Supporting Information

Synthesis and Antiplasmodial Activity of Aminoalkylamino-Substituted Neocryptolepine Derivatives

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Purity data for the target compounds.

Purity was verified using two diverse HPLC systems using respectively a mass and UV-detector. Water (A) and ACN (B), were used as eluents.
LC-MS spectra were recorded on an Agilent 1100 Series HPLC system using a Alltech Prevail C18 column (2.1 X 50 mm, 3 µm) coupled with an Esquire 3000plus as MS detector and a 5-100% B, 20 min-gradient was used with a flow rate of 0.2 mL/min. 0.1% Formic acid was added to solvent A and B.
Reversed phase HPLC was run on a Gilson instrument equipped with an Ulthrasphere ODS column (4.6 X 250 mm, 5µm). A 10-100% B, 35 min gradient was used with a flow rate of 1mL/min. 0.1% TFA was added to solvent A and B. 214 nm was used as wavelength.

Compound	**HPLC (214 nm) (t_r (min), peak area (%))**	**LC-MS (t_r (min), peak area (%))**
10a	16.39 min, 100%	12.5 min, 100%
10b	15.95 min, 100%	12.1 min, 100%
10c	19.72 min, 100%	12.1 min, 96%
10d	19.67 min, 100%	13.2 min, 100%
11a	15.03 min, 100%	9.15 min, 100%
11b	15.68 min, 100%	11.2 min, 100%
11c	16.04 min, 100%	10.4 min, 96%
11d	15.95 min, 100%	13.2 min, 97%
16b	19.67 min, 100%	13.2 min, 100%
17a	16.79 min, 100%	11.9 min, 94%
17b	20.55 min, 98.0%	13.2 min, 100%
17c	19.47 min, 71.0%;	13.5 min, 85%
17d	17.86 min, 82.5%	13.2 min, 87%
18a	14.22 min, 100%	10.3 min, 100%
18b	14.8 min, 95%	13.2 min, 100%
18c	15.29 min, 97.4%	15.2 min, 93%
18d	14.23 min, 100%	14.58 min, 97%
19b	14.57 min, 94.3%	13.2 min, 100%
19c	15.41 min, 94.1%	13.9 min, 100%
19d	14.63 min, 99.1%	14.2 min, 100%
20a	11.67 min, 100%	9.2 min, 100%
20b	14.57 min, 94.3%	13.2 min, 100%
20c	11.89 min, 100%	10.7 min, 97%
20d	12.44 min, 100%	9.7 min, 100%
20e	9.98 min, 100%	8.8 min, 100%
20f	9.67 min, 100%	8.7 min, 94%
20g	12.64 min, 100%	9.7 min, 95%
21a	12.09 min, 100%	9.6 min, 94%
21b	12.1 min, 100%	10.2 min, 97%
21c	12.28 min, 100%	11.6 min, 100%
21d	12.25 min, 100%	9.8 min, 100%
21e	11.31 min, 100%	11.3 min, 100%
21f	10.57 min, 100%	8.7 min, 100%
21g	13.46 min, 100%	13.1 min, 100%

***In vivo* drug screening model against *Plasmodium berghei* in Swiss mice**

Parasite and animals

Plasmodium berghei (ANKA strain, chloroquine-sensitive) is maintained in the lab by weekly sub-passage in Swiss mice. Blood from a clinically ill donor mouse (approximately 20% parasitaemia) is collected in a heparin-coated tube and further diluted in PBS to prepare the infection inoculum containing about $4x10^8$ infected erythrocytes in 0.2 ml. The infection is administered either intraperitoneally or intravenously.

Compound solutions and reference drugs

Compound formulations are prepared in PEG400 at 10 mg/ml and administered intraperitoneally. Chloroquine was used as the standard reference drug and is formulated at 5 mg/ml in PEG400.

Primary evaluation

Male Swiss mice (5/group) are intraperitoneally infected with $4x10^8$ infected erythrocytes at day 0. About 4-6 hours later, intraperitoneal treatment with the test compound is started and continued for 5 consecutive days at 80 mg/kg (or at lower dose levels in case of toxicity). The reference compound chloroquine (10 mg/kg IP) is included in the same treatment regimen. Untreated infected controls generally die before day 7 of infection. On days 4, 7, 10 and 14, a drop of blood is obtained from the tail vein for determination of the levels of parasitaemia (microscopic reading of Giemsa-stained blood smears). Compounds are considered active if the parasitaemia is reduced by >80% on day 4 (i.e. during dosing) or if the mean survival time in the treated exceeds that of the untreated controls by at least 50%.

Parameters

Clinical symptoms: the animals are observed for the occurrence/presence of clinical and adverse effects during the course of the experiment. The occurrence of mortality is monitored daily. Deaths before day 5 are likely related to drug toxicity. Obviously ill animals are euthanized and survival time is set at the next day. The mean survival time (MST) of treated versus control animals is indicative for efficacy.

Parasitaemia: on day 4, 7, 10 and 14 (or longer in survivors) – reduction as compared to infected control animals is a measure for drug activity. Parasitaemia will be determined microscopically by counting 5 fields of approximately 400 erythrocytes per field. The difference between the mean value of the control group (taken as 100 %) and those of the experimental groups is expressed as percent reduction using the equation:

$$\text{Activity} = 100 - \left(\frac{\text{mean parasitaemia treated}}{\text{mean parasitaemia control}} \times 100\right)$$

Body weight: on days 0, 4, 7, 10, 14 (or longer in survivors).

Spectroscopic details of intermediate compounds

2-(1*H*-Benzotriazol-1-yl)-6-chloroquinoline (8a). Yield: 1.30 g (93%), colourless crystals; ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 1H), 7.72 (m, 2H), 7.88 (d, 1H, *J* = 1.6 Hz), 8.10 (d, 1H, *J* = 8.8 Hz) 8.17 (d, 1H, *J* = 8.8 Hz), 8.30 (d, 1H, *J* = 8.8 Hz), 8.54 (d, 1H, *J* = 8.8 Hz), 8.92 (d, 1H, *J* = 8.4 Hz); MS (ESI): *m/z* = 303 $[M+Na]^+$.

2-(1*H*-Benzotriazol-1-yl)-7-chloroquinoline (8b). Yield: 1.25 g (88.5%), colourless crystals; ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 2H), 7.68 (m, 1H), 7.81 (d, 1H, *J* = 8.4 Hz), 8.16 (m, 2H), 8.33 (d, 1H, *J* = 8.8 Hz), 8.48 (d, 1H, *J* = 8.4 Hz), 8.9 (d, 1H, *J* = 8.0 Hz); MS (ESI): *m/z* = 303 $[M+Na]^+$.

2-(5-Chloro-1*H*-benzotriazol-1-yl)quinoline and 2-(6-chloro-1*H*-benzotriazol-1-yl)quinoline (8c,d). Yield: 1.10 g (79%), colourless crystals obtained as an inseparable 1:1 mixture of two regioisomers; ^{1}H NMR ($CDCl_3$), δ 7.45 (d, 1H, *J* = 2.0 Hz), 7.47 (d, 1H, J = 2.0 Hz), 7.6 (m, 3H), 7.80 (m, 2H), 7.88 (d, 1H, *J* = 8.4 Hz), 8.05 (d, 1H, *J* = 8.8 Hz), 8.12 (m, 2H), 8.17 (d, 1H, *J* = 8.8 Hz), 8.35 (s, 1H), 8.37 (s, 1H), 8.43 (d, 1H, *J* = 2.8 Hz), 8.45 (s, 1H, *J* = 2.8 Hz), 8.88 (d, 1H, *J* = 8.8 Hz), 8.96 (d, 1H, *J* = 2.0 Hz); MS (ESI): *m/z* = 303 $[M+Na]^+$.

2-Chloro-6*H*-indolo[2,3-*b*]quinoline (9a). Yield: 0.22 g (29%), light yellow solid; ^{1}H NMR (DMSO-d_6) δ 7.27 (m, 1H), 7.50 (m, 2H), 7.70 (m, 1H), 7.94 (m, 1H), 8.18 (s, 1H), 8.24 (m, 1H), 9.01 (s, 1H), 11.77 (s, 1H); MS (ESI): *m/z* = 253 $[M+H]^+$, 275 $[M+Na]^+$.

3-Chloro-6*H*-indolo[2,3-*b*]quinoline (9b). Yield: 0.23 g (30%), light yellow solid; ^{1}H NMR (DMSO-d_6) δ 7.53 (m, 2H), 7.70 (m, 1H), 7.94 (m, 1H), 7.92 (m, 1H), 8.21 (m, 2H), 9.01 (s, 1H), 11.77 (s, 1H); MS (ESI): *m/z* = 253 $[M+H]^+$, 275 $[M+Na]^+$.

8- and 9-Chloro-6*H*-indolo[2,3-*b*]quinoline (9c-d). Yield: 0.25 g (33.2%), light yellow solid obtained as an inseparable 1:1 mixture of two regioisomers; ^{1}H NMR (DMSO-d_6); δ 7.29 (m, 1H), 7.75 (m, 1H), 7.51 (m, 3H), 7.74 (m, 2H), 7.98 (s, 1H), 8.00 (s, 1H), 8.10 (m, 2H), 8.28 (m, 2H), 8.37 (m, 1H), 9.07 (s, 1H), 9.11 (s, 1H), 11.81 (s, 2H); MS (ESI): *m/z* = 253 $[M+H]^+$, 275 $[M+Na]^+$.

Methyl 2-(phenylamino)-1*H*-indole-3-carboxylate (14a). Yield: 1.77 g (56%); ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 7.05 (m, 1H), 7.15 (m, 1H), 7.27 (d, 1H, *J* = 7.6 Hz), 7.42 (m, 5H), 7.70 (d, 1H, *J* = 7.6 Hz), 8.11 (s, 1H), 9.33 (s, 1H); MS (ESI): *m/z* = 289 $[M+Na]^+$.

Methyl 2-[(3-chlorophenyl)amino]-1*H*-indole-3-carboxylate (14b). Yield: 1.68 g (47%); ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 7.09 (m, 3H), 7.15 (m, 2H), 7.23 (m, 2H), 7.80 (d, 1H, *J* = 8.4 Hz), 8.37 (s, 1H), 9.02 (s, 1H); MS (ESI): *m/z* = 323 $[M+Na]^+$.

Methyl 2-[(4-chlorophenyl)amino]-1*H*-indole-3-carboxylate (14c). Yield: 1.75 g (49%); ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 7.02 (m, 1H), 7.12 (m, 4H), 7.29 (m, 2H), 7.78 (d, 1H, *J* = 7.6 Hz), 8.41 (s, 1H), 8.91 (s, 1H); MS (ESI): *m/z* = 323 $[M+Na]^+$.

5,6-Dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one (15a). Yield: 0.60 g (65%); ^{1}H NMR (DMSO-d_6) δ 7.32 (m, 2H), 7.29 (m, 1H), 7.45 (d, 1H, *J* = 7.6 Hz), 7.63 (d, 2H, *J* = 3.6 Hz), 8.16 (d, 1H, *J* = 8.0 Hz), 8.28 (d, 1H, *J* = 8.0 Hz), 11.7 (s, 1H), 12.30 (s, 1H); MS (ESI): *m/z* = 235 $[M+H]^+$.

1-Chloro-5,6-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one and 3-chloro-5,6-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one (15b-c).
Yield: 0.94 g (88%), as an inseparable 1:1 mixture of two regioisomers; ^{1}H NMR (DMSO-d_6); δ 7.33 (m, 4H), 7.54 (m, 4H), 7.63 (m, 1H), 7.72 (s, 1H), 8.21 (m, 1H), 8.30 (d, 1H, J = 8.4 Hz), 11.7 (s, 1H), 11.88 (s, 1H), 12.43 (s, 1H), 12.47 (s, 1H); MS (ESI): m/z = 269 $[M+H]^+$.

2-Chloro-5,6-dihydro-11*H*-indolo[2,3-*b*]quinolin-11-one (15d). Yield: 0.57 g (53%); ^{1}H NMR (DMSO-d_6); δ 7.00 (d, 1H, J = 8.8 Hz), 7.25 (m, 2H), 7.39 (m, 1H), 7.48 (d, 1H, J = 8.0 Hz), 8.17 (d, 1H, J = 7.6 Hz), 8.21 (s, 1H), 11.76 (s, 1H), 12.45 (s, 1H); MS (ESI): m/z = 269 $[M+H]^+$.