SYNTHESIS PHARMACOLOGICAL EVALUATION, MOLECULAR DOCKING AND CYTOTOXICITY STUDIES ON SOME N-SUBSTITUTED 5-[(4-CHLOROPHENOXY)METHYL]-1,3,4-OXADIAZOLE-2YL-2-SULFANYL ACETAMIDES

Sabahat Zahra Siddiquiᵃ, Muhammad Athar Abbasiᵃ, Aziz-ur-Rehmanᵃ, Misbah Irshadᵃ, Babar Shahzadᵃ, Muhammad Ashrafᵇ, Irshad Ahmadᶜ, Muhammad A. Lodhiᵈ, Bushra Mirzaᵉ, Hammad Ismailᵉ, Muhammad N. Akhtarᶠ

ᵃDepartment of Chemistry, Government College University, Lahore-54000, Pakistan.
ᵇDepartment of Biochemistry and Biotechnology, The Islamia University of Bahawalpur, Bahawalpur-63100, Pakistan.
ᶜDepartment of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur-63100, Pakistan.
ᵈDepartment of Biochemistry, Abdul Wali Khan University, Mardan-23200, Pakistan.
ᵉDepartment of Biochemistry, Quaid-i-Azam University, Islamabad, 45320, Pakistan.
ᶠFaculty of Industrial Sciences & Technology, University Malaysia Pahang, Leburaya TunRazak 26300, Kuantan Pahang, Malaysia.

ABSTRACT
The framework of our systematic efforts focuses on the synthesis of N-substituted 5-[(4 chlorophenoxy) oxadiazole-2yl-2-sulfanyl acetamides. 4-Chlorophenoxyacetic acid (1) was utilized as a precursor for the 1,3,4-oxadiazole moiety. Esterification of 1 in the presence of catalytic amount of concentrated sulfuric acid and absolute alcohol generated ethyl 2-(4-chlorophenoxy)acetate (2) which was treated with hydrazine hydrate to yield 2-chlorophenoxy)acetohydrazide (3). Ring closure reaction of 3 with carbon disulfide and alcoholic potassium hydroxide afforded [5-(4-chlorophenoxy)methyl]-1,3,4-oxadiazole-2-thiol (4). Finally, substitution at thiol position electrophiles, N-substituted-2-bromoacetamides (6a-p) in polar aprotic solvent and LiH yielded various chlorophenoxy)methyl]-1,3,4-oxadiazole-2yl-2-sulfanyl acetamides (7a-p). IR, 1H-NMR and EI-MS spectral analysis data unequivocally confirmed all the substitutions on 1,3,4-oxadiazole-2-thiol core. It was recognized that the synthesized derivatives are potential antibacterial agents against both gram negative and gram positive bacteria and moderate inhibitors of α-chymotrypsin enzyme. In vitro screening against various bacterial strains unleashed their potential, especially 5-[(4-chlorophenoxy)methyl]-1,3,4-oxadiazol-2yl-N-(3,4-dimethylphenyl)-2-sulfanyl exhibited marvelous activity when compared with standard ciprofloxacin against S.typhi (-), K.pneumon (+). Compounds were computationally docked with the α-chymotrypsin enzyme protein to unravel the α which displayed significant correlation with the bioactivity data. It can be envisioned that the amalgamation of chlorophenoxy)methyl]-1,3,4-oxadiazole-2-thiol with N-substituted-2-bromoacetamides generated N-substituted-[(4-chlorophenoxy)methyl]-1,3,4-oxadiazole-2yl-2-sulfanyl acetamides having tremendous antibacterial act anti-enzymatic potential. Moreover, substitutions on the oxadiazole moiety lead to the discovery of less compounds as evident from the cytotoxicity data.

KEYWORDS: N-Substitute5- [(4-Chlorophenoxy)Methyl]-1,3,4-Oxadiazole-2yl-2-Sulfanyl Acetamides, Spectral Analysis, Pharmacological Screening, Molecular Docking.