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Dual histamine H_3 and sigma-1 receptor ligands as novel pharmacological tools in the treatment of central nervous system disorders with the focus on neuropathic pain

The philosophy "one molecule—one target—one disease" was the dominant approach in medicinal chemistry for several decades up till the end of the twentieth century. This strategy was based on the identification and optimization of small chemical entities able to specifically recognize one target believed to be fully responsible for one certain disease. The aim of the "one drug—one target" approach was to find bioactive compounds endowed with a limited risk of off-target properties, frequently responsible for drug side-effects. Since central nervous system disorders are characterized by diverse physiological dysfunctions and deregulations of a complex network of signaling pathways, optimal multipotent drugs should simultaneously and peculiary modulate selected group of biological targets. This assumption gave birth to polypharmacology – a new scientific area focused on discovery, development, and pharmacological study of Multiple Targeting Designed Ligands, able to simultaneously modify the activities of several interacting pharmacological targets. While their identification has long been the result of serendipity, nowadays medicinal chemistry tends to design desirable polypharmacology.

With the recent market approval of Pitolisant, the interest in clinical application of novel multifunctional histamine H_3 receptor antagonists has clearly increased. Such designed molecule might express improved pharmacological effects and reduced unwanted side-effects. Up to date, several combinations of different H_3 receptor pharmacophores with pharmacophoric elements of other G-protein coupled receptors, transporters or enzymes have been synthesized by numerous companies and academic institutions. Unfortunately, none of them have reached the pharmaceutical market so far. Therefore, the search for new, multifunctional histamine H_3 receptor ligands, while maintaining the appropriate pharmacokinetic parameters, is desired. Interestingly, the latest studies have shown that some clinically evaluated histamine H_3 receptor antagonists possess nanomolar affinity at sigma-1 receptor binding sites, suggesting this property might play important role in their overall efficacy. These two different biological structures, histamine H_3 and sigma-1 receptors, are both highly expressed in the central nervous system, and can represent potential, fruitful targets for therapeutic developments in tackling numerous human diseases.

Neuropathic pain affects approximately 7-10% of the adult population. Multiple causes of neuropathic pain have been described and its incidence is likely to increase owing to the global ageing of population, increased incidence of diabetes mellitus and improved survival from cancer after chemotherapy. The burden of chronic neuropathic pain seems to be related to the complexity of neuropathic symptoms, poor outcomes and difficult treatment decisions. Importantly, quality of life is impaired in patients with neuropathic pain owing to increased drug prescriptions resulting from more frequent visits to health care providers, as well as the morbidity from the pain itself and the inciting disease. Several studies have suggested a potential therapeutic use of sigma-1 antagonists for the treatment of pain conditions including neuropathic, inflammatory and visceral pain, also as adjuvants to opioid therapy. Being localized in many central nervous system regions involved in nociception, histamine H_3 receptors are also associated with pain being involved in central sensitization of pain.

As the result of this Project, we will identify new pharmacological tools with high affinity at both histamine H_3 and sigma-1 receptors that can improve existing therapies of the neuropathic pain. Secondly, we will determine whether such dual-acting ligands are more effective in the treatment of neuropathic pain compared to selective ones. This Project also aims at creating necessary structural requirements of obtained compounds, responsible for their biological activity, that might play a role in the overall efficacy of histamine H_3 recptor antagonists and facilitate the design of further compounds with this activity profile. Furthermore, by fulfilling the tasks, we will obtain a library of novel ligands whose effectiveness can also be tested in various other central nervous system disorders.