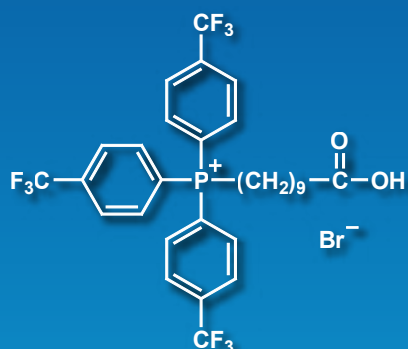
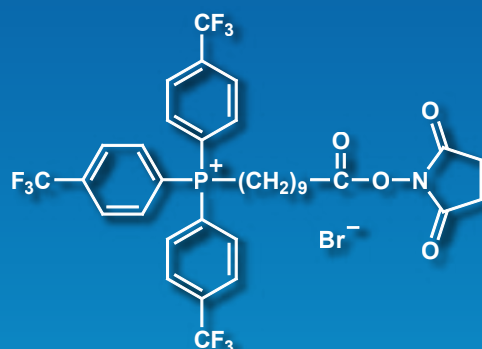


Mitochondria-Targeting Carriers that Do Not Induce Mitochondrial Uncoupling and Depolarization Even at High Concentrations



(9-Carboxynonyl)tris[4-(trifluoromethyl)phenyl]phosphonium Bromide
200mg [C4077]



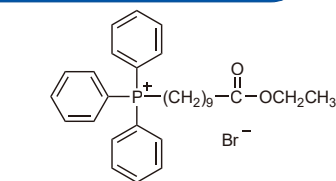
[10-[(2,5-Dioxopyrrolidin-1-yl)oxy]-10-oxodecyl]tris[4-(trifluoromethyl)phenyl]phosphonium Bromide
50mg / 200mg [D6410]

Advantages

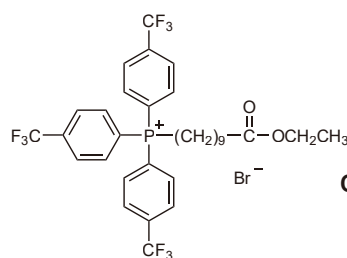
- Less likely to induce mitochondrial uncoupling ¹⁾
- Less likely to induce depolarization
- Lower toxicity than non-trifluoromethyl-substituted triphenylphosphonium (TPP⁺)
- Carboxylic acid and NHS ester forms — easily conjugatable to fluorescent dyes and other compounds

Reference Data 1

Comparison of the functionality of unsubstituted TPP⁺ and CF₃-substituted TPP⁺

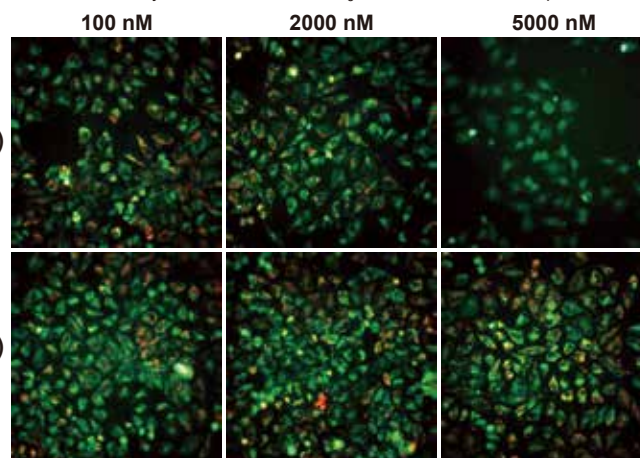


Unsubstituted TPP⁺ compound (1)



CF₃-substituted TPP⁺ compound (2)

Figure. Changes in Mitochondrial Membrane Potential Induced by Unsubstituted and CF₃-Substituted TPP⁺ Compounds



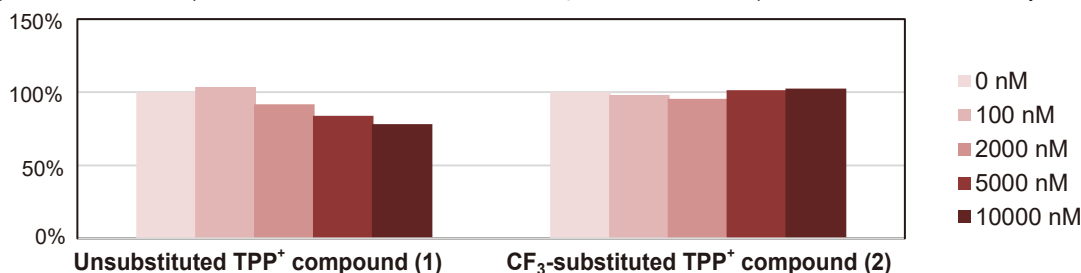
HeLa cells were cultured overnight with either the unsubstituted TPP⁺ compound (1) or the CF₃-substituted TPP⁺ compound (2) at the indicated concentrations. Mitochondrial membrane potential was observed using JC-1. Compound 2 maintained the membrane potential even at 5000 nM, resulting in red staining. Compound 1 showed almost no detectable red color.

- References**
- 1) C. A. Kulkarni, R. J. Kerns, *et al.*, *J. Med. Chem.* **2021**, *64*, 662. <https://doi.org/10.1021/acs.jmedchem.0c01671>
 - 2) M. AbuEid, M. B. Dwinell, *et al.*, *iScience.* **2022**, *25*, 105670. <https://doi.org/10.1016/j.isci.2022.105670>
 - 3) D. Huang, Y. He, *et al.*, *J. Med. Chem.* **2022**, *65*, 9955. <https://doi.org/10.1021/acs.jmedchem.2c00640>
 - 4) W. Chyan, R. J. Radford, *et al.*, *Proc. Natl. Acad. Sci. USA.* **2014**, *111*, 143. <https://doi.org/10.1073/pnas.1310583110>

Mitochondrial-Targeting Carriers that Do Not Induce Mitochondrial Uncoupling and Depolarization Even at High Concentrations

Reference Data 2

Figure. Concentration-dependent cell survival of unsubstituted and CF₃-substituted TPP⁺ compounds, measured via MTT assay

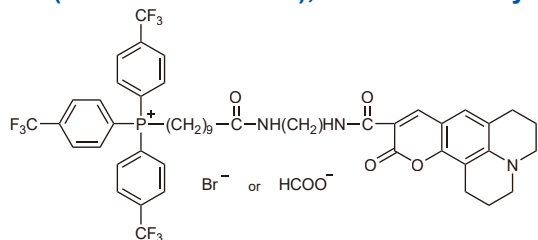


HeLa cells were cultured overnight with the indicated concentrations of unsubstituted (1) and CF₃-substituted (2) TPP⁺ compounds. Relative cell numbers were measured using an MTT assay.

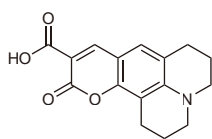
The relative cell count for each condition was calculated as a ratio of the survival rate of cells cultured without additives. Compound 2 maintained high survival rates at all concentrations, while compound 1 showed a concentration-dependent decrease in survival rate.

Reference Data 3

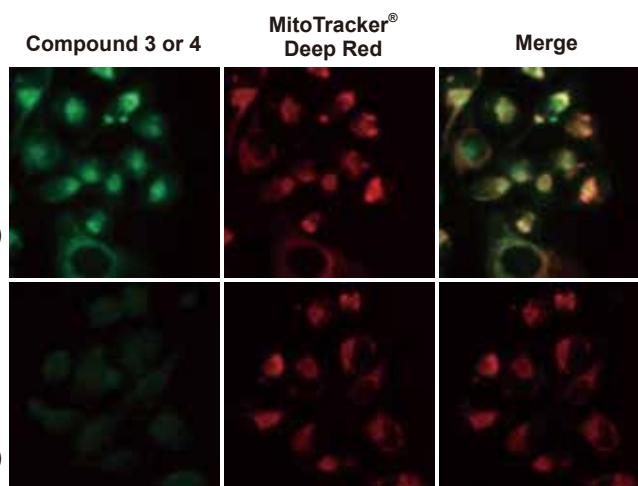
Confirmation that CF₃-substituted TPP⁺ compounds accumulate in mitochondria using Coumarin 343 (Product No. C2899), a fluorescent dye conjugated with CF₃-substituted TPP⁺.



CF₃-substituted TPP⁺-Coumarin 343 conjugate (3)



Coumarin 343 (4)



Top row: HeLa cells were co-stained with a CF₃-substituted TPP⁺ coumarin 343 conjugate and MitoTracker[®] Deep Red.

Bottom row: HeLa cells were co-stained with Coumarin 343 (4) and MitoTracker[®] Deep Red.

Staining was observed at an excitation wavelength of 470 nm and an emission wavelength of 525 nm for Coumarin 343, while MitoTracker[®] Deep Red was observed at an excitation wavelength of 640 nm and an emission wavelength of 690 nm. Compound 4 showed almost no staining; however, the staining patterns of compound 3 and MitoTracker[®] Deep Red largely overlapped, suggesting that they target the same cellular regions.

† MitoTracker[®] is a registered trademark of Molecular Probes, Inc.

‡ The mitochondrial targeting of molecules conjugated with TPP⁺ is known to be influenced by the charge and hydrophobicity of the molecular species.⁴⁾

We confirmed that, while accumulating in mitochondria, CF₃-substituted TPP⁺ compounds are less likely to induce mitochondrial depolarization and exhibit lower cytotoxicity than unsubstituted TPP⁺ compounds. There are reports of cases where metformin modified with CF₃-substituted TPP⁺ showed reduced *in vivo* toxicity while maintaining antitumor efficacy,²⁾ and cases where a CF₃-substituted TPP⁺-based phenylbutyric acid (PBA) conjugate displayed greatly enhanced mitochondrial accumulation compared to PBA alone, resulting in strong tumor growth inhibition.²⁾ These compounds are also valuable for studying heart failure, ischemia-reperfusion injury, and Alzheimer's disease, as reactive oxygen species (ROS) arising from mitochondrial dysfunction or abnormalities are implicated in these conditions.

Related Products

Coumarin 343

200mg [C2899]

TMRM Perchlorate (= Tetramethylrhodamine Methyl Ester Perchlorate)

10mg / 50mg [T3608]

JC-1 Mitochondrial Membrane Potential Assay Kit

1kit [J0043]

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