Preparation of pyrazolo[3,4-*b*]pyridines and integration in late-stage functionalization

Supervisors: **Dr. Maïwenn JACOLOT** and **Prof. Florence POPOWYCZ**

Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), UMR 5246
Institut National des Sciences Appliquées de Lyon, Université Lyon 1, CNRS, CPE Lyon
Bâtiment Lederer, CampusLyonTech La Doua, F-69621 Villeurbanne, France
E-mail : maïwenn.jacolot@insa-lyon.fr; florence.popowycz@insa-lyon.fr

Context of the PhD proposal: The PhD position described below will be funded by the Chinese Scholarship Council and expected to start in October 2025 for 42 months. The candidate will be hosted at ICBMS (Université de Lyon - INSA Lyon).

Scientific content:

A multitude of aromatic heterocycles have a bicyclic nitrogen structure. Among these, the pyridine-[*b*]-bicyclic unit is extremely common, and consists of a pyridine fused to another aromatic ring. The pyrazolo[3,4-*b*]pyridine ring has a pyridine ring attached to a pyrazole. This motif is present in a multitude of compounds with biological activity, such as anxiolytics,[1] antifungals,[2] anti-leishmaniases[3] and even as anti-influenza agents[4] (Figure 1). For our part, in collaboration with the Microbiology, Adaptation and Pathogenesis team (UMR5240), we have been able to show that certain molecules have bactericidal or bacteriostatic properties.

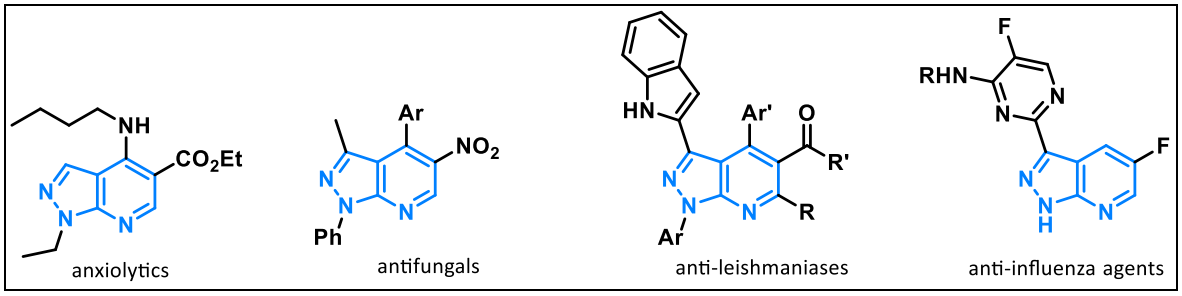


Figure 1. Examples of bio-active pyrazolo[3,4-b]pyridines

Despite the importance of the pyrazolo[3,4-*b*]pyridine nucleus present in many active pharmaceutical ingredients (APIs) covering a wide range of biological activities, synthetic transformations on this scaffold are few and far between. **Today's challenges lie on the development of more eco-compatible methods (saving steps and atoms) while offering more chemical diversity**. In response to this ambitious synthetic challenge and given the interest of these bicyclic nitrogen structures for the

[1] (a) Patel, J. B.; Malick, J. B.; Salama, A. I.; Goldberg, M. E. *Pharmacol. Biochem. Behav.* **1985**, *23*, 675–680. (b) Bare, T. M.; McLaren, C. D.; Campbell, J. B.; Firor, J. W.; Resch, J. F.; Walters, C. P.; Salama, A. I.; Meiners, B. A.; Patel, J. B. *J. Med. Chem.* **1989**, *32*, 2561–2573.
[2] Quiroga, J.; Villarreal, Y.; Gálvez, J.; Ortíz, A.; Insuasty, B.; Abonia, R.; Raimondi, M.; Zacchino, S. *Chem. Pharm. Bull.* **2017**, *65*, 143–150.
[3] Anand, D.; Yadav, P. K.; Patel, O. P. S.; Parmar, N.; Maurya, R. K.; Vishwakarma, P.; Raju, K. S. R.; Taneja, I.; Wahajuddin, M.; Kar, S.; Yadav, P. P. *J. Med. Chem.* **2017**, *60*, 1041–1059
[4] Bandarage, U. K.; Clark, M. P.; Perola, E.; Gao, H.; Jacobs, M. D.; Tsai, A.; Gillespie, J.; Kennedy, J. M.; Maltais, F.; Ledeboer, M. W.; Davies, I.; Gu, W.; Byrn, R. A.; Nti Addae, K.; Bennett, H.; Leeman, J. R.; Jones, S. M.; O'Brien, C.; Memmott, C.; Bennani, Y.; Charifson, P. S. *ACS Med. Chem. Lett.* **2017**, *8*, 261–265

development of a drug candidate, this project will focus on the development of **innovative** and **direct metallo-catalysed late stage functionalization methodologies on this bicyclic scaffold** (Figure 2).

Based on our preliminary work on Suzuki cross-coupling reaction on 4-chloro-5-carbethoxy pyrazolopyridine,[5] other pallado-catalyzed reactions such as **Sonogashira** and **Heck** will be examined for C-4 functionalization. Another part of the project, dedicated to the **decarboxylative coupling** in C-5 position will be performed in collaboration with COBRA-Rouen.

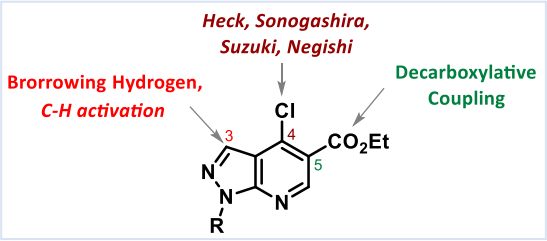
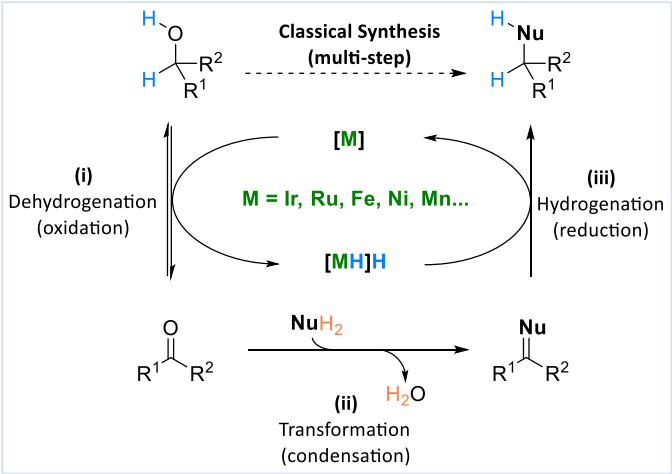


Figure 2. Pyrazolopyridine functionalizations

Finally, functionalization in C-3 position will be envisioned using the **borrowing hydrogen (BH) methodology** with various primary and secondary alcohols. This one-pot transformation has emerged as an attractive strategy for the construction of novel C-N[6] and C-C[7] bonds from an alcohol and an amine or a *C*-nucleophile. A first step of catalytic dehydrogenation converts an unreactive alcohol into the corresponding carbonyl. Subsequent aldol condensation with a C-nucleophile gives the corresponding α,β-unsaturated ketone which upon hydrogenation affords the expected C-alkylated compound (Scheme 1). We thus propose to take advantage of the pyrazolopyridine as a novel C-nucleophile.



Scheme 1. *C*-alkylation using the BH methodology

A wide range of late-stage transformations will be evaluated in the framework of this PhD program and the library of compounds will be integrated in the Chimiothèque Nationale for biological screening.

---

[5] Lavrard, H.; Popowycz, F. *Eur J Org Chem* **2017**, *2017*, 600–608.

[6] (a) Bahé, F.; Grand, L.; Cartier, E.; Jacolot, M.; Moebs-Sanchez, S.; Portinha, D.; Fleury, E.; Popowycz, F. *Eur. J. Org. Chem.* **2020**, 599-608. (b) Grand, L.; Powderly, M.; Popowycz, F.; Jacolot, M. *J. Org. Chem.* **2023**, *88*, 2642-2647. (c) Larduinat, M.; François, J.; Jacolot, M.; Popowycz, F. *J. Org. Chem.* **2023**, *88*, 11, 7512–7517

[7] François, J. ; Rio, J. ; Jeanneau, E. ; Perrin, M.-È. L. ; Jacolot, M. ; Payard, P.-A. ; Popowycz, F. *Org. Chem. Front.* **2023**, *10*, 4732–4739.