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In silico investigations of silylated analogues of the anti-Alzheimer's drug donepezil.

Alzheimer's disease (AD) has been extensively studied, as it is the most prevalent form of dementia in the world1. Potentially the best treatment available is based on the FDA approved drug donepezil, which was identified by Sugimoto et al2. Donepezil (shown if figure 1) is a reversible acetylcholinesterase inhibitor.

Figure 1: Donepezil

Studies in the mid-1970's report substantial neocortical deficits of choline acetyltransferase, which is responsible for the production of acetylcholine3. Further studies illustrated reduced choline uptake and subsequently reduced acetylcholine release, confirming a substantial presynaptic cholinergic deficit3. The discovery of the role of acetylcholine in learning and memory, with previous discoveries lead to the development of the cholinergic hypothesis of Alzheimer's disease3. The hypothesis proposes that the degradation of the cholinergic neurons in the basal forebrain and the correlated decline in cholinergic neurotransmission in the cerebral cortex together with other factors significantly contribute to the deterioration of cognitive function of Alzheimer's patients3.
Extensive research has been done on the modification of the donepezil structure, but little has been done with regard to the nature of the substituents on the aromatic ring in the indanone moiety (indicated in figure 1), in particular very little is reported pertaining to silicon substitution1. Silane substitution has been shown in literature to increase the availability of compounds in the brain by facilitating blood brain barrier (BBB) penetration,4 the development of sila-derivatives of donepezil is therefore an attractive target for the development of potent cholinesterase inhibitors with good BBB penetration.
The aim of this study is to utilise in silica studies in the identification of potential silicon analogues and their subsequent synthesis. The program suite Schrodinger is used with three approaches in the prediction of the best analogues, mainly glide docking, mmgbsa and the induced fit approach. Identified compounds are currently being synthesised.

References:

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HPC content

The study entails the use of the Schrodinger suite for computer aided drug discovery (CADD) and utilises glide docking, mmgbsa and the induced fit approach. Approximately 50 ligands are under study, but because of the limited amount, a higher accuracy algorithm is used, such as induced fit docking. In the normal docking algorithms, the residues are assumed to be rigid, while in induced fit approach the residues are flexible. This

flexibility increases the computational power and run time exponentially, as more residues are indicated as important in the binding site.

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