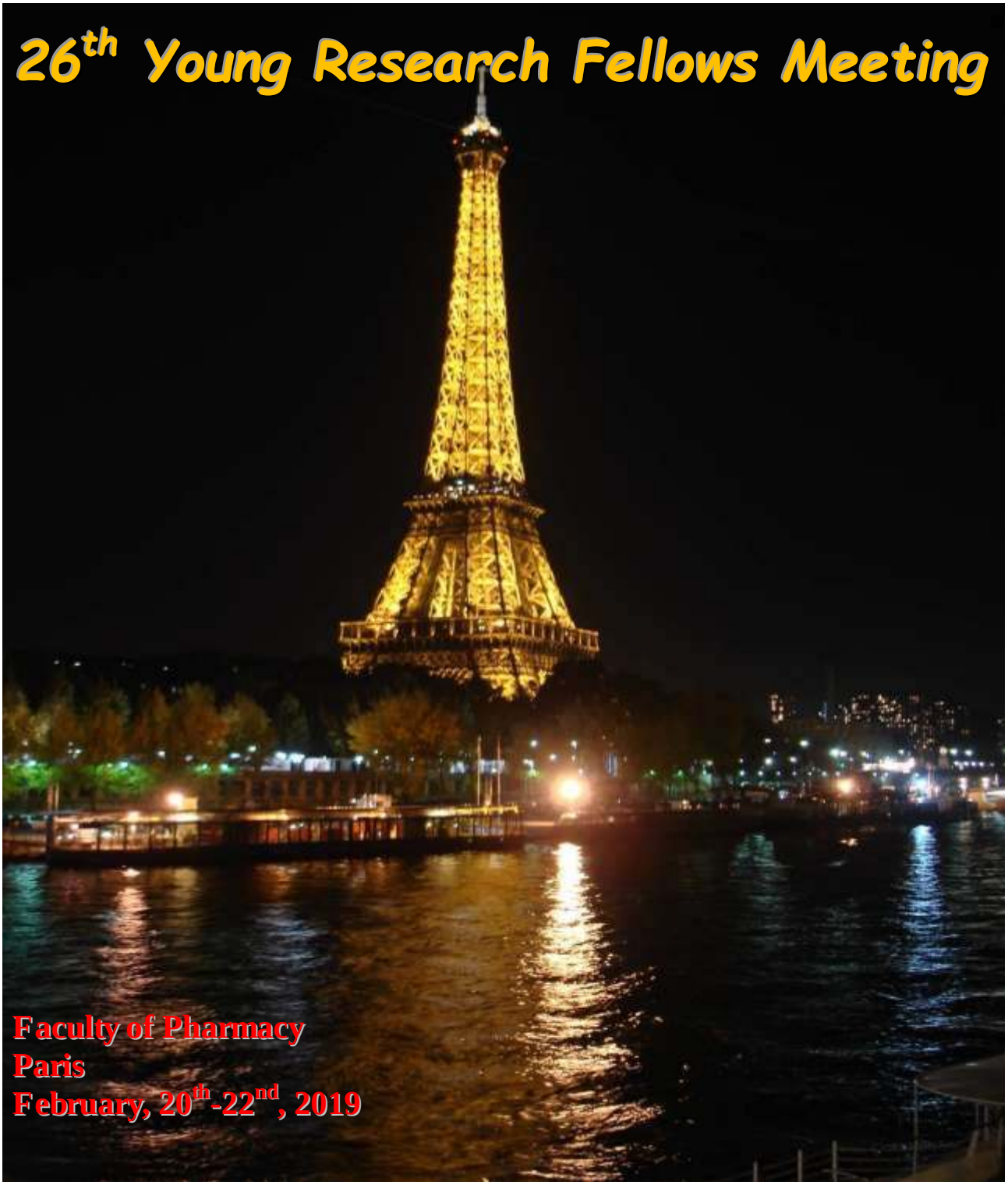
26th Young Research Fellows Meeting



Faculty of Pharmacy
Paris
February, 20th-22nd, 2019

Welcome to the 26th Young Research Fellows Meeting!

The YRFM Organizing Committee is very proud to welcome in Paris 350 young investigators issued from all the European countries to celebrate the twenty-sixth edition of this annual meeting! This meeting aims at offering both top-quality scientific and career sessions. Therefore, we are very grateful to Pr. E. Mikros (Greece), Pr. F. Borges (Portugal), Pr. Gilles Pagès, Dr. C. Andraud and Dr. G. Guichard (France) for accepting to give plenary session lectures. Their presence is the guarantee of the scientific excellence of the conference! Many thanks to them!
We also welcome several prestigious keynote lectures (see program below). In addition, many among you will have the opportunity to present your results by means of "oral communications", "flash poster presentation" and "poster sessions". Take the opportunity to highlight your projects in this outstanding environment, and maybe to receive awards for your work! We received many abstract, and sincerely, the selection has been very difficult. This is one of the reasons for which the sessions start early in the morning, and end late in the evening. We made the choice to select a maximum of lectures!
The career session will enable you, in a friendly atmosphere, to be interviewed and to discuss with professional recruiters belonging to pharmaceutical companies, biotechs and start-ups. It will be also for you an opportunity to learn from people who created successfully their own company.
The success of this meeting is indicated by the number of sponsors issued from institutional (including Fondation ARC, Paris Descartes University) and industrial partners (including Institut de Recherches Servier, Sanofi and IRIS Biotech), that you can discover in this book.
Nevertheless, the SCT and the YRFM Organizing Committee are particularly indebted to Prof. Jean Louis Beaudeux, the Dean of the Faculty of Pharmacy, who opened the doors of his faculty.
We are also proud of our Pharmacist's students. They will highlight their faculty during the Show "Pharma Welcomes You", with the participation of dancers and musicians. You will also eat traditional pancakes thank to their cooking skills! Please note, that the fund collected when you will purchase pancakes will be used to fund their social actions in Europe and Africa! So, do not hesitate to be "gourmand"…. Indeed, in the Faculty of Pharmacy, the Young Research Fellows Meeting has truly the feeling to be "at home"!
Finally, we introduced in our program this year two social events. We hope, you will enjoy the evening "sharing food and science" followed by the show made by our pharmacist's students. We also hope that you will not forget your gala dresses and your tuxedo for the Party, on Thursday evening!!
We sincerely hope you will never forget these three days in Paris!
"Bienvenue à Paris!"
Luc Demange and Philippe Belmont on behalf of the organizing committee

UNIVERSITÉ PARIS DESCARTES

FACULTÉ DE PHARMACIE DE PARIS

It is with great pleasure that I welcome you to the Faculty of Pharmacie of Paris for this important congress.

In the heart of Paris, as part of Paris Descartes University, the Faculty of Pharmacy of Paris prepares its students for the degree of Doctor in pharmacy. Created in 1803, it is looking for excellence in the field of pharmaceutical research and teaching and offers a wide range of professional opportunities.

In a historic building with an exceptional botanical garden, the faculty welcomes 4500 students, supervised by 250 teachers and a 400 technical/administrative staff. The department of Chemistry and Physical Chemistry is one of the six departments dedicated to both scientific research and educational programs.

The Research Center plays a crucial role in the research and innovation related to drugs and health. Il is constituted of 10 academic research units, engaged in partnerships with prestigious research institutions such as the CNRS, Inserm and the IRD, and numerous technical platforms (Animal platform and Imagery of the little animal, Structural biology, Cellular and molecular imagery, Mass spectrometry and -omics, , Phospho-imaging…). The scientific production reaches 300 publications a year, ranking the faculty at the 28th international rank of pharmaceutical science institutions, and ranking first at the national level.

Coordinated by Professors Philippe Belmont and Luc Demange, the Scientific and Organizational Committee has prepared a very attractive scientific program. I hope that this congress will be an exceptional forum for your research in chemistry. I wish you a very good time in Paris!

Jean-Louis Beaudeux
Dean of the Faculty of Pharmacy of Paris

Discover the French Medicinal Chemistry Society (S.C.T.)!

Thank you for joining the 26th *Young Research Fellows Meeting community…*
As an immediate consequence, you become a new member of the French Medicinal Chemistry Society (S.C.T.) for one year. This is now the time for you to discover your society, and your subsequent advantages and privileges! We sincerely hope that you will enjoy this year of membership and that you will choose to stay with us for a long time!

Welcome to S.C.T.!

Société de Chimie Thérapeutique

ACTIVITIES

The **French Medicinal Chemistry Society** (Société de Chimie Thérapeutique, **S.C.T.**) was founded in 1966, with the aim to disseminate scientific results and promote interdisciplinary knowledge in the major pharmaceutical research and development domains covering the whole panel of Drug Discovery and related sciences from target identification to drug registration. The SCT is also involved in advancing medicinal chemistry by initiating cooperation, networking, providing training and rewarding scientific excellence. The S.C.T. is interested in developing and maintaining scientific contacts with industrial and academic research groups, medicinal chemistry related associations, federations, both on national and international level. The S.C.T. is an active member of the European Federation of Medicinal Chemistry (E.F.M.C.).

Our Society organises each year **three** to **four** dedicated **scientific events**. By offering to young scientist reduced registration fees, lodging in low-cost hotels and a large admissibility to poster and career sessions, the S.C.T. strongly supports and promotes their participation to its conferences.

The most prestigious conference organized by the SCT is the "**Rencontres Internationales de Chimie Thérapeutique**" (RICT) an international congress devoted to the main scientific areas in medicinal chemistry. Usually, RICTs bring together internationally recognized speakers from Europe, Asia and North-America presenting their outstanding results in every aspect of modern drug discovery chemistry. In 2015, the 55th RICT will be held in Nantes (July, 3-5) and will be entitled "**interfacing chemical biology and drug discovery**". Please visit our website for more details and to discover the updated scientific program ! www.rict2019.org

The "**Young Research Fellows Meeting**", formerly "**Journées Jeunes Chercheurs**", provides a unique opportunity for attendees to present their research results in an outstanding environment provided by more than 25 years of S.C.T. expertise in organizing young fellows meetings. In addition, this meeting gives the young scientists the opportunity to meet human resources representatives of pharmaceutical companies, small biotechs, start-ups for simulated job interviews. Many special and personalized advices are given to upgrade their CV. Round-tables have also been organised. This event is alternatively held in Paris and in French Regions. Thus,

in 2018, the conference was held in Orléans, and in **2019 the "Young Research Fellows Meeting" community will be welcomed in Caen** for its conference!

Last years, S.C.T. was re-organized and consequently strongly modernized. Several series of measures have been introduced such as the reorganisation of the S.C.T. Board, and the creation of a new **Scientific Advisory Board** (SAB) of experts covering the main fields of medicinal chemistry. Lastly, a prestigious prize has been launched: the "**Pierre Fabre Award for Therapeutic Innovation**". Consequently, new partnership contracts have been established with pharmaceutical companies, public administrations and governmental institutions as well as sister societies in neighbouring countries. The communication of ongoing activities has been intensified to encourage subscriptions and thus power up the position of the SCT within the European Federation of Medicinal Chemistry and French Federation for Chemical Societies.

Importantly, the S.C.T. communicates through its modern website and through the social networks (LinkedIn, Facebook). Recruitment opportunities are frequently disseminated by our reactive communication team! Please read below the dedicated section.

Lastly, another important facet of the SCT is to promote and to support research by means of several prestigious prizes attributed to scientists for the excellence in their research! Moreover, in partnership with "Institut de Recherche Servier" the SCT launches yearly a specific call in drug discovery chemistry to support a 3-years PhD or post-doctoral research program!

To summarize, you belong now to a very dynamic society which organizes conferences, gives awards, supports excellence in drug discovery chemistry and provides to young scientists the unique opportunity to extend their professional network. We are sure that you want to stay connected with the worldwide drug discovery chemistry network and therefore that you will stay with us for long time!

Welcome to your society!

Prof. Luc Demange,
SCT Treasury Deputy,
Head of Junior Scientists Actions
Co-Chair of YRFM

Website

Société de Chimie Thérapeutique

http://www.sct-asso.fr

The S.C.T. website has been designed as a platform presenting the activities of the Society as well as a relay of communication between members. It is divided in two parts: a public part, and a private part which is accessible only to S.C.T. members with a login and a password. Everyone has a direct access to the News and Events directly on the homepage. They are classified in three categories (from the S.C.T., from our privileged partners, or from others).

Going to **http://www2.sct-asso.fr** provides access in French or in English to the membership application, or to the registration form for some of our meetings such as "Young Research Fellows Meeting" or one-day thematic meeting). S.C.T. members have access to the coordinates of all S.C.T. members that have accepted to share their address by filling out the form as below:

S.C.T. members can also retrieve their membership number required to pay the reduced fee for SCT organized meetings (such as RICT). By filling out the form "Find your membership number" they will receive an e-mail where are mentioned the membership number, login, password, and status of the membership for the current year.

Société de Chimie Thérapeutique

Social Networks

SCT is also present on the 2 most popular **social networks**, **LinkedIn** and **Facebook**.

You can become a "**Com. Committee SCT**" relation on **LinkedIn** and a member of the "RICT - International Conference on Medicinal Chemistry" and "SCT - Journées Jeunes Chercheurs" groups.

On **Facebook**, make "**Societe Chimie-Therapeutique**" a friend of yours and become a member of "Journées Jeunes Chercheurs" groups.

You will thus be permanently connected to the S.C.T. and its members: you will so have the opportunity to be linked to French (and European) medicinal and biotech community. You will be informed of News and Events organized by the S.C.T. : RICT and YRFM speaker profiles and sponsors will be made immediately available to you and you will be alerted to new job offers and to other information concerning particularly young medicinal chemistry scientist career.

« Young Research Fellows Meeting », formerly "Journées Jeunes Chercheurs" group on **Facebook**:

https://www.facebook.com/login.php?next=http%3A%2F%2Fwww.facebook.com%2Fgroups%2F235361546525890%2F

"RICT" group on **LinkedIn**:

http://www.linkedin.com/groups/RICT-International-Conference-on-Medicinal-3734237/about

RICT on LinkedIn **YRFM on Facebook**

The SCT Communication Board:
Dr. Frédéric Schmidt
Pr. Nicolas Willand

S.C.T. Awards

Société de Chimie
Thérapeutique

To promote excellence, but also to support young researchers at the dawn of their careers, the French Medicinal Chemistry Society provides each year prestigious prizes and grants to the academic and to the industrial "Drug Discovery chemistry" community. In this duty, the S.C.T. is highly supported by its generous sponsors, among them "**Janssen, a pharmaceutical company of Johnson & Johnson**", "**Pierre Fabre Médicament**", and "**Institut de Rescherche Servier**".
You can discover the full list of the laureates of each prize and each grant on the S.C.T. website!

Main S.C.T. Prizes

Ehrlich Prize.
This is a prestigious award, sponsored by "**Janssen**", which is attributed each year during the RICT to a researcher or to a research team for an outstanding contribution to medicinal chemistry.

Pierre Fabre Award for Therapeutic Innovation.
This prize, launched in 2014, is sponsored by the company "**Pierre Fabre Médicament**", in memory of its founder. It awards a confirmed researcher (junior or senior scientist) who has accomplished a decisive action, a scientific discovery, an innovative technology contributing to a substantial therapeutic innovation.

« ***Prix d'Encouragement à la recherche en chimie thérapeutiq*ue ».**
This prize is sponsored by **SCT**, and is devoted to European junior scientists, no older than 36 years. It awards the dawn of the laureate's career and considers globally his research contributions. This prize might be attributed to one, two... or more (!) young scientists. During the 26th Young Research Fellows Meeting, you will enjoy the lecture given by Dr. Cyril Ronco (ICN, Nice, France) who will receive this prize in 2019.

Research Grants
Yearly, the "**Institut de Recherche Servier**" launches a research call in spring. The S.C.T. is responsible for the announcements and takes part of the selection procedure. The final choice is in the hands of Servier. One or two projects are finally selected. The subsequent financial support corresponds to a 3-year PhD Fellowship or a 2-year Postdoctoral Fellowship.

Keep in mind that S.C.T awards the excellence in Drug Discovery Chemistry!

ACKNOWLEDGMENTS

Member of the organizing committee would like to thank all the partners who have supported the implementation of this Congress.

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About Servier
Servier is an international pharmaceutical company governed by a non-profit foundation, with its headquarters in France (Suresnes). With a strong international presence in 149 countries and a turnover of 4.152 billion euros in 2017, Servier employs 21,700 people worldwide. Entirely independent, the Group reinvests 25% of its turnover (princeps drugs) in research and development and uses all its profits for development. Corporate growth is driven by Servier's constant search for innovation in five areas of excellence: cardiovascular, immune-inflammatory and neuropsychiatric diseases, cancer and diabetes, as well as by its activities in high-quality generic drugs. Servier also offers eHealth solutions beyond drug development.

More information: www.servier.com

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Prestwick Chemical:
Screening Libraries and successful medicinal chemistry

Prestwick Chemical is a premium provider of medicinal chemistry services for 15 years, and started as spin-off of the University of Strasbourg, France. We also offer innovative smart screening libraries and research tools to pharmaceutical & biotechnology companies, as well as academic research laboratories and institutions.

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Contract research services in medicinal chemistry: Hit validation – Lead optimisation – Ligand profiling

Prestwick's team of well-trained medicinal chemists develops innovative medicinal chemistry strategies tailored to clients' needs. They are supported by state-of-art computational ligand design, including large scale virtual screening and take into account ADME/Tox as well as selectivity issues. This helps to minimize time and maximize results (in average 18 months from inception to acceptable drug candidate). Possible contracts include '"no string attached" programs (FTE based) and public funded projects.
Any chemistry offer is optimally tailored for pharma, biotech companies, TTOs or academia.
Eleven (11) optimized leads coming from our research ended in clinical phase (I to III) or on the market;

Various screening libraries (compound collections):

Prestwick has a portfolio of smart Libraries designed to ensure maximal chemical diversity, possibly to access new IP while remaining within reach of both low and high throughput screening processes. They are constantly updated and improved. Our clients have reported high quality hit generation rate.
The Prestwick Chemical Library® is our flagship and is mentioned in > 400 publications worldwide.

www.prestwickchemical.com
contact: infochem@prestwickchemical.fr

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Internet: www.iris-biotech.de

Who we are ....

On 24th July 1788 the first chemical factory in Germany has been founded in Marktredwitz as CFM (Chemische Fabrik Marktredwitz). IRIS Biotech has been established in 2001 as an offspring, in order to strengthen the position in the Peptide and Life Science market.

What we do for our customers ...

IRIS Biotech is specialized in reagents for Drug Discovery, Drug Delivery, and Diagnostics. We have specific know-how and production capabilities to manufacture and supply products from the following areas from grams to multi-ton lots:

1. Starting Materials for Peptide Synthesis, Peptidomimetic and Medicinal Chemistry

Protected amino acids, coupling reagents, linkers and resins for solid phase chemistry, natural & unusual amino acids, as well as building blocks used in Peptide Synthesis, Peptidomimetic and Medicinal Chemistry.

2. Technologies for Drug Delivery

With approx. 1000 different polymer carriers we provide the widest portfolio for drug delivery technologies used in Polymer Therapeutics for small API molecules, as well as for large biopharmaceuticals for latest state-of-the-art application areas like combination therapy and personalize medicine.

We carry the worldwide largest portfolio of PEGylating reagents from short monodisperse to long polydisperse poly(ethylene glycol) derivatives.

Poly(amino acids) like homopolymers of Arginine, Glutamic acid, and Ornithine, are modern drug carrier systems providing the advantages of polymer therapeutics also to small drug molecules.

PEG based Dendrimes offer a new possibility to synchronized multiple and parallel applications in diagnostics and combination therapy.

Our latest highlight : Poly(2-oxazolines) , where hydrophilicity and surface activity can be fine-tuned to application's requirements, as well as linkers for the synthesis of Antibody-Drug-Conjugates (ADCs).

3. Reagents for Life Sciences and Diagnostics

Substrates for reporter enzymes and drug interaction studies, metabolites, glucuronides and inhibitors, inducers, antibody conjugates and cross-linkers, natural products, with biological and pharmacological activity, carbohydrates, dyes and fluorescent labels as Tools in Immunology, Diagnostic, Biochemistry and Molecular Biology.

4. Contract Manufacturing

We are carrying out many Contract Manufacturing projects in these areas; our strong points are unusual derivatives with one or several chiral centers.

medicina

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Message from the Editor-in-Chief

The journal *Medicina*, has been issued since 1920, and is a peer-reviewed, bi-monthly journal that mainly focuses on publishing reviews and clinical and experimental studies. *Medicina* publications cater to clinicians, diagnosticians and researchers, and serves as a forum to discuss the current status of health-related matters and their impact on a global and local scale. The journal aims to report advanced knowledge related to problems in medicine, disseminate research on global health, and promote and foster prevention and treatment of diseases worldwide. Please consider *Medicina* for your next publication of novel and innovative research.

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- **Free of charge publication** The APC for Medicina is financed by a European Union grant, and papers are being published free of charge.

EFMC Yearbook 2019 Presentation Unit

Material delivery deadline: November 15, 2018

Company name	MercachemSyncom
Two-sentence description	MercachemSyncom is the leading European organic chemistry solution service provider for drug discovery. Our scope of activities ranges from hit finding to medicinal chemistry to API synthesis. As your preferred chemistry partner, we aim to create your value by combing our synthetic power, collective intelligence, medchem insights and CMC know-how.
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Fax	+31 24-372 3305
Email	Norimasa.morita@mercachem.com
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Interchim is a multinational company whose heart beats in France, dedicated to Sciences with its own Research and Development Laboratories. Interchim manufacture and distribute consumables and instruments for Research and Industry.

The Techno-Quality of the French multinational exported to the world.

Since its creation in 1970, by Jean Boch, PhD in Organic Chemistry and Mrs. Colette Boch, Interchim has repeatedly demanded to offer its customers products that meet their daily ambitions and challenges in the field of Chemistry, Analytical Sciences or BioSciences.

The specificity of Interchim is to remain faithful to its motivation: to anticipate and to remain attentive to the needs of its customers by proposing the most efficient and innovative technologies through a meticulous selection of the best existing products or by its own manufacture of consumables and instruments, which are now marketed on all continents, guaranteeing their quality and success.

If around the world, laboratories are colored blue and carry its standard, Interchim is a multinational whose heart sits in France. Its products and services are available in more than 50 countries, either directly as in France, Germany, Austria, Belgium or through its subsidiaries such as the United States or the United Kingdom, or in partnership thanks to Its network of distributors. This family-business company, headed by Lionel Boch (Chairman of the Management Board), Corinne Boch-Jourdain (Chief Executive Officer) and Véronique Boch (Chief Executive Officer), also strengthens its leadership position in Analytical Sciences, Chromatography and Purification. Interchim was the first manufacturer of instruments to market a system of Flash purification, whose collection is triggered by a mass spectrometer.

In a perpetual dynamic world, Interchim's aspirations are constant: to facilitate everyday life and to think of service as essential.

The website www.interchim.com gives access to more than 3.5 million scientific articles with prices updated daily. It is a unique window to discover the products essential to the research of scientists in the field of Fine Chemistry, Analytical Sciences and BioSciences.

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Bio-reagents Uptima®

In order to enable its customers to concentrate fully on their core business, by facilitating and reducing administrative tasks, Interchim has set up e-Procurement or Procurement Grouping solutions at the level of a laboratory (One lab Shop) or a company or entity (One Store Shop).

Accompanying customers around the globe so that their challenges today become tomorrow's success.

Beyond rigorous selection of the best consumables and instruments, Interchim's main objective is to provide the best solution for the application, technology or product solution that is most relevant for each of our customers to achieve their objectives or better exceed. For this, the technical services and support of the company are available to share their knowledge and give their advice.

Offer personalized services

Interchim proposes to its customers to carry out preparations upstream or downstream of their process in their laboratories so that they can devote themselves to their core business, reducing costs and increasing their flexibility. These services are reviewed on a case-by-case basis.

Encourage the sharing of knowledge and enrich its knowledge.

Interchim, training organization

Interchim, as an accredited organization, now offer training courses (notably in Flash-purification) to offer its customers even more and to benefit from the maximum capacities of their consumables and instruments.

Interchim Forum & FAQ

Along with this desire to share knowledge, Interchim provide a database and knowledge in the form of a forum that can be consulted to share its questions, experiences or recommendations.

Blogs & Social Networks

Interchim also offer a blog (in English and French) with numerous articles to consult which also allows to follow the news of the company as well as its innovations. Interchim also has a Youtube channel, where you can find demonstration videos Ration and presentation of products.
The French multinational is also present on all social networks linkedin, facebook and twitter.

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HUMA PHARMA

Huma Pharma is the local and international solidarity association from the Faculty of Pharmacy in Paris.

For 25 years, this association has been gathering volunteer students who collaborate with communities of young and disadvantaged people to create awareness, information and support missions.
It is an association in which each member shares his creativity and open-mindedness while learning from himself and others. This furthers the common solidarity cause.

Our fundamental aim is to try to bring others a reflection and an awareness on the world surrounding us and especially on the following subjects : solidarity, social exclusion, public health issues.

Mission

Huma Pharma has 8 missions according to 3 distinctive scales :

-Locally, the K'die, the Sensib' and the Handivalides missions, the Cultural Festival

-Nationally, the Collecte, the Hopital des Nounours missions, the humanitarian forum

-Internationally, Mada'ction and Togo missions

SOLIDARITE DES ETUDIANTS DE PHARMACIE DE PARIS V

Who are you ?

Our members are students who spend their time helping bigger associations of public health and sensibilizing the students of the Univsersity of Pharmacy in Paris.

Our six missions :

- Téléthon
- Sidaction
- La Journée Rose to fight against breast cancer
- Two days for blood donation with l'Établissement Français du Sang
- Opération Bouchon inside the University of Pharmacy
- Nez Pour Sourire with HumaPharma association

Why should you eat our crepes during this congress ?

All the money will be directly given to Sidaction, a very important mission of SEPPV.
During two days, on the 7th and 8th March 2019, our aim is to prevent and sensibilize people on AIDS and Sexually Transmitted Disease.

The Young Research Fellows Meeting Organizing Committee

The National Committee
L. Demange, Université Paris-Descartes
F. Huguenot, Université Paris-Descartes.
Ch. Cavé, Université Paris-Saclay

The Local Committee
F. Kateb, Université Paris-Descartes
N. Serradji, Université Paris-Diderot
E. Guenin, Université Paris 13.
P. Belmont, Université Paris-Descartes
S. Broussy, Université Paris-Descartes
E. Brachet, Université Paris-Descartes
E. Braud, Université Paris-Descartes

The Organizing Committee gratefully acknowledges the members of this jury for their precious help in order to award the best works!

26th Journées Jeunes Chercheurs
Young Research Fellow Meeting

PROGRAMME

Wednesday February 20, 2019

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10h00 – 12h30 : **Registration; welcome snacks and drinks**

12h30 – 12h45 : **Introductive remarks**
Ph. Belmont and L. Demange,
on behalf of the Organizing Committee

12h45 – 13h15 : **Opening Keynote Lecture.**
Dr. Bart Roman, Ghent University, Belgium
Pharmacology of motor proteins: a fast-moving field

13h15 – 14h55 : **Oral Communication session**

13h15 – 13h35 : **CO 1 : Sergio Ortiz, CiTCoM, Faculté de Pharmacie, Paris-Descartes, Paris, France.**
Inhibition of Arf1-BigSec7 interaction by natural and semisynthetic sesquiterpene lactones

13h35 – 13h55 : **CO 2 : Mathieu Bordy, Ecole Nationale Supérieure, Lyon, France.**
Fluorogenic probes for high-sensitivity imaging of enzymatic activity

13h55 – 14h15 : **CO 3 : Willi Smeralda, CERMN, Caen, France.**
Alzheimer's Disease: Development and application of a Multistep Procedure to Characterize Modulators of Amyloid Peptide Aggregation.

14h15 – 14h35 : **CO 4 : Bérénice Hattat, IBMM, Montpellier, France & CERMN, Caen, France.**
Synthesis and biological evaluation of multi-target directed ligands as potential treatment for alzheimer's disease.

14h35 – 14h55 : **CO 5 : Pascal Dao, Institut de Chimie de Nice, Nice, France.**
Development of highly sensitive fluorescent probes for the real-time monitoring of senescence in live cells.

14h55 – 15h05 : **Flash Poster Presentation. Session 1.**

15h05 – 15h15 : **Commercial presentation :** Fluorochem

15h15 – 16h05 : **Coffee break, poster session & commercial exhibition.**

16h05 – 16h45 : **Plenary lecture.**
Dr. C. Andraud, ENS Lyon, France.
Biphotonic molecules in the service of biophotonics.

16h45 – 17h45 : **Oral Communications session.**

16h45 – 17h05 : **CO 6 : Krzystof Chmiel, University of Silesia, Chorzow, Poland.**
Amorphization as a Tool in Service of Pharmaceutical Industry. Corresponding Issues and proposed Solutions

17h05 – 17h25 : **CO 7 : David Fallon, GSK R&D, Stevenage, United Kingdom.**
The Design and Synthesis of Bromodomain Photoaffinity Probes

17h25 – 17h45 : **CO 8 : Alice Legru, IBMM, Montpellier, France.**
Inhibition of metallo-β-lactamases (MBLs) to flight the bacterial resistance to β-lactam antibiotics.

17h45 – 17h50 : **Welcome talk**
Pr. Jean-Louis Beaudeux, Faculty's Dean

17h50 – 18h30 : **EFMC lecture.**
Pr. Emmanuel Mikros, Faculty of Pharmacy, Athens, Greece.
Using advanced and analytical tools for efficient discovery of new bioactive compounds

18h30 – 19h30 : **Sharing science and food session.**
You own food buffet in front of the posters. Discuss science, wine and food together… Bring delights from your country and share it with your colleagues!

19h30 – 20h30 : **Pharma welcomes you!**
Enjoy the artists of the faculty of Pharmacy, music and show by our pharmacy's students.

Thursday February 21, 2019

08h30 – 09h00 : **Keynote lecture.**
S. Huvelle, Faculty of Pharmacy, Tours, France.
Original site-specific antibody-drug conjugates.

09h00 – 10h20 : **Oral Communications session.**

09h00 – 09h20 : **CO 9 : Clara Van Hoey, University of Vienna, Vienna, Austria.**
Drug Fragment-based Discovery of Enterovirus Inhibitors

09h20 – 09h40 : **CO 10 : Mathus Hlavac, Comenius University of Bratislava, Slovakia & ECPM, Strasbourg, France.**
Synthesis and biological activity of predicted ALR2 inhibitors.

09h40 – 10h00 : **CO 11 : Lucia Ferrazzano, Alma Mater Studiorum, University of Bologna, Italy.**
Mixtures of green solvent for solid phase peptide synthesis.

10h00 – 10h20 : **CO 12 : Manon Réau, Conservatoire National des Arts et Métiers, Paris, France.**
NR-DBIND : A database dedicated to nuclear receptor binding data including negative data and pharmacological profile

10h20 – 10h40 : **Flash Poster Presentation. Session 2.**

10h40 – 11h30 : **Coffee break, poster session & commercial exhibition.**

11h30 – 12h50 : **Oral Communications session.**

11h30 – 11h50 : **CO 13 : Daniele Di Marino, USI, Lugano, Switzerland.**
Deciphering the mechanisms of allosteric modulation of HSP90.

11h50 – 12h10 : **CO 14 : Salomé Azoulay-Ginsburg, Bar Ilan University, Ramat Gan, Israël.**
Lipophilic phenylbutyric acid derivative as a drug candidate for the treatment of misfolded proteins related diseases.

12h10 – 12h30 : **CO 15 : Xiaowei Chen, CiTCoM, Faculté de Pharmacie, Paris Descartes, Paris, France.**
Interaction between HIV Maturation Inhibitors and GAG precursor.

12h30 – 12h50 : **CO 16 : Florian Descamps, UMR-S1172, Université de Lille, France.**
Discovery of new compounds that promote non-amyloidogenic processing of the amyloid precursor protein for the treatment of Alzheimer‘s disease.

12h50 – 14h00 : **Lunch break**

14h00 – 18h30 : **Cancer Session, "New Frontier in Oncology" Granted by Fondation ARC.**

14h00 – 14h40 : **Plenary lecture.**
Pr. Fernanda Borges, Faculty of Pharmacy, Porto, Portugal.
Drug discovery and neurodegenerative diseases: time for a change of tack.

14h40 – 15h40 : **Oral Communications session.**

14h40 – 15h00 : **CO 17 : Laura Gallego Yerga, University Castilla la Mancha, Albacete, Spain.**
Nanomedicine for the treatment of glioblastoma: glycol-targeted cyclodextrin-calixarene heterodimers for controlled drug delivery.

15h00 – 15h20 : **CO 18 : Chloé Maucort, ICN, Nice, France.**
Synthetic small molecules interfering with oncogenic microRNAs for the induction of glioblastoma stem cells differentiation.

15h20 – 15h40 : **CO 19 : Daniil Bazanov, Moscow State University, Moscow, Russia.**
Novel cis-imidazoline derivatives as precursors for potent inhibitors of mdm2-p53 interaction

15h40 – 16h05 : **Flash Poster Presentation. Session 3.**

16h00 – 16h45 : **Coffee break, poster session & commercial exhibition.**

16h45 – 17h25 : **Plenary lecture.**
Pr. Gilles Pagès, IRCAN, Nice, France.
New therapeutic approaches in resistant kidney cancer care.

17h25 – 18h25 : **Oral Communications session.**

17h25 – 17h45 : **CO 20 : Aurore Dumond, CSM, Monaco, Principality of Monaco.**
Opposite effect of NRP-1 and NRP-2 in the aggressiveness of clear cell Renal Cell Carcinoma

17h45 – 18h05 : **CO 21 : Maria Karelou, National and Kapodistrian University of Athens, Greece.**
Design, synthesis and pharmacological evaluation of novel tdp1 and 2 inhibitors.

18h05 – 18h25 : **CO 22 : Karine Porte, CEA – DRF – JOLIT – SCBM, Gif-sur-Yvette, France.**
Bioorthogonal Cleavable Micelles for Double Targeted Controlled in Vivo Delivery

18h25 – 18h55 : **SCT Award for young investigators in medicinal chemistry lecture.**
Dr. Cyril Ronco, Institut de Chimie de Nice, France.
ER Stress inducers targeting resistant cancers

19h00 – 20h30 : **Round Table :** How to get funds from the European Union, the H2020 scientific program. **Pascale Massiani and Laura Molinari** (French Ministry of Research), **Alain Cimino** (Cimbiose, a company specialized in H2020 projects) and **Pr. Matthieu Montes** (CNAM, ERC Starting Grant Laureate).

20h30 – 01h00 : **Let's go to the XVIth YRFM Party !**
Food, music, dance and drinks into the Orpheus Club

Friday February 22, 2019

08h30 – 10h10 : **Oral Communications session.**

08h30 – 8h50 : **CO 23 : Sandi Brudar, Faculty of Chemistry and Chemical Technology, Ljubjana, Slovenia.**
The influence of the solution conditions on the fibrillization of hen egg-white lysozyme.

08h50 – 09h10 : **CO 24 : Juliane Sousa Lanza, BIOCIS, Faculté de Pharmacie, Châtenay-Malabry, France.**
Combined antileishmanial chemotherapy: mixed micellar system of known actives allows oral treatment of leishmaniasis.

09h10 – 09h30 : **CO 25 : Pedro Soares, Faculty of Sciences, Porto, Portugal.**
Improving the activity of dietary cinnamic and benzoic acids for the treatment of neurodegenerative disorders.

09h30 – 09h50 : **CO 26 : Thi-Hong-Lien Han, ITODYS, Paris-Diderot, Paris, France.**
Oxidation Stress in Friedreich Ataxia: role of Frataxin.

09h50 – 10h10 : **CO 27 : Aine Mahon, University College Dublin, Ireland.**
The Synthesis of Aromatic Lipoxin A4 Analogues with Upper Chain Modifications.

10h10 – 11h00 : **Coffee break, poster session & commercial exhibition.**

11h00 – 11h40 : **Plenary lecture.**
Dr. Gilles Guichard, IECB, Bordeaux, France.
Foldamers for mimicking and engineering the backbone of biologically active peptides.

11h40 – 13h00 : **Oral communications session.**

11h40 – 12h00 : **CO 28 : Ana Carolina Ruberte, University of Navarra, Pampelona, Spain.**
Selenium heteroaryl derivatives as potent cytostatic and antioxidant agents.

12h00 – 12h20 : **CO 29 : Gianina Dodi, Grigore T. Popa University, Iasi, Romania.**
Synthesis and characterization of multifunctional hybrid magnetic nanoparticles designed for multimodal imaging.

12h20 – 12h40 : **CO 30 : Merve Saylam, Izmir Katip Celebi University, Izmir, Turkey.**
Targeting Myeloperoxidase: Studies on Novel Benzimidazole Derivatives as MPO Inhibitors.

12h40 – 13h00 : **CO 31 : Roberta Ibba, University of Sassari, Sassari, Italy.**
Screening of UGGT binding fragments as chemical leads for the development of novel broad-spectrum antivirals.

13h00 – 14h00 : **Lunch break**

14h00 – 16h30 : **Multi-targeted drug Keynote lectures session in coordination with the COST MuTaLig European Action.**

14h00 – 14h30 : **Pr. Stefano Alcaro, University of Catanzaro, Italy.**
From the MuTaLig COST Action ton the Net4Science academic spin-off: one evolution branch of a research project for multi-target drug discovery.

14h30 – 15h00 : **Pr. Danijel Kikelj, University of Ljubjana, Slovenia.**
Discovery of dual gyrase A/gyrase B inhibitors with antibacterial activity.

15h00 – 15h30 : **Dr. Eugenio Gaudio, Institute of Oncology Research, Bellinzona, Swizzerland.**
Selection of biological targets and assessments of biological data: a case study.

15h30 – 16h00 : **Pr. Hanoch Senderowitz, Bar Ilan University, Tel Aviv, Israël.**
Title to be announced.

16h00 – 16h30 : **Dr. Sharon Bryant, Inte:Ligand, Wien, Austria.**
Advanced 3D-pharmacophores & the MuTaLig chemoteca: enhancing virtual screening efficacity in multitarget drug discovery.

16h30 – 17h00 : **Coffee break, poster session & commercial exhibition.**

17h00 – 18h20 : **Oral communications session.**

17h00 – 17h20 : **CO 32 : Maxime De Abreu, CiTCoM, Faculté de Pharmacie, Paris Descartes, Paris, France.**
Straightforward access to phthalazine scaffold under visible-light irradiation.

17h20 – 17h40 : **CO 33 : Patricia Serra, iMed, Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal.**
Structure-based virtual screening toward Hexokinase 2 inhibitors: targeting metabolism and apoptosis signaling in cancer cells.

17h40 – 18h00 : **CO 34 : Richard Botar, University of Debrecen, Hungary.**
A novel PC2A-derivative ligand as pH-responsive „smart" MRI probe: synthesis and characterization.

18h00 – 18h20 : **CO 35 : Agnieszka Zak, ICOA, Orléans, France.**
Synthesis and biological evaluation of new fluorinated ligands targeting P2X7R.

18h20 – 18h50 : **Closing Keynote lecture.**
Dr. Fayna Mammeri, ITODY, Paris-Diderot University, France.
Design of star-shaped magneto-plasmonic nanoparticles made of gold and iron oxide for biomedicine. A focus on photothermia application.

18h50 – 19h00 : **Awards and concluding remarks**

PLENARY LECTURES

Biphotonic molecules in the service of biophotonics

Dr. Chantal Andraud

Laboratory of Chemistry, Ecole Normale Supérieure de Lyon, CNRS, Lyon 1 University, 46 allée *d'Italie, 69364 Lyon, France*

This presentation will illustrate our different recent approaches in order to fulfill main chemical requirements for in vivo biophotonics. We will present our results based on : (1) molecular engineering approaches for enhancing organic[1] or lanthanides[2] based chromophores biphotonic properties and further spectrocopic requirements for imaging or photodynamic therapy in the NIR ; (2) methods of hydrosolubilisation and biocompatibility for these biphotonic chromophores[3] . Intravital fluorescence imaging or photodynamic therapy will be then discussed as a function of chromophores characteristics.

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Wednesday February 20, 2019

« EFMC » Lecture

Using advanced and analytical tools for efficient discovery of new bioactive compounds

Pr. Emmanuel Mikros
Department of Pharmacy, University of Athens,
Panepistimiopolis Zografou, Greece.

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Drug discovery is a laborious and lengthy process spread over a sequence of phases. In the last decades the preclinical stages of drug discovery pipeline have been considerably shortened by successful implementation of innovative physicochemical methods for screening of compound libraries as well as chemoinformatics and bioinformatics methods for primary hit identification, hit-to-lead optimization and rational drug design. Of utmost importance in the discovery of new and promising drug candidates are the various computational algorithms used for predicting the chemical affinity of small molecules to therapeutically relevant biological targets in silico. The aim of this presentation is to illustrate examples of the implementation of computational tools in conjunction with screening, structural and spectroscopical techniques for the identification and optimization of bioactive compounds.

In a first example we address issues related to robustness of virtual screening (VS) in a systematic manner by comparing in silico calculations performed under a consensus ranking scheme with the in vitro experimental evaluation of a small chemical library against four well validated kinase targets. In a second example, we shall demonstrate how consensus ranking can be used in close relation with computational mapping of the binding site solvation to hit-to lead optimization of emerging epigenetic targets like the bromodomain PB1 and UHRF1. Solvation mapping can suggest possible lead modifications to optimize protein−ligand interactions by identifying hydration sites in the vicinity of the ligand, providing modification hints for increasing enthalpic gain and decreasing unfavorable entropy.

Finally, in a completely different context, we will present how statistical tools utilized in -omic technologies, can be applied for the identification of active components in complex mixtures. The application of Statistical Total Correlation Spectroscopy (STOCSY) and statistical heterospectroscopy (SHY) based on data from NMR and MS complemented with their heterocovariance against bioactivity may facilitate structural identification of the active components of a natural extract prior to purification, resulting to acceleration of bioactives discovery.

EFMC
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Thursday February 21, 2019

Drug discovery and neurodegenerative diseases: time for a change of tack.

Pr. Fernanda Borges
CIQUP/Department of Chemistry and Biochemistry
Faculty of Sciences, University of Porto

Neurodegenerative diseases (ND) are a large group of disorders of the central nervous system (CNS) with heterogeneous clinical and pathological expressions, affecting specific neuronal groups and brain signaling networks. Albeit each ND exhibits its own disease mechanisms and pathological hallmarks, it is consensual that the etiology of ND is multifactorial and that neuronal death occurs as a result of a complex network of cross-talking damaging stimuli over an extended period of time. Nevertheless, no exact causes have yet been identified and the current knowledge on ND pathology is still based on a cascade of hypothesis. Furthermore, the existing single-target drugs in therapy are only palliative, and fail to modify disease progression.

For some time, drug discovery players have been questioning the success of the reductionist philosophy to ameliorate disease states with multifactorial and polygenic nature. Consequently, it is intuitive that by targeting different regions or modules of the disease network a better regulation of the system can be achieved. One of the main limitations with this approach is the ability to define the set of targets and the design compounds that will hit the key targets with a desirable potency ratio. This is certainly a daunting challenge but given the current unmet medical needs, and the possible gains, such a venture is worthwhile.

In this context, our research group have been focused in the discovery of new chemical entities based on nature-inspired scaffolds and centered on one target and multi-target design associated to neurodegenerative diseases. The most relevant data attained so far will be briefly depicted in this communication.

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New therapeutic approaches in resistant kidney cancer care.

Maeva Dufies[1], Sandy Giuliano[1], Luc Demange[3], Rachid Benhida[4] and **Gilles Pagès**[1-2]

1- Centre Scientifique de Monaco, Biomedical department
2-University Cote d'Azur, Institute for research on cancer and aging of Nice CNRS UMR 7284/INSERM U 1081
3- University Paris-Descartes, Faculty of Pharmacy, UMR 8038 CNRS.
4- University Cote d'Azur, Institute of Chemistry of Nice CNRS UMR 7272

Clear cell Renal Cell carcinomas (RCC) are characterized by a pro-angiogenic/pro-inflammatory context. Despite conventional or targeted therapies, metastatic RCC and remain incurable. Identification of molecular mechanisms associated with resistance to the current treatment may highlight innovative therapeutic strategies. We demonstrated that almost immediate sunitinib sequestration in lysosomes prevent the accessibility of the drug to its targets and inhibits autophagic processes resulting in a strong dependency on the proteasome for physiological homeostais. Hence, combination of sunitinib with drugs that prevent lysosome trapping or that inhibit the proteasome (bortezomib/Velcade used in myeloma) prevent sunitinib resistance. Anti-angiogenic drugs adaptation renders tumor cells addict to the EGF receptor signaling pathway. Hence, resistance is bypassed through combination with EGFR inhibitor used for lung cancers (erlotinib/Tarceva). Finally, redundant angiogenic cytokines of the ERL+CXCL family are highly produced by resistant cells. These cytokines exert their effects through the G-protein coupled receptors CXCR1/2. Targeting the most important ELR+CXCL cytokine (ie: CXCL7) or its receptors demonstrated a high anti-tumor efficacy. CXCR1/2 inhibitors were developed for the treatment of inflammatory diseases but to a lower extent for cancers. We more performant inhibitors than the available one. We aimed to used them in early clinical trials for patients in therapeutic impasses.
Our translational strategy is dedicated to precision medicine and the improvement in patient care for "chronicization" of the pathology or long-term remissions.

Foldamers for mimicking and engineering the backbone of biologically active peptides, and application to some cancer-related targets

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Dr. Gilles Guichard

Univ. Bordeaux, CNRS, CBMN, UMR 5248, Institut Européen de Chimie et Biologie, 33607 Pessac, France

Our ability to synthesize sequence-specific synthetic oligomers (i.e. foldamers[1]) that fold into well-defined secondary structures akin to those found in proteins opens up enticing opportunities for mimicking peptides and addressing some of their limitations such as short in vivo half-lives. In particular, many foldamer backbones are endowed with useful properties such as structure predictability and improved resistance to enzymatic degradation that make them well suited as new modalities for therapeutic applications. However, the design of foldamers that recapitulate the activities of biologically active peptides (e.g. targeting protein-protein interactions or activating receptors) is far from trivial. One emerging approach pioneered by Gellman and coworkers consists in redesigning peptides by combining α-peptide and foldamer backbones in a single chain. We have recently started to explore this concept of foldamer/α-peptide chimeras with aliphatic oligoureas, a class of foldamers that adopt a well-defined helical secondary structure with good similarity to the α-helix.[2] In this presentation, we will show how key beneficial features of both species — such as natural epitope recognition of α-peptides and the innate helical stability of oligoureas — can be exploited in single chimeric constructs (i.e. block co-foldamers) to design original and effective α-helix mimics[3,4] that can recognize protein surfaces including some cancer-related targets. These findings provide a rationale for the use of oligoureas to improve the properties of biologically active peptides such as resistance to proteolytic degradation and duration of action, and may lead to new therapeutic applications.

Acknowledgements: This work has received support from the CNRS, Univ. Bordeaux, Conseil Régional Nouvelle-Aquitaine (Project 20091102003) and ANR (ANR-12-ASTR-0024, ANR-12-BS07-0019 and ANR-15-CE07-0010). Support from UREkA, Sarl is also gratefully acknowledged.

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KEYNOTE LECTURES

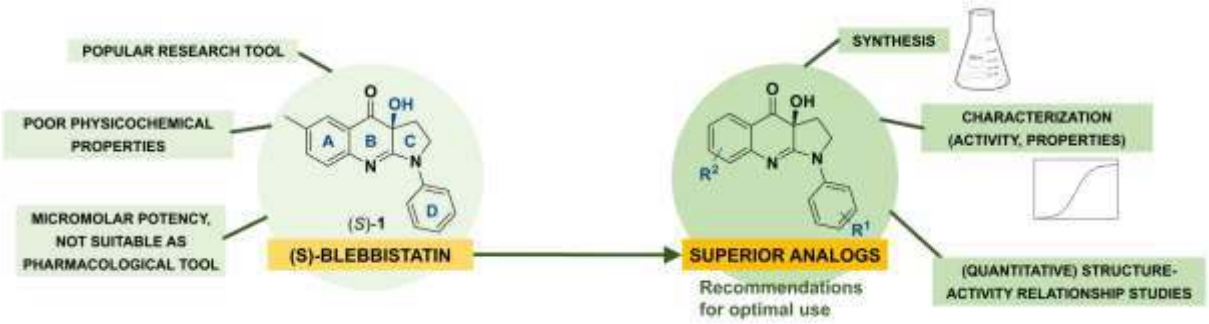
Wednesday February 20, 2019

Pharmacology of motor proteins: a fast-moving field

Dr. Bart Roman

Ghent University, Department of Green Chemistry and Technology
SynBioC Research Group, Coupure Links 635, 9000 Gent, Belgium

This talk is an introduction to the pharmacology of motor proteins, in particular to the medicinal chemistry of blebbistatin. (*S*)-Blebbistatin (*S*)-**1**, a chiral tetrahydropyrroloquinolinone, is a widely used and well-characterized ATPase inhibitor selective for myosin II.[(a)] The central role of myosin II in many normal and aberrant biological processes has been revealed with the aid of this small molecule.



Given the multiple roles of myosin II in a diverse range of motility-based diseases, potent and drugable inhibitors of particular isoforms of this protein could be valuable pharmacological tools. The potency of (*S*)-blebbistatin is however too low to serve this goal. (*S*)-blebbistatin also has severe physicochemical deficiencies that trouble its use as a research tool in advanced biological systems: low solubility, fluorescence interference, (photo)toxicity and stability issues. As a consequence, there is a large unmet need for better myosin inhibitors.

Over the last years we have developed and field-tested a toolbox of (*S*)-blebbistatin analogs as improved myosin inhibitors in which several of the above shortcomings have been addressed. We have designed a user's guide for their optimal application.[(a,b,c)] We have also strived for potency enhancement via modification of rings A, C and D of the molecule, in search of lead compounds.[(a,d,e)] We have analyzed the resulting structure-activity relationships using *in silico* methods.[(f)]
The present talk will provide an overview of these efforts, as well as an outlook to future developments in the fast moving area of motor pharmacology.

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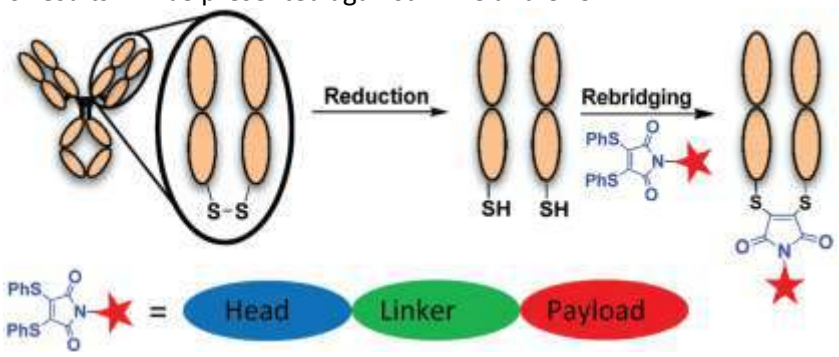
Original site-specific antibody-drug conjugates.

Steve Huvelle[(1)]*, Camille Marti [(1)], Francesca Bryden[(1)], Imène Ait Mohamed Amar[(1)], Stéphanie Letast[(1)], Maguy Del Rio[(2)], Valérie Laurent-Matha[(2)], Emma-Liaudet-Coopman[(2)], Sandrine Valsesia-Wittmann[(3)], Marie-Claude Viaud-Massuard[(1)], Nicolas Joubert[(1)].

(1) GICC EA 7501, Team Molecular Innovation and Therapy, University of Tours, 31 avenue Monge, Tours, France. ***(2)*** *IRCM, INSERM U1194, Team Proteases Microenvironment and Cancer, Campus Val D'Aurelle, Montpellier, France .(3) Centre Léon Bérard, 28 rue Laennec, Lyon, France.*

Developing innovating treatments to avoid systemic toxicity still remains a challenge in anticancer chemotherapy. Antibody-Drug Conjugates (ADCs) are a new class of vectorised chemotherapy, designed to reach this goal by taking advantages of the high specificity of an antibody (mAb) for its antigen overexpressed in tumor, and a cytotoxic agent grafted on the mAb generally through a stochastic bioconjugation method.[a] Our team developed new site-specific bioconjugation technics using a modular approach, giving access to a large variety of original site-specific ADCs from any native mAb of interest.[b,c] Among them, our site-specific anti-HER2 ADCs were able to efficiently kill HER2-positive cancer cells (BT-474) *in vitro* with a picomolar activity (IC_{50} = 17 pM) and induced a total remission with 100 % survival in an *in vivo* study (BT-474 mouse model).
However, HER2 is over-expressed in only 20 % of breast cancers. Therefore, encouraged by our previous results and using our modular approach to build ADCs, we decided to expand the field of application of our ADCs to other cancers. To reach that goal, we designed and developed two new ADCs able to target several breast cancers including triple-negative breast cancer (TNBC), a very challenging disease for which no treatment is yet available.
In addition, a similar approach will be considered to target colorectal cancer (CRC). Because EGFR is too ubiquitous, a mAb has been recently developed against an original antigen more selective for tumor, and then conjugated to give two ADCs.
Preliminary *in vitro* results will be presented against TNBC and CRC.



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Design of star-shaped magneto-plasmonic nanoparticles made of gold and iron oxide for biomedicine. A focus on photothermia application.

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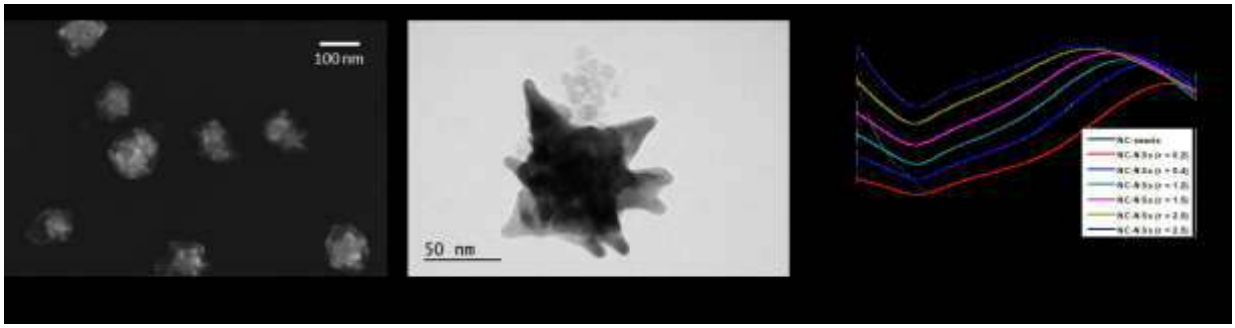
Iron oxide (IO) nanoparticles (NPs) have demonstrated their strong potential for diagnostic and therapeutic applications. However, one of the significant limitations of these NPs in biomedical applications is their poor colloidal stability in physiological conditions. An interesting approach to ensuring such colloidal stability as well as biocompatibility is to cover IO NPs with a noble metal such as gold that is non-toxic and chemically stable under physiological conditions. Moreover, tuning the shape of the gold shell is expected to provide photoactivity in the near-infrared (NIR) spectral region, making them valuable for photothermia in addition to their ability to be used as contrast agent for magnetic resonance imaging (MRI).

We describe here the preparation and the characterization of non-spherical Fe3-xO4-Au core-shell nanoparticles, exhibiting both superparamagnetic behavior and plasmonic absorption in the NIR region. These nanostructures are based on 10 nm in diameter magnetic iron oxide nanoparticles, produced by forced hydrolysis of metallic salts in polyol [1], subsequently self-assembled as nanoclusters (NCs) by citrate surface modification. Negatively charged spherical aggregates were obtained for a critical citrate concentration. The addition of tetrachloroauric acid to the NCs in presence of dimethylformamide (DMF) led to the formation of a star-shaped gold shell NPs. The optimization of the synthesis conditions has been studied [2].

These star-shaped particles, able to absorb light in the NIR spectral region (820 nm) and exhibiting a non-negligible magnetization at room temperature (>10 emu g-1), can be easily dispersed in water at physiological pH as stable colloids and are particularly valuable for both *in vivo* MRI and photothermia applications. *In vitro* photothermal measurements carried out on the best sample resulted in a promising conversion efficiency of 25% under an 808 nm laser illumination and will be presented in this communication.



TEM pictures and UV-Vis spectra of NC-NSs.

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Friday February 22, 2019

« SCT Award for young investigators in medicinal chemistry » Lecture

Dr. Cyril Ronco

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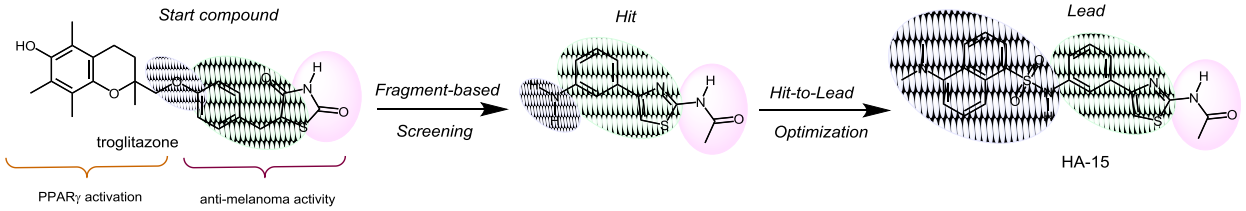
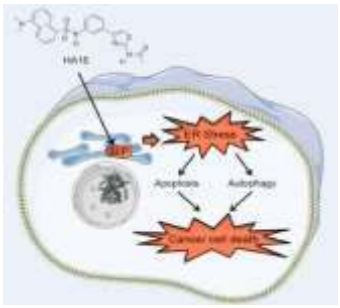
ER Stress inducers targeting resistant cancers

Despite dramatic improvement in its care over the last two decades, the treatment of resistant forms of cancer is still an unmet challenge. [1] Thus, efficient treatments, especially relying on innovative modes of action are needed to overcome these resistance phenomena. We have discovered that troglitazone shows **apoptosis of melanoma cell lines,** in addition to its known PPARγ receptors activation. We have modified its structure by fragment-based screening in order to define the phenylthiazole core as anticancer pharmacophore. Then, this Hit has been optimized by extensive structure−activity and structure-pharmacological properties relationships to obtain a Lead compound: **HA15**.[2,3]





HA15 shows an efficient activity in vivo in melanoma xenografts, including on resistant cells models. This prompted us to study the mode of action of this drug. Transcriptomics, SiRNA, western blots, cytotoxic activity measurements and microscopy methods disclosed an original mode of action: induction of **Endoplasmic Reticulum (ER) stress** and selective death of cancer cells by concomitant apoptosis and autophagy.[4] Then, the molecular target was identified by proteomics, immunoprecipitation, fluorescence co-localization, ITC, DSC and ATPase activity inhibition techniques: ER-chaperone **GRP78/BiP**. This pivotal enzyme in the Unfolded Protein Response is an original drug-target that controls the ER-stress adaptation of cancer cells.

The activity of HA-15 led us to study this molecule in other pathologies[5,6] and to evaluate its synergy with immune checkpoint inhibitors. This study highlights the role of UPR in cancer cells metabolism and paves the way for the design and evaluation of new ER-stress inducers to target resistant cancers.

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COST MuTaLig European Action

Multi-targeted drug Keynote

COST MuTaLig specific session – www.mutalig.eu

Discovery of Dual Gyrase A/Gyrase B Inhibitors with Antibacterial Activity

B. Fois[1,2*] , Ž. Skok[2], M. Durcik, L. Peterlin Mašič, T. Tomašič[2], Á. Nyerges[3], J. Ilaš[2] and D. Kikelj[2]

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Bacterial DNA gyrase, an ATP-fueled heterotetrameric protein, composed of two A subunits (GyrA) and two B subunits (GyrB), is essential for cell viability because it introduces negative supercoils in DNA in front of the replication fork. The GyrA subunit is the target of fluoroquinolone antibiotics, while the GyrB ATP-binding site is a target of novobiocin and a number of recently reported GyrB inibitors. Noviobicin, discovered in the mid-1950s, was withdrawn from the market primarily due to its toxicity and due to the high resistance development and so far, no GyrB inhibitor has been introduced into the clinic. In previous works we reported the binding mode of several structural types of pyrrole-2-carboxamide derivatives e.g. 2-((2-(4,5-dibromo-1H-pyrrole-2-carboxamido)benzo[d]thiazol-6-yl)amino)-2-oxoacetic acid with E. coli GyrB.[1] Unfortunately, all these inhibitors did not show in vitro antibacterial activity, because of insufficient penetration and effluxing. It is assumed that dual targeting could reduce bacterial resistance because mutations at two different sites are less probable to occur than single mutation in GyrA and GyrB sites. These observations evoked our interest in dual targeting of gyrase A and gyrase B that could open new avenues for gyrase inhibition and fighting bacterial resistance.

Since gyrase A inhibitors (fluoroquinolones) and our pyrrole-2-carboxamide gyrase B inhibitors do not share common structural features, ciprofloxacin was combined through a methylene linker with our recently reported benzothiazole-based gyrase B inhibitors, placing a pyrrole-2-carboxamide moiety at position 2 or 6 of the benzothiazole scaffold. Further, we hoped that ciprofloxacin would enable the molecules to penetrate into the bacteria and boost their antibacterial activity. All four prepared dual compounds displayed potent bioactivity against Gram negative E.coli. Moreover one compound showed good in vitro activity against Gram negative Shigella flexneri and Klebsiella pneumoniae and Gram-positive S. aureus. The lack of bioactivity change in presence of GyrB E136 mutant and the lack of bioactivity in the case of the mutated fluoroquinolone binding site (E.coli K-12 MG1655 GyrA S83L+D87N; ParC S80I+E84G) indicates that the primary binding site of these dual inhibitors in bacterial cell is GyrA and/or topoisomerase IV ParC although inhibition of ATP-ase inhibitory activity provided evidence also for inhibition of gyrase B. We have demonstrated that hybrids obtained by merging a gyrase B inhibitor with ciprofloxacin enter Gram negative and Gram positive bacteria and are not intensively effluxed. Further optimization of compounds is in progress.

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COST MuTaLig specific session – www.mutalig.eu

Selection of biological targets and assessment of biological data: a case study.

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Despite the big improvements obtained in the last years, the outcome of patients affected by hematological cancers is still far to be optimal. TCL1 (T-cell leukemia/ lymphoma 1) is an oncogene codifying for a co-activator of both AKT downstream of the PI3K and of NF-KB pathways through its interaction with IKB and ATM. TCL1 is often over-expressed in T- and B-cell malignancies, including chronic lymphocytic leukemia (CLL) but also aggressive lymphomas such as Burkitt (BL) and diffuse large B-cell lymphoma (DLBCL). TCL1 results to be an important target of therapy due to its role in the activation of pathways up-regulated in most hematologic malignancies. TCL1 interacts with multiple protein partners and the identification of new compounds able to inhibit TCL1 activity would also affect the activity of TCL1 interacting partners by exerting an indirect multi-targeting effect. Following the computational analysis to uncover the physical interaction between TCL1 and putative inhibitors, a series of both biological and molecular biology tests were performed to validate the in silico data and highlight the values both of TCL1 as target of therapy and of the selected small molecules as inhibitors.

COST MuTaLig specific session – www.mutalig.eu

Computational Tools for Multi-Target Drug Discovery

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(2)

The MuTaLig cost action[1] was formulated based on the paradigm that modern, successful drugs should interact with more than a single pharmaceutical target preferably in a synergic fashion. The resulting poly-pharmacology is likely to increase drug efficiency and at the same time reduce the probability for the development of drug resistance. However, this requirement adds another layer of complexity to the drug development process which already involves the simultaneous optimization of multiple parameters (e.g., efficacy, solubility, membrane permeability, metabolic stability, toxicity) some of which are at odds with one another (e.g., solubility and membrane permeability). The development of multi-target drugs could therefore be best formulated as a multi objective optimization problem (MOOP).[2]

Multi objective optimization problems do not have a single solution, i.e., there is no single solution that is better than all other solutions in all objectives. Rather, a set of equally good solutions is typically obtained. In drug discovery this basically means that compounds with different pharmacological profiles are suggested each excelling in one or more (but not all) properties, and it is up to the developer to select the compound with best combination of properties.

The purpose of this seminar is to present the concept of multi objective optimization as it is related to the different stages of the drug discovery process (hit identification and lead optimization) and the computational tools used to address it. Selected examples from the literature as well as from the work performed within the framework of the MuTaLig Cost Action will be presented. The role of databases such as ChEMBL and the MuTaLig-generated Chemotheca,[3] will be highlighted.

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COST MuTaLig specific session – www.mutalig.eu

From the MuTaLig COST Action to the Net4Science academic spin-off: one evolution branch of a research project for multi-target drug discovery

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www.net4science.com

An important and emerging issue in modern drug discovery is to design novel or identify existing bioactive compounds, endowed with the capability to interact selectively with two or more macromolecular targets, exerting their effects against certain therapeutic goals in a synergic fashion.[a] This innovative concept stimulated the creation of a COST Action focusing on novel ligands able to recognize selected multiple targets, to promote closer scientific links among European research groups involved in medicinal chemistry field at both academic and industrial level. The repurposing issue is extremely interesting especially at this level, since many compounds, obtained by means of consistent scientific investigations, could be revaluated and eventually have a new future.[b] The aim of the COST Action MuTaLig (Multi-target paradigm for innovative ligand identification in the drug discovery process) is to join highly-qualified research teams working in disciplines around the field of medicinal chemistry, into a novel network devoted to the multi-target issue in drug discovery. The choice of this theme is related to its marked multidisciplinary character, which can ensure a strong interaction among all COST Action participants, started as 5 co-proposing European research teams and recently expanded up to more than 30 countries. Additional details about the recently launched MuTaLig COST CA15135 Action with the support of the EU Framework program Horizon 2020 are available on line.[c] The research competencies of the network will span around medicinal chemistry, from synthetic chemistry, natural products and biophysics to theoretical chemistry, molecular modelling and biological screening. They are linked to each other by means of a unique additional networking tool related to the chemotheca[d] developed at the Università Magna Graecia di Catanzaro, that will be presented in the WG3 discussion.
One of the most stimulating goals included in the COST Action is related to the involvement of stakeholders working in the field of pharmaceutical, fine chemicals and biotech companies. This issue is always critical due to the objective difficulties to share in a large scientific community their contents that, by definition, are protected by intellectual property. So last year my team, mostly composed by young investigators, decided to constitute the academic spin-off Net4Science that could better care about the innovation and research requests of companies interested to perform multi-target drug discovery activities.[e]

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(c) www.cost.eu/actions/CA15135 and www.mutalig.eu
(d) chemotheca.unicz.it
(e) www.net4science.com

* Correspondence: alcaro@unicz.it

COST MuTaLig specific session – www.mutalig.eu

Advanced 3D-Pharmacophores & the Mu.Ta.Lig Chemotheca: Enhancing Virtual Screening Efficacy in Multitarget Drug Discovery

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The concept of developing a small molecule to selectively interact with a target responsible for disease has been a strategic approach used in industry since the beginning of drug research and one of the driving forces in industrial drug discovery for decades. It is now widely accepted that polypharmacology is fundamentally important when considering therapeutic efficacy. Successful drugs that were designed with target selectivity in mind, including blockbusters like imantinib and sunitinib, are now known to interact with many physiological targets. In modern drug discovery research, the multi-target approach involves developing compounds that embody the 'right' selectivity profiles, i.e., interact with several targets in a converging biological pathway while at the same time avoiding adverse outcomes.[a] Pharmacophore-based compound modeling, virtual screening, and target bioactivity profiling[b] have evolved into successful in silico methodologies used in industry and academia to support multi-target based compound hit finding and lead optimization research (Fig. 1). The molecular design tool LigandScout[c] successfully addresses one of the most important issues in multi-target based parallel virtual screening: Enhancing early enrichment (identification of bioactive molecules) while maintaining high computational speed as well as intuitive ease of use, as shown by reference studies.[d] Selected examples of multi-target approaches from literature and our own research including initiatives from the Mu.Ta.Lig COST Action[e], involving advanced 3D-pharmacophores, the IL Pharm DB (IL Pharmacophore database)[f] and the Mu.Ta.Lig COST Action Chemotheca[g] will be covered.

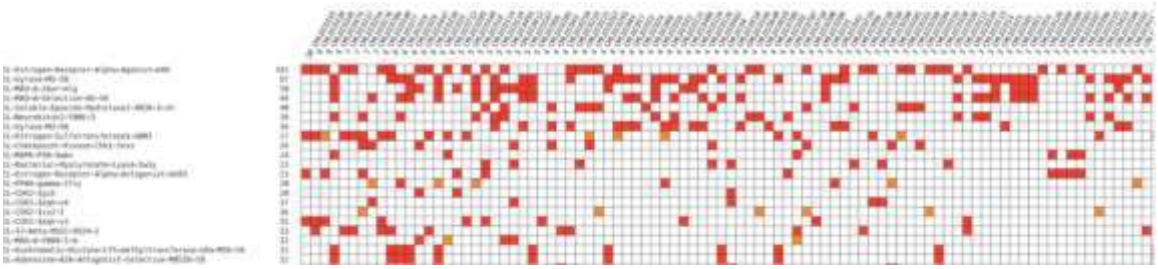

Fig.1 *Multi-target profiling of the Mu.Ta.Lig Chemotheca using LigandScout 3D-pharmacophores and activity profiling algorithms. Target models (left) have identified compounds (top): Red indicates high likelihood to have activity at that target, orange lower likelihood, white likely to be inactive. Compounds hitting multiple targets can be visualized easily.*

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ORAL COMMUNICATIONS

Inhibition of Arf1-BigSec7 interaction by natural and semisynthetic sesquiterpene lactones.

Sergio Ortiz[(1)]*, Euzébio Guimarães Barbosa [(2)], Pascale Lemoine [(3)], Raphaël Grougnet [(1)], Jacqueline Cherfils [(4)], Sabrina Boutefnouchet [(1)].

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(2) Department of Pharmacy, Universidade Federal do Rio Grande do Norte (UFRN), Natal, 59010-180, Brazil.
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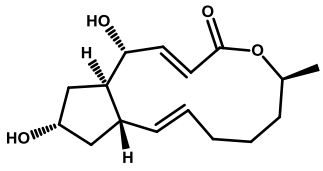
OC_01

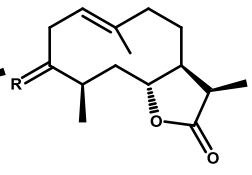
The ADP-ribosylation factor (ARF) family of proteins belongs to the Ras super family of small GTPase. GTP loading on ARF proteins is regulated by a family of evolutionary conserved GEFs (BIG1-2, GBF, ARNO, BRAG1, etc.) with a well conserved catalytic Sec7 domain, encountered in several sub-compartment and involved in the expression of different cellular function [(a-b)]. GEF (guanine nucleotide-exchange factor) actives ARF1, localized in the trans-Golgi network, leads to the recruitment of coat polymers involved in vesicular traffic and in the activation of membrane-modifying enzymes. Impairment of ARF1 functions result in secretion, endocytosis, cell adhesion and tumor-cell invasion processes.

Brefeldin A (BFA) is a known uncompetitive inhibitor of ARF1-BIGSec7 interaction. BFA has been deeply studied from a medicinal chemistry point of view. Unfortunately, poor pharmacokinetic profile have limited further development[(c)]. Ketopelenolide B (**KB1**) [(d)], a sesquiterpene lactone isolated from *Pentzia monodiana*, is closely related to BFA. Docking studies revealed that **KB1** is able to inhibit ARF1 activation by BIGSec7. This *in silico* result was confirmed by *in vitro* experiments showing 20% inhibition of ARF1 activation by **KB1** at 50 µM. Several structural modifications of **KB1** allowed us to obtain 14 new sesquiterpene lactones derivatives (**KB2**-**15**). **KB9** (3-ethoxyimino derivative) was able to inhibit 35 % of ARF1-BIGSec7 activation at 50 µM. Additionally, regarding others GEFs as ARF1-ARNOSec7 (10%) and ARF1-BRAGSec7 (5%) **KB9** seems to be a selective inhibitor under the same conditions. Thus, **KB9** may be considered as a new lead for ARF1-BIGSec7 interaction inhibitors.



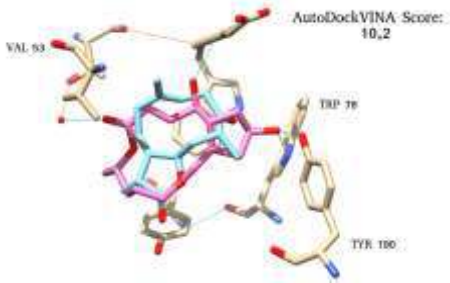
Brefeldin A (BFA)

1



KB1, R = O, Ketopelenolide A
KB9, R = $NOCH_2CH_3$

2



3

Figure 1: Brefeldin A structure. Figure 2: **KB1** and **KB9** structures. Figure 3: Docking with ARF1, illustrating the resemblance between the **BFA** and **KB1**. In red the original ligand and in green **KB1**.

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Fluorogenic probes for high-sensitivity imaging of enzymatic activity	***OC_02***

Mathieu Bordy[(1)]*, Corentin Gondrand [(1)], Damien Curton[(1)], Alix Tordo [(1)], Lea Mélin[(1)], Jens Hasserodt [(1)].

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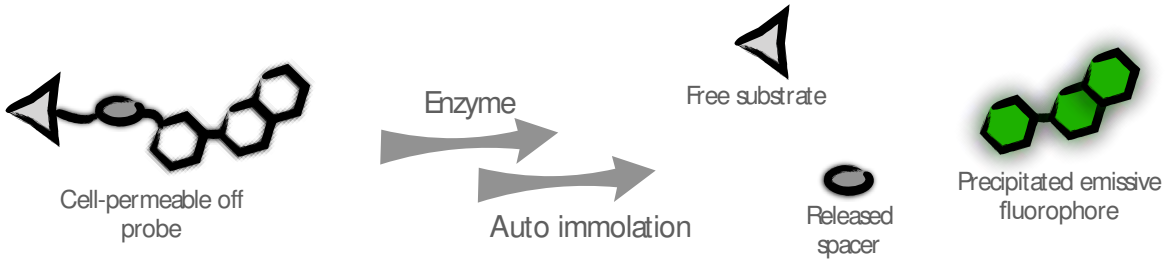
In order to understand the biological mechanisms underlying certain pathologies, it is of prime importance to detect and precisely localize a particular enzyme activity within a live cell or organism. The habitually employed molecular probes suffer from a number of weaknesses, including signal diffusion away from the enzyme locus, or the formation of a fluorophore with a small Stokes shift that decreases detection sensitivity.

To meet these challenges, we have designed three-component probes that release an unique solid-state fluorophore that is highly insoluble under physiological conditions. Its fluorescence can be masked by acylation of its phenolic hydroxyle. In addition, it benefits from the ESIPT (Excited State Intramolecular Proton Transfer) effect which generates a large Stokes shift. However, it has not been widely used because of the difficulty to incorporate it into responsive probes that are stable. We reported on a structural solution to this problem that resulted in a quickly responding probe while remaining silent over many hours in the absence of the target enzyme. Our design is based on a smart spacer that cyclizes immediately upon enzymatic removal of the substrate portion, thus resulting in the release of the precipitating fluorophore (see Figure).



We here report on significant improvements of our probe technology, consisting in the use of other triggering enzymatic substrates to increase the range of targetable enzymes. Especially, we are now able to detect and image enzymes from the glycosidase family, such as beta-galactosidase, known to be a highly important target for its role as a biomarker of certain cancers and as a control product in gene expression experiments.

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Development of highly sensitive fluorescent probes for the real-time monitoring of senescence in live cells.	***OC_03***

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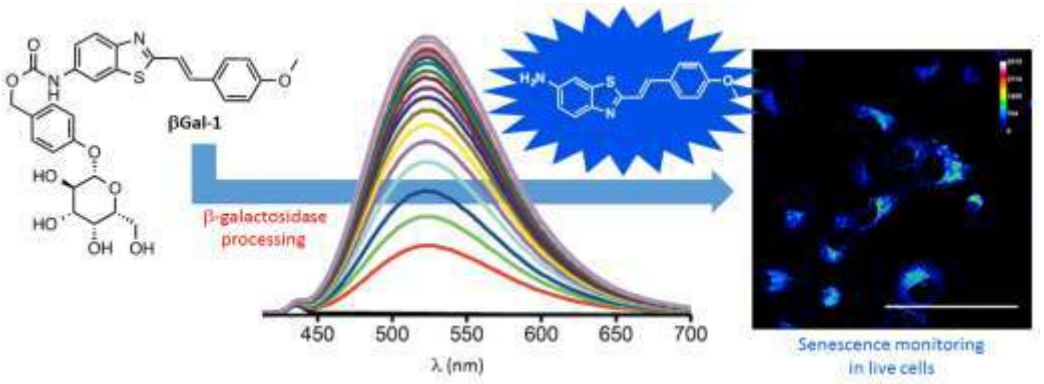
Aging is the major risk for chronic disease, neurodegenerative disorders, cardiovascular disease and cancer. Aging is characterized by a gradual functional decline, although we are far from understanding the biological basis of aging. Cellular senescence has been characterized as a central hallmark of aging. Senescence is a persistent cytostasis which results from a non-lethal stress. It is characterized by a morphological and biochemical phenotype that include an abnormally accumulated β-gal activity called senescence-associated β-galactosidase (SA-β-gal).[1] This SA-β-gal activity is a widely accepted marker of cellular senescence.[2] Indeed, a limiting factor in the better understanding of senescence has been the lack of powerful methods for the characterization and quantification of senescence.

We report the development of four novel fluorescent probes to monitor the activity of the β-galactosidase enzyme (β-gal), in vitro and in living cells.[3] The fluorophores are based on a 6-amino-styryl-benzothiazole push–pull core and display a strong ICT emission. The probes encompass the fluorescent motif that is connected to a β-D-galactopyranoside moiety through a self-immolative benzyl carbamate linker. Our probes, βGal-1, exhibited an extremely fast response and over 200-fold fluorescence enhancement following the enzymatic cleavage of the β-D-galactopyranoside unit. This rapid and extremely sensitive response allowed the detection of senescence-associated β-galactosidase (SA-β-gal) activity. More importantly, βGal-1 also enabled us to monitor, in real-time, the emergence of senescence in live cells, i.e. the phenotypic transformation from normal to senescent cell. These findings underpin the fact that βGal-1 may find useful applications in biomedical research.



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Synthesis And Biological Evaluation Of Multi-Target Directed Ligands As Potential Treatment For Alzheimer's Disease.	***OC_04***

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Targeting more than one molecular cause implied in the pathogenesis of Alzheimer's disease (AD) with a sole drug is considered a promising challenge, because it could address the failures that recently occurred during clinical trials. Within this framework, we recently reported the design of donecopride, a pleiotropic agent that both displays acetylcholinesterase (AChE) inhibition and 5-HT_4R agonist activity.[1] Based on its procognitive and antiamnesiant in vivo properties, donecopride is currently under preclinical investigation. A pharmacomodulation study allowed to establish the structure-activity relationships in the donecopride series and to enlarge the latter with some other potent ligands.[2] Taking into account the clinical interest of idalopirdine, a 5-HT6R antagonist, in Alzheimer's Disease (AD) treatment, we undertook a new program aiming at designing novel Multi-Target Directed Ligands targeting selectively AChE, 5-HT4 and 5-HT6 receptors.

Considering the pharmacophores established for each of the three targets, we performed the synthesis of numerous donecopride derivatives. The pharmacomodulation of these compounds led to first pluripotent derivatives with in vitro submicromolar activities towards the three designated targets.

The TRIAD program, funded by the Ligue Européenne contre la Maladie d'Alzheimer and the French Fondation Plan Alzheimer, recently led to one novel promising agent which has demonstrated good in vitro results. The first in vivo results will also be presented.

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Bioorthogonal Cleavable Micelles for Double Targeted Controlled in Vivo Delivery	***OC_05***

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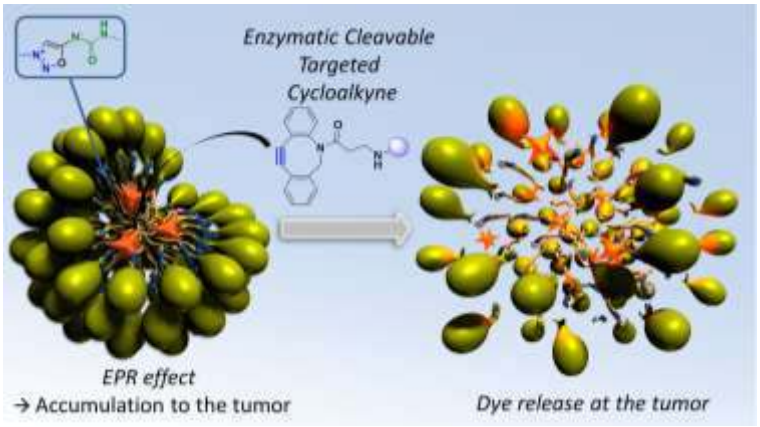
In recent years, our group has extensively explored the chemistry of mesoionic compounds. In 2017, we described for the first time the reactivity between iminosydnones and cycloalkynes.[(a)] This reaction, defined as a "click and release reaction", has the particularity to allow simultaneous formation of a new compound and release of a second one. Despite its novelty and the many potential biological applications, this reaction cannot be used for *in vivo* due to low reaction speed. The main goal of my work has been to increase the reaction rate of this click and release process and to explore its potential as a powerful tool for drug delivery. With this in mind, we designed an amphiphilic compound, containing an iminosydnones moiety, able to self-assembly in water and form micelles. After reacting theses micelles with cycloalkynes, we observed a dramatic increase of the reaction kinetics due to the high local concentration of the cycloalkyne inside the micelles. When the click and release occurs we observed the rapid cleavage of the nanoparticles, which can be used for the controllable release of drugs or dyes. We developed an *in vivo* approach for an "on demand" release of dyes by using the iminosydnone micelles and a cyclooctyne designed to target the tumor. The first *in vivo* proof of concept gives us encouraging results for a potential drug release application.



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Amorphization as a Tool in Service of Pharmaceutical Industry. Corresponding Issues and Proposed Solutions	*OC_06*

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Low bioavailability due to limited water solubility of drugs remains one of the serious problems of modern pharmacy. Transformations of crystalline drugs to the amorphous form is the most promising strategie to overcome this issue. In contrast to crystals, amorphous solids does not exhibits long-range ordering (presents molecular arrangement similar to that of liquids), and as a consequences are characterized by better water solubility. However, the main drawback of the amorphous solids is their psychical instability.[a] Active Pharmaceutical Ingredients (APIs) in amorphous form may go through re-crystallization over the time of processing, storage, and use of the product, losing at the same time their superior properties.[b,c]

Throughout this presentation we will demonstrate : i) easy and efficient way to transform crystalline sample into amorphous form ; ii) methods usefull in order to determine physical stability of the amorphous sample in both glassy and supercooled liquid state ; iii) possible paths to enhance physical stability of the measured sample.

ACKNOWLEDGEMENT

K.C., and M.P., are grateful for the financial support received within the Project No. 2015/16/W/NZ7/00404 (SYMFONIA 3) from the National Science Centre, Poland. J.K-K. thanks the FNP for awarding grants within the framework of the START Program (2017).

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The Design and Synthesis of Bromodomain Photoaffinity Probes	OC_07

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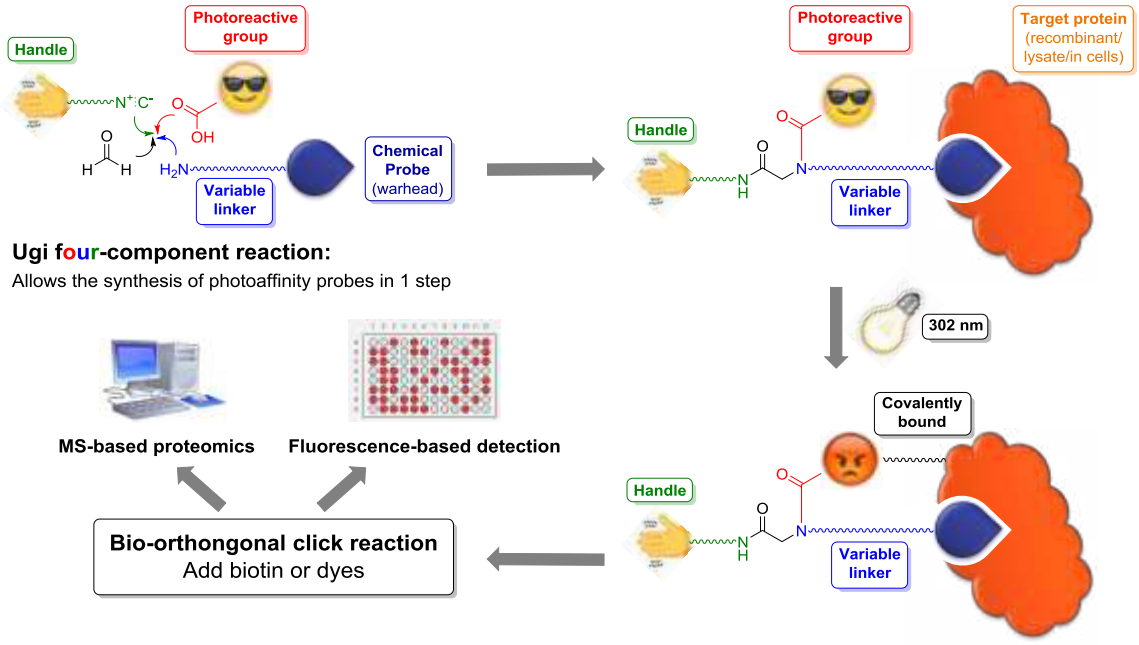
In recent years, photoaffinity probes have become powerful tools in the field of chemical biology, allowing a greater understanding of the proteome. These tools can provide a wealth of information regarding on/off target affinity, especially when coupled with modern mass spectrometry-based proteomics. Inherently, photoaffinity probes are highly functionalised molecules, usually containing an affinity function, photoreactive moiety, and a bio-orthogonal handle. The stability, compatibility and ease-of-synthesis of these tri-functional molecules can prove extremely challenging. A general protocol for the bringing-together of the three separate functional components in a single synthetic step to synthesise fully elaborated photoaffinity probes has not been reported.

Herein we present the use of the Ugi multi-component reaction to combine various commercially available photoreactive groups with a bromodomain-targeting chemical probe in a single synthetic step. This robust protocol allowed for a two-dimensional synthetic array to study the photocrosslinking yields of five commonly used photoreactive groups, in combination with three different linker-lengths. The results and implications from this linker length study are discussed, along with the direct applications of these bromodomain-targeting photoaffinity probes. This includes their use in high-throughput assays with recombinant protein, and in proteomic studies to determine on- and off-targets in live cells.



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Inhibition of metallo-β-lactamases (MBLs) to fight the bacterial resistance to β-lactam antibiotics.	***OC_08***

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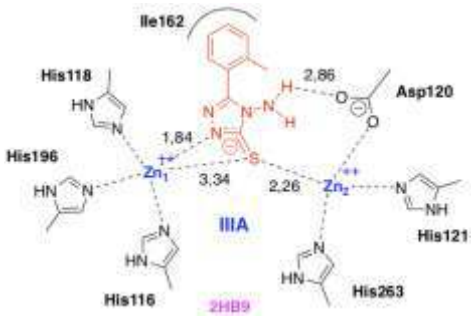
Bacterial resistance to antibiotics is a highly worrying threats to public health and the risk of return to the pre-penicillin era is real. In 2017, WHO has published a Global priority list of antibiotic-resistant bacteria to fight and placed carbapenem-resistant Gram-negative bacteria first.[(a)] The main mode of resistance to the β-lactam antibiotics Carbapenems, which are last-resort antibiotics at hospital, is the production of β-lactamases, among which the class of metallo-β-lactamases (MBLs) is of extreme concern. One major approach to fight this resistance consists of combination therapy in which a β-lactam antibiotic is given along with a β-lactamase inhibitor, which protects the former from inactivation. Although numerous series of MBL inhibitors have been developed, there are no MBL inhibitors marketed yet.



In 2008, the crystallographic structure of the MBL L1 with compound IIIA (2HB9.pdb) revealed the original binding mode of the triazole-thione scaffold, which simultaneously coordinates the two zinc atoms in the enzyme active site (*figure 1*).[(b)] Since then, our laboratory developed various series based on this scaffold.[(c),(d)] Among these, several compounds were found to inhibit several important MBLs (NDM- and VIM-types) with Ki in the μM to sub-μM range. In addition, some compounds were shown to restore the susceptibility of MBL-producing clinical Enterobacteriaceae strains to meropenem. Finally, the resolution of the crystallographic 3D structure of VIM-2 in complex with one inhibitor confirmed the binding mode of these compounds.

We will present and discuss the synthesis and biological evaluation of triazole-thione-based MBLs inhibitors.

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Design, Synthesis And Pharmacological Evaluation Of Novel Tdp1 And 2 Inhibitors.

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OC_09

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. Given that Tyrosyl-DNA phosphodiesterase 1 and 2 (TDP1 and 2 respectively) repairs stalled topoisomerase - DNA complexes, the inhibition of these two DNA repair enzymes could have deadly effects in cancer cells. 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 is a DNA repair enzyme that removes many covalent adducts from DNA through hydrolysis of complexes between DNA and the Top2 active site tyrosine residue. Here, we describe the design, synthesis and pharmacological evaluation of novel compounds as TDP1 and/or 2 inhibitors [(a,b)]. The new compounds bear the acridine or aza-acridine core, possessing one or two basic side chains. The early results suggest, in accordance to In Silico calculations, that the second basic side chain is essential for the activity against TDP1 whilst, the first side chain slightly enhances the activity.

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Synthesis and biological activity of predicted ALR2 inhibitors	OC_10

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Inhibition of an aldose reductase (ALR2), the first enzyme of a polyol pathway, is a promising approach in the treatment of late diabetic complications. Several of ALR2 inhibitors contain an important carboxylic group, which interacts with an anion binding pocket in an active site of ALR2. Recently, 2-(3-thioxo-2*H*-[1,2,4]triazino[5,6-*b*]indol-5(3*H*)-yl)acetic acid (**CMTI or cemtirestat**) was identified as a powerful ALR2 inhibitor possessing a good ALR2 / ALR1 selectivity and drug-like properties.[(a)] Based on the structure drug design, several potential analogues of **CMTI** were proposed. Among them, compound **1 (OCMTI,** IC_{50} = 42 nM**)** showed almost 3-fold higher inhibitory activity in an *in vitro* ALR2 enzymatic assay and more as 8-fold higher selectivity relative to ALR1 (IC_{50} >100 µM) than **CMTI (1)** (IC_{50} = 116 nM ALR2 and 35.10 µM ALR1). Based on these results we can conclude, that isosteric replacement of sulphur with oxygen plays an important role in the inhibition of ALR2 and its selectivity.

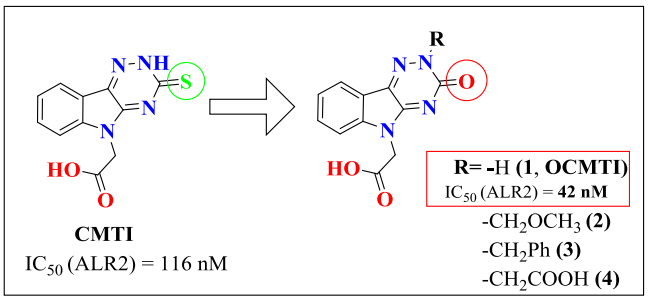

Figure 1. The structures of CMTI, its oxygen analogue derivatives 1-4 and some of determined ALR2 IC_{50} activities.

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Acknowledgements

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Mixtures of green solvent for solid phase peptide synthesis	***OC_11***

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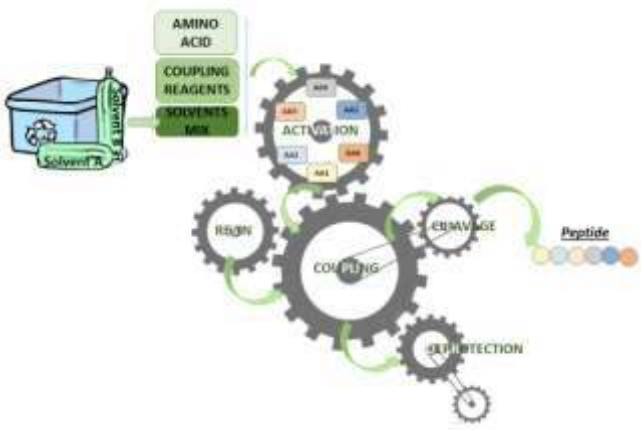
In pharmaceutical industry, the solvents represent the main waste of a synthetic chemical process playing a key role in the toxicity of the overall process as consequence of their use only as medium in which the reactions occur[(a)]. Due to the increasing demand from the chemical and pharamceutical markets for chemically synthesized peptide therapeutics, great attention as been paid to the use of greener solvents for their synthesis. Usually, the solid-phase peptide synthesis (SPPS) is the most employed approach introduced by Merrifield in 1963 and developed by Carpino et al.[(b)] : it consists of Fmoc orthogonal protecting strategy that provides a C-terminal amino acid anchored onto the solid support, that grows with removal of N-protecting group and coupling of the subsequent amino acid, until completion of peptide. All the excess of reagents and byproducts can be removed by filtratation and washings of the functionalized solid support. For this reason, a large amount of solvent will be required during the intere synthetic process. In order to substitute the most employed solvents, like DMF (classified as high reprotoxic solvents), several attempts have been set during the last years, using water, acetonitrile, tetrahydrofuran, ethyl acetate, N-Butylpyrrolidone as examples[(c)]. Anyway, since the role of the solvent in SPPS is to efficiently assist the swelling of the resins[(d)], the couplings, the deprotections and the washings, it's difficult to find new single green solvents able to simultaneously do well in all these different steps. In order to include green solvents that have been excluded from the previous studies, we tested mixtures of solvents showing efficient properties as swelling agents and solubilization media.

We reported a study on the replacement of DMF in solid phase peptide synthesis with mixtures of green solvents (GM-SPPS), obtained by mixing Cyrene™, Sulfolane or Anisole with Dimethyl or Diethyl carbonate, testing their efficiency in the synthesis of a model peptide (Aib-enkephalin) and evaluated in terms of swelling of the resins, coupling, deprotection and washings processes.



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[(d)] S. Lawrenson, M. North, F. Peigneguy, A. Routledge, *Green Chem.*, 2017, **19**, 952.

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NR-DBIND : A database dedicated to nuclear receptor binding data including negative data and pharmacological profile.	*OC_12*

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Nuclear receptors (NRs) are transcription factors capable of regulating gene expression in various key physiological processes through their interaction with small hydrophobic molecules. They constitute an important class of targets for drugs and endocrine disruptors and they are widely studied for both human health and environmental risks. Today, the NR family is among the most studied protein families, and the quantity of experimental binding and activity data published in the literature should be valuably used to boost NRs compounds profiling, ligand-based and structure-based drug design, and SAR studies. In the present work, we gathered diverse NR experimental data that have been published in the literature in a database named Nuclear Receptor DataBase Including Negative Data (NR-DBIND) to help extracting qualitative information for chemists, biologists and toxiciologists. Since the integration of negative data can be critical for accurate modeling of ligand activity profiles, we manually collected and annotated affinity data for molecules experimentally tested against NRs, including both positive and negative results. The NR-DBIND contains the most extensive information about interaction data on NRs, with 15 116 positive and negative interactions data provided for 28 NRs together with 593 PDB structures. The entire database is freely available at http://www.nr-dbind.drug-design.fr and propose multiple datasets.

In the future, the NR-DBIND and all the knowledge it brings to the scientific community should facilitate rational drug discovery for documented NRs and help predicting the NR-related risk of endocrine disruption.

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Opposite effect of NRP-1 and NRP-2 in the aggressiveness of clear cell Renal Cell Carcinoma

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OC_13

Anti-angiogenic therapies are used for the treatment of metastatic ccRCC (mccRCC). The current reference therapy in the first line is the multi-kinase inhibitor sunitinib (Sutent®). However, relapses appear after a few months. We recently describe that VEGF-C, the main pro-lymphangiogenic factor, represents one of the main actors of a progressive disease with dissemination of tumour cells through the neo-formed VEGF-C dependent lymphatic network[(a)]. These results highlight the urgent need to develop alternative therapeutic strategies for mccRCC at relapse on conventional treatment.

Moreover, a distinct family of VEGFs co-receptors, the Neuropilins (NRPs), has emerged as a relevant oncology target. NRPs form complexes with VEGFs and their receptors and induce cell migration, survival, and tumour growth. In this study, we show that NRP-1 and NRP-2 have an opposite effect in the aggressiveness of ccRCC. Indeed, NRP-1/VEGF-A pathway is pro-proliferative and pro-migrative, on the contrary NRP-2/VEGF-C pathway is anti-proliferative and anti-migrative. From this, NRP-1/VEGF-A pathway should be targeted to reduce ccRCC aggressiveness but not NRP-2/VEGF-C pathway. At the same time we developed and tested a NRP inhibitor, NRP-a308 that is targeting both NRPs. In the case of ccRCC expressing NRP-1 and NRP-2, NRP-a308 has good *in-vitro* effects, but it has no effect on tumorigenesis of ccRCC xenograft on nude mice. However, it was previously shown to exert anti-cancer effects on human aggressive breast cancer expressing only NRP-1[(b)]. This result on ccRCC can be explained by the opposite effect of NRP-1 and NRP-2 pathways in term of proliferation. Indeed, NRP-a308 targeting both NRPs, the compensatory effect is present and the inhibitor has no effect on ccRCC xenograft tumorigenesis. Thus, our objective is to synthesize and test new inhibitor targeting specifically NRP-1 to reduce its pro-proliferative and pro-migrative effect in ccRCC.

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Lipophilic phenylbutyric acid derivative as a drug candidate for the treatment of misfolded proteins related diseases

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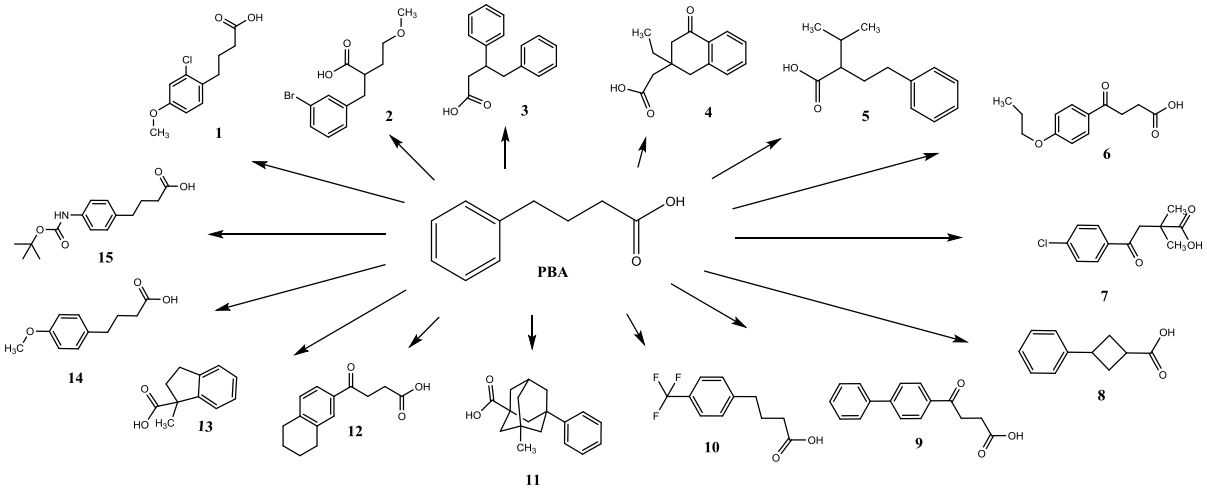
OC_14

Chemical chaperones have shown the ability to prevent protein aggregation and induce therapeutic effect in many misfolded protein related diseases by controlling the correct folding and assembly of proteins, ensuring their appropriate intracellular trafficking and functions. Protein refolding by chemical chaperones has enabled proteolytic enzymes and proteasome systems to cleave misfolded proteins properly. However, using chemical chaperones as drugs are limited due to their very high active concentrations (mM range) required for their efficacy. One of the known chemical chaperones is phenylbutyric acid (PBA) or its sodium salt. This chemical chaperone is used for the treatment of urea cycle diseases, although it seems that its therapeutic effect is not related only to its chaperoning activity. Alternatively, PBA as a chemical chaperone showed very impressive therapeutic effects in cystic fibrosis, amyotrophic lateral sclerosis, parkinson disease and many others misfolded protein disorders. Yet, due to its non-favorable pharmacokinetic properties, PBA was not approved as a drug to treat those diseases. Therefore, the search for more effective and more potent PBA derivatives is intense.
In this work, we report the discovery of lipophilic PBA derivative: 3-methyl-2-phenethylbutanoic acid (compound 5) which shows impressive protein chaperoning activity in several in vitro models in much lower concentrations comparing to PBA.
Importantly, one of the in vitro systems in which 3-methyl-2-phenethylbutanoic acid was found to be active is autism cellular model (i.e. the overexpression of mutated neuroligin-3 in neurons). Compound 5 decreased by a factor of 4 the concentration of secreted mutated neuroligin-3 compared to PBA.



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Interaction between HIV Maturation Inhibitors and GAG precursor

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OC_15

The maturation of human immunodeficiency virus type 1 (HIV-1) particle is a key step for viral infectivity. During this process[(a, b)], the polyprotein Gag is cleaved by the viral protease into four proteins MA, CA, NC and p6 and 2 spacer peptides SP1 and SP2 between CA and NC and NC and p6 respectively. Interestingly, the last cleavage between CA and SP1 could be blocked by maturation inhibitors[(c)]. We identified EP39, a derivative of Bevirimat, as a new maturation inhibitor that interferes with the process of the cleavage between CA and SP1[(d)]. However, the mechanism of interaction between CA-SP1 and maturation inhibitors is still unknown.

To decipher this mechanism, we determined, by NMR, the structure of the domain spanning CActer, SP1 and NC (CActer-SP1-NC) without and with EP39. Briefly, the structure of the protein without EP39 showed that CActer-SP1-NC had three major segments. The CActer that contains four stable α-helices, the flexible domain (82-109) comprising the last seven amino acids of CA, the whole SP1 and the first seven amino acids of NC and finally the NC with its two stable zinc fingers. The CA-SP1 junction in the flexible domain is in a dynamic equilibrium of coil-helix[(e)]. In the presence of EP39, CActer and NC retain the same conformation while the domain (82-109) folds into a stable α-helix. Besides, we also studied the dynamics of the protein alone and in complex with EP39. The relaxation experiments showed that there was no obvious change in the dynamics of CActer and NC proteins after binding EP39 while a net decrease of the dynamics of domain (82-109) confirms EP39 binding.

Taken together, our results suggest that EP39 inhibits the maturation of HIV particles by interfering with the dynamics equilibrium of coil-helix in CA-SP1 junction and driving this domain to fold into a helix conformation. Further studies to identify the precise interaction site of EP39 with the junction CA-SP1 within Gag need to be performed to help the development and optimization of these new HIV maturation inhibitors.

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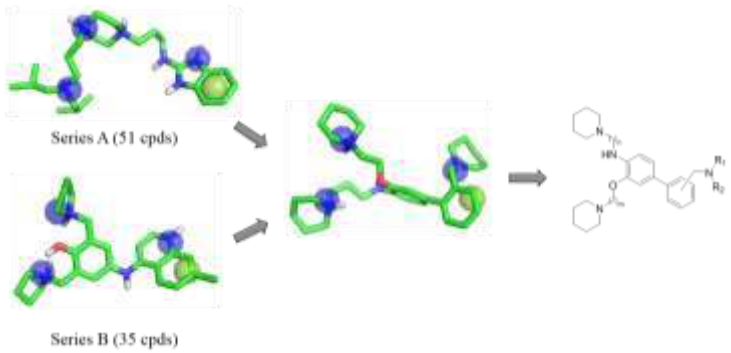
Discovery of new compounds that promote non-amyloidogenic processing of the amyloid precursor protein for the treatment of Alzheimer's disease. **Florian Descamps (1)*, Marion Gay (1), Caroline Evrart (1), Pascal Carato (1), Nicolas Renault (2), Mathilde Coevoet (1), Sabiha Eddarkaoui (1), Catherine Baud (1), Paul-Emmanuel Larchanché (1), Luc Buée (1), Jamal El Bakali (1), Valérie Vingtdeux (1), Nicolas Sergeant (1), Patricia Melnyk (1).** *(1) Université de Lille, Inserm, CHU Lille, UMR-S 1172 - JPArc - Centre de Recherche Jean-Pierre AUBERT Neurosciences et Cancer, F-59000 Lille, France* *(2) Université de Lille, Inserm, CHU Lille, U995 - LIRIC - Lille Inflammation Research International Center, F-59000 Lille, France*	***OC_16***

Dysregulation of the Amyloid Precursor Protein (APP) processing leading to toxic species of Aβ peptides is central to Alzheimer's disease etiology**.** Aβ are produced by sequential cleavage of APP by β-secretase (BACE-1) and γ-secretase. Indirect inhibition of β-secretase by lysomotropic molecules such as chloroquine (CQ) through the endosome/lysosome-mediated degradation has been reported to inhibit Aβ peptide production. Following on from the promising activity of two series of APP metabolism modulators (Series A and B) derived from CQ, new series of compounds able to retain the inhibitory effects on Aβ production without altering lysosome functions were developped. Biaryl compounds were designed using a ligand-based pharmacophore modeling approach coupled with *de novo* design that led to the discovery of a series of biaryl compounds.

Ligand-based approach leading to biaryl



structure-activity relationship studies revealed that minor modifications allowed for the identification of compounds with the desired profile. finally, this work shows that it is possible to dissociate the lysosomotropic effect of cq-derived compounds from their action on aβ secretion, providing a new profile of indirect β-secretase inhibitors for ad treatment.(b)

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Nanomedicine for the treatment of glioblastoma: glyco-targeted cyclodextrin-calixarene heterodimers for controlled drug delivery.	***OC_17***

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Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor with a median survival for patients of 1-2 years. The standard treatment is based on surgical resection followed by radiotherapy plus concomitant chemotherapy with temozolomide. However, tumor heterogeneity, angiogenesis and infiltration in the surrounding tissues avoid a complete resection by surgery or an efficient radiotherapy. Moreover, the short have-life of temozolomide, the lack of specificity, the resistance to treatment and the adverse effects make the chemotherapy inefficient. A very interesting alternative is based on drug delivery systems able to improve bioavailability of drugs and avoid secondary effects through targeted transport. We have developed calixarene-cyclodextrin heterodimers filled with the capacity to self-assemble in water media to form functional nanoparticles, as confirmed by AFM and Cryo-TEM microscopy. These nanostructures have an inner core formed by hydrophobic calix[4]arene (CA_4) units and an external hydrophilic shell exposing β-cyclodextrin (βCD) moieties. The CA_4 scaffold is very well suited to promote tight packing of fatty chains installed at the narrower ring, providing a lipid matrix where hydrophobic drugs can be entrapped, whereas the presence of hydrophilic bCD moieties at the surface allows nanoparticle solubilization in water as well as ligand incorporation by inclusion complex formation. The potential of the new systems in nanomedicine is illustrated by their capacity to encapsulate and provide sustained release of anticancer drugs such as temozolomide and undergo supramolecular post-modification with adamantane-armed glycoligands targeting the human macrophage mannose receptor, which is overexpressed in the tumour-associated macrophagues. Studies in human glioblastoma cell lines demonstrated its potential as a new nanomedical therapy for the GBM.

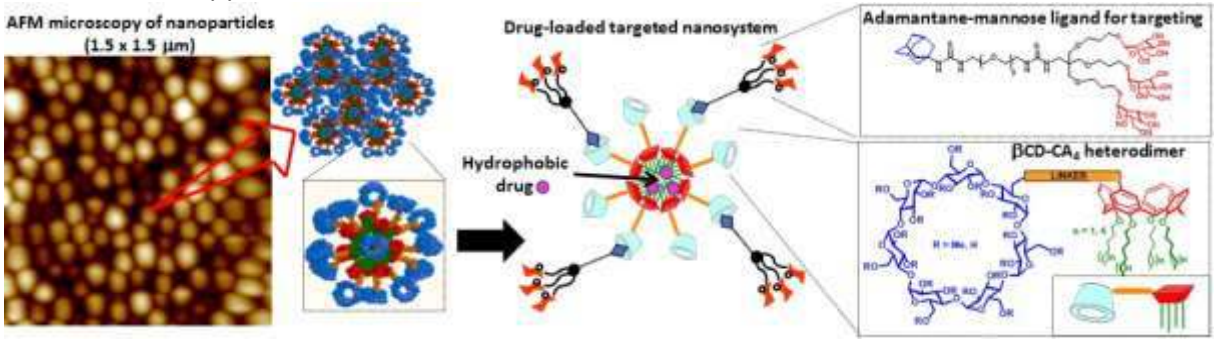

Figure 1. AFM image and structure of targeted nanosystems self-assembled from heterodimers.

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Synthetic small molecules interfering with oncogenic microRNAs for the induction of glioblastoma stem cells differentiation.	***OC_18***

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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.[(a)] 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.[(b)] Recently, our team identified original compounds able to interfere with miRNAs biogenesis.[(c)] 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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Deciphering the Mechanisms of Allosteric Modulation of HSP90

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OC_19

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

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Oxidation Stress in Friedreich Ataxia: role of Frataxin	*OC_20*

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Friedreich ataxia (FRDA) is the most common of the inherited ataxias. Mitochondrial dysfunction and oxidative tissue damage are observed in pathologic cells. Until now, there is no approved pharmacological treatment for this neurodegenerative disease. The use of antioxidants has been explored as a potential therapy with however a limited benefit in patient clinical trials. Thus, it is crucial to understand the mechanism of oxidative stress in the pathophysiology of FRDA. This disease is caused by the decreased expression of a mitochondrial protein, frataxin, whose specific function remains controversial. Several functions have been proposed, among which, the control of oxidative stress in mitochondria.

We establish here, in cell free assays, the existence of molecular interactions between yeast frataxin (Yfh1) and superoxide dismutases (SODs), the gate keepers in regulation ROS. We, furthermore, report, by kinetic and thermodynamic approaches, the rate and affinity constants involved in the molecular interactions between Yfh1 and CuZnSOD and MnSOD, respectively. Yfh1 increases the enzymatic activity of CuZnSOD while slightly affecting that of MnSOD. Frataxin binds metal without any specificity.[(a)] We show here that the stabilities of the Yfh1-SOD adducts as well as the impact of Yfh1 on superoxide dismutase depend on the nature of the metal present in the mitochondrium. We consequently demonstrate the participation of frataxin in cellular defence against oxidative stress.

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he influence of the solution conditions on the fibrillization of hen egg-white lysozyme	OC_21

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Proteins are biological macromolecules that are essential to life. For their proper operation their native structure needs to be maintained. Intra- and intermolecular interactions in protein solutions play a key role in stabilizing proteins, as they can trigger their unfolding or association into aggregates[a]. Under certain conditions proteins can form amyloid fibrils, highly organized protein aggregates, which are most known for their close intertwining with the onset of several neurodegenerative diseases, e.g. Alzheimer's disease[b]. Although cardiovascular diseases and cancer are still the main cause of death, age-related neurodegenerative disorders, due to a considerable increase in the number of elderly people in practically every country in the world, present a growing threat to mankind. Knowledge about the formation of amyloid fibrils is of key importance for disease prevention and treatment.

In our study we have focused on the formation of hen egg-white lysozyme (HEWL) fibrils in aqueous solutions of different buffers in both, acidic and basic pH range. By using UV-Vis spectroscopy, CD spectroscopy and emission fluorescence measurements we have ascertained that HEWL fibrils form only under specific solution conditions (agitated sample in Figure 1). Our results point out several parameters that determine the onset of HEWL fibrillation: solution pH, sample incubation (agitated vs. static), added excipients (NaCl and PEG), and also buffer identity (glycine, TRIS, PBS, cacodylate, acetate and HEPES), which has been shown to play an important role in biological systems[c].

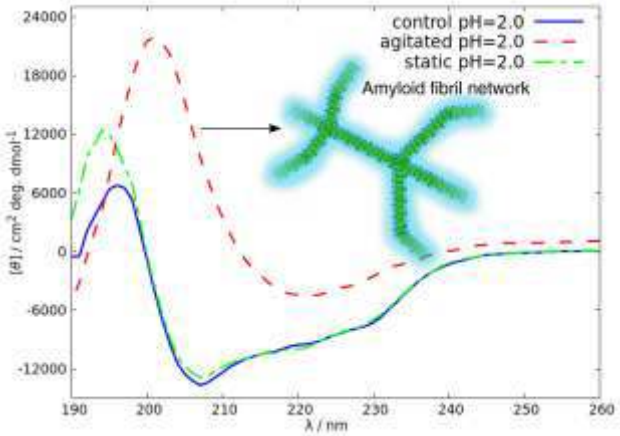

Figure 2 : CD spectra of three HEWL samples in 0.5 M glycine buffer, pH=2.0. Control and static sample exhibit native lysozyme with predominant α-helix secondary structure. Agitated sample displays amyloid fibril formation as a distinct signal for the anti-parallel β-sheet is observed.

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Alzheimer's Disease: Development and application of a Multistep Procedure to Characterize Modulators of Amyloid Peptide Aggregation

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OC_22

Abstract: Alzheimer's disease is the most widespread form of senile dementia worldwide and represents the leading socioeconomic problem in healthcare. The onset and the progression of this neurodegenerative disease is associated with the aggregation of the amyloid-β peptide (Aβ).
An attractive therapeutic strategy against this disorder is the development of molecules able to interfere at specific steps of this fibrillization pathway. To identify such molecules, experimental methods are required to precisely follow and characterize the Aβ peptide during its fibrillization process. In the same time, these methods must be simple enough to remain compatible with the High Throughput Screening (HTS) of new compounds.
In the present study, we propose to combine experimental methods to allow a multiparameter characterization of potential modulators of Aβ1-42 fibrillization.
Kinetic studies were performed by implying liposomes as membranes models since it has been established that neuronal lipids are an important factor in the formation of the amyloid fibers. Thus, fluorescence of Thioflavin T, a specific dye for amyloid species, was monitored to follow the Aβ fibrillization pathway. In parallel, a liposome leakage assay supported by partition coefficient determination studies was carried out to evaluate the impact of the interactions between the peptide and membranes to predict any destabilization effect.
From results obtained to date, it appears that the tested modulators present a range of effects that can affect defined stages of the aggregation of the Aβ1-42 peptide. Considering that the toxic fibers formed by Aβ are mainly organized into β-sheets, assays were correlated with the secondary structure analysis of the peptide using ATR-FTIR spectroscopy. All of these experiments will provide a multiparametric test allowing the characterization and the discrimination of newly Aβ aggregation modulators synthetized by chemists and could even be expanded to other amyloid diseases.

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Drug Fragment-based Discovery of Enterovirus Inhibitors

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OC_23

Enteroviruses infections can lead to several diseases such as poliomyelitis, hand-foot-and-mouth disease, aseptic meningitis and myocarditis. Currently, no antiviral drugs targeting these viruses are available on the market.

A novel broad-spectrum non-nucleoside inhibitor targeting enterovirus polymerases was identified[(a)], but improvements in drug-like properties were required to continue the development. This study aimed to identify new chemical scaffolds retrieving the interaction with enterovirus polymerases while presenting drug-like properties.

Through a **structure-based drug design** approach, pharmacophore models were built with LigandScout software[(b)] to contain the relevant features responsible for the biological activity, based on the crystal structure of the polymerase. This model was then used for virtual High Throughput Screening (vHTS) to identify potential bio-active molecules.

Taking advantage of a database of virtually combined **drugs fragments** issued from the Prestwick Drug-Fragment Library, several scaffolds were considered in the hit list. Some of the virtual compounds were synthesized to evaluate their **antiviral activity**. The use of related and shared starting materials enabled to obtain various scaffolds, even with a limited number of reactions.

Synthesized compounds were evaluated by *in vitro* experiments against two strains of enterovirus. Besides investigation of new scaffolds, hit validation and derivatization of most promising hits can afford new potential anti-enterovirus leads.

With the aim to optimize the hit discovery process, this project associated computational chemistry techniques to an innovative use of fragments.

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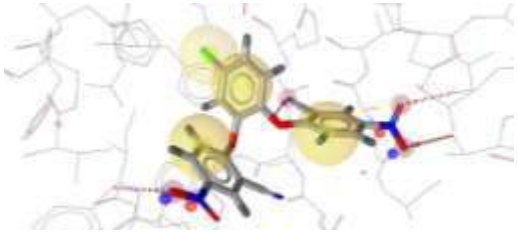
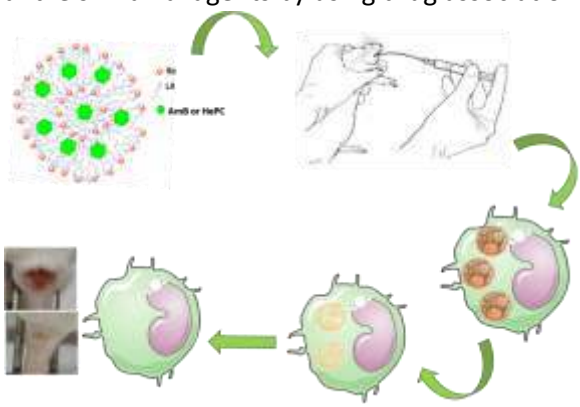


Structure-based pharmacophore model from Coxsackie Virus B3 polymerase

Combined antileishmanial chemotherapy: mixed micellar system of known actives allows oral treatment of leishmaniasis **Juliane Sousa Lanza[(1,2)*], Virgínia Mendes Carregal[(2)], Arshad Islam[(2)], Lucas A. M. Ferreira[(2)], Cynthia Demicheli[(2)], Sébastien Pomel[(1)], Philippe Loiseau[(1)] and Frédéric Frézard[(1,2)]** *(1) Chimiotherapie Antiparasitaire, BioCIS, Faculté de Pharmacie, UPSud, Chatenay-Malabry, France.* *(2) Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.*	***OC_24***

Leishmaniasis are chronic diseases with basically cutaneous (CL) and visceral (VL) manifestations, caused by flagellate protozoa of the Leishmania genus. This disease affects more than 12 million people mainly in developing countries. Human chemotherapy has several limitations as high toxicity, recurrence and development of resistance by the parasites. Therefore, efforts have been made to decrease the toxicity and increase the efficacity of these drugs. One strategy consists in formulating existing active agents in a biocompatible nanodelivery systems and combining them in lower ratios. In this context, this work aimed to study pharmacologically the type of interaction between either amphotericin B (AmB) or miltefosine (HePC) in association with a micelle-like system consisting in amphiphilic antimony(V) complex (SbL10) that was previously reported to be orally-active. For that, in vitro assays using macrophages, intramacrophage and axenic Leishmania donovani parasites were performed to determine IC50, CC50, FICI and SI (Selectivity Index). The reduction of HePC and AmB IC50s upon increasing SbL10 concentration demonstrated additive effects of the drugs (0.5<FICI<4). The 100-fold higher SI value for SbL10 in intramacrophage parasites in comparison with axenic parasites supports participation of the host cell in the drug activation through reduction of Sb(V) to Sb(III) active form and in micelle-mediated intracellular accumulation of Sb. The in vivo treatment with SbL10/AmB given orally showed significant reduction of liver and spleen parasite loads compared to the saline control ($p<0.0001$) in a murine model of VL. Oral treatment with SbL10/HePC led to a significant reduction of the lesion parasite load, in a murine model of CL, in relation to treatment with saline, HePC or SbL10 given alone at the same dose ($p<0.001$). This work shows that it is possible to increase the efficacy of antileishmanial agents by using drug association in versatile nanodelivery systems.



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Improving the activity of dietary cinnamic and benzoic acids for the treatment of neurodegenerative disorders	***OC_25***

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

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

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

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Novel cis-imidazoline derivatives as precursors for potent inhibitors of mdm2-p53 interaction.	***OC_26***

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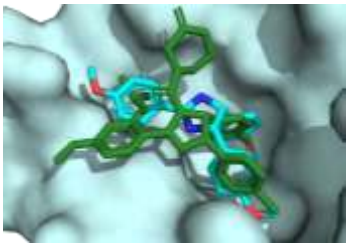
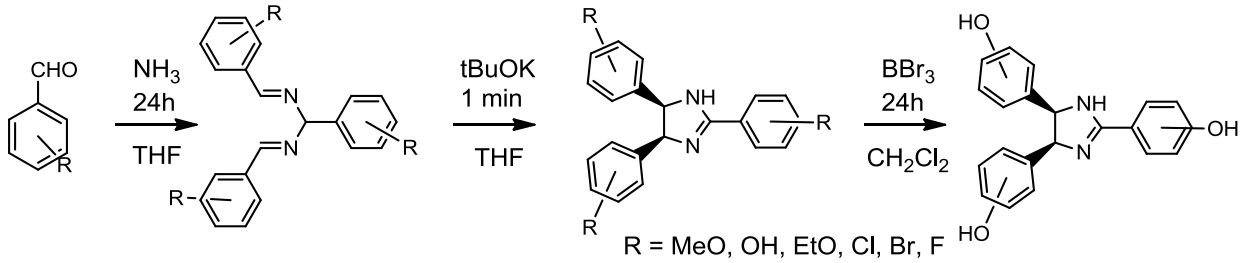


Figure 3: Docking of 4-MeO derivative (cyan) versus Nutlin-3a (green) in mdm2 binding site

Preparation of cis-imidazoline derivatives using the reaction of aromatic aldehydes with ammonia is a convenient and simple synthesis of the imidazolines, precursors of the known inhibitors Mdm2-p53 interaction. We report docking studies, synthetic approach, cytotoxicity and mechanism of action analysis. Docking studies showed the possibility of proposed structures to occupy p53 binding pockets. Using the proposed synthetic approach, we synthesized various cis-imidazoline structures containing halogens, alkoxy and hydroxy groups and investigated their cytotoxicity.



R = MeO, OH, EtO, Cl, Br, F

Despite the fact that both derivatives (R = 4-Cl, 4-MeO) showed cytotoxicity and increased p53 level, chlorine derivatives induced necrotic cell death, while alkoxy derivative was not toxic and demonstrated the best efficacy for p53 stabilization.

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The Synthesis of Aromatic Lipoxin A_4 Analogues with Upper Chain Modifications.

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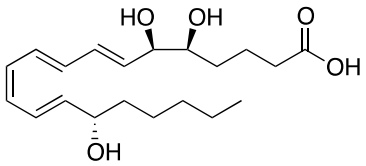
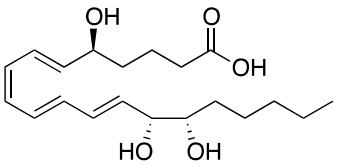
OC_27

Lipoxins, a group of bioactive compounds enzymatically derived from arachidonic acid by a family of lipoxygenase enzymes, were first isolated from human leukocytes by Serhan and Samuelsson in 1984.[(a)] The two naturally occurring Lipoxins, Lipoxin A_4 (LXA_4) (**1**) and Lipoxin B_4 (LXB_4) (**2**) are trihydroxytetraene-containing eicosanoids. Lipoxins regulate components of both the innate and adaptive immune systems to initiate the resolution of inflammation by activating the FPR2/ALX receptor.[(b,c)] Although a healthy bodily response, the effective resolution of inflammation is essential for maintaing normal tissue homeostasis and the prevention of chronic inflammatory diseases.



Lipoxin A_4, (**1**)



Lipoxin B_4, (**2**)

The major obstacle associated with using Lipoxins to treat diseases caused by chronic inflammation is the rapid metabolism observed *in vivo*, which is characteristic of all autacoids. These LX metabolites exhibit dramatically decreased biological activity and are considered inactive metabolites, rendering them poor potential pharmacological agents.[(d)] Within our research group the rapid metabolic inactivation has been overcome by synthesizing aromatic and heteroaromatic analogues of LXA_4.[(e)] The aim of this project is to synthesise a range of aromatic LXA_4 analogues with varied upper chain lengths to probe the stability *in vivo*, in particular the β-oxidation of the upper chain of which is known to be another source of metabolic instability in LXA_4.

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Selenium heteroaryl derivatives as potent cytostatic and antioxidant agents

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OC_28

Selenium heteroaryl derivatives have received great attention owing to their possible usefulness as therapeutic drugs for cancer treatment. Some emblematic examples include ebselen, ethaselen and 1,2,5-selenadiazole derivatives. The purpose of this study is to perform structural modifications over 1,2,5-selenadiazole derivatives to improve its anticancer and antioxidant characteristics.

Twenty-seven novel benzo[*c*][1,2,5]selenodiazole-5-carboxamide derivatives were designed and synthesized. These novel derivatives were tested *in vitro* against a panel of five human tumor cell lines (PC-3, HT-29, CCRF-CEM, HTB-54 and MCF-7) and two non-malignant cell lines (184B5, BEAS-2B) in order to determine their anti-proliferative activity and their selectivity. For MCF-7 cells, the apoptotic process and cell cycle analysis of the cells were based on the TUNEL technique. The capability of the synthesized compounds to interact with the stable radical 2, 2-diphenyl-1-picrylhydrazyl was also examined.

Some compounds exhibited higher cytostatic activity than ebselen and ethaselen in solid tumors, along with higher selectivity indexes. Likewise, the radical scavenging values of four compounds were greater than EBS.

The cytostatic activity of hit compound was significant in MCF-7 cells, with a growth inhibitory 50% (GI_{50}) of 3.7 µM. Nevertheless, the induction of cell death was independent on the apoptotic status. Furthermore, the lethal dose (LD_{50}) of hit derivative in the non-tumoral cell line 184B5 was more than 100 µM [(a)].

Given the moderate antioxidant and cytostatic activity and low toxicity, these selenium heteroaril derivatives can be use as an excellent scaffold to achieve novel and effective antioxidant compounds for numerous diseases, such as cancer, neurodegenerative and heart diseases.

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Synthesis and characterization of multifunctional hybrid magnetic nanoparticles designed for multimodal imaging.

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OC_29

Summary

Over the last decade, the field of nanomedicine imaging is focused on the design of all-in-one multifunctional agents that can be detected by multimodal techniques. Dual-modality radiolabeled nanoparticles with large surface areas and multiple functional moieties are promising candidates since they combine synergistic advantages, for non-invasive, high sensitive, high-resolution, and quantitative imaging of two different imaging modalities, namely, single-photon emission computed tomography and magnetic resonance imaging (SPECT and MRI). An ideal nanoparticle imaging probe for next-generation multifunctional radiotracer, should include the following functionalities: easy administration, excellent *in vivo* and radiolabeling stability,[(a)] biocompatibility,[(b)] selectivity, sensitivity,[(c)] ability to observe its accumulation in real-time and to monitor disease progression,[(d)] biodegradable or rapidly excreted after the imaging is complete, minimal to no side effects, and cost-effectiveness, while producing a strong imaging signal.[(e)] Although significant breakthrough has been made toward the development of various radiolabeled and/or fluorescent nanoparticles which can be used as promising diagnostic tools,[(f)] multifunctional imaging agents that simultaneously exhibit all the desired features are extremely rare.

The main objective of this paper was to design a new multifunctional hybrid magnetic tracer that will be further radiolabeled and used as dual-modality SPECT and MRI imaging probe. Hybrid magnetic nanoparticles were synthesized using iron oxide core and multifunctional silica shell chains available for fluorescent marking and ^{99m}Tc radiolabeling. The structure, external morphology, size distribution, colloidal and magnetic properties were characterized by FT-IR, SEM, TEM, XRD, DLS and VSM analyses. TEM and DLS results showed that the hybrid complex has nanostructure with broad distribution. Formation of crystalline magnetite nanoparticles was confirmed by XRD analysis. Magnetization measurements on the obtained samples show a straightforward correlation between the saturation magnetization and morphology of the samples. These positive findings suggest that the multifunctional hybrid magnetic nanoparticles could be applied as a dual imaging probe for targeting tumoral tissues.

Acknowledgement: This work was supported by a grant of Ministery of Research and Innovation, CNCS - UEFISCDI, project number PN-III-P1-1.1-PD-2016-1642, within PNCDI III.

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Targeting Myeloperoxidase: Studies on Novel Benzimidazole Derivatives as MPO Inhibitors

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OC_30

Myeloperoxidase (MPO) is a heme-containing enyzme and a member of peroxidase enzyme family. It is stored in neutrophils and plays significant role in human antimicrobial and antiviral system by oxidizing vital molecules of microorganisms due to its catalysing activity of hydrogen peroxide which results in the production of highly oxidative hypochlorous acid (HOCl). On the other hand, MPO can be released outside of neutrophils generating HOCl in extracellular fluids that leads to damage to biomolecules such as DNA, RNA, proteins, lipids. This oxidative damage causes many inflammatory diseases for instance atherosclerosis, rheumatoid arthritis, neurodegenerative diseases (Alzheimer's and Parkinson), renal failure etc. As the understanding of the role of MPO/H_2O_2/Cl^- system on these diseases expanded, MPO became a promising target for the development new anti-inflammatory agents[(a,b)].

Literature survey indicated that potential MPO inhibitors commonly have thiourea group and fused rings such as indole, indazole and indazolone[(c,d,e,f)]. Based on these findings, we combined benzimidazole ring and thiourea function and then synthesized a group of novel N,N'-disubstituted benzimidazole-2-thione derivatives. MPO inhibitory activity of the final compounds have been determined by taurine chloramine assay.

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Screening of UGGT binding fragments as chemical leads for the development of novel broad-spectrum antivirals

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OC_31

UDP-glucose glycoprotein glucosyltransferase (UGGT) is the only known endoplasmic reticulum (ER) folding checkpoint for misfolded glycoproteins and forms part of the ER quality control (ERQC). Targeting the ERQC is pursued as a broad-spectrum antiviral strategy. For example, inhibiting ER alpha-glucosidase II, the counter player of UGGT in the so-called calnexin cycle, leads to an accumulation of misfolded viral glycoproteins that are retained inside the ER, compromising secretion and infectivity of many viruses[(a)]. UGGT has never been tested as an antiviral target, and there are no known UGGT inhibitors apart from its product UDP. Preliminary unpublished proof-of-principle experiments on UGGT1 knockout mammalian cells showed that certain viruses could not replicate any longer. These results encouraged us to initiate the search for potent and selective small molecule inhibitors of UGGT. We decided to perform a Fragment Based Lead Discovery (FBLD) to find ligands of the catalytic domain of *Chaetomium thermophilum* UGGT (*Ct*UGGT-GT24): the fungal protein and its human homologue *Hs*UGGT1 share high sequence identity in this domain. X-ray crystallography was selected for ligand screening. We developed a protocol to reliably grow thousands of high-resolution diffracting *Ct*UGGT-GT24 crystals suitable for soaking with fragments. At the XChem Diamond facility in Harwell UK, we then soaked 768 crystals with as many fragments from the DSi-Poised Library. X-ray diffraction data were collected from 692 of these soaked crystals, processed by the autoPROC suite of programs and analysed by using the XChem suite provided by Diamond facility and a custom-written shell script pipeline named COaLLA which enabled the best automated choice of crystal polymorph for each soaked crystal. Any fragment hits obtained will be subjected to hit expansion, i.e. close analogues of these hits will be identified, synthetized and evaluated, and in subsequent rounds of chemical modifications, we hope to obtain a strong and selective ligand.

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Straightforward Access To Phthalazine Scaffold Under Visible-Light Irradiation

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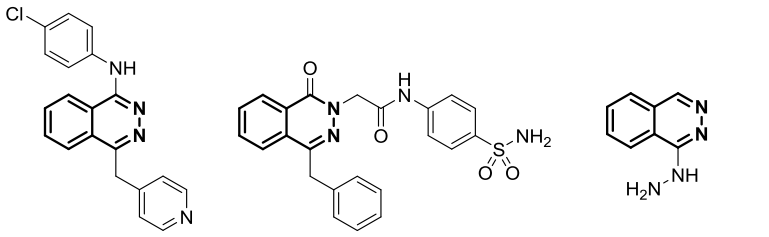
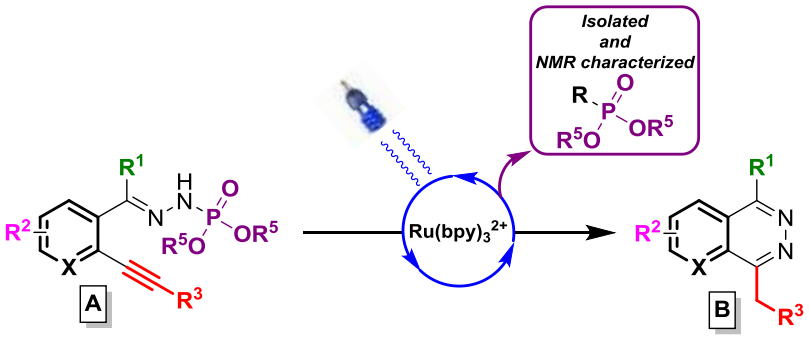
OC_32

Therapeutic properties of nitrogen-containing heterocycles have been known for decades[(a)]. The phthalazine scaffold is no exception since it has been proved to have anticancer[(b)] and antibacterial[(c)] properties, in addition to its antihypertensive[(d)] properties for which it is already marketed in Europe and in the USA.



Our laboratory is involved in the development of new photochemical reactions[(e)] and has reported in 2016 the synthesis of the phthalazine scaffold *via* an innovative visible-light induced amination followed by a Smiles rearrangement[(f)]. Here we describe a new way to access the phthalazine B, starting from phosphonohydrazone derivatives A.



In this work, we will describe the reaction conditions' optimization, the scope and the mechanistic proposal for this reaction[(g)].

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

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OC_33

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

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

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A novel PC2A-derivative ligand as pH-responsive ,,smart" MRI probe: synthesis and characterization

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OC_34

The Magnetic Resonance Imaging (MRI) is the most widely used imaging technique in the biomedical studies to get anatomical and functional images. Nowadays, the application of the molecular imaging is seeking for information about the molecular levels. We need deeper understanding of the biochemical and physiological abnormalities of diseases for earlier diagnosis. The molecular imaging - instead of anatomical imaging - requires molecular imaging probes. (a)

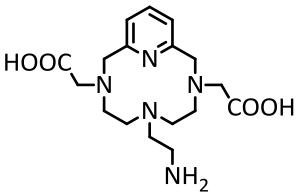

Figure 1: Structure of PC2A-EA ligand

In this work the newly synthesized PC2A-EA ligand (Figure 1.) was studied. The synthetic scheme was designed to prepare some intermediate compounds that can be used to prepare new smart imaging agent candidates. The alkylation of the cis-nitrogen atoms of the macrocycle was performed by using ethyl-bromoacetate which allowed the primary amine nitrogen to be functionalized after removal of the Boc protecting group.

The protonation constants of the ligand and the stability and protonation constants of the complexes formed with essential metal ions were determined using pH-potentiometric titration method. The stability constant of [Mn(PC2A-EA)] was found to be $\log K_{MnL}$=19.01. The pH-dependence of the relaxivity of the [Mn(PC2A-EA)] was also investigated by using ^{1}H relaxometry. These results showed that the complex was formed in 100% around pH=5.0, and a significant (~1.5 unit) decrease in the relaxivity could be observed due to the deprotonation and coordination of the primer amine group in the pH range of 6.0-8.0 ($\log K_{MnLH}$=7.12). Neither the extent nor the pH range of the given pH response was affected by Human Serum Albumin (HSA).

The half-life of dissociation ($t_{1/2}$) of the [Mn(PC2A-EA)] (at near to physiological pH) is calculated to be 8054 h at 25 °C. An estimation (based on the results obtained for Gd(III) complexes) gives about 1600 hours at 37 °C. This results makes the [Mn(PC2A-EA)] complex a promising candidate for *in vivo* applications.

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Synthesis and biological evaluation of new fluorinated ligands targeting P2X7R.	***OC_35***

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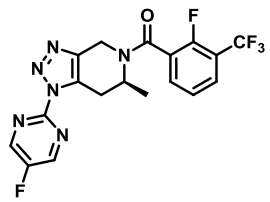
The central nervous system (CNS) is the part of the nervous system consisting of the brain and spinal cord. Neurodegenerative diseases as Parkinson's, Alzheimer's or epilepsy are typically associated with chronic inflammation of the CNS (neuroinflammation). Neuroinflammation is a part of the complex biological response of body tissues to pathogens or damaged cells. The function of inflammation is to eliminate the initial cause of cell injury and initiate tissue repair. The initial microglial response that occurs in neuroinflammation is characterized by microglial accumulation in the injured sites of the brain.[(a)]

Inflammatory conditions are associated with the extracellular release of nucleotides, particularly ATP. Extracellular ATP is activated by ionotropic P2X receptors. Among seven members of P2XR family, P2X7 is expressed by variety of cells type in brine as neurons and microglial cells. Although several other P2XRs are functional during inflammation, P2X7R in particular has been shown to affect the outcomes of inflammatory or infectious diseases.[(b)]

In the literature, there are few described references targeting this receptor (Fig. 1). Based at literature research, we designed and synthesized new scaffolds and series of original fluorinated compounds. The activity of all the molecules was evaluated. The most promising ligands will become a potential ^{18}F probes to early diagnosis CNS disorders.



$P2X_7$ IC_{50} = 5,9 nM
Janssen Pharmaceutical NV

Fig. 1. Reference molecule

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FLASH POSTER ABSTRACT

Study of relevant structural information from a large set of bioactive molecules using a network-based approach.

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FP01

It has been adopted that drugs interact with multiple targets i.e. polypharmacology [1]. In this area, bipartite drug-target network became a popular approach in target prediction studies [2, 3] drug repurposing [4], or searching for secondary target causing side effect [5]. But few studies used a multilayer network, that include a decomposition of the structure of a molecule using for example pharmacophore or scaffold [6].

In this work, we have developed a multilayer network that allows to identify substructure of a molecule that is relevant for a given bioactivity. To develop the network, we considered the ChEMBL database and more specifically the structure and bioactivities of the compounds (only compounds with a bioactivity < 1 □M) given a total of 202536 bioactives molecules for 503 708 compounds in our network. Each molecule was then represented with a pharmacophore (using pipeline pilot [7] and a scaffold (using Scaffold Hunter [8]). Then, a similarity of the molecules represented by a same scaffold or pharmacophore was computed using the Tversky index (based on the ECFP4 fingerprints). This protocol allows to identify the diversity of bioactive molecules associated to a scaffold and/or a pharmacophore and so to prioritize structure key elements of a molecule to a target. Some examples will be discussed in the poster.

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A_{2A} receptor antagonists for the treatment of neurodegenerative diseases: design, synthesis and biological evaluation

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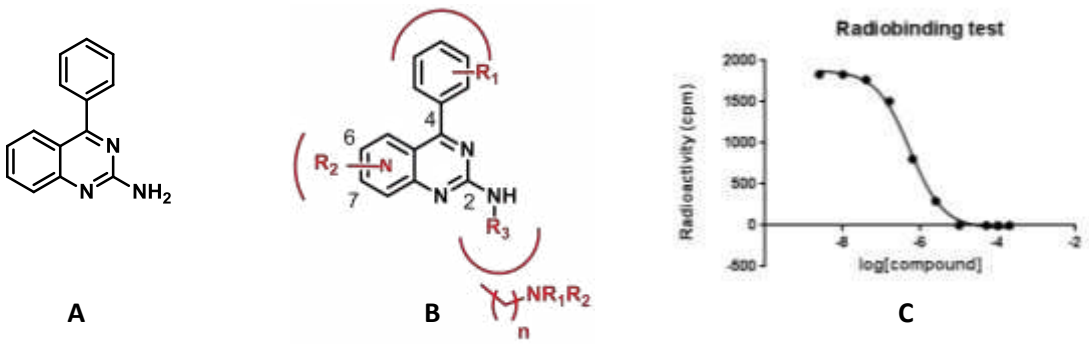
FP02

The past fifty years have been marked by the breakthrough of neurodegenerative diseases as Alzheimer and Parkinson. Unfortunately, current treatments are symptomatic. Hence, the search for new and innovative therapeutic targets becomes a major challenge. The adenosine A_{2A} receptor ($A_{2A}R$) has been the subject of much research in recent years. Indeed, it has been found that A_{2A} receptor antagonists, such as caffeine improves memory performance as it reduces β-amyloid deposits and Tau-phosphorylation. Though several $A_{2A}R$ antagonists have reached clinical trials[(a)], current research efforts are focusing on developing new antagonists with relevant ADME properties. Thus, based on the recently published crystalline structure of the $A_{2A}R$ complexed with the selective and high-affinity antagonist triazine[(b)], a virtual screening followed by a first optimization step allowed us to design a lead compound (**A**). This compound showed a high affinity towards $A_{2A}R$ (Ki($hA_{2A}R$) = 198 nM). Our aim is to improve its affinity and selectivity towards other adenosine receptors subtype, while keeping good ADME properties.



A **B** **C**

In this aim, we modulated the lead compound (**A**) in various position (**B**). Mainly, a series of 2-aminoquinazoline has been developed and exhibiting nanomolar affinities with potentially interesting pharmacokinetic properties including a high solubility. Affinities were measured using a radiobinding test (**C**). Recently, two compounds have been evaluated for blood-brain barrier crossing.

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Drugs and mucus: understanding the way of interaction	
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Mucus is a complex viscoelastic hydrogel that covers all mucosal surfaces of the human body. Its biological function is to act as a selective barrier for nutrients, as well to confer protection against pathogens and air pollutants [(a)]. Drugs administered by oral or airway routes have to overcome the interactional, the steric, and the dynamic barriers exposed by mucus in order to be effective (Figure 1). Alteration of mucus physico-chemical properties are associated with diseases, such as cystic fibrosis, where hyper-viscous mucus accumulates and obstructs airways and intestine. Moreover, the altered mucus prevents the absorption and activity of drugs [(b), (c)]. The design of effective CF drugs must take into account the diffusion across the pathologic mucus layer. Therefore, aiming to improve the design of new drugs as well the current CF therapies, in this work, we present a biosimilar mucus model that mimics both composition and rheological properties of pathological mucus. The biosimilar mucus could be employed as an economic and fast screening tool for assessments of effective drugs. The parallel artificial membrane permeability assay (PAMPA) in presence of the biosimilar mucus was employed to investigate the permeability of several drugs for interest in CF therapy.

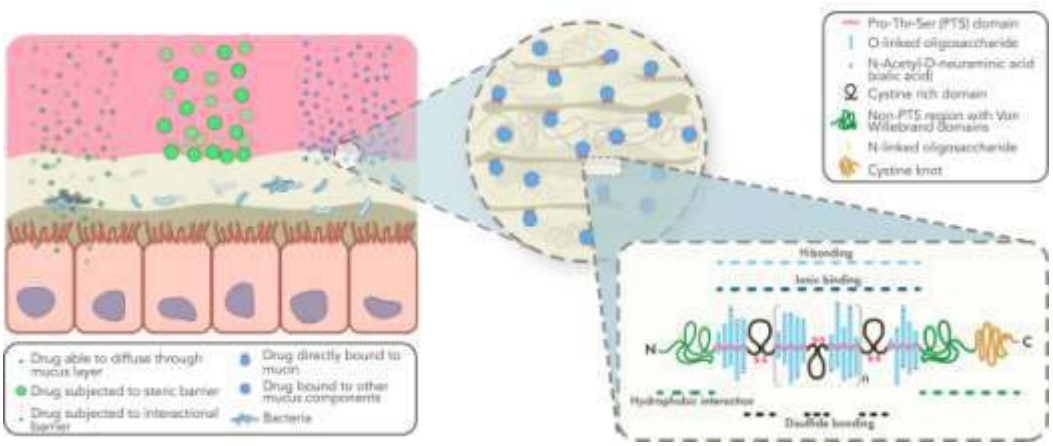

Figure 1: mucus barrier properties.

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Quinone-based derivatives : a new class of multi-target agents against Alzheimer's disease

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FP04

Alzeheimer's disease (AD) is a progressively invalidant pathology characterized by a neuronal and synaptic loss in the cholinergic system due to the accumulation of β-amyloid (Aβ) aggregates and hyperphosforilated tau proteins. This multifactorial syndrome derives from an intricate array of neurochemical factors, which continue to inspire the development of new anti-AD agents with diverse mechanisms of action. The present work has concerned the design and synthesis of new multi-target ligands addressed with structural requirements for tackling at different levels the intricate network of AD. Pursuing our studies on a previous series of quinone-containing derivatives[(a)], herein we have developed new naphtho- and anthraquinone derivatives connected through a polymethylene chain to an aromatic or heteroaromatic ring (Figure 1). These hydrophobic features have been explored with the aim of establishing suited hydrophobic interactions with a sequence of aromatic aminoacids of Aβ that is involved in the initial phases of aggregation process[(b)]. The novel derivatives have been tested for the direct inhibition of Aβ aggregation and for the inhibition of both cholinesterases. Most of the them have shared low micromolar IC_{50} values against Aβ and some of them also have proven to inhibit both cholinesterases, thus fulfilling the fundamental requisite for a multi-target mechanism of action. Four promising compounds have been undergone to the evaluation of inhibition of Aβ oligomeric species during aggregation and of their safety profile.

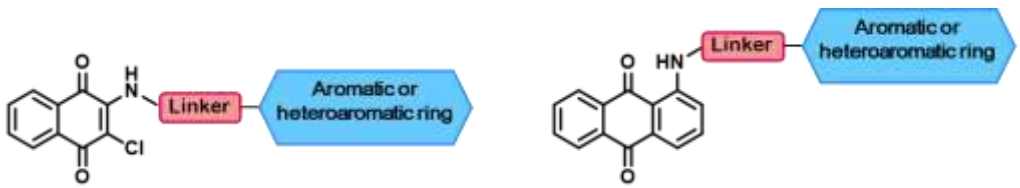

Figure 1: Scaffold of the investigated chemical classes.

Bibliographic references:

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Evaluation of the antimicrobial potential for some new compounds with xanthine scaffold	*FP05*

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Introduction. The diabetes mellitus is frequently associated with an increased risk for common infections development such as respiratory, dermal or genito-urinary ones. These infections can be also a trigger factor for different metabolic complications of this malady. **Aim.** The aim of this study was the *in vitro* evaluation of the antibacterial and antifungal activity of some new thiazolidine-4-one derivatives with xanthine scaffold. **Material and methods.** The antimicrobial potential was evaluated using two in vitro assays: disk diffusion method by measuring the inhibition area diameter of microbial growing and broth microdilution method by minimum inhibitory and bactericidal/fungicidal concentration determination. The tests were performed on different bacterial (*Staphylococcus aureus, Sarcina lutea, Escherichia coli*) and fungal (*Candida albicans, glabrata* and *parapsilosis*) strains, using as positive controls ciprofloxacin, ampicillin, nystatin and fluconazole. **Results.** The results revealed that 4-fluoro and 4-methyl derivatives presented a notable antibacterial activity, these compounds proving more bacteriostatic and less bactericidal action. In comparison with theophylline, the parent compound, the 4-fluoro compound showed to be 16 times more active on *Staphylococcus aureus*, while the methylate one 2 times and 4 times more active on *Escherichia coli* and *Candida albicans* respectively. **Conclusions.** In this research, 11 new thiazolidine-4-one with xanthine structure were evaluated for the antibacterial and antifungal activity, for some compounds the structural modulation of the theophylline scaffold being associated with an improvement of the antimicrobial effect.

Bibliographic references:

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Synthesis of peptidomimetic integrin ligands as delivery systems

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FP06

Nowadays, one of the most important challenges in the treatment of several diseases is the selectivity. In the case of tumours, their treatment involves the use of cytotoxic agents that interfere with events in cell proliferation or survival; these therapeutic agents can be toxic for unhealthy cells or healthy cells indiscriminately.

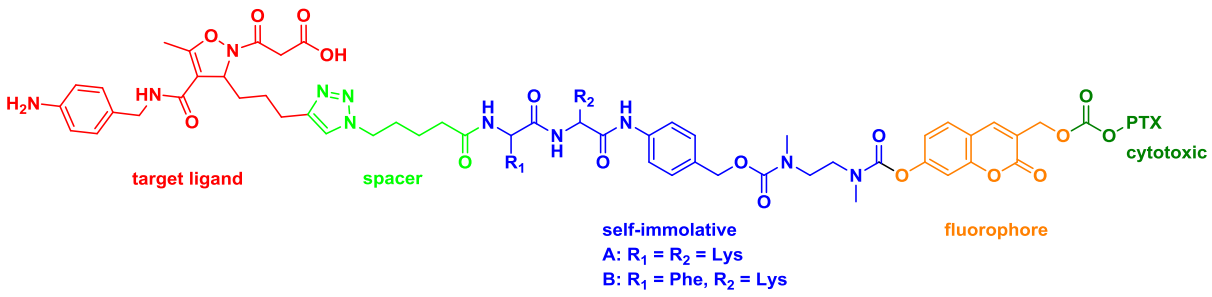
Targeting the cytotoxic agent to cancer cells as selectively as possible is needed in order to minimize the side effects. For this reason, *Drug Delivery Systems* (*DDSs*) have been developed[a].

These systems are able to inactivate the drug in the blood flow, sending it to cancer tissue where it is released in the active form by the cleavege of a proper spacer able to separate the drug from the ligand. In fact, selective targeting is obtained by means of the specifically ligands planned to interacting with a receptor or a bio-maker overexpressed on the surface of cancer cells.

In particular, receptors $\alpha_v\beta_3$ are largely used as target for DDSs because they are overexpressed in a large number of cancer cell subtypes. These receptors recognize RGD (Arg-Gly-Asp) sequence in endogenous molecules of the extracellular matrix by the guanidinic function of Arg and carboxylic function of Asp.

In order to reproduce a DDSs, we developed the syntesis of RGD peptidomimetic that can be selectively recognized by integrins receptors $\alpha_v\beta_3$ by means of isoxazolinic system conveniently functionalized with basic and acid side chains able to mimic the pharmacophore groups of endogenous ligand[b] and a functionalizable chain in position 3 carrying the spacer and the drug.

The system has been planned as theranostic agent for in vitro analysis.



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Elaboration and study of glycosylated fluorescent organic nanoparticles toward bright labelling of bacteria

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FP07

Fast and selective detection of pathogens represents high challenges given the considerably high proliferation rate of bacteria and their mutation potential against antibiotics. Moreover, to be fully efficient, detection needs to be selective for bacteria. In this study, we are interesting in pathogenic *Escherichia coli*, responsible for gastrointestinal and urinary tract infections. These bacteria express *fimbriae* that display strong binding to mannose. Recently, we have developed fluorescent organic nanospheres (FONs) functionalized with phosphonic acid units[(a)] that interact within 5 minutes with *Staphylococcus aureus*[(b)]. Our aim here is to extend this strategy to glycosylated FONs to label *E. coli* membrane.

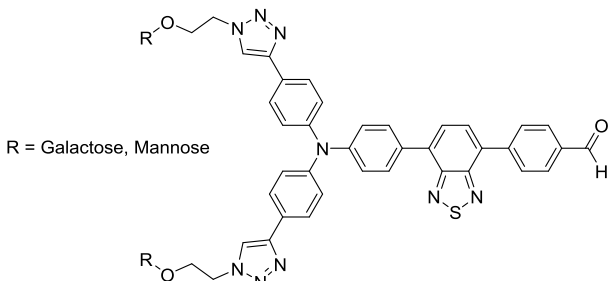

Figure 4 : Structure of the glycosylated fluorophores.

For this purpose, we have fabricated two kinds of glycosylated fluorophores which incorporate a benzothiadiazole unit, known for its high photostability and red fluorescence efficiency (Figure 1). A modular approach based on rapid and versatile Click-Chemistry allowed us to graft glycosylated moieties (galactose and mannose).

These fluorophores were self-assembled as FONs upon nanoprecipitation. Compared to free dyes in solution, they provide higher brightness and near-infrared emission (λ_{max} = 640-680 nm), which limits the autofluorescence signal in living organisms. Moreover, these ultrabright dots are nontoxic and show high potential recognition due to a high payload of glycosylic groups.

Concanavalin A, a lectin specific to mannose[(c)], was used as a nonpathogenic model to apprehend interactions between FONs and *fimbriae* of *E. coli*. Preliminary results involving fluorescent *ConA* show significant fluorescence resonance energy transfer (FRET) from mannose-FONs to the lectin, proving close vicinity of both partners and thus complexation of mannose-FONs by *ConA*. Comparative studies on galactose-FONs show no such FRET, evidencing high selectivity of the recognition process. This feature offers promising perspectives to use mannose-FONs as diagnostic agents to label *E. coli* cells in a rapid and specific way.

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Synthesis, Structures and Cytotoxicity Studies of Novel NHC*-Gold(I) Dithiocarbamate Complexes	
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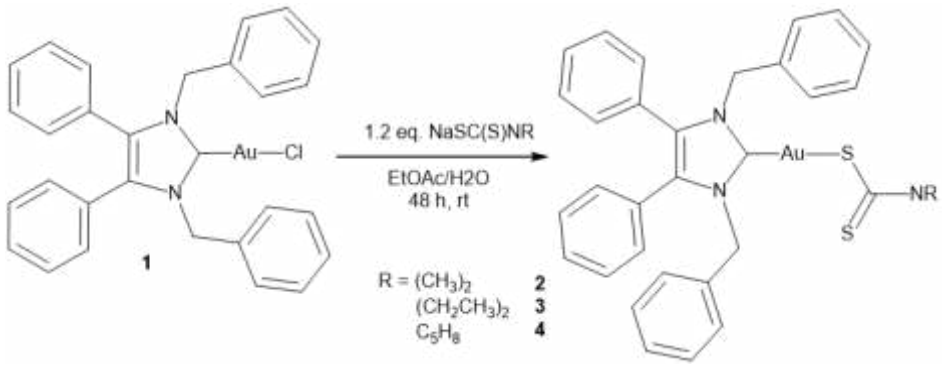
Metal-based drugs are an important tool in the development of new therapeutic drugs. Auranofin, the successful gold(I)-based drug, exhibits both high potency antiarthritic and antitumour properties. Auranofin analogues have been investigated for their interesting coordination to both a phosphine and a thioglucoside. In many cases, *N*-heterocyclic carbenes (NHCs) have been utilized as alternatives to the phosphine ligand. Recent work in the Tacke group has employed these NHCs as ancillary ligands to develop novel gold(I) complexes similar to those of Auranofin.[a] The unique mechanism of action of gold(I) and its high affinity for thiols results in promising anticancer drugs.

Herein we present novel NHC-gold(I) dithiocarbamate complexes (**2-4**), based on our NHC* system, (1,3-dibenzyl-4,5-diphenylimidazol-2-ylidene)gold(I) chloride (**1**), with full characterisation and biological testing.[b] The cytotoxicity was evaluated against the multidrug-resistant MCF-7^{topo} breast cancer, HCT-116^{wt} and its p53 knockout mutant HCT-116$^{-/-}$ colon carcinoma cell lines. Across all three cell lines tested single-digit micromolar IC50 values were observed.[b]



Scheme 1. General reaction scheme for the synthesis of NHC*-Au(I)-dithiocarbamates **2**-**4**.

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[a] O. Dada, G. Sánchez-Sanz, M. Tacke, X. Zhu, *Tetrahedron Lett.* **2018**, *59*, 2904.

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Antitumour activity and structure-activity relationship of styryl lactones related to goniofufurone	***FP09***

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(+)-Goniofufurone (**1**) and 7-*epi*-(+)-goniofufurone (**2**) are natural styryl lactones, while (-)-goniofufurone (***ent*-1**) and 7-*epi*-(-)-goniofufurone (***ent-2***) are their opposite enantiomers, which are obtained by synthesis. Herein, we want to present results of antitumour activity and structure-activity relationship (SAR) of **1**, ***ent*-1**, **2**, ***ent*-2** and analogues (**3**-**7**, ***ent*-3** – ***ent*-7**) that are synthesized in our laboratory. It is noticeable that (-)-goniofufurone mimics are more active comparing to (+)-goniofufurone analogues.

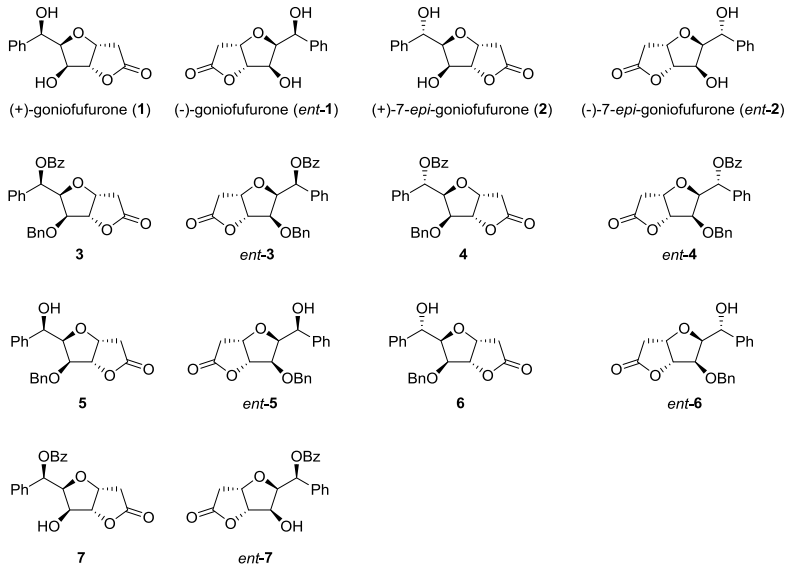

Figure 1. Structures of (+)-goniofufurone (**1**), 7-*epi*-(+)-goniofufurone (**2**) and analogues (**3**-**7**, ***ent*-1** - ***ent*-7**).

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

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Towards 5-HT$_6$ receptor modulators in the treatment of neurodegenerative diseases: let's do it with flow!

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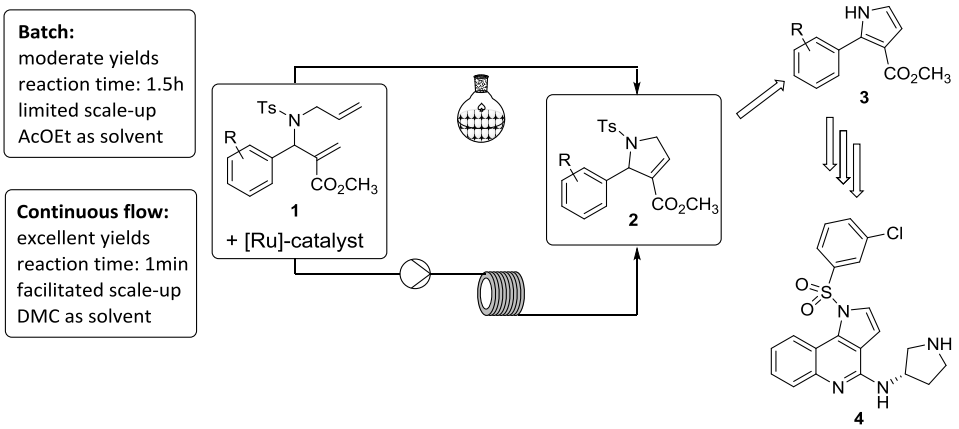
FP10

A large body of evidences support the role of 5-HT$_6$ receptor (5-HT$_6$R) in the treatment of cognitive decline associated with neurodegenerative diseases, as well as cognitive disorders caused by genetic abnormalities.[1,2] These issues, depending on the association of 5-HT$_6$R with interacting proteins and its high level of constitutive activity, underscore the need of developing ligands with neutral antagonist *vs*. inverse agonist properties in order to compare their action in different *in vitro* and *in vivo* settings.[3]

We recently demonstrated the synthesis of high value pyrroles (**3**) and pyrroloquinolines via generation of 2,5-dihydro-1H-pyrrole-3-carboxylates (**2**), in ring-closing metathesis (RCM), as structural frameworks for providing of potent 5-HT$_6$R neutral antagonist (**4, CPPQ**).



In the study, we present a highly efficient continuous flow RCM using dimethyl carbonate as green solvent. We demonstrated that reaction could be completed within 1 min at 120°C and scaled-up from 1 to 23mmol, without changing the outcomes, yielded the cyclized compound in 91% yield.[4]

The study was partially supported by the University of Montpellier, CNRS, National Science Centre, Poland (grant no. 2016/21/B/NZ7/01742), Institut Carnot Chimie Balard (ANR programme no. 11 CARN 0001-01), PHC Polonium program and BGF program.

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Chemical probes of ribosomes biogenesis and their application as potential anti-cancer therapeutics	***FP11***

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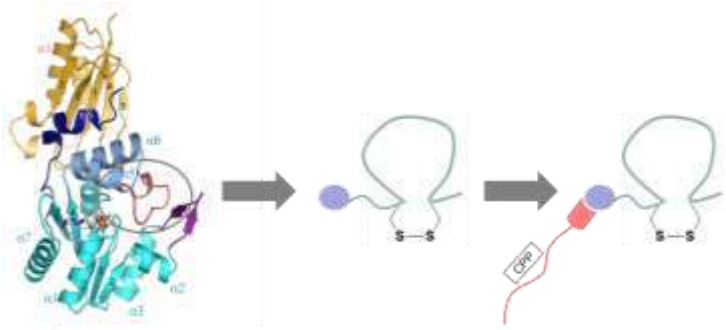
The ribosome is the cell's huge ribonucleic machinery in charge of synthesizing proteins from mRNA. The ribosome biogenesis pathway is closely tied to regulation of p53 by HDM2. The tumour suppressor p53 is activated as a result of stress cell to regulate transcription of many proapoptotic genes. In the 50% of cancers, p53 function is inhibited by deregulation of the HDM2, oncoproteins responsible for the degradation of p53. Therefore, the design of small molecules to block HDM2-p53 interaction to activate p53 in tumour cells is an area of intense research.
Several studies have shown that inhibition at different levels of ribosome biogenesis leads to the stabilization and accumulation of p53 through a mechanism involving the inhibition of the ubiquitin ligase activity of HDM2 by ribosomal proteins[a]. Therefore, targeting the ribosome biogenesis/p53 regulation pathway is an attractive and complementary alternative to targeting the p53/HDM2 interaction for anticancer therapies.



The different steps of ribosomes biogenesis require the coordinated action of over 200 non ribosomal proteins, named Assembly Factor (AF)[b]. It has been reported that hCINAP, an AF, inhibits p53 activity through the regulation of ribosomal protein S14 (Rps14)[c]. Based on the resolved complex structure of their yeast homologs (Fap7/Rps14)[d], we are currently investigating the C-terminus domain of Rps14, by designing small cyclic peptides as potential antitumor therapeutics. Combining peptide design and cell penetrating peptide (CPP) strategy[e], these mimicking peptides exhibited preliminary results on HCT-116 cancer cells, a suitable cell model for ribosome biogenesis.

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Design, synthesis and biological evaluation of tetrasubstituted pyrazoles as inhibitors of HIV-1 replication

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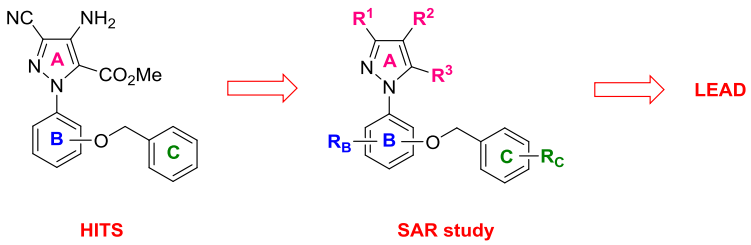
FP12

AIDS caused by HIV is a major pandemic that is still active with 2 millions persons being newly infected each year. Antiretroviral combination therapy allows to reduce HIV replication and therefore significantly improves the life expectancy and quality of HIV-infected patients. However, the rapid development of resistant strains and the need to maintain life-long treatment urges the need for new molecules.

In this context, the screening of our laboratory chemolibrary of 112 heteroaromatic compounds[(a)] allowed the identification of two pyrazole-based hits able to inhibit HIV-1 replication *in cellulo*. Within the frame of our hit-to-lead optimization program, we designed and synthesized analogues that were modified on the three main cycles A, B and C in order to get a complete SAR study.



In this communication we will describe the chemical synthesis of new analogues, as well as their inhibition activity and toxicity. The main lines of the resulting SAR regarding the different positions on the scaffold will also be discussed. We will finally disclose the structure of a promising new lead.

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* Correspondence: jeanne.fichez@parisdescartes.fr, patricia.busca@parisdescartes.fr

Synthesis and biological evaluation of a new series of 1-2-dihydropyridine carboxamide derivatives as CB2 receptor allosteric modulators.	***FP13***

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The endocannabinoid system (ECS) is a complex lipid signaling system comprising at least two cannabinoid receptors (CBRs), (CB1Rs and CB2Rs), lipid mediators known as endocannabinoids (ECs), and their synthesizing and degrading enzymes and transport systems. The ECS was found to be implicated in several pathologies such as obesity, cancer, mental illnesses, pain, drug addiction and neurodegenerative diseases. Therefore, since the discovery of CBRs, drugs directly targeting CBRs have been frequently studied. However, this approach led to the development of some compounds producing serious adverse effects, such as anxiety, depression, suicidal ideation, psychotropic effects or immune dysfunction, that have limited their clinical development. One possible new strategy for avoiding problems arising from the use of traditional orthosteric drugs, would be to develop CBR allosteric modulators as new medicines. Allosteric ligands, modulate the affinity and/or efficacy of specific orthosteric ligands by binding to topographically distinct allosteric sites. Recently, our research group reported compound **C2** as the first synthetic CB2R allosteric modulator[(a)]. In order to better understand the structural requirements for the binding of a ligand to the CB2R allosteric site, we synthesized new derivatives of general structure **A**, **B**, **C** and **D** (Figure 1).

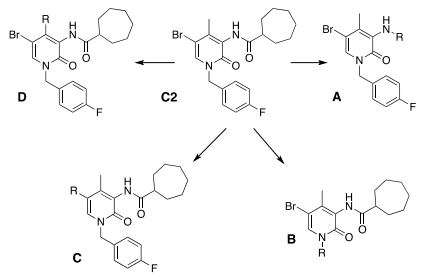

Figure 1 : Chemical structure of compound **C2** and **A**, **B**, **C** and **D** analogues.

The new compounds have been tested for their CB2R functional activity. The results reported in this work might be useful for computational studies regarding the pharmacology and crystal structure of the CB2R's allosteric site.

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[(a)] Gado F *et al. J. Med. Chem.* (2018). doi: 10.1021/acs.jmedchem.8b00368

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Sulfonamides as new Tubulin Binding Drugs: a privileged scaffold	FP14

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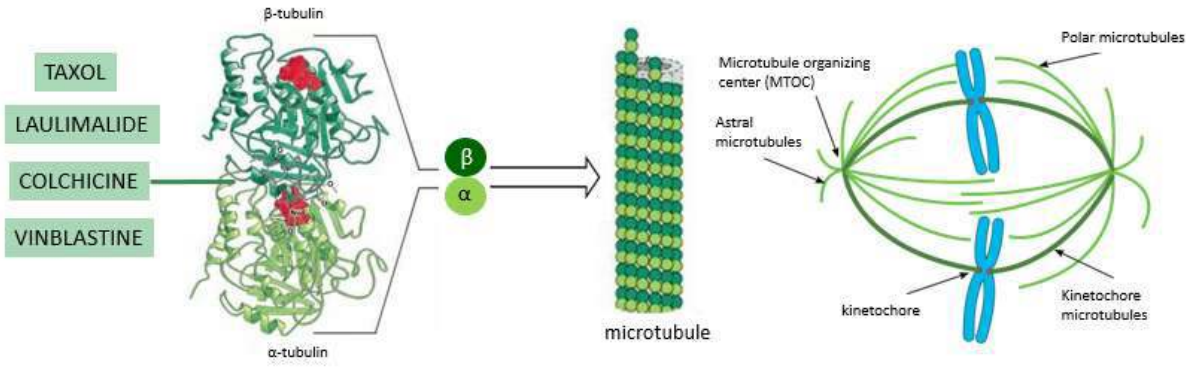
The sulfonamide moiety is considered a privileged scaffold in medicinal chemistry due to a combination of favorable and highly tunable physical–chemical and biological properties. It is common to find it as a part of a large number of biological activities and drugs.

Following the initial discovery of prontosil and the antibacterial sulfa drugs, new activities were described for the sulfonamide scaffold, such as, hypoglycemic effects, diuretics, antihypertensives, antiinflammatory, anticonvulsant, antithyroid, herbicidal, antiviral and anticancer.

The favorable properties that make sulfonamides a frequent pick in the design of drug–like molecules include a suitable combination of accessibility, stability, hydrogen bonding capability, polarity, hydrophobic-hydrophilic balance and conformational preferences, among others.

With the aim to improve one of the main drawbacks of Tubulin Binding Drugs (TBDs), its pharmacokinetics properties, we have designed, synthetized and evaluated new TBDs with a sulfonamide moiety in its structure. Based on the potent, natural, antimitotic agent the Combretastatin-A4. The bridge between the two aromatic rings has been substituted by a sulfonamide bridge, contributing several benefits to the molecule and maintaining the antimitotic effect.
The hydrosolubility values of the new compounds, stability studies and pKa prediction, together with the tubulin polymerization inhibitory activity *in vitro* and the citotoxicity will be presented.



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Developing probabilistic restraint optimization protocols for comparative modelling in MODELLER	***FP15***
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We have developed a framework for comparative modelling on top of MODELLER [1], which extends exploration of spatial restraints and the conformational space. Restraints are optimized by diverse protocols in a model-creation-restraint-evaluation feedback loop (Figure 1) using probabilistic graphs, heuristic optimization algorithms and quantitative quality gauges. The framework is written in Python, and restraints operationalized with a relational PostgreSQL database. The performance of the method is evaluated for its ability to reconstruct GPCR structures.

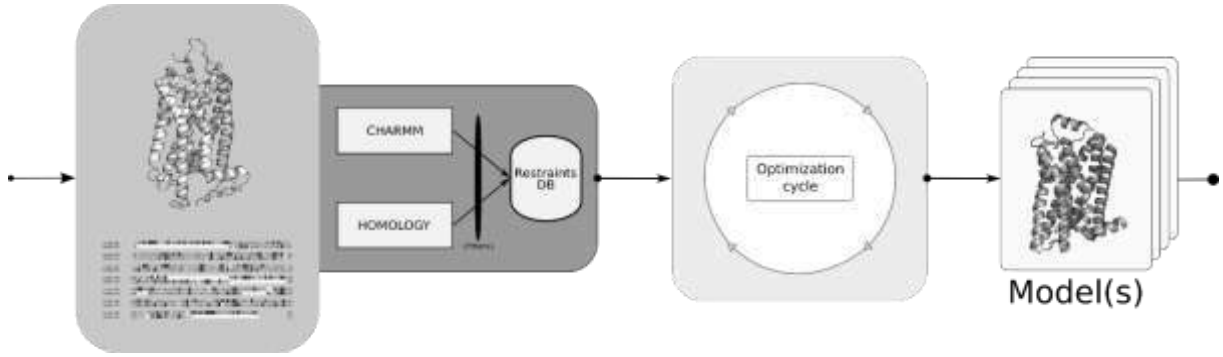

Figure 1 Initialization and the modeling cycle. Input consists of a template and the sequence alignment to the target. Restraints are created by MODELLER and stratified into CHARMM and homology types. In addition to these restraints, we create custom restraints, which are then subjected to the optimization protocols.

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Design Of Antiviral Compounds Against Bunyavirales Supported By Ligand-Nuclease Interactions Studies.

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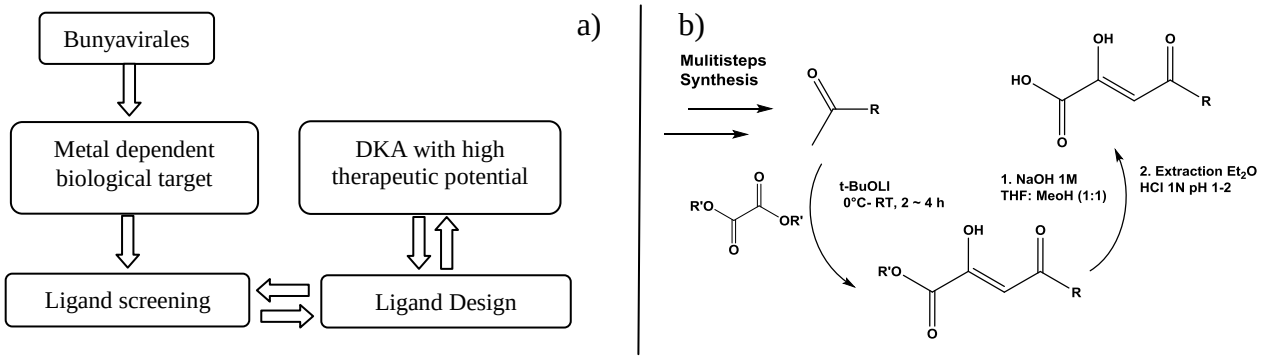
FP16

Bunyavirales, is an order of viruses that are enveloped and have a negative stranded RNA genome divided into two or three segments. In 2017, the world health organization (WHO) classified some of the bunyavirales genus as highly pathogenic viruses for human and declared that "medicine does not currently have any means of action" [(a)].

In this context, structural studies of the viral proteins demonstrated that the viral genome encodes an endonuclease. The latter is located in the N terminal domain of the multifunctional viral (L) protein and it was highly conserved among the other families under this order. Moreover, it has an important role at the earlier stages of the viral trascription mechanism[(b)(c)]. In the other hand, Biophysical and biochemical assays proved that the activity of the endonuclease was Mn+2 and/or Mg+2 dependent. Rational design of Diketo acid (DKA) ligand Derivatives, based on studies performed *in vitro*[(d)], in minigenome and in infected cells, demonstrates a high therapeutic potential[(e)] and a promising strategy to fight against the bunyavirales Schema.1(b).



Schema.1 a) The design strategy of the bunyavirales antivirals, b) synthesis of DKA ligand derivatives.

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Novel Tacrine Inhibitors of Acetylcholinesterase with Potential Implication against Organophosphorous Poisoning	
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Organophosphorus nerve agents (OPNAs) still represent potential threats in military, terrorism situations and civilian sphere. OPNAs act as potent irreversible inhibitors of central and peripheral cholinesterases. Up-to-date, the prophylaxis against OPNAs poisoning relies on administration of the reversible acetylcholinesterase (AChE) inhibitor pyridostigmine. The major drawback of this compound is no penetration into the brain. With this regard, some other non-charged reversible AChE inhibitors such as huperzine or physostigmine proved their efficacy as prophylactic agents against OPNAs. Moreover, these compounds are also able to cross the blood-brain barrier (BBB). Encouraged by these results, we have prepared novel, potent AChE reversible inhibitors based on tacrine scaffold as potential prophylactic agents against incapacitating effects of OPNAs. Additionally, most of them also displayed inhibition of plasmatic butyrylcholinesterase (BChE), thus preserving its capacity to act scavenger of OPNAs. Within our contribution, we will report the synthesis and biological data for AChE/BChE inhibition, prediction of the binding modes using in silico methods and the ability to cross the BBB for novel tacrine hybrids as potential prophylactic agents against OPNAs.

Supported by the Long-term development plan (Faculty of Military Health Sciences, University of Defence, Czech Republic), by MH CZ - DRO (University Hospital Hradec Kralove, No.00179906) and by Technology Agency of the Czech Republic project no. TG02010020.

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Isosteric replacement of sulphur with oxygen in the thioxotriazinoindole-based aldose reductase inhibitors markedly improved inhibition selectivity

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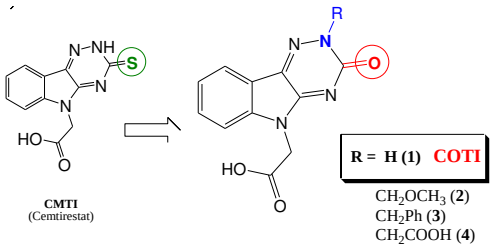
FP18

Inhibition of aldose reductase (ALR2), the first enzyme of the polyol pathway, is a promising approach in the treatment of diabetic complications. In our previous study [(a)], carboxymethylated thioxotriazinoindoles were identified as ALR2 inhibitors with high efficacy and selectivity. We proceeded with optimization of the thioxotriazinoindole scaffold by replacement of sulphur with oxygen, with the aim to improve the inhibitory efficacy and selectivity. The aim of this study was to synthesize a series of 2-(3-oxotriazinoindol-5-yl)acetic acid derivatives (COTIs), determine ALR2 inhibitory effects of and examine SAR. ALR2 inhibitory activities of the compounds were characterized by the IC_{50} values in the submicromolar range. Molecular docking simulations and optimization were used to identify key interactions of the compounds located in the inhibitor binding site of the enzyme. In COTIs derivatives, less bulky oxygen compared to the sulfur of the original thioxotriazinoindoles rendered larger rotational flexibility of the carboxymethyl group which enabled better fitting of the molecular structure into the active site of ALR2. On the other hand, poor interaction with the active site of the structurally related ALR1 resulted in significantly enhanced selectivity of COTIs. Cation-π interaction of protonated Arg312 in ALR1 with aromatic ring of COTIs supported by two H-bonds keeps COTI off $NADP^+$. To conclude, structure modification of the original carboxymethylated thioxotriazinoindoles by isosteric replacement of sulphur with oxygen provided novel derivatives with markedly increased ALR2 inhibition efficacy and selectivity.



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Design and Synthesis of Allosteric Inhibitors of Cell Cycle Proteins as Potential Cancer Therapeutics

Lin, S.,[1] Berdini, V.,[2] Endicott, J. A.,[1] Golding, B. T.,[1] Hardcastle, I. R.,[1] Harnor, S. J.,[1] Martin, M. P.,[1] Noble, M. E. M.,[1] Waring, M.,[1] Wedge, S. R.,[1] Wood, D.[1] and Cano, C.[1]

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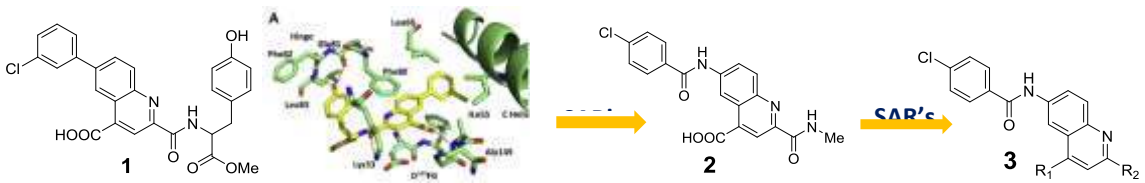
FP19

Cyclin-dependent kinases (CDKs) are key regulators of cell cycle progression and transcription, with functionality that is strictly dependent on association with their partner proteins, the cyclins.[1] Cyclin E1 and low molecular weight isoforms thereof are overexpressed in many breast cancers, and their interaction with CDK2 has been linked to unfavourable patient prognosis. Recent studies have also documented high cyclin E1 protein expression in ovarian cancer, osteosarcoma, non-small cell lung cancer (NSCLC), bladder, oesophageal, colorectal, and gastric cancer. In high-grade serous ovarian cancer (HGSC) cyclin E1 (CCNE1) amplification occurs in approximately 20% of patients.[2] This is clinically associated with poor overall survival and primary treatment failure. CDK inhibitors currently in clinical trials exclusively target the ATP site and suffer from issues of selectivity and associated off-target toxicity. They also inhibit catalytic, but not scaffolding functions of CDK/cyclin complexes. There is, therefore, a significant need to identify novel ways to interfere with CDK/cyclin function. Recent research has revealed a hydrophobic pocket in CDK2 that is independent of the ATP site. Compounds that bind to this allosteric site cause structural rearrangements that render the enzyme unable to interact with cyclin E1.[4] The CDK2 allosteric site offers an alternative route to CDK2 inhibition that has the potential to lead to a new class of anticancer drug, potentially avoiding the off-target effects seen with the current CDK inhibitors. Research conducted at Merck identified that quinoline-based compound **1** could disrupt the CDK2-cyclin A interaction and act as an ATP competitive inhibitor. As revealed in the crystal structure, **1** binds to the hinge region of CDK2 inducing several conformational changes to the CDK2 protein (in particular the C-helix) that would prevent binding of cyclin A.[5] Structure Activity Relationship (SAR) studies around this compound were carried out by introducing an amide linker between the chlorophenyl and quinoline rings, and modifying the quinoline scaffold to investigate whether compound **3** could occupy solely the allosteric pocket without binding to the ATP site and engaging with the hinge. The syntheses of proposed targets as well as co-crystal structures will be disclosed.



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Synthesis of new piperazine-based siderophores : a promising therapeutic strategy to fight antimicrobial resistance

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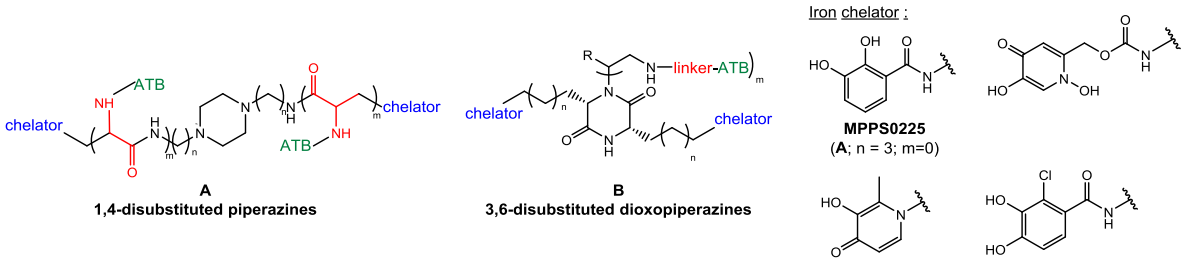
FP20

Resistance to antibiotics is an increasing phenomenon and a major medical problem. Resistance to conventional antibiotics of Gram-negative bacteria such as *Pseudomonas aeruginosa* and the *Burkholderia* group leads to therapeutic failure and requires new antibiotic therapies. Using iron transport systems is a promising strategy to overcome these issues. The TonB-dependent receptors, essential for the survival of microorganisms, allow specific recognition of ferric siderophore complexes in order to transport iron within bacteria.[a] According to their kind, bacteria express different types of receptors that recognize their endogenous siderophores but also xenosiderophores. In particular, *Pseudomonas aeruginosa* and *Burkholderia pseudomallei* possess FptA receptors allowing the recognition of pyochelin.[b] These specific systems may allow the introduction of antibacterial agents, by forming antibiotic-siderophore conjugates or toxic complexes such as gallium complexes.[c]

Siderophores have three types of chelating function: catecholates, hydroxamates and α-hydroxy-carboxylates. Previous work in the laboratory has shown that piperazine 1,4-dicatechol structures (MPPS0225) are recognized by *P. aeruginosa* strains. To further investigate this piperazine platform, we have synthesized iron chelators bearing 3-hydroxypyridin-4-one and 1,3-dihydroxypyridin-4-one ligands. At the same time, we were interested in the rhodotorulic acid (RA), a natural siderophore produced by *Rhodotorula pilimanae* showing an interesting iron affinity (p*Fe* = 21,8). Two RA synthesis strategies will be developed that also provide access to the corresponding 3,6-disubstituted analogs. Through the synthesis of these chelators, we want to study the influence on the iron complexation of: i) the nitrogenous platform (piperazine or dioxopiperazine), ii) the presence of stereogenic centers (3,6-disubstituted dioxopiperazines *vs* 1,4 -disubstituted piperazines) and iii) the nature of the iron ligands (hydroxypyridinone *vs* catechol). An evaluation of the siderophore-like potential and a measurement of the complexing force will be carried out.



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Synthesis and Evaluation of Antiplasmodium Assay of 4-Aminoquinoline-Isoindolinone Hybrids

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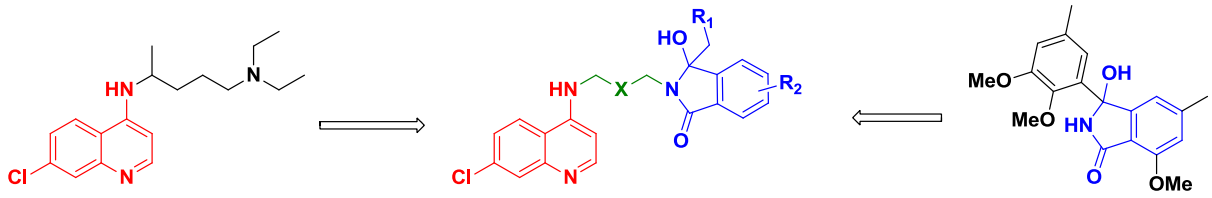
FP21

Malaria is one of the global leading causes of death particularly in young children and pregnant women in many developing countries. The control of malaria is mainly constrained on the rapid spread of parasitic resistance (*Plasmodium falciparum*) to standard antimalaria drugs such as chloroquine and artemisinine. One of strategies to address this problem is developing new antimalaria candidate by linking two pharmacophore units with the main aim to improve the therapeutic properties.[1] In this context, the pharmacophore hybridization was conducted by combining 4-aminoquinoline unit and isoindolinone scaffold. While the former is widely known as the core structure of antimalaria of chloroquine, the latter can be found in numbers of natural products which display good biological activities, such as Entonalactam C as antiplasmodium.[2] In this study, several 4-aminoquinoline-isoindolinone hybrids have been synthesized *via* three step synthesis in good yields.[3–5] The hybrids were then subjected to *in vitro* antiplasmodial assay.



Chloroquine **4-Aminoquinoline-isoindolinone hybrids** **Entonalactam C**

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Development Of Fluorescent Probes As Diagnostic Tools To Track Bcl-2 Dependency In Breast Cancer	*FP22*

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Breast cancer remains the leading cause of death by cancer among women. Actually, triple negative breast cancers (TNBCs) and Luminal B (LumB) cancers remain difficult to treat with standard chemotherapy which is used almost systematically. Although initial results may be promising, progression and dissemination are not prevented in the long term.

Philippe Juin's team in Nantes currently studies the Bcl-2 family of proteins which act at the core of the therapeutic response of cancer cells and significantly contribute to their adaptation to stress.[a] Anti-apoptotic members of this family, which include Bcl-2, Bcl-xL and Mcl-1, exert a survival activity that relies on their ability to bind and antagonize pro-apoptotic members by engaging a network of intracellular interactions. The binding interfaces have been targeted through the use of small-molecules BH3 mimetics (ABT-737/navitoclax dual Bcl-2/Bcl-xL, ABT-199/venetoclax selective Bcl-2). Their studies with breast tumors slices ex vivo suggests that Bcl-2 inhibitors would be useful for the treatment of breast cancers that are refractory to the acute effects of chemotherapy. It is therefore necessary to develop tools that could track Bcl-2 dependency in breast cancer. Sylvain Routier's team in Orleans has synthesized several fluorescent probes based on ABT-199 and linked to two fluorophores (*Figure 1*). The CRCINA has validated their efficacy to modulate the interaction between Bcl-2 and its intracellular partners. Work is in progress to develop new probes based on small molecule BH3 mimetics.

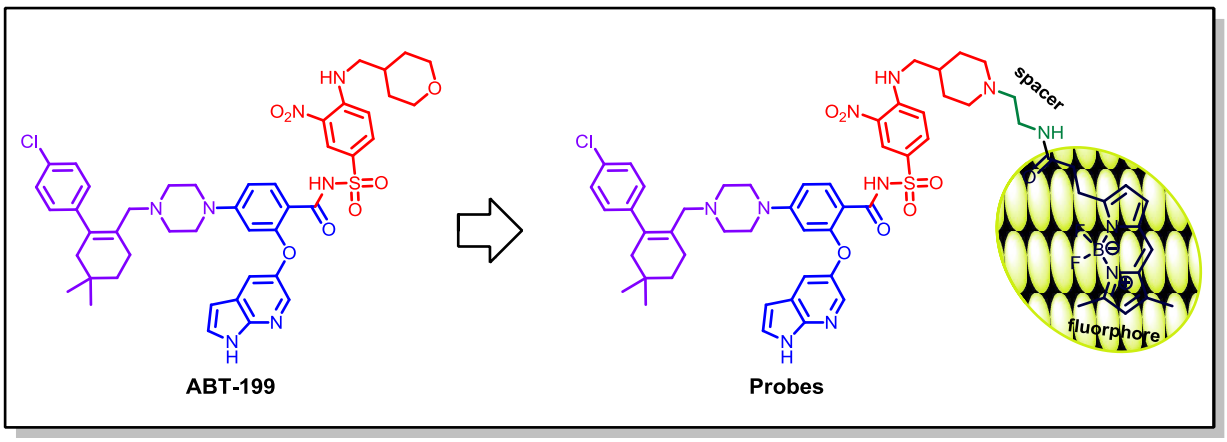

Figure 1 : fluorescent probe based on ABT-199

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Dual agents against HIV and HCMV

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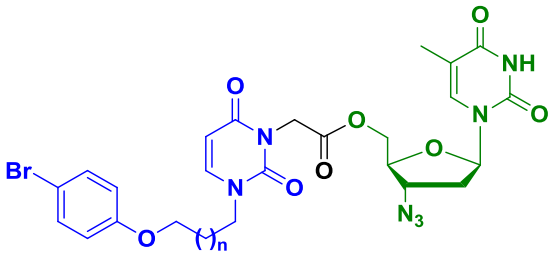
FP23

Introduction

Human cytomegalovirus (HCMV, or human herpesvirus-5) belongs to the viral family known as *Herpesviridae*. Despite modern prevention and treatment strategies, it remains a common opportunistic pathogen associated with serious morbidity and mortality in immunocompromised individuals such as transplant recipients and AIDS patients. Also convincing evidence has been obtained that the presence of such viruses as HSV-2 and HCMV in the donor facilitates the transmission of HIV, regardless of the level of immunosuppression. In general, opportunistic infections play an important role not only at the time of HIV transmission, but also during the development of the disease.



n= 1-10

Anti-HCMV EC_{50} 3-12μM

Anti-HIV EC_{50} 0.2-0.83 μM

Materials and methods

Compounds were synthesized starting from corresponding 1-[ω-(4-bromophenoxy)alkyl]uracil derivatives and 2',3'-dideoxy-3'-azidothymidine (AZT). Stability of compounds was studied in the presence of different esterases.

Results

Here we present new conjugates of non-nucleoside HCMV replication inhibitors and AZT, a classical nucleoside inhibitor of DNA biosynthesis, catalyzed by HIV reverse transcriptase.

Conclusions

The proposed conjugates are depot forms and are able to be hydrolyzed by the action of cellular enzymes, releasing components that have high antiviral activity. The creation of these molecules improved both the solubility of non-nucleoside inhibitors and the pharmacokinetic parameters of the modified nucleoside.

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Targeting orexin receptor type 2 in the treatment of narcolepsy

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FP24

Narcolepsy is a chronic neurologic disorder characterized by excessive daytime sleepiness and other symptoms such as cataplexy, vivid hallucinations and paralysis.[(a)] Narcolepsy is considered as the rare disease affecting approximately 1 in 3000 people.[(b)] It is believed that narcolepsy is based on autoimmune response mediated by loss of a specific hypothalamic neuropeptide, orexin (also called hypocretin).[(c,d)] Two orexins have been described – orexin A and orexin B. Accordingly, there are two specific receptors for the orexin peptides, orexin receptor tape 1 (OX1R) and orexin receptor type 2 (OX2R). However, patients with narcolepsy are currently treated only symptomatically. Compounds such as modafinil (non-amphetamine wake promoting compound for excessive daytime sleepiness) and sodium oxybate (short-acting sedative for fragmented nighttime sleep and cataplexy) are preferentially used.[(a)] An alternative to the symptomatic treatment of narcolepsy with cataplexy would be a direct orexigenic system-targeted therapy in the form of non-peptide small-molecule orexin agonists able to cross the blood brain barrier.

The aim of this work was to design, synthetize and biologically evaluate a novel class of the orexin receptor 2 type agonists. From the group of proposed novel structures, we selected those that fulfill several criteria including CNS multiparameter optimization desirability with predicted proper interaction with OX2R as shown by *in silico* methods.[(e,f)] Solubility profile was also one considered as one of the key parameters with logS values higher than -4. Within our contribution, all the achieved results in syntheses and biological evaluations of prepared derivatives will be presented.

Supported by grant GA CR No. 17-08596S given by Grant Agency CR.

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Preclinical studies of new diselenide compounds as promising leishmanicidal agents

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FP25

Leishmaniasis encompasses a number of poverty-associated diseases caused by different species of flagellate protozoa parasites of the genus Leishmania[1]. The disease affects both animals as well as humans, provoking a series of clinical manifestations. Even though exact statistical data are lacking within the 350 million people that live in areas where leishmaniasis is endemic approximately 12 million people are infected. The current chemotherapy is far from being satisfactory and present several problems including toxicity, many adverse side effects, high costs and resistances. That's why drug development against parasitic diseases is needed[2].

A series of novel diselenide compounds bearing interesting bioactive scaffolds showed promising activity values against L. infantum amastigotes with high values of selectivity. On the basis of these results, these work evaluates the appropriate dose and route of administration of the lead two compounds for the in vivo toxicity and efficacy assays in female BALB/c mice. Both compounds, 2h and 2m, showed low toxicity values against THP-1, Vero and Caco-2 cell lines. Intestinal permeability assays were carried out by Ussing Chamber method and results measured by selenium atomic absorbance. Unfortunately, compounds were not suitable for oral administration, since they exhibited poor values of intestinal permeability. Therefore, intraperitoneal route has been explored. Acute toxicity and repeat dose toxicity assays lead us the dose to perform efficacy assays in *L. infantum* infected mice. After treated, leishmanisis-infected mice's parasitemia decreased considerably in liver, spleen and bone marrow.

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Continuous-flow Enabled Efficient Chemical Reactivities and Entities

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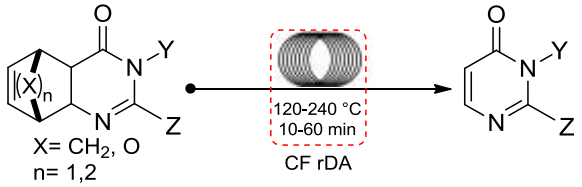
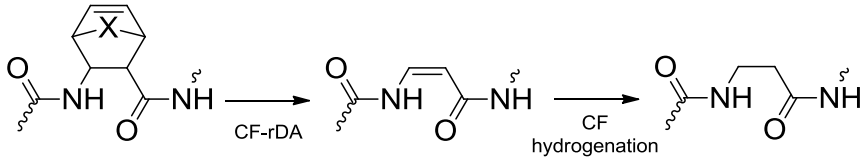
FP26

Continuous-flow (CF) technology has gained significant importance in modern synthetic chemistry. This technology allows a quick optimization, acceleration,[(a)] and easy scale-up with an inherently safe and green nature.[(b)] The accurate tuning of residence time can further broaden the versatility of CF processes.[(c)] Thus, flow chemistry has long been selected to provide a simple means to use more rigorous reaction conditions such as the retro-Diels-Alder (rDA) reaction. Our aim was to exploit the flexibility of flow-based reactors for the synthesis of functionalized pyrimidinone as potentially bioactive products through the precisely controlled CF-rDA reactions (Scheme 1).



Scheme 1.

As a next step, we wanted to investigate the applicability extent of our CF protocols. Thus, the construction of six new pentameric β-peptide systems containing [1*R*,2*R*]-2-aminocyclohexanecarboxylic acid building blocks possessing an enantiomer of norbornene residue in the middle of the peptide chain was reported, in which the ability of 14-Helix formation was investigated (Scheme 2).



Scheme 2.

The results confirmed the viability of preparing the desired pyrimidinones in excellent yields and shorter reaction times. Furthermore, we proved the versatility of the CF rDA protocol by providing distinct peptidic structures. We conclude that the CF reactor set-up ensured enhanced safety and afforded yields higher than those for the batch and microwave processes. Moreover, this approach allowed the replacement of high-boiling and toxic solvents by environmentally benign solvents.

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Synthesis of 3,3-disubstituted 2-oxindoles: privileged structures with biological activities.

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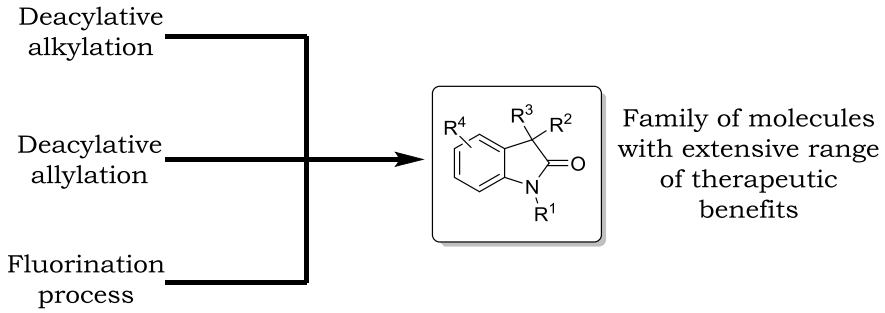
FP27

Disubstituted 2-oxindoles at the 3-position are present in many natural products[a] and pharmaceuticals.[b] In this work, different efficient syntheses of 3,3-disubstituted 2-oxindoles have been developed. First, an innovative monoalkylation and nonsymmetrical 3,3-dialkylation of oxindoles through a deacylative alkylation[c] process have been achieved.[d] Then, a Pd-catalyzed deacylative allylation using allylic alcohols as electrophiles was carry out, obtaining important intermediates for the synthesis of biological active oxindoles.[e] Finally, a similar methodology has been applied for the synthesis of 3-substituted 3-fluoro-2-oxindoles,[f] because the introduction of a fluorine atom at the 3-position of the oxindole rings enhances their biological activity as is the case in many drugs. The family of 3,3-disubstituted 2-oxindoles has shown significative biological activity in more than 15 diseases as cancer, diabetes, HIV, acetylcholinesterase inhibitors, among others.



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Synthesis, antioxidant and Aβ anti-aggregation properties of new ferulic, caffeic and lipoic acid derivatives obtained by Ugi four-component reaction.

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FP28

Alzheimer's disease (AD) is a neurodegenerative disease characterized by decline of key neurotransmitters, beta-amyloid (A□) aggregation and neurofibrillary tangles deposition. Due to its complex nature of AD, multi-target small molecules (MTSM) may enable therapeutic efficacy[(a)]. Accordingly, compounds possessing among others, anticholinergic activity, A□-aggregation inhibition properties, biometal chelating, and NO releasing properties, antioxidant capacity, beta-secretase and monoamine oxidase inhibition power, serotonin and sigma receptor modulation capacities have been developed [(b)].

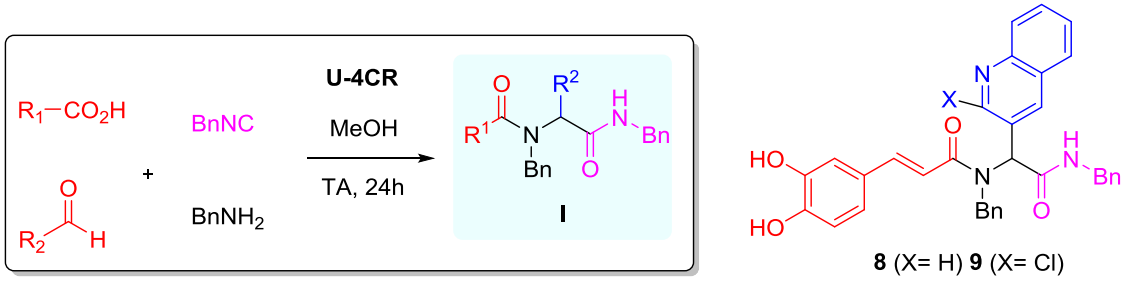

Figure 1. Structure of compounds of type 1, 8 and 9.

In this context, we have recently embarked in a project targeted to the synthesis of (E)-N-benzyl-N-[2-(benzylamino)-2-oxoethyl]-3-(aryl)acrylamides of type I bearing phenyl, pyridine and quinoline motifs (Figure 1), assembled by U-4CR [(c)], where we have incorporated typical antioxidant motifs from naturally occurring ferulic, caffeic and lipoic acids, that have been shown to be effective antioxidant agents [(d)]. Thus, in this communication we will show the synthesis of twelve new adducts of type I, and their antioxidant properties using the DPPH and ORAC assays. As a result, we have identified adducts 8 and 9 (Figure 1), as potent antioxidant agents showing in addition strong A□□□□□ self- aggregation inhibition [(e)].

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Synthesis and biological evaluation of inhibitors targeting STAT5 proteins in the treatment of myeloid leukemias

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FP29

Myeloid leukemias are myeloproliferative diseases that affect hematopoietic stem cells (HSC) and are divided in two types acute (AML) and chronic (CML) according respectively to a fast or slower cell growth.

CML is mainly due to the t(9,22) genomic translocation-derived BCR-ABL fusion oncogene coding for the tyrosine kinase BCR-ABL which activates the transcription factors STAT5 (Signal Transducers and Activators of Transcription 5). This latter plays a crucial role in the initiation and maintenance[(a)] of CML and mediate resistance to Bcr-Abl kinase inhibitors such as Imatinib Mesylate (IM, Glivec®).[(b)] For its part, AML is resulting mainly from internal tandem duplication (Itd) mutations in the juxtamembrane region or point mutation in FLT3. This oncoprotein FLT3-Itd has a tyrosine kinase activity, which activates STAT5. [(c)] As a result, inhibiting STAT5 would contribute to reduce the survival of CML and AML cells and moreover tackle their potential chemoresistance.

A first structure-activity relationship study, allowed us to identify one compound, **17f**, which inhibited the growth of AML and CML cell lines as well as phosphorylation and transcriptional activity of STAT5. These results suggest that **17f** might be a new lead molecule targeting STAT5 signaling in myeloid leukemias.[(d, e)]

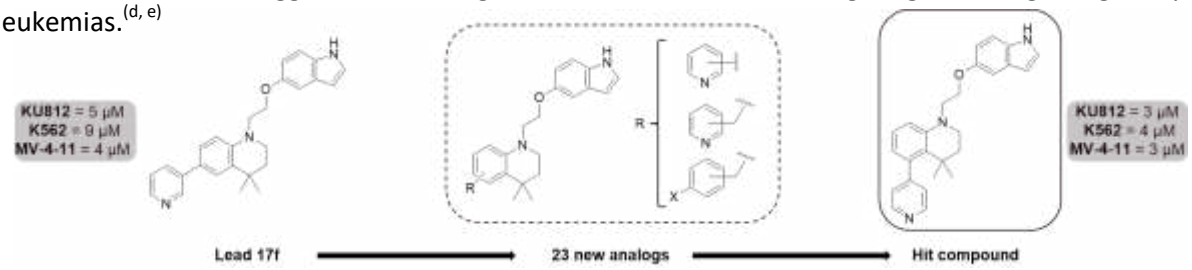

Figure 5. Lead 17f, new analogs and hit compound

Thanks to these results, synthesis of **17f** new analogs with modulation around the tetrahydroquinoleine (THQ) ring have been undertaken and their biological evaluation by proliferation and viability studies were carried out on model CML (KU812, K562) and AML (MV-4-11) cell lines. [(f)] Among these new results, one compound, with the 4-pyridinyl in the position 5 on the THQ ring, shows slightly better results than **17f** on all cell lines. This outcome will guide further modulation work on the THQ ring with others nitrogen heterocycles (pyridazine, triazine, etc.).

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

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FP30

Predicting the thermodynamic properties of the binding process of a drug to its molecular target is of primary relevance to shed light on its mechanism of action and develop new medications. In 2013 our group developed Funnel-Metadynamics (FM).[(a)] Using FM the ligand binding mode and the accurate estimate of the absolute protein-ligand binding free energy are provided within an affordable computer time. From its development FM has been successfully used by different groups to study ligand/protein and ligand/DNA binding complexes, identifying crystallographic binding modes and predicting experimental binding free energies.[(a-e)] The rapid diffusion of FM and the feedback from the users prompted us to develop the Funnel-Metadynamics Automated Protocol (FMAP) that is presented in this talk. FMAP allows disclosing in three steps the whole pharmacodynamics process of a drug to its molecular target, from its unbound state to its final binding mode. FMAP makes use of a graphical user interface (GUI) that allows the interactive preparation of the input files for the FM simulation and the interactive analysis of the results. The GUI guides even inexpert investigators through a step-by-step procedure that is composed of 3 phases: pre-processing, simulation, and post-processing. The final outcome of FMAP is the identification of the ligand binding mode, the metastable states found during the ligand binding mechanism and the accurate estimate of the ligand binding free energy.

In conclusion, FMAP is an accurate, flexible and user-friendly protocol that is expected to impact computer-aided drug design studies in the near future.

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Development of riboflavin-based nanoplatforms for biomedical applications

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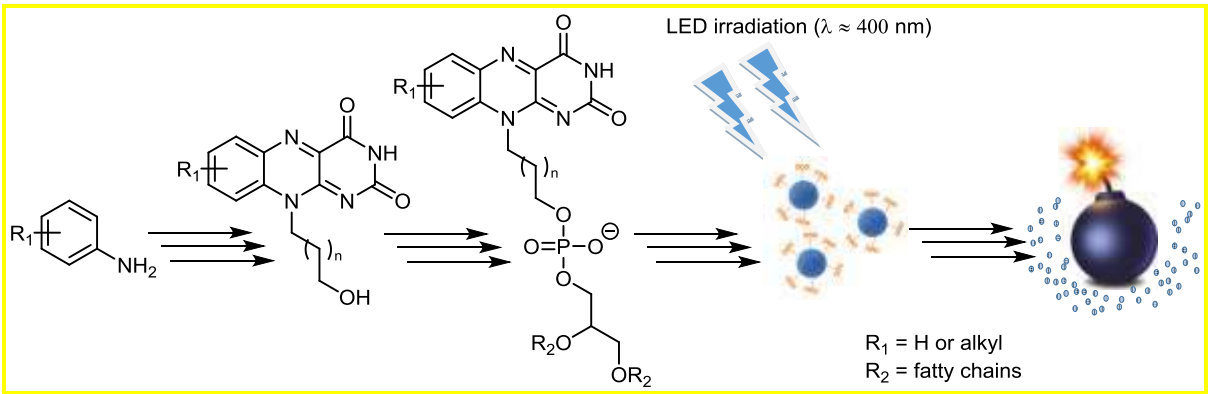
FP31

Riboflavin (RF) is an essential vitamin which, along with its derivatives (flavin mononucleotide and flavin adenine dinucleotide) participate in fundamental physiological events. The presence of isoalloxazine ring in their structures induce redox, photosensitizing and fluorescence properties that can be exploited in tissue engineering and cancer therapies. Moreover, numerous preclinical studies indicate that RF is internalized through RF transporters, which are highly upregulated in prostate, breast cancer cells and neovasculature.[(a)] By irradiation with low energy blue light (*e.g.* LED), RF is also able to generate reactive oxygen species (ROS).

Our group is interested in exploiting the above mention physico-chemical properties of RF and its cancer targeting abilities. We are particularity focused on developing self-assembled nano-systems for biomedical applications starting from RF (or analogs)-conjugated phospholipids.[(b)] We already demonstrated that a home-made amphiphilic RF phospholipid (*e.g.* RfdiC14) formulated with other lipids was able to generate targeted liposomes with applications in photo acoustic imaging of tumor. [(c)] However self-assemblies of this amphiphile used alone induce a compact lamellar morphology because of the π-stacking between the isoalloxazine rings, that quenches fluorescence and ROS production.

Our current hypothesis is to prevent the π-stacking between the isoalloxazine rings by incorporating bulky substituents in 3, 7 or 8 positions. This would conduct to nano-assemblies having enhanced ROS generating properties. The current communication will present the design and our initial synthetical studies of such "**ROS nano-bombs**". Briefly, synthetic phospholipids were generated *via* a multi-steps approach. The key isoalloxazine intermediates were synthesized from commercially available anilines, then conjugated to artificial phospholipids using the phosphoramidite chemistry (Schema).



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Blp1 protein as new vaccine candidate against infections caused by multidrug-resistant *Acinetobacter baumannii*	***FP32***

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Gram-negative bacterium *Acinetobacter baumannii* is a difficult to treat infection agent, causing nosocomial infections world-wide[a]. It has a high propensity for the spread and is often multidrug-resistant (MDR). Therefore, *A. baumannii* has been considered as top priority pathogen for which new drugs and therapeutic options are urgently needed[b]. The success of several pathogen antigen-based vaccines inspired the search of *A. baumannii* specific-antigens as vaccine candidates. However, bacterium displays a high degree of genome plasticity which allows the expression of highly variable surface-associated proteins and capsular polysaccharides. Furthermore, *A. baumannii* express a capsular layer, which covers the surface of bacteria and protects it from the host immune system. To overcome this we propose Blp1 protein as new vaccine candidate against *A. baumannii* infections.

The Blp1 from *A.baumannii* is a large outer membrane protein (~ 3300 amino acids), consisting of multiple Ig-like domains, usually found in extended bacterial adhesins, which might penetrate the capsule layer. We have tested over 100 clinical *A. baumanni* isolates and confirmed the possession of Blp1 coding gene in all tested strains. Importantly, the sequence at the very end of Blp1 protein C-terminus (~ 150 a. a.) is fully conserved. We have purified the C-terminus of Blp1 protein and used it for the mice vaccinations. We have analyzed the serum, obtained from immunized mice and the results indicated the presence of Blp1-specif IgG antibodies. Mice, immunized with C-terminus of Blp1 protein, demonstrated the higher survival rate after challenging with *A. baumannii* comparing to the control group.

In conclusion, the results represent Blp1 protein as a promising target for vaccine development against *A. baumannii* infections.

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Efficient And Regeoselective Synthesis Of Novel Sulfonamide-Isoxazoline/Isoxazole/ Pyrazoline And Pyrazole Through 1,3-Dipolar Cycloaddition Reactions

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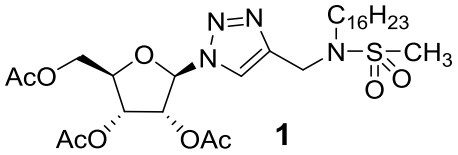
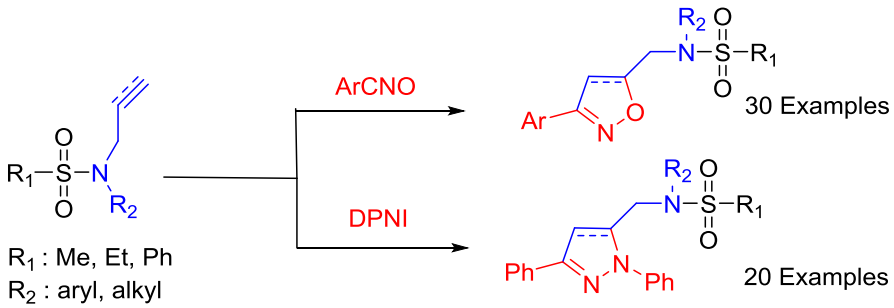
FP33

Sulfonamides received significant attention in modern organic chemistry as they constitute a very privileged class of compound in synthetic and medicinal chemistries. Sulfonamides and Aza-heterocycles are omnipresent motifs found in many natural products and pharmaceutically active compounds. [1] Recently, we reported that the compound 1 exhibits a 19 to 66-fold increased activity compared with AICAR (marketed anticancer drug) - IC50 of 13-15 ⍰M (RCC4 cells). [2]



1

In continuation of our research program focused on the discovery of new bioactive molecules harboring anticancer activities, [3] we synthesized a novel series of five-membered *Aza*-heterocycles linked to sulfonamide moiety. The synthetic access involves a 1,3-dipolar cycloaddition reaction (Scheme 1) between benzonitrile oxides (ArCNO) or diphenylnitrile imine (DPNI) and N-allyl or N-propargyl-sulfonamides as the dipolarophile. In view of our earlier work, this strategy may grant access to novel small libraries of sulfonamide analogs.



Scheme

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***Citrus × clementina (*Rutaceae) leaves a source of bioactive compounds**	
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Citrus × clementina is a hybrid between orange and mandarin, belonging to the Rutaceae family. In Calabria (South of Italy) the cultivation of clementine is widespread for to optimal climatic conditions that have contributed to developing of food product awarded with protected geographical indications (PGI) certification by the European Union as "Clementine di Calabria" [(a)]. Recently, great attention was been paid to *C. × clementina* fruits for their nutritional properties and medicinal value [(b,c,d)].

In this work, *C. × clementina* leaves extracts were investigated for their chemical composition (HPLC-DAD and HPLC-UV) and antioxidant activity using ABTS, DPPH and FRAP tests [(b)]. The total phenols, flavonoids, and carotenoids were also quantified. For this purpose, *C. × clementina* leaves collected in Cetraro, Calabria (Southern Italy) were extracted by maceration with EtOH and EtOH/H_2O (80:20).

Hesperidin, quercetin-3-*O*-glucoside and tangeretin were the most abundant compounds. The HPLC-UV-DAD analysis excluded the presence of furanocoumarins. In addition, *C. × clementina* hydroalcoholic extract showed a promising radical scavenging activity in ABTS and DPPH, while the EtOH extract exhibited the highest activity in FRAP assay. Collectively, compared to the literature for the juice [(c)], our data showed that *C. × clementina* leaves extracts represent a good source of bioactive compounds that will be further explored for future development as nutraceutical products.

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Nanoemulsions, as carriers for compounds with pharmacological interest: formulation, structural study and *in vitro* testing

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FP35

The subject of the study is the development and structural characterization of biocompatible O/W nanoemulsions as carriers, efficient for the encapsulation and delivery of lipophilic substances with pharmacological interest (a). O/W nanoemulsions have been formulated, using generally recognized as safe "GRAS" ingredients namely: distilled water as the aqueous phase, polysorbate 80, labrasol and lecithin as the emulsifier mix and medium chain triglycerides (MCT) as the dispersed oil phase. The study of structural characteristics is performed by Dynamic Light Scattering (DLS) and Electron Paramagnetic Resonance (EPR) spectroscopy. DLS technique is used to determine the diameter of the oil nanodroplets, to evaluate system's homogeneity by measuring the polydispersity index value (PdI) but also to determine nanoemulsion's stability during storage and time. EPR spectroscopy is used in order to evaluate interfacial properties of the surfactants monolayer and investigate the degree of encapsulation of the chosen bioactive compounds (b, c). Furthermore, in vitro tests (in presence and absence of lipophilic compounds) for cell viability and cell toxicity in various cancer cell lines, among them the MW 164 skin melanoma cell line and the Caco-2 human epithelial colorectal adenocarcinoma cell line were carried out. Percentage of cell survival is measured in order to determine the effect of nanoemulsions' ingredients and the effective release of the chosen lipophilic compounds in cell cultures.

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* Correspondence : jtheohari@eie.gr

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

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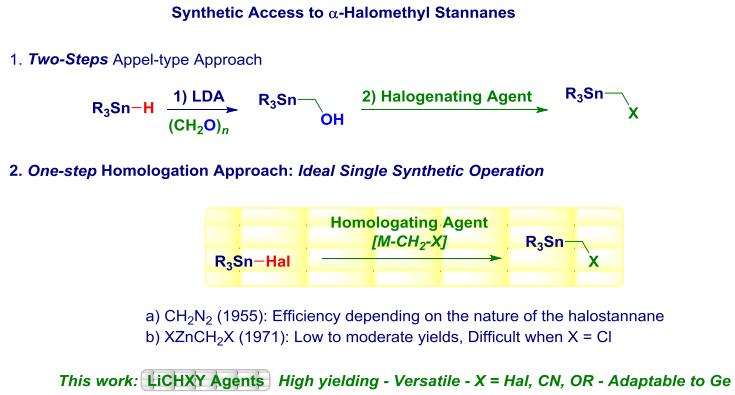
FP36

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



Scheme 1

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Design And Synthesis Of Novel 4-Methylbenzothiazole-Piperazine Propanamides And Their Biological Evaluation As Acetylcholinesterase Inhibitors

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FP37

Alzheimer's Disease (AD) is a progressive fatal neurodegenerative disorder which is characterized clinically by behavioral and cognitive deterioration[a]. Despite many factors affecting the disease progression such as; beta amyloid accumulation leading senile plaques, neurofibrillary tangles, drugs that meet the cholinergic deficiency are widely used currently for the symptomatic treatment of AD[b]. According to recent studies, benzothiazole as the core ring, piperazine derivatives as basic terminus with acetamide linker showed potent AChEI activity and good selectivity against acetylcholinesterase (AChE) rather than butyrylcholinesterase (BuChE)[c,d]. In this regard, we synthesized ten novel 4-methylbenzothiazole-piperazine propanamides and determined their biological activities by modified *in vitro* spectrophotometric method of Ellman[e], also docking studies were performed on AChE (Fig.). As a result, dimethylaminoalkyl piperazine derivatives ; dimethylaminopropyl **2d** (IC_{50}: 410 nM) and dimethylaminoethyl **2e** (IC_{50}: 480 nM) were found to be more potent AChE inhibitors than Galantamine (IC_{50}: 740 nM) and showed a comparable activity with Donepezil (IC_{50}: 103 nM).

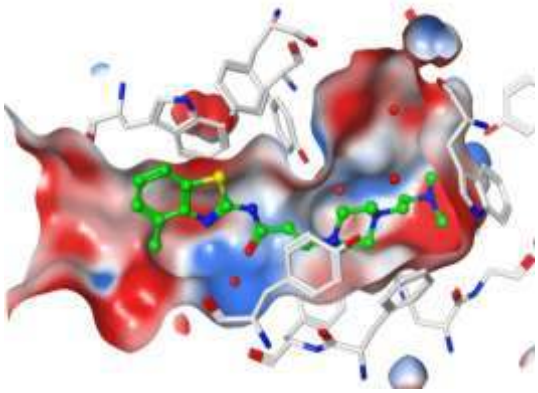

Figure. Docking results for **2e** in the TcAChE enzyme.

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Urocanic acid derivatives based on adamantane and bycyclo[3.3.1]nonane as novel cytotoxic agents

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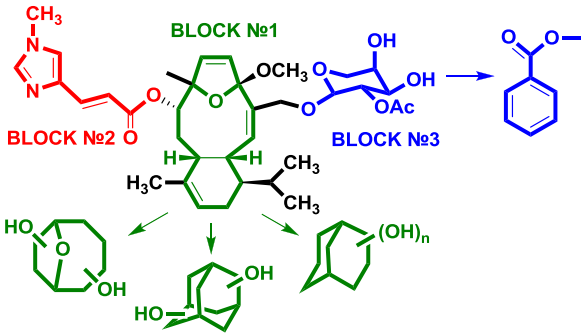
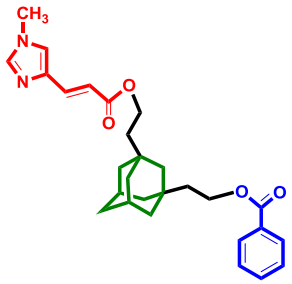
FP38

Cancer is the second major cause of death in highly industrialized countries. Chemotherapy of cancer usually involves the use of cytotoxic agents that destroy rapidly dividing cells. Despite some progress in the development of alternative therapies, cytotoxic agents (such as tubulin ligands taxol and eleutherobin[a]) will remain the main and most popular method of treatment in the near future.

During molecular modeling we formulated the main principles of design of simplified eleutherobinanalogues. We assumed that some polycyclic structures (e.g. adamantane, oxabicyclooctane, bicyclononane) could play the role of the central block. They should contain at least two hydroxyl groups, one of them esterified with N-methylurocanic acid (as in eleutherobin, Block №2) and the other one with benzoic acid (as in taxol, Block №3).



We synthesised a series of individual novelanalogs of eleutherobin which are toxic against three human tumor cell lines (breast MCF7, ovarian SKOV and colon HCT116) in the micromolar range of concentrations. These compounds caused cell rounding and death which could be an evidence of taxol-like effect on tubulin polymerization.



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Acknowledgments: This work was supported by the Russian Foundation for Basic Research (Project 17-03-01320)

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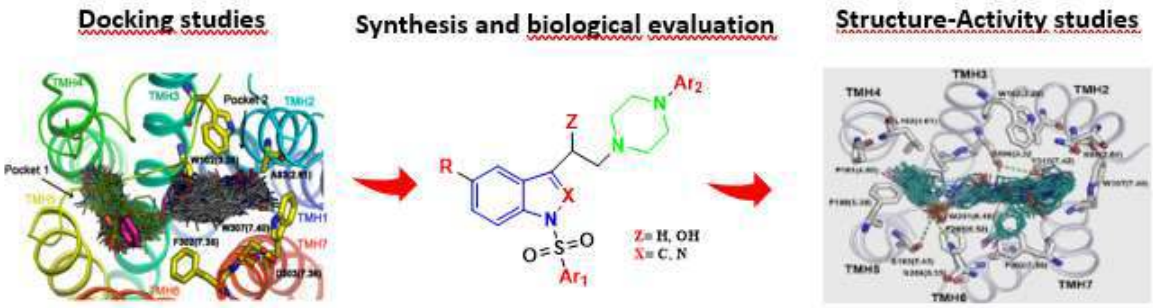
***N*-arylsulphonylindoles and derivatives as a potential anti-obesity drugs: Design, synthesis and biological assessment**	
<u>Gonzalo Vera</u>[(1)], Gonzalo Recabarren-Gajardo[(1)], Carlos F. Lagos[(2)], Jaime Mella-Raipán[(3)] *(1) Synthesis of bioactive heterocycles, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, box 306, Avda. Vicuña Mackenna 4860, Macul, Santiago 7820436, Chile* *(2) Department of Endocrinology, Facultad de Medicina y Ciencia, Universidad San Sebastián, Lota 2465, Providencia, Santiago 7510157, Chile* *(3) Institute of Chemistry and Biochemistry, Science Faculty, Universidad de Valparaíso, box 5030, Av. Gran Bretaña 1111, Playa Ancha, Valparaíso 2360102, Chile*	***FP39***

Currently, obesity is considered as a high priority public health issue due to the exponential growth that has occurred in the last 40 years, increasing more than 10 times the percentage of obese people around the world. It has been shown that obesity is one of the major causes in the development of insulin resistance, diabetes, hypertension, dyslipidemia and other metabolic disorders. In the search for an effective treatment for this health problem, it has been discovered that antagonist 5-HT_6 receptor ligands can cause a profound and sustained weight loss in obese animals.[a]

In this context, we designed, through comparative modeling studies, a new pharmacophore for 5-HT_6 receptor antagonists, that has been used as a pivotal for the synthesis of more than 60 *N*-arylsulfonylindole type ligands[b]. These new series of compounds exhibited moderate to high binding affinities and displayed antagonist profile in 5-HT_6 receptor functional assays. These results were also used to carry out structure-activity studies[c].



The promising biological results obtained so far have encouraged us to make structural modifications of these ligands, based on our computational studies, in order to improve their activity and their pharmacokinetic properties.

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Palladium catalyzed intramolecular allylic amination: diastereoselective synthesis of 2,6-disubstituted 1,2,3,6-tetrahydropyridines	***FP40***

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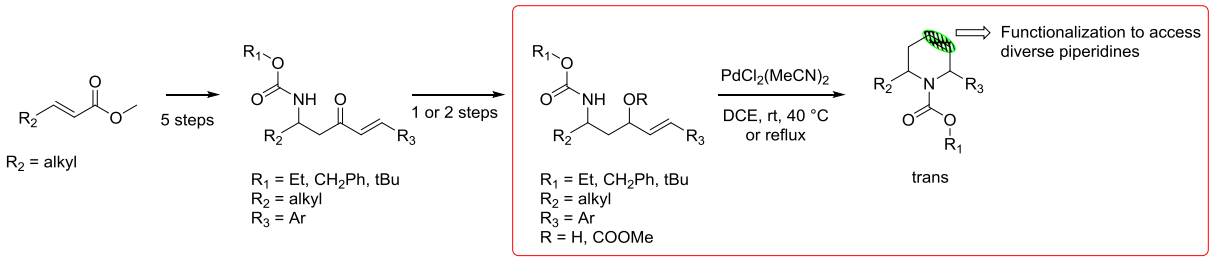
1,2,3,6-Tetrahydropyridines (THP) are an important class of heterocycles found in numerous alkaloids and pharmaceutical compounds[a,b]. These structures could also be used as intermediates in the synthesis of piperidines, and even polysubstituted piperidines or iminosugars with the possible reduction or functionalization of the double bond. Consequently, many strategies for the synthesis of THP have been proposed. Among them, the 2,6-disubstituted-THP and 2,6-disubstituted piperidines have attracted much attention because they are found in many interesting products with a wide range of pharmacological activities. Many methods have been described for the preparation of 2,6-disubstituted-THP but few of them report the synthesis of *trans*-2,6-disubstituted-THP and piperidines, because *trans*-2,6-disubstituted-THP are thermodynamically disfavored[c]. Knowing the importance of the stereoselectivity for the biological activities, the development of new stereoselective syntheses of *trans*-2,6-disubstituted-THP and the corresponding piperidines remains an important challenge.



During our previous studies, we have developed a methodology to prepare stereoselectively either *cis*-2,6 or *trans*-2,6-disubstituted piperidines *via* a Michael-type cyclization[d] from β'-carbamate-α,β-unsaturated ketones easily obtained from the corresponding α,β-unsatured methyl ester in 5 steps. We will present a new methodology using these same ketones as key precursors. We have shown that the corresponding alcohols and carbonates of these ketones could form a *trans*-2,6-disubstituted-THP by palladium catalyzed intramolecular allylic amination. In order to establish this new approach as a general method for the preparation of *trans*-2,6-disubstituted-THP, various conditions and starting products were tested. Based on the obtained results, a proposition of mechanism will also be presented.

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Chemoenzymatically synthesized novel ganglioside GM3 analogues with antitumor activities

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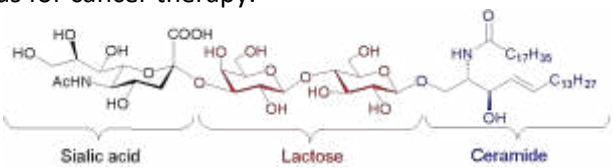
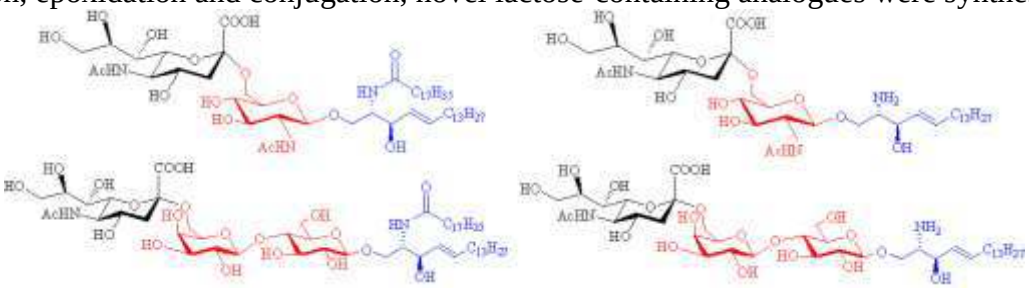
FP41

Ganglioside GM3, belonging to glycosphingolipids family, has been considered as tumor-associated carbohydrate antigen (TACA) on several types of tumor. In addition, several studies have revealed that GM3 can inhibit epidermal growth factor receptor tyrosine kinase (EGFR-TK), which is strongly related with uncontrolled tumor growth[(a)]. Furthermore, our previous studies demonstrated that some GM3 analogues containing galactose or mannose with α-2,6 sialoside have significant inhibitory effects on tumor cell growth and migration[(b)]. Recently we designed and synthesized new GM3 analogues containing glucosamine or lactose with α-2,6 sialoside in order to study their antitumor activities and search new leading compounds for cancer therapy.



Structure of ganglioside GM3

At first, the sialic acid was activated as sialyl xanthate form. Then the lipid precursor azidosphingosine was synthesized from the commercial D-(+)-galactose. Finally, glucosamine and lactose moieties were prepared by enzymatic hydrolysis, and the enzyme is specific for removing the acetyl group at C-6 position. The glucosamine residue bearing a free 6-OH was obtained from 2-phthalimido-2-deoxy-α-D-glucopyranoside tetraacetate by enzyme, further through α-sialylation reaction and conjugation with lipid precursor, after several step manipulations, the novel glucosamine-containing analogues were synthesized. Next, the lactal with free 6-OH at galactose was obtained from peracetylated lactal using enzyme, further also by α-sialylation, epoxidation and conjugation, novel lactose-containing analogues were synthesized.


Structures of synthesized glucosamine- and lactose- containing analogues

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I

POSTER ABSTRACT

Individual p*K*a values of aminoglycosides determined by different NMR spectroscopy

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PO 001

The biological activities of the natural product alkaloid aminoglycoside antibiotics depend upon the amino functional group substituents located around the various rings. The ionisation constant (p*K*a) is the pH at which each functional group is 50% ionized. Any medication's p*K*a values have an important role to play in their physicochemical data and they are also important in the biological activities of drugs. Various NMR reporter nuclei have been used to ascertain the individual p*K*a values which cannot be obtained through the use of potentiometric methods, particularly the order in which the functional groups either gain or shed protons. These data have the capacity to enhance comprehension of the order of target mRNA binding of the basic functional groups. The aim is to measure the p*K*a values of individual amines on selected aminoglycoside alkaloids from *Streptomyces* and *Micromonospora* by using new combinations of 1H, 13C, and 15N NMR spectroscopic data.

Aminoglycoside analyte solutions (0.15-0.73 M aminoglycoside in 99.97% D2O) were prepared at a ~10 mg/mL concentration. NMR spectra including 1H, 13C, HSQC, HMBC, NOESY, and 15N-HMBC were recorded on Bruker Avance III 400 and 500 MHz spectrometers. Trimethylsilylpropanoic acid (TMSP) was used as a reference at δ 0.00 ppm for 1H and 13C NMR spectroscopy. 15N chemical shift values were measured relative to external CH3NO2 set at -511.72 ppm. The pH values were adjusted using 0.5 M NaOD/DCl. MestReNova was used for analysis of the recorded spectra. The nonlinear sigmoidal curve and the inflection point of the sigmoidal curve were determined using GraphPad Prism 7 (Version 2017), after subtraction of 0.5 to convert the measured pD values into pH values.[1]

The p*K*a values of 1-NH2 and 3-NH2 of 2-deoxystreptamine are 9.26 and 7.00. The order of ionisation constants for neamine is: N-6' (8.31) > N-1 (7.60) > N-2' (7.11) > N-3 (6.50), for neomycin is: N-6''' (8.76) > N-6' (8.65) > N-1 (8.08) ≈ N-2' (7.98) ≈ N-2''' (8.03) > N-3 (6.86), for tobramycin is: N-6' (9.10) > N-2' (7.75) ≈ N-3'' (7.68) > N-1 (7.55) > N-3 (6.70), and for sisomicin is: N-6' (9.30) > N-3'' (8.50) > N-2' (8.00) > N-1 (7.42) > N-3 (6.22).

In conclusion, 1H, 13C, and 15N NMR spectroscopy is a powerful technique when it comes to measuring distinct p*K*a values. Also, owing to of its sensitivity, 1H NMR spectroscopy requires less time taking only two minutes for each sample, in comparison to 13C which requires 30 minutes for each sample, and 15N-HMBC, requiring 45 minutes per sample. Unambiguous assignments have been made for each amine substituent on these clinically significant aminoglycoside antibiotics.

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Synthesis of bisubstrate-type analogues as inhibitors of RNA methyltransferases from emerging viruses

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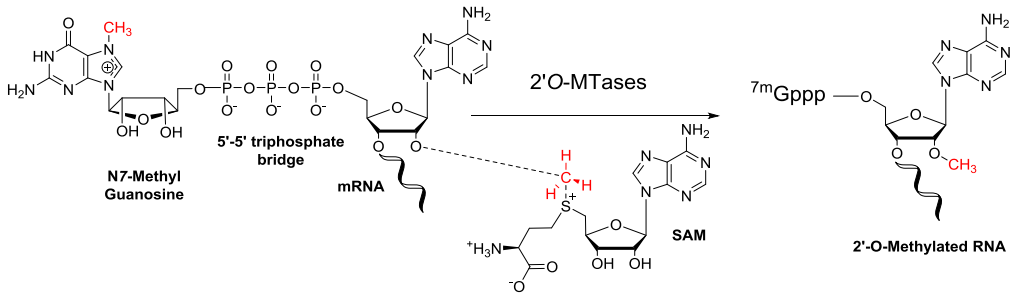
PO 002

Emerging RNA viruses (eg., Dengue, Zika, SARS, MERS, Ebola viruses) are important human pathogens causing substantial health and economic burden. Their emergence is linked to rapid evolution and escape of antiviral response by hiding their RNA from detection by antiviral sensors. Their viral replication/transcription complex contains enzymes essential for virus replication, which are involved in RNA synthesis (polymerase) and epitranscriptomic RNA modifications (capping enzymes, RNA methyltransferases) responsible for luring the host cell. Knowledge on these key enzymes will aid antiviral drug-design, and connect the mechanistics of viral epitranscriptomic RNA modification to innate immunity (1). Particularly, our research aims at studying and targeting viral RNA methyltransferases (RNMTs) which play a crucial role by catalyzing the methylation of the cap structure using S-adenosyl-L-methionine (SAM) as the methyl donor. This cap structure, consisting of a guanosine linked by a 5'-5'-triphosphate bridge to the 5'-end of messenger RNAs, is essential for their translation into proteins. The cap is methylated at the nitrogen in position N7 of guanosine and at the 2'-*O*-position of the N1 residue (adenosine or guanosine) of the viral RNA sequence. These methylations are essential for RNA stability, protection against innate immune system and stimulation of the translation into viral proteins. Small-molecule RNMTs inhibitors (Sinefungin, MTA) have been described but these SAM analogs show inadequate selectivity due to the high homology of SAM binding domain of different RNMTs. To overcome this lack of selectivity, we developed another approach with bisubstrate analogues as 2'-*O*-methyltransferase inhibitors by mimicking the transition state of the 2'-*O*-methylation of the RNA with each substrate (2). We thus synthesized several dinucleosides by coupling an analog of SAM to the 2' hydroxyl of adenosine unit *via* various sized linkers containing diverse heteroatoms (S, N), group of atoms or even the amino acid side chain of the SAM. All compounds were fully characterized and were subjected to biological activity assays. Inhibition activity IC_{50} of 2'-*O*-MTases from several viruses was determined.



Schematic representation of the 2'-*O*-methylation reaction of an adenosine in the cap structure of a mRNA

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The optimization of the synthesis of some new thiazolidin-4-one derivatives of diclofenac

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PO 003

Introduction: Diclofenac is one of the most prescribed nonsteroidal anti-inflammatory drug for the treatment of pain and inflammation from various rheumatic diseases. Despite of the pharmacological effects, the therapeutic use of diclofenac is often associated with several side effects, especially at gastrointestinal and renal level. In order to improve the toxicological profile of diclofenac, the researchers have focused on synthesis of new derivatives through modulation of free carboxyl group. **Aim:** The optimization of the synthesis of some new thiazolidine-4-one derivatives of diclofenac, in view of the optimal conditions of reaction. **Material and methods:** The synthesis of thiazolidin-4-one derivatives of diclofenac was performed in several steps: reaction of ethyl ester of diclofenac with hydrazine hydrate; condensation of resulted hydrazide with different aromatic aldehydes when corresponding hydrazones were formed and finally cyclization of hydrazones of diclofenac with excess of mercaptoacetic acid. In order to optimize the synthesis, the reaction conditions were varied (molecular ratio between reagents, time, temperature, solvent, catalyst etc.). **Results:** The most favorable method was proved to be the reaction between diclofenac hydrazones with excess of mercaptoacetic acid, at 135-140°C, for 6 h, when the thiazolidine-4-one derivatives were obtained in good yield. **Conclusions:** The structure of the synthesized compound was proved using spectral methods (IR, ^{1}H NMR, ^{13}C NMR, HR-MS).

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Gloeophyllum trabeum: a potential source for novel antibiotics.

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PO 004

Abstract:

There is an increasing interest in utilizing fungal secondary metabolites in the battle against emerging superbugs [1]. *G. trabeum* is a wood decay basidiomycete that established compact network with its environment [2]. However, information on its secondary metabolites synthesis is scare. In our study, we investigated *G. trabeum* antagonistic towards *Escherichia coli*, *Saccharomyces services* and *Bacillus subtilis*, highlighting its ability to produce antimicrobial agents. We further examined *G. trabeum* sensitivity against two antibiotics; glufosinate and hygromycin B, to find that hygromycin, is a reliable and cost-effective selectable marker for genetic manipulation in *G. trabeum*. We then chemically analyzed *G. trabeum* fermentation culture. This leads to the characterization of four previously undescribed rare coumarin based polyketides (Gt-1= oospoglycol, Gt-2= oosponol, Gt-3= FD48 and Gt-4), of which, Gt-2 showed antimicrobial activity against *B. subtilis*. *G. trabeum* whole genome sequences, represents the only available genomic data from the Gloeophyllales [3], characterizing these unique compounds in this species, would provide further support towards the quest for high yield and fast production of novel antibiotics via synthetic biology platform.

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4-

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α-CCl_3-*N*-Heterocycles pharmacomodulation for discovering novel antimalarials.

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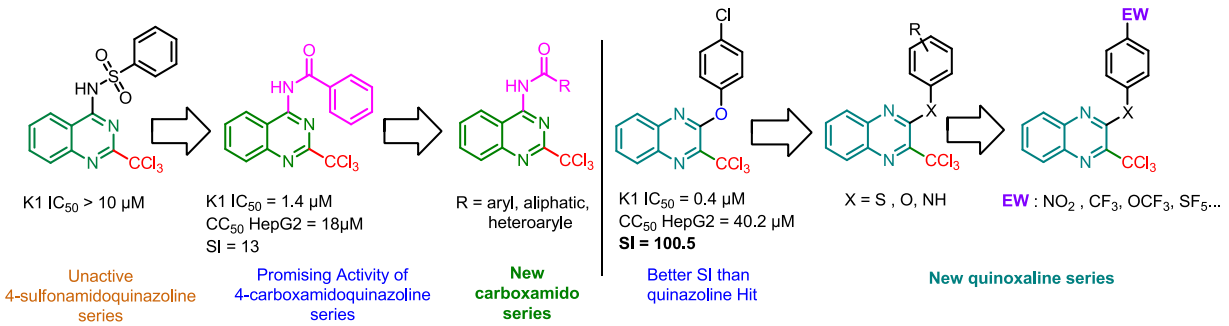
PO 005

Among infectious diseases, malaria is still the leading cause of death.[1] Due to the emergence of drug resistances including the ACTs, new treatments displaying original mode of action are urgently required. Aiming at developing new antiplasmodials, our laboratory previously described the synthesis and the biological activities of a library of 2-trichloromethylquinazoline derivatives which highlighted a Hit molecule (IC_{50} = 0.4 µM, CC_{50} = 16 µM).[2] In previous work, we reported that sulfonamide group at position 4 of the 2-trichloromethylquinazoline scaffold led to inactive compounds.[3] Isosteric replacement with carboxamide moiety showed promising activity. Thus, we prepare a new series of aliphatic and aromatic carboxamide derivatives.

Moreover, a scaffold hopping strategy previously showed that the replacement of the quinazoline moiety by a quinoxaline one improved the cytotoxicity profile.[4] Thus, we synthetize a new series of 2-trichloromethylquinoxaline analogues. The *in vitro* biological evaluations against the multi-resistant K1 *P. falciparum* strain highlighted two new hit molecules substituted with an electron-withdrawing group in *para* position. According to this result, we prepare new 2-trichloromethylquinoxaline analogues bearing other electron-withdrawing group such as -CF_3, -SF_5, or OCF_3. We report herein our pharmacomodulation work: the synthesis of the corresponding derivatives and the biological results will be described in the poster.



This work was supported by the ANR NINTARMAL project, grant ANR-17-CE11-0017.

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Development of Staphylococcal immune evasion protein Sbi as a potential immunotherapeutic agent.

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PO 006

Background Information: Sbi stands for Staphylococcus Aureus Binder of IgG. Sbi is a unique 436-residue immune evasion protein expressed by the gram-positive bacterium and is made up by four domains. Domains I and II are IgG binding domains that bind on the Fc region of antibodies, whereas domains III and IV bind complement protein C3. Previous research done on mutated truncated forms of Sbi, showed that domain IV (residues 198-266) alone inhibits activation of the complement alternative pathway by binding the C3 breakdown product, C3b opsonin. Hence inhibiting the interaction of CR2 of B cells and their complement recruitment on the bacterial surface.

Purpose: Even though the main function of Sbi is to enable the evasion of the host immune response by the futile consumption of the complement protein C3, through alternative pathway activation, the aim of this project is to produce a truncated form of the evasion protein fused and expressed recombinantly with eGFP fluorescent protein. This fusion protein will provide a targeted complement deposition detection on the surface of HER2+/BT474 cancer cells

Methods: Recombinant fusion protein expression was achieved by the use of a pET15-b plasmid containing the engineered eGFP/SbiIVCys fusion gene transformed into E.coli SHuffle T7 cells (NEB). Cells cultured and induced for protein production by IPTD as per manufacturer guidelines. The Fusion protein was purified by FPLC APAKTA prime purification using the GE HisTag FF column as per manufacturer guidelines. HER2+/BT474 breast cancer cell line was grown with Hyclone complete media as per ATCC guidelines.

Results: The eGFP/SbiIVCys protein was expressed and purified as monomer and dimer of approximately 50% ratio at a high purity and yield of 18mg per 1L culture Preliminary in vitro confocal microscopy experiments have shown a clear difference of C3b deposition on the surface of the HER2+ BT474 breast cancer cells in the presence of varying percentage of human complement.

Conclusions: This unique immune response protein and its mutants are easily produced and each with a different activity level, allowing for different applications and drug production targets. Novel antibody-drug conjugate was produced with proven efficacy and results effectively visualised

Acknowledgements: Many thanks for the Santander Postgraduate fund that allowed to attend this conference.

Topic Area: Microbial protein production and Confocal Microscopy.

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New insights into a potential therapeutic target regulating Unfolded Protein Response and subsequent inflammation in liver and muscle

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PO 007

As a result of growing life expectancy, rise of lifestyle-related diseases can be attributable to prolonged abnormal exposure to toxic stimuli, resulting in endoplasmic reticulum (ER) stress. As a consequence, ER stress triggers the activation of interconnected pathways collectively called Unfolded Protein Response (UPR) which is an adaptive physiological process initiated to maintain proper ER function. However, when prolonged or severe, UPR can also induce deleterious responses like inflammation[(a)]. Hence, UPR has been proposed as a pharmacological target but druggable proteins still need to be identified to modulate UPR signaling in order to control or prevent ER stress and its detrimental consequences. In the lab, we study a protein that could represent an attractive therapeutic target for UPR modulation in particular in skeletal muscle and liver.

To this purpose, we evaluated the effect of a proprietary protein inhibitor in C2C12 myocytes and HepG2 hepatocytes stressed by tunicamycin, a glycosylation inhibitor. In addition, we analyzed the effect of the invalidation of this protein of interest in two strains of mice (C57BL/6 and NOD).

As expected, UPR markers were increased in tunicamycin-stimulated myocytes and hepatocytes. Moreover, we observed that treatment with the protein inhibitor further induced UPR genes expression both in myocytes and hepatocytes compared to vehicle. In parallel, we found an increase in UPR genes expression (*Xbp1s*, *Gadd34*) compared to wild-type animals in liver and muscle from invalidated mice. Interestingly, we also noticed a strong induction of inflammation markers (*IL-1β*, *Mcp1*, *IL-6*) in liver and muscle from invalidated mice.

These results suggest that this protein could be an attractive therapeutic target since it seems to play a role in UPR pathway induction and in subsequent inflammatory response.

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Antiinflammatory properties of some phenazone derivatives containing thiazolidine moiety, in the carrageenan-induced acute inflammation model

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PO 008

Introduction. The phenazone was the first pure synthetic worldwide, introduced in therapy as an analgesic agent, and later as antipyretic. It was followed by other derivatives containing the pyrazole and pyrazolidione cycle which were used as analgesic, antipyretic and nonsteroidal anti-inflammatory agents[(a)]. As regards the thiazolidine moiety, it has been shown its importance in antimicrobial, anti-inflammatory, anticonvulsant, antimalarial, analgesic, anti-HIV and anticancer activity of the derivative compound[(b)]. The aim of this study was to investigate the anti-inflammatory properties of thiazolidines derivatives of phenazone in an attempt to develop new anti-inflammatory compounds with less side effects. Methods. The Antiinflammatory activity was tested in acute model of inflammation induced by carrageenan[(c)]. The tested compounds (ten new synthetic compounds; phenazone and 4-aminophenazone were used as positive control) were administrated as suspension in tween 80 prior induced of acute edema by injected of 0.1 ml of carrageenan solution 1%, in right paw of rats. The anti-inflammatory activity was established by determination of right paw volume edema at 2h, 4h, 6h and 24h and comparison with the paw volume edema determined before carrageenan being injected. The capacity of edema inhibition was compared with phenazone and 4-aminophenazone. The compounds showed the highest anti-inflammatory activity at 4h or 6h. This was observed in particular at compound 3-(2-methoxyphenyl-4-oxo-1,3-thiazolidine-3-yl)-N-(2,3-dimethyl-1-phenyl-5-oxo-pyrazolin-4-yl)propionamide. Conclusion. Many of the compounds showed good anti-inflammatory activity and the substitution of orto position on phenyl ring and the methoxy radical seems to have a good influence on the anti-inflammatory activity of the compounds.

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Synthesis of pyrroloquinolinone derivatives via *ortho*-quinonemethides

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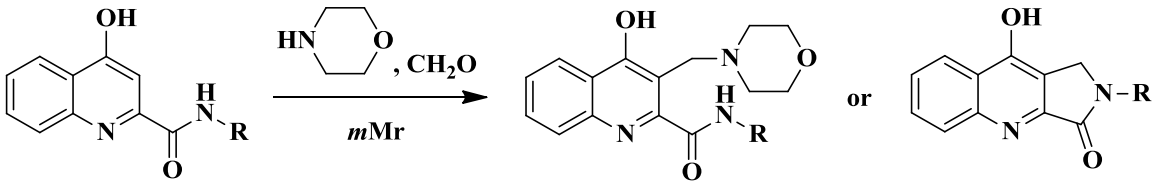
PO 009

Kynurenic acid (KYNA) is an endogenous neuroprotective compound and the deviation from its normal level in the human body can contribute to neurological disorders like Alzheimer's, Parkinson's and Huntington's disease.[(a)] The direct medical use of KYNA is inhibited because of its poor penetration through the blood-brain-barrier. There have already been several attempts trying to solve this problem, with the synthesis of derivatives through the alteration of the quinoline structure.[(b)]

Previous works in our institute have proven that derivatives containing tertiary nitrogen in amide sidechains show promising biological activities. In order to insert new cationic centers into position 3, the ethyl esther of KYNA was aminoalkylated using secondary amines and aldehydes in a modified Mannich reaction (*m*Mr).

As a further extension of this work it has been proven that the aminoalkylation can also be achieved if the kynurenic skeleton contains an amide unit at position 2. Starting from 4-hydroxy-*N*-(2-(pyrrolidin-1-yl)ethyl)quinoline-2-carboxamide or *N*-(2-(dimethylamino)ethyl)-4-hydroxyquinoline-2-carboxamide and formaldehyde in the presence of morpholine, the aminoalkylation of position 3 could be performed.



During these reactions the formation of a new side product containing a pyrrolidinone ring have been observed. It was proven synthetically, that the formation of the new pyrroloquinolinone derivatives undergoes faster via an *ortho*-quinonemethide intermediate formed by the elimination of morpholine. Furthermore, the reaction was extended by the alteration of the amide unit.

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

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PO 010

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

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

Acknowledgment

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Ena/VASP as novel antimetastatic target addressed by structure-optimized ProM scaffolds

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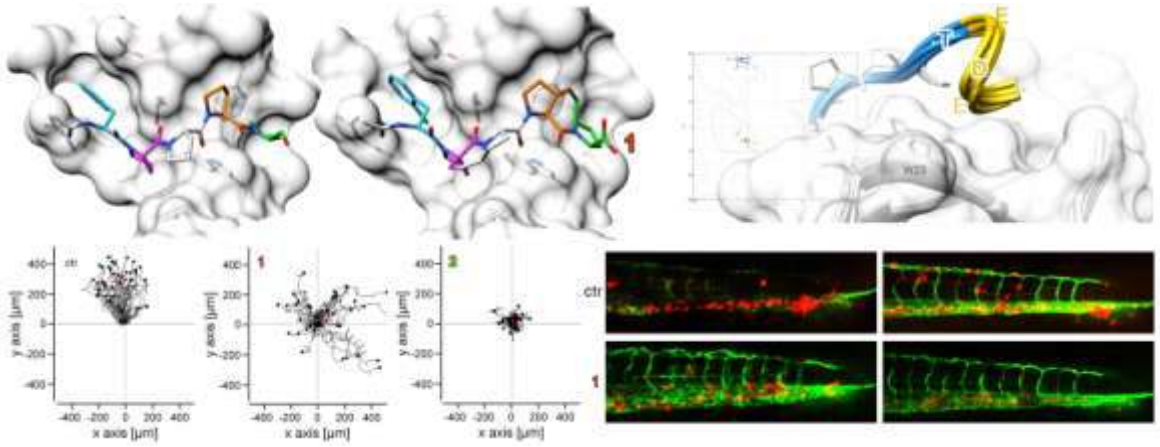
PO 011

Metastasis is the major lethal attribute of cancer. Yet, the progress of metastasis-directed drug development efforts is limited, making new approaches in drug design essential. Recently, we showed that interfering with the actin regulatory protein family Ena/VASP causes significant reduction in breast cancer cell invasion. To inhibit the proline-mediated protein-protein interaction of Ena/VASP EVH1, we designed an extendable scaffold toolbox composed of di-proline mimicking scaffolds, coined ProMs [1]. However, the moderate affinity of the initial inhibitor (**1**, top panel) restricts the validation of Ena/VASP as novel cancer target. Here, we solve crystal structures of ENAH EVH1 in complex with C-terminally elongated high-affinity peptides derived from *Listeria monocytogenes* (top right panel) and mimic the newly found interaction sites by *in silico* designed scaffold modifications (**2**, lower panel). We then evaluated the published and the structure-optimized inhibitors both in cellular assays as well as in zebrafish studies. We can show that the boosted affinity nicely correlates with the potency to inhibit MDA-MB-231 cancer cell invasion. Our current work demonstrates the power of our modular scaffold toolbox to develop a novel class of antimetastatic drugs acting at the very end of converging receptor kinase signaling and integrin pathways.



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

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PO 012

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

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

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

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Studies of a fluorescent analogue of an anticancer glycoglycerolipid.

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PO 013

SK3 channels, a small conductance activated potassium channels which are activated by low intracellular calcium concentration, are expressed in several cancer cell lines (breast cancer cells, human metastatic melanoma cell lines). Previous studies have shown that SK3 channels are involved in cancer cell migration and are expressed in cancer cell lines known for their invasive properties [a]. Thus, SK3 channel represents a potential target for a new class of anticancer agents that would reduce cancer cell migration and potentially, metastasis formation. Ohmline was the first efficient and non-toxic SK3 inhibitor that exhibits an amphiphilic structure (Figure 6) [b, c]. This compound is quite selective since it strongly inhibits SK3 channels whereas SK1 is weakly inhibited and SK2 or BKCa are not modulated with this compound. *In vivo* experiments, carried out on a metastatic breast cancer murine model, have shown that the administration of Ohmline eliminated the occurrence of bone metastasis and reduced by 50% the occurrence of lung metastases [d]. These outstanding results still need to be better understood. If Ohmline is likely incorporated in the plasma membrane, its localization at a cellular scale still needs to be assessed. With this view in mind, we report herein the synthesis of a fluorescent analogue of Ohmline and the first biological results obtained.

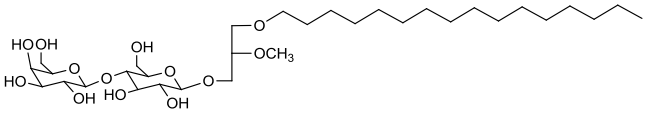

Figure 6 : Structure of Ohmline

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Synthesis of new O,N- or N,N-heterocycles via in situ generated ortho-quinonemethids

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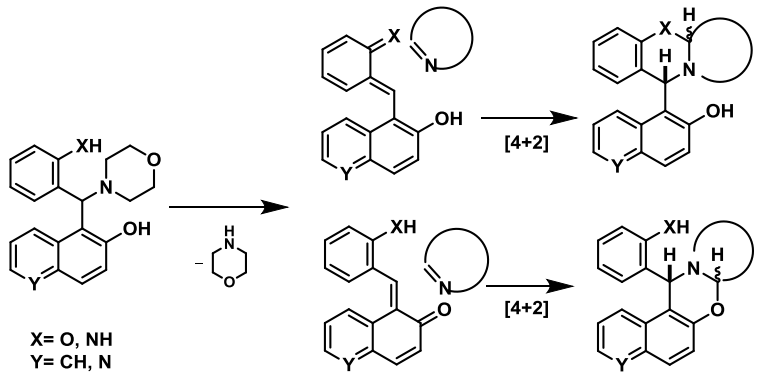
PO 014

The preparation of novel condensed poliheterocycles is a relatively new area of chemistry of *ortho*-quinonemethids (*o*-QMs) generated from Mannich bases.[(a)] In this case, the cycloaddition take place between the *o*-QMs and cyclic imines. Our research group developed for the first time the reaction of 1-aminoalkyl-2-naphthols with 3,4-dihydroisoquinoline as cyclic imine obtaining naphth[1,2-*e*]oxazino[1,3]isoquinolines as new heterocycles.[(b)] Therefore we planned to synthesize new aminonaphthol derivatives that can serve two different type of *o*-QMs. Our further aim was to investigate their reactivity in [4+2] cycloaddition with different cyclic imines.



The syntheses of the starting compounds were achieved by the reactions of 2-naphthol and 6-hydroxyquinoline with salicylic aldehyde and/or *o*-nitrobenzaldehyde in the presence of morpholine. These functionalyzed Mannich bases were then reacted with partially saturated cyclic amines such as: 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine, 4,5-dihydro-3*H*-benz[*c*]azepine and 3,4-dihydro-β-carboline. The regio- and diastereoselectivity of the reactions were tested by using different reaction conditions. All of the reactions could be accelerated by using microwave irradiation and in all cases the reactions lead to the formation of a single product.

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Mechanistic Insight Enables Practical, Scalable, Room Temperature Chan-Lam *N*-Arylation of *N*-Aryl Sulfonamides

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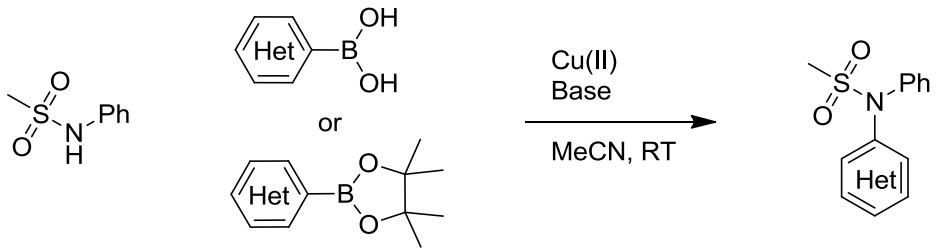
PO 015

The importance of the *N*-aryl sulfonamide group is demonstrated by its presence in marketed drugs to treat a range of pathologies; including infections, cancer and cardiovascular diseases. To the best of our knowledge, literature reports of Pd-catalysed *N*-arylation of sulfonamides are scare and Ullman-based approaches require undesirable forcing conditions which limit their applicability. An inexpensive, ligand-free and mild Chan-Lam cross-coupling would be more appealing, however low or unreported yields are observed across the literature. There is therefore the need to develop mild, broadly applicable and scalable chemistry that enables the *N*-arylation of *N*-arylsulfonamides to facilitate SAR analysis and large-scale synthesis of pharmaceuticals.

Here, we provide a mechanistically informed, rationally designed system for practical and scalable Chan-Lam *N*-arylation of *N*-arylsulfonamides.[1] Traditional copper acetate-catalysed Chan-Lam reaction conditions were optimized to improve yields. Moreover, the generality of the optimized protocol was assessed by application to a series of substrates and scaled up. The result showed high conversion, functional group tolerability and scalability. This optimized Chan-Lam protocol is envisioned as a practical, scalable and mild *N*-arylation of *N*-arylsulfonamides with broad substrate tolerability and broad applicability to medicinal chemistry.



1 equiv 2 equiv

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Potentiometric properties and substrate specificity of *E. coli* nitroreductase A, a candidate for gene-directed enzyme prodrug anticancer therapy

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PO 016

NfsA, a major FMN-associated nitroreductase of *E. coli*, catalyzes 2e- reduction of quinones and 2-/4-electron reduction of nitroaromatics. In the latter reaction, nitroso intermediates are reduced mainly in a non-enzymatic way by NADPH. NfsA has potential applications in the biodegradation of nitroaromatic environment pollutants, e.g. explosives, and is also of interest for the anticancer strategy gene-directed enzyme prodrug therapy. However, the catalytic mechanism of NfsA is poorly characterized. Here we examined the NADPH-dependent reduction of quinones (n = 16) and nitroaromatic compounds (n = 12) by NfsA. The reactivity of quinones (k_{cat}/K_m = 2.3 x 10^3 – 1.4 x 10^7 M^{-1} s^{-1}) was lower than that of nitroaromatics (k_{cat}/K_m = 9.6 x 10^3 – 7.9 x 10^6 M^{-1} s^{-1}) having similar E^1_7 values, except for the significantly enhanced reactivity of 2-OH-1,4-naphthoquinones, consistent with observations previously made for the group B nitroreductase of *Enterobacter cloacae*. Reaction followed "ping-pong" scheme. NfsA photoreduction with 5-deazaflavin did not yield semiquinone, which points to its instability. Also we determined the redox potential of NfsA, using its reactions with oxidized and reduced forms of 3-acetylpyridine adenine dinucleotide phosphate ($APADP^+$ and APADPH, respectively). Reaction rates were characterized by k_{cat} = 5.5 s^{-1} and k_{cat}/K_m = 1.35 x 10^6 M^{-1} s^{-1} for the reduction half-reaction and k_{cat} = 25 s^{-1} and k_{cat}/K_m = 4.3 x 10^4 M^{-1} s^{-1} for the oxidation half-reaction. Redox potential was calculated by Haldane method, according to the ratio of k_{cat}/K_m and the Nernst equation. Given that $APADP^+$/APADPH potential is -0.258 V we were able to determine NfsA potential, which was equal to -214 mV ± 11 mV.

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Gaiacol : Chemical Syntheses And Analytical Control Of Raw Materials Synthesized

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PO 017

Discovery or design of new drugs and their synthesis is one of the main objectives of therapeutic chemistry.

Le gaiacol, derived from the phenol nucleus, can be obtained by chemical synthesis, a laboratory scale, products synthesized will be tested according to the tests described in the EP 6th Edition 2008.The system "Quality Assurance" ensures quality, efficacy and safety of pharmaceuticals products.

Gaiacol can be obtained by two methods, the first being the diazotaion of orthoanisidine, and the second was the application of DAKIN's reaction on the orthoanisaldehyde.

Gaiacol synthesized was controlled, according to the tests described in the European Pharmacopoeia by different identification tests, the dosage of the raw material and the determination of the purity.

The first synthesis method was rejected because it was obtained an oxidation product, confirmed by a spectroscopic technique (IR) and a chromatographic technique (TLC). .

By cons, the protocol of the DAKIN's oxidation reaction was optimized and yielded satisfactory results with a yield equal to **65%.**

The analytical control of the product synthesized by various physicochemical tests, spectroscopic and chromatographic which proved compliance with the standards required by the European Pharmacopoeia 6th Edition 2008. Therefore, the product is of Synthesized Satisfactory quality.

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Development of Small Molecule Inhibitors of the NLRP3 Inflammasome

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PO O18

The NLRP3 (NOD-Like Receptor Pyrin Domain Containing Protein 3) inflammasome is a multi-protein complex responsible for the processing of the proinflammatory cytokine IL-1β (interleukin-1β).[(a)] The NLRP3 inflammasome is implicated in a number of morbidities, including Alzheimer's disease.[(b,c)] Inhibiting the NLRP3 inflammasome could be a new approach in neuroscience drug discovery.[(d)] We recently showed that the fenamates, a series of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), selectively and effectively inhibit the NLRP3 inflammasome through inhibition of VRAC (Volume Regulated Anion Channel), independently of their effect on COX (cyclooxygenase) enzymes.[(e)]

A number of analogues (Novel VRAC compounds, NVRs) were synthesised, based on the fenamates (Fig. 1). Alternatives to the amine linker present in the fenamates were considered, as well as a number of other alterations in order to explore the SAR (Structure Activity Relationship) of the NVR series. Favoured alterations include a bioisosteric replacement to the carboxylic acid, and an alternative to the amine linker. The leading NVRs inhibit the release of IL-1β with an IC_{50} of 0.5 - 2 μM.

Future work is planned on the NVR series, with the aim to improve potency, to assess selectivity for VRAC over COX, and to establish good pharmacokinetic properties of the lead compounds.

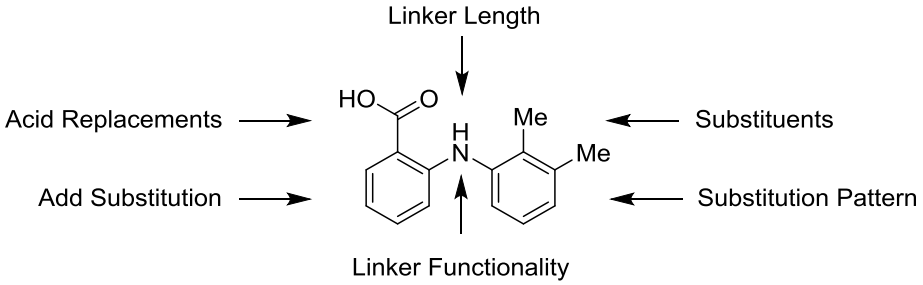

Fig. 1: NVR Analogues. Alterations made in the indicated areas of mefenamic acid, one of the fenamate lead compounds.

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Design of a drug eluting stent : A nanostructured medical device composed of functionalized gold nanoparticles for a nitric oxide controlled release

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PO 019

Each year in France 300 000 patients suffer from myocardial ischemia. About 200 000 of those patients require the implantation of a medical device. However, cardiovascular medical devices implanted for a long time are associated to high risk of thrombosis or restenosis. These complications are due to known mechanisms such as endothelial lesions, protein adsorption, coagulation and leukocyte activation and hyperproliferation of smooth muscle cells leading to the vessel occlusion. In this physiopathological context, nitric oxide (NO), an endogenous radical gas-transmitter, plays a key role. Due to its very short half-life (< 1 s), NO cannot be used directly in therapy. This issue can be overcome with the help of *S*-nitrosothiols (RSNO) also called NO-donors thanks to their ability to carry and deliver NO. Our aim is to design an active NO eluting stent composed of functionalized gold nanoparticles for a NO controlled release.

Nanostructured medical devices are a full expansion field. Up to now, 33 marketed medical devices contain nanoparticles or are nanostructured. A key to produce active devices is the use of layer-by-layer polyelectrolyte films with immobilized metallic nanoparticles such as silver, gold or cupper … The surface chemistry of gold nanoparticles (AuNP) allows them to be easily incorporated into surface coatings and also to be grafted with drugs at very high yields. In this way, we showed that 7500 molecules of glutathione can be grafted on a gold nanoparticle [1].

We hypothesized that RSNO functionalized AuNP entrapped into LbL are a good approach to improve efficiency of cardio-vascular medical device (figure 1.). The optimal construction for the film was already defined using poly(allylamine) as polycationic layer and poly(acrylic acid) as polyanionic layer. Preliminary studies gave encouraging results. This LbL is stable under physiological conditions during more than 1 year. It remains also unchanged when exposed to shear stress [2]. At the same time, early data on biocompatibility are promising. Films showed a low protein adsorption and induction of hemolysis [3].However, improvements are still required. Biocompatibility of devices will be enhanced with the help of a pegylated out layer. The optimization of the NO storage capacity of the LbL is also investigated. AuNP-RSNO synthesis is already known but their physico-chemical properties restrict their inclusion on the film. Thus, in situ functionalization of gold nanoparticles is currently developed. *In fine,* the target is to reach a sustain NO release of 6 weeks to be suitable with a therapeutic effect [4] (6 µmol.cm^{-2} are needed to prevent both thrombosis and restenosis).

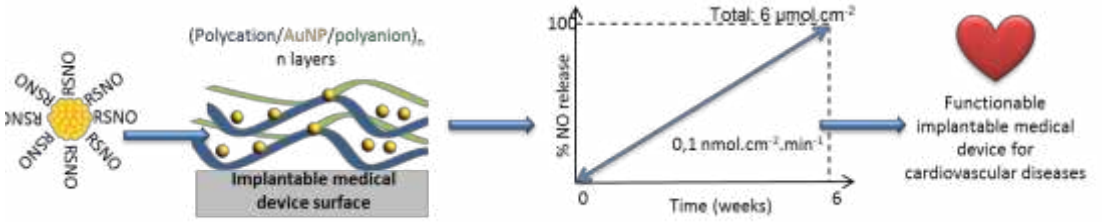

Figure 7: Strategy of development of a device with a nanostructured surface for a NO controlled release applicable to cardiovascular devices. AuNP : gold nanoparticles , RSNO : S-nitrosothiols.

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Synthesis and biological evaluation of 3-substituted 2-oxindole derivatives as new glycogen synthase kinase 3β inhibitors

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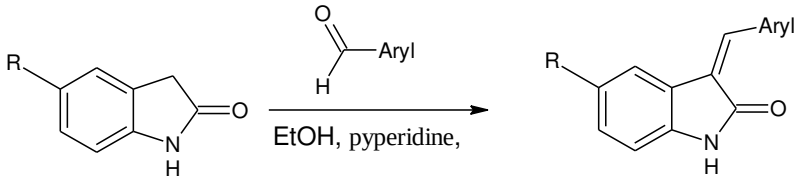
PO 020

A number of novel glycogen synthase kinase 3*б* *(*GSK-3*б)* inhibitors with promising activity were synthesized using the 3-arylidene-2-oxindole scaffold. The lead compound (**1**) was shown to inhibit GSK-3*б* with IC_{50} 4.19 nM. with moderate cytotoxity in a cell-based assay. Compound **1** was evaluated in oral glucose tolerance test in rat model of type 2 diabetes mellitus and demonstrated significant antidiabetic effect. The results attest to the potential for further development of **1** as a therapeutic agent for treatment of diabetes[1,2] and cancer[3,4].



43 - 99 %

Compound	R	Ar	Yield %	% Inhibition at 10 μM	IC_{50} (μM)
1	H	2-pyridyl	79	95.70	0.00419
2	BzNH	4-OH-Ph	99	58.94	4.343
3	$CH_3C(O)NH$	3,4,5-tri-MeO-Ph	43	84.16	0.2329
4	MeOC(O)NH	4-OH-Ph	44	91.82	0.1554
5	MeOC(O)NH	4-NO_2-Ph	49	69.29	0.3479

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Targeting DOT1L in MLL rearranged leukaemia cells

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PO 021

DNA and histone methylation are aberrantly regulated in many diseases such as cancer. Epigenetic modifications contribute to the onset and progression of cancer and appeared as a promising target for several diseases because of the reversibility of the chemical epigenetic marks[1-3]. Thus, to develop new therapeutic strategies, proteins responsible for DNA and histone methylation are extensively studied. Both DNMT and HMT catalyse the transfer of a methyl group from the co-factor *S*-5'-adenosyl-L-methionine (SAM). Based on the available structures of DNMTs and HMTs proteins co-crystallized with *S*-5'-adenosyl-L-homocystein (SAH), we identified differences in the catalytic sites and of the pharmacophoric groups involved in the SAH recognition. These observations allowed us to design a new focused chemical library to target selected DNMT and HMT. The lysine HMT (HKMT) DOT1L was selected in order to validate our approach. DOT1L is necessary for the proliferation of the MLLr cells. Epizyme developed two specific inhibitors EPZ-4777 and EPZ-5676[4-5] the latter entered clinical trials for the treatment of MLLr, but both show a poor metabolic stability and phase I clinical trial ended. A couple of inhibitors were designed to avoid this instability and were characterized on a molecular and cellular basis.

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Design of Bioinspired pH-responsive Foldamers for Intracellular Delivery of Biomacromolecules[1]

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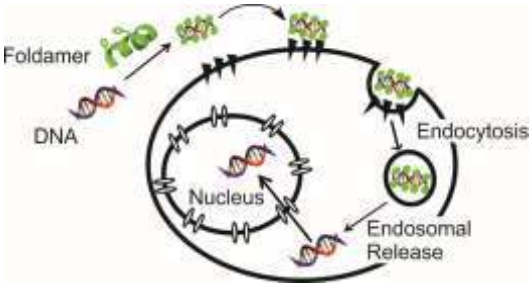
PO 022

Among the huge diversity of non-viral systems conceived to deliver Nucleic Acids (NA) into cells for therapeutic purposes, Cell-Penetrating Peptides (CPPs), exhibiting amphipathic α-helical conformation, have emerged as potent NA transfection agents. Compared to purely cationic amphiphilic lipids or polymers, CPPs are generally less cytotoxic and their length and size can be easily optimized by sequence modifications. Moreover, it has been highlighted that the presence of His residues at defined positions along the peptide sequence facilitates the release of the NA-assemblies (*i.e* proton sponge effect) from the endosomes. This is particularly the case of the synthetic peptide LAH4 that exhibits good transfection efficiency in numerous cell lines[1]. However, despite recent significant improvement, CPPs still suffer from limitations in part due to their poor biostability. *N,N'*-oligourea foldamers have been introduced to mimic the amino acid composition and α-helical conformation of biological relevant peptide sequences while exhibiting high resistance to proteolysis[2]. A pH-responsive bio-reducible Cell Penetrating Foldamer (CPF) was recently developed by thiol-dimerization of a short (*8-mer*) amphipathic oligourea sequence bearing histidine-type urea-residues. This CPF exhibits a high capacity to assemble with plasmid DNA (*pDNA*) and mediates efficient NAs delivery into cells without negatively affecting cell viability[3].



To further explore the DNA transport properties of urea-based foldamers, we have developed a methodology on solid support using Boc chemistry that facilitates access to CPFs without resorting to final HF cleavage. This method which makes use of a disulfide bridge-type resin was successfully applied to the preparation of new CPFs among which a oligourea-peptide conjugate with remarkably high transfection efficiency in various cell lines and serum-enriched medium (up to 50%). Furthermore, we found that the activity of urea-based CPFs is not restricted to DNA transfection and preliminary results suggest that our foldamers are also effective in delivering other biomolecules (*e.g.* proteins) into cells.

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Study interaction of synthetic antihypertensive and natural molecules from *Innula Viscosa* L. with dipeptidyl carboxypeptidase (ACE)

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PO 023

Abstract

Hypertension (HTN) also known as high blood pressure has been reported among the most chronic disease in the world increasing other risk as strokes, coronary disease, heart failure, renal failure, etc. Treatment of hypertension consists generally in administration of antihypertensive which are synthetic inhibitors of dipeptidyl carboxypeptidase enzyme (ACE). *Inula Viscosa L.* is plant used traditionally to treat hypertension by North African population. In present work interaction between chemical compounds from *Inula Viscosa L.* and dipeptidyl carboxypeptidase enzyme has been studied by molecular docking using scoring function in order to identify new ACE inhibitors candidate. Score interaction between natural compounds with ACE has been compared to score of complexes formed between ACE and famous active substance from commercialized antihypertensive drugs. Using Molecular Operating Environment software (MOE), dipeptidyl carboxypeptidase enzyme (4BZR PDB code) and ligands (natural and synthetic molecules) were performed and optimized under default condition (temperature, pH, salt, cutoff…etc). Docking results given by MOE software show that many compounds from *Inula Viscosa L.* which satisfy Lipinski rules of 5 have better affinity with ACE and may form stable complexes than many known inhibitors. Obtained results encourage further investigation for *in-vitro* and *in-vivo* tests.

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Synthesis of avibactam derivatives and activity on β-lactamases and peptidoglycan biosynthesis enzymes of mycobacteria

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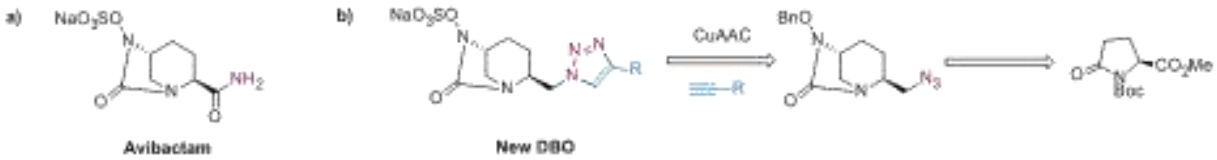
PO 024

The β-lactams remain the first-line treatment for numerous bacterial infections despite the emergence of multiple resistance mechanisms resulting from an intensive use of the drugs in the last 70 years. Thus, there is a renewed interest for β-lactams for treating infections due to *Mycobacterium tuberculosis* and *M. abscessus* because their β-lactamases can be inhibited. Avibactam (*scheme 1a*), a recently approved β-lactamase inhibitor, is original in its structure since it is based on a diazabicyclooctane (DBO) scaffold containing a cyclic urea rather than a β-lactam ring found in classical inhibitors[1].

The potential of avibactam for improving the efficacy of β-lactams against mycobacterial infections prompted us to further investigate DBOs and to develop a synthetic route to easily obtain functionalized DBOs (*scheme 1b*). We described the access to an azido derivative of the DBO scaffold of avibactam and we report a versatile route for their functionalization via the copper(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) [2].



In this work, we synthesized the azido DBO from a commercially available oxopyrrolidine in 12 steps followed by a CuAAC as a key step, providing an easy access to structural diversity in the DBO side chain. New DBOs have been prepared and showed that the resulting triazole linker retain the capacity to reach the periplasm of *M. tuberculosis* and *M. abscessus* and to inhibit their β-lactamases. In addition, to their activities against β-lactamases, we exhibited that DBOs act as slow-binding inhibitors of a model L,D-transpeptidases (Ldt_{fm}) opening an attractive strategy to obtain drugs selectively active on mycobacteria.

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Stapled Peptides to Inhibit $PCSK_9$/LDLR Interaction	
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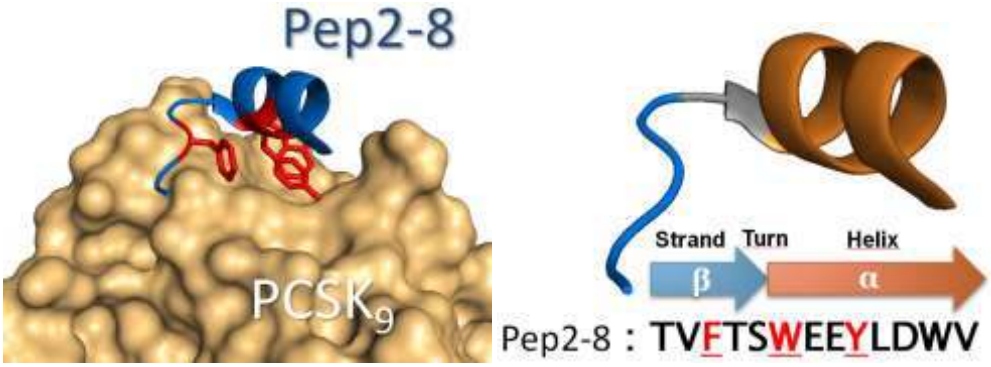
Cardiovascular diseases (CVD) represent 31% of the world mortality, being the first cause of death in the world[(a)]. Proprotein convertase subtilisin/kexin type 9 ($PCSK_9$) has been identified as a regulator of low density lipoprotein receptor (LDL_R) on the cell membrane and therefore plays a major role in CVD[(b)]. In this project, our aim is to target the interaction between $PCSK_9$ and the LDL_R. By inhibiting this protein-protein interaction (PPI), we prevent LDL_R degradation allowing the circulating LDL to recover its homeostasis and preventing cardiovascular diseases (CVD)[(c)]. As an alternative strategy to monoclonal antibodies (mAb)[(d)], our approach consists in blocking the PPI between $PCSK_9$/LDL_R with specific therapeutic peptides. In particular, we developed and strongly enhanced the affinity of the peptide Pep2-8 which was previously described as a potent $PCSK_9$/LDL_R inhibitor[(e)]. This strand-turn-helix peptide composed of 13 residues was modified by combining the stapling strategy and other approaches such as the structure inducing probes (SIP) technology[(f)]. The structures of the various synthesized peptides were analysed by circular dichroism and NMR, and their affinity for $PCSK_9$ was determined by Surface Plasmon Resonance (SPR). At last, the LDL-uptake rate obtained from the best compounds was measured.



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Transition state analogues for the structural study of m^{6}A-RNA methyltransferases.

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PO 026

Exploration of RNA modifications is one of the most fast growing field in biology. To date, a hundred of these modifications have been identified and among them, methylation is certainly one of the most studied.[(a)] RNA methyltransferases (RNMTs) catalyze the methylation of RNA using S-adenosyl-L-methionine (SAM) as the cofactor.[(b)] It has been shown that deregulation of the methylation process leads to the development of human diseases such as cancers, metabolic disorders or neurodegenerative diseases.[(c)] The formation of N6-methyladenosine (m^{6}A) is the most prevalent internal modification observed in RNA (including rRNA, tRNA, mRNA and long-non-coding RNA) in eukaryotes, viruses and bacteria. Recently, it was defined as a dynamic process[(d)] and its disturbance correlated to human diseases, such as cancer emphasizing its dramatic importance.[(e)] However, despite the key biological roles of m^{6}A RNA modification, RNMTs remain underexplored by the medicinal chemistry community because of the lack of structural data. Indeed, no crystal structure involving the three partners of the reaction of methylation has been solved yet.

In this context, one of our goals consists in the synthesis of new tools for the study of these RNMTs. Here, we will present the design and the synthesis of the first transition state analogues for RNMTs that catalyze the methylation of adenosine at position 6.[(f)] Structural studies have been conducted on the model bacterial methyltransferase RlmJ and the first crystal structures between RlmJ and two of the synthesized SAM-adenosine conjugates have been obtained.

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Conception, synthèse et évaluation de peptides vecteurs et conjugués vectorisés qui facilitent la délivrance de molécules d'intérêt thérapeutique dans les organes, en particulier le cerveau et les tumeurs.	***PO 027***

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Summary:

Addressing active substances to target organs is a major challenge for the modern pharmaceutical industry. Indeed, the number of "biomolecule" drugs (proteins, antibodies, oligonucleotides, peptides, etc.) represents each year an increasingly important share of all evaluated drug-candidates compared to conventional therapeutic molecules derived from organic synthesis of drugs. These biomolecules are, by their very nature, unable to cross biological barriers, be it the plasma membrane to reach an intracellular target or the blood-brain barrier, gateway to the central nervous system. Thus these new forms of active ingredients require specific addressing that allows them to reach their target and thus obtain the desired therapeutic effect, with a minimum of side effects.

VECT-HORUS has created a unique VECTrans® technology platform in Europe, specializing in the development of "vector" molecules targeting specific receptors, particularly the LDL (Low Density Lipoprotein) receptor family. The aim of this thesis will be to conjugate Vect-Horus peptides-vectors to imaging or therapeutic agents, in order to favor their specific targeting to the brain and other pathological organs or tissues such as tumors. This thesis, at the interface chemistry-biology, will use organic synthesis, peptide synthesis, bioconjugation chemistry but also biochemistry techniques to evaluate the molecules prepared. It will benefit from the strong support of the Vect-Horus biologist teams who will be able to test these molecules in vitro and in vivo, so as to be at their best in the evaluation of molecules.

Bibliographic references:
(a)
(b)
(c)

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Synthesis and evaluation of macrocycle peptide disrupting LDH tetramerization

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PO 028

The alteration of the elements involved in metabolic pathways is one of the strategies adopted by cancer cells to sustain their anabolic growth and proliferation. Lactate dehydrogenase (**LDH**) is involved in these metabolic adaptations. **LDH** is a tetrameric enzyme constituted of two isoforms, LDHA and LDHB. It catalyzes the interconversion of lactate to pyruvate and is involved in various pathogenic pathways such as invasiveness1[1,2], angiogenesis[2] and autophagy[1] and constitutes therefore a promising target for cancer therapy. **LDH** is active only in its tetrameric state. An octapeptide (**LB8**) was recently identified to interact directly with LDH tetramerization site. From these results a new strategy targeting LDH tetrameric state to inhibit its activity is emerging.

The aim of our project is to constrain **LB8** into its active conformation in order to improve its potency. We therefore designed, synthetized and evaluated a library of cyclic peptide that shows increased potency compared to **LB8** in addition to prevent the formation of LDH tetramers. Using F-moc solide phase peptide synthesis, we performed a cysteine scan by replacing LB8 non interacting amino acids to cysteines. Using a-helix promoting alkylating agents we then cyclized and constrained the linear peptide into a-helical conformation. Cyclic peptides are then analyzed and purified using HPLC-MS. The cyclic peptides are then evaluated for their potency using MicroScale Thermophoresis (MST).

Preliminary results show a 30 fold increase in potency compared to **LB8**. Further optimization is therefore being conducted to reach for the best interacting macrocycle. These macrocycle will then undergo further evaluation in order to validate LDH tetrameric disruption as a new strategy in anticancer therapy.

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Novel Selenoureas As Chemotherapeutic Agents In Several Tumor Cancer Cell Lines

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PO 030

KEYWORDS: antioxidant, cancer, selenium, selenourea

Oxidative stress is a common pathogenic factor associated with aging processes and is involved in various diseases, including cancer. Several selenocompounds, such as ebselen and PBISe, have demonstrated to regulate the cell redox status and they are promising compounds for therapy and prevention of diseases directly related with reactive oxygen species (ROS) generation [1, 2]. For these reasons, we consider that Se might be an important tool for the development of new drugs.

Moreover, *N*,*N*'-disubstituted selenourea derivatives have been reported as nontoxic polyfunctional antioxidants with higher potency than sulfur or oxygen analogs [3]. In our research group different acylselenourea derivatives have been proven as potent agents against different types of cancer, such as breast, colon or prostate [4].

Taking all these facts into account, herein we present the design, synthesis and *in vitro* cell growth inhibition and radical scavenging activity for 32 new *N*,*N*'-disubstituted selenoureas (*Figure 1*).

Eight compounds achived IC_{50} values lower than 10 µM in HTB-54 (lung) and MCF-7 (breast) and different colon cancer cell lines. Additionally, at low doses most of the synthesized compounds shown outstanding radical scavenging capacity, comparable to the reference ascorbic acid.

To conclude, selenourea-based analogs might be consider as privileged frameworks to develop dual antioxidant and antitumoral agents.

R_1= H, CH_3, OCH_3, Cl, CN
R_2= Aromatic, heteroaromatic, aliphatic

Figure 8 : *General scheme of the N,N´-disubstituted selenoureas.*

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Design of Antibody Radiolabeled Drug Conjugates using ^{195m}Pt-Carboplatin for cancerology.	***PO 031***

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

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

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

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

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Interaction of functionalized naphthalenophanes with abasic sites in DNA and their cytotoxic effects

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PO 032

In the context of cancer therapy, most DNA-alkylating drugs (e.g., MMS or temozolomide) induce DNA damage leading to the formation of abasic (AP: apurinic / apyrimidinic) sites. The latter are processed by the base excision repair (BER) pathway thanks to the action of a key enzyme, APE1 (AP endonuclease 1). The DNA repair activity of APE1 was identified as the major source of radio- and chemoresistance in certain cancers, especially in glioblastoma. Several studies validated the BER pathway and, particularly, APE1 as important drug targets for improvement of efficacy of anti-cancer drugs. However, instead of direct inhibition of the enzyme, an alternative strategy can rely on targeting its substrate: the AP sites in DNA (Fig. 1a).[a] Herein, we systematically studied a novel generation of AP-site ligands, sharing the common naphthalenophane scaffold but bearing a variety of substituents (Fig. 1b). Our results demonstrate that most of these ligands strongly and selectively bind to AP-sites in DNA and inhibit the APE1-induced hydrolysis *in vitro* (Fig. 1a, *i*).[b] On the other hand, we evidenced the intrinsic AP-site cleavage activity of macrocycles by a mechanism different from that of APE1 (*ii*) and whose efficiency could be modulated by the molecular design of naphthalenophanes. At the same time, we observed an unprecedented formation of a covalent DNA-ligand adduct with one of ligands (*iii*). Finally, most of these bis-naphthalene ligands showed a cytotoxic effect on cancerous cell lines in the µM range and of interest, one of them showed a synergetic effect *in cellulo* with a DNA-alkylating drug in a resistant glioblastoma cell line (T98G).

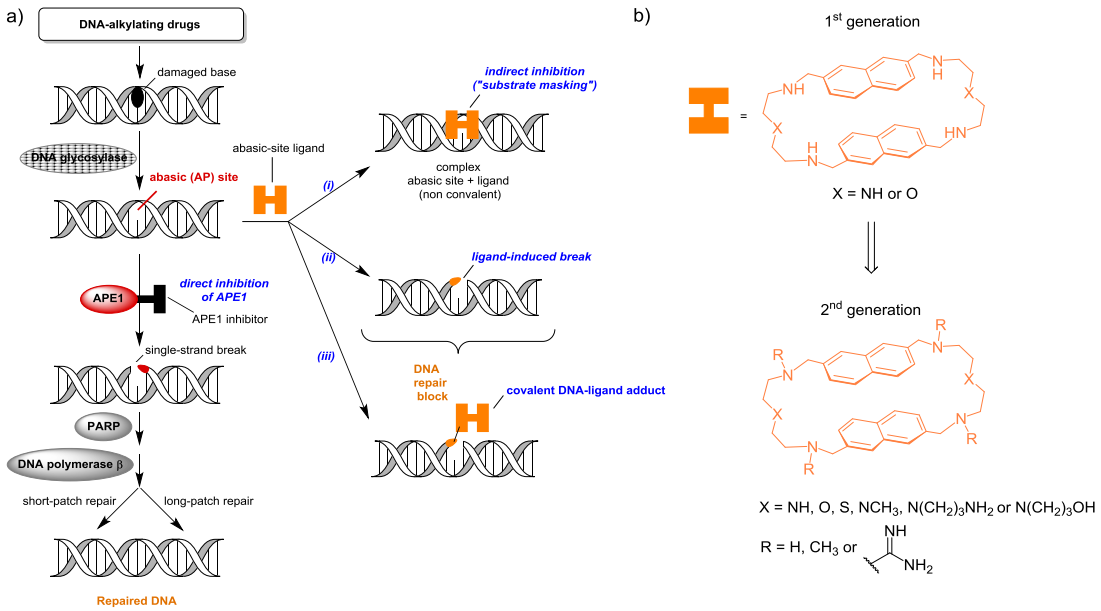

Fig. 1. a) Scheme of the BER DNA repair pathway and ligand-induced interference; b) structures of naphthalenophanes.

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Synthesis of new aminopyrazole analogues with promising anti-leishmaniosis activity: A University-DNDi Open Synthesis Project

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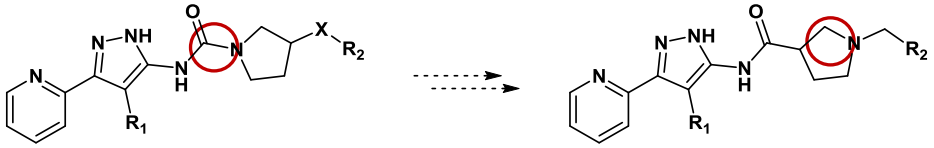
[1] School of Pharmaceutical Sciences, University of Geneva, Rue Michel-Servet 1, 1206 Genève [2] Students from the second year of the bachelor in Pharmaceutical Sciences performing pharmaceutical chemistry practical exercise, University of Geneva, Rue Michel-Servet 1, 1206 Genève [3] Drugs for Neglected Diseases initiative, 15 Chemin Louis-Dunant, 1202 Geneva

PO 033

Introduction: Leishmaniosis is a neglected tropical disease, an illness that kills up to 30,000 people yearly. Existing drugs have serious drawbacks in terms of safety, resistance, stability, difficulty of administration and cost. Thus, there is a need for new treatments. The aminopyrazole class of compounds originally from Pfizer has shown promising early profiles for the treatment of both visceral and cutaneous leishmaniosis. [1,2,3]

Aim: In the frame of an Open Synthesis Network (OSN) between the University of Geneva and the Drugs for Neglected Diseases initiative (DNDi), we aimed at synthetizing new aminopyrazole analogues for early stage discovery for new treatments for leishmaniosis.



DNDi lead chemotype — Targeted analogues

Methods: In order to explore the aminopyrazole chemotypes, we set up a 5-steps synthesis starting from (R/S)-β-proline, 14 different aldehydes and 3 different aromatic cores to obtain 42 different products. The two key reactions are reductive amination, during which a first structural diversification occurs and the last coupling by amidation that led to the final expected compounds. Compounds biological activity has been assessed on *Leishmania infantum* and cytotoxicity on human and murine fibroblasts.

Results: This multi-steps synthesis led to 14 new compounds that have been fully characterized by HRMS, ^{1}H-NMR, ^{13}C-NMR, IR and HPLC. Despite difficulties occurring in the amidation coupling, a new valid protocol was found to obtain the expected compounds in a sufficient yield (32-36%) and purities > 95%. All final compounds have been tested *in vitro* for both efficacy and toxicity. Two of them showed high potency against *Leishmania infantum* (IC_{50} 0.3 and 1.5 microM) and a selectivity index (CC_{50}/IC_{50}) ranging from 27 to 213.

Conclusions: The open source nature of this project aimed at deepening the learning of laboratory work in the context of students R&D practical work. The collaborative spirit of the students has led to the successful synthesis output and the development of a scientific rigor of work, which includes the preparation and the follow-up plans of experiment. The promising anti-leishmaniosis activity clearly indicates an SAR and the possibility of further exploring the current chemotype to improve compounds efficacy and selectivity. The two most potent compounds are undergoing in vitro ADME studies to prepare for subsequent *in vivo* efficacy testing.

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Endogenous albumin as a bioorthogonal platform for the *in vivo* synthesis of enzyme-responsive drug delivery systems

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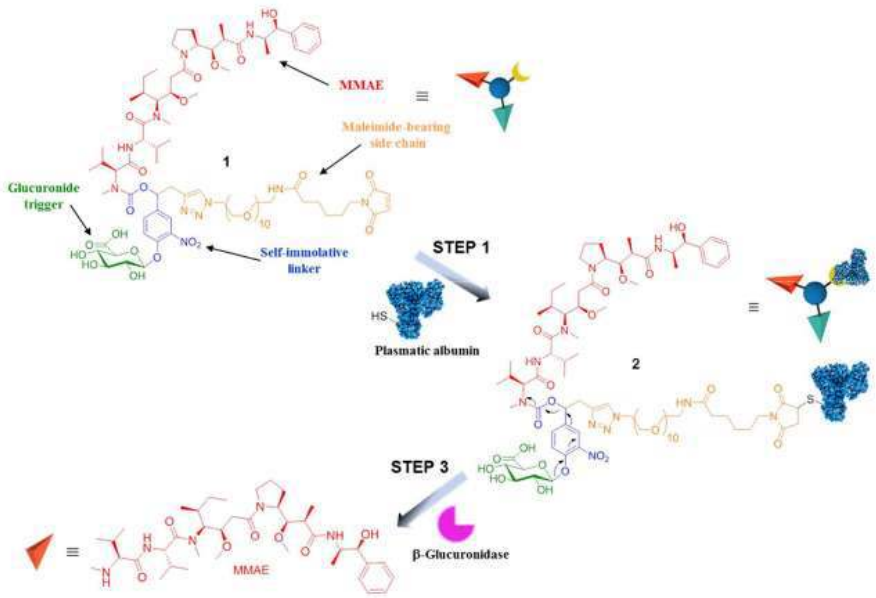
PO 034

The controlled delivery of anticancer agents in malignant tissues is an emerging therapeutic strategy that reduces dose-limiting adverse effects associated with traditional chemotherapy. The vast majority of drug delivery systems have been designed to recognize a specific cell surface marker (*e.g.* antigens and receptors), penetrate inside cancer cells through endocytosis and trigger the release of highly toxic compounds in response to an intracellular biochemical stimulus. Numerous internalizing ligand- and antibody-drug conjugates have been assessed in humans, leading recently to the marketing of brentuximab vedotin and trastuzumab emtansine for applications in oncology. However, the scope of such targeting devices is restricted to only the treatment of tumors expressing a high level of the targeted cell surface marker.

Recently, we demonstrated that the targeting of the tumor microenvironment by means of β-glucuronidase-responsive albumin-binding prodrug is a selective, efficient and potentially versatile therapeutic strategy.[1, 2] This targeting strategy produces outstanding therapeutic efficacy on orthotopic triple-negative mammary and pancreatic tumors in mice, leading to impressive reduction or even disappearance of tumors without inducing side effects.

As an extension of this work, we designed a multivalent chemical platform allowing the construction of various β-glucuronidase-responsive albumin-binding prodrugs *in vivo* using biorthogonal chemistry. This study will be presented.



Scheme 1 : The principle of tumour targeting with the *β*-glucuronidase-responsive β-glucuronidase-responsive albumin-binding prodrugs

Bibliographic references:

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Searching for New Neuroprotective Agents: Design, Synthesis and Biological Evaluation of Piperine-derived Cationic Compounds

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PO 035

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

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

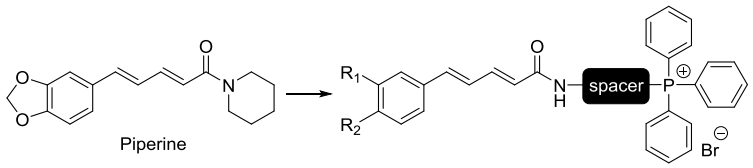

Figure 1: Chemical structure of piperine and derivatives thereof.

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

Acknowledgements: This project was supported by Foundation for Science and Technology (FCT) and FEDER/COMPETE (Grants UID/QUI/00081/2015, POCI-01-0145-FEDER-006980, and NORTE-01-0145-FEDER-000028). D. Chavarria (SFRH/BD/108119/2015) grant was also supported by FCT and FEDER/COMPETE funds.

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Development and characterization of new polymeric systems containing lipoic acid	PO 036

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Objectives: In recent years, the interest in using different polymeric systems in order to improve the pharmacokinetic and pharmacological profile of some drugs significantly increased. Chitosan is a non-toxic, biocompatible, biodegradable biopolymer for which significant pharmacological effects have been revealed**.** For lipoic acid, the literature data offer scientific evidence concerning its role in amelioration of diabetic neuropathy, decreasing insulin resistance, reducing the oxidative stress. The aim of the study was the development and characterization of some polymeric systems represented by microparticles, using chitosan matrix which included lipoic acid. **Material and Method:** Drug-polymer systems were obtained by inotropic gelation, using pentasodium tripolyphosphate (TPP) as cross-linking agent. Medium molecular weight chitosan 1.5% was used, the concentration of cross-linking agent was 2% and the chitosan: lipoic acid ratio was 1:0.5. The microparticles obtained were characterized in terms of size, structure and morphology using IR Spectroscopy and Scanning Electronic Microscopy (SEM). The hydration ability was studied in distilled water and simulated gastric fluid. The percentage of drug loading and the release of the drug from the polymeric matrix was determined using a HPLC method. **Results:** The size of the microparticles obtained ranged between 723.1 and 916.3 µm. The IR analyses proved the drug encapsulation and the SEM analyses showed the surface morphology. The drug loading percentage was 35.84%; the systems obtained showed good hydration ability and the percentage of drug release from the polymeric matrix was 84.79%. **Conclusions:** The developed chitosan-lipoic acid systems represent a step in the attempt to modulate the pharmacokinetic and pharmacological profile of lipoic acid.

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Identification of Small Allosteric Inhibitors of Cell Cycle Proteins for the Treatment of CCNE1-amplified Cancers

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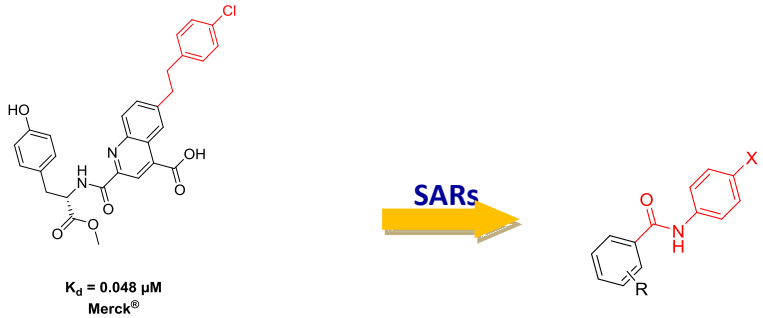
PO 037

CCNE1 encodes for the cell cycle regulator cyclin E which binds to cyclin-dependent kinase-2 (CDK2) to drive cells through a G1/S cell cycle transition.[1] Genetic perturbation of CDK2 indicates that its function is not essential for mitosis to complete in normal tissue development and homeostasis. In contrast, tumour cells in which CCNE1 is amplified are critically-dependent on CDK2 and cyclin E for survival. Such "oncogene-addiction" to CCNE1 occurs in a significant cohort of high-grade serous ovarian cancer (HGSOC) and confers a particularly poor patient outcome to current therapy. An estimated 190,000 women are diagnosed with HGSOC each year and approximately 20 -25% of these tumours contain an amplification of the CCNE1 gene.[2] Although there have been many attempts to pharmacologically-inhibit CDK2 kinase activity, these have resulted in the development of ATP-competitive inhibitors that do not have sufficient selectivity against other CDKs (involved in essential cellular processes) to exert amplicon-dependent activity.[3] There is, therefore, a significant need to identify novel ways to interfere with CDK/cyclin function.

Recent research has revealed a hydrophobic pocket in CDK2 that is independent of the ATP binding site. Importantly, compounds that bind to this allosteric site have been shown to cause structural rearrangements that render the enzyme unable to interact with cyclin E1.[4] This newly identified allosteric site offers an alternative route to CDK2 inhibition that could potentially lead to a new class of anticancer drug. In 2014, Merck® published a series of quinoline ATP competitive inhibitors which bind to the hinge region of the CDK2 protein and stretch into the allosteric pocket.[5] A pharmacophore mapping approach was undertaken and fragments bearing the *para*-chloro phenyl hydrophobic 'head' were synthesised. The syntheses developed and a recently resolved co-crystal structure of one of the new inhibitors bound in the allosteric site of CDK2 will be disclosed.



K_d = 0.048 µM
Merck®

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Access to tricyclic fused 1,4-Benzodiazepin-5-ones from pipecolic derivatives.

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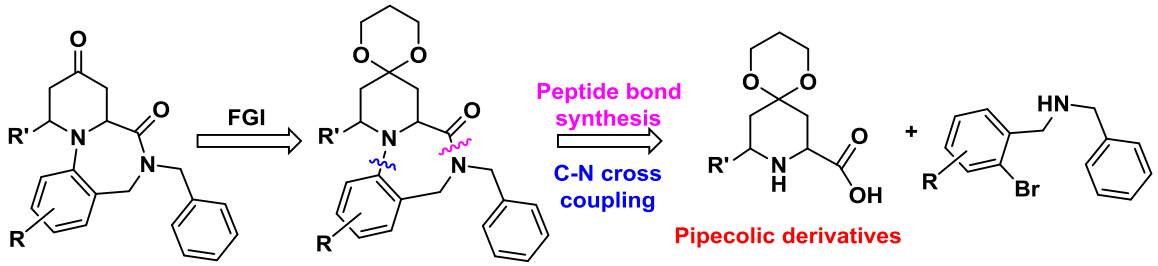
PO 039

The 1,4-benzodiazepin-one scaffold is still regarded as a "privileged structure"[a] for drug discovery and development. Though, as a consequence, this skeleton is used as core of several pharmaceutically important families. It can be divided into three different sub-families, namely 1,4-diazepin-2-one, 1,4-diazepin-3-one and 1,4-diazepin-5-one. The literature showed that 1,4-diazepin-2-one and 1,4-diazepin-5-one types are well described but only few reports are devoted to 1,4-diazepin-3-one type compounds which has been used mainly as □-turn peptidomimetics. Moreover, fused polycyclic benzodiazepinones which have shown inhancement in their biological activities have promoted interest in such heterocyclic structures and consequently new structural analogs with new applications have appeared in the literature. [b] We have recently reported chiral routes for the synthesis of 2,6-disubstituted piperidin-4-one [c] and its application to the synthesis of natural products. So, we can extend the methodology to chiral compounds which can be medicinally relevant heterocycles.



Inspired by these concepts, we will present a new series of fused heterocyclic 1,4-benzodiazepin-3-one in which the heterocyclic ring is a substituted piperidine based on a new strategy starting from pipecolic acid derivatives and substituted bromo di-benzylamines.

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Synthesis of anti-tuberculosis compounds

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PO 040

Although the development of drugs and vaccine to fight against tuberculosis has permitted to decrease the number of people contaminated, its eradication is still a myth. Indeed, it remains one of the ten leading causes of death worldwide [(a)]. *Mycobacterium tuberculosis* (*M.tb*) also named Koch's Bacillus is responsible for this infectious disease. The current treatments meet severe problems of observance, latency and resistance, which is a very worrying problem. Indeed, the WHO estimated that in 2016, 600 000 patients were infected by a resistant strain of *M.tb* [(a)]. One of the challenges of the century is to succeed in finding new drugs, to propose a new first-line regimen.

In that purpose, a phenotypic screening on *Mycobacterium tuberculosis* [(b)] allowed us to find new scaffolds that have not yet been described in the literature. More than 25 000 compounds were tested on macrophages infected by the virulent strain of *M.tb H37Rv-GFP*. The results of the screening revealed three families of compounds that are active on *M.tb*. One of them displays a benzotriazepine core (*Figure 1*) substituted in positions 2 and 5. Nevertheless, the compounds present two important physico-chemical drawbacks: the lack of solubility and the lack of chemical stability in biological media. To solve the solubility issue, we present the synthesis of new pyridinotriazepine analogs and benzotriazepines substituted in position 2 by a pyridine using two different pathways, in order to decrease the lipophilicity of the molecules. Then, for the instability problems, analysis of the degradation products revealed that the benzotriazepine core is prone to hydrolysis. Therefore, we tried to replace it by a benzodiazepine core. A new synthetic pathway was therefore required and we present herein the optimization of the first steps.

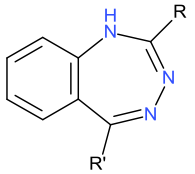

Figure 9.General structure of the benzotriazepines.

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Incorporation of dichloroacetate-units into polysaccharides and humic substances for achieving its controllable release.

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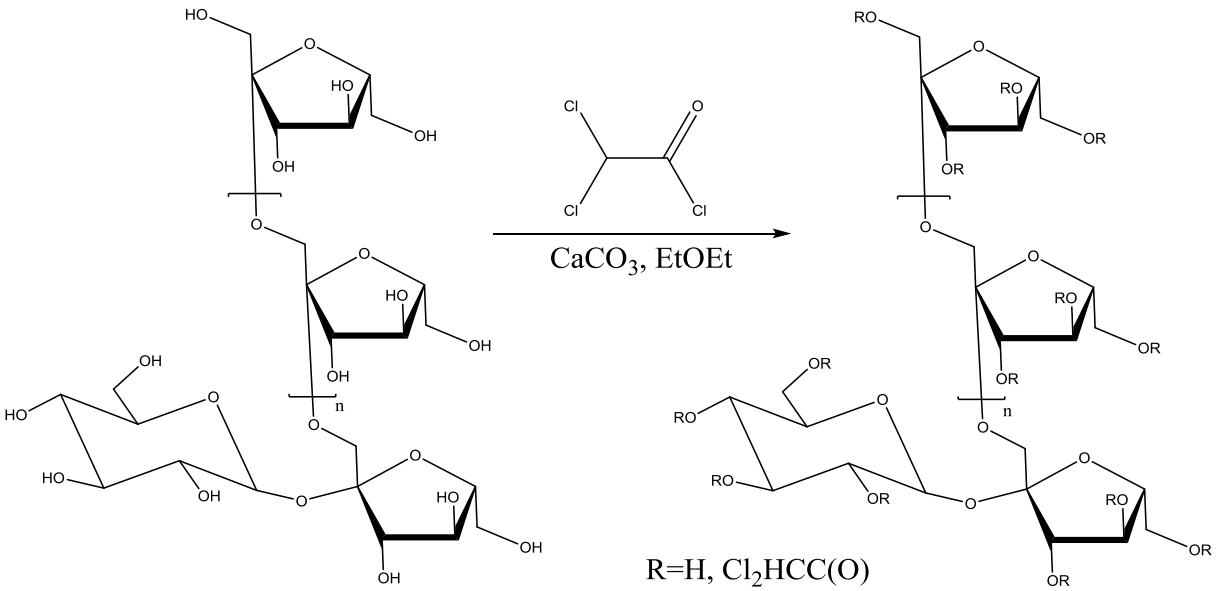
PO 041

Dichloroacetate (DCA) acts selectively on tumor cells, which possess reverse metabolism. However, the therapeutic doses in clinical trials remain very high. This may be associated with low bioavailability and poor penetration of DCA-anion through the cell membrane. In addition, the structure of this compound is not optimal for binding with the site of the protein target. Therefore, it was proposed to modify DCA by incorporation into natural non-toxic polymeric carriers which are enriched with alcoholic hydroxyls or phenolic groups. It is assumed that such a modification will slow down the release of DCA, as well as expand its therapeutic window and reduce toxicity. We have tried few approaches to incorporate DCA into polysaccharide structure (inulin). Direct acylation of inulin with 1,2-dichloroacetic acid chloride (solvent - THF, catalytic amounts of Py as the base) did not lead to formation of the expected product. The reaction products were identified using 1H and 13C NMR spectroscopy . Allternative technique was applied for inulin acylation (diethyl ether was used as a solvent, and calcium carbonate – as a base). The acylated product was analyzed using 2D NMR which showed the presence of acetylated inuline. This improved method will befurther applied to acylation of humic substances. This will allow changing the content of components, since humic substances contain not only carbohydrate groups, but also phenolic ones. The next task is to measure the rate of DCA release from the modified carriers.



Acknowledgments: This work was supported by the Russian Foundation for Basic Research (Project 17-03-01320)

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Metal Complexes With Enantiopure Oxime Ligands And Its Applications As Anticancer Agents.	***PO 042***

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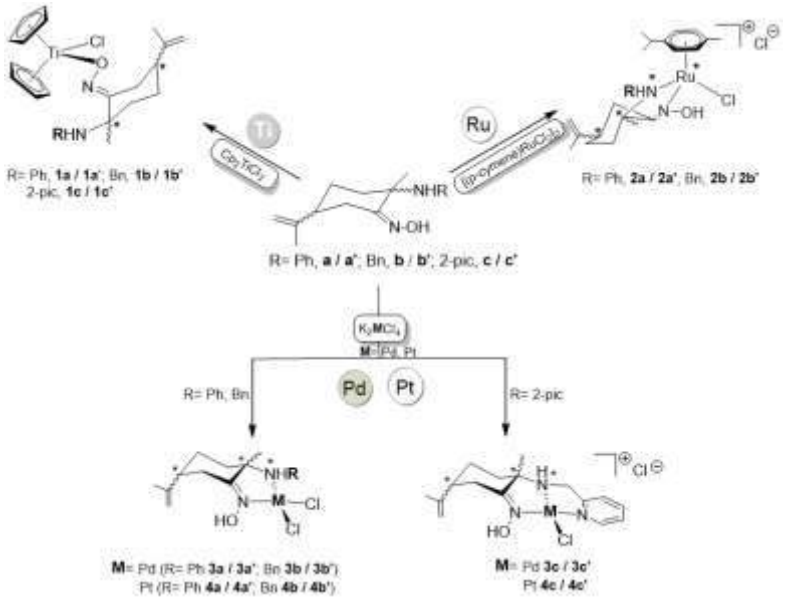
Chemically modified natural substances are promising ligands for the synthesis of novel coordination compounds with potential clinical applications. In this regard, chiral ligands are of particular interest[a], since the effect of stereochemistry on biological activity is of great importance in medicinal chemistry. Terpenes, in particular R- and S-limonene, are inexpensive natural products, commercially available in optically pure form and easily tailored by stereoselective functionalization[b]. Amine and oxime functional groups are attractive ligands for the synthesis of potential metal-based anticancer drugs. Both functions can improve water solubility[c] of the resulting metal compounds due to their ability to stablish hydrogen bonds. Furthermore, some reported oxime compounds caused beneficial biological effects for cancer treatment[d-g].



Scheme 1. Synthesis of novel optically active amino-oximato titanium compounds and amino-oxime ruthenium, palladium and platinum compounds.

Herein, we report a comparative study of the anticancer activity, DNA-drug interactions and possible binding modes of novel chiral titanium[f], ruthenium[e,g], palladium and platinum compounds with amino-oxime ligands (Scheme 1). A comparative study of the *in vitro* effect of different metal complexes and of their respectives enantiomers will be reported.

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Novel arene Ru(II) compounds with N- phenanthroline glycosylamine ligands as potential anticancer agents

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PO 043

The search of new metal compounds which could act as antitumor drugs with novel mechanisms of action different from those found in cis-platin, has become an emerging area of research. Many carbohydrates are known to be generally good binders for nucleic acids while Warburg effect is recognized as one of the hallmarks of cancer. Thus, functionalization of drugs with carbohydrates is an anticancer strategy that has gained great interest in recent years[(a-c)]. On the other hand, polypyridyl compounds such as 1,10-phenanthroline are powerful bidentate metal chelating ligands, and a variety of metal compounds have been extensively studied for their anticancer properties, usually related with their ability to act as DNA intercalators and groove binders[(d)]. Furthermore, they serve as scaffolds for several potent stabilizers of DNA G-quadruplexes, which are being investigated as potential targets for anticancer drug development[(e)]. Herein, we report the synthesis and characterization of a new family of water soluble arene Ru(II) compounds of general formula [RuCl(p-cymene){(N-R)5-amino-1,10-phenanthroline}]Cl; R = Glc, Rham, Xyl, Man (glucose Glc, rhamnose Rham, xylose Xyl and mannose Man). A comparative study of their DNA interactions and cytotoxic activity with those of N-phenanthroline glycosylamine organic derivatives[(f)] is currently under investigation.

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Development and characterization of olive oil-in-water nanoemulsions as delivery vehicles of lipophilic compounds

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PO 044

Nowadays, the interest in improving the efficiency of bioactive compounds has gained the attention of pharmaceutical industry. For that purpose, of particular interest is the development and use of biocompatible food-grade systems that will serve as carriers of compounds of pharmaceutical interest and various bioactive substances such as antioxidants, vitamins etc. One of the most widespread ways of administering drugs is by oral route because of the benefits it offers. However, to overcome the disadvantages and restrictions of this particular method, notable useful is the development of nanoemulsions in which it is possible to encapsulate the desired substances, while offering advantages such as increasing bioavailability and solubility, protecting the functional substance from degradation and efficient delivery of active ingredients (a).

The purpose of the study is to develop and structurally characterize biocompatible, non-toxic oil-in-water (O/W) nanoemulsions in order to encapsulate lipophilic compounds. The proposed system consists of: a continuous aqueous phase, a mixture of Tween 20 and lecithin as surfactants and extra virgin olive oil (EVOO) of high concentration of polyphenols as the dispersed oil phase. To examine the efficiency of the system, Vitamin D was used as a model lipophilic compound for encapsulation. Vitamin D (cholecalciferol) was dissolved within the lipid phase prior to emulsification.

Structural and antioxidant studies of the nanoemulsions were conducted both in the presence and in absence of the vitamin. Using the Dynamic Light Scattering Technique (DLS), the nanodroplet diameter, the polydispersity index, and the stability of the nanoemulsions over time were examined. Also, interfacial properties of nanoemulsions were investigated using Electron Paramagnetic Resonance (EPR) spectroscopy employing the amphiphilic spin probe, 5-doxylstearic acid (5-DSA) (b). From the characteristics of the EPR spectra we have calculated the order parameter (S) and the rotational correlation time (τ_R) in order to investigate membrane dynamics and the degree of vitamin's embedment. Using EPR and the free radical TEMPOL we have also evaluated the antioxidant activity of vitamin D upon encapsulation in EVOO nanoemulsions (c).

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Synthesis of 3D Fragments for the Exploration of Novel Chemical Space

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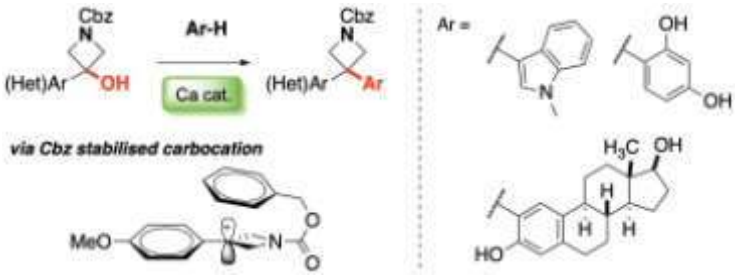
PO 045

New synthetic methodology is necessary in order to synthesize innovative scaffolds capable of exploring novel chemical space. Saturated nitrogen heterocycles are among the most abundant pharmacophores in pharmaceutical products, dominated by five- and six-membered rings.[(a)] In marked contrast, 4-membered azetidines are much less explored, despite offering attractive physicochemical properties for drug discovery.[(b)]

We focused on 3,3-diarylazetidine derivatives because their potential to have 3D shape, good solubility and low molecular weight. The nitrogen atom provides an additional vector for functionalization. 3,3-Diaryloxetanes have recently received interest within medicinal chemistry[(c)] as novel scaffolds and we were intrigued by possible rapid, efficient and robust routes to produce 3,3-diarylazetidines.

3,3-Diarylazetidines are prepared in high yield from *N*-Cbz azetidinols in a calcium(II)-catalyzed Friedel–Crafts alkylation of (hetero)aromatics and phenols, including complex phenols such as β-estradiol.[(d)] The product azetidines can be derivatized to druglike compounds through the azetidine nitrogen and the aromatic groups. The *N*-Cbz group is crucial to reactivity by providing stabilization of an intermediate carbocation on the four-membered ring.



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pH Low Insertion Peptides (pHLIP) drug conjugates as drug delivery system for cancer therapy

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PO 046

Targeted drug delivery is a very promising area of research for cancer therapy.[a] In the field of cancer, the specific targeting of tumors allows to reduce potential side effects of non-selective cytotoxic drugs. In this context, pH Low Insertion Peptide (pHLIP) recently emerged as a very promising strategy to deliver drugs into the tumors.[b] These peptides have the capacity to structure themselves and insert into membranes upon weak acidification of the extracellular media, that is a characteristic of cancer cells. This family, derived from the bacteriorhodopsin C helix, represents a unique class of water-soluble membrane polypeptides which were found to insert across a membrane to form a stable transmembrane α-helix.

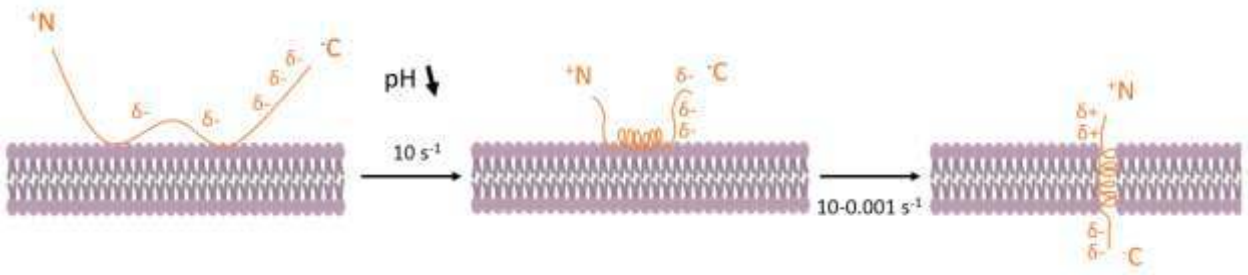

Figure 1. Representation of pHLIP interaction with lipid bilayer of membrane.[c]

Specifically, we aim to study, develop and apply the pHLIP technology in two particular fields of research: the lipid tumor metabolism and the T cell response to acidification. It should be noted that this technology might also prove to be relevant in other diseases such as ischemia, stroke or infection.

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5-lipoxygenase inhibitors derived from ω-oxidized tocotrienols

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PO 047

Prostaglandins and leukotriens (LTs), produced from arachidonic acid by cyclo-oxygenase and 5-lipoxygenase (5-LOX) pathways respectively, are key mediators in inflammation[1]. Our recent results showed an anti-inflammatory activity of ω-oxidized tocotrienols by inhibiting 5-LOX[2]. Amongst these compounds, δ-garcinoic acid (δ-GA) was the most active one. It inhibited LTs formation in 5-LOX and polymorphonuclear leukocyte assays with IC_{50} at 0.04 ± 0.02 μM and 0.35 ± 0.08 μM respectively. In order to further understand the mode of action and to improve the 5-LOX inhibitory activity of δ-GA, the rational design of a series of the corresponding amides followed by their semisynthesis were performed. Here, we present a dataset of novel δ-GA-based anti-inflammatory agents with promising *in vitro* and *in cellulo* anti-inflammatory activity.

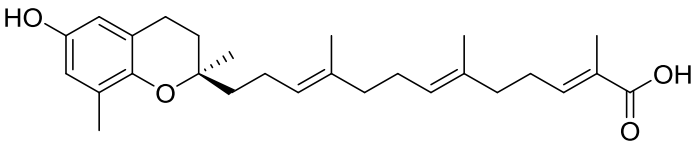

Figure 10 : Structure of δ-garcinoic acid

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Synthesis of new derivatives of phenolic metabolites: Modulating neuroinflammation, increasing neuroprotection

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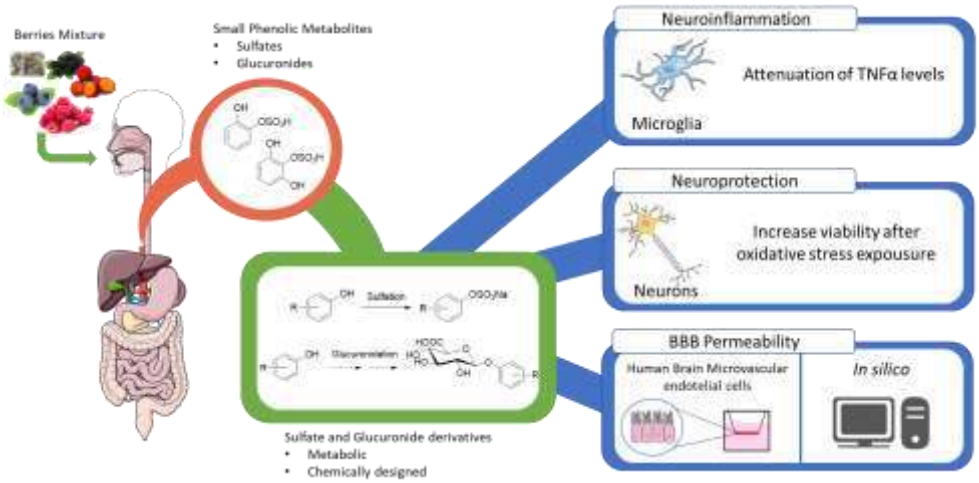
PO 048



Dietary molecules have been described to alter multiple markers of neuroinflammation thus modulating microglia response and neuronal cytotoxicity. Nonetheless, information considering small dietary metabolites, shown in human blood circulation, have been limited. Previously, in a human intervention study, we have shown small phenolic metabolites, capable of crossing the blood brain barrier and decrease the release of inflammatory markers, such as TNFα, at physiological concentrations, in microglia cells upon an inflammatory insult. [(a)]

Novel phenolic derivatives, including sulphate and glucuronide conjugates were chemically synthesized. The molecules were evaluated for their role in reducing TNFα released by microglia cells while their ability to cross the blood brain barrier conducted through an *in silico* study and are currently being analysed in a transwell model using human brain microvascular endothelial cells. Furthermore, these compounds were also evaluated in differentiated SH-SY5Y neuroblastoma cells, for the ability to prevent oxidative damage hence demonstrating their neuroprotection capacity.

Together our results elucidate the effects of small dietary metabolites and derivatives in mitigating neuroinflammation and deciphering their role in the prevention of neurodegenerative diseases.

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Novel approach for the synthesis of new indolo[2,3-*b*]quinolines and evaluation of their antimicrobial properties	***PO 049***

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Neocryptolepine, which possesses an indolo[2,3-*b*]quinoline structure, is an alkaloid isolated from the roots of *Cryptolepis sanguinolenta* by Pieters in 1996. Since this discovery these structures have raised the interest of several research teams[(a)] due to their numerous biological properties such as anticancer, antimalaria or antibacterial activities. In regard to those interesting biological properties we propose an innovative process for the synthesis of new indolo[2,3-*b*]quinolines based on a radical domino reaction as key step. This reaction, developed by our team combines an 5-*exo*-*trig* cyclization and a Smiles rearrangement.[(b)] This strategy permitted the access to a scaffold possessing various sites of pharmacomodulations for the elaboration of SAR studies. Fighting against the resistance phenomenon of antimicrobial agents, first representatives were screened in collaboration with Bios team (EA 4691, URCA) against multiple bacterial targets and showed interesting properties.

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Synthesis, characterization and *in vitro* biological evaluation of 3- (4-hydroxy-3-methoxy-phenyl) acrylic acid derivatives with thiazolidin-4-one structure

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PO 050

The study objective. By structural modulation of 4-hydroxy-3-methoxycinnamic acid (AF) new compounds having thiazolidin-4-one structure have been synthesized. The compounds were physiochemically and spectral characterized and biologically assessed by *in vitro* methods. **Materials and methods:** The 2- (R-phenyl) -3- [3- (4-hydroxy-3-methoxyphenyl) acrylamido] thiazolidin-4-one derivatives were obtained by condensing 3- (4-hydroxy-3-methoxyphenyl) acryloyl hydrazine (3), aromatic aldehydes (R = H, 4-chloro-4-fluorobenzyl) 2,6-dichloro-4-dimethylamino / 2,3-dihydroxy / 4-hydroxy-3-methoxy) and excess thioglycolic acid in freshly distilled toluene medium. The formation of the 1,3-thiazolin-4-one ring is favored by removing the water resulting from the condensation and cyclization reaction by azeotropic distillation using the Dien-Stark device. The *in vitro* antioxidant potential was assessed by determining the antioxidant effect against the $ABTS^+$ cation radical and the DPPH radical. The *in vitro* anti-inflammatory potential was evaluated using the erythrocyte membrane stability test and the inhibition of serum albumin degradation. **Results**: Twelve derivatives of 2- (R-phenyl) -3- [3- (4-hydroxy-3-methoxyphenyl) acrylamido] thiazolidin-4-one (**5a-l**) were synthesized. They were physico-chemical and spectral (IR and ^{1}H-NMR) characterized. Several of the synthesized compounds showed good antiradical activity, which supports the favorable influence of structural modulations of 4-hydroxy-3-methoxycinnamic acid (AF) with regard to the antioxidant effect. The most intense capacity to inhibit protein denaturation was demonstrated by compounds **1e** (R = 2-NO_2), **1f** (R = 2-OH) and **1d** (R = 4-NO_2), whose anti-denaturing activity was more intense than ferulic acid and comparable to diclofenac. Regarding the ability of the test compounds to stabilize the erythrocyte membrane, it was comparable or more intense than the diclofenac and 4-hydroxy-3-methoxycinnamic acid (AF) ability at the concentration of 500 µg/mL. **Conclusions**: New 2- (R-phenyl)-3-[3-(4-hydroxy-3-methoxyphenyl)acrylamido]thiazolidin-4-one(5a-l) were synthesized, physico-chemical and spectral characterized and biologically assessed using in vitro methods. **Key words:** thiazolidin-4-one, *in vitro* biological evaluation.

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New biocompatible isoniazid derivatives for the treatment of tuberculosis

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PO 051

Introduction: Tuberculostatic drugs are the most common drug groups with idiosyncratic global hepatotoxicity. The treatment problems that may arise, within this class of medicines, are mainly of two types: adverse reactions (collateral, toxic or hypersensitive reactions) and the initial or acquired resistance of *Mycobacterium tuberculosis* to one or more antituberculosis drugs. Prevention of adverse reactions to TB treatment, increase treatment adherence and success rates, providing better control of TB [a]. In this regard, obtaining new drugs with low toxicity and high tuberculostatic potential, is essential. Thus, the main objective of this study is obtaining new isoniazid (HIN) condensation products, to improve its biocompatibility and tuberculostatic potential. *Materials and methods:* The condensation reaction between isoniazid and the three aromatic benzaldehydes (benzaldehyde (a), 2-nitro-benzaldehyde (b) and 4-bromo-benzaldehyde (c)) was carried out in a molar ratio of 1: 1, in absolute ethyl alcohol medium [b]. Chemical structure confirmation, of the synthesized compounds was performed using spectral methods: infrared spectroscopy and nuclear magnetic resonance (^{1}H-NMR). For biocompatibility assay and cell morphology examination of the samples, we used a stabilized line of mouse fibroblasts NCTC (929 clones) cell. Cytotoxicity testing evaluation of the samples was preformed by exposing cultured cells directly to the samples followed by cell viability MTT (thiazolyl tetrazolium bromide) assay [c]. *Results:* By structural modulation of isoniazide, three isonicotinoylhydrazones have been obtained (HIN-a, HIN-b and HIN-c) and their spectral analysis have highlighted the structural elements of each compound. In vitro biocompatibility evaluation, using MTT cell viability assay, revealed the most noncytotoxic sample, HIN-c, while cell morphology aspects of HIN-c sample treatment, suggest a good biocopatibility of it. *Conclusions:* The obtained isonicotinoylhydrazones, from the study, are original and with potential biological application as antimicrobial agents, in the treatment of tuberculosis.

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A relational database structure for fast and efficient mining of molecular interactions in the PDB.

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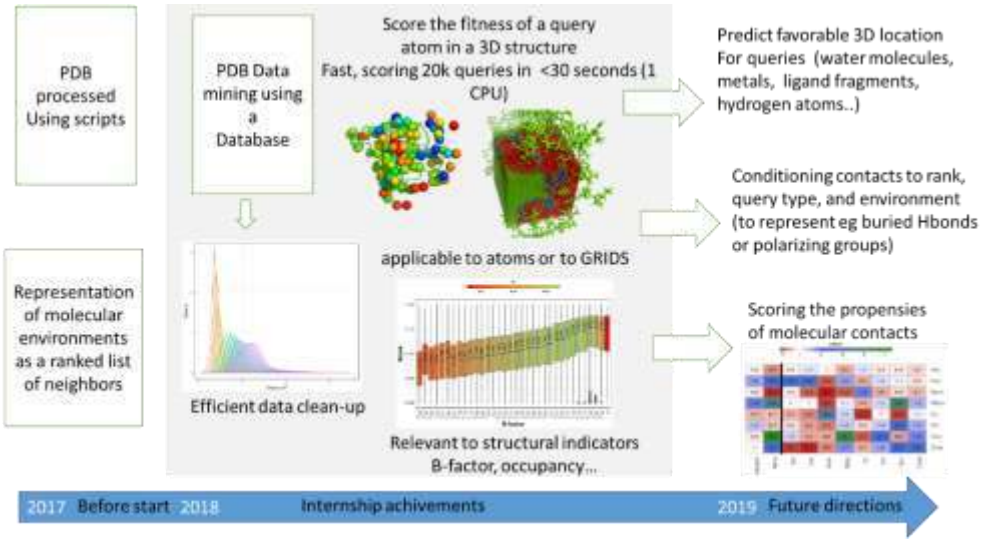
PO 052

There are around 130,000 protein structures in the protein data bank (PDB)[a] that provide a wealth of information about molecular interactions. Filtering the complexes of interest is usually conducted at different levels in order to build datasets where for example the resolution, protein chain and ligand redundancies[b], interactions with metals, or simply associated features have been controlled. This is usually done using collections of scripts organized into workflows[c-d]. Examples of organizing the data into databases are rare[e], yet they represent a powerful and time-efficient ways to conduct data mining studies. Here, we present a relational database, developed in PostgreSQL to mine molecular interactions in the PDB, as well as the key features.



Bibliographic references:

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New 2-heteroaryl-4-quinolones as potential antibiotics targeting bacterial communication systems

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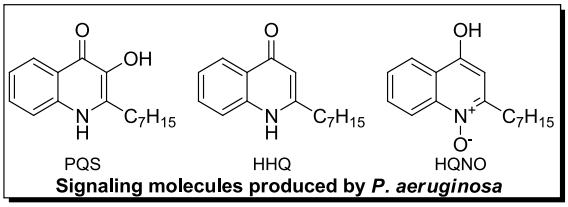
PO 053

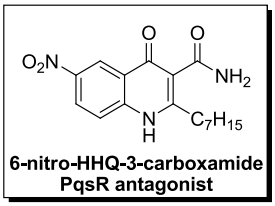
The availability of effective therapies against multidrug resistant bacteria, including ESKAPEE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, *Enterobacter spp.* and *Escherichia coli*), is an important unmet medical need.[(a)] The development of new antimicrobial molecules active towards novel pharmacological targets seems to be a promising strategy to overcome antibiotic resistance. The communication systems of bacteria, called Quorum Sensing (QS), appear to be of great interest. Indeed, many pathogenic microorganisms use QS to control the expression of virulence factors, the bacterial multiplication and/or the development of biofilms. QS relies on small molecules to regulate gene expression in response to population density and environmental factors.

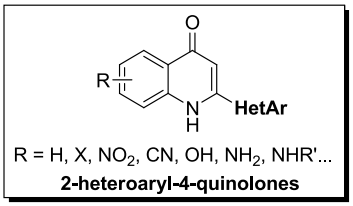
For *P. aeruginosa*, three main QS circuits are studied: the *las*, *rhl* and *pqs*.[(b)] The *pqs* system is based on two signaling molecules, the *Pseudomonas* quinolone signal (PQS) and its precursor 2-heptyl-4(1*H*)-quinolone (HHQ). Extracellular HHQ synthesized by *P. aeruginosa* is internalized by neighboring bacteria and converted into PQS. High concentrations of PQS in the cell will then activate the transcriptional regulator PqsR and trigger the expression of virulence factors.[(b)] Recently, HHQ analogues such as 6-nitro-HHQ-3-carboxamide synthesized by Hartmann *et al.* have been described as PqsR antagonists.[(c)] Furthermore, *P. aeruginosa* produces a secondary metabolite, the 2-heptyl-4-hydroxyquinoline-*N*-oxide (HQNO), which has been found to be toxic for various competing microorganisms such as *S. aureus*. In fact, HQNO disrupts the flow of electrons through the respiratory chain of many bacteria at the cytochrome *bc1* complex. As a consequence, reactive oxygen species are generated in the cell leading to apoptosis.[(d)]

Taking these studies into account, we decided to develop a new 2-heteroaryl-4-quinolone family with potential antibacterial properties. These promising compounds could inhibit the respiratory chains of bacteria and/or modulate the communication systems, especially in *P. aeruginosa.* In the poster, the synthesis of the first expected derivatives using metal-catalysed coupling reactions is reported.



Signaling molecules produced by *P. aeruginosa*


6-nitro-HHQ-3-carboxamide
PqsR antagonist



2-heteroaryl-4-quinolones

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Study of a novel agent for TCA precipitated proteins washing - comprehensive insights into the role of ethanol/HCl on molten globule state by multi-spectroscopic analyses

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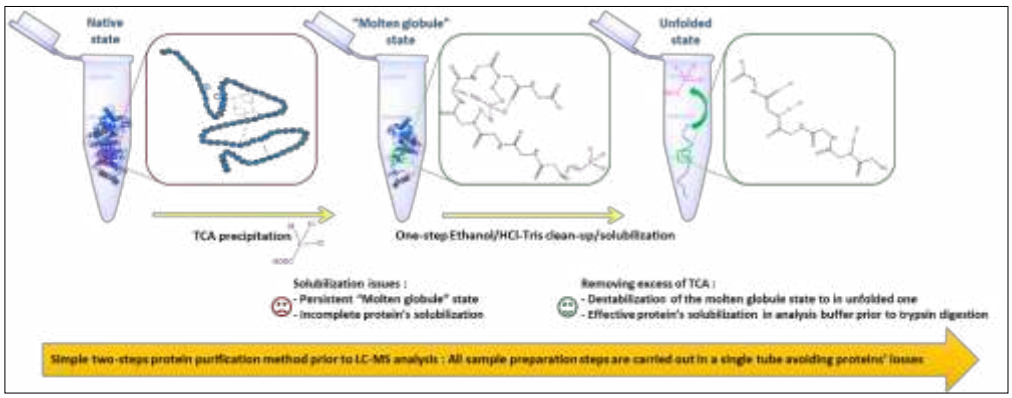
PO 054

Sample preparation for mass spectrometry-based proteomics is a key step for ensuring reliable data [1] [2]. In gel-free experimental workflows, protein purification often starts with a precipitation stage using trichloroacetic acid (TCA). In presence of TCA, proteins precipitate in a stable molten globule state making the pellet difficult to solubilize in aqueous buffer for proteolytic digestion and MS analysis. In this context, the objective of this work was to study the suitability of a novel agent, ethanol/HCl, for the washing of TCA-precipitated proteins. This method optimized the recovery of proteins in aqueous buffer (50 to 96%) while current organic solvents led to losses of material. Following a mechanistic study, the effect of ethanol/HCl on the conformation of TCA-precipitated proteins was investigated. It was shown that the reagent triggered the unfolding of TCA-stabilized molten globule into a reversible intermediate, characterized by a specific Raman signature, which favored protein subsequent resolubilization. Finally, the efficiency of ethanol/HCl for the washing of TCA-precipitated proteins extracted from a biofilm, a soil or a mouse liver was demonstrated. Being versatile and simple, it could be of great interest to include an ethanol/HCl wash-step to produce high-quality protein extracts.



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[2] C. Qian, R.L. Hettich, Optimized extraction method to remove humic acid interferences from soil samples prior to microbial proteome measurements, J. Proteome Res. (2017).

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Microwave-assisted decarboxylative condensation of isatins as an express method for novel antiglaucomic drug discovery.

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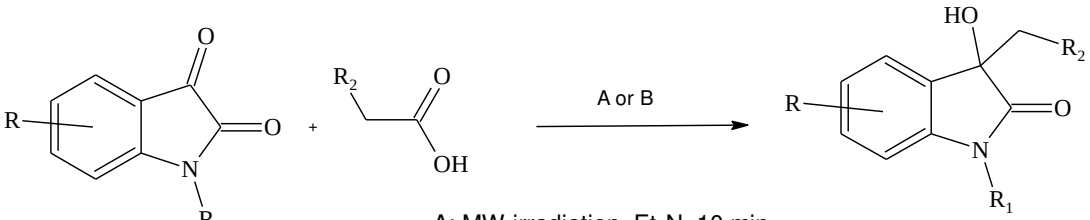
PO 055

The microwave-assisted (MW) decarboxylative condensation of isatins with malonic and cyanoacetic acids is reported for the first time in order to obtain the new 3-hydroxy-2-oxindole derivatives. Various compounds were synthesized with high yields (up to 98%). The methods of MW and conventional synthesises were optimised. The influence of novel compounds on intraocular pressure (IOP) was studied in vivo on normotensive rabbits. The obtained compounds were found to reduce the IOP nearly as fine as melatonin and timolol (reference drug). Time-dependent study revealed the prolonged effect (more than 7 h) of the synthesized compound. This effect in combination with high IOP reducing effect with high water solubility represents a great potential of low-cost oxindole derivatives as potent antiglaucoma agents.



R= H; 5-NO_2; 5,7-NO_2; 7-NO_2; 5-Br; 5-OMe; 5-OMe-7-NO_2; 5-OMe-4-NO_2

R_1= H; Bn

R_2= COOH; CN

A: MW irradiation, Et_3N, 10 min

B: conventional, Et_3N, 3 h

A: 85-98%

B: 70-93%

Reduction of IOP:

oxindole compounds - 1,53-3,93 Torr

melatonin - 3,13 Torr

timolol - 3 Torr

Bibliographic references:

(a) Bioorganic and Medicinal Chemistry Letters, 2017, Vol. 27, P. 3787–3793.

(b) Tetrahedron, 2017, Vol. 73, P. 6887–6893

(c) Biochemistry, Supplemental Series B, 2017, Vol. 11, no. 3, P. 272–278

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Regioselective synthesis of new 2,4-(Het)aryl-3*H*-pyrido[1',2':1,5]pyrazolo[4,3-*d*]pyrimidine involving palladium-catalyzed cross-coupling reactions.

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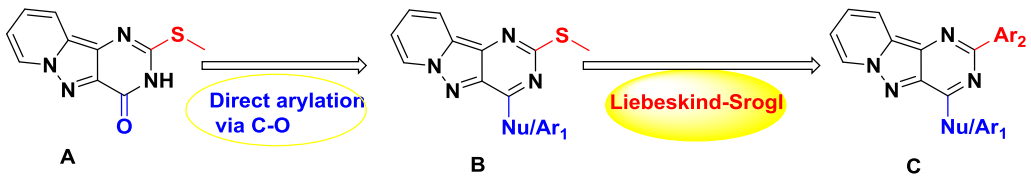
PO 056

The exploration of chemical space is a key prior step in the discovery of biologically active molecules. This strategy in heterocyclic chemistry includes the design and the functionalization of polynitrogen structures, which are chosen for their similarity with major biomarkers and may contain scaffolds such as indoles, imidazoles, pyrimidine or imidazopyrimidine as well as tricyclic folate cores [1]. In view of their potential for the design of bioactive molecules, a variety of polynitrogenated skeletons have received considerable attention due to the synthetic challenge that they represent [2], In this area, tricyclic fused heteroaromatic derivatives with a bridgehead nitrogen have less often been examined [3]. There is therefore a need to provide synthetic methods for their functionalization through reproducible and versatile strategies.

On the basis of our group's interest in rare heterocyclic structures and the results of our previous research [4], we present in this work the design of pyridopyrazolopyrimidines which have emerged to provide high potential bioactive compounds. In particular, we focused our efforts to develop a versatile platform **A** and then, to explore its multiple substitution using C–O activation with PyBroP as activator followed by a Suzuki-Miyaura cross coupling reaction. This strategy will allow to design future original bioactive molecules containing pyrido[1',2':1,5]pyrazolo[4,3-*d*]pyrimidine scaffold.



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Meeting the DNA methylation readers

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(4) Institute for Biochemistry and Technical Biochemistry, University of Stuttgart, Germany

PO 057

Epigenetics has received a lot of attention in the last decade. Many insights on epigenetic (dys)regulation in disease have been obtained[(a)] and clinical therapies targeting epigenetic dysregulations are in place. However, the readers of the epigenetic marks are lacking behind this revolution. In particular it is poorly understood how DNA methylation is being read and translated to chromatin function and cellular responses[(b)]. To study this mechanism, we are developing a chemical strategy to target the methyl-CpG readers, in particular the Methyl-CpG Binding Domain proteins (MBD). We have designed analogues of 5-methylcytosine. Using NMR and DSF, we are screening them for their ability to bind MBD2 to identify a starting point for the development of chemical probes for MBDs.

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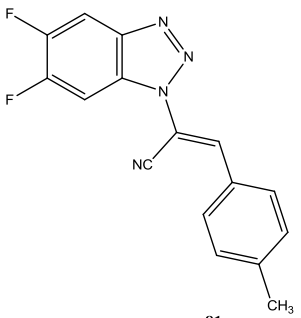
* Correspondence: diane.erdmann@pasteur.fr

Functionalization of some aromatic antiproliferative compounds with antimitotic activity: design, synthesis and biological evaluation of new 2-(5,6-difluoro-1*H*(2*H*)-benzo[*d*][1,2]triazol-1(2)-yl)-3-(4-*R*-phenyl)acrylonitriles	***PO 058***

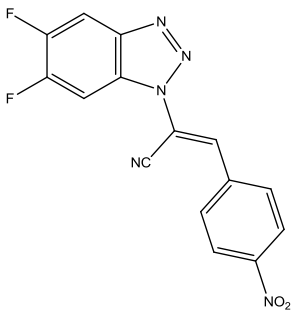
Federico Riu[(1)]*, Roberta Ibba[(1)], Sandra Piras[(1)], Paola Corona[(1)], Antonio Carta[(1)]

(1) Department of Chemistry and Pharmacy, University of Sassari, via Muroni 23/A, 07100 Sassari, Italy

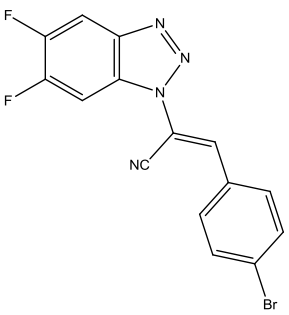
Among the anticancer drug treatments, antimitotic therapies are efficient against the abnormal proliferation of transformed cells, as cell-cycle deregulation is a property of cancer cells. Even if mitosis is the shortest cell-cycle phase, it is an elaborate process in actively proliferating cells, so damages activate the spindle assembly checkpoint (SAC), which brings to a long mitotic arrest. The process known as mitotic cell death (MCD) is largely exploited as an antiproliferative strategy for the development of new chemotherapeutic drugs. Microtubule-targeting agents (MTAs), the most classical yet, reliable antimitotics, interrupt correct microtubule dynamics, resulting in chromosome misalignment, wrong spindle formation, and continuous activation of SAC. This class of drugs can be subcategorized into microtubule-destabilizing agents, like Vinca alkaloids and microtubule-stabilizing agents, like taxanes[(a)]. The challenge is to identify or design more specific and potent drugs. This work is part of a project based on the synthesis of some benzotriazolacrylonitrile derivatives compounds that first demonstrated cytotoxicity against MT-4 cells, and then exhibited a potent antiproliferative activity against a panel of cell lines of several solid and haematological tumors, with an antimitotic activity[(b)]. A new series of variously substituted 2-(5,6-difluoro-1*H*(2*H*)-benzo[*d*][1,2]triazol-1(2)-yl)-3-(4-*R*-phenyl)acrylonitrile derivatives was synthesized, starting from 3,4-difluoroaniline, as part of this project. The *in vitro* activity of the derivatives was evaluated on a panel of 60 human cancer cell lines at the National Cancer Institute in Bethesda, Maryland, USA. In this work we report the preliminary screening of the compounds **81a,b,c,e,f,g** and **82a**, which showed an interesting activity at 10 µM, with a percentage of growth inhibition in tumor cells between 50% and 100%. Some of them, **81a,e,h**, have been selected to be screened on the same 60 tumor cell lines, but at 5 different concentrations down to 0.01 µM, to measure CC_{50} values. These antiproliferative screenings show that compound **81a** is still very potent on 4 tumor lines, in particular leukemia, with percentages of proliferation inhibition between 53% and 97% with a concentration of 1 µM. Compound **81h** instead maintains a percentage over 50% on the SR leukemia line, while the derivative **81e**, the most potent in the preliminary test, still show percentage values over 50% inhibition with 0.1 µM concentration on HOP-92 line from non-small cell lung cancer. General values of GI_{50} are up to 0.1 µM, while those of LC_{50} reach up to 1 µM.



81a



81e



81h

Bibliographic references:a-.-. -

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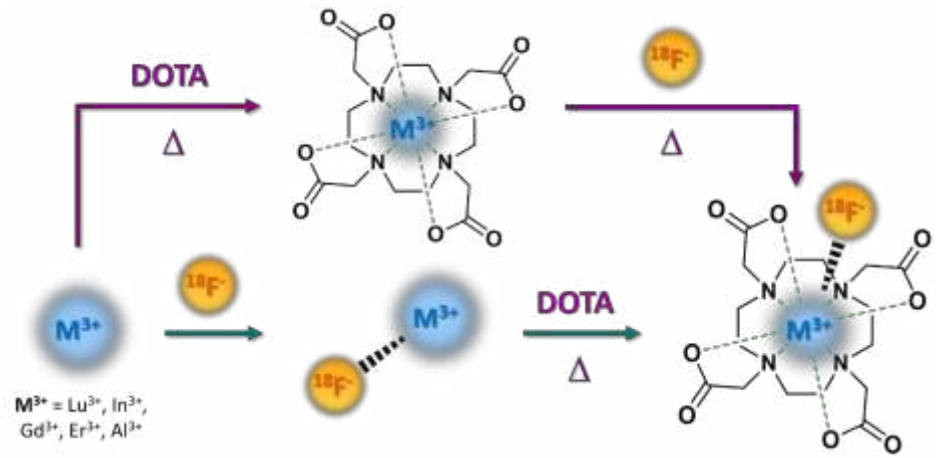
* Correspondence: federicoriu1@gmail.com

Non-covalent radiofluorination: is Al^{18}F the only possible strategy?	***PO 059***
Cyril FERSING$^{(1,2)*}$, Ahlem BOUHLEL$^{(2)}$, Philippe GARRIGUE$^{(2)}$, Benjamin GUILLET$^{(2)}$. *(1) Aix-Marseille Université, CNRS, ICR UMR 7273, Laboratoire de Pharmaco-Chimie Radicalaire, Faculté de Pharmacie, Marseille.* *(2) Aix-Marseille Université, INSERM 1263, INRA 1260, C2VN, Faculté de Pharmacie/CERIMED, Marseille.*	

Because of its ideal physical properties (110 min half-life, decay profile with 97% positron emission and a low positron energy), fluorine-18 turns out to be a key radionuclide for positron emission tomography (PET) imaging,[(a)] for both preclinical and clinical applications. However, usual radiofluorination procedures require the formation of covalent bonds, through the use of fluorinated prosthetic groups. This drawback makes radiofluorination impractical for routine radiolabeling.

In response to this limitation, aluminum [^{18}F]fluoride chemistry was developed in the late 2000s.[(b)] This approach is based on the formation of a $Al^{18}F^{2+}$ cation (usually written Al^{18}F), complexed with a 9-membered cyclic chelator such as NOTA, NODA or their analogs. Due to the small size of the $Al^{18}F^{2+}$ cation, this radiolabeling methodology is poorly compatible with the 12-membered cyclic chelators like DOTA. Radiopharmaceutical preparation kits containing this type of complexing agent, such as SOMAKIT-TOC® (edotreotide), used for PET imaging of neuroendocrine tumors, cannot therefore be labeled with Al^{18}F. Thus, in order to transpose the Al^{18}F methodology to DOTA-conjugated biomolecules, the replacement of aluminum by larger metal ions was envisaged. After a careful study of the experimental radiolabelling conditions that could be applied to this approach, the TLC method for reaction monitoring has been validated, allowing to discriminate free $^{18}F^-$, metal-[^{18}F]fluoride (M^{18}F) and radiocomplex between M^{18}F and a cyclic chelator. Then, a series of 60 reaction tests involving indium, gadolinium, erbium or lutetium was carried out. Both the M^{18}F formation and its complexation in DOTA were studied by varying several parameters such as metal, chelator and [^{18}F]fluoride amount, reaction temperature, pH and co-solvent addition. This work represents the starting point for the optimization of this original non-covalent radiolabeling approach with [^{18}F]fluorine, in the perspective of a routine application.



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[(b)] W. J. McBride *et al.*, *J. Nucl. Med.* 50 (2009), 991–8.
[(c)] M. M. Graham *et al.*, *J. Nucl. Med.* 58 (2017), 1452–1458.

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Radiolabeling optimization with cyclotron produced ^{44}Sc	PO 060
Viktória Forgács(1)*, Anikó Fekete(1), György Baranyai(1), Dezső Szikra(1) (1) University of Debrecen, Faculty of Medicine, Medical Imaging Department, Division of Nuclear Medicine, Debrecen, Hungary	

The PET (Positron Emission Tomography) camera gives excellent resolution images with gamma photons which come from the positron annihilation. This phenomenon is an interaction between a positron and an electron resulting gamma photons with 511 keV energy. In case of small molecules fluorine-18 and carbon-11 were used for the radiolabeling. However, the labeling of antibodies, peptides and proteins with radiometals instead of ^{18}F and ^{11}C can be more effective[(a)].

Scandium-44 (^{44}Sc) decays with positron emission and has good PET imaging properties. Advantages of this radionuclide are for example the relatively long half-life (t1/2 = 3,97 h) and the rapid radiolabeling with appropriate chelators. ^{44}Sc is produced by cyclotron from the proton irradiation of solid target (^{44}Ca(p,n)^{44}Sc)[(b)]. For this reason we built our own solid target system, which is cheap and simple consturction compared to the the commercially available ones. No modifications on the cyclotron was needed, no adjustments were made on the proton beam, and ^{18}F production was not compromised. The target was prepared by pressing approximately 120 mg natural metal calcium into a pellet and this pellet was pressed into an aluminum target holder. After the irradiation, target is placed into a teflon holder and 3 M u.p. HCl is pumped through the cavity between the calcium surface and the target holder (Fig. 1.). The critical parameters are: amount and flow rate of the acid. Activity remaining on target holder: 1-3 MBq.

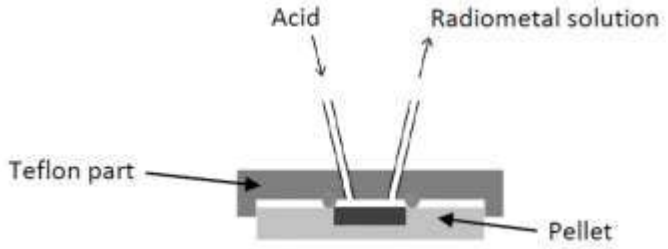

Figure 1: Dissolution of the pellet

DOTA chelator was used as model compound to compare the purity and reactivity of the produced scandium isotope. The reaction mixture is injected onto an analytical column for the determination of radiochemical yield. We developed generally applicable liquid chromatographic methods that allow the detection of free- and biomolecular conjugated chelators labeled with metal isotopes. For this purpose several methods were developed for various mixed stationary phases (ex.: Adsorbosphere SCX)[(c)] using Waters Acquity UPLC I-class with radioactivity detector.

^{44}Sc was successfully produced and purified for labeling using DGA resin. The contaminating inactive metal ions were determined with ion chromatography on a Dionex CS5A column, and the results were used to fine tune the purification method.

Bibliographic references:

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[(b)] Rösch F., *Current Radiopharmaceuticals*, 2012, (5), 187-201.

[(c)] Vlad Orlovsky, Yury Zelechonok, *Chromatography Today,* 2011, *Aug./Sept.*, 24-28.

* Correspondance : forgacs.viktoria@med.unideb.hu

Host DHFR-targeting (2-aminotriazino)benzimidazoles as new antiviral agents	
Valeria Francesconi (1)*, Elena Cichero (1), Lieve Naesens (2), Maria Paola Costi (3), Michele Tonelli (1). *(1) Dipartimento di Farmacia, Università di Genova, Viale Benedetto XV 3, 16132 Genova, Italy.* *(2) Rega Institute for Medical Research, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium.* *(3) Dipartimento di Scienze della Vita, Università di Modena e Reggio Emilia, Via Campi 103, 41100 Modena, Italy.*	***PO 061***

In the fight against viral disease, the traditional therapeutic approaches are mainly focused on targeting specific viral components or enzymes involved in the replication process. This virus-directed approach, while being highly successful in many cases, in many others suffers from the emergence of drug-resistance, due to the high mutation rate of viral genome, which may lead to the selection of resistant strains. As emerging strategy, host factor-directed therapy may provide new agents able to counteract the evolution of viral resistance also endowed with broad-spectrum antiviral properties. In this context, we started a research program studying the activity of diamino dihydrotriazine-based derivatives as host (human) DHFR inhibitors [(a,b)]. This enzyme has been recently identified by us as novel molecular target for influenza and RSV therapy [(a)]. Taking into account our previous findings, now we have synthesized a new series of (2-aminotriazino)benzimidazoles in an attempt to discover new antiviral compounds that may exert their mechanism of action through a direct inhibition of the host (human) DHFR enzyme. The new compounds were tested in enzyme inhibition assays against the hDHFR and have shown K_i values in the range 0.69–3.34 μM. In order to explore species-selectivity preferences they have been assayed against two protozoan DHFRs (Leishmania DHFR and Trypanosoma cruzi DHFR), displaying a different trend of potencies. Then they have been evaluated *in vitro* for the cytotoxicity and the antiviral activity against influenza viruses and other RNA and DNA viruses. Finally, molecular docking studies have enlightened the key interactions of this new series and the target enzyme.

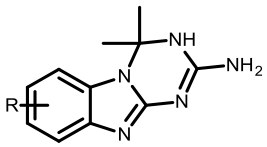

Figure 1. General structure of the newly synthesized (2-aminotriazino)benzimidazoles

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Structure-based virtual screening toward Hexokinase 2 inhibitors: targeting metabolism and apoptosis signaling in cancer cells

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PO 062

Glucose is regarded as the main fuel of cancer cells and the glycolytic pathway has been demonstrated as a potential target to be explored for cancer treatment. Several enzymes involved in glycolysis are overexpressed in different types of cancer cells, namely hexokinase 2 (HK2)[1]. This enzyme is not only involved in the first and most determinant step of glycolysis and subsequently in the different branched 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, avoiding the normal pro-apoptotic signalling. HK2-VDAC disruption would facilitate the binding of pro-apoptotic proteins to VDAC, promoting the enhancement of apoptosis in cancer cells[4].

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

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

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Benzimidazole and benzoxazole derivates as anti-proliferative compounds: synthesis and biological assessment

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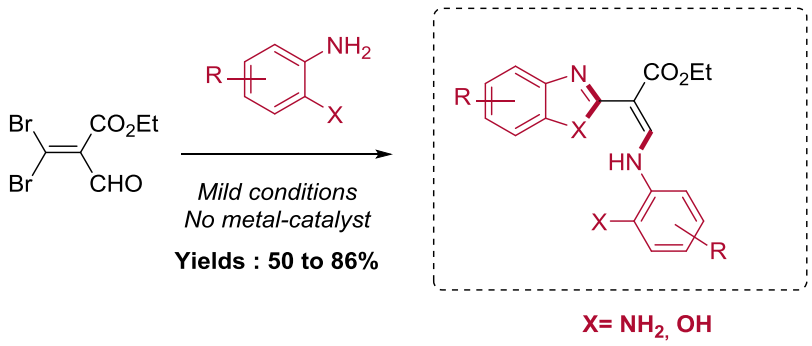
PO 063

Benzimidazole is a well-known heterocyclic ring commonly encountered in medicinal chemistry[(a)]. Indeed, nitrogen atoms of the benzimidazole represent a crucial pharmacophore for many drugs. Its functionalization around 1, 2, 5 and/or 6 positions provides a wide range of molecules of biological interest as antihypertensive (sartan), antiulcer (proton pump inhibitor), anticancer (alkylating agent), anticoagulant (Direct Oral AntiCoagulant), antiviral, anthelmintic etc…. All these outstanding achievements strongly suggest the infinite potential of developing benzimidazole derivates in medicinal field.

In this context, we set out to synthetize highly functionalized benzimidazole and benzoxazole moieties starting from original β-β'-dihalogenoacroleine scaffolds with diaminobenzene or 2-aminophenol derivatives. In this present study, we unveil a one pot, metal-free reaction that enables to access the expected heterocyclic compounds with valuable yields.

The originality of our work lies in generating 3 new C-heteroatom bonds without metal-catalysts. We extended this scheme on a wide array of dinucleophile aromatic rings in order to scrutinize the scope of the reaction. The biological assessment revealed a promising anti-proliferative effect on breast cancer cells, that encouraged us to go further with this project.



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Syntheses of fluorescent probes for cellular imaging of peroxide hydrogen: kinetic evaluations towards H_2O_2.

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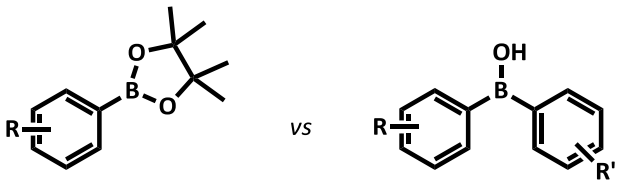
PO 064

Reactive oxygen species (ROS: hydrogen peroxide, hydroxyl and superoxide radicals) play a crucial role in a wide range of physiological process in human. However, when our cells are subjected to oxidative stress conditions, the overproduction of these species is directly or indirectly responsible for numerous oxidative damages at the molecular level (nucleic acids, proteins, lipids, etc.), which can affect cellular mechanisms. This process is associated with aging, as well as cancer and several neuro-degenerative diseases such as Alzheimer's or Parkinson's. [1]

In order to detect hydrogen peroxide, many probes have been developed, based on several type of trigger. Among them, the probes based on the boronate trigger allowed the detection of an oxidative stress *in cellulo*. [2] But these probes also suffered from lack of reactivity (activation superior than hours), which is not fully satisfactory for biological applications. The goal of this project is to improve the reactivity of the trigger by developing probes possessing a borinic trigger.



boronate trigger borinic trigger

We present here an efficient synthetic pathway to access to dissymmetric borinate derivatives. We also synthetized a methylcoumarin-based borinic acid as a fluorescent probe. *In vitro* kinetic evaluations towards hydrogen peroxide have been evaluated.

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Design and synthesis of CD73 inhibitors.	
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CD73 is a member of 5'-nucleotidases that is overexpressed in several cancers.[1] It is a cell surface anchored enzyme catalyzing the irreversible hydrolysis of extracellular adenosine-5'-monophosphate (AMP) into adenosine (Ado) and inorganic phosphate.[2] Then, adenosine is able to interact with several adenosine receptors (A1, A2a, A2b and A3) expressed in tumor microenvironment, thus inducing an immunosuppressive effect leading to tumor cells growth and proliferation.[3,4]

So far, many analogues of adenosine diphosphate (ADP) have been described as potent inhibitors. However, these compounds suffer from poor bioavailability and enzymatic hydrolysis. Herein we will present the synthesis and the inhibitory activities of new substrate analogue as potential CD73 inhibitors.

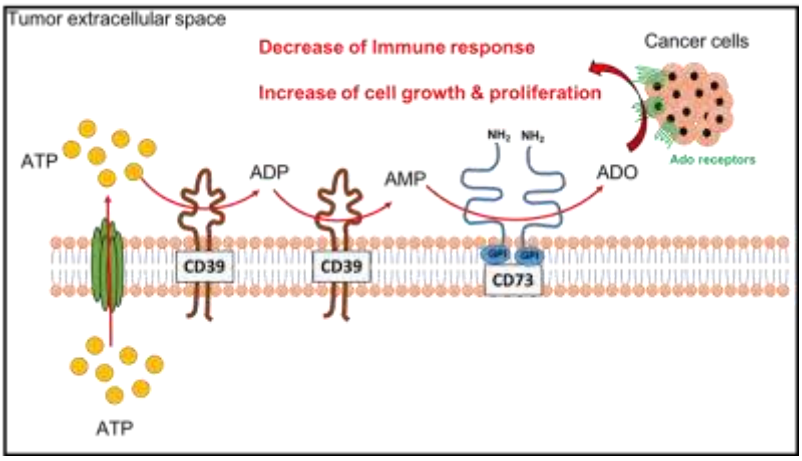

Figure 11 : CD73 function in tumor environment.

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Design, synthesis and characterization of protein-protein interaction disruptors related to early amyloidogenic phenomena in Alzheimer's disease	***PO 066***

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Alzheimer's disease is a slow neuronal degeneration characterized by short-term memory troubles, executive performance disruptions and time and space orientation function disturbance. Outbreak and spread of the disease damages are related to the evolution of the disease symptoms. Brain study of patients with Alzheimer's disease has shown two types of damages which decisively identify the diagnosis: amyloid plaques and neurofibrillary tangles. Each of those two types of lesions are associated to a protein compound: beta-amyloid peptide (Aβ) for senile (amyloid) plaques and hyperphosphorylated tau protein for neurofibrillary tangles. For both of these protein compounds, key-peptide sequences were identified as responsible for early oligomerization initiating the whole amyloidogenic process[(a,b)]. In this process, these peptide sequences shape in a beta sheet structuration. We are aiming to design and synthetize small peptidomimetic molecules as protein-protein interaction disruptors in order to prevent oligomerization responsible for the disease.

The present work was initiated by a conformational analysis of the key peptide sequences implied in aggregation. The various aggregates were built and their stabilities were assessed through molecular dynamic simulations. Then the intra- and intermolecular interaction analyses in aggregate core were carried out and they will be presented in the poster. From the unit expertise in rational design of abiotic foldamers, molecular aromatic scaffolds that could disturb the interactions defined for the proteins will then be designed, synthesized and biologically tested.

This strategy involving medicinal chemistry and molecular modelling at the same time and used for molecule design as secondary structure mimicries (alpha helix and beta sheet) has shown great interest for oncology application[(c)] and now supports the laboratory to enlarge its scientific goals to design new molecular frames aiming protein-protein interactions.

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Integration of in silico structure-based and machine-learning approaches to predict interactions of small molecules with drug metabolizing enzymes

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PO 067

Drug metabolizing enzymes (DME) (1) play a key role in the metabolism, elimination and detoxification of xenobiotics, drugs and endogenous molecules. While their principal role is to detoxify organisms by modifying compounds, such as pollutants or drugs, for a rapid excretion, in some cases they render their substrates more toxic thereby inducing adverse drug reactions, or their inhibition can lead to drug-drug interactions. Predicting potential inhibition of DME is important in early-stage drug discovery. We focus on Cytochrome P450 (CYP) (2) responsible for the metabolism of 90 % drugs and on sulfotransferases (SULT) (3), phase II metabolizing enzymes, acting on a large number of drugs, hormones and natural compounds. We developed an original in silico approach for the prediction of CYP2C9 and SULT1A1 inhibition combining the knowledge of the protein structure and its dynamic behavior in response to the binding of various ligands and machine learning modeling (4). This approach includes structural information for CYP2C9 (5) and SULT1A1 (6) based on the available crystal structures and molecular dynamic simulations (MD) that we performed to take into account conformational changes of the binding site. We performed modeling using two learning algorithms, Support Vector Machine (SVM) and RandomForest, and we constructed combined models based on physico-chemical descriptors and predicted binding energies computed by docking on both X-ray and MD protein conformations. Inhibition models based on classical molecular descriptors and predicted binding energies were able to predict CYP2C9 and SULT1A1 inhibition with an accuracy of >77 % using RandomForest and >73.8 % using SVM on external validation sets.

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Role of melatonin in the prevention of noise-induced hearing loss

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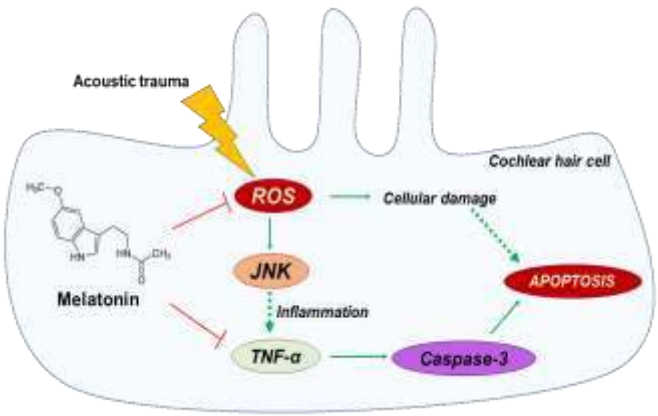
PO 068

Melatonin is a hormone produced by the pineal gland in animals that regulates sleep and wakefulness. However other physiological roles have been described for melatonin such as antioxidant protection of nuclear and mitochondrial DNA and anti-inflammatory effects by TNF-α inhibition. Because an increasing number of studies have demonstrated that antioxidants may serve as effective compounds to block cochlear inflammation and hair cell apoptosis, targeting members of antioxidant pathways could be a feasible option for the treatment of several types of hearing loss. For this reason, the aim of this study is to determine the effect of melatonin in hearing impairment, and anxiety induced by acoustic trauma.

We also aim to assess the preventive effect of melatonin in hearing loss induced by a bilateral acoustic trauma at 4 -8 kHz and 119 dB in Wistar rats. Auditory Brainstem Responses (ABR) at and the Distortion Product Otoacoustic Emissions (DPOAE) were measured 24h and 21 days after acoustic trauma. Rats were subcutaneously treated with melatonin (10 mg/kg) one day before acoustic trauma and for 10 days post trauma. Therefore, anxiety was assessed and finally, cochleae were fixed for scanning electron microscopy observation.

Daily melatonin injections significantly reduced the increase of ABR thresholds and the decrease of DPOAE amplitudes. Melatonin treatment reduced anxiety 21 days after acoustic trauma with no effect on locomotor activity and protected cochlear outer and inner hair cell functionality.

These results suggest that melatonin prevents hearing loss induced by acoustic trauma. We hypothesized that melatonin could reduce oxidative stress of IHC and OHC induced by the acoustic trauma. However, as melatonin plays a key role in TNF-α and c-fos inhibition, we cannot discard other complementary molecular mechanisms protecting hair cells and neurons.



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The story of tacroximes; novel unique compounds for the recovery of organophosphorus-inhibited acetylcholinesterase.

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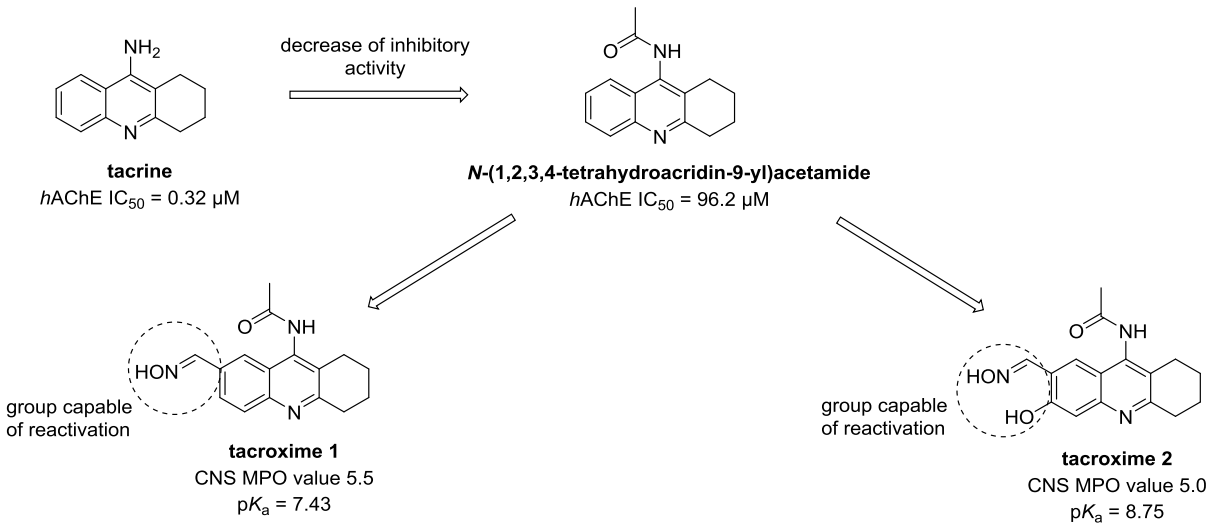
PO 069

The nerve agents (NA), the most toxic chemical warfare agents, are known for over 70 years. Their deadly effect was demonstrated several times during the history. Another member of the organophosphorus compound (OPC) family, OP pesticides, likewise represent serious burden for the mankind. Though, there is still no reliable antidote that would offer efficient medical assurance for the intoxicated patients. Herein, we describe two novel compounds, tacroximes, as unique merged molecules of tacrine against organophosphorous intoxication. These reactivators of acetylcholinesterase have balanced physico chemical properties, should be able to cross blood brain barrier and have slightly lower cytotoxicity. Their efficiency was proved against dichlorvos as compared with pralidoxime and obidoxime. Tacroxime represents interesting starting point to spur the development of novel, centrally active reactivators/or prophylactic agents with potential to become interesting drug candidates for *in vivo* studies.



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Water-soluble fluorescent ligands for the development of antitumor agents based on platinated oligonucleotides

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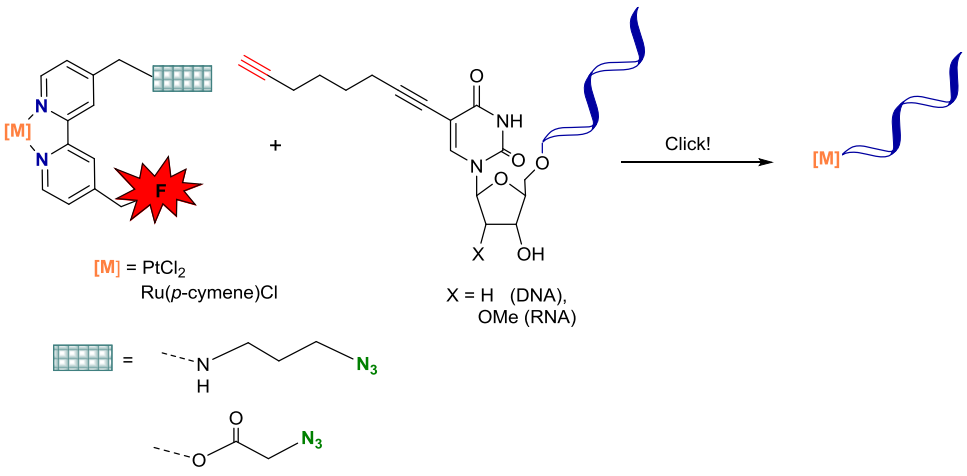
PO 070

The search of novel cisplatin analogs with potential applications as anticancer agents is still an area of intensive investigation. In the last years, several strategies have been developed based on the use of targeted platinum(II) compounds, nanoparticle delivery or platinum(IV) prodrugs, to name only a few examples.[(a)] The main goal is to discover new compounds endorsed with significant activity and selectivity, albeit with less toxicity than cisplatin.

As part of our research program, we propose the assembly of biologically active Pt(II) or Ru(II) metal complexes to modified nucleic acid sequences targeting the telomere-telomerase system. To this end, we are currently working in the bioconjugation of these two components by using the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction ("click chemistry"). The first part of the synthesis of these conjugate systems requires the preparation of a water-soluble ligand with a pendant azide, along with a modified oligonucleotide incorporating the alkyne function at the 5' and/or 3-ends.

In this communication, we report our recent results regarding the design and synthesis of the precursor ligands, including the incorporation of a fluorescent tag to allow easy tracking of the compounds inside the cell.



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Development of pleiotropic (pro)drugs MAO-B inhibitor/AChE inhibitor for Alzheimer's disease.	PO 072

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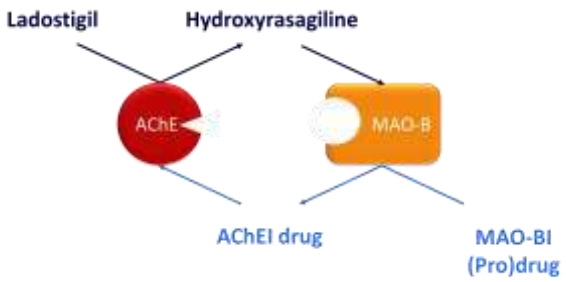
Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder, leading to the most common[(a)] form of dementia in the elderly. Given AD's multifactorial causes, the classical pharmacological approach consisting in interacting very selectively with a single target has shown clinical limitations, failing to restore such a complex biological system. As a result, more and more examples illustrate the concept of Multi-Target Directed Ligands (MTDLs), molecules which display several activities by interacting with different biological in order to obtain a synergy of action[(b)]. For example, our group described the donecopride, first MTDL inhibiting acetylcholinesterase (AChE) and activating 5-HT_4 serotoninergic receptors, and now in preclinical evaluation [(c)].

Ladostigil (Figure 1) is a novel type of MTDL currently in phase II clinical trials. It is the first compound able to release an active compound, the hydroxyrasagiline, a Mono Amine Oxidase B (MAO-B) inhibitor, through the interaction with a first target, the acetylcholinesterase (AChE), which is temporarily inhibited during the process[(d)].

The objective of this project is to illustrate the concept the concept of molecules which are both drugs and prodrugs: the action on a first target will release a second agent acting on another target. Our objective remains original by leading to the design of (pro)drugs interacting with MAO-B to inhibit it and release another anti-AD drug. Using AChE inhibitors, we may then obtain an action similar to ladostigil but in an opposite mechanistic way.



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Targeting Cancer Stem Cells with Antibiotics

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PO 073

Compelling evidence suggests that cancer stem cells (CSC) are the roots of current shortcomings in advanced and metastatic colorectal cancer treatment. CSC represent a minor subpopulation of tumor cells endowed with self-renewal and multi-lineage differentiation capacity, which can escape from both conventional and targeted therapies (cetuximab, avastin), disseminate and seed metastasis. For that reason, **targeting CSC has become a major goal** to design new therapeutic routes **that may prevent tumor relapse and metastasis development**.

Most drugs possess off-target effects that might provide substantial benefit for cancer treatment. **Drug repositioning now became a powerful alternative strategy** to deliver cheaper and faster drug development. Amongst potential candidates, antibiotics are of particular interest. We focused our attention on aminoglycosides, and most particularly streptomycin (SM), a potent bactericidal antibiotic generally administered for the treatment of individuals with moderate to severe infections such as tuberculosis. Our work on commercial and patient derived cancer cell lines clearly established that **SM interferes with stem-like properties -such as self-renewal- inherent to CSC phenotype**. Furthermore, SM affects with equal effectiveness colorectal, breast and lung cancer cell lines, suggesting a **"pan-cancer" effect**, independent of tissue origin and mutation profile. At the sub-cellular level, SM triggers an increased production of mitochondrial reactive oxygen species (ROS) in CSC, causing oxidative stress and leading to cell apoptosis. Remarkably, catalytic reduction of the aldehyde moiety of SM abolishes ROS production and prevents cell death while maintaining bactericidal properties.

Because SM is an aminoglycoside endowed with RNA-binding ability, we speculate that the underlying mechanism involves targeting of CSC-specific RNAs and subsequent alteration of their processing and/or function. In order to identify SM target(s), we successfully designed and synthesized a tagged-SM which retains anti-CSC properties. This compound contains an alkyne residue and will be employed to identify the intracellular target of SM. Furthermore, the synthetic strategy that has been developed for its preparation allows for the synthesis of analogues and for future SAR studies.

Based on the literature and these preliminary results [(a)], our main objective is to further study the impact of SM on CSC and validate this antibiotic as a potential adjuvant chemotherapy agent in advanced and metastatic colorectal cancer. From a molecular perspective, by connecting the association of SM with certain(s) RNA(s) to inhibition of stem-like properties, we might discover unexpected mechanisms or pathways involved in acquisition or maintenance of these properties. This may in particular lead to the identification of new RNA(s) target for cancer therapy.

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Fragment based approaches for 14-3-3 PPIs stabilization as a new strategy in targeted cancer therapies	***PO 074***

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Protein-protein interactions (PPIs) modulation is one of the most promising and active fields in modern drug discovery and chemical biology. However, it is in many instances understood synonymously with PPIs inhibition, disregarding the complementary strategy of stabilizing PPIs despite the fact that successful drugs such as Rapamycine (Figure 1a.) and Lenalidomide are established stabilizers.[(a)] A multitude of natural products and a growing number of synthetic compounds further validate the feasibility and value of small-molecule PPI stabilization.[(b)] Stabilizers also display a number of advantages like their uncompetitive nature and their potential for higher specificity. They bind to composite pockets in the interface of their target complexes which naturally show a higher structural variability than, for example, active sites of enzymes or ligand binding pockets of receptors. However, how such interface-binding molecules can be designed in a rational, bottom-up manner remains an unanswered question.

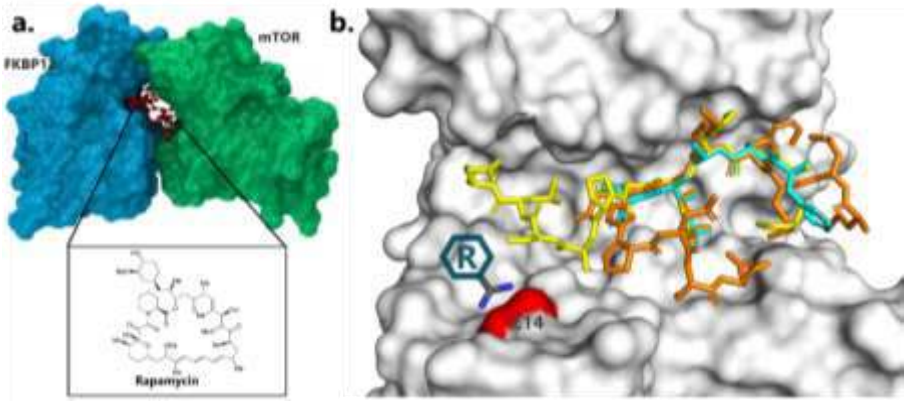

Figure 12. ***a. Structure of the ternary complex of FKBP12•rapamycin•mTOr, b. Overlay of the structurally different binding*** **epitopes of p53 (orange), TAZ (yellow) and ERa (cyan) with 14-3-3.**

An especially interesting target for PPI modulation is the adapter protein 14-3-3. This "hub" protein interacts with several hundred partner proteins and regulates the activity of many disease-related proteins like C-Raf (cancer), Tau (Alzheimer) and CFTR (cystic fibrosis).[(c)] Using a fragment-based drug discovery (FBDD) approach, we identified by x-ray crystallography fragments that bind in a differential manner to the distinct interfaces of 14-3-3 with three major proto-oncogenic proteins, namely p53, TAZ and ER (figure 1b.). Additionally, biophysical assays demonstrated that these fragments already show small but selective stabilizing activity. These preliminary results on the adapter protein 14-3-3 hint at the possibility of introducing selectivity at an early stage of the optimization cycle of PPIs stabilizing ligands.

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Synthesis and biological evaluation of bioactive ferrocenyl analogues of bisacodyl

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PO 075

The global situation of bacterial diseases has become a major issue in the last years due to the lack of new drugs and the antibiotic resistance. Since the year 2000, only eight antibacterial molecules have obtained a marketing authorization (AMM). [1-3]

Currently, pharmaceutical companies are developing new approaches from existing drugs, in order to accelerate the discovery of interesting leads with low costs and reduced risks. Particularly, repositioning strategy can identify novel indications for existing drugs with known pharmacokinetic profiles.[4]

In this work we present the synthesis and the biological study of ferrocenyl analogues of bisacodyl, a drug used in therapeutic as laxative. Ten original ferrocenyl compounds have been designed and synthesized *via* an efficient synthetic procedure using the McMurry coupling reaction. The antibacterial activity was investigated against Gram-positive and Gram-negative pathogens including *Listeria monocytogenes*, *Listeria ivanovii*, *Enteroccus faecalis*, *Staphylococcus aureus* and *Escherichia coli*. Most of compounds showed an excellent antimicrobial activity comparing to doxycycline and the bisacodyl analogues seemed to be more bactericides than bacteriostatic.[5]

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Access to new diagnostic tools in oncology through (radio)-iodination of Bcl-2 inhibitors.

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PO 076

Labelling of (bio)molecules with radioactive isotopes is of high interest to the scientific community, as it strongly impacts the discovery process in life science and nuclear medicine. Radiolabelled molecules have been extensively used to assess biochemical reactions, to measure in vivo distribution of a substance or to perform RIA (RadioImmunoAssay). In nuclear medicine, radio-therapeutics for RIT (RadioIsotope Therapy) and radio-tracers for molecular imaging experiments such as PET (Positron Emission Tomography), SPECT (Single Photon Emission Computed Tomography) or scintigraphy have been described. Several useful isotopes of iodine can be used for both diagnosis and therapy: 123I for SPECT imaging, 124I for PET imaging, 125I for biological assays and nuclear medicine and 131I for radio-therapy and scintigraphy. Our group has recently developed a method to radio-iodinate *N*-acylsulfonamides through a room temperature palladium mediated C-H radio-iodination. This original strategy allows radiolabelling in very mild conditions without the use of chemical precursors.

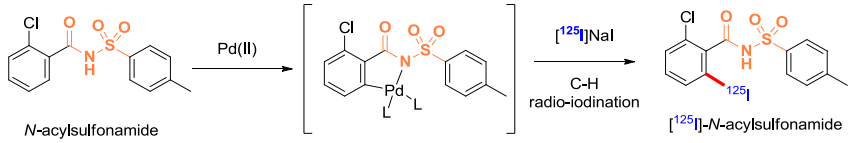

Figure 13 : Palladium mediated C-H radio-iodination.

In this context, we are currently enlarging the scope of this methodology toward the radio-iodination of antitumoral agents containing a *N*-acylsulfonamide group. Thus, an antiproliferative agent LY32262[1], a Bcl-xL/Mcl-1 dual inhibitor[2] and ABT-737[3] have been selected and progress toward the (radio-)iodination of these molecules will be presented.

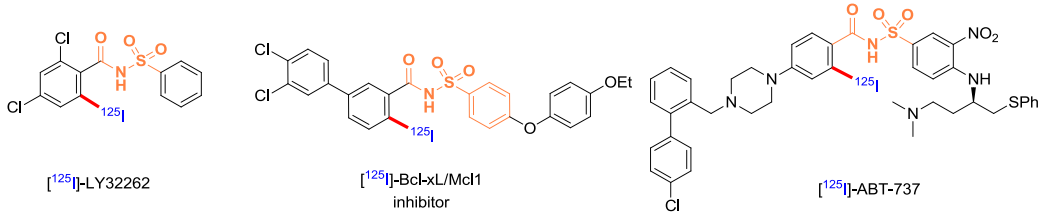

Figure 14 : Structure of [^{125}I]-LY32262, a [^{125}I]-Bcl-xL/Mcl-1 and [^{125}I]-ABT-737.

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Electrospun nanofibers based on Chitosan/PEO and arginine-optimal formulation parameters

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PO 078

Objectives: In the last decades the electrospinning techinque of producing fibrilar materials has achieved widespread popularity in academia as well as industries. Electrospinning is a centenary technology that basically consists in an electrostatic fiber manufacture technique that has displayed extra attention and interest in recent years due to its simplicity, versatility and potential for applications in different fields from a large variety of polymer compositions. The aim of the present paper is the development of new chitosan and arginine based nanofibres by electrospinning and establishing optimal formulation parameters. **Material and Method:** The nanofibers formulation was carried out in 2 steps: the first step consisted in the preparation of chitosan (3% w/v) and PEO (1% w/v) polymer solutions (molar ratio 1: 1 chitosan: PEO) using as solvent: acetic acid (50% v/v, 30% v/v), followed by the second step: the inclusion of arginine in various concentrations (1%, 3%, 5% w/v) in the colloidal dispersion obtained. For the electrospinning process (nanospinner INOVENSO), a syringe with different ranges of gauge needle was filled with the solution and then applied different flow rates, different values of applied voltage and also different tip-to-collector distance (to probe the impact of this three important parameters on the active substance electrospinnability). During this process, also the humidity was monitorised, due to the importance recorded in many studies on the electrospun nanofibers formation. The electrospun nanofibers were characterized in terms of morphology using scanning electronic microscopy (SEM). **Results:** Following the researches, new electrospun nanofibres systems based on chitosan were performed, in which the arginine was incorporated in a concentration of 1 %, 3%, 5% (w/v). From the analysis of the obtained results it was found that the obtaining of homogeneous nanofibres depends on the chitosan and arginine concentration as well as the formulation parameters: feed rate (ml/h), the applied voltage and the needle-collector distance. **Conclusions:** The studies and results obtained justify the evaluation of the biological, antibacterial and pro-healing potential in the treatment of various wounds, starting from the antibacterial effects of chitosan and the beneficial role of applied topical arginine in the treatment of wounds.

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Regioselective C-H functionalization of nitro heterocycles and further transformation of manipulable nitro group.	***PO 079***

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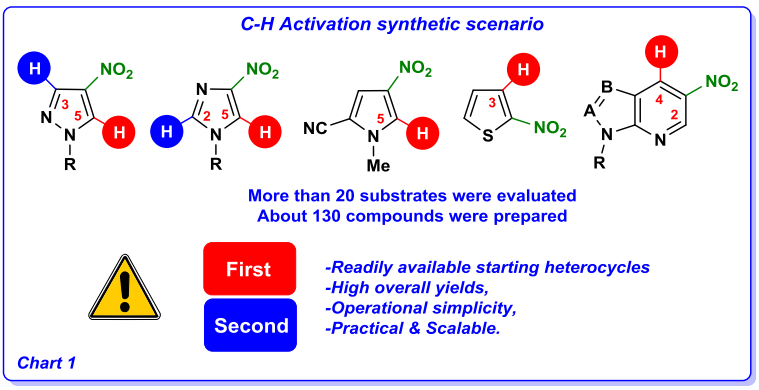
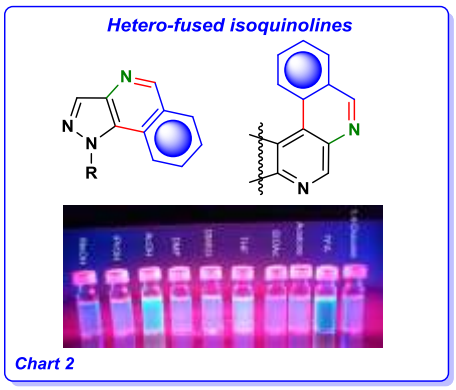
In recent years, transition metal catalysed C-H activation emerged as one of the most important methodologies of modern organic chemistry. The issue of selectivity in C-H activation of complex organic substrates containing two or more reactive C-H bonds, in particular drug-like heterocyclic scaffolds, is a pivotal topic to contemporary organic synthesis[(a)].





The Pd and Ni catalysed, guided and regioselective C-H arylation protocols for series of 4-nitropyrazoles, 4-nitroimidazoles, annulated 3-nitropyridines and several other nitro heterocycles were developed (Chart 1). The method described here is a facile tool for chemical functionalization of drug-like 5- and 6-membered nitro heterocycles. Scope and limitations of the developed methodologies along with reaction mechanism were studied. Quintessential, the elaborated routes had been utilized for construction of several hetero-fused isoquinolines – scaffolds with materials relevant photoelectronic properties (Chart 2) [(b-d)]. Furthermore, TM-catalysed C–H arylselenation of the title heterocyclic substrates was also successfully elaborated[(e)]. Finally, we demonstrated the chemical potential of manipulable nitro group transforming it into different functionalities[(f)]. Part of this work was supported by NCN SONATA 10 grant no. 2015/19/D/ST5/02774.

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Novel acyclic peptidomimetics as inhibitors of hIAPP aggregation: interest in type II diabetes.	PO 080

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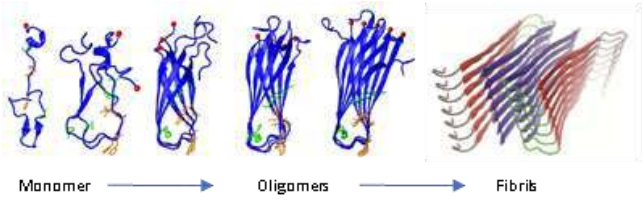
Amyloidosis is the general term used to refer to more than 20 serious human diseases, and Type 2 Diabetes (T2D) belongs to this group of pathologies. In amyloidosis, misfolded proteins rich in β-sheet secondary structures are present and due to this wrong folding, these proteins form erroneous interaction which led to the formations of insoluble and toxic oligomers and fibrils.[(a)]



Worldwide, over 422 million people are affected by T2D, and this value is set to grow year by year with an impressive impact on the economy. T2D represents 90% of the cases of diabetes and apoptosis of pancreatic β cells, related to human islet amyloid polypeptide (hIAPP) deposits, is observed in 95% of the cases. Taking in account these values and the absence of therapies able to avoid side effects and complications, it is well understandable why new treatments are desirable.[(b)] Nowadays, targeting the aggregation process of hIAPP has become an interesting strategy for T2D treatment in order to decrease β cells death. Some heterogeneous classes of compounds have been proposed to inhibit hIAPP aggregation.[(c)] In this work, we are presenting a new class of hIAPP inhibitors that mimic β-hairpin structures, being based on a piperidine-pyrroline β turn mimic. Encouraged by our results obtained using this strategy to target Aβ1-42[(d,e)] (amyloid peptide involved in Alzheimer's disease), we decided to keep the same β turn inducer in order to design, synthesize and evaluate new selective inhibitors of hIAPP oligomers formation and fibrillization. As already done for Aβ1-42, we first investigated compounds with two peptidic arms linked to the piperidine-pyrroline scaffold with the aim to evidence the applicability of this class as aggregation inhibitors in hIAPP aggregation. Secondly, we substituted one of the peptidic arm with a peptidomimetic arm in order to try to modulate the metabolic stability and to improve the anti-aggregation activities of our compounds.

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Recombinant synthesis and purification of hTFF2 protein in S. Cerevisiae

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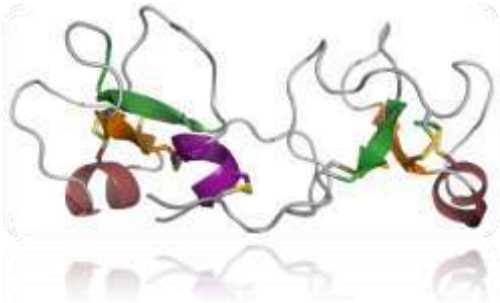
PO 081

Summary: Human trefoil factor family protein 2 (hTFF2) belongs to a family of peptides containing one or more characteristic trefoil domains —a distinctive three-leaved structure formed and stabilized by three disulfide bonds.[1] hTFF2 contains 106 amino acid residues and two trefoil domains formed by 6 disulfide bonds and these domains are interconnected with a 7th disulfide bond.[1b] Because of these disulfide bonds, they are stable secretory proteins expressed in gastrointestinal mucosa. Their physiological functions are not defined,[3] but they may protect the mucosa from insults, stabilize the mucus layer and affect healing of the epithelium.[2,4] Their size and cysteine-rich character are the main reason why these peptides have never been successfully synthesized. Only very limited amounts of hTFF2 can be prepared from human tissue extraction. Here, we describe a yeast expression system designed for the production of sufficient amounts of hTFF2 for physiological and biochemical studies.



To obtain natively folded hTFF2 protein, we chose to express it in *S. cerevisiae*. We designed the hTFF2 gene encoding a fusion protein consisting of a hybrid leader sequence and the hTFF2 sequence. Recombinant plasmids were constructed. The leader sequence served to direct the fusion protein in to the secretory pathway of cell and to expose it to the Kex 2 processing enzyme system. We optimized conditions for protein expression. The secreted hTFF2 was found in a glycosylated and an non-glycosylated form.[5] The two forms of hTFF2 were purified from the yeast fermentation broth by a combination of ultrafiltration, ion-exchange chromatography & preparative HPLC. The hTFF2 and glycosylated hTFF2 were analyzed by HR-MS.[5] Subsequently, we have synthesized N15 enriched analogue of hTFF2 protein and currently, we are analyzing its three dimensional structure by NMR.
Moreover, this recombinant hTFF2 would serve to identify its receptor by using LRC-TRICEPs method and elucidate its role in intestinal wound healing.

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Design And Synthesis Of Novel Staurosporine And Rutaecarpine Hybrids As Therapeutic Leads In The Treatment Of Cancer

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PO 083

Cancer is one of the major problems these days, thus there is an indispensable need to synthesize new drugs with intended anticancer activity. Very important natural compounds with such characteristics and properties are Staurosporine and Rebeccamycin, as well as Rutaecarpine and Evodiamine and their analogues. Staurosporine and Rebeccamycin are indolocarbazole or bisindole antibiotics with broad spectrum antitumor activity. Rebeccamycin and its analogues stabilize the DNA-topoisomerase cleavage complex, whilst Staurosporine and other bisindole alkaloids (i.e. topsentin) are some of the strongest known protein kinases inhibitors. In addition, indoloquinazoline compounds, Rutaecarpine and Evodiamine possess anti-cancer activities both *in vitro* and *in vivo* by inhibiting proliferation, invasion and metastasis. Prompted by the above, here we describe the design and synthesis of several hybrids of the above leads. The new compounds showed important anticancer activity against a variety of molecular targets and cancer cell lines, especially TDP2 enzyme, WM2664 malignant metastatic melanoma (<1 μM) and T24 urinary bladder cell line. According to *in silico* studies, depending on the substitution of the main core, the new compounds bind in a great manner in the active sites of TDP2, CDK2, b-raf, Aurora B and PIM1 kinases (*Figure 1*). All these experiments will contribute to exclude safer structure activity relationships and to a further synthesis of new compounds which will be evaluated against the determined molecular targets.

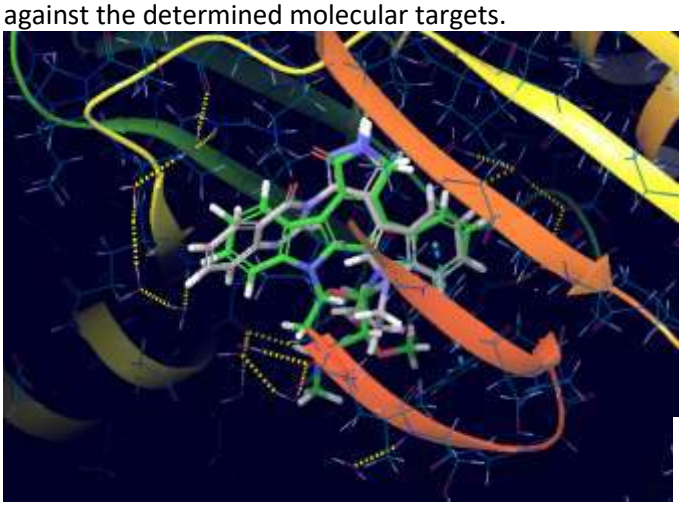

Figure 1: Our compound in the active site of PIM1 in comparison with

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Synthesis and antiproliferative activity of novel (–)-goniofufurone analogue

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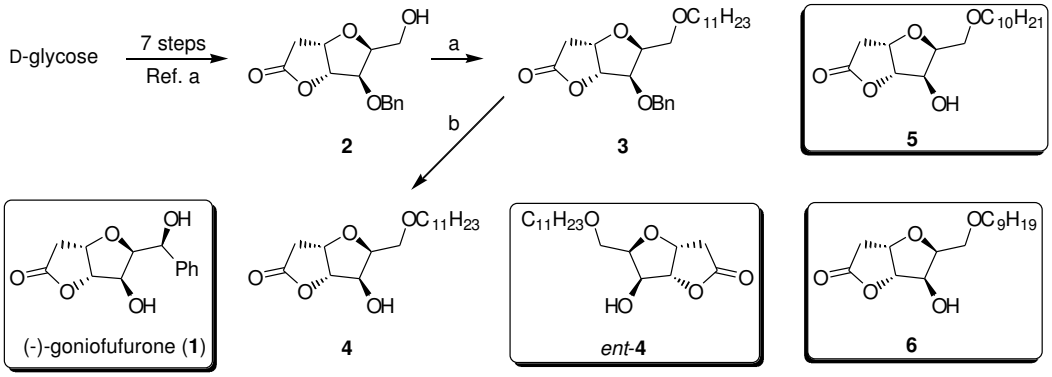
PO 084

As a part of our ongoing program in the synthesis of oxygenated lactones as potential antitumour agents from abundant monosaccharides, D-glucose was converted to analogue **4** (*Sheme 1*). Furanolactone **4** might be considered as a non-styryl analogue of (–)-goniofufurone (**1**), the opposite enantiomer of naturally occurring cytotoxic lactone (+)-goniofufurone.

Target **4** was evaluated for its *in vitro* cytotoxicity against a number of tumour cell lines, as well as against normal foetal lung fibroblasts. Also, we will present results of antiproliferative activity and structure–activity relationship (SAR) of **1**, **4**, its opposite enantiomer *ent*-**4** and analogues **5** and **6**, that were previously synthesized in our laboratory.



Sheme 1. Reagents and conditions: (a) $C_{11}H_{23}Br$, Ag_2O, AgOTf, Et_2O, reflux; (b) H_2, 10% Pd/C, MeOH, rt.

Acknowledgement: The work was supported by a grant from the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project 172006).

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Cinnamic acid derivatives as cytoprotective agents in doxorubicin-damage cardiomyocytes – a correlation with the inhibition of CBR1 mediated metabolism

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PO 086

Doxorubicin (DOX) is common therapeutic agent, frequently used in cancers treatment. Despite a great efficacy against a wide spectrum of neoplasms, its application is limited by adverse effects – cardiotoxicity, which affect patients treated with approved doses and cancer cell resistance which decreases response to treatment [1,2]. Dose-dependent cardiac toxicity of DOX becomes a major obstacle for its clinical use. Currently, many therapeutic strategies emphasise on combination therapy with DOX and other agents, that would improve the clinical efficacy of chemotherapeutic by protecting patients from cardiotoxicity [3].

One of the hypothesis that explains the emergence of side effects, indicate an important role of cytosolic enzyme - carbonyl reductase (CBR). Human carbonyl reductase 1 (CBR1), a member of the short-chain dehydrogenase/reductase superfamily, reduces DOX to their less potent anticancer C-13 hydroxy metabolite –doxorubicinol (DOXol), what is linked with pathogenesis of cardiotoxicity [2]. Due to the undesirable activity of DOXol, there is a clear need for searching a new carbonyl reductase inhibitors that will improve the effectiveness of DOX therapy[4].To take up such a challenge in our group a new potential inhibitors of CBR1 in a group of cinnamic acid derivatives (CA) have been designed and synthesized.

The aim of the present study was to explore the effects of CA on DOX-induced cardiotoxicity. Firstly, the biotransformation process of DOX in the presence of CA in human cytosol fraction was examined and molecular modeling analysis was conducted to predict the potential interaction of CA with an active site of CBR1 enzyme. Then, cytotoxic and cytostatic activities of DOX+CA were investigated in human lung cancer cells (A549). Finally, cytoprotective effect of CA on DOX-induced cardiotoxicity in rat cardiomyocytes (H9c2) was determined using: cytotoxicity, apoptosis and ATP level analysis. Furthermore, human iPSC differentiation procedure into cardiomyocytes were provide to establish specific, unique and clinically relevant cellular model system that allowed to translate data from animal cellular models to complex cellular physiology of human cardiomyocytes. Preliminary studies have shown that synthetic cinnamic acid analogues (1-8) exhibit differentiated synergistic effects with doxorubicin increasing cytotoxicity against cancer cells. All analyzed compounds exert multidirectional, cytoprotective effect against DOX-induced cardiotoxicity in H9c2 cells and iPSC derived- cardiomyocytes.

Taking into account these results, it can be concluded that CA, a new potential inhibitors of CBR1, are thought to be a promising agents for adjuvant therapy with a double beneficial effect in improving the therapeutic response to DOX and reducing the cardiotoxic effects in patients undergoing chemotherapy.

Acknowledgements: This work was supported by funds granted for the Faculty of Pharmacy of Jagiellonian University Medical College by the Polish National Science Centre no. 2016/21/D/NZ7/01546

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Optimization of synthesis of D2AAK1, a multi-target ligand of aminergic GPCRs.

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PO 087

Careful characterization of GPCR ligands revealed that many compounds can interact with more than one receptor. At first it was considered a difficulty in discovering drugs acting through these receptors. Nowadays it is known that in diseases with complex pathomechanisms, such as Alzheimer's and Parkinson's diseases and schizophrenia, drugs acting through several molecular targets are more efficient than selective drugs. In search for novel multi-target antipsychotics we performed structure-based virtual screening[(a)] and found, among others, compound D2AAK1 (Fig. 1). This compound has affinity to human dopamine D_2 receptor with K_i of 58 nM. D2AAK1 possesses additional nanomolar or low micromolar affinity to D_1, D_3, 5-HT_{1A} and 5-HT_{2A} receptors[(a,b)].

In the light of above, the aim of studies was synthesis optimization of the compound D2AAK1. This compound was synthesized in two steps (Fig. 1). The first steps was reaction of 5-methoxyindole with piperidin-4-one hydrochloride in MeOH/KOH leading to 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole following the previously described procedure[c]. This intermediate was reacted with 3-(chloromethyl)-2(1H)-quinolinone in DMF/K_2CO_3 at room temperature. For both steps different solvents, proportions of reagents and reaction times were tried. The final yield of the first step was 40% and the second one 53%.

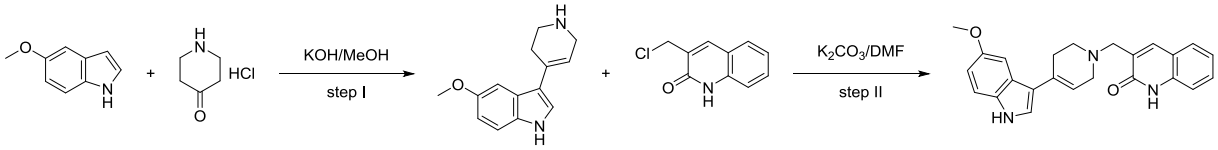

Figure. 1. Reaction scheme.

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Novel quinazolin-4-one derivatives as potentiating agents of doxorubicin cytotoxicity

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PO 088

DNA-dependent protein kinase (DNA-PK) is a member of the phosphatidylinositol 3-kinase (PI3K) related protein kinase family (PIKK). With two other members of this group, ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR), they take care of DNA maintenance and manage DNA damage response (DDR).[(a)] DNA-PK is the major regulator of the cellular answers to DNA double strand breaks (DSBs), where both strands of the DNA helix are severed. DSBs, often caused by ionizing radiation (IR) or chemotherapeutic drugs, are the most lethal type of DNA lesion and if unrepaired, they can lead to cell death or to genome rearrangements with subsequent malignant transformation. DDR is a highly studied area of current cancer research. Within our contribution, we will report the design, synthesis and biological evaluation of 17 novel 8-aryl-2-morpholino-3,4-dihydroquinazoline derivatives based on the standard model of DNA-PK and PI3K inhibitors. Novel compounds are sub-divided into two series where the second series of five derivatives was designed to have a better solubility profile over the first one. A combination of in vitro and in silico techniques suggested a plausible synergistic effect with doxorubicin of the most potent compound **14d** on cell proliferation via DNA-PK and poly(ADP-ribose) polymerase-1 (PARP-1) inhibition, while alone having a negligible effect on cell proliferation.[(b)]

Supported by the Long-term development plan (Faculty of Military Health Sciences, University of Defence, Czech Republic), by MH CZ - DRO (University Hospital Hradec Kralove, No.00179906) and by Technology Agency of the Czech Republic project no. TG02010020.

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Pharmacological studies of novel ligands of aminergic GPCRs

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PO 089

G protein-coupled receptors (GPCRs) are an important drug target for neuropsychatric disorders, such as schizophrenia, Parkinson's disease, bipolar disorder or depression. In particular, multi-target drugs which interact with several GPCRs simultaneously reflecting a complex pathomechanism of these diseases, are a hot topic in current medicinal chemistry.

In search for novel antipsychotics and antidepressants we performed structure-based virtual screening to identify multi-target ligands of aminergic GPCRs[a]. Seven best compounds with *in vitro* confirmed affinity to dopamine D_2 receptor as well as D_1, D_3, 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptors were subjected to further *in vitro* and *in vivo* studies[b].

Here we present preliminary results of *in vitro* and *in vivo* studies for these compounds and their selected derivatives, including cytotoxicity evaluation and investigation of the effect of these compounds on amphetamine-induced hyperactivity, anxiety processes in elevated plus maze test, memory processes in passive avoiding test and depressive processes in forced swim test in mouse models.

Regarding four compounds tested as potential antipsychotics (D2AAK1-D2AAK4), they decrease amphetamine-induced hyperactivity (when compared to the amphetamine-treated group) measured as spontaneous locomotor activity in mice. In addition, passive avoidance test demonstrated that all the compounds improve memory consolidation after acute treatment in mice. Elevated plus maze tests indicated that all the compounds induce anxiogenic activity 30 minutes after acute treatment. 60 minutes after administration D2AAK1 displays anxiolytic activity, D2AAK3 no activity and the anxiogenic activity continues for D2AAK2 and D2AAK4.

The obtained results indicate that the studied compounds are promising as hits for further elaboration into pharmacological tools or potential drugs.

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[(a)]Kaczor AA, Silva AG, Loza MI, Kolb P, Castro M, Poso A (2016) ChemMedChem 11:718-729.

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Development of a new cancer diagnostic and pronostic system: study of the molecular dynamics of solid tumors by chemobiology

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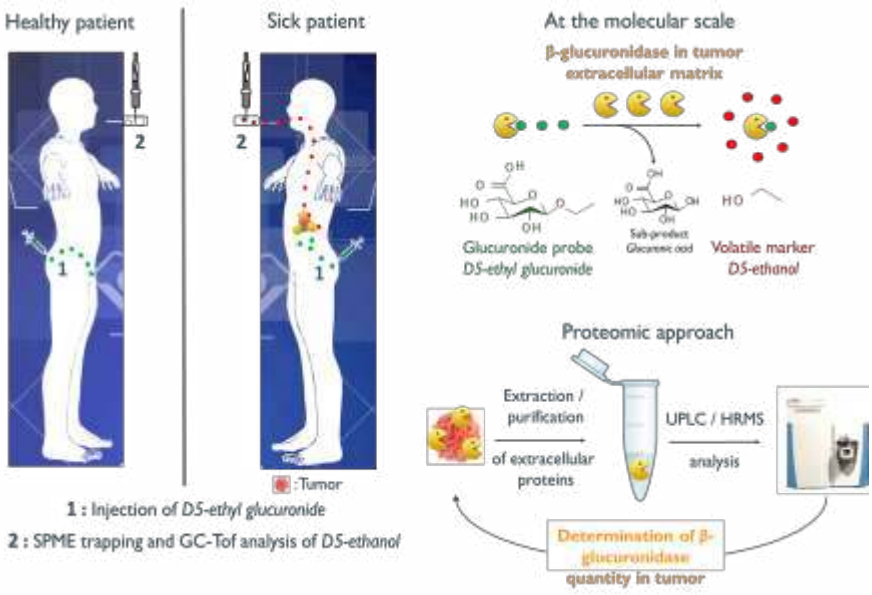
PO 090

Despite significant advances in therapeutic approaches, cancer remains a major problem of public health with 8.8 million deaths in 2015 according to the World Health Organization (data from February 2018). Another way to reduce this mortality rate is to improve cancers diagnosis.

Within this framework, we propose a new concept of chemical biology to (1) detect almost all solid tumors at early steps of development and (2) monitor their dynamics, particularly during a chemotherapeutic protocol.



Our concept relies on a direct correlation between the tumor progression and the amount in patient's breath of an exogenous volatile marker (i.e. ethanol in figure). This molecule comes from the hydrolysis of its glucuronide derivative in cancer cells extracellular matrix by a specific enzyme present in the microenvironment of almost all solid tumors, the β-glucuronidase[a]. The volatile compound further diffuses in the blood stream and ends up in patient's breath (figure 1).

In this presentation, the public health context will first be introduced. Our chemo-biological strategy, which combines metabolomics and proteomics approaches, will then be presented. Finally, results obtained on model animals will be shown.

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Design and synthesis of novel Benzisoxazole compounds with antioxidant properties in Alzheimer's disease.

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PO 091

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

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

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

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Quinoline-anti microbial peptide conjugates : synthesis and microbiological activities

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PO 092

Infectious diseases are a part of the main causes of death worldwide. Among them, tuberculosis and nosocomial infections are particularly worrying. Indeed, mycobacteria and ESKAPE bacteria kill millions of people each year[1].

The aim of this work is to study new antibacterial compounds, especially effective against Gram-negative bacteria and mycobacteria in replicating and latent form.

We have previously synthesized some aminoquinoline-methanols (AQM) with good antibacterial properties against Gram-positive bacteria.

Using antimicrobial peptides (AMP) can be an interesting strategy to restore or broaden antibacterial activity of any sort of antibiotics. For example, conjugates like dpMtx or chloramphenicol-ubiquicidin$_{29\text{-}41}$ (fig 1.) have shown the possibility respectively (1): to enhance antimicrobial activity (about 10 fold against *M. tuberculosis*) and (2): to reduce cytotoxicity (about 75% against neutrophils) [2].

We would like to broaden antibacterial spectrum of our aminoquinoline-methanols by conjugation with short sequence antimicrobial peptide[3]. Herein we will present our main results concerning the synthesis and biological results of these AQM-AMP conjugates (fig 1.)

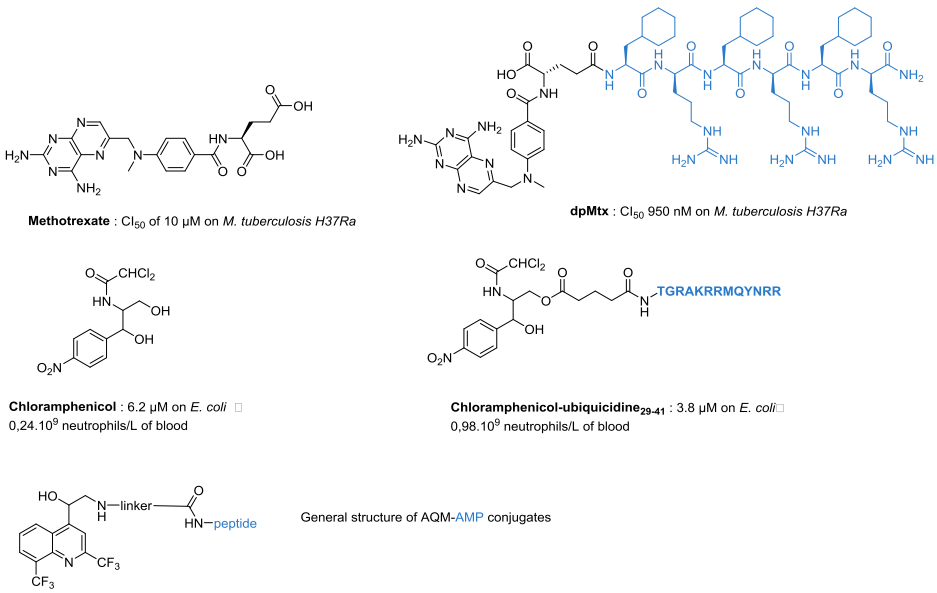

Figure 15 : Some examples of conjugates with antimicrobial peptides

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Modelization, application and transposition of a continuous flow chemistry process to pharmaceutical industry.

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PO 093

As part of the perspectives of sustainable development and green chemistry, continuous flow chemistry has recently emerged in the field of fine and pharmaceuticals chemicals and cosmetics, offering to these industrial specialities many advantages such as processes more efficient, fast, reliable, safe and eco-friendly. [1]

Compared to the batch process, these main advantages of this novel technologies allowed: i) to easily and safely control the heat transfer during exothermic reactions; ii) to reproduce some reaction conditions with precision; iii) to increase the kinetic rate of classical reactions; iv) to perform high pressure reactions with high level of security; v) to perform easily and quickly extrapolations to industry. [2]

However, despite this large number of advantages, the implementation of flow process by industrial partners is often seen as a constraint because it impacts both the know-how and the socio-economic benefits of the company. To overcome this feeling and to facilitate the transfer of known batch process to flow chemistry, we have established a computer model predicting the temperature profile according to the chemical species generated during a reaction. This model will accelerate the extrapolation and promote the transposition at the industrial level of sensitive reactions such as the genesis and use of diazonium salts. [3]

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Design and synthesis of fluorinated foldamers as inhibitors of hIAPP aggregation: interest in Type 2 diabetes

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PO 094

Today around half a billion people are suffering from Type 2 diabetes (T2D).[1] T2D is an amyloid disease like Alzheimer's, and Parkinson's diseases which are characterized by the aggregation of a peptide (amyloid β, α-sinuclein, …). In its random or α-helix conformation, the human islet amyloid polypeptide (hIAPP, or amylin) plays a role in glucose homeostasis. But by an unknown mechanism it can change to a β-sheet conformation and aggregate to form amyloid deposit in pancreas of more than 95% of type II diabetic patients. Amyloid aggregates of hIAPP contribute to β-cells dysfunction and death leading to type 2 diabetes and cardiovascular complications.[2] No causal treatment of TD2 exists. Therefore, it is a major international issue to find new drugs to treat this fatal disease.

Since few years, foldamers have emerged as useful secondary structure mimetics of proteins[3]. Peptidic foldamers could be particularly interesting in trying to meet the challenge of finding new classes of drugs targeting protein-protein interactions as in T2D.

On the other hand, introducing fluorine atom(s) into bioactive organic compounds has become a leading strategy for drug design. Due to its unique properties, fluorine is frequently employed to modify biologically relevant properties such as metabolic stability, basicity, lipophilicity, and bioavailability.[4] Nevertheless, in the literature, there is still no fluorinated peptide used as a drug.

Herein, we report the design and the synthesis of fluorinated peptidomimetics foldamers as potential inhibitors of hIAPP aggregation.

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Structural optimization and biological evaluation of *Mycobacterium tuberculosis* MabA inhibitors	***PO 095***

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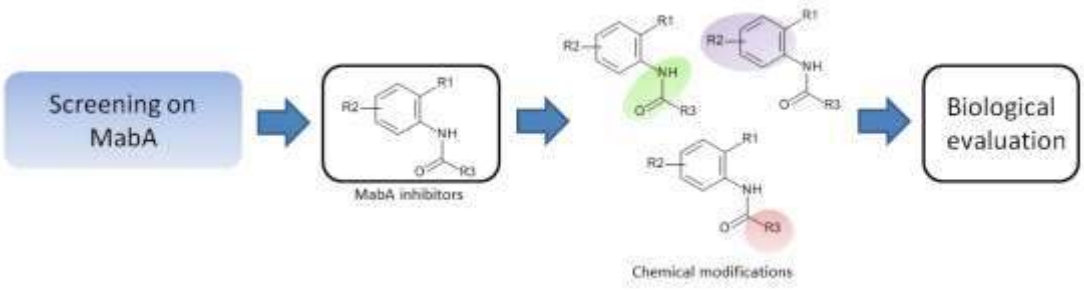
Tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis*, remains one of the major causes of mortality worldwide, killing each year 1.6 million people[(a)]. A treatment, involving a combination of drugs for a minimum of six months, is available but the rapid emergence of multidrug resistant (MDR) strains of *M. tuberculosis* stresses the need for alternative therapies.

The enzyme MabA (FabG1) is involved in the biosynthesis of mycolic acids[(b)], which are very long-chain fatty acids playing an essential role in the architecture and permeability of the envelope of *M. tuberculosis*. The gene coding for this enzyme has been shown to be essential for the bacteria[(c)], therefore our objective is to discover drug-like inhibitors of MabA active on mycobacteria in order to propose an innovative strategy to treat tuberculosis.

In a previous work we described the screening of a 1280 fragment-library on MabA using a new enzymatic assay allowing the identification of several families of inhibitors. In order to further optimize one of this series, over one hundred analogues were synthesized and tested on MabA and *M. tuberculosis*. The synthesis of the compounds and the structure-activity relationships will be presented. The bacterial activity of the series will also be discussed.



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Imaging and quantifying aggresome in an automated miniaturized microscopy assay.	***PO 096***

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Aggresome is a subcellular perinuclear structure where misfolded proteins accumulate by retrograde transport on microtubule[(a)]. The function of aggresome is primarily protective by sequestration of accumulated misfolded proteins which can be then undertaken by the autophagy pathway. But when the capacity of cell is exceeded, in case of prolonged cellular stress or disruption of autophagy pathway for example, it could become toxic. It has thus been observed that the apoptotic effect of proteasome inhibitors, that increase the load of misfolded proteins in cells, go along with an increase of aggresome formation.

We used the Proteostat® Aggresome detection kit to detect aggresomes. The kit provides a red fluorescent molecular rotor dye, which becomes brightly fluorescent when it binds to aggregated proteins cargo[(b)]. This test was initially developed by the supplier for cell analysis by flow cytometry or by fluorescence microscopy with glass slides. We optimized the assay for microscopy-based high content screening applications in 384 well plates. We have developed a script that measures the intensity of the Proteostat® reagent labeling in individual cells, but also finds spots in cells which correspond to aggresome and measures their intensity and area. Ultimately we can calculate the percentage of cells with aggresome for each incubates and consequently an EC_{50} on aggresome formation induced by drugs.

To conclude, we have optimized and validated the Proteostat® aggresome detection kit utilization, to monitor easily aggresome formation in a miniaturized, automated and quantitative assay. We tested different conditions that increase aggresome formation (proteasome inhibitors, ER-stress inducers) in adherent cells and in cells that grow in suspension. So it is possible now to test faster a large number of conditions that could promote aggresome formation, in order to find pharmacological compounds for cancer therapy. Also, we can suppose that we could apply this assay to find compound that decrease aggresome in protein misfolding disorders.

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Computing free energies and water-maps in minutes: building upon rigorous liquid state stat-mech and pragmatic machine learning.	***PO 097***

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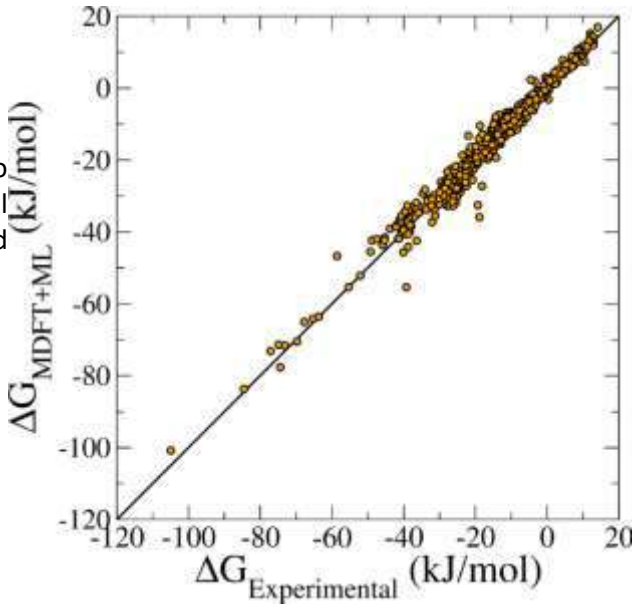
Biochemical processes in the human body happen in large number of solvent molecules, not to say water. To account for this embedding medium at the molecular scale, several possibilities are offered to in-silico experimentalists:

(i) One can forget about the molecular nature of the solvent: no hydrogen bonding, no crowding effect ... Those primitive models, like the polarizable continuums, focus on macroscopic properties of the solvent like its dielectric permittivity. It's a crude approximation but is numerically cheap, fast, and arbitrarily configurable.

(ii) One can use atomistic simulations like molecular dynamics. The numerical cost increases by 4 to 5 orders of magnitude with respect to the previous solution but you gain insight into all the molecular details... If it fits into your computers.

(iii) I will present a new paradigm, the molecular density functional theory (MDFT). I will show how to compute rigorously and within minutes some equilibrium solvation properties of a solute (e.g. a protein or a small molecule). I will focus on two key properties: the solvation *free* energy and the solvation profile, also called water-map.

I will discuss advantages of MDFT (fast, rigorous, systematically improvable), its drawbacks (it's a theory and thus rely on approximations), and how we use machine learning to improve its predictability to move toward in silico drug discovery and binding free energies.



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Rational design of VRAC inhibitors for the potential treatment of Alzheimer's Disease

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PO 098

Inflammation occurs as a result of released inflammatory cytokines such as IL-1β and IL-18. This is a result of inflammasome activation, mainly the NLRP3 inflammasome which has become a major target as it contributes to the pathophysiology of several diseases, including several microbial diseases, gout, type 2 diabetes, CNS diseases including Alzheimer's disease (AD), as well as autoimmune diseases. Volume Regulated Chloride Channel (VRAC) has been shown to activate NLRP3 inflammasome through the efflux of chloride ions and mefenamic acid has been shown to inhibit VRAC and show promising results in a mouse model of AD.[1] Recently, Cryo-EM has been used to determine the structure of VRAC.[2] The aim of this work is focused on the rational design of novel VRAC inhibitors with increased selectivity and potency for the potential treatment of Alzheimer's Disease. Molecular modelling using docking techniques (MOE software) has been used to design novel inhibitors of VRAC, which have been synthesised and evaluated both for their inhibition of IL-1β and VRAC.

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Spiropyrazoline oxindoles – *in silico* optimization for p53 activation

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PO 099

The tumour suppressor protein p53 is involved in many biological processes which are important to maintain the normal function of the cells (e.g. apoptosis, cell arrest and DNA repair). In 50% of all types of human cancers, wt p53 is inactivated by negative regulators such as MDM2 and MDMX Currently, the most popular approach to activate the wt p53 is the inhibition of the protein-protein interaction (PPI) of p53 with these two regulators using small molecules[(a)]. The design of these small molecules passes by mimicking the three critical amino acids (Phe19, Trp23 and Leu26) of p53 essential for the binding of both proteins. Among them, spiropyrrolidine oxindoles were shown to act as potent inhibitors of the p53-MDM2 PPI[(b)].

Our research group has been working in the development and optimization of spiropyrazoline oxindoles to obtain dual p53-MDM2/X interaction inhibitors. Previously, the antiproliferative activity of a library of twenty-three derivatives was evaluated in HCT-116 p53(+/+) human colon cancer cell line. Two compounds showed to induce apoptosis and cell cycle arrest at G0/G1 phase and upregulated p53 steady-state levels, leading to a decrease in MDM2 level[(b)].

In this communication, we report the synthesis and structure-based computational optimization of spiropyrazoline oxindole family for the development of novel p53-MDM2/X protein-protein interaction inhibitors. Our studies will shed lights on the possible binding mode of spirooxindole derivatives to MDM2 and MDMX, and will drive the hit-to-lead optimization strategy.

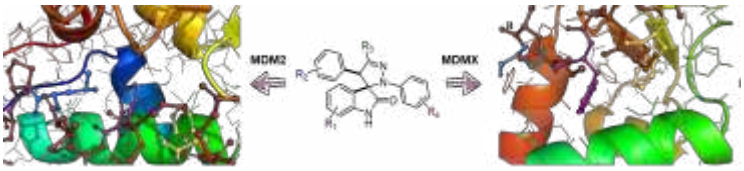

Figure – Binding of a spiropyrazoline oxindole derivative to MDM2 (left) and MDMX (right)

Acknowledgements: FCT (Fundação para a Ciência e a Tecnologia, Portugal) the grant PTDC/QUI-QOR/29664/2017, and the PhD fellowship SFRH/BD/137544/2018 and COST Action CM1407 through STSM 39244 grant (EA Lopes).

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Candida antarctica lipase B as a reusable biocatalyst for xylose palmitate synthesis.

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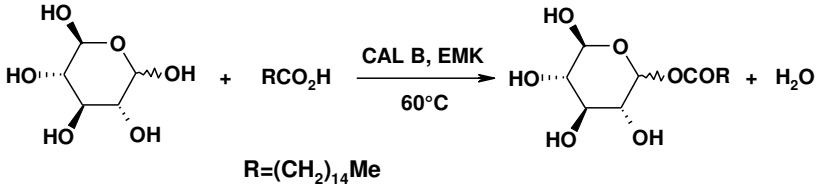
PO 100

Summary

Enzymes such as lipases often exhibit innovative catalytic functions in organic solvents[a] as improvement the solubility of hydrophobic substrates and facilitation of product recovery. Lipase immobilization appears to be a promising method for protecting lipases.

immobilization of lipases on appropriate solid supports is one way to improve their stability and activity(b). they can be reused for large scale applications. immobilized candida antartica lipase type b (cal b) has proven to be a versatile catalyst for a wide range of biotransformations. this lipase is commercially immobilized on acrylic resin and used as an efficient biocatalyst for sugar ester synthesis(c).

In this work, the lipase-catalyzed esterification of D-xylose with palmitic acid (Scheme-I) was selected as a model reaction to investigate the activity and stability of CAL B. The reuse of the immobilized lipase was studied. The enzyme suspended in ethylmethylketone could be reused several times with less than 10% loss of activity per cycle.



Scheme-I -Lipase catalyzed synthesis of xylose palmitate ester.

Butanol (log P = 0.88) was used to wash the immobilized lipase. Highest enzyme activities and stabilities are generally observed in solvents with high log P values. In this lipase-recycling system, the enzyme was repeatedly used four times (Table 1) without any decrease in reactivity when washed with Butanol.

TABLE 1. Enzyme reuse in the esterification reaction of xylose with palmitic acid

Used	Conversion (%)	Specific activity ($\mu mols \cdot min^{-1} \cdot g^{-1}$)
1	65	8.67
2	63,42	8.57
3	62	8.25
4	60,48	7.90

More than 90 % of initial activity of the lipase was still be retained after four cycle reuse. The conversion reached 60%.

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Synthesis and biological study of new bioisosters of melatonin	***PO 101***

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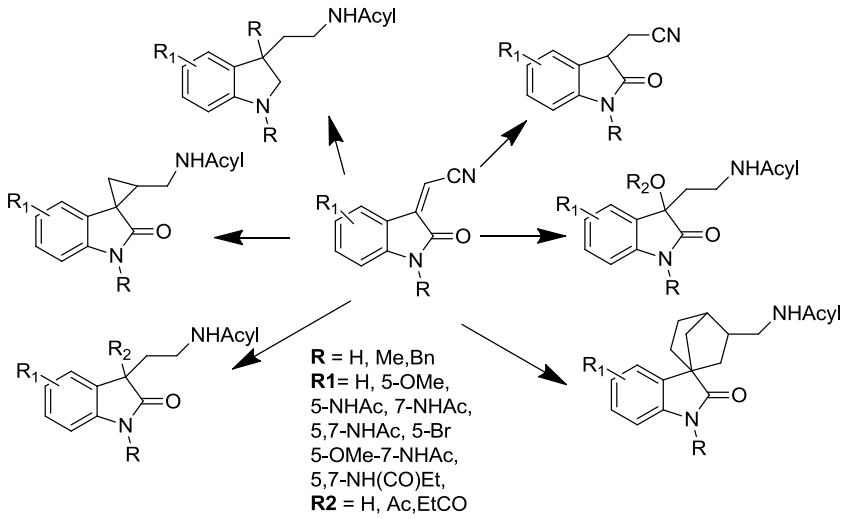
The indolinone scaffold was used to create melatonin analogs with strong biological response. The binding affinity of synthesized compounds to melatonin receptors of MT1, MT2 type and to quinone reductase 2 (proposal MT3 receptor)along with their antioxidant properties was investigated. The ability of selected compounds to reduce the intraocular pressure (IOP) was studied in vivo in normotensive rabbits. The lead compound was found to reduce IOP at 41% (more, then melatonin (30%) and reference drug timolol (32%)). The long-lasting hypotensive effect of 2-oxindole-based melatonin bioisosters (>6 h) along with their high antioxidant properties making they a perspective scaffold for design of new antiglaucoma agents.



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Acknowledgments: This work was supported by the Russian Foundation for Basic Research (Project 17-03-01320)

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Pharmacokinetic study of Pegylated TGR5 agonists

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PO 102

The aim of polyethylene glycol (PEG) conjugation in therapeutic strategy is to improve the therapeutic effect of drugs through a modulation of their pharmacokinetic properties. While the main PK profiling studies of this strategy are described for large molecules with large PEG, we report in the present work the impact of the PEGylation with short PEG (<5 000Da) on PK properties of small molecules, agonist of the bile acids receptor TGR5. The activation of TGR5 located in the distal part of the intestine lead to secretion of glucagon-like peptide-1 (GLP-1). Thus, TGR5 agonist development became an attractive therapeutic approach for the treatment of type 2 diabetes and its metabolic complications. Aiming at targeting selectively intestinal TGR5, we used the kinetophore concept to design new topical intestinal TGR5 agonists[(a)]. The keystone of this PEGylation strategy was the identification of a "mute" position where the introduction of PEG kinetophore could modulate the PK properties without impacting interactions with the target. From a SAR study performed on several ligands synthesized in the lab, we designed chimeric analogs with the same pharmacophore scaffold linked on the mute position to various mPEG moities.

A thorough evaluation of these PEGylated TGR5 agonists enabled us to draw crucial conclusions on the effect of the PEG length on the physicochemical and *in vitro* and *in vivo* pharmacokinetic properties of these compounds. Thus, this study provides informations which could be used as guideline for the design of topical intestinal compounds that could be transposable to modulators of other intestinal targets.

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1,3-Diazepines for the treatment of metastatic melanoma

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PO 103

Malignant melanoma is the most aggressive and life-threatening skin cancer. It represents about 5% of skin cancers, and over the last 50 years, it increases by ~7% per year in industrialized countries.(a) In 2012, 232 000 new cases of melanoma were diagnosed worldwide.(b) On the local stage (stage I/II), surgical resection provides more than 90% survival at 5 years. However, melanoma metastasis may spread rapidly into the liver, lungs, brain, etc. (stage IV), and survival falls down dramatically, with a median survival of less than one year.(a) Until recently, the therapeutic options in stage IV melanoma were very limited, mostly centered on dacarbazine, a chemotherapeutic alkylating agent, used as monotherapy, and in various combinations. Since 2011, new therapies acting against metastatic melanoma have emerged and offer promising results. Among them, small compounds inhibiting the RAF/MEK pathway (vemurafenib and dabrafenib, two BRAF inhibitors, and cobimetinib and trametinib, two MEK inhibitors) have greatly improved median overall survival of mutated BRAF (V600E) metastatic melanoma patients.(c) Immunotherapy based on immune checkpoint inhibitors (like ipilimumab, nivolumab, pembrolizumab) and on the first oncolytic virus TVEC authorized by the FDA, also offers encouraging results.(d) However, initial resistance or emergence often occur leading to a partial patient benefit.(e) The development of new drugs acting against melanoma is still in demand.

In this context, we have recently identified a new family of compounds, based on the pyridoimidazo-1,3-diazepinone scaffold, with potential anticancer activity.[f, g] One of our compounds, JMV5038, demonstrated an *in vitro* anti-cancer activity, more particularly active on melanoma cell lines (*e.g.* IC50 on MDA-MB-435 cell line = 1.3 ± 0.5 µM), while no significant cytotoxicity was found on the "healthy" fibroblast NIH3T3 cells (IC50 > 100 µM). Preliminary results on a xenograft of A375 melanoma cells on chicken embryo chorioallantoic membrane (CAM), suggested the anti-cancer potential of JMV5038. We now focused on structure-activity relationship (SAR) studies of these chemical series to potentially develop new analogues of JMV5038 with better activity and also to increase the hydrosolubility of these compounds.

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Design of PET radiotracers for brain 5-HT$_4$ receptors: influence of fluorine introduction on an indazole scaffold

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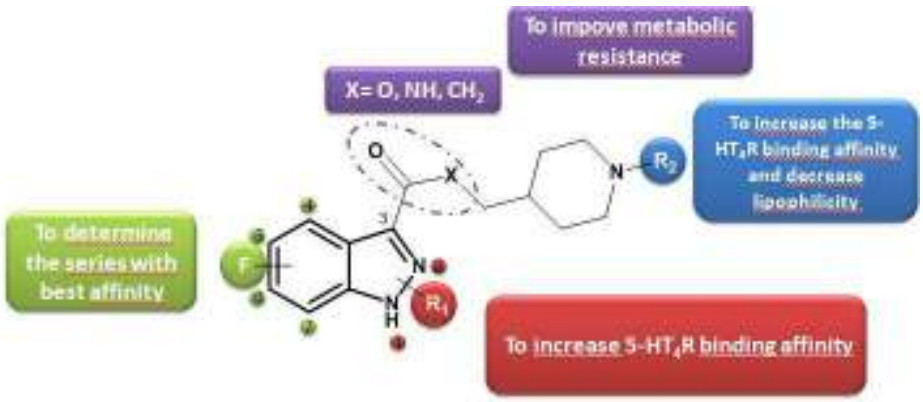
PO 104

Since its discovery in 1988, the serotonin 4 receptor subtype (5-HT$_4$R) has emerged as a promising target for drug discovery and development resulting from their implications in cognition, learning, memory processes and many neuropsychiatric disorders such as Alzheimer's disease, anxiety, depression or anorexia nervosa.[a] Thus, discovery of active 5-HT$_4$R agonists and antagonists remains a continuing interest in clinical research. To this end, positron emission tomography (PET)[b,c] coupled with effective radioligands constitutes a valuable tool, both in clinical studies and drug discovery's program. Based on previous works in CERMN,[d] we aimed to develop new fluorinated indazole derivatives as potential brain 5-HT$_4$R PET tracers.



Scheme 2. Pharmacomodulations in fluoroindazoles series

A convergent synthesis pathway to obtain fluorinated analogues has been established. A methodology allowing selective functionalization at position 3 leading to polyfunctional indazoles within a minimum of step has been developed. New pharmacomodulations studies were realized in order to increase receptor affinity, decrease lipophilicity and increase metabolic resistance.

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Integrin-mediated adhesive properties of neutrophils are reduced by hyperbaric oxygen therapy in patients with chronic non-healing wound

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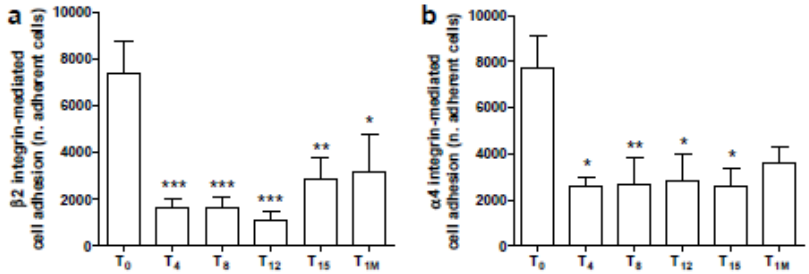
PO 105

Hyperbaric oxygen therapy (HBOT) in the treatment of patients with chronic wounds and diabetic ulcers demonstrated to reduce inflammatory cytokine and neutrophil recruitment in damaged areas. The adhesion of neutrophils to the extracellular matrix is mediated by α_4 and β_2 integrins, hence the effects of HBOT on their expression and function in neutrophils could be promising for the design of new anti-inflammatory therapeutic protocols.[(a,b)] In this context we evaluated α_4 and β_2 integrin function and expression in human primary neutrophils obtained from patients affected by chronic wounds and followed throughout a prolonged HBOT. The effect of a peptidomimetic $\alpha_4\beta_1$ integrin antagonist[(c)] was also analyzed under these conditions: a significant decrease in β_2 integrin expression on neutrophils was observed during the treatment with HBOT, while α_4 integrin levels remained unchanged. However, the cell adhesion function of both integrins $\alpha_4\beta_1$ and β_2 was strongly reduced, while $\alpha_4\beta_1$ sensitivity to antagonist inhibition was maintained, suggesting that a combined therapy between HBOT and integrin antagonists could have greater antinflammatory efficacy.



HBOT reduces integrin-mediated neutrophil adhesion to fibrinogen(Fg) or Fibronectin(FN)

[(a)] S. R. Thom, *Plast. Reconstr. Surg*. 2011, 127, 131S–141S.
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Targeting toxin-antitoxin systems with new RNA ligands in bacteria: towards new antibiotic therapies.	***PO 106***

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There is currently an urgent need for new antibiotics in order to overcome the steady emergence of multidrug-resistant bacteria and the associated human and economic cost.[(a)] The purpose of this project is the discovery of new antibiotics targeting original and so far unexploited targets: **bacterial toxin-antitoxin (TA) systems**.[(b)] TA systems are small genetic elements composed of a toxin gene and its related antitoxin both coding for corresponding toxin and antitoxin products. The toxins of all known TA systems are proteins able to inhibit bacterial cell growth or lead to cell death, whereas the antitoxins are either proteins or small regulatory RNAs that neutralize the toxin. Here, we decided to target **type I TA systems** where **the antitoxin is a non-coding RNA that binds to the messenger RNA (mRNA) coding for the toxin** thus inhibiting its translation. In order to validate the proposed strategy, we propose to target a particular type I TA system of the major **human gastric pathogen *Helicobacter pylori*** which is a gram-negative bacterium infecting about 50% of the entire world population.

Based on the experience our research group in the design and the synthesis of selective RNA ligands, a large library of new compounds constituted of various known RNA binding domains is currently in preparation using a **multicomponent synthetic methodology**.[(c)] The synthesized compounds will be evaluated for their ability **to disrupt the loop-loop interaction** between the antitoxin and the toxin mRNA using *in vitro* assays. The most active compounds will be finally optimized thanks to the proposed highly versatile synthetic methodology in order to improve their biological activity and their pharmacodynamic/pharmacokinetic properties toward a future therapeutic application. In conclusion, we present here an original approach toward **the discovery of new antibacterial compounds** against *H. pylori* infections. The same approach could be further applied to other major pathogens such as *Staphylococcus aureus* and *Mycobacterium tuberculosis*.

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Design and Synthesis of Pyrrolidine-Based Nucleotide Mimetics for Use as Inhibitors of the DNA Repair Enzyme AAG

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PO 107

The action of the DNA repair enzyme alkyladenine DNA glycosylase (AAG), as part of the Base Excision Repair pathway, on alkylation-induced DNA damage has been shown in mice to lead to cell death in the retina, spleen, thymus and cerebellum.[1,2] The action of AAG has also been linked to damage caused by ischaemia/reperfusion (I/R) events in liver, brain and kidney.[3] As a result, small molecule inhibitors of AAG are required for ongoing studies into the biological mechanism of this cellular damage, as well as to become potential drug leads for some types of retinal degeneration, I/R-related tissue damage, or as protective agents for patients undergoing alkylative chemotherapy.

Pyrrolidine-based inhibitors were designed based on the published X-ray crystal structures of AAG in complex with DNA oligomers containing etheno-cytidine or an abasic pyrrolidine, which show potent AAG inhibition *in vitro*.[4] Here we report the rationale behind the design and synthesis of the resulting fragment-sized pyrrolidine-based nucleotide mimetics (Figure 16). These candidates were subsequently tested *in vitro* against AAG, with one of them showing promising inhibition and good ligand efficiency.

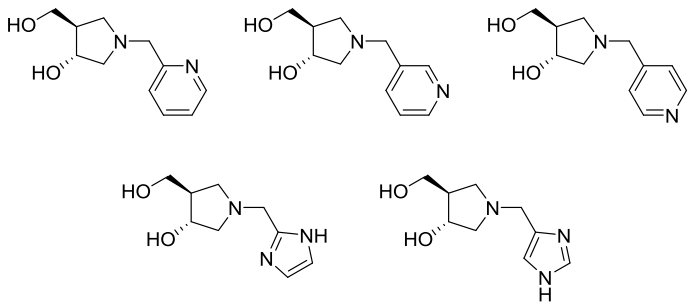

Figure 16: Fragment-like nucleotide mimetics synthesised and tested against AAG

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From *In Vitro* to *In Cellulo*: Evaluation of Anti-TNFα Activity of a New Series of Small Molecules.

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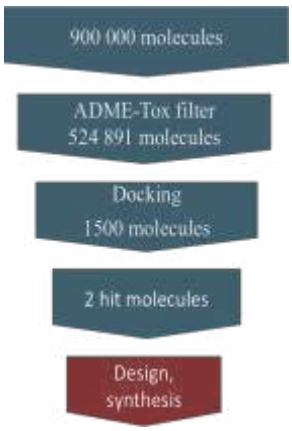
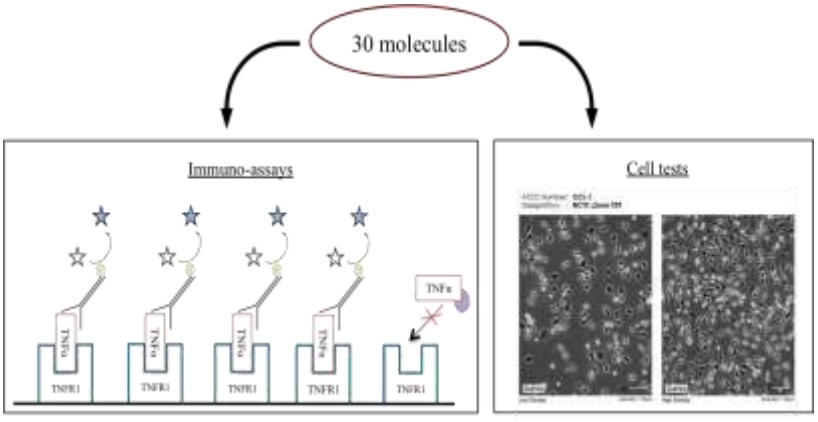
PO 108

The Tumor Necrosis Factor alpha (TNFα) is a relevant clinical target for the treatment of chronic inflammatory diseases, as rheumatoid arthritis or Crohn's disease. Anti-TNFα biotherapies are used for the treatment of these diseases. They considerably improve patient living conditions but they are not without drawbacks. They cause side effects like accrue risk of infection, some patient develop resistance to these biotherapies and they are expensive [1]. Small molecules inhibitors of TNFα would present fewer drawbacks than existing biotherapies, less side effects, no resistance, oral administration and would probably lead to less expensive treatments. Today only few small molecules are known as direct inhibitors of TNFα. SPD304 was the first small molecule described by He *et al* in 2005 [2]. None of these molecules showed both an efficient activity and a low toxicity, necessary to yield them into clinical trial [3] [4].

The Bioinformatics team of GBCM laboratory has set-up a program aiming at finding new small molecules inhibitors of TNFα. A preview *in silico* docking study led to the identification of potential anti-TNFα molecules. Based on the docking results, new small molecules have been designed, synthetized and biologically evaluated in collaboration with the Molecular Chemistry team of GBCM laboratory.
Herein we describe the biological evaluation of a series of thirty new synthetized compounds for their capacity to inhibit the TNFα. These molecules were evaluated *in vitro* using two different immuno-assays (binding and shifting) and cell tests on two different cell lines.





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Synthesis and studies of new CXCR1/CXCR2 antagonists for an application in oncology.

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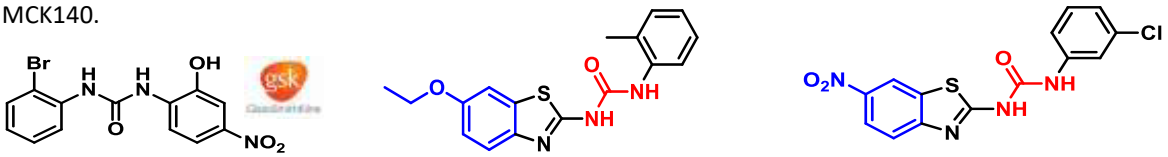
PO 109

The current anti-angiogenic therapies fail to fully eradicate cancer cells, since the tumors always relapse after an initial period of clinical benefit. Therefore, new therapeutic approaches are urgently needed to overcome drug resistances. In this context, our project aims at developing news antagonists of CXCR1 and CXCR2 receptors, to interfere with the ERL+CXCL cytokines signaling pathway.[(a)] This strategy will concomitantly tackle inflammation and angiogenesis. The rational design and the synthesis of a series of new CXCR1/CXCR2 antagonists, structurally-related to SB-225002, a CXCR antagonist developed by GSK,[(b)] led us to obtained two potential hits, MCK 133 and MCK140.



Compound SB225002
IC_{50} > 90 µM (786-O)

Compound MCK133

Compound MCK140
IC_{50} = 2 µM (786-O)

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

These molecules exert *in vitro* cytotoxic effects against a panel of human solid tumors and hematological malignancies, but they are less toxic against healthy cells (human fibroblasts). MCK140 reduces *in vivo* tumor growth in mice xenografted with aggressive human A-498 kidney cancer cell line by more than 30% (Figure. 2).

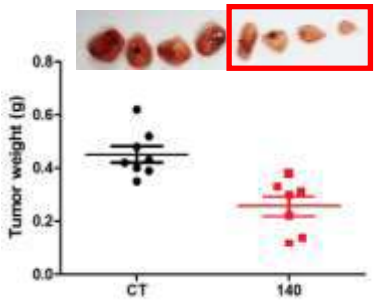


Figure 2: Evaluation of the tumor growth in presence of MCK140.

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

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Evaluation of benzopyrone pharmacophore features on MAO-B inhibition

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PO 110

Parkinson disease (PD) is a multifactorial neurodegenerative disorder pathologically characterized by the loss of dopaminergic neurons in the *substancia nigra* and of dopamine in the *striatum*. Currently, the clinical management of PD is symptomatic and mainly based on restoring dopamine levels. The key pharmacological therapy of PD is the administration of L-dopa in monotherapy or in combination with enzymatic inhibitors, as an L-aromatic amino acid decarboxylase (L-AAAD), catechol-O-methyltransferase (COMT) or monoamine oxidase-B (MAO-B) inhibitors[a]. Existing drug treatments are associated with a gradual loss of efficacy and long term side effects.

Stimulatingly, it was described that MAO-B inhibitors can postpone, in the early stages of the disease, and delay the need for levodopa by a few months and that some MAO-B inhibitors act as disease-modifying agents[b]. However, there is no conclusive evidence from clinical trials.

Considering the importance of MAO-B inhibitors for PD treatment, and the side effects shown by the drugs in therapy, the search of new MAO-B inhibitors is still an active area. In this context, chromone and coumarin were validated as privileged scaffolds for the design and development of new, potent, selective, and reversible MAO-B inhibitors[c-f]. However, the role of the carbonyl and double bound of the benzopyrone ring remain unknowable.

Therefore, a small library of benzopyran-based compounds was synthesized to build up a robust structure-activity relationship and identify the key structural features of the pharmacophore. In addition, benzopyran isosteres were synthesized to study the effect of the replacement of the oxygen atom of the benzopyran motif on MAO inhibition. The results obtained so far will be presented in this communication.

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In silico screening and Hit to lead development of small molecules neurotrophin receptors ligands

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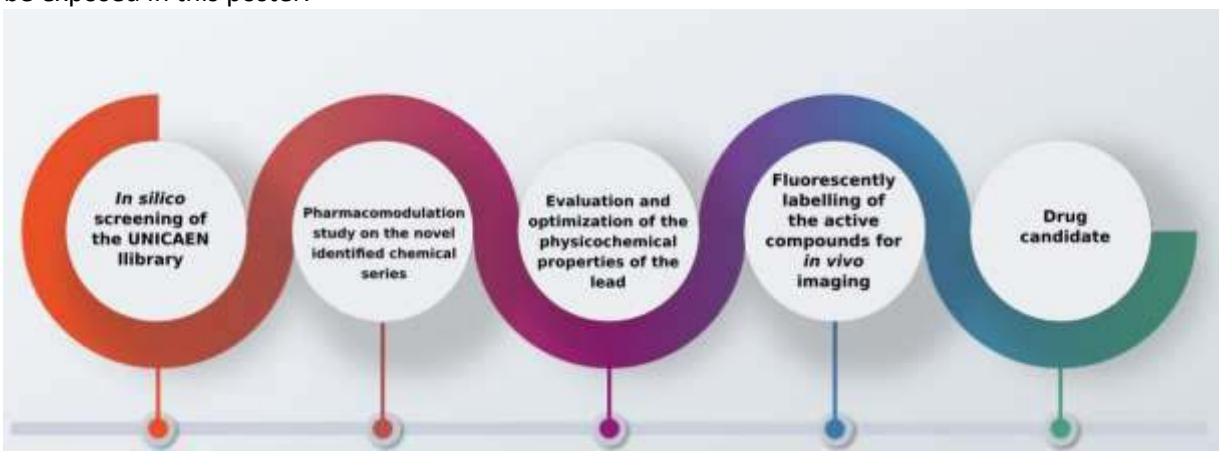
PO 111

Neurodegenerative diseases (ND), like Alzheimer's disease, Parkinson's disease, Multiple Sclerosis and motor neuron disease, are on the rise worldwide. Alzheimer's disease alone affects 36 million people in the world and 7 million in Europe. Currently, there is no cure for any ND and most of the available drugs fail to tackle ND pathogenesis. Numerous studies have been published about the implication of the neurotrophin receptors in the pathogenesis of several neurodegenerative conditions pointing to the therapeutic potential of neurotrophin receptor ligands[(a,b,c)]. There are two types of neurotrophin receptors: a non-enzymatic, trans-membrane protein of the tumour necrosis receptor (TNFR) family – p75; and the tyrosine kinase receptors (Trks) A, B, and C. Trk receptors are activated, specifically, and with high affinity, by nerve growth factor (NGF) (TrkA), brain-derived growth factor and neurotrophin 4 (BDNF and NT4) (TrkB), and neurotrophin 3 (NT3) (TrkC), while p75 is activated by all mentioned neurotrophins[(d)]. A number of properties limit the therapeutic application of the neurotrophins: short half-life in the plasma, poor blood-brain barrier penetration [(e)]. Because of this reasons, there is a huge need to develop a data set of the non-peptide, small molecules capable of interacting with neurotrophin receptors with high potency and specificity. The objectives of our project will be to identify and develop novel small molecules mimetics of neurotrophin in the context of the European network Euroneurotrophin. Our first results obtained from the *in silico* screening of CERMN Chemical Library will be exposed in this poster.



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New hope for knee osteoarthritis: IGF-1-regulating chimeric peptides showing therapeutic activity on knee osteoarthritis are well tolerated in vivo.

PO 112

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Introduction: Osteoarthritis (OA) is a chronic musculoskeletal disease characterized by matrix components degradation (proteoglycans and type II-collagen) responsible for the loss of cartilage. There is no curative treatment available for early and moderate knee OA and because Insulin-like growth factor-1 (IGF-1) is involved in the mechanisms leading to the production of matrix components, we designed and developed a new chimeric peptide targeting IGF-1 pathways as a disease modifying osteoarthritis drug (DMOAD). This peptide (REG-O3) combines a short amino acid sequence derived from animal growth hormone (GH) and an analog of somatostatin (SST), both molecules being involved in IGF-1 pathways regulation. We already demonstrated that REG-O3 induces *in vitro* an increase of both IGF-1 expression and matrix components synthesis (type II-collagen), improves knee joint function and significantly preserves cartilage from degeneration in two knee OA animal models. Therefore, we hypothesized that REG-O3 might be a candidate DMOAD in Human. However, the GH fragment used for REG-O3 is not conserved during evolution. To overcome this limitation, we designed and synthesized new humanized REG-O3 chimeric peptides and selected the lead candidate based on its ability to induce matrix components synthesis. Finally, we studied the systemic exposure of this lead candidate as well as its local/general tolerance.

Methods: The humanized chimeric REG-O3 peptides (h1-REG-O3, h2-REG-O3 and h6-REG-O3) have been designed by replacing the animal GH sequence used for REG-O3 by the corresponding Human one. While h1-REG-O3 exhibits a sequence derived from the wild-type human GH, h2-REG-O3 and h6-REG-O3 contain a sequence derived from the polymorphic human GHs. Those peptides were synthesized chemically using automated microwave peptide synthesizer and products were characterized by reverse phase high performance liquid chromatography with UV detector coupled with mass spectrometry. To test the ability of these humanized peptides to induce matrix component synthesis, human articular chondrocytes were grown with each peptide for eight days. These cells were then fixed and stained with Alcian blue to visualize, by microscopy, matrix proteoglycans. h6-REG-O3 tolerance and its systemic exposure were studied in dogs (Beagle). h6-REG-O3 was administered by a single intravenous (IV) injection at dose levels up to 10 times the targeted therapeutic dose. After a week of washout, h6-REG-O3 was administered by a unique intra-articular (IA) injection in the left knee joint at dose levels up to 10 times the targeted therapeutic dose.

Results: Based on the Alcian blue staining, h6-REG-O3 was selected as the lead candidate since the treated cells with this peptide displayed the higher production of proteoglycans. *In vivo*, h6-REG-O3 showed a safe profile. At dose levels up to 10 times the targeted therapeutic dose, there was no side effect of neither a single IV nor IA injection of h6-REG-O3 on general clinical signs, food consumption, body weight, organ weight and clinical pathology parameters. Furthermore, no adverse macroscopic nor microscopic findings could be attributed to h6-REG-O3. Interestingly, h6-REG-O3 exhibited a fast leakage from knee to systemic circulation but at very low level and a very short lifetime in systemic circulation.

Conclusions: h6-REG-O3 peptide was selected as the candidate to be tested as a DMOAD in Human. It was shown to be safe upon either a single IV or IA injection up to 10 times the targeted therapeutic dose. Even if repeated toxicity study needs to be performed, the present work provides important information for the future clinical trials regarding h6-REG-O3 safety.

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Investigating the mode of action of antimalarial drug Plasmodione using the yeast model

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PO 113

Abstract

Malaria is an infectious disease that causes more than 400,000 deaths per year, according to WHO. The disease is caused by an apicomplex protozoan parasite of the genus *Plasmodium*. Numerous antimalarial drugs have been developed. Unfortunately, many cases of resistance have been reported. New drugs are thus urgently needed.

Plasmodione (3- [4- (trifluoromethyl) benzyl] –menadione) or PD is a new antimalarial molecule developed by the team of E. Davioud in Strasbourg. It is a potent inhibitor of the proliferation of *Plasmodium* sp. especially at the gametocyte phases. Development of drugs active at gametocyte stages and thus blocking the transmission to mosquitoes is a priority defined by WHO. The mode of action of PD is not fully understood. *In vitro* studies showed that PD would act as a redox cycler of the flavoprotein NADPH-dependent glutathione reductase (GR) and the methemoglobin (Bielitza et al., 2015). PD activity pathway was proposed to start with the benzylic oxidation of PD to form PDO (3-benzoylmenadione), which acts as a subversive substrate of the GR or other flavoenzymes .

Using the yeast (*Saccharomyces cerevisiae*) model, we are investigating the mode of action of PD and its putative metabolites PDO and PD-bzol. We observed that PD inhibits yeast respiratory growth (but not fermentation growth), and this *via* an oxidative stress. We found that the respiratory chain NADH-dehydrogenases (NDH) are involved in PD sensitivity. These flavoenzymes can use PD and its metabolites as substrate, the reaction resulting in ROS production. The study of the role of NDH in PD activity in the parasite *P. falciparum* will start soon.

More work is also in progress to identify, in the yeast model first, other actors in PD sensitivity and resistance.

Synthesis of S-containing 2'-deoxyuridines as potential antibacterial inhibitors.

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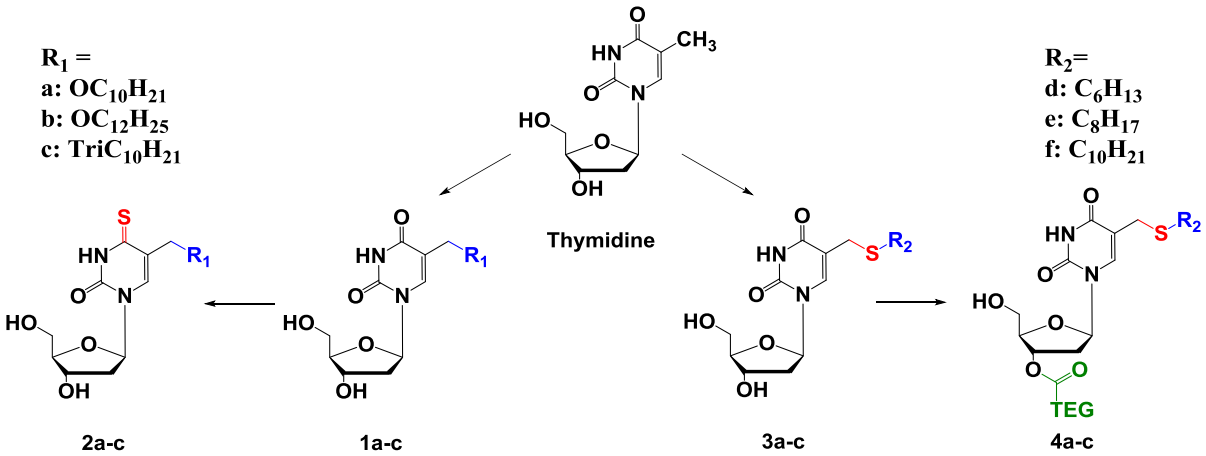
PO 114

Pyrimidine nucleosides bearing substituents in position C-5 display various antimicrobial activities[1]. A series of pyrimidine nucleoside analogues **1a-c** with lengthy flexible alkyloxymethyl and alkyltriazolylmethyl substituents obtained in our laboratory demonstrated *in vitro* inhibitory properties towards a group of microorganisms including *M. tuberculosis*[1-2]. The goal of this work was changing of the oxygen atom at certain positions to bioisosteric sulfur atom which can lower the polarity and enhance the lipophilicity in order to obtain more active compounds.

Substitution of the C-4 carbonyl group to thiocarbonyl appeared to be a challenging task, because using standard thiation reagents (such as Lawesson`s reagent or P_2S_5) did not lead to the desired products. Using a different route, we obtained compounds **2a-c**, which were tested against H37Rv strain of *M. tuberculosis*.

A series of 5-thioalkyl derivatives of 2'-deoxyuridine **3a-c** was also obtained as potential microorganism growth inhibitors. However, these compounds were poorly soluble in water which made the biological investigations complicated. A non-toxic triethylene glycol group was used as a hydrophilic substituent in order to increase their solubility to give derivatives **4a-c**. Their antibacterial activity, cytotoxicity and water solubility values will be reported.



Acknowledgment: The study was supported by the Russian Foundation for Basic Research [grant № 17-04-00536].

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Novel 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazines bearing thiazolidine-2,4-dione or thiosemicarbazone functions as antiparasitic agents **Felipe N. Coutinho (1,2)*, Marlene S. Araújo Neta (1,2)*, Antônio R. de Faria (2), Carine Picot (1), Fabrice Pagniez (1), Patrice Le Pape (1), Teresinha G. da Silva (3), Pascal Marchand (1).** *(1) EA1155 – IICiMed, IRS2, University of Nantes, France, 44200.* *(2) Department of Pharmaceutical Sciences, University of Pernambuco, Recife-PE, Brazil, 50740-520.* *(3) Department of Antibiotics, University Federal of Pernambuco, Recife-PE, Brazil, 50740-520.*	***PO 115***

Neglected Tropical Diseases (NTDs) affect mainly underdeveloped or developing countries located in Africa, Asia and Latin America. Worldwide, there are more than one billion people affected by these diseases[(a)]. These include Chagas disease and leishmaniasis, caused by protozoa. Difficult of treatment due to the amount of side effects of the drugs currently used, the resistance of the parasite and late detection are concerns to address. Therefore, the development of new substances for the treatment of NTDs is extremely necessary. Thus, using medicinal chemistry tools such as molecular hybridization, novel 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine/thiazolidine-2,4-dione or aryl-thiosemicarbazone molecular hybrids were synthesized (Figure 1).

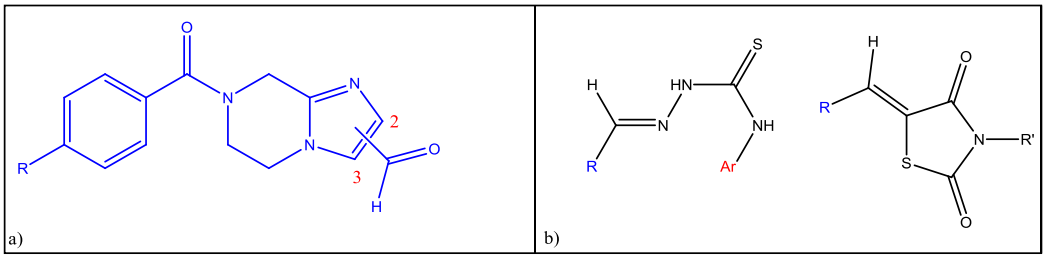

Figure 1. a) 5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazine-carboxaldehyde before coupling. b) General structures of target compounds.

According to the literature, such compounds would display antichagasic[(b)] and antileishmanial activities[(c,d)]

The first developments of this novel series of hybrid molecules will be discussed.

Acknowledgements: CAPES-COFECUB Program, Brazil-France

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Design, synthesis and *in vitro* evaluation of a promising new class of bifunctional uncharged hybrid reactivators for nerve agent-inhibited human acetylcholinesterase.

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PO 116

Summary: Acetylcholinesterase (AChE) is a key enzyme of neurotransmission hydrolyzing the neurotransmitter acetylcholine.[1] By targeting AChE, organophosphorus nerve agents and pesticides disrupt the cholinergic transmission leading to a certain death if untreated. The current treatment available in the French army consists of an auto-injector containing 2-PAM for AChE reactivation, atropine as an anticholinergic drug, and avizafone, a prodrug of diazepam for stopping convulsions. However, this treatment is limited in terms of CNS bioavailability, spectrum of action and effectiveness.

The aim of this project is to develop a new class of efficient reactivators for nerve agent-inhibited human acetylcholinesterase. We designed, synthesized and evaluated bifunctional uncharged hybrid reactivators composed of a 3-hydroxypyridinaldoxime linked to tacrine derivatives.[2,3] The *in vitro* efficacy of this reactivators have been assessed. We show that this new class of reactivators outperform HI-6 in restoring the human AChE activity inhibited by VX, sarin, tabun surrogates and paraoxon. Using a human *in vitro* model of BBB, we showed that our leading compound could reach the CNS as efficiently as Diazepam. By X-ray crystallography, we have been able to observe some of this new hybrids bound in the active site gorge of *Tc*AChE.

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Synthesis and Antimicrobial Activity of Novel NHC*- and Ph_3P-Ag(I)-Benzoate Derivatives

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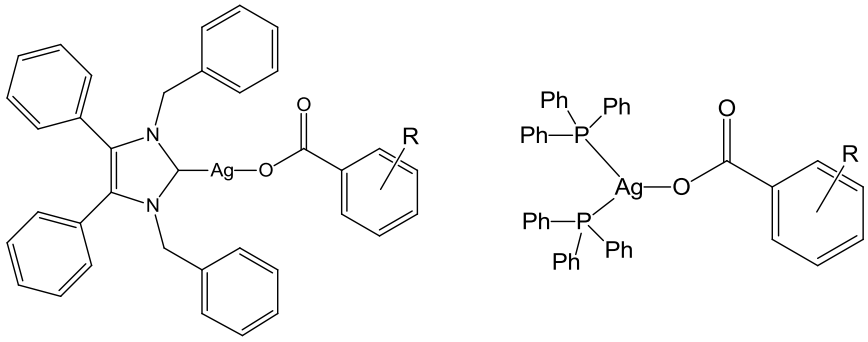
PO 117

The rising threat of Antimicrobial Resistance (AMR) requires a novel approach to the treatment of infectious diseases.[1] Covalently bonded silver, which has known antibacterial and antifungal properties and multiple mechanisms of action, may provide a treatment strategy when used alone or in combination with already known antimicrobial compounds.[2] We present the synthesis of eight novel silver(I) complexes and the encouraging antimicrobial *in vitro* activities against two pathogenic bacterial strains, *Methicillin-resistant Staphylococcus aureus* (*MRSA*) and *Escherichia coli* (*E. coli*), and against two pathogenic fungal strains, *Candida albicans* and *Candida parapsilosis*.[3]



NHC*-Ag(I) Benzoate and Ph_3P-Ag(I)-Benzoate Derivatives for Targeting Infectious Microbial Strains

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Ullman-Derived Inhibitors Of Er-Aminopeptidases (Eraps)

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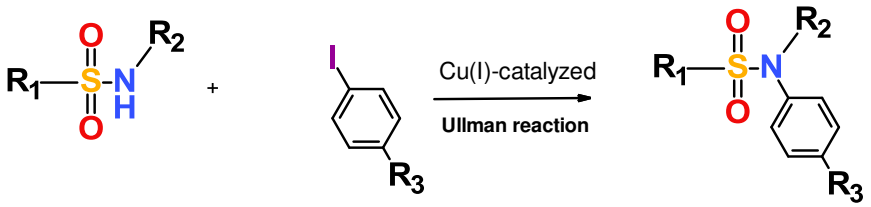
PO 118

Endoplasmic reticulum aminopeptidases (ERAP1 and 2) are M1 family zinc metalloproteases playing a key role in the antigen presentation pathway. These intracellular aminopeptidases trim peptide precursors resulting from proteins degraded by the proteasome, and generate mature antigenic epitope of appropriate length for presentation on the cell surface by major histocompatibility complex class I (MHCI) molecules. The cytotoxic T-cells recognition of the extracellular peptide triggers immune response against infected or diseased cells through biological cascades leading to cell apoptosis. Thereby, ERAPs are major regulators of adaptive immune response in humans. GWAS studies have associated polymorphism of ERAPs with predisposition to immune diseases (i.e. ankylosing spondylitis, Behcet syndrome, Birdshot uveitis and type1 diabetes). ERAP1 inhibition was shown to delete Th17 response in a model of spondylarthritis (Chen, L., et al. (2016) Annals of the Rheumatic Diseases 75(5): 916-923). On the contrary, cancer cells can evade the immune system by stopping the generation of antigenic peptides, and ERAP1 inhibitors have been shown to affect antigen processing in cultured cells and elicit cytotoxic T-cell responses in a dose- and affinity-dependent manner (Zervoudi E. *et al. PNAS.* 2013, *110*, 19890-5). Thus, ERAPs have emerged in the past years as potential targets for cancer immunotherapy, that may lead to treatments for autoimmune diseases acting upstream inflammatory chemokine production.

Up to now, the ERAP2 inhibitors bear either a phosphinic group or a 1,4-diaminobenzoic acid motif, to bind the catalytic zinc atom. They display good to excellent activities against ERAP2 (IC_{50} of 240 to 11nM). However, these inhibitors need to be optimized to achieve better selectivity and druggable properties. In parallel to these efforts, we developed a fast enzyme-efficient 384-well plate HTS assay, and we screened a focused in-house library to discover new chemical templates able to inhibit ERAP2. One of the hits identified during the screening campaign displayed an *N*-aryl-sulfonamide group. Thus, we designed and synthesized analogues of this hit and explored their potency to inhibit ERAP1, 2 and their selectivity towards related IRAP and LAP enzymes.



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Detection of Vancomycin Resistance, what can we do?

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PO 119

Summary : Glycopeptides are last resort bactericidal antibiotics in hospital medium.[a] Among them, vancomycin is the most important. The resistance to vancomycin, which is in progression, constitutes a serious problem of public health in Europe.[b] Enterococcus faecium resistant to the glycopeptides was classified as an emergent highly resistant bacterium (BHRe).[c] Therefore it occupies the first place of priorities list of WHO in the fight against resistances to antibiotics.[b] Methods of detection of resistances to the glycopeptides were developed but they are slow and/or expensive. A fast detection of these resistances will make it possible to isolate and take charge of patient precociously, and limit the dissemination of the resistant stock thus. In order to contribute to the ousting of epidemics and possibly of endemic diseases, the objective of this study is to develop methods of fast detection of vancomycin resistance. The concept of methods base on the detection of resistance through the D-Ala-D-Ala dipeptidase activity of VanX will be developed, evaluated and validated. VanX activity will be detect by releasing a chromogenic agent [figure 1].

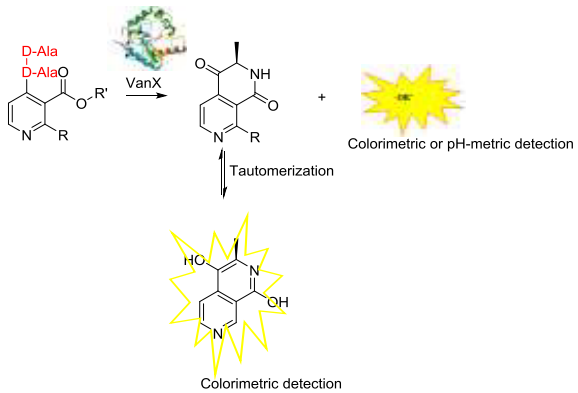

Figure 17 : Scientific approach

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Design, Synthesis And Structure-Activity Relationships Of Quinoxaline Analogues As Pim-1 Kinase Inhibitors

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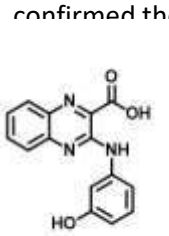
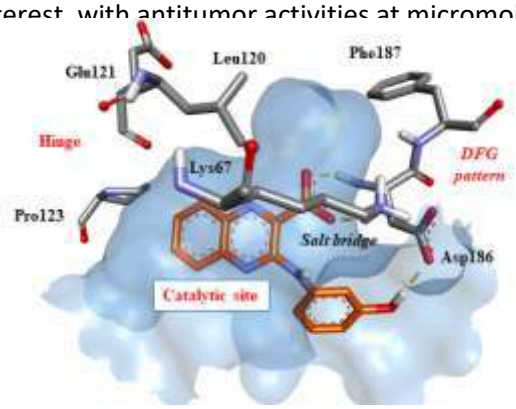
PO 120

The oncoprotein Pim-1 is a serine/threonine protein kinase involved in cell cycle regulation, cell survival, proliferation, and differentiation.[1] This kinase is overexpressed in a large range of human tumors[2], plays a crucial role in resistance to chemotherapy drugs[3], and is thus considered as a relevant target for cancer therapy. We identified the quinoxaline-2-carboxylic acid **1** as a new lead compound by performing an *in vitro* screening on a panel of kinases, comprising *Homo sapiens Hs*Pim-1. This molecule was able to inhibit the *in vitro* enzymatic activity of *Hs*Pim-1 with an IC_{50} of 74 nM. Docking studies realized in the ATP pocket of *Hs*Pim-1 suggested an unclassical binding mode of this inhibitor. We then determined a study model, based on fragment growing studies, to elucidate the structure-activity relationships of our compounds. Thus, 21 new derivatives were synthesized, and evaluated *in vitro* on *Hs*Pim-1, and on a panel of mammalian kinases to determine their selectivity profile. Finally, *in vitro* studies of the most potent inhibitors on the human chronic myeloid leukemia cell line KU812, overexpressing Pim-1, confirmed their interest, with antitumor activities at micromolar concentrations.[4]



Lead 1

IC50	µM
*Hs*Pim-1	0,074
KU812	38,9



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Thiols in food matrices: A new separative and quantitative method based on nanostructured polymeric films.

PO 121

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Thiols (RSH) are characterized by the presence of a sulfhydryl group (-SH). Depending on the size of the R group, thiols are available in low molecular weight (cysteine, homocysteine or glutathione) or high molecular weight (proteins with cysteine groups). In the food industry and especially in beverages, thiols are considered as key markers in olfaction. These so-called volatile thiols are characterized by a low molecular mass (100-300 DA) and play a major role in the quality of different food like wine, beer, coffee, or tropical fruit. Since their perception thresholds are very low, their influence on the aroma can be considerable on the final perception of a product This is the reason why various complex technics have been developed to detect and quantify those thiols. However, those technics implied high solvent amounts along with the use of mercury-based reagents and are time consuming.

In this project, we developed a new sensitive method dedicated to concentrate specifically food thiols and analyze them. To achieve this objective, we used the properties of gold nanoparticles (AuNP) which have a high affinity towards -SH groups. This catalytic activity of colloidal AuNP has already been demonstrated in our lab (1). To overcome colloidal AuNP lack of stability, they were immobilized on a cellulosic membrane with the help of polymeric films. Those films were built in two steps: first, deposition of a cationic layer using 0.1 M poly(allylamine) hydrochloride (PAH) solution and second, deposition of citrate stabilized AuNP. Membranes were monitored with Transmission and Surface Electronic Microscopy (TEM – SEM) (Figure 1). Deposited AuNP were individualized on the surface and gold quantification (2) led to a magnitude of 10^{14} AuNP/cm² of film.

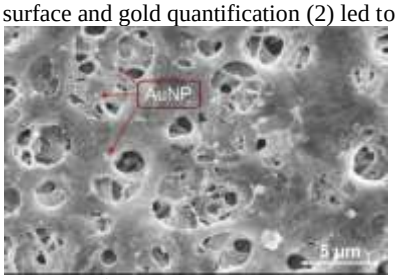

Figure 18: SEM picture of immobilized AuNP on a cellulosic membrane

This immobilization is of great interest in terms of stability of AuNP under real sample conditions and creating a reservoir containing high amounts of AuNP. These two points have been the subject of previous studies in our laboratory (3). Finally, immobilization on a support generates a device that can be easily handled and eliminates many sample processing steps. The full strategy is illustrated in Figure 2.

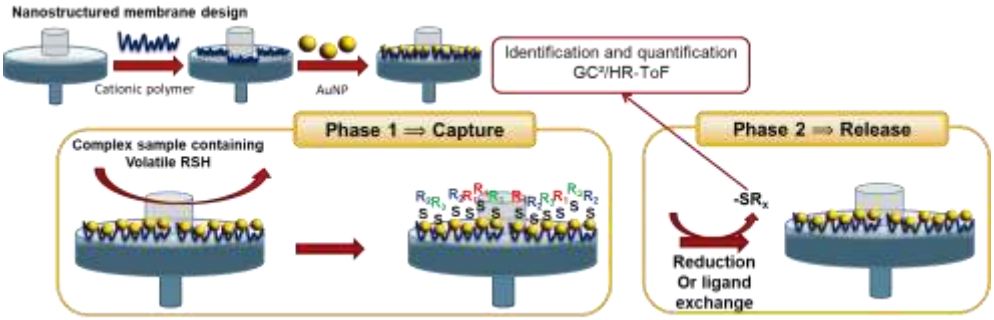

Figure 19: Strategy of detection and quantification of volatile thiols in complex matrices.

As a proof of concept reduced glutathione (GSH) was used as model thiol. The kinetic capture of GSH at 5 µM appeared to be very quick (95 ± 5 % of GSH captured in less than 5 min of contact). To release immobilized GSH, membranes were treated with dithiothreitol (DTT) and resulting filtrate was analyzed using HPLC coupled to UV detection. The recovery yield was 60 ± 10 % in reduced GSH.

It is of common knowledge that reduced thiols have a low stability in complex matrices. However, this new separation process coupled with an efficient detection method will allow us reaching thresholds of volatile thiols required by food industry.

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Genetic Code Expansion of novel recombinant Human Arylsulfatase B

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PO 122

Lysosomal Storage Diseases (LSDs) are inborn metabolic disorders (a). LSDs are caused by a lysosome enzyme dysfunction which leads to substrate aggregation in lysosome (b). Mucopolysaccharidosis VI (also named Maroteaux-Lamy syndrome) is one of LSDs with autosomal recessive inheritance pattern. Patients suffer from Maroteaux-Lamy syndrome have mutations in Arylsulfatase B gene (c). Arylsulfatase B (ASB, EC 3.1.6.1) is a lysosomal hydrolase that breaks sulfate ester bond in N-acetylgalactosamine 4-sulfate residues of dermatan sulfate (d). Dermatan sulfate aggregation due to ASB's dysfunction will lead to various symptoms in different organ and tissues (e) such as bone dysplasia, heart problems and neural disorders. Though these symptoms reduce life quality remarkably and most patients lose their lives early (f,g),there is no permanent cure for the disease. Currently, gene therapy is used to arrest further deterioration by supplying the sufficient concentration of functional enzyme which is called Enzyme Replacement Therapy (ERT) (g). Galsulfase (Naglazyme®) is FDA-approved drug for Maroteaux-Lamy syndrome patients (h). Genetic code expansion is dedicating a genetic code to non-natural amino acids. Incorporation of non-natural amino acids in proteins contribute to a better control of protein's chemical structure. Based on the type of non-natural amino acid that is used, protein function could be changed (i). In other words, genetic code expansion method is considered as an important tool in protein engineering since non-natural amino acids provide wider range of chemical functionality. We applied genetic code expansion to produce a novel recombinant human Arylsulfatase B with superior therapeutic features.

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Polyol-made luminescent lanthanide based nanocrystals and their evaluation as efficient nanoprobes for optical imaging	***PO 123***

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Polygonal-shaped about 75 nm sized and highly crystallized Ln-doped β-$NaYF_4$ particles with three different Lanthanides (Ln), Eu, Er and Yb, were directly prepared under mild conditions using the polyol process [1]. A set of operating parameters are optimized to have a very stable β allotropic form with a small and controlled size in one-step. A double layer of oleic acid is applied on the surface which will induce the hydrophilicity of the nanocrystals. Depending on the nature of the lanthanides used, strong emissions are observed at different wave length under 2-photons excitation (Fig. 1). These luminescent properties are extremely advantageous for biological imaging applications due to their narrow emission bands with a specific energy in the NIR region, long life-time and good resistance. Any accurate cytotoxicity was observed when incubated with healthy human foreskin fibroblast (BJH) cells for doses as high as 50 $\mu g.mL^{-1}$ with 48 h of contact for the Ln doped nanocrystals.

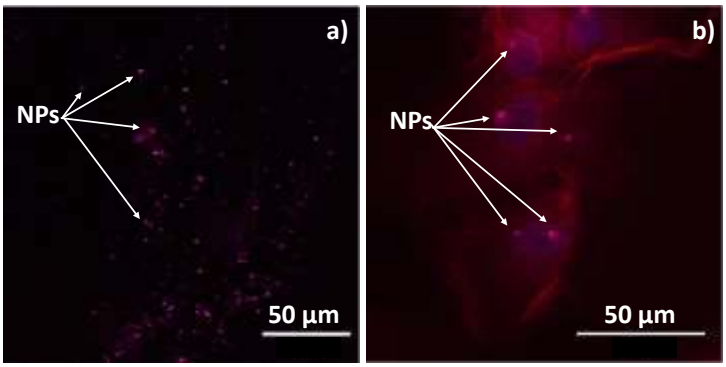

Figure 1. Two photon images using 830 nm as excitation wavelength collected on β-$NaY_{0.8}Eu_{0.2}F_4$ particles contacted with particles BJH cells counterstained with the blue DAPI and red TRITC dyes.

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* Correspondence: parvizian.mahsa21@gmail.com

Synthesis Of Polyfunctionalized Imidazo[2,1-*B*][1,3,4]Thiadiazoles As Novel Dyrk1a/Clk1 Dual Inhibitors.

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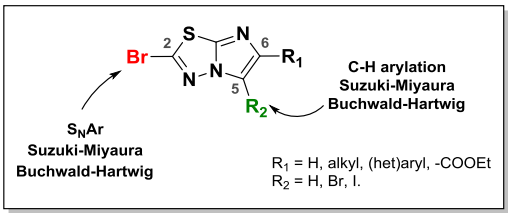
PO 124

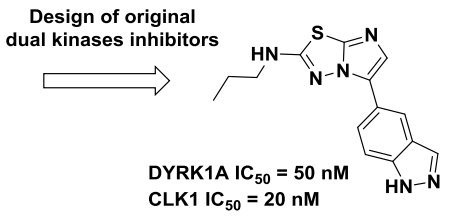
The interest in the imidazo[2,1-*b*][1,3,4]thiadiazole[a] moiety for application in pharmaceutical products makes this scaffold a highly useful building block for organic chemistry. Such derivatives have found applications in oncology[b], infectiology[c] or neurodegenerative diseases.[d] However, the synthetic tools for accessing of highly functionalized imidazothiadiazoles are very limited, and only few functionalization methods are described.[e] In order to increase the molecular diversity of these derivatives, there is consequently tremendous interest in developing efficient synthetic methodologies.

Consequently, we developed several methodologies to modulate regioselectively the *C-2*, *C-5* and *C-6* positions of this scaffold.[f] In order to create C-C, C-N, C-O or C-S bounds, we used various reactions as S_NAr, C-H arylation, palladium catalyzed cross coupling. We investigated the reactivity of each position and showed the influence of previously introduced groups.

Finally, we implemented these efficient methodologies to design dual inhibitors. Indeed, the functionalized scaffold could be a strong inhibitor of DYRK1A and CLK1 kinases, involved in the neuronal degeneration pathway observed especially in the Alzheimer disease.

These methodologies, the synthesis of the compounds and the results of biological tests will be presented in this communication.





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Frags2Drugs, from fragment database to new potent and selective protein kinase inhibitors

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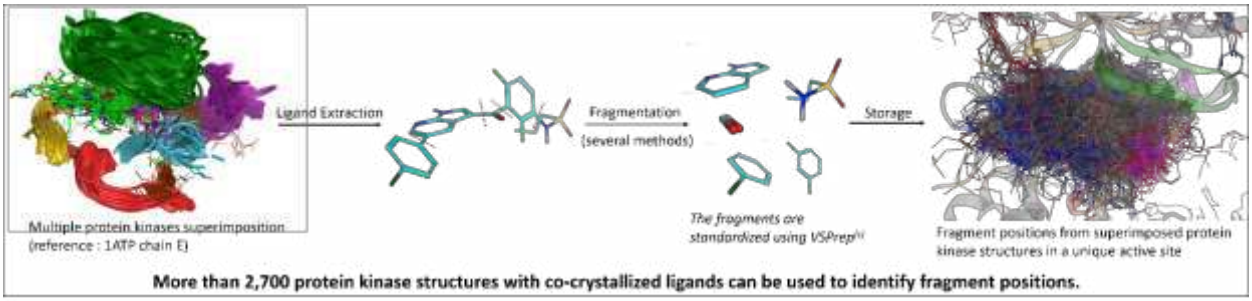
PO 125

Over the last two decades, Fragment-Based Drug Design (FBDD) approach has been widely developed in academic laboratories and pharmaceutical companies[(a)]. Today, several drugs approved by the FDA or in advanced clinical trials were discovered from FBDD. For instance, vemurafenib was developed by Plexxikon and approved by the FDA in 2011[(b)].

Fragments are molecules with low molecular weight (≈ 300 Da). Thanks to their size, they bind more efficiently to their targets, but weaker compared to drug-like molecules. Fragments can be optimized (growing) or combined (linking) in the active site of the target to generate potent and selective new inhibitors.

Frags2Drugs (F2D) is an *in silico* FBDD tool that uses fragment positions extracted from co-crystallized ligands or molecular docking. Relations between thousands of fragments are divided in two categories, exclusion or inclusion, and stored in a graph-oriented database.



More than 2,700 protein kinase structures with co-crystallized ligands can be used to identify fragment positions.

Starting from an initial fragment, called seed, this database allows finding back all the connections with other fragments in the target. The seed is chosen by a medicinal chemist as a molecular scaffold. At the end of the growing, in-house kinase-like filters, extracted from PKIDB[(d)], are applied to the proposed molecules in order to target only the kinase chemical space.

F2D was validated by reconstructing all known co-crystallized protein kinase inhibitors. Recently, it was successfully applied on 3 protein kinases implicated in cancer and neurodegenerative diseases. New patentable series were synthesized and excellent kinase activity (nM range) and selectivity (S(10)=0.011 @1□M on 93 kinases) were obtained *in vitro*.

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Volatile compound probe for the prediction of chemotherapy efficacy.

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PO 126

Cancer remains a major problem of public health, being the leading cause of death worldwide with 8.8 million deaths in 2015 according to the World Health Organization (data from February 2018). Despite significant advances, therapeutic approaches, including chemotherapy, still show some ineffectiveness against tumours especially at a late stage of the disease.
Parallel to the development of smart drug delivery systems, emerging approaches have been designed to predict the efficacy of chemotherapeutic strategies [(a-d)]. Within this framework, we deviated the primary function of a chemobiological concept we have developed to diagnose all solid tumours, to give it a predictive function with the aim to anticipate the efficacy of chemotherapies.
This concept, inspired by prodrug monotherapy (PMT) strategies, involves the detection in exhaled air of an exogenous volatile organic compound (VOC), ethanol, after its intra-tumour metabolization *via* a targeted enzyme specific to this environment. Following on, by quantifying the amount of exhaled VOC during a chemotherapeutic protocol, the dynamics of tumour growth or regression could be monitored.
In this proposal, we will briefly present the overall concept and the *in vivo* results obtained on model animals. We will finally show the potential of this companion tool to predict, survey and improve the efficacy of novel chemotherapeutic agents.

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Design, synthesis and biological evaluation of new RNA ligands as inhibitors of oncogenic microRNAs production.

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PO 127

MicroRNAs (miRNAs) are a class of small non-coding RNAs that act as regulators of gene expression at the post-transcriptional level. Increasing evidence has indicated that the deregulation of miRNAs expression is linked to various human cancers and therefore, miRNAs represent a new class of potential drug targets. In this context, we focused on the discovery of new inhibitors of oncogenic miRNAs production. We choose to target two miRNAs (miRNA-372 and miRNA373) implicated in various types of cancer, such as gastric cancer. Their precursor pre-miRNAs are overexpressed in cancer cells and lead to mature miRNAs after cleavage of their stem-loop structure by the enzyme Dicer in the cytoplasm.[(a)]

Our group previously demonstrated that conjugates of the aminoglycoside neomycin with artificial nucleobases were able to efficiently inhibit the production of oncogenic miRNAs upon binding to their precursors and inhibiting Dicer-mediated processing. This activity has been directly linked to a decrease in the production of oncogenic miRNA-372 and -373 in adenocarcinoma cells and the decrease of cancer cells proliferation was observed.[(b)] While these compounds were efficient inhibitors, their physicochemical properties were not favorable for future therapeutic applications.

Here we describe a new series of drug-like conjugates where the previously employed neomycin was replaced with 2-desoxystreptamine (Figure 1). This latter belongs to neomycin, it is known to be particularly important in the interaction with RNA and bears a reduced size. The synthesized compounds have been studied for their ability to inhibit Dicer processing of pre-miRNAs *in vitro* and for their affinity and selectivity for these targets. We were able to demonstrate that some of these compounds maintain the biological activity of their neomycin analogs opening new perspectives for the synthesis of new efficient and selective RNA binders.

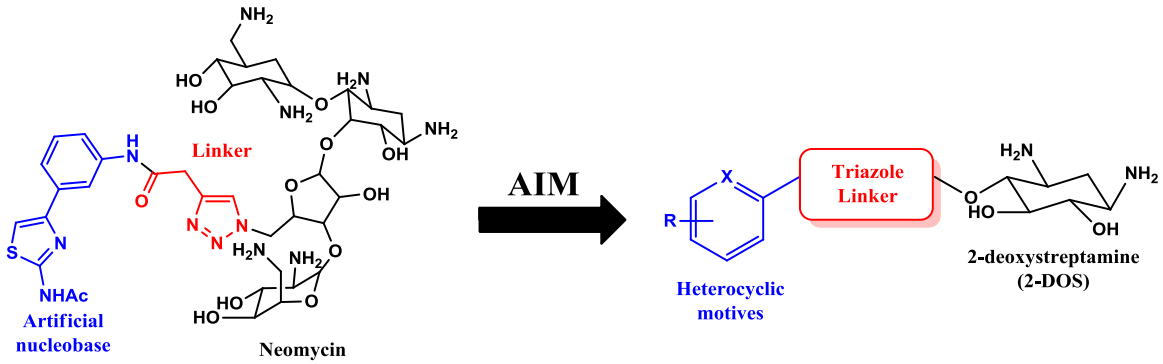

Figure 1 : New inhibitor structure of oncogenic miRNAs

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Design and synthesis of boronic acid substituted heterocycles as Arginase 1 inhibitors.	***PO 128***

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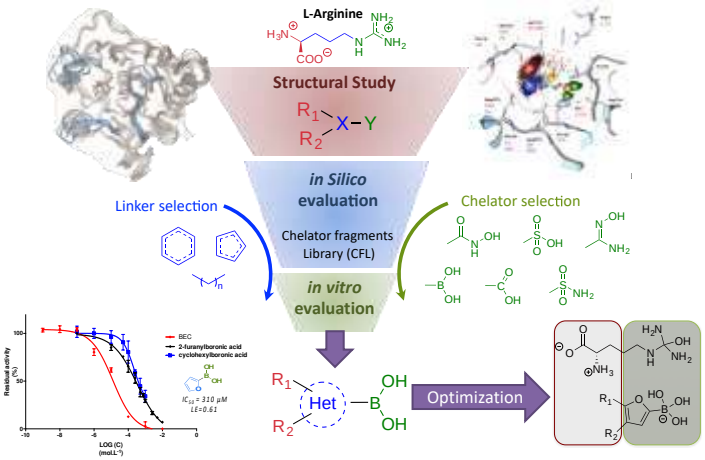
Despite major advances in understanding the mechanisms leading to tumor immunity, the discovery of effective therapies is confronted to numerous difficulties. Such obstacles include the ability of tumors to foster a tolerant microenvironment and the activation of a plethora of immunosuppressive mechanisms. Among others major mechanisms, immunosuppression involves the catabolism of L-tryptophan and L-Arginine. In the context of L-arginine depletion, Arginase 1 (ARG1) is a therapeutically relevant target in tumor tolerance, synergistically associated with tumor growth.



Our current strategy leading to better understanding of molecular mechanism of ARG1 will be presented as well as our advancements in the discovery of inhibitors to use as pharmacological tools. A rational structure based drug design was combined with a in depth computer-aided investigation, including molecular dynamics and construction of dynamic 3D pharmacophore (dynophores). Building up Chelator Fragments Library (CFL) as innovative approach specifically targeting metals of ARG1 highlighted the interest of study the linker moiety. Assessment of cycle and heterocycle derivatives was confirmed by experimental testing with a targeted fragment library focused on the more efficient chelating function, *i.e.* boronic acid.

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Branched peptidomimetics as VEGF-A_{165}/NRP-1 complex inhibitors.

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PO 129

Neuropilin-1 (NRP-1) is a surface receptor involved in the angiogenesis process in physiological and pathological conditions, including cancer.[(a)] It is admitted that vascular endothelial growth factor A_{165} (VEGF-A_{165}) is the most important NRP-1 ligand with pro-angiogenic activity.[(b)] Some reports have suggested that VEGF-A_{165}/NRP-1 complex on the surface of cancer cells is responsible for inducing tumour growth and metastasis.[(c)] These results indicate that searching for new VEGF-A_{165}/NRP-1 complex inhibitors, including functional peptides, could play a crucial role in drug development (e.g. in oncology). Peptides, which specifically bind to the VEGF-binding region of NRP-1, require C-terminal exposure of so-called CendR motif.[(d)]

Biologically active peptides might be good candidates for potential drugs, but sequences containing natural amino acids usually have short biological half-life due to the enzymatic degradation. Peptidomimetics containing unnatural amino acids and/or amide bond mimetics are considered to be more resistant to enzymatic degradation, due to the fragments unrecognizable by the enzymes. We have recently developed branched peptides with the K(*h*R)XXR sequence, which exhibit a significant $VEGF_{165}$/NRP-1 binding inhibitory effect.[(e)] Therefore, to improve enzymatic stability and affinity to NRP-1, peptidomimetics based on K(*h*R)XXR with unnatural amino acids and amide bond mimetics have been synthesized. We have also compared methods used in determining the affinity of ligands for NRP-1.

Obtained results of structure-activity relationship studies provide new insight into structural requirements for the ligand/NRP-1 b1-domain interactions. Acquired data are highly useful for designing new active compounds, able to inhibit VEGF-A_{165}/NRP-1 complex at low concentrations.

Acknowledgements: This work was financially supported by grant no. 2017/27/N/NZ7/02473 from Narodowe Centrum Nauki (National Science Centre, Poland) and by STSM Grant from the MuTaLig COST Action CA15135.

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Design and synthesis of putative inhibitors for the human Endosulfatatase H-Sulf 2, a new therapeutic target

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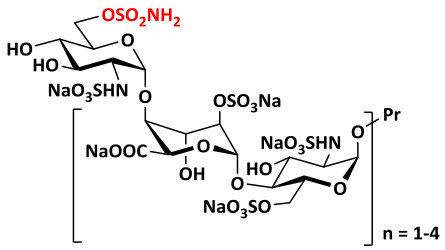
PO 130

Heparan Sulfate proteoglycans (HSPGs) interact with many proteins, especially growth factors or cytokines via specific sulfation patterns. They can be remodeled in the pericellular space by a novel class of extracellular enzymes, the Endosulfatases (HSulf 1 and 2), which selectively remove the 6-*O*-sulfate groups from glucosamine residues within the HSPGs chains [1-3]. HSulfs expression/production is deregulated in many human cancers including breast, lung, ovarian and hepatocarcinoma [4-5]. Thus, this family of enzymes represents an interesting therapeutic target.

The endosulfatase catalytic mechanism involves a Cα-formylglycine residue and efficient inhibitors have been designed by replacing the sulfate's moiety by a sulfamate function [7-8]. In order to optimize the recognition between the enzyme and the inhibitor and study the structure/activity relationship, the synthesis of Heparan Sulfate fragments of different length, with a 6-*O*-sulfamate at the non-reducing end have been designed.

Herein we report the synthesis of HS fragments integrating a sulfamate moiety.



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In-silico modelling of a slow-onset, tight-binding human asparagine synthetase inhibitor: A medicinal chemistry perspective.

PO 131

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Hight bioavailability of L-asparagine and enforced expression of the enzyme asparagine synthetase (ASNS) has been strongly correlated with metastatic progress in a functional model of breast cancer and RNA interference screens. These findings strongly suggest emerging potential of ASNS and urgent need for the development of small molecule inhibitors of ASNS and their significant clinical application in the prevention of metastasis, and perhaps more broadly in cancer chemotherapy. We report molecular dynamics simulations that reveal how a slow-onset, tight binding inhibitor with nanomolar affinity binds to the synthetase active site of human ASNS. Further on, advanced Free energy estimation identified the important of chiral selectivity. We also discuss the implications of these findings for the development of novel ASNS inhibitors that can be used to understand the metabolic changes that take place as cells undergo metastatic progression and as lead compounds for identifying novel anti-cancer drugs.

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Synthèse et étude du mécanisme d'action de complexes d'Iridium semi-sandwich aux propriétés cytotoxiques

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PO 132

Depuis les 5 dernières années, un intérêt croissant a été porté sur les complexes semi-sandwich d'iridium comme agents anticancéreux potentiels car certains d'entre eux présentent des propriétés antiprolifératives prometteuses. Toutefois leur mécanisme d'action reste encore à découvrir.

Des résultats préliminaires ont été établis par les deux équipes au cours des 6 derniers mois. Ils rendent compte du large panel de molécules synthétisables et de la diversité des fonctions chimiques qu'il est possible de leur adjoindre. La stabilité des molécules a également été établie vis-à-vis du solvant d'administration (DMSO), et des résultats de cytotoxicité encourageants ont été obtenus sur plusieurs lignées cellulaires cancéreuses (notamment une lignée de cancer du sein MDA-MB231, la lignée HeLa et deux variants isogéniques p53+/+ et p53-/- de la lignée dérivée de cancer colorectal HCT-116). Certains composés sont capables de perturber l'équilibre redox cellulaire, et entraînent une accumulation rapide et irréversible de peroxyde d'hydrogène, détecté in vivo à l'aide d'une sonde ratiométrique du peroxyde d'hydrogène (sonde Hyper). Des modifications de la morphologie cellulaire, un arrêt du cycle cellulaire et une mort cellulaire rapide ont aussi été observés par des approches d'imagerie et de cytométrie, suggérant que leur mécanisme d'action diffère de celui du Cis-Platine.

Pour aller plus loin et comprendre comment ces molécules interagissent avec le vivant et exercent leur activité biologique, nous proposons de synthétiser des molécules bifonctionnelles résultant de l'assemblage judicieux d'un complexe d'iridium et d'une entité fluorescente agissant comme sonde optique. Des études poussées de biologie cellulaire combinées à l'imagerie moléculaire seront mises en œuvre afin de dresser un panorama exhaustif du mécanisme d'action de ces molécules aux niveaux cellulaire et moléculaire.

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Synthesis, characterization and biological evaluation of new PEGylated triarylmethanes for antibacterial purposes

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PO 133

The emergence and dissemination of multidrug resistant (MDR) Gram-negative bacterial pathogens observed in recent years is a major challenge for antimicrobial chemotherapy and is today considered as a major public health issue. This "antibiotic resistance crisis" has been intensified by the gap between the burden of infections due to MDR bacteria and the development of new antibiotics to tackle the problem. Moreover, despite the discovery over the last twenty years of compounds with an interesting antibiotic activity, few of them belong to new chemical classes or have the required properties to become drugs or to avoid resistance problems. That's why the need for new antibiotics is urgent. [(1-3)]

Small molecular drugs often suffer some problems, such as low solubility, high toxicity, rapid excretion or untargeted biodistribution. To overcome these obstacles, one promising approach is to use a PEGylation strategy. Thanks to their favorable properties (nontoxic, nonimmunogenic, non-antigenic and amphiphilic), PEG as modifying polymer plays an important role in drug discovery. PEG-drug conjugates have several advantages: prolonged residence in body, decreased degradation by metabolic enzymes, reduction or elimination of protein immunogenicity, and so on.[(4)]

We describe herein the synthesis and the antibacterial evaluation of a series of PEGylated triarylmethanes, analogues of bisacodyl, a drug used in therapeutic as laxative and with a demonstrated antibacterial activity.[(5)] The new compounds were synthesized from saponified bisacodyl followed by a functionalization with PEG fragments in order to increase solubility and efficacy. The antimicrobial evaluation was performed using polystyrene micro-assay plates (96 well) using levofloxacine, a broad-spectrum antibiotic, as a control. The synthetized PEGylated molecules revealed a promising antibacterial activity compared to bisacodyl

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Probing Functional Cellular Uptake of Small Molecules Using Heterobivalent Constructs	
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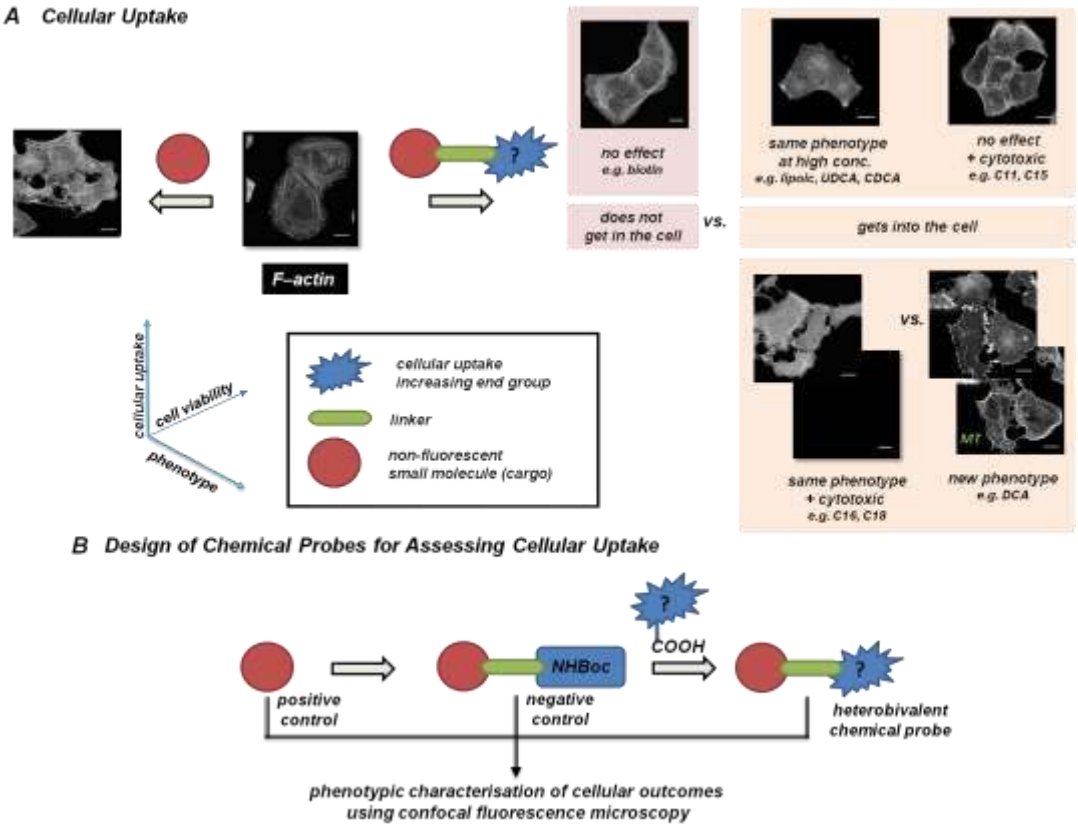
Cellular uptake of small molecules and their linker- extended derivatives is defined by their chemical properties including lipophilicity and molecular weight. While modification of constructs by simple fatty acids may improve cellular uptake, it remains poorly understood whether such conjugates actually deliver the in-cell biological activity. With a wide range of chemical modifications to increase cellular uptake, we profile a selection of them using hetero-bifunctional constructs approach. We identify that conjugation to various moieties may act differentially on the cellular uptake as well as the ultimate intracellular functionality of such chemical probes within the context of a living cell.



1. Bhadoria, R.; Ping, K.; Lohk, C.; Järving, I.; Starkov, P. *submitted*

Improved synthesis, resolution, absolute configuration determination and biological evaluation of HLM006474 enantiomers.

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PO 135

HLM006474 is a small molecule pan-inhibitor of E2F-DNA binding and it is a potent inhibitor of melanocytes proliferation[a] that may have efficacy in lung cancer.[b] This compound is chiral but has only been evaluated on biological systems as a racemic. HLM006474 synthesis was first described in 2008 by a one-step three-component Betti reaction,[a] in very low yield (12%) and important reaction time (14 days). Here we present an improved synthetic access to this compound in good yields, the separation of the enantiomers, their absolute configuration determination and their biological activity. Biological evaluation of both enantiomers on E2F1 transcriptional activity reveals that the (+)-R, but not the (-)-S enantiomer is biologically active in repressing E2F1 transcriptional activity.[c]

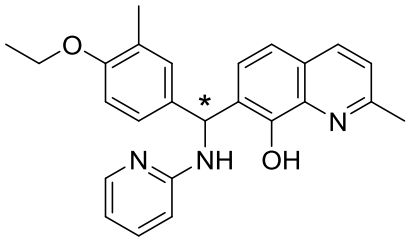

Figure 1: Structure of HLM006474

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Formation of radicals from endoperoxide ascaridole in a 3D epidermis model : an EPR spin trapping study

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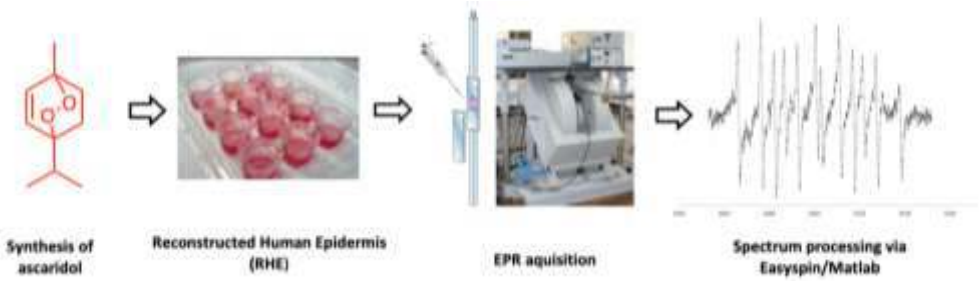
PO 136

Skin contact allergy is a major public health problem and is considered as the most important immunotoxicity reaction in humans[1].Because of the increase in the prevalence, it is necessary to predict the sensitizing potential of all chemicals before their use in consumer products. Thus, understanding all the mechanisms leading to allergic reactions is essential in order to evaluate the molecules at risk[2]. Chemicals form antigenic triggers inducing sensitization and further contact dermatitis by binding to skin proteins through nucleophilic-electrophilic mechanisms but also by radical-mediated processes. Ascaridole, the oxidative metabolite of α-terpinene, is considered to be one of the components responsible for contact allergy to essential oils derived from *Chenopodium* and *Melaleuca* species[3]. The endoperoxide chemical function of ascaridole can be degraded and form radical intermediates evolving via different mechanisms to form carbon centered radical intermediates together with electrophilic reactive compounds[4]. The aim of this study was to understand the role of free radical intermediates derived from ascaridole in the sensitization processes by evaluating the reactivity profile towards amino acids and by studying their formation in a reconstructed human epidermis 3D model closer to what may happen *in vivo*. For this, the spin trapping technique combined with Electronic Paramagnetic Resonance was used[5].



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The impact of amidation on the activity of L,D-transpeptidases in *Mycobacterium tuberculosis*

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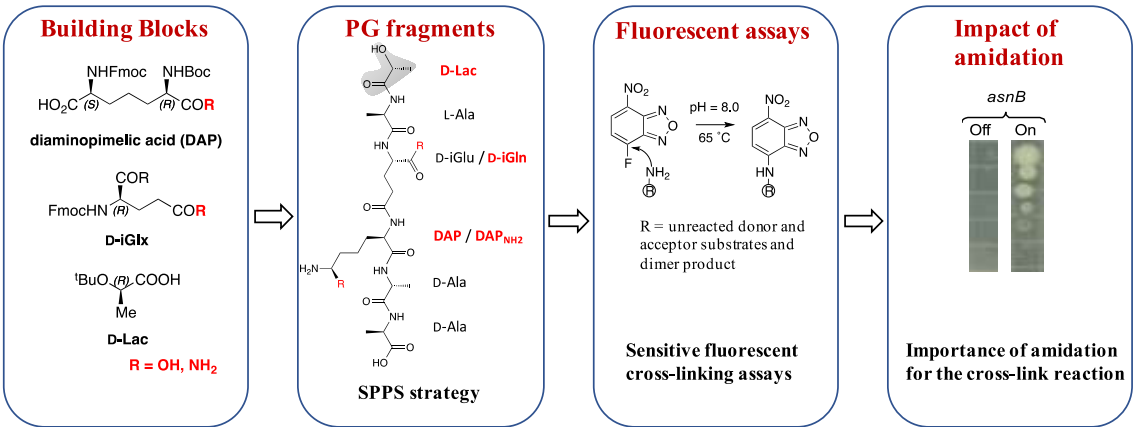
PO 137

Peptidoglycan (PG) is an attractive and validated target for antibacterial drug development for two main reasons. First, it is an essential and unique bacterial cell wall polymer with no counterpart in human cells, minimizing the risk of drug toxicity. Second, the essential PG synthases are exposed at the outer surface of the cytoplasmic membrane, making them highly accessible for antibiotic inhibition. Formation of the PG network requires transpeptidases for peptide cross-linking between two stem peptides, a donor and an acceptor. In this context, our groups have already shown that L,D-transpeptidases of Mycobacterium tuberculosis can be irreversibly inhibited by β-lactams of the carbapenem class and are important targets for the development of anti-tuberculosis agents.



Therefore, in this work, we will describe the synthesis of chemical tools, notably peptidoglycan fragments synthesis based on solid phase peptide synthesis (SPPS) strategy using suitably protected amino acid building blocks and sensitive fluorescent assays that provided crucial information about the impact of the amidation on peptidoglycan precursors toward the activity of L,D-transpetidases in *Mycobacterium tuberculosis* and *Enterococcus faecium.*[a] This study allowed us to establish that AsnB amidotransferase is an attractive target for the development of anti-mycobacterial drugs.

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Small molecules containing selenium as cytotoxic agents against cancer

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PO 138

Cancer is currently one of the major health problems of the human population and a prominent cause of death worldwide. The introduction of a selenium atom (Se) in the structure of organic molecules has demonstrated to be a valid approximation in the design of new compounds with several biological effects, including antitumoral activity[(a)].

On the basis of these results, and taking into account previous studies developed by our research group[(b)], we have designed 15 new acylselenourea derivatives bonded to heterocyclic nuclei with reported antitumoral efficacy (thiophene, furan and benzothiophene). These compounds have been modulated with an *N*-substitution in the selenourea group with different aromatic rings functionalized with electron withdrawing or electron donating groups in the 'para' position.

The 15 new organoselenic compounds were screened at 2 concentrations in 3 different cancer cell lines (MCF-7, HT29 and HTB54) *in vitro* as a first approach to evaluate their cytotoxic effect.

From the results obtained in this preliminary experiment, 3 hit compounds were selected and their dose-response curves were determined against two human breast cancer cell lines (MCF-7 and T47D) and their IC_{50} values were also calculated. These experiments were carried out using the MTT assay after 48h of treatment. All of the 3 leaders showed IC_{50} values below 10 μM, meaning that these derivatives containing selenium could act as potential antitumoral agents.

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Developments of new nitric-oxide-indomethacin drugs

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PO 139

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of osteoarthritis, rheumatoid arthritis and musculoskeletal pain. However, chronic use of NSAIDs has been associated with an increased risk of gastrointestinal complications (which range from dyspepsia to gastrointestinal bleeding, obstruction, and perforation) renal side effects (including a wide range of tubular, interstitial, glomerular, and vascular lesions) and a large number of additional side effects.

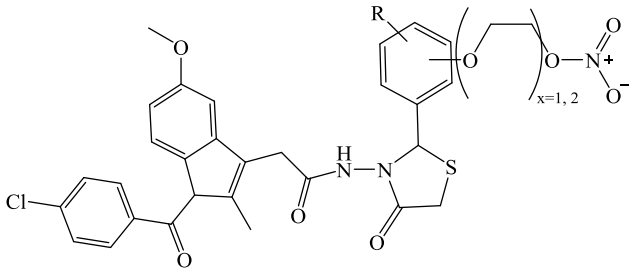
The inhibition of the arachidonic acid cascade is one of the most used strategies for the treatment of the inflammatory diseases. The classical type of NSAIDs exerts the anti-inflammatory effects through inhibition of both constitutive COX-1 and inductive COX-2 but in a non-selective manner. The discovery of celecoxib, valdecoxib, and rofecoxib (as Coxibs candidates), confirms the concept of preparation of more selective COX-2 inhibitors with a minimal gastric effect. Unfortunately, Valdecoxib and rofecoxib are withdrawn from the market due to cardiovascular complications (1).

Nitric oxide (NO) is a biologically active molecule involved in modulating the plethora of physiological responses including maintenance of blood pressure in the cardiovascular system, stimulating host defenses in the immune system, regulating neural transmission in the brain, platelet aggregation, learning and memory, male sexual function, cytotoxicity and cytoprotection, development of arteriosclerosis among others, inflammation, gastroprotection (2,3).

A novel approach to reduce the side effects of NSAIDs, especially their gastric toxicity consists to link, *via* a chemical spacer, a known NSAID molecule and a NO-releasing group (typically $–NO_2$). This original approach is known as Nitric Oxide-releasing Non-Steroidal Anti-Inflammatory Dugs (NO-NSAIDs).

The rationale for NO-NSAIDs development was based on the observation that NO possesses some of the same properties as PGs within the gastric mucosa. NO increases mucosal blood flow, mucous release, and repair of the mucosa, whereas it inhibits neutrophil activation and adherence. These effects can theoretically compensate for gastric PG reduction. Coupling a NO-releasing moiety to a NSAID might deliver NO to the site of NSAID-induced damage and thus decrease gastric toxicity (4).

The objective of this study is the synthesis of a new NO-NSAIDs entities containing indomethacin as NSAID associated with 1,3-thiazolidin-4-one moiety containing a nitric ester group. The synthesis and the NO release capacity will be present in this communication.



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New Concepts in Synthetic Medicinal Chemistry: from Chemoselectivity to Applications

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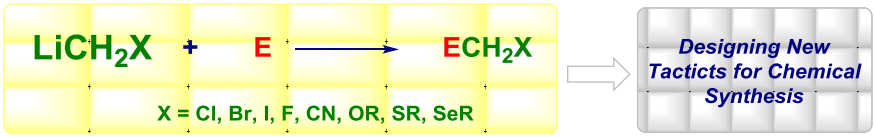
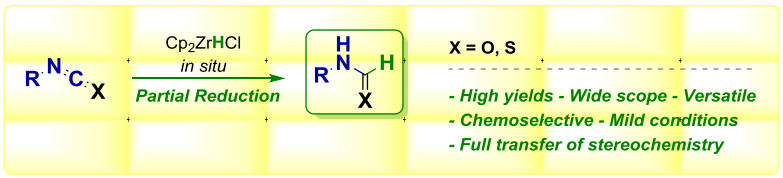
PO 140

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

Introducing a Functionalized CH2X Fragment via a Single Synthetic Operation



Schwartz Reagent mediated Reduction of Iso(thio)cyanates to (Thio)Formamides



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Synthesis of Dual Acting COMT Inhibitors and Iron Chelators

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PO 141

Dopamine (DA) deficiency-neurological disorders such as Parkinson disease (PD) are usually symptomatically treated with the biosynthetic dopamine precursor levodopa that is extensively metabolized by catechol O-methyltransferase (COMT).[1] Nitrocatechols are second generation inhibitors of COMT and act as co-adjuvant drugs.[2] Tolcapone, a potent, blood-brain barrier (BBB) permeable and the only centrally-active COMT inhibitor, is associated with a severe risk of hepatotoxicity and its use is very restricted. Commercially available alternatives entacapone and opicapone although safer only act peripherally.[1] Albeit the nitrocatechol pharmacophore yields potent tight-binding COMT inhibitors, it raises toxicological concerns, particularly for compounds with increased lipophilicity. This makes it particularly difficult to develop BBB-permeable nitrocatechol COMT inhibitors. Non-nitrocatechol COMT inhibitors such as heterocycle catechol mimics (HetCAMs) may thus provide a safer alternative. Moreover, as brain iron accumulation has been acknowledged to contribute to DA depletion, this type of compounds can also operate as iron chelators, resulting in a disease-modifying outcome.

Accordingly, our project is focused in the development of centrally active dual target drug candidates able to remove accumulated iron in the brain and inhibit COMT, while mitigating the toxicological risks of currently available tolcapone. To achieve the goal two HetCAMs, N-substituted and NH- or O-containing HetCAMs substituted at the C2 position, libraries are being synthesized from a naturally-occurring, cheap and commercially available starting material: kojic acid. The synthetic strategy was designed and optimized. The results obtained so far will be presented in this communication.

Acknowledments:
This project was supported by Foundation for Science and Technology (FCT) and FEDER/COMPETE (Grants UID/QUI/00081/2015, POCI-01-0145-FEDER-006980, NORTE-01-0145-FEDER-000028, and POCI-01-0145-FEDER-029164). T. Silva grant was also supported by FCT, FEDER/COMPETE and NORTE-2020 funds. L.Sequeira grant was supported by Univerità degli Studi di Cagliari (funds from the Italian Ministry of Education, University and Reasearch).

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Dimethylaminobenzophenones as antimitotic agents: modifications of the A ring.	***PO 142***

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The anti-mitotic natural product combretastatin A4 (Fig. 1) and its benzophenone analogues (phenstatins) are both potent inhibitors of tubulin polymerization and cytotoxic compounds. [1] However, their structure-activity relationships differ due to a distinct arrangement of the phenyl rings. [2] Thus, the effect on the potency of diverse substitution patterns is different for the two families of compounds.

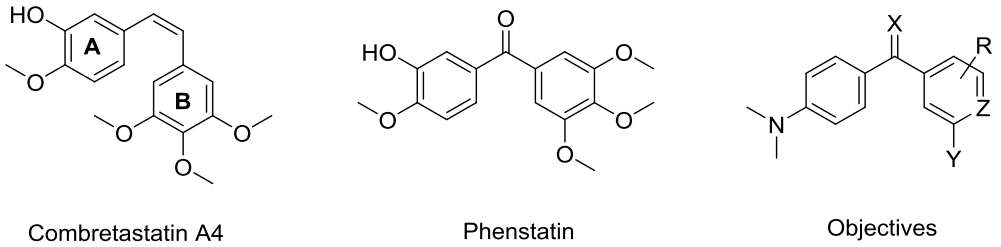

Figure 20. Structure of reference compounds and objective of this project.

With the aim of obtaining new analogues with improved pharmacokinetic profiles, in this communication we have synthesized and evaluated novel benzophenones carrying out modifications on the methoxy group substitution patterns and with replacements of the methoxy groups by alternative moieties such as dimethylamino groups. Moreover, variations on the carbonyl bridge were performed. Results of the design, synthesis, tubulin polymerization and cytotoxic activity will be presented.

Acknowledgements

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AVB thanks the Spanish Ministerio de Educación, Cultura y Deporte for a predoctoral FPU fellowship.

MG and SM acknowledge Junta de Castilla y León for a predoctoral fellowship.

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Synthesis of fluorinated β-lactam derivatives towards potentially bioactive compounds

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PO 143

The β-lactam ring synthesized for the first time by Staudinger in 1907[a], belongs to the most important classes of antibiotic agents since the incidental discover in 1928 and isolation in 1938 of naturally existing penicillin by Alexander Fleming and co-workers. In a short time, β-lactam antibiotics have gained a significant role in a treatment of various diseases caused by bacterial infections. In addition, due to their specific properties, these compounds are also applied in a treatment of malaria, cancer and HIV.[b,c] The β-lactam derivatives can also take part a significant role in intestinal cholesterol uptake inhibition as e.g Ezetimibe, which is employed in a treatment of hypercholesterolemia.[d] Nevertheless, these compounds are very interest not only because of their specific biological properties, but also their practical applications in organic synthesis, as good precursors for the synthesis of a wide range of acyclic and heterocyclic compounds containing nitrogen such as e.g. α-amino acids, peptidomimetics. The reactivity of these four-membered compounds results from the presence of high strain in the small ring. Therefore these compounds can undergo nucleophilic ring opening reactions *via* different kinds of nucleophiles or bacterial enzymes and act as an enzyme inhibitors.[e] Moreover, the introduction of fluorinated substituent into these aza-heterocyclic compounds can cause a significant modification in the physico-chemical and particularly biological properties of the parent compounds. It is known that the introduction of the CF_3 group into well-known drugs improved their pharmaceutical properties such as Efavirenz (antiviral agent), Fluoxetine (antidepressant) and CF_3-Ac-Docetaxel (anticancer agent).[f] Moreover, these four-membered reactive compounds stabilized by the fluorinated group are still reactive enough to undergo different type of functionalization reactions. Thus various of valuable heterocyclic and acyclic compounds are prepared and could be used in a design of therapeutic potential compounds.[g,h]

For that reason, the aim of this work is to carry out the functionalization of the CF_3-β-lactams in C-3 position. These new CF_3-β-lactam derivatives could exhibit potential biological activities and could be considered in the design of important useful compounds.

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Design and synthesis of original spirocycles for sigma-1 receptors	*PO 144*

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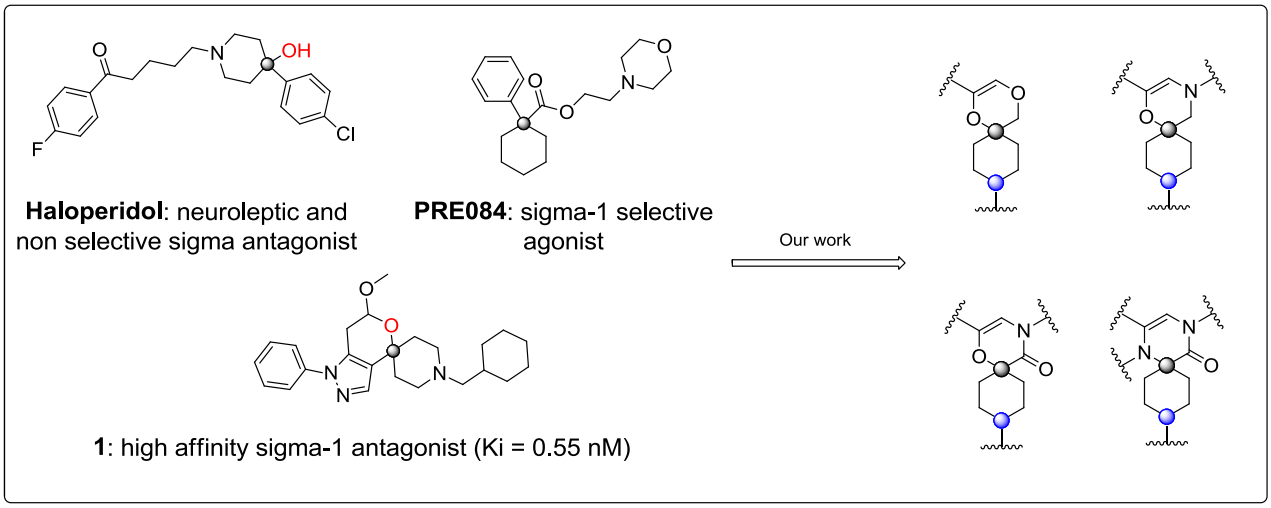
Sigma-1 receptors are highly expressed in the central nervous system [1-3]. When activated, they can offer neuroprotection against neurodegenerative diseases such as Huntington's and Alzheimer's disease as well as Amyotrophic Lateral Sclerosis (ALS) [4, 5]. Many compounds bearing a quaternary carbon atom such as **haloperidol**, **PRE084** and the spirocycle **1** have been found active on those receptors. In addition, more and more spirocycles such as Irbesartan, a very powerful antihypertensive drug, have been proposed in the therapeutic arsenal but for ease of synthesis and purification they often lack chirality. In order to tackle the challenges encountered in this field, our research focuses on the development of general methods for the synthesis of chiral spirocycles with an application, eventually, in drug design. Our research focuses on spirocycles in which a heteroatom is directly attached to the quaternary carbon. The substrates for the synthesis of the desired spirocycles were prepared from N-protected piperidone. Several transition metals (Au, Pt, Cu) were tested for the metal catalyzed cyclization and the best catalyst was selected after an optimization step. The stereoselective methods for the synthesis of the chiral spirocycles are under development in order to obtain the first candidates for the biological evaluation.



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D2AAK3 as a multi-functional ligand of aminergic GPCRs

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PO 145

Schizophrenia is a chronic mental disorder with complex and still not fully understood pathomechanism. Currently available antipsychotics are often not sufficiently effective against symptoms of the disease. In search for novel potential antipsychotics, structure-based virtual screening was performed in order to identify new antagonists of dopamine D_2 receptor[(a)]. The compound D2AAK3 with 115 nM affinity to dopamine D_2 receptor was found. D2AAK3 may be considered as an ideal candidate for a multi-target drug, since it exhibits nanomolar or low micromolar affinity also to D_1, D_3, 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptors. The compound possesses also some affinity to M_1 and H_1 receptors. D2AAK3 exhibits favorable profile in functional in vitro studies. To study interactions of D2AAK3 with its molecular targets at the molecular level, homology modeling, molecular docking and molecular dynamics were performed. The main interaction of D2AAK3 with all studied receptors is the electrostatic interaction between the protonatable nitrogen atom of the ligand and the conserved Asp(3.32), what is typical for orthosteric ligands of aminergic GPCRs. Behavioral studies[(b)] showed that D2AAK3 decreases hyperactivity induced by administration of amphetamine (when compared to the amphetamine-treated group) measured as spontaneous locomotor activity in mice. Moreover, in passive avoidance test D2AAK3 was demonstrated to improve memory consolidation after acute treatment in mice. In elevated plus maze tests studied compound exhibited anxiogenic activity 30 minutes after acute treatment in mice. However, 60 minutes after administration of D2AAK3 this effect was reversed.

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Novel Tacrine Inhibitors of Acetylcholinesterase with Potential Implication against Organophosphorous Poisoning

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PO 146

Organophosphorus nerve agents (OPNAs) still represent potential threats in military, terrorism situations and civilian sphere. OPNAs act as potent irreversible inhibitors of central and peripheral cholinesterases. Up-to-date, the prophylaxis against OPNAs poisoning relies on administration of the reversible acetylcholinesterase (AChE) inhibitor pyridostigmine. The major drawback of this compound is no penetration into the brain. With this regard, some other non-charged reversible AChE inhibitors such as huperzine or physostigmine proved their efficacy as prophylactic agents against OPNAs. Moreover, these compounds are also able to cross the blood-brain barrier (BBB). Encouraged by these results, we have prepared novel, potent AChE reversible inhibitors based on tacrine scaffold as potential prophylactic agents against incapacitating effects of OPNAs. Additionally, most of them also displayed inhibition of plasmatic butyrylcholinesterase (BChE), thus preserving its capacity to act scavenger of OPNAs. Within our contribution, we will report the synthesis and biological data for AChE/BChE inhibition, prediction of the binding modes using in silico methods and the ability to cross the BBB for novel tacrine hybrids as potential prophylactic agents against OPNAs.

Supported by the Long-term development plan (Faculty of Military Health Sciences, University of Defence, Czech Republic), by MH CZ - DRO (University Hospital Hradec Kralove, No.00179906) and by Technology Agency of the Czech Republic project no. TG02010020.

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Enzymatic approach to synthesize glycoconjugates useful as potential tuberculosis vaccine.

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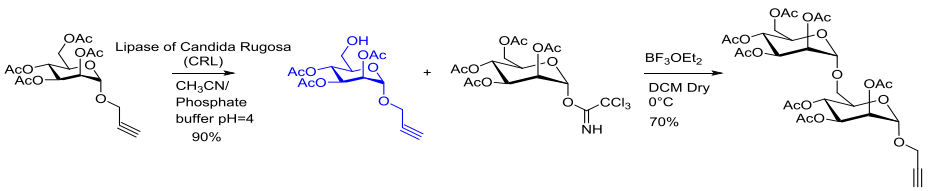
PO 148

New roles have been attributed to oligosaccharides as glycoconjugates, above all in immune response. Mannose receptor (MR) is important for this function: due to its expression on Antigen Presenting cells surfaces, APC cells, it is possible to consider MR involved in immune process. The interaction between oligosaccharides and mannose receptor induces the internalization, processing and exposition of the antigen on the APC cells surface.

In order to prepare innovative multivalent glycoconjugates useful as anti-bacterial vaccines (against tuberculosis) and composed by immunogenic oligosaccharides and antigenic peptides, it is necessary to synthesize several mannose-containing oligosaccharides: their synthesis is not so simple because of some intermediates that must have a specific free hydroxyl group.
The classical chemistry with protecting groups involves the use of many steps and leads to low yield products.

Instead enzymatic approach resulted efficient: by using immobilized enzymes (Lipase from *candida rugosa* immobilized on octyl agarose or Acetyl Xylan Esterase from *Bacillus pumilus* immobilized on epoxy support), aqueous solvent (Phosphate buffer) and a low and variable percentage of organic solvent (acetonitrile), it is possible to synthesize mannoside with specific free hydroxyl group.
Through a screening of enzymatic hydrolysis on mannose derivatives presenting different anomeric functional groups, we obtained the intermediates with simple procedure and higher yields.
In this way, it was easier to synthesize disaccharides and trisaccharides useful for the conjugation with antigenic proteins, *via* thiocyano methyl group in anomeric position, and for the conjugation with nanomaterials as Fullerene, *via* click chemistry by using propargyl group in anomeric position.



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Towards the validation of a new anticancer strategy: Designed peptides targeting Lactate Dehydrogenase tetramerization process

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PO 149

Lactate metabolism is a pathway of major significance for most cancer cells. In glycolytic cancer cells, lactate dehydrogenase A (LDHA) catalyzes the reduction of pyruvate to lactate. In addition, oxidative cancer cells can take up extracellular lactate, which is then oxidized by LDHB to pyruvate to fuel oxidative phosphorylation (OXPHOS). Active LDHA and LDHB are tetrameric enzymes. In cancer, their catalytic activity promotes a metabolic symbiosis between glycolytic and oxidative cancer cells[1], autophagy[2], angiogenesis[3] and invasiveness[4]. These enzymes are considered as safe and validated targets for cancer therapy. However, their highly polar catalytic site makes it a challenging target for small molecule inhibitors. We aimed therefore at developing allosteric site inhibitors capable of interfering with LDH tetramerization, hence LDH activity in cancer cells.
In vitro and *in silico*, we initially identified a 19 amino-acid dominant-negative peptide (**LB19**) that inhibits LDH tetramerization. Based on this unprecedented observation, we aimed to optimize the interaction between **LB19** and LDH tetramerization sites in order to yield potent and druggable LDH tetramerization inhibitors. To this end, an inactive dimeric recombinant LDH was produced in *E.coli* rosetta strain and used in nuclear magnetic resonance (NMR) experiments to characterize the interaction between **LB19** and LDH tetramerization site. This led to a sequence optimization of **LB19**, yielding an 8 amino-acid peptide (**LB8**) retaining all the key interactions motifs for LDH inhibition. This minimal interacting sequence was used to detail hot spot protein residues and establish preliminary structure activity relationships (SARs) for the inhibition of LDH tetramerization. Finally, these preliminary SARs data were used to design potent cyclic analogs of LB8, among which macrocycle **LT-018** that proved to be a micromolar inhibitor of LDH tetramerization.

Conclusively, our work provides a proof-of-principle that LDH tetramerization state can be targeted by small peptides, which could lead to innovative anticancer applications.

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From melatonergic and serotonergic receptors to the development of new therapeutics for Alzheimer's disease: a polypharmacological approach.	*PO 150*

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Alzheimer's disease (AD) is the most common form of dementia affecting 50 million of patients worldwide, for which only symptomatic treatments are currently on the market. Among the biological targets implied in the physiopathology, melatonergic MT1 and MT2 and serotonergic 5-HT_{2c} receptors present a growing interest, since their modulations have been shown to promote the non-amyloidogenic cleavage of Amyloid Protein Precursor (APP) and to alleviate the symptoms through several actions such as anti-oxidant effect and regulation of the general neurotransmission.[a,b] As AD is a multifactorial disorder, a simultaneous action on these two types of receptors with Multi-Target Directed Ligands (MTDLs) could represent a novel therapeutic approach. In this objective, we screened our chemical library in order to identify both potent MT1 and MT2 receptors agonists and 5-HT_{2c} receptors antagonists. We performed docking studies of the selected molecules into homology models of MT1 and MT2 receptors and into the crystal structure of 5-HT_{2c} receptors[c]. Using Norns[d], a new chemo-informatics software we developed, we then extracted their structure-activity relationships (SARs). Both the resulting ligand-receptor interactions and SARs are in agreement with the literature and allow to understand the polypharmacological profile of this promising new series of compounds.[e,f] Our hypothesis and SARs towards these targets as well as the design of novel MTDLs will be presented in this communication.

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Detection of glycosidase activities by precipitating fluorogenic probes.

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PO 151

Over- or under-expression of enzymes is today well-known as disease biomarkers but also as reporters for many cellular processes. In this context, fluorogenic probes developed in our team appear as a rapid, efficient and non-toxic method to quantify and localize enzyme activity by releasing a solid-state fluorophore, which ensures the retention of the signal around the enzyme locus[(a),(b)].

This model of OFF-ON probe has shown its applicability *in vitro* and *in cellulo* to many enzymes such as leucine aminopeptidase (LAP) or lipases, and our current work is targeting glycosidases family which hydrolyze glycosidic bonds in complex sugars. Especially, three probes developed for this family in our lab will be presented: one for β-galactosidase, an enzyme overexpressed in senescent cells and mainly used as a product of reporter gene; another one targeting cellulase for a bioenergetics project in collaboration with a biology team (ENS), and the last one for maltase activity which plays a pivotal role in biological systems and widely used in food industries.

Synthesis aspects and biological experiments will be presented to explain their mode of action and their applicability.

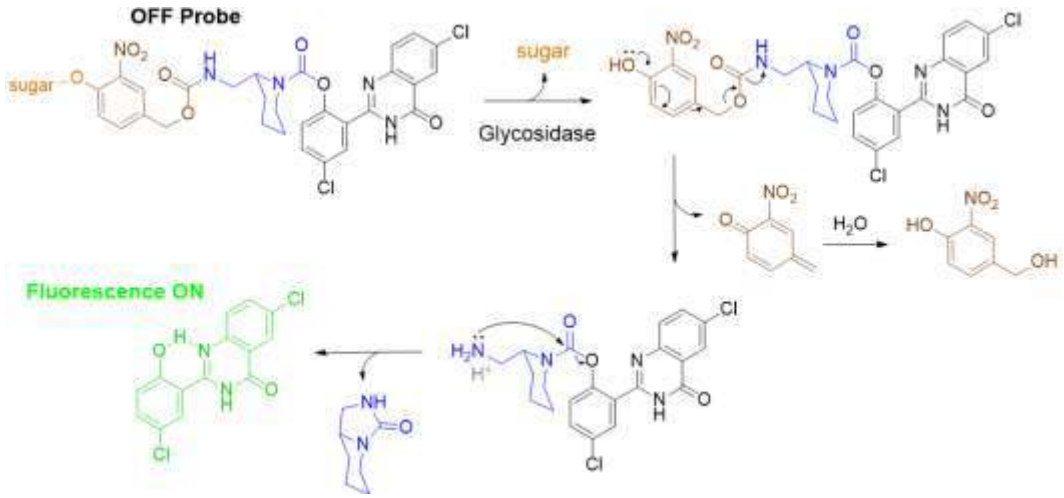

Figure 1 – Mode of action of glycosidase fluorogenic probes.

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Synthesis and biological evaluation of novel concept: prodrugs with multi-target activites in Alzheimer's disease.	***PO 152***
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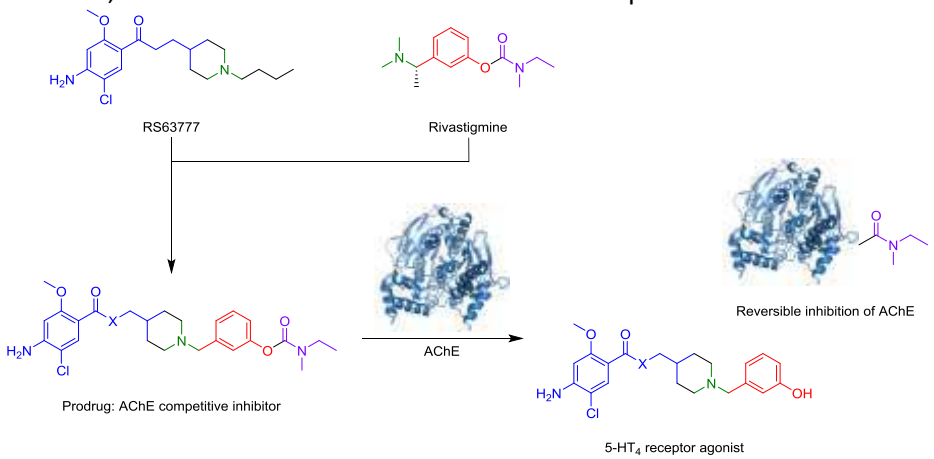
In 1906, Alois Alzheimer described the disease for the first time: the patient had particular disorders of memory and had brain pathologic deposits called amyloid plaques. As a result of multiple research, the disease has proved to be more and more complex: plaque formation is due to hyperactivation of β-secretase resulting in the formation of the amyloid peptide. In addition, we have hyperphosphorylation of the tau protein, causing disaggregation of microtubules, a neuronal death and a decreased cholinergic transmission.[(a)]

In order to treat Alzheimer's disease, a multitude of molecules have been synthesized but only 4 are currently marketed:[(b)] they are inhibitors of acetylcholinesterase (AChE), as for example rivastigmine a covalent pseudo-irreversible inhibitor, and a NMDA inhibitor, memantine.

Faced to the complexity of the disease and the lack of effectiveness of the current molecules, we have developed multi-target directed ligands (MTDLs) a new strategy based on describing a drug with several therapeutic targets of interest to treat a disease. Thus, our laboratory synthesized Donecopride[(c)] a molecule inhibiting AChE and simultaneously activating 5-HT_4 serotoninergic receptors.

Our present project is to design, synthesize and evaluate biologically prodrugs having a structural analogy between rivastigmine and RS67333[(d)] (a 5-HT_4 receptor agonist). These drugs, only active on AChE, possess a carbamate group comparable to rivastigmine. The action of AChE will cause the release of a second biologically molecule specifically active on serotonin receptors. For this work, three series were studied: ketones, esters and amides. The first results will be presented in this communication.



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GENERATION AND INVESTIGATION OF PROTEIN-BASED CAVITY PHARMACOPHORES.	PO 153

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Identifying the very first ligands of pharmacologically important targets in a fast and cost-efficient manner is an important issue in drug discovery. In absence of structural information on either endogenous or synthetic ligands, computational chemists have not many possible choices other than docking compound libraries to a binding site of interest, with well-known biases arising from the usage of scoring functions. Recent international docking challenges agree to conclude that the success in ranking ligands by a structure-based approach is strongly related to the level of available knowledge of both the target and its existing ligands, thereby promoting the development of knowledge-based strategies in prioritizing docking poses. For ligand-orphan targets, such approaches are no more possible and novel algorithms need to be developed to find putative ligands from the simple knowledge of a protein structure. We herewith propose a novel approach consisting in the generation of simple cavity-based pharmacophores to which potential ligands could be aligned by the use of a smooth Gaussian function. The method, embedded in the IChem toolkit,[(a)] automatically detects ligand-binding cavities, then predicts their structural druggability, and last creates a structure-based pharmacophore for predicted druggable binding sites. A companion tool (Shaper2) was designed to align ligands to cavity-derived pharmacophoric features. The proposed method is as efficient as state-of-the-art virtual screening methods (ROCS, Surflex-Dock) in both posing and virtual screening challenges.[(b,c)] Interestingly, IChem-Shaper2 is clearly orthogonal to these latter methods in retrieving unique chemotypes from high-throughput virtual screening data.

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Polymeric analogues of antimicrobial peptides with therapeutic	PO 154

potential against *Clostridium difficile*.

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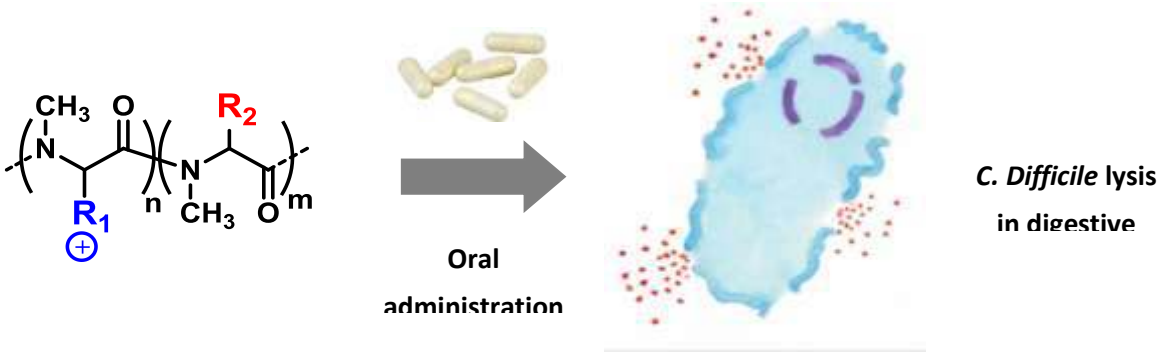
Clostridium difficile (CD) is a strict anaerobic Gram-positive bacterium that is able to sporulate.[1] It is responsible for epidemic nosocomial diarrhea and pseudomembranous colitis in elderly patients that are treated with large spectrum antibiotics. CD is responsible for nearly 500,000 infections and approximately 15,000 to 30,000 deaths each year in the USA due to its high resistance to the currently used antibiotics.[2,3]

Antimicrobial peptides (AMPs) are produced by various micro-organisms that are able to display selective antibacterial activity against all types of bacteria, including CD.[4,5] Recent studies have suggested that, rather than their primary amino-acid sequence, the cationic/hydrophobic amino-acid ratios in AMP would be a major factor to explain their anti-bacterial mechanism of action,[6] as cationic surfactant analogues. However, their oral administration remains an important concern, due to their sensitivity to proteases or peptidases.

This research program (Therapeptics) aims at synthesizing original orally active amino-acid polymers, as simplified analogues of AMPs that could selectively target CD. These molecules will be synthetized from activated cationic (R_1) and hydrophobic (R_2) bio-sourced amino acid derivatives, leading to *N*-carboxyanhydrides (NCAs) that will be copolymerized by a "ring-opening polymerization" (ROP) reaction, to afford a polymer library in a cost-efficient way.[7]

Amphiphilic amino acid polymers as simplified AMP analogues that is resistant against proteases or peptidases



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Synthesis of novel ligands for human quinone reductase 2 (MT3/QR2) through specific cyanation and selective reduction

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PO 155

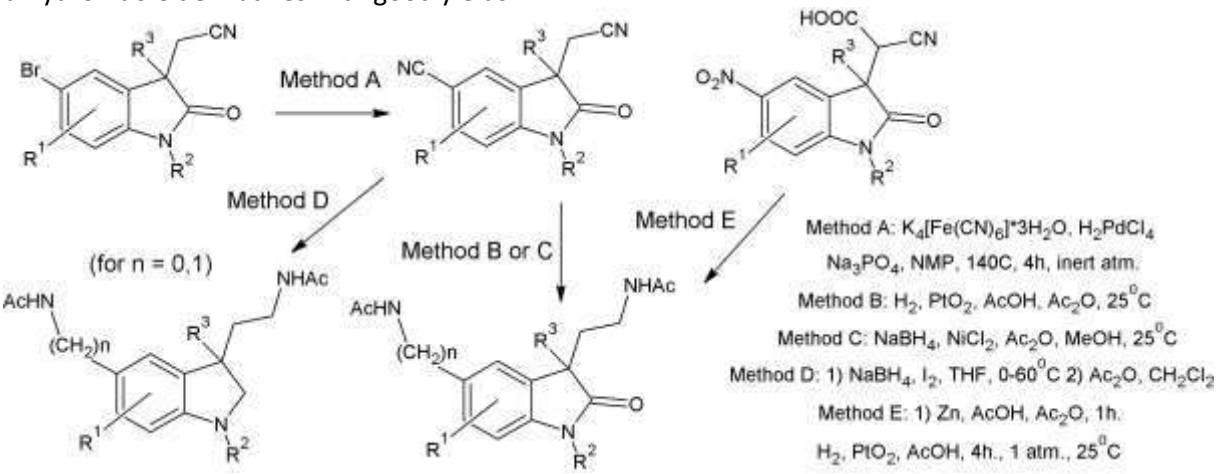
MT3/QR2 is a low-affinity melatonin receptor, which functions include, according to some research, neuroprotective and antioxidant activity, as well as decreasing of the intraocular pressure (IOP).

A new method of obtaining MT3/QR2 (and MT1, MT2 in case of 2,3-dihydroindoles) affinic ligands is proposed in this work. It was previously shown, that amido-group in 5-position is a pharmacophore one and is necessarily present in many MT3-active compounds[a]. The aim of this study is the synthesis of new melatonin analogues containing the amido-group in 5-position of indole ring.

According to molecular docking and X-ray crystal diffraction analysis[b], the substituent in 5-position of the indole scaffold must be modified by adding a -CH2- spacer before the amido-group. Supposedly, when the amido-group is situated one carbon atom further from the indole core, less water can be confined in the binding site of QR2 (less free space), making the binding more efficient.

Cyano- and nitro-derivatives were chosen as precursors for this modification, as they can be reducted to amines and then acylized together with the other cyano-group in 3-position, which leads to minimization of reaction stages. Palladium-catalyzed cross-coupling with hexacyanoferrate (II) ion was chosen as the main cyanation method because of its high yields and absence of free CN- ions, traces of which in the medication can be toxic. Thus, many new bioisosters of melatonin can be obtained with good yields.

Also, a new method of selective reduction of cyano-groups and the amido-group in 2-position of the indole scaffold is proposed. The conditions of these reactions were optimized to obtain indole- or 2,3-dihydroindole derivatives with good yields.



This work was supported by the Russian Foundation for Basic Research (Project 17-03-01320)

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Development of new compounds based on nonsteroidal antiinflammatory drugs and symptomatic slow acting drugs.	***PO 156***

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It is known that osteoarthritis is one of the most common articular degenerative disease that appears at elderness. Some evidence also shows that it is characterized by inflammation, pain and articular cartillage degradation. The treatment includes relieving symptoms drugs (analgesics and non-steroidal anti-inflammatory drugs) and symptomatic slow acting drugs (SSAD) such as glucosamine and chondroitin sulfate.

The aim of this project is developing of new therapeutic agents for arthritis diseases, more safe and efficiently than current therapy. The designed formulations combine three important compounds with pharmacological effects: non-steroidal anti-inflammatory drug (ibuprofen), sulfur amino-acid (methionine, cysteine) / aminothiol (cysteamine) and glycosaminoglycans (glucosamine, chondroitin sulfate) in order to obtain new compounds that can be theraputic candidates for arthritis. Some studies have shown that certain sulfur containing amino acids (SAA), such as methionine and cysteine, can exert anti-inflammatory effect.

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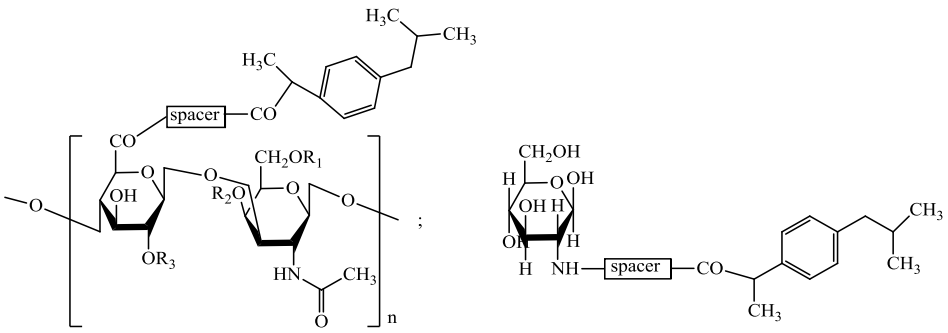

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Spectral analysis of some extracts from *Glinus oppositifolius* (L.) Aug. DC.	***PO 157***

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Introduction. *Glinus oppositifolius* is used in traditional medicine of Mali in the treatment of some disease characterized by immune dysfunctions: intestinal parasitoses, intestinal pain, diarrhea, joint pain, inflammation, fever, skin disease, open wounds, malaria, urinary infections, liver dysfunction. Our objective was to investigate the phenolic and saponin profile of two extracts obtained from the aerial part of this African plant.

Material and methods.

Chloroform (GC) and aqueous (GA) extracts of *G. oppositifolius* were chemically characterized using Fourier transform infrared spectroscopy (FT-IR). The extracts were then separated on a Phenomenex Gemini C18 column. Gradient elution was adopted using H_2O/acetonitrile with 0.1% formic acid. ESI-Q-TOF-MS/MS analysis was performed in positive and negative ion mode.

Results and discussions.

FT-IR spectral data highlights the presence of triterpene saponins and sterols in GC and triterpene saponins and carbohydrates in GA. HPLC-DAD-ESI-Q-TOF-MS/MS metabolite profiling of both extracts revealed the presence of several flavonoid *C*-glycosides, such as vitexin and vicenin-2, as well as a high abundance of hopane-type tritepernoid saponin glycosides, notably glinosides A-B and spergulin B. Two polar amino acids (phenylalanine, *N*-cinnamoyl-arginine) were characteristically evidenced in GA, whereas free and esterified fatty acids (linolenic acid, hydroxylinolenic acid, glyceryl stearate) were solely identified in GC.

Conclusions. A number of compounds with potential biological activity were found in the obtained extracts following this phytochemical screening. Sub-fractionation of the plant extracts is further necessary to identify novel compounds.

Keywords: *Glinus oppositifolius*, HPLC-MS, vitexin.

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Structure-based drug design: mechanism of action of novel antitumor biaryl sulfonamides

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PO 158

Cancer is the second cause of death worldwide, and despiste the wide range of antitumor drugs, chemotherapy remains a challenge as tumor cells are very prone to mutate. This drawback may be overcome by designing drugs targeting the high-conserved protein tubulin. This protein is a heterodimer formed by two globular subunits that dynamically polymerizes to constitute microtubules. Microtubule-dynamics disruption leads to cell division blockage, halting tumor progression. The colchicine site is one of the seven binding pockets for exogen ligands that have been described within the structure of tubulin. We have focused on the design of novel molecules able to bind at the colchicine site with the aim of improving the potency of the already known reference ligands and increasing their aqueous solubility. The *in silico* aided docking experiments and conformational studies led us to propose biaryl molecules with a sulfonamide bridge, which have been synthetised for further evaluation (Fig.1).

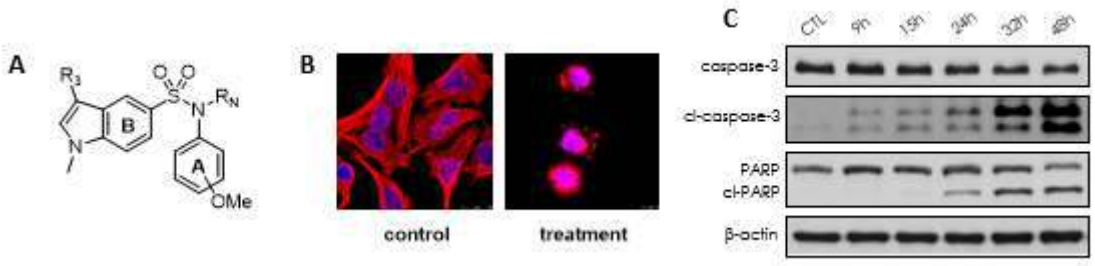

Fig.1. A. Main scaffold of the novel family of biaryl sulfonamides. B. Effect on tubulin cytoskeleton (red). C. Time-course for the expression levels of some apoptosis related proteins after treatment.

These new ligands have shown *in vitro* nanomolar IC_{50} values against different tumor cells, causing a prolonged cell cycle arrest that lasts at least 72 hours due to cytoskeleton organization disruption (Fig.1). We have studied how cells switch from mitotic arrest to apoptosis induction, suggesting that mitochondria might have a key role in this process. Some other pathways have shown to be altered after treatment, such as autophagy, so we have evaluated the signaling pathways involved not only in the pharmacological response, but also in the reversion of the mitotic arrest after drug removal. All these studies allowed us to identify some lead compounds with higher potencies than reference ligands and also, with improved pharmacokinetic properties, as evidenced by aqueous solubility evaluation.

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Optimisation of a broad-spectrum inhibitor of toxins selected from a CNF1-induced Rac1 modulator

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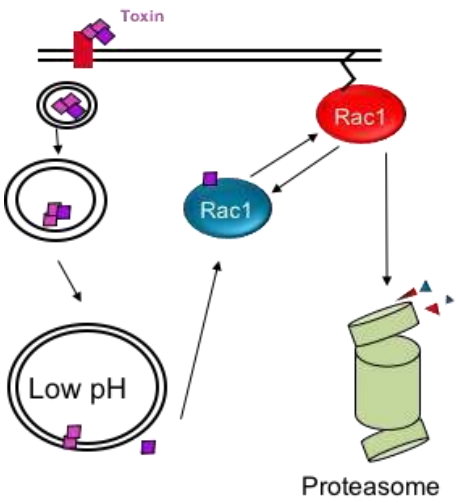
PO 159

Summary :



Bacterial toxins are virulence factors responsible for human diseases and potential bioterror weapons. Through their ability to reach the cytosol, they exert their enzymatic effects and disrupt the normal metabolism of host cells producing deleterious effects and generally leading to their death. This study aims to develop a drug candidate capable of blocking the action of a broad range of bacterial toxins. A High Throughput Screening[a] identified a compound named C910 with broad spectrum inhibitory properties against many bacterial toxins (LT, BoNT/A, DT, CNF1, TcdB, Stx). Thus, it constitutes a good starting point to develop a drug candidate by medicinal chemistry . This chemical optimization based on structure-activity relationship studies is currently underway. In order to identify chemical groups essential for bioactivity and to get more potent molecules, twenty eight analogs were synthesized so far and their bioactivity as well as toxicity evaluated *in vitro* in cellular assays. The results obtained open up prospects for improving the activity of the parent molecule.

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Direct interaction between LAT3 and unknown partners revealed by optoproteomics

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PO 161

In cancer metabolisms, besides glucose, amino acids play key roles in maintaining high metabolic processes of cancer cells in comparison to normal cells. The LATs family have been found to be specifically in charge of supplying amino acids from extracellular to intracellular side of the cells. Among four variants, LAT3 is highly expressed proteins in several cancers including esophageal and prostate cancers, ideal as therapeutic target, as well as specific biomarkers of cancer detection.

One avenue of research that we have focused on LAT proteins is what interactive proteins inside cells that are tuned to respond to amino acids transportation. We started with the LAT3 variant. Since there are no 3D structures available for LAT3, we first applied bioinformatics tools to predict the topology, structure and putative functional sites including phosphorylation and ubiquitination. We then worked on the establishment of optoproteomics technique utilizing our specialty in genetic code expansion. Site-specific incorporation of light-activatable *p*-azido-L-phenylalanine (AzF) as cross-linkers into proteins makes an attractive solution for the generation of protein complexes for mass-spectrometric analysis, in terms of the precise spatial and temporal control of complex formation provided by the light induction, as well as specific crosslinking interface between the protein complexes.

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Chemoenzymatically synthesized novel ganglioside GM3 analogues with antitumor activities	***PO 163***

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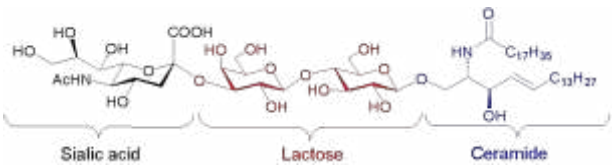
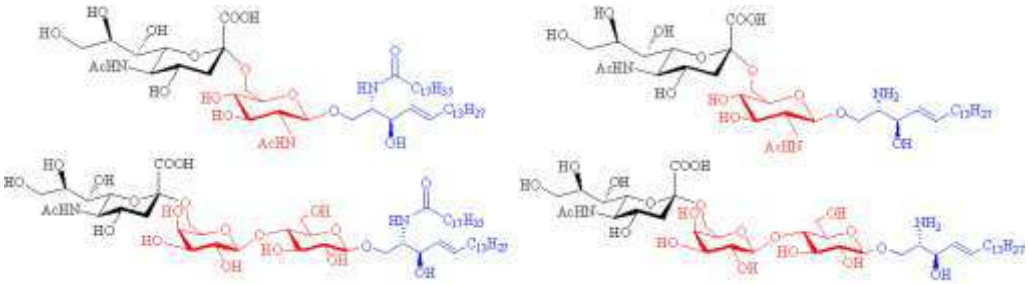
Ganglioside GM3, belonging to glycosphingolipids family, has been considered as tumor-associated carbohydrate antigen (TACA) on several types of tumor. In addition, several studies have revealed that GM3 can inhibit epidermal growth factor receptor tyrosine kinase (EGFR-TK), which is strongly related with uncontrolled tumor growth[(a)]. Furthermore, our previous studies demonstrated that some GM3 analogues containing galactose or mannose with α-2,6 sialoside have significant inhibitory effects on tumor cell growth and migration[(b)]. Recently we designed and synthesized new GM3 analogues containing glucosamine or lactose with α-2,6 sialoside in order to study their antitumor activities and search new leading compounds for cancer therapy.



Structure of ganglioside GM3

At first, the sialic acid was activated as sialyl xanthate form. Then the lipid precursor azidosphingosine was synthesized from the commercial D-(+)-galactose. Finally, glucosamine and lactose moieties were prepared by enzymatic hydrolysis, and the enzyme is specific for removing the acetyl group at C-6 position. The glucosamine residue bearing a free 6-OH was obtained from 2-phthalimido-2-deoxy-α-D-glucopyranoside tetraacetate by enzyme, further through α-sialylation reaction and conjugation with lipid precursor, after several step manipulations, the novel glucosamine-containing analogues were synthesized. Next, the lactal with free 6-OH at galactose was obtained from peracetylated lactal using enzyme, further also by α-sialylation, epoxidation and conjugation, novel lactose-containing analogues were synthesized.


Structures of synthesized glucosamine- and lactose- containing analogues

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Study of LAM-mimetics glycovaccines against Tuberculosis (TB)

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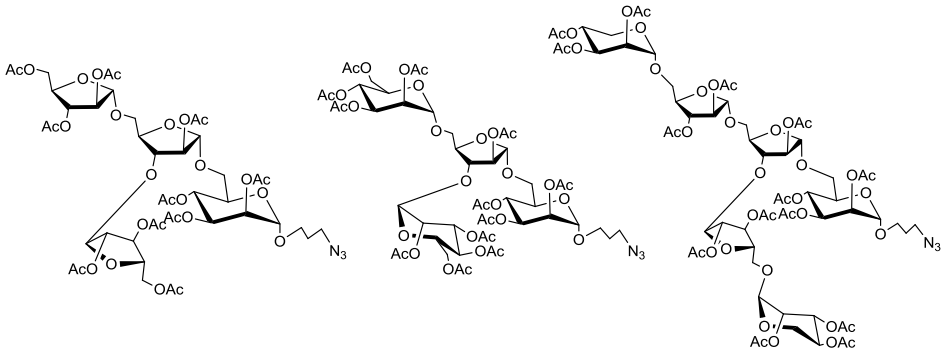
PO 164

Lipoarabinomannan (LAM) is a kind of lipoglycans found in the mycobacterial cell wall[a]. As an important immuno-modulating compound, it plays key roles in mycobacterial infections, which gives a direction for future vaccines development[b]. Due to the complicated structure of LAM, its mimetic is more likely to be prepared and studied as vaccine candidates. In this work, a core building block is prepared using flow chemistry with high yield. Then it is used as the acceptor to combine with three different donors and the newly prepared compounds are finally combined to a monosaccharide for further use with carrier proteins.



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Membrane-type 5-matrix metalloproteinase (MT5-MMP) inhibition: an emerging strategy in Alzheimer's therapy.

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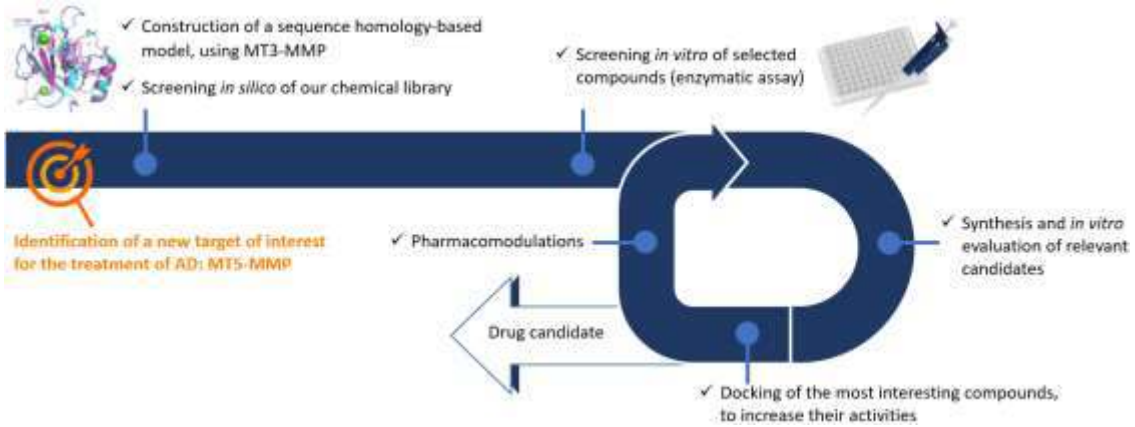
PO 165

In 2018, the number of people living with dementia in the world is estimated at 47 million and Alzheimer's disease (AD) is the most common form of dementia in France with about 900,000 cases. AD is a neurodegenerative and incurable brain disorder; only treatments for symptoms are available at this time. Because of the heavy economic and societal impacts, there is an urgent need to find new treatments that target the molecular causes of neuronal cell death.

Two abnormal structures in the brain called β-amyloid (Aβ)-containing plaques and neurofibrillary tangles are considered as two of the main features of AD. In this context, several studies support the hypothesis that alterations in the processing of amyloid precursor protein (APP), resulting in the accumulation of β-amyloid peptides (Aβ) and other proteolytic products contributes to AD pathogenesis. Thus, current research focuses on the enzymes involved in APP cleavage such as α-, β-, and γ-secretases. However, recent studies have revealed the existence of another physiological APP processing pathway, mediated by a novel AD-related enzyme, membrane-type 5-matrix metalloproteinase (MT5-MMP), that can process APP and promote Aβ and CTFβ accumulation, as well as the inflammatory process in AD transgenic mice.[(a),(b),(c)] Moreover, MT5-MMP can cleave APP upstream from the β-secretase cleavage site (the so called η-cleavage site)[(d)] and release a N-terminally elongated Aβ fragment (Aη-α), which appears to be synaptotoxic.[(e)]

We aim to design and synthesize the first MT5-MMP inhibitor through an interdisciplinary approach including molecular modelling, medicinal chemistry and biology. Starting from a hit compound identified by *in silico* screening, we are now investigating the pharmacomodulations on that scaffold to gain in affinity and selectivity for MT5-MMP.



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In silico studies of allosteric modulation of aminergic GPCRs

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PO 166

Dopamine receptors belong to monoamine GPCRs and in the human brain they play an important role in the pathophysiology and treatment of psychosis and movement disorders. Currently one of the hot topics in drug discovery is design of allosteric modulators of GPCRs instead of orthosteric ligands. Positive allosteric modulators (PAMs) of dopamine D_2 receptor have been proposed as a method of treatment of Parkinson's disease (PD), however there are no registered antiparkinsonian drugs which are D_2 receptor PAMs. Moreover, only few PAMs of D_2 receptor are known and they are mostly peptidomimetics, such as PAOPA. The studies on benzothiazole racemic compound and its enantiomers (Fig.1.) showed that R enantiomer acts as a PAM of dopamine D_2 receptor by enhancing the effect of dopamine on G protein activation, cAMP signaling, and enhancing the binding of [^{3}H] - dopamine[(a)].

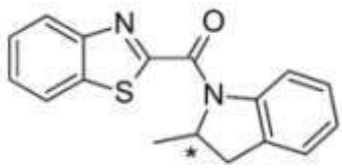

Fig.1. The studied dopamine D_2 receptor positive allosteric modulator (PAM).

The aim of studies was to investigate the allosteric effect of this PAM on D_2 dopamine receptor D_{2LONG} (the isoform with long intracellular IL3 loop) in active conformation in complex with respective G protein. The homology model of D_{2LONG} receptor was created by Modeller using crystal structures of β_2-adrenergic receptor in complex with G_s protein (PDB ID: 3SN6) and D_2, D_3, D_4 in inactive conformation (PDB ID: 6CM4, 3PBL and 5WIU, respectively). The IL3 long loop was generated with Yasara software. Dopamine was docked to the receptor model as the orthosteric ligand. Several allosteric binding sites for PAM were considered. The membrane environment for the ligand-receptor complexes was constructed using the Charm-Gui membrane builder server. Molecular dynamics simulations were performed using Gromacs in order to study the effect of the allosteric ligand on the receptor. An Amber03 force field was used for receptors, Slipids for the membrane and General Amber Force Field for dopamine and modulator.

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Design of GSK9742, a Chemical Probe for the TAF1/TAF1L Bromodomains.	***PO 167***

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A chemical probe is a tool molecule that selectively binds to a target and is used to elucidate its biological function, helping bridge together chemical biology and drug discovery.[(a)] TATA binding protein (TBP) associated factor 1 (TAF1) and TAF-1-like (TAF1L) are multidomain proteins that have been implicated with oncology and neurodegenerative diseases.[(b)] The biological role of these proteins and their bromodomain regions within disease is still unknown with further target validation required. Herein we report the discovery of GSK9742, a potent, selective and cell penetrant TAF1/TAF1L bromodomain chemical probe and accompanying negative control GSK5121 for pre-clinical target validation.

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(b) Oh, H. R.; An, C. H.; Yoo, N. J.; Lee, S. H. *Pathol. Oncol. Res.* 2017, *23*, 125–130

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