www.chemmedchem.org

CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY

EFMC | ISMC 2012

XXIInd International Symposium on Medicinal Chemistry

Berlin, Germany September 2-6, 2012

ISMC 2012 Book of Abstracts

A Journal of

ChemPubSoc Europe

WILEY-VCH

References

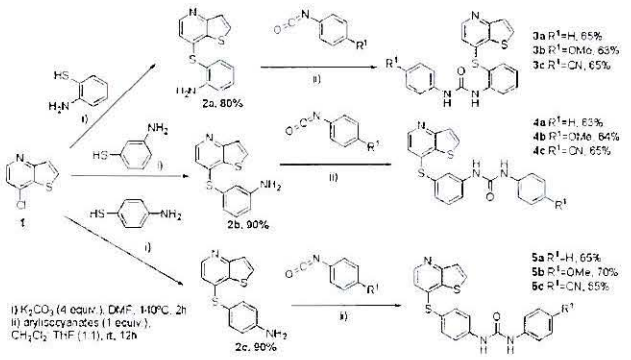
[1] M.-J. R. P. Queiroz, R. C. Calhelha, L. A. Vale-Silva, E. Pinto, R. T. Lima, M. H. Vasconcelos, *Eur. J. Med. Chem.* **2010**, *45*, 5628–5634.
[2] M.-J. R. P. Queiroz, R. C. Calhelha, L. A. Vale-Silva, E. Pinto, G. Almeida, M. H. Vasconcelos, *Eur. J. Med. Chem.* **2011**, *46*, 236–240.
[3] R. M. V. Abreu, I. C. F. R. Ferreira, R. C. Calhelha, R. T. Lima, M. H. Vasconcelos, F. Adega, R. Chaves, M.-J. R. P. Queiroz, *Eur. J. Med. Chem.* **2011**, *46*, 5800–5806.
[4] H. R. Heyman, et al., *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1246–1249.

P023

Synthesis of Novel 1-Aryl-3-[2-,3- or 4-(thieno[3,2-*b*]pyridin-7-ylthio)phenyl]ureas and Evaluation as VEGFR2 Tyrosine Kinase Inhibitors

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

[a] Centro de Química, Universidade do Minho, Campus de Gualtar 4710-057 Braga, Portugal
[b] CIMO/ESA, Inst. Politécnico de Bragança Campus de Santa Apolónia, Apt 1172, 5301-855 Bragança, Portugal



Vascular endothelial growth factor receptor 2 (VEGFR2) tyrosine kinase is involved in cancer and in angiogenesis.[1] Herein, we report the synthesis of novel 1-aryl-3-[2-, 3- or 4-(thieno[3,2-*b*]pyridin-7-ylthio) phenyl]ureas as VEGFR2 inhibitors by promoting the regioselective attack of the thiol group of the 4-aminothiophenol in the chlorine nucleophilic displacement on 7-chlorothieno[3,2-*b*]pyridine **1**, obtaining the aminated compounds **2a–c**. These were reacted with arylisocyanates to give the corresponding 1,3-diarylureas **3a–c**, **4a–c** and **5a–c** (see scheme).

1-Aryl-3-[3-(thieno[3,2-*b*]pyridin-7-ylthio)phenyl]ureas **4a–c** with the arylurea in the *meta* position relative to the thioether showed the lowest IC_{50} values (0.4–0.9 μM) in enzymatic assays using VEGFR2 tyrosine kinase domain, and the binding mode for these compounds was predicted by docking simulations.

Acknowledgements: The Foundation for Science and Technology (FCT–Portugal) is acknowledged for financial support through the NMR Portuguese network (Bruker 400 Avance III-Univ Minho). The FCT and FEDER (European Fund for Regional Development)-COMPETE/QREN/EU are acknowledged for financial support through the research unities PEst-C/QUI/UI686/2011 and PEst-OE/AGR/UI0690/2011, the research project PTDC/QUI- QUI/111060/2009 and the postdoctoral grant to R.C.C. (SFRH/BPD/68344/2010).

References

[1] G. Giamas, Y. L. Man, H. Hirner, J. Bischof, K. Kramer, K. Khan, S. S. L. Ahmed, et al., *Cell. Signalling* **2010**, *22*, 984–1002.

P024

In Silico Design of Neuroplasticity Modulators

Josep Prous, Marceli Carbo, Antoni Valencia

Prous Institute for Biomedical Research, Rambla Catalunya 135, 08008 Barcelona, Spain

Neuroplasticity, defined as the changing of the structure, function, and organization of neurons, has emerged as an interesting target for the development of new and effective treatments for multiple neurodegenerative diseases.

In this study, we have applied our proprietary computational platform, Symmetry®, to assess more than 30 molecular and cellular targets involved in neuroplasticity and start designing potential small-molecule modulators.

This chemoinformatics technology is applied on top of large amounts of factual data and is able to characterize multiple molecular mechanisms of action and other important pharmacological endpoints. The system enables the generation of focused libraries covering a wide range of chemical diversity patterns around specific conditions, mechanisms of action or selected chemical scaffolds.

The screening of generated virtual compounds has demonstrated a strong correlation between predicted and real mechanisms of action, along with a convenient ADMET profile.

The corresponding synthesis and experimental validation has led to a series of small-molecule BDNF modulators which have been selected for further pharmacological evaluation.