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A number of thienopyrimidine derivatives have shown potent vascular endothelial growth factor receptor 2 (VEGFR2) inhibition activity. Here, we present the synthesis of new 1-aryl-3-[6-(3,2-dihydropyrimidin-4-yl)(4-amino)phenyl]-1H-pyrazoles by promoting the regioselective attack of the hydroxy group of the 6-aminothieno(3,2-d)pyrimidine-4-yl moiety on two-chlorinated thieno(3,2-d)pyrimidines, obtaining compounds 1a and 1b which were reacted with enolacetonates to give the corresponding 1,3-dinylarenes 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 IC50 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 labeled by ELISA assay. Given the established role of VEGFR2 in proliferation and migration of endothelial cells, these molecules are promising antiproliferative agents that can be used for therapeutic purposes in pathological conditions where angiogenesis is exacerbated, such as cancer.

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The synthesis of versatile 2-aminobenzyl phenyl 2 has been achieved via highly regioselective Gomberg-Bachmann arylation. Through a new type of the Meerwein arylation, nitrogen monoxide can be used for the preparation of aromatic amino acids. The process is also a potential tool for the recycling of NO occurring as waste gas on multi-ton scale every day.

References