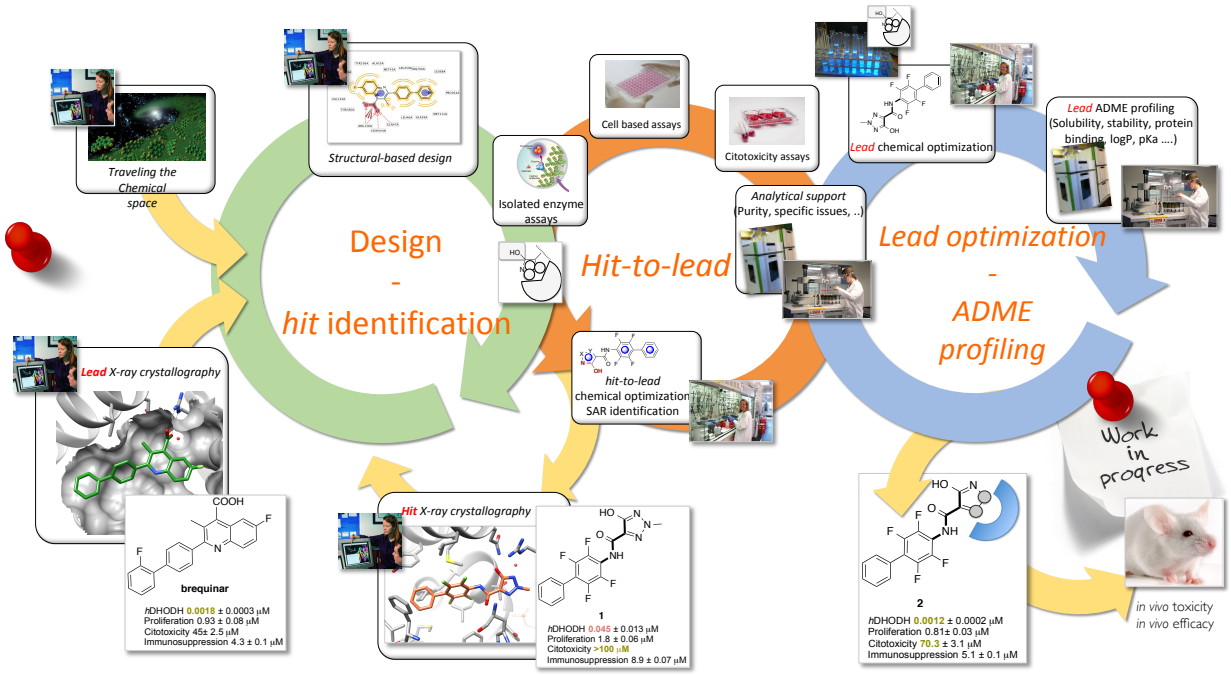
Drug Design at MEDSynth group

The design of biologically active molecules is a challenging task that expose the **chemist** to a multicultural environmental, opening by reflex his/her mind. In the following the pathways we recently followed for the design of potent *Dihydroorotate Dehydrogenase* inhibitors…...

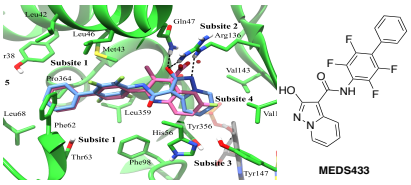


Master Thesis - Organic synthesis / Medicinal Chemistry

Targeting Leukemia

Acute myelogenous leukemia (AML) is a clinically most 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 by Sykes et al. (Cell **2016**, 167, 171) who demonstrated that inhibition of human *dihydroorotate dehydrogenase* (*h*DHODH) enables myeloid differentiation in both human and mouse AML models.

What we have done so far. Our best candidate, designed by a bioisosteric approach, **MEDS433** is able to inhibit *h*DHODH at IC_{50} **0.0012 ± 0.0002 µM** , just comparable to *brequinar*. However, it is able to restore the myeloid differentiation in leukemia cell lines at a one-log lower concentration compared to the lead brequinar, causing a massive death of leukemic cells. To our knowledge, **MEDS433** is one of the most potent and safe *h*DHODH inhibitor so far discovered.



What we have still to do.

- Improve drug-like properties (solubility, protein binding, …)
- Design PET tracer ligands based on **MEDS433** (*New York University*)
- Design a third generation compound series.
- Move the best candidate to *in vivo* experiments (soon….).

Bibliography/project status

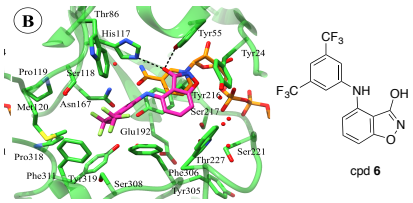
Sainas, Stefano; Lolli, Marco *et al* *"Targeting myeloid differentiation using potent 2-hydroxypyrazolo[1,5-a]pyridine scaffold-based human dihydroorotate dehydrogenase (hDHODH) inhibitors]*. Medicinal Chemistry **2018**, 61 (14), 6034-6055.

Master Thesis - Organic synthesis / Medicinal Chemistry

Targeting Prostatic cancer

The **aldo-keto reductase 1C3 (AKR1C3)** isoform plays a vital role in the biosynthesis of androgens and is considered an attractive target in prostate cancer (PCa). No AKR1C3-targeted agent has to date been approved for clinical use. Flufenamic acid and indomethacine are non-steroidal anti-inflammatory drugs known to inhibit AKR1C3 in a non-selective manner as COX off-target effects are also observed.

What we have done so far. Following a scaffold hopping approach, we designed a new series focused around an acidic hydroxybenzoisoxazole moiety, which was rationalised to mimic the benzoic acid role in the flufenamic scaffold. The most promising compound of the series (6) was found to be highly selective (up to 450-fold) for AKR1C3 over the 1C2 isoform with minimal COX1 and COX2 off-target effects. Crystallography supported the biochemical data.



What we have still to do.

- Design a third generation compounds able to reach nM activity
- Design PET tracer ligands based on cpd **6** (*New York University*)
- Improve drug-like properties (solubility, protein binding, …)
- Move the best candidate to in vivo experiments.

Bibliography/project status

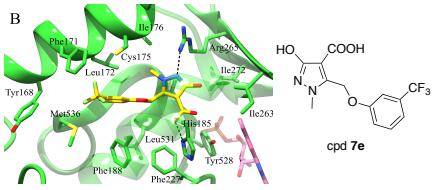
Pippione Agnese; Lolli, Marco *et al Potent and selective aldo-keto reductase 1C3 (AKR1C3) inhibitors based on the benzoisoxazole moiety: Application of a bioisosteric scaffold hopping approach to flufenamic acid.* European Journal of Medicinal Chemistry **2018**, 150, 930-945.

Master Thesis - Organic synthesis / Medicinal Chemistry

Targeting Malaria

Malaria is one of the world's "*biggest three infectious diseases*" (HIV/AIDS, tuberculosis, and malaria) that kill millions of people every year. Effective vaccines have not been developed and drug resistance to almost every known antimalarial agent has compromised the effectiveness of control programs. *Plasmodium falciparum* dihydroorotate dehydrogenase (*Pf*DHODH) has been clinically validated as a target for **antimalarial** drug discovery, as a triazolopyrimidine class inhibitor (DSM265) is currently undergoing clinical development.

What we have done so far. We have identified new hydroxyazole scaffold-based *Pf*DHODH inhibitor **7e** active in the low µM range (IC_{50} 2.8 µM) on the enzyme. Cpd **7e** showed clear selectivity over human isoform (*h*DHODH IC_{50} > 200 µM), low cytotoxicity, and retained micromolar activity in *P. falciparum*-infected erythrocytes.



What we have still to do.

- Design a second generation compounds able to reach nM activity
- Improve drug-like properties (solubility, protein binding, …)
- Move the best candidate to *in vivo* experiments.

Bibliography/project status

Pippione Agnese; Lolli, Marco *et al Hydroxyazole scaffold-based Plasmodium falciparum dihydroorotate dehydrogenase inhibitors: synthesis, biological evaluation and X-ray structural studies.* European Journal of Medicinal Chemistry, **2018**, *in press*

Research lines:

The group is focused on *oncologic* (**Leukemia, Prostatic** and **Breast Cancer**), *Neglected diseases* (**Malaria, Lehismaniosis**) and *neurodegenerative* (**Gaba, Glu**) targets.

for recent advances, see www.medsynth.unito.it

Collaborations:

The group is involved in many collaborations with groups both European as worldwide. In particular, we use intensively the **Erasmus program** to exchange Master students with our European partners. In these case, the student is involved in the commune research line that join the two groups.

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.. and more.

Contact:

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