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1-Aryl-3-[4-(thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl]ureas as VEGFR2 inhibitors: synthesis, docking enzymatic and cellular assays

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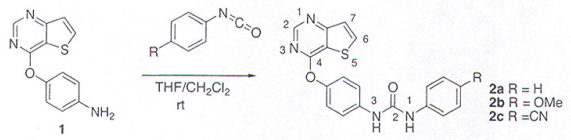
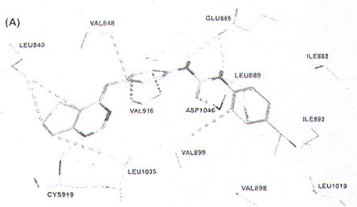
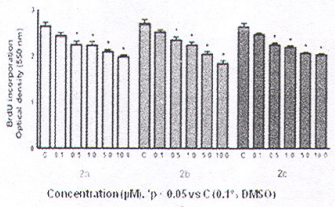
A number of thienopyrimidines derivatives have shown potent VEGFR2 (Vascular Endothelium Growth Factor Receptor2) tyrosine kinase inhibition activity.[1] VEGF is a surrogate marker of angiogenesis that activates VEGFR2 in endothelial cells.

Here we present the synthesis of new 1-aryl-3-[4-(thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl]ureas from the aminodi(hetero)arylether **1**, also prepared by us, which was reacted with arylisocyanates to give the corresponding 1,3-diarylureas **2a-c**.





(C) Superimposition of the docking poses at the VEGFR2 kinase domain for compounds **2a-c**.



(B) Proliferation of HUVECs with VEGF supplementat.

Compounds **2a-c** were evaluated for inhibition of VEGFR2 tyrosine kinase activity using enzymatic assays and showed good inhibition ability. The rational for the inhibition is discussed using docking (A). To examine the activity of compounds **2a-c** in endothelial cells, HUVECs were cultured in M199 medium (supplemented with 2% FBS and 60 ng/mL of VEGF) in the absence (control) or presence of each compound at different concentrations. A reduction above 0.5 μM in the proliferation of HUVECs was observed, evaluated by the incorporation of BrdU in cell culture. These molecules are promising anti-angiogenic agents that may be used for therapeutic purposes.

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