
Multi-target fragment-based design of novel inhibitors for AChE and SSAO/VAP-1 enzymes

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Abstract

We described the identification of novel multi-target inhibitors of human semicarbazide-sensitive amine oxidase/vascular adhesion protein-1 (SSAO/VAP-1) and acetyl cholinesterase (AChE) using fragment-based drug design. The known structurally diverse inhibitors of each protein were deconstructed into small fragments. Each fragment was docked into the active site of both enzymes and they were then sorted based on the scoring function. Eleven fragments were selected from each protein. These fragments were combined and resulted in 121 compounds. The docking poses of these compounds showed that seven compounds interacted in the binding site of both AChE and SSAO/VAP-1 enzymes. ADMET properties of these compounds were then calculated. The results showed that four of these inhibitors need to be synthesized for further experimental evaluation.

Key words: Please provide up to 6 key words. Please try to stick to one line.

Introduction

Alzheimer's disease (AD), the most common form of dementia, is a chronic neurodegenerative disorder which is characterized by progressive cognitive impairment in elderly people [1]. In AD increased human semicarbazide-sensitive amine oxidase/vascular adhesion protein-1 (SSAO/VAP-1) expression has been found to co-localise with abnormal amyloid deposition. In addition, inhibition of AChE in AD treatment should allow the lowered levels of ACh in the synapses a chance to induce a signal in the downstream nerve. The design of novel multi-target inhibitors has been proposed for AD [2]. The multi-target inhibitor approach is based on designing an inhibitor for the multiple targets. Multi-target inhibitors are more appropriate for addressing the complexity of AD and may provide new drugs for controlling the multifactorial nature of AD, stopping its progression [3]. Recent years have seen a tremendous increase in the discovery of novel drug technologies. Fragment-based approaches have rapidly become a proven technique to identify such starting points in a variety of research programs.

Results and discussion

The crystal structure of the AChE (PDB code 1B41) and SSAO/VAP-1 (PDB code 2C10) was taken from the protein data bank. In order to obtain conformation of AChE and SSAO/VAP-1 in a water environment, 10 ns MD simulation were performed in a cubic water box. The known inhibitors of each enzyme from published results were used to generate fragments. Fragments were obtained by dividing the original active inhibitors into two different fragments. 185 and 176 fragments were obtained from AChE and SSAO/VAP-1 inhibitors, respectively. Fragments

were screened based on the docking studies using AutoDock Vina. Based on the protein-fragment affinity, the fragments that show the low free energy of binding with the two target proteins are selected as the active fragments. The new inhibitors were constructed by linking the active fragments. In this way, 121 new molecules were designed.

Table 1. Lipinski's parameters of the proposed inhibitors

No.	Hydrogen bond acceptor	Hydrogen bond donor	TPSA	Refractivity	LogP	MW
4	6	1	63.69	136.146	3.823	505.62
5	6	2	80.32	141.486	3.997	507.56
25	6	1	67.87	137.525	4.243	578.51
41	6	2	92.88	122.815	3.876	460.55
43	9	3	128.35	126.889	1.032	489.55
102	5	0	36.02	126.391	4.064	505.56
121	5	2	63.25	126.178	4.086	447.55

These molecules were docked to AChE and SSAO/VAP-1 by the blind docking. The docked pose of these molecules showed that 7 molecules interacted in the binding site of the both enzymes. ADMET properties of the selected compounds were predicted using the rule of five formulated by Lipinski [4]. The results of these calculations are listed in Table 1. These results revealed that compounds 41, 43, 102 and 121 have the potential to be synthesized. This methodology could help to design multi-target inhibitors for other diseases.

References

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