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Novel pyrazinamide condensed azetidinones inhibit the activities of cholinesterase enzymes

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Abstract

A series of novel pyrazinamide condensed azetidinones was prepared with pyrazinamide Schiff's bases and chloroacetylchloride in the presence of catalytic amounts of 1,4-dioxane and triethylamine. The chemical structures of the synthesized compounds (**6a–6m**) were confirmed by melting point analysis, TLC, IR, ^{1}H NMR, mass spectrometry, and elemental analysis. The synthesized compounds were evaluated for acetyl and butyl cholinesterase inhibitory activities. The compounds showed a range of inhibitory activities that could be categorized as weak, moderate, or high. Compound 6l exhibited potent acetyl and butyl cholinesterase inhibitory activities, with IC_{50} values of 0.09 μM and 3.3 μM, respectively, when compared with the current therapeutic agent donepezil HCl. Our present study suggests that pyrazinamide condensed azetidinones might be interesting and have potential as acetyl and butyl cholinesterase inhibitory compounds.

Keywords: Alzheimer's disease; Azetidinones; Acetylcholinestrase inhibitor; Pyrazinamide

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia among older people [1]. It is a chronic and progressive neurodegenerative disease that is neuropathologically characterized by the extracellular deposition of β-amyloid aggregates and intraneuronal neurofibrillary tangles. Neuronal loss at the affected regions causes a deficit in the production of the neurotransmitter acetylcholine, leading to cortical cholinergic dysfunction [2]. Based on the cholinergic hypothesis, acetylcholinesterase inhibitors were developed to sustain or enhance acetylcholine levels. The crucial role

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of cholinesterases in neural transmission makes them a primary target of a large number of cholinesterase-inhibiting drugs and toxins [3]. The toxins are useful for agricultural purposes and for the preparation of novel drugs, although there is little interest in new toxins [4]. The neuropathology of AD is generally characterized by the presence of numerous amyloid β-peptide (Aβ) plaques, neurofibrillary tangles (NFT), and degeneration or atrophy of the basal forebrain cholinergic neurons. The loss of basal forebrain cholinergic cells results in a significant reduction in acetylcholine (ACh) levels, which plays an important role in the cognitive impairment associated with AD [5]. Disruption of cholinergic transmission in AD has been proven in many clinical and neuropathological studies [6,7]. A deficit in Ach and the loss of presynaptic M2 muscarinic and nicotinic receptors has also been observed [8]. There is also evidence of an interaction between AChE and Aβ, which participates in plaques and plays an essential role in AD pathophysiology. AChE constitutes a stable complex with senile plaque components and may even enhance the aggregation of Aβ peptides and amyloid formation. The neurotoxicity of amyloid components may be increased by the presence of AChE [9,10]. In contrast to the overall decrease in AChE in AD brains, at least in its later stages, the local concentration of AChE around the plaques increases as the lesions occur [11]. In addition to hydrolysing ACh, AChE may also be involved in other functions such as cell proliferation, differentiation, and responses to various damaging factors including stress and amyloid formation [12]. Hence, for the most part, AChE inhibitors enhance ACh concentrations in the brain and have been introduced to the market for treating mild-to-moderate AD. Acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine are currently the best available pharmacotherapies for AD patients [13].

The name lactam is given to cyclic amides. In older nomenclature, the second carbon in an aliphatic carboxylic acid is designated as α, the third as β, and so on. Thus, a β-lactam is a cyclic amide with four atoms in its ring. The contemporary name for this ring system is azetidinone. β-Lactam has come to be a generic descriptor for the penicillin family. The ring ultimately proved to be the main component of the pharmacophore [14,15], so the term possesses both medicinal and chemical significance. Ketene–imine cycloaddition was reported by Staudinger to be a smooth, well-documented route to synthesize substituted β-lactam derivatives. In an effort to investigate the suitably of substituted monocyclic β-lactams as a minimum requirement for biological activity, many scientists have reported trans-stereo selective syntheses of butadienyl azetidinones and their Diels–Alder cycloaddition [16,17]. This includes the preparation of a series of Schiff's bases and their reaction with dienyl ketene to produce a trans-azetidinone. This reaction involved the in situ formation of the ketene and its subsequent addition to the imine [18,19].

The 2-azetidinone skeleton, otherwise known as the β-lactam ring, has been recognized as a useful building block in the synthesis of biologically important compounds. Azetindin-2-one derivatives display interesting biological activities, including antimicrobial [20,21], antitubercular [22,23], analgesic, anti-inflammatory [24], chymase inhibitory [25], antitumor [26], and antinociceptive [27] activities. The chemical structure of pyrazinamide provides a valuable molecular template for the development of agents that are able to interact with a wide variety of biological activities [28]. Hence, it was thought worthwhile to synthesize new congeners by incorporating pyrazinamide and azetidinone moieties into a single molecular framework and to evaluate their acetyl and butyl cholinesterase inhibitor activities.

2. Experimental

2.1. Materials and methods

All of the chemicals were supplied by E. Merck (Germany) and S.D. fine chemicals (India). The melting points of the synthesized compounds were determined in open capillaries using a Veego VMP-1 apparatus, are expressed in °C, and are uncorrected. The IR spectra of the compounds were recorded on a Shimadzu FT-IR spectrometer using the KBR pellet technique and are expressed in cm^{-1}. ^1H NMR spectra were recorded on a Bruker DRX-300 (300 MHz FT-NMR) spectrometer using DMSO-d6 as the solvent and TMS as an internal standard. The chemical shifts were reported in ppm. Mass spectra were obtained using a Shimadzu LCMS 2010A with the ESI ionization technique.

2.2. Synthesis of the Schiff's bases (*3a–3m*)

A mixture of equimolar quantities of compound pyrazinamide [1] (0.01 M) and the appropriate aryl or heteroaryl aldehyde [2] (0.01 M) were dissolved in ethanol (95%). The contents were relaxed for a period of 3 h in a steam bath. The obtained solid was separated from the ethanol and crystallized. The percent yield for the compounds was 66–82% and the compounds melted at 158–204 °C. The IR spectra of compounds **3a–3m**