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Abstract

Design of Potential Antimalarial Agents Based on a Homology Model of *Plasmodium falciparum* Glucose-6-Phosphate Dehydrogenase †

Caterina Pont [1], Nelson Alencar [2,3], Irene Sola [1], María Linares [4], Luca Di Palma [1], Carla Barbaraci [1], Cristina Sampedro [1], Jordi Juárez-Jiménez [2], Paloma Abad [4,5], Susana Pérez-Benavente [5], Jerónimo Lameira [3], José M. Bautista [4,5], F. Javier Luque [2] and Diego Muñoz-Torrero [1,*]

1 Laboratory of Pharmaceutical Chemistry (CSIC Associated Unit), Faculty of Pharmacy and Food Sciences and Institute of Biomedicine (IBUB), University of Barcelona (UB), Av. Joan XXIII 27-31, E-08028 Barcelona, Spain; aitak1989@gmail.com (C.P.); irenesola872@gmail.com (I.S.); lucadipalma92@gmail.com (L.D.P.); carlabarbaraci@rocketmail.com (C.B.); cristinasampedrogarcia@gmail.com (C.S.);

2 Department of Nutrition, Food Science and Gastronomy, Faculty of Pharmacy and Food Sciences, and IBUB, University of Barcelona, Av. Prat de la Riba 171, E-08921 Santa Coloma de Gramenet, Spain; nelsonalencar@gmail.com (N.A.); jordi.juarez@gmail.com (J.J.-J.); fjluque@ub.edu (F.J.L.)

3 Laboratório de Planejamento e Desenvolvimento de Fármacos-LPDF, Instituto de Ciências Exatas e Naturais-ICEN, Universidade Federal do Pará—UFPA, Av. Augusto Correa, Nº 1-Bairro: Guamá, Cep: 66.075-900 Belém-Pará, Brazil; lameira@ufpa.br

4 Research Institute Hospital 12 de Octubre, Avda. de Cordoba s/n, 28041 Madrid, Spain; marialinares@vet.ucm.es (M.L.); paloma.abadg@gmail.com (P.A.); jmbau@ucm.es (J.M.B.)

5 Department of Biochemistry and Molecular Biology, Universidad Complutense de Madrid, Facultad de Veterinaria, Ciudad Universitaria, 28040-Madrid, Spain; susipz@ucm.es

* Correspondence: dmunoztorrero@ub.edu

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There currently exists a dire need for safe and inexpensive new antimalarial drugs, which are effective against multiple life cycle stages of *Plasmodium falciparum*, and act through mechanisms that differ from those of the available drugs to prevent drug resistance. The enzyme glucose-6-phosphate dehydrogenase (G6PD) of *P. falciparum* has emerged as a promising target for antimalarial drug discovery, due to its key role in parasite development and survival and its protective effect against malaria infection observed under human G6PD deficiency conditions. Here, we describe the construction of a homology model of *Pf*G6PD, which has enabled the identification of key structural differences as compared with the human enzyme. We have exploited these changes to rationally design a novel family of substrate analog-based inhibitors that can be endowed with selectivity towards *Pf*G6PD. Several compounds display micromolar affinity, good selectivity, and low cytotoxicity, but weak antiplasmodial activity in phenotypic assays, likely as a result of a poor internalization of the compounds in the parasite cell. Future hit optimization should focus on improving the physicochemical/pharmacokinetic properties of this class of compounds.

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