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Synthesis of 1-Benzyl-4-[2-(3-thienylcarbonylamino)ethyl]piperidine as a Novel Potential Cholinesterase Inhibitor

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Potentiating of cholinergic activity which increases the acetylcholine level in the brain has been regarded as an approach for the palliative treatment of alzheimer's disease. Accordingly, inhibition of the acetyl cholinesterase enzyme is considered to be a viable and attractive therapeutic strategy for alzheimer's disease patients. In an attempt to find a new acetyl cholinesterase inhibitor (AChEI), 1-benzylpiperidin-4-yl-ethylamine has been reacted with thiophen-3-carbonylchloride to prepare 1-benzyl-4-[2-(3-thienylcarbonyl-amino)ethyl]piperidine, as potential acetyl cholinesterase inhibitor. The structure of target compound was confirmed by mass, NMR and IR spectra.

Key Words: Synthesis, Thiophenes, Piperidine, Acetyl cholinesterase inhibitor.

INTRODUCTION

Alzheimer's disease (AD) is described as a multifunctional neurodegenerative disease of central nervous system characterized specially by decline in cognitive ability and behavioural abnormalities. Alzheimer's disease accounts for the majority of dementia diagnose after the age of 60[1-6]. It has been demonstrated that alzheimer's disease is associated with a selective loss of cholinergic nervous and reduced level of acetylcholine (ACh) neurotransmitter in cerebral cortex and hippocampus[7]. Potentiating of cholinergic activity which increases the ACh level in the brain has been regarded as an approach for the palliative treatment of alzheimer's disease. Accordingly, augmentation of the cholinergic neurotransmission, through inhibition of the acetyl cholinesterase (AChE) enzyme, is considered to be a viable and attractive therapeutic strategy for alzheimer's disease patients[8,9]. Four currently administrated acetyl cholinesterase inhibitors (AChEIs) for alzheimer's disease, tacrin, donepezil, rivastigmine and galantamine (Fig. 1) are centrally active and have been shown to improve memory and cognition in some patients with mild to moderate alzheimer's disease[2,5,10,11].

A family of AChEIs, the N-benzylpiperidines, have exhibited superior efficacy for AChE[3]. According to the previous findings by Hachiro Sugimoto and co-workers, 1-benzyl-4-[2-(N-benzoylamino)ethyl]piperidine (**1**), has shown anti AChE activity[12]. Replacing the phenyl ring of benzoyl moiety with pyridine-3-yl (**2**) and pyridine-4-yl (**3**), enhanced the inhibitory effect on AChE. When phenyl ring was replaced by a cyclic alkyl group (*e.g.*, cyclohexyl, **4**), the activity of anti AChE was decreased. For the amide moiety, when the CONH group was replaced by a CH_2NH group **5**, AChEI activity disappeared. For benzylpiperidine moiety, the basicity of the nitrogen atom of piperidine group appears to have an important role in the degree of activity; N-benzoylpiperidine analogue (**6**) was almost inactive. Therefore, replacing the phenyl moiety with other hetero-aromatics has been regarded as one of the most promising method for increasing anti AChE activity[3,4,12] (Table-1).

The purpose of present study is to replace phenyl ring of benzoyl moiety with thiophene-3-yl **7**, to find new anti AChE agent with higher activity according to described structure activity relationship for this family of acetyl cholinesterase inhibitors.

EXPERIMENTAL

All chemical reagents and solvents used in this study were purchased from Merck AG (Darmstadt, Germany). The purity

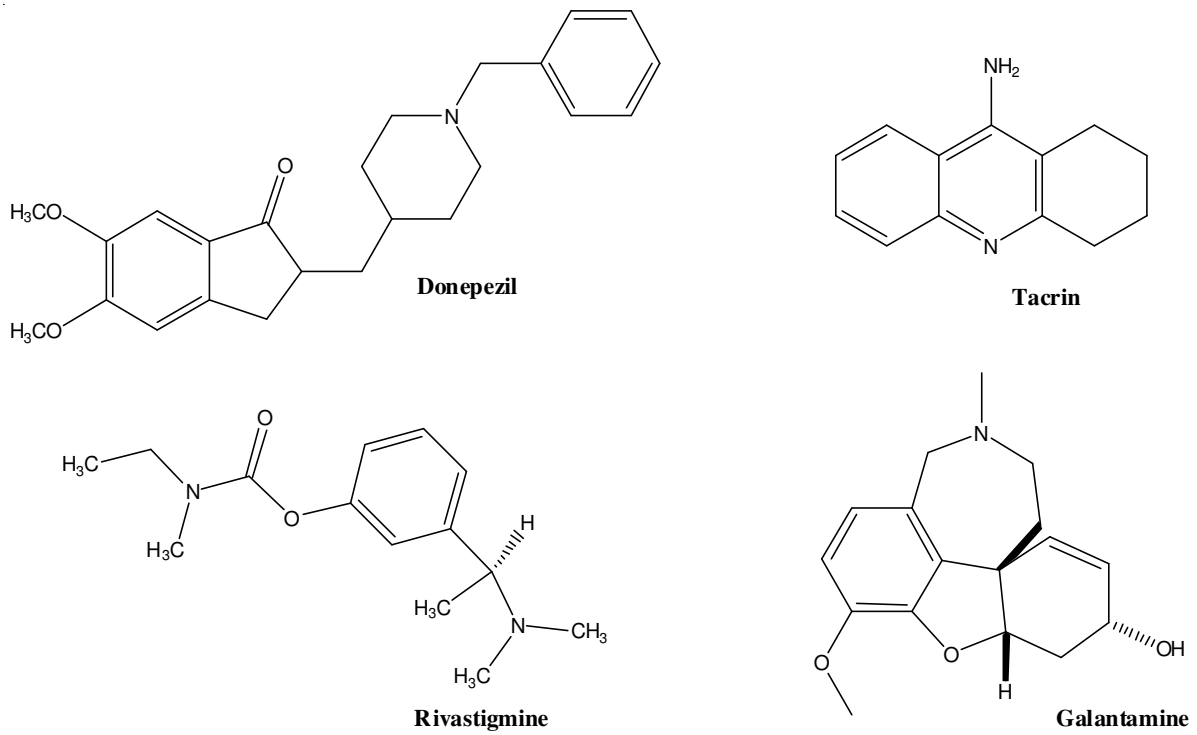
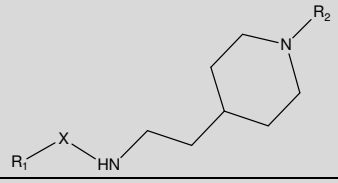
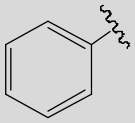
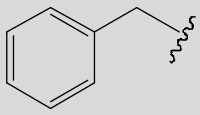
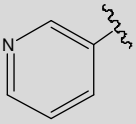
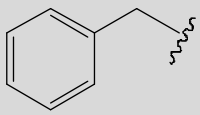
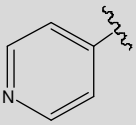
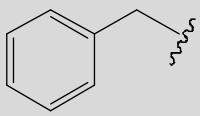
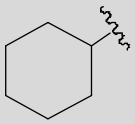
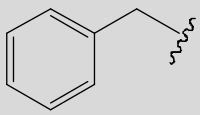
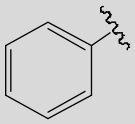
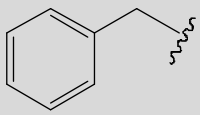
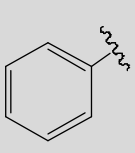
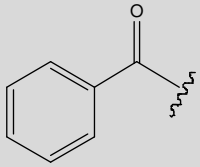


Fig. 1. Food and drug administration approved AChEIs[2]

TABLE-1
PIPERIDINE BASED AChEIs



Comp.	R_1	X	R_2
1		C=O	
2		C=O	
3		C=O	
4		C=O	
5		CH_2	
6		C=O	

of the synthesized compounds was confirmed by thin layer chromatography using various solvents of different polarities. Merck silica gel 60 F_{254} plates were applied for analytical TLC. Column chromatography was performed on Mercksilica 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.

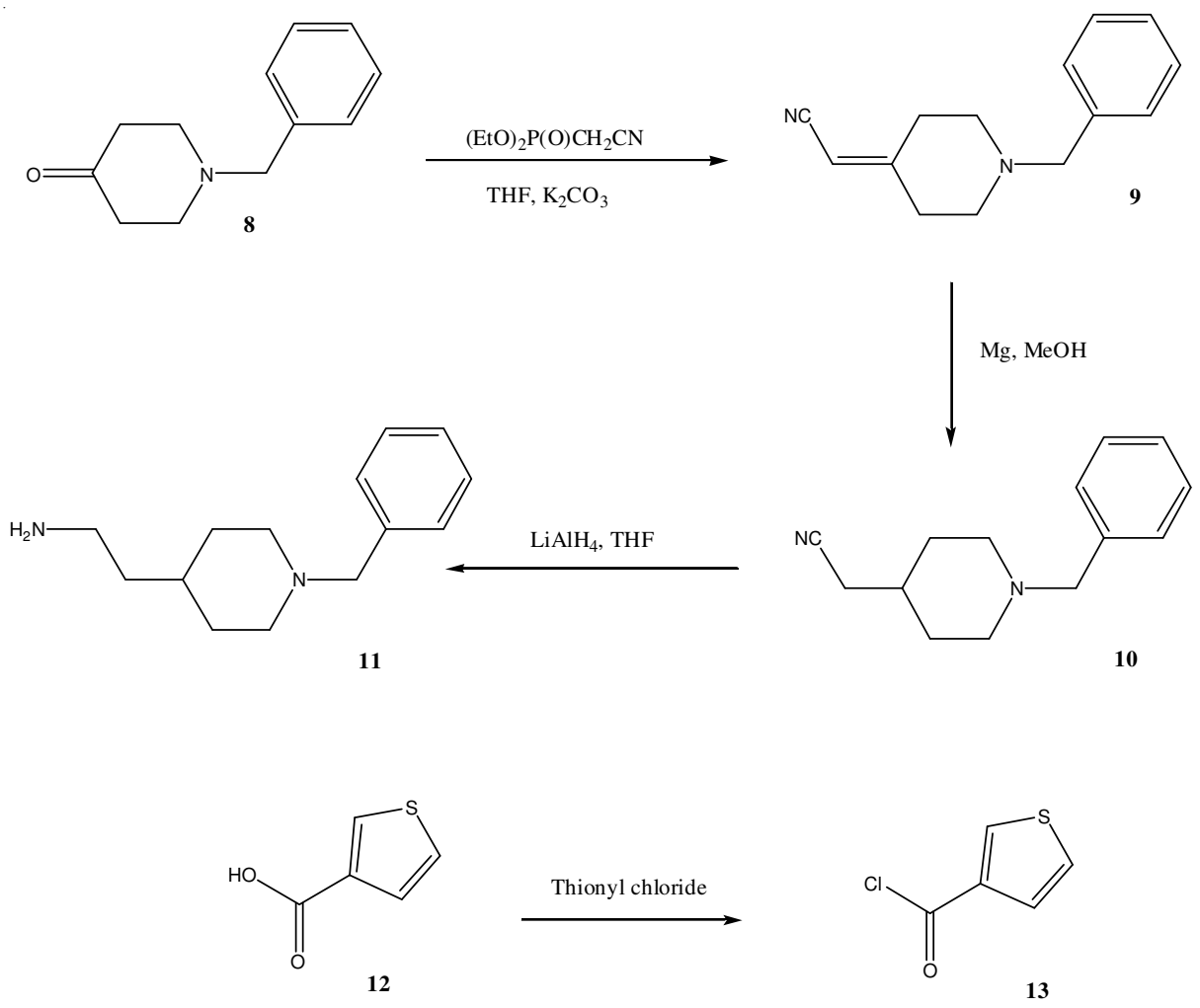
Synthesis of thiophene-3-carbonylchloride (13): To a stirring mixture of thiophene-3-carboxylic acid **12** (0.1 mol, 11.6 g) in benzene (20 mL), was added thionyl chloride (20 mL) and the resulting mixture was refluxed for 2 h. The solvent and excess of thionyl chloride was removed in reduced pressure and the residue was dissolved in CH_2Cl_2 and was washed with $NaHCO_3$ solution and water. The solution was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The residue was passed from a short silica gel column using chloroform as eluent. Chloroform was removed and the remaining oil was used without further purification in next step: yield 53 %; m.p. 50-52 ºC, ^{1}H NMR ($CDCl_3$): δ 8.37 (m, 1H), 7.57 (m, 1H), 7.39 (m, 1H).

Synthesis of 1-benzyl-4-[2-(3-thienylcarbonylamino) ethyl]piperidine (7): To a mixture of **11** (1.10 g, 5 mmol) in 10 % aqueous potassium carbonate (7.0 mL) and $CHCl_3$ (7.0 mL) a solution of **13** (0.78 g, 104.52 mmol) in $CHCl_3$ was added dropwise at 0 ºC. After stirring for 0.5 h, the $CHCl_3$ layer was washed with water, dried over K_2CO_3 and evaporated. The crude residue was purified by silica gel column chromatography

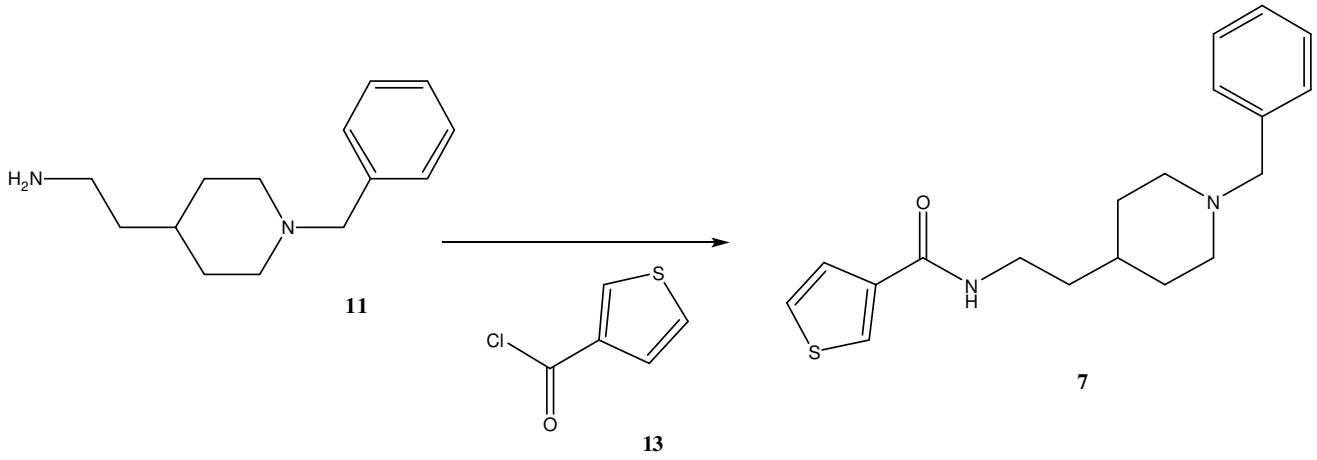
(CH_2Cl_2-MeOH, 99:1) to give 1.16 g of oily compound, yield 65 %. ^{1}H NMR (DMSO-d_6): δ 9.15 (brs, 1H), 8.05 (m, 1H), 7.36 (m, 7H), 4.02 (m, 2H), 3.36 (m, 4H), 2.38 (m, 2H), 1.82 (m, 1H), 1.70 (m, 4H), 1.25 (m, 2H); MS (m/e, %): 328 (M^+, 100); IR (KBr, ν_{max}, cm^{-1}): 3302 (NH), 1631 (C=O).

RESULTS AND DISCUSSION

Our synthetic routes to the intermediates compounds **11** and **13** are presented in **Scheme-I**. The synthesis of target compound **7** is depicted in **Scheme-II**. Compound **11** was obtained with a slightly modified procedure described by Contreras *et al.*[13]. Thus, the reaction of 1-benzyl-4-piperidone (**8**) with diethylcyanomethyl phosphonate afforded compound **9**. Hydrogenation of ethylene bond was achieved *via* reduction using magnesium powder in ethanol to afford compound **10**. Reduction of the cyano group using $LiAlH_4$ afforded amine **11**. Reaction of 2-(1-benzylpiperidine-4-yl)-ethylamine (**11**), with thiophene-3-carbonylchloride (**13**), in chloroform in the



Scheme-I: Synthetic routes for the intermediates **11** and **13**



Scheme-II: Synthetic route for target compound **7**

presence of aqueous potassium carbonate, gave the target compound **7**.

Conclusion

Target compound **7** was synthesized as a potential acetyl cholinesterase inhibitor and its structure was confirmed by mass, ^{1}H NMR and IR spectra.

ACKNOWLEDGEMENTS

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