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Identification of novel acetylcholinesterase inhibitors: Indolopyrazoline derivatives and molecular docking studies

Sridevi Chigurupati [a,*], Manikandan Selvaraj [b,c,*], Vasudevan Mani [c,d], Kesavanarayanan Krishnan Selvarajan [c], Jahidul Islam Mohammad [e], Balaji Kaveti [a], Hriday Bera [f], Vasanth Raj Palanimuthu [f], Lay Kek Teh [b,c], Mohd Zaki Salleh [b,c]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, AIMST University, Semeling, 08100 Bedong, Kedah, Malaysia
[b] Integrative Pharmacogenomics Institute (iPROMISE), Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia
[c] Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia
[d] Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Buraidah 51452, Saudi Arabia
[e] Department of Pharmacology, Faculty of Medicine, AIMST University, Semeling, 08100 Bedong, Kedah, Malaysia
[f] Department of Pharmaceutics, Faculty of Pharmacy, AIMST University, Semeling, 08100 Bedong, Kedah, Malaysia

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ABSTRACT

The synthesis of novel indolopyrazoline derivatives (**P1-P4** and **Q1-Q4**) has been characterized and evaluated as potential anti-Alzheimer agents through *in vitro* Acetylcholinesterase (AChE) inhibition and radical scavenging activity (antioxidant) studies. Specifically, **Q3** shows AChE inhibition (IC_{50}: 0.68 ± 0.13 μM) with strong DPPH and ABTS radical scavenging activity (IC_{50}: 13.77 ± 0.25 μM and IC_{50}: 12.59 ± 0.21 μM), respectively. While **P3** exhibited as the second most potent compound with AChE inhibition (IC_{50}: 0.74 ± 0.09 μM) and with DPPH and ABTS radical scavenging activity (IC_{50}: 13.52 ± 0.62 μM and IC_{50}: 13.13 ± 0.85 μM), respectively. Finally, molecular docking studies provided prospective evidence to identify key interactions between the active inhibitors and the AChE that furthermore led us to the identification of plausible binding mode of novel indolopyrazoline derivatives. Additionally, *in-silico* ADME prediction using QikProp shows that these derivatives fulfilled all the properties of CNS acting drugs. This study confirms the first time reporting of indolopyrazoline derivatives as potential anti-Alzheimer agents.

1. Introduction

Cholinergic dysfunction and increased oxidative stress play an important role in the pathogenesis of Alzheimer's disease (AD). Acetylcholinesterase (AChE) is an enzyme that is responsible for the termination of cholinergic signalling by hydrolyzing acetylcholine (ACh). Therefore, inhibition of both AChE and oxidative stress could be effective in the treatment and management of AD [1]. Until recently, reversible AChE inhibitors (e.g. Donepezil, Rivastigmine and Galantamine) were used to treat the symptoms caused by cholinergic dysfunction in AD [2]. However, the related enzyme butyrylcholinesterase also hydrolyses Ach but, AChE inhibitors are commonly prescribed to improve the cholinergic signalling in AD. The use of the above class of drugs for the treatment of AD has been limited by its serious side effects, so the search for novel compounds remains as an emerging demand for the treatment of AD. Indole alkaloids and its analogues are well known for their AChE inhibitory [3–5] and antioxidant effects [5–7]. Pyrazolines are also well known for various biological activities including antioxidant [8] and cholinesterase and selective monoamine oxidase B inhibitors for the treatment of AD [9,10] and Parkinson's disease [11]. There are various report which showed that the hybrid of two active moiety enhance the activity like hybrids of indole, quinoline, bisindole, benzothiazole, benzimidazole, biscoumarin, oxadiazole showed potent activity [12–18].

Both pyrazoline and indole nucleus are potent AChE inhibitors. Till date, no studies are reported in hybrid of these two nuclei and investigated either as an AChE inhibitor or antioxidant.

In the present study, the 3-acetylindole moiety is modified into indolopyrazolines (**P1-P4** and **Q1-Q4**) *via* indolochalcones as

* Corresponding authors at: Integrative Pharmacogenomics Institute (iPROMISE), Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia. Tel.: +60 33258 4652; fax: +60 33258 4658 (S. Manikandan), Department of Pharmaceutical Chemistry, Faculty of Pharmacy, AIMST University, Semeling 08100, Bedong, Kedah, Malaysia. Tel.: +60 4429 8000x1284 (Ch. Sridevi).

E-mail addresses: sridevi.phd@gmail.com (S. Chigurupati), manifans@gmail.com (M. Selvaraj).

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intermediate compounds. The synthesized compounds were characterized and evaluated for their possible *in vitro* antioxidant and AChE inhibitory potentials.

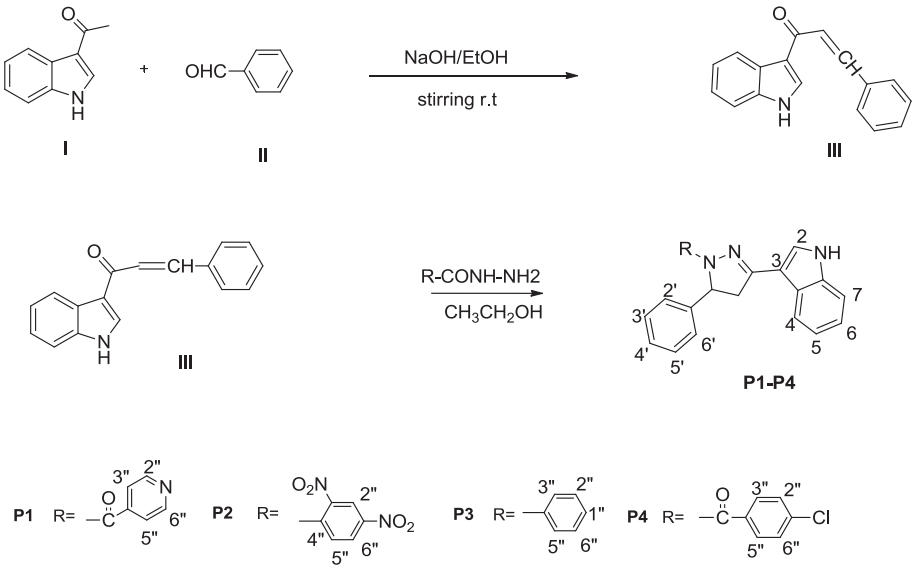
Each experimental value is expressed as the mean ± Standard error mean and all experiments are carried in triplicates (n = 3). Statistical analysis was performed using Graph Pad prism 5.0.

Molecular docking studies were carried out [15] further to explore the feasibility of the structural topographies required for the interaction of the indolopyrazoline derivatives with the AChE enzyme. It also permits to elucidate the possible key active site residues involved in the intermolecular interactions with the ligand [19]. So furthermore, the synthesized compounds were evaluated for their possible QikProp prediction of ADME properties for all the eight indolopyrazoline derivatives [20].

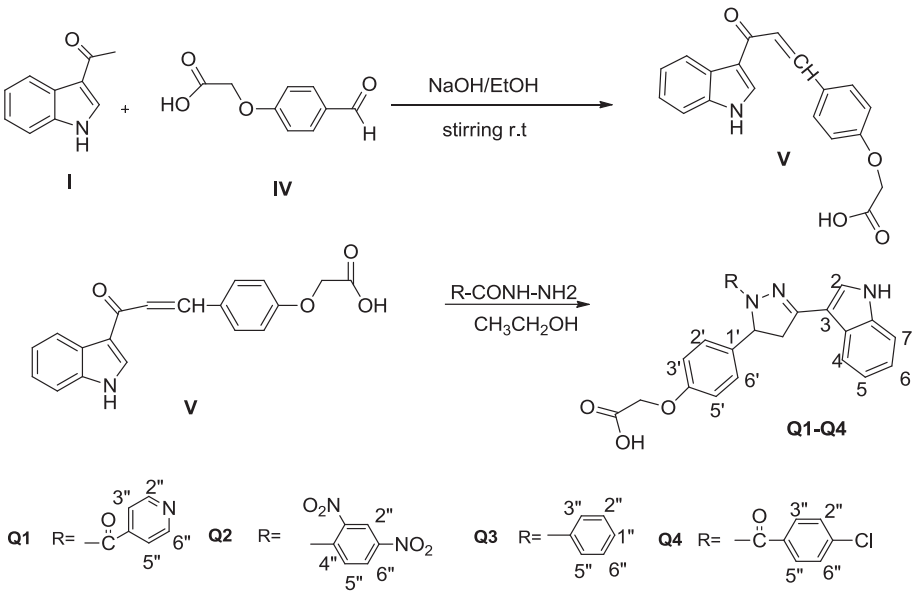
2. Results and discussion

2.1. Chemistry

Indolopyrazolines (**P1-P4** and **Q1-Q4**) were obtained by refluxing the indolochalcones (**III** and **V**) and acid hydrazides in 1:2 ratio respectively in the presence of glacial acetic acid (see Schemes 1 and 2). The mechanism involved in the conversion of chalcone to pyrazole is given in Fig. 1 The indolochalcones were obtained by Aldol condensation of 3-acetyl indole and substituted benzaldehydes in the presence of aqueous NaOH Solution. Solidified crude products were recrystallized from aqueous ethanol. The indolopyrazolines were obtained in high yields. The purity of the indolopyrazoline compounds was checked by the R_f value of TLC (Thin Layer



Scheme 1. Synthesis of indolopyrazolines (**P1-P4**).



Scheme 2. Synthesis of indolopyrazolines (**Q1-Q4**).