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A comparative study of p53 and nutlin-3 interaction with MDM2 towards drug design

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The tumor suppressor protein p53 is inhibited while mouse double minute 2 (MDM2) protein binds on its transactivation domain. Over expression of MDM2 impairs p53 function and are observed in many human tumors. Disruption of MDM2-p53 interaction leads to increased p53 level and restore p53 transcriptional activity. Restoration of p53 activity through inhibiting the interaction between p53 and MDM2 represents a promising approach for cancer therapy. A number of small-molecule p53-MDM2 binding inhibitors have been developed during the past several years. Nutlin-3 has shown a potent and selective small-molecule MDM2 antagonist which has a considerable promise in pre-clinical studies. In this study we investigated theoretically the interaction of nutlin-3 with MDM2 at atomistic level, and compared to the interaction of MDM2 with p53 to explore the molecular basis of inhibition. In MDM2-p53 model, p53 residues has three hydrogen bonding interaction with MDM2. The lengths of the hydrogen bonds are found 2.45 Å, 2.46 Å and 1.89 Å whereas interaction energies are -3.82 kcal/mol, -3.76 kcal/mol, -5.32 kcal/mol respectively. The sum of three hydrogen bonding energy is -12.90 kcal/mol. On the other hand in MDM2-nutlin model, there are four hydrogen bond interactions between MDM2 and nutlin. The bond lengths are found 2.29 Å, 1.77Å, 2.48 Å and 2.39 Å whereas interaction energies are -4.21 kcal/mol, -6.63 kcal/mol, -3.65 kcal/mol. -3.63 kcal/mol. respectively. Interaction energy among MDM2 residues and nutlin-3 is calculated to be -18.12 kcal/mol. From the comparison between two models it is revealed that MDM2-nutlin3 model has four hydrogen bonds where as MDM2-p53 model has three hydrogen bonds. The interaction energy in MDM2-nutlin-3 is relatively more stable than MDM2-p53 interaction. Due to stronger hydrogen bond interaction with higher interaction energy, nutlin-3 blocks the p53-binding pocket of MDM2 thus disrupts the MDM2-p53 interaction and helps to activate p53 pathway of apoptosis.

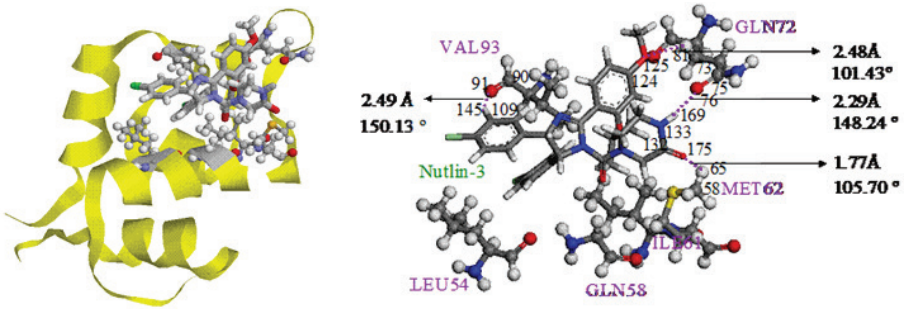

Fig. 1) Final structure of MDM2-Nutlin-3 (docked) after UA-QCMD, Fig. 2) Interaction of Nutlin-3 with surrounding MDM2 residues (Truncated model). Hydrogen bonding is represented by dashed line.

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