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Research Article

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Design, molecular modelingand docking studies of novel Tacrine –aryl hybrids as multifunctional agents for the treatment of Alzheimer's disease

Samaneh Zali[1*], Azar Mostoufi[1], Farshid Afshoon[1], Masood Fereidoonnezhad[1]

[1]School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran.
*Corresponding Author

Abstract

A series of novel tacrin-arylhybrids were designedas multifunctional agents for the treatment of Alzheimer'sdisease(AD)and drug-likeness, molecular docking of them were performed to find out a drug candidate with better binding affinity than tacrine. We found that these newdesigned hybrids inhibit human acetylcholinesterase, butyrylcholinesterase (h-AChE , h-BuChE) being more potent than the parent inhibitor, tacrine.

Keywords: tacrine,aryl, AD,drug-likeness, molecular docking, h-AChE, h-BuChE and BACE-1.

Introduction

AD is a complex neurodegenerative process occurring in the centeral nervous system (CNS), Characterized by deposits of aberrant proteins namely β- amyloid (Aβ) andTau-protein, oxidative stress, loss of synapses, and death of cells, especially cholinergic neurons.

Most therapeutic treatment for AD are drugs that aim to inhibit enzymes AChE and BuChE, thereby increasing acetylcholine concentration in cholinergic synaptic clefts. Tacrine is a potent inhibitor of both AChE and BuChE that suffers from therapy-limiting liver toxicity, which can be prevented with free radical scavengers. Thus the development of tacrine based dimers and hybrids with improved pharmacological propertis has been the focus of a great deal of research in recent years.

The multifunctional nature of AD provides the logical foundation for the development of an innovative drug design strategy centered on multi-target-directed-ligands (MTDLs). The multitarget approach has been proposed as particularly suitable to combat the heterogeneity of AD. In recent years, the MTDL concept has been exploited to design different ligands hitting different biological targets. On the basis of our knowledge of the well-knownstructure of AChE ,BuChEwe decided to connect the tacrine and aryl fragments with a linker.

Materials and Methods

a) drug design

More than 1000 ligands were designed based on the fig 1.

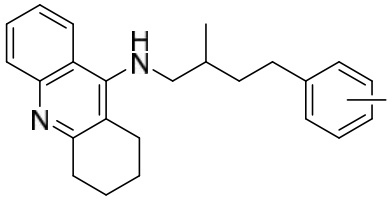

Fig 1. Drug design

b) Optimization of the ligands

The two dimensional structures of the ligands were drawn using ACD chemsketch software. Then the ligands were subjected to minimization procedures by means of an in house TCL script using Hyperchem8.

c) Drug-likeness calculations

Drug-likeness rules are set of guidelines for the structural properties of compounds, used for fast calculation of drug-like properties of a molecule. They can be quite effective and efficient. Using DruLiTo an open source virtual screening tool, we calculated druglikeness descriptors (fig 2).

Fig 2.DruLiTo an open source virtual screening tool for calculating Drug-likness

d) Docking procedure

The docking simulations were carried out by means of an in house batch script (DOCKFACE) for automatic running of AutoDock 4.2 in a parallel mode using all system resources. The dimensional crystal structures of AChE(**PDB ID:1ACJ**), BuChE(**PDB ID:4bds2**) were retrieved from protein data bank .

Results and Discussion

Having completed the docking process, then the protein–ligand complex was analyzed to investigate the type of interactions. Top ranked binding energies (kcal/mol) in AutoDockdlg output file were considered as response in each run.

	AChE	BuChE
Lig1	-15.47	-13.25
Lig2	-14.43	-12.78
Lig3	-14.91	-13.03
Lig4	-14.59	-11.51
Lig5	-14.76	-12.49
Lig6	-14.03	-12.74
Lig7	-14.77	-12.06
Lig8	-15.29	-12.06
Lig9	-14.44	-13.61
Lig10	-14.48	-12.51
Lig11	-14.24	-14.09
Lig12	-14.08	-13.66
Lig13	-13.89	-12.69
ligandcocrystal	-8.71	-9.2

Fig 3.dock results on AChE, BuChE

Docking Validation

For our target, 33 active ligands and 139 inactive decoys were retrieved from ChEMBL database as SMILES format. Compared to ROC plot, EF_{max} factor is highly dependent to the number of actives in a data set. Since ROC values do not depend to the number of actives and decoys, they are more valuable in making decisions about the validity of the methods than EF_{max} analysis.

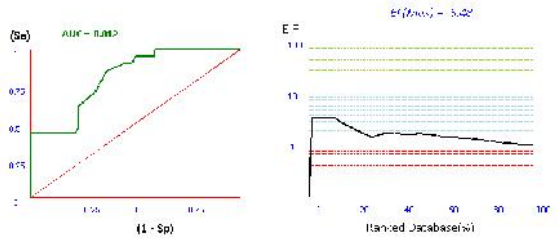

Fig 4.Docking validation on AChE

Conclusion

The docking analyses of tacrin-aryl hybrids showed that more than 30 compounds are effective in their docking scores high binding nature. Thus these compounds are good candidates for synthesis and should be considered for further evaluation using in vitro and in vivo studies to develop an effective anti-Alzheimer's drug.

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