Programmed multiple C–H bond functionalisation of the privileged 4-hydroxyquinoline template

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Abstract

The introduction of substituents on bare heterocyclic scaffolds can selectively be achieved by directed C–H functionalisation. However, such methods have only occasionally been used, in an iterative manner, to decorate various positions of a medicinal scaffold to build chemical libraries. We herein report the multiple, site selective, metal-catalyzed C–H functionalisation of a "programmed" 4-hydroxyquinoline. This medicinally privileged template indeed possesses multiple reactive sites for diversity-oriented functionalisation, of which four were targeted. The C-2 and C-8 decorations were directed by an N-oxide, before taking benefit of an O-carbamoyl protection at C-4 to perform a Fries rearrangement and install a carboxamide at C-3. This also released the carbonyl group of 4-quinolones, the ultimate directing group to functionalise position 5. Our study highlights the power of multiple C–H functionalisation to generate diversity in a biologically relevant library, after showing its strong antimalarial potential.

Introduction

The confluence of chemical libraries and biological screenings holds huge promises for drug discovery. The development of medicinally relevant compound collections can be addressed by smart synthetic strategies,[1] while late-stage functionalisation approaches provide a useful complement for library diversification.[2,3] Indeed, achievements empowered by transition-metal-catalysis[4] during the past two decades have permitted the site-selective $C(sp^2)$–H bond functionalisation of aromatic and heteroaromatic scaffolds by the use of directing groups.[5,6,7,8,9] These methods allow diversity to be introduced on medicinal targets with minimal functional group manipulations. The concept was initially applied by Yu to the divergent C–H functionalisation of the non-steroidal anti-inflammatory drug celecoxib, directed by a sulfonamide function present on the molecule.[10] Several methodology-driven C–H functionalisations then allowed the straightforward diversification of many pharmaceutical and biologically relevant substrates.[11] Overall, these approaches constitute a paradigm in diversity-oriented synthesis strategies, permitting the late-stage diversification of key pharmaceutical scaffolds.
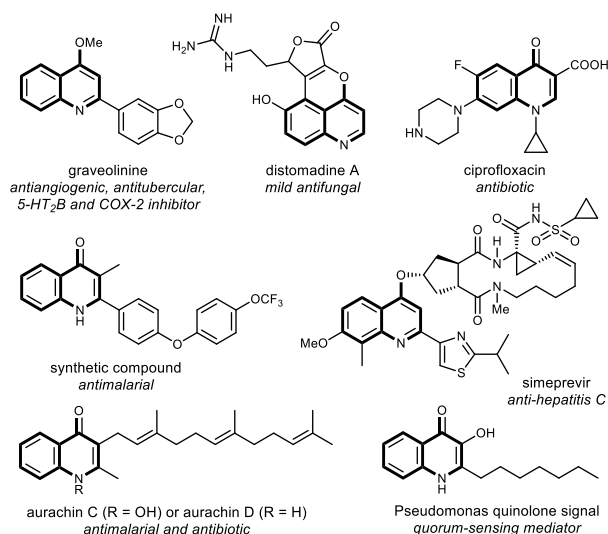
Multiple C–H functionalisations have however more rarely been used to decorate a bare heterocyclic template in an iterative manner, especially in the medicinal context. For example (Fig. 1, top), multiple arylations were reported on thiazole N-oxide,[12] thiazoles,[13,14] azaindoles N-oxide,[15] imidazole,[16] 3-methoxythiophene,[17] imidazo[1,2-a]pyrazines,[18] or 3-acetylpyrrole.[19]
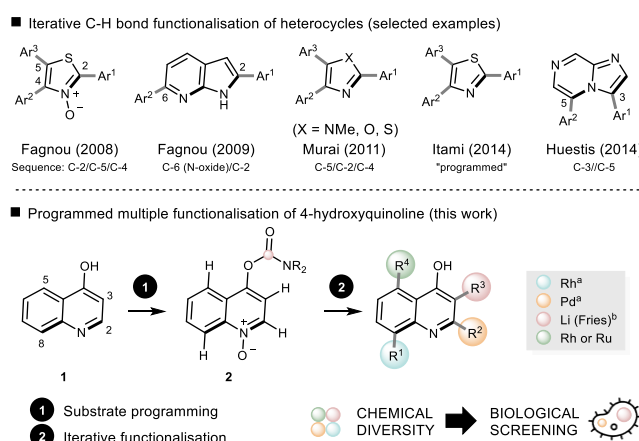
Fig. 1 Divergent multiple C–H bond functionalisation of heterocycles. Notes: [a] Steps can be inverted; [b] After N-oxide removal.

We report herein the programmed multiple C–H bond functionalisation of the 4-hydroxyquinoline (1) pharmacophore. After introducing a carbamate and an N-oxide (2) for site-selectivity, this scaffold was successively decorated at positions 8, 2, 3 and 5 (Fig. 1, bottom).

Importantly, *4-hydroxy*quinoline-based substrates have rarely been addressed by methodological studies, despite significant interests for this scaffold. Compounds possessing the 4-hydroxyquinoline core or its 4-quinolone tautomer have been associated to numerous activities, especially in the field of cancer, infectious and parasitic, or cardiovascular diseases (Fig. 2).[20] Some of them were taken as an inspiration for substituent choice during this work.

graveolinine
*antiangiogenic, antitubercular,
5-HT_{2B} and COX-2 inhibitor*

distomadine A
mild antifungal

ciprofloxacin
antibiotic

synthetic compound
antimalarial

simeprevir
anti-hepatitis C

aurachin C (R = OH) or aurachin D (R = H)
antimalarial and antibiotic

Pseudomonas quinolone signal
quorum-sensing mediator

Fig. 2 Examples of decorated 4-hydroxyquinoline and 4-quinolone structures with medicinal values, taken as an inspiration for this work.[21]

In 2009, Fagnou and co-workers reported the selective C-2 arylation of unsubstituted quinoline *N*-oxide, using the Pd(OAc)$_2$/P(*t*Bu)$_2$Me·HBF$_4$ (1:1) catalytic system (5 mol%) in presence of an aryl bromide and K$_2$CO$_3$ in toluene at 110°C.[22] In this seminal study, an excess of the *N*-oxide (3 equiv. relatively to ArBr) was necessary to maintain high yields. Numerous studies involving metal catalysis have demonstrated the efficiency of the C-2 functionalisation of quinoline *N*-oxide to introduce aryl, alkenyl, alkyl, acyl groups or heteroatoms, using palladium, copper and rhodium catalysts.[21a,23] Overall, these methods were rarely exemplified with an oxygenated substitution at C-4.[21a]

Alternatively, the *N*-oxide could serve as a directing group to functionalise position 8.[24,25] Shibata and Matsuo reported in 2014 the alkenylation of quinoline *N*-oxides in presence of the [Rh(cod)$_2$]OTf/DM-BINAP catalytic system (10 mol%) and diphenylalkyne.[26] This study was followed by numerous reports describing the introduction of aryl, alkyl, alkenyl, alkynyl, allyl, acyl, indolyl, halide, nitrogenated or other heteroatom groups using rhodium, iridium, ruthenium, palladium, or cobalt catalysis.[27] This field is rapidly growing but applications to 4-oxy-substituted quinoline substrates are still rare.[27c,l]

The C-H functionalisation of position 3 by metal catalysis has been less frequently studied. The C-3 selective arylation of unsubstituted quinoline was first reported by Yu, using a Pd(OAc)$_2$/phenanthroline catalytic system in presence of aryl bromides.[28] Alternative strategies to functionalise position 3 used of the *ortho* lithiation of *O*-carbamates followed by a Fries rearrangement,[29] or that of *O*-phosphorodiamidates prior to the electrophile addition.[30] In principle, a carbamate group could also offer the possibility to direct an alkenylation at C-3, as done on electron-rich arenes in presence of cationic ruthenium(II) and an acrylate ester.[31]

With a 4-hydroxyl group, the C–H functionalisation could be directed at position 5 by using [RuCl$_2$(p-cymene)]$_2$ or [Cp*RhCl$_2$]$_2$ in presence of alkynes, promoting an alkynylation[32] or an annulation,[33,34] respectively. Alkylations were also reported in presence of diazocarbonyl derivatives.[35] Finally, it is not surprising that the C–H functionalisation of the two remote positions 6 and 7 are still poorly reported.[36] Recently Yu described a catalyst supporting a remote directing template allowing the functionalisation of position 6.[37]

Considering this broad functionalisation scope and the high medicinal potential of the quinoline ring, we envisioned a programmed approach for its multiple, divergent functionalisation (Fig. 1, bottom). Our strategy is centred on the putative 4-hydroxyquinoline *N*-oxide template, which bears two directing groups for the functionalisation of positions 2/8 (the *N*-oxide group) and 3/5 (the 4-OH group). To avoid any interference between the two groups and take full benefits of the *N*-oxide as a directing group, the 4-hydroxyl was protected as a carbamate, which later offered the possibility to functionalise position 3 with a carboxamide by a Fries rearrangement. This step would also release the 4-OH directing group to further functionalise position 5. Overall, this approach offers a powerful mean to generate chemical diversity, whose significance will be demonstrated by the discovery of potent antimalarial compounds.
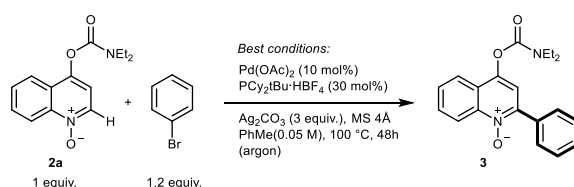
Results and Discussion

C-2 Functionalisation: optimisation and scope of the arylation

4-Hydroxyquinoline (**1**) was first converted into *N*-oxides **2a** and **2b** by carbamoylation in presence of diethyl and dimethyl carbamoyl chloride, respectively, followed by *N*-oxidation with *m*-chloroperbenzoic acid (Scheme S1).[22,29,38] The C-2

functionalisation of **2a** was then attempted in presence of bromobenzene. We tested variations of solvents, ligands, bases and the Pd/ligand ratio, all playing a critical role in the efficiency of the reaction (Table 1). The best yield (96% by NMR) was obtained when employing 1.2 equivalent of PhBr and a catalytic amount of Pd(OAc)$_2$ (10 mol%) in presence of electron-rich phosphine ligand PCy$_2$tBu (30 mol%, used as the HBF$_4$ salt according to Fu and Netherton[39]), Ag$_2$CO$_3$ (3 equiv.) and 4Å molecular sieves (MS) in dry toluene at 100 °C (entry 1). By contrast, under Fagnou's conditions (entry 2),[22] no C-2 arylation was observed on substrate **2a**,‡ but an undesired rearrangement product in 54% yield resulting from the *O*-carbamyl migration onto the *N*-oxide (*i.e.* 1-diethylcarbamyloxy-4(1*H*)-quinolone **S3**, Scheme S2)§ and the reduction of the *N*-oxide (10%). A similar rearrangement was observed with **2b**, providing suitable crystals for crystallographic confirmation of the rearranged structure (see Supporting information).

Any variation from our successful condition resulted in dropping yields. The use of phenyl iodide instead of phenyl bromide gave a satisfactory, yet lower, yield of 81% (entry 3). The absence of ligand or the use of bidentate ligands (entry 4) was unable to provide any quantifiable amount of product, while other phosphine ligands, including bulky and electron-rich ligands like PtBu$_2$Me (used by Fagnou[22]) or PtBu$_3$ (used by Schneider[21a]), proved less effective than PCy$_2$tBu (entries 5, 6). Yields were affected by lowering the catalyst loading (entry 7) and changing the [Pd]/PR$_3$ ratio (entry 8). Furthermore, we show that Ag(I) cations are essential in this catalytic reaction, as the reaction in the presence of AgOAc instead of Ag$_2$CO$_3$ still proceeds in good yields (entry 9), but does not occur with K$_2$CO$_3$ (entry 10). Finally, arene solvents were preferred, especially toluene at an optimal substrate concentration of 0.05 M (entry 11-14). In addition, the use of 4Å MS was necessary (3Å MS could also be used), suggesting that traces of water are deleterious to the reaction (entry 15). Finally, performing the reaction under an air atmosphere decreased the yield to 44% (entry 16).

Table 1 Optimization of conditions for the C-2 functionalisation of substrate **2a**.


Entry	Deviation from best conditions	Yield %^{a}
1	none	96
2	Fagnou's conditions[22]: 3 equiv. of **2a**, Pd(OAc)$_2$ (5 mol%), P(tBu)$_2$Me·HBF$_4$ (5 mol%), K$_2$CO$_3$, PhMe (0.3 M), 110°C	0^b
3	PhI instead of PhBr	81
4	no ligand or Phen or Bbbpy^c instead of PCy$_2$tBu^d	0^e
5	ddpe, dppf, PCyPh$_2$, PPh$_3$, TFP or XantPhos^c instead of PCy$_2$tBu^d	20-33
6	PtBu$_2$Me,^{d} PtBu$_3$,^{d} PCy$_3$,^{d} or BINAP^c instead of PCy$_2$tBu^d	37-66
7	2 or 5 mol% instead of 10 mol% of Pd(OAc)$_2$	42, 44
8	Pd(OAc)$_2$/PCy$_2$tBu ratio: 1:1, 1:2 or 1:4 instead of 1:3	58, 69, 73
9	AgOAc instead of Ag$_2$CO$_3$	77
10	K$_2$CO$_3$ instead of Ag$_2$CO$_3$	0^e
11	mesitylene, xylene instead of toluene	64, 75
12	1,2-DCE, PhCF$_3$ or DMF^c instead of toluene	21-35
13	THF, 1,4-dioxane instead of toluene	38, 44
14	0.5 M, 0.25 M or 0.1 M instead of 0.05 M (toluene)	39, 55, 65
15	no 4Å MS	0^e
16	air instead of argon atmosphere	44

^{a} ^{1}H NMR yields measured with dichloroethane as an internal standard. ^{b} Rearranged product **S3** was isolated in 54% yield, accompanied by 10% of the corresponding quinoline product (from the *N*-oxide reduction). ^{c} Abbreviations: BINAP: *rac*-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene; 1,2-DCE: 1,2-dichloroethane; DMF: *N,N*-dimethylformamide; dppe: 1,2-bis(diphenylphosphino)ethane; dppf: 1,1'-ferrocenediyl-bis(diphenylphosphine); Phen: 1,10-phenanthroline; TFP: tris-(2-furyl)phosphine; XantPhos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. ^{d} Used as the HBF$_4$ salt. ^{e} Entry 4: No reaction; Entry 10: **S3** observed in 68% yield, accompanied by 15% of *N*-oxide reduction; Entry 15: **S3** observed in 13% yield.

The mechanism of the Pd-catalyzed arylation of azine *N*-oxide has been thoroughly discussed in the literature. The acetate counter-anion could have an active role as a base during the palladium-catalyzed C–H activation, in a concerted metalation-deprotonation mechanism hypothesized by Fagnou.[40] The use of a *t*-butylphosphinepalladium(II) complex, by readily undergoing cyclometallation, could yet imply a cooperative palladium catalysis involving two distinct palladium complexes, as proposed by Hartwig on pyridine *N*-oxides.[41] Furthermore, as we found that Ag(I) salts are needed to achieve this functionalisation, the silver cation could have an active role as a halide scavenger or as a catalyst for C-H activation, as discussed by Larrosa,[42] Sanford[43] and Hartwig.[44,45]

With these optimized conditions in hand, we evaluated the scope of this functionalisation. It could be applied to a wide range of aryl donors (**3-26**, Scheme 1) including polyaromatic (**4,5**), electron-rich (**9-13**) or electro-deficient (**16-26**) substrates. Some of them were specifically chosen for biological purposes, when incorporating aryl or long-chain alkyl substituents sharing similarities with biologically relevant compounds (see Fig. 2). Limitations were observed with arene containing free phenols (**12**), or

heteroarenes like the 2-furyl (**29**), 2-thiophenyl (**30**), 4-(*N*-methyl)imidazole (**31**) or 2-(3-hydroxy)pyridyl (**32**) rings which were poorly or not reactive. However, a 2-thiazolyl substituent (**28**) could be introduced in 52% yield. *Ortho* substituents on phenyl rings were tolerated, except the most electron-deficient ones in **20** (NO$_2$), **25** (F), and **27** (CF$_3$). Remarkably, we were able to introduce an aryl group bearing an *O*-geranyl substituent, without losing the geranyl group and in a good yield of 78% (**15a**). The reaction was also possible when an amide function was present in position 8 (**33**), or a methyl group in a multiple functionalisation perspective (see discussion below). As for the influence of the carbamate group on the efficiency of the reaction, we observed that the diethyl carbamate (**2a**) gave better yields than the dimethyl carbamate (**2b**, mainly due to uncomplete conversion), giving products **6a-8a** or **6b-8b**, respectively. The diethyl carbamate was thus preferred for this C-2 functionalisation. To complete this work, after hydrolysis of the corresponding diethylcarbamate, 4-hydroxyquinoline *N*-oxide derivatives were obtained for biological screening (**S5-S16**, Scheme S3).
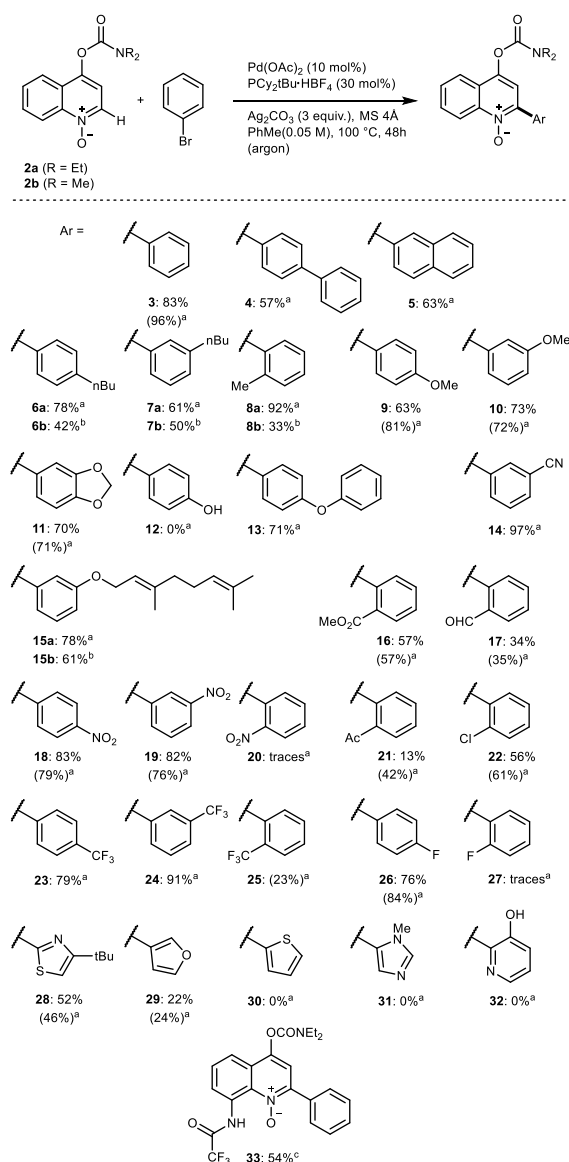
Scheme 1 C-2 functionalisation of substrate **2a** (NMR yields in parentheses). Notes: [a] From **2a**. [b] From **2b**. [c] After [Rh]-catalyzed amidation at C-8.

C-8 Functionalisation: introduction of amide and methyl groups

Next, we turned our attention to the functionalisation of C-8, again directed by the *N*-oxide, focusing on readily affordable Rh(III)-catalyzed amidations and methylations (Scheme 2).[27c,n] We introduced a trifluoroacetamide group at C-8 by using Cui's oxidative conditions[27n] in presence of CF$_3$CONH$_2$ (1.2 equiv.), PhI(OAc)$_2$ (2 equiv.) and Li$_2$CO$_3$ (0.4 equiv.), with [RhCp*Cl$_2$]$_2$ (4 mol%) and AgOTf (16 mol%) as a catalytic system, in 1,2-DCE at room temperature. These conditions would involve the formation of an intermediary rhodium complex **A** (Scheme 2) following rhodium insertion and nitrene formation.[27n,46] After a successful attempt on substrate **2a** giving amide **34** in 77% yield, they were applied to 2-arylated substrates bearing 4-diethylcarbamoyloxy (**11**, **13**, **24**, **28**) and 4-dimethylcarbamoyloxy (**6b**, **7b**, **15b**) substituents, affording products (**35-42**). Geranylated substrate **42** was obtained with a lower yield of 31%, as expected owing to the sensibility of this aryl ether.
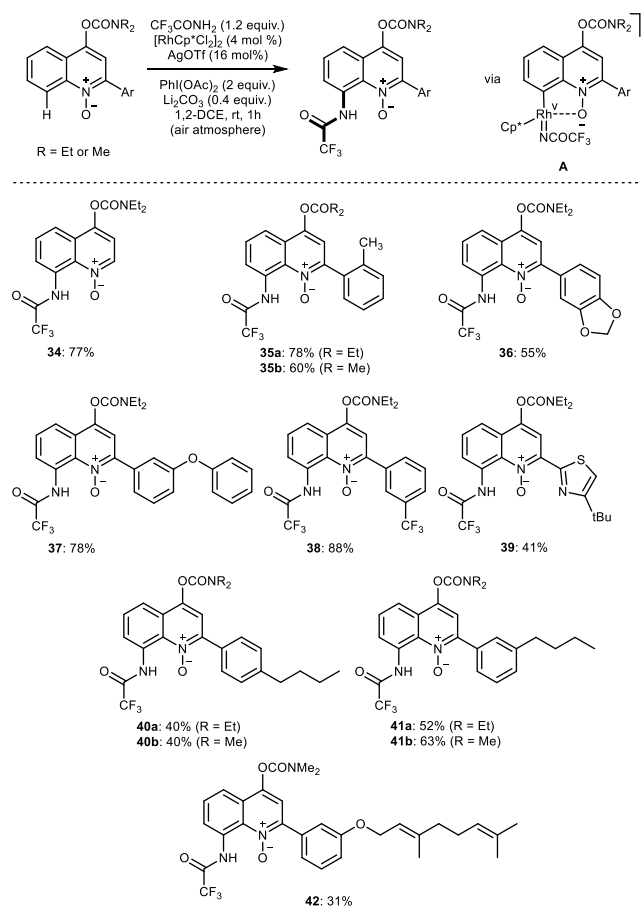
**Scheme 2** Trifluoroamidation at C-8: method and scope.

Alternatively, the methylation at C-8, expected from complex intermediate **B** (Scheme 3), was performed in presence of CH_3BF_3K (3 equiv.), AgOAc (2 equiv.) and a catalytic system composed of $[RhCp*Cl_2]_2$ (10 mol%) and $AgSbF_6$ (20 mol%) in 1,2-dimethoxyethane at 65 °C, according to Liu.[27c] Substrate **3** gave mitigated results due to the undesired extra methylation observed at the *ortho* position of the 2-phenyl substituent, presumably through rhodium complex **C** although this assumption needs further investigation (Scheme 3). An inseparable mixture of both compounds **43** and **44** (1:2 ratio) was thus obtained in 37% yield (Scheme 3). This result suggested that our multiple C–H functionalisation strategy should first target position 8, before the arylation of position 2. Consequently, the methylation was performed on quinoline *N*-oxide scaffolds **2a** and **2b** to furnish 8-methylquinoline derivatives **45a** and **45b** in 87% and 85% yields, respectively (Scheme 3). The next functionalisation of position 2 was then performed on substrate **45b** under our previously optimized palladium-catalyzed arylation conditions, to furnish 2-aryl derivatives **46**-**50** in moderate to good yields (Scheme 3, condition b). The choice of **45b** instead of **45a** to make this functionalisation was motivated by the next anionic Fries rearrangement, which was reputed to work well with *O*-dimethylcarbamyl derivatives, but not with their diethyl analogues.[29]
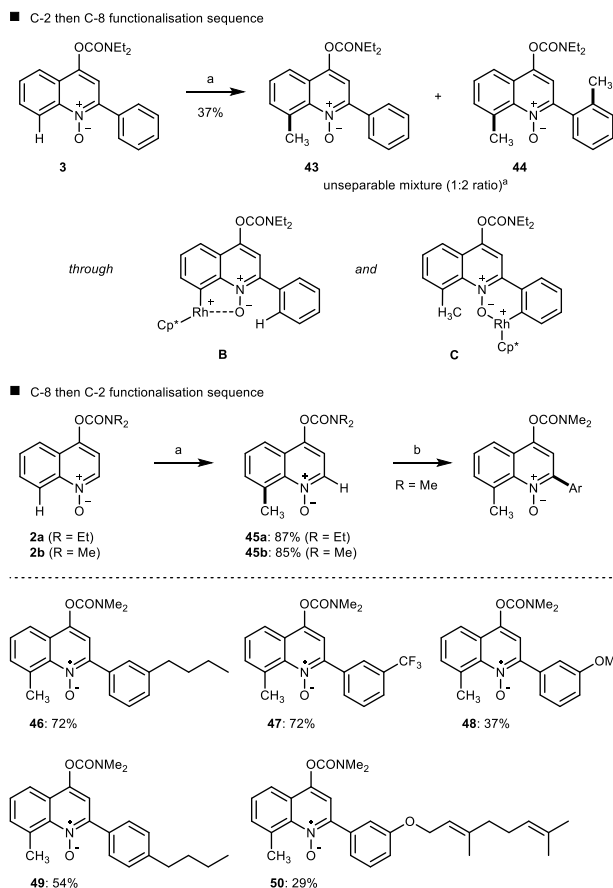
Scheme 3 Methylation at C-8. *Conditions:* a. CH_3BF_3K (3 equiv.), $[RhCp*Cl_2]_2$ (10 mol %), $AgSbF_6$ (20 mol%), AgOAc (2 equiv.), DME, 65°C, 16h; b. ArBr (1.1 equiv.), $Pd(OAc)_2$ (10 mol%), $PCy_2tBu \cdot HBF_4$ (30 mol%), Ag_2CO_3 (3 equiv.), MS 4Å, PhMe (0.05 M), 100 °C, 48h (argon atmosphere). Note: [a] HPLC ratio (210 nm).

Functionalisation of C-3 by the *ortho*-Fries rearrangement

To perform the anionic *ortho* Fries rearrangement,[29,47,48] the *N*-oxide was first reduced in presence of PCl_3 (Scheme 4). Subsequently, the lithiation of position 3 in presence of LDA initiated the carbamoyl migration, providing quinolone products **53-56** in moderate to good yields (38-73%) over two steps. Only geranyl ethers **57a** and **57b** were obtained in lower yields due to substantial decomposition during the *N*-oxide reduction. Gratifyingly, compound **56b** (R = Me) furnished crystals for X-ray analysis, showing the prevalence of the quinolone form in the solid state, co-crystalizing with a molecule of water (Figure 3).§§ Incidentally, we attempted to use the *N,N*-dimethylcarbamate as a directing group for other C–H functionalisation at C-3, but without success despite large condition screening (lithiation of *ortho* position 3 followed by addition of electrophiles,[48] or directed metal-catalyzed arylations[31]).§§§ Overall, the Fries rearrangement finally provided a straightforward access to various substituted 4-quinolones bearing a carboxamide moiety at position 3, which are commonly found in biologically relevant compounds.[21c] Most importantly, it also released the 4-oxo directing group needed for the functionalisation of position C-5.
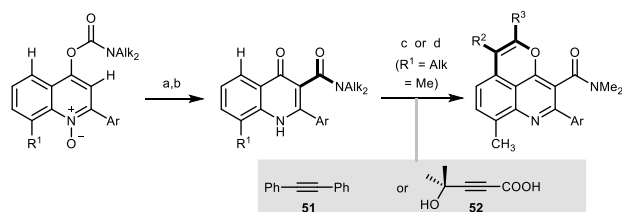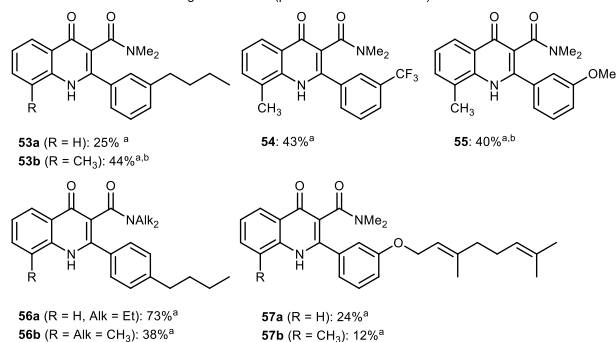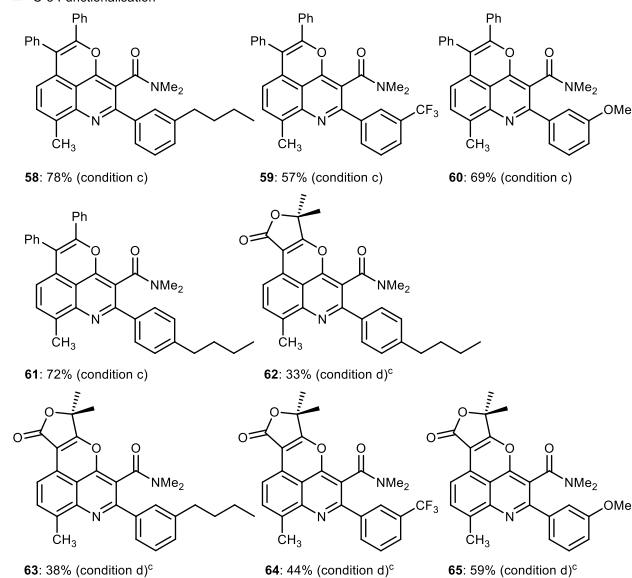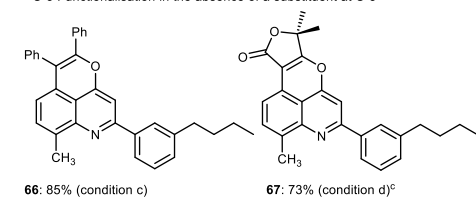
Scheme 4 Functionalisation of positions C-3 and C-5. *Conditions:* a. PCl₃ (2 equiv.), toluene, 0 °C→rt, 1h; b. LDA (2 equiv.), THF, -78 °C→rt, 16h; c. **51** (1.2 equiv.), [RuCl₂(p-cymene)]₂ (5 mol%), Cu(OAc)₂ (1 equiv.), 1,2-DCE, 110 °C, 20h; d. **52** (2 equiv.), [RhCp*Cl₂]₂ (5 mol%), AgSbF₆ (20 mol%), Cu(OAc)₂ (2 equiv.), KF (0.4 equiv.), DME, 100 °C, 16h. Notes: [a] Yields over two steps; [b] **53b**, **55** and **56a** were accompanied by hydrolysed products **S17**, **S18** and **S19**, respectively; [c] Isolated compounds, formed in a 3.5:1 ratio with the other regioisomeric lactone.

56b   **59**
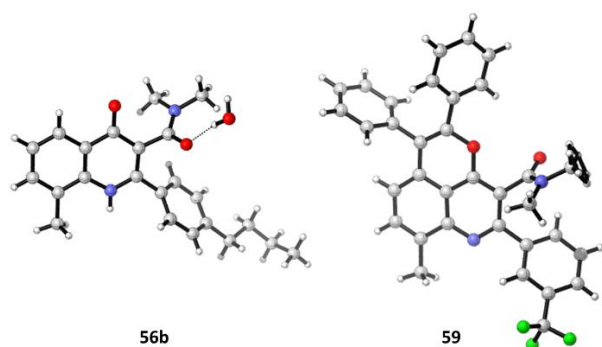
Fig. 3 X-ray crystallographic structures of **56b** and **59**. Compound **56b** co-crystallised with a molecule of water. Compound **59** shows one disordered methyl group on the amide nitrogen (a mask was used during the refinement of structure **59**, removing the contribution of 42 electrons from the unit-cell content. This might correspond with a molecule of dichloromethane per formula unit. This disorder could not be treated in another way).§§

C-5 Functionalisation through annulation reactions

To complete this functionalisation program, we ended up with an alkenylation of position C-5 in presence of alkynes under rhodium or ruthenium catalysis.[32,33,34,49] In fact, these reactions allowed an annulation with the adjacent 4-hydroxyl group, to give fused pyran ring systems **58-65**. The reaction with diphenylacetylene (**51**) was performed under the conditions defined by Patel,[33] in presence of [RuCl$_2$(*p*-cymene)]$_2$ (5 mol%), Cu(OAc)$_2$ (1 equiv.) in 1,2-DCE at 110 °C, to give annulated compounds **58-61** in good yields generally ranging from 69 to 78%, except for CF$_3$-substituted substrate **54** giving **59** in 57% yield. This last product gave suitable crystals for X-ray crystallography (Figure 3).§§ Alternatively, the reaction with dissymmetric alkyne **52** was undertaken under conditions inspired by Shi's work[34] in presence of [RhCp*Cl$_2$]$_2$ (5 mol%), AgSbF$_6$ (20 mol%), Cu(OAc)$_2$ (2 equiv.) and KF (0.4 equiv.) in DME at 100 °C, providing lactones **62-65** in moderate yields ranging from 33 to 59% after separation from the minor regioisomeric lactones (3.5:1 ratio, major isomer drawn on Scheme 4). Interestingly these compounds are structurally related to natural product distomadines (Fig. 2).[21b] In addition, in the absence of carboxamide substituent at position 3, the annulation reactions of 4-hydroxyquinoline substrate **S17** (see note b in Scheme 4 and the supporting information) performed well with both alkynes **51** and **52**, giving products **66** and **67** in 85 and 73% yields, respectively.

Biological relevance of our library

Overall, we show that the multiple C–H bond functionalisation of a well-designed quinoline substrate is an efficient strategy to obtain a diverse collection of natural product- and drug-inspired compounds. Some of them are obviously structurally related to natural products like aurachin D, graveolinine, distomadine A, and the menaquinone analogues 2-alkyl-4-quinolones and their *N*-oxides, or to the heterocyclic core of sipremevir (Fig. 2). Quinolone derivatives have been described as antimalarial compounds in many reports.[21d-e,50] More than 50 compounds of our collection were thus engaged in a screening against the parasite *Plasmodium falciparum*. First, we measured the percentage of growth inhibition of the chloroquine-resistant *P. falciparum* FcB1 strain by each compound at 10 µM and 1 µM (Table S24). These experiments showed that 33% of all compounds have a percentage of inhibition of the parasite above 75% at the concentration of 10 µM, and 7% at 1 µM (**57a**, **S12**, **S19** and aurachin D that was available as a positive quinolone control from a previous study[21d]). These results show the prevalence of active compounds bearing a long lipophilic substituent on carbon 2, and the favorable effect of the free 4-OH group on the antimalarial activity. Based on these data, 8 promising compounds were selected for IC$_{50}$ evaluation on *P. falciparum* FcB1 and on the chloroquine-sensitive strain *P. falciparum* 3D7 (**53a**, **56a**, **57a**, **S6**, **S7**, **S11**, **S12**, **S19** and aurachin D, all being 4-hydroxyquinoline *N*-oxides or 4-quinolones, see Figure S4). In addition, the cytotoxicity of these compounds was evaluated on primary human fibroblast cell line AB943. The results are shown in Table 2.

Table 2 Mean IC$_{50}$ values (µM) of selected compounds (see Figure S4) on *Plasmodium falciparum* strains FcB1 and 3D7, and on the primary human fibroblast cell line AB943 (the selectivity index, SI, was calculated by dividing the IC$_{50}$ obtained from human cell line AB943 by that from *P. falciparum* FcB1).

Compounds	FcB1[a]	3D7[a]	AB943[b]	SI
53a	1.10	1.32	>100	>91
56a	2.15	2.92	97	45
57a	0.07	0.16	34.5	492
S6	0.32	0.47	>100	>312
S7	0.34	0.75	38.5	113
S11	0.65	0.92	63	96
S12	0.08	0.12	48	600
S19	0.24	0.32	99	412
Aurachin D	0.09	0.21	>100	>1111
Chloroquine	0.048	0.011	25	520

[a] From quadruplicate values. [b] From duplicate values.

These data first demonstrate that our compounds target both chloroquine-resistant and sensitive *P. falciparum* strains, mainly at submicromolar concentrations, despite slight differences indicating a better activity against the FcB1 strain. This observation suggests that the biological target of these compounds could be different from that of chloroquine. Indeed, being structural analogues of menaquinone, they are susceptible to target the mitochondrial electron transport chain,[21d] especially cytochrome B and type II NADH dehydrogenase.[50] Furthermore, it is striking that compounds **57a** and **S12**, like aurachin D, have the best activity, at low concentrations <0.1 µM. These compounds all share a crucial polyisoprenyl chain. Incidentally, the 2-aryl linker in **57a** and **S12** may also increase their metabolic stability.[50a] As for *n*-butyl-substituted derivatives (**53a**, **56a**, **S6**, **S7**, **S19**), they are informative on the impact of the amide in position 3 and of the *N*-oxide on the activity. The presence of the amide seems to have a strong negative impact (**53a** *vs.* **S19**), while the *N*-oxide could have a limited positive influence (**S6** *vs.* **S19**). Finally, all compounds were poorly cytotoxic against the fibroblastic cell line AB943, resulting in high selectivity indexes, especially for compounds **57a** (SI = 492), **S12** (SI = 600) and aurachin D (SI = >1111). At the concentrations used to inhibit the parasites, these compounds could therefore have a limited impact on the human cells.

Conclusions

During this multiple functionalisation approach, the 4-hydroxyquinoline scaffold was used as a valuable template to build a substantial chemical diversity in a minimum of steps. Comparatively, traditional approaches would have necessitated a dedicated synthetic route for each compound synthesized. Four positions were thus successfully functionalised, applying a programmed sequence on dedicated substrates **2a** and **2b**, taking benefit of two weakly coordinating directing groups. Two C-H functionalisations at C-2 and C-8 were first guided by the *N*-oxide. Then, after removal of the *N*-oxide, an anionic *ortho* Fries rearrangement of a 4-*O*-carbamyl moiety allowed the functionalisation of position C-3, which released the 4-oxo group within the quinolone core. This was taken as a new directing group for the functionalisation of position C-5. Taking into consideration the medicinal potential of this collection of quinoline and quinolone products, they were engaged in a biological screening against the agent of malaria, revealing compounds (**57a**, **S12**) with strong activities in the submicromolar range. In addition, the low cytotoxicity found on human cells revealed high selectivity indexes in favour of the antimalarial activity, demonstrating that these compounds hold promising properties for additional drug developments. This work shows that the multiple functionalisation strategy, associated to substrate design, is a powerful mean to quickly generate biologically relevant libraries.

Author Contributions

BN designed and supervised the project. QR and WZ performed the experiments and structure analysis. NC performed the crystallographic analyses. EM and IF designed and performed the antimalarial and cytotoxicity essays. BN and QR wrote the article. The analysis of results was performed by all authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

‡ We must point out that Fagnou's reaction (ref. 22) were reproduced on quinoline *N*-oxide (3 equiv.), giving 89% yield of 2-phenylquinoline *N*-oxide. Our conditions worked similarly on this substrate, giving 94% yield of product when 3 equiv. of substrate were used (vs. 60% with 1.1 equiv.), suggesting our method could be general to quinoline substrates.

§ This *O*-carbamyl rearrangement was not reported before, but Hammersmith and co-worker showed a related transformation of 4-(ethoxycarbonyloxy)quinoline *N*-oxides into 1-(ethoxycarbonyloxy)-4(1*H*)-quinolones (see ref. 38). In fact, our rearrangement occurred spontaneously in trace amounts when substrates **2a** and **2b** were left in dichloromethane at room temperature for several hours. Surprisingly, it was not observed under our C-2 functionalisation conditions.

§§ Crystallographic structures were deposited on the Cambridge Crystallographic Data Centre under CCDC numbers 2042478 for **56b** and 2042479 for **59**.

§§§ When applying the conditions previously developed for C-2 functionalisation (Table 1) to carbamate **2a**, the 3-phenylquinoline product was observed in max. 5-10% yields. We were unable to improve this reaction.
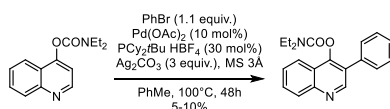
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