Štipendija za doktorski študij »Pharmaceutical and Biomolecular Sciences" na Univerzi v Torinu (Rok za prijavo: 6. 4. 2018)

Dear colleagues,

At the **PhD programme in Pharmaceutical and Biomolecular Sciences** of the **University of Turin** - UniTO (Italy) we have reserved scholarships for **International students**. We are looking for motivated students for the upcoming academic year, starting **October 1, 2018**, to be involved in the project named:

Targeting leukemia myeloid differentiation using innovative human Dihydroorotate Dehydrogenase (hDHODH) inhibitors

Inside the three years Ph.D, the candidate will be involved in *state-of-the-art* drug design research, exposing him/herself to the design of *in vivo* effective preclinical candidates for *acute myelogenous leukemia* (AML). In the specific, he/she will asked to design and synthesize the target *h*DHODH inhibitors. During the three years PhD, he/she will spend his/her research at the *Department of Science and Drug Technology* of UniTo (tutor Marco L. Lolli) and at least 6-12 months in a second research group, selected inside the connection we have with European/India/USA groups. He/she will fully involved in the group research, tutoring Master student figures, participating to project writing and disseminating the project results in international meetings.
Keywords: Medicinal Chemistry, Drug Design, advanced organic synthesis, Bioisosterism, NMR, MS, Molecular modeling, ADME.

The candidate.
The optimal candidate must be well motivated, in presence of a **Master degree in Chemistry** or similar and with **basic experience of *Practical Organic synthesis***, performed during the Master thesis. Because the application is quite competitive, **he/she must have acquired a top valuation** during his/her Master owing a CV already **enriched by some publication in Medicinal Chemistry field** (also poster are counted in this case).

The Project.
The project is focused on *human* Dihydroorotate Dehydrogenase (*h*DHODH), a flavin-dependent mitochondrial enzyme involved in *de novo* pyrimidine biosynthesis. Being already validated as a therapeutic target for the treatment of autoimmune diseases, such as *rheumatoid arthritis* and *multiple sclerosis,* recently *h*DHODH was associated (Sykes et al., **2016**, Cell 167, 171–186) with *acute myelogenous leukemia* (AML), a disease where the standard of intensive care has not changed in the last four decades. In the spring **2017**, by applying a scaffold hopping approach, we described a new class of potent and selective *h*DHODH inhibitors based on a hydroxyazole scaffolds (Stefano Sainas *et al Eu. J. Med. Chem.* 2017, (129), 287-302). Following a similar strategy, in the following we introduced a novel class of inhibitors based on other hydroxyazoles systems as an unusual bioisostere of carboxylic group. The most interesting compound the series was able to reach *in vitro* the *brequinar h*DHODH potency levels. Owing low cytotoxicity at cellular level, moving of leukemia cells was found able to specifically induce a massive death already at 0.1 mM, i.e., at a 1-log inferior concentration compared to *brequinar*. The DHODH project will be orally

presented at the **New Orleans American Society Meeting ACS meeting** https://plan.core-apps.com/acsnola2018/abstract/8af5604b51d341b62607bc1c43442212 on March 21th, 2018.
During the PhD project the candidate will move such outstanding results to *in vivo* AML animal models, designing a third generation of ADME optimized compounds.

Where.
The Ph.D research will be performed at **MEDSynth**, is a *medicinal chemistry* group born in the 2012 in occasion of the winning of 7FP project, at the *Dept Science and Drug Technology* of the University of Turin. The MEDSynth group is able to offer a complete technological platform, from the *in silico* design, throughout the synthesis until the *in vitro* / *in vivo* pharmacological characterization, for the design of ***preclinical drug candidates***. See here www.medsynth.unito.it for details on out research and news.
DHODH-AML project financial support.
The *h*DHODH - AML project is financially supported by **a three years grant** inside the *science and technology cooperation programme between Italy and the kingdom of Sweden* (see here: https://www.esteri.it/mae/resource/garegemellaggi/2017/06/bando_italia_svezia_2018_2020.pdf, PIs Marco L. Lolli and Salam Al-Karadaghi).

Ph.D details.
Position Type: PhD program
Salary: €10'000 - €20'000.
Application opening: March 6, 2018
Application deadline: April 6, 2018
Position Category: Pharmaceutical and Bimolecular Sciences
How to apply: http://dott-sfb.campusnet.unito.it/do/home.pl
Application details: https://en.unito.it/postdegree/phd/pharmaceutical-and-biomolecular-sciences

If you think to be an eligible candidate that want to be involved in this project, please **contact us sending your cv** (marco.lolli@unito.it) so, in case, we can support your application. Put in the message subject" *DHODH-AML PhD scholarship*" so that we can immediately track you.

Marco L. Lolli

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