# Novel selenium-based molecules as drug candidates for Alzheimer`s Disease (AD)

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- **Abstract:** Although Alzheimer's disease (AD) was firstly diagnosed over 100 years ago, the number of therapeutic options remains very limited, and the drug discovery process for AD is painstakingly slow. This is attributed to the complexity of the disease pathophysiology. Consequently, AD research has shifted from a monotherapy approach into a multi-targeted approach where one molecule is able to hit multiple targets. **Organoselenium compounds** as multi-targeted drug ligands (MTDLs) have been developed as potential inhibitors of Aβ aggregation and to reduce oxidative stress in AD, and to provide novel scaffolds for designing promising disease-modifying agents. By utilizing computational chemistry principles, organoselenium tricyclic scaffolds were designed that exhibited promising binding affinity, and efficiency toward **Aβ protein**, different organic chemistry procedures were applied to develop synthetic methods to obtain the target derivatives. Further studies include structure-activity relationship (SAR) optimization by carrying out in vitro fluorescence kinetic studies to determine the inhibition of Aβ40 aggregation, transmission electron microscopy (TEM) studies, evaluation of antioxidant properties, and cell culture studies to identify novel organoselenium derivatives as MTDLs. Preliminary studies demonstrate significant reduction in the Aβ40 aggregation suggesting their application in the development of novel therapeutic agents for the treatment of AD.
- **Keywords:** Alzheimer`s Disease (AD), organoselenium, MTDL, Aβ protein, structure-activity relationship (SAR) , ROS, antioxidant properties
- **Background:** Alzheimer`s disease (AD) is a chronic neurodegenerative disorder that starts slowly and gradually worsens over time. It is characterized clinically by the presence of two common pathological hallmarks that can be detected in AD patient`s brains: extracellular senile plaques and intracellular neurofibrillary tangles (NFT). In the market, there are only four available drugs that have been approved by the US Food and Drug Administration (FDA), donepezil (Aricept®), rivastigmine (Exelon®), galantamine (Razadyne®), and tacrine (Cognex®) that had been withdrawn from the market due to its hepatotoxicity (Fig. **1**). Another approved medication for AD is memantine (Namenda®) (Fig. **1**) which is mainly prescribed for moderate to severe stages of AD These medications are only effective for the management of AD symptoms, neither curing AD nor halting the disease progress. Interestingly, all of the currently marketed AD therapeutics is based on the classical "one drug, one target" concept that is no longer effective for the treatment of AD due to the multi-factorial nature of the disease. Consequently, AD research has shifted from a monotherapy approach into a multi-targeted approach that provide us with great opportunities to modulate a plethora of therapeutic targets to facilitate the discovery of novel agents for AD. Based on our previous research, tacrine, Fig. **1 (A)**, has been utilized as a template for the design of novel anti-AD hybrid molecules that exhibited very promising inhibitory activities against cholinesterase, and Aβ aggregation. In this regard, some novel organoselenium derivatives, as multi-targeting ligands to treat AD, have been developed which utilize the promising tricyclic nucleus with the incorporation of selenium atom to provide intrinsic antioxidant properties for the designed compounds Fig. **1 (B,C)**.

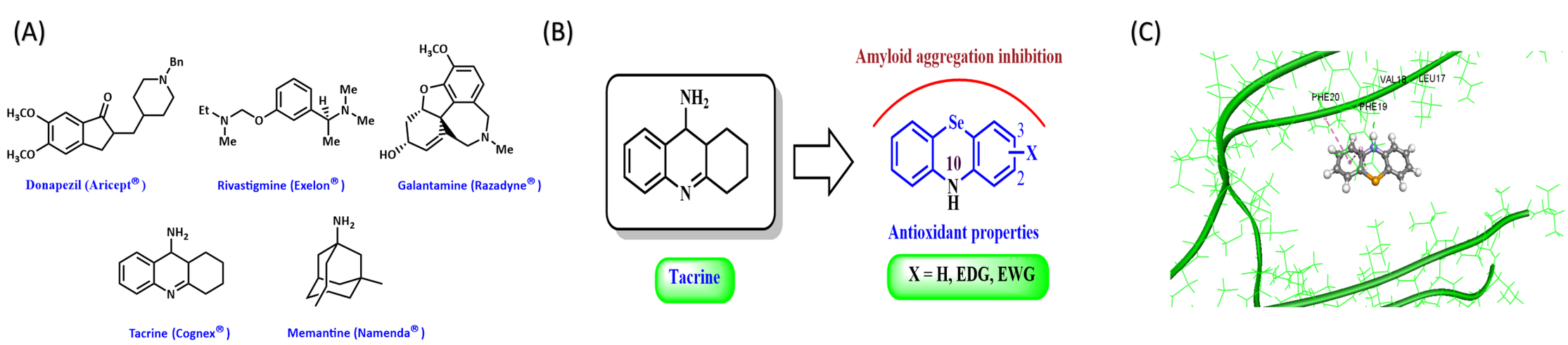
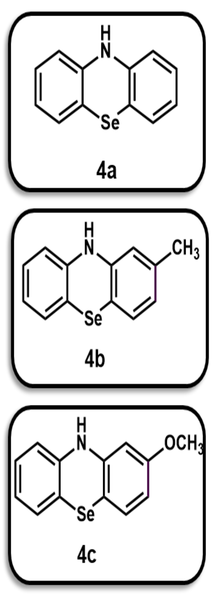



**Fig 1:** (**A**) Chemical structures of the FDA approved medications for AD, (**B**) Structural design for the organoselenium scaffold, (**C**) Binding mode of 10H-phenoselenazine compound (ball and stick cartoon) with Aβ40 dimer (PDB ID: 2LMN), CDOCKER interaction energy = −14.23 kcal $mol^{-1}$

**Table 1:** ThT-based Aβ40 aggregation kinetic assay for the PSZ compounds **4a-c**, Resveratrol, and Methylene blue (MB) at concentrations 1-25 µM over 24 h




| Compound | % inhibition at: [a] 1 µM | 5 µM | 10 µM | 25 µM |
|---|---|---|---|---|
| **4a** | 55.7 | 72.2 | 60.2 | 20.2 |
| **4b** | 68.9 | 31.4 | 77.7 | **89.8** |
| **4c** | NA | 44.5 | 50.4 | 28.5 |
| **MB** | 77.5 | 93.9 | 96.5 | 98.5 |
| **Resveratrol** | NA | 70.6 | 88 | 94.5 |

[a] Percent aggregation inhibition values are average of (n = 3) for one experiment.
NA = not active

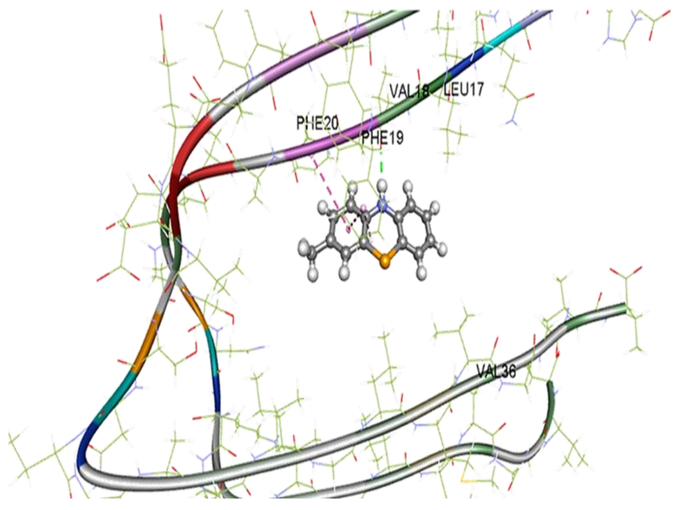



**Fig 2:** Binding mode of 2-Methyl-10*H*-phenoselenazine compound (ball and stick cartoon) with Aβ40 dimer model (PDB ID: 2LMN), CDOCKER interaction energy = −15.15 kcal mol−1

**Results:** Biological screening of our synthesized phenoselenazine compounds **4a-c** showed a good inhibition against Aβ40 aggregation compared to our standard compounds, Resveratrol and Methylene blue (MB), Particularly methyl derivative (4b) which exhibited ~ 90% inhibition at 25 µM (Table **1**). Our biological results were compatible with the docking studies against Aβ40 dimer model that show favourable interaction with different amino acid residues (Fig. **2**).

**Conclusions:** Based on computational studies, tricyclic scaffold is a promising nucleus for developing novel anti-AD therapeutics capable of exhibiting disease-modifying properties. Our proposed PSZ compounds have the potential to prevent Aβ aggregation with a good scavenging capability towards ROS; therefore, they can act as multi-targeted ligands against AD.

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