SECTION 1

INTRODUCTION
Alzheimer’s disease (AD), characterised by Alois Alzheimer in 1907, is a progressive neurodegenerative disorder of the brain and is the most common form of dementia among the elderly. It affects over 20 million individuals worldwide and this number will substantially increase in the future along with the increase of the number of elderly in the population. Its prevalence increases with age, from 10% at 65 years to nearly 50% at 85 years [1, 2]. According to the “cholinergic hypothesis”, impairment in the cholinergic function is of critical importance in AD especially the brain areas dealing with learning, memory, behavior and emotional responses that include the neocortex and the hippocampus. Brain atrophy is the most obvious clinical finding in AD in which the levels of acetylcholine (ACh) are decreased due to its rapid hydrolysis by acetylcholinesterase (AChE) enzyme [3]. Furthermore, a broad range of evidences have shown that enzyme AChE produces secondary non-cholinergic functions that include promotion in beta-amyloid (Aβ) deposition in the form senile plaques/neurofibrillary tangles in the brain of afflicted individuals [4,5,6,7]. Thus, AChE inhibition has been documented as a critical target for the effective management of AD by an increase in the availability of acetylcholine in the brain regions and decrease in the Aβ deposition [8].

The previous studies had shown that meta, ortho- and para-aminobenzoic acid derived arylamides and arylimides exhibit potent acetylcholinesterase inhibitory activities [9,10,11]. It has also been documented that p-aminobenzoic acid derived arylamides and arylimides are more potent as compared to corresponding m-aminobenzoic acid and o-aminobenzoic acid derivatives [9, 11]. Furthermore, the studies have shown that addition of different chemical moieties to tacrine including addition of substituted pyrazolo groups enhances the effectiveness of tacrine, one of the standard AChE inhibitor [12]. Therefore, it is proposed that substituted pyrrolo groups (bioisostere of pyrazolo) may be added to the arylimides of p-aminobenzoic acid to derive pyrrolo-isoxazole derivatives with potential acetylcholinesterase
inhibitory activities (Figure 1). The studies have suggested that different chemical moieties with central nucleus related to pyrrolo-isoxazole possess acetylcholinesterase inhibitory properties. The different derivatives of pyrrolo-benzisoxazols such as CP-118,954 and CP-126,998 have been reported as potent AChE inhibitor and are used for in-vivo imaging of AChE [13,14,15]. The pyrazolo-pyridine and pyrazolo-naphthyridine derivatives have been shown to be very effective in inhibiting AChE [12]. Furthermore, derivatives of pyrrolo-quinoline have been demonstrated to significantly ameliorate scopolamine-induced amnesia suggesting its acetylcholinergic dysfunction improving properties [16].

Figure 1: Proposed design strategy for obtaining pyrrolo-isoxazole derivatives from arylimide of p-aminobenzoic acid derivatives

Coumarins are naturally occurring phytochemicals in many plant species with a wide range of biological activities such as anti-inflammatory [17], anti-tumour [18], hepatoprotective, anti-allergic, anti-HIV-1, antiviral, antifungal, antimicrobial, anti-asthmatic,
anti-oxidant, anti-nociceptive [19], anti-diabetic and anti-depressant effects [20]. The studies have also shown that naturally occurring as well as the chemically synthesised coumarin analogs exhibit potent AChE inhibitory activity [21]. Furthermore, functionalization of the aromatic center of coumarins has led to development of novel analogs that are capable of inhibiting Aβ aggregation [22]. The studies have also documented the anti-amnestic and the memory restorative functions of coumarin derivatives in different experimental models of amnesia [23]. The recognition of key structural features within coumarin template has helped in designing and synthesizing new analogues with improved AChE inhibitory activity and additional pharmacological activities that are important for AD management. Furthermore, coumarin derivatives also provide protection to neurons against Aβ-induced oxidative stress and free radicals [24]. A plant derived coumarin is reported to attenuate intracerebroventricular injection of Aβ-induced memory impairment in mice [25].

Flavonoids are polyphenolic natural phytochemical compounds possessing $C_{15}$ skeleton in which either two benzene rings are joined by a linear three carbon atoms chain or chromane ring bears second aromatic ring B at 2$^{nd}$, 3$^{rd}$ or 4$^{th}$ position. These are widely distributed in fruits, vegetables, whole grains and are classified into six categories including flavones, flavonols, flavanones, isoflavones, flavanols and anthocyanins [26]. Flavonoids are natural phytochemicals that are distributed in fruits, vegetables and whole grains with a wide range of pharmacological properties including anti-inflammatory, anti-tumor, hepatoprotective, antiviral, antifungal, antimicrobial and anti-oxidant [27]. The studies have also shown that natural as well as the chemically synthesised flavonoid analogues exhibit neuroprotective effects, AChE inhibitory [28] along with Aβ fibril formation inhibitory activities [29, 30]. Several studies have also documented the anti-amnestic and memory restorative functions of flavonoid derivatives in different experimental models of amnesia along with prevention/slowing of progressive neurodegeneration in AD [31]. Furthermore,
the studies have shown that addition of different chemical moieties to flavonoid scaffold such as benzyl piperidine [32] and amino alkyl groups at para and meta positions enhance the effectiveness of flavonoid nucleus for AChE inhibition [33].

A number of studies have revealed that carbamate is an important structural constituent imparting AChE inhibitory properties. Infact, carbamate is an integral part of clinically employed AChE inhibitor, rivastigmine. The various research groups have synthesised carbamate derivatives by incorporating other chemical moieties to produce potent AChE inhibitors that included phenyl ring [34], benzopyrano [4,3-b] pyrroles [35], 1,2-phenylalkyl-substituted piperidines [36], N-propargylaminoindan and N-propargylphenethylamine [37]. Based on these, it may be proposed that the addition of carbamate moiety to coumarin and flavonoid molecule may produce potent AChE inhibitors (Figures 2a and 2b) that in turn may be beneficial for memory restoration in amnesia of diverse etiology including AD.
Figure 2a: Design strategy of carbamate derivatives of coumarin

Figure 2b: Design strategy of carbamate derivatives of flavanone.