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In Vitro Myeloid Differentiation Using a New Generation of Potent *Human* Dihydroorotate Dehydrogenase Inhibitors

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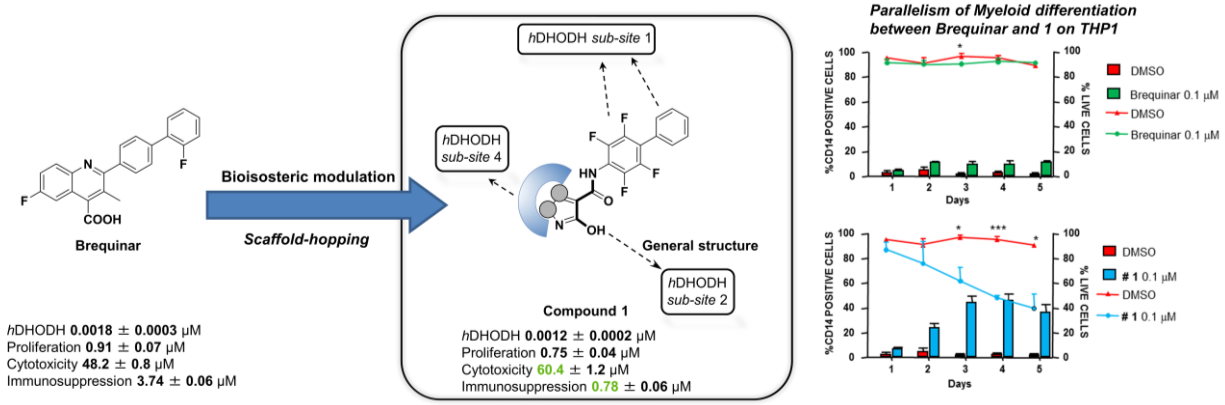
Human dihydroorotate dehydrogenase (*h*DHODH) catalyses the fourth step in the de novo pyrimidine biosynthesis where dihydroorotate (DHO) is converted to orotate (ORO).(1) Being already validated as therapeutic target for the treatment of autoimmune diseases, as rheumatoid arthritis or multiple sclerosis,(2) quite recently *h*DHODH was associated to acute myeloid leukaemia (AML),(3) a disease where the standard of intensive care has not changed in the last four decades.(4) The success of brequinar (Figure 1), one of the most potent known *h*DHODH inhibitors, to induce in vitro and in vivo differentiation in mouse AML models,(3) highly encourages researches to design *h*DHODH inhibitors with better drug-like profiles. Starting from brequinar, by applying innovative scaffold-hopping replacement, we recently designed a first generation of potent *h*DHODH inhibitors presenting nM activity on the isolated *h*DHODH. (5) Following that early affords, in this occasion we are presenting a second generation of inhibitors (Figure 1) able to reach the brequinar *h*DHODH potency levels. Compound **1**(6), the best of two series, was found able to restore the myeloid differentiation in leukaemia cell lines (U937 and THP-1) at concentrations one digit lower than those achieved in experiments with brequinar. Theoretical design, modeling, synthesis, SAR, X-ray crystallographic data, biological assays, preliminary Drug-Like proprieties and in vivo toxicity are here presented and discussed.



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