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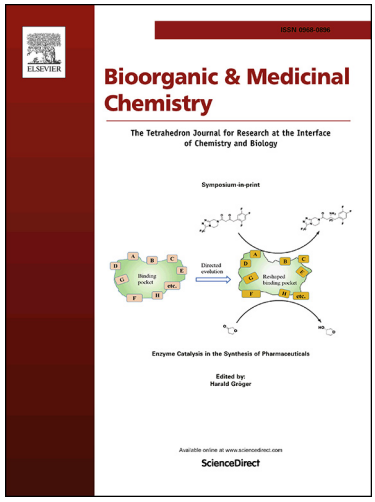

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PII: S0968-0896(18)31818-2
DOI: https://doi.org/10.1016/j.bmc.2019.01.044
Reference: BMC 14736

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 26 October 2018
Revised Date: 21 January 2019
Accepted Date: 31 January 2019

Please cite this article as: da Silva, R.M.R., Gandi, M.O., Mendonça, J.S., Carvalho, A.S., Coutinho, J.P., Aguiar, A.C.C., Krettli, A.U., Boechat, N., New hybrid trifluoromethylquinolines as antiplasmodium agents, *Bioorganic & Medicinal Chemistry* (2019), doi: https://doi.org/10.1016/j.bmc.2019.01.044

New hybrid trifluoromethylquinolines as antiplasmodium agents

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keywords: malaria; P. falciparum; quinoline; hybrids; mefloquine; amodiaquine

Abstract

*Malaria remains a major public health problem worldwide, and it is responsible for high rates of morbidity and mortality. Resistance to current antimalarial drugs has been identified, and new drugs are urgently needed. In this study, we designed and synthesized seventeen novel quinolines based on the structures of mefloquine ((2,8-bis(trifluoromethyl)quinolin-4-yl)(piperidin-2-yl)methanol) and amodiaquine (4-((7-chloroquinolin-4-yl)amino)-2-((diethylamino)methyl)phenol) using ring bioisosteric replacement and molecular hybridization of the functional groups. The compounds were evaluated in vitro against Plasmodium falciparum and in vivo in mice infected with P. berghei. All derivatives presented anti-P. falciparum activity with IC_{50} values ranging from 0.083 to 33.0 µM. The compound with the best anti-P. falciparum activity was N-(5-methyl-4H-1,2,4-triazol-3-yl)-2,8-bis(trifluoromethyl)quinolin-4-amine (**12**) which showed an IC_{50} of 0.083 µM. The three most active compounds were selected for antimalarial activity tests against P. berghei-infected mice. Compound **12** was the most active on the 5th day after infection, reducing parasitemia by 66%, which is consistent with its in vitro activity. This is an important result as **12**, a simpler molecule than mefloquine, does not contain the stereogenic center, and consequently, its synthesis in the laboratory is easier and less expensive. This system proved promising for the design of potential antimalarial compounds.*

1. Introduction

Malaria is an important infectious disease globally, and approximately 3.2 billion people are at risk of infection.[1,2] In 2016, an estimated 216 million cases of malaria and 445 thousand deaths occurred worldwide. However, US$ 2.7 billion have been invested in malaria control and elimination efforts globally by governments of malaria endemic countries and international partners.[1,2] For decades, the treatment of malaria was based on chloroquine (**CQ**), which has rapid efficacy and low toxicity and is safe even for children and pregnant women. A number of other quinolines, such as amodiaquine (**AQ**), primaquine (**PQ**) and mefloquine (**MQ**), have been developed to treat chloroquine-resistant strains (CQR) of *P. falciparum.* However, the parasite has developed resistance to most antimalarials around the world.[3,4,5,6] Artemisinin and its derivatives, such as artesunate (**AS**), have reached prominence in the antimalarial arsenal due to their efficacy with high parasitic reduction rates.[7] **AS** reduces parasitemia more quickly than any other therapeutic options, as it acts on more phases of the parasite cycle, and it can be used against severe malaria in adults and children.[8] **AS** has an extremely short half-life, being almost completely eliminated in 24 h, and it is not used as a monotherapy since at least seven days of treatment are needed to adequately eliminate all parasites from circulation.[7,9] Artemisinin derivatives are used in association with a quinoline compound, which has a high efficacy and a long half-life in plasma. These combinations are known as artemisinin- based combination therapies (ACTs).[9] The different ACT combinations, such as artesunate-amodiaquine (**ASAQ**) and artesunate-mefloquine (**ASMQ**), share the fact that they have high efficacy and excellent safety profiles, and they have been recommended by the WHO (World Health Organization) as first-line treatments against *P. falciparum*.[10] However, drug resistance has

significantly increased, and the emergence and spread of parasite strains resistant to ACTs highlight the need for new drugs with different structural characteristics and modes of action.[11,12,13,14,15,16]

Hybridization is an important tool in medicinal chemistry and is based on combining two pharmacophoric chemical entities into a single skeleton.[17] Studies have been conducted using synthetic hybrid compounds designed to have increased efficacy over quinoline derivatives such as AZT-chloroquinoline[18] and quinine-dihydroartemisinin.[19] We have demonstrated the importance of some new compounds against *P. falciparum* based on molecular hybrids, such as salts of mefloquine and artesunate,[20] primaquine and artesunate,[21] 2-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidine,[22] 1*H*-1,2,3-triazole-quinoline,[23] quinoline-sulfonamide[24] and aminoquinolines-atorvastatin.[25]

Thus, aminoquinolines are still attractive lead compounds in the search for new antimalarial drugs.[18-29] The development of new bioactive substances by modifications of the chemical structure of a prototype using molecular hybridization and bioisosterism as tools[17,30] has become common, and this technique has been successfully used in the search for compounds with higher activity and/or better pharmacological profiles.[14-23] As an extension of our efforts to develop novel compounds to fight malaria,[14-23] we present herein the synthesis and biological evaluation of novel *N*-substituted-2,8-bis(trifluoromethyl)-quinolin-4-amines derivatives **1-14** and 4-substituted 2,8-bis(trifluoromethyl)quinoline derivatives **15-16**.

2. Results and discussion

These novel quinolines were designed using molecular hybridization and ring bioisosterism as tools for combining two pharmacophoric chemical entities into a single skeleton. The pharmacophoric subunit 2,8-bis-(trifluoromethyl)quinoline, which is present in the structure of **MQ** (in blue), plus the aminoheteroaromatic or aromatic function contained in **AQ** (in red) could generate potent antimalarial drugs (**Fig. 1**). An analysis of the nature of the aliphatic, aromatic and heteroaromatic substituents in the **AQ** moiety (in red) will provide the electronic and lipophilic properties to determine the distinct contributions of each fragment to the desired activity profile of each member of this new class of compounds (**Fig. 1A**). On the other hand, we investigated the influence of the absence of the NH group by preparing compounds **15** and **16**, as shown in **Fig. 1B**. Compound **17** was also prepared to compare the importance of 2,8-bis(trifluoromethyl)quinoline versus 7-chloroquinoline in the antiplasmodial (**Fig. 1C**).

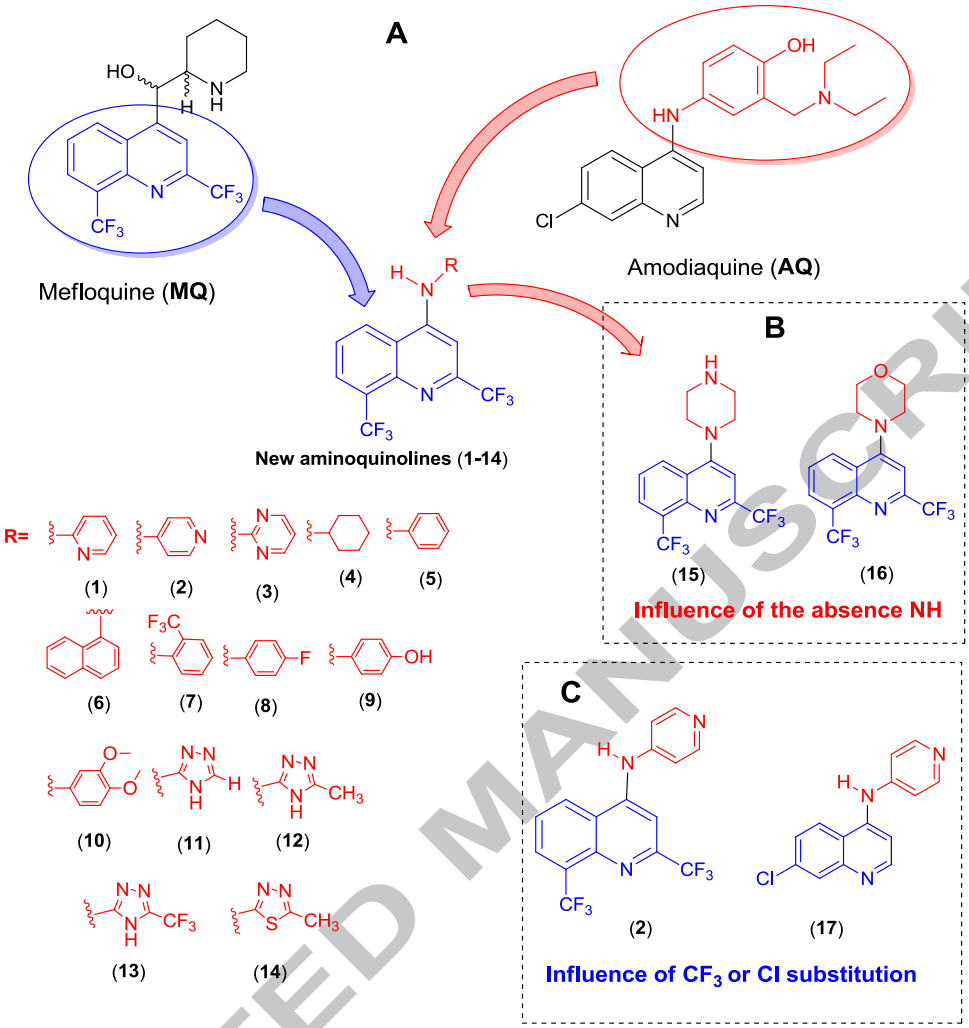
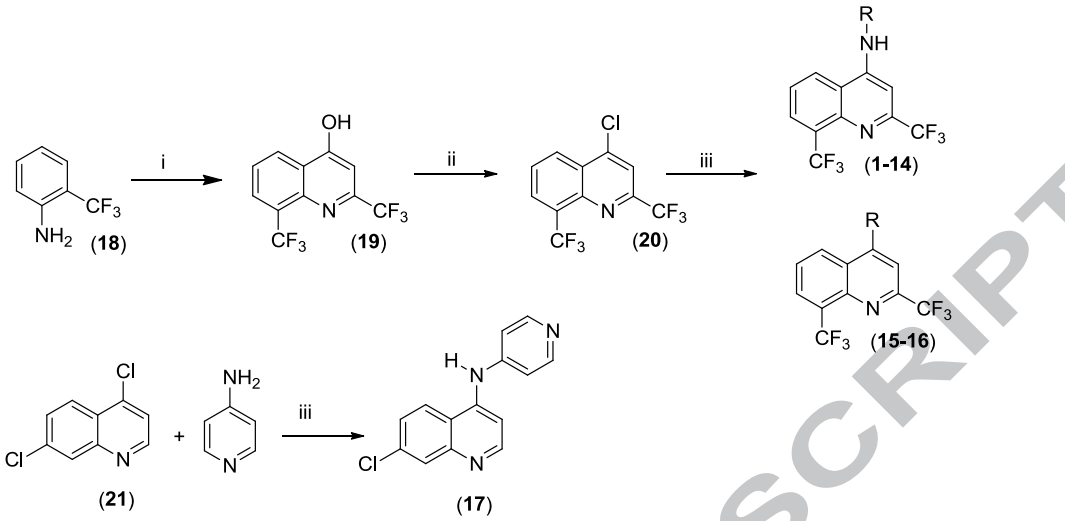


Figure 1. Rational approach to the design of *N*-substituted-2,8-bis(trifluoromethyl)-quinolin-4-amines derivatives **1-14** in **A**, 4-substituted-2,8-bis(trifluoromethyl)quinoline **15-16** in **B** and 7-chloro-N-(pyridin-4-yl)quinolin-4-amine (**17**) in **C**.

2.1 Chemistry

The synthetic route to prepare *N*-substituted-2,8-bis(trifluoromethyl)-quinolin-4-amines derivatives **1-14** is shown in Scheme 1. The 2,8-bis(trifluoromethyl)quinoline core was prepared by cyclization of commercially available 2-(trifluoromethyl) aniline (**18**) with ethyl 4,4,4-trifluoroacetoacetate in the presence of polyphosphoric acid (PPA) to give **19** in 91% yield.[31] Intermediate **19** was chlorinated with phosphorus oxychloride at 80°C to obtain 4-chloro derivative **20** in 98% yield.[32] The last step was an aromatic nucleophilic substitution reaction between 4-chloro derivative **20** and the corresponding amine in NaH and DMSO to afford desired products **1-16** in good yields.[33,34]

To obtain 7-chloro-N-(pyridin-4-yl)quinolin-4-amine **(17)**, the nucleophilic substitution of 4-aminopyridine with commercial 4,7-dichloroquinoline (**21**) was used to give **17** in 89% yield. The structures of all the prepared compounds were confirmed by spectral analyses, namely, ^{1}H, ^{19}F and ^{13}C NMR, FTIR and mass spectrometry, and the obtained data were in full agreement with the proposed structures.



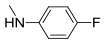
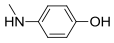
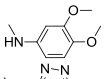
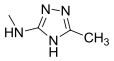
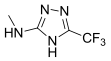
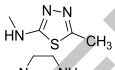
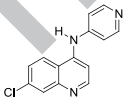
Reagents and conditions: (i) PPA, ethyl 4,4,4-trifluoroacetoacetate, 150 ^{o}C, 3 h, 91%; (ii) $POCl_3$, 80 ^{o}C, 4 h, 98%; (iii) 3 eq NaH, DMSO, 3eq R-NH_2, r.t, 42-98%.

Scheme 1. Synthesis of *N*-substituted-2,8-bis(trifluoromethyl)-quinolin-4-amines derivatives **1-14**, 4-substituted-2,8-bis(trifluoromethyl)quinoline **15-16** and 7-chloro-N-(pyridin-4-yl)quinolin-4-amine (**17**).

2.2 Antiplasmodial assays

Studies have been conducted using synthetic compounds, which were designed to have the increased efficacy of quinoline derivatives.[35,36] A total of 16 quinoline derivatives containing a **MQ** pharmacophoric entity in combination with an aromatic moiety from the lipophilic region of **AQ** were synthesized and evaluated *in vitro* against the intraerythrocytic stages of CQ-resistant *P. falciparum* parasites (W2 clone). Their efficacies were compared with those of **MQ** and **AQ**, and these results are shown in Table 1.

Table 1. *In vitro* activities (IC_{50} values) of synthesized compounds **1**-**17** and references antimalarials **CQ**, **MQ** and **AQ** against a chloroquine-resistant *Plasmodium falciparum* clone (W2), cytotoxicity against the BGM cell line (EC_{50}), and selectivity index (SI), which is the ratio between the EC_{50} and IC_{50}.

Compound Code	R^1	IC_{50} ± SD [μM]	EC_{50} BGM [μM]	SI
1		19.6±2.8	<44.8	<2.29
2		8.4±1.7	>560	>66.7
3		8.4±2	>559	>66.5
4		11.0±8.3	127±44	11.5
5		28.0±2.8	<22.5	<0.83
6		9.6±1.0	12.3	1.2
7		33.0±2.4	<18.9	<0.57
8		16.0±0.0	<42.8	<2.67
9		24.1±9.4	672	<27.88
10		4.8±1.0	129.8	27
11		2.9±0.0	<23.1	<8
12		0.083±0.006	11±3.9	132
13		11.5±1	84.2±29	7.3
14		1.8±1.0	1.5	0.8
15		31.5±2.9	17.2±2.9	0.5
16		>143	1680±131	<11.74
17		11.7±3	784.3	67
MQ		0.019±0.003	15±5.3	163
CQ		0.25±0.06	907±166	3628
AQ		0.006±0.002	-	-

The importance of the 2,8-bis(trifluoromethyl)quinoline moiety in **MQ** versus the 7-chloroquinoline present in the **CQ** core was the first consideration investigated in this study. When the results of compounds **2** and **17** were compared, where the substitution pattern of the quinolinic ring was changed from 7-chlorine to 2,8-diCF_3, respectively, **2** was equipotent than **17** demonstrating that substitution in the quinoline core was not relevant for anti-*plasmodium* activity.

Another important factor was the presence of the quinoline-NH group in this class of molecules. Compounds **15** (IC_{50} = 31.5 μM) and **16** (IC_{50} >143 μM), which are tertiary amines, were less active and inactive, respectively. Comparing these biological results, we propose two hypotheses for the lack of anti-*P. falciparum* activity of compounds that do not have an NH group between the trifluoromethylquinoline ring and the hydrophobic region: (i) the cyclic tertiary amines of **15** and **16** lack conformational freedom because they

are more rigid than the other compounds, and this rigidity interferes with their ability to interact with the biomacromolecule receptor; and (ii) the NH group could interact with the bioreceptor via hydrogen bonding.

The most active compound in the 2,8-bis-(trifluoromethyl)quinoline series was **12** (IC_{50} = 0.083 µM) containing a 3-methyl-1,2,4-triazole substituent. Despite being less potent than **MQ**, the antiplasmodium activity of **12** proved to be relevant as it is 3-fold more potent than **CQ**. Moreover, its chemical structure is simpler than that of **MQ** as it does not contain a stereogenic center, and consequently, its synthesis in the laboratory is easier and less expensive. If the 5-H or 5-CF_3 in the triazole ring in derivatives **11** (IC_{50} = 2.9 µM) and **13** (IC_{50} = 11.5 µM), respectively, were substituted, significantly lower activities were observed relative to when 5-CH_3 remained intact as it is in **12** (IC_{50} = 0.083 µM). The investigation of the isosteric replacement of the 5-methyltriazole unit in **12** with a 5-methylthiadiazole unit in **14** (IC_{50} = 1.8 µM) proved to be deleterious to the activity, showing the importance of the triazole nucleus in the antiplasmodial activity. This fact corroborates previous literature results[37,38,39] showing the importance of the triazole nucleus against the *Plasmodium* parasite.

When comparing different substituents on the phenyl group, the following results were observed: 3,4-di-OCH_3 in **10** (IC_{50} = 4.8 µM); *p*-F in **8** (IC_{50} = 16.0 µM); *p*-OH in **9** (IC_{50} = 24.1); H in **5** (IC_{50} = 28.0 µM); and *o*-CF_3 in **7** (IC_{50} = 33.0 µM). The replacement of the phenyl group in **5** (IC_{50} = 28.0 µM) with a ß-naphthyl group afforded **6** (IC_{50} = 9.6 µM), which was three times more active, showing the importance of lipophilicity in this region to biological activity; however, it was not selective and showed high toxicity.

Concerning the location of the nitrogen atom on the pyridine, when the nitrogen was in the 4-position, as in **2** (IC_{50} = 8.4 µM), the compound was 2.5 times more active than when the nitrogen was in the 2-position, as in **1** (IC_{50} = 19.6 µM), and it was much more selective. Moreover, when we evaluated the effect of a pyrimidine derivative, as in **3** (IC_{50} = 8.4 µM), with two adjacent nitrogen atoms, the compound showed equipotent anti-*P. falciparum* activity and toxicity with **2**. The LogP, LogD (pH 7.4 and 5.2) pKa were calculated for all substances. However, it fails to correlate with the biological activity.

2.3 Antimalarial tests

Due to the high SI value of compounds **2, 3,** and **12,** they were selected for antimalarial activity tests against *P. berghei* in experimentally infected mice. Compound **3** inhibited parasitemia by 61% on day 5 after inoculation, whereas compound **2** was less active with a maximum of 25% parasitemia inhibition. Compound **12** was the most active on the 5th day after infection, reducing parasitemia by 66%, which is consistent with its *in vitro* activity (Table 2).

Table 2. Antimalarial activity of the compounds that were most selective *in vitro* in mice infected with *Plasmodium berghei* treated daily (doses of 50 mg/kg body weight) for three consecutive days. The antimalarial mefloquine was used as a standard drug.

Compound	Dose (mg/kg)	Parasitemia on days[a] Mean ± SD (% Reduction)			Survival (Mean ± SD)
		5th	7th	9th	
2	50	1.3 ± 0.9 (25)	12.3 ± 5.4 (42)	29.5 ± 19 (11)	15±2
3	50	0.9 ± 0.7 (61)	16.2 ± 11 (35)	22.9 ± 14 (31)	13±4
12	50	0.3 ± 0.2 (66)	15 ± 4.9 (30)	31 ± 13 (23)	19±4
CQ	20	0.01± 0.02 (99)	0.14 ± 0.1 (99)	6.3 ± 3.8 (84)	24±3
MQ	20	0.04 ± 0.04 (98)	0.46 ± 0.6 (98)	0.43 ±0.9 (99)	>30
Non-treated		0.88 ± 0.3	21.5 ± 2.7	40.4 ± 12	13±3

[a]Reduction of parasitemia in relation to untreated controls; when < 30%, the compound was considered inactive, 30-40% was partially active and > 40% was active. The data from compounds 2 and 3 are from one experiment. The compound 12 was tested in two individual experiments.

3. Conclusions

We have successfully designed, synthesized and characterized a series of 17 novel quinolines **1-17** that are structural analogues of **MQ** and **AQ**. These compounds were obtained in only three steps with good yields and are of great importance because they are simpler and less expensive to produce than **MQ**. Final costs cannot be disregarded in the area of drug development, and this parameter depends on (i) the production process of the specific drug, which is directly related to its structural complexity; (ii) less complex drugs require fewer steps to produce and, consequently, reduce the consumption of reagents, solvents, energy, water, and personnel hours and reduce safety concerns; and (iii) these new aminoquinolines were synthesized in only three steps. Based on initial data reported in this paper, the selected potent analogues may represent new leads for the development of synergistic drug partners in antimalarial combination therapies.

All compounds exhibited anti-*P. falciparum* activity *in vitro* against chloroquine-resistant parasites, with IC_{50} values ranging from 0.083 to 33.0 µM. The compound in their series with the most potent anti-plasmodium activity was N-(5-methyl-4*H*-1,2,4-triazole-(4-amino-(2,8-bis(trifluoromethyl)-quinoline) (**12**), although less potent than **MQ**, it was 3-fold more potent than to **CQ**, and it is simpler and less expensive to synthesize, as it lacks the stereogenic center present in **MQ**. Another relevant observation is that 2,8-diCF_3 quinoline **2** was equipotent than 7-Cl quinoline **17** demonstrating that substitution in the quinoline core was not relevant for anti-*plasmodium* activity. Furthermore, the absence of the quinoline-NH group, molecules of this class are less active and more toxic (**15** and **16**). Comparing the lipophilic region of the phenyl substituent (**5-10**) and different substituents on the phenyl ring, improvements in activity were observed when larger groups were present in this region, as in **6** and **10**; however, these compounds are toxic. In addition, the location of the nitrogen atom in the pyridine core influences the activity; when the nitrogen is in position 4, the compound is more active and selective. Finally, the 5-methyltriazole core provided superior antimalarial activity compared with the other groups tested in this study, confirming that it is an important fragment for the development of

new antiparasitic drugs. The antimalarial activities of the compounds that were most selective *in vitro* (**2**, **3** and **12**) in mice infected with *Plasmodium berghei* showed that **12** was the most active on the 5th day after infection, and it reduced parasitemia by 66%, which was consistent with its *in vitro* activity. Ultimately, this system proved promising for the design of potential antimalarial drugs.

4. Experimental

4.1 Chemistry

Reagents were purchased from Aldrich or Merck and were used without further purification. Thin-layer chromatography separations were performed on silica gel plates (Merck, Kieselgel 60 F254), and the spots were visualized using ultraviolet light (UV, 254 nm). Yields were determined after purification. Melting points were obtained on a Buchi melting point apparatus model B-545 and are uncorrected. Infrared spectra were obtained on a Shimadzu FTIR spectrophotometer model Prestige-21 through KBr reflectance. Gas chromatography with mass spectrometry detection (GC-MS) was performed using an Agilent® Model 6890 Chromatograph with an Agilent® Model 5973 at 70 eV. The values of the fragmentation and molecular ions are expressed as the mass/load (m/z) values. The column used was an Agilent® 122e5532 DB-5MS (5% diphenyl: 95% dimethylpolysiloxane), and analyses were performed using a temperature ramp of 50°C and 350°C. The electron ionization mass spectrometry (ESI-MS, scan ES þ capillary (3.0 kV)/cone (30 V)/ extractor (1 V)/RF lens (1.0 V)/source temperature (150°C)/desolvation temperature (300°C)) data were recorded using a Micromass/Waters Spectrometer model: ZQ-4000. High-resolution mass spectrometry (HRMS) data were obtained using an LC-MS Bruker Daltonics MicroTOF (time of flight analyzer). ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were obtained at 400, 100 and 376 MHz, respectively, using a BRUKER Avance instrument equipped with a 5-mm probe. Tetramethylsilane was used as an internal standard. The chemical shifts (d) are reported in ppm. The coupling constants (J) are reported in hertz along with the apparent peak multiplicities.

2,8-bis(trifluoromethyl)quinolin-4-ol (19)

To a solution of polyphosphoric acid (637.7 mmol) in 2-trifluoromethyl aniline (77.6 mmol) was added ethyl 4,4,4-trifluoroacetoacetate (77.7 mmol). The reaction mixture was stirred for 3 hours at 150 °C. Completion of the reaction was monitored by TLC. After, the reaction mixture was poured into iced distilled water slowly with vigorous stirring to form yellow precipitate. The precipitate was vacuum filtered and washed with cold distilled water to give yellow solid in 91% yield. m.p 128-130 ^{o}C; ^{1}H-NMR (400 MHZ; DMSO-d_6, ppm): δ 7.30 (s, 1H, H-3); 7.80 (t, 1H, H-6; *J* = 7.9 Hz); 8.28 (d, 1H, H-5; J = 7.2 Hz); 8.52 (d, 1H, H-7, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): *δ* 101.0 (C-3); 119.9 (C-4a); 121.9 (C-6); 122.6 (q, C-9, *J* = 273 Hz); 125.3 (q, C-10, *J* = 276 Hz); 127.3 (C-7); 130.0 (q, C-8, *J* = 58 Hz); 144.5 (C-5); 148.4 (q, C-2, *J* = 67 Hz); 163.3 (C-4); ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): δ -58.98 (s, 3F; F-10); -67.03 (s, 3F; F-9).

4-chloro-2,8-bis(trifluoromethyl)quinoline (20)

A mixture of 2,8-bis(trifluoromethyl)quinolin-4-ol (2g) and $POCl_3$ (108.2 mmol) was heated at 80 °C for 4 h. The reaction was monitored by TLC. After completion of the reaction was poured into iced distilled water slowly with vigorous stirring to form dark brown precipitate. The precipitate was collected by filtration to give yellow solid in 98% yield. m.p 45-46^{o}C; GC-MS m/z (%): 299 (100); 280 (23); 230 (54); 210 (16);^{1}H-

NMR (400 MHZ; DMSO-d_6, ppm): δ 7.92 (s, 1H, H-3); 7.84 (t, 1H, H-6, *J* = 7.9 Hz); 8.28 (d, 1H, H-5, *J* = 7,2 Hz); 8.54 (d, 1H, H-7, *J* = 8.2 Hz); ^{19}F-NMR (376 MHZ; MeOH, ppm): δ - 58.98 (s, 3F; F-10); -67.00 (s, 3F; F-9).

General procedure for the synthesis of *N*-substituted-2,8-bis(trifluoromethyl)-quinolin-4-amines (1-16) and 7-chloro-*N*-(pyridin-4-yl)quinolin-4-amine (17).

To a suspension of sodium hydride in mineral oil (80%, 3.33 mmol) in dry DMSO (2 ml) at 0 °C, the appropriate amine (3.33 mmol) was slowly added. The mixture was stirred for 15 min at 0 °C and then at room temperature for 1 h. After this time, 4-chloro-2,8-bis(trifluoromethyl)quinoline or 4,7-dichloroquinoline (1 mmol) in dry DMSO (2 ml) was added to the reaction mixture, and it was stirred at room temperature for an additional 24 h. The reaction was monitored by TLC. After it was complete, the reaction was poured into iced distilled water to form a precipitate, which was isolated by filtration and dried. When no precipitation occurred, the reaction mixture was extracted with ethyl acetate (3 x 20 ml), washed with water (3 x 15 ml), and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and solid **1-17** precipitated in 56-87% yields.

***N*-(pyridin-2-yl)-2,8-bis(trifluoromethyl)quinolin-4-amine (1)**

Yellow solid**;** 77 % yield; m.p 170-172 °C; GC-MS m/z (%): 356 (100); 357 (80); 288 (87); 78 (16); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): *δ* 7.12-7.09 (m, H-5', *J* = 5.2 Hz); 7.46 (d, 1H, H-6'); 7.86-7.82 (m, H-6; H-4'); 8.27 (d, 1H, H-5, *J* = 7.2 Hz); 8.43 (d, 1H, H-3', *J* = 4.8 Hz); 8,95 (d, H-7, *J* = 8.6 Hz); 9.01 (s, H-3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): *δ* 101.7 (C-3); 114.6 (C-5'); 118.1 (C-3'); 122.5 (q, C-9, *J* = 273 Hz); 122.6 (q, C-10, *J* = 276 Hz); 123.4 (C-4a); 125.5 (C-6); 126.6 (q, C-8, *J* = 29 Hz); 127.4 (C-5); 129.2 (q, C-7, *J* = 5.1 Hz); 138.2 (C-4'); 144.3 (C-4); 147.2 (C-6'); 147.6 (q, C-2, *J* = 33.5 Hz); 148.0 (C-1'); 158.4 (C-8a); ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): - 58.79 (s, 3F; F-10); -66.94 (s, 3F; F-9); FTIR (KBr, cm^{-1}): 3326 (ν NH_2); 2861 (ν CH); 1618 (C=C); ν 1588(ν C=N); 1369 (ν C-N); 1301 (ν C-N); 1092, 1105 and 1119 (ν CF); 724 (ν CF_3); HRMS: calculated for $C_{16}H_{10}F_6N_3$: 358.0773, found: 358.0771.

***N*-(pyridin-4-yl)-2,8-bis(trifluoromethyl)quinolin-4-amine (2)**

Yellow solid**;** 87 % yield; m.p 146-148 °C; GC-MS m/z (%): 357 (100); 358 (17); 288 (19); 78 (12); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): *δ* 7.40 (d, 2H, H-1'; H-4', J = 7.40 Hz); 7.65 (s, 1H, H-3); 7.88 (t, 1H, H-6, J = 7.8 Hz); 8.32 (d, 1H, H-5, J = 7.2 Hz); 8.52 (d, 2H, H-2', H-3', J = 5.92 Hz); 8.74 (d, 1H, H-7, J = 8.5 Hz); 9.98 (1H, N-H). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): *δ* 100.9 (C-3); 114.3 (C-2', C-6'); 121.4 (q, C-9, J = 273 Hz); 122.8 (q, C-10, J = 276 Hz); 125.2 (C-6); 126.4 (q, C-8, J = 29 Hz); 127.6 (C-5); 129.6 (q, C-7, J = 5.0 Hz); 144.3 (C-4); 147.4 (q, C-2, J = 33.5 Hz); 148.5 (C-1'); 150.8 (C-3', C-5'). ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): -58.84 (s, 3F, F-10); - 66.98 (s, 3F, F-9). HRMS: calculated for $C_{16}H_{10}F_6N_3$: 358.0773, found: 358.0771.

***N*-(pyrimidin-2-yl)-2,8-bis(trifluoromethyl)quinolin-4-amine (3)**

Yellow solid**;** 87 % yield; m.p 118-120 °C; GC-MS m/z (%): 357 (100); 358 (76); 289 (59); 278 (5); 79 (6); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): *δ* 7.20 (t, 1H, H-4', J = 4.84 Hz); 7.83(t, 1H, H-6, J = 8 Hz); 7.30 (d, 1H, H-5, J = 7.2 Hz); 8.76 (d, 2H, H-3', H-5', J = 4.8 Hz); 8.90 (s, 1H, H-3); 9.00(d, 1H, H-7, J = 8,5 Hz); 9.98 (1H, N-H). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): *δ* 104.6 (C-3); 115.6 (C-4'); 121.1 (C-4a); 121.4 (q, C-

9, J = 272 Hz); 122.4 (q, C-10, J = 274 Hz); 126.1 (C-6); 126.7 (q, C-8, J = 29 Hz); 127,9 (C-5); 129.5 (q, C-7, J = 9.1 Hz); 143.9 (C-4); 146.4 (C-8a); 147.4 (q, C-2, J = 33.3 Hz); 158.4 (C-3'; C-5'); 159.3 (C-1'). ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): -58.76 (s, 3F, F-10), - 66.83 (s, 3F, F-9); FTIR (KBr, cm^{-1}): 3448 (ν NH), 3236 (ν NH), 2923 (ν CH), 1591 (ν C=C), 1501-1533 (ν NH), 1340-1252 (ν C-N), 1189, 1113 e 994 (ν CF), 756 (ν CF_3). HRMS: calculated for $C_{15}H_9F_6N_4$: 359,2412, found: 359.2410.

N-cyclohexyl-2,8-bis(trifluoromethyl)quinolin-4-amine (4)

Yellow solid**;** 79 % yield; m.p 84-85 °C; GC-MS m/z (%): 362 (68); 343 (15); 319 (100); 299 (18); 236 (10); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): *δ* 1.41- 1.43 (ms, 10H, H-2', H-3', H-4', H-5', H-6'); 1.78 (bs, 1H, H-1'); 6.91 (s, 1H, H-3); 7.56 (d, 1H, NH, J = 7.8 Hz); 7.66 (t, 1H, H-6, J = 7.9 Hz); 8.14 (d, 1H, H-5, J = 7.2 Hz); 8.72 (d, 1H, H-7, J = 8.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): *δ* 24.5 (C-4'); 25.2 (C-3' C-5'); 31.5 (C-2' C-6'); 51.8 (C-1'); 94.2 (C-3); 119.3 (C-4a); 120.9 (q, C-9, J = 263 Hz); 123.3 (q, C-10, J = 268 Hz); 124.1 (C-6); 126.3 (q, C-8, J= 28 Hz); 127.2 (C-5); 128.8 (q, C-7, J = 5 Hz); 144.0 (C-4); 147.8 (q, C-2, J = 32.5 Hz); 151.2 (C-8a), ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): - 58.88 (s, 3F; F-10); -66.96 (s, 3F; F-9). HRMS: calculated for $C_{17}H_{17}F_6N_2$: 363.3127, found: 363.3129.

***N*-phenyl-2,8-bis(trifluoromethyl)quinolin-4-amine (5)**

Brown solid; 78 % yield; m.p 94-96 °C; GC-MS m/z (%): 356 (100); 335 (10); 288 (75); 217 (1); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 7.07 (s, 1H, H-3), 7.32 (t, 1H, H-4', J = 10 Hz), 7.44 (d, 2H, H-2';H-6', J = 10 Hz), 7.52 (t, 2H, H-3', H-5', J = 10 Hz), 7.79 (t, 1H, H-6, J = 5.0 Hz), 8.25 (d, 1H, H-5, J = 5.0 Hz), 8.80 (d, 1H, H-7, J = 5.0 Hz) 9,79 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 96.5 (C-3), 114.8 (C-4'), 120.0 (C-3'; C-5'), 121.4 (q, C-9, J = 273 Hz), 123.9 (q, C-10, J = 290 Hz), 125.3 (C-2', C-6'), 125.8 (C-6), 126.5 (q, C-8, J = 28.7 Hz), 127.3 (C-5), 129.6 (q, C-7, J = 5.0 Hz), 130.1 (C-1'); 138.8 (C-4a), 144.3 (C-4), 147.6 (q, C-2, J = 33.7 Hz), 151.2 (C-8a). ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): -58.76 (s, 3F, F-10), - 66.83 (s, 3F, F-9); FTIR (KBr, cm^{-1}): 3450 (ν NH), 1580 (ν C=C), 1502-1532 (ν NH), 1363 (ν C=N), 1315 (ν C=N), 1106, 1132 e 1155 (ν CF), 722 (ν CF_3); HRMS: calculated for $C_{17}H_{11}F_6N_2$: 357.0820, found: 357.0827.

***N*-(naphthalen-2-yl)-2,8-bis(trifluoromethyl)quinolin-4-amine (6)**

White solid; 49 % yield; m.p 124-126 ^{o}C; GC-MS *m/z* (%): 406 (100), 336(36); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.35 (s, 1H, H-3); 7.53 (t, 1H, H-3', J = 7.1Hz); 7.59-7.70 (ms, 3H, H-6', H-7', H-2'); 7.84 (t, 1H, H-6, J = 7.9 Hz); 7.89 (d, 1H, H-4', J = 8.3 Hz); 8.03 (d, 1H, H-5', J = 7.6 Hz); 8.06 (d, 1H, H-8', J = 8.1 Hz); 8.27 (d, 1H, H-5, J = 7.2 Hz); 9.01 (d, 1H, H-7, J = 8.4 Hz); 10.05 (bs, 1H, N-H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 96.4 (C-3); 119.6 (C-4a'); 122.6 (C-8a'); 122.7 (q, C-9, J = 263 Hz); 124.8 (q, C-10, J = 263 Hz); 125.3 (C-5'); 126.3 (C-3'); 126.40 (C-6); 126.7 (q, C-8, J = 28 Hz), 127.3-127.8 (C-6', C-7'), 128.6 (C-2'), 129.4 (C-5), 129.5 (q, C-7, J = 5.1 Hz); 134.4-134.4 (C-4', C-8'); 138.6 (C-4a); 144.1 (C-4); 147.9 (q, C-2, J = 33.2 Hz); 152.9 (C-8a); ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): δ – 58.90 (s, 3F, F-10); - 67.38 (s, 3F, F-9). HRMS: calculated for $C_{21}H_{13}F_6N_2$: 407.0977, found: 407.0961.

2,8-bis(trifluoromethyl)-*N*-(2-(trifluoromethyl)phenyl)quinolin-4-amine (7)

White solid; 76 % yield; m.p. 119-120 ^{o}C; GC-MS m/z (%): 424 (100); 385 (31); 354 (59); 335 (25);315 (22); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.29 (s, 1H, H-3); 7.76 (ms, 2H, H-5'; H-6', J = 7 Hz); 7.84 (t, 1H, H-4', J = 8 Hz); 7.92 (t, 1-H, H-6, J = 7.5 Hz); 8.00 (d, 1H, H-3', J = 8 Hz); 8.29 (d, 1H, H-5, J =

7.0 Hz); 8.86 (d, 1H, H-7, J = 8.5 Hz); 9.77 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 96.7 (C-3); 122.3 (q, C-9, J = 273 Hz); 122.7 (q, C-7' J = 236 Hz); 124.4 (q, C-10, J = 276 Hz), 125.6 (C-4'); 126.4 (C-6); 127.0 (q, C-8, J = 28.7 Hz); 128.2 (q, C-3', J = 5.1 Hz); 128.8 (C-6'); 129.6 (q, C-7, J = 5.0 Hz); 131.4 (C-5); 134.7 (C-5'); 136.4 (q, C-2', J = 31.2); 139.3 (C-4a); 143.9 (C-4); 147.7 (q, C-2, J = 33.1 Hz); 151.3 (C-1'); 152.9 (C-8a); ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): δ -58.96 (C-7'); -59.76 (C-10); -67.34 (C-9); FTIR (KBr, cm^{-1}): 3477 (ν NH); 1584 (ν C=C); 1506-1541 (ν NH); 1310-1334 (ν CF_3); 1179; 1134 and 1118 (ν CF); 758 (ν CF_3). HRMS: calculated for $C_{18}H_{10}F_9N_2$: 425.0694, found: 425.0690.

***N*-(4-fluorophenyl)-2,8-bis(trifluoromethyl)quinolin-4-amine (8)**

Brown solid; 87 % yield; m.p 121-122 °C; GC-MS m/z (%): 372 (100); 108 (62); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.97 (s, 1H, H-3); 7.34-7.40 (ms, H-2'; H-6'); 7.46-7.51 (ms, H-3'; H-5'), 7.80 (t, H-6, J = 7,9 Hz), 8.25 (d, H-5, J = 7.2 Hz), 8.79 (d, H-7, J = 8.4 Hz); 9.75 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 96.2 (C-3); 116.7 (d, C-3'; C5', J = 29 Hz); 119.8 (q, C-9, J = 273 Hz); 122.7 (q, C-10, J = 276 Hz); 125.2 (C-6); 126.5 (d, C-2'; C-6' J = 8.0 Hz); 127.2 (q, C-8, J = 29 Hz); 129.4 (q, C-7, J = 5.4 Hz); 130.1 (C-5); 135.0 (C-4a); 144.2 (C-4); 147.4 (q, C-2, J = 32.9 Hz); 151.5 (C-8a); 158.6 (C-1'); 161.03 (C-4'); ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): 58.94 (s, 3F, F-10); - 67.29 (s, 3F, F-9); -116.11 (s, 1F, F-4'); FTIR (KBr, cm^{-1}): 3299 (ν NH); 1607 (ν C=C); ν 1509-1547 (ν NH); 1360 (ν C-N); 1311 (ν C-N); 1114, 1136 and 1136 (ν CF); 729 (ν CF_3). HRMS: calculated for $C_{17}H_{10}F_7N_2$: 375.0726, found: 375.0717.

4-((2,8-bis(trifluoromethyl)quinolin-4-yl)amino)phenol (9)

Brown solid; 77 % yield; m.p 121-122 °C; GC-MS m/z (%):372 (100), 108 (62); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): *δ* 2.50 (bs, 1H, OH or NH); 5.30 (bs, 1H, NH or OH); 6.72 (d, 2H, H-2';3', J = 8,7 Hz); 6.86 (s, 1H, H-3); 7.05 (d, 2H, H-5';6', J = 8.7 Hz); 7.94 (t, 1H, H-6, J = 7.9 Hz); 8.40 (d, 1H, H-5, J = 7.2 Hz); 8.73 (d, 1H, H-7, J = 8.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): *δ* 99.7 (C-3); 114.6 (C-3'); 119.5 (C-5'); 120.8 (q, C-9, J = 273 Hz); 121.5 (C-4'); 122.2 (q, C-10, J = 276 Hz); 126.2 (C-2'); 126.5 (C- 6'); 126.9 (C-6); 127.5 (q, C-8, J = 58 Hz); 127.7 (C-5); 130.5 (q, C-7, J = 5.0 Hz); 142.4 (C-4a); 144.0 (C-4); 147.4 (C-1'); 148.1 (q, C-2, J = 33 Hz); 164.8 (C-8a); ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): - 58.91 (s, 3F, F-10); - 67.00 (s, 3F, F-9); FTIR (KBr, cm^{-1}): 3445 (ν OH); 3369 (ν NH); 1624 (ν C=C); 1538-1580 (ν NH); 1369 (ν C-N); 1312 (ν C-N); 1105; 1119 and 1142 ν CF); 722 (ν CF_3); HRMS: calculated for $C_{17}H_{11}F_6N_2O$: 373.0770, found: 373.0772.

***N*-(3,4-dimethoxyphenyl)-2,8-bis(trifluoromethyl)quinolin-4-amine (10)**

Brown solid; 88 % yield; m.p 180-181 °C; GC-MS m/z (%):416 (100); 417 (20); 401 (80); 385 (16); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): *δ* 3.76 (s, 3H, H4'); 3.81 (s, 3H, H3'); 6.94 (s, 1H, H-3), 6.96 (dd, 1H, H6', J = 2.3 Hz, J= 8.5 Hz); 7.02 (d, 1H, H2', J = 2.3 Hz); 7,09 (d, 1H, H-5', J = 8.5 Hz), 7.77 (t, 1H, H-6, J = 7.8 Hz), 8.24 (d, 1H, H-5, J = 7.1 Hz), 8.80 (d, 1H, H-7, J = 8.4 Hz); 9.65 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): *δ* 55.6 (CH_3); 96.1 (C-3); 122.8 (q, C-9, J = 263.6 Hz); 125.0 (q, C-10, J = 273.5 Hz); 125.5 (C-6); 126.6 (q, C-8, J = 58 Hz); 127.1 (C-5); 129.3 (q, C-7, J = 5.0 Hz); 131.4 (C-1'); 140.0 (C-4a); 143.4 (C-5'); 144.2 (C-4); 146.0 (C-2'); 147.7 (q, C-2, J = 31 Hz); 149.5 (C-4'); 151.2 (C-8a); 151.9 (C-3'); ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): -58.92 (s, 3F, F-10); - 67.29 (s, 3F, F-9). HRMS: calculated for $C_{19}H_{15}F_6N_2O_2$: 417.1032, found: 417.1021.

***N*-(4*H*-1,2,4-triazol-3-yl)-2,8-bis(trifluoromethyl)quinolin-4-amine (11)**

White solid; 67 % yield; m.p 150-152 °C; GC-MS m/z (%):347 (100), 305 (88), 278 (57), 251 (1); ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 6.14 (bs, 2H, NH); 7.97 (t, 1H, H-6, J = 7.9 Hz); 8,32 (s, 1H, H-3); 8.42 (d, 1H, H-5, J = 7.2 Hz); 9,01 (s, 1H, H-5'); 9.14 (d, 1H, H-7, J = 8.7 Hz); ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 110.3 (C-3); 119.7 (q, C-9, J = 273 Hz); 122.5 (q, C-10, J = 276 Hz); 126.5 (q, C-8, J = 30 Hz); 128.1 (C-6), 130.2 (C-5), 130.5 (q, C-7, J = 5.0 Hz), 143.2 (C-4a), 144.4 (C-4), 147.4 (q, C-2, J = 35 Hz), 151.5 (C-5'), 156.5 (C-8a), 165.7 (C-3'). ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): -60.29 (s, 3F; F-10); -67.82 (s, 3F; F-9); FTIR (KBr, cm^{-1}): 3409 (ν OH); 3334 (ν NH); 3097 (ν NH); 1628 (ν C=C); 1521-1585 (ν NH); 1376 (ν C-N); 1309 (ν C-N); 1101; 1102; 1131 ν CF); 725 (ν CF_3); HRMS: calculated for $C_{13}H_8F_6N_5$: 348.2186, found: 348.2189.

***N*-(5-methyl-4H-1,2,4-triazol-3-yl)-2,8-bis(trifluoromethyl)quinolin-4-amine (12)**

White solid; 67 % yield; m.p 172-173 °C; GC-MS m/z (%):361 (100), 342 (22), 278 (78), 251 (32); ^{1}H NMR (500 MHz, MeOD, ppm): δ 2.34 (s, 3H, CH_3); 3.31 (bs, 2H, NH); 7.92 (t, 1H, H-6, J = 7.5 Hz); 8.18 (s, 1H, H-3); 8.25 (d, 1H, H-5, J = 8.5 Hz); 8.36 (d, 1H, H-7, J = 7.5 Hz); ^{13}C NMR (125 MHz, MeOD, ppm): δ 12.5 (CH_3); 117.0 (C-3); 121.4 (q, C-9, J = 268 Hz); 123.4 (q, C-10, J = 273 Hz); 126.1 (C-6); 126.9 (q, C-8, J = 30 Hz); 129.9 (C-5); 130.2 (q, C-7, J = 5 Hz); 145.2 (C-4); 146.3 (C-4a); 150.1 (q, C-2, J = 33.5 Hz); 151.2 (C-8a); 156.0 (C-3'); 165.4 (C-5'); ^{19}F-NMR (376 MHZ; MeOD, ppm): -61.61(s, 3F; F-10), -69.40 (s, 3F; F-9). HRMS: calculated for $C_{14}H_{10}F_6N_5$: 362.0834, found: 362.0851.

2,8-bis(trifluoromethyl)-*N*-(5-(trifluoromethyl)-4*H*-1,2,4-triazol-3-yl)quinolin-4-amine (13)

Yellow solid**;** 72 % yield; m.p 167-168 °C; GC-MS m/z (%): 415 (72), 345 (32), 278 (100), 209 (1); ^{1}H NMR (500 MHz, MeOD, ppm): δ 3.3 (bs, 2H, N-H).7.95 (t, 1H, H-6, J = 7.9 Hz); 8.16 (d, 1H, H-5, J = 8.1 Hz); 8.22 (s, 1H, H-3); 8.38 (d, 1H, H-7, J = 8.2 Hz); ^{13}C NMR (125 MHz, MeOD, ppm): δ 117.5 (C-3), 121.4 (q, C-9, J = 268 Hz), 123.4 (q, C-10, J = 273 Hz); 126.6 (C-6); 126.9 (q, C-8, J = 29 Hz); 129.3 (C-5); 130.1 (q, C-6', J = 276 Hz); 131.8 (q, C-7, J = 5 Hz); 144.1 (C-4); 146.5 (C-4a); 150.2 (q, C-2, J = 33.5 Hz), 154.3 (C-3'), 159.5 (q, C-5', J= 38.7 Hz); ^{19}F-NMR (376 MHZ; MeOD, ppm): -61.59 (s, 3F; F-6'); -68.09 (s, 3F; F-10), -69.41 (s, 3F, F-9). HRMS: calculated for $C_{14}H_7F_9N_5$: 416.2165, found: 416.2168.

***N*-(2,8-bis(trifluoromethyl)quinolin-4-yl)-5-methyl-1,3,4-thiadiazol-2-amine (14)**

White solid**;** 42 % yield; m.p 124-126°C; GC-MS m/z (%): 378 (100); 359 (43); 337 (39); 310 (22); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.67 (s, 3H, CH_3); 7.93 (t, 1H, H-6, J = 7,8 Hz); 8.34 (d, 1H, H-5, J = 7.20 Hz); 8.87 (d, 1H, H-7, J = 8.56 Hz); 9.07 (s, 1H, H-3), 11.21 (bs, 1H, N-H).^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 15.1 (CH_3); 102.7 (C-3); 121.3 (q, C-9, J = 273 Hz); 122.5 (q, C-10, J = 276 Hz); 126.6 (C-6); 126.9 (q, C-8, J = 31,4 Hz); 127.3 (C-5); 129.6 (q, C-7, J = 5.0 Hz); 143.7 (C-4a); 146.0 (C-4); 148.0 (q, C-2, J = 33.5 Hz); 159.2 (C-2'); 163.2 (C-5'); ^{19}F-NMR (376 MHZ; DMSO-d_6, ppm): -58.75 (s, 3F; F-10); -66.98 (s, 3F; F-9); HRMS: calculated for $C_{14}H_8F_6N_4NaS$: 401.0266, found: 401.0274.

4-(piperazin-1-yl)-2,8-bis(trifluoromethyl)quinoline (15)

Yellow solid; 56% yield; m.p 133-134 °C; GC-MS m/z (%): 350 (100), 331 (30), 392 (100), 264 (28), 223 (100), 196 (33); ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 2.99 (s, 4H, H-2', H-6'); 3.27 (s, 4H, H-3', H-5'); 3.37 (bs, 1H, N-H); 7.36 (s, 1H, H-3); 7.80 (t, 1H, H-6, J = 7.8 Hz), 8.26 (d, 1H, H-5, J = 7.2 Hz), 8.37 (d,

1H, H-7, J = 8.4 Hz); ^{13}C NMR (100 MHz, DMSO-d6, ppm): δ 45.3 (C-2', C- 6'); 53.2 (C-3'C-5'); 104.6 (C-3), 121.3 (q, C-10, J = 273 Hz); 122.7 (q, C-9, J = 276 Hz); 123.4 (C-4a); 125.8 (C-6); 126.9 (q, C-8, J = 28.5 Hz), 127.8 (C-5); 129.3 (q, C-7, J = 5.0 Hz); 139.2 (C-4a); 144.4 (C-4); 147.5 (q, C-2, J = 33.7 Hz); 159.4 (C-8a); ^{19}F-NMR (376 MHZ; DMSO-d6, ppm): δ 58.76 (s, 3F, F-10); - 66.65 (s, 3F, F-9); FTIR (KBr, cm−1): 3073 (ν NH); 2984, 2954 (ν C-H); 1591 (ν C-N); 1299 (ν CH_2); 1033 (ν C-N); 1097, 1112 and 1182(ν CF); 724 (ν CF_3; HRMS: calculated for $C_{15}H_{14}F_6N_3$: 350.1086, found: 350.1083.

4-(2,8-bis(trifluoromethyl)quinolin-4-yl)morpholine (16)

Yellow solid; 69% yield; m.p 198-200 °C; GC/MS m/z (%):349 (40); 330 (13); 307 (100); 238 (25); ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 3.36 (t, 4H, C-3', C-5' J = 4.3 Hz); 3.91 (s, 4H, C-2', C-6' J = 4.5 Hz); 7.42 (s, 1H, H-3); 7.80 (t, 1H, H-6, J = 7.9 Hz); 8.27 (d, 1H, H-5, J = 7.2 Hz); 8.42 (d, 1H, H-7, J = 8.5 Hz); ^{13}C NMR (100 MHz, DMSO-d6, ppm): δ 52.1 (C-3', C-5'); 65.8 (C-2', C-6'); 105.0 (C-3); 122.6 (q, C-10, J = 276 Hz); 122.4 (q, C-9, J = 273 Hz); 123.4 (C-4a); 126.2 (C-6); 126,9 (q, C-8, J = 28.7 Hz); 129.3 (C-5); 129.4 (q, C-7, J = 5.0 Hz); 144.3 (C-4); 147.6 (q, C-2, J = 33.0 Hz); 158.9 (C-8a); ^{19}F-NMR (376 MHZ; DMSO-d6, ppm): δ – 58.75 (s, 3F; F-10); -66.63 (s, 3F; F-9); FTIR (KBr, cm−1): 2952 (ν NH); 2813 (ν NH); 1590 (ν NH); 1112 (ν CH); 1097, 1112 and 1129 (ν CF); 724 (ν CF_3); HRMS: calculated for $C_{15}H_{12}F_6N_2NaO$: 373.0746, found: 373.0751.

7-chloro-N-(pyridin-4-yl)quinolin-4-amine (17)

Yellow solid**;** 89 % yield; m.p 157-158°C; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): *δ* 7.26 (d, 2H, H-2', H-6', J = 6.2 Hz); 7.38 (d, 1H, H-3, J = 5.2 Hz); 7.64 (d, 1H, H-6, J = 9.0 Hz); 7.98 (s, H-8); 8.34 (d, 1H, H-5, 3 J = 9.2 Hz); 8.40 (d, 2H, H-3', H-5', J = 6.2 Hz); 8.66 (d, 1H, H-2, 3 J = 5.2 Hz); ^{13}C NMR (125 MHz, MeOD, ppm): *δ* 106.6 (C-2', C-6'); 112.9 (C-3); 119.7 (C-4a); 124.7 (C-6); 125.8 (C-5); 127.8 (C-8); 134.3 (C-7); 145.0 (C-3', C-5'); 148.3 (C-4); 149.6 (C-8a); 150.5 (C-2); 152.0 (C-1'); HRMS: calculated for $C_{14}H_{11}ClN_3$: 256.0636, found: 256.0624.

4.2 Biological evaluation

4.2.1 Continuous cultures and *in vitro* assays with *P. falciparum*-infected erythrocytes.

A CQ-resistant and MQ-sensitive *P. falciparum* clone W2[40] was cultivated as described[41] in human erythrocytes (A^+) in complete medium (RPMI 1640 supplemented with 1% ALBUMAX II), and the tests followed a protocol[42] that was slightly modified as follows. Human erythrocytes (A^+) were kindly donated by the Center of Hemotherapy and Hematology of Minas Gerais (HEMOMINAS-http://www.hemominas.mg.gov.br) under the mutual cooperation term number 18/09.

The molecules were diluted in dimethyl sulfoxide (DMSO) (Sigma-Aldrich) to obtain a stock solution of 10 mg/mL and further diluted to the specified concentrations with RPMI 1640 medium supplemented with 25 mM Hepes, 21 mM sodium bicarbonate, 11 mM glucose, 2% glutamine (Sigma-Aldrich), and 40 mg/L gentamicin (Schering-Plough, Kenilworth, New Jersey, USA) to a final concentration of 0.02% DMSO for the assays against *P. falciparum*.

The sorbitol-synchronized ring-stage parasites[43] were adjusted for parasitemia and hematocrit, according to the specifications of the test, and then distributed in 96-well microtiter plates (Corning, Santa Clara, CA, USA). The plates had been prepared previously and contained dilutions of the test compounds (20 µL/ well). Triplicate tests were used for each dose. **CQ**, **MQ** and **AQ**, the standard antimalarials, were tested in

parallel each time. The drug activity was determined in comparison to untreated parasite cultures in complete medium, as described previously.[44] Parasite growth was measured through the anti-HRPII test[45] in cultures adjusted to 1.5% hematocrit and 0.05% parasitemia with monoclonal antibodies (MPFM-55A and MPFG-55P) that were commercially acquired (ICLLABH, USA) and TMB chromogen (3,39,5,59-tetramethylbenzidine), which was purchased from KPL (Gaithersburg, MD, USA). The reaction was stopped with the addition of 50 µL/L of 1 M sulfuric acid, and the absorbance of each well was read at 450 nm using a spectrophotometer (SpectraMax340PC384, Molecular Devices).

Sigmoid dose-response curves were generated with curve-fitting software (Microcal Origin Software 5.0, Inc.) and were used to determine the 50% inhibitory concentrations of parasite growth (IC_{50} values). The activities were calculated by comparing the growth in the drug-exposed cultures and the drug-free control cultures.

4.2.2 Cell Cultures and Cytotoxicity Tests

The monkey kidney cell line (BGM) was cultured in 75-cm^2 sterile flasks with RPMI 1640 supplemented with 10% heat-inactivated fetal serum and 40 mg/L gentamicin in a 5% CO_2 atmosphere at 37 °C. For the *in vitro* cytotoxicity experiments, the cell monolayer was trypsinized, washed with culture medium, distributed in a flat-bottomed 96-well plate (5×10^3 cells/well), and finally incubated for 18 h at 37 °C to achieve cell adherence.

For cytotoxicity testing, we used the (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay described in the literature[46]. The BGM cells were incubated with 20 µL of the test compounds at different concentrations (200–25 µg/mL) for 24 h under an atmosphere of 5% CO_2 at 37°C. For the molecules dilution a stock solution of 20 mg/mL in DMSO was made. Next, the compounds were solubilized in culture medium RPMI 1640 supplemented with 10% heat-inactivated fetal serum.

For the MTT assay, which evaluates mitochondrial viability, 20 µL of MTT solution (5 mg/mL) was added, and the plates were incubated for an additional 3 h. After incubation, the supernatant was carefully removed from the wells, and 100 µL of DMSO was added and mixed thoroughly. Optical densities at 570 and 630 nm (background) were determined by an ELISA reader. Cell viability is expressed as the percentage of the control absorbance obtained in untreated cells after subtracting the absorbance from the appropriate background. Finally, half maximal effective concentration (EC_{50}) was determined as previously described.[47] The ratio between the EC_{50} and IC_{50} values was used to determine the selectivity index (SI).

4.2.3 *P. berghei* and antimalarial tests in mice

The suppressive test was performed, as described.[48] The *P. berghei* NK65 strain used was maintained through weekly blood passages, as described.[49] For these experiments, groups of up to 30 mice were inoculated i.p. with 1×10^5 infected erythrocytes, kept together for approximately 24 h, and then randomly distributed into groups of five per cage. The mice were treated daily for three consecutive days with the compounds freshly diluted in 3% DMSO (Sigma-Aldrich) in RPMI medium and administered orally at 50 mg/kg; the control groups received either the drug vehicle or the antimalarials **CQ** and **MQ** at 20 mg/kg. On days 5, 7, and 9 after the parasite inoculation, a blood sample was taken from the tail of each mouse and used to prepare thin smears that were methanol-fixed, Giemsa-stained, and examined microscopically (1000X) to determine parasitemia. The inhibition of parasite growth was determined relative to parasitemia in the untreated mice, which was

considered to be 100% parasite growth. Compounds reducing parasitemia by >40% were considered active, between 30-40% were partially active, and by less than 30% were considered inactive.

Acknowledgments

This study was financed in part by the Coordenacao de Aperfeiçoamento de Pessoal de Nivel Superior - Brasil (CAPES) - Finance Code 001. The authors thank the National Council for Scientific and Technological Development (CNPq) for the fellowships granted to the authors and financial support of the projects. We are also thankful to the Foundation for Research of the State of Rio de Janeiro (FAPERJ), Coordination of Improvement of Higher-Level Personnel (CAPES), the Foundation for Research of the State of Minas Gerais (FAPEMIG) and the Foundation for Scientific and Technological Development in Health (FIOTEC) for their financial support.

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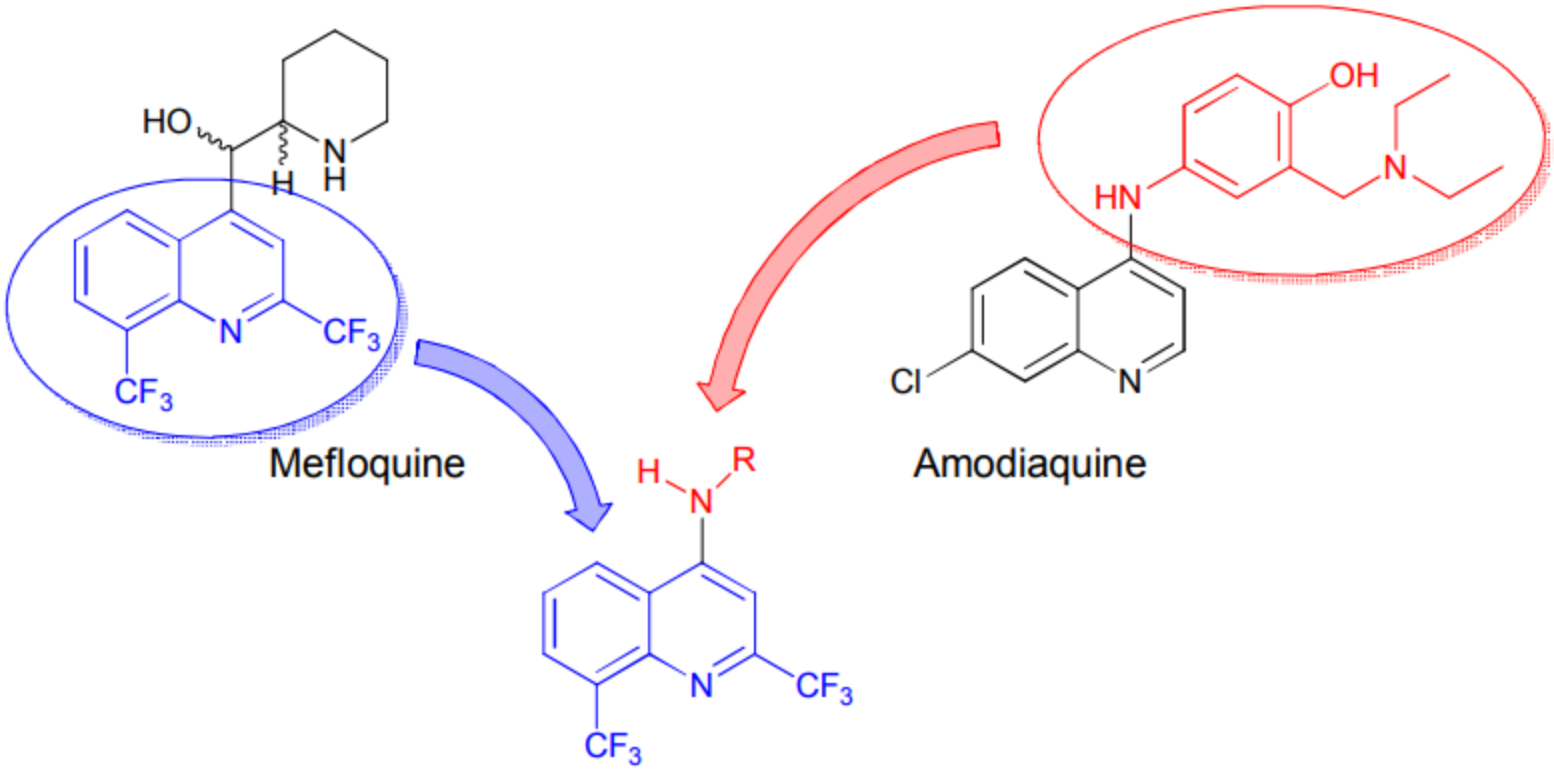

New aminoquinolines (1-14)