Pharmacomodulation of ellagic acid: a total synthesis approach.

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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 µg/mL), helped by inter-/intramolecular bonds and planar aspect of this structure[1]. Different strategies could be employed to enhance solubility and by extension, improving PK/PD properties (Figure 2)[2].

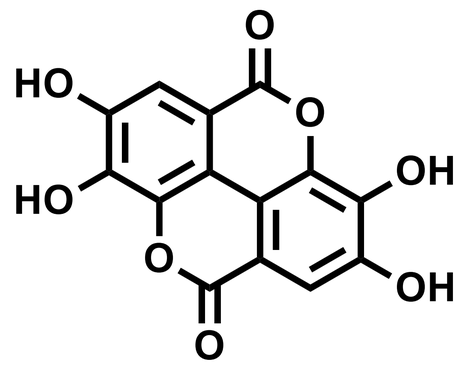


Figure 1 : Ellagic acid (EA)

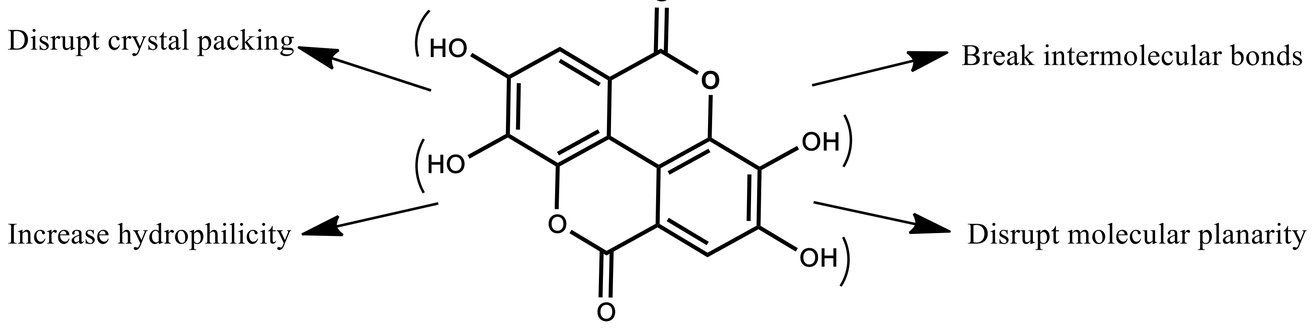
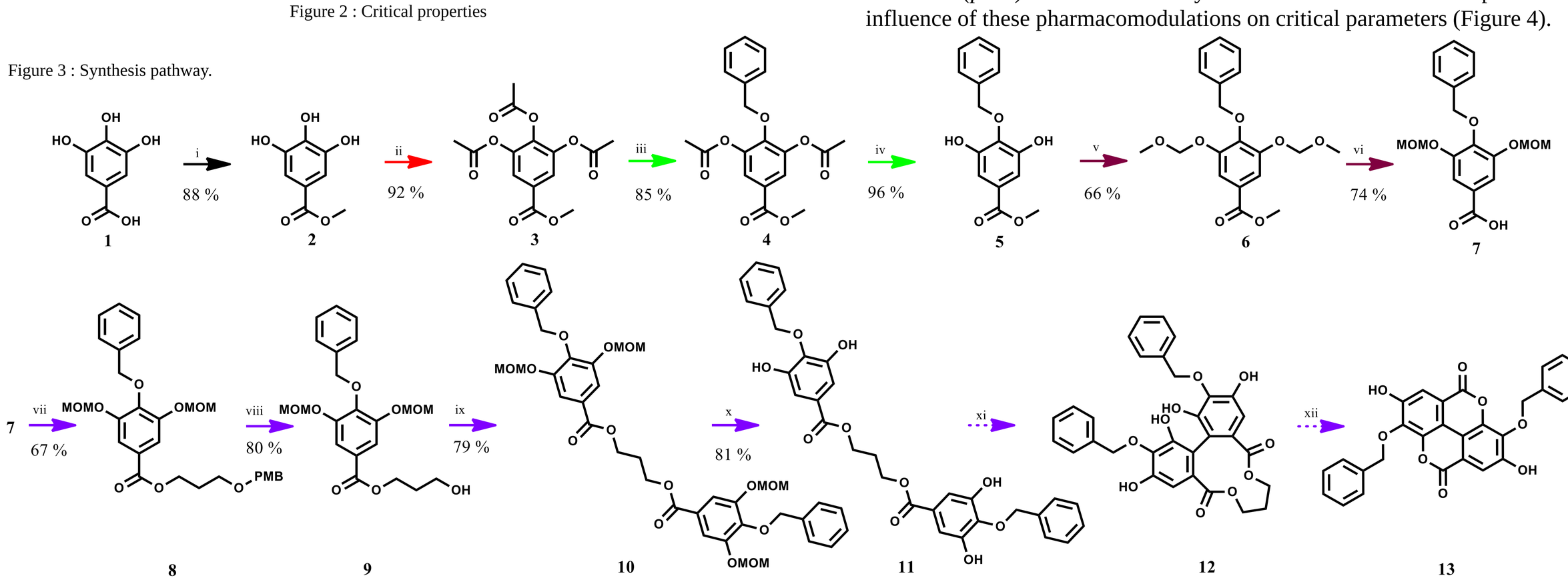


Figure 2 : Critical properties

A total synthesis approach (Figure 3) was finally selected, based on EA's natural monomer, gallic acid and inspired by ellagitanins synthesis[3]. Following this strategy, we expect to obtain (a)symetric 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).

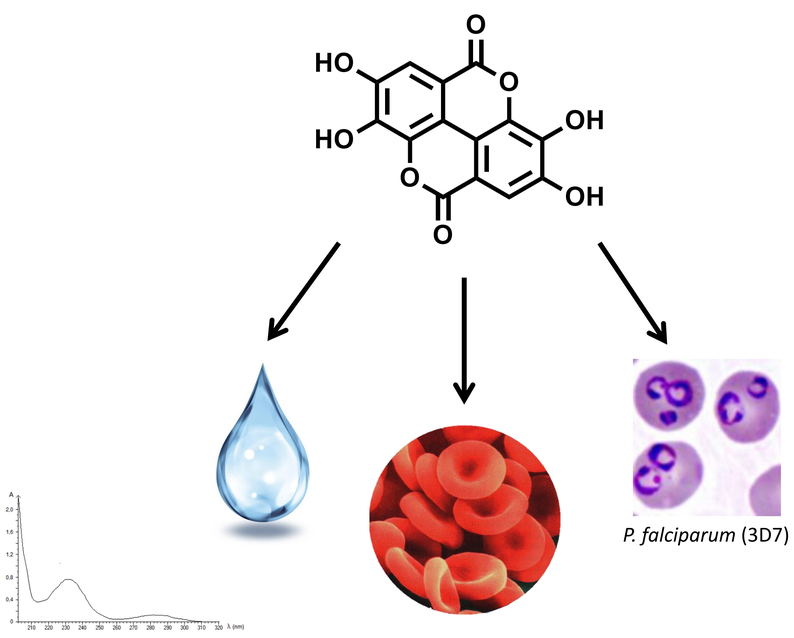
Figure 3 : Synthesis pathway.



Gokcen et al, 2016[4] Pearson et al., 1991[5] Yamada et al., 2008[5] Hirokane et al., 2014[3]

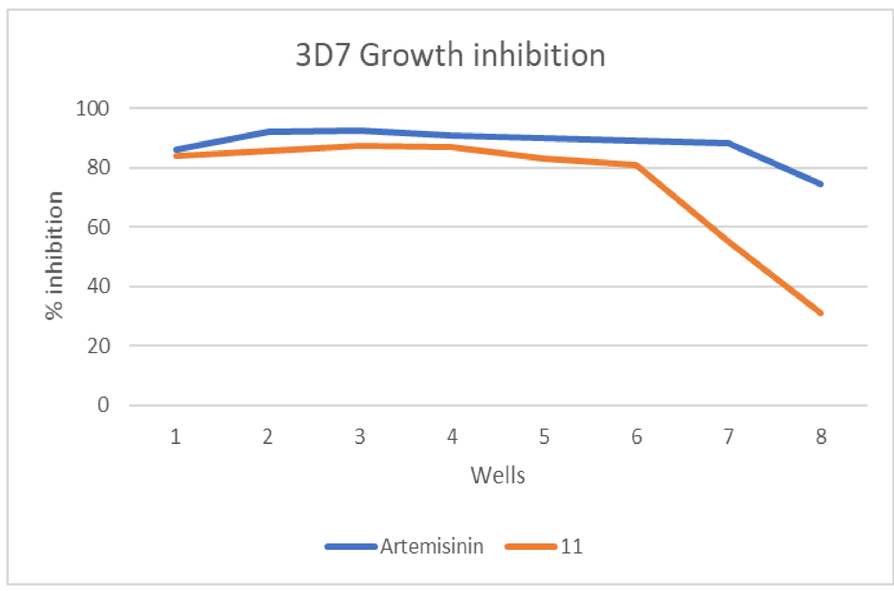
i CH_3OH, H_2SO_4 ii Ac_2O, H_2SO_4 iii BnBr, KI, K_2CO_3, DMK iv K_2CO_3 , CH_3OH, H_2O v NaH, MOMCl, DMF vi LiOH, CH_3OH, THF, H_2O vii 1,3-propanediol-PMB, DMAP, EDCI-HCl, CH_2Cl_2 viii DDQ, Sorenson's buffer, CH_2Cl_2 ix DMAP, EDCI-HCl, CH_2Cl_2 x THF, IPA/HCl xi $CuCl_2$, *n*-$BuNH_2$, CH_3OH xii LiOH, CH_3OH, THF, H_2O.

Figure 4: Bioassays



	Solubility (µM)	*P. falciparum* (µM)	Hemolysis (100 µg/mL)
EA	18.1 ± 3.06	4.05 ± 2.18	< 1%
1	70.2 10^3 ± 8.2 10^3	63.96 ± 4.31	< 1%
2	74.2 10^3 ± 7.7 10^3	26.84± 1.81	< 1%
3	585 ± 75	9.30 ± 3.03	< 1%
4	461 ± 224	56.38 ± 2.15	< 1%
5	3.72 10^3 ± 0.79 10^3	34.94 ± 5.97	< 1%
6	Liq.	54.33 ± 10.10	< 1%
7	646± 153	7.61	< 1%
8	Liq.	12.1	< 1%
9	Liq.	8.17 ± 1.80	< 1%
10	9.30 ± 0.15	1.90 ± 0.90	< 1%
11	/	1.75 ± 0.94	< 1%

Liq. = Liquid/oil



Artemisinin : 0.1 to 7.8 10^{-4} µg/mL; 11 : 100 to 0.78 µg/mL;
in 96-wells plate (8 two-folds dilutions).

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 IC_{50} 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.

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