

EXPANDING THE BILE ACID CHEMICAL SPACE: SYNTHETIC STRATEGIES FOR LEAD DISCOVERY AND DEVELOPMENT

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Bile acid-responsive receptors are widely recognized as relevant targets for drug discovery. The key members of this family, namely FXR and TGR5, are exploited for the treatment of several liver and metabolic diseases including non-alcoholic steatohepatitis (NASH) and diabetes.[1] Following the success of obeticholic acid (OcalivaTM),[2] in the last years our efforts have been devoted to exploring the structure–activity relationships of bile acids as FXR/TGR5 ligands, to identifying functional hot spots responsible for selectivity and efficacy, and to disclosing powerful chemical probes for phenotypic studies in biochemical, cell-based and animal models. The development of these compounds has also revealed how apparently minor chemical modifications of the steroidal cholanoic scaffold greatly influence the physicochemical, pharmacokinetic, and biodistribution profile of the resulting molecules thereby determining their fate in clinical settings of metabolic disorders.[3]

Unquestionably, an important challenge for the discovery and development of new bile acids with improved properties is to solve synthesis designs that enable to expand the bile acid chemical space and simultaneously ensure the synthetic accessibility of unexplored ‘hidden’ positions of the biliary scaffold. In this communication, case studies related with the synthesis and optimization of novel, nature-inspired bile acid lead candidates are reported and discussed.

[1] a) Massafra, V.; Pellicciari, R.; Gioiello, A.; van Mil, S.W.C. *Pharmacol Ther.* **2018**, *191*, 162. b) van Nierop, F. S.; Scheltema, M. J.; Eggink, H.M. *et al. Lancet Diabetes Endocrinol.* **2017**, *5*, 224.

[2] Pellicciari, R.; Pruzanski, M.; Gioiello, A. *Successful Drug Discovery* **2018**, *3*, 197 Ed. Wiley-VCH Verlag GmbH & Co. KGaA.

[3] Roda, A.; Pellicciari, R.; Gioiello, A.; Neri, F. *et al. J. Pharmacol. Exp. Ther.* **2014**, *350*, 56.