MULTITARGET CELL-CYCLE REGULATORS MODELING

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Nutlins is a family of *cis*-imidazoline derivatives which inhibit the interaction between MDM2 and p53 tumor suppressor protein. These compounds have been found by virtual screening of the diverse library of synthetic chemicals [1]. Currently, Nutlins are in clinical trials as anticancer drugs. Among them Nutlin-3 is the first potent and selective MDM2 inhibitor.

Recently, there is evidence that Nutlin-3 is not only involved in the induction of p53-mediated apoptosis, but also acts independently of p53 pathway, causing apoptosis in cancer cells. It was also shown that Nutlin-3 inhibits protein Bcl-xL, a member of the Bcl-2 family of apoptosis regulator proteins [2].

We suggested that the other well-known MDM2 inhibitors may also have cross-effects. We tested Nutlins, inhibitors MI-series (spiro-oxindole derivatives), Priaxon's inhibitors and α-helix mimetics in our work. The protein targets chosen were MDM2, Bcl-xL, MDM4 which is a negative regulator of p53 and has a high degree of homology to MDM2, and Bcl-2 which is a homologue of Bcl-xL, possessing anti-apoptotic effect like Bcl-xL. We tested MDM2 inhibitors for interaction with the selected targets by docking and compared them with each other. The aim of this work was to compare the compounds developed in our laboratory with well-known leaders for the ability to inhibit multiple targets (MDM2, MDM4, Bcl-xL, Bcl-2). Computer experiment showed that our developed compounds fit into the multitarget conception and can efficiently compete with inhibitors from leading drug-design laboratories.

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References

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