DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF ANTIPARASITIC DINITROANILINE-ETHER PHOSPHOLIPID HYBRIDS

Magoulas George E.,[a] Roussaki Marina,[a] Fotopoulou Theano[a], Santarem Nuno.[b] Barrias Emile,[c] Pöhner Ina,[h] Luelmo Sara,[b] Afroudakis Pantelis,[a] Tejera Nevado Paloma,[d] Eick Julia,[d] Bifeld Eugenia,[d] Corral María J.,[e] Jiménez-Antón María Dolores,[e] Ellinger Bernhard,[f] Kuzikov Maria,[f] Fragiadaki Irini,[g] Scoulica Effie,[g] Gul Sheraz,[f] Clos Joachim,[d] Prousis Kyriakos C.[a], Torrado Juan J.,[e] Alunda José María,[e] Wade Rebecca C.,[h] de Souza Wanderley,[c] da Silva Cordeiro Anabela,[b] Calogeropoulou Theodora[a]

a. National Hellenic Research Foundation, Institute of Chemical Biology, Athens, Greece;
b. i3S and IBMC Universidade do Porto, Porto, Portugal
c. Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil;
d. Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany
e. Universidad Complutense de Madrid, 28040 Madrid, Spain.
f. Fraunhofer Institute for Translational Medicine and Pharmacology, Hamburg, Germany
g. University of Crete, Heraklion, Crete, Greece;
h. Heidelberg Institute for Theoretical Studies (HITS), Heidelberg, Germany

In the context of our ongoing research on the design and synthesis of new antiparasitic agents against Neglected Tropical Diseases (NTDs) with improved potency and safety,[1,2] a series of nine novel ether phospholipid-dinitroaniline hybrids were prepared. The compounds were evaluated for their *in vitro* antiparasitic activity against *L. infantum, L.donovani, L. amazonensis, L. major* and *L. tropica* promastigotes, *L. infantum* and *L. donovani* intracellular amastigotes, *Trypanosoma brucei brucei* and against different developmental stages of *Trypanosoma cruzi*. The nature of the oligomethylene spacer between the dinitroaniline moiety and the phosphate group, the length of the side chain substituent on the dinitroaniline and the choline or homocholine head group were found to affect both the activity and the toxicity of the hybrids. The early ADMET profile of the derivatives did not reveal major liabilities. The derivative bearing an 11-carbon oligomethylene spacer, a butyl side chain and a choline head group, was the most potent analogue of the series. It exhibited a safe toxicological profile and a broad spectrum antiparasitic profile with micromolar activity against the intracellular amastigotes of the two *L. infantum* strains, against *T. brucei* and against *T. cruzi* Y strain epimastigotes, intracellular amastigotes and trypomastigotes. Computational analysis of binding sites and docking indicated that the interaction of the compound with trypanosomatid *α*-tubulin may contribute to its mechanism of action.

References

1. T. Calogeropoulou *et al. J. Med. Chem.* **2008**, *51*, 897-908.
2. G.E. Magoulas *et al. Molecules*. **2021**, *26*, 4204.

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