PERSONA CIÈNCIA EMPRESA
UNIVERSITAT RAMON LLULL

Master Thesis (TFM) Projects (2020-2021)

Master's Degree in Pharmaceutical Chemistry

TFM at IQS

TFM-1
Title: Design and synthesis of MNK inhibitors for treatment of cancer
Summary: The oncogene eIF4E is a key factor in the regulation of protein synthesis and is found to be overexpressed in many cancers. MAP Kinase Interacting Kinases 1/2 (MNK1/2) regulate the function of eIF4E by phosphorylation and, for this reason, the pharmacological inhibition of MNKs is considered a new therapeutic strategy for the treatment of cancer. During the past years, our group in collaboration with Hospital de la Vall d'Hebron has been working on the pyrazolo[3,4-*b*]pyridinic systems as MNK inhibitors. The present project is focused on the design and synthesis of new pyrazolo[3,4-*b*]pyridine derivatives with potential activity against MNK1/2. This project is open to a PhD position.
Director: Dr. Roger Estrada, Dr. Raimon Puig de la Bellacasa
Laboratory: Laboratory of Molecular Design and Laboratory of Synthesis
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TFM-2
Title: Synthesis of novel inhibitors to target key proteins in pancreatic cancer
Summary: Pancreatic cancer is the one cancer type with worse prognosis. Targeted therapies consist in blocking the signal transduction pathways overexpressed in cancer, particularly those triggered by FGFR2 and IGFR receptors. This project is focused on the synthesis of new dual inhibitors targeting key proteins in pancreatic cancer using straightforward microwave assisted synthetic methodologies.
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TFM-3
Title: Synthesis of novel inhibitors to target a key protein in peripheral T-cell lymphomas
Summary: Peripheral T-cell lymphoma is a group of lymphomas derived from mature T and NK cells, usually associated with an aggressive clinical course and for which effective treatments are not yet available. ZAP-70 is an essential kinase in the proximal signaling of the T cell receptor (TCR). The application of drug design methods allowed our research group to identify a set of compounds with potential activity against ZAP-70. This project is focused in obtaining these compounds by organic synthesis, including the design of the synthetic route and product characterization.
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TFM-4
Title: Synthesis of new potential CXCR4 inhibitors
Summary: Cytokines receptors are involved in many regulatory pathways. Particularly, the G-protein-coupled receptor CXCR4 are related with tumour growth, HIV-1 infectivity, inflammation, stem cell migration, among other processes. Although our research group has wide experience in designing and synthesizing new drug candidates in this area of research. In this project, we will develop new synthetic strategies allowing us obtaining a new family of potential and selective CXCR4 antagonists.
Director: Dr. Raimon Puig de la Bellacasa, Dr. Albert Gibert
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TFM-5
Title: New approaches to face myotonic dystrophy
Summary: Myotonic dystrophy (DM) is a rare disease which pathogenic mechanism relies on the formation of poly(CUG) RNA triplets during the transcription of the DMPK gene. These RNA expansions sequestrate MBNL proteins, which play a pivotal role in alternative splicing. Downregulation of MBNL in muscle cells provokes myotonia and leads to a multisystem disorder. For this reason, gaining insights into RNA druggability caught our attention and the application of molecular modeling techniques allowed us to design small molecules able to target the pathogenic RNA and DM protein-related targets. In this regard, this project is focused on the synthesis of new chemical compounds with potential activity against DM.
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TFM-6
Title: Design and synthesis of a family of analogues for cancer inhibitors via rational selection
Summary: Neoplasms have been in the last decade the main topic of study in research. In fact, these diseases are the target of 26% of the last FDA approved drugs. As an example, Tazverik & Ayvakit, have recently been accepted (January 2020) to treat epithelioid sarcoma and metastatic gastrointestinal stromal tumor respectively. However, the active principle ingredient (API) of a drug consists in a molecule selected from a large combinatorial library defined by the Markush structure described as a claim in the patent of the drug. By this project, it is expected to demonstrate there is part in this chemical space protected that has not been explored which can hide more active molecules. Therefore, a family of cancer inhibitors will be firstly selected, its combinatorial library developed, and a rational selection will be performed using Python coding in order to select a group of feasible synthetic analogues that represent the chemical space. Finally, the student will synthesize the selection in the laboratory to further test their activity and contrast with the original hit in the search for new leads.
Directors: Dr. Jordi Teixidó, Dr. Roger Estrada
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TFM-7
Title: Covalent binding strategy: Synthesis of suitable linkers for pyrido[2,3-*d*]pyrimidines structures as a potential anticancer agents
Summary: During the last years, our group has designed and developed many compounds with pyrido[2,3-*d*]pyrimidine as a main scaffold. Among several applications, some of these compounds showed good activity as tyrosine kinase inhibitors, which are one of the main targets to fight against cancer. Until now, reversible interaction between drug and protein has been the most extended one (hydrogen bond, van der Waals, …). Recently, a new approach is emerging, focusing the research efforts on designing new entities with the ability to create an irreversible interaction with their therapeutic targets. The covalent inhibitors possess numerous advantages: increased biochemical efficacy, longer duration of action, the high potential for improved therapeutic index due to lower effective dose, and the potential to inhibit certain drug resistance mechanisms. This project is focused on the introduction into the pyrido[2,3-*d*]pyrimidine scaffold suitable linkers allowing a covalent binding with tyrosine kinase FGFR.
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TFM-8
Title: Synthesis and study of a new family of Hexaphyrins for Cancer Therapies
Summary: Porfirinoids are conjugated macrocycles with a wide range of applications in many fields, from phototherapy to materials science (*Chem. Rev*. **2017**, *117*, 2481-2516). In the present work, it is proposed to prepare a new hexapyrrolic porphyrinoid with potential applications in biomedicine. Furthermore, the structure and electronic properties of the new macrocycle will be studied by computational calculations and single-crystal X-ray diffraction.
Director: Dr. David Sánchez-García
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TFM-9
Title: Dual Release Nanocontainers for Combined Therapy of Cancer
Summary: The primary objective of the project is taking advantage of nanotechnology for the development of dual release devices. The combined administration of drugs enhances their therapeutic activity because of synergetic mechanisms (*Drug delivery* **2018***, 25 (1),* 1137-1146). In this work, a new stimuli-responsive nano-container for the dual release of two antitumoral drugs will be prepared and characterized.
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TFM-10
Title: Preparation and characterization of mesoporous silica nanoparticles decorated with proteins
Summary: The aim of the project is the use of proteins as valves to control the release of a drug from the pores of mesoporous silica nanoparticles. The proteins, attached to the surface of the particle by means of a stimulus-sensitive linker, would act as intelligent caps and would endow of an enhanced biocompatibility to the system.
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TFM-11
Title: Synthesis of novel polymeric nanoformulatios as mRNA vaccines for lung cancer immunotherapy
Summary: Lung cancer is the most devastating cancer type worldwide. Current standard-of-care, consisting on systemic chemotherapy, produces severe side effects without increasing patients' survival. for this reason, cancer immunotherapy aroused as a promising alternative. Although it demonstrated great results for easy-to-access tumors, such as melanoma, specifically for lung cancer, its efficacy remains limited, mainly due to the poor performance of delivery vectors. For this reason, in the current project we propose the use of targeted polymeric nanoparticles as cancer vaccines. The main aim of the project. is to design novel polymeric formulations able to selectively target dendritic cells and promote their (re)activation against tumor associated antigens. Within this project, the student will be in charge of the synthesis of the new polymers, as well as the in vitro tests required to confirm the the immunogenic tumor cell death.
Director: Dr. C. Fornaguera, Dr. S. Borrós, Dr. N. Artzi
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TFM-12
Title: Applications of the Aza-Michael Reaction I Flow Chemistry for the Synthesis of API
Summary: Analogues of histamine are important API used for vasodilation and fall in blood pressure, sleep-wake regulation, controlling gastric acid release or for the treatment of erection disfunction and sexual function, schizophrenia or multiple sclerosis. Their synthesis usually involves an aza-Michael reaction, which produces some undesired byproducts. Our group recently discovered specific conditions for the retro-aza-Michael reaction which can be used in combination of Flow Chemistry to improve the industrial production of histamine analogues. This project involves the use of different Michael acceptors and aza-donors to spread the applicability of the method in collaboration with the industrial company LEBSA.
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TFM-13
Title: Cyclic peptides with new scaffolds for drug delivery to the brain
Description: Brain diseases affect one out of five people at some point in life. Almost all drugs designed to treat brain diseases are unable to reach the brain in therapeutically relevant amounts because they cannot cross the blood-brain barrier (BBB). Thus, delivery systems that enable transport across the BBB are highly coveted. In this project you will develop new protease-resistant peptides that enable drug transport across the BBB. For such purpose, you will learn how to generate peptides with non-canonical amino acids via solid-phase peptide synthesis and work on several cyclization strategies. Furthermore, you will conjugate the peptides to relevant therapeutic cargoes and study the transport of the constructs in cellular models of the BBB. For more information on the project and the team please contact us and see https://www.oller-salvia.com/
Director: Dr. Benjamí Oller-Salvia
Laboratory: Biomaterials lab, Bioengineering Department
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TFM-14
Title: Development of a hydrophillic tuneable coating for systemic gene delivery to brain tumours
Description: Glioblastoma (GBM) is the most malignant form of brain tumour and life expectancy upon diagnosis is roughly 15 months. Gene therapy has a great potential to overcome the limitations of current treatments and to provide an efficient therapy for GBM. Poly(beta-amino ester)s (PBAE)s are among the most promising non-viral gene delivery vectors. However, selectivity and stability of PBAEs for systemic administration is limited. In this project you will develop pH-sensitive coatings to decrease the transfection promiscuity of the pBAE-oligonucleotide polyplex. The pH-sensitive coating will be guided to the tumour with targeting ligands and shed at the target site unleashing the full transfecting potential of the polyplex. In this project you will synthetize polymers, generate nanoparticles, modify them using bioorthogonal chemistry, and study their stability and transfection capacity in cells. For more information on the project and the team please contact us and see https://www.oller-salvia.com/
Director: Dr. Benjamí Oller-Salvia, Dr. Salvador Borrós
Laboratory: Biomaterials lab, Bioengineering Department
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TFM-15
Title: Development of caged antibodies targeting cancer stem cells
Summary: Cancer stem cells are the main cause of tumor resistance and relapse. Drug delivery systems targeting these cells must avoid affecting other stem cells in healthy tissues. Hence, developing drug delivery systems that only release the drug in the tumour site is critical. In this project **you will develop caged targeting antibodies (pro-antibodies) that are only activated in the tumor microenvironment**, thereby providing a safe and efficient treatment. You will learn how to engineer antibodies and how to site-specifically modify them to incorporate chemical handles. You will link these handles to masking peptides that will only be shed in the tumour. You will test the selectivity of these caged antibodies in a variety of cell

types. For more information on the project and the team please contact us and see https://www.oller-salvia.com/
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TFM-16
Title: Modification of a multilayered biomembrane in order to reproduce some human skin characteristics.
Summary: Since 2013, ethical considerations regarding the use of animals or volunteers for scientific research are being reinforced in the European Union. In the field of Dermatology, the use is ethically regulated for drugs. In Cosmetics field, it is already forbidden. Notwithstanding that, 80% of countries still allow cosmetics to be tested on animals. Recent news are stating out that the European Parliament is adopting a resolution calling for a global ban on animal testing for cosmetics products before 2023.
For these reasons, Regulatory Authorities and Industry are demanding artificial skin alternatives to human skin as there is a serious need for skin substitutes.
The present project consists of modifying the construction method of a 3-layered biomembrane, in order to change some specific parameters of the membrane so it can reproduce real human skin characteristics. These parameters can be; the nº of pores or pore size, the hydrophobic/hydrophilic capacity, the layers thickness, the inclusion of different biomaterials in each layer, etc. Afterwards, the membrane will be characterized. Lastly, some permeation studies of different molecules will be performed.
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Laboratory: Chemical engineering and Material Science.
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TFM-17
Title: Study of hydrophilic and hydrophobic drugs permeation through a synthetic skin.
Summary: Since 2013, ethical considerations regarding the use of animals or volunteers for scientific research are being reinforced in the European Union. In the field of Dermatology, the use is ethically regulated for drugs. In Cosmetics field, it is already forbidden. Notwithstanding that, 80% of countries still allow cosmetics to be tested on animals. Recent news are stating out that the European Parliament is adopting a resolution calling for a global ban on animal testing for cosmetics products before 2023.
For these reasons, Regulatory Authorities and Industry are demanding artificial skin alternatives to human skin as there is a serious need for skin substitutes.
The present project is focused on the permeation of a multilayered biomembrane, which can mimic human skin permeation when applying hydrophilic or hydrophobic topical drugs.
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TFM-18
Title: Modification of a 3-layered biomembrane for testing different kinds of skin defects: wrinkles/scars/stretching marks and hydrolipidic layer alteration.
Summary: Since 2013, ethical considerations regarding the use of animals or volunteers for scientific research are being reinforced in the European Union. In the field of Dermatology, the use is ethically regulated for drugs. In Cosmetics field, it is already forbidden. Notwithstanding that, 80% of countries still allow cosmetics to be tested on animals. Recent news are stating out that the European Parliament is adopting a resolution calling for a global ban on animal testing for cosmetics products before 2023.
For these reasons, Regulatory Authorities and Industry are demanding artificial skin alternatives to human skin as there is a serious need for skin substitutes.
The present project consists on simulating certain aspects of a wrinkle/scar/stretch mark skin and of dry/dehydrated skin on a 3-layered biomembrane. Afterwards, the efficacy of some APIS/final products applied on the membrane will be tested.
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TFM-19
Title: Synthesis of potential psychoactive compounds and development of analytical methods to evaluate their purity
Summary: The illicit drug market has changed remarkably in the last decade, and a huge number of new psychoactive substances (NPS) have been labeled and marketed as legal highs, bath salts or research chemicals. NPS is a new term used to describe analogues of traditionally abused drugs, not controlled by the 1961 Single Convention on Narcotic Drugs of USA and most of them may have strong rewarding effects, be toxic, have abuse liability, and may be potentially lethal, posing an imminent threat to public health. However, information about long-term adverse effects or risks are still unknown or very limited.
The aim of this project is to synthesize a family of potentially new psychoactive substances (NPS) from the group of synthetic cathinones. Moreover, the development of new analytical methodologies based on liquid chromatography (HPLC) coupled to diode array detector (DAD) and mass spectrometry (MS) will be carried out in order to characterize and evaluate their purity. The mechanism of action of these compounds will be evaluated in further studies.
Director: Dr. Xavier Berzosa (xavier.berzosa@iqs.url.edu) / Dr. Cristian Gómez Canela (cristian.gomez@iqs.url.edu)

TFM-20
Title: Evaluation of the effect of variations in the structure of synthetic cathinones in their psychoactive properties
Summary: The illicit drug market has changed remarkably in the last decade, and a huge number of new psychoactive substances (NPS) have been labeled and marketed as legal highs, bath salts or research chemicals. NPS is a new term used to describe analogues of traditionally abused drugs, not controlled by the 1961 Single Convention on Narcotic Drugs of USA and most of them may have strong rewarding effects, be toxic, have abuse liability, and may be potentially lethal, posing an imminent threat to public health. However, information about long-term adverse effects or risks are still unknown or very limited.

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The aim of this project is to synthesize a family of potentially new psychoactive substances (NPS) from the group of synthetic cathinones. Once synthesized, the effect of the different moieties/functionalities in their mechanism of action will be evaluated, especially regarding the potential to inhibit monoamine (dopamine, noradrenaline and/or serotonin) uptake and the interaction with monoamine transporters and receptors involved in drug abuse, as well as their psychostimulant and rewarding effects in animal models.
Director: Dr. Xavier Berzosa (xavier.berzosa@iqs.url.edu) / Dr. Raul López Arnau (raullopezarnau@ub.edu)

TFM-21
Title: *Exploring of new routes to precursors for rapid PET ^{18}F-radiofluorination*
Summary: Positron Emission Tomography (PET) is a powerful imaging technique capable of *in vivo* probing of biological processes. Among the active radionuclide employed, fluorine-18 (***^{18}F***) is one of the most popular PET radiotracers with a half-life of $t_{1/2}$ = 110 min. In our group, an on-going line of research aims to use either the high-valent iodine or boron-based molecules as precursors for rapid [^{18}F]-radiofluorination. Despite these exciting advances, synthetic access to many such structures is still highly challenging, particularly for the more complex biologically active cores. To explore strategies to overcome these hurdles, we have teamed up with the Radiochemistry and Nuclear Imaging Platform at CIC biomaGUNE San Sebastián. In this TFM project, we are seeking a motivated chemistry student to join this project to synthesize new classes of hypervalent iodane precursors to advanced radiotracers.
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TFM-22
Title: *BN isosterism: New Synthetic Opportunities in Drug Discovery*
Summary: The chemistry of organoboron compounds has been primarily dominated by their use as powerful reagents in synthetic organic chemistry. However, recently, the incorporation of boron as part of functional targets has emerged as a useful way to generate diversity in organic compounds. An interesting strategy is the replacement of a CC unit with its isoelectronic BN unit, so called BN/CC isosterism. Such strategy has emerged as a viable approach to increase the chemical space of compounds relevant to materials science and biomedical research. Successful incorporation of BN-heterocyclic building blocks into key structures is intimately associated with the elaboration of versatile synthetic routes to access these molecules. So, the aim of this proposal is to contribute to the development of this promising area in two ways: a) the implementation of new chemical methodologies to gain access to BN isosteric structures and b) study some interesting potsfunctionalization of stablished BN cores to enlarge their potential applications in biomedical sciences.
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