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Screening Cholinesterase Inhibitory Potential of Selected Amines

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Abstract

Cholinesterase inhibition has gained attention in the treatment of some disease states, covering cholinergic deficiency. Alzheimer's disease (AD) can be counted as the most important one among them. Indeed, the current drugs used in the treatment of AD are cholinesterase inhibitor molecules, besides memantine, and biological new drugs. Many pharmacophores have been suggested so far for cholinesterase inhibition and many of them possess a basic center with an amine function. In the present study, we have selected some simple amines and investigated their potential to inhibit acetylcholinesterase and butyrylcholinesterase enzymes. The results indicated that simple amines by themselves do not have strong potential unless they are used with other pharmacophores.

Keywords

Alzheimer's Disease, cholinesterases, selected amines, pharmacophore.

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INTRODUCTION

Athough Alzheimer's disease (AD) was first discovered and diagnosed over a century ago, there are still a lot of unanswered concerns, particularly in relation to its pathophysiology (Gulcan and Orhan 2020). Unfortunately, AD-related dementia, which impairs cognition, is the most prevalent kind of dementia. Given that AD is a progressive disease, symptoms of dementia deteriorate over time and can be classified as mild, moderate, or advanced (Pagani *et al.*, 2017).

Many validated and non-validated targets have been proposed so far for the therapy of AD, despite the fact that the pathophysiology of the illness is too complex to completely comprehend. However, cholinesterase inhibition still stays as the major validated system. From this perspective, cholinesterase inhibitors are still important, and they are the only drugs used in the treatment of AD, besides memantine, and the new biological drugs offered for amyloid beta clearance in the mild stage of the disease (Krall *et al.*, 1999).

Four cholinesterase inhibitors have been available on the market since the 1980s to treat dementia associated with AD (Gulcan and Orhan 2021). Tacrine was the first one, however it was withdrawn from the clinic with respect to its hepatotoxicity (Blackard *et al.*, 1998). From the perspectives of source, target, dose, pharmacokinetics, and pharmacodynamics, the remaining three (i.e., donepezil, galantamine, rivastigmine) exhibit a variety of characteristics (Figure 1). Therefore, there has been a continuous interest in the screening of diverse structures (Gao *et al.*, 2021).

There have been many scaffolds used so far with diverse heterocycles to obtain potent cholinesterase inhibitor molecules. Among the pharmacophores employed, amine portion is indispensable in the majority of them (Norouzbahari *et al.*, 2018). Within this study, we have employed ten simple amine molecules and aimed to investigate their potential to inhibit cholinesterase enzymes.

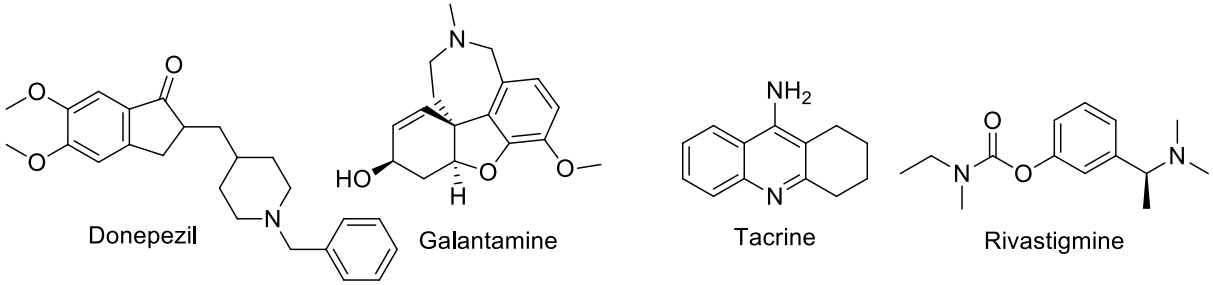

Figure 1: Cholinesterase inhibitor drugs.

MATERIALS AND METHODS

All reagents and organic solvents were obtained from Sigma Aldrich through the aid of local vendors and used directly unless otherwise stated.

Enzyme assays

The title compounds' potential to inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) enzymes was measured employing Ellmann's method. Accordingly, each enzymatic reaction was prepared with a 200 µL total volume. 168 µL of 50 mM Tris HCl buffer (pH 8.0), 10 µL of 6.8 mM DTNB solution (0.34 mM final), 20 mM $MgCl_2$, and 100 mM NaCl, and 10 µL of AChE or BuChE solution were mixed. The reactions were initiated by the addition of 10 µL of either 10 mM acetylthiocholine iodide or 10 µL of 1.5 mM butyrylthiocholine iodide. Measurements were achived using UV absorptions at 412 nm following incubation for 15 minutes at 27°C (Varioskan Flash, Thermo Scientific, USA). By comparing the rates of reaction of samples relative to blank samples (DMSO and methanol), the percentage of inhibition of AChE and BuChE was calculated. The compounds were tested at 40 µM level. Each concentration was evaluated in triplicate using each measurement. The mean ± standard deviation was calculated.

RESULTS AND DISCUSSION

The title compounds employed and the percent inhibition results obtained are summarized in Table 1.

Table 1: The compounds and inhibitions of AChE and BuChE (%).

Compound	AChE	BuChE
1-Naphtylamine HCl	10.63 ± 0.011	34.84 ± 0.038
Dimethylamine HCl	18.33 ± 0.035	26.04 ± 0.021
N-benzylpiperazine 2HCl	25.12 ± 0.024	21.86 ± 0.012
6,7-Dimethoxy-1,2,3,4-tetrahydoisoquinoline	41.74 ± 0.019	41.85 ± 0.014
Hydroxylamine HCl	32.83 ± 0.026	11.40 ± 0.024
N benzyl methyl amine	39.38 ± 0.032	13.92 ± 0.027
Aniline	21.51 ± 0.048	6.06 ± 0.011
Morpholine	31.61 ± 0.036	11.72 ± 0.025
Triethylamine	40.69 ± 0.002	34.59 ± 0.027
1,2,3,4-Tetrahidraisoquinoline	44.69 ± 0.051	35.22 ± 0.028
Donepezil 10 µM	100 ± 0.007	83.10 ± 0.002
Galantamine 10 µM	96.11 ± 0.006	54.59 ± 0.002

Accordingly, none of the simple amines displayed superior activity over the standards (donepezil and galantamine) employed. The most active amines were

found to be the ones possessing benzylamine moiety. As seen in 1-naphtylamine and aniline examples, direct amine attached substituents generated lower potential. The most active compound was found to be an isoquinoline derivative.

Overall, the results definitely displayed that those simple amines alone are not potential inhibitors of cholinesterases. However, they are important components of pharmacophores in drug design to inhibit cholinesterase enzymes.

CONCLUSION

Within this limited research work, 10 amines have been selected and screened for their potential to inhibit acetylcholinesterase and butyrylcholine-esterase enzymes. With respect to the standards employed, low potential inhibitions were measured. The results clearly stated their function as a pharmacophore, since they are employed as an important scaffold in cholinesterase inhibitors. However, they have limited potential by themselves to inhibit cholinesterase enzymes.

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