Targeting the *human* Dihydroorotate Dehydrogenase (*h*DHODH) by a Scaffold Hopping Bioisosteric approach using Hydroxy-azoles

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The human isoform of the dihydroorotate dehydrogenase enzyme (hDHODH) catalyses the fourth step of the de novo pyrimidine synthesis, a biosynthetic pathway enhanced in proliferating cells such as activated T-lymphocytes, and cancer cells. The efficacy of hDHODH inhibitors in the treatment of rheumatoid arthritis and multiple sclerosis has been evaluated, and leflunomide (Arava®) and its active metabolite teriflunomide (Aubagio®) have been already approved for therapy. Brequinar is another well-studied hDHODH inhibitor, but it was unsuccessfully evaluated against a number of tumour categories due to several drug-related side effects.[1]
Inside the inhibitor-binding site, conventionally divided into five subsites, two different binding-modes have been described in literature.[2]. Starting from structural information from both brequinar and teriflunomide, a scaffold hopping approach was applied using hydroxy-azoles system, affording a new series of products able to establish additional interactions with subsites **3** and **4**. The general model of these compounds (**1**) is a hydroxylated heterocycle linked to a biphenyl system through an amide bond.[3] According to molecular modelling studies, the deprotonated acidic moiety should interact with residues Arg**136** and Gln**47** of subsite **2** (Brequinar-like binding-mode[2]), while the biphenyl system may establish lipophilic interactions with residues of subsites **1** and **5** (*Figure* **a**). New compounds showed inhibitory activity on recombinant *h*DHODH with IC_{50} values in the nanomolar range and inhibition of human T-cell proliferation comparable to brequinar and teriflunomide. Our theoretical design, modelling, synthesis, SAR, X-Rays and biological assays, as well as cell viability, proliferation, cytotoxicity and immunosuppression results are presented in detail.

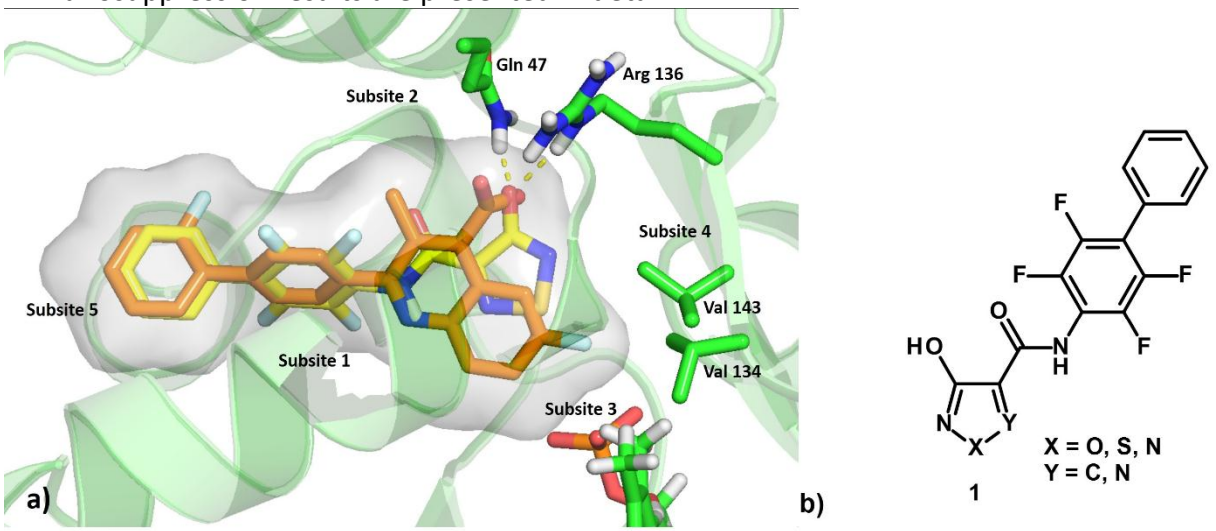

Fig. 1. a) The lipophilic patch of the hDHODH binding site in complex with brequinar (green) and our best compound (yellow). b) General structure of new inhibitors (1).

References

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