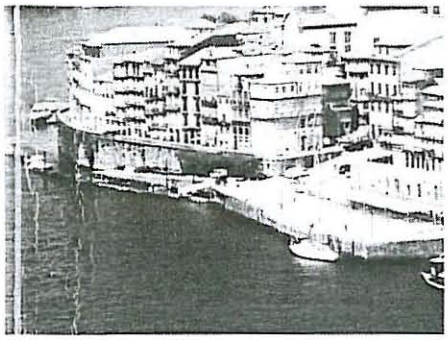

2nd Iberic Meeting on Medicinal Chemistry:

G Protein-Coupled Receptors and Enzymes in Drug Discovery

Porto, Portugal
12 – 15 June, 2011

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Program and Abstracts

Methyl 3-amino-6-[4 or 3 or 2-(3-arylureido)phenyl]thieno[3,2-b]pyridine-2-carboxylates: synthesis and molecular modelling studies using VEGFR-2

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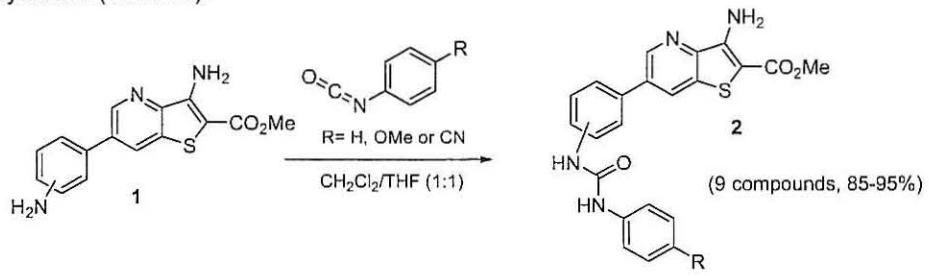
The membrane receptor tyrosine kinases (RTKs), possess both extracellular and intracellular domains and selectively catalyze the phosphorylation of tyrosine hydroxyl groups in response to binding of certain extracellular growth factors. RTK signalling pathways are normally highly regulated, yet their over-activation has been shown to promote the growth, survival, and metastasis of cancer cells, and has been associated with the progression of various human cancers. Recently some thieno[3,2-c]pyridine 1,3-diarylurea derivatives were prepared as VEGFR-2 (vascular endothelium growth factor receptor-2) inhibitors.[1] Here we present the synthesis of methyl 3-amino-6-[4 or 3 or 2-(3-arylureido)phenyl]thieno[3,2-*b*]pyridine-2-carboxylates **2** by reaction of the methyl 3-amino-6-(4 or 3 or 2-aminophenyl)thieno[3,2-*b*]pyridine-2-carboxylates **1**, synthesized earlier by our group,[2] with arylisocyanates (Scheme).



Scheme

Compounds **2** were evaluated as potential VEGFR-2 inhibitors using AutoDock Vina as molecular docking software. The enzyme 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 VEGFR2, 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[3], LIF: 2 nM[4]) were negligible, validating the protein structures for virtual screening with the synthesised compounds. The potential use of the compounds as future drugs was studied by applying the Lipinski's Rule of Five analysis and it was observed that all compounds respected this rule.Comparing the three compounds of the three different substituted positions, the best results for Ki were observed for the compounds **2** with R = H when the amino group was in the 2 or 3-position in compounds **1** (214 and 180 nM, respectively) while when the amino group was in the 4-position of compounds **1** the best compound **2** was the one with R = OMe (253 nM).
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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References

[1] Heyman, H.R. et al. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1246-1249. [2] Queiroz, M.-J.R.P.; Calhelha, R.C.; Vale-Silva, L.A.; Pinto E.; Lima R.T.;Vasconcelos, M.H. *Eur. J. Med. Chem.* **2010**, *45*, 5628-5634. [3] Fabian, MA; Biggs, WH; Treiber, DK; Atteridge, CE; Azimioara et al. *Nat. Biotechnol.* **2005**, *23*, 329-336. [4] Miyazaki, Y; Tang, J; Maeda, Y; Nakano, M; Wang, L et al. *Bioorg. Med. Chem. Lett.* **2007**,*17*,1773-1778.








Certificate

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