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Microwave Synthesis and Molecular Docking Studies of Azetidinone Analogous Bearing Diphenyl Ether Nucleus as a Potent Antimycobacterial and Antiprotozoal Agent

Authors : Vatsal M. Patel, Navin B. Patel

Abstract : The present studies deal with the developing a series bearing a diphenyl ethers nucleus using structure-based drug design concept. A newer series of diphenyl ether based azetidinone namely N-(3-chloro-2-oxo-4-(3-phenoxyphenyl)azetidin-1-yl)-2-(substituted amino)acetamide (2a-j) have been synthesized by condensation of m-phenoxybenzaldehyde with 2-(substituted-phenylamino)acetohydrazide followed by the cyclisation of resulting Schiff base (1a-j) by conventional method as well as microwave heating approach as a part of an environmentally benign synthetic protocol. All the synthesized compounds were characterized by spectral analysis and were screened for in vitro antimicrobial, antitubercular and antiprotozoal activity. The compound 2f was found to be most active M. tuberculosis (6.25 µM) MIC value in the primary screening as well as this same derivative has been found potency against L. mexicana and T. cruzi with MIC value 2.09 and 6.69 µM comparable to the reference drug Miltefosina and Nifurtimox. To provide understandable evidence to predict binding mode and approximate binding energy of a compound to a target in the terms of ligand-protein interaction, all synthesized compounds were docked against an enoyl-[acyl-carrier-protein] reductase of M. tuberculosis (PDB ID: 4u0j). The computational studies revealed that azetidinone derivatives have a high affinity for the active site of enzyme which provides a strong platform for new structure-based design efforts. The Lipinski's parameters showed good drug-like properties and can be developed as an oral drug candidate.

Keywords : antimycobacterial, antiprotozoal, azetidinone, diphenylether, docking, microwave
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