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Abstract

Design, Synthesis and Structure—Activity Relationships of a Phenotypic Small Library against Protozoan Infections †

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Protozoan infections (*Plasmodium* spp., *Leishmania* spp., and *Trypanosoma* spp.) remain one of the most pressing global health concerns, affecting billions of people and producing unsustainable economic burdens [1]. Current pharmacotherapy is inadequate, and appropriate technologies should be exploited to identify novel drug candidates in a cost- and time-effective manner. Accordingly, an effective strategy could exploit privileged structures to generate libraries of high-quality compounds, combined with the feasibility of a phenotypic assay, and the early evaluation of the ADME-tox profile.

On these bases, we generated an 18-membered combinatorial library by fast assembling phenothiazine, biphenyl and phenylpiperazine anti-protozoan privileged scaffolds via a Huisgen cycloaddition. Thanks to NMTrypI [2] and SPHTI [3] screening facilities, we tested **1–18** against *T. brucei* and *cruzi*, *L. infantum* and *donovani*, and *P. falciparum*, and counter-screened selectivity against mammalian cells (L6 and A549). In parallel, ADME-tox properties were assessed by testing hERG, CYP inhibition, and mitochondrial viability.

Despite the small number of synthesized compounds, this strategy led to the successful identification of interesting hits with promising profiles. Particularly, **4** and **9** showed IC_{50} values of 3.8 and 3.4 μM against *T. cruzi*, together with an excellent selectivity (SI (IC_{50} (L6)/IC_{50} (*Tc*)) >48 and % A549 cell growth at 10 μM > 100%).

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conceived the experiments. M.K., R.B., C.B.M. and L.H.F.-J. performed whole-cell assays. S.G. and B.E. carried out the early tox-profiling.

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References

1. Field, M.C.; Horn, D.; Fairlamb, A.H.; Ferguson, M.A.; Gray, D.W.; Read, K.D.; De Rycker, M.; Torrie, L.S.; Wyatt, P.G.; Wyllie, S.; Gilbert, I.H. Antitrypanosomatid Drug Discovery: An Ongoing Challenge and a Continuing Need. *Nat. Rev. Microbiol.* **2017**, *15*, 217–231.
2. The Anti-Parasitic Activity and the Early-Toxicity Profiling of the Compounds Were Developed within the International Collaborative Effort of the European Union's Seventh Framework Programme under Grant Agreement n° 603240 (NMTrypI—New Medicines for Trypanosomatidic Infections). Available online: http://fp7-nmtrypi.eu (accessed on 16 October 2017).
3. SPHTI—Swiss Tropical & Public Health Institute, Parasite Chemotherapy Unit. Available online: https://www.swisstph.ch/en/ (accessed on 16 October 2017).