Synthesis of Novel 1-Aryl-3-[2-,3- or 4-(thieno[3,2-b]pyridin-7-ylthio)phenyl]ureas and Evaluation as VEGFR2 Tyrosine Kinase Inhibitors


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Vascular endothelial growth factor receptor 2 (VEGFR2) tyrosine kinase is involved in cancer and in angiogenesis.[1] Herein, we report the synthesis of novel 1-aryl-3-[2-, 3- or 4-(thieno[3,2-b]pyridin-7-ylthio)phenyl]ureas as VEGFR2 inhibitors by promoting the regioselective attack of the thiol group of the 4-aminothiophenol in the chlorine nucleophilic displacement on 7-chlorothieno[3,2-b]pyridine 1, obtaining the aminated compounds 2a–c. These were reacted with arylisocyanates to give the corresponding 1,3-diarylureas 3a–c, 4a–c and 5a–c (see scheme).

1-Aryl-3-[3-(thieno[3,2-b]pyridin-7-ylthio)phenyl]ureas 4a–c with the arylurea in the meta position relative to the thioether showed the lowest IC50 values (0.4–0.9 μM) in enzymatic assays using VEGFR2 tyrosine kinase domain, and the binding mode for these compounds was predicted by docking simulations.

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