27th SCT Young Research Fellows Meeting

27ièmes Journées Jeunes Chercheurs, JJC

January 29 – 31, 2020, Caen

BOOK OF ABSTRACT

www. cermn.unicaen.fr ..... www.sct-asso.fr

Welcome to the 27th Young Research Fellows Meeting!

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

Thank you for joining the 27th 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

Société de Chimie Thérapeutique

Website

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 thérapeutique ».
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

Acknowledgements

Members of the organizing committee would like to thank all the partners who have supported the organizition of this meeting.

Institution

Industrial sponsor

Synthenova SAS
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Website : www.synthenova.com
Email : synthenova@orange.fr

Located in Hérouville Saint Clair near Caen, the SYNTHENOVA company proposes various services in fine organic chemistry addressed to companies specialized in biotechnology and for pharmaceutical, cosmetic and chemical industries.

Synthenova provides mainly two services: Research and Development of new molecules and custom synthesis of building blocks or reference molecules.

In such a competitive industry, Fluorochem have worked hard to keep pace with market developments, continuously expanding our catalogue making sure we can offer some of the most weird, wonderful and novel products. With around 200,000 products in our catalogue, we offer, but are not limited to; organic research intermediates, NMR solvents and tubes, silica gel and silanes.

A competitive chemical supplier of reagent and building blocks for research and development to the pharmaceutical companies, Universities and those performing contract research. We currently have over 30,000 products in UK stock and with this number continuously increasing we aim to have your order with you next day.

One of Fluorochem's most recent projects is its new search facility "Doug Discovery". The site still offers the traditional methods of searching such as; the sketcher tool or searching by product identifiers. However, Doug offers chemists a totally different method of searching, the 'Concept Search'. This option provides a speedy process to browse the product catalogue by selecting a combination of structure and functional groups; an entirely new concept for chemical supplier websites.

Home of the new search facility "Doug Discovery". Come and ask for a demo alternatively check it out yourself www.dougdiscovery.com

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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.

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

Follow us on Social Media:

https://servier.com/en/company/

About TCI

Tokyo **C**hemical **I**ndustry is a global manufacturer of research chemicals, offering more than 30,000 reagents including 8,000 unique products using our own facilities. Many of these chemicals are highly specialised, including a large number of reagents available only through TCI. The company's high quality chemicals for chemistry, life science, materials science, and analytical chemistry are available in benchtop-to-bulk scale. TCI is known worldwide for its organic reagents, high product reliability and availability, and fast delivery.

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+


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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
C. Rochais, Université de Caen Normandie
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P. Dallemagne, Université de Caen Normandie
A. Malzert-Fréon, Université de Caen Normandie
T. Cailly, Université de Caen Normandie
M. Since, Université de Caen Normandie
Students and members of the CERMN

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

27th *Journées Jeunes Chercheurs*
Young Research Fellow Meeting

PROGRAMME

Wednesday January 29, 2020

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11h30 – 12h45 : **Registration**

12h45 – 13h00 : **Opening**
Prof Michel Boulouard – Dean of the School of Pharmacy – Université de Caen Normandie
Prof Sébastien Papot – President of the Société de Chimie Thérapeutique

Session 1: Chairman Benjamin Guieu

13h00 – 13h40 : **Plenary lecture.**
Dr. S. Ongeri, BioCIS, Université Paris Saclay, France.
Mimicking beta-hairpin and helix with designed peptidomimetics to inhibit the aggregation of amyloid proteins: interest in Alzheimer's disease and type 2 Diabetes.

13h40 – 13h40 **Oral Communication session 1**

13h40 – 13h55 : **CO 1 : Raphaël Bolteau, Univ. Lille, INSERM, CHU Lille, France**
Design, synthesis and pharmacological evaluation of promising A_{2A} receptor antagonists based on the quinazoline scaffold.

13h55 – 14h10 : **CO 2 : Gulsah Bayraktar, Ege University, Izmir, Turkey.**
Potential Anti-Alzheimer Tacrine-Donepezil Hybrids with MTDL Profile

14h10 – 14h25 : **CO 3 : Mazarine Laurent, ICOA, Orléans, France.**
Design and functionalization of new heterocycles fused with a quinuclidine moiety as analogs of SK inhibitors.

14h25 – 14h40 : **CO 4 : Caroline Lanthier, CERMN, Caen, France**
New potent benzisoxazole derivatives as pleiotropic compounds with $5HT_4R$ agonism and *in cellulo* antioxidant properties to fight Alzheimer's disease.

14h40 – 15h10 : **Flash Poster Presentation. Session 1.**

FP1: Laetitia Lesire
FP2: Johanna Giovannini
FP3: Rossella Castagna
FP4: Mirjana Antonijevic

15h10 – 16h00 : **Coffee break, poster session & commercial exhibition.**

Session 2: Chairwoman Gülşah Bayraktar

16h00 – 16h40 : **Plenary lecture.**
Pr. Michael Decker (University of Wurzburg, Germany).
Photopharmacology in Alzheimer Research

16h40 – 17h40 : **Oral Communications session 2**

16h40 – 16h55 : **CO 5 : Pauline Zipfel, CERMN, Caen, France.**
Matrix metalloproteinases as new biological targets in Alzheimer's disease: Opportunities and Challenges.

16h55 – 17h10 : **CO 6 : Davia Prischich, *IBEC, CIBER-BBN, Spain*.**
Photocontrol of clathrin-mediated endocytosis using Traffic Light peptides**.**

17h10 – 17h25 : **CO 7 : Fabio Riefolo, IBEC, Barcelona, Spain.**
Photocontrol of Muscarinic Receptors and Applications in vivo

17h25 – 17h40 : **CO 8 : Line Séguy, CERMN, Caen.**
Development of safe and brain-targeting nanovectors for Alzheimer's disease treatment

17h40 – 18h10 : **Flash Poster Presentation. Session 2**
FP5: Clémentine Pescheteau
FP6: Sangeetha Thirumaran
FP7: Nicolas Probst
FP8: Jean-Pierre Jourdan

18h10 – 19h30 : **Welcome Reception and poster session.**
Food buffet in front of the posters. Discuss science, wine and food together…

Thursday January 30, 2019

Session 3: Chairman Nicolas Guedeney

09h00 – 09h30 : **Plenary lecture.**
Sophie Faure (ICCF, Université Clermont Auvergne, France)
Peptoids: oligoamides with designable architecture to mimic structure and function of natural peptides

09h30 – 10h30 : **Oral Communications session 3.**

09h30 – 09h45 : **CO 9 : Carlo Matera, Institute for Bioengineering of Catalonia, Spain**.
Phototrexate®: a novel drug candidate for cancer and psoriasis**.**

09h45 – 10h00 : **CO 10 : Stéphane Duflocq, CiTCoM, U 1268, Paris, France.**
Oxime bond in peptide vectorization: unveiling an antitumoral effect through ribosome biogenesis impairment.

10h00 – 10h15 : **CO 11 : Amanda Garrido, University of Tours, Tours, France.**
Design of original imidazophtalazine compounds as promising therapies for breast cancers

10h15 – 10h30 : **CO 12 : Charlotte Juillet, ICSN, Université Paris-Saclay , France.**
Synthesis of Simplified Analogs of Marine Metabolites for Aurora B Kinase Inhibition

10h30 – 11h00 : **Coffee break, poster session & commercial exhibition.**

Session 4: Chairwoman Marie Jouanne

11h00 – 11h30 : **Plenary lecture.**
Dr. C. Kieffer, (CERMN Université de Caen Normandie, France)
Design of Protein-Protein Interaction modulators: two applications in cancerology

11h30 – 12h00 : **Flash Poster Presentation. Session 3**
FP9: Sergio Ramos Varela
FP10: Nicolas Guedeney
FP11: Maxime Neuville
FP12: Alexander Efremov

12h00 – 13h00 : **Lunch break – Poster Session**

Session 5: Chairwoman Emmanuelle Dubost

13h00 – 13h40 : **Plenary lecture.**
Pr. A. Sutherland (University of Glasgow, Scotland).
Molecular Tracers for Neuroinflammation: From Synthesis to Human Tissue Imaging

13h40 – 14h40 : **Oral Communications session 4.**

13h40 – 13h55 : **CO 13 : Laura Gallego Yerga, Dept of Pharmaceutical Sciences, , Salamanca, Spain.**
Design of potent colchicine-site ligands to overcome multi-drug resistance of colon cancer cells with improved intrinsic water solubility

13h55 – 14h10 : **CO 14 : Antoine Versini, Institut Curie, Paris, France.**
Salinomycin derivatives kill cancer stem cells via lysosomal iron targeting

14h10 – 14h25 : **CO 15 : Jason Muller, PEPITE EA4267, Besançon, France.**
Binding study and optimisation of piceatannol as inhibitor of arginase.

14h25 – 14h40 : **CO 16 : Marion Polomski, GICC EA 7501, Tours, France.**
Synthesis and biological evaluation of 17f new analogs as STAT5 proteins inhibitors in myeloid leukemias treatment

14h40 – 15h10 : **Flash Poster Presentation. Session 4.**

FP13: Clément Vigier
FP14: Martha Hernandez Carrillo
FP15: Quentin Ibert
FP16: Antoinette Keita

15h10 – 16h00 : **Coffee break, poster session & commercial exhibition.**

Session 6: Chairman Jean-Pierre Jourdan

16h00 – 16h40 : **Plenary lecture.**
Dr. L. Jean (COBRA, Université de Rouen Normandie, France)
Design, biological evaluation and X-ray crystallography of multifunctional ligands targeting simultaneously acetylcholinesterase and glycogen synthase kinase-3

16h40 – 17h40 : **Oral Communications session 5**

16h40 – 16h55 : **CO 17 : Gianina Dodi, University of Medicine and Pharmacy of Iasi, Romania**

Magnetic hybrid nanoparticles: facile preparation, toxicity and MRI biodistribution.

16h55 – 17h10 : **CO 18 : Reynald Mangeant, CERMN, Caen, France**
MR35806: a new fluorinated indazole compound as a potential 5-HT_4R PET radiotracer.

17h10 – 17h25 : **CO 19 : Aziza Saber, GEOPAC Research Center, Rabat, Morocco**.
New eco-sustainable synthesis of indole derivatives using green catalysts.

17h25 – 17h40 : **CO 20 : Veselin Nasufovic, Friedrich Schiller Universität, Jena, Germany.**
Opportunities in targeting actin with unexpected species selectivity

17h40 – 18h10 : Flash Poster Presentation. Session 5

FP17: Marine Duplantier
FP18: Léo Faïon
FP19: Kristina Mihajlović
FP20: Antoine Tronnet
FP21: Emilija Milovic
FP22: Marion Polomski CO 16

Journées Jeunes Chercheurs

Friday January 31, 2019

Session 7: Chairman Gonzalo Vera

09h00 – 10h30 : Oral Communications session 6.

09h00 – 09h15 : **CO 21 : Ofelia Feuillatre, University of Tours, Tours, France.**
Benefits of using innovative bioconjugation technology for antibody-drug conjugates: proof of concept with MF-BTX-MMAE in CD30-positive lymphoma model.

09h15 – 09h30 : **CO 22 : Aurore Dreneau, Institut Pasteur de Lille, Lille, France.**
Discovery, optimization and biological evaluation of the first boosters of the nitroimidazole anti-tb drug pretomanid**.**

09h30 – 09h45 : **CO 23 : Dyhia Amrane, Faculté de Pharmacie, Marseille, France..**

Pharmacomodulation and *in vitro* antiplasmodial evalution of α-CCl_3-*N*-heterocycles using a scaffold-hopping strategy.

09h45 – 10h00 : **CO 24 : Guillermo Nunez Mojica, Universidad Autónoma de Nuevo León, Mexico.**
Antibacterial and antimycobacterial activities of extracts and steroid saponins from *Solanum chrysotrichum*

10h00 – 10h15 : CO 25 : Shafi Ullah Khan, School of Pharmacy, Monash University, Selangor, Malaysia
In search of G protein-coupled estrogen receptor (GPER-1) modulators: Insilco and Invitro approach

10h15 – 10h30 : **CO 26 : Marie Fabre, Institut de Chimie de Nice, Nice, France.**
Synthesis of new CXCR1/2 receptors antagonists for wet AMD treatment

10h30 – 11h00 : Coffee break, poster session.

Session 8: Chairman SCT

11h00 – 11h30 : Plenary lecture.
SCT Award for young investigator in Medicinal Chemistry
Dr Bart Roman – Ghent University, Belgium
Biology-driven chemistry: new molecules and reactions to better understand and modulate health and disease

11h30 – 12h00 : Oral Communications session 7.

11h30 – 11h45 : **CO 27 : Kossi Efouako Soklou, ICOA, UMR 7311, Orléans, France.**
Synthesis of heterospirocycles for molecular diversity and medicinal chemistry.

11h45 – 12h00 : **CO 28 : Margot Boujut, COBRA, Rouen University, Mont St Aignan France.**
Indazoles: From medicinal chemistry to fluorescent probes.

12h00 – 12h30 : Awards and concluding remarks

12h30 – 13h30 : Lunch break

13h30 End of the meeting


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PLENARY LECTURES

Professor Sandrine ONGERI

EDUCATION/CAREER

Since 2011	**Full Professor in Medicinal Chemistry** - BioCIS UMR 8076, Faculty of Pharmacy, Univ. Paris Sud (became Univ. Paris Saclay the 1st January 2020)
2001-2011	**Associate Professor in Medicinal Chemistry** - BioCIS UMR 8076, Faculty of Pharmacy, Univ. Paris Sud.
1999/2001	**Post-Doctoral researcher**. Univ Milan (Italy). **Pr. C. Gennari. European Grant**
1995-1999	**PhD** in Organic Chemistry, Univ. Paris Descartes. **Pr. H-P Husson**
1995/1996	Dyson-Perrins Laboratory, **Oxford** (UK). **Pr. Sir J. E. Baldwin**
1994/1995	**Master Degree** in Organic Chemistry Univ. Paris 5. **Research period (12 months) in Pharmaceutical Company** (SERVIER Laboratories).
1989-1995	**Pharmacy Degree,** Faculty of Pharmacy - Univ. Paris 5

VARIOUS ACTIVITIES

Since 2010	Co-**DIRECTION** (with Dr. B. Crousse) of the team FLUOPEPIT OF BIOCIS UMR 8076, LabEx LERMIT. http://www.biocis.u-psud.fr/?-Molecules-Fluorees-et-Chimie-. 2 Full Prof, 1 DR CNRS, 3 MCU, 1 IE, PhDs (4-7), Masters (2-3).
Since 2015	**Deputy director of the Doctoral school** "Therapeutic innovation" ED569. 300 PhD students. Organization of their multidisciplinary training (scientific and transferable skills). Recruitment management. Conflict management between PhD students and their supervisor. In charge of the International relations and programmes.

Partner of ITN "TubInTrain" : https://www.tubintrain.eu/ (2019-2023)
Partner of FETOPEN "NoPest" : https://www.h2020nopest.org/ (2019-2024)

Professor Michael DECKER

EDUCATION

- Habilitation in Pharmacy at University of Jena, Germany 2007
- Ph. D. in Pharmaceutical Chemistry 2001
  University of Bonn, Germany
- University of Cambridge (St. John`s College), UK 1996 - 97
  M. Phil. at the Department of Chemistry
- Undergraduate studies in Chemistry at University of Bonn 1993 - 96

PROFESSIONAL EXPERIENCE

- Professor of Pharmaceutical and Medicinal Chemistry, since 2012
  Julius-Maximilians-Universität Würzburg, Germany
- "Privatdozent" in Pharmaceutical Chemistry at Regensburg 2010 - 2012
  University, Germany
- Lecturer in Medicinal Chemistry, School of Pharmacy, 2008 - 2009
  Queen's University Belfast, UK
- Visiting Scientist at the Medicinal Chemistry Laboratory 2007 – 2008
  of McLean Hospital, Harvard Medical School, USA
  as a research fellow of the German Academy of Natural Scientists Leopoldina

Dr Sophie FAURE

Sophie Faure, studied chemistry at the University of Reims-Champagne-Ardennes where she received her PhD degree in 1999 under the supervision of Prof. O. Piva, working on photocycloadditions and photoisomerisations to access natural sesquiterpenes. She joined the group of Prof. D. Enders in Aachen as a postdoctoral fellow in 2000. After a second post-doctoral position in medicinal chemistry in Prof. H.-P. Husson group at Paris V University, she joined the CNRS in 2002 as “Chargé de Recherche” in the group of Prof. David J. Aitken in Clermont-Ferrand to work on natural macrocyclic peptides total synthesis and conformationally constrained □-amino acids for the development of original foldamers. In 2007, she turned her interest toward peptoid-type peptidomimetics and foldamers with Prof. C. Taillefumier and passed her habilitation in 2012. She is since 2017 head of the group “peptoid” at the Chemistry Institute of Clermont-Ferrand.

Dr Charline KIEFFER

Charline KIEFFER was born in Epinal (France) in 1986. She studied pharmacy at the Henry Poincaré University (Nancy, France), and went in 2009 to Aix-Marseille University to complete her pharmacy residency. In 2014, she received her PharmD and Pharmacy Residency Diploma. In the same year, she obtained her PhD in Organic Chemistry, under the supervision of Pr Pascal Rathelot and Pr Pierre Verhaeghe (Faculty of Pharmacy, Marseille), for research on antiprotozoal pharmacochemistry in quinazoline and quinolone series. After completing a postdoctoral period in Medicinal Chemistry in the Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN) (Caen, France) in the group of Pr Anne Sophie Voisin-Chiret, she was appointed Lecturer in Medicinal Chemistry in the school of Pharmacy at the University of Caen Normandie in 2017. Her research interests include medicinal chemistry in the field of protein-protein interactions, in order to design abiotic compounds with an interest in cancerology and neurosciences.

Dr Andrew SUTHERLAND

Andrew Sutherland was born in 1972 in Wick, Scotland. After graduating with a 1st class B.Sc. Honours degree in chemistry at the University of Edinburgh, he undertook a Ph.D. at the University of Bristol under the supervision of Professor Christine Willis. This was followed by postdoctoral studies with Professor John Vederas at the University of Alberta and Professor Timothy Gallagher at the University of Bristol. In 2003, he was appointed to a lectureship in the School of Chemistry at the University of Glasgow and currently holds the position of Reader. His research group's interests are on the discovery of new radionuclide-based and fluorescent molecular imaging agents for medical applications and, the development of new synthetic methodology, including processes applicable for radiohalogenation.

Dr Ludovic JEAN

Ludovic Jean received his PhD degree from the University of Caen Normandy (France) in 2004 under the supervision of Prof. Marie-Claire Lasne and Prof. Jacques Rouden. After several post-doctoral periods at l'Institut de Chimie des Substances Naturelles (ICSN), Gif-sur-Yvette, France (2005-2006) with Prof. Angela Marinetti, at the Max-Planck-Institut, Mülheim an der Ruhr, Germany (2006-2007) with Prof. Alois Fürstner, at the University of Paris Descartes (2007-2008) with Prof. Janick Ardisson. Ludovic Jean has been appointed as assistant professor in 2008 in the bio-organic chemistry team at the Laboratory COBRA, UMR CNRS 6014, University of Rouen Normandy, France. His research interests are focused on medicinal chemistry: reactivators of cholinesterases inhibited by organophosphorus nerve agents; inhibitors of cholinesterases; multi-target directed ligands (MTDLs) against neurodegenerative diseases; peptidomimetics; fluorescent probes; click chemistry). He is co-author of 55 peer reviewed articles and 4 international patents.

Mimicking β-hairpin and helix with designed peptidomimetics to inhibit the aggregation of amyloid proteins: interest in Alzheimer's disease and type 2 Diabetes

Dr. Sandrine ONGERI
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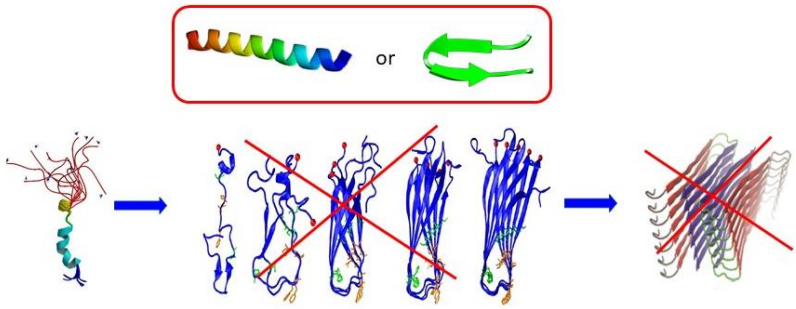
At least 20 human degenerative diseases, named amyloidosis, have been currently identified and involve misfolding and misassembly into various aggregate structures of more than 30 proteins. Among these diseases, Alzheimer's disease (AD) and type 2 diabetes (T2D), affecting approximately 47 and 400 million people respectively worldwide, are major public health issues. No etiological treatment exists against these two diseases which lead irremediably to the death of neuronal and pancreatic β-cells respectively. Clinical studies suggest that they are linked and that T2D might be an increased risk for AD. Aggregates of $A\beta_{1\text{-}42}$ and hIAPP amyloid proteins**,** involved in AD and T2D respectively, share similar structural characteristics and aggregation process. In particular, soluble oligomers of $A\beta_{1\text{-}42}$ and hIAPP are highly suspected to be involved in neuronal and pancreatic β-cells death respectively, by a similar mechanism of toxicity.
We demonstrate here that peptidomimetic foldamers are attractive molecules to reduce efficiently the aggregation process of $A\beta_{1\text{-}42}$ and hIAPP and to maintain the presence of their non toxic monomer species. β-hairpin and β-strands mimics were designed to interact with β-sheet rich toxic aggregates (oligomers and fibrils). Helix mimics have been also investigated as an alternative strategy for trapping the non-toxic monomeric forms before the switch to β-sheet conformation. This presentation will give an overview of : 1- the design and the synthesis of β-hairpin and helix peptidomimetics targeting either $A\beta_{1\text{-}42}$ and/or hIAPP; 2- the development of new biophysical techniques to identify and separate soluble monomer and oligomer species of $A\beta_{1\text{-}42}$ and hIAPP; 3- the evaluation of our peptidomimetics on $A\beta_{1\text{-}42}$ and hIAPP aggregation using these new techniques.



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Photopharmacology in Alzheimer Research

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In the last years the field of "photopharmacology" has emerged. Photoswitchable units, such as azobenzenes and diarylethenes, are chemically incorporated into biologically active molecules to obtain photoswitchable molecules that can reversibly change their structure and concomitantly their activity upon irradiation with light, normally UV light. Within our research efforts for anti-Alzheimer drugs targeting the human cannabinoid receptor subtype 2 (hCB_2R) [a] and the human muscarinic acetylcholine receptor subtype 1 (hM_1R) [b], we have incorporated azobenzene units into hCB_2R agonists and both dualsteric and bivalent hM_1R agonists [c], the latter simultaneously address both the orthosteric and allosteric binding sites of the receptor.

Applying computational studies, such as molecular dynamics, as well as a portfolio of pharmacological assays, such as radioligand binding, functional studies, as well as FRET techniques, we were able to develop the first selective photoswitchable hCB_2R "affinity on-switch" [d], i. e. a small molecule that bind swith higher affinity after irradiation with UV light. Furthermore, a dualsteric photoswitchable hM_1R ligand was developed, the activity of which can be regulated by light as demonstrated in a set of FRET studies [e]. A dualsteric ligand interacts with the orthosteric binding site of the neurotransmitter and of classical ligands, but at the same time with a distinct binding site, the allosteric one [b]. We also synthesized, photophysically and pharmacologically characterized bivalent hM_1R ligands based on the agonist iperoxo. and incorporated fluorine atoms to yield "red-shifted" ligands that show a considerably higher extent of photoconversion and can be switched by visible light [f]. We observed for the first time that "red-shifted" ligands can also differ significantly in their pharmacological activity [f]. Ongoing work on hM_1R orthosteric agonists yielded "on-switches" regarding potency.
These findings show that photopharmacology can be successfully applied to various GPCR ligands of interest in Alzheimer research. The field is moving beyond proof-of-concept, since it seems possible to specifically design GPCR ligands as "on- or off-switches", and to compounds that are "affinity switches" and/or "efficacy switches". This significantly expands the toolbox of GPCR investigation with specialized molecular tools supporting the investigation of the molecular basis of receptor function. The underlying principles seem generally applicable, since also a photoswitchable dualsteric hM_2R ligand was developed and applied to optically control cardiac function, even in vivo [g].

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Peptoids: oligoamides with designable architecture to mimic structure and function of natural peptides

Sophie FAURE

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Peptoids are *N*-substituted glycine oligomers, developed in the early 1990s, structurally related to peptides with the side-chains located on the amide nitrogen rather than on the α-carbon.[(a)] Peptoids are well-suited peptidomimetics since they possess undeniable advantages such as proteolytic stability and cost-effective synthesis with a great potential for diversity.[(b)] However, peptoids are inherently more flexible than peptides due to achiral backbone and, above all, the presence of *N*,*N*-disubstituted amides that are prone to cis-trans isomerism and prevent stabilisation by internal hydrogen bonding. This intrinsic flexibility could in fact be turned into a key advantage to access different type of folded architectures. A set of chemical tools have been introduced to improve folding propensities of peptoids and access a large variety of secondary structures. In particular, specific side-chains were developed to generate robust polyproline-type helical structures.[(c)] Among them, the triazolium-type side-chain was exploited to design cationic amphipathic helical peptoids as mimics of natural antimicrobial peptides.[(d)]

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Design of Protein-Protein Interaction modulators: two applications in cancerology

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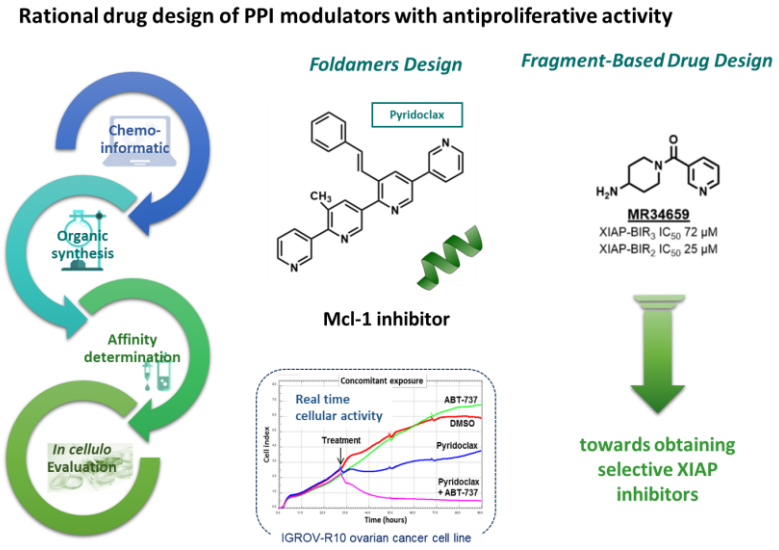
Protein-Protein Interactions (PPIs) are defined as "interactions between two identical or dissimilar proteins at their domain interfaces that regulates the function of the protein complex". They constitute the interactome.[a] PPIs disorders are implicated in many pathological processes, such as neurodegenerative diseases, diabetes, or cancers. Today, PPIs are considered as the next generation of therapeutic targets, and most pharmaceutical industries have now extended their drug discovery programs to PPIs.

Disrupting PPIs with small molecules to design drugs is a challenge: indeed, the interaction surfaces between proteins are flat, hydrophobic and large, which makes the conception of molecules more complex than with a conventional target. Nowadays, rational drug design strategies play an important role in obtaining PPIs modulators.[b]

During the talk, the design of antiproliferative molecules disrupting PPIs involved in cancerization process will be shown, through two examples of molecules obtained at CERMN lab.[c,d]



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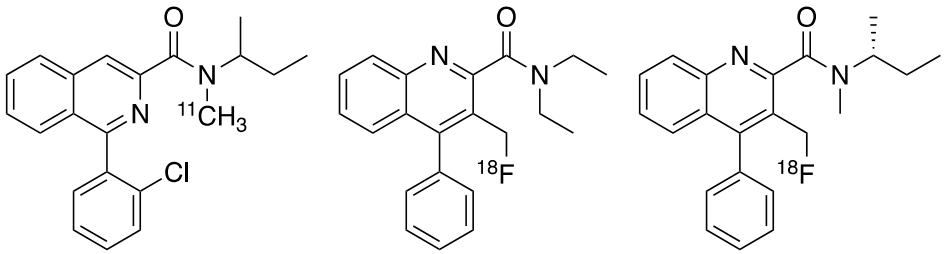
Molecular Tracers for Neuroinflammation: From Synthesis to Human Tissue Imaging

Andrew SUTHERLAND

WestCHEM, School of Chemistry, The Joseph Black Building,
University of Glasgow, G12 8QQ, UK

The translocator protein (TSPO, 18 kDa) is a hydrophobic, tryptophan-rich outer mitochondrial membrane protein found in many of the major organs.[a] In healthy brain tissue, TSPO is expressed at low concentration, however, in response to chronic neurodegeneration or acute brain injury, TSPO expression is dramatically increased. Therefore, TSPO is considered an attractive target for molecular imaging of neuroinflammation and neurodegenerative diseases. Over the last three decades, the most commonly used tracer for TSPO is [^{11}C]PK11195. However, this suffers from low brain uptake and poor signal to noise ratio. More recently, efforts have focused on the development of second-generation tracers. While showing affinity and selectivity for TSPO, many of these have mixed affinity binding in humans.[b] We developed a research programme to investigate the factors associated with binding of small organic molecules with TSPO.[c] This led to the discovery of quinoline-2-carboxamides as high affinity agents with optimal physicochemical properties. In particular, [^{18}F]AB5186 was used to image TSPO in an intracranial glioma bearing mouse and was able to penetrate the intact blood brain barrier in a non-human primate.[d] This presentation will describe the development of AB5186 and the recently discovered analogue, LW223 as PET imaging agents of TSPO. Results of binding affinity profile in both human brain and heart tissue will also be discussed.



PK11195 **AB5186** **LW223**

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Design, biological evaluation and X-ray crystallography of multifunctional ligands targeting simultaneously acetylcholinesterase and glycogen synthase kinase-3

Ludovic JEAN[(1)]

Killian Oukoloff[(1)], Nicolas Coquelle[(2)], Jacques-Philippe Colletier[(2)], Buron Frédéric[(3)], Sylvain Routier[(3)], Manuela Bartolini[(4)], Marco Catto[(5)], Pierre-Yves Renard[(1)]

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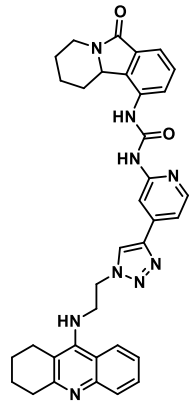
Alzheimer's disease (AD) is a complex and progressive neurodegenerative disorder. The available therapy is limited to the symptomatic treatment and its efficacy remains unsatisfactory. In view of the prevalence and expected increase in the incidence of AD, the development of an effective therapy is crucial for public health. Due to the multifactorial etiology of this disease, the multi-target-directed ligand (MTDL) approach is a promising method in search for new drugs for AD. One of our research projects is the development of MTDLs targeting acetylcholinesterase and glycogen synthase kinase-3.



IC_{50} (hAChE) = 11 nM
IC_{50} (GSK-3 α/β) = 16 nM
Good BBB penetration

Bibliographic references:
Eur. J. Med Chem. **2019**, *168*, 58-77. DOI: 10.1016/j.ejmech.2018.12.063

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Friday January 31, 2020

SCT Award for young investigator in Medicinal Chemistry

Biology-driven chemistry: new molecules and reactions to better understand and modulate health and disease.

Bart I. Roman[(1,2)*]

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(2) Cancer Research Institute Ghent, Corneel Heymanslaan 10, B-9000 Gent, Belgium.

My overall goal is to develop innovative (bio)chemical matter and technologies to interrogate, understand and pharmacologically modulate the cellular and molecular events driving normal physiology and pathogenesis. This translates into the development of research tools and pharmacological tools for in vivo studies. These goals are pursued via 'biology-driven chemistry': tackling real-life biological (oncology) needs using novel chemistry.

During this talk I will give an overview of the medicinal chemistry projects I have been working on, since I started being active in the field in 2005. These projects each use a different ‘angle of attack’: e.g. different entities (small molecules or immunoconjugates), different roles of chemistry (methodology or scaffold optimization), different screening technologies (in silico, phenotypic, target-based).

Bibliographic references:
An overview of relevant publications can be found at https://users.ugent.be/~biroman/

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ORAL COMMUNICATIONS

Design, synthesis and pharmacological evaluation of promising A_{2A} receptor antagonists based on the quinazoline scaffold	*CO 01*

Bolteau, R.(1)*, Liberelle, M.(1), Melnyk, P.(1), Yous, S.(1)

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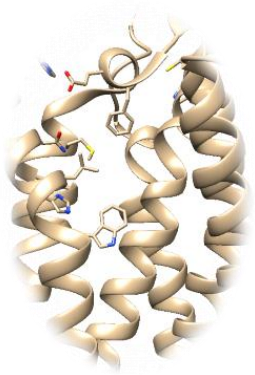
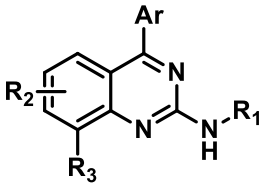
The past fifty years have been marked by the breakthrough of neurodegenerative diseases as Alzheimer and Parkinson[(a)]. Unfortunately, current treatments are symptomatic. Hence, the search for new and innovative therapeutic targets becomes a major challenge. Among these targets, the adenosine A_{2A} 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[(b)]. Though several $A_{2A}R$ antagonists have reached clinical trials[(c)], current research efforts are focusing on developing new antagonists with relevant ADME properties. Based on the co-crystallized structure of the A_{2A} receptor with a selective and high affinity antagonist, a virtual screening allowed us to identify a quinazoline scaffold as a privilege structure. A hit to lead synthesis optimization lead to nanomolar affinity compounds with potentially interesting pharmacokinetic properties including a high solubility. Furthermore, the structure–affinity relationships obtained through a competition binding assay allowed us to better understand the binding mode of our compounds, which was confirmed by obtaining a new co-crystallized structure.



Structure based-design



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Potential Anti-Alzheimer Tacrine-Donepezil Hybrids with MTDL Profile	
Gülşah Bayraktar(1)*, Mümin Alper Erdoğan(2), Ece Bayır(3), Barbara Monti(4), Güliz Armağan(5), Aylin Şendemir(6), Maria Laura Bolognesi(4), Vildan Alptüzün(1). *(1)Department of Pharmaceutical Chemistry, Ege University, Izmir, Turkey* *(2) Department of Physiology, İKÇÜ, Izmir, Turkey* *(3) EGE-MATAL, Izmir, Turkey* *(4) Department of FaBiT, University of Bologna, Bologna, Italy* *(5) Department of Biochemistry, Ege University, Izmir, Turkey* *(6) Department of Biomedical Technologies, Ege University, Izmir, Turkey*	***OC 02***

Alzheimer's disease (AD), is a neurodegenerative disorder mainly characterized by decreased ACh levels, toxic amyloid-β (Aβ) plaques and neurofibrillary tangles (NFT). Apart from these, oxidative stress, neuroinflammation and metal ion dyshomeostasis contribute to AD pathogenesis [(a,b)].

Considering the multifaceted nature of the AD pathogenesis, design of novel scaffolds using Multi-Target-Directed Ligands (MTDL) concept that target more than one therapeutically active site is getting more and more attention in the recent years to obtain disease modifying effect [(a,b)].

Although tacrine is no longer used in the treatment of AD due to its hepatotoxicity, it is still a widely used scaffold in the design of MTDLs thanks to its high affinity to AChE. Donepezil, the first choice medication in the treatment of AD, is a dual inhibitor of AChE with its ability to bind both catalytic active site and peripheral anionic site of the enzyme, simultaneously [(a,b)].

In our previous study, we have reported hydrazone containing structures with good inhibition towards ChEs and Aβ aggregation inhibition potency [(c)]. Moreover, there are some examples of hydrazone containing compounds with antioxidant, metal-binding properties in the literature [(d)].

Previously, a small library of tacrine-donepezil hybrids was designed and synthesized. Benzylpiperidine moiety of donepezil and tacrine were selected as core structures and connected with hydrazone functional group to aim dual inhibition of AChE as well neuroprotective and metal complex formation properties. The compounds have exhibited AChE and BChE inhibition at very low micromolar concentrations. Neuroprotective properties of selected compounds on SH-SY5Y cell line against H_2O_2-induced oxidative stress were evaluated. Additionally, ADME properties of the title compounds were predicted theoretically. Based on this theoretical prediction, BBB penetration of selected compounds were tested on HBEC-5i cell line. In the context of this communication, ChE inhibitory activity structure activity relationships, neuroprotective properties and BBB penetration of the selected compounds will be discussed.

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* Correspondence: bayraktargulsah@gmail.com, gulsah.bayraktar@ege.edu.tr

Design and functionalization of new heterocycles fused with a quinuclidine moiety as analogs of SK inhibitors

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(1) Institut de Chimie Organique et Analytique (ICOA), Université d'Orléans, UMR CNRS 7311, rue de Chartres, BP 6759, 45067 Orléans, France.
(2) Institut de Combustion, Aérothermique, Réactivité et Environnement (ICARE), 1c avenue de la recherche scientifique, 45071 Orléans Cedex 2, France.
(3) PMC ISOCHEM, 4 rue Marc Sangnier, BP 16729, 45300 Pithiviers, France.

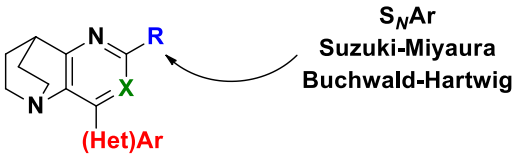
OC 03

Derivatives containing a quinuclidine scaffold are molecules of interest in medicinal chemistry. Indeed, this heterocycle is present in many natural molecules such as quinine, and have many different biological properties such as antimalarials, antipyretic or analgesic. Its high potential and its physicochemical properties have led chemists to develop synthetic molecules targeting, in particular, central nervous system receptors such as the α7 nicotinic acetylcholine receptor. [a]

Despite its potential, few fused polycyclic structures containing the quinuclidine scaffold are described in the literature.[b] There is therefore a great interest in developing novel structures and associated synthetic methodologies to increase the molecular diversity of these families and to study their biological potentials.

To remove this lock, we have developed the synthesis of versatile platforms with a quinuclidine moiety fused with heterocycle containing nitrogen atom. We focused our research to create C-C or C-heteroatom bounds with several functionalization methodologies such as palladium-catalyzed cross-coupling or S_NAr using modern synthesis techniques.

All of these methodologies will be applied to design original analogs of SK inhibitors.



X = C, N
R = OH, Cl

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New potent benzisoxazole derivatives as pleiotropic compounds with 5HT$_4$R agonism and *in cellulo* antioxidant properties to fight Alzheimer's disease.

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OC 04

In a world where life expectancy is increasing, Alzheimer disease (AD) is the main cause of dementia in the world. 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. The medical need is thus strong in AD population.

In this context, the concept of Multi-Target Directed Ligands (MTDLs) was applied to design a drug with several therapeutic targets. The envisaged MTDL (Targeted structure – fig 1) should be able in first hand, to limit the development of ß-amyloid plaques obtained by the aggregation of ß-amyloid peptides (Aß). Indeed, 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 5HT4R agonists which are already studied in the CERMN in other MTDL projects and led to the discovery of Donecopride[1] (blue part – fig 1.). In another hand, it appears that the oxidative stress plays a central role in AD.[2] Adding antioxidant moiety such as polyphenol, lipoic and ferulic acid (red part- fig 1.) could trap free radicals or reactive oxygen species (ROS) and also have a neuroprotective effect. This aspect has been widely studied in Prof. Maria-Laura Bolognesi's laboratory over the years.[3] To that end, different compounds will be designed and synthesized, with both the expertise of CERMN and Prof Maria-Laura Bolognesi, in order to evaluate theirs in vitro/in vivo properties regarding their agonist activity on 5-HT$_4$R and antioxidant properties. The development and promising in vitro/in cellulo results of the benzisoxazoles's moieties lines will be described in this presentation.

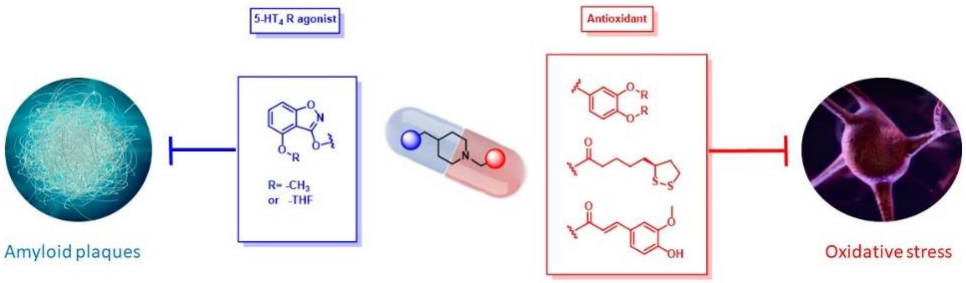

Figure 1- Targeted structure, with 5-HT$_4$R agonist moiety in blue and antioxidant moieties in red.

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Matrix metalloproteinases as new biological targets in Alzheimer's disease: Opportunities and Challenges.	***CO 05***

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In 2018, the number of people living with dementia in the world was estimated at 50 million and Alzheimer's disease (AD) is the most common form of dementia. 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.

Our colleagues from the Institute of Neuropathophysiology (INP) reported recently that some matrix metalloproteinases (MMPs), particularly MT5-MMP and MT1-MMP, are highly involved in the pathogenesis of AD as they have an impact on both the metabolism of Amyloid Precursor Protein (APP) into neurotoxic fragments and on the inflammatory response.[(a),(b),(c)] Our innovative project aims therefore to design first inhibitors of these MMPs that have an impact on AD and that could be promising novel drug candidates.

However, the design of selective inhibitors of MMPs remains quite challenging, considering the homology some of these MMPs share.[(d)] Recent molecular modelling and medicinal chemistry studies seem nevertheless likely to pave the route for deciphering the structural requirements of this enzyme inhibition and open the way to novel and selective inhibitors with an original mechanism of action towards AD molecular causes.[(e),(f)]

During my PhD, I'm exploring different drug design strategies in the search for new inhibitors of specific MMPs. In the first part of my thesis, I have focused on an ambitious *in silico* approach, starting with the virtual screening of the chemolibrary of our laboratory (>19,000 molecules) on a homology model of the enzyme created in our laboratory. I'm currently investigating a more "traditional" approach in drug design, also called "ligand based drug design".

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Photocontrol of clathrin-mediated endocytosis using Traffic Light peptides.	***OC 06***

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Clathrin-mediated endocytosis (CME) is crucial to all eukaryotic cells. It is implicated in a variety of cellular processes that range from nutrient uptake, signal transduction and regulation of the membrane components including surface proteins. The functioning of this transient machinery requires a complex network of proteins that cannot be untangled only by means of genetic modification and immunological depletion. Although pharmacological tools can aid studying the dynamics of biological responses by acute inhibition or stimulation of the upstream processes, the freely diffusing nature of these molecules poses limits on the control of their activity. In this sense, photopharmacology offers powerful tools to manipulate endogenous processes with high spatio-temporal resolution and in a non-invasive manner.

Traffic Lights (TLs) peptides are cell-permeable, photoswitchable inhibitors of the main adaptor complex in the CME machinery. Based on the structure of β-arrestin C-terminal peptide (BAP-long), they bind to the β-appendage of AP2 (β-adaptin), which mediates the binding of clathrin to the membrane or to cargo receptors. When tested in mammalian cells, TL1 and TL2 were spontaneously internalised and proved capable of inhibiting CME in a light-regulated manner[(a) (b)].

Here we show that TL peptides can be used as a tool to further investigate the molecular mechanisms behind CME in an extremely versatile eukaryotic model system, i.e. yeast. *S. cerevisiae* cells were deprived of the cell wall and the resulting spheroplasts were allowed to internalise the peptides as confirmed by fluorescence microscopy imaging. Subsequently, mutants expressing fluorescently tagged Sla1 - a coat-associated endocytic protein - were used to observe kinetic delays in the dynamics of vesicle formation, confirming the possibility of photoregulating CME events by means of TL2. We now aim to achieve *in situ* activation of the peptide so to directly address the role of endocytosis in cellular processes such as cytokinesis or cell migration.

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[(b)] Martín-Quirós et al. (2015) *Chem. Biol.* 22, 31-37

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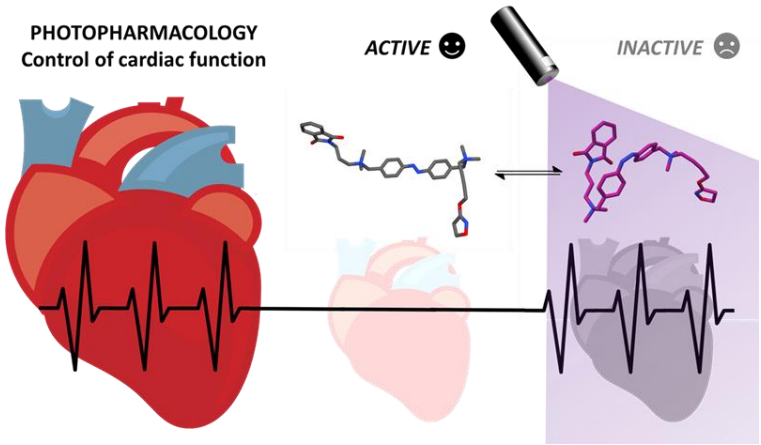
Photocontrol of Muscarinic Receptors and Applications in vivo **F. Riefolo[1,2,+], C. Matera[1,2,+], A. Garrido-Charles[1,2], A. M.J. Gomila[1,2], R. Sortino[1,2], L. Agnetta[3], E. Claro[4], R. Masgrau[4], U. Holzgrabe[3], M. Batlle[5], M. Decker[3], E. Guasch[5,6], and P. Gorostiza[1,2,7]*** *[1] Institute for Bioengineering of Catalonia (IBEC). [2] Network Biomedical Research Center in Bioengineering, Biomaterials, and Nanomedicine. [3] Pharmaceutical and Medicinal chemistry, Julius Maximilian University of Würzburg. [4] Institut de Neurociències (INc), Universitat Autònoma de Barcelona (UAB). [5] Cardiovascular Institute, Hospital Clinic; University of Barcelona (UB); IDIBAPS. [6] Network Biomedical Research Center in Cardiovascular Diseases (CIBER-CV). [7] Catalan Institution for Research and Advanced Studies (ICREA). [+] Contributed equally to this work.*	***OC 07***

Remote control of physiological functions with light offers the promise of unveiling their complex spatiotemporal dynamics *in vivo*, and enabling highly focalized therapeutic interventions with reduced systemic toxicity. Optogenetic methods have been implemented in the heart, but the need of genetic manipulation jeopardizes clinical applicability. We present a method to modulate cardiac function with light through a photoswitchable compound and without genetic manipulation. A new light-regulated drug, named PAI, was designed and synthesized to be active on M2 muscarinic acetylcholine receptor (mAChR). PAI can be reversibly photoisomerized between *cis* and *trans* conformations under UV and visible light. In cell lines overexpressing M2 receptors, PAI is able to photocontrol the cytosolic calcium oscillations, indicative of M2 activation, in a light dependent manner. We show that PAI has different light-dependent cardiac effects in a mammalian animal model. Finally, we demonstrate the reversible, real-time photocontrol of cardiac function in translucent wildtype tadpoles: PAI induced bradycardia and this effect could be reversibly switched using UV and visible illumination. PAI can also effectively activate M2 receptors using two-photon excitation with near-infrared light, which overcomes the scattering and low penetration of short-wavelength illumination. Such a new approach may enable enhanced spatial and temporal selectivity for cardiovascular drugs.[a]



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*** Correspondence:** pau@icrea.cat

Development of safe and brain-targeting nanovectors for Alzheimer's disease treatment	
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Alzheimer's disease (AD) is on the rise worldwide whereas to date, no curative treatment exists. The development of an efficient treatment for AD is a huge challenge, in particular due to the limited access of drugs through the blood-brain barrier (BBB). To improve their bioavailability and to deliver therapeutic payloads by targeting the brain, drug delivery systems like nanocarriers can be advantageously proposed.

Recently, we have identified a serotonin receptor agonist as a drug of interest for AD. Considering its poor druggability properties, we propose to encapsulate this drug in two innovative formulations, nanoemulsions and liposomes. These formulations must be administrable by intranasal and intravenous (IV) routes (Fig. 1). The intranasal drug delivery will bypass the BBB. In parallel, to pass through the BBB after IV administration, we aim to functionalize the nanoparticles by BBB shuttle peptides (BBBSP). These peptides, that we have synthesized, are able to bind the low-density lipoprotein receptor on the BBB[1] (Fig. 2).

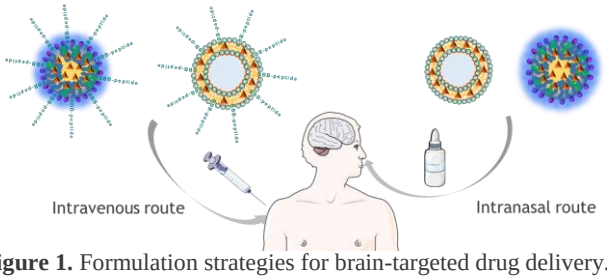

Figure 1. Formulation strategies for brain-targeted drug delivery.

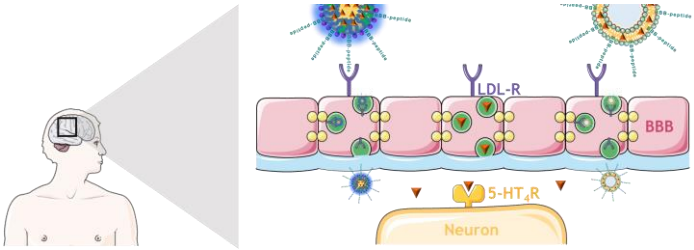

Figure 2. Receptor-mediated transcytosis through the BBB.
▲ Drug for AD

After original development, both drug-loaded formulations appear monodisperse in size and they present high encapsulation efficiency abilities. The coating with BBBSP can be performed using a one-step process, as we realized successfully. It can be also performed using a post-insertion method, as we previously reported[2]. In this goal, a DSPE-PEG_{3400}-peptide conjugate was synthetized to facilitate the insertion of the peptide into the surface of the nanocarriers. The evaluation of the transport through the BBB will be soon performed on a human BBB model[3].

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(3)Gosselet F. *Médecine/sciences*, **2017**, 33, 423-431.
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Phototrexate®: a novel drug candidate for cancer and psoriasis.	***OC 09***

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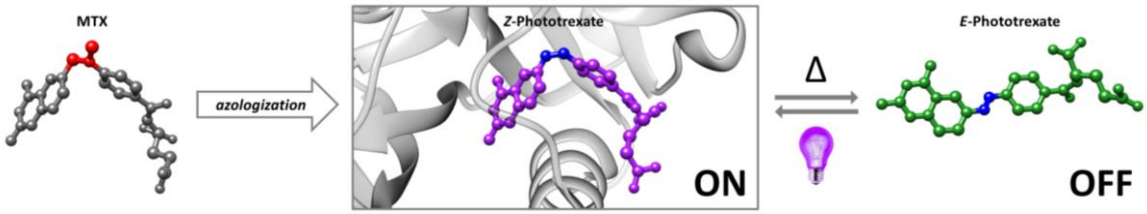
Antifolates are structural analogs of folates, essential one-carbon donors in the synthesis of DNA in mammalian cells, and they work as inhibitors of key enzymes in folate metabolism, such as dihydrofolate reductase and thymidylate synthetase. Methotrexate (MTX) was one of the first agents of this class and is still extensively used in the treatment of a variety of tumors, including acute lymphocytic leukemia, breast cancer, osteosarcoma, primary central nervous system lymphoma, and head and neck cancer. Above all, it is also commonly used in certain autoimmune diseases, such as rheumatoid arthritis or psoriasis.[1] However, the clinical efficacy of MTX is often limited and compromised by toxic dose-related side effects, which leads to morbidity, interruption of the treatment, and occasional mortality. A promising approach to tackle this problem is to activate the drug exclusively at its desired place of action. In fact, in those diseases that would benefit from a highly localized treatment, a precise spatiotemporal control over the activity of a chemotherapeutic agent would allow reducing the concentration of active compound outside the target tissue, improving the tolerability and hence the efficacy of the treatment. Light is a powerful tool in this respect: it offers unparalleled opportunities as a non-invasive regulatory signal for pharmacological applications because it can be delivered with high precision regarding space, time, intensity and wavelength.

We have recently developed Phototrexate®, the first photoswitchable antifolate, by incorporation of a photochromic unit into the structure of MTX. Phototrexate® was designed to be constitutively inactive in its thermodynamically stable configuration (*E* isomer), while it can be activated with light (*Z* isomer) to locally provide the pharmacological effects of the parent drug, as confirmed in our earlier experiments *in vitro* and in zebrafish larvae.[2] Studies are currently underway to assess safety/tolerability, pharmacokinetics, pharmacodynamics, and efficacy of our compound *in vitro* and in preclinical animal models. All current results indicate that Phototrexate® is a drug candidate with high potential for development as an innovative light-regulated antifolate for cancer and psoriasis.



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Oxime bond in peptide vectorization: unveiling an antitumoral effect through ribosome biogenesis impairment.	***OC 10***

Stéphane Duflocq[(1,2)]*, Wang-Qing Liu[(1,2)], Florent Huguenot[(1,2)], Elodie Olivier[(1)], Mélody Dutot[(1)], Lila Delbos[(1)], Magali Blaud[(1)], Patrice Rat[(1)], Nicolas Leulliot[(1)], Michel Vidal[(1,2)].

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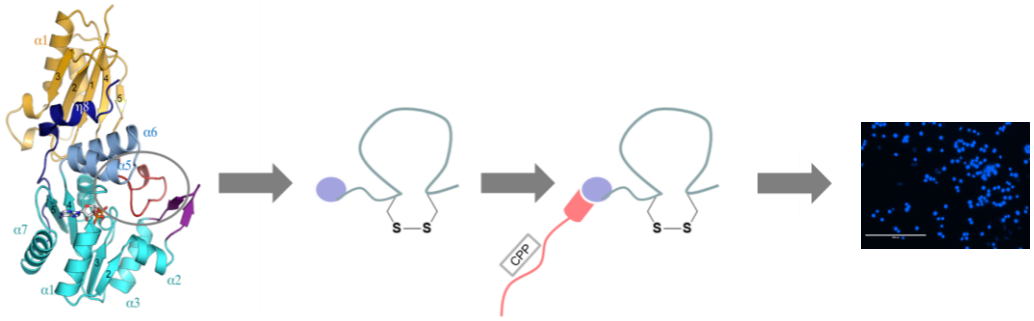
Ribosomes are the cell's huge ribonucleic machinery in charge of synthesizing proteins from mRNA. The different steps of ribosome biogenesis require the coordinated action of over 200 non ribosomal proteins, named Assembly Factor (AF)[a]. Among the AFs, it has been reported that yeast protein Fap7 inhibits p53 activity through the regulation of ribosomal protein S14 (Rps14)[b]. Tumour suppressor p53 is physiologically activated as a result of stress cell to regulate transcription of many pro-apoptotic genes but in the 50% of cancers, p53 remains inhibited by HDM2, an oncoprotein bearing a ubiquitin ligase activity that promotes p53 degradation. It has been shown that inhibition at different levels of ribosome biogenesis leads to the stabilization and accumulation of p53 by ribosomal proteins including Rps14[c]. As cancer cells have disproportionate ribosome biogenesis, inhibitors of Fap7/Rps14 interaction are under investigation in order to restore p53 activity in cancer cells and selectively trigger their apoptosis through hCinap, the human homologue of Fap7.
Based on the resolved complex structure of Fap7/Rps14[d], we are currently designing small cyclic peptides that mimic the C-terminus domain of Rps14. Combining peptide design and cell penetrating peptide (CPP) strategy[e], this work provides new methods for convenient oxime vectorization[f] and biochemical assays were set up to provide tools for SARs studies.



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(f) Manuscript submitted

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Design of original imidazophtalazine compounds as promising therapies for breast cancers	OC 11

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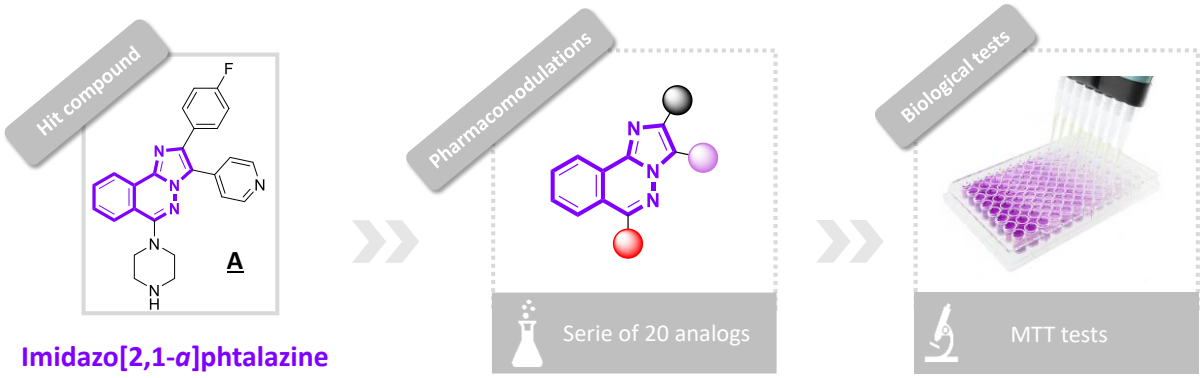
A selectivity screening on a panel of kinases of our home-made library revealed one original compound **A** displaying good inhibition on casein kinase 1ε (**CK1ε**). CK1ε was found to play a critical role in cancer signaling pathways especially in breast cancers.[(a)]
Breast cancers are a worldwide burden issue, accounting for the most commonly diagnosed cancer (2.1 million newly diagnosed cases in 2018) and the leading cause of cancer death among females.[(b)] In developed countries, 9 women out of 10 are cured thanks to better prevention promotion and targeted drug development. Nevertheless, some breast cancers cannot benefit from these medical improvements. Namely, the **triple negative breast cancer** challenges medical research because of chemotherapy resistance and poor life span.
In this context, we performed pharmacomodulations of our hit **A** to provide a serie of 20 analogs, all containing the **imidazophtalazine scaffold**. Our chemistry project involves exploring the influence of various groups on three different positions in our moiety. Biological investigations are carried out to assess **cell viability** in two breast cancer cell lines and highlighted 3 compounds with micromolar activities.



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Synthesis of Simplified Analogs of Marine Metabolites for Aurora B Kinase Inhibition.

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OC 12

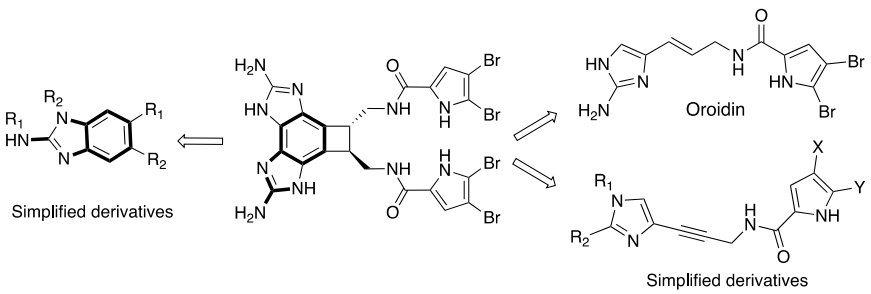
Natural products chemistry is crucial for drug discovery. Indeed many successful drugs are bio-inspired from natural metabolites. Marine natural products constitute a tremendous source of bioactive compounds for pharmaceutical purposes.

The pyrrole-2-aminoimidazole (P-2-AI) alkaloids are exclusively isolated from marine sponges and well known for their high structural diversity, high nitrogen-to-carbon ratio and interesting biological activities.[a] We focused our efforts on the synthesis of fragments of benzosceptrins[b] and oroidin[c] for their kinase inhibitory activities.

Some of the numerous synthetic analogs of isolated P-2AI have been found to inhibit various kinases including Aurora B, CK1 or RIPK1.

Here we present new inhibitors of Aurora B, which is essential for cell division via mitosis regulation. Thus it plays a crucial role in tumorigenesis and has shown great promise over the past two decades as a new target for cancer therapy.[d-f]

The presentation will be devoted to the improvement of inhibitory potency and specificity of the selected scaffold. Some results of the characterization of the mechanism of action leading will be presented as well.



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Design of potent colchicine-site ligands to overcome multi-drug resistance of colon cancer cells with improved intrinsic water solubility	***OC 13***

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The microtubule targeting agents are known as antimitotic drugs because they bind to the main constituent of the microtubules, the αβ-tubulin dimers, which is essential in the formation of the mitotic spindle during cell division. The colchicine binding of the αβ-tubulin has received special attention since the recent discovery that some colchicine site ligands are not only anti-cancer drugs but are also able to shut down tumor neovasculature. The most potent candidate, Combretastatin A4 (CA-4), suffers from low aqueous solubility due to the high hydrophobic nature of the binding site. The water soluble phosphate CA-4 prodrugs exhibit drug resistance, one of the more important problems of cancer chemotherapy. We present a new strategy to improve the water solubility of antimitotic colchicine site ligands and overcome multi-drug resistance (MDR) in several cancer cells. The chemical design is based in increasing molecular polarity without exposing polar groups. [(a)] It has been applied to diaryl derivatives having polar moieties such as pyridine or indole rings and bulky substituents that hinder the polar groups from the hydrophobic pocket while increasing molecular polarity and water solubility. The resulting molecules showed high antiproliferative activity against several cancer cell lines (HeLa cervix epithelioid carcinoma, HT-29 colon adenocarcinoma, MCF-7 breast adenocarcinoma and HL-60 human acute myeloid leukemia) and very low toxicity against primary pancreatic cells. Those compounds were able to overcome multidrug resistance, specially in less sensitive HT-29 cells, as demonstrated by proliferation assays in presence of verapamil, a known MDR protein inhibitor. The mechanism of action was assessed by tubulin inhibition polymerization experiments and immunofluorescence confocal microscopy. The observed microtubule disruption was accompanied by a cell cycle arrest at G2/M phase and subsequently apoptotic cell death was confirmed by cells gathered at the subG0/G1 population and Annexin V/Propidium Iodide double-positive cells observed after 48 h/72 h of treatment. Docking studies support the binding of the ligands at the colchicine site of tubulin. These results validate the proposed strategy for the design of water soluble colchicine site ligands with antimitotic effects in resistant cancer cells and open a new road to increasing the aqueous solubility of ligands binding in apolar environments.

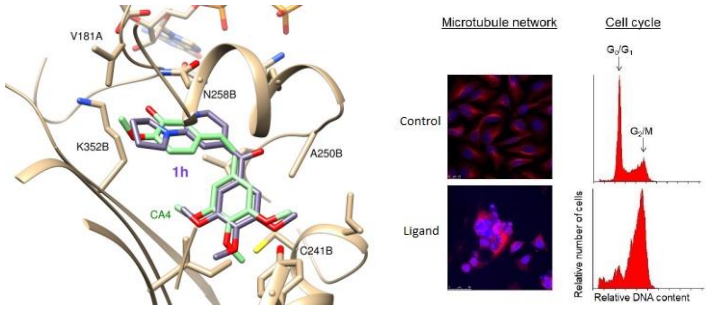

Figure 1. Left: docking poses of one of the new synthesized ligands (purple) superimposed with the X-ray pose of CA-4 (green). Right: effects of the ligands on the microtubule network and cell cycle in HeLa cells.

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Salinomycin derivatives kill cancer stem cells via lysosomal iron targeting

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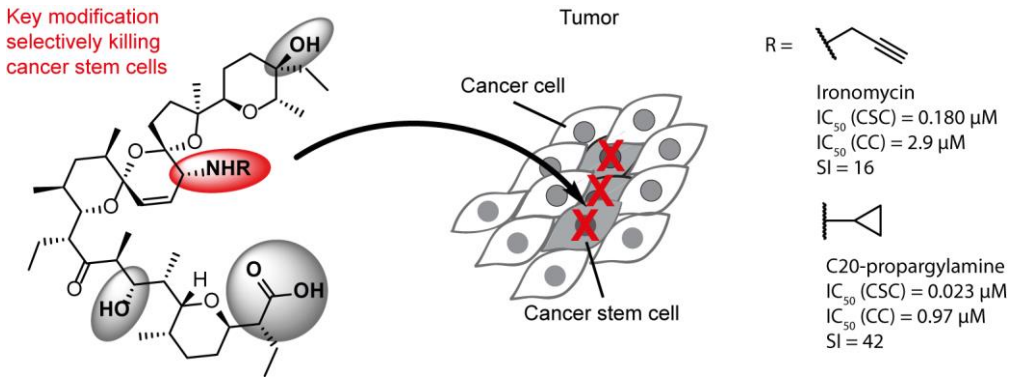
Salinomycin (Sal) is a polyether ionophore, which exhibits a large spectrum of biological activities including the capacity to selectively eradicate cancer stem cells (CSC).[1] There is increasing evidence that Sal and its derivatives are promising candidates for the development of drug leads against CSC. It has been demonstrated that Sal and its C20-propargylamine derivative (Ironomycin) accumulate in lysosomes and sequester iron in this organelle.[2] We synthetized a library of derivatives of Sal, including products of C20-amination, C1-esterification, C9-oxidation and C28-dehydration. We have then evaluated the biological activity of these compounds against transformed human mammary epithelial cells HMLER $CD24^{low}/CD44^{high}$, a well-established model of breast CSC, and HMLER $CD24^{high}/CD44^{low}$ cancer cells deprived of CSC properties.[3] Unlike other structural alterations, derivative displaying cyclopropylamine at position C20 showed a strikingly low IC_{50} value of 23 nM against HMLER $CD24^{low}/CD44^{high}$ cells leading to a 42-fold selectivity over HMLER $CD24^{high}/CD44^{low}$ cells. Thus, this study reports highly selective molecules to target the CSC niche, potentially providing the basis for the development of drugs that can tackle cancer resistance.



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Binding study and optimisation of piceatannol as inhibitor of arginase.	***OC 15***

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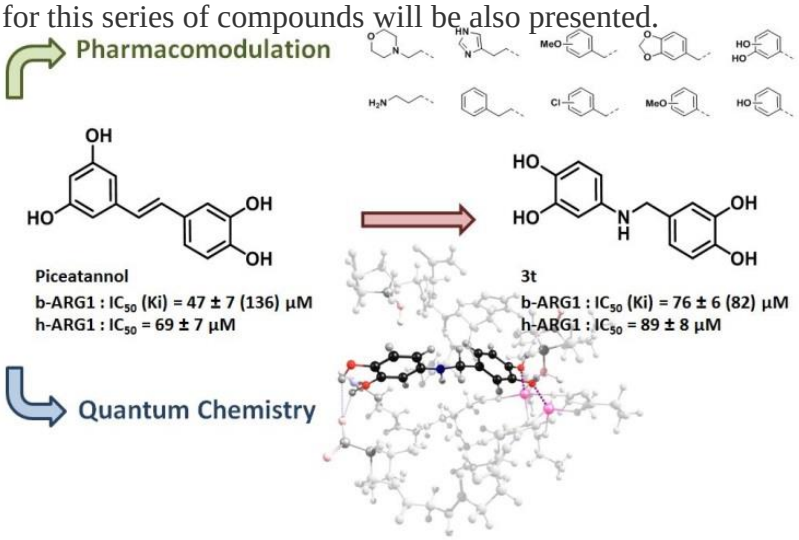
Arginase (EC 3.5.3.1) is a binuclear manganese transaminidase which catalyses the hydrolysis of L-arginine into urea and L-ornithine and it is a promising target to overcome cancer immuno-resistance. Reference inhibitors are 2(S)-amino-6-boronohexanoic acid (ABH), R-(2-boronoethyl)-L-cysteine (BEC) and nor-Nω-Hydroxy-Arginine (nor-NOHA). Recently Guo *et al.*(b) described suicide inhibitors based on an 1,6-elimination and Van Zandt *et al.*(c) described an α,α-disubstituted amino acid-based arginase inhibitors, directly inspired from ABH, which is in a Phase I/II clinical trial in solid tumour patients (CX-1158-101). In parallel, natural polyphenols as inhibitor of arginase have been discovered. Among them piceatannol, a stilbene derivative, is one of the most efficient. Here we will present our recent effort combining quantum chemistry modelling and pharmacomodulation to generate analogues of piceatannol as inhibitors of arginase. The best candidate, N-(3,4-dihydroxyphenyl)-3,4-dihydroxybenzylamine (**3t**) inhibits bovine and human arginase 1 with IC_{50} of 76 and 89 µM respectively. Synthesis and structure-activity relationship and mechanistic study for this series of compounds will be also presented.



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Synthesis and biological evaluation of 17f new analogs as STAT5 proteins inhibitors in myeloid leukemias treatment

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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)]

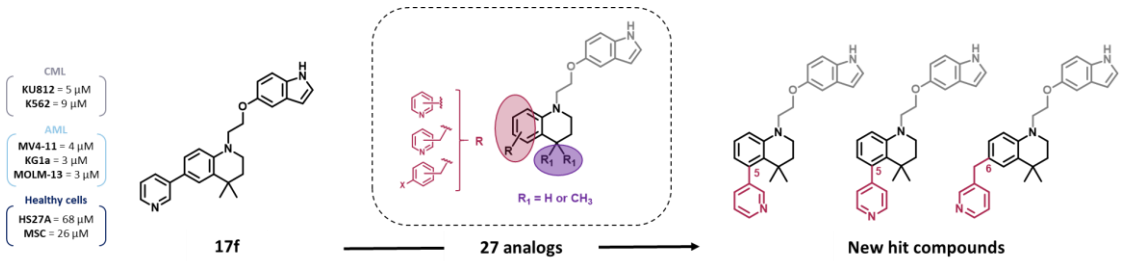

Figure 2. Lead **17f**, analogs and hit compounds

17f derivatives synthesis was undertaken by pharmacomodulation work around the tetrahydroquinoline (THQ) ring and biological evaluation of these new analogues by proliferation and viability studies were carried out on CML (KU812, K562) and AML cell lines (MV4-11, MOLM-13, KG1a). These results allowed us to determine the influence of the pyridine and its nitrogen position on the THQ aromatic part, the impact of an additional degree of freedom with benzyl derivatives and the importance of the THQ dimethyl group.[(f)] Furthermore, STAT5 phosphorylation and apoptosis assays along with biological evaluation on stromal cell lines (HS27A, MSC) will be presented.

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[(e)] Brachet-Botineau *et al*. *Cancers* **2019**, 11, 2043.
[(f)] Polomski *et al.* Article in preparation.

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Magnetic hybrid nanoparticles: facile preparation, toxicity and MRI biodistribution.	
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Summary:

Currently, magnetic iron oxide nanoparticles bare and/or polymer conjugated appear to play an important role in nanomedicine by serving as magnetic resonance imaging (MRI) contrast agents. Herein, we report an innovative strategy divided in several steps, for achieving the MRI candidate:
- first, hybrid magnetic nanoparticles were synthesized using iron oxide core obtained by co-precipitation method followed by glucose-silica shell chains coverage;
- then, the structure and physicochemical properties of the obtained magnetic based nanoparticles were studied by multiple methods;
- citotoxicity of the multifunctional hybrid magnetic tracer was investigated on normal V79 cell line;
- further, in situ stability of the magnetic hybrid nano-systems was explored over time by size quantification;
- in vivo toxicity studies of the synthesized nanoparticles in animal healthy models over short and long term periods;
- toxicity assessment by evaluating changes in blood chemistries and variation of blood cell parameters, profiles in liver and kidney or change in gross or histologic features of organs as well as monitoring clinical and weight changes after intravenous administration of the potential hybrid contrast agents;
- in vivo biodistribution of the obtained hybrid magnetic nanoparticle probe was determined after intravenous administration on healthy experimental animals by *in vivo* MRI.

Overall, the magnetic iron oxide nanoparticles conjugated with silica and glucose chains exhibited high colloidal stability in biological simulated medium, low toxicity depended on dosage, improved relaxation rate comparing to commercially available contrast agent, proving that these nanoplatforms can be used for MRI.

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MR35806: a new fluorinated indazole compound as a potential 5-HT$_4$R PET radiotracer	OC 18

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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 learning, cognition, memory processes and many neuropsychiatric disorders such as Alzheimer's disease, anxiety, depression or anorexia.[a] Thus, discovery of active 5-HT$_4$R agonists and antagonists remains an important axis of research in clinical development. To that 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 at CERMN[d], we aimed to develop new fluorinated indazole derivates as potential brain 5-HT$_4$R PET tracers.

This synthesis was carried out following three essential steps described in Figure 1. First, a convergent synthesis pathway to obtain cold ligands (CL) was established using a regioselective functionalization at position 3. Then, new pharmacomodulations studies were realized in our compounds in order to increase receptor affinity, metabolic resistance and decrease lipophilicity.

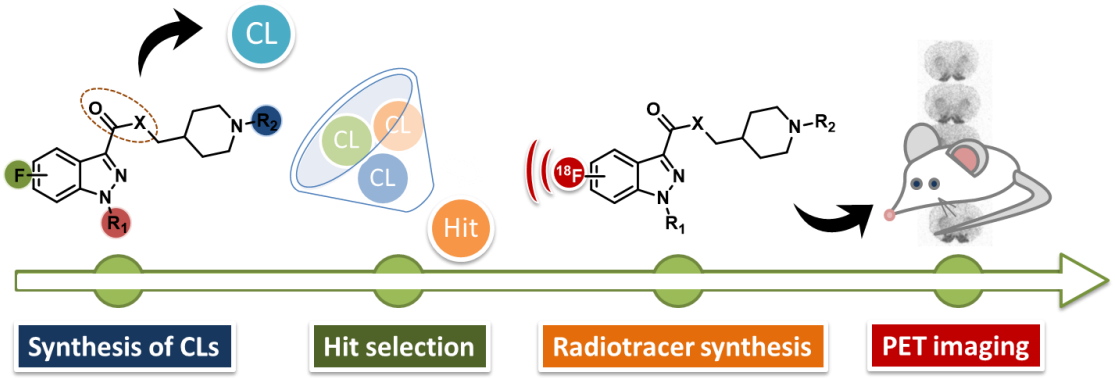

Figure 3. Essential steps to obtain radiotracers

More than thirty compounds have been synthesized and their affinities for 5-HT$_4$R have been determined. MR35806, is currently radiolabeled with fluorine 18 to obtain our first brain PET radiotracer. In a near future, this compound will be tested on mouse's brains.

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New eco-sustainable synthesis of indole derivatives using green catalysts.

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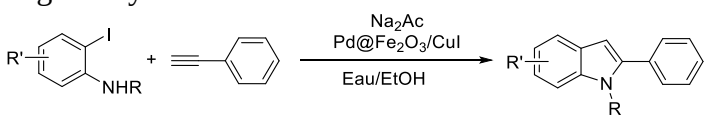
OC 19

The transition metal catalysts emerged two decades ago for applications in heterocyclisation (including indole synthesis),[3] due to their wide tolerance and the use of simplified procedures leading to improved yields compared to classical approaches. However, their use is not compatible with sustainable chemistry processes (green chemistry), because they require the use of toxic solvents (eg toluene), and also because certain metals exhibit significant toxicity. Therefore, we aim at developing new processes based on eco-compatible, recyclable metallic nanoparticles supporting Pd(0) as catalysts (NPs). Interestingly, NPs have an increased interface with the solvent, which facilitates reactions and allows low catalyst loads. They also proved very active for couplings and reductions in mild conditions and with TOF (Turn Over Frequency) of up to 100,000 h^{-1}.

Highly functionalized indoles show a large spectrum of biological activities, and some of them are used in therapy.[1] However, despite the widespread development of synthetic methodologies leading to them,[2] only few examples of "partly" green processes have been disclosed. These indole syntheses involved the use of NPs and/or micellar systems, requiring very high catalytic loads, the use of chemical additives and toxic solvents. They also need long reaction times and complex work-ups. Therefore, these processes can't be considered as really green. However, using our own NPs, we have been able to synthesize indoles using a very low amount of NPs supporting Pd(0) as catalysts (0.05%) and CuI (0.5 eq.), and using a mixture of ethanol and water as green solvents. The scope of this methodology is currently in evaluation, however these optimized conditions maybe from now considered as a real breakthrough for indoles green synthesis.



Schema 1: Sonogashira cross-coupling reaction catalysed by palladium nanoparticles

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(3) Y. H. Jang, S. W. Youn, *Org. Lett.* 2014, *16*, 3720 – 3723.

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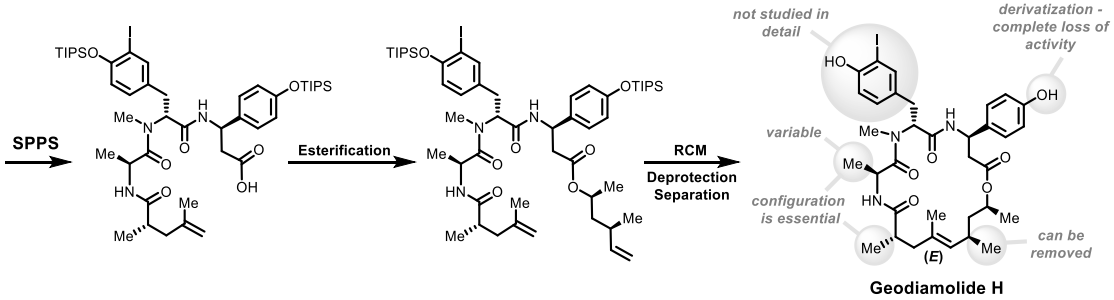
pportunities in targeting actin with unexpected species selectivity **Veselin Nasufovic[(1)], Florian Küllmer[(1)], Rosa Herbst[(2)], Pierre Stallforth[(2)], Hans-Dieter Arndt[(1)*].** *(1) Friedrich Schiller Universität, Institut für Organische Chemie und Makromolekulare Chemie, Humboldtstr. 10, D-07743 Jena,* *(2) Leibniz Institute for Natural Product Research and Infection Biology, Hans-Knöll-Institute, Beutenbergstraße 11a, D-07745 Jena*	***OC 20***

Globular actin (G-actin) polymerizes in highly regulated manner to give filamentous actin (F-actin) in the process on which depend numerous cell functions but mainly connected with moving or transport. Being the most abundant protein in eukaryotic cells and responsible for important cell processes actin represents challenging target.[1]

The family of F-actin binding cyclodepsipeptides features more than 50 natural products.[2] The jaspamides, seragamides, chondramides, and geodiamolides feature high structural similarities and similar stereochemistry. High affinity to F-actin leads to high toxicity in cancer cell lines, high antifungal activity as well as insecticidal activity.[3] Although interesting high activities were demonstrated these molecules have not found application in drug development. Major reason is high abundance of actin protein and low structural difference between actin isoforms which limits possibilities for achieving selectivity. We have launched campaign with goal of full understanding of SAR of actin binding cyclodepsipeptides and understanding possibilities for achieving selectivity using these molecules.



Geodiamolide H

New total synthesis of Geodiamolide H and Jasplakinolide will be presented. These methodologies allowed us generation of the focused library of more than 50 analogues. Biological profiling of all analogues led to rationalization of previous SAR information for this natural product class and to generation of useful biology tools for studying structure and function of actin (fluorescence markers, EPR probes, photoswitchable ligands). Promising data on amoebicidal activity will be presented as well, highlighting differences in activity and selectivity, compared to human cancer cell lines.

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Benefits of using innovative bioconjugation technology for antibody-drug conjugates: proof of concept with MF-BTX-MMAE in CD30-positive lymphoma model.	***OC 21***

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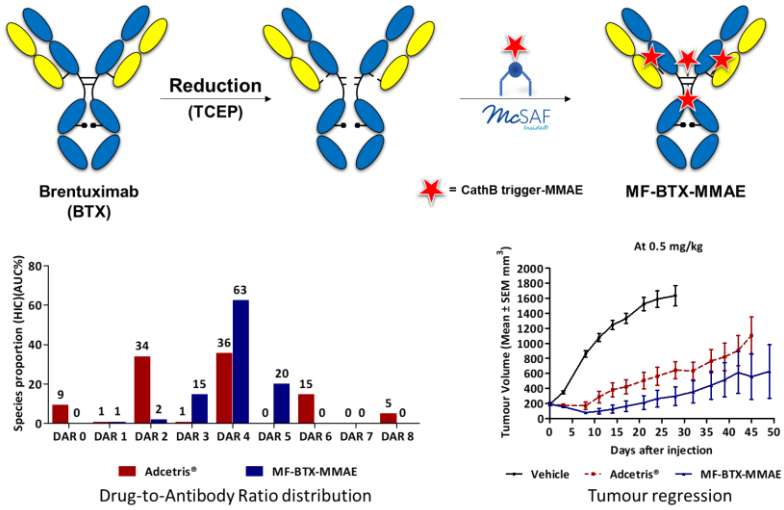
Antibody-drug conjugates (ADCs) are the spearhead of targeted therapies. According to the technology used, the conjugation of a cytotoxic drug to an antibody can produce suboptimal heterogeneous species impacting the overall efficacy.[(a)] In this work, we describe a new technology, called McSAF Inside®, that allows conjugation at previously reduced interchain cysteines of native antibody, resulting in disulfide re-bridging.[(b)] It permits the obtention of homogeneous ADCs, more stable than the existing bioconjugation technologies incorporating a maleimide motif. This technology was exemplified in a CD30-positive model with the ADC MF-BTX-MMAE and compared to Adcetris®, an ADC used to treat CD30-positive lymphoma. In this work, we demonstrated that MF-BTX-MMAE displays improved homogeneity as well as enhanced stability in several conditions including thermal stress or the presence of free thiol (*e.g.* DTT and HSA). Using McSAF Inside® solution, MF-BTX-MMAE showed antigen-binding, *in vitro* and *in vivo* efficacy similar to Adcetris®. Thanks to its better stability profile compared to maleimide incorporating technologies, we expect an improved safety profile in further PK/PD and toxicology studies for MF-BTX-MMAE.



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DISCOVERY, OPTIMIZATION AND BIOLOGICAL EVALUATION OF THE FIRST BOOSTERS OF THE NITROIMIDAZOLE ANTI-TB DRUG PRETOMANID.

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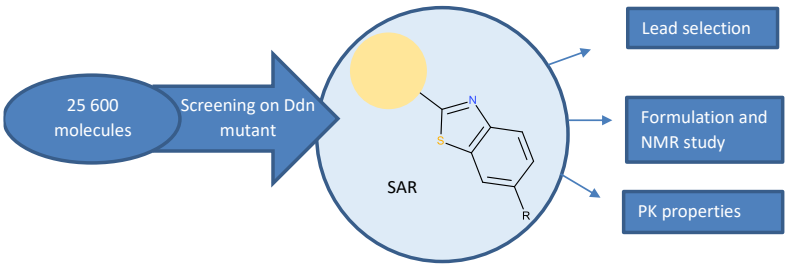
OC 22

Tuberculosis (TB), caused by the pathogenic bacteria *Mycobacterium tuberculosis*, has been responsible for the death of 1.6 million persons in 2017 and remains one of the major cause of mortality.[(a)] The current treatment lasts more than six months and is often associated with serious side effects. Over the past fifty years, many resistant strains have appeared and in 2017, 580 000 persons have been infected with multi-drug resistant (MDR) TB. Therefore, there is a real need to find new treatments and alternative therapies to stop this phenomenon.

The most striking peculiarity shared by most of the drugs used to treat TB is that they are prodrugs, and that they become inactive when mutations arise in the pathway of bioactivation. Our approach lies on the discovery of boosters that are able to trigger new bioactivating enzymes in the mycobacteria. The concept has already been validated with the thioamide drugs[(b)] (ethionamide and prothionamide) and has been extended to pretomanid (PA-824), a new anti-TB drug recently approved to treat MDR/XDR TB in combination with bedaquiline and linezolid. PA-824, is a nitroimidazole derivative,[(c)] that is bioactivated by the Ddn (Deazaflavin dependant nitroreductase) leading to the impairment of the growth of the bacteria by release of toxic NO and by inhibition of the mycolic acid synthesis.[(d)]

Apparition of Ddn mutants has been shown to lead to PA-824 loss of activity. The screening of 25,600 molecules from our in house library in combination with PA-824 on a Ddn mutant has led to the identification of hits exhibiting no bactericidal activity by themselves but allowing PA-824 to become active again. In order to improve the potency of the hits and study the structure activity relationships, we have performed modifications of the hit and the identification of a potent lead has been possible. The mechanism of action is currently unknown and under investigation.



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Pharmacomodulation and *in vitro* antiplasmodial evalution of α-CCl_3-*N*-heterocycles using a scaffold-hopping strategy

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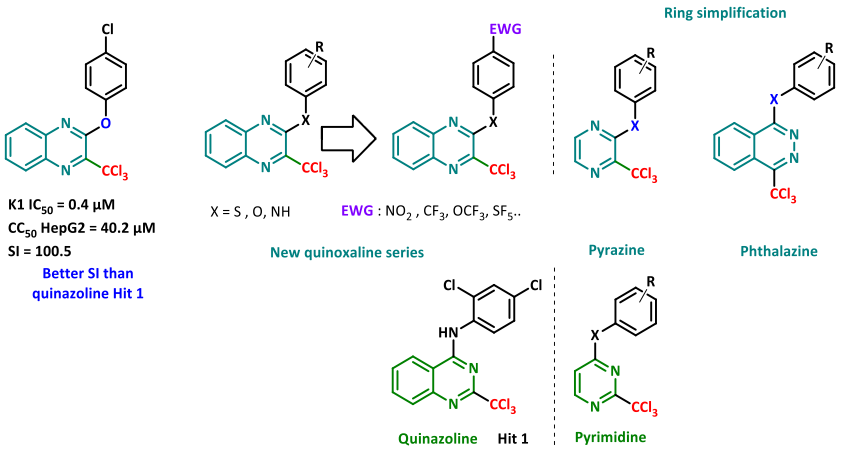
OC 23

Malaria is still the leading cause of death among parasitic infections worldwide.[1] The subsequent emergence and expansion of *Plasmodium* strains resistant to the Artemisinin-based Combination Therapies (ACTs), are now threatening the efficacy of malaria treatment. Therefore, new molecules displaying original mode of action are urgently required. Aiming at developing new antiplasmodial molecules, our laboratory previously described the synthesis and the biological activities of a library of 2-trichloromethylquinazoline derivatives which highlighted a Hit molecule 1 (IC_{50} = 0.4 µM, CC_{50} = 16 µM).[2] Moreover, a scaffold hopping strategy showed that the replacement of the quinazoline moiety by a quinoxaline one improved the cytotoxicity profile.[3] 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. In a view to evaluate the new hits in a mouse model of malaria (*P.berghei*), physicochemical and *in vitro* pharmacokinetic properties were assessed and detailed in the communication.

In parallel, to complete the global SAR study using the scaffold hopping approach, we replaced the quinoxaline ring by a phthalazine one. The importance for the antiplasmodial activity of the phenyl ring in quinazoline and quinoxaline scaffolds was also studied by structural simplification. Thus, we synthesized the related pyrazine and pyridine analogs.

The synthesis details of the new analogs of Hit 1 in various series and the biological results will be described in the communication.



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

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Antibacterial and antimycobacterial activities of extracts and steroid saponins from *Solanum chrysotrichum*	*OC 24*

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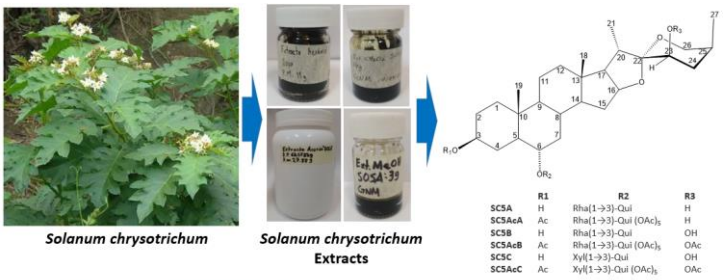
From *S. chrysotrichum* were prepared the hexane extract, dichloromethane extract, methanol extract, and aqueous extract. The methanol extract was fractioned yielding 5.1 g of a mixture of three steroid saponins which were acetylated in order to purify and characterize the constituents as derivatives. The obtained compounds were deacetylated by saponification to obtain the *neo*-steroid saponins SC5A, SC5B and SC5C which were the *neo* forms of previously reported compounds[a,b]. The antibacterial activity of extracts and compounds was evaluated *in vitro*[c] against clinical isolates of drug-resistant bacteria, displaying the organic extracts good antibacterial activity against carbapenem resistant *Acinetobacter baumanni* and *Pseudomonas aeruginosa* (MIC: 125 µg/mL), and good activity for SC5C against gram-positive bacteria (MIC: 25-12.5 µg/mL). The *in vitro* antimycobacterial activity[d] was determined against *Mycobacterium tuberculosis* H37Rv and the multidrug-resistant strain G122, and good activity was observed for the hexane extract against both strains (MIC: 125 µg/mL). This work represents the first report of antimycobacterial activity for *S. chrysotrichum* extracts and good antibacterial activity for the *neo*-steroid saponin SC5C.



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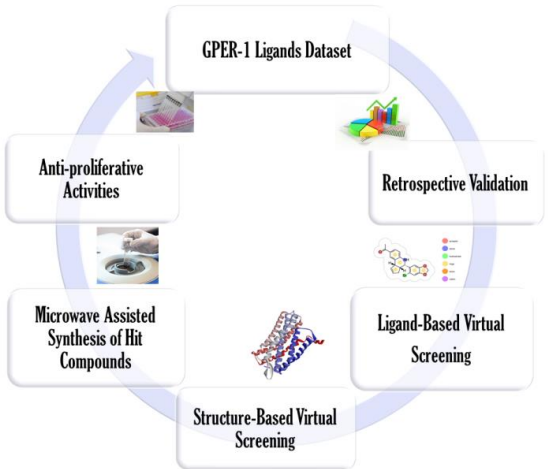
In search of G protein-coupled estrogen receptor (GPER-1) modulators: Insilco and Invitro approach **Shafi Khan[1], Nafees Ahemad[1], Lay-Hong Chuah[1], Rakesh Naidu[2], Thet Thet Htar[1]** *(1) School of Pharmacy, Monash University, Malaysia, Subang Jaya, Selangor, Malaysia* *(2) Jeffrey Cheah School of Medicine and Health Sciences, Monash University, Malaysia, Subang Jaya, Selangor, Malaysia*	***OC 25***

G protein-coupled estrogen receptor-1 (GPER-1) is a seven transmembrane receptor, responsible for mediating rapid estrogen signaling in many physiological responses in reproductive, nervous, endocrine, immune and cardiovascular systems. Due to unavailability of the crystal structure of GPER-1, a sequential ligand-based virtual screening (LBVS) and structure-based screening (SBVS) approach was used to identify potential GPER-1 modulators. LBVS and SBVS approaches were first validated retrospectively using the Receiver Operating Curve (ROC) plot and the early Enrichment Factor (EF) as statistical matrices. LBVS was performed based on a GPER-1 agonist, G1, as a query model for screening of the eMolecules library using the Rapid Overlay of Chemical Structure (ROCS) and the electrostatic potential screening (EON) approaches. Topscored hits from LBVS were further screened by SBVS. SBVS was based on generating the homology models of GPER-1 and subsequent molecular docking studies. Using Chemguass4 score, final hit compounds having higher score than the query G1 complound (Chemguass4 score = -11.575) were filtered out. The topranked hits were clustered based on the similarity in their scaffolds. Prospective validation was also performed by synthesizing the top hit scaffolds followed by investigating the antiproliferative activity in three different GPER-1 specific cancer cell lines. Preliminary results of this study discovered five new scaffolds which may be serve as ideal lead compounds for further development of novel GPER-1 modulators.



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Synthesis of new CXCR1/2 receptors antagonists for wet AMD treatment.	***OC 26***

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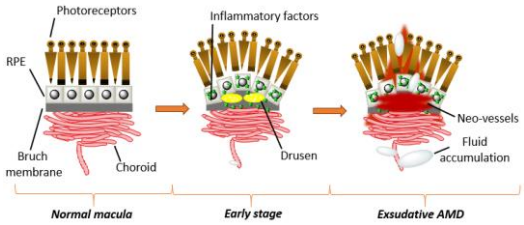
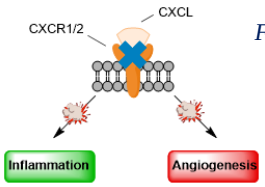
In western countries, wet age-related macular degeneration (AMD) is one of the leading causes of blindness in the elderly. This disease is characterized by an abnormal vascularization of the choroid and a strong intraocular inflammation (Fig. 1). Currently, only symptomatic treatments exist, which rely on humanized monoclonal antibodies (mAbs) targeting pro-angiogenic factors. Moreover, only 30% of the patients present a durable response to this treatment.



Figure



Figure

The blockage of the ERL+ CXCL cytokines signalling pathway has been proposed as promising alternative to target simultaneously choroid vascularization and inflammation[1]. Indeed, this sub-family of cytokines is specifically involved both in inflammation and in early stage of the pro- angiogenic signal[1] (Fig. 2).

Two hits were already developed[2] and validated both *in vitro* and *in vivo*, (MCK133 and MCK140). However, they suffer from limited solubility for further eye related applications. We have demonstrated that the drawbacks of these compounds are mainly due to the inherent structure of arylurea. Therefore, a new series of compounds has been designed that futures the same pharmacophore but with new chemical functions to enhance the activity and the physicochemical properties.

A new straightforward synthetic pathway has been developed to prepare a series of compounds presenting 2 types of modulation. These compounds have been biologically evaluated both on XTT cell viability assays and for their migration potential on a Boyden chamber model. Encouraging preliminary results have been obtained, showing that 2 compounds, with improved PK properties, efficiently block the cell migration related to CXCR-CXCL interaction.

In this context, further structure modification is ongoing for in depth studies of the structure activity relationships of this series. The final aim of the project is to obtain a derivate with improved activity and suitable properties to be evaluated on a *in vivo* retinopathy model.

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(2) Benhida, R., Pages, G., Dufies, M., Ronco, C., Demange, L., Grytsai, O. European Patent 2018 EP18306362.7.

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Synthesis of heterospirocycles for molecular diversity and medicinal chemistry.	OC 27

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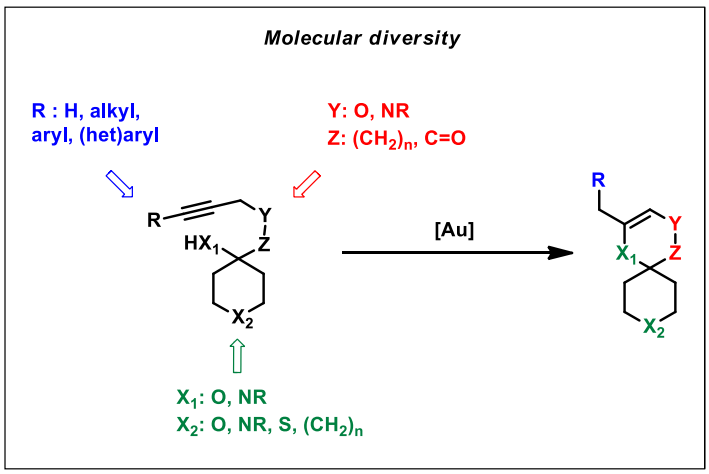
The conception and synthesis of new biologically active molecules, coupled with an increased exploration of new chemical space is an important goal in medicinal chemistry. The advantage of 3D fragments over 2D fragments, giving better physicochemical properties, has been widely documented. [(a), (b)] Due to their molecular rigidity, and an increased number of Csp^3 carbons, interest in the synthesis of new and original spirocyclic compounds is constant, in academia as well as in the pharmaceutical industry. The increasing occurrence of heterospirocycles that possess a heteroatom directly attached to the quaternary spirocyclic carbon is a driving force for the development of general synthetic strategies for these heterospirocycles. Starting from commercial piperidone derivatives and quinic acid, suitable substrates for the target heterospirocycles were prepared. A screening of different transition metal catalysts and the tuning of different reaction parameters led to the best cyclization conditions. The optimized strategy was applied to several substrates, exploring molecular diversity and studying the scope of the reaction. Selected heterospirocycles were directed towards a medicinal chemistry program exploring new potent kinases inhibitors.



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Indazoles: **From medicinal chemistry to fluorescent probes.**	***OC 28***
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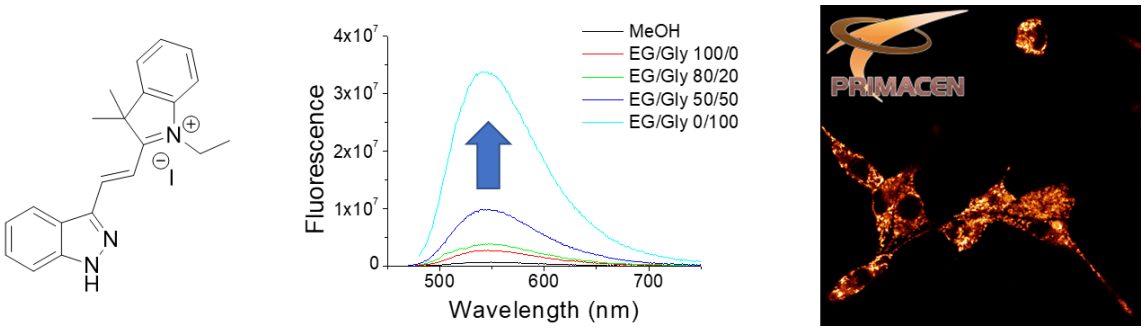
Indazole is a common scaffold in medicinal chemistry because it is a bioisostere of indole and because of its ability to interact with biomolecules. Both these properties make it an interesting building block to design selective molecular probes with strong affinity to biomolecules. Yet, indazoles' optical properties remain largely unknown[a] and to this day, very few chromophores take advantage of their unique extended π-system and electron donating ability.[b]

I developed a fast and direct synthesis to substituted indazoles[c] in order to build a library of new fluorophores. These exotic donor-acceptor molecules present pro-fluorescent properties and can probe the viscosity, polarity and pH of their environment.[d]

In cellulo, two families of molecular probes were identified, giving promising results for lipidic environments or mitochondria imaging.



<u>Figure:</u> (left) Structure of a push-pull indazole derivative, (center) Effect of the solvent viscosity on its fluorescence, (right) Fluorescence image on live cells.

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FLASH POSTER ABSTRACT

Imaging and quantifying aggresome in an automated miniaturized microscopy assay	*FP 01*

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Background: Aggresome is a perinuclear structure where misfolded proteins are accumulated by retrograde transport on microtubule follwing different stress[(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.

Objectives and method: 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 EC50 on aggresome formation induced by drugs.

Results and conclusions: 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. We performed a screening of 1280 pharmacological compounds on HeLa cells and we identified compounds that promote aggresome formation in cancer cells. Also, we can suppose that we could apply this assay to find compound that decrease aggresome in protein misfolding disorders.

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Design, synthesis and characterization of small molecules as new Tau aggregation disruptors	FP 02

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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. Brain study of patients with Alzheimer's disease has shown two types of damages: amyloid plaques and neurofibrillary tangles. Each of those lesions is associated to one protein compound: beta-amyloid peptide (Aβ) for senile (amyloid) plaques and hyperphosphorylated tau protein for neurofibrillary tangles. For both of these proteins, key-peptide sequences were identified as responsible for early oligomerization initiating the whole amyloidogenic process [(a, b)]. In this process, these peptides shape in a beta sheet structuration.

We are aiming to synthesize small molecules as protein-protein interaction disruptors in order to prevent aggregation in early stages.

The present study was initiated by a conformational analysis of the Tau key peptide sequences implied in aggregation. Various aggregates were built, their stabilities were assessed through Molecular Dynamic (MD) simulations and the analyses of intra- and intermolecular interaction in various aggregate cores were carried out and will be presented. Furthermore, MD simulations of Tau aggregates with palmatine, a Tau aggregation disruptor[(c)], were launched and mechanisms of aggregation disruption will be proposed.

Then, similarity screening of our in-house chemical library[(d)] based on palmatine and *in vitro* tests made as a part of collaboration with Bari University provided 40 scaffolds as starting points for rational design of abiotic foldamers that could disturb the interactions between amyloid fibrils.

From the first results of *in vitro* tests, we synthesized several series of new molecules. These compounds will then be tested for their ability to disrupt Tau oligomerization.

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[(c)] Haj, E., Losev, Y. et al. BBA – General Subjects 2018, *1862*, 1565-1575.

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Design of photoswitchable acetylcholinesterase inhibitors	
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The possibility to photocontrol biological activity has driven research both towards the use of light to interact with light-sensitive photoreceptors (optogenetics) and towards the design of photoswitchable drugs that can interact with native receptors (photopharmacology). Photopharmacology has been used to manipulate biological activity at the cellular level by targeting ion channels, G protein-coupled receptors and metabolic enzymes. Several applications of photopharmacology have been reported, including sight restoration, control of cardiac rate, and focalized chemotherapy against psoriasis and cancer[(a)].

The possibility to control synaptic communication is appealing for interfering with neuron communication and with the cellular excitability/inhibition that is mediated by the exchange of neurotransmitters. One of the most important neurotransmitters is acetylcholine (ACh), which after being released at the synaptic cleft and activating cholinergic receptors is hydrolyzed to choline by the action of the acetylcholinesterase (AChE) enzyme. ACh is indeed involved in cognitive functions such as perception, learning and memory. Therefore, regulating ACh levels can be beneficial, for instance in patients suffering from Alzheimer's disease[(b)].

In the literature, there are few examples of photoswitchable AChE inhibitors based on azobenzenes[(c)] or diarylethenes[(d)] as light-sensitive scaffolds and quaternary ammonium compounds or a tacrine moiety as pharmacologically active units. However, the enzyme activity is photocontrolled by illuminating the drug with high-energy light (UV-blue), which causes two important problems: i) tissue and cell damage ii) poor tissue penetration due to scattering and absorption by endogenous chromophores. Both problems would be overcome by using more penetrating and less harmful red light as switching trigger.

In this work, we take advantage of the many small-molecule AChE inhibitors reported in the literature to explore the design of red-shifted compounds via a molecular docking approach. We have studied three azobenzene dyes that absorb in the green-red spectral region (510-650 nm). We investigated the photochemical properties, the solubility and the photostability of these molecules in order to identify the most promising scaffold for drug design.

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Development of TrkB/5-HT$_4$ receptors ligands, a new approach in the treatment of neurodegenerative diseases

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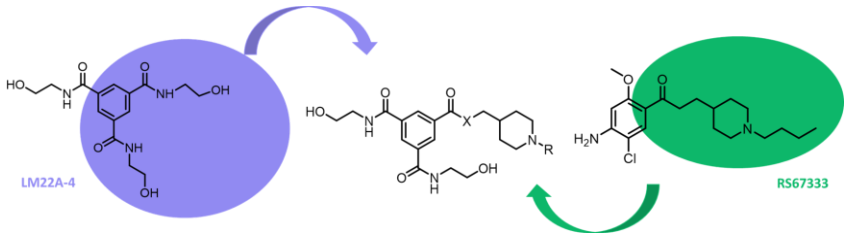
FP 04

Numerous studies have been published about the implication of the neurotrophin tyrosine kinase receptor - TrkB in the pathogenesis of several neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, Multiple Sclerosis and motor neuron disease[a,b,c]. Brain-derived neurotrophic factor (BDNF) and neurotrophin-4/5 (NT-4/5) activate the TrkB receptor with high potency and specificity, promoting neuronal survival, differentiation and synaptic function. On the other side activation of the p75 neurotrophin receptor (member of tumour necrosis factor receptor family), is mainly inducing cell death[d]. Based on the main structural characteristics of LM22A-4[e], a known activator of the TrkB receptor, we have designed and synthesised a small data set of compounds. The lead idea for the design of the new compounds was to modify the third position of the LM22A-4 (by introducing N-alkyl or N-cycloalkyl piperidine substituent) in order to obtain the compounds which will be not only ligands for TrkB receptor, but also indirect activators of α-secretase (partial 5-HT$_4$ receptor agonists) (Fig. 1). Many research findings have shown that the cleavage of p75 receptor is normally occurring in the presence of α-secretase (ADAM17). As a result of this cleavage the extracellular part of p75 acts as neuroprotective agent while intracellular part can increase phosphorylation of TrkB if this receptor is in its activated state (in the presence of TrkB ligands)[d,f,g]. Also, there are evidences that partial 5-HT$_4$ receptor agonist (RS67333) can increase concentration of BDNF[h]. As a result of our study, we have developed a new data set of small molecules, potential TrkB/ 5-HT$_4$ receptors ligands, which will be used for further biological research and hit to lead optimisation studies.



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IMIDAZO[2,1-*b*][1,3,4]THIADIAZOLES : CONCEPTION AND SYNTHESIS OF NOVEL DYRK1A/CLK1 DUAL INHIBITORS

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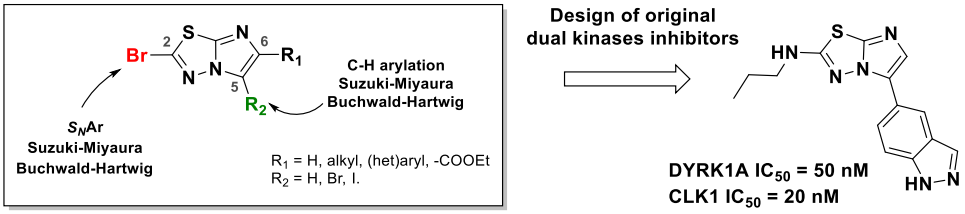
FP 05

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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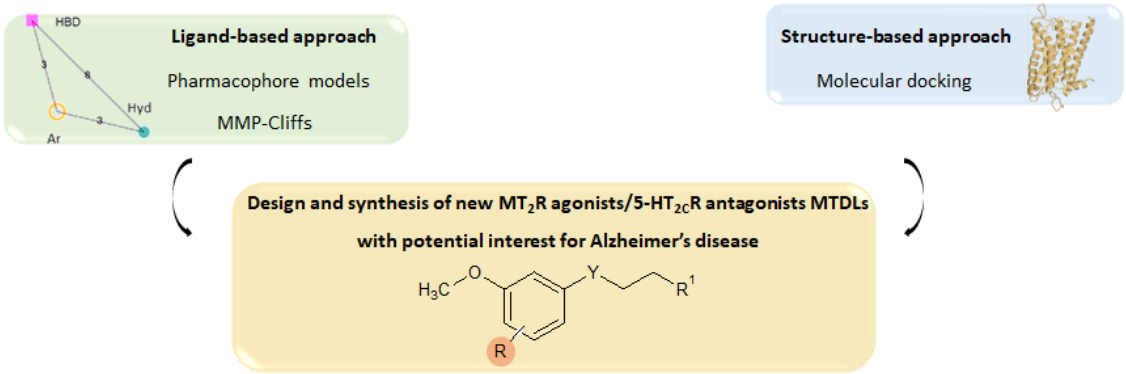
In silico design and synthesis of original MT_2R/5-$HT_{2C}R$ MTDLs as potential therapeutics for Alzheimer's disease. **THIRUMARAN Sangeetha-Laura*, BUREAU Ronan, LEPAILLEUR Alban, ROCHAIS Christophe.** *Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN), Normandie Univ, UNICAEN, 14000 Caen, France.*	***FP 06***

Alzheimer's disease (AD) is the most common form of dementia, affecting more than 50 million of patients worldwide, and for which the current treatments produce only symptomatic benefits. Among the biological targets implied in the pathophysiology, and especially among the G-protein coupled receptors (GPCRs), melatonergic MT_1 and MT_2 receptors (MT_1R and MT_2R) and serotonergic 5-HT_{2c} receptors (5-$HT_{2c}R$) present a growing interest. Indeed, their modulation could lead to positive effects on cognition through several actions, such as the promotion of neurogenesis and of the non-amyloidogenic cleavage of the Amyloid Protein Precursor (APP).[a,b] As AD is a multifactorial disorder, a simultaneous action on these two types of receptors with potent and selective Multi-Target Directed Ligands (MTDLs) could represent a novel therapeutic approach.

With this objective, we analyzed the structure-activity relationships (SARs) of an in-house chemical library constituted of more than 1200 MT_1R agonists, MT_2R agonists and 5-$HT_{2C}R$ antagonists. Firstly, a ligand-based approach was used, including an analysis of Matched Molecular Pairs-based Activity Cliffs (MMP-Cliffs), and an automatic computation of pharmacophores with an in-house chemoinformatics tool, Norns[c]. Secondly, a structure-based approach, consisting in docking studies into the crystal structures of the three receptors, was used in order to understand the polypharmacological profile of this promising series of compounds. On this basis, we designed and synthesized an original chemical family of MT_2R agonists and 5-$HT_{2C}R$ antagonists MTDLs which could exert pro-cognitive effects. All these results will be presented in this communication.



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Uncharged Reactivators of OP-inhibited Cholinesterases.

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FP 07

The development of medical countermeasure against both acute and chronic intoxications by organophosphorus (OP) nerve agents continues to be a challenge. Only strong nucleophiles (typically oximes) are able to reactivate the phosphylated-enzyme. After 50 years of research, there is no broad spectrum reactivator. Furthermore the currently used reactivators (pyridinium aldoximes) are unable to cross the blood brain barrier (BBB) efficiently in order to reach phosphylated central AChE. The aim of this project is to find new and more efficient reactivators focusing on the synthesis of new uncharged reactivators able to cross the BBB, and to evaluate their *in vitro* and *in vivo* efficacy.
These reactivators, composed of an AChE peripheral site binder (e.g. tetrahydroisoquinoline, piperazine, piperidine, morpholine…) linked to an oxime through a linker have been evaluated *in vitro* against several OP-inhibited enzymes. In order to have an accurate and rapid evaluation of their potential *in vivo* efficacy, the therapeutic window for each compound has been estimated. The previous generation suffers some drawbacks as an uncompleted protection against different OP, exemplified by oxime JR595. The new generation of uncharged oximes presented in this communication shows reactivation within the therapeutic window for several OP, indeed at 100µM concentration, more than 30% of the enzyme is reactivated in less than 5 min.

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Drug repositioning based on real life side effects, identifying unkown butyrylcholinesterase inhibitors useful in alzheimer's disease treatment.	***FP 08***

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Drug repositioning, repurposing, reprofiling, redirecting or switching are words to characterize the principle to propose an active drug already on the market for a novel indication[(a)]. Some 94 drugs are yet taking the way of repositioning use in new commercialization to date. The global turnover in 2014 is about $ 250 billion.[(b),(c)]
Drug repositioning application to Alzheimer's disease is a route to find therapeutic solutions to treat this non-reversible degenerative neuronal disorder. The literature relates, to date, 26 cases in the clinical trials pipeline of anti-Alzheimer's drugs are already marketed as drugs and are therefore subject to a repositioning process.

The aim of the research was to search new indications for commercialized medicine. Adverse effects of a drug are mostly related to pharmacological activities. The rational of drug repositioning according to drug adverse effects is that similar pharmacological properties of drugs will reflect in similar safety profiles. Here, we performed an integrated approach of pharmacovigilance database data mining of a panel of adverse effects and in vitro testing of drugs to efficiently identify candidates with anticholinesterasic properties for drug repositioning in Alzheimer's disease.

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NOVEL CONFIGURATIONALLY STABLE CA-4 ANALOGUES: MODIFICATIONS IN THE AROMATIC RING SUBSTITUTION PATTERNS

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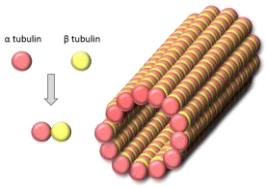
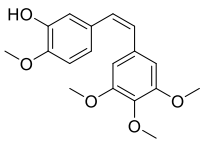
FP 09

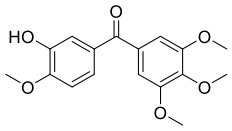
Microtubules, which are built up by polymerization of α-β tubulin heterodimers, play an essential role in several cell functions such as formation of the mitotic spindle or cell motility. Combretastatin A-4, also known as CA-4, is a natural product that binds at the colchicine site of tubulin strongly inhibiting tubulin polymerization. However, CA-4 presents several drawbacks, such as low aqueous solubility, high toxicity or configurational instability, which prevent it from being used as a drug. [(a)]



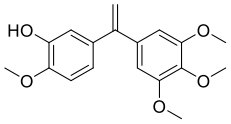


Combretastatin A-4

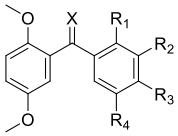
One-atom bridged CA-4 analogues are potent inhibitors of tubulin polymerization and cytotoxic compounds with the advantage of avoiding configurational instability. Thus, in this communication we have synthesised and evaluated novel CA-4 analogues in order to improve the pharmacokinetic profile by replacing the original 1,2-substituted olefinic bridge by different moieties such as oximes, 1,1-substituted olefins (isocombretastatins) or a carbonyl group (phenstatins). Moreover, modifications on the methoxy group substitution patterns were carried out. Results of the design, synthesis, tubulin polymerization and cytotoxic activity will be presented. [(b)]



Phenstatin



Isocombretastatin



Objectives

Acknowledgements

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Design of small protein-protein interaction disruptors to overcome apoptosis resistance	*FP 10*
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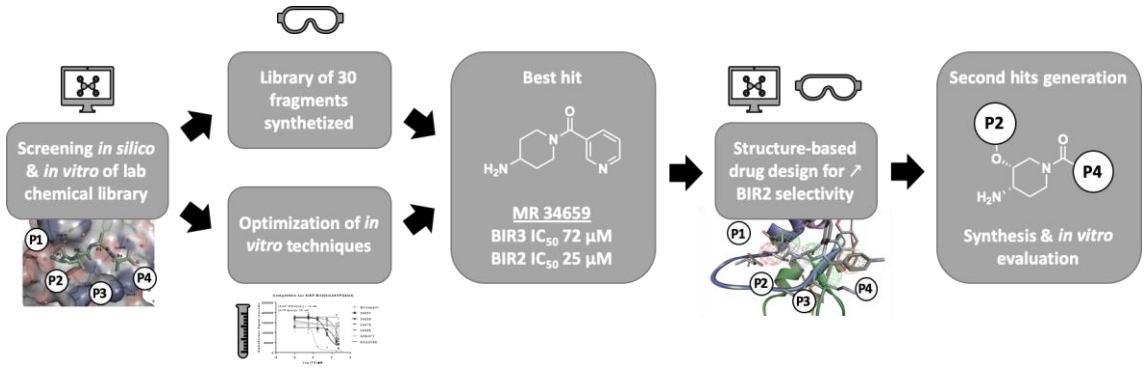
Apoptosis, an essential form of programmed cell death, is a tightly regulated cellular process to eliminate unwanted or damaged cells. Resistance of apoptosis is a hallmark of cancer cells.[a] X-linked inhibitor of apoptosis proteins (XIAP) is one of key apoptosis regulators that promote cancer cell resistant to apoptosis when overexpressed.[b] Disrupting the binding of XIAP with their functional partners (caspase 3/7/9) therefore is a promising strategy to restore the apoptotic response to proapoptotic stimuli.[c]

In medicinal chemistry approaches, the most successful example is the use of small molecules to mimic interactions between BIR2 or BIR3 XIAP domains and the binding motif of SMAC, an endogenous peptidic disruptor. If many peptidomimetic compounds have been developed last years, recurrent drawbacks are: the difficulty to achieve selectivity between members of the IAP proteins family, or between XIAP-BIR2 or XIAP-BIR3 domains, and unfavorable pharmacokinetic parameters.[d]

This past year, we have been conducted a rational approach to develop original non-peptidic inhibitors of XIAP-BIR2 domain. A first step of fragment-based drug design and optimization of *in vitro* evaluation (FPA, Alphascreen®) allowed us to obtain a first compounds library. As the fragment MR-34659 showed a promising selectivity for XIAP-BIR2, we conducted a pharmacomodulation study, based on difference between BIR2 and BIR3 domains,[e,f] in order to optimize structure-activity relationships. Our second generation of compounds is actually going on biological evaluation.



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Structural basis for peptide mimicry and Vitamin D receptor recognition by helical foldamers	
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The vitamin D receptor (VDR) is a ligand-activated transcription factor and a member of the nuclear hormone receptor family. It is implicated in the regulation of many biological functions including bone homeostasis, cell growth and immunity. Transcriptional activity of VDR upon binding to 1,25-dihydroxyvitamine D3, its natural ligand is enhanced by molecular association of the ligand binding domain (LBD) with coactivators such as steroid receptor coactivator (SRC) family members[1, 2] which interact with LBD though a conserved LXXLL motif. The LXXLL motif adopt a helical conformation upon binding to the LBD hydrophobic pocket. Peptide ligands derived from the LXXLL motif and designed to inhibit the VDR–coactivator interaction and thus genomic activation may find application as anticancer therapies. However, peptides suffer from several drawbacks and various chemical approaches are developed to improve their properties. Foldamers, sequence-based oligomers with precise folded conformation have emerged as a promising approach[3]. Here we have used oligourea foldamers which are readily synthesized and can be interfaced with peptides as α-helix mimics[4].

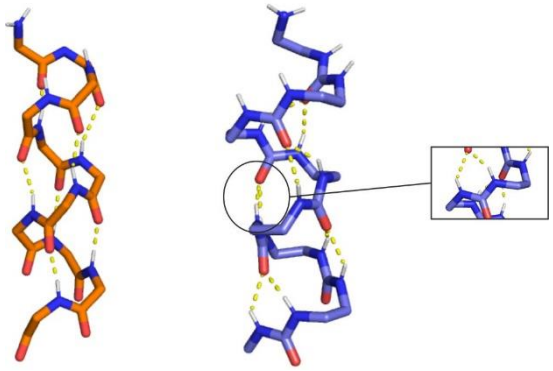

Figure 4 : α-Helical structure of peptide (Orange) and Oligo-urea (Blue)

We show that peptides with oligourea inserts of various lengths may be designed to retain high affinity for their protein target and report several crystal structures of peptide-oligoureas hybrids bonded to VDR LBD. This work should enable and facilitate the generation of effective foldamer-based disruptors of PPIs in the context of peptide lead optimization.

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QR2 (putative MT3) Inhibitors in the Treatment of Glaucoma: Achievements and Prospects

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FP 12

Glaucoma is a neurodegenerative eye disease responsible for 15% of blindness worldwide. One of the crucial factors of this disease is the increased intraocular pressure (IOP). All available anti-glaucoma medications act only as IOP lowering agents. However, we have discovered that 2-oxindoles, being the ligands of the quinone reductase II (QR2, putative melatonin MT3 receptor), not only significantly reduce IOP, but also possess antioxidant neuroprotective properties[a-c]. We have developed effective synthetic method for the preparation of oxindole-based melatonin bioisosteres[e-d]. More than 75 new compounds were tested in vivo on normotensive rabbits. A group of compounds with high IOP reducing effect (>40%) at low concentrations (0.1 wt%) and prolonged action (up to 28 h) was identified[a]. The obtained lead compounds are even less toxic than melatonin (LD_{50} = 2400 mg/kg and 800 mg/kg, respectively)[a]. All tested compounds have great antioxidant properties – 100 times higher than melatonin. These results allow us to state that we are on the way to developing a new generation anti-glaucoma drug.

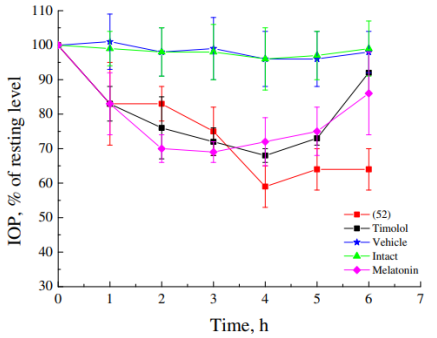
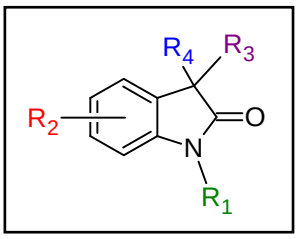


Fig. 1. Time-dependent study for (5-acetamido-2-oxindole-3-yl)acetic acid (52) [a]



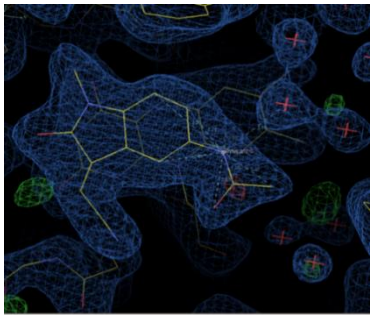


Fig. 2. X-ray crystal structures of (5-acetamido-2- oxoindolin-3-yl) acetonitrile in complex with QR2 (PDB ID: 4GQI, 4GR9) [a]

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Exploring Brain – Immune interaction with hyper – polarized Xenon – 129 Magnetic Resonance Imaging

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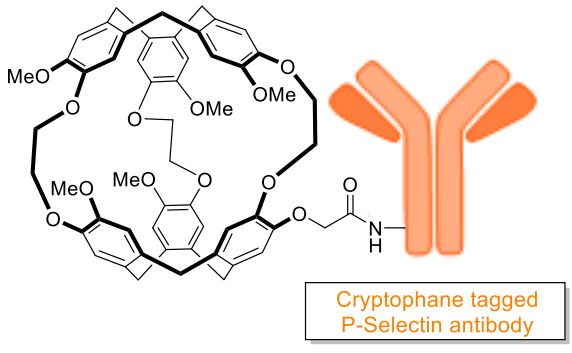
FP 13

Inflammation is a hallmark of most neurological disorders and the ability to detect, quantify and monitor the inflammatory response of the central nervous system (CNS) could have large implication for both diagnosis and therapeutic response prediction [1]. Among the different diagnostic modalities suitable to detect neuroinflammation, plasmatic biomarkers can be used but no reliable and specific plasmatic biomarker of neuroinflammation has been identified to date. Recently, molecular imaging of neuro-inflammation has been developed: the in vivo detection of a protein, the P-selectin, that is over-expressed at the luminal surface of endothelial cells during neuro-inflammation, was performed using micro-sized particles of iron – oxide (MPIO) [2]. However, this biosensor can't be used in human because of its toxicity.

Hyper-polarized xenon-129 (HP-129Xe) has recently emerged as a promising biocompatible contrast agent to improve sensitivity of MRI, successfully used to acquire images of the Human pulmonary system [3] and brain [4]. However, this gas is not specific of a biological target, and therefore to be a valuable biosensor, it has to be vectorized using a molecular host. Among them, cryptophanes showed very good xenon encapsulations properties, leading to a number of in vitro studies using HP-129Xe cryptophane based biosensors reported in the literature since the 2000's [5].

Here we propose the design and the synthesis of a new biocompatible MRI biosensor composed of a cryptophane core, able to encapsulate xenon, and a well-characterized P-selectin antibody able to selectively bind endothelial P-selectin with high affinity.



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Larrea tridentata lignan semi-synthetic amino ether derivatives and their antibacterial activity against drug-resistant bacteria

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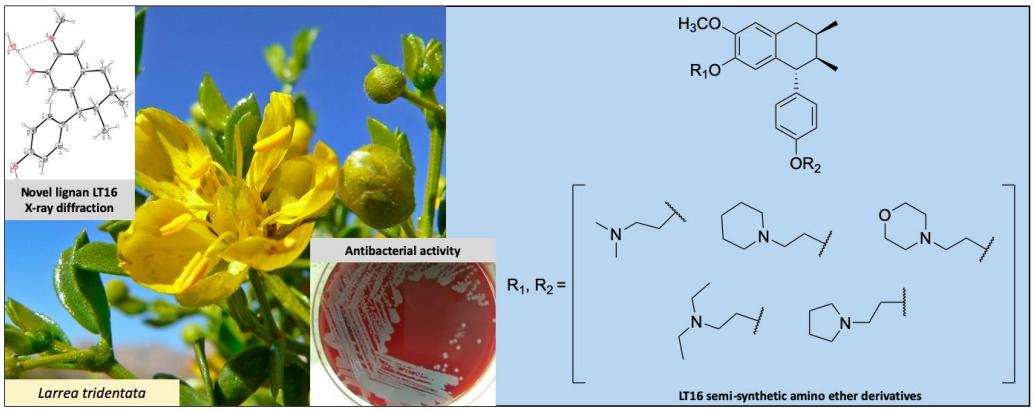
FP 14

Resistance to antibiotics has attracted the attention of international agencies, such as the World Health Organization (WHO), which in 2018 reported the widespread presence of resistance to antibiotics in 22 countries in its Global Antimicrobial Resistance Surveillance System (GLASS). This system confirmed the seriousness of antibiotic resistance and established that some bacteria responsible for causing common infections such as pneumonia, blood infections or urinary tract infections, are now drug resistant. Research groups have been obtaining extracts from plants used in traditional medicine and have evaluated them against different microorganisms. *Larrea tridentata* chloroform extract showed activity against different drug-resistant bacteria strains. Lignans were responsible for the antibacterial activity on this plant. In this work, we decided to carry out structural modifications on one of those lignans to increase their antibacterial activity and to test against nine drug-resistant bacteria from clinical isolates strains. Currently, we have done the semi-synthesis of new eleven amino-ethers (Figure 1) using as starting material 4,4'-dihydroxy-3-methoxy-6,7'-cyclolignan (LT16). We also tested them against drug-resistant bacteria and eight of them showed antibacterial activity compared with reference drug Levofloxacin.

Figure 1



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Synthesis of Ureas *N*-Substitued from Primary Amides	
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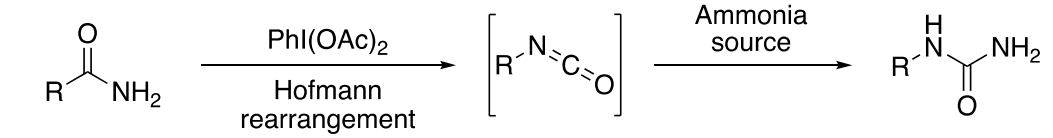
Due to their physicochemical and biological properties, ureas are increasingly used in medicinal chemistry.[a,b] A new method to form ureas from primary amides in one-pot synthesis has been developed, employing diacetoxyiodobenzene and ammonia (from methanolic ammonia or ammonium carbamate). These ureas are the result of nucleophilic attack of an intermediate isocyanate generated by a Hofmann rearrangement of the starting amide. The reaction has been tested on various compounds to determinate the extent of method, allowing to get a large scope of ureas in good to excellent yields.



R : Alk, Ar, HetAr

16 examples

Aryl : 52-99%
Alkyl : 77-86%

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Dextromethorphan and his derivatives as new antimalarial drugs targeting the hepatic stage of *Plasmodium falciparum*

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FP 16

Malaria remains one of the major human infectious diseases and is responsible for half a million deaths each year. As resistance to available drugs increases, there is an urgent need to identify new antimalarial molecules and to explore new strategies. In this context, targeting the *Plasmodium* liver stage could represent a valuable entry for preventing malaria[1]. Indeed, parasite liver stages precede the appearance of blood stages which are responsible for the clinical symptoms of the disease. Most current drugs target these blood stages which feature a constant genetic reprogramming and ultimately select chemoresistance mutations. The antimalarial activity of the highly functionalized natural product tazopsine[2,3] (Fig. 1), an *ent*-morphinane alkaloid, led to the identification of dextromethorphan (DXM, Fig. 1) as a new lead for the development of simplified analogs against *Plasmodium falciparum*[4].

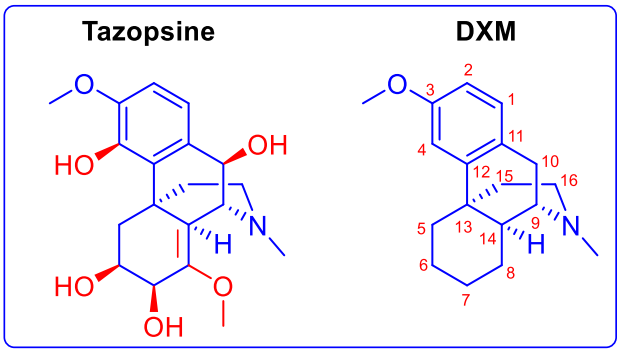

Fig. 1: Structure of tazopsin and DXM

Herein, we propose a semisynthetic approach to diversify the DXM skeleton using simple chemical reactions. A first generation of compounds functionalized on the *N* position was prepared and their antimalarial activities evaluated in prescreen on 2D+ cell culture constituted of cryopreserved human hepatocytes infected by *P. berghei* – GFP. The results are represented here.

*** Correspondence** antoinette.keita@parisdescartes.fr

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New 2-heteroaryl-4-quinolones as potential antibacterial agents targeting ESKAPEE pathogen communication systems

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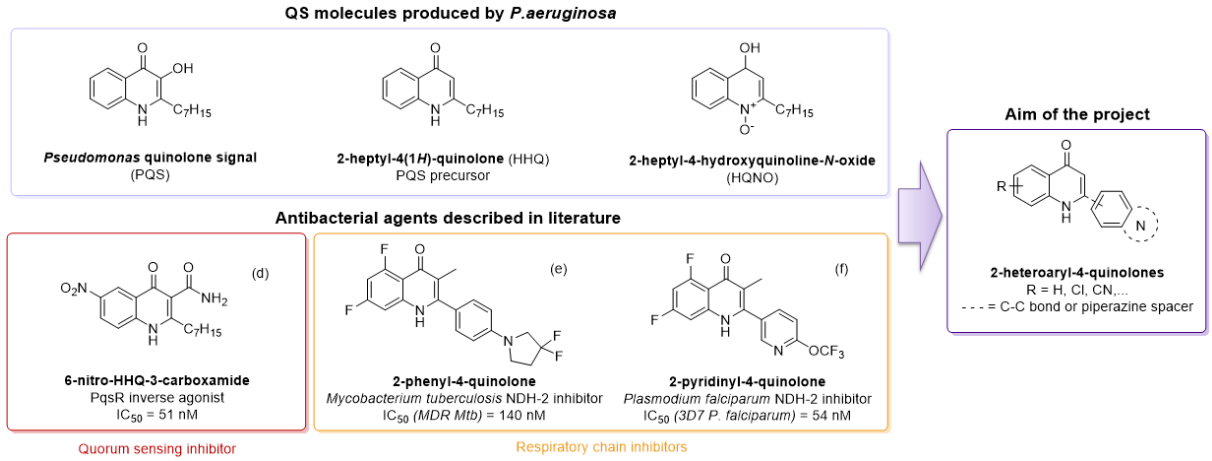
FP 17

Various nosocomial infections are due to multi-drug resistant ESKAPEE pathogens. Considering this serious threat to public health, new efficient treatments are urgently needed.[(a)] The quorum sensing (QS), that refers to bacterial communication systems, constitute a pool of new promising pharmacological targets for the development of antibacterial agents. The inhibition of QS could disrupt several intra/inter-species protective interactions (biofilm formation and multiplication of microorganisms) and virulence pathways (synthesis of pyocyanin, proteases or rhamnolipids).

The intervention of two main small signaling molecules was described in the *pqs* intercellular communication system of *P. aeruginosa*: the *Pseudomonas* quinolone signal (PQS) and its precursor 2-heptyl-4(1*H*)-quinolone (HHQ).[(b)] Those molecules are part of a HHQ/PQS pathway that regulate gene expression *via* the PQS receptor (PqsR) in response to population density and environmental factors. Interestingly, a secondary metabolite produced by *P. aeruginosa*, the 2-heptyl-4-hydroxyquinoline-*N*-oxide (HQNO), appears to be a potent respiratory chain inhibitor for various competing microorganisms such as *Staphylococcus aureus* or *Mycobacterium abscessus*.[(c)] Furthermore, HHQ analogues and different 2-heteroaryl-4-quinolone series revealed efficient as PqsR antagonists or type II NADH/quinone oxidoreductase inhibitors.[(d),(e),(f)]



Taking these literature data into account, we aim to develop a new antibacterial 2-heteroaryl-4-quinolone family. These compounds could be active against ESKAPEE pathogens by inhibiting QS or respiratory chain. The synthesis of the first final products carrying out palladocatalyzed coupling reactions from 2-bromo-4-chloroquinoline precursors diversely substituted in position 5 to 8 will be described in the presentation.

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Structure-activity relationship studies within the first chemical family of boosters of the nitroimidazole anti-tb drug pretomanid

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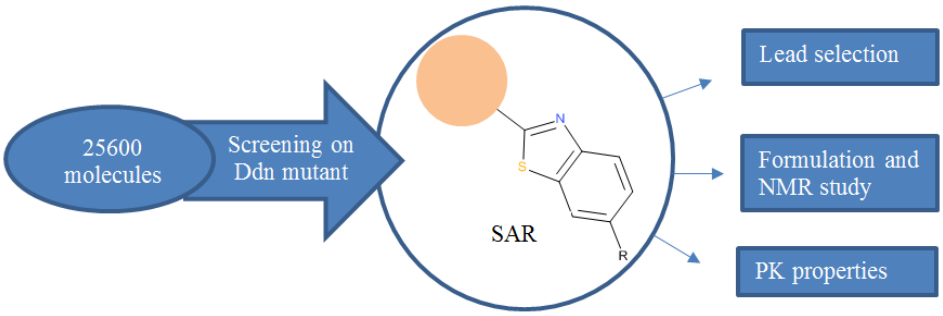
FP 18

Tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis*, remains a major cause of mortality killing each year 1.6 million people.[(a)] The treatment of this disease involves multidrug chemotherapy regimen often associated with serious side-effects. Difficulties with adherence to treatment favor the selection of resistant strains, and in 2017, 580 000 persons were infected with MDR (Multi-Drug Resistant) strains. The search for new alternative therapies is therefore urgently needed.

PA-824, known as pretomanid,[(b)] is one of the new nitroimidazole derivatives that was just approved to treat MDR/XDR TB in combination with bedaquiline and linezolid. It is a prodrug, which requires to be bioactivated by the mycobacterial enzyme Ddn (deazaflavin dependent nitro-reductase). This bioactivation leads to the production of nitrogen monoxide, which poisons the respiratory chain of the bacteria.[(c)]

One of the most common way for bacteria to resist to prodrugs is to mute genes in the corresponding bioactivation pathway, and Ddn mutated strains were selected *in vitro*, and were shown to be insensitive to PA-824. Our idea was to find molecules that will circumvent these mutations by triggering new bioactivation pathways. The concept has already been successfully demonstrated with the thioamide prodrugs,[(d)] ethionamide and prothionamide and has been extended to pretomanid (PA-824).

The screening of 25,600 molecules from our in house library in combination with PA-824, on a Ddn mutant, has led to the identification of hits, exhibiting no bactericidal activity alone but able to boost PA-824 activity. In order to optimize the hits and study the structure-activity relationships, we have performed pharmacomodulations that led to the identification of a more potent lead compound. The mechanism of action is currently unknown and under investigation.



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The Synthesis of potentially biologically active *trans*-PdL_2Cl_2 type of complex with 6-(Phenylseleno)hexahydro-2H-cyclopenta[b]furan-2-one as a ligand

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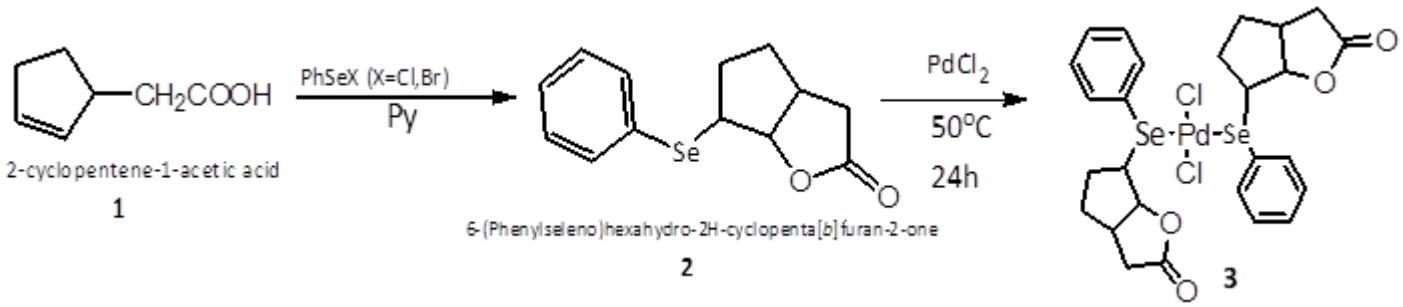
FP 19

Lactonization plays an important role in modern organic synthesis, not only because lactones are widespread compounds in nature, but also because they represent a useful class of synthons. One method for the preparation of lactones is the reaction of cycliyation of unsaturated acids with an eletrophilic oranoselenium reagent, where by products containing the organoselenium group in the side chain are formed. Obtained compounds have shown diverse and interesting biological activities such as antitumor, antibacterial activity, etc.[(a)]

Previous studies have shown good pharmacological properties of synthesized Pd(II) complexes with ligands having an organoseleneium group in the side chain. The purpose of this study is to obtain a Pd(II) complex with lactone, which is obtained by reaction intramolecular cyclization, using 2-cyclopentene-1-acetic acetic (**1**) acid as a substrate and PhSeCl or PhSeBr as reagents, in the presence of pyridine as an additive. The use of pyridine as an additive, results in almost quantitative yields of reaction product. Similar compounds from that group which already have been used in the synthesis of the complex show good biological activity. The synthesized Pd(II) complexes showed moderately good antioxidant, antimicrobial and antibacterial activity. The aim of our present study is to examine the biological activity of the synthesized Pd(II) complex (**3**) with 6-(Phenylseleno)hexahydro-2H-cyclopenta[b]furan-2-one (**2**) as a potentially better pharmacological agent.[(b)]



2-cyclopentene-1-acetic acid
1

6-(Phenylseleno)hexahydro-2H-cyclopenta[b]furan-2-one
2

3

Bibliographic references:

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Toward orally active polypeptide polymers as analogues of antimicrobial peptides targeting *Clostridium difficile*

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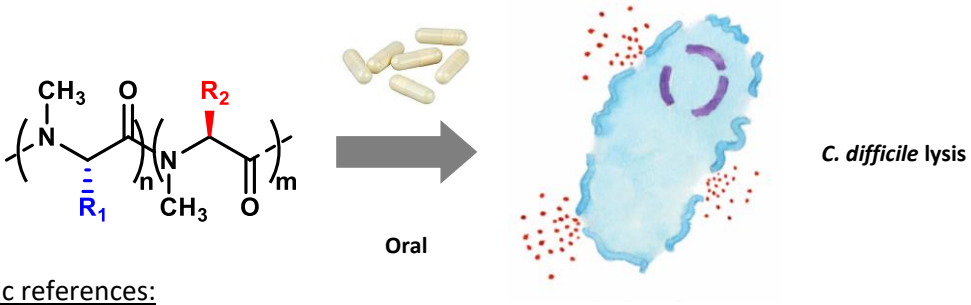
FP 20

Clostridium difficile (CD) is a strict anaerobic Gram-positive bacterium that can form endospores.[1] It is responsible for epidemic nosocomial diarrhea and pseudomembranous colitis in elderly patients treated with large spectrum antibiotics. Every year, 500,000 infections and approximately 15,000 to 30,000 deaths are attributed to CD infections in US where CD becomes more and more resistant to current treatments.[2] Moreover, it is estimated that acute care of CD infected patients reaches about 5 billion $/year in the USA.[3]

Antimicrobial peptides (AMPs) are produced by various micro-organisms and can display selective antibacterial activity including activity against CD.[4, 5] Recent studies evidence that, the cationic/hydrophobic amino-acid ratios in AMPs would be a major factor to explain their mechanism of action, which involves bacterial membrane destabilization.[6] Nevertheless, high production cost, sensitivity to proteases or peptidases and systemic toxicity are strong limitations for their therapeutic use.

This project aims at synthesizing a new class of peptidic polymers that can be orally administrated to target CD infections. To allow their oral administration, peptide bonds of the macromolecules will be *N*-methylated to afford significant resistance to proteases once in the digestive tract. These *N*-methylated polypeptides are synthesized from cationic and hydrophobic *N*-Carboxyanhydride amino acids monomers using "ring-opening copolymerization". Overall, the use of a single polymerization step permits to easily access library of polymeric analogues of AMPs composed of various cationic (R_1)/hydrophobic (R_2) ratios.[7] These libraries are being tested *in vitro* i.e., 1) on different bacteria, including CD, to evaluate their selectivity, 2) in the presence of peptidases, to confirm their resistance to proteolysis and 3) on a Caco-2 human epithelial intestinal cell line, to assess their cytotoxicity.

Amphiphilic amino acid polymers as simplified AMP analogues



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(7) Yong S. *et al*., *Chem. Soc. Rev.* (**2015**), *44*, 612

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Synthesis, characterization and anticancer activity of selected pyrrolin-2-ones

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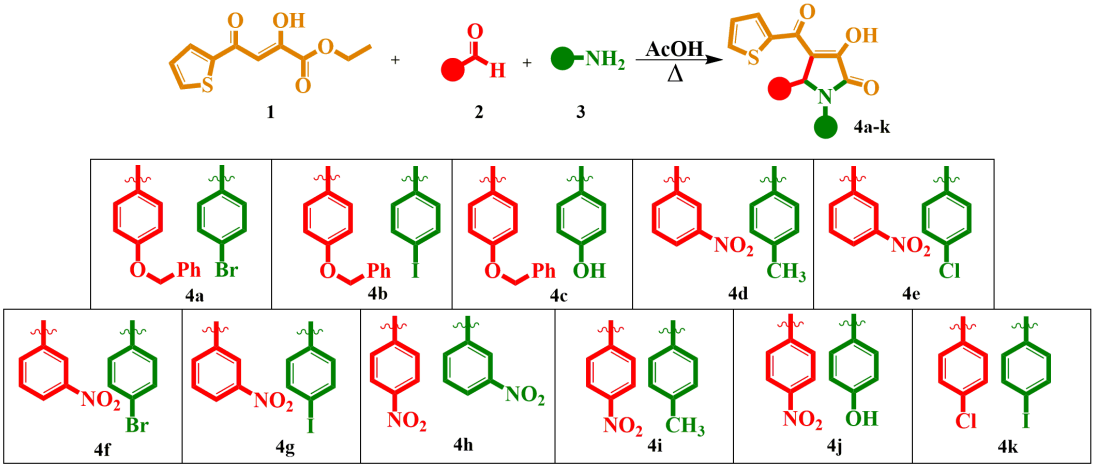
FP 21

One of the biggest problem in our society nowadays is cancer, so it is not surprising that scientists from all over the world have been trying to discover new agents with antitumor activities. These new agents have to be more selective, because chemotherapeutics that are used these days have many side effects such as neurotoxicity, nephrotoxicity, etc. The main goal is to find a novel drugs with better properties. Compounds such as pyrrolidinone have been studied in this area due to their derivates possess many interesting and different biological activities such as antimicrobial, anticancer, anti-inflammatory and antiviral activity.[(a,b)] In addition, some of them could be used to treat certain neurodegenerative disorders. Bearing in mind the previous we synthesized eleven novel 3-hydroxy-3-pyrrolin-2-ones (**4a-k**) by multicomponent one-pot reaction of enol ester (**1**) with aromatic aldehydes (**2**) and aromatic amines (**3**) (Shema 1). All compounds were examined for their cytotoxic effect on human colorectal cancer cell line SW480 and normal fibroblasts (MRC-5). Three compounds (**4h**, **4i** and **4j**) that showed cytotoxicity against malignant cells and the best selectivity towards normal cells were selected for further experiments. Moreover, to observe the suitability of these molecules for clinical use in the future, the mechanism of action of these molecules with biomacromolecules such as deoxyribonucleic acid (DNA) and bovine serum albumine (BSA) was examined.

Shema 1. Synthesis of novel 1,5-diaryl-4-(2-thienylcarbonyl)-3-hydroxy-3-pyrrolin-2-ones



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POSTER ABSTRACT

*

Novel sigma-1 fluorescent ligands: tools for non-radiative biological assays.

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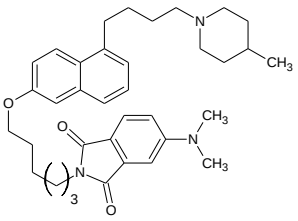
PO 01

Background : The Sigma-1 receptor (Sig-1R) is a chaperone protein involved in different patologies, such as cancer and neurodegenerative disorders. Despite the growing interest for its therapeutic possible exploitation, Sig-1R mode of action needs clarification. Evidence has shown how Sig-1R is a modulator of many signaling pathways, involving G protein-coupled receptors (GPCR) and ion channels, in particular. Sig-1R indeed is not only involved in intracellular calcium signaling and inositol triphosphate (IP_3) tournover, but can also inhibit potassium channels. The need to better understand the role and mechanism of this receptor, has stimulated the impulse to synthesize fluorescent ligands, which give the possibility to identify complex formation or observe conformational changes in live cells, without the use of radioligand binding techniques.

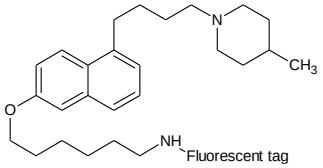
With this aim in 2016, LM1 has been synthesized in our laboratories. This compound consists of two different parts: a scaffold, which is PB212 (a subnanomolar Sig-1R antagonist, 10-fold selective towards the Sigma-2 receptor) and a fluorophore (N,N-dimethilaminophtalimide) which are connected by an hexamethylenes chain. LM1 has been used on human breast adenocarcinoma cells (MCF7_Sig-1R) by flow cytometry, where it provided curves which allowed to calculate the IC_{50} values of sigma-1 reference compounds for the human Sig-1R.

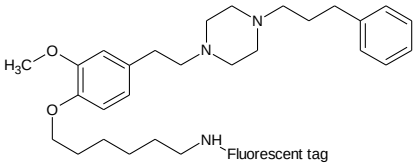


LM1

Aim of the study : In order to extend the applicability of these compounds in different tecniques, new fluorescent ligands have been synthesized. They are based either on PB212 or SA4503, a well known reference nanomolar Sig-1R agonist. The avaiability of fluorescent ligands based on a Sig-1R agonist and antagonist may provide useful tools to better understand cellular pathways involving Sig-1R.

The fluorescent compounds herein sythesized will provide versatile tools to be used in flow cytometry and confocal microscopy experiments, likely overcoming the limitations that LM1 showed in confocal microscopy (ongoing experiments) and extending the use to differently equipped instruments.





Conclusions : New fluorescent ligand herein sythesized will give the possibility to detect the presence of Sig-1R in live cells and perform binding assays without classical radioligand-based technque.

Modulations of a piperidine-based hit identified from a phenotypic-screening, for the treatment of tuberculosis.	**PO 02**

Théo Abdesselam[1*], Marion Michel[1], Céline Lenglart[1], Catherine Piveteau[1], Benoît Déprez[1], Sushovan Dam[2], Marion Flipo[1], Nicolas Willand[1], Ruben C. Hartkoorn[2], Baptiste Villemagne[1]

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Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb). First-line treatment is made of a polychemotherapy which lasts for several months. This treatment causes serious side effects, resulting in observance issues and ultimately in a growing emergence of drug-resistant bacterial strains, threatening our ability to tackle this globally present disease. To address these issues, new antibiotics with novel mechanisms of action are urgently needed. In order to identify such new molecules, we carried out a phenotypic screening on Mtb, in collaboration with the team of Dr. Ruben C. Hartkoorn, using our own in-house library of over 9,000 original compounds. This led to the identification of a hit bearing a N-benzylated-3,4-substituted piperidine central ring, and displaying an MIC of 1.5 µM. Metabolic studies conducted on this molecule unsurprisingly showed it to be prone to oxidation on position 4 of the benzyl group. Thus, in order to improve its activity and metabolic stability, we focused our efforts on the modification of the metabolically weak benzyl moiety. 29 analogs were synthetized and tested, resulting in a fiftyfold activity enhancement and a noticeable microsomal stability improvement. Herein are presented the different analogs synthetized in this project, and the associated structure-activity and structure-property relationships.

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Design and production of innovative armed scFv to target HER2-positive breast cancer	PO 03

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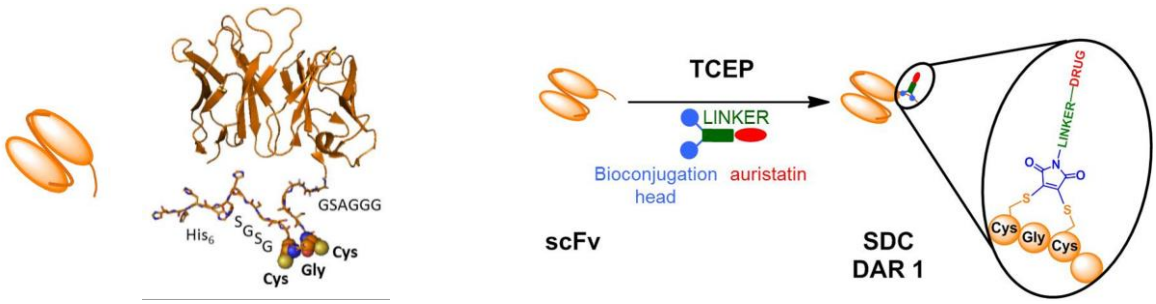
The combination of a highly potent cytotoxic agent (drug) with a specific therapeutic monoclonal antibody (mAb) *via* a suitably constructed spacer arm (linker) (Fig 1) appear to be an ideal embodiment of the "magic bullet" concept leading to the development of a novel therapeutic class named Antibody-Drug-Conjugates (ADCs) [(a)]. These armed antibodies can be viewed as a way to improve tumor-cell killing while sparing normal tissues. While ADC have been successfully implemented in clinical strategies for the treatment of hematological cancers, the case of solid tumors suffer from insufficient ADCs activity at the maximum doses that can be tolerated. Currently, almost all ADCs in clinical trials are based on canonical IgG molecules associated with limitations including bad tumor penetration as well as Fc-mediated off target toxicities, due to an increase of normal tissue exposure (due to long half-life *via* FcRn recycling) and cross reaction with immune cells (due to FcγR interactions). Thereby, the aim of our project is to use antibody fragments to try to circumvent these limitations.



Our strategy is based on a site-specific conjugation [(b,c)] of monomethyl auristatin F (MMAF) onto an engineered anti-HER2 antibody fragment including single chain fragment variable (scFv) of the trastuzumab antibody, generating new scFv-drug conjugates (SDCs). Cysteines were judiciously incorporated in the scFv aminoacid sequence to allow controlled bioconjugation of a non-cleavable heterobifunctional linker carrying MMAF. Ours results showed efficient targeting of site-specific SDCs against HER2-positive breast cancer cells. This work represents a first important step in the design of more effective small conjugates, paving the way for future *in vivo* translation to evaluate their full potential.

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Biopharmaceutical characterization and evaluation of antioxidant activity of some diclofenac derivatives with hydrazone structure	PO 04

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Introduction: Natural and synthetic compounds are widely used as a source of therapeutic tools to prevent or treat multiple diseases. Experimental and epidemiological studies have shown that many natural and synthetic drugs are involved in reducing oxidative stress developed due to free radicals and act as antioxidants. **Aim:** Biopharmaceutical characterization using the prediction program MedChemDesigner 5.5 and the evaluation of the antioxidant potential of hydrazones derivatives with diclofenac structure have been performed. **Material and methods:** The synthetized compounds were characterized biopharmaceutical, *in silico*, by estimation of the partition coefficient octanol/water, distribution coefficient octanol/water, absorption capacity at digestive level and topological polar surface area.The evaluation of the antioxidant potential was also performed using *in vitro* methods: total antioxidant capacity and reducing power. **Results:** The biopharmaceutical features suggest an optimal pharmacokinetic profile with a lipophilic character for studied derivatives, which allows both crossing cell membranes and digestive absorption. In addition, several compounds have proven notable antioxidant activity, higher than diclofenac, the parent compound. It is found that the most active compounds were **4s** (R = 2-Br-3-OH-4-OCH_3), **4c** (R = 3-NO_2) and **4g** (R = 4-OCH_3). **Conclusions:** The biopharmaceutical study revealed promising characteristics regarding the pharmacokinetic profile of the studied compounds. Moreover, it was noticed that the antioxidant effect increases with concentration and it is influenced by the nature of the substituent on the aromatic ring.

Acknowledgments
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Regioselective ortho-nitroanilines reduction as way to novel biologically active heterocycles

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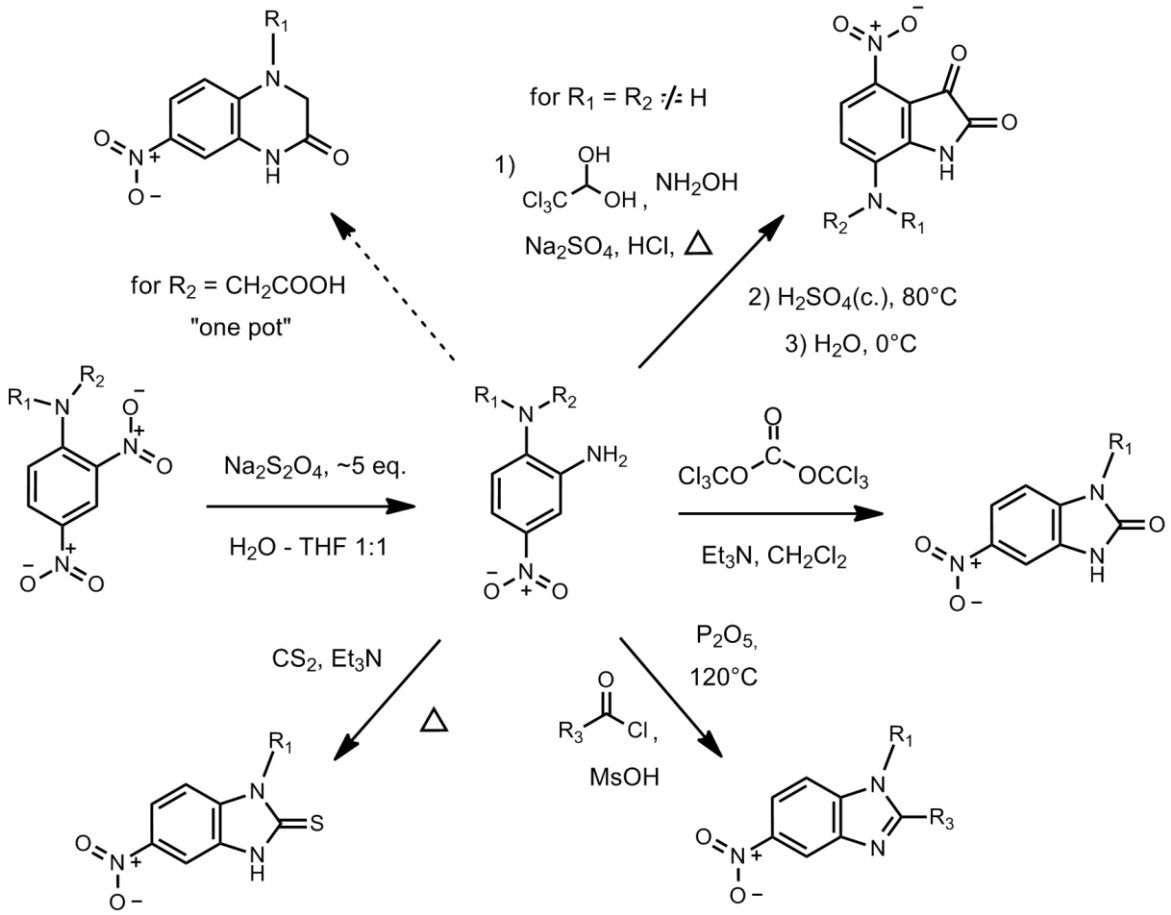
PO 05

Currently, many types of drugs on the market have heterocycles in their structure. Our method allows the obtaining of different biologically active heterocycles from one source – 2,4-dinitrochlorobenzene, which is inexpensive and commercially available. Nucleophilic substitution of chlorine with nucleophilic amines followed by regioselective ortho-nitro group reduction lead to 2-amino-4-nitroanilines – useful building blocks for various heterocycles indicated in the scheme below. Thus, we can get scaffolds of biologically active compounds such as benzimidazolones/tions, benzimidazoles, and benzoxazoles (see scheme). In the last few years benzimidazoles and benzimidazolones have been studied extensively for their antitumor, antiviral and antimicrobial activities such as the antiprotozoal and antibacterial.
In this way, we proposed a simple method for design of new compounds with a wide spectrum of activity.



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Synthesis of Simplified Analogs of Marine Metabolites for Aurora B Kinase Inhibition.

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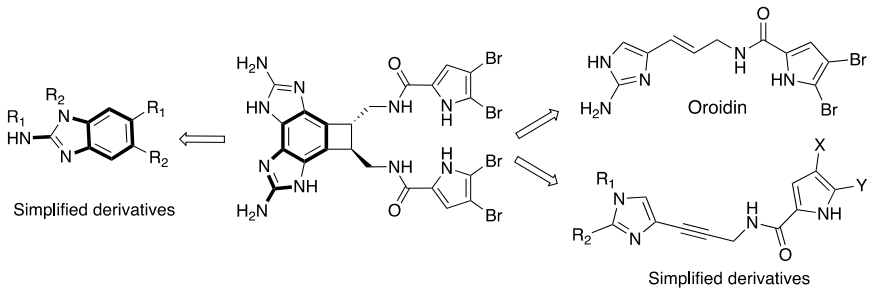
PO 06

Natural products chemistry is crucial for drug discovery. Indeed many successful drugs are bio-inspired from natural metabolites. Marine natural products constitute a tremendous source of bioactive compounds for pharmaceutical purposes.
The pyrrole-2-aminoimidazole (P-2-AI) alkaloids are exclusively isolated from marine sponges and well known for their high structural diversity, high nitrogen-to-carbon ratio and interesting biological activities.[a] We focused our efforts on the synthesis of fragments of benzosceptrins[b] and oroidin[c] for their kinase inhibitory activities.
Some of the numerous synthetic analogs of isolated P-2AI have been found to inhibit various kinases including Aurora B, CK1 or RIPK1.
Here we present new inhibitors of Aurora B, which is essential for cell division via mitosis regulation. Thus it plays a crucial role in tumorigenesis and has shown great promise over the past two decades as a new target for cancer therapy.[d-f]
The presentation will be devoted to the improvement of inhibitory potency and specificity of the selected scaffold. Some results of the characterization of the mechanism of action leading will be presented as well.



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Qualitative and quantitative comparison of extracts obtained from dry and fresh walnut leaves	PO 07

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The Walnut tree (*Juglans regia* L.), commonly known '***Al-Djouz'*** in Algeria, has a long history of medicinal uses that treat a wide range of health complaints. Different parts of this tree, especially the leaves, are used in traditional medicine to treat several diseases including diabetes and cancer **[a]**. The use of dry plant material has always been useful in the discovery of new bioactive molecules that are absent in its fresh state. In order to see the influence of the presence of water in the fresh walnut leaves, we compared the extracts obtained from them with the extracts obtained from the dry leaves of walnut. The study is conducted on the extracts obtained by the cold maceration extraction method and the analysis is carried out under the same operating conditions, using the same chromatographic equipment (HPLC) **[b]**. We notice that, we do not have a qualitative difference between the two extracts, since we could identify the same compounds in both samples namely; two phenolic acids (caffeic acid and p-coumaric acid) and three flavonoids (rutin, ± naringenin and luteolin). On the other hand, a quantitative distinction was observed in the extraction yield as well as in the analyzed phenolic content. Indeed, the extraction yield of the extract of dry leaves obtained by the MF technique and almost twice that of the fresh leaves (9.60% versus 5.44%). As for the compounds of phenolic acids and flavonoids quantified, we find that all these compounds are strongly present in the extract of dry leaves relative to the extract of fresh leaves with a total of 165.22 ppm / mg versus 61.72 ppm / mg.

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Biological evaluation of new polymeric systems based on chitosan and lipoic acid

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PO 08

Objectives: Recent studies are focused on the use of natural polymers as drug delivery systems, in order to improve the pharmacokinetic and pharmacological profile of some drugs. Chitosan is a natural polymer with some important properties as biocompatibility, biodegradability, lack of toxicity and low immunogenicity. In addition to this, chitosan presents some pharmacological effects including hypoglycemic, cholesterol-lowering, antihypertensive, antioxidant, antimicrobial and favorable effects in reducing obesity, making it suitable for the development of different multi-target drug-polymer systems. The aim of this study was the biological evaluation of some polymeric systems containing chitosan and lipoic acid. **Material and Method:** The new polymeric systems were prepared as microparticles, using medium molecular weight chitosan in whose matrix was included lipoic acid. The microparticles obtained were evaluated *in* vivo on diabetic Wistar rats. After the induction of diabetes, the microparticles were administered orally for 30 days. During the experiment and at the end of it, it was evaluated the influence of the systems developed on the blood glucose and glycosylated hemoglobin values, body weight, food and water consumption. **Results:** The polymeric system developed proved a favourable influence on the glycaemic profile, reducing significantly the blood glucose and glycosylated hemoglobin values. Also, the lipoic acid – chitosan microparticles showed the benefit on body weight and food consumption. **Conclusions:** The developed chitosan-lipoic acid systems present all the theoretical premises to act as a multi-target treatment of diabetes mellitus.

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ANTIOXIDANT AND ANTIMICROBIAL POTENTIAL OF NEW AZETIDIN-2-ONE OF FERULIC ACID

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PO 09

The study objective. The objective of our study was to evaluate the antioxidant and antimicrobial potential for six new azetidin-2-one derivatives of ferulic acid. **Materials and methods:** The *in vitro* antioxidant potential of the compounds was assessed by using total antioxidant capacity and total reducing power assays. Antimicrobial activity was investigated using Gram positive bacteria (*Staphylococcus aureus* ATCC 25923), Gram negative bacteria (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853) and pathogenic yeast (*Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019). Several of the synthesized compounds showed a good antioxidant activity, exceeding the ferulic acid antioxidant potential. All the investigated compounds proved a good activity against Gram positive bacteria. **Results**: The results revealed that newly synthesised compounds showed a greater antioxidant activity at low concentrations as compared to ferulic acid. Good antioxidant activity showed the compounds resulting from the condensation reaction with 4-chlorobenzaldehyde **1c** (EC_{50}=19.67±0.07 µg/mL), 2-nitrobenzaldehyde **1d** (EC_{50}=19.89±0.05 µg/mL), 4-fluorobenzaldehyde **1b** (EC_{50}=20.007±0.03 µg/mL) and 2-hydroxybenzaldehyde **1f** (EC_{50}= =23.004±0.06 µg/mL). These compounds are about 1.4 to 1.2 times more active than ferulic acid (EC_{50}=27.62±0.05 µg/mL) at the same concentration and so the results support the initial premise. The antimicrobial assays show a evident difference in terms of antibacterial and antifungal activity, implying that the tested compounds act differently on various types of microorganisms. All new six tested compounds have good antibacterial activity against *S. aureus* ATCC 25923 and medium activity against *E. coli*. The most active compound against *S. aureus* proved to be **1d** (2-nitrobenzaldehyde) and against *E. coli* was **1e** (4-brombenzaldehyde). Against *P. aeruginosa* ATCC 27853 the tested compounds had no activity, except **1a** (H-benzaldehyde) and **1d** (2-nitrobenzaldehyde). Also, the tested compounds demonstrated a good activity against the *Candida* strains, except **1e** (4-brombenzaldehyde). The obtained results indicate that the new ferulic acid azetidin-2-one derivatives possess good antimicrobial properties. **Conclusions**: Our results indicate that the new six azetidin-2-one derivatives of ferulic acid possess good antioxidant activity at low concentrations and good antimicrobial activity against Gram positive bacteria. **Key words:** azetidin-2-one, ferulic acid, antioxdant activity, antimicrobial activity.

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Evaluation of the antiangiogenetic activity of some nanoparticle-type polymeric matrices, using in vivo model of the chick choroallantoic membrane

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PO 10

Introduction: Angiogenesis is a complex process, with an essential role in tumor growth and metastasis. The mechanisms of antitumor activity are varied, such as inhibition of carbonic anhydrase, cell cycle arrest in G1 phase, disruption of the microtubule assembly, functional suppression of the NF-Y transcriptional activator, and inhibition of angiogenesis. Four types of nanoparticles, corresponding to previously synthesized chitosan-sulfonamide derivatives (a), were obtained in this work, characterized by IR and in vivo evaluated for their antiangiogenetic activity. ***Matherial and methods:*** Nanoparticles corresponding to the 4 derivatives (CLA, CLB, CLC and CLD) were obtained using the method of crosslinking with sodium tripolyphosphate (b), separated by centrifugation, dried by lyophilization and characterized by IR in order to highlight the functional groups specific of the obtained nanoparticles. Chick Chorioallantoic Membrane (CAM) model was used to assess the antiangiogenic activity of chitosan derivatives nanoparticles, by using nine-day-old fertilized chick eggs (c). At the end, the embryos with nanoparticles were compared with those without nanoparticles (respectively the corresponding CAM membranes), in order to observe the new vessel formation, using histopathological analysis with a Nikon Eclipse 50i microscope. ***Results and discussion:*** The obtained results revealed the ability to inhibit angiogenesis in the four types of nanoparticles. In additon, samples CLC and CLD were highlighted (nanoparticles corresponding to chitosan-sulfamethoxydiazine and chitosan- sulfisoxazole derivatives); for these, significant decrease of blood vessels presence, was recorded.

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Uncharged Reactivators of OP-inhibited Cholinesterases.	
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The development of medical countermeasure against both acute and chronic intoxications by organophosphorus (OP) nerve agents continues to be a challenge. Only strong nucleophiles (typically oximes) are able to reactivate the phosphylated-enzyme. After 50 years of research, there is no broad spectrum reactivator. Furthermore the currently used reactivators (pyridinium aldoximes) are unable to cross the blood brain barrier (BBB) efficiently in order to reach phosphylated central AChE. The aim of this project is to find new and more efficient reactivators focusing on the synthesis of new uncharged reactivators able to cross the BBB, and to evaluate their *in vitro* and *in vivo* efficacy.

These reactivators, composed of an AChE peripheral site binder (e.g. tetrahydroisoquinoline, piperazine, piperidine, morpholine…) linked to an oxime through a linker have been evaluated *in vitro* against several OP-inhibited enzymes. In order to have an accurate and rapid evaluation of their potential *in vivo* efficacy, the therapeutic window for each compound has been estimated. The previous generation suffers some drawbacks as an uncompleted protection against different OP, exemplified by oxime JR595. The new generation of uncharged oximes presented in this communication shows reactivation within the therapeutic window for several OP, indeed at 100µM concentration, more than 30% of the enzyme is reactivated in less than 5 min.

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Development of targeted nanoemulsions for Molecular Resonance Imaging of neuro-inflammation using hyperpolarized xenon-129.	***PO 12***

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Inflammation is a hallmark of number of neurological disorders (1) and our ability to detect, quantify and monitor the inflammation within the central nervous system (CNS) should have large implication for diagnosis, prognosis and therapeutic responsiveness of these diseases (2). Among the different diagnostic modalities suitable to detect neuro-inflammation (NI), a powerful molecular magnetic resonance imaging (MRI) tool targeting the adhesion molecules P-selectin and vascular-cell adhesion molecule-1 (VCAM-1), proteins that are over-expressed at the luminal surface of endothelial cells during processes of NI, were developed and characterized recently. This tool, designed from paramagnetic contrast agent micron-sized particles of iron oxide (MPIO), have shown convincing preclinical proofs of concepts and appeared as a promising for diagnosis and prognosis of CNS disorders. (3),(4) However, the use of non-biodegradable MPIO as contrast agent remains an unsolved limitation for translation to the clinic.

In this project, we postulate that the use of hyper-polarised xenon-129 (HP-129Xe) as contrast agent is relevant for translation of molecular-MRI of NI from bench to bed side. Indeed, HP-129Xe has recently emerged as a promising biocompatible contrast agent to improve sensibility of MRI, successfully used to acquire images of the Human pulmonary system (5) and brain (6). This gas is not specific of a biological target, and therefore has to be vectorised to be a valuable biosensor. Despite a great number of in vitro studies using HP-129Xe biosensors reported in the literature (7), an in vivo demonstration is still lacking.

Thus, the aim of our project is to develop a biocompatible contrast agent for MRI of NI, composed of nanoemulsions (NE) of HP-129Xe molecular hosts linked to P-selectin and VCAM-1 antibodies. Our preliminary results will be presented in this presentation.

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***In Silico* investigation type of interaction between Au(III) complexes and DNA/SA molecules.**	***PO 13***

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During the last 20 years much interests have been focused on gold(III) compounds and their biological role, due to their in vitro cytotoxicity toward different human tumor cell lines.[(a)] In comparison with well know cisplatin,[(b)] gold complexes exhibit different properties (pharmaco-dynamic or kinetic) that include strong cell growth inhibiting effects, which makes them promising compounds for biological examination.[(c)] Antitumor activity of gold complexes[(d)] is based on their interaction with DNA molecule and serum albumin protein as a main drug transporting compound throughout a body. Therefore, understanding the type of their interactions can improve our knowledge of the biochemical processes that occur in the body during the application of transition metal complexes as antitumor drugs. From this point of view, a molecular docking simulations emerge as a very powerful tool for testing how small molecules perform interaction with biomacromolecules, in our case with DNA and BSA molecules.[(e)]

The principal objective of our study was to investigate the type of interaction between two Au(III) complexes, $[Au(DPP)Cl_2]^+$ (**1**) and $[Au(DMP)Cl_3]$ (**2**) (4,7-diphenyl-1,10-phenanthroline (DMP) and 2,9-dimethyl-1,10-phenanthroline (DPP) with two different fragments of DNA, a canonical B-DNA (PDB: 1BNA) and a DNA fragment with an intercalation gap (PDB: 1Z3F), and additionally with bovine serum albumin (PDB: 4F5S) using Molegro Virtual Docker (MVD, version 2013.6.0.1)[(e)] as a molecular docking simulations tool. The estimation of interaction strength between investigated complexes and DNA/BSA was described by the MVD-related scoring functions, where further analyses of non-covalent interactions between best docked poses and DNA molecule were performed with a Multiwfn program.[(f)] The obtained results were discussed in order of find connection between different geometrical structure of studied complexes and their ability to effective bind to biomacromolecules.

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Discovery of hERAP2 inhibitors by Kinetic Target guided synthesis and hit optimization.	***PO 14***

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Endoplasmic Reticulum aminopeptidase 2 (ERAP2) is an intracellular aminopeptidase that belongs to the M1 family of zinc metalloproteases. In combination with ERAP1, it processes antigenic peptide precursors to generate antigenic peptides for presentation by MHC-I molecules[a]. These enzymes can thus regulate adaptive immune responses in humans and influence cytotoxic responses against healthy or aberrant cells.

During recent years, ERAP2 has been associated, via genome-wide association studies, with the development of autoimmunity, immune evasion by cancer and resistance to HIV infection[b]. As a result, development of potent and selective hERAP2 inhibitors as potential pharmacological tools and well as lead compounds is of high interest.

Recently hERAP2 inhibitors displaying either a phosphinic group and a 3,4-diaminobenzoic acid moiety were published[c,d]. Despite good to excellent activity on hERAP2, these inhibitors are either non-selective regarding other aminopeptidases or have low druggability properties.

To discover hits, the kinetic Target-Guided Synthesis (TGS) was used[e]. This method is commonly described with the Huisgen cycloaddition where a mixture of alkyne are mixed with azides and with the targeted enzymes. On the 2160 possible combinations, 7 hits were identified. These hits were synthesized by chemical synthesis and tested against ERAP 2 to confirm them activities leading to the discovery of 4 hits.

To optimize the activity against ERAP 2 and the selectivity several analogs were synthesized, allowed us to uncover new hERAP2 inhibitors with IC_{50} up to 76nM and good druggable profiles.

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Design of original imidazophtalazine compounds as promising therapies for breast cancers	PO 15

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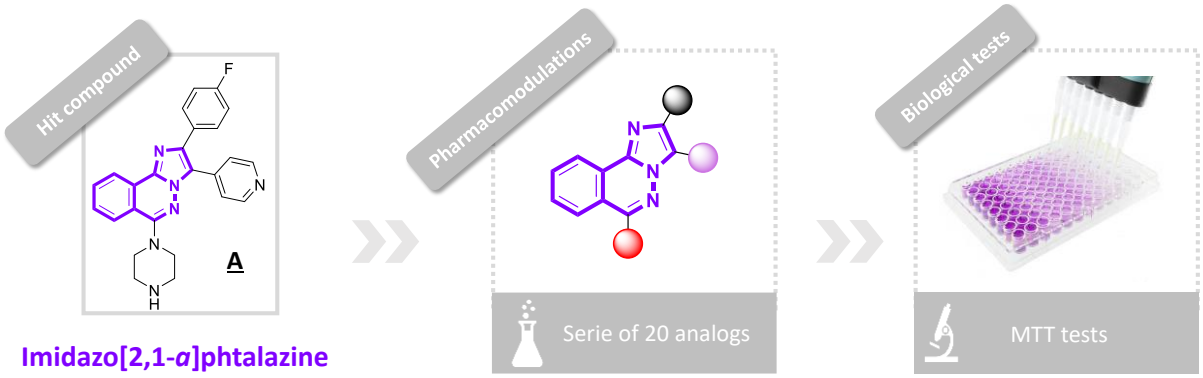
A selectivity screening on a panel of kinases of our home-made library revealed one original compound **A** displaying good inhibition on casein kinase 1ε (**CK1ε**). CK1ε was found to play a critical role in cancer signaling pathways especially in breast cancers.[a]
Breast cancers are a worldwide burden issue, accounting for the most commonly diagnosed cancer (2.1 million newly diagnosed cases in 2018) and the leading cause of cancer death among females.[b] In developed countries, 9 women out of 10 are cured thanks to better prevention promotion and targeted drug development. Nevertheless, some breast cancers cannot benefit from these medical improvements. Namely, the **triple negative breast cancer** challenges medical research because of chemotherapy resistance and poor life span.
In this context, we performed pharmacomodulations of our hit **A** to provide a serie of 20 analogs, all containing the **imidazophtalazine scaffold**. Our chemistry project involves exploring the influence of various groups on three different positions in our moiety. Biological investigations are carried out to assess **cell viability** in two breast cancer cell lines and highlighted 3 compounds with micromolar activities.



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Evaluation of nanoemulsion formulation of a new MCL-1 inhibitor derived from natural products for the treatment of B cell Lymphomas

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PO 16

B cell lymphomas make up most (about 85%) of the non-Hodgkin lymphomas (NHL). In 2018, in France, NHL was the 9th cause of cancers, with 14,745 new cases, and 5,660 deaths per year (Globocan, 2018). Research of effective treatments is crucial…

In regard of the biological results, NA1-115-7 (NA), a selective MCL-1 inhibitor, appears as a very promising lead with a real therapeutic interest, in particular for B cell lymphoproliferations[a]. However, considering its lipophilic structure, and its sensitivity to acid conditions, the drugability parameters of this lead could hamper its preclinical development. We propose to engineer NA-loaded nanoemulsions (NE) to ensure solubilization and stabilization of NA in biological media, in particular after oral administration and also after intravenous (iv) injection, increasing drug bioavailability, and ferry efficient doses[b].

At 2.0 ± 0.1 wt% drug loading rate, NA-loaded NE were obtained with a monodisperse diameter (average diameter of 42.4 ± 0.4 nm, polydispersity index of 0.152 ± 0.005), and a good encapsulation efficiency (91.2 ± 1.8 %), equivalent to a colloidal solution of 4.04 ± 0.08 mg/mL or 10.19 ± 0.19 mM of NA. Kinetic solubility of NA dissolved in DMSO, and NA-NE was evaluated at 37°C in PBS, in simulated gastric fluids (concentration of 100 µM of NA in all cases). In PBS, both free and encapsulated NA remained solubilized in time. In acid gastric media, the solubilized drug proportion progressively decreased in time very rapidly all the more for the free API. After 3 h, only 14 % of the initial drug amount was recovered if free and 56 % if encapsulated. Cellular toxicity and mechanism of action of free NA and NA encapsulated in NE was evaluated on lymphoid cell lines. Apoptosis induction after 24h of treatment was analyzed by Annexin V/IP labelling and BAK activation after 4h of treatment was detected with conformational antibody and analyzed by FACS. Encapsulation of NA in NE increases its efficacy.

In fine, thanks to nanoemulsions newly developed, the increase in stability and recovery of NA in physiological conditions should be obtained. The ability of nanoemulsions to transport NA leads to improve activity. From results of these preclinical studies, a new drug candidate should be identified and in vivo determination of the therapeutic effects in mice could be performed.

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Development of pleiotropic MAO-B/AChE inhibitors for Alzheimer's disease.	PO 17

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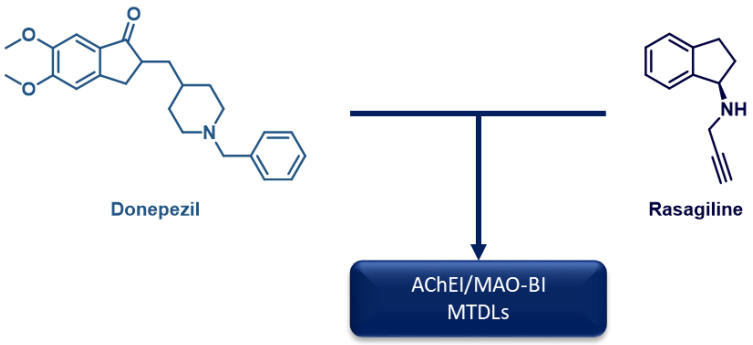
Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder, leading to the most common[(a)] form of dementia in the elderly. Given AD's multifactorial causes, the classical pharmacological approach consisting in interacting very selectively with a single target has shown clinical limitations, 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)].

The objective of this project is to develop new molecules interacting with two identified targets : Acetylcholinesterase (AChE) and Mono Amine Oxidase B (MAO-B) . AChE inhibition is the mechanism of action of the main anti-Alzheimer's drugs, preventing acetylcholine degradation. MAO-B inhibition provides a neuroprotective effect and was also identified as implied in the amyloid cascade, comforting the growing interest of this target for Alzheimer's disease[(d)]. The association of the symptomatic effect of AChE inhibitors and the neuroprotective effect of MAO-B inhibitors appears as a promising path towards the discovery of new drug candidates for Alzheimer's disease.

The targeted molecules are based on the scaffolds of Donepezil, an AChE inhibitor and rasagiline, a known MAO-B inhibitor. We started to develop a new series of molecules which are compromise between the two structures in order to display both activities.



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Development of new inhibitors of SK3 channel to prevent metastasis occurrence

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PO 18

Currently, there is no treatment able to prevent bone metastasis. We discovered that while the abnormal expression of the SK3 channel by cancer cells promotes cancer cell migration and bone metastasis development, its suppression reduces them. Here, we propose to develop SK3 channel inhibitors as a new class of anti-metastatic drugs in targeted and personalized cancer therapy (targeted to SK3 channel and dedicated to patients with cancer cells expressing the SK3 channel).

Lead compound NS8593 is currently one of the SK negative modulator inhibitor. However, the selectivity is current limitation in order to use this compound as anti-metastatic agent.

Our team is developing new synthetic strategies in order to provide novel polyfunctionalized pyridopyrimidines to explore structure-activity relationships and to improve the selectivity of final compounds. To achieve these objectives, we have developed efficient and modular strategies using S_NAr and palladium-catalyzed coupling reactions to modulate the main scaffold.

Among all the 25 compounds tested using patch clamp technique we identified GF495, a chiral compound, as strong inhibitor of SK3 channel with an IC_{50} = 18.4 nM (n=12). This compound was also found to inhibit the SK2 channel with an IC50 of around 1nM (n=7). In vitro experiments showed that this compound was not toxic until 10 µM. Our results show that GF495 (100nM) significantly reduces the migration of five cancer cell lines, expressing SK3 channel including the MDA-MB435s. Furthermore, GF495 has on effect on the migration of breast cancer cells that do not expressed SK3 (MDA-MB231) or in which SK3 channel were knockdown (MDA-MB435-shSK3). In vivo experiments showed that GF495 was not toxic until 20 mg/Kg (i.p. 5 times a week for 2 weeks). Finally, GF495 was tested on a murine model of metastatic breast cancer (i.p.1 mg/kg, 3 times a week for 15 weeks). GF495 treatment reduces dramatically bone metastasis (88.8%) and suppresses uterine and ovarian metastases,

To conclude, GF495 is a new and potent inhibitor of SK3 channel, that show a capacity to reduce the development of metastasis. These promising results encourage us to develop analogues of GF495 molecule, with at least a better selectivity (no effect on SK2 channel). In addition, it seems necessary to characterize the role of SK2 channel in cancer cell biology.

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Evaluation of the antiradical ability of new electrospun nanofibers used as potential wound healing dressings	PO 19

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Aim: Nanotechnology offers a superlative approach to hasten the healing of acute and chronic wounds, by stimulating proper movement through the different healing phases. In nanotechnology, the small sized nanomaterials, nanoscaffolds, nanofibers are used for topical drug delivery for wound healing. The goal of this work is the development of new active electrospun nanofibers based on chitosan and polyethylene oxide (CH/PEO) and their antiradical ability evaluation as new dressing materials in the treatment of wounds. **Materials and methods:** The CH/PEO matrices preparation will be done in two steps: (i) the biopolymeric solutions formation starts by the disolution of CH and PEO in 50% acetic acid by stirring at rt. The two solutions will be mixed in suitable ratios then, over the resulting mixture it was added the active substances (arginine, propolis and insulin) and stirred until an homogeneous solution is obtained;(ii) the electrospun nanofiber formation, where for the electrospinning process it was used a nanospinner INOVENSO, a syringe with different ranges of gauge needle filled with the solution and then applied different flow rates, different values of applied voltage and also different tip-to-collector distance , depending of each sample. The evaluation of the antiradical ability was achieved using the free radical DPPH and radical cation $ABTS^{\cdot+}$ assays. Antiradical capacity was calculated as a inhibition percentage (I%) using the formula: $I\% = (A_0 - A_s/A_0) \times 100$ wherein, A_0=the absorbance value of the 0.1 mM DPPH methanolic solution/ethanolic solution of $ABTS^{\cdot+}$; As=the absorbance value of the sample, read at 30 minutes after adding the methanol solution of DPPH/read at 6 min after adding the solution of $ABTS^{\cdot+}$. **Results and discussions:** Following the researches, new electrospun nanofibres systems based on chitosan and different active substances were performed and evaluated in terms of antioxidant activity, using 2 *in vitro* assays. After analyzing the data obtained, it was concluded that the nanofibers with propolis and *Calendula* extract obtained the best results. **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 propolis and *Calendula* extract in the treatment of wounds. **Acknowledgment:** Scientific research funded by the University of Medicine and Pharmacy "Grigore T Popa Iasi", based on contract no. 27496/20.12.2018.

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Chemical biology of hTFF2 protein: Synthesis, purification and role in inflammatory bowel disorders	PO 20

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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.[a] hTFF2 contains 106 amino acid residues and two trefoil domains formed by 7 disulfide bonds and 15Asn is glycosylated (see Figure). hTFF2 is secreted into gastrointestinal tract and plays important role in protecting the mucosa from insults, stabilize the mucus layer and affect healing of the epithelium and hence holds promise in inflammatory bowel disorders (IBD).[b] However, its 3D-structure, mode of action and receptor are yet unknown.

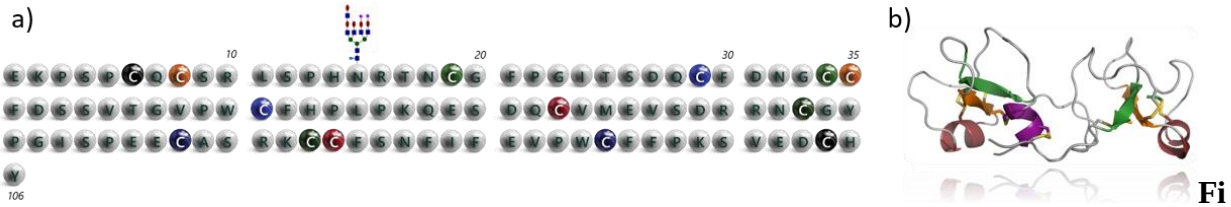

Figure: hTFF2 protein: a) sequence b) structure modeled after homologous porcine TFF2

Their size and cysteine-rich character are the main reason why these peptides have never been successfully synthesized. Only a very limited amounts of hTFF2 can be prepared from human tissue extraction. Here, we describe our chemical synthesis and recombinant synthesis (a yeast expression system designed) for the production of hTFF2 for physiological and biochemical studies. We designed the hTFF2 gene encoding a fusion protein and constructed recombinant plasmids and optimized conditions for protein expression. The secreted hTFF2 was found in a glycosylated and an non-glycosylated form.[c] 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.[c] Subsequently, we have synthesized ^{15}N enriched analogue of hTFF2 protein. Furthermore, we also describe our chemical synthesis approach to synthesize hTFFF2 protein by 4 segment condensation NCL.

Recombinant hTFF2 would serve to identify its receptor by using LRC-TRICEPs method and elucidate its role in intestinal wound healing. Access to ^{15}N enriched analogue of hTFF2 would facilitate analysis of its three dimensional structure by NMR.

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Development of screening assays to identify inhibitors of protein-protein interactions.

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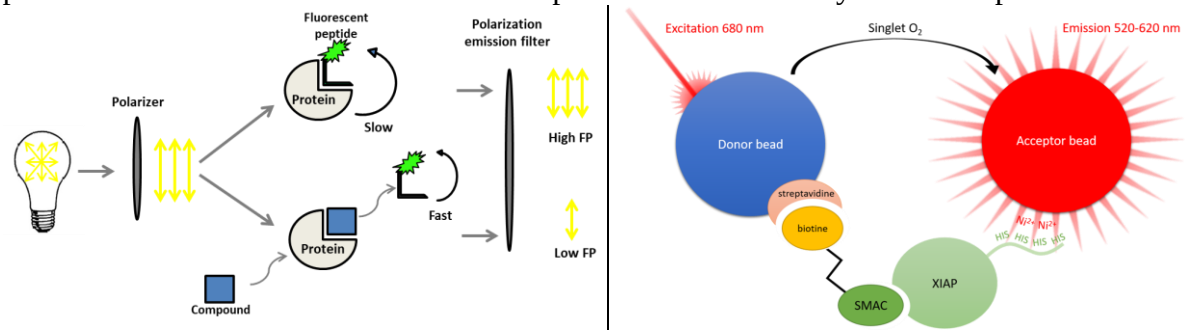
PO 21

For few years, our laboratory is interested in design and synthesis of small molecules as potential disruptors of Protein Protein Interactions (PPIs). Particularly, we are interested in proteins involved in apoptosis process such as anti-apoptotic Bcl-2 family proteins or more recently the X-linked inhibitor of apoptosis protein (XIAP).
Based on its expertise in molecular modelling and in medicinal chemistry, our team has developed a large library of abiotic foldamers able to mimic the secondary structures of proteins.[a] The biological evaluation of these compounds has been realized with our partner (binding affinity by SPR, cellular tests…) and some of them have been shown very interesting anti-proliferative activities against Mcl-1 protein.[b] New molecules are still synthesized in order to disrupt targeted proteins. To study biomolecular interactions in a microplate format, we decided recently to implement screening binding affinities using fluorescence polarization or Alpha technology® (scheme 1). The results obtained allow us to select best compounds before to perform cellular and *in vivo* tests and to improve structure-activity relationship.



Scheme 1. Fluorescence polarization (left) and Alpha technology (right).

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Single-electron reduction of aromatic *N*-oxides by *Plasmodium falciparum* ferredoxin: $NADP^+$ oxidoreductase **Mindaugas Lesanavičius [(1)]*, Alessandro Aliverti [(2)], Jonas Šarlauskas [(1)], Narimantas Čėnas [(1)].** *(1) Department of Xenobiotics Biochemistry, Institute of Biochemistry, Life Sciences Center, Vilnius University, Saulėtekio 7, LT-10257, Vilnius, Lithuania.* *(2) Universita degli Studi di Milano, via Celoria 26, 20133, Milano, Italy*	***PO 22***

Malaria is affecting millions of people worldwide every year and is caused by an apicoplastan parasite *Plasmodium falciparum.* Because of a weak antioxidant system of the parasite, a number of redox cycling compounds including aromatic *N*-oxides are being investigated as possible antiplasmodial agents[a]. To the best of our knowledge a flavoenzyme ferredoxin:$NADP^+$ oxidoreductase of *P. falciparum* (*Pf*FNR) could be the most active generator of free radicals of xenobiotics in the parasite[b]. Here we present the data on its reactions with the derivatives of 3-amino-1,2,4-benzotriazine-1,4-dioxide (tirapazamine, TPZ) and related *N*-oxides (n = 13). The reactions proceed in a single-electron way and are accompanied by the reduction of added cytochrome *c* at 180-195% of NADPH oxidation rate. This reaction is partly inhibited by superoxide dismutase. The bimolecular rate costants of reduction (k_{cat}/K_m) range from 800 $M^{-1}s^{-1}$ (quinoxaline-1,4-dioxide, QDO) to 6.3×10^4 $M^{-1}s^{-1}$ (3-$NHCOCH_3$-TPZ). The reactivity of TPZ, its 1-oxide, QDO, 1,2,4-benzotriazine-1,4-dioxide and 7-substituted TPZ derivatives (n = 5) increases with their single-electron reduction midpoint potential (E^1_7) with a relationship of $\Delta\log(k_{cat}/K_m)/\Delta E^1_7$ = 6.07 ± 1.05 V^{-1}. Alternatively, the reactivity of BTRDO, TPZ and its 7-substituted derivatives including 7-CF_3O-TPZ (n = 7) increases with the σ_p value of substituents ($\Delta\log(k_{cat}/K_m)/\Delta\sigma_p$ = 1.53 ± 0.35). This shows that the reactivity of these compounds is not structurally specific and is governed mainly by their electron-accepting properties. On the other hand, the reactivity of BTRDO, TPZ and 3-substituted derivatives of TPZ (n = 3) does not possess well-expressed dependences on either σ_p or σ_m values for substituents on C3. In our opinion, our data could be instrumental in the design of new representatives of aromatic *N*-oxides with high reactivity in *Pf*FNR-catalyzed reactions thereby possibly being efficient antiplasmodial agents.

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Synthetic design of novel biologically active compounds based on reaction of aromatic aldehydes with ammonia

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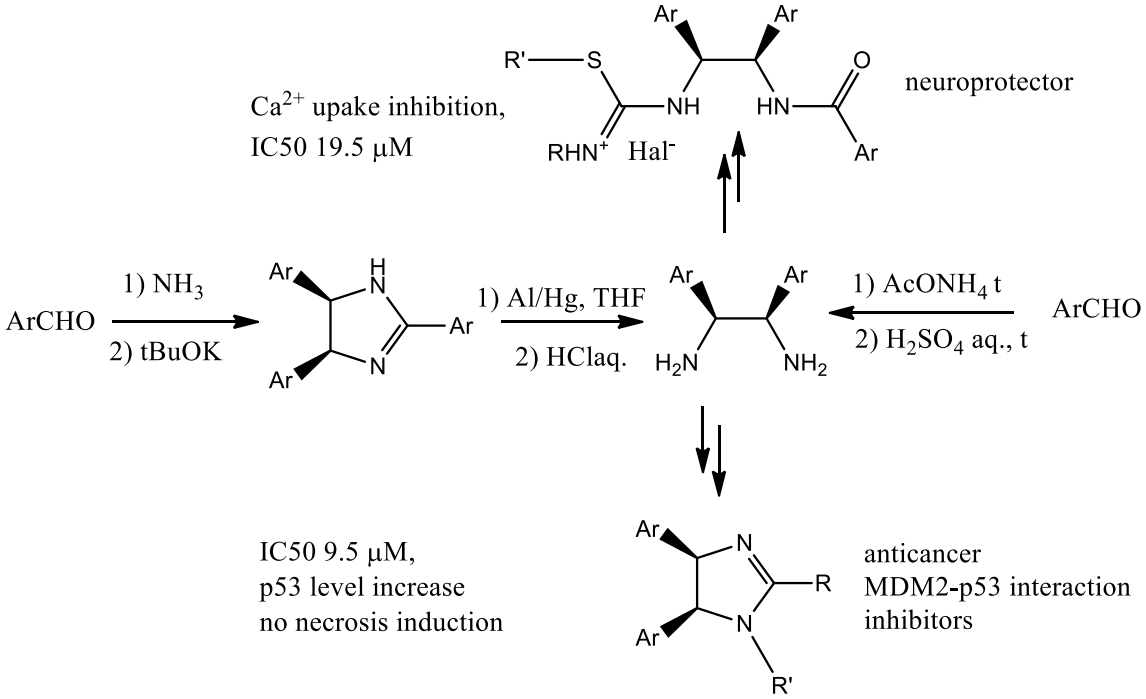
PO 23

Vicinal diamines are versatile tools for synthesis of novel compounds with different types of biological activity. The simple stereoselective synthesis of novel vicinal diamines derivatives was used to obtain new compounds with promising antitumor and neuroprotective activity.



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(b) Russian Chemical Bulletin. — *2009. — Vol. 58, no. 1. — P. 152–155*

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(d) Russian Chemical Bulletin. — 2003. — Vol. 52, no. 3. — P. 674–678

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OPTIMIZED METHOD FOR OBTAINING CHITOSAN NANOPARTICLES	*PO 24*

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Nano delivery systems are widely used to deliver therapeutic agents to specific targeted sites in a controlled manner. **Aim**: This research was focused on the development of an optimized method for chitosan nanoparticles (CSNPs) preparation by ionic gelation method. **Materials and method**: In order to develop appropriate method different parameters such as the concentration of chitosan and tripolyphosphate as well as the stirring speed were varied. The aggregation of the nanoparticles was prevented by using Tween 80 as a surfactant. **Results**: Following the CSNPs optimization process nanoparticles in the range of 231-244 nm were obtained. In presence of the surfactant, the nanoparticles size decrease slightly to 193 nm with increasing the concentration of Tween 80 and remain stable after 72 h of storage. **Conclusions**: The CSNPs obtained after the optimization method by modifying several independent variables can be characterized as having small size and a good stability over time. Given these important features CSNPs are promising materials for targeted drug delivery system.

Acknowledgments: Scientific research was funded by the grant of "Grigore T. Popa" University of Medicine and Pharmacy Iasi, based on contract no 23401/07.11.2018

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[(a)] Anand M, Sathyapriya P, Maruthupandy M, Hameedha Beevi A, Synthesis of chitosan nanoparticles by TPP and their potential mosquito larvicidal application. Front Lab Med., 2018; 2(2): 72-78

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Design, synthesis and biological evaluation of fluorescent probes as diagnostic tools to track bcl-2 dependency in breast cancer	PO 25

Hamid Marzag[(1)*], Karen Plé[(1)], Laurent Maillet[(2)], Sabine Sévère[(2,3)], Patricia Gomez-Bougie[(2)], François Guérard [(2)], Michel Chérel [(2)], Martine Amiot[(2)], Philippe Juin[(2,4)] and Sylvain Routier[(1)]

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Breast cancer remains the leading cause of death by cancer among women. In particular, triple negative breast cancers (TNBCs) and Luminal B (LumB) cancers are difficult to treat with standard chemotherapy although this is almost systematically used as a first line of treatment. For these cases, initial results may be promising, but 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.

There is thus a need to confirm that responsive tumors encompass chemosensitive ones and to define tools that could diagnose BCL-2 dependency to stratify patients. Sylvain Routier's team in Orleans has synthesized several fluorescent probes based on ABT-199 structure and using two chromophores (***Figure 1***) and the CRCINA has evaluated their efficacy to modulate the interaction between Bcl-2 and its intracellular partners. Work is in progress to develop new probes based on fluorescent and radiolabeled BH3 mimetics.

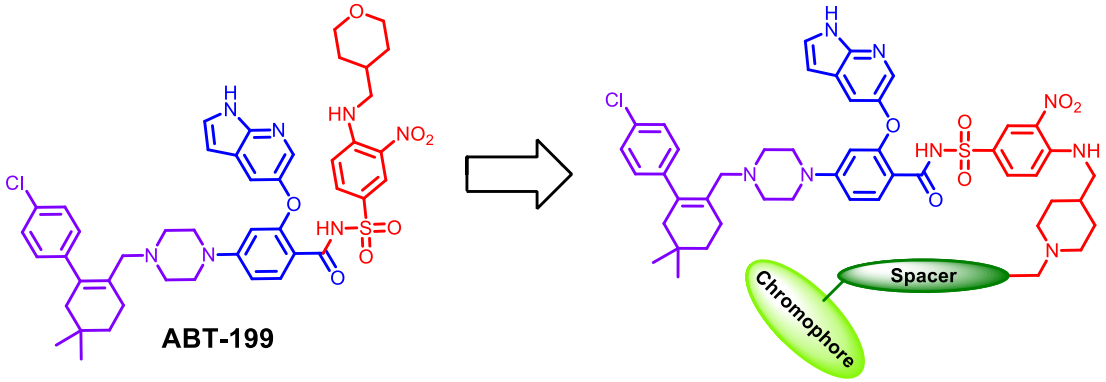

Figure 1: Design of fluorescent probes from ABT-199

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Tools and cancer models for assessment of Mcl-1 targeting molecules biological effects

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Cancers are responsible for 9.6 million deaths each year worldwide, mainly due to their chemoresistance. Protection against apoptosis cell death plays an essential role in this chemoresistance. The anti-apoptotic protein Mcl-1 is involved in this protection against apoptosis and is over-expressed in a wide variety of tumor locations. This protein is therefore a promising therapeutic target for cancer treatment, as shown by the development programs for Mcl-1 inhibitors lead by pharmaceutical industry. In this context, our teams have been collaborating for several years to determine the biological efficacy of innovative Mcl-1 inhibitors.

In order to screen these molecules, the model of interest chosen is a chemoresistant ovarian tumor line (IGROV1-R10) whose survival depends on two anti-apoptotic proteins: Bcl-xL and Mcl-1. In these cells, it is therefore necessary to inhibit the two proteins concomitantly to promote cell death by apoptosis. The use of a pharmacological molecules known to inhibit one of them thus makes it possible to identify molecules likely to inhibit the second. The screening of a library of compounds on cells in which Bcl-xL has been inhibited thus allows the identification of molecules potentially inhibiting Mcl-1. This is made possible by techniques studying apoptosis such as morphological observation or cell cycle distribution monitoring. Other techniques allow the acquisition of numerous parameters in real time and in high throughput manner (cell adhesion and growth by impedancemetry, cell imaging with the use of probes specific to cell death).

However, the specificity of molecules as inhibitors of Mcl-1 must be verified by techniques that allow specific understanding of protein-protein interactions, such as Fluorescence Polarization Assay (FPA), Surface Plasmon Resonance (SPR), Bioluminescence Resonance Energy Transfer (BRET) or immunoprecipitations.

Finally, the interest of the molecules identified can be validated on other models, closer to clinical reality, such as tumor organoid (micro-tumors obtained from patient tumors) or patient tumors implanted in immunodeficient mice (PDX).

These different models and tools thus make it possible to screen molecules designed by chemists on the basis of their Mcl-1 inhibition potential and to validate their antitumor effects on more complex models in order to provide preclinical evidence of their efficacy.

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Drug/β-amyloïd peptide/membranes interactions: Development and application in drug discovery of multiparametric tools enabling the characterization of this interactome of interest for Alzheimer's disease	PO 27

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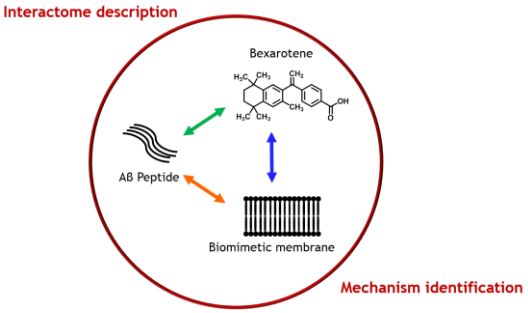
The study of molecular interactions at the level of biological membranes is a key issue for the screening and the development of new drugs. Alzheimer's disease (AD) is the most common form of senile dementia in the world and is the leading socio-economic problem in health care. The appearance and progression of this neurodegenerative disease are associated with the aggregation of the amyloid-β peptide (Aβ).

A therapeutic strategy against AD consists in the development of molecules able to interfere with specific steps of Aβ aggregation. To identify such compounds, experimental methods are required to monitor and characterize the Aβ peptide during its fibrillation process. These methods must be simple enough to remain compatible with drug discovery. We propose to combine experimental methods to allow a multiparametric characterization of potential $A\beta_{1\text{-}42}$ fibrillation modulators, by integrating liposomes of defined composition as biomimetic neuronal membranes. It is indeed established that neuronal lipids are an important factor in the formation of amyloid fibers and their toxicity.[a]

Two liposomal formulations models of neuronal membrane were defined, developed, and characterized.[b] Effects of both on $A\beta_{1\text{-}42}$ peptide or an oligomeric mutant, oG37C, aggregation process were evaluated through studies of aggregation kinetic, membrane toxicity, and peptide conformation (ATR-FTIR). The data were correlated to precisely describe the peptide/membrane interactions. A known aggregation inhibitor, bexarotene, was analyzed through our procedure to highlight some original interactome insights.



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[(b)] W. Smeralda *et al.* Eur. J. Pharm. Sci. **2019**

* Correspondence: marc.since@unicaen.fr

Study of new 4-aminoalcohol quinoline hybrids as antimalarial drugs	PO 28

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Malaria is a deadly infection caused by parasites of the genus *Plasmodium*. Amoung five species able to infect humans, *P. falciparum* is the most virulent and common. Despite being avoidable and treatable, malaria continues to be one of the most widespread infectious disease in the world with 228 millions of cases in 2018.[(a)] This tropical illness affects highly Africa (93 %), mainly pregnant women and children. The main challenge of the fight against malaria is the parasite resistance to antimalarial medicines. The World Health Organization recommends artemisinin-based combination therapy (ACT) to prevent and reduce this risk.[(a)(b)] However, the efficiency of these therapies failed due to the emergence of parasites with both decreased sensibily to artemisinin and resistance to the partner drug.[(c)] Mefloquine (MQ) is an aminoalcohol quinoline used in combination with artesunate. Genic mutations or overexpression of efflux pump are the main cause of quinoline resistance. Thus, covalent conjugation of quinoline-based antiplasmodial drug with efflux pumps inhibitors or reversal agent can allow to struggle resistant parasites.[(d)]

Our laboratory has previously developped an asymmetric synthesis to prepare 4-aminoalcohol quinoline enantiomers as MQ analogs.[(e)(f)(g)] Some of them were active on nanomolar range against 3D7 (chloroquine-sensitive) and W2 (chloroquine-resistant) *P. falciparum* strains with a good selectivity index.[(f)(h)(i)] Interestingly, (*S*)-enantiomers were 2 to 15 fold more active than (*R*)-enantiomers and some quinolines remain actives against MQ-resistant or multidrug resistant strains.[(f)]

Follow this previous work, we are interested to develop a new class of 4-aminoalcohol quinolines as hybrid compounds able to limit the resistance with efflux transporters. We are focus on conjugaison of efflux pump inhibitor patterns with a 4-aminoalcohol quinoline scaffold. The design of these hybrids will be discussed and their synthesis will be described. First results concerning their antimalarial activity against *Pf*3D7 and PfW2 and their cytotoxicity will be debated.

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Synthesis of novel benzimidazolone-based quinone reductase 2 (QR2/MT3) ligands	PO 29

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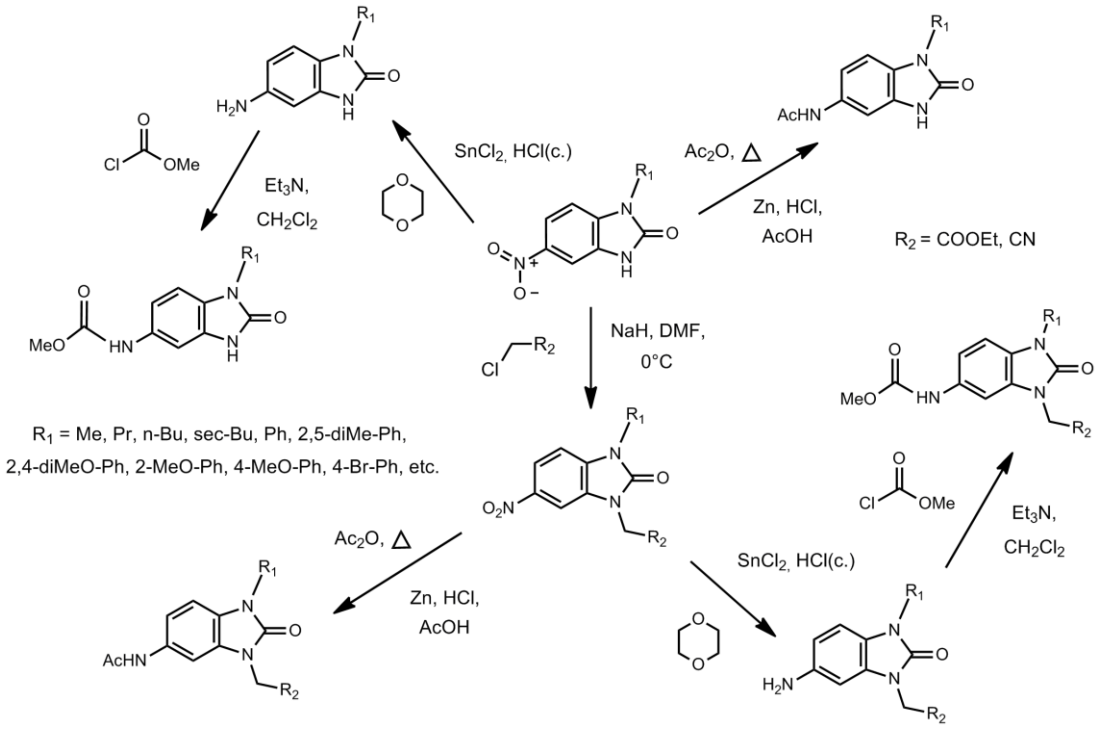
QR2 is a low-affinity melatonin receptor (MT3), that has neuroprotective, antioxidant, and IOP-decreasing properties. It is one of the perspective molecular targets for therapy of several diseases, such as glaucoma and Alzheimer's disease, that are of great social importance.

Recently it was shown, that 2-oxindole derivatives express noticeable MT3 activity, as an amide group is important for active site binding[(a)]. Therefore, it was reasonable to search for bioisosters with that fragment, as they have high chances to maintain the activity levels – so are benzimidazolones. The simple method of synthesis for 5-nitrobenzimidazolones was developed earlier in our group.

Further modifications include one-pot reduction and acylation of the nitrogroup in 6-position or 2-step synthesis of carbamoyl-derivatives. These substituents were chosen as they have shown the highest activity on 2-oxindoles. To increase the solubility of benzimidazolone derivatives in water, the nitrogen in 1-position was modified by a -CH_2COOEt fragment, as it can be hydrolyzed in the last step to obtain soluble salts, or by a -CH_2CN fragment. These substituents were also rationally chosen, because 2-oxindole leaders have the -CH_2COOH or -CH_2CN group in 3-position.



This work was supported by the Russian Foundation for Basic Research (Project 20-03-00915).

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Tirapazamine derivatives as substrates of mammalian thioredoxin reductase	
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Mammalian thioredoxin reductases (TrxRs) contain FAD, catalytic disulfide and selenosulfide in the active center, and catalyze NADPH-dependent reduction of disulfide protein thioredoxin, which performs antioxidant, protein repair and other functions. In addition, TrxRs reduce quinones, nitroaromatics and other prooxidant compounds, thus initiating their redox cycling and oxidative stress [a,b]. These reactions confer prooxidant properties to TrxRs, and may comprise a certain approach in cancer chemotherapy. The derivatives of 3-amino-1,2,4-benzotriazine-1,4-dioxide (tirapazamine, TPZ) are mainly considered as redox active hypoxia-selective anticancer agents [c], however, possessing certain prospects in the treatment of oxic tumours. In order to characterize their possible targets, we examined the reactions of recombinant human cytosolic TrxR (TrxR-1) with 7 TPZ derivatives, whose single-electron reduction potentials (E^1_7) ranged from -0.575 V to -0.345 V. The reactions were accompanied by superoxide dismutase-sensitive cytochrome *c* reduction which points to the formation of free radicals. The reactivity of compounds (k_{cat} = 0.02-0.1 s^{-1}, k_{cat}/K_m = 110-1140 $M^{-1}s^{-1}$) did not depend on their E^1_7 values. However, in a broad sense this correlated with higher reactivity of other oxidants possessing higher E^1_7 values, *e.g.* juglone (E^1_7 = -0.09 V, k_{cat} = 10.3 s^{-1}, k_{cat}/K_m = 2.73x10^5 $M^{-1}s^{-1}$), menadione (E^1_7 = -0.20 V, k_{cat} = 13.6 s^{-1}, k_{cat}/K_m = 4.94x10^4 $M^{-1}s^{-1}$), and *p*-dinitrobenzene (E^1_7 = -0.26 V, k_{cat} = 1.1 s^{-1}, k_{cat}/K_m = 2000 $M^{-1}s^{-1}$). Interestingly, low m.w. TrxR from *Thermotoga maritima* also reduced 7-CF_3-TPZ (E^1_7 = -0.345 V) with low rate (k_{cat} = 0.28 s^{-1}, k_{cat}/K_m = 330 $M^{-1}s^{-1}$, thus pointing to a limited importance of these reactions for cytotoxicity of TPZs.

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Optimization of the synthesis of chitosan-tripolyphosphate nanoparticles.	***PO 31***

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In the last time current researches focused on nanotechnology, based on its important applications in different fields including drug delivery systems. Nanotechnology improved some properties of the drugs such as solubility, bioavailability, biological effects and toxicity degree. Nanoparticles (NPs) are one of the most intense studied nanosystems, which are frequently used due to their important advantages such as small particle size (1 - 1000 nm), large ratio active surface area/volume, high stability, feasibility of different drugs encapsulation, high carrier capacity and efficacy.
The aim of this study was to optimize the synthesis of chitosan-based nanoparticles (CSNPs) and to study the influence of different parameters on the formulation process. The CSNPs were prepared by ionic gelation method using sodium tripolyphosphate (TPP) as cross-linking agent and two types of chitosan (CS) (low and medium molecular weight).
In order to optimize the preparation method, several parameters such as the CS and TPP concentration, pH of CS solution, stirring speed and reticulation time have been varied. The CSNPs synthesis was monitored by dynamic light scattering (DLS) technique.
The optimized CSNPs with size of 208.8 ± 8.5 nm were obtained using the following parameters: 0.1% CSLMW (pH = 4.7 - 4.8), 0.1% TPP, stirring for 1 h at 1000 rpm. Based on this optimized method, the synthesized CSNPs will be used in the next applications, as drug delivery systems for antidiabetic and anti-inflammatory drugs.

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Total Synthesis of (±)-Thallusin

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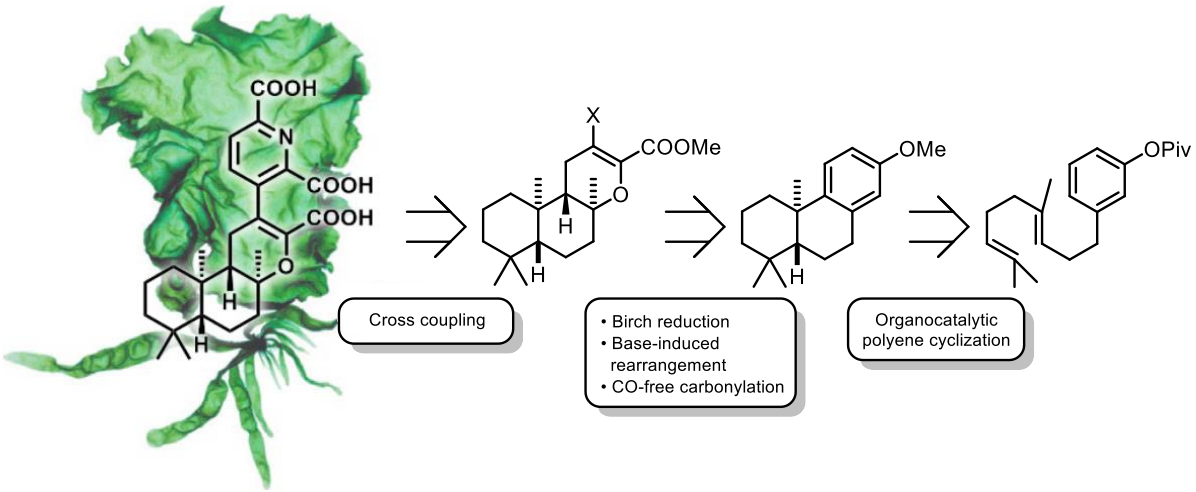
(-)-Thallusin, a terpenoid-hybrid metabolite, was isolated from epiphytic marine bacteria YM2-23 in 2005 and triggers the development of algal tissue (thallus) at concentrations as low as 10^{-15} g/L in macroalgae.[a] Thallusin mediates highly relevant symbiotic chemical communication between macroalgae and epiphytic bacteria in the marine environment.[b-e] However, its general impact on the underlying processes and its mode of action remains to be clarified. Thus, with growing interest in this area[f], synthetic access of (-)-thallusin and analogues, is highly desirable in order to study structure-activity-relationships in depth.



We developed a novel, concise and scalable total synthesis of (±)-thallusin with a biomimetic polyene cyclization catalyzed by an artificial cyclase[g] as the key step. Further steps are a base-induced rearrangement[h] to obtain the oxygen-containing C-ring, a CO-free carbonylation[i] and a transition-metal catalyzed cross coupling. Efforts towards an enantioselective total synthesis will be presented.

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Trimethoprim analogues as novel DHFR inhibitors: Synthesis, Biological Activity and Molecular Modeling Study.

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Folate metabolism has long been recognized as an important and attractive target for the development of therapeutic agents against bacterial, parasitic infections [1], and cancer therapy [2]. Dihydrofolate reductase (DHFR) is an essential enzyme which catalyses the reduction of dihydrofolate acid (7,8-dihydrofolate, DHF) to tetrahydrofolic acid (5,6,7,8-THF) using reduced nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor [3,4].
The most successful inhibitor against bacterial DHFR is trimethoprim (**TMP**) [2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine], which belongs in a synthetic, broad-spectrum antimicrobial agent [5]. This work was targeted to design novel candidates of antitumor drugs, which are structurally related to netropsin (NT) and TMP (**Figure 1**). In this work, we intended to obtain new series of **TMP** analogues (**1-6**). Solid phase synthesis seems to be a good method to obtain **TMP** analogues containing amide bonds [6]. Molecular docking was used to confirm their affinity to bind dihydrofolate reductase enzyme, as well as DHFR inhibition assay. Data from the ethidium displacement test showed their DNA binding capacity. A test confirming the possibility of DNA binding in a minor groove as well as determination of association constants were performed using calf thymus DNA, T4 coliphage DNA, poly(dA-dT)$_2$ and poly(dG-dC)$_2$. Additionally, the mechanism of action of the new compounds was studied. In conclusion, some of new analogues inhibited DHFR activity stronger than **TMP**, what confirmed that the addition of amide bond into the analogues of **TMP** increases their affinity towards DHFR.

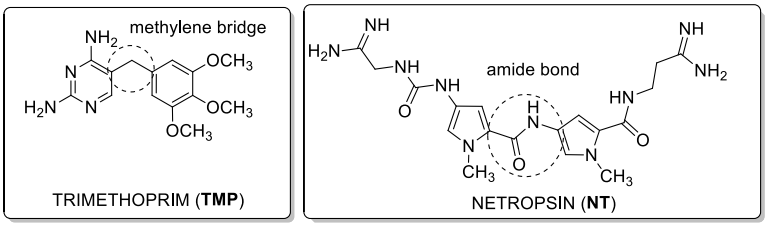

Figure1. Structure of trimethoprim (**TMP**) and netropsin (**NT**) as model compounds.

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Synthesis of a new potent clickable analogue of 5-OP-RU for the study of MAIT cells biology

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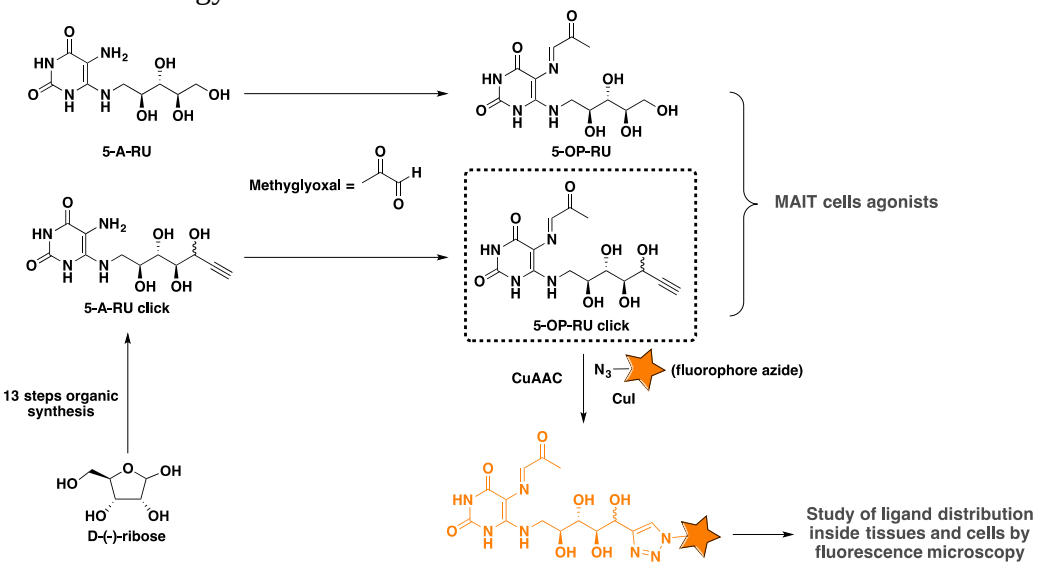
Mucosal Associated Invariant T Cells (MAITs) are an abundant subset of innate like T lymphocytes expressing a semi-invariant T cell receptor. It is now well established that these cells play a key role in antimicrobial immunity since they recognize small organic molecules derived from microbial vitamin metabolism[(a)]. So far, the most potent MAIT cells agonist known is the riboflavin (vitamin B2) derived metabolite 5-OP-RU (5-oxopropylideneamino-ribityluracil) [(b)]. It is obtained from the condensation reaction between the metabolite 5-A-RU (5-amino-ribityluracil) and endogenous methylglyoxal.

Since the last two decades, there has been a growing interest in the study of MAIT cells notably to understand their protective role against infection diseases and their potential implication in pathogenesis. Despite all these efforts, many fundamental questions are still remaining. To investigate some of them, we decided to develop new chemical tools that could allow us to track and visualize MAIT cells ligands inside biological tissues and cells. To this end, we managed to synthetize an active "clickable" analogue of 5-OP-RU in which we added an alkyne group so that the molecule can react with azide functionalized fluorophore by CuAAC (copper-catalyzed alkyne-azide cycloaddition). Biological evaluation of the new synthetized ligand showed a similar potency in activating MAIT cell *in vitro* compare to 5-OP-RU. Moreover, first bio-orthogonal experiments allowed us to visualize the ligand into murine fibroblasts by epifluorescence microscopy after click reaction. We therefore proved that this interesting tool can now be used in cell biology and will potentially give us new information about MAIT cells biology.



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Kinetic reactions of Rh(III) complexes in presence of an ionic liquid with biologically important ligands

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Interactions between biomolecules and transition metal complexes, such as Rh(III) complexes that attract increasing attention as potential pharmacological agents, represent a very important part of medicinal chemistry.(a) Ionic liquids (ILs) are a family of liquid compounds consisting solely of ions at room temperature, and they provide an attractive alternative to traditional organic solvents for both laboratory and industrial purposes because of their potential as "green" solvent and reaction media. (b) Within this study, we examined the kinetics of the substitution reaction for Rh(III) complexes containing different tridentate N-donor ligands with 5'-GMP, as a biologically important ligand. To show if the presence of 1-Ethyl-3-methylimidazolium ethyl sulfate (ionic liquid) had an effected on the kinetics of these reactions, experimentally obtained results in HEPES buffer and in HEPES buffer in presence of this ionic liquid were compared. Analysis of the interaction capabilities of these complexes with CT-DNA and BSA were also performed using Uv-Vis spectrophotometry, fluorescence spectroscopy, and viscosity measurement. To better understand these reactions, docking measurement were made.

Acknowledgments
This research was financially supported by Ministry of Education, Science and Technological Development Project No. 172011.

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Development of novel therapeutic strategy for the selective delivery of anticancer drugs	PO 36

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During the last decades, numerous anticancer agents have been developed in order to fight against cancer. However, most of these drugs lacks any intrinsic selectivity causing severe side effects as the consequence of the destruction of healthy tissues. With the aim to solve this issue, vectorization strategies have been designed to selectively destroy the tumor without affecting normal cells. Within this framework, our team has designed recently a multivalent platform consisting in three cyclodextrins able to non-covalently encapsulate hydrophobic cytotoxic agents within their cavities and a maleimide allowing the *in situ* binding to plasmatic albumin through Michael addition (**Figure 1**). In combination with doxorubicin, our molecular platform produced a higher therapeutic efficiency than doxorubicin injected alone for the treatment of lung tumors in mice, without inducing side effects. These preliminary results indicated that this novel targeting strategy may be useful to enhance the therapeutic index of currently used anticancer drugs.

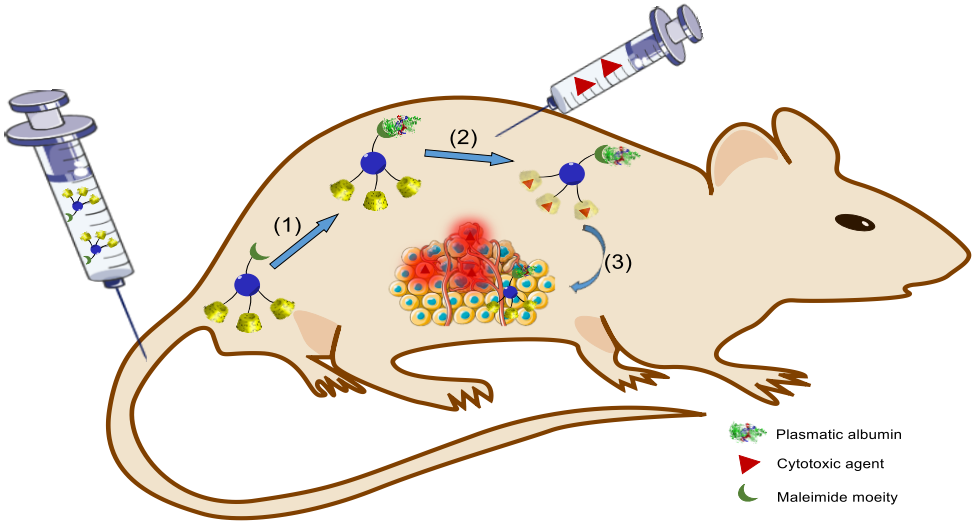

Figure 1 : Principle of the tumor targeting. (1) : After i.v administration, the maleimide moiety covalently binds to plasmatic albumin. (2) Injection of the drug and *in vivo* complexation *with cyclodextrins*. (3) Selective accumulation in tumors and drug release.

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Contribution of three (3) medicinal plants of Senegalese flora in the management of sickle cell disease

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Abstract

Sickle cell disease is a major public health problem in Africa and many other areas across the world. Many drugs that are available for treating the disease are insufficiently effective, toxic, or too expensive. Therefore, there is a pressing need for safe, effective, and inexpensive therapeutic agents from indigenous plants used in traditional medicines. In Senegal, a lot of plants are proposed by traditional healers to manage the sickle cell disease, among them *Combretum glutinosum*, *Leptadenia hastate and Maytenus senegalensis*. These plants were studied in this work. Methanolic and ethyl acetate extracts of part of these plants were evaluated on SS sickles type to determine their anti-sickling potential. Antiradical properties of methanolic extract of *C glutinosum* were evaluated using the DPPH radical as oxidant. Total phenolic content of the methanol extract was determined. Phytochemical screening of the crude extract of methanol revealed the presence of tannins, saponins, phenols, anthracenics and flavonoids. Results show a good antisickling effect of methanol extracts with a maximum antisickling revers of 72, 80 and 81% for respectively *M senegalensis*, *L hastate* and *C glutinosum* at 10 mg/mL in 120 min incubation while ethyl acetate extract at the same conditions has 62, 66 and 77% of sickling reverse. Arginine used as the positive reference has 67% sickling reverse activity at 120 min of incubation. The measured IC_{50} were 0.65 and 0.163 for respectively the methanol extract and ascorbic acid. Antiradical powers 0.155 and 0.62 respectively for methanol extract and ascorbic acid were calculated from the effective concentrations. The results of this study confirm the traditional use these three plants in the management of sickle cell disease.

Keywords: Sickle cell disease; oxidative stress; medicinal plant; antisickling activity; antioxidant activity.

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Synthesis, characterization, oxidase biomimetic catalytic activity and optoelectronic properties of metal(II) complexes with 1,10 – phenanthroline derivatives

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ABSTRACT

A novel bioactive metal(II) complexes with the molecular formulae of $[M^{II}L]$ where M= Cu(II), Ni(II), Co(II) and Zn(II); L = 1,10 - phenanthroline derivative were synthesized. They were characterized using elemental, thermal analysis, molar conductance, cyclic voltammetry, magnetic moment measurements as well spectral (FT-IR, UV–Vis and ESR) techniques. Physico-chemical studies suggested that an octahedral geometry for the cobalt(II), nickel(II), copper(II) and zinc(II) complexes. Powder X-ray diffraction spectral data has been used for structural elucidation of the phenantroline complexes. The DNA interaction study performed by UV–visible spectroscopy as well as by molecular docking suggests the tested compounds interact with DNA through intercalation mode. All compounds including ligand and complexes were also engaged with different bacterial (Escheria coli, Staphylococcus aureus, Bacillus subbtilis) and fungal strains (Candida albicans, Aspergillus flavus and Aspergillus niger) in order to check the inhibitory action of titled compounds. The results showed that the metal complexes have greater antimicrobial activities than ligand. Additionally, the superoxide dismutase (SOD) mimetic activity of the complexes was measured and discussed herein. The green emission of the materials was confirmed by using UV light as well as fluorescence spectrophotometers. Bandgap energies of these materials were obtained by both experimental and theoretical calculation of cyclic voltammetry, UV–Visible spectrophotometer and DFT calculation. I–V characteristic analysis used to determine the threshold voltage (V_{on}) of the materials. The observed experimental results of the materials have promising to be applicable for opto-electronic applications.

Keywords: Complexes; catalytic; copper enzymes; optoelectronic; mimetic.

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New insights into a potential therapeutic target regulating Unfolded Protein Response and subsequent inflammation in liver and muscle	PO 39

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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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Antibacterial and antimycobacterial activities of extracts and steroid saponins from *Solanum chrysotrichum*

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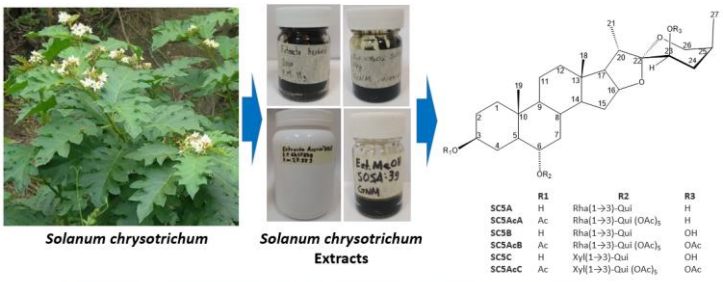
From *S. chrysotrichum* were prepared the hexane extract, dichloromethane extract, methanol extract, and aqueous extract. The methanol extract was fractioned yielding 5.1 g of a mixture of three steroid saponins which were acetylated in order to purify and characterize the constituents as derivatives. The obtained compounds were deacetylated by saponification to obtain the *neo*-steroid saponins SC5A, SC5B and SC5C which were the *neo* forms of previously reported compounds[a,b]. The antibacterial activity of extracts and compounds was evaluated *in vitro*[c] against clinical isolates of drug-resistant bacteria, displaying the organic extracts good antibacterial activity against carbapenem resistant *Acinetobacter baumanni* and *Pseudomonas aeruginosa* (MIC: 125 µg/mL), and good activity for SC5C against gram-positive bacteria (MIC: 25-12.5 µg/mL). The *in vitro* antimycobacterial activity[d] was determined against *Mycobacterium tuberculosis* H37Rv and the multidrug-resistant strain G122, and good activity was observed for the hexane extract against both strains (MIC: 125 µg/mL). This work represents the first report of antimycobacterial activity for *S. chrysotrichum* extracts and good antibacterial activity for the *neo*-steroid saponin SC5C.



Determination of antibacterial and antimycobacterial activities by microdilution methods

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Salinomycin derivatives kill cancer stem cells via lysosomal iron targeting	PO 41

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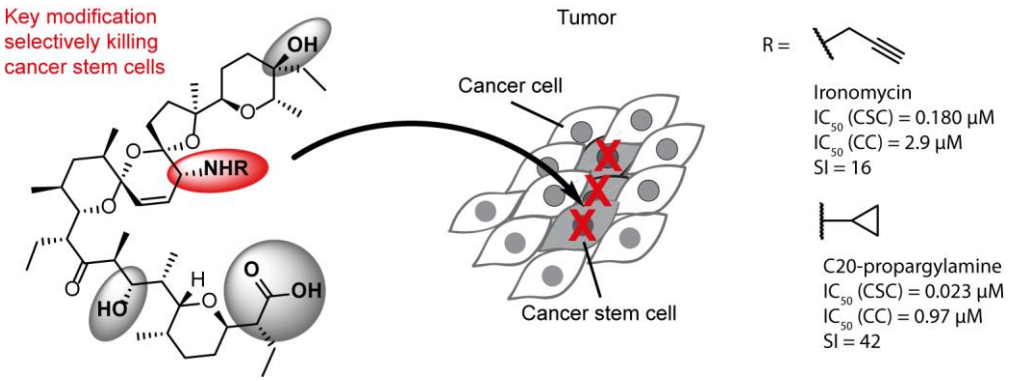
Salinomycin (Sal) is a polyether ionophore, which exhibits a large spectrum of biological activities including the capacity to selectively eradicate cancer stem cells (CSC).[1] There is increasing evidence that Sal and its derivatives are promising candidates for the development of drug leads against CSC. It has been demonstrated that Sal and its C20-propargylamine derivative (Ironomycin) accumulate in lysosomes and sequester iron in this organelle.[2] We synthetized a library of derivatives of Sal, including products of C20-amination, C1-esterification, C9-oxidation and C28-dehydration. We have then evaluated the biological activity of these compounds against transformed human mammary epithelial cells HMLER $CD24^{low}/CD44^{high}$, a well-established model of breast CSC, and HMLER $CD24^{high}/CD44^{low}$ cancer cells deprived of CSC properties.[3] Unlike other structural alterations, derivative displaying cyclopropylamine at position C20 showed a strikingly low IC_{50} value of 23 nM against HMLER $CD24^{low}/CD44^{high}$ cells leading to a 42-fold selectivity over HMLER $CD24^{high}/CD44^{low}$ cells. Thus, this study reports highly selective molecules to target the CSC niche, potentially providing the basis for the development of drugs that can tackle cancer resistance.



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