

Design, Synthesis and Evaluation of 4-(Phenylsulfonamido)Benzamide Derivatives as Selective Butyrylcholinesterase Inhibitors

Authors : Sushil Kumar Singh, Ashok Kumar, Ankit Ganeshpurkar, Ravi Singh, Devendra Kumar

Abstract : In spectrum of neurodegenerative diseases, Alzheimer's disease (AD) is characterized by the presence of amyloid β plaques and neurofibrillary tangles in the brain. It results in cognitive and memory impairment due to loss of cholinergic neurons, which is considered to be one of the contributing factors. Donepezil, an acetylcholinesterase (AChE) inhibitor which also inhibits butyrylcholinesterase (BuChE) and improves the memory and brain's cognitive functions, is the most successful and prescribed drug to treat the symptoms of AD. The present work is based on designing of the selective BuChE inhibitors using computational techniques. In this work, machine learning models were trained using classification algorithms followed by screening of diverse chemical library of compounds. The various molecular modelling and simulation techniques were used to obtain the virtual hits. The amide derivatives of 4-(phenylsulfonamido) benzoic acid were synthesized and characterized using ^1H & ^{13}C NMR, FTIR and mass spectrometry. The enzyme inhibition assays were performed on equine plasma BuChE and electric eel's AChE by method developed by Ellman et al. Compounds 31, 34, 37, 42, 49, 52 and 54 were found to be active against equine BuChE. N-(2-chlorophenyl)-4-(phenylsulfonamido)benzamide and N-(2-bromophenyl)-4-(phenylsulfonamido)benzamide (compounds 34 and 37) displayed IC_{50} of 61.32 ± 7.21 and 42.64 ± 2.17 nM against equine plasma BuChE. Ortho-substituted derivatives were more active against BuChE. Further, the ortho-halogen and ortho-alkyl substituted derivatives were found to be most active among all with minimal AChE inhibition. The compounds were selective toward BuChE.

Keywords : Alzheimer disease, butyrylcholinesterase, machine learning, sulfonamides

Conference Title : ICMCP 2020 : International Conference on Medicinal Chemistry and Pharmacology

Conference Location : Dublin, Ireland

Conference Dates : August 17-18, 2020