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In-Silico Studies and Anticancer Evaluation of some Newly Synthesized Indolin-2-One Derivatives as Potential VEGFR-2 Inhibitors

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Statement of Research: Tyrosine kinase inhibitors and their potential in clinical application are well documented by dramatic examples like, Gleevec, Iressa and Nexavar etc. Several tyrosine kinase inhibitors are undergoing human trials and several are in the pipeline of drug discovery. Quick selection of epidemiologically relevant, drugable tyrosine kinase targets coupled to efficient lead finding and optimization needs more intervention in the area of high throughput cancer genome based molecular therapeutics. All these concerted effort may pave the silver lining to tailor made personalized cancer therapeutics.

Experimental & Theoretical Orientation: Keeping in view their importance, twenty new substituted indolin-2-one containing imine derivatives **(2a-2t)** were synthesized and docked with eight different tyrosine kinase enzymes (*Aurora A Kinase* PDB: 3FDN, *Aurora B Kinase* PDB: 2VRX, *human Abl kinase* PDB: 3CS9, *human CDK6-VCYCLIN* PDB: 2EUF, *C-MET* PDB: 4XMO, *EGFR*

PDB: 1M17, *Focal Adhesion Kinase* PDB: 2JKK, *human VEGFR-2* PDB: 3VHE). On the basis of docking results, VEGFR-2 target was selected out of all kinase targets for the *in-vitro* enzyme assay. Enzymatic inhibition assay was performed for all twenty compounds using VEGFR-2 enzyme inhibition assay kit and IC_{50} was obtained for all compounds. Simultaneously, all compounds were sent to NCI, USA for sixty-cell line based anticancer screening, out of which fifteen compounds were selected for one dose anticancer assay.

Findings: Compounds **2a** (NSC: D-795068/1) and **2g** (NSC: D-795071/1) were found potent during one dose anticancer screening and fulfilled the specified threshold for growth inhibition criteria of NCI and further selected for full panel five dose assay at 10-fold dilutions of five different concentrations. Both compounds **2a** and **2g** displayed Mid GI_{50} values of 1.69 µM & 1.54 µM respectively against the cell lines of Leukemia, Non-Small Cell Lung Cancer, Colon Cancer, CNS Cancer, Melanoma, Ovarian Cancer, Renal Cancer, Prostate Cancer and Breast Cancer.

Conclusion: The results were found even better than the standard used (Fluorouracil) by NCI. *In silico* studies and ADME prediction also supported the potential of these compounds as tyrosine kinase inhibitors. It is expected that Tyrosine Kinase inhibition by the said compounds may deliberate a substantial therapeutic benefit over existing treatments for cancer.

Biography:

Nishtha Shalmali is presently working on development of new tyrosine kinase inhibitor compounds as a PhD Scholar in the Department of Pharmaceutical Chemistry, School of Pharmaceutical Education & Research, Jamia Hamdard. She has recently qualified CSIR-SRF and secured 2nd Best Poster Award for her group's research work on thiazole-5-carboxylate derivatives as selective MAGL inhibitors at ITS, Ghaziabad (India). She has emerged as an effective presenter during various conferences. Nishtha has attained hands on specific skills in the field of Green Chemistry, Scale up techniques and Bulk drugs during her Post Graduation & has achieved impressive hold on medicinal, pharmaceutical & analytical laboratory techniques during her doctoral research.