Combination of FAAH inhibition with action via serotonin 5-HT_6 receptor as pioneering approach to fight with Alzheimer Disease

Recent statistics report that nearly 50 million people worldwide are affected by Alzheimer's disease (AD). This condition is the most common form of neurodegenerative disease characterized by progressive cognitive impairment and mental disorders caused by the death of nerve cells in the brain. However, the actual causes and cascade of events in the development of this pathology are not fully understood due to the wide array of biochemical factors that are revealed during its progression.

Currently available drugs for AD are primarily inhibitors of acetylcholinesterase, an enzyme that breaks down one of the primary neurotransmitters, acetylcholine. However, their effectiveness is limited due to the potential for adverse side effects and the lack of significant and long-term improvement. A therapeutic target that has recently gained much popularity is the serotonin 5-HT_6 receptors (5-HT_6R) located almost exclusively in brain. Their main role is the regulation of cholinergic and glutamatergic transmission, which is of particular importance for patients suffering from various cognitive disorders. Despite this, none of the known 5-HT_6R ligands has yet been approved as a drug due to unsatisfactory therapeutic effects. However, inhibition of the enzyme fatty acid amide hydrolase (FAAH), which is an important part of the endocannabinoid system, may be of great importance in the treatment of AD. It breaks down endogenous cannabinoids, which are involved in reducing nervous system inflammation, pain, and regulation of other neurological functions, including memory processes and motor activity.

Continued failures in the process of developing a new drug for such a complex disease as Alzheimer's disease have resulted in a break from the classic "one drug, one target, one disease" paradigm. Instead, the polypharmacology approach, which involves the use of a pharmaceutical that simultaneously target several therapeutic targets associated with the given disease, has gained popularity.

Following the new trend that offers hope for a breakthrough in AD therapy and set by polypharmacology, this research is focused on the search for multitarget molecules acting on the 5-HT_6 receptor and the FAAH enzyme. Our team, through many years of work, has been able to develop a number of compounds with a unique 1,3,5-triazine backbone that are highly active 5-HT_6R antagonists. Analysis of the available literature pointed out some analogies to known FAAH inhibitors, which allowed for preliminary design of chemical modifications allowing for increasing this similarity. Results of pharmacological tests for the synthesised pilot compounds confirmed the accuracy of the modifications, thus emerging a lead structure of dual 5-HT_6/FAAH agent that will be a good started point for further studies. Due to the combined dual action on 5-HT_6R and FAAH is a unique approach not described before, thus the dual ligands may represent a breakthrough direction in the treatment of central nervous system (CNS) diseases.

Hence, the aim of this project is the rational design supported by advanced molecular modelling techniques, chemical synthesis, and determination of the pharmacological activity of a series of compounds with potential dual activity against 5-HT_6R and FAAH. The compounds with the highest activity will undergo further extended biological studies including in vivo animal testing. Such multipronged efforts will allow for a detailed analysis of the applicability and efficacy of the resulting potential drugs useful in the treatment of AD and may bring researchers closer to a solution to neurodegenerative diseases. In turn, patients affected by AD, which is so complex and incurable at the moment, will be given new hope.