Synthesis and Antimalarial Activity of New Amino Analogues of Amodiaquine

E. Paunescu[a], S. Susplugas[b], E. Boll[a], R. A. Varga[c], E. Mouray[b], P. Grellier[b] and P. Melnyk[a,*]

[a]*UMR CNRS 8161 - Universités de Lille I & II - Institut Pasteur de Lille, 1 rue du Professeur Calmette, B.P. 447, 59021 Lille cedex, France ;* [b]*USM 0504-EA 3335, Département Régulations, Développement, Diversité Moléculaire, CP52 Muséum National d'Histoire Naturelle, 61 rue Buffon, 75005 Paris, France;* [c]*National Centre for X-Ray Diffractometry, "Babes-Bolyai" University, Faculty of Chemistry and Chemical Engineering, Arany Janos Str. No. 11, RO-400028 Cluj-Napoca, Romania*

Abstract: Amodiaquine remains one of the most prescribed antimalarial 4-aminoquinoline. To assess the importance of the 4'-hydroxyl group and subsequent hydrogen bond in the antimalarial activity of amodiaquine (AQ), a series of new analogues in which this functionality was replaced by various amino groups was synthesized. The incorporation of a 3'-pyrrolidinamino group instead of the 3'-diethylamino function of AQ allowed the development of a parallel series of amopyroquine derivatives. The compounds were screened against both chloroquine (CQ)-sensitive and –resistant strains of Plasmodium falciparum and their cytotoxicity evaluated upon the MRC5 cell line. Antimalarial activity in a low nanomolar range was recorded showing that the 4'-hydroxy function can be successfully replaced by various amino substituents in terms of activity without any influence of the level of CQ-resistance of the strains. Furthermore the ability of the compounds to inhibit beta-hematin formation was measured in order to discuss the mechanism of action of these new compounds. Compounds **7d** and **8d** exhibit a high selectivity index and may be considered as promising leads for further development.

Key Words: Antimalarials, 4-aminoquinolines, amodiaquine, *Plasmodium falciparum*.

INTRODUCTION

More than a third of world's population is at risk of contracting malaria and according to recent estimates, this disease affects more than 2,400 million people in more than 100 countries [1]. It is estimated that approximately 7000 people, mainly children under the age of 5 years and pregnant women in Africa, die of malaria every day [2]. Malaria is one of the main obstacles to socio-economic development in sub-Saharian Africa and other tropical regions in the world.

Chloroquine (CQ, Chart **1**) was a mainstream drug in the fight against *Plasmodium falciparum*, but its efficacy is eroded by the emergence of resistant parasites. In fact, the emergence of *Plasmodium falciparum* strains resistant to almost all the antimalarials currently in use has prompted researchers around the world to search for new antimalarial drugs. Meanwhile last WHO's guidelines for malaria treatment recommend the use of combination of at least two drugs [3].

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 [4]. The lack of an enzyme drug target for quinoline antimalarials is probably a chief reason why resistance development to these drugs is relatively slow. Chloroquine resistance is associated with the K76T mutation in the transporter *pfcrt* gene [5-7]. Whether this mutation is responsible alone for resistance or not, it is always associated with CQ-resistant phenotypes of *P. falciparum* strains.

Hemoglobin degradation and interaction with heme still remain a fruitful area for drug discovery as relatively small changes in structure can enhance compound uptake into the food vacuole of CQ-resistant parasites [8]. A metallocenic analog of CQ, i.e. Ferroquine, is now under clinical trials [9].

The spread of CQ-resistance has prompted the re-examination of alternative antimalarials such as amodiaquine (AQ, Chart **1**), another 4-aminoquinoline proved to be effective against CQ-resistant strains [10, 11]. Recent comparative trials of CQ and AQ for the treatment of acute, uncomplicated infections in Gambia, in Chad and in Nigeria found AQ to be superior to CQ, displaying lower parasitological and clinical failure rates [12-14]. However, in the 1980s, cases of agranulocytosis, neutropenia and hepatisis were reported associated with AQ prophylaxis and its use was halted [15].

AQ toxicity has been explained by the presence of its 4-hydroxyanilino moiety, which is believed to undergo extensive metabolization to its quinoneimine variant [16, 17]. Formation of this reactive species *in vivo* and subsequent binding to cellular proteins and lipids could affect cellular functions either directly or by immunological response [18, 19]. This bio-activation was found to be accompanied by the expression of a drug-related antigen on the cell surface, suggesting a type II hypersensitivity reaction and causing the myelotoxicity of AQ [20, 21].

*Address correspondence to this author at the UMR CNRS 8161 - Universités de Lille I & II - Institut Pasteur de Lille, 1 rue du Professeur Calmette, B.P. 447, 59021 Lille cedex, France; Tel: (33) 3 20 87 12 19; Fax: (33) 3 20 87 12 35; E-mail: patricia.melnyk@ibl.fr

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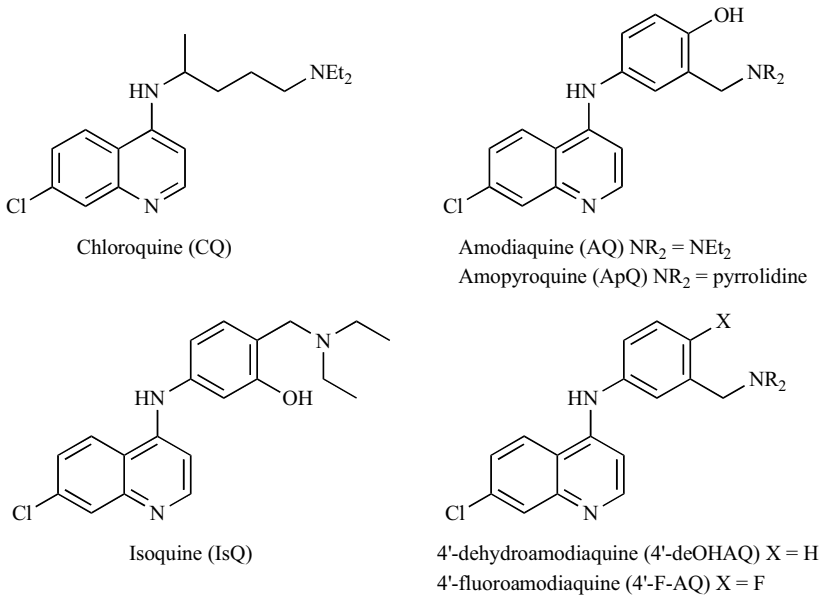


Chart 1. Structure of Chloroquine, Amodiaquine and derivatives.

However, detailed investigations have shown that AQ presents a toxicity similar to that of CQ when used therapeutically to treat uncomplicated *P. falciparum* malaria. In fact, results collated from 40 different clinical trials held in the late 1980s suggest that adverse drug reactions to AQ are likely to occur only during prophylaxis [22].Thus, AQ was reintroduced for therapeutic use only. To date, there is no evidence for serious toxicity associated with amodiaquine therapy [22, 23]. Thought resistance to AQ is developing, last WHO's guidelines for malaria treatment still recommend its use in combination with artemisinin derivatives or if not available with sulfadoxine/pyrimethamine.

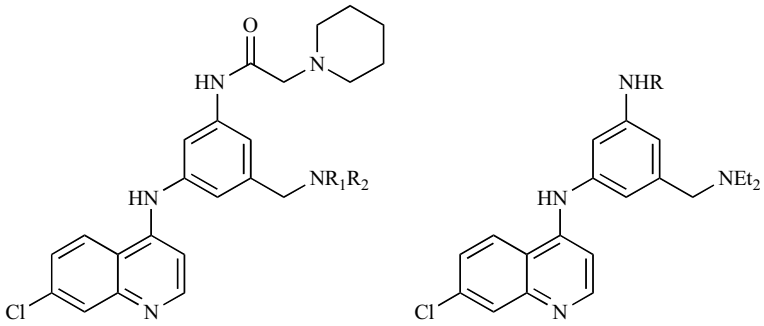
Besides, activity of AQ is described to be linked to an active conformation in which the internitrogen separation between the quinoline nitrogen and the diethylamino nitrogen, is approximately 8.30 Å, like in CQ [24]. This distance is similar to that measured by X-ray crystallography between the central iron and the oxygens of the carboxylate groups of heme [25], the putative "receptor" of these 4-aminoquinolines. This active conformation is the result of an intramolecular hydrogen bond between the hydroxyl and the proton of the charged diethylamino function [26]. This hypothesis is at the basis of the design of fluoro analogs [27] and isoquine (Chart **1**).

Isoquine (IsQ), is an amodiaquine regioisomer that can not form toxic metabolites by simple oxidation and which is potent against CQ-resistant parasites *in vitro*. Interchange of the hydroxyl group and the Mannich side chain prevented oxidation to toxic metabolites while retaining possible bonding interactions with the aromatic hydroxyl function. For IsQ and analogs, X-ray crystallography studies demonstrated the presence of the internal hydrogen bond between the hydroxyl function and the diethylamino side-chain [28]. The t-butylamino side-chain analog is now planned for clinical trials [29].

To maintain intramolecular hydrogen bond, the 4'-hydroxyl group was replaced with fluorine (4'-dehydroxy-4'-fluoroamodiaquine, Chart **1**) [27,30]. A decrease of drug potency was observed compared to that of AQ for both CQ-sensitive and CQ-resistant strains. The idea that incorporation of an intramolecular hydrogen-bonding motif in the side chain of 4-aminoquinolines could increase the basicity of amino side chain and thus enhance the activity of the compound against drug resistant strains of *P. falciparum* has been recently reevaluated by Madrid [31].

We recently evaluated the effects of the 4'-hydroxyl group substitution and demonstrated that derivatives substituted in 5'-position with an amido (**1**-**4**, Chart **2**) [32] or an amino (**5**-**6**, Chart **2**) [33] functionality presented good *in vitro* antimalarial activities (Table **1**). Compounds **4** and **5** provided an interesting *in vivo* activity thought modest compared to AQ [27, 28]. It is important to note that this type of derivatives do not retain the possible hydrogen bonding interaction due to the absence of the aromatic hydroxyl function. This does not exclude a possible oxidation *in vivo* to a hydroxyl derivative. Moreover, removal of the 4'-position hydroxyl group (to produce 4'-deOH-AQ) led to reduction in activity against CQ-sensitive strains without having a significant effect on potency against CQ-resistant strains.

In light of the SAR studies established around compounds **1-6**, we were interested in determining the effects induced by the introduction of an amino group in the 4'-position of an AQ-like structure upon the antimalarial activity. Thus, a new series of AQ analogs bearing in this position various amino substituents (primary or secondary, cyclic or acyclic) was synthesized (Chart **3**, compounds **7a-h**). It is important to note here that compounds bearing secondary amine could not form intramolecular hydrogen bound. Furthermore, as AQ-analogs obtained by the replacement of the *N*-diethylamino function of the side chain, with a pyrrolidine cycle or a *N-tert*-butyl group were proved to be metabolically less labile [34, 35], we completed our study with the development of parallel amopyroquine-analogues series (compounds **8a-h**). Amopyroquine (ApQ), a structural ana-



1 $NR_1R_2 = NEt_2$
2 NR_1R_2 = pyrrolidine
3 $NR_1R_2 = NMeCH_2CH_2NMe_2$
4 NR_1R_2 = morpholine

5 R = H
6 R = $-(CH_2)_2$-piperidine

Chart 2. Structure of compounds **1-6**.

logue of AQ in which the diethylamino group in the side chain is replaced with a pyrrolidine cycle, was shown to be more active than both CQ and AQ against 11 CQ-resistant isolates of *P. falciparum* [36, 37]. 4'-deOH AQ **9** and 4'-deOHApQ **10** were also synthesized and evaluated to enrich the SAR discussion.

CHEMISTRY

Low-cost preparation and easy accessibility were the main criteria for the design of the molecules. The 4'-amino substituted AQ analogues **7a-h** and, respectively, ApQ analogues **8a-h** were easily synthesised following a multiple step procedure starting from commercially available 2-fluoro-5-nitrobenzaldehyde as described in Scheme **1**.

We were interested in developing an effective and simple synthetic strategy that could be used for the obtainment of both series of desired compounds. The first challenge was the obtainment of key intermediates **13** and **14**. In the preliminary assays of reductive amination (conditions described by Keenan *et al.* [38]) conducted on 2-fluoro-5-nitrobenzaldehyde, in the presence of diethylamine, the only isolated product was the alcohol **11**, resulted by the aldehyde reduction, with a medium yield of 41%. The same reaction conducted in the presence of pyrrolidine, provided very low yields of expected compound **14**. In this case the major side product isolated was 1-(4-nitro-2-pyrrolidin-1-ylmethyl-phenyl)-pyrrolidine. In these conditions (basic, polar and protic medium), the high nucleophilicity of the secondary cyclic amine, favored the aromatic nucleophilic substitution of the fluorine atom activated by the presence of a strong electron withdrawing nitro group in *para* position. The yield of the desired compound could be improved by reducing the reaction temperature, but not enough to be satisfying.

Aldehyde reduction in classical conditions ($NaBH_4$) followed by the activation of alcohol **11** as a tosylated derivative **12** and substitution with the appropriate amine (diethylamine or pyrrolidine) provided the key intermediates **13** and **14** in good yields. Substitution reaction of the tosylated intermediate **12** with pyrrolidine was conducted at room temperature, in order to avoid the side reaction of aromatic nucleophilic substitution of the fluorine atom. In the case of the synthesis of the intermediate **13** in similar conditions, higher temperature could be used.

In the next step an aromatic nucleophilic substitution reaction of the fluorine atom in intermediates **13** and **14** with various primary and secondary amines, gave the diethylami-

Table 1. ***In Vitro*** **Antimalarial Activity Upon** ***P. falciparum*** **CQ-sensitive and Resistant Strains and Cytotoxicity of Compounds 1-6**

Compd.	IC_{50} F32 (nM) [a]	IC_{50} FcB1 (nM) [a]	IC_{50} K1 (nM) [a]	CC_{50} (μM) [c]	SI (FcB1) [d]
CQ	7.0 ± 1.4 [b]	126 ± 26 [b]	125.3 ± 6.4 [b]	> 32	254
AQ	8.1 ± 0.7 [b]	7.9 ± 2.7 [b]	9.0 ± 0.6 [b]	13	1645
1	nd	8.2 ± 1.4 [b]	nd	4	488
2	nd	6.9 ± 3.3 [b]	nd	4	580
3	nd	5.0 ± 0.8 [b]	nd	2	400
4	12.8 ± 1.1 [b]	9.5 ± 3.4 [b]	12.4 ± 1.1 [b]	20	2105
5	16.3 ± 2.1 [b]	18.1 ± 0.8 [b]	32.3 ± 4.2 [b]	> 25	1381
6	15.1 ± 0.6 [b]	19.1 ± 0.6 [b]	26.4 ± 5.9 [b]	4	209

[a] Parasites were considered resistant to CQ for IC_{50} > 100 nM; [b] number of experiments between 3 and 6; [c] CC_{50} is the IC_{50} value for cytotoxicity upon MRC5 cells calculated on the basis of three experiments; [d] SI (selectivity index) = CC_{50} / IC_{50} (FcB1).

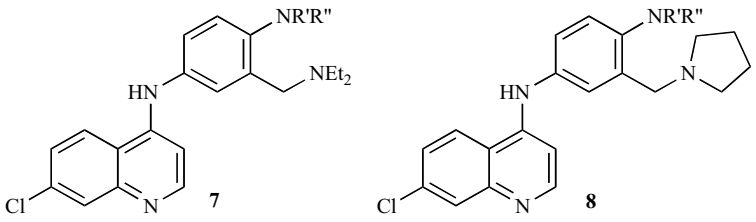


Chart 3. General structures of target compounds **7** and **8**.

nomethyl (**15a-h**) and, respectively, pyrrolidinylmethyl (**16a-h**) intermediates. Secondary amines, and especially more nucleophilic cyclic ones, necessitated shorter reaction times.

Next, a two step sequence, reduction of the nitro group in the intermediates (**17a-h**) and (**18a-h**) and, subsequently condensation of the obtained amines with 4,7-dichloroquinoline, allowed the synthesis of the target AQ and ApQ analogues.

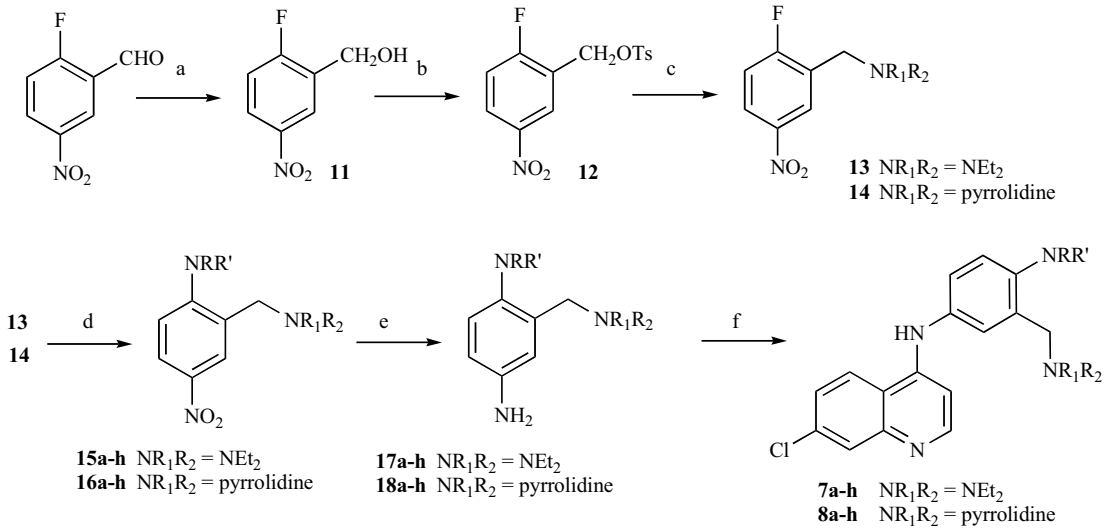
As references, unsubstituted compounds 4'-deOHAQ **9** and 4'-deOHApQ **10** were synthesized according to published procedure (Scheme **2**), starting from commercially available 3-nitro-benzyl bromide [33]. Nucleophilic substitution of the activated bromide atom in benzylic position with the appropriate amine allowed the construction of the amino side chain, and subsequent reduction of the nitro group and then condensation of the obtained amine with 4,7-dichloroquinoline provided compound **10**.

BIOLOGICAL RESULTS AND DISCUSSION

In order to study the influence of the CQ-resistance level on the compound activities, all the compounds were tested against two CQ-sensitive strains (F32, Thai) and three CQ-resistant strains (PFB, FcB1R and K1) of *P. falciparum* (Fig. **1**). As IC_{50} values could lead to erroneous conclusions in the efficacy of the compounds, IC_{90} values were also calculated and discussed for the F32 and K1 strains (Table **2**). In parallel, the cytotoxicity of the different compounds was evaluated upon the human MRC-5 cells (diploid embryonic lung cell line) (Table **3**).

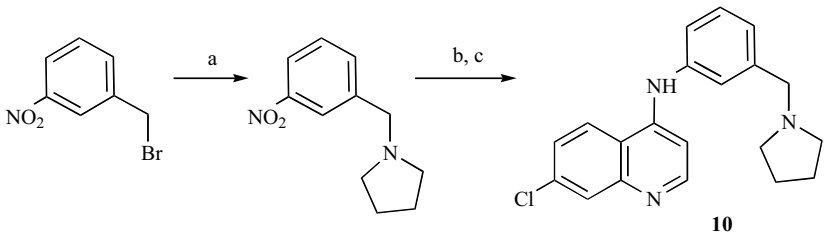
These compounds were also evaluated for their ability to inhibit β-hematin formation, the commonly accepted mechanism of action of 4-aminoquinolines and *in silico* calculations of the Vacuolar Accumulation Ratio (VAR) [39] were performed according to the hypothesis of weak-base model (Fig. **1**).

IC_{50} values for AQ and ApQ were found to be quiet constant whatever the CQ-resistance status of strains tested, with a better 2 times activity for ApQ (IC_{50}s ranging from 4-5 nM) (Tables **1**, **2**). As already described, 4'-deOHAQ (compound **9)** showed a slight decrease of activity compared to AQ. The same observation was made for 4'-deOHApQ (compound **10)** and ApQ. All the compounds were more efficient than CQ to inhibit the CQ-resistant strains and except compounds substituted by cyclohexylethylamino or benzylamino group, they provided activity in the low nanomolar range (IC_{50}s below 20 nM) and showed similar IC_{50}s values upon all the strains tested. Generally ApQ analogs **8a-h** showed better antimalarial activity than AQ analogs **7a-h**. A notable difference appears among derivatives corresponding to tertiary aromatic or secondary aromatic moiety. The



[a]Reagents: (a) $NaBH_4$, MeOH, 0°C [38]; (b) TsCl, NaOH, THF, H_2O, 5-10°C; (c) NEt_2, TEA, 1,4-dioxane, 55°C or pyrrolidine, TEA, 1,4-dioxane, r.t.; (d) diamines, K_2CO_3, EtOH, reflux, or monoamines, K_2CO_3, CH_3CN, reflux; (e) $SnCl_2$, HCl (1M, aq.), THF, reflux; (f) 4,7-dichloroquinoline, HCl (1M, aq.), CH_3CN, reflux.

Scheme 1. Synthesis of Compounds **7** and **8**[a].



[a]Reagents: (a) pyrrolidine, K_2CO_3, CH_3CN, reflux; (b) $SnCl_2$, HCl (1M, aq.), THF, reflux; (c) 4,7-dichloroquinoline, HCl (1M, aq.), CH_3CN, reflux.

Scheme 2. Synthesis of 4'-deOH-ApQ **10** [a].

N-methylpiperazine-substituted compounds (**7e** and **8e**) were the most potent derivatives of both series with IC_{50} values lower or similar to AQ depending upon the strains tested. Compounds substituted by morpholine (**7d** and **8d**), dimethylamine (**7a** and **8a**), pyrrolidine (**7b** and **8b**) or piperidine (**7c** and **8c**) were slighty less active. Secundary amino compounds (**7f** and **8f**, **7g** and **8g**) were much less active with IC_{50} values ranging from 70 to 140 nM. The same observations could be made for the IC_{90} values, which remain lower than 50 nM except for the compounds bearing benzylamino or cyclohexylamino substitution (Table **3**).

Considering tertiary aromatic amines, cyclisation increases the activity (compare **7a** and **7b**, **8a** and **8b**). Enlargement of the size of the cycle has little impact (compare **7b** and **7c**, **8b** and **8c**) but the introduction of an heteroatom is favorable for activity (compare compounds **c** with compounds **d** and **e**). For compounds **7e** and **8e**, the presence of a supplementary basic center, changing the ability of the compounds to be protonated and therefore their subsequent accumulation into the food vacuole of the parasite, seems beneficial to the activity as for secondary amines **7h** and **8h**. The better accumulation offsets the negative effect of the NH group. Indeed, in the case of secondary amines **7f** and **8f**, **7g** and **8g** a dramatic loss of activity was observed. A difference should be noticed for these compounds as cyclohexylamino substitution provided IC_{50}s increasing with the CQ-resistance level whereas benzylamino analogs showed almost constant IC_{50}s.

The cytotoxicity of the different compounds was evaluated upon human MRC-5 cells (diploid embryonic lung cell line) (Table **3**). Surprisingly but reproducible low toxicity was measured for benzylamino compound **7g.** Pyrrolidine analogs (**7b** and **8b**) and the morpholino ApQ-analog **8d** were found to be equally toxic to AQ while the other compounds displayed lower CC_{50} values. Among the compounds, the morpholine derivative **8d** revealed a selectivity index (ratio CC_{50} / IC_{50}K1) similar to that of AQ. Hence, it is of valuable interest to consider compounds with selectivity indexes greater than 1000 (compounds **7b**, **8b**, **7c**, **7d** and **7e**).

Amino analogs showed interesting capacity to inhibit β-hematin polymerisation (Fig. **1**). Except in the case of benzylamino substituant, IC_{50}s of the compounds were higher than IC_{50}s of AQ but in the same range as CQ. Perhaps because of steric hinderance of free diethylamino group, AQ analogs are lower inhibitors than ApQ analogs (except in the case of compounds **c**). Interestingly, compound **7h** showing higher antimalarial activity is one of the poorer β-hematin polymerization inhibitor.

DISCUSSION

The hemoglobin degradation pathway in *P. falciparum* is a specialized parasite process with a proven background as an efficient therapeutic target as exemplified by the development of 4-aminoquinolines and endoperoxides. Furthermore, the parasite has difficulty in developing resistance to these classes of drug (compared with the speed of resistance development to atovaquone or pyriméthamine). Resistance to CQ was first reported in the late 50's but is now widely established. 4-aminoquinoline amodiaquine remains efficient in an important part of the world and is still recommended by WHO (in combination with artemisinin derivatives artesucam® or if not available with sulfadoxine/pyrimethamine). For several years our group has been engaged in the identification of new 4-aminoquinoline antimalarials, able to escape CQ-resistance mechanism. Some of our SAR studies showed that the replacement of 4'-OH group in AQ structure by several amino substituants, particularly in 5'-position, could provide interesting activities. As the presence of intramolecular hydrogen bond seems important for activity we designed a new series of 4'-amino analogs of AQ and ApQ.

4-aminoquinolines inhibit the crystallisation of the heme to form hemozoin (and its synthetic equivalent β-hematin). Several compounds could be considered as good antimalarial candidates and particularly compounds **d**, **e** and **h**. Studies on the inhibition of β-hematin formation revealed that most of compounds were as potent inhibitors as CQ.

4-aminoquinolines accumulate at high concentrations into the parasite's acid food vacuole, which is their site of action. It is generally admitted that a stronger basicity of the molecule increases the antimalarial activity due to a better uptake in the vacuole owing to the pH gradient between cytosol and the acidic vacuole. By taking this into account, mono or biamino substituants were introduced in 4'-position. To evaluate the contribution to antimalarial activity of the component accumulation in the food vacuole, *in silico* lipophilic calculations (logD at vacuolar and cytosolic pHs) and vacuolar accumulation ratios (VAR) based on a weak-base model were carried out. Compounds of series **e** and **h**, as expected, are susceptible of accumulating like AQ and 40-200 times more than the others, which show VAR values similar to that of CQ. For example, compound **8h** (VAR = 2733 x 10^3, $logD_{5.2}$ = -0.94, $logD_{7.4}$ = -0.05), displaying a

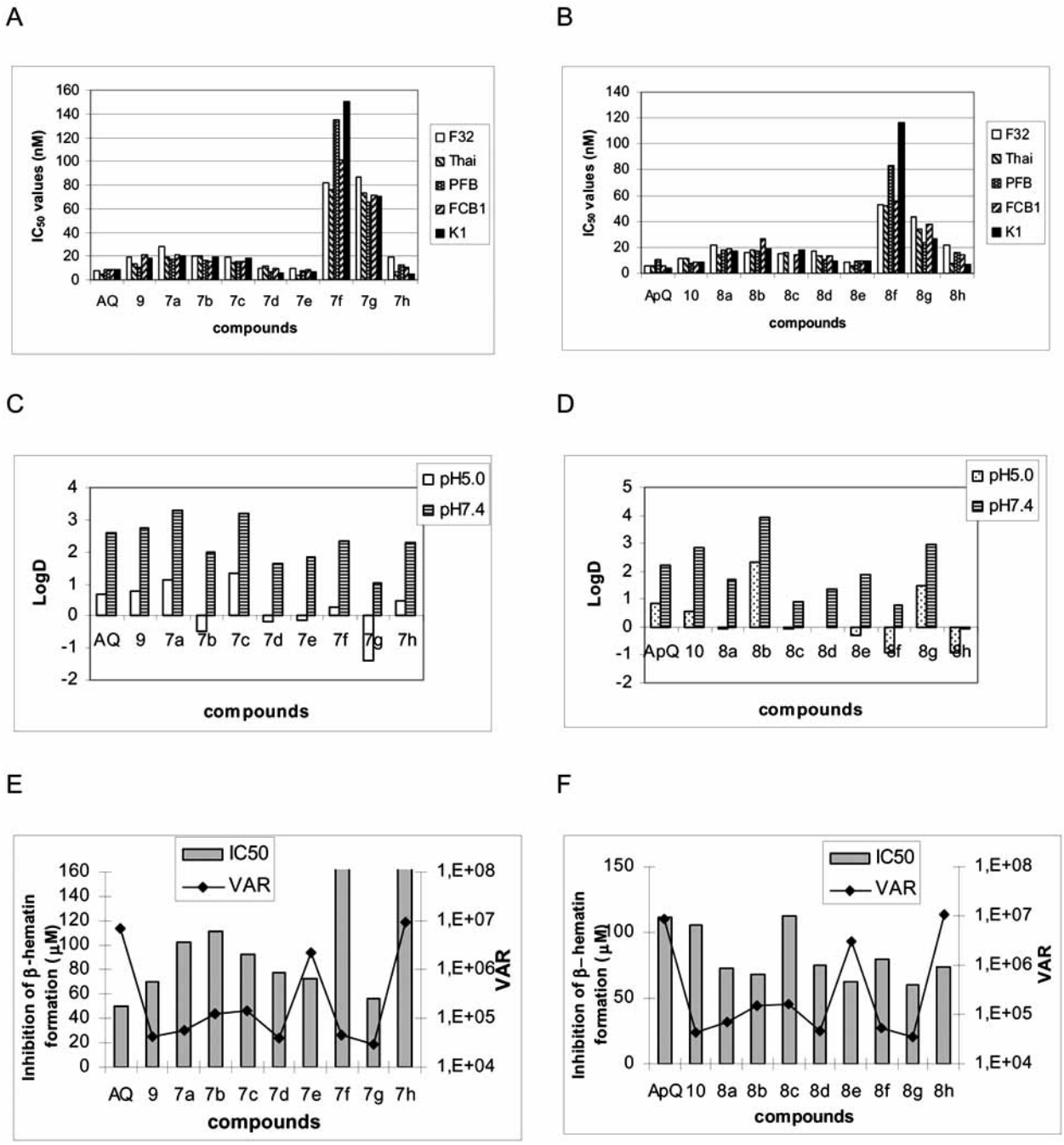


Fig. (1). Comparison between *in vitro* antimalarial activity, lipophilicity and *in vitro* inhibition of β-hematin formation.

A and B) Efficiency (IC_{50}s) of AQ and ApQ analogs, respectively, to inhibit growth of parasites expressing different degrees of resistance to CQ.

C and D) Calculated logD at pH 5.0 and 7.4 of AQ and ApQ analogs, respectively.

E and F) *In vitro* inhibition of β-hematin formation (IC_{50}s) and calculated Vacuolar Accumulation Ratio of AQ and ApQ analogs.

greater potential accumulation than compound **8a** (VAR = 23 x 10^3, $logD_{5.2}$ = -0.06, $logD_{7.4}$ = 1.71) and a comparable inhibition of β-hematin formation (IC_{50}s around 70 μM), is about 4 times more active. Thus, introduction of the additional amine center notably increases ion-trapping of molecules.

Interestingly, compound **7h** provide exception to this general trend. Indeed, while it accumulates less than its ApQ conterpart **8h** and display almost the same antimalarial activity, it inhibits β-hematin formation three times less. These results suggest that additional mechanisms may be involved for this compound. It must be noticed that compounds of

Table 2. In Vitro Antimalarial Activity Upon *P. falciparum* CQ-Sensitive F32 and CQ-Resistant K1 Strains

cpd	NR'R"	F32		K1	
		IC_{50} ± SD (nM) [a,b]	IC_{90} ± SD (nM) [a,b]	IC_{50} ± SD (nM) [a,b]	IC_{90} ± SD (nM) [a,b]
AQ analogs					
AQ	OH	8.1 ± 0.7	28.3 ± 1.3	9.0 ± 0.6	11.8 ± 2.5
9	H	19.2 ± 2.0	29.8 ± 0.6	18.1 ± 1.0	31.5 ± 0.8
7a	dimethylamine	27.6 ± 10.8	41.1 ± 16.8	20.0 ± 2.2	31.5 ± 1.3
7b	pyrrolidine	19.8 ± 2.3	27.0 ± 4.2	19.1 ± 1.4	38.6 ± 10.1
7c	piperidine	18.8 ± 0.1	27.7 ± 6.1	18.7 ± 4.4	25.5 ± 5.7
7d	morpholine	9.4 ± 0.6	13.0 ± 3.7	6.0 ± 1.6	12.2 ± 2.9
7e	N-methyl-piperazine	9.5 ± 1.1	14.7 ± 0.4	6.3 ± 2.4	10.5 ± 4.2
7f	cyclohexylmethylamine	81.6 ± 10.6	128.5 ± 4.2	149.9 ± 7.4	236.3 ± 8.6
7g	benzylamine	86.6 ± 2.1	130.2 ± 2.6	70.0 ± 8.2	117.1 ± 5.7
7h	piperidinethylamine	19.1 ± 1.5	29.2 ± 1.4	5.0 ± 0.2	7.5 ± 0.1
ApQ analogs					
ApQ	OH	5.7 ± 1.5	10.0 ± 2.4	4.2 ± 1.4	9.6 ± 3.6
10	H	11.8 ± 3.5	15.5 ± 0.9	8.7 ± 2.4	22.5 ± 6.4
8a	dimethylamine	21.8 ± 0.3	31.0 ± 0.4	16.6 ± 2.6	26.4 ± 4.3
8b	pyrrolidine	16.2 ± 5.6	21.6 ± 7.1	19.1 ± 1.4	31.1 ± 1.8
8c	piperidine	15.6 ± 0.6	23.6 ± 7.6	17.8 ± 2.4	36.7 ± 14.4
8d	morpholine	17.3 ± 1.2	31.1 ± 0.4	9.1 ± 2.8	16.7 ± 1.5
8e	N-methyl-piperazine	8.7 ± 1.1	15.6 ± 0.2	9.7 ± 1.1	16.5 ± 2.9
8f	cyclohexylmethylamine	53.4 ± 13.5	104.5 ± 26.3	116.8 ± 6.2	197.6 ± 4.2
8g	benzylamine	43.8 ± 1.0	66.6 ± 0.8	26.6 ± 6.3	43.9 ±12.9
8h	piperidinethylamine	21.3 ± 0.2	30.3 ± 0.1	6.6 ± 0.4	9.9 ± 1.0

[a] Parasites were considered resistant to CQ for IC_{50} > 100 nM; [b] number of experiments between 3 and 6.

series **h** provide a higher toxicity than all the other compounds.

Compounds **7e** and **8e** show a typical 4-aminoquinoline mechanism of action with high accumulation component, good β-hematin formation inhibition capacities and high antimalarial activity (IC_{50} and IC_{90} values around 10 nM against the CQ-resistant K1 strain).

Compounds **8h** and **8d** are among the most active compounds and were successfully crystallized. X-ray crystallography studies of compound **8h** demonstrated as expected the presence of the internal hydrogen bond between the 4'-amino function and the pyrrolidino side-chain. This compound provides one more time the evidence of the importance of this hydrogen linkage. The presence of another hydrogen bond between 4'-amino function and piperazine nitrogen atom is also noteworthy (Fig. **2**). On the other hand, in the case of other compounds, as for compound **8d**, the structure of the compound is incompatible with hydrogen bound and the conformation of the compound is very different from compound **8h** (Fig. **3**).

In conclusion, the study of these two series of derivatives shows that (i) the 4'-hydroxy function can be successfully replaced by various amino substituents in terms of activity on CQ-resistant strains, (ii) the antimalarial activity of these compounds is not influenced by the level of CQ-resistance of the strains and (iii) morpholine substituent lead to compounds of same selectivity index as AQ (around 3000). The possible formation of an intramolecular hydrogen bound seems not a major parameter for activity as most interesting compounds' structures are not compatible with this internal linkage. Among compounds synthesized in this study, seven of them (**7b**, **8b**, **7c**, **7d**, **8d**, **7e**, **7g**) exhibited a selectivity

Table 3. Cytotoxicity on MRC-5 Cells and Selectivity Index Calculated from IC_{50} Values Against the CQ-Resistant K1 Strain of *P. falciparum*

No.	NR'R"	Cytotoxicity	SI (K1) [b]
		CC_{50} ± SD (μM) [a]	CC_{50} / IC_{50}
AQ analogs			
AQ	OH	29.4 ± 2.1	3267
9	H	31.3 ± 0.8	1729
7a	dimethylamine	17.4 ± 1.2	870
7b	pyrrolidine	28.3 ± 1.2	1482
7c	piperidine	23.2 ± 1.0	1241
7d	morpholine	16.7 ± 0.2	2783
7e	N-methyl-piperazine	7.1 ± 1.7	1127
7f	cyclohexylmethylamine	15.5 ± 0.7	103
7g	benzylamine	76.6 ± 17	1094
7h	piperidinethylamine	2.8 ± 0.7	560
ApQ analogs			
ApQ	OH	23.5 ± 1.3	5595
10	H	29.8 ± 6.2	3425
8a	dimethylamine	14.7 ± 1.2	886
8b	pyrrolidine	26.5 ± 1.3	1387
8c	piperidine	10.4 ± 3.1	584
8d	morpholine	31.8 ± 0.9	3495
8e	N-methyl-piperazine	8.6 ± 0.8	887
8f	cyclohexylmethylamine	15.1 ± 0.6	129
8g	benzylamine	12.7 ± 4.1	477
8h	piperidinethylamine	2.1 ± 0.1	318

[a] CC_{50} is the IC_{50} value for cytotoxicity calculated on the basis of three experiments; [b] SI (selectivity index) = CC_{50} / IC_{50} (K1).

index higher than 1000 and may be considered for further development. These compounds have now to be modified by the introduction of a small substituent (methyl group for instance) in 5'-position in order to avoid bioactivation, metabolisation and subsequent potential hepatotoxicity. Work is in progress to evaluate this strategy.

MATERIALS AND METHODS

Chemistry

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. Thick-layer chromatography (TLC) was performed using silica gel from Merck, from which the compounds were extracted by the following solvent system: CH_2Cl_2/MeOH/NH_4OH, 75:25:4. All melting points were determined on a Büchi melting point apparatus and were uncorrected. ^1H 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. Mass spectra were recorded on a MALDI-TOF Voyager-DE-STR spectrometer. 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). Analytical HPLC was performed on a Shimadzu system equipped with a UV detector set at 254 nm. Compounds were dissolved in MeOH/water or ethyl acetate and injected through a 50 μL loop. The following eluent systems were used: A (H_2O/TFA, 100:0.05) and B (CH_3CN/H_2O/TFA, 80:20:0.05). HPLC retention times (HPLC t_R) were obtained, at flow rates of 1 mL/min, using the following conditions: for the 10min method : a gradient run from 100% eluent A during 30s, then to 100% eluent B over the next 8 min and for the 40 min

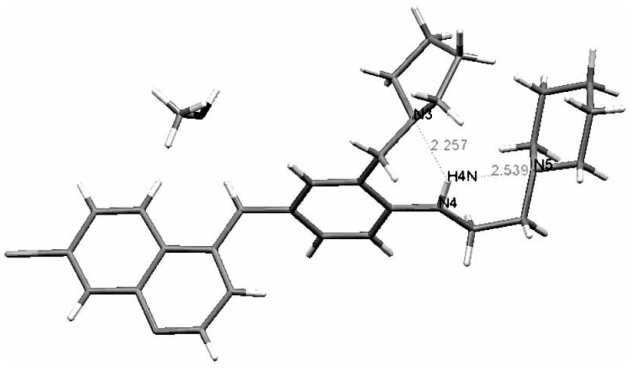


Fig. (2). X-ray crystallography studies of compound **8h**.

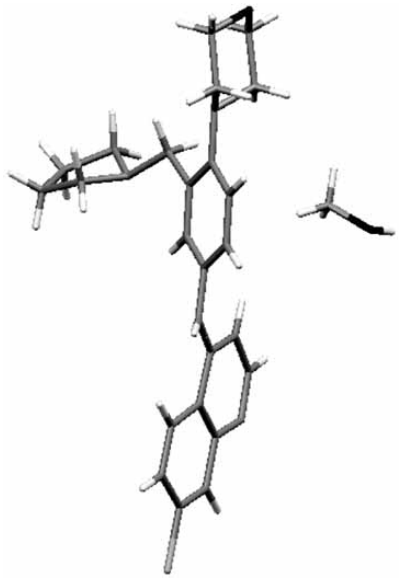


Fig. (3). X-ray crystallography studies of compound **8d**.

method : a gradient run from 100% eluent A during 1 min, then to 100% eluent B over the next 30 min. Reagents were obtained from Acros, Aldrich, Lancaster, Novabiochem and Avocado.

The following abbreviations were used: EP (petroleum ether), AcOEt (ethyl acetate), Hex (n-hexane), Cyh (cyclohexane), DCM (dichloromethane), ACN (acetonitrile), Quin (quinoline).

Toluene-4-sulfonic acid 2-fluoro-5-nitro-benzyl Ester 12

To a solution of NaOH (0.537g, 2.3eq) in H_2O (4 mL) was added, at 0°C, a solution of alcohol **11** [33] (0.999g, 5.84mmol) in THF (20 mL). When the temperature was below 5°C for 20 min, a solution of TsCl (1.892g, 1.7eq) in THF (10 mL) was added over 3h. After stirring at 5°C for 2 h, the mixture was hydrolysed with water (50 mL), extracted in DCM (3x100 mL). The organic layers were then combined, dried over $MgSO_4$, the solvent was evaporated. Most of the compound was precipited in methanol and filtered. The resulting solution was concentrated and purified by TLC (Hex/AcOEt//7/3) to yield compound **12** as a yellow-white solid (1.7 g, 90% yield); R_f 0.6 (Hex/AcOEt//7/3); HPLC (C18-10min) P_{HPLC} 98%, t_R 6.45 min; ^{1}H NMR ($CDCl_3$) δ 8.18-8.26 (2H, m, Ar-H_4, Ar-H_6), 7.82 (2H, d, Tos-H), 7.35 (2H, d, Tos-H), 7.20 (1H, dd, 3-CH, $^3J_{3,4}$ = 8.7Hz, $^3J_{3,F}$ = 8.7Hz), 5.17 (2H, s, CH_2), 2.46 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 130.1 (2C, Tos), 128.1 (2C, Tos), 126.7 (d, Ar-C_4, $^3J_{C4,F}$ = 10.0Hz), 126.3 (d, Ar-C_6, $^3J_{C6,F}$ = 5.0Hz), 116.7 (d, Ar-C_3, $^2J_{C3,F}$ = 23.6Hz), 64.1 (d, CH_2, $^3J_{C7,F}$ = 4.1Hz), 22.2 (CH_3).

Diethyl-(2-fluoro-5-nitro-benzyl)-amine 13

To a solution of tosyl compound **12** (0.696g, 2.13mmol) in 1,4-dioxane (20mL), was added triethylamine (0.45mL, 1.5eq) and diethylamine (0.33mL, 1.5eq). After stirring the mixture at 55°C for 8h, the solvent was evaporated. The residue was purified by TLC (EP/AcOEt/NH_4OH//8/2/0.2) to yield compound **13** as a yellow oil (0.365g, 76% yield); R_f 0.8 (EP/AcOEt/NH_4OH//8/2/0.2); HPLC (C18-10min) P_{HPLC} 99%, t_R 2.84 min; ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, dd, Ar-H_6, $^4J_{6,4}$ = 2.9Hz, $^4J_{6,F}$ = 6.3Hz), 8.12 (1H, ddd, Ar-H_4, $^3J_{4,3}$ = 8.9Hz, $^4J_{4,6}$ = 2.9Hz, $^4J_{4,F}$ = 4.4Hz), 7.15 (1H, dd, Ar-H_3, $^3J_{3,4}$ = 8.9Hz, $^3J_{3,F}$ = 8.9Hz), 3.67 (2H, s, CH_2), 2.58 (4H, qv, CH_2, $^3J_{9,10}$ = 7.1Hz), 1.08 (6H, t, CH_3, $^3J_{10,9}$ = 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 126.7 (d, Ar-C_6, $^3J_{C6,F}$ = 6.9Hz), 124.1 (d, Ar-C_4, $^3J_{C4,F}$ = 10.2Hz), 115.9 (d, Ar-C_3, $^2J_{C3,F}$ = 24.6Hz), 49.6 (CH_2), 47.1 (2C, CH_2), 11.8 (2C, CH_3); m/z 227.1 (M^++1).

1-(2-Fluoro-5-nitro-benzyl)-pyrrolidine 14

To a solution of tosyl compound **12** (0.696g, 2.31mmol) in 1,4-dioxane (20mL), was added triethylamine (0.32mL, 1eq) and pyrrolidine (0.19mL, 1eq). After stirring the mixture at room temperature for 24h, the solvent was evaporated. The residue was purified by TLC (EP/AcOEt/ NH_4OH//8/2/0.2) to yield compound **14** as a yellow oil (0.399g, 77% yield); R_f 0.8 (EP/AcOEt /NH_4OH//8/2/0.2); HPLC (C18-10min) P_{HPLC} > 99%, t_R 2.86 min; ^{1}H NMR ($CDCl_3$) δ 8.38 (1H, dd, Ar-H_6, $^4J_{6,4}$ = 2.9Hz, $^4J_{6,F}$ = 6.2Hz), 8.15 (1H, ddd, Ar-H_4, $^3J_{4,3}$ = 8.9Hz, $^4J_{4,6}$ = 2.9Hz, $^4J_{4,F}$ = 4.4Hz), 7.17 (1H, dd, Ar-H_3, $^3J_{3,4}$ = 8.9Hz, $^3J_{3,F}$ = 8.9Hz), 3.76 (2H, d, CH_2, $^4J_{CH2,F}$ = 1.3Hz), 2.57-2.64 (4H, m, N-CH_2), 1.80-1.87 (4H, m, CH_2).; ^{13}C NMR ($CDCl_3$) δ 127.0 (d, Ar-C_6, $^3J_{C6,F}$ = 6.4Hz), 124.5 (d, Ar-C_4, $^3J_{C4,F}$ = 10.1Hz), 116.2 (d, Ar-C_3, $^2J_{C3,F}$ = 24.9Hz), 54.1 (2C, N-CH_2), 52.2 (CH_2), 23.5 (2C, CH_2); m/z 225.1 $[M+H]^+$.

AROMATIC SUBSTITUTION OF FLUORINE ATOM : GENERAL PROCEDURE A

To a solution of fluoro compound in EtOH or ACN was added K_2CO_3 (2eq) and appropriate amine (1.1eq). The reaction medium was refluxed and the evolution was followed by TLC and HPLC. The reaction medium was filtered and concentrated. $NaHCO_3$ sat solution (50mL) was added and the compound was extracted with DCM (3x100mL or 5x50mL).

Combined organic layers were dried over $MgSO_4$ and evaporated. The compound was purified by preparative TLC.

(2-Diethylaminomethyl-4-nitro-phenyl)-dimethyl-amine 15a

Synthesized from compound **13** (100mg, 0.446mmol), K_2CO_3 (367mg, 6eq) and dimethylamine (0.442mL, solution 2M MeOH, 2eq) according to general procedure **A** (reflux for 16h). The residue was purified by TLC (EP/AcOEt/ NH_4OH//9/1/0.2) to yield expected compound **15a** as a yellow solid (104mg, 94% yield); R_f 0.6 (EP/AcOEt/NH_4OH// 8/2/0.2); HPLC (C18-10min) P_{HPLC} 99%, t_R 3.57 min; ^{1}H NMR ($CDCl_3$) δ 8.53 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.8Hz), 8.03 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.9Hz, $^4J_{4,6}$ = 2.8Hz), 6.96 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.9Hz), 3.61 (2H, s, CH_2), 2.85 (6H, s, N-CH_3), 2.55 (4H, q, N-CH_2, ^3J = 7.1Hz), 1.05 (6H, t, CH_3, ^3J = 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 126.3 (Ar-C_6), 123.0 (Ar-C_4), 117.3 (Ar-C_3), 53.3 (CH_2), 47.3 (2C, N-CH_2),44.1 (2C, N-CH_3), 11.8 (2C, CH_3); m/z 252.2 $[M+H]^+$.

Diethyl-(5-nitro-2-pyrrolidin-1-yl-benzyl)-amine 15b

Synthesized from compound **13** (100mg, 0.442mmoles), K_2CO_3 (122mg) and pyrrolidine (0.041mL) according to general procedure **A** (reflux for 4h). The residue was purified by TLC (Cyh/AcOEt/NH_4OH//8/2/0.2) to yield expected compound **15b** as a yellow solid (89mg, 73% yield); R_f 0.5 (Cyh/AcOEt/ NH_4OH//8/2/0.2); mp = 77-78°C; HPLC (C18-10min) P_{HPLC} 98%, t_R 4.11 min; ^{1}H NMR ($CDCl_3$) δ 8.31 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.9Hz), 7.98 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 9.2Hz, $^4J_{4,6}$ = 2.9Hz), 6.61 (1H, d, Ar-H_3, $^3J_{3,4}$ = 9.2Hz), 3.62 (2H, s, CH_2), 3.54 – 3.58 (4H, m, N-CH_2), 2.51 (4H, q, N-CH_2, ^3J = 7.1Hz), 1.96 - 2.00 (4H, m, CH_2), 1.01 (6H, t, CH_3, ^3J = 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 128.4 (Ar-C_6), 124.0 (Ar-C_4), 113.4(Ar-C_3), 56.8 (CH_2), 51.1 (2C, N-CH_2), 46.2 (2C, N-CH_2), 25.7 (2C, CH_2),11.5 (2C, CH_3); m/z 278.2 $[M+H]^+$.

Diethyl-(5-nitro-2-piperidin-1-yl-benzyl)-amine 15c

Synthesized from compound **13** (100mg, 0.442mmol), K_2CO_3 (122mg) and piperidine (0.051mL) according to general procedure **A** (reflux for 3h). The residue was purified by TLC (Cyh/AcOEt/NH_4OH//8/2/0.2) to yield expected compound **15c** as a yellow solid (117mg, 91% yield); R_f 0.7 (Cyh/AcOEt/ NH_4OH//8/2/0.2); mp = 55-56°C; HPLC (C18-10min) P_{HPLC} 97%, t_R 4.56 min; ^{1}H NMR ($CDCl_3$) δ 8.52 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.8Hz), 8.03 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.9Hz, $^4J_{4,6}$ = 2.8Hz), 6.98 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.9Hz), 3.54 (2H, s, CH_2), 2.95 (4H, m, N-CH_2), 2.52 (4H, q, N-CH_2, ^3J = 7.2Hz), 1.71 - 1.76 (4H, m, CH_2), 1.61 - 1.65 (2H, m, CH_2), 1.03 (6H, t, CH_3, ^3J = 7.2Hz); ^{13}C NMR ($CDCl_3$) δ 126.7 (Ar-C_6), 125.0 (Ar-C_4), 123.6 (Ar-C_3), 54.2 (2C, N-CH_2), 53.0 (CH_2), 48.0 (2C, N-CH_2), 27.0 (2C, CH_2), 24.9 (CH_2),12.7 (2C, CH_3); m/z 292.2 $[M+H]^+$.

Diethyl-(2-morpholin-4-yl-5-nitro-benzyl)-amine 15d

Synthesized from compound **13** (100mg, 0.442mmol), K_2CO_3 (122mg) and morpholine (0.043mL) according to general procedure **A** (reflux for 6h). The residue was purified by TLC (Cyh/AcOEt/NH_4OH//8/2/0.2) to yield expected compound **15d** as a yellow solid (97mg, 75% yield); R_f 0.4 (Cyh/AcOEt/ NH_4OH//8/2/0.2); mp = 47-48°C; HPLC (C18-10min) P_{HPLC} 97%, t_R 3.39 min; ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.8Hz), 8.07 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.8Hz, $^4J_{4,6}$ = 2.8Hz), 7.04 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.8Hz), 3.88 (4H, m, O-CH_2), 3.57 (2H, s, CH_2), 3.05 (4H, m, N-CH_2), 2.53 (4H, q, N-CH_2, ^3J = 7.1Hz), 1.03 (6H, t, CH_3, ^3J = 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 126.5 (Ar-C_6), 123.3 (Ar-C_4), 118.6 (Ar-C_3), 67.2 (2C, O-CH_2), 52.8 (CH_2), 52.6 (2C, N-CH_2), 47.3 (2C, N-CH_2), 12.0 (2C, CH_3); m/z 294.2 $[M+H]^+$.

Diethyl-[2-(4-methyl-piperazin-1-yl)-5-nitro-benzyl]-amine 15e

Synthesized from compound **13** (187mg, 0.825mmol), K_2CO_3 (228mg) and *N*-CH_3-piperazine (0.101mL) according to general procedure **A** (reflux for 16h). The residue was purified by TLC (AcOEt/ NH_4OH//10/0.2) to yield expected compound **15e** as a yellow oil (231mg, 91% yield); R_f 0.4 (AcOEt/NH_4OH//10/0.2); HPLC (C18-10min) P_{HPLC} 98%, t_R 0.67-2.61 min; ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.8Hz), 8.02 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.9Hz, $^4J_{4,6}$= 2.8Hz), 7.05 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.9Hz), 3.58 (2H, s, CH_2), 3.10 (4H, m, N-CH_2), 2.65 (4H, m, N-CH_2), 2.54 (4H, q, N-CH_2, ^3J = 7.1Hz), 2.40 (3H, s, N-CH_3), 1.04 (6H, t, CH_3, ^3J= 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 126.0 (Ar-C_6), 122.9 (Ar-C_4), 118.5 (Ar-C_3), 55.1 (2C, N-CH_2), 52.5 (1C, CH_2), 51.9 (2C, N-CH_2), 47.2 (2C, N-CH_2), 46.0 (N-CH_3),11.9 (2C, CH_3); m/z 307.3 $[M+H]^+$.

Cyclohexylmethyl-(2-diethylaminomethyl-4-nitro-phenyl)-amine 15f

Synthesized from compound **13** (100mg, 0.442mmol), K_2CO_3 (244mg, 4eq) and cyclohexylmethylamine (0.069mL) according to general procedure **A** (reflux for 48h). The residue was purified by TLC (Cyh/AcOEt/NH_4OH//8/2/0.2) to yield expected compound **15f** as a yellow solid (133mg, 75% yield); R_f 0.4 (Cyh/AcOEt/NH_4OH//8/2/0.2); HPLC (C18-10min) P_{HPLC} 95%, t_R 5.69 min; ^{1}H NMR ($CDCl_3$) δ 8.06 (1H, dd, Ar-H_4, $^3J_{4,3}$= 9.0Hz, $^4J_{4,6}$ = 2.7Hz), 7.85 – 7.98 (1H, t large, NH), 7.89 (1H, d, Ar-H_6, $^4J_{6,4}$= 2.7Hz), 6.45 (1H, d, Ar-H_3, $^4J_{3,4}$= 9.0Hz), 3.61 (2H, s, CH_2), 3.03 (2H, dd, NH-CH_2, ^3J = 6.0Hz), 2.50 (4H, q, N-CH_2, ^3J = 7.2Hz), 1.54 - 1,84 (6H, m, Cyh), 1.16 – 1.34 (3H, m, Cyh), 1.04 (6H, t, CH_3, ^3J = 7.2Hz), 0.98 - 1,04 (2H, m, Cyh); ^{13}C NMR ($CDCl_3$) δ 126.1 (2C, Ar-C_6, Ar-C_4), 107.7 (Ar-C_3), 57.8 (CH_2),49.7 (CH_2), 46.3 (2C, N-CH_2), 37.8 (CH), 31.4 (2C, CH_2), 26.6 (CH_2), 26.1 (2C, CH_2), 11.5 (2C, CH_3); m/z 320.4 $[M+H]^+$.

Benzyl-(2-diethylaminomethyl-4-nitro-phenyl)-amine 15g

Synthesized from compound **13** (100mg, 0.442mmol), K_2CO_3 (244mg, 4eq) and benzylamine (0.058mL) according to general procedure **A** (reflux for 72h). The residue was purified by TLC (EP/AcOEt/ NH_4OH//9/1/0.2) to yield expected compound **15g** as a yellow solid (122mg, 75% yield); R_f 0.5 (EP/AcOEt/NH_4OH//9/1/0.2); mp = 75-77°C; HPLC (C18-10min) P_{HPLC} 95%, t_R 4.76 min; ^{1}H NMR ($CDCl_3$) δ 8.32 (1H, m large, NH), 8.05 (1H, dd, Ar-H_4, $^3J_{4,3}$= 9.1Hz, $^4J_{4,6}$ = 2.6Hz), 7.94 (1H, d, Ar-H_6, $^4J_{6,4}$= 2.6Hz), 7.27-7,39 (5H, m, Ar), 6.48 (1H, d, Ar-H_3, $^4J_{3,4}$= 9.1Hz), 4.43 (1H, d, CH_2, ^3J = 5.2Hz), 3.66 (1H, s, CH_2), 2.48 (4H, q, N-CH_2, ^3J = 7.0Hz), 0.96 (6H, t, CH_3, ^3J= 7.0Hz); ^{13}C NMR ($CDCl_3$) δ 128.7 (2C, Ph), 127.4 (Ph), 127.1 (2C, Ph), 125.8 (Ar-C_6),

125.7 (Ar-C_4), 108.2 (Ar-C_3), 57.4 (CH_2), 47.0 (NH-CH_2), 46.0 (2C, N-CH_2), 11.2 (2C, CH_3); m/z 314.3 $[M+H]^+$.

(2-Diethylaminomethyl-4-nitro-phenyl)-(2-piperidin-1-yl-ethyl)-amine 15h

Synthesized from compound **13** (100mg, 0.442mmol), K_2CO_3 (244mg, 4eq) and 1-(2-aminoethyle)-piperidine (0.075 mL) according to general procedure **A** (reflux for 48h). The residue was purified by TLC (Hex/AcOEt/NH_4OH//8/2/0.2) to yield expected compound **15h** as a yellow solid (147mg, 99% yield); R_f 0.6 (Hex/AcOEt/NH_4OH//8/2/0.2); mp = 43-45 °C; HPLC (C18-10min) P_{HPLC} 99%, t_R 2.96 min; ^{1}H NMR ($CDCl_3$) δ 8.08 (1H, dd, Ar-H_4, $^3J_{4,3}$= 9.1Hz, $^4J_{4,6}$ = 2.7Hz), 7.93 – 8.03 (1H, m, NH), 7.91 (1H, d, Ar-H_6, $^4J_{6,4}$= 2.7Hz), 6.47 (1H, d, Ar-H_3, $^4J_{3,4}$= 9.1Hz),3.60 (2H, s, CH_2), 3.27 (2H, td, NH-C$\underline{H}_2$, ^3J= 6.0Hz), 2.60 (2H, t, N-CH_2, ^3J= 6.4Hz), 2.50 (4H, q, N-CH_2, ^3J= 7.1Hz), 2.43 - 2.49 (4H, m, N-CH_2),1.56 - 1.63 (4H, m, CH_2), 1.44-1.50 (2H, m, CH_2), 1,06 (6H, t, CH_3, ^3J= 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 126.2 (Ar-C_4), 126.1 (Ar-C_6), 108.0 (Ar-C_3), 57.5 (CH_2), 57.2 (CH_2), 54.6 (2C, N-CH_2), 46.5 (2C, N-CH_2), 40.2 (1C, NH-CH_2), 26.1 (2C, CH_2), 24.5 (CH_2), 11.6 (2C, CH_3); m/z 335.2 (M^++1).

Dimethyl-(4-nitro-2-pyrrolidin-1-ylmethyl-phenyl)-amine 16a

Synthesized from compound **14** (100mg, 0.446mmol), K_2CO_3 (367mg, 6eq) and dimethylamine (0.45mL, 2M in MeOH, 2eq) in ACN (25mL) according to general procedure **A** (reflux for 16h). The residue was purified by TLC (EP/AcOEt/NH_4OH//9/1/0.2) to yield expected compound **16a** as a yellow solid (83mg, 94% yield); R_f 0.5 (AcOEt/EP/NH_4OH//1/9/0.2); mp = 72-74°C; HPLC (C18-10min) P_{HPLC} 99%, t_R 3.52 min; ^{1}H NMR ($CDCl_3$) δ 8.35 (1H, d, 6 Ar-H_6, $^4J_{6,4}$= 2.8Hz), 8.04 (1H, dd, Ar-H_4, $^3J_{4,3}$= 9.0Hz, $^4J_{4,6}$ = 2.8Hz), 6.94 (1H, d, Ar-H_3, $^3J_{3,4}$= 9.0Hz), 3.69 (2H, s, CH_2), 2.92 (6H, s, N-CH_3), 2.58 – 2.62 (4H, m, N-CH_2), 1.79 – 1.84 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 126.8 (Ar-C_6), 123.5 (Ar-C_4), 117.2 (Ar-C_3), 56.2 (CH_2), 54.2 (2C, N-CH_2), 43.9 (2C, N-CH_3), 24.7 (2C, CH_3); m/z 250.2 $[M+H]^+$.

1-(4-Nitro-2-pyrrolidin-1-ylmethyl-phenyl)-pyrrolidine 16b

Synthesized from compound **14** (100mg, 0.446mmol), K_2CO_3 (123mg) and pyrrolidine (0.041mL) in EtOH (5mL) according to general procedure **A** (reflux for 20h). The residue was purified by TLC (Cyh/AcOEt/ NH_4OH//8/2/0.2) to yield expected compound **16b** as a yellow solid (81mg, 66% yield); R_f 0.4 (Cyh/AcOEt/NH_4OH//8/2/0.2); HPLC (C18-10min) P_{HPLC} 99%, t_R 4.03 min; ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, d, Ar-H_6, $^4J_{6,4}$= 2.7Hz), 7.99 (1H, dd, Ar-H_4, $^3J_{4,3}$= 9.3Hz, $^4J_{4,6}$ = 2.7Hz), 6.57 (1H, d, Ar-H_3, $^3J_{3,4}$= 9.3Hz), 3.63 – 3.67 (6H, m, CH_2, N-CH_2), 2.50 (4H, m, N-CH_2), 1.96 – 2.01 (4H, m, CH_2), 1.74 – 1.79 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 129.2 (Ar-C_6), 124.6 (Ar-C_4), 113.3 (Ar-C_3), 59.2 (CH_2), 53.7 (2C, N-CH_2), 50.9 (2C, N-CH_2), 25.8 (2C, CH_2), 23.5 (2C, CH_2); m/z 276.2 $[M+H]^+$.

1-(4-Nitro-2-pyrrolidin-1-ylmethyl-phenyl)-piperidine 16c

Synthesized from compound **14** (100mg, 0.446mmol), K_2CO_3 (123mg) and piperidine (0.049mL) in EtOH (5mL) according to general procedure **A** (reflux for 3h). The residue was purified by TLC (Cyh/AcOEt/ NH_4OH//8/2/0.2) to yield expected compound **16c** as a yellow solid (108mg, 84% yield); R_f 0.6 (Cyh/AcOEt/NH_4OH//8/2/0.2); mp = 103-104°C; HPLC (C18-10min) P_{HPLC} 96%, t_R 4.60 min; ^{1}H NMR ($CDCl_3$) δ 8.36 (1H, d, Ar-H_6, $^4J_{6,4}$ = 3.0Hz), 8.05 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.9Hz, $^4J_{4,6}$ = 3.0Hz), 6.98 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.9Hz), 3.63 (2H, s, CH_2), 3.03 (4H, m, N-CH_2), 2.53 – 2.58 (4H, m, N-CH_2), 1.76 – 1.82 (4H, m, CH_2), 1.70 – 1.76 (4H, m, CH_2), 1.59 – 1.65 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 126.2 (Ar-C_6), 123.4 (Ar-C_4), 118.5 (Ar-C_3), 55.4 (CH_2), 54.4 (2C, N-CH_2), 53.5 (2C, N-CH_2), 26.4 (2C, CH_2), 24.3 (CH_2), 23.8 (2C, CH_2); m/z 290.2 $[M+H]^+$.

4-(4-Nitro-2-pyrrolidin-1-ylmethyl-phenyl)-morpholine 16d

Synthesized from compound **14** (100mg, 0.446mmol), K_2CO_3 (123mg) and morpholine (0.043mL) in EtOH (5mL) according to general procedure **A** (reflux for 6h). The residue was purified by TLC (Cyh/AcOEt/NH_4OH//8/2/0.2) to yield expected compound **16d** as a yellow solid (107mg, 82% yield); R_f 0.4 (Cyh/AcOEt/NH_4OH//8/2/0.2); mp = 70-72°C; HPLC (C18-10min) P_{HPLC} 77%, t_R 3.37 min; ^{1}H NMR ($CDCl_3$) δ 8.33 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.7Hz), 8.09 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.7Hz, $^4J_{4,6}$ = 2.7Hz), 7.03 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.7Hz), 3.88 (4H, m, O-CH_2), 3.65 (2H, s, CH_2), 3.15 (4H, m, N-CH_2), 2.52 – 2.58 (4H, m, N-CH_2), 1.76 – 1.82 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 126.6 (Ar-C_6), 123.6 (Ar-C_4), 118.6 (Ar-C_3), 67.3 (2C, O-CH_2), 55.7 (CH_2), 54.3 (2C, N-CH_2), 52.6 (2C, N-CH_2), 23.8 (2C, CH_2); m/z 292.2 $[M+H]^+$.

1-Methyl-4-(4-nitro-2-pyrrolidin-1-ylmethyl-phenyl)-piperazine 16e

Synthesized from compound **14** (105mg, 0.470mmol), K_2CO_3 (130mg) and *N*-CH_3-piperazine (0.058mL) in ACN (20mL) according to general procedure **A** (reflux for 16h). The residue was purified by TLC (AcOEt/NH_4OH//10/0.2) to yield expected compound **16e** as a yellow solid (118mg, 82% yield); R_f 0.4 (AcOEt/NH_4OH//10/0.2); HPLC (C18-10min) P_{HPLC} 99%, t_R 0,64 - 2,36 min; ^{1}H NMR ($CDCl_3$) δ 8.33 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.8Hz), 8.06 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.9Hz, $^4J_{4,6}$= 2.8Hz), 7.04 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.9Hz), 3.66 (2H, s, CH_2), 3.18 (4H, m, N-CH_2), 2.64 (4H, m, N-CH_2), 2.56 – 2.61 (4H, m, N-CH_2), 2.40 (3H, s, N-CH_3), 1.77 – 1.82 (4H, m, N-CH_2); ^{13}C NMR ($CDCl_3$) δ 126.3 (Ar-C_6), 123.5 (Ar-C_4), 118.7 (Ar-C_3), 55.5 (CH_2), 55.3 (2C, N-CH_2), 54.3 (2C, N-CH_2), 51.9 (2C, N-CH_2), 46.1 (N-CH_3), 23.7 (2C, CH_2); m/z 305.3 $[M+H]^+$.

Cyclohexylmethyl-(4-nitro-2-pyrrolidin-1-ylmethyl-phenyl)-amine 16f

Synthesized from compound **14** (100mg, 0.446mmol), K_2CO_3 (247mg, 4eq) and cyclohexylmethylamine (0.070mL) in ACN (25mL) according to general procedure **A** (reflux for 46h). The residue was purified by TLC (Cyh/AcOEt/NH_4OH// 8/2/0.2) to yield expected compound **16f** as a yellow solid (134mg, 95% yield); R_f 0.6 (Cyh/AcOEt/NH_4OH//8/2/0.2); (C18-10min) P_{HPLC} 99%, t_R 5.51 min; ^{1}H NMR ($CDCl_3$) δ 8.08 (1H, dd, Ar-H_4, $^3J_{4,3}$= 9.1Hz, $^4J_{4,6}$ = 2.6Hz), 7.85-7,95 (1H, m, NH),7.90 (1H, d, Ar-H_6, $^4J_{6,4}$= 2.6Hz), 6.45 (1H, d, Ar-H_3, $^4J_{3,4}$= 9.1Hz), 3.65 (2H, s, CH_2), 3.05 (2H, dd, NH-C$\underline{H}_2$, ^3J = 5.9Hz), 2.47 (4H, m, N-CH_2), 1.56 – 1.80 (10H, m, CH_2, Cyh), 1.15 – 1.43 (3H, m, Cyh), 1.06 – 1.14 (2H, m,

Cyh); ^{13}C NMR ($CDCl_3$) δ 126.1 (Ar-C_4), 125.5 (Ar-C_6), 107.7 (Ar-C_3), 59.5 (CH_2),53.5 (2C, N-CH_2),49.6 (NH-CH_2), 37.7 (CH), 31.2 (2C, CH_2), 26.6 (CH_2), 26.1 (CH_2), 23.8 (CH_2); m/z 318.3 $[M+H]^+$.

Benzyl-(4-nitro-2-pyrrolidin-1-ylmethyl-phenyl)-amine 16g

Synthesized from compound **14** (100mg, 0.446mmol), K_2CO_3 (247mg, 4eq) and benzylamine (0.059mL) in ACN (25mL) according to general procedure **A** (reflux for 72h). The residue was purified by TLC (EP/AcOEt/NH_4OH// 9/1/0.2) to yield expected compound **16g** as a yellow solid (125mg, 90% yield); R_f 0.6 (EP/AcOEt/NH_4OH//9/1/0.2); mp = 42 - 45°C; HPLC (C18-10min) P_{HPLC} 99%, t_R 4.59 min; ^{1}H NMR ($CDCl_3$) δ 8.22 (1H, m large, NH), 8.03 (1H, dd, Ar-H_4, $^3J_{4,3}$= 9.1Hz, $^4J_{4,6}$ = 2.6Hz), 7.94 (1H, d, Ar-H_6, $^4J_{6,4}$= 2.6Hz), 7.26 – 7.39 (5H, m, Ph), 6.48 (1H, d, Ar-H_3, $^4J_{3,4}$= 9.1Hz), 4.46 (1H, d, NH-CH_2, ^3J= 5.5Hz), 3.72 (1H, s, CH_2),2.50 (4H, m, N-CH_2), 1.71 – 1.81 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 128.6 (2C, Ph), 127.3 (1C, Ph), 126.7 (Ph), 125.3 (Ar-C_6), 124.3 (Ar-C_4), 108.2 (Ar-C_3), 59.1 (CH_2), 53.2 (2C, N-CH_2), 46.9 (NH-CH_2), 24.4 (2C, CH_2); m/z 312.4 $[M+H]^+$.

(4-Nitro-2-pyrrolidin-1-ylmethyl-phenyl)-(2-piperidin-1-yl-ethyl)-amine 16h

Synthesized from compound **14** (100mg, 0.446mmol), K_2CO_3 (247mg, 4eq) and 1-(2-aminoethyl)-piperidine (0.076 mL) in ACN (25mL) according to general procedure **A** (reflux for 48h). The residue was purified by TLC (Hex/AcOEt/ NH_4OH//8/2/0.2) to yield expected compound **16h** as a yellow solid (190mg, 98% yield); R_f 0.5 (Hex/AcOEt/NH_4OH// 8/2/0.2); mp = 63-65°C; HPLC (C18-10min) P_{HPLC} 99%, t_R 2.95 min; ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, dd, Ar-H_4, $^3J_{4,3}$= 9.1Hz, $^4J_{4,6}$ = 2.7Hz), 7.93 (1H, d, Ar-H_6, $^4J_{6,4}$= 2.7Hz), 7.65-7,82 (1H, m, NH), 6.48 (1H, d, Ar-H_3, $^4J_{3,4}$= 9.1Hz), 3.62 (2H, s, CH_2), 3.27 (2H, q, NH-CH_2, ^3J= 5.9Hz), 2.59 (2H, t, N-CH_2, ^3J= 6.3Hz), 2.46 - 2.52 (4H, m, N-CH_2), 2.41 - 2.44 (4H, m, N-CH_2), 1.73 – 1.81 (4H, m, CH_2),1.55 - 1.63 (4H, m, CH_2),1.45 - 1.49 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 125.8 (Ar-C_4), 125.3 (Ar-C_6), 107.7 (Ar-C_3), 59.1 (CH_2), 57.1 (N-CH_2), 54.3 (2C, N-CH_2), 53.3 (2C, N-CH_2), 39.8 (NH-CH_2), 25.8 (2C, CH_2), 24.2 (CH_2), 23.6 (2C, CH_2); m/z 333.2 $[M+H]^+$.

REDUCTION OF NITRO GROUP : GENERAL PROCEDURE B

To a solution of nitro compound **15** or **16** (1eq) in THF was added a solution of tin chloride (4eq) in THF with HCl 1M (3eq). After stirring at reflux, the mixture was concentrated, alcalinized with $NaHCO_3$ (pH 8) and the aqueous layer extracted with DCM (5x50 mL). The organic layers were then combined, dried over $MgSO_4$, the solvent was evaporated and the residue purified by TLC.

2-Diethylaminomethyl-N^1,N^1-dimethyl-benzene-1,4-diamine 17a

Synthesized from compound **15a** (99mg, 0.394mmol) and $SnCl_2$ (298mg) in HCl (1.18mL) and THF (25mL) according to general procedure **B** (reflux for 5h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9/1/0.2) to yield expected compound **17a** as a yellow oil (39mg, 55% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 95%, t_R 2.30 – 2.41 min; ^{1}H NMR ($CDCl_3$) δ 6.97 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz), 6.96 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.8Hz), 6.56 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,6}$ = 2.8Hz), 3.80 - 4,10 (2H, s large, NH_2), 3.72 (2H, s, CH_2), 2.64 (4H, q, N-CH_2, ^3J = 7.2Hz), 2.58 (6H, s, N-CH_3), 1.10 (6H, t, CH_3, ^3J = 7.2Hz); ^{13}C NMR ($CDCl_3$) δ 120.3 (Ar-C_3), 116.4 (Ar-C_6), 114.2 (Ar-C_4), 51.4 (CH_2), 46.8 (2C, N-CH_2), 45.6 (2C, N-CH_3), 11.1 (2C, CH_3); m/z 222.4 $[M+H]^+$.

3-Diethylaminomethyl-4-pyrrolidin-1-yl-phenylamine 17b

Synthesized from compound **15b** (74mg, 0.268mmol) and $SnCl_2$ (203mg) in HCl (0.81mL) and THF (10mL) according to general procedure **B** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/ NH_4OH//9/1/0.2) to yield expected compound **17b** as a yellow oil (28mg, 43% yield); R_f 0.2 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 93%, t_R 2.52 – 2.78 min; ^{1}H NMR ($CDCl_3$) δ 7.03 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.8Hz), 6.92 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz),6.54 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,6}$ = 2.8Hz), 3.60 - 3,70 (2H, s large, NH_2), 3.63 (2H, s, CH_2), 2.92 - 2,96 (4H, m, N-CH_2), 2.59 (4H, q, N-CH_2, ^3J = 7.1Hz), 1.85 – 1,90 (4H, m, CH_2), 1.07 (6H, t, CH_3, ^3J = 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 119.5 (Ar-C_3), 116.9 (Ar-C_6), 114.2 (Ar-C_4), 53.0 (2C, N-CH_2),52.3 (CH_2),47.0 (2C, N-CH_2),24.4 (2C, CH_2),11.5 (2C, CH_3); m/z 248.2 $[M+H]^+$.

3-Diethylaminomethyl-4-piperidin-1-yl-phenylamine 17c

Synthesized from compound **15c** (102mg, 0.349mmol) and $SnCl_2$ (265mg) in HCl (1.05mL) and THF (10mL) according to general procedure **B** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/ NH_4OH//9/1/0.2) to yield expected compound **17c** as a yellow oil (35mg, 39% yield); R_f 0.2 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 95%, t_R 3.23 min; ^{1}H NMR ($CDCl_3$) δ 6.93 (1H, d, Ar-H_6, $^4J_{6,4}$ = 3.0Hz), 6.91 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz), 6.54 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,6}$ = 3.0Hz), 3.62 (2H, s, CH_2), 3.50 – 3.60 (2H, s large, NH_2), 2.71 (4H, m, N-CH_2), 2.57 (4H, q, N-CH_2, ^3J = 7.2Hz), 1.62 – 1.69 (4H, m, CH_2), 1.52 – 1.55 (2H, m, CH_2), 1.07 (6H, t, CH_3, ^3J = 7.2Hz); ^{13}C NMR ($CDCl_3$) δ 120.8 (Ar-C_3), 116.8 (Ar-C_6), 114.1 (Ar-C_4), 54.7 (2C, N-CH_2), 51.0 (CH_2), 46.8 (2C, N-CH_2), 26.7 (2C, CH_2), 24.3 (CH_2), 11.4 (2C, CH_3); m/z 262.3 $[M+H]^+$.

3-Diethylaminomethyl-4-morpholin-4-yl-phenylamine 17d

Synthesized from compound **15d** (79mg, 0.269mmol) and $SnCl_2$ (204mg) in HCl (0.81mL) and THF (10mL) according to general procedure **B** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/ NH_4OH//9/1/0.2) to yield expected compound **17d** as a yellow oil (42mg, 60% yield); R_f 0.3 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 95%, t_R 0.62 – 2.38 min; ^{1}H NMR ($CDCl_3$) δ 6.94 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz),6.90 (1H, d, Ar-H_6, $^4J_{6,4}$ = 3.0Hz), 6.55 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,6}$ = 3.0Hz), 3.81 (4H, m, O-CH_2), 3.60 (2H, s, CH_2), 3.40 – 3.60 (2H, s large, NH_2), 2.82 (4H, m, N-CH_2), 2.54 (4H, q, N-CH_2, ^3J = 7.1Hz), 1.05 (6H, t, CH_3, ^3J = 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 121.0 (Ar-C_3), 117.0 (Ar-C_6), 114.1 (Ar-C_4), 67.6 (2C, O-CH_2), 53.7 (2C, N-CH_2), 51.6 (CH_2), 46.9 (2C, N-CH_2),11.6 (2C, CH_3); m/z 264.3 $[M+H]^+$.

3-Diethylaminomethyl-4-(4-methyl-piperazin-1-yl)-phenylamine 17e

Synthesized from compound **15e** (231mg, 0.753mmol) and $SnCl_2$ (571mg) in HCl (2.26mL) and THF (20mL) according to general procedure **B** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9/1/0.2) to yield expected compound **17e** as a yellow oil (114mg, 55% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 99%, t_R 0.63 – 1.43 min; ^{1}H NMR ($CDCl_3$) δ 6.95 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz), 6.90 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.8Hz), 6.53 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,6}$= 2.8Hz), 3.80 – 4.20 (2H, s large, NH_2), 3.62 (2H, s, CH_2), 2.84 (4H, m, N-CH_2), 2.58 (4H, q, N-CH_2, ^3J = 7.0Hz), 2.55 (4H, m, N-CH_2), 2.34 (3H, s, N-CH_3), 1.06 (6H, t, CH_3, ^3J =7.0Hz); ^{13}C NMR ($CDCl_3$) δ 121.9 (Ar-C_3), 117.7 (Ar-C_6), 115.0 (Ar-C_4), 56.6 (2C, N-CH_2),53.9 (2C, N-CH_2),52.1 (CH_2),47.5 (2C, N-CH_2),47.0 (N-CH_3),12.2 (2C, CH_3); m/z 277.3 $[M+H]^+$.

***N*^{1}-Cyclohexylmethyl-2-diethylaminomethyl-benzene-1,4-diamine 17f**

Synthesized from compound **15f** (131mg, 0.409mmol) and $SnCl_2$ (310mg) in HCl (1.23mL) and THF (25mL) according to general procedure **B** (reflux for 22h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9/1/0.2) to yield expected compound **17f** as a violet oil (97mg, 82% yield); R_f 0.6 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} 96%, t_R 3.91 min; ^{1}H NMR ($CDCl_3$) δ 6.56 (1H, m, Ar-H_4), 6.41 – 6.46 (2H, m, Ar-H_3, Ar-H_6), 3.48 (2H, s, CH_2), 2.86 (2H, d, NH-C<u>H</u>$_2$, ^3J= 6.3Hz), 2.46 (4H, q, N-CH_2, ^3J=7.2Hz), 1.52 – 1.86 (6H, m, Cyh), 1.19 – 1.34 (3H, m, Cyh), 1.00 (6H, t, CH_3, ^3J= 7.2Hz), 0.98 – 1.90 (2H, m, Cyh); ^{13}C NMR ($CDCl_3$) δ 119.2 (Ar-C_6), 115.7 (Ar-C_4), 110.9 (Ar-C_3), 58.0 (CH_2), 51.1 (NH-CH_2), 46.5 (2C, N-CH_2), 38.0 (CH), 31.8 (2C, CH_2), 26.9 (CH_2), 26.3 (2C, CH_2), 11.7 (2C, CH_3); m/z 289.3 $[M+H]^+$.

N1-Benzyl-2-diethylaminomethyl-benzene-1,4-diamine 17g

Synthesized from compound **15g** (105mg, 0.335mmol) and $SnCl_2$ (254mg) in HCl (1.00mL) and THF (25mL) according to general procedure **B** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/ NH_4OH//9.5/0.5/0.2) to yield expected compound **17g** as a brown oil (32mg, 33% yield); R_f 0.7 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} 99%, t_R 3.30 min; ^{1}H NMR ($CDCl_3$) δ 7.20 - 7,41 (5H, m, Ph), 6.44 - 6,57 (3H, m, Ar-H_3, Ar-H_4, Ar-H_6), 4.27 (2H, s, NH-C<u>H</u>$_2$), 4.10 - 4,40 (2H, s large, NH_2), 3.57 (1H, s, CH_2), 2.51 (4H, q, N-CH_2, ^3J= 7.2 Hz), 0.98 (6H, t, CH_3, ^3J= 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 128.8 (2C, Ph), 127.6 (2C, Ph), 126.9 (1C, Ph), 119.2 (Ar-C_4), 115.9 (Ar-C_6), 112.1 (Ar-C_3), 57.5 (CH_2), 48.6 (NH-CH_2), 46.4 (2C, N-CH_2), 11.4 (2C, CH_3); m/z 283.4 $[M+H]^+$.

2-Diethylaminomethyl-*N*^{1}-(2-piperidin-1-yl-ethyl)-benzene-1,4-diamine 17h

Synthesized from compound **15h** (131mg, 0.392mmol) and $SnCl_2$ (297mg) in HCl (1.18mL) and THF (25mL) according to general procedure **B** (reflux for 6h). The residue was purified by TLC (DCM/MeOH/ NH_4OH//9/1/0.2) to yield expected compound **17h** as a yellow solid (70mg, 59% yield); R_f 0.6 (DCM/MeOH/NH_4OH//9/1/0.2); mp = 49-50°C; HPLC (C18-10min) P_{HPLC} 98%, t_R 0.66 - 2.48 min; ^{1}H NMR ($CDCl_3$) δ 6.58 (1H, dd, Ar-H_4, $^3J_{4,3}$= 8.4Hz, $^4J_{4,6}$ = 2.7Hz), 6.45 - 6.49 (2H, m, Ar-H_3, Ar-H_6), 3.48 (2H, s, CH_2), 3.15 (2H, t, NH-CH, ^3J = 6.4Hz), 2.59 (2H, t, N-CH_2, ^3J = 6.4Hz), 2.47 (4H, q, N-CH_2, ^3J = 7.1Hz), 2.43 - 2.52 (4H, m, CH_2),1.55 - 1.63 (4H, m, CH_2), 1.44 - 1.47 (2H, m, CH_2), 1.03 (6H, t, CH_3, ^3J = 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 119.3 (1C, Ar-C_6), 115.6 (Ar-C_4), 111.4 (Ar-C_3), 58.6 (N-CH_2), 57.4 (CH_2), 54.9 (2C, N-CH_2), 46.7 (2C, N-CH_2), 41.5 (NH-CH_2), 26.2 (2C, CH_2), 24.7 (CH_2),11.9 (2C, CH_3); m/z 305.2 (M^++1).

N^1,N^1-Dimethyl-2-pyrrolidin-1-ylmethyl-benzene-1,4-diamine 18a

Synthesized from compound **16a** (81mg, 0.323mmol) and $SnCl_2$ (245mg) in HCl (0.97mL) and THF (25mL) according to general procedure **B** (reflux for 5h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9/1/0.2) to yield expected compound **18a** as a yellow oil (39mg, 55% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 92%, t_R 0,63 - 2,35 min; ^{1}H NMR ($CDCl_3$) δ 6.96 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz),6.89 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.8Hz), 6.56 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,6}$ = 2.8Hz), 3.70 – 4.00 (2H, s large, NH_2), 3.79 (2H, s, CH_2), 2.62 – 2.72 (4H, m, N-CH_2), 2.59 (6H, s, N-CH_3), 1.78 – 1.88 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 120.4 (Ar-C_3), 116.5 (Ar-C_6), 114.3 (Ar-C_4), 54.3 (CH_2), 53.9 (2C, N-CH_2), 45.6 (2C, N-CH_3), 23.4 (2C, CH_2); m/z 220.3 $[M+H]^+$.

4-Pyrrolidin-1-yl-3-pyrrolidin-1-ylmethyl-phenylamine 18b

Synthesized from compound **16b** (68mg, 0.248mmol) and $SnCl_2$ (188mg) in HCl (0.75mL) and THF (20mL) according to general procedure **B** (reflux for 22h). The residue was purified by TLC (DCM/MeOH/ NH_4OH//9/1/0.2) to yield expected compound **18b** as a yellow oil (47mg, 77% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 99%, t_R 0.63 – 2.69 min; ^{1}H NMR ($CDCl_3$) δ 6.92 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.7Hz), 6.90 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz), 6.53 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,5}$ = 2.7Hz), 3.68 (2H, s, CH_2), 3.40 – 3.60 (2H, s large, NH_2), 2.94 – 2.99 (4H, m, N-CH_2), 2.58 – 2.62 (4H, m, N-CH_2), 1.85 – 1.92 (4H, m, CH_2),1.75 – 1.82 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 119.4 (Ar-C_3), 117.0 (Ar-C_6), 114.3 (Ar-C_4), 55.7 (CH_2), 54.4 (2C, N-CH_2), 52.9 (2C, N-CH_2), 24.6 (2C, CH_2), 23.7 (2C, CH_2); m/z 246.2 $[M+H]^+$.

4-Piperidin-1-yl-3-pyrrolidin-1-ylmethyl-phenylamine 18c

Synthesized from compound **16c** (93mg, 0.320mmol) and $SnCl_2$ (242mg) in HCl (0.96mL) and THF (10mL) according to general procedure **B** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/ NH_4OH//9/1/0.2) to yield expected compound **18c** as a yellow oil (42mg, 50% yield); R_f 0.3 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 96%, t_R 3.22 min; ^{1}H NMR ($CDCl_3$) δ 6.91 - (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz),6.84 (1H, d, Ar-H_6, $^4J_{6,4}$ = 3.0Hz), 6.54 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,6}$ = 3.0Hz), 3.68 (2H, s, CH_2), 3.30 – 3.60 (2H, s large, NH_2), 2.74 (4H, m, N-CH_2), 2.55 – 2.61 (4H, m, N-CH_2), 1.73 – 1.83 (4H, m, CH_2), 1.62 – 1.69 (4H, m, CH_2), 1.48 – 1.55 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 120.9 (Ar-C_3), 116.9 (Ar-C_6), 114.1 (Ar-C_4), 54.7 (2C, N-CH_2), 54.4 (CH_2), 54.1 (2C, N-CH_2),

26.8 (2C, CH_2), 24.4 (CH_2), 23.5 (2C, CH_2); m/z 260.3 $[M+H]^+$.

4-Morpholin-4-yl-3-pyrrolidin-1-ylmethyl-phenylamine 18d

Synthesized from compound **16d** (93mg, 0.319mmol) and $SnCl_2$ (242mg) in HCl (0.96mL) and THF (10mL) according to general procedure **B** (reflux for 5h). The residue was purified by TLC (DCM/MeOH/ NH_4OH//9/1/0.2) to yield expected compound **18d** as a yellow oil (56mg, 94% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 96%, t_R 0,62 -2,34 min; ^{1}H NMR ($CDCl_3$) δ 6.92 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz),6.82 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.8Hz), 6.55 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,6}$ = 2.8Hz), 3.80 (4H, m, O-CH_2), 3.67 (2H, s, CH_2), 3.50 – 3.70 (2H, s large, NH_2), 2.85 (4H, m, N-CH_2), 2.51 – 2.58 (4H, m, N-CH_2), 1.72 – 1.80 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 120.9 (Ar-C_3), 116.9 (Ar-C_6), 114.0 (Ar-C_4), 67.6 (2C, O-CH_2), 54.6 (CH_2), 54.1 (2C, N-CH_2), 53.5 (2C, N-CH_2), 23.5 (2C, CH_2); m/z 262.2 $[M+H]^+$.

4-(4-Methyl-piperazin-1-yl)-3-pyrrolidin-1-ylmethyl-phenylamine 18e

Synthesized from compound **16e** (118mg, 0.386mmol) and $SnCl_2$ (293mg) in HCl (1.16mL) and THF (20mL) according to general procedure **B** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9/1/0.2) to yield expected compound **18e** as a yellow oil (52mg, 49% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 97%, t_R 0,67 - 1,27 min; ^{1}H NMR ($CDCl_3$) δ 6.97 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz), 6.85 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.8Hz), 6.57 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,6}$= 2.8Hz), 4.00 – 4.40 (2H, s large, NH_2), 3.78 (2H, s, CH_2), 2.86 (4H, m, N-CH_2), 2.68 – 2.72 (4H, m, N-CH_2), 2.64 (4H, m, N-CH_2), 2.35 (3H, s, N-CH_3), 1.80 – 1.86 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 121.4 (Ar-C_3), 117.0 (Ar-C_6), 114.7 (Ar-C_4), 55.8 (2C, N-CH_2), 54.1 (CH_2), 53.9 (2C, N-CH_2), 53.1 (2C, N-CH_2), 46.2 (N-CH_3), 23.4 (2C, CH_2); m/z 275.3 $[M+H]^+$.

N^1-Cyclohexylmethyl-2-pyrrolidin-1-ylmethyl-benzene-1,4-diamine 18f

Synthesized from compound **16f** (131mg, 0.412mmol) and $SnCl_2$ (313mg) in HCl (1.24mL) and THF (25mL) according to general procedure **B** (reflux for 22h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **18f** as a violet oil (100mg, 84% yield); R_f 0.5 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} 97%, t_R 3.81 min; ^{1}H NMR ($CDCl_3$) δ 6.50 – 6.52 (1H, m, Ar-H_4), 6.37 -6.41 (2H, m, Ar-H_3, Ar-H_6), 3.60 – 4.50 (2H, s large, NH_2), 3.47 (2H, s, CH_2), 3.82 (2H, d, NH-CH_2, ^3J = 5.7Hz), 2.36 – 2.38 (4H, m, N-CH_2), 1.53 – 1.75 (10H, m, CH_2, Cyh), 1.10 – 1.25 (3H, m, Cyh), 0.87 – 0.99 (2H, m, Cyh); ^{13}C NMR ($CDCl_3$) δ 118.4 (Ar-C_6), 115.7 (Ar-C_4), 111.2 (Ar-C_3), 59.7 (CH_2), 53.7 (2C, N-CH_2), 51.1 (NH-CH_2), 37.5 (CH), 31.5 (Cyh), 26.9 (Cyh), 26.3 (Cyh), 23.8 (2C, CH_2); m/z 288.3 $[M+H]^+$.

N^1-Benzyl-2-pyrrolidin-1-ylmethyl-benzene-1,4-diamine 18g

Synthesized from compound **16g** (108mg, 0.347mmol) and $SnCl_2$ (263mg) in HCl (1.04mL) and THF (25mL) according to general procedure **B** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **18g** as a brown oil (42mg, 43% yield); R_f 0.7 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} 98%, t_R 3.14 min; ^{1}H NMR ($CDCl_3$) δ 7.20 – 7.43 (5H, m, Ph), 6.43 – 6.59 (3H, m, Ar-H_3, Ar-H_4, Ar-H_6), 4.41 (2H, s, NH-CH_2), 4.10 – 4.40 (2H, s large, NH_2), 3.63 (1H, s, CH_2), 2.51 – 2.55 (4H, m, N-CH_2), 1.71 – 1.82 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 128.6 (2C, Ph), 127.4 (1C, Ph), 126.9 (Ph), 118.6 (Ar-C_4), 116.0 (Ar-C_6), 112.4 (Ar-C_3), 59.2 (CH_2), 53.8 (2C, N-CH_2), 48.5 (NH-CH_2), 23.7 (2C, CH_2); m/z 284.4 $[M+H]^+$.

N^1-(2-Piperidin-1-yl-ethyl)-2-pyrrolidin-1-ylmethyl-benzene-1,4-diamine 18h

Synthesized from compound **16h** (130mg, 0.390mmol) and $SnCl_2$ (296mg) in HCl (1.17mL) and THF (25mL) according to general procedure **B** (reflux for 6h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9/1/0.2) to yield expected compound **18h** as a orange solid (63mg, 53% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9/1/0.2); mp = 70-72°C; HPLC (C18-10min) P_{HPLC} 99%, t_R 0.66 - 2.50 min; ^{1}H NMR ($CDCl_3$) δ 6.57 (1H, dd, Ar-H_4, $^3J_{4,3}$= 9.1Hz, $^4J_{4,6}$ = 2.7Hz), 6.47 - 6.50 (2H, m, Ar-H_3, Ar-H_6), 3.70 - 4.40 (2H, s large, NH_2), 3.50 (2H, s, CH_2), 3.15 (2H, t, NH-CH_2, ^3J = 6.4Hz), 2.57 (2H, t, N-CH_2, ^3J = 6.4Hz), 2.43 - 2.45 (8H, m, N-CH_2, N-CH_2), 1.69 - 1,80 (4H, m, CH_2), 1.54 - 1.62 (4H, m, CH_2), 1.43 - 1.49 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 118.2 (Ar-C_6), 115.4 (Ar-C_4), 111.4 (Ar-C_3), 59.2 (CH_2), 58.2 (N-CH_2), 54.6 (2C, N-CH_2), 53.7 (2C, N-CH_2), 41.4 (NH-CH_2), 26.0 (2C, CH_2), 24.4 (CH_2),23.7 (2C, CH_2); m/z 333.2 $[M+H]^+$.

AROMATIC SUBSTITUTION OF CHLORINE ATOM: GENERAL PROCEDURE C

A solution of amine **17** or **18** (1eq) in ACN was added a solution of 4,7-dichloroquinoline (4,7-diClQ, 1eq) in ACN and HCl 1M (1eq). After stirring at reflux, the mixture was concentrated and purified by TLC to yield target compound.

N^4-(7-Chloro-quinolin-4-yl)-2-diethylaminomethyl-N^1,N^1-dimethyl-benzene-1,4-diamine 7[a]

Synthesized from compound **17a** (48mg, 0.216mmol) and 4,7-diClQ (43mg) in HCl (0.22mL) and ACN (15mL) according to general procedure **C** (reflux for 4h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **7a** as yellow solid (65mg, 79% yield); R_f 0.6 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} >99%, t_R 3.48 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 15.93 min; HPLC (C4-40min) P_{HPLC} >99%, t_R 14.78 min; ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.4Hz), 8.01 (1H, d, Quin-H_5, $^3J_{5,6}$ = 8.9Hz), 7.94 (1H, d, Quin-H_8, $^4J_{8,6}$ =2.1Hz), 7.57 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.5Hz), 7.34 (1H, dd, Quin-H_6, $^3J_{6,5}$ = 8.9Hz, $^4J_{6,8}$ = 2.1Hz), 7.19 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.5Hz, $^4J_{4,6}$ = 2.5Hz), 7.11 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.5Hz), 6.84 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.4Hz), 3.75 (2H, s, CH_2), 2.68 (6H, s, N-CH_3), 2.63 (4H, q, N-CH_2, ^3J = 7.2Hz), 1.07 (6H, t, CH_3, ^3J = 7.2Hz); ^{13}C NMR ($CDCl_3$) δ 151.7 (Quin-C_2), 128.4 (Quin-C_8), 125.8 (Quin-C_6), 125.3 (Ar-C_6), 122.6 (Ar-C_4), 122.1 (Quin-C_5), 120.1 (Ar-C_3), 101.8 (Quin-C_3), 51.9 (CH_2), 47.2 (2C, N-CH_2),45.3 (2C, N-CH_3), 11.4 (2C, CH_3); m/z 383.3 - 385.3 $[M+H]^+$.

(7-Chloro-quinolin-4-yl)-(3-diethylaminomethyl-4-pyrrolidin-1-yl-phenyl)-amine 7b

Synthesized from compound **17b** (28mg, 0.114mmol) and 4,7-diClQ (23mg) in HCl (0.12mL) and ACN (10mL) according to general procedure **C** (reflux for 7h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **7b** as a yellow-white solid (65mg, 72% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); mp = 177-178 °C; HPLC (C18-10min) P_{HPLC} 95%, t_R 3.94 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 17.29 min; HPLC (C4-40min) P_{HPLC} 98%, t_R 16.03 min; ^{1}H NMR ($CDCl_3$) δ 8.46 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.4Hz), 7.98 (1H, d, Quin-H_8, $^4J_{8,6}$ = 2.1Hz), 7.88 (1H, d, Quin-H_5, $^3J_{5,6}$ = 8.9Hz), 7.58 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.5Hz), 7.40 (1H, dd, Quin-H_6, $^3J_{6,5}$ = 8.9Hz, $^4J_{6,8}$ = 2.1Hz), 7.10 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.6Hz, $^4J_{4,6}$ = 2.5Hz), 6.99 (1H, d, Ar-H_3, $^4J_{3,4}$ = 8.6Hz), 6.80 – 6.95 (1H, s large, NH), 6.78 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.4Hz), 3.62 (2H, s, CH_2), 3.12 – 3.16 (4H, m, N-CH_2), 2.56 (4H, q, N-CH_2, ^3J=7.1Hz), 1.92 – 1.97 (4H, m, CH_2), 1.04 (6H, t, CH_3, ^3J =7.1Hz); ^{13}C NMR ($CDCl_3$) δ 151.9 (Quin-C_2), 128.8 (Quin-C_8), 125.8 (Ar-C_6), 125.7 (Quin-C_6), 122.6 (Ar-C_4), 121.4 (Quin-C_5), 117.6 (Ar-C_3), 101.6 (Quin-C_3), 53.7 (CH_2), 52.2 (2C, N-CH_2), 47.3 (2C, N-CH_2), 24.9 (2C, CH_2), 11.9 (2C, CH_3); m/z 409.3 - 411.3 $[M+H]^+$.

(7-Chloro-quinolin-4-yl)-(3-diethylaminomethyl-4-piperidin-1-yl-phenyl)-amine 7c

Synthesized from compound **17c** (35mg, 0.135mmol) and 4,7-diClQ (27mg) in HCl (0.14mL) and ACN (10mL) according to general procedure **C** (reflux for 6h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **7c** as a yellow-white solid (51mg, 89% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} 98%, t_R 4.17 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 18.09 min; HPLC (C4-40min) P_{HPLC} 98%, t_R 16.99 min; ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.4Hz), 8.00 (1H, d, Quin-H_8, $^4J_{8,6}$ = Hz), 7.90 (1H, d, Quin-H_5, $^3J_{5,6}$ = 8.7Hz), 7.54 (1H, d, Ar-H_6, $^4J_{6,4}$ = Hz), 7.41 (1H, d, Quin-H_6, $^3J_{6,5}$ = Hz, $^4J_{6,8}$ = Hz), 7.17 (1H, dd, Ar-H_4, $^3J_{4,3}$ = Hz, $^4J_{4,6}$ = Hz), 7.09 (1H, d, Ar-H_3, $^4J_{3,4}$ = 8.4Hz), 6.86 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.4Hz), 6.9-7,00 (1H, s large, NH), 3.67 (2H, s, CH_2), 2.84 (4H, dd superposé, N-CH_2, $^3J_{2',3'}$ = Hz),2.59 (4H, q, N-CH_2, ^3J =6.9Hz), 1.71-1,74 (4H, m, N-CH_2), 1.57-1,60 (2H, m, CH_2),1.07 (6H, t, CH_3, ^3J =6.9Hz). ^{13}C NMR ($CDCl_3$) δ 151.8 (Quin-C_2), 128.7 (Quin-C_8), 125.7 (Quin-C_6), 125.1 (Ar-C_6), 122.1 (Ar-C_4), 121.3 (Quin-C_5), 120.3 (Ar-C_3), 101.7 (Quin-C_3), 54.3 (2C, N-CH_2), 51.2 (CH_2), 47.0 (2C, N-CH_2), 26.5 (2C, CH_2), 24.2 (CH_2), 11.4 (2C, CH_3); m/z 423.3 - 425.3 $[M+H]^+$.

(7-Chloro-quinolin-4-yl)-(3-diethylaminomethyl-4-morpholin-4-yl-phenyl)-amine 7d

Synthesized from compound **17d** (42mg, 0.160mmol) and 4,7-diClQ (32mg) in HCl (0.16mL) and ACN (10mL) according to general procedure **C** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **7d** as a yellow-white solid (65mg, 95% yield); R_f 0.5 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} 98%, t_R 5.35 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 15.28 min; HPLC (C4-40min) P_{HPLC} 99%, t_R 14.25 min; ^{1}H NMR ($CDCl_3$) δ 8.47 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.4Hz), 7.96 (1H, d, Quin-H_8, $^4J_{8,6}$ = 2.2Hz), 7.93 (1H, d, Quin-H_5, $^3J_{5,6}$ =9.0Hz), 7.52 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.6Hz), 7.37 (1H, dd, Quin-H_6, $^3J_{6,5}$ = 9.0Hz, $^4J_{6,8}$ = 2.2Hz), 7.20 – 7,30 (1H, s large, NH), 7.18 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.5Hz, $^4J_{4,6}$ = 2.6Hz), 7.10 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.5Hz), 6.86 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.4Hz), 3.87 (4H, m, O-CH_2), 3.64 (2H, s, CH_2), 2.93 (4H, m, N-CH_2), 2.55 (4H, q, N-CH_2, ^3J = 7.1Hz), 1.03 (4H, t, CH_3, ^3J = 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 151.9 (Quin-C_2), 128.7 (Quin-C_8), 125.9 (Quin-C_6), 125.6 (Ar-C_6), 122.5 (Ar-C_4), 121.8 (Quin-C_5), 120.7 (Ar-C_3), 102.0 (Quin-C_3), 67.6 (2C, O-CH_2), 53.4 (2C, N-CH_2), 52.0 (CH_2), 47.2 (2C, N-CH_2), 11.9 (2C, CH_3); m/z 425.3 – 427.3 $[M+H]^+$.

(7-Chloro-quinolin-4-yl)-[3-diethylaminomethyl-4-(4-methyl-piperazin-1-yl)-phenyl]-amine 7e

Synthesized from compound **17e** (114mg, 0.412mmol) and 4,7-diClQ (82mg) in HCl (0.41mL) and ACN (10mL) according to general procedure **C** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9/1/0.2) to yield expected compound **7e** as a white solid (132mg, 73% yield); R_f 0.6 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 97%, t_R 3.11 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 12.60 min; HPLC (C4-40min) P_{HPLC} 98%, t_R 11.38 min; ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.4Hz), 8.02 (1H, d, Quin-H_5, $^3J_{5,6}$ = 9.0Hz), 7.92 (1H, d, Quin-H_8, $^4J_{8,6}$ = 2.1Hz), 7.51 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.5Hz), 7.32 (1H, dd, Quin-H_6, $^3J_{6,5}$ = 9.0Hz, $^4J_{6,8}$ = 2.1Hz), 7.17 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.5Hz, $^4J_{4,6}$= 2.5Hz), 7.09 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.5Hz), 6.84 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.4Hz), 3.64 (2H, s, CH_2), 2.94 (4H, m, N-CH), 2.58 (4H, m, N-CH_2), 2.56 (4H, q, N-CH_2, ^3J= 7.1Hz), 2.37 (3H, s, N-CH_3), 1.03 (6H, t, CH_3, ^3J = 7.1Hz). ^{13}C NMR ($CDCl_3$) δ 151.6 (Quin-C_2), 128.3 (Quin-C_8), 125.7 (Quin-C_6), 125.6 (Ar-C_6), 122.6 (Ar-C_4), 122.2 (Quin-C_5), 120.7 (Ar-C_3), 101.8 (Quin-C_3), 55.7 (2C, N-CH_2), 52.8 (2C, N-CH_2),51.6 (CH_2),47.0 (2C, N-CH_2),46.2 (1C, N-CH_3),11.6 (2C, CH_3). m/z 438.4 - 440.4 $[M+H]^+$.

***N*^{4}-(7-Chloro-quinolin-4-yl)-*N*^{1}-cyclohexylmethyl-2-diethylaminomethyl-benzene-1,4-diamine 7f**

Synthesized from compound **17f** (97mg, 0.336mmol) and 4,7-diClQ (67mg) in HCl (0.34mL) and ACN (15mL) according to general procedure **C** (reflux for 18h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **7f** as a white solid (97mg, 64% yield); R_f 0.6 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} > 99%, t_R 5.22 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 21.47 min; HPLC (C4-40min) P_{HPLC} 99%, t_R 20.45 min; ^{1}H NMR ($CDCl_3$) δ 8.35 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.7Hz), 7.93 (1H, d, Quin-H_5, $^3J_{5,6}$ = 9.0Hz), 7.92 (1H, d, Quin-H_8, $^4J_{8,6}$ = 2.1Hz), 7.32 (1H, dd, Quin-H_6, $^3J_{6,5}$ = 9.0Hz, $^4J_{6,8}$ = 2.1Hz), 7.06 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,6}$ = 2.7Hz), 6.91 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.7Hz), 6.56 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz), 6.56 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.7Hz), 3.54 (2H, s, CH_2), 3.48 (1H, s, NH), 2.94 (2H, d, NH-C<u>H</u>$_2$, ^3J = 6.3Hz), 2.47 (4H, q, N-CH_2, ^3J=7.2Hz), 1.57 - 1.89 (6H, m, Cyh), 1.18 - 1.36 (3H, m, Cyh), 1.02 (6H, t, CH_3, ^3J=7.2Hz), 1.00 - 1.21 (2H, m, Cyh). ^{13}C NMR ($CDCl_3$) δ 150.2 (Quin-C_2), 126.9 (Quin-C_8), 126.6 (Ar-C_6), 124.7 (Quin-C_6), 124.7 (Ar-C_4), 120.9 (Quin-C_5), 109.1 (Ar-C_3), 100.1 (Quin-C_3),

56.9 (CH_2),49.4 (NH-CH_2), 45.5 (2C, N-CH_2),36.9 (CH), 30.7 (2C, CH_2), 25.8 (CH_2), 25.2 (2C, CH_2), 11.7 (2C, CH_3); m/z 451.3 – 453.3 $[M+H]^+$.

N^1-Benzyl-N^4-(7-chloro-quinolin-4-yl)-2-diethylaminomethyl-benzene-1,4-diamine 7g

Synthesized from compound **17g** (32mg, 0.112mmol) and 4,7-diClQ (22mg) in HCl (0.11mL) and ACN (10mL) according to general procedure **C** (reflux for 20h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **7g** as a white solid (42mg, 84% yield); R_f 0.9 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} 96%, t_R 4.34 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 19.05 min; HPLC (C4-40min) P_{HPLC} 99%, t_R 18.42 min; ^{1}H NMR ($CDCl_3$) δ 8.28 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5,9Hz), 8.08 (1H, d, Quin-H_5, $^3J_{5,6}$ = 9Hz), 7.92 (1H, d, Quin-H_8, $^4J_{8,6}$ = 2,1Hz), 7.23-7.39 (6H, m, Quin-H_6, Ph), 7.05 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8,4Hz, $^4J_{4,6}$ = 2,5Hz), 6.97 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2,5Hz), 6.59 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5,9Hz), 6.56 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8,4Hz), 4.40 (2H, s, NH-C<u>H</u>$_2$), 3.58 (2H, s, CH_2), 2.47 (4H, q, N-CH_2, ^3J =7,1Hz), 0.96 (6H, t, CH_3, ^3J =7,1Hz); ^{13}C NMR ($CDCl_3$) δ 148.9 (Quin-C_2), 128.4 (3C, Ph), 127.2 (2C, Ph), 127.1 (Quin-C_6), 126.9 (Ar-C_6), 125.9 (Quin-C_8),125.2 (Ar-C_4), 122.3 (Quin-C_5), 110.4 (Ar-C_3), 100,6 (Quin-C_3), 57.4 (CH_2),47.5 (1C, NH-CH_2), 46.1 (2C, N-9), 11.3 (2C, CH_3); m/z 445.1 - 447.1 $[M+H]^+$.

N^4-(7-Chloro-quinolin-4-yl)-2-diethylaminomethyl-N^1-(2-piperidin-1-yl-ethyl)-benzene-1,4-diamine 7h

Synthesized from compound **17h** (70mg, 0.231mmol) and 4,7-diClQ (46mg) in HCl (0.23mL) and ACN (15mL) according to general procedure **C** (reflux for 4h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **7h** as a orange solid (86mg, 80% yield); R_f 0.6 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} 99%, t_R 3.21 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 13.73 min; HPLC (C4-40min) P_{HPLC} 98%, t_R 12.57 min; ^{1}H NMR ($CDCl_3$) δ 8.65-8.75 (1H, s large, 1'-NH),8.38 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.5Hz), 7.97 (1H, d, Quin-H_8, $^4J_{8,6}$ = 2.1Hz), 7.87 (1H, d, Quin-H_5, $^3J_{5,6}$ = 9.0Hz), 7.39 (1H, d, Quin-H_6, $^3J_{6,5}$ = 8.9Hz, $^4J_{6,8}$ = 2.1 Hz), 7.09 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4 Hz, $^4J_{4,6}$ = 2.5 Hz), 6.96 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.5 Hz), 6.84 -7.04 (1H, s large, NH),6.62 (1H, d, Ar-H_3, $^4J_{3,4}$ = 8.4Hz), 6.56 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.5Hz), 3.56 (2H, s, CH_2), 3.25 (2H, t, NH-CH_2, ^3J = 6.4Hz), 2.70 (2H, t, 3N-CH_2, ^3J = 6.4Hz), 2.51 (4H, q, N-CH_2, ^3J = 7.1Hz), 2.47 - 2.58 (4H, m, N-CH_2), 1.59 - 1.67 (4H, m, CH_2),1.47 - 1.51 (2H, m, CH_2), 1.09 (6H, t, CH_3, ^3J= 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 150.8 (Quin-C_2), 127.9 (Quin-C_8), 127.3 (Ar-C_6), 125.4 (Quin-C_6), 125.2 (Ar-C_4), 121.2 (Quin-C_5), 110.1 (Ar-C_3), 100.8 (Quin-C_3), 57.7 (N-CH_2), 56.9 (CH_2), 54.2 (2C, N-CH_2), 46.3 (2C, N-CH_2), 40.3 (NH-CH_2), 25.6 (2C, CH_2), 24.1 (CH_2),11.4 (2C, CH_3); m/z 466.2 – 468.2 (M^++1).

N^4-(7-Chloro-quinolin-4-yl)-N^1,N^1-dimethyl-2-pyrrolidin-1-ylmethyl-benzene-1,4-diamine 8[a]

Synthesized from compound **18a** (39mg, 0.177mmol) and 4,7-diClQ (35mg) in HCl (0.18mL) and ACN (15mL) according to general procedure **C** (reflux for 4h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **8a** as an orange solid (54mg, 81% yield); R_f 0.5 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} 99%, t_R 3.45 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 15.96 min; HPLC (C4-40min) P_{HPLC} 98%, t_R 14.64min; ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.5Hz), 8.01 (1H, d, Quin-H_5, $^3J_{5,6}$ = 8.9Hz), 7.93 (1H, d, Quin-H_8, $^4J_{8,6}$ =2.1Hz), 7.48 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.5Hz), 7.32 (1H, dd, Quin-H_6, $^3J_{6,5}$ = 8.9Hz, $^4J_{6,8}$ = 2.1Hz), 7.21 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.5Hz, $^4J_{4,6}$ = 2.5Hz), 7.11 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.5Hz), 6.82 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.5Hz), 3.85 (2H, s, CH_2), 2.69 – 2.73 (4H, m, N-CH_2), 2.68 (6H, s, N-CH_3), 1.80 – 1.83 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 151.5 (Quin-C_2), 128.2 (Quin-C_8), 125.6 (Quin-C_6), 125.2 (Ar-C_6), 123.8 (Ar-C_4), 122.8 (Quin-C_5), 120.1 (Ar-C_3), 101.6 (Quin-C_3), 54.3 (CH_2), 54.0 (2C, N-CH_2),45.1 (2C, N-CH_3), 23.4 (2C, CH_2); m/z 380.2 – 382.1 $[M+H]^+$.

(7-Chloro-quinolin-4-yl)-(4-pyrrolidin-1-yl-3-pyrrolidin-1-ylmethyl-phenyl)-amine 8b

Synthesized from compound **18b** (47mg, 0.191mmol) and 4,7-diClQ (38mg) in HCl (0.19mL) and ACN (15mL) according to general procedure **C** (reflux for 5h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9/1/0.2) to yield expected compound **8b** as a yellow solid (30mg, 39% yield); R_f 0.5 (DCM/MeOH/NH_4OH//9/1/0.2); mp = 179-181 °C; HPLC (C18-10min) P_{HPLC} 99%, t_R 3.92 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 17.15 min; HPLC (C4-40min) P_{HPLC} 98%, t_R 15.97 min; ^{1}H NMR ($CDCl_3$) δ 8.46 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.4Hz), 7.98 (1H, d, Quin-H_8, $^4J_{8,6}$ =2.1Hz), 7.86 (1H, d, Quin-H_5, $^3J_{5,6}$ = 9.0Hz), 7.41 (1H, d, Quin-H_6, $^3J_{6,5}$ = 9.0Hz, $^4J_{6,8}$ = 2.1Hz), 7.39 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.7Hz), 7.09 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.6Hz, $^4J_{4,6}$ = 2.7Hz), 6.94 (1H, d, Ar-H_3, $^4J_{3,4}$ = 8.6Hz), 6.78 (1H, s large, NH), 6.74 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.4Hz), 3.68 (2H, s, CH_2), 3.19 – 3.24 (4H, m, N-CH_2), 2.53 – 2.58 (4H, m, N-CH_2), 1.90 – 2.01 (4H, m, CH_2), 1.72 – 1.82 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.0 (Quin-C_2), 128.9 (Quin-C_8), 126.4 (Ar-C_6), 125.7 (Quin-C_6), 123.1 (Ar-C_4), 121.3 (Quin-C_5), 117.3 (Ar-C_3), 101.6 (Quin-C_3), 57.0 (CH_2), 54.4 (2C, N-CH_2), 51.9 (2C, N-CH_2), 25.1 (2C, CH_2), 23.7 (2C, CH_2); m/z 407.3 - 409.3 $[M+H]^+$.

(7-Chloro-quinolin-4-yl)-(4-piperidin-1-yl-3-pyrrolidin-1-ylmethyl-phenyl)-amine 8c

Synthesized from compound **18c** (42mg, 0.160mmol) and 4,7-diClQ (32mg) in HCl (0.16mL) and ACN (10mL) according to general procedure **C** (reflux for 6h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **8c** as a yellow solid (68mg, 72% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} >99%, t_R 4.18 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 18.10 min; HPLC (C4-40min) P_{HPLC} >99%, t_R 17.10 min; ^{1}H NMR ($CDCl_3$) δ 8.49 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.4Hz), 7.99 (1H, d, Quin-H_8, $^4J_{8,6}$ = 2.1Hz), 7.86 (1H, d, Quin-H_5, $^3J_{5,6}$ = 8.9Hz), 7.41 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.6Hz), 7.41 (1H, dd, Quin-H_6, $^3J_{6,5}$ = 8.9Hz, $^4J_{6,8}$ = 2.1Hz), 7.17 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.5Hz, $^4J_{4,6}$ = 2.6Hz), 7.09 (1H, d, Ar-H_3, $^4J_{3,4}$ = 8.5Hz), 6.84 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.4Hz), 6.75 – 6.90 (1H, s large, NH), 3.74 (2H, s, CH_2), 2.87 (4H, m, N-CH_2), 2.58 – 2.62 (4H, m, N-CH_2), 1.77 – 1.82 (4H, m, CH_2), 1.71 – 1.74 (4H, m, CH_2), 1.57 – 1.60 (2H, m, CH_2) ;

^{13}C NMR ($CDCl_3$) δ 151.9 (Quin-C_2), 128.8 (Quin-C_8), 125.7 (Quin-C_6), 125.3 (Ar-C_6), 122.4 (Ar-C_4), 121.2 (Quin-C_5), 120.5 (Ar-C_3), 101.7 (Quin-C_3), 54.5 (CH_2), 54.2 (4C, N-CH_2), 26.6 (2C, CH_2), 24.2 (CH_2), 23.5 (2C, CH_2); m/z 421.3 - 423.2 $[M+H]^+$.

(7-Chloro-quinolin-4-yl)-(4-morpholin-4-yl-3-pyrrolidin-1-ylmethyl-phenyl)-amine 8d

Synthesized from compound **18d** (56mg, 0.214mmol) and 4,7-diClQ (42mg) in HCl (0.22mL) and ACN (10mL) according to general procedure **C** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9/1/0.2) to yield expected compound **8d** as a yellow-white solid (77mg, 85% yield); R_f 0.5 (DCM/MeOH/NH_4OH//9/1/0.2); mp = 187-188 °C; HPLC (C18-10min) P_{HPLC} 96%, t_R 3.53 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 15.24 min; HPLC (C4-40min) P_{HPLC} 99%, t_R 14.26 min; ^{1}H NMR ($CDCl_3$) δ 8.47 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.4Hz), 7.95 (1H, d, Quin-H_8, $^4J_{8,6}$ =2.1Hz), 7.94 (1H, d, Quin-H_5, $^3J_{5,6}$ =8.7Hz), 7.40 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.4Hz), 7.37 (1H, dd, Quin-H_6, $^3J_{6,5}$ = 8.7Hz, $^4J_{6,8}$ = 2.1Hz), 7.18 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4Hz, $^4J_{4,6}$ = 2.4Hz), 7.08 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz), 6.83 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.4Hz), 3.84 – 3.88 (4H, m, O-CH_2), 3.70 (2H, s, CH_2), 2.96 – 2.99 (4H, m, N-CH_2), 2.52 – 2.54 (4H, m, N-CH_2), 1.73 – 1.76 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.0 (Quin-C_2), 128.8 (Quin-C_8), 125.9 (2C, Quin-C_6, Ar-C_6), 122.9 (Ar-C_4), 121.9 (Quin-C_5), 120.7 (Ar-C_3), 102.0 (Quin-C_3), 67.6 (2C, O-CH_2), 55.0 (CH_2), 54.4 (2C, N-CH_2),53.4 (2C, N-CH_2), 23.7 (2C, CH_2); m/z 423.3 - 425.3 $[M+H]^+$.

(7-Chloro-quinolin-4-yl)-[4-(4-methyl-piperazin-1-yl)-3-pyrrolidin-1-ylmethyl-phenyl]-amine 8e

Synthesized from compound **18e** (52mg, 0.189mmol) and 4,7-diClQ (38mg) in HCl (0.19mL) and ACN (10mL) according to general procedure **C** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9/1/0.2) to yield expected compound **8e** as a yellow solid (68mg, 83% yield); R_f 0.2 (DCM/MeOH/NH_4OH//9/1/0.2); HPLC (C18-10min) P_{HPLC} 97%, t_R 3.03 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 12.63 min; HPLC (C4-40min) P_{HPLC} 98%, t_R 11.39 min; ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.4Hz), 7.98 (1H, d, Quin-H_5, $^3J_{5,6}$ = 9.0Hz), 7.93 (1H, d, Quin-H_8, $^4J_{8,6}$ =2.1Hz), 7.41 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.5Hz), 7.32 (1H, dd, Quin-H_6, $^3J_{6,5}$ = 9.0Hz, $^4J_{6,8}$ = 2.1Hz), 7.19 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.5Hz, $^4J_{4,6}$= 2.5Hz), 7.10 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.5Hz), 6.82 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.4Hz), 3.77 (2H, s, CH_2), 2.95-2.98 (4H, m, N-CH_2), 2.64 (4H, m, N-CH_2), 2.59 (4H, m, N-CH_2), 2.37 (3H, s, N-CH_3), 1.79 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 151.6 (Quin-C_2), 128.3 (Quin-C_8), 125.7 (Quin-C_6), 125.5 (Ar-C_6), 122.8 (Ar-C_4), 122.0 (Quin-C_5), 120.8 (Ar-C_3), 101.8 (Quin-C_3), 55.6 (2C, N-CH_2), 54.4 (CH_2), 54.1 (2C, N-CH_2), 52.7 (2C, N-CH_2), 46.1 (N-CH_3), 23.5 (2C, CH_2); m/z 436.4 - 438.4 $[M+H]^+$.

***N*^{4}-(7-Chloro-quinolin-4-yl)-*N*^{1}-cyclohexylmethyl-2-pyrrolidin-1-ylmethyl-benzene-1,4-diamine 8f**

Synthesized from compound **18f** (100mg, 0.348mmol) and 4,7-diClQ (69mg) in HCl (0.35mL) and ACN (15mL) according to general procedure **C** (reflux for 18h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **8f** as a yellow solid (104mg, 66% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} 99%, t_R 5.16 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 21.38 min; HPLC (C4-40min) P_{HPLC} >99%, t_R 20.36 min; ^{1}H NMR ($CDCl_3$) δ 8.35 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.5Hz), 7.92 (1H, d, Quin-H_8, $^4J_{8,6}$ =2.1Hz), 7.91 (1H, d, Quin-H_5, $^3J_{5,6}$ = 8.9Hz), 7.90 (1H, s, NH), 7.32 (1H, dd, Quin-H_6, $^3J_{6,5}$ = 8.9Hz, $^4J_{6,8}$ = 2.1Hz), 7.06 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.5Hz, $^4J_{4,6}$ = 2.4Hz), 6.92 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.4Hz), 6.57 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.5Hz), 6.56 (1H, d, Quin-H_3, $^3J_{3,2}$ =5.5Hz), 3.58 (2H, s, CH_2), 3.48 (1H, s, NH), 3.96 (2H, d, NH-CH_2, ^3J= 6.3Hz), 2.44 (4H, m, N-CH_2), 1.59-1,84 (10H, m, CH_2, Cyh), 1.16-1.34 (3H, m, Cyh), 1.01-1.09 (2H, m, Cyh); ^{13}C NMR ($CDCl_3$) δ 150.8 (Quin-C_2), 127.5 (Quin-C_8), 126.5 (Ar-C_6), 125.3 (Ar-C_4), 125.2 (Quin-C_6), 121.5 (Quin-C_5), 109.7 (Ar-C_3), 100.6 (Quin-C_3), 59.2 (CH_2),53.2 (2C, N-CH_2),49.9 (NH-CH_2), 37.2 (CH), 31.0 (2C, CH_2), 26.3 (CH_2), 25.8 (2C, CH_2), 23.4 (2C, CH_2); m/z 449.3 – 451.3 $[M+H]^+$.

***N*^{1}-Benzyl-*N*^{4}-(7-chloro-quinolin-4-yl)-2-pyrrolidin-1-ylmethyl-benzene-1,4-diamine 8g**

Synthesized from compound **18g** (42mg, 0.151mmol) and 4,7-diClQ (3mg) in HCl (0.15mL) and ACN (10mL) according to general procedure **C** (reflux for 16h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **8g** as an orange solid (24mg, 72% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} 99%, t_R 4.26 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 19.04 min; HPLC (C4-40min) P_{HPLC} 97%, t_R 18.28 min; ^{1}H NMR ($CDCl_3$) δ 8.24 (1H, d, Quin-H_2, $^3J_{2,3}$ = 6.0Hz), 8.12 (1H, d, Quin-H_5, $^3J_{5,6}$ = 9.0Hz), 7.90 (1H, d, Quin-H_8, $^4J_{8,6}$ =2.1Hz), 7.23 - 7.38 (6H, m, Quin-H_6, Ph), 7.01 - 7.06 (2H, m, Ar-H_4, Ar-H_6), 6.58 (1H, d, Quin-H_3, $^3J_{3,2}$ = 6.0Hz), 6.55 (1H, d, Ar-H_3, $^3J_{3,4}$ = 8.4Hz), 4.38 (2H, s, NH-CH_2), 3.67 (2H, s, CH_2), 2.52 (4H, m, N-CH_2), 1.76 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 147.8 (Quin-C_2), 128.5 (2C, Ph),126.9 (3C, Ph), 126.6 (Ar-C_6), 126.3 (Quin-C_6), 125.4 (Ar-C_4), 125.0 (Quin-C_8),122.7 (Quin-C_5), 110.8 (Ar-C_3), 100.5 (Quin-C_3), 58.9 (CH_2), 53.4 (2C, N-CH_2), 47.4 (NH-CH_2), 23.5 (2C, CH_2); m/z 443.3 – 445.2 $[M+H]^+$.

***N*^{4}-(7-Chloro-quinolin-4-yl)-*N*^{1}-(2-piperidin-1-yl-ethyl)-2-pyrrolidin-1-ylmethyl-benzene-1,4-diamine 8h**

Synthesized from compound **18h** (63mg, 0.207mmol) and 4,7-diClQ (41mg) in HCl (0.21mL) and ACN (15mL) according to general procedure **C** (reflux for 4h). The residue was purified by TLC (DCM/MeOH/NH_4OH//9.5/0.5/0.2) to yield expected compound **8h** as a orange solid (80mg, 83% yield); R_f 0.4 (DCM/MeOH/NH_4OH//9.5/0.5/0.2); HPLC (C18-10min) P_{HPLC} >99%, t_R 3.19 min; HPLC (C18-40min) P_{HPLC} 98%, t_R 13.70 min; HPLC (C4-40min) P_{HPLC} 98%, t_R 12.54 min; ^{1}H NMR ($CDCl_3$) δ 8.65 - 8.75 (1H, s large, NH), 8.32 (1H, d, Quin-H_2, $^3J_{2,3}$ = 5.7Hz), 7.93 - 7.96 (2H, m, Quin-H_5, Quin-H_8), 7.37 (1H, d, Quin-H_6, $^3J_{6,5}$ = 9.0Hz, $^4J_{6,8}$ = 2.1Hz), 7.10 (1H, dd, Ar-H_4, $^3J_{4,3}$ = 8.4 Hz, $^4J_{4,6}$ = 2.5 Hz), 6.99 (1H, d, Ar-H_6, $^4J_{6,4}$ = 2.5 Hz), 6.62 (1H, d, Ar-H_3, $^4J_{3,4}$ = 8.4Hz), 6.55 (1H, d, Quin-H_3, $^3J_{3,2}$ = 5.7Hz), 3.61 (2H, s, CH_2), 3.29 (2H, t, NH-CH_2, $^3J_{2',3'}$= 6.3Hz), 2.70 (2H, t, N-CH_2, ^3J = 6.3Hz), 2.52 - 2.56 (8H, m, N-CH_2), 1.77 - 1,80 (4H, m, CH_2), 1.62 - 1.69 (4H, m, CH_2), 1.49 - 1.52 (2H, m,

CH_2); ^{13}C NMR ($CDCl_3$) δ 150.3 (Quin-C_2), 127.4 (Quin-C_8), 127.2 (Ar-C_6), 126.1 (Quin-C_6), 125.8 (Ar-C_4), 122.2 (Quin-C_5), 110.8 (Ar-C_3), 101.1 (Quin-C_3), 59.2 (CH_2), 57.8 (N-CH_2), 54.7 (2C, N-CH_2), 53.9 (2C, N-CH_2), 40.6 (NH-CH_2), 25.8 (2C, CH_2), 24.4 (CH_2), 24.0 (2C, CH_2); m/z 464.2 – 466.2 $[M+H]^+$.

BIOLOGICAL EVALUATION

In Vitro P. falciparum Culture and Drug Assays

P. falciparum strains were maintained continuously in culture on human erythrocytes as described by Trager and Jensen [40]. *In vitro* antiplasmodial activity was determined using a modification of the semi-automated microdilution technique of Desjardins [41]. *P. falciparum* CQ-sensitive (F32/Tanzania and THAI/Thailand) and CQ-resistant (PFB/Brazil, FcB1R/Colombia and K1/Thailand) strains were used in sensitivity testing. Stock solutions of chloroquine diphosphate and test compounds were prepared in sterile distilled water and DMSO, respectively. Drug solutions were serially diluted with culture medium and introduced to asynchronous parasite cultures (1% parasitaemia and 1% final hematocrite) on plates comprising 96-well plates for 24 h at 37°C prior to the addition of 0.5 μCi of [^{3}H]hypoxanthine (1 to 5 Ci/mmol; Amersham, Les Ulis, France) *per* well, for 24 h. The growth inhibition for each drug concentration was determined by comparison of the radioactivity incorporated into the treated culture with that in the control culture (without drug) maintained on the same plate. The concentrations causing 50% inhibition (IC_{50}) or 90% inhibition (IC_{90}) were obtained from the drug concentration-response curve and the results were expressed as the mean ± the standard deviations determined from several independent experiments. The DMSO concentration never exceeded 0.1% and did not inhibit the parasite growth.

Cytotoxicity Test upon MRC-5 Cells

A human diploid embryonic lung cell line (MRC-5, Bio-Whittaker 72211D) were used to assess the cytotoxic effects towards host cells. MRC-5 cells were seeded at 5,000 cells *per* well. After 24 h, the cells were washed and two-fold dilutions of the drug were added in 200 μL standard culture medium (RPMI + 5% FCS). The final DMSO concentration in the culture remained below 0.5%. The cultures were incubated with several concentrations of compounds (between 32 and 1.6 μM) at 37°C in 5% CO_2-95% air for 7 days. Untreated cultures were included as controls. The cytotoxicity was determined using the colorimetric MTT assay [42] and scored as a % reduction of absorption at 540 nm of treated cultures *versus* untreated control cultures.

Heme Polymerization Inhibition

The ability of a compound to inhibit heme polymerization induced by lipids [43] was determined using the methods developed by Ayad [44]. To a suspension of 1-monooleoyl glycerol 1 mM in 90 mM sodium acetate at pH 5 (500 μL) was added a solution of hemin 700 μM in NaOH 25 mM (500 μL). Drugs were added from stock solutions in DMSO (10 μL). Samples were incubated for 24 hours at 37°C. Controls contained an equal amount of DMSO. Following incubation, samples are centrifuged at 27,000*g* at 4°C for 15 min. The precipitate of β-hematin was washed several times with 10 mM sodium phosphate, pH 7.4, containing 2.5% SDS vortexed for 10 min at 20°C before repelleting, until supernatant was colorless. Dissolution of β-hematin was achieved by addition of 900 μL of 10 mM sodium phosphate, pH 7.4, containing 2.5% SDS and 50 μL of NaOH 1M. Concentration of heme was calculated from absorbance at 405 nm. Experiments were done in duplicates.

X-ray crystallography studies

Yellow, block crystals of **8h** and **8d** were mounted on a cryoloop. Data collection and processing for both compounds was carried out using a Bruker AXS SMART APEX system, with graphite-monochromated MoKa radiation at 297 K. The structures were solved by direct methods SHELXS- 97 [45] and successive difference Fourier syntheses. Refinement applied full-matrix least-squares methods SHELXL-97 [46]. The details of the crystal structure determination and refinement for both compounds are given in supplementary materials. The structures were refined with anisotropic thermal parameters. All C-bound H atoms were placed in calculated positions (C—H = 0.93–0.97 Å) and treated using a riding model with U_{iso}= 1.5U_{eq}(C) for methyl and U_{iso}= 1.2U_{eq}(C) for aryl H atoms; the methyl groups were allowed to rotate but not to tip. For compound **8h** atoms H2N and H4N bonded to the N2 and N4 atoms, respectively, were calculated and fixed at the standard N—H distance of 0.85(2) and 0.87(2) Å. For compound **8d** atom H1 bonded to the N2 atom was calculated and fixed at the standard N—H distance of 0.87(2) Å. Atomic scattering factors for neutral atoms and real and imaginary dispersion terms were taken from international tables for X-ray crystallography [47]. The drawings were created with the ORTEP [48] and DIAMOND [49] programs. Crystallographic data for the structural analysis of compounds **8d** and **8h** have been deposited with the Cambridge Crystallographic Data Centre (CCDC no 649121, 649122). Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk; or www.ccdc.cam.ac.uk).

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ABBREVIATIONS

AQ = Amodiaquine

CQ = Chloroquine

DIEA = Diisopropylethylamine

MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (thiazolyl blue)

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$$VAR = \frac{1 + \sum_{n=1}^{4} \sum_{i=1}^{n} 10^{pkai - pHv}}{1 + \sum_{n=1}^{4} \sum_{i=1}^{n} 10^{pKai - pH0}}$$

Where: pHv = pH inside the vacuole (assumed to be pH 5.0)

pHo = pH externally (assumed to be pH 7.4)

This equation proceeds from a derivation of the Henderson-Hasselbach equation, based on predicted values of drug pKa according to previous works of Hawley *et al*. [30]

Values of pKa were calculated using ACD/pKa DB software from Avanced Chemistry Development Inc., Toronto, Canada.

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