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Analysis of Intermolecular Binding Interactions for Novel Cytotoxic 2,5-disubstituted Oxadiazoles versus Cancer Relevant Targets

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Introduction and background: Oxadiazole nucleus is a privileged structure in medicinal chemistry. In continuation to our interest in bioactive heterocycles, a few novel synthesized 1,3,4-oxadiazole derivatives were subjected to structure based modeling with the aim of elucidating intermolecular interactions into chemotherapeutic targets. Selected targets were previously demonstrated to be inhibited by 1,3,4-oxadiazoles. Quantitative and qualitative structure binding relationship analysis of docked oxadiazole derivatives proposed binding affinity/mode for cytotoxic oxadiazole molecules within diverse validated targets.

Methods: Ligand-flexible docking studies were performed using the molecular docking software, AutoDock 4.2. To elucidate the interactions of selected targets with 1,3,4-oxadiazole molecules (**1**-**17**), all the related structures were docked into the active site of validated decuple receptors. Besides, AutoDock driven binding affinities (ΔG_b, k_i, and LE) were subjected to linear regression analysis with *in vitro* target inhibitory activities.

Results: Structure–binding relationship (SBR) studies confirmed that chemical structures possessing chlorine and bromine atoms on 5-phenyl ring and *N*-benzyl moieties (**4** and **17**) exhibited superior binding modes/energies in the majority of studied targets. Amine & pyrrole NH, and N3 of oxadiazole ring were the most frequent atoms participated in H-bond interactions necessary for the enzyme inhibition. Moreover; linear regression analysis demonstrated that telomerase, epidermal growth factor (EGF), and BCL-2 were desirable targets with relatively acceptable affinity toward oxadiazoles on A549 cell line.

Discussion and Conclusion: Multi-target oriented study revealed some insights into binding mode of novel cytotoxic oxadiazole derivatives. On the basis of obtained results, a general structure activity relationship (SAR) pattern for candidate 1,3,4-oxadiazoles were represented and a few novel structures were proposed and virtually validated as potential anticancer agents. Since the assessed macromolecular targets were previously proved to be blocked by 1,3,4-oxadiazoles, the results of this study might be useful in further design of more potent cytotoxic 1,3,4-oxadiazole derivatives.

Keywords: Cancer; Target, Oxadiazole; Docking

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