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Optimized and convergent synthesis of potent anti-malarial aminoquinoline compounds: easy access to analogs

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Abstract

Amodiaquine is one of the most active antimalarial 4-aminoquinoline. Previously we have described new analogs of amodiaquine and amopyroquine, in which the hydroxyl group was replaced by various amino groups and identified highly potent compounds. Here we describe a more efficient synthesis of this family of compounds allowing the rapid and convergent access of new analogs bearing a piperazine or a morpholine ring at the 4′-position and diverse heterocyclic amino side chains.

Keywords: antimalarials; 4-aminoquinolines; morpholine; piperazine.

Introduction

In spite of the recent decline of the pathology, malaria remains a major health problem. In 2008, there were an estimated 243 million cases of malaria worldwide and about 860 000 deaths in more than 100 countries (Vangapandu et al., 2007; 2009 WHO report), but 85–90% of cases and deaths were in the African Region. Malaria is one of the main obstacles to socio-economic development in sub-Saharian Africa and other tropical regions in the world. The need for new therapy is still relevant.

Chloroquine (CQ, Figure 1) was a mainstream drug in the fight against *Plasmodium falciparum*, but its efficacy is eroded by the emergence of resistant parasites. Quinoline antimalarials are concentrated in the parasite food vacuole and are thought to exert their activity by preventing effective formation of hemozoin by interacting to heme through π-π stacking of their planar aromatic structures, resulting in heme-mediated toxicity to the parasite (Vippagunta et al., 1999). The lack of an enzyme drug target for quinoline antimalarials is probably a chief reason why resistance development to these drugs is relatively slow. Amodiaquine (AQ, Figure 1), another 4-aminoquinoline proved to be effective against CQ-resistant strains (Rieckmann, 1971; Ridley, 2002). But in the 1980s, cases of agranulocytosis, neutropenia and hepatisis were reported associated with AQ prophylaxis and its use was halted (Hatton et al., 1986; Thomas et al., 2004). AQ toxicity has been explained by the presence of its 4-hydroxyanilino moiety, which is believed to undergo extensive metabolization by cytochrome P450 to its quinoneimine variant (Maggs et al., 1988; Harrison et al., 1992). Nevertheless AQ is commercialized in combination with an artemisinin derivatives as Arsucam® speciality.

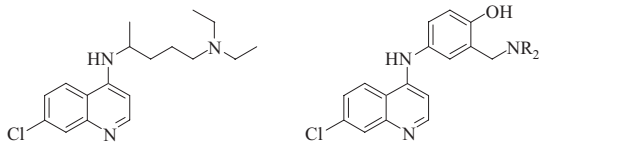
We recently evaluated the effects of the 4′-hydroxyl group substitution (Delarue-Cochin et al., 2008a,b) and demonstrated that derivatives substituted in 4′-position with an alkyl, aryl or heteroaryl group **1** (Paunescu et al., 2009) or 5′-position with an amido **2** (Delarue et al., 2001) or an amino **3** (Delarue-Cochin et al., 2008a,b) functionality presented good *in vitro* nanomolar antimalarial activities (Figure 2). More excitingly, we developed a series of analogs where 4′-hydroxy group was replaced by various amino substituents **4** (Paunescu et al., 2008). Furthermore, as AQ-analogs obtained by the replacement of the *N*-diethylamino function of the side chain, with a pyrrolidine cycle (amopyroquine, ApQ) or a *N-tert*-butyl group were proved to be as active and metabolically less labile (Hawley et al., 1996; Verdier et al., 1989), we completed our study with the development of parallel ApQ-analogs series. The substitution of 4′-hydroxy by *N*-methylpiperazine (compound **5**) or morpholine (compound **6**) provided low nanomolar activity upon K1 chloroquino-resistant strain and low cytotoxicity (Paunescu et al., 2008).

In this study, we optimized the synthetic process and synthesized a family of analogs (Figure 3).

Results and discussion

A first synthesis of 4′-amino analogs was described as a six-step procedure and global yields were about 30% (Paunescu et al., 2008). Moreover, the introduction of the amino functions was the third and fourth step, avoiding convergent and rapid access to analogs. We developed a process in which the diverse amino function NR_3R_4 was introduced in the last synthetic step.

Starting from commercially available 2-fluoro-5-nitrobenzaldehyde, the target compounds could be obtained in a 5 step-synthesis with high yields (Scheme 1). As previously described by our laboratory, benzyl alcohol **7** could easily be obtained with a quantitative yield (Paunescu et al., 2008). Aromatic nucleophilic substitution of fluorine atom with *N*-methylpiperazine or morpholine provided intermediates **8** and **14** with high yield of 94% and 99% respectively. Next several conditions for the reduction of the nitro group were



Chloroquine (CQ)

Amodiaquine (AQ): NR_2=NEt_2
Amopyroquine (ApQ): NR_2=pyrrolidino

Figure 1 Structure of some aminoquinoline anti-malarial compounds.

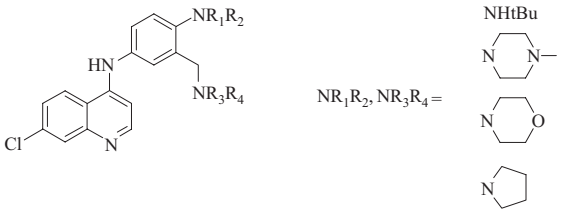


Figure 3 Target compounds.

tested: tin chloride, iron chloride. Optimized conditions were obtained using hydrogen transfert with ammonium formate and Pd/C in ethanol. Compounds **9** and **15** were obtained in quantitative yield without need of purification. Nucleophilic aromatic substitution of the chlorine atom in position 4 of the 4,7-dichloroquinoline allowed the synthesis of derivatives **10** and **16**. In this case, the use of acidic conditions to enhance the electrophilic character of quinoline C-4 was not necessary. In the last step, benzyl alcohol was activated with thionyl chloride and substituted in one pot by various amines in NMP (*N*-methylpyrrolidone) with yields over 80%. With this synthetic route compounds **5** and **6** were obtained with global yield of 65% and 75% respectively, compared with only 23% and 37% in the last procedure.

Conclusion

Despite recent progress, malaria still remains a major health problem. Aminoquinoline derivatives are historically interesting compounds to treat his pathology. We have described a new synthesis of a potent amodiaquine analogs devoided of potential metabolic instability and the convergent access to analogs. Further work will evaluate the metabolic stability and the anti malarial activity of these new analogs.

Experimental section

All reactions were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker 300 MHz spectrometer, chemical shifts (δ) were expressed in ppm relative to TMS used as an internal standard. Purity and identity of intermediate compounds were checked by LCMS, using a Waters Alliance 2695 system (X-Terra column, ionization mass spectrometer). The following eluent systems were used: a (H_2O/TFA, 100:0.01) and B (CH_3CN/H_2O/TFA, 80:20:0.01). Retention times (t_R) were obtained, at flow rate of 0.3 ml/min, using the following conditions: a gradient run from 100% eluent A to 100% eluent B over 8 min, then 100% eluent B for 90 s. The purity of final compounds was verified by two types of high pressure liquid chromatography (HPLC) columns: C18 Deltapak (C18N) and C4 Interchrom UP5WC4-25QS (C4) on a Shimadzu system equipped with a UV detector set at 254 nm, same eluents as for LCMS method, at flow rate of 1 ml/min, with a 40 min method: a gradient run from 100% eluent A during 1 min, then to 100% eluent B over the next 30 min. For some compounds mass spectra were recorded on a MALDI-TOF Voyager-DE-STR (Applied Biosystems) apparatus.

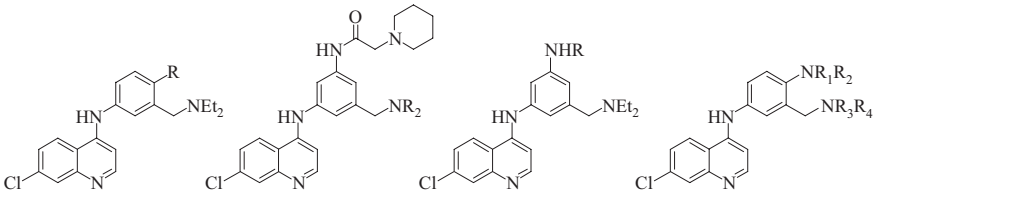
Reagents were obtained from Acros, Aldrich, Lancaster, Novabiochem and Avocado.

The following abbreviations were used: AcOEt (ethyl acetate), DCM (dichloromethane), rt (room temperature), Quino (quinoline).

Aromatic nucleophilic substitution

2-Fluoro-5-nitrobenzyl alcohol **7** (Paunescu et al., 2008) (1 g, 5.84 mmol) and amine (2 eq) were heated at 130°C for 1 h. The reaction mixture was then diluted with 25 ml of THF and washed with a saturated aqueous solution of Na_2CO_3 and then with brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was thoroughly washed with pentane and filtered off to yield expected compound.

[2-(4-Methylpiperazino)-5-nitrophenyl]methanol (8) Orange powder (94% yield). **LC/MS** t_R=5.0 min; P_{HPLC} >99%; m/z (ESI) 252.1 $[M+H]^+$. **^{1}H NMR** (300 MHz, MeOH-d_4) δ 8.46 (d, *J*=2.8 Hz, 1H, H-6), 8.18 (dd, *J*=8.9 and 2.9 Hz, 1H, H-4), 7.26 (d, *J*=8.90 Hz, 1H, H-3), 4.75 (s, 2H, O-CH_2), 3.20-3.10 (m, 4H, N-CH_2), 2.75-2.65 (m, 4H, N-CH_2), 2.44 (s, 3H, CH_3); **^{13}C NMR** (75 MHz, MeOH-d_4)



1 R=alkyl, aryl

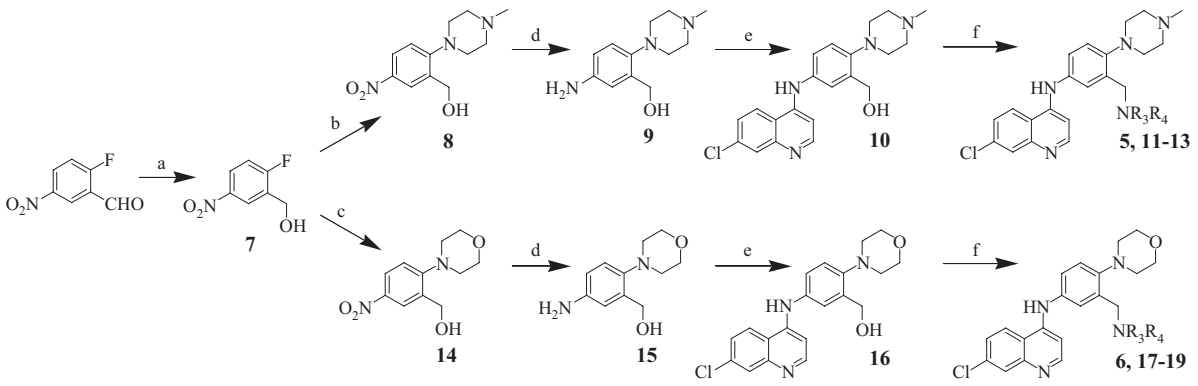
2

3

4

5 NR_1R_2=*N*-methylpiperazino; NR_3R_4=pyrrolidino
6 NR_1R_2=morpholino; NR_3R_4=pyrrolidino

Figure 2 Structure of some potent amodiaquine analogs.



Scheme 1 Reagents: (a) Paunescu et al., 2008; (b) *N*-methylpiperazine, 130°C; (c) morpholine, 115°C; (d) $HCOONH_4$, Pd/C (10%), EtOH, r.t.; (e) 4,7-dichloroquinoline, *n*-pentanol, reflux; (f) $SOCl_2$, NMP, r.t., then amine, NMP, 0°C to r.t.

δ 156.5 (C), 143.4 (C), 136.6 (C), 124.1 (C-6), 123.6 (C-4), 119.0 (C-3), 59.5 (O-CH_2), 55.2 (N-CH_2), 51.7 (N-CH_2), 45.2 (CH_3).

[2-Morpholino-5-nitrophenyl]methanol (14) Yellow oil (99% yield). **MALDI-TOF** m/z 206.1 $[M\text{-}O_2+H]^+$, 223.1 $[M\text{-}O+H]^+$; **^{1}H NMR** (300 MHz, MeOH-d_4) δ 8.44 (d, *J*=2.7 Hz, 1H, H-6), 8.16 (dd, *J*=9.0 and 2.8 Hz, 1H, H-4), 7.23 (d, *J*=8.7 Hz, 1H, H-3), 4.75 (s, 2H, O-CH_2), 3.89 (m, 4H, O-CH_2), 3.09 (m, 4H, N-CH_2); **^{13}C NMR** (75 MHz, MeOH-d_4) δ 156.5 (C), 143.4 (C), 136.6 (C), 124.1 (C-6), 123.5 (C-4), 118.8 (C-3), 67.0 (O-CH_2), 59.4 (O-CH_2), 52.6 (N-CH_2).

Reduction of nitro function

Nitro compound **8** or **14** (3.98 mmol) was hydrogenated using ammonium formate (2.51 g, 10 eq) and Pd/C (10% Pd, 0.43 mg, 0.1 eq) in 50 ml of EtOH. The mixture was stirred overnight at room temperature and then filtered through a celite pad. The filtrate was evaporated and the residue was dissolved in DCM and washed with a saturated aqueous solution of Na_2CO_3. The aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to yield expected compound.

[5-Amino-2-(4-methylpiperazino)phenyl]methanol (9) Pale yellow oil (0.85 g, 97% yield). **^{1}H NMR** (300 MHz, MeOH-d_4) δ 7.00 (d, *J*=8.4 Hz, 1H, H-3), 6.78 (d, *J*=2.7 Hz, 1H, H-6), 6.64 (dd, *J*=8.7 and 2.7 Hz, 1H, H-4), 4.65 (s, 2H, O-CH_2), 2.95-2.85 (m, 4H, N-CH_2), 2.70-2.50 (m, 4H, N-CH_2), 2.34 (s, 3H, N-CH_3); **^{13}C NMR** (75 MHz, MeOH-d_4) δ 144.5 (C), 142.2 (C), 137.1 (C), 121.2 (C-3), 115.7 (C-6), 115.2 (C-4), 61.2 (O-CH_2), 55.8 (2 N-CH_2), 52.7 (2 N-CH_2), 45.2 (N-CH_3).

(5-Amino-2-morpholinophenyl)methanol (15) Brown powder (1.21 g, 99% yield). **LC/MS** t_R=2.8 min; P_{HPLC}=95%; m/z (ESI) 209.2 $[M+H]^+$. ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.02 (d, *J*=9.0 Hz, 1H, H-3), 6.83 (d, *J*=3.0 Hz, 1H, H-6), 6.68 (dd, *J*=9.0 and 3.0 Hz, 1H, H-4), 4.71 (s, 2H, CH_2), 3.82 (m, 4H, O-CH_2), 2.87 (m, 4H, N-CH_2); **^{13}C NMR** (75 MHz, MeOH-d_4) δ 121.1 (C-3), 115.7 (C-6), 115.2 (C-4), 67.6 (O-CH_2), 60.9 (2 O-CH_2), 53.7 (2 N-CH_2).

Aromatic substitution of the chlorine atom

Aniline derivatives **9** or **15** (0.45 mmol) and 4,7-dichloroquinoline (94 mg, 1.1 eq) were refluxed in 1 ml of *n*-pentanol overnight. The reaction mixture was then evaporated and purified by flash chromatography (DCM/MeOH/NH_4OH//8/2/0.1) to yield expected compound.

{5-[(7-Chloroquinolin-4-yl)amino]-2-(4-methylpiperazino) phenyl}methanol (10) Pale brown solid (143 mg, 83% yield). **LC/MS** t_R=5.8 min; P_{HPLC}>99%; m/z (ESI) 383.1-385.1 $[M+H]^+$. **^{1}H NMR** (300 MHz, MeOH-d_4) δ 8.38 (d, *J*=5.4 Hz, 1H, Quino-2), 8.36 (d, *J*=2.5 Hz, 1H, Quino-5), 7.89 (d, *J*=2.0 Hz, 1H, Quino-8), 7.58 (dd, *J*=9.1 and 2.1 Hz, 1H, Quino-6), 7.55-7.53 (m, 1H, H-6), 7.35-7.28 (m, 2H, H-3, H-4), 6.89 (d, *J*=6.1 Hz, 1H, Quino-3), 4.78 (s, 2H, O-CH_2), 3.20-3.02 (m, 8H, N-CH_2), 2.69 (s, 3H, N-CH_2); **^{13}C NMR** (75 MHz, MeOH-d_4) δ 152.1 (C), 149.3 (Quino-5), 148.0 (C), 146.7 (C), 138.3 (C), 137.0 (C), 135.7 (C), 126.4 (Quino-6), 124.9-124.8 (Quino-8, C-6), 124.2-124.1 (Quino-2, C-4), 121.1 (C-3), 117.9 (C), 117.5 (C), 101.2 (Quino-3), 59.9 (O-CH_2), 55.0 (2 N-CH_2), 51.4 (2 N-CH_2), 44.0 (N-CH_3).

{5-[(7-Chloroquinolin-4-yl)amino]-2-morpholinophenyl} methanol hydrochloride (16) Yellow powder (1.90 g, 80% yield). **LC/MS** t_R=6.3 min; P_{HPLC} >99%; m/z (ESI) 370.3 $[M+H]^+$. **^{1}H NMR** (300 MHz, MeOH-d_4) δ 8.55 (d, *J*=9.0 Hz, 1H, Quino-5), 8.33 (d, *J*=6.0 Hz, 1H, Quino-2), 7.93 (d, *J*=1.8 Hz, 1H, Quino-8); 7.77 (dd, *J*=9.0 and 2.1 Hz, 1H, Quino-6), 7.58-7.56 (m, 1H), 7.57 (d, *J*=2.2 Hz, 1H, H-6); 7.40-7.28 (m, 2H, H-3, H-4), 6.86 (d, *J*=6.2 Hz, 1H, Quino-3), 4.78 (s, 2H, O-CH_2), 3.85 (m, 4H, O-CH_2), 2.97 (m, 4H, N-CH_2); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 154.9 (C), 149.0 (C), 143.2 (Quino-2), 139.0 (C), 138.3 (C), 138.2 (C), 131.8 (C), 127.2 (Quino-6), 126.2 (C-6), 124.8-124.3 (C-3, Quino-5), 119.8 (C-4), 119.1 (Quino-8), 115.9 (C), 100.1 (Quino-3), 66.5 (2 O-CH_2), 58.2 (O-CH_2), 52.4 (2 N-CH_2).

Synthesis of target compounds

To benzyl alcohol **10** or **16** (0.78 mmol) in 6 ml of NMP at 0°C was added thionyl chloride (0.28 ml, 5 eq). The reaction mixture was warmed up to room temperature and stirred for 2 h. The solvent was evaporated. The residue was suspended in 6 ml of NMP and amine (20 eq) was added at 0°C. The solution was stirred overnight at room temperature, evaporated and the residue was purified by flash chromatography to yield expected compound.

7-Chloro-N-[4-(4-methylpiperazino)-3-(pyrrolidinomethyl) phenyl]quinolin-4-amine (5) (Paunescu et al., 2008). Yellow

solid (97 mg, 86% yield). ***LC/MS*** t_R=5.2 min; P_{HPLC}=98%; m/z (ESI) 436.4-438.4 $[M+H]^+$. **HPLC** (C4) t_R=7.1 min; P_{HPLC}=99%; **HPLC** (C18) t_R=12.3 min; P_{HPLC} >99%.

N-{3-[(tert-Butylamino)methyl]-4-(4-methylpiperazino) phenyl}-7-chloroquinolin-4-amine (11) Yellow solid (101 mg, 74% yield). **LC/MS** t_R=5.4 min; P_{HPLC}=99%; m/z (ESI) 438.4-440.4 $[M+H]^+$. **HPLC** (C4) t_R=6.3 min; P_{HPLC} >99%; **HPLC** (C18) t_R=15.4 min; P_{HPLC}=99%; **^{1}H NMR** (300 MHz, MeOH-d_4) δ 8.36 (d, *J*=5.6 Hz, 1H, Quino-2), 8.27 (d, *J*=9.1 Hz, 1H, Quino-5), 7.85 (d, *J*=2.1 Hz, 1H, Quino-8), 7.49 (dd, *J*=9.1 and 2.1 Hz, 1H, Quino-6), 7.39-7.24 (m, 3H, H-3, H-4, H-6), 6.90 (d, *J*=5.6 Hz, 1H, Quino-3), 3.82 (s, 2H, N-CH_2), 3.02 (m, 4H, N-CH_2), 2.67 (m, 4H, N-CH_2), 2.39 (s, 3H, N-CH_3), 1.24 (s, 9H, 3 CH_3); **^{13}C NMR** (75 MHz, MeOH-d_4) δ 151.5 (Quino-2), 150.4 (C), 149.2 (C), 148.9 (C), 137.2 (C), 136.7 (C), 135.7 (C), 126.8 (Quino-5), 126.1 (Quino-6), 125.6-123.8-123.7-122.2 (Quino-8, C-3, C-4, C-6), 118.4 (C), 101.5 (Quino-3), 55.8 (N-CH_2), 52.7 (2 N-CH_2), 51.1 (C), 45.3 (N-CH_3), 43.4 (2 N-CH_2), 27.9 (3 CH_3).

7-Chloro-N-[4-(4-methylpiperazino)-3-(morpholinomethyl) phenyl]quinolin-4-amine (12) Yellow solid (97 mg, 86% yield). **LC/MS** t_R=5.3 min; P_{HPLC} >99%; m/z (ESI) 452.2-454.3 $[M+H]^+$. **^{1}H NMR** (300 MHz, MeOH-d_4) δ 8.51 (d, *J*=5.3 Hz, 1H, Quino-2), 8.00 (d, *J*=2.0 Hz, 1H, Quino-8), 7.89 (d, *J*=9.0 Hz, 1H, Quino-5), 7.5-7.4 (m, 2H, Quino-6, H-6), 7.2-7.1 (m, 2H, H-3, H-4), 6.9-6.8 (m, 2H, Quino-3, NH), 3.7-3.6 (m, 4H, O-CH_2), 3.57 (s, 2H, N-CH_2), 3.0-2.9 (m, 4H, N-CH_2), 2.7-2.4 (m, 8H, N-CH_2), 2.36 (s, 3H, N-CH_3); **^{13}C NMR** (75 MHz, MeOH-d_4) δ 154.5 (C), 150.1 (C), 144.9 (Quino-2), 141.5 (C), 139.1 (C), 134.8 (C), 132.8 (C), 128.0-127.4 (Quino-6, C-6), 125.6 (Quino-5), 124.8 (C-3 or C-4), 122.3 (C-3 or C-4), 121.0 (Quino-8), 116.6 (C), 100.7 (Quino-3), 63.6 (2 O-CH_2), 57.1 (N-CH_2), 54.1 (2 N-CH_2), 53.1 (2 N-CH_2), 43.4 (2 N-CH_2), 42.6 (N-CH_3). **HPLC** (C4) t_R=6.0 min; P_{HPLC}=99%; **HPLC** (C18) t_R=14.6 min; P_{HPLC} >99%.

7-Chloro-N-[4-(4-methylpiperazino)-3-[(4-methylpiperazino) methyl]phenyl] quinolin-4-amine (13) Yellow solid (94 mg, 78% yield). **LC/MS** t_R=5.3 min; P_{HPLC}=98%; m/z (ESI) 465.1-467.2 $[M+H]^+$. **^{1}H NMR** (300 MHz, MeOH-d_4) δ 8.56 (d, *J*=9.1 Hz, 1H, Quino-5), 8.42 (d, *J*=6.7 Hz, 1H, Quino-2), 7.97 (d, *J*=2.0 Hz, 1H, Quino-8), 7.76 (dd, *J*=9.1 and 2.1 Hz, 1H, Quino-6), 7.59 (s, 1H, H-6), 7.5-7.4 (m, 2H, H-3, H-4), 6.90 (d, *J*=6.7 Hz, 1H, Quino-3), 3.81 (s, 2H, N-CH_2), 3.5-3.4 (m, 4H, N-CH_2), 3.3-3.1 (m, 8H, N-CH_2), 2.99 (s, 3H, N-CH_3), 2.9-2.8 (m, 4H, N-CH_2), 2.87 (s, 3H, N-CH_3); **^{13}C NMR** (75 MHz, MeOH-d_4) δ 154.1 (C), 149.8 (C), 145.8 (Quino-2), 142.5 (C), 138.8 (C), 134.5 (C), 134.5 (C), 127.6-127.3 (Quino-6, C-6), 125.1-125.0 (Quino-5, C-3 or C-4), 122.2 (C-3 or C-4), 121.7 (Quino-8), 116.9 (C), 100.8 (Quino-3), 56.5 (N-CH_2), 54.6 (2 N-CH_2), 53.9 (2 N-CH_2), 50.4 (2 N-CH_2), 50.0 (2 N-CH_2), 42.8 (N-CH_3), 42.6 (N-CH_3). ***HPLC*** (C4) t_R=5.7 min; P_{HPLC} >99%; ***HPLC*** (C18) t_R=11.9 min; P_{HPLC} >99%.

7-Chloro-N-[4-morpholino-3-(pyrrolidinomethyl)phenyl] quinolin-4-amine (6) (Paunescu et al., 2008). Yellow solid (105 mg, 96% yield). **LC/MS** t_R=6.0 min; P_{HPLC}=99%; m/z (ESI) 423.3-425.3 $[M+H]^+$. **HPLC** (C4) t_R=8.0 min; P_{HPLC} >99%; **HPLC** (C18) t_R=15.0 min; P_{HPLC}=99%.

N-{3-[(tert-Butylamino)methyl]-4-morpholinophenyl}-7-chloroquinolin-4-amine (17) Yellow solid (103 mg, 92% yield). **LC/MS** t_R=5.9 min; P_{HPLC}=99%; m/z (ESI) 425.2-427.2 $[M+H]^+$. **^{1}H NMR** (300 MHz, MeOH-d_4) δ 8.36 (d, *J*=5.6 Hz, 1H, Quino-2), 8.29 (d, *J*=9.0 Hz, 1H, Quino-5), 7.85 (d, *J*=2.1 Hz, 1H, Quino-8), 7.49 (dd, *J*=9.1 and 2.4 Hz, 1H, Quino-6), 7.43 (d, *J*=1.7 Hz, 1H, H-6), 7.4-7.3 (m, 2H, H-3, H-4); 6.91 (d, *J*=5.6 Hz, 1H, Quino-3), 3.96 (s, 2H, N-CH_2), 3.9-3.8 (m, 4 H, O-CH_2), 3.0-2.9 (m, 4H, N-CH_2), 1.30 (s, 9H, CH_3); **^{13}C NMR** (75 MHz, MeOH-d_4) δ 152.5 (Quino-2), 151.2 (C), 150.2 (C), 150.1 (C), 138.0 (C), 136.8 (C), 136.0 (C), 127.8 (Quino-8), 127.1 (C-6), 126.7 (Quino-6), 125.3 (C-3 or C-4), 124.7 (Quino-5), 123.5 (C-3 or C-4), 119.5 (C), 102.6 (Quino-3), 68.5 (O-CH_2), 54.7 (N-CH_2), 50.8 (C), 43.7 (2 N-CH_2), 28.1 (3 CH_3). **HPLC** (C4) t_R=7.3 min; P_{HPLC} >99%; **HPLC** (C18) t_R=15.1 min; P_{HPLC}=97%.

7-Chloro-N-[4-morpholino-3-(morpholinomethyl)phenyl] quinolin-4-amine (18) **Y**ellow solid (83 mg, 77% yield). **LC/MS** t_R=5.9 min; P_{HPLC}=99%; m/z (ESI) 439.1-441.1 $[M+H]^+$. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.49 (d, *J*=5.6 Hz, 1H, Quino-2), 8.02 (d, *J*=2.0 Hz, 1H, Quino-8), 7.88 (d, *J*=9.1 Hz, 1H, Quino-5), 7.5-7.4 (m, 2H, Quino-6, H-6), 7.22 (dd, *J*=8.5 and 1.8 Hz, 1H, H-4); 7.15 (d, *J*=8.6 Hz, 1H, H-3); 6.83 (d, *J*=5.8 Hz, 1H, Quino-3), 3.87 (m, 4H, O-CH_2), 3.69 (m, 4H, O-CH_2), 3.59 (s, 2H, N-CH_2), 2.9-2.8 (m, 4H, N-CH_2), 2.5-2.4 (m, 4H, N-CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.5 (Quino-2), 149.7 (C), 148.6 (C), 135.7 (C), 134.9 (C), 134.7 (C), 128.7 (Quino-8), 126.6-125.8 (Quino-6, C-6), 123.0 (C-3 or C-4), 121.4-121.2 (Quino-5, C-3 or C-4), 117.9 (C), 102.0 (Quino-3), 67.6 (2 O-CH_2), 67.2 (2 O-CH_2), 57.9 (N-CH_2), 53.9 (2 N-CH_2), 53.5 (2 N-CH_2). **HPLC** (C4) t_R=9.4 min; P_{HPLC}=99%; **HPLC** (C18) t_R=14.3 min; P_{HPLC}=99%.

7-Chloro-N-{3-[(4-methylpiperazino)methyl]-4-morpholinophenyl}quinolin-4-amine (19) Yellow solid (120 mg, 99% yield). **LC/MS** t_R=5.7 min; P_{HPLC}=99%; m/z (ESI) 452.2-454.2 $[M+H]^+$; **^{1}H NMR** (300 MHz, MeOH-d_4) δ 8.33 (d, *J*=5.7 Hz, 1H, Quino-2), 8.27 (d, *J*=9.0 Hz, 1H, Quino-5), 7.85 (d, *J*=2.1 Hz, 1H, Quino-8), 7.49 (dd, *J*=9.0 and 2.1 Hz, 1H, Quino-6), 7.45 (d, *J*=2.2 Hz, 1H, H-6), 7.3-7.2 (m, 2H, H-3, H-4); 6.81 (d, *J*=5.7 Hz, 1H, Quino-3), 3.9-3.8 (m, 4H, O-CH_2), 3.68 (s, 2H, N-CH_2); 3.0-2.9 (m, 4H, N-CH_2), 2.7-2.5 (m, 8H, N-CH_2), 2.37 (s, 3H, N-CH_3); **^{13}C NMR** (75 MHz, MeOH-d_4) δ 152.0 (Quino-2), 151.8 (C), 151.0 (C), 149.8 (C), 136.9 (C), 136.7 (C), 135.3 (C), 127.4-127.3 (Quino-8, C-6), 126.7 (Quino-6), 124.9-124.8 (Quino-5, C-3 or C-4), 122.3 (C-3 or C-4), 119.3 (C), 103.3 (Quino-3), 68.5 (2 O-CH_2), 57.9 (N-CH_2), 55.7 (2 N-CH_2), 54.6 (2 N-CH_2), 53.1 (2 N-CH_2); 28.1 (N-CH_3).

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