

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

**Probing salicylamide bioisosteric replacement in the design of Plasmodium Falciparum dihydroorotate dehydrogenase (pfDHODH) inhibitors**

**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/147167> since

*Publisher:*

Amean Chemical Society

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

# Probing salicylamide bioisosteric replacement in the design of *Plasmodium Falciparum* dihydroorotate dehydrogenase (*p*fDHODH) inhibitors.

Marco L. Lolli,<sup>\*1</sup> Donatella Boschi,<sup>1</sup> Ulf J. Nilsson,<sup>2</sup> Ingela Fritzson,<sup>3</sup> Anders P. Sundin<sup>2</sup> and Salam Al-Karadaghi.<sup>4</sup>

<sup>1</sup> DSTF - Science and Drug Technologies Department, University of Turin, Via Pietro Giuria, 9 – 10125 Torino, Italy.

<sup>2</sup> Centre for Analysis and Synthesis, Department of Chemistry, Lund University, PO Box 124, 221 00 Lund, Sweden.

<sup>3</sup> Active Biotech AB, PO Box 724, 220 07 Lund, Sweden.

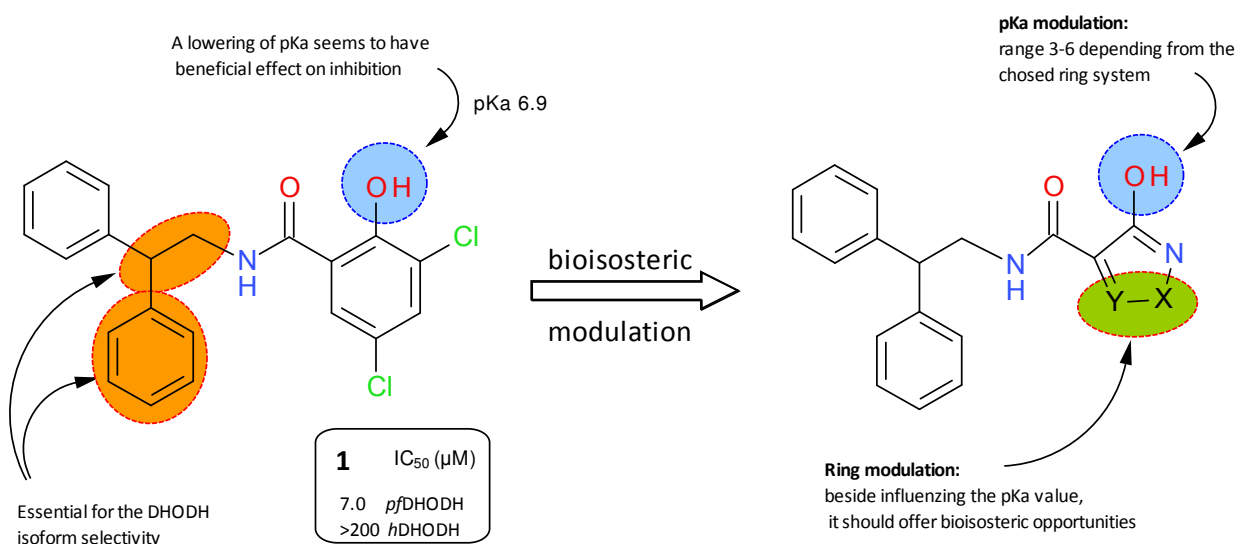
<sup>4</sup> Center for Molecular Protein Science, Department of Chemistry, Lund University, PO Box 124, 221 00 Lund, Sweden.

@ marco.lolli@unito.it

Malaria causes great suffering with estimated annual mortalities of over 800.000 people, principally in Africa and Asia. A major problem in the fight against malaria is resistance to current drug treatments and several strategies have been employed to combat this problem. Beside these, inhibitors of the newly validated target *dihydroorotate dehydrogenase* (DHODH) could play an important role as future single or combinatory treatment of malaria. A continuing program of ours investigates *Plasmodium Falciparum* dihydroorotate dehydrogenase (*p*fDHODH) inhibitors based on N-substituted salicylamides scaffold.<sup>1</sup> Recently, the most active model of the series (**1**) showed low micromolar range activity over *p*fDHODH together with a quite interesting selectivity over human DHODH (*h*DHODH).<sup>1</sup>

Isosteric replacement is a widely used approach within *Medicinal Chemistry* for improving properties of a lead compound such as bioavailability, selectivity, and potency.<sup>2</sup> Since 2006, the *Med Chem* group at DSTF directed its efforts towards the investigation of hydroxylated pentatomic heterocyclic systems in order to create a sophisticated tool able to iso/bioisosterically mimic the carboxylic group, both electronically and sterically.<sup>3</sup> More recently, attentions were directed in the application of this technology to other acidic systems.<sup>4</sup>

In this poster, the salicylamide moiety of highly selective *p*fDHODH where identified as a possible occasion for a bioisosteric modulation. The synthesis, the dissociation constant (pKa) as well as the preliminary *p*fDHODH *in vitro* inhibition assays are presented and discussed.



## References

- Ingela Fritzson, Paul T. P. Bedingfield, Anders Sundin, Glenn McConkey, Ulf J. Nilsson *N-Substituted salicylamides as selective malaria parasite dihydroorotate dehydrogenase inhibitors*, *MedChemComm* **2011**, 2(9), 895-898.
- Meanwell NA. *Synopsis of some recent tactical application of bioisosteres in drug design*. *J Med Chem*. **2011**, 54(8), 2529-91.
- Lolli ML, Giordano C, Pickering DS, Rolando B, Hansen KB, Foti A, Contreras-Sanz A, Amir A, Fruttero R, Gasco A, Nielsen B, Johansen TN. *4-Hydroxy-1,2,5-oxadiazol-3-yl moiety as bioisoster of the carboxy function. Synthesis, ionization constants, and molecular pharmacological characterization at ionotropic glutamate receptors of compounds related to glutamate and its homologues*. *J Med Chem*. **2010**, 53(10), 4110-8.
- Lolli ML, Giorgis M, Tosco P, Foti A, Fruttero R, Gasco A. *New inhibitors of dihydroorotate dehydrogenase (DHODH) based on the 4-hydroxy-1,2,5-oxadiazol-3-yl (hydroxyfurazanyl) scaffold*. *Eur J Med Chem*. **2012**, 49, 102-9.