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INDOLINONE DERIVATIVES AS PROMISMING ANTI VEGFR-2 AGENTS TARGETING TUMOR ANGIOGENESIS : A COMPREHENSIVE *IN SILICO* CASE STUDY

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ABSTRACT : Tumor angiogenesis is a complicated process involving several interconnected pathways and interactions between RTKs and signaling factors that contribute to tumor formation. After being shown to be a crucial mediator in the angiogenesis phenomenon, RTKs such as VEGFR-2 have been recognized as a primary therapeutic target for lowering angiogenesis in different tumors. Despite the fact that past case studies and research have shed light on the function of VEGFR-2 in tumor angiogenesis and its suppression mechanism, much more research and knowledge is required to improve cancer treatment. There are several FDA-approved drugs in the market that target VEGFR-2. However, their substantial side effects and adverse reactions are a worry, if taken long-term. Peer scientists are doing multiple in-silico, *in vivo* and *in vitro* studies in order to provide a better anti-VEGFR-2 drug with more accuracy and fewer adverse effects. Computational approaches have aided in the production of medications as well as the discovery of multi-targeted inhibitors of several over expressed proteins. In this research work, we have performed structure based virtual screening, molecular docking and metabolic reactivity studies of indolinone derivatives to identify the potential leads possessing anti-VEGFR2 activity. This investigation revealed three compounds *viz.* SUN153, SUN69 and SUN147 with significant binding strengths against the VEGFR2 than sunitinib, control drug. These virtual hits may be investigated for early therapeutic development against tumor angiogenesis *in vitro* and *in vivo* due to their strong modulating and target inhibiting characteristics, as expected after testing.

Key words : Tumor angiogenesis, embryogenesis, vesculogenesis, molecular docking, UCSF Chimera, virtual screening, pharmacokinetics.

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INTRODUCTION

Angiogenesis is the process by which new blood vessels are formed from pre-existing ones as a result of the interplay of several angiogenic pathways and angiogenic substances. Angiogenesis is involved in the formation and development of physiological cellular structures as well as the development of several forms of cancer (Gordon *et al*, 2010). During embryogenesis, vascular formation begins with vasculogenesis, which includes denovo differentiation of endothelial cells from angioblast and is followed by angiogenesis (Abhinand *et al*, 2016). Angiogenesis has been discovered to be involved in both non-pathological and pathological body circumstances (Rosen, 2004). This process involves a number of angiogenic stimulators or signaling molecules, as well as their receptors. Several angiogenic stimulators or signaling molecules, as well as their receptors, are involved in this process, resulting in distinct signaling pathways that allow endothelial cells to be rapidly recruited to the formation of mature blood vessels (Shah *et al*, *2021*). Endoglin, endostatin, angiostatin, tissue inhibitors of metalloproteins, interferons, interleukins, and other proteins all have an effect on the normal angiogenic pathway. In non-pathological contexts, an angiogenic switch maintains the normal balance of angiogenic and anti-angiogenic factors, but it is disturbed in pathological

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