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Use of the 4-hydroxy-triazole moiety as a bioisosteric tool in the development of selective ligands for subtypes AMPA receptor

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(Article begins on next page)

25 April 2024

EFMC-YMCS

6th

EFMC Young Medicinal Chemist Symposium

September 5-6, 2019 | Athens, Greece

Book of Abstracts

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Welcome

Dear participant,

On behalf of the European Federation for Medicinal Chemistry (EFMC) and the Organising Committee, we warmly welcome you to Athens for the 6th edition of the EFMC Young Medicinal Chemist Symposium (EFMC-YMCS).

Since the first edition of the EFMC-YMCS in 2014, the symposium has gone from strength to strength with increased participation from EFMC-National Adhering Organisations, and it is now firmly established as the premier forum in Europe for young Medicinal Chemistry and Chemical Biology researchers to promote their science.

Our principal aims are:
- Creating a network of young European investigators in Medicinal Chemistry and Chemical Biology
- Stimulating young European investigators to share their scientific work with peers, and inspiring them to become leaders in their field
- Creating competition, excellence and European Champions in Medicinal Chemistry and Chemical Biology

This year, more than 170 scientists from 30 nations will gather in Athens for the latest edition. The symposium will consist of 3 keynote lectures, 20 oral communications given by prize winners from national competitions around Europe, 20 flash poster presentations, and more than 100 poster presentations showcasing the latest advances in drug discovery advances.

We also invite you to attend the different soft-skills training sessions organised in collaboration with the EFMC Young Scientists Network:
- How to boost your presentation skills
- Tips for a successful job interview
- How to get your paper published.

Finally, there will be a networking reception with senior representatives from academia and industry, giving you the opportunity of informal networking, which could shape your future career.

During the closing ceremony, the following prizes will be awarded to the European Champions in Medicinal Chemistry and Chemical Biology:
- EFMC-YMCS Presentation Prize, sponsored by the EFMC & Idorsia
- EFMC-YMCS Poster Prizes, sponsored by MedChemComm & Wiley
- EFMC-YMCS Public's Prize, sponsored by Roche

We thank our sponsors (American Elements, ChemPubSoc Europe, Evotec, Idorsia, Janssen, Merck, MDPI, MedChemComm, Novartis, Sanofi, Sygnature Discovery and Roche), the Hellenic Society of Medicinal Chemistry and all the participating National Adhering Organisations for their support, without which we could not run this event, and we look forward to your participation!

Emmanouil FOUSTERIS
University of Patras, GR
Symposium Chairman

On behalf of the EFMC-YMCS Organising committee:

David ALKER (David Alker Associates, UK),
Dennis GILLINGHAM (University of Basel, CH),
Kristina GONCHARENKO (SpiroChem AG, CH),
Cassandra LEE FLEMING (University of Gothenburg, SE),
Brieuc MATAGNE (LD Organisation, BE),
Eleni PONTIKI (Aristotele University of Thessaloniki, GR),
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Programme

Thursday September 5, 2019

14:15 Registration

15:00 Welcome and Opening

Session Chair: Dr Emmanouil FOUSTERIS (UNIVERSITY OF PATRAS, Patras, Greece)

15:05 **KL01 - The Emergence of Antibody-Drug Conjugates (ADCs) as Targeted Cancer Therapies From Ehrlich's "Magic Bullet" Concept to Calicheamicin γ^{I}_{1} and Mylotarg**
Prof. K.C. NICOLAOU (RICE UNIVERSITY, Houston, United States)

EFMC-YMCS Competition Presentation Session I

15:35 **OC01 - Functionalization of Tumour-Targeting Antibodies Via Enzymatic Oxidation of Tyrosine to 1,2-Quinones**
Winner of the Young Medicinal Chemist Meeting in The Netherlands
Mr Jorick BRUINS (WAGENINGEN UNIVERSITY, Wageningen, The Netherlands)

15:55 **OC02 - Synthetic Small Molecules Interfering with Oncogenic Microrna for the Induction of Glioblastoma Stem Cells Differentiation**
Winner of the Young Medicinal Chemist Meeting in France
Ms Chloé MAUCORT (INSTITUTE OF CHEMISTRY OF NICE, Nice, France)

16:15 **OC03 - New Ruthenium-Cyclopentadienyl Complexes Bearing Biotinylated (Macro)Ligands: Targeting Strategies to Fight Metastatic Breast Cancer**
Winner of the Young Medicinal Chemist Meeting in Portugal
Dr Leonor CORTE-REAL (CENTRO DE QUÍMICA ESTRUTURAL, Lisboa, Portugal)

16:35 **Flash Poster Presentations** (01-10)

- **FP01 - A New Life for Diazaborines: the Next Generation of Serine Protease Inhibitors**
  Mr Joao ANTONIO (UNIVERSITY OF LISBON, Lisbon, Portugal)
- **FP02 - From Peptides to Peptidomimetics: Structure-Activity Relationship of a Factor H-Binding Peptide to Modulate Undesired Host Complement Activity**
  Mr Clément BECHTLER (UNIVERSITY OF BASEL, Basel, Switzerland)
- **FP03 - Matrix Metalloproteinase-12 Inhibitors: Synthesis, Structure-Activity Relationships and Intestinal Absorption of Novel Sugar-Based Biphenylsulfonamide Carboxylates**
  Dr Doretta CUFFARO (UNIVERSITY OF PISA, Pisa, Italy)
- **FP04 - Photophysical Properties and Antiparasitic Activity of Bodipy-Tethered Dinuclear Trithiolato-Bridged Ruthenium(II)-Arene Complexes**
  Mrs Oksana DESIATKINA (UNIVERSITY OF BERN, Bern, Switzerland)
- **FP05 - N-ALKYL L-Iminosugars as Novel Anti-Inflammatory and Anti-Biofilm Tools for Cystic Fibrosis Lung Infections**
  Ms Anna ESPOSITO (UNIVERSITY OF NAPOLI FEDERICO II, Napoli, Italy)
- **FP06 - Design, Synthesis and Biological Evaluation of Novel Substituted Purine Isosters as EGFR Kinase Inhibitors, with Promising Pharmacokinetic Profile and In Vivo Efficacy**
  Dr Efthymios-Spyridon GAVRIIL (NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS, Athens, Greece)
- **FP07 - Metal Chelating Acetohydroxamic Acids Against Hepatitis C Virus and Flaviviruses**
  Ms Erofili GIANNAKOPOULOU (NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS, Athens, Greece)
- **FP08 - Discovery of Small-Molecule Modulators of 14-3-3 PPIs Via Dynamic Combinatorial Chemistry**
  Mr Alwin HARTMAN (UNIVERSITY OF GRONINGEN, Groningen, The Netherlands)
- **FP09 - Purine Nucleoside Analogs as Highly Potent Leads for the Treatment of Human African Trypanosomiasis**
  Mr Fabian HULPIA (UGENT, Ghent, Belgium)
- **FP10 - Development of Allosteric Inhibitors of ColH Using DCC Strategy**
  Dr Jelena KONSTANTINOVIC (HELMHOLTZ INSTITUTE FOR PHARMACEUTICAL RESEARCH SAARLAND (HIPS), Saarbrücken, Germany)

Programme

16:55 Coffee Break

EFMC-YMCS Competition Presentation Session II

Session Chair: Dr Kristina GONCHARENKO (SPIROCHEM AG, Basel, Switzerland)

17:10 **OC04 - Novel Acridine Derivatives as TDP 1 and/or 2 Inhibitors**
Winner of the Young Medicinal Chemist Meeting in Greece
Mrs Maria KARELOU (NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS, Athens, Greece)

17:30 **OC05 - Discovery of a Novel Chemotype of Non-Acidic, Neutral and Macrocyclic Keap1 Inhibitors**
Winner of the Young Medicinal Chemist Meeting in Sweden
Mr Fabio BEGNINI (UPPSALA UNIVERSITY, Uppsala, Sweden)

17:50 **OC06 - Directed Evolution of Short Peptides for Selective Detoxification of Lead**
Winner of the Young Medicinal Chemist Meeting in Switzerland
Dr Michal SHOSHAN (ETH ZÜRICH, Zürich, Switzerland)

18:10 **Flash Poster Presentations (11-20)**

- **FP11 - Identification, Synthesis and Optimization of Inhibitors of the Protein Tyrosine Phosphatase SHP2**
  Dr Yelena MOSTINSKI (LEIBNIZ-FORSCHUNGSINSTITUT FÜR MOLEKULARE PHARMAKOLOGIE, Berlin, Germany)
- **FP12 - Multitarget Triazoles: an Innovative Approach for the Treatment of Alzheimer's Disease**
  Ms Vanesa NOZAL GARCIA (CIB - CSIC, Madrid, Spain)
- **FP13 - TDP-43 Modulation by CDC7 Inhibitors as a Therapeutic Strategy for Amyotrophic Lateral Sclerosis**
  Ms Elisa ROJAS (CIB - CSIC, Madrid, Spain)
- **FP14 - Use of the 4-Hydroxy-Triazole Moiety as a Bioisosteric Tool in the Development of Selective Ligands for Subtypes Ampa Receptor**
  Dr Stefano SAINAS (UNIVERSITY OF TORINO, Torino, Italy)
- **FP15 - In Vitro and In Ovo Evaluation of Ros-Activatable Anticancer Boronate Prodrugs of Doxorubicin**
  Dr Charles SKARBEK (UNIVERSITY PARIS SUD, Orsay, France)
- **FP16 - Design and Synthesis of Tead's Ligands for the Treatment of Cancers**
  Mrs Manon STURBAUT (UNIVERSITY OF LILLE, Lille, France)
- **FP17 - Drug-Fragment Based Explorations for Novel Enterovirus Inhibitors**
  Ms Clara VAN HOEY (UNIVERSITY OF VIENNA, Vienna, Austria)
- **FP18 - Gemcitabine-GnRH Bioconjugates Bearing Oxime Bond Linkages: Synthesis, In Vitro Stability, Drug Release and Cytotoxic Effect**
  Mr Eirinaios VRETTOS (UNIVERSITY OF IOANNINA, Ioannina, Greece)
- **FP19 - Development of GSTO1-1 Inhibitors for the Treatment of Inflammatory Conditions**
  Ms Yiyue XIE (MONASH UNIVERSITY, Melbourne, Australia)
- **FP20 - Identification of a Novel Quinoline-Based DNA Demethylating Compound Highly Potent in Cancer Cells**
  Dr Clemens ZWERGEL (UNIVERSITY OF ROME LA SAPIENZA, Rome, Italy)

18:30 **EFMC-YMCS Poster Presentation Session 1 (Odd), Drinks & bites**

19:30 **EFMC-YMCS Poster Presentation Session 2 (Even), Drinks & bites**

20:30 End of the Scientifc Programme

Programme

EFMC-YSN Soft Skills Training Session (1)

20:30 **How to Boost Your Oral Presentation Skill, and Create a Good Slideshow**
Dr Kristina GONCHARENKO (SPIROCHEM AG, Basel, Switzerland)

20:45 **Getting the Job You Deserve!**
Dr David ALKER (DAVID ALKER ASSOCIATES, Birchington, United Kingdom)

21:15 **EFMC-YSN Networking Event**

22:30 End of the day

Friday September 6, 2019

EFMC-YMCS Competition Presentation Session III
Session Chair: Dr Cassandra LEE FLEMING (UNIVERSITY OF GOTHENBURG, Gothenburg, Sweden)

08:30 **KL02 - Medicinal Chemistry Between Serendipity and (Artificial) Intelligence**
Dr Cornelia ZUMBRUNN (IDORSIA PHARMACEUTICALS, Allschwil, Switzerland)

09:00 **OC07 - Antiplasmodial Activity of SAHAquines, Novel SAHA - Primaquine Hybrids**
Winner of the Young Medicinal Chemist Meeting in Croatia
Ms Maja BEUS (UNIVERSITY OF ZAGREB, Zagreb, Croatia)

09:20 **OC08 - Hybrdization Approach Towards Novel Antituberculars: Design, Synthesis, And Antimicrobial Evaluation Hybrid Compounds Combining Pyrazinamide and p Aminosalicylic Acid**
Winner of the Young Medicinal Chemist Meeting in Czech Republic
Ms Ghada BOUZ (CHARLES UNIVERSITY, Hradec Kralove, Czech Republic)

09:40 **OC09 - Synthesis, Computational and Biological Evaluation of Novel Benzimidazole Compounds for the Treatment of Cryptococcus Neoformans**
Winner of the Young Medicinal Chemist Meeting in the United Kingdom
Ms Gina WASHBOURN (UNIVERSITY OF LIVERPOOL, Liverpool, United Kingdom)

10:00 **OC10 - N'-Benzylated Derivatives of N-(7-Chloroquinolin-4-Yl)Octane-1,8-Diamine as Quorum Sensing Inhibitors in Pseudomonas Aeruginosa**
Winner of the Young Medicinal Chemist Meeting in Serbia
Ms Marta SPASIC (UNIVERSITY OF BELGRADE, Nis, Serbia)

10:20 Coffee Break

EFMC-YMCS Competition Presentation Session IV
Session Chair: Dr Eleni PONTIKI (ARISTOTELE UNIVERSITY OF THESSALONIKI, Thessaloniki, Greece)

10:40 **OC11 - Geometric Isomers of N-Propargyl-4-Syrylpiperidine Discriminate Between Monoamine Oxidase Isoforms A and B**
Winner of the Young Medicinal Chemist Meeting in Slovenia
Dr Damijan KNEZ (UNIVERSITY OF LJUBLJANA, Ljubljana, Slovenia)

11:00 **OC12 - A Fusing Strategy Application: Towards Potent ChE Inhibitors With MTDL Profile**
Winner of the Young Medicinal Chemist Meeting in Turkey
Ms Gülsah BAYRAKTAR (EGE UNIVERSITY FACULTY OF PHARMACY, Izmir, Turkey)

Programme

11:20 **OC13 - Development of Unique Molecular Probes: Low-Basicity Agonists for the Study of 5-HT7 Receptor Function**
Winner of the Young Medicinal Chemist Meeting in Poland
Dr Adam HOGENDORF (MAJ INSTITUTE OF PHARMACOLOGY, POLISH ACADEMY OF SCIENCES, Krakow, Poland)

11:40 **OC14 - The Establishment of Tocopherol Reference Intervals for Hungarian Adult Population Using Validated HPLC Method**
Winner of the Young Medicinal Chemist Meeting in Hungary
Dr Gábor VERES (HUNGARIAN ACADEMY OF SCIENCES, Budapest, Hungary)

12:00 Lunch

EFMC-YSN Soft Skills Training Session (2)

13:00 **Why Was My Paper Rejected? Tips from an Editor on How to Get Published**
Dr David PERALTA (WILEY-VCH VERLAG GMBH & CO. KGAA, Weinheim, Germany)

EFMC-YMCS Competition Presentation Session V

Session Chair: Prof. Grigorios ZOIDIS (UNIVERSITY OF ATHENS, Athens, Greece)

13:45 **OC15 - Expanding the Chemical Space of DNA-Encoded Small Molecule Libraries**
Winner of the Young Medicinal Chemist Meeting in Germany
Dr Andreas BRUNSCHWEIGER (TU DORTMUND, Dortmund, Germany)

14:05 **OC16 - Finding the Right Candidate for the Right Position: a Fast NMR-Assisted Combinatorial Method for Optimizing Nucleic Acids Binders**
Winner of the Young Medicinal Chemist Meeting in Spain
Dr Andrés GONZALEZ SANTANA (IQOG - CSIC, Madrid, Spain)

14:25 **OC17 - From ZINC to ZINClick: Our Way to Explore the Chemical Space**
Winner of the Young Medicinal Chemist Meeting in Italy
Dr Alberto MASSAROTTI (UNIVERSITY OF EASTERN PIEDMONT, Novara, Italy)

14:45 **OC18 - Extended Glucuronides: Achieving Site-Selectivity Through Extracellular Drug Release**
Winner of the Young Medicinal Chemist Meeting in Denmark
Mr Raoul WALTHER (AARHUS UNIVERSITY, Aarhus, Denmark)

15:05 **OC19 - Cyclopropenium-Based Polymers**
Winner of the Young Medicinal Chemist Meeting in Israel
Mr Noam STEINMAN (HEBREW UNIVERSITY OF JERUSALEM, Jerusalem, Israel)

15:25 **Voting Break**

15:40 **KL03 - Chemical Tools to Target and Image Tumours**
Prof. Stuart CONWAY (UNIVERSITY OF OXFORD, Oxford, United Kingdom)

16:10 Closing and Award Ceremony

16:20 End of the Symposium

EFMC Young Scientists Network

All EFMC-YMCS participants are invited to participate to the EFMC-YSN (Young Scientists Network) Soft-Skills Training Sessions:

Thursday September 5, 2019

How to Boost Your Oral Presentation Skill, and Create a Good Slideshow

Dr Kristina GONCHARENKO (SPIROCHEM AG, Basel, Switzerland)

Don't just present your results - tell a story with your data! This workshop focuses on visualizing and communicating with your results in a better way. How much information can you put onto one slide? How to determine the appropriate type of graph for your situation? How to direct your audience to the most important parts of your data? As a chemist you can think like a designer! During this workshop we will leverage the power of storytelling and learn how to help your message resonate with your audience.

Getting the job You Deserve!

Dr David ALKER (DAVID ALKER ASSOCIATES, Birchington, United Kingdom)

Starting your career following postgraduate study can often look like a challenging even impossible step, with fierce competition for places and many talented applicants. However, there are simple things you can do which will dramatically improve your chance of getting an exciting and worthwhile position. Following a successful career as a medicinal chemist, Dave Alker spent 15 years as Recruitment Manager for Pfizer so come along and find out how you can improve your chances of getting the job you deserve.

Thursday's sessions will be followed at 21:15 by a **Networking Event,** giving you the opportunity to interact with the keynote lecturers and some senior profiles of all horizons (Academia, Big Pharma, CRO's).

Friday September 6, 2019

Why Was My Paper Rejected? Tips from an Editor on How to Get Published

Dr David PERALTA (WILEY-VCH VERLAG GMBH & CO. KGAA, Weinheim, Germany)

Have you ever wondered why your last journal submission was directly rejected? Or how editors pick referees and conduct peer review? Or what exactly do editors and publishing houses do? In this talk, Dr. David Peralta, Editor-in-Chief of ChemMedChem (a Wiley-VCH and ChemPubSoc Europe journal) talks from his experience as a scientific editor and opens up the "black box" of science publishing. Dr. Peralta will provide concrete tips on how to optimize your manuscript submission to journals and also how to deal with rejected papers. This is also a great opportunity to learn about editorial work, which is an excellent career option for those with graduate degrees in the sciences.

EFMC YOUNG SCIENTISTS NETWORK

"Crossing boundaries to Build Strong Networks for Early Career Researchers"

EFMC launched the **EFMC-Young Scientists Network** to **inspire**, **connect** and **facilitate** medicinal chemists and chemical biologists in their Early Career.

Registration is **free of charge** and open to all!

Our actitivites

- **Networking**
  - Open forum
  - "Meet & Greet" events for young people
  - Networking evenings at the EFMC-YMCS
- **Training**
  - "Soft-skills" workshops
  - Career fairs
  - Mentoring programs
- **Support**
  - Travel grants to attend EFMC Events
  - YSN Prize for best PhD/Post-doc
  - Job & academic positions portal
- **Events & Meetings**
  - EFMC-YMCS (www.efmc-ymcs.org)
  - YSN-Members assembly

Visit www.efmc.info/ysn for more information, or mail us at ysn@efmc.info

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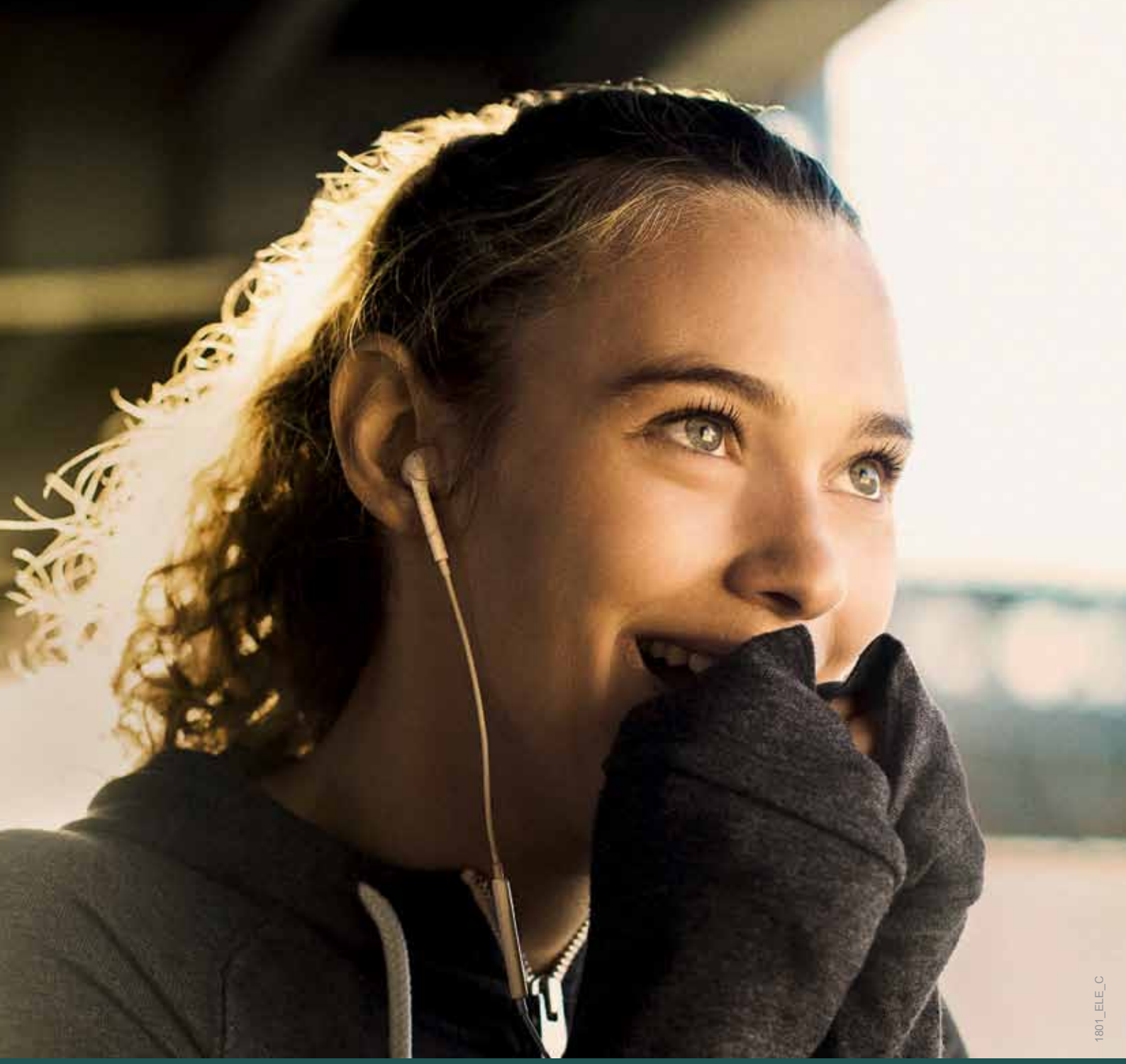

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Notes

Keynote Lectures

Keynote Lectures' Biographies

Prof. K.C. NICOLAOU (RICE UNIVERSITY, Houston, United States)
KL01 - The Emergence of Antibody-Drug Conjugates (ADCs) as Targeted Cancer Therapies: From Ehrlich's "Magic Bullet" Concept to Calicheamicin γ1I and Mylotarg

K. C. Nicolaou is currently the Harry C. Olga K. Wiess Professor of Chemistry at Rice University. He previously served concurrently as the founding chairman of the Chemistry Department at the Scripps Research Institute, a distinguished Professor of Chemistry at the University of California, San Diego (1989-2013), and the founding Director of the Chemical Synthesis Laboratory at ICES, A*STAR at Biopolis, Singapore. His research activities focus on the discovery and development of new synthetic strategies and technologies, and their applications to the total synthesis of natural and designed molecules of biological and medical importance. He is a co-author of *The Classics in Total Synthesis series* (I, II, III) and *Molecules that Changed the World*.

Dr Cornelia ZUMBRUNN (IDORSIA PHARMACEUTICALS, Allschwil, Switzerland)
KL02 - Medicinal Chemistry Between Serendipity and (Artificial) Intelligence

Cornelia Zumbrunn holds a position as Principal Scientist (medicinal chemist and project leader) in the field of antibacterial research and cardiovascular diseases. Since 2004 she worked in the research department of Actelion Pharmaceuticals Ltd, now Idorsia Pharmaceuticals Ltd. (Allschwil, Switzerland). Previous positions include Morphochem AG and Hoffmann-LaRoche, after a postdoc at Cambridge University (UK). Cornelia obtained her PhD from Hoffmann-LaRoche and the University of Zürich after having completed studies in organic chemistry in Fribourg (CH) and Neuchâtel (CH). Her research focused on the discovery of antibiotics with novel modes of action and other projects in the areas of central nervous systems and cardiovascular research. She is a board member and the secretary of the Division of Medicinal Chemistry and Chemical Biology of the Swiss Chemical Society (DMCCB).

Prof. Stuart CONWAY (UNIVERSITY OF OXFORD, Oxford, United Kingdom)
KL03 - Chemical Tools to Target and Image Tumours

Stuart Conway is a Professor of Organic Chemistry at the University of Oxford, and the E. P. Abraham Cephalosporin Fellow in Organic Chemistry at St Hugh's College, Oxford. He studied Chemistry with Medicinal Chemistry at the University of Warwick before undertaking PhD studies with Professor David Jane and Professor Jeff Watkins FRS at the University of Bristol. Stuart completed post-doctoral studies with Professor Andrew Holmes FRS at the University of Cambridge. In 2003, he was appointed as a Lecturer in Bioorganic Chemistry at the University of St Andrews, in 2008 was appointed as an Associate Professor at Oxford, and in October 2014 he was promoted to Full Professor. Between March and August 2013 Stuart was a Visiting Associate at the California Institute of Technology. Since 2016 he has been an Associate Editor for the Journal of Medicinal Chemistry and he is the President-elect of the RSC Organic Division. His research focuses on the development of chemical tools to study biological systems.

THE EMERGENCE OF ANTIBODY DRUG CONJUGATES (ADCS) AS TARGETED CANCER THERAPIES FROM EHRLICH'S "MAGIC BULLET" CONCEPT TO CALICHEAMICIN γ_1^I AND MYLOTARG AND BEYOND

K. C. Nicolaou

Rice University, Department of Chemistry, BioScience Research Collaborative, Ste. 363, 6100 Main Street, MS-602, TX 77005-1827 Houston, United States

The emergence and development of the antibody–drug conjugate (ADC) paradigm for targeted cancer therapies will be presented beginning with Paul Ehrlich's "magic bullet" concept proposed by him more than a century before Mylotarg, the first example of such therapy was approved for clinical use. Today three additional ADCs are approved for the treatment of various cancers, Adcetris, Kadcyla and Besponsa. The fascinating history of ADCs follows the emergence and development of organic synthesis and immunology, and related disciplines as they advanced themselves to high levels of performance, an occurrence that allowed the realization of Ehrlich's dream of the "magic bullet." To be sure improvements are still needed in the field of antibody–drug conjugates as scientists strive to expand their applications to treat patients with other types of cancers and various other medical indications.[1–3]

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1) The Role of Organic Synthesis in the Emergence and Development of Antibody–Drug Conjugates as Targeted Cancer Therapies, K.C. Nicolaou, S. Rigol, *Angew. Chem. Int. Ed.* **2019**, DOI: 10.1002/anie.201903498.
2) Total Synthesis Endeavors and Their Contributions to Science and Society: A Personal Account, K.C. Nicolaou, S. Rigol, R. Yu, *CCS Chem.* **2019**, *1*, 3–37.
3) Total Synthesis in Search of Potent Antibody–Drug Conjugate Payloads. From the Fundamentals to the Translational, K.C. Nicolaou, S. Rigol, *Acc. Chem. Res.* **2019**, *52*, 127–139.

MEDICINAL CHEMISTRY BETWEEN SERENDIPITY AND (ARTIFICIAL) INTELLIGENCE

Cornelia Zumbrunn

Idorsia Pharmaceuticals Ltd., Hegenheimermattweg 91, CH-4123 Allschwil, Switzerland

The job of a medicinal chemist is generally regarded as “designing and making bioactive molecules”. Owing to the complexity of developing a new drug, many different types of expertise are key in this process, making drug discovery an extremely interdisciplinary and fascinating field of activity.

The know-how about biological processes underlying diseases as well as the availability of novel data, technologies and modalities increase the possibilities and scope of drug discovery.

Dealing with the many dimensions and parameters during optimization is a real challenge in which machine learning and “Artificial Intelligence” may play a significant role.[1]

Most of the times however, our knowledge is fragmented and based on models representing but a part of the “truth”. Curiosity and creativity will remain important aspects in medicinal chemistry on the long path of drug development.

Certain aspects of this fascinating job will be discussed with the help of real-life examples from the NBTI project (Novel bacterial topoisomerase inhibitors[2-3]) at Actelion/Idorsia which led to the discovery of highly potent and broad-spectrum antibacterial compounds covering the most problematic ESKAPE pathogens.[4]

The focus will be put on specific challenges such as the understanding the multiple parameters that influence the intracellular concentration of antibiotics in different Gram-negative species as well as the structure-based design of novel inhibitors with an unusual mode of action.

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2) Bax, B. et al, Nature 2010, 466, 935-940. https://doi.org/10.1038/nature09197
3) Gibson, E.G. et al., ACS infect. Dis. 2019, 5, 570. https://doi.org/10.1021/acsinfecdis.8b00315
4) Zumbrunn, C.; Ritz, D.; Rueedi, G.; et al., unpublished results

THE CHEMISTRY OF TARGETING AND IMAGING TUMOUR HYPOXIA

Stuart Conway

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Epigenetics, defined as “stably heritable phenotype resulting in changes in a chromosome without alterations in the DNA sequence”, comprises regulatory mechanisms of chromatin state that control access to DNA, mediated by noncoding RNA, DNA methylation, nucleosome remodelling histone variants, and some histone post-translational modifications (PTMs). Histone PTMs are dynamic, with cellular machinery identified that can add these modifications and that can remove them. A third class of proteins, termed “readers”, has been identified, that binds to PTMs and thus stabilise large protein assemblies, which are often involved in transcriptional regulation.

Histone or lysine deacetylase (H/KDAC) inhibitors inhibit the removal of acetyl groups from lysine residues, and have been approved for use in a number of oncology indications. Despite the success of these compounds, there are two potential issues with this class of drugs. Firstly, the inhibitors are almost all based on the zinc-binding hydroxamic acid group, which can bind to other zinc-containing enzymes potentially causing off-target effects and toxicity. Secondly, KDAC inhibitors are broad epigenetic remodifies that affect the expression of a multitude of genes. In untargeted drugs such as Panobinostat these effects are present in both cancerous and healthy cells, leading to unwanted short-term and long-term effects. To overcome this issue we have developed a hypoxia-activated pro-drug of Panobinostat (NI-Pano). This compound releases Panobinostat selectively in regions of hypoxia (low oxygen), such as those found in solid tumours. In conditions of normal oxygen concentration NI-Pano has no effect on the survival of cancer cell line (at a concentration of 5 μM), whereas in hypoxia NI-Pano (5 μM) causes complete killing of cancer cells. These results indicate that NI-Pano represents a promising new targeted therapy for oncology indications that will have fewer unwanted effects. The design, synthesis, *in vitro* and *in vivo* studies on NI-Pano will be presented. In addition, complemenatry methods for imaging tumour hypoxia will be reported.

Notes

Oral Communications

FUNCTIONALIZATION OF TUMOUR-TARGETING ANTIBODIES VIA ENZYMATIC OXIDATION OF TYROSINE TO 1,2-QUINONES

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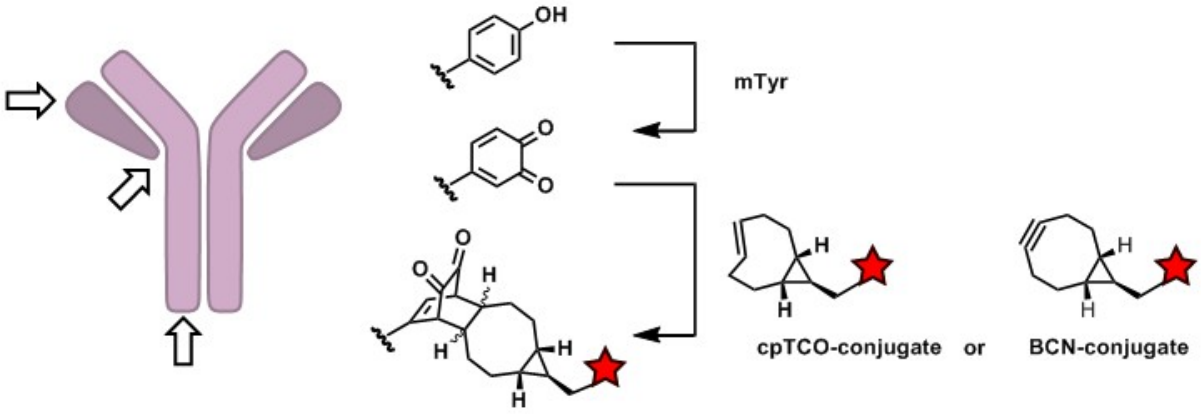
Antibodies have been utilized for treatment of cancers and other diseases in either its native form (*e.g.* AstraZeneca's Fasenra and Imfinzi), or with potent cytotoxic agents conjugated for targeted therapy (*e.g.* Pfizer's Ifixi). We have developed a new method of rapid, site-selective and high-yielding conjugation by oxidizing tyrosine residues expressed at the termini of antibodies.[1]



By exposing tyrosine residues via a tetra-glycyltyrosine (G_4Y) tag, they become prone to selective enzymatic oxidation by mushroom tyrosinase, which converts the phenol moiety to a quinone.The quinone can perform rapid strain-promoted oxidation-controlled cyclooctyne-1,2-quinone cycloaddition (SPOCQ) with bicyclo[6.1.0]nonyne (BCN),[1a, 2] or cyclopropanated trans-cyclooctene (cpTCO),[1b] resulting in a stable conjugation of a selected probe to an antibody with yields of over 95%.

This method was applied to prepare i.e. antibody-drug conjugates (ADCs) and fluorescently labelled antibodies, and is being used to bi-functionalize antibodies with immunologically relevant proteins such as interleukins, cytotoxic agents and others.

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SYNTHETIC SMALL MOLECULES INTERFERING WITH ONCOGENIC MICRORNAS FOR THE INDUCTION OF GLIOBLASTOMA STEM CELLS DIFFERENTIATION

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Glioblastomas (GBM) are the most common form of primary brain tumors afflicting adult patients of all ages and inevitably lead to a fatal outcome in less than 18 months. These highly vascularized and infiltrating tumors are resistant to current therapies which combines surgery, radiotherapy and chemotherapy with Temozolomide as alkylating agent.(1) The aggressive behavior of GBM, including resistance to treatments and tumor recurrences, has been attributed to the presence of GBM stem-like cells (GSCs), which remain persistent and even more aggressive following conventional cytotoxic treatments.

A complex network of small non-coding RNAs, named microRNAs, is involved in the differentiation/dedifferentiation process in GSCs and it would be particularly interesting to interfere with microRNAs expression using small-molecule drugs able to cross the blood-brain barrier.(2) Recently, our team identified original compounds able to interfere with miRNAs biogenesis.(3) Some of them induce GSCs differentiation, inhibit clonal proliferation and strongly increase the sensitivity of these cells to Temozolomide. The purpose of this research project is to develop new drug candidates starting from these original and validated hits and to increase GSCs sensitivity to current chemotherapies by interfering with the microRNAs network. To date, we already synthesized a first series of derivatives bearing chemical modifications at various positions and identified the first structure-activity relationships using in vitro studies. The biological assays on primary glioblastoma cultures are currently in progress. From the achievement of this project, we expect the identification of druggable compounds for anti-GSC strategies bearing an extremely original mechanism of action and directed toward a so far incurable cancer.

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NEW RUTHENIUM-CYCLOPENTADIENYL COMPLEXES BEARING BIOTINYLATED (MACRO)LIGANDS: TARGETING STRATEGIES TO FIGHT METASTATIC BREAST CANCER

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One of the major challenges in chemotherapy is the design of drugs that are able to target cancer cells while sparing healthy cells and thus avoiding side effects. The lack of selectivity of the drugs towards cancer may be circumvented by the use of biomolecules and/or macromolecules to benefit from the active and/or passive targeting strategies, respectively.[1] In this frame, our research group has been engaged in the design of 'Ruthenium-cyclopentadienyl' compounds bearing a macromolecule and/or a biomolecule.[2],[3] Here we will present our recent results regarding the possible targets and mechanism of action of two novel Ru compounds with the general formula $[Ru(Cp)(PPh_3)(bipy\text{-}R)]^+$, where R = biotin or polylactide, aimed to target triple-negative breast cancer cells. Thus, to assess the biological potential of the new Ru compounds an array of *in vitro* studies in hormone and nonhormone-responsive breast cancer cell lines was performed. These studies encompass the assessment of cytotoxicity, cell death mechanism, intracellular distribution (drug internalization), F-actin staining (cytoskeleton morphology changes) and anti-metastatic ability (colony formation assay). The ability of the compounds to overcome multidrug resistance and preliminary *in vivo* studies to assess the toxicity of the compounds in the zebrafish model will also be presented.

Acknowledgments: This work was financed by the Portuguese Foundation for Science and Technology (FCT) - projects UID/QUI/00100/2019, PTDC/QUI-QIN/28662/2017 and UID/BIA/04050/2013 (POCI-01-0145-FEDER-007569. L. Côrte-Real and A.R. Brás thank FCT for their Ph.D. Grants (SFRH/BD/100515/2014 and SFRH/BD/139271/2018, respectively). A. Valente acknowledges the CEECIND 2017 Initiative (CEECIND/01974/2017).

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NOVEL ACRIDINE DERIVATIVES AS TDP 1 AND/OR 2 INHIBITORS

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Cancer is a one of the most deadly diseases, responsible for about 13% of all deaths worldwide. It is normally caused by genetic abnormalities related to DNA of the affected cells; therefore, targeting the repair pathways of DNA could improve the efficacy of DNA-damaging anticancer drugs, such as clinically significant Topoisomerase-I (Top1) and Topoisomerase-II inhibitors. Among the most recently discovered DNA repair enzymes are Tyrosyl-DNA phosphodiesterases TDP1 and 2, which function is excising irreversible protein tyrosyl-DNA complexes involving topoisomerase 1 and/or 2 respectively. TDP1 catalyzes the hydrolysis of the phosphodiester bond between Top1 and DNA-3′-phosphate, suggesting a role in repairing of DNA double-strand breaks. Additionally, TDP2 removes many covalent adducts from DNA through hydrolysis of complexes between DNA and the Top2 active site tyrosine residue. TDP inhibitors reduce the destabilization and cleavage of stalled topoisomerase - DNA complexes, making them irreversible and thereby driving cancer cells into apoptosis.[1] Here, we describe the design, synthesis and pharmacological evaluation of novel amino substitutent tricyclic analogues as TDP1 and/or 2 inhibitors. The new compounds bear the the acridine or aza-acridine core, possessing one or two basic side chains. All compounds were tested for their activity against TDP1 and 2 and most of them showed significan activity. These results suggest in accordance with *In Silico* calculations, that the second basic side chain is essential for this activity, while also crucial is the presence of a methoxy substitution.

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DISCOVERY OF A NOVEL CHEMOTYPE OF NON-ACIDIC, NEUTRAL AND MACROCYCLIC KEAP1 INHIBITORS

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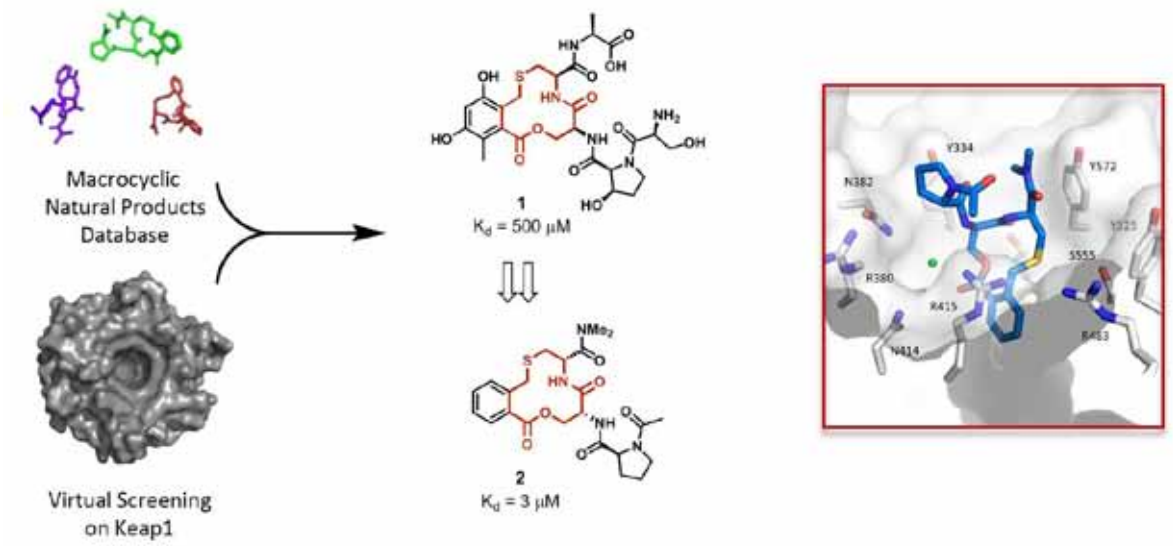
The Keap1-Nrf2 protein-protein interaction is well characterized, but development of ligands for the binding site on Keap1 is challenging due to its polar and charged nature. Activation of Nrf2 through inhibition of the complex with Keap1 offers opportunities to reduce oxidative stress, which is involved in a number of diseases.[1,2]

The natural product cyclothialidine (**1**), which contains a 12-membered lactone, was identified as a ligand for Keap1 in a virtual screen of a set of natural product derived macrocyclic cores. More than 30 simplified analogues of cyclothialidine were synthesized and evaluated as inhibitors of the binding of a peptide from Nrf2 to Keap1. This provided an optimized lead compound (**2**) that showed a 100-fold improvement in potency as compared to cyclothialidine, together with good solubility and moderate cell permeability.[3]



Moreover, the conformational ensemble in solution of compound **2** and its structure when bound to Keap1 were determined. This structural information allows the rationalization of the SAR studies and will be used for further optimization of the lead compound.

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DIRECTED EVOLUTION OF SHORT PEPTIDES FOR SELECTIVE DETOXIFICATION OF LEAD

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Affecting enormous populations worldwide, lead (Pb) poisoning currently poses a major challenge for medicinal chemistry. Although chelation therapy is the most efficient way to handle metal toxicity, the approved chelating agents suffer from many drawbacks. As relatively small molecules, these chelators cannot distinguish between essential and toxic metal ions, causing the deactivation of essential metal ions in the body. As a result, most of these compounds are highly toxic and many segments of the population, such as pregnant women and children, who are the most susceptible to metal poisoning, are prohibited from treatment with them.

Peptides and short proteins serve as common scaffolds for metal detoxification in many organisms. As peptides are biocompatible, flexible and contain a variety of potential functionalities, developing a peptide for this purpose is highly advantageous. Taking advantage of the power of large numbers, we used directed evolution for combinatorial screening to test more than 10^6 different peptides through a survival-selection system. Upon challenging bacteria that harbor the library plasmids with toxic Pb(II) ions, the gene sequences from surviving colonies were decoded to identify peptides that not only complex with the toxic ions, but also do not independently harm the bacteria. The identified peptides underwent extensive structure-activity relationship studies towards relevant characteristics in order to determine the best ligands for the goal, which is the establishment of a new potential generation of compounds for chelation therapy.

ANTIPLASMODIAL ACTIVITY OF SAHAQUINES, NOVEL SAHA - PRIMAQUINE HYBRIDS

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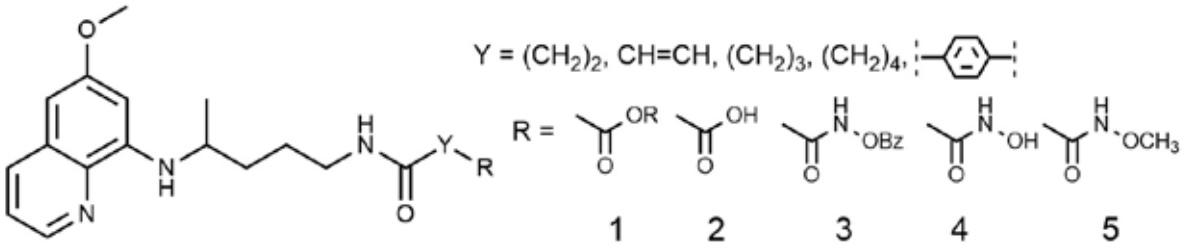
SAHAquines are novel hybrid compounds that combine moieties of suberoylanilide hydroxamic acid (SAHA), an anticancer agent with weak antiplasmodial activity, and primaquine, an antimalarial drug with low antiproliferative activity (1-3). The prepared SAHAquines differ in linker length/type and/or functional groups: compounds **1** are esters, **2** are carboxylic acids, **4** are unsubstituted and **3** and **5** are *O*-benzyl and *O*-methyl substituted hydroxamic acids.

To evaluate their antiplasmodial activity, SAHAquines were tested *in vitro* against *P. falciparum* erythrocytic stages (3D7 and Dd2 strains) and against *P. berghei* hepatic stages. Overall, our results show that SAHAquines with free hydroxamic acid were the most potent, out of which SAHAquine **4b** had the lowest IC_{50} values (0.4 μM for *Pf*3D7, 1.9 μM for the *PfD*d2 strain (erythrocytic stage) and 0.43 μM (hepatic stage)). SAHAquine **1b** from the ester subclass was the only compound out of hydroxamic acid series with IC_{50} values in a low micromolar range. This is probably due to α,β-unsaturated carbonyl group (Michael acceptor moiety), capable of conjugate addition.

This work has been fully supported by the Croatian Science Foundation under the project number IP-09-2014-1501. The work of doctoral student Maja Beus has been fully supported by the Young researcher's career development project – training of doctoral students of the Croatian Science Foundation founded by the European Union from the European Social Fund.



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HYBRDIZATION APPROACH TOWARDS NOVEL ANTITUBERCULARS: DESIGN, SYNTHESIS, AND ANTIMICROBIAL EVALUATION HYBRID COMPOUNDS COMBINING PYRAZINAMIDE AND p AMINOSALICYLIC ACID

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The white plaque, tuberculosis, remains the number one killer of all infectious diseases according to the World Health Organization.[1] As part of our long-term research, we discuss the design, synthesis, antimycobacterial evaluation, structure-activity relationships, and docking studies of a series of hybrid compounds combing pyrazinamide, a first line agent, and *p*-aminosalicylic acid, a second line agent (Fig. below).[2,3] Title compounds were obtained by reacting different pyrazinecarboxylic acids, activated by 1,1'-carbonyldiimidazole, with *p* -aminosalicylic acid in dimethylsulfoxide as a solvent. A further modification step to the general structure of obtained compounds was the formation of a cyclic lactone in the *p*-aminosalicylic acid fragment. All obtained products were *in vitro* evaluated for their antimycobacterial activities against *Mycobacterium tuberculosis* H37Rv and four other non-tubercular mycobacterial strains. As complementary testings, prepared compounds were *in vitro* screened for antibacterial, antifungal, and cytotoxicity in HepG2 liver cancer cell line. Most compounds showed moderate to excellent antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv and *Mycobacterium kansasii* with no *in vitro* cytotoxicity. Cyclized compounds were found more active against the latter mycobacterial strains than their corresponding non-cyclic parent compounds [6-chloro-*N*-(4-oxo-4*H* -benzo[*d*][1,3]dioxin-7-yl)pyrazine-2-carboxamide was the most active compound with minimum inhibitory concentration against *Mycobacterium tuberculosis* H37Rv ≤ 0.78 μg/mL (2.5 μM)]. This finding may be attributed to the increased lipophilicity of lactone compounds and hence improved penetration through the lipophilic mycolic cell walls of mycobacteria. No antibacterial or antifungal activities were observed for any of the prepared compounds, suggesting selectivity. Docking studies were conducted to have an insight regarding possible targets of active compounds.

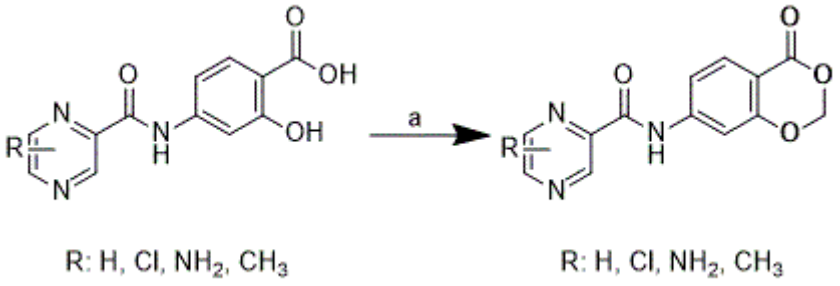

Fig.: The general structures of hybrid compounds combining pyrazinamide and *p*-aminosalicylic acid; a) $K_3PO_4.3H_2O$, DCM, DMF, 100 °C, reflux for 10 hrs.

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SYNTHESIS, COMPUTATIONAL AND BIOLOGICAL EVALUATION OF NOVEL BENZIMIDAZOLE COMPOUNDS FOR THE TREATMENT OF CRYPTOCOCCUS NEOFORMANS

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Cryptococcus neoformans is opportunistic fungal infection that is prominent in sub-Saharan Africa, were co-infection with AIDS exacerbates the condition further. The disease is currently treated by the drugs amphotericin B, fluconazole and flucytosine, all of which present issues due to toxicity and lack of efficacy. Despite being a major cause of morbidity, research is poorly funded and thus there have been no novel treatments discovered for many years.

Benzimidazoles, such as albendazole (MIC = 0.5 mg/L) and flubendazole (MIC = 0.125 mg/L) have previously been used to treat helminthic infections in veterinary medicine. However research has suggested that derivatives of these can be used to treat a number of fungal infections including *C. neoformans*. Mechanistically they bind to β-tubulin and prevent mitosis from occuring causes fungal cell death.[1]

The aim of this project was to develop a library of benzimidazole drugs as novel treatment for *C. neoformans*, developing novel synthetic routes. Potent compounds have been identified with favourable measured DMPK characteristics (Table 1), with future work seeking to improve aqueous solubility. Understanding of whether the compounds show selectivity for *C. neoformans* β-tubulin over human β-tubulin has been achieved using both biological and computational methods.[1] Work is still ongoing to understand this selectivity, which should aid design for compounds that are both efficacious and well-tolerated.

Overall, the project has resulted in the successful synthesis of a variety of novel benzimidazole analogues, which display excellent activity against *C. neoformans* compared to flubendazdole. Computational modelling has also been employed to understand this interaction with the β-tubulin target (Figure 1).

Compound Code	MIC (mg/L)	Log D7.4	Aq Sol (μM)	Human Microsomal Cl_{int} (μl/min/mg)	Rat Hepatocyte Cl_{int} (μl/min/10^6 cells)
Flubendazole	0.125	2.9	0.8	44	39
GW-07-07*	0.03	4	0.3	17	12
GW-07-17	0.03	4.8	0.1	9.07	21.9
GW-09-79	0.06	3.6	0.3	26	8
GW-09-73	0.25	3.1	39.4	18.9	59

*Predicted DMPK data

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N'-BENZYLATED DERIVATIVES OF N-(7-CHLOROQUINOLIN-4-YL)OCTANE-1,8-DIAMINE AS QUORUM SENSING INHIBITORS IN PSEUDOMONAS AERUGINOSA

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Development of resistance to antibiotics that are currently used for clinical treatment is one of the major health problems and creates a necessity for a new strategy for treatment and prevention of bacterial infections. *Pseudomonas aeruginosa* is opportunistic pathogen which causes nosocomial infections and serious diseases, especially among immunocompromised patients (cystic fibrosis, cancer, AIDS), and its resistance is mainly associated with biofilms formation. Quorum sensing (QS) is a complex, hierarchically organized, cell-density-dependent communication system, through which bacteria control production and secretion of their virulence factors, motility, and biofilm formation. The QS network of *P. aeruginosa* consists of four interconnected signalling pathways: Las, Rhl, the PqsR-controlled quinolone system (PQS), and Integrated QS system (IQS). Since virulence and biofilm production of *P. aeruginosa* is regulated by QS, the disruption of these signalling pathways may be a promising novel approach in the treatment of multi-drug resistant infections. Anti-virulence agents do not target vital functions, therefore selective pressure is reduced.

We have previously reported that long-chained 4-aminoquinolines inhibited biofilm formation and virulence factors production in *P. aeruginosa* through inhibition of PQS signalling.[1] In order to further optimize the activity, new derivatives of 7-Cl and 7-CF_3-substituted *N*-alkylamino-4-aminoquinolines were synthesized by introducing different *N'*-benzyl substituents, and/or by changing the length of the aminoalkyl chain. The tested derivatives showed low bactericidal activity, thus resulting as candidates for anti-virulence agents. It was demonstrated that the tested compounds can significantly reduce the production of bacterial pigment pyocyanin, and most active derivative caused the inhibition >90% at 50 μM, with IC_{50} value of 12 μM. Inhibition of specific QS pathway was evaluated and the compounds reduced Rhl activity by 35-49%. The effect on PqsR was the most prominent with the most active compounds causing the inhibition of 66-80%. It was shown that small structural modifications cause significant differences in anti-QS activity, which enables several directions for further optimization of anti-QS activity of 4-aminoalkylquinolines.

Acknowledgments

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GEOMETRIC ISOMERS OF N-PROPARGYL-4-SYRYLPIPERIDINE DISCRIMINATE BETWEEN MONOAMINE OXIDASE ISOFORMS A AND B

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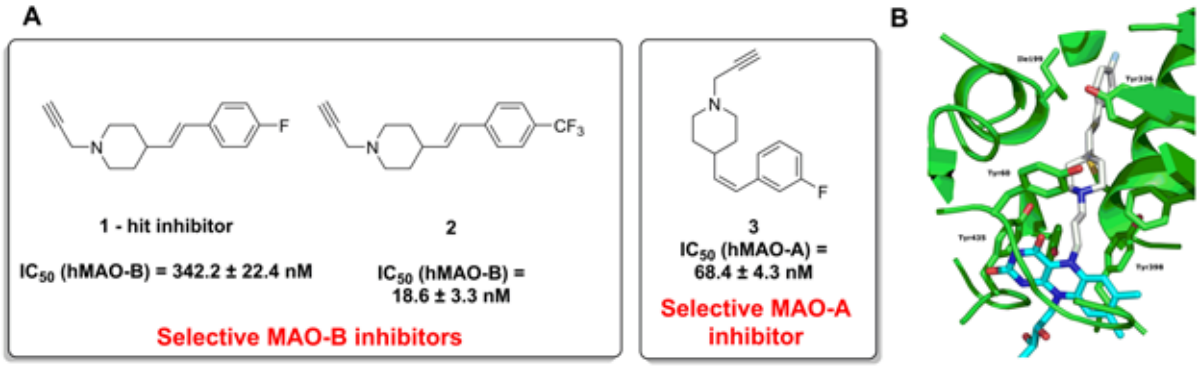
Monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) are important targets in the therapy of neurological disorders such as depression and Parkinson's disease.[1,2] As a part of our screening program, 1-propargyl-4-((*E*)-styryl)-piperidine **1** (Figure 1A) was identified as a selective human (h)MAO-B inhibitor. Interestingly, *cis* isomer selectively inhibited human (h)MAO-A. The preferential activity of each isomer towards MAO isoforms was explained by molecular modelling. This distinct inhibitory activity of geometric isomer pair prompted us to study the structure-activity relationships by synthesizing a focused library of piperidines and close analogues. 1-Propargyl-4-((*E*)-styryl)-piperidines with various substituents on the benzene ring inhibited hMAO-B with low nanomolar IC_{50} values (e.g., **2**, Figure 1A). On the other hand, *cis* isomers with small substituents on the benzene ring (e.g., fluorine in compound **3**, Figure 1A) irreversibly inhibited hMAO-A with high selectivity over hMAO-B (Figure 1A). Crystal structures of five derivatives in complex with hMAO-B were resolved and confirmed covalent modification of the FAD cofactor (Figure 1B).

Compounds were not cytotoxic to SH-SY5Y cells (EC_{50} > 100 μM) and showed neuroprotective properties in 6-hydroxydopamine (6-OHDA) cell-based model of Parkinson's disease. They also displayed favorable *in-vitro* pharmacokinetic parameters in terms of oral bioavailability and BBB permeability. *Ex-vivo* experiments demonstrated MAO-A and MAO-B inhibition in mice brain homogenates after *i.p.* and *per oral* administration. Importantly, selective hMAO-A inhibitor **3** (Figure 1A) showed antidepressant activity in mice in chronic 10-day treatment regime (*i.p.*, 0.3 mg/kg) with no apparent toxic effects.



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A FUSING STRATEGY APPLICATION: TOWARDS POTENT CHE INHIBITORS WITH MTDL PROFILE

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

Considering the multifaceted nature of the AD pathogenesis, targeting more than one therapeutically active site is getting more and more attention in the recent years to design novel scaffolds in the treatment of AD [1,2]. Multi-Target-Directed Ligands (MTDL) concept describes those compounds that are effective in treating complex diseases such as AD thanks to their ability to interact with the multiple targets responsible for the disease pathogenesis to obtain disease modifying effect [1,2]. There are four approved AChE inhibitors for the symptomatic treatment of AD: Tacrine, donepezil, rivastigmine, and galantamine. Although tacrine is no longer used in the treatment of AD due to its hepatotoxicity, it is still a widely used scaffold in the design of MTDLs thanks to its high affinity to AChE. Donepezil, the first choice medication in the treatment of AD, is a dual inhibitor of AChE with its ability to bind both catalytic active site and peripheral anionic site of the enzyme, simultaneously [1,2].

Previously, we have reported hydrazone containing structures with good inhibition towards ChEs and Aβ aggregation inhibition potency [3,4]. Moreover, there are several examples of hydrazone containing compounds with metal-binding properties in the literature [5,6].

In this study, we chose the benzylpiperidine moiety of donepezil and tacrine as core structures and connected them with hydrazone functional group to aim dual inhibition of AChE as well as inhibition of Aβ aggregation and with metal complex formation properties.

According to the ChE assay results, all of the compounds exhibited good inhibitory activity in nanomolar range against both ChEs. In respect to the Thioflavin T Fluorescence Assay, tested compounds exhibited moderate inhibitory potency towards β-amyloid aggregation. Moreover, metal complex formation properties of the compounds were investigated. Additionally, the neurotoxicity and hepatotoxicity profiles were evaluated. On the other hand, ADME properties of the title compounds were predicted theoretically, docking studies and dynamic simulations were performed.

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DEVELOPMENT OF UNIQUE MOLECULAR PROBES: LOW-BASICITY AGONISTS FOR THE STUDY OF 5-HT7 RECEPTOR FUNCTION

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Aminergic receptors (G-protein coupled receptors activated by endogenous amines: serotonin, histamine, acetylcholine, catecholamines: dopamine, adrenalin, noradrenalin and trace amines) are the targets of ~25% of drugs. There is a common mechanism (anchoring salt bridge with Asp3.32) underlying the formation of ligand-aminergic receptor complex, which has inhibited the discovery of truly selective and drug-like ligands, in particular agonists.

A paradigm shift came with the discovery of the first non-basic ligands of histamine and serotonin receptors over the last years. Our work on aromatic basic groups in the design of aminergic GPCR ligands led to the discovery of unique ligands of the 5-HT_7R: the first weakly basic (non protonable under physiological conditions) full agonists of an aminergic receptor.[1,2] Lead compounds, derivatives of 3-(1-alkyl-1*H*-imidazol-5-yl)-4-fluoro-1*H*-indole exhibit nanomolar affinity together with unusually high selectivity and full-agonist function, high water solubility, high BBB permeation and oral bioavailability, high metabolic stability, a good safety profile, are easily synthesized and can be radiolabelled which renders them perfect molecular probes for the study of 5-HT_7R function.[3] Compound AGH-194 has been shown useful in electrophysiology, research on neuronal plasticity and behavioural studies.

The question of the possible binding mechanism of the weakly basic 5-HT_7R agonists has been addressed using homology modelling, derivative synthesis, mutagenesis, potentiometric titrations, and crystallography.

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THE ESTABLISHMENT OF TOCOPHEROL REFERENCE INTERVALS FOR HUNGARIAN ADULT POPULATION USING VALIDATED HPLC METHOD

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Background and Objectives - Evidence suggests that decreased α-tocopherol (the most biologically active substance in the vitamin E group) level can cause neurological symptoms, most likely ataxia. The aim of the current study was to first provide reference intervals for serum tocopherols in the adult Hungarian population with appropriate sample size recruiting healthy control subjects and neurological patients suffering from conditions without symptoms of ataxia, myopathy or cognitive deficiency.

Materials and Methods - A validated HPLC method applying a diode array detector and rac-tocol as internal standard was utilized for the measurement of serum α-, β/γ- and δ-tocopherol levels. Furthermore, serum cholesterol levels were determined as well for data normalization.

Results - The calculated 2.5-97.5% reference intervals for α-, β/γ- and δ-tocopherols were 24.62 – 54.67 μM, 0.81 – 3.69 μM and 0.29 – 1.07 μM, respectively, whereas the tocopherol/cholesterol ratios were 5.11 – 11.27 μmol/mmol, 0.14 – 0.72 μmol/mmol and 0.06 – 0.22 μmol/mmol, respectively.

Conclusions - The establishment of these reference intervals may improve the diagnostic accuracy of tocopherol measurements in certain neurological conditions with decreased tocopherol levels. Moreover, the current study draws special attention to the possible pitfalls in the complex process of the determination of reference intervals as well, including the selection of study population, the application of internal standard and method validation and the calculation of tocopherol/cholesterol ratios.

EXPANDING THE CHEMICAL SPACE OF DNA-ENCODED SMALL MOLECULE LIBRARIES

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The identification of bioactive small molecules is often a challenging task. Compound libraries barcoded with DNA, called DNA-encoded libraries (DELs), offer an efficient, high-throughput platform for target-based screening.[1] DELs combine the efficiency of combinatorial synthesis routines[2] with molecular biology techniques such as enzymatic DNA barcode ligation, and DNA amplification for compound synthesis and identification. Ready availability of advanced sequencing technologies enables handling of numerically vast compound libraries, but requires computer-based statistics tools as a must-have to analyze the massive amounts of sequencing data for screening outcome interpretation (Figure 1a). The productivity of (encoded) screening libraries depends largely on chemical space coverage. Access to diverse compound structures depends in turn on the availability of starting materials and synthesis methodology. To be DNA-encodable, any chemical reaction must be DNA-compatible, and water-tolerant. Ideally, it furnishes target compounds from diverse starting materials with high yields and in spite of high dilution of DNA-tagged compounds. In order to expand methodology for encoded compound synthesis, we are developing DEL coding strategies that are initiated with solid phase-bound DNA strands.[3,4] This enables the use of a broad scope of organic solvents for target compound synthesis, facilitating encoded heterocyclic chemistry (Figure 1b). In a second strategy, we develop bespoke catalysts for encoded library synthesis based on oil-in-water micelles. Micellar catalysis is an attractive principle for DEL synthesis due to both reaction acceleration and DNA shielding. Amphiphilic block copolymers form spherical nanoreactors and immobilize a sulfonic acid catalyst in the DNA-inaccessible hydrophobic core. DNA-tagged aldehydes could be reacted by micelle-mediated Povarov and Groebke reactions to diverse substituted tetrahydroquinolines and imidazopyridines (Figure 1c). The concept holds promise to be extended to further acid-mediated reactions and also to other catalysts.[5]

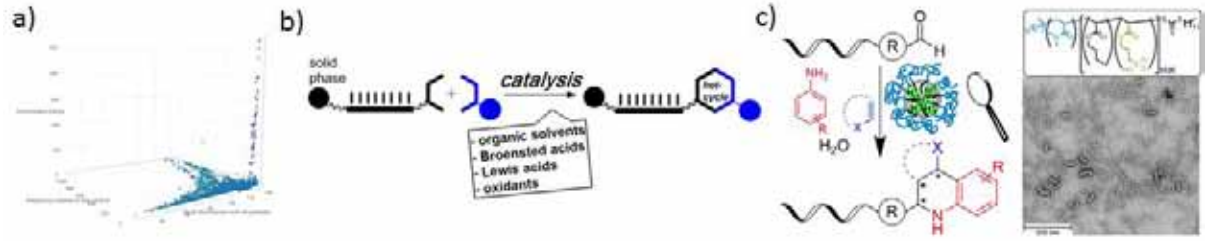

Figure 1: DNA-encoded compound libraries - a chemistry-focused interdisciplinary technology. a) Algorithms translate large sequencing data sets into plots for screening result interpretation. b) Solid phase-based synthesis approaches. c) A micelle-based reaction system for encoded synthesis.

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FINDING THE RIGHT CANDIDATE FOR THE RIGHT POSITION: A FAST NMR-ASSISTED COMBINATORIAL METHOD FOR OPTIMIZING NUCLEIC ACIDS BINDERS

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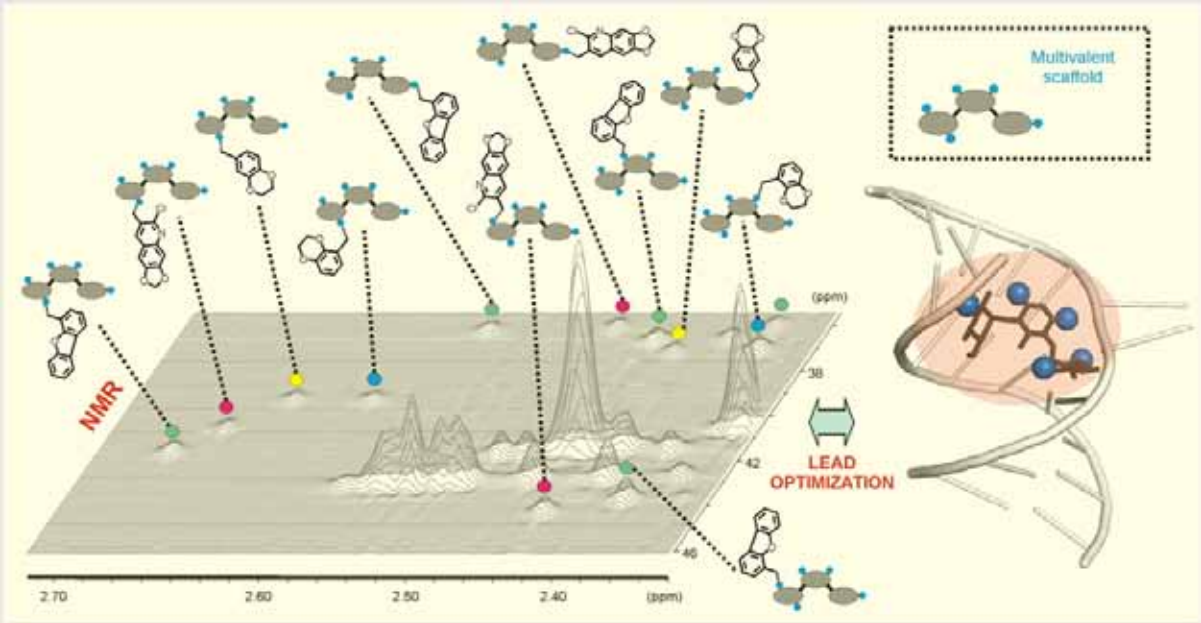
The development of strong and selective binders from promiscuous lead compounds represents one of the most expensive and time-consuming tasks in drug discovery. We herein present a novel fragment-based combinatorial strategy for the optimization of multivalent polyamine scaffolds as DNA/RNA ligands. Our protocol provides a quick access to a large variety of regioisomer libraries that can be tested for selective recognition by combining microdialysis assays with simple isotope labeling and NMR experiments. To illustrate our approach, 20 small libraries comprising 100 novel kanamycin-B derivatives have been prepared and evaluated for selective binding to the ribosomal decoding A-Site sequence. Contrary to the common view of NMR as a low-throughput technique, we demonstrate that our NMR methodology represents a valuable alternative for the detection and quantification of complex mixtures, even when integrated by highly similar or structurally related derivatives, a common situation in the context of a lead optimization process. Furthermore, this study provides valuable clues about the structural requirements for selective A-site recognition, which ultimately aims at a more efficient way to produce much-needed new antibiotics able to overcome multidrug resistance.



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FROM ZINC TO ZINCLICK: OUR WAY TO EXPLORE THE CHEMICAL SPACE

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We all know that the chemical space is an almost infinite set of all possible chemical entities, and it is not possible to create all molecules to subsequently search for the interesting ones. There are plentiful chemical databases available online that are useful for assessing (and accessing) different areas of the chemical space.[1] One of the most widespread approaches involves the use of the ZINC database and, through virtual screening, going to identify which molecules within it have a potential activity on a specific target.

Over the years we have successfully pursued this strategy by identifying, for example, new inhibitors of DGKα suitable for clinical trials in X-linked lymphoproliferative disease 1 (XLP1).[2] Pharmacological inhibition of DGKα in XLP1 animal models limits CD8+ T cell expansion and interferon-γ production, suggesting the development of DGKα inhibitors for XLP1 therapy.

Besides the idea to select compounds "easy to buy" we have focused our attention also on the creation of a new library of compounds which represent an unknown portion of chemical space. We have already demonstrated the ability of the 1,2,3-triazole scaffold to give important and pivotal binding interactions with biological targets.[3]

In the last years, we have investigated the click-chemical space covered by molecules containing the triazole ring, we generated a database of 1,2,3-triazoles called ZINClick,[4] starting from literature-reported alkynes and azides synthesizable in no more than three synthetic steps from commercially available products. This combinatorial database contains millions of 1,4-disubstituted-1,2,3-triazoles that are easily synthesizable, new and patentable. The library is regularly updated and it is freely downloadable (http://www.ZINClick.org).[5] The new implementation of ZINClick will be discussed as well as our new strategy about clustering the chemical space covered by 1,4-disubstituted-1,2,3-triazoles around their availability: from direct purchase to different degree of synthetic feasibility of the compounds (Figure 1).

Figure 1. Detailed view of the ZINClick v.18 webpage: (A) details of the subsets available to download, and (B) details page of a ZINClick triazole.

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EXTENDED GLUCURONIDES: ACHIEVING SITE-SELECTIVITY THROUGH EXTRACELLULAR DRUG RELEASE

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The majority of approved drugs on the market were designed to maximize pharmacokinetic and pharmacodynamic potency. However, as is the case for cancer therapeutics, cytostatic drugs generally suffer from a poor therapeutic window. This is where prodrugs come into play and by design modulate these pitfalls.

In my talk, I will demonstrate how extracellular drug release provides an elegant method to achieve site-selectivity and how exploitation of a human metabolite, namely glucuronides, achieves this goal.[1] I will demonstrate how self-immolative linkers serve as a key blueprint in prodrug design and consolidates a modular and robust synthetic platform. This culminated in an antibiotic prodrug platform, which in combination with biocatalytic surface coatings[2], nanoparticles[3], or specifically designed metal-coatings[4] provide a short-term solution to the inevitable rise of antimicrobial resistance. Moreover, I will shortly present how self-immolative linkers facilitate the synthesis of O-aryl glucuronides and I illustrate this on the example of SN-38.[5]

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CYCLOPROPENIUM-BASED POLYMERS

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Cationic polymers offer a wide range of potential biomedical applications, and so their continued development is of paramount importance. We describe here the synthesis and characterization of a series of novel polymers bearing cationic cyclopropenium either along a polyester backbone, both linear and crosslinked, or as a tri-functional crosslinker of secondary amine-containing polymers. Polymers containing cyclopropenium along the polymer backbone are synthesized stepwise via the reaction between diol-functionalized tris(amino)-cyclopropenium (TAC) monomers and diacyl chlorides. Incorporation of cyclopropenium as a chemical crosslinker of secondary amine-containing polymers was performed in a rapid one-step crosslinking reaction that requires no subsequent purification. When dispersed in aqueous media, polymers form spherical nanoparticles with highly positive charge that is maintained even in alkaline conditions. Biodegradable cyclopropenium polymers undergo hydrolytic degradation and swell significantly, displaying an important framework for the drug-delivery capabilities of a hydrolytically degradable cationic polyester. One polymer displayed potent antimicrobial activity against *Staphylococcus epidermidis*, and one displayed improved transfection capabilities compared to poly(ethylene imine). These synthetic strategies will enable the incorporation of cyclopropenium into a wide variety of macromolecules.

Flash Poster Presentations

Flash Poster Presentation

FP01	**A New Life for Diazaborines: the Next Generation of Serine Protease Inhibitors** *Mr Joao ANTONIO (UNIVERSITY OF LISBON, Lisbon, Portugal)*	**P003**
FP02	**From Peptides to Peptidomimetics: Structure-Activity Relationship of a Factor H-Binding Peptide to Modulate Undesired Host Complement Activity** *Mr Clément BECHTLER (UNIVERSITY OF BASEL, Basel, Switzerland)*	**P006**
FP03	**Matrix Metalloproteinase-12 Inhibitors: Synthesis, Structure-Activity Relationships and Intestinal Absorption of Novel Sugar-Based Biphenylsulfonamide Carboxylates** *Dr Doretta CUFFARO (UNIVERSITY OF PISA, Pisa, Italy)*	**P016**
FP04	**Photophysical Properties and Antiparasitic Activity of Bodipy-Tethered Dinuclear Trithiolato-Bridged Ruthenium(II)-Arene Complexes** *Mrs Oksana DESIATKINA (UNIVERSITY OF BERN, Bern, Switzerland)*	**P018**
FP05	**N-ALKYL L-Iminosugars as Novel Anti-Inflammatory and Anti-Biofilm Tools for Cystic Fibrosis Lung Infections** *Ms Anna ESPOSITO (UNIVERSITY OF NAPOLI FEDERICO II, Napoli, Italy)*	**P024**
FP06	**Design, Synthesis and Biological Evaluation of Novel Substituted Purine Isosters as EGFR Kinase Inhibitors, with Promising Pharmacokinetic Profile and In Vivo Efficacy** *Dr Efthymios-Spyridon GAVRIIL (NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS, Athens, Greece)*	**P031**
FP07	**Metal Chelating Acetohydroxamic Acids Against Hepatitis C Virus and Flaviviruses** *Ms Erofili GIANNAKOPOULOU (NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS, Athens, Greece)*	**P032**
FP08	**Discovery of Small-Molecule Modulators of 14-3-3 PPIs Via Dynamic Combinatorial Chemistry** *Mr Alwin HARTMAN (UNIVERSITY OF GRONINGEN, Groningen, The Netherlands)*	**P036**
FP09	**Purine Nucleoside Analogs as Highly Potent Leads for the Treatment of Human African Trypanosomiasis** *Mr Fabian HULPIA (UGENT, Ghent, Belgium)*	**P039**
FP10	**Development of Allosteric Inhibitors of ColH Using DCC Strategy** *Dr Jelena KONSTANTINOVIC (HELMHOLTZ INSTITUTE FOR PHARMACEUTICAL RESEARCH SAARLAND (HIPS), Saarbrücken, Germany)*	**P049**
FP11	**Identification, Synthesis and Optimization of Inhibitors of the Protein Tyrosine Phosphatase SHP2** *Dr Yelena MOSTINSKI (LEIBNIZ-FORSCHUNGSINSTITUT FÜR MOLEKULARE PHARMAKOLOGIE, Berlin, Germany)*	**P062**
FP12	**Multitarget Triazoles: an Innovative Approach for the Treatment of Alzheimer's Disease** *Ms Vanesa NOZAL GARCIA (CIB - CSIC, Madrid, Spain)*	**P069**
FP13	**TDP-43 Modulation by CDC7 Inhibitors as a Therapeutic Strategy for Amyotrophic Lateral Sclerosis** *Ms Elisa ROJAS (CIB - CSIC, Madrid, Spain)*	**P080**
FP14	**Use of the 4-Hydroxy-Triazole Moiety as a Bioisosteric Tool in the Development of Selective Ligands for Subtypes Ampa Receptor** *Dr Stefano SAINAS (UNIVERSITY OF TORINO, Torino, Italy)*	**P081**
FP15	**In Vitro and In Ovo Evaluation of Ros-Activatable Anticancer Boronate Prodrugs of Doxorubicin** *Dr Charles SKARBEK (UNIVERSITY PARIS SUD, Orsay, France)*	**P085**
FP16	**Design and Synthesis of Tead's Ligands for the Treatment of Cancers** *Mrs Manon STURBAUT (UNIVERSITY OF LILLE, Lille, France)*	**P088**
FP17	**Drug-Fragment Based Explorations for Novel Enterovirus Inhibitors** *Ms Clara VAN HOEY (UNIVERSITY OF VIENNA, Vienna, Austria)*	**P094**
FP18	**Gemcitabine-GnRH Bioconjugates Bearing Oxime Bond Linkages: Synthesis, In Vitro Stability, Drug Release and Cytotoxic Effect** *Mr Eirinaios VRETTOS (UNIVERSITY OF IOANNINA, Ioannina, Greece)*	**P096**
FP19	**Development of GSTO1-1 Inhibitors for the Treatment of Inflammatory Conditions** *Ms Yiyue XIE (MONASH UNIVERSITY, Melbourne, Australia)*	**P098**
FP20	**Identification of a Novel Quinoline-Based DNA Demethylating Compound Highly Potent in Cancer Cells** *Dr Clemens ZWERGEL (UNIVERSITY OF ROME LA SAPIENZA, Rome, Italy)*	**P108**

Posters Presentations

TOWARDS THE TOTAL SYNTHESIS OF MYCAPOLYOL A

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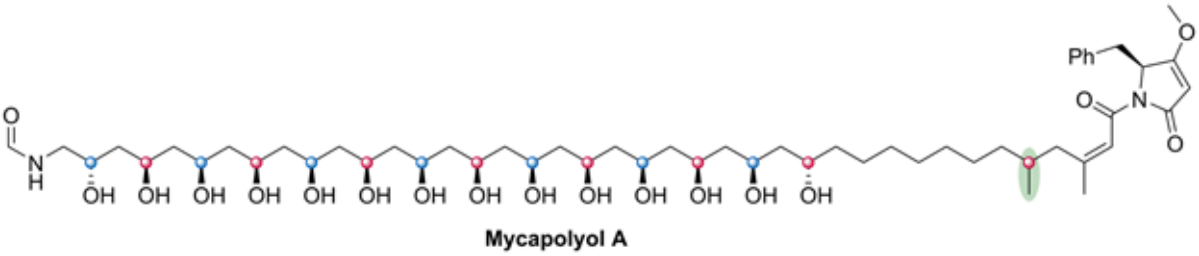
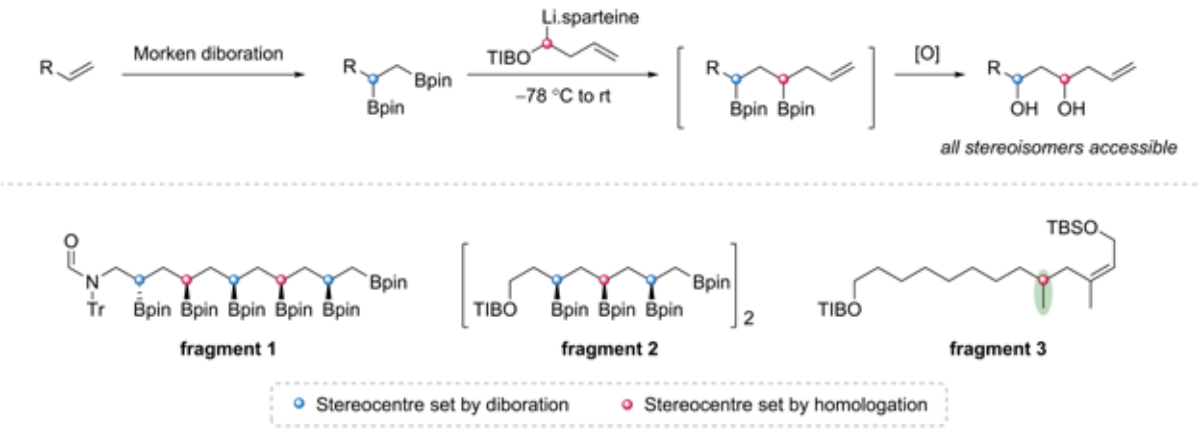


Mycapolyol A

Mycapolyols A-F are 6 unusual PKS metabolites which exhibit cytotoxicity against HeLa cells, isolated by Fusetani and co-workers from the marine sponge *Mycale izuensis* in 2005.[1] There are no reported syntheses of any mycapolyols in the literature to date.

The key synthetic challenge in mycapolyol A is the extended 1,3-polyol unit, comprising 14 stereodefined contiguous but skipped hydroxyl groups. Previous work in the Aggarwal group demonstrated the stereocontrolled synthesis of secondary-secondary and secondary-tertiary 1,3-diols by performing lithiation–borylation reactions with 1,2-bis(boronic esters),[2] which can be obtained through asymmetric diboration of terminal alkenes.[3] Iterative enantioselective alkene diboration and reagent-controlled homologation with a homoallylic benzoate would enable the construction of a stereodefined 1,3-polyol. No repetitive oxidation level changes or functional group interconversions are necessary between iterations, since the boronic esters both mask the hydroxyl functionality, which can be revealed in a later stereospecific oxidation, and enable the homologation through lithiation–borylation reactions.



Retrosynthetic analysis of mycapolyol A suggested a modular approach; fragments 1, 2 and 3 will be prepared separately and then coupled together. The optimized synthesis of the 3 key fragments and their combination through lithiation–borylation reactions will be presented, along with model studies for the endgame steps. In addition, fragment 3 contains the one undefined stereocentre at C-5 in mycapolyol A (highlighted); its configuration can be set unambiguously through the choice of either enantiomer of α-stannyl ethyl benzoate for the homologation and so this stereocentre has now been assigned through synthesis.

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DESIGN, SYNTHESIS AND EVALUATION OF 5-ALKYLAMINO-N-PHENYLPYRAZINE-2-CARBOXAMIDES AS POTENTIAL ANTIMYCOBACTERIAL AGENTS

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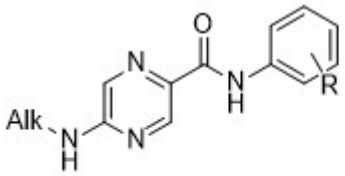
Tuberculosis is the second leading cause of death among all infectious diseases worldwide. It is caused by *Mycobacterium tuberculosis* and due to its rapid build of resistance to antibiotics it is necessary to develop new drugs and new therapies[1]. One of the strategies is to design new inhibitors of mycobacterial fatty acid synthase I (FAS I) like 5-Chloropyrazinamide (5-Cl-PZA)[2]. With an appropriate substitution of this compound it is possible to increase antimycobacterial activity and reduce cytotoxicity of this moiety[2,3]. The series of 49 compounds derived from the 5-chloropyrazinamide skeleton was obtained. Modifications were made to two places in the structure. First modification was adding in amide position moieties consist of a phenyl ring substituted with various function groups. Second modification was substitution of chlorine attached to pyrazine ring by alkylamines. Preparation included synthesis of 5-chloro-*N*-phenylpyrazine-2-carboxamides as intermediate compounds and substitution of chlorine bonded to pyrazine ring by aliphatic amine. 5-Alkylamino-*N*-phenylpyrazine-2-carboxamides (Fig. 1) have been tested for activity against *Mycobacterium tuberculosis* H37Rv, *M. kansasii, M. avium, M. smegmatis* and *M. aurum*. Detailed description of obtained results will be presented on the poster.



Alk: propyl, butyl, pentyl, hexyl, heptyl, octyl
R: 3-OH,4-OH, 3-CF_3, 4-Cl-2-OH, 5-Cl-2-OH, 4-CH_3, 4-C_2H_5

Fig. 1: 5-alkylamino-*N*-phenylpyrazine-2-carboxamide

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A NEW LIFE FOR DIAZABORINES: THE NEXT GENERATION OF SERINE PROTEASE INHIBITORS

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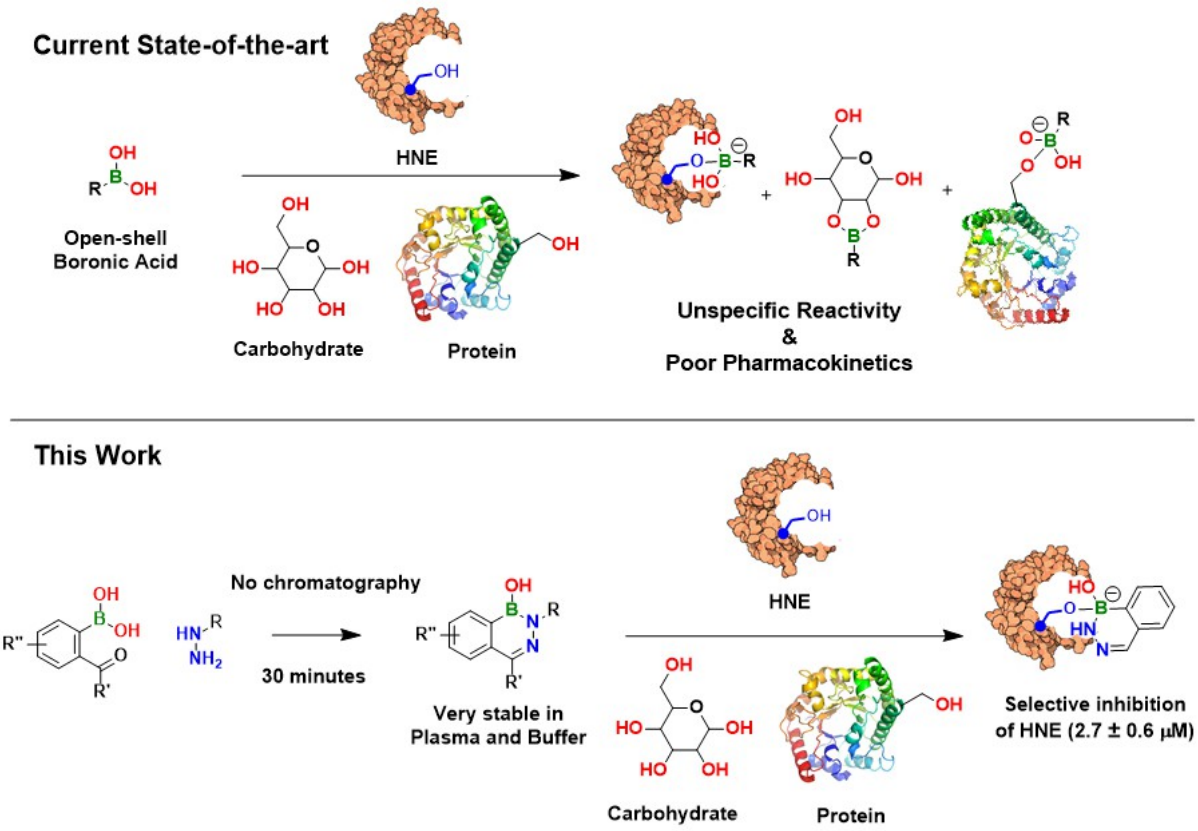
Boronic Acids are a preeminent functionality extensively used to design biologically active compounds such as the FDA-approved Bortezomib and Ixazomib. However, due to boron's open shell, this class of inhibitors also exhibits unspecific reactivity with endogenous nucleophiles that often results in poor pharmacokinetic profiles and off-target toxicity. Here diazaborines are presented as a new class of boron-based warheads for serine proteases inhibition, in which the boron functionality is stabilized in the form of an aromatic BN heterocycle. In this study, diazaborines were readily synthesized in a single step in yields up to 96%, without any chromatographic operation and were shown to selectively inhibit Human Neutrophil Elastase with IC_{50}'s values in the low μM range. Synthetic and theoretical studies performed on this system suggest that, like boronic acids, the reaction mechanism involves the formation of a reversible covalent bond between the diazaborine boron center and the catalytic serine oxygen. Finally and differently from boronic acids who have half-lifes of 2h in buffer, diazaborines were shown very stable in different biocompatible conditions like buffer and human plasma. This work demonstrates that diazaborines are an interesting starting point for the development of the next generation of serine proteases[1].



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SIMULATIONS OF THE TRKA RECEPTOR TO ELUCIDATE THE MECHANISM OF ACTION OF NEUROTROPHIN MIMETICS

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The tropomyosin receptor kinase A (TrkA) belongs to a superfamily of tyrosine kinase receptors, which when bound to their native ligands, called Neurotrophins, can modulate several signaling pathways that regulate neuronal survival, axonal and dendritic network maintenance, as well as synaptic plasticity.[1,2] Preclinical studies have demonstrated the therapeutic potential of neurotrophins in preventing or slowing down the progression of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Multiple Sclerosis and Motor Neuron disease.[3,4] However, the use of neurotrophins as drugs is hindered by their poor pharmacokinetic properties. Therefore, novel, low molecular weight neurotrophin mimetics are promising anti-neurodegeneration drug candidates. Previous studies have identified several steroid compounds with neurotrophin mimetic activity.[5] However, their exact mechanism of action remains unclear. In the present work, molecular simulations of the TrkA receptor have been performed in order to investigate the conformational changes that lead to the activation of the receptor upon Neurotrophin binding. Since the active conformation of the receptor is not known, this study is a crucial step for the examination of the mechanism through which steroidal compounds lead to TrkA activation and the triggering of subsequent signal transduction pathways.

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NEW ANTI-CANCER AGENTS FROM DAFFODILS. SYNTHESIS & BIOLOGICAL EVALUATION

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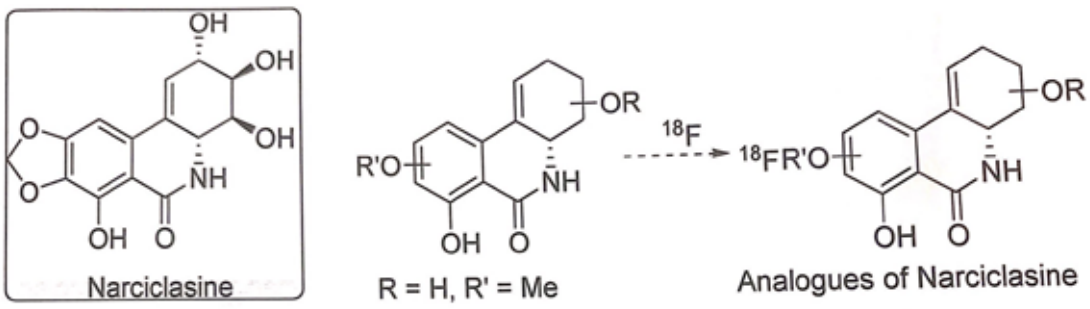
Narciclasine is a compound obtained from daffodil (narcissus) that exhibits potent and selective anticancer activity against a range of cancers.[1] It is of particular interest due to its potent anti-tumour properties against the most aggressive form of brain cancer, glioblastoma multiforme, which at present has an extremely poor prognosis.[2]

Under current treatment regimes, the average survival rate from brain metastasis is only about 7 months.[2] The current drug of choice for glioblastoma, Temozolomide, acts an alkylating agent producing cytotoxic effects in glioma cells. Narciclasine, however, displays good potential as a cytostatic agent due to its interaction with GTPases with little toxicity to normal cells.[2,3]

Limited availability from natural sources and complex chemical synthesis of the natural products and related current analogues have prevented detailed biological evaluation and clinical development. Hence the need for efficient chemical synthesis. Our group has established synthetic methodology to generate the Narciclasine core in a single high-yielding step from the corresponding dihydrocinnamic acid, *via* a modified Curtius rearrangement. Formation and capture of an isocyanate intermediate with a Lewis acid by the electron rich aromatic ring forms the desired lactam, initially as a BF_2-complex.[4] We have also explored a highly efficient Pd-catalysed route to Narciprimine, a natural related analogue of Narciclasine. We are now exploiting our expertise and generating a number of novel Narciclasine derivatives which we are fine-tuning to make more drug-like analogues thus improve both selectivity and potency. We have sent initial compounds to our collaborators at Exeter Medical School where our compounds are tested against a model blood brain barrier and glioblastoma cell lines and have received preliminary results. Our synthetic approach also allows us to label analogues with ^{18}F. We are currently investigating fluorinated derivatives. We will use our ^{18}F compounds as tracker to investigate the activity and mode of action *in vivo* on mice orthotopically xenografted with highly invasive human glioblastomas.



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FROM PEPTIDES TO PEPTIDOMIMETICS: STRUCTURE-ACTIVITY RELATIONSHIP OF A FACTOR H-BINDING PEPTIDE TO MODULATE UNDESIRED HOST COMPLEMENT ACTIVITY

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The complement system is a self-amplifying, fast reacting protein network, generally known for its pivotal role in host defence pathways. However, its adverse clinical implications in transplantation, hemodialysis and other conditions have been increasingly recognized, and strategies for taming complement attack of non-self surfaces are therefore actively pursued. We previously achieved such protection by recruiting the complement's master regulator Factor H (FH) to cellular and artificial surfaces through a 14 amino acid-long disulphide-bridged phage display-derived cyclic peptide (5C6). 5C6 showed nanomolar binding affinity to FH and was able to act as a molecular bridge between FH and implant or transplant surfaces when combined with appropriate tethering motifs.

To further develop 5C6 towards a preclinical candidate, we identified and addressed three key aspects for improving affinity and stability. First, we replaced the disulphide with several other functional groups such as alkenes, lactams, thioacetals or triazoles, affecting activity to different degrees. Second, we varied the size of the macrocycle, which had a profound impact on activity, enabling us to define the maximally tolerated ring size. Third, we replaced individual amino acids with natural and unnatural amino acids to successfully improve the affinity of 5C6. The compounds were prepared by solid-phase peptide synthesis and further modified using solution-phase reactions. Binding affinities were determined by direct SPR binding and competitive microscale thermophoresis assays.

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OPEN SOURCE MALARIA SERIES 3: A PROMISING AMINOTHIENOPYRIMIDINE LEAD

Mathamsanqa Bhebhe (1), James Cronshaw (1), Alice Williamson (1), Murray Robertson (1), Althea Tsang (1), Angela Butera (1), Matthew Tarnowski (1), Carmen Tran (1), Patrick Thomson (2), Tom Foley (2), Peter Rutledge (1), Matthew Todd (3)

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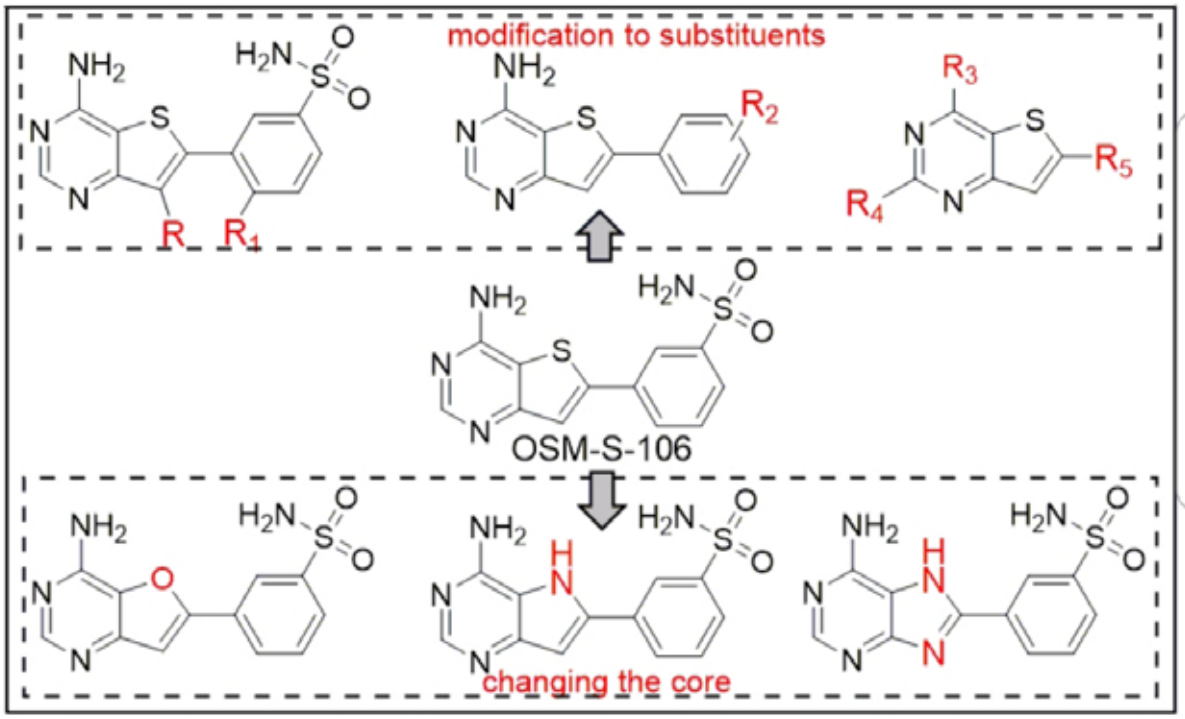
In 2010 GSK released data on 13,500 antimalarial hits. One of these was potent and was used to start Series 3 of the Open Source Malaria Consortium, where the activity was confirmed (OSM-S-106). We will present all the research carried out to date on this aminothienopyrimidine core. All modifications to the substituents have decreased the potency of the drug. We are now conducting SAR studies by changing the core of the original hit compound and seeking the mechanism of action of the series through computational, biochemical and genetic approaches.



NOVEL PYRAZOLO [3,4-D] PYRIMIDINE NUCLEOSIDES: PROMISING HITS FOR CHAGAS DISEASE AND LEISHMANIASIS

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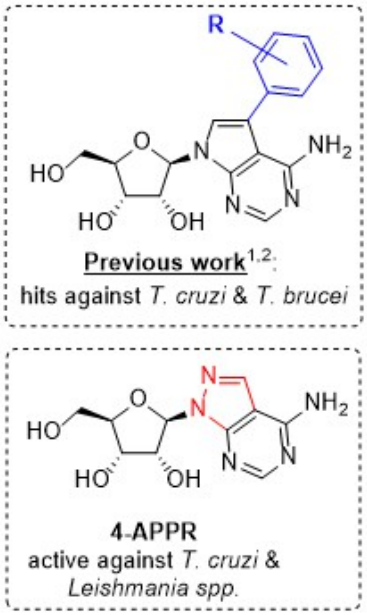
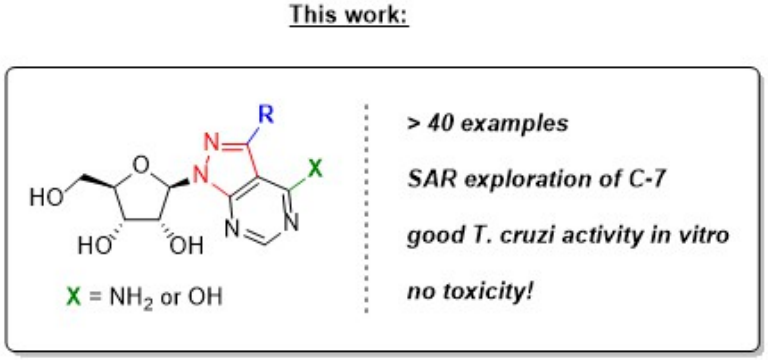
Our group recently reported several tubercidin (7-deazaadenosine) analogues with activity against *Trypanosoma brucei* and *Trypanosoma cruzi* parasites, the causative agents of sleeping sickness and Chagas disease.[1,2] The introduction of aromatic substituents on the C-7 position of the nucleobase (purine numbering) resulted in potent compoundswith a favorable selectivity profile. Remarkably, activity against the related *Leishmania* parasites was lacking.

In the 1980's, the nucleoside analogues allopurinol riboside (7-deaza-8-azainosine) and 4-aminopyrazolo[3,4-*d*]pyrimidine riboside (4-APPR, 7-deaza-8-aza-adenosine) were found to display activity against *T. cruzi* and *Leishmania* spp.[3] The pyrazolo[3,4-*d*]pyrimidine structure closely mimics a purine ring and, similar to 7-deazapurines, allows for modification on the C-7 carbon atom. In the hope of discovering new nucleoside analogs with activity against *Leishmania spp.*, we set out to construct a library of novel pyrazolo[3,4-*d*]pyrimidine nucleosides. The compounds were synthesized via $BF_3.OEt_2$-mediated glycosylation of a 7-bromo- or 7-iodopyrazolopyrimidine. The halogen atom was then used as a synthetic handle to introduce substituents on the C-7 position.





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COMPUTATIONAL DESIGN OF THE CONFORMATIONAL AND TAUTOMERIC VARIABILITY OF THE QUERCETIN MOLECULE

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Quercetin (3, 3′, 4′, 5, 7-pentahydroxyflvanone, $C_{15}H_{10}O_7$) is a plant flavonoid compound and is known to act as a natural drug molecule. Its chemical structure contains two aromatic A and B rings linked through the C ring and five hydroxyl groups.

However, up to date its physico-chemical properties, defining its functionality, have been investigated only fragmentarily. Obviously, such state of affairs does not allow to identify the biologically important conformers or tautomers with potentially important pharmacological properties.

In this study using the quantum-chemical calculations at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) it was defined structural and tautomeric specificities of the quercetin molecule. Also, by using Bader's Quantum Theory of Atoms in Molecules we have revealed and analysed intramolecular specific contacts – hydrogen bonds and van der Waals contacts.

Altogether, it was established 48 conformers of the quercetin molecule with the relative Gibbs free energy in the range of 0.0-25.3 kcal•mol^{-1}. Moreover, we revealed that these conformers can acquire dozens of tautomeric forms by the proton transition to different sites of the quercetin molecule – oxygen and carbon atoms. It was observed the rupture of the ring or formation of the CH_2 exocyclic groups for the most exotic tautomers. Main physico-chemical properties of the established novel conformers and tautomers have been defined in details using bioinformatics tools.

Obtained results can be useful for the formulation of the general rules of the formation and importance of conformational and tautomeric states, which can be applied for different heterocyclic molecules with potential biological or pharmaceutical activity.

SYNTHESIS, MOLECULAR DOCKING AND EGFR KINASE INHIBITORY ACTIVITY STUDIES OF BENZIMIDAZOLE DERIVATIVES BEARING PROPYL-LINKED TO OXADIAZOLE RING

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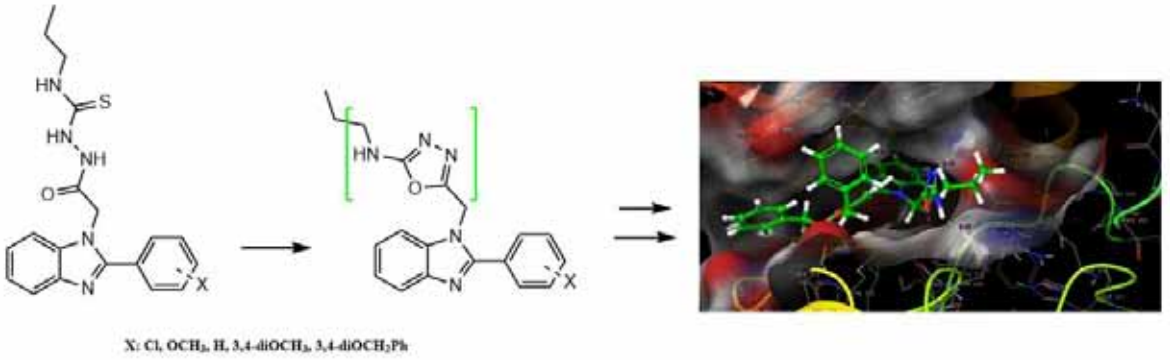
Benzimidazole derivatives have many pharmacological effects, including the inhibitory activity of highly expressed egfr kinases in many types of cancer, such as lung and breast cancer (1). A series of novel 5-((2-(substitutedphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-N-propyl-1,3,4-oxadiazol-2-amine were synthesized, molecular docking studies were performed and their EGFR inhbitor activity will be evaluated.



X: Cl, OCH_3, H, 3,4-diOCH_3, 3,4-diOCH_2Ph

Synthesis

First, 2-phenyl/substituted phenyl-1H-Benzo[*d*]imidazole was prepared by oxidative condensation of o-phenylenediamine, benzaldehyde and sodium metabisulfite in DMF. In the second step, K_2CO_3 and ethyl chloroacetate were added to the reaction medium, refluxed for 5 h, and the reaction end with TLC was observed. In the third step, hydrazine hydrate was added to the same reaction medium, refluxed for 3 hours, and the reaction end with TLC was observed. After cooling, acid hydrazide was precipitated by adding water to the reaction medium. Thiosemicarbazides were obtained by condensing acyl hydrazides with the propyl isothiocyanate in ethanol or DMF. The oxadiazole bearing benzimidazole compounds was synthesized from thiosemicarbazides in the presence of $Hg(CH_3COO)_2$ in ethanol by reflux (2).

Molecular Docking

The binding mode of compounds was investigated through docking study using Schrodinger program Maestro Version 11.5.011. For the validation, the protein was re-docked with the co-crystallized ligand erlotinib. The compounds were docked into the active site of the kinase domain of EGFR kinase domain (PDB:1M17). According to docking results, **5a** compound was highest docking score with -7.380 and made up two hydrogens bonds between LYS721 and oxadiazole aromatic N as well ASN818 and oxadiazole N-H (3).

Biological Activity

Benzimidazole compounds containing oxadiazole will be tested by comparing with erlotinib for their EGFR kinase inhibitory activities by using ADP-Glo™ Kinase Assay (4).

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TAILORING GEMCITABINE BIOCONJUGATES TO SENSE AND KILL CANCER CELLS

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Gemcitabine(dFdC) is an antimetabolite, a nucleoside analogue and is widely used as an anticancer agent against several solid tumors. Although its potency, it has two main therapeutic limitations: it lacks cancer cell selectivity and is rapidly transformed to an inactive uridine(dFdU) metabolite. To surmount these drawbacks we generated several novel gemcitabine bioconjugates with tumor homing peptides and their pharmacokinetic profile have been extensively explored. Furthermore, we constructed a theranostic molecular device that is able to sense and kill cancer cells integrating both photo regulated drug dosing properties and cancer microenvironment sensing characteristics.

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DESIGN AND SYNTHESIS OF 4-THIATOCOPHEROL/HYDROXYTYROSOL HYBRIDS AS PROTEASOME ACTIVATORS

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Aging is a natural, inevitable progressive deterioration of physiological function with increasing age for any organism. Aging and longevity are controlled by a multitude of molecular mechanisms and signaling pathways combined with endogenous and exogenous factors in order to maintain cellular homeostasis. Protein homeostasis (proteostasis), is the cellular process that controls the accumulation of damaged or misfolded proteins that contributes to aging and age-related diseases such as Huntington's disease (HD), Alzheimer's disease (AD), Parkinson's disease (PD) and Amyotrophic lateral sclerosis.[1,2]

The identification, labeling and degradation of non-functional proteins or normal proteins that have completed their mission is achieved through specific degradation mechanisms such as the **U**biquitin **P**roteasome **S**ystem (UPS) or the lysosomal system. The UPS is the primary pathway for the degradation of normal, damaged or non-functional structures in eukaryotic cells. Regulation of proteasome function may prolong life expectancy by delaying the onset of symptoms associated with proteasome disorders[3]. Thus, the development of new compounds that can activate the main proteasome core, namely, 20S complex may result in beneficial and/or therapeutic effect against human aging and/or in age-related diseases and pathologies.

The present work involves the design and synthesis of new bio-inspired 4-thiatocopherol/ hydroxytyrosol hybrids. Hydroxytyrosol, is the main antioxidant phenolic constituent of olive oil and structural component of oleuropein and 4-thiatocopherol is a bioisostere of the chroman ring of Vitamin E. The two pharmacophores were connected through five-membered heterocyclic rings which are bioisosteres of the amide or ester bonds or possess biological activity. The new compounds were examined for their proteasome activating properties (a) *in cellulo* in human primary HFL-1 fibroblasts and (b) *in vitro* through direct activation of highly purified 20S proteasome and initial results are promising.[4]

Acknowledgement

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NEW ENANTIOPURE HYDROXYETHYL-PIPERAZINES AS CARBONIC ANHYDRASE INHIBITORS

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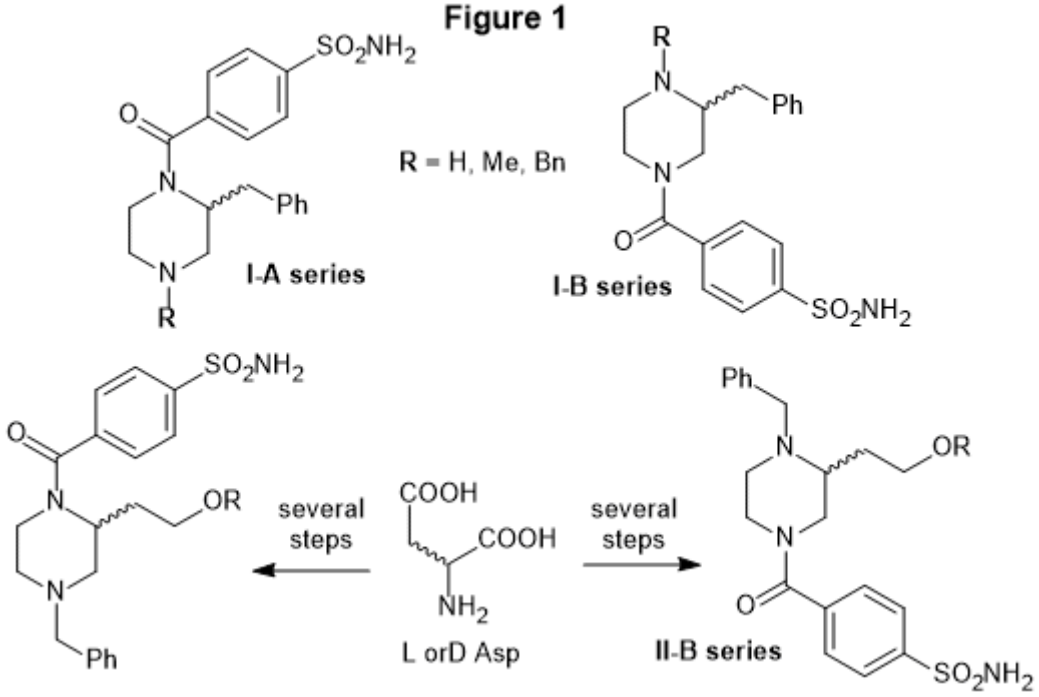
The hydration of CO_2 into bicarbonate and protons and the optimal equilibrium between these chemical species is essential for the vitality of organisms in all life kingdoms [1]. This reaction is catalyzed by the metalloenzyme Carbonic Anhydrase (CA), one of the most efficient enzyme known in nature, evolved in seven genetically different families (α-θ). A large number of isoforms are described among the different organisms, their presence being crucial for pH regulation, secretion of electrolytes and for other essential physiological or pathological processes [2]. For these reasons, CAs are important targets for drugs that can be used for different pathologies, providing that it could be possible to exploit the existent differences between families or isoforms to achieve a selective activity. This may not be an easy task, since the catalytic sites are well conserved, at least among the sixteen human α isoforms (I-XVI); however, variability can be found in hydrophilic and lipophilic accessory sites close to the Zn-binding domain.

Aiming to further investigate the structure activity relationships (SAR) of a previously synthesized series of CA inhibitors **I-A** and **I-B**, bearing an enantiopure benzyl-piperazine scaffold [3], two series of new chiral hydroxyethyl-piperazine **II-A** and **II-B**, carrying a 4-sulfamoylbenzoyl moiety on one nitrogen (**Figure 1**) have been designed and prepared from L or D Aspartic Acid [4]. In this communication the synthesis and inhibitory activity of the new compounds, assessed against four physiological relevant human CA isoforms (I, II, IV, IX), will be reported and compared to the already characterized benzyl-piperazine analogues **I-A** and **I-B**.

Figure 1



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IDENTIFYING INHIBITORS OF BACE1 FOR ALZHEIMER'S DISEASE BY A CUSTOMIZED PHARMACOPHORE-BASED VIRTUAL SCREENING AND MOLECULAR DOCKING SIMULATION

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Alzheimer's disease (AD) is a devastating neurodegenerative disorder, characterized by a progressive neuronal dysfunction and consecutive cognitive impairment[1]. Since no drugs have been approved for AD treatment, it is imperative that disease-modifying strategies should be actively pursued[2,3].The *Amyloid cascade hypothesis* has been disseminated as the basis of AD since the evidence that amyloid-β (Aβ) vastly contribute to the neurodegerative process[4]. The Aβ peptide is generated by the metabolism of amyloid precursor protein (APP) by BACE1 and γ-secretase. A recognized way to reduce the Aβ levels is targeting the BACE1 (figure 1), which has emerged as a promising therapeutic approach for AD[5,6].

Thus, the main goal of this research project is the discovery of new small molecules that effectively reach the brain and inhibit BACE1. The project focuses on a validated multiple-step protocol of virtual screening, which includes: i) a combination of a structure-based (SB) and ligand-based (LB) pharmacophore modeling to screen several druglike compound databases; ii) a subsequent filter to predict their ability to cross the blood-brain barrier (BBB), a pharmacokinetic property required for these drugs; and iii) molecular docking simulations to predict the binding mode and affinity of those molecules, which enable the selection of the best candidates for further biological evaluation. Moreover, while the SB approach is based on receptor-ligand key interactions of several BACE1-ligand crystal complexes, the LB strategy captures the essential features of structurally diverse known active compounds that inhibit BACE1. To evaluate the quality of the generated pharmacophore models' multiple metrics were considered. Hence, the chances of finding new compounds that effectively bind to BACE1 are enhanced by considering simultaneously the structure of the BACE1 enzyme and the known inhibitors.

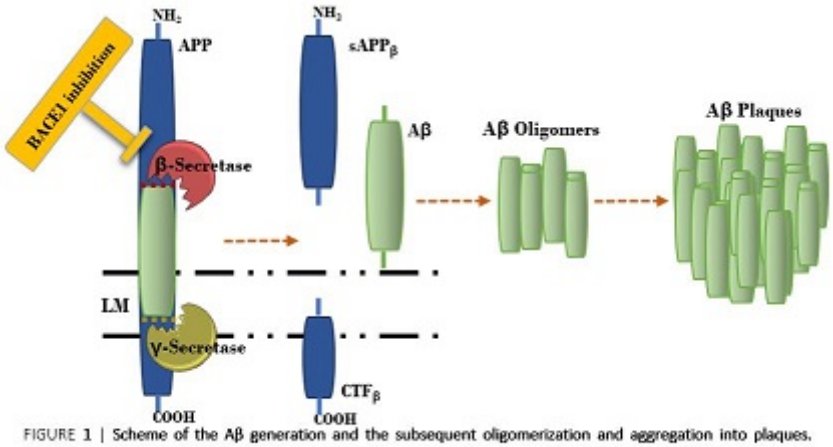

FIGURE 1 | Scheme of the Aβ generation and the subsequent oligomerization and aggregation into plaques. Generation of Aβ by consecutive proteolytic process of APP by β- and γ-secretase. Potential therapeutic interventions for AD may involve the inhibition of BACE1.

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TARGETING NON-CYSTEINE RESIDUES IN PI4K IIIβ USING FLUOROSULFATES AS COVALENT WARHEADS

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A range of novel fluorosulfate based inhibitors were synthesised and their stability to buffers and reactivity to amino acids were investigated (Figure 1). To determine the potential for covalent modification of PI4K IIIβ, the compounds were incubated with the protein and profiled by mass spectrometry to identify adducts. The time and concentration dependency of this labelling was investigated too.

X-ray crystallography identified the inhibitor (c) binding to lysine in the active site of PI4K IIIβ. On analysis of the X-ray crystal structure, a nearby tyrosine residue was identified that showed an intermolecular hydrogen bond with the para-pyridyl head group. An alternative fluorosulfate inhibitor (d) was synthesised to target this tyrosine residue. The inhibitor was profiled by protein mass spectrometry and a crystal structure was obtained with the desired covalent modification.

Building upon this result, a novel bis-covalent fluorosulfate compound (e) was synthesised to target both tyrosine and lysine with one inhibitor. The same profiling techniques were carried out on the inhibitor, with the crystal structure showing it bound to both residues. This bifunctional covalent inhibitor could lead to many interesting applications in chemical biology.

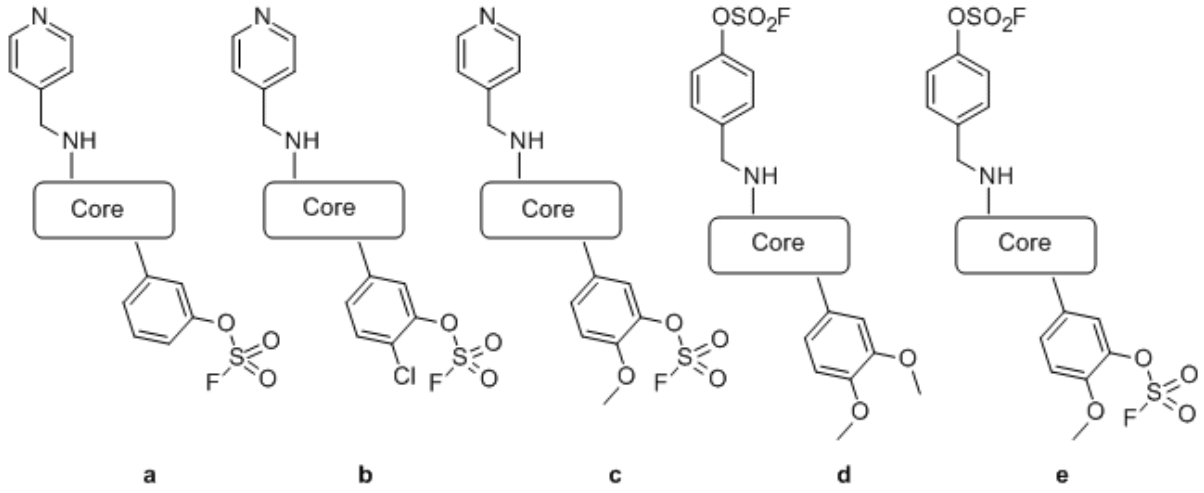

Figure 1: Series of novel fluorosulfate inhibitors.

* Full structures disclosed in the poster.

MATRIX METALLOPROTEINASE-12 INHIBITORS: SYNTHESIS, STRUCTURE-ACTIVITY RELATIONSHIPS AND INTESTINAL ABSORPTION OF NOVEL SUGAR-BASED BIPHENYLSULFONAMIDE CARBOXYLATES

Doretta Cuffaro (1), Caterina Camodeca (1), Felicia D'Andrea (1), Eugenia Piragine (1), Lara Testai (1), Vincenzo Calderone (1), Elisabetta Orlandini (2), Elisa Nuti (1), Armando Rossello (1)

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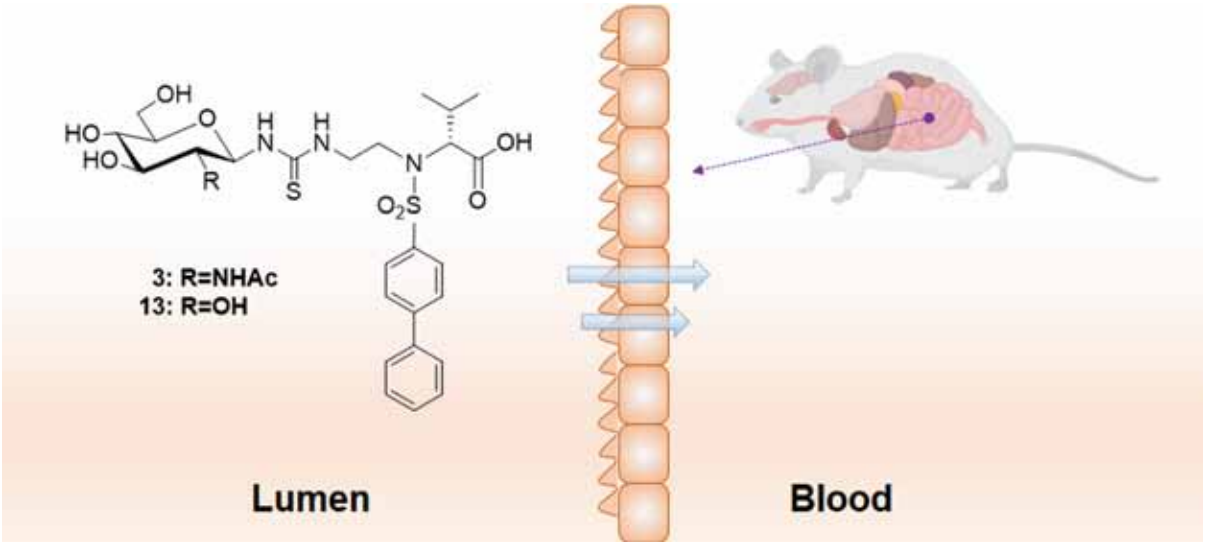
MMP-12, or macrophage metalloelastase, belongs to the matrix metalloproteinases (MMPs), a family of endopeptidases able to degrade the structural components of the extracellular matrix (ECM). This enzyme is mainly produced by macrophages and is involved in acute and chronic pulmonary inflammatory diseases.[1] Moreover, MMP-12 upregulation is implicated in atherosclerosis and cardiovascular diseases.[2]Oral administration of selective MMP-12 inhibitors might be useful to treat pulmonary and cardiovascular pathologies. The principal obstacles to clinical development of MMP-12 inhibitors are an inadequate selectivity for the target enzyme and a poor water solubility, with consequent poor oral bioavailability. In order to overcome these drawbacks, we recently reported[3] a new class of sugar-based arylsulfonamide carboxylates with a nanomolar activity for MMP-12, a good selectivity and an improved water solubility. Successively, we designed and synthesized new derivatives to characterize the structure-activity relationships (SARs) within this class of glycoconjugate inhibitors. All the new derivatives were tested on human recombinant MMP-12 and MMP-9 in order to evaluate their affinity and the selectivity for the target enzyme. Given their nanomolar activity and selectivity for MMP-12, the four most promising compounds were selected to assess their intestinal permeability using an *ex vivo* everted gut sac model. Considering the high polarity and structural similarity to glucose, compound **3** was demonstrated to cross the intestinal membrane by using the facilitative GLUT2 transport.[4] Further studies to determine the pharmacokinetic characteristics of this lead compound before in vivo testing are ongoing.



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PHARMACOMODULATION OF ELLAGIC ACID : A TOTAL SYNTHESIS APPROACH.

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The fight against malaria persists for more than 20000 years in Africa,[1] where 90% of reported cases and deaths are still located today. Even if mortality and incidence have been reduced worldwide, the progress in this context were rather limited the couples last decades. As a matter of illustration the number of cases has recently increased, after 10 years of constant reduction (211 million in 2015 versus 219 million in 2017). This phenomenon may be linked to well-documented drug-resistances. As all the current medicines are concerned in these emerging resistances, there is an urgent need of new therapeutic entities.[2]

Considering this overall picture, we have selected an antiplasmodial prototype to develop a new antimalarial treatment. Taking advantage of opportunities offered by Mother Nature, we have initiated a project focused on the development of analogues of ellagic acid.This common tannin precursor shows a great inhibitory effect both *in vitro* (105-330 nM) and *in vivo* with no adverse effects, even at high doses. The major drawback consists in its poor hydrosolubility, quantified as 9 µg/mL, impeding its oral use.[3]

As this feature may be due to the planar crystal packing which promotes intra- and intermolecular bonds, we decide to introduce bulky and/or hydrophilic chains on the phenolic functions. After unfruitful attempts towards direct hemisynthesis approach, a total synthesis approach starting from gallic acid was investigated (Fig 1.).[4]

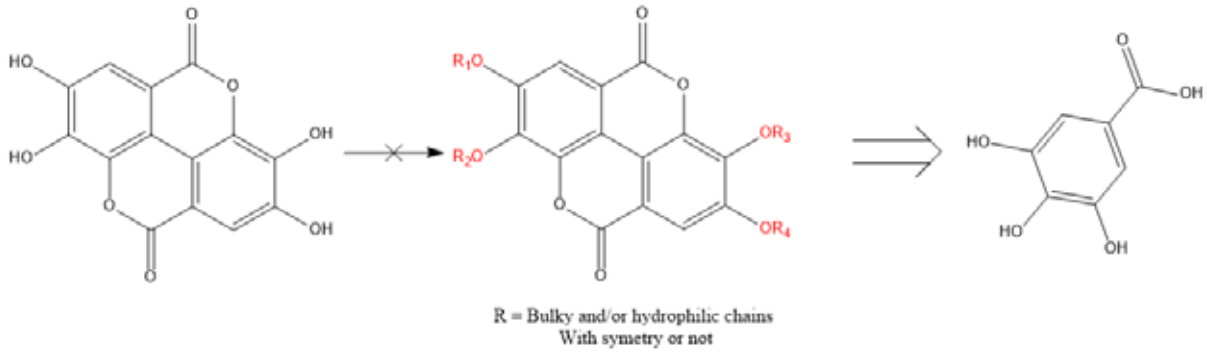

Figure 1: Pharmacomodulation of ellagic acid.

The antiplasmodial activity (3D7 strain) as well as cytotoxic and hemolytic effects were determined for all intermediates and final compounds and the water solubility has been quantified using a UV-spectrophotometric method. From these evaluations, it turns out that the range of antiplasmodial activity is 60 µM-1 µM and that this effect is not linked with hemolysis nor cytotoxic effect. This gain in activity was however found counterbalanced by a reduction of hydrosolubility (60 mM to 10 µM).

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PHOTOPHYSICAL PROPERTIES AND ANTIPARASITIC ACTIVITY OF BODIPY-TETHERED DINUCLEAR TRITHIOLATO-BRIDGED RUTHENIUM(II)-ARENE COMPLEXES

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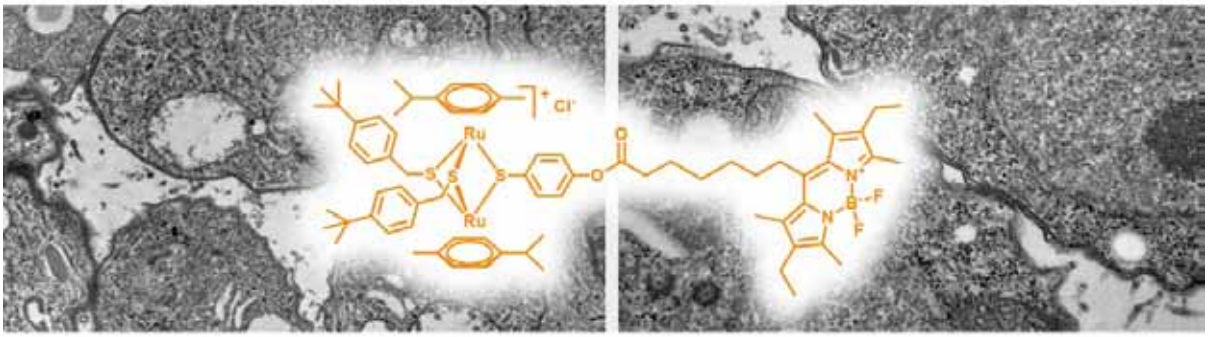
Cationic trithiolato-bridged dinuclear ruthenium(II)-arene complexes presenting symmetric or 'mixed' structures (general formula $[(\eta^6\text{-arene})_2Ru_2(\mu_2\text{-SR})_3]^+$ and, respectively, $[(\eta^6\text{-arene})_2Ru_2(\mu_2\text{-SR}^1)_2(\mu_2\text{-SR}^2)]^+$) were recently acknowledged as prospective antiparasitic agents against *Toxoplasma gondii*[1] and *Neospora caninum.*[2] Interestingly, the mitochondrion was identified as the major target in both parasites. We aim now to identify their possible mechanism of action and to monitor their fate in cells.

Fluorophore-labeled conjugates were shown to be a versatile approach for the intracellular visualization of organometallic compounds by means of confocal fluorescence microscopy. BODIPY-tethered ruthenium complex conjugateswere shown to be a useful tools for cellular bioimaging.[3-6] A series of eleven trithiolato-bridged dinuclear ruthenium(II)-*p*-cymene conjugates tagged with BODIPY fluorophores was synthesized. The impact of various structural features (i.e. the nature of connecting bond (ester *vs* amide), the length of the linker between the fluorophore and the organometallic moiety) upon the photophysical and antiparasitic properties of the conjugates was evaluated. Fluorescence measurements revealed that anchoring the organometallic moiety to the BODIPY dye was accompanied by an important fluorescence quenching for all conjugates.

In a first biological activity screening, human foreskin fibroblast (HFF) host cells and *T. gondii* apicomplexan parasite grown in HFF cells were exposed to each compound of interest (BODIPY-tethered conjugates, non-modified thiolato-bridged dinuclear ruthenium(II)-arene complexes and free BODIPY dyes) at two concentrations (1 and 0.1 μM). From this early assessment, five conjugates emerged as interesting for further biological studies. While none of the compounds affected HFF host cells at dosages of up to 2.5 μM, they inhibited *T. gondii* proliferation with 50% inhibitory concentrations (IC_{50}s) in the 0.34-0.54 μM range, the four ester conjugates being slightly more active compared to the amide derivative. Transmission electron microscopy of *T. gondii*tachyzoites exposed to two ester conjugates detected ultrastructural alterations in the matrix of the parasite mitochondria already 24 h after initiation of the treatment.



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A NOVEL NIR PROBE FOR TARGETED CANCER DIAGNOSIS

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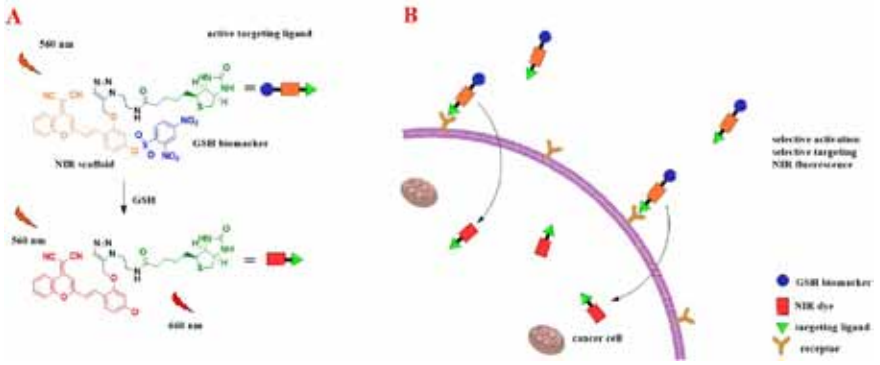

In 2019, cancer remains one of the most important causes of death worldwide. According to the latest estimation about 1.8 million new cases and 600 thousand deaths will appear in USA while the number is expected to increase significantly by 2025[1]. To minimize the high mortality and morbidity of this disease, a large number of chemotherapeutic agents are available on the market, however, the complete neutralization of rapidly growing cancer cells remains a major barrier. The main reasons behind this include delayed detection, the metastatic nature of cancer cells as well as the lack of targeted therapeutic agents[2]. In order to prevent cancer in early stages, diagnosis is essential and can be done through a variety of imaging techniques including . Among the exhisted non-invasive techniques optical imaging possesses several advantages including increased selectivity and the low cost for obtaining the right equipment[3]. In the last decade, near infrared fluorescence imaging (NIRF) has received great attention, as an imaging tool since it has extremely high sensitivity, permits deep tissue *in vivo* imaging and annihilates auto fluorescence interference[4] . Tumor cells are characterized by the overexpression of membrane bound receptors that are recognized by particular ligands, therefore a great number of tumors targeted prodrugs and diagnostics has been reported[5-7]. Targeting ligands such as peptides and small molecules including vitamins and triphenylphosphine derivatives have received great attention. Compared to peptides that are characterized by increased production and purification cost, vitamins based targeting ligands can overcome theses drawbacks and thus are more efficacious. Vitamin B9, commercial known as folic acid is most widely used vitamin based targeting unit, however the majority of cancer cell lines over express B-7 (biotin) receptors[8].Considering that cancer cells are defined by unique characteristics including the lower extracellular pH levels and the overexpression of specific biomarkers and enzymes a great number of prodrugs and diagnostic compound have been recently developed. Among these biomarkers, glutathione (GSH), the most abundant thiol, displays a vital role in the redox biology of cancer cells. The elevated level of GSH is directly linked with the appearance of this deathful disease, thus it is important to establish molecular probes that possess real time response high selectivity towards biothiols probes. Herein, we synthesized a novel NIR fluorescent optical reporter that is selectively delivered in the tumor microenvironment and released by glutathione.

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IMPRESSIVE BIOFILM-GROWING BACTERIA INACTIVATION

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The worldwide emergence of multidrug-resistant (MDR) bacteria are considered by the World Health Organization (WHO) one of the main causes of mortality by infectious diseases. It has been estimated that more than 80 % of all microbial infections are caused by formation of bacteria biofilms.[1] According to WHO recommendations, an urgent investment in R&D is essential for the development of new antibacterial entities with alternative mechanisms of action, to avoid that around 10 million people will die annually worldwide by 2050.[2,3] Antimicrobial photodynamic therapy is one of the methodologies that has received significant attention, for not being associated with the development of microorganism resistance after treatment.[4] The present work intends to overcome these challenges by the development of new photosensitizers based on cationic imidazolyl moieties with different amphiphilicities, molecular weights and number of charges. Their antimicrobial activity was tested towards a panel of pathogenic microorganisms: Gram-positive *(Staphylococcus aureus)*, Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and *S.aureus* biofilms. Total inactivation was found for concentrations as low as 100 nM in planktonic bacteria. On the other hand, in *S.aureus* biofilm, we observed an impressive destruction of the biofilm (~99,43 %) in the presence of just 5.2 nM of the photosensitizer. Additionally, confocal microscopy and computational studies were performed to understand this unprecedented inactivation. These outstanding results open the way to overcome the problem of resistance.

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SYNTHESIS AND BIOLOGICAL EVALUATION OF FUSED COUMARIN DERIVATIVES

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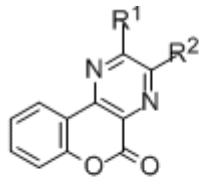
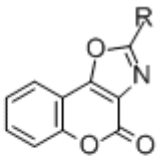
Fused coumarin derivatives containing pyran or pyridine or oxazole ring present interesting biological activities, [1-4] such as chemopreventive for carcinogenesis, through inhibition of P450 1A2, antiiflammatory, antimicrobial, photosensitizing etc. We have reported recently the synthesis of fused pyranocoumarins,[5] oxazolocoumarins[6,7] and pyridocoumarins.[8] In continuation to our interest in the synthesis of fused coumarin derivatives in order to examine their biological properties we would like to present here the syntheses of several fused pyrazinocoumarins **1a-e**, oxazolocoumarins **2a,b**, and bis-fused pyridopyranocoumarins **3a-d, 4** from 4-amino-3-nitrocoumarin, 4-hydroxy-3-nitrocoumarin and 6-amino-7-hydroxycoumarin, respectively. The prepared new compounds were tested as soybean lipoxygenase, lipid peroxidation and serine proteases inhibitors.



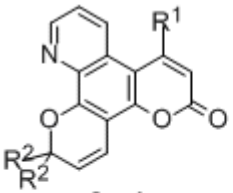
1a-e

1a: R^1=R^2=H
b: R^1=Me, R^2=H
c: R^1=Ph, R^2=H
d: R^1=R^2=Me
e: R^1=R^2=Ph



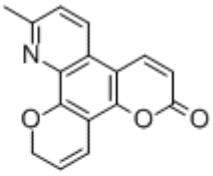
2a,b

2a: R=Me
b: R=OEt



3a-d

3a: R^1=R^2=H
b: R^1=Me, R^2=H
c: R^1=H, R^2=Me
d: R^1=R^2=Me



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SYNTHESIS OF NEW KAPPA OPIOID RECEPTOR-SELECTIVE FLUORESCENT PROBES AND APPLICATION FOR HOMODIMERIZATION STUDIES UNDER PHYSIOLOGICAL CONDITIONS VIA SINGLE MOLECULE MICROSCOPY

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G protein-coupled receptors (GPCRs) are a major class of drug targets. The four opioid receptor (OR) subtypes (μ, δ, κ and the nociception receptor subtype) located on neuronal cells represent important targets for pain management. The classic viewpoint on GPCRs functioning as single units is nowadays shifting to certain GPCRs forming oligomeric complexes with distinct pharmacology. [1]

The main goal of our project is investigating κOR homodimerization in neutral state (i.e. the non-activated state of the receptor, as bound to an G-protein and β-arrestin antagonist and not to an inverse agonist). We designed, synthesized and characterized a set of subtype-selective fluorescent ligands using the antagonist 5'GNTI (figure) linked to Cy3 and Cy5 dyes (figure) via suitable spacers (aliphatic, biglycine, tetraglycine). [2-5]

Subsequently, two of the compounds were used to study receptor localization, dynamics and potential dimerization via Single Molecule Microscopy (SMM). This technique allows individual receptor visualization on the surface of living cells. Our results do not support neutral-state κOR dimerization on the plasma membrane at physiological receptor densities.

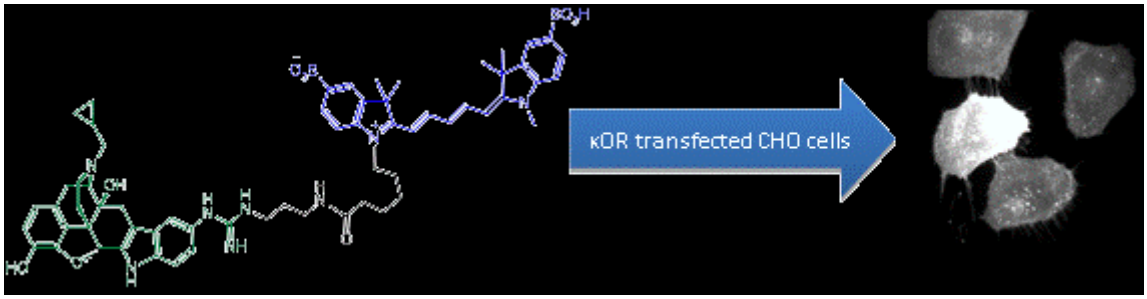

Figure: 5'GNTI (green) linked to Cy5 dye (blue) with an aliphatic spacer (black). CHO cells after overnight transfection with κOR are incubated with the probe (20 min incubation / 1 nM). High affinity κOR binding and very good optical properties are exhibited by the fluorescent probe

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NEW SMALL-MOLECULE DUAL INHIBITORS OF THE p53–MDM2/X INTERACTIONS TO REACTIVATE THE p53 PATHWAY

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Cancer is still the major global health problem with high mortality rate. The search for more effective therapeutic approaches featuring alternative or synergistic anticancer agents with minimal side-effects continues.

The p53 protein has an important role in the tumor suppression and regulation of cell processes and, nowadays, it is well established that the p53 signaling pathway is activated under cellular stress.Although, the p53 inactivation due to negative regulation by the proteins MDM2 and MDMX is a common event in 50% of human cancers.[1] In the last years, medicinal chemistry approaches to regulate the p53 pathway have been mainly focused on inhibiting the p53-MDM2 interaction, however, it is now clear that for targeting effectively the p53 pathway it is required the dual inhibition of p53-MDM2/X interactions.[2]

To address this challenge, in the last years our group has been working on the development of MDM2/X dual inhibitors. A preliminary screening of enantiopure tryptophanol derivatives in yeast cell models led to the identification of a hit tryptophanol-derived oxazoloisoindolinone.[3] In search of more potent p53 activators, an optimization process was carried out in order to improve the anticancer activities of the hit compound. In this communication, we will present our most recent results related with the lead generation. The chemical libraries of enantiopure tryptophanol derivatives were easily obtained through a chiral-pool cyclocondensation strategy, in good to excellent yields. This synthetic approach is highly efficient and an economic way to obtain enantiopure compounds.

The anticancer activity of the new compounds was studied in HCT116 cells with wild-type p53 and respective p53-null isogenic derivative cells. Two compounds were identified as selective p53-activators. Both compounds were able to cause growth inhibition, mediated by p53 stabilization and upregulation of p53 transcriptional targets involved in cell cycle arrest and apoptosis, in wt p53-expressing tumor cells (including MDM2- or MDMX-overexpressing cells). The results also indicated that the tryptophanol-derived small molecules potentially activated p53 by disruption of the p53-MDM2/MDMX interactions.[4-5] *In vivo* studies using human tumor xenograft mice models confirmed a p53-dependent antitumor activity of tryptophanol derivatives through induction of apoptosis and inhibition of proliferation and angiogenesis.[4]

Therefore, tryptophanol-derived compounds can be considered promising drug candidates for the treatment of cancer and a good starting point to develop more potent anticancer agents based on the p53 activation.

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N-ALKYL L-IMINOSUGARS AS NOVEL ANTI-INFLAMMATORY AND ANTI-BIOFILM TOOLS FOR CYSTIC FIBROSIS LUNG INFECTIONS

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Chronic inflammation of airways and polymicrobial infections greatly contribute to the irreversible lung damage in Cystic Fibrosis (CF) disease.[1] Accordingly, increasing attention is currently devoted to development of novel anti-inflammatory as well as antibiofilm agents for the treatment of CF lung infections. In this context, D-iminosugars (sugar analogues with an amino function in place of the endocyclic oxygen) have recently shown interesting *in vitro* and *in vivo* anti-inflammatory effect, by targeting β-glucosidase 2 (NLGase).[2] However, as widely reported, the poor *in vivo* selectivity of D-iminosugars hampers their long-term use as therapeutics.[3] Conversely, their non-superimposable mirror images, L-iminosugars, have shown higher selectivity than their D-counterparts toward specific enzymes acting as either inhibitors or enhancers.[3,4] Based on these findings, in order to explore role of iminosugar configuration on the therapeutic potential of these molecules in the treatment of CF lung infections, we tuned up a novel synthetic procedure for the preparation of L-DNJ, i.e. L-deoxynojirimycin, and its *N*-alkylated derivatives (**Figure 1**).

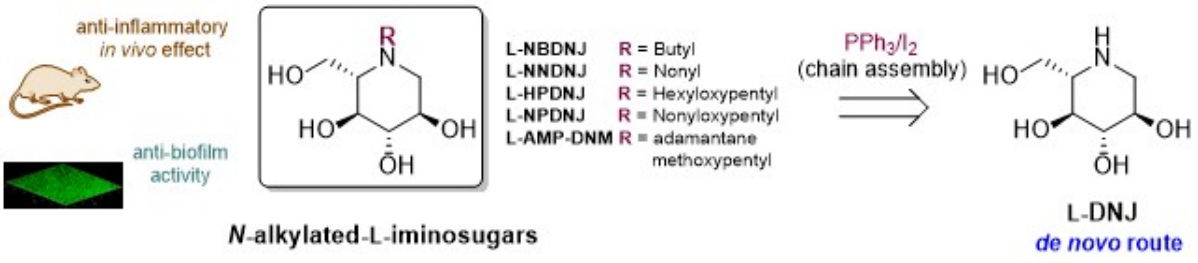

Figure 1 *De novo* route to L-DNJ and its *N*-alkyl derivatives.

Particularly, access to the iminosugar core has been devised through a stereocontrolled *de novo* procedure,[4] while the use of polymer-bound triphenylphosphine/iodine complex has been conceived for the assembly of the alkyl chains. Biological assays for some derivatives revealed, on one hand, an anti-inflammatory activity in CF bronchial cells as well as in murine models of lung infection, on the other, promising antibiofilm activity against some pathogens involved in chronic lung infections characterizing CF patients.

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SMALL MOLECULE STABILISATION OF THE p53 – 14-3-3σ INTERACTION AS A THERAPEUTIC MODALITY FOR CANCER

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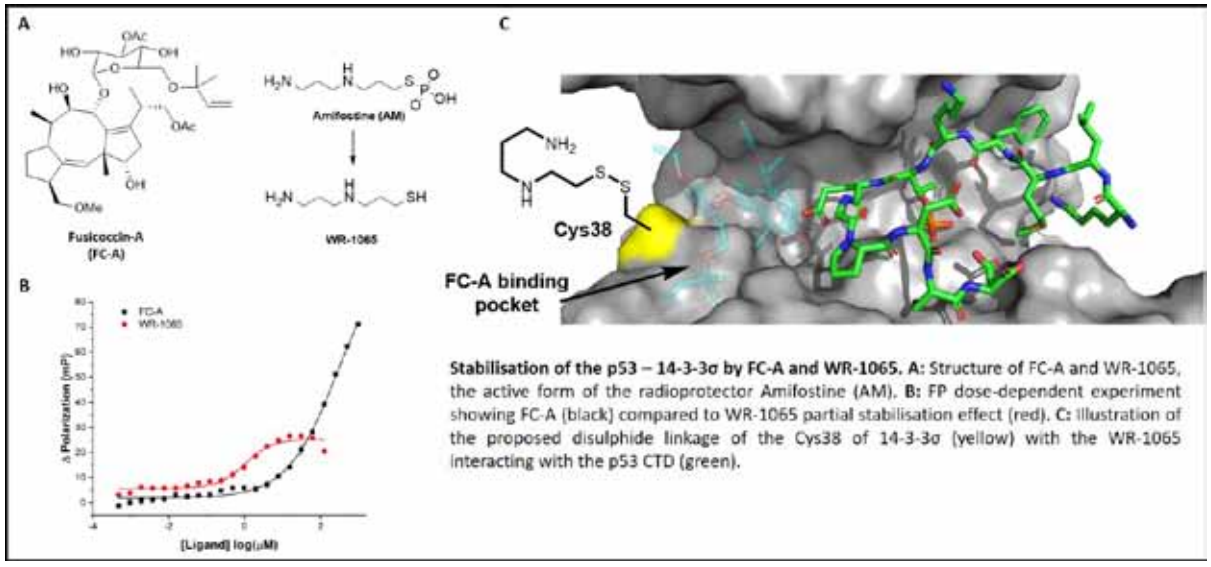
Protein-protein interactions (PPIs) play a significant role in many biological processes and consequently in many diseases. In the last decades, the modulation of PPIs with small molecules has gained substantial interest in pharmaceutical research, providing opportunities for new treatments[1]. An interesting case of PPIs as an oncology target for small molecules is given by the tumour suppressor factor p53 and its positive or negative regulators. When the gene encoding for p53 carries a mutation on its sequence, p53 cannot bind properly to the DNA and therefore, the cell starts to divide uncontrollably in response to oncogenic stimuli, forming malignant tumours. Considerable efforts are being made in recovering p53 function in anticancer therapy. One successful approach is to inhibit the interaction between p53 and its negative regulator MDM2[2].

However, this poster describes an alternative strategy: stabilising the PPI between p53 and the adapter protein 14-3-3σ, its positive regulator. It has been shown that this PPI enhances p53 transcriptional activity and its level in cells[3], consequently reducing the oncogene-induced tumourigenicity in mice[4]. The fungal metabolite Fusicoccin A (FC-A), represents the first example of a small-molecule that stabilises the interaction between p53 and 14-3-3σ. Isothermal Titration Calorimetry (ITC) and Fluorescence Polarization (FP) has shown a four-fold stabilisation of the PPI in the presence of FC-A[5] and a partial stabilising effect in presence of another unrelated compound WR-1065[6,7]. Interestingly, high-resolution mass spectrometry (HRMS) experiments suggest that WR-1065 binds to 14-3-3σ in a covalent manner stabilising its interaction with p53. Based on these results, new WR-1065 analogues bearing different electrophiles have been designed and are now being synthesised and tested to determine if they also bind to 14-3-3σ. No further work has been done to validate the effect of these molecules on p53 expression/activity in cellulo. Hence, this is one of the principal aims of this work along with the development of a novel library of new selective and more potent small molecule stabilisers of the interaction between p53 and 14-3-3σ.



Stabilisation of the p53 – 14-3-3σ by FC-A and WR-1065. A: Structure of FC-A and WR-1065, the active form of the radioprotector Amifostine (AM). **B:** FP dose-dependent experiment showing FC-A (black) compared to WR-1065 partial stabilisation effect (red). **C:** Illustration of the proposed disulphide linkage of the Cys38 of 14-3-3σ (yellow) with the WR-1065 interacting with the p53 CTD (green).

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF QUATERNARY AMMONIUM FLUOROQUINOLONES

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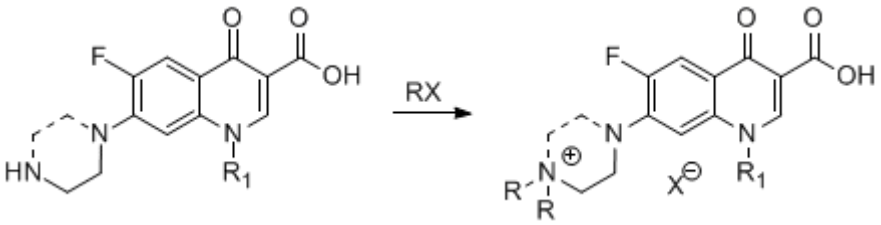
Fluoroquinolones are broad-spectrum antibiotics (effective for both gram-negative and gram-positive bacteria) that play an important role in the treatment of serious bacterial infections, especially hospital-acquired infections and others in which resistance to older antibacterial classes is suspected. Since the discovery of nalidixic acid by George Lesher in 1962 over ten thousand analogues have been synthesized from which four generations of chemotherapeutics with a broad spectrum of antibacterial activities have emerged.

Safirinium dyes are water-soluble and inexpensive fluorophores that possess triazolo-pyridinium core (1-2). Recently we have synthesized a series of fluorescent *Safirinium*-fluoroquinolone hybrid compounds featuring fused quaternary quinolone-triazolinium moiety that exhibited biological effects. Novel derivatives showed a pronounced in vitro antibacterial and antibiofilm activity against various pathogens, including *Pseudomonas aeruginosa*. The obtained conjugates were potent *E. coli* DNA gyrase inhibitors and caused a defect in DNA decatenation. The most active compounds were found to be comparable to the reference drug, ciprofloxacin (unpublished results). Moreover, the presence of quaternary nitrogen atom in the structure should prevent distribution to the brain (3) and such hybrid agents should not elicit the direct CNS side effects after intravenous administration.

In view of the above, we have synthesized a series of quaternary analogues of fluoroquinolones with dimethylpiperazinium moiety. Antibiofilm activity of obtained compounds was investigated. Molecular docking experiments were undertaken to confirm the mode of action of the novel antibacterials.



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NEW NIFURTIMOX-ADAMANTANE HYDRAZONE ADDUCTS: DESIGN, SYNTHESIS AND EVALUATION OF TRYPANOCIDAL ACTIVITY

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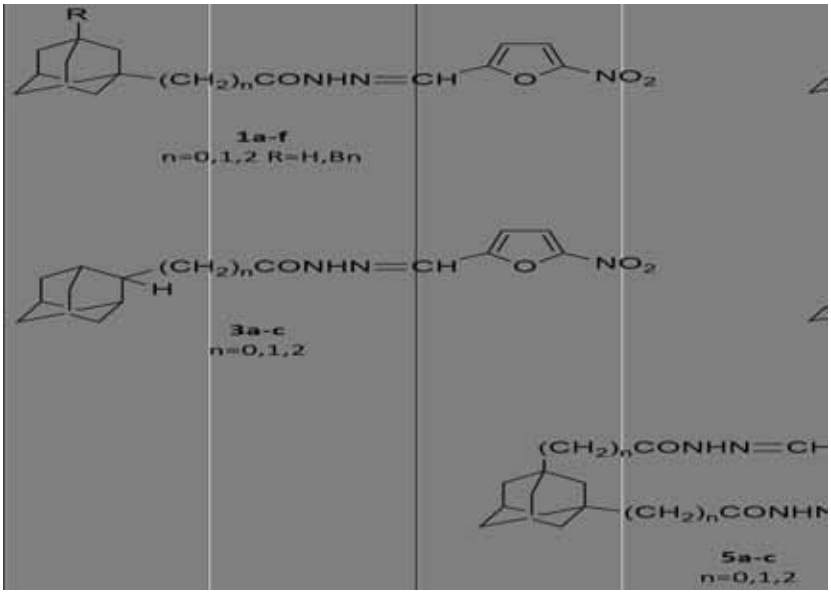
Five to eight million people in Latin America are infected with the protozoan parasite Trypanosoma cruzi, the aetiologic agent of Chagas disease. Although the disease occurs mainly in Latin America, migration and travel have extended the distribution to other continents including North America, Europe and parts of the Western Pacific, where significant numbers of Chagas disease sufferers can now be found. The current drugs, benznidazole and nifurtimox, are characterized by limited efficacy and toxic side-effects, and treatment failures are frequently observed. This has led the World Health Organization (WHO) to coordinate public sector and private partnerships as part of a global effort to develop new and safer drugs.

Over the past 10 years we have been interested in adamantane chemistry and have prepared numerous adamantane derivatives with antitrypanosomal potency [1-2], exploiting adamantane's role in bioactivity. Herein, the synthesis and pharmacological evaluation of the C-1 substituted adamantane hydrazones **1a-f**, **2a-d**, C-2 substituted hydrazones **3a-c**, **4a-d** and the C-1,3 1,3-disubstituted derivatives **5a-c** is described [3-4].

The nifurtimox-adamantane hydrazone adducts are more potent trypanocidals than the parent drug, nifurtimox. The effect of the presence of the phenyl ring, in conjugation with the hydrazone side chain, on activity, shows an adamantane position substitution dependence. The insertion of a phenyl ring between the adamantane core and the hydrazone side chain has improved the pharmacological profile, in terms of activity and toxicity. The most active adduct with the best selectivity is the phenylacetoxy hydrazone **2b** (EC_{50}=11 ± 0.9 nM and SI_{Tb}=770).



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SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,2-DIHYDROPYRIDINE CARBOXAMIDE DERIVATIVES AS NOVEL POTENTIAL ALLOSTERIC MODULATORS OF CANNABINOID RECEPTOR 2

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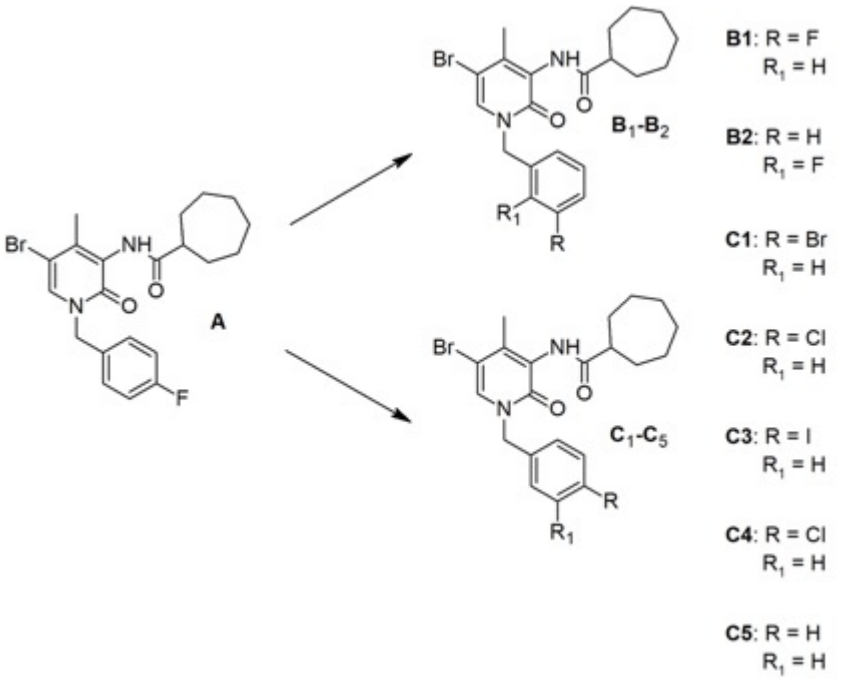
The endocannabinoid system (ECS) is a neuromodulatory retrograde lipidsignaling system comprising at least two cannabinoid receptors (CBRs), (CB1Rs and CB2Rs), a class of lipid mediators calledendocannabinoids (ECs), their synthesizing and degrading enzymes and the EC membrane transporter (EMT). Over the past few years, the role of the ECS in several pathologies such as obesity, cancer, mental illnesses, pain, drug addiction and neurodegenerative diseases has emerged. Therefore, soon after the discovery of CBRs, drugs directly targeting CBRs have been firstly studied. Unfortunately, the new compounds developed following this approach were characterized by serious adverse effects, such as anxiety, depression, suicidal ideation, psychotropic effects or immune dysfunction, that have consequently limited their clinical development. To overcome the side effects due to the use of traditional orthosteric drugs, a possible new strategy would be to develop CBR allosteric modulators as potential medicines. Allosteric ligands, are able modulate the affinity and/or efficacy of specific orthosteric ligands by binding to topographically distinct allosteric sites. Recently, our research group reported the synthesis and the biological evaluation of the first synthetic CB2R allosteric modulator (**A**)(1). In order to better understand the role of the fluorine in position 4 of the benzyl group, we synthesized new derivatives changing the position of the fluorine in the ring (**B1**, **B2**) or replacing it with other halogens (**C1**, **C2**, **C3**, **C4**) or without any substituents (**C5**).



The new compounds have been tested for their CB2R binding affinity and functional activity at the University of Aberdeen in Prof. Pertwee's lab. The results might be useful for computational studies regarding the pharmacology and crystal structure of the CB2R's allosteric site.

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INSIGHTS INTO THE ILK–PARVIN INTERACTION AS A NEW STRATEGY AGAINST CHRONIC KIDNEY DISEASE

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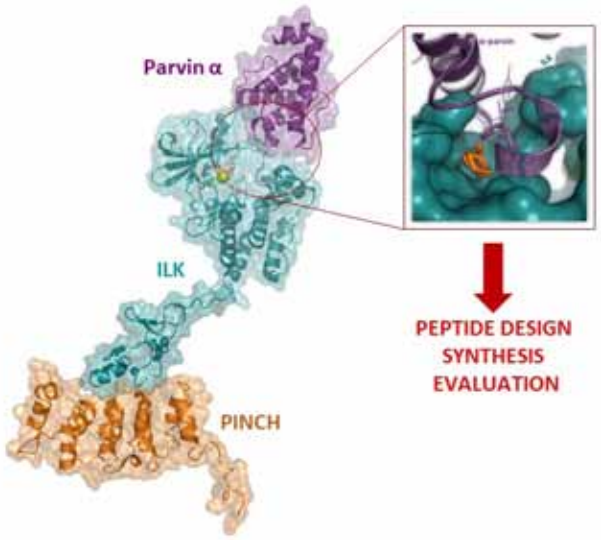
Chronic kidney disease (CKD) is the non–transmissible global cause of death that raised the most within the past 20 years. It increases the risk of all–cause mortality and may progress to end–stage of renal failure. There is no effective therapy for CKD and current approaches do not prevent its progression. Then, the search of new and validated targets against CKD has become a milestone in academic groups and industry. This pathology has been related, at least partially, to integrin–linked kinase (ILK) [1]. This is an intracellular pseudokinase which forms the ternary complex IPP (ILK–PINCH–parvin) with two adaptor proteins. On the other hand, disrupting protein–protein interactions have emerged as very promising strategy against different types of diseases due to its high selectivity and specificity. We have focused our efforts in disrupting the ILK–parvin interaction to validate this protein as target for CKD. Starting from the crystal structure and the sequences of both proteins, an extensive analysis on the interaction surface was carried out using molecular modelling approaches to identify the most favourable regions of interaction, cavities and hot–spots. These data allowed the design and synthesis of peptides for the study of this interaction using SPR and biological assays.



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TARGETING GLUCOSE METABOLISM AND MITOCHONDRIA-INDUCED APOPTOSIS IN CANCER CELLS: STRUCTURE-BASED VIRTUAL SCREENING VALIDATION TOWARD HEXOKINASE 2 INHIBITORS

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Glucose is regarded as the main fuel of cancer cells and the glycolytic pathway has been demonstrated as a potential target to be explored for cancer treatment. Several enzymes involved in glycolysis, namely hexokinase 2 (HK2), are overexpressed in different types of cancer cells[1]. This enzyme is not only involved in the first and most determinant step of glycolysis and subsequently in the different branched pathways[2,3], but also in the immortalization of cancer cells. When catalytically active, HK2 is able to bind to the voltage-dependent anion channel (VDAC) in the mitochondrial outer membrane, preventing the normal pro-apoptotic signalling. HK2-VDAC disruption should promote the binding of pro-apoptotic proteins to VDAC, therefore enhancing apoptosis in cancer cells[4].

For this reason, the inhibition of the HK2 catalytic centre is proposed as a strategy to reduce the main source of energy to cancer cells, thus significantly decreasing cancer cell proliferation, avoiding HK2 binding to VDAC, and enhancing the apoptosis process. As an effort to find hit compounds able to interfere with the HK2 catalytic activity, a structure-based drug design strategy was implemented, leading to the virtual screening of several general databases such as DrugBank (~2000 molecules), NCI (~265 000 molecules), Chemoteca (~800 molecules) and some specific databases of natural product derivatives such as Ambinter (~10 000 000 molecules) and InterBioScreen Natural Products (~84 000 molecules). The virtual screening was carried out using molecular docking calculations through Gold 5.20 software. Molecules were prepared using Molecular Operating Environment (MOE2016 0802) and then docked into the HK2 catalytic site. Our results have suggested 2981 molecules with the potential to act as new HK2 inhibitors. Biochemical validation of the above-mentioned protocol is being conducted with 64 selected molecules, using the ADP-Glo™ kinase assay, a luminescence-based approach. Some of these compounds have displayed comparable or higher inhibition than a known HK2 inhibitor.

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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL SUBSTITUTED PURINE ISOSTERS AS EGFR KINASE INHIBITORS, WITH PROMISING PHARMACOKINETIC PROFILE AND IN VIVO EFFICACY

Efthymios-Spyridon Gavriil (1), Aris Doukatas (2), Theodoros Karampelas (2), Vassilios Myrianthopoulos (1), Spyridon Dimitrakis (1), Emmanuel Mikros (1), Panagiotis Marakos (1), Constantin Tamvakopoulos (2), Nicole Pouli (1)

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Epidermal Growth Factor Receptor (EGFR) is the first member of the HER-family of receptors, consisting of four members (HER1-4, ErbB1-4), which are key regulators of important cellular functions and have been implicated in a number of the most lethal tumors [1]. Lapatinib (Fig. 1A), an approved drug, acts as dual EGFR/HER2 inhibitor and is indicated for HER2 overexpressing advanced or metastatic breast cancer [2]. Taking into account the binding mode of lapatinib [3], a number of modified purines were designed by converting the central quinazoline core of the drug to purine isoster (Fig. 1C, I-III) or purine (Fig. 1C, IV) hinge binders in order to investigate the effect of an isosteric replacement of the quinazoline core by a ring system with the capacity to accommodate additional hydrogen bonds with the kinase hinge (Fig. 1B-C).

For the synthesis of the compounds, suitably substituted pyridine or pyrimidine derivatives were used as starting materials, while each group of derivatives required its own synthetic procedure. The target compounds were evaluated for their direct inhibitory action on the intracellular receptor kinase domain, as inhibitors of receptor phosphorylation at the cellular level, and for their cytotoxicity in the non-small cell lung cancer cell line A549 and breast cancer HCC1954, which are associated with overexpression of $EGFR^{WT}$ and HER-2, respectively. The most potent derivatives were further studied for their cellular uptake levels and *in vivo* pharmacokinetic properties. One compound distinguished among the others as it displayed a noteworthy pharmacokinetic profile as well as higher intracellular accumulation in comparison to lapatinib in the A549 cells, possibly due to its higher lipophilicity. This compound was finally assessed for its efficacy in an EGFR positive xenograft model, where it successfully inhibited tumor growth, with similar efficacy with that of lapatinib and with minimal phenotypic toxicity.

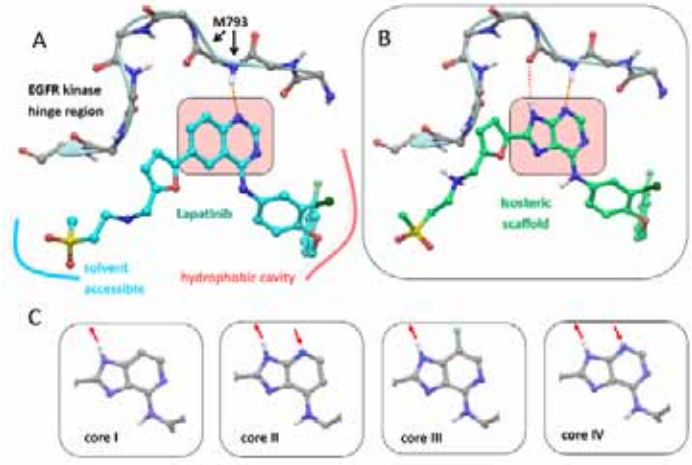

Fig. 1. A) A simplified depiction of the experimental binding mode of lapatinib in EGFR kinase domain. **B)** The designed isosteric modification of quinazoline into a purine-like system carried by the novel analogues. **C)** The four distinct heterocyclic ring systems considered and evaluated in this study.

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METAL CHELATING ACETOHYDROXAMIC ACIDS AGAINST HEPATITIS C VIRUS AND FLAVIVIRUSES

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Hepatitis C Virus (HCV) infections pose a major public health threat globally, with infected individuals being at risk of developing chronic liver disease, cirrhosis and hepatocellular carcinoma. There is no vaccine available and despite advances in current chemotherapy, the global burden of HCV infections remains high, due to their partial effectiveness or viral resistance. The flaviviruses Dengue (DENV), Yellow fever (YFV), and the re-emerging Zika virus (ZIKV) cause diseases ranging from mild febrile illness to severe encephalitis or hemorrhagic syndromes. Despite the extensive research on flaviviral diseases, there is no clinically approved therapy, thus, they constitute high priority targets for drug discovery. Because of all the above and based on literature reports on metal-chelating agents inhibiting HCV NS5B-polymerase,[1],[2] the development of novel scaffolds of metal-chelators with antiviral properties was undertaken.

By utilizing docking-scoring calculations, structural insight regarding HCV inhibition was obtained, prompting the rational design and synthesis of novel carbocyclic-(spiro)substituted hydantoin-derivatives, bearing the acetohydroxamic acid metal-chelating group upon the imidic nitrogen, and a variety of lipophilic substitutions at the amidic nitrogen atom.

The compounds were evaluated for their effect on HCV RNA replication and cell viability (ATP and luciferase assays), exhibiting EC_{50} values ranging from 0.08 to 4.50 μM, in Huh7 reporter subgenomic replicon cell lines of genotype 1b, and remarkable Selectivity Indexes rising up to 781. The fact that flaviviruses are members of the Flaviviridae family, along with HCV, and they share several similarities among their homologous metalloenzymes (NS5B/NS5 RNA-dependent RNA polymerase and NS3 protease/helicase)[3],[4] prompted the evaluation of the most potent anti-HCV compounds against DENV, YFV and ZIKV.

The preliminary anti-flaviviral results of low μM EC_{50} values, observed for many compounds (representative EC_{50} values 0.07 μM, 2.76 μM, and 0.44 μM for DENV, YFV and ZIKV respectively), are highly encouraging and, along with theoretical simulations, suggest that the novel framework of metal-chelators we developed offers a highly promising starting point for the design of potent and broadly effective antiviral agents with dual-target potential. Analysis of resistance mutations and modeling studies are currently underway to further characterize their inhibition mechanism.

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STUDIES TOWARDS THE TOTAL SYNTHESIS OF THE ANTI-INFLAMMATORY DITERPENOID NEOROGIOLTRIOL AND DERIVATIVES

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A number of natural products derived from marine organisms have been reported to exhibit a broad spectrum of pharmacological activity, including anti-inflammatory effects.[1] Algae, and in particular red algae, represent a rich source of different secondary metabolites, the majority of which consists of acetogenins, halogenated diterpenes and sesquiterpenes.[2]

Recently, we isolated neorogioltriol (Fig 1), a new tricyclic brominated diterpenoid with analgesic activity[3] from the organic extract of the red algae *Laurencia glandulifera*. Subsequently, we investigated the anti-inflammatory activity of neorogioltriol *in vitro* on lipopolysaccharide (LPS)-treated Raw264.7 macrophages and *in vivo* using carrageenan-induced inflammation in the rat paw. The *in vivo* study demonstrated that the administration of 1 mg/kg of neorogioltriol resulted in a significant reduction of carrageenan-induced rat edema.[4]

Thus, we set out to identify the molecular features of neorogioltriol responsible for its anti-inflammatory properties. This objective can be achieved either by chemical modification of neorogioltriol or through total synthesis and evaluation of the biological activity of intermediates. The second approach, though more time-consuming, offers the possibility of synthesizing a variety of analogues of the natural product on a large scale without having to collect it from the marine environment. Therefore, we embarked on the total synthesis of neorogioltriol using a convergent approach. In the current work we will present our synthetic efforts towards this goal as well as the preparation of derivatives of the natural product in order to obtain structure activity relationships.

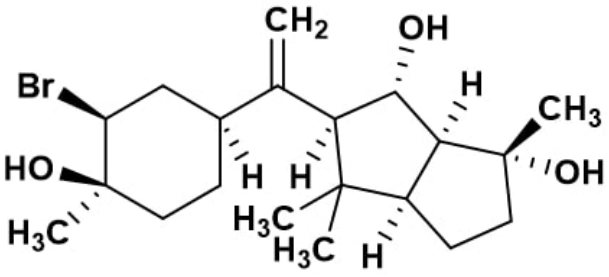

Figure 1. Structure of neorogioltriol

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TRANSFORMATION OF BIOMASS DERIVED FURANS TO KEY BIOACTIVE SCAFFOLDS

Rafael Gomes, Kessia Andrade, Raquel Frade, Alexandre Trindade, Jaime Coelho, Carlos Afonso

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Preparation of biologically active products from biomass allows for cheaper and accessible drug products. Carbohydrates have been seen has a possible source of bulk chemicals *via* dehydration to levulinic acid and furans such as furfural and 5-hydroxymethylfurfural (HMF). Our group has been working on the valorization of biomass derived furans (BDF). In particular our group prepared HMF[1] from fructose or glucose and developed a family of antitumoral triarylmethanes[2] from this monomer. We recently reported a family of highly complex δ-Lactone-fused cyclopentenones[3] (CPs). Also furfural is currently prepared in industrial scale from lignocellulosic material and our group have developed methodologies for the preparation of *trans* -4,5-diamino-CPs including a very mild procedure in aqueous media[4]. This CPs show remarkable antimicrobial activity[5]. Further derivatization of the CPs through a Michael addition allow the formation of new families of antitumoral CPs[5]with optimal drug-like properties. In this way we hope to show the potential of biomass in the development of valuable scaffolds for Medicinal Chemistry that are in pair with the environmentally friendly demands of nowadays.

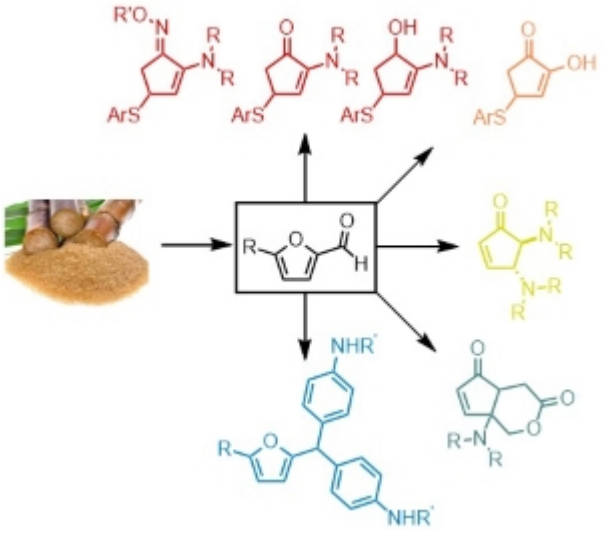

Fig 1. Transformation of biomass to bioactive scaffolds

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SYNTHESIS OF NOVEL 2-SUBSTITUTED INDOLE DERIVATIVES AS POTENTIAL ANTITUMOUR AND ANTIBACTERIAL AGENTS

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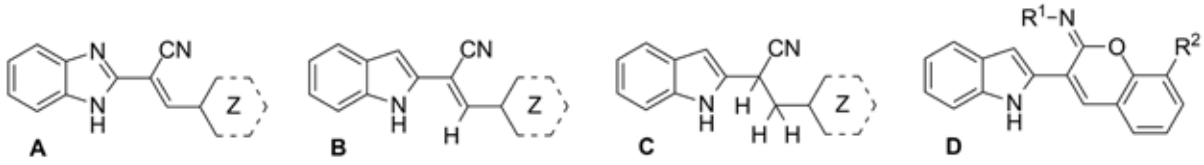
The indole moiety represents an extraordinary fragment in several promising classes of compounds with an interesting pharmacological profile. 2-substituted indoles have been shown to possess spasmolytic, hypotensive, antioxidative, tuberculostatic, insecticidal and anticancer activities. Recently, we have described syntheses and pronounced antitumour properties of 3-arylacrylonitriles either with triazole or benzimidazole substituents in position 2 of the acrylonitrile moiety [1][2].

In particular, 2-benzimidazole substituted acrylonitriles of type **A** were effective at inhibiting the growth of various human cancer cell lines *in vitro*. Additionally, these compounds have been found to be active against *Staphylococcus epidermidis* and *Staphylococcus aureus*. With the above information in mind, we have decided to prepare a new series of 2-substituted indole analogues (structure **B**) to identify compounds with potential antitumour and/or antibacterial activities. To investigate the importance of the acrylonitrile double bond on the biological activity, derivatives lacking this group have also been synthesized (structure **C**). It should be noted that antitumour activity also exhibit variously substituted imino-coumarins [3]. Therefore we reasoned that compounds synthesized by linking indol-2-yl moiety compounds with 2-imino-coumarin ring system could be effective as potential antitumour agents (structure **D**).



R^1 = H, benzoyl, phenylsulfonyl, phenylcarbamoyl; **R**^{2} = H, Me, OMe, Cl; **Z** = aryl, heteroaryl

The structures of novel 2-substituted indole derivatives were confirmed by IR, NMR and MS spectroscopic data as well as single X-ray analysis.

The *in vitro* antitumour properties of the obtained compounds were tested at the Department of Medicinal Chemistry, University of Greifswald (Germany) and National Cancer Institute (USA). The prominent compound with remarkable anticancer activity (GI_{50} = 0.26-6.60 μM, TGI = 0.64-9.49 μM) to all investigated human tumour cell lines was (*Z*)-3-[4-(dimethylamino)phenyl]-2-(1*H*-indol-2-yl)acrylonitrile of type B (Z = 4-$(CH_3)_2$ N-C_6H_4). The newly prepared compounds were also evaluated for their potential antimicrobial activities against Gram-negative and Gram-positive bacteria. The greatest antibacterial activity displayed 2-(1H-indol-2-yl)-3-(1*H* -pyrrol-2-yl)acrylonitrile of type **B** (Z = pyrrol-2-yl).

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DISCOVERY OF SMALL-MOLECULE MODULATORS OF 14-3-3 PPIs VIA DYNAMIC COMBINATORIAL CHEMISTRY

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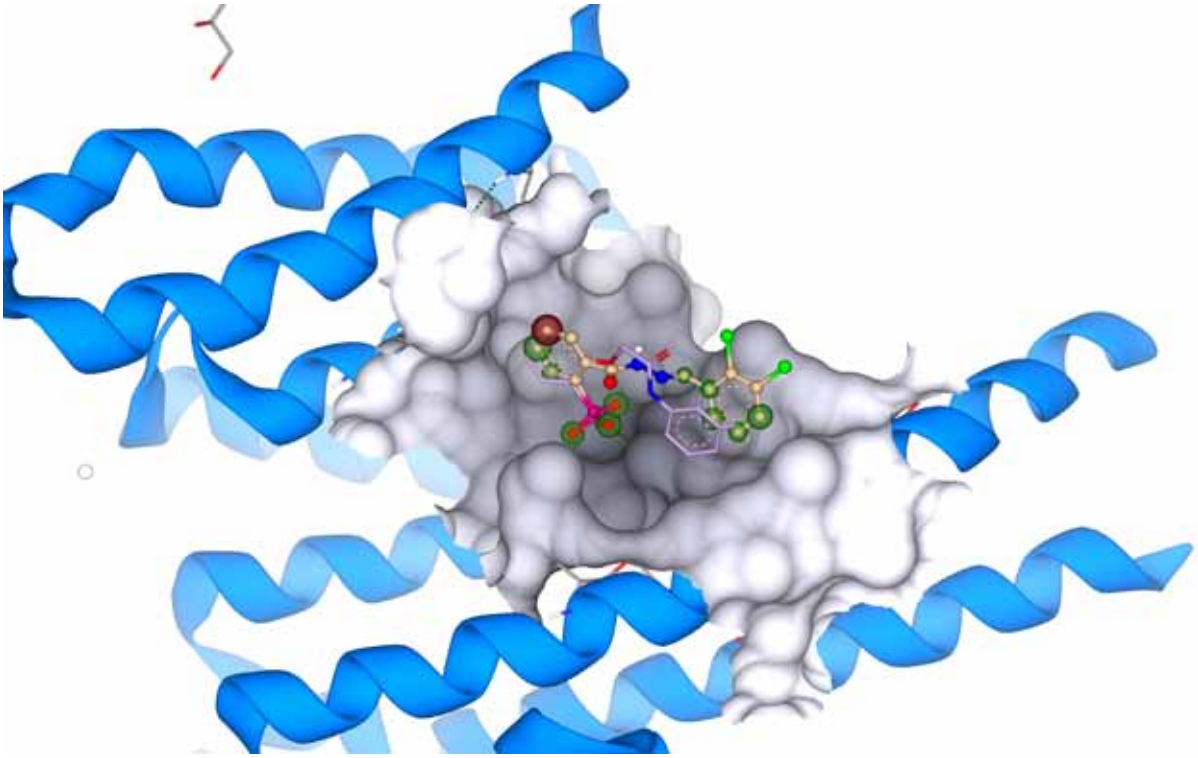
Protein-Protein Interactions (PPIs) can be found in many biological processes. It is assumed that between 130,000 and 600,000 PPIs exist, some play a role in carcinomas others for example in cell-cycle regulation. The 14-3-3 protein family is known for its PPIs, as it is implicated in several diseases and biological processes. Proteins of this family do not have any enzymatic activity, however, they interact and regulate the activity of other proteins.[1] Finding modulators, which could stabilize or inhibit [2] the PPIs, would constitute a tool to modulate these interactions and possibly interfere with undesired biological processes by targeting the corresponding PPIs. Dynamic Combinatorial Chemistry (DCC) is a powerful tool to identify biologically active compounds. The strength of this technique is the amplification of the best binders by the target. We pioneered, DCC for the identification of small-molecule stabilizers of 14-3-3 proteins, representing its first application to a PPI. To mimic a typical PPI of 14-3-3, we used synaptopodin, a 21 amino acid long peptide, in complex with 14-3-3. The activities of the amplified hits of the DCC experiment were confirmed via surface plasmon resonance (SPR) studies.[3] Optimization of promising compounds and crystallography studies are ongoing.



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4) Picture made in SeeSAR 8.1, BioSolveIT GmbH

DEHYDROABIETYLAMINE-BASED CELLULOSE NANOFIBRIL FILMS: A NEW CLASS OF SUSTAINABLE BIOMATERIALS FOR HIGHLY EFFICIENT, BROAD-SPECTRUM ANTIMICROBIAL EFFECTS

Ghada Hassan (1), Nina Forsman (2), Xing Wan (3), Leena Keurulainen (1), Luis M. Bimbo (6), Leena-Sisko Johansson (2), Nina Sipari (4), Jari Yli-Kauhaluoma (1), Ralf Zimmermann (5), Susanne Stehl (5), Carsten Werner (5), Per E. J. Saris (3), Monika Österberg (2), Vânia M. Moreria (1,6)

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Antibacterial coatings are needed in the manufacturing of biomedical devices and tissue engineering-related materials which continuously suffer from microbial colonization.[1] They are also needed to limit the destructive effect of biofilms accumulating onto various surfaces, causing health risks and losses in several industries including food, water and paper. [2]

Nanofibrillated cellulose (CNF) is a renewable biomaterial with high potential to reach commercialization. [3] Currently, it is investigated for its potential applications in the biomedical field due to its biocompatibility, low cytotoxicity and unique chemical properties. [4]

Abietanes, naturally occurring diterpenoids extracted from pine resin, have demonstrated antimicrobial and anti-biofilm activity. [5-6] The approach of surface protection with an antimicrobial coating material includes attaching antimicrobial compounds to a surface. [7] When linked to a surface, the antimicrobial agent is not released or consumed, providing effective and long-lasting surface protection. [8]

Herein we report the discovery of a new class of ecofriendly antimicrobial materials based on the modification of nanofibrillated cellulose (CNF) films with (+)-dehydroabietylamine, a commercially available diterpenic amine with weak antimicrobial activity. [9] With a minimal surface coverage (14 - 25%) and good biocompatibility the materials exhibited clear antimicrobial activity against the gram positive *Staphylococcus aureus*, the gram negative *Escherichia coli*, and the methicillin-resistant *S. aureus* MRSA14TK301. The immobilization of antimicrobial diterpenes on the surface retained the original physicochemical properties of the CNF including moisture buffering and strength.

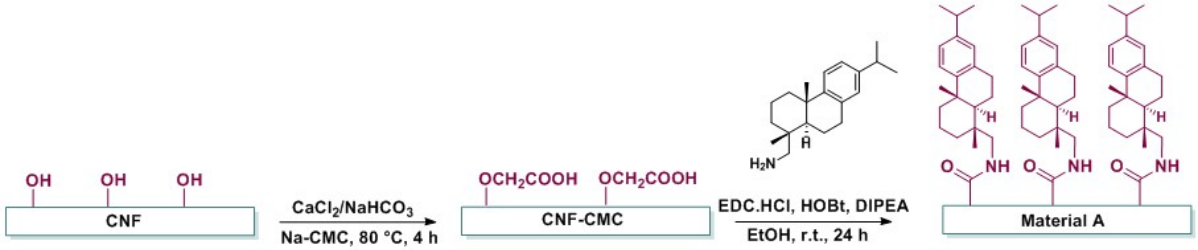

Figure 1. Example showing synthesis of CNF and (+)-dehydroabietylamine hybrid material.

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IN VITRO XENOBIOTIC DOSING PARADIGMS: ANOTHER LAYER OF COMPLEXITY DUE TO THE CELLULAR STAGE

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Over the years of clinical practice, a number of optimal drug dose determination methods have been developed [1,2]. However, the same is not true for *in vitro* experiments on cellular models. It is a well-established paradigm to compare the activity of compounds by effective (EC) or inhibitory concentration (IC). Such methodology assumes the cellular activity of a compound is based on its reversible interaction with the target, which is often either not true or a naïve simplification of cellular events leading to observed effects. This, in turn, raises substantial issues with the scaling of experiments. The usual approach in drug discovery is to first perform high-throughput screening using small-volume, small-culture-surface multi-well plates. Moving to larger culture dishes with different geometric parameters for more detailed experiments then often requires a reassessment of EC/IC. A more universal paradigm has been already proposed by Doskey *et al.* to use effective dose (ED) expressed as mol of substance per cell [3].

Here we add another layer of complexity to the issue raised. It is assumed that established cell lines are either homogeneous or stably heterogeneous. HL-60 cell line is an acute myeloid leukemia model characterized by a well-defined hierarchy of maturation stages. We have shown that stage profile is sensitive to culture density. In particular, low cell culture density increased the fraction of primitive cells (which include clinically critical leukemia stem cells (LSCs)). Three HL-60 sublines have been established: Primitive, Standard and Mature. They were next used as a screening platform for novel anthrapyridazone derivatives. A potential LSC-active compound was found (C123). Furthermore, we have confirmed the usefulness of ED expressed as moles of substance per cell. We have tested three xenobiotics: ethanol (EtOH), dimethylsulfoxide (DMSO) and idarubicin (IDA). While EtOH dose was well-described by IC, IDA required the use of ED. However, neither of these standards was adequate for DMSO which is a known differentiation inducer [4].

The additional layer of complexity described in our work requires a novel paradigm of dose expression which we propose as mol of substance per cell in a specific maturation stage.

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PURINE NUCLEOSIDE ANALOGS AS HIGHLY POTENT LEADS FOR THE TREATMENT OF HUMAN AFRICAN TRYPANOSOMIASIS

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Human African Trypanosomiasis (HAT) is a deadly infectious disease caused by *Trypanosoma brucei* spp. parasites. This vector-borne disease, prevalent in sub-Saharan Africa is spread via bites of infected tsetse flies. The disease course is characterized by a two-stage disease progression, linked to parasite distribution in the body. A first, often non-symptomatic stage occurs when parasites enter the haemolymphatic system. Later, when parasites cross the blood-brain barrier (stage-II), patients develop neurological symptoms such as altered sleep-wake cycles, hence the more common name for HAT being sleeping sickness.

Available therapeutics suffer from major drawbacks such as: they only show efficacy in stage-I disease; high inherent toxicity (arsenicals); the need for systemic administration, which is challenging in rural areas in Africa. Finally, drug resistance against available treatments is on the rise. This showcases the pressing need for novel therapeutic options.

Nucleoside analogues have found wide-spread use as antivirals and in oncology. While some nucleoside analogues were reported to have activity against *T. brucei* spp., systematic screening of nucleoside libraries is not a common practice. *T. brucei* parasites are unable to assimilate the purine ring (no *de novo* purine synthesis), and therefore must rely on salvage of host purines to meet their high demand. Hence, purine nucleosides analogues might interact with this highly developed salvage pathway, either as inhibitors of specific enzymes or as subversive substrates. This presents a interesting rationale to investigate purine nucleoside analogues as a means to discover new bio-active hits.

In this presentation, we will discuss the discovery of a new class of purine nucleoside analogues characterized by potent *in vitro* activity against *T. brucei*. Additionally, results from the evaluation of the frontrunner analogue in acute as well as CNS-stage mouse models of HAT will be presented. This derivative was shown to be orally bioavailable and able to cross the blood-brain-barrier, marking it as a highly promising lead for the treatment of HAT.

OPEN SOURCE TUBERCULOSIS (OSTB) SERIES 3: SMALL MOLECULE INHIBITORS OF NON-REPLICATING MYCOBACTERIUM TB

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3) GSK Tres Cantos, Madrid, Spain

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (*Mtb*) and is one of the top 10 causes of death worldwide.[1] The World Health Organisation estimates that 25% of the world's population have latent TB, with a 5–15% lifetime risk of those individuals falling ill with the disease due to regrowth of the dormant, non-replicating (NR) *Mtb* residing in their tissues. Therefore, treatment of the latent TB infection represents an important strategy for preventing the progression of the disease. Current treatments involve administering isoniazid, rifapentine, or rifampin over 3 to 9 months, depending on the regimen.[2] Hence, an urgent need for short-term therapies to eliminate dormant bacilli and reduce the global burden caused by TB.

Guided by open source principles, the Open Source Tuberculosis (OSTB) consortium is trying a different approach to curing TB. All data is open, and anyone can contribute.[3] Research follows the 'Six Laws'[4] with the aim of speeding up the drug discovery process. OSTB Series 3 arose from collaborative work performed by GSK and Cornell University in 2015.[5] Nine novel bactericidal scaffolds were discovered by a high-throughput screen of 270,000 compounds from GSK's library. Amongst these, **OSTBS83** was identified as a selective and potent inhibitor of NR *Mtb* with low toxicity towards human hepatocellular carcinoma cell line, HepG2 (**Figure 1a**). These desirable properties make **OSTBS83** an attractive starting point for lead optimisation. Herein, we present our structure activity relationship studies to date, with current synthetic efforts focusing on making subtle changes to the aromatic core and amide tether to improve potency (**Figure 1b**).

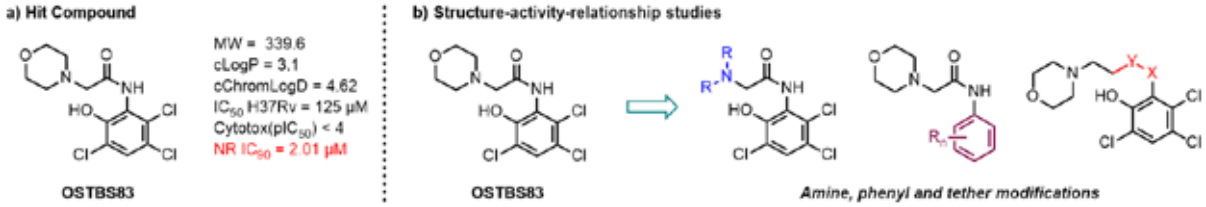

Figure 1: Lead optimisation of **OSTBS83**.

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STRUCTURE OF MEMBRANE BOUND PYROPHOSPHATASE FROM THERMOTOGA MARITIMA IN COMPLEX WITH IMIDODIPHOSPHATE AND N-[(2-AMINOBENZO[d]THIAZOL -6-YL)METHYL]-1H-INDOLE-2-CARBOXAMIDE

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Membrane bound pyrophosphatases (mPPases) are large homodimeric integral membrane proteins and can be found in human pathogens such as *Plasmodium* species (malaria).[1] These enzymes couple the hydrolysis of pyrophosphate (PP_i) to pumping of H^+ or Na^+ ions, generating an electrochemical potential across the acidocalcisomal membrane. This task is necessary for the parasites since PP_i, a by-product from many biosynthetic pathways, in too high concentrations may disturb physiological reactions. Although mPPases play an essential role for many pathogenic protozoan parasites they do not exist in humans, thereby making them promising drug targets.The first structure of a mPPase was solved in the Goldman laboratory.[2]

Our aim is to develop novel mPPase inhibitors capable of disrupting this key ion gradient of pathogenic protozoan parasites in order to decrease their viability. So far, mainly phosphorus-containing inhibitors of mPPases have been reported, limiting their therapeutic utility. However, through screening efforts of *Thermotoga maritima* PPase we found novel organic inhibitors. The best hit compound inhibited the enzyme activity uncompetitively with an IC_{50} of 1.7 μM.[3] The binding mode was solved by X-ray crystallography at 3.7 Å resolution together with the substrate analogue imidodiphosphate. The hit compound binds to the protein monomer near the exit channel, forming a hydrophobic clamp that locks the enzyme conformation in the closed state and thereby prevents hydrolysis and sodium pumping activity.

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SYNTHESIS, ANTICANCER EVALUATION AND MECHANISM OF CYTOTOXIC ACTIVITY OF 3-HYDROXY-3-PYRROLIN-2-ONES BEARING THENOYL FRAGMENT

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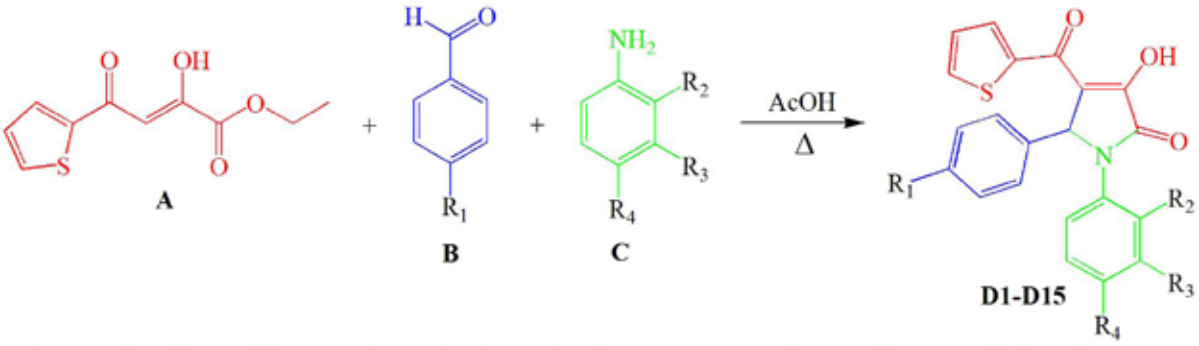
In order to make a progres in discovering a new agents for chemotherapy with improved properties and bearing in mind the fact that substituted 3-hydroxy-3-pyrrolin-2-ones belong to a class of biologically active compounds [1,2], series of novel 1,5-diaryl-4-(2-thienylcarbonyl)-3-hydroxy-3-pyrrolin-2-ones were synthesized (**Scheme 1**) and characterized. All compounds were examined for their cytotoxic effect on human cancer cell lines HeLa and MDA-MB 231 and normal fibroblasts (MRC-5). Four compounds (**D10**, **D13**, **D14**, and **D15)** that showed the highest cytotoxicity were selected for further experiments. Results obtained by investigating mechanisms of cytotoxic activity suggest that selected 3-hydroxy-3-pyrrolin-2-one derivatives in HeLa cells induce apoptosis that is associated with S phase arrest (**D13**, **D15**, and **D10**) or unrelated to cell cycle distribution (**D14**). Additionally, to better understand their suitability for potential use as anticancer medicaments we studied the interactions between biomacromolecules (DNA or BSA) and **D13** and **D15**.



D1 R_1=R_3=R_4= H, R_2= CH_3
D2 R_1=R_2=R_3= H, R_4= CH_3
D3 R_1=R_2=R_3= H, R_4= OH
D4 R_1=R_2=R_3= H, R_4= Cl
D5 R_1=R_2=R_3= H, R_4= Br

D6 R_1=R_2=R_3= H, R_4= I
D7 R_1= NO_2, R_2=R_3= H, R_4= Cl
D8 R_1= NO_2, R_2=R_3= H, R_4= Br
D9 R_1= NO_2, R_2=R_3= H, R_4= I
D10 R_1= Cl, R_2=R_3= H, R_4= CH_3

D11 R_1= Cl, R_2=R_3= H, R_4= Cl
D12 R_1= Cl, R_2=R_3= H, R_4= Br
D13 R_1= OCH_2Ph, R_2=R_4= H, R_3= NO_2
D14 R_1= OCH_2Ph, R_2=R_3= H, R_4= NO_2
D15 R_1= OCH_2Ph, R_2=R_3= H, R_4= Cl

Scheme 1 **S**ynthetic pathway towards 1,5-diaryl-4-(2-thienylcarbonyl)-3-hydroxy-3-pyrrolin-2-ones (**D1-D15**).

Acknowledgments: The authors are grateful to the Ministry of Education, Science and Technological Development of the Republic of Serbia for financial support (Grant 172011).

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STRUCTURE-ACTIVITY RELATIONSHIP-GUIDED SYNTHESIS AND IN VITRO CHARACTERIZATION OF GATA4 AND NKX2-5 PROTEIN-PROTEIN INTERACTION MODULATORS

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Cardiovascular disease is today the major cause of death and disease in developed as well as developing countries.[1] Heart failure alone affects more than 23 million people globally and imposes a huge economic burden for societies.[2] Cardiac transcription factors (TF), such as GATA4 and NKX2-5, regulate both physiological and pathophysiological processes in the heart. For example, a physical interaction of these two TFs is involved in stretch-induced cardiomyocyte hypertrophy. In our previous studies we have demonstrated that isoxazole hit compound inhibiting the GATA4-NKX2-5 transcriptional synergy attenuates cardiomyocyte hypertrophy in vitro[3] and improves cardiac function in vivo in experimental models of myocardial infarction and hypertension.[4]

In this work, we continued the optimization of the original isoxazole hit compound by synthesizing alternative northern, central and southern parts. The compounds were tested in the luciferase assay to examine the inhibition of the transcriptional synergy of the GATA4 and NKX2-5. Additionally, the most potent compounds were tested in luciferase assays for NKX2-5 and GATA4 activity individually. Furthermore, when cytotoxicity of the compounds was evaluated in MTT assay in the COS-1 cell line, it correlated with the inhibition of GATA4 activity. Finally, the most promising compounds were tested for antihypertrophic response in a cell-based assay by measuring BNP promoter activity in a rat neonatal cardiomyocytes.

In summary, we have synthesized and successfully identified inhibitors of GATA4 and NKX2-5 transcriptional synergy, which potently inhibit hypertrophic response in neonatal cardiomyocytes.

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APPROACH TO THE TOTAL SYNTHESIS OF GULMIRECIN B

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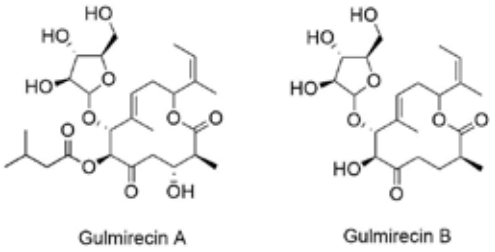
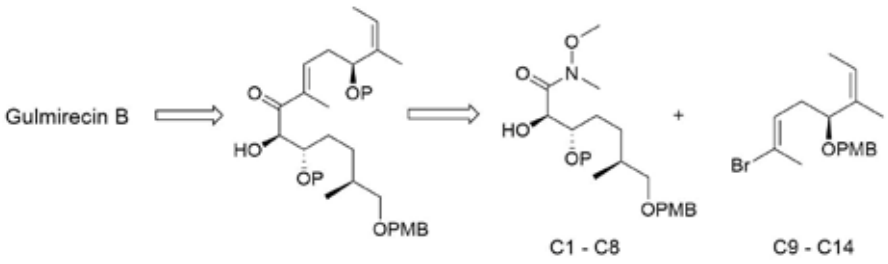
Multinational hospitals have had to deal with the number of resistant bacteria growing and evolving, leading to sickness and death caused by multiresistant bacteria.[1] The organic compounds Gulmirecin A and B were isolated by Nett et al. in 2013[2] with both substances demonstrating antimicrobial activity, especially against MRSA (Methicillin-resistant-stapphyloccocus aureus).[2]



The Gulmirecins are twelve-membered macrolactones with four stereocenters. Each macrocycle contains two alkene functions, therefore, they are interesting target molecules for a total synthesis.Up to this point there are two total synthesises published for the analog structures of disciformycin.[3][4] In Prof. Maiers working group, different approaches are investigated to build up the core structure of Gulmirecin B and recently the synthesis of the C1-C12 fragment was published.[5]



In our current approach, the macrolactone is constructed from two parts. A C1-C8 fragment and a C9-C14 fragment. The first fragments containing the C6-C7 diol originated from D-tartrate whereas the second part is synthesized from D-malic acid.

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STUDY OF THE 3-(PYRAZOL-4-YL)INDOLE PHARMACOPHORE MOIETY: DEVELOPMENT OF NOVEL ANTICANCER AGENTS

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Pyrazole and indole are known moieties, which have found interest as pharmacophores in drug discovery. These days, cancer is one of the main causes of deaths worldwide; thus there is an indispensable need to synthesize new drugs with intended anticancer activity. Very important compounds with such characteristics and properties, including indole or/ and pyrazole core in their main scaffold, are Doramapimod, Bisindole maleimides, Staurosporine, Meridianines, etc. These compounds, have the ability to inhibit proliferation, invasion, and metastasis in cancerous cells, by interfering in complex biological signaling pathways, but with the problems of toxicity and limited use, still remaining.

Our goal is the development of potent and selective inhibitors, based on these two interesting cores, which depending on their substitution and their physicochemical characteristics, will be specific for the treatment of different types of malignant diseases. Prompted by the above, here we describe the design and synthesis of several analogues of the above leads, including both pyrazole and indole scaffolds in their main scaffold. The new compounds showed significant anticancer activity against several cancer cell lines (WM2664 malignant metastatic melanoma0 (less than 1 μM), T24 urinary bladder cell line) and a variety of molecular targets (TDP2, PIM1, CLK1, CLK4, and GSK3b kinases). According to SAR, and in silico studies, the new inhibitors, depending on the substitution of the 3-(pyrazol-4-yl)indole moiety, bind selectively in the active sites of the above enzymes (Figure 1).

Figure 1: Our compound in the active site of PIM1.

SYNTHESIS AND ANTITUMOUR POTENTIAL OF MONO- AND TRI-O-BENZOYLATED CLEISTENOLATE ANALOGUES

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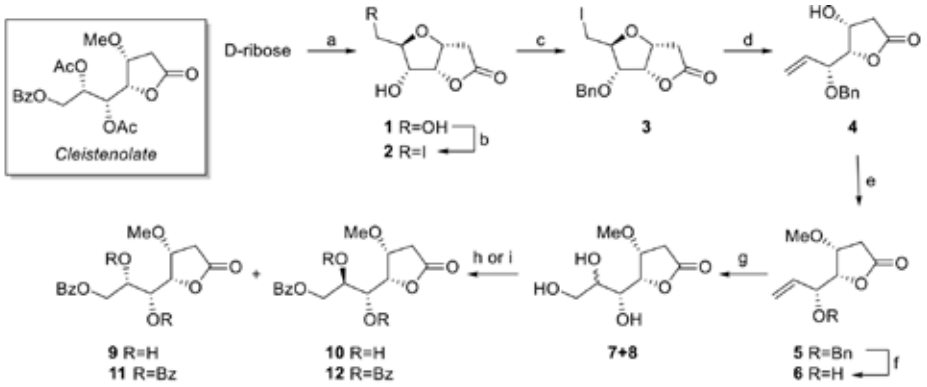
Naturally occurring butanolide, (−)-cleistenolate, was isolated from the leaves of subtropical plant *Cleistochlamys kirkii* (Benth.) Oliv., Annonaceae in 2017.[1] Herein, we report the synthesis of its mono- and tri-*O* -benzoylated analogues from the commercially available chiral precursor, d-ribose (Scheme 1).

In vitro antiproliferative activities of synthesized compounds against a number of human tumour cell lines and single normal cell line are recorded and compared with those recorded for the commercial antitumour agent doxorubicin. These results will be presented and discussed in detail.



Scheme 1. (a) Meldrum's acid, t$BuNH_2$, DMF; (b) I_2, Imidazole, Ph_3P, THF; (c) BnBr, Ag_2O, AgOTf, CH_2Cl_2; (d) Zn dust, 4:1 THF/H_2O; (e) MeI, Ag_2O, AgOTf, Et_2O; (f) $TiCl_4$, CH_2Cl_2; (g) OsO_4, NMO, 10:1 Me_2CO/H_2O; (h) BzCl (1.05 eq), CH_2Cl_2, Py, **9** and **10**; (i) BzCl (10 eq), CH_2Cl_2, Py, **11** and **12**.

Acknowledgment: The work was supported by a grant from Ministry of Education, Science and Technological Development (Project 172006), and (in part) by a research project from the Serbian Academy of Sciences and Arts (Grant No. F-130).

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DESIGN, SYNTHESIS AND EVALUATION OF MICRONEUROTROPHINS, NOVEL SYNTHETIC AGONISTS OF NEUROTROPHIN RECEPTORS

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Neuronal cell death by apoptosis is the “end point” of many human neurological disorders, including Alzheimer’s, Parkinson’s, and Huntington’s diseases, stroke/trauma, amyotrophic lateral sclerosis and ocular pathologies as glaucoma, retinitis pigmentosa, diabetic retinopathy and age-related macular degenaration. Neurotrophins control neuronal cell fate and function acting through two classes of cell surface receptors, the Trk family of receptor tyrosine kinases and the p75NTR, a member of the tumour necrosis factor receptor superfamily. The neurotrophin NGF sends its survival signals through activation of TrkA and can induce death by binding to p75NTR.1 Its therapeutic usefulness though is compromised by its polypeptidic nature and limited penetrance to the blood-brain barrier (BBB).
Based on our previous studies, BNN27 an analog of the neurosteroid dehydroepiandrosterone featuring a 17-spiro epoxy moiety, has been shown to bind specifically the NGF receptors TrkA and p75NTR at nanomolar concentrations (Kd: 1.86±0.4nM and 3.9±1.2nM respectively). Upon binding BNN27 induces down-stream neuronal survival-related TrkA signaling and controls specific p75NTR-mediated signaling of neuronal cell fate. In vitro experiments have shown that BNN27 effectively rescues from apoptosis NGF dependent and TrkA positive sympathetic and sensory neurons and in vivo studies evidence that BNN27 synergizes with NGF in promoting axonal outgrowth and effectively rescued NGF-dependent and TrkA-positive sympathetic and sensory neurons from apoptosis, in vitro, ex vivo and in vivo in NGF-KO mice. The efficacy of synthetic microneurotrophins in protecting neurons from apoptosis was tested in various experimental animal models of neurodegenerative diseases with excellent results. Biomolecular STD-NMR and in silico studies have provided evidence for the potential hot spots of interaction of BNN27 at the neurotrophin receptors and their complexed forms with NGF.2-4
In the context of our ongoing efforts for microneurotrophins development we have conducted a lead optimization phase comprising a steroidal focused library with analogs bearing structural modifications at the 17 position of the steroidal core, which led to the more potent lead compound BNN237. The design was guided by the increase of the van der Waals interactions in the predicted binding sites and the improvement of the pharmacokinetic profile i.e. lipophilicity tuning, optimized BBB membrane permeability, metabolic stability.
Microneurotrophins BNN27 and BNN237 are lead molecules for the development of neurotrophin receptor modulators, with potential therapeutic applications in neurodegenerative diseases, brain trauma and neuropathic pain.

Acknowledgement
This work was supported by the project “DINNESMIN: under the Action “Action for the Strategic Development on the Research and Technological Sector”, funded by the Operational Programme "Competitiveness, Entrepreneurship and Innovation" (NSRF 2014-2020) and co-financed by Greece and the European Union (European Regional Development Fund).

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THE IMPACT OF INFLUENZA A M2 TRANSMEMBRANE DOMAIN AND ADAMANTANE-BASED LIGANDS ON PROPERTIES OF DMPC BILAYERS: DSC, ssNMR SPECTROSCOPY, X-RAY SCATTERING, AND MD SIMULATIONS

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The effects in dimyristoylphosphatidylcholine (DMPC) bilayers of including the influenza A M2 protein transmembrane domain (M2TM) with or without an six-fold excess of amantadine (*Amt*) or the synthetic analog spiro[pyrrolidine-2,2′-adamantane] (*AK13*) were studied using differential scanning calorimetry (DSC), small- and wide-angle x-ray scattering (SAXS and WAXS), solid state NMR (ssNMR) and molecular dynamics (MD) simulations. The influence of the M2TM on the DMPC bilayers without or with drug was evaluated by DSC and SAXS. At low peptide concentrations, two lipid domains were observed that likely correspond to the M2TM boundary lipids and the bulk-like lipids. At high peptide concentrations, one domain was identified which constitute essentially all of the lipids which behave as boundary lipids. MD simulations, and ^{1}H, ^{31}P ssNMR showed that M2TM in apo form or drug-bound form span the membrane interacting strongly with lipid acyl chain tails and the phosphate groups of the polar head surface. The ^{13}C ssNMR experiments allow the inspection of excess drug molecules and the assessment of its impact on the lipid head-group region. The MD simulations showed that the drugs anchor through their ammonium group with the lipid phosphate and occasionally with M2TM asparagine-44 carboxylate groups. According to SAXS, WAXS and DSC, in the absence of M2TM both drugs exerted a similar perturbing effect on the bilayer at low concentrations. Interestingly, at the same concentrations when M2TM is present, the *Amt* and, to a lesser extent, *AK13* caused a significant disordering of chain stacking. This effect is likely to the stronger ionic interactions of *Amt* primary ammonium group with phosphate groups, compared with the secondary buried ammonium group in *AK13*, and to the preference of *AK13* to locate in closer vicinity to M2TM compared to *Amt*.

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DEVELOPMENT OF ALLOSTERIC INHIBITORS OF ColH USING DCC STRATEGY

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The growing number of antibiotic-resistant bacteria represents one of the biggest risks to public health, leading to rapid emergence of infections that are impossible to treat.[1] Therefore, there is an urgent need for discovering novel targets and antibiotics with novel mechanisms of action. Due to the arising problem of antibiotic resistance, particular emphasis has been put on targeting bacterial virulence as an alternative approach for fighting microbial infections.[2] The resulting anti-virulence agents will preserve the commensal microbiome and are expected to be less prone to the development of resistance than conventional antibiotics. The Gram-positive bacterium *Clostridium histolyticum* is responsible for high mortality rates worldwide. It produces collagenase ColH as a virulence factor, an attractive target for the treatment of *C. histolyticum*-derived infections.[3]
The main problem with protease inhibitors is their lack of stability under physiological conditions, as well as their lack of selectivity towards human matrix metalloproteases (MMPs), which makes them unsuitable candidates for antibacterial treatment in *in vivo* models. In our work, we aim to discover allosteric inhibitors of ColH, which do not have to contain a zinc-binding motif. To reach this goal, we are using dynamic-combinatorial chemistry strategy (DCC), a powerful tool that accelerates drug discovery in its early stages to a significant extent.[4,5,6] The overall idea is to block the active site of ColH with a known inhibitor and to screen the resulting complex against a dynamic combinatorial library (DCL). This results in shifting of the equilibrium and leads to selection and amplification of the strongest allosteric binders (Figure 1). Among various reactions that can be performed using this method, we selected the acylhydrazone formation. The reaction is performed in acetate buffer (pH=5), as by using the thermal shift assay we observed the protein to be stable under these conditions. In each DCC experiment, we use approximately 2–3 aldehydes and 8–12 hydrazides (Figure 2). Experiments are analyzed by using a liquid chromatography-mass spectrometry technique (LC-MS), which allows separation of complex mixtures of possible products, as well as assignment of compounds by their mass.

Figure 1. Novel DCC approach for discovering allosteric inhibitors of ColH

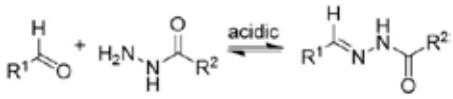

Figure 2. Reversible reaction to be used in protein-templated DCC

By using this strategy, we obtained several hits with amplification up to 800%. These hits were synthesized and will be further examined for their potency against ColH. Having these results in hand, we will thoroughly modify the structures of the initial hits to obtain more potent inhibitors. This will represent the first application of DCC for the discovery of novel inhibitors of ColH and for allosteric inhibitors in general.

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A NEW APPROACH TO ACCESS α-ARYLATED AMINES. ATOM-ECONOMIC ZIRCONIUM CATALYZED HYDROAMINOALKYLATION

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α-Arylated amines are important building blocks in pharmaceuticals, and consequently several routes have been developed for their preparation, including organic and organometallic processes. Organic methods involve reductive amination reactions (Mignonac reaction), Mannich-like reactions and reactions between phenyllithium derivatives and imines.[1] In organometallic chemistry, both excited and ground state transition metals have been reported to introduce the aryl group via $C_{sp}^3 - C_{sp}^2$bond formation at the α-carbon of the amine.[2] Another approach to obtain these α-arylated amines is to activate the C-H bond of a benzylamine to introduce the alkyl group via $C_{sp}^3 - C_{sp}^3$ bond formation.[3] Here we show that α-arylated primary and secondary amines can be prepared via the zirconium catalyzed hydroaminoalkylation of alkenes. This is a 100% atom economic reaction that makes use of common commercially available starting materials and catalysts. With $Zr(NMe_2)_4$ the catalytic hydroaminoalkylation of alkenes with a variety of N-substituted benzylamines has been achieved (**Figure 1**). Substrate controlled regioselectivity in this reaction will be demonstrated with different substituents on the alkene and amine starting materials (alkyl, aryl, SiR_3). Efforts to apply this synthetic approach toward the efficient assembly of pharmaceutically relevant α-arylated amine building blocks and heterocycles will be reported.

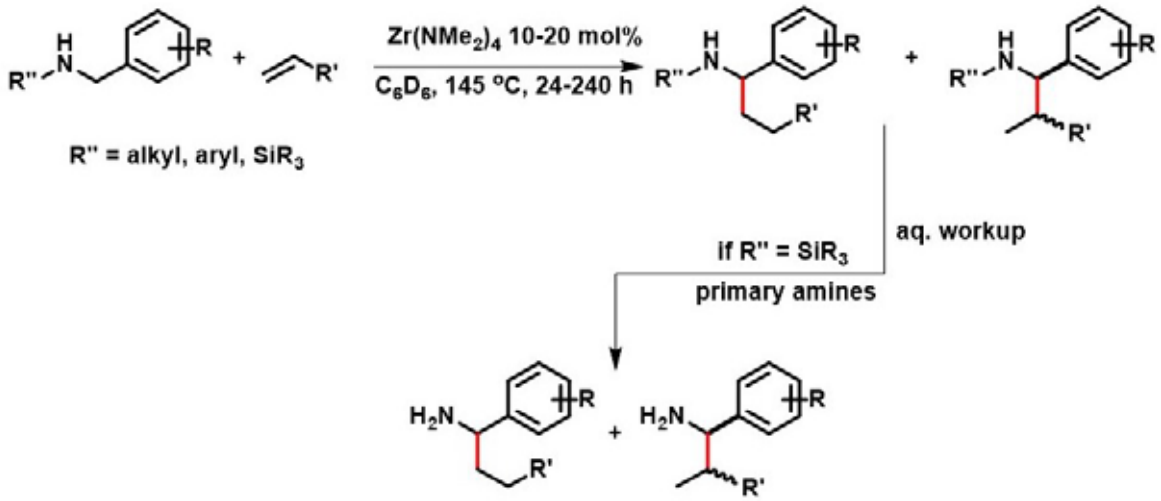

Figure 1. Zirconium-catalyzed hydroaminoalkylation of alkenes with benzylamine derivatives as substrates.

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INDOLE-BASED BIFUNCTIONAL ALDOSE REDUCTASE INHIBITORS AS PROMISING THERAPEUTIC DRUGS OF DIABETIC COMPLICATIONS: STRUCTURE – ACTIVITY RELATIONSHIPS

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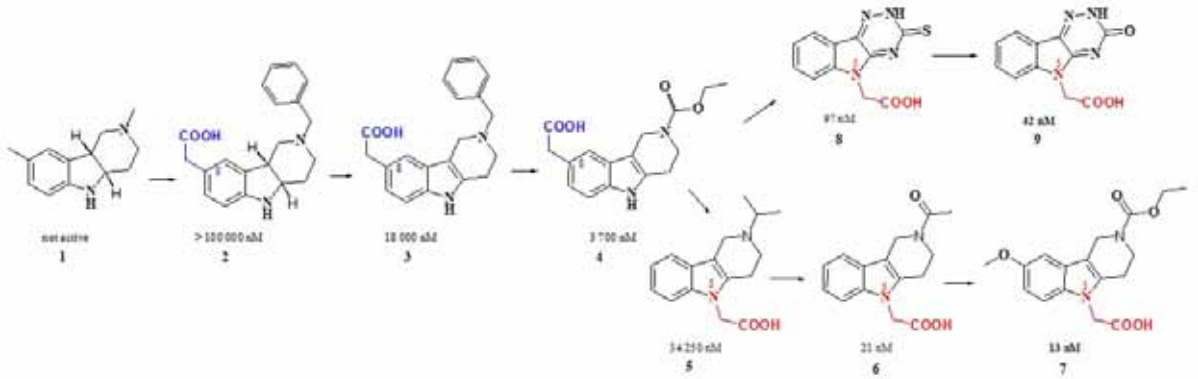
Aldose reductase (AR), the first enzyme of the polyol pathway, has been implicated in the pathophysiology of diabetic complications. Aldose reductase inhibitors thus present a promising therapeutic approach to treat a wide array of diabetic complications. Substituted pyridoindoles are an interesting group of compounds with a plethora of biological activities. Starting from the efficient hexahydropyridoindole antioxidant stobadine (**1**), a series of tetrahydro- and hexahydropyridoindoles carboxymethylated in position 8 (compounds **2-4**) was synthesized and characterized as AR inhibitors with mild efficacy (IC/50/s depicted) and selectivity yet with significant antioxidant (AO) effect as an additional biological activity.[1]



Structure optimization of the tetrahydropyridoindole scaffold by shifting the carboxymethyl pharmacophore from position 8 to position 5, yielded derivatives (compounds **5-7**) with markedly enhanced inhibition efficacy and selectivity, yet with abolished AO activity.[2] In this series, the AR inhibition efficacy increased with decreasing basicity of N-2 nitrogen. Mercaptotriazine structural alternative (compound **8**) yielded highly efficient AR inhibitor with high selectivity and reasonable AO activity.[3] In further structure optimization efforts, isosteric replacement of sulfur in compound **8** with oxygen provided compound **9** with increased AR inhibition efficacy and markedly improved selectivity, yet with diminished AO activity. Molecular obesity indices along with the criteria of Lipinski's 'rule of five' point to an excellent "drug-likeness" of the compounds, even with prospects of further structure optimizations.

Acknowledgement: This work was supported by VEGA 2/0005/2018, VEGA 1/0670/18, VEGA 1/0127/18 and Slovak Research and Development Agency under the contract NO. APVV-15-0455.

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NOVEL PYRIDAZINONE DERIVATIVES AS SELECTIVE BUTYRYLCHOLINESTERASE INHIBITORS

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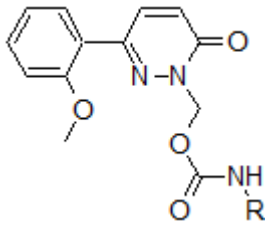
In the current study, new (6-oxo-3-(2-methoxyphenyl)pyridazin-1(6*H*)-yl)methyl substitutedcarbamate derivatives were synthesized and evaluated for their ability to inhibit electric eel acetylcholinesterase (*Ee*AChE) and equine butyrylcholinesterase (eqBuChE) enzymes. According to the inhibitory activity results, compound 16c (76.96%; IC_{50}= 12.83 mM) was the most active eqBuChE inhibitor among the synthesized compounds. Furthermore, compounds 13c, 14c, and 16c selectively inhibited the eqBuChE enzyme, while the compounds 3c, 6c, and 7c were found to be dual inhibitors of *Ee*AChE and eqBuChE. Obtained biological activity results were also supported by molecular docking studies.



R: Phenyl (3c), 4-fluorophenyl (4c), 4-chlorophenyl (5c), 4-methoxyphenyl (6c), 4-methylphenyl (7c), methyl (8c), ethyl (9c), propyl (10c), 2-propyl (11c), butyl (12c), pentyl (13c), hexyl (14c), cyclohexyl (15c), heptyl (16c).

This work was supported by The Scientific and Technological Research Council of Turkey (TUBITAK) (grant number 117S872).

SYNTHESIS AND BIOLOGICAL POTENTIAL OF NOVEL STEROIDAL 6,19-EPOXY DERIVATIVES

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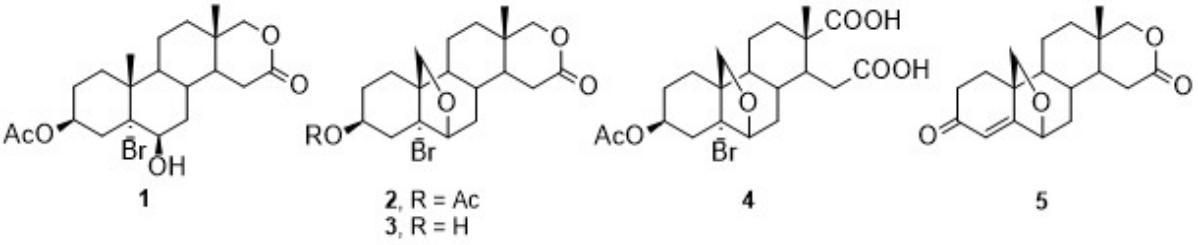
According to World Health Organisation, cancer is the second leading cause of death globally. Having in mind this fact and large number of cancer types, one of the main goals of medicinal chemists research is obtaining effective and selective antitumor agent. Steroidal compounds are commonly used in treatment of hormone dependent cancers. For these compounds is very important their good antiproliferative activity, as well as absence of hormonal activity. Taking into account this fact, we have conducted multistep synthesis in order to obtain some D-modified steroids with 6,19-epoxy moiety **2**-**5** (Fig. 1). As a starting compound 5α-bromo-6β-hydroxy derivative **1** was used [1, 2]. Furthermore, *in silico* ADME profile was determined for newly synthesised compounds, as well as, their antiproliferative activity against selected human cancer cells, that was measured *in vitro*. Finally, relative binding affinities of newly synthesized 6,19-epoxides for selected steroid receptors were estimated using fluorescent cell assay in yeast.



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SYNTHESIS AND BIOLOGICAL EVALUATION OF DEHYDROEPIANDROSTERONE 17-SPIRO-CYCLOPROPYL DERIVATIVES WITH NEUROTROPHIC AND NEUROPROTECTIVE ACTIVITY

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Neurosteroids affect survival, development and function of neurons and it has been found that their levels in the brain reduce with aging and in neurodegenerative diseases.Recent studies have shown that the neurosteroid dehydroepiandrosterone (DHEA) acts as neurotrophic factor in the brain and prevents neuronal apoptosis by interacting with the neurotrophin receptors TrkA and $p75^{NTR}$.[1] Neurotrophins are a family of growth factors that regulate proliferation, differentiation and survival of neural cells. This family consists of four growth factors, namely nerve growth factor (NGF), brain-derived growth factor (BDNF), neurotrophin-3 (NT3) and neurotrophin-4/5 (NT-4/5). Each neurotrophin binds to its respective high affinity Trk receptor (NGF to TrkA, BDNF and NT3 to TrkB, and NT4/5 to TrkC) and all neurotrophins withlow affinity to $p75^{NTR}$ receptor. A number of studies corroborated that neurodegeneration is due, at least in part, to changes in expression of neurotrophins and/or their receptors. Nevertheless, DHEA is metabolized in humans into estrogens and androgens, thus its long-term administration is increasing the risk for hormone-dependent cancer. Therefore, DHEA analogues with modifications at position C17 of the steroid skeleton were synthesized aiming to improve the neuroprotective and antiapoptotic activity of the parent molecule, without the undesired hormonal side effects.[2,3,4]

In the current work the synthesis of chiral 17-spirocyclopropyl DHEA derivatives will be described. A variety of pharmacophore groups as substituents of the cyclopropyl moiety were introduced, in order to obtain Structure-Activity-Relationships for neurotrophin mimetic activity. The new compounds were evaluated for their agonistic activity on neurotrophin receptors TrkA, TrkB and $p75^{NTR}$ on NIH-3T3 -stable transfected with each receptor- cells, while their anti-apoptotic activity was evaluated using the neural crest-derived PC12 cell line. Moreover, we tested their effect on inflammatory responses of LPS-stimulated microglial cells.[5] Furthermore, preliminary *in silico* screening studies were performed to examine the possible binding sites of the new compounds on neurotrophin receptors.

Acknowledgement
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NEW ANTI-ALZHEIMER BIOLOGICAL ACTIVE HYBRIDS COMBINING ENONE AND CINAMMATE SCAFFOLDS

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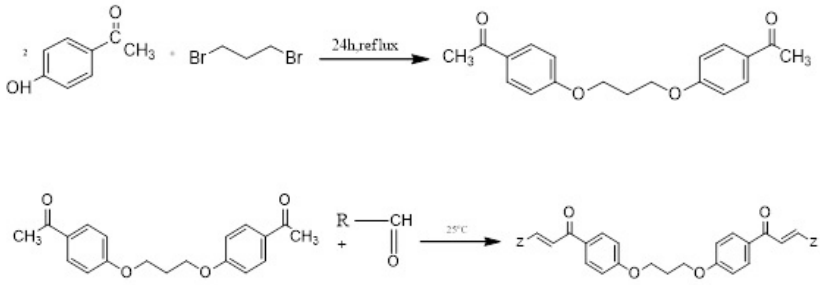
Epidemiological and experimental studies have already established the functional relationship between Alzheimer disease, oxidative stress and inflammation. [1,2,3] The reason that creates AD and other dementias is not fully discovered as well as the links among all these paths. Thus, we attempted to clarify these relationships and introduce new therapeutic agents. Multitarget therapeutic strategy can be used to inhibit two or more biological targets, acting on an enzyme and/or a receptor, or affect an ion channel and a transporter. [4] Therefore it is evident that the treatment of Alzheimer Disease (AD) could benefit from the use of multipotent drugs that present free radical scavenging, anti-inflammatory and AChE inhibitory activity. In the present study it has been synthesized a series of new pleiotropic compounds which have multiple biological activities that uses the enone moiety as basic scaffold. [5,6] Using computer aided drug design and previous biological data from known chalcones and flavonoid derivatives we designed a series of chalcones and bis-substituted chalcone ethers with possible inhibition on achetylocholinasterase and lipoxygenase as well as antioxidant activity. [5,6].



The compounds were tested in vitro for their ability to react with DPPH, ABTS+·, to inhibit lipid peroxidation and their ability to react with luminol. Compounds were evaluated for their ability to inhibit soybean Lipoxygenase, h-15-LOX and AChE, to interact with GSH and to inhibit β-amyloid accumulation. The compounds were studied for cytotoxicity. In vivo anti-inflammatory and behavioral tests were also conducted. The results were characterized based on the structural characteristics and physicochemical properties of the molecules.

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ENCAPSULATION OF 4-MU IN FUNCTIONALIZED PLGA NANOPARTICLES FOR TARGETING LIVER CANCER

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Hepatocellular Carcinoma (HCC) is the most frequent primary liver cancer in adults, and represents the third cause of cancer-related death worldwide. It occurs in the setting of chronic liver disease or cirrhosis due to chronic hepatitis B and C viral infection, alcohol abuse, and nonalcoholic fatty liver disease.[1] The liver injury is characterized by an excessive accumulation of extracellular matrix components including hyaluronic acid (HA). An abnormal production of HA is also closely linked to a cancerous condition, because

stromal HA may create a permissive extracellular microenvironment for tumor progression and metastasis through cancer cell proliferation, migration, and invasion. Thus, HA signaling is expected to be a target for anticancer therapy.[2]

4-Methylumbelliferone (4-MU) is a synthetic coumarin derivative (7-hydroxy-4-methylcoumarin), and it is an effective inhibitor of HA synthesis with potential therapeutic benefits for treating cancer.[3] In spite its positive effects against different diseases, 4-MU manifests a very poor bioavailability in vivo, due to its low aqueous solubility and minimal absorption in gastrointestinal tract, that definitely limits its use in biomedical applications.

The objective of this work is to propose a drug delivery system based on poly(lactic-co-glycolic acid) nanoparticles (PLGA-NPs) loaded with 4-MU, for the treatment of HCC. PLGA-NPs with hydrodynamic diameter of

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OPTIMIZATION OF KINASE INHIBITION AND METABOLIC STABILITY OF PYRAZOLOPYRIDINE INHIBITOR OF YEAST KINASE YCK2

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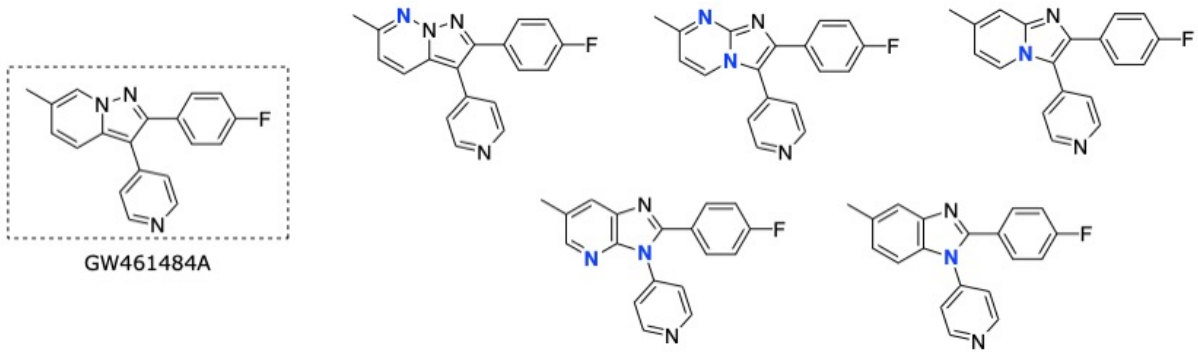
The fungus Candida albicans is a leading cause of nosocomial infections, with mortality rates often exceeding 40% despite treatment.[1] Emerging resistance to existing therapies necessitates the identification of new antifungal mechanisms and the development of new antifungal drugs.[2] Towards this aim we screened the first and second generation Published Kinase Inhibitor Set (PKIS)[3,4]against caspofungin-resistant C. albicans strains. We identified pyrazolopyridimidines that had both single-agent activity and the ability to potentiate the effects of caspofungin. The lead compound GW461484A exhibited 85% growth inhibition in combination with caspofungin relative to caspofungin as a single agent control. However, GW461484A was revealed to have several limitations. First, the compound was rapidly metabolized in liver S9 fractions, potentially due to oxidation of its electron-rich ring system. Secondly, while GW461484 had high activity, the lack of complete inhibition may allow for resistance mechanisms to develop. We sought to address these two issues with a program of iterative medicinal chemistry. We now describe our medicinal chemistry program to improve metabolic stability and increase activity.



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SCALE-UP SYNTHESIS OF INT-767, A POTENT DUAL FXR/TGR5 AGONIST ADVANCED IN CLINICAL STUDY

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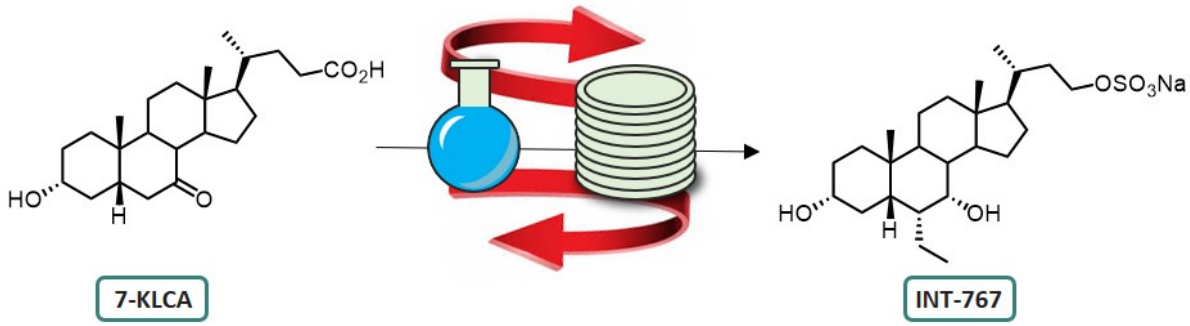
3α,7α,23-Trihydroxy-6α-ethyl-24-nor-5β-cholan-23-sulphate (INT-767) is a semisynthetic bile salt characterized by the presence of a sulphate moiety at C23 position. INT-767 is a dual agonist being able to activate the nuclear receptor FXR with an EC_{50} of 30 nM, and the G-protein coupled receptor TGR5 with EC_{50} of 630 nM.[1,2]

INT-767 has shown promising preclinical activity in both preventing and reversing organ damage due to fibrosis. Recent data demonstrated that INT-767 treatment reduces body weight, improves hepatic bile acid, lipid and glucose metabolism and increases insulin sensitivity in high fat diet-induced obese mice, thus suggesting a great therapeutic potential for treating NAFLD, diabetes, and obesity.[3]

In this communication, we report our ongoing efforts aimed at improving and expediting the large-scale synthesis of INT-767 from readily available 7-keto-lithocholic acid (7-KLCA). A particular attention will be devoted to the discussion of critical steps and the illustration of flow chemistry application in order to perform reactions not feasible or problematic under standard batch conditions.



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NEW ANTICANCER COMPOUNDS WITH DUAL MECHANISMS OF ACTION AS INHIBITORS OF TYROSINE KINASE PROTEIN AND TELOMERASE: IN SILICO STUDIES AND BIOLOGICAL EVALUATION

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Protein tyrosine kinase (PTK) is a pervasive family of signaling enzymes, which catalyze the transfer of the γ phosphate of ATP to tyrosine residues of the substrate protein. Phosphorylation plays a significant role in a wide range of cellular processes, regulating cell division, growth, and differentiation. However, abnormal expression of PTK has relevance to several human diseases, most notably, cancers. Dysregulation is usually linked to tumor formation and progression to metastasis (1). Cancer cell immortalization is also a result of increased activity of telomerase, which is present in about 85% of all tumors. Separately inhibiting telomerase or PTK is often not enough to cell death, therefore combined dual action of inhibiting both enzymes remains a desirable target for cancer therapeutics.

Recent studies imply that anthraquinones derivatives are promising drugs targeting tyrosine kinases (2). To discover new and potent PTK inhibitors, several 9,10-antracenedione derivatives, previously tested in telomerase activity assay, were virtually tested using computational protein-ligand docking by AutoDock Vina to predict bound conformations and free energies of binding for small-molecule compounds to various kinases. The screening included docking to Epidermal Growth Factor Receptor (EGFR), Platelet-Derived Growth Factor Receptor (PDGF-R), AKT-1, c-Kit, B-Raf, and ERK-2. The best results were obtained to c-Kit kinase with combination to 9,10-dioxo-9,10-dihydroanthracen-1-yl pyrrolidine-1-carbodithioate and 9,10-dioxo-9,10-dihydroanthracen-2-yl pyrrolidine-1-carbodithioate with similar scoring. Molecular modeling studies have been confirmed by *in vitro* Universal Tyrosine Kinase Assay Kit and Western blot using specific antibodies.

Overall, our results indicate that novel anthraquinones-based derivatives represent promising anticancer drugs with a new dual mechanism of action.

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IDENTIFICATION OF NEW PSNCBAM-1 DERIVATIVES AS CB1 RECEPTOR ALLOSTERIC MODULATORS

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Cannabinoid receptor type 1 (CB1) can be exploited as a therapeutic target for many pathologies such as obesity, nicotine and alcohol addiction, pain of various origin, nausea and multiple sclerosis. Starting from the CB1 allosteric modulator PSNCBAM-1,[1] compounds **1-4**[2] and **5-8**[3] were designed and biologically evaluated in two recent works. Given their good results in enhancing the binding affinity for the orthosteric reference compound CP 55,940 and in decreasing the receptor functionality, we took in account and combined their structural features, with the aim to synthesize new CB1 allosteric modulators with higher potency and subtype selectivity and to extend the structure requirements for this class of compounds. We designed, synthesized and biologically evaluated three series of derivatives: biphenyl compounds (A), bipyridinyl compounds provided of an amine spatial linker (B) and pyrrolidine-lacking compounds, carrying an amine spatial linker as well (C) (Fig. 1).

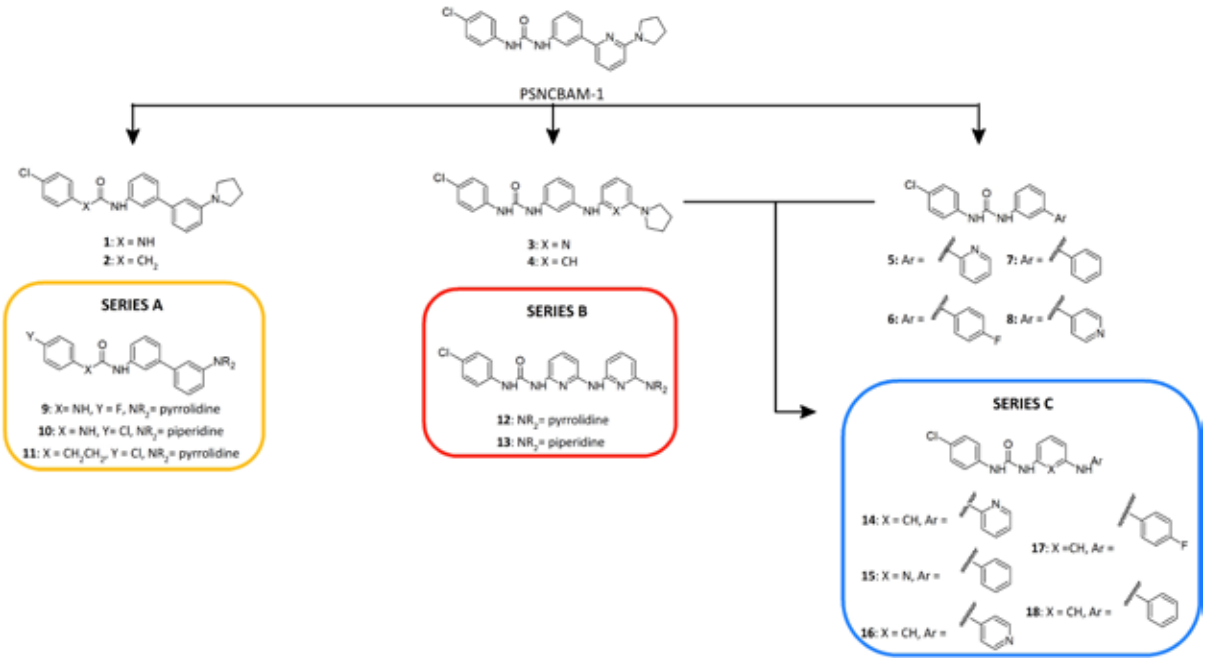

Figure 1. Design of novel structural modifications of PSNCBAM-1 based on the derivatives **1-4**[2] and **5-8**,[3] recently reported in literature.

The new derivatives were tested in radioligand binding assays in hCB1-CHO cell membranes to evaluate their ability to modulate the binding affinity of CP55,940. Then, we assessed their ability to influence the cellular response at CB1 receptor in absence and in presence of different concentrations of the orthosteric compound, by [^{35}S]GTPγS functional assays. **10** and **17** (series A and C, respectively) displayed a positive modulation of agonist binding and a negative influence of the receptor functionality, with a behavior similar to the parental compound PSNCBAM-1.[1] These results might indicate that both the biphenyl moiety in association with the piperidine ring and the contemporary presence of the *p*-fluorophenyl system and the amine spacer, are relevant structural features which could be exploited for future optimizations of this class of compounds.

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DESIGN AND SYNTHESIS OF SMALL-MOLECULES AS TUBULIN COLCHICINE SITE BINDERS FOR CANCER TREATMENT

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Microtubule-targeting agents (MTAs), one of the most common class of drugs used to treat cancer, exert their activity by interfering with microtubule dynamics leading to cell death, in particular during mitosis[1]. Although the great success in the clinic, toxicity and resistance development are their two well-known drawbacks. To overcome these limitations, fragment-based drug discovery (FBDD) represents an interesting approach for finding new starting points for MTAs development, as widely applied in drug discovery[2].

Here, we firstly present the promising outcomes from a FBDD campaign based on X-ray crystallography targeting tubulin, which allowed identifying some compounds able to bind different pockets of tubulin. In particular, it was observed the ability of Fragment 1 (Figure 1) to allocate in the well-known colchicine site, previously validated for tumor treatment[3]. Structural similarity of Fragment 1 with Nocodazole, a well-known antineoplastic agent that has been recently co-crystallized with tubulin at the colchicine site[4], and the capability of both molecules to bind the same tubulin pocket inspired the idea of superimposing both X-ray structures (Figure 1). The good-matching superposition of the X-ray structures guided us in the rational development of new potential antimitotic agents. In particular, we designed and synthesized two series of molecules by introducing different structural modifications on Fragment 1. In the first series, our goal was to identify Fragment 1 key structural features required for target engagement. In the second series, we moved to fragment growth using a computer-aided drug design approach. X-ray crystallography and resazurin assay studies were respectively proposed to evaluate binding ability and interference with cell viability of all synthetized compounds.

Further results from these studies are likely to offer an opportunity for improving antimitotic properties of colchicine site ligand and, hopefully, expand this strategy to new tubulin binders.

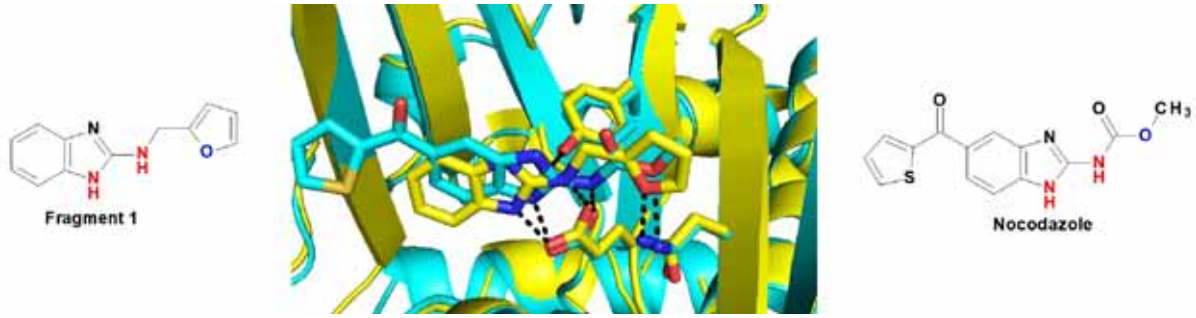

Figure 1 Superimposition of crystal structures of Nocodazole-tubulin (PDB code: 5CA1)[4] and Fragment 1-tubulin complexes.

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IDENTIFICATION, SYNTHESIS AND OPTIMIZATION OF INHIBITORS OF THE PROTEIN TYROSINE PHOSPHATASE SHP2

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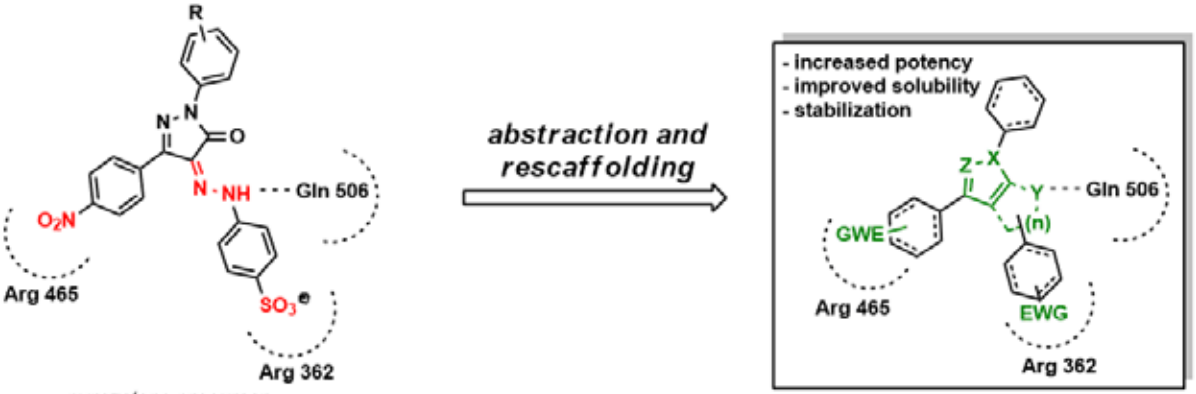

pyrazolone precursor

indole, aza-indole, indazole and aza-indazole derivatives

Protein tyrosine phosphorylation and de-phosphorylation are key events in cellular signal transduction and are often aberrant in cancer. The non-receptor tyrosine phosphatase SHP2 (the PTPN11 gene product) mediates growth factor and cytokine signals, and regulates the activity of the Ras-MAPK pathway. The oncogenic function of mutated SHP2 is related to sustained activation of Ras/MAPK signaling and SHP2 is for example widely up-regulated in infiltrating breast carcinomas. SHP2 activity is responsible for acquired drug resistance to medications targeting MAPK-pathway (like MEK and BRAF inhibitors)[i]. The pharmacological inhibition of SHP2 suppresses mammary gland tumor development by reducing cancer stem cells. By a virtual screening effort with a database of 2.7 million compounds using a homology model of SHP2, the lead structure PHPS1 was identified as a highly active and selective pyrazolone derived SHP2 inhibitor(2). However, this compound class bears three unwanted, non-druglike structural features: (1) a nitro group (ii) a sulfonic acid (iii) and a hydrazone based scaffold. In general, the presence of these functional groups account for chemical and metabolic liability, cytotoxicity as well as low cell permeability. Here we report the development of very potent, selective and in particular drug-like inhibitors of SHP2 by replacing these unfavorable structural features by a rescaffolding of the core unit and searching for bioisosteric substitutes of the unwanted fragments.

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DISCOVERY OF LIGAND STRUCTURE-ACTIVITY RELATIONSHIP BY MASS SPECTROMETRY: IDENTIFICATION OF NEW TUBERCULOSIS INHIBITORS

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A set of tuberculosis fragment inhibitors has been discovered by mass spectrometry. The method is based on the observation of protein-ligand complexes by mass spectrometry.[1] These fragments may compete for common binding sites on the target protein or bind at different sites. Mass spectrometry enables identification of ternary complexes in which two ligands bind to different sites of a target.[2-3]

For a specific target, the result $(P+L_1) + (P+L_2)$ indicates binding to the same site (competitive), while the result $(P+L_1) + (P+L_2) + (P+L_1+L_2)$ shows that L_1 and L_2 bind to different sites (non-competitive). Compound design relies on using a number of competitive fragments linked to a non-competitive fragment. In the next step, the structures of these fragments will be modified using synthetic methods to enhance their activities and produce novel inhibitors.

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PHOTODYNAMIC ACTIVITY OF FREE-BASE AND Zn(II) COMPLEXES OF N-METHYLATED TETRA- AND TRIPYRIDYLPORPHYRINS

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Photodynamic therapy (PDT) is a relatively new, minimally invasive therapeutic procedure that is based on a cytotoxic effect against malignant cells using three main components, photosensitiser (PS), light and oxygen. Porphyrins and other related tetrapyrrole molecules present highly investigated group of PSs for PDT, due to their characteristic photophysical and photochemical properties. Some of their desirable properties are stability, negligible or no toxicity in dark, absorption and fluorescence spectra in visible region and efficient production of the singlet oxygen ($^1O_2$)[1].

Another useful characteristic of porphyrins is a relatively easy chelation on their pyrrole nitrogen atoms that leads to different photophysical and photochemical properties in comparison to free-base porphyrins. It was shown that chelation with Zn(II) and other paramagnetic metals could increase the lifetime of the PS's excited triplet state (^{3}PS*), which increases the possibility of ^{3}PS* to react with molecular oxygen and cellular targets. Chelation can also change the lipophilicity of the molecule, thus it could have two possible ways in improving PDT activity of the PS[2].

Since it was proven that the presence of alkyl chain and overall amphiphilicity plays an important role for PDT[3], the impact of chain length as well as Zn(II) chelation of *N*-methylated pyridylporphyrins was further investigated[4]. Their photophysical and photochemical properties relevant for use in PDT, such as absorption and fluorescence spectra, singlet oxygen production using 1,3-diphenylisobenzofurane (DPBF) fluorescence decrease method, and lipophilicity using *Rf* value and *n*-butanol/water partition coefficient methods will be presented[4].

Finally, photodynamic activity and dark toxicity of both free-base and Zn(II) pyridylporphyrins against melanoma cells will be presented as a part of a study of the effect of a chain length and chelation with Zn(II).

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DESIGN AND SYNTHESIS OF DEHYDROEPIANDROSTERONE-BASED NEUROTROPHIN MIMETICS

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Neuro**t**rophins (NTs) belong to a family of secreted proteins associated by structure and function that bind with high affinity and selectivity to the **T**yrosine **R**eceptor **K**inases (TrkA, TrkB and TrkC), and exert powerful neuroprotective and neurogenic activity, both centrally and peripherally. Furthermore, they bind with low affinity to the **P**an **N**euro**t**rophin **R**eceptor **75** ($p75^{NTR}$), in contrast to their immature forms (pro-neurotrophins), which show high selectivity and affinity for $p75^{NTR}$. However, due to their polypeptidic nature, NTs are not suitable for therapeutic use. Thus, small druggable molecules, mimicking neurotrophin beneficial actions are highly desirable.[1]

The endogenous sex steroid precursor **De**h**y**dro**e**pi**a**ndrosterone (DHEA) is able to activate the neurotrophin receptor TrkA exhibiting neuroprotective activity,[2] while, it inhibits acute microglia-mediated inflammation.[3] We have recently synthesized 17-spiro-epoxy-dehydroepiandrosterone derivatives with anti-apoptotic and neuroprotective activity, selectively mediated through the neurotrophin receptors.[4-6] These compounds, in contrast to the parent molecule DHEA, are not metabolized to estrogens and androgens and exhibit high affinity for the NGF receptor, TrkA.

As a continuation of our studies on steroidal neurotrophin mimetics, we embarked on the synthesis of 17-spiro DHEA derivatives substituted by 6- or 5-membered rings, decorated with a variety of pharmacophores, in order to probe the stereo-electronic requirements for optimum neurotrophic/neuroprotective/neurogenic activity. Preliminary *in silico* studies were performed to examine the possible binding sites of the compounds to neurotrophin receptors.

The new derivatives were evaluated for their agonistic activity for TrkA, TrkB and $p75^{NTR}$, on NIH-3T3 -stable transfected with each receptor- cells, while, their anti-apoptotic activity was evaluated using the neural-crest-derived PC12 cell line. Moreover, their effect on inflammatory responses were tested in microglia cells.

Acknowledgement. This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 765704 (www.euroneurotrophin.eu).

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IDENTIFICATION OF NOVEL PPAR-α/γ AGONIST USING COMPUTATIONAL APPROACH

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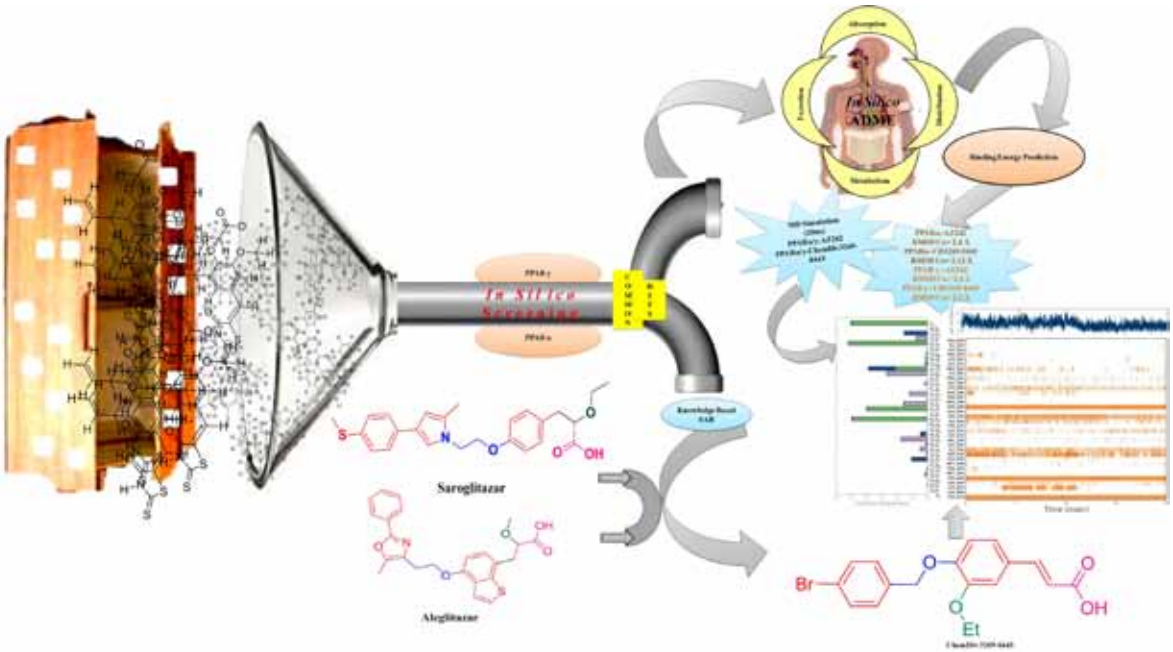
The high incidence of mortality and morbidity due to type 2 diabetes mellitus in the world as well as the increasing risk about the undesirable effects of the current medications have prompted the researcher to develop the more potential drug(s) against the disease. The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptors family and take part in a vital role in the regulation of metabolic equilibrium. They can induce or repress genes associated in adipogenesis, lipid and glucose metabolism. In this study, the PPARα/γ agonistic hits were screened by hierarchical virtual screening followed by molecular dynamics simulation and knowledge-based structure-activity relation analysis. The key amino acid residues of binding pockets of both targets PPARα/γ were acknowledged as essential and were found to be associated in the key interactions with the most potential dual hit (ChemDiv-3269-0443). Obtained potential hit have comparable binding energy and ADME. Stability studies using molecular dynamics (MD) simulation of PPARα and γ complex was performed with the most promising hit. Further, comparative analysis of approved PPARα/γ agonists was done for knowledge-based SAR, which may useful for designing of PPARγ agonistic candidates with anti-hyperlipidemic potential.



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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF POSITIONAL DERIVATIVES OF A SERIES OF N-(PYRAZIN-2-YL)CARBOXAMIDES

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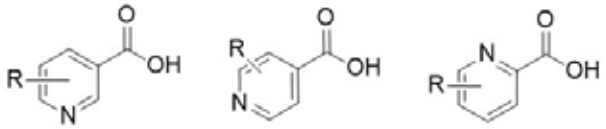
Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*, and is the number one killer of infectious diseases. According to the Global tuberculosis report[1] published by the World Health Organization in 2017 1.6 million deaths were caused by TB and 10 million people developed TB. The disease was successfully controlled by a combination of anti-infective drugs, yet the emerging issues of AIDS, antimicrobial resistance and dropping number of global treatment success prevented the eradication of this disease. TB is a serious health security threat and alternative pathways to induce mycobacterium vulnerability to the treatment must be discovered. As an attempt to develop new antituberculars effective against drugs-sensitive and drug-resistant Mtb, we report on this poster the synthesis of a novel series of compounds based on positional derivatives of picolinic acid that were linked to pyrazine by amidic bond(1). Compounds were prepared by reacting 2-aminopyrazine with different nitrogen containing derivatives of aromatic carboxylic acids (i.e. picolinic acid, 6-chloropyridine-3-carboxylic acid) after activation by carbonyldiimidazole. Reactions were carried out in dichloromethane and stirred overnight. The reaction solution was then evaporated and obtained solid was washed with water (final compounds). All compounds were evaluated for biological activity against selected strains of *Mycobacterium* (*M. tuberculosis* H37Ra, *M. kansasii*, *M. smegmatis)* and chosen bacterial and fungal strains of clinical importance. The minimum inhibitory concentration (MIC) was determined for all tested compounds beside isoniazid, ciprofloxacin and rifampicin as standards. Results of the biological testing and structure activity relationships are discussed on the poster.



R = selection of substituents

(1)

The study was supported by the Ministry of Education, Youth and Sports of the Czech Republic (SVV 260 401) and by Grant Agency of Charles University (project C-C3/1572317).

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ANTIMICROBIAL PROPERTIES OF A CATIONIC STEROID

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Currently, multidrug-resistant infections are one of the most important threats, driving the search for new antimicrobials. Cationic peptide antibiotics (CPAs) and ceragenin contain in their structures cationic groups and adopt a facially amphiphilic conformation, conferring the ability to permeate the membrane of bacteria and fungi [1]. These features confer to these compounds the ability to permeate the membranes of bacteria and fungi. Keeping these features in mind, we have screened a series of *in-house* synthesized steroid derivatives and discovered an amine steroid, DOCA-NH_2 to be active against reference strains and multidrug-resistant isolates of Gram-positive *Enterococcus faecalis* and *Staphylococcus aureus* and Gram-negative *Escherichia coli*, *Pseudomonas aeruginosa* and *Campylobacter jejuni*. The prevention of biofilm formation was measured by the crystal violet method [2] and potential synergies between the compounds tested and clinically relevant antibiotics were evaluated as well. Antifungal activity was evaluated for reference and multidrug-resistant isolates of *Candida albicans*, *C. krusei*, *Aspergillus fumigatus* and *Trichophyton rubrum*. The inhibition of germ tube formation in *C. albicans* was also performed.

DOCA-NH_2 was synthesized in two steps, in 50% overall yield. Firstly, Fisher esterification was performed, following by refluxing the ester in the adequate amine.

The compound was active against all the tested microorganisms, having bactericidal and fungicidal activity. Minimal inhibitory concentrations (MIC) ranged between 16 and 128 µg/mL. No synergy with clinically relevant antibacterial drugs was found, however, the compound was able to completely inhibit biofilm formation of bacteria exposed to MIC of the compound. For *E. coli* and *E. faecalis* inhibition of biofilm formation occurred at half the MIC. In addition, DOCA-NH_2 inhibited dimorphic transition of *C. albicans* at concentrations 4 times lower than the MIC, which can reduce the microorganism virulence and biofilm formation.

These results call for a more in-depth study of DOCA-NH_2, including the mechanism of action, which can be related with the mechanism of action of CPAs and ceragenins [3].

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MULTITARGET TRIAZOLES: AN INNOVATIVE APPROACH FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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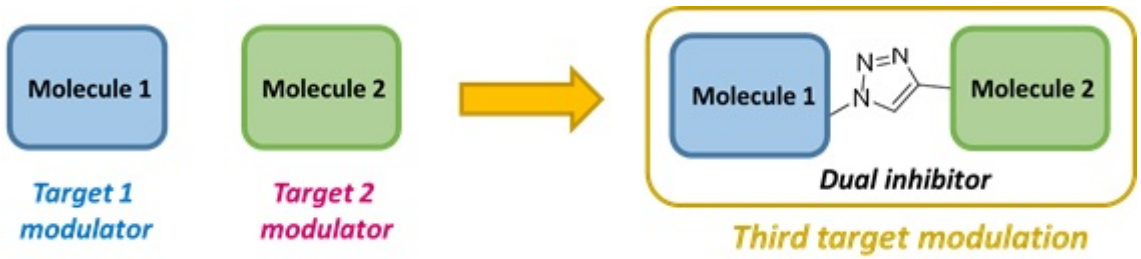
Multitarget drugs are molecular entities that are designed to present more than one biological activity. They are arising as powerful tools to tackle complex diseases including bacterial resistances, cancer or neurodegenerative diseases. Typically, the rational strategies to design multitarget drugs are linkage, fusion and incorporation or merge. Here we present the creation of a multitarget drug combining active fragments in a way that could inhibit an additional third target with the objective to create powerful modulating agents for neurodegenerative diseases. Multitarget compounds are ideally suited for the treatment of these pathologies due to their unknown etiology, multifactorial pathology and lack of efficient treatments. To achieve this aim we have combined fragments that inhibit kinases involved in the main pathomolecular pathways of Alzheimer's disease such as tau aggregation, neuroinflammation and decreased neurogenesis, looking for a third action in BACE1, responsible of β-amyloid production. To synthesize the multitarget compounds we have employed the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC)[1,2] methodology to obtain the 1,4-disubstituted triazoles. The synthesized triazoles exhibited three inhibitory activities against the desired targets.
Finally, and after the successful results obtained using this methodology, we have started to implement the in situ click chemistry technique[3] to better select the multitarget compounds using BACE1 as a template.



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NOVEL DERIVATIVES OF ANTRACENODIONE AS INHIBITORS OF TYROSINE KINASE PROTEIN

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The primary modulators of the cell signaling processes are reactions of phosphorylation and dephosphorylation. The phosphate group is enzymatically transferred from ATP to the amino acid residue of the protein. Protein tyrosine kinases play a crucial role in the process of signal processing and control many vital pathways in cell (e.g. regulating cell cycle, growth, differentiation and apoptosis of cells). The oncogenic forms of protein tyrosine kinases express in various malignant tumors and the regulation of their activity can be essential in the treatment of cancer with molecular targeted therapy [1].

The new derivatives of anthracenodione were tested using computational protein-ligand docking by AutoDock Vina in order to find if they can be new and potent protein tyrosine kinases inhibitors (Epidermal Growth Factor Receptor (EGFR), Platelet-Derived Growth Factor Receptor (PDGF-R), AKT-1, c-Kit, B-Raf, and ERK-2). The most promising docking scores were found for i19 and i42 compounds bound to Epidermal Growth Factor Receptor (EGFR) kinase and c-kit kinase with similar results. The similar high scores for i84 and i19 compounds were obtained in docking to B-Raf kinase. The studies of molecular modeling have been confirmed by *in vitro* biological assays.

The presented studies show that novel synthesized derivatives of antracenodione exhibit promising antitumor properties.

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NEW IMIDAZOPYRIDINE NUCLEOSIDE DERIVATIVES AND EVALUATION OF THEIR ANTIVIRAL ACTIVITY

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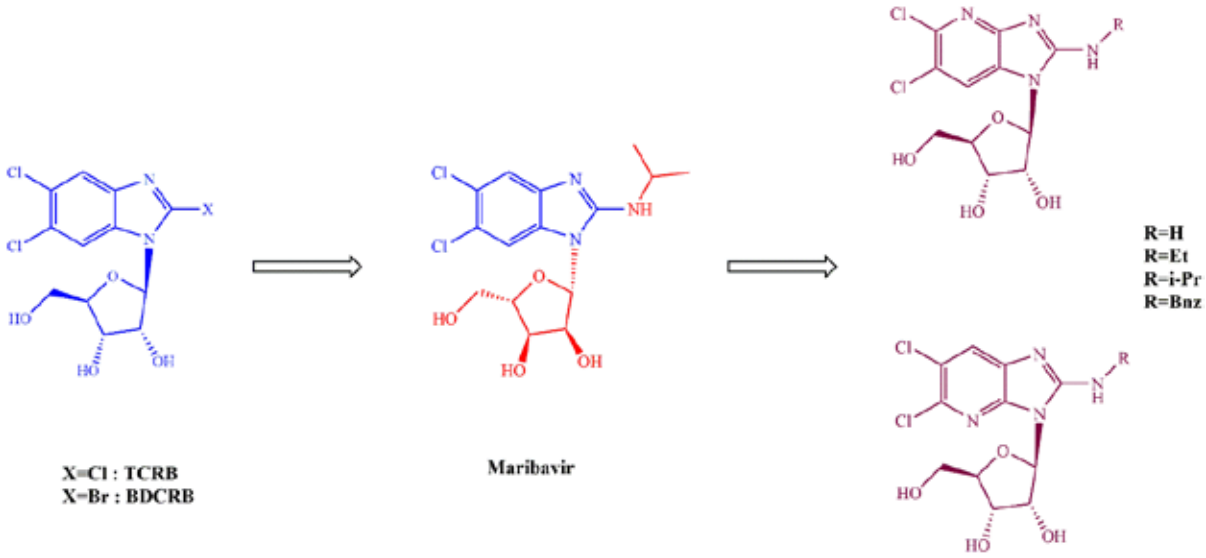
Human Cytomegalovirus (HCMV) is the most common sight- and life-threatening opportunistic pathogen in immunocompromised individuals[1]. Ganciclovir is still the gold standard for the treatment of HCMV infectious manifestations, while Cidofovir and Foscarnet serve as second-line therapies. However, the clinical effectiveness of these compounds is limited[2] and the recent approval of the terminase inhibitor Letermovir with fast-track procedures[3] highlights the urgent need for anti-HCMV agents with novel modes of action and improved clinical safety. In this scope, research efforts led to the development of polyhalogenated benzimidazole nucleosides, exemplified by 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB) and its 2-bromo analogue (BDCRB), that were found to strongly inhibit viral replication[4]. The 2-isopropylamine substituted derivative of the β-L-series Maribavir has proven to be more potent than BDCRB, reducing HCMV DNA synthesis via the inhibition of the viral kinase UL97 and has entered clinical trials[5].



In order to expand the structure-activity relationships of the benzimidazole series to the less studied and more "purine-like" imidazo[4,5-*b*]pyridine scaffold, we have developed a number of novel nucleoside derivatives, which can be considered as 4-aza-D-isosters of Maribavir. Our aim is to explore the spatial limitations of the target enzymes and gain insight on the network of interactions developed. Within this context, we disclose herein the preparation and pharmacological evaluation of the 1- and 3-regioisomeric β-D-ribosides of 5,6-dichloroimidazo[4,5-*b*]pyridine, introducing various aminosubstituents at the vacant position of the imidazole ring.

**This work has been carried out in the framework of the author's M.Sc. Scholarship granted by the Onassis Foundation*

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DESIGN AND SYNTHESIS OF NON-NUCLEOSIDE DERIVATIVES OF IMIDAZO[4,5-b]PYRIDINE AND EVALUATION OF THEIR ACTIVITY AGAINST HEPATITIS B VIRUS

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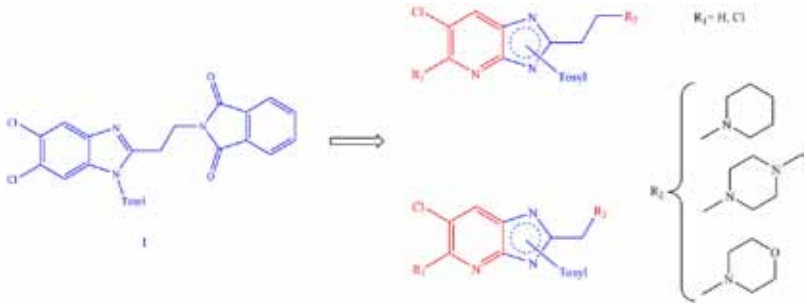
Hepatitis B virus (HBV) infection is a world leading cause of chronic liver disease. The employment of vaccination strategies has not resulted in eradication of the virus and infection still poses serious health problems, especially in developing countries[1]. Consequently, pharmacological intervention is an effective way to reduce mortality from cirrhosis and hepatocellular carcinoma. Two major classes of antiviral agents are utilized in chronic hepatitis B, namely interferons and nucleos(t)ide derivatives. However, severe side effects related to interferon treatment[2] and the high emergence of HBV drug-resistant strains underline the clinical need for novel classes of compounds[3]. Within this context, the development of non-nucleoside benzimidazole inhibitors of HBV provides a promising therapeutic strategy. Among them, compound I exhibited high antiviral potency and selectivity index[4].



In an effort to contribute to the structure-activity relationship studies of these series we have prepared a number of novel compounds possessing the imidazo[4,5-*b*]pyridine scaffold and investigated their biological activity as potential HBV inhibitors. The new compounds bear different substitution patterns on the fused pyridine ring, while the phthalimide moiety has been replaced by alicyclic amines. Furthermore, in order to identify the optimal chain length between the imidazopyridine core and the amino group, different alkyl linkers have been introduced. Target compounds are also considered the corresponding tosyl derivatives, which have been prepared from the tosylation of the heterocyclic bases, leading to both 1- and 3-regioisomers of imidazo[4,5-*b*] pyridine.

**This work has been carried out in the framework of the author's M.Sc. scholarship granted by the Onassis Foundation*

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TOWARDS THE DEVELOPMENT OF NOVEL ANTI-HBV AGENTS: BLOCKAGE OF VIRUS REPLICATION BY N-HYDROXYIMIDES THROUGH INHIBITION OF RIBONUCLEASE H

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Hepatitis B Virus (HBV) is a DNA virus in the *Hepadnaviridae* family. Long-term HBV infections constitute a major cause of end-stage liver disease and chronic carriers are at risk of developing cirrhosis, liver failure and hepatocellular carcinoma. Current antiviral therapy (immunomodulators, nucleos(t)ide analogues) rarely eradicates the virus and apparently cleared HBV infections can be reactivated during immunosuppression. Moreover, HBV's high mutation rate can lead to drug resistance. To cure HBV infection, it is crucial to develop new strategies, including achieving profound viral suppression.

HBV Ribonuclease (RNaseH) is a metalloenzyme that belongs to the nucleotidyl transferase superfamily and its active site contains four carboxylates that bind to two Mg^{2+} ions required for the RNA cleavage. However, the potential of RNaseH as a drug target for HBV treatment, was never seriously explored until recently. The importance of the RNaseH, along with the fact that there is no discernable amino acid homology between the HBV enzyme and the cellular RNaseHs, prompted the development of novel scaffolds, bearing a metal-chelating motif, as potent inhibitors.[1]

Utilizing findings in the literature and our previous publications,[2] we have rationally designed and synthesized a series of metal chelating agents (*N*-hydroxyimides) to optimize our lead compound. The novel analogues were evaluated for their anti-HBV activity, and they were considerably potent with EC_{50} values in the mid nM range. All the compounds were also tested for their activity against the human ribonuclease H1 (huRNaseH1) and they were found to be quite selective. Our studies indicate that this class of compounds holds significant potential for antiviral development. Our future studies will be informed by our growing structure activity relationships.

Acknowledgments: Ms. V. Pardali would like to thank the Greek State Scholarships Foundation for providing her a Ph.D. fellowship within the framework of the Action "Doctoral Research Support" (MIS 5000432), ESPA 2014-2020 Program and the National Institute of Health (NIH) for funding this project.

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BIGINELLI HYBRIDS AS ANTITUMOR AGENTS:MECHANISM OF ACTION

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In order to investigate potential therapeutically agents, the newly synthesized Biginelli compounds (**4a-l**) were evaluated for in vitro cytotoxic activity against HeLa, LS174, A549 and on normal cell line, human fetal lung fibroblast cell line (MRC-5) by employing a MTT assay. Compounds **4c**, **4d**, **4f**, **4k** and **4l** showed strong activity against all tested malignant cell lines, similar to the activity of control compound cisplatin. Also, the compounds **4f-i** exhibit low cytotoxicity according to the MRC-5 and consequently very good selectivity. Compound **4f** have up to three times higher selectivity index (SI) towards cancer cells than cisplatin (on HeLa, LS174 and A549 SI=18.2, 13.5 and 11.2, respectively). Additionally, the molecular docking was performed to support the interactions and to find out the preferred binding modes of ligands (**4c** and **4d**) with DNA[1] and BSA. Obtained results show that for both compounds only benzene rings interact through intercalation with DNA. Analysis of results for BSA shows that all ligands interact with BSA in the same binding pocket.

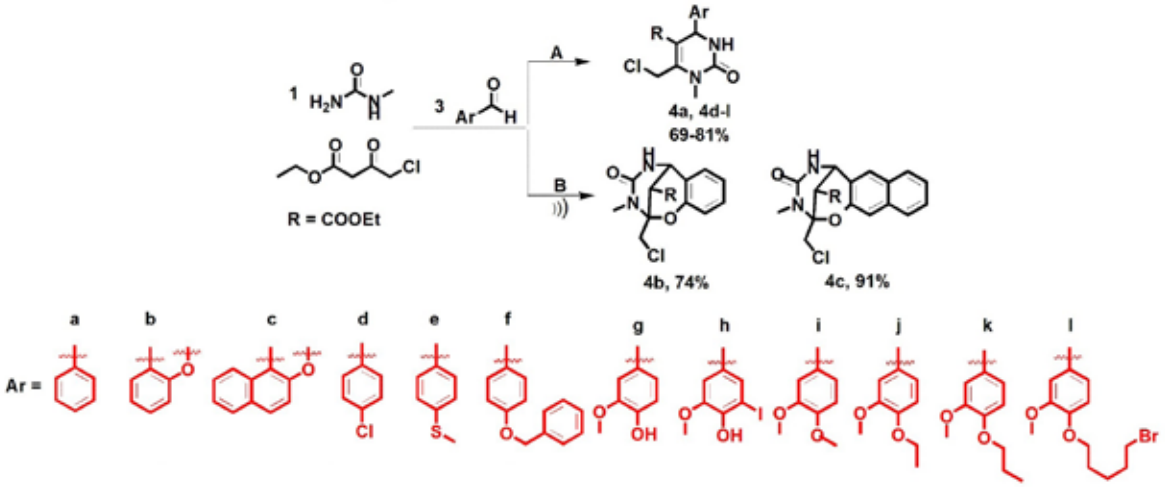

Fig. 1. Synthesis of the 2-oxo-1,2,3,4-tetrahydropyrimidines **4a**, **4d-l** and 1,3,5-oxadiazocine **4b** and **4c**.

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SYNTHETIC APPROACHES OF PYRROLE-IMIDAZOLE ALKALOIDS: OXIDATIVE OPENING OF PYRIDINE

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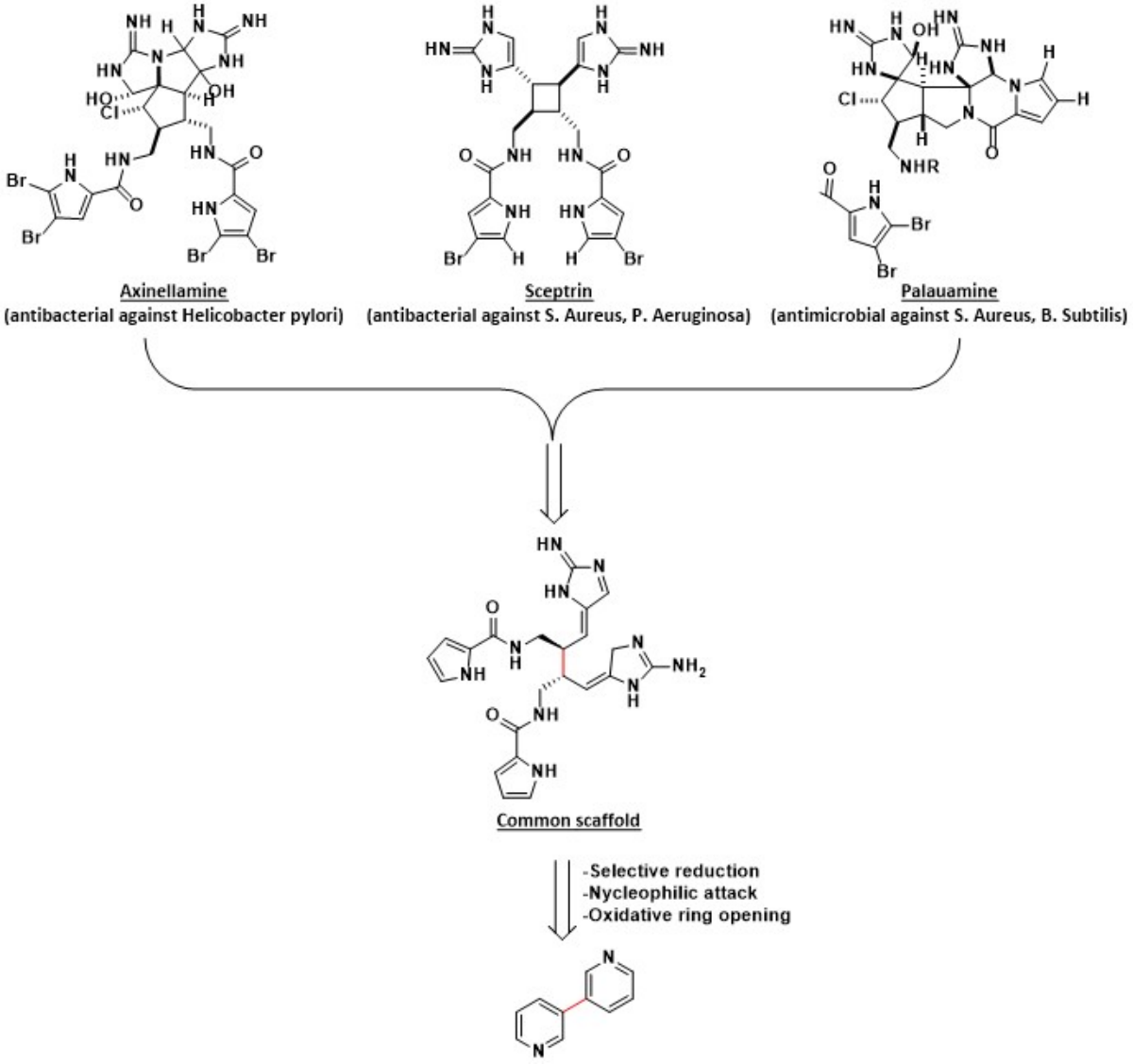
Pyrrole-imidazole alkaloids are an important subcategory of marine alkaloid natural products.[1] Of particular interest are their dimeric, trimeric and polymeric derivatives not only for their structural complexity, but also due to their important biological properties as anticancer[2], antibiotic[3] and antibacterial[4] agents.

A new synthetic approach is presented for the composition of their dimeric derivatives, which may in future allow the collective synthesis of a variety of natural products of this family. The process is based on the oxidative opening of bispyridine's substituted derivatives to form conjugated dimers.



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DESIGN AND SYNTHESIS OF NEW COMPOUNDS CONTAINING THE CINNAMIC PHARMACOPHORE WITH POSSIBLE MULTI-TARGET ACTIVITY

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Inflammation is believed to be involved in numerous diseases such as cancer, and senile dementia Alzheimer's type. Lipoxygenase (LOX) and Cycloxygenase (COX) pathways play an important role in inflammatory sites in correlation with the reactive oxygen species (ROS) produced during the inflammation by phagocytic leukocytes. ROS are involved in the LOX and COX mediated conversion of arachidonic acid into pro-inflammatory intermediates. Acetylcholinesterase (AchE) was used as another target implicated in the dementia and Alzheimer's disease.

The aim of our study is to synthesize compounds combining the cinnamic and curcumin pharmacophore, the coumarin and thiazole nucleus, the azomethine linkage as well as hybrids of cinnamic acids, and drug like moieties. Computer-aided drug design was used for the candidates' synthesis selection, which was partly based on published procedures. The curcumin, cinnamic, coumarin, thiazole and hydrazone derivatives play a vital role in the formation of commercially important intermediate molecules which are necessary for the production of different bioactive compounds and drugs. Cinnamic acid derivatives present a wide range of biological activities: antituberculosis, antidiabetic, antioxidant, antimicrobial, hepatoprotective, central nervous system stimulant (CNS), antidepressant, anticholesterolemic, antimalarial, antiviral, anxiolytic, cytotoxic, and anti-inflammatory. Furthermore, the combination of appropriate pharmacophore groups led to conjugates with multi-target activities. In recent years, intensive research on hybrids has been conducted in order to create new multifunctional drugs. The results of our synthetic efforts are several groups of newly synthesized compounds that were subjected to further optimization.

The new derivatives were characterized based on the structural characteristics and physicochemical properties of the molecules.

Preliminary antioxidant and AchE inhibitory activity *in vitro* tests have been performed followed by inhibition of soybean LOX and COX. The physicochemical properties of the compounds were analyzed in terms of Lipinski's rule. Further investigation is in progress concerning their multi-target profile.

Acknowledgements: Biobyte Corp., 201 West 4th St, Suite 204, Claremont CA 91711, USA

EPIGENETICS IN CANCER: DESIGN AND BIOLOGICAL EVALUATION OF PROSPECTIVE EZH2 INHIBITORS

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The role of epigenetic pathways in the development and progression of cancer have been extensively studied and new anticancer targets have been proposed for exploitation. Polycomb repressive complex 2 (PRC2) is such an epigenetic regulator which catalyzes the trimethylation of lysine 27 in Histone 3 (H3K27me3), a process that facilitates chromatin compaction and gene silencing. Cancers with poor prognosis are related with overexpression and gain of function mutation of EZH2, which is the functional enzymatic component of the PRC2 [2]. Thus, the development of new small-molecule inhibitors of the EZH2 catalytic subunit offers promising opportunities as anticancer drugs [1].

To contribute to the discovery of new EZH2 inhibitors, we carried out a computer-aided drug design (CADD) campaign to find hit molecules for testing in biological assays and/or for synthesis. First, a panel of unique 3D-pharmacophore models were generated, validated and optimized using LigandScout Advanced 4.2.1 software [3] and information relating to the key interactions and the 3D-geometries associated with inhibition of EZH2 activity were obtained. The prioritized models were used in two computational hit finding campaigns: Virtual Screening and De Novo Design. During the Virtual Screening, a unique 3D-pharmacophore-based method (iscreen) from LigandScout was used and several databases (e.g., DrugBank, NCI, MuTaLig Chemotheca, and our in-house libraries) were computed and screened. The interesting virtual hit molecules with high inhibition potential totaled more than 60 compounds, been evaluated in vitro in a variety of assays and benchmarked against two known EZH2 inhibitors. Many of these compounds were inhibited EZH2 in biochemical and cell-based assays. Notably, many of the putative EZH2 hits from the in silico studies yielded clean off-target and safe ADME-Tox profiles.

In parallel to the above, a de novo design campaign has been initiated based on selected pharmacophore models, and new scaffold cores for EZH2 inhibition have been identified. The structures obtained from these studies will be synthesised and evaluated in vitro in EZH2, off-target and ADME-Tox assays.

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SYNTHESIS OF FUNCTIONALIZED PROBES TO IDENTIFY AND VALIDATE NOVEL THERAPEUTIC AND DIAGNOSTIC TARGETS FOR DRY EYE DISEASE AND IRRITABLE BOWEL SYNDROME

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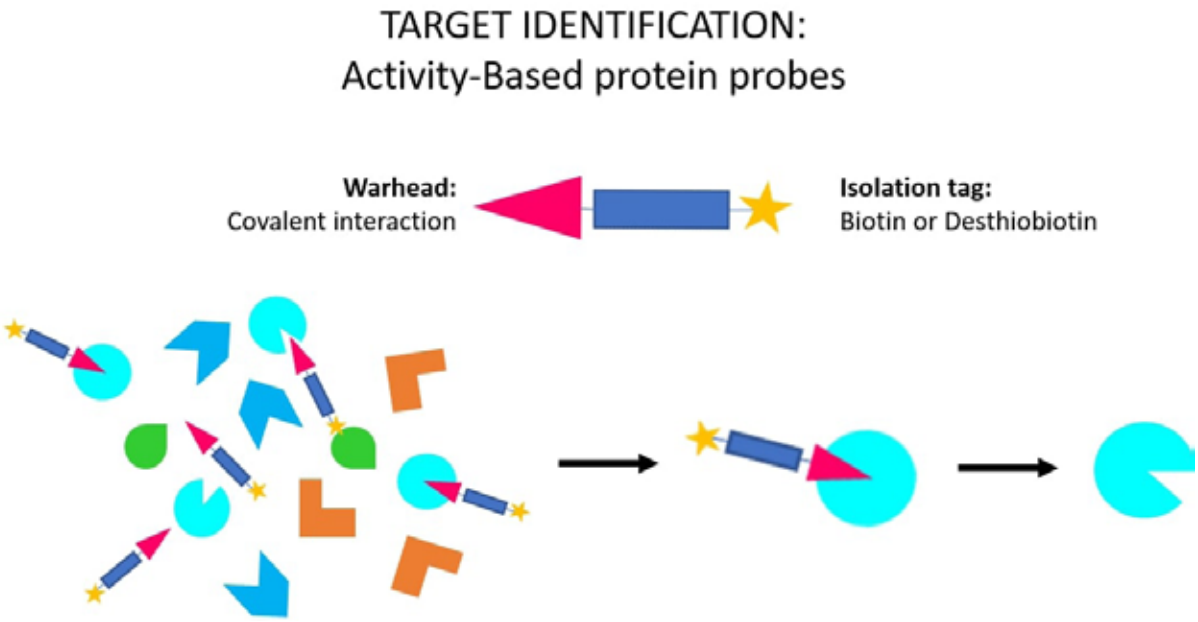
Serine proteases are a subgroup of the protease family involved in several physiological processes, including immune response, cell death and tissue healing. [1] The upregulation of these proteases can increase inflammatory cytokines, degradation of extracellular matrix components, activation of PAR2 or MMP-9, among others. [2,3]

We recently obtained an *in vivo* proof of concept with a multi-target serine protease inhibitor in Dry Eye Disease (DED). Topical application of this compound in the eye of a tear-deficient dry eye rat animal model gave a significant reduction of both tissue damage and of inflammatory parameters. [4] Moreover, serine protease inhibitors also cause a decrease in visceral hypersensitivity in a rat model of post-inflammatory visceral hypersensitivity. [5] Therefore, we hypothesized that serine proteases play an important role in both DED and Irritable Bowel Disease (IBS).

In order to characterize the proteases involved in DED and IBS, a series of serine protease-targeted activity-based probes (ABPs), analogues from our inhibitors, have been synthesized. The probes were designed to target chymotrypsin, trypsin, and elastase-like serine peptidases, with biotin or desthiobiotin as reporting tag and a diaryl phosphonate as a warhead. The synthesis of ABPs with a basic side-chain amino acid analogue was quite challenging and required extensive optimization of the synthetic route. We will also report on the potency of these probes on a few isolated serine proteases.



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SYNTHETIC STUDIES TOWARDS AN ENANTIOSPECIFIC TOTAL SYNTHESIS OF CHABROLONAPHTHOQUINONE B

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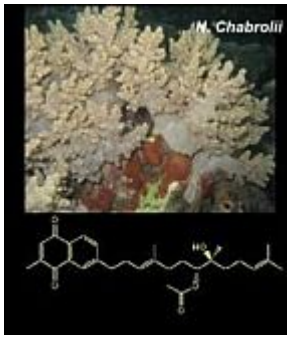
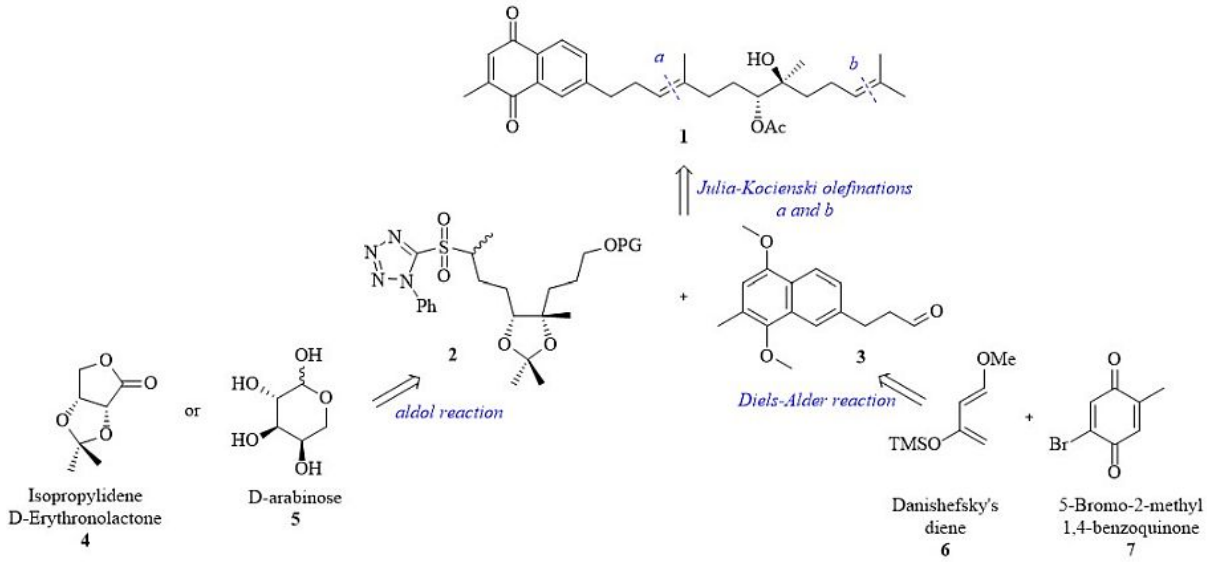
Chabrolonaphthoquinone B (**1**) is a natural product isolated in South Taiwan from the organic extract of the soft coral *Nephthea chabrolii.* Biological evaluation showed that **1** exhibits very good cytotoxic activity against MDA-MB-231 (human breast cancer cell line) (IC_{50}~4.7 μM), Hep-G2 (human liver cancer cell line) (IC_{50}~12.4 μM) and A549 (human lung cancer cell line) (IC_{50}~33.9 μM).



Herein, we describe our synthetic studies towards the first enantiospecific total synthesis of this natural product employing a chiral pool approach. The key step of our synthetic route is a modified Julia olefination (*a*) of the sulfone bearing aliphatic fragment **2** and the aromatic aldehyde **3**, leading to a facile construction of the *E* -trisubstituted double bond. A Julia-Kocienski protocol (*b*) was also used for the introduction of the dimethyl side-chain from a key-aldehyde precursor, whereas the quinone moiety was reached via a regioselective Diels-Alder reaction of Danishefsky's diene **6** and bromoquinone **7**. D-Arabinose (**5**) or isopropylidene-D-erythronolactone (**4**) served as the as starting materials for the preparation of the required PT-intermediate **2** via a stereoselective aldol reaction. Besides **1**, our synthetic strategy allows for facile synthesis of analogues of the natural product, and is expected to facilitate structure-activity relationships studies.



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TDP-43 MODULATION BY CDC7 INHIBITORS AS A THERAPEUTIC STRATEGY FOR AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by loss of motor neurons, leading to muscle wasting and early death due to respiratory failure. Listed as a “rare disease”, ALS affects 2 to 3 people of every 100.000 citizens in Europe and North America. However, the etiology remains unknown and no effective treatment exists to date, thus the search for new drugs able to modulate this neurodegeneration is needed. Approximately, between 5 to 10% of ALS cases have a genetic link, while the sporadic ones represent 90% of all cases [1].

TDP-43 has been recognized to play a key role in the disease, in both familiar and sporadic cases. In normal conditions, TDP-43 is a nuclear protein and regulates the expression of many genes, but it’s hyperphosphorylated, ubiquitinated and N-terminally truncated in the cytoplasm of motor neurons in ALS patients [2].

Protein kinases are important targets for several neurodegenerative disorders, as well as inflammatory diseases, diabetes and cancer. The reason is that aberrant protein kinase signaling is implicated in many of these human diseases [3]. In this context, it has been recently discovered that cell division cycle kinase 7 (CDC7) is responsible for pathological TDP-43 phosphorylation [4]. So that, CDC7 inhibition by brain permeable small molecules will be a good strategy for the treatment of ALS, as they could strongly reduce TDP-43 phosphorylation, preventing TDP-43-dependent neurodegeneration.

In our laboratory, CDC7 inhibitors have been designed and synthesized showing a low micromolar activity against this kinase. Furthermore, these compounds were predicted as able to cross the blood brain barrier based on PAMPA assays and selective against other kinases. Here, we present the ability of these compounds to reduce TDP-43 phosphorylation both in vitro and in vivo in ALS models as well as restore its nuclear location. Additionally, this same behavior is observed when FTLD patient´s lymphoblasts are treated [5][6].

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USE OF THE 4-HYDROXY-TRIAZOLE MOIETY AS A BIOISOSTERIC TOOL IN THE DEVELOPMENT OF SELECTIVE LIGANDS FOR SUBTYPES AMPA RECEPTOR

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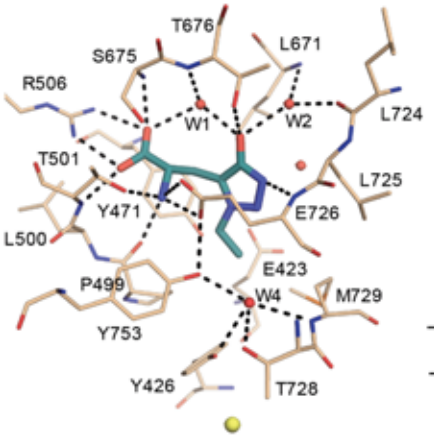
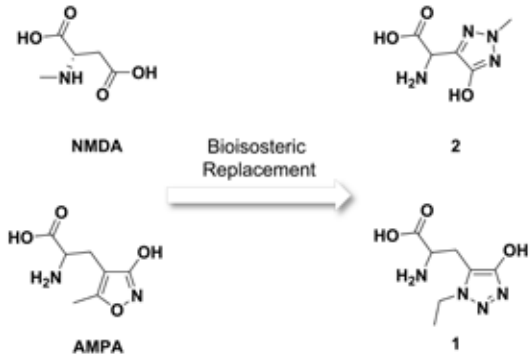
(S)-Glutamic acid is the major excitatory neurotransmitter in the central nervous system (CNS); it is crucial to normal brain functions and altered neurotransmissions are involved in a number of brain disorders. The Glu effects are mediated by a highly heterogeneous receptor population comprising G protein-coupled metabotropic (mGluRs) and ionotropic Glu receptors (iGluRs).[1] The iGluRs are ligand-gated ion-channels that are divided into three major classes: NMDA, (S)-AMPA and kainic acid. Inside a large number of ligands showing selectivity among the three classes of iGluRs, only few have been developed owing subtypes specificity. In this sense, the design of subtypes selective iGluRs ligands remains an unsolved need. In recent years, we have been focusing on improving the scaffold hopping replacement of the acidic moieties, present in many lead compounds, by acidic hydroxylated azoles. In light of the promising results obtained in previous work[2] and in an attempt to explore the selectivity towards iGluRs, the hydroxy-1,2,3-triazole scaffold was used to bioisosterically replace the distal carboxylic group of Glu.[3] In the design of the AMPA analogues, oppositely of the isoxazolol moiety the hydroxy-1,2,3-triazole scaffold provides the opportunity to place a substituent oriented in two different directions as opposed to the isoxazolol moiety in AMPA. Compound **1** showed unprecedented selectivity among AMPA receptor subtypes; and crystal structures of the AMPA receptor GluA2 agonist binding domain in complex with **1** disclosed an unusual binding mode. Moreover, the triazole aspartate analogue **2** was unexpectedly able to activate both the glutamate and glycine agonist binding sites of the NMDA receptor. These observations demonstrate novel features that arise when employing a hydroxyl-triazole moiety as bioisostere for the distal carboxylic acid in glutamate receptor agonists. The synthesis and extensive pharmacological characterization at native and recombinant iGluRs of the hydroxytriazole Glu analogues and the aspartate triazole analogue will be describe along with X-ray crystallographic studies of two compounds bound in the GluA2 ABD.





Ligand	GluA1$_o$ K_i (μM)	GluA2(R)$_o$ K_i (μM)	GluA3$_o$ K_i (μM)	GluA4$_o$ K_i (μM)
S-AMPA	0.022	0.017	0.021	0.040
1	9.02 ± 2.27	**0.71 ± 0.22**	1.91 ± 0.44	9.47 ± 1.95

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VALORIZATION OF OLEUROPEIN VIA TUNABLE ACID-PROMOTED METHANOLYSIS

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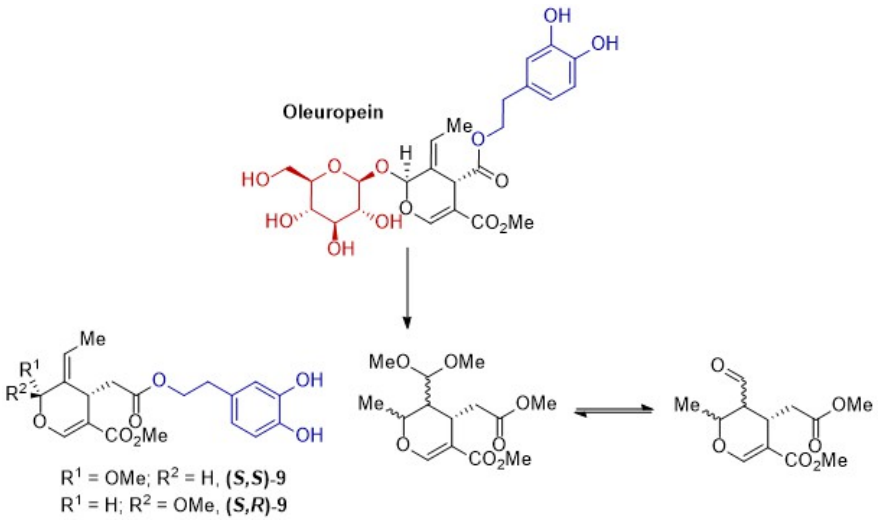
Oleuropein is one of the major secoiridoids found in the olive leaf (0.5-2% (w/w) on dry basis).1 Oleuropein structure can be divided in three subunits – glucoside, monoterpene and hydroxytyrosol (red, black and blue, respectively, Figure 1).2 The monoterpene unit is a highly functionalized moiety that includes two esters, one alkene, one enol ether, one acetal and a stable chiral center at C-4. This multifunctional structure makes it difficult to be obtained by other means than extraction from natural sources.3 In this context, we became interested in the valorization of oleuropein towards the synthesis of diverse and synthetically rich building blocks.

The acid-promoted methanolysis of oleuropein was studied using a variety of homogeneous and heterogeneous acid catalysts. Exclusive cleavage of the acetal bond between the glucoside and the monoterpene subunits or further hydrolysis of the hydroxytyrosol ester and subsequent intramolecular rearrangement were observed upon identification of the most efficient catalyst and experimental conditions. Furthermore, selected conditions were tested using Oleuropein under continuous flow and using a crude mixture extracted from olive leaves under batch.

Formation of (-)-methyl elenolate was also observed in this study, which is a reported precursor for the synthesis of the antihypertensive drug (-)-ajmalicine.4



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DISCOVERY OF NOVEL, DRUG-LIKE FERROPTOSIS INHIBITORS WITH IN VIVO EFFICACY

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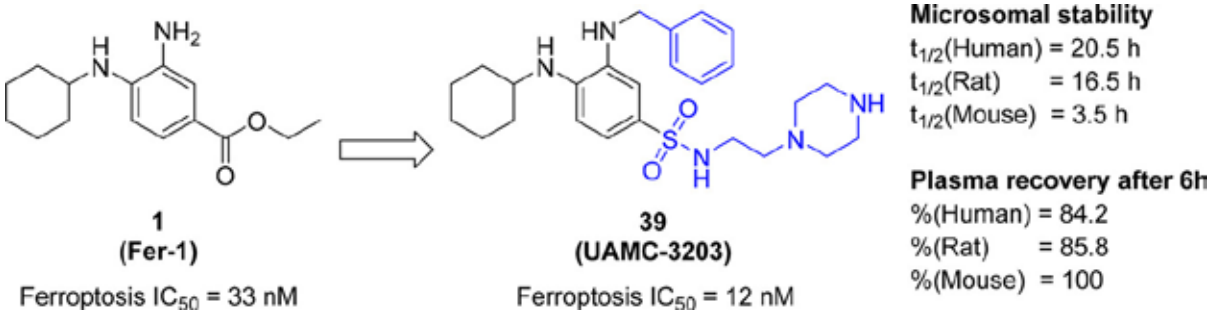
Nowadays, the field of cell death is facing new pathways: Ferroptosis is an iron-catalyzed, nonapoptotic form of regulated necrosis that results in oxidative lipid damage in cell membranes that can be inhibited by different class of molecules.[1] Between those, Ferrostatin-1 (Fer-1) emerged as a novel potent radical-trapping antioxidant (RTAs) suffered from solubility issues.[2] The reported study focused on the synthesis of a more stable and readily soluble series of Fer-1 analogues that potently inhibit ferroptosis enhancing the solubility.[3] The design of the new compounds starts from: 1) The replacement of the labile ester moiety with a sulfonamide to improve stability as well as potency. 2) The cyclohexyl moiety was deemed to be the most ideal substituent with regard to both potency and lipophilicity. 3) The introduction of an aromatic group on the 3-amino position greatly improved potency but also further decreased the solubility of the compounds

The most promising compounds, **UAMC-3234, UAMC-3206** and **UAMC-3203** showed a remarkable improvement in stability when compared to Fer-1 in the microsomal and plasma stability incubated with both human and rat microsomes. Compounds **UAMC-3234, UAMC-3206** and **UAMC-3203** also showed an improved protection compared to Fer-1 against multiorgan injury in mice and no toxicity was observed in mice after daily injection of **UAMC-3203** for 4 weeks. In silico study confirm the rapid insertion of **UAMC-3203** in a phospholipid bilayer, which aligns with the current understanding of the mechanism of action of these compounds.[4]

In conclusion, by introducing both a solubility improving group and a sulfonamide moiety to the Fer-1 scaffold, we were able to synthesize novel molecules that are more potent than Fer-1, while simultaneously improving solubility and stability.[5] These analogues have superior properties compared to Fer-1, showing in vivo efficacy, and represent novel lead compounds with therapeutic potential in relevant ferroptosis-driven disease models.



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SMALL BUT SELECTIVE: DEVELOPING CHEMICAL PROBES FOR PKN/PRK2

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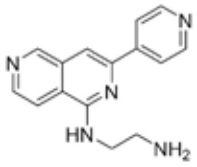
Chemical probes/tools help biologists answer mechanistic questions to validate disease pathways and new drug targets. They need not possess all the physiochemical properties of a drug-like molecule as these can been incorporated into a compound later in the drug discovery process. Chemical tools must be sufficiently stable, potent and selective against their given target protein.[1]

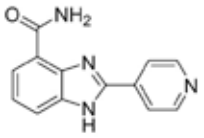
Collaborative efforts across academia and industry such as the Structural Genomics Consortium Human Kinase Chemical Probe Programme and PKIS/PKIS2 chemogenomic set[2] are currently undertaking the mammoth task of finding chemical probes for the 518 human protein kinases.

Protein kinase C-related kinase 2 (PKN/PRK2) is an AGC serine/threonine protein kinase. It is one of 3 homologues (PKN1-3) within the AGC kinase involved in a variety of pathways such as cytoskeleton regulation, transcription, migration and cell invasion. PKN2 is also a target of interest across several types of cancer. It currently does not have a selective chemical probe to help define its biological role.[3]

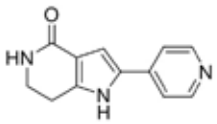
Three series of highly ligand efficient compounds selected from a ChEMBL screen (Fig. 1) have been developed and shown to bind potently to PKN2, with promising levels of selectivity against PKN1, and wider kinase panels. Their unusually small size challenges traditional criteria for drug-like compounds but can be utilised to design potent and selective molecular probes for PKN2 to help elucidate its role in disease.



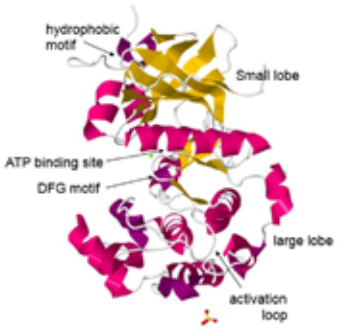
PRK2 IC_{50} 7 nm
J. Med. Chem., 2010, **53**, 5400–5421



PRK2 K_i = 40 nM
J. Med. Chem., 2000, **43**, 4084-4097



PRK2 K_i = 5 nM
J. Med. Chem., 2007, **50**, 2647-2654



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IN VITRO AND IN OVO EVALUATION OF ROS-ACTIVATABLE ANTICANCER BORONATE PRODRUGS OF DOXORUBICIN

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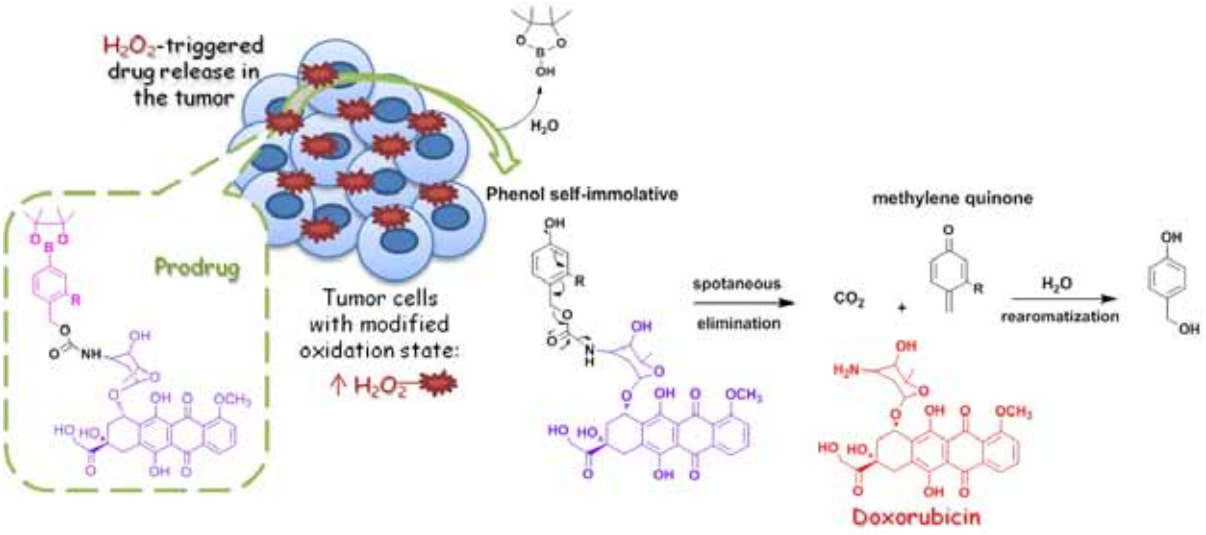
Pharmaceutical industries and public research centers have made oncology one of their priorities. Many drugs have been introduced on the market in order to treat cancer, however, many still suffer from a lack of selectivity for tumor cells over normal cells resulting in insufficient drug concentrations in tumors, systemic toxicity and appearance of drug-resistant tumor cells. To circumvent these drawbacks, a relevant strategy relying on the development of prodrugs designed to be activated after an enzymatic or a chemical reaction near the site of action has rose [1]. This strategy allows a specific release of the drug at its target site and could increase the therapeutic index of anticancer drugs. Among the different metabolic pathways, the activation by reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2), appears particularly interesting and recent studies have shown that this property could be exploited for therapeutic benefits [2]. Arylboronates, in which the oxidation of the carbon-boron bond allows the formation of an electron donor alcohol group, act as quinone methide-based self-immolative spacers, leading to the release of the conjugated moiety after an electronic delocalization within the aromatic nucleus. As the cleavage of arylboronic acids and their ester derivatives takes place in presence of H_2O_2, we studied the design and development of new anticancer prodrugs consisting in the coupling of a pinacol boronate ester (trigger unit) to doxorubicin (active entity). On the basis of established structure-activity relationships[3], our study led to the design of a benzeneboronate profluorescent probe and three doxorubicin arylboronate prodrugs containing either, an unsubstituted bezenboronic acid, a fluorinated bezene homologue or a furan ring. The proof of concept of oxidation of the carbon-boron bound was investigated by adding increasing amounts of H_2O_2 to the profluorescent probe and by measuring the release kinetic of the fluorescent moiety. The capacity of cell line to produce ROS was also studied using the profluorescent probe. The in vitro evaluation of the designed doxorubicin prodrugs was investigated on a panel of cell line by determination of their IC_{50}value in comparison to doxorubicin. Finally, the efficacy of the most potent prodrug was evaluated in ovo on pancreatic cancer tumor model using the HET-CAM assay.



Scheme 1: Self-immolative mechanism of arylboronate-doxorubicin prodrugs.

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IS THE 5-BROMO-4-THIO-2'-DEOXYURIDINE A POTENTIAL RADIOSENSITIZER OF DNA DAMAGE?

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Cancers are the main cause of death in the developed regions of the world.[1] Thousands of people, doctors and scientists, are looking for new drugs and therapies that could help to overcome this disease. However, the number of deaths increases from year to year.

One of the most common modalities used in the cancer treatment is radiotherapy. It is estimated that about 50% of cancer patients are treated with ionizing radiation (IR) during the treatment. Thus, it is important to search for and employ compounds – radiosensitizers – which increase the efficacy of radiotherapy, reduce radiation dose necessary to kill cancer cells and minimize its dangerous side effects. Incorporation of modified nucleosides into DNA followed by exposure to X-rays or UV radiation leads to the formation of various types of DNA damage like crosslinks, single or double strand breaks. The mentioned above damage frequently leads to lethal effects in the labeled cells.[2,3]

One of the group of potential radiosensitizers are derivatives of 4-thio-2'-deoxyuridine (SdU).[4] Promising experimental results on 5-iodo-4-thio-2'-deoxyuridine (ISdU) (radiolysis, clonogenic assay, MTT assay, Histone H2A.X Phosphorylation and Cell Death Assays) supported by computational studies prompted us to investigate another analogue of SdU – 5-bromo-4-thio-2'-deoxyuridine (BrSdU).[5] We carried out steady-state radiolysis on aqueous solutions of BrSdU as well as cellular studies. Unlike for ISdU, the products of dissociative electron attachment (DEA) to BrSdU were not present in the respective radiolytes. Consequently, we did not observe a reduced survival of the cells treated with X-rays in clonogenic assay. The height of barrier for the C5-Br bond dissociation in the DEA process seems to be responsible for the observed difference between BrSdU and ISdU.

Supported by the Polish National Science Center (NCN) under the Grant No. UMO-2014/14/A/ST4/00405 (J. R.)

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DESIGN AND SYNTHESIS OF NEW SQ109 DERIVATIVES AGAINST TUBERCULOSIS AND OTHER INFECTIONS

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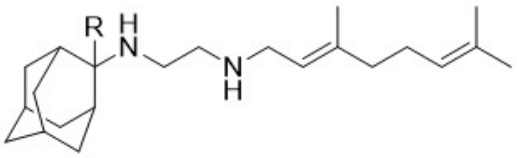
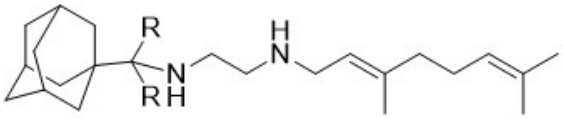
Despite the introduction of an effective treatment 40 years ago, tuberculosis (TB) is spreading globally. Over the past 10 years, recent efforts from various groups have generated a promising TB drug pipeline [1]. SQ109 (N-geranyl-N-(2-adamantyl)ethane-1,2-diamine) proved to be more active than ethambutol both in vitro and in vivo and has more favorable pharmacokinetic properties and, importantly, has been shown to accumulate in the lung, the site of M. tuberculosis infection. SQ109 proved to be active against both drug-susceptible (MIC ranging from 0.2 to 0.39 mg/mL) and drug-resistance (MIC ranging from 0.2 to 0.78 mg/mL) M. tuberculosis strains in vitro and clinical isolates of M. tuberculosis [2-4]. SQ109 showed a distinctive pharmacological profile in mice, while it showed poor oral bioavailability in rats and dogs. In both single and multi-dose Phase I and Phase II clinical trials, SQ109 proved to be both safe and well- tolerated [2-4].



SQ109: R=H
AK116: R=Me
AK118: R=Pr



AK117: R=Me
AK119: R=Et

Recently an x-ray structure of SQ109 in complex with MmpL3 provided a platform for structure-based drug design [5]. Using the MmpL3-SQ109 structure we designed and synthesized new analogues as a part of an ongoing project to develop highly potent anti-tuberculosis therapeutics, with SQ109 being optimized.

To achieve these analogues of SQ109, geranylamine was synthesized from the low cost geraniol. The desired aminoadamantane conjugates were obtained through a mild reduction, applied for the first time in these derivatives. The derivatives are under testing against Trypanosoma brucei, Mycobacterium smegmatis and TB and the currently obtained results showed that the derivatives are 10-fold more potent than SQ109 against T. brucei and M. smegmatis.

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DESIGN AND SYNTHESIS OF TEAD'S LIGANDS FOR THE TREATMENT OF CANCERS

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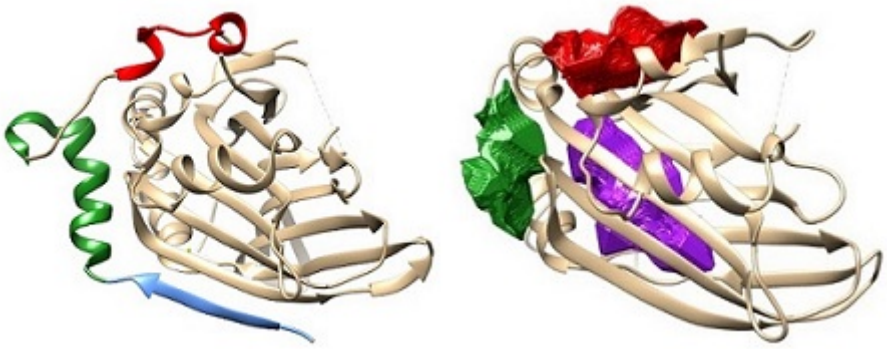
Transcriptional enhancer associate domain (TEAD) is the final actor of the highly conserved Hippo signaling pathway which regulates organ growth, cell proliferation, differentiation, apoptosis and cancer stem cell (CSC). TEAD family proteins bind directly to YAP and TAZ and induce gene expression. Since YAP, TAZ and TEAD have been found to be overexpressed in several cancers[1] (breast, colon, lung, liver, etc…), targeting the YAP/TAZ-TEAD complexes appears as an attractive anticancer strategy.

Structures of the YAP/TAZ-TEAD complexes show three external interfaces[2] between both proteins (interfaces 1 (in blue), 2 (in green) and 3 (in red)). Recently, crystal structures of different TEAD have highlighted the presence of an internal hydrophobic cavity (in purple) that contains a conserved cysteine residue which can be S-palmitoylated or myristoylated. This acylation seems to be important for protein stability and the loss of this post-traductional modification affects the YAP/TAZ-TEAD interaction[3]. Consequently, the TEAD structure contains several promising druggable sites which can be targeted[4].



We designed novel and original small molecules and crystallized them with the YAP/TAZ binding domain of TEAD2 using the soaking approach. Several crystals were obtained and X-ray crystallography analysis has shown that our compounds actually fit in different druggable pockets. Moreover, some of the designed molecules proved to be active in a cellular assay and exhibit moderate to low cytotoxicity.

To conclude, this crystallographic screening by soaking proved to be very efficient and allowed the discovery of several new TEAD ligands. The identified hits will serve as starting points for the development of potent compounds that could disrupt YAP/TAZ-TEAD interactions.

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DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITY STUDIES OF NOVEL NAPHTOQUINONE-AMINO ACID DERIVATIVES AS PROTEASOME INHIBITORS

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The ubiquitine–proteasome pathway (UPP) is the main proteolytic system in eukaryotic cells. The 26S proteasome unit is responsible for the degradation of polyubiquitinated proteins and has multicatalytic proteinase activities. It has been shown that UPP is involved in many important biological processes such as cell growth, cell differentiation, apoptosis, signal transduction, DNA repair, antigen process and inflammatory response. Apart from these physiological roles, this enzyme has been associated with many pathological conditions such as inflammation, neurodegenerative diseases, immune diseases and cancer. Therefore, the ubiquitine-proteasome pathway has recently become a remarkable therapeutic target, especially for cancer treatment (1).

Bortezomib is the first proteasome inhibitor approved by FDA for the treatment of multiple myeloma. Although it has achieved significant clinical success, Bortezomib has some undesirable effects (2). Thus, the development of new and selective proteasome inhibitors is still an important subject. Recent literature has shown that a proteasome inhibitor coded PI-083, bearing naphthoquinone group, has a broader antitumor activity and is more selective against cancer cells compared to Bortezomib (3-5). Based on these findings, using PI-083 as the lead compound, we designed and synthesized some naphtoquinone-amino acid (glycine/alalnine) derivatives bearing anilide functional group. We will present the synthesis procedure and preliminary biological activity results of the designed compounds.

Acknowledgement

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COMPUTER-AIDED DRUG DESIGN OF SMALL-MOLECULE NEUROTROPHIN MIMETICS

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Neurotrophins are growth factors that are expressed in the central and peripheral nervous systems. Among their roles are the control of dendritic growth and synapse formation and, ultimately, cell survival and apoptosis. Neurotrophins bind selectively to the three tropomyosin receptor kinase (Trk) receptors, TrkA, TrkB, TrkC, and collectively to the p75 receptor. Usually, binding to Trk receptors leads to cell protection and survival, while binding to the p75 receptor leads to apoptosis.[1,2] In neurodegenerative diseases, apoptotic cells show a decline in Trk receptor expression, so there has been an effort to treat neurodegenerative diseases with neurotrophins as therapeutic agents. However, this effort is hindered by the poor pharmacokinetic profile of neurotrophins, and their ability to induce immune reactions. For this reason, the use of small molecules as neurotrophin mimetics has been followed.[2] One class of neurotrophin mimetics is neurosteroids, and especially dehydroepiandrosterone (DHEA), which has been shown to protect cells against apoptosis via interaction with NGF receptors.[3,4] DHEA, however, can be metabolized to androgens and estrogens, so there is the need to modify the molecule. BNN-27 is a lead compound that possesses a modification at the C17 position of DHEA, thus abolishing unwanted metabolism.[5] BNN-27 has been shown to protect cells against apoptosis, acting selectively through the TrkA and p75 receptors.[6,7] The aim of our studies is to understand the molecular mechanism of action of BNN-27, from binding to causing an effect, as well as optimizing it for increased affinity and selectivity. For this purpose, docking studies have been carried out in order to assess probable binding sites for BNN-27. Moreover, derivatives and molecular fragments have been docked to deduce a basic Structure-Activity Relation and guide the design of analogues of BNN-27.

Acknowledgement

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ENCAPSULATION OF TEMOZOLOMIDE IN A CALIXARENE NANOCAPSULE IMPROVES ITS STABILITY AND ENHANCES ITS THERAPEUTIC EFFICACY AGAINST GLIOBLASTOMA

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Background: The alkylating agent temozolomide (TMZ) is currently the first-line chemotherapeutic for glioblastoma (GBM), the most common and aggressive primary brain tumour in adults. However, its poor stability and unfavourable pharmacokinetic profile limit its clinical efficacy (1). There is therefore an unmet need to tailor the therapeutic window of TMZ, either through complex derivatization or by utilizing pharmaceutical excipients.

Methods: To enhance stability and aqueous solubility, we encapsulated TMZ in a p-sulphonatocalix[4]arene (Calix) nanocapsule. ^{1}H-NMR, LC-MS and UV-Vis spectroscopy were employed to chart the stability of this novel TMZ@Calix complex according to FDA and EMA guidelines. LC-MS/MS plasma stability assays were conducted in mice to further explore the stability profile of TMZ@Calix *in vivo*. Therapeutic efficacy was compared to that of unbound TMZ in GBM cell lines and patient derived primary cells with known *O* 6-methylguanine-DNA methyltransferase (*MGMT*) expression status and *in vivo* in an intracranial U87 xenograft mouse model.

Results: Encapsulation significantly enhanced the stability of TMZ in all conditions tested. TMZ@Calix was more potent than native TMZ at inhibiting the growth of both established GBM cell lines and patient derived primary lines that express MGMT and are normally highly resistant to TMZ. In vivo, native TMZ was rapidly degraded in mouse plasma, whereas the stability of TMZ@Calix was enhanced 3-fold with increased therapeutic efficacy in an intracranial model of GBM.

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DESIGN OF MULTIFACETED ANTIOXIDANTS: SHIFTING TOWARDS ANTI-INFLAMMATORY AND ANTIHYPERLIPIDEMIC ACTIVITY

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The contribution of oxidative stress and inflammation in a multitude to pathological conditions is well established over the last decades. The correlation between various oxidative and inflammatory mechanisms and the development of multifactorial diseases such as atherosclerosis, diabetes, neurodegenerative and rheumatoid arthritis, has shifted research interest from a “one molecule-one target” to a “one molecule-multiple targets” approach. In these terms, the focus of this work is the design and study of pluripotent antioxidants which combine different properties including anti-inflammatory, free radical scavenging and antihyperlipidemic action. A series of 15 new derivatives by combining non-steroidal anti-inflammatory bioactive molecules with antioxidant functional moieties have been designed, synthesized and evaluated both *in vitro* and *in vivo*. This incorporation of multiple pharmacophores in the same structure led to an increase (2-10 fold) in both antioxidant and antiinflammatory profile, compared to reference bioactives/drugs, while some derivatives exhibited an interesting antihyperlipidemic activity. This work may compliment the latest trends in antioxidant drug development and may benefit our rational drug design strategy and practice.

DEVELOPMENT OF BENZOIMIDAZOLIC STRUCTURE INHIBITORS OF HUMAN FATTY ACID AMIDE HYDROLASE ENZYME (h-FAAH)

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During the last few years, the endocannabinoid system has emerged as a highly relevant topic in the scientific community, due to the fact that many different regulatory actions have been attributed to it and it is involved in several pathophysiological conditions [1]. The relevance of the system is further strengthened by the notion that drugs interfering with the activity of the endocannabinoid system are considered as promising candidates for the treatment of various diseases, including obesity, Parkinson's disease, Alzheimer's and others [1,2].

Based on this background, our research group has designed series of compounds aimed at the direct modulation of CB_1 and CB_2 receptors [3, 4, 5]. The modulation strategy has been extended to indirect agonist action through the design of FAAH inhibitors. The interest in designing this last type of molecules is due to the fact that FAAH inhibitors generate a specific increase of anandamide in tissues where endocannabinoids are produced by physiological protection mechanisms, giving a finer response in terms of site-selectivity. This characteristic makes it possible to suppose that the pharmacological effects associated with the inhibition of FAAH would be less adverse than those commonly associated with the direct activation of the CB_1 receptor. In addition, FAAH inhibitors have already shown anti-inflammatory effects by suppressing the release of inflammatory chemical mediators by stimulating CB_2 receptors in immune cells [5].

Based on the same work line and having the in-silico model of the FAAH enzyme, we designed 2 series of new benzoimidazole central core molecules with inhibitory capacity on FAAH.

The work carried out so far, has consisted mainly in the synthesis of 2 families of compounds, containing the basic structure of a ring of benzoimidazole associated through a connector to various substituted arylpiperazines. In addition, the docking studies of the compounds with the protein is reported and their subsequent evaluation as inhibitors of the fatty acid amide hydrolase enzyme.

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FONDECYT (Grant 1150121)

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DRUG-FRAGMENT BASED EXPLORATIONS FOR NOVEL ENTEROVIRUS INHIBITORS

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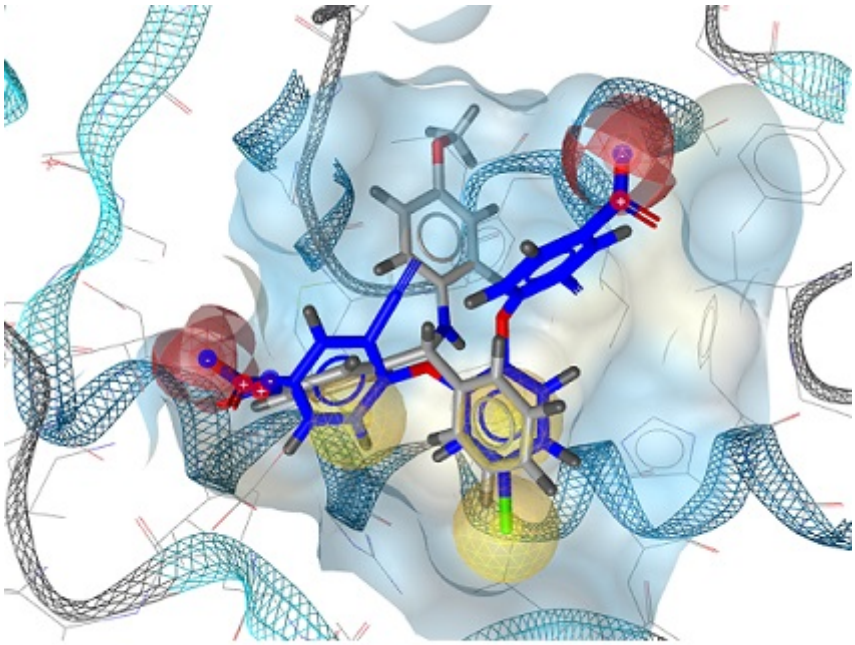
Enterovirus infections can lead to several diseases such as poliomyelitis, hand-foot-and-mouth disease, myocarditis or aseptic meningitis. Due to the absence of marketed drugs against these viruses, the identification of enterovirus inhibitors remains an unmet medical need.

A non-nucleoside inhibitor, recently identified as a broad-spectrum inhibitor of enterovirus polymerases (1), presents a lack of drug-like properties. This study aimed to identify new chemical scaffolds while keeping biological interactions identified between the initial ligand and enterovirus polymerases.

To proceed, the crystal structure of the reference inhibitor was the starting point for a **structure-based drug design** approach, using the LigandScout software (2). After the validation of the pharmacophore model, virtual screening performed on a database of combined **drugs fragments**, issued from the Prestwick Drug-Fragment Library, afforded hits presenting optimal drug-like properties.



Structure-based pharmacophore of enterovirus polymerase, illustrated with the reference inhibitor and a screening hit.

Some of these virtual compounds were then prepared to evaluate the **antiviral activity** of diverse scaffolds. Primary assays led to the identification of hits, which allowed to move further to the hit validation step.

Thus, this project combines the innovative use of fragments with computational chemistry for optimizing the hit discovery process.

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SALINOMYCIN DERIVATIVES: NEW ANTICANCER AGENTS TARGETING RELAPSE AND METASTASIS FORMATION

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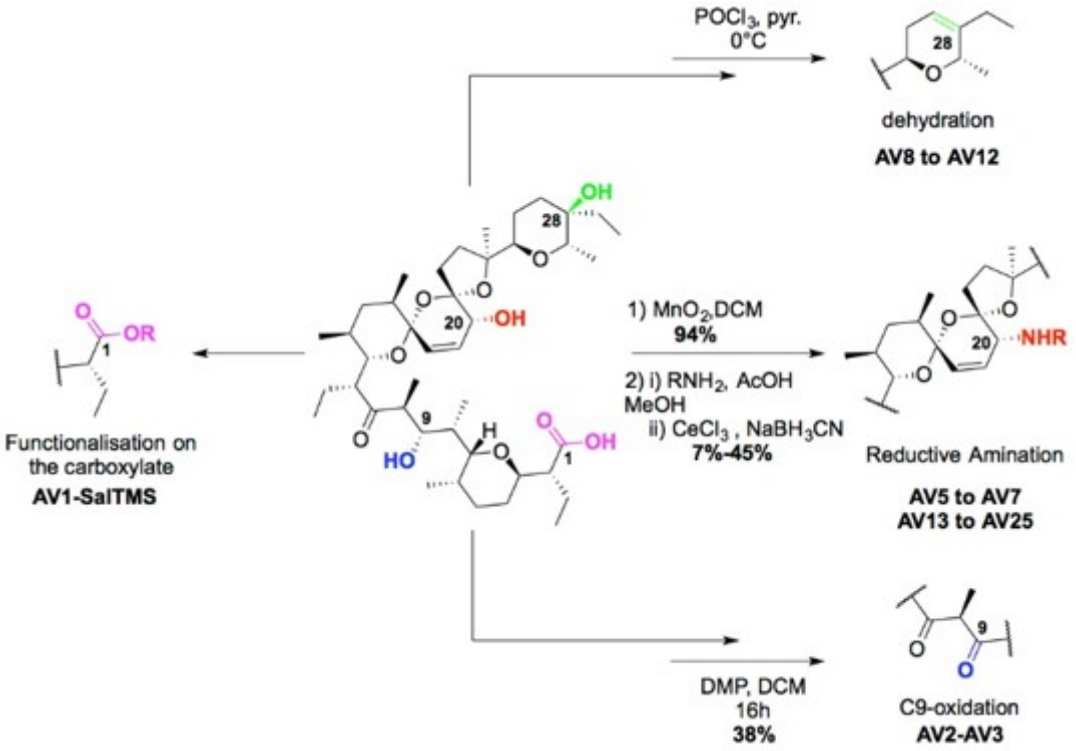
Cancer Stem Cells (CSC) present a subpopulation of cells within a tumor that can be responsible for cancer relapse after therapy and for metastasis formation. These cells show an inherent plasticity and are capable of undergoing epithelial-to-mesenchymal transition in some cancers. In this context, the natural product Salinomycin (Sal) isolated from *S. Albus* has intrigued scientists around the world since 2009, when it was identified by Gupta *et al.* as a promising agent against breast CSC among over 16,000 compounds tested, using a high throughput screen.[1] Since this discovery, Sal has been widely studied and proved its significant anticancer property with high selectivity toward CSC. Natural products, such as Sal, are an excellent source of bioactive compounds with a potential for drug discovery.

Recently, our lab discovered a mechanism where Sal interacts with iron and sequesters this metal in lysosomes.[2] Leading on from this work, we herein present specific modifications that can fit with this recently established mechanism. Four main positions of the molecule were investigated, including dehydration of C28, esterifications of the carboxylate, oxidation of the C9 hydroxyl and amination of the C20 alcohol.[3-5] We evaluated the IC_{50} activity of cell proliferation of all these molecules against transformed human mammary epithelial HMLER cells sorted into control and CSC cell lines.[6] We discovered that the activity of Sal derivatives was significantly improved by the replacement of the C20 hydroxyl by an amine.



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GEMCITABINE-GNRH BIOCONJUGATES BEARING OXIME BOND LINKAGES: SYNTHESIS, IN VITRO STABILITY, DRUG RELEASE AND CYTOTOXIC EFFECT

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Cancer is the second leading cause of death worldwide and as a result a variety of strategies are currently being exploited to concur it. Current treatment processes involve a combination of treatments like surgical intervention, radiation and chemotherapeutic drugs. Notably, drugs used for this purpose are inevitably cytotoxic in order to eliminate cancer cells, but they lack selectivity and inevitably cause severe side effects on the patient's health. A rapidly emerging field of therapy involves Peptide-Drug Conjugates (PDCs), which are considered as an inextricable part of the oncologic armamentarium and are continuously explored as a viable approach to target malignant tumours[1, 2]. Gemcitabine is one of the most frequently used nucleoside analogues in chemotherapy for various types of solid tumors[3] but there are certain limitations in its usage mostly due to its collateral cytotoxicity, the drug resistance and its conversion to the inactive metabolite (dFdU). Towards this end, we rationally designed and synthesized three Peptide – Drug Conjugates bearing oxime bond, consisted of gemcitabine (drug), D-Lys^6-GnRH (tumour-homing peptide) and aminooxy acetic acid (acid-labile linker). This concept was based on the fact that D-Lys^6-GnRH selectively binds on GnRH-Receptor, overexpressed in various cancer cells[4], and gets internalized via endocytosis, dragging gemcitabine intracellularly and therefore surpassing the drug resistance limitation by introducing an alternative entrance path. To halt its unwanted deamination to dFdU, its free -NH_2 moiety was capped with the linker. Last, the utilized linker gets hydrolysed in the slightly acidic pH of the tumour microenvironment, enhancing the drug accumulation in malignancies. Finally, we evaluated the biological profile of the three conjugates regarding their *in vitro* cytotoxicity, stability in cell culture and human plasma, as well as their consequent drug release in prostate cancer cell lines.

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PROOXIDATIVE EFFECTS, DNA AND HSA BINDING OF NAPHTHOQUIONONE DERIVATIVES

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Our previous study provided a strong indication of the potential use of a-methylbutyrylshikon (**1**), acetylshikonin (**2**) and b-hydroxyisovalerylshikonin (**3**) as antitumor agents.[1] Many compounds decrease the viability of tumors cells by binding to DNA and/or by inducing the ascending level of oxidant stress in exposed cells. Also, HSA can play a main role in drug transportation. Accordingly, in this study we have investigated the possible mechanisms of antitumor activity of these shikonin derivatives by estimating concentrations of superoxide anion radical ($O2^{\cdot-}$), nitrite ($NO2^{-}$) and glutathione in HCT-116 cell line. Compounds **1** and **3** expressed significant prooxidative activity, while all tested compounds exhibited significant increase in nitrite levels. Also, all examined compounds significantly increased the concentration of oxidized glutathione (GSSG) suggesting significant prooxidative disbalance. The levels of reduced glutathione (GSH) was also elevated as a part of antioxidative cell response. The data indicate that induced oxidative imbalance could be one of the triggers for previously recorded decreased viability of HCT 116 cells exposed to tested naphthoquinone derivatives. Moreover, we examined interactions of compounds **1**, **2** and **3** with CT-DNA and HSA by molecular docking and spectroscopic analysis. Based on the obtained results, it can be concluded that these compounds have established important interactions with HSA through various amino acids such as LYS195, ARG222, TRP214, GLU153, TIR452, while the most important interactions with the DNA molecule are achieved through DG12, DA13, DT14.

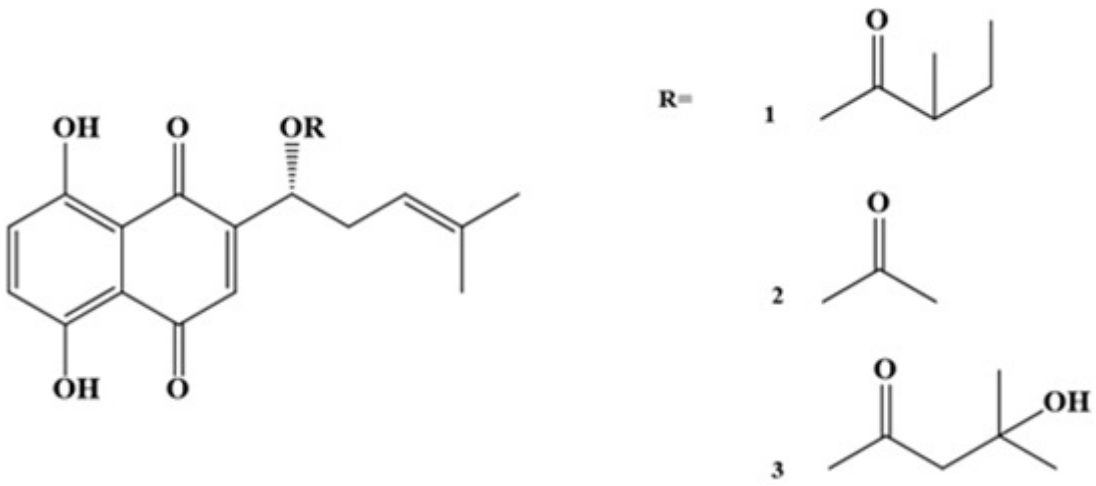

Figure 1. Chemical structures of examined naphthoquinones

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DEVELOPMENT OF GSTO1-1 INHIBITORS FOR THE TREATMENT OF INFLAMMATORY CONDITIONS

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Glutathione transferase omega 1-1 (GSTO1-1) is an enzyme which has recently been shown to have an essential role in bacterial lipopolysaccharide (LPS) stimulated inflammatory responses,[1] as well as to mediate the activation of NLRP3 inflammasome by deglutathionylating NEK7.[2] The inhibition of this enzyme could potentially target various diseases, including acute and life-threatening inflammatory responses such as those involved in sepsis, NLRP3 inflammasome involved diseases such as type 2 diabetes and Alzheimer's disease, and diverse human cancers.[3] So far, a diverse array of small molecules have been reported as GSTO1-1 inhibitors, although they are all relatively underdeveloped.[3] The most extensively investigated inhibitors were discovered as activity-based probes, which function by covalently labeling the active site GSTO1-1 cysteine (Cys32) thiol with their chloroacetamide warheads.[4,5] In this work, we chose one of these chloroacetamides, termed C1-27, as the lead compound for medicinal chemistry optimization towards novel GSTO1-1 inhibitors with better inhibitory activity. We researched the potential for decreasing ligand reactivity, as well as using structure-guided design aimed to increase non-covalent interactions, in order to improve the chances of selectivity and safety while maintaining potency. In the work to be presented, we investigated the lead-likeness of C1-27 in depth, synthesized three series of novel C1-27 analogues to study its structure-activity relationship (SAR) and evaluated their enzymatic inhibitory activities by 4-NPG assay. The k_{inact}/K_I values of selected compounds were measured as a more accurate potency evaluation of covalent inhibitors. We also tested the inhibitory activities of selected compounds in cell.

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DESIGN AND SYNTHESIS OF ARYLOXY BENZAMIDE DERIVATIVES WITH POTENTIAL INHIBITORY EFFECT AGAINST SIRT2

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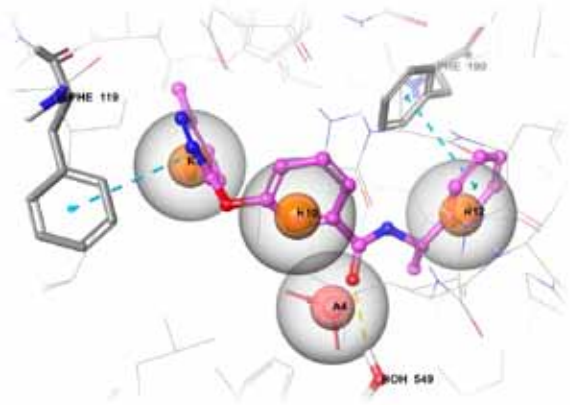
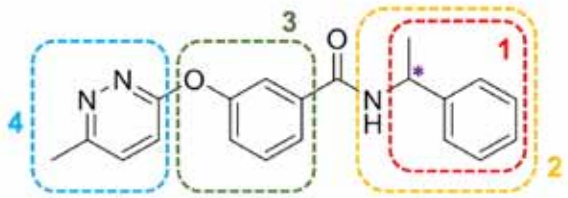
Sirtuins (SIRTs) are a class of nicotinamide adenine dinucleotide (NAD^+)-dependent protein histone deacetylases (HDACs) that catalyses the reversible deacetylation of lysine residues in the histones or non-histone substrates. Mammalian sirtuins consist of seven isoforms (SIRT1-7), which show different subcellular localizations and enzymatic functions. Among the seven human sirtuins, SIRT2 predominantly located in the cytoplasm but is enriched in the nucleus during mitosis. [1] Its activity has been found to be deregulated in a variety of cancers, metabolic and neurodegenerative disorders such as Parkinson's disease and Huntington's disease. Therefore, selective SIRT2 inhibitors are of growing interest as potentially candidate therapeutic agents to treat SIRT2-dependent pathologies as well as valuable tools to investigate and define the biological roles of SIRT2. In our preliminary study [2], a virtual screening campaign was performed by using the pharmacophore model which was generated by a strategy combining ligand- and structure-based features. Three SIRT2 inhibitors were identified among the hits and selected as lead compounds. The lead optimization studies were done according to binding modes of inhibitors in SIRT2 active site and aryloxy benzamide derivatives were designed and synthesized which are expected to be potent and selective inhibitors.





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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW BENZOTHIAZOLE AMIDE DERIVATIVES AS BRAFV600E INHIBITORS

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BRAF mutations are present in 8% of human cancers and they appear in different malignant tumors, more frequently in melanoma (>50%).[1] So far, two selective BRAF inhibitors have been approved by the FDA for the treatment of metastatic melanoma with BRAFV600E mutation and also combination therapy with MEK inhibitors.[2] However, due to the rapid development of resistance to treatment and the various side effects that come along with therapy, the interest in this field has focused in the discovery of new inhibitors of the MAPK pathway that overcome the problems mentioned above. In order to contribute in this field, we designed and synthesized a series of compounds using the benzothiazole ring as a scaffold, a functional group that is present in many approved drugs (Figure 1). In the present study, we describe the synthesis of novel benzothiazole derivatives containing side chains with amide, sulfonamide or other groups. Synthetic schemes as well as biological evaluation of the target molecules will be discussed.

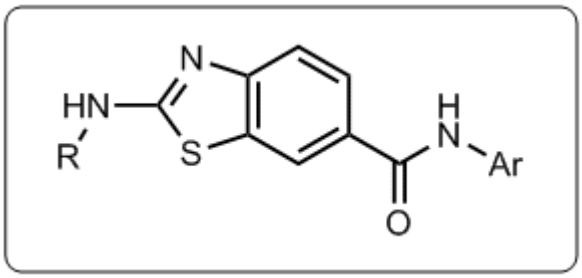

Figure 1: General structure of new benzothiazole derivatives.

Acknowledgements

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THE INTERACTIONS BETWEEN DIFFERENT FLUOROQUINOLONES AND SELECTED TEMPO AND PROXYL DERIVATIVES – FLUORESCENCE QUENCHING STUDIES

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The interactions between a group of different fluoroquinolone antibiotics (ciprofloxacin, danofloxacin, enrofloxacin, levofloxacin, marbofloxacin, norfloxacin and ofloxacin) and various 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,2,5,5-tetramethyl-1-pyrrolidinyloxy (PROXYL) derivatives have been studied mainly in aqueous solutions with the use of spectroscopic techniques – namely UV-Vis absorption as well as steady-state and time-resolved fluorescence spectroscopy – and supported by theoretical calculations of molecular radii and ionization potentials. Since it has been found that the fluorescence intensity of the chosen fluoroquinolones is efficiently decreased by the nitroxides, the mechanism of fluorescence quenching has been determined. The work constitutes a continuation of our previous experiments on the interactions between different antibiotics and 4-hydroxy-TEMPO[1]. The biological significance of this work is proven by the fact that TEMPO and PROXYL nitroxides have already many applications and their detection and quantitative determination under physiological conditions might help to understand the mechanism of an oxidative stress.

This work was supported by the Polish National Science Centre (NCN) under the Grant No. 2016/23/D/ST4/01576.

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STRUCTURAL CHARACTERIZATION OF NUCLEOBASE TRANSPORTER UAPA USING METADYNAMICS

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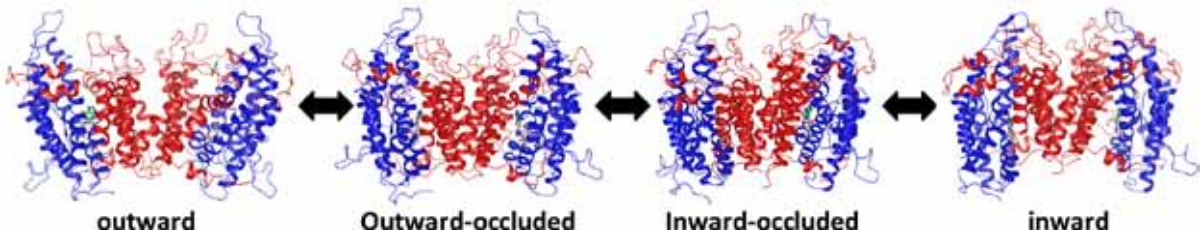
Transmembrane transporters are proteins mediating the selective uptake or efflux of solutes, metabolites, drugs, or ions across cellular membranes. Among them, NCS2/NAT proteins are H+ or Na+ symporters responsible for the uptake of purines, pyrimidines or related metabolites in bacteria, fungi and some plants. In particular, the UapA transporter of Aspergillus nidulans is specific for the transport of xanthine and uric acid in the fungi cells. While A.nidulans is harmless for humans, A.fumigatus, another member of the Aspergilli family, is the most common airborne fungal pathogen and can cause severe and usually fatal invasive infections in immunocompromised hosts. For this reason, elucidating the molecular mechanism of the A.nidulans' transporters is important to illustrate how to exert an exogenous control of its activity, thus paving the way to the development of anti-fungal drugs.

UapA works as a dimer, each unit consisting of 14 transmembrane segments folded in a rigid core domain and a flexible gate domain. Its biological function is based on a transportation mechanism called "elevator", which implies the relative motion of the gate domains sliding on the core. The entire transportation process can be divided in four protein states: Outward-Open (OOp), Outward-Occluded (OOc), Inward-Occluded (IOc), and Inward-Open (IOp). The endogenous ligand approaches the dimer from outside the cell to the OOp conformation, which progressively evolves into the IOp conformation allowing the molecule to enter the cytoplasm. Importantly, a crystal structure of the IOp conformation was recently resolved and several mutations have been reported, identifying key residues in the transportation mechanism. However, the exact translocation pathway remains elusive and the transportation mechanism is still unclear.

In this project, the objective is to reproduce the "elevator" mechanism from the OOp to the IOp state of the protein, by employing cutting-edge metadynamics simulations. In this way, we aim to correlate computational and experimental data and gain insight into this large-scale and complex phenomenon. Structures of the missing steps in the translocation pathway, namely OOp, OOca and IOc states, were built using targeted MD simulations starting from the UapA pdb (PDBID 5i6c) and using as template the crystal structures of the homologous transporters Band3, Bor1, UraA, respectively. A Path Collective Variable defined in the space of the root main square deviation of selected protein's backbone atoms was chosen to reproduce the large-scale conformational changes of the core-gate domains. Interestingly, we observed in the simulation an asynchronous behaviour of the dimers, in which they undertake the transportation mechanism only one per time. Furthermore, simulating the Xanthine in the binding site with the receptor in the IOp state, we found that Gln 408 plays a key role in the ligand unbinding, confirming data previously reported in literature. In particular, its flexibility allows to lead the ligand throughout most of the transportation process and deliver it to Arg481, which finally releases the molecule inside the cell.



5-IODO-4-THIO-2'-DEOXYURIDINE AS A SENSITIZER OF X-RAY INDUCED CANCER CELL KILLING

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Radiotherapy is the most common modality for treating human cancers. However, oxygen levels in solid tumors are very low, and therefore tumor cells become resistant to X-rays. This fact calls for introducing radiosensitizers, i.e. chemical agents capable of radiosensitizing cancer cells to the effects of high-energy radiation, and in consequence, effectively reducing the therapeutic dose of ionizing radiation, which is not neutral to normal cells adjacent to the tumor.[1]

In this communication, we report 5-iodo-4-thio-2'-deoxyuridine (ISdU) as a compound that can effectively lead to X-ray induced cellular death, which is proved by a clonogenic assay. The Histone H2A.X phosphorylation assay showed that ISdU sensitizes MCF-7 cells to ionizing radiation, at least in part, by increasing the formation of double strand breaks (DSBs) while the MitoDamage cell detah assay confirmed that pretreatment of MCF-7 cells with ISdU leads to the induced by X-ray reduction of cell viability and increase in the population of cells in early apoptosis. Additionally, the studied derivative turned out to be non-cytotoxic towards both normal and cancer cells; therefore, only after irradiation the lethal effects are observed inside the cell.

In order to elucidate the molecular mechanism behind the increased radiosensitivity of cells treated with the sensitizer, we performed radiation chemistry experiments for aqueous solutions of ISdU combined with theoretical studies. One of the major products of ISdU irradiation, SdU, results from the dissociative electron attachment process. Besides ISOdU and IdU (oxidation products), the $(ISdU)_2$ and ISdU-SdU dimers were identified. The decomposition of ISdU is almost 1.5-fold more effective compared to BrdU, a well-known radiosensitizer.[2]

The present studies established ISdU as a potential radiosensitizer that after incorporation into DNA and exposure to IR should cause lethal damage, such as strand breaks, both intra- and interstrand DNA crosslinks as well as DNA-protein crosslinks. The use of effective radiosensitizers results in an increase of the efficacy of radiotherapy, allowing the reduction of the employed radiation dose, which eventually gives radiological protection to healthy tissues.

Supported by the Polish National Science Center (NCN) under the Grant No. UMO-2014/14/A/ST4/00405 (J. R.)

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OXINDOLE SYNTHESIS VIA ORGANOCATALYTIC REACTIONS WITH THIOESTER ENOLATES

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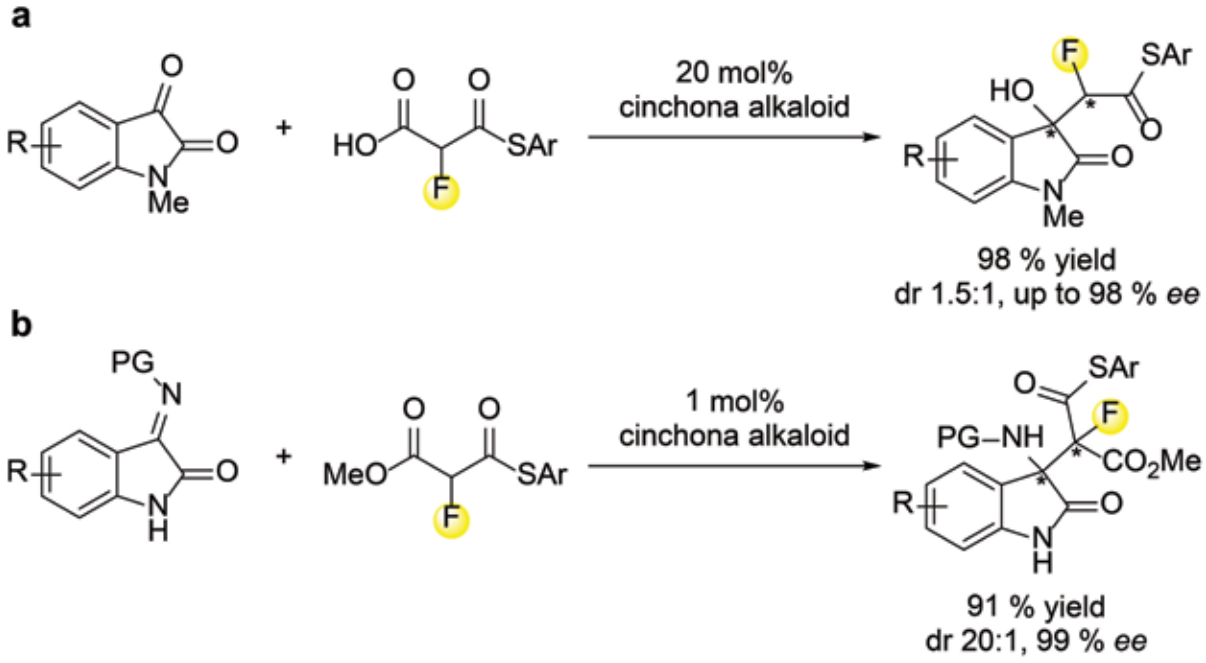
Thioester enolate surrogates are utilized by nature for the synthesis of polyketides or fatty acids[1] and are valuable in organic chemistry for C-C bond formations.[2] Our group developed alkylated and fluorinated malonic acid half thioesters (MAHTs) and monothiomalonates (MTMs) as masked thioester enolate equivalents and used them in organocatalytic addition reactions to several electrophiles, including nitroolefins, imines, isatin-ketimines and aldehydes. The products were obtained in excellent yields and stereoselectivities.[3]

We are currently expanding this methodology to reactions of fluorinated thioester enolate equivalents with isatins and isatin-ketimines to access fluorinated oxindoles. Oxindoles are prominent motifs in many therapeutically active compounds[4] and fluorine substituents can be expected to further enhance their potency.[5]

Fluorinated malonic acid half thioesters (F-MAHTs) undergo decarboxylative addition to protected isatins using cinchona alkaloid catalysts in excellent yields and moderate to excellent stereoselectivities (Scheme 1a).

The addition of fluorinated monothiomalonates (F-MTMs) to isatin-ketimines using cinchona alkaloids as catalysts, provided 3-amino oxindoles in excellent yields and stereoselectivities (Scheme 1b). Remarkably low catalyst loadings and short reaction times sufficed to obtain the product with two adjacent tetrasubstituted stereocenters without the need for a protecting group at the isatin lactam.

The poster will present the scope of the organocatalytic reactions and the preparation of downstream analogs of the chiral 3-hydroxy and 3-amino oxindoles.



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DEVELOPMENT OF L-741,626 ANALOGUES SELECTIVELY TARGETING THE DOPAMINE D2 RECEPTOR

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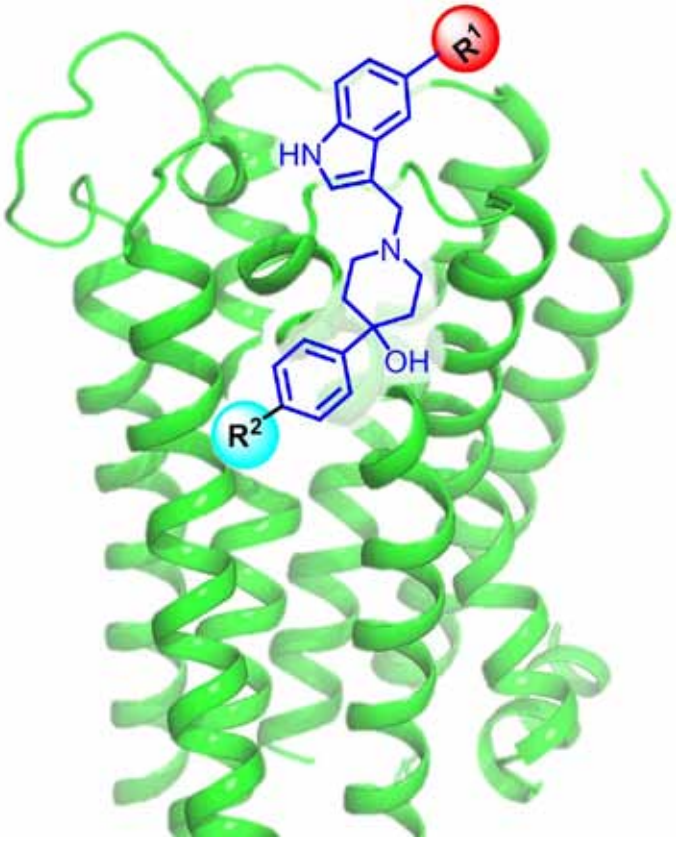
Dopamine receptors belong to the 'Class A' rhodopsin family of G protein-coupled receptors (GPCRs) and are essential for many neurological processes. Among the five dopamine receptor subtypes, the dopamine D_2 receptor (D_2R) is a crucial target for treating schizophrenia and Parkinson's disease. However, despite the evident therapeutic importance, there is scarcity of highly selective compounds targeting D_2R.

The antagonist L-741,626 displays selectivity for the D_2R over the structurally related dopamine D_3 receptor (D_3 R) and dopamine D_4 receptor (D_4R) subtypes.[1-2] This pattern of subtype selectivity is distinct from the majority of ligands designed to target the D_2-like dopamine receptors that do not display selectivity across this receptor family. In this research, we aimed to design and synthesize a focused library of L-741,626 analogues and study their binding mode to the D_2R, to develop ligands with enhanced receptor selectivity as a potential treatment for schizophrenia. Additionally, this research could provide a source of new pharmacological tools for exploring the structure and physiological role of the D_2R. We successfully synthesized and pharmacologically characterized several rationally designed L-741,626 analogues. Some of these compounds are able to bind to D_2R with high affinity and selectivity over the highly homologous D_3R and D_4R subtypes. These results provide insights into the binding directions of this important compound.



SYNTHESIS, PHOTOCHEMICAL REACTIVITY AND BIOLOGICAL ACTIVITY OF QUINONE METHIDE PRECURSORS CONTAINING BODIPY CHROMOPHORE - POTENTIAL ANTICANCER DRUGS

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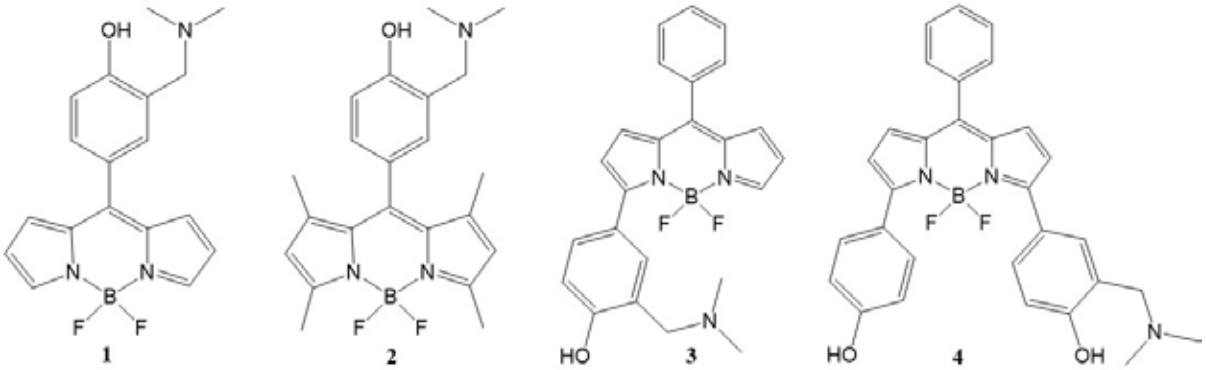
Quinone methides (QMs) are reactive intermediates that have been shown as useful synthons in organic synthesis,1 as well as biologically active agents applicable in biochemistry and medicine.[1,2]

It has been shown that QMs react with nucleotides and induce DNA alkylation and cross-linking, leading to cytotoxicity.[3-5] The generation of QMs under mild conditions can be facilitated by photochemical elimination reactions.[6] On the other hand, BODIPY derivates are commonly used dyes for biomolecular labeling since they are characterized by good photochemical stability and excellent photophysical and spectral properties.[7]

To obtain molecules which can be excited by visible light of >650 nm which is needed for the penetration through tissue, we incorporated BODIPY chromophore into the QM precursor units.[8]

BODIPY-QM precursor molecules **1-4** have been synthesized in the multi step synthetic pathway that includes condensation of an aldehyde and pyrrole to dipyrromethane moiety, its transformation to the BODIPY chromophore and subsequent functionalization. For **1** and **2**, the target molecules were obtained in a Mannich reaction. On the other hand, **3** and **4** were prepared in a reaction sequence involving chlorination with N-chlorosuccinimide, Suzuki coupling, deprotection of the benzyl group from the phenol and the Mannich reaction. Synthesized precursor molecules **1-4** undergoe photodeamination reactions and deliver the corresponding QMs that react with nucleophiles in a Michael addition, which may lead to biological effects. Antiproliferative activity of synthesized BODIPY-QM precursors was investigated using MTT assay on several cell lines with and without irradiation. An enhancement of the activity was observed for the cells that were irradiated. The MTT results will be discussed in light of the photochemical reactivity of the molecules and some structure-photoreactivity-biological activity relationship will be demonstrated.



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DESIGN, CHEMICAL SYNTHESIS AND FUNCTIONAL CHARACTERIZATION OF NOVEL AGENTS TARGETING PERSISTER AND PATHOGENIC BACTERIA

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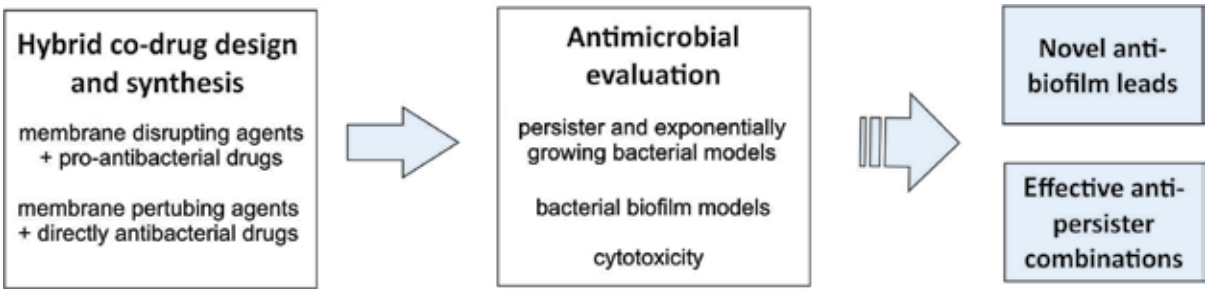
Antimicrobial resistance is a major global threat for public health and it is associated with soaring treatment and extensive societal costs. Infections caused by antibiotic-tolerant, biofilm forming Gram-negative bacteria, such as *P. aeruginosa*, are alarmingly rising and increasingly dependent on the use of last-resort drugs, such as colistin, which have also encountered evolving resistance [1]. On the other hand, the multidrug-resistant, biofilm-forming Gram-positive *S. aureus*, the causative species of various hospital-associated infections, is of especially serious concern. It has been now demonstrated that a bacterial phenotype known as "persister cells" exists, consisting of specialized survivor cells which cannot be eliminated by antibiotic therapy [2]. Studies of dose-dependent killing of *P. aeruginosa* biofilm have shown the presence of a small subpopulation of bacterial cells completely tolerant to antibiotics such as ofloxacin and ciprofloxacin [3]. The currently existing antimicrobial drugs possess only limited activity, if any, against persister cells. Thus, after a typical course with antibiotics, persister cells remain unaffected and they can switch into a metabolically active state as soon as the antimicrobial therapy is terminated, thus prompting the relapse of the infection and prolonged treatment periods [4].

The aim of the project is to design, synthesize and evaluate novel compounds against persister and rapidly multiplying pathogens of *S. aureus* and *P. aeruginosa*. Several antimicrobial co-drugs of membrane disrupting agents, pro-antibacterial and directly antibacterial drugs can be designed and synthesized, as indicated in the scheme below. Successfully synthesized compounds will be evaluated for their antimicrobial activity to determine their effect on persister and exponentially growing bacteria, bacterial biofilms and their use in the protection of clinically relevant biomaterials. Cytotoxicity of the selected drugs will be determined in mammalian cell lines as well.



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IDENTIFICATION OF A NOVEL QUINOLINE-BASED DNA DEMETHYLATING COMPOUND HIGHLY POTENT IN CANCER CELLS

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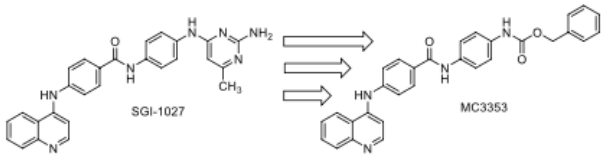
Background: DNA methyltransferases (DNMTs) are epigenetic enzymes involved in embryonic development, cell differentiation, epithelial to mesenchymal transition and control of gene expression, whose overexpression or enhanced catalytic activity has been widely reported in cancer initiation and progression.[1] To date, two DNMT inhibitors (DNMTi), 5-azacytidine (5-AZA) and 5-aza-2'- deoxycytidine (DAC), are approved for treatment of myelodysplastic syndromes and acute myeloid leukemia. Nevertheless, they are chemically instable and quite toxic for healthy cells, thus the discovery of novel DNMTi is urgent. [1,2]



Scheme1: Design of MC3353

Results: We will present the identification of a new quinoline-based molecule, MC3353, as a non- nucleoside inhibitor and downregulator of DNMT. The design of MC3353 is based on the known non nucleosidic DNMTi SGI-1027 replacing the 4-methyl-2,6-diaminopyrimidine moiety of the template with a benzyl carbamate function. This compound was able, in promoter demethylating assays, to induce enhanced green fluorescence protein (EGFP) gene expression in HCT116 cells and transcription in a cytomegalovirus (CMV) promoter-driven luciferase reporter system in KG-1 cells. Moreover, MC3353 displayed strong antiproliferative activity when tested on HCT116 colon cancer cells after 48 h of treatment at 0.5 μM. At higher doses, this compound provided a cytotoxic effect in double DNMT knockout HCT116 cells. MC3353 was also screened on a different panel of cancer cells (KG-1 and U-937 acute myeloid leukemia, RAJI Burkitt's lymphoma, PC-3 prostate cancer, and MDA-MB- 231 breast cancer), where it arrested cell proliferation and reduced viability after 48 h of treatment with IC50 values ranging from 0.3 to 0.9 μM. Compared to healthy cell models, MC3353 induced apoptosis (e.g., U-937 and KG-1 cells) or necrosis (e.g., RAJI cells) at lower concentrations. Importantly, together with the main DNMT3A enzyme inhibition, MC3353 was also able to downregulate the DNMT3A protein level in selected HCT116 and PC-3 cell lines. Additionally, this compound provided impairment of the epithelial-to-mesenchymal transition (EMT) by inducing E-cadherin while reducing matrix metalloproteinase (MMP2) mRNA and protein levels in PC-3 and HCT116 cells. Last, tested on a panel of primary osteosarcoma cell lines, MC3353 markedly inhibited cell growth with low single-digit micromolar IC_{50} ranging from 1.1 to 2.4 μM. Interestingly, in Saos-2 osteosarcoma cells, MC3353 induced both expression of genes and mineralized the matrix as evidence of osteosarcoma to osteoblast differentiation.

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TOWARDS THE SYNTHESIS OF NOVEL PROTEASE INHIBITORS: LATE-STAGE MODIFICATIONS ALLOWING DIVERGENT SYNTHESIS FROM PEPTIDE-CARBOXYLIC ACIDS

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Protease inhibition is an emerging and promising tool in the development of novel antivirals. Orthosteric protease inhibitors are often peptide-like molecules mimicking fragments of the protease natural substrate. Inhibition is generally attained introducing on the carboxylic acid terminus of the peptido-mimetic backbone reactive moieties towards the active site of the protease (covalent inhibitors) or unreactive amide bioisosters (non-covalent inhibitors). Library generation of such inhibitors is often hampered by the need of centering the synthesis on the first amino-acid derivative, forcing the chemist to tailor-make each compound since the very beginning. Herein we present the successful development of a library of viral protease inhibitors stemming from the late stage functionalization of peptide-carboxylic acids, deploying the most recent developments in organic synthesis.

DESIGN AND SYNTHESIS OF MULTISUBSTITUTED 1,2,3,4-TETRAHYDROPYRIMIDINES AS NOVEL ALLOSTERIC MODULATORS TARGETED TO THE C1 DOMAIN OF PKC

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Protein kinase C (PKC) isoforms represent highly attractive drug targets as they modulate numerous cellular functions including metabolism, growth, apoptosis and differentiation.[1] Utilizing the crystal structure of the PKCδ C1B domain (PDB ID: 1PTR),[2] we have developed and previously reported hydrophobic isophthalic acid derivatives which allosterically modulate PKC activity by targeting its C1 domain.[3, 4] Recently, we synthesized and characterized the binding affinities of a series of multisubstituted pyrimidines as isophthalate analogs.[5] In contrast to our docking experiments, scaffold hopping from a phenyl to a pyrimidine core diminished the binding affinity of the compounds. However, since phospholipid bilayers play a key role during PKC activation, a deeper investigation with molecular dynamics simulations suggested that non-favorable ligand-bilayer interactions may contribute to the diminished affinity of those pyrimidine derivatives.[6] Based on the new insight, in the present study, we designed and synthesized a set of 1,2,3,4-tetrahydropyrimidines as novel derivatives targeting the C1 domain.

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