

2nd Iberic Meeting on Medicinal Chemistry:

G Protein-Coupled Receptors and
Enzymes in Drug Discovery

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Program and Abstracts

1-Aryl-3-[4-(thieno[3,2-d]pyrimidin-4-yloxy)phenyl]ureas as potential inhibitors of VEGFR-2: synthesis and molecular modelling studies

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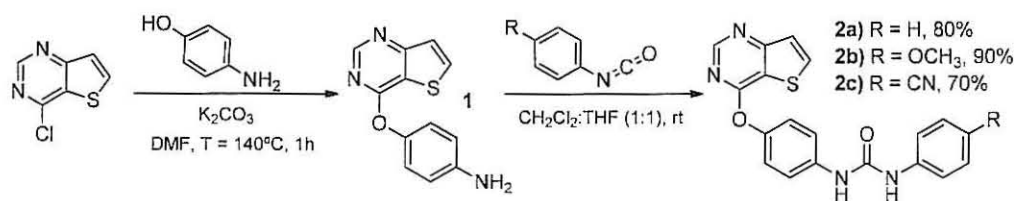
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Angiogenesis is a requirement for tumor growth and metastasis and occurs through several signalling pathways. One key pathway that initiates proliferation and migration of endothelial cells is signalling through the vascular endothelial growth factor receptor-2 (VEGFR-2).¹ Therefore, small molecules that block this signalling pathway through inhibition of the VEGFR tyrosine kinase activity could potentially inhibit angiogenesis and tumour growth. Recently works describing thienopyrimidines² and thienopyridine ureas³ as inhibitors of VEGFR-2 have appeared in the literature. Here we present the synthesis of new 1,3-diarylureas **2** starting by regioselective nucleophilic substitution of the 4-chlorothieno[3,2-d]pyrimidine with 4-aminophenol to obtain 4-(thieno[3,2-d]pyridin-4-yloxy)aniline **1** which reacts with different arylisocyanates (Scheme).



Scheme

The synthesized 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 (K_i) 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 K_i (Sorafenib: 109 nM; LIF: 7 nM) and experimental K_i (Sorafenib: 93 nM⁴, LIF: 2 nM⁵) were negligible, validating the protein structures for virtual screening with the synthesised compounds. Their potential use as future drugs was studied by applying the Lipinski's Rule of Five analysis and it was observed that all compounds respected this rule. The estimated values of K_i were 180 nM for **2a**, 214 nM for **2b** and 66 nM for **2c**, showing that the presence of the nitrile group significantly lowers the K_i value when compared to the methoxy group of **2b**. In this series compound **2c** is the most promising one. 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.

Acknowledgments: FCT (Portugal) and COMPETE/QREN/EU for financial support through research project PTDC/QUI-QUI/111060/2009.

References

- [1]Giaccone, G; Rodriguez, JA. *Nature Clinical Practice Oncology*, **2005**, *2*, 554-561.
- [2]Munchhof, MJ et al. *Bioorganic and Medicinal Chemistry Letters*, **2004**, *14*, 21-24.
- [3] Heyman, HR et al. *Bioorganic and Medicinal Chemistry Letters*, **2007**, *17*, 1246-1249.
- [4]Fabian, MA; Biggs, WH; Treiber, DK; Atteridge, CE; Azimioara et al. *Nature Biotechnology*, **2005**, *23*, 329-336.
- [5] Miyazaki, Y; Tang, J; Maeda, Y; Nakano, M; Wang, L et al. *Bioorganic and Medicinal Chemistry Letters*, **2007**, *17*, 1773-1778.

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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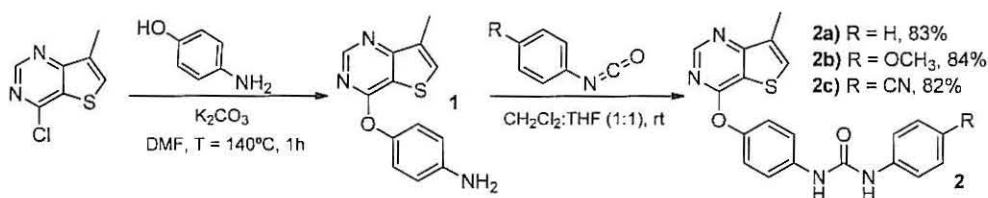
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The development of anticancer drugs inhibiting angiogenesis has been an area of extensive research in the past decade. Angiogenesis is a requirement for tumor growth and metastasis and occurs through several signalling pathways. One key pathway that 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 thienopyrimidines² and thienopyridine 1,3-diaryureas³ 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 (K_i) 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 K_i (Sorafenib: 109 nM; LIF: 7 nM) and experimental K_i (Sorafenib: 93 nM⁴, LIF: 2 nM⁵) 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 K_i 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.

Acknowledgments: FCT (Portugal) and COMPETE/QREN/EU for financial support through research project PTDC/QUI-QUI/111060/2009.

References

- [1]Giaccone, G; Rodriguez, JA. *Nature Clinical Practice Oncology*, **2005**, *2*, 554-561.
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Certificate

2nd Iberic Meeting on Medicinal Chemistry

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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.

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