SYNTHESIS OF NEW NITRONES TARGETING MITOCHONDRIA WITH LOW CYTOTOXICITY

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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-butylnitrone 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[1]. As mitochondrial dysfunction is involved in many disorders, efforts have been concentrated on developing tools (pH probes[2,3]) or pharmacological agents targeting-mitochondria.

Materiel-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.

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