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Synthesis of 1-Benzyl-4-[2-(5-phenyl-1,3,4-thiadiazole-2-yl)aminoethyl]piperidine as Potential Alzheimer's Disease Modifying Agent

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A number of pharmacological agents are available for clinical use in the treatment of alzheimer's disease. The cognitive impairment associated with alzheimer's disease is characterized by reduced levels of acetylcholine in CNS. Acetyl cholinesterase inhibitors increase the level of acetyl choline at the synapses by blocking the breakdown of the neurotransmitter. The aim of this study is the synthesis of 1-benzyl-4-[2-(5-phenyl-1,3,4-thiadiazole-2-yl)aminoethyl]piperidine, as potential acetyl cholinesterase inhibitor, from the reaction of 2-chloro-5-phenyl-1,3,4-thiadiazole and 1-benzyl(piperidin-4-yl)ethylamine. The structure of obtained compound was identified by its ^{1}H NMR, mass and IR spectra.

Key Words: Synthesis, 1,3,4-Thiadiazole, Piperidine, Alzheimer's disease.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of neurodegenerative disorders that affects up to 5 % of people over 65 years[1,2]. The cognitive impairment associated with alzheimer's disease is characterized by a loss of basal forebrain neurons and reduced cortical and hypocampal levels of acetylcholine (ACh)[3,4]. One strategy to enhance cholinergic neurotransmitter is to inhibit acetylcholinesterase (AChE). Accordingly, acetyl cholinesterase inhibitors (AChEIs) increase the level of acetylcholine at the synapses by blocking the breakdown of the neurotransmitter[5-8].

A number of pharmacological agents are already available for clinical use in the treatment of alzheimer's disease. Some medications are currently approved by regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) to treat the cognitive manifestations of alzheimer's disease, like tacrine and donepezil (Fig. 1)[5,6,8,9]. Donepezil, marketed under the trade name Aricept® by its developer Eisai and partner Pfizer, is a centrally acting reversible acetylcholinesteraseinhibitor. Its main therapeutic use is in the treatment of alzheimer's disease. Donepezil is generally better tolerated than others in its class[10,11]. Thus, such AChE inhibitors with central bioavailability represent still a promising approach to the treatment of alzheimer's disease[7,8].

In a research by Jean-Marie Contreras and co-workers[12], some aminopyridazines have been reported as active AChEI agents. Among these compounds, 3-[2-(1-benzylpiperidin-4-yl)ethylamino]-6-phenylpyridazine **2**, was about 600 times more potent toward 3-[2-(piperidin-1-yl)ethylamino]-6-phenylpyridazine **1**. It appears that in these compounds the most favourable lipophilic side chain is the ethyl-N-benzyl-piperidinyl chain which is also present in donepezil, 5-phenyl-2-[2-(piperidin-1-yl)ethylamino]-1,3,4-thiadiazole (**3**), which is 1,3,4-thiadiazole analogue of **1**, showed moderate activity in Jean-Marie Contreras and co-workers research[12]. Herein, we would like to report the synthesis of 1-benzyl-4-[2-(5-phenyl-1,3,4-thiadiazole-2-yl)aminoethyl]piperidine (**4**), as potential AChEI agent for the treatment of alzheimer's disease.

EXPERIMENTAL

Chemical and solvents used in this study were purchased from Merck AG and Aldrich chemical. The purity of the synthesized compounds was confirmed by thin layer chromatography using various solvents of different polarities. Merck silica gel

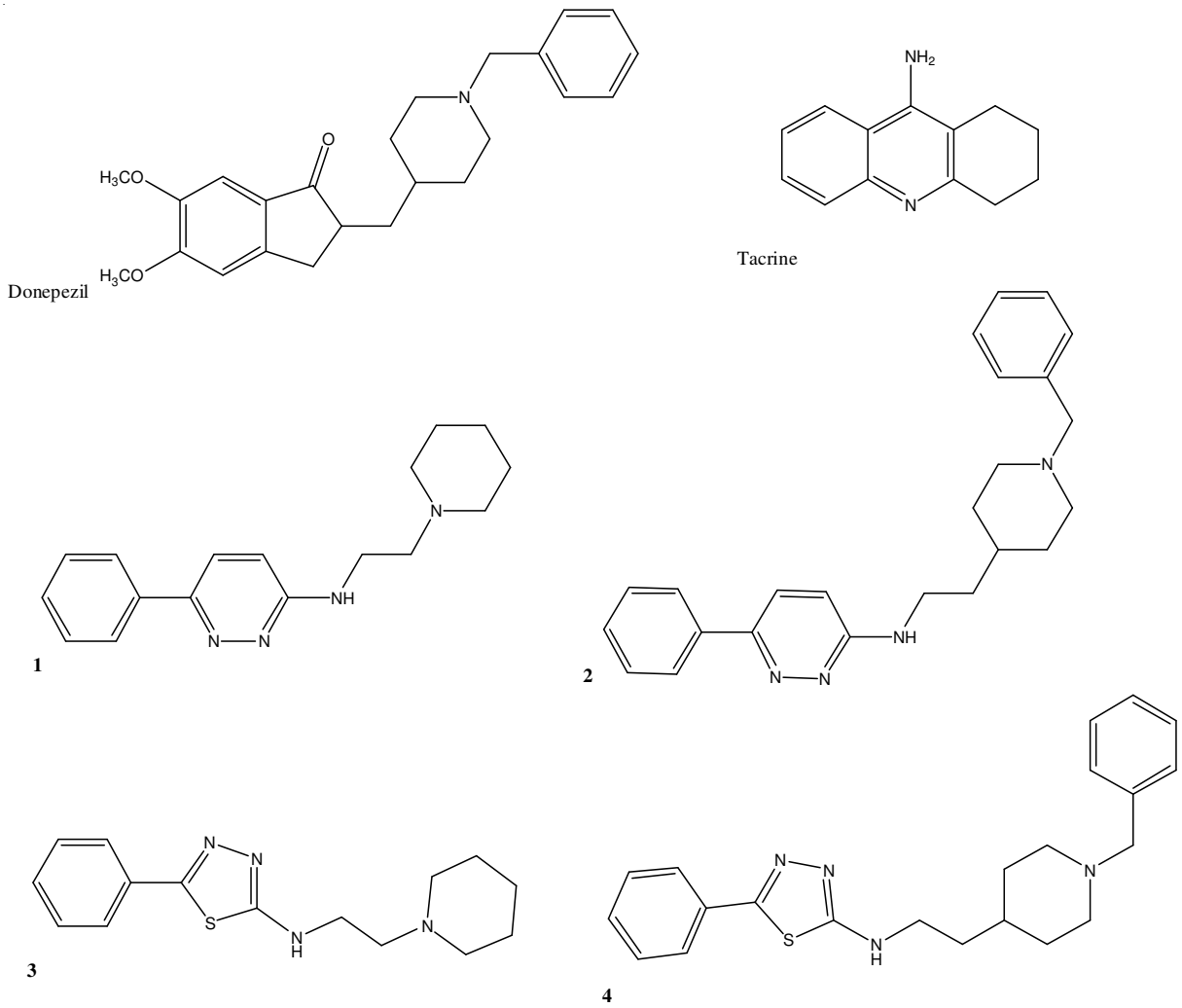


Fig. 1. Chemical structures of some AChEIs and target compound **4**

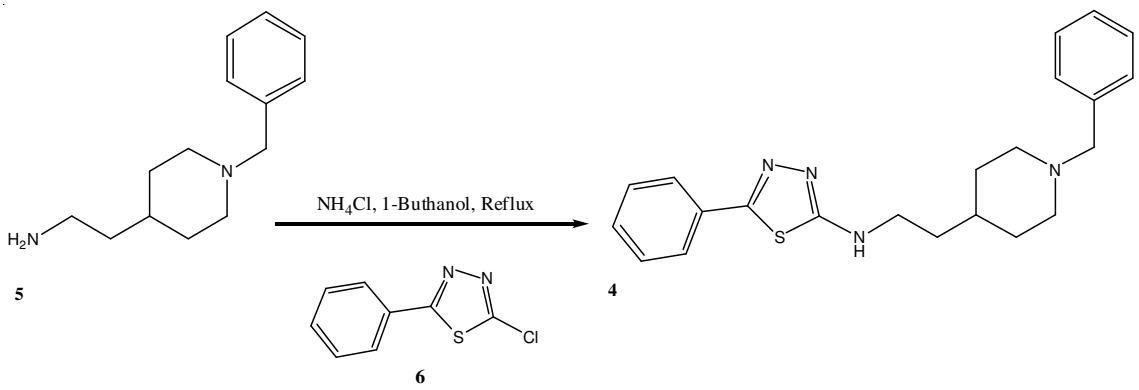
60 F_{254} plates were applied for analytical TLC. Column chromatography was performed on Merck silica gel (70-230 mesh). Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR spectra were measured using a Bruker 500 spectrometer and chemical shifts are expressed as δ (ppm) with tetramethylsilane as internal standard. The IR spectra were obtained on a Shimadzu 470 spectrophotometer (potassium bromide disks). The mass spectra were run on a Finigan TSQ-70 spectrometer (Finigan, USA) at 70 eV. Elemental analyses were carried out on a CHN-O-rapid elemental analyzer (GmbH-Germany) for C, H and N and the results are within ± 0.4 % of the theoretical values.

Synthesis of phenylcarbaldehyde thiosemicarbazone (8): To a mixture of benzaldehyde (0.01 mol) and thiosemicarbazide (0.01 mol) in ethanol (30 mL), was added conc. HCl (0.5 mL) and the resulting mixture was refluxed for 1 h. The reaction was cooled and the precipitate was filtered and crystallized from ethanol.

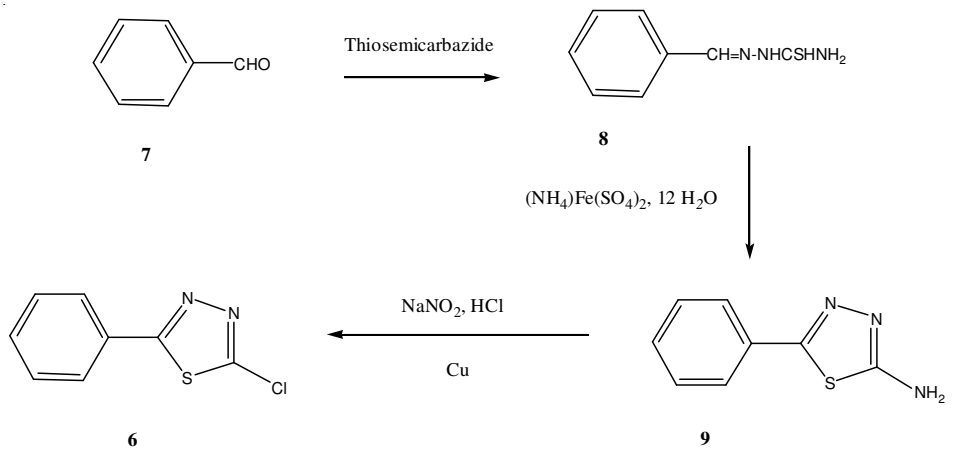
2-Amino-5-phenyl-1,3,4-thiadiazole (9): A mixture of phenylcarbaldehyde thiosemicarbaone **8** (0.1 mol) and ammonium ferric sulfate (0.4 mol) in H_2O (500 mL) was refluxed for 8 h. The reaction mixture was cooled and the solids isolated by filtration were washed with water, air dried and crystallized from ethanol to give 80 % of **9**.

2-Chloro-5-phenyl-1,3,4-thiadiazole (6): Compound **9** (0.1 mol) was ground with a large excess of $NaNO_2$ (0.5 mol) and the mixture was introduced, in small portions and with stirring, into a large excess of conc. HCl (300 mL) and water (150 mL), containing Cu powder (0.2 times the weight of 6c), at about -5 ºC. The reaction mixture was allowed to reach room temperature and heated to 65 ºC until the evolution of gas ceased. The mixture was cooled and extracted with $CHCl_3$. The combined extracts were washed with $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated to give crude **6**. If necessary, purification was achieved by passage through a short silica gel column with either $CHCl_3$ or ether-petroleum ether (b.p. 40-60 ºC) as eluent. The product were crystallized from ethanol: yield 68 %, m.p. 86-88 ºC.

Synthesis of 1-benzyl-4-[2-(5-phenyl-1,3,4-thiadiazole-2-yl)aminoethyl]piperidine (4): A mixture of 2-chloro-5-phenyl-1,3,4-thiadiazole **6** (3.1 mmol), 1-benzyl(piperidin-4-yl)ethylamine (**5**) (6.2 mmol) and ammonium chloride (3.1 mmol) in 1-butanol (10 mL) was refluxed for 48 h. The solvent was removed by evaporation. The residue was diluted with 10 % K_2CO_3 (100 mL) and extracted with EtOAc. The organic layer was washed with a 10 % citric acid solution and the combined aqueous phases were extracted with EtOAc. The aqueous layer was rendered alkaline with K_2CO_3 and then



Scheme-I: Synthetic route to target compound **4**



Scheme-II: Synthesis of compound **6**

extracted with EtOAc. After drying over Na_2SO_4, the obtained crude free base was purified by flash chromatography using two different eluents (EtOAc and then a mixture of EtOAc-MeOH, 9:1, with 2 % (v) triethylamine): yield 28 %, oily compound, ^{1}H NMR ($CDCl_3$): δ 7.15-7.85 (m, 10H), 3.48 (s, 2H), 3.40 (m, 2H), 2.87 (m, 4H), 1.94 (m, 4H), 1.65 (m, 3H); MS (m/e, %): 378 (M^+, 100); IR (KBr, ν_{max}, cm^{-1}): 3024 (NH).

RESULTS AND DISCUSSION

In our previous work[13] on the same class of N-benzyl piperidine AChEIs, we described the synthesis of "1-benzyl-4-[2-(3-thienylcarbonylamino)ethyl]piperidine" as potential AChEI. Herein, the key intermediate "1-benzylpiperidin-4-yl-ethylamine" has been reacted with 2-chloro-5-phenyl-1,3,4-thiadiazole to yield target compound 1-benzyl-4-[2-(5-phenyl-1,3,4-thiadiazole-2-yl)aminoethyl]piperidine (**4**), as potential AChEI agent for the treatment of alzheimer's disease.

Our synthetic route to target compound **4** is presented in **Scheme-I**. The requisite 2-(1-benzylpiperidine-4-yl)-ethyl-amine **5** was prepared according to the described method by Jean-Marie Contreras and co-workers[12]. The preparation of 2-chloro-5-phenyl-1,3,4-thiadiazole (**6**) depicted in **Scheme-II**. Reaction of 2-(1-benzylpiperidine-4-yl)-ethylamine **5**, with 2-chloro-5-phenyl-1,3,4-thiadiazole 6, in 1-butanol in the presence of ammonium chloride at reflux condition, gave compound **4**. Structure of target compound has been confirmed by ^{1}H NMR, mass and IR spectra.

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