Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **34** (5): 924-33 (2015)

Regular article
Received: March 9, 2015
Revised version: March 17, 2015
Accepted: March 18, 2015

Synthesis, Docking, Metal Chelating and Biological Activity of New Oxalamide Analogues for Alzheimer Disease

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SUMMARY. A series of new oxalamide (**1**-**15**) derivatives were synthesized and evaluated as dual cholinesterase inhibitors for Alzheimer's disease. The anticholinesterase activity of oxalamide derivatives was determined against Electric Eel acetylcholinesterase (EeAChE) and horse serum butyrylcholinesterase (hBuChE) and some of the compounds appeared as moderately potent inhibitors of EeAChE and hBuChE. The compound **13** (*N,N'*-dibenzyl-*N,N'*-bis-(4-chloro-phenyl)-oxalamide) showed maximum activity against hBuChE with an half maximal inhibitory concentration (IC_{50}) = 1.19 μM whereas the compound **12** (*N,N'*-dibenzyl-*N,N'*-bis-(4-fluoro-phenyl)-oxalamide) exhibited optimum dual ChE (AChE IC_{50}= 8.31 μM, BuChE IC_{50}= 1.34 μM) inhibition. To better understand the enzyme-inhibitor interaction of the most active compounds towards cholinesterases, molecular modeling studies were carried out on high-resolution crystallographic structures. The docking simulation showed that the compounds **11** and **13** created many hydrogen bond and π-π stacking interactions with the catalytic and the peripheral anionic site gorges of 1ACJ and 1P0I, confirming its high inhibitor potency and supporting the mixed-type inhibition.

RESUMEN. Una serie (**1**-**15**) de nuevos derivados de oxalamida fueron sintetizados y evaluados como inhibidores duales de la colinesterasa para la enfermedad de Alzheimer. La actividad anticolinesterasa de los derivados de oxalamida se determinó frente a acetil- colinesterasa de anguila eléctrica (EeAChE) y butirilcolinesterasa de suero de caballo (hBuChE) y algunos de los compuestos aparecieron como inhibidores moderadamente potentes de EeAChE y hBuChE. El compuesto **13** (*N, N'*-dibencil-*N, N'*-bis- (4-cloro-fenil) -oxalamida) mostró una actividad máxima contra hBuChE con una concentración máxima media inhibidora (IC_{50}) = 1,19 μM mientras que el compuesto **12** (*N, N'*-dibencil-*N, N'*-bis- (4-fluoro-fenil) -oxalamida) exhibió óptima inhibición dual ChE (AChE IC_{50} = 8,31 M, BuChE IC_{50} = 1,34 M). Para entender mejor la interacción enzima-inhibidor de los compuestos más activos hacia las colinesterasas, se llevaron a cabo estudios de modelos moleculares en estructuras cristalográficas de alta resolución. La simulación de acoplamiento demostró que los compuestos **11** y **13** crearon muchos enlaces de hidrógeno e interacciones π-π de apilamiento con el catalizador y los sitios aniónicos periféricos de 1ACJ y 1P0I, confirmando su alta potencia inhibidora y la inhibición de tipo mixto.

KEY WORDS: AChE, BuChE, mixed-type inhibition, molecular modeling, oxalamide.

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ISSN 0326 2383 (printed ed.)
ISSN 2362-3853 (on line ed.)