Acute myelogenous leukemia (AML) is a clinically devastating disease with dismal prognosis and survival rate. Efforts to identify new therapeutic targets to overcome myeloid differentiation blockade were largely unsuccessful until the breakthrough study in 2016 (Sykes et al., 2016, Cell 167, 171–186) who demonstrated that brequinar, the most potent dihydroorotate dehydrogenase (hDHODH) inhibitor known, was able to enable myeloid differentiation in vivo on mouse AML models. In this lecture will be presented the state-of-the-art designing paradigms (including synthesis, SAR, crystallographic and molecular modelling studies, biological assays (cell viability, proliferation, cytotoxicity, immunosuppression and myeloid differentiation), and physicochemical characterization) that we have recently followed during the discovery a new generation of hDHODH inhibitors based on the hydroxypyrazole-pyridine scaffold. The most representative compound the series, although being comparable to brequinar in terms of hDHODH inhibitory activity, is able to restore the myeloid differentiation in leukemia cell lines U937 at a 1-log lower concentration compared to its lead brequinar, causing a massive death of cells. To our knowledge, this compound is one of the most potent hDHODH inhibitor so far discovered and, because its safety profile, a valuable candidate for in vivo experiments.