# Towards the total synthesis of ellagic acid analogues – regioselective functionalisation of gallic acid's phenolic functions

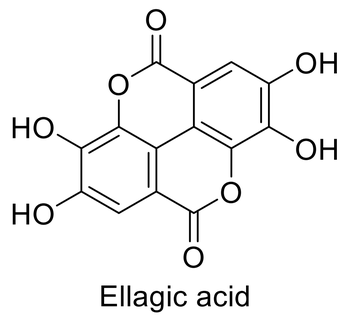
Schmitz A.[1], Colson T.[1], Lesenfants C.[1], Mankulu Kakumba J.[1], Frédérich M.[2], Pirotte B.[1], Francotte P.[1]

[1] *Laboratory of Medicinal Chemistry, CIRM, Department of Pharmacy, University of Liège*

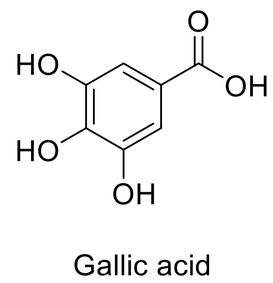
[2] *Laboratory of Pharmacognosy, CIRM, Department of Pharmacy, University of Liège*

## State of the art

As malaria remains a worldwide major health issue, there is a significant need to develop new **antimalarial drugs**. For this purpose, a wide range of natural substances have been tested through screenings. Such a screening has highlighted **ellagic acid** (EA) as a good starting point for the development of antiplasmodial drugs. Previous works have shown that direct modulation of the ellagic acid structure was challenging. Therefore, a **total synthesis approach**, starting from **gallic acid** was considered. Based on this strategy, different open-ring EA analogues and gallate derivatives were prepared, amongst which interesting structures have emerged.



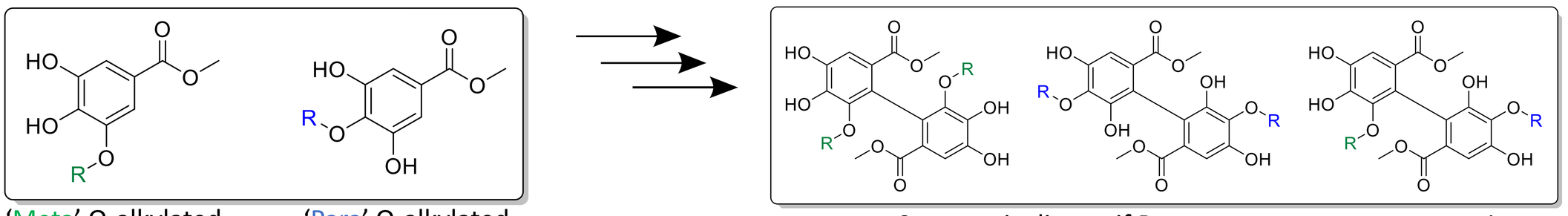
Ellagic acid



Gallic acid

## Aim of the present work

Taking opportunities from the previous studies, this work aims to **regioselectively modulate the phenolic functions of the gallic acid** in order to obtain a range of **monomers grafted with small groups of various sizes and polarities**. These different monomers could then be coupled to form **symmetric or asymmetric dimers open-ring (or not) EA analogues**.



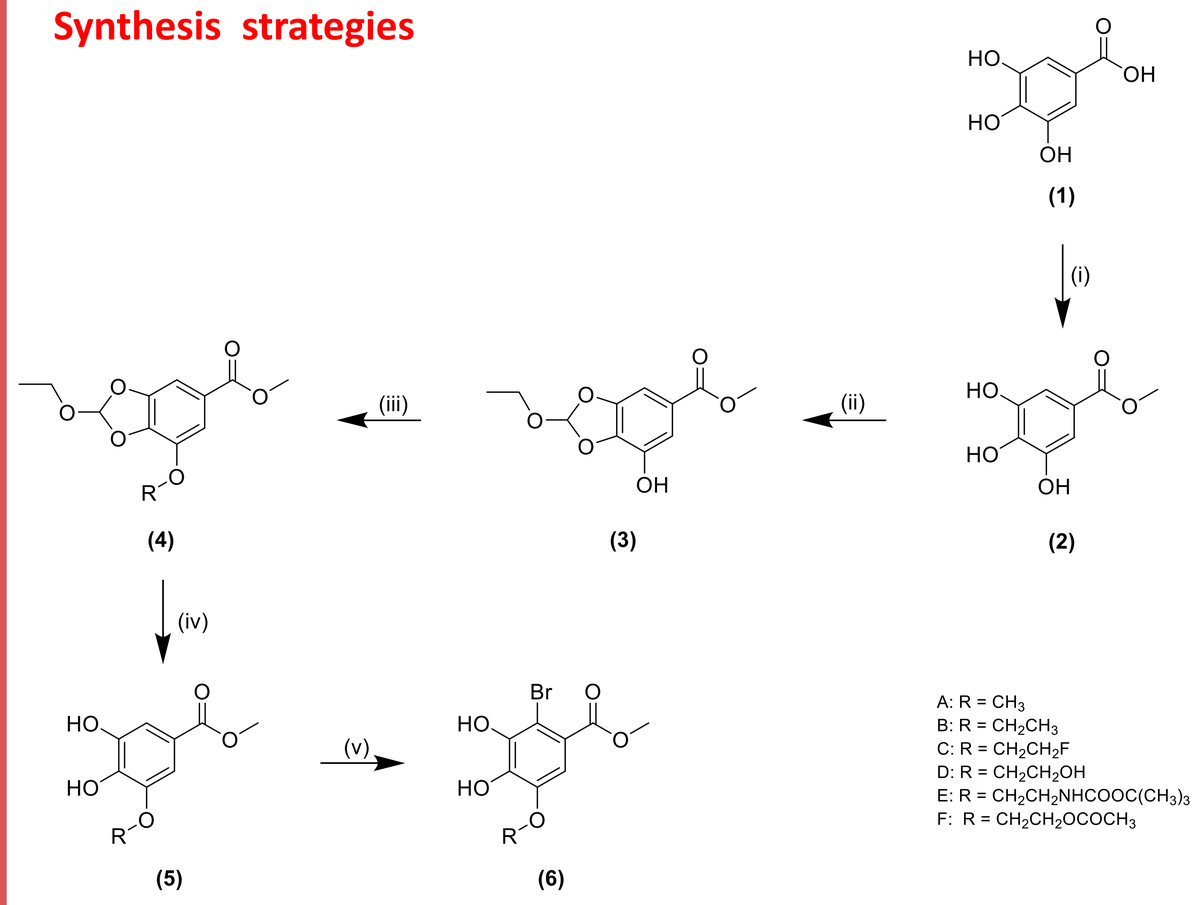
'Meta' O-alkylated Gallate derivatives

'Para' O-alkylated Gallate derivatives

Symmetric dimers if R are the same

Assymmetric dimers if R are different

## Synthesis strategies

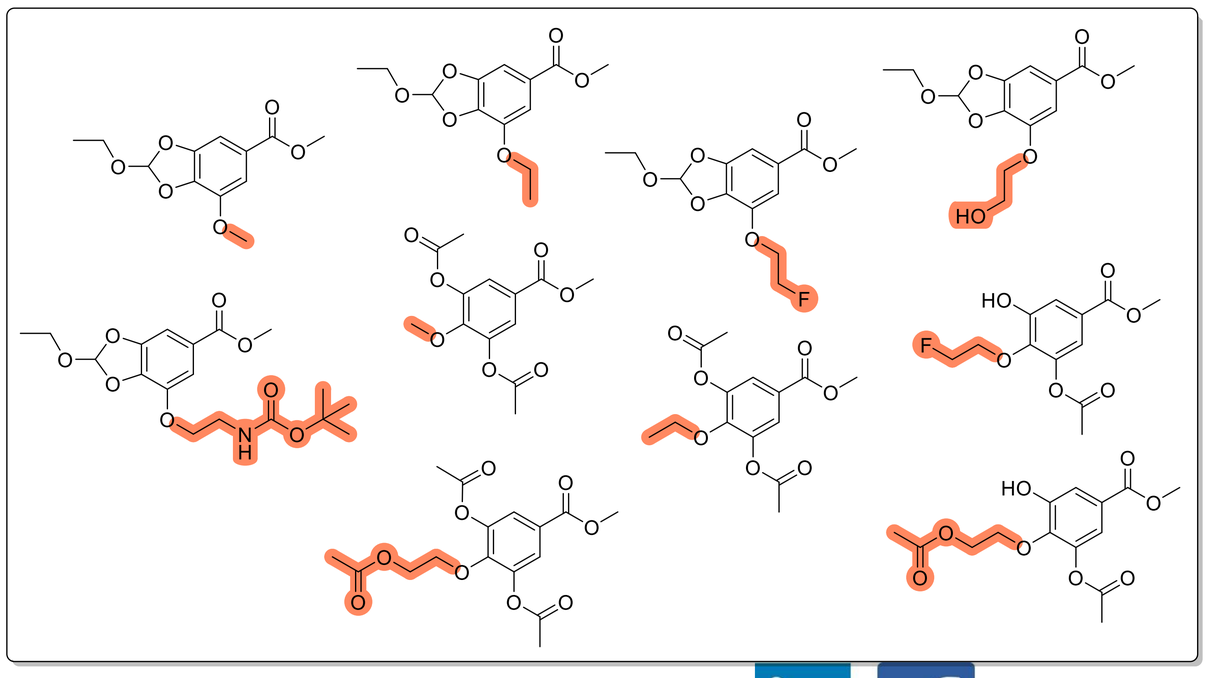



The first step consists in the protection of the carboxylic function of gallic acid through its **esterification**.

Then, depending on the target compounds (para or meta alkylated, compared to the carboxylic ester), a full **protection** is achieved using acetyl moieties or a reaction with triethyl orthoformate gives access to compound **3**. **Regioselective insertion of the** different **alkyl groups** may be then achieved in alcaline medium, leading to compounds **4** and **8**. After **removing the protective groups** from the phenols, the selective **bromination** in position 2 occurs, enabling a subsequent Ullmann's coupling.

*(i) MeOH, $H_2SO_4$ cat ; (ii) Triethylorthoformate (11 eq.) ; (iii) X-R (2,15 eq.), anhydrous $K_2CO_3$, anhydrous acetone, reflux, 12h ; (iv) concentrated HCl, methanol ; (v) NBS (1,5 eq.), ACN ; (vi) Acetic anhydride (2 éq.), $H_2SO_4$ ; (vii) X-R (2,15 eq.), anhydrous $K_2CO_3$, anhydrous acetone, reflux, 12h ; (viii) $K_2CO_3$, MeOH ; (ix) NBS (1,5 eq.), ACN.*

## Conclusion and perspectives



The preparation of a focused chemical library has been initiated; the first diverse alkyl chains inserted on the various phenol positions should allow a comprehensive study of the **influence of their lipophilic and electronic factors**. Moreover, we plan to study the spontaneous potential **ring closure of dimers**, leading to EA structures.

A study is planned to **optimize reaction conditions** (KI addition to the medium to obtain compounds **8**, bromination/purification to obtain compounds **6** or **10**) and a **scale up** of the alkylation step. Our next goal is the development of the **Ullmann's coupling reaction** in order to prepare the final **dimers**.

And last but not least, we plan to investigate the antiplasmodial activity of the gallate derivatives (compounds **4-6** and **8-10)**.

fnrs LA LIBERTÉ DE CHERCHER

CIRM ULiège

WEBSITE: www. cirm.uliege.be

CENTER FOR INTERDISCIPLINARY RESEARCH ON MEDICINES