Project objectives

In the progress of research on the function of the central nervous system (CNS), the availability of appropriate tool compounds which selectively interact with a particular type of receptor located in the CNS allow clarification of its physiological functions and involvement in CNS pathological processes.
The main purpose of the project is to obtain a number of 3-(1-alkyl-1H-imidazol-5-yl)-1H-indole derivatives as selective 5-HT_7 serotonin receptor agonists which, due to their high activity, selectivity, and favorable pharmacokinetic parameters, meet the criteria of high quality tool compounds for investigating the role of the 5-HT_7 receptor in the CNS. Due to the low basicity of the investigated compounds, which is a unique feature for agonists of the aminergic GPCR receptors (the 5-HT_7 receptor is a member of this group), the essence of the work will be to clarify the mechanism of direct ligand binding at the appropriate receptor site.

Description of the research

The synthesis of the new series of compounds will allow a detailed analysis of the relationship between the chemical structure and activity, and studies using genetically modified 5-HT_7 receptors conducted in collaboration with Professor Levy team (Department of Pharmacology, Institute of Clinical Medicine, University of Oslo, Norway) will help explain their mechanism of action.
Biochemical studies will determine the activity of the new compounds to the 5-HT_7 receptor and their selectivity in relation to other types of receptors. Electrophysiological experiments will determine the effect of the receptor activation induced by the tested compounds, and studies using animal models of depression, anxiety, and cognitive function will clarify the role of the 5-HT_7 receptor in selected disease processes.

Rationale

The basis of the research is the recent discovery (at the Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences) of low-basicity compounds with high affinity for the 5-HT_7 receptor. These compounds are likely to have an unprecedented selectivity profile due to a different mode of action (relative to that commonly accepted as required for receptor activation). The most active derivative in the published series, compound AGH-107, in terms of affinity, selectivity, and efficacy for 5-HT_7 receptor activation, is almost equal to two AS-19, LP-211 – selective tool compounds used so far in pharmacological studies. Improved metabolic stability and blood-brain barrier permeability as well as water solubility make AGH-107 a better candidate for pharmacological testing. Preliminary studies have shown that new AGH-107 analogs, will be even more active 5-HT_7 receptor agonists than those currently used.