INVESTIGATION OF A POSSIBLE MITOCHONDRIAL MECHANISM OF ACTION OF NAPHTOQUINONE-ANACARDIC ACID HYBRIDS COMPOUNDS AGAINST TRYPANOSOMIASIS.

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In a search for new effective and low-cost drug-hybrids for Neglected Tropical Diseases, we aimed at designing and synthezing a focused combinatorial chemical library of 15 naphtoquinone-anacarcic acid hybrids to treat trypanosomiases. By following a merging strategy, the naphthoquinone scaffold derived from an in-house hit anti-trypanosomatid compound, named B6, has been combined to the natural phenols of cardanol derivatives, a renewable food production waste product from *Anacardum Occidentale*. In particular, B6 has been identified (i) to inhibit trypanosomal glyceraldehyde-3-phpsphate dehydrogenase (GAPDH) (IC_{50} of 7.25 μM); (ii) to exhibit potent trypanocidal activity (EC_{50} of 80 nM against *T. brucei rhodesiense*); (iii) to possess a promising selectivity index (SI of 74); (iv) to generate oxygen radicals in the trypanosomal mitochondrion.[1] Furthermore, the anacardic acid derivatives, extracted from cashew nut shell liquid (CNSL), are endowed of many biological activities. They proved to be micromolar inhibitors (IC_{50} 28.0 μM) of GAPDH of *Trypanosoma cruzi*.[2] Some of the newly synthetized compound have been preliminary tested against *T. brucei* GAPDH, showing an interesting inhibitory activity (micromolar range).[3]

Given the profile of the starting hit compounds, we decide to evaluate their mechanism of action at the mitochondrial level, as the drug design strategy is inspired to be a synergistic inhibition of energy metabolism. All compounds are designed on the ubiquinone-ubiquinol scaffold, in order to inhibit its electron transporter activity in the respiratory chain pathway. In particular, the naphtoquinon moiety is hypothesized to target Trypanosome Alternative Oxidase (TAO), the key respiratory enzyme of the T. brucei mitochondrion, and the phenol moiety on glycerol-3-phosphate-dehydrogenase. Thus, all the compounds have been tested against *T. brucei* for the cell viability and investigated for their mitochondrial mechanism of action**.**

References

[1] Pieretti, S. et al., 2013.
[2] Pereira, J. M. et al., 2008.
[3] Prati, F. et al., 2015