Design and Synthesis of Small Molecule Inhibitors against the Protective Antigen of *Bacillus anthracis*

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Abstract
Bacillus anthracis carries a special type of bacterial toxin and is considered to be a potential biological weapon. The highly lethal spores of *B. anthracis* cause severe diseases such as cutaneous, gastrointestinal, and inhalation anthrax. The multicomponent binary toxin (AB-type) of *B. anthracis* consists of two separate components: component A with enzymatic activity (edema factor and lethal factor) and component B (protective antigen, PA—the binding portion). Component B is essential for the formation of transmembrane channels (PA pores) that translocate component A from endosomes to the cytoplasm, thereby causing lethal effects in the target cells. We have designed and synthesized small molecule inhibitors belonging to a novel class of aminoquinolinium substances that block the entry of the enzymatic components through the PA pore.

Keywords: *Bacillus anthracis*, anthrax, binary toxins, aminoquinoline, aminoquinolinium salts

Introduction

In the past decades, anthrax gained special attention for being a highly lethal[1] threat as a bacterial infectious disease[2] and most importantly for being categorized as a bioweapon.[3] The intentional dissemination of spores of *Bacillus anthracis* via mailing letters and packages,[4] followed by anthrax outbreaks in the USA[4] after September 11, 2001,[5] strongly emphasized the ease of infection and the difficulty to effectively protect the population from this infection.[4] Such biological agents are highly lethal, they are noiseless and invisible; thus leading to an indiscernible spread which prevents an early detection and causes mass hysteria at the same time.[6]

The pathogen *B*. *anthracis* is an ubiquitous, gram-positive, immobile, spore-forming, aerobic, and facultative anaerobic bacterium.[7] One threatening characteristic of *B*. *anthracis* is represented by the nature of its highly infectious spores. Mostly resistant to common disinfection and sterilization methods,[7] they remain alive for decades in the environment,[6] able to infect mammals, especially humans.[7] The transmission doesn't occur directly among humans.[8]

B. *anthracis* secretes binary toxins of the AB-type, which consists of the following three separate portions: component A consists of two enzymatic active factors (edema factor, EF, and lethal factor, LF) and component B consists of one binding portion (protective antigen, PA).[7] During a multi-step process, the component B forms an heptameric PA_{63}-channel through which the toxic enzymes of component A (EF and LF) are translocated from the endosome into the cytoplasm.[9]

The clinical picture of a *B*. *anthracis* infection is characterized by different syndroms with an incubation period of one to seven days (up to 60 days is also possible).[8] Among the cutaneous, gastrointestinal, and inhalation forms of anthrax,[7] the cutaneous form is the most common,[7] usually treated with antibiotics;[8] if it is untreated, it can be lethal in about five to 20 % of cases.[8] Uncharacteristic symptoms during the initial stage complicate the early diagnosis of gastrointestinal and inhalation anthrax, followed by a severe course of the disease if the medical treatment is delayed.[7,8] For gastrointestinal and

inhalation anthrax, and in systemic cases of cutaneous anthrax, hospitalization and intravenous antibiotics are immediately administered.[10] No vaccine is available for the civilian population worldwide,[11] but only for military personnel in the United States and the United Kingdom.[10]

The only option to prevent and to treat a *B. anthracis* infection is to use antibiotics against the bacterium itself. A delayed treatment can be lethal in cases of a fulminant course of the disease with a massive release of toxins. Antibiotics only limit the number of bacteria but not the amount of toxins. The simultaneous application of antibiotics together with inhibitory molecules active against intracellular binary toxins can be effective in treating infections caused by binary toxins produced by microorganisms.[12]

Herein, we present the design, synthesis, and characterization of compounds effective against the transport channels formed by PA components. Binding affinity and binding kinetic profiles of our inhibitory compounds, measured by bilayer titration experiments by our collaborators, showed an effective and persistent blockade and ability to prevent the translocation of the enzymatic components, which would normally be followed by cell death. These data are part of a more comprehensive study described and published in our patent application.[13]

Results and discussion

Basic considerations

The ϕ-clamp, a radial symmetric heptad, consisting of seven aromatic phenylalanine amino acids within the heptameric PA_{63}-channel lumen, is essential for protein-protein interaction of the components A, LF and EF, with the pore and for their translocation through the channel.[14,15] Bilayer membrane experiments showed that aminoquinolines, such as chloroquine (**1**; Figure 1), are able to successfully block the pore.[16] Negatively charged functional groups within the channel vestibule ionically interact with cationic inhibitors, but only one ligand can bind to the channel.[16] The inner pore diameter is about 15 Å,[15] its narrowest diameter is 11 Å;[14] therefore, molecules with similar extension and symmetry of the pore provide the best coverage and can be effective in blocking the pore.[14,17]

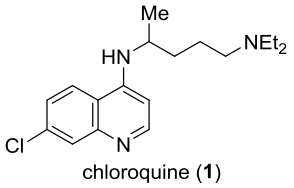
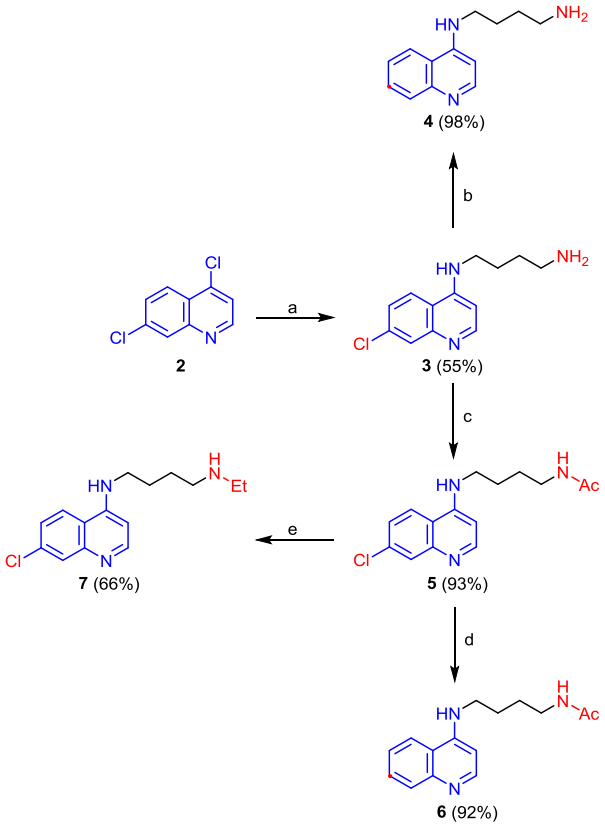


Figure 1. Structure of chloroquine (1), a known inhibitor molecule binding to the PA_{63}-channel that blocks the entry of components A, used as the reference drug in the bioactivity study.

For the design of small molecule inhibitors against the PA-channel of *B. anthracis*, we considered the following properties to be important: an aromatic, hydrophobic basic structure for hydrophobic interactions,[18] a cationic substituted side chain for ionic interactions within the pore binding site, enrichment in acidic compartments, optional heteroatoms for the formation of additional hydrogen bonds, and a sterically demanding moiety to cover the pore.

Starting from the known inhibitor molecule chloroquine (**1**) as a lead structure, we designed several derivatives with various substitution patterns at the side chain, and diverse aminoquinolinium salts containing a permanent positively charged nitrogen of the aminoquinoline structure.

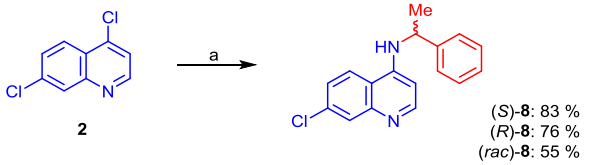


Scheme 1. Synthesis of desmethylchloroquine analogs for structure activity relationship studies. Reagents and conditions: (a) 1,4-diaminobutane, neat, 80 °C; (b) H_2, Pd/C, MeOH (dry), 25 °C; (c) Ac_2O, NaOAc, DCM (dry), 25 °C; (d) H_2, Pd/C, MeOH (dry), 25 °C; (e) 1. BH_3–DMS, THF (dry), 0-80 °C, 2. HCl conc., MeOH (dry), 80 C.

Synthesis

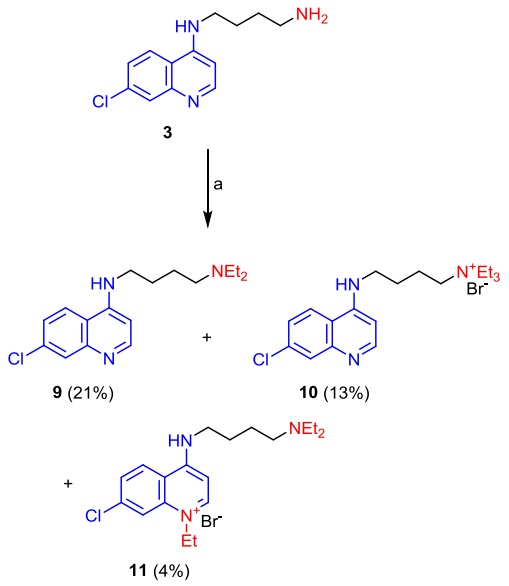
A known nucleophilic substitution reaction of 4,7-dichloroquinoline (**2**) using 1,4-diaminobutane as a reagent and as the solvent gave compound **3** with a 55 % yield as the starting material for the synthesis of further derivatives (Scheme 1).[19-21] Acetylation of the primary amine was obtained with a 93 % yield using acetic anhydride in DCM (dry) at room temperature (**5**). The chlorine-free molecules **4** (98 %) and **6** (92 %) were synthesized by reductive dehalogenation reactions on derivatives **3** and **5**, respectively, with Pd/C as a catalyst, hydrogen gas in MeOH (dry) at room temperature. The acetylated amine of **5** was reduced to amine **7** in a two-step procedure retaining the chlorine atom by first using BH_3–DMS in THF (dry) from 0 °C up to 80 °C, removal of the THF solvent as well as of all volatile components under reduced pressure and followed by acidic hydrolysis of the boron complexes using HCl conc. in MeOH at 80 °C.

A Buchwald-Hartwig amination reaction protocol using $Pd_2(dba)_3$, (±)-BINAP, KO*t*Bu in 1,4-dioxane (dry) at 70 °C introduced a racemic and an enantiopure α-methylbenzylamine moiety as a simple, shortened, and non-basic aromatic side chain analog to 4,7-dichloroquinoline (**2**; Scheme 2). The racemic product (*rac*)-**8** was obtained with 55 % yield, the enantiopure derivatives (*R*)-**8** and (*S*)-**8** with 76 % and 83 % yields, respectively. The higher yields for the enantiopure compounds (*R*)-**8** and (*S*)-**8** were obtained using a new batch of the $Pd_2(dba)_3$ catalyst, and higher yields could be obtained also for *rac*-**8**.



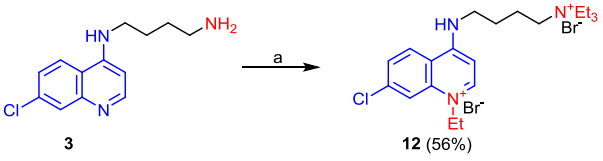
Scheme 2. Racemic and enantiopure synthesis of compound 8. Reagents and conditions: (a) (*rac*)-/ (*S*)-/ (*R*)-α-methylbenzylamine, $Pd_2(dba)_3$, (±)-BINAP, KO*t*Bu, 1,4-dioxane (dry), 70 C.

First representatives with a permanent positively charged nitrogen atom in the side chain (**10**, 13 %) at the aminoquinolinium moiety (**11**, 4 %) and a non-charged structure (desmethylchloroquine (**9**), 21 %) were synthesized with the reaction of compound **3** with two equivalents of ethyl bromide and DIPEA as a base in DMF (dry) at room temperature (Scheme 3). The obtained yields were low in all cases due to the high hydrophilicity of the synthesized substances; this event caused problems for the purification by column chromatography using alumina oxide (activity level V) followed by recrystallization.



Scheme 3. Synthesis of side chain derivatives: desmethylchloroquine (**9**), compound **10**, and the first aminoquinolinium salt (**11**) with di-ethylated tertiary amine function and the ethylated quinoline nitrogen atom. Reagents and conditions: (a) EtBr (2 equivalents), DIPEA, DMF (dry), 25 °C.

The synthesis of the double positively charged compound **12** yielded in 56 % by the reaction of compound **3** with six equivalents of ethyl bromide in DMF (dry) at room temperature and an heterogenous base, as Cs_2CO_3, that could be easily filtered (Scheme 4).



Scheme 4. Synthesis of the first double positively charged compound 12. Reagents and conditions: (a) EtBr (6 equivalents), Cs_2CO_3, DMF (dry), 25 C.

The formerly introduced ethyl substituent was replaced by diverse and more complex residuesat the positively charged quinoline nitrogen atom in *para*-postion to the free amine function (position B, Figure 2). A substituent with similar chain length (four carbon atoms) and a terminal amine function still protected, as phthalimide functionality, was used (Figure 2, Scheme 5).

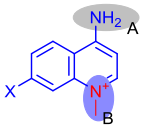
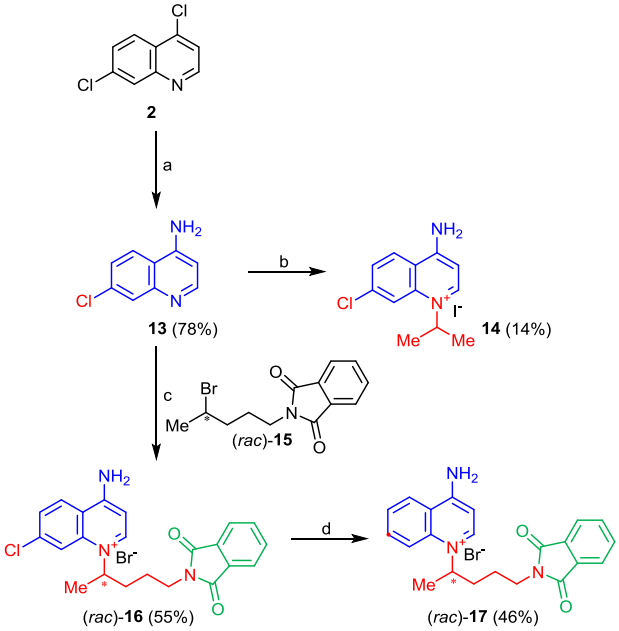


Figure 2. Position A and B used for derivatization.

To obtain **13** with 78 % yield, we used 4,7-dichloroquinoline (**2**) in phenol as solvent, gaseous ammonia as reagent and heated the mixture from 170 °C up to 200 °C (Scheme 5).[22,23] The nucleophilic substitution reaction at the quinoline nitrogen atom required harsher conditions than the ones used before.

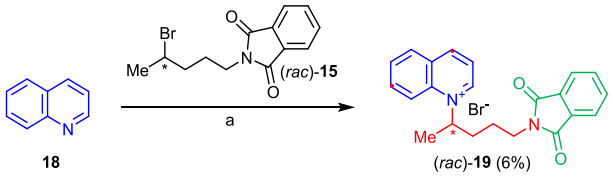


Scheme 5. Synthesis of the most highly active inhibitor derivative (*rac*)-16. Reagents and conditions: (a) NH_3 (g), phenol, 170–200 °C; (b) *i*-PrI, neat, 100 °C; (c) (*rac*)-**15**, neat, 160 °C; (d) H_2, Pd/C, MeOH (dry), 25°C.

Conditions and solvents that are typically used for nucleophilic substitution reactions were applied to the reaction between **13** with (*rac*)-**15**, but this reaction did not produce (*rac*)-**16**. The desired reaction with a 55 % yield occurred only when the mixture was stirred at a higher temperature under neat conditions (Scheme 5). A larger amount of reaction mixture, which facilitated stirring, leaded to higher conversion of the starting material and to higher yields. (*Rac*)-**16** was the most active inhibitor molecule with a high binding affinity and a long retention time to the channel, nearly completely blocking the pore.[Error! Bookmark not defined.] Reductive dehalogenation of (*rac*)-**16** to (*rac*)-**17** was performed by hydrogen gas, Pd/C as catalyst in MeOH (dry) at room temperature yielding in 46 % of (*rac*)-**17**.

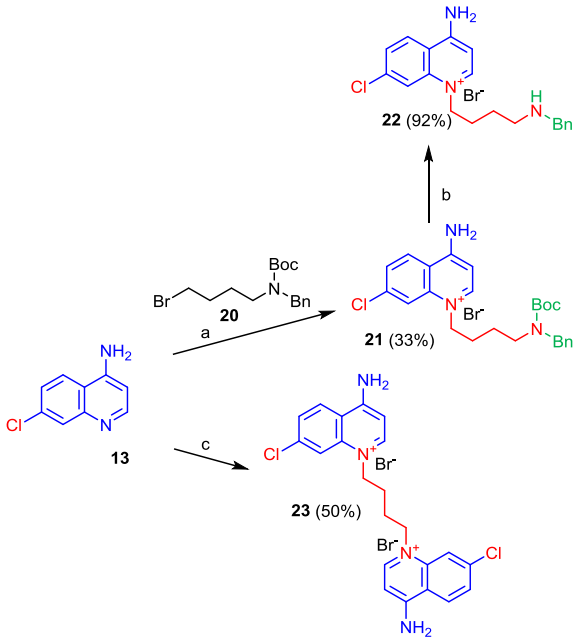
The simplified molecule **14** with an isopropyl residue attached to the quinoline nitrogen atom revealed the necessity of the terminal phthalimide group and a longer side chain with terminal amine function for the activity of these compounds, because the activity decreased significantly (Scheme 5).[13] **14** was obtained with only a 14 % yield. Isopropyl iodide, which has a lower boiling point than the required conversion temperature, had to be slowly dropped into the melted **13** in great excess at 100 °C.

To further investigate required substituents for activity, analog (*rac*)-**19** without a 7-chlorine atom and without a 4-amine function was prepared in low yields, since the electron-donating effect of the former 4-amine function was lacking and thus reduced the nucleophilicity of the quinoline nitrogen atom (Scheme 6).



Scheme 6. Synthesis of compound (*rac*)-19 without a 7-chlorine atom and without a *para*-amine function for structure activity relationship studies. Reagents and conditions: (a) (*rac*)-**15**, neat, 100 C.

Applying a similar procedure as for **16** (Scheme 5, c) at 150 °C, the analogs **21** followed by **22** were produced, and they provided different substituents with greater steric hindrance and different basic nitrogen atoms at the end of the side chain (Scheme 7). The reaction with the bromine derivative **20** yielded compound **21** (33 %), followed by the removal of the Boc protecting group using HCl conc. in MeOH to give **22** (92 %). The dimer **23** was obtained with 50 % yield by using 4-amino-7-chloroquinoline (**13**) and 1,4-dibromobutane at 150 °C.



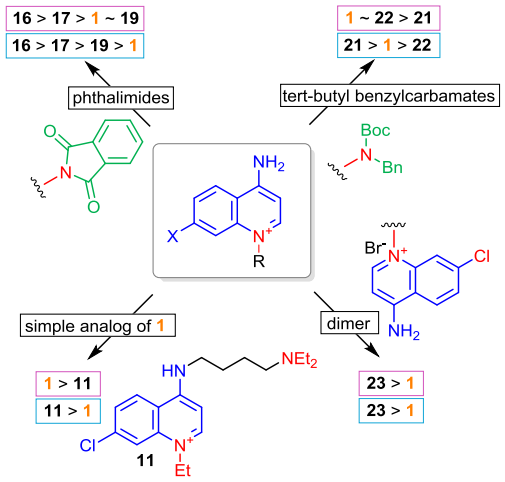
Scheme 7. Synthesis of the aminoquinolinium salts 21 and 22, and of the first aminoquinolinium dimer 23. Reagents and conditions: (a) **20**, neat, 150 °C; (b) HCl conc., MeOH, 25 °C; (c) 1,4-dibromobutane, neat, 150 C.

Conclusion

In order to design inhibitor molecules with increasing binding affinities (K) and increasing retention times (reciproke to k_{off}) into the PA_{63}-channel binding site (see overview Scheme 9), a

permanent positive charge in the quinoline moiety and diverse terminal substitution patterns of the side chain are essential.

The simplified desmethylchloroquine analogs with altered terminal amine functions with or without a 7-chlorine atom (**3**, **5**, **8**, **11**) showed binding affinity values in the range of the known inhibitor substance chloroquine (**1**) or slightly lower values. Of those compounds, **11** showed the highest activity with an ethylated positively charged quinoline nitrogen atom and a tertiary amine functionality for additional protonation in acidic compartments.[13] The basic building block of **13** showed minimal activity, compound **14** with a permanent positive charge and the isopropyl residue attached to the quinoline nitrogen atom was even more active than compound **13**.



Scheme 8. Inhibitory molecules of the study and reference drug chloroquine (1) in order from the highest to the lowest binding affinity (K in M^{-1}) and from the lowest to the highest retention time (referring to the reciproke binding kinetic constant k_{off} in s^{-1}) respectively. Only molecules with K > 10^5 M^{-1} and k_{off} < 10^{-3} s^{-1}. The best compound **16** binds 33.1 times stronger and 100 times longer than reference drug chloroquine (**1**).

The compound (*rac*)-**16** showed the highest activity of all inhibitor molecules (Figure 3). The positive charge on the aminoquinolinium structure, the phthalimide substituent as a hydrogen bond donor, and the length of the molecule close to the pore diameter contributed to the highest binding affinity to and longest retention time in the pore among all synthesized inhibitor analogs.[13]

The removal of the 7-chlorine atom from compound (*rac*)-**16** produced a lower activity, further reduced by the loss of both the 7-chlorine atom and the 4-amine function. A higher steric hindered terminal substituent such as that of compound (*rac*)-**21** had no higher activity than compound (*rac*)-**16**. A second positively charged quinoline nitrogen, as in dimer **23**, did not further increase the activity.

In conclusion, effective substituents should have a spatial orientation similar to that of the phthalimide group with a plane, bicyclic structural component with the ability to form hydrogen bonds, and compounds should have the 7-chlorine and the 4-amine substituents at the quinoline moiety. These properties are essential not only for the high binding affinity to the channel but also for the long retention times of the inhibitor molecules in the pore. Long retention times of the inhibitors are crucial in reducing the risk for component A to pass through the channel as soon as the inhibitor molecules detache from the binding site and the channel opens again.

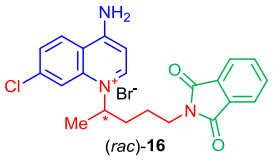


Figure 3. The most effective inhibitor molecule (*rac*)-16. The structure represents the

novel substance class of 4-amino-7-chloroquinolinium salts active against the protective antigen of *B. anthracis*.

Experimental Section

General Information

All used solvents were distilled before use. Commercially available materials were purchased from Sigma Aldrich and were used without further purification. Thin-layer chromatography was carried out using silica gel 60 F_{254} or alumina with fluorescent indicator. Detection of the compounds was achieved by flourescence quenching at 254 nm, flourescence at 356 nm, or staining with iodine or ninhydrin. Flash chromatography was performed using silica gel (20-63 mesh) or using ICN neutral or basic alumina, deactivated with 15 % H_2O. NMR spectra were obtained on a Bruker DMX 600 apparatus and are reported in ppm relative to internal solvent signal with coupling constants (*J*) in Hertz (Hz); in case of D_2O, 1,4-dioxane was added as internal solvent signal. Spectra were usually obtained at 25 °C, compound **21** was measured at (calibrated) 2 °C. EI mass spectrometry was carried out on a Finnigan MAT 8200; ESI-HRMS was measured on a Bruker Daltonik micrOTOF-focus.

Synthesis

N-(7'-Chloroquinolin-4'-yl)butane-1,4-diamine (3)[20]

4,7-dichloroquinoline (**2**, 7.599 g, 0.384 mol) and 1,4-diaminobutane (23.669 g, 0.268 mol) were stirred at 80 °C for 15 hours. The beige reaction mixture was suspended in chloroform, filtered, and concentrated. Recrystallization from water gave compound **3** (5.200 g, 55 %) as beige crystals. – Mp 122 °C (H_2O) – IR (ATR-FTIR): $\tilde{\nu}$ = 3253 (w, br), 3009 (w, br), 2930 (w), 2857 (w), 2360 (w), 1609 (w), 1576 (s), 1541 (m), 1489 (w), 1471 (m), 1450 (m), 1432 (m), 1369 (m), 1332 (m), 1285 (w), 1254 (w), 1199 (w), 1160 (w), 1132 (m), 1085 (w), 1072 (w), 1016 (w), 975 (m), 899 (s), 875 (m), 851 (s), 818 (w), 795 (m), 767 (m), 647 (w), 621 (m) cm^{-1} – ^{1}H-NMR (400 MHz, MeOD-d_4): δ = 1.57-1.64 (m, 2 H, CH_2), 1.74-1.81 (m, 2 H, CH_2), 2.70 (t, $^3J_{H-H}$ = 7.20 Hz, 2 H, 4-CH_2), 3.37 (t, $^3J_{H-H}$ = 7.08 Hz, 2 H, 4-CH_2), 6.50 (d, $^3J_{H-H}$ = 5.68 Hz, 1 H, 3'-H), 7.38 (dd, $^3J_{H-H}$ = 8.96 Hz, $^4J_{H-H}$ = 2.16 Hz, 1 H, 6'-H), 7.76 (d, $^4J_{H-H}$ = 2.12 Hz, 1 H, 8'-H), 8.09 (d, $^3J_{H-H}$ = 9.08 Hz, 1 H, 5'-H), 8.34 (d, $^3J_{H-H}$ = 5.68 Hz, 1 H, 2'-H) ppm – ^{13}C-NMR (100 MHz, MeOD-d_4): δ = 27.00, 31.53, 42.45, 44.00, 99.77, 118.94, 124.45, 126.05, 127.75, 136.42, 149.88, 152.59, 152.88 ppm – MS (EI, 70 eV): m/z (%) = 250.1/249.1 $[M]^{+\cdot}$ (14/75), 206.1/205.1 $[M\text{-}C_2H_6N]^+$ (37/100), 192.1/191.1 $[M\text{-}C_3H_8N]^+$ (22/99), 179.1/178.1 $[M\text{-}C_4H_9N]^+$ (99/30) – CHN calcd. ($C_{13}H_{16}ClN_{3)}$ C: 62.52 H: 6.46 N: 16.83; found C: 61.77 H: 6.35 N: 16.54.

N^1-(Quinolin-4'-yl)butane-1,4-diamine (4)

A solution of **3** (35.4 mg, 0.142 mmol) in MeOH (dry, 5 ml) was stirred 16 hours at 25 °C using Pd/C (4.5 mg, 13 % m/m) as catalyst under hydrogen gas atmosphere. The reaction mixture was filtered and concentrated. Purification with flash column chromatography on alumina (activity level V, MeOH 100 %) gave compound **4** (31.0 mg, 98 %) as beige crystals. – Mp 221 °C (MeOH) – IR (ATR-FTIR): $\tilde{\nu}$ = 3253 (w, br), 3058 (w), 2926 (w), 2855 (w), 2359 (w), 2341 (w), 1697 (w), 1580 (s), 1540 (m), 1509 (w), 1456 (w), 1437 (w), 1393 (w), 1375 (w), 1338 (w), 1299 (w), 1249 (w), 1172 (w), 1127 (w), 1038 (w), 869 (w), 809 (w), 763 (w), 735 (w), 698 (w), 668 (w), 654 (w), 610 (w) cm^{-1} – ^{1}H-NMR (600 MHz, MeOD-d_4): δ = 1.62-1.67 (m, 2 H, 3-H), 1.76-1.81 (m, 2 H, 2-H), 2.75 (t, $^3J_{H-H}$ = 7.32 Hz, 2 H, 4-H), 3.39 (t, $^3J_{H-H}$ = 7.05 Hz, 2 H, 1-H), 6.50 (d, $^3J_{H-H}$ = 5.52 Hz, 1 H, 3'-H), 7.42-7.44 (m, 1 H, 6'-H), 7.61-7.64 (m, 1 H, 7'-H), 7.80 (d, $^3J_{H-H}$ = 8.16 Hz, 8'-H), 8.10 (d, $^3J_{H-H}$ = 8.46 Hz, 5'-H), 8.34 (d, $^3J_{H-H}$ = 5.52 Hz, 1 H, 2'-H) ppm – ^{13}C-NMR (150 MHz, MeOD-d_4): δ = 26.94 (C-2), 30.58 (C-3), 42.13 (C-4), 43.82 (C-1), 99.27 (C-3'), 120.41 (C-4'a), 122.37 (C-5'), 125.72 (C-6'), 128.87 (C-8'), 130.63 (C-7'), 148.98 (C-8'a), 151.30 (C-2'), 152.81 (C-4') ppm – MS (EI, 70 eV): m/z (%) = 216.1/215.1 $[M]^{+\cdot}$ (7/42), 172.1/171.1 $[M\text{-}C_2H_6N]^+$ (13/48), 158.1/157.1 $[C_{10}H_9N_2]^+$ (17/100), 145.1/144.0 $[C_9H_8N_2]^{+\cdot}$ (46/30) – HRMS (ESI) calcd. $[M+H]^+$ 216.14952; found 216.14952.

N-(4-(7'-Chloroquinolin-4'-ylamino)butyl)-acetamide (5)

A suspension of amine **3** (506.7 mg, 2.03 mmol) and NaOAc (249.3 mg, 3.04 mmol) in DCM (dry, 30 ml) was stirred under nitrogen atmosphere at 0 °C and a solution of acetanhydride (216.0 mg, 2.12 mmol, 200.0 µl Ac_2O, corresponding to 2.2 ml of a solution with 1.0 ml Ac_2O in 10.0 ml DCM, dry) was dropped into the mixture. The mixture was stirred for 30 min at 25 °C, filtered, and concentrated. Purification with flash column chromatography on neutral alumina (activity level V, DCM/MeOH 10:1) and recrystallization (MeOH/H_2O) gave **5** (547.2 mg, 93 %) as colourless crystals. – Mp 195 °C (MeOH/H_2O) – IR (ATR-FTIR): $\tilde{\nu}$ = 3360 (w), 3329 (w), 3185 (w, br), 3035 (w, br), 2926 (w, br), 2870 (w), 1658 (s), 1612 (w), 1577 (s), 1555 (s), 1537 (s), 1488 (m), 1472 (m), 1448 (m), 1429 (m), 1382 (w), 1362 (s), 1324 (m), 1305 (m), 1279 (m), 1251 (m), 1199 (m), 1168 (w), 1137 (m), 1103 (m), 1077 (m), 1038 (w), 1020 (w), 999 (w), 902 (m), 868 (m), 851 (s), 821 (w), 811 (m), 795 (m), 767 (m), 740 (m), 647 (w), 630 (w), 621 (w) cm^{-1} – ^{1}H-NMR (400 MHz, MeOD-d_4): δ = 1.61-1.68 (m, 2 H, 2-CH_2), 1.74-1.81 (m, 2 H, 3-CH_2), 1.92 (s, 3 H, Me), 3.24 (t, $^3J_{H-H}$ = 6.94 Hz, 2 H, 1-CH_2), 3.40 (t, $^3J_{H-H}$ = 7.00 Hz, 2 H, 4-CH_2), 6.53 (d, $^3J_{H-H}$ = 5.68 Hz, 1 H, 3'-H), 7.39 (dd, $^3J_{H-H}$ = 8.96 Hz, $^4J_{H-H}$ = 2.12 Hz, 1 H, 6'-H), 7.77 (d, $^4J_{H-H}$ = 2.04 Hz, 1 H, 8'-H), 8.10 (d, $^3J_{H-H}$ = 8.96 Hz, 1 H, 5'-H), 8.35 (d, $^3J_{H-H}$ = 5.68 Hz, 1 H, 2'-H) ppm – ^{13}C-NMR (100 MHz, MeOD-d_4): δ = 22.68 (Me), 26.80 (C-3), 28.21 (C-2), 40.27 (C-1), 43.75 (C-4), 99.80 (C-3'), 118.95 (C-4'a), 124.47 (C-5'), 126.11 (C-6'), 127.73 (C-8'), 136.48 (C-7'), 149.85 (C-8'a), 152.57 (C-2'), 152.92 (C-4'), 173.48 (amide CO) ppm – MS (EI, 70 eV): m/z (%) = 293.1/292.2/291.2 $[M]^{+\cdot}$ (9/7/30), 207.1/206.1/205.1 $[M-C_4H_8NO]^+$ (33/18/100), 193.1/192.1/191.1 $[M-C_5H_{10}NO]^+$ (17/10/54) – CHN calcd. ($C_{15}H_{18}ClN_3O$) C: 61.75 H: 6.22 N: 14.40; found C: 61.62 H: 6.05 N: 14.31.

N-(4-(Quinolin-4'-ylamino)butyl)acetamide (6)

Compound **5** (28.3 mg, 0.097 mmol) in MeOH (dry, 5 mL) was stirred for 17 h at 25 °C using Pd/C (3.5 mg, 12 % m/m) as catalyst under hydrogen gas atmosphere; the mixture was then filtered and concentrated. Purification with flash column chromatography on alumina (activity level V, MeOH 100 %) gave **6** (23.1 mg, 92 %) as colourless crystals. – Mp 168 °C (MeOH) – IR (ATR-FTIR): $\tilde{\nu}$ = 3194 (w, br), 3057 (w, br), 2922 (w), 2859 (w), 2359 (s), 2341 (s), 1616 (s), 1592 (s), 1549 (s), 1497 (w), 1452 (s), 1372 (m), 1354 (m), 1308 (m), 1286 (m), 1261 (w), 1222 (m), 1198 (w), 1169 (w), 1150 (w), 1122 (w), 1040 (w), 1010 (w), 965 (w), 890 (w), 872 (w), 796 (w), 761 (s), 668 (m), 649 (m), 629 (m), 602 (s) cm^{-1} – ^{1}H-NMR (600 MHz, MeOD-d_4): δ = 1.64-1.69 (m, 2 H, 2-H), 1.80-1.85 (m, 2 H, 3-H), 1.94 (s, 3 H, Me), 3.25 (t, $^3J_{H-H}$ = 6.96 Hz, 2 H, 1-H), 3.60 (t, $^3J_{H-H}$ = 7.29 Hz, 2 H, 4-H), 6.85 (d, $^3J_{H-H}$ = 6.96 Hz, 1 H, 3'-H), 7.66-7.69 (m, 1 H, 6'-H), 7.84 (d, $^3J_{H-H}$ = 8.28 Hz, 1 H, 8'-H), 7.89-7.92 (m, 1 H, 7'-H), 8.37-8.39 (m, 2 H, 2'-H, 5'-H) ppm – ^{13}C-NMR (150 MHz, MeOD-d_4): δ = 22.72 (Me), 26.53 (C-3), 28.07 (C-2), 40.02 (C-1), 44.44 (C-4), 99.36 (C-3'), 118.69 (C-4'a), 122.02 (C-8'), 123.83 (C-5'), 128.02 (C-6'), 134.55 (C-7'), 140.44 (C-8'a), 144.08 (C-2'), 157.32 (C-4'), 173.55 (amide CO) ppm – MS (EI, 70 eV): m/z (%) = 258.2/257.2 $[M]^{+\cdot}$ (7/34), 172.1/171.1 $[M-C_4H_8NO]^+$ (16/92), 158.1/157.1 $[C_{10}H_9N_2]^+$ (14/100), 145.1/144.1 $[C_9H_8N_2]^{+\cdot}$ (27/20) – HRMS (ESI) calcd. $[M+H]^+$ 258.16009; found 258.16009.

N^1-(7'-Chloroquinolin-4'-yl)-N^4-ethylbutane-1,4-diamine (7)

To a solution of amide **5** (110.4 mg, 0.38 mmol) in THF (dry, 30 ml) a commercially available solution of BH_3–DMS (1.90 mmol, 950 µl, 2 mmol/ml THF) was dropped at 0 °C under nitrogen atmosphere. The mixture was heated up to 80 °C and stirred for 5 h under nitrogen atmosphere. The BH_3–DMS excess was hydrolysed with small amounts of water, and the mixture was concentrated. The residue was suspended in MeOH (30 mL) and HCl conc. (1.5 ml) stirring for further 2 hours at 80 °C. The mixture was concentrated, suspended in aqueous Na_2CO_3 solution, and exhaustively extracted using chloroform. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification with flash column chromatography on basic alumina (activity level V, DCM/MeOH 40:1) and recrystallization (acetone/H_2O) gave **7** (69.1 mg, 66 %) as creamy

white crystals. – Mp 88-90 °C (acetone/H_2O) – IR (ATR-FTIR): $\tilde{\nu}$ = 3064 (w, br), 2928 (w, br), 2863 (w, br), 2362 (w), 2342 (w), 1612 (w), 1578 (s), 1539 (m), 1477 (m), 1450 (m), 1430 (m), 1413 (m), 1368 (m), 1331 (m), 1310 (m), 1283 (m), 1246 (w), 1203 (w), 1136 (m), 1079 (w), 904 (w), 869 (w), 854 (m), 803 (m), 787 (m), 765 (m), 745 (m), 643 (m), 621 (m) cm^{-1} – ^{1}H-NMR (400 MHz, MeOD-d_4): δ = 1.11 (t, $^3J_{H-H}$ = 7.16 Hz, 3 H, Me), 1.61-1.69 (m, 2 H, 3-CH_2), 1.74-1.81 (m, 2 H, 3-CH_2), 2.60-2.65 (m, 4 H, 4-CH_2, Et-CH_2), 3.38 (t, $^3J_{H-H}$ = 6.98 Hz, 2 H, 1-CH_2), 6.51 (d, $^3J_{H-H}$ = 5.64 Hz, 1 H, 3'-H), 7.38 (dd, $^3J_{H-H}$ = 9.08 Hz, $^4J_{H-H}$ = 2.24 Hz, 1 H, 6'-H), 7.77 (d, $^4J_{H-H}$ = 2.08 Hz, 1 H, 8'-H), 8.09 (d, $^3J_{H-H}$ = 9.08 Hz, 1 H, 5'-H), 8.34 (d, $^3J_{H-H}$ = 5.60 Hz, 1 H, 2'-H) ppm – ^{13}C-NMR (100 MHz, MeOD-d_4): δ = 14.82 (Me), 27.39 (C-2), 28.23 (C-3), 43.98 (C-1), 44.89 (CH_2), 50.26 (CH_2), 99.79 (C-3'), 118.95 (C-4'a), 124.45 (C-5'), 126.06 (C-6'), 127.77 (C-8'), 136.43 (C-7'), 149.89 (C), 152.60 (C-2'), 152.88 (C) ppm – MS (EI, 70 eV): m/z (%) = 279.1/278.2/277.2 $[M]^{+\cdot}$ (6/8/17), 250.1/249.1/ 248.1 $[M\text{-}C_2H_5]^+$ (6/3/18), 221.1/220.1/219.1 $[M\text{-}C_3H_8N]^+$ (4/4/12), 207.1/206.1/205.1 $[M\text{-}C_4H_{10}N]^+$ (15/12/45), 193.0/192.0/ 191.0 $[M\text{-}C_5H_{12}N]^+$ (23/47/50), 180.0/179.0/178.0 $[C_9H_7ClN_2]^+$ (13/69/14) – HRMS (ESI) calcd. $[M+H]^+$ 278.14185; found 278.14186.

7-Chloro-N-(1-phenylethyl)quinolin-4-amine [(rac)-8, (R)-8 and (S)-8]

Compound **8** was produced in a racemic and in enantiopure forms. Exemplarily described is the procedure for the synthesis of (*rac*)-**8**.

To a beige solution of 4,7-dichloroquinoline (**2**, 712.5 mg, 3.60 mmol) in 1,4-dioxane (dry, 10 mL), a 10 min stirred purple colored suspension of $Pd_2(dba)_3$ (81.0 mg, 0.09 mmol) and (±)-BINAP (113.6 mg, 0.18 mmol) in 1,4-dioxane (dry, 2 mL) was added at 25 °C and under nitrogen atmosphere. (*rac*)-α-methylbenzyl-amine (654 mg, 5.40 mmol, 687 µl) was added, observing the changing of color to yellowish, followed by the addition of KO*t*Bu (807.6 mg, 7.20 mmol). The mixture was stirred for 8 hours at 70 °C, filtered, and concentrated. The residue was suspended in dichloromethane, the organic layer was washed with water several times, dried ($MgSO_4$), filtered and concentrated. Purification with flash column chromatography on silica gel (petroleum ether/EtOAc 2:1) and recrystal-lization (acetone/MeOH) gave (*rac*)-**8** (840 mg, 83 %) as colourless crystals. – Mp 148-149 °C (acetone/MeOH) – (*S*)-Enantiomer: $[\alpha]_D^{20}$ = +350.8 (*c* = 0.5, MeOH), (*R*)-Enantiomer: $[\alpha]_D^{20}$ = -342.5 (*c* = 0.5, MeOH) – IR (ATR-FTIR): $\tilde{\nu}$ = 3205 (w, br), 3085 (w, br), 3056 (w, br), 2980 (w, br), 2928 (w, br), 1608 (w), 1567 (s), 1535 (m), 1489 (m), 1446 (m), 1423 (m), 1375 (m), 1348 (m), 1324 (m), 1276 (m), 1247 (m), 1213 (m), 1177 (w), 1165 (w), 1155 (w), 1138 (m), 1121 (w), 1078 (m), 1028 (w), 1009 (w), 965 (w), 940 (w), 897 (w), 872 (m), 850 (m), 808 (m), 770 (m), 755 (m), 697 (s), 659 (w), 645 (w), 632 (w), 620 (w), 604 (w) cm^{-1} – ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.68 (d, $^3J_{H-H}$ = 6.66 Hz, 3 H, Me), 4.68-4.72 (m, 1 H, 1'-H), 5.53 (s, br, 1 H, NH), 6.21 (d, $^3J_{H-H}$ = 5.52 Hz, 1 H, 3-H), 7.25-7.27 (m, 1 H, *p*-Ph-H), 7.31-7.38 (m, 5 H, *o*-Ph-H, *m*-Ph-H, 6-H), 7.83 (d, $^3J_{H-H}$ = 9.00 Hz, 1 H, 5-H), 7.94 (d, $^4J_{H-H}$ = 2.04 Hz, 1 H, 8-H), 8.33 (d, $^3J_{H-H}$ = 5.46 Hz, 1 H, 2-H) ppm –^{13}C-NMR (150 MHz, $CDCl_3$): δ = 24.68 (Me), 53.48 (C-1'), 100.93 (C-3), 117.16 (C-4a), 121.29 (C-5), 125.85 (C-6), 127.83 (*p*-Ph-CH), 128.46 (C-8), 129.22 (*o*-Ph-CH, *m*-Ph-CH), 135.40 (C-7), 143.06 (Ph-C), 148.48 (C-8a), 149.13 (C-4), 151.37 (C-2) ppm – MS (EI, 70 eV): m/z (%) = 284.2/283.2/282.2 $[M]^{+\cdot}$ (10/6/29), 180.1/179.1/178.1 $[C_9H_7ClN_2]^{+\cdot}$ (6/2/17), 106.1/105.1 $[C_8H_9]^+$ (8/100) – HRMS (ESI) calcd. $[M+H]^+$ 283.09965; found 283.09965.

Ethylated derivatives 9, 10, and 11

To a solution of amine **3** (337.4 mg, 1.35 mmol) and DIPEA (526.0 mg, 4.07 mmol, 709 µL) in DMF (dry, 2 mL), ethyl bromide (323.6 mg, 2.97 mmol, 222 µL) was added and stirred for 18 h at 25 °C. DMF was removed using high vacuum, the residue was suspended in dichloromethane, filtered, and concentrated. Purification with flash column chromatography on neutral alumina (activity level V, DCM/MeOH 50:1, followed by DCM/MeOH 20:1) gave compounds **9** (85.9 mg, 21 %) as beige crystals, **10** (72.9 mg, 13 %) as colourless oil, and **11** (22.5 mg, 4 %) as yellowish oil.

N^1-(7-Chloroquinolin-4-yl)-N^4,N^4-diethylbutane-1,4-diamine (9)

Mp 85 °C (DCM/MeOH) – IR (ATR-FTIR): $\tilde{\nu}$ = 3725 (w), 3702 (w), 3649 (w), 3628 (w), 3208 (w, br), 3060 (w), 2952 (m), 2926 (m), 2864 (m), 2794 (m), 2724 (w), 2360 (s), 2341 (s), 1612 (w), 1578 (s), 1542 (m), 1489 (w), 1452 (m), 1428 (m), 1379 (m), 1369 (m), 1355 (m), 1329 (m), 1300 (m), 1276 (m), 1254 (m), 1231 (m), 1197 (m), 1164 (m), 1138 (s), 1105 (w), 1089 (m), 1080 (m), 1041 (w), 991 (w), 946 (w), 920 (w), 898 (m), 867 (m), 852 (m), 826 (m), 803 (s), 763 (m), 750 (m), 720 (w), 680 (m), 669 (m), 653 (m), 639 (m), 620 (m), 608 (w) cm^{-1} – ^{1}H-NMR (400 MHz, MeOD-d_4): δ = 1.04 (t, $^3J_{H-H}$ = 7.18 Hz, 6 H, Me), 1.58-1.66 (m, 2 H, 3-CH_2), 1.70-1.78 (m, 2 H, 2-CH_2), 2.49-2.59 (m, 6 H, 4-CH_2, Et-CH_2), 3.38 (t, $^3J_{H-H}$ = 6.92 Hz, 2 H, 1-CH_2), 6.51 (d, $^3J_{H-H}$ = 5.60 Hz, 1 H, 3'-H), 7.38 (dd, $^3J_{H-H}$ = 9.00 Hz, $^4J_{H-H}$ = 1.96 Hz, 1 H, 6'-H), 7.77 (d, $^4J_{H-H}$ = 2.08 Hz, 1 H, 8'-H), 8.09 (d, $^3J_{H-H}$ = 9.08 Hz, 1 H, 5'-H), 8.34 (d, $^3J_{H-H}$ = 5.64 Hz, 1 H, 2'-H) ppm – ^{13}C-NMR (100 MHz, MeOD-d_4): δ = 11.35 (Me), 25.12 (CH_2), 27.66 (CH_2), 43.99 (C-4), 47.85 (Et-CH_2), 53.66 (C-1), 99.81 (C-3'), 118.95 (C-4'a), 124.45 (C-5'), 126.06 (C-6'), 127.77 (C-8'), 136.44 (C-7'), 149.89 (C-8'a), 152.60 (C-2'), 152.88 (C-4') ppm – MS (EI, 70 eV): m/z (%) = 307.1/306.1/305.1 $[M]^{+\cdot}$ (3/5/8), 234.0/233.0 $[M-C_4H_{10}N]^+$ (4/7), 191.0 $[C_{10}H_8ClN_2]^+$ (3), 87.1/86.1 $[C_5H_{12}N]^+$ (10/100) – HRMS (ESI) calcd. $M+H]^+$ 306.17315; found 306.17314.

4-(7'-Chloroquinolin-4'-ylamino)-N,N,N-triethylbutane-1-aminium bromide (10)

IR (ATR-FTIR): $\tilde{\nu}$ = 3265 (w, br), 2985 (w, br), 2950 (w, br), 1610 (m), 1577 (s), 1539 (m), 1484 (w), 1451 (m), 1426 (w), 1394 (w), 1367 (m), 1330 (m), 1279 (w), 1249 (w), 1217 (w), 1199 (w), 1188 (w), 1160 (w), 1138 (w), 1078 (w), 1006 (w), 956 (w), 901 (w), 880 (w), 851 (m), 807 (m), 772 (w), 729 (w), 700 (w), 646 (w), 633 (w), 622 (w), 612 (w), 601 (w) cm^{-1} – ^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 1.26 (t, $^3J_{H-H}$ = 7.18 Hz, 9 H, Et-CH_3), 1.85-1.90 (m, 4 H, 2-CH_2, 3-CH_2), 3.26 (q, $^3J_{H-H}$ = 7.28 Hz, 6 H, Et-CH_2), 3.43-3.47 (m, 4 H, 4-CH_2), 6.30 (d, $^3J_{H-H}$ = 5.44, 1 H, 3'-H), 7.32 (dd, $^3J_{H-H}$ = 9.00 Hz, $^4J_{H-H}$ = 2.20 Hz, 1 H, 6'-H), 7.81 (d, $^4J_{H-H}$ = 2.20 Hz, 1 H, 8'-H), 7.90 (t, $^3J_{H-H}$ = 5.00 Hz, 1 H, NH), 8.39 (d, $^3J_{H-H}$ = 5.36 Hz, 1 H, 2'-H), 8.87 (d, $^3J_{H-H}$ = 9.04 Hz, 1 H, 5'-H) ppm – ^{13}C-NMR (100 MHz, CD_2Cl_2): δ = 8.32 (Et-CH_3), 20.11 (CH_2), 24.73 (CH_2), 41.67 (C-4), 53.93 (Et-CH_2), 58.17 (C-1), 98.87 (C-3'), 118.66 (C-4'a), 125.04 (C-6'), 125.91 (C-5'), 128.32 (C-8'), 134.93 (C-7'), 150.13 (C-4'), 151.23 (C-8'a), 152.37 (C-2') ppm – MS (EI, 70 eV): m/z (%) = 306.1/305.1/304.1 $[M-C_2H_6-Br]^+$ (10/11/23), 235.1/234.1/233.1 $[C_{13}H_{14}ClN_2]^+$ (8/9/28), 221.1/220.1/219.0 $[C_{12}H_{12}ClN_2]^+$ (4/4/11), 207.1/206.0/205.0 $[C_{11}H_{10}ClN_2]^+$ (9/9/4), 193.0/192.0/191.0 $[C_{10}H_8ClN_2]^+$ (4/4/10), 87.1/86.1 $[C_4H_{10}N_2]^{+\cdot}$ (6/100) – HRMS (ESI) calcd. $[M]^+$ 334.20445; found 334.20433.

7-Chloro-4-(4'-(diethylamino)butylamino)-1-ethylquinolinium bromide (11)

IR (ATR-FTIR): $\tilde{\nu}$ = 3404 (w, br), 3153 (w, br), 3046 (w, br), 2965 (m), 2934 (m), 2868 (m), 2799 (m), 2360 (s), 2341 (m), 1610 (s), 1578 (s), 1468 (m), 1441 (m), 1379 (m), 1287 (w), 1261 (m), 1226 (s), 1197 (w), 1165 (m), 1116 (m), 1083 (m), 1039 (m), 996 (w), 948 (m), 898 (w), 866 (m), 847 (m), 805 (m), 774 (m), 730 (m), 679 (m), 668 (m), 651 (m), 616 (m) cm^{-1} – ^{1}H-NMR (600 MHz, MeOD-d_4): δ = 1.05 (t, $^3J_{H-H}$ = 7.20 Hz, 6 H, Et-CH_3), 1.52 (t, $^3J_{H-H}$ = 7.20 Hz, 3 H, N^1-Et-CH_3), 1.61-1.66 (m, 2 H, 3'-CH_2), 1.76-1.81 (m, 2 H, 2'-CH_2), 2.51-2.54 (m, 2 H, 4'-CH_2), 2.58 (q, $^3J_{H-H}$ = 7.20 Hz, 4 H, Et-CH_2), 3.59 (t, $^3J_{H-H}$ = 7.20 Hz, 2 H, 1'-CH_2), 4.54 (q, $^3J_{H-H}$ = 7.20 Hz, 2 H, N^1-CH_2), 6.84 (d, $^3J_{H-H}$ = 7.56 Hz, 1 H, 3-H), 7.71 (dd, $^3J_{H-H}$ = 8.94 Hz, $^4J_{H-H}$ = 1.62 Hz, 1 H, 6-H), 8.14 (d, $^4J_{H-H}$ = 1.44 Hz, 1 H, 8-H), 8.39 (d, $^3J_{H-H}$ = 7.56 Hz, 1 H, 2-H), 8.43 (d, $^3J_{H-H}$ = 9.0 Hz, 1 H, 5-H) ppm – ^{13}C-NMR (150 MHz, MeOD-d_4): δ = 11.37 (Et-CH_3), 14.99 (N^1-Et-CH_3), 25.06 (C-3'), 27.62 (C-2'), 45.52 (C-1'), 47.82 (Et-CH_2), 50.87 (N^1-CH_2), 53.51 (C-4'), 100.48 (C-3), 118.76 (C-8), 118.98 (C-4a), 127.05 (C-5), 128.34 (C-6), 140.18 (C-8a), 141.57 (C-7), 147.28 (C-2), 157.28 (C-4) ppm – MS (EI, 70 eV): m/z (%) = 335.3/334.3/333.3 $[M-HBr]^{+\cdot}$ (16/11/42), 306.2/305.2/304.2 $[M-HBr-Et]^+$ (33/22/100), 235.1/234.1/233.1 $[M-HBr-Et-NEt_2]^+$ (22/15/60), 221.1/220.1/219.1 (11/12/29), 208.1/207.1/206.1 (11/22/21) – HRMS (ESI) calcd. $[M-Br]^+$ 334.20445; found 334.20445 $[M-Br]^+$.

7-Chloro-N^1-ethyl-4-(4'-(triethylammonio)-butylamino)-quinolinium dibromide (12)

To a solution of amine **3** (205.0 mg, 0.82 mmol) in DMF (dry, 2 mL), Cs_2CO_3 (804.4 mg, 2.47 mmol) and ethyl bromide (554.8 mg, 5.09 mmol, 380 µl) were added and stirred for 24 h at 25 °C. The solvent was removed using high vacuum, the residue was suspended in dichloromethane, filtered, and concentrated. Purification with flash column chromatography on neutral alumina (activity level V, DCM/MeOH 20:1) and recrystalization (DCM/petroleum ether) gave **12** (241.2 mg, 56 %) as a beige solid. – Mp 127 °C (DCM/petroleum ether) – IR (ATR-FTIR): $\tilde{\nu}$ = 3725 (w), 3708 (w), 3312 (w, br), 3214 (w, br), 3088 (w, br), 2977 (w, br), 2360 (s), 2341 (s), 1608 (s), 1578 (m), 1465 (m), 1439 (m), 1399 (m), 1377 (m), 1342 (w), 1281 (w), 1256 (w), 1224 (m), 1164 (w), 1116 (w), 1022 (w), 957 (w), 934 (w), 866 (m), 817 (m), 767 (w), 749 (w), 720 (w), 669 (m), 651 (m), 615 (m), 602 (m) cm^{-1} – ^{1}H-NMR (600 MHz, MeOD-d_4): δ = 1.32 (t, $^3J_{H-H}$ = 7.26 Hz, 9 H, Et-CH_3), 1.54 (t, $^3J_{H-H}$ = 7.26 Hz, 3 H, N^1Et-CH_3), 1.88 (m, 4 H, 2'-CH_2, 3'-CH_2), 3.31 (m, 2 H, 4'-CH_2), 3.36 (q, $^3J_{H-H}$ = 7.26 Hz, 6 H, Et-CH_2), 3.69-3.71 (m, 2 H, 1'-CH_2), 4.61 (q, $^3J_{H-H}$ = 7.26 Hz, 2 H, N^1CH_2), 7.00 (d, $^3J_{H-H}$ = 7.56 Hz, 1 H, 3-H), 7.77 (dd, $^3J_{H-H}$ = 9.00 Hz, $^4J_{H-H}$ = 1.80 Hz, 1 H, 6-H), 8.22 (d, $^4J_{H-H}$ = 1.80 Hz, 1 H, 8-H), 8.55 (d, $^3J_{H-H}$ = 7.56 Hz, 1 H, 2-H), 8.57 (d, $^3J_{H-H}$ = 9.00 Hz, 1 H, 5-H) ppm – ^{13}C-NMR (150 MHz, MeOD-d_4): δ = 7.94 (Et-CH_3), 15.10 (N^1Et-CH_3), 20.64 (C-2'), 26.20 (C-3'), 44.48 (C-1'), 51.23 (N^1CH_2), 54.16 (Et-CH_2), 57.75 (C-4'), 100.74 (C-3), 118.44 (C-4a), 119.02 (C-8), 127.27 (C-5), 128.78 (C-6), 140.11 (C-8a), 141.98 (C-7), 148.10 (C-2), 157.27 (C-4) ppm – MS (EI, 70 eV): m/z (%) = 335.2/334.2/333.2 [M-2HBr-Et]$^{+\cdot}$ (6/4/15), 306.1/305.1/304.1 [M-2HBr-Et_2]$^+$ (16/10/46), 235.1/234.1/233.1 [M-2HBr-Et-NEt_3]$^+$ (10/7/27), 221.1/220.1/219.1 (4/5/14), 86.1 [$NCH_2(CH_3)_2$]$^+$ (100) – HRMS (ESI) calcd. [M-H]$^+$ 362.23575; found 362.23579.

7-Chloroquinolin-4-amine (13)[22-24]

Gaseous ammonia was directed through a solution of 4,7-dichloroquinoline (**2**, 11.907 g, 0.060 mmol) in phenol (58.000 g, 0.616 mol) at 170 °C, the mixture was heated up to 200 °C and stirred for 2.5 hours. After addition of glacial acetic acid (15 mL), water (30 mL), and diethyl ether (100 mL), a colorless solid was obtained and filtered. The residue was dissolved in water, alkalized using aqueous NaOH solution and exhaustively extracted using diethyl ether. The combined organic extracts were dried ($MgSO_4$) and concentrated. Recrystallization (H_2O) gave **13** (8.359 g, 78 %) as colourless crystals. – Mp 152 °C (H_2O) – IR (ATR-FTIR): $\tilde{\nu}$ = 3447 (w), 3355 (w), 3060 (w, br), 1637 (m), 1612 (m), 1574 (s), 1507 (m), 1442 (m), 1369 (w), 1326 (m), 1284 (m), 1200 (m), 1129 (w), 1077 (w), 1019 (w), 909 (m), 877 (m), 855 (m), 837 (m), 812 (s), 760 (m), 732 (m), 643 (m), 626 (m) cm^{-1} – ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.56 (d, $^3J_{H-H}$ = 5.16 Hz, 1 H, 3-H), 7.37 (dd, $^3J_{H-H}$ = 8.96 Hz, $^4J_{H-H}$ = 2.16 Hz, 1 H, 6-H), 7.67 (d, $^3J_{H-H}$ = 8.96 Hz, 1 H, 5-H), 7.96 (d, $^4J_{H-H}$ = 2.04 Hz, 1 H, 8-H), 8.49 (d, $^3J_{H-H}$ = 5.20 Hz, 1 H, 2-H) ppm – ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 104.18 (C-3), 117.34, 121.89, 125.91, 128.99, 135.49 (C-7), 149.71, 149.84 (C-4), 151.96 (C-2) ppm – ^{15}N-NMR: (40.5 MHz, DMSO-d_6): -310.0 (4-NH_2), -110.0 (N-1) ppm – MS (EI, 70 eV): m/z (%) = 180.1/179.1/178.1 [M]$^{+\cdot}$ (34/14/100).

4-Amino-7-chloro-N^1-isopropylquinolinium iodide (14)

2-Iodopropane (1.768 g, 10.40 mmol, 1038 µL) was added dropwise to melted 4-amino-7-chloroquinoline (**13**, 103.2 mg, 0.58 mmol) at 100 °C and the reaction mixture was stirred at 100 °C for 1 hour. The residue was suspended in methanol, alkalized using a small amount of ammonia solution, concentrated, and purified with flash column chromatography on neutral alumina (activity level V, DCM/MeOH 25:1). Recrystallization (MeOH/H_2O) gave **14** (26.2 mg, 14 %) as beige crystals. – Mp 342 °C (decomposition; MeOH/H_2O) – IR (ATR-FTIR): $\tilde{\nu}$ = 3245-3037 (w, br), 2921 (w), 2852 (w), 2472 (w), 2416 (w), 2368 (w), 2312 (m), 1648 (w), 1606 (s), 1562 (m), 1527 (w), 1502 (w), 1459 (m), 1394 (w), 1363 (m), 1334 (w), 1290 (m), 1214 (m), 1178 (m), 1133 (w), 1083 (m), 1025 (m), 1006 (m), 954 (w), 885 (w), 858 (m), 823 (s), 765 (w), 727 (w), 674 (m), 651 (m) cm^{-1} – ^{1}H-NMR (600 MHz, MeOD-d_4): δ = 1.62 (d, $^3J_{H-H}$ = 6.60 Hz,

6 H, *i*Pr-Me), 5.30-5.37 (m, 1 H, *i*Pr-H), 6.90 (d, $^3J_{H-H}$ = 7.44 Hz, 1 H, 3-H), 7.75 (dd, $^3J_{H-H}$ = 8.97 Hz, $^4J_{H-H}$ = 1.83 Hz, 1 H, 6-H), 8.35 (d, $^4J_{H-H}$ = 1.74 Hz, 1 H, 8-H), 8.39 (d, $^3J_{H-H}$ = 8.94 Hz, 1 H, 5-H), 8.56 (d, $^3J_{H-H}$ = 7.44 Hz, 1 H, 2-H) ppm – ^{13}C-NMR (150 MHz, MeOD-d_4): δ = 22.35 (*i*Pr-Me), 54.79 (*i*Pr-CH), 104.54 (C-3), 117.55 (C-4a), 118.59 (C-8), 127.61 (C-5), 128.50 (C-6), 141.11 (C-8a), 142.65 (C-7), 143.29 (C-2), 159.77 (C-4) ppm – MS (EI, 70 eV): m/z (%) = 222.1/221.1/220.1 [M-HI] (13/25/24), 179.0 [M-I-*i*Pr] (100) – HRMS (ESI)calcd. $[M]^+$ 221.08400; found 221.08400 – HRMS (EI) calcd. $[M-H]^{+\cdot}$ 220.07618; found 220.07622.

2-(4'-Bromopentyl)-isoindolin-1,3-dione ((rac)-15)[25,26]

(*Rac*)-1,4-dibromopentane (10.122 g, 0.044 mol, 6.0 mL) was added to a solution of potassium phthalimide (6.050 g, 0.033 mol) in acetone (dry, 35 ml), the reaction mixture was stirred at 80 °C for 24 h, filtered, and concentrated. The residue was purified by distillation and (*rac*)-**15** (6.806 g, 70 %) as yellowish oil was obtained. – Bp 180 °C ($3.4\cdot10^{-1}$ mbar) – IR (ATR-FTIR): $\tilde{\nu}$ = 2955 (w), 2938 (w), 2864 (w), 1771 (w), 1702 (s), 1615 (w), 1465 (w), 1433 (m), 1394 (s), 1376 (m), 1360 (s), 1322 (m), 1303 (w), 1286 (w), 1264 (m), 1243 (m), 1186 (m), 1169 (w), 1157 (w), 1138 (w), 1127 (m), 1083 (m), 1034 (s), 994 (w), 972 (w), 926 (m), 897 (w), 882 (m), 831 (w), 795 (w), 776 (m), 712 (s), 693 (m), 648 (s), 604 (m) cm^{-1} – ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.68 (d, $^3J_{H-H}$ = 6.68 Hz, Me), 1.76-1.95 (m, 4 H, 2'-CH_2, 3'-CH_2), 3.68-3.72 (m, 2 H, 1'-CH_2), 4.10-4.18 (m, 1 H, 4'-CH), 7.69-7.71 (m, 2 H, ar-H), 7.82-7.84 (m, 2 H, ar-H) ppm – ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.66, 27.22, 37.39, 38.31, 50.69 (C-4'), 123.48 (ar-CH), 132.30 (ar-Cq), 134.19 (ar-CH), 168.59 (imide CO) ppm – ^{15}N-NMR: (40.5 MHz, DMSO-d_6): -219.0 (N-2) ppm – MS (EI, 70 eV): m/z (%) = 295.1$[M]^{+\cdot}$ (4), 216.1 $[M-Br]^+$ (74), 160.0 $[M-(CH_2)_2CHBrCH_3]^+$ (100) – CHN calcd. for $C_{13}H_{14}BrNO_2$ C: 52.72 H: 4.76 N: 4.73; found C: 53.64 H: 4.66 N: 4.96.

4-Amino-7-chloro-1-(5'-(1'',3''-dioxoisoindolin-2''-yl)pentan-2'-yl)quinolinium bromide ((rac)-16)

4-Amino-7-chloroquinoline (**13**, 103.0 mg, 0.58 mmol) and the bromine compound (*rac*)-**15** (80.4 mg, 0.27 mmol) were stirred at 160 °C for 30 min. Purification of the remaining solid on deactivated silica gel (petroleum ether/EtOAc 5:1, followed by EtOAc 100 % and chloroform/acetone/methanol 6:3:1) and recrystallization (methanol/EtOAc) gave (*rac*)-**16** (59.1 mg, 55 %) as light beige solid. – Mp 303 °C (decomposition; MeOH/EtOAc) – IR (ATR-FTIR): $\tilde{\nu}$ = 3248 (w), 3073 (w), 2357 (w), 1767 (w), 1707 (s), 1650 (m), 1611 (s), 1558 (w), 1538 (w), 1509 (w), 1477 (w), 1465 (w), 1438 (w), 1402 (m), 1380 (m), 1358 (m), 1331 (m), 1216 (s), 1186 (w), 1170 (m), 1156 (w), 1110 (m), 1050 (s), 988 (w), 886 (w), 859 (m), 840 (w), 820 (m), 720 (m), 712 (m), 661 (w), 641 (m), 614 (w) cm^{-1} – ^{1}H-NMR (600 MHz, MeOD-d_4): δ = 1.59 (d, $^3J_{H-H}$ = 6.36 Hz, 3 H, 1'-Me), 1.63-1.71 (m, 2 H, 4'-CH_2), 1.98-2.10 (m, 2H, 3'-CH_2), 3.63-3.71 (m, 2 H, 5'-CH_2), 5.28 (s, br, 1 H, 2'-H), 6.88 (d, $^3J_{H-H}$ = 7.44 Hz, 1 H, 3-H), 7.70 (dd, $^3J_{H-H}$ = 8.88 Hz, $^4J_{H-H}$ = 1.22 Hz, 1 H, 6-H), 7.78-7.82 (m, 4 H, 4''-H, 5''-H, 6''-H, 7''-H), 8.35-8.37 (m, 2 H, 5-H, 8-H), 8.51 (d, $^3J_{H-H}$ = 7.44 Hz, 1 H, 2-H) ppm – ^{13}C-NMR (150 MHz, MeOD-d_4): δ = 20.75 (C-1'), 25.84 (C-4'), 34.08 (C-3'), 38.27 (C-5'), 57.84 (C-2'), 104.73 (C-3), 117.41 (C-4a), 118.44 (C-5), 124.27 (C-4''), 127.67 (C-8), 128.50 (C-6), 133.41 (C-3''a, C-7''), 135.57 (C-5'', C-6''), 141.50 (C-4), 142.78 (C-7), 143.51 (C-2), 159.78 (C-8a), 169.99 (C-1'', C-3'') ppm – ^{15}N-NMR: (40.5 MHz, DMSO-d_6): -269.0 (4-NH_2), 218.3 (N-2''), 216.6 (N^+-1) ppm – MS (EI, 70 eV): m/z (%) = 395.3/394.3/393.3 $[M-HBr]^{+\cdot}$ (17/13/48), 180.1/179.1/178.1 $[C_9H_7ClN_2]^{+\cdot}$ (12/7/35), 160.1 $[C_9H_6NO_2]^+$ (100) – HRMS (ESI) calcd. $[M-Br]^+$ 394.13168; found 394.13167 $[M-Br]^+$.

4-Amino-1-(5'-(1'',3''-dioxoisoindolin-2''-yl)-pentan-2'-yl)quinolinium bromide ((rac)-17)

A suspension of (*rac*)-**16** (70.0 mg, 0.15 mmol) and Pd/C (7.7 mg, 11 % m/m) as catalyst in MeOH (dry, 6 ml) was stirred at 25 °C for 23 hours under hydrogen gas atmosphere. Filtration, concentration purification with flash column chromatography on neutral alumina (activity level V, (DCM/MeOH 20:1) and recrystallization (MeOH/EtOAc) gave **(***rac***)-17** (30.5 mg, 46 %) as light beige crystals. – Mp 137 °C (MeOH/EtOAc) – IR (ATR-FTIR): $\tilde{\nu}$ = 3330 (w, br), 3093 (w, br), 2938 (w), 2360 (w), 1770 (w),

1700 (s), 1660 (m), 1612 (s), 1563 (w), 1546 (w), 1498 (w), 1465 (w), 1436 (w), 1398 (m), 1361 (w), 1332 (w), 1268 (w), 1245 (w), 1218 (w), 1172 (m), 1049 (m), 1000 (w), 881 (w), 838 (w), 779 (w), 717 (s), 651 (m), 626 (m) cm^{-1} – ^{1}H-NMR (600 MHz, MeOD-d_4): δ = 1.60-1.61 (m, 4 H, Me, 4'-H), 1.65-1.72 (m, 1 H, 4'-H), 2.00-2.06 (m, 2 H, 3'-H), 3.66 (t, $^3J_{H-H}$ = 6.90 Hz, 2 H, 5'-H), 5.35 (m, 1 H, 2'-H), 6.90 (d, $^3J_{H-H}$ = 7.32 Hz, 1 H, 3-H), 7.69-7.72 (m, 1 H, 6-H), 7.77-7.80 (m, 4 H, 4''-H, 5''-H, 6''-H, 7''-H), 8.00-8.03 (m, 1 H, 7-H), 8.27 (d, $^3J_{H-H}$ = 9.12 Hz, 1 H, 8-H), 8.37 (dd, $^3J_{H-H}$ = 8.40 Hz, $^4J_{H-H}$ = 1.14 Hz, 1 H, 5-H), 8.52 (d, $^3J_{H-H}$ = 7.44 Hz, 1 H, 2-H) ppm – ^{13}C-NMR (150 MHz, MeOD-d_4): δ = 20.82 (Me), 25.97 (C-4'), 34.23 (C-3'), 38.29 (C-5'), 57.46 (C-2'), 104.15 (C-3), 118.57 (C-8), 118.86 (C-4a), 124.24 (CH), 125.79 (C-5), 127.88 (C-6), 133.38 (C-3''a, C-7''a), 135.55 (C-4'', C-7''), 136.10 (C-7), 140.66 (C-8a), 142.89 (C-2), 159.86 (C-4), 169.93 (C-1'', C-3'') ppm – MS (EI, 70 eV): m/z (%) = 361.2/360.2/359.2 $[M-H]^{+\cdot}$ (4/24/97), 161.0/160.0 $[C_9H_6NO_2]^+$ (12/100) – HRMS (ESI) calcd. $[M]^+$ 360.17065; found 360.17062.

N^1-(5'-(1'',3''-Dioxoisoindolin-2''-yl)pentan-2'-yl)quinolinium bromide ((rac)-19)

Quinoline (21.2 mg, 0.16 mmol) and the bromine derivative (*rac*)-**15** (106.2 mg, 0.36 mmol) were stirred for 2.5 h at 100 °C. Purification of the remaining solid with flash column chromatography on neutral alumina (activity level V, DCM/MeOH 20:1) gave (*rac*)-1**9** (3.8 mg, 6 %) as a reddish brown solid. – Mp 215 °C (DCM/MeOH) – IR (ATR-FTIR): $\widetilde{\nu}$ = 3729 (w, br), 3592 (w, br), 3311 (w, br), 2921 (m), 2852 (m), 2360 (s), 2337 (s), 2107 (w), 1760 (w), 1708 (s), 1594 (w), 1523 (w), 1459 (m), 1402 (m), 1371 (s), 1220 (m), 1051 (s), 983 (s), 881 (s), 804 (m), 775 (m), 717 (m), 619 (s) cm^{-1} – ^{1}H-NMR (600 MHz, MeOD-d_4): δ = 1.69 (m, 2 H, 4'-H), 1.81 (d, $^3J_{H-H}$ = 5.22 Hz, 3 H, Me), 2.24 (m, 2 H, 5'-H), 3.70-3.72 (m, 2 H, 3'-H), 5.90 (m, br, 1 H, 2'-H), 7.78-7.82 (m, 4 H, 4''-H, 5''-H, 6''-H, 7''-H), 8.03-8.06 (m, 1 H, 7-H), 8.12-8.14 (m, 1 H, 3-H), 8.27-8.32 (m, 1 H, 6-H), 8.44 (d, $^3J_{H-H}$ = 8.16 Hz, 1 H, 8-H), 8.72 (d, $^3J_{H-H}$ = 9.18 Hz, 1 H, 5-H), 9.20 (d, $^3J_{H-H}$ = 8.28 Hz, 1 H, 4-H), 9.50 (d, $^3J_{H-H}$ = 5.94 Hz, 1 H, 2-H) ppm – ^{13}C-NMR (150 MHz, MeOD-d_4): δ = 21.31 (Me), 25.96 (C-4'), 34.90 (C-5'), 38.16 (C-3'), 62.21 (C-2'), 119.23 (C-5), 123.45 (C-3), 124.30 (CH), 131.44 (C-7), 132.08 (C-4a), 132.61 (C-8), 133.43 (C-3''a, C-7''a), 135.59 (CH), 137.62 (C-6), 140.16 (C-8a), 147.15 (C-2), 149.10 (C-4), 169.99 (C-1'', C-3'') ppm – MS (EI, 70 eV): m/z (%) = 161.0/160.0 $[C_9H_6NO_2]^+$ (15/100), 130.0/129.0 $[C_9H_7N]^{+\cdot}$ (14/41) – HRMS (ESI) calcd. $[M]^+$ 345.15975; found 345.16016.

tert-Butyl benzyl(4-bromobutyl)-carbamate (20)

To a solution of Boc protected benzylamine (4.789 g, 21.6 mmol) in DMF (dry, 50 ml), NaH (3.048 g of a 55 % oily dispersion, 69.8 mmol) was added at 0 °C under nitrogen atmosphere and stirred at 0 °C for 30 min. 1,4-dibromobutane (8.3 mL, 15.006 g, 69.5 mmol) was added at 0°C, and the reaction mixture was stirred for 3 h. The excess of NaH was carefully hydrolyzed using water, and the aqueous phase was exhaustively extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), and the solvent was azeotropically removed as a mixture with toluene. Purification with flash column chromatography on silica gel (petroleum ether/EtOAc 10:1) gave **20** (2.019 g, 27 %) as colourless oil. – IR (ATR-FTIR): $\widetilde{\nu}$ = 2971 (w), 2931 (w), 1687 (s), 1454 (m), 1413 (m), 1363 (m), 1299 (w), 1241 (m), 1151 (s), 1108 (w), 1074 (w), 1029 (w) cm^{-1} – ^{1}H-NMR (600 MHz, $CDCl_3$, +2 °C): δ = 1.41 (s, 9 H, *t*Bu-Me), 1.48 (s, 9 H, *t*Bu-Me), 1.56-1.66 (m, 4 H, 2-CH_2), 1.75-1.82 (m, 4 H, 3-CH_2), 3.12 (t, $^3J_{H-H}$ = 7.08 Hz, 2 H, 1-CH_2), 3.22 (t, $^3J_{H-H}$ = 7.20 Hz, 2 H, 1-CH_2), 3.34-3.39 (m, 4 H, 4-CH_2), 4.38 (s, 2 H, CH_2Ph), 4.43 (s, 2 H, CH_2Ph), 7.18-7.25 (m, 6 H, *o*-Ph-H, *p*-Ph-H), 7.29-7.32 (m, 4 H, *m*-Ph-H) ppm – ^{13}C-NMR (150 MHz, $CDCl_3$, +2 °C): δ = 26.54 (C-2), 26.77 (C-2), 28.56 (*t*Bu-Me), 28.63 (*t*Bu-Me), 30.05 (C-3), 33.67 (C-4), 33.92 (C-4), 45.41 (C-1), 45.50 (C-1), 49.74 (CH_2Ph), 50.39 (CH_2Ph), 80.03 (*t*Bu-C), 80.05 (*t*Bu-C), 127.29 (Ph-CH), 127.35 (Ph-CH), 127.41 (Ph-CH), 127.85 (Ph-CH), 128.68 (*m*-Ph-CH), 128.71 (*m*-Ph-CH), 138.34 (Ph-C), 138.57 (Ph-C), 155.84 (Boc CO), 156.19 (Boc CO) ppm – MS (EI, 70 eV): m/z (%) = 287.1/286.1/285.1 $[M-C_4H_8]^{+\cdot}$ (30/8/29), 91.1 $[C_7H_7]^+$ (100) – HRMS (ESI) calcd. $[M+H]^+$ 342.10632; found 342.10631 $[M+H]^+$.

4-Amino-1-(4'-(benzyl(tert-butoxycarbonyl)-amino)butyl)-7-chloroquinolinium bromide (21)

A solution of the bromine derivative **20** (256.6 mg, 0.75 mmol in 0.5 ml DCM) was added by drops to the melted 4-amino-7-chloroquinoline (**13**, 88.3 mg, 0.49 mmol) at 150 °C, and the reaction mixture was stirred for 1 hour at 150 °C. The residue was suspended in methanol, alkalized using ammonia solution, and concentrated. Purification with flash column chromatography on neutral alumina (activity level V, EtOAc 100 %, followed by DCM/MeOH 20:1 and DCM/MeOH 10:1) and recrystallization (DCM/MeOH/petroleum ether) gave **21** (81.3 mg, 33 %) as a colorless crystals. – Mp 207 °C (DCM/MeOH/petroleum ether) – IR (ATR-FTIR): $\tilde{\nu}$ = 3531 (w, br), 3466 (w, br), 3272 (w, br), 3090 (m, br), 3033 (m), 2975 (w), 2944 (w), 2359 (w, br), 2342 (w, br), 1669 (s), 1647 (s), 1613 (s), 1558 (m), 1536 (m), 1508 (m), 1496 (w), 1479 (m), 1465 (m), 1421 (m), 1382 (m), 1364 (m), 1310 (w), 1289 (w), 1272 (w), 1224 (s), 1158 (s), 1129 (m), 1103 (m), 1076 (w), 1051 (m), 1010 (w), 978 (w), 922 (w), 897 (w), 868 (s), 842 (w), 819 (s), 777 (w), 765 (w), 752 (w), 727 (w), 695 (m), 668 (w), 647 (w), 616 (m) cm^{-1} – ^{1}H-NMR (600 MHz, MeOD-d_4, +2 °C): δ = 1.42-1.49 (m, 20 H, *t*Bu-Me, 3'-CH_2), 1.53-1.56 (m, 2 H, 3'-CH_2), 1.77-1.82 (m, 4 H, 2'-CH_2), 3.20-3.22 (m, 2 H, 4'-CH_2), 3.29-3.31 (m, 2 H, 4'-CH_2), 4.40 (s, br, 2 H, CH_2Ph), 4.42 (s, br, 2 H, CH_2Ph), 4.49-4.54 (m, 4 H, 1'-CH_2), 6.78 (d, $^3J_{H-H}$ = 7.26 Hz, 2 H, 3-H), 7.19-7.28 (m, 10 H, Ph-H), 7.75-7.77 (m, 2 H, 6-H), 8.17 (s, br, 1 H, 8-H), 8.21 (s, br, 1 H, 8-H), 8.33-8.40 (m, 4 H, 2-H, 5-H) ppm – ^{13}C-NMR (150 MHz, MeOD-d_4, +2 °C): δ = 26.13 (C-3'), 26.74 (C-3'), 27.48 (C-2'), 27.74 (C-2'), 28.75 (*t*Bu-Me), 47.46 (C-4'), 48.05 (C-4'), 51.53 (CH_2Ph), 51.98 (CH_2Ph), 55.47 (C-1'), 55.56 (C-1'), 81.49 (*t*Bu-C), 81.59 (*t*Bu-C), 103.96 (C-3), 117.53 (C-4a), 119.06 (C-8), 127.63 (C-5), 127.69 (C-5), 128.40 (Ph-CH), 128.45 (Ph-CH), 128.63 (C-6), 128.68 (C-6), 129.66 (Ph-CH), 139.82 (Ph-C), 140.05 (Ph-C), 140.70 (C-8a), 140.79 (C-8a), 142.44 (C-7), 147.88 (C-2), 157.68 (Boc CO), 157.78 (Boc CO), 160.11 (C-4) ppm – MS (EI, 70 eV): m/z (%) = 180.3/179.3/178.2 $[C_9H_7ClN_2]^{+\cdot}$ (42/63/57), 162.3/161.3 $[C_{11}H_{15}N]^{+\cdot}$ (6/ 42), 92.2/91.2 $[C_7H_7]^+$ (16/100) – HRMS (ESI) calcd. $[M]^+$ 440.20993, found 440.20993 $[M]^+$.

4-Amino-1-(4'-benzylamino)butyl)-7-chloro-quinolinium bromide (22)

HCl conc. (0.5 ml) was added to a solution of **21** (38.0 mg, 0.073 mmol) in MeOH (5 mL) at 25 °C, the reaction mixture was stirred for 15 h at 25°C and concentrated. Purification with flash column chromatography on alumina (activity level V, DCM/MeOH 10:1) and recrystallization (DCM/MeOH/petroleum ether) gave **22** (25.1 mg, 92 %) as light beige crystals. – Mp 222 °C (CH_2Cl_2/MeOH/petroleum ether) – IR (ATR-FTIR): $\tilde{\nu}$ = 3017 (w, br), 2358 (w), 2256 (w), 1660 (m), 1610 (s), 1558 (m), 1535 (m), 1512 (m), 1463 (m), 1383 (m), 1339 (w), 1230 (m), 1173 (w), 1100 (m), 1050 (m), 1027 (w), 909 (w), 869 (m), 822 (s), 733 (m), 719 (m), 695 (s), 651 (m), 626 (m), 616 (m) cm^{-1} – ^{1}H-NMR (600 MHz, MeOD-d_4): δ = 1.57-1.62 (m, 2 H, 3'-CH_2), 1.90-1.95 (m, 2 H, 2'-CH_2), 2.63 (t, $^3J_{H-H}$ = 7.32 Hz, 4'-CH_2), 3.74 (s, 2 H, CH_2Ph), 4.54 (t, $^3J_{H-H}$ = 7.41 Hz, 2 H, 1'-CH_2), 6.82 (d, $^3J_{H-H}$ = 7.26 Hz, 1 H, 3-H), 7.22-7.26 (m, 1 H, *p*-Ph-H), 7.30-7.31 (m, 4 H, *o*-Ph-H, *m*-Ph-H), 7.74 (dd, $^3J_{H-H}$ = 8.96 Hz, $^4J_{H-H}$ = 1.82 Hz, 1 H, 6-H), 8.20 (d, $^4J_{H-H}$ = 1.68 Hz, 1 H, 8-H), 8.38-8.40 (m, 2 H, 2-H, 5-H) ppm – ^{13}C-NMR (150 MHz, MeOD-d_4): δ = 27.27 (C-3'), 28.16 (C-2'), 49.25 (C-4'), 54.54 (CH_2Ph), 55.75 (C-1'), 104.06 (C-3), 117.55 (C-4a), 119.06 (C-8), 127.62 (C-5), 128.40 (*p*-Ph-CH), 128.64 (C-6), 129.63 (Ph-CH), 129.71 (Ph-CH), 140.56 (Ph-C), 140.87 (C-8a), 142.51 (C-7), 147.86 (C-2), 160.16 (C-4) ppm – MS (EI, 70 eV): m/z (%) = 180.0/179.0/178.0 $[C_9H_7ClN_2]^{+\cdot}$ (16/15/46), 162.1/161.1 $[C_{11}H_{15}N]^{+\cdot}$ (7/ 15), 92.1/91.1 $[C_7H_7]^+$ (11/100) – HRMS (ESI) calcd. $[M]^+$ 340.15750; found 340.15748.

1,1'-(Butane-1'',4''-diyl)bis(4-amino-7-chloroquinolinium) dibromide (23)

1,4-Dibromobutane (38.0 mg, 0.18 mmol, 21 µL) was added to melted 4-amino-7-chloroquinoline (**13**, 125.3 mg, 0.70 mmol) at 150 °C, and the reaction mixture was stirred for 1 h at 150 °C. The remaining solid was suspended in methanol, alkalized using ammonia solution, and concentrated. Recrystallization (acetone/H_2O/ petroleum ether) gave **23** (51.8 mg, 50 %) as

yellow crystals. – Mp > 350 °C (decomposition; acetone/H_2O/petroleum ether) – IR (ATR-FTIR): $\tilde{\nu}$ = 3241 (w, br), 3065 (m, br), 2452 (w), 2358 (w), 2321 (w), 2270 (w), 1793 (w), 1650 (m), 1610 (s), 1560 (m), 1531 (m), 1509 (m), 1460 (m), 1381 (m), 1310 (w), 1251 (w), 1227 (s), 1159 (w), 1097 (m), 1049 (m), 1018 (w), 929 (w), 868 (m), 850 (m), 823 (s), 760 (w), 717 (w), 691 (w), 668 (w), 641 (m), 628 (m), 611 (m) cm^{-1} – ^{1}H-NMR (600 MHz, D_2O): δ = 1.84-1.89 (m, 4 H, 2''-CH_2, 3''-CH_2), 4.41-4.46 (m, 4 H, 1''-CH_2, 4''-CH_2), 6.68 0 eV): m/z (%) = 412.1/411.1/410.1 $[M\text{-}2HBr]^{+\cdot}$ (29/21/40), 180.0/179.0/178.0 $[C_9H_7ClN_2]^{+\cdot}$ – HRMS (ESI) calcd. $[M\text{-}H]^+$ 411.11378; found 411.11378.

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(d, $^3J_{H\text{-}H}$ = 7.24 Hz, 2 H, 3-H, 3'-H), 7.60 (dd, $^3J_{H\text{-}H}$ = 9.00 Hz, $^4J_{H\text{-}H}$ = 1.68 Hz, 2 H, 6-H, 6'-H), 7.68 (d, $^4J_{H\text{-}H}$ = 1.52 Hz, 8-H, 8'-H), 7.92 (d, $^3J_{H\text{-}H}$ = 9.00 Hz, 2 H, 5-H, 5'-H), 8.12 (d, $^3J_{H\text{-}H}$ = 7.24 Hz, 2 H, 2-H, 2'-H) ppm – ^{13}C-NMR (150 MHz, D_2O): δ = 22.47 (C-2'', C-3''), 54.73 (C-1'', C-4''), 102.53 (C-3, C-3'), 115.36 (C-4a, C-4'a), 117.91 (C-8, C-8'), 126.58 (C-5, C-5'), 127.75 (C-6, C-6'), 137.96 (C-8a, C-8'a), 141.05 (C-7, C-7'), 147.46 (C-2, C-2'), 157.79 (C-4, C-4') ppm – MS (EI, 7

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