

Total synthesis approach: development of new antimalarial compounds.

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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...) impeded by a low water solubility (6 µg/mL), helped by inter-/intramolecular bonds and planar aspect of this structure¹. Different strategies could be employed to enhance solubility and by extension, improving PK/PD properties (Fig. 2)².

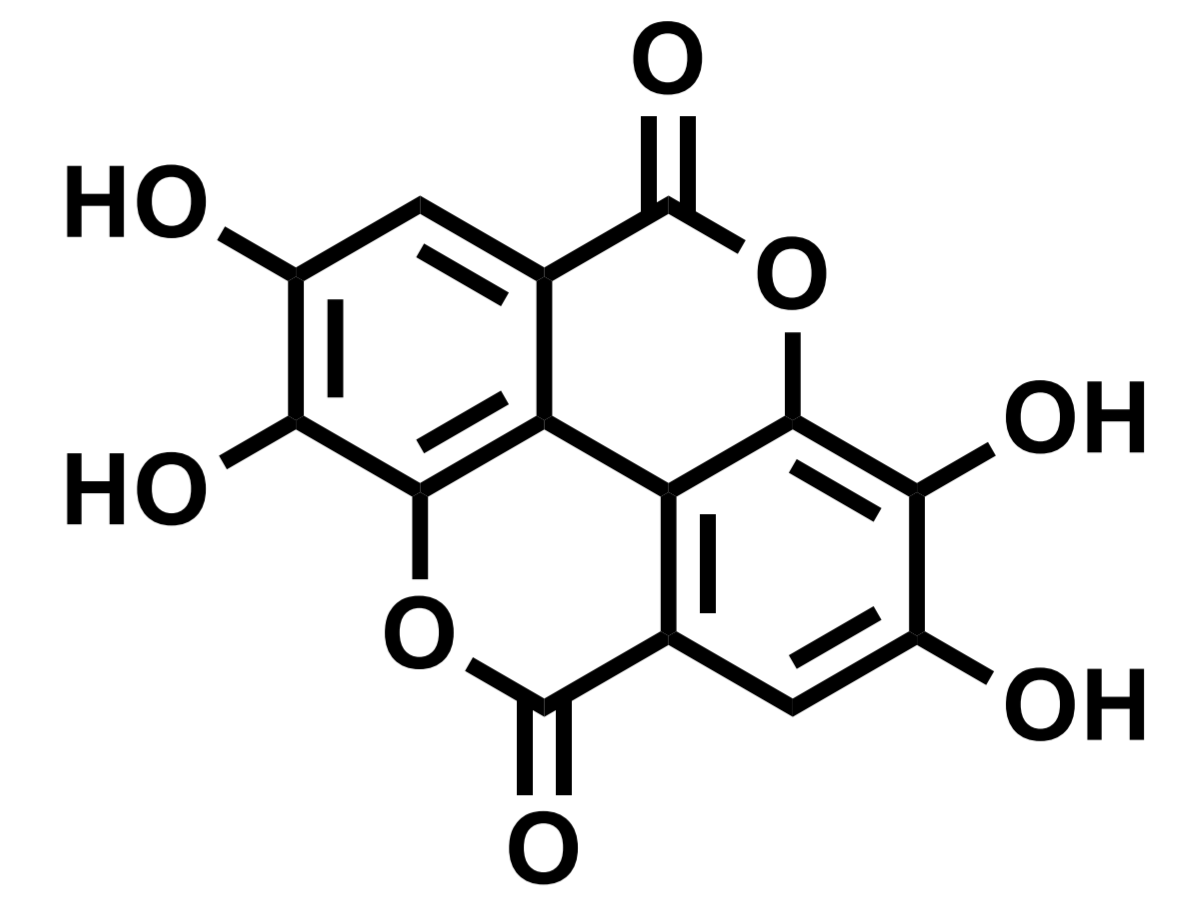


Figure 1 : Ellagic acid (EA)

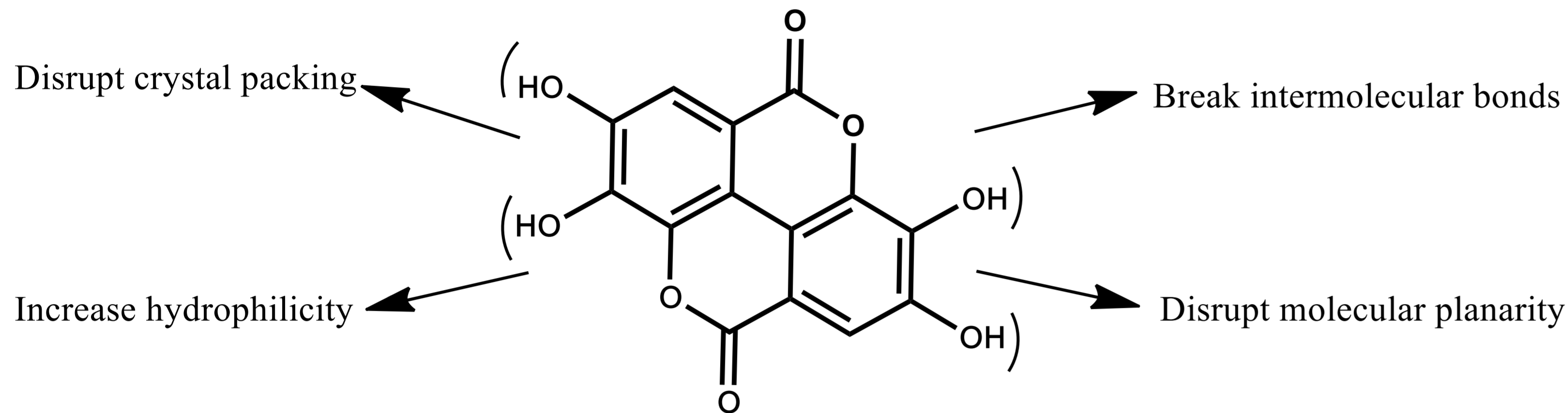
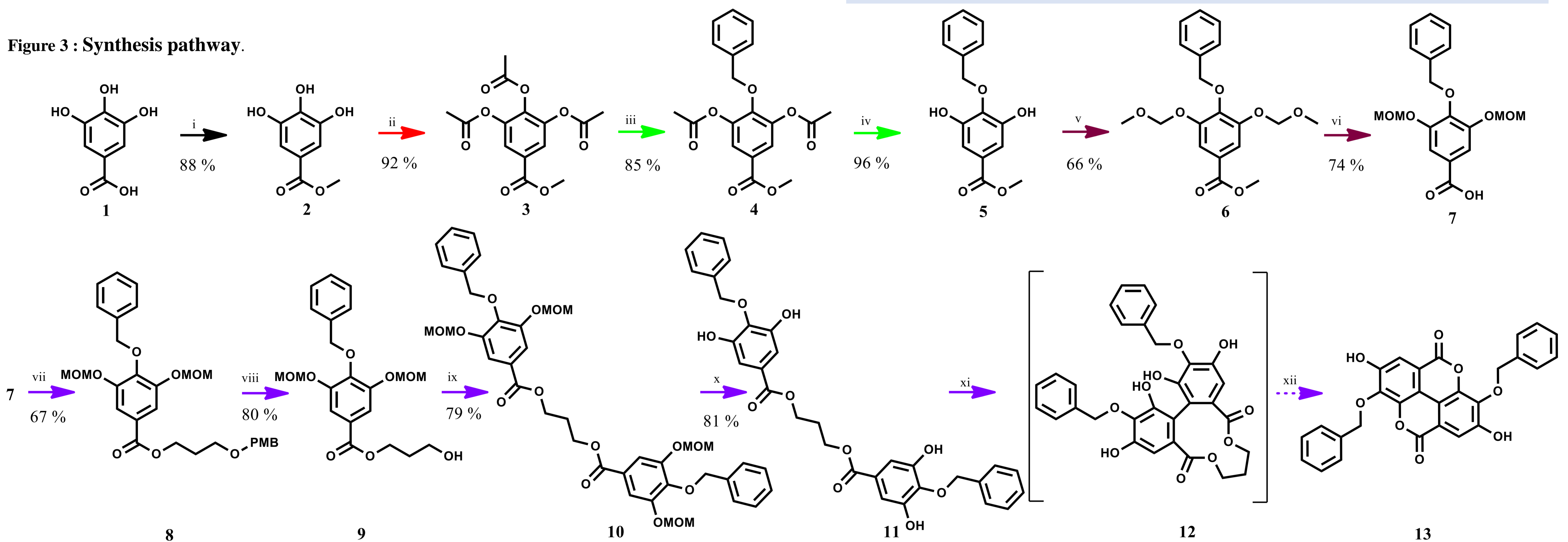


Figure 2 : Critical properties

A total synthesis approach (Fig. 3) was finally selected, based on EA's natural monomer, gallic acid and inspired by ellagitannins synthesis³. Following this strategy, we expect to obtain (a)symmetric 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 (Fig. 4).

Figure 3 : Synthesis pathway.



Gokcen et al., 2016⁴

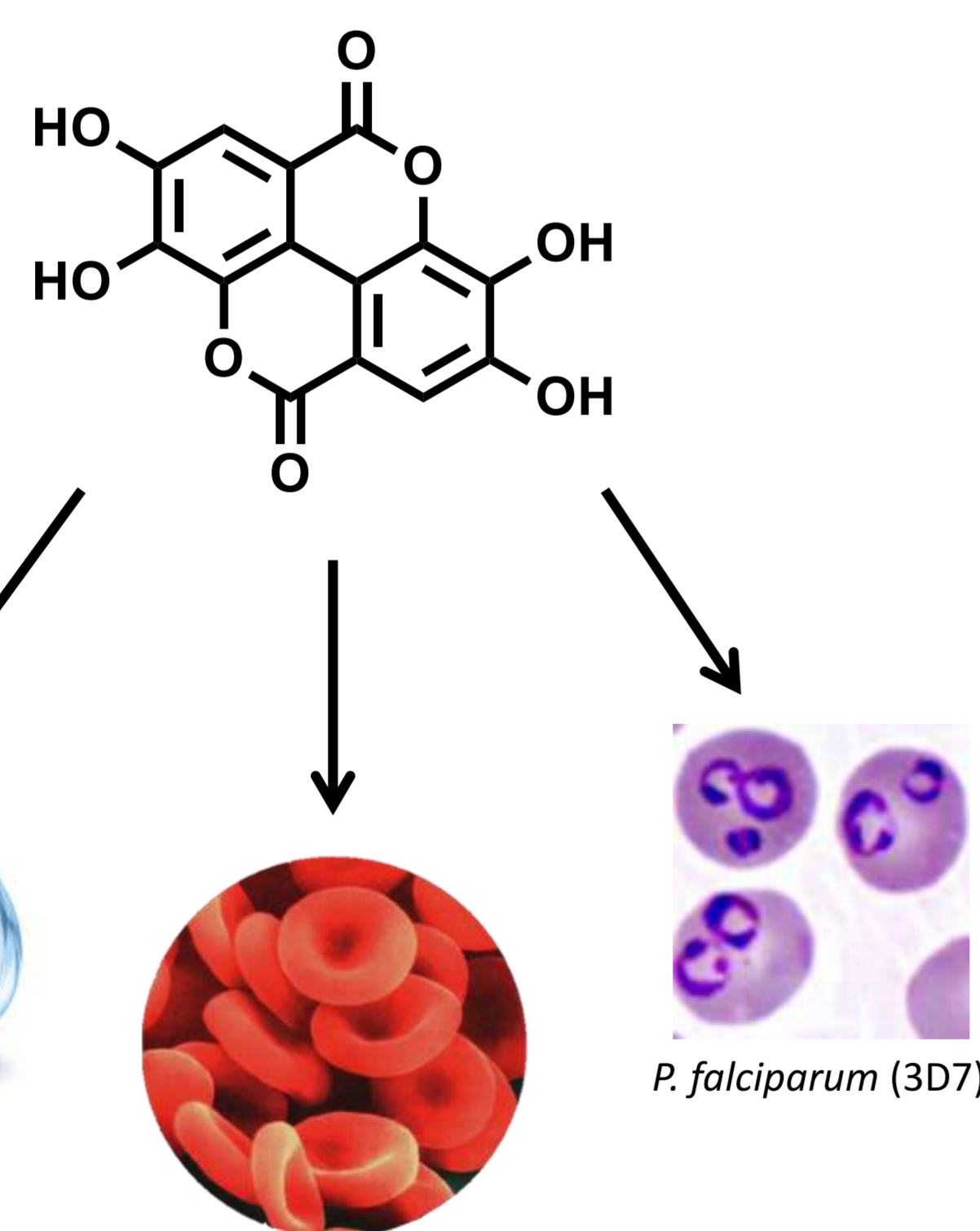
Pearson et al., 1991⁵

Yamada et al., 2008⁵

Hirokane et al., 2014³

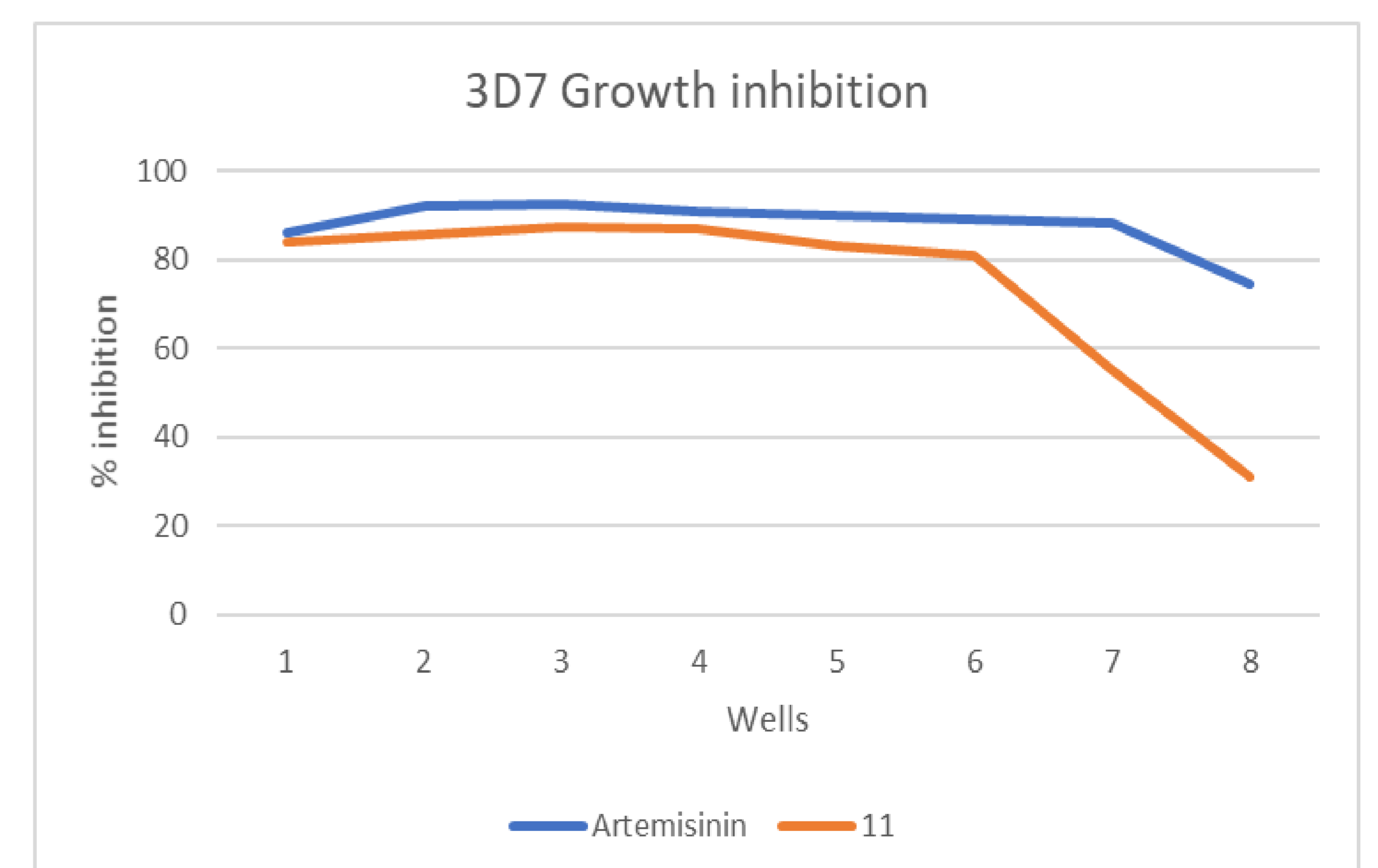
i CH₃OH, H₂SO₄ ii Ac₂O, H₂SO₄ iii BnBr, KI, K₂CO₃, DMK iv K₂CO₃, CH₃OH, H₂O v NaH, MOMCl, DMF vi LiOH, CH₃OH, THF, H₂O vii 1,3-propanediol-PMB, DMAP, EDCI-HCl, CH₂Cl₂ viii DDQ, Sorenson's buffer, CH₂Cl₂ ix DMAP, EDCI-HCl, CH₂Cl₂ x THF, IPA/HCl xi CuCl₂, *n*-BuNH₂, CH₃OH xii LiOH, CH₃OH, THF, H₂O.

Figure 4: Bioassays



	Solubility (µM)	<i>P. falciparum</i> (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).

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

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.

References:

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