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Synthesis and biological evaluation of new oxopyrrolidine derivatives as inhibitors of acetyl cholinesterase and β amyloid protein as anti – Alzheimer's agents

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ABSTRACT

A new series of oxopyrrolidines was synthesized and evaluated for their effect on Alzheimer's disease by measuring their inhibitory activity against acetyl cholinesterase enzyme and amyloid β 42 protein. Most of the compounds showed good inhibitory activity with ethyl 2-(2-(2, 6-dimethylphenylcarbamoyl)- 5-oxopyrrolidin-1-yl) acetate (**V**) having the highest activity against acetyl cholinesterase with IC_{50} value 1.84 ng/g tissue compared to standard donepezil 3.34 ng/g tissue. Furthermore, compound 1-((4-(4-chlorophenyl) piperazin-1-yl) methyl)-N-(2,6-dimethylphenyl)-5- oxopyrrolidine- 2-carboxamide **(IIIe)** displayed the highest activity against β 42 protein with IC_{50} value of 11.3 Pg/g tissue compared to 18.4 Pg/g tissue of donepezil.

1. Introduction

Alzheimer's disease (AD), is one of the most severe conditions affecting elderly people. It is estimated that around 24 million people worldwide are suffering from AD. The figure is expected to increase significantly over the next 50 years due to increasing life expectancy [1]. Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by abnormal accumulation of β amyloid (A β) peptide, neurofibrillary tangles and cholinergic neurons loss [2]. Among many pharmacological agents, acetyl cholinesterase inhibitors AChEI) are the only class of compounds that have consistently proven to be efficacious in treating the cognitive and functional symptoms of Alzheimer's disease [3,4]. In patients with Alzheimer's disease, large numbers of senile plaques are found throughout the cerebral cortex and hippocampus the principal proteinaceous component of the amyloid deposited is β amyloid protein A β) [5]. According to the amyloid hypothesis, the neuronal loss observed in AD is caused by deposition of extracellular aggregates of the A β protein [6]. Strong evidence has been obtained that the deposition of A β in senile plaques plays a seminal role in AD pathogenesis [7]. The current pharmacological treatment of Alzheimer's disease (AD) comes down to four marketed drugs (tacrine, donepezil, rivastigmine and galantamine) (Fig. 1) all of which are acetyl cholinesterase inhibitors, conforming to the cholinergic hypothesis [8]. Donepezil, an acetyl cholinesterase inhibitor, is an approved drug for the treatment of Alzheimer's disease AD) [9] and is the current first choice drug for AD since it is a very potent, low toxic and well tolerated. [11] donepezil was found also to significantly improve Aβ induced memory impairment [12].

Several researchers also debated piperazine derivatives as potential neuroprotective agents [13].

Donepezil, which is a benzylpiperidine derivative, was chosen as a reference standard drug it is thought to mimic the binding mode of Ach by structural similarity and therefore, is a competitive inhibitor of AChE [17] the main features of donepezil were taken into consideration while designing the new derivatives. The four main parts essential for its activity, the indanone moiety (a), a spacer (b), positive charge center (c) and a phenyl moiety (d) [18] Fig. 2.

From the previous we designed and synthesized new oxopyrrolidine derivatives with structural resemblance to donepezil bearing substituted piperazine to investigate structure modification of the

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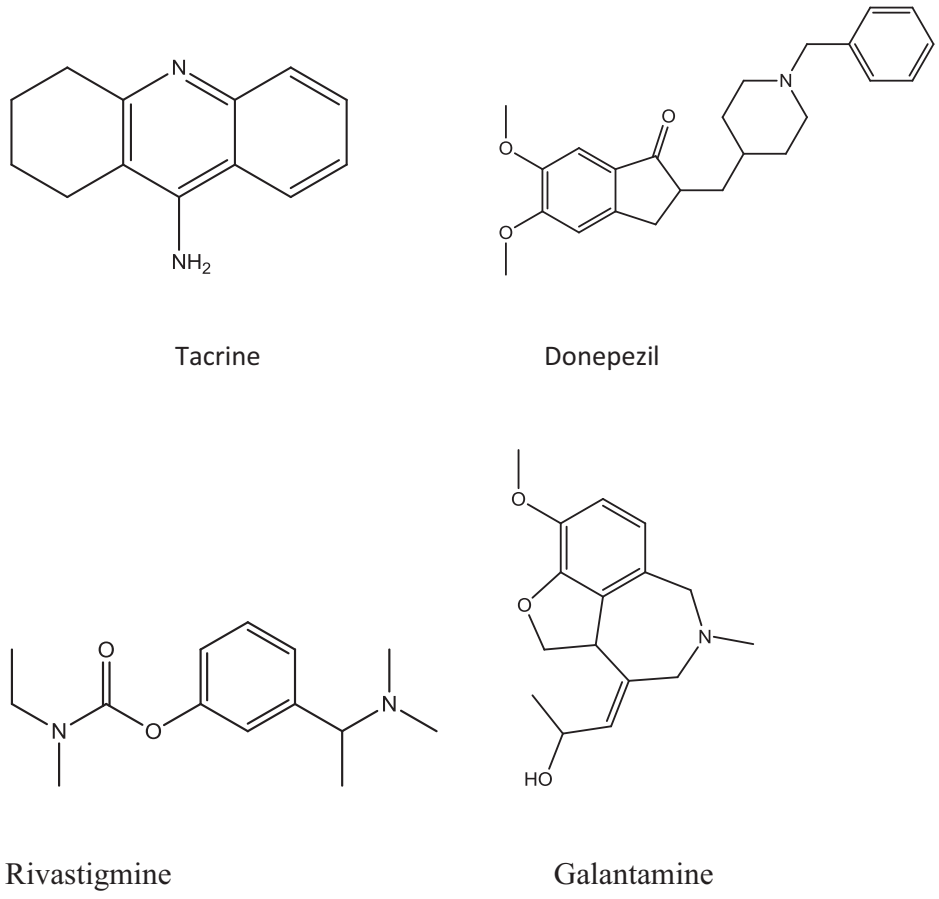

Fig. 1. Structure of tacrine, donepezil, rivastigmine and galantamine.

new derivatives. The new derivatives were tested for inhibition of acetyl cholinesterase enzyme and amyloid β 42 protein.

2. Materials and methods

2.1. Chemistry

All melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer spectrophotometer using potassium bromide discs. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 300 MHz and Bruker 400 MHz using DMSO-d_6 as solvent. The chemical shifts were reported as parts per-million δ ppm, tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a Jeol-SX-102 instrument. Elemental analysis was performed on a Perkin-Elmer 2400 C, H, N analyzer and values were within ±0.4% of theoretical percentages. The progress of the reaction was monitored on readymade Silica –gel plates fluorescent (Merck) using $CHCl_3$/CH_3OH (9.5:0.5) as solvent using, UV lamp.

Pyroglutamic acid **I** was purchased from Aldrich chemicals,1-(2-ethoxy-2-oxoethyl)-5-oxopyrrolidine-2-carboxylic acid **IV** and ethyl 2-(2,3-dioxoindolin-1-yl)acetate **VIII** were synthesized according to reported procedures [15,10].

2.2. General procedure for the synthesis of (IIa-d)

To a solution of **(I)** (0.1 mol, 1.29 gm) in ethanol (5 ml) was added a solution of formalin (0.1 mol, 0.03 gm) and the appropriate piperazine derivative (0.1 mol) in ethanol (5 ml), the reaction was then heated under reflux for 2 h. The reaction was allowed to cool, filtered, the separated solid was dried and finally crystallized from ethanol.

2.2.1. 5-Oxo-1-((4-phenylpiperazin-1-yl) methyl) pyrrolidine-2-carboxylic acid (IIa)

Mp 102 °C, yield 85%, IR(KBr, cm^{-1}): 3406(OH), 3087 (CH aromatic), 2970 (CH alphatic), 1710, 1680 (CO). ^{1}H NMR 400 MHz (DMSO-d_6): 1.94–2.35 (m,4H, 2CH $_2$), 2.59(d, *j = 6* Hz, 4H, piperazine), 3.05 (d, *j = 5* Hz, 4H, piperazine),4.28(s, 2H, CH_2),6.74(t, 1H, Ar-H),6.89 (d, *j = 6* Hz, 2H, Ar-H), 6.92 (s,1H,CHCO)7.18((d, *j = 7.2* Hz, 2H, Ar-H), 8.10 (s,1H,OH, D_2O exchangeable). MS: *m/z* (% abundance): *m/z* 302 (M^+−3, 28.16%). Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.02; H, 6.99; N, 13.80.

2.2.2. 1-((4-(4-Methoxyphenyl) piperazin-1-yl) methyl)-5-oxopyrrolidine-2-carboxylic acid (IIb)

Mp 115 °C, yield 80%, IR (KBr, cm^{-1}): 3400(OH), 3080 (CH aromatic), 2980 (CH alphatic), 1710,1680 (CO). ^{1}H NMR 300 MHz (DMSO-d_6): 1.95–2.23 (m,4H, 2CH_2), 2.33(d, *j = 5.1* Hz, 4H, piperazine), 3.10 (d, *j = 6.5* Hz, 4H, piperazine),3.67 (s, 3H, OCH_3),4.18 (s, 2H, CH_2),6.80(d, *j = 9* Hz, 2H, Ar-H),6.84 (s, 1H,CHCO), 6.85 (d, *j = 8.4* Hz, 2H, Ar-H), 7.9 (s,1H,OH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, δ ppm): 22.75 (CH_2 Pyrrolidine), 29.38 (CH_2 Pyrrolidine), 49.26 (2CH_2Piperzine), 50.96(2CH_2Piperzine), 55.12 (CH Pyrrolidine), 59.79 (OCH_3), 63.11 (NCH_2), 114.20 (2 C Ar) 117.35 (2 C Ar), 118.02 (C-Ar), 145.26 (C Ar), 173.88 (CO), 175.30 (CO). MS: *m/z* (% abundance): *m/z* 333(M^+, 0.01%), Anal.Calcd for $C_{17}H_{23}N_3O_4$; C, 61.25; H, 6.95; N, 12.60. Found: C, 61.22; H, 6.96; N, 12.60.