Identification of Inhibitors of the Mitotic Kinesin HSET. Synthesis of Biologically Active Compound Libraries

Before talking about the project that I am working on it, I would like to introduce a little bit of my background. During my PhD I worked in two projects: the first one was the studio of catalytic and stoichoimetric transmetallation reactions with enaminocarbene complexes using different catalysts (**López-Alberca, M. P.**; Fernández, I.; Mancheño, M. J.; Gómez-Gallego, M.; Casarrubios, L.; Sierra, M. A. *Eur. J. Org. Chem.* **2011**, 3293–3300; **López-Alberca, M. P.**; Mancheño, M. J.; Fernández, I.; Gómez-Gallego, M.; Sierra, M. A.; Torres, R. *Chem. Eur. J.* **2009***, 15*, 3595–3604; **López-Alberca, M. P.**; Mancheño, M. J.; Fernández, I.; Gómez-Gallego, M.; Sierra, M. A.; Torres, R. *Org. Lett*. **2007**, *9*, 1757–1759), and the second one was the synthesis of macrocycles compounds from Fischer carbene complexes (**López-Alberca, M. P.**; Mancheño, M. J.; Fernández, I.; Gómez-Gallego, M.; Sierra, M. A.; Hemmert, C.; Gornitzka, H. *Eur. J. Inorg. Chem.* **2011**, 842–849; **López-Alberca, M. P.**; Mancheño, M. J.; Fernández, I.; Gómez-Gallego, M.; Sierra, M. A. *Org. Lett*. **2007**, *10*, 365–368; Llordes, A.; Sierra, M. A.; **López-Alberca, M. P.**; Molins, E.; Ricart, S. *J. Organomet. Chem.* **2005**, *690,* 6096–6100).

After Fischer and Maasböl described for the first time the metal-transition-carbene complexes, these compounds became a really useful tool in organic synthesis. Prof. Sierra´s group developed a few years ago the first example of transfer of the alcoxicarbene ligand to different compounds using different palladium catalysts. The study of the transmetalation reactions let us describe different ways of reactivity due to the presence of dfferent centers able to react with the different catalysts. So, palladium or rhodium catalyzed transmetalation reactions lead the formation of quinolines with moderate yield. In the other hand, the stoichiometric transmetallation reactions from tungsten or chromium fisher carbene complexes to $[PdCl_2(MeCN)_2]$, $[PtCl_2(MeCN)_2]$ or $PtCl_2$, gave new mononuclear palladium or platinum alcoxi-*bis*-carbenes complexes.

The second project I worked on was based on the synthesis of macrocycle structures from Fischer carbene complexes. In recent years, the use of transition metals in the construction of cyclophanes and macrocyclic structures has attracted many interest because the metal centers are an excellent tool for synthesizing organic molecules. However, there are no so many examples of using Fischer carbene complexes for the preparation of structures with cavities that can be used in the design of supramoleculares architectures. Therefore, in this project a general, versatil and effective methodology was developed to synthesize metal-carbene complexes bimetallic or tetrametallic.

After my PhD I joined Prof. Gregory Fu´s group (MIT and Caltech). During my first months working as a postdoctoral research fellow in Prof. Fu´s lab I worked on asymmetric Ni-catalyzed Sonogashira cross-coupling reactions of secondary electrophiles. A few months later, I moved to another project: Preparation of Small-Ring Heterocycles and Exploration of Their Efficacy as Selective Inhibitors of Serine-Esterases, Exploring the Scope of [2+2] Cycloadditions of Ketenes and Azo-Compounds (some of the results of this project resulted in a publication: Zuhl, A. M.; Mohr, J. T.; Bachovchin, D. A.; Niessen, S.; Hsu, K.-L.; Berlin, J. M.; Dochnahl, M.; **López-Alberca, M. P.**; Fu, G. C.; Cravatt, B. F. *J. Am. Chem. Soc***. 2012***, 134,* 5068). In addition, I prepared different Organic Synthesis Procedures: Synthesis of Biaryls and Styrenes via Pd-catalyzed Negishi cross-coupling of arylzinc reagents with aryl and vinyl chlorides (it will give rise to a *Organic Synthesis* paper), Synthesis of β,γ-unsaturated ketones via coupling of alkenylzirconium reagents with α-bromoketones (it will give rise to two *Organic Synthesis* papers) and Synthesis of Aza-β-lactams by means of [2+2] Cycloaddition of Alkyl Aryl Ketenes and Azodicarboxylates (*Organic Synthesis*, *manuscript in preparation*).

In November 2012, I moved into Max-Planck Institute (Dortmund, Germany) to work in Prof. Waldmann´s group, where I started working on the **Identification of Inhibitors of the Mitotic Kinesin HSET**. Kinesins are eukaryotic microtubule-dependent motor proteins that employ ATP hydrolysis for unidirectional movement along microtubules. Kinesin family members are important for intracellular vesicle and organelle transport and during cell division, e.g. in bipolar spindle formation, chromosome alignment and segregation and cytokinesis. The mitotic spindle is a validated target in cancer chemotherapy and spindle poisons like taxol and vinca alkaloids are clinically successful anti-cancer drugs. However, their usage is limited by innate or acquired drug resistance and drug toxicity. Kinesins represent an emerging target for chemotherapy. The most advanced mitotic kinesin inhibitors target the Eg5 (also known as KIF11) and centromere-associated protein E (CENP-E). The kinesin HSET (human spleen embryo testes) was shown to be essential for the viability of cells containing supernumerary centrosomes while it is non-essential for the cell division in normal cells. HSET is important for clustering extra centrosomes and ensures bipolar cell division. Thus, inhibition of HSET and consequently inhibition of centrosome clustering may selectively kill tumour cells with multiple centrosomes. This kinesin can crosslink microtubules at the mitotic spindle and it is responsible for spindle pole formation by aligning and focusing of microtubule minus ends. HSET controls spindle length through microtubules crosslinking and sliding. There are hardly any HSET inhibitors reported. To find small molecules that bind to the human HSET protein the chemical array approach was employed to screen 25.224 compounds of the RIKEN NPDepo and the COMAS libraries for binding to HSET. The 84 hit compounds were evaluated for the ability to modulated HSET's activity. One compound inhibited the microtubule-dependent ATPase activity of HSET and a second inhibitor was identified after assaying 23 compounds embodying a similar scaffold. Recently the first small molecule inhibitor AZ82 for KIFC1 has been reported.