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HETEROARYLETHER 1,3-DIARYLUREAS IN THE THIENO[3,2-d]PYRIMIDINE SERIES AS VEGFR2 TYROSINE KINASE INHIBITORS: SYNTHESIS, DOCKING STUDIES, ENZYMATIC AND CELLULAR ASSAYS

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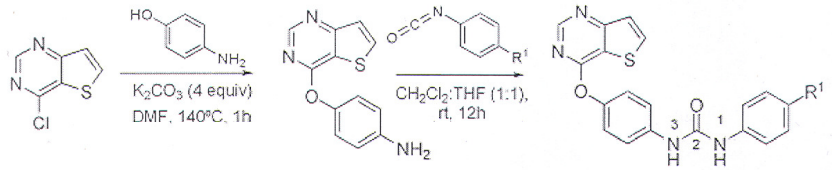
A number of thienopyrimidines derivatives have shown potent VEGFR2 (Vascular Endothelium Growth Factor Receptor2) inhibition activity [1]. VEGF is a surrogate marker of angiogenesis that activates VEGFR2 in endothelial cells. VEGF induces proliferation, migration and anastomosis of these cells. Here we present the synthesis of new 1-aryl-3-[4-(thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl]ureas, by reaction of 4-aminophenol with 4-chlorothieno[3,2-*d*]pyrimidine giving compound **1**, which was reacted with arylisocyanates to give the corresponding 1,3-diarylureas **2a-c** (Scheme).



1, 91%

2a R^1 = H, 79%
2b R^1 = OCH_3, 90%
2c R^1 = CN, 70%

These were evaluated for inhibition of VEGFR2 tyrosine kinase activity using enzymatic assays and showed good inhibition ability. The rational for the inhibition is also discussed using docking. To examine the activity of these compounds in endothelial cells, Human Umbilical Vein Endothelial Cells (HUVECs) were cultured in M199, supplemented with 20% FBS containing 60 ng/mL of VEGF, in the presence or absence of each compound and in the concentrations 0.1 μM, 1.0 μM and 10 μM or control (0.1% DMSO). Cell viability was measured by MTS assay at 24h, revealing a decrease in the percentage of viable cells upon incubation with higher concentrations. This was accompanied by a reduction above 0.5 μM in the proliferation of HUVECs evaluated by the incorporation of BrdU quantified by ELISA assay. These findings suggest that these compounds are able to inhibit proliferation. Given the established role of VEGFR2 in proliferation and migration of endothelial cells, these molecules are promising anti-angiogenic agents that can be used for therapeutic purposes in pathological conditions where angiogenesis is exacerbated, such as in cancer.

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References

1) Munchhof, M.J. et al. Bioorg. Med. Chem. Lett. 2004, 14, 21–24.