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Extended Abstract

Discovery of a Selective NEK6 Kinase Inhibitor by Virtual Screening †

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NIMA-related kinases (Neks) are a conserved serine/threonine protein kinase family related to cell cycle progression and cell division. Among these, NEK6 was shown to be overexpressed in human cancers; its involvement in tumorigenesis has also been demonstrated, thus making NEK6 an emerging attractive target for cancer drug development [1]. The selective inhibitors of NEK6 may therefore become important compounds for identifying novel therapeutic agents. Several natural and synthetic molecules have been reported in literature with inhibitory activity on NEK6, but no potent scaffold has emerged and to date, no inhibitor of NEKs has entered clinical trials for the treatment of cancer. In an effort to identify novel NEK6 inhibitors, we performed a virtual screening study, on a generated homology model of the kinase, adopting both structure- and ligand-based techniques. An in silico study, followed by biochemical screening, led to the identification of (5Z)-2-hydroxy-4-methyl-6-oxo-5-[(5-phenylfuran-2-yl)methylidene]-5,6-dihydropyridine-3-carbonitrile), able to selectively inhibit NEK6, with respect to the homologous NEK7, at micromolar order of magnitude [2,3]. Notably, the compound shows antiproliferative activity against a panel of human cancer cell lines and displays a synergistic effect with cisplatin and paclitaxel in a BRCA2 mutated ovarian cancer cell line, thus supporting a possible use for personalized therapy.

References

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