4,9-diaminoacridines and 4-aminoacridines as antiplasmodial dual-stage hits

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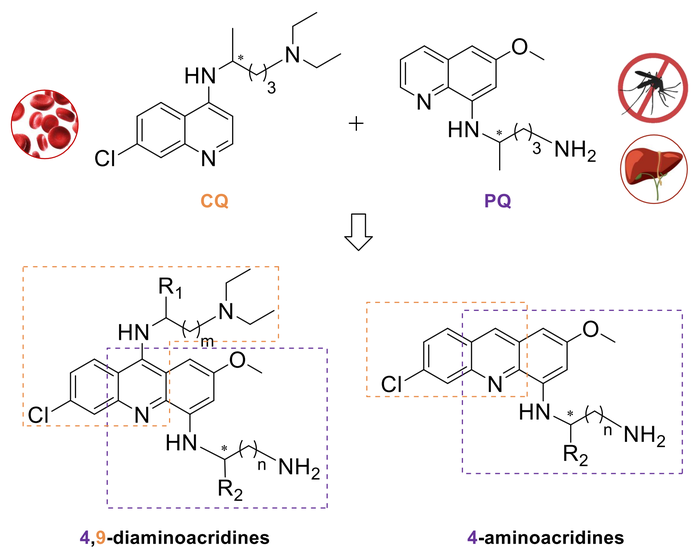
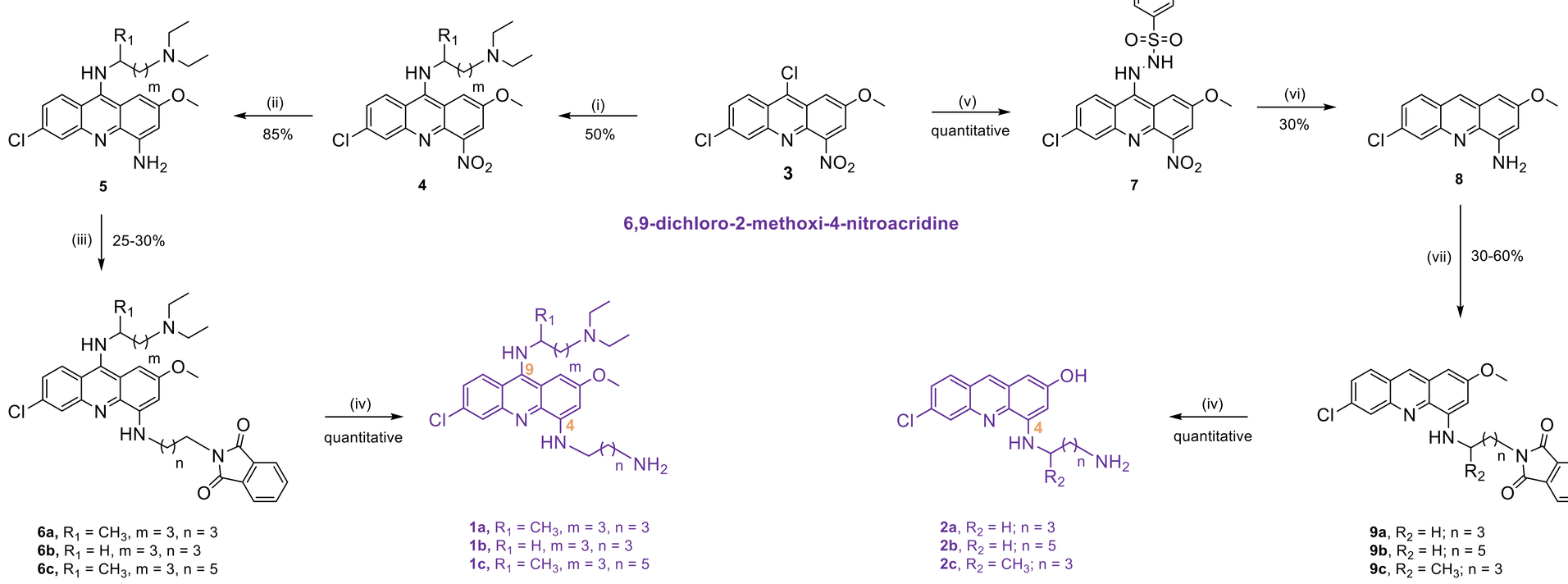
Aim

Malaria is one of the deadliest infectious diseases in the world. The eradication of malaria has not yet been achieved, mainly due to the emergence of resistant parasites. Therefore, **multi-target drugs** have being prioritized in antimalarial drug discovery, as targeting more than one process in the Plasmodium life cycle is likely to **increase efficiency**, while **decreasing** the chances of emergence of **resistance** by the parasite.[1] In this sense, and keeping in mind that the one cost-effective strategy is to repurpose existing drugs for malaria, or to rescue antimalarial pharmacophores,[1] we reported the synthesis and in vitro evaluation of two novels acridines families (**4,9-diaminoacridines** and **4-aminoacridines**) though the combination of primaquine (**PQ**) and chloroquine (**CQ**), two well-known antimalarial drugs with activities in different stages of the parasite life cycle,[2] hence acting as dual-stage antiplasmodial hits.



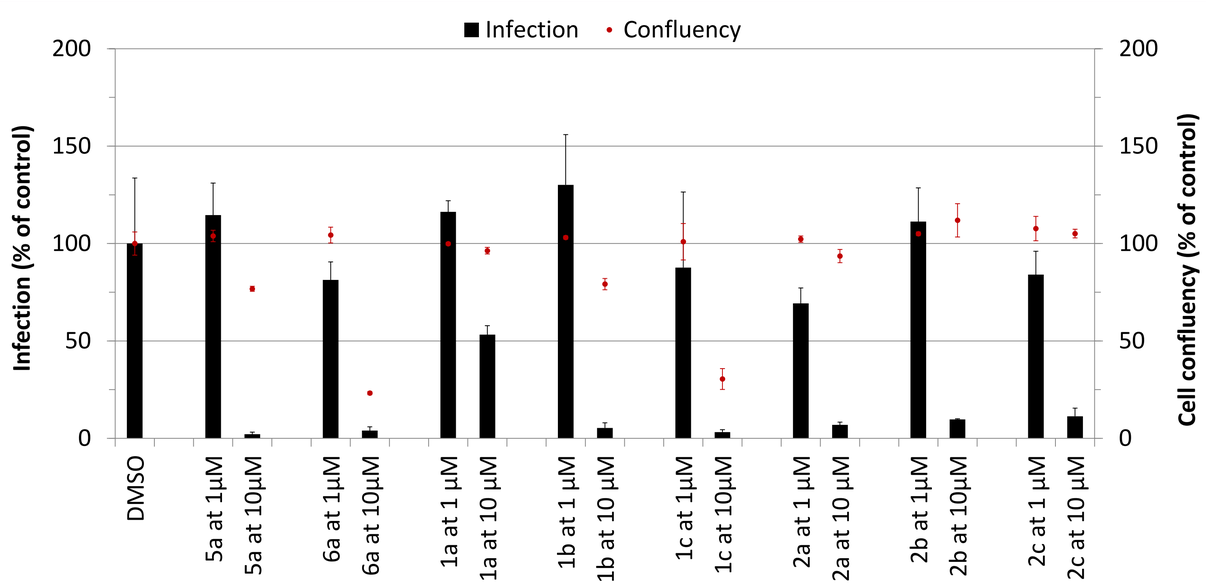
Synthetic route



In vitro results

Compound	IC_{50} (µM) blood-stage *Pf* 3D7	IC_{50} (µM) blood-stage *Pf* W2	IC_{50} (µM) liver-stage
5a	0.45 ± 0.22	0.49 ± 0.24	ND*
6a	0.16 ± 0.22	0.98 ± 0.24	ND
1a	0.68 ± 0.24	6.17 ± 0.23	11.02 ± 0.44
1b	0.44 ± 0.21	0.66 ± 0.25	ND
1c	0.26 ± 0.35	0.49 ± 0.23	ND
2a	5.64 ± 0.22	5.14 ± 0.23	2.22 ± 0.51
2b	>10	4.17 ± 0.23	1.64 ± 0.30
2c	>10	2.39 ± 0.24	2.04 ± 0.38
CQ	0.02	0.23	-
PQ	-	-	7.5

*ND – Not determined



Conclusions

- Synthesized compounds retained the activity of the parent compounds, which makes them potential antimalarial **dual-stage** hits;
- Activity is dependent of the nature and length of side chain introduced in position 4 and 9 of the acridine ring;

References: [1] Teixeira, C. et al. Chem Rev. **2014**, *114*, 11164-11220; [2] Fonte, M. et al. Tetrahedron Lett., **2019**, *60*, 1166-1169.

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