Tetrahedron: *Asymmetry* xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric synthesis of new antimalarial aminoquinolines through Sharpless aminohydroxylation

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ARTICLE INFO

Article history:
Received 3 October 2015
Accepted 12 November 2015
Available online xxxx

ABSTRACT

Recently, the asymmetric synthesis and biological activity of (*R*)- and (*S*)-4-aminoquinolinemethanols **1** as mefloquine analogues were reported. Several compounds showed very promising antimalarial activity, in the nanomolar range, against *Plasmodium falciparum* 3D7 and W2. Enantiomers with an (*S*)-absolute configuration were more active than their (*R*)-counterparts by a factor ranging from 2 to 15-fold, according to the compound and the plasmodial strain considered. In continuation of our work, three novel series of enantiopure aminoquinolines **2a**, **2b,** and **3** were synthesized via an asymmetric aminohydroxylation reaction. These compounds were obtained in 2 or 4 steps from a common amidoalcohol key-intermediate **4**. They displayed IC_{50} values close to the micromolar against the two *P. falciparum* strains 3D7 and W2. The study of the structure–activity relationships allows us to better understand the importance of the substitution and of the stereochemistry at C11 and C12 position of the quinoline and gives tracks for the design of new compounds more active against the plasmodial strains.

1. Introduction

Malaria is a neglected tropical disease that remains a leading cause of morbidity and mortality among the world's poorest populations. More than 100 tropical and sub-tropical countries are endemic for this infectious disease. Pregnant women and children are the most sensitive to this infection and more than 750,000 people die of malaria each year. Among the five species of *Plasmodium* responsible for human malaria, *P. falciparum* is the parasite, which causes the most serious form of the disease. Unfortunately this one is difficult to eradicate because of its capacity to develop varying degrees of resistance to many classes of antimalarial drugs. More recent efforts have focused on the development of antimalarial vaccines and since 2006,[1] the World Health Organization recommends artemisinin-based combination therapies.[2] However, artemisinin resistant strains of *Plasmodium* emerged in some malaria endemic areas of South East Asia and efficacy of artemisinin-based combination therapies might be lowered. This phenomenon increased the urgency to discover and develop new drugs against this disease.[3]

Mefloquine (Fig. 1) was proposed, for a long time, as the drug of choice for chloroquine-resistant malaria and artesunate–mefloquine combination was the most prescribed artemisinin-based combination therapy in areas of highest parasite resistance. This antimalarial drug possesses good pharmacokinetic properties such as a longer half-life compared to other antimalarial drugs, which permits weekly administration and facilitates a better observance for prophylactic treatment.[4] Mefloquine is relatively safe during pregnancy and can be given to children of more than three years.[5] However, the emergence of resistance to mefloquine and its associated neuropsychiatric side effects limit its use.

Mefloquine is commercially available as a racemate (Lariam®), although both enantiomers have shown differences in biological activities. On the one hand, the antimalarial activities of the two isomers are close[2] but (+)-mefloquine is more active by a factor of 1.6–1.8 on D6, W2 and 3D7 strains.[6,7] On the other hand, the neuropsychiatric side effects correspond with a greater accumulation of (−)-mefloquine compared to (+)-mefloquine in the central nervous system due to a stereoselective cerebral transport of

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http://dx.doi.org/10.1016/j.tetasy.2015.11.003
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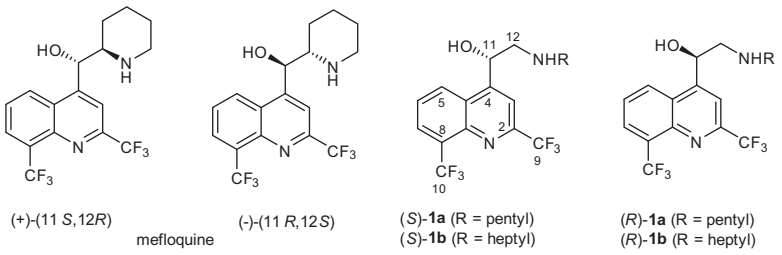


Figure 1. Mefloquine and aminoquinolinemethanol **1**.

mefloquine.[8–10] Moreover, (−)-mefloquine is 100 to 400-fold more potent than (+)-mefloquine as an adenosine receptor agonist.[11]

Among several approaches to lower the mefloquine neurotoxicity and to improve its resistance profiles,[12] modulation of the mefloquine core as a pure enantiomer is an attractive strategy.[13]

Our team recently reported the asymmetric synthesis and the biological activity of (*R*)- and (*S*)-4-aminoquinolinemethanols as mefloquine analogues.[14,15] Several compounds, such as **1a** and **1b**, showed a promising antimalarial activity, in the nanomolar range, against *P. falciparum* W2 and 3D7 strains. Some structure–activity relationships were highlighted: (i) the importance of the absolute configuration of the stereogene centers (*S*) versus (*R*); and (ii) the impact of the electron density around the amine (R = alkyl vs R = aryl). The most active molecule synthesized is the aminoquinolinemethanol **1a** with an (*S*)-configuration and a pentylamino group at C12 position of the quinoline (Fig. 1, Table 1).

Table 1
The in vitro antimalarial activity of (*S*)- and (*R*)-**1**

Entry	Compounds	IC_{50}[a] (nM) *Plasmodium falciparum*	
		3D7	W2
1	(*S*)-**1a**	8.33 ± 0.44[b]	6.98 ± 0.62
2	(*R*)-**1a**	74.7 ± 4.71	38.2 ± 3.63
3	(*S*)-**1b**	33.0 ± 1.55	ND[c]
4	(*R*)-**1b**	254 ± 26.9	ND
5	Chloroquine	25.7 ± 7.81	572 ± 112
6	Mefloquine	52.2 ± 4.18	26.5 ± 2.44

[a] Isotope micromethod that measures inhibition of parasite uptake of tritiated hypoxanthine in the presence of antimalarial agents.
[b] The 50% inhibitory concentrations were calculated using Pk-Fit software. Results expressed as mean ± standard deviation.
[c] Not determined.

Compound (*S*)-**1a** was more active than chloroquine and mefloquine, whatever the strain and was 5 to 9-fold more active (IC_{50} = 6.98 nM (W2) and 8.33 nM (3D7)) than its (*R*)-enantiomer (*R*)-**1a** (IC_{50} = 38.2 nM (W2) and 74.7 nM (3D7)), depending on the strain (entries 1 and 2, Table 1).[16] These results confirmed the importance of the stereochemistry in the design of mefloquine analogues in malaria treatment. Interestingly, (*S*)-**1a** and its (*S*)-heptyl analogue (*S*)-**1b** exhibited a steady activity against a panel of *P. falciparum* strains with varying resistance profiles to chloroquine and mefloquine.[17] Furthermore, we showed an additive or synergic effect of in vitro (*S*)-**1a**/dihydroartemisinin and (*S*)-**1b**/dihydroartemisinin combinations. Hemolysis tests pointed toward a rather safe use compared to mefloquine. In order to elucidate the mechanism of action of compounds **1**, their effects on β-hematin formation and on peroxidative-degradation of haemin were studied.[16] All derivatives tested were more efficient than mefloquine at inhibiting β-hematin formation and haemin degradation pathway. No significant difference in the inhibiting activity of the (*R*)- or (*S*)-enantiomer carrying the same side chain was observed. Further investigations were performed to highlight the mechanism of action that could explain the difference in activity of the enantiomers.

In continuation of our work concerning the research of new chiral antimalarial drugs and to better understand the biological mechanism of compounds **1**, we were interested in the synthesis of aminoquinolinethanols (*R*)- and (*S*)-**2** and quinolinethanamines (*R*)- and (*S*)-**3** to establish new structure–activity relationships (Fig. 2). Compared to the previous family of aminoquinolinemethanol **1**, we decided to study the importance of the amine and the alcohol function positions grafted at the C11 and C12 positions of quinoline. Herein, we describe the synthesis and antimalarial activity of a new series of quinolines **2** and **3** with a pentyl and/or heptyl chain (Fig. 2).

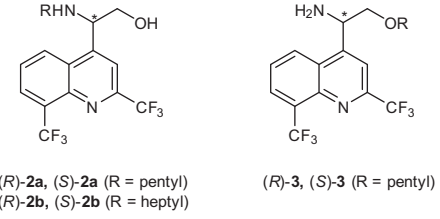


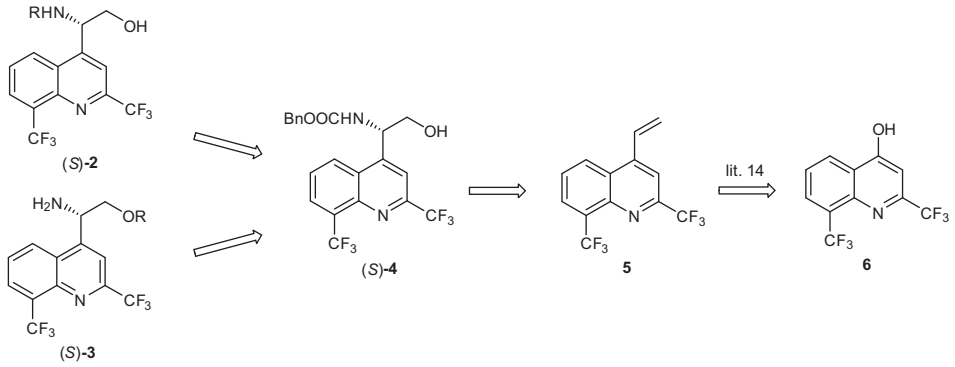
Figure 2. Aminoquinolinethanols **2** and quinolinethanamines **3**.

2. Results and discussion

2.1. Chemistry

The retrosynthetic route chosen shows that the enantiopure aminoquinolinethanols **2** and quinolinethanamines **3** can be prepared from a common key intermediate **4** [for an example see the (*S*)-enantiomers in Scheme 1] which could be obtained from 4-vinylquinoline **5**. We have previously described a two step synthesis of this vinylarene from 4-hydroxyquinoline **6** in 80% global yield.[14]

Our strategy is based on the aminohydroxylation reaction.[18,19] This one permits the sequential or simultaneous addition of both nitrogen and oxygen on an alkene compound. The sequential addition, developed by Davies et al., consists of the addition of a chiral amide anion to an α,β-unsaturated ester. The resulting enolate is trapped by an oxygen electrophile such as an oxaziridine, to lead to the corresponding aminoalcohol in excellent diastereoselectivity.[18] The simultaneous addition is based on an asymmetric Sharpless dihydroxylation reaction: the asymmetric Sharpless aminohydroxylation.[19] For this, Sharpless used a chiral amine ligand such as phthalazine ligands $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ to generate the asymmetric addition of an amide and a hydroxyl group on the alkene double bond. Various nitrogen sources were described in the aminohydroxylation reaction: sulfonamides,



Scheme 1. Retrosynthesis of (11*S*)-enantiopure aminoquinolinethanols **2** and quinolinethanamines **3**.

carbamates, and amides. Optimal yields and enantioselectivities were observed with α,β-unsaturated esters and phosphonates as substrates. For vinylarene substrates, the yield and the regioselectivity are highly dependent on both the nature and the substitution of the arene moiety, as well as the choice of ligand, solvent, and ligand-solvent combination.[20]

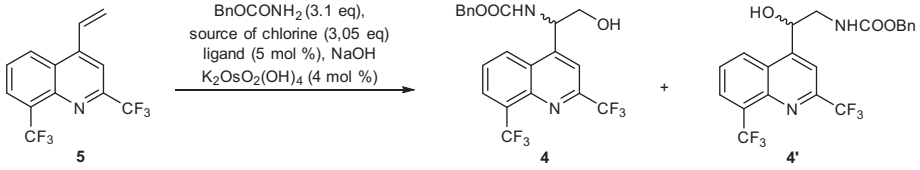
For the synthesis of the key intermediate **4**, we decided to use the Sharpless methodology using benzylcarbamate as the nitrogen source since this is: (i) more appropriate in the case of terminal alkenes;[20] and (ii) easily cleavable under mild conditions.

The aminohydroxylation reaction assays of 4-vinylquinoline **5** to **4** are summarized in Table 2. In each case, the reactions were achieved using 4 mol % of the osmium(VI) pre-catalyst, potassium osmate(VI) dihydrate, 5 mol % of alkaloid ligand (1,4-bis(9-*O*-dihydroquininyl)-phthalazine $(DHQ)_2PHAL$ or 1,4-bis(9-*O*-dihydroquinidinyl)-phthalazine $(DHQD)_2PHAL$), and 3.1 equiv of benzylcarbamate in an *n*-PrOH or acetonitrile/H_2O solvent mixture at 25 °C. The benzylcarbamate was converted in situ into the corresponding *N*-chlorosodiocarbamate salt in the presence of sodium hydroxide and freshly prepared *tert*-butyl hypochlorite.

All tests led to the desired compound **4** in poor yield ranging from 26% to 48% (Table 2). These low chemical yields could be explained by the formation of two principal by-products: the diol and the regioisomer **4′**. The quantification and separation of these by-products were often difficult because they form a non-separable mixture with benzylcarbamate in excess. Hence, regioisomer **4′** was isolated only twice (entries 5 and 6).

The first assay was carried out in a mixture of 1:1 *n*-PrOH/H_2O with $(DHQ)_2PHAL$ as ligand and led to (−)-**4** in 48% yield and with 80% ee (entry 1). In order to improve the carbamate-based aminohydroxylation, the addition of an excess of mercury salt was carried out. In this reaction, the *N*-chlorosodiocarbamates react in situ with the metallic salt to form more reactive *N*-chloro-*N*-metallocarbamates. The beneficial effect of excess mercury salt was previously reported by Sharpless.[21] Unfortunately in our case, this addition had a deleterious effect since no product was formed (entry 2). Aminohydroxylation was also carried out by changing the solvent mixture to 2:1 *n*-PrOH/H_2O (entry 3) or 1:1 acetonitrile/H_2O (entry 4) hoping to limit the by-product formation. In these two cases, the reaction proceeded with lower yield

Table 2
Reagents and conditions used to prepare **4**



Entry	Source of chlorine	Ligand	Solvent	$Hg(NO_3)_2$ (equiv)	Yield[a] (%)		ee[b] (%)	$[\alpha]_D^{20}$[c]	
					4	**4′**		**4**	**4′**
1	^{t}BuOCl	$(DHQ)_2PHAL$	*n*-PrOH/H_2O 1:1		48	ND[d]	80	−28.9	
2	^{t}BuOCl	$(DHQ)_2PHAL$	*n*-PrOH/H_2O 1:1	3.05	0	ND	/	/	
3	^{t}BuOCl	$(DHQ)_2PHAL$	*n*-PrOH/H_2O 2:1		36	ND	74		
4	^{t}BuOCl	$(DHQ)_2PHAL$	MeCN/H_2O 1:1		31	ND	60	/	
5	1,3-Dichloro-5,5-dimethylhydantoin	$(DHQ)_2PHAL$	*n*-PrOH/H_2O 1:1		26	19	76		+12.4
6	^{t}BuOCl	$(DHQD)_2PHAL$	*n*-PrOH/H_2O 1:1		33	24	70	+9.5	−15.4

[a] After chromatography purification.
[b] Enantiomeric excesses of compounds **4** were determined by HPLC (Chiralpak IB column, heptane/*i*-PrOH 9:1; 1 mL/min, 278 nm) $t_R(S)$ = 14.6 min; $t_R(R)$ = 16.6 min.
[c] *c* 0.1, MeOH. Determined after chromatography purification.
[d] Observed but not quantified.

(31% and 36% vs 48%) and with the poorest enantioselectivity. In a last assay, the source of chlorine was changed and 1,3-dichloro-5,5-dimethylhydantoin was used in place of *tert*-butyl hypochlorite (entry 5). In this case, compound **4** was obtained in 26% yield and the regioisomer **4′** was isolated with 19% of yield. The best results were obtained with a 1:1 ratio of *n*-PrOH/H_2O as the solvent and *tert*-butyl hypochlorite as the source of chlorine (entry 1). Thus, these same conditions were used to prepare the (+)-**4** enantiomer in 33% yield and with 70% ee (entry 6, Table 2).

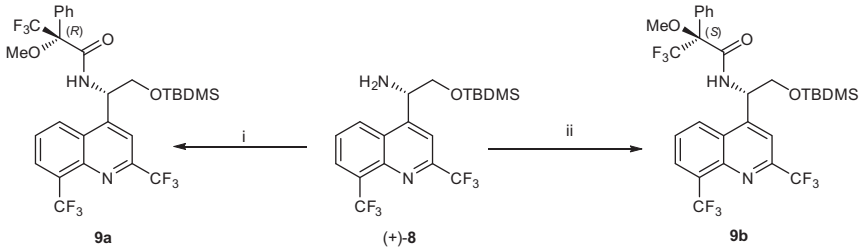
As in the catalytic asymmetric dihydroxylation, the chiral ligands favoured the addition to one face of the prochiral alkene substrate.[22] Thus, vinylquinoline **5** was converted into the corresponding (*S*)-**4** {$[\alpha]_D^{20} = -28.9$ (*c* 0.1, MeOH)} when $(DHQ)_2PHAL$ was used as a ligand (entry 1, Table 2) and to (*R*)-**4** {$[\alpha]_D^{20} = +9.5$ (*c* 0.1, MeOH)} when $(DHQD)_2PHAL$ was employed (entry 6, Table 2). Concerning the regioselectivity of the aminohydroxylation, it was reported that the amination of the more substituted carbon for monosubstituted alkenes, such as styrene, is preferred.[23]

Thus, provisionally, the majority of compound obtained (entries 1 and 6) was assigned as the (−)-(*S*)-**4** when $(DHQ)_2PHAL$ was employed and (+)-(*R*)-**4** when (DHQD)PHAL was used. In order to achieve X-ray studies to prove the structure of **4**, several assays of crystallization were achieved but no solvent system used was efficient. Thus, the stereoselectivity and the regioselectivity of the aminohydroxylation reaction will be confirmed later by the preparation of the Mosher amides **9** from amine (+)-**8** (Scheme 2).

The obtained enantiomers **4** were used in reaction with *tert*-butyldimethylsilyl chloride to give (−)-**7** and (+)-**7** (Table 3). After removal of the benzylcarbamate group with hydrogen in the presence of palladium on charcoal, (−)-**8** and (+)-**8** were afforded in good yields.

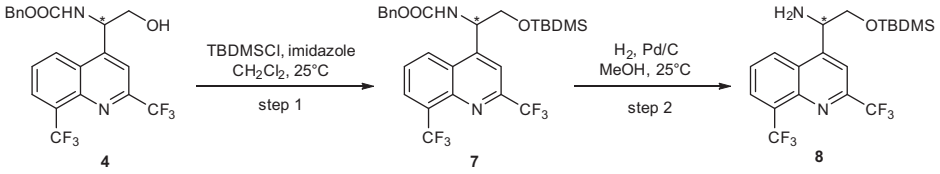
At this step, we decided to establish the absolute configuration of (+)-**8** and (−)-**8**, and indirectly those of (+)-**4** and (−)-**4**. Thus, the preparation of Mosher amides **9a** and **9b** from (+)-**8** was achieved. This amine was reacted with 1.5 equiv of Hünig's base (DIPEA) and (*S*)-methoxy(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) as well as (*R*)-MTPA-Cl (Scheme 2).[24] The two diastereomers **9a** and **9b** were obtained in 79% and 69% yields, respectively. Their NMR spectra were compared according to the Mosher method: the interpretation of the significant chemical shift differences in the individual diastereomeric MTPA amides **9a** and **9b** derived from the (+)-**8** clearly confirmed the supposed configuration *S*. Consequently, (−)-**8** should present the *R*-absolute configuration. These results permit also to conclude that (−)-**4** and (+)-**4** can be assigned as (*S*)-**4** and (*R*)-**4**, respectively.

After confirmation of the configuration of the key intermediates **4** and **8**, two steps were necessary to obtain final compounds **2** and **3**. For compounds **2**, the substitution of enantiomers **8** with alkyl chains was followed by the deprotection of the alcohol moiety. In order to optimize the alkylation step, several assays were achieved using (*S*)-**8** as the substrate and bromopentane as the halo-compound reagent (entries 1–4, Table 4). All tests were performed in acetonitrile as the solvent. Our first experiments (entries 1 and 2) were carried out in the presence of 1 or 2 equiv of triethylamine or potassium carbonate in acetonitrile at reflux, but none of the products were obtained. The addition of potassium iodide as a catalyst slightly reduced the reaction time (15 h vs 20 h) and led to the product (*S*)-**10a** in a poor yield of 19% (entry 3). Finally, to accelerate the reaction and improve the yield, we used microwave irradiation (entry 4). The reaction was optimized with respect to the temperature (100–150 °C) and the total conversion of reactant (*S*)-**8** was observed after 3 h of reaction at 150 °C and (*S*)-**10a** was obtained in 62% yield (entry 4).



Scheme 2. Reagents and solvents: (i) (*S*)-MTPA-Cl (1.2 equiv), DIPEA (1.5 equiv), CH_2Cl_2, 25 °C, 79%; (ii) (*R*)-MTPA-Cl (1.2 equiv), DIPEA (1.5 equiv), CH_2Cl_2, 25 °C, 69%.

Table 3
Reagents and conditions used to prepare **8**

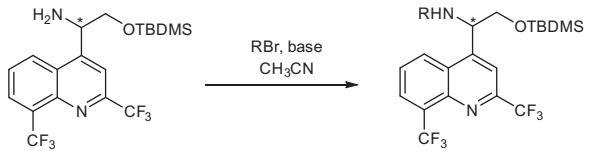


Entry	Step 1					Step 2				
	4	**7**	Yield (%)	ee[a] (%)	$[\alpha]_D^{20c}$	**7**	**8**	Yield (%)	ee[b] (%)	$[\alpha]_D^{20d}$
1	(−)-**4**	(−)-**7**	89	76	−7.8	(−)-**7**	(+)-**8**	81	74	+37.8
2	(+)-**4**	(+)-**7**	80	70	+4.9	(+)-**7**	(−)-**8**	81	70	−36.9

[a] Enantiomeric excesses of compounds **7** were determined by HPLC (Chiralpak IB column, heptane/EtOH 95:5; 1 mL/min, 278 nm) $t_R(S) = 5.9$ min; $t_R(R) = 7.5$ min.
[b] Enantiomeric excesses of compounds **8** were determined by HPLC (Chiralpak IB column, heptane/EtOH 95:5; 1 mL/min, 278 nm) $t_R(S) = 6.6$ min; $t_R(R) = 7.3$ min.
[c] *c* 0.1, MeOH. Specific rotation of compounds **7**.
[d] *c* 0.1, MeOH. Specific rotation of compounds **8**.

Please cite this article in press as: Bentzinger, G.; et al. *Tetrahedron: Asymmetry* (2015), http://dx.doi.org/10.1016/j.tetasy.2015.11.003

Table 4
Reagents and conditions used to the synthesis of **10**



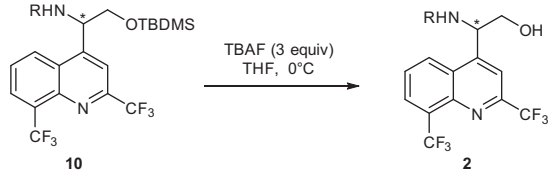
Entry	Reactant	R	Base (equiv)	Catalyst (0.1 equiv)	Temperature (°C)	Time (h)	Product	Yield[b] (%)	ee (%)
1	(*S*)-**8**	C_5H_{11}–	Et_3N (1)	/	Reflux	20	–	0	–
2	(*S*)-**8**	C_5H_{11}–	K_2CO_3 (2)	/	Reflux	20	–	0	–
3	(*S*)-**8**	C_5H_{11}–	K_2CO_3 (2)	KI	Reflux	15	(*S*)-**10a**	19	–
4	(*S*)-**8**	C_5H_{11}–	K_2CO_3 (2)	KI	150 °C (MW)[a]	3	(*S*)-**10a**	62	78[c]
5	(*S*)-**8**	C_7H_{15}–	K_2CO_3 (2)	KI	150 °C (MW)	3	(*S*)-**10b**	67	74[d]
6	(*R*)-**8**	C_5H_{11}–	K_2CO_3 (2)	KI	150 °C (MW)	3	(*R*)-**10a**	60	62[c]
7	(*R*)-**8**	C_7H_{15}–	K_2CO_3 (2)	KI	150 °C (MW)	3	(*R*)-**10b**	64	70[d]

[a] Reaction was performed using microwave heating at 150 °C (200 W).
[b] Yield of isolated product.
[c] Enantiomeric excesses of compounds **10a** were determined by HPLC (Chiralpak IB column, heptane/*i*-PrOH 99:1; 1 mL/min, 278 nm) $t_R(S)$ = 3.8 min; $t_R(R)$ = 4.2 min.
[d] Enantiomeric excesses of compounds **10b** were determined by HPLC (Chiralpak IB column, heptane/*i*-PrOH 99:1; 1 mL/min, 278 nm) $t_R(S)$ = 3.7 min; $t_R(R)$ = 4.0 min.

These microwave conditions were selected to prepare analogues (*R*)-**10a**, (*S*)-**10b,** and (*R*)-**10b**, which were achieved in the same range of yield (60–67%) and with an enantiomeric excess between 62% and 78% (entries 5–7, Table 4).

Deprotection of the alcohol moiety was performed using tetrabutylammonium fluoride in THF at 0 °C. After 1 h, the final compounds **2** were obtained in good yields and with enantiomeric excesses ranging from 56% to 86% (Table 5).

Table 5
Reagents and conditions used to the synthesis of **2**



Entry	Reactant	R	Product	Yield (%)	ee (%)	$[\alpha]_D^{20}$[c]
1	(*S*)-**10a**	C_5H_{11}–	(*S*)-**2a**	83	86[a]	+22.0
2	(*S*)-**10b**	C_7H_{15}–	(*S*)-**2b**	73	74[b]	+25.6
3	(*R*)-**10a**	C_5H_{11}–	(*R*)-**2a**	100	70[a]	−29.0
4	(*R*)-**10b**	C_7H_{15}–	(*R*)-**2b**	85	56[b]	−28.9

[a] Enantiomeric excesses of compounds **2a** were determined by HPLC (Chiralpak IB column, heptane/EtOH 99:1; 1 mL/min, 278 nm) $t_R(R)$ = 31.9 min; $t_R(S)$ = 34.3 min.
[b] Enantiomeric excesses of compounds **2b** were determined by HPLC (Chiralpak IB column, heptane/EtOH 99:1; 1 mL/min, 278 nm) $t_R(R)$ = 29.5 min; $t_R(S)$ = 32.3 min.
[c] *c* 0.1, MeOH. Specific rotation of compounds **2**.

In order to reinforce the regiochemistry established for the aminohydroxylation reaction (Table 2), NMR data of the final product (*S*)-**2a** and the lead compound (*S*)-**1a** were compared (Fig. 3). Significant differences were raised between the chemical shift of H11 [47.7 ppm for (*S*)-**2a** vs 5.68 ppm for (*S*)-**1a**] and H12 [3.66 and 3.85 ppm for (*S*)-**2a** vs 2.83 and 2.99 ppm for (*S*)-**1a**]. These differences validate the structure of compounds **2**, as regioisomers of compounds **1**.

Finally, the *O*-alkylated compounds **3** were synthesized in two steps from the aminohydroxylation products **4**: alkylation, and carbamate cleavage (Table 6). Concerning the O-alkylation of **4**, three

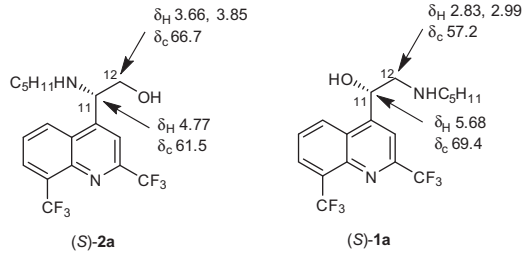


Figure 3. (*S*)-**2a** and (*S*)-**1a** NMR data.

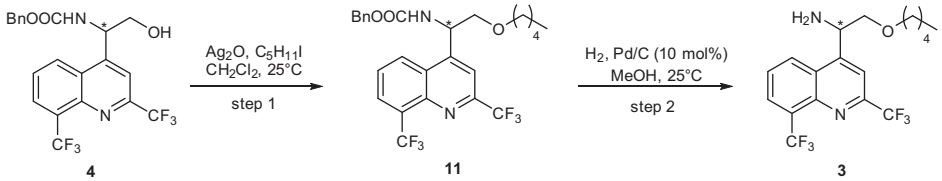
conditions were attempted: (i) bromopentane with Et_3N as the base in acetonitrile at reflux; (ii) iodopentane in the presence of a phase transfer catalyst (tetrabutylammonium sulfate) with sodium hydroxide as the base in a biphasic solvent system (THF/H_2O); and (iii) iodopentane with silver oxide in dichloromethane. Only the third assay allowed us to obtain the desired compounds **11** in yields ranging from 41% to 53%. Deprotection of amine moiety was carried out in a hydrogen atmosphere with palladium on charcoal as the catalyst. Compounds **3** were obtained in 74% yield and with moderate enantiomeric excesses up to 54%.

Thus, the key intermediates (*R*)-**4** and (*S*)-**4** were obtained in one step from 4-vinylquinoline **5**, through the aminohydroxylation reaction in 33% (70% ee) and 48% (80% ee) yields, respectively. Six novel compounds **2** and **3** were synthesized from **4** in 4 or 2 steps, respectively, in moderate yield and with enantiomeric excesses higher than 54%.

2.2. Biological evaluation

The in vitro antimalarial activity of the aminoquinolinethanols (*R*)- and (*S*)-**2**, quinolinethanamine (*R*) and (*S*)-**3** and some intermediates during the synthesis were evaluated against *P. falciparum* strains W2 and 3D7 (Table 7). W2 is a chloroquine resistant strain and is mefloquine sensitive while 3D7 is chloroquine sensitive and displays a decreased susceptibility to mefloquine. The biological activity of the new products **2**, **3,** and intermediates (*S*)-**8** and (*S*)-**10a** was evaluated with a SYBR Green I fluorescence-based method.[25,26] Chloroquine and mefloquine were routinely included as positive controls as well as negative controls using the solvent. The resulting IC_{50}s were calculated using a regression program available online and are reported in Table 7.[27]

Table 6
Reagents and conditions used to the synthesis of **3**



Entry	Step 1				Step 2				
	4	**11**	Yield (%)	Ee[a] (%)	**11**	**3**	Yield (%)	ee[b] (%)	$[\alpha]_D^{20c}$
1	(*S*)-**4**	(*S*)-**11**	41	64	(*S*)-**11**	(*S*)-**3**	74	58	+28.1
2	(*R*)-**4**	(*R*)-**11**	53	68	(*R*)-**11**	(*R*)-**3**	74	66	−43.3

[a] Enantiomeric excesses of compounds **11** were determined by HPLC (heptane/*i*-PrOH, 90:10; flow 1 mL/min, 210 nm) $t_R(S)$ = 7.3 min, $t_R(R)$ = 10.0 min.
[b] Enantiomeric excesses of compounds **3** were determined by HPLC (heptane/*i*-PrOH, 95:5; flow 1 mL/min, 278 nm) $t_R(S)$ = 8.1 min, $t_R(R)$ = 9.0 min.
[c] *c* 0.1, MeOH. Specific rotation of compounds **3**.

Table 7
In vitro antimalarial activity of compounds (*S*)-**8**, (*S*)-**10,** and series **2**–**3**

Entry	Compounds	IC_{50}[a] (nM) *Plasmodium falciparum*	
		3D7	W2
1	(*S*)-**8**	746 ± 58[b]	ND[c]
2	(*S*)-**10a**	5042 ± 243	ND
3	(*S*)-**2a**	10,535 ± 721	2801 ± 255
4	(*R*)-**2a**	5454 ± 322	2007 ± 299
5	(*S*)-**2b**	26,541 ± 6972	>40,000
6	(*R*)-**2b**	15,532 ± 1754	2446 ± 940
7	(*S*)-**3**	4069 ± 289	1730 ± 369
8	(*R*)-**3**	13,605 ± 1329	3175 ± 914
9	Chloroquine	75.9 ± 3	198.8 ± 27
10	Mefloquine	79.7 ± 8	31.8 ± 1

[a] SYBR Green I in vitro test was used.
[b] IC_{50}s were calculated using WinNonlin software. Results expressed as mean ± standard deviation.
[c] Not determined.

With mefloquine, all tested compounds were more active against *P. falciparum* strains W2 than against *P. falciparum* strains 3D7 (Table 7). Unfortunately, this novel series displayed lower activities [IC_{50}s = 746–26541 nM (3D7) and 1730–3175 nM (W2)] than mefloquine and the lead compound **1a** [IC_{50} = 8.33 nM (3D7) and 6.98 nM (W2)] (Tables 1 and 7). Among these new tested compounds, two quinolinethanamines with an (*S*)-configuration were the most potent: the intermediate (*S*)-**8** (IC_{50} = 746 nM) on the 3D7 strain followed by the (*S*)-**3** [IC_{50}s = 4069 nM (3D7) and 1730 nM (W2)] on the two strains.

As previously observed for compounds **1** (Table 1), the (*R*)- and (*S*)-enantiomers of compounds **2** and **3** showed different antimalarial activities. For compounds **3** as for compounds **1**, (*S*)-derivatives were more active than their (*R*)-counterparts (entries 7 and 8, Table 7). The IC_{50} ratio (*R*)/(*S*) ranged from 1.8 to 3 according to the strain considered, which is slightly less than the ratio found for compounds **1a** and **1b**. In the case of the aminoquinolinethanols **2**, enantiomers with an (*R*)-absolute configuration were more potent by a factor of 1.7 for **2b** to 1.9 for **2a** on the 3D7 strain. Compounds **1** and **3** possess a polar group (–OH or $–NH_2$) at the C11 position of the quinoline and a substituted heteroatom (–OR or –NHR) at C12. For compounds **2**, the position of these groups is reversed. Thus, a polar group at C11 of the quinoline seems to support a better activity for the (*S*)-enantiomers. This group should not be substituted, otherwise the antimalarial activity decreases [(*S*)-**1** and (*S*)-**3** vs (*S*)-**2a** or -**2b**, (*S*)-**8** vs (*S*)-**10a**]. Compounds (*S*)-**1** were by far the most potent and carry a –OH group at C11. In the novel series, (*S*)-**8** and (*S*)-**3** carrying a $–NH_2$ at the C11 position were more active than other (*S*)-enantiomers with pentyl or heptylamino group at this position (Table 7). For the (*S*)-enantiomers, the C11 position of the quinoline should be substituted preferably by an –OH group followed by $–NH_2$ and finally by –NHR.

For (*R*)-compounds, this trend is less evident in the novel series. Compounds of the series **1** (*R*)-**1a** and (*R*)-**1b** [IC_{50}s = 74 and 254 nM (3D7)] are still much more active than (*R*)-**2** (IC_{50} up to 5454 nM on 3D7) and (*R*)-**3** [IC_{50} = 13605 nM (3D7)]. However, (*R*)-**2a** which is substituted at C11 by a pentylamino group, is more active than (*R*)-**3** with an $–NH_2$ group at this position.

Evidently, the better substitution at the C11 position of the quinoline is the –OH group, whatever the stereochemistry of the compounds. An $–NH_2$ group or an –NHR in this position has a deleterious effect on the antimalarial activity. Thus, a hydrogen interaction seems to be essential for the antimalarial activity of this type of quinoline. Furthermore, the more the heteroatom is electron withdrawing, the stronger this interaction is.

The C11 substitution of the quinoline by a –OH group is essential for the antimalarial activity but not sufficient. Indeed, the weak antimalarial activity of the racemic quinolines **12** and **13** (Fig. 4) carrying an –OH group at C11 and a polar group (–OH or $–NH_2$) at C12 was previously described by Milner et al.[13c] The IC_{90}s of these two compounds is up to 1400 nM against W2 strains.

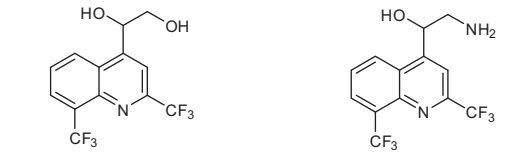


Figure 4. Antimalarial activity of **12** and **13**.

Thus, a hydrophilic group such as –OH or $–NH_2$, at C12 seems unfavorable to the antimalarial activity. The lead compounds **1** possess an –NHR group (R = alkyl) at C12. For the (*S*)-enantiomers of the new series, the silylated compound (*S*)-**8** was the most potent followed by (*S*)-**10a** and (*S*)-**3** with an –OTBDMS and an $–OC_5H_{11}$ group at C12. Compounds **2** with a –OH group were lesser active. Thus, we confirmed through the synthesis of this novel series of quinoline that a hydrophobic group at C12 position of the quinoline led to more potent compounds. The –NHR group, where R is an alkyl, remains the most effective substituent (Fig. 5).

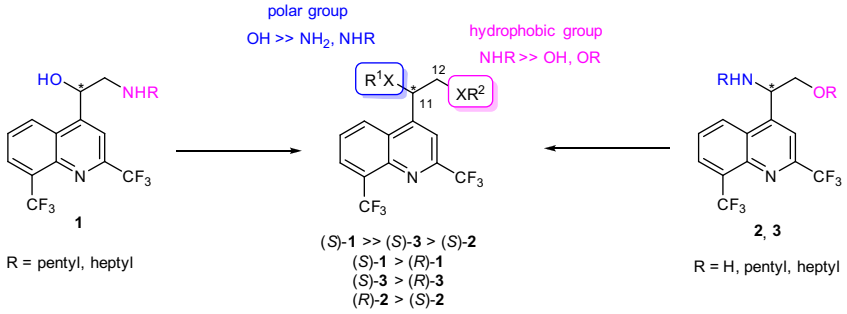


Figure 5. Structure–antimalarial activity relationships for **1**–**3**.

3. Conclusion

Three news series of enantiopure aminoquinolines **2a**, **2b,** and **3** were synthesized and evaluated for their antiplasmodial activity toward two *P. falciparum* strains, W2 and 3D7. We obtained these compounds **2** and **3** in 2 or 4 steps from the key intermediate **4**, which was successfully obtained via aminohydroxylation. All compounds displayed IC_{50}s close to the micromolar and were less active than the previous series **1**. This novel series of compounds allowed us to establish new structure–activity relationships. The best substitution at the C11 position of the quinoline is the –OH group, whatever the stereochemistry of the compounds. The C12 position of the quinoline should be substituted by a hydrophobic group, preferably an –NHR group. The lead compound (*S*)-**1a** remains the most active one [IC_{50} = 6.98 nM (W2) and 8.33 nM (3D7)], whatever the strain. However, other structure–antimalarial activity relationships have been highlighted and give tracks for the design of new compounds.

4. Experimental

4.1. Chemistry

Nuclear magnetic resonance (NMR) spectra were recorded using Bruker 400 MHz NMR instrument (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) and Bruker 300 MHz NMR instrument (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz). Chemical shifts are expressed in parts per million (δ, ppm) downfield from tetramethylsilane and are referenced to the deuterated solvent. ^{1}H NMR and ^{13}C NMR data were reported in the order of chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet), integration, coupling constants in hertz (Hz). High performance liquid chromatography (HPLC) was carried out on a Schimadzu LC-20AD equipped with a Chiralpak IB column. Specific rotations were measured on a Jasco P1010 polarimeter. Melting points were determined on Electrothermal Stuart SMP30 digital melting point apparatus and are uncorrected. Infrared spectra were recorded with a Jasco FTIR-4200 and are reported using the frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from a Micromass-Waters Q-TOF Ultima spectrometer.

Routine monitoring of reactions was performed using Merck silica gel 60 F254 plates, thin layer chromatography (TLC) and visualized under UV light (254 nm), with ethanolic phosphomolybdic acid (PMA). Flash column chromatography was carried out on Kielselgel 60 (40–63 μm) ASTM (Merck). All the moisture sensitive reactions were performed using oven dried glassware and under an inert gas atmosphere. In this case, solvents were dried with a Serlabo PS-MD-5 drier.

4.1.1. Preparation of (−)-(*S*)-4 and (+)-(*R*)-4

4.1.1.1. Preparation and titration of *tert*-butylhypochlorite. To a solution of 500 mL of NaOCl (4.00–4.99% of available chlorine), cooled to 0 °C and placed in the dark, were added a solution of 20 mL of acetic acid and 31 mL of *t*-butyl alcohol in one single portion. The solution was stirred for 10 min. The mixture was then poured into a separatory funnel. The aqueous layer was discarded and the organic layer washed, once, with 50 mL of an aqueous solution of $NaHCO_3$ 10% and then with 50 mL of water. The organic layer was dried over $CaCl_2$ and filtered. A yellow liquid was obtained (32 g, 0.29 mol, 75%) and stored over $CaCl_2$, under Ar atmosphere in a fridge.

Before each aminohydroxylation reaction, ^{t}BuOCl was titrated: To 20.0 mL of a solution of potassium iodide (100 g/L) were added 15 drops of acetic acid, and 114.0 μL of ^{t}BuOCl. The solution was titrated with a solution of $Na_2S_2O_3$ (0.1 M), after which 20.0 mL of sodium thiosulfate were added to give a pure product.

4.1.1.2. (*S*)-Benzyl (1-(2,8-bis(trifluoromethyl)quinolin-4-yl)-2-hydroxyethyl)carbamate (−)-(*S*)-4. To a solution of 804 mg (5.32 mmol, 3.1 equiv) of benzyl carbamate in propanol (7 mL) was added a solution of 210 mg (5.24 mmol, 3.05 equiv) of NaOH in water (13 mL). The solution was stirred for 5 min at 25 °C. Then 0.62 mL (5.24 mmol, 3.05 equiv) of freshly prepared ^{t}BuOCl and 70.0 mg (0.09 mmol, 5 mol %) of $(DHQ)_2PHAL$ in propanol (6 mL) were added. The solution was placed into a water bath and stirred for 10 min. To this solution were added 200 mg (1.72 mmol, 1 equiv) of vinyl **5** and 26.0 mg (0.07 mmol, 4 mol %) of $K_2OsO_2(OH)_4$. The suspension was stirred in a water bath for 15 h. The mixture was then extracted with AcOEt (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel (cyclohexane/ethyl acetate 2:1) afforded 378 mg (0.82 mmol) of (−)-(*S*)-**4** as a white solid. Yield 48%; ee 80%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 90:10, flow 1 mL/min, 278 nm, $t_R(S)$ = 14.6 min, $t_R(R)$ = 16.6 min); $[\alpha]_D^{20} = -28.9$ (*c* 0.1, MeOH). R_f 0.23 (cyclohexane/ethyl acetate 2:1); mp 135 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 3.89 [AB(ABX), J = 11.4, 6.4, 4.8 Hz, 2H], 5.08 (s, 2H), 5.62–5.80 [X(ABX), J = 6.4, 4.8 Hz, 1H], 7.14–7.41 (m, 5H), 7.77 (t, J = 7.8 Hz, 1H), 8.02 (s, 1H), 8.19 (d, J = 7.8 Hz, 1H), 8.57 (d, J = 7.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 54.6, 65.1, 67.9, 116.3, 120.9 (q, J = 274.8 Hz), 123.1 (q, J = 272.9 Hz), 126.8, 127.2, 127.3, 127.6, 128.4, 138.0, 144.9, 147.2 (q, J = 35.1 Hz), 151.9, 158.4 ppm; IR $\sqrt{}_{max}$: 3306, 1680, 1545 cm^{-1}; HRMS calcd for $C_{21}H_{17}F_6N_2O_3$ $(M+H)^+$ 459.1132, found 459.1134.

4.1.1.3. (*R*)-Benzyl (1-(2,8-bis(trifluoromethyl)quinolin-4-yl)-2-hydroxyethyl)carbamate (+)-(*R*)-4. Compound (+)-(*R*)-**4** was prepared from **5** according to the same procedure as that of

(−)-(*S*)-**4** with $(DHQD)_2PHAL$ as ligand. Yield 33%; ee 70%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 90:10, flow 1 mL/min, 278 nm, $t_R(S)$ = 14.6 min, $t_R(R)$ = 16.6 min); $[\alpha]_D^{20}$ = +9.5 (*c* 0.1, MeOH); R_f 0.23 (cyclohexane/ethyl acetate 2:1); mp 135 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 3.89 [AB (ABX), *J* = 11.4, 6.4, 4.8 Hz, 2H], 5.08 (s, 2H), 5.62–5.80 [X(ABX), *J* = 6.4, 4.8 Hz, 1H], 7.14–7.41 (m, 5H), 7.77 (t, *J* = 7.8 Hz, 1H), 8.02 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.57 (d, *J* = 7.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 54.6, 65.1, 67.9, 116.3, 120.9 (q, *J* = 274.8 Hz), 123.1 (q, *J* = 272.9 Hz), 126.8, 127.2, 127.3, 127.6, 128.4, 138.0, 144.9, 147.2 (q, *J* = 35.1 Hz), 151.9, 158.4 ppm; IR $\sqrt{}_{max}$: 3306, 1680, 1545 cm^{-1}; HRMS calcd for $C_{21}H_{17}F_6N_2O_3$ $(M+H)^+$ 459.1132, found 459.1136.

Regioisomer (*R*)-**4′** was isolated as a yellow oil. Yield: 24%; $[\alpha]_D^{20}$ = −15.4 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 3.42 [AB(ABX), *J* = 14.2, 7.8, 3.7 Hz, 2H], 4.97–5.07 (m, 2H), 5.68 [X (ABX), *J* = 7.8, 3.7 Hz, 1H], 7.19–7.32 (m, 5H), 7.76 (t, *J* = 7.9 Hz, 1H), 8.15 (s, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 8.65 (d, *J* = 7.9 Hz, 1H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 67.6, 69.6, 115.7 (q, *J* = 1.9 Hz), 122.8 (q, *J* = 274.7 Hz), 125.1 (q, *J* = 272.9 Hz), 128.2, 128.7, 128.9, 129.0, 129.4, 129.7 (q, *J* = 30.0 Hz), 130.1 (q, *J* = 5.2 Hz), 138.1, 144.7, 149.2 (q, *J* = 34.9 Hz), 154.0, 159.1 ppm. IR $\sqrt{}_{max}$: 3344, 1683, 1144, 1100 cm^{-1}; HRMS calcd for $C_{21}H_{16}F_6N_2O_3Na$ $(M+Na)^+$ 481.0963, found 481.0941.

4.1.2. Preparation of (−)-(*S*)-7 and (+)-(*R*)-7

4.1.2.1. (*S*)-Benzyl(1-(2,8-bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)-ethyl)carbamate (−)-(*S*)-7.

At first, (−)-(*S*)-**4** (625 mg, 1.36 mmol, 1 equiv) was dissolved under an argon atmosphere, in dry CH_2Cl_2 (5 mL) and 102 mg (1.50 mmol, 1.1 equiv) of imidazole were added. The solution was stirred at 25 °C for 5 min before the addition of 225 mg (1.50 mmol, 1.1 equiv) of TBDMSCl. The mixture was stirred for 15 h at 25 °C. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel (cyclohexane/ethyl acetate 4:1) afforded 693 mg of (−)-(*S*)-**7** as a colorless oil. Yield 89%; ee 76%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 95:5, flow 1 mL/min, 278 nm, $t_R(S)$ = 5.9 min, $t_R(R)$ = 7.5 min); $[\alpha]_D^{20}$ = −7.8 (*c* 0.1, MeOH); R_f 0.77 (cyclohexane/ethyl acetate 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.19 (s, 3H), −0.11 (s, 3H), 0.79 (s, 9H), 4.02 [AX(ABX), *J* = 10.3, 3.8, 2.9 Hz, 2H], 5.13 (s, 2H), 5.54–5.77 [X(ABX), *J* = 3.8, 2.9 Hz, 1H], 7.28–7.58 (m, 5H), 7.75 (t, *J* = 7.1 Hz, 1H), 7.87 (s, 1H), 8.19 (d, *J* = 7.1 Hz, 1H), 8.35 (d, *J* = 7.1 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6, 29.7, 51.9, 64.7, 67.4, 115.6, 121.3 (q, *J* = 271.6 Hz), 123.5 (q, *J* = 273.7 Hz), 126.8, 127.4, 128.4, 128.8, 129.8 (q, *J* = 30.0 Hz), 35.9, 143.9, 148.0 (q, *J* = 35.5 Hz), 149.1, 155.7 ppm. IR $\sqrt{}_{max}$: 3330, 2902, 1684, 1530 cm^{-1}. HRMS calcd for $C_{27}H_{31}F_6N_2O_3Si$ $(M+H)^+$ 573.1995, found 573.2008.

4.1.2.2. (*R*)-Benzyl(1-(2,8-bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)-ethyl)carbamate (+)-(*R*)-7.

Compound (+)-(*R*)-**7** was prepared from (+)-(*R*)-**4** according to the same procedure as that of (−)-(*S*)-**7**. Colorless oil; yield 80%; ee 70%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 95:5, flow 1 mL/min, 278 nm, $t_R(S)$ = 5.9 min, $t_R(R)$ = 7.5 min); $[\alpha]_D^{20}$ = +4.9 (*c* 0.1, MeOH); R_f 0.77 (cyclohexane/ethyl acetate 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.19 (s, 3H), −0.11 (s, 3H), 0.79 (s, 9H), 4.02 [AX(ABX), *J* = 10.3, 3.8, 2.9 Hz, 2H], 5.13 (s, 2H), 5.54–5.77 [X(ABX), *J* = 3.8, 2.9 Hz, 1H], 7.28–7.58 (m, 5H), 7.75 (t, *J* = 7.1 Hz, 1H), 7.87 (s, 1H), 8.19 (d, *J* = 7.1 Hz, 1H), 8.35 (d, *J* = 7.1 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6, 29.7, 51.9, 64.7, 67.4, 115.6, 121.3 (q, *J* = 271.6 Hz), 123.5 (q, *J* = 273.7 Hz), 126.8, 127.4, 128.4, 128.8, 129.8 (q, *J* = 30.0 Hz), 35.9, 143.9, 148.0 (q, *J* = 35.5 Hz), 149.1, 155.7 ppm. IR $\sqrt{}_{max}$: 3330, 2902, 1684, 1530 cm^{-1}. HRMS calcd for $C_{27}H_{30}F_6N_2O_3SiNa$ $(M+Na)^+$ 595.1828, found 595.1851.

4.1.3. Preparation of (+)-(*S*)-8 and (−)-(*R*)-8

4.1.3.1. (*S*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)ethan-amine (+)-(*S*)-8.

To 10 mL of dried MeOH under an Ar atmosphere were added 63.0 mg (10% w/w) of Pd/C. The suspension was placed under H_2 atmosphere and stirred for 5 min. A solution of 630 mg (1.21 mmol, 1 equiv) of (−)-(*S*)-**7** in 10 mL of dried MeOH was added slowly to the suspension and stirred for 8 h. The mixture then was filtered, and the filtrate concentrated in vacuo. Flash chromatography on silica gel (cyclohexane/ethyl acetate 2:1) afforded 430 mg of (+)-(*S*)-**8** as a colorless oil. Yield 81%; ee 74%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 95:5, flow 1 mL/min, 278 nm, $t_R(S)$ = 6.6 min, $t_R(R)$ = 7.3 min); $[\alpha]_D^{20}$ = +37.8 (*c* 0.1, MeOH). R_f 0.27 (cyclohexane/ethyl acetate 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.02 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.66–1.99 (m, 2H), 2.08–2.11 (s, 2H), 3.79 [AB(ABX), *J* = 9.8, 6.6, 3.9 Hz, 2H], 5.01 [X(ABX), *J* = 6.6, 3.9 Hz, 1H], 7.74 (t, *J* = 7.7 Hz, 1H), 8.04–8.25 (m, 2H), 8.39 (d, *J* = 8.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7, 29.7, 52.8, 67.9, 115.5, 121.1 (q, *J* = 276.1 Hz), 123.5 (q, *J* = 273.2 Hz), 127.0, 127.1, 128.6, 143.8, 148.4 (q, *J* = 33.7 Hz), 151.7 ppm. IR $\sqrt{}_{max}$: 2887, 1307 cm^{-1}. HRMS calcd for $C_{19}H_{25}F_6N_2OSi$ $(M+H)^+$ 439.1619, found 439.1613.

4.1.3.2. (*R*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)ethan-amine (−)-(*R*)-8.

Compound (−)-(*R*)-**8** was prepared from (+)-(*R*)-**7** according to the same procedure as that of (+)-(*S*)-**8**. Colorless oil; yield 81%; ee 70%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 95:5, flow 1 mL/min, 278 nm, $t_R(S)$ = 6.6 min, $t_R(R)$ = 7.3 min); $[\alpha]_D^{20}$ = −36.9 (*c* 0.1, MeOH); R_f 0.27 (cyclohexane/ethyl acetate 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.02 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.66–1.99 (m, 2H), 2.08–2.11 (s, 2H), 3.79 [AB (ABX), *J* = 9.8, 6.6, 3.9 Hz, 2H], 5.01 [X(ABX), *J* = 6.6, 3.9 Hz, 1H], 7.74 (t, *J* = 7.7 Hz, 1H), 8.04–8.25 (m, 2H), 8.39 (d, *J* = 8.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7, 29.7, 52.8, 67.9, 115.5, 121.1 (q, *J* = 276.1 Hz), 123.5 (q, *J* = 273.2 Hz), 127.0, 127.1, 128.6, 143.8, 148.4 (q, *J* = 33.7 Hz), 151.7 ppm. IR $\sqrt{}_{max}$: 2887, 1307 cm^{-1}; HRMS calcd for $C_{19}H_{25}F_6N_2OSi$ $(M+H)^+$ 439.1650, found 439.1640.

4.1.4. Preparation of Mosher amides 9a and 9b

4.1.4.1. (*R*)-*N*-((*S*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide 9a.

To a solution, under argon, of 60.0 mg (0.14 mmol, 1 equiv) of amine (+)-(*S*)-**8** in 2 mL of anhydrous CH_2Cl_2 were added 0.04 mL (0.21 mmol, 1.5 equiv) of *N*,*N*-diisopropylethylamine and 0.03 mL (0.17 mmol, 1.2 equiv) of (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The solution was stirred at 25 °C for 1 h and then concentrated under reduced pressure. The resulting oil was taken up in 1 M NH_4Cl and then extracted into methylene chloride. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 5:1) to afford 73.0 mg of **9a** as a colorless oil. Yield 79%; $[\alpha]_D^{20}$ = +39.9 (*c* 0.1, MeOH); R_f 0.27 (cyclohexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.10 (s, 3H), 0.01 (s, 3H), 0.89 (s, 9H), 3.41 (s, 3H), 4.04 [AB(ABX), *J* = 10.4, 4.20, 3.4 Hz, 2H], 5.84–5.91 (m, 1H), 7.41–7.50 (m, 3H), 7.52–7.57 (m, 2H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.93, −5.90, 18.0, 25.5, 50.1, 54.9, 64.0, 84.2 (q, *J* = 26.5 Hz), 115.6 (q, *J* = 1.6 Hz), 121.2 (q, *J* = 275.5 Hz), 123.5 (q, *J* = 273.7 Hz), 123.7

(q, J = 290.3 Hz), 126.8, 127.5, 127.7, 128.8, 128.9 (q, J = 5.4 Hz), 129.6 (q, J = 30.2 Hz), 129.7, 131.6, 143.9, 148.0 (q, J = 35.4 Hz), 148.2, 166.2 ppm; IR ν_{max}: 2932, 1700, 1142 cm^{-1}; HRMS calcd for $C_{29}H_{32}F_9N_2O_3Si$ $(M+H)^+$ 655.2039, found 655.2019.

4.1.4.2. (*S*)-*N*-((*S*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide 9b. To a solution, under argon, of 50.0 mg (0.11 mmol, 1 equiv) of amine (+)-(*S*)-**8** in 2 mL of anhydrous CH_2Cl_2 were added 0.03 mL (0.17 mmol, 1.5 equiv) of *N*,*N*-diisopropylethylamine and 0.02 mL (0.13 mmol, 1.2 equiv) of (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The solution was stirred at 25 °C for 1 h and then concentrated under reduced pressure. The resulting oil was taken up in 1 M NH_4Cl and then extracted into methylene chloride. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 5:1) to afford 50.0 mg of **9b** as a colorless oil. Yield 69%; $[\alpha]_D^{20}$ = −37.3 (*c* 0.1, MeOH); R_f 0.34 (cyclohexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.08 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 3.49 (s, 3H), 4.05 [AB(ABX), J = 10.4, 4.2, 3.3 Hz, 2H], 5.86–5.95 (m, 1H), 7.29–7.45 (m, 5H), 7.69 (t, J = 8.0 Hz, 1H), 7.75 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.9, −5.8, 18.0, 25.5, 49.8, 55.0, 64.0, 84.0 (q, J = 26.5 Hz), 115.5 (q, J = 1.9 Hz), 121.1 (q, J = 275.6 Hz), 123.4 (q, J = 273.7 Hz), 123.7 (q, J = 290.1 Hz), 126.9, 127.2, 127.5, 128.8, 128.9 (q, J = 5.4 Hz), 129.3 (q, J = 30.1 Hz), 129.8, 131.8, 143.9, 147.8 (q, J = 35.3 Hz), 148.3, 166.2 ppm; IR ν_{max}: 2932, 1700, 1142 cm^{-1}; HRMS calcd for $C_{29}H_{32}F_9N_2O_3Si$ $(M+H)^+$ 655.2039, found 655.2033.

4.1.5. General procedure for preparation of compounds 10

To a microwave vessel were added 210 mg (0.48 mmol, 1 equiv) of (−)-(*S*)-**8** or (+)-(*R*)-**8**, 6 mL of CH_3CN, 133 mg (0.96 mmol, 2 equiv) of K_2CO_3, 8.00 mg (0.05 mmol, 0.1 equiv) of KI and 0.06 mL (0.48 mmol, 1 equiv) of the appropriate bromoalkane. The solution was heated at 150 °C for 3 h with a power of 200 W. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude compound was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 5:1).

4.1.5.1. (*S*)-*N*-(1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)ethyl)pentan-1-amine (+)-(*S*)-10a. Yellow oil; yield 62%; ee 78%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 99:1, flow 1 mL/min, 278 nm, $t_R(S)$ = 3.8 min, $t_R(R)$ = 4.2 min); $[\alpha]_D^{20}$ = +30.7 (*c* 0.1, MeOH); R_f 0.62 (cyclohexane/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.86–0.90 (m, 12H), 1.19–1.40 (m, 4H), 1.44–1.60 (m, 2H), 2.17 (s_{br}, 1H), 2.39–2.57 (m, 2H), 3.74 [AB(ABX), J = 10.1, 8.2, 4.1 Hz, 2H], 4.68 [X(ABX), J = 8.2, 4.1 Hz, 1H), 7.73 (t, J = 8.1 Hz), 8.11–8.19 (m, 2H), 8.52 (d, J = 8.1 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.5, 25.7, 29.3, 29.8, 47.8, 60.8, 66.8, 116.2, 121.3 (q, J = 275.7 Hz), 123.5 (q, J = 273.7 Hz), 126.8, 127.2, 128.5, 129.5 (q, J = 30.2 Hz), 144.0, 148.5 (q, J = 35.1 Hz), 150.5 ppm; IR ν_{max}: 2929, 1308, 632 cm^{-1}; HRMS calcd for $C_{24}H_{35}F_6N_2OSi$ $(M+H)^+$ 509.2423, found 509.2418.

4.1.5.2. (*R*)-*N*-(1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)-ethyl)pentan-1-amine (−)-(*R*)-10a. Yellow oil; yield 60%; ee 62%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 99:1, flow 1 mL/min, 278 nm, $t_R(S)$ = 3.8 min, $t_R(R)$ = 4.2 min); $[\alpha]_D^{20}$ = −15.4 (*c* 0.1, MeOH); R_f 0.62 (cyclohexane/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.86–0.90 (m, 12H), 1.19–1.40 (m, 4H), 1.44–1.60 (m, 2H), 2.17 (s_{br}, 1H), 2.39–2.57 (m, 2H), 3.74 [AB(ABX), J = 10.1, 8.2, 4.1 Hz, 2H], 4.68 [X(ABX), J = 8.2, 4.1 Hz, 1H), 7.73 (t, J = 8.1 Hz), 8.11–8.19 (m, 2H), 8.52 (d, J = 8.1 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.5, 25.7, 29.3, 29.8, 47.8, 60.8, 66.8, 116.2, 121.3 (q, J = 275.7 Hz), 123.5 (q, J = 273.7 Hz), 126.8, 127.2, 128.5, 129.5 (q, J = 30.2 Hz), 144.0, 148.5 (q, J = 35.1 Hz), 150.5 ppm; IR ν_{max}: 2929, 1308, 632 cm^{-1}; HRMS calcd for $C_{24}H_{35}F_6N_2OSi$ $(M+H)^+$ 509.2423, found 509.2418.

4.1.5.3. (*S*)-*N*-(1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)ethyl)heptan-1-amine (−)-(*S*)-10b. Yellow oil; yield 67%; ee 74%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 99:1, flow 1 mL/min, 278 nm, $t_R(S)$ = 3.7 min, $t_R(R)$ = 4.0 min); $[\alpha]_D^{20}$ = +18.0 (*c* 0.1, MeOH); R_f 0.69 (cyclohexane/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.84–0.91 (m, 12H), 1.19–1.40 (m, 4H), 1.44–1.58 (m, 2H), 1.92 (s_{br}, 1H), 2.39–2.58 (m, 2H), 3.73 [AB(ABX), J = 10.1, 8.2, 4.1 Hz, 2H], 4.66 [X(ABX), J = 8.2, 4.1 Hz, 1H], 7.73 (t, J = 8.1 Hz), 8.11–8.20 (m, 2H), 8.52 (d, J = 8.1 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.6, 25.8, 27.1, 29.1, 30.1, 31.8, 47.8, 60.8, 66.8, 116.2, 121.3 (q, J = 274.8 Hz), 123.5 (q, J = 273.8 Hz), 126.8, 127.2, 128.6, 129.5 (q, J = 29.8 Hz), 144.0, 148.5 (q, J = 35.6 Hz), 150.4 ppm; IR ν_{max}: 2931, 1309, 632 cm^{-1}; HRMS calcd for $C_{26}H_{38}F_6N_2OSiNa$ $(M+Na)^+$ 559.2555, found 559.2539.

4.1.5.4. (*R*)-*N*-(1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)ethyl)heptan-1-amine (−)-(*R*)-10b. Yellow oil; yield 64%; ee 70%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 99:1, flow 1 mL/min, 278 nm, $t_R(S)$ = 3.7 min, $t_R(R)$ = 4.0 min); $[\alpha]_D^{20}$ = −30.1 (*c* 0.1, MeOH); R_f 0.69 (cyclohexane/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.84–0.91 (m, 12H), 1.19–1.40 (m, 4H), 1.44–1.58 (m, 2H), 1.92 (s_{br}, 1H), 2.39–2.58 (m, 2H), 3.73 [AB(ABX), J = 10.1, 8.2, 4.1 Hz, 2H], 4.66 [X(ABX), J = 8.2, 4.1 Hz, 1H], 7.73 (t, J = 8.1 Hz), 8.11–8.20 (m, 2H), 8.52 (d, J = 8.1 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.6, 25.8, 27.1, 29.1, 30.1, 31.8, 47.8, 60.8, 66.8, 116.2, 121.3 (q, J = 274.8 Hz), 123.5 (q, J = 273.8 Hz), 126.8, 127.2, 128.6, 129.5 (q, J = 29.8 Hz), 144.0, 148.5 (q, J = 35.6 Hz), 150.4 ppm; IR ν_{max}: 2931, 1309, 632 cm^{-1}; HRMS calcd for $C_{26}H_{38}F_6N_2OSiNa$ $(M+Na)^+$ 559.2555, found 559.2539.

4.1.6. General procedure for the preparation of compounds 2

To a solution of 114 mg (0.22 mmol, 1 equiv) of silylated alcohol **10a** or **10b** in dried THF (6 mL), under an Ar atmosphere and cooled to 0 °C, were added 0.67 mL (0.67 mmol, 3 equiv) of TBAF (1 M in THF). The reaction was stirred at 0 °C for 1 h and then quenched with water. The mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude compound was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 99:1).

4.1.6.1. (*S*)-2-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(pentylamino)ethanol (+)-(*S*)-2a. White solid; yield 83%; ee 86%, HPLC analysis was performed with Chiralpak IB column (heptane/ethanol, 99:1, flow 1 mL/min, 278 nm, $t_R(R)$ = 31.9 min, $t_R(S)$ = 34.3 min); $[\alpha]_D^{20}$ = +22.0 (*c* 0.1, MeOH); R_f 0.37 (CH_2Cl_2/MeOH 99:1); mp 50 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82–0.95 (m, 3H), 1.20–1.40 (m, 4H), 1.46–1.60 (m, 2H), 2.16–2.39 (s_{br}, 2H), 2.45–2.63 (m, 2H), 3.78 [AB(ABX), J = 10.8, 7.9, 4.0 Hz, 2H], 4.75 [X(ABX), J = 7.9, 4.0 Hz, 1H], 7.75 (t, J = 8.0 Hz), 8.04 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.46 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.4, 29.3, 29.8, 47.7, 60.1, 65.7, 115.4, 121.2 (q, J = 275.5 Hz), 123.7 (q, J = 273.7 Hz), 127.0, 127.2, 128.1,

128.8 (q, J = 5.4 Hz), 129.6 (q, J = 30.1 Hz), 144.0, 148.4 (q, J = 35.2 Hz), 150.0 ppm; IR $\sqrt{}_{max}$: 2929, 1308, 1140, 629 cm^{-1}; HRMS calcd for $C_{18}H_{21}N_2OF_6$ $(M+H)^+$ 395.1558; found 395.1538.

4.1.6.2. (*R*)-2-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(pentylamino)ethanol (−)-(*R*)-2a. White solid; yield 100%; ee 70%, HPLC analysis was performed with Chiralpak IB column (heptane/ethanol, 99:1, flow 1 mL/min, 278 nm, $t_R(R)$ = 31.9 min, $t_R(S)$ = 34.3 min); $[\alpha]_D^{20}$ = −29.0 (c 0.1, MeOH); R_f 0.37 (CH_2Cl_2/MeOH 99:1); mp 50 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82–0.95 (m, 3H), 1.20–1.40 (m, 4H), 1.46–1.60 (m, 2H), 2.16–2.39 (s_{br}, 2H), 2.45–2.63 (m, 2H), 3.78 [AB(ABX), J = 10.8, 7.9, 4.0 Hz, 2H], 4.75 [X(ABX), J = 7.9, 4.0 Hz, 1H], 7.75 (t, J = 8.0 Hz), 8.04 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.46 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.4, 29.3, 29.8, 47.7, 60.1, 65.7, 115.4, 121.2 (q, J = 275.5 Hz), 123.7 (q, J = 273.7 Hz), 127.0, 127.2, 128.1, 128.8 (q, J = 5.4 Hz), 129.6 (q, J = 30.1 Hz), 144.0, 148.4 (q, J = 35.2 Hz), 150.0 ppm; IR $\sqrt{}_{max}$: 2929, 1308, 1140, 629 cm^{-1}; HRMS calcd for $C_{18}H_{21}N_2OF_6$ $(M+H)^+$ 395.1558; found 395.1540.

4.1.6.3. (*S*)-2-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(heptylamino)ethanol (+)-(*S*)-2b. Colorless oil; yield 73%; ee 74%, HPLC analysis was performed with Chiralpak IB column (heptane/ethanol, 99:1, flow 1 mL/min, 278 nm, $t_R(R)$ = 29.5 min, $t_R(S)$ = 32.3 min); $[\alpha]_D^{20}$ = +25.6 (c 0.1, MeOH); R_f 0.17 (CH_2Cl_2/MeOH 99:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75–0.99 (m, 3H), 1.19–1.40 (m, 8H), 1.44–1.61 (m, 2H), 2.46–2.63 (m, 2H), 2.72 (s_{br}, 2H), 3.79 [AB(ABX), J = 10.9, 7.9, 3.9 Hz, 2H], 4.75 [X(ABX), J = 7.9, 3.9 Hz, 1H], 7.75 (t, J = 7.9 Hz), 8.06 (s, 1H), 8.18 (d, J = 7.9 Hz, 1H), 8.46 (d, J = 7.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 27.1, 29.1, 30.0, 31.8, 47.7, 60.1, 65.7, 115.5, 121.2 (q, J = 275.5 Hz), 123.5 (q, J = 273.7 Hz), 126.9, 127.2, 128.1, 128.8 (q, J = 5.4 Hz), 129.7 (q, J = 30.4 Hz), 144.0, 148.3 (q, J = 35.4 Hz), 149.6 ppm; IR $\sqrt{}_{max}$: 2928, 1308, 1142 cm^{-1}; HRMS calcd for $C_{20}H_{25}N_2OF_6$ $(M+H)^+$ 423.1871, found 423.1849.

4.1.6.4. (*R*)-2-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(heptylamino)ethanol (−)-(*R*)-2b. Colorless oil; yield 85%; ee 56%, HPLC analysis was performed with Chiralpak IB column (heptane/ethanol, 99:1, flow 1 mL/min, 278 nm, $t_R(R)$ = 29.5 min, $t_R(S)$ = 32.3 min); $[\alpha]_D^{20}$ = −28.9 (c 0.1, MeOH); R_f 0.17 (CH_2Cl_2/MeOH 99:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75–0.99 (m, 3H), 1.19–1.40 (m, 8H), 1.44–1.61 (m, 2H), 2.46–2.63 (m, 2H), 2.72 (s_{br}, 2H), 3.79 [AB(ABX), J = 10.9, 7.9, 3.9 Hz, 2H], 4.75 [X(ABX), J = 7.9, 3.9 Hz, 1H], 7.75 (t, J = 7.9 Hz), 8.06 (s, 1H), 8.18 (d, J = 7.9 Hz, 1H), 8.46 (d, J = 7.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 27.1, 29.1, 30.0, 31.8, 47.7, 60.1, 65.7, 115.5, 121.2 (q, J = 275.5 Hz), 123.5 (q, J = 273.7 Hz), 126.9, 127.2, 128.1, 128.8 (q, J = 5.4 Hz), 129.7 (q, J = 30.4 Hz), 144.0, 148.3 (q, J = 35.4 Hz), 149.6 ppm; IR $\sqrt{}_{max}$: 2928, 1308, 1142 cm^{-1}. HRMS calcd for $C_{20}H_{25}N_2OF_6$ $(M+H)^+$ 423.1871, found 423.1849.

4.1.7. Preparation of (−)-(*S*)-11 and (+)-(*R*)-11

4.1.7.1. (*S*)-2-((1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(pentyloxy)ethyl)imino)-1-phenylethanone (−)-(*S*)-11. To a solution of 100 mg (0.22 mmol, 1 equiv) of (*S*)-**4** in 4 mL of CH_2Cl_2, under argon and placed in the dark, were added 255 mg (1.10 mmol, 5 equiv) of silver oxide and 0.29 mL (2.20 mmol, 10 equiv) of iodopentane. The suspension was stirred at 25 °C for 63 h, filtered off through a Celite pad, and washed with CH_2Cl_2. The filtrate was concentrated in vacuo. Flash chromatography on silica gel (cyclohexane/ethyl acetate 4:1) afforded (−)-(*S*)-**11** as a white solid. Yield 41%; ee 64%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 90:10, flow 1 mL/min, 210 nm, $t_R(S)$ = 7.3 min, $t_R(R)$ = 10.0 min); $[\alpha]_D^{20}$ = −12.6 (c 0.1, MeOH); R_f 0.67 (cyclohexane/ethyl acetate 2:1); mp 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–0.89 (m, 3H), 1.13–1.31 (m, 4H), 1.44–1.57 (m, 2H), 3.24–3.52 (m, 2H), 3.64–3.97 (m, 2H), 5.12 (s, 1H), 5.76–5.84 (m, 1H), 5.92 (s, 1H), 7.26–7.45 (m, 5H), 7.75 (t, J = 7.0 Hz, 1H), 7.91 (s, 1H), 8.18 (d, J = 7.0 Hz, 1H), 8.39 (d, J = 7.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 22.4, 28.2, 29.0, 50.6, 67.4, 71.5, 71.8, 115.5, 120.9 (q, J = 275.6 Hz), 123.5 (q, J = 273.8 Hz), 126.8, 127.3, 127.6, 128.2, 128.4, 128.6, 128.7 (q, J = 5.4 Hz), 129.6 (q, J = 30.2 Hz), 135.9, 143.9, 148.1 (q, J = 35.3 Hz), 149.2, 155.8 ppm; IR $\sqrt{}_{max:}$ 2943, 1683, 1552, 1104 cm^{-1}; HRMS calcd for $C_{26}H_{26}F_6N_2O_3Na$ $(M+Na)^+$ 551.1745, found 551.1761.

4.1.7.2. (*R*)-2-((1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(pentyloxy)ethyl)imino)-1-phenylethanone (+)-(*R*)-11. Compound (+)-(*R*)-**11** was prepared from (*R*)-**4** according to the same procedure as that (−)-of (*S*)-**11**. White solid; yield 53%; ee 68%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 90:10, flow 1 mL/min, 210 nm, $t_R(S)$ = 7.3 min, $t_R(R)$ = 10.0 min); $[\alpha]_D^{20}$ = +3.2 (c 0.1, MeOH); R_f 0.67 (cyclohexane/ethyl acetate 2:1); mp 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–0.89 (m, 3H), 1.13–1.31 (m, 4H), 1.44–1.57 (m, 2H), 3.24–3.52 (m, 2H), 3.64–3.97 (m, 2H), 5.12 (s, 1H), 5.76–5.84 (m, 1H), 5.92 (s, 1H), 7.26–7.45 (m, 5H), 7.75 (t, J = 7.0 Hz, 1H), 7.91 (s, 1H), 8.18 (d, J = 7.0 Hz, 1H), 8.39 (d, J = 7.0 Hz, 1H,) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 22.4, 28.2, 29.0, 50.6, 67.4, 71.5, 71.8, 115.5, 120.9 (q, J = 275.6 Hz), 123.5 (q, J = 273.8 Hz), 126.8, 127.3, 127.6, 128.2, 128.4, 128.6, 128.7 (q, J = 5.4 Hz), 129.6 (q, J = 30.2 Hz), 135.9, 143.9, 148.1 (q, J = 35.3 Hz), 149.2, 155.8 ppm; IR $\sqrt{}_{max:}$ 2943, 1683, 1552, 1104 cm^{-1}; HRMS calcd for $C_{26}H_{26}F_6N_2O_3Na$ $(M+Na)^+$ 551.1745, found 551.1761.

4.1.8. Preparation of (+)-(*S*)-3 and (−)-(*R*)-3

4.1.8.1. (*S*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(pentyloxy)ethanamine (+)-(*S*)-3. To a solution of 115 mg (0.22 mmol, 1 equiv) of (*S*)-**11** in 4 mL of EtOH, under argon, were added 46.0 mg of Pd/C (40% w/w). The mixture was placed under an H_2 atmosphere and stirred at 25 °C for 8 h. The reaction mixture was filtered off through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 2:1). Orange oil; yield 74%; ee 58%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 95:5, flow 1 mL/min, 278 nm, $t_R(S)$ = 8.1 min, $t_R(R)$ = 9.0 min); $[\alpha]_D^{20}$ = +28.1 (c 0.1, MeOH); R_f 0.45 (cyclohexane/ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77–0.96 (m, 3H), 1.16–1.38 (m, 4H), 1.55–1.65 (m, 2H), 1.83–2.09 (s_{br}, 2H), 3.37–3.56 (m, 3H), 3.72 (dd, J = 9.4, 3.6 Hz, 1H), 5.06–5.12 (m, 1H), 7.74 (t, J = 7.9 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H), 8.21 (s, 1H), 8.41 (d, J = 7.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 28.3, 29.2, 51.1, 71.7, 75.3, 115.4, 121.3 (q, J = 275.6 Hz), 123.5 (q, J = 273.7 Hz), 127.0, 127.1, 127.5, 128.6 (q, J = 5.5 Hz), 129.5 (q, J = 30.1 Hz), 143.8, 148.5 (q, J = 35.2 Hz), 151.6 ppm; IR $\sqrt{}_{max}$: 2935, 2866, 1313, 1135, 1100 cm^{-1}; HRMS calcd for $C_{18}H_{20}F_6N_2ONa$ $(M+Na)^+$ 417.1378, found 417.1360.

4.1.8.2. (*R*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(pentyloxy)ethanamine (−)-(*R*)-3. Compound (−)-(*R*)-**3** was prepared from (*R*)-**11** according to the same procedure as that of (−)-(*S*)-**11**. Colorless oil; yield 74%; ee 66%, HPLC analysis was performed with Chiralpak IB column (heptane/isopropanol, 95:5, flow 1 mL/min, 278 nm, $t_R(S)$ = 8.1 min, $t_R(R)$ = 9.0 min); $[\alpha]_D^{20}$ = −43.3 (c 0.1, MeOH); R_f 0.45 (cyclohexane/ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77–0.96 (m, 3H), 1.16–1.38 (m, 4H),

1.55–1.65 (m, 2H), 1.83–2.09 (s_{br}, 2H), 3.37–3.56 (m, 3H), 3.72 (dd, J = 9.4, 3.6 Hz, 1H), 5.06–5.12 (m, 1H), 7.74 (t, J = 7.9 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H), 8.21 (s, 1H), 8.41 (d, J = 7.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 28.3, 29.2, 51.1, 71.7, 75.3, 115.4, 121.3 (q, J = 275.6 Hz), 123.5 (q, J = 273.7 Hz), 127.0, 127.1, 127.5, 128.6 (q, J = 5.5 Hz), 129.5 (q, J = 30.1 Hz), 143.8, 148.5 (q, J = 35.2 Hz), 151.6 ppm; IR $\sqrt{}_{max}$: 2935, 2866, 1313, 1135, 1100 cm^{-1}; HRMS calcd for $C_{18}H_{20}F_6N_2ONa$ $(M+Na)^+$ 417.1378, found 417.1374.

4.2. The in vitro antiplasmodial activity

The in vitro antiplasmodial activities were first tested over concentrations ranging from 39 nM to 40 μM and then, if molecule efficacy warranted it, further checked over a concentration range of 1 nM to 1 μM. The reference strains used were culture-adapted *Plasmodium falciparum* 3D7 and W2. The former strain is susceptible to chloroquine but displays a decreased susceptibility to mefloquine, while the latter is considered as resistant to chloroquine. Parasites were cultivated in RPMI medium (Sigma–Aldrich, Lyon, France) supplemented with 0.5% Albumax I (Life Technologies corporation, Paisley, United Kingdom), hypoxanthine (Sigma–Aldrich), gentamicin (Sigma–Aldrich), and human erythrocytes. They were incubated at 37 °C in a candle jar, as described previously.[28] The *P. falciparum* drug susceptibility test was carried out in 96-well flat bottom sterile plates under a final volume of 250 μL. After 48-h incubation with the drugs, quantities of DNA in treated and control cultures of parasites in human erythrocytes were compared according to the SYBR Green I (Sigma–Aldrich) fluorescence-based method.[25,26] Briefly, after incubation, plates were frozen at −20 °C until use. They were then left to thaw for 2 h at room temperature after which 100 μL of the homogenized culture were transferred to 96-well flat bottom sterile black plates (Nunc Inc.) already containing 100 μL of the SYBR Green I lysis buffer (2xSYBR Green, 20 mM Tris base pH 7.5, 5 mM EDTA, 0.008% w/v saponin, 0.08% w/v Triton X-100). A negative control, controls treated by solvents (DMSO and H_2O, typically), and positive controls (chloroquine and mefloquine) were added to each set of experiments. Plates were incubated for 1 h at room temperature and the SYBRGreen fluorescence was then read on a fluorescence plate reader (Tecan, Austria) using excitation and emission wavelengths of 485 and 535 nm, respectively. Concentrations inhibiting 50% of the parasite's growth (half maximal inhibitory concentration or IC_{50} values) were then calculated from the obtained experimental results using a regression program available on line.[27]

Acknowledgements

The authors thank the financial supports from DGA (Direction Générale de l'Armement, Ministère de la Défense, France), ANR Astrid (project ANR-12-STR-003) and Région Picardie. Guillaume Bentzinger was the recipient of a grant from the Région Picardie. We thank Sophie Da Nascimento for mass spectra recording.

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