BIOINSPIRED ACETYLENIC MOLECULES FOR ANTITUBERCULOSIS DRUG DEVELOPMENT

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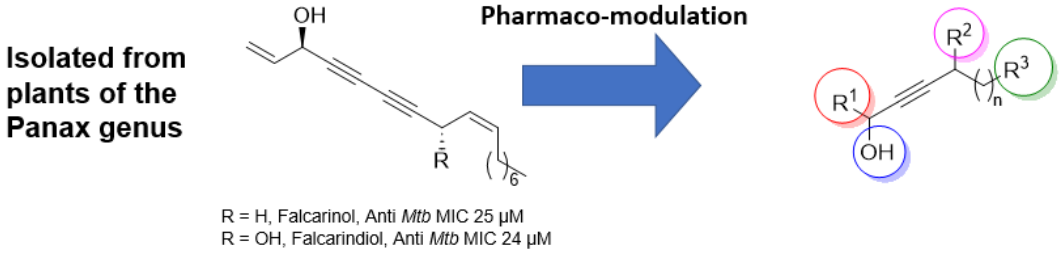
Tuberculosis (TB) is caused by the airborne bacteria *Mycobacterium tuberculosis (Mtb)* and has claimed more than 1.3 million lives in 2022, making it one of the deadliest infectious diseases in the world[1]. Although TB has almost been wiped out in developed countries, it remains an important threat in underdeveloped communities and immunocompromised individuals. Since 1921, the only prophylactic treatment remains the Bacille Calmette-Guérin (BCG) vaccine, showing variable efficiency among individuals. Currently available curative treatment requires a 6-months drug combination of isoniazid, rifampicin, pyrazinamide and ethambutol, becoming increasingly ineffective with the rising burden of antibiotic resistance. Over the last 50 years, only three new drugs (pretomanid, delamanid and bedaquiline) were approved highlighting the urgent need to enrich the therapeutic arsenal against TB[2].

This project aims to develop novel anti-TB drugs taking inspiration from nature as a source of bioactive compounds, in particular Lipidic AlkynylCarbinols (LACs). These compounds are characterized by a long carbon backbone containing at least one triple bond in α position of a primary or secondary carbinol. Some of them isolated from medicinal plants and fungi show only modest *in vitro* toxicity against pathogenic bacteria however, given their unusual chemical structure, they can be expected to act through an original and unexplored mode of action (MOA)[3]. Two synthetic hits were already selected.



R = H, Falcarinol, Anti *Mtb* MIC 25 µM
R = OH, Falcarindiol, Anti *Mtb* MIC 24 µM

Fig. 1 : Structure of falcarinol and falcarindiol[4] and their biological activities and the planned pharmaco-modulation

This multidisciplinary project will face four main objectives: **Obj. 1:** Expand the chemical library and improve the previous hits (selectivity index = IC_{50}/MIC); **Obj. 2:** improve their physico-chemical and pharmacokinetic properties (solubility, half-life) using a prodrug strategy; **Obj. 3:** elucidate their unknown MOA and target and **Obj. 4:** validate their therapeutic efficacy in a mouse model of TB infection.

References:

[1]World Health Organization (WHO), Global Tuberculosis Report, **2022**.

[2]Furin J., Cox H., Pai M. Tuberculosis, *Nature*, **2019**, 393, 1642-1656.

[3]Margaux Bossuat *et al*. Phenyl dialkynylcarbinols, a Bioinspired Series of Synthetic Antitumor Acetylenic Lipids, *J. Med. Chem.*, **2023**, 66, 13918-13945.

[4]Li H *et al.* Anti-mycobacterial diynes from the Canadian medicinal plant *Aralia nudicaulis*, *J. Ethnopharmacol.*, **2012,** 140, 141-144.