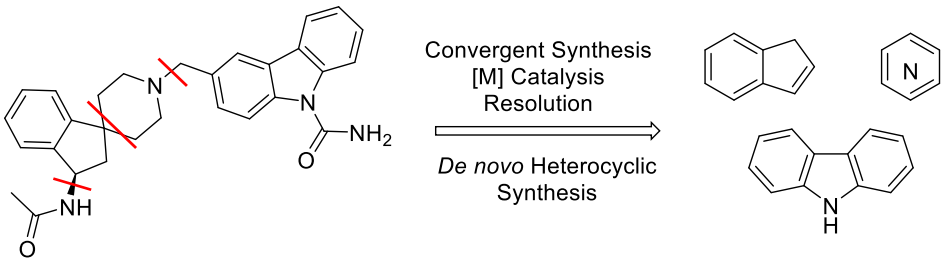
SYNTHESIS OF AN MCHR2 ANTAGONIST VIA SCALABLE & GREEN CHEMISTRY PRINCIPALS

Rowan Coupez,[1] Ruslan Popenko,[1] Marie-Anne Solliec,[2] Françoise Presse,[2] Sophie Martini,[1] Jean-Louis Nahon,[2] Véronique Michelet[1]

[1] Université Côte d'Azur, Institut de Chimie de Nice, CNRS UMR 7272 - veronique.michelet@univ-cotedazur.fr
[2] Université Côte d'Azur, Institut de Pharmacologie Moléculaire et Cellulaire IPMC UMR 7275
rcoupez@univ-cotedazur.fr

The Melanin-Concentrating Hormone (MCH) is a regulator of energy balance in mammals[1,2] of the two receptor subtypes, the role of MCHR2 is poorly understood. Following our interest in the synthesis of heterocycles and bioactive molecules,[3] we envisaged the synthesis of an identified MCHR2 antagonist[4] according to scalable and green chemistry principles. Installation of the key functional groups was envisaged via abundant transition-metal catalysis as well as the application of an efficient chiral resolution for isolation of an enantiomerically pure product. *De novo* synthesis of heterocyclic derivatives, for continued SAR exploration, as well as preparation of fluorescently labelled compounds for pharmacokinetic distribution studies are also described. These compounds can be used to help reduce the existing knowledge-gap in the understanding of the role of MCHR2 via *in-vivo* studies using an *hMCHR2* mouse model developed by Nahon's team.



[1] Nahon J.-L, Presse F., Bittencourt J. C., Sawchenko P. E., Vale W., *Endocrinology*, **1989**, 125, 2056. Haussen A.C., Ruud J., Jiang H., Hess S., Varbanov H., Kloppenburg P., Brüning J. C., *Cell Rep.*, **2016**, *17*, 2512.
[2] MacNeil, D., *Front. Endocrinol.* **2013**, *4*, 49.
[3] Heinrich, C. F., Durand, D., Starck, J., Michelet, V. *Org. Lett.* **2020**, *22*, 7064. Laher, R., Marin, C., Michelet V. *Org. Lett.* **2020**, *22*, 4058. Tang Y., Benaissa I., Huynh M., L. Vendier L., Lugan N., Bastin S., Belmont P., César V., Michelet V., *Angew. Chem. Int. Ed.* **2019**, *58*, 7977.
[4] Chen, X.; Mihalic, J.; Fan, P.; Liang, L.; Lindstrom, M.; Wong, S.; Ye, Q.; Fu, Y.; Jaen, J.; Chen, J. L.; Dai, K.; Li, L. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 363.