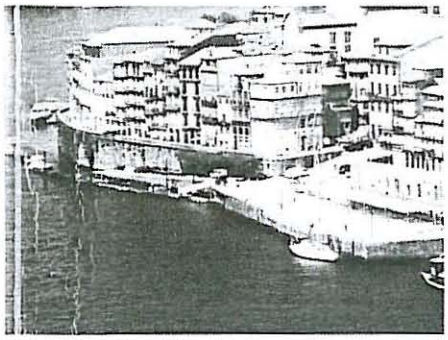

2nd Iberic Meeting on Medicinal Chemistry:

G Protein-Coupled Receptors and Enzymes in Drug Discovery

Porto, Portugal
12 – 15 June, 2011

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Program and Abstracts

1-aryl-3-(4-(7-methylthieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)ureas: synthesis and molecular modelling studies using VEGFR-2

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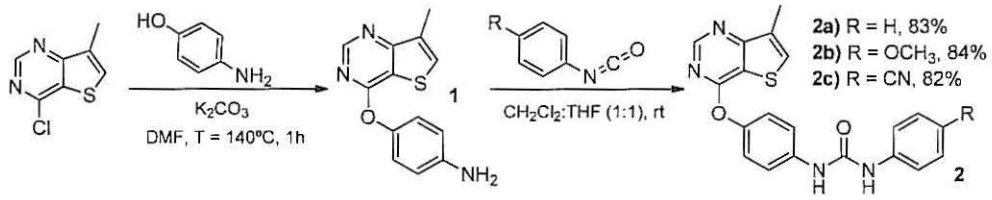
The development of anticancer drugs inhibiting angiogenesis has been an area of extensive research in the past decade. Angiogenesis is a requirement for tumor growth and metastasis and occurs through several signalling pathways. One key pathway that initiates proliferation and migration of endothelial cells is signalling through the vascular endothelial growth factor receptor-2 (VEGFR-2).[1] Therefore, small molecules that block this signalling pathway through inhibition of VEGFR-2 tyrosine kinase activity could potentially inhibit angiogenesis and tumor growth. Recently works describing thienopyrimidines[2] and thienopyridine 1,3-diarylureas[3] as VEGFR-2 inhibitors have emerged in the literature. Here we present the synthesis of new 1-aryl-3-(4-(7-methylthieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)ureas **2** in high yields by reaction of 4-[(7-methylthieno[3,2-*d*]pyridin-4-yl)oxy]aniline **1** with arylisocyanates. The former was prepared by regioselective nucleophilic substitution of 4-chloro-7-methylthieno[3,2-*d*]pyrimidine with 4-aminophenol (Scheme).



Scheme

Compounds **2** were evaluated as potential VEGFR-2 tyrosine kinase inhibitors using AutoDock Vina as molecular docking software. The receptor X-ray 3-D structure was obtained from the Protein Data Bank: VEGFR2 (PDB: 1YWN) and the estimated inhibition constants (Ki) of the synthesised compounds were obtained. In order to validate the molecular docking approach, the respective co-crystallized ligand (LIF) and Sorafenib, a known drug that inhibit VEGFR-2, were docked to the kinase domain. The difference between the X-ray conformation and the predicted docked conformations of both ligands as well as the difference between estimated Ki (Sorafenib: 109 nM; LIF: 7 nM) and experimental Ki (Sorafenib: 93 nM[4], LIF: 2 nM[5]) were negligible, validating the protein structures for virtual screening with the synthesised compounds.
The potential use of compounds **2** as future drugs was studied by applying the Lipinski's Rule of Five analysis and it was observed that all the compounds respected this rule. The estimated values of Ki were 109 nM for **2a**, 354 nM for **2b** and 47 nM for **2c**, showing that the presence of the nitrile group makes this compound the most promising of this series.
Moreover, the docking pose of the compounds with the best docking score was analyzed in order to understand the key interactions between the compounds and the VEGFR-2 kinase domain structure.

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Certificate

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We certify that:

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Attended the *2nd Iberic Meeting on Medicinal Chemistry — G Protein-Coupled Receptors and Enzymes in Drug Discovery* and presented a poster communication.

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