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1-Aryl-3-[4-(thieno[3,2-*d*]pyrimidin-4-yloxy) phenyl]ureas as VEGFR2 Tyrosine Kinase Inhibitors: Synthesis, Docking Studies, Enzymatic and Cellular Assays

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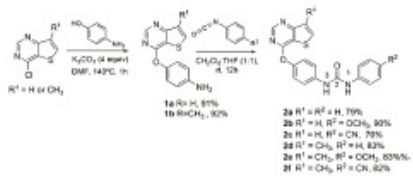
A number of thienopyrimidines derivatives have shown potent vascular endothelial growth factor receptor 2 (VEGFR2) inhibition activity.[1] Here, we present the synthesis of new 1-aryl-3-[4-(thieno[3,2-*d*] pyrimidin-4-yloxy)phenyl]ureas by promoting the regioselective attack of the hydroxy group of the 4-aminophenol in the chlorine nucleophilic displacement on two 4-chlorinated thieno[3,2-*d*]pyrimidines, obtaining compounds **1a** and **1b** which were reacted with arylisocyanates to give the corresponding 1,3-diarylureas **2a–f** (see scheme).

These compounds were evaluated for inhibition of VEGFR2 tyrosine kinase activity using enzymatic assays, and **2a–c** showed good inhibition ability with IC_{50} values in the range of hundreds of nanomolar. The rationale for the inhibition activity is also discussed using docking. To examine the activity of **2a–c** in endothelial cells, human umbilical vein endothelial cells (HUVECs) were cultured in the presence or absence of each compound in different concentrations. A decrease in the proliferation of HUVECs was observed by the incorporation of BrdU quantified by ELISA assay. Given the established role of VEGFR2 in proliferation and migration of endothelial cells, these molecules are promising antiangiogenic agents that can be used for therapeutic purposes in pathological conditions where angiogenesis is exacerbated, such as cancer.



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Green Chemistry in Pharmaceutical Research—Inspirations from Radical Reactions

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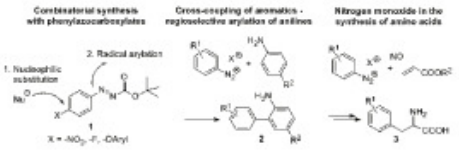
Chemical transformations in medicinal chemistry and pharmaceutical manufacturing have to meet ever more complex demands such as sustainability and selectivity in order to be applied to the multifaceted challenges of today.[1] To address theses issues, radical chemistry has been a largely neglected discipline. Herein, we would like to present three recent examples showing the suitability of metal-free radical reactions for pharmaceutical purposes. Phenylazocarboxylates **1**, which are valuable building blocks for combinatorial synthesis, can be modified by nucleophilic substitution and radical reactions under mild conditions.[2,3]



The synthesis of versatile 2-aminobiphenyls **2** has been achieved via a highly regioselective Gomberg-Bachmann arylation.[4] Through a new type of the Meerwein arylation, nitrogen monoxide can used for the preparation of aromatic amino acids **3**.[5] This process is also a potential tool for the recycling of NO occuring as waste gas on multi-ton-scale every day.

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