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# SYNTHESIS OF NEW NITRONES TARGETING MITOCHONDRIA WITH LOW CYTOTOXICITY

THÉTIOT-LAURENT, Sophie, DELEHEDDE, Caroline, ESGULIAN, Mathieu, CASSIEN, Mathieu,  
CULCASI, Marcel, PIETRI, Sylvia

Aix Marseille Université – Institut de Chimie Radicalaire - France

sophie.thetiot-laurent@univ-amu.fr

**Introduction:** The free radicals (FR) occurrence in biological signalling or as pathologies triggers is well-documented and the design of specific scavengers to limit oxidative stress is enthralling. Because FR become inactivated upon addition to nitrones, efforts have focused on developing alpha-phenyl-*N*-tert-butyl-nitronone derivatives (PBNs) with promising pre-clinical data. To improve efficacy, a new generation of nitrones derived from 2-(diethoxyphosphoryl)-*N*-(benzylidene)propan-2-amine-*N*-oxide (PPNs) incorporating an antioxidant framework, gave rise to multipotent drugs exhibiting EPR-spin-trapping properties<sup>1</sup>. As mitochondrial dysfunction is involved in many disorders, efforts have been concentrated on developing tools (pH probes<sup>2,3</sup>) or pharmacological agents targeting-mitochondria.

**Material-Methods:** A series of mitochondria-targeted PPNS was synthesized based on the improved biocompatibility of P-containing nitrones and the expected benefits of introducing a cationic vector. Spin-adducts EPR-parameters toward biologically-relevant FR were established. Cytotoxicity was determined on cells and mitochondria-permeation assessed in isolated rat organs.

**Results:** a) synthesis of a series of vectorized PPNS with different linkers and vectors, b) spin-adducts EPR-parameters determination with various FR, c) comparative cytotoxicity studies in various normal and cancer cells and mitochondria permeation according to vectors.

**Conclusion:** New mitochondria-targeting nitrones appeared as lower cytotoxic alternative to the commonly used mito-PBN and were safely applied for investigating the anticancer-mechanism of new drugs impacting mitochondria.

## References

1. Cassien, M.; Petrocchi, C.; Thétiot-Laurent, S.; Robin, M.; Ricquebourg, E.; Kandouli, C.; Asteian, A.; Rockenbauer, A.; Mercier, A.; Culcasi, M.; Pietri, S. *Eur. J. Med. Chem.* 2016, 119, 197-217.
2. Culcasi, M.; Casano, G.; Lucchesi, C.; Mercier, A.; Clément, J.-L.; Pique, V.; Michelet, L.; Krieger-Liszkay, A.; Robin, M.; Pietri, S. *J. Med. Chem.* 2013, 56, 2487-2499.
3. Culcasi, M.; Thétiot-Laurent, S.; Atteia, A.; Pietri, S. *Mitochondrial Medicine: Volume II Methods and Protocols, in Methods in Molecular Biology (MIMB)*, Walker, J. M., ed. Humana Press, Springer Protocols. 2015, pp135-147.