3º Encontro Nacional de Química Terapêutica

3rd Portuguese Meeting on Medicinal Chemistry
1st Portuguese-Spanish-Brazilian Meeting on Medicinal Chemistry.

Sociedade Portuguesa de Química

universidade de aveiro

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Supported by The Portuguese Society of Chemistry and the University of Aveiro

Scientific program

Wednesday, November 28th

09:00-10:50	Registration
10:50-11:15	Opening ceremony
	Chairperson Artur Silva
11:15-12:00	PL1 – Gerhard Ecker Department of Medicinal Chemistry, University of Vienna *The medicinal chemistry of drug transport – knowledge driven ligand design*
12:00-12:30	IL1 – Maria M. M. Santos Research Institute for Medicines and Pharmaceutical Sciences (iMed.UL), Faculty of Pharmacy, University of Lisbon *Design of novel compounds to modulate apoptosis*
12:30-13:00	IL2 – Ana Peixoto Gomes Department of Chemistry & QOPNA, University of Aveiro *Synthesis of biologically active porphyrin derivatives in photodynamic Therapy*
13:00-14:30	Lunch
	Chairperson Sérgio Simões
14:30-15:15	PL2 – Mathias Montenarh Medical Faculty, University of Saarland *Protein kinase CK2 as a pharmacological target in different cellular processes*
15:15-15:45	IL3 – José Alberto Martins Department of Chemistry, University of Minho *Gold nanoparticles functionalised with Gd^{3+} chelates as contrast agents for magnetic resonance imaging: fool's gold?*
15:45-17:00	Posters discussion and coffee break
	Chairperson Luísa Sá e Melo
17:00-17:15	OC1 – Patrícia M. R. Pereira Department of Chemistry, University of Aveiro *Albumin and monoclonal antibody conjugated porphyrin: synthesis, characterization and biological potential against human bladder cancer cell line*
17:15-17:30	OC2 – Gonçalo N. Costa Luzitin, SA, Edifício Blupharma, São Martinho do Bispo, Coimbra *Synthesis of stable meso-aryl bacteriochlorin photosensitisers: 3rd generation compounds for photodynamic therapy*

17:30-17:45 OC3 – Paula Gomes

Centro de Investigação em Química da Universidade do Porto, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto
Old drugs with new faces: boosting the antiparasitic activity of "antimalarial classics"

17:45-18:00 OC4 – M. Manuel Cruz Silva

CNC-Centre for Neuroscience and cell Biology and Faculdade de Farmácia, Universidade de Coimbra
Cytotoxic oxysterols: combining chemical and enzymatic approaches to obtain new derivatives with improved activity

18:00-18:15 OC5 – Ana Sofia Leal

Grupo de Química Farmacêutica, Faculdade de Farmácia da Universidade de Coimbra, Pólo das Ciências da Saúde, Coimbra, Portugal and Centro de Neurociências e Biologia Celular, Universidade de Coimbra, Coimbra, Portugal and Department of Medicine, Mount Sinai School of Medicine, New York, NY USA
Novel ursolic acid derivatives with potent anticancer activity

18:15-18:30 OC6 – Inês Martins

Centro de Química Estrutural, Instituto Superior Técnico, UTL, Lisboa, Portugal and Faculdade de Ciências e Tecnologia, UNL, Lisboa
New co-crystal forms and molecular salts of azelaic acid and nalidixic acid with potential medicinal application

19:00 Welcome reception

Thursday, November 29th

Chairperson Hans Peter Wessel

09:00-09:45 PL3 – Torsten Hoffmann

F. Hoffmann-La Roche Ltd, Pharma Research & Early Development (pRED), Basel, Switzerland
Future role of medicinal chemistry and its maturation to chemical biology

09:45-10:15 IL4 – Claus Jacob

Bioorganic Chemistry, School of Pharmacy, Saarland State University, Saarbruecken, GERMANY
Redox signaling via the cellular thiolstat – the special relationship in group 16

10:15-10:45 IL5 – Gonçalo Bernardes

Institute of Pharmaceutical Sciences, (ETH), Zürich, Switzerland
Traceless antibody-drug conjugates for cancer therapy

10:45-11:15 Coffee break

Chairperson Fernanda Proença

11:15-11:30 OC7 – Vasco Cachatra

Universidade de Lisboa, Faculdade de Ciências, Departamento de Química e Bioquímica/Centro de Química e Bioquímica, Carbohydrate Chemistry Group, Lisboa, Portugal
Synthetic studies on miharamycins sugar moiety and analogues

11:30-11:45	OC8 – Raquel G. Soengas
	Department of Chemistry & QOPNA, University of Aveiro, Portugal *Novel domino reaction of iodo glycosides: formal synthesis of aminocyclopentitols*
11:45-12:00	OC9 – Daniela Ribeiro
	REQUIMTE, Department of Chemical Sciences, Faculty of Pharmacy, University of Oporto, Oporto, Portugal *Flavonoids and inflammation: a structure-activity relationship study*
12:00-12:15	OC10 – Maria do Carmo Barreto
	CIRN/DCTD, Universidade dos Açores, Ponta Delgada, Portugal *Synthesis, biological evaluation and docking studies of oxygen heterocyclic compounds as acetylcholinesterase inhibitors*
12:15-14:00	Lunch

Chairperson William Heggie

14:00-14:45	PL4 – Rob Leurs
	Amsterdam Institute of Molecules, Medicines and Systems, Division of Medicinal Chemistry, VU, University of Amsterdam *Parasite-specific cyclic nucleotide phosphodiesterase inhibitors to target Trypanosoma brucei*
14:45-15:15	IL6 – João Nuno Moreira
	Faculty of Pharmacy and Center for Neurosciences and Cell Biology (CNC), University of Coimbra *Tumor targeting with nanoparticles: making novel therapeutics from "old" drugs*
15:15-15:30	OC11 – Francisco Peixoto
	Department of Chemistry and CQ-VR, UTAD, Vila Real, Portugal *Toxicological evaluation of new tacrine analogues from 4-amino-1H-pyrrole-3-carbonitrile*
15:30-15:45	OC12 – Daniel J. V. A. Dos Santos
	Research Institute for Medicines and Pharmaceutical Sciences (iMed.UL), Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal *A unified view on P-glycoprotein efflux: blending experimental, pharmaphore, molecular dynamics and molecular docking results*
15:45-17:00	Posters discussion and coffee break

Chairperson Madalena Pinto

17:00-17:15	OC13 – Maria João R. P. Queiroz
	Centro de Química, Univ. do Minho, Braga, Portugal *Synthesis, docking, enzymatic and celular assays of thieno[3,2-b]pyridine-thioether-1,3-diarylureas as VEGFR2 inhibitors*
17:15-17:30	OC14 – Tiago Rodrigues
	Swiss Federal Institute of Technology (ETH Zürich), Institute of Pharmaceutical Sciences, Zürich, Switzerland *Ligand-based de novo design of kinase lead structure candidates*

17:30-17:45	OC15 – Susana D. Lucas
	Research Institute for Medicines and Pharmaceutical Sciences (iMed.UL), Faculty of Pharmacy, University of Lisbon, Lisboa, Portugal *In silico approach toward lead generation for COPD drug discovery*
17:45-18:00	OC16 – M. Manuel B. Marques
	REQUIMTE - Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Portugal *Unveiling the role of a peptidoglycan involved in cellular recognition*
18:00-18:15	OC17 – Mariana Leão
	REQUIMTE, Department of Biological Sciences, Laboratory of Microbiology, Faculty of Pharmacy, University of Porto, Porto, Portugal *A new small-molecule inhibitor of p53-MDM2 interaction discovered using a yeast cell-based screening assay*
18:15-18:30	OC18 – Ana Isabel Tomaz
	Centro de Ciências Moleculares e Materiais, DQB, Faculty of Sciences, Lisbon University, Lisbon, Portugal *Promising organometallic ruthenium metallodrugs: [RuII(η5-Cp)(bpy)(PPh$_3$)]$^+$ a large spectrum antitumor agent*
18:40- …	Meeting of the Medicinal Chemistry Group (SPQ)
19:30- …	Congress dinner

Friday, November 30th

1st Portuguese-Spanish-Brazilian Meeting on Medicinal Chemistry

Chairperson Artur Silva

09:00-09:35	PL1-PSB – Carlos Montanari
	Institute of Chemistry of São Carlos, University of São Paulo, Brazil *"On the integration of in silico and in vitro assays for new trypanocidal agents discovery"*
09:35-10:10	PL2-PSB – Antoni Torrens
	President of the Spanish Society of Medicinal Chemistry (SEQT); ESTEVE, R & D, Barcelona, Spain *Discovery of new and selective 5-HT$_7$ agonists for the treatment of pain*
10:10-11:30	Posters discussion and coffee break

Chairperson Fernanda Proença

11:30-12:05	PL3-PSB – João Rocha
	CICECO, Department of Chemistry, University of Aveiro *Materials for medicinal chemistry: some case studies*

12:05-12:40	PL4-PSB – Andrei Leitão
	Institute of Chemistry of São Carlos, University of São Paulo, Brazil *Cell-based assays and cheminformatics approaches of novel anticancer compounds*
12:40-14:30	Lunch

Chairperson Rui Moreira

14:30-14:40	Rui Moreira
	Faculty of Pharmacy, University of Lisbon, Portugal *International symposium on medicinal chemistry, Lisbon, 2014*
14:40-15:15	PL5-PSB – Madalena Pinto
	Faculty of Pharmacy, University of Porto *Chiral derivatives of xanthones: bioactive small molecules and analytic tools*
15:15-15:50	PL6-PSB – María José Camarasa
	Instituto de Química Médica (CSIC), Madrid, Spain *A prodrug approach based on the DPPIV/CD-26 enzyme*
15:50-16:10	Closing ceremony

Synthesis, docking, enzymatic and cellular assays of thieno[3,2-*b*]pyridine-thioether-1,3-diarylureas as VEGFR2 inhibitors

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

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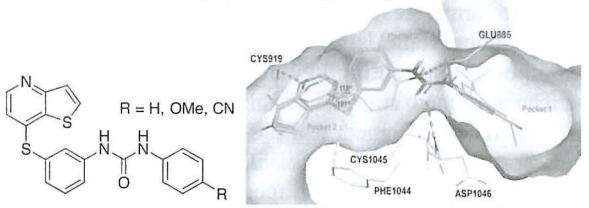
Vascular endothelial growth factor receptor 2 (VEGFR2) is a class of tyrosine kinase receptors, expressed primarily in endothelial cells, and is activated by the specific binding of VEGF to the VEGFR2 extracellular regulatory domain, undergoing autophosphorylation, triggering signaling pathways leading to endothelial cell proliferation and subsequent angiogenesis.[1] Small molecules may act as inhibitors by competing for the ATP-binding site of the VEGFR2 intracellular tyrosine kinase domain, thereby preventing the intracellular signaling that leads to angiogenesis.[2] Herein, we report the synthesis of novel nine 1-aryl-3-[2-, 3- or 4-(thieno[3,2-*b*]pyridin-7-ylthio)phenyl]ureas as VEGFR2 inhibitors. The compounds presented below, with the arylurea in the meta position to the thioether, showed the lowest IC_{50} values (0.4-0.9 μM) in enzymatic assays. Using molecular docking (A) and molecular dynamics simulations, a convincing rationalization was achieved to explain the highest potency of these compounds.



(A) Docking pose superimposition at the VEGFR2 kinase binding site for the 3 compounds and Sorafenib (a known inhibitor).

(B) Proliferation of HUVECs with VEGF supplementation

To examine the activity of the three compounds in endothelial cells, HUVECs were cultured in M199 medium (supplemented with 2% FBS and 60 ng/mL of VEGF) in the absence or presence of each compound at different concentrations. A remarkable reduction in the proliferation of HUVECs was observed for the compound with R=OMe at 0.5 μM or higher, evaluated by the incorporation of BrdU in cell culture. For compounds with R=H or R=CN, a decrease in cell growth was only observed at 1 μM or higher concentrations. These findings indicate that the methoxylated compound is the most promising. Further studies are ongoing to examine whether these molecules affect the expression and activity of VEGFR2.

Acknowledgments: To FCT–Portugal for financial support through the PTNMR network. To FCT and COMPETE/QREN/EU for financial support through the research unities PEst-C/QUI/UI686/2011, PEst-OE/AGR/UI0690/2011, PEst-OE/SAU/UI0038/2011, the research project PTDC/QUI-QUI/111060/2009 and the post-Doctoral grant attributed to R.C.C. (SFRH/BPD/68344/2010) also financed by POPH and FSE.

References

[1] Strawn, L.M. *et al. Cancer Res.* **1996**, *56*, 3540-3545.

[2] Baka, S.; Clamp, A.R.; Jayson, G.C. *Expert Opin. Ther. Targets* **2006**, *10*, 867-876.

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1-Aryl-3-[4-(thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl]ureas as VEGFR2 inhibitors: synthesis, docking enzymatic and cellular assays

Daniela Peixoto,[a] Ricardo C. Calhelha,[a,b] Pedro Soares,[a,c] Rui M.V. Abreu,[b] Hugo Froufe,[b] Isabel C. F. R. Ferreira,[b] Raquel Costa,[d] Raquel Soares,[d] Maria João R. P. Queiroz[a]

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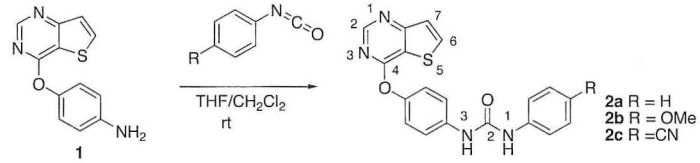
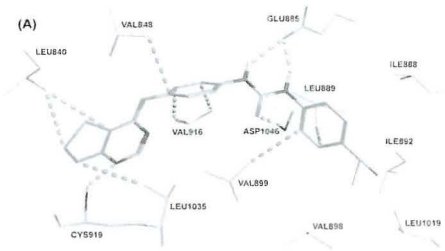
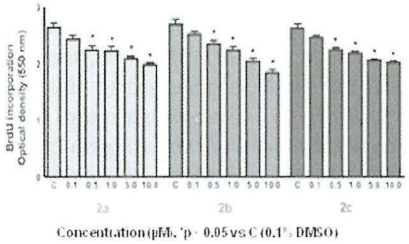
A number of thienopyrimidines derivatives have shown potent VEGFR2 (Vascular Endothelium Growth Factor Receptor2) tyrosine kinase inhibition activity.[1] VEGF is a surrogate marker of angiogenesis that activates VEGFR2 in endothelial cells.

Here we present the synthesis of new 1-aryl-3-[4-(thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl]ureas from the aminodi(hetero)arylether **1**, also prepared by us, which was reacted with arylisocyanates to give the corresponding 1,3-diarylureas **2a-c**.





(C) Superimposition of the docking poses at the VEGFR2 kinase domain for compounds **2a-c**.



(B) Proliferation of HUVECs with VEGF supplementat.

Compounds **2a-c** were evaluated for inhibition of VEGFR2 tyrosine kinase activity using enzymatic assays and showed good inhibition ability. The rational for the inhibition is discussed using docking (A). To examine the activity of compounds **2a-c** in endothelial cells, HUVECs were cultured in M199 medium (supplemented with 2% FBS and 60 ng/mL of VEGF) in the absence (control) or presence of each compound at different concentrations. A reduction above 0.5 μM in the proliferation of HUVECs was observed, evaluated by the incorporation of BrdU in cell culture. These molecules are promising anti-angiogenic agents that may be used for therapeutic purposes.

Acknowledgments: To the FCT–Portugal for financial support through the PTNMR network. To FCT and COMPETE/QREN/EU for financial support through the research unities PEst-C/QUI/UI686/2011, PEst-OE/AGR/UI0690/2011, PEst-OE/SAU/UI0038/2011, the research project PTDC/QUI-QUI/111060/2009 and the post-Doctoral grant attributed to R.C.C. (SFRH/BPD/68344/2010) also financed by POPH and FSE.

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[1] Dai, Y. *et al. J. Med.Chem.* **2005**, *48*, 6066–6083.