

UMR 7042

Laboratoire d'Innovation
Moléculaire et Applications



LIMA

LIMA, *Laboratoire d'Innovation Moléculaire & Applications*

Gathering a roughly 90 collaborator staff, the *Laboratoire d'Innovation Moléculaire & Applications* (LIMA, UMR 7042) is a three-tiered Unistra/UHA/CNRS laboratory which is localized both in Strasbourg and Mulhouse.

This laboratory results from the merger of the *Laboratoire de Chimie Moléculaire* (LCM, UMR 7509) of *Université de Strasbourg* and the *Laboratoire de Chimie Organique et Bioorganique* (COB, EA 4566) of *Université de Haute-Alsace* in Mulhouse.

The LIMA is a decisive actor for the scientific site coherence and becomes the largest laboratory dedicated to research in molecular chemistry in Alsace. One of the LIMA's priorities is to support the emergence of new research fields, to promote fundamental research and to stimulate fruitful interactions with the socio-economic environment. The overall scientific aim of the LIMA is to develop innovative methods dedicated to molecular synthesis, to validate new therapeutic strategies and to apply them in different fields (pharmaceutical and agro-chemistry, eco-responsible chemistry and materials chemistry).

The laboratory is organized in 9 research teams (6 in Strasbourg and 3 in Mulhouse) related to specific scientific domains. In addition to this, a strong technical support is provided by an analytical platform at the cutting edge of modern techniques, dedicated to molecular chemistry and biochemistry, which is spread over the two Alsatian sites.

Frédéric Leroux
Director



Strasbourg

Jean-Philippe Goddard
Deputy-director



Mulhouse

7

Full professors

11

Lecturers

12

CNRS researchers

12

Support staff

10

Post-Docs

35

PhD Students

> 60

Research papers/year

16

Patents

8

Industrial partnerships

> 60

Academic partnerships

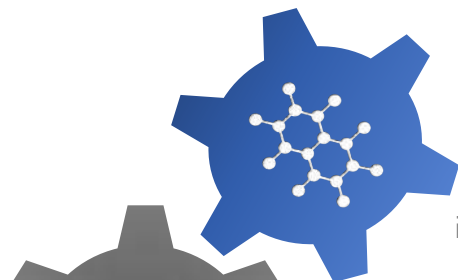
Financial supports



European collaborations



From **fundamental research** to **leading innovations**



Our teams are specialized in numerous fields of organic chemistry, from **methodology developments** to their applications in the fields of **life science, agriculture, catalysis, materials** ...

The laboratory is world recognized for its work on **chirality, synthesis** of naturally and/or biologically related compounds, **glycochemistry, fluorine chemistry, radical chemistry** and **material synthesis** with application in electronics and photovoltaics.

Through that research process, many **universities and companies** already collaborate with us to **create knowledge** but also to develop the **innovations of the future**.

... also training the leaders of tomorrow

Fully integrated in the French and international research landscape, our teams are also dedicated to the programs of partner universities. Teaching in chemistry faculties or in the two chemical engineering schools (ECPM & ENSCMu), our staff give high level courses to train the chemistry leaders of tomorrow into a European research campus, EUCOR.



Chimie Médicinale & Phytopharmaceutique (S. Albrecht)

• “Medicinal Chemistry”

Target-based approaches focused on the design of metalloenzyme inhibitors with particular emphasis on inhibiting the M1(alanyl) and M17(leucyl) aminopeptidase families involved in many metabolic disorders (angiogenesis, inflammation, autoimmune diseases, and cognitive decline) and essential for the development of pathogenic agents (*Plasmodium*, *Toxoplasma*, *Neisseria*). We have discovered a modular platform, based on aminobenzosuberone scaffold, inhibiting potently and selectively each aminopeptidase family. Several medicinal chemistry programs (recombinant enzymes, SAR studies, prodrugs) are currently in progress.

Phenotypic approach against *Plasmodium falciparum* to identify novel fast acting, transmission blocking anti-malarial agents as well as exploration of their mode of action.

• “Phytopharmaceutical activities”

We are focalized on grapevine trunk diseases. We developed different strategies to address these issues: i) mode of action investigation on known fungicides, ii) new specific fungal target identification, iii) plant-pathogen interactions analysis and iv) resistance study of *Vitis Vinifera* subspecies.

Keywords: Metalloenzyme inhibitors, multi-omic approach, metabolic and parasitic diseases.

Biomolécules, Synthèse & Méthodologie (N. Blanchard)

The “Biomolecules, synthesis and methodology” (BSM) team focuses on **2 research areas** with an emphasis on new concepts of reactions having applications in natural product chemistry, life- or material sciences.

• “New synthetic methods”

In a first area of research, we develop synthetic methods based on cycloaddition reactions, metal-catalyzed cross-couplings (with a special focus on copper) and hydroelementation of heterosubstituted alkynes, allowing a straightforward preparation of heterocyclic synthons of interest for the pharmaceutical and agrochemical industries

• “Natural products”

The second area of research is centered on natural products. This area is sub-divided in two themes, the first one deals with the total synthesis of mycolactone A/B, a polyketidic natural product of importance in a mycobacterial disease, Buruli ulcer. The second theme aims at the identification, analysis and applications of natural products (bioactive natural products from endophytes; chemotaxonomy and phytochemical studies of plants; studies on hybrid organic-inorganic materials for cosmetic or medical uses).

Keywords: Pericyclic reactions, catalysis, heterocycles, total synthesis, natural products.

Chimie Organométallique Appliquée (M. Chetcuti)

Research is focused on the synthesis of organometallic compounds, the discovery of new reaction pathways, and the applications of organo-transition metal chemistry to homogeneous catalysis.

• “Nickel chemistry”

Our recent research has focused on the chemistry of relatively thermally- and air-stable nickel(II) complexes which bear both cyclopentadienyl ligands and N-heterocyclic carbene ligands. Nickel is a cheap and abundant metal and exhibits a unique reactivity due to its ability to access Ni(I) and Ni(III) oxidation states in comparison to Pd and Pt.

• “C-H Activation”

A serendipitous discovery has led us into the field of C–H activation. A number of readily prepared nickel(II) complexes are able, in the presence of a base, to activate sp^3 C–H bonds that are in an alpha-position relative to a coordinated nitrile or ketone group. This subsequently led to the development of nickel(II) based catalysts for the alpha-arylation of aromatic ketones.

• “New catalytically active organometallics”

Current and future projects are based on enlarging our library of nickel NHC complexes; grafting of NHC ligands onto calixarenes to investigate the catalytic, and the complexation-of-anion and studying the chemistry of other metals.

Keywords: Ni Chemistry, homogeneous catalysis, NHC complexes.

Synthèse & Catalyse Asymétrique (F. Colobert)

- **“Total synthesis of biologically active compounds”**

Our ambition is to address unsolved and persisting challenges in the synthesis of complex organic scaffolds hence allowing preparation of biologically relevant compounds and their analogues i.e. complex pimaranes or neoclerodanes as well as cyclophanes for which the challenging atroposelective ring closure of their *seco*-precursors is studied.

- **“Medicinal Chemistry”**

Synthesis of selective low molecular weight inhibitors of VEGFR as antiangiogenic products and of CDC25 phosphatases as anti-cancer compounds. We designed new antagonists and agonists of the hedgehog pathway for cancer stem cells inhibition. Another axis focuses on the preparation of fluorinated analogs of antibacterial pristinamycin IA to provide better pharmacokinetic parameters.

- **“Development of new stereoselective methods”**

Our research focuses on metal catalyzed asymmetric C-H functionalization to control both axial and central chirality (design of new bicoordinating stereogenic directing groups and new ligands). Besides a new approach based on the *design and synthesis of chiral hypervalent iodines* pave the way towards both metal free and metal-catalyzed stereoselective unprecedented couplings. In addition, mild C-C couplings by means of dual catalysis combining C-H activation and photocatalysis are targeted.

Keywords: C-H activation, chiral hypervalent iodine, medicinal chemistry, total synthesis

Synthèse Organique & Molécules Bioactives (P. Compain)

Our research projects combine the development of new synthetic methodologies and the design of natural-like heterocycles of biological and therapeutic interest.

The overall aim is to develop efficient synthetic access to original glycomimetics in order to accelerate the discovery of potent inhibitors of carbohydrate-processing enzymes and then target diseases (mainly rare genetic disorders).

- **“New synthetic methodologies”**

We have recently synthesized unprecedented four-membered carbasugars and spiranic iminosugars. As organic chemists, we were attracted by the number of synthetic challenges that such structures represent with several contiguous asymmetric centres, small cycles and a high density of functional groups.

- **“Multivalency”**

Recent studies in SYBIO team concerning multivalent effect in glycosidase inhibition showed that cyclopeptoid platforms displaying up to 48 copies of an iminosugar inhibitor are up to 170,000 fold more potent than the corresponding monovalent model. Application to glycosidases of therapeutic interest in the field of cystic fibrosis has led to the first description of a multivalent effect for correcting protein folding defects in cells. This approach should find applications for the treatment of a number of protein folding disorders.

Keywords: Glycomimetics, multivalency, synthetic methodologies, enzyme inhibitors.

Chimie Bioorganique & Médicinale (E. Davioud-Charvet)

- **“Anti-infective drugs & redox chemistry”**

A research applied to medicinal chemistry, in particular, to the synthesis of inhibitors of NADPH-dependent oxido-reductases is conducted with the aim to develop anti-infectious agents (e.g. menadione series) and to identify new targets for antiparasitic chemotherapy. Our interdisciplinary activity spans from the synthesis (inhibitors, redox-cyclers, fluorescent tools, photoaffinity labels of targeted proteins) to enzymology and understanding of the mechanisms of action *in situ* in living parasites. Among our recent major achievements, we showed that potent antiparasitic drug-candidates, displaying a 3-benzyl-menadione scaffold, induce distinct phenotypic effects in parasites according to their substitution patterns. Our research efforts are now focused on the optimization of our antimalarial lead plasmodione, a fast acting and transmission blocking agent, and on the development of chemical tools for metabol- and proteo-omics *via* a click & fish strategy.

- **“(Bio)(in)organic chemistry & fluorescent tools”**

Unraveling the mechanisms of action is also guided by physicochemical approaches under quasi-physiological conditions to describe the interactions of anti-infectious agents with relevant biotargets. Structure-activity relationships are synergized to chemo informatics (local collaboration) to optimize the drug design. Efforts are also directed to the development of ratiometric fluorescent probes for local pH or redox measurements in living parasites.

Keywords: Anti-infective drugs, bio(in)organic chemistry, fluorescent tools, redox chemistry.

Chimie Radicalaire, Hétérocyclique et Interfaces (J.-P. Goddard)

The research activity of the Radical, Heterocyclic Chemistry and Interfaces team follows two main axes related to organic synthesis and its applications.

- **“Radical Chemistry and Photoredox Catalysis”**

Our efforts are focused on the development of new methodologies for the generation of free radicals based on environmentally friendly and sustainable pathways. We have been concerned for many years with the development of different aspects of SET processes with light for synthetic applications. Biomimetic organic synthesis is also developed by the team for radical and ionic transformations with artificial enzymatic catalyst.

- **“Organic Chromophores”**

We study new chromophores as photoacids or for non-linear quadratic optics. Specific aromatic compounds are applied to doped materials in the fields of optical electronics but also to the transport and processing of information. The photoacid aspect of these compounds is studied to confine photoreaction in submicron volumes, to control and spatially direct the photo-generated acid gradient, with a shorter writing time.

Keywords: Radical chemistry, photochemistry, methodology, chromophore chemistry.

Chimie Organique & Hétérochimie Appliquées (F. Leroux)

The philosophy of our research is based on a fruitful interplay of several objectives:

- **“Heterochemistry”**

This axis is mainly dedicated to fluorine chemistry. Due to the increasing importance of fluorine in pharmaceutical and agrochemical active ingredients, we develop new, mild and cost-effective methods to access high-value building blocks bearing emergent fluorinated substituents, either on heteroaromatic scaffolds or stereogenic C_{sp3} centers. A large part of the work in this axis is carried out in the context of a CNRS-Unistra-Bayer joint laboratory.

- **“Organometallic Chemistry”**

In this research topic, both transition metal-catalyzed and transition metal-free methods are investigated, especially to access diversely functionalized aromatic compounds. In particular, we developed a transition metal-free and stereoselective synthesis of chiral biaryls via aryllithiums and arynes, which allowed access to axially chiral biaryls of high interest.

- **“Frustrated Lewis Pairs”**

FLPs were discovered a decade ago as a Lewis acid and a Lewis base able to operate synergistically to activate small molecules such as dihydrogen. They are the focus of intense interest since they can serve as an alternative or a complement to transition metal-based catalysts. The young field of FLPs and related Lewis superacids is still very limited in terms of asymmetric catalytic applications. This is the objective we tackle in our group.

Keywords: Fluorine, heteroelements, asymmetric synthesis, FLP.

Chimie des Matériaux Moléculaires (J.-F. Nierengarten)

Traditionally centered on fullerene chemistry, significant efforts have also been focused on dendrimers, luminescent transition metal complexes, macrocyclic compounds and π -conjugated systems. The group has also successfully crossed interdisciplinary boundaries to pioneer new areas at the interfaces with biology and materials science.

- **“Fullerene chemistry”**

Our expertise includes the design and synthesis of versatile fullerene building blocks that can be easily derivatized and incorporated within molecular constructs having applications in biology or materials science.

- **“Phosphorescent metal complexes”**

The group has combined fullerenes with transition metal complexes to generate photoactive molecular devices, and has become increasingly involved in the field of phosphorescent metal complexes. In particular, he has developed strongly luminescent Cu^I complexes and has been among the first to show the potential of such compounds for light emitting applications.

- **“Fullerene & pillar[n]arene nanoscaffolds”**

The group has designed versatile fullerene and pillar[n]arene scaffolds that allow the combination of multiple molecular entities to rapidly generate sophisticated multifunctional molecules.

Keywords: Fullerene, macrocycles, dendrimers, luminescent complexes.

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