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# Exploring chemical space using in silico studies to identify novel inhibitors of Acetylcholinesterase, a target for Alzheimer's disease

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Alzheimer's disease (AD) is the leading cause of dementia.[1] The number of AD cases is increasing at an alarming rate, which is mostly the result of increases in both the population and the average life expectancy due to advances in modern medicine. AD has been shown to be twice as prevalent in African-Americans, calling it the "Silent Epidemic of Alzheimer's Disease".[2] This suggests that the disease is particularly relevant to South Africa and Africa due to its demographics. As such, there is a dire need for the development of effective treatments of AD.

Acetylcholinesterase (AChE) is a protein that has been identified for the treatment of AD, with four AChE inhibitors having been approved for treatment by the FDA. These inhibitors have significant side-effects and/or short-term bio-availability. It is suggested that AChE inhibitors can act as dual inhibitors by both inhibiting AChE and prevent Amyloid Beta (Aβ) aggregation also associated with AD.

The binding pocket of AChE is ~20 Å deep gorge which is highly solvated. It has been shown that the majority of the side-chain residues are highly flexible and this flexibility should be considered when screening is performed. In addition, the entrance of the binding pocket known as the Peripheral Anionic Site (PAS) contributes to Aβ aggregation. Using High Through-put Virtual Screening (HTVS), potential inhibitors of AChE from the BioFocus library of 20'000 housed at the CSIR were identify by using ensemble docking. Ensemble docking involves using multiple conformations of the same protein to take the flexibility of the active site into account. In doing so, an improved enrichment in the results is obtained where fewer false negatives occur and alternative interactions are also considered. Furthermore, ensemble docking scales linearly with increasing number of receptor conformations, whereas if screening of compounds was performed with the active site being considered flexible the computational resources would increase exponentially with increasing number of flexible residues.

Significant validation testing was initially done on the HTVS model to check that an acceptable enrichment was obtained by testing the model against known active compounds and decoys. The majority of the receptor structures were obtained from the Protein Database (PDB). To improve the model further, more receptor structures were generated by performing Inducted Fit Docking (IFD) with compounds that were false negatives during the initial HTVS model.

Promising hits identified from the BioFocus library will be submitted for bioassay to confirm the inhibition against AChE and Aβ aggregation.

References

(1) Anand, R.; Gill, K. D.; Mahdi, A. A. Neuropharmacology 2014, 76 (PART A), 27.

(2) Alzheimer's Association. Alzheimer's Dement. 2014, 10 (2), 1.

## HPC content

The computational recourse which has been accessed through the CHPC has been critical to this project. Thus far a million compounds have already been docked into receptors for model validation and screening.

Screening this number of compounds requires a significant number of computational cores to obtain results in a reasonable time and with acceptable accuracy.

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