DEVELOPMENT OF MEDICAL CHEMISTRY PROGRAMS

Description

The Laboratory of Medical Chemistry of the Universidad Complutense de Madrid (MedChemLab) carries out research projects based on the development of new therapeutic strategies aimed at the achievement of effective treatments for diseases of high incidence. The approach of this ambitious objective is structured from the perspectives of medical chemistry and biological chemistry.

The different medical chemistry projects encompass drug discovery programs in which, through the development of new compounds with activity in different therapeutic targets, their potential for the treatment of specific pathologies such as Parkinson's disease (allosteric receptor modulators Of dopamine D1), diabetes (allosteric modulators of glucagon-like peptide-1 receptor, GLP-1), spinal cord injury (lysophosphatidic acid receptor antagonists, especially the LPA1 and LPA2 subtypes), bacterial infections Multi-resistant (inhibitors of the bacterial protein FtsZ) and tuberculosis (antibodies conjugated with antibiotics) is addressed.

Medicinal Chemistry Lab – UCM

How does it work

The different programs of medical chemistry are carried out using methodologies developed in the MedChemLab:

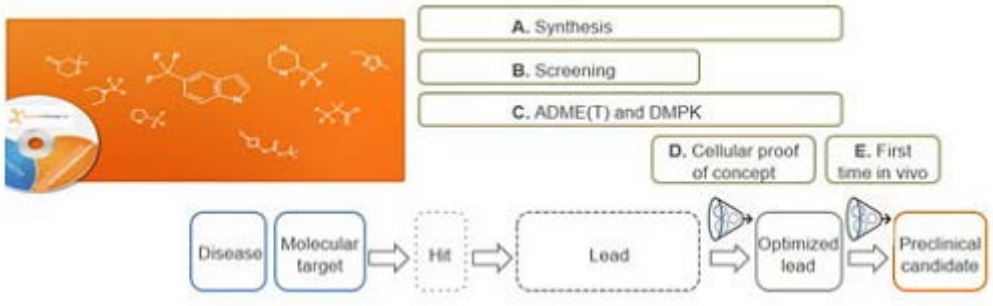
Design of new compounds using computer models: pharmacophore, virtual screening, docking, ADME parameter analysis (clogP, solubility, stability, permeability, bioavailability).

Synthesis of the proposed new compounds: approach of the synthetic routes, preparation of the reactions, preparation and purification of the desired products.

In vitro screening of the new synthesized compounds: binding assays, cellular cytotoxicity, enzymatic ELISA inhibition, calcium mobilization, cAMP levels, protein expression levels, nuclear magnetic resonance (STD, HSQC, ...) experiments, etc.

ADME (T) properties and pharmacokinetic (PK) study of active compounds: solubility, chemical, serum and metabolic stability in hepatic microsomes (LM), albumin binding (HSA), cellular permeability (PAMPA), plasma and brain levels B / P), cytochrome inhibition (CYP), cardiotoxicity (hERG).

In vitro pharmacological characterization of selected compounds: functional activity (dose-response curves), selectivity, signaling pathways (cAMP levels, calcium mobilization, protein phosphorylation), insulin secretion in pancreatic cells, phenotypic antibacterial study.



Stages of the preclinical phase in a medical chemistry drug discovery program

Advantages

The most innovative aspects of the different research lines developed in the Laboratory of Medical Chemistry are: (i) contribution of compounds generated by rational design with novel structural skeletons that represent an extension of the pharmacologically active chemical space and, therefore, for the potential interest for complete development by the pharmaceutical industry; (ii) contribution of different mechanisms of action derived from the developed structural diversity, thus differentiating them from other drugs available in the market; (iii) contribution of drugs of potential usefulness for the treatment of pathologies that do not have adequate therapies at present and (iv) development of new methodologies of interest at academic level but simultaneously extrapolable to real problems in the pharmaceutical industry and therefore of potential Interest for this.

Where has it been developed

The present work is developed in the Laboratory of Medical Chemistry (MedChemLab) located in the Department of Organic Chemistry of the Faculty of Chemical Sciences of the Universidad Complutense de Madrid. The research team is led by Professor María Luz López Rodríguez and composed by the professors Bellinda Benhamú Salama and Silvia Ortega Gutiérrez, the professors contracted Mar Martín-Fontecha Corrales and Angeles Canales Mayordomo, two postdoctoral researchers, four predoctoral researchers, two Students of masters, two students of degree, two Erasmus students and a technician. The group includes researchers with different areas of specialization (organic chemistry, medical chemistry, biochemistry, cell and structural biology and molecular modeling).

The laboratory has all the equipment and instrumentation of a modern laboratory of organic chemistry and biological chemistry, necessary to carry out all the experiments of the different programs of medical chemistry in development. Robotic purification systems, microwave reactor, hydrogenation systems, polarimeter, infrared, ultraviolet and fluorescence spectrometers and a high efficiency liquid chromatography coupled to mass spectrometry are available. We also have access to the different Research Support Centers (CAI) of the UCM of nuclear magnetic resonance, proteomics, microanalysis, X-rays, electron microscopy, cytometry, etc.

The solid trajectory of the research group is reflected in the funding of 14 projects financed by public entities and private companies (UCB Pharma, Italfarmaco, Vivia Biotech) in the last 10 years, as well as in its scientific productivity. During the last 5 years, 36 articles have been published in the most prestigious journals in the areas of medical chemistry and biological chemistry (Nature, Nat. Commun., Nat. Neurosci., J. Natl. Cancer Inst., Angew. Chem. Int. Ed., J. Am. Chem. Soc., Allergy Clin. Immunol., Proc. Natl. Acad Sci. USA, J. Neurosci., Chem. Commun., Oncotarget, Breast Cancer Res. Int J. Cancer, Chem. Eur. J. Med. Chem., ACS Chem. Biol., J. Biol. Chem.), With an average impact index of 10.82.

Among the most relevant contributions of the last 10 years are the contribution to the study of the G protein-coupled receptors (GPCRs), in particular the clinical phase progression of several 5-HT1A agonists in collaboration with SchwarzPharma and UCB Pharma (4 patents And 9 articles in J. Med. Chem.); The identification of a new type of cannabinoid receptor located in mitochondria (5 articles in Science, J. Neurosci., J. Biol. Chem., Nat. Neurosci. And Nature); The validation of the FASN and ICMT enzymes as new targets for the treatment of cancer (2 international patents and 7 articles in Clin. Cancer Res. Breast Cancer Res., J. Med. Chem., Int. J. Cancer and Oncotarget.) ; The validation of the MAGL enzyme in the treatment of multiple sclerosis (an article in Angew. Chem. Int. Ed.) and the development, together with Vivia Biotech, of a powerful allosteric modulator of the GLP1 receptor for the treatment of type diabetes 2 (two patents).

And also

Partners are sought from public or private organizations related to the pharmaceutical industry and interested in the development of new drugs.

Responsible Researchers

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