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Novel Hybrid Molecules of Cholinesterase Inhibitor for Alzheimer's Disease: A Systematic Review.

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ABSTRACT

Acetylcholinesterase (AChE) inhibitor is a basic drug design recently used in treating Alzheimer's disease (AD). However, butyrylcholinesterase (BuChE) also suggested to be responsible for the hydrolysis of acetylcholine (ACh) and its inhibition may benefit in the latter stage of AD. Nonetheless, the search for potent AChE and BuChE inhibitor is still in need, in curing this neurodegenerative disorders. Numerous hybrid molecules were designed for the dual inhibition of AChE and BuChE. However, these molecules have different selectivity towards AChE and BuChE. Therefore, this systematic review aims to determine a rational design that can exhibit high inhibition against AChE and BuChE activity. ScienceDirect, Pubmed, Medline & Ovid and ISI Web of Science database from January 2006 to September 2016 were searched systematically with some specific inclusive and exclusive criterias. The synthesis of hybrid molecules and anticholinesterase (AChE and BuChE) test conducted in human AChE and BuChE with IC_{50} values were included in this review. Two reviewers independently evaluated the studies and extracted the data using a standardized data collection form. Only one study was identified from the search with IC_{50} value recorded lower than rivastigmine. Compound **1** (showed high inhibition against AChE (IC_{50} = 0.34 µM) and BuChE (IC_{50} = 0.88 µM). This review has successfully determined a novel hybrid molecule containing 2-arylbenzofuran skeleton, which possess dual inhibition of anticholinesterase for neurodegenerative disorders especially Alzheimer disease.

Keywords: Hybrid molecules; anticholinesterase; Alzheimer

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder affecting elderly, mostly at the age of 65 and above [1]. AD is often manifested by the reduced levels of acetylcholine, β-amyloid senile plaques and neurofibrillary tangles formation within the brain of afflicted individuals. Accordingly, the enhancement of cholinergic neurotransmission and the inhibition of β-amyloid peptide formation are considered as main approaches for effective treatment of Alzheimer's disease [2].

It has been reported that acetylcholinesterase (AChE) level decreases while butyrylcholinesterase (BuChE) activity increases during AD progression. The gradual shift from AChE to BuChE responsible for the degradation of ACh could be the reason for the inefficacy of AChE selective inhibitor. Therefore, hybrid molecule with dual inhibition of AChE and BuChE may afford several advantages including greater and broader symptomatic effects, particular behavioural benefits and the absence of AChE upregulation [3-6]. In 2003, there are five AChE inhibitors approved by U.S. Food and Drug Administration (FDA) to treat Alzheimer's symptoms including donepezil (Aricept®), rivastigmine (Exelon®), tacrine (Cognex®), galantamine (Razadyne®) and memantine (Namenda®). Rivastigmine is the only AChE inhibitor which also inhibit BuChE and demonstrated beneficial effects on memory acquisition and consolidation. Nevertheless, like any other drugs, rivastigmine may cause several side effects such as nausea, diarrhoea and dizzinesss [7-8].

Following the production of rivastigmine, more studies started to develop novel anti-Alzheimer's drugs with dual inhibition of AChE and BuChE. Tacrine derivatives [9], donepezil derivatives [3], [10], coumarin derivatives [11,12], thiazole compounds [12,13] and organoselenium compounds [14,15] are among various synthetic compounds that have been synthesized and tested to serve as an anticholinesterase. However, there are no synthesized compounds which exhibit better activity than rivastigmine. Therefore, our intention is to propose a rational design among previous studies conducted that showed high dual inhibition of AChE and BuChE.

METHODOLOGY/DESIGN

Search strategy

The following electronic databases were searched: ScienceDirect, Pubmed, Medline & Ovid and ISI web of Science (2006 to September week four 2016).

Inclusion and exclusion criteria

All articles were published in English medium. The synthesis of hybrid molecules and anticholinesterase test using human AChE and BuChE with IC_{50} values were described and included. However, reviews, proceedings, letters and editorials were excluded from this study.

Data extraction

Two reviewers (NIH, NZA) independently screened the title and abstract of all records identified by the search strategy. Full text copies of all potentially relevant articles were obtained and screened by the two authors. Any disagreements were resolved by discussion between the reviewers and external reviewer (NASI). A data extraction sheet was developed and refined accordingly. Outcome measured includes type of hybrid molecule and IC_{50} values. For each study, two reviewers independently extracted data. Disagreement was resolved by discussion between the two reviewers.

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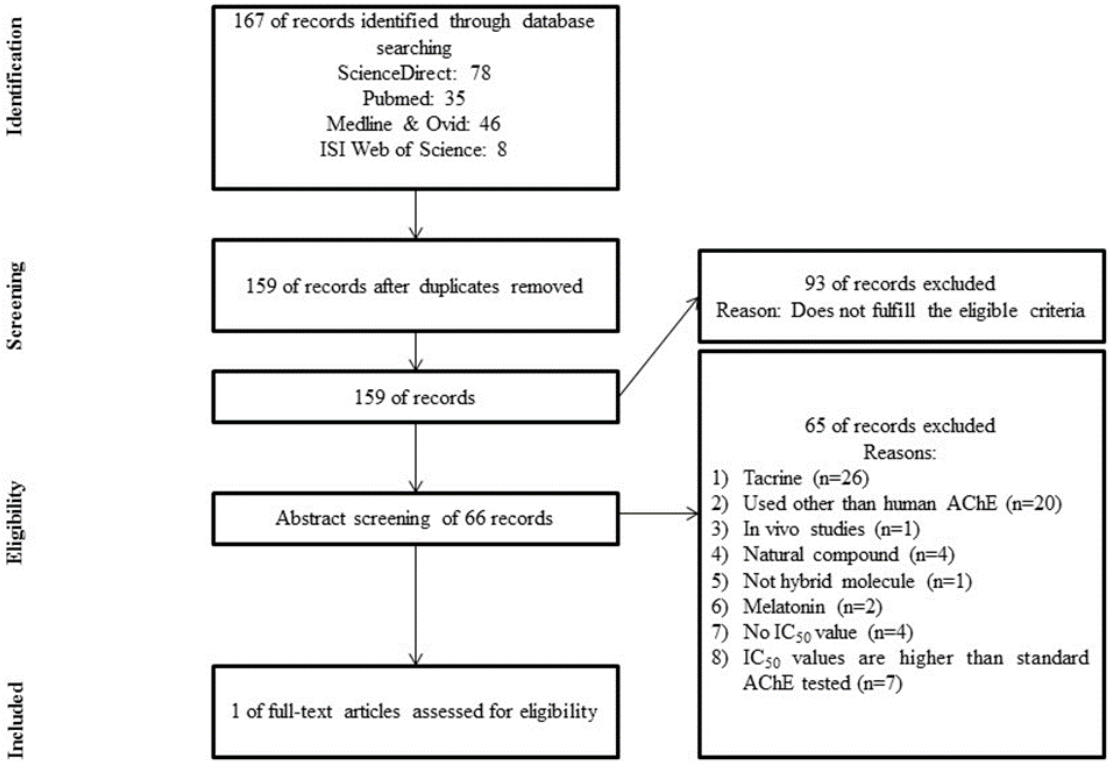
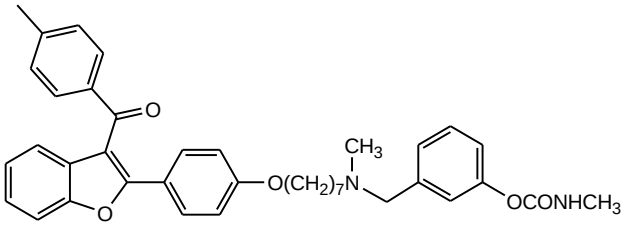


Figure 1: Flow chart of the selection process for the systematic review

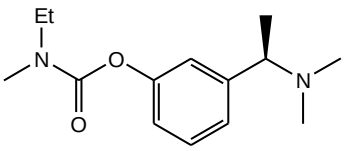
Study selection

From 167 abstracts, only one relevant study was identified in this review (Figure 1). The structure is provided in Figure 2. The structure selected have lower IC_{50} value for AChE and comparable IC_{50} value for BuChE with rivastigmine. Further explanation is discussed in the result and discussion section.



1

IC_{50} (AChE) = 0.34 ± 0.03 µM
IC_{50} (BuChE) = 0.88 ± 0.10 µM



Rivastigmine

IC_{50} (AChE) = 3.01 ± 0.21 µM
IC_{50} (BuChE) = 0.30 ± 0.01 µM

Figure 2: Selected hybrid molecule with IC_{50} value as dual inhibitor for AChE and BuChE compared with rivastigmine (Rizzo et al. 2012).

RESULTS AND DISCUSSION

Compound 1 is the most active compound in the series which possesses dual inhibition of AChE and BuChE with IC_{50} value of 0.34 µM and 0.88 µ, respectively compared to rivastigmine (IC_{50} for AChE, 3.01 µM; IC_{50} for BuChE, 0.30 µM) [4]. Although the IC_{50} value for BuChE is slightly higher than rivastigmine but it is in the same order of magnitude with rivastigmine. The compounds were compared with IC_{50} of rivastigmine because it is the only marketed AChE inhibitor with dual inhibition [3-4]. Hence, compound with IC_{50} value lower than rivastigmine have a potency to inhibit both enzymes.

It is important to note that there is only one compound selected as a potential inhibitor for both enzymes in the series and from the screening of 66 records. From eight eligible records, four of them have distinct selectivity between AChE and BuChE [3], [13], [16], [17]. The plausible explanation that it is caused by the different size of active site for the two enzymes. BuChE has a significantly larger gorge at the active site which allows larger groups to accommodate preferably with the active site of BuChE while AChE has smaller active site which best fits a smaller molecule [16]. Similarly, the inhibitory activity on AChE seems to be strongly dependant on the size and polarizability of the halogen substituent at the *para* position of the phenyl ring [13]. However, this relationship was not observed for BuChE as more volume is allowed in the active site of BuChE. Therefore, it can be concluded that a slight change on the hybrid molecules can generate compounds with specific selectivity towards AChE or BuChE.

CONCLUSION

Overall, our main aim to determine a rational design of a hybrid molecule that able to exhibit high inhibition against both AChE and BuChE activities was successful. Thus, we can explore more on this skeleton (2-arylbenzofuran) in designing new cholinesterase derivatives for future work.

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