Rational Designing, Synthesis and Multibiological Profiling of Novel Benzothiazole-Piperazine Hybrids against Alzheimer's disease

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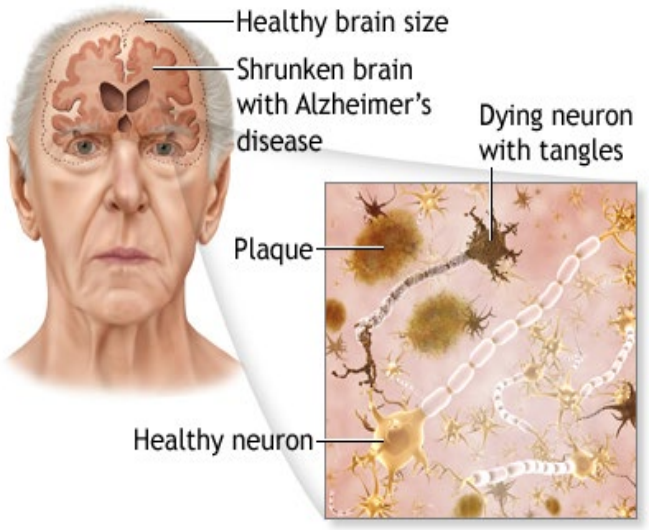
Alzheimer's Disease

- Age related neurodegenerative disorder.
- Loss of memory, impairment of language, personality changes and decline in intellectual ability.
- 50 million people affected worldwide.
- Projected to reach 152 million by the year 2050.

(2018 world Alzheimer's Report)



(Jack Jr CR et al 2010)

Current therapeutic options for the treatment of AD :

- Cholinesterase inhibitors : Donepezil, Rivastigmine, and Galantamine and an NMDA receptor antagonist – Memantine

✓ Modest improvement in memory and cognitive function

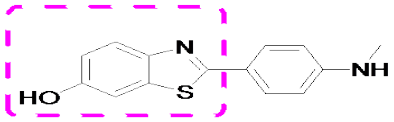
✓ They do not prevent progressive neurodegeneration

- To scuffle with this multifactorial disease, a new horizon in drug research involving **Multi-Target-Directed Ligand (MTDL)** has their potential advancements in the treatment of AD.

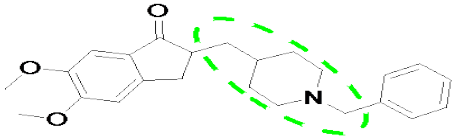
Objectives and Methodology

Design and Synthesis → Biochemical assays → *In-silico* studies → Cell-culture studies → *In-vivo* studies

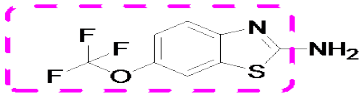
Design and synthesis of the Benzothiazole-piperazine derivatives



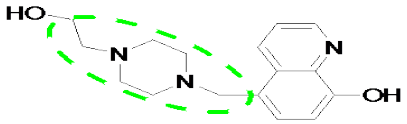
PIB (Potent amyloid binding agents)



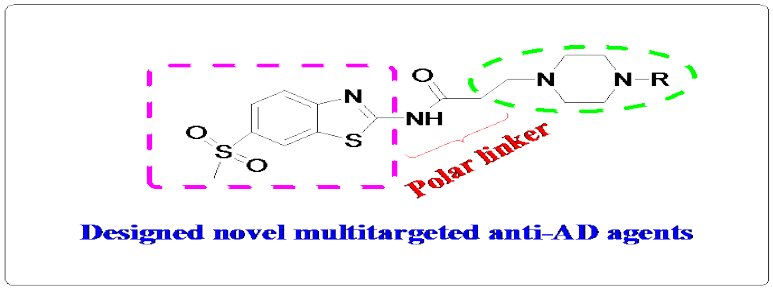
Donepezil (Standard AChE inhibitor)



Riluzole (Potent neuroprotective Drug)

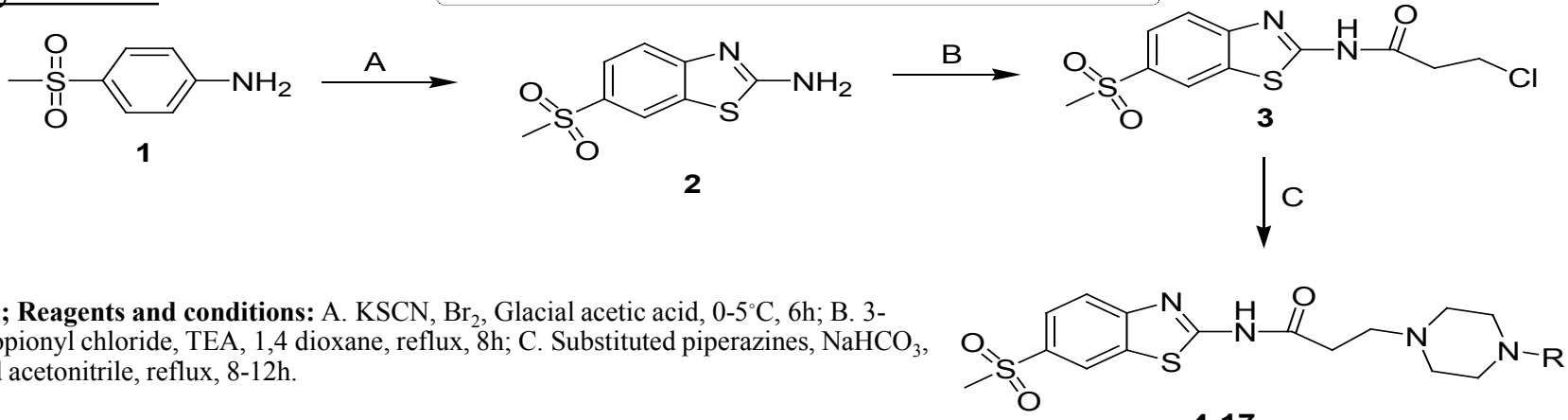


VK-28 (Potent neuroprotective agent)



Designed novel multitargeted anti-AD agents

Synthesis



Scheme 1; Reagents and conditions: A. KSCN, Br_2, Glacial acetic acid, 0-5°C, 6h; B. 3-Chloropropionyl chloride, TEA, 1,4 dioxane, reflux, 8h; C. Substituted piperazines, $NaHCO_3$, NaI, dried acetonitrile, reflux, 8-12h.

AChE and BuchE inhibition and Abeta aggregation inhibition studies

a

Compounds	IC_{50} ± SD(μM) AChE [a]	IC_{50} ± SD(μM) BuChE [b]	Self $A\beta_{1-42}$ aggregation inhibition(%) [c]
4	24.14 ± 0.721	>100	54.29502 ± 0.265
5	18.31 ± 0.777	>100	55.53029 ± 0.134
6	13.05 ± 0.813	>100	51.74112 ± 0.289
7	11.25 ± 1.803	>100	54.34428 ± 0.427
8	20.18 ± 1.435	>100	54.43522 ± 0.159
9	14.45 ± 1.032	>100	52.31708 ± 0.114
10	7.834 ± 0.810	>100	53.40836 ± 0.322
11	4.548 ± 0.984	**>100**	52.22614 ± 0.513
12	**2.319 ± 0.410**	**>100**	**53.30605 ± 0.541**
13	10.87 ± 0.657	>100	53.6736 ± 0.228
14	14.59 ± 0.438	>100	54.48827 ± 0.885
15	19.48 ± 0.452	>100	52.44591 ± 1.203
16	5.244 ± 0.690	>100	45.3109 ± 0.241
17	26.43 ± 0.551	>100	53.40836 ± 0.805
Donepezil	0.049 ± 0.05	8.71 ± 1.36	n.a
Curcumin	n.a	n.a	50.23 ± 1.201

[a] 50% inhibitory concentration (means ± SD of three experiments) of AChE from electric eel.
[b] 50% inhibitory concentration (means ± SD of three experiments) of BuChE from equine serum.
[c] Inhibition of self-induced $A\beta 1_{-42}$ aggregation (50 μM) by tested inhibitors at 50 μM by Thioflavin-T based fluorescence method (means ± SD of three experiments).

b

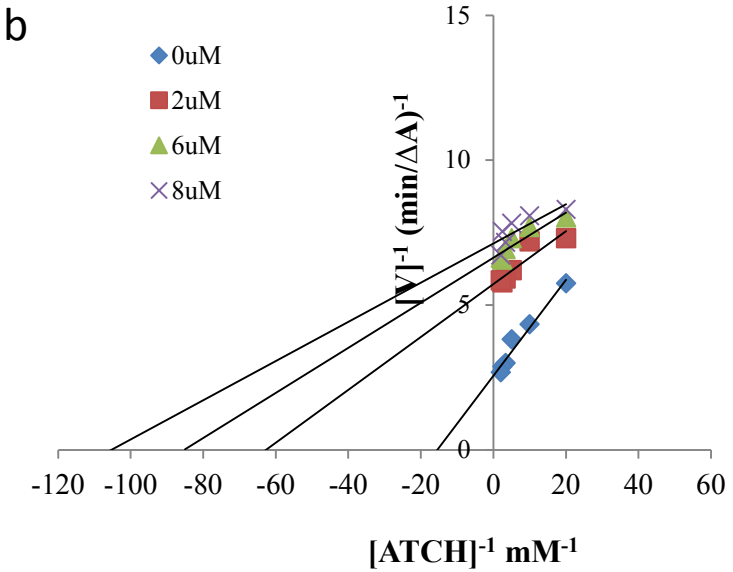


Fig: Kinetics of Compound 12

c

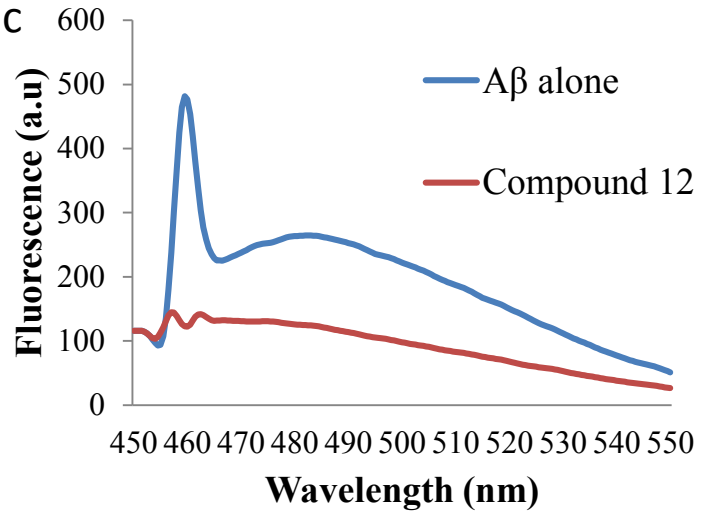
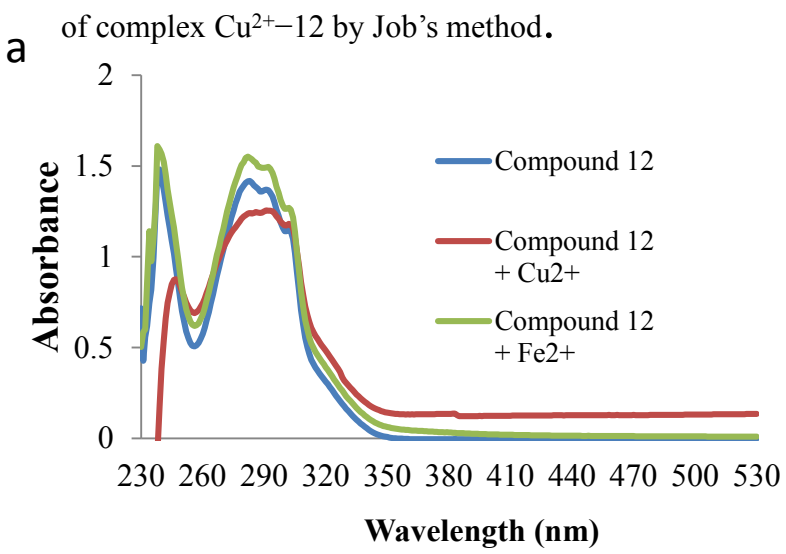
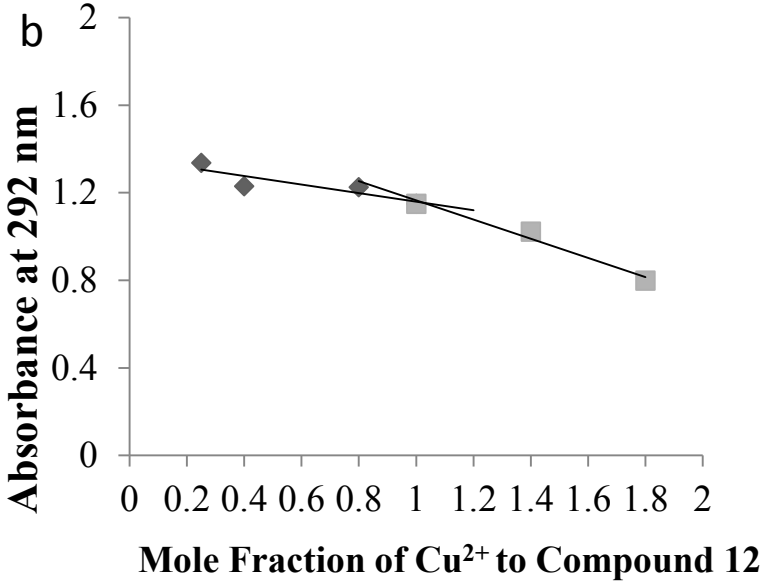


Fig: ThT emission fluorescence spectra

Metal Chelation studies:

(a)UV absorbance spectrum of compound 12 alone and in the presence of CuSO4 & FeSO4 (b) Determination of the stoichiometry of complex Cu^{2+}−12 by Job's method.





Molecular Docking studies:

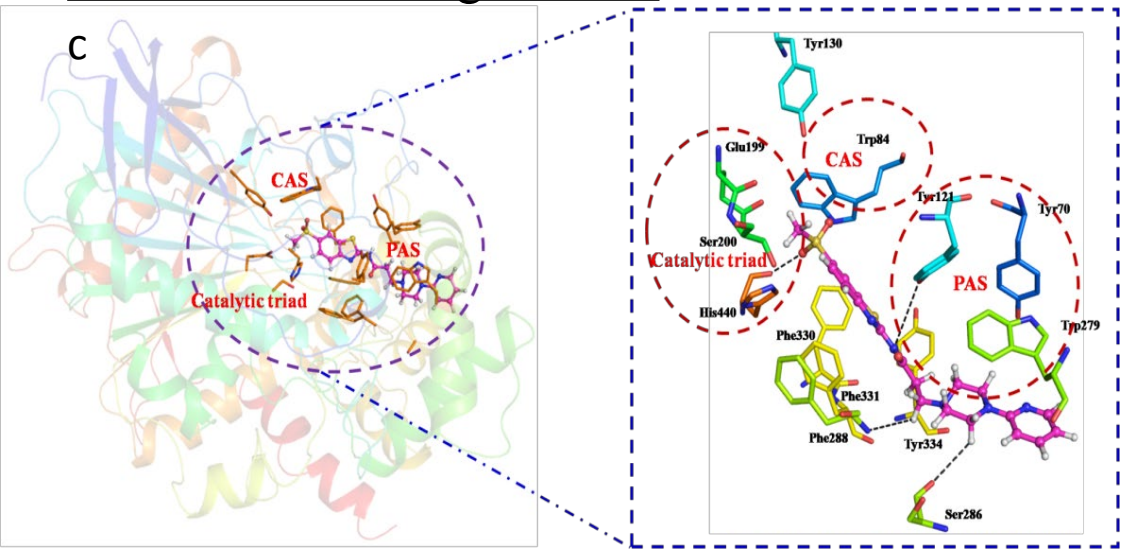


Fig: Proposed binding mode of compound 12 in the active site of AChE (PDB: 1EVE).

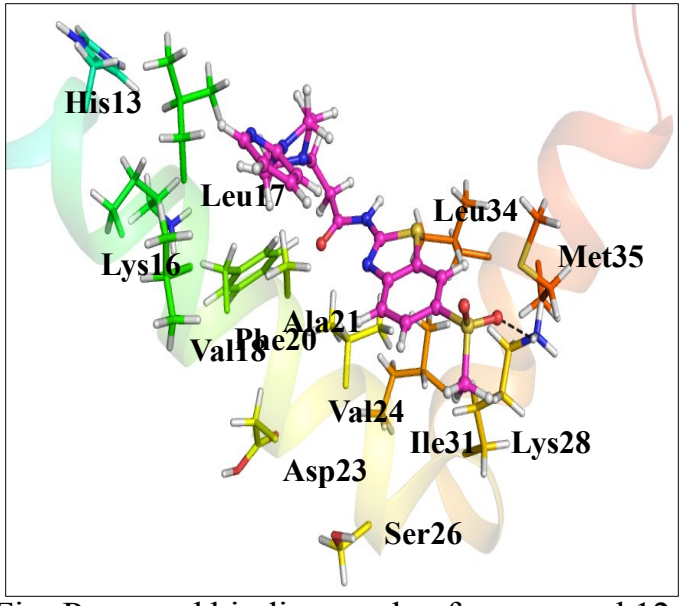
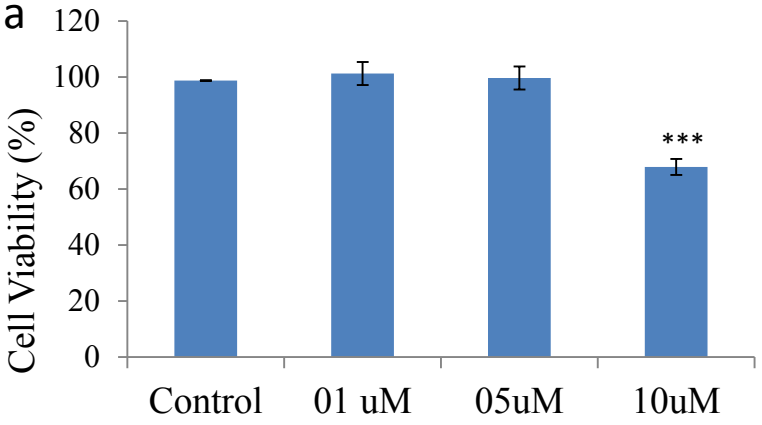


Fig: Proposed binding mode of compound 12 in the active site of $A\beta_{1-42}$ (PDB: 1IYT).

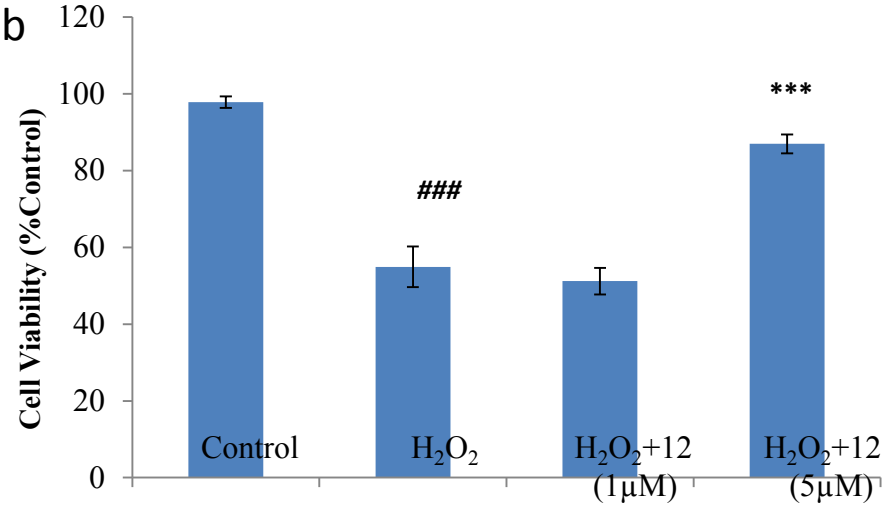
In-vitro studies

a



Effect of different concentrations of compound 12 on cell viability in SHSY5Y cells after treatment for 24 hrs.

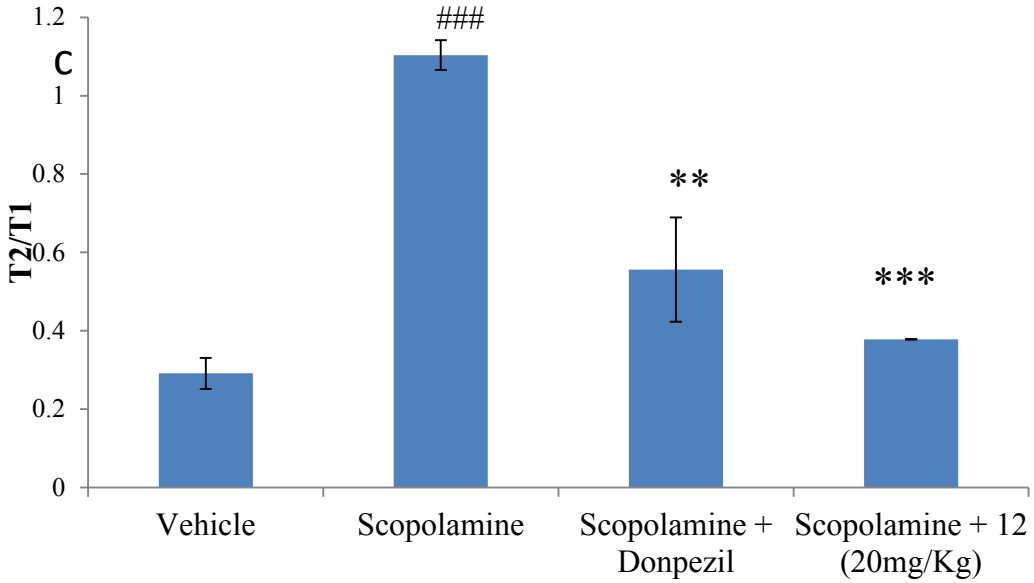
b



Protective effects of compound 12 on H_2O_2-induced cell death in SHSY5Y cells.

In-vivo studies

c



Treatment effect of test compound 12 at 20mg/kg on the T2/T1 (second interaction trial/ first interaction trial ratio) in social recognition test in scopolamine induced model.

d

Groups	Transfer Latency (T_L) in Seconds
Group 1 Vehicle	9.82 ± 1.42
Group 2 Scopolamine	22.00 ± 0.81
Group 3 Scopolamine + Donepezil	15.08 ± 1
Group 4 Scopolamine + 12 (10mg/Kg)	12.81 ± 2.08
Group 5 Scopolamine + 12 (20mg/Kg)	12.62 ± 2.60

Treatment effect of test compound 12 at 10mg/kg and 20mg/kg on the transfer latency (TL) in elevated plus maze task in scopolamine induced model.