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Repurposing antiplasmodial leads for cancer: Exploring the antiproliferative effects of *N*-cinnamoyl-aminoacridines

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ABSTRACT

Drug repurposing and rescuing have been widely explored as cost-effective approaches to expand the portfolio of chemotherapeutic agents. Based on the reported antitumor properties of both *trans*-cinnamic acids and quinacrine, an antimalarial aminoacridine, we explored the antiproliferative properties of two series of *N*-cinnamoyl-aminoacridines recently identified as multi-stage antiplasmodial leads. The compounds were evaluated *in vitro* against three cancer cell lines (MKN-28, Huh-7, and HepG2), and human primary dermal fibroblasts. One of the series displayed highly selective antiproliferative activity in the micromolar range against the three cancer cell lines tested, without any toxicity to non-carcinogenic cells.

Cancer remains a pervasive and life-threatening disease worldwide.[4,5] Alongside surgery and radiotherapy, chemotherapy is one of the most common anticancer therapeutic approaches employed. However, it faces several limitations, such as high cost, low efficacy, resistance issues, and poor selectivity, translating into high toxicity.[6] Therefore, in spite of a constant quest for highly efficacious anticancer drugs and biopharmaceuticals, the traditional development pipeline is a costly, complex, and extensive process.[7] As such, drug repurposing and rescuing are being increasingly explored as strategies to find new uses for known drugs and pharmacophores, including for cancer. When rescuing or repurposing a well-known drug, prior knowledge regarding its safety, efficacy, and suitable administration route translates into a fast track towards more affordable medicines to treat conditions other than that for which the drug was originally licensed.[7–11] Indeed, there is growing evidence that several drugs may interact with multiple biological targets, which, in turn, may be implicated in more than one pathophysiological process.[12,13] Therefore, a single bioactive molecule holds the potential to play a therapeutic role in a wide range of diseases as diverse as, e.g., cancer and malaria.[14,15] For instance, the repurposing of antimalarials like chloroquine[16–19] or quinacrine (QN) [20–24] as anticancer agents has been widely explored.

QN (Fig. 1) and *trans*-cinnamic acids (CA, Fig. 1) are well-known bioactive scaffolds that have been extensively described for diverse medicinal purposes, including for cancer treatment.[20–22,25–33] Following its discovery in the 1920s as an antimalarial agent, QN has been widely documented for its anticancer potential.[21,34] Despite the exact mechanism(s) of action (MoA) underlying the anticancer activity of QN remaining unclear, it has been suggested that it may hinder cancer cell growth through (i) regulation of autophagy, (ii) intercalation into DNA, (iii) suppression of the nuclear factor-kappa B (NF-κB), (iv) alkalization of cellular compartments, (v) inhibition of topoisomerases, and (vi) activation of protein p53.[20–22, 35] In turn, the antineoplastic activity of CA derivatives has been linked to their ability to (i) induce apoptosis and cell cycle arrest through DNA damage in cancer cells, (iii) inhibit

Abbreviations: CA, cinnamic acid; DOX, doxorubicin; IC_{50}, half maximal inhibitory concentration; MoA, mechanism of action; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; QN, quinacrine; SI, selective index.

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hypoxia-induced angiogenesis, (iv) modulate crucial signaling pathways involved in cell survival, proliferation, and migration, and (v) exert antioxidant and anti-inflammatory actions important for the inhibition of tumor growth.[30–33].

Given the features of the QN and the CA moieties, their combination into a single molecule may offer advantages in the formulation of novel therapeutic candidates, including as antitumor agents. Thus, our research group has previously explored the antiproliferative properties of QN-CA conjugates, with very promising findings.[36,37] We have now investigated the *in vitro* antiproliferative effects of two families of *N*-cinnamoyl-aminoacridines (**1a-j** and **2a-h**, Fig. 1), recently reported by us as multi-stage antiplasmodial leads.[1] These compounds result from linking either the acridine core (**1a-j**) or the whole QN structure (**2a-h**) to a CA moiety through a 4-aminobutylamine spacer. Since these two sets of compounds showed different antiplasmodial profiles,[1] differences in their antiproliferative effects were equally anticipated.

Compounds **1a-j** and **2a-h** were prepared using a synthetic route previously developed and fine-tuned by us, and their analytical and structural data were consistent with previous reports.[1–3, 38]

Both sets of compounds were first screened *in vitro* against the gastric adenocarcinoma cell line MKN-28 and human dermal fibroblasts (HDF), at two different concentrations, 12.5 and 25 (**1a-j**) or 50 (**2a-h**) μM, using the colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (see SI). Conjugates **1a-j** displayed solubility issues, which prevented us to obtain reliable data at the highest concentration, 50 μM. Still, based on previous work, [1,2] we were not expecting compounds **1** to show any significant activity against cancer cell lines, in contrast with conjugates **2a-h**, which had already shown toxicity against a cancer cell line at 10 μM.[2] Therefore, although we could not compare both sets of conjugates at the highest concentration, the results depicted in Fig. 2 show that conjugates **1a-j** (embedding only the acridine core of QN) did not exhibit any toxicity against either MKN-28 or HDF cells, whereas conjugates **2a-h** (embedding the whole QN structure) displayed a notably selective action against the cancer cells. These results indicate that the aminoalkyl side chain linked to the acridine'sC-9 in the QN structure has a relevant role in the potency and selectivity of the antiproliferative effects of these compounds.

In face of these results, *N*-cinnamoyl-4,9-diaminoacridines (**2a-h**) were selected for determination of their growth inhibition IC_{50} values against the MKN-28, Huh-7 (hepatocyte-derived carcinoma), HepG2 (hepatocellular carcinoma), and HDF cell lines; the antineoplastic agent doxorubicin (DOX) and QN were included as controls in these experiments (Table 1). Overall, all compounds were active in the low micromolar range against the three cancer cell lines (MKN-28: 9.998 < IC_{50} (μM) < 15.540; Huh-7: 7.260 < IC_{50} (μM) < 12.905; HepG2: 3.328 < IC_{50} (μM) < 7.642), whereas no toxic effects to non-carcinogenic HDF cells could be detected up to the maximum concentration tested, 50 μM. Thus, these compounds displayed a remarkably selective action against cancer cells (SI > 4–15, Table 1), as well as marked antiproliferative potency, especially against hepatic cancer cell lines Huh-7 and HepG2. Compounds **2d** and **2b**, the most potent ones against Huh-7 and HepG2 respectively, were more active than the reference drug QN (Huh-7: IC_{50}(**2d**) = 7.260 ± 0.410 μM, IC_{50}(QN) = 8.696 ± 0.284 μM; HepG2: IC_{50}(**2b**) = 3.328 ± 1.505 μM, IC_{50}(QN) = 4,480 ± 0,680 μM). In fact, **2d** was equipotent to DOX, a reference antineoplastic drug (IC_{50}(DOX) = 6.053 ± 0.401 μM), against Huh-7 cells.

The small set of compounds studied does not allow for the establishment of meaningful structure–activity relationships and, consequently, no obvious correlation between the stereoelectronic properties of the cinnamoyl substituents (R_1) or the length of the amino side chain (R and n) and antiproliferative activity could be devised. Nonetheless, the following observations were made:

(a) for compounds with the longer side chain (n = 3, **2a-d**), the introduction of a substituent (R_1) in the cinnamoyl moiety is not advantageous for their antiproliferative activity, as **2d** (R_1 = H) was the most active of this set against the three cancer cell lines;
(b) the alteration of the aryl substituent (R_1) from *para* to *meta* position, as in **2a** (R_1 = *p*-F) versus **2c** (R_2 = *m*-F), does not have any significant impact on the *in vitro* activity against the three cell lines;
(c) for compounds with the shorter side chain (n = 2, **2e-h**), an electron-withdrawing aryl substituent R_1, such as fluorine in **2e**, appears to lead to higher activity against MKN-28 cells than an electron-donating one, such as methoxy in **2f**.

Overall, antiproliferative activities were stronger against HepG2 cells compared to other cell lines, whereas compound **2d** stood out as the most potent compound against all the three cancer cell lines included in this study.

As previously highlighted, both families of conjugates **1a-j** and **2a-h** displayed antiplasmodial effects across three distinct phases of parasite life cycle, as previously reported by us.[1,2] The presence of the aminoalkyl substituent at the acridine ring's C-9 in conjugates **2a-h** increased both antiplasmodial blood stage activity and toxicity to Huh-7 hepatocytes; in turn, conjugates **1a-j** that lack this aminoalkyl side chain were not toxic. Results herein reported therefore suggest that the same structural feature, i.e., the basic aminoalkyl side chain, is equally important for the selective action of conjugates **2a-h** against carcinogenic cells. Although the MoA underlying either the antiplasmodial or the antiproliferative activity of these conjugates are yet to be established, our results are in line with the crucial role that has been ascribed to the basic aminoalkyl side chain for antiplasmodial activity, namely, by facilitating the accumulation of the compounds in the acidic digestive vacuole of the malaria parasite during its intraerythrocytic stage.[39,40] A similar effect could be hypothesized as the reason behind the selective action of conjugates **2a-h** against carcinogenic cells: tumor acidity has

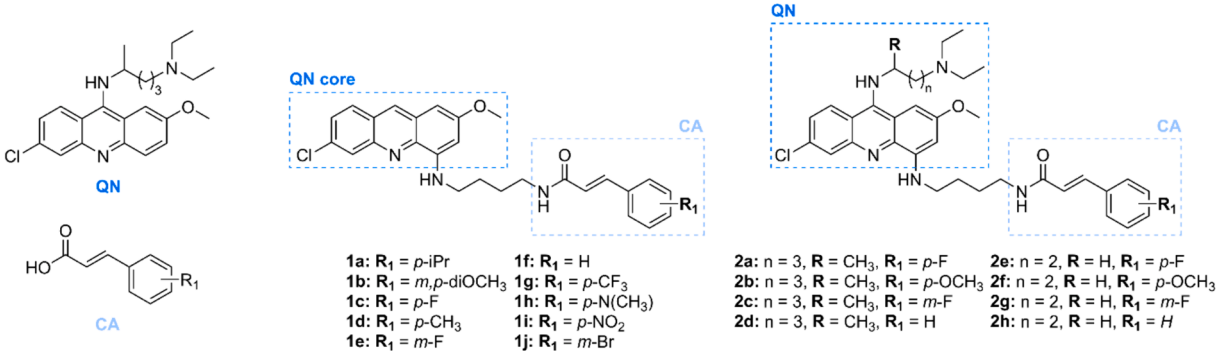

Fig. 1. Multi-stage antiplasmodial *N*-cinnamoyl-aminoacridines (**1a-j** and **2a-h**) herein investigated for their antiproliferative effects *in vitro*. The structures of the QN and CA scaffolds are also included, for reference.[1–3.]

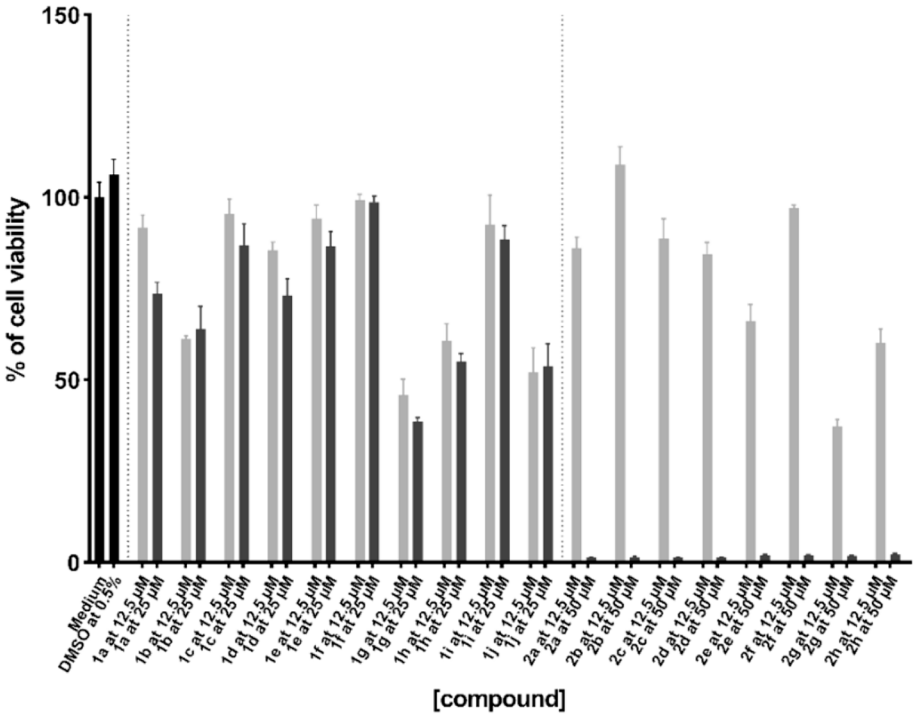

Fig. 2. Initial screening of conjugates **1a-j** (at 12.5 and 25 μM) and **2a-h** (at 12.5 and 50 μM) on MKN-28 cells.

Table 1
In vitro antiproliferative activity (IC_{50}) and selectivity (SI) of compounds **2a-h** against MKN-28, Huh-7, HepG2 and HDF cell lines. The antineoplastic drug doxorubicin (DOX) was included for reference.

Comp.	R	n	R_1	$IC_{50} \pm$ SD, μM[a] MKN-28[b]	SI[c]	Huh-7[d]	SI[c]	HepG2[d]	SI[c]	HDF[b, e]
2a	CH_3	3	*p*-F	12.483 ± 1.366	> 4.0	12.425 ± 2.963	> 4.0	7.642 ± 2.420	> 6.5	> 50
2b	CH_3	3	*p*-OCH_3	13.667 ± 1.665	> 3.6	12.125 ± 0.983	> 4.1	3.328 ± 1.505	> 15.0	> 50
2c	CH_3	3	*m*-F	12.720 ± 0.276	> 3.9	12.905 ± 0.757	> 3.9	5.064 ± 0.107	> 9.9	> 50
2d	CH_3	3	H	9.998 ± 0.359	> 5.0	7.260 ± 0.410	> 6.9	4.166 ± 0.879	> 12.0	> 50
2e	H	2	*p*-F	12.250 ± 1.300	> 4.1	11.172 ± 1.964	> 4.5	6.319 ± 2.198	> 7.9	> 50
2f	H	2	*p*-OCH_3	15.540 ± 1.933	> 3.2	12.375 ± 2.199	> 4.0	5.383 ± 0.670	> 9.3	> 50
2 g	H	2	*m*-F	12.960 ± 1.964	> 3.8	11.535 ± 2.836	> 4.3	5.215 ± 0.612	> 9.6	> 50
2 h	H	2	H	15.430 ± 1.814	> 3.2	12.130 ± 0.693	> 4.1	4.110 ± 0.730	> 12.2	> 50
QN	–	–	–	2.46 ± 0.11[e]	–	8.696 ± 0.284	–	4.480 ± 0.680	–	nd
DOX	–	–	–	0.34 ± 0.01[e]	–	6.053 ± 0.401	–	0.425 ± 0.045	–	nd

[a] IC_{50}: compound concentration causing inhibition of cell growth by 50 %; [b] antiproliferative activity evaluated at the Escola Superior de Saúde (ESS), using the MTT assay; [c] Selectivity index (SI): IC_{50}(HDF cells)/IC_{50} (cancer cells); [d] antiproliferative activity evaluated at the Institute of Molecular Medicine (iMM), using the Alamar Blue assay in; [e] 50 μM was the highest concentration tested; [d] taken from reference [37]; nd, not determined.

been highlighted as both a hallmark and a therapeutic target for anti-cancer agents.[41] Yet, one cannot rule out other relevant factors or MoA (s) for these or similar compounds. Indeed, the MoA(s) through which *N*-cinnamoyl-4,9-diaminoacridines **2a-h** exert their antiproliferative activity remains to be elucidated. One possibility is that, due to the planarity of their heteroaromatic core, and resemblance to QN, these compounds might be able to intercalate into DNA, disrupting its structure and interfering with its replication and transcription.[20–22,35] On the other hand, the presence of a CA moiety that may act as Michael acceptor through its α,β-unsaturated carbonyl moiety might induce formation of covalent complexes with nucleophilic groups (e.g., cysteine side-chain thiols) in key proteins directly or indirectly involved in cell signaling, apoptosis, and other cellular processes relevant for the growth of carcinogenic cells.[30–33] Still, other possibilities cannot be ruled out, as the acridine (QN) and Michael acceptor (CA) moieties might further (or alternatively) engage in other biochemical processes contributing to the hindrance of tumor cell growth; an additional and relevant observation is that both these moieties are equally present in conjugates **1a-j** that do not display the same bioactivity profile. This further reinforces the hypothesis that the aminoalkyl side chain present in **2a-h** and absent in **1a-j** could be making a difference in regard to the ability of the former to accumulate inside their target cells. Anyway, this highlights the need to carry out further studies envisaging the establishment of the mechanisms of internalization and action of these compounds.

In summary, two families of *N*-cinnamoyl-aminoacridines (**1a-j** and **2a-h**), previously reported as potent multi-stage antiplasmodial leads, were evaluated for their antiproliferative activity. While conjugates **1a-j** were not cytotoxic against either cancer (MKN-28) or healthy (HDF) cells, conjugates **2a-h** exhibited selective low micromolar activity against MKN-28, Huh-7, and HepG2 cancer cells. As such, compounds **2a-h**, particularly **2d**, represent a promising starting point for the pursuit of novel affordable leads against malignant tumor cells. Further structural optimization, and elucidation of their MoA(s) may pave the way towards more selective and potent antineoplastic candidates. Altogether, our findings reinforce the therapeutic value of repurposing scaffolds based on QN for cancer therapy.

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CRediT authorship contribution statement

Mélanie Fonte: Writing – original draft, Methodology, Investigation, Data curation. **Catarina Rôla:** Investigation, Formal analysis, Data curation. **Sofia Santana:** Validation, Investigation, Formal analysis, Data curation. **Miguel Prudêncio:** Writing – review & editing, Supervision, Resources, Formal analysis. **Joana Almeida:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis. **Ricardo Ferraz:** Writing – review & editing, Resources, Methodology, Formal analysis. **Cristina Prudêncio:** Validation, Supervision, Resources. **Cátia Teixeira:** Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Paula Gomes:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2024.129894.

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