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Hadda, T.B.[a] , Talhi, O.[b] , Silva, A.S.M.[b] , Senol, F.S.[c] , Orhan, I.E.[c] , Rauf, A.[d] , Mabkhot, Y.N.[e] , Bachari, K.[f] , Warad, I.[g] , Farghaly, T.A.[h i] , Althagafi, I.I.[i] , Mubarak, M.S.[j]

Cholinesterase inhibitory activity of some semi-rigid spiro Heterocycles: POM analyses and crystalline structure of pharmacophore site

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[a] LCM Laboratory, Sciences Faculty, Mohammed Premier University, Oujda, 60000, Morocco
[b] QOPNA, Department of Chemistry, University of Aveiro, Aveiro, 3810-193, Portugal
[c] Department of Pharmacognosy, Pharmacy Faculty, Gazi University, Ankara, 06330, Turkey
[d] Department of Chemistry, University of Swabi, Anbar, Khyber Pakhtunkhwa 23561, Pakistan
[e] Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh, 11451, Saudi Arabia
[f] Centre de Recherche Scientifique et Technique en Analyses Physico-Chimiques, BP 384, Tipaza, RP 42004, Algeria
[g] Department of Chemistry, Science College, An-Najah National University, P.O. Box 7, Nablus, Palestine
[h] Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt
[i] Department of Chemistry, Faculty of Applied Science, Umm Al-Qura University, Makkah Almukkarramah, Saudi Arabia
[j] Department of Chemistry, The University of Jordan, Amman, 11942, Jordan

Abstract
Background: Cholinesterase family consists of two sister enzymes; acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) which hydrolyze acetylcholine. Since deficit of acetylcholine has been evidenced in patients of Alzheimer's disease (AD), cholinesterase inhibitors are currently the most prescribed drugs for the treatment of AD. Objective: our aim in this article was to investigate the inhibitory potential of five known compounds (2-6) with spiro skeleton against AChE and BChE using ELISA microplate assays. In addition to their ChE inhibitory effect, their physico-chemical properties were also calculated. Moreover, the present work aims at investigating the charge/geometrical effect of a hypothetical pharmacophore or bidentate site in a bioactive group, on the inhibition efficiency of spiro compounds 2-6 by using Petra/Osiris/ molinspiration (POM) and X-ray analyses. Method: In the present study, five compounds (2-6) with spiro skeleton have been synthesized and tested in vitro for their inhibitory potential against AChE and BChE using ELISA microtiter plate assays at 25 µg/mL. Results: Results revealed that three of the spiro compounds tested exert more than 50% inhibition against one of cholinesterases. Compound 5 displayed 68.73 ± 4.73% of inhibition toward AChE, whereas compound 6 showed 56.17 ± 0.83% of inhibition toward BChE; these two previously synthesized compounds have been the most active hits. Conclusions: Our data obtained from screening of compounds 2-6 against the two cholinesterases indicate that three of these show good potential to selectively inhibit AChE or BChE. Spiro compounds 2, 5, and 6 exhibited the most potent activity of the series against AChE or BChE with inhibition values in the range 55-70%. © 2018 Bentham Science Publishers.

Author Keywords
Alzheimer's disease (AD); Cholinesterases; Crystalline structure; Petra/Osiris/Molinspiration (POM) analyses; Pharmacophore; Spiro heterocycles