4-aminoacridines and 4,9-diaminoacridines derivatives as potential antiproliferative hits

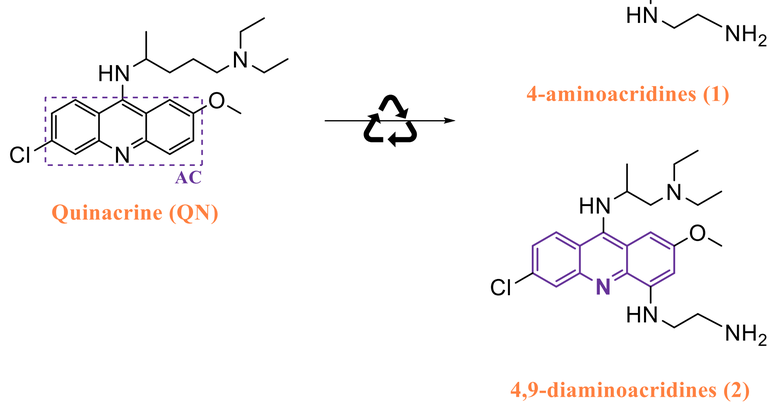
Mélanie Fonte,[a]* Natália Tassi,[a] Hélder Oliveira,[a] Iva Fernandes,[a] Nuno Mateus,[a] Ricardo Ferraz,[b] Maria J. Araújo,[a] Paula Gomes,[a] Cátia Teixeira[a]

a) LAQV-REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Portugal; b) Ciências Químicas e das Biomoléculas, Escola Superior de Saúde, Politécnico do Porto, Portugal.

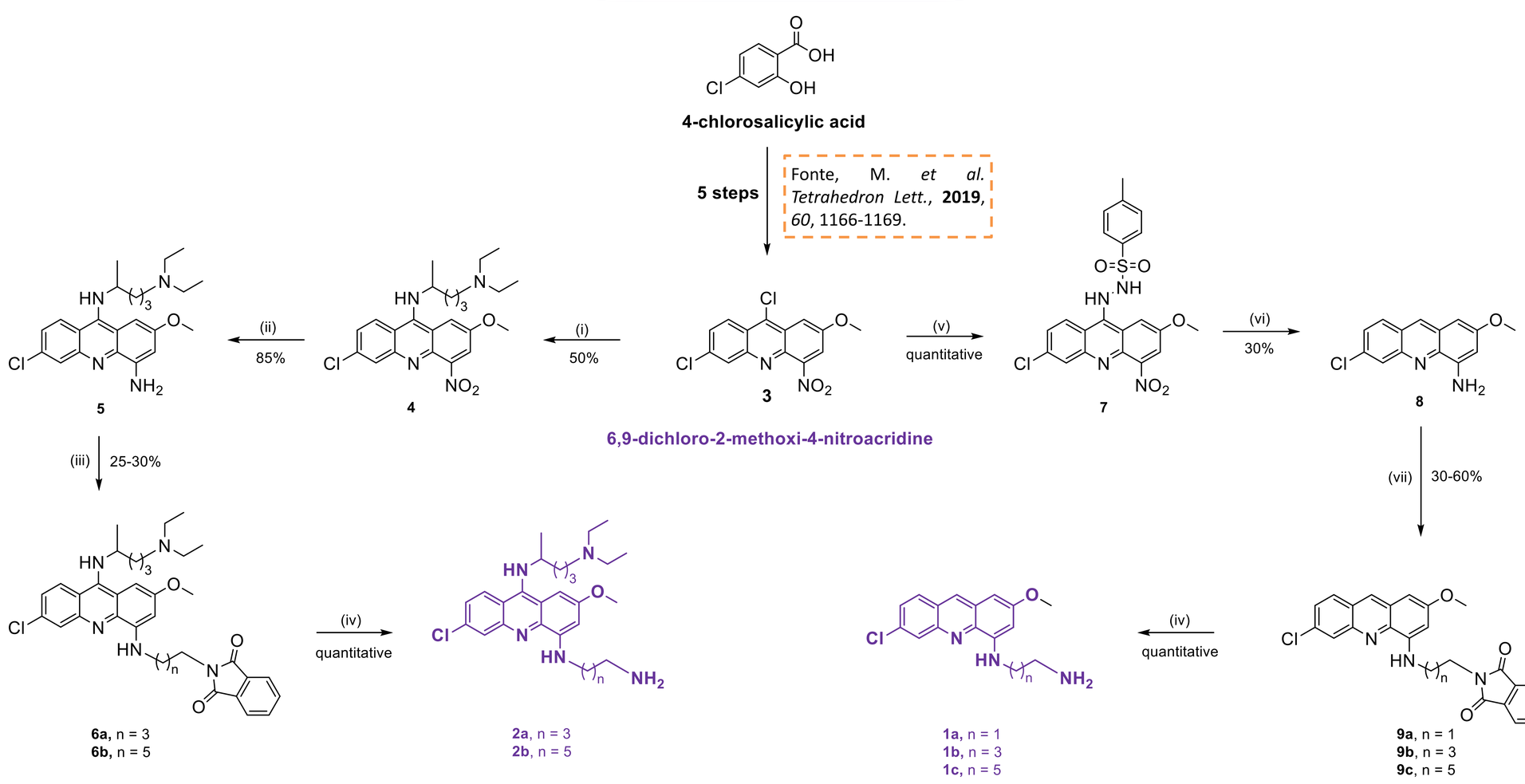
*melanie.fonte@fc.up.pt

Aim

Acridine (**AC**) derivatives have attracted much attention due to their broad spectrum of biological activity. Though **Quinacrine** (**QN**), an AC derivative, was the first clinically tested synthetic antimalarial drug, this heteroaromatic core is well-know to exhibit other interesting bioactivities, such as **antiproliferative properties**.[1] One cost-effective strategy to accelerate drug development is to repurposed/rescued compounds originally developed against a given disease and abandoned owing resistance issues or toxicity.[2] In this context, our research group has been working on the chemical modifications of the classical antimalarial no longer used QN.[3,4] Here, we report the synthesis of **4-aminoacridine (1)** and **4,9-diaminoacridines (2)** derivatives that were further evaluated for their *in vitro* activity against MKN-28 and Caco-2 cell lines.



Synthetic route



In vitro results

Compound	IC_{50} (µM)			
	HFF-1	Caco-2	MKN-28	SI[a]
4	14.05 ± 0,26	4.43 ± 0.51	2.93 ± 0,15	3.17
5	16.02 ± 0,49	5.49 ± 0.26	6.19 ± 0,04	2.59
6a	18.46 ± 0,20	7.28 ± 0.46	6.59 ± 0,01	2.54
2c	13.64 ± 0,65	10.01 ± 0.52	4.70 ± 0,61	1.36
1a	> 100	51.33 ± 2,34	25.12 ± 2,08	1.95
1b	51.67 ± 0.63	7.18 ± 0,59	3.74 ± 0.748	7.20
1c	66.08 ± 1.53	44.37 ± 2,05	16.22 ± 1.47	1.49
QN	10.59 ± 0.73	2.37 ± 0.02	2.46 ± 0.11	4.30

[a] Selectivity index (SI): reason between cytotoxicity in HFF-1 / cytotoxicity in cell lines, using IC_{50} value determined to the less potent compound.

Conclusion

- Both families confirmed their potential by showing **antiproliferative activity** in the **µM range**.
- Derivatives **1** presented **lower toxicity** against normal HFF-1 cells than their parent compound **QN**.
- The interactions of derivatives with **DNA** are under study.

References: **1.** B.Oien D. *et al. Sem Cancer Biol.*, **2021**, *68*, 21-30. **2.** Teixeira, C. *et al. Chem Rev.*, **2014**, *114*, 11164-11220. **3.** Fonte, M. *et al. Tetrahedron Lett.*, **2019**, *60*, 1166-1169. **4.** Fonte, M. *et al. ChemMedChem*, **2021**, *16*, 788.

Acknowledgement: This work was developed within the scope of projects UIDB/50006/2020 and PTDC/BTM-SAL/29786/2017, financed by national funds through the Fundação para a Ciência e Tecnologia (FCT). MF thanks the FCT for the doctoral grant SFRH/BD/147345/2019.