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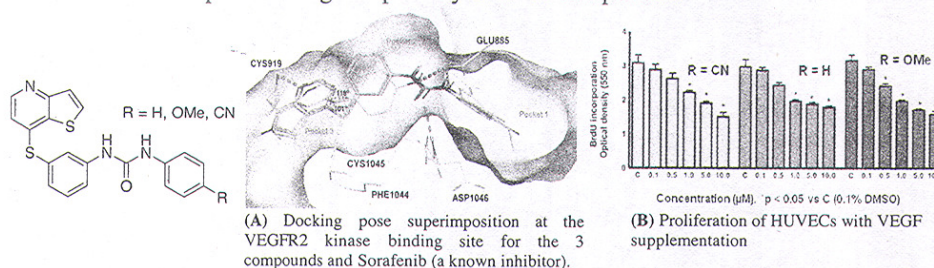
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Synthesis, docking, enzymatic and cellular assays of thieno[3,2-*b*]pyridine-thioether-1,3-diaryljureas as VEGFR2 inhibitors

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Vascular endothelial growth factor receptor 2 (VEGFR2) is a class of tyrosine kinase receptors, expressed primarily in endothelial cells, and is activated by the specific binding of VEGF to the VEGFR2 extracellular regulatory domain, undergoing autophosphorylation, triggering signaling pathways leading to endothelial cell proliferation and subsequent angiogenesis.^[1] Small molecules may act as inhibitors by competing for the ATP-binding site of the VEGFR2 intracellular tyrosine kinase domain, thereby preventing the intracellular signaling that leads to angiogenesis.^[2] Herein, we report the synthesis of novel nine 1-aryl-3-[2-, 3- or 4-(thieno[3,2-*b*]pyridin-7-ylthio)phenyl]ureas as VEGFR2 inhibitors. The compounds presented below, with the arylurea in the meta position to the thioether, showed the lowest IC₅₀ values (0.4-0.9 μM) in enzymatic assays. Using molecular docking (A) and molecular dynamics simulations, a convincing rationalization was achieved to explain the highest potency of these compounds.



To examine the activity of the three compounds in endothelial cells, HUVECs were cultured in M199 medium (supplemented with 2% FBS and 60 ng/mL of VEGF) in the absence or presence of each compound at different concentrations. A remarkable reduction in the proliferation of HUVECs was observed for the compound with R=OMe at 0.5 μM or higher, evaluated by the incorporation of BrdU in cell culture. For compounds with R=H or R=CN, a decrease in cell growth was only observed at 1 μM or higher concentrations. These findings indicate that the methoxylated compound is the most promising. Further studies are ongoing to examine whether these molecules affect the expression and activity of VEGFR2.

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