Towards discovery of novel scaffold with potent antiangiogenic activity; design, synthesis of pyridazine based compounds, impact on hinge interaction, and accessibility of their bioactive confirmation on VEGFR-2 activities

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Abstract

Pyridazine scaffolds are considered privileged structures pertaining to its novelty, chemical stability, and synthetic feasibility. In our quest towards the development of novel scaffolds for effective vascular endothelial growth 2 (VEGFR-2) inhibition with antiangiogenic activity, four novel series of pyridazines were designed and synthesised. Five of the synthesised compounds; namely (8c, 8f, 15, 18b, and 18c) exhibited potent VEGFR-2 inhibitory potency (>80%); with IC50 values ranging from low micromolar to nanomolar range; namely compounds 8c, 8f, 15, 18c with (1.8¡ÕM, 1.3¡ÕM, 1.4¡ÕM, 107¡nM), respectively. Moreover, 3-[4-{(6-oxo-1,6-dihydropyridazin-3-yl)oxy}phenyl]urea derivative (18b) exhibited nanomolar potency towards VEGFR-2 (60.7¡nM). In cellular assay, the above compounds showed excellent inhibition of VEGF-stimulated proliferation of human umbilical vein endothelial cells at 10¡εM concentration. Finally, an extensive molecular simulation study was performed to investigate the probable interaction with VEGFR-2.

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