Weight:  | 204.62   |
| Target:            | STING; IFNAR; Mitochondrial Metabolism; Bacterial; Apoptosis; Oxidative Phosphorylation; PINK1/Parkin                |
| Pathway:           | Immunology/Inflammation; Metabolic Enzyme/Protease; Anti-infection; Apoptosis; Others; Autophagy; Neuronal Signaling |
| Storage:           | Powder    -20°C    3 years<br>4°C    2 years<br>In solvent   -80°C    2 years<br>-20°C    1 year                     |



## SOLVENT & SOLUBILITY

|   |   |  |           |            |            |
|---|---|--|-----------|------------|------------|
| In Vitro  | DMSO : 50 mg/mL (244.36 mM; Need ultrasonic)  |  |           |            |            |
|   | H <sub>2</sub> O : < 0.1 mg/mL (ultrasonic;warming;heat to 60°C) (insoluble)  |  |           |            |            |
|   | Preparing Stock Solutions   | <div><div>Solvent</div><div>Concentration</div><div>Mass</div></div> | 1 mg      | 5 mg       | 10 mg      |
|   |   | 1 mM   | 4.8871 mL | 24.4355 mL | 48.8711 mL |
|   |   | 5 mM   | 0.9774 mL | 4.8871 mL  | 9.7742 mL  |
|   |   | 10 mM  | 0.4887 mL | 2.4436 mL  | 4.8871 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<br>Solubility: ≥ 2.5 mg/mL (12.22 mM); Clear solution |  |           |            |            |

## BIOLOGICAL ACTIVITY

|                           |  |
|---------------------------|--|
| Description               | CCCP is an oxidative phosphorylation (OXPHOS) uncoupler. CCCP induces activation of PINK1 leading to Parkin Ser65 phosphorylation <sup>[1]</sup> .   |
| IC <sub>50</sub> & Target | STING <sup>[1]</sup><br>IFN-β <sup>[1]</sup>   |
| In Vitro                  | CCCP inhibits IFN-β production induced by various types of the STING pathway activators. CCCP suppresses the phosphorylation of STING, TBK1, and IRF3 via disrupting the association of STING and TBK1. CCCP inhibits activation of STING and its downstream signaling molecules, TBK1 and IRF3, but not STING translocation to the perinuclear region. CCCP |

impairs the interaction between STING and TBK1 and concomitantly triggers mitochondria fission. Importantly, the knockout of the crucial mitochondria fission regulator Drp1 restored the STING activity, indicating that CCCP down-modulates the STING pathway through DRP1-mediated mitochondria fragmentation. The protonophore CCCP that disrupts membrane potential suppresses the DMXAA-triggered STING signaling pathway. CCCP drastically suppresses the production of IFN- $\beta$  in DMXAA-treated RAW264.7 cells and MEFs<sup>[1]</sup>.

As low as 1  $\mu$ M CCCP is enough to induce mitocytosis. In cells treated with 10  $\mu$ M CCCP, which is the dose used for inducing mitophagy, mitocytosis is barely induced. Mechanistically, mitocytosis requires positioning of damaged mitochondria at the cell periphery, which occurs because damaged mitochondria avoid binding to inward motor proteins<sup>[4]</sup>.

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

#### In Vivo

The same dosage of 3 mg/kg.bw each of CCCP and PPEF is used. In both the cases 1 log reduction is observed in the bacterial load. However, when 3 mg/kg.bw of PPEF is used in combination with 3 mg/kg.bw of CCCP, 6 log<sub>10</sub> reduction is observed in the bacterial count. The developed model validates the enhanced antibacterial activity of combination therapy<sup>[2]</sup>. <sup>99m</sup>Tc-MIBI signals in the hearts of SD rats administered CCCP (4 mg/kg intraperitoneally) or vehicle is also measured. <sup>99m</sup>Tc-MIBI signals decrease in rat hearts administered CCCP, and the ATP content, as measured by <sup>31</sup>P magnetic resonance spectroscopy, decreased simultaneously. To investigate whether CCCP decreased the <sup>99m</sup>Tc-MIBI signals in rats, we analyzed the radioisotope activity of excised heart tissue from rats administered CCCP. At 180 min after <sup>99m</sup>Tc-MIBI injection, the <sup>99m</sup>Tc-MIBI signals from the hearts in the CCCP group are significantly lower than those in the vehicle group<sup>[3]</sup>. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

## PROTOCOL

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

MEFs (5 $\times$ 10<sup>5</sup>), Raw264.7 cells (1 $\times$ 10<sup>6</sup>), and HeLa cells stable expressing STING (1.5 $\times$ 10<sup>5</sup>) are stimulated with DMXAA (100  $\mu$ g/mL) for 2 or 3 h, or transfected with c-di-GMP (5  $\mu$ M), cGAMP (5  $\mu$ g/mL), or poly (dA:dT) (2  $\mu$ g/mL) for 6 h. CCCP (50  $\mu$ M) is co-treated with DMXAA (100  $\mu$ g/mL), or treated for the last 5 h in case of treatment of c-di-GMP or poly (dA:dT)<sup>[1]</sup>. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

#### Animal Administration <sup>[2][3]</sup>

Mice<sup>[2]</sup>

Female Balb/c mice n=6, per dosing group weighing 20-25 g are rendered neutropenic with 2 intraperitoneal injections of cyclophosphamide 150 mg/kg.bw and 100 mg/kg.bw on 4 days and 1 day prior to bacterial infection. 0.1 mL of the 10<sup>6</sup> CFU/mL bacterial suspension is injected into right posterior thigh muscle. After 2 h post-infection mice are treated with PPEF (3 mg/kg.bw), CCCP (3 mg/kg.bw) and in combination PPEF+CCCP (3 mg/kg.bw+3 mg/kg.bw) dissolved in 0.1 mL sterile water by single bolus intravenous injection. Twenty-four hours after antibacterial administration, the mice are humanely sacrificed. Right thigh muscles from each mouse are aseptically collected, homogenized and serially diluted and processed for quantitative cultures.

Rats<sup>[3]</sup>

Rats are randomly divided into three groups. One group is euthanized 15 min after a dose of 12.5 MBq (337.8  $\mu$ Ci) <sup>99m</sup>Tc-MIBI injection (n=6). The other two groups are administered 4 mg/kg CCCP (CCCP group; n=7) or vehicle (vehicle group; n=7) by intraperitoneal (i.p.) injection 90 min after the same dose of <sup>99m</sup>Tc-MIBI injection and are euthanized after an additional 90 min (180 min after the <sup>99m</sup>Tc-MIBI injection). Hearts are excised and weighed, and radioactivity is measured between 110 and 170 keV with an auto-well gamma counter. <sup>99m</sup>Tc-MIBI signals are corrected for physical decay (half-life=6 h). MCE has not independently confirmed the accuracy of these methods. They are for reference only.

## CUSTOMER VALIDATION

- Nature. 2019 Nov;575(7782):375-379.
- Cell Res. 2021 Jun;31(6):703-712.
- Cell Metab. 2023 Jan 3;35(1):200-211.e9.

- Nat Commun. 2024 Jan 23;15(1):686.
- J Clin Invest. 2020 Jun 1;130(6):3253-3269.

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## REFERENCES

- [1]. Haifeng Jiao, et al. Mitocytosis, a migrasome-mediated mitochondrial quality-control process. Cell. 2021 May 27;184(11):2896-2910.e13.
- [2]. Kwon D, et al. Carbonyl cyanide 3-chlorophenylhydrazone (CCCP) suppresses STING-mediated DNA sensing pathway through inducing mitochondrial fission. Biochem Biophys Res Commun. 2017 Aug 30. pii: S0006-291X(17)31704-7.
- [3]. Sinha D, et al. Synergistic efficacy of Bisbenzimidazole and Carbonyl Cyanide 3-Chlorophenylhydrazoncombination against MDR bacterial strains. Sci Rep. 2017 Mar 17;7:44419.
- [4]. Kawamoto A, et al. Measurement of technetium-99m sestamibi signals in rats administered a mitochondrial uncoupler and in a rat model of heart failure. PLoS One. 2015 Jan 16;10(1):e0117091.
- [5]. Kondapalli C, et al. PINK1 is activated by mitochondrial membrane potential depolarization and stimulates Parkin E3 ligase activity by phosphorylating Serine 65. Open Biol. 2012 May;2(5):120080.

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

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