Andrade-Jorge *et al.*
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Crystal structure, DFT calculations and evaluation of 2-(2-(3,4-dimethoxyphenyl) ethyl)isoindoline-1,3-dione as AChE inhibitor

Erik Andrade-Jorge[1], José Bribiesca-Carlos[1], Francisco J. Martínez-Martínez[2], Marvin A. Soriano-Ursúa[3], Itzia I. Padilla-Martínez[4] and José G. Trujillo-Ferrara[1*]

Abstract

Dioxoisoindolines have been included as a pharmacophore group in diverse drug-like molecules with a wide range of biological activity. Various reports have shown that phthalimide derivatives are potent inhibitors of AChE, a key enzyme involved in the deterioration of the cholinergic system during the development of Alzheimer's disease. In the present study, 2-(2-(3,4-dimethoxyphenyl)ethyl)isoindoline-1,3-dione was synthesized, crystallized and evaluated as an AChE inhibitor. The geometric structure of the crystal and the theoretical compound (from molecular modeling) were analyzed and compared, finding a close correlation. The formation of the C6–H6···O19 interaction could be responsible for the non-negligible out of phenyl plane deviation of the C19 methoxy group, the O3 from the carbonyl group lead to C16–H16···O3^{i} intermolecular interactions to furnish *C(9)* and *C(14)* infinite chains within the (− 4 0 9) and (− 3 1 1) families of planes. Finally, the biological experiments reveal that the isoindoline-1,3-dione exerts a good competitive inhibition on AChE (Ki = 0.33–0.93 mM; 95% confidence interval) and has very low acute toxicity (LD_{50} > 1600 mg/kg) compared to the AChE inhibitors currently approved for clinical use.

Keywords: AChE inhibitor, Alzheimer's disease, Crystal structure, Isoindoline-1, 3-Dione, Kinetic

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder. Since the gradual damage to neurons leads to an irreversible deterioration of memory and learning, the afflicted person is eventually unable to carry out cognitive functions [1, 2]. AD is the most common form of dementia in the elderly population [3], accounting for 60–80% of all cases [4–6].

The pathogenesis of AD involves the accumulation of soluble amyloid-β peptide [7], the dysfunction of the cholinergic system, and the deposition of tau neurofibrillary tangles in the brain [8]. These physiological changes lead to confusion, memory loss, impaired cognitive and emotional function, and finally dementia [9].

The main drug target is acetylcholinesterase (AChE) [8], which hydrolyzes the neurotransmitter acetylcholine (ACh) at cholinergic synapses and thus terminates nerve transmission. Since low levels of this signaling molecule are associated with the development of AD, high levels of the same are considered desirable in patients [10–13].

According to the cholinergic hypothesis, impairments in the cholinergic pathway play a pivotal role in the pathogenesis of AD [14]. The main mechanism for enhancing the level of ACh is the inhibition of AChE, which is presently the most effective strategy for treating AD. Hence, the current treatments are cholinesterase inhibitors that target AChE and butyrylcholinesterase (BuChE), and antagonists of *N*-methyl-D-aspartate (NMDA) receptor [1, 2].

In addition to depleting Ach (low concentrations), human AChE accelerates the metabolic rate of

*Correspondence: jtrujillo@ipn.mx
[1] Laboratorio de Investigación en Bioquímica, Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina del Instituto Politécnico Nacional, Plan de San Luis y Díaz Mirón s/n Casco de Santo Tomás, 11340 Mexico City, Mexico
Full list of author information is available at the end of the article