Synthesis and evaluation of new macrocyclic compounds based on jatrophane scaffold

Summary description of the project objectives:

1) **Synthesis of an advanced intermediate for the preparation of potentially Multi Drug Resistance Jatrophane analogues**
2) **Synthesis of migrastatin analogues and their evaluation as Pgp inhibitors**
3) **Biologically evaluation of migrastatin as antimetastatic agents**

Description of the work performed since the beginning of the project and main results achieved so far.

The occurrence of resistance to anticancer agents is a major obstacle for successful cancer chemotherapy. The emergence of resistance to anticancer drugs, in particular multidrug resistance (MDR) has made many of the available anticancer drugs ineffective.

Jatrophane and Lathyrane natural products have been found to be potent and specific P-glycoprotein modulators with potential as Multi Drug Resistance modulators.

Carbohydrates are chiral natural products. After the proper chemical manipulation, the chirality can be transferred from the starting material to the target molecule. Our synthetic strategy is based on the synthesis of an advanced intermediate that can be used for the preparation of jatrophane analogues. L-Sorbose is a naturally occurring carbohydrate, and is the starting material for the industrial synthesis of Vitamin C. Its production is approximately 60000 tons/year. Despite the similarity with the well exploited D-Fructose, only few methods were developed for the modification of this economic sugar. We decide so to develop a new synthetic approach for the manipulation of L-sorbose. We apply this method for the synthesis of the advanced intermediate showed in figure 1.

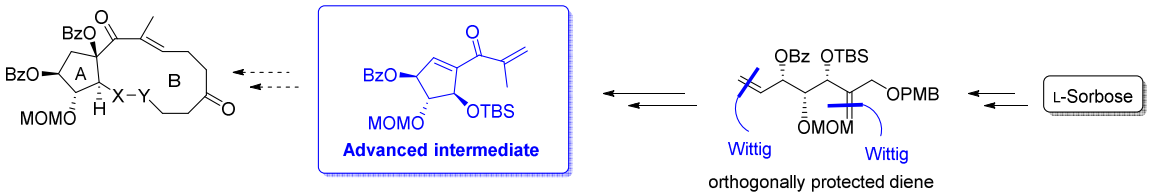


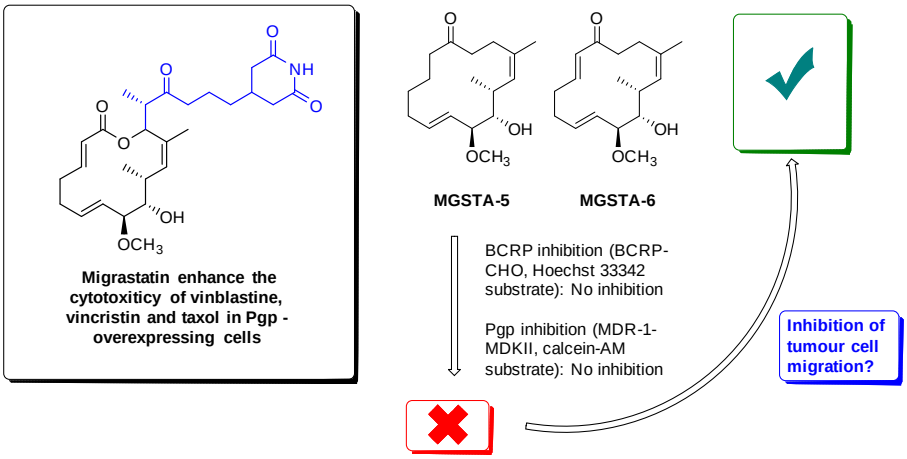
Figure 1

Final results and their potential impact and use

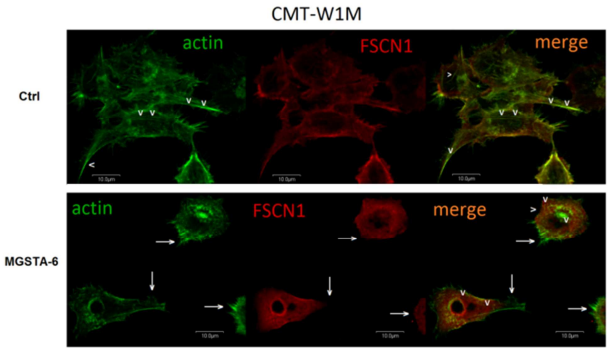
A novel synthetic approach for the manipulation of L-sorbose was developped. The advanced intermediate for the preparation of potential Multi Drug Resistance Modulators was prepared through the orthogonally protected diene shown in figure 1. Importantly, the synthetic route developed herein provides an access to cyclopentitols, polyhydroxylated cyclopentanes, which are of particular significance because of their presence in a variety of medicinally relevant natural products. The synthetic route developed herein is expected to have a significant impact in the scientific community devoted to monosaccharides manipulation and chiral pool synthesis.

Objective: Synthesis of Migrastatin analogues.

Migrastatin analogues were synthesized in order to evaluate their biological property as MDR modulator (inhibitors of Pgp). Migrastatin analogues failed to inhibit Pgp, however they were tested as inhibitor of cell migration: an important target in cancer metastasis.

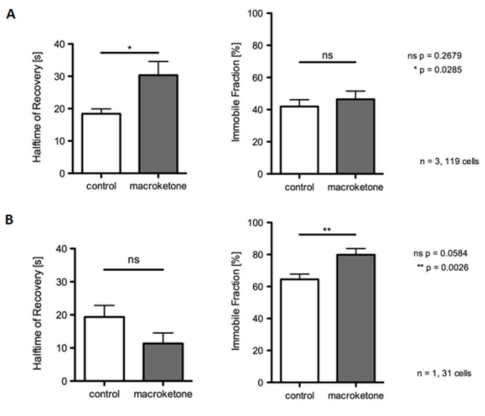


Objective: Biological evaluation of Migrastatin analogues.



Synthesized Migrastatin analogues were found to inhibit cell migration in human (MDA-MB-231 human breast cancer) and canine (CMT-W1, CMT-W2 and CMTW1M) cell lines. The Interference with fascin1 dependent actin cross-linking in canine mammary cancer cells by **MGSTA-6** was studied using confocal microscopy. Administration of **MGSTA-6** caused decrease in the number of filopodial protrusions in CMT-W1M cells. The same effect was observed in CMT-W1 and CMT-W2 cell lines.

In addition, the effect of treatment with a Migrastatin analogue on E-Cadherin dinamics was studied using fluorescence recovery after photobleaching (FRAP) *in vitro* and *in vivo*. We observed that *in vivo* **MGSTA-5** treatment significantly increased the immobile fraction of E-cadherin in cell-cell junctions an effect expected to strengthen cell-cell adhesion and therefore antagonize metastasis.



Final results and their potential impact and use

In conclusion, we develop a scalable route for the preparation of migrastatin core analogues. In addition, the mechanism by which this class of compounds inhibits cell migration was studied. We expect that these results have significant impact in the scientific community devoted to the study of cancer metastasis and cell migration in pathological conditions.