Discovery and optimization of benzoylpiperidine derivatives as new reversible, potent and selective MAGL inhibitors

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The serine hydrolase monoacylglycerol lipase (MAGL) is the main responsible of the degradation of 2-arachidonoylglycerol, an endocannabinoid implicated in several physiological processes. Moreover, MAGL is involved in the formation of pro-tumorigenic signaling molecules. MAGL inhibition is considered a valid therapeutic approach to treat several pathological conditions, including several types of cancer.[1] So far, only a limited number of MAGL inhibitors have been discovered and most of them are characterized by an irreversible mechanism of action, determining the occurrence of undesired effects. In this study we identified a reversible MAGL inhibitor by a structure-based virtual screening analysis. With the aim of identifying more potent and selective MAGL inhibitors, chemical modifications were introduced to the original compound to improve both potency and selectivity.[2] The structural optimization led to the obtainment of nanomolar inhibitors (Figure 1), which are selective over other hydrolases and cannabinoid receptors. These new inhibitors exert an appreciable antiproliferative activity in cancer cells and are able to inhibit MAGL in *in vivo* assays.

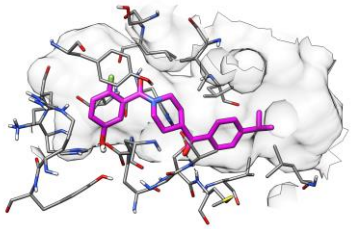

Figure 1: Putative binding disposition of one of the best inhibitors in MAGL active site.

[1] Mulvihill MM, Nomura DK, *Life Sci.* **2013**; 92(8-9):492-497.
[2] Granchi C, Rizzolio F, Palazzolo S, Carmignani S, Macchia M, Saccomanni G, Manera C, Martinelli A, Minutolo F, Tuccinardi T, *J Med Chem.* **2016**; 59(22):10299-10314.