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Synthesis and antiplasmodial evaluation of aziridine–(iso)quinoline hybrids and their ring-opening products†

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Aziridine–(iso)quinoline hybrid systems were prepared as novel synthetic intermediates *en route* to functionalized (iso)quinolines with potential antimalarial activity. Various quinolinecarboxaldehydes were converted into quinoline–aziridine–pyrazole, –pyridazinone or –pyrimidinone hybrids, and the three-membered azaheterocyclic moiety in these compounds was finally subjected to ring opening by either methanol or water to provide the corresponding functionalized quinolines. In addition, 5-hydroxyisoquinoline was used for the preparation of isoquinoline–aziridine chimeras, which were further transformed into a variety of functionalized isoquinolines *via* regioselective aziridine ring opening by various nucleophiles. Antiplasmodial evaluation of these new aziridine–(iso)quinoline hybrids and their ring-opening products revealed micromolar potency (0.22–30 μM) for all representatives against a chloroquine-sensitive strain of the malaria parasite *Plasmodium falciparum*. The six most potent compounds also showed micromolar activity against a chloroquine-resistant strain of *P. falciparum* with IC_{50}-values ranging between 1.02 and 17.58 μM.

Introduction

An emerging strategy within drug discovery programs comprises the synthesis of novel chemical entities *via* combination of two biologically relevant moieties. This strategy has recently been used in the development of, for example, new anticancer, anti-Alzheimer, antimalarial and antiviral agents.[1–5] An important motive for the application of molecular hybridization is the development of active drugs which can obviate drug resistance by linking bioactive units into molecules that are recognized and transported into the desired cells. However, in addition to these biological perspectives, molecular hybridization also allows for selective modification of the more reactive entity within hybrid systems, thus providing an easy access to new functionalized target compounds with biological interest because of the conservation of the second bioactive moiety.[5]

The importance of the quinoline class of compounds in the treatment of malaria (as exemplified by chloroquine **1**, mefloquine **2**, quinine **3** and quinidine **4**; Fig. 1) has unequivocally been established and has been a source of inspiration for medicinal chemists for many years.[6] As a result, a large variety of functionalized quinolines and quinoline-based hybrid molecules[7–10] has been designed, and several antiplasmodial quinoline drugs have been commercialized.[6,11,12] Although less frequently encountered as the core structure in bioactive substances as compared to quinolines, isoquinolines have also been associated with a range of biological activities such as anticancer, anti-inflammation, anti-diabetes, anti-HIV, *etc.*[13–17] In addition, diverse studies have ratified the antimalarial properties of isoquinoline derivatives, making these systems attractive templates in antimalarial research as well.[11,17]

The combination of a(n) (iso)quinoline scaffold with a bioactive heterocyclic moiety in a hybrid system *via* an aziridine linker and the study of their applications comprises an unexplored field of research. As (iso)quinolines are known to be suitable templates for the synthesis of antimalarial agents, antimalarial evaluation of novel aziridine–(iso)quinoline chimeras could potentially provide new leads in this field. Moreover, the inherent reactivity of the aziridine nucleus allows for selective transformations of these hybrids to provide novel functionalized (iso)quinoline derivatives.[18–25] Hence, the objective of this study comprises the design, synthesis and antiplasmodial evaluation of a set of new aziridine–(iso)quinoline systems and the corresponding aziridine ring-opening products.

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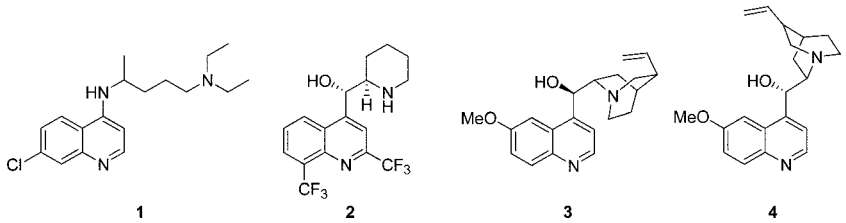
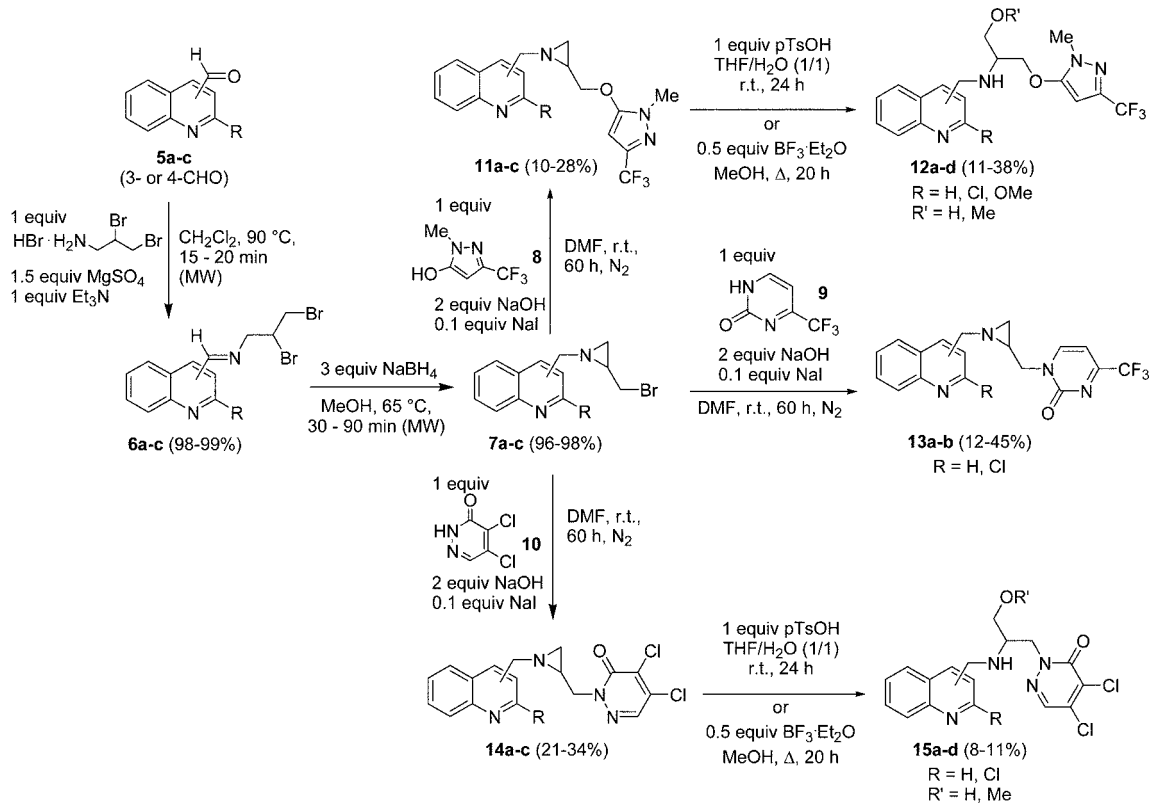


Fig. 1 Important quinoline-based antimalarials.

Results and discussion

The synthetic strategy used to construct the aziridine–quinoline chimera consists of the initial synthesis of {[2-(bromomethyl)-aziridin-1-yl]methyl}quinolines starting from quinolinecarboxaldehydes. From a synthetic perspective, the 2-(bromomethyl) aziridine core has proven to be an excellent synthon in organic chemistry,[26,27] especially toward the preparation of functionalized aminopropanes which in turn are known to possess a wide variety of biological activities, for example as β-blockers, antibiotics, antimalarials, anti-cancer agents, *etc.*[28–38] Condensation of quinoline-3- and quinoline-4-carboxaldehydes **5** with 2,3-dibromopropylamine hydrobromide in dichloromethane in the presence of magnesium sulfate and triethylamine resulted in the formation of dibromoimines **6** after 15–20 min in a closed recipient at 90 °C applying microwave irradiation. These imines **6** were immediately treated with sodium borohydride in methanol in a closed recipient to produce the desired new {[2-(bromomethyl)aziridin-1-yl]methyl}quinolines **7** after 30–90 min at 65 °C under microwave irradiation (Scheme 1 and Table 1). Optimization of the reaction conditions showed that full conversion was only obtained when the reducing agent was sequentially added (2 × 1.5 equiv., with an interval of 45 min). This method afforded aziridines **7** in excellent yields (96–98%) and purities (>95%, NMR). All newly synthesized {[2-(bromomethyl)aziridin-1-yl]methyl}quinolines **7** appeared to be rather unstable, even when stored at low temperatures (−20 °C); so further synthetic modification of these hybrids **7** was performed immediately through substitution with heteroaromatic nucleophiles. Three nucleophiles, *i.e.*, 5-hydroxy-1-methyl-3-(trifluoromethyl)pyrazole **8**, 4-trifluoromethyl-1*H*-pyrimidin-2-one **9** and 4,5-dichloro-2*H*-pyridazin-3-one **10**, were selected because of their known antimalarial potency,[12] which could be beneficial within the concept of biological hybrid formation. To



Scheme 1 Synthesis of racemic aziridine–quinoline hybrids and their ring-opening products.

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Table 1 Substitution pattern and isolated yields of quinolines **7**, **11**, **12**, **13**, **14** and **15**

Entry	Compound	Quinolin-3- or 4-yl	R	R′	Yield
1	**7a**	3-yl	H	—	96%
2	**7b**	3-yl	Cl	—	98%
3	**7c**	4-yl	H	—	96%
4	**11a**	3-yl	H	—	10%
5	**11b**	3-yl	Cl	—	28%
6	**11c**	4-yl	H	—	12%
7	**12a**	3-yl	H	H	11%
8	**12b**	3-yl	Cl	H	24%
9	**12c**	3-yl	Cl	CH_3	12%
10	**12d**	3-yl	OMe	CH_3	38%
11	**13a**	3-yl	H	—	45%
12	**13b**	3-yl	Cl	—	12%
13	**14a**	3-yl	H	—	32%
14	**14b**	3-yl	Cl	—	21%
15	**14c**	4-yl	H	—	34%
16	**15a**	3-yl	H	H	8%
17	**15b**	3-yl	Cl	H	9%
18	**15c**	4-yl	H	H	11%
19	**15d**	4-yl	H	CH_3	10%

accomplish the desired bromide displacement reaction, one equiv. of nucleophile **8**, **9** or **10** was first treated with 2 equiv. of sodium hydroxide and 0.1 equiv. of sodium iodide in DMF at room temperature under inert atmosphere (N_2). After one hour, (aziridin-1-ylmethyl)quinolines **7** were added to the mixture and further stirring for 60 h at room temperature afforded the desired novel quinoline–aziridine–pyrazole/pyrimidinone/pyridazinone hybrid compounds **11**, **13** and **14** in moderate to good yields (37–82%). Finally, column chromatography on silica gel was performed to afford analytically pure samples for spectroscopic analysis and biological testing, although this purification step accounted for reduced yields (10–45%) due to the strong polarity of these novel compounds **11**, **13** and **14** (Scheme 1). Literature reports show that deprotonation of pyrimidin-2-one **9** and pyridazin-3-one **10** leads to selective *N*-alkylation, supporting the formation of *N*-functionalized pyrimidinones **13** and pyridazinones **15**.[39–42] It should be noted that moderate to low yields were obtained after column chromatographic purification (Scheme 1 and Table 1), and that the initially obtained reaction yields were considerably higher.

An interesting feature of these novel hybrid structures **11**, **13** and **14** involves the attachment of the quinoline ring to the heteroaromatic moiety (pyrazole, pyrimidine or pyridazine) by an aziridine linker. This small azaheterocycle represents a useful synthon since the strained three-membered ring can be opened toward functionalized aminopropanes, a moiety which has already proven its broad therapeutic relevance in the past.[28–38] Therefore, {[2-(1-methyl-3-trifluoromethyl-1*H*-pyrazol-5-yloxymethyl)aziridin-1-yl]methyl}quinolines **11** and 4,5-dichloro-2-[1-(quinolinylmethyl)aziridin-2-ylmethyl]-2*H*-pyridazin-3-ones **14** were selected for further elaboration and subjected to two types of regioselective ring opening. In the first approach, the aziridine ring was activated by protonation with an equimolar mixture of *para*-toluenesulfonic acid followed by ring opening by water at the less sterically hindered aziridine carbon atom,[43] affording the desired functionalized aminopropanes **12a,b** and **15a–c** (R′ = H) in good yields (60–82%) after 24 h at room temperature in a THF–water (1/1) solvent mixture (Scheme 1). Perilous column chromatography on silica gel was performed in order to obtain analytically pure samples, resulting in low overall yields of 8–24% after purification. To evaluate a second approach toward the ring opening of azaheterocycles **11** and **14**, the aziridine ring was activated using the Lewis acid $BF_3 \cdot Et_2O$. Aziridine–quinoline chimeras **11** and **14** were thus treated with 0.5 equiv. of $BF_3 \cdot Et_2O$ in methanol at reflux temperature for 20 h, affording functionalized aminopropanes **12c** and **15d** (R′ = Me) through ring opening by methanol in good yields (74–83%). It should be noted that lower Lewis acid loadings (<0.5 equiv.) resulted in longer reaction times and/or lower overall yields. Once again, a tedious purification step affected the overall yields (10–24%) of the finally obtained products (Scheme 1 and Table 1).

Notably, the $BF_3 \cdot Et_2O$-mediated ring opening of the aziridine–quinoline–pyrazole hybrid **11b** under microwave irradiation (MeOH, 90 °C, 1 h) yielded quinoline **12c** (R = Cl, 12%) only as the minor product, while the major product **12d** (R = OMe, 38%) was formed through replacement of chloride by methanol at the 2-position of the quinoline ring. Similar reactions have been reported in the literature.[44]

A second approach toward aziridine-containing hybrids as intermediates for the synthesis of potential novel antimalarials was based on the use of the isoquinoline template. As mentioned above, the antiplasmodial activity of isoquinoline derivatives has by far not been described as extensively as that of the quinoline class, although diverse literature reports have mentioned their antimalarial properties.[11,17] Therefore, functionalization of the isoquinoline nucleus *via* molecular hybridization was considered a new and interesting tool to provide an entry to new representatives of this class of compounds. In order to achieve this objective, a reactive moiety had to be introduced and, in analogy with the first part of this work, a strained aziridine ring was proposed.

As an isoquinoline source, the readily available 5-hydroxyisoquinoline **16** was employed. The hydroxyl group was first deprotonated using sodium hydroxide, and nucleophilic substitution then occurred after adding 1 equiv. of an 1-arylmethyl-2-(bromomethyl)aziridine.[26,27] Reaction for 2–4 h in DMF at 100 °C thus afforded novel 5-(aziridin-2-ylmethoxy)isoquinolines **17** in good yields (65–90%) (Scheme 2 and Table 2).

Finally, different strategies for the opening of the constrained ring in these aziridine–isoquinoline hybrids **17** were evaluated. Firstly, the aziridine system in compound **17** was activated by *N*-protonation using *para*-toluenesulfonic acid in a THF–water (1/1) solvent mixture. Reaction at reflux for 6 h caused water to open the activated aziridine ring at the less substituted position, which afforded isoquinoline–aminopropanols **18** in high yields (85–94%) (Scheme 2 and Table 2). Secondly, the aziridine ring of hybrids **17** was activated by complexation of the nitrogen atom with a Lewis acid (*e.g.*, $BF_3 \cdot Et_2O$), which allowed the strained three-membered ring to be opened at the less hindered aziridine carbon atom by the solvent (methanol) after 30 min at 90 °C

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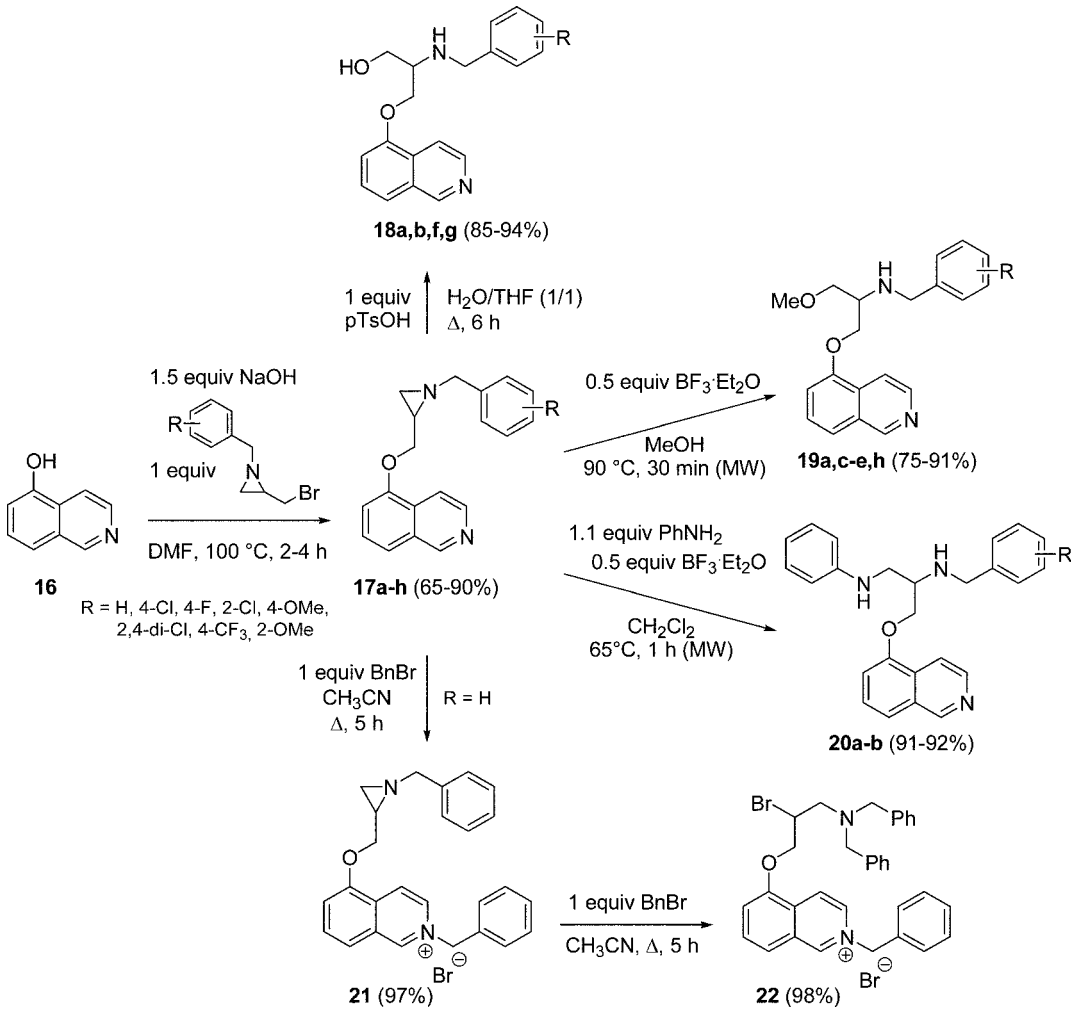

Scheme 2 Synthesis of racemic aziridine–isoquinoline hybrids and their ring-opening products.

under microwave conditions,[43] yielding functionalized isoquinolines **19** in high yields (75–91%). In addition to the oxygen-based nucleophiles H_2O and MeOH, aniline was used as a nitrogen-based nucleophile to induce ring opening of aziridines **17** *en route* to 1,2-diaminopropanes. To that end, aziridine–isoquinoline hybrids **17** were dissolved in dichloromethane in the presence of 0.5 equiv. of $BF_3 \cdot Et_2O$, after which 1.1 equiv. of aniline was added. Reaction occurred under microwave irradiation (1 h at 65 °C), providing new isoquinoline derivatives **20** in high yields (91–92%). As reported in the literature, Lewis acid-mediated ring opening of 2-alkylaziridines by aromatic amines occurred *via* a nucleophilic attack at the less substituted aziridine carbon atom.[43] When $Yb(OTf)_3$ was used instead of $BF_3 \cdot Et_2O$, yields dropped to 68% applying the same reaction conditions, while $Cu(OTf)_2$ did not result in conversion at all. Furthermore, after evaluating the effect of different amounts of Lewis acid (0.2, 0.5, 1 and 2 equiv.) on the overall reaction efficiency, ring opening utilizing 0.5 equiv. of $BF_3 \cdot Et_2O$ was found to provide optimal results.

A final method to activate the aziridine moiety in systems **17** involved alkylation of the aziridine nitrogen atom. Upon addition of 1 equiv. of benzyl bromide to the aziridine–isoquinoline chimera **17** in CH_3CN, selective alkylation of the isoquinoline nitrogen atom was observed, resulting in the formation of the isoquinolinium salt **21**.[17] Still containing a reactive aziridine linker, this isoquinolinium bromide **21** was again treated with an equimolar amount of benzyl bromide in acetonitrile for 5 h at reflux temperature, affording the desired ring-opening product, *i.e.*, β-bromoamine **22**, in excellent yield (98%) (Scheme 2 and Table 2). According to the literature, ring opening of *N*,*N*-dialkylaziridinium salts by bromide proceeds at the more hindered aziridine carbon atom.[43,45,46] It should be noted that isoquinolinium salts have been reported to exhibit potent antiplasmodial activities.[17]

With a small library of aziridine–(iso)quinoline chimeras **11a–c**, **13a,b**, **14a–c**, **17a–h**, **21** and their ring-opening products **12a–d**, **15a–d**, **18a,b,f,g**, **19a,c–e,h**, **20a–b**, **22** in hand, antiplasmodial screening was undertaken. All samples were tested in triplicate against a chloroquine-sensitive (CQS) strain of *Plasmodium falciparum* (NF54). Subsequently, only those samples showing promising antiplasmodial activity were tested against a chloroquine-resistant (CQR) strain of *P. falciparum*

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Table 2 Substitution pattern and isolated yields of isoquinolines **17**, **18**, **19**, **20**, **21** and **22**

Entry	Compound	R	Yield
1	**17a**	H	90%
2	**17b**	4-Cl	80%
3	**17c**	4 F	75%
4	**17d**	2-Cl	74%
5	**17e**	4-OMe	77%
6	**17f**	2,4-di-Cl	82%
7	**17g**	4-CF_3	84%
8	**17h**	2-OMe	65%
9	**18a**	H	94%
10	**18b**	4-Cl	85%
11	**18f**	2,4-di-Cl	89%
12	**18g**	4-CF_3	93%
13	**19a**	H	91%
14	**19c**	4-F	79%
15	**19d**	2-Cl	82%
16	**19e**	4-OMe	85%
17	**19h**	2-OMe	75%
18	**20a**	H	92%
19	**20b**	4-Cl	91%
20	**21**	—	97%
21	**22**	—	98%

(Dd2) and screened for *in vitro* cytotoxicity against a mammalian cell-line, Chinese Hamster Ovarian (CHO), using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT)-assay. Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen.[47] Quantitative assessment of antiplasmodial activity *in vitro* was determined *via* the parasite lactate dehydrogenase assay using a modified method described by Makler *et al.*[48] The test samples were tested in triplicate on one occasion.[49] The MTT-assay was used to measure all growth and survival, and compares well with other available assays.[50,51] The tetrazolium salt MTT was used to measure growth and chemosensitivity. The test samples were tested in triplicate on one occasion.[52]

The results of the biological evaluation are summarized in Table 3. All compounds exhibited micromolar potencies against a chloroquine-sensitive NF54 strain of *P. falciparum*, with 21 of the 37 samples having IC_{50}-values between 220 nM and 20 μM. Subsequently, the activity of the six most potent compounds was determined against a chloroquine-resistant strain of *P. falciparum* (Dd2), again resulting in micromolar activities with IC_{50}-values ranging between 1.02 and 17.58 μM. Isoquinolinium salts **21** and **22** in particular displayed promising *in vitro* activities (1.09 μM and 220 nM against a NF54 strain and 1.02 μM and 1.17 μM against a Dd2 strain, respectively). These six representatives also appear to have high selectivity indices toward *P. falciparum* and low resistance indices, illustrating the potential of these compounds as novel templates in antimalarial drug design.

From a structure–activity relationship viewpoint, a few observations can be made. Firstly, it is clear that isoquinolinium-based hybrids display the most potent bioactivities, and that this class of compounds holds the most promising potential upon further investigation. Secondly, aziridine ring opening by both water and aniline mostly results in slightly more active compounds as compared to methanol-induced ring-opening products, although the difference is small. Finally, both the introduction of a chloro atom at the 2-position of the quinoline ring and the choice of the heterocyclic moiety (pyrazole, pyrimidinone, pyridazinone) in quinoline-based hybrids does not seem to have a pronounced effect on the biological activity.

In conclusion, a new approach to functionalize (iso)quinolines *via* molecular hybridization with a small reactive heterocycle, *i.e.* a strained aziridine ring, was elaborated. With aziridines being useful synthons in organic synthesis, further

Table 3 IC_{50}-values of aziridine–(iso)quinoline hybrids **11a–c**, **13a,b**, **14a–c**, **17a–g**, **21** and their ring-opening products **12a–d**, **15a–d**, **18a,b,f,g**, **19a,c–e**, **20a,b**, **22** tested for *in vitro* antimalarial activity and cytotoxicity[a]

Entry	Compound	NF54: IC_{50} (μM)	Dd2: IC_{50} (μM)	CHO: IC_{50} (μM)	SI[b]	RI[c]
1	**11a**	>27.60	ND	ND	ND	ND
2	**11b**	>25.20	ND	ND	ND	ND
3	**11c**	9.66	ND	ND	ND	ND
4	**12a**	4.73	15.25	181.14	38.28	1.23
5	**12b**	>24.11	ND	ND	ND	ND
6	**12c**	17.02	ND	ND	ND	ND
7	**12d**	>23.56	ND	ND	ND	ND
8	**13a**	>27.75	ND	ND	ND	ND
9	**13b**	9.12	ND	ND	ND	ND
10	**14a**	12.73	ND	ND	ND	ND
11	**14b**	22.75	ND	ND	ND	ND
12	**14c**	26.85	ND	ND	ND	ND
13	**15a**	15.29	ND	ND	ND	ND
14	**15b**	14.99	ND	ND	ND	ND
15	**15c**	24.52	ND	ND	ND	ND
16	**15d**	14.49	ND	ND	ND	ND
17	**17a**	9.99	ND	ND	ND	ND
18	**17b**	>30.79	ND	ND	ND	ND
19	**17c**	15.89	ND	ND	ND	ND
20	**17d**	12.93	ND	ND	ND	ND
21	**17e**	9.99	ND	ND	ND	ND
22	**17f**	>27.84	ND	ND	ND	ND
23	**17g**	>27.90	ND	ND	ND	ND
24	**17h**	5.29	8.46	52.27	9.88	1.60
25	**18a**	6.81	17.58	148.19	21.76	2.58
26	**18b**	22.75	ND	ND	ND	ND
27	**18f**	>26.51	ND	ND	ND	ND
28	**18g**	11.69	ND	ND	ND	ND
29	**19a**	13.03	ND	ND	ND	ND
30	**19c**	24.38	ND	ND	ND	ND
31	**19d**	16.53	ND	ND	ND	ND
32	**19e**	>28.37	ND	ND	ND	ND
33	**19h**	>28.38	ND	ND	ND	ND
34	**20a**	4.69	8.21	237.03	50.50	1.75
35	**20b**	10.53	ND	ND	ND	ND
36	**21**	1.09	1.02	51.80	47.70	0.94
37	**22**	0.22	1.17	45.06	205.04	5.32
38	CQ ($n = 14$)	0.03	0.53	ND	ND	21.25
39	Artunesate ($n = 8$)	0.02	ND	ND	ND	ND
40	Emetine	ND	ND	0.40	ND	ND

[a] ND = not determined; CQ = chloroquine. [b] SI (Selectivity Index) = IC_{50} CHO/IC_{50} NF54. [c] RI (Resistance Index) = IC_{50} Dd2/IC_{50} NF54.

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functionalization of these novel aziridine–(iso)quinoline chimeras was effected by ring opening of the aziridine moiety by water, methanol, aniline or bromide affording new functionalized (iso)quinolines. Furthermore, the antiplasmodial activity and cytotoxicity of the novel aziridine–(iso)quinoline class of compounds and their ring-opening products were demonstrated. All tested compounds displayed micromolar activity against a chloroquine-sensitive strain of *P. falciparum*, and six compounds also showed micromolar activity against a chloroquine-resistant strain of *P. falciparum*. High selectivity indices asserted the low cytotoxicity of these compounds, demonstrating the promising potential of these new compounds as potential novel antimalarial lead structures.

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