

Medicinal Chemistry I and Analytical Chemistry Section



Sonia Martínez

Section Head

Sonia Martínez was born in Horguen (Switzerland) in 1968. She graduated from the *Universidad Autónoma de Madrid* in Organic Chemistry in 1991.

She then worked at the chemical company Exchem Ltd, New Oakley (UK), and returned to Spain after eight months to study for her Master's Degree at the *Instituto de Química Orgánica (CSIC)* in Madrid.

In 1993 she joined GlaxoWellcome (now GlaxoSmithKline) as a PhD student to search for Phosphomannose Isomerase inhibitors as antifungal targets. As a result of this work she was awarded her PhD in 1998 at the *Universidad Autónoma de Madrid*.

She was then appointed as a laboratory Head at the Spanish biotechnology company *Roviall Química*, Murcia, where she focused on the design and synthesis of libraries of compounds applying High Throughput Synthetic Technologies.

One year later she joined Johnson & Johnson Pharmaceutical Research (a division of Janssen Cilag, Toledo, Spain) where she worked for 10 years as a Senior Scientist in the High Throughput Medicinal Chemistry Department. During this time she led the HTMC group for 1 year in medicinal chemistry working mainly on CNS projects as well as on metabolic disorders and oncology projects. She is co-holder of 8 patents.

Sonia Martínez joined the CNIO as Head of Section of Medicinal Chemistry I and Analytical Chemistry in October 2009.

Summary

We are involved in two main projects: PIM inhibitors (in an advanced hit-to-lead phase) and the CDK8 project (in the hit generation phase). For the PIM project, we have obtained two types of inhibitors: very strong and selective PIM inhibitors (PIM1 selective and pan-PIM), with no FLT3 activity; and other inhibitors with a similar profile to reference compound SGI-1776 (FLT3 active), which was discontinued from phase I clinical trials due to cardiotoxicity.

We are now biologically profiling both types of inhibitors at the cellular level, as single agents and/or in combination with other chemotherapeutics. Preliminary results have shown activity in the low nanomolar range for p-Bad inhibition in the H1299 cell line (mechanistic studies), as well as good FLT3 activity results in MV411 cells. Representative compounds from each series demonstrated a strong synergistic behaviour in anti-proliferative combination settings with important anticancer therapeutic potential.

For the CDK8 project, we ran an HTS campaign and obtained a good number of hits, but in general with poor chemical space diversity and non-free Intellectual Property (IP). There were some hits however with good IP space. We are currently trying to design compounds with free IP, and to explore the IP free series.

Main Objectives

- Generate proprietary chemical series in the field of PIM inhibitors
- Select several compounds and promote them for *in vivo* studies, to reach proof-of-concept for their target
- To solve ADME issues during the optimisation of these chemical series, in particular metabolic stability, with special focus on the potential for cardiovascular toxicity



Staff scientists: M. Teresa Aranda (until February), Ana B. García, Ana M. García, Cristina A. Gómez (since September), Esther González, Jose I. Martín, Beatriz Noya, Miguel A. Ortega, M. Rosario Rico, Antonio Rodríguez, Antonio Salgado and Carmen Varela. **Post-doctoral fellow:** Francisco J. Ramos. **Technician:** Milagros Lorenzo.

Highlights

PIM-CNIO-01: High PIM1 inhibitory activity and no FLT3 component. Metabolic stability is an issue. ETP-45299 was obtained through chemical optimisation and used as a tool compound in anti-proliferative combination studies, demonstrating encouraging synergistic results. The figure illustrates the structure and biological profile of this compound (Figure).

PIM-CNIO-02: Dual inhibitors for PIM-FLT3 but they are also selective against other kinases. This dual activity is responsible for the good cellular response of the series in MV411 cells. The ADME profile indicates moderate metabolic stability and permeability. New compounds with improved properties have been prepared and will be further evaluated.

PIM-CNIO-03: Highly potent panPIM inhibitory activity, no activity was found in FLT3. These compounds are also selective against a panel of 24 kinases. Anti-proliferative cell-based combination studies disclosed a remarkable synergistic behaviour of selected compounds. We have generated subseries with different ADME or PK properties.

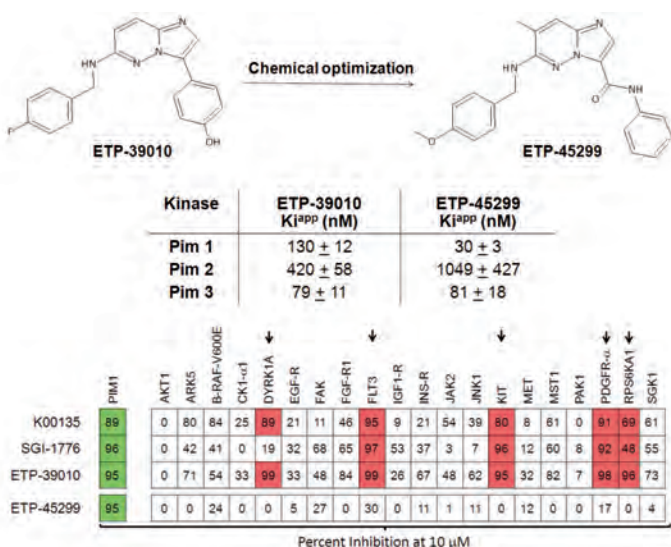


Figure: Chemical structure of ETP-39010 and ETP-45299; biochemical potency towards PIM kinases; and the selectivity profile of several imidazopyridazines.

PIM-CNIO-06: Series generated by proprietary scaffold-hopping techniques. Potent PIM1 inhibitors, showed different selectivity regarding FLT3 activity. Good metabolic stability and permeability. Compounds with acceptable PK have been selected for *in vivo* studies of the mechanism of action.

PIM-CNIO-07: PIM1PIM3 inhibitors, selective vs PIM2 and Flt3. Metabolically stable in microsomes and good PK properties for a compound tested.

These series are currently protected by their corresponding patent applications.

CDK8 project, a small set of compounds – focused and diverse – was screened for hits from our library (approximately 1000 cpds). We detected 130 hits (>50% inhibition @ 10mM) and determined their IC₅₀ values, finding hits in the low nanomolar to micromolar range of activity and different intellectual property states. These results are currently under analysis.

Publications

Ramos-Lima FJ, et al. (2010). The role of p53 in the cellular toxicity by active trans-platinum complexes containing isopropylamine and hydroxymethylpyridine. *Eur J Med Chem* 45, 134-141.

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Patent

Pastor Fernández J, Kurz G, Martínez González S (2010). Preparation of imidazo[2,1-b][1,3,4]thiadiazole derivatives as P13-K inhibitors for treating cancer and other diseases. PCT Int Appl WO 2010112874 A1 20101007.