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Guillaume Bentzinger, Etienne Pair, Jean Guillon, Mathieu Marchivie, Catherine Mullié, et al.. Enantiopure substituted pyridines as promising antimalarial drug candidates. Tetrahedron, 2020, 76 (15), 131088 (10 p.). 10.1016/j.tet.2020.131088 . hal-03611926

HAL Id: hal-03611926
https://u-picardie.hal.science/hal-03611926

Submitted on 20 May 2022

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Version of Record: https://www.sciencedirect.com/science/article/pii/S004040202030209X
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Tetrahedron
journal homepage: www.elsevier.com



Enantiopure substituted pyridines as promising antimalarial drug candidates

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Malaria
P. falciparum
Arylaminoalcohols
Enpiroline
Asymmetric synthesis

ABSTRACT

We describe the enantioselective synthesis and biological evaluation of 4-(2-amino-1-hydroxyethyl)pyridines (4 AHPs) as new antimalarial drug candidates. In particular, two routes to obtain the key-intermediate 4-vinyl-pyridine were studied. These routes are based on a Kröhnke-type cyclization or on metal-catalyzed reactions. The Kröhnke-type cyclization route is faster but only efficient at low scale since this pathway involves a Wittig reaction that requires severe temperature-control. Consequently, we designed a second route based on metal-catalyzed reactions. This way is longer but the 4-vinyl-pyridine can be obtained on a 5 g scale at least. Finally, a regioselective S_N2 ring-opening of enantiopure epoxides by alkyl primary amines allowed the synthesis of eight 4-AHPs with global yields up to 41%. These compounds show strong *in vitro* antimalarial activity against *P. falciparum* strains and are more active that chloroquine and mefloquine. These results demonstrate that 4-AHPs are promising antimalarial drug candidates.

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1. Introduction

Malaria is still today a major public health threat on a worldwide scale. In 2018, 228 million cases of malaria were reported worldwide and led to 405,000 deaths, 67% of them children aged under 5 years.[1] Since 2014, investments for malaria control and elimination were robust and resolute (2.7 billion dollars in 2018) but falling far the 5 billion dollars funding target of the World Health Organization (WHO) global strategy. *Plasmodium falciparum* is the most prevalent malaria parasite in Africa and is responsible for most malaria cases. It has shown great adaptive potential and the apparition of resistances towards antiplasmodial molecules always calls for new drug candidates. In the fight against malaria, the family of arylaminoalcohol (AAA) drugs including quinine (QN), mefloquine (MQ) and lumefantrine play an important role.[1] Not only do they have good activities against *P. falciparum* but their slow clearance makes them perfect partners for artemisinin-based combination therapy (ACT), widely recommended by the WHO since 2006.[2] MQ-artesunate and lumefantrine-artemether are among the six ACT commercially available.[1,3]

The first AAA used in antimalarial therapy was the enantiomerically pure quinine, one of the four cinchona alkaloids. Quinidine (QD), the dextrorotatory diastereomer of quinine, was discarded because it differs from QN in many pharmacological respects. Although, QD is about three to four times more active as an antimalarial drug,[4] the QT (Q wave-T wave interval) prolongation observed with it is about four times more than with QN.[5] Accordingly, QN was used as antimalarial drug while QD was for years available as an anti-arrhythmic. For the MQ, another AAA, several studies highlighted that the (*R*,*S*) enantiomer of MQ is the least active (Fig. 1) and crosses more easily the blood-brain barrier.[6-10] This latter ability making it, in part, responsible for the important neurological side effects of MQ.[11-13] Despite important disparities in activities, toxicities and pharmacokinetic profiles of the AAA stereoisomers, current commercial drugs containing MQ or lumefantrine are still used as racemates.

For those reasons, our group works on the enantioselective synthesis of new AAA analogs. Previously, the synthesis of 4-(2-amino-1-hydroxyethyl)quinolines (4-AHQs) as enantiopure open analogs of MQ was achieved (Fig. 1). Structure-activity-relationship (SAR) studies on the aminoalcohol moiety allowed us to identify a few molecules **1a-d** with alkyl side chains, as active as MQ *in vitro* and *in vivo* on the selected *P. falciparum* strains 3D7 and W2.[14-18] These compounds **1a-d** also showed a clearer (*S*)/(*R*) selectivity *in vitro* than MQ with IC_{50} up to 15-fold higher for the more active enantiomer.

The importance of the aminoalcohol stereochemistry for the antimalarial activity was reinforced with our study on the pyrroloquinoxaline family.[18] Although their corresponding activity was low (micromolar range), strong (*S*)/(*R*) disparities have been observed (eudysmic ratio up to 15.5).

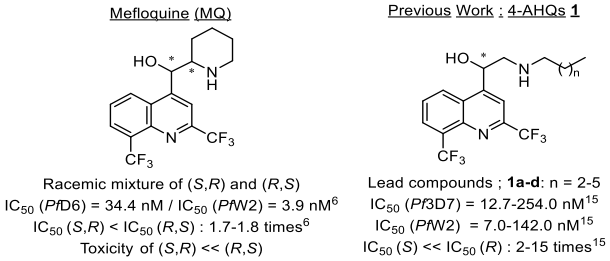


Fig. 1. Previous work: mefloquine and 4-AHQs **1a-d**.

As a continuation of our SAR studies, we decided now to focus our work on the aromatic ring role by restructuring the ring system. Dissociation of the quinoline core by splitting the benzo compound could lead to new antimalarial drugs such as 4-(2-amino-1-hydroxyethyl)pyridines (4-AHPs) **2a-d**. Furthermore, 4-AHPs could also be considered as enpiroline (ENP) analogs (Fig. 2). ENP is an AAA based on a pyridine core and was previously studied as a drug candidate.[19-22] Surprisingly, this compound was never fully exploited despite promising activities, good pharmacokinetic parameters, and low toxicity. Also, ENP enantiomers have similar activities with eudysmic ratios around 1.2.[6,23] We thought that 4-AHPs **2a-d** could display improved antimalarial activities and enhanced eudysmic ratios compared to 4-AHQs **1a-d** and lower long-term toxicity than MQ.[15] Herein, we describe the enantioselective synthesis and biological evaluation of 4-AHPs **2a-d** as new antimalarial potential drugs.

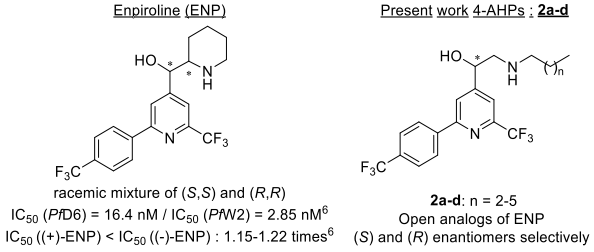


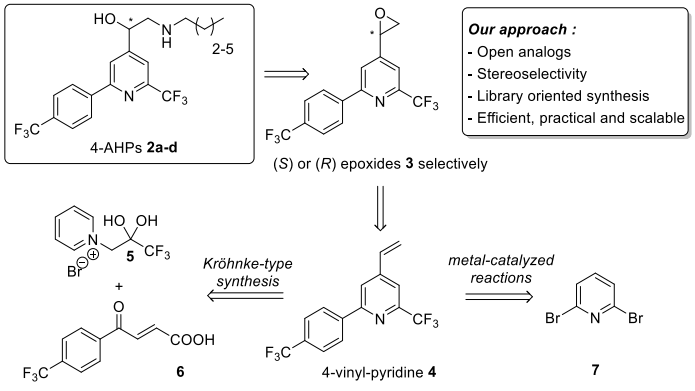
Fig. 2. Present work: Enpiroline and 4-AHPs **2a-d**.

In order to take advantage of the strategy we had optimized for generating the library of enantiopure 4-AHQs **1** for making the enantiopure 4-AHPs **2**, we needed to access to the epoxides **3** through an indirect asymmetric epoxidation of the 4-vinyl-pyridine **4** (scheme 1).[14] Two routes to obtain the key-intermediate 4-vinyl-pyridine **4** are studied based on a Kröhnke-type cyclization[24] or metal-catalyzed reactions. The respective advantages and inconveniences of these ones are discussed below. Finally, the 4-AHPs **2a-d** were prepared in three steps from the vinyl pyridine **4** and their *in vitro* activities were measured against *P. falciparum* 3D7 and W2 strains. Thus, novel SAR were highlighted with regard to their stereochemistry, alkyl substitution and in comparison with the corresponding quinolines 4-AHQs **1**.

2. Results and discussion

2.1. Chemistry

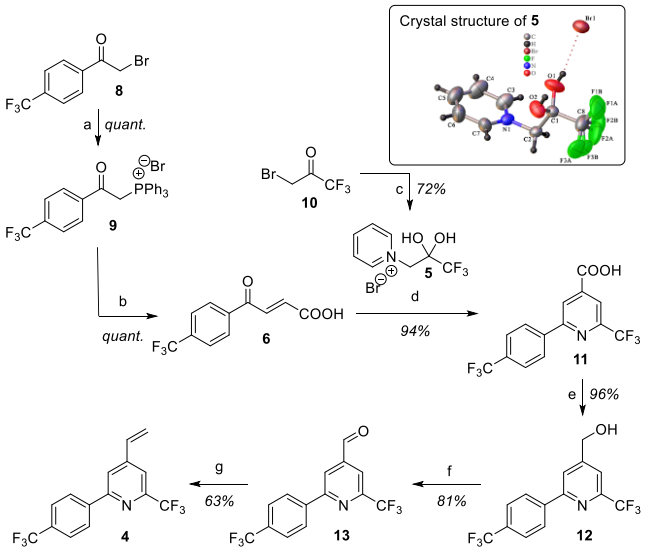
Two ways of making the 4-vinylpyridine **4** were explored either *via* a Kröhnke-type cyclization (7 steps, 46% overall yield)[24] or metal-catalyzed reactions (9 steps, 37% overall yield).



Scheme 1. Retrosynthesis strategies for the 4-AHPs **2a-d**.

*2.1.1. Synthesis of **4** using a Kröhnke-type cyclization*

Having a Wittig reaction in mind for the synthesis of the enone **6**, the commercial 2-bromo-4'-(trifluoromethyl)acetophenone **8** was treated with PPh_3 (Scheme 2). The resulting phosphonium salt **9**, obtained quantitatively, was then reacted with glyoxylic acid to obtain **6** as the Wittig product in quantitative yield. The ^1H NMR analysis and the coupling constant between the ethylenic protons ($^3J_{H1/H2}$ = 15.6 Hz) confirmed the selective formation of the *(E)*-isomer. In parallel, the commercially available 3-bromo-1,1,1-trifluoroacetone **10** was reacted with pyridine in EtOH at 70 °C. The corresponding pyridinium salt **5** was afforded in 72% yield with the ketone function completely hydrated due to its electro-withdrawing environment.[19,24,25] This structure was confirmed by ^{13}C NMR ($\delta C(C(OH)_2)$: 148.2 ppm) and X-ray diffraction (Scheme 2, supplementary material). With the enone **6** and the pyridinium salt **5** in hands, a Kröhnke-type cyclization was performed in order to form the isonicotinic acid **11** in 94% yield. Thereafter, the acid function is converted into aldehyde in order to introduce the vinyl group with a Wittig reaction. Different reducing agents were tested to achieve the direct reduction of the acid moiety to the aldehyde **13**, but mixtures of the aldehyde **13** and the alcohol **12** were afforded systematically. Thus, a two steps aldehyde synthesis was performed: i) borane (BH_3) was used as reducing agent to obtain the primary alcohol **12** in 96% yield and ii) Dess-Martin Periodinane as selective oxidant allowed to afford the aldehyde **13** in 81% yield. For the Wittig reaction, the methyltriphenylphosphonium bromide was deprotonated *in situ* with *n*-BuLi as the base at 0 °C in THF to generate the corresponding ylide. Due to the high reactivity of this ylide with aldehydes, the reaction required serious optimization (temperature, additives, reaction times). In our best conditions, the addition of aldehyde **13** was carried out dropwise at -78 °C. Then, the Wittig reaction itself was performed at -30 °C for six hours. Thus, the vinyl derivative **4** was obtained in 63% yield. When one gram or more of aldehyde were used, yields dropped between 15% and 30%. This reaction being very temperature sensitive, it proved to be hard to reproduce when scaled-up, probably due to a lack of temperature-control. With this synthetic pathway, the desired vinyl intermediate **4** is accessible in a 46% yield in an overall 7 steps sequence. Because of the scalability issues with the final Wittig step, we considered this method to be unsuitable for making a library of compounds and devised a new route to obtain the key derivative **4,** based on robust and reliable metal-catalyzed reactions.



Scheme 2. Preparation of the vinyl **4** by Kröhnke-type cyclization. Reagents and conditions: (a) PPh_3, THF, 70 °C. (b) Glyoxylic acid, NEt_3, $CHCl_3$/MeOH (1/1), 25 °C. (c) Pyridine, EtOH, 80 °C. (d) NH_4OAc, THF, 70 °C. (e) BH_3.DMS, THF, 25 °C. (f) DMP, CH_2Cl_2, 0 °C. (g) 1) $BrPPh_3CH_3$, *n*-BuLi, LiOH, THF, 0°C, 2) **13**, -78 °C, 1 h then -30 °C, 6 h.

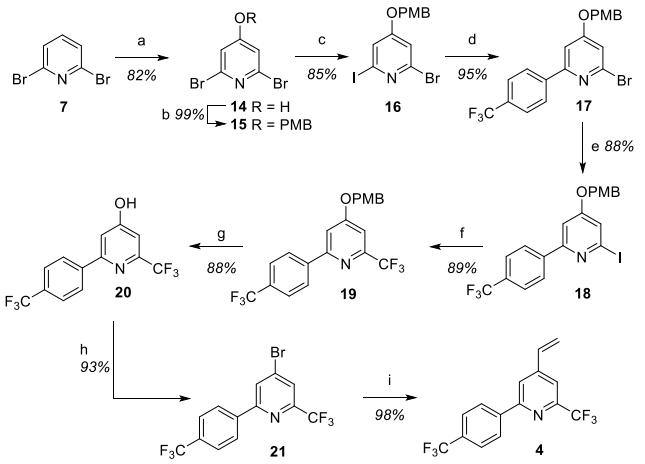
*2.1.2. Synthesis of **4** using metal-catalyzed reactions.*

The commercially available 2,6-dibromopyridine **7** was converted into 4-hydroxypyridine **14** *via* the formation of a boronate intermediate using the $[Ir(cod)Cl]_2$ catalyst in the presence of pinacolborane and 4,4′-di-tert-butyl-2,2′-dipyridyl (dtbpy). Then, a one-pot oxidative cleavage of the boronate was performed with Oxone® to afford **14** in an 82% yield.[26] An *O*-protecting reaction was carried out with 4-methoxybenzyl chloride to give **15**. A mono-halogen exchange, using Grignard reagent in the presence of I_2, afforded the mono-iodinated compound **16** in 85% yield. After optimization, the best conditions were found by using 1.6 equivalents of both Turbo Grignard and I_2.[27] The mono-iodination allowed to perform a selective Suzuki coupling with 4-(trifluoromethyl)phenylboronic acid affording **17** in 95% yield.[28] At that point, direct conversion of **17** into **19** using reaction conditions described by Z. Gonda *et al.*[29] was unsuccessful. Consequently, a copper-catalyzed aromatic Finkelstein reaction was used in order to convert **17** into **18** in 88% yield.[30,31] The iodo derivative **18** proved to be more reactive and was converted into a $-CF_3$ affording **19** in a satisfactory 89% yield.[29] After removal of the –PMB group, the resulting alcohol **20** was reacted with $POBr_3$ to isolate the bromo compound **21** in 93% yield. This allowed a Suzuki coupling with potassium (vinyl)trifluoroborate affording the key intermediate **4** in 98% yield. The global yield for this new synthetic pathway is of 37% over 9 steps. The selected reactions proved to be very robust whatever the scale (up to 5 g of vinyl **4** per sequence).

*2.1.3. Synthesis of 4-(2-amino-1-hydroxyethyl) pyridines **2** (4-AHPs).*

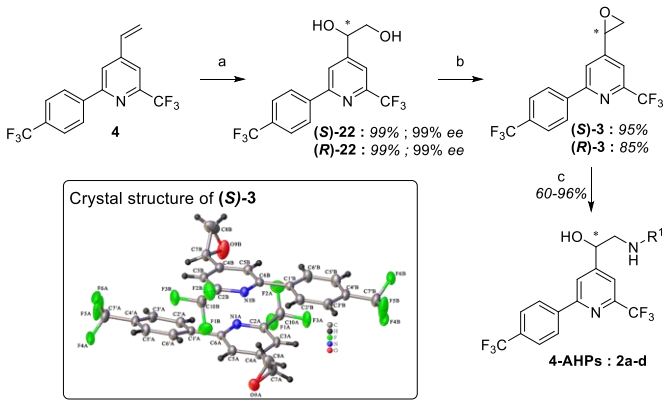
With intermediate **4** in hands, the diols ***(S)*-22** and ***(R)*-22** were obtained enantioselectively using a Sharpless dihydroxylation in the presence of AD-mix-α or -β respectively in 99% yield and 99% *ee*. A ring-closure was carried out in order to form the epoxides ***(S)*-3** and ***(R)*-3** by means of a slightly modified "one-pot" reaction, previously described.[14] Those were obtained with complete retention of configuration in 95% and 85% yield from

(*S*)-22 and **(*R*)-22** respectively. X-ray diffraction of epoxide ***(S)*-3** was performed and the *(S)*-geometry was ascribed unambiguously (Scheme 4, supplementary material).



Scheme 3. Preparation of the vinyl **4** using metal-catalyzed reactions. Reagents and conditions: (a) 1) $[Ir(cod)Cl]_2$, pinacolborane, dtbpy, cyclohexane, 80 °C, 2) Oxone, THF/H_2O (1/1), 25 °C. (b) 4-methoxybenzyl chloride, K_2CO_3, DMF, 110 °C. (c) *i*PrMgCl.LiCl, I_2, THF, 25 °C. (d) 4-(trifluoromethyl)phenyl boronic acid, Na_2CO_3, $Pd(PPh_3)_4$, toluene/H_2O/EtOH (6/1/1), 110 °C. (e) CuI, NaI, *N*,*N*'-dimethylethylenediamine, 1,4-dioxane, 110 °C. (f) KF, CuI, $TMSCF_3$, 1,10-phenantroline, $B(OMe)_3$, DMSO, 60 °C. (g) TFA, DCM, 25 °C. (h) $POBr_3$, DMF, 110 °C. (i) Potassium (vinyl)trifluoroborate, Na_2CO_3, $Pd(PPh_3)_4$, toluene/EtOH/H_2O (6/1/1), 110 °C.

The last step of the synthesis consisted in a regioselective S_N2 ring-opening with diverse primary amines (Scheme 4, Table 1). Using microwave irradiations allowed for reduced reaction times compared to the classical heating that was used for making the corresponding quinoline derivatives. Eight **(*S*)**- or (***R*)**-4-AHPs **2a-d** were thus synthesized using four alkylamines of growing size in good to excellent yields (60-96%) and with enantiomeric excesses superior to 98%.

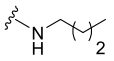
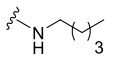
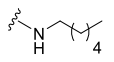
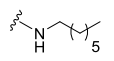


Scheme 4. Synthesis of 4-AHPs **2a-d**. Reagents and conditions: (a) AD-mix-α or -β, $K_2OsO_2(OH)_4$, *t*BuOH/H_2O (1/1), 0 °C to 25 °C, 15 h. (b) i) trimethyl orthoacetate, *p*TsOH, DCM, 25 °C, 7 h, ii) TMSBr, DCM, 25 °C, 15 h, iii) K_2CO_3, MeOH, 25 °C, 4 h. (c) R^1-NH_2, EtOH, 130 °C (M.W.), 30 min.

2.2. Biological evaluation.

The activities of all 4-AHPs **2a-d** were evaluated against *P. falciparum* 3D7 and W2 using the SYBR Green I method.[32] *Pf*W2 is a chloroquine (CQ) resistant strain and is MQ sensitive while *Pf*3D7 is chloroquine sensitive and displays a decreased susceptibility to MQ. The two antiplasmodial compounds CQ and MQ were used as references. The half maximal inhibitory concentration (IC_{50}) calculated are reported in Table 2.

Table 1.
Yields and enantiomeric purities of the synthesized 4-AHPs **2a-d.**

Entry	Compound	-NHR[1]	Yield	%*ee* [a]
1	**(*S*)-2a**		78%	99
2	**(*R*)-2a**		96%	99
3	**(*S*)-2b**		94%	99
4	**(*R*)-2b**		85%	99
5	**(*S*)-2c**		67%	99
6	**(*R*)-2c**		65%	98
7	**(*S*)-2d**		60%	99
8	**(*R*)-2d**		85%	99

[a]determined by chiral HPLC, see experimental part.

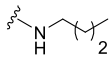
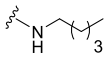
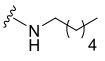
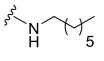
Pleasingly, all IC_{50} are in the nanomolar range and all compounds are more active than the references whatever the strain. As previously observed for the AHQs **1a-d**,[15] the 4-AHPs **2a-d** are more active against *Pf*W2 than *Pf*3D7, the CQ-resistant strain, with IC_{50} ranging from 3.5 (entry 8) to 10.0 nM (entry 2). For the *Pf*3D7 strain, less sensitive to MQ, the IC_{50} are between 17.7 (entry 7) and 56.7 nM (entry 2). In general, it appears that a longer side chain enhances the efficacy of the compound and the differences between (*S*)- and (*R*)- enantiomers. Interestingly, this trend correlates with a higher calculated logP of the corresponding molecules. Compound **2d,** with a heptyl side chain, shows the best activities against both *Pf*3D7 and *Pf*W2 and has a clear difference between (*S*)- and (*R*)- enantiomers against *Pf*3D7 with a eudysmic ratio of 3.1. The newly synthesized 4-AHPs **2a-d** are as much active as their quinoline counterparts 4-AHQs **1**, but clearly show less differences between (*S*)- and (*R*)- enantiomers which had a eudysmic ratio between 2.2 and 15.1.[15] Nonetheless, disparities could appear more clearly in pharmacokinetic properties like in the case of MQ. These pharmacokinetic studies are currently under progress.

3. Conclusion

The synthesis of eight enantiopure AHPs **2a-d** with varying alkyl substituents was achieved from the 4-vinylpyridine **4**. This key-intermediate was obtained by two routes using either a Kröhnke-type cyclization or metal-catalyzed reactions. The cyclisation route led to **4** in a 46% yield in an overall 7 steps sequence. However, this pathway was not suitable for making a library of compounds, as the scaling-up was limited by the last step of the sequence. The metal-catalyzed route proved to be more robust. However, **4** was obtained in a lower yield of 37% yield over 9 steps. Nonetheless, this new synthesis allowed us to obtain large quantities of the AHPs precursor **4** (up to 5 g per sequence). Consecutively, a regioselective S_N2-ring opening of enantiopure epoxides **3** with four alkyl primary amines gave 4-AHPs **2a-d** with good yields and excellent *ee*. These pyridines **2a-d** showed strong antimalarial activity with IC_{50} ranging from 3.5 to 10.0 nM against *Pf*3D7 and 17.7 to 56.7 nM against *Pf*W2. Compared with their quinoline counterparts AHQs **1**, the differences between (*S*)- and (*R*)- enantiomers IC_{50} are less marked with eudysmic ratio between 1.1 and 3.1. These novel

promising antimalarial 4-AHPs **2a-d** and derivatives were recently patented.[32] Pharmacokinetic studies and *in vivo* experiments in a mouse model are under progress to validate their potential as antimalarial drug candidates.

Table 2.
In vitro antiplasmodial activities of the 4-AHPs **2a-d** and references **CQ** and **MQ** against a chloroquine sensitive *Plasmodium falciparum* clone (3D7) and a chloroquine-resistant *Plasmodium falciparum* clone (W2), eudysmic ratio and clogP values.

Entry	Compound code	-NHR[1]	IC_{50} ± SD (nM)[a,b]		eudysmic ratio[c]		clogP[d]
			*Pf*3D7[e]	*Pf*W2[f]	*Pf*3D7	*Pf*W2	
1	**(*S*)-2a**		45.8 ± 2.3	9.0 ± 0.4	1.2	1.1	4.74
2	**(*R*)-2a**		56.7 ± 2.3	10.0 ± 0.7			
3	**(*S*)-2b**		52.4 ± 1.7	8.6 ± 1.0	1.3	1.2	5.26
4	**(*R*)-2b**		41.8 ± 5.5	7.2 ± 0.5			
5	**(*S*)-2c**		47.1 ± 13.2	N.D.[g]	1.5	N.D.	5.81
6	**(*R*)-2c**		32.3 ± 2.0	8.3 ± 0.8			
7	**(*S*)-2d**		17.7 ± 4.7	5.6 ± 0.3	3.1	1.6	6.08
8	**(*R*)-2d**		54.4 ± 3.2	3.5 ± 0.5			
9	**Mefloquine (MQ)**		75.9 ± 3,0	198.8 ± 27.0	-	-	3.91
10	**Chloroquine (CQ)**		79.7 ± 8.5	31.8 ± 1.0	-	-	4.40

[a] *in vitro* measurements against *P. falciparum* using the SYBR Green I method, see experimental part. [b] Results expressed as mean ± standard deviation. [c] ratio between the IC_{50} of the more active enantiomer and the less active. [d] Predicted octanol/water partition coefficient calculated with Maestro Material Sciences 2.9.011 software. [e] *P. falciparum* strain with decreased sensibility to MQ and sensitive to CQ. [f] *P. falciparum* strain resistant to CQ and sensitive to MQ. [g] Not determined

4. Experimental

4.1. Chemistry

Reactions were monitored by thin-layer chromatography with silica gel 60 F_{254} pre-coated aluminium plates (0.25 mm). Visualization was performed under UV light and PMA oxidation. Filtrations were performed on Celite® 545. Chromatographic purification of compounds was achieved with 60 silica gel (40-63 μm). Unless otherwise noted, all reagent-grade chemicals and solvents were used as supplied (analytical or HPLC grade) without prior purification. Melting points were measured on a Stuart SMP3 apparatus with a precision of +/- 1.5 °C and are uncorrected. Infrared spectra (IR) were recorded on a FT/IR-4200 Jasco with an ATR-Golden gate. Liquids and solids were applied on the Single Reflection Attenuated Total Reflectance (ATR) Accessories. Data are reported in cm^{-1}. Optical rotations were determined with a Jasco P1010 polarimeter with a 10 cm cell. Specific rotations are reported in 10^{-1} deg.cm^2.g^{-1} and concentrations in g per 100 mL. ^{1}H NMR Spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on a Bruker 400 MHz NMR. The field was locked by external referencing to the relevant deuteron resonance. Data appear in the following order: chemical shifts in ppm which were referenced to the internal solvent signal, number of protons, multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *dd*, doublet of doublet, *ddd*, doublet of doublet of doublet, *ddt*, doublet of doublet of triplet, *m*, multiplet) and coupling constant *J* in Hertz. The abbreviation *Ar* is used to denote aromatic, *br.* to denote broad and *app.* to denote apparent. Coupling constants, *J*, are measured to the nearest 0.1 Hz and are presented as observed. LC-HRMS analyses were performed on an ACQUITY UPLC H-Class system (Waters-Micromass, Manchester, UK) coupled with a SYNAPT G2-Si Q-TOF hybrid quadrupole time-of-flight instrument (Waters-Micromass, Manchester, UK), equipped with an electrospray (ESI) ionization source (Z-spray) and an additional sprayer for the reference compound (Lock Spray)., Torrance, CA, USA) heated at 50 °C. High-resolution mass spectra (HRMS) were obtained from a Micromass-Waters Q-TOF Ultima spectrometer, in electrospray ionization (ESI) mode (positive or negative). Enantiomeric excesses were measured with Schimadzu LC-20AD equipped with a Chiralpak column (IA, IB, IC, ID or IG).

*4.1.1. (2-Oxo-2-(4-(trifluoromethyl)phenyl)ethyl) triphenyl phosphonium bromide (**9**)*

To a solution of 2-bromo-1-(4-(trifluoromethyl)phenyl)-ethanone **8** (1.00 g, 3.70 mmol, 1 eq.) in THF (20 mL) were added triphenylphosphine (1.08 g, 4.10 mmol, 1.1 eq.). The reactional mixture was heated to reflux for 15 h and concentrated under reduced pressure. The residue was washed with Et_2O. The solid was filtered, washed with toluene and then with Et_2O to afford **9** (2.00 g, quant.) as a white solid. m.p. 136 °C; NMR ^{1}H (400 MHz, $CDCl_3$): δH 6.41 (d, *J* = 12.1 Hz, 2H), 7.49-7.57 (m, 11H), 7.84-7.93 (m, 6H), 8.49 (d, *J* = 7.5 Hz, 2H) ppm ; NMR ^{13}C (100 MHz, $CDCl_3$): δC 38.7 (d, *J* = 61.3 Hz), 118.4 (d, *J* = 89.3 Hz), 123.3 (q, *J* = 272.9 Hz), 125.8 (q, *J* = 3.6 Hz), 130.1 (d, *J* = 13.1 Hz), 130.4, 133.4 (d, *J* = 10.7 Hz), 134.8 (d, *J* = 2.9 Hz), 135.4 (q, *J* = 32.7 Hz) 137.6 (d, *J* = 5.6 Hz), 191.2 (d, *J* = 10.9 Hz) ppm; IR ν_{max} : 3435, 3057, 2722, 1680, 1409, 1316, 1107 cm^{-1}; HRMS calcd. for $C_{27}H_{21}F_3OP$ $[M+H]^+$ 449.1282, found 449.1285.

*4.1.2. (E)-4-oxo-4-(4-(trifluoromethyl)phenyl)but-2-enoïc acid (**6**)*

To a solution of 6.00 g (11.4 mmol, 1 eq.) of **9** in 30 mL of $CHCl_3$ were added 2.00 mL (1.45 g, 17.0 mmol, 1.5 eq.) of NEt_3. The solution was stirred at 25 °C for 5 min, before to add 1.57 g (17.0 mmol, 1.5 eq.) of glyoxylic acid in 30 mL of MeOH. The reactional mixture was stirred at 25 °C for 15 h and then concentrated in *vacuo*. AcOEt (30 mL) were added before to be treated with 4 x 30 mL sat. aq. $NaHCO_3$. The aqueous layers were combined and acidified (pH ~ 1) with 1 M aq. HCl. The solid was filtered and dried to afford **6** (3.07 g, quant.) as a white solid. m.p. 154 °C; NMR ^{1}H (300 MHz, CD_3OD): δH 6.80 (d, *J* = 15.6 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 15.6 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 2H) ppm; NMR ^{13}C (75 MHz, CD_3OD): δC 129.4 (q, *J* = 272.0 Hz), 127.0 (q, *J* = 3.8 Hz), 130.5, 134.8, 135.7 (q, *J* = 32.5 Hz), 137.0, 140.9, 168.2, 190.3 ppm; IR ν_{max} : 2982, 1691, 1665, 1504, 1170, 1134, 1111 cm^{-1}; HRMS calcd. for $C_{11}H_7F_3O_3Na$ $[M+Na]^+$ 267.0245, found 267.0238.

*4.1.3. 1-(3,3,3-Trifluoro-2,2-dihydroxypropyl) pyridin-1-ium bromide (**5**)*

To a solution of 5.00 g (26.3 mmol, 1.3 eq.) of 3-bromo-1,1,1-trifluoropropan-2-one **10** in 20 mL of EtOH were added 1.60 mL (20.2 mmol, 1 eq.) of pyridine. The mixture was heated to reflux for 10 h, before to be cooled to 25 °C. Et_2O was then added until to obtain a murky solution. The mixture was stirred at 25 °C for 15 h. The solid was then filtered to afford **5** (6.35 g, 72%) as a white solid. m.p. 193 °C; NMR ^{1}H (300 MHz, D_2O): δH 1.19 (t, *J* = 7.0 Hz, 3H), 3.62 (q, *J* = 7.0 Hz, 2H), 4.99 (s, 2H), 8.18 (t , *J* = 6.9 Hz, 2H), 8.71 (t, *J* = 6.9 Hz, 1H), 8.91 (d, *J* = 6.9 Hz, 2H) ppm ; NMR ^{13}C (75 MHz, D_2O): δC 18.4, 58.3, 63.8, 94.9 (q, *J* = 32.0 Hz), 125.0 (q, *J* = 291.1 Hz), 128.9, 148.2 ppm; IR ν_{max} : 3157, 1300, 1239, 1152, 1087 cm^{-1}.

*4.1.4. 2-(Trifluoromethyl)-6-(4-(trifluoromethyl) phenyl) isonicotinic acid (**11**)*

In 300 mL of MeOH were added 2.92 g (9.24 mmol, 1 eq.) of **5**, 3.38 g (13.9 mmol, 1.5 eq.) of **6** and 5.70 g (73.9 mmol, 8 eq.) of NH_4OAc. The reaction mixture was heated to reflux for 24 h before to concentrate it in *vacuo*. The residue was directly purified by flash chromatography (cyclohexane/AcOEt/AcOH 1/1/0.01) to afford **11** (2.92 g, 94%) as an orange solid. m.p. 205 °C; NMR ^{1}H (300 MHz, CD_3OD): δH 7.69 (d, *J* = 8.2 Hz, 2H), 8.10 (s, 1H), 8.16 (d, *J* = 8.2 Hz, 2H), 8.46 (s, 1H) ppm ; NMR ^{13}C (75 MHz, CD_3OD): δC 120.0, 122.4 (q, *J* = 273.6 Hz), 123.9, 125.6 (q, *J* = 271.6 Hz), 126.8, 128.6, 132.9 (q, *J* = 32.4 Hz), 141.5, 143.1, 150.5 (q, *J* = 35.2 Hz), 158.2, 166.3 ppm; IR ν_{max} : 2980, 1714, 1128 cm^{-1}; HRMS calcd. for $C_{14}H_8F_6NO_2$ $[M+H]^+$ 336.0459, found 336.0466.

*4.1.5. (2-(Trifluoromethyl)-6-(4-(trifluoromethyl) phenyl)pyridin-4-yl)methanol (**12**)*

To a solution, at 0 °C and under argon, of 78.0 mg (0.23 mmol, 1 eq.) of **11** in 2 mL of anhydrous THF were added 0.58 mL (1.15 mmol, 5 eq.) of BH_3.DMS (2M in THF). The solution was stirred at 25 °C for 8 h, cooled to 0 °C and treated with an of excess MeOH. The reactional mixture was stirred for 5 min at 0 °C and 5 min at 25 °C, before concentrated in *vacuo*. The residue was extracted with Et_2O. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (cyclohexane/AcOEt 2/1) to afford **12** (71 mg, 96%) as a light orange solid. m.p. 83 °C; NMR ^{1}H (400 MHz, $CDCl_3$): δH 4.90 (s, 2H), 7.66 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.95 (s, 1H), 8.18 (d, *J* = 8.2 Hz, 2H) ppm; NMR ^{13}C (100 MHz, $CDCl_3$): δC 63.1, 116.8 (q, *J* = 2.7 Hz), 120.2, 121.5 (q, *J* = 274.5 Hz), 124.0 (q, *J* = 272.2 Hz), 125.6 (q, *J* = 3.8 Hz), 127.5, 131.6 (q, *J* = 32.6 Hz), 141.0, 148.6 (q, *J* = 34.7 Hz), 153.0, 156.4 ppm; IR ν_{max}: 3249, 2918, 2850, 1323, 1116 cm^{-1}; HRMS calcd. for $C_{14}H_9F_6NONa$ $[M+Na]^+$ 344.0486, found 344.0496.

4.1.6. 2-(Trifluoromethyl)-6-(4-(trifluoromethyl)

*phenyl) isonicotinaldehyde (**13**)*

To a solution, at 0 °C, of 90.0 mg (0.28 mmol, 1 eq.) of **12** in 2 mL of CH_2Cl_2 were added 132 mg (0.31 mmol, 1.1 eq.) of Dess-Martin Periodinane. The suspension was stirred at 0 °C for 1.5 h before to be treated with sat. aq. $NaHCO_3$. The reaction mixture was stirred at 25 °C for 5 min. The solid was then filtered and the filtrate extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (cyclohexane/AcOEt 1/1) to afford **13** (72.0 mg, 81%) as a white solid. m.p. 69 °C; NMR ^{1}H (300 MHz, $CDCl_3$): δH 7.77 (d, *J* = 8.2 Hz, 2H), 8.06 (s, 1H), 8.24 (d, *J* = 8.2 Hz, 2H), 8.35 (s, 1H), 10.21 (s, 1H) ppm; NMR ^{13}C (75 MHz, $CDCl_3$): δC 118.0, 120.2 (q, *J* = 272.0 Hz), 121.6, 123.9 (q, *J* = 274.5 Hz), 126.0, 127.6, 132.1 (q, *J* = 32.7 Hz), 139.8, 144.2, 150.0 (q, *J* = 35.9 Hz), 158.0, 189.6 ppm; IR ν_{max}: 1711, 1319, 1118 cm^{-1}.

*4.1.7. 2-(Trifluoromethyl)-6-(4-(trifluoromethyl) phenyl)-4-vinylpyridine (**4**)*

Method A: Wittig reaction: To a suspension, at 0 °C and under argon, of 729 mg (2.04 mmol, 1.3 eq.) of methyltriphenylphosphonium bromide, 75.0 mg (3.14 mmol, 2 eq.) of LiOH in 30 mL of distilled THF were added 1.96 mL (3.14 mmol, 2 eq.) of *n*-BuLi (1.6 M in hexane). The reaction mixture was stirred at 0 °C for 10 min, at 25 °C for 10 min and cooled to -78 °C. A solution of 500 mg (1.57 mmol, 1 eq.) of **13** in 10 mL of distilled THF were added dropwise. The solution was stirred for 20 min at -78 °C before to be heated to -30 °C. The reaction mixture was stirred at -30 °C for 6 h, heated to 25 °C in 5 h (0.2 °C/min) and stirred at 25 °C for 15 h. The solution was treated with a MeOH excess before to be extracted with AcOEt. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (cyclohexane/AcOEt 10/1) to afford **4** (270 mg, 63%) as an oil, solidifying over time into a light yellow solid.

Method B: Suzuki coupling: An argon-purged mixture of **21** (6.0 g, 16.3 mmol, 1 eq.), potassium vinyltrifluoroborate (2.4 g, 17.9 mmol, 1.1 eq.), Na_2CO_3 (3.5 g, 32.6 mmol, 2 eq.) and $Pd(PPh_3)_4$ (0.94 g, 0.81 mmol, 0.05 eq.) in a mixture of toluene/EtOH/H_2O (6/1/1, 280 mL) was stirred at 110 °C for 16 h. The reaction mixture was cooled to 25 °C and extracted with AcOEt. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 10/1) affording **4** (5.08 g, 98%) as a yellow oil, solidifying over time into light yellow solid. m.p. 37 °C; NMR ^{1}H (400 MHz, $CDCl_3$): δH 5.66 (d, *J* = 10.9 Hz, 1H), 6.15 (d, *J* = 17.6 Hz, 1H), 6.78 (dd, *J* = 17.6 Hz, 10.9 Hz, 1H), 7.65 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.83 (s, 1H), 8.15 (d, *J* = 8.2 Hz, 2H) ppm; NMR ^{13}C (100 MHz, $CDCl_3$): δC 116.2 (q, *J* = 2.7 Hz), 120.3, 120.7, 121.3 (q, *J* = 272.2 Hz), 123.9 (q, *J* = 272.2 Hz), 125.7 (q, *J* = 3.4 Hz), 127.4, 131.5 (q, *J* = 32.5 Hz), 133.7, 141.0, 147.7, 148.9 (q, *J* = 34.5 Hz), 156.7 ppm; IR ν_{max}: 1321, 1108 cm^{-1}; HRMS calcd. for $C_{16}H_{10}F_6N$ $[M+H]^+$ 318.0717, found 318.0725.

*4.1.8. 2,6-Dibromopyridin-4-ol (**14**)*

An argon-purged mixture of 2,6-dibromopyridine **7** (2.0 g, 8.44 mmol, 1 eq.), pinacolborane (2.20 mL, 15.2 mmol, 1.8 eq.), $[Ir(cod)Cl]_2$ (56.7 mg, 0.08 mmol, 0.01 eq.) and 4,4′-di-tert-butyl-2,2′-dipyridyl (45.3 mg, 0.017 mmol, 0.02 eq.) in cyclohexane (15 mL) was stirred at 80 °C for 18 h. The reaction mixture was cooled back to 25 °C and concentrated under reduced pressure. The residue was dissolved in THF (20 mL) before adding dropwise a solution of oxone monopersulfate (2.9 g, 9.3 mmol, 1.1 eq.) in H_2O (30 mL). The resulting mixture was stirred at 25 °C for 30 min, quenched with 1 M $NaHCO_3$ aq. and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting solid was purified by flash chromatography on silica gel (cyclohexane/EtOAc 4/1) affording **14** (1.75 g, 82%) as a white solid. m.p. 207 °C; ^{1}H NMR (400 MHz, CD_3OD): δH 6.97 (s, 2H, H_3, H_5) ppm; ^{13}C NMR (100 MHz, CD_3OD): δC 116.0 (C_3, C_5), 141.8 (C_2, C_6), 168.6 (C_4) ppm; IR ν_{max} : 2838, 1540, 1147, 769 cm^{-1}; HRMS calcd. for $C_5H_4NO^{79}Br_2$ $[M+H]^+$ 251.8660, found 251.8663.

*4.1.9. 2,6-Dibromo-4-((4-methoxybenzyl)oxy) pyridine (**15**)*

To a solution of **14** (8.0 g, 31.6 mmol, 1 eq.) in DMF (100 mL) were added 4-methoxybenzyl chloride (4.3 mL, 31.6 mmol, 1 eq.) and K_2CO_3 (5.7 g, 41.1 mmol, 1.3 eq.). The suspension was stirred at 110 °C for 15 h, cooled back to 25 °C, filtered over a celite pad and the filtrate was concentrated under reduced pressure. The residue was placed in EtOAc and washed with 0.5 M NaOH. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 9/1) affording **15** (11.7 g, 99%) as a white solid. m.p. 69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δH 3.83 (s, 3H), 5.00 (s, 2H), 6.94 (d, ^3J = 8.7 Hz, 2H), 7.04 (s, 2H), 7.31 (d, ^3J = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δC 55.3, 70.8, 114.0, 114.2, 126.3, 129.5, 141.1, 160.0, 166.7 ppm; IR ν_{max} : 2925, 1572, 1514, 982, 826 cm^{-1}; HRMS calcd. for $C_{13}H_{11}{}^{79}Br_2NO_2Na$ $[M+Na]^+$ 395.9054, found 395.9065.

*4.1.10. 2-Bromo-6-iodo-4-((4-methoxybenzyl)oxy) pyridine (**16**)*

To a solution of **15** (4.97 g, 13.1 mmol, 1 eq.) in anhydrous THF (13 mL) were added *i*PrMgCl.LiCl (1.3 M in THF) (16.2 mL, 21.0 mmol, 1.6 eq.). The reaction mixture was stirred at 25 °C for 2 h and cooled to 0 °C before adding portionwise I_2 (5.33 g, 21.0 mmol, 1.6 eq.). The resulting mixture was stirred at 0 °C for 5 min, at 25 °C for 15 h and quenched with 0.5 M $Na_2S_2O_3$ aq. (3 x 40 mL). The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 10/1) affording **16** (4.68 g, 85%) as a white solid. m.p. 96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δH 3.83 (s, 3H), 4.99 (s, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 1.9 Hz, 1H), 7.26-7.34 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δC 55.3, 70.6, 114.3, 114.3, 115.5, 121.2, 126.4, 129.5, 141.0, 160.0, 165.6 ppm; IR ν_{max} : 2928, 1563, 1516, 1251, 983, 826 cm^{-1}; HRMS calcd. for $C_{13}H_{12}{}^{79}BrINO_2$ $[M+H]^+$ 419.9096, found 419.9097.

*4.1.11. 2-Bromo-4-((4-methoxybenzyl)oxy)-6-(4-(trifluoromethyl)phenyl)pyridine (**17**)*

An argon-purged mixture of **16** (2.74g, 6.52 mmol, 1 eq.), 4-(trifluoromethyl)phenylboronic acid (1.11g, 5.87 mmol, 0.9 eq.), Na_2CO_3 (1.38 g, 13.0 mmol, 2 eq.) and $Pd(PPh_3)_4$ (377 mg, 0.33 mmol, 0.05 eq.) in a mixture of toluene/EtOH/H_2O (6/1/1) (109 mL) was stirred at 110 °C for 15 h. The reaction mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was directly purified by flash chromatography on silica gel (cyclohexane/EtOAc 8/1) affording **17** (2.73 g, 95%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δH 3.83 (s, 3H), 5.08 (s, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 2.0 Hz, 1H), 7.27

(d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 8.04 (d, *J* = 8.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δC 55.3, 70.5, 108.1, 112.7, 114.3, 124.0 (q, *J* = 272.2 Hz), 125.6 (q, *J* = 3.8 Hz), 126.8, 127.2, 129.5, 131.3 (q, *J* = 32.6 Hz), 141.0, 143.1, 157.4, 160.0, 166.6 ppm; IR ν_{max}: 2935, 1580, 1321 cm^{-1}; MS (ESI$^+$) m/z: 439 $[M+H]^+$.

*4.1.12. 2-Iodo-4-((4-methoxybenzyl)oxy)-6-(4-(trifluoromethyl) phenyl)pyridine (**18**)*

To a solution of **17** (453 mg, 1.03 mmol, 1 eq.), CuI (10.0 mg, 0.05 mmol, 0.05 eq.) and NaI (309 mg, 2.06 mmol, 2 eq.) in anhydrous 1,4-dioxane (1.3 mL) were added *N*,*N*'-dimethylethylenediamine (11.0 µL, 0.10 mmol, 0.1 eq.). The solution was stirred at 110 °C for 28 h, cooled to 25 °C, treated with NH_4OH (28% in H_2O) (10 mL) and diluted with water. The mixture was extracted with DCM. The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 8/1) affording **18** (442 mg, 88%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δH 3.74 (s, 3H), 4.96 (s, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.93 (d, *J* = 8.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δC 55.3, 70.3, 108.4, 114.2, 118.8, 119.7, 124.0 (q, *J* = 272.3 Hz), 125.6 (q, *J* = 3.7 Hz), 126.9, 127.2, 129.5, 131.2 (q, *J* = 32.5 Hz), 141.0, 157.9, 160.0, 165.5 ppm; IR ν_{max} : 2935, 1575, 1319, 1110, 993, 827 cm^{-1}; HRMS calcd. for $C_{20}H_{16}F_3BrINO_2$ $[M+H]^+$ 486.0178, found 486.0190.

*4.1.13. 4-((4-Methoxybenzyl)oxy)-2-(trifluoro methyl)-6-(4-(trifluoromethyl)phenyl)pyridine (**19**)*

To a solution, under argon, of **18** (2.28 g, 4.70 mmol, 1 eq.), KF (1.64 g, 28.2 mmol, 6 eq.), CuI (0.36 g, 1.88 mmol, 0.4 eq.) and 1,10-phenantroline (0.34 g, 1.88 mmol, 0.4 eq.) in anhydrous DMSO (68 mL) were added $B(OMe)_3$ (3.14 mL, 28.2 mmol, 6 eq.) and $TMSCF_3$ (2 M in THF) (14.1 mL, 28.2 mmol, 6 eq.). The solution was stirred at 60 °C for 24 h. The reaction mixture was treated with NH_4OH (28% in H_2O) (20 mL) and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 4/1) affording **19** (1.78 g, 89%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δH 3.75 (s, 3H), 5.07 (s, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δC 55.3, 70.5, 106.6 (q, *J* = 2.8 Hz), 109.7, 114.3, 121.4 (q, *J* = 274.6 Hz), 124.0 (q, *J* = 272.2 Hz), 125.7 (q, *J* = 3.8 Hz), 126.7, 127.4, 129.5, 131.5 (q, *J* = 32.6 Hz), 141.2, 150.0 (q, *J* = 34.5 Hz), 157.9, 160.0, 166.7 ppm; IR ν_{max}: 2935, 1604, 1324, 1126 cm^{-1}; MS (ESI$^+$) m/z: 428 $[M+H]^+$.

*4.1.14. 2-(Trifluoromethyl)-6-(4-trifluoromethyl) phenyl)pyridin-4-ol (**20**)*

To a solution of **19** (1.78 g, 4.17 mmol, 1 eq.) in DCM (42 mL) were added TFA (1 mL). The reaction mixture was stirred at 25 °C for 7 h and treated with 1 M NaOH aq. (3 x 20 mL). The aqueous layers were acidified with 1 M HCl until pH~6 and concentrated under reduced pressure. The residue was washed with MeOH and the solid filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 1/1) affording **20** (1.03 g, 80%) as a white solid. m.p.: 170 °C; ^{1}H NMR (400 MHz, CD_3OD): δH 7.14 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 8.20 (d, *J* = 8.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δC 108.8 (q, *J* = 2.8 Hz), 111.7, 123.0 (q, *J* = 273.5 Hz), 125.7 (q, *J* = 271.3 Hz), 126.7 (q, *J* = 3.8 Hz), 128.7, 132.4 (q, *J* = 32.2 Hz), 143.0, 150.8 (q, *J* = 34.2 Hz), 159.2, 168.1 ppm; IR ν_{max}: 3097, 1611, 1582, 1323, 1108, 1061, 849 cm^{-1}; HRMS calcd. for $C_{13}H_8F_6NO$ $[M+H]^+$ 308.0510, found 308.0523.

*4.1.15. 4-Bromo-2-(trifluoromethyl)-6-(4-(trifluoro methyl)phenyl)pyridine (**21**)*

To a solution, under argon, of **20** (6.5 g, 21.2 mmol, 1 eq.) in DMF (130 mL) were added $POBr_3$ (24.3 g, 84.6 mmol, 4 eq.). The suspension was stirred at 110 °C for 16 h and quenched with H_2O. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 9/1) affording **21** (6.02 g, 93%) as a white solid. m.p.: 59 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δH 7.76 (d, ^3J = 8.2 Hz, 2H), 7.83 (s, 1H), 8.12 (s, 1H), 8.16 (d, ^3J = 8.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δC 120.7 (q, ^1J = 275.1 Hz), 122.9 (q, ^3J = 2.8 Hz), 123.9 (q, ^1J = 272.4 Hz), 126.0 (q, ^3J = 3.8 Hz), 126.4, 127.6, 132.2 (q, ^2J = 32.7 Hz), 134.9, 139.7, 149.3 (q, ^2J = 35.4 Hz), 157.5 ppm; IR ν_{max} : 1573, 1320, 1119, 1057, 843 cm^{-1}..

*4.1.16. (S)-1-(2-(Trifluoromethyl)-6-(4-(trifluoro methyl)phenyl)pyridin-4-yl)ethane-1,2-diol (**(S)-22**)*

To a suspension of AD-mix α (1.26 g) in a *t*BuOH/H_2O mixture (1/1) (22 mL) was added potassium osmate (3.00 mg, 0.09 mmol, 0.01 eq.). The mixture was cooled to 0 °C and **4** (285.0 mg, 0.90 mmol, 1 eq.) was added. The reaction mixture was stirred at 0 °C for 5 min and at 25 °C for 15 h. The reaction was cooled to 0 °C and quenched with Na_2SO_3 (980 mg). The suspension was stirred for 10 min at 0 °C, 10 min at 25 °C and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was precipitated with cyclohexane. The resulting solid was filtered affording **(*S*)-22** (316 mg, 99%) as a white solid. m.p. 101 °C; ^{1}H NMR (400 MHz, CD_3OD): δH 3.77 (m, 2H), 4.89 (m, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.84 (s, 1H), 8.20 (s, 1H), 8.29 (d, *J* = 8.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD) : δC 67.8, 74.2, 118.7 (q, *J* = 2.8 Hz), 122.5, 123.2 (q, *J* = 273.6 Hz), 125.6 (q, *J* = 271.3 Hz), 126.8 (q, *J* = 3.8 Hz), 128.7, 132.5 (q, *J* = 32.3 Hz), 142.7, 149.2 (q, *J* = 34.3 Hz), 157.0, 157.2 ppm; IR ν_{max} : 3293, 1323, 1097 cm^{-1}; HRMS calcd. for $C_{15}H_{11}F_6NO_2Na$ $[M+Na]^+$ 374.0578, found 374.0583; $[\alpha]_D^{20}$: +29.1° (c 0.1 ; MeOH); Chiral HPLC 99% *ee*, Chiralpak IB column, heptane/*i*-PrOH, 90/10, flow 1 mL/min, *tr*(*R*) = 10.6 min, *tr*(*S*) = 11.6 min.

*4.1.17. (R)-1-(2-(Trifluoromethyl)-6-(4-(trifluoro methyl)phenyl)pyridin-4-yl)ethane-1,2-diol (**(R)-22**)*

To a suspension of AD-mix β (8.85 g) in a *t*BuOH/H_2O mixture (1/1) (160 mL) was added potassium osmate (23.2 mg, 0.06 mmol, 0.01 eq.). The mixture was cooled to 0 °C and **4** (2.00 g, 6.30 mmol, 1 eq.) was added. The reaction mixture was stirred at 0 °C for 5 min and at 25 °C for 15 h. The reaction was cooled to 0 °C and quenched with Na_2SO_3 (7 g). The suspension was stirred for 10 min at 0 °C, 10 min at 25 °C and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was precipitated with cyclohexane. The resulting solid was filtered affording **(*R*)-22** (2.21 g, 99%) as a white solid. m.p., ^{1}H NMR, ^{13}C NMR and IR spectra are the same that those of **(*S*)-22**. HRMS calcd. for $C_{15}H_{11}F_6NO_2Na$ $[M+Na]^+$ 374.0578, found 374.0583; $[\alpha]_D^{20}$: -29.3° (c 0.1 ; MeOH); Chiral HPLC >98,5% *ee*

(incomplete separation), Chiralpak IB column, heptane/*i*-PrOH, 90/10, flow 1 mL/min, *tr*(*R*) = 11.0 min, *tr*(*S*) = 12.7 min.

4.1.18. (S)-4-(Oxiran-2-yl)-2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridine ***(S)-3***

To a solution, under argon, of **(*S*)-22** (1.20 g, 3.42 mmol, 1 eq.) in anhydrous DCM (35 mL) were added trimethylorthoacetate (1.3 mL, 10.25 mmol, 3 eq.) and *p*TsOH (32.5 mg, 0.17 mmol, 0.05 eq.). The reaction mixture was stirred at 25 °C for 30 min and then concentrated under reduced pressure. The residue was placed under argon, dissolved in anhydrous DCM (35 mL) and cooled to 0 °C. TMSBr (1.35 mL, 10.25 mmol, 3 eq.) was then added dropwise. The solution was stirred at 0 °C for 5 min, at 25 °C for 30 min and concentrated under reduced pressure. The residue was placed under argon and dissolved in anhydrous MeOH (35 mL). K_2CO_3 (2.36 g, 17.08 mmol, 5 eq.) was then added. The suspension was stirred at 25 °C for 1 h, quenched with sat. aq. NH_4Cl and extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 6/1) affording **(*S*)-3** (1.08 g, 95%) as a white solid. m.p. 81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δH 2.84 (dd, *J* = 5.6, 2.5, 1H), 3.29 (dd, *J* = 5.6, 4.3, 1H), 4.02 (dd, *J* = 4.3, 2.5 Hz, 1H), 7.59 (m, 1H), 7.75 d, *J* = 8.3 Hz, 2H), 7.86 (m, 1H), 8.18 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δC 48.1 (q, *J* = 4.1 Hz), 50.9, 121.9 (q, *J* = 275.6 Hz), 123.1, 124.0 (q, *J* = 272.2 Hz), 125.9 (q, *J* = 3.7 Hz), 127.3, 131.6 (q, *J* = 32.5 Hz), 132.1, 135.5, 140.6, 145.6 (q, *J* = 34.6 Hz), 154.3 ppm; IR ν_{max}: 2928, 1319, 1105, 1068 cm^{-1}; HRMS calcd. for $C_{15}H_{11}F_6NO_2Na$ $[M+H]^+$ 334.0667, found 334.0679.; $[\alpha]_D^{20}$: +23.5° (c 0,1 ; MeOH).

4.1.19. (R)-4-(Oxiran-2-yl)-2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridine ***((R)-3)***

To a solution, under argon, of **(*R*)-22** (1.00 g, 2.85 mmol, 1 eq.) in anhydrous DCM (30 mL) were added trimethylorthoacetate (1.10 mL, 8.50 mmol, 3 eq.) and *p*TsOH (27.0 mg, 0.14 mmol, 0.05 eq.). The reaction mixture was stirred at 25 °C for 30 min and then concentrated under reduced pressure. The residue was placed under argon, dissolved in anhydrous DCM (30 mL) and cooled to 0 °C. TMSBr (1.13 mL, 8.54 mmol, 3 eq.) was then added. The solution was stirred at 0 °C for 5 min, at 25 °C for 30 min and concentrated under reduced pressure. The residue was placed under argon and dissolved in anhydrous MeOH (30 mL). K_2CO_3 (1.97 g, 14.25 mmol, 5 eq.) was then added. The suspension was stirred at 25 °C for 2 h, quenched with sat. aq. NH_4Cl and extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 6/1) affording **(*R*)-22** (804 mg, 85%) as a white solid. m.p. 81 °C; NMR and HRMS data in accordance with **(*S*)-22**; IR ν_{max} : 2928, 1319, 1105, 1068 cm^{-1}; HRMS calcd. for $C_{15}H_{11}F_6NO_2Na$ $[M+H]^+$ 334.0667, found 334.0679. $[\alpha]_D^{20}$: -20.8° (c 0,1 ; MeOH).

4.1.20. General Procedure for the ring-opening reactions: Preparation of 4-AHPs (2)

To a solution of the epoxide **3** in ethanol (0.05 M) was added the desired amine. The reaction mixture was stirred at 130°C using microwaves for 30 min and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel affording the corresponding 4-AHP.

4.1.21. (S)-2-(Butylamino)-1-(2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridin-4-yl)ethanol ***((S)-2a)***

Following the general method for the preparation of 4-AHPs and starting from **(*S*)-3** (200.0 mg, 0.60 mmol, 1 eq.) and *n*-butylamine (0.30 mL, 3.00 mmol, 5.0 eq.), the residue was purified by flash chromatography on silica gel (DCM/MeOH 9/1) affording **(*S*)-2a** (191.4 mg, 78%) as a white solid. m.p. 129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δH 0.93 (t, *J* = 7.3 Hz, 3H), 1.31-1.44 (m, 2H), 1.45-1.56 (m, 2H), 2.61-2.79 (m, 3H), 3.06 (dd, *J* = 12.3, 3.7 Hz, 1H), 3.07 (s_{br}, 2H), 4.84 (dd, *J* = 9.2, 3.6 Hz, 1H), 7.67 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.99 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) : δC 13.9, 20.2, 32.0, 49.0, 56.2, 69.7, 116.6 (q, *J* = 2.6 Hz), 120.0, 124.0 (q, *J* = 272.3 Hz), 124.2 (q, *J* = 274.8 Hz), 125.6 (q, *J* = 3.8 Hz), 127.5, 131.5 (q, *J* = 32.6 Hz), 141.1, 148.5 (q, *J* = 34.6 Hz), 155.0, 156.4 ppm; IR ν_{max} : 2921, 1328, 1109 cm^{-1}; HRMS calcd. for $C_{19}H_{21}F_6N_2O$ $[M+H]^+$ 407.1558, found 407.1551; $[\alpha]_D^{20}$: +31.1° (c 0.1 ; MeOH); Chiral HPLC 99% *ee*, Chiralpak IB column, heptane/*i*-PrOH/EDA, 99/1/0.1, flow 1 mL/min, *tr*(*R*) = 17.8 min, *tr*(*S*) = 20.8 min.

4.1.22. (R)-2-(Butylamino)-1-(2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridin-4-yl)ethanol ***((R)-2a)***

Following the general method for the preparation of 4-AHPs and starting from **(*R*)-3** (40.0 mg, 0.12 mmol, 1 eq.) and *n*-butylamine (0.071 mL, 0.72 mmol, 6 eq.), the residue was purified by flash chromatography on silica gel (DCM/MeOH 9/1) affording **(*R*)-2a** (47 mg, 96%) as a white solid. m.p., ^{1}H NMR, ^{13}C NMR and IR spectra are the same that those of **(*S*)-2a**. HRMS calcd. for $C_{19}H_{21}F_6N_2O$ $[M+H]^+$ 407.1558 , found 407.1551; $[\alpha]_D^{20}$: -31.0° (c 0.1 ; MeOH); Chiral HPLC 99% *ee*, Chiralpak IB column, heptane/*i*-PrOH/EDA, 99/1/0.1, flow 1 mL/min, *tr*(*R*) = 17.7 min, *tr*(*S*) = 21.2 min.

4.1.23. (S)-2-(Pentylamino)-1-(2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridin-4-yl)ethanol ***((S)-2b)***

Following the general method for the preparation of 4-AHPs and starting from **(*S*)-3** (200.0 mg, 0.60 mmol, 1 eq.) and *n*-pentylamine (0.36 mL, 3.10 mmol, 5.15 eq.), the residue was purified by flash chromatography on silica gel (DCM/MeOH 9/1) affording **(*S*)-2b** (236.6 mg, 94%) as a white solid. m.p. 112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δH 0.89 (t, *J* = 7.0 Hz, 3H), 1.20-1.42 (m, 4H), 1.52-1.62 (m, 2H), 2.60-2.81 (m, 3H), 3.09 (dd, *J* = 12.2, 3.1 Hz, 1H), 3.87 (s_{br}, 2H), 4.94 (dd, *J* = 9.2, 3.2 Hz, 1H), 7.68 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 8.00 (s, 1H), 8.18 (d, *J* = 8.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δC 13.9, 22.5, 29.3, 29.6, 49.3, 56.2, 69.7, 116.6 (q, *J* = 2.5 Hz), 120.0, 124.0 (q, *J* = 272.2 Hz), 124.2 (q, *J* = 274.5 Hz), 125.7 (q, *J* = 3.7 Hz), 127.5, 131.5 (q, *J* = 32.5 Hz), 141.1, 148.5 (q, *J* = 34.6 Hz), 155.0, 156.4 ppm; IR ν_{max}: 2930, 1327, 1126 cm^{-1}; HRMS calcd. for $C_{20}H_{22}F_6N_2O$ $[M+H]^+$ 421.1715, found 421.1720; $[\alpha]_D^{20}$: +23.7° (c 0.1 ; MeOH); Chiral HPLC 99% *ee*, Chiralpak IB column, heptane/*i*-PrOH/EDA, 99/1/0.1, flow 1 mL/min, *tr*(*R*) = 12.4 min, *tr*(*S*) = 14.3 min.

4.1.24. (R)-2-(Pentylamino)-1-(2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridin-4-yl)ethanol ***((R)-2b)***

Following the general method for the preparation of 4-AHPs and starting from **(*R*)-3** (200.0 mg, 0.60 mmol, 1 eq.) and *n*-pentylamine (0.36 mL, 3.10 mmol, 5.15 eq.), the residue was purified by flash chromatography on silica gel (DCM/MeOH 9/1) affording **(*R*)-2b** (214.0 mg, 85%) as a white solid. m.p., ^{1}H NMR, ^{13}C NMR and IR spectra are the same that those of **(*S*)-**

2b. HRMS calcd. for $C_{20}H_{22}F_6N_2O$ $[M+H]^+$ 421.1715, found 421.1720; $[\alpha]_D^{20}$: -27.9° (c 0.1 ; MeOH); Chiral HPLC 99% *ee*, Chiralpak IB column, heptane/*i*-PrOH/EDA, 99/1/0.1, flow 1 mL/min, *tr*(*R*) = 11.9 min, *tr*(*S*) = 14.0 min.

4.1.25. (S)-2-(Hexylamino)-1-(2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridin-4-yl)ethanol ((S)-2c)

Following the general method for the preparation of 4-AHPs and starting from **(*S*)-3** (40.0 mg, 0.12 mmol, 1 eq.) and *n*-hexylamine (0.05 mL, 0.36 mmol, 3 eq.), the residue was purified by flash chromatography on silica gel (DCM/MeOH 9/1) affording **(*S*)-2c** (35 mg, 67%) as a white solid. m.p. 84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δH 0.86 (t, *J* = 6.6 Hz, 3H), 1.21-1.37 (m, 6H), 1.53-1.61 (m, 2H), 2.63-2.82 (m, 3H), 3.11 (dd, *J* = 12.2, 3.4 Hz, 1H), 4.76 (s_{br}, 2H), 5.00 (dd, *J* = 9.4, 3.0 Hz, 1H), 7.67 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.99 (s, 1H), 8.16 (d, *J* = 8.1 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δC 13.9, 22.5, 26.7, 29.4, 31.6, 49.3, 56.0, 69.5, 116.5 (q, *J* = 2.6 Hz,), 120.0, 124.0 (q, *J* = 272.2 Hz), 124.2 (q, *J* = 274.6 Hz), 125.7 (q, *J* = 3.8 Hz), 127.5, 131.6 (q, *J* = 32.6 Hz), 141.0, 148.5 (q, *J* = 34.6 Hz), 154.7, 156.4 ppm; IR ν_{max}: 2925, 1325, 1112 cm^{-1}; HRMS calcd. for $C_{21}H_{25}F_6N_2O$ $[M+H]^+$ 435.1871, found 435.1857; $[\alpha]_D^{20}$: +30.8° (c 0.1 ; MeOH); Chiral HPLC 99% *ee*, Chiralpak IB column, heptane/*i*-PrOH/EDA, 99/1/0.1, flow 1 mL/min, *tr*(*R*) = 9.7 min, *tr*(*S*) = 10.8 min.

4.1.26. (R)-2-(Hexylamino)-1-(2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridin-4-yl)ethanol ((R)-2c)

Following the general method for the preparation of 4-AHPs and starting from **(*R*)-3** (50.0 mg, 0.15 mmol, 1 eq.) and *n*-hexylamine (0.06 mL, 0.45 mmol, 3 eq.), the residue was purified by flash chromatography on silica gel (DCM/MeOH 9/1) affording **(*R*)-2c** (42 mg, 65%) as a white solid. m.p., ^{1}H NMR, ^{13}C NMR and IR spectra are the same that those of **(*S*)-2c**. HRMS calcd. for $C_{21}H_{25}F_6N_2O$ $[M+H]^+$ 435.1871, found 435.1857; $[\alpha]_D^{20}$: -28.6° (c 0.1 ; MeOH); Chiral HPLC 98% *ee*, Chiralpak IB column, heptane/*i*-PrOH/EDA, 99/1/0.1, flow 1 mL/min, *tr*(*R*) = 9.6 min, *tr*(*S*) = 10.7 min.

4.1.27. (S)-2-(Heptylamino)-1-(2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridin-4-yl)ethanol ((S)-2d)

Following the general method for the preparation of 4-AHPs and starting from **(*S*)-3** (50.0 mg, 0.15 mmol, 1 eq.) and *n*-heptylamine (0.13 mL, 0.90 mmol, 6 eq.), the residue was purified by flash chromatography on silica gel (DCM/MeOH 9/1) affording **(*S*)-2d** (40 mg, 60%) as a white solid. m.p. 76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δH 0.78-0.97 (m, 3H), 1.06-1.43 (m, 8H), 1.45-1.66 (m, 2H), 2.62-2.70 (m, 2H), 2.89 [AB(ABX), *J* = 12.2, 8.6, 2.7 Hz, 2H], 3.25-3.80 (s_{br}, 2H), 4.86 [X(ABX), *J* = 8.6, 2.7 Hz, 1H], 7.67 (s, 1H), 7.74 (d, *J* = 7.8 Hz, 2H), 8.00 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δC 14.0, 22.6, 27.1, 29.1, 29.8, 31.7, 49.3, 56.1, 69.6, 116.6 (q, *J* = 2.6 Hz), 120.0, 124.0 (q, *J* = 272.2 Hz), 124.2 (q, *J* = 274.6 Hz), 125.8 (q, *J* = 3.8 Hz), 127.5, 131.2 (q, *J* = 32.6 Hz), 141.1, 148.5 (q, *J* = 34.7 Hz), 154.9, 156.4 ppm; IR ν_{max} : 2928, 1324, 1114 cm^{-1}; HRMS calcd. for $C_{22}H_{27}F_6N_2O$ $[M+H]^+$ 449.2028, found 449.2040; $[\alpha]_D^{20}$: + 24.9° (c 0.1 ; MeOH); Chiral HPLC 99% *ee*, Chiralpak IB column, heptane/*i*-PrOH/EDA, 99/1/0.1, flow 1 mL/min, *tr*(*R*) = 11.7 min, *tr*(*S*) = 13.5 min.

4.1.28. (R)-2-(Heptylamino)-1-(2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridin-4-yl)ethanol ((R)-2d)

Following the general method for the preparation of 4-AHPs and starting from **(*R*)-3** (31.0 mg, 0.09 mmol, 1 eq.) and *n*-heptylamine (0.08 mL, 0.54 mmol, 6 eq.), the residue was purified by flash chromatography on silica gel (DCM/MeOH 9/1) affording **(*R*)-2d** (34 mg, 85%) as a white solid. m.p., ^{1}H NMR, ^{13}C NMR and IR spectra are the same that those of **(*S*)-2d**. HRMS calcd. for $C_{22}H_{27}F_6N_2O$ $[M+H]^+$ 449.2028, found 449.2040; $[\alpha]_D^{20}$: -27.4° (c 0.1 ; MeOH); Chiral HPLC 99% *ee*, Chiralpak IB column, heptane/*i*-PrOH/EDA, 99/1/0.1, flow 1 mL/min, *tr*(*R*) = 11.6 min, *tr*(*S*) = 13.5 min.

4.2. Biological assay

The *in vitro* antiplasmodial activities were first tested over concentrations ranging from 39 nM to 40 µM and then, if the 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 and displays a decreased susceptibility to mefloquine, while the latter is susceptible to mefloquine and 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.[33] 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.[33,35] 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.[36]

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Acknowledgments

This project was financed in part from DGA (Direction Générale de l'Armement, Ministère de la Défense, France), ANR Astrid (project ANR-12-STR-003), région Picardie and the SATT Nord. G. B. was the recipient of a grant from Région Picardie. The authors thank Philippe Grellier (Muséum National d'Histoire Naturelle) who graciously provided *P. falciparum* strains. We thank Sophie Da Nascimento for mass spectra recording.

Supplementary Material

The supplementary material contains general procedure information, NMR spectra, HPLC analysis about the principal compounds and the X-ray analysis of (S)-**3** and **5**.

Graphical Abstract

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Enantiopure substituted pyridines as promising antimalarial drug candidates

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