Third WG Meeting CA15135

BOOK OF THE ABSTRACTS

COST ACTION CA15135

Activities of young investigators within the WG

MuTaLig COST Action

Faculté de Pharmacie de Paris, Université Paris DESCARTES,
February 23-24 2019

www.mutalig.eu

INTRODUCTION

The MuTaLig COST Action concludes the cycle of meetings of the third year with a special event dedicated to the activities of young investigators working in all parties. The third WG meeting was diffused to the full list of participants, increased up to more than 600 units. As planned in the Memoradum of Understanding document three annual meetings (Lugano, Porto, La Valletta), three training schools (Vienna, Siena and Hamburg) and three WG meetings (Budapest, Tenerife and Paris) were organized in the first three grant years. More STSM programs have been supported as well as additional European connections have been potentiated. Novel dissemination activities were activated too.

The WG meeting in Paris is the appropriate occasion to focus mainly on the status of the work done by young investigators, in order to properly fulfill all issues of the COST Action basing on the second progress report. Along with 18 selected oral communications of ECI, belonging to research institutions located in different places of the MuTaLig network, according to the gender balance, 2 relevant local experts present plenary lectures and some MC members give their stimuli too. Moreover, 40 poster communications from all four WGs complete the scientific program. A final round table and the CORE meeting conclude the two intense days of the third WG meeting.

As Chair of this COST Action, I want to express my gratitude especially to the local organizer and LOS (Prof. Luc Demange, MC member for France) for his enthusiastic work, to his local team, to the Grant Holder from University of Porto (Prof. Fernanda Borges and Dr. Joana Maria Neves Moreira Abrantes) and to the COST Association (Dr. Lucia Forzi, Science Officer and Dr. Svetlana Voinova, Administrative Officer) for their efforts in the meeting organization. A special thank is also due to the young investigator Dr. Antonio Lupia (Università “Magna Græcia” di Catanzaro, Italy) for the support in the organization of this abstract book.

I wish a fruitful and stimulating WG meeting to all participants!

Stefano Alcaro
Università “Magna Græcia” di Catanzaro (Italy)
Chair of CA15135 COST Action
alcaro@unicz.it

PROGRAM

Friday February 22nd 2019

MuTaLig Session at the Young Research Fellows Meeting, French Medicinal Chemistry Society
Moderator: Luc DEMANGE (MC member FR – LOS) - Université Paris DESCARTES (France)

15:00 - 17.30 Information at the web site www.sct-asso.fr/yrfm.html

Saturday February 23rd 2019

8.30 Registration

9.00 **Introduction to the MuTaLig COST Action 3nd WG meeting**
Stefano ALCARO (CA15135 Chair) - Università "Magna Græcia" di Catanzaro (Italy)
Luc DEMANGE (MC member for France and local organizer) - Université Paris DESCARTES (France)

Session I "Drug repositioning and kinase opportunities"
Moderator: David MAGRI (MC member MT) - University of Malta (Malta)

9.30 PL1 **Repositioning approach to fish new multitarget bioactive molecules: Application to the development of analogues to bisacodyl.**
Maité SYLLA - Conservatoire national des arts et métiers, Paris (France)

10.00 PL2 **Towards selective Kinase Inhibitors. Elucidation of their Molecular Mechanism of Action**
Hervé GALONS (Editor in Chief of Eur J Med Chem) - Université Paris DESCARTES (France)

10.30 *Coffee break and Poster session*

Session II "Selected WG1 and WG2 young investigators in anticancer field"
Moderator: Gilles HANQUET (MC member FR) - Université de Strasbourg (France)

11:00 OC1 **Synthesis and Antagonist Study of CXCR1 and CXCR2 Receptors for Oncology Applications**
Lou MATEO - Université côte d'Azur, Nice (France)

11.20 OC2 **A branching inhibitor in plants as a new antiangiogenic and antitumoral drug candidate**
Paloma CARRILLO - University of Malaga (Spain)

Session II "Selected WG1 young investigators in CNS field"
Moderator: Hoger STARK (MC member DE) - Heinrich-Heine University, Düsseldorf (Germany)

11.40 OC3 **Development of novel MTDL combining 5-HT4R agonism and antioxidant properties in Alzheimer's disease**
Caroline LANTHIER - (CERMN), Normandie Univ, UNICAEN, Caen (France)

12.00 OC4 **Development of Dual-Target Agents Based on Piperine Scaffold**
Daniel CHAVARRIA - University of Porto (Portugal)

12.20 OC5 **Studies on novel tacrine-donepezil hybrids with potent MTDL profile**
Gülşah BAYRAKTAR - Ege University, Izmir (Turkey)

12.40 OC6 **Design and development of new chemical entities for the treatment of Parkinson disease**
Francesco MESITI - Università "Magna Græcia" di Catanzaro (Italy)

13.00 OC7 **Highly Selective and Antioxidant BChE Inhibitors with Controllable Duration of Action Showing Neuroprotective Properties *in vivo***
Matthias HOFFMANN - Julius-Maximilians University, Würzburg (Germany)

13.20 *Lunch and Poster session*

Session III "Selected WG2, WG3 and WG4 young investigators"
Moderator: Emmanuel MIKROS (MC member EL) - University of Athens (Greece)

15.00 OC8 **Novel Fubinaca/Rimonabant Hybrids as Endocannabinoid System Modulators**
Azzurra STEFANUCCI - "G. d'Annunzio" University, Chieti (Italy)

15.20 OC9 **Tracking the Oxypeucedanin: from ethnobotanical studies to pharmacological target**
Elif ALANÇAY - Ege University, Izmir (Turkey)

15.40 OC10 **Targeting metabolism and apoptosis signaling in cancer cells: a structure-based virtual screening approach toward Hexokinase 2 inhibitors**
Sara N. GARCIA - Universidade de Lisboa (Portugal)

16.00 OC11 **The Mu.Ta.Lig. Chemotheca: Chemoinformatic tool for Multi-Target Drugs Identification and Compounds Repurposing**
Raffaella CATALANO - Università "Magna Græcia" di Catanzaro (Italy)

16.20 OC12 **Funnel-Metadynamics Automated Protocol (FMAP): three steps to disclose drug pharmacodynamics**
Stefano RANIOLO - Università della Svizzera italiana (USI), Lugano (Switzerland)

16.40 OC13 **The *in silico/in vitro* metabolism identification of the series promising xanthine- and tert-amylphenoxyalkyl piperidine derivatives with confirmed multi target directed activity**
Gniewomir LATACZ - Jagiellonian University Medical College, Kraków (Poland)

17.00 *Jazz free event (organized by the student's associations of the Faculty of Pharmacy)*

18.30 **Core meeting (for the MuTaLig Core group only)**

19.30 *Optional social activity (cruise & dinner)*

Sunday February 24th 2019

Session IV: "New ideas and updates from Working Groups"
Moderator: Stefano ALCARO (CA15135 Chair) - Università "Magna Græcia" di Catanzaro (Italy)

9:00 OC14 **Zn(II) complexes with pyridine-based thiazolyl-hydrazones as potent multi-targeting anticancer agents**
Nenad FILIPOVIĆ (MC substitute SR) - University of Belgrade (Serbia)

9.20 OC15 **Pyridoindole compounds with multi-target effects**
Magdaléna MÁJEKOVÁ (MC member SK) - Institute of Exp Pharm and Tox, Bratislava (Slovakia)

9.40 OC16 **Recent Progress on Naphthalimide Molecular Logic Gate Anticancer Agents**
David MAGRI (MC member MT) – University of Malta (Malta)

10.00 OC17 **Multi-Target Qualities and Ligand Pharmacology for Neurodegenerative, Cancer, and Other Inhibitors in the Chemotheca**
Alfonso T. GARCÍA-SOSA (MC member EE, communication manager) - University of Tartu (Estonia)

10.20 OC18 **Isatin-Triazole Hybrids: Lymphoma Anti-Proliferation and BuChE Inbibition**
Antony BURKE - University of Évora (Portugal)

10.40 *Coffee break*

11.15 **Round table and best poster awarding ceremony**
Moderator: Fernanda BORGES (CA15135 Vice-Chair) - University of Porto (Portugal)
Danijel KIKELJ (WG1 leader) - University of Ljubljana (Slovenia)
Eugenio GAUDIO (WG2 leader) - Oncology Research Institute, Bellinzona (Switzerland)
Sharon BRYANT (WG3 leader) - Inte:Ligand GmbH, Vienna (Austria)
Hanoch SENDEROWITZ (WG4 leader) - Bar-Ilan University, Ramat-Gan (Israel)
Alfonso T. GARCÍA-SOSA (MC member EE, communication manager) - University of Tartu (Estonia)
Maria Laura BOLOGNESI (STSM coordinator) - "Alma Mater" Università di Bologna (Italy)

12.30 **Concluding remarks**

Plenary lectures

Plenary Lecture 1

Repositioning approach to fish new multitarget bioactive molecules: application to the development of analogues to Bisacodyl

Maité Sylla Iyarreta Veitía [a]

[a] *Equipe de Chimie Moléculaire du Laboratoire de Génomique Bioinformatique et Chimie Moléculaire, GBCM, EA7528, Conservatoire national des arts et métiers (Cnam), 2 rue Conté, 75003 Paris, France.*

maite.sylla@lecnam.net

The discovery and development of new drugs is a lengthy, expensive and financially risky process. Currently, pharmaceutical companies implement new approaches from existing drugs, in order to accelerate the discovery of interesting leads with relatively low costs and decrease risks. Drug repositioning allows the development of new indications for existing drugs with identified pharmacokinetic profiles, known safety profile, already resolved manufacturing issues. [1-3]

Herein we described *in silico* repositioning, design, synthesis, biological evaluation and structure-activity relationship of an original class of anti-inflammatory agents based on a polyaromatic pharmacophore structurally related to bisacodyl (BSL) drug used in therapeutic as laxative. We describe the potential of TOMOCOMD-CARDD methods to find out new anti-inflammatory drug-like agents from a diverse series of compounds using the total and local atom based bilinear indices as molecular descriptors. The models obtained were validated by biological studies, identifying BSL as the first anti-inflammatory lead-like using in silico repurposing from commercially available drugs. Several biological *in vitro* and *in vivo* assays were performed in order to understand its mechanism of action. A set of analogues of BSL was prepared using low-cost synthetic procedures and further biologically investigated in zebrafish models. The obtained results defined these compounds as new promising anti-inflammatory agents for further preclinical development. [4] The antibacterial activity of a new series of triarylmethane analogues of BSL is also presented. Compounds were evaluated against Gram-positive and Gram-negative foodborne pathogens and the promising results showed that synthesized compounds exhibit a higher bacteriostatic activity. [5]

References

[1] Wermuth, C.G. *J. Med. Chem.*, **2004**, 47(6), 1303-1314.

[2] L.T. Friedhoff, J. Dailey, Eur. Neuropsychopharm., **2015**, 25, 1035-1038.

[3] J.W. Scannell, A. Blanckley, H. Boldon, B. Warrington, Diagnosing the decline in pharmaceutical R&D efficiency, Nat Rev Drug Discov, **2012**, 11, 191-200; C.A. Lipinski, Drug Discov. Today: Therapeutic Strategies, **2011**, 8, 57-59.

[4] M. Sylla-Iyarreta Veitía, D. Siverio-Mota, V. Lerari, M. Marín, R. M. Giner, F. Dumas, C. Ferroud, L. Vicet-Muro, Y. Rivero-Guerra, P. A. M. de Witte, A. D. Crawford, V. J. Arán and Y. Marrero-Ponce. Curr. Top. Med. Chem., **2017**, 17(25), 2866-2887,

[5] Görmen, M; Sylla Iyarreta Veitía, M; Trigui, F; El Arbi, M; Ferroud, C, *Organomet Chem.* **2015***, 794, 274-281.*

Plenary Lecture 2

Towards selective kinase inhibitors. Elucidation of their molecular mechanism of action

Galons Hervé

INSERM U1022, Paris Descartes University, 4, avenue de l'Observatoire, 75006 Paris, France

herve.galons@parisdescartes.fr

The development of precision medicine is boosting the kinase inhibitor field. Not less than 7 kinase inhibitors were approved by the FDA in 2018, adding to the 4 which reached the market in 2017. Cyclin despendent kinase (CDKs) have recently attracted interest as 3 CDK4/CDK6 inhibitors have been approved against estrogen positive breast cancer[1]. In Manros-Therapeutics, we are conducting a phase IIa clinical test with (R)-Roscovitine (CYC202, Seliciclib) in the treatment of cystic fibrosis[2].

New series of compounds were designed based on crystal structure determinations of kinase-inhibitor complexes[3]. Their molecular mechanism of action was investigated through affinity chromatography assays. The probes prepared to identify molecular targets were also useful for a better understanding of the mechanism of targeted diseases.[4] These experiments guided us in the search of new inhibitors with distinct inhibition profiles. This led to the discovery of selective compounds. In particular, following a kinome scan against 250 kinases, selective inhibitors of CDK7 were discovered. CDK7 is a promising target as this kinase controls CDK2, CDK4, CDK6 and transcription. Unexpectedly, this series of compounds exhibited anti-angiogenic activity. Several of them were found more antiangiogenic than Sunitinib.

References

[1]Sherr, C.J.; Beach, D.; Shapiro, G.I.; Targeting CDK4 and CDK6: From Discovery to Therapy. *Cancer Discovery* **2016**; *6*, 353-67.

[2]Meijer , L.; Nelson D.J.; Riazanski, V.; Gabdoulkhakova, A.G; Hery-Arnaud, G; Le Berre, R; Loaëc, N; Oumata N.; Galons, H.; Nowak, E.; Gueganton, L.; Dorothée, G.; Prochazkova, M.; Hall, B.; Kulkarni, A.B.; Gray, R.D.; Rossi, A.G.; Witko-Sarsat, V.; Norez, C.; Becq, F.; Ravel, D.; Mottier, D.; Rault. G. *J Innate Immun*. **2016**; *8*, 330-49.

[3]El Hage, K.; Piquemal J-P., Oumata, N.; Meijer, L.; Galons, H.; Gresh, N. A Simple Isomerization of the Purine Scaffold of a Kinase Inhibitor, Roscovitine, Affords a Four- to Seven-Fold Enhancement of Its Affinity for Four CDKs. Could This Be Traced Back to Conjugation-Induced Stiffenings/Loosenings of Rotational Barriers? *ACS Omega* **2017**; *2*, 3467-3474.

[4]Delehouzé, C.; Godl, K.; Loaëc, N.; Bruyère, C.; Desban, N.; Oumata, N.; Galons, H.; Roumeliotis, T.I.; Giannopoulou, E.G.; Grenet, J.; Twitchell, D.; Lahti, J.; Mouchet, N.; Galibert, M.D.; Garbis, S.D.; Meijer, L. CDK/CK1 inhibitors roscovitine and CR8 downregulate amplified MYCN in neuroblastoma cells. *Oncogene*. **2014** ;33, 5675-87.

Short communications

Short communication 1

Synthesis and Antagonist Study of CXCR1 and CXCR2 Receptors for Oncology Applications

Lou MATEO,[a] Rachid BENHIDA [a] , Luc DEMANGE,[a] Cyril RONCO,[a] Gilles PAGES,[b] Maëva DUFFIES,[b].

[a] *Institut chimie de Nice, Université côte d'Azur, 28 avenue Valrose 06100 Nice, FRANCE.*

[b] *. Institute for Research on Cancer and Aging of Nice, IRCAN UMR CNRS 728 INSERM U1081, Université Côte d'Azur, Nice, France*

lou.mateo@univ-cotedazur.fr

The current anti-angiogenic therapies fail to fully eradicate cancer cells, since the tumors always relapse after an initial period of clinical benefit. Therefore, new therapeutic approaches are urgently needed to overcome drug resistances. In this context, our project aims at developing news antagonists of CXCR1 and CXCR2 receptors, to interfere with the ERL+CXCL cytokines signaling pathway.[1] This strategy will concomitantly tackle inflammation and angiogenesis.

The rational design and the synthesis of a series of new CXCR1 and CXCR2 antagonists, structurally-related to SB-225002, a CXCR antagonist developed by GSK,[2] led us to obtained two potential hits, MCK 133 and MCK140.

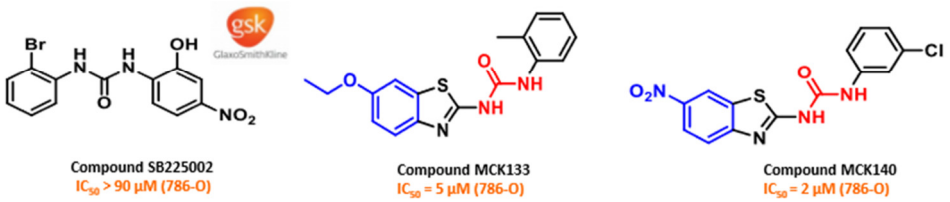


Figure 1: IC_{50} of compound SB225002 and the two potential hits MCK133 and MCK140.

These molecules exert *in vitro* cytotoxic effects against a panel of human solid tumors and hematological malignancies, but they are less toxic against healthy cells (human fibroblasts). On the other hand, the compound MCK140 reduces HUVECs motility by specifically interfering with its CXCR1/2 receptors, highlighting its antiangiogenic potential. Lastly, MCK140 reduces *in vivo* tumor growth in mice xenografted with aggressive human A-498 kidney cancer cell line by more than 30% (Figure. 2).

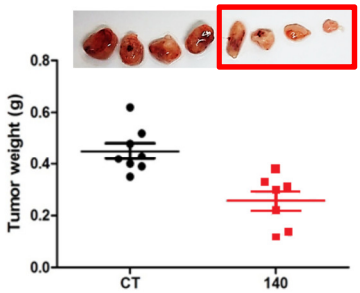


Figure 2: Evaluation of the tumor growth in presence of MCK140.

Based on these encouraging results, the main objective of my PhD is to design, develop, and synthesize new CXCR1/CXCR2 antagonists, with a special emphasis on the improvement of the aqueous solubility and the pharmacokinetics properties. In particular, chemical functions bioisosteric of the urea have been designed.

References

[1] Vandercappellen, J.; Van Damme, J.; Struyf, S. The role of CXC chemokines and their receptors in cancer. *Cancer Lett*, **2008**, *267*, 226-244.

[2] Campbell, L.M. et al. *Pharmaceuticals*, **2013**, *6*, 929-959.

Short communication 2

A Branching Inhibitor in Plants as a New Antiangiogenic and Antitumoral Drug Candidate

Paloma Carrillo[a], Beatriz Martínez-Poveda[a], Miguel Ángel Medina[a,b], Ana R. Quesada[a,b]

[a] *University of Malaga, Andalucía Tech, Department of Molecular biology and Biochemistry, Faculty of Sciences, Campus de Teatinos sn, Málaga, Spain*

[b] *U741 (CB06/07/0046) CIBER de Enfermedades Raras, Málaga, ES*

pcarrillo@uma.es

An increased formation of new blood vessels caused by a persistent and deregulated activation of angiogenesis is related to diseases such as proliferative retinopathies, psoriasis, diabetes, rheumatoid arthritis or cancer. For this reason, angiogenesis inhibition is an attractive target in cancer and other angiogenesis-dependent diseases[1]. Strigolactones, plant hormones derived from carotenoids that are involved in the inhibition of root branching and sprouting, have shown great potential in cancer prevention and therapy[2]. In this work, we have investigated the antiangiogenic and antitumoral potential of GR24, a synthetic analogue of strigolactones.

Our results show that GR24 inhibits the growth of endothelial and tumor cells *in vitro*. This strigolactone is a multitarget angiogenesis inhibitor, interfering several key steps of the angiogenic process *in vitro* such as proliferation, migration and differentiation of endothelial cells, and inhibiting the activation of the vascular endothelial growth factor receptor VEGFR2. GR24 affects the endothelial cytoskeleton organization and induces changes in the expression levels of adhesion proteins. In the *in vivo* tests, GR-24 shows a great inhibitory effect on the formation of blood vessels in the chicken chorioallantoic membrane and on *Danio rerio*, both in the formation of intersegmental vessels in embryos and in the caudal fin regeneration in adults. Taken together, these results suggest that GR-24 may be a promising new multitarget compound for the treatment of cancer and other angiogenesis-dependent diseases.

Our work is supported by grants PIE P12-CTS-1507 (Andalusian Government and FEDER) and BIO2014-56092-R (MINECO and FEDER). The “CIBER de Enfermedades Raras” is an initiative from the ISCIII (Spain).

References

[1] Quesada, A.R.; Medina, M.Á.; Muñoz-Chápuli R.; Ponce, Á.L. Do not say ever never more: the ins and outs of antiangiogenic therapies. *Curr Pharm Des*. **2010**,*16(35),* 3932-57.

[2] Mayzlish-Gati, E. *et al*. Strigolactone analogs act as new anti-cancer agents in inhibition of breast cancer in xenograft model. *Cancer Biol. Ther.* **2015**, *16,* 1682–1688.

Short communication 3

Development of novel MTDL combining 5-HT4R agonism and antioxidant properties in Alzheimer's disease.

Caroline Lanthier [ab], Cédric Lecoutey[a], Julien Lalut[a], Marc Since[a], Audrey Davis[a], Maria-Laura Bolognesi[b], Patrick Dallemagne[a], Christophe Rochais[a].

[a] *Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN), Normandie Univ, UNICAEN, 14000 Caen, France.*

[b] *Department of Pharmaceutical Sciences, University of Bologna, Via Belmeloro 6, 40126 Bologna, Italy.*

caroline.lanthier@unicaen.fr

In a world where life expectancy is increasing, Alzheimer disease (AD) is the main cause of dementia, and touch approximatively 17% of people who are more than 75 years in France. This is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline. Despite the fact that the physiopathology of AD is not entirely known at the time, some molecular causes were found such as the ß-amyloid peptides aggregation, tau-dependent neurofibrillary tangles, as well as oxidative stress and neuroinflammation. Currently, treatments available for patients are mainly acetylcholine esterase (AChE) inhibitor, which only have symptomatic benefits and do not cure AD. Then there is still a strong medical need in the AD population.

In this context, the concept of Multi-Target Directed Ligands (MTDLs) was applied to design a drug with several therapeutic targets. The envisaged MTDL (Targeted structure – fig 1) should be able in first hand, to limit the development of ß-amyloid plaques obtained by the aggregation of ß-amyloid peptides (Aß). Our compounds are designed to promote the cleavage of amyloid protein precursor (APP) by α -secretase activation in order to produce a neuroprotective and soluble peptide sAPPα. This is the role of the $5HT_4R$ agonists (blue part – fig 1.) which are already studied in the CERMN in other MTDL projects and led to the discovery of Donecopride[1]. In another hand, it appears that the oxidative stress has a central role in AD[2]. Adding antioxidant moiety such as polyphenol, lipoic and ferulic acid (red part- fig 1.) could trap free radicals or reactive oxygen species (ROS) and also have neuroprotective effect. This aspect has been widely studied in Prof. Maria-Laura Bolognesi's laboratory over the years[3]. To that end, different compounds will be designed and synthesized, with both the expertise of CERMN and Prof Maria-Laura Bolognesi, in order to evaluate their in vitro/in vivo properties regarding their agonist activity on $5\text{-}HT_4R$ and antioxidant properties. The first promising results of the chloroaniline's moiety line will be described in this poster.

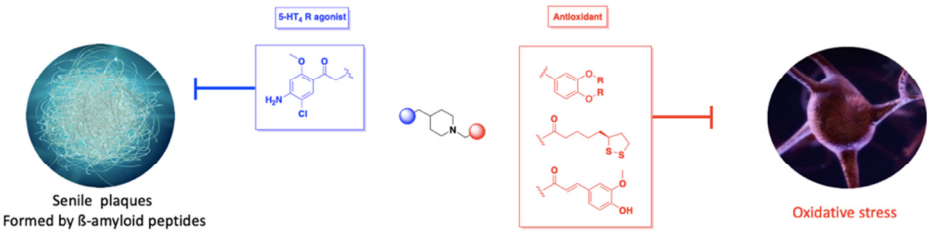


Figure 1. Targeted structure, with $5\text{-}HT_4R$ agonist moiety in blue and antioxidant moieties in red.

References

[1] Rochais, C. et al. *J. Med. Chem.*, **2015**, 58, 3172-3187.

[2] Rosini, M. et al. *J. Med. Chem.*, **2014**, 57, 2821-2831

[3] Bolognesi, M-L. et al. *J. Med. Chem.*, **2009**, 52, 7883-7886

Short communication 4

Development of Dual-Target Agents Based on Piperine Scaffold

Daniel Chavarria,[a] Carlos Fernandes, [a] Fernando Cagide,[a] Fernando Remião,[b] Paulo Jorge Oliveira[c] and Fernanda Borges[a]

[a] *CIQUP/Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, 4169-007 Porto, Portugal.*

[b] *UCIBIO-REQUIMTE, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal.*

[c] *CNC – Center for Neuroscience and Cell Biology, University of Coimbra, UC-Biotech Building, Biocant Park, Cantanhede, Portugal.*

danielfchavarria@gmail.com

Alzheimer's disease (AD) is a progressive and multi-factorial age-related disorder characterized by the loss of memory and cognitive functions[1]. Despite the unclear molecular mechanisms involved in the pathogenesis of AD, numerous targets for potential therapeutics have been identified[2]. These include, among others, the decline of cholinergic transmission and oxidative stress[1,3], as well as mitochondrial dysfunction in particular, a process that precedes the establishment of tau and amyloid beta pathologies[4] and contributes to the synaptic degeneration[5]. Given the multifactorial nature of AD, the modulation of several targets using multitarget directed ligands may enable the desired therapeutic outcome[1]. Therefore, reducing mitochondrial injury may have beneficial effects on neuronal dysfunction and cognitive decline observed in AD patients.

As part of our drug discovery program and following an AD multi-target strategy, novel piperine-based mitochondriotropic antioxidants endowed with cholinesterase inhibitory activity were designed (**Figure 1**).

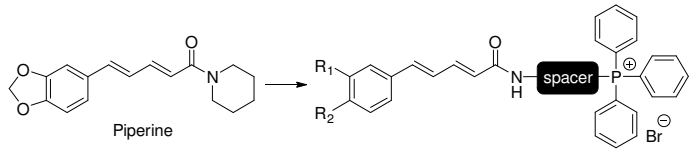


Figure 1: Chemical structure of piperine and derivatives thereof.

Lipophilic triphenylphosphonium conjugates based on piperine were successfully synthesized. The antioxidant profile was assessed using fluorometric and cell-based assays. In addition, the Ellman assay was used to evaluate the acetylcholinesterase and butyrylcholinesterase inhibitory activity and the mechanism of action of the compounds under study. The results obtained so far will be presented in this communication.

Acknowledgements: This project was supported by Foundation for Science and Technology (FCT) and FEDER/COMPETE (Grants UID/QUI/00081/2015, POCI-01-0145-FEDER-006980, and NORTE-01-0145-FEDER-000028). D. Chavarria, C. Fernandes and F. Cagide grants were also supported by FCT, FEDER/COMPETE and NORTE-2020 funds.

References:

[1] Guzior, N.; Wieckowska, A.; Panek, D.; Malawska, B. *Curr Med Chem* **2015**, *22*, 373-404.
[2] Ismaili, L.; Refouvelet, B.; Benchekroun, M.; Brogi, S.; Brindisi, M.; Gemma, S.; Campiani, G.; Filipic, S.; Agbaba, D.; Esteban, G.; Unzeta, M.; Nikolic, K.; Butini, S.; Marco-Contelles, J. *Prog Neurobiol* **2017**, *151*, 4-34.
[3] Oliveira, C.; Cagide, F.; Teixeira, J.; Amorim, R.; Sequeira, L.; Mesiti, F.; Silva, T.; Garrido, J.; Remiao, F.; Vilar, S.; Uriarte, E.; Oliveira, P. J.; Borges, F. *Front Chem* **2018**, *6*, 1-17.
[4] Yao, J.; Irwin, R. W.; Zhao, L.; Nilsen, J.; Hamilton, R. T.; Brinton, R. D. *PNAS* **2009**, *106*, 14670-14675.
[5] Cai, Q.; Tammineni, P. *J Alzheimers Dis* **2017**, *57*, 1087-1103.

Short communication 5

Studies on novel Tacrine-Donepezil hybrids with potent MTDL profile

Gülşah BAYRAKTAR,[a] Sülünay PARLAR [a], Donatella Bagetta [b], Francesco Ortuso [b], Stefano Alcaro [b], Vildan ALPTÜZÜN.[a]

[a] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ege University, IZMIR, TURKEY*

[b] *Department of Health Science, "Magna Graecia" – University of Catanzaro, Catanzaro, ITALY*

bayraktargulsah@gmail.com

gulsah.bayraktar@ege.edu.tr

Alzheimer's disease (AD), is a neurodegenerative disease characterized by various pathologic pathways. The oldest theory regarding AD pathophysiology is the cholinergic hypothesis, relies on decreased Ach levels at the synaptic cleft. Apart from this, there are several other pathways in the pathology of AD including formation and accumulation of toxic amyloid-β (Aβ) plaques, neurofibrillary tangles (NFT), oxidative stress, metal ion dyshomeostasis, inflammation, etc [1,2].

Tacrine, donepezil, rivastigmine, and galantamine are AChE inhibitors approved by FDA for the symptomatic treatment of AD. Considering the complex pathology of the disease, it is essential to target more than one pathological pathway with one molecule to obtain disease modifying effect [2,3].

In our previous study, benzylpiperidine moiety of donepezil and tacrine were selected as core structures and merged with hydrazone functional group to aim dual inhibition of AChE as well as inhibition of Aβ aggregation and metal complex formation properties. Considering all these data, newly synthesized hybrids showed a promising MTDL profile against AD. As lead-like structures should possess drugability properties in order to attain a certain degree of therapeutic efficacy and avoid poor pharmacokinetics, low bioavailability, high toxicity, etc., ADME properties of the title compounds were investigated theoretically to obtain bioavailability and BBB permeability profiles of the compounds. Docking studies were performed on the selected compounds with both AChE and BuChE.

References

[1] Schelterns, P.; Feldman, H. Treatment of Alzheimer's Disease: Current Status and New Perspectives. Lancet Neurol. **2003**, 2, 539-47.

[2] A, Cavalli.; M.L, Bolognesi.; A, Minarini.; M, Rosini.; V, Tumiatti.; M, Recanatini.; C, Melchiorre. Multi-Target-Directed Ligands to Combat Neurodegenerative Diseases. J. Med. Chem., **2008**, 51, 347-72.

[3] Morphy, R.; Rankovic, Z. Designed Multiple Ligands. An Emerging Drug Discovery Paradigm. J. Med. Chem., **2005**, 48, 6523–6543.

Short communication 6

Design and development of new chemical entities for the treatment of Parkinson disease

F. Mesiti,[1,2*] A. Gaspar[1], D. Chavarria[1], T. Silva[1], S. Alcaro[2], F. Borges[1]

[1]*CIQUP/Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, Porto, Portugal;*

[2] *Department of "Scienze della Vita", University "Magna Græcia" of Catanzaro, 88100 Catanzaro, Italy;*

francesco.mesiti@hotmail.it

Parkinson's disease (PD) is an age-related neurodegenerative illness characterized by four cardinal motor features (bradykinaesia, rigidity, resting tremor and postural instability) and several non-motor symptoms[1]. Although the depletion of dopamine is described as the key neurochemical impairment in PD, significant deficits in cholinergic transmission have been associated with the cognitive decline and gait dysfunction [1].

Currently, the clinical management of PD is symptomatic and mainly based on restoring dopamine levels[2]. However, as a significant deficit in cortical acetylcholinesterase activity has been described it was hypothesized that AChE inhibitors can be beneficial to manage the non-motors symptoms associated to the disease. Rivastigmine has been licensed by FDA for the treatment of patients with mild to moderately severe dementia associated with PD, although several lines of evidence have also pointed out clinical benefits for donepezil and galantamine[1].

Taken into account PD multifactorial nature and the need of disease-modifying drugs our group started a project focused on the design and development of dual-target-directed ligands aimed to restore dopamine and cholinergic levels. As chromone and coumarin scaffolds were validated as MAO-B or AchE inhibitors[3-6] the first step of our project was aimed to identify the key structural of benzopyrone ring important for each activity and attain novel hybrid chemical templates which can be of great value in surmounting the paucity of effective disease-modifying agents in the pipeline of PD. The results obtained so far will be presented in this communication.

[1]G. Paganom, G. Rengo, G. Pasqualetti, et al., J Neurol Neurosurg Psychiatry **2014**, 0, 1–7.

[2]T. Müller, Transl Neurodegener, **2012**, 1, 10.

[3]A. Fonseca, J Reis, T Silva, et al., J. Med. Chem., **2017**, 60, 7216-7217.

[4]A. Gaspar, T. Silva, M. Yáñez, et al., J. Med. Chem., **2011**, 54, 5165-5173.

[5]A.Gaspar, M.J. Matos, J. Garrido, et al., Chem Reviews 2014, 114, 4960-4992.

[6]J. Reis, F. Cagide, D. Chavarria, et al., J. Med. Chem **2016,** 59, 5879-5893.

Short communication 7

Highly Selective and Antioxidant BChE Inhibitors with Controllable Duration of Action Showing Neuroprotective Properties *in vivo*

Matthias Hoffmann,[a] Carina Stiller,[a] Matthias Scheiner,[a] Sandra Gunesch,[a] Tangui Maurice,[b] Michael Decker[a]*

[a] *Institute of Pharmacy and Food Chemistry, Julius-Maximilians University Würzburg, Am Hubland, D-97074 Würzburg, Germany*

[b] *INSERM UMR-S1198, University of Montpellier, Place Eugène Bataillon, F-34095 Montpellier, France*

Matthias.Hoffmann@uni-wuerzburg.de

Previous studies could show that both, antioxidant properties as well as inhibition of BChE can improve cognition in *in vivo* studies of dementia.[1–4] Therefore, hybrid molecules combining the features above might offer opportunities for over-additive pharmacological effects.

In this study, we present highly selective and nanomolar carbamate-based inhibitors of *h*BChE which exhibit high antioxidant properties *in vitro*. We synthesized a set of compounds bearing a) an antioxidant carrier scaffold, and b) a carbamate residue with different heterocyclic amines (*e.g.*, morpholine, tetrahydroisoquinoline, benzimidazole, piperidine) connected via alkylene spacers (2 to 10 methylene groups) probing a peripheral binding site (PAS) in *h*BChE. The inhibitors were characterized *in vitro* for inhibitory potency, binding kinetics, carbamate re-hydrolysis off the enzyme, and neuroprotectant properties. Not only selectivity for BChE over AChE is achieved, but the results also confirm the existence of a peripheral binding site yielding short, medium and long-acting nanomolar *h*BChE inhibitors (ranging from the half-life of 1 to 28 h of carbamoylated enzyme). The long-binding inhibitor **B** (figure) shows *in vivo* neuroprotective properties already at a dose of 0.3 mg/kg in a mouse model of Alzheimer´s disease (AD) outreaching lead compound **A** (figure). These findings suggest a significant benefit of hybrids combining BChE inhibition and antioxidant properties for disease-modifying treatment of AD.

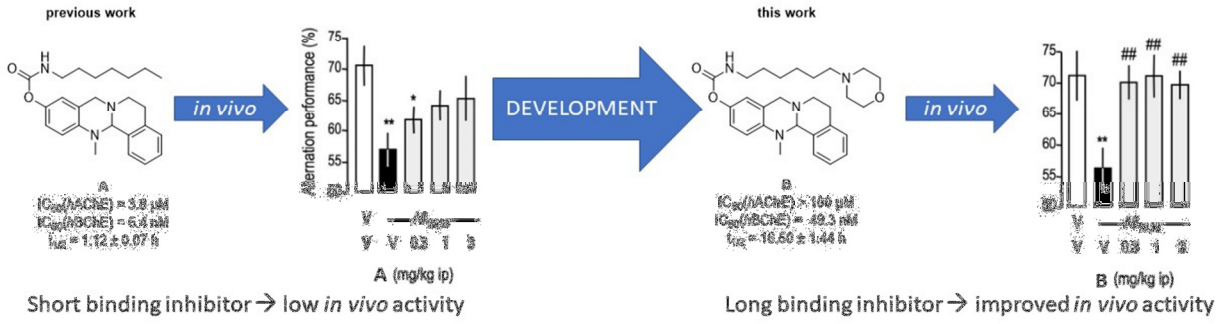


Figure 1: Optimization of short-acting BChE inhibitor **A**[5,6] to long-acting morpholine compound **B** improves *in vivo* neuroprotective properties

References

[1] Jin, G.; Bai, D.; Yin, S.; Yang, Z.; Zou, D.; Zhang, Z.; Li, X.; Sun, Y.; Zhu, Q. Silibinin rescues learning and memory deficits by attenuating microglia activation and preventing neuroinflammatory reactions in SAMP8 mice. *Neurosci. Lett.*, **2016**, *629*, 256–261.

[2] Tönnies, E.; Trushina, E. Oxidative Stress , Synaptic Dysfunktion, and Alzheimer´s Disease. *J. Alzheimers Dis.*, **2017**, *57*, 1105-1121.

[3] Košak, U.; Brus, B.; Knez, D.; Šink, R.; Žakelj, S.; Trontelj, J.; Pišlar, A.; Šlenc, J.; Gobec, M.; Živin, M.; Tratnjek, L.; Perše, M.; Sałat, K.; Podkowa, A.; Filipek, B.; Nachon, F.; Brazzolotto, X.; Więckowska, A.; Malawska, B.; Stojan, J.; Raščan, I. M.; Kos, J.; Coquelle, N.; Colletier, J.-P.; Gobec, S. Development of an in-vivo active reversible butyrylcholinesterase inhibitor. *Sci. Rep.*, **2016**, *6*, 39495.

[4] Dolles, D.; Hoffmann, M.; Gunesch, S.; Marinelli, O.; Möller, J.; Santoni, G.; Chatonnet, A.; Lohse, M. J.; Wittmann, H.-J.; Strasser, A.; Nabissi, M.; Maurice, T.; Decker, M. Structure-Activity Relationships and Computational Investigations into the Development of Potent and Balanced Dual-Acting Butyrylcholinesterase Inhibitors and *h*CB_2R Agonists with Pro-Cognitive *in vivo* Profile. *J. Med. Chem.*, **2018**, *61*, 1646–1663.

[5] Darras, F.-H.; Kling, B.; Heilmann, J.; Decker, M. Neuroprotective Tri- and Tetracyclic BChE Inhibitors Releasing Reversible Inhibitors upon Carbamate Transfer. *ACS Med. Chem. Lett.*, **2012**, *3*, 914-919.

[6] Sawatzky, E.; Al-Momani, E.; Kobayashi, R.; Higuchi, T.; Samnick, S.; Decker, M. A Novel Way to Radiolabel Human Butyrylcholinesterase for Positron Emission Tomography through Irreversible Transfer of the Radiolabeled Moiety. *ChemMedChem*, **2016**, *11*, 1540–1550.

Short communication 8

Novel Fubinaca/Rimonabant Hybrids as Endocannabinoid System Modulators

Azzurra Stefanucci,[a] Giorgia Macedonio,[a] Szabolcs Dvorácskó,[b] Csaba Tömböly,[b] Adriano Mollica[a]

[a] *Department of Pharmacy, "G. d'Annunzio" University of Chieti-Pescara, Via dei Vestini 31, 66100 Chieti, Italy.*

[b] *Institute of Biochemistry, Biological Research Centre of the Hungarian Academy of Sciences, Temesvári krt. 62. 6726 Szeged, Hungary.*

a.stefanucci@unich.it

The discovery of novel modulators of the cannabinoid system is a current topic in medicinal chemistry.[1,2] Here we report the design and synthesis of nine chemical entities (**LONI 1-9**) as hybrids of Fubinaca family compounds and Rimonabant, obtained by linking the 1-benzyl-2,5-dichloroindazole-3-carboxylic acid scaffold to different amino acids bearing a hydrophobic side chain and three different *C*-terminus (Figure 1). *In vitro* biological tests were performed to evaluate their cannabinoid activity by receptor binding assays and [^{35}S]GTPγS stimulation to reveal their affinity and potency. We found that all the novel compounds are able to bind to the cannabinoid receptors in the low nanomolar range with a marked selectivity towards the CB1 cannabinoid receptor. Some of them are full agonists, whereas the others act as partial agonists. These molecules could be potentially used as anti-obesity agents, antiemetic and analgesics.

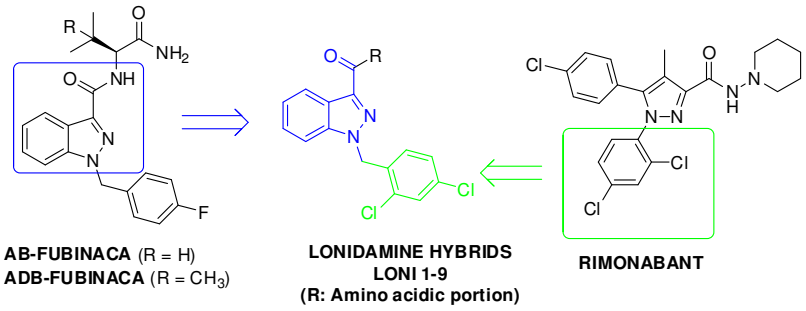


Figure 1. Structures of Lonidamine hybrids and related compounds **ADB-FUBINACA**, **AB-FUBINACA.**

References:

1. Banister SD, Moir M, Stuart J, Kevin RC, Wood KE, Longworth M, Wilkinson SM, Beinat C, Buchanan AS, Glass M, Connor M, McGregor IS, Kassiou M (**2015**). Pharmacology of indole and indazole synthetic cannabinoid designer drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB-PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. *ACS Chem Neurosci* 6 (9): 1546-1559.

2. Huffman JW, Szklennik PV, Almond A, Bushell K, Selley DE, He H, Cassidy MP, Wiley JL, Martin BR (**2005**). 1-Pentyl-3-phenylacetylindoles, a new class of cannabimimetic indoles. *Bioorg Med Chem Lett* 15(18): 4110-4113.

Short communication 9

Tracking the Oxypeucedanin: from ethnobotanical studies to pharmacological target

Alancay E. [a], Demiroz T.[b], Demir S.[b], Belen N.[a], Sevin G.[a], Baykan S.[b], Yetik-Anacak G.[a]
[a] *Dept of Pharmacology, Ege University, Faculty of Pharmacy, Izmir, Turkey*
[b] *Dept of Pharmaceutical Botany, Ege University, Faculty of Pharmacy, Izmir, Turkey*
elif.alancay@gmail.com

Ethnobotanical studies show that *Prangos* roots are traditionally used as an aphrodisiac in Anatolia (1). We found that oxypeucedanin (oxy) is the major compound in the chloroform extract of the roots of *P. pabularia* by HPLC analysis, which is an endemic species of Prangos (Umbelliferae) in Turkey.

A new gasotransmitter Hydrogen sulfide (H_2S) has been shown to play a role in erectile function (2). Thus we investigated first whether extract of the roots of *P. pabularia* and oxy increase erectile function through vasorelaxation in mice penile tissue and if so the role of H_2S in these effect. Because both H_2S (2) and oxy share similar therapeutic potential in oxidative stress, inflammation and inhibition of cholinesterase enzyme (3).

Air dried roots of *P. pabularia* were extracted with hexane, chloroform and methanol sequentially. Pharmacological studies were performed on chloroform extract of the plant. Erectile function of mice penile tissue was evaluated by vasorelaxation response measured by DMT strip myograph. Aminooxyacetic acid; AOAA CSE and CBS dependent enzyme inhibitor of H_2S synthesis was used to investigate the role of H_2S. We found that *P.Pabularia* (10^{-7}-10^{-4} g/mL, n=6) and oxy (10^{-7}- 10^{-4} M, n=10) caused relaxation in mice corpus cavernosum precontracted with phenylephrine ($3x10^{-6}$-10^{-4}) compared to vehicle (n=4). *P. pabularia* or oxy induced vasodilatations were significantly inhibited by AOAA (10 mM, 30 min. n=3 and 6)(Emax=74.28 ± 3.93 vs 47.91±3.73 and 70.32± 2.95 vs 47.02±7.16, extract and oxy with or without AOAA respectively, P<0.001, 2 way ANOVA).

We also examined effect of oxy (100 µM, 30 minutes, n=5) on basal and L-cysteine (L-cyst; 10 mM) stimulated H_2S formation in the presence or absence of; AOAA (10 mM, after oxy treatment, n=5) in mouse penile homogenates by an amperometric H_2S microsensor for 30 minutes at 37°C (UnisenseA/S, Aarhus, Denmark). Oxy caused a significant increase in H_2S formation induced by L-cysteine but not in basal condition (E_{max}= 33.77±1.34 and 40.93±2.32, L-cyst control and oxy, respectively, P<0.05, Unpaired T test L-cyst control vs oxy). L-cysteine-induced augmentation of endogenous H_2S formation was reversed back by H_2S synthesis inhibitor AOAA significantly (E_{max}=13.07±0.733, P<0.001, Unpaired T test, oxy vs AOAA)

We found that chloroform extract of the roots of *P. pabularia* and its major component oxy cause very well vasorelaxation in penile tissue, suggesting a potential in treatment of erectile dysfunction. Further our result demonstrated that both extract and major component have a capability to induce L-cysteine induced H_2S formation. Since H_2S has several physiological and pharmacological effects, our result may lead further studies to investigate the effect of extract of *P.pabularia* and oxy in other pathological conditions where H_2S is beneficial, such as myocardial infarction, diabetes, and hypertension.

Acknowledgement: We thank TUBITAK (Grant no: 117s116) for the financial support and #114s448 as a grant allowing to join MuTaLig COST Action.

References

1. Tabanca,N.; Tsikolia,M.; Ozek,G.; Ozek,T.; Ali,A.; R. Bernier,U.; Ahmet Duran,A.; Baser K.H.C.; A. Khan I. The Identification of Suberosin from Prangos pabularia Essential Oil and Its Mosquito Activity Against Aedes aegypti. Records of Natural Products, **2016**, 3 May-June, 311 – 325.
2. Czabo C.; Papapetropoulos A. International Union of Basic and Clinical Pharmacology. CII: Pharmacological Modulation of H2S Levels: H2S Donors and H2S Biosynthesis Inhibitors. Pharmacol Rev, **2017**, Oct;69(4), 497-564.
3. Choi JS.; Shin HY.; Kwon KS.; Shin S.; Choung SY.; Kwon YS.; Lee JW.; Choi BH.; Lee CK. Effects of oxypeucedanin on global gene expression and MAPK signaling pathway in mouse neuroblastoma Neuro-2A cells. Planta Med, **2011**, Sep;77(13), 1512-8.

Short communication 10

Targeting metabolism and apoptosis signaling in cancer cells: a structure-based virtual screening approach toward Hexokinase 2 inhibitors

Sara N. Garcia[a,b], M. Matilde Marques[a], Rita C. Guedes[b]

[a]*Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal*

[b]*iMed.ULisboa, Faculdade de Farmácia, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*

sara.garcia@tecnico.ulisboa.pt

Glucose is regarded as the main fuel of cancer cells and the glycolytic pathway has been demonstrated as a potential target to be explored for cancer treatment. Several enzymes involved in glycolysis are overexpressed in different types of cancer cells, namely hexokinase 2 (HK2)1. This enzyme is not only involved in the first and most determinant step of glycolysis and subsequently in the different branched pathways2,3, but also in the immortalization of cancer cells. When catalytically active, HK2 is able to bind to the voltage-dependent anion channel (VDAC) in the mitochondrial outer membrane, avoiding the normal pro-apoptotic signaling. HK2-VDAC disruption would facilitate the binding of pro-apoptotic proteins to VDAC, promoting the enhancement of apoptosis in cancer cells4.

Therefore, the inhibition of the HK2 catalytic centre is proposed as a strategy to reduce the main source of energy to cancer cells, thus substantially decreasing cancer cell proliferation and preventing HK2 binding to VDAC, enhancing the apoptosis process. As an effort to find hit compounds able to interfere with the HK2 catalytic centre, a structure-based drug design strategy was implemented, leading to the virtual screening of several general databases such as DrugBank (~2000 molecules), NCI (~265 000 molecules), Mu.Ta.Lig Chemotheca (~800 molecules) and some specific natural product databases such as Ambinter (~10 000 000 molecules) and Inter Bio Screen Natural Products (~84 000 molecules). The virtual screening was carried out using molecular docking calculations through Gold 5.20 software. Molecules were prepared using Molecular Operating Environment (MOE2016 0802) and then docked into the HK2 catalytic site. Prior validation of the above-mentioned protocol was conducted, by testing different three-dimensional (crystallographic) HK2 structures, the amino acids at the catalytic pocket centre, scoring functions and catalytic pocket radius. Our results have suggested 2981 molecules with the potential to act as new HK2 inhibitors. From those, 50 compounds were selected to progress to biochemical evaluation.

Acknowledgements

We thank Fundação para a Ciência e a Tecnologia for financial support (PD/BD/135284/2017, UID/DTP/04138/2013, UID/QUI/00100/2013, and SAICTPAC/0019/2015).

References

[1] Hay, N. Nat. Rev. Cancer 2016, 16 (10), 635–649.

[2] Martinez-Outschoorn, U. E.; Peiris-Pagès, M.; Pestell, R. G.; Sotgia, F.; Lisanti, M. P. Nat. Rev. Clin. Oncol. 2017, 14 (1), 11–31.

[3] Hamanaka, R. B.; Chandel, N. S. J. Exp. Med. 2012, 209 (2), 211-215.

[4] Krasnov, G. S., Dmitriev, A. A., Lakunina, V. A., Kirpiy, A. A. & Kudryavtseva, A. V. Expert Opin. Ther. Targets 17, 1221–1233 (2013).

Short communication 11

The Mu.Ta.Lig. CHEMOTHECA: chemoinformatic tool for Multi-Target drugs identification and compounds repurposing

Raffaella Catalano,[a] Donatella Bagetta,[a] Antonio Lupia,[a] Annalisa Maruca,[a] Roberta Rocca,[a,b] Francesco Ortuso,[a] Stefano Alcaro.[a]

[a] *Dept. of Health Sciences, University Magna Græcia, Viale Europa/88100-Catanzaro, Italy*

[b] *Dept. of Experimental and Clinical Medicine, University Magna Græcia and Translational Medical Oncology Unit, Viale Europa/88100-Catanzaro, Italy*

catalano@unicz.it

The use of multi-target drugs against multiple selective targets have shown promising potential in facilitating drug discovery due to the better profiles of therapeutic efficacy and safety.[1] The Mu.Ta.Lig Chemotheca was developed within the COST ACTION CA15135 framework. It is focused on the identification of multi-target ligands and compound-repurposing, stimulating new collaborations between researchers while saving intellectual property of all involved researchers. The Chemotheca is accessible on the web (http://chemotheca.unicz.it) either by REGISTERED and GUEST users with different level of offered functionalities (Figure 1). The database permits registered users only, to upload their own data and to use the advanced search interface, with highly customizable filter criteria, storable and loadable for next searches. Instead, guest access only provides basic information such as compound IDs and related 2D or 3D chemicals structures.

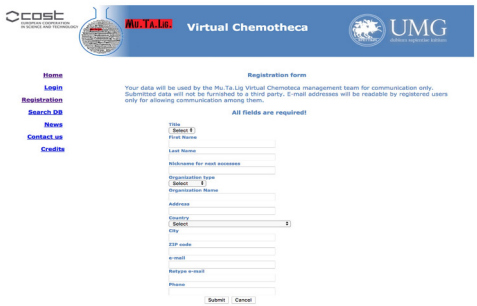


Figure 1: registration form to the Virtual Chemotheca.

All Chemotheca data are stored in a MySQL database. An *ad hoc* developed Python code computes 90 molecular descriptors, including physico-chemical and ADME properties as well as substructure-based PAINS evaluations for each new uploaded compound.

References

[1] Ma, X. H., Shi, Z., Tan, C., Jiang, Y., Go, M. L., Low, B. C., & Chen, Y. Z. In-Silico approaches to multi-target drug discovery. *Pharmaceutical research*, **2010**, *27(5)*, 739-749.

Short communication 12

Funnel-Metadynamics Automated Protocol (FMAP): three steps to disclose drug pharmacodynamics

Stefano Raniolo,[a] Vittorio Limongelli[a]

[a] *Faculty of Biomedical Sciences, Institute of Computational Science, Università della Svizzera italiana (USI), Lugano, Switzerland*

stefano.raniolo@usi.ch

Predicting the thermodynamic properties of the binding process of a drug to its molecular target is of primary relevance to shed light on its mechanism of action and develop new medications. In 2013 our group developed Funnel-Metadynamics (FM).[1] Using FM the ligand binding mode and the accurate estimate of the absolute protein-ligand binding free energy are provided within an affordable computer time. From its development FM has been successfully used by different groups to study ligand/protein and ligand/DNA binding complexes, identifying crystallographic binding modes and predicting experimental binding free energies.[1-5]

The rapid diffusion of FM and the feedback from the users prompted us to develop the Funnel-Metadynamics Automated Protocol (FMAP) that is presented in this talk. FMAP allows disclosing in three steps the whole pharmacodynamics process of a drug to its molecular target, from its unbound state to its final binding mode. FMAP makes use of a graphical user interface (GUI) that allows the interactive preparation of the input files for the FM simulation and the interactive analysis of the results. The GUI guides even inexpert investigators through a step-by-step procedure that is composed of 3 phases: pre-processing, simulation, and post-processing. The final outcome of FMAP is the identification of the ligand binding mode, the metastable states found during the ligand binding mechanism and the accurate estimate of the ligand binding free energy.In conclusion, FMAP is an accurate, flexible and user-friendly protocol that is expected to impact computer-aided drug design studies in the near future.

References

[1] Limongelli, V.; Bonomi, M.; Parrinello, M. Funnel-Metadynamics as accurate binding free energy method. *PNAS*, **2013**, *110*, 6358-6363.

[2] Troussicot, L.; Gullière, F.; Limongelli, V.; Walker, O.; Lancelin, J.M. Funnel-Metadynamics and solution NMR to estimate protein-ligand affinities. *JACS*, **2015**, *137*, 1273-1281.

[3] Comitani, F.; Limongelli, V.; Molteni, C. The Free Energy Landscape of GABA Binding to a Pentameric Ligand-Dated Ion Channel and its Disruption by Mutations. *JCTC*, **2016**, *12*, 3398-3406.

[4] Moraca, F.; Amato, J.; Ortuso, F.; Artese, A.; Pagano, B.; Novellino, E.; Alcaro, S.; Parrinello, M.; Limongelli, V. Ligand binding to telomeric G-quadruplex DNA investigated by Funnel-Metadynamics simulations. *PNAS*, **2017**, *114*, E2136-E2145.

[5] Yuan, X.; Raniolo, S.; Limongelli, V.; Xu, Y. The Molecular Mechanism Underlying Ligand Binding to the Membrane-Embedded Site of a G-Protein-Coupled Receptor. *JCTC*, **2018**, *14*, 2761-2770.

Short communication 13

The *in silico/in vitro* metabolism identification of the series promising xanthine- and tert-amylphenoxyalkyl piperidine derivatives with confirmed Multi Target Directed activity

Gniewomir Latacz,[a] Dorota Łażewska,[a] Agnieszka Olejarz-Maciej,[a] Michał Załuski,[a] Christa E. Müller,[b] Katarzyna Kieć-Kononowicz[a]

[a]*Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, Kraków 30-688, Poland*

[b]*PharmaCenter Bonn, Pharmaceutical Institute, Pharmaceutical Chemistry I, University of Bonn, An der Immenburg 4, 53121 Bonn, Germany*

glatacz@cm-uj.krakow.pl

The series of new xanthine- and tert-amylphenoxyalkylamine piperidine derivatives were synthesized and their Multi Target Directed activities as A_1/A_{2A} adenosine receptor antagonists/MAO-B inhibitors (xanthines) and H_3 receptor antagonists/MAO-B inhibitors (piperidines) were confirmed.[1-3] As very important part of the performed studies the metabolic stability and the metabolic pathways of the most active compounds were determined. The compounds were examined first using MetaSite 4.1.1 software to calculate the most likely sites of metabolism. In the next step the examined Multi Target Directed Ligands (MTDLs) were incubated for 2 h with human (HLMs) or rat liver microsomes (RLMs). The UPLC/MS of the reaction mixtures and ion fragments analyses of the obtained metabolites allowed with support of the *in silico* data to identify the metabolic stability and probable metabolic pathways of tested MTDLs. The metabolic stability of xanthine derivatives differed depending on the structures and was found to be from excellent to moderate. The metabolic pathways were determined to include hydroxylation, dealkylation, dehydrogenation, dealkylation and deamination followed by oxidation. The tert-amylphenoxyalkylamine piperidine derivatives showed from moderate to good metabolic stability with the hydroxylation at tert-amyl substituent as most frequently occurring metabolic biotransformation. Our studies have shown *in silico* preliminary metabolism prediction as very useful tool for appropriate interpretation of the *in vitro* results. Moreover, the obtained data will be helpful for the future design of new xanthine- and piperidine- derivatives with MTD activity and desired high metabolic stability.

Financial support by: Jagiellonian University statutory funds K/ZDS/007121 is kindly acknowledged

References:

[1]Kuder, K.J.; Łażewska, D.; Kaleta, M. et al. Synthesis and biological activity of novel tert-amylphenoxyalkyl (homo)piperidine derivatives as histamine H_3R ligands. *Bioorg Med Chem*, **2017**, *25,* 2701-2712.

[2]Łażewska, D.; Olejarz-Maciej, A.; Kaleta, M. et al. 4-tert-Pentylphenoxyalkyl derivatives - Histamine H3 receptor ligands and monoamine oxidase B inhibitors*. Bioorg Med Chem Lett*, **2018**, *28*, 3596-3600.

[3]Załuski, M.; Stanuch, K.; Karcz, T. et al. Tricyclic xanthine derivatives containing a basic substituent: adenosine receptor affinity and drug-related properties. *Medchemcomm.* **2018**, *9*, 951-962.

Short communication 14

Zn(II) complexes with pyridine-based thiazolyl-hydrazones as potent multi-targeting anticancer agents

Nenad Filipović,[a,✉] Aleksandar Višnjevac,[b] Jasminka Popović,[b] Jovana Araškov,[c] Goran Janjić,[d] José M. Padrón,[e] Tamara Todorović[d]

[a]*Department of Chemistry and Biochemistry, Faculty of Agriculture, University of Belgrade, Nemanjina 6, 11000 Belgrade, Serbia*

[b] *Ruđer Bošković Institute, Bijenička 54, 10000 Zagreb, Croatia*

[c]*Faculty of Chemistry, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia*

[d]*Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia*

[e]*BioLab, IUBO AG, CIBICAN, Universidad de La Laguna, C/ Astrofisico Fco. Sanchez 2, 38206 La Laguna, Spain*

nenadf.chem@gmail.com

In our previous study we demonstrated potent anticancer activities and dual targeting nature of benzylidene-based selenazolyl-hydrazones.[1] In this work, we prepared unprecedented Zn(II) complexes of their pyridine-based sulfur analogues (L1–L3, Fig. 1) starting from two Zn salts. Single crystal X-ray diffraction analysis revealed that, among six novel complexes, geometry of the central metal ion is an octahedral in five complexes, while in the case of complex obtained from L1 and zinc chloride the geometry is trigonal-bipyramidal. In a preliminary cytotoxicity screening against several human solid tumor cell lines, all complexes showed GI_{50} values in the range 2–4 μM, being much more potent in comparison to the corresponding ligands. Computational methods have been used to indicate possible anticancer targets.

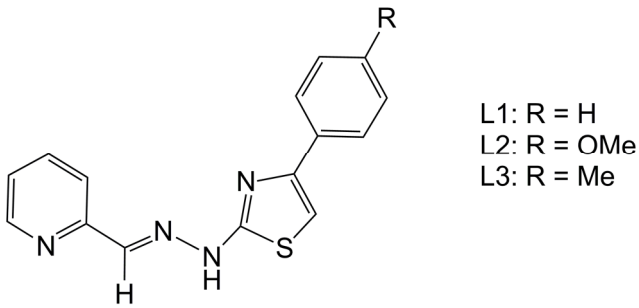


Figure 1: Structure of pyridine-based thiazolyl-hydrazones L1–L3.

References

[1] Elshaflu, H.; Todorović, T.; Nikolić, M., Lolić, A.; Višnjevac, A.; Hagenow, S.; Padrón, J. M.; García-Sosa, A. T.; Djordjević, I.; Grubišić, S.; Stark, H.; Filipović, N. Selenazolyl-hydrazones as Novel Selective MAO Inhibitors with Antiproliferative and Antioxidant Activities: Experimental and In-silico Studies. *Frontiers in Chemistry,* **2018**, 6, 247.

Short communication 15

Pyridoindole compounds with multi-target effects

Magdaléna Májeková,[a] Lucia Račková,[a] Lucia Kováčiková,[a] Jana Balleková,[a] Pavel Májek,[b] Milan Štefek[a]

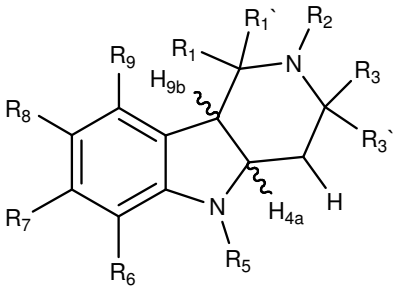
[a]*Department of Biochemical Pharmacology, Centre of Experimental Medicine, Institute of Experimental Pharmacology and Toxicology, SAS, Dubravska Cesta 9, Bratislava, Slovakia*

[b] *Institute of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinskeho 9, Bratislava, Slovakia*

magdalena.majekova@savba.sk

Fifteen years ago, a group of 82 pyridoindole derivatives was designed and synthesized at the Institute of Experimental Pharmacology and Toxicology of Slovak Academy of Sciences. The original goal was to enhance the antioxidant properties of the original compound stobadine (4aR,9bS isomer of carbidine) and to obtain a possible drug candidate for the treatment of brain injury. The excellent antioxidant and neuroprotective properties were observed for a number of congeners. The group was virtually screened for the specific therapeutic effects and later new substituents were introduced in order to hit specific targets. Some compounds were tested by in vivo model experiments. The promising results were obtained in the prevention of diabetic complications, protection of vascular injury and suppression of depressive-like behavior. Good pharmacodynamics behavior in animal experiments proved also the satisfactory bioavailability of these compounds. Here we bring a survey of the most important properties of this group from the point of view of theoretical study.

Hexahydropyridoindoles



Tetrahydropyridoindoles

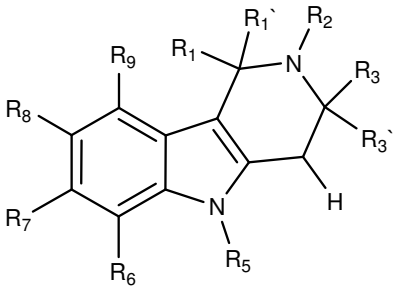


Figure 1: Structure of pyridoindole compounds

References

[1] Štolc S, Šnirc V, Májeková M, Gáspárová Z, Gajdošíková A, Štvrtina S. Development of the new group of indole-derived neuroprotective drugs affecting oxidative stress. *Cell Mol Neurobiol.* **2006,** 26, 1495-1504.

Acknowledgement

This work was supported by the COST action CA15135, the Scientific Grant Agency VEGA 2/0127/18 and the Slovak Research and Development Agency under the contract No. APVV-15-0455.

Short communication 16

Recent Progress on Naphthalimide Molecular Logic Gate Anticancer Agents

Alex D. Johnson,[a] Jake C. Spiteri,[a] A. Joseph Buhagiar, [b] David C. Magri[a]

[a] *Department of Chemistry, Faculty of Science, University of Malta, Msida, MSD2080, Malta*

[b] *Department of Biology, Faculty of Science, University of Malta, Msida, MSD2080, Malta*

david.magri@um.edu.mt

Compounds with naphthalimide (benz[de]isoquinolin-1,3-diones)[1] and ferrocene[2] moieties are potential multi-ligand target agents. Our aim is to develop novel naphthalimide-ferrocene derivatives as fluorescent markers for cell imaging[3] and as potential therapeutic cancer agents.[1] The molecules are rationally designed to detect two or more analytes (or potential targets) according to Boolean algebra functions (i.e. AND, OR, XOR, INH etc.) and report successful multi-detection by fluorescence emission. Our series of naphthalimide-based molecules incorporate a secondary or tertiary amine, which is susceptible to protonation for improved water solubility, and a ferrocenyl moiety for promoting redox chemistry.[4] In this presentation, the importance of field effects on the physiochemical properties of molecules will be highlighted in addition to recent cytotoxicity and fluorescent cell imaging results in MCF-7 and K562 cells.

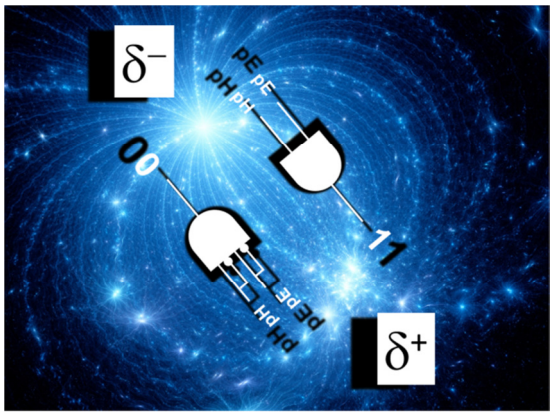


Figure 1: Cover art for ref. 4 depicting the symbolic logic functions of the molecular logic gates depending on the orientation with respect to the electric field.

References

[1] Gellerman, G. Recent Developments in the Synthesis and Applications of Anticancer Amonafide Derivatives. A Mini Review, *Lett. Drug. Des. Discov*., **2016**, *13*, 47-63.

[2] Ornelas, C. Application of ferrocene and its derivatives in cancer research, *New. J. Chem*., **2011**, *35*, 1973-1985.

[3] Magri, D. C.; Johnson, A. D.; Spiteri, J. C. Fluorescent Photoinduced Electron Transfer (PET) Logic Gates for Acidity (pH) and Redox Potential (pE), *J. Fluoresc.,* **2017**, *27*, 551-559.

[4] Spiteri, J. C.; Denisov, S.A.; Jonusauskas, G.; Klejna, S.; Szaciłowski, K.; McClenaghan, N. D. Magri, D.C. Molecular engineering of logic gate types by module rearrangement in 'Pourbaix Sensors': the effect of excited-state electric fields, *Org. Biomol. Chem*., **2018**, *16*, 6195-6201.

Short communication 17

Multi-Target Qualities and Ligand Pharmacology for Neurodegenerative, Cancer, and Other Inhibitors in the Chemotheca

Alfonso T. García-Sosa [a]

[a] *Institute of Chemistry, University of Tartu, Ravila 14a, Tartu, 50411, Estonia*

alfonsog@ut.ee

Multi-target drug design requires the consideration of several on- and off-targets for a desired specificity. Ligands can have multiple beneficial, even synergistic, interactions with several targets be they in the same or separate pathways or families. One example are series of ligands with nM MAO B inhibition, that could have additional targets in neurodegenerative diseases, such as KCCN1, as well as cancer-related target inhibition through 5-NT and EIF4E.[1] These extra targets were found through a ligand-based similarity ensemble approach, and then further enhanced through docking.[1] Such extended multiple target space can be predicted for ligands such as those in the Chemotheca [http://chemotheca.unicz.it/index.php], and thus speed up the multi-target development of compounds in databases.

Ligands can have mechanisms which may not be immediately apparent, for example, though complexation and delivery via metal, in this case cobalt, to their site of action (bacterial quorum-sensing, Figure 1).[2] All of these considerations can also be used in addition to profiling compounds for their ADME properties, PAIN filters, as well as organ or disease-category profiling though relationships including machine-learning.[3,4] The Chemotheca can automatically include predictions of multiple targets for the deposited ligands and possibly their metabolites, in order to facilitate multi-target design for compounds.

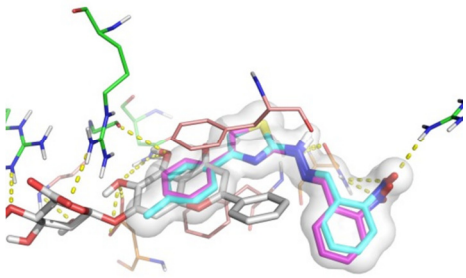


Figure 1: Docked ligand HL (cyan), docked known inhibitor furvina (magenta), docked known binder 3-oxo-C12-HSL (slate), co-crystallized known binder 3-oxo-C12-HSL (yellow), in the binding site of LasR

References

[1] Elshaflu H.; Todorović T.R.; Nikolić M.; Lolić A.; Višnjevac A.; Hagenow S.; Padrón J.M.; García-Sosa A.T.; Djordjević I.S.; Grubišić S.; Stark H.; Filipović N.R. "Selenazolyl-hydrazones as Novel Selective MAO Inhibitors With Antiproliferative and Antioxidant Activities: Experimental and In-silico Studies", *Front. Chem.*, **2018**, *6*, 247

[2] Borges A., Simões M., Todorovic T. R., Filipovic, N. R., García-Sosa A. T.,* "Cobalt Complex with Thiazole-Based Ligand as New Pseudomonas aeruginosa Quorum Quencher, Biofilm Inhibitor, and Virulence Attenuator", *Molecules*, **2018**, *23*, 1385

[3] Yosipof, A.; Guedes, R.C.; García-Sosa, A.T., "Data Mining and Machine Learning Models for Predicting Drug Likeness and Their Disease or Organ Category", *Front. Chem.*, **2018**; *6*: 162, 10.3389/fchem.2018.00162

[4] García-Sosa, A.T.; Maran, U. "Drugs, Non-Drugs, and Disease Category Specificity: Organ Effects by Ligand Pharmacology", *SAR QSAR Environ. Res.*, **2013**, 24, 319-331

Short communication 18

Isatin-Triazole Hybrids: Lymphoma Anti-Proliferation and BuChE Inbibition

Burke, A.J.[a,b], Marques, C.S.[a], Bagetta, D.[c], Gaudio, E.[d], López, Ó.[e], Carreiro, E.P.[a], Bertoni, F.[d], Alcaro, S.[c]

[a] Centro de Química de Évora, University of Évora, Institute for Research and Advanced Training, Rua Romão Ramalho 59, 7000 Évora, Portugal. [b] Department of Chemistry, Rua Romão Ramalho 59, 7000 Évora, Portugal. [c] Università Magna Græcia di Catanzaro, Viale Europa 88100 Catanzaro ,Italy, [d] Universita' della Svizzera italiana, Institute of Oncology Research, Via Vela 6, 6500 Bellinzona, Switzerland. [e] Department of Organic Chemistry. Faculty of Chemistry, Profesor García González, 1. 41012. Seville, Spain.

ajb@uevora.pt

Isatins (including their oxindole analogues) and triazoles are privileged skeletons in medicinal chemistry.[1] However, hybrids that contain both units for the moment are quite rare, despite their large therapeutic potential and are thus highly desirable. Two of the most notorious disease categories at the current time are cancer and Alzheimer's disease (AD), which affect a significant portion of the world population, and thus new medicines are required. We have developed a family of *oxindole-triazole* molecules (**1**) that were shown to be dual inhibitors for butrylcholinesterase (BuChE) (important target for treating AD symptoms) and arresting lymphoma proliferation, but recently our studies have shown that the *isatin-triazole analogues* (**2**) particularly compound (**2b**), seem to be more potent in this context. Some of the key results are shown in **Figure 1**.[2]

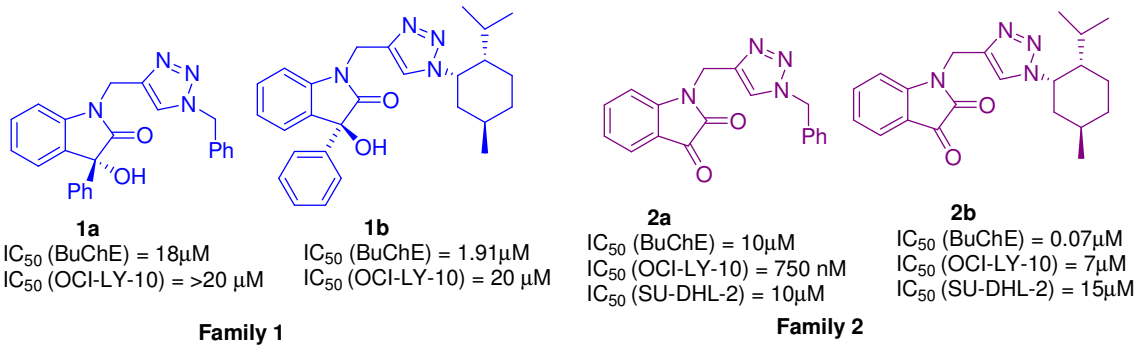


Figure 1

To gain greater insignt into the differences obsereved in the activities of these two framilies of compounds, we also carried out key Molecular Modelling studies and Saturation Transfer Difference NMRs, which were highly revealing. These results together with the biassay studies and the underlining medicinal chemistry will be discussed in this presentation.

References

[1] Abadi, A. H.; Abou-Seri, S. M.; Abdel-Rahman, D. E.; Klein, C.; Lozach, O.; Meijer, L. *Eur. J. Med. Chem.* **2006**, *41*, 296-305. Brandão, P.; Burke, A.J., *Tetrahedron,* **2018**, *74*, 4927-57.

[2] Marques, C.S.; Burke, A.J. *ChemCatChem,* **2016**, *8*, 3518-26. Marques, C.S.; Busto, N.; Gaudio, E.; Bertoni, F.; Burke, A.J. EP11006317.

Poster communications

Poster communication 1 – WG 1

Synthesis Characterization and study of the Nickel-Diimine-Dithiolate Complex, its DNA Binding and Cell Viability properties

Balou Sophie[a], Eleni Efthimiadou[b], Christina Anna Mitsopoulou[c]

[a b c] *Dept of Chemistry, National and Kapodistrian University of Athens, Panepistimioupolis Zografou 15771, Athens, Greece*

sbalou@chem.uoa.gr

The fact that the human genome is the cornerstone of all livings things has come to be widely accepted among the scientific community. The knowledge of specific targets in rational design of molecules can be used as anticancer agents. [1] In the last decades, the potential use of inorganic complexes as drugs has come under the scope of scientific research. The search for an alternative to cisplatin and its derivatives, which exhibit lower toxicity and less adverse effects, has produced an impressive number of metal-based compounds, which have been evaluated for their anticancer activity. It was surprising that nickel found to be cofactor of the enzyme urease, in 1970. [3,4] Nowadays, a substantial list of nickel enzymes has been found. The biology of nickel is expanding beyond the enzyme metal centers to include cellular homoeostasis mechanisms that are deployed by the organism that use nickel. [4,5]. However, the biological function of nickel is still unclear. The interactions of nickel (II) complexes with DNA mainly depend on the structure of the ligand exhibiting intercalative nature. [5]

Herein the synthesis of the complex [Ni(dppz)(qdt)] is presented, where the ligand dppz is the dypyrido[3,2-a:2',3'-c] phenazine and qdt is the ligand quinoxaline-2,3-dithiol. The above complex was characterized by utilizing spectroscopic and electrochemistry methods. Moreover, binding studies of the complex with Calf Thymus (C.T. DNA) were conducted employing a variety of different techniques, namely UV-visible absorption spectra, Viscosity analysis, Cyclic Voltammetry, Fluorescence and Cyclic Dichroism. DNA cleavage experiments have also been conducted by agarose gel electrophoresis using pBR322 DNA both dark conditions, as well as after illumination, in which the wavelength was greater than 400nm. In addition, an MTT assay was implemented, aiming at the investigation of cell viability after incubation within the complex.

References

[1] Juan Carlos García-Ramos, R.G.-M., Fernando Cortés-Guzmán and Lena Ruiz-Azuara, *Metal-Based Drug-DNA Interactions.* J. Mex. Chem. Soc., **2013**, 57(3)

[2] Nielsen, F.H., *Essentiality and function of nickel.* Trace Element Metabolism in Animals, **1974**.

[3] Zamble, D.B., *Nickel in biology.* Metallomics, **2015,** 7(4): p. 588-9.

[4] Skyrianou, K.C., et al., *Nickel-quinolones interaction. Part 1 - Nickel(II) complexes with the antibacterial drug sparfloxacin: structure and biological properties.* J. Inorg Biochem, **2009**, 103(12): p. 1617-25.

[5] Rudolf K.Thauer, G.D., Peter Schönheit, *Biological role of nickel.* Trends in Biochemical Sciences, **1980**, 5(11): p. 304-306.

Poster communication 2 – WG 1

Superior tools to modulate normal and aberrant myosin II function

Bart Roman[a,b]

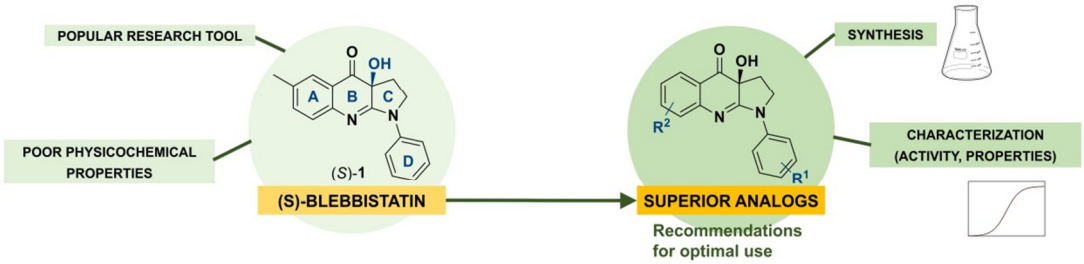
[a] *SynBioC Research Group, Department of Green Chemistry and Technology, Faculty of Bioscience Engineering, Coupure Links 653, 9000 Gent, Belgium.*

[b] *Cancer Research Institute Ghent (CRIG), Corneel Heymanslaan 10, 9000 Gent, Belgium*

bart1.roman@ugent.be

(S)-Blebbistatin (S)-**1**, a chiral tetrahydropyrroloquinolinone, is a widely used and well-characterized ATPase inhibitor selective for myosin II.[1] The central role of myosin II in many normal and aberrant biological processes has been revealed with the aid of this small molecule.

Unfortunately, (S)-blebbistatin has severe physicochemical deficiencies that trouble its use in advanced biological settings: low solubility, fluorescence interference, (photo)toxicity and stability issues. We and others have developed a large toolbox of (S)-blebbistatin analogs in which particular shortcomings have been addressed.[2-4] The present communication provides an overview of the synthesis and characterization of these molecules, and a user's guide for their optimal application in in vitro and in vivo model systems.[1]



References

[1] Roman, B.I.; Verhasselt, S.; Stevens, C.V. Medicinal Chemistry and Use of Myosin II Inhibitor (*S*)-Blebbistatin and Its Derivatives. *J Med Chem*, **2018**, *61*, 9410-9428.

[2] Verhasselt, S.; Roman, B.I.; Bracke, M.E.; Stevens, C.V. Improved synthesis and comparative analysis of the tool properties of new and existing D-ring modified (*S*)-blebbistatin analogs. *Eur J Med Chem*, **2017**, 136:85-103.

[3] Verhasselt, S.; Roman, B.I.; De Wever, O.; Van Hecke, K.; Van Deun, R.; Bracke, M.E.; Stevens, C.V. Discovery of (*S*)-3'-hydroxyblebbistatin and (*S*)-3'-aminoblebbistatin: polar myosin II inhibitors with superior research tool properties. *Org Biomol Chem*, **2017**, *15*, 2104-2118.

[4] Verhasselt, S.; Stevens, C.V.; Van den Broecke, T.; Roman, B.I. Insights into the myosin II inhibitory potency of A-ring-modified (*S*)-blebbistatin analogs. *Bioorg Med Chem Lett*, **2017**, *27*, 2986-2989.

Poster communication 3 – WG 1

Systematic Design and Synthesis of Novel Small Molecule Inhibitors of Chikungunya Virus

Verena Battisti,[a] Julia Moesslacher,[b] Charlotte Vanderheydt,[c] Ernst Urban[a] and Thierry Langer[a]

[a] *University of Vienna, Faculty of Life Sciences, Department of Pharmaceutical Chemistry, Althanstraße 14 (UZA II) A-1090 Vienna, Austria*

[b] *University of Innsbruck, Faculty of Chemistry and Pharmacy, Innrain 80-82 A-6020 Innsbruck, Austria*

[c] *KU Leuven, Rega Institute for Medical Research, Herestraat 49 3000 Leuven, Belgium*

verena.battisti@univie.ac.at

The Chikungunya virus (CHIKV) is the causative agent of the Chikungunya fever, an illness characterized not only by a rapid onset of high fever but also by severe myalgia and leads in some cases also to death. Even years after the infection, some patients suffer under recurrent and persistent myalgia, which causes an impaired quality of life. Since its re-emerging in 2005, the disease had massive outbreaks infecting millions of people in more than 40 countries not only in Asia and Africa but also in America and Europe (France and Italy). Currently there are no specific antiviral drugs or vaccine available to prevent or treat the infection, although the predicted outbreak of a new epidemic in a Mediterranean city like Rome is highly probable. Therefore, the design and development of an effective antiviral drug are immensely needed. [1, 2, 3, 4]

In 2014 Dr. Julia Moesslacher discussed in her Ph.D. thesis a series of small molecules, how they could be synthesized and evaluated in biological assays. From her starting point the hit CIM016321, described by HTS by the Centrum voor Innovatie en Stimulatie van Medicijnonwikkeling (CISTIM) and the Katholieke Universiteit Leuven, she produced 59 analogues by a hit to lead optimization. [5]

Based on her most successful compounds, a series of new promising molecules were now designed, synthesized and tested against only on the Chikungunya virus but also on Enterovirus 71, Zikavirus and Norovirus. Hereby the concept of bioisosterism and the Topliss tree of decision where used for a systematic variation of substitution pattern. Also, her established 4-step-synthesis was optimized, resulting in a higher, purer yield.

References

[1] Bakar, F.; Ng, L. “Nonstructural Proteins of Alphavirus—Potential Targets for Drug Development.” *Viruses*, **2018**, *vol.10*, *no. 10,* p.71-86

[2] Powers, A. “Vaccine and Therapeutic Options To Control Chikungunya Virus.” *Clin. Microbiol. Rev.,* **2018**, *vol. 31, no.1*, p.104-116.

[3] Thiberville, M.; Moyen, F. et al. “Chikungunya fever: Epidemiology, clinical syndrome, pathogenesis and therapy”. *Antiviral Res.*, **2013**, *vol. 99*, pp. 345-370.

[4] Solimini, A. G.; Manica, M.; Rosà, R.; et al. “Estimating the risk of Dengue, Chikungunya and Zika outbreaks in a large European city.,” *Sci. Rep*., **2018**, *vol. 8, no. 1*, p. 16435.

[5]Kirchebner, J.; “Novel Small Molecule Inhibitors of Chikungunya Virus,” University of Innsbruck, **2014**.

Poster communication 4 – WG 1

Design of Antibody Radiolabeled Drug Conjugates using 195mPt-Carboplatin for cancerology.

Christophe Cantelli[a,b]*, Lisa-Maria Rečnik[a,b], Isabelle Navarro-Teulon[b], Jean-Pierre Pouget[b], Vincent Lisowski[a].

[a] *IBMM, UMR 5247, CNRS, Université de Montpellier, ENSCM, UFR des Sciences Pharmaceutiques et Biologiques, Montpellier, France.*

[b] *IRCM, INSERM U1194, Université de Montpellier, Institut Regional du Cancer de Montpellier, Montpellier, France.*

christophe.cantelli@etu.umontpellier.fr

The past decade has seen significant advances in the field of antibody-drug conjugates (ADCs) with the launch of four drugs, namely Kadcyla® for breast cancer, Adcetris® for Hodgkin lymphoma, Mylotarg® for acute myelogenous leukemia and Besponsa® for acute lymphoblastic leukemia. ADCs combine the high selectivity of monoclonal antibodies (mAbs) for their target with a highly potent cytotoxic payload. This allows minimisation of the drug's side effects by specifically delivering the drug to cancer cells.[1]

Platinum derivatives (Carboplatin and Oxaliplatin) are mainly used in ovarian and colorectal cancers. However, these drugs lead to some drawbacks with resistances and side effects that can limited their use.[2] To decrease these drawbacks and improve efficiency, we conjugated carboplatin with a monoclonal antibody. Furthermore, switching the stable platinum atom for a radioisotope (e.g. 195mPt) in such chemotherapeutic agents could be a way to improve DNA damages of cancer cells. These radioisotopes also allows imaging experiments like single positon emission computed tomography (SPECT) for a theranostic approach.

Two kinds of ADCs will be presented, the first one, is directed against colorectal cancers cells and is not able to be internalised. The deleterious effect of 195mPt effect at the membrane by emission of Auger electrons can be explored. The second construction links a mAb directed against human Müllerian Inhibiting Substance type II receptor (MISRII) to a functionalized carboplatin derivative with a cleavable and self-immolative linker. This ADC can be internalised by the cell and liberate the platinated drug inside the cancer cell.

Preliminary results (synthetic and biological) of this project will be presented.

References (Calibri 10)

[1] Beck, A et al.; Nat. Rev. Drug Discov, **2017**, 16, 315-337.

[2] Oun, R et al.; Dalton Trans, 2018, 47, 6645–6653.

Poster communication 5 – WG 1

RP-HPLC evaluation of lipophilicity of a series of dual DNA gyrase and topoisomerase IV inhibitors

Vladimir Dobričić,[a] Jelena Savić,[a] Tihomir Tomašič,[b] Nace Zidar,[b] Lucija Peterlin Mašič,[b] Janez Ilaš,[b] Danijel Kikelj,[b] Olivera Čudina[a]

[a] *Dept of Pharmaceutical Chemistry, University of Belgrade – Faculty of Pharmacy, Vojvode Stepe 450, 11000 Belgrade, Serbia*

[b] *University of Ljubljana, Faculty of Pharmacy, Chair of Pharmaceutical Chemistry, Aškerčeva 7, SI-1000 Ljubljana, Slovenia*

vladimir@pharmacy.bg.ac.rs

In this study, lipophilicity of twenty-three DNA gyrase and topoisomerase IV ATPase inhibitors was estimated at two pH values (5.5 and 7.4) using reversed-phase high-performance liquid chromatography (RP-HPLC) [1,2]. Retention behavior was tested on HP 1100 HPLC chromatograph, using column Zorbax Eclipse Plus C8 (150 X 4.6 mm, 5 µm particle size). Mobile phase consisted of acetonitrile and phosphate buffer (pH was adjusted to 5.5 or 7.4). Each compound was tested in four different ratios of acetonitrile and buffer (acetonitrile ranged from 20% to 65%). Column temperature was 25 °C, flow rate 1 mL/min, injection volume 20 µL and detection was performed at 254 nm. For each compound, capacity factor (*k*) was calculated and *logk* values were plotted against percentage of acetonitrile. Finally, following chromatography parameters were calculated: $logk_w$ (y-axis intercept), *a* (slope) and ϕ_0 ($-logk_w/a$).

Derivatives with the highest lipophilicity were TEL-28 and NDL-20, whereas NZ97 had the lowest lipophilicity (at both pH values, Figure 1). The majority of compounds possess similar or slightly different lipophilicities at both pH values, but the highest differences were observed for TAZ-7, LMD-17 and NCH-4d, which could significantly affect their biological properties (particularly gastrointestinal absorption, distribution and biological activity).

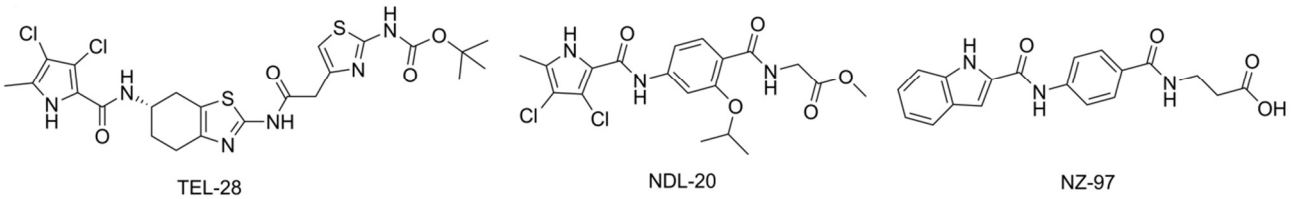


Figure 1: Chemical structures of underlined compounds

References

[1] Pallicer, J. M.; Sales, J.; Roses, M.; Rafols, C.; Bosch, E. Lipophilicity assessment of basic drugs (log Po/w determination) by a chromatographic method. *J.Chromatogr.A*, **2011**,1218, 6356-68.

[2] Han, S.-Y.; Qiao, J.-Quin.; Zhang, Y.-Y.; Yang, L.-L.; Lian, H.-Z.; Ge, X.; Chen, H.-Y. Determination of n-octanol/water partition coefficient for DDT-related compounds by RP-HPLC with a novel dual-point retention time correction. *Chemosphere*, **2011**, *83*, 131-6.

Poster communication 6 – WG 1

Design and synthesis of benzothiazole-based dual DNA gyrase and topoisomerase IV inhibitors with broad spectrum antibacterial activity

Martina Durcik,[a] Ákos Nyerges,[b] Žiga Skok,[a] Nace Zidar,[a] Janez Ilaš,[a] Päivi Tammela,[c] Tamás Révész,[b] Gábor Draskovits,[b] Danijel Kikelj,[a] Csaba Pál,[b] Tihomir Tomašič,[a] Lucija Peterlin Mašič[a]

[a] *University of Ljubljana, Faculty of Pharmacy, Aškerčeva cesta 7, 1000 Ljubljana, Slovenia*

[b] *Synthetic and Systems Biology Unit, Institute of Biochemistry, Biological Research Centre of the Hungarian Academy of Sciences, Szeged H-6726, Hungary*

[b] *Centre for Drug Research, Faculty of Pharmacy, University of Helsinki, 00014 Helsinki, Finland*

martina.durcik@ffa.uni-lj.si

DNA gyrase and topoisomerase IV are validated targets for antibacterial drug discovery. These enzymes are highly homologous, thus offering an opportunity for dual-targeting to reduce the rate of resistance acquisition. They are heterotetramers composed of two catalytic GyrA/ParC subunits and two GyrB/ParE subunits with ATPase activity. The ATP-binding site became an attractive target especially after successful introduction of novobiocin into the therapy. However, novobiocin, which was the only marketed GyrB/ParE inhibitor until now, was later withdrawn from the clinic due to toxicity, low effectivity and rapid resistance-acquisition.

Using structure-based design, we have discovered and optimized several structural classes of potent GyrB and ParE inhibitors.[1-4] We optimized a series of benzothiazole-based potent dual DNA gyrase B and topoisomerase IV (ParE) inhibitors. The most potent compounds possess low µg/mL antibacterial activity against the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) as well as potent activity with MIC values lower than 0.5 µg/mL against many Gram-positive strains (e.g. *S. aureus*, *Streptococcus pneumoniae*, *Clostridium difficile*, *Neisseria gonorrhoeae*, and several MRSA strains). They display remarkably low frequency-of-resistance (i.e., $<10^{-12}$ at 2 × MIC, for certain MRSA isolates), moreover, the most promising compounds show no cross-resistance with the fluoroquinolones.

References

[1] Tomašič, T.; Katsamakas, S.; Hodnik, Ž.; et al. Discovery of 4,5,6,7-tetrahydrobenzo[1,2-*d*]thiazoles as novel DNA gyrase inhibitors targeting the ATP-binding site. *J. Med. Chem.*, **2015**, *58*, 5501-5521.

[2] Zidar, N.; Macut, H.; Tomašič, T.; et al. *N*-Phenyl-4,5-dibromopyrrolamides and *N*-phenylindolamides as ATP competitive DNA gyrase B inhibitors: Design, synthesis, and evaluation, *J. Med. Chem.*, **2015**, *58*, 6179-6194.

[3] Gjorgjieva, M.; Tomašič, T.; Barančoková, M.; et al. Discovery of benzothiazole scaffold-based DNA gyrase B inhibitors. *J. Med. Chem.*, **2016**, *59*, 8941-8954.

[4] Durcik, M.; Lovison, D.; Skok, Ž.; et al. New *N*-phenylpyrrolamide DNA gyrase B inhibitors : optimisation of efficacy and antibacterial activity. *Eur. J. Med. Chem.*, **2018**, *154*, 117-132.

Poster communication 7 – WG 1

Radiofluorination using metal fluorides: a way to radiolabel DOTA-conjugates?

Cyril FERSING,[a] Ahlem BOUHLEL,[b] Philippe GARRIGUE,[c] Benjamin GUILLET.

[a] *Aix-Marseille Université, CNRS, ICR UMR 7273, Laboratoire de Pharmaco-Chimie Radicalaire, Faculté de Pharmacie, Marseille.*

[b] *Aix-Marseille Université, INSERM 1263, INRA 1260, C2VN, Faculté de Pharmacie/CERIMED, Marseille.*

cyril.fersing@inserm.fr

Fluorine-18 is amongst the most frequently used positron-emitting radionuclides for PET imaging.(1) Because of the non-metallic properties of this atom, radiofluorination implies covalent labeling strategies(2) that are hardly compatible with routine use. Overcoming this limitation, aluminum [^{18}F]fluoride chemistry is based on the formation of a $Al^{18}F^{2+}$ cation that can be complexed with a 9-membered cyclic chelator such as NOTA, NODA or their analogs. Due to the small size of the $Al^{18}F^{2+}$ cation, this radiolabeling methodology is poorly compatible with the 12-membered cyclic chelators like DOTA. Radiopharmaceutical preparation kits containing this type of complexing agent, such as SOMAKIT-TOC® (edotreotide), used for PET imaging of neuroendocrine tumors, cannot therefore be labeled with $Al^{18}F^{2+}$. Thus, in order to transpose this methodology to DOTA-conjugated molecules, the replacement of aluminum by larger metals was envisaged. Around 60 reaction tests involving indium, gadolinium, erbium or lutetium was carried out to optimize the reaction conditions of both the metal-[^{18}F]fluoride ($M^{18}F$) and the $M^{18}F$-DOTA complex formation. Two distinct strategies were considered: (i) the formation of $M^{18}F$ followed by its complexation with DOTA, and (ii) the synthesis of a M-DOTA complex followed by its radiolabeling using [^{18}F]fluoride. This work represents the starting point for the optimization of this original non-covalent radiolabeling approach with metal-[^{18}F]fluorides.

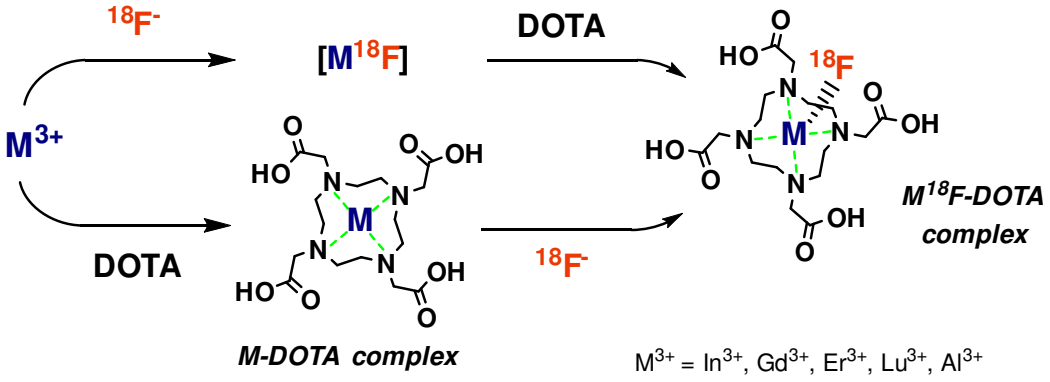


Figure 1: Considered strategies for the non-covalent radiofluoration of DOTA-conjugates.

References

[1] Alauddin, M. M. Positron emission tomography (PET) imaging with (^{18})F-based radiotracers. *Am J Nucl Med Mol Imaging.* **2011**, *2*, 55-76.

[2] van der Born, D.; Pees, A.; Poot, A. J.; Orru, R. V. A.; Windhorst, A. D., Vugts, D. J. Fluorine-18 labelled building blocks for PET tracer synthesis. *Chem Soc Rev.* **2017**, *46*, 4709-4773.

Poster communication 8 – WG 1

Targeted cyclodextrin-calixarene-based nanoparticles: a new nanomedical approach for the treatment of glioblastoma

Laura Gallego-Yerga,[a] Cristina de la Torre,[a] Carmen Ortiz Mellet,[b] José Manuel García Fernández,[b] Inmaculada Posadas,[a] Valentín Ceña.[a]

[a] *Neurodeath, Faculty of Medicine, University of Castilla-La Mancha, Albacete, Spain; CIBERNED-ISCIII, Madrid, Spain.*

[b] *Departament of Organic Chemistry, Faculty of Chemistry, University of Seville, Seville, Spain.*

lgallegoyerga@gmail.com

Cyclodextrins (CD) and calixarenes (CA) have the capacity to form host-guest superstructures and the possibility to be tailored to achieve a controlled non-covalent organization, which makes them privileged scaffolds to develop nanosystems. In this work we report the synthesis of nanocarriers based on CD-CA amphiphilic heterodimers which self-assemble in water to form nanospheres or nanocapsules.[1] These nanoparticles consist of an inner core composed by hydrophobic calix[4]arene (CA_4) units functionalized with alkyl chains, where hydrophobic drugs can be entrapped, and an external hydrophilic shell exposing β-cyclodextrin (βCD) motifs that allows the solubilization of the system and post-functionalization by complex inclusion formation. The potential of the new systems in nanomedicine is illustrated by their capacity to encapsulate and provide sustained release of anticancer drugs such as docetaxel, whose clinical applications are limited by its low water solubility and its toxicity to normal cells, and undergo modification with adamantane-armed glycoligands targeting the macrophage mannose receptor which is overexpressed in tumour-associated macrophages. The nanoparticles where characterized by Dynamic Light Scattering (DLS), AFM and cryo-TEM microscopy whereas *in vitro* studies demonstrated its potent anti-cancer activity in glioblastoma cell lines.[2]

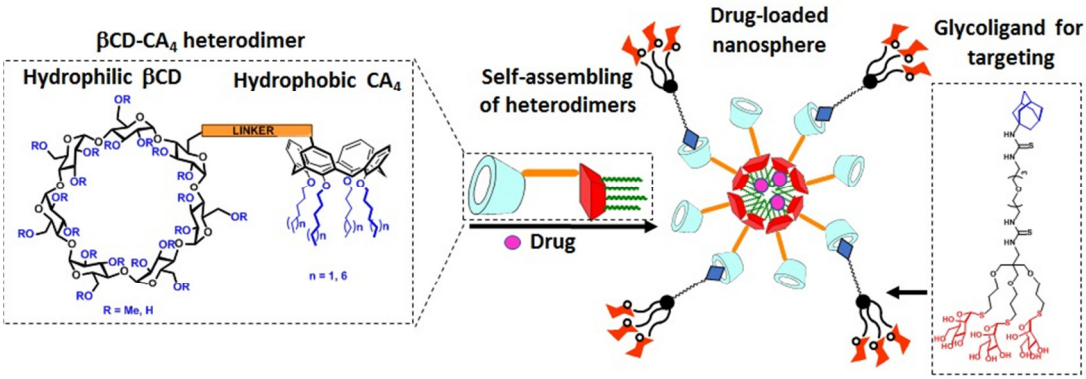


Figure 1: Self-assembling of βCD-CA_4 based heterodimers to form drug-loaded nanospheres.

References

[1] Gallego Yerga, L.; Posadas, I.; De la Torre, C.; Ruiz Almansa, J.; Sansone, F.; Ortiz Mellet, C.; Casnati, A.; García Fernández, J.M.; Ceña, V. Docetaxel-loaded nanoparticles assembled from β-cyclodextrin/calixarene giant surfactants: physicochemical properties and cytotoxic effect in prostate cancer and glioblastoma cells. *Frontiers in Pharmacology*, **2017**, *8* (249), 1-13.

[2] Jativa, P.; Ceña, V. Use of nanoparticles for glioblastoma treatment: a new approach. *Nanomedicine (Lond.)*, **2017**, 12 (20), 2533–2554.

Poster communication 9 – WG 1

Synthesis of fluorescent ligands to investigate μ-opioid receptor dimerization

Christian Gentzsch[a], Kerstin Seier[b], Antonios Drakopoulos[a], Marie-Lise Jobin[b], Damien Maurel[c], Rémy Sounier[c], Sebastien Granier[c], Davide Calebiro[b,d,e], Michael Decker[a]

[a] *Institute of Pharmacy and Food-Chemistry, University of Würzburg*

[b] *Institute of Pharmacology and Toxicology, University of Würzburg*

[c] *Institut de Génomique Fonctionnelle, Université de Montpellier*

[d] *Institute of Metabolism and Systems Research, University of Birmingham*

[e] *Centre of Membrane Proteins and Receptors (COMPARE), Universities of Birmingham and Nottingham*

christian.gentzsch@uni-wuerzburg.de

The μ-opioid receptor (μ-OR) represents an important target in medicinal chemistry, particularly for its ability to modulate pain transmission. The question, if this receptor exists as monomer or dimer, is highly debated and answers may be crucial to completely understand the variety of complex effects mediated by the μ-OR.[1,2] In this study, we chose a ligand based on the antagonist E-*p*-Nitrocinnamoylamino-dihydrocodeinone and attached two fluorophores on the core by a tetraglycine-linker (Figure 1).

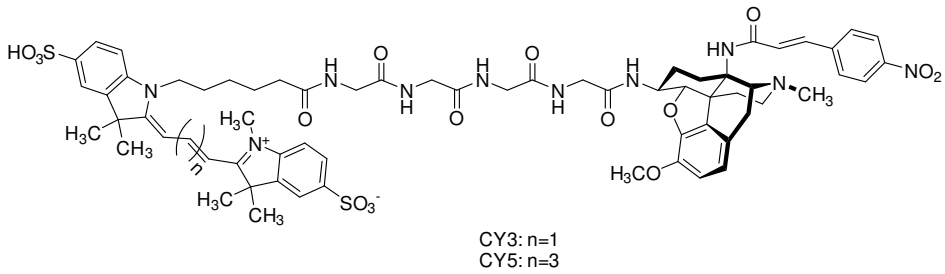


Figure 1: Structure of fluorophore-labelled ligands.

Despite these chemical modifications, the fluorescent ligands still exhibit good affinity values (K_d = 112 ± 31 and 45 ± 9 nM). Furthermore, the selectivity for the μ-OR over δ- and κ-subtypes has been retained, making the compounds suitable to investigate μ-OR dimerization by single-molecule microscopy techniques. With the help of two-colour single-molecule movies combined with computation methods, μ-dimerization events have been precisely traced.[3,4] It could be shown by single-particle tracking and computational analyses, that μ-ORs labelled with the fluorescent ligands on the surface of living cells show a heterogenous diffusion behavior. The two-colour experiments revealed rare co-localization of two receptors labelled with each dye, indicating an absence of stable dimers.

References

[1] I. Gomes, B. Jordan, A. Gupta, N.Trapaidze, V. Nagy, L. Devi, *J Neurosci.* **2000**, *20 (22)*, RC110.

[2] A. Kuszak, S. Pitchiaya, J. P. Anand, H. I. Mosberg, N. G. Walter, R. K. Sunahara, *J Biol Chem.* **2009**, *284*, 26732-26741.

[3] T. Sungkaworn, M.-L. Jobin, K. Burnecki, A. Weron, M. J. Lohse, D. Calebiro, *Nature* **2017**, *550*, 543-547.

[4] D. Calebiro, F. Rieken, J. Wagner, T. Sungkaworn, U. Zabel, A. Borzi, E. Cocucci, A. Zürn, M. J. Lohse, Proc Natl Acad Sci U S A **2013**, *110*, 743-748.

Poster communication 10 – WG 1

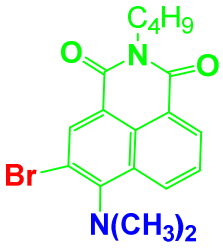
Poly(propyleneamine) dendrimers modified with 3-bromo-4-dimethylamino-1,8-naphthalimide units as antimicrobial agents

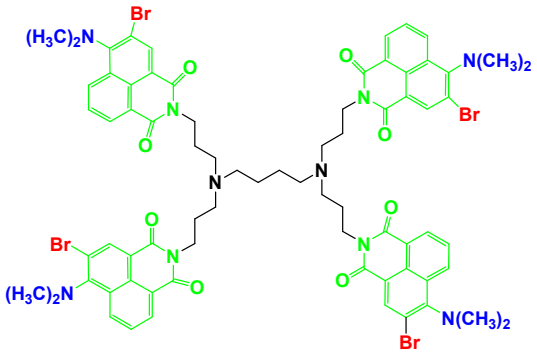
Ivo Grabchev[a], Desislava Staneva[b], Evgenia Vasileva-Tonkova[c]

[a]*Sofia University "St. Kliment Ohridski", Faculty of Medicine, 1407 Sofia, Bulgaria*
[b]*University of Chemical Technology and Metallurgy, 1756 Sofia, Bulgaria*
[c]*The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria*
[d]*Institute of Experimental Morphology, Pathology and Anthropology with Museum, Bulgarian Academy of Sciences, Acad. G. Bonchev Street, Bl. 25, Sofia 1113, Bulgaria*

i.grabchev@chem-uni-sofia.bg

1,8-naphthalimides and their derivatives are an important heterocyclic of class organic compounds finding diverse pharmacological and biomedical applications. In the last years especial attention has been paid to investigations on their capacities as antibacterial, antifungal, antiviral, anti-inflammatory or anticancer therapeutics. Recently dendrimers have been a part of a very important research area due to their promising biological and biomedical activities. Their unique structure facilitates an important role in the fields of nanomedicine, pharmaceutical and medical chemistry. These compounds are also considered an effective tool for anticancer therapy or drug delivery systems. Complimenting those two interesting structures into one molecule enables the preparation of new compounds containing a large number of substances with considerably enhanced biological activity.





In the present study, the synthesis and characterisation of a new poly(propyleneamine) modified with 3-bromo-4-dimethylamino-1,8-naphthalimides units and its monomer analogue 3-bromo-4-dimethylamino-N-butyl-1,8-naphthalimide have been presented. The antimicrobial activity of the new compounds has been investigated against different pathogens and human cancer cells. Both compounds have been deposited onto the surface of a 100% cotton fabric and tested viewing their potential application in production of antibacterial wound dressings.

Acknowledgments: *The authors acknowledge Grant № КОСТ, 01/3-2017, Scientific Research Fund, Ministry of Education and Science of Bulgaria.*

Poster communication 11 – WG 1

Structural and pharmacological studies of Multi-Target ligands of aminergic GPCRS for potential treatment of mental diseases

Agnieszka A. Kaczor,[a,b] Magda Kondej,[a] Piotr Stępnicki,[a] Oliwia Koszła[a], Justyna Żuk,[a] Agata Bartyzel,[c] Katarzyna M. Targowska-Duda,[d] Tomasz M. Wróbel,[a] Damian Bartuzi[a], Ewa Kędzierska[e], Grażyna Biała,[e] Dariusz Matosiuk,[a] Andrea G. Silva,[f] Marián Castro[f]

[a]Department of Synthesis and Chemical Technology of Pharmaceutical Substances, [d]Department of Biopharmacy and [e]Department of Pharmacology and Pharmacodynamics, Medical University of Lublin, 4A Chodźki St., PL-20059 Lublin, Poland; [b]University of Eastern Finland, Yliopistonranta 1, FI-70211 Kuopio, Finland; [c]Department of General and Coordination Chemistry, M. Curie-Skłodowska University, M. Curie-Skłodowskiej Sq. 2, PL-20031 Lublin, Poland; [f]Department of Pharmacology, Universidade de Santiago de Compostela, , Avda de Barcelona, E-15782 Santiago de Compostela, Spain

agnieszka.kaczor@umlub.pl

Central nervous system (CNS) diseases are an important medical, economic and social problem and belong to most costly medical conditions. In particular, mental diseases, such as schizophrenia, bipolar disorder and depression are cured today with moderate success. As a part of our research on CNS agents we performed structure-based virtual screening to identify multi-target ligands of aminergic G protein-coupled receptors with affinity to different dopamine and serotonin receptors.[1] As a result we identified 10 active compounds, confirmed their affinity *in vitro* and four of them were studied as otential antipsychotics while other three were investigated as potential antidepressants. Here we present structural (X-ray and molecular modeling), thermal and pharmacological (*in vitro* and *in vivo*) studies of these compounds. The compounds were docked to the orthosteric binding sites of respective receptors and molecular dynamics simulations of the obtained ligand-receptor complexes were performed. Next, the compounds were subjected to *in vivo* evaluation. All the potential antipsychotics (D2AAK1-D2AAK4) decrease amphetamine-induced hyperactivity (when compared to the amphetamine-treated group) measured as spontaneous locomotor activity in mice. In addition, passive avoidance test demonstrated that all the compounds improve memory consolidation after acute treatment in mice. Elevated plus maze tests indicated that all the compounds induce anxiogenic activity 30 minutes after acute treatment. 60 minutes after administration D2AAK1 displays anxiolytic activity, D2AAK3 no activity and the anxiogenic activity continues for D2AAK2 and D2AAK4. Potential antidepressants (SER1-SER3) were tested for their anti-depressive properties in the forced swimming test and for their anxiolytic properties as above. In order to optimize the structures of the lead compounds, we also designed, synthesized and tested their modifications.

References

[1] Kaczor, A.A.; Silva, A.G.; Loza, M.I.; Kolb, P.; Castro, M.; Poso, A. Structure-based virtual screening for dopamine D_2 receptor ligands as potential antipsychotics. *ChemMedChem*, **2016**, *11*, 718-729.

Poster communication 12 – WG 1

Piperazine derivatives as a novel active histamine H_3 receptor ligands

Katarzyna Szczepańska,[a] Tadeusz Karcz,[a] Szczepan Mogilski,[b] Kamil J. Kuder,[a] Stefanie Hagenow,[c] Magdalena Kotańska,[b] Holger Stark,[c] Katarzyna Kieć-Kononowicz[a]

[a] *Department of Technology and Biotechnology of Drugs,* [b] *Department of Pharmacodynamics, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, Kraków 30-688, Poland*

[c] *Institute of Pharmaceutical and Medicinal Chemistry, Heinrich-Heine-University Düsseldorf, Universitaetsstr. 1, 40225 Düsseldorf, Germany*

szczepanskatarzyna@gmail.com

Histamine H_3 receptors (H_3R) are constitutively active G-protein coupled receptors (GPCR) mostly expressed in CNS. Interaction with these receptors results in modulation of histamine levels as well as that of other neurotransmitters. Therefore, blockade of these receptors might provide useful pharmacological target in treatment of many CNS-based diseases such as schizophrenia, Alzheimer´s and Parkinson's diseases, obesity, narcolepsy and attention-deficit hyperactivity disorder (ADHD) [1], also as dual or multiple acting ligands [2].

Undoubtedly, the imidazole ring replacement with other heterocyclic moieties was a milestone in the search for new histamine H_3R ligands. The piperazine moiety is such a replacement, being a significant versatile chemical scaffold in rational drug design for numerous GPCR ligands.

Based on the results of the research so far, it is assumed that the 4-pyridylpiperazine moiety in the basic part of the compound determines their high affinity at and selectivity for human H_3R. The position of the nitrogen atom in an aromatic ring attached to piperazine moiety has turned out to be a key structural element for suitable interaction with its biological target [3]. In order to determine the influence of substituents located in the "eastern part" of the molecule, structural modifications of previously obtained compounds including replacement of branched alkyl benzene substituents, with bulky aromatic groups were undertaken. Moreover, subsequent extension of alkyl linker in the range of five to eight methylene groups was also performed. Taking into account structural similarity of our compounds to other GPCR ligands, determination of affinity to histamine H_1, dopamine D_2 and α_1 adrenergic receptors was also carried out.

We kindly acknowledge the generous support of National Science Center, Poland granted on the basis of decision No. 2016/23/N/NZ7/00469.

[1] Łażewska, D.; Kieć-Kononowicz, K. New developments around histamine H_3 receptor antagonists/inverse agonists: a patent review (2010 – present). *Expert Opin. Ther. Patents*. **2014**, 24(1): 89-111.
[2] Bautista-Aguilera, ÓM.; et.al. Multitarget-Directed Ligands Combining Cholinesterase and Monoamine Oxidase Inhibition with Histamine H_3R Antagonism for Neurodegenerative Diseases. *Angew. Chem. Int. Ed*. **2017**; 56: 12765-12769.
[3] Szczepańska, K.; et.al. Synthesis and biological activity of novel *tert*-butyl and *tert*-pentylphenoxyalkyl piperazine derivatives as histamine H_3R ligands. *Eur. J. Med. Chem*. **2018**, 152: 223-234.

Poster communication 13 – WG 1

Isoquinolinequinones as Multitargeted Anticancer Agents

Ryan D. Kruschel,[a] Florence O. McCarthy,[a]

[a]*School of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.*

r.kruschel@umail.ucc.ie

The isoquinolinequinone (IQQ) pharmacophore is a privileged framework in known cytotoxic natural product metabolites, caulibugulones and mansouramycins both isolated from marine sponges (Figure 1).[1] Both series exhibit cytotoxicity in the sub-micromolar range across multiple cancer cell lines including renal, breast and ovarian. A multi-targeted approach is often adopted to explain the IQQ's potent cytotoxicity. This includes mitochondrial destruction through redox cycling and enzyme inhibition through electrophilic addition to critical amino acids *in vivo* for example in cell division cycle 25 (CDC25) isoforms, whose function is crucial in normal cell cycle regulation.[2,3,4]

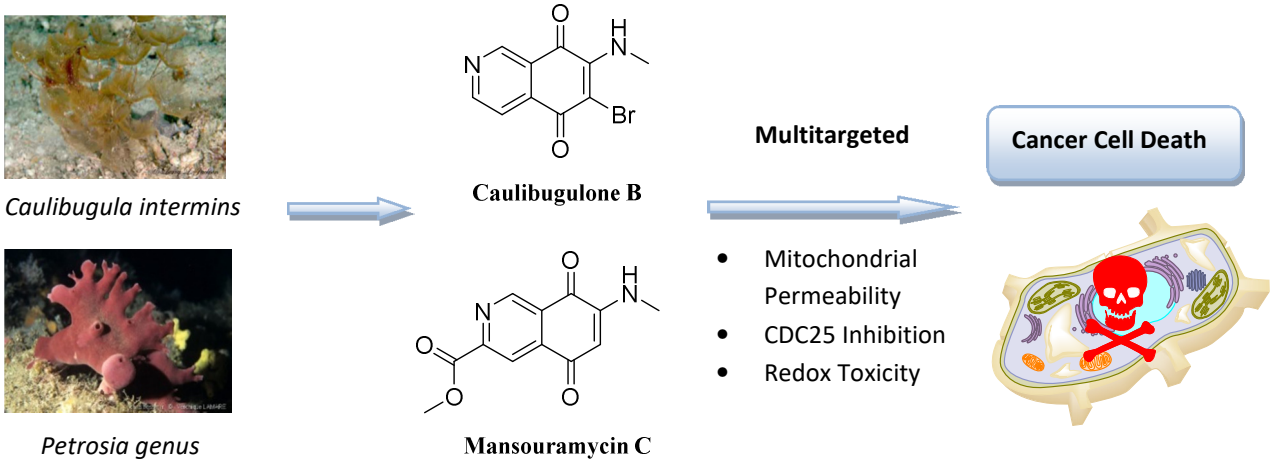


Figure 1: Marine metabolites Caulibugulone B (IC_{50} 0.82 µM against the Murine IC-2^{WT} Cell Line) and Mansouramycin C (IC_{50} 0.089 µM (mean of 36 tumour cell lines))

We report on the generation of a versatile IQQ framework utilising a one-pot silver (I) oxide mediated oxidation and the discovery of a potent novel anticancer framework. A library of novel IQQ's were synthesised analogous to known caulibugulones and mansouramycins exhibiting nM cytotoxic activity against breast, melanoma and ovarian cancer cell lines. A lead compound has been identified to conduct further structure activity relationship studies in view of progression towards clinical development.

Financial Support :This work was supported by the Irish Research Council (Project I.D. GOIPG/2015/3148)

References

1. Milanowski, J.D. *et al*., *Journal of Natural Products,* **2004**, *67*, 70-73
   Hawas *W.U. et al, Journal of Natural Products*, **2009**, *72*, 2120-2124
2. Kuang S. *et al*, *Oncotarget*, **2017**, 61, 104057-104071
3. Brisson M. *et al.*, *Molecular Pharmacology*, **2007**, *71*, 184-192
4. K. Kristjansdottir k. *et al.*, *Chemistry & Biology*, **2004,** *11 (8)*, 1043-1051

Poster communication 14 – WG 1

Human histamine H3 receptor affinity and choline esterase inhibitory activities of (homo)piperidinyl-hexyloxybenzophenone derivatives

Dorota Łażewska,[a] Paula Zaręba,[b] Stefanie Hagenow,[c] Maria Kaleta,[a] Barbara Malawska[b], Holger Stark[c], Katarzyna Kieć-Kononowicz[a]

[a]Department of Technology and Biotechnology of Drugs, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland; [b]Department of Physicochemical Drug Analysis, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland; [c]Institute of Pharmaceutical and Medicinal Chemistry, Heinrich-Heine-University Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf , Germany

dlazewska@cm-uj.krakow.pl

Histamine H_3 receptors (H_3Rs) are mostly expressed in CNS and regulate the release of histamine itself and other neurotransmitters (e.g., acetylcholine, dopamine or serotonin). Blockade of these receptors could be useful in the treatment of various central nervous system (e.g. Alzheimer's Disease), metabolic, pain and allergic disorders.[1] So far, many structurally diverse H_3R ligands have been synthesized and pharmacologically evaluated. As a continuation of our previous works we synthesized a series of (homo) piperidinyl-hexyloxybenzophenone derivatives. Compounds were designed as multi-target-directed ligands (MTDLs) combining antagonism of H_3Rs with inhibitory activities at cholinesterases (acetylcholinesterase, AChE, and butyrylcholinesterase, BuChE). H_3Rs affinity of compounds was evaluated at recombinant human H_3Rs stably expressed in HEK-239 cells whereas cholinesterase inhibitory activity (AChE and BuChE) was evaluated using the method established by Ellman et al.[2] Tested compounds showed moderate to good human H_3R affinities (25 nM ≤ K_i hH_3R ≤ 162 nM), and most of them exhibited cholinesterases inhibitory activities with IC_{50} values in low micromolar range. Generally homopiperidine derivaitves were stronger cholinesterase inhibitors than corresponding piperidine analogues although showing (with one except) comparable human H_3R affinities. Compound **E321** (4-(-6-(azepan-1-yl)hexyloxy)phenyl)(4-fluorophenyl)methanone) was in this respect of special interest (**Figure 1**).

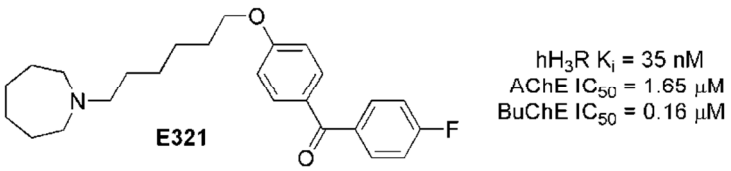


Figure 1: Structure and biological activity of **E321**.

Acknowledgement: Partly supported by National Science Center on the basis of decision DEC-2016/23/B/NZ7/02327.

References

[1]Panula P, Chazot PL, Cowart M, Gutzmer R, Leurs R, Liu WLS, Stark H, Thurmond RL, Haas HL. International Union of Basic and Clinical Pharmacology. XCVIII. Histamine Receptors. *Pharmacol. Rev.* **2015**; *67*, 601-655.

[3]Ellman, G.L.; Courtney, K.D.; Andres, V.; Featherstone, R.M. A new and rapid colorimetric determination of acetylcholinesterase activity, *Biochem. Pharmacol.* **1961**, *7*, 88-95.

Poster communication 15 – WG 1

DNA-binding and anticancer evaluationof bis- and tris-heteroleptic RU-diimine complexes bearing 2-(2-pyridyl)-quinoxaline.

Christiana A. Mitsopoulou[a]* Athanasios Zarkadoulas[a], Maria Koukouvitaki[a], Luciano Marchio[b], Eleni K. Efthimiadou[c.]

[a], *Inorganic Chemistry Laboratory, Chemistry Department, National and Kapodistrian University of Athens, Panepistimiopolis, Zografou 157 71, Greece.*

[b] *Dipartimento di Chimica, Università degli Studi Parma, Parco Area delle Scienze 17A, I43124 Parma, Italy*

[c] Institute of Nanoscience and Nanotechnology, National Center for Scientific Research Demokritos

cmitsop@chem.uoa.gr

Ruthenium diimine complexes have long attracted interest due to their various applications in catalysis[1] and in metal-based drugs[2]. More specifically, ruthenium diimine complexes exhibit both telomerase and topoisomerase inhibition and can induce apoptosis in cancer cells in various stages of replication cell cycle via intercalation or after photoexcitation, leading to applications in photodynamic therapy[3].

Focusing on the ligand framework, peripheral functionalization of diimines has led to the development of multi-potent metal based drugs containing third row transition elements bearing dipyridophenazine (dppz), 1,10-phenanthroline-5,6-dione[3], or quinoxaline ligands [4]. More specifically, 2-(2-pyridyl)-quinoxaline (pq) has proved a versatile ligand that can bind to a plethora of transition metals. The quinoxaline moiety is found in many molecules of medicinal interest that exhibit antibacterial, antiviral, antifungal, antihelmintic, and anticancer properties[4].

Inspired by proven affinity of pq-containing metal complexes for DNA and the diversity of opportunities opening from incorporating a tris-heteroleptic ligand manifold around Ru(II), in this work we report the preparation and characterization of the tris–heteroleptic $[Ru(bpy)(phen)(pq)](PF_6)_2$ complex along with its $[Ru(bpy)_2(pq)](PF_6)_2$ counterpart. Both complexes have been structurally characterized and the interaction of the tris-heteroleptic complex with CT-DNA and against MCF-7, U87-MG, and HEK-293 cancer cells is reported. Moreover, its ability to localize inside the cell in vitro was revealed by confocal microscopy.

References

[1] Elgrishi,N., Chambers, M.B., Wang, X., Fontecave, M, Chem. Soc. Rev., **2017**, 761-796.

[2] White, K., Schmehl, R.H, Turro, C., Inorganica Chim. Acta, **2017**,454, 7–20.

[3]Kaplanis, M., Stamatakis, G., Papakonstantinou, V.D., Paravatou-Petsotas, M., Demopoulos, C.A. . Mitsopoulou, C.A, J. Inorg. Biochem., **2014**, 135, 1–9.

[4]Mitsopoulou, C.A. Dagas, C.E., Makedonas, C., J. Inorg. Biochem. **2008**, 102, 77–86

Poster communication 16 – WG 1

3-Phenylcoumarin as a Scaffold for Building Potent Inhibitors for 17-β-Hydroxysteroid Dehydrogenase 1 and Monoamine Oxidase B

Pekka A. Postila[a], Sanna Rauhamäki[a], Sanna Niinivehmas[a], Mira Ahinko[a], Pasi Koskimies[b], Markku Pasanen[c], Risto O. Juvonen[c], Hannu Raunio[c], Juhani Huuskonen[d], Olli T. Pentikäinen[a,e]

[a] *Depart. of Biological and Environmental Science & Nanoscience Center, University of Jyväskylä, Jyväskylä, Finland.*
[b] *Forendo Pharma Ltd., Turku, Finland.*
[c] *School of Pharmacy, University of Eastern Finland, Kuopio, Finland.*
[d] *Dept. of Chemistry & Nanoscience Center, University of Jyväskylä, Jyväskylä, Finland.*
[e] *MedChem.fi, Institute of Biomedicine, University of Turku, Turku, Finland.*
pekka.a.postila@jyu.fi

3-phenylcoumarin is a privileged scaffold that can be functionalized via carefully selected substitutions (R1-R6 in Figure 1) to block various biological targets with both selectivity and potency.

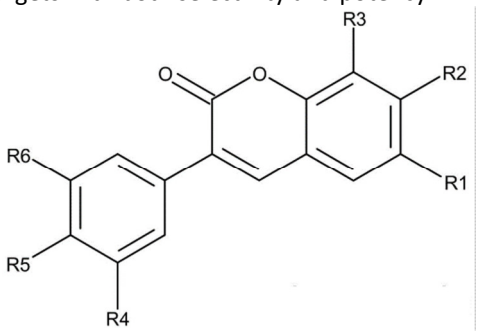


Figure 1: 2D structure of 3-phenylcoumarin.

Here, this malleability of the 3-phenylcoumarin is demonstrated using 17-β-hydroxysteroid dehydrogenase 1 (HSD1)[1] and monoamine oxidase B (MAO-B)[2] as the drug discovery targets. Potent HSD1 inhibitors, preventing selectively the estradiol synthesis in the sulphatase pathway, have potential for breast cancer and endometriosis treatment. Likewise, novel MAO-B inhibitors could be used to treat dopamine-linked diseases such as Parkinson's disease. A vast set of 3-phenylcoumarin analogs with diverse substitutions at the ring systems were designed de novo or using virtual combinatorial chemistry and synthetized using microwave chemistry. With the HSD1, five analogs inhibit the enzyme at 5 µM and three of them at 1 µM. With the MAO-B, the analogs inhibit the enzyme at 100 nM-1 µM and, notably, one of them produced IC50 value of 56 nM. A docking-based structure-activity relationship analysis was done for the analogs using the activity data acquired for both of the target enzymes. Furthermore, the cross-reactivity and selectivity of the analogs was tested for a specific subset of enzymes with known coumarin activity such as estrogen receptor, aromatase, cytochrome P450 1A2, MAO-A and HSD2. This comprehensive analysis led to the design and discovery of 3-imidazolecoumarin as a potent aromatase inhibitor. As a whole, the results show that the 3-phenylcoumarin is a suitable scaffold for building small-molecule inhibitors for blocking both HSD1 and MAO-B activity while retaining a necessary level of selectivity.

References

[1] Niinivehmas, S.; Postila, P.A.; Rauhamäki, S.; Manivannan, E.; Kortet, S.; Ahinko, M. *et al*., Blocking oestradiol synthesis pathways with potent and selective coumarin derivatives. *J. Enzyme Inhib. Med. Chem.* **2018**, *33*, 743.
[2] Rauhamäki, S.; Postila, P.A.; Niinivehmas, S.; Kortet, S.; Schildt, E.; Pasanen, M. *et al*., Structure-Activity Relationship Analysis of 3-Phenylcoumarin-Based Monoamine Oxidase B Inhibitors. *Front. Chem.* **2018**, *6*, 1.

Poster communication 17 – WG 1

A cascade reaction based Multi-Target Salen-Manganese complexes for controlling ROS damage

Lara Rouco,[a] Ana M. González-Noya,[b] Rosa Pedrido,[b] Rebeca Alvariño,[c] Luis M. Botana,[c] Marcelino Maneiro[a]

[a] Dept. de Química Inorgánica, Facultade de Ciencias, Campus Terra, University of Santiago de Compostela, Lugo, Spain; [b] Dept. de Química Inorgánica, Facultade de Química, Campus Vida, University of Santiago de Compostela, Santiago de Compostela, Spain; [c] Dept. de Farmacología, Facultade de Veterinaria, Campus Terra, University of Santiago de Compostela, Lugo, Spain.

lara.rouco.mendez@usc.es

Salen-manganese complexes are known as multi-target antioxidant agents[1] which can behave as SOD, catalases or peroxidases mimics. We have studied the neuroprotective effects of six of these artificial models in SH-SY5Y neuroblastoma cells. Three of them can meaningfully improve the mitochondrial function and decreasing reactive oxygen species levels. During studies aimed to getting a better understanding of the kinetics of the processes involved in this antioxidant behavior, evidences were found showing a cascade reaction pathway in which the MnSB (SB = Schiff base) react with the photochemically generated $OH^{\bullet}$ radicals[2] yielding a new MnSB* species (Figure 1). Interestingly, although the MnSB parent compounds act as $OH^{\bullet}$ radical scavengers, they cannot disproportionate hydrogen peroxide; but, the MnSB* complexes formed in the previous step behave as efficient catalase mimics, inducing the formation of oxygen and water from hydrogen peroxide. As a result of this cascade process, MnSB and MnSB* detoxify $OH^{\bullet}$ radicals and H_2O_2, respectively.

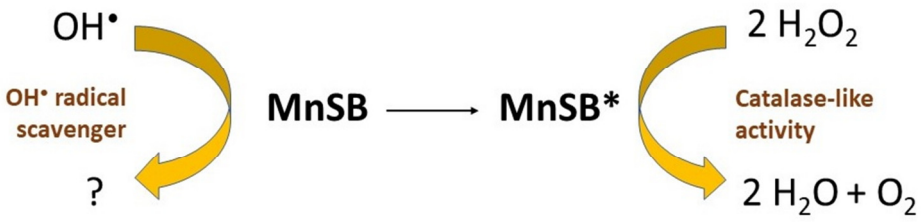


Figure 1

References

[1] Bani, D.; Bencini, A. Developing ROS scavenging agents for pharmacological purposes: recent advances in design of manganesebased complexes with anti-inflammatory and anti-nociceptive activity. *Curr. Med. Chem*., **2012**, *19*, 4431−4444.

[2] Liberato, A.; Fernández-Trujillo, M. J.; Máñez, A.; Maneiro, M.; Rodríguez-Silva, L.; Basallote, M. G. Pitfalls in the ABTS peroxidase activity test: interference of photochemical processes. *Inorg. Chem*., **2018**, *57*, 14471-14475.

Poster communication 18 – WG 1

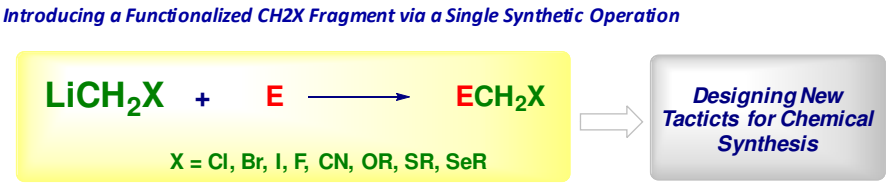
New Concepts in Synthetic Medicinal Chemistry: from Chemoselectivity to Applications

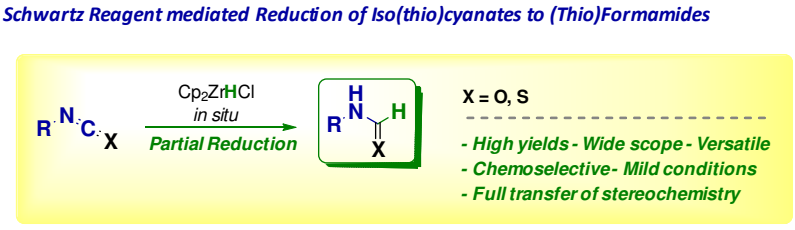
Raffaele Senatore, Thierry Langer, Wolfgang Holzer, Ernst Urban and Vittorio Pace

Department of Pharmaceutical Chemistry, University of Vienna, Althanstrasse, 14, Vienna, Austria

raffaele.senatore@univie.ac.at

Herein, we present the reactivity of α-functionalized lithium reagents, including halocarbenoids, ($LiCH_2X$, X = Cl, Br, I, F, CN, OR^1, SR^1, SeR^1) as nucleophilic homologating agents towards several different electrophilic carbonyl-type compounds, with focus on Weinreb Amides. In addition, we disclose a reliable and high-yielding method for preparing various functionalized (Thio)Formamides through the chemoselective reduction of Iso(thio)cyanates mediated by the Schwartz reagent.





Bibliographic references:

(a) Castoldi, L.; Monticelli, S.; Senatore, R.; Ielo, L.; Pace, V., *Chem. Commun*. **2018**, 54, 6692.
(b) Pace, V.; Castoldi, L.; Holzer, W., *J. Org. Chem.* **2013**, 78, 7764
(c) Pace, V.; Holzer, W.; Verniest, G.; Alcántara A. R.; De Kimpe N., *Adv. Synth. Catal*. **2013**, 355, 919
(d) Mamuye A.D.; Castoldi L.; Azzena U.; Holzer W.; Pace V., *Org. Biomol. Chem.*, **2015**, 13, 1969
(e) Pace V.; Murgia I.; Westermayer S.; Langer T.; Holzer W., *Chem. Commun.*, **2016**, 52, 7584
(f) Senatore, R.; Ielo, L.; Urban, E.; Holzer, W.; Pace, V., *Eur. J. Org. Chem.*, **2018**, 2018, 2466
(g) Senatore, R.; Castoldi, L.; Ielo, L.; Holzer, W.; Pace, V., *Org. Lett*, **2018**, 20, 2685 - Highlighted in *Synfacts* **2018**, 14, 769
(h) Castoldi, L.; Holzer, W.; Langer, T.; Pace, V. Chem. Commun. **2017**, 53, 9498 - Highlighted in *Synfacts* **2017**, 13, 1185
(i) Castoldi, L.; Ielo, L.; Hoyos, P.; Hernáiz, M. J.; De Luca, L.; Alcántara, A. R.; Holzer, W.; Pace, V., *Tetrahedron*, **2018**, 74, 2211 - Highlighted in *Nat. Prod. Rep.* **2018**, 35, 496
(j) Pace, V.; Castoldi, L.; Holzer, W., *Chem. Commun*. **2013**, 49, 8383 - Highlighted in *Synfacts* **2013**, 9, 1218
(k) Pace, V.; Castoldi, L.; Mamuye, A. D.; Holzer, W., *Synthesis* **2014**, 46, 2897 - Feature Article
(l) Pace, V.; Monticelli, S.; De la Vega-Hernandez, K.; Castoldi, L., *Org. Biomol. Chem*. **2016**, 14, 7848
(m) De la Vega-Hernandez, K.; Senatore, R.; Miele, M.; Urban, E.; Holzer, W.; Pace, V.; ***Org. Biomol. Chem.*** **2018**, in press

Poster communication 19 – WG 1

Synthesis of 2-(7-hydroxy-4,8-dimethyl-2-oxo-2*H*-chromen-3-yl)acetate Derivatives With Potential Anticancer Activity

Lisa Sequeira ,[a]Rita Meleddu,[a]Elias Maccioni[a]

[a]*Department of Life and Environmental Sciences, University of Cagliari, Cagliari, Italy*

lisa.sequeira@unica.it

Carbonic anhydrases (CAs) are a class of metallo-enzymes that catalyze the reversible hydration of carbon dioxide into bicarbonate and a proton and are widely distributed in all living organisms[1, 2]. These enzymes are involved in numerous physiological processes such as ion transport, regulation of pH, bone resorption, and secretion of gastric, cerebrospinal fluid and pancreatic juice[3]. In mammals CAs have 16 different isoforms and multiple ones implicated in a range of diseases, including cancer[2]. In particular, the trans-membrane CAs IX and XII are key pH regulators that create a differential pH microenvironment within solid tumors and allow for tumor cell survival under stressful conditions[2].For this reason CAs became an increasing interest to researchers as drug targets, and, as a result, a number of CAs inhibitors have been designed[1]. Coumarins are a group of heterocyclic compounds commonly found in nature and have relevant pharmacological activity such as antiviral, antimycotic, and antitumor[4].

Accordingly, our project is focused in the development of CAs inhibitors based on the chromene scaffold. To achieve this goal several 2-(7-hydroxy-4,8-dimethyl-2-oxo-2*H*-chromen-3-yl)acetate derivatives (**Figure 1**) are being synthesized. The results obtained so far will be presented in this communication.

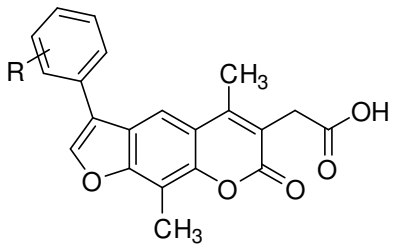


Figure 1: General structure of the compounds proposed for synthesis.

Acknowledgements:
L.Sequeira grant was supported by Univerità degli Studi di Cagliari (funds from the Italian Ministry of Education, University and Reasearch).

References

[1]Meleddu, R., et al., Tuning the Dual Inhibition of Carbonic Anhydrase and Cyclooxygenase by Dihydrothiazole Benzensulfonamides. Acs Medicinal Chemistry Letters, 2018. 9(10): p. 1045-1050.
[2]Singh, S., et al., Cancer Drug Development of Carbonic Anhydrase Inhibitors beyond the Active Site. Molecules, 2018. 23(5).
[3]Bianco, G., et al., N-Acylbenzenesulfonamide Dihydro-1,3,4-oxadiazole Hybrids: Seeking Selectivity toward Carbonic Anhydrase Isoforms. Acs Medicinal Chemistry Letters, 2017. 8(8): p. 792-796.
[4]Melis, C., et al., Targeting Tumor Associated Carbonic Anhydrases IX and XII: Highly Isozyme Selective Coumarin and Psoralen Inhibitors. ACS Medicinal Chemistry Letters, 2018. 9(7): p. 725-729.

Poster communication 20 – WG 1

From nature inspiration to multitarget small molecules: upgrading the activity of dietary cinnamic and benzoic acids for the treatment of neurodegenerative disorders

Pedro Soares,[a] Catarina Oliveira,[a] Sofia Benfeito,[a] Fernando Cagide,[a] Carlos Fernandes,[a] Jose Teixeira,[b] Ricardo Amorim,[b] Paulo J. Oliveira,[b] Fernanda Borges[a].

[a] *Department of Chemistry and Biochemistry, Faculty of Sciences University of Porto, Rua do Campo Alegre 1021/1055, 4169-007 Porto, Portugal.*

[b] *CNC – Center for Neuroscience and Cell Biology, University of Coimbra, UC-Biotech, Biocant Park, Cantanhede 3060-197, Portugal.*

pedro.soares@fc.up.pt and fborges@hotmail.com

Neurodegenerative disorders (NDs) are a group of age-related neurological disorders caused by a multiplicity of genetic and environmental factors, among others. In our days, NDs became more prevalent due to the steady increase of the world population life expectancy. Consequently, the social and economic burden over the families of the patients became more severe. Therefore, the discovery of therapeutic agents that could ameliorate or prevent neurodegenerative diseases, are urgently needed.

Hydroxycinnamic and benzoic acids, two families of naturally occurrent phenolic antioxidants, for long had a huge potential for the development of new therapies for NDs.[1] However, the low permeability and bioavailability of these antioxidants in biological systems for long limited their use in potential therapies. Hence, in the recent years, in order to create a novel therapeutic window for NDs our group designed a range of small molecules using hydroxycinnamic and benzoic acids present in human diet as a scaffold.[2–4] Based on this approach a range of hybrid compounds were obtained by linking the phenolic core to a triphenylphosphonium (TTP^+) cation via different size aliphatic chain spacers.

The new antioxidants retained the *in vitro* antioxidant activity of the parent compounds. Subsequent studies revealed that the new antioxidants were able to directly act in mitochondria preventing oxidative stress damage and inhibited the activity of cholinesterase enzymes (AChE and BChE) two relevant targets in a range of NDs.[2–4] In this communication are presented the most recent results obtain in our drug discovery efforts.

References (coloca 2 ou 3 artigos publicados por nos

1. Benfeito, S. *et al.* Antioxidant therapy: Still in search of the 'magic bullet'. *Mitochondrion* **13,** 427–435 (2013).
2. Teixeira, J. *et al.* Discovery of a new mitochondria permeability transition pore (mPTP) inhibitor based on gallic acid. *J. Enzyme Inhib. Med. Chem.* **33,** 567–576 (2018).
3. Teixeira, J. *et al.* Development of a mitochondriotropic antioxidant based on caffeic acid: Proof of concept on cellular and mitochondrial oxidative stress models. *J. Med. Chem.* **60,** 7084–7098 (2017).
4. Teixeira, J. *et al.* Development of hydroxybenzoic-based platforms as a solution to deliver dietary antioxidants to mitochondria. *Sci. Rep.* **7,** (2017).

Poster communication 21 – WG 1

Synthesis of the Tetracyclic Ring-System of Isocryptolepine and Regioisomers

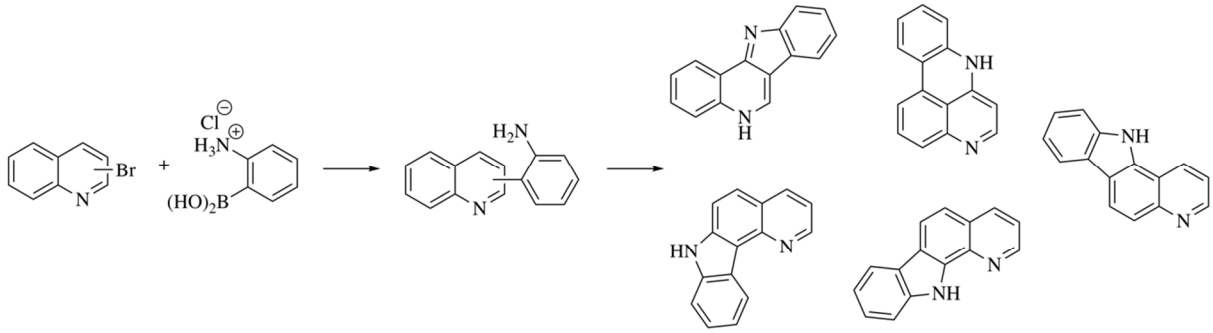
Katja S. Håheim,[a] Ida T. Urdal Helgeland,[a] Emil Lindbäck[a] and Magne O. Sydnes[a]

[a] *Faculty of Science and Technology, Department of Chemistry, Bioscience and Environmental Engineering, University of Stavanger, NO-4036 Stavanger, Norway*

magne.o.sydnes@uis.no

The quinoline core represents an attractive scaffold for the synthesis of compounds containing significant antimalarial and anticancer activity,[1] the natural alkaloids cryptolepine, neocryptolepine and isocryptolepine are examples of such compounds.[2,3] In an attempt to facilitate the synthesis of the aforementioned heterocycles and regioisomers, the activity of the quinoline ring-system was explored using readily available quinolines as a starting materials.

Under standard Suzuki-Miyaura cross-coupling conditions, the desired biaryls were synthesized starting from bromoquinolines and 2-aminophenylboronic acid hydrochloride. When subjecting the biaryls to intramolecular cyclization via a palladium-catalyzed C-H activation and C-N bond formation, the activity towards formation of the corresponding tetracyclic ring-systems varied tremendously. It was rationalized that the observed differences in reactivity could be explained by the electron density of the various carbons in the quinoline ring-system, with low electron density promoting cyclization.



References

[1]Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem*. **2010**, *45*, 3245-3264.

[2]Pousset, J. L.; Martin, M. T.; Jossang, A.; Bodo, A. *Phytochemistry* **1995**, *39*, 735-736.

[3]Sharaf, M. H. H.; Schiff, P. L.; Tackie, Jr. A. N.; Phoebe, C. H.; Johnson, Jr. R. L.; Minick, D.; Andrews, C. W.; Crouh, R. C.; Martin, G. E. *J. Heterocycl. Chem*. **1996**, *33*, 789-797.

Poster communication 22 – WG 1

From melatonergic and serotonergic receptors to the development of new therapeutics for Alzheimer's disease: a polypharmacological approach.

Sangeetha-Laura THIRUMARAN, Feng XIAO, Stéphane LEMAITRE, Jana SOPKOVA-DE OLIVEIRA SANTOS, Ronan BUREAU, Sylvain RAULT, Alban LEPAILLEUR, Christophe ROCHAIS.

Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN), Normandie Univ, UNICAEN, 14000 Caen, France

sangeetha-laura.thirumaran@unicaen.fr

Alzheimer's disease (AD) is the most common form of dementia diagnosed in 50 million of patients worldwide, for which the current treatments are only symptomatic ones. Among the biological targets implied in the physiopathology, melatonergic MT1 and MT2 and serotonergic 5-HT_{2c} receptors present a growing interest, as they have been shown to alleviate the symptoms through several actions such as the promotion of the non-amyloidogenic cleavage of the Amyloid Protein Precursor (APP).[1,2] As AD is a multifactorial disorder, a simultaneous action on these two types of receptors with Multi-Target Directed Ligands (MTDLs) could represent a novel therapeutic approach. In this objective, we screened our chemical library in order to identify original and potent MT1/MT2/5-HT_{2c} MTDLs. Then, we performed docking studies of the selected molecules, and using Norns[3], a new chemo-informatics software we developed, we extracted their structure-activity relationships (SARs) (Figure 1). All these results allow to understand the polypharmacological profile of this promising new series of compounds.

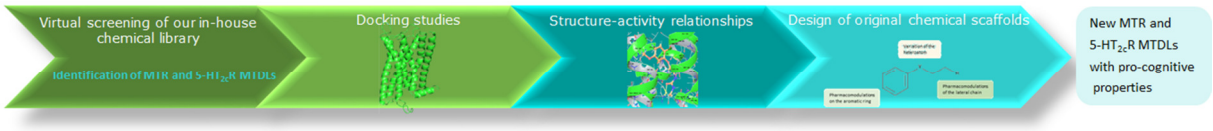


Figure 1. Design of new MTDLs of potential interest for Alzheimer's disease.

References

[1] Shukla, M.; Govitrapong, P.; Boontem, P.; Reiter, R.J.; Satayavivad, Mechanisms of Melatonin in Alleviating Alzheimer's Disease. J. *Curr Neuropharmacol.* **2017***, 15*, 1010- 1031.

[2] Švob Štrac, D.; Pivac, N.; Mück-Šeler, D. The serotonergic system and cognitive function. *Transl Neurosci.* **2016**, *7*, 35–49.

[3] Métivier, J.-P. ; Cuissart, B. ; Bureau, R. ; Lepailleur, A.*;* The Pharmacophore Network: A Computational Method for Exploring Structure-Activity Relationships from a Large Chemical Data Set*. J. Med. Chem*. **2018**, *61*, 3551-3564.

Poster communication 23 – WG 1

Prodrug MTDLs a potential strategy to treat Alzheimer's disease

François-Xavier Toublet,[a] Julien Lalut,[a] Cédric Lecoutey,[a] Audrey Davis,[a] Marc Since,[a] Bérénice Hatat,[a,b] Patrick Dallemagne,[a] Christophe Rochais[a]

[a] *Normandie Univ, UNICAEN, Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN), 14000 Caen, France*

[b] *CNRS, UMR-5203, Institut Génomique Fonctionnelle, F-34000 Montpellier, France*

francois-xavier.toublet@unicaen.fr

In 1906, Alois Alzheimer described the disease for the first time: his patient was suffering from particular memory disorders and present brain pathologic deposits. As a result of multiple research, the disease has proved to be more and more complex: amyloid plaque formation is due to hyperactivation of β-secretase resulting in the formation of the amyloid peptide (Aβ). In addition, hyperphosphorylation of the tau protein was observed, causing disaggregation of microtubules, a neuronal death and a decreased cholinergic transmission.[1] In order to treat Alzheimer's disease, a multitude of molecules have been developed but only 4 are currently marketed:[2] they are mostly acetylcholinesterase inhibitors (AChE), as for example rivastigmine a covalent pseudo-irreversible inhibitor, and a NMDA inhibitor, memantine. Facing the complexity of the disease and the lack of effectiveness of the current molecules, we have developed multi-target directed ligands (MTDLs) as new strategy based on a drug with several therapeutic targets of interest to treat a disease. Thus, our laboratory synthesized Donecopride[3] a molecule inhibiting AChE and simultaneously activating 5-HT_4 serotoninergic receptors.

My project consists in the development, the synthesis and the biological evaluation of new molecules with novel mechanism: prodrug MTDLs. Normally a prodrug is an inactive molecule activated by an enzyme.[4] In this context, the first target of interest is inactivated by prodrug, which finds itself cut in half, releasing the second active drug.

This poster will detail the various prodrugs and explain in more details this new notion of MTDL prodrugs.

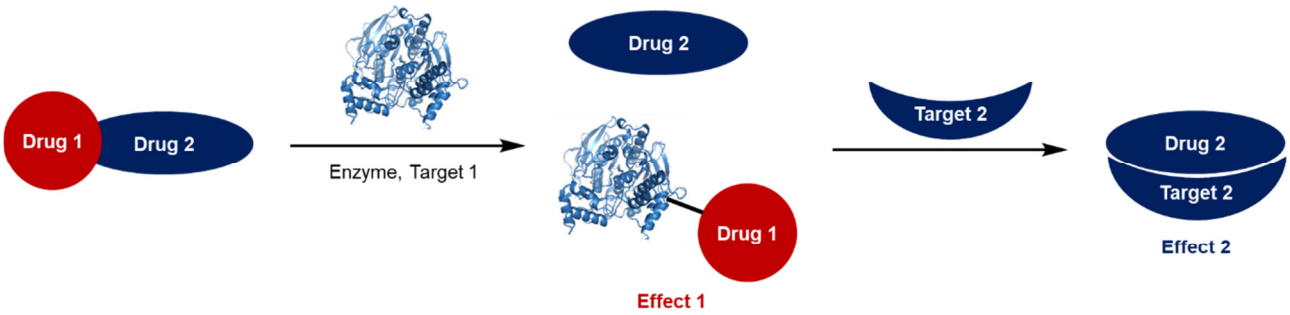


Figure 1: Prodrug MTDLs

References

[1] Yun, H. *et al. Experimental Neurobiology* **2011**, *20* (4), 159–168.

[2] Cummings, J. *et al. Alzheimer's Dement. Transl. Res. Clin. Interv.* **2017**, *3* (3), 367–384.

[3] Lecoutey, C. *et al. Proc. Natl. Acad. Sci.* **2014**, *111* (36), E3825–E3830.

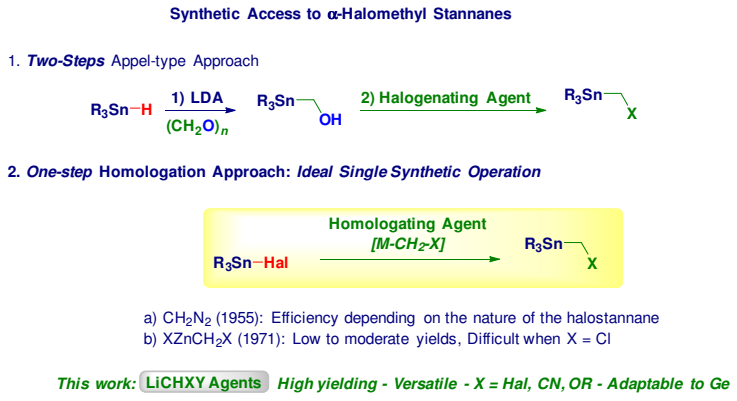
Poster communication 24 – WG 1

Homologation of halostannanes and halogermanes with lithium carbenoids: a convenient and straightforward one-step access to α-functionalized organotin reagents

Saad Touqeer, Laura Castoldi, Thierry Langer, Wolfgang Holzer and Vittorio Pace

Department of Pharmaceutical Chemistry, University of Vienna, Althanstrasse 14, 1090 Vienna (Austria).
a01647317@unet.univie.ac.at

The unique reactivity of the C-Sn bond together with the good stability makes organotin compounds highly versatile entities across the chemical sciences.[1] Accordingly, their use in synthetic processes is not limited to pivotal synthetic operations (*in primis* the Stille coupling)[2] but also encompasses fundamental organometallic techniques.[3] In this context, α-halomethyl stannanes (R_3Sn-CH_2-X) represent privileged tin-containing reagents because of the formal analogy with metal carbenoids (MCH_2X). In fact, the excellent stability they feature allows to overcome *de facto* important limitations of classical metal carbenoids (M = Li, MgY, ZnY) such as the thermal depending α-elimination.[4] As a consequence of this significant advantage, the reactivity portfolio of these stannanes has been considerably exploited in a series of synthetic processes ranging from the equivalence with alkoxymethyl anions[5] to electrophilic carbon units suitable for the preparation of multifunctionalized organotin compounds via nucleophilic substitutions.[6] Herein, we report the effectiveness of the nucleophilic substitution on halostannanes with lithium carbenoids and related reagents (LiCH2X, X = halogen, OR, CN) for accomplishing a direct, one-step and straightforward formation of R3Sn-CH2-X type reagents. We anticipate the applicability of the protocol to the homologation of analogous organogermanium derivatives. Conceptually, the overall process can be regarded as a transmetallation of Li into Sn or Ge carbenoids, in which the products retain the α-halomethyl unit susceptible of late functionalization.



Scheme 1

Bibliographic references:

(a) A. de Meijere, S. Brase and M. Oestreich, eds., *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH, Weinheim, 2014.
(b) a) P. Espinet and A. M. Echavarren, *Angew. Chem. Int. Ed.*, 2004, **43**, 4704; b) C. Cordovilla, C. Bartolomé, J. M. Martínez-Ilarduya and P. Espinet, *ACS Catalysis*, 2015, **5**, 3040.
(c) a) M. S. Jensen, C. Yang, Y. Hsiao, N. Rivera, K. M. Wells, J. Y. L. Chung, N. Yasuda, D. L. Hughes and P. J. Reider, *Org. Lett.*, 2000, **2**, 1081; b) M. Cormier, M. Ahmad, J. Maddaluno and M. De Paolis, *Organometallics*, 2017, **36**, 4920.
(d) V. Pace, L. Castoldi, S. Monticelli, M. Rui and S. Collina, *Synlett*, 2017, **28**, 879.
(e) J. Clayden, M. N. Kenworthy and M. Helliwell, *Org. Lett.*, 2003, **5**, 831.
(f) a) A. Wieczorek and F. Hammerschmidt, *J. Org. Chem.*, 2012, **77**, 10021; b) H. Kobayashi, J. A. Eickhoff and A. Zakarian, *J. Org. Chem.*, 2015, **80**, 9989.

Poster communication 25 – WG 2

Lovastatin and Fluvastatin as promising inhibitors of 2D- and 3D- growth of retrovirus-transformed rat sarcoma cells

Radostina Alexandrova[1], Milena Glavcheva[1], Zdravka Petrova[1], Desislav Dinev[1], Rossen Spassov[1,2]

[1]*Institute of Experimental Morphology, Pathology and Anthropology with Museum, Bulgarian Academy of Sciences, Sofia, Bulgaria*

[2]*Medical Faculty, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria*

rialexandrova@hotmail.com

Statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, are efficient and widely used drugs in the treatment of lipid disorders. They have also been found to exhibit antineoplastic activity against wide variety of cell culture and animal tumor models as well as the ability to potentiate the antitumor effects of some cytokines and chemotherapeutics.

The aim of our study was to evaluate the influence of Lovastatin and Fluvastatin on viability and proliferation of cultured LSR-SF-SR rat sarcoma cells. The cells express v-src gene which cellular analogues (when disregulated) have been suggested to play important role in cancerogenesis and tumor progression.

The investigations were performed by MTT test, double staining with acridine orange and propidium iodide, haematoxylin and eosin staining, Annexin/FITC method and 3D-colony-forming method. The results obtained revealed that applied at a concentration range of 0.75-200 µg/mL for 24, 48 and 72 h both statins significantly reduced the percent of viable cells as compared to the untreated control. The long-term experiments lasting 20 days demonstrated that administered at concentrations ≥ 200 µg/mL (Lovastatin) and ≥ 100 µg/mL (Fluvastatin) both compounds completely suppressed 3D growth of rat sarcoma cells in a semi-solid medium.

In conclusion we can assume, that Lovastatin and Fluvastatin exhibit promising cytotoxic activity in v-src expressing tumor cells, so that their anticancer potential deserve further in-dept research.

Acknowledgement: Supported by Grant № DFNI Б 02 30/ 12.12.2014, National Science Fund, Ministry of Education and Science, Bulgaria.

Poster communication 26 – WG 2

Identification of phenolic compounds from nettle as new candidate inhibitors of main enzymes responsible on type-II diabetes.

Salim Bouchentouf [a, 1], Said Ghalem [b,1] ,Nadia Kambouche [c], Soumaya Kerese[c]

[a] *Faculty of Technology, Doctor Moulay Tahar University, Saida, Algeria*
[b] *Department of Chemistry, Faculty of Sciences, Aboubekr Belkaid University, Tlemcen, Algeria*
[c] *Departement of Chemistry, Faculty of Applied Exacts Sciences, University Ahmed Benbella of Oran, Algeria*
[1] *Laboratory of Naturals products and bioactives, University Aboubekr Belkaid of Tlemcen. Algeria*
bouchentouf.salim@yahoo.fr

In medicinal chemistry, the discovery of small organic molecules that can be optimized and lead to a future drug capable of effectively modulating the biological activity of a therapeutic target remains as major challenge. Because of harmful secondary effects of synthesized therapeutic molecules, the development of research has been oriented towards phytomedicines. Phenolic compounds from medicinal plants are constantly explored for new therapeutic use.In this paper, we studied interactions between main enzymes responsible on type 2 diabetes mellitus (T2DM) and phenolic compounds from nettle (Urtica dioica L.) using molecular Docking with Molecular Operating Environment Software (MOE).Docking results show a common molecule (secoisolariciresinol) which may form stable complexes with depeptidyl peptidase 4 (DPP-4), alpha-amylase and beta-glucosidase with binding energy of -7.04732084 kcal/mol, -3.82946181 kcal/mol and -4.16077089 kcal/mol respectively. Besides secoisolariciresinol other phenolic compounds give better docking score than the original co-crystallized ligand for alpha-amylase (PDB ID 5U3A) and beta-glucosidase (PDB ID 1OGS).The obtained results are promising for the discovery of new alpha-amylase and beta-glucosidase inhibitors. This study confirms also folk use of nettle as antidiabetic agent.

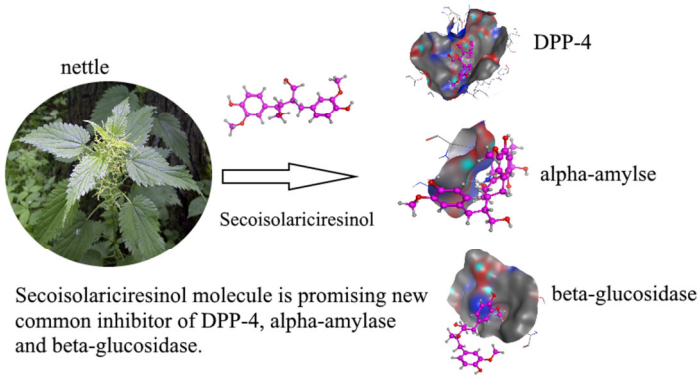


Figure 1: Graphical Abstract

References

[1] Tarighat Esfanjani A, Namazi N, Bahrami A, Ehteshami M. Effect of hydroalcoholic extract of nettle (Urtica dioica) on glycemic index and insulin resistance index in type 2 diabetic patients. Iranian journal of endocrinology and metabolism. **2012**;6(13):561-8. (In Persian).
[2] Franciškovi M, Gonzalez-Pérez R, Orčić D, Sánchez de Medina F, Martínez-Augustin O, Svirčev E et al. Chemical Composition and Immuno-Modulatory Effects of Urtica dioica L. (Stinging Nettle) Extracts. Phytotherapy Research. **2017**;31(8):1183-1191
[3] Molecular Operating Environment (MOE), 2014.09; Chemical Computing Group Inc., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, **2014**.

Poster communication 27 – WG 2

Effect of polyphenols on pancreatic INS-1E beta cells by modulation of intracellular calcium concentration

Vladimir Heger [ab], Jana Viskupicova[a], Magdaléna Májeková,[a], Attila Hunyadi[c],, Lubica Horakova[a],

[a] *Institute of Experimental Pharmacology and Toxicology, Centre of Experimental Medicine of the Slovak Academy of Sciences, Dubravska cesta 9, 841 04 Bratislava, Slovakia*

[b] *Department of Biochemistry, Faculty of Natural Sciences, Comenius University in Bratislava, Mlynska dolina, Ilkovicova 6, 842 15 Bratislava 4, Slovakia*

[c] *Institute of Pharmacognosy, University of Szeged, Eötvös u. 6, 6720 Szeged, Hungary*

heger3@uniba.sk

T Calcium is an important second messenger in signal transduction pathways which regulate a wide variety of processes, including gene expression, protein synthesis, secretion, muscle contraction, metabolism and apoptosis. Maintenance of calcium homeostasis is of crucial importance in the proper functioning of cells, and its dysfunction is associated with many pathological conditions.

Polyphenols, (94 compounds) were tested using molecular docking followed by experimental studies of top-scoring compunds. SERCA activity was established in non-cellular system. Cell viability, apoptosis, intracellular calcium level, insulin secretion, and calcium-related protein expression were assessed in pancreatic INS-1E beta cell line.

The results may indicate a key role of SERCA in regulation of events associated with impairment of beta-cells. Understanding the molecular regulation of calcium homeostasis via SERCA and its impairment may be a novel therapeutic approach to treating diseases related to ER dysfunction.

This work is a result of collaboration within COST Action CM1407: www.natchem.eu. Supported in the frame of OPVaV for the project ITMS 26240220040, jointly financed from the sources of EFRR, supported from the Slovak National grantsVEGA 2/0111/16 and APVV-15-0455, and from the National Research, Development and Innovation Office, Hungary (NKFIH; K119770). AH acknowledges the János Bolyai fellowship of the Hungarian Academy of Sciences, and the Kálmán Szász Prize.

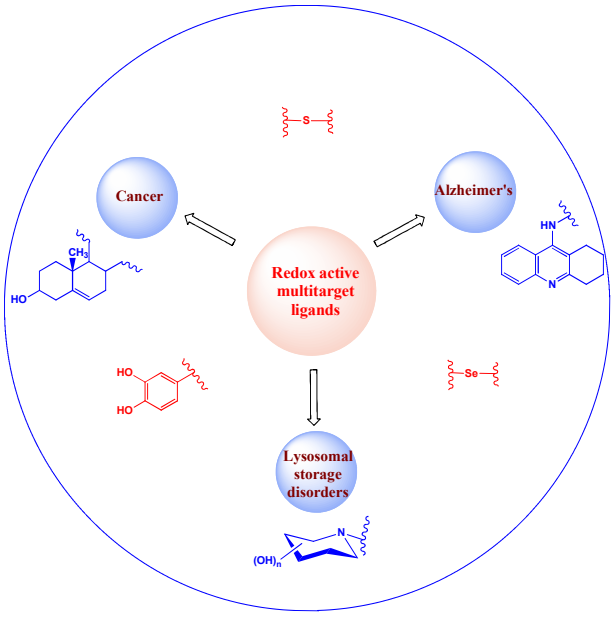
Poster communication 28 – WG 2

Design of redox active multitarget directed ligands

Óscar López,[a] Paloma Begines[a], Jesús Roldán-Peña,[a] Inés Maya,[a] Laura L. Romero-Hernández,[b] Penélope Merino-Montiel,[b] Socorro Meza-Reyes,[b] José Luis Vega Báez,[b] Sara Montiel-Smith,[b] Alexis R. Galán,[c] Miguel X. Fernandes,[c] Irene Lagunes,[c] Luis E. Peña-Altamira,[d] Manuela Bartolini,[d] Bárbara Monti,[d] María L. Bolognesi,[d] José M. Padrón,[c] José G. Fernández-Bolaños[a]

[a] Depto. de Química Orgánica, Facultad de Química, Univ. de Sevilla Apartado 1203, E-41071, Seville, Spain [b] Facultad de Ciencias Químicas, Ciudad Universitaria, BUAP, 72570 Puebla, PUE, Mexico; [c]BioLab, IUBO-AG, CIBICAN, Univ. La Laguna, C/Astrofísico Fco. Sánchez 2, Apto. 456, 38200 La Laguna; [d] Dep. Pharmacy and Biotechnology, Alma Mater Studiorum Univ. Bologna, via Belmeloro 6, 40126 Bologna, Italy
osc-lopez@us.es

The enormous complexity associated to multifactorial diseases, like cancer or Alzheimer's, featured with numerous and even unknown etiologies has obliged to introduce hybrid molecules, bearing different pharmacophores in order to tackle them. One common feature of such diseases is the prevalence of high levels of ROS, leading to the oxidative degradation of biomolecules. Accordingly, a rational design of new drugs can lead to the incorporation of redox active fragments to modify the redox status. In this context, we have successfully applied[1-3] this concept by combining polyphenolic or chalcogen-containing motifs with a second pharmacophore, like iminosugars, or steroids (Figure 1), achieving new drugs prototypes with bioactivities ranging from the low micromolar-nanomolar range.



Acknowledgements. We thank the DGI of Spain (CTQ2016-78703-P, the Junta de Andalucía (FQM134), FEDER, and the Italian MIUR for financial support. JMR-P and P.B. thank Fundacion Cámara-Urzáiz, Spanish Ministry of Education and University of Seville for the award of fellowships

References

[1] Roldán-Peña *et al.*, *Eur. J. Med. Chem.*, **2017**, *138*, 761-773; [2]Olsen *et al.*, *Eur. J. Med. Chem.* **2016**, *123*, 155-160; [3]Romero Hernández *et al.*, *Eur. J. Med. Chem.* **2015**, *99*, 67-81.

Poster communication 29 – WG 2

ADME analisys and toxicological evaluation of a new synthetic antifungal compound active against azole-resistant candida strains

Francesco Orofino,[a] Giuseppina I. Truglio[a] and Maurizio Botta[a,b,c]

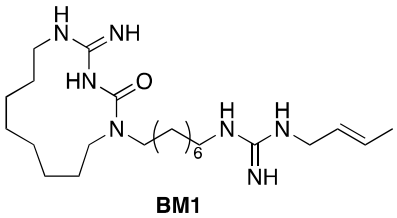
[a] *Department of Biotechnology, Chemistry and Pharmacy, University of Siena, I-53100 Siena, Italy*

[b] *Sbarro Institute for Cancer Research and Molecular Medicine, Temple University, Philadelphia, PA, USA.*

[c] *Lead Discovery Siena s.r.l, Via Vittorio Alfieri 31, I-53019 Castelnuovo Berardenga, Italy*

francesco.orofino@icloud.com

Among the opportunistic fungi, *Candida* species represent one of the most common cause of nosocomial bloodstream infections. The large use of antifungal agents, most of them launched on the market more than twenty years ago, led to the selection of drug-resistant or even multidrug-resistant fungi. We have already described a novel class of antifungal macrocyclic compounds bearing an amidinourea moiety, highly active against various azole-resistant *Candida* strains. After setting up a novel gram-scale synthetic approach, one representative of this family, compound **BM1**, has been investigated on its *in vitro* activity and *in vivo* safety. Our research highlights the *in vivo* low toxicity profile of compound **BM1**, its affinity for the renal system in rats and its good ADME features. Moreover, we confirm that the molecular target is new and not shared by any other antifungal compound on the market, since our compound preserves a potent activity also against azole-resistant fungal strains, including *C. auris* isolates, which makes it and its sibling compounds a promising novel antifungal class.



BM1

Figure 1: Chemical structure of compound **BM1**.

References

[1] Manetti, F.; Castagnolo, D.; Raffi, F.; Zizzari, A. T.; Rajamaki, S.; D'Arezzo, S.; Visca, P.; Cona, A.; Fracasso, M. E.; Doria, D.; Posteraro, B.; Sanguinetti, M.; Fadda, G.; Botta, M. Synthesis of New Linear Guanidines and Macrocyclic Amidinourea Derivatives Endowed with High Antifungal Activity Against Candida Spp. and Aspergillus Spp. *J. Med. Chem.* **2009**, *52* (23), 7376–7379.

[2] Sanguinetti, M.; Sanfilippo, S.; Castagnolo, D.; Sanglard, D.; Posteraro, B.; Donzellini, G.; Botta, M. Novel Macrocyclic Amidinoureas: Potent Non-Azole Antifungals Active Against Wild-Type and Resistant Candida Species. *ACS Med. Chem. Lett.* **2013**, *4* (9), 852–857.

[3] Deodato, D.; Maccari, G.; De Luca, F.; Sanfilippo, S.; Casian, A.; Martini, R.; D'Arezzo, S.; Bonchi, C.; Bugli, F.; Posteraro, B.; Vandeputte, P.; Sanglard, D.; Docquier, J. D.; Sanguinetti, M.; Visca, P.; Botta, M. Biological Characterization and in Vivo Assessment of the Activity of a New Synthetic Macrocyclic Antifungal Compound. *J. Med. Chem.* **2016**, *59* (8), 3854–3866.

Poster communication 30 – WG 2

Modified ELISA-like assay for investigation of peptidomimetics inhibiting NRP-1/VEGF-A_{165} complex

Anna Puszko,[a] Piotr Sosnowski,[b] Yves Lepelletier,[c,d] Olivier Hermine,[c,d] Gérard Hopfgartner,[b] Karolina Pułka-Ziach,[a] Aleksandra Misicka[a]

[a] *Faculty of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland*

[b] *Department of Inorganic and Analytical Chemistry, University of Geneva, 24 Quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland*

[c] *Imagine Institute, INSERM UMR 1163, Paris Descartes University–Sorbonne Paris Cité, 24 Boulevard Montparnasse 75015 Paris, France*

[d] *CNRS ERL 8254, 24 Boulevard Montparnasse, 75015 Paris, France*

apuszko@chem.uw.edu.pl

Neuropilin-1 (NRP-1) is a receptor found on the surface of vascular endothelial cells, involved in the angiogenesis process in physiological and pathological conditions, such as tumor growth and metastasis.[1,2] Overexpression of the most stimulating pro-angiogenic factor, VEGF-A_{165}, occurs in several diseases, including cancer.[3,4] This indicates that searching for new molecules, able to interact with NRP-1 as inhibitors of pathological angiogenesis, could play a crucial role in novel drug development. Biologically active peptides might be appropriate candidates for potential drugs. We have recently developed branched peptides with the K(*h*R)XXR sequence, which exhibit a significant $VEGF_{165}$/NRP-1 binding inhibitory effect.[5]

In our research, NRP-1/VEGF-A_{165} binding inhibition assay was optimized. We compared the importance of NRP-1 receptor origin and detection methods. Next, we synthesized branched peptidomimetics with general K(*h*R)XXR sequence, containing unnatural amino acids and amide bond mimetics, and examined inhibitory effect on $VEGF_{165}$/NRP-1 binding. The results of structure-activity relationship study provide new insight into structural requirements for inhibition of $VEGF_{165}$/NRP-1.

References

[1] Ferrara, N.; Gerber, H.P.; Le Couter, J. The biology of VEGF and its receptors. *Nat Med*, **2003**, *9*, 669-676.

[2] Prud'homme, G.J.; Glinka Y. Neuropilins are multifunctional coreceptors involved in tumor initiation, growth, metastasis and immunity. *Oncotarget*, **2012**, *3*, 921-939.

[3] Ziyad, S.; Iruela-Arispe, M.L. Molecular mechanisms of tumor angiogenesis. *Genes Cancer*, **2011**, *2*, 1085-1096.

[4] Grun, D.; Adhikary, G.; Eckert R.L. VEGF-A acts via neuropilin-1 to enhance epidermal cancer stem cell survival and formation of aggressive and highly vascularized tumors. *Oncogene*, **2016**, *35*, 4379-4387.

[5] Tymecka, D.; Puszko, A.K.; Lipiński, P.F.J.; Fedorczyk, B.; Wileńska, B.; Sura, K.; Perret, G.Y.; Misicka A. Branched pentapeptides as potent inhibitors of the vascular endothelial growth factor 165 binding to Neuropilin-1: Design, synthesis and biological activity. *Eur J Med Chem*, **2018**, *158*, 453-62.

Poster communication 31 – WG 2

Modulation of relaxation activity of human Topoisomerases by Pt(II)-based complexes

Claudia Sissi,[a] Nicholas P. Farrell,[b]

[a] *Dept of Pharmaceutical and Pharmacological Sciences, v. Marzolo 5, 35131 Padova, Italy*

[b] *Department of Chemistry, Virginia Commonwealth University, 1001 W. Main Street, Richmond, VA, 23284-2006, USA*

claudia.sissi@unipd.it

The clinical efficiency of Pt(II)-based drugs is based on articulate mechanism of action that results from metal ion reactivity towards protein and nucleic acid. Here we analyzed the effect of two TPAs in comparison to cisplatin and transplatin on the DNA processivity by human topoisomerases I and IIα. Each tested metal complex produces DNA adducts with unique geometrical features and, consistently, they exert different effects on the enzymes activity. Moreover, our results highlighted more subtle consequences on the enzymatic activity by the tested metal complexes which derive from a combination of preferential DNA or protein platination. As a result, in physiological environment, we can expect different pathways according to the chemical reactivity profile of each single metal complex.

References

[1] Pinato, O.; Musetti, C; Sissi, C. Pt-based drugs: the spotlight will be on proteins, *Metallomics*, **2014**, *6*, 380-395.

[2] Pinato, O.; Musetti, C.; Farrell, N. P.; Sissi, C. Platinum-based drugs and proteins: reactivity and relevance to DNA adduct formation, *J Inorg Biochem*, **2013**, *122*, 27-37.

Poster communication 32 – WG 2

1,4-dihydropyridine-benzylidenhydrazon derived AChE inhibitor induces H_2S formation

Gulnur Sevin[a], Elif Alancay[a], Sulunay Parlar[b], Emine Nur Ozbek[a], Oguzhan Kaya[b], Vildan Alptuzun[b], Gunay Yetik Anacak[a]

[a]*Department of Pharmacology, Faculty of Pharmacy, Ege University, Izmir Turkey;*

[b]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ege University, Izmir Turkey*
gunayyetik@gmail.com

H_2S-signaling pathways have been described to offer protection against Alzheimer's amyloid vasculopathy and neurodegeneration. H_2S can work in the central nervous system as a neuromodulator to promote long-term potentiation and protect the nervous system from oxidative stress, apoptosis, or degeneration (1). Dysregulation of H_2S homeostasis is implicated in the pathological processes of AD. Both *in vivo* and *in vitro* studies shows that H_2S prevents neuronal impairment and attenuates cognitive dysfunction in the experimental model of AD (1). Previously we have shown that 1,4-dihydropiridine-benzylidenhidrazon derived C1 coded chemical that we synthesized inhibits AChE, Aβ fibril formation and causes destruction of already formed fibrils (IC50: 0.27 µM) (2). Thus we now would like to study whether C1 causes H_2S formation and have potential to be effective in alzheimer treatment by polypharmacological effects of H_2S.

We investigated the effect of C1 (10uM) on basal or L-cysteine (L-cyst;10 mM) induced H_2S formation in the presence and absence of Cystathionine-gamma-lyase (CSE) inhibitor PAG (2 mM) in mouse aorta and lung homogenates by methylene blue assay. C1 induced basal H_2S formation both in lung (1.302±0.05 vs 1.522±0.07, n=6) and aorta homogenates (0.695± 0.03 vs 0.782±0.02, n=8-4, P<0.05 Unpaired t-test,). C1-induced basal H_2S formations were inhibited by PAG significantly in both lung and aorta (0.854±0.05 and 0.622±0.06, P<0.001 and P<0.05, Unpaired t-test n=6 and 4, respectively,). C1 significantly increased L-cyst induced H_2S formation both in aorta (6.173±0.15 vs 8.046±0.28, P<0.001 Unpaired t-test, n=9) and lung homogenates (1.784±0.06 vs 2.286±0.12, P<0.001 Unpaired t-test, n=8). Augmentation of L-cyst induced H_2S formation by C1 was inhibited by PAG significantly in both aorta (5.999±0.29, P<0.001 One way ANOVA, n=4) and lung (1.279±0.03, P<0.001 One way ANOVA, n=3), confirmed that C1 causes endogenous H_2S synthesis.

We conclude that C1 can augment L-cysteine-induced H_2S formation in vascular tissues and thereby have a potential to be effective in Alzheimer. Because H_2S level is decreased in Alzheimer and H_2S production have protective effects in Alzheimer through inhibition of oxidation and inflammation as well as increasing neuronal dysfunction.

Acknowledgement: We thank Turkish Scientific Research Council TUBITAK for the grant #114S448 and COST action CA15135.

References

1 Wei HJ, Li X, Tang XQ. Therapeutic benefits of H_2S in Alzheimer's disease. J Clin Neurosci. 2014 Oct;21(10):1665-9. (11):1069-77.

2. Prinz M, Parlar S, Bayraktar G, et all. 1,4-Substituted 4-(1H)-pyridylene-hydrazone-type inhibitors of AChE, BuChE, and amyloid-β aggregation crossing the blood-brain barrier. Eur J Pharm Sci. 2013, 49:603-613.

Poster communication 33 – WG 3

Pyrrolo[2',3':3,4]cyclohepta[1,2-*d*][1,2]oxazoles as potential multitargeting agents

Spanò V.,[a] Giallombardo D.,[a] Carbone A.,[a] Montalbano A.,[a] Gaudio E.,[b] Ortuso F.,[c] Alcaro S.,[c] Barraja, P [a]

[a] *Dept of Biological, Chemical and Pharmaceutical Sciences and Technologies (STEBICEF), Via Archrafi 32, 90123 University of Palermo*
[b] *Lymphoma Genomics, Institute of Oncology Research (IOR), USI University Bellinzona, 6500-CH Switzerland*
[b] *Dept of Health Science, University of Magna Græcia Viale Europa 88100 Catanzaro (Italy)*
paola.barraja@unipa.it

[1,2]Oxazoles represent the core structure of many drug candidates with multiple targets, demonstrating an attractive scaffold in medicinal chemistry. Diaryl[1,2]oxazoles have emerged as potent analogues of the antitubulin compound Combretastatin A4 (CA4)[2] and several examples of compounds incorporating the isoxazole core are effective against kinases. 3-Amino-benzo[*d*]isoxazoles displayed potent inhibitory effects both at enzymatic and cellular levels towards c-Met tyrosine kinase,[3] and isoxazolo-quinazolines emerged as potent modulators of MSK1 and PERK kinases.[3] The [1,2]oxazolo[4,5-*g*]indole system, previously investigated by us, gave excellent results in preclinical studies[4] reducing in vitro cell growth, impairing cell cycle progression and inducing apoptosis, as a consequence of the inhibition of tubulin polymerization, in experimental models of diffuse malignant peritoneal mesothelioma (DMPM). Moreover, a significant in vivo antitumor activity of selected derivatives at well-tolerated doses in a DMPM xenograft model. A further modification of the original structure led to the new tricyclic derivatives pyrrolo[2',3':3,4]cyclohepta[1,2-d][1,2]oxazoles, which were synthetized with the aim of exploring both the antimitotic activity and their kinases seletivity. A series of 26 compounds was screened at the NCI of Bethesda on a panel of 60 human cell lines. Six compounds showed potent activity with GI_{50} reaching the nanomolar level with mean graph mid-points (MG_MID) of 0.08–0.41 µM. All compounds were further tested at the Lymphoma Genomics, Institute of Oncology Research (IOR, Switzerland) on a panel of linphoma cel lines and some compounds showed potent growth inhibitory effect on selected cell lines. Additionally computational studies will indicate the best predicted selectivity against specific kinases, which will be confirmed by enzymatic assays. Investigation on the mechanism of action will be carried out to confirm the new class of heterocycles as multitargeting agents.

References

[1] Sun, C. –M.; Lin, L. –G.; Yu, H. –J.; Cheng, C. –Y.; Tsai, Y. –C.; Chu, C. –W; Din, Y. –H.; Chau, Y. –P.; Don, M. –J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1078–1081; Kaffy, J.; Pontikis, R.; Carrez, D.; Croisy, A.; Monneret, C.; Florent, J. –C. *Bioorg. Med. Chem.* **2006**, *14*, 4067–4077.
[2] Jiang, X.; Liu, H.; Song, Z.; Peng, X.; Ji, Y.; Yao, Q.; Geng, M.; Ai, J.; Zhang, A. *Bioorg. Med. Chem.* **2015**, *23*, 564–578.
[3] Beria, I.; Caldarelli, M.; Colombo, N.; Piutti, C.; Salsa, M.; Tarquandi, G. PCT Int. Appl. WO 2012013557
[4] Spanò, V.; Pennati, M.; Parrino, B.; Carbone, A.; Montalbano, A.; Cilibrasi, V.; Lopergolo, A.; Cominetti, D.; Diana, P.; Cirrincione, G.; Barraja, P.; Zaffaroni N., *J. Med. Chem.* **2016**, *59*, 7223−7238; Spanò, V.; .; Pennati, M.; Parrino, B.; Carbone, A.; Montalbano, A.; Lopergolo, A.; Zuco, V.; Cominetti, D.; Diana, P. ; Cirrincione, G.; Zaffaroni, N.; Barraja, P. *Eur. J. Med. Chem.* **2016**, *124*, 840.

Poster communication 34 – WG 3

Deciphering the Mechanisms of Allosteric Modulation of HSP90.

Ilda D'Annessa,[a] Stefano Raniolo,[b] Vittorio Limongelli, [b,c] Daniele Di Marino, [b] Giorgio Colombo,[a,d]

[a] *Istituto di Chimica del Riconoscimento Molecolare, CNR, Via Mario Bianco 9, 20131 Milano, Italy.*

[b] *Faculty of Biomedical Sciences, Institute of Computational Science - Center for Computational Medicine in Cardiology, Università della Svizzera Italiana (USI), CH-6900 Lugano, Switzerland.*

[c] *Dipartimento di Farmacia, Università di Napoli "Federico II", 80131 Napoli, Italy.*

[d] *Dipartimento di Chimica, Università di Pavia, V.le Taramelli 12, 27100 Pavia, Italy.*

daniele.di.marino@usi.ch

The molecular chaperone HSP90 plays a critical role in controlling proteins folding and their functional activation, thus in cellular proteostasis. As such, it is involved in most cellular vital pathways having a direct role in the onset and progression of different pathological processes, like cancer and neurodegeneration. The allosteric modulation of the enzymatic reaction promoted by HSP90 is an emerging strategy for the development of new therapies. A deep understanding of the molecular basis of the allosteric mechanism exerted by designed drugs is fundamental to provide new molecules with increased efficiency and specificity. Because of its high conformational plasticity HSP90 is difficult to study from a structural point of view and this causes a lack of information on the precise protein-ligand interaction and dynamical effects. Here, by applying a fully theoretical approach we embarked in a study aimed at defining the molecular basis of the allosteric effect of an O-aryl rhamnoside benzofuran scaffold, known to be an activator of HSP90. Using Funnel-Metadynamics we could follow several binding/unbinding events of the ligand and from that we derived an accurate estimation of the absolute binding free energy. More importantly, we unveiled the molecular basis behind the allosteric mechanism of the compound. To the best of our knowledge, this work for the first time presents a study in which an extensive theoretical approach is applied to put in relation the dynamical profile of a receptor in response to binding/unbinding of a ligand and to decipher the allosteric effects of such process.

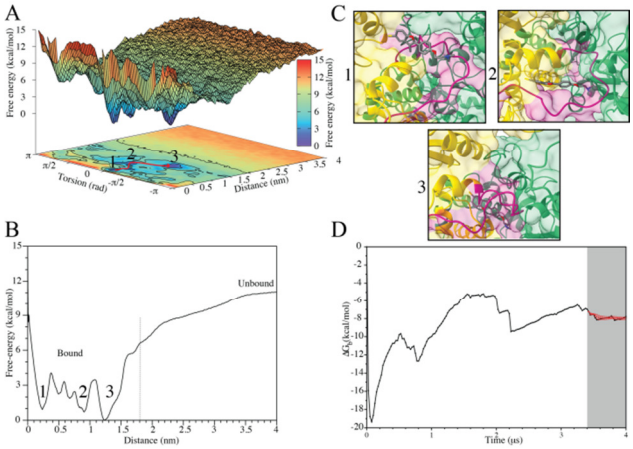


Figure 1: Free-energy surface and binding modes description of the HSP90 allosteric modulator

References

[1]Sattin, S.; Tao, J.; Vettoretti ,G.; Moroni, E.; Pennati M, Lopergolo, A.; Morelli, L.; Bugatti, A.; Zuehlke, A.; Moses, M.; Prince, T.; Kijima, T.; Beebe, K.; Rusnati, M.; Neckers, L.; Zaffaroni, N.; Agard, DA.; Bernardi, A.; Colombo, G. Activation of Hsp90 Enzymatic Activity and Conformational Dynamics through Rationally Designed Allosteric Ligands. *Chemistry*, **2015,** 21, 13598-13608.

[2]Limongelli, V.; Bonomi, M.; Parrinello, M. Funnel metadynamics as accurate binding free-energy method. *Proc Natl Acad Sci U S A*, **2013,** 16, 6358-6363.

Poster communication 35 – WG 3

Evolution of the Chemotheca model for the technological transfer in a spin-off academic reality

Annalisa Maruca,[a,b] Anna Artese,[a,b] Bagetta Donatella,[a,b] Catalano Raffaella,[a,b] Costa Giosuè,[a,b] Lupia Antonio,[a,b] Mesiti Francesco,[a,b] Moraca Federica,[b] Rocca Roberta,[a,b] Romeo Isabella,[a,b] Rotundo Salvatore,[b] Ortuso Francesco,[a,b] Alcaro Stefano [a,b]

[a] *Department of Health Sciences, University Magna Græcia, Viale Europa, 88100-Catanzaro, Italy*

[b] *Net4Science srl, University Magna Græcia, Viale Europa, 88100-Catanzaro, Italy*

maruca@unicz.it

Multi-target drugs have aroused considerable interest in the last decade, both in academia and in companies, since their advantages in the treatment of complex diseases and health conditions linked to resistance issues. A further application of multi-target ligands is their repurposing in the treatment of concomitant diseases.[1] N4S is a spin-off of the Magna Graecia University of Catanzaro proposed by the research group of Medicinal Chemistry of the Department of Health Sciences, which provides services to public and private parties in the pharmaceutical and nutraceutical sector, nationally and internationally. Its main activity consists in carrying out and accelerating the processes of drug discovery in the field of polypharmacological and multi-targeting, training professional figures in this sector and enhancing the use of typical products in a nutraceutical perspective.

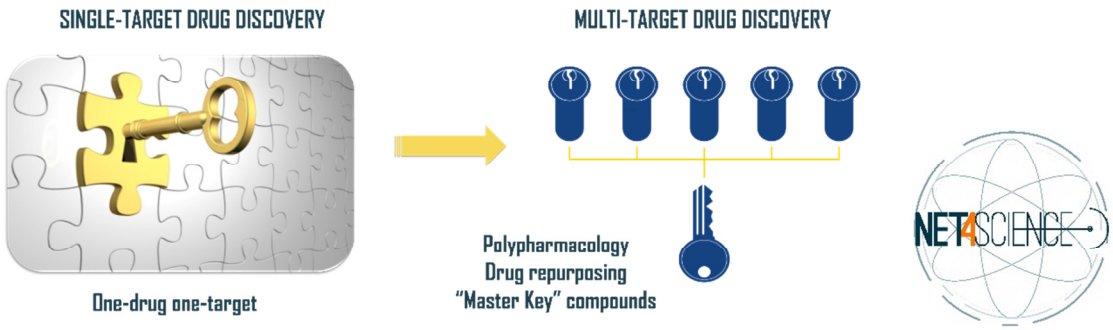


Figure 1: Multi-target drug discovery and Net4Science Brand.

N4S offers innovative high-tech services aimed at: a) develop specific platforms to carry out innovative drug discovery activities; b) enhance the bioactive components of typical products in order to increase their use as functional or nutraceutical foods; c) train specialists in the pharmaceutical and nutraceutical sectors.

References

[1]Ramsay, R.R.; Popovic-Nikolic, M.R.; Nikolic, K.; Uliassi, E.; Bolognesi, M.L. A perspective on multi-target drug discovery and design for complex diseases. *Clin Transl Med,* **2018**, *7(1)*, 3.

Poster communication 36 – WG 3

The Metabolites' Exploration from Chemotheca Database

Črtomir Podlipnik,[a] Marko Jukič[b]

[a] *Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, 1000 Ljubljana*

[b] *Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana*

crtomir.podlipnik@fkkt.uni-lj.si

The prediction of the metabolic profiles of designed molecules is an essential part of all drug discovery projects. The knowledge about drug metabolic pathways is extremely important for a better understanding of pharmacokinetics as well as pharmacodynamics of drugs. Metabolism can also contribute to multidrug resistance in infectious disease and chemotherapy of cancer. Finally, drug metabolites can bestow toxic effects on the human.

In our study, we explore a library of *In silico* metabolites derived from Virtual Chemotheca Database. Meteor Nexus, a knowledge-based software for metabolite prediction from Lhasa Limited, has been used for generation of metabolite database. We analysed around 800 compounds from Virtual Chemotheca, and the Meteor Nexus returned more than 14 000 entries with more than 7 400 unique metabolite structures with a molecular weight between below 871.84 g/mol. An example of a metabolic transformation of compound CMLID459 is shown as Fig 1.

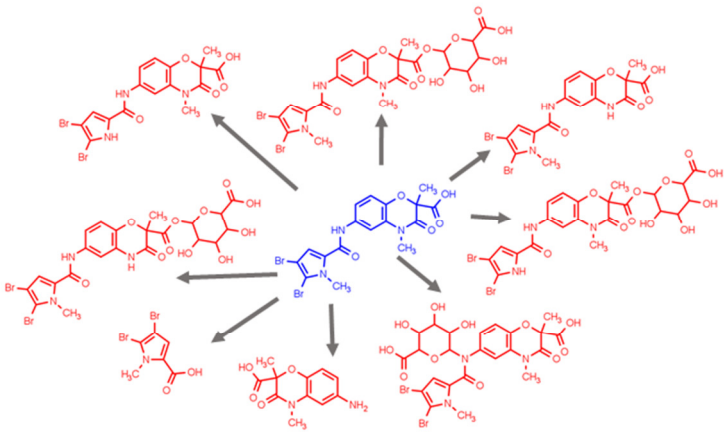


Figure 1: An example of metabolic transformation for compound CMLID459.

We have used the chemoinformatics tools for the analysis of the database of metabolites derived from Virtual Chemotheca.

Poster communication 37 – WG 4

Molecular Modeling and STD-NMR combined approach for the identification of HuR inhibitors compounds

Francesca Alessandra Ambrosio,[a] Giosuè Costa,[a] Simona Collina,[b] Stefano Alcaro[a]

[a] *Dept of Health Sciences, University Magna Graecia of Catanzaro, Viale Europa 88100, Catanzaro, Italy*

[b] *Dept of Drug Sciences, Medicinal Chemistry and Technology Section, University of Pavia, Via Taramelli 12, Pavia, Italy.*

ambrosio@unicz.it

The Human RNA-binding protein (HuR), a ubiquitously expressed member of the Hu protein family, plays an important role in mRNA degradation and has been implicated as a key post-transcriptional regulator. HuR protein is higher expressed in several pathologies such as cancer and neurodegeneration[1-2]. Focusing on the interactions of HuR-mRNA interactions, combining molecular modeling and STD-NMR approaches we studied the ability of structurally-related compounds (i.e., flavonoids and coumarins), naturally decorated with different functional groups, as new potential inhibitor of HuR-mRNA complex. Starting from the Crystal structure of the two N-terminal RRM domains of HuR complexed with RNA, deposited in the Protein Data Bank (PDB) with the 4ED5 pdb code[2], Molecular Dynamics simulations and Molecular Docking studies were performed in order to investigate the protein rearrangement and the theoretical binding affinity of the studied compounds versus HuR protein, respectively. Our results represent the foundation for the development of potent and selective ligands able to interfere with ELAV–RNA complexes.

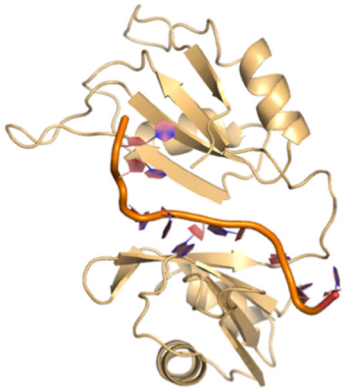


Figure 1: 3D representation of HuR-mRNA complex; the protein and the m-RNA are showed as light orange and orange cartoon, respectively.

References

[1] Preet, L.; Linda, C.; Vito Giuseppe, D.; Chiara, Z.; Carmelo, F.; Isabelle, B.; Erik, D.; Stefano, G.; Danilo, D.; Vikal, V.; Ranjan, P.; Sha, W.; Max, F.; Rachel, M.; Elin, L.; Kotb. A.; Saioa, E.; Claudio, L.; Ettore, N.; Alessandra, Q.; Emiliano, B.; Leonardo, M.; Myriam, G.; Dan, D.M.; Pierfausto, S.; Luciana, M.; Marco, F.; Alessandro, P. Regulation of HuR structure and Function by dihydrotanshinone-I. *Nucleic Acid Research*, **2017**, *45*, 9514-9527.

[2] Wang, H.; Zeng, F.; Liu, H.; Niu, L.; Teng, M.; Li, X. The structure of the ARE-binding domains of Hu antigen R (HuR) undergoes change during RNA binding. *Acta Crystallogr D Biol Crystallogr*. **2013**. *69*, 373-80.

Poster communication 38 – WG 4

Recent validations of the ab initio-grounded SIBFA polarizable molecular mechanics/dynamics potential for inhibitor Zn-metalloenzyme complexes. Perspectives for large-scale, massively parallel, molecular dynamics simulations.

Nohad Gresh[a], Karolina Kwapien[a], Léa El Khoury[a], Louis Lagardère[a], Laurent Salmon[b], Jean-Philip Piquemal[a]

[a]*Laboratoire de Chimie Théorique, Sorbonne Universités, UPMC, UMR7616 CNRS, Paris, France*

[b]*Laboratoire de Chimie Bioorganique et Bioinorganique, ICMMO, Université Paris-Saclay*

e-mail address gresh@lct.jussieu.fr

In the SIBFA polarizable molecular mechanics/dynamics procedure, the interaction energy is formulated as a sum of five distinct contributions: electrostatic, short-range repulsion, polarization, charge-transfer and dispersion, formulated, calibrated and validated on the basis of ab initio QC energy decomposition analyses (EDA). Inhibitor-metalloenzyme complexes are a major domain for its applications. We present validation tests in two cases: the complexes of hydroxamate-based inhibitors to the Zn-dependent phosphomannose-isomerase (PMI) enzyme, which is involved in bacterial and parasitic diseases [1, 2], and the complexes of anionic triazole thione derivatives to the Zn(II)-binding sites of L1 and VIM-2 metallo-□-lactamases, which are responsible for the acquired resistance of bacteria to antibiotics [3]. For the PMI-complexes, the QC validations can encompass up to 280 atoms. □E(SIBFA) matches □E(QC) with relative errors <2-3% and the trends in interaction energies of 12 different complexes (four inhibitors in three poses from MD) are closely reproduced. For the MBL complexes, SIBFA closely reproduces the values of □E(QC) for the binding of three triazole thione derivatives in the two monozinc and in the dizinc binding site, and the trends of the separate □E(QC) contributions. SIBFA is being ported into the massively parallel 'Tinker-HP' code [4]. Perspectives for large-scale molecular dynamics simulations in this context are discussed.

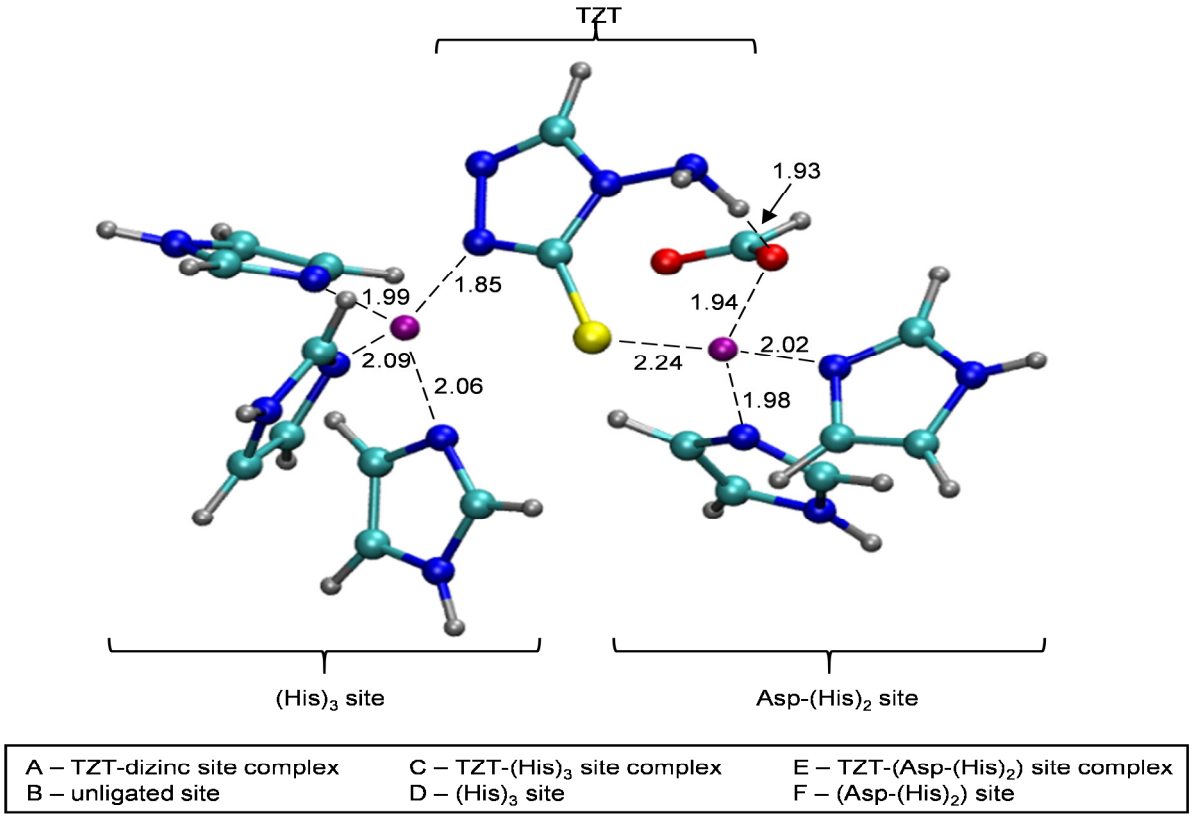


Figure 1: *Complex of the dizinc binding site of VIM-2 Zn-metallo-beta-lactamase with a triazole thione ligand*

References.

[1]. Complexes of a Zn-Metalloenzyme Binding Site with Hydroxamate-Containing Ligands. A Case for Detailed Benchmarkings of Polarizable Molecular Mechanics/ Dynamics Potentials When the Experimental Binding Structure is Unknown. N.Gresh, D. Perahia, B. de Courcy, J. Foret, C. Roux, L. El-Khoury, J-P. Piquemal, L. Salmon, *J. Comput. Chem.*, **2016**, *37*, 2770-2782.

[2] Importance of explicit smeared lone-pairs in anisotropic polarizable molecular mechanics. Torture track angular tests for exchange-repulsion and charge transfer contributions. L. El Khoury, S. Naseem-Khan, K. Kwapien, Z. Hobaika, R. Maroun, J-P. Piquemal, N. Gresh, *J. Comput. Chem.*, **2017**, 38, 1897-1920. (COVER)

[3]. Calibration of 1,2,4-triazole-3-thione, an original Zn-binding group of metallo-□-lactamase inhibitors. Validation of a polarizable MM/MD potential by *ab initio* quantum chemistry (QC). K. Kwapien, M. Damergi, S. Nader, L. El Khoury Z. Hobaika,R. G. Maroun, J.-P. Piquemal, L.Gavara, D. Berthomieu, J.-F. Hernandez, N. Gresh**,** *J. Phys. Chem. B*, **2017,** *121,* 6295-6312.

[4] Tinker-HP: a Massively Parallel Molecular Dynamics Package for Multiscale Simulations of Large Complex Systems with Advanced Polarizable Force Fields.L. Lagardere, L.-H. Jolly, F. Lipparini, F. Aviat, B. Stamm, Z. F. Jing, M. Harger, H. Torabifard, G. A. Cisneros, M. J. Schnieders, N. Gresh, Y. Maday, P. Ren, J. W. Ponder, J.-P. Piquemal, *Chem. Sci.,* **2018**, *9*, 956-972.

Poster communication 39 – WG 4

Small-molecule immune system modulators to fight Cancer

R. Acúrcio[a], A. Scomparin[b], R.Satchi-Fainaro[b], H. F. Florindo[a], Rita C. Guedes[a]

[a]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal.*
[b]*Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
rguedes@ff.ulisboa.pt

Immunotherapy is nowadays a powerful strategy in cancer therapy with very exciting outcomes. In particular, modulation of immune checkpoint receptors have gain special attention. These immune regulators limit activation and proliferation of T cells and other immune cells enrolled in these signaling pathways. Under normal conditions, they are essential in modulating immune responses; however, they are also one of the major mechanisms used by tumors to evade immune system recognition and destruction. To date, several immune checkpoint receptors have been identified and used as therapeutics in oncology, as programmed cell death protein 1 (PD-1). When engaged by one of its ligands (PD ligand 1 (PD-L1) and PD ligand 2) PD-1 limits autoimmunity. PD-1 ligands are upregulated in many human cancers and their blockade could lead to activation of T cells and therefore enforce tumor recognition. In fact, PD-1/PD-L1 pathway is one of the most successful pathways in the context of clinical cancer immunotherapy with several approved drugs. The most successful therapies relay on the use of antibodies. However, despite their outstanding success, they still have numerous disadvantages as severe immune-related adverse [1, 2].
Recently, the hypothesis of small-molecule modulators as safer therapeutic alternatives has been raised. However, limited efforts have been directed toward immune checkpoint receptors. Our study is focused on the discovery of small molecules targeting PD-L1 that can block PD-1/PD-L1 interaction in order to overcome antibody therapy disadvantages. The limited structural information concerning PD-L1 led us to a detailed structural characterization based on *in silico* studies in order to assess structural flexibility, gating or binding pockets. Following a computer assisted drug discovery approach to achieve PD-L1 inhibitors, we accomplished a de novo design campaign based on the (2-methyl-3-biphenylyl)methanol derivatives generating several scaffolds. Potential PD-L1 inhibitors were selected using several parameters.
The binding affinity and functionality of selected PD-L1 inhibitors were assessed on different human and mice cancer cell lines by ELISA and Flow Cytometry. A multi-target approach have been used to target simultaneously other immune checkpoint receptors

References

[1] Pardoll D. et al., Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell*, **2015**, *27*, 450-61.

[2] Sharma P. et al., Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell*, **2015**, *161*, 205-14.

Poster communication 40 – WG 4

The viral surface glycoproteins on HIV-1 and HIV-2 infections: Computer aided structural elucidation and molecular dynamics

Patrícia Serra[1], Andreia Martins[1], Nuno Taveira[1,2], Rita C. Guedes[1]

(1) iMed.ULisboa, Research Institute for Medicines and Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal, (2) Instituto Superior de Ciências da Saúde Egas Moniz (ISCSEM), Quinta da Granja, 2829-511 Monte da Caparica, Portugal

pfserra@ff.ulisboa.pt

None of the current drugs effectively prevents entry into the cells and the efficacy of the available drugs is very limited against HIV-2. HIV envelope glycoproteins mediate binding to the receptor CD4 and co-receptors at the surface of the target cell, enabling fusion with the cell membrane and viral entry.(1,2,3) The discovery of multiple new hit compounds that can be used as useful starting points towards drug candidates for HIV-1 and HIV-2 therapy is the main goal of this work. The viral gp120 and gp125 are critical to the receptors recognize and allowing internalization of viral content into the cell. Its modulation can lead to the disturbance of the entry viral mechanism.

In the absence of a crystallographic structure of HIV-2 envelope gp125 comprising variable domains, computer aided modulation is crucial to identify structural features in the variable regions that correlate with HIV-2 tropism and susceptibility. A 3D structure of HIV-2ROD gp125 was generated by homology modelling, using MOE2016 and MODELLER 9v19. Additionally, to disclose the importance of the main structural features and compare with experimental results, 3D-models of six mutants were also generated. These mutations revealed selectively impact in the behaviour of the protein. Additionally, molecular dynamics is being performed, using Gromacs 2006.3, in order to better characterize the full protein and disclose its the biological dynamic behaviour. It is primordial to understand the structural behaviour of these domains inserted in the main structure. The mutations revealed selectively impact in the behaviour of the protein. Structurally, the mutations studied leads to a loss of aromatic features, very important for the establishment of π-π interactions, which could induce a structural preference by a specific coreceptor.

Bibliographic references:

1) Kwong, P. D. et al. Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. Nature 1998; 393: 648–59. 2) Uchtenhagen, H. et al. Crystal structure of the HIV-2 neutralizing Fab fragment 7C8 with high specificity to the V3 region of gp125. PLoS One 2011;6: e18767. 3. Davenport, Y. W., West, A. P. & Bjorkman, P. J. Structure of an HIV-2 gp120 in Complex with CD4. J. Virol. 2016;90: 2112–18.

Acknowledgements: Fundação para a Ciência e a Tecnologia for PhD Grant SFRH/BD/100643/2014 of Patrícia Serra and UID/DTP/04138/2013.

Author index

Legend Prefix_# progressive number
PL Plenary communication SC Short communication PC Poster communication

Acúrcio R.
PC_39 67
Ahinko M.
PC_16 43
Alancay E.
PC_32 59
SC_9 17
Alcaro F.
SC_11 19
SC_5 12
Alcaro S.
PC_33 60
PC_35 62
PC_37 64
SC_18 26
SC_6 13
Alexandrova R.
PC_25 52
Alptuzun V.
PC_32 59
Alptüzün V.
SC_5 12
Alvariño R.
PC_17 44
Ambrosio F.A.
PC_37 64
Amorim R.
PC_20 47
Anacak G.Y.
PC_32 59
SC_9 17
Araškov J.
SC_14 22
Artese A.
PC_35 62
Bagetta D.
PC_35 62
SC_11 19
SC_18 26
SC_5 12
Balleková J.
SC_15 23
Balou S.
PC_1 28
Barraja P.
PC_33 60
Bartolini M.
PC_28 55
Bartuzi D.
PC_11 38
Bartyzel A.
PC_11 38
Battisti V.
PC_3 30
Baykan S.
SC_9 17
Bayraktar G.
SC_5 12
Begines P.
PC_28 55
Belen N.
SC_9 17
Benfeito S.
PC_20 47
Benhida R.
SC_1 8
Bertoni F.
SC_18 26
Biała G.
PC_11 38
Bolognesi M.L.
PC_28 55
SC_3 10
Borges F.
PC_20 47
SC_4 11
SC_6 13
Botana L.M.
PC_17 44
Botta M.
PC_29 56
Bouchentouf S.
PC_26 53
Bouhlel A.
PC_7 34
Bureau R.
PC_22 49
Burke A.J.
SC_18 26

Cagide F.
PC_20 47
SC_4 11
Calebiro D.
PC_9 36
Cantelli C.
PC_4 31
Carbone A.
PC_33 60
Carillo P.
SC_2 9
Carreiro E.P.
SC_18 26
Castoldi L.
PC_24 51
Castro M.
PC_11 38
Catalano R.
PC_35 62
SC_11 19
Ceña V.
PC_8 35
Chavarria D.
SC_4 11
SC_6 13
Collina S.
PC_37 64
Colombo G.
PC_34 61
Costa G.
PC_35 62
PC_37 64
Čudina O.
PC_5 32
D'annessa I.
PC_34 61
Dallemagne P.
PC_23 50
SC_3 10
Davis A.
PC_23 50
SC_3 10
De La Torre C.
PC_8 35
Decker M.
PC_9 36
SC_7 14
Demange L.
SC_1 8
Demiris S.
SC_9 17
Demiroz T.
SC_9 17
Di Marino D.
PC_34 61
Dinev D.
PC_25 52
Dobričić V.
PC_5 32
Drakopoulos A.
PC_9 36
Draskovits G.
PC_6 33
Duffies M.
SC_1 8
Durcik M.
PC_6 33
Dvorácskó S.
SC_8 16
Efthimiadou E.
PC_1 28
Efthimiadou E.K.
PC_15 42
El Khoury L.
PC_38 65
Farrell N.
PC_31 58
Fernandes C.
PC_20 47
SC_4 11
Fernandes M.X.
PC_28 55
Fernández-Bolaños J.G.
PC_28 55
Fersing C.
PC_7 34
Filipović N.
SC_14 22
Florindo H.F.
PC_39 67
Galán A.R.
PC_28 55
Gallego-Yerga L.
PC_8 35
Galons H.
PL_2 6
García Fernández J.M.
PC_8 35

Garcia S.N.
SC_10 18
García-Sosa A.T.
SC_17 25
Garrigue P.
PC_7 34
Gaspar A.
SC_6 13
Gaudio E.
PC_33 60
SC_18 26
Gentzsch C.
PC_9 36
Ghalem S.
PC_26 53
Giallombardo D.
PC_33 60
Glavcheva M.
PC_25 52
González-Noya A.M.
PC_17 44
Grabchev I.
PC_10 37
Granier S.
PC_9 36
Gresh N.
PC_38 65
Guedes R.C.
PC_39 67
PC_40 68
SC_9 18
Guillet B.
PC_7 34
Guillet V.
PC_27 54
Gunesch S.
SC_7 14
Hagenow S.
PC_12 39
PC_14 41
Håheim K.S.
PC_21 48
Hatat B.
PC_23 50
Helgeland Urdal I.T.
PC_21 48
Hermine O.
PC_30 57
Hoffmann M.
SC_7 14
Holzer W.
PC_18 45
PC_24 51
Hopfgartner G.
PC_30 57
Horakova L.
PC_27 54
Hunyadi A.
PC_27 54
Huuskonen J.
PC_16 43
Ilaš J.
PC_5 32
PC_6 33
Janjić G.
SC_14 22
Jobin M.L.
PC_9 36
Johnson A.D.
SC_16 24
Joseph Buhagiar A.
SC_16 24
Jukič M.
PC_36 63
Juvonen R.O.
PC_16 43
Kaczor A.A.
PC_11 38
Kaleta M.
PC_14 41
Kambouche N.
PC_26 53
Karcz T.
PC_12 39
Kędzierska E.
PC_11 38
Kerese S.
PC_26 53
Kieć-Kononowicz K.
PC_12 39
PC_14 41
SC_13 21
Kikelj D.
PC_5 32
PC_6 33
Kondej M.
PC_11 38
Koskimies P.
PC_16 43

Koszła O.
PC_11 38
Kotańska M.
PC_12 39
Koukouvitaki M.
PC_15 42
Kováčiková L.
SC_15 23
Kruschel R.
PC_13 40
Kuder K.J.
PC_12 39
Kwapien K.
PC_38 65
Lagardère L.
PC_38 65
Lagunes I.
PC_28 55
Lalut J.
PC_23 50
SC_3 10
Langer T.
PC_18 45
PC_24 51
PC_3 30
Lanthier C.
SC_3 10
Latacz G.
SC_13 21
Łażewska D.
PC_14 41
SC_13 21
Lecoutey C.
PC_23 50
SC_3 10
Lemaitre S.
PC_22 49
Lepailleur A.
PC_22 49
Lepelletier Y.
PC_30 57
Limongelli V.
PC_34 61
SC_12 20
Lindbäck E.
PC_21 48
Lisowski V.
PC_4 31
López Ó.
PC_28 55
SC_18 26
Lupia A.
PC_35 62
SC_11 19
Maccioni E.
PC_19 46
Macedonio G.
SC_8 16
Magri D.C.
SC_16 24
Májek P.
SC_15 23
Májeková M.
PC_27 54
SC_15 23
Malawska B.
PC_14 41
Maneiro M.
PC_17 44
Marchio L.
PC_15 42
Marques C.S.
SC_18 26
Marques M.M.
SC_9 18
Martins A.
PC_40 68
Maruca A.
PC_35 62
SC_11 19
Mašič L.P.
PC_5 32
PC_6 33
Mateo L.
SC_1 8
Matosiuk D.
PC_11 38
Maurel D.
PC_9 36
Maurice T.
SC_7 14
Maya I.
PC_28 55
McCarthy F.O.
PC_13 40
Medina A.M.
SC_2 9

Meleddu R.
PC_19 46
Mellet C.O.
PC_8 35
Merino-Montiel P.
PC_28 55
Mesiti F.
PC_35 62
SC_6 13
Meza-Reyes S.
PC_28 55
Misicka A.
PC_30 57
Mitsopoulou C.A.
PC_1 28
PC_15 42
Moesslacher J.
PC_3 30
Mogilski S.
PC_12 39
Mollica A.
SC_8 16
Montalbano A.
PC_33 60
Monti B.
PC_28 55
Montiel-Smith S.
PC_28 55
Moraca F.
PC_35 62
Müller C.E.
SC_13 21
Navarro-Teulon I.
PC_4 31
Niinivehmas S.
PC_16 43
Nyerges Á.
PC_6 33
Oguzhan K.
PC_32 59
Olejarz-Maciej A.
SC_13 21
Oliveira C.
PC_20 47
Oliveira P.J.
PC_20 47
SC_4 11
Orofino F.
PC_29 56
Ortuso F.
PC_33 60
PC_35 62
SC_11 19
SC_5 12
Ozbek E.N.
PC_32 59
Pace V.
PC_17 45
PC_24 51
Padrón J.M.
PC_28 55
SC_14 22
Pages G.
SC_1 8
Pál C.
PC_6 33
Parlar S.
PC_32 59
SC_5 12
Pasanen M.
PC_16 43
Pedrido R.
PC_17 44
Peña-Altamira L.E.
PC_28 55
Pentikäinen O.T.
PC_16 43
Petrova Z.
PC_25 52
Piquemal J.-P.
PC_38 65
Podlipnik Č.
PC_36 63
Popović J.
SC_14 22
Posadas I.
PC_8 35
Postila P.A.
PC_16 43
Pouget J.P.
PC_4 31
Poveda B.M.
SC_2 9
Pułka-Ziach K.
PC_30 57
Puszko A.
PC_30 57
Quesada A.R.
SC_2 9

Račková L.
SC_15 23
Raniolo S.
PC_34 61
SC_12 20
Rauhamäki S.
PC_16 43
Rault S.
PC_22 49
Raunio H.
PC_16 43
Rečnik L.M.
PC_4 31
Remião F.
SC_4 11
Révész T.
PC_6 33
Rocca R.
PC_35 62
SC_11 19
Rochais C.
PC_22 49
PC_23 50
SC_3 10
Roldán-Peña J.
PC_28 55
Roman B.
PC_2 29
Romeo I.
PC_35 62
Romero-Hernández L.L.
PC_28 55
Ronco C.
SC_1 8
Rotundo S.
PC_35 62
Rouco L.
PC_17 44
Salmon L.
PC_38 65
Satchi-Fainaro R.
PC_39 67
Savić J.
PC_5 32
Scheiner M.
SC_7 14
Scomparin A.
PC_39 67
Seier K.
PC_9 36
Senatore R.
PC_18 45
Sequeira L.
PC_19 46
Serra P.
PC_40 68
Sevin G.
PC_32 59
SC_9 17
Silva A.G.
PC_11 38
Silva T.
SC_6 13
Since M.
PC_23 50
SC_3 10
Sissi C.
PC_31 58
Skok Ž.
PC_6 33
Soares P.
PC_20 47
Sopkova De Oliveira Santos J.
PC_22 49
Sosnowski P.
PC_30 57
Sounier R.
PC_9 36
Spanò V.
PC_33 60
Spassov R.
PC_25 52
Spiteri J.C.
SC_16 24
Staneva D.
PC_10 37
Stark H.
PC_12 39
PC_14 41
Stefanucci A.
SC_8 16
Štefek M.
SC_15 23
Stępnicki P.
PC_11 38
Stiller C.
SC_7 14
Sydnes M.O.
PC_21 48

Sylla Iyarreta Veitía M.
PL_1 5
Szczepańska K.
PC_12 39
Tammela P.
PC_6 33
Targowska-Duda K.M.
PC_11 38
Taveira N.
PC_40 68
Teixeira J.
PC_20 47
Thirumaran S.L.
PC_22 49
Todorović T.
SC_14 22
Tomašič T.
PC_5 32
PC_6 33
Tömböly C.
SC_8 16
Toublet F.-X.
PC_23 50
Touqeer S.
PC_24 51
Tuglio G.I.
PC_29 56
Urban E.
PC_18 45
PC_3 30
Vanderheydt C.
PC_3 30
Vasileva-Tonkova E.
PC_10 37
Vega Báez J.L.
PC_28 55
Viskupicova J.
PC_27 54
Višnjevac A.
SC_14 22
Wróbel T.M.
PC_11 38
Xiao E.
PC_22 49
Załuski M.
SC_13 21
Zaręba P.
PC_14 41
Zarkadoulas A.
PC_15 42
Zidar N.
PC_5 32
PC_6 33
Żuk J.
PC_11 38