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Design and synthesis of newer potential 4-(*N*-acetylamino)phenol derived piperazine derivatives as potential cognition enhancers

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ABSTRACT

A series of novel hybrids has been designed, synthesized and evaluated for cognition enhancing activities through the inhibition of acetylcholinesterase (AChE) and by passive avoidance mouse model. All the compounds showed excellent AChE inhibition activities and potentially reversed the scopolamine induced memory deficit. Enzyme kinetic and molecular docking studies have confirmed their dual binding affinity and mixed type inhibition. Among them, compounds **1b** and **2d** displayed excellent IC_{50} values of 1.66 μM and 0.49 μM and competitive inhibitor constant K_i 43.66 μM and 4.10 μM respectively. *Ex vivo* study confirmed their CNS penetration and brain AChE inhibition abilities. Furthermore, **1b** and **2d** showed significant antiamnesic activity at a dose of 1.0 mg/kg as compared to the reference compounds piracetam and rivastigmine. The results indicate that these two compounds emerged to be developed as cognition enhancers worthy of future pursuit.

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1. Introduction

Cognition is a combination of skills, including knowledge, acquisition, attention, memory, learning, language, perception, skilled motor behaviours, decision making, goal setting, planning and judgements [1]. Cognitive dysfunction is one of the most functionally infirm aspect of many neuropsychiatric disorders and neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson disease (PD), schizophrenia, depression, seizure disorders and traumatic brain injury [2]. It is a very common problem in the over 65 year age group and creates a symptomatic clinical situation that a person has complaints about memory loss and shows the evidence for cognitive impairment. It subsequently progresses towards the most devastating form of clinical dementia, i.e. Alzheimer dementia, shown by around 5% of the population and can be considered as the preclinical stage of AD and the risk factors for AD could also be risk factors for the development and progression of cognitive dysfunction [3–8].

The most excited approach towards the discovery of new cognition enhancers has been based on the functions of the central cholinergic system [9]. It has been found that central cholinergic depletion is the hallmark of AD and experimentally induced cholinergic dysfunction produces cognitive deficits both preclinically and clinically [10]. Although, in the past several decades many cognition enhancers have been discovered, recently research intend has turned towards the development of new acetylcholinesterase inhibitors (AChEIs) as these are capable of suppressing the normal break down of ACh from the synaptic cleft, thereby increasing overall level of ACh available to the relevant postsynaptic receptors [11–14].

The X-ray crystallographic structure of AChE has revealed that its active site gorge lined with aromatic residues about 20 Å deep contains two ligand binding sites. *I.e.* the acylation site (AS) and the peripheral anionic site (PAS). The acylation site (Phe288, Phe290, Phe299) lies at the bottom of the gorge, consisting of a catalytic triad (His440-Glu327-Ser200), and the PAS (Trp279, Tyr70, Tyr121, Asp72, Glu197, Phe290) is located at the entrance of the gorge. The AS also has a quaternary ammonium binding locus consisting of Glu199, Phe330 and Trp84. Ligands can bind selectively to either the acylation site or the peripheral site [15–17]. However recent research has revealed that dual binding site inhibitors of AChE facilitate cholinergic transmission as well as interfere with the synthesis, deposition and aggregation of toxic beta-amyloid (Aβ). Rivastigmine, ensaculin and donepezil (Fig. 1) are well known clinically used AChEIs for AD therapeutics [18]. Rivastigmine is a 'pseudo-irreversible' inhibitor of AChE and approved for the treatment of mild to moderate cognition deficit [19,20]. Similarly, ensaculin, a piperazine based molecule has shown improvement in memory and cognitive functions including slow down of progressive neurodegeneration. It is reported a dual binding site inhibitor of AChE and has been used to treat AD

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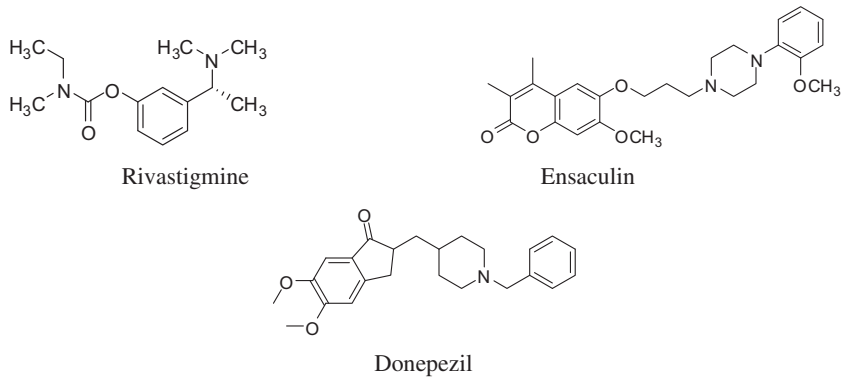

Fig. 1. Structure of clinically used marketed drugs for AD therapeutics.

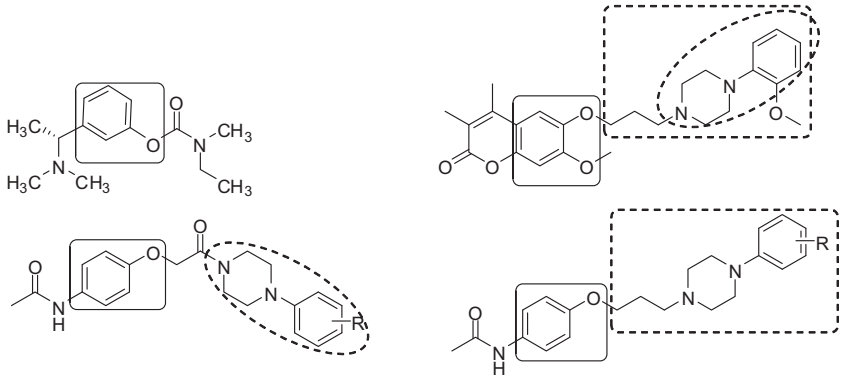

Fig. 2. Pharmacophoric hybrid design strategy of the target compounds.

clinically for a long time [18]. Donepezil is a centrally acting reversible AChEI and reported as a potent anti-amnesic and neuroprotective agent [21]. On this basis, pharmacophoric hybrid (Fig. 2) approach has been made to design the novel molecules by hybridizing the pharmacophoric fragments of rivastigmine and ensaculin. 4-(*N*-acetylamino)phenol was selected for the aryloxy fragment with the hope of its possibility to form favourable hydrogen bond, π–π stacking interactions and simultaneously may show free radical scavenging activity. Therefore, *p*-(*N*-acetylamino)phenol derived piperazine derivatives have been synthesized and screened for cognition enhancing activities.

2. Results and discussion

2.1. Chemistry

Two series of 4-(*N*-acetylamino)phenol derived piperazine derivatives were designed and synthesized as depicted in Schemes 1 and 2. In both schemes, 4-(*N*-acetylamino)phenol was used as the starting material, anhydrous K_2CO_3 as catalyst and ethyl methyl ketone as the solvent to afford the key intermediates **1** and **2**. The compounds have been synthesized by the fusion (an excellent green chemistry approach; completely avoiding use of any organic solvent) of intermediate **1** with different monosubstituted piperazines (Scheme 1) whereas the compounds of Scheme 2 were synthesized by refluxing the intermediate **2** with different monosubstituted piperazines in the presence of anhydrous K_2CO_3 in ethyl methyl ketone. All the synthesized compounds are in accordance with the IR, ^{1}H NMR, ^{13}C NMR, Mass and CHN analysis data. The synthesized ligands are enlisted in Tables 1 and 2.

2.2. Docking

Docking studies of all the hybrids (**1a–1g** and **2a–2g**) on *Tc*AChE demonstrated that they emerged as good dual binding site inhibitors. The ligands were docked with *Tc*AChE through H-bond interaction and π–π stacking interaction at both AS and PAS. The carbonyl oxygen and nitrogen atoms of 4-(*N*-acetylaminophenoxy) moiety was involved in H-bond interaction with the amino acids His440, Arg289, Phe228, Tyr70, Tyr130 and Trp84, Phe228, Ser122, Ser286 respectively. Similarly, the aromatic fragments of the ligands showed π–π stacking interaction with Trp84, Trp279, Phe330, Phe331 and Tyr334. The N_4 atom of piperazine ring showed H-bond interaction with Glu199 (**1a**, **2a**), Phe288 (**2a**) and His440 respectively. The F atom of **1c** also involved in H-bonding with Glu199. The phenoxy oxygen atom of compound **2b** showed H-bond interaction with Tyr121. Molecular docking images of most active compounds of both series **1b** and **2d** are given in (Figs. 3 and 4) respectively.

2.3. Inhibition of AChE

2.3.1. In vitro AChE Inhibition

To determine the AChE inhibitory activity of the synthesized compounds (**1a–1g** and **2a–2g**), *in vitro* assay was conducted using Ellman spectrophotometric method [22]. Enzyme kinetics study was also performed to elucidate the mechanism of AChE inhibition. The IC_{50} values and the kinetic parameters were calculated using GraphPad Prism 5 (Table 3). All the compounds exhibited excellent IC_{50} values. Compounds **1b** and **2d** showed IC_{50} values of 1.66 μM and 0.49 μM respectively. It affirmed that the relationship between

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