Title: Discovery and optimization of new GPBAR1 agonists for the treatment of inflammatory and metabolic diseases

In the last two decades bile acids have been identified as important nutrient and metabolic sensors that play a critical role in maintaining metabolic homeostasis. In addition to their primary functions in absorption of lipids and fat-soluble vitamins from the gastrointestinal tract, bile acids also play an important role as signal molecules and endogenous ligands of various receptors and channels, above all the nuclear farnesoid X receptor (FXR) and membrane G protein-coupled bile acid receptor-1 (GPBAR1, also known as Takeda G protein-coupled receptor 5, TGR5). GPBAR1, a member of the rhodopsin-like superfamily, is widely expressed in various cells types, including cholangiocytes, gallbladder smooth muscle cells, intestinal cells, nerve cells and brown adipose cells. The role of GPBAR1 in metabolic diseases has always been a hot topic of research.[1] GPBAR1 regulates the control of different metabolic and enterohepatic functions such as energy and glucose homeostasis and exerts a protective role in gastrointestinal tract by attenuating inflammatory processes. For these reasons, GPBAR1 agonists are valuable drugs for the treatment of different diseases ranging from type 2 diabetes mellitus, nonalcoholic steatohepatitis, cholestasis and inflammatory bowel disease. However, the pharmacologic utility of GPBAR1 agonists has been limited by systemic undesirable side effects, such as excessive gallbladder filling, blockade of gallbladder emptying, itching and cardiovascular issues. The design of molecules targeting GPBAR1 in the bowel and that are not absorbed in the systemic blood stream is an attractive approach to obtain therapeutic drugs useful for the treatment of diabetes mellite or IBD, allowing to reach higher drug concentrations in the bowel and minimizing undesired effects.[2-4]

On these bases, we purpose to carry out an interdisciplinary research activity, focused on the discovery and optimization of new intestinal-restricted GPBAR1 agonists that avoid the systemic side effects maintaining the potential therapeutic effect and, consequently, developing drugs with acceptable safety profiles.

1. *Nutrients* **2020**, 12, 3709
2. *J. Med. Chem*. **2015**, 58, 3315
3. *RSC Med. Chem*., **2021**, 12, 394–405
4. *J. Med. Chem.* **2021**, 64, 3, 1593