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The purpose of this study was to explore the chemical space of naturally derived compounds with a special focus on a region populated by butyrylcholinesterase inhibitors. Recent evidences suggest that butyrylcholinesterase plays a role in the progression of Alzheimer’s disease. Hence, the development of selective butyrylcholinesterase inhibitors can provide a new effective strategy to treat cognitive impairments associated with Alzheimer’s disease. The study was commissioned by Drug Discovery and Pharmaceutical Biology at Åbo Akademi University.

In this thesis, we first set off to develop a chemical database (named as TE subset) containing nearly 1000 unique molecules synthesized by the group of Prof. Thomas Erker at the University of Vienna, Austria, followed by the exploration of its chemical space, with a focus on a region populated by butyrylcholinesterase inhibitors. The chemical database was prepared and structure data files as well as other essential chemical properties were included. This generated chemoinformation was used to explore the chemical space using ChemGPS-NP. The ChemGPS-NP concept is based on eight principal components, each of them representing different predicted properties. These principal components were analyzed and compared in 2-dimensional and 3-dimensional graphs. Comparisons to strictly defined natural and synthetic libraries were carried out, to define the properties of the TE subset. The space occupied by known butyrylcholinesterase inhibitors was analyzed mathematically based on Euclidean distance values.

The exploration of the chemical space of the TE subset revealed that it had more synthetic-like than natural-like properties. Natural compounds were shown to cover a wider, more diverse chemical space than the TE subset or two model libraries of synthetic compounds. Butyrylcholinesterase inhibitors seemed to occupy a well-defined region characterized by low size, high aromaticity and relatively high lipophilicity. An attempt was made to mathematically define this privileged chemical space with the aid of control inhibitors. By setting a threshold Euclidean distance value, distances could be pre-calculated prior to in vitro screening and compared to the threshold value. This would allow filtering out distant compounds with lower chances to act as butyrylcholinesterase inhibitors.

Keywords: Chemical space, ChemGPS-NP, Butyrylcholinesterase, Natural compound, Drug discovery, Alzheimer’s disease