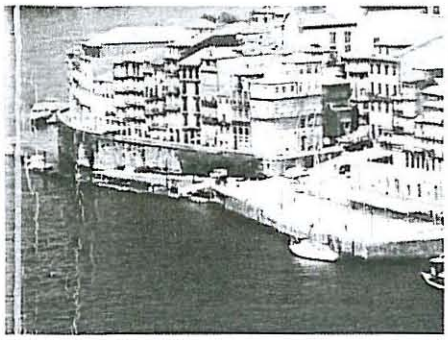


2nd Iberic Meeting on Medicinal Chemistry:

G Protein-Coupled Receptors and Enzymes in Drug Discovery

Porto, Portugal
12 – 15 June, 2011

http://2immc.fc.up.pt

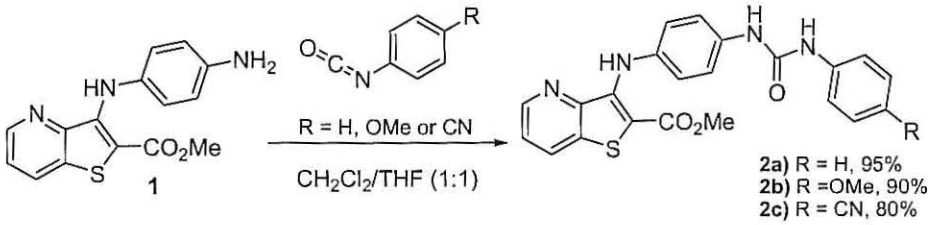
Program and Abstracts

Methyl 3-[4-(3-arylureido)phenylamino]thieno[3,2-*b*]pyridine-2-carboxylates as potential inhibitors of VEGFR-2: synthesis and molecular modelling studies

Daniela Peixoto,[a] Ricardo C. Calhelha,[a,b] Sofia Dias,[a] Hugo Froufe.[b] Rui M.V. Abreu, [b] Isabel C.F.R. Ferreira,[b] Maria-João R.P. Queiroz[a]

[a]*Centro de Química, Universidade do Minho, Campus de Gualtar 4710-057 Braga*
[b]*CIMO-ESA, Instituto Politécnico de Bragança, Campus de Santa Apolónia, 1172, 5301-855 Bragança*
e-mail:mjrpq@quimica.uminho.pt

When overexpressed or mutated, protein tyrosine kinases become potent oncoproteins that cause deregulated cell growth angiogenesis and metastasis. Because of these characteristics, they are targets for small molecule inhibitors in the treatment of cancer. 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-[4-(3-arylureido)phenylamino]thieno[3,2-*b*]pyridine-2-carboxylates **2** in excellent yields, by reaction of the methyl 3-(4-aminophenylamino)thieno[3,2-*b*]pyridine-2-carboxylate **1**, prepared also by us, with different arylisocyanates (Scheme).



Scheme

In this study we used AutoDock Vina to perform molecular docking in order to evaluate the capacity of compounds **2** to inhibit VEGFR-2, a protein related to tumour angiogenesis. The protein tyrosine kinase domain X-ray 3-D structure was obtained from the Protein Data Bank (PDB: 1YWN) and the estimated inhibition constants (Ki) of the compounds were obtained. In order to validate the molecular docking approach, the respective co-crystallized ligand (LIF) and Sorafenib, a known drug that inhibits 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^2,LIF: 2 nM^3) were negligible, validating the protein structure for virtual screening with the synthesised compounds. An initial drug-like analysis was performed by calculating several property parameters of the compounds and it was observed that all compounds **2** obey the Lipinski's Rule of Five. In this series compound **2c** is the most promising one presenting an estimated Ki value of 214 nM against 5276 nM for **2a** and 497nM for **2b**. The presence of the nitrile group lowers significantly the Ki value in this series.
Furthermore, the docking pose of the compound with the best docking score was analyzed in order to understand the key interactions between the compounds and the VEGFR-2 kinase domain structure.

Acknowledgments: FCT (Portugal) and COMPETE/QREN/EU for financial support through research project PTDC/QUI-QUI/111060/2009. RC Calhelha thanks to FCT, POPH-QREN and FSE for his grant (SFRH/BPD/68344/2010.

References

[1] Heyman, HR et al. *Bioorganic and Medicinal Chemistry Letters* **2007**, *17*, 1246-1249.
[2]Fabian, MA; Biggs, WH; Treiber, DK; Atteridge, CE; Azimioara et al. *Nature Biotechnology* **2005**, *23*, 329-336.
[3] Miyazaki, Y; Tang, J; Maeda, Y; Nakano, M; Wang, L et al. *Bioorganic and Medicinal Chemistry Letters*, **2007**,*17*,1773-1778.








Certificate

2nd Iberic Meeting on Medicinal Chemistry

G Protein-Coupled Receptors and Enzymes in Drug Discovery

12 to 15 June 2011 Porto, Portugal

We certify that:

Isabel Ferreira

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

The Organizing Committee