Pharmacomodulation of ellagic acid: a total synthesis approach.

Gilles Degotte1,2; Bernard Pirotte1; Michel Frederich2; Pierre Francotte3

1Laboratoire de Chimie Pharmaceutique, Centre Interdisciplinaire de Recherches sur le Médicament (CIRM), Liège – Quartier Hôpital – B36 Tower 4, Avenue Hippocrate 15, 4000 Liège, Belgium.
2Laboratoire de Pharmacognosie, Centre Interdisciplinaire de Recherches sur le Médicament (CIRM), Liège – Quartier Hôpital – B36 Tower 4, Avenue Hippocrate 15, 4000 Liège, Belgium.
Email: gdegotte@doct.uliege.be

Nature remains the main source of pharmacological molecules. Unfortunately, highly active is often linked to poor oral bioavailability, mostly explained by low hydrosolubility. Thus, pharmacomodulation of natural scaffolds is often reported to increase these properties. Ellagic acid (Fig. 1) is one of them: numerous biological effects (anticancer, antimicrobial, antiplasmodial…) impede by a low water solubility (6 g/mL), helped by inter-/intramolecular bonds and planar aspect of this structure. Different strategies could be employed to enhance solubility and by extension, improving PK/PD properties (Figure 2). A total synthesis approach (Figure 3) was finally selected, based on EA’s natural monomer, gallic acid and inspired by ellagittannins synthesis. Following this strategy, we expect to obtain (asymmetric compounds with hydrophilic/alkyl chains to disrupt crystal packing, in addition to loss of molecular planarity. The modifications have been performed on phenolic functions (para) and several assays have been achieved to explore the influence of these pharmacomodulations on critical parameters (Figure 4).

Disrupt crystal packing
Increase hydrophilicity
Break intermolecular bonds
Disrupt molecular planarity

Figure 2: Critical properties

Figure 3: Synthesis pathway.

Figure 4: Bioassays

Total synthesis approach led to several promising compounds. Indeed, considering key properties, all intermediates showed a non-toxic profile against red blood cells with a low to great inhibitory effect on Plasmodium falciparum (3D7). A low IC50 value seems to be linked to a dimer-like structure i.e. two gallic moieties with a short linker. In addition, most compounds exhibited a better water solubility than EA. However, one of the most active molecules was also found poorly soluble. The C–C bond between the 2 aromatic rings has now to be achieved and evaluated to follow evolution of these properties. Moreover, cytotoxicity against human healthy cells will be performed to determine selectivity of our intermediates.

Authors are grateful to FRS-FNRS and Fondation Léon Fredericq for financial support.

References: