Preparation of ellagic acid derivatives through a total synthesis approach to improve bioavailability.

Gilles Degotte[1,2] ; Annabelle Halleux[2]; Aurore Hans[2] ; Olivia Jansen[1] ; Allison Ledoux[1] ; Pauline Desdemoustier[1] ; Bernard Pirotte[2] ; Pierre Francotte[2] ; Michel Frederich[1].

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

Context [1-3]

- Malaria is a vector-borne parasitosis, responsible of 435 000 deaths and 219 million of cases in 2017.
- Disease mainly caused by *Plasmodium falciparum* for which a resistance phenomenon to artemisinin is documented.
- Considering this resistance and the prevalence of malaria, development of new antiplasmodials represents an urgent need.
- Ellagic acid (EA, **1**) seems to be one of the most promising candidates: 105-330 nM *in vitro* and no toxic.
- Poor oral bioavailability due to a reduced water solubility (9.7 µg/mL).

Objectives

1. Synthesis of steric-hindered EA analogues or EA prodrugs using phenolic positions.

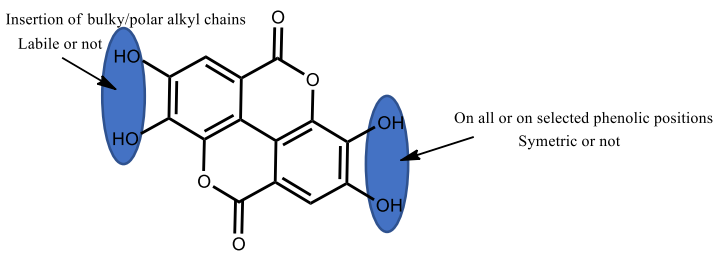
   Direct synthesis approach vs **total synthesis strategy**

2. Evaluation of antiplasmodial effect against 3D7 strain (chloroquine-sensitive)[4]

3. Measuring impact of pharmacomodulations on water solubility thanks to UV-spectrophotometer.

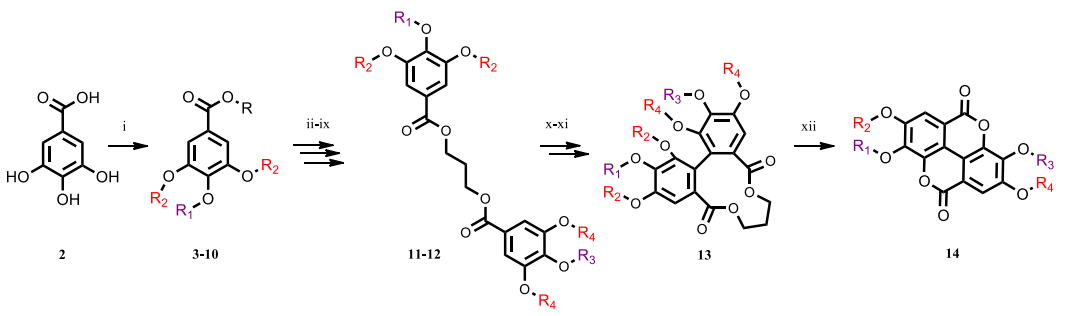
Pharmacomodulation

- The hunt for the pharmacophore

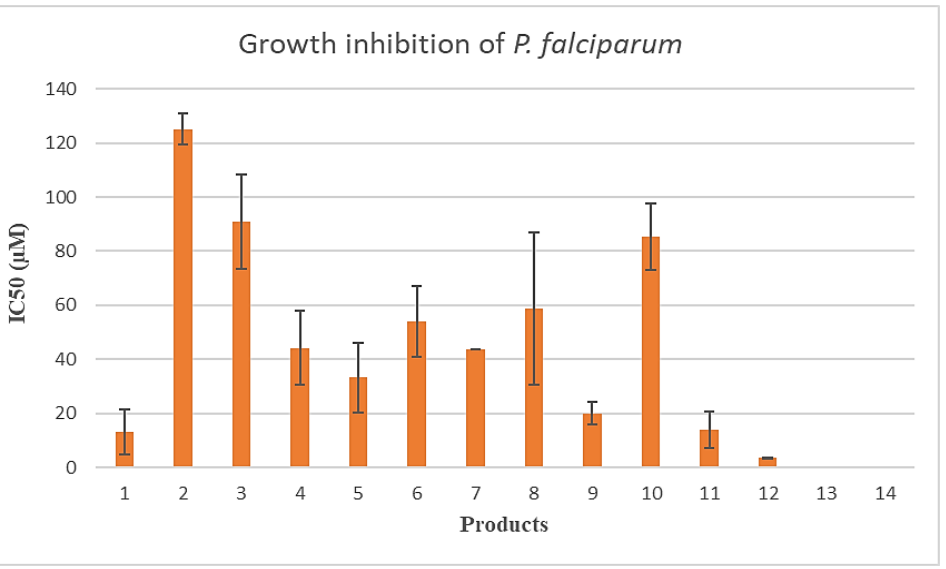


1

Synthesis



i CH_3OH, H_2SO_4 ii Ac_2O, H_2SO_4 iii BnBr, KI, K_2CO_3, acetone iv K_2CO_3, CH_3OH, H_2O v NaH, MOMCl, DMF vi LiOH, CH_3OH, THF, H_2O vii 1,3-propanediol-PMB, DMAP, EDCI-HCl, CH_2Cl_2 viii DDQ, Sorenson's buffer, CH_2Cl_2 ix DMAP, EDCI-HCl, CH_2Cl_2 x THF, IPA/HCl xi $CuCL_2$, *n*-$BuNH_2$, CH_3OH xii LiOH, CH_3OH, THF, H_2O



Product	R	R_1/R_3	R_2/R_4	IC_{50} (µM) (n=)	Solubility (µg/mL) (n=3)
1	/	H	H	13.24±8.37 (2)	267.72±21.52
2	H	H	H	125.19±5.76 (3)	9658.79±983.38
3	CH_3	H	H	90.87±17.52 (3)	11654.95±2560.76
4	CH_3	CH_3CO	CH_3CO	44.27±13.75 (3)	957.52±151.72
5	CH_3	$BnCH_2$	CH_3CO	33.27±12.86 (3)	14.70±3.20
6	CH_3	$BnCH_2$	H	54.11±13.02 (3)	163.21±9.22
7	CH_3	$BnCH_2$	MOM	43.83 (1)	Liq.
8	H	$BnCH_2$	MOM	58.74±28.25 (3)	wip
9	$CH_2CH_3CH_2OPMB$	$BnCH_2$	MOM	19.89±4.16 (4)	liq.
10	$CH_2CH_3CH_2OH$	$BnCH_2$	MOM	85.29±12.42 (3)	liq.
11	$CH_2CH_3CH_2$	$BnCH_2$	MOM	13.93±6.75 (3)	wip
12	$CH_2CH_3CH_2$	$BnCH_2$	H	3.59±0.14 (4)	wip
13	$CH_2CH_3CH_2$	$BnCH_2$	H	wip	wip
14	/	$BnCH_2$	H	wip	wip

wip = Work In Progress; Liq. = liquid

Conclusion & Prospects

- Increase of inhibitory effect from gallic acid (**2**) (125.2 µM), especially when a linker is present between 2 gallate moieties. "Dimer look-alike" importance to observe the same rank of potency of EA.
- Substituents on the phenolic functions negatively impact this effect (**11** vs **12**).
- Solubility seems to be mainly dependent of phenolic functions.
- In the near future: Assay of final substituted compound and synthesis of other derivatives of EA's scaffold.

Thanks to FNRS and Fondation Léon Fredericq for financial support.

References :
1.World Health Organisation. *World Malaria Report 2018.* (2018).
2.Soh, P. N. *et al.* In vitro and in vivo properties of ellagic acid in malaria treatment. *Antimicrob. Agents Chemother.* **53,** 1100–1106 (2009).
3.Bala, I., Bhardwaj, V., Hariharan, S. & Kumar, M. N. V. R. Analytical methods for assay of ellagic acid and its solubility studies. *J. Pharm. Biomed. Anal.* **40,** 206–210 (2006).
4.Frédérich, M. *et al.* Antiplasmodial Activity of Alkaloids from Various Strychnos Species. *J. Nat. Prod.* **65,** 1381–1386 (2002).

CIRM ULiège

WEBSITE: www.cirm.uliege.be

CENTER FOR INTERDISCIPLINARY RESEARCH ON MEDICINES