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Piperidine Derivatives as Next-Generation Dual Cholinesterase Inhibitors: From Rational In Silico Design to In Vitro Validation

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INTRODUCTION & AIM

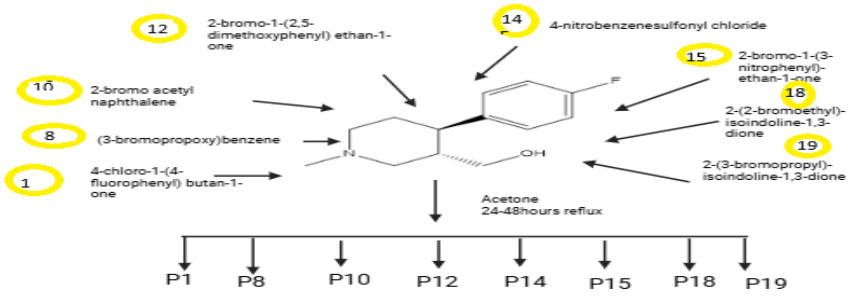
Alzheimer's disease (AD) necessitates novel therapeutics. This study aimed to design and develop new heterocyclic cholinesterase inhibitors using a rational, integrated computational and experimental approach, with a focus on achieving potency and selectivity, particularly for butrylcholinesterase (BuChE).

METHOD

Study is divided into three phases.

1-Synthesis

Synthesis of (3S,4R)4-flouromethyl-piperidinemethanol Derivatives and characterization through spectral analysis.



2-In-vitro studies

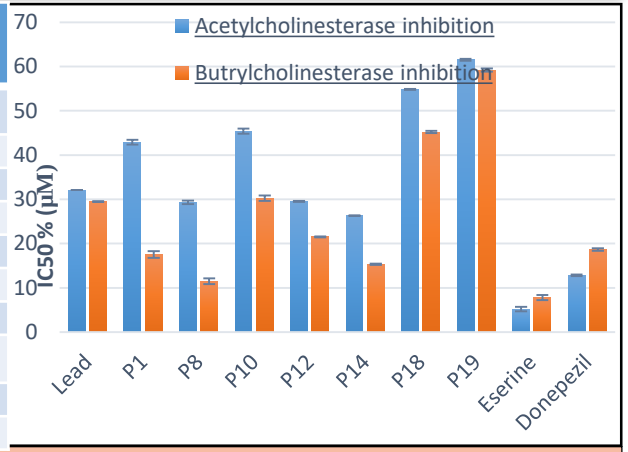
Ellman's method is use for acetylcholinesterase and butrylcholinesterase inhibitory activity

3-In-silico studies

Molecular modelling of, P8 and p14 against human recombinant acetylcholinesterase (PDB ID: 4EY7), and human recombinant butrylcholinesterase (PDB ID: 4BDS), were carried out to evaluate the ligand-protein interaction using molecular operating environment (MOE 2014) software.

RESULTS & DISCUSSION

Sr. #	COMPOUND	Acetylcholinesterase Inhibition Activity IC_{50} (µM) ± SEM[b]	Butrylcholinesterase Inhibition Activity IC_{50} value(uM)±SEM[b]	Similarity Index (SI)[c] (AChE/BuChE)	Preference
1	Lead	32.1 ± 0.56	29.5 ± 0.76	1.088	AChE/BuChE
2	P 1	42.9 ± 0.39	17.5 ± 0.67	2.451	BuChE
3	P 8	29.3 ± 0.56	11.5 ± 0.62	2.547	BuChE
4	P 10	45.4 ± 0.11	30.24 ± 0.14	1.501	BuChE
5	P 12	29.5 ± 0.09	21.5 ± 0.16	1.372	BuChE
6	P 14	26.3 ± 0.11	15.3 ± 0.26	1.718	BuChE
7	P18	54.8 ± 0.22	45.2 ± 0.36	1.21	BuChE
8	P19	61.5 ± 0.51	59.2 ± 0.61	1.038	BuChE(weak)
9	Eserine	5.2 ± 0.18	7.8 ± 0.28	0.667	AChE
10	Donepezil	12.83 ± 0.44	18.66 ± 0.66	0.687	AChE



Docking studies elucidated a binding mode involving anchoring in the catalytic site and π–π interactions in the peripheral site. In vitro testing identified two potent dual inhibitors, P8 (IC_{50} = 11.5 µM for BuChE) and P14 (IC_{50} = 15.3 µM for BuChE), which outperformed donepezil for BuChE inhibition. The series exhibited a selective profile favoring BuChE. Structure-activity relationship (SAR) confirmed terminal group planarity as critical for potency. All compounds exhibited favorable drug-like properties.

CONCLUSION

The study successfully identifies P8 and P14 as promising, drug-like lead compounds with a superior BuChE-inhibitory profile, making them viable scaffolds for developing next-generation AD therapeutics. The work validates the combined computational and experimental framework for rational inhibitor design

FUTURE WORK / REFERENCES

Islam, M. T., Aktaruzzaman, M., Barai, C., Rafi, F. I., Hasan, A. R., Tasnim, T., Sarder, P., Albadrani, G. M., Al-Ghadi, M. Q., & Sayed, A. A. (2025). In silico screening of naturally derived dietary compounds as potential butyrylcholinesterase inhibitors for Alzheimer's disease treatment. Scientific Reports, 15(1), 17134.

Yekta, R., Sadeghi, L., & Dehghan, G. (2020). The inefficacy of donepezil on glycated-AChE inhibition: Binding affinity, complex stability and mechanism. International Journal of Biological Macromolecules, 160, 35-46.