SYNTHESIS AND ANTIMALARIAL ACTIVITY OF NEW 4,6-DIALKOXY- AND 4,6-BIS(ALKYLTHIO)PYRIDO[3,2-*g*]QUINOLINE DERIVATIVES

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Abstract - A set of 4,6-dialkoxy- and 4,6-bis(alkylthio)pyrido[3,2-*g*]quinoline derivatives was prepared from 2,8,10-trimethylpyrido[3,2-*g*]quinoline-4,6-dione as starting material. The latter was synthesized in a simple and convenient two step procedure. These compounds were tested *in vitro* on chloroquinosusceptible and chloroquinoresistant strains of *Plasmodium falciparum*. Two of them possess a 50 % inhibitory concentration (IC_{50}) lower than 100 nM against both strains.

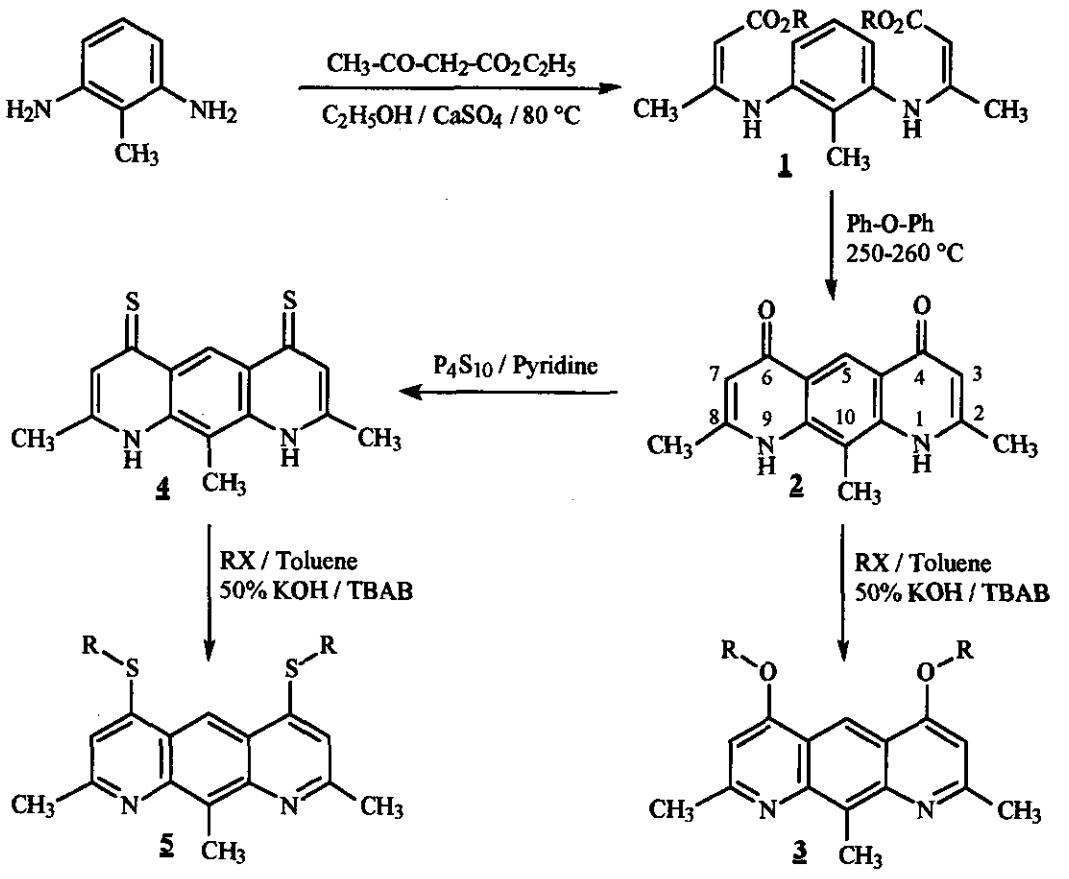
The spread of chloroquine-resistant *Plasmodium falciparum* is a serious problem with respect to prophylaxy and in the treatment of malaria in many endemic regions.[1,2] Resistance to alternative drugs has already occurred in several parts of the world.[3,4] On the one hand, there are only a few alternative drugs which are effective against chloroquine-resistant *Plasmodium falciparum*. On the other hand, the use of antimalarial drugs is difficult owing to the fact that side effects are frequent.[5,6] Thus, an urgent search for new drugs is needed. That is why new pyrido[3,2-*g*]quinoline derivatives were synthesized and tested against *Plasmodium falciparum* chloroquinosusceptible and chloroquinoresistant clones.

RESULTS AND DISCUSSION

Chemistry

The 2,8,10-trimethylpyrido[3,2-*g*]quinoline-4,6-dione **(2)** was readily prepared in a two step procedure (Scheme 1) : addition of 2,6-diaminotoluene on ethyl acetoacetate which led to the 2,6-bis (carboethoxymethylvinylamino)toluene **(1)**, followed by a thermal cyclization. Yield approximates 80 %.

Scheme 1



a : R = $(CH_2)_2$-$N(CH_3)_2$ **d** : R = $(CH_2)_2$-$N[CH(CH_3)_2]_2$ **g** : R = $(CH_2)_3$-N⟨ ⟩

b : R = $(CH_2)_3$-$N(CH_3)_2$ **e** : R = $(CH_2)_2$-N⟨ ⟩ **h** : R = $(CH_2)_2$-N⟨O⟩

c : R = $(CH_2)_2$-$N(C_2H_5)_2$ **f** : R = $(CH_2)_2$-N⟨ ⟩ **i** : R = $(CH_2)_3$-N⟨NH⟩

Compound **(2)** was then alkylated on the carbonyl functions in positions 4 and 6 under phase transfer catalysis (PTC) conditions[7] with tetrabutylammonium bromide (TBAB) as catalyst to give the 4,6-dialkoxypyrido[3,2-*g*]quinolines **(3)**.

Thiation of **2** with tetraphosphorus decasulfide led to 2,8,10-trimethylpyrido[3,2-*g*]quinoline-4,6-dithione **(4)**. The dithione **(4)** can be used without purification, the more so as this compound is quite insoluble in pure or mixed usual solvents.

Alkylation of **4** on the thio functions in positions 4 and 6 under PTC conditions gave the 4,6-bis(alkylthio)pyrido[3,2-*g*]quinolines **(5)**.

Compounds **(5)** were characterized by ^{1}H and ^{13}C nmr spectroscopies. In particular, chemical shifts for C-4 and C-6 are 144 ppm while they are 162 ppm for the same carbons in the alkoxy derivatives **(3)**. These values are closed to those pointed out for C-O in the 9-alkoxyacridines (169 ppm)[8] and for C-S in the 9-alkylthioacridines (144 ppm).[9] Hence, in spite of a tautomeric equilibrium between C=O,[4,6] or C=S,[4,6] and NH[1,9] functions, alkylation only led to S- and O-substituted derivatives (Scheme 1). No *N*-alkylated derivatives have been isolated nor identifyed by nmr of the crudes. Added to this, it must be noted that alkylation under phase transfer catalysis conditions is better for preparing alkylthio derivatives **(5)** than for preparing alkoxy derivatives **(3)**. This is clearly demonstrated comparing yields of these compounds.

Chemical data of compounds prepared are gathered in Tables 1 and 2.

Parasitology

Fifteen compounds were tested against chloroquine-susceptible D6 clone. The *in vitro* activity of these compounds and that of chloroquine as drug reference is given in Table 3. The IC_{50} values against D6 clone allowed to establish structure-activity relationships. The 2,8,10-trimethylpyrido[3,2-*g*]quinoline is the common structure for the drugs tested. Only changes are those of alkoxy (O-R) and alkylthio (S-R) substituents in positions 4 and 6. Comparison between ethers **(3)** and thioethers **(5)** with the same substituent R **(3b-5b ; 3c-5c ; 3e-5e ; 3f-5f ; 3g-5g)** shows that heteroatoms O and S have similar influence on activity under investigation. However this activity mainly depends upon the nature of the side-chain. Two compounds showed an attractive activity : **3g** and **5g** (mean IC_{50} 74 nM and 88 nM, respectively). These two compounds were tested concurrently against chloroquine-resistant W2 clone. *In vitro* activity against W2 clone is given in Table 4. Compound **(3g)** showed similar IC_{50} against both

clones. In contrast the D6 clone (mean IC_{50} 88 nM) was more susceptible to compound **(5g)** than the W2 clone (mean IC_{50} 290 nM). Compound **(3g)** might be an attractive therapeutic drug against malaria.

Table 1 : Chemical data of compounds (1) , (2) and 4,6-dialkoxy-2,8,10-trimethylpyrido[3,2-*g*] quinolines (3)

Compd	Time (h)	Yield (%)	mp (°C)	^{1}H Nmr ($CDCl_3$/TMS)* - δ (ppm) - J (Hz)
1	2	83	113-115	1.25(t, 6H, J = 7.1, CH_3) ; 1.85(s, 6H, CH_3) 2.20(s, 3H, CH_3) ; 4.15(q, 4H, J = 7.1, CH_2) 4.70(s, 2H, CH) ; 6.95(d, 2H, J = 7.8, H Ar) 7.10(t, 1H, J = 7.8, H Ar) ; 10.10(s, 2H, NH)
2	1	95	>260	3.10(s, 6H, CH_3) ; 3.20(s, 3H, CH_3) 7.35(s, 2H, H Ar) ; 9.80(s, 1H, H Ar)
3b	48	33	133-135	2.15(qt, 4H, J = 6.6 and 7.0, CH_2) ; 2.30(s, 12H, N-CH_3) 2.55(t, 4H, J = 7.1, CH_2-N) ; 2.75(s, 6H, CH_3) 3.30(s, 3H, CH_3) ; 4.25(t, 4H, J = 6.4, O-CH_2) 6.55(s, 2H, H Ar) ; 8.85(s, 1H, H Ar)
3c	24	62	144-146	1.10(t, 12H, J = 7.1, CH_3) ; 2.70(m, 8H, CH_2) 2.75(s, 6H, CH_3) ; 3.10(t, 4H, J = 6.1, CH_2-N) 3.30(s, 3H, CH_3) ; 4.25(t, 4H, J = 6.1, O-CH_2) ; 6.55(s, 2H, H Ar) ; 8.85(s,1H, H Ar)
3d	24	68	176-178	1.10(d, 24H, J = 6.5, CH_3) ; 2.75(s, 6H, CH_3) 3.10(m, 8H, CH_2-N + CH) ; 3.30(s, 3H, CH_3) 4.15(t, 4H, J = 6.9, O-CH_2) ; 6.55(s, 2H, H Ar) 8.90(s, 1H, H Ar)
3e	24	40	175-177	1.70(m, 8H, CH_2) ; 2.60(m, 14H, N-CH_2 + CH_3) 2.95(t, 4H, J = 5.1, CH_2-N) ; 3.10(s, 3H, CH_3) 4.40(t, 4H, J = 5.1, O-CH_2) ; 6.90(s, 2H, H Ar) 8.80(s, 1H, H Ar)
3f	24	51	188-190	1.45(m, 4H, CH_2) ; 1.65(qt, 8H, J = 4.8 and 5.6, CH_2) 2.65(t, 8H, J = 5.1, N-CH_2) ; 2.75(s, 6H, CH_3) 3.00(t, 4H, J = 5.8, CH_2-N) ; 3.30(s, 3H, CH_3) 4.35(t, 4H, J = 5.8, O-CH_2) ; 6.55(s, 2H, H Ar) 8.85(s, 1H, H Ar)
3g	24	40	159-161	1.45(m, 4H, CH_2) ; 1.60(m, 8H, CH_2) 2.15(qt, 4H, J = 6.4 and 7.6, CH_2) ; 2.45(m, 8H, N-CH_2) 2.60(t, 4H, J = 6.9, CH_2-N) ; 2.70(s, 6H, CH_3) 3.30(s, 3H, 10-CH_3) ; 4.25(t, 4H, J = 6.4, O-CH_2) 6.50(s, 2H, H Ar) ; 8.85(s, 1H, H Ar)
3h	24	40	202-204	2.70(t, 8H, J = 4.6, CH_2) ; 2.75(s, 6H, CH_3) 3.00(t, 4H, J = 5.6, CH_2-N) ; 3.30(s, 3H, CH_3) 3.75(t, 8H, J = 4.6, CH_2) ; 4.35(t, 4H, J = 5.6, O-CH_2) 6.55(s, 2H, H Ar) ; 8.85(s, 1H, H Ar)

* Except for **1** (DMSO-d_6/TMS) and **2** (TFA-d/TMS)

Table 2 : Chemical data of 4,6-bis(alkylthio)-2,8,10-trimethylpyrido[3,2-*g*]quinoline (5)

Compd	Time (h)	Yield (%)	mp (°C)	^{1}H Nmr ($CDCl_3$/TMS) - δ (ppm) - J (Hz)
5a	24	50	180-182	2.35(s, 12H, N-CH_3) ; 2.75(t, 4H, J = 6.8, CH_2-N) 2.75(s, 6H, CH_3) ; 3.20(t, 4H, J = 6.3, S-CH_2) 3.30(s, 3H, CH_3) ; 7.05(s, 2H, H Ar) 8.75(s, 1H, H Ar)
5b	24	60	112-114	2.00(qt, 4H, J = 7.0 and 7.1, CH_2) ; 2.30(s, 12H, N-CH_3) 2.50(t, 4H, J = 6.8, CH_2-N) ; 2.75(s, 6H, CH_3) 3.20(t, 4H, J = 7.1, S-CH_2) ; 3.30(s, 3H, CH_3) 7.05(s, 2H, H Ar) ; 8.70(s, 1H, H Ar)
5c	24	69	117-119	1.10(t, 12H, J = 7.1, CH_3) ; 2.60(q, 8H, J = 7.1, CH_2) 2.70(s, 6H, CH_3) ; 2.85(t, 4H, J = 6.6, CH_2-N) 3.25(t, 4H, J = 6.6, S-CH_2) ; 3.30(s, 3H, CH_3) 7.05(s, 2H, H Ar) ; 8.70(s, 1H, H Ar)
5e	24	61	162-164	1.85(qt, 8H, J = 3.2 and 6.5, CH_2) 2.65(t, 8H, J = 6.4, N-CH_2) ; 2.75(s, 6H, CH_3) 2.90(t, 4H, J = 5.6, CH_2-N) ; 3.30(s, 3H, CH_3) 3.30(t, 4H, J = 5.6, S-CH_2) ; 7.10(s, 2H, H Ar) 8.75(s, 1H, H Ar)
5f	24	50	170-172	1.45(m, 4H, CH_2) ; 1.55(qt, 8H, J = 5.1 and 5.2, CH_2) 2.50(t, 8H, J = 5.2, CH_2) ; 2.75(s, 6H, CH_3) 2.80(t, 4H, J = 5.3, CH_2-N) ; 3.25(t, 4H, J = 3.1, S-CH_2) 3.35(s, 3H, CH_3) ; 7.15(s, 2H, H Ar) 8.75(s, 1H, H Ar)
5g	24	70	146-148	1.47(m, 4H, CH_2) ; 1.60(m, 8H, CH_2) 2.00(qt, 4H, J = 7.2 and 7.3, CH_2) ; 2.40(m, 8H, N-CH_2) 2.50(t, 4H, J = 7.2, CH_2-N) ; 2.75(s, 6H, CH_3) 3.15(t, 4H, J = 7.3, S-CH_2) ; 3.30(s, 3H, CH_3) 7.05(s, 2H, H Ar) ; 8.75(s, 1H, H Ar)
5h	24	70	160-162	2.60(t, 8H, J = 4.6, CH_2-O) ; 2.75(s, 6H, CH_3) 2.80(t, 4H, J = 7.8, CH_2-N) ; 3.25(t, 4H, J = 7.8, S-CH_2) 3.30(s, 3H, CH_3) ; 3.85(t, 8H, J = 4.6, N-CH_2) 7.05(s, 2H, H Ar) ; 8.75(s, 1H, H Ar)
5i	24	56	86-88	2.00(qt, 4H, J = 7.1 and 7.2, -CH_2-) ; 2.45(m, 8H, CH_2) 2.55(t, 4H, J = 7.1, CH_2-N) ; 2.75(s, 6H, CH_3) 2.90(t, 8H, J = 4.8, CH_2) ; 3.20(t, 4H, J = 7.2, S-CH_2) 3.30(s, 3H, CH_3) ; 7.10(s, 2H, H Ar) 8.75(s, 1H, H Ar)

Table 3 : ***In vitro*** **activity of compounds against the D6 chloroquinosensitive strain of** ***P. falciparum***

Compounds	IC_{50} (nM)
Chloroquine	20
3b	250
3c	215
3d	260
3e	340
3f	255
3g	74
3h	6000
5a	310
5b	375
5c	235
5e	295
5f	3000
5g	88
5h	5000
5i	1100

Table 4 : ***In vitro*** **activity of compounds against the W2 chloroquinoresistant strain of** ***P. falciparum***

Compounds	IC_{50} (nM)
3g	90
5g	290

EXPERIMENTAL

Chemistry

Melting points were determined on a Köfler hot bench and are given uncorrected. Nmr spectra were recorded on a Bruker ARX 200 spectrometer with tetramethylsilane as internal standard. Microanalyses

were performed on a Technicon CHN autoanalyzer. The ^1H nmr abbreviations used, are as follows : s(singlet), d(doublet), t(triplet), q(quartet), qt(quintet), m(multiplet).

Mass spectrometry was achieved on a HP 5987 spectrometer either by direct introduction with temperature controled from 60 °C to 280 °C or by chemical ionization in methane as vector, under 1 torr pressure at 200 °C temperature of the source.

2,6-Bis(carboethoxymethylvinylamino)toluene (1)

A stirred mixture of 3.05 g (25 mmol) of 2,6-diaminotoluene, 7.4 g (57 mmol) of ethyl acetoacetate, 10 g (58 mmol) of calcium sulfate, 30 ml of ethanol and few drops of acetic acid, was heated at 80°C for 2 h. After filtration, the calcium sulfate was washed with ether. After evaporation of ether, solution was kept cool for a night. Precipitate was collected by filtration, washed with cold ethanol and recrystallized from absolute ethanol (7.35 g, 85 %). *mp* 113-115 °C *Anal. Calcd for* $C_{19}H_{26}N_2O_4$: C, 65.89 ; H, 7.52 ; N, 8.09. Found : C, 65.86 ; H, 7.56 ; N, 8.08.

2,8,10-Trimethylpyrido[3,2-*g*]quinoline-4,6-dione (2)

In a three necked round bottom flask, with a gas inlet and a thermometer, 125 ml of diphenyl ether were heated at 120°C. Then, 3.46 g (10 mmol) of **1** were added and the temperature was quickly raised and kept at 250°C for 50 min under nitrogen flow. After cooling to 60-70°C, 300 ml of petroleum ether were added. Precipitate obtained was filtered off, washed with methanol, petroleum ether. No recrystallization solvent have been found but the compound was analytically pure (2.42 g, 95 %). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.86 ; H, 5.51 ; N, 11.02. Found : C, 70.89 ; H, 5.48 ; N, 11.07. ^{13}C Nmr (TFA-d) : 11.87(10-CH_3) ; 22.85(2,8-CH_3) ; 108.1(C-3, C-7) ; 119.37(C-5) 120.27(C-5a, C-5b) ; 124.75(C-10) ; 140.5(C-10a, C-10b) ; 167.54(C-2, C-8) ; 173.58(C-4, C-6).

4,6-Dialkoxy-2,8,10-trimethylpyrido[3,2-*g*]quinoline (3). General procedure

A stirred mixture of 0.635 g (2.5 mmol) of **2**, 7.5 mmol of alkylating agent, 0.3 g (0.9 mmol) of TBAB, 30 ml of toluene, 15 ml (7.5 mmol) of 50 % aqueous potassium hydroxide was refluxed for 24 h. The organic layer was separated, washed with water and dried over magnesium sulfate. After evaporation of solvent, the residue obtained was recrystallized from absolute ethanol to give the expected compounds **(3)**.

4,6-Bis(dimethylaminopropyloxy)-2,8,10-trimethylpyrido[3,2-*g*]quinoline (3b)

Anal. Calcd for $C_{25}H_{36}N_4O_2$: C, 70.75 ; H, 8.49 ; N, 13.20. Found : C, 70.79 ; H, 8.45 ; N, 13.15. ^{13}C Nmr ($CDCl_3$) : 12.58(10-CH_3) ; 26.85(2,8-CH_3) ; 27.45(CH_2) ; 45.63(N-CH_3) ; 56.48(CH_2-N) ; 66.71(O-

CH_2) ; 99.46(C-3, C-7) ; 112.65(C-5) ; 118.31(C-5a, C-5b) ; 132.69(C-10) ; 146.66(C-10a, C-10b) ; 160.29(C-2, C-8) ; 162.18(C-4, C-6). Ms (m/z) : 424.

4,6-Bis(diethylaminoethoxy)-2,8,10-trimethylpyrido[3,2-*g*]quinoline (3c)

Anal. Calcd for $C_{27}H_{40}N_4O_2$: C, 71.68 ; H, 8.84 ; N, 12.38. Found : C, 71.65 ; H, 8.87 ; N, 12.35. ^{13}C Nmr ($CDCl_3$) : 12.41(CH_3) ; 12.58(10-CH_3) ; 26.85(2,8-CH_3) ; 48.23(CH_2) ; 51.72(CH_2-N) ; 67.54(O-CH_2) ; 99.43(C-3, C-7) ; 112.97(C-5) ; 118.30(C-5a, C-5b) ; 132.69(C-10) ; 146.68(C-10a, C-10b) ; 160.24(C-2, C-8) ; 162.20(C-4, C-6). Ms (m/z) : 452.

4,6-Bis(diisopropylaminoethoxy)-2,8,10-trimethylpyrido[3,2-*g*]quinoline (3d)

Anal. Calcd for $C_{31}H_{48}N_4O_2$: C, 73.23 ; H, 9.45 ; N, 11.02. Found : C, 73.28 ; H, 9.47 ; N, 11.07. ^{13}C Nmr ($CDCl_3$) : 12.64(10-CH_3) ; 21.14(CH_3) ; 26.91(2,8-CH_3) ; 44.28(CH_2-N) ; 49.72(CH) ; 69.86(O-CH_2) ; 99.53(C-3, C-7) ; 113.01(C-5) ; 118.31(C-5a, C-5b) ; 132.60(C-10) ; 146.67(C-10a, C-10b) ; 160.36(C-2, C-8) ; 162.32(C-4, C-6). Ms (m/z) : 508.

4,6-Bis(pyrrolidinoethoxy)-2,8,10-trimethylpyrido[3,2-*g*]quinoline (3e)

Anal. Calcd for $C_{27}H_{36}N_4O_2$: C, 72.32 ; H, 8.03 ; N, 12.50. Found : C, 72.35 ; H, 8.06 ; N, 12.51. ^{13}C Nmr ($CDCl_3$) : 12.56(10-CH_3) ; 23.89(CH_2) ; 26.87(2,8-CH_3) ; 54.72(N-CH_2) ; 55.05(CH_2-N) ; 68.04(O-CH_2) ; 99.40(C-3, C-7) ; 113.06(C-5) ; 118.20(C-5a, C-5b) ; 132.72(C-10) ; 146.67(C-10a, C-10b) ; 160.27(C-2, C-8) ; 162.31(C-4, C-6). Ms (m/z) : 448.

4,6-Bis(piperidinoethoxy)-2,8,10-trimethylpyrido[3,2-*g*]quinoline (3f)

Anal. Calcd for $C_{29}H_{40}N_4O_2$: C, 73.10; H, 8.40 ; N, 11.79. Found : C, 73.13 ; H, 8.39 ; N, 11.83. ^{13}C Nmr ($CDCl_3$) : 12.57(10-CH_3) ; 24.33(CH_2) ; 26.27(CH_2) ; 26.94(2,8-CH_3) ; 55.23(N-CH_2) ; 57.77(CH_2-N) ; 66.98(O-CH_2) ; 99.45(C-3, C-7) ; 112.97(C-5) ; 118.30(C-5a, C-5b) ; 132.68(C-10) ; 146.64(C-10a, C-10b) ; 160.28(C-2, C-8) ; 162.07(C-4, C-6). Ms (m/z) : 476.

4,6-Bis(piperidinopropyloxy)-2,8,10-trimethylpyrido[3,2-*g*]quinoline (3g)

Anal. Calcd for $C_{31}H_{44}N_4O_2$: C, 73.80 ; H, 8.73 ; N, 11.11. Found : C, 73.82 ; H, 8.77 ; N, 11.15. ^{13}C Nmr ($CDCl_3$) : 12.61(10-CH_3) ; 24.52(CH_2) ; 26.11(CH_2) ; 26.66(CH_2) 26.94(2,8-CH_3) ; 54.84(N-CH_2) ; 56.02(CH_2-N) ; 66.90(O-CH_2) ; 99.41(C-3, C-7) ; 112.71(C-5) ; 118.29(C-5a, C-5b) ; 132.34(C-10) ; 146.47(C-10a, C-10b) ; 160.08(C-2, C-8) ; 162.08(C-4, C-6). Ms (m/z) : 504.

4,6-Bis(morpholinoethoxy)-2,8,10-trimethylpyrido[3,2-*g*]quinoline (3h)

Anal. Calcd for $C_{27}H_{36}N_4O_4$: C, 67.50 ; H, 9.16. Found : C, 67.48 ; H, 9.15 ; N, 11.67. ^{13}C Nmr ($CDCl_3$)

: 12.59(10-CH_3) ; 26.85(2,8-CH_3) ; 54.34(N-CH_2) ; 57.48(CH_2-N) ; 66.81(O-CH_2) ; 67.10(CH_2-O) ; 99.53(C-3, C-7) ; 112.71(C-5) ; 118.19(C-5a, C-5b) ; 132.83(C-10) ; 146.55(C-10a, C-10b) ; 160.33(C-2, C-8) ; 161.87(C-4, C-6). Ms (m/z) : 480.

2,8,10-Trimethylpyrido[3,2-*g*]quinoline-4,6-dithione (4)

A stirred mixture of 1.27 g (5 mmol) of **2**, 2.22g (5 mmol) of tetraphosphorus decasulfide and 30 ml of pyridine, was heated at 100°C for 5 h. Precipitate obtained was filtrated off and plentifully washed with water.

4,6-Bis(alkylthio)-2,8,10-trimethylpyrido[3,2-*g*]quinoline (5). General procedure

The 4,6-bis(alkylthio) derivatives **(5)** were prepared from **4** (2.5 mmol) according to the procedure described for preparing 4,6-bis(alkoxy) derivatives **(3)**.

4,6-Bis[(dimethylaminoethyl)thio]-2,8,10-trimethylpyrido[3,2-*g*]quinoline (5a)

Anal. Calcd for $C_{23}H_{32}N_4S_2$: C, 64.48 ; H, 7.47 ; N, 13.08 ; S, 14.95. Found : C, 64.46 ; H, 7.53 ; N, 13.12 ; S, 15.01. ^{13}C Nmr ($CDCl_3$) : 12.77(10-CH_3) ; 26.37(2,8-CH_3) ; 29.62(S-CH_2) ; 45.45(N-CH_3) 57.58(CH_2-N) ; 116.05(C-5) ; 116.1(C-3, C-7) ; 122.74(C-5a, C-5b) ; 134.8(C-10) ; 144.7(4,6-C) ; 147.85(C-10a, C-10b) ; 157.94(C-2, C-8). Ms (m/z) : 428.

4,6-Bis[(dimethylaminopropyl)thio]-2,8,10-trimethylpyrido[3,2-*g*]quinoline (5b)

Anal. Calcd for $C_{25}H_{36}N_4S_2$: C, 65.79 ; H, 7.89 ; N, 12.28 ; S, 14.03. Found : C, 65.76 ; H, 7.92 ; N, 12.24 ; S 14.06. ^{13}C Nmr ($CDCl_3$) : 12.76(10-CH_3) ; 26.4(2,8-CH_3) ; 26.47(CH_2) ; 29.19(S-CH_2) ; 45.59(N-CH_3) ; 58.58(CH_2-N) ; 115.86(C-5) ; 116.20(C-3, C-7) ; 122.70(C-5a, C-5b) ; 134.78(C-10) 144.69(C-4, C-6) ; 147.85(C-10a, C-10b) ; 157.97(C-2, C-8). Ms (m/z) : 456.

4,6-Bis[(diethylaminoethyl)thio]-2,8,10-trimethylpyrido[3,2-*g*]quinoline (5c)

Anal. Calcd for $C_{27}H_{40}N_4S_2$: C, 66.94 ; H, 8.26 ; N, 11.57 ; S, 13.22. Found : C, 66.96 ; H, 8.22 ; N, 11.60 ; S, 13.19. ^{13}C Nmr ($CDCl_3$) : 11.89(CH_3) ; 12.72(10-CH_3) ; 26.28(2,8-CH_3) ; 29.39(S-CH_2) ; 47.15(CH_2) ; 51.04(N-CH_2) ; 115.96(C-5) ; 116.03(C-3, C-7) ; 122.68(C-5a, C-5b) ; 134.70(C-10) ; 144.63(C-4, C-6) ; 147.67(C-10a, C-10b) ; 157.84(C-2, C-8). Ms (m/z) : 484.

4,6-Bis[(pyrrolidinoethyl)thio)]-2,8,10-trimethylpyrido[3,2-*g*]quinoline (5e)

Anal. Calcd for $C_{27}H_{36}N_4S_2$: C, 67.50 ; H, 7.50 ; N, 11.66 ; S, 13.33. Found : C, 67.53 ; H, 7.46 ; N, 11.69 ; S, 13.30. ^{13}C Nmr ($CDCl_3$) : 12.79(10-CH_3) ; 23.59(CH_2) ; 26.42(2,8-CH_3) ; 31.01(S-CH_2) ; 54.(N-CH_2) ; 54.67(CH_2-N) ; 116.23(C-3, C-7) ; 116.38(C-5) ; 122.83(C-5a, C-5b) ; 134.87(C-10) ; 144.78(C-4, C-6) ; 147.77(C-10a, C-10b) ; 158.0(C-2, C-8). Ms (m/z) : 480.

4,6-Bis[(piperinoethyl)thio)]-2,8,10-trimethylpyrido[3,2-*g*]quinoline (5f)

Anal. Calcd for $C_{29}H_{40}N_4S_2$: C, 68.50 ; H, 7.87 ; N, 11.02 ; S, 12.59. Found : C, 68.48 ; H, 7.90 ; N, 11.06 ; S, 12.55. ^{13}C Nmr ($CDCl_3$) : 12.79(10-CH_3) ; 24.34(CH_2) ; 26.0(CH_2) ; 26.44(2,8-CH_3) ; 28.9(S-CH_2) ; 54.68(N-CH_2) ; 57.46(CH_2-N) ; 116.07(C-5) ; 116.32(C-3, C-7) ; 122.82(C-5a, C-5b) ; 134.85(C-10) ; 144.75(C-4, C-6) ; 144.71(C-10a, C-10b) ; 158.03(C-2, C-8). Ms (m/z) : 508.

4,6-Bis[(piperidinopropyl)thio]-2,8,10-trimethylpyrido[3,2-*g*]quinoline (5g)

Anal. Calcd for $C_{31}H_{44}N_4S_2$: C, 69.40 ; H, 8.20 ; N, 10.44 ; S, .11.94. Found : C, 69.42 ; H, 8.16; N, 10.41 ; S, 11.96. ^{13}C Nmr ($CDCl_3$) : 12.74(10-CH_3) ; 24.48(CH_2) ; 25.85(CH_2) ; 26.07(CH_2) ; 26.41(2,8-CH_3) ; 29.43(S-CH_2) ; 54.72(N-CH_2) ; 58.20(CH_2-N) ; 115.90(C-5) ; 116.11(C-3, C-7) ; 122.70(C-5a, C-5b) ; 134.73(C-10) ; 144.67(C-4, C-6) ; 147.92(C-10a, C-10b) ; 157.92(C-2, C-8). Ms (m/z) : 536.

4,6-Bis[(morpholinoethyl)thio]-2,8,10-trimethylpyrido[3,2-*g*]quinoline (5h)

Anal. Calcd for $C_{27}H_{36}N_4O_2S_2$: C, 63.28 ; H, 7.03 ; N, 10.93 ; S, 12.5. Found : C, 63.31 ; H, 7.00; N, 10.96 ; S, 12.52. ^{13}C Nmr ($CDCl_3$) : 12.79(10-CH_3) ; 26.40(2,8-CH_3) ; 28.86(S-CH_2) 53.62(N-CH_2) ; 56.98(CH_2-N) ; 66.94(CH_2-O) ; 116.08(C-5) ; 116.59(C-3, C-7) ; 122.86(C-5a, C-5b) 135.05(C-10) ; 144.77(C-4, C-6) ; 147.50(C-10a, C-10b) ; 158.04(C-2, C-8). Ms (m/z) : 512.

4,6-Bis[(piperazinopropyl)thio]-2,8,10-trimethylpyrido[3,2-*g*]quinoline (5i)

Anal. Calcd for $C_{29}H_{44}N_6S_2$: C, 64.68 ; H, 7.80 ; N, 15.61 ; S, 11.89. Found : C, 60.04 ; H, 9.14 ; N, 17.52 ; S, 13.31. ^{13}C Nmr ($CDCl_3$) : 12.77(10-CH_3) ; 26.44(2,8-CH_3) ; 29.33(S-CH_2) ; 31.02(CH_2) ; 46.16(CH_2-NH) ; 54.68(N-CH_2) ; 57.96(CH_2-N) ; 115.95(C-3, C-7) ; 116.29(C-5) ; 122.79(C-5a, C-5b) ; 134.86(C-10) ; 144.74(C-4, C-6) ; 147(C-10a, C-10b) ; 158.01(C-2, C-8). Ms (m/z) : 568.

Parasitology

Culture-adapted strains of *p. falciparum*

Two reference clones of *P. falciparum* were maintained in continuous culture : the chloroquine-susceptible D6 (Sierra Leone) clone and the resistant W2 (Indochina) clone. The drug susceptibility patterns of our reference clones have been described. Stock cultures were grown with type A^+ human erythrocytes suspended in RPMI (Gibco BRL, Paisley, UK) supplemented with 10% human serum (A^+) and buffered with 25 mM HEPES and 25 mM $NaHCO_3$. Cultures were incubated at 37°C in an atmosphere of 10% O_2, 6% CO_2, 84% N_2, and a humidity of 95%. Prior to the *in vitro* assay, parasitized erythrocytes were

diluted with uninfected, fresh erythrocytes to an initial parasite density of 0.5% and resuspended in culture medium to hematocrit of 1.5%.

Drugs

Chloroquine diphosphate was provided by Sigma Chemical (St. Louis, MO, USA). Stock solutions and two-fold serial dilutions of chloroquine diphosphate and of compounds were prepared in sterile distilled water and distributed in triplicate into flat-bottomed, 24 well plates (Nunc, ref. 13124).

***In vitro* assay**

The procedures of semimicro *in vitro* test were previously described by Le Bras and Deloron.[10] The suspension of parasitized erythrocytes was distributed under 750 µl/well. The plates were incubated for 42 h. ^{3}H-Hypoxanthine (specific activity 52.17×10^{10} Bq/mmol, 3.7×10^{4} Bq/well ; NEN Products, Dreiech, W. Germany) was added 18 hr latter to assess parasite growth. At the end of the incubation period, the plates were frozen and thawed to lyse erythrocytes. The contents of each well were collected on filter discs and washed using a cell harvester (PHD^{TM} cell harvester, Cambridge Technology Inc., Watertown, MA, USA). The filter discs were dried and placed in a scintillation vial containing 2 ml of liquid scintillation cocktail (Ultima Gold F, Packard Instrument Compagny, Meriden, CT, USA). The amount of radioactivity incorporated by parasites was measured using a liquid scintillation counter (Minaxi b Tricarb^{R} 4000, Packard).

The 50% inhibitory concentration (IC_{50}) values, defined as the drug concentration corresponding to 50% of the uptake of ^{3}H-Hypoxanthine by the parasites in drug-free control wells, were determined by linear regression analysis of log-dose/response curves.

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