MedChem 2022 Barcelona

XI Paul Ehrlich Euro-PhD Network

BOOK OF ABSTRACTS

Institut Químic de Sarrià – Universitat Ramon Llull (IQS-URL)
Barcelona, July 14th-16th 2022

www.pehrlichmedchem.eu
medchem2022@iqs.url.edu
WELCOME PREFACE

“The Organizing Committee cordially invites you to participate at MedChem 2020 (X Meeting of the Paul Ehrlich Euro-PhD Network) to be held in Barcelona from the 11th to the 13th of June 2020…”

Little could I have imagined when I wrote these sentences in an, already distant, 2019 that the rumors that something was not right in China were going to turn into a global pandemic that would force firstly to postpone and then to cancel the said meeting.

The COVID pandemic has affected the lives of all humanity, it has affected our freedoms, it has produced immense economic damages but, above all, it has meant the loss of millions of lives. On behalf of the IQS School of Engineering and the Organizing Committee, our support, and condolences to all members of the Paul Ehrlich Community who have lost family and/or friends during this pandemic.

Within this drama, we have also seen that Medicinal Chemistry, Biotechnology, Pharmacology, and Medicine have responded to this enormous challenge by developing, in record time, vaccines and treatments to reduce the impact of the pandemic and help those who suffered the most acute versions of the illness. Once again science has responded to a challenge for humanity. Now, that the situation seems to be improving rapidly all over the planet and it is time to launch the MedChem 2022 (XI Meeting of the Paul Ehrlich Euro-PhD Network) next July 2022.

The MedChem2022 will be hosted by the Department of Organic and Pharmaceutical Chemistry of IQS School of Engineering of the Universitat Ramon Llull and held in Barcelona from the 14th to the 16th of July 2022.

Although all kinds of communications in the area of Medicinal Chemistry can be submitted, the Organizing Committee has decided to focus this meeting on two areas of research that are major health issues: Cancer and Anti-infectives, so communications in these two topics are especially welcomed.

The venue for the meeting will be the Conference Room of IQS School of Engineering and the adjacent hall for the poster session. The accommodation selected
is within a walking distance of IQS. We are located very close to the hills that surround Barcelona but directly connected by subway with the city center (20 min).

A social program has been prepared for the night of Friday 15th including the visit to an emblematic Barcelona monument and a dinner.

The number of participants is limited to 170. Save the dates in your calendar and come to enjoy “the Mediterranean, beautiful and big Barcelona (Antonio Gaudí 1852-1926)”.

José I. Borrell

*IQS School of Engineering (Barcelona)*

*Chair of MedChem2022 joint meeting*

Jose.borrell@iqs.url.edu
Supporting institutions
MedChem 2022

XI Paul Ehrlich Euro-PhD Network Meeting

Scientific program

Paul Ehrlich Euro-PhD Network

IQS, Barcelona (Spain), July 14th-16th
https://medchem2022.org/
Thursday, July 14th

14:00 Registration

15:00 Opening and Welcome

Introduction to the XI Paul Ehrlich Euro-PhD network meeting

J.I. Borrell  IQS School of Engineering, Universitat Ramon Llull

Welcome greeting from the authorities

J. A. Rom  Vice-Rector for Research and Innovation, Universitat Ramon Llull

J. Diaz  Dean of IQS School of Engineering

S. van Calenbergh  Coordinator of the Paul Ehrlich Network

15:30 PLENARY LECTURE 1

Chair: S. Alcaro

From enzyme inhibition to degradation: MMPs, CK and HDAC as anticancer targets

B. de Pascual-Teresa  Professor of Organic and Pharmaceutical Chemistry, Universidad San Pablo CEU, President of the Spanish Society of Medicinal Chemistry, SFQT

SESSION A — Mini-Symposium Cancer

16:00 Invited Lecture A

Tackling oncogenic signaling and tumor-stroma crosstalk in aggressive B-cell lymphoma

G. Roué  Lymphoma Translational lab, Josep Carreras Leukaemia Research Institute, IJC

16:30 Flash Posters in 2 min (FP-1 → FP-12)

17:00 Coffee break and Poster Session A

17:45 OC-A1/ R. Listro  Towards the identification of novel compounds targeting HuR-RNA complexes

18:00 OC-A2/ D. Secci  Molecular hybrids as a valid strategy to modulate carbonic anhydrase isozyme inhibitors selectivity


18:30 OC-A4/ J. Ceramella  Anti-melanoma and antioxidant properties of Annona cherimola Mill. leaves extracts

18:45 OC-A5/ R. Cosials  PET imaging of self-assembled 18F-labelled Pd2L4 metallacages for anticancer drug delivery

19:00 Welcome Party  Cloister of the Casa d’Exercícis dels Jesuïtes
**Friday, July 15th**

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<tr>
<th>Time</th>
<th>Session</th>
<th>Chair</th>
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<tbody>
<tr>
<td>9:00</td>
<td><strong>PLENARY LECTURE 2</strong></td>
<td>J.J. Borrell</td>
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<td><em>Another awakening: Discovering a new drug for narcolepsy</em></td>
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<td></td>
<td><strong>Y. Auberson</strong> Executive Director in Global Discovery Chemistry, Novartis Institutes for BioMedical Research. Past President of the European Federation for Medicinal Chemistry and Chemical Biology, EFMC</td>
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<tr>
<td>9:30</td>
<td><strong>SESSION B — Mini-Symposium Anti-infectives</strong></td>
<td>P. Marchand</td>
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<td>9:30</td>
<td><strong>Invited Lecture B</strong></td>
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<td><em>Pan-antiviral strategies: the future ahead</em></td>
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<td><strong>N. Izquierdo</strong> Pathogen Immunity, Signaling and Therapeutic Applications, IRSi Caixa</td>
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<td>10:00</td>
<td><strong>Flash Posters in 2 min (FP-13 → FP-32)</strong></td>
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<td>10:30</td>
<td><strong>Coffee break and Poster Session B</strong></td>
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<td>11:15</td>
<td><strong>OC-B1/ Martina Pacetti</strong></td>
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<td></td>
<td>Cycloheptatriphene-3-carboxamides exert potent anti-influenza activity by interfering with polymerase PA-PB1 heterodimerization</td>
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<td>11:30</td>
<td><strong>OC-B2/ Silvia Cammarone</strong></td>
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<td>Resorc[4]arene-functionalized MWCNTs for the development of high selective and sensitive immunosensors</td>
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<td><strong>OC-B3/ Roberta Bivacqua</strong></td>
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<td><em>In silico approaches for the identification of HSV-1 Glycoprotein D inhibitors</em></td>
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<td>12:00</td>
<td><strong>OC-B4/ Bárbara Nunes</strong></td>
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<td>Antibacterial activity of ionic liquids against Staphylococcus aureus</td>
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<td>12:15</td>
<td><strong>OC-B5/ Leticia Manén</strong></td>
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<td>Looking for new anti-marial drugs in the Tafenoquine Chemical Space: the Markush Dilemma.</td>
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<td>12:30</td>
<td><strong>Keynote: mRNA vaccines beyond Covid19</strong></td>
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<td><strong>R. Magaña</strong> Group of Materials Engineering, Gemat, IQS School of Engineering</td>
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<td>13:00</td>
<td><strong>Lunch</strong> IQS Bar-Restaurant</td>
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<td>14:30</td>
<td><strong>Meeting of PE Coordinators and Free Time</strong></td>
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**SESSION C — Mini-Symposium Other Diseases**

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<th>Time</th>
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<th>Speaker/Title</th>
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<tr>
<td>15:30</td>
<td>Invited Lecture C</td>
<td>Chair D. Secci</td>
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<td>Harnessing multi-target drug discovery for neurodegeneration</td>
<td>M. L. Bolognesi, Professor of Medicinal Chemistry, Università di Bologna</td>
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<td>16:00</td>
<td>OC-C1/ Rosa Purgatorio Synthesis and biological evaluation of novel</td>
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<td>piperazine-containing selective BChe inhibitors as potential multimodal</td>
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<td>neuroprotective agents for Alzheimer's disease</td>
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<td>16:15</td>
<td>OC-C2/ Emanuela Berrino Carbon Monoxide Releasing Molecular Hybrids,</td>
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<td>Synthesis and Biological Evaluation of New Potent Anti-Inflammatory</td>
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<td>Agents</td>
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<td>16:30</td>
<td>Flash Posters in 2 min (FP-33 → FP-44)</td>
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<td>17:00</td>
<td>Coffee break and Poster Session A</td>
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<td>17:45</td>
<td>OC-C3/ Rebecca Appiani Pyrrolidinyl benzofurans and benzodioxanes:</td>
<td>Selective α4β2 nAChR ligands with different activity profiles at the two</td>
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<td>Multi-target 5-HT2A/D2 receptor ligands</td>
<td>receptor stoichiometries</td>
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<td>18:00</td>
<td>OC-C4/ Agata Zięba The 3D-QSAR studies aimed to assist the development</td>
<td>novel multi-target 5-HT2A/D2 receptor ligands</td>
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<td>of novel multi-target 5-HT2A/D2 receptor ligands</td>
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<td>18:15</td>
<td>OC-C5/ Raúl Ondoño Novel MD-based drug candidates against DM1 toxic</td>
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<td>18:30</td>
<td>Social Program Visit To MNAC and dinner at Hotel La Florida</td>
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**Saturday, July 16th**

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<th>Time</th>
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<th>Chair/Presenter</th>
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<tr>
<td>9:30</td>
<td>PLENARY LECTURE 3</td>
<td>Chair X. Berzosa</td>
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<td>Going with the Flow – The Use of Continuous Processing for Making</td>
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<td>APIs</td>
<td>C. O. Kappe, Professor of Chemistry, University of Graz</td>
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<td>10:30</td>
<td>Coffee break</td>
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<td>11:00</td>
<td>Presentation of the SEQT B. Pascual-Teresa</td>
<td>Chair E. Maccioni</td>
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<td>PE MedChem Euro-PhD Label communications</td>
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<td>PEA-1/ A. Corcione Natural products in drug discovery In Silico</td>
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<td>approaches for the detection of new hits against unexplored molecular</td>
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<td>PEA-2/ M.G. Nizi Discovery of potent and selective PARP inhibitors as</td>
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<td>valuable pharmacological tools</td>
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<td>PEA-3/ M. Rullo MAO B-centered multitargeting ligands against</td>
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<td>neurodegenerative disorders</td>
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<td>PEA-4/ M. Barreca Insight on pyrrole[1,2]oxazole derivatives in</td>
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<td>multiple lymphoma subtypes</td>
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<td>PEA-5/ S. Mirabile Structure- and Ligand-based optimization of</td>
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<td>fragment binding Tyrosinase from Agaricus bisporus to develop</td>
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<td>anti-melanogenic agents</td>
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<td>13:00</td>
<td>Closing Remarks</td>
<td>Chair A. B. Cuencía</td>
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7
Plenary Lectures
Plenary Lecture 1

From enzyme inhibition to degradation: MMPs, CK and HDAC as anticancer targets

Beatriz de Pascual-Teresa, Claire Coderch, Irene Ortín, José María Zapico, Laura Marquez-Cantudo, Lourdes Acosta, Alba Gil, Mateusz Daško and Ana Ramos

Departamento de Química y Bioquímica, Facultad de Farmacia, Universidad San Pablo-CEU, Urbanización Montepríncipe, 28668 Madrid, Spain.

bpaster@ceu.es

Traditional anticancer drug design based on small molecules continues to be a powerful strategy for the development of novel chemotherapeutics. However, these anticancer therapies are facing major problems such as drug resistance, especially in advanced cancers [1]. This is mainly due to the alterations in the target, ineffective apoptosis or activation of different pathways, among others. Furthermore, the lack of active targeting to tumor cells from conventional chemotherapy hinders candidates chances of success in the clinic.

Based on these considerations, and bearing in mind the role of Protein kinase 2 (CK2), Histone DeAcetylases (HDACs) and Matrix Metalloproteases (MMPs) enzymes in the development and progression of tumors, we work on the design of compounds based on different strategies.

We have developed potent and selective matrix metalloproteinase MMP2 inhibitors based on the use of click chemistry as a synthetic tool to connect the scaffold containing a Zinc Binding Group (ZBG), with appropriate subunits designed to interact with the hydrophobic S1’ pocket of the enzyme [2]. Following this strategy we have also found an interesting hit for the future development of potent and selective MMP13 inhibitors with application in osteoarthritis [3].

We are now working on the development of more efficient cancer therapies such as dual CK2/HDAC inhibitors [4], PROteolysis TArgeting Chimeras (PROTACs), and the synthesis of Folate Conjugates (FCs) to target the therapeutic agent towards tumor cells.

Financial support from RTI2018-093539-B-I00 and PID2021-123786OB-I00 (MICIU/FEDER, UE) is kindly acknowledged.


The discovery of LML134, a drug for narcolepsy patients.

Yves P. Auberson

Novartis Institute for Biomedical Research

WSJ-88.10, Novartis Campus, 4058 Basel, Switzerland

yves.auberson@novartis.com

Histamine H3 receptor (H3R) inverse agonists that have been in clinical trials for the treatment of excessive sleep disorders, have been plagued with insomnia as a mechanism-based side effect. We focused on the identification of compounds that achieve high receptor occupancy within a short time, followed by rapid disengagement from the receptor, a target profile that ended up providing therapeutic benefits without the undesired side effects. This talk will describes the optimization work and medicinal chemistry principles that led to the discovery of LML134.

Plenary Lecture 3

Going with the Flow – The Use of Continuous Processing for Making APIs

C. Oliver Kappe

Institute of Chemistry, University of Graz
Heinrichstrasse 28, 8010 Graz, Austria
oliver.kappe@uni-graz.at

Continuous flow processes form the basis of the petrochemical and bulk chemicals industry where strong competition, stringent environmental and safety regulations, and low profit margins drive the need for highly performing, cost effective, safe and atom efficient chemical operations. In contrast to the commodity chemical industry, however, the fine chemical industry primarily relies on its existing infrastructure of multipurpose batch or semi-batch reactors. Fine chemicals, such as drug substances and active pharmaceutical ingredients (APIs), are generally considerably more complex than commodity chemicals and usually require numerous, widely diverse reaction steps for their synthesis. These requirements generally make versatile and reconfigurable multipurpose batch reactors the technology of choice for their preparation. However, the advantages of continuous flow processing are increasingly being appreciated also by the pharmaceutical industry and, thus, a growing number of scientists, from research chemists in academia to process chemists and chemical engineers in pharmaceutical companies, are now starting to employ continuous flow technologies on a more routine basis [1].

In this lecture, contributions from our research group in the field of continuous flow processing will be highlighted. Emphasis will be given to highly atom efficient and process intensified chemical transformations useful for the synthesis of APIs or key intermediates that are often too hazardous to be executed in a batch reactor. These involve azide, diazomethane and nitration chemistry, oxidation reactions involving pure oxygen, and flow photochemistry/electrochemistry applications.

Session A

Mini-Symposium Cancer

Invited Lecture
Invited Lecture A

Tackling oncogenic signaling and tumor-stroma crosstalk in aggressive B-cell lymphoma

Gaël Roué

Lymphoma Translational lab
Josep Carreras Leukaemia Research Institute
Ctra de Can Ruti, Camí de les Escoles s/n, 08916 Badalona, Spain

groue@carrerasresearch.org

Aggressive B-cell lymphomas are clinically and pathologically diverse and reflect multiple pathways of transformation involving, among others, oncogenic signalling, lymphoma-stroma crosstalk and intrinsic protein homeostasis. Alterations in these highly regulated processes play a key role in the progression of the malignant clone and correlate with a high failure rate in treatment protocols. In the last decade, new therapies applied to the treatment of B-cell lymphoma have significantly improved the overall survival of these patients, but so far no single agent can cure these diseases. At the origin of the gap between promising preclinical results and failure in clinical phase II/III, conventional preclinical models lack predictive value in the main trials carried out in these cancer subtypes.

To foster the bench-to-bedside translation of innovative therapeutic strategies more selective and more suited to the biology of B-cell lymphoma, our team has been focused on the development of innovative in vitro (2D and 3D multicellular co-cultures) and in vivo (mice and chicken embryo xenografts) models of the most prevalent and/or aggressive subtypes of B-cell non-Hodgkin lymphoma (NHL). In the last 10-15 years, these models allowed us to unravel some crucial aspects of the interplay between lymphoma cells and their stroma, and to decipher the mechanism of action of several agents directed against specific tumour-associated processes like protein homeostasis, microenvironment signalling, or epigenetic control of cancer cell growth [1-3].

Session A
Mini-Symposium Cancer
Oral Communications A
Towards the identification of novel compounds targeting HuR–RNA complexes

Roberta Listro, Martina Garbagnoli, Pasquale Linciano, Daniela Rossi, Simona Collina

Department of Drug Sciences, University of Pavia, Via Taramelli, 12, 27100 Pavia, Italy
roberta.listro01@universitadipavia.it

RNA Binding Proteins (RBPs) are key mediators of RNA metabolism and play a relevant role in post-transcriptional process of gene expression. Particularly, HuR, belonging to the family of ELAV proteins, has attracted the attention of the scientific community as innovative target against cancer, owing to its regulatory role in various aspects of tumorigenesis, i.e. cell proliferation, angiogenesis and metastasis. In particular, the identification of novel small molecules able to modulate HuR activity generate much interest[1].

In this context, we design and synthesized novel promising HuR ligands taking advantages of STD-NMR as a powerful technique for evaluating the ability of compounds to interact with HuR. Particularly, compound RBA-4 was selected and properly investigated, highlighting its interaction with HuR protein. Thus RBA-4 was used as template molecule to develop compounds able to modulate the stability of HuR–mRNA complexes. Combining SPR screening, STD NMR spectroscopy, molecular modeling, novel compounds able to bind HuR have been identified. Moreover, the capability of the new compounds to interfere with the formation of the HuR-mRNA complex have been evaluated by fluorescence polarization (FP) [2].

Herein we present our efforts in optimization of compounds belonging to RBA series and in evaluation of their ability to interfere with HuR–mRNA complexes.

Oral Communication A2 (OC-A2)

Molecular hybrids as a valid strategy to modulate carbonic anhydrase isozyme inhibitors selectivity

Daniela Secci, a Simona Distinto, a Erica Sanna, a Alessia Onali, a Rita Meleddu, a Stefano Alcaro, b Claudiu T. Supuran c e Elias Maccioni a

a Department of Life and Environmental Sciences, University of Cagliari, Cagliari, Italy; A Building-Cittadella Universitaria di Monserrato S.P. 8 km 0.700, 09042 Monserrato, Italy

b Department of Health Sciences, University “Magna Græcia” of Catanzaro, Campus Universitario “S. Venuta, “Viale Europa, I-88100 Catanzaro, Italy

c Department of Neurosciences, Area del Farmaco e Salute del Bambino (NEUROFARBA) Via Ugo Schiff, 6 50019 Sesto Fiorentino, Italy
daniela.secci@unica.it

As part of our ongoing project, we investigated new scaffolds able to interact and inhibit the hCA IX and XII isozymes. Indeed, hCA IX and XII are highly overexpressed in hypoxic solid tumours and their inhibitors may act as anticancer agents by disrupting cancer cell ability to avoid apoptosis in hypoxic conditions [1]. Molecular hybridization represents a valid approach in drug design [2], [3] and, pursuing our research on hybrid molecules [4], we designed and synthesized two series of compounds with heteroaromatic-benzen sulphonamide scaffold hybridised with a substituted thiazolidinone core. Two series of compounds, EMAC10204 and EMAC10205 were synthesised, and the effect of the substitution pattern on the inhibition and selectivity towards hCA I, hCA II, hCA IX, and hCA XII isozymes have evaluated. Results showed a promising inhibitory activity in the nanomolar range on carbonic anhydrases IX and XII. In particular, the nature of substituent in the position 3 of the thiazolidinone ring appeared as determinant for the selectivity of compounds towards hCA IX and XII. Furthermore, a computational study was performed to clarify the interactions of substitutes on enzyme biding site, to gain more information about the structural requirements for both activity and selectivity.

Oral Communication A3 (OC-A3)

Haloperidol metabolite II Valproate ester-loaded NLC as promising strategy for the treatment of Uveal Melanoma

Cinzia Cimino\textsuperscript{b,b}, Claudia Giovanna Leotta\textsuperscript{c}, Carla Barbaracci\textsuperscript{id,e}, Teresa Musumeci\textsuperscript{ib,f}, Giovanni Mario Pitari\textsuperscript{c}, Claudia Carbone\textsuperscript{ib,f}, Agostino Marrazzo\textsuperscript{d}

\textsuperscript{a} PhD in Biotechnology, Department of Biomedical and Biotechnological Sciences, University of Catania

\textsuperscript{b} Laboratory of Drug Delivery Technology, Department of Drug and Health Sciences, University of Catania

\textsuperscript{c} Vera Salus Ricerca S.r.l., Siracusa

\textsuperscript{d} Medicinal Chemistry Laboratory, Department of Drug and Health Sciences, University of Catania

\textsuperscript{e} Laboratory of Medicinal Chemistry (CSIC Associated Unit), Faculty of Pharmacy and Food Sciences, and Institute of Biomedicine (IBUB), University of Barcelona

\textsuperscript{f} NANO-i, Research Centre for Ocular Nanotechnology, University of Catania

cinzia.cimino@phd.unict.it

Uveal melanoma (UM) represents one of the most common malignancies in the eye, with mortality in 50\% of patients within a year [1]. The involvement of both $\sigma$ receptors in modulating proliferation and angiogenesis suggested a possible use of $\sigma_1$ antagonist in the treatment of this disease; together with HDAc inhibitors, which seem to play an important role as adjuvants, inducing cancer cells death. In particular, the $\sigma_1$ receptor antagonists and HDAc inhibitors (±)-MRJF22, (S)-(−)-MRJF22 and (R)-(+)‐MRJF22 – prodrugs of (±)-haloperidol metabolite II conjugated with valproic acid – showed an interesting antiangiogenic effect in 92-1 uveal melanoma (UM) cells [2]. However, due to the physiological difficulties related to ophthalmic administration, nanoencapsulation into drug delivery systems represents a potential solution to efficiently reach the target site. Therefore, the aim of our work was the encapsulation of (S)-(−)-MRJF22 and (R)-(+)‐MRJF22 into nanostructured lipid carriers (NLC), selected for their advantages in ophthalmic application [3], thus obtaining S-NLC and R-NLC, respectively. The preliminary physical-chemical characterization of the compounds by Differential Scanning Calorimetry (DSC) allowed assessing their thermal behaviour, demonstrating that the temperature used in the NLC preparation method did not affect the molecules. NLC prepared with Softisan and Isopropyl myristate were produced using TRIS buffer pH 7.2-7.4 as aqueous phase, thus guaranteeing...
physiological pH and osmolarity values (respectively 7.2 and 0.260 mOsm/kg) and confirming their suitability with the intended administration route. The produced platforms had homogeneous (PDI=0.230) small particles (100-150 nm) with almost neutral zeta potential (-5 mV). Since this zeta potential value does not assure particles repulsion and long-term stability [4], accelerated stability studies were required. Following the ICH guidelines Q1A (R2), samples were stored for 6 months at 40 ± 2 °C and 75 ± 5% RH, and it emerged a great long-term stability with size and PDI values substantially unaffected. After the assessment of a good encapsulation efficiency (EE%), in vitro release studies performed using Franz cells showed a sustained release with an initial burst effect for R-NLC (65% at 24 h) reaching 87% plateau after 3 days, while a slower release rate was observed for S-NLC, with 28% of drug released after 24 h and a plateau of 34% maintained for 7 days. Finally, in vitro cytocompatibility studies were performed on 92-1 uveal melanoma cell line using blank and loaded NLC, confirming a good cell viability at concentrations below 5 µM. Finally, the activity of S-NLC and R-NLC on UM 92-1 cell proliferation were examined in vitro by crystal violet staining. Results indicate that S-NLC and R-NLC exhibited higher antiproliferative effects compared to the free compounds. In particular, at sub-micromolar concentrations, loaded-NLC were able to significantly reduce 92-1 cell proliferation compared to both the unloaded NLC and the free compounds.

The obtained results suggest that the prepared NLC are suitable for the ophthalmic delivery of (R)-(+-)MRJF22 and (S)-(--)MRJF22 enantiomers and represent a promising treatment for UM. Further studies will be performed to assess cellular uptake and in vivo eye biodistribution using fluorescent probe.

Oral Communication A4 (OC-A4)

Anti-melanoma and antioxidant properties of *Annona cherimola* Mill. leaves extracts

Jessica Ceramella\(^a\), Chiara La Torre\(^a\), Domenico Iacopetta\(^a\), Alexia Barbarossa\(^b\), Carmela Saturnino\(^c\), Alessia Fazio\(^a\), Stefano Alcaro\(^d\), Maria Stefania Sinicropi\(^a\)

\(^a\)Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, 87036 Arcavacata di Rende, Italy

\(^b\)Department of Pharmacy-Drug Sciences, University of Bari “Aldo Moro”, 70126 Bari, Italy

\(^c\)Department of Science, University of Basilicata, 85100 Potenza, Italy

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Malignant melanoma represents one of the most aggressive and deadly skin cancers among the different type of cancers. Unfortunately, the long-term efficacy of melanoma treatments is limited by the lack of clinical effects, together with the onset of side effects and resistance [1]. Thus, the research efforts are aimed at exploring of new potent and safer anticancer agents. Recently, numerous plant species, rich in various nutraceuticals, have been widely studied for their interesting biological properties. With this in mind, we identified numerous bioactive compounds in three *Annona cherimola* Mill. leaves extracts (ethanolic, methanolic and aqueous). In particular, the ethanolic extract showed the most promising and interesting anticancer activity, mostly on the malignant A2058 melanoma cell line (IC\(_{50}\)=5.6±0.8 ng/mL), together with a negligible cytotoxicity on the normal cells. It was also able to block the melanoma cells migration process, modulating the expression levels of proteins implicated in migration and angiogenesis processes, namely E-cadherin, N-cadherin, vimentin and VEGF. In addition, the A2058 cells treated with the ethanolic extract showed a clear disorganization of tubulin and actin cytoskeleton, inducing cell apoptosis. Finally, the methanolic and ethanolic extracts also showed the highest scavenging activity against the DPPH and ABTS radicals and reduced the oxidative stress induced by menadione treatment in 3T3-L1 murine fibroblasts. These interesting results demonstrate that *Annona Cherimola* Mill. leaves extracts could represent safe and valid adjuvants/alternatives to toxic chemotherapy drugs, commonly used for melanoma treatment.

Oral Communication A5 (OC-A5)

PET imaging of self-assembled \(^{18}\text{F}\)-labelled Pd\(_2\text{L}_4\) metallacages for anticancer drug delivery

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Positron emission tomography (PET) is a powerful imaging technique capable of exploring biological processes \textit{in vivo}. Recently, this technique has been used as a high-precision tool to evaluate the biodistribution of drug delivery systems. Although fluorine-18 (\(^{18}\text{F}\)) is one of the most widely used radionuclides in PET, its incorporation into the system of study through well-established chemical reactions is not always evident. Among the possible \(^{18}\text{F}\) labelling strategies, our attention was drawn away from the common \(^{18}\text{F}\)-carbon bond forming processes, focusing instead on the \(^{19}\text{F}\)-to-\(^{18}\text{F}\)-boron isotopic exchange using ammonium trifluoroborate functionalities (AMBF\(_3\)) \[1\].

With the aim of designing self-assembled metallosupramolecular architectures for drug delivery, the straightforward synthesis of AMBF\(_3\)-\(^{18}\text{F}\)-labelled [Pd\(_2\text{L}_4\)]\(^{4+}\) metallacages capable to encapsulate the anticancer drug cisplatin \[2\] is herewith reported. Combined NMR spectroscopy, high-resolution electrospray mass spectrometry (HR-ESI-MS), radio-HPLC and inductively coupled mass spectrometry (ICP-MS) studies allowed to assess the formation of the cage-drug complex. The biodistribution profiles of the cages and respective ligands have been studied by PET/CT imaging in healthy mice \textit{in vivo}, in combination to ICP-MS \textit{ex vivo}. 

Session B

Mini-Symposium Anti-infectives

Invited Lecture
Invited Lecture B

Pan-antiviral strategies and the future ahead

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Pan-antiviral strategies can counteract different viruses, and could be ready to deploy when novel outbreaks arise. This would allow to save lives until specific treatments are developed and approved. In this talk, I will present two strategies with pan-antiviral potential already tested in clinical trials identified by our group while searching for antivirals against SARS-CoV-2.

First, we analysed the virucidal potential of oral mouthwashes containing cetylpyridinium chloride (CPC), which reduced the infectivity of different variants of concern in vitro by disrupting the integrity of the SARS-CoV-2 membrane [1]. In non-hospitalized patients, CPC oral rinse, compared to placebo, was associated with a significant detection of an internal viral protein in saliva, indicating enhanced disruption of viral particles [2]. CPC-containing mouth rinses could therefore represent a cost-effective measure to reduce SARS-CoV-2 infectivity in saliva, aiding to reduce viral transmission.

In addition, we have assayed more than 72 compounds in a repurposing screening that identified plitidepsin as a potent antiviral against SARS-CoV-2 [3]. This antitumoral agent of marine origin had nanomolar activity against different variants of concern in vitro [4]. Cells exposed to SARS-CoV-2 and treated with plitidepsin did not form double membrane vesicles (DMV) required for intracellular viral replication [4]. Given that many viruses use DMV as platforms for viral replication, we are currently exploring the pan antiviral potential of plitidepsin. Phase I clinical trial in COVID-19 patients already showed safety of the treatment with plitidepsin [5]. Pan-antiviral approaches identified herein along with those yet to come may represent effective measures to be prepared for future viral outbreaks.

Session B

Mini-Symposium Anti-infectives

Oral Communications B
Oral Communication B1 (OC-B1)

Cycloheptathiophene-3-carboxamides exert potent anti-influenza activity by interfering with polymerase PA-PB1 heterodimerization


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Influenza viruses (flu) are responsible for seasonal epidemics and severe pandemic outbreaks causing high rate of morbidity and mortality. The limited therapeutic armamentarium, emergence of viral variants and development of drugs resistance prompt the urgency need to develop new anti-flu drugs. The viral RNA-dependent RNA polymerase (RdRP), a heterotrimer composed by PB1, PB2, and PA subunits, is as an attractive drug-target playing an essential role within flu replication, transcription, and evolution. A successful approach to interfere with RdRP functions is hampering protein-protein interactions involving its subunits [1]. In this context, our group focused on developing disruptors of PA-PB1 subunits interface with the best compounds characterized by a cycloheptathiophene-3-carboxamide (cHTC) scaffold. cHTC compounds showed the ability to disrupt PA-PB1 complex formation, to potently inhibit flu RdRP and viral growth, and a high barrier to drug resistance[2-4].

In the present study, additional cHTC compounds were synthesized by alternately modifying the moieties at the C-2 and C-3 position of the cHTC core, but also combining the best moieties emerged into an additional set of analogues. The study led to identify new potent anti-flu compounds characterized by the ability to interfere with PA-PB1 association and to inhibit the RdRP functions [4]. In depth studies were performed to determine their activity against a panel of fluA and fluB strains and their ability to interfere with PA-PB1 heterodimerization in a cellular context. Finally, the pharmacokinetic profile was investigated to assess the drug-like properties of the new small molecules.

Oral Communication B2 (OC-B2)

Resorc[4]arene-functionalized MWCNTs for the development of high selective and sensitive immunosensors

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One of the main problems in the development of immunosensors is to overcome the complexity of binding antibodies onto the sensor surface, thus leading to a loss of sensitivity. For this reason, in the last twenty years, macrocyclic species such as calix[4]arene has been used for the site-directed immobilization of antibodies in the correct end-on orientation. In the last years, due to their configuration and unique molecular recognition properties, resorcinol-based cyclooligomes, namely resorc[4]arenes, have been used for the development of highly sensitive immunosensors. In this project, new resorc[4]arene-based derivatives have been designed and synthesized for covalent grafting by nucleophilic substitution or cycloadDITION of multi-walled carbon nanotubes, a versatile material endowed with great electric properties, high electroactive surface area and biocompatibility. The prepared materials have been fully characterized by both morphological (FE-SEM and AFM) and spectroscopical (XPS) techniques before the construction of the immunosensors. Finally, the modified electrodes have been characterized by DPV and CV and IgG antibodies for the SARS-CoV-2 spike protein S1 (SPS1) were immobilized on their surface. The developed immunodevice was then employed in the analysis of SPS1 standard solutions as a proof of concept for COVID-19 immunosensor.

Oral Communication B3 (OC-B3)

In silico approaches for the identification of HSV-1 Glycoprotein D inhibitors

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Herpes simplex virus (HSV-1) infections are a significant public health concern. Currently available antiviral drugs are used to reduce the severity of the symptoms but unfortunately do not represent a permanent cure for the infection [1]. The emergence of drug-resistant HSV-1 strains and drug toxicity issues highlight the need for new therapeutic approaches. A promising strategy to overcome these drawbacks is the inhibition of virus entry into the host cell. This complex process is mediated by the binding of the viral envelope glycoprotein D (gD) to cell surface receptors HVEM (herpes virus entry mediator) and Nectin-1 (Figure 1) [2].

Figure 1. Crystal structures of HSV-1 gD in complex with A) HVEM and B) Nectin-1.

A protein-protein docking analysis was carried out to investigate the binding affinity of gD for its surface receptors. A structure-based virtual screening of an in-house library of synthetic [1,2,3]triazolo[4,5-h][1,6]naphthyridines and [1,2,3]triazolo[4,5-b]pyridines against the binding interfaces of gD with HVEM
(PDB:1JMA [3]) and Nectin-1 (PDB:3U82 [4]) was subsequently performed to identify the most promising compounds. Finally, Molecular Dynamics simulation (MDs) of the best docked compounds for each binding pocket were carried out for 100 ns, proving that selected triazolo[4,5-b]pyridin-6-yl)methanol derivatives were able to better recognize and stabilize gD. Antiviral screening assays against HSV-1 are currently ongoing.

Oral Communication B4 (OC-B4)

Antibacterial activity of ionic liquids against Staphylococcus aureus

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Antibacterial resistance is a challenge that is associated with high morbidity and mortality. There is currently a shortage of efficient therapies, lack of successful prevention measures, and the availability of only a few effective antibiotics for some bacteria, which require the development of alternative antimicrobials and novel therapeutic strategies [1].

Accordingly, this study has been focused on the design and synthesis of a series of forty-nine alkyl cationic derivatives (ionic liquids—ILs) as potential antibiotics. The effects of these compounds in the control of planktonic bacterial growth of Staphylococcus aureus have been studied and a structure-activity relationship was established. To achieve this goal, structural modifications were performed by inserting an aliphatic carbon chain spacer (C₆ to C₁₈) linked to different cations (triphenylphosphonium, pyridinium, picolinium, quinolinium, methylimidazolium, isoquinolinium and quaternary ammonium salts). In the study, the triphenylphosphonium cation (TPP⁺) was used due to its relevant enzymatic and antimicrobial inhibition properties [2]. The number of the aliphatic carbon chain spacers was modified to increase the lipophilicity of the new compounds as this property has a marked influence on the permeability and, therefore, on the bioavailability properties.

The ILs were synthetized in good yields and with high purity (≥ 98%). Their structural elucidation was carried out by Nuclear Magnetic Resonance (NMR) and Mass Spectroscopy (MS). The antibacterial activities of the ILs against S. aureus were determined by measuring their minimum inhibitory/bactericidal concentrations (MIC and MBC) by the broth microdilution method. TPP⁺ derivatives proved to be effective antimicrobial compounds against S. aureus in a planktonic state. Bacterial susceptibility to these TPP⁺ derivatives was much superior to that observed for the other derivatives tested. Moreover, a clear tendency to improve antimicrobial activity with the increasing length of the alkyl side chain was verified. Indeed, bacterial growth inhibition and bactericidal activity in the planktonic state gradually increase, until reaching a reasonable limit (C₁₀-C₁₄).
Acknowledgments: This work was funded by FEDER funds through the Operational Programme Competitiveness Factors-COMPETE and national funds by FCT – Foundation for Science and Technology under research grantsUIDB/00081/2020 and PTDC/ASP-PES/28397/2017, LA/P/0045/2020 (ALiCE), UIDB/00511/2020, UIDP/00511/2020 (LEPABE), PTDC/BII-BTI/30219/2017 - POCI-01-0145-FEDER-030219 and POCI-01-0247-FEDER-072237

Looking for new anti-malarial drugs in the Tafenoquine Chemical Space: the Markush Dilemma.

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Tafenoquine is a single-dose 8-aminoquinoline that was approved by the FDA in 2018 for the radical cure of \textit{P. vivax} malaria. This disease is the most widespread human malaria, there were an estimated 241 million cases and 627 000 related deaths in 2020, being Africa the most affected continent. This drug belongs to 8-aminoquinoline antimalarial drugs, and it is highly related to primaquine. Hence, it has inherited one of the main drawbacks of its predecessor causing severe hemolytic anemia in people with G6PD deficiency. Consequently, an alternative to this original hit is aimed in order to lower this side effect and, optimally, find a more active drug candidate.

When looking into the patents containing Tafenoquine’s analogs (US4617394, US6376511), we realized that although drug’s patent tend to describe wide chemical space through Markush structures, the optimization of new principal active ingredient is frequently driven by a simple Free Wilson approach. This procedure leads to a highly focused study on the chemical space nearby a hit compound leaving many regions unexplored which may present highly biological active reservoirs.

Hence, in this study we apply and defend an alternative methodology which may be more efficient in the early drug discovery stages. Through the deep exploration of the Tafenoquine chemical space described by its combinatorial library, seven compounds with expected antimalarial activity have been rationally selected and synthesized being more representative than the 59 reported analogs until date. After their biological assessment, the obtained results have evidenced that rational selection has proven to be a more efficient methodology of exploration suitable for the early drug discovery stages.
mRNA vaccines beyond Covid19: How to design and use polymeric nanoparticles as cancer therapeutic vaccines

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Vaccination has been one of the main successes of modern society. Traditional vaccines were composed of entire or fractions of the infectious agent. However, they account for unsolvable disadvantages, such as safety issues and low immunogenic potential that require the addition of adjuvants. In this context, the use of mRNA for immunizing purposes has shown an enhanced performance, as demonstrated by the very fast approval of two mRNA vaccines preventing SARS-CoV-2 infection. Beyond success in preventing viral infection, mRNA has also spread the use of vaccination for therapeutic cancer applications. In this context, our project aims to build up a mRNA vaccination platform by the development of a mRNA vaccine based on proprietary polymeric nanoparticles, with demonstrated safety, efficacy and selectivity to target dendritic cells. Based on our experience in biomaterials engineering, we developed a library of oligopeptide-end modified poly (beta aminoesters) (OM-pBAE), followed by oligopeptides end-capping. In parallel, we set up the methodology for the in vitro transcribed mRNA synthesis, which enables the synthesis of different mRNAs encoding for different personalized antigens. The proprietary OM-pBAE demonstrated high efficiency in the encapsulation of various mRNA, by electrostatic interaction between the cationic polymers and the anionic nucleic acid, for the formation of small nanometric particles, able to be freeze-dried without losing their integrity and functionality [1]. By the selection of the appropriate oligopeptide composition, we found a formulation that selectively targets dendritic cells [2]. In addition, it promotes dendritic cells maturation and generates a specific immune response against encoded model antigens in mice. In conclusion, we have been able to design a platform for the production of mRNA vaccines based on polymeric nanoparticles able to overcome the main limitations that traditional vaccines present. Our platform represents a turning point in the era of vaccination for infectious diseases prophylaxis and tumor therapies.


Session C
Mini-Symposium Other Diseases
Invited Lecture C
Invited Lecture C

Harnessing multi-target drug discovery for neurodegeneration

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From the beginning of the 2000s onwards, many medicinal chemists have become fascinated with the potential of so-called multi-target-directed ligands (MTDLs) for treating neurodegenerative diseases [1]. The founding principles were that ligands simultaneously directed to multiple targets can more efficiently tackle intricate network pathological effects, but with the benefits of single molecules. Over the years, this has become one of the most burgeoning fields of neurodegenerative drug discovery. We have applied these concepts to the development of small molecules for both Alzheimer’s disease and amyotrophic lateral sclerosis, which differ for their intrinsic features and design concepts: i.e., hybrids and conjugates. In this talk, we will showcase examples from our recent research and provide medicinal chemistry considerations on how to bridge the "valley of death" from lab research to pharmaceutical development [2].

Session C

Mini-Symposium Other Diseases

Oral Communications C
Oral Communication C1 (OC-C1)

Synthesis and biological evaluation of novel piperazine-containing selective BChE inhibitors as potential multimodal neuroprotective agents for Alzheimer’s disease

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Alzheimer’s disease (AD) is a neurodegenerative and devastating disorder, accounting for the majority of the dementias. The identification of a disease-modifying agent still represents a medical unmet need \cite{1}. Despite the efforts, only two classes of drugs have been approved for the symptomatic treatment of AD, namely the acetylcholinesterase (AChE) inhibitors and the N-methyl-d-aspartate receptor (NMDAR) antagonist memantine \cite{2}.

Recently, we reported the activities as ChE’s inhibitors of 6-substituted 3,4,5,6-tetrahydroazepino[4,3-b]indol-1(2H)-one (THAI) derivatives\cite{3}. Some of them proved to be highly potent selective inhibitors of human BChE. To overcome some drawbacks, such as a very low aqueous solubility and a strong interaction with human serum albumin, several analogues bearing a piperazine moiety have been synthesized. Herein, synthesis, physicochemical properties, and biological activities (ChE inhibition and protective effects against NMDA and H\textsubscript{2}O\textsubscript{2} insults to SH-SY5Y cell line) are presented and discussed. Finally, compound 12c and 12d showed potential as multimodal neuroprotective agents.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{BChE IC\textsubscript{50} (\textmu M) for compounds 12c and 12d.}
\end{figure}

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Compound & \text{BChE IC\textsubscript{50} (\textmu M)} & \text{SH-SY5Y cell viability} & \text{BChE IC\textsubscript{50} (\textmu M)} \\
\hline
12c & 0.163 & 100 & 12d & 0.065 & 100 \\
\hline
\end{tabular}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{SH-SY5Y cell viability and BChE IC\textsubscript{50} (\textmu M) for compounds 12c and 12d.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{SH-SY5Y cell viability and BChE IC\textsubscript{50} (\textmu M) for compounds 12c and 12d.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{SH-SY5Y cell viability and BChE IC\textsubscript{50} (\textmu M) for compounds 12c and 12d.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{SH-SY5Y cell viability and BChE IC\textsubscript{50} (\textmu M) for compounds 12c and 12d.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{SH-SY5Y cell viability and BChE IC\textsubscript{50} (\textmu M) for compounds 12c and 12d.}
\end{figure}

Carbon Monoxide Releasing Molecular Hybrids: Synthesis and Biological Evaluation of New Potent Anti-Inflammatory Agents

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Controlled release of Carbon Monoxide (CO) from a metallo-organic scaffold by using CO releasing molecules (CORMs) is a widely applied strategy to treat inflammatory based diseases (i.e. Rheumatoid Arthritis (RA))[1]. With the aim to obtain a synergistic antihyperalgesic effect and taking into account the Carbonic Anhydrase (CA) involvement in RA, we designed small molecule hybrids consisting of a CA inhibitor head linked to a CORM tail section [2]. The in vitro anti-inflammatory and antioxidant evaluation of such hybrids using different cell lines revealed some compounds to enhance cellular viability and decrease LDH release[3,4] The CO releasing properties of the synthetized CORMs were assessed by means of the Myoglobin (Mb) carbonylation assay, improved by using K-means and multivariate curve resolution-purity based algorithm, with excellent results (Figure 1)[6]. Taken together, these data justify further investigations in this field and pave the way for the use of CORM hybrids in inflammatory related diseases.

**Figure 1.** A) CAI-CORMs and representative in vitro anti-inflammatory studies; B) Chemometrics methods applied to the qualitative and quantitative evaluation of Mb-CO.
Oral Communication C3 (OC-C3)

Pyrrolidinyl benzofurans and benzodioxanes: Selective α4β2 nAChR ligands with different activity profiles at the two receptor stoichiometries

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A series of racemic benzofurans bearing \textit{N}-methyl-2-pyrrolidinyl residue at C(2) or C(3) has been synthesized and tested for affinity at the α4β2 and α3β4 nicotine acetylcholine receptors (nAChRs). As previously reported for the benzodioxane based analogues, hydroxylation at proper position of benzene ring results in high α4β2 nAChR affinity and α4β2 vs. α3β4 nAChR selectivity\cite{1}. 7-Hydroxy-\textit{N}-methyl-2-pyrrolidinyl-1,4-benzodioxane 1 and its 7- and 5-amino benzodioxane analogues 2 and 3, which are all α4β2 nAChR partial agonists, and 2-(\textit{N}-methyl-2-pyrrolidinyl)-6-hydroxybenzofuran 4 were selected for functional characterization at the two α4β2 stoichiometries, the high sensitivity (α4)\textsubscript{2}(β2)\textsubscript{3} and the low sensitivity (α4)\textsubscript{3}(β2)\textsubscript{2}. The benzene pattern substitution, which had previously been found to control α4β2 partial agonist activity and α4β2 vs. α3β4 selectivity, proved to be also involved in stoichiometry-selectivity. The 7-hydroxybenzodioxane derivative 1 selectively activates (α4)\textsubscript{2}(β2)\textsubscript{3} nAChR, which cannot be activated by its 5-amino analogue 3. A marginal structural modification, not altering the base pyrrolidinyl benzodioxane scaffold, resulted in opposite activity profiles at the two α4β2 nAChR isoforms providing an interesting novel case study\cite{2}.

\begin{center}
\begin{tabular}{cccc}
\textbf{1} & \textbf{2} & \textbf{3} & \textbf{4} \\
\end{tabular}
\end{center}

\[\text{[1]}\text{ F. Bavo, M. Pallavicini, C. Gotti et al., \textit{J. Med. Chem.} \textbf{2020}, 63, 15668-15692.}\]

Oral Communication C4 (OC-C4)

The 3D-QSAR studies aimed to assist the development of novel multi-target 5-HT2A/D2 receptor ligands

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One can say, that the identification of complex disorders has revolutionized the world of pharmacotherapy. The single-target ligands affecting only one pharmacological pathway appeared to be relatively ineffective, since the pathomechanism of such disorders was correlated with the impairment in numerous pathways [1]. Thus, another concept was created, encouraging to create ligands acting through numerous molecular targets, in order to more effectively reconstruct natural homeostasis. Currently, certain promising combinations of molecular targets are available, and it is highly desirable for novel ligands to exhibit such pleiotropic activity [2]. 3D-quantitative structure-activity relationship (abbrev. 3D-QSAR) methods have been applied in the field of drug discovery for decades. These techniques are based on the construction of statistically valid computational models reliably representing relationships between physicochemical properties of chemical substances and their biological activities. Such information, regarding favorable and unfavorable structural features, assists the development of novel potent ligands and helps to reduce the overall cost of the discovery process by eliminating from further studies derivatives exhibiting numerous undesired features [3,4].

The serotonin 5-HT2A and the dopamine D2 receptors belong to the G-protein coupled receptors superfamily. Both of these proteins are considered attractive therapeutic targets for numerous brain disorders such as e.g. depression, schizophrenia, and anxiety [5-8]. Hence, the identification of features responsible for high potency of ligands capable of modifying D2 and 5-HT2A mediated signaling could assist the development of numerous therapeutic agents e.g. novel antipsychotics or antidepressants [9,10].

Taking note of this information, we decided to perform a meticulous analysis of the data available regarding the relationship between the structure and biological activity in ligands exhibiting activity toward both 5-HT2A and D2 receptors. Furthermore, we decided to take the incentive of the information regarding dual D2/5-HT2A receptor
ligands as well as experimentally solved protein structures and construct a docking-based universal 3D-QSAR model to quantitatively analyze the relationship between the structure and biological activity of these molecules.

Oral Communication C5 (OC-C5)

Novel MD-based drug candidates against DM1 toxic ncRNA

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Although gene therapy is a rising alternative to traditional chemotherapy for the treatment of genetic diseases such as DM1, there is still a road to pave in this field. Meanwhile, the chemotherapeutic approach has already proven its value. One of the main therapeutic strategies is targeting the DM1 characteristic ncRNA transcripts. This pathogenic CUG expansion can be stabilized by falling compounds into U•U mismatches forming Janus-Wedge interactions. This approach has been thoroughly described and it can confer additional selectivity to DM1 drug candidates [1]. Molecular design approaches have been applied to obtain potential anti-DM1 compounds composed of two pyrido[2,3-d]pyrimidines moieties as U•U recognizers joined by a set of linkers. Molecular dynamics simulations coupled with MMPBSA analysis allowed the identification of high-binding energy compounds and the description of their binding mechanism. Those compounds have been synthesized using click chemistry techniques and their biological activity in releasing MBNL1 protein was tested in-vitro using a well-established protein-RNA binding assay. Furthermore, biological characterization was performed using patient-derived cells [2].


Paul Ehrlich MedChem Euro-PhD Label
Communications
Natural products in drug discovery. In Silico approaches for the detection of new hits against unexplored molecular targets.

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The aim of this PhD research project was the identification of compounds from datasets of natural products and FDA approved drugs as new candidate hits against three different molecular targets respectively involved in three different kinds of pathogenic mechanisms. The first part of the project was focused on HuD, an ELAV-Like RNA-binding protein specifically expressed in nervous tissues and involved in the pathogenesis of Alzheimer’s Disease. [1] The work led to the identification of new molecules able to recognize and bind HuD, thus interfering with its activity. Virtual screening, molecular dynamics, and STD-NMR techniques were combined, and folic acid was eventually found to be a most interesting hit. The second part of the project was aimed at the detection of human Asparagine Synthetase (hASNS) inhibitors. hASNS is the enzyme responsible of the production of L-Asparagine in healthy cells. The misfunctioning and the overexpression of the enzyme have been correlated to resistant forms of ALL, sarcoma, and metastatic breast cancer. [2] Despite the initial difficulties encountered during the development of the project, the structural information obtained after the optimization of the model and the site mapping undoubtedly helped in the choice of a better method of prediction. Eventually, thanks to the release of a patent featuring several potent inhibitors of the enzyme, a new pharmacophore model was developed which will certainly be useful in future studies for the identification of new hits able to potently inhibit hASNS. DNA Ligase III is an enzyme involved in DNA repairing mechanisms as well as Alternative Non-Homologous End-Joining when the physiological mechanisms are compromised. This enzyme seems to be involved in the pathogenesis of multiple myeloma. [3] The catalytic region of the three mammalian ligases shows high similarity among the three enzymes. The presence of a unique site of interaction between two domains of Ligase III may represent a specific target for the selective inhibition of this enzyme. Indeed, this site of the enzyme was the focus of the computational approaches carried out in this work.

Discovery of potent and selective PARP inhibitors as valuable pharmacological tools

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Poly-(ADP-ribose)polymerase (PARP) is a class of 17 post-translational modifications enzymes, able to covalently attach ADP-ribose to the target proteins in form of monomer or polymers (MARylaton and PARylation, respectively). Their overexpression is related to a series of human diseases, with a key role in the cancer progression [1].

Efforts in the elucidation of PARylation roles, with a main focus on PARP1/2 and their involvement in DNA damage repair, have successfully led to the approval of four PARP inhibitors (PARPi) as anticancer agents [2].

On the other hand, the enzymes catalysing MARylation remained understudied although their potentiality as drug targets is clearly emerging [3]. In this context, the identification of compounds able to specifically inhibit the single PARP subfamilies is essential for better understanding the physio-pathological roles of these enzymes.

To this aim, by working around three different scaffolds, a large series of compounds were designed and synthesised during my thesis work. When biologically evaluated, some of them emerged with a very interesting profile, being able to specifically inhibit some PARP subfamilies with low nM potency, coupled with a good safety profile. All the best compounds were able to penetrate HeLa cells and engage the intracellular target.

Worthy of note, the most promising compounds were based on a very innovative tricyclic structure, which led to identify the most potent PARP10, PARP15 and PARP12 inhibitors ever reported to date. This new chemotype also imparted a favourable preliminary pharmacokinetic profile, highlighting its great potentiality in giving new PARPi.

MAO B - centered multitargeting ligands against neurodegenerative disorders

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Among neurodegenerative diseases, a key role is played by Alzheimer’s Disease (AD), representing nowadays the major cause of senile dementia. Given the multifactorial nature of AD and the lack of disease-resolving therapies, research has recently been focused on the development of unique chemical entities able to correct at the same time more than a single pathological mechanism, termed multitarget-directed ligands (MTDLs) [1]. The goal of this PhD project was to identify new small molecules capable of inhibiting two or more key enzymes in the onset and progression of AD. Specifically, the research activity was divided into two sub-projects involving the development of multitarget agents with two different bioactivity profiles sharing the inhibition of monoamine oxidase B (MAO B) as a common feature. The rational lies in the attempt to counteract AD-related oxidative stress conditions that may result also from MAO B catalytic cycle by-products. The first sub-project, displayed in Figure 1A, addressed the synthesis of dual MAO B - AChE inhibitors in order to study the effect of fluorinated isosteres on both in vitro potency and drug-like features of the most active dual hits previously developed in our research group [2]. The other one, shown in Figure 1B, aimed at identifying dual MAO B - JNK3 inhibitors as multitargeting tools for neuroprotection against AD.

Figure 1. Schematic representation of (A) fluorine-bearing MTDLs as MAO B - AChE inhibitors and (B) of the design strategy for dual MAO B - JNK3 blockers.

Insight on pyrrole[1,2]oxazole derivatives in multiple lymphoma subtypes

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Lymphomas are a heterogeneous group of blood cancers and among the ten most common human cancers. Despite significant treatment evolution and improvements during the years, still too many individuals are not cured by standard therapies and succumb due to the disease, highlighting the need for novel therapeutic agents. Anti-tubulin agents are the cornerstone of treatment for different lymphoma types, since they are included in both chemotherapy schemes (R-CHOP, ABVD, BEACOP) and antibody-drug conjugates (ADCs) such as brentuximab vedotin and polatuzumab vedotin. Herein, we present the structural optimization, evaluation and modelling of a large family of pyrrole[1,2]oxazole derivatives, with wide variability of chemical scaffolds and substituents. In vitro cytotoxicity tests against four lymphoma histotypes (germinal center B-cell-DLBCL, activated-DLBCL, marginal zone lymphoma and mantle cell lymphoma) identified several derivatives with prominent antiproliferative activity in at least one lymphoma model, with IC50 values between the
low micromolar and nanomolar range. Furthermore, insights on the mechanism of action revealed G2/M phase arrest and induction of apoptosis through strong inhibition of tubulin polymerization and colchicine binding to tubulin. In particular, compound SIX2-F elicited at 5 μM a colchicine binding inhibition similar to that of CA-4 (88% vs 97%). Molecular modeling approaches identified a strong interaction with tubulin and a binding mode similar to that of colchicine, characterized by the methoxybenzyl portion oriented towards the C241 residue. Crystallographic data confirmed the clear perturbation of the colchicine site with the βT7 and αT5 loops of tubulin rotated to accommodate the ligands. Overall, these results indicate the discovery of a new class of anti-tubulin agents with strong antitumor effect against lymphoma histotypes.

PE Award Label Communication 5 (PEA-5)

Structure- and Ligand-based Optimization of Fragment Binding Tyrosinase from Agaricus bisporus to Develop Anti-Melanogenic Agents

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Tyrosinases (TYR, EC 1.14.18.1) are copper-containing enzymes expressed in bacteria, fungi, plants and animals. The human TYRs have been in depth-studied to find therapeutics against hyper-pigmentation and related diseases. In this context, we have disclosed a collection of TYR inhibitors (TYRIs) possessing the 4-fluorobenzyl and 4-(1-piperazinyl)phenol fragments as key moieties, to bind the active site of TYR [1-5]. All synthesized compounds have been preliminary in vitro evaluated using Agaricus bisporus TYR (AbTYR). Many of the obtained compounds were more potent than the reference kojic acid (IC50= 17.76 µM). Some of them displayed anti-melanogenic effects in B16F10 mouse melanoma cells. By means of experimental and theoretical studies we investigated the recognition within TYR cavity. All the collected data culminated in SAR advancements for both the classes of inhibitors and might be useful to obtain TYRIs for human applications.

Session A

Mini-Symposium Cancer

Poster Communications A
Poster Communication 1 (FP-1)

Design of novel dual COX-2 and 5-LOX inhibitors using quantitative structure-activity relationships analysis

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Inflammation is a part of immune system’s response to harmful intrinsic and extrinsic stimuli, such as infection or injury. It has an important role in progression of some diseases, such as cancer, arthritis, stroke [1]. It is considered that inhibition of COX-2 and 5-LOX pathways of production of inflammation mediators provides a new strategy for development of more effective anticancer drugs [2]. The aim of this study was designing of novel COX-2/5-LOX inhibitors with improved activity towards both enzymes using quantitative structure-activity relationships (QSAR). QSAR modeling was applied on a literature data set consisting of 28 dual COX-2/5-LOX inhibitors and obtained pharmacophoric features were used in design of novel compounds. Regarding prediction of activity of novel COX-2 and 5-LOX inhibitors, two models were developed. Based on values of $Q^2$ (0.53 (COX-2 model) and 0.71 (5-LOX model)) and $R^{2}_{\text{pred}}$ (0.85 (for both COX-2 and 5-LOX models)), developed models have good predictive ability and can be used for activity prediction of novel designed compounds. Obtained values of $r^2_{\text{pred}}, r^2_{\text{Hold}}$ and $\Delta r^2_{\text{Hold}}$ were higher than 0.5 and $\Delta r^2_{\text{Pred}}$ was lower than 0.2 indicating high predictive quality of developed models. Applicability domain (AD) was defined using Leverage approach and all compounds were inside the AD. In order to get more potent dual inhibitors of COX-2 and 5-LOX enzymes, compounds with high pIC$_{50}$ values were chosen for design of novel compounds. As a result, 32 novel compounds were designed and according to predicted pIC$_{50}$ values can be considered promising dual COX-2 and 5-LOX inhibitors.

Small interfering RNA (siRNA) represents revolutionary tool for gene therapy with a wide array of potential applications in the regulation of gene expression. However, a successful clinical application of nucleic acid-based therapy requires novel delivery options, because of the extremely labile nature of siRNA under physiological conditions, which hamper its efficient and sustained delivery. With the aim to
physically entrap siRNA duplexes in the inner cavity of an engineered Humanized ferritin from *Archaeoglobus fulgidus* (HumAfFt), piperazine-based compounds featuring one or two piperidine rings (PAs) were rationally designed and these rigid-rod-like amines were functionalized with thiol-reactive crosslinkers (*i.e.* maleimide and fluorobenzene sulfonamide) for chemoselective conjugation of cysteine residues located inside the HumAfFt cavity. These systems allowed siRNA delivery into HeLa, HepG2 and MCF-7 cancer cells with improved silencing effect on glyceroldehyde-3-phosphate dehydrogenase (GAPDH) gene expression with respect to traditional transfection methodologies and provided a promising TfR1-targeting system for multifunctional siRNA delivery to therapeutic applications. It is envisioned that the reported nanodelivery systems might be employed to multiple siRNA-based silencing for a wide range of biotechnological applications.
Poster Communication 3 (FP-3)

Development of new CK2 fluorescent probes as potential cancer theranostic agents

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Fluorescent small-molecule compounds used as probes or biosensors to label targets involved in human diseases could be the key to understanding biological events in cells through a non-invasive, rapid, and real time analysis. This not only enables the design and development of more selective drugs that minimize the side effects of the treatment, but also the diagnosis of the disease at the early stages [1,2].

Scheme 1. Development of fluorescent probes.

In this regard, we proposed the design and synthesis of new theranostic fluorescent probes targeting CK2, a protein kinase overexpressed in multiple cancers. For this purpose, we combine in a single entity a derivative of CX-4945 as a CK2-binding component and different chromophores as signaling components [3]. Both fragments are connected through azide-alkyne “click” cycloaddition reaction (Scheme 1) [4]. This strategy is an easy and versatile way to synthesize a large chemical library that includes a fluorophore with interesting electronic properties due to the large π-conjugated system [4].

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Novel insights on the pyran-2-one scaffold for potent and selective inhibition of tumor-related carbonic anhydrase isoforms IX and XII

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Human carbonic anhydrase (hCA) isoforms IX and XII are known for their over-expression in solid hypoxic tumors [1]. For this reason, their selective inhibition has been recognized as a promising therapeutic tool for the treatment of cancer. Based on a molecular simplification of the well-known coumarin scaffold [2], we developed a new series of the pyran-2-one core. The latter has been endowed with a carboxamidic linker to achieve a final structure able to mime the coumarin nucleus but also to interact with the active site (Figure 1) [3]. The new compounds are endowed with potent and selective inhibitory activity against the tumor-related human carbonic anhydrase isoforms IX and XII in the low nanomolar range, whereas being inactive against the two cytosolic off-target isoforms hCA I and II. The compounds exhibiting the best results in the hCA inhibition assay were further investigated against breast adenocarcinoma cell line (MCF7) in mimic hypoxic conditions, evaluating their ability to synergize with doxorubicin. Furthermore, the possible binding mode of all compounds to the active site of the tumor-associated human CA IX was investigated by molecular docking and by molecular dynamics (MD) simulations.
Figure 1. Synthetic scheme of the synthesis and studies employed on the pyran-2-one scaffold.

Poster Communication 5 (FP-5)
Targeted protein degradation of aurora kinase A using PROTACS as a novel approach for precision medicine in neuroblastoma

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Neuroblastoma is a pediatric tumor of the sympathetic nervous system that arises during early embryonic development with very limited options for precision medicine. Aurora kinase A (AURKA) is a highly overexpressed protein in neuroblastoma and its potential as therapeutic target has already been demonstrated. Though several inhibitors exist, these mainly target AURKA’s mitotic functions by blocking its kinase domain. Targeted protein degradation may result in a more pronounced effect by additionally targeting AURKA’s kinase-independent functions, including its ability to bind and stabilize the MYCN oncogene.

Here, we make use of the Proteolysis Targeting Chimeras (PROTAC) technology to develop AURKA protein degraders. Towards this end, we envisioned two distinct AURKA inhibitors (inhibitor A and B) to design AURKA degraders. Known co-crystal and SAR studies allowed to identify a suitable solvent exposed moiety as linker attachment point. Several PROTACs were synthesized by connecting the AURKA inhibitor with an E3-ligase recruiter tethered by linkers of varying lengths and nature.

Impact on cell viability was assessed using the IncuCyte® Live-Cell Imaging system and intracellular protein degradation was evaluated by Simple Western. While PROTACs based on inhibitor A were unsuccessful, the majority of the PROTACs in the inhibitor B - series resulted in strongly reduced viability of a neuroblastoma cell line (NGP) with IC50 values in the low nanomolar ranges, outperforming parent inhibitors. Remarkably, a significantly lower sensitivity profile is observed in a non-tumor-derived cell line (HEK293T), which may point to hypothesized favorable therapeutic window. Subsequent analysis reveals potent AURKA protein degradation starting at a concentration of 10nM. Interestingly, the parent inhibitor but not the PROTAC resulted in a strong upregulation of AURKA, further supporting possible advantages of degraders. Prospectively, we will further design and synthesize analogs in order to
improve potency, physicochemical properties, selectivity and metabolic stability. Further validation of the PROTACs’ mode-of-action will be performed.
Discovering of new potential kinases binding sites

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Due to the pivotal role as modulators of cell signaling as well as their involvement in various type of cancer, the protein kinases represent a primary group of therapeutical targets in drug discovery efforts. Widely studied is the notable conformational change of the protein active site, related with the orientation of a conserved motif known as DFGmotif (Asp-Phe-Gly) in kinase activation loop. In the most simplified convention the active, intermediate, and inactive conformational status are labelled as DFGin, DFGinter and DFGout, respectively (Fig.1).

To date, several protein kinase inhibitors have been identified, classified according to their binding mode. The so-called type I, type I 1/2 and type II kinase inhibitors are ATP competitive because they bind at the kinase ATP-binding site. Despite the discovery of allosteric binding sites is still challenging, the development of allosteric inhibitors represents a promising approach in the drug discovery. Nowadays, the majority of identified allosteric inhibitors are classified as type III and type IV inhibitors based on the distance of their targeted allosteric site from the ATP-binding pocket. Herein, the X-ray models of kinases in different conformations complexed with the inhibitors were collected. Our purpose is to provide computational methods and experimental validation to identify potential kinase binders targeting novel theoretical binding sites and a detailed in silico structure-based description of kinase modulators.


Targeting transcription factors in acute leukemia

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Acute leukemia is a clonal hematopoietic neoplasm and nowadays the prognosis remains poor.

Two AML/ALL dependency factors have recently been identified and validated in our laboratories: RUNX2 \textsuperscript{[1]} and ZEB2 \textsuperscript{[2]} \textsuperscript{[3]}. These transcription factors (TFs) are involved in the onset and progression of acute leukemias. Historically, TFs were considered ‘undruggable’, but new therapeutic approaches are changing the rules of ‘druggability’. We are exploring the possibility to develop proteolysis targeting chimera (PROTACs) that are able to degrade these TFs.

This poster will highlight the multidisciplinary approach we follow for the design, synthesis and evaluation of these PROTACs.

\textsuperscript{[2]} ZEB2 drives immature T-cell lymphoblastic leukaemia development via enhanced tumour-initiating potential and IL-7 receptor signalling. Nat Commun 6, 5794 (2015)
Poster Communication 9 (FP-9)

Discovery of a potent 14-3-3 modulator as anticancer agent in lymphoma

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Many of the cancer drivers, particularly kinases, have provided druggable targets that have yielded significant clinical benefits. However, more than 50% of the patients relapse and die of their disease within few years of diagnosis. Due to the limited efficacy of the current therapies, it is imperative to expand the horizon of the treatment options for cancers with substantial unmet needs. On this basis, and following a phenotypic drug discovery (PDD) approach we have screened a library of hundred molecules previously synthesized by our group against a panel of glioblastoma, lymphoma, thyroid, and lung cancer cell lines. Few molecules, across the library tested, showed nanomolar activities in nine cell lines (lymphoma and Ewing sarcoma). The most promising compound (FC86), with a 2-oxo-indole privileged structure already used for the synthesis of PDK1/AurA kinase inhibitors [1], was subjected to a kinome profiling and DARTS (Drug Affinity Responsive Target Stability) experiment to prioritize the identification of its key targets. The kinome profiling showed a complete lack of kinase activity at 0.1μM against 410 kinases, whereas the target proteins profiled by DARTS resulted in the identification of human protein class 14-3-3 as specific target of. The versatile functions of 14-3-3 proteins in the regulation of cell growth, cell division, cell death and cell migration make them candidate proteins, although the low number of modulators currently available [2]. Pre-clinical evidence of the importance of 14-3-3 protein-protein interaction (PPI) modulation in a wide range of physiological processes has been accumulating at several levels: cell proliferation, cell cycle control and cell apoptosis [3], suggesting that active compounds able to target the complex formation between 14-3-3 and a protein partner (“interactome”), could regulate and execute biological processes with a right intrinsic specificity. Herein we present the design and synthesis of FC86 and analogs. Moreover, results from in vitro target deconvolution as well as in vitro and in vivo
anticancer activity are discussed, thus proving FC86 as a lead-compound for design and synthesis of novel pharmacological interventions for lymphoma.


Two targets or not two targets? A pharmacophoric approach towards cancer signaling inhibition

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Cancer is a primary cause of death worldwide and multiple cellular pathways influence growth and metastatic potential of tumors, creating heterogeneity, redundancy, and the potential for tumors to bypass signaling pathway blockade, resulting in primary or acquired resistance. Combining therapies that inhibit different signaling pathways is more effective than targeting a single pathway to overcome tumor resistance.

The aim of this work is to identify novel dual inhibitors toward two key elements in the growth and dissemination of tumors: vascular endothelial growth factor receptor (VEGF) and epidermal growth factor receptor (EGFR), both TK receptors [1]. Computer-aided drug discovery approach was applied, and a ligand-based pharmacophore modeling was performed by employing Sunitinib (a VEGFR inhibitor) [2] and Vandetanib (both VEGFR and EGFR inhibitors) [3] as input ligands in the LigandScout software training set [4]. The shared-pharmacophore (Figure 1) was applied for a virtual/pharmacophoric screening of a small library of designed molecules. As a result of the virtual screening the most promising molecules were selected to be synthesized.

Figure 1- Espresso ligand-based pharmacophore with training compounds.

Poster Communication 11 (FP-11)

Targeting the dimer-monomer equilibrium of thymidylate synthase, to accelerate protein degradation and cancer cell growth inhibition

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Thymidylate synthase (hTS) is an homodimeric protein existing in a dimer-monomer equilibrium. This equilibrium can be altered when specific ligands can bind at the protein interface. Drugs that target the hTS are widely used in anticancer therapy. However, treatment with classical substrate site-directed TS inhibitors such as 5fluorouracil and others, induces, among other mechanisms, protein over-expression and the development of drug resistance. Previous results suggest that the monomeric form of the protein is involved in process leading to protein level regulation. We expect that dimer to monomer shift can cause protein level reduction and anticancer efficacy. To discover interface binding hTS inhibitors that can shift the equilibrium to the monomer and reduce drug resistance development, we started a tethering-based approach targeting the interface residues. We mutated the tyrosine residue to cysteine and developed a disulfide covalent library screening. Then a medicinal chemistry program delivered an optimized lead. By combining structural, spectroscopic and kinetic investigation of the effects of the small molecules we confirmed the dissociative mechanism towards the hTS target. Then we showed that the best inhibitor, \textbf{E7}, accelerates the proteasomal degradation of hTS in cancer cells. \textbf{E7} showed a superior anticancer profile to 5fluorouracil in a mouse model of human pancreatic and ovarian cancer. Thus, over sixty years after the discovery of the first TS prodrug inhibitor, fluorouracil, \textbf{E7} breaks the link between TS inhibition and enhanced expression in response, providing a strategy to fight drug-resistant cancers. [1]

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Poster Communication 12 (FP-12)

Disclosing the role of *Cannabis sativa* L. polyphenols as new antiproliferative agents

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*Cannabis sativa* L. is a well-known plant that belongs to the *Cannabaceae* family. Based on its chemical composition, it is classified in both psychoactive and non-psychoactive varieties. This plant is a source of different bioactive compounds, including cannabinoids, polyphenols and terpenes. Regarding polyphenols, the most representative ones in *C. sativa* are cannflavins A and B, which are prenylated flavones [1]. Phenolic compounds are known to possess several biological properties, with the antiproliferative activity being the most interesting one from a medicinal point of view. For this reason, the interest in the bioactivity of polyphenols from *C. sativa* is fully justified in a medicinal chemistry ambit [1,2]. In the light of this, the aim of this study is to obtain an enriched fraction of polyphenols from inflorescences of a non-psychoactive *C. sativa* variety and to test its bioactivity, together with the isolation of pure compounds. The work was initially focused on the optimization of the extraction method for polyphenols, with the objective to remove as many co-extracted compounds as possible, followed by preparative flash column chromatography under normal phase conditions. Both a targeted and an untargeted analysis by ultra-high performance liquid chromatography coupled high-resolution mass spectrometry (UHPLC-HRMS) was applied to fully characterize both the raw extract and the polyphenols-enriched fraction, which was mainly composed of flavonoids. The antiproliferative activity of the latter was assessed on human adenocarcinoma Caco-2 and SW480 cells, providing an IC_{50} value of 4.8 and 5.7 µg/mL, respectively. The antiproliferative activity of the polyphenols-enriched fraction and pure compounds in both cell lines will be further investigated and the mechanism/s of action will be elucidated. Based on the results of the biological assays, pure compounds from *C. sativa* can represent new hits/leads for a further optimisation of their bioactivity using synthetic methods.

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Poster Communication 13 (FP-13)

From bench-to-bedside: ADME free online prediction tools for academic or small biotech environments

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For a drug candidate to become a new chemical entity (NCE) it is not only essential that it be safe, effective, and non-toxic; it is also required to have a favourable pharmacokinetic (PK) profile. In the early 1990s, inappropriate PK profiles were responsible for 40% of discontinuities in clinical trials of drug candidates [1], a figure that drops to 11% in 2007 and 1% of pharmacokinetic failures in 2010 [2]. Administration, distribution, metabolism, and elimination (ADME) are the critical parameters that describe the drug-like character along with other physicochemical and biological properties (such as aqueous solubility, ionization constant, or chemical stability). Consequently, a successful strategic drug design and discovery approach should evaluate the PK aspects of potential drug candidates as early as possible. For this purpose, ADME-related \textit{in silico} models, based on empirical methods or molecular models, have become the fastest and most reliable way to assess properties before compounds are further investigated \textit{in vitro}.

Thus, developing trustworthy and accurate \textit{in silico} prediction tools has been one of the greatest challenges for the scientific community in recent years due to the complexity of biological systems and the limited amount and chemical diversity of ADME available. In this sense, private companies both the pharmaceutical industry and small CROs have developed their own specialized software that small laboratories or academia do not have access to. On the other hand, many free tools have become accessible to research centres and universities that allow them to predict the most relevant PK parameters.

Therefore, we have collected and present here the free software and online tools capable of predicting ADME properties, its advantages and disadvantages, its model-based calculations, and its degree of accuracy. In the current work, experimental tyrosine kinase inhibitors against pancreatic cancer, developed by our research group, were used to evaluate the goodness of the predictions.

Expanding the diversity at C-4 position of pyrido[2,3-d]pyrimidin-7(8H)-ones to achieve biological activity against ZAP-70

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Pyrido[2,3-d]pyrimidin-7(8H)-ones are ortho-fused bicyclic heterocycles consisting of a pyridone and a pyrimidine rings. This kind of structure presents up to 5 diversity centers (R\textsuperscript{2}, R\textsuperscript{4}, R\textsuperscript{5}, R\textsuperscript{6}, and R\textsuperscript{8}) and two possible degrees of unsaturation between C5 and C6 (1). Functionalized pyrido[2,3-d]pyrimidines are considered privileged heterocyclic scaffolds for drug discovery due to their well-known activity as tyrosine kinase inhibitors along with many others.

In this work, a general synthetic methodology for the synthesis of 4-substituted-2-(phenylamino)-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-ones (2) is described. By using cross-coupling reactions such as Ullman’s, Buchwald’s, Suzuki’s, or Sonogashira’s reactions catalyzed by Pd or Cu we have been able to describe new potential biologically active compounds. The resulting pyrido[2,3-d]pyrimidin-7(8H)-ones present N-alkyl, N-aryl, O-aryl, S-aryl, aryl, and arylethynil substituents at C4, which have never been explored in connection with the biological activity of such heterocycles as tyrosine kinase inhibitors, in particular as ZAP-70 inhibitors [1].

\[ \text{C4-amino} \leftrightarrow \text{C4-leaving group} \]

\[ \text{Cross-coupling reactivity} \rightarrow \text{potential biologically active compounds} \]

Poster Communication 15 (FP-15)

Identification of potential drug repurposing opportunities for the treatment of advanced-stage prostate cancer through big data analysis

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Prostate cancer (PC) is the second most common type of tumor in men. Unfortunately, the efficacy of currently available therapeutic approaches often remains limited against the advanced stages of the disease and castration-resistant prostate cancer (CRPC), mainly due to the establishment of drug resistance [1,2]. Consequently, research efforts have been put forward for identifying novel and more effective compounds against CRPC, especially among already approved drugs and clinically candidates with a favorable safety profile (i.e., drug repurposing) [3]. Computational approaches, when framed in integrated workflows, have demonstrated to provide significant advantages in this respect, as they allow to efficiently exploit the structural, biological and chemical information already reported into public databases [4].

On these premises, we developed a computational workflow to analyze information reported in public databases in search of drug repurposing possibilities against PC and CRPC. To this aim, we firstly collected information about ligands and targets related to PC from the ChEMBL, DrugBank and Therapeutic Target Database (TTD). Then, we performed extensive 2D fingerprints (ECFP4 and MACCS) and 3D-shape based similarity estimations on the collected compounds, identifying 276 DrugBank ligands similar to molecules that are already reported to be active against established PC cell lines. Of note, similarity data allowed us to identify 105 DrugBank compounds that have already been tested against PC, thus confirming that the developed protocol is able to retrieve active compounds. Besides, 161 of the identified molecules have never been tested against PC, thus representing completely new and potentially valuable candidates for drug repurposing. We also found a significant degree of similarity with compounds active on targets not directly related to PC. These DrugBank compounds may provide an even higher novelty at the expense of a higher risk of inactivity A set of selected candidates will be tested experimentally on selected PC cell lines.


Session B
Mini-Symposium Anti-infectives
Poster Communications B
Application of computational approaches for the identification of antiviral compounds

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Computer-aided Drug Design (CADD) methods are largely applied to accelerate the drug development process [1]. In the last decades both ligand and structure-based strategies have been successfully exploited for the identification of new hits and in the hit-to-lead process [2]. In our lab we are carrying out several projects focused on the discovery and study of potential antiviral compounds toward validated targets such as HIV-1 Reverse Transcriptase (RT), VP24 and VP35 of Ebola virus (EBOV) and, recently, the Human Stimulator of Interferon Genes (hSTING) protein (Figure 1).

The results obtained demonstrated the efficacy of computational methods for the identification of hits, rationalization of their activity and investigation of molecular mechanism.

For the specific targets we applied different methods combination according to the information in our hands. Therefore, specific workflows will be analysed.

**Figure 1**: 3D representation of the studied targets (a) HIV-1 RT (PDB code: 1VRT), (b) VP35 (PDB code: 3L25), VP24 (PDB code: 4M0Q) and STING (PDB code: 6UKZ).

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2-Phenylquinolines as promising broad-spectrum anti-Coronaviruses agents

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Recently the world has been overwhelmed by a pandemic caused by an emerging virus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Belonging to the Coronaviridae family, Coronavirus genus (CoV) is classified into four sub-genera (alpha-, beta-, gamma- and delta-CoV) and able to cause respiratory, enteric, renal, and neurological diseases on both humans and animals. Nowadays, the development of effective therapies represents a crucial step to fight these viruses and the discovery of broad-spectrum anti-coronavirus agents is increasingly required not only to combat SARS-CoV-2, but also to prevent the onset of future pandemics caused by emerging CoVs. With this in mind, we decided to evaluate through phenotypic-based screening assay, a selection of structurally different compounds from in-house library. Among them, 2-Phenylquinoline scaffold emerged as the most promising with compound 1a showing EC50 and CC50 of 6 and 18 µM, respectively. Additional analogues were then selected along with ad hoc synthesized derivatives with the aim of acquire SAR information around 2-phenylquinoline core and discover novel SARS-CoV-2 replication inhibitors endowed with low cytotoxicity. The most promising compounds proved to be potential broad-spectrum antiviral agents showing antiviral activity also against further two human coronaviruses (HCoV-229E and HCoV-OC43) with EC50 ranging from 0.2 to 9.4 µM. From investigations about the mechanism of action, the SARS-CoV-2 helicase (nsp13) emerged as potential target with compound 6g having IC50 of 0.42 µM [1].
2,3-Diarylimidazo[1,2-α]pyrazines as promising antiparasitic agents targeting

*Leishmania* casein kinase 1

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Leishmaniasis - visceral leishmaniasis (VL), cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (MCL) - are classified as one of the 20 so-called neglected tropical diseases of the WHO program. These parasitic diseases are endemic in nearly 100 countries worldwide and constitute a serious public health problem with 12 million people infected, 350 million others at risk of infection and 40,000 deaths each year. In 2012, mainly due to global warming, visceral leishmaniasis (VL) was declared as a new emerging disease in Europe. Current treatments are toxic, costly and lead to the development of parasite resistance. Therefore, it's important to rapidly develop new and more effective drugs with new mechanisms of action to resolve this emerging resistance. Previously, we reported the discovery of CTN1122\(^1\), an imidazo[1,2-α]pyrazine derivative with promising antileishmanial properties and targeting a protein of interest: *Leishmania* Casein Kinase 1 paralog 2 (L-CK1.2)\(^2\). In this context, we decided to synthesize CTN1122 analogues (Figure 1) in order to improve the pharmacological activity profile.
Figure 1. Modulation from the hit compound CTN1122.

Thirteen new analogues resulting from the optimization of CTN1122, mainly by the modification of the substituents in positions 3 and/or 8 of the imidazo[1,2-a]pyrazine ring, were obtained. The study of these analogues will allow to discuss the structure-activity relationship regarding their antileishmanial properties, their LmCK1 target protein inhibition capacities and taking into account their toxicity profile.

Quaternary phosphonium conjugates: a new class of antimicrobial agents?

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Antimicrobial resistance is currently posing a serious threat to public health. The abuse and misuse of antimicrobial agents in animals and humans is among the leading causes of the development and spread of antimicrobial resistance. Unfortunately, the speed of the innovation in antibiotic research has failed to match that of the emergence of multidrug-resistant bacteria, which have been difficult to treat with conventional therapies [1]. Therefore, the development of new antimicrobial agents able to act on multidrug-resistant bacteria is urgently needed.

As part of our drug discovery program, we designed and synthesized a small library of phytochemical-based triphenylphosphonium (TPP\textsuperscript{+}) conjugates with the aim of finding new antimicrobial agents. Then, the preliminary screening of their antimicrobial activity against Gram-positive methicillin-resistant S. aureus (MRSA) and different Gram-negative bacteria (\textit{E. coli}, \textit{K. pneumoniae}, \textit{P. aeruginosa}, \textit{A. baumannii}) and fungi (\textit{C. albicans} and \textit{C. neoformans var. grubii}) was performed. The best performing conjugates were selected for the preliminary evaluation of their cytotoxicity in human embryonic kidney cells (HEK293) and their haemolytic activity in human red blood cells (RBC). Based on the results obtained, robust structure-activity-toxicity relationships were established. Dihydrocinnamic acid-based conjugates were selected for mechanistic studies since they exhibited potent and selective antimicrobial activity towards \textit{S. aureus} (MRSA) and safe cytotoxicity profiles. With this endeavour several bacterial physiological indices were measured on \textit{S. aureus} XU212 cells, namely MBC, surface charge, PI uptake and intracellular K\textsuperscript{+} release.

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Session C

Mini-Symposium Other Diseases

Poster Communications C
Poster Communication 31 (FP-31)

Two Approaches towards new in-depth Investigations of Monoamine Neurotransmitter Transporters

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The three monoamine neurotransmitters serotonin, norepinephrine and dopamine play a major role in our bodies’ everyday functions. Malfunctions of their respective transporters SERT (serotonin transporter), NET (norepinephrine transporter) and DAT (dopamine transporter) are associated with diseases like depression, epilepsy, anxiety, ADHD and Parkinson’s disease \cite{Kristensen2011}. This makes in-depth understanding of SERT, NET and DAT indispensable for the design of novel drugs.

Our first approach towards control and investigation of SERT, NET and DAT utilizes methods and principles of photopharmacology. Photopharmacology enables light-induced, highly precise temporal and spatial control of e.g. ion channels and transporters \cite{Huell2018}. By introduction of photoswitchable azo-handles into the known NET-selective substrate Reboxetine, we obtained photoswitchable inhibitors for NET.

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\includegraphics[width=0.8\textwidth]{fig1}};
\end{tikzpicture}
\end{center}

\textbf{Fig. 1: Photoswitchable modified Reboxetine as its E- and Z-isomer}

Investigating the SERT transport cycle, serotonin derivatives with different sidechain lengths were synthesized. Biological tests revealed that minor changes of only one or two carbons can lead to severely different binding behavior. This supports new hypotheses regarding the SERT transport cycle.

\begin{thebibliography}{9}
\end{thebibliography}
Poster Communication 32 (FP-32)

Non-Chiral Components of Bergamot Essential Oil: Identification of a Novel, Selective Human Monoamine Oxidase B Inhibitor

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The burden of neurological disorders has rapidly increased over the past years becoming one of the major causes of disability and death worldwide. Among the pharmacological strategy, the inhibition of monoamine oxidases (hMAOs) is used for the clinical management of neuropsychological disorders including depression, anxiety, Parkinson's disease, and Alzheimer's disease [1,2]. Since the discovery of iproniazide, the first recognized hMAO inhibitor, the low selectivity and lack of reversibility of hMAO inhibitors have made it difficult to develop new active molecules. In the present work, a computational workflow was used with the aim to identify MAO inhibitors among the non-chiral constituents of Bergamot Essential Oil (BEO) [3]. First, the selected constituents were subjected to molecular docking studies with both hMAO-A and hMAO-B active sites to predict ligand-target binding affinity and mode of binding interactions. The theoretical binding affinity was used to select the most promising compounds. According to this, the furcoumarin Bergamottin resulted in a selective hMAO-B inhibitory activity. A post-docking molecular dynamics simulation analysis was carried out on the Bergamottin-hMAOs complexes to further characterize the target recognition and to rationalize the selectivity preference. The biological assay confirmed both the never reported hMAO inhibition properties of Bergamottin and its preference for the isoform B. Our results identified a novel activity for Bergamottin providing a basis for the identification of new hMAOs inhibitors.

Design, synthesis and human monoamine oxidase inhibitory activity of 2-aroylbenzofuran-3-ol and 2-aroylbenzofuran derivatives: a new route towards hMAOs inhibition

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Two novel libraries of benzofuran-based compounds were designed and synthesized starting from previously developed benzo[b]thiophen-3-oles [1], through the isosteric replacement of sulfur atom with the oxygen one (Library 1) and successive removal of the enol OH moiety (Library 2). (Figure 1)

Figure 1. Design of the hMAO inhibitors based on benzofuran scaffold.
Currently, the 2-arylbenzofurans (Library 2) have been assessed towards hMAO-A and hMAO-B enzymes and their inhibition rates expressed as IC_{50}. Most of the compounds belonging to Library 2 showed selective hMAO-B inhibitory activity in low nanomolar range. Activities for compounds belonging to Library 1, as well molecular docking studies, are in progress.

Poster Communication 34 (FP-34)

Novel approach for targeted drug delivery: MOF-monoclonal antibody conjugation

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Metal–organic frameworks (MOFs) are porous crystalline solids made by the assembly of inorganic ions or clusters and organic ligands. This class of materials possesses an exceptional surface area (up thousands of m²/g) due to the highly porous structure and the possibility to prepare tunable cavities opens endless opportunities. Magnetic nanoparticles (MNs) combined with MOFs lead to magnetic framework composites (MFCs) that could be utilized for targeted drug delivery to carry active agents directly to target organs or specific locations in the body. In previous work, MN@Fe-BTC composite containing iron oxide nanoparticles (MN, Fe₃O₄) covered by iron(III) carboxylate framework (Fe-BTC) was synthesized by an unconventional mechanochemical processes for this purpose (*Figure 1*)[1]. Pursuing our efforts in MOF research field we attempted another strategy to obtain drug targeting by linking the MOF Fe-BTC nanoparticles with monoclonal antibody (mAb) taking advantage of EDC/N-hydroxysulfosuccinimide mediated conjugations on carboxylate groups located at the surface of Fe-BTC.

![Mechanochemical preparative process of MN@Fe-BTC and subsequent doxorubicin loading.](image)

*Figure 1*: Mechanochemical preparative process of MN@Fe-BTC and subsequent doxorubicin loading.

Poster Communication 35 (FP-35)
Tackling dopamine depletion and oxidative stress with innovative caffeic acid derivatives

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Parkinson’s disease (PD) is a multifactorial age-related disorder clinically characterized by motor dysfunction. Increased oxidative stress and depletion of nigrostriatal dopamine (DA) are closely linked to the neurodegeneration observed in PD [1]. The management of PD symptoms include the use of drugs that inhibit monoamine oxidase B (MAO-B) and catechol-O-methyltransferase (COMT), two enzymes involved in DA metabolism [2], as a mean to increase the synaptic levels and the half-life of DA [3]. However, the therapeutic benefit of these drugs are impaired by pharmacokinetic, pharmacodynamic, clinical efficacy or safety issues.

Following our line of research related with the development of multitarget agents based on natural scaffolds, we designed a small caffeic acid (CA)-based library aimed to find out new molecules able to act as dual MAO-B/COMT inhibitors and as antioxidants.

A small library of CA derivatives was successfully obtained. Then, their inhibitory activities towards MAO and COMT isoforms were assessed. The antioxidant activity of all compounds was evaluated using the ORAC assay and voltammetric methods. Cell-based assays in human neuroblastoma cells were performed to assess...
the cytotoxicity of the bioactive compounds. Finally, the parallel artificial membrane permeability assay was used to predict the compounds’ ability to cross the blood-brain barrier by passive diffusion.

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Targeting Antioxidants to Mitochondria: a new therapeutic track for Amyotrophic Lateral Sclerosis

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Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by the progressive loss of motor neurons (MNs) in the motor cortex, spinal cord, and brainstem, leading to severe muscle atrophy, paralysis, and ultimately death by respiratory failure 3 to 5 years after diagnosis [1]. Riluzole and Edaravone are the only two drugs approved for ALS and, respectively, extend a few months of the life expectancy of the patients or ameliorate the symptoms in the initial stages of the disease [2]. Therefore, there is an urgent need for more efficient therapies.

Recently, growing evidence about the involvement of the cross-talking between mitochondria and oxidative stress (OS), in the pathology of several neurodegenerative diseases, including ALS, emerged. Mitochondria dysfunction has been identified as one of the major hallmarks of ALS and, therefore, mitochondria have been identified as a promising target for the development of novel therapeutics for the disease [3].

Over the last twenty years, considerable efforts have been made to develop effective antioxidant therapies. However, disappointing results associated with the antioxidants’ poor bioavailability and target specificity were obtained so far. To overcome these limitations, a mitochondria-targeted antioxidant (MitoQ), which consists of a ubiquinone moiety conjugated to a triphenylphosphonium (TPP+) cation to facilitate accumulation within the mitochondria, was developed and promising results in ALS models were attained [4]. Following these observations, we design a novel library of mitochondriotropic antioxidants using natural phenolic antioxidants as
cargo and TPP+ and isoquinolinium cations as carriers. Herein, we present the synthesis and initial studies on the evaluation of antioxidant profile and ADME properties.

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A molecular hybridization approach for the design of selective Aldose reductase (ALR2) inhibitors and exploration of their activities against Protein Tyrosine Phosphatase 1B (PTP1B)

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Type II diabetes mellitus is a metabolic disease associated with insulin resistance and high blood glucose levels. Under hyperglycemic conditions the polyol pathway is significantly activated resulting in a series of stress conditions and, finally, in cellular damage. Aldose reductase is the first enzyme of the polyol pathway which is implicated in the onset of long-term diabetic complications. Although many efforts have been focused on developing clinical aldose reductase inhibitors in previous years, they were fruitless due to the poor selectivity profile over the detoxifying aldehyde reductase enzyme. A series of novel benzothiazole-based 4-oxothiazolidin-2-yl-imino acetic acid derivatives has been designed based on our experience from previously reported (Z)-2-(benzo[d]thiazol-2-ylimino)thiazolidin-4-one derivatives. In addition, we followed a molecular hybridization of two well-known aldose reductase inhibitors by replacing toxicophore moieties and combining crucial fragments for aldose reductase inhibitory activity as well as selectivity. The most promising compounds in this series exhibited potent aldose reductase inhibitory activity with IC50 values of 46 and 67 nM, respectively, and optimal selectivity towards aldehyde reductase. Moreover, inspired by the idea that certain pharmacophoric features of aldose reductase inhibitors overlap with that of protein tyrosine phosphatase 1B inhibitors, we investigated the inhibitory activity of synthesized compounds towards this enzyme.
Zopodrestat

Epalrestat

Molecular Hybridization Modifications

Targeting AUR2 selectivity pocket essential for AUR2 inhibitory activity

Remove Michael acceptor moiety and potential toxicity

\[ R = H, F, Cl, CF_3, OCF_3, OCH_3 \]
Eremurus persicus: a source of agents acting as proteasome activators

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Eremurus persicus (Jaub & Spach) Boiss is an herbaceous plant used in Kurdish folk medicine for the treatment of genitourinary diseases, atherosclerosis, skin infections and inflammations [1]. Driven by this ethnomedicinal evidence, we conducted phytochemical study on E. persicus and confirmed that its roots extract is endowed with anti-inflammatory properties, being able to inhibit hPBMC proliferation, cytokine secretion and TNF-α activity [1]. Moreover, we isolated and characterized (R)-aloesaponol-III-8-methyl-ether [(R)-ASME, Fig. 1] as its main secondary metabolite and confirmed its anti-inflammatory activity. Moreover, we extended the biological investigation of (R)-ASME and evidenced its potential against leishmanial infections. To dispose of sufficient amount of (R)-ASME to better investigate its mechanism of action, we revised the extraction methods. The results are herein presented.

As a first step, we optimize the preparation of E. persicus roots extracts testing both maceration and microwave assisted extraction (MAE) and then properly fractionated the raw extracts. In such a way, we isolated (R)-ASME, and a second metabolite, identified as (R)-Germichrysone (Fig. 1). The best yields of both metabolites were obtained adopting a MAE approach (2x20min cycles, 60°C).

Figure 1. Chemical structure of (R)-ASME and (R)-Germichrysone

Successively, we assessed their effect on proteasome, being proteasome dysfunction associated with chronic inflammation [2]. Unexpectedly, both metabolites showed the ability to significantly activate the target in a dose dependent manner.
These compounds are under investigation for better understanding the potential of proteasome activators in different pathologies.

Poster Communication 39 (FP-39)

D-π-D-A imidazole-based phenothiazine derivatives as potential fluorescent dyes in biological applications - synthesis and characterization

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Heterocycles play a crucial role in many fields of science due to their electron abundance, bioactivity and wide possibilities of structure functionalization. They are frequently used as building blocks in donor-acceptor (D-A) systems [1]. Among the heterocyclic compounds, phenothiazine and imidazole moieties draw considerable attention. They are linked to the group of widely used fluorophores, increasingly attractive for designing new materials for organic electronics and bioimaging [2].

The novel series of imidazole-based phenothiazine derivatives (3a-3e) with D-π-D-A architecture was designed and synthesized in a multistep synthetic path. The central core was a donor phenothiazine ring connected through an acetylene linker with an imidazole unit at position 7 and possesses the formyl group at position 3. The obtained compounds differed in the length of the alkyl chain at the imidazole auxiliary donor. The photophysical properties of the new compounds were investigated. Absorption and fluorescence spectra were performed in various solvents, indicating the positive solvatochromism of compounds. Derivatives 3a-3e showed a broad emission band in the range of 450-600 nm, a high quantum yield of fluorescence (41-93%) and fluorescence decay time of 4.01 and 7.55 ns. The best photophysical parameters were distinguished among fluorophores by 3b and 3c with hexyl and decyl alkyl chains, respectively. Moreover, novel 3a-3e compounds demonstrated a comparative lack of cytotoxicity, indicating their promising suitability in bio-imaging combined with their high fluorescence.

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Neurotoxic profile of psychedelic phenethylamine derivatives

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New psychoactive substances (NPS) represent a constant danger to public health, with phenethylamine derivatives ranking third in number of monitored substances by the EU Early Warning System in 2020 [1]. Among phenethylamines are the 2,5-dimethoxyphenethylamine-based (2C) and the N-benzylphenethylamine-based (NBOMe) drugs, both substituted phenethylamines with psychedelic effects. Although there are several reports of acute intoxication and deaths related with the consumption of these compounds, their toxicological profile remains uncharacterized [2,3].

Thus, the main goal of this project was the synthesis of a group of psychedelic phenethylamines and the assessment of their neurotoxic profile in two in vitro models: human neuronal SH-SY5Y cells, differentiated into a dopaminergic phenotype and primary cultures of cortical neurons. SH-SY5Y cells and primary rat cortical neurons were exposed to the compounds for 24 h, and their cytotoxicity was evaluated by the neutral red uptake and MTT reduction assays, drawing concentration-response curves and estimating their EC₅₀ values. Moreover, their potential to generate free radicals was assessed using the DCFH-DA fluorescent probe. The impact of MAO-mediated metabolism on the compounds’ cytotoxicity was evaluated in the presence of MAO-A and MAO-B inhibitors, clorglyline and rasagiline, respectively. The compounds’ lipophilicity (log D, pH=7.4) was also determined through the chromatographic hydrophobicity index (CHI) data acquired by HPLC. The overall results of this study will be presented in this communication.

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Novel Aryl Piperazine Derivatives For The Treatment Of Schizophrenia - Design, Synthesis And Biological Evaluation

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N-phényl piperazines constitue un noyau de base dans un ensemble de composés biologiquement actifs. Particulièrement dans le domaine de la neurosciences, ils sont fréquemment présents dans des structures de ligands de récepteurs sérotonine et de dopamine. Un travail de sélection virtuelle précédent a permis l'identification de nouveaux antipsychotiques, dont la dérivé de N-phényl piperazine, le composé D2AAK3, avec une affinité de 115 nM pour le récepteur D2, ainsi que des affinités nanomolaires ou basses micromolaires pour D1, D3, 5-HT₁A, 5-HT₂A et 5-HT₇. La dérivé a été trouvé [1]. Les études comportementales ont révélé que D2AAK3 diminue l'hyperactivité amphetamine-induite in vivo, améliore la consolidation de la mémoire en test de mémoire passée et expose un comportement anxieux dans le labyrinthe élevé 30 minutes après un traitement aigu (cet effet a été inversé 60 minutes après l'administration) [2]. Dans la campagne d'optimisation de D2AAK3, une série de ses analogues, avec un substituant arylique modifié au piperazine et un lien alkyle étendu, ont été synthétisés. Les composés obtenus ont été évalués dans des tests d'assay de ligands radioactifs vis-à-vis leurs affinités pour les cibles de l'intérêt. Les études comportementales des composés les plus actifs compléteront les résultats des tests in vitro.
Influence of selected substances on the activity of tyrosinase

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Melanin belongs to a group of photo protective compounds. They protect against harmful effects of ultraviolet light. Unfortunately, in some cases, this pigment can accumulate, causing discoloration. The cosmetics industry is looking for more and more effective and safer solutions in the fight against hyperpigmentation. Many of the brightening agents are of natural origin, but their derivatives are increasingly used [1]. Melanin is formed because of reactions taking place in the melanogenesis pathway. The key enzyme and regulator in this process is tyrosinase (TYR). Many of the lightening compounds used affect the activity of tyrosinase. Tyrosinase is a glycoprotein produced only by specialized cells - melanocytes. Substances with bleaching potential can influence the TYR at various stages. Melanogenesis can be regulated in the steps of TYR expression, maturation, degradation, or direct inhibition of activity [2]. Melanogenesis is a very complex and multistep process. Several brightening compounds, despite proven activity, do not have an impact on TYR activity, inhibiting the process of melanin formation at a different stage. The use of antioxidants can modify melanogenesis by reducing oxidative stress. The resulting free radicals may stimulate tyrosinase activity. In addition, antioxidants can decrease the process of the photo-oxidation process of melanin deposited in melanosomes [3]. The strongest whitening agents include hydroquinone, azelaic acid, arbutin and kojic acid. Unfortunately, long-term use of hydroquinone causes many side effects, which is why it has been restricted or banned for use in cosmetic products by many countries [4].

Poster Communication 44 (FP-44)

Evaluation of cytotoxic and neuroprotective profile of potential dual-acting ligands for the treatment of Parkinson’s disease

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Parkinson's Disease (PD) is the second most common neurodegenerative disorder, characterized by the selective loss of dopaminergic neurons in the brain's substantia nigra pars compacta [1]. PD has pathophysiological hallmarks that includes iron accumulation within the brain, which triggers a specific form of regulated cell death called ferroptosis, further leading to dopamine (DA) depletion [2]. Currently, the available drugs are predominantly directed to symptoms relief, keeping the course of the disease unchanged [2].

The main goal of this study was the evaluation, in vitro, of the cytotoxic effects of novel dual-acting molecules based on 3-hydroxypyridin-4-one and the assessment of their neuroprotective profile in human neuronal SH-SYSY cells, differentiated into a dopaminergic phenotype with retinoic acid and 12-O-tetradecanoylphorbol-13-acetate (TPA). These compounds previously demonstrated the ability of chelate iron and inhibit catechol O-methyltransferase (COMT), allowing to restore DA levels.

SH-SYSY cells were exposed to the compounds for 24h and their cytotoxicity was evaluated by the neutral red uptake and resazurin reduction assays, to select non-cytotoxic concentrations. To evaluate the potential neuroprotective effects against iron (III)-induced cytotoxicity, the cells were exposed to ferric nitritotriacetate (FeNTA 24h), a ferric (Fe³⁺) iron aggressor, in the presence and absence of compounds. Also, the cells were exposed to MPP⁺, a neurotoxin that induces an in vitro PD model, with or without simultaneous exposure to the tested compounds, and their potential neuroprotective effects further evaluated 24h after exposure. Moreover, the compounds effects on the activity of P-glycoprotein, an efflux transporter impacting several neurodegenerative diseases [3], were also assessed through the rhodamine 123 accumulation assay.

The overall results of this study will be presented in this poster communication.
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