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Design, synthesis and pharmacological evaluation of some novel indanone derivatives as acetylcholinesterase inhibitors for the management of cognitive dysfunction

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ABSTRACT

The present study reports the effect of indanone derivatives on scopolamine induced deficit cholinergic neurotransmission serving as promising leads for the therapeutics of cognitive dysfunction. Eleven compounds **54**–**64** have been designed, synthesised and evaluated against behavioural alterations using step down passive avoidance protocol at a dose of 0.5 mg/kg with Donepezil (**1**) as the reference standard. All the synthesised compounds were evaluated for their in vitro acetylcholinesterase (AChE) inhibition at five different concentrations using mice brain homogenate as the source of the enzyme. Compounds **54**, **56**, **59** and **64** displayed appreciable activity with an IC_{50} value of 14.06 μM, 12.30 μM, 14.06 μM and 12.01 μM, respectively towards acetylcholinesterase inhibition. The molecular docking study performed to predict the binding mode of the compounds suggested that these compounds could bind appreciably to the amino acids present at the active site of recombinant human acetylcholinesterase (rhAChE). The behavioural, biochemical and in silico pharmacokinetic studies were in concordance with each other.

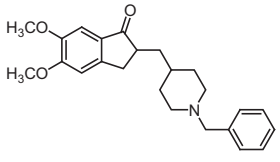
1. Introduction

Cognition is the mental action or process of acquiring knowledge and understanding through thought, experience, and senses.[1] Cognitive decline is manifested in various neurodegenerative debilities mainly in Alzheimer's disease (AD), Parkinson's disease (PD), traumatic brain injury, schizophrenia, depression etc.[2]

The therapeutic strategies towards cognitive decline have been directed to two main targets: reduced cholinergic neurotransmission and aggregation of β amyloid proteins which destroy the structural proteins of the neurons.[3] Since acetylcholine (ACh) is a neurotransmitter associated with learning and memory, treatment approaches have been focused on the compensation of deficit cholinergic neurotransmission in the CNS.

The past several decades have witnessed the development of several cognition enhancers, but the discovery and development of several potential AChEIs has paved the way for a better therapeutic and treatment approach towards cognitive decline.[4] Acetylcholinesterase (AChE) is one of the most crucial enzyme of the family serine hydrolases involved in the hydrolytic cleavage of ACh, depleting the levels of ACh implicated in memory and learning.[5] The existence of both the anionic and the peripheral binding sites in AChE encouraged the design of ligands, which can interact simultaneously with both the sites. The catalytic active site (CAS) of the enzyme AChE is actively involved in the maintenance of cholinergic neurotransmission. It has been postulated that AChE binds through its peripheral site to alleviate the amyloidogenic pathway which promotes cognitive decline.[6,7]

Indanone nucleus has been apperceived as a privileged structure which attracts significant scientific interest arising from its broad spectrum of pharmacological activities. In the last few years, indanone derivatives and their structural analogues have been widely used in medicine, agriculture and in natural products synthesis.[8] Donepezil (**1**) (Aricept®) possessing the indanone pharmacophore, is used for all stages of Alzheimer's disease.[9]



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Scientists therefore reconsidered AChE enzyme as a target mediating two important effects in the neurotoxic cascade, β amyloid fibrils formation and ACh breakdown. Because the indanone nucleus is essential for cognition disorders, a number of studies with regard to substitutions on indanone and aryl residues have been performed.[10–12] Following the strategy that the aromatic ring residue would resemble the benzyl moiety of Donepezil (1) and in order to examine the effect of variation in the electronic environment on the activity parameters our research group designed indanone conjugated benzoyl chlorides, leading to a better interaction with both the sites of AChE.

2. Results and discussion

2.1. Design

Pharmacophore mapping has been employed for designing these compounds. It is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response.

The diversity and complexity of molecular structures that characterize drug discovery today have led to the development of sophisticated computer algorithms for the elucidation, manipulation, and use of pharmacophore models. The elucidation algorithms include (a) representing the ligands (i.e. placing points on or around the molecules to represent the various pharmacophoric features), (b) searching for candidate alignments, (c) scoring those alignments. The aim being to superimpose a set of active ligands, all of which bind to the same protein of unknown 3D structure, so that the features they have in common become evident. Pharmacophore models containing three, four and five sites were generated using a terminal box size of 1 Å with 9 highly active molecules, reported as AChEIs,[13] selected using a tree based partition algorithm (Fig. 1).

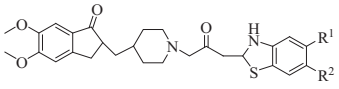
Pharmacophore model containing more than four sites (five and six sites) could not be generated and the three featured CPHs (common pharmacophore hypotheses) were rejected, as they were unable to define the complete binding space of the selected molecules. A total of seven probable four-featured CPHs belonging to different types were subjected to stringent scoring function analysis with respect to actives using default parameters for site, vector, and volume. Reference relative conformational energy (kJ/mol) was included in the score with a weight of 0.01, and ligand activity, expressed as pIC_{50}, was incorporated with a weight of 1.0.

The hypotheses that survived the scoring process were used to build the ADDR (Hydrogen bond acceptor, hydrogen bond donor and ring aromatic) based QSAR model. Features of the hypotheses were used to design a novel series of indanone derivatives using the developed four sites ADDR pharmacophore as depicted in Fig. 2.

By considering the pharmacophoric features of four sites hypothesis, a novel series of indanone derivatives has been designed and the general structure is given in Fig. 3.

2.2. Chemistry

The synthetic pathway for the synthesis of compounds **54–64** has been depicted in Scheme 1. The key intermediate 2-(3-hydrox-



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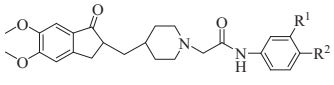
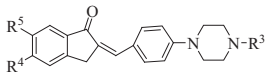


(9-15)

No.	R^1	R^2	AChE % inhibition at 10^{-3} M
2	-H	-H	4.62
3	-H	$-CH_3$	5.82
4	-H	$-OCH_3$	3.72
5	-H	-F	1.24
6	-H	-Cl	2.13
7	-H	-NO2	5.90
8	$-OCH_3$	$-OCH_3$	3.20

No.	R^1	R^2	AChE % inhibition at 10^{-3} M
9	-H	-H	5.81
10	-H	$-CH_3$	13.91
11	-H	$-OCH_3$	12.81
12	-H	-F	6.19
13	-H	-Cl	2.74
14	-H	-NO2	8.67
15	$-OCH_3$	$-OCH_3$	7.33



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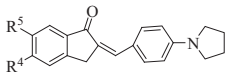

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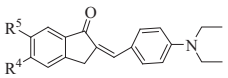

(37-39)

No.	R^3	R^4	R^5	AChE % inhibition at 10^{-3} M
16	CH_3	OCH_3	H	17.87
17	CH_3	H	OCH_3	15.52
18	CH_3	OCH_3	OCH_3	54.66
19	C_2H_5	OCH_3	H	18.61

No.	R^3	R^4	R^5	AChE % inhibition at 10^{-3} M
28	$C_2H_6N(CH_3)_2$	OCH_3	H	87.05
29	$C_2H_6N(CH_3)_2$	H	OCH_3	88.02
30	$C_2H_6N(CH_3)_2$	OCH_3	OCH_3	90.31
31	C_6H_5	OCH_3	H	6.88

Fig. 1. Data set of training compounds used for generation of pharmacophore along with their AChE % inhibition values.