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PAPER

Synthesis and antiplasmodial activity of streptocyanine/peroxide and streptocyanine/4-aminoquinoline hybrid dyes†

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Two series of streptocyanine dyes incorporating cyclic peroxide or 4-aminoquinoline moieties are prepared and X-ray diffraction structures for three compounds are determined. All hybrid dyes show good antiplasmodial activity (0.06 to 0.66 μM) and are not or are slightly cytotoxic, except **10a**.

Introduction

Malaria is one of the most serious infectious diseases in tropical and subtropical regions. Every year, 300 million people are afflicted leading to 880 000 deaths, especially among young children.[1] An urgent need exists to develop new classes of antimalarial drugs that operate, or not, by novel mechanisms of action because malaria parasites develop resistance to clinically used chemotherapeutic agents and prophylactic drugs such as chloroquine, mefloquine or sulfadoxine–pyrimethamine, and recently to artemisinin.[2] Nowadays, drug combinations are recommended to avoid the emergence of resistant parasite strains. But the two independent drugs may present different pharmacokinetics profiles which hamper the full benefit of the drug combinations. A recent rational approach involves "covalent bitherapy". This new strategy is based on using hybrid molecules with a dual mode of action. The two active entities are covalently linked. These drugs allow bypassing the development of resistance, enhancing patient compliance and reducing drug–drug interactions.[3]

We previously described the synthesis of streptocyanine dyes as a potential new class of antimalarial drugs.[4] SAR studies have shown the influence of the polymethine chain length (5C-, 7C- or 9C-) and also the great importance of the structural modifications at the nitrogen end groups (Fig. 1). The most active compounds displayed sub-micromolar *in vitro* activities against *P. falciparum* and the best selectivity was obtained for 5C-streptocyanines with morpholino end groups.

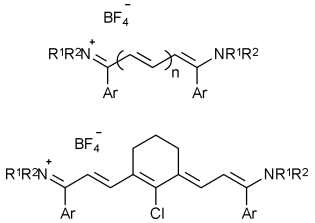

Fig. 1 5C- ($n = 1$),[5] 7C- ($n = 2$)[6] and 9C-[7] chain streptocyanine dyes.

Here we report our results on the synthesis and *in vitro* antiplasmodial activities of two series of new hybrid molecules. Firstly, a cyclic peroxide moiety and secondly, a 4-aminoquinoline moiety, were chosen to be tagged on the streptocyanines with the aim to induce a synergic effect and/or to create molecules with a dual mode of action. We are also interested in antiplasmodial agents acting in a similar way to artemisinin and we focused on the syntheses of modified bicyclic peroxide G-factors (G1, G2, G3). These natural bicyclic peroxides are easily extracted from the leaves of *Eucalyptus grandis*[8] (Fig. 2). We have previously reported the crucial role of the peroxyketal function for this activity.[9] But the most significant differences were those observed between the natural product G3 (IC_{50} 30 μM) and the methyl ether analogue G3Me (IC_{50} 0.28 μM). The latter compound was found to be one hundred times more active than G3, indicating the crucial role of the ether function compared to the hydroxyl one. Some of the previously synthesised α-spiro derivatives present moderate

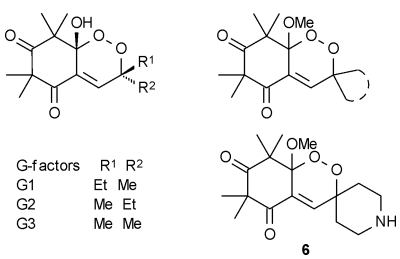

Fig. 2 Natural G-factors and α-spirobicyclic peroxide analogues of G3-factor.

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to good antiplasmodial activities.[10] We decided to synthesise the α-spiropiperidine analogue allowing the tag of the streptocyanine and obtaining only one compound, avoiding the presence of two diastereoisomers.

The 4-aminoquinoline moiety[11] was introduced to the streptocyanine dyes *via* cyclic or acyclic linkers (Fig. 3).

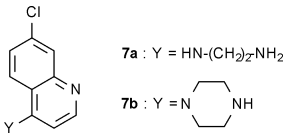


Fig. 3 4-Amino-7-chloroquinolines **7a** and **7b**.[11]

Results and discussion

Synthesis

Because streptocyanine dyes are synthesised by reacting various nitrogen nucleophiles with hemicarboxonium or carboxonium salts,[5] the functionalization of peroxide and 4-aminoquinoline moieties by a reactive primary or secondary amino group has been necessary (Scheme 1 and Fig. 3, respectively).

The functionalized cyclic peroxide **6** (peroxo) is obtained by the following procedure (Scheme 1). 1-BOC-4-hydroxymethylpiperidine is first oxidized to aldehyde **1** in quantitative yield. Then, modified Knoevenagel reaction between syncarpic acid and the iminium obtained from aldehyde **1** and piperidine leads to Mannich base **2**, which after acidic treatment and elimination of piperidine, furnishes the enone precursor **3** in equilibrium with the dienol form in dichloromethane solution. The solution is kept under air, and after twelve days at room temperature ^{1}H NMR analysis indicates that auto-oxidation is complete. Bicyclic peroxide **4** is obtained in 68% yield after purification by silica gel column chromatography. The peroxide is then methylated on the peroxyhemiketal position, using butyllithium solution then methyl triflate at low temperature. Methylated bicyclic peroxide **5** is obtained in 65% yield after purification by silica gel column chromatography. Then BOC is cleaved using trifluoroacetic acid at room temperature furnishing peroxide **6** in 92% yield, which is used in the next coupling without further purification.

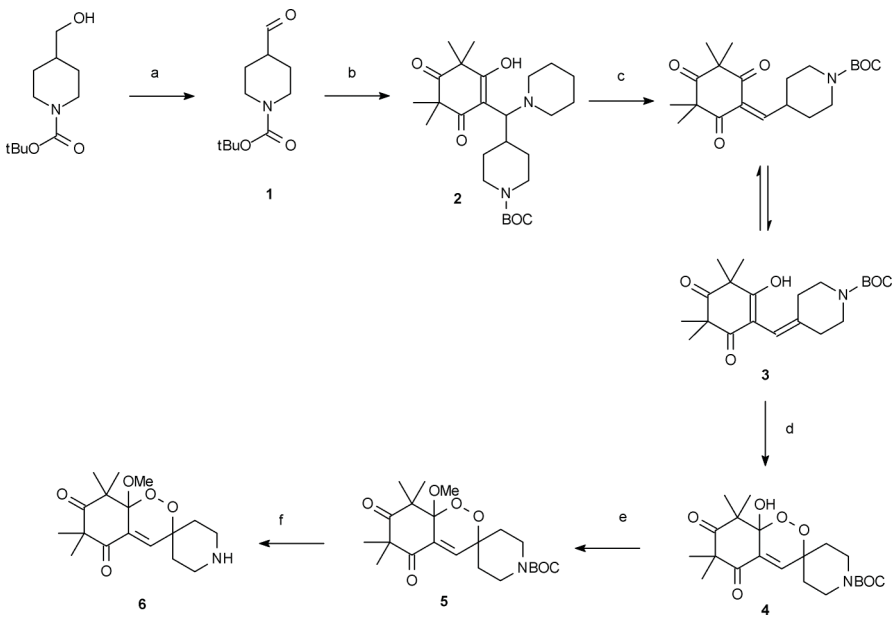
The synthesis of functionalized 4-aminoquinoline **7a, b** (Fig. 3) was achieved by the nucleophilic substitution of the 4-Cl atom of 4,7-dichloroquinoline with ethylenediamine or piperazine according to Chauhan's procedures.[11]

Hybrid peroxo-streptocyanine dyes **10a, b**, **11b** and **12b** were synthesised by the synthetic procedures as shown in Scheme 2. Unsymmetrical compounds **10a, b** and **11b** were obtained in respective yields of 22, 28 and 48% *via* a hemicarboxonium salt which is isolated (**13a**) or not (**9b**). The symmetrical hybrid peroxo-streptocyanine dye **12b** was obtained by reacting peroxide **6** with carboxonium salt **8b** in 14% yield. To obtain the compounds **10a** and **12b**, Hünig's base activation of **6** was necessary to achieve the substitution of the second ethoxy group.

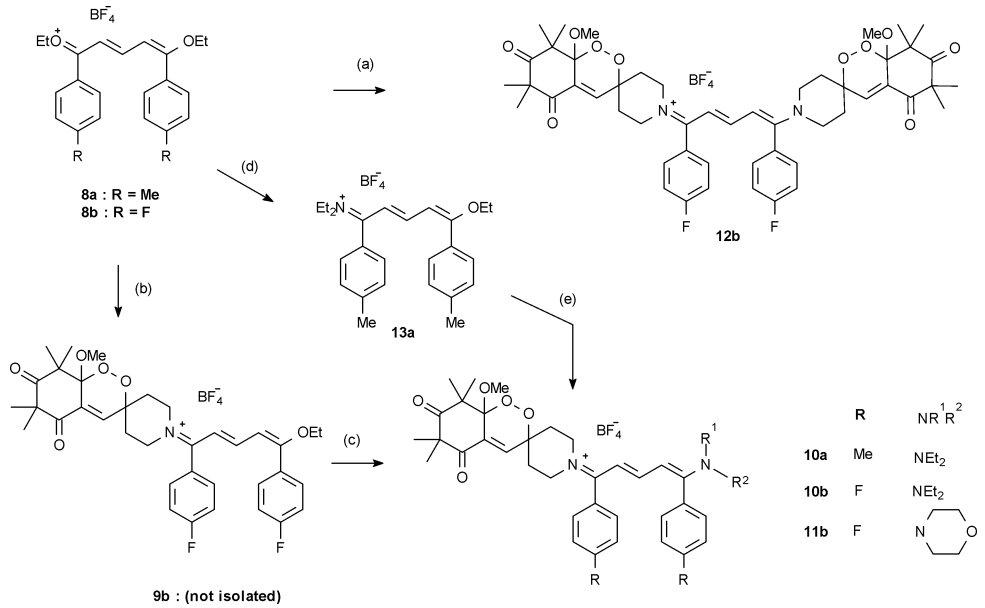
Nucleophilic substitution of the ethoxy group of hemicarboxonium salts **13b** and **14b** with **7a** (quino) or **7b** (pipequino) gives unsymmetrical hybrid 4-aminoquinoline–streptocyanine dyes **15b, 16b** and **18b, 19b** in 26, 59, 30 and 50% yield, respectively (Scheme 3).

To introduce two 4-aminoquinoline groups, the reaction was carried out from the carboxonium salt **8b** and the symmetrical hybrid 4-aminoquinoline–streptocyanine dyes **17b** and **20b** were obtained in 30 and 70% yield respectively, depending on the acyclic or cyclic linker used (Scheme 4).

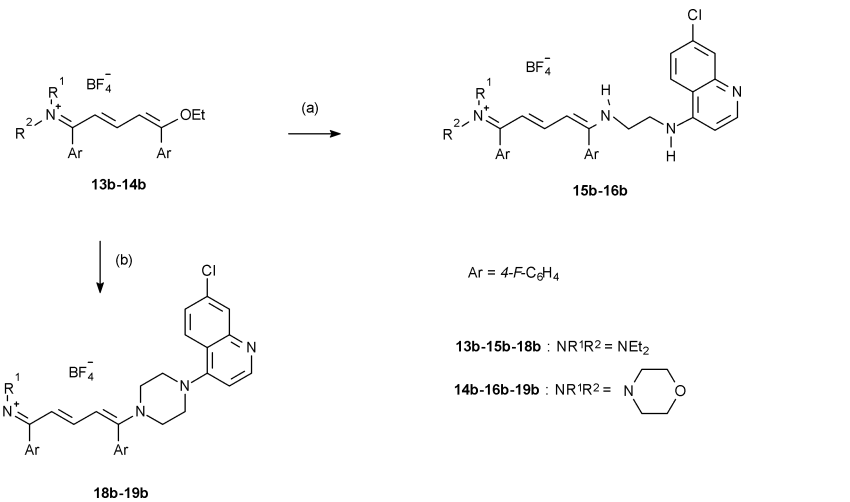
As was previously observed for streptocyanine dyes,[6,7,12] X-ray diffraction structures of **17b** (Fig. 4), **18b** (Fig. 5) and **19b** (Fig. 6) reveal "all *trans*" 5C carbon chains, with angles of about 120°. The polymethine chains are almost planar and the aryl groups are roughly perpendicular to the chains, except for **17b**. The C–C and C–N bond lengths of the conjugated system have intermediate



Scheme 1 Synthesis of peroxo compound **6**. *Reagents and conditions*: (a) SO_3–Py, Et_3N, DMSO; (b) syncarpic acid, piperidine; (c) NH_4Cl, HCl; (d) O_2; (e) BuLi, TfOMe; (f) TFA, CH_2Cl_2.



Scheme 2 Synthesis of hybrid peroxo-streptocyanine dyes **10a**, **10b–12b**. **8a**, **8b** and **13a** were synthesised following previously described procedures.[5] *Reagents and conditions*: argon, RT (a) CH_3CN, iPr_2NEt 2 eq., **6** 2 eq., 10 d, (b) CH_3CN, **6** 1 eq., 24 h; (c) Et_2NH or morpholine 1 eq., 24 h; (d) CH_3CN, Et_2NH 1 eq., 15 min; (e) DMF, iPr_2NEt 1 eq., **6** 1 eq., 30 d.



Scheme 3 Synthesis of unsymmetrical hybrid 4-aminoquinoline–streptocyanine dyes **15b**, **16b**, **18b** and **19b**. *Reagents and conditions*: RT (a) CH_3CN/DMF, **7a** 1 eq., 24 h; (b) CH_3CN, **7b** 1 eq., 24 h.

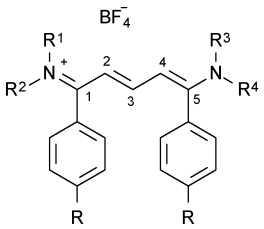
values between those of single and double bonds, expressing the delocalisation of the positive charge of the 5C carbon chain.

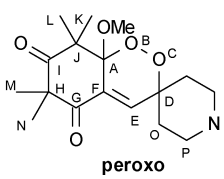
Biological activity

All the biological results are summarized in Tables 1 and 2. The antimalarial activity of the hybrid streptocyanines was evaluated *in vitro* against *P. falciparum* on a chloroquine-sensitive (Nigerian) strain[13] and on chloroquine resistant strains (FcB1-Colombia and FcM29),[14] according to the procedures described by Desjardins and co-workers.[15] The antiplasmodial specificity of the drugs was evaluated by comparing antiplasmodial activities toward the mammalian MCF7 and Vero cell lines *versus* parasite (IC_{50} cells)/(IC_{50} *P. falciparum*). Two cell lines were used, the human breast cancer cell line MCF7 and a normal cell line of simian origin (Vero cells), as described.[16] These two cell lines were chosen for *in vitro* culture ease and because one is a transformed cancerous cell line (McF7) while the other (Vero) is not of cancerous origin, this allowed comparisons of the two origins in the selectivity index. A resistance index was also calculated as the ratio $IC_{50\ Fcb1}/IC_{50\ Nigerian}$ or $IC_{50\ FcM29}/IC_{50\ Nigerian}$. This ratio is 4.4 for chloroquine with the FcB1 strain (K76T mutation at the PfCRT locus) and 8.7 for the FcM29 strain (K76T mutation at the PfCRT locus, resistance-associated mutations on the Pf-MDR gene) which has IC_{50} constantly higher than FcB1.[17]

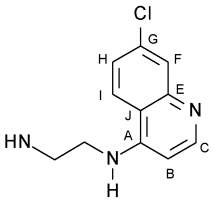
All hybrid molecules exhibit good *in vitro* antiplasmodial activities (0.06 to 0.66 μM) similar to those of regular streptocyanines. Moreover, they are not toxic or are slightly cytotoxic, except **10a**. Hemicarboxonium salts **13b** and **14a** are neither active nor toxic. They are characterised by a less conjugated polymethine chain

Table 1 *In vitro* activity of the synthesised compounds against chloroquine-sensitive (Nigerian) and chloroquine-resistant (FcB1, FcM29) strains of *Plasmodium falciparum*

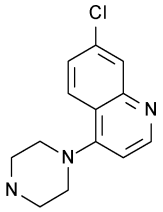




peroxo



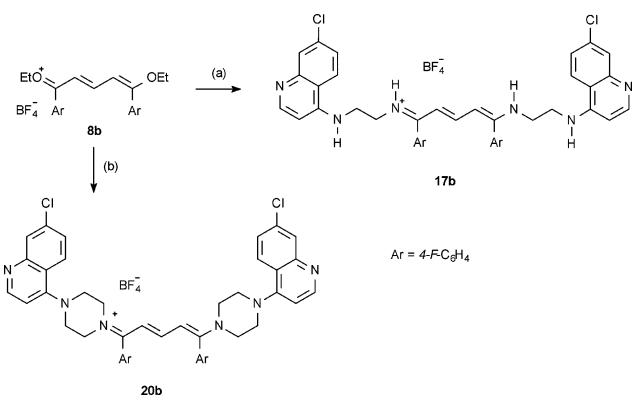
quino



pipequino

Compound	NR^1R^2	NR^3R^4	R	IC_{50} *P. falciparum* (μM) Nigerian[a]	FcB1[b]	FcM29[b]	Resistance index $IC_{50\ FcB1}/IC_{50\ Nigerian}$	$IC_{50\ FcM29}/IC_{50\ Nigerian}$
10a	NEt_2	peroxo	Me	—	0.057	0.039	—	—
10b	NEt_2	peroxo	F	0.10	0.436	0.422	4.27	4.14
11b		peroxo	F	0.305	0.427	0.374	1.40	1.23
12b	peroxo	peroxo	F	0.645	0.294	0.366	0.46	0.57
13b	NEt_2	OEt	F	4.15	4.921	6.451	1.19	1.55
14a		OEt	Me	23.5	49.642	58.275	2.11	2.48
15b	NEt_2	quino	F	0.15	0.695	—	4.60	—
16b		quino	F	0.63	0.526	3.942	0.83	6.21
17b	quino	quino	F	0.66	1.152	1.459	1.75	2.21
18b	NEt_2	pipequino	F	0.13	0.470	0.281	3.59	2.14
19b		pipequino	F	0.235	0.550	0.892	2.34	3.79
20b	pipequino	pipequino	F	0.35	0.444	0.468	1.27	1.34
21b[4]			F	0.73	5.466	3.221	7.49	4.41
22a[4,5]	NEt_2	NEt_2	Me	0.13	0.420	0.085	3.36	0.68
22b	NEt_2	NEt_2	F	0.15	0.248	0.465	1.65	3.10
Artemisinin[20]	—		—	0.008	—	0.004	—	0.5
chloroquine	—		—	0.03	0.132	0.26	4.40	8.67

[a] Values reflect the mean of two experiments carried out in duplicate. [b] Values reflect the mean of three independent experiments, as SD was constantly lower than 15% they were not indicated in the table.



Scheme 4 Synthesis of symmetrical hybrid 4-aminoquinoline–streptocyanine dyes **17b** and **20b**. *Reagents and conditions*: argon, RT (a) DMF, **7a** 2 eq., 6 d; (b) CH_3CN, **7b** 2 eq., 24 h.

compared to streptocyanines, with a positive global charge located to a greater extent on the nitrogen end of the molecule than the oxygen end. The difference in activities between hemicarboxonium salts and streptocyanines is in agreement with the π-delocalized lipophilic cation (DLC) hypothesis.[18]

Hybrid peroxo-streptocyanine dyes are ten- to one hundred-fold more active than the cyclic peroxide **6** (IC_{50} 5.7 μM) which is too hydrophilic. The molecules with *para*-fluorophenyl groups are less cytotoxic than the *para*-methylated compound **10a**. The latter, in spite of its good antiplasmodial activity (62 nM), is 47-fold more cytotoxic toward MCF7 cells than its fluoro homologue **10b**, so it has the worst selectivity index among this hybrids series. Interestingly, unsymmetrical compounds **10a**, **10b**, and **11b** showed increasing activity with regard to the corresponding symmetrical streptocyanines **22a**, **22b**, **21b**, or to the hybrid molecule **12b**. The selectivity index of hybrid dyes **11b** and **12b** was lower than the selectivity index of the two morpholino end groups streptocyanine **21b**. In contrast, the association of diethylamino

Table 2 *In vitro* activity of the synthesised compounds against the mammalian cells, MCF7 and Vero

Compound	IC_{50} (μM)		Selective toxicity					
	MCF7[a]	Vero[a]	$IC_{50\ MCF7}$ / $IC_{50\ Nigerian}$	$IC_{50\ Vero}$ / $IC_{50\ Nigerian}$	$IC_{50\ MCF7}$ / $IC_{50\ Fcb1}$	$IC_{50\ Vero}$ / $IC_{50\ Fcb1}$	$IC_{50\ MCF7}$ / $IC_{50\ FcM29}$	$IC_{50\ Vero}$ / $IC_{50\ FcM29}$
10a	0.095	2.8	—	—	1.7	48	2.5	71
10b	4.5	46	44	454	0.7	7	0.8	8
11b	12	24	42	79	30	56	34	64
12b	22	36	35	55	76	121	61	97
13b	7.4	24	2	6	2	5	1	4
14a	7.5	50	0.3	2	0.1	1	0.8	1
15b	5.1	5.2	33	35	7	8	—	—
16b	5.3	5.7	8	9	10	11	1	1
17b	41	41	62	62	36	36	28	28
18b	5.0	38	38	290	11	81	18	135
19b	26.8	46	114	196	49	84	30	52
20b	9.5	41	27	117	21	92	20	87
21b[4]	67	139	92	190	12	25	21	43
22a[4,5]	0.62	1.07	5	9	1	3	7	13
22b	0.43	11	3	72	2	43	1	23
chloroquine	>10	43	—	1433	—	326	—	165

[a] Values reflect the mean of three experiments, SD was consistently < 15% (thus omitted for clarity); doxorubicin (positive control) IC_{50}: 55 nM for MCF7 and 120 nM for Vero.

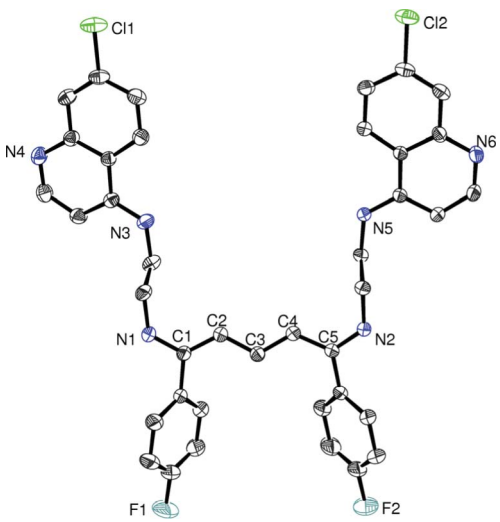


Fig. 4 ORTEP view of **17b**. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms, tetrafluoroborate anion and solvent molecules are omitted for clarity. Selected bond lengths (Å) and angles (°): N1–C1 1.3389(19), C1–C2 1.398(2), C2–C3 1.392(2), C3–C4 1.389(2), C4–C5 1.401(2), C5–N2 1.3382(19), N1–C1–C2 122.39(14), C1–C2–C3 124.53(14), C2–C3–C4 121.55(14), C3–C4–C5 125.86(14), C4–C5–N2 120.63(13); deviation of the chain carbons from the mean plane: 7.6 pm.

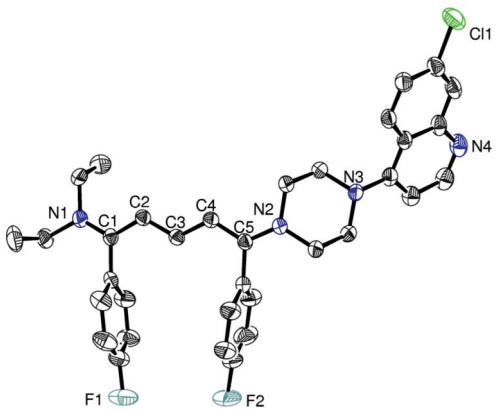


Fig. 5 ORTEP view of **18b**. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms, tetrafluoroborate anion and solvent molecules are omitted for clarity. Selected bond lengths (Å) and angles (°): N1–C1 1.335(3), C1–C2 1.398(3), C2–C3 1.391(3), C3–C4 1.382(3), C4–C5 1.401(3), C5–N2 1.335(3), N1–C1–C2 122.9(2), C1–C2–C3 121.9(2), C2–C3–C4 125.2(2), C3–C4–C5 121.1(2), C4–C5–N2 123.7(2); deviation of the chain carbons from the mean plane: 2.68 pm.

and peroxo groups has been beneficial because the hybrid molecule **10b** has retained the good antiplasmodial activity of **22b** with less cytotoxicity. So, **10b** exhibits high selectivity indices of 44 and 454, respectively, to MCF7 and Vero cells. For most of the tested drugs (except **10b**, **15b**, and **21b**), the resistance ratio was lower than 4 or 8 for FcB1 or FcM29, respectively. This indicated the absence of a chloroquine-like resistance pathway for these molecules. The resistance index of **12b** is less than one, which is a characteristic of artemisinin-like compounds.[19,20] It seems that **12b** present an artemisinin-like action mode, whereas the peroxo moiety of **10b**, and to a lesser extent of **11b**, doesn't seem to be responsible for the observed antiplasmodial activity.

The antiplasmodial activities of the hybrid 4-aminoquinoline–streptocyanine dyes range from 0.13 to 0.66 μM, *i.e.*, between the streptocyanines **22b** and **21b** activities. These values are close to those obtained with other promising antimalarial compounds. In the regular 5C-, 7C-, 9C-streptocyanines series,[4] compounds with secondary amino groups at the end of the polymethine chain have shown a better activity than molecules with primary amino groups. In the same way, pipequino hybrid dyes are more active than the ones with quino moieties (**20b**/**17b** IC_{50} 0.35/0.66 μM, **19b**/**16b** 0.23/0.63 μM). Moreover, their cytotoxicities are lower, except for **20b**, leading to better selective toxicity profiles. Hybrid molecules with quino moieties, **17b** and **16b**, have similar activities to the one with two morpholino end groups, **21b**, but are more cytotoxic against MCF7 as well as Vero cells. Although hybrid molecules with pipequino moieties, **20b** and **19b**, are respectively 2- and

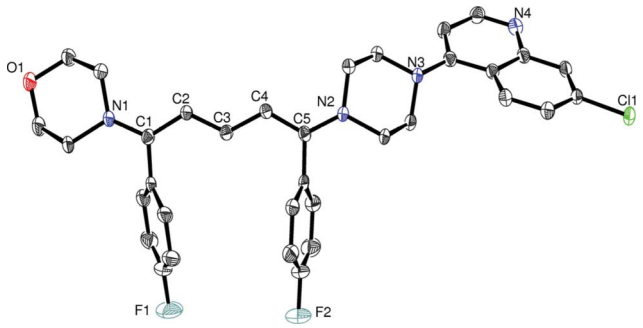


Fig. 6 ORTEP view of **19b**. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms, tetrafluoroborate anion and solvent molecules are omitted for clarity. Selected bond lengths (Å) and angles (°): N1–C1 1.337(3), C1–C2 1.415(3), C2–C3 1.388(3), C3–C4 1.402(3), C4–C5 1.398(3), C5–N2 1.350(3), N1–C1–C2 123.3(2), C1–C2–C3 121.3(2), C2–C3–C4 124.9(2), C3–C4–C5 121.3(2), C4–C5–N2 123.1(2); deviation of the chain carbons from the mean plane: 3.68 pm.

3-fold more active than **21b**, their selectivity indices are of the same order for **19b** and weaker for **20b**. Symmetrical hybrid compounds **17b** and **20b** are respectively 4- and 2-fold less active than **22b**, but absence of cytotoxicity on MCF7 cells gives them selectivity indices 20- and 10-fold higher. Against Vero cells, only **20b** shows a better selectivity (117). As observed in peroxo-streptocyanine dyes, unsymmetrical hybrid compounds with diethylamino groups, **15b** and **18b**, are more interesting than the corresponding symmetrical dyes **22b** because of the decrease in MCF7 cells cytotoxicity afforded by the 4-aminoquinoline moiety. Against Vero cells, **15b** is twice as cytotoxic as **22b**, but **18b** is four-fold less cytotoxic and this compound shows the best selectivity index (289) of the series of 4-aminoquinoline–streptocyanines synthesised.

Conclusion

We have designed and synthesised two novel series of streptocyanine dyes incorporating cyclic peroxide or 4-aminoquinoline moieties. The resulting hybrid compounds take advantage of the preservation of the good antiplasmodial activities of the streptocyanines while decreasing their cytotoxicity. If two active moieties are introduced, the corresponding symmetrical hybrid streptocyanines (**12b**, **17b**, **20b**) have submicromolar activities but stay less selective than the two morpholino end group streptocyanine (**21b**). The latter was found to be the most selective compound (92 and 189 to MCF7 and Vero cells, respectively) in previous RSA studies. However, with our synthetic method, we can easily obtain unsymmetrical compounds to act separately on activity and cytotoxicity. So, the unsymmetrical hybrids, which combine the active but toxic diethylamino group with peroxide or aminoquinoline moieties, have better selectivity index (44 and 454 for **10b**, 38 and 289 for **18b** against MCF7 and Vero cells, respectively).

Experimental

All experiments were performed under dry conditions (argon atmosphere, anhydrous solvents) to avoid degradation of the carboxonium salt. Melting points were determined with a Büchi capillary apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC 200, Bruker AC 250, AM 300 WB, AM 400 WB or AVANCE 500 spectrometers. Chemical shifts are given in ppm from TMS. Mass spectra were obtained on a Perkin-Elmer SCIEX API 365 apparatus with electrospray (positive mode, CH_3CN), a Nermag R10–10 apparatus for DCI and a GC TOF Waters and Waters Q/TOF Ultima apparatus for high resolution electrospray. Elemental analysis was performed by the microanalysis service from the Laboratoire de Chimie de Coordination (LCC) in Toulouse.

Preparation of tetrafluoroborate carboxonium salts 8a, b

These compounds were synthesised following previously described procedures.[5]

Preparation of tetrafluoroborate hemicarboxonium salts 13a, b and 14a–, b

These compounds were synthesised following previously described procedures.[5] One equivalent of amine (morpholine, diethylamine) was added dropwise onto carboxonium salt in solution in dry acetonitrile at room temperature, under argon atmosphere. After 15 min stirring, the solvent was removed under reduced pressure and the solid was washed with pentane and dried. The crude streptocyanine was crystallized in 100% ethanol and dried under vacuum at 40 °C. Only characterizations for new compounds are described below.

1-Ethoxy-5-diethylamino-1,5-bis(4-fluorophenyl)-penta-1,3-dienylium tetrafluoroborate 13b. **13b** was obtained as a yellow powder (1.65 g, 69%). (Found: C, 60.26, H, 6.02, N, 3.09. $C_{23}H_{26}BF_6NO$ requires C, 60.41, H, 5.73, N, 3.06%); mp 146 °C (dec); δ_H(300 MHz; CD_3CN) 1.20 (3H, t, ^3J 7.2, NCH_2CH_3), 1.44 (3H, t, ^3J 7.1, OCH_2CH_3), 1.48 (3H, t, ^3J 7.2, NCH_2CH_3), 3.48 (2H, q, ^3J 7.2, NCH_2CH_3), 3.95 (2H, q, ^3J 7.2, NCH_2CH_3), 4.22 (2H, q, ^3J 7.2, OCH_2CH_3), 6.23 (1H, part X of ABX syst., ^3J 11.7, H_2), 6.65 (1H, part B of ABX syst., ^3J 11.7 and 14.1, H_3), 6.84 (1H, part A of ABX syst., $^3J_{AB}$ 14.1, H_4) and 7.00–7.30 (8H, m, H_{arom}); δ_C(75 MHz; CD_3CN) 12.3, 12.9 (NCH_2CH_3), 13.5 (OCH_2CH_3), 47.3, 50.8 (NCH_2CH_3), 66.6 (OCH_2CH_3), 103.6 (C_2), 115.3, 116.2 (2d, $^2J_{CF}$ 22.2, CH_{arom}), 116.5 (C_4), 127.2, 129.9 (2d, $^4J_{CF}$ 3.3; C_{arom}–C_{1-5}), 130.4, 131.8 (2d, $^3J_{CF}$ 8.9, CH_{arom}), 160.6 (C_3), 163.8, 164.0 (2d, $^1J_{CF}$ 248.3, F–C_{arom}), 173.1 and 174.7 (C_{1-5}); *m/z* (ESI+; CH_3CN) 370.3 (M^+, 100%).

1-Ethoxy-5-morpholino-1,5-bis(4-methylphenyl)-penta-1,3-dienylium tetrafluoroborate 14a. **14a** was obtained as a yellow powder (1.50 g, 70%). (Found: C, 64.93, H, 6.66, N, 3.00. $C_{25}H_{30}BF_4NO_2$ requires C, 64.81, H, 6.53, N, 3.02%); mp 192 °C; δ_H(300 MHz; CD_3CN) 1.44 (3H, t, ^3J 7.1, OCH_2CH_3), 2.37 et 2.42 (6H, 2 s, CH_3–C_6H_4), 3.62 (2H, m, NCH_2CH_2), 3.77 (2H, m, NCH_2CH_2), 3.99 (2H, m, OCH_2CH_2), 4.10 (2H, m, OCH_2CH_2), 4.24 (2H, q, ^3J 7.1, OCH_2CH_3), 6.23 (1H, m, H_3), 6.91 (2H, m, H_{2-4}), 7.16–7.43 (8H, m, H_{arom}) and δ_C(75 MHz; CD_3CN) 13.5 (OCH_2CH_3), 20.4 (CH_3–C_{arom}), 51.1, 53.8 (NCH_2CH_2), 65.8, 66.4 (OCH_2CH_2), 66.5 (OCH_2CH_3), 103.4, 115.5 (C_{2-4}), 127.9, 130.6 (C_{arom}–C_{1-5}), 128.6, 128.9, 129.5, 129.8 (CH_{arom}), 141.8, 142.2 (C_{arom}–CH_3), 162.0 (C_3), and 175.0, 175.5 (C_{1-5}); *m/z* (ESI+; CH_3CN) 375.5 (M^+, 100%).

1-Ethoxy-5-morpholino-1,5-bis(4-fluorophenyl)-penta-1,3-dienylium tetrafluoroborate 14b. **14b** was obtained as a yellow powder (1.60 g, 70%). (Found: C, 58.61, H, 5.44, N, 2.91. $C_{23}H_{24}BF_6NO_2$ requires C, 58.62, H, 5.13, N, 2.97%); mp 221 °C (dec); δ_H(250 MHz; CD_3CN) 1.45 (3H, t, ^3J 7.0, OCH_2CH_3), 3.60 (2H, m, NCH_2CH_2), 3.77 (2H, m, NCH_2CH_2), 4.00 (2H, m, OCH_2CH_2), 4.11 (2H, m, OCH_2CH_2), 4.25 (2H, q, ^3J 7.0, OCH_2CH_3), 6.26 (1H, part X of ABX syst., ^3J 11.4, H_2), 6.83 (1H, part B of ABX syst., ^3J 11.4 and 14.1, H_3), 6.95 (1H, part A of ABX syst., ^3J 14.1, H_4), 7.13–7.41 (8H, m, H_{arom}) and δ_C(75 MHz; CD_3CN) 13.5 (OCH_2CH_3), 51.3, 54.0 (NCH_2CH_2), 65.8, 66.3 (OCH_2CH_2), 66.7 (OCH_2CH_3), 103.8 (C_2), 115.3, 116.5 (2d, $^2J_{CF}$ 22.2, CH_{arom}), 116.1 (C_4), 126.9, 129.9 (C_{1-5}-C_{arom}), 131.3, 131.9 (2d, $^3J_{CF}$ 9.0, CH_{arom}), 161.4 (C_3), 164.1, 164.2 (2d, $^1J_{CF}$ 248.8, F–C_{arom}) and 173.6, 174.3 (C_{1-5}); *m/z* (ESI+; CH_3CN) 384.4 (M^+, 100%).

Preparation of tetrafluoroborate streptocyanine dyes 21a, b and 22a, b

These compounds were synthesised following previously described procedures.[4] Two equivalents of amine (morpholine, diethylamine) were added dropwise onto carboxonium salt in solution in dry acetonitrile at room temperature, under argon atmosphere. After stirring for 24 h, the solvent was removed under reduced pressure and the solid was washed with pentane and dried. The crude streptocyanine was crystallized from 100% ethanol and dried under vacuum at 40 °C. Only characterization for the new compound is described below.

1,5-Bis(diethylamino)-1,5-bis(4-fluorophenyl)-penta-1,3-dienylium tetrafluoroborate 22b. **22b** was obtained as a yellow powder (1.60 g, 50%). (Found: C, 61.67, H, 6.92, N, 5.55. $C_{25}H_{31}BF_6N_2$ requires C, 62.00, H, 6.45, N, 5.78%); mp 258 °C; δ_H(300 MHz; CD_3CN) 1.05 (6H, t, ^3J 7.2, NCH_2CH_3), 1.36 (6H, t, ^3J 7.2, NCH_2CH_3), 3.21 (4H, q, ^3J 7.2, NCH_2CH_3), 3.67 (4H, q, ^3J 7.2, NCH_2CH_3), 5.87 (1H, part X of AXX′ syst., ^3J 13.8 and 12.0, H_3), 6.18 (2H, part AA′ of AA′X syst., ^3J 13.0, H_{2-4}) and 7.06–7.11 (8H, m, H_{arom}); δ_C(75 MHz; CD_3CN) 11.6, 13.2 (NCH_2CH_3), 44.9, 48.1 (NCH_2CH_3), 105.2 (C_{2-4}), 115.5 (d, $^2J_{CF}$ 22.4, CH_{arom}), 129.1 (d, $^4J_{CF}$ 3.5, *C*–C_{1-5}), 130.5 (d, $^3J_{CF}$ 8.9, CH_{arom}), 161.4 (C_3), 163.1 (d, $^1J_{CF}$ 242.8, F–C_{arom}) and 168.3 (C_{1-5}); *m/z* (ESI+; CH_3CN) 397.3 (M^+, 100%).

Preparation of hybrid molecules with peroxide moiety 10a, b, 11b and 12b

4-Formylpiperidine-1-*tert*-butyl carboxylate 1. Under argon, 1-BOC-4-hydroxymethylpiperidine (0.40 g, 1.9 mmol, 1eq.) is dissolved in anhydrous dichloromethane (1.6 mL $mmol^{-1}$). DMSO (2 mL $mmol^{-1}$), triethylamine (1.29 mL, 9.3 mmol, 5 eq.) and SO_3–pyridine complex (1.48 g, 9.3 mmol, 5 eq.) are successively added. After 30 min stirring at room temperature, the mixture is diluted in ethyl ether then treated with a saturated NaCl solution. The organic phase is dried on magnesium, filtered then concentrated. Aldehyde **1** (0.40 mg, 1.9 mmol) is obtained as a yellow oil in a quantitative yield. δ_H(300 MHz; $CDCl_3$) 1.44 (s, 9H, $3CH_3$), 1.55 (m, 2H, ABX syst., CH_2–CHCHO), 1.87 (m, 2H, ABX syst., CH_2–CHCHO), 2.39 (m, 1H, CHCHO), 2.91 (m, 2H, ABX syst., CH_2–N) and 3.99 (m, 2H, ABX syst., CH_2–N); δ_C(75 MHz; CD_3Cl_3) 25.1 (CH_2–CHCHO), 28.4 (CH_3), 42.8 (CH_2–N), 48.0 (CHCHO), 79.7 (C), 154.6 (C=O) and 202.9 (CH=O); *m/z* (ESI+, MeOH) 236 ($[MNa]^+$, 100%).

4-(3,5,6,7,8,8a-Hexahydro-8a-hydroxy-6,6,8,8-tetramethyl-5,7-dioxobenzo[*c*][1,2]dioxin-3-yl)piperidine-1-*tert*-butyl carboxylate 4. Under argon, at room temperature, aldehyde **1** (0.38 mg, 1.8 mmol, 1 eq.) dissolved in anhydrous dichloromethane (9 mL) is added to piperidine (0.09 mL, 0.9 mmol, 0.5 eq.). Piperidine (0.09 mL, 0.9 mmol, 0.5 eq.) is added to a suspension of syncarpic acid (0.32 g, 1.8 mmol, 1 eq.) in dichloromethane (9 mL). After 45 min, the solution of syncarpic acid is poured into the solution of iminium. After 30 min stirring, the mixture is concentrated under vacuum. Mannich base **2** is obtained as a white powder. The Mannich base is then solubilised in dichloromethane and treated with a saturated solution of NH_4Cl in HCl 1 M. The biphasic mixture is stirred for 15 min; the organic phase is recovered, dried on $MgSO_4$, filtered and concentrated. Enone **3** is obtained as a yellow oil. It is then dissolved in dichloromethane, and kept under air for thirteen days. After evaporation, the crude mixture is purified by silica gel column chromatography using petroleum ether/ethyl acetate: 8/2 as eluent. *Endo*-peroxide **4** (0.49 g, 1.2 mmol) is obtained in 68% yield as a white solid. mp 152 °C; R_f (PE/AcOEt) = 0.46; δ_H(300 MHz; $CDCl_3$) 1.03 (s, 3H, $CH_{3\,K/L}$), 1.32 (s, 3H, $CH_{3\,K/L}$), 1.35 (s, 3H, $CH_{3M/N}$), 1.37 (s, 3H, $CH_{3M/N}$), 1.45 (s, 9H, $3CH_3$), 1.61–2.04 (m, 4H, ABX syst., CH_{2O}), 3.00–4.10 (m, 5H, ABX syst., CH_{2P} and OH) and 7.06 (s, 1H, CH_E); δ_C(75 MHz; $CDCl_3$) 15.1–21.0 ($CH_{3\,K/L}$), 24.1–26.6 ($CH_{3M/N}$), 28.4 ($C(CH_3)_3$), 30.5–32.5 (CH_{2O}), 38.7 (CH_{2P}), 51.7 (C_J), 55.0 (C_H), 78.7 (C_D), 80.1 ($C(CH_3)_3$), 97.7 (C_A), 132.8 (C_F), 140.9 (CH_E), 154.5 (NC=O), 198.1 (C_G) and 210.3 (C_I); IR (KBr, *ν*): 3394 (OH), 2978 to 2877 (CH_2 and CH_3), 1731 (C=O), 1691 (α,β-unsaturated C=O), 1669 (NC=O), 1636 (C=C), 1276 (C–N) and 1099 (C–O peroxide); HRMS (DCI/CH_4, CH_2Cl_2, negative mode) 409.2101 (M^+. $C_{21}H_{31}NO_7$ requires 409.2101).

4-(3,5,6,7,8,8a-Hexahydro-8a-methoxy-6,6,8,8-tetramethyl-5,7-dioxobenzo[*c*][1,2]dioxin-3-yl)piperidine-1-*tert*-butyl carboxylate 5. Under argon, *endo*-peroxide **4** (1.25 g, 3.0 mmol, 1 eq.) is dissolved in anhydrous tetrahydrofuran (100 mL). At −78 °C, butyllithium solution (1.3 M in hexane) (2.10 mL, 3.3 mmol, 1.1 eq.) is slowly added. After 15 min stirring, methyl triflate (0.38 mL, 3.3 mmol, 1.1 eq.) is added. The mixture is stirred for 4 h at −78 °C and then hydrolysed with saturated NH_4Cl solution. The aqueous phase is extracted with dichloromethane, the organic phases gathered, washed, dried over $MgSO_4$, filtered and evaporated. Methylated *endo*-peroxide **5** is obtained after purification by silica gel column chromatography (PE/AcOEt 9/1) as a white solid (0.80 g, 1.9 mmol) in 65% yield. R_f (PE/AcOEt: 8/2) = 0.39; δ_H(300 MHz; C_6D_6) 0.71 (s, 3H, $CH_{3\,K/L}$), 1.08 (m, ABX syst., 1H, CH_{2O}), 1.17–1.31 (m, ABX syst., 2H, CH_{2O}), 1.34 (s, 3H, $CH_{3M/N}$), 1.39 (s, 3H, $CH_{3M/N}$), 1.47 (s, 9H, $3CH_3$), 1.49 (s, 3H, $CH_{3\,K/L}$), 1.59 (m, ABX syst., 1H, CH_{2O}), 2.87 (m, ABX syst., 1H, CH_{2P}), 3.10 (m, ABX syst., 1H, CH_{2P}), 3.50–4.14 (m, ABX syst., 2H, CH_{2P}) and 6.93 (s, 1H, CH_E); δ_C(75 MHz; C_6D_6) 16.1–21.6 ($CH_{3\,K/L}$), 24.9–26.2 ($CH_{3M/N}$), 28.4 (CH_3), 30.4–32.3 (CH_{2O}), 39.2 (CH_{2P}), 53.2 (C_J), 54.5 (OCH_3), 54.8 (C_H), 77.9 (C_D), 79.4 ($C(CH_3)_3$), 101.1 (C_A), 129.7 (C_F), 143.4 (CH_E), 154.4 (NC–O), 197.8 (C_G) and 209.1 (C_I); IR (KBr, *ν*): 2973 to 2840 (CH_2 and CH_3), 1726 (C–O), 1692 (α,β-unsaturated C=O and carbamoyl), 1634 (C=C), 1279 (C–N) and 1102 (C–O peroxide); *m/z* (ESI+, CH_2Cl_2/MeOH) 446 ($[MNa]^+$,

100%); HRMS (ESI+, MeOH) 446.2155 ([MNa]$^+$. $C_{22}H_{33}NO_7Na$ requires 446.2192).

3-Piperidin-4-yl-8,8a-dihydro-8a-methoxy-6,6,8,8-tetramethyl-benzo[*c*][1,2]dioxine 5,7(3*H*,6H)-dione 6. Under argon at room temperature, trifluoroacetic acid (0.66 mL, 8.8 mmol, 20 eq.) is added to *endo*-peroxide **5** (0.19 g, 0.4 mmol, 1 eq.) dissolved in anhydrous dichloromethane (22 mL). After 24 h, the mixture is neutralized with saturated $NaHCO_3$ solution. The aqueous phase is extracted with dichloromethane, the organic phases gathered, washed, dried over $MgSO_4$, filtered and evaporated. Amine **6** (0.13 g, 0.4 mmol) is obtained as a yellow solid in 92% yield. mp 55 °C; R_f (CH_2Cl_2/MeOH saturated with NH_4OH 19/1) = 0.18; δ_H(300 MHz; C_6D_6) 0.75 (s, 3H, $CH_{3\,K/L}$), 1.10–1.39 (m, ABX syst., 2H, CH_{2O}), 1.37 (s, 3H, $CH_{3M/N}$), 1.42 (s, 3H, $CH_{3M/N}$), 1.53 (s, 3H, $CH_{3\,K/L}$), 1.40–1.71 (m, ABX syst., 2H, CH_{2O}), 2.38–2.83 (m, 4H, ABX syst., CH_{2P}), 3.21 (s, 3H, OCH_3) and 7.14 (s, 1H, CH_E); δ_C(75 MHz; C_6D_6) 16.1–21.7 ($CH_{3\,K/L}$), 25.0, 26.2 ($CH_{3M/N}$), 31.4, 32.8 (CH_{2O}), 41.2, 41.3 (CH_{2P}), 53.2 (C_J), 54.5 (OCH_3), 54.8 (C_H), 78.1 (C_D), 101.1 (C_A), 129.5 (C_F), 143.9 (CH_E), 198.0 (C_G) and 209.3 (C_I); IR (KBr, ν): 2973 to 2873 (CH_2 and CH_3) and 1718 (C═O), 1690 (α,β-unsaturated C═O), 1636 (C═C), 1278 (C–N), 1102 (C–O peroxide); *m*/*z* (DCI/CH_4, CH_2Cl_2, positive mode): 324 ([M + 1]$^+$, 100%); HRMS (DCI/CH_4, CH_2Cl_2, positive mode) 324.1811 ([M + 1]$^+$. $C_{17}H_{26}NO_5$ requires 324.1806).

1,5-Bis(4-methylphenyl)-1-diethylamino-5-3-piperidin-4-yl-8,8a-dihydro-8a-methoxy-6,6,8,8-tetramethylbenzo[*c*][1,2]-dioxine-5,7-(3*H*,6*H*)-dione-penta-1,3-dienylium tetrafluoroborate 10a. 6 (0.04 g, 0.13 mmol) was added to **13a** (0.05 g, 0.13 mmol) in DMF (5 cm^3) at room temperature. Diisopropylethylamine (0.02 cm^3, 0.13 mmol) was then added to the mixture. After 30 days stirring, the solvent was removed at reduced pressure. Water was added and extraction with dichloromethane performed, followed by washing the organic phases, drying on $MgSO_4$ and evaporation to furnish a solid. This was washed with pentane and precipitated in ethyl acetate/petroleum ether (4/1) to give **10a** as an orange powder (0.03 g, 32%).

δ_H(300 MHz; $CDCl_3$) 0.90–1.15 (6H, $CH_{3\,K/L}$ + N–CH_2–CH_3), 1.23–1.38 (9H, $CH_{3\,K/L/M/N}$), 1.44 (3H, t, ^3J 6.6, N–CH_2–CH_3), 1.70–2.30 (4H, m, CH_{2O}), 2.35 (6H, s, CH_3–C_6H_4), 3.23 (2H, q, ^3J 6.6, N–CH_2–CH_3), 3.30–4.50 (9H, m, N–CH_2–CH_3 + OCH_3 + CH_{2P}), 6.09 (1H, t, ^3J 12.6, H_3), 6.55, 6.60 (2H, 2d, ^3J 12.6, $H_{2\text{-}4}$), 6.70–7.15 (8H, m, H_{arom}) and 7.25 (1H, s, CH_E); δ_C(125 MHz; $CDCl_3$) 11.7, 13.2 (N–CH_2–*C*H_3), 15.1, 21.2, 21.3, 24.3, 25.3 (CH_3), 20.4 (2 s, *C*H_3–C_6H_4), 29.6, 30.6, 31.3, 32.3 (C_O), 43.3, 43.5, 46.3, 46.4 (C_P), 45.0, 46.4 (N–*C*H_2–CH_3), 52.8 (C_J), 54.4 (C_H), 54.6 (O–CH_3), 77.9 (C_D), 100.9 (C_A), 104.7, 106.3 ($C_{2\text{-}4}$), 128.0–129.1 (massif, CH_{arom}), 129.2, 129.8 ($C_{1\text{-}5}$–*C*$_{arom}$), 129.9 (C_F), 139.9, 140.4 (CH_3–*C*$_{arom}$), 143.1 (C_E), 162.5 (C_3), 168.8, 170.3 ($C_{1\text{-}5}$), 198.0 (C_G) and 210.0 (C_I); δ_F(300 MHz; $CDCl_3$) –152.99, –153.05 (BF_4); *m*/*z* (ESI+; MeOH) 639.6 (M$^+$, 100%); HRMS (DCI/NH_3, MeOH, positive mode) 639.3768 (M$^+$. $C_{40}H_{51}N_2O_5$ requires 639.3798).

1,5-Bis(4-fluorophenyl)-1-diethylamino-5-3-piperidin-4-yl-8,8a-dihydro-8a-methoxy-6,6,8,8-tetramethylbenzo-[*c*][1,2]-dioxine-5,7-(3*H*,6*H*)-dione-penta-1,3-dienylium tetrafluoroborate 10b. A solution of **6** (0.07 g, 0.20 mmol) in dry CH_3CN (5 cm^3) was added dropwise to a solution of **8b** (0.09 g, 0.20 mmol) in dry CH_3CN (35 cm^3) at room temperature. Diisopropylethylamine was then added to the mixture (0.04 cm^3, 0.20 mmol). After 24 h stirring, diethylamine (0.03 cm^3, 0.20 mmol) was added to the mixture. 24 h later, the solvent is removed under reduced pressure. Water is added and extraction with dichloromethane performed, followed by washing the organic phases, drying on $MgSO_4$ and evaporation to furnish a solid which was precipitated in ethyl acetate/petroleum ether (4/1). **10b** was obtained as an orange powder (0.04 g, 28%). δ_H(300 MHz; $CDCl_3$) 0.90–1.17 (6H, $CH_{3\,K\,L^{-1}}$ + N–CH_2–CH_3), 1.20–1.40 (9H, $CH_{3\,K/L/M/N}$), 1.44 (3H, t, ^3J 6.3, N–CH_2–CH_3), 1.50–2.60 (4H, m, CH_{2O}), 3.20–4.50 (11H, CH_{2P} + N–CH_2–CH_3 + OCH_3), 5.99 (1H, t, ^3J 12.9, H_3), 6.50, 6.56 (2H, 2d, ^3J 12.9, $H_{2\text{-}4}$), 6.95–7.25 (8H, m, H_{arom}) and 7.31 (1H, s, CH_E); δ_C(75 MHz; $CDCl_3$) 12.5, 14.2 (N–CH_2–*C*H_3), 15.6, 21.7, 24.8, 24.9, 25.9 ($C_{K/L/M/N}$), 31.2, 32.2 (C_O), 43.8, 46.6 (C_P), 45.6, 48.3 (N–*C*H_2–CH_3), 53.1 (C_J), 54.8 (C_H), 55.1 (O–CH_3), 77.6 (C_D), 100.9 (C_A), 107.2, 108.5 ($C_{2\text{-}4}$), 115.8, 115.9 (2d, $^2J_{CF}$ 21.7, CH_{arom}), 128.6, 128.8 (2d, $^4J_{CF}$ 3.4, $C_{1\text{-}5}$-*C*$_{arom}$), 130.0 (C_F), 130.2 (CH_{arom}), 142.4 (C_E), 162.7 (C_3), 163.5, 164.9 (2d, $^1J_{CF}$ 250.7, F–C_{arom}), 167.2, 168.8 ($C_{1\text{-}5}$), 198.2 (C_G) and 210.0 (C_I); δ_F(300 MHz; CD_3CN) –152.7, –152.6 (BF_4), –109.7, –109.2 (F_{arom}); HRMS (ESI+, MeOH) 647.3287 (M$^+$. $C_{38}H_{45}N_2O_5F_2$ requires 647.3297).

1,5-Bis(4-fluorophenyl)-1-morpholino-5-3-piperidin-4-yl-8,8a-dihydro-8a-methoxy-6,6,8,8-tetramethylbenzo-[*c*][1,2]-dioxine-5,7-(3*H*,6*H*)-dione-penta-1,3-dienylium tetrafluoroborate 11b. A solution of **6** (0.07 g, 0.20 mmol) in dry DMF (10 cm^3) was added dropwise to a solution of **8b** (0.09 g, 0.20 mmol) in dry DMF (40 cm^3) at room temperature. After 6 h stirring, morpholine (0.02 cm^3, 0.20 mmol) was added to the mixture. 24 h later, the solvent was removed under reduced pressure, and the crude solid was purified by silica gel chromatography (dichloromethane/ethyl acetate/acetonitrile 4/1/2). **11b** was obtained as an orange powder (0.07 g, 48%). TLC R_f (CH_2Cl_2/AcOEt/CH_3CN 4/1/2) 0.31; δ_H(500 MHz; $CDCl_3$) 0.94, 1.03 (3H, 2 s, $CH_{3\,K\,L^{-1}}$), 1.12–1.38 (9H, massif, $CH_{3\,K/L/M/N}$), 1.60–2.50 (4H, m, CH_{2O}), 3.30–4.50 (15H, 2 N–CH_2 + 2 O–CH_2 + OCH_3 + CH_{2P}), 6.15 (1H, part A of AMX syst., $^3J_{AX}$ 12.5 and $^3J_{AM}$ 13.0, H_3), 6.65 (1H, part M of AMX syst., $^3J_{AM}$ 13.0, H_2 or H_4), 6.71 (1H, part X of AMX syst., $^3J_{AX}$ 12.5, H_2 or H_4), 7.00–7.25 (8H, m, H_{arom}) and 7.28 (1H, s, CH_E); δ_C(125 MHz; $CDCl_3$) 15.6, 21.6, 21.9, 24.8, 25.9 ($C_{K/L/M/N}$), 30.3, 32.3 (C_O), 44.2, 46.8 (C_P), 49.1, 51.5 (N–CH_2), 53.1 (C_J), 54.8 (C_H), 55.1 (O–CH_3), 66.5, 66.9 (O–CH_2), 77.5 (C_D), 101.0 (C_A), 108.4, 108.7 ($C_{2\text{-}4}$), 116.1 (d, $^2J_{CF}$ 21.7, CH_{arom}), 128.2, 128.5 (2d, $^4J_{CF}$ 3.7, $C_{1\text{-}5}$-*C*$_{arom}$), 130.0 (C_F), 130.6, 131.0 (m, CH_{arom}), 142.1 (C_E), 163.1 (C_3), 163.6 (d, $^1J_{CF}$ 257.0, F–C_{arom}), 168.1 ($C_{1\text{-}5}$), 198.0 (C_G) and 209.9 (C_I); δ_F(300 MHz; CD_3CN) –151.88, –151.83 (BF_4), –111.9, –111.8 (F_{arom}); HRMS (ESI+, MeCN) 661.3088 (M$^+$. $C_{38}H_{43}N_2O_6F_2$ requires 661.3089).

1,5-Bis(4-fluorophenyl)-1, 5-bis(3-piperidin-4-yl-8,8a-dihydro-8a-methoxy-6,6,8,8-tetramethylbenzo-[*c*][1,2]-dioxine 5,7 (3*H*,6*H*)-dione-penta-1,3-dienylium tetrafluoroborate 12b. A solution of **6** (0.14 g, 0.40 mmol) in dry CH_3CN (10 cm^3) was added dropwise to a solution of **8b** (0.09 g, 0.20 mmol) in dry CH_3CN (40 cm^3) at room temperature. Diisopropylethylamine (0.08 cm^3, 0.40 mmol) was then added to the mixture. After 10 days at room temperature, the solvent was removed under reduced pressure. Water was added and extraction with dichloromethane performed, followed by washing the organic phases, drying on $MgSO_4$ and evaporation to furnish a solid. This was washed with diethyl ether and precipitated in

ethyl acetate/petroleum ether (4/1) to give **12b** as a yellow powder (0.026 g, 14%). δ_H(300 MHz; $CDCl_3$) 0.90–1.50 (24H, $CH_{3\,K/L/M/N}$), 1.50–2.60 (8H, m, CH_{2O}), 3.20–4.60 (14H, CH_{2P} + OCH_3), 6.13 (1H, part A of AX_2 syst., $^3J_{AX}$ 12.6, H_3), 6.68 (2H, part X of AX_2 syst., $^3J_{AX}$ 12.6, $H_{2\text{-}4}$) and 7.05 (10H, m, H_{arom} + CH_E); δ_C(125 MHz; $CDCl_3$) 15.6, 21.8, 24.9, 25.9 ($C_{K/L/M/N}$), 26.9, 29.2, 31.3, 32.4 (C_O), 39.8, 39.9, 44.2, 46.7 (C_P), 53.1 (C_J), 54.8 (C_H), 55.0 (O–CH_3), 75.7 (C_D), 101.0 (C_A), 108.6 ($C_{2\text{-}4}$), 116.1 (CH_{arom}), 128.4 ($C_{1\text{-}5}$-C_{arom}), 130.4 (C_F), 130.8 (m, CH_{arom}), 142.0 (C_E), 163.4 (C_3), 163.6 (d, $^1J_{CF}$ 251.4, F–C_{arom}), 168.0 ($C_{1\text{-}5}$), 198.1 (C_G) and 209.7 (C_I); δ_F(300 MHz; CD_3CN) −151.7, −151.6 (BF_4), −108.5 (F_{arom}); HRMS (ESI+, MeOH) 897.4136 (M^+. $C_{51}H_{59}N_2O_{10}F_2$ requires 897.4138).

Preparation of hybrid molecules with quinoline moiety 15b–20b

Compounds **7a** and **7b** were synthesised following previously described procedures.[11]

1 equivalent of **7a** in solution in DMF, or **7b** in solution in CH_3CN (around 2 cm^3), was added to 1 equivalent of **13b** or **14b** in solution in CH_3CN (around 30 cm^3) at room temperature. After 24 h stirring, the solvent was removed under reduced pressure, and the solid was washed with diethyl ether and dried. The crude streptocyanine was crystallized from 100% MeOH and dried under vacuum at 40 °C. **15b** was obtained as a yellow powder (0.03 g, 26%), **16b** as an orange powder (0.12 g, 59%), **18b** as yellow crystals (0.04 g, 30%) and **19b** as yellow crystals (0.14 g, 50%).

5-(*N*-(7-Chloroquinolin-4-yl)ethane-1,2-diamine)-1-diethylamino-1,5-bis(4-fluorophenyl)penta-1,3-dienylium tetrafluoroborate 15b. (Found: C, 57.77, H, 5.24, N, 8.68. $C_{32}H_{32}BClF_6N_4{\cdot}1.8H_2O$ requires C, 57.77, H, 5.39, N, 8.42%); mp 160 °C; δ_H(300 MHz; MeOD) 1.12 (3H, m, N–CH_2–CH_3), 1.36 (3H, m, N–CH_2–CH_3), 3.25 (2H, m, N–CH_2–CH_3), 3.68 (2H, m, N–CH_2–CH_3), 3.85 (4H, m, NH–CH_2), 5.79, 6.00 (2H, 2d, ^3J 12.9, $H_{2\text{-}4}$), 6.19 (1H, t, ^3J 12.9, H_3), 6.77 (1H, d, ^3J 6.0, H_B), 7.15 (8H, m, H_{arom}), 7.47 (1H, dd, ^3J 9.0 and ^4J 1.8, H_H), 7.83 (1H, d, ^4J 1.8, H_F), 8.03 (1H, d, ^3J 9.0, H_I) and 8.45 (1H, d, ^3J 6.0, H_C); δ_C(75 MHz; MeOD) 11.2, 12.9 (N–CH_2–CH_3), 41.4, 42.1 (NH–CH_2), 41.2, 44.8 (N–CH_2–CH_3), 98.6 (C_B), 102.4, 105.8 ($C_{2\text{-}4}$), 115.1, 115.4 (2d, $^2J_{CF}$ 28.2, CH_{arom}), 117.5 (C_J), 123.3 (C_I), 125.1 (C_H), 125.9 (C_F), 128.8, 130.1 (2d, $^4J_{CF}$ 3.4, C_{arom}), 130.3, 131.0 (d, $^3J_{CF}$ 8.6, CH_{arom}), 135.4 (C_G), 147.8 (C_E), 150.7 (C_C), 151.5 (C_A), 161.2 (C_3), 163.3, 164.0 (2d, $^1J_{CF}$ 248.7, F–C_{arom}) and 168.4, 168.6 ($C_{1\text{-}5}$); δ_F(300 MHz; MeOD) −154.2, −154.1 (BF_4), −112.1, −110.9 (F_{arom}); *m/z* (ESI+; MeOH) 545.5 (M^+, 100%), 547.5 (37, $[M+2]^+$).

5-(*N*-(7-Chloroquinolin-4-yl)ethane-1,2-diamine)-1,5-bis(4-fluorophenyl)-1-morpholino-penta-1,3-dienylium tetrafluoroborate 16b. (Found: C, 58.39, H, 4.73, N, 8.29. $C_{32}H_{30}BClF_6N_4O{\cdot}0.75H_2O$ requires C, 58.28, H, 4.80, N, 8.50%); mp 204 °C (dec); δ_H(300 MHz; CD_3CN) 3.30–3.90 (12H, m, O–CH_2, N–CH_2 et NH–CH_2), 5.73, 5.89 (2H, 2d, ^3J 12.9, $H_{2\text{-}4}$), 6.32 (2H, m, H_3 + NH), 6.66 (1H, d, ^3J 5.4, H_B), 7.15 (8H, m, H_{arom}), 7.44 (1H, dd, ^3J 9.0 and ^4J 2.1, H_H), 7.82 (1H, d, ^3J 9.0, H_I), 7.88 (1H, d, ^4J 2.1, H_F) and 8.53 (1H, d, ^3J 5.4, H_C); δ_C(75 MHz; MeOD) 41.3, 42.2 (NH–CH_2), 66.1 (O–CH_2), 98.7 (C_B), 104.0, 105.2 ($C_{2\text{-}4}$), 115.2, 115.7 (2d, $^2J_{CF}$ 22.3, CH_{arom}), 117.6 (C_J), 123.3 (C_I), 125.0 (C_H), 126.2 (C_F), 128.5, 129.9 (2d, $^4J_{CF}$ 3.3, C_{arom}), 131.0, 131.1 (d, $^3J_{CF}$ 9.4, CH_{arom}), 135.1 (C_G), 148.2 (C_E), 151.1 (C_C), 151.2 (C_A), 161.4 (C_3), 163.6, 164.2 (2d, $^1J_{CF}$ 249.1, F–C_{arom}) and 167.9, 169.6 ($C_{1\text{-}5}$); δ_F(300 MHz; MeOD) −154.4, −154.3 (BF_4), −111.4, −110.4 (F_{arom}); *m/z* (ESI+; MeOH) 559.5 (M^+,100%), 561.3 (38 $[M+2]^+$).

5-(7-Chloro-4-(piperazin-1-yl)quinoline)-1-diethylamino-1,5-bis(4-fluorophenyl)penta-1,3-dienylium tetrafluoroborate 18b. (Found: C, 60.54, H, 5.47, N, 8.26. $C_{34}H_{34}BClF_6N_4{\cdot}1H_2O$ requires C, 60.33, H, 5.36, N, 8.28%); mp 206 °C; δ_H(300 MHz; CD_3CN) 1.08 (3H, t, ^3J 7.0, N–CH_2–CH_3), 1.38 (3H, t, ^3J 7.0, N–CH_2–CH_3), 3.22–3.52 (8H, m, N–CH_2–CH_3, N–CH_2–CH_2), 3.73 (2H, q, ^3J 7.0, N–CH_2–CH_3), 4.03 (2H, m, N–CH_2–CH_2), 6.05 (1H, part A of AMX syst., $^3J_{AM}$ 12.9 and $^3J_{AX}$ 12.6, H_3), 6.28 (1H, part M of AMX syst., $^3J_{MA}$ 12.9, H_4 or H_2), 6.30 (1H, part X of AMX syst., $^3J_{XA}$ 12.6, H_2 or H_4), 6.98 (1H, d, ^3J 4.8, H_B), 7.15 (8H, m, H_{arom}), 7.53 (1H, dd, ^3J 9.0, ^4J 2.1, H_H), 8.05 (1H, d, ^4J 2.1, H_F), 8.09 (1H, d, ^3J 9.0, H_I) and 8.75 (1H, d, ^3J 4.8, H_C); δ_C(75 MHz; CD_3CN) 11.4, 12.8 (N–CH_2–CH_3), 44.9, 48.2 (N–CH_2–CH_3), 47.4, 50.2, 50.6, 51.4 (N–CH_2–CH_2), 104.6, 106.6 ($C_{2\text{-}4}$), 109.3 (C_B), 115.2, 115.4 (2d, $^2J_{CF}$ 22.2, CH_{arom}), 121.3 (C_J), 125.4, 125.8 ($C_{I\text{-}H}$), 128.2 (C_F), 128.4, 128.6 (2d, $^4J_{CF}$ 3.6, C_{arom}), 130.1, 131.0 (d, $^3J_{CF}$ 8.7, CH_{arom}), 134.1 (C_G), 149.8 (C_E), 151.9 (C_C), 155.4 (C_A), 161.7 (C_3), 162.8, 163.1 (2d, $^1J_{CF}$ 247.0, F–C_{arom}) and 167.4, 169.1 ($C_{1\text{-}5}$); δ_F(300 MHz; CD_3CN) −151.7, −151.6 (BF_4), −112.5, −112.1 (F_{arom}); *m/z* (ESI+; MeOH) 571.3 ($[M]^+$, 100%), 573.3 (40, $[M+2]^+$).

5-(7-Chloro-4-(piperazin-1-yl)quinoline)-1,5-bis(4-fluorophenyl)-1-morpholino-penta-1,3-dienylium tetrafluoroborate 19b. (Found: C, 59.52, H, 4.80, N, 8.05. $C_{34}H_{32}BClF_6N_4O{\cdot}0.75H_2O$ requires C, 59.49, H, 4.92, N, 8.16%); mp 208 °C; δ_H(300 MHz; CD_3CN) 3.20–4.20 (16H, m, O–CH_2, N–CH_2), 6.26 (3H, m, ABX syst., $H_{2\text{-}3\text{-}4}$), 6.98 (1H, d, ^3J 4.8, H_B), 7.17 (8H, m, H_{arom}), 7.54 (1H, dd, ^3J 9.0, ^4J 2.4, H_H), 8.05 (1H, d, ^4J 2.4, H_F), 8.10 (1H, d, ^3J 9.0, H_I) and 8.75 (1H, d, ^3J 4.8, H_C); δ_C(75 MHz; CD_3CN) around 51.2 (broad signal, N–CH_2), around 66.0 (broad signal, O–CH_2), 106.1, 106.3 ($C_{2\text{-}4}$), 109.7 (C_B), 115.8 (d, $^2J_{CF}$ 22.2, CH_{arom}), 121.7 (C_J), 125.7 (C_I), 126.2 (C_H), 128.6 (C_F), 128.5, 128.8 (2d, $^4J_{CF}$ 3.4, C_{arom}), 131.2, 131.3 (2d, $^3J_{CF}$ 8.6, CH_{arom}), 134.5 (C_G), 150.2 (C_E), 152.2 (C_C), 155.7 (C_A), 162.7 (C_3), 163.5 (d, $^1J_{CF}$ 247.6, F–C_{arom}) and 168.7, 169.0 ($C_{1\text{-}5}$); δ_F(300 MHz; CD_3CN) −151.7, −151.6 (BF_4), −111.8 (F_{arom}); *m/z* (ESI+; MeOH) 585.3 ($[M]^+$, 100%), 587.3 (44, $[M+2]^+$).

1,5-Bis(*N*-(7-chloroquinolin-4-yl)ethane-1,2-diamine)-1,5-bis(4-fluorophenyl)penta-1,3-dienylium tetrafluoroborate 17b. **7a** (0.21 g, 0.95 mmol) in solution in dry DMF (20 cm^3) was added dropwise to **8b** (0.20 g, 0.47 mmol) in solution in dry DMF (20 cm^3) at room temperature. After 6 days stirring, the solvent was removed under reduced pressure, and the solid was washed with dichloromethane and dried. The crude product was crystallized from 100% MeOH and dried under vacuum at 40 °C. **17b** was obtained as yellow crystals (0.11 g, 30%). (Found: C, 56.66, H, 4.58, N, 10.18. $C_{39}H_{33}BCl_2F_6N_6{\cdot}2.5H_2O$ requires C, 56.68, H, 4.63, N, 10.17%); mp 142 °C; δ_H(300 MHz; MeOD) 3.82–3.88 (8H, m, N–CH_2–CH_2), 5.48 (2H, part A of A_2X syst., $^3J_{AX}$ 12.9, $H_{2\text{-}4}$), 6.49 (1H, part. X of A_2X syst., $^3J_{AX}$ 12.9, H_3), 6.86 (2H, d, ^3J 6.0, H_B), 7.17 (8H, m, H_{arom}), 7.51 (2H, d, ^3J 9.0, H_H), 7.85 (2H, m, H_F), 8.07 (2H, d, ^3J 9.0, H_I) and 8.51 (2H, d, ^3J 6.0, H_C); δ_C(75 MHz; D_6DMSO) 41.7, 42.5 (NH–CH_2),

99.4 (C_B), 103.1 (C_{2-4}), 116.0 (d, $^2J_{CF}$ 21.9, CH_{arom}), 117.2 (C_J), 124.4 (C_I), 125.1 (C_H), 126.0 (C_F), 130.2 (d, $^4J_{CF}$ 3.0, C_{arom}), 132.1 (d, $^3J_{CF}$ 8.9, CH_{arom}), 136.0 (C_G), 145.0 (C_E), 148.8 (C_C), 152.8 (C_A), 159.8 (C_3), 163.9 (d, $^1J_{CF}$ 246.5, F–C_{arom}) and 168.0 (C_{1-5}); δ_F(300 MHz; MeOD) −153.94, −153.89 (BF_4), −110.3 (F_{arom}); *m/z* (ESI+; MeOH) 693.3 ([M]$^+$, 100%), 695.2 (68, [M+2]$^+$), 697.1 (14, [M + 4]$^+$).

1,5-Bis(7-chloro-4-(piperazin-1-yl)quinoline)-1,5-bis(4-fluorophenyl)penta-1,3-dienylium tetrafluoroborate 20b. **7b** (0.12 g, 0.50 mmol) in solution in dry CH_3CN (20 cm^3) was added dropwise to **8b** (0.11 g, 0.25 mmol) in solution in dry CH_3CN (20 cm^3) at room temperature. After 24 h stirring, the solvent was removed under reduced pressure and the solid was washed with pentane and dried. The crude product was crystallized from 100% MeOH and dried under vacuum at 40 °C. **20b** was obtained as yellow crystals (0.15 g, 70%). (Found: C, 58.04, H, 4.49, N, 9.66. $C_{43}H_{37}BCl_2F_6N_6\cdot 3H_2O$ requires C, 58.19, H, 4.88, N, 9.47%); mp 150 °C; δ_H(300 MHz; CD_3CN) 3.00–4.20 (16H, m, N–CH_2), 6.28 (3H, m, syst. AA′X, H_{2-3-4}), 6.98 (2H, d, ^3J 5.2, H_B), 7.20 (8H, m, H_{arom}), 7.54 (2H, dd, ^3J 9.0, ^4J 2.1, H_H), 8.05 (2H, d, ^4J 2.1, H_F), 8.10 (2H, d, ^3J 9.0, H_I) and 8.73 (2H, d, ^3J 5.2, H_C); δ_C(75 MHz; CD_3CN) around 50.8 (broad signal, NH–CH_2), 106.4 (C_{2-4}), 109.3 (C_B), 115.9 (d, $^2J_{CF}$ 22.3, CH_{arom}), 121.3 (C_J), 125.9 (C_I), 126.2 (C_H), 127.9 (C_F), 128.7 (d, $^4J_{CF}$ 3.6, C_{arom}), 131.3 (d, $^3J_{CF}$ 8.9, CH_{arom}), 134.9 (C_G), 149.4 (C_E), 151.4 (C_C), 156.0 (C_A), 162.8 (C_3), 163.6 (d, $^1J_{CF}$ 247.6, F–C_{arom}) and 169.0 (C_{1-5}); δ_F(300 MHz; CD_3CN) −151.7, −151.6 (BF_4), −111.7 (F_{arom}); *m/z* (ESI+; MeOH) 745.3 ([M]$^+$, 100%), 747.3 (80, [M + 2]$^+$), 748.3 (18, [M+4]$^+$).

For all the structures, data were collected at low temperature on a Bruker-AXS APEX II diffractometer or on a Bruker APEX II Quazar with IμS, using Mo-Kα radiation (λ = 0.7103 Å). The selected crystals were mounted on a glass fiber using perfluoropolyether oil and cooled rapidly to 193(2) K or 100(2) K in a stream of cold N_2. Semi-empirical absorption corrections were employed.[21] Structures were solved by direct methods (SHELXS–97)[22] and refined using the least-squares method on F^2.[23]

Crystallographic data for 17b

$C_{39}H_{33}BCl_2F_4N_6$ 2(CH_3OH), M = 845.51, T = 193(2) K, monoclinic, space group $P21/c$, a = 10.6578(2) Å, b = 32.0622(6) Å, c = 12.1186(3) Å, β = 100.604(1)°, V = 4070.36(15) Å^3, Z = 4, ρ_c = 1.3080 Mg m^{-3}, μ = 0.231 mm^{-1}, 134094 reflections, 13147 unique ($R(int)$ = 0.0368), R_1 [$I > 2\sigma(I)$] = 0.0526, wR_2 [all data] = 0.1581.

Crystallographic data for 18b

$C_{34}H_{34}BClF_6N_4O_{0.5}$, M = 666.91, T = 193(2) K, monoclinic, space group $P21/c$, a = 17.3524(3) Å, b = 11.5299(2) Å, c = 18.2276(3) Å, β = 112.482(1)°, V = 3369.66(10) Å^3, Z = 4, ρ_c = 1.315 Mg m^{-3}, μ = 0.178 mm^{-1}, 49681 reflections, 7401 unique ($R(int)$ = 0.0366), R_1 [$I > 2\sigma(I)$] = 0.0683, wR_2 [all data] = 0.2135.

Crystallographic data for 19b. $C_{34}H_{32}BClF_6N_4O$ (0.5 CH_3OH, 1 H_20), M = 706.93, T = 100(2) K, monoclinic, space group $C2/c$, a = 21.3858(4) Å, b = 11.0501(2) Å, c = 30.9188(7) Å, β = 108.770(1)°, V = 6918.0(2) Å^3, Z = 8, ρ_c = 1.357 Mg m^{-3}, μ = 0.182 mm^{-1}, 30548 reflections, 7013 unique ($R(int)$ = 0.0723), R_1 [$I > 2\sigma(I)$] = 0.0532, wR_2 [all data] = 0.1333.

CCDC 805391 for **17b**, 805392 for **18b** and 805393 for **19b** contain the supplementary crystallographic data for this paper.†

Drug inhibition of *in vitro* cultured *P. falciparum* parasite

The three strains of *P. falciparum* (Nigerian, chloroquino-sensitive, and FcB1 and FcM29, both being chloroquino-resistant) were asexually cultured in human blood in complete medium (RPMI 1640 supplemented with 25 mM Hepes, pH 7.4) and 10% AB+ human serum.[24] Drug effects were measured in microtiter plates on suspensions of asynchronous *P. falciparum* infected red blood cells (1.5% final haematocrit, 0.6% parasitemia) according to Desjardins *et al.*[15,25] Drugs (previously dissolved in DMSO) were diluted in culture medium so that the final DMSO concentration never exceeded 0.25%. After 48 h incubation at 37 °C, parasite viability was assayed by the incorporation of (^{3}H)Hypoxanthine (0.5 μCi/well, 22.2 kBq) in parasitic nucleic acids for 18 h. Cells were then lysed using an automatic cell harvester and the parasite radioactive nucleic acids were retained on glass fiber filters (Filtermate collector, Packard Biosciences). The filters were counted for radioactivity (TopCount NXT, Packard Biosciences). The radioactivity background was obtained by incubation of non-infected erythrocytes under the same conditions, and deducted. Analyses of dose–effect curves were performed with the Graphpad Prism analytical software. The results are expressed as IC_{50}, corresponding to the drug concentration leading to 50% parasite growth inhibition. Values are the means of at least two independent experiments (different cell cultures, different drug dilution stocks), each performed in duplicate.

In vitro cytotoxicity assay

Cytotoxicity was estimated, on one hand, on human MCF7 breast cancer cells and, on the other hand, on Vero cells (monkey kidney normal cells). The cells were cultured in the same conditions (same culture medium) as those used for *P. falciparum*, except that the 10% human serum was replaced by 5% foetal calf serum (Cambrex, Belgium). Cells were distributed in 96-well plates (20×10^3 cells/well and 5×10^3 cells/well for MCF7 and Vero, respectively) and the streptocyanines were added at various concentrations in triplicate. Cell growth was estimated by [^{3}H]-Hypoxanthine (9250 Bq/well added 24 h before the end of the experiment) incorporation after 48 h incubation.[15] The [^{3}H]-hypoxanthine incorporation, in the presence of streptocyanine, was compared with that of control cultures without extract (positive control being doxorubicin (Sigma)). IC_{50} was determined graphically on growth inhibition *vs.* concentration curves. The experiments were repeated three times.

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