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Research Article

In Silico Studies - Molecular Docking Of Novel Alkaloids As Potential Candidates For Treatment Of Alzheimer Diseases

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ABSTRACT

Objective: Alzheimer disease (AD) is a progressive neurodegenerative condition. Acetylcholine (Ach), a neurotransmitter that is essential for many cognitive and neuropsychiatric function, is significantly reduced is AD patient's brains.

Method: In the present insilico study, 43 bioactive compounds of Eburnane type of Natural bioactive alkaloids were analyzed for their inhibitory role on Acetylcholinesterase (AChE) activity by applying the molecular docking studies. Other parameters viz. protein-ligand interactions, determination of molecular interaction-based binding affinity values, Lipinski rule of five, functional properties and biological activities for the above compounds were also calculated by employing the appropriate bioinformatics tools.

Result: The results of docking analysis clearly showed that 13 chemical molecules model Out of 43 model shows the more binding affinity but molecule 4ey7_A11 has highest binding affinity with AChE (-11.9 kcal/mole) has least percentage activity on AD and neurodegenerative disease. Whereas, the 4ey7_A35 has been second qualified binding affinity (-10.9 kcal/mol).

Conclusion: We have determined that 4ey7_A11 is the best molecular fit to investigate further for the treatment of AD based on docking results.

INTRODUCTION

Alzheimer disease (AD) is a neurodegenerative, progressive, and fatal disorder, characterized by marked atrophy of the cerebral cortex and loss of basal forebrain cholinergic neurons. The major pathological features of AD are related to neuronal degeneration and include extracellular deposition of amyloid beta (Aβ) plaques, intracellular formation of neurofibrillary tangles (NFTs), which are made up of hyper phosphorylated tau protein, and neuro inflammation. Neurodegenerative diseases are characterized by the progressive and

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irreversible loss of neurons from specific regions of the brain. The pattern of neuronal loss is selective, affecting mainly the subcortical areas (nuclei of the base) and cerebral cortex, resulting in abnormality in the control of voluntary movement, impairment of memory, and cognitive ability. The progression of these debilitating and incurable conditions gives rise to dementia. The most known dementias are amyotrophic lateral sclerosis, Parkinson's disease, and Huntington's disease. AD is the most prominent of these dementias. New approaches including the observation of amyloid beta Aβ and neurofibrillary tangles (NFTs) lead to the amyloid and tau hypotheses as causes for AD development. Approaches based on the development of multi-target ligands (MTLs), molecules capable of binding to multiple targets involved in the pathology of AD. Multi-target molecules able to inhibit cholinesterases and interfere with Aβ aggregation and/or tau protein hyper phosphorylation or neuro inflammation may be useful tools in the treatment of AD. Natural products have been a constant source of new approaches for the treatment of AD, especially plant alkaloids. In this vast field of possibilities, natural products may, once again, be the source of potential MTL drug candidates. Alkaloids are a particular group of low–molecular weight, nitrogen-containing compounds, active at different cellular levels within organisms. They take part in the biological processes of plants, animals, and microorganisms living in different environments. This class of compounds is found in approximately 25% of the species of higher plants, being especially abundant in the Apocynaceae, Asteraceae, Fabaceae, Papaveraceae, Rubiaceae, and Solanaceae families. Because of the influential and multiple actions of alkaloids, they possess a variety of pharmacological potentials in modern medicine and the effects includes analgesic (e.g., morphine), anti-hyperglycemic (e.g., piperine), anticancer (e.g., berberine), antiarrhythmic (e.g., quinidine), antibacterial (e.g., ciprofloxacin). Some other alkaloids exhibit stimulant effects to CNS (e.g., cocaine, caffeine, and nicotine) as well as psychotropic effects (e.g., psilocin). Alkaloids is ancholinesterase enzyme inhibitors(IChE) and allosteric modulator of the central nicotinic receptor and selective inhibitor of acetylcholinesterase. Of the three anticholinesterase agents approved by the FDA for the treatment of AD, galanthamine is an amaryllidaceae alkaloid and rivastigmine is a derivative of the indole alkaloid physostigmine. Physostigmine (Physostigmavenenosum, Papilionaceae) was the first cholinesterase inhibitor used to treat AD, but its short half-life in plasma and low therapeutic index limited its use.

Eburnane:

Eburnane is the type of alkaloid which contains indole ring and ethyl side chain. Kopsialarutens is gave predominantly alkaloids of the eburnane. Kopsialarutensis is a species of plant in the family Apocynaceae. It is found in Peninsular Malaysia, Borneo and Thailand. Five alkaloids of the eburnan type, viz., (+)-eburnamonine, (+)-eburnamonineN(4)-oxide, (−)-eburnamine, (+)-isoeburnamine and larutenine have been isolated from the leaves of Kopsialarutensis. Larutenine is a new alkaloid, while (+)-eburnamonineN(4)-oxide is isolated as a natural product for the first time.

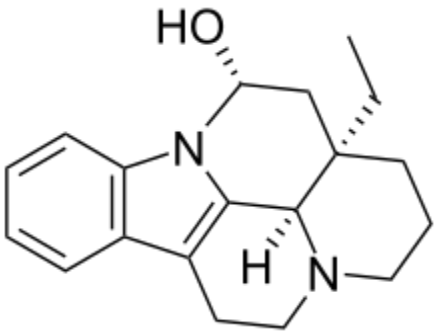


Fig 1: Eburnane Alkaloid

MATERIAL AND METHOD'S

Molecular Docking

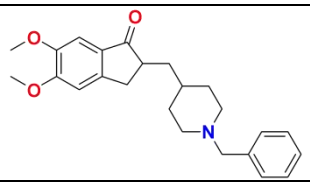
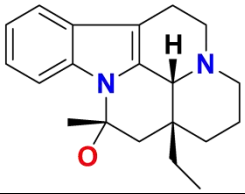
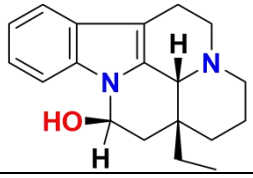
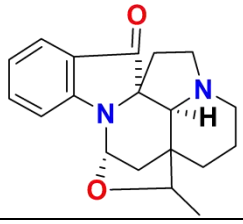
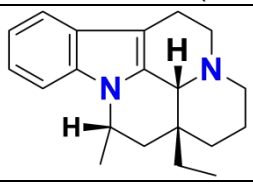
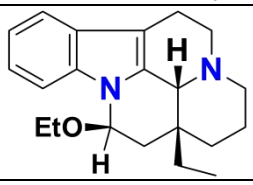
Selection of ligands and preparation of therapeutic target proteins

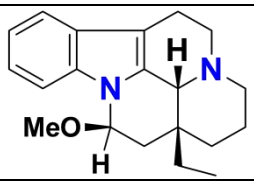
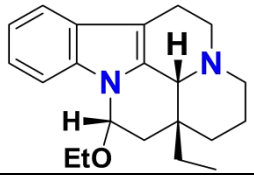
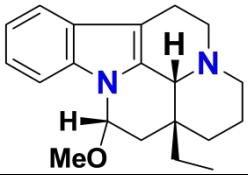
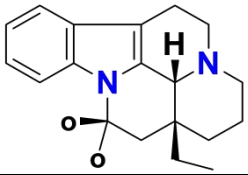
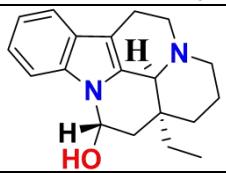
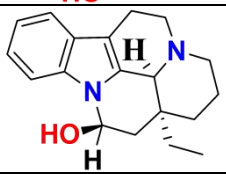
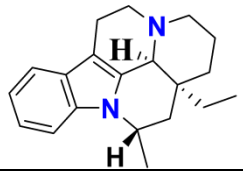
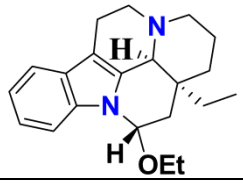
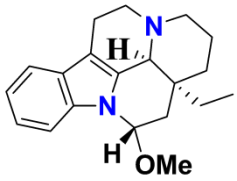
The lead compounds were collected from an article published by Kam-WengChong,Joanne Soon-Yee Yeap and his co-workers (2017). The compounds were selected from Eburnane alkaloids derivatives from the Malaysian Kopsia and LeuconoticsSpicies plant which includes eburnamonine, eburnamine, isoeburnamine, eburnamenine. All these structures were draw by chemdraw with possible structure definition file format for docking studies. The subsequent docking molecules viz. AChE were downloaded from protein databank (PDB) with a resolution of 2.20Å. The protein is a Crystal Structure of Recombinant Human Acetylcholinesterase in Complex with Donepezil included hetero atoms and its inhibitors were removed in an Discovery Studio Visualizer. Hetero atoms and inhibitor free protein structures were subjected to energy minimization using Avogadro Software.

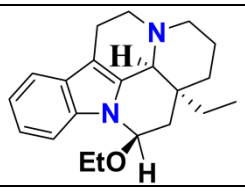
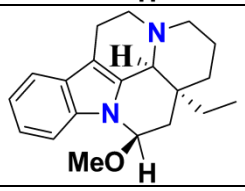
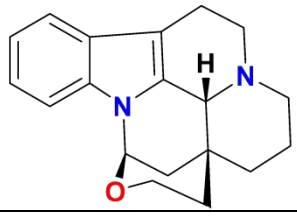
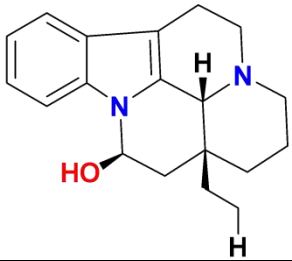
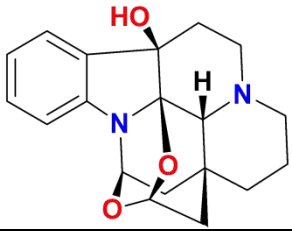
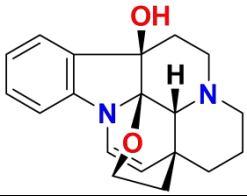
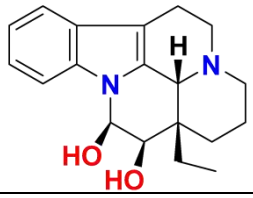
Ligand molecules

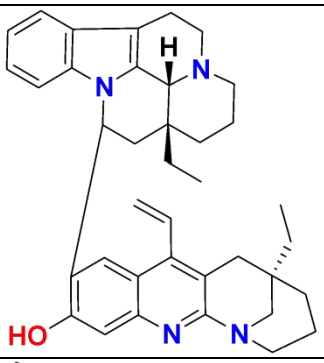
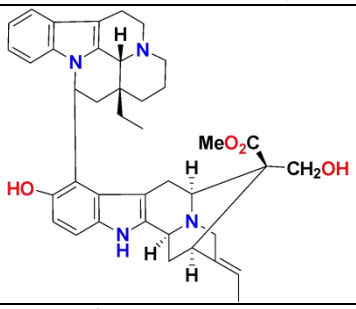
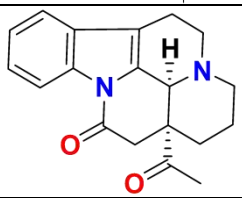
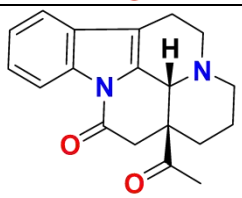
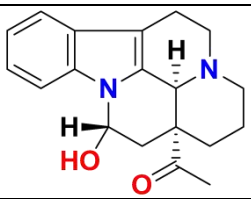
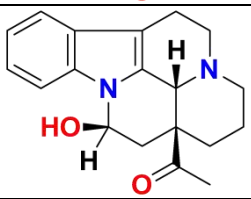
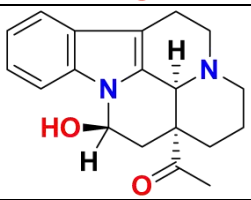
About 43 novel compounds containing Eburnane alkaloids were designed using CHEMDRAW software. Chemical formula and IUPAC name are listed below.

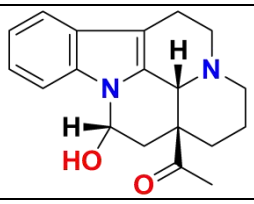
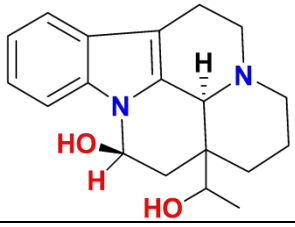
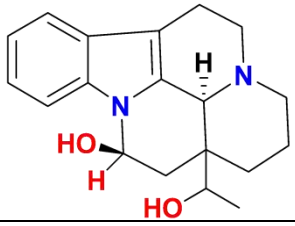
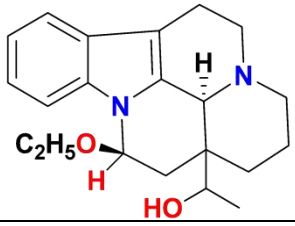
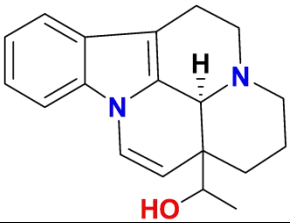
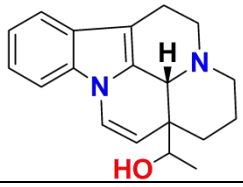
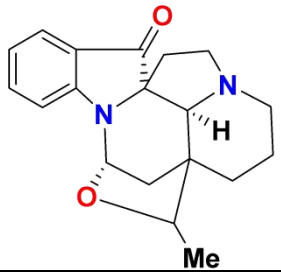
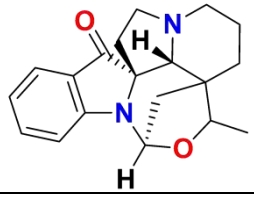
Table 1: Structure of Eburnane alkaloids, molecular formula and IUPAC name

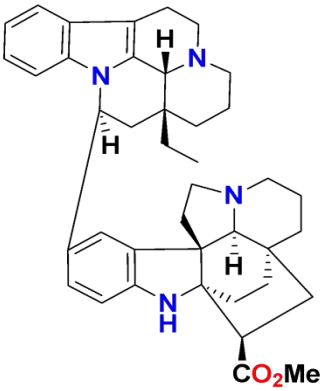
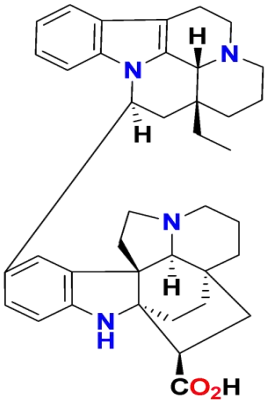
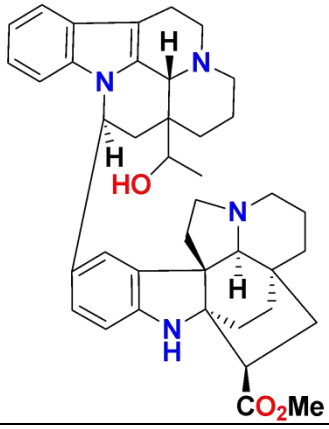
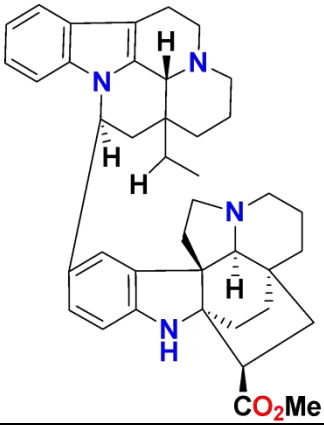
Compound Name	Structure	Molecular Formula	IUPAC Name
Donepezil		$C_{24}H_{29}NO_3$	2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one
4ey7_A1		$C_{20}H_{25}N_2O$	(41R,12S,13aR)-13a-ethyl-12-methyl-12-(l1-oxidaneyl)-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine
4ey7_A2		$C_{19}H_{24}N_2O$	(41R,12R,13aR)-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-ol
4ey7_A3		$C_{19}H_{22}N_2O_2$	(3a1S,6S,12aS)-4-methyl-2,3,13,14-tetrahydro-1H,3a1H,4H,6H,12H-3a,6-methanoindolizino[1',8':4,5,6][1,3]oxazepino[3
4ey7_A4		$C_{20}H_{26}N_2$	(41R,12S,13aR)-13a-ethyl-12-methyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine
4ey7_A5		$C_{21}H_{28}N_2O$	(41R,12R,13aR)-12-ethoxy-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine

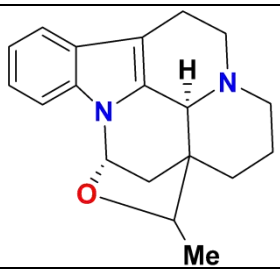
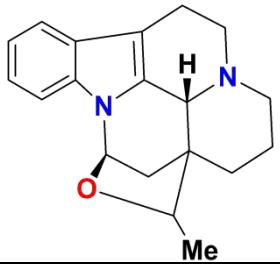
4ey7_A6		$C_{20}H_{26}N_2O$	(41R,12R,13aR)-13a-ethyl-12-methoxy-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine
4ey7_A7		$C_{21}H_{28}N_2O$	(41R,12S,13aR)-12-ethoxy-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine
4ey7_A8		$C_{20}H_{26}N_2O$	(41R,12S,13aR)-13a-ethyl-12-methoxy-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine
4ey7_A9		$C_{19}H_{22}N_2$	(41R,12S,13aR)-13a-ethyl-12-methoxy-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[1-de]pyrido[3,2,1-ij][1,5]naphthyridine
4ey7_A10		$C_{19}H_{24}N_2O$	(41S,12S,13aS)-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-ol
4ey7_A11		$C_{19}H_{24}N_2O$	(41S,12R,13aS)-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-ol
4ey7_A12		$C_{20}H_{26}N_2$	41S,12S,13aS)-13a-ethyl-12-methyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine
4ey7_A13		$C_{21}H_{28}N_2O$	(41S,12S,13aS)-12-ethoxy-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine
4ey7_A14		$C_{20}H_{26}N_2O$	(41S,12S,13aS)-13a-ethyl-12-methoxy-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine

4ey7_A15		$C_{21}H_{28}N_2O$	41S,12R,13aS)-12-ethoxy-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine
4ey7_A16		$C_{20}H_{26}N_2O$	(41S,12R,13aS)-13a-ethyl-12-methoxy-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine
4ey7_A17		$C_{19}H_{22}N_2O$	(41R,12R,13aS)-2,3,41,6,12,13-hexahydro-1H,5H-12,13a-(epoxyethano)indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine
4ey7_A18		$C_{19}H_{24}N_2O$	(41R,12R,13aR)-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-ol
4ey7_A19		$C_{19}H_{22}N_2O_3$	(7R,7aR,7bR,9R,11R,16bR)-1,2,5,6-tetrahydro-4H,7aH,11H,16bH-7,9:7,11-dimethano[1,3,5]dioxazino[5',4':1,2]indolo[2,3-a]quinolizin-16b-ol
4ey7_A20		$C_{19}H_{22}N_2O_2$	(41R,6aR,11aR,14aS)-2,3,5,6,13,14-hexahydro-1H,41H,6aH-11,14a-ethenoindolo[2,3-a]pyrano[4,3,2-ij]quinolizin-6a-ol
4ey7_A21		$C_{19}H_{24}N_2O_2$	(41R,12R,13R,13aS)-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine-12,13-diol

4ey7_A22		$C_{38}H_{44}N_4O$	(5R)-5-ethyl-9-((41R,13aR)-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-yl)-7-vinyl-3,4,5,6-tetrahydro-2H-1,5-methanoazocino[2,3-b]quinolin-10-ol
4ey7_A23		$C_{40}H_{46}N_4O_4$	methyl (6S,10R,11S,11aS,E)-1-((41R,13aR)-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-yl)-9-ethylidene-2-hydroxy-11-(hydroxymethyl)-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-b]quinolizine-11-carboxylate
4ey7_A24		$C_{19}H_{20}N_2O_2$	(41S,13aR)-13a-acetyl-2,3,5,6,13,13a-hexahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12(41H)-one
4ey7_A24A		$C_{19}H_{20}N_2O_2$	(41R,13aS)-13a-acetyl-2,3,5,6,13,13a-hexahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12(41H)-one
4ey7_A25		$C_{19}H_{22}N_2O_2$	1-((41S,12S,13aR)-12-hydroxy-2,3,5,6,12,13-hexahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-13a(41H)-yl)ethan-1-one
4ey7_A25A		$C_{19}H_{22}N_2O_2$	1-((41R,12R,13aS)-12-hydroxy-2,3,5,6,12,13-hexahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-13a(41H)-yl)ethan-1-one
4ey7_A26		$C_{19}H_{22}N_2O_2$	1-((41S,12R,13aR)-12-hydroxy-2,3,5,6,12,13-hexahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-13a(41H)-yl)ethan-1-one

4ey7_A26A		$C_{19}H_{22}N_2O_2$	1-((41R,12S,13aS)-12-hydroxy-2,3,5,6,12,13-hexahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-13a(41H)-yl)ethan-1-one
4ey7_A27		$C_{19}H_{24}N_2O_2$	(41S,12S)-13a-(1-hydroxyethyl)-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-ol
4ey7_A28		$C_{19}H_{24}N_2O_2$	(41S,12R)-13a-(1-hydroxyethyl)-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-ol
4ey7_A29		$C_{21}H_{28}N_2O_2$	1-((41S,12R)-12-ethoxy-2,3,5,6,12,13-hexahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-13a(41H)-yl)ethan-1-ol
4ey7_A30		$C_{19}H_{22}N_2O$	1-((41S)-2,3,5,6-tetrahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-13a(41H)-yl)ethan-1-ol
4ey7_A30A		$C_{19}H_{22}N_2O$	1-((41R)-2,3,5,6-tetrahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-13a(41H)-yl)ethan-1-ol
4ey7_A31		$C_{19}H_{22}N_2O_2$	(3a1S,6S,12aS)-4-methyl-2,3,13,14-tetrahydro-1H,3a1H,4H,6H,12H-3a,6-methanoindolizino[1',8':4,5,6][1,3]oxazepino[3,4-a]indol-12-one
4ey7_A31A		$C_{19}H_{22}N_2O_2$	(3a1R,6R,12aS)-4-methyl-2,3,13,14-tetrahydro-1H,3a1H,4H,6H,12H-3a,6-methanoindolizino[1',8':4,5,6][1,3]oxazepino[3,4-a]indol-12-one

4ey7_A32		$C_{40}H_{48}N_4O_2$	methyl (3aR,3a1S,5R,5aR,10bR)-9-((41R,12S,13aR)-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-yl)-2,3,4,5,11,12-hexahydro-1H,3a1H,6H-3a,5a-ethanoindolizino[8,1-cd]carbazole-5-carboxylate
4ey7_A33		$C_{39}H_{46}N_4O_2$	(3aR,3a1S,5R,5aR,10bR)-9-((41R,12S,13aR)-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-yl)-2,3,4,5,11,12-hexahydro-1H,3a1H,6H-3a,5a-ethanoindolizino[8,1-cd]carbazole-5-carboxylic acid
4ey7_A34A		$C_{40}H_{48}N_4O_3$	methyl (3aR,3a1S,5R,5aR,10bR)-9-((41R,12S)-13a-(1-hydroxyethyl)-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-yl)-2,3,4,5,11,12-hexahydro-1H,3a1H,6H-3a,5a-ethanoindolizino[8,1-cd]carbazole-5-carboxylate
4ey7_A35		$C_{40}H_{48}N_4O_2$	methyl (3aR,3a1S,5R,5aR,10bR)-9-((41R,12S)-13a-ethyl-2,3,41,5,6,12,13,13a-octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-yl)-2,3,4,5,11,12-hexahydro-1H,3a1H,6H-3a,5a-ethanoindolizino[8,1-cd]carbazole-5-carboxylate

4ey7_A36		$C_{19}H_{22}N_2O$	(3a1S,10S)-12-methyl-2,3,3a1,5-tetrahydro-1H,4H,10H,12H-11-oxa-3a,9b-diaza-10,12a-methanobenzo[a]naphtho[2,1,8-cde]azulene
4ey7_A36 A		$C_{19}H_{22}N_2O$	(3a1R,10R)-12-methyl-2,3,3a1,5-tetrahydro-1H,4H,10H,12H-11-oxa-3a,9b-diaza-10,12a-methanobenzo[a]naphtho[2,1,8-cde]azulene

Molecular docking studies

Docking is a kind of computational modelling, which facilitates the prediction of the preferred binding orientation of one molecule (e.g. Ligand) to another (e.g. Receptor) when both interact with each other to form a stable complex. Molecular docking studies on the above-mentioned selected compounds against AChE was done in auto-dock vina in PyRx software, which is freely accessible and designed for molecular docking studies. PyRx includes docking wizard with an easy-to-use user interface which makes it a valuable tool for computer-aided drug design. PyRx also includes chemical spreadsheet-like functionality and powerful visualization engine that are essential for rational drug design. The selected drug targets were energy minimized, and converted them into pdbqt format in PyRx.

Molecular interactions visualization

Autodockvina generated docking pair of protein and ligands was saved in pdb format, and were visualized in PyMOL visualization tool i.e. python-enhanced molecular graphics tool. It excels at three-dimensional visualization of proteins, small molecules, density, surfaces and trajectories. It also includes molecular editing, ray tracing, and movies. The ligand binding sites and surrounding amino acids of ligands were also visualized. Molecular interactions in the form of hydrogen bonds between proteins and ligands were characterized and the distance of hydrogen bonds was also calculated.

Active site prediction

Proteins have specific sites, the amino acid residue side chains that form an active cavity or cleft where the ligands or atoms or other proteins are capable to bind and are called active sites. The active sites of the AChE proteins were identified. Identified active sites were visualized in PyMOL molecular visualization tool.

RESULT AND DISCUSSION

Over the past few years, a number of reviews on the recently identified AChE inhibitors derived from marine, fungal, and plant sources have also

been published. Most of these AChE inhibitors are alkaloid compounds, such as steroidal alkaloids, indole, isoquinoline, quilizidine, and piperidine. Other metabolites that inhibit AChE include the alkaloids αchaconine, α-solanine, tomatine, berberine, palmatine, and jatrorrhizine. In this study, we performed docking studies in between 43 selected plant bioactive alkaloid compounds against the cholinergic enzyme's viz. AChE active sites. 43 ligands were docked against the acetylcholinesterase enzyme. The enzyme 4EY7 obtained from PDB is prepared. The ligands were prepared for docking. The docking using the Autodock 1.5.6 software was carried out. The binding energy by ranking along with the ligand efficiency, inhibition constant, intermolecular energy, desolvation, electrostatic, torsional, and total internal energies of the ranked docking pose. All these energies were recorded for the best fit of the model for all the 43 compounds (Table. 10). The binding energies of the compounds ranged between **-11.9** to **-7.7** kcal/mol. The compound *4ey7_A11* shows the highest binding energy of *–11.9* kcal/mol. The compounds 4ey7_A2 4ey7_A4 4ey7_A6 4ey7_A10 4ey7_A11 4ey7_A14 4ey7_A16 4ey7_A17 4ey7_A18 4ey7_A20 4ey7_A24 4ey7_A26 4ey7_A28 4ey7_A34A 4ey7_A35 exhibited the best binding energies of -10.1, -10.2, -10.2, -8.2, -10.5, -11.9, -10.3, -10.5, -10.6, -10.1, -10.5, -10.6, -10.4, -10.7, -10.6 and -10.9 kcal/mol respectively. The compound 4ey7_A11 with maximum inhibition constant binds AchE with the binding energy of -11.9 kcal/mol. The interactions between the target AchE and the ligands visualized by BIOVIA Discovery Studio were recorded in the table. The interactions with the acetylcholinesterase were based on two main positions in the gorge of the target

Table 2: The interactions between the target AchE and the ligands visualized by BIOVIA

Compound name	Binding energy (kcal/mol)	Ligand efficiency	Inhibition constant (µm)	Inter-molecular energy	Desolvation energy	Electro-static energy	Total internal energy	Torsional energy
4ey7_ Donepezil	-9.8	-0.11	56.343	-6.67	-6.28	-0.38	2.32	2.39
4ey7_A1	-8.8	29.77	389.05	-7.96	-7.48	-0.48	-1.52	1.79
4ey7_A2	**-10.1**	-0.15	575.44	-7.03	-6.41	-0.63	-2.61	1.79
4ey7_A3	-8.1	-0.14	524.81	-6.54	-5.9	-0.64	-2.55	1.79
4ey7_A4	**-10.2**	-0.15	8912.51	-6.81	-6.26	-0.54	-2.46	1.79
4ey7_A5	-8.3	-0.15	323.36	-6.78	5.73	-1.04	-1.42	1.79
4ey7_A6	**-10.2**	-0.17	23928	-7.48	-6.91	-0.57	-2.55	1.79
4ey7_A7	-8.2	-0.12	53703.2	-6.38	-5.43	-0.95	-4.15	2.39
4ey7_A8	-8.7	-0.08	109648	-6.18	-6.01	-0.18	2.97	2.98
4ey7_A9	-9.1	-0.28	12022	-10.29	-9.83	-0.46	-2.74	1.79
4ey7_A10	**-10.5**	-0.22	31622.8	-10.07	-9.32	-0.75	-1.26	1.79
4ey7_A11	**-11.9**	-0.24	1445.44	-9.37	-8.74	-0.62	-2.07	1.19
4ey7_A12	-8.5	-0.24	3019.95	-9.26	-8.66	-0.61	-1.08	1.19

4ey7_A13	-7.7	-0.25	758.58	-9.58	-8.94	-0.64	-0.6	1.19
4ey7_A14	**-10.3**	-0.15	30.903	-6.24	-5.83	-0.4	-2.54	1.19
4ey7_A15	-8	-0.25	3801.89	-9.75	-8.94	-0.81	-1.17	1.19
4ey7_A16	**-10.5**	-0.21	2691.53	-8.99	-8.37	-0.62	-2.65	1.79
4ey7_A17	**-10.6**	-0.22	1380.38	-9.33	-8.59	-0.75	-1.98	1.79
4ey7_A18	**-10.1**	-0.17	10000	-8.93	-8.16	-0.77	-2.42	2.39
4ey7_A19	-8.1	-0.22	794.33	-7.73	-7.17	-0.56	-1.9	1.19
4ey7_A20	**-10.5**	-0.2	4466.84	-7.51	-7.51	0	-1.92	1.79
4ey7_A21	-8.8	-0.15	2187.76	-6.54	-5.9	-0.64	-2.55	1.79
4ey7_A22	-9	-0.14	151356	-6.81	-6.26	-0.54	-2.46	1.79
4ey7_A23	-9.5	-0.15	1995.26	-6.78	5.73	-1.04	-1.42	1.79
4ey7_A24	**-10.6**	-0.15	6025.6	-7.48	-6.91	-0.57	-2.55	1.79
4ey7_A24A	-9.7	-0.17	6760.83	-6.38	-5.43	-0.95	-4.15	2.39
4ey7_A25	-9.7	-0.12	2290.87	-6.18	-6.01	-0.18	2.97	2.98
4ey7_A25A	-8.6	-0.08	1584.89	-10.29	-9.83	-0.46	-2.74	1.79
4ey7_A26	**-10.4**	-0.28	1258.93	-10.07	-9.32	-0.75	-1.26	1.79
4ey7_A26A	-8.7	-0.22	794.33	-9.37	-8.74	-0.62	-2.07	1.19
4ey7_A27	-9.2	-0.25	70.79	-9.26	-8.66	-0.61	-1.08	1.19
4ey7_A28	**-10.7**	-0.21	85.11	-9.58	-8.94	-0.64	-0.6	1.19
4ey7_A29	-9.5	-0.22	66.07	-6.24	-5.83	-0.4	-2.54	1.19
4ey7_A30	-8.2	-0.17	1000	-9.75	-8.94	-0.81	-1.17	1.19
4ey7_A30A	-8	-0.22	1000	-8.99	-8.37	-0.62	-2.65	1.79
4ey7_A31	-9.1	-0.25	741.31	-6.67	-6.28	-0.38	2.32	2.39
4ey7_A31A	-8.3	-0.15	44.67	-7.96	-7.48	-0.48	-1.52	1.79
4ey7_A32	-9.1	-0.25	60.26	-7.03	-6.41	-0.63	-2.61	1.79
4ey7_A33	-7.8	-0.21	2344.23	-6.54	-5.9	-0.64	-2.55	1.79
4ey7_A34A	**-10.6**	-0.22	114.82	-6.81	-6.26	-0.54	-2.46	1.79
4ey7_A35	**-10.9**	-0.17	457.09	-6.78	5.73	-1.04	-1.42	1.79
4ey7_A36	-8.4	-0.23	147.91	-7.48	-6.91	-0.57	-2.55	1.79
4ey7_A36A	-9.6	-0.32	63.1	-6.38	-5.43	-0.95	-4.15	2.39

Table 3:Dockingresultsof all the compounds using Auto dock 4.0software

COMPOUND NAME	VANDERWAALS	CONVENTIONALHYDROGEN BOND	STACKED INTERACTION	OTHERS
4ey7_ Donepezil	GLY B:448 HIS B:447 PHE B:297 PHE B:295 ARG B: 296 TYR B:124 VAL B:294 TRP B:286 SER B:293 GLU B:292	GLN B:291	TYR B:337 TRP B:86	LEU B:289 PHE B:338 TYR B:341
4ey7_A1	GLYA:448 GLY B:122 GLY B:12 PHE A:297 PHE A:295 TYR A:337	SER A:203 TYR A:124	TYR A:341 PHE A:338	HIS A:447 TRP A:86

	TRP A:286 GLU B:202			
4ey7_A2	GLYA:448 GLY B:122 GLY B:121 PHE A:297 PHE A:295 TYR A:337 TRP A:286 GLU B:202	SER A:203 TYR A:124	TYR A:341 PHE A:338	HIS A:447 TRP A:86
4ey7_A3	SER B:293 TYR B:341	VAL B:294 GLU B:292		LEU B:289 TRP B:286 TYR B:72
4ey7_A4	PHE A:297 TYR A:341 LEU A:76 TYR A:72 PHE A:295 SER A:293 VALA:294 TYR A:338 ARG A:296	SER A:203 TYR A:124	TYR A:124	TRP A:286
4ey7_A5	ASP A:74 THR A:75 TYR A:124 PHE A:297 TYR A:341 LEU A:289 TYR A:72 PHE A:295 SER A:293 VALA:294 PHE A:338 ARGA:296	TYR A:72		TRP A:286
4ey7_A6		ASP A:74 TYR A:124 TYR A:341 SER A:203	PHE A:338	HIS A:447 TRP A:86
4ey7_A7	ASP A:74 THR A:75 TYR A:124 TYR A:341 LEU A:289 GLU A:292		TYR B:341 TRP B:286	

	TYR A:72 PHE A:295 SER A:293 VAL A:294 ARGA:296			
4ey7_A8	ASP A:74 THR A:75 TYR A:72 TYR B:124 PHE B:295 TYR B:341 LEU B:76 TYR A:72 PHE A:295 SER B:293 VALB:294 PHE A:338 ARGA:296			TRP B:286
4ey7_A9				TRP A:286 TYR A:341
4ey7_A10				TRP A:286 TYR A:341
4ey7_A11	TYR B:124	SER B:125 HIS B:447 PHE B:297 ASP B:74 PHE B:338 GLYB:121 GLY B:122PHE A:295 SER A:293 TYR B:337 TRP B:286	TYR B:341	TRP B:86
4ey7_A12			TRP A:286 TYR A:341	
4ey7_A13	GLN A:291			TRP A:286 TYR A:341
4ey7_A14	GLN A:291			TRP A:286 TYR A:341
4ey7_A15	ASP B:74 ASN B:87 THR A:75 TYR B:124	SER B:125 TYR B:124		TRP A:286 TYR B:337

	PHE A:297 TYR B:341 TYR B:133 TYR B:72 GLY B:126 GLY B:448 GLY B:121 GLY B:120			PHE B:338 HIS B: 447 LEU B:130 TRP B: 86
4ey7_A16	ASP A:74 ASN A:87 PRO A:88 THR A:83 PHE A:297 TYR A:341 TYR A:133 GLY A:126 GLY A:448 GLY A:121 GLY A:120	SER A: 125 GLU A:202 TYR A:337	TRP A:86	HIS B: 447
4ey7_A17	TYR B:341			TRP A:286
4ey7_A18	TYR B:341		TRP A:286	
4ey7_A19	ASP B:74 ASN B:87 THR A:75 TYR A:124 SER A:125 PHE A:297 TYR B:341 TYR B:133 TYR B:72 GLY B:126 GLY B:448 GLY B:121 GLY B:120	SER B:125 TYR B:124	GLY A:120	TYR A:337 PHE A:338
4ey7_A20	TRP B:286 TYR B:124 HIS B:447 SER B:125 PHE B:29 PHE B:295 TYR B:337 TYR B:133 GLY B:122 GLY B:121		TYR B:341	TYR B:341 TRP B:86

	GLY B:120			
4ey7_A21	GLU A:292 LEU A:28 TYR A:124 TYR A:72 PHE A:297 PHE A:338 PHE A:295 VAL A:294 GLY A:342		TYR A:341 TRP A:286	SER A:293
4ey7_A22	ARG B:296 GLN B:369 HIS B:405 PRO B:410 PRO B:537 PRO B:368 PRO B:312 PRO B:232 ALA B:237 THR B:238 THR B:311 GLU B:313 GLU B:243 GLY B:234 GLY B:240 ARG B:247 VAL B:239 VAL B:370	ASN B:233 PRO B:235		
4ey7_A23				TYR A:341 TRP A:286
4ey7_A24	ASP A:74 ASN A:87 PRO A:88 PHE A:338 HIS A:447 TYR A:341 GLY A:126 GLY A:448 GLY A:121 GLY A:120	GLU A:202 TYR A:124	TRP A:86	TYR A:337
4ey7_A24A	LEU A:76 ASP A:74 ARG A:296 PHE A:297 PHE A:338 PHE A:295 HIS A:447 TYR A:72			TRP A:286

	TYR A:341 TRP A:124 VAL A:294 SER A:293			
4ey7_A25	LEU A:76 ASP A:74 ARG A:296 PHE A:297 PHE A:338 PHE A:29 TYR A:72 TYR A:341 TRP A:124 VAL A:294 SER A:293		TRP A:286	
4ey7_A25A	LEU B:280 HIS A:381 GLN A:527 HIS B:381 ASP A:384	GLN B:527		
4ey7_A26	ASP A:74 ASN A:87 PRO A:88 PHE A:338 HIS A:447 TYR A:341 GLU A:202 GLY A:126 GLY A:448 GLY A:121 GLY A:120	SER A:125 TYR A:124	TRP A:86	TYR A:337
4ey7_A27	LEU A:76 ASP A:74 ARG A:296 PHE A:297 PHE A:295 PHE A:338 PHE A:29 TYR A:72 TYR A:341 TRP A:124 VAL A:294 SER A:293		TRP A:286	4ey7_A27
4ey7_A28	GLU A:292 LEU A:289 ASP A:74 ARG A:296 PHE A:297 PHE A:295 PHE A:338 PHE A:29 TYR A:341 TRP		TRP A:286	

	A:124 VAL A:294 SER A:293			
4ey7_A29	LEU A:76 ASP A:74 ARG A:296 PHE A:297 PHE A:295 PHE A:338 PHE A:29 TYR A:72 TYR A:341 TRP A:124 VAL A:294 SER A:293			TRP A:286
4ey7_A30	ASP B:400 GLN B:527 GLN A:527 HIS A:381 HIS B:381 ALA B:528 THR B:383 ASP B:384 ARG B:525		TYR B:382	ALA B:397
4ey7_A30A	ALA B:397 ASP B:400 GLN B:527 LEU B:380 THR B:383 GLN A:527 TYR B:382 HIS A:381 HIS B:381 ALA B:528 THR B:383 ASP B:384 ARG B:525			
4ey7_A31	LEU A:289 GLY A:342 ARG A:296 PHE A:297 PHE A:295 PHE A:338 TYR A:72 TYR A:341 TRP A:124 VAL A:294 SER A:293			TRP A:286
4ey7_A31A	GLN B:413 ASN B:233 CYS B:409 PRO B:410	PRO B:235		HIS B:405 PRO B:537 GLU B:313

	TRP B:432 LEU B:536 PRO B:235			
4ey7_A32	GLY A :342 SER A:293 LEU A:289 VAL A:294 TYR A:341 ARG A:296 PHE A:295 PHE A:338 PHE A: 297 TYR A:124 TYR A: 72		TRP A:286	
4ey7_A33	LEU B:540 LEU B:536 PRO B: 537GLU B:313 PRO B:410 ASN B:233 GLY B:234 ASN B:533 TRP B:532 AGR B:296 VAL B:370			HIS B:405 PRO B:235
4ey7_A34A	GLN B:413 ASN B: 233 PRO B:410 CYS B:409 TRP B:532 LEU B:536 PRO B:235	ASN B:533		GLU B:313 HIS B:405 PRO B:537
4ey7_A35	ARG B:525 ALA B:528 HIS B:381 LEU B:380 GLN B:527 TRP A:385 THR A:383 HIS A:381 ASP A:384 ALA A:528 GLN A:527 THR B:383 ASP B:384 ALA B:397	TYR B:382		
4ey7_A36	TYR B:510 GLY B:523	ARG B:525	VAL B:408	VAL B:429

	LEU B:524 VAL B:330 VAL B:331 LYS B:332 ARG B:521			
4ey7_A36A	HIS A:447 GLY A:121 TYR A:133 TYR A:119 LEU A:130 GLY A:126 TYR A:124	SER A:125 ASP A:74	GLY A:120 TYR A:341 PHE A:338	TRP A:86 TYR A:337

CONCLUSION

Based on Insilco docking interaction and binding affinity studies, all the Eburnane type alkaloids have exhibited good binding affinity with the cholinergic enzymes AChE, the key therapeutic targets of AD. However, the compound 4ey7_A11 shows the highest binding energy of –11.9 kcal/mol and qualified all predicted drug property parameters. So, 4ey7_A11 compound is confirmed as the best to inhibit AChE targets to treat AD.

REFERENCES

1. Kam-Weng Chong, Joanne Soon-Yee Yeap, Siew-Huah Lim, Jean-Frédéric F. Weber, Yun-Yee Low, and Toh-SeokKamJournal of Natural Products 2017 80 (11), 3014-3024
2. Mishra CK, Shrivastava B, Sasmal D. PharmacognosticalStandarization and Phytochemical Identification of Fruit and Root of Carissa carandas Linn. Int J Pharm Pharm Sci. 2013;5(3):347–350.
3. Parvin MN. Phytochemical screening, antinociceptive, anthelmintic and cytotoxicity studies of the leaves of Carissa carandas Linn. (Family: Apocynaceae) Int. J. Sci. 2018;4(5):119.
4. Agarwal T, Singh R., Shukla AD, Waris I. In Vitro Study of Antibacterial activity of Carissa carandas leaf extracts. Pelagia Research Library. 2012;2(1):36–40.
5. Joglekar SN, Gaitonde BB. Histamine Releasing Activity of Carissa carandas Roots (Apocyaneceae) The Japanese journal of Pharmacology. 1970;20:367–372.
6. Mcgleenon BM., Dynan KB, Passmore AP. Acetyl cholinesterase inhibitors in Alzheimer's disease. Br J ClinPharmacol. 1999;48:471–480.
7. Sharma S., Nehru B., Saini A. Inhibition of Alzheimer's amyloid-beta aggregation in-vitro by carbenoxolone: Insight into mechanism of action. Neurochem. Int. 2017;108:481–493.
8. Lanctot KL, Herrmann N, Yau KK, Khan LR, Liu BA, Loulou MM, Einarson TR. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: A meta-analysis. Can. Med. Assoc. J. 2003;169(6):557–564.
9. Hubbard BM., Fentonm GW, Anderson JM. A Quantitative Histological Study of Early Clinical and Preclinical Alzheimer's disease. Neuropathol. Appl. Neurobiol. 1990;16(2):111 121.
10. Mcgleenon BM., Dynan KB, Passmore AP. Acetyl cholinesterase inhibitors in Alzheimer's disease. Br J ClinPharmacol. 1999;48:471–480.

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