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Research paper

Looking for new antiplasmodial quinazolines: DMAP-catalyzed synthesis of 4-benzyloxy- and 4-aryloxy-2-trichloromethylquinazolines and their *in vitro* evaluation toward *Plasmodium falciparum*

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SARs

ABSTRACT

A DMAP catalyzed synthesis of new 4-benzyloxy- and 4-aryloxy-2-trichloromethylquinazolines was studied, in a view to react 4-chloroquinazolines with poorly nucleophilic alcohols such as benzylic alcohols, *via* a simple and cheap S_NAr reaction approach. A fast (1 h) general operating procedure, affording good reaction yields, was achieved under microwave irradiation. Thus, a series of 35 molecules was obtained and evaluated *in vitro* on the K1 multi-resistant *Plasmodium falciparum* strain, in parallel with a cytotoxicity assessment on the human HepG2 cell line. 5 hit-molecules were identified, presenting both promising antiplasmodial activity (1.5 μM < IC_{50} < 2 μM) and low cytotoxicities (25 μM < CC_{50} < 45 μM). Apart for 2 molecules, the global series displayed a satisfying solubility in the aqueous biological media. Structure-activity relationships showed that the molecules presenting a benzyloxy moiety were less cytotoxic than the ones bearing a phenoxy moiety at position 4 of the quinazoline ring. It also appeared that the introduction of a heteroaryl moiety afforded inactive compounds. Finally, the most active and selective molecules (Selectivity Index = 22–27) were the ones presenting either an unsubstituted benzyloxy group or a phenoxy group, this last bearing a *p*-bromo or an *o*-acetyl substituent.

1. Introduction

Plasmodium falciparum is the protozoa responsible for cerebral malaria, the leading cause of death among parasitic infections worldwide. According to the 2015 World Malaria Report [1], 214 million people were infected by *Plasmodium* in 2014. It was also estimated that 438.000 people died from this parasitic infection, mainly because of the cerebral form of the disease. About 88% of the estimated deaths occurred in Africa, children under five representing a large majority of the victims.

Since the beginning of 2000, a very significant improvement of the situation has been reached, thanks to the WHO intervention and the involvement of several non-governmental organizations (Bill and Melinda Gates Foundation, Roll Back Malaria, Medicines for Malaria Venture …).

Nevertheless, the emergence of drug-resistant strains of the parasite in Africa, South-East Asia and South America remains a serious concern for the medical and scientific community, in a view to keep on controlling the infection and to try to eradicate the disease. For that purpose, the treatment of the patients infected by *P. falciparum* is based on combination therapies including

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artemisinin derivatives, in order to cure the disease and avoid the selection of resistant strains and their spreading in the exposed population, which would lead to a very worrying sanitary situation. Concerning artemisinin derivatives, which are nowadays key-molecules for the treatment of *P. falciparum* malaria, resistances are emerging in Asia [2], and it has been demonstrated that they are responsible for therapeutic failures in several infected patients [3]. Moreover, it has also recently been highlighted that the African *Anopheles gambiae* mosquito could transmit such Asian resistant parasites [4], indicating a major worldwide spreading risk. Thus, research efforts have to be maintained so as to discover new chemical entities presenting novel antiplasmodial mechanisms of action, to use in combination therapies with the existing antimalarial drugs, to guaranty their durable efficiency.

Considering all the scaffolds which were studied for their antiplasmodial potential, several bioactive molecules are based on a quinazoline ring. For example, febrifugine is natural alkaloid including a quinazolinone moiety which is extracted from the Chinese herb *Dichroa febrifuga,* and which was employed by local people as a medicine against fevers caused by malaria. Some synthetic febrifugine derivatives were prepared and displayed good *in vitro* and *in vivo* potential [5]. Many other quinazoline derivatives were synthesized and evaluated toward *P. falciparum*, in particular, quinazolines bearing, an amino group [6], an alkylamine moiety [7,8] or an anilino substituent [9–11] at position 4 of the quinazoline ring.

In continuation with our research activity focusing on the synthesis of new nitrogen-containing heterocycles with anti-infective potential [12–14], our research group previously reported the synthesis and *in vitro* study of numerous antiplasmodial molecules based on a 2-trichloromethylquinazoline scaffold. Thus, several series bearing an anilino [10], aryl [15], thiophenol [16], sulfonamide [17] or alkynyl moiety [18] at position 4 of the quinazoline ring were prepared and revealed several hit-molecules which are presented in Table 1. Among the antiplasmodial hit-molecules which were identified, a 4-phenoxy-2-trichloromethylquinazoline derivative was also discovered [19], presenting a 50% inhibitory concentration (IC_{50}) of 1.1 μM and a 50% cytotoxicity concentration (CC_{50}) of 50 μM (Table 1), reaching an encouraging selectivity index of 45, in comparison with chloroquine and doxycycline. Then, searching for novel analogs presenting an oxygen-containing substituent at position 4 of the quinazoline ring, we present herein the synthesis work which was conducted for reacting 4-chloro-2-trichloromethylquinazoline with poorly nucleophilic benzylic alcohols, to afford the target molecules in a fast, simple and cheap way, using the S_NAr reaction. The *in vitro* biological evaluation and the SARs will then be presented and discussed.

2. Results and discussion

2.1. Synthesis

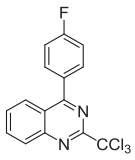
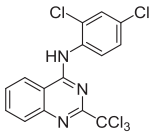
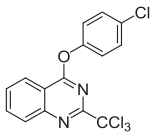
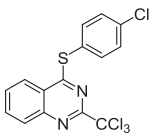
As aliphatic alcohols display poor nucleophilicity, reacting them with chlorinated azaheterocycles, to provide the corresponding S_NAr products, is difficult and usually requires the preliminary *in situ* formation of the corresponding alcoholate anion. Thus, in quinazoline series, various operating procedures were reported in the literature, using methylate sodium in methanol [20], sodium hydride in dry DMF [21], sodium hydride in dry THF [22,23] or sodium in dry THF [24]. These protocols, leading to the expected products in moderate to good yields (32–84%), present several disadvantages as they consist in 2 step-reactions (formation of the anion followed by the S_NAr), require the use of perfectly dry organic solvents and involve highly reactive and flammable reagents. Moreover, we tried to react 4-chloro-2-trichloromethylquinazoline with benzyl alcohol, using the reaction conditions we previously reported for the synthesis of 4-phenoxyquinazolines [19] (NaH, DMSO, RT, 24 h) and obtained the expected product in a very low 11% yield (Table 2, entry 13).

Among the available alternative strategies, palladium cross-coupling reactions could have been considered. Nevertheless, because of the expensive costs of both palladium catalysts and ligands, in order to set up a cheap and simple operating procedure, we decided to study the one pot S_NAr reaction between 4-chloro-2-trichloromethylquinazoline **1** and benzyl alcohol. To facilitate the S_NAr reaction between **1** and poorly nucleophilic species like amino-substituted heterocycles, our group recently reported a synthetic procedure using *N*-*N*-dimethylaminopyridine (DMAP) as an efficient catalyst, involving the formation of a highly reactive quinazoline intermediate which we isolated and characterized by X-ray diffraction [25]. Then, benefiting from our experience in the use of microwave irradiation for introducing substituents at position 4 of the quinazoline ring [26], and considering that a successful microwave-assisted S_NAr reaction between a 4-chloroquinazoline derivative and ethylene glycol had been reported [27], we focused on a S_NAr reaction protocol combining a DMAP catalysis with microwave irradiation. For that purpose, we first prepared substrate **1** (Fig. 1), from commercial 2-methylquinazolin-4(3*H*)-one, according to a previously reported microwave synthesis using PCl_5 in $POCl_3$ [28].

Then, the DMAP-catalyzed S_NAr reaction between **1** and benzyl alcohol was studied (Fig. 2) by varying the solvent nature, the amount of catalyst, the amount of benzyl alcohol, the reaction temperature, the microwave irradiation mode and the reaction time. The experimental results are presented in Table 2.

When using 0.1 equiv. DMAP in the presence of toluene, the

Table 1
In vitro antiplasmodial profiles of the previously identified hit-molecules in 2-trichloromethylquinazoline series.

				
Antiplasmodial activity *P. falciparum W2 or K1 IC_{50} (μM)*	2.5	0.4	1.1	0.9
Cytotoxicity *HepG2 CC_{50} (μM)*	>125	16	50	>25
Selectivity index *(CC_{50}/IC_{50})*	50	40	45	>28

Reference molecules: Chloroquine (IC_{50} K1 *P. falciparum* = 0.6 μM, CC_{50} HepG2 = 30 μM, SI = 50); Doxycycline (IC_{50} K1 *P. falciparum* = 6 μM, CC_{50} HepG2 = 20 μM, SI = 3.3).

Table 2
Studied parameters for the DMAP-catalyzed reaction of **1** with benzyl alcohol.

Entry	DMAP (equiv.)	Reaction conditions[a]	Alcohol equiv.	Solvent	Yield (%)
1	0.1	1 h, 130 °C/monomode MW	2	toluene	23
2	0.1	1 h, 150 °C/monomode MW	2	DMSO	5[b]
3	0.1	1 h, 150 °C/monomode MW	2	DMF	3[b]
4	0.1	1 h, 80 °C/monomode MW	2	THF	Traces[c]
5	0.2	1 h, 130 °C/monomode MW	2	toluene	42
6	0.3	0.5 h, 130 °C/monomode MW	2	toluene	27
7	0.4	1 h, 130 °C/monomode MW	2	toluene	51
8	**0.3**	**1 h, 130 °C/monomode MW**	**1.2**	**toluene**	**53**
9	0.3	1 h, 130 °C/monomode MW	2	toluene	53
10	0.3	2 h, 110 °C/monomode MW	2	toluene	39[b]
11	0.4	0.5 h, 150 °C/monomode MW	2	toluene	18[b]
12	0.4	2 h, 800 W, 110 °C/multimode MW	2	toluene	27
13	–	NaH 95% (2 equiv.), RT, 24 h [19]	1	DMSO	11

The values in bold indicate best results.
[a] The monomode microwave oven used was a Biotage Initiator. The multimode microwave oven used was a Milestone SynthLab Station.
[b] Formation of resins.
[c] Detected by LC/MS.

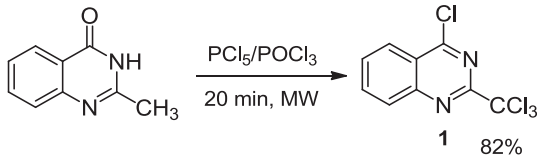


Fig. 1. Microwave-assisted synthesis of substrate **1** from commercial 2-methylquinazolin-4(3*H*)-one.

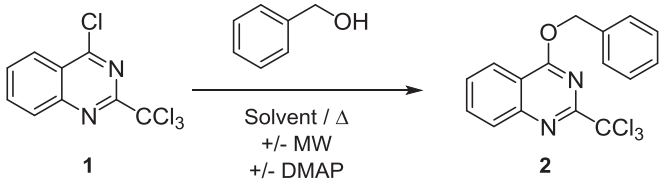


Fig. 2. Studied reaction: preparation of 4-benzyloxy-2-trichloromethylquinazoline **2** from substrate **1.**

reaction yield reached 23%, higher than with DMSO, DMF, or THF. Then, by increasing the amount of DMAP to 0.2 equiv., the reaction yield was improved to 42%. Finally, *via* a 1 h monomode microwave irradiation at 130 °C, the use of 0.3 equiv. of DMAP, allowed a decrease in the amount of alcohol (1.2 equiv.) needed and a 53% reaction yield was reached. From that point, decreasing reaction temperature, reaction time, or using a multimode microwave irradiation did not provide satisfying reaction yields.

For comparison purposes, the same reaction was carried out without DMAP and then conducted with other tertiary amine derivatives (DBU, DABCO and TEA). Indeed, DMAP was the only tertiary amine which allowed the reaction to proceed.

According to this general procedure, summarized in Fig. 3, the S_NAr reaction of **1** with aliphatic alcohols (mainly benzyl alcohols) was then extended to the synthesis of a series of 18 derivatives (molecules **2**–**19**). As presented in Table 3, the reaction yields varied from moderate (35%) to excellent (97%). In addition, the same protocol was applied to the synthesis of a series of 13 derivatives bearing a phenoxy moiety at position 4 of the quinazoline ring (molecules **20**–**32**). These molecules were obtained in 38–99% yields. Finally, 4 more derivatives were prepared, bearing a heteroaryloxy moiety at position 4 of the quinazoline ring (molecules **33**–**36**), in 55–98% yields. Thus, this DMAP-catalyzed operating procedure appeared as generally applicable to aliphatic alcohols, phenols and hydroxyheteroaryl reagents.

Among the 35 synthesized molecules, 2 were previously reported. Thus, compound **2** was mentioned in a 2001 publication [29] but no experimental data is available. Concerning quinazoline **27**, it is to note that it had previously been synthesized, according to another protocol [19], in 25% yield. As shown in Fig. 4, from the same substrate, the presently described DMAP protocol led to the formation of product **27** in 98% yield and only 1 h, indicating its high efficiency for preparing most of 4-phenoxyquinazolines (apart for molecules **23** and **26**).

2.2. Biological evaluation

All synthesized molecules were then evaluated *in vitro* on the multi-resistant K1 *P. falciparum* strain, by determining their 50% inhibitory concentration (IC_{50}), and compared with 2 antimalarial drug-compounds: chloroquine and doxycycline. In parallel, these molecules were assessed *in vitro* on the HepG2 human hepatocyte cell line, by determining their 50% cytotoxic concentrations (CC_{50}) and comparing them to the one of doxorubicin, used as a cytotoxic reference drug-compound, in order to calculate their respective Selectivity Index ($SI = CC_{50}/IC_{50}$). The results are presented in Table 3 and highlight 5 hit-molecules (**2, 6, 16, 20, 26**), presenting both IC_{50} values < 2 μM and CC_{50} values > 25 μM, reaching selectivity indexes ranging between 17 and 27.

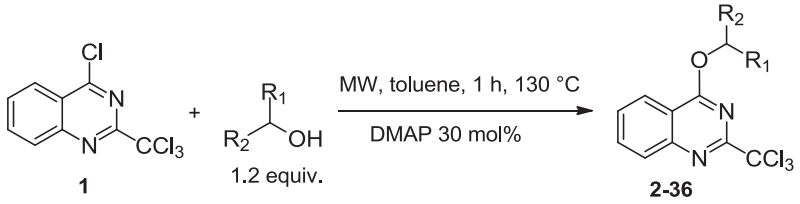
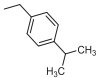
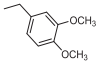
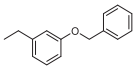


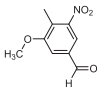
Fig. 3. Optimal conditions for preparing derivatives belonging to the 4-benzyloxy-2-trichloromethylquinazoline series from substrate **1.**

Table 3
Reaction yields, *in vitro* antiplasmodial and *in vitro* cytotoxicity evaluations of all synthesized quinazolines.

Molecule N	R-	Yield (%)	HepG2 CC_{50} (μM)	*Pf*K1 IC_{50} (μM)	SI[e]
2		53	43.8	2.0	21.9
3		72	50.9	4.0	12.7
4		65	90.3	>10[d]	<9
5		97	33.4	2.5	13.4
6		**96**	**34.9**	**1.8**	**19.4**
7		91	29.9	2.2	13.6
8		87	>10[c]	2.3	>4.3
9		83	27.8	2.8	9.9
10		81	33.3	>10[d]	<3.3
11		64	118.4	3.9	30.6
12		35	39.9	3.3	12.1
13		68	25.1	3.5	7.2
14		69	30.2	4.2	7.2
15		84	24.6	2.4	10.2
16		**41**	**25.7**	**1.5**	**17.1**
17		85	28.7	3.1	9.3
18		45	31.25	2.6	12.0
19		68	62.5	3.8	16.4
20		**99**	**45**	**1.8**	**25**
21		99	36.7	2.3	16.0

(*continued on next page*)

Table 3 (*continued*)

Molecule	R-	Yield (%)	HepG2 CC_{50} (μM)	*Pf*K1 IC_{50} (μM)	SI[e]
22		99	26.2	1.9	13.8
23		38	>8[c]	1.6	>5
24		95	49.5	2.3	21.5
25		99	1.0	1.7	0.6
26		**47**	**40.0**	**1.5**	**26.7**
27		98	0.5	1.9	0.3
28		78	75.0	10.0	7.5
29		94	43.7	4.4	9.9
30		79	57.0	>10[d]	<5.7
31		92	5.3	0.9	5.9
32		89	22.1	1.2	18.4
33		67	62.7	>10[d]	<6.3
34		98	4.9	>10[d]	<0.5
35		67	30.3	>10[d]	<3.0
36		55	59.0	>10[d]	<5.9
Doxorubicine[a]			0.2	–	–
Chloroquine[b]			30.0	0.6	50
Doxycycline[b]			20.0	6.0	3.3

In bold: hit-compounds ($IC_{50} \leq 2$ μM, $CC_{50} \geq 25$ μM and $SI \geq 17$).

[a] Doxorubicine was used as a cytotoxic reference-drug.

[b] Chloroquinine and doxycycline were used as antimalarial reference-drugs.

[c] CC_{50} could not be determined because of a lack of solubility of the tested molecule in the culture medium.

[d] IC_{50} was not reached at the highest tested concentration (10 μM).

[e] Selectivity index (SI) was calculated according to the formula: $SI = CC_{50}/IC_{50}$.

2.3. Structure-activity relationships

Apart compounds **8** and **23**, all tested molecules presented satisfying solubilities in the biological media as the determination of their *in vitro* activities was not hindered by any precipitation. In the benzyloxy series, no cytotoxicity was identified whereas, in the phenoxy series, compounds **25**, **27** and **31**, presenting a substituent at the *meta* position of the benzene ring, displayed low CC_{50} values (0.5–5.3 μM). In the heteroaryloxy series, compound **34** also appeared slightly cytotoxic (CC_{50} = 4.9 μM), because of the presence of two bromine atoms.

Concerning antiplasmodial activity, the molecules belonging to the heteroaryloxy series were not active. In the benzyloxy series, compounds **2**, **6** and **16** appeared as hit-molecules with IC_{50} values ranging from 1.5 to 2 μM and selectivity indexes being around 20, in comparison with the values noted for reference drugs. Compound **2**, bearing a benzyloxy group at position 4 of the quinazoline ring, was found more active and selective than its phenyloxy analog

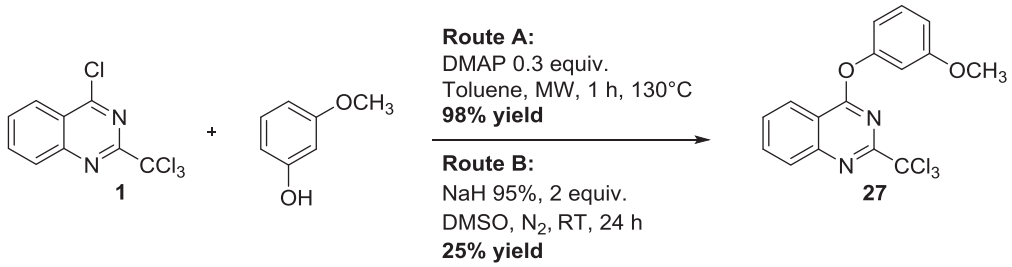


Fig. 4. Comparison of synthetic routes A and B [19] for the synthesis of compound **27**.

(IC_{50} = 3,1 μM/SI = 16) [19]. In most cases (apart for nitrated molecule **6**), the substitution of the benzene ring of the benzyloxy group was globally deleterious toward antiplasmodial activity, nevertheless, considering compound **16**, it can be noted that the introduction of a substituent on the benzylic carbon, for example *via* a nitrile function, is compatible with maintaining biological activity.

In the phenoxy series, compounds **20** and **26** were identified as hit-molecules, displaying IC_{50} values of 1.8 and 1.5 μM and selectivity indexes above 25. When comparing *para*-brominated molecule **20** to its chlorinated analog (Table 1), in accordance with the SAR conclusions that we previously reported [19], it can be concluded that the substitution of the benzene ring by a chlorine or bromine atom is favorable toward the antiplasmodial activity if located at the *para* position of the benzene ring, chlorine remaining slightly more favorable. Indeed, we also identified that the introduction of an acetyl substituent at the *ortho* position of the benzene ring (compound **26**) allowed antiplasmodial activity. This selective activity is decreased when changing the substitution position or when changing the acetyl group into a formyl analog (compound **28**). To validate the key role play67ed by the 2-trichloromethylquinazoline scaffold of hit-molecule **26**, its dehalogenated analog **37** was prepared in two steps (Fig. 5).

As presented in Fig. 6, the antiplasmodial activity of compound **26** depends from the presence of a trichloromethyl group at position 2 of the quinazoline ring, in accordance with the results that we previously reported. Thus, compounds **2** (in the original benzyloxy series) and **26** (first active *o*-substituted phenoxy derivative) appear as novel hit-molecules and extend the available SAR data in the 2-trichloromethylquinazoline series.

3. Conclusion

Five antiplasmodial hit-molecules were identified from an *in vitro* screening of 35 new 2-trichloromethylquinazoline derivatives bearing an oxygen-containing moiety at position 4 of the quinazoline ring. Structure-activity relationships showed that the derivatives presenting a benzyloxy, a *p*-bromophenoxy or an *o*-acetylphenoxy moiety were the most active and selective ones. The global series was prepared from 4-chloro-2-trichloromethylquinazoline *via* a DMAP catalyzed S_NAr reaction with benzylic alcohols, phenols or hydroxyheterocycles, under microwave irradiation. This operating procedure appears as an efficient, simple, fast and cheap operating protocol for introducing a large diversity of alkoxy, phenoxy or heteroaryloxy substituents at position 4 of 4-chloroquinazolines, substrates of wide pharmaceutical interest.

4. Experimental

4.1. Chemistry

4.1.1. General

Melting points were determined on a Köfler melting point apparatus and are uncorrected. Elemental analyses were carried out at the Spectropole, Faculté des Sciences de Saint-Jêrome (Marseille) with a Thermo Finnigan EA1112 analyzer and a Brucker Nonius diffractometer. NMR spectra were recorded on a Bruker ARX 200 spectrometer at the Faculté de Pharmacie of Marseille (200 MHz ^{1}H NMR: reference $CHCl_3$ δ = 7.26, and 50 MHz ^{13}C: reference $CHCl_3$ δ = 76.9). The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC was performed on 5 cm × 10 cm aluminum plates coated with silica gel 60F-254 (Merck) in an appropriate eluent. Visualization was performed with ultraviolet light (234 nm). Purity of synthesized compounds was checked by LC/MS analyses, which were realized at the Faculté de Pharmacie of Marseille with a Thermo Scientific Accela High Speed LC System® coupled using a single quadrupole mass spectrometer Thermo MSQ Plus®. The RP-HPLC column is a Thermo Hypersil Gold® 50 × 2.1 mm (C18 bounded), with particles of a diameter of 1.9 mm. The volume of sample injected on the column is 1 μL.

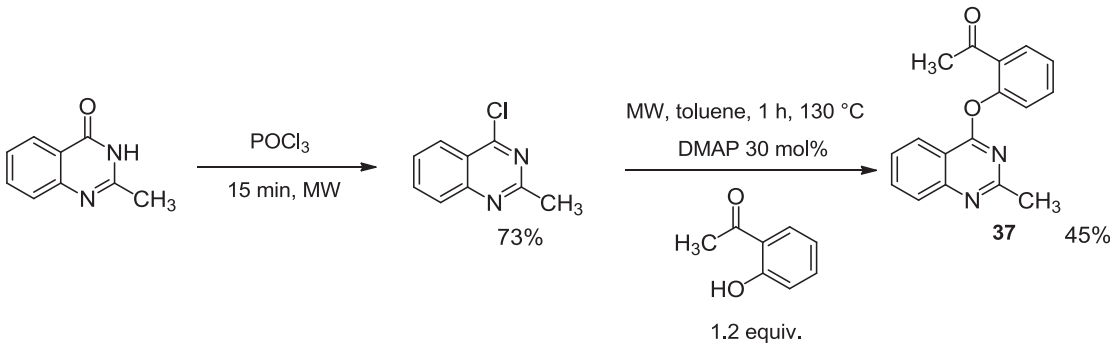
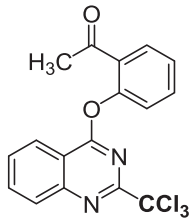
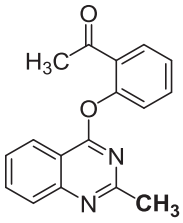


Fig. 5. Two step synthesis of molecule **37**.



26

IC50 *P. falciparum K1* = 1.5 μM



37

IC50 *P. falciparum K1* > 15 μM

Fig. 6. Comparison of the *in vitro* antiplasmodial activities of molecules **26** and **37.**

Chromatographic analysis, total duration of 8 min, is on the gradient of the following solvents: t = 0 min, methanol/water 50:50; 0 < t < 4 min, linear increase in the proportion of water to a methanol/water ratio of 95:5; 4 < t < 6 min, methanol/water 95:5; 6 < t < 7 min, linear decrease in the proportion of water to return to a methanol/water ratio of 50:50; 6 < t < 7 min, methanol/water 50:50. The water used was buffered with ammonium acetate 5 mM. The flow rate of the mobile phase was 0.3 mL/min. The retention times (t_R) of the molecules analyzed are indicated in min. The microwave reactions were performed using multimode reactors: ETHOS Synth Lab station and MicroSYNTH® Lab terminal 1024 (Ethos start, Milestone Inc.); or monomode reactors: Biotage Initiator® classic in sealed vials.

2-Methylquinazolin-4(3*H*)-one was purchased from Sigma Aldrich.

4.1.2. 4-Chloro-2-trichloromethylquinazoline (1)

4-Chloro-2-trichloromethylquinazoline **1** was prepared as described in the literature [28]. Yield 82%. White solid. Mp 127 °C (lit. 127 °C).[6] ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.82–7.90 (m, 1H), 8.03–8.12 (m, 1H), 8.20–8.24 (m, 1H), 8.33–8.38 (m, 1H). $C_9H_4Cl_4N_2$, MW: 282.18 g/mol.

4.1.3. General procedure for the preparation of compounds 2 to 34

A mixture of 4-chloro-2-trichloromethylquinazoline **1** (0.2 g, 0.71 mmol), DMAP (26 mg, 0.21 mmol, 0.3 equiv) and adequate alcohol derivative (0.85 mmol, 1.2 equiv) in toluene (3 mL) was introduced in miniaturized sealed reactor (5 mL). The reaction mixture was irradiated in a monomode microwave oven, for 1 h at 130 °C. After removal of the toluene under reduced pressure, the residue was purified by silica gel column chromatography and recrystallized from appropriate solvent.

4.1.4. 4-(Benzyloxy)-2-(trichloromethyl)quinazoline (2)

Yield 53%. Beige powder. Mp 115 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.23 (dd, *J* = 1 Hz; 8 Hz, 1H), 8.07 (d, *J* = 8 Hz, 1H), 7.88 (dd, *J* = 1 Hz; 5 Hz, 1H), 7.66–7.58 (m, 3H), 7.45–7.37 (m, 3H), 5.74 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.7, 160.1, 150.4, 135.6, 134.4, 129.0, 128.7, 128.6, 123.7, 115.5, 97.3, 69.4. LC-MS (ESI+) t_R 5.38 min, *m/z* $[M+H]^+$ 351.79/354.40/355.98. MW: 353.63 g/mol. Anal. Calcd for $C_{16}H_{11}Cl_3N_2O$: C, 54.34; H, 3.14; N, 7.92. Found: C, 54.45; H, 3.11; N, 7.98.

4.1.5. 4-(4-Methylbenzyloxy)-2-(trichloromethyl)quinazoline (3)

Yield 72%. Pale beige powder. Mp 130 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 8 Hz, 1H), 8.07 (d, *J* = 8 Hz, 1H), 7.90 (t, *J* = 8 Hz, 1H), 7.67–7.53 (m, 1H), 7.53–7.49 (d, *J* = 8 Hz, 3H), 7.23–7.19 (d, *J* = 8 Hz, 1H), 5.70 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.6, 160.1, 150.4, 138.5, 134.4, 132.6, 129.2, 129.3, 128.7, 128.6, 123.7, 115.6, 97.6, 69.5, 27.3. LC-MS (ESI+) t_R 5.68 min, *m/z* $[M+H]^+$ 367.11/368.98/371.30. MW: 367.66 g/mol. Anal. Calcd for $C_{17}H_{13}Cl_3N_2O$: C, 55.54; H, 3.56; N, 7.62. Found: C, 55.39; H, 3.53; N, 7.51.

4.1.6. 4-(4-Methoxybenzyloxy)-2-(trichloromethyl)quinazoline (4)

Yield 65%. Pale beige powder. Mp 86 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.21 (d, *J* = 8 Hz, 1H), 8.06 (d, *J* = 8 Hz, 1H), 7.90 (t, *J* = 8 Hz, 1H),7.67–7.54 (m, 3H), 6.94–6.90 (d, *J* = 8 Hz, 2H), 5.68 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.6, 159.9, 150.4, 134.4, 131.0, 128.7, 128.6, 127.7, 126.9, 123.7, 115.6, 114.1, 114.0, 97.2, 69.4, 55.3. LC-MS (ESI+) t_R 5.33 min, *m/z* $[M+H]^+$ 382.94/384.77/386.88. MW: 383.66 g/mol. Anal. Calcd for $C_{17}H_{13}Cl_3N_2O_2$: C, 53.22; H, 3.42; N, 7.30. Found: C, 53.13; H, 3.39; N, 7.51.

4.1.7. 4-(4-Chlorobenzyloxy)-2-(trichloromethyl)quinazoline (5)

Yield 97%. Beige powder. Mp 95 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.22 (d, *J* = 8 Hz, 1H), 8.08 (d, *J* = 8 Hz, 1H), 7.90 (dd, *J* = 2 Hz; 7 Hz, 1H), 7.69–7.61 (m, 1H), 7.57–7.53 (d, *J* = 8 Hz, 2H), 7.39–7.34 (d, *J* = 8 Hz, 2H), 5.69 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.4, 160.0, 150.4, 134.5, 134.1, 130.5, 128.8, 128.7, 123.6, 115.5, 97.1, 68.7. LC-MS (ESI+) t_R 5.59 min, *m/z* $[M+H]^+$ 386.61/388.96/390.91. MW: 388.08 g/mol. Anal. Calcd for $C_{16}H_{10}Cl_4N_2O$: C, 49.52; H, 2.60; N, 7.22. Found: C, 49.70; H, 2.58; N, 7.14.

4.1.8. 4-(4-Nitrobenzyloxy)-2-(trichloromethyl)quinazoline (6)

Yield 96%. Yellow powder. Mp 199 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.34–8.30 (m, 3H), 8.18–8.15 (m, 1H), 8.04–7.98 (m, 1H), 7.85–7.74 (m, 3H), 5.88 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.1, 159.8, 150.5, 147.9, 142.8, 134.8, 129.3, 129.1, 129.0, 123.9, 123.4, 115.3, 97.0, 68.0. LC-MS (ESI+) t_R 5.06 min, *m/z* $[M+H]^+$ 397.93/399.91/402.06. MW: 398.63 g/mol. Anal. Calcd for $C_{16}H_{10}Cl_3N_3O_3$: C, 48.21; H, 2.53; N, 10.54. Found: C, 48.33; H, 2.55; N, 10.41.

4.1.9. 4-(3-Nitrobenzyloxy)-2-(trichloromethyl)quinazoline (7)

Yield 91%. Yellow powder. Mp 147 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.27–8.24 (m, 1H), 8.19–8.14 (m, 2H), 7.88–7.81 (m, 3H), 7.69–7.54 (m, 2H), 5.95 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.1, 159.7, 150.3, 148.0, 134.9, 133.5, 131.7, 130.1, 129.3, 128.9, 128.8, 124.9, 123.2, 115.1, 97.2, 67.8. LC-MS (ESI+) t_R 4.95 min, *m/z* $[M+H]^+$ 397.94/399.89/401.96. MW: 398.63 g/mol. Anal. Calcd for $C_{16}H_{10}Cl_3N_3O_3$: C, 48.21; H, 2.53; N, 10.54. Found: C, 48.03; H, 2.56; N, 10.66.

4.1.10. 4-(2-Nitrobenzyloxy)-2-(trichloromethyl)quinazoline (8)

Yield 87%. Yellow powder. Mp 141 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.28–8.23 (m, 1H), 8.14–8.07 (m, 2H), 7.94 (dd, *J* = 2 Hz; 7 Hz, 1H), 7.82–7.48 (m, 4H), 6.13 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.0, 159.9, 150.5, 148.2, 134.7, 133.6, 131.7,

130.3, 129.2, 129.0, 128.9, 125.1, 123.5, 115.3, 96.9, 66.1. LC-MS (ESI+) t_R 4.82 min, m/z $[M+H]^+$ 397.91/400.02/401.86. MW: 398.63 g/mol. Anal. Calcd for $C_{16}H_{10}Cl_3N_3O_3$: C, 48.21; H, 2.53; N, 10.54. Found: C, 48.31; H, 2.50; N, 10.39.

4.1.11. 2-(Trichloromethyl)-4-(4-(trifluoromethyl)benzyloxy) quinazoline (9)

Yield 83%. Pale yellow powder. Mp 130 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.27–8.23 (m, 1H), 8.18–8.12 (m, 1H), 8.04–7.98 (m, 1H), 7.97–7.89 (m, 1H), 7.75–7.64 (m, 4H), 5.79 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.3, 160.0, 150.4, 139.6, 134.7, 129.0, 128.9, 126.7, 125.6, 125.5, 123.5, 121.3, 115.4, 97.1, 68.5. LC-MS (ESI+) t_R 5.52 min, m/z $[M+H]^+$ 420.88/422.92/424.93. MW: 421.63 g/mol. Anal. Calcd for $C_{17}H_{10}Cl_3F_3N_2O$: C, 48.43; H, 2.39; N, 6.64. Found: C, 48.59; H, 2.41; N, 6.58.

4.1.12. 4-(4-Isopropylbenzyloxy)-2-(trichloromethyl)quinazoline (10)

Yield 81%. Pale beige powder. Mp 121 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.23 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.93–7.85 (m, 1H), 7.67–7.53 (m, 3H), 7.28 (d, J = 8 Hz, 2H), 5.72 (s, 2H), 2.94 (sept, J = 7 Hz, 1H), 1.27 (d, J = 7 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.6, 160.2, 150.4, 149.5, 134.4, 133.0, 129.3, 128.7, 128.6, 126.7, 123.8, 115.6, 97.3, 68.5, 34.0, 24.0. LC-MS (ESI+) t_R 5.73 min, m/z $[M+H]^+$ 395.10/396.96/399.02. MW: 395.71 g/mol. Anal. Calcd for $C_{19}H_{17}Cl_3N_2O$: C, 57.67; H, 4.33; N, 7.08. Found: C, 57.76; H, 4.35; N, 7.21.

4.1.13. 4-(3,4-Dimethoxybenzyloxy)-2-(trichloromethyl) quinazoline (11)

Yield 64%. Beige powder. Mp 127 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.22 (d, J = 8 Hz, 1H), 8.06 (d, J = 8 Hz, 1H), 7.90 (t, J = 8 Hz, 1H), 7.63 (t, J = 8 Hz, 1H), 7.20–7.16 (m, 2H), 6.89 (d, J = 8 Hz, 1H), 5.68 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H) . ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.6, 160.1, 150.4, 149.4, 149.0, 134.4, 129.0, 128.7, 128.6, 128.1, 126.8, 123.7, 122.2, 115.6, 112.6, 111.0, 97.3, 69.7, 56.0, 55.9. LC-MS (ESI+) t_R 4.95 min, m/z $[M+H]^+$ 413.00/414.75/416.93. MW: 413.68 g/mol. Anal. Calcd for $C_{18}H_{15}Cl_3N_2O_3$: C, 52.26; H, 3.65; N, 6.77. Found: C, 52.09; H, 3.64; N, 6.72.

4.1.14. 4-(1-Phenylethoxy)-2-(trichloromethyl)quinazoline (12)

Yield 35%. Beige powder. Mp 141 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.28 (dd, J = 1 Hz; 8 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 7.89 (t, J = 8 Hz, 1H), 7.70–7.56 (m, 3H), 7.41–7.29 (m, 3H), 6.58 (q, J = 7 Hz, 1H), 1.84 (d, J = 7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.1, 160.1, 150.4, 141.2, 135.5, 134.3, 129.2, 129.0, 128.8, 128.5, 128.1, 126.9, 126.8, 123.7, 115.7, 97.2, 76.0, 22.1. LC-MS (ESI+) t_R 5.83 min, m/z $[M+H]^+$ 366.97/368.97/371.04. MW: 367.66 g/mol. Anal. Calcd for $C_{17}H_{13}Cl_3N_2O$: C, 55.54; H, 3.56; N, 7.62. Found: C, 55.59; H, 3.59; N, 7.71.

4.1.15. 4-(1-(4-Chlorophenyl)ethoxy)-2-(trichloromethyl) quinazoline (13)

Yield 68%. Brown powder. Mp 86 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.22 (d, J = 8 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 7.90 (dd, J = 1 Hz; 7 Hz, 1H), 7.66 (td, J = 1 Hz; 7 Hz, 1H), 7.52 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 6.53 (q, J = 7 Hz, 1H), 1.82 (d, J = 7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.9, 160.0, 150.4, 139.7, 134.4, 133.9 128.8, 128.7, 128.3, 123.5, 115.6, 97.1, 75.2, 22.0. LC-MS (ESI+) t_R 5.83 min, m/z $[M+H]^+$ 400.96/402.81/404.83. MW: 402.10 g/mol. Anal. Calcd for $C_{17}H_{12}Cl_4N_2O$: C, 50.78; H, 3.01; N, 6.97. Found: C, 50.48; H, 3.03; N, 6.90.

4.1.16. 4-(1-(2,4-Dichlorophenyl)ethoxy)-2-(trichloromethyl) quinazoline (14)

Yield 69%. Brown powder. Mp 123 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.31 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.96–7.87 (m, 1H), 7.69 (t, J = 7 Hz, 1H), 7.49–7.39 (m, 2H), 7.20 (dd, J = 2 Hz; 8 Hz, 1H), 6.78 (q, J = 7 Hz, 1H), 1.81 (d, J = 7 Hz, 3H) . ^{13}C NMR (50 MHz, $CDCl_3$) δ = 165.3, 159.2, 150.8, 135.3, 131.6, 130.8 129.4, 129.3, 129.0, 128.6, 123.4, 115.4, 96.9, 72.7, 21.0. LC-MS (ESI+) t_R 6.02 min, m/z $[M+H]^+$ 434.74/436.86/438.81. MW: 436.55 g/mol. Anal. Calcd for $C_{17}H_{11}Cl_5N_2O$: C, 46.77; H, 2.54; N, 6.42. Found: C, 46.41; H, 2.52; N, 6.51.

4.1.17. 4-(1-Phenylprop-2-ynyloxy)-2-(trichloromethyl)quinazoline (15)

Yield 84%. Pale yellow powder. Mp 120 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.28–8.24 (m, 1H), 8.07 (d, J = 8 Hz, 1H), 7.95–7.87 (m, 1H), 7.82–7.77 (m, 2H), 7.69–7.61 (m, 1H), 7.47–7.39 (m, 3H), 7.26–7.24 (m, 1H), 2.75 (d, J = 2 Hz, 1H) . ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.3, 159.7, 150.6, 136.3, 134.7 129.4, 128.8, 128.7, 128.4, 123.8, 115.4, 97.0, 80.1, 76.4, 68.6. LC-MS (ESI+) t_R 5.20 min, m/z $[M+H]^+$ 377.11/379.05/381.08. MW: 377.65 g/mol. Anal. Calcd for $C_{18}H_{11}Cl_3N_2O$: C, 57.25; H, 2.94; N, 7.42. Found: C, 57.61; H, 2.95; N, 7.35.

4.1.18. 2-Phenyl-2-(2-(trichloromethyl)quinazolin-4-yloxy) acetonitrile (16)

Yield 41%. Pale yellow powder. Mp 141 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.36–8.21 (m, 1H), 8.14 (d, J = 8 Hz, 1H), 7.99 (td, J = 2 Hz; 8 Hz, 1H), 7.80–7.68 (m, 3H), 7.54–7.49 (m, 3H), 7.14 (s, 1H) . ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.3, 159.7, 150.6, 136.3, 134.7 129.4, 128.8, 128.7, 128.4, 123.8, 116.0, 114.7, 96.5, 65.9. LC-MS (ESI+) t_R 4.73 min, m/z $[M+H]^+$ 377.99/380.01/381.99. MW: 378.64 g/mol. Anal. Calcd for $C_{17}H_{10}Cl_3N_3O$: C, 53.93; H, 2.66; N, 11.10. Found: C, 53.89; H, 2.70; N, 11.12.

4.1.19. 4-((6-Nitrobenzo[d][1,3]dioxol-5-yl)methoxy)-2-(trichloromethyl) quinazoline (17)

Yield 85%. Pale yellow powder. Mp 181 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.25 (d, J = 8 Hz, 1H), 8.10 (d, J = 8 Hz, 1H), 7.98–7.92 (m, 1H), 7.74–7.65 (m, 2H), 7.27–7.24 (m, 1H), 6.13 (s, 2H), 6.08 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.1, 159.9, 152.2, 150.5, 147.8, 142.3, 134.8 129.0, 128.9, 123.5, 115.3, 109.1, 106.0, 103.2, 96.9, 66.2. LC-MS (ESI+) t_R 5.00 min, m/z $[M+H]^+$ 441.87/443.97/445.95. MW: 442.64 g/mol. Anal. Calcd for $C_{17}H_{10}Cl_3N_3O_5$: C, 46.13; H, 2.28; N, 9.49. Found: C, 45.91; H, 2.27; N, 9.57.

4.1.20. (E)-4-(3-(4-Nitrophenyl)allyloxy)-2-(trichloromethyl) quinazoline (18)

Yield 45%. Yellow powder. Mp 140 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.29 (m, 4H), 7.98–7.89 (m, 1H), 7.73–7.65 (m, 1H), 7.58–7.24 (m, 2H), 6.98 (d, J = 16 Hz, 1H), 6.80–6.66 (m, 1H), 5.41 (dd, J = 1 Hz; 6 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.3, 160.0, 150.4, 147.4, 142.6, 134.6, 133.0, 131.9, 129.6, 129.1, 128.9, 128.8 127.6, 127.3, 124.1 123.8, 123.5, 115.4, 96.3, 67.7. LC-MS (ESI+) t_R 5.34 min, m/z $[M+H]^+$ 423.94/425.92/427.96. MW: 424.67 g/mol. Anal. Calcd for $C_{18}H_{12}Cl_3N_3O_3$: C, 50.91; H, 2.85; N, 9.89. Found: C, 51.08; H, 2.86; N, 9.75.

4.1.21. 4-(3-(Benzyloxy)benzyloxy)-2-(trichloromethyl)quinazoline (19)

Yield 68%. Yellow powder. Mp 96 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.23 (dd, J = 1 Hz; 8 Hz, 1H), 8.10 (d, J = 8 Hz, 1H), 7.91 (td, J = 1 Hz; 8 Hz, 1H), 7.69–7.61 (m, 1H), 7.47–7.18 (m, 8H), 5.72 (s, 1H), 5.72 (s, 2H), 5.10 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.6, 160.1, 159.0, 150.4, 137.2, 136.9, 134.5, 130.0, 129.7, 128.9,

128.8, 128.6, 128.0, 127.5, 123.7, 121.4, 115.5, 115.3, 115.0, 97.2, 70.1, 69.3. LC-MS (ESI+) t_R 5.87 min, m/z $[M+H]^+$ 458.74/460.72/462.84. MW: 459.75 g/mol. Anal. Calcd for $C_{23}H_{17}Cl_3N_2O_2$: C, 60.09; H, 3.73; N, 6.09. Found: C, 59.87; H, 3.70; N, 5.98.

4.1.22. 4-(4-Bromophenoxy)-2-(trichloromethyl)quinazoline (20)

Yield 99%. White powder. Mp 179 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.42–8.38 (m, 1H), 8.16 (d, J = 8 Hz, 1H), 8.02 (td, J = 1 Hz; 8 Hz, 1H), 7.81–7.73 (m, 1H), 7.59 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.9, 160.1, 151.4, 151.3, 134.9, 132.5, 129.2, 129.1, 123.5, 123.3, 118.9, 115.3, 96.7. LC-MS (ESI+) t_R 5.38 min, m/z $[M+H]^+$ 418.26/420.82/422.93. MW: 418.5 g/mol. Anal. Calcd for $C_{15}H_8BrCl_3N_2O$: C, 43.05; H, 1.93; N, 6.69. Found: C, 43.25; H, 1.95; N, 6.58.

4.1.23. 4-(3-Bromophenoxy)-2-(trichloromethyl)quinazoline (21)

Yield 99%. White powder. Mp 114 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41–8.37 (m, 1H), 8.18–8.14 (m, 1H), 8.01 (td, J = 1 Hz; 8 Hz, 1H), 7.81–7.73 (m, 1H), 7.63–7.62 (m, 1H), 7.48–7.30 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.8, 160.0, 152.5, 151.2, 135.1, 130.5, 129.3, 129.1, 125.1, 123.6, 122.3, 120.4, 115.2, 96.6. LC-MS (ESI+) t_R 5.43 min, m/z $[M+H]^+$ 418.18/420.78/422.82. MW: 418.5 g/mol. Anal. Calcd for $C_{15}H_8BrCl_3N_2O$: C, 43.05; H, 1.93; N, 6.69. Found: C, 42.91; H, 1.92; N, 6.76.

4.1.24. 4-(2-Bromophenoxy)-2-(trichloromethyl)quinazoline (22)

Yield 99%. White powder. Mp 138 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.51–8.47 (m, 1H), 8.17 (d, J = 8 Hz, 1H), 8.02 (td, J = 1 Hz; 8 Hz, 1H), 7.84–7.67 (m, 2H), 7.49–7.39 (m, 2H), 7.28–7.17 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.7, 159.9, 151.1, 149.4, 135.0, 133.4, 129.2, 128.9, 128.4, 127.4, 123.8, 123.7, 116.2, 114.9, 96.5. LC-MS (ESI+) t_R 5.05 min, m/z $[M+H]^+$ 418.07/420.73/422.87. MW: 418.5 g/mol. Anal. Calcd for $C_{15}H_8BrCl_3N_2O$: C, 43.05; H, 1.93; N, 6.69. Found: C, 42.89; H, 1.91; N, 6.81.

4.1.25. 4-(2-(Trichloromethyl)quinazolin-4-yloxy)benzonitrile (23)

Yield 38%. White powder. Mp 194 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41 (d, J = 8 Hz, 1H), 8.19 (d, J = 8 Hz, 1H), 8.07–8.00 (m, 1H), 7.84–7.78 (m, 3H), 7.57 (d, J = 8 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.4, 159.7, 155.4, 151.3, 135.4, 133.8, 129.6, 129.2, 123.5, 122.7, 118.3, 115.0, 109.9, 96.5. LC-MS (ESI+) t_R 4.46 min, m/z $[M+H]^+$ 364.10/365.99/367.99. MW: 364.61 g/mol. Anal. Calcd for $C_{16}H_8Cl_3N_3O$: C, 52.71; H, 2.21; N, 11.52. Found: C, 52.71; H, 2.21; N, 11.52.

4.1.26. 1-(4-((2-(Trichloromethyl)quinazolin-4-yl)oxy)phenyl) ethanone (24)

Yield 95%. White powder. Mp 149 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41 (d, J = 8 Hz, 1H), 8.18–7.97 (m, 4H), 7.78 (t, J = 8 Hz, 1H), 7.52 (d, J = 8 Hz, 2H), 2.65 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 196.9, 166.7, 159.9, 155.8, 151.2, 135.2, 134.7, 130.0, 129.4, 129.1, 123.6, 121.6, 115.2, 96.6, 26.7. LC-MS (ESI+) t_R 4.48 min, m/z $[M+H]^+$ 381.07/383.07/385.02. MW: 381.64 g/mol. Anal. Calcd for $C_{17}H_{11}Cl_3N_2O_2$: C, 53.50; H, 2.91; N, 7.34. Found: C, 53.71; H, 2.89; N, 7.41.

4.1.27. 1-(3-(2-(Trichloromethyl)quinazolin-4-yloxy)phenyl) ethanone (25)

Yield 99%. White powder. Mp 106 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.43 (dd, J = 1 Hz; 8 Hz, 1H), 8.17 (d, J = 8 Hz, 1H), 8.05–7.89 (m, 3H), 7.83–7.75 (m, 1H), 7.67–7.54 (m, 2H), 2.64 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 197.1, 167.0, 159.9, 151.1, 138.5, 135.1, 129.7, 129.3, 129.0, 126.3, 125.8, 123.6, 121.5, 115.2, 96.7, 26.8. LC-MS (ESI+) t_R 4.47 min, m/z $[M+H]^+$ 381.07/383.05/384.98. MW: 381.64 g/mol. Anal. Calcd for $C_{17}H_{11}Cl_3N_2O_2$: C, 53.50; H, 2.91; N, 7.34. Found: C, 53.21; H, 2.90; N, 7.42.

4.1.28. 1-(2-(2-(Trichloromethyl)quinazolin-4-yloxy)phenyl) ethanone (26)

Yield 47%. White powder. Mp 147 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.46 (d, J = 8 Hz, 1H), 8.12 (d, J = 8 Hz, 1H), 8.05–7.89 (m, 2H), 7.83–7.75 (m, 1H), 7.68–7.59 (m, 1H), 7.46–7.33 (m, 2H), 2.50 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 197.4, 167.5, 159.9, 151.2, 150.6, 135.1, 133.6, 131.3, 130.4, 129.4, 129.0, 126.3, 123.7, 115.2, 96.8, 29.7. LC-MS (ESI+) t_R 4.16 min, m/z $[M+H]^+$ 381.03/383.03/384.99. MW: 381.64 g/mol. Anal. Calcd for $C_{17}H_{11}Cl_3N_2O_2$: C, 53.50; H, 2.91; N, 7.34. Found: C, 53.27; H, 2.93; N, 7.29.

4.1.29. 4-(3-Methoxyphenoxy)-2-trichloromethylquinazoline (27)

Yield 98%. White powder. Mp 101 °C (Lit. 101 °C [19]), (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.39–8.43 (m, 1H), 8.13–8.17 (m, 1H), 7.95–8.03 (m, 1H), 7.72–7.80 (m, 1H), 7.32–7.40 (m, 1H), 6.96–7.05 (m, 2H), 6.83–6.89 (m, 1H), 3.83 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.4, 160.4, 160.1, 153.1, 151.0, 134.8, 129.7, 129.1, 128.9, 123.7, 115.4, 113.5, 112.0, 107.2, 96.8, 55.5 LC-MS (ESI+) t_R 5.10 min, m/z $[M+H]^+$ 369.01/371.15/373.09. MW: 369.63 g/mol. Anal. Calcd for $C_{16}H_{11}Cl_3N_2O_2$: C, 51.99; H, 3.00; N, 7.58. Found: C, 52.16; H, 3.07; N, 7.67.

4.1.30. 2-(2-(Trichloromethyl)quinazolin-4-yloxy)benzaldehyde (28)

Yield 78%. White powder. Mp 111 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 10.19 (s, 1H), 8.47 (dd, J = 1 Hz; 8 Hz, 1H), 8.17 (d, J = 8 Hz, 1H), 8.06–7.98 (m, 2H), 7.87–7.69 (m, 2H), 7.52–7.45 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 188.4, 167.5, 163.1, 153.3, 151.2, 146.7, 135.5, 130.1, 129.5, 129.1, 126.7, 123.6, 123.3, 120.9, 114.9, 96.5. LC-MS (ESI+) t_R 4.20 min, m/z $[M+H]^+$ 367.03/369.02/371.03. MW: 367.61 g/mol. Anal. Calcd for $C_{16}H_9Cl_3N_2O_2$: C, 52.28; H, 2.47; N, 7.62. Found: C, 52.59; H, 2.45; N, 7.68.

4.1.31. 4-(Perfluorophenoxy)-2-(trichloromethyl)quinazoline (29)

Yield 94%. White powder. Mp 139 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.43 (dd, J = 1 Hz; 8 Hz, 1H), 8.22 (d, J = 8 Hz, 1H), 8.07 (td, J = 1 Hz; 8 Hz, 1H), 7.88–7.80 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 165.4, 159.5, 151.4, 135.7, 129.9, 129.2, 123.4, 114.0, 96.0. LC-MS (ESI+) t_R 5.49 min, m/z $[M+H]^+$ 428.71/430.78/432.67. MW: 429.56 g/mol. Anal. Calcd for $C_{15}H_4Cl_3F_5N_2O$: C, 41.94; H, 0.94; N, 6.52. Found: C, 42.12; H, 0.97; N, 6.42.

4.1.32. 3-Methoxy-5-nitro-4-(2-(trichloromethyl)quinazolin-4-yloxy)benzaldehyde (30)

Yield 79%. Yellow powder. Mp 171 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 10.28 (s, 1H), 8.49–8.46 (m, 2H), 8.24–8.05 (m, 3H), 7.86 (t, J = 6 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 186.2, 166.6, 159.6, 152.8, 151.4, 148.0, 146.5, 135.6, 135.1, 129.8, 129.6, 129.3, 123.5, 115.6, 114.3, 111.5, 96.2, 56.9. LC-MS (ESI+) t_R 4.01 min, m/z $[M+H]^+$ 441.87/443.71/445.72. MW: 442.64 g/mol. Anal. Calcd for $C_{17}H_{10}Cl_3N_3O_5$: C, 46.13; H, 2.28; N, 9.49. Found: C, 45.95; H, 2.30; N, 9.55.

4.1.33. 4-(4-Chloro-3-methylphenoxy)-2-(trichloromethyl) quinazoline (31)

Yield 92%. White powder. Mp 98 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.37 (dd, J = 1 Hz; 8 Hz, 1H), 8.16–8.12 (m, 1H), 8.02–7.94 (m, 1H), 7.79–7.70 (m, 1H), 7.41 (d, J = 8 Hz, 1H), 7.31–7.30 (m, 1H), 7.20 (dd, J = 1 Hz; 8 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.9, 159.9, 151.0, 150.4, 137.3, 134.9, 131.1, 129.6, 129.1, 128.9, 123.7, 123.5, 120.1, 115.2, 96.7, 20.3. MW: 388.08 g/mol. HRMS (ESI): m/z $[M+Na]^+$ calcd for $[C_{16}H_{10}Cl_4N_2O]^+$:

408.94395; found: 408.94429.

4.1.34. 4-[(2,4-Dichlorophenyl)oxy]-2-(trichloromethyl)quinazoline (32)

Yield 89%. White powder. Mp 110 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.43–8.48 (m, 1H), 8.18 (d, *J* = 8 Hz, 1H), 8.06–7.98 (m, 1H), 7.84–7.75 (m, 1H), 7.54–7.33 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.5, 159.8, 151.2, 147.0, 135.2, 131.9, 130.2, 129.4, 129.0, 128.0, 127.9, 124.6, 123.6, 114.8, 96.4. LC-MS (ESI+) t_R 4.60 min, *m/z* $[M+H]^+$ 408.05/410.09/411.98. MW: 408.49 g/mol. Anal. Calcd for $C_{15}H_7Cl_5N_2O$: C, 44.10; H, 1.73; N, 6.86. Found: C, 44.50; H, 1.71; N, 6.97.

4.1.35. 2-Methyl-3-(2-(trichloromethyl)quinazolin-4-yloxy)-4H-pyran-4-one (33)

Yield 67%. Beige powder. Mp 202 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41 (dd, *J* = 1 Hz; 8 Hz, 1H), 8.15 (d, *J* = 8 Hz, 1H), 7.99 (td, *J* = 1 Hz; 8 Hz, 1H), 7.82–7.72 (m, 2H), 6.49 (d, *J* = 4 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 171.9, 165.9, 159.8, 154.4, 151.3, 135.4, 135.1, 129.2, 128.9, 126.8, 123.8, 117.0, 113.0, 96.5, 15.2. LC-MS (ESI+) t_R 3.29 min, *m/z* $[M+H]^+$ 370.97/372.99/375.00. MW: 371.60 g/mol. Anal. Calcd for $C_{15}H_9Cl_3N_2O_3$: C, 48.48; H, 2.44; N, 7.54. Found: C, 48.38; H, 2.41; N, 7.62.

4.1.36. 4-(5,7-Dibromoquinolin-8-yloxy)-2-(trichloromethyl) quinazoline (34)

Yield 98%. Brown powder. Mp 186 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.77–8.55 (m, 3H), 8.21–8.12 (m, 2H), 8.04 (t, *J* = 8 Hz, 1H), 7.83 (t, *J* = 6 Hz, 1H), 7.56–7.53 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.13, 159.6, 151.4, 151.3, 146.5, 142.2, 136.2, 135.1, 133.3, 129.3, 128.9, 127.8, 124.1, 122.8, 119.5, 116.9, 114.8, 96.4. LC-MS (ESI+) t_R 5.37 min, *m/z* $[M+H]^+$ 546.08/547.52/549.54. MW: 548.44 g/mol. Anal. Calcd for $C_{18}H_8Br_2N_3O$: C, 39.42; H, 1.47; N, 7.66. Found: C, 39.49; H, 1.50; N, 7.51.

4.1.37. 4-(Quinolin-2-yloxy)-2-(trichloromethyl)quinazoline (35)

Yield 67%. Yellow powder. Mp 163 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.52 (d, *J* = 8 Hz, 1H), 8.34 (d, *J* = 8 Hz, 1H), 8.18 (d, *J* = 8 Hz, 1H), 8.07–7.72 (m, 5H), 7.64–7.49 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.9, 159.8, 157.4, 151.3, 146.3, 140.1, 135.3, 130.5, 129.4, 129.0, 128.4, 127.3, 126.8, 124.0, 115.7, 115.2, 96.5. LC-MS (ESI+) t_R 4.60 min, *m/z* $[M+H]^+$ 389.95/391.95/394.06. MW: 390.65 g/mol. Anal. Calcd for $C_{18}H_{10}Cl_3N_3O$: C, 55.34; H, 2.58; N, 10.76. Found: C, 55.13; H, 2.56; N, 10.91.

4.1.38. 4-(2-(Trichloromethyl)quinazolin-4-yloxy)-2H-chromen-2-one (36)

Yield 55%. Yellow powder. Mp 237 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.45 (d, *J* = 8 Hz, 1H), 8.26 (d, *J* = 8 Hz, 1H), 8.10 (t, *J* = 8 Hz, 1H), 7.92–7.80 (m, 2H), 7.68–7.60 (m, 1H), 7.47–7.30 (m, 2H), 6.96 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 165.3, 161.6, 159.7, 153.7, 151.7 135.9, 133.0, 130.1, 129.6, 124.4, 123.1, 122.9, 117.3, 115.5, 115.1, 104.3, 96.1. LC-MS (ESI+) t_R 4.60 min, *m/z* $[M+H]^+$ 406.93/408.93/411.18. MW: 407.63 g/mol. Anal. Calcd for $C_{18}H_9Cl_3N_2O_3$: C, 53.04; H, 2.23; N, 6.87. Found: C, 52.86; H, 2.24; N, 6.92.

4.1.39. Preparation of 1-(2-(2-methylquinazolin-4-yloxy)phenyl) ethanone (37)

Molecule **37** was prepared in two steps from commercial 2-methylquinazolin-4(3*H*)-one. This last was first chlorinated at position 4, by using $POCl_3$, according to a previously microwave-assisted reported procedure [25], leading to 4-chloro-2-methylquinazoline in 73% yield. Then, the general DMAP-catalyzed operating procedure described in § 3.1.3. was applied to this intermediate product, leading to molecule **37** in 45% yield, as a beige powder. Mp 118 °C, (isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.33 (d, *J* = 8 Hz, 1H), 7.95–7.83 (m, 3H), 7.65–7.56 (m, 2H), 7.42–7.25 (m, 2H), 2.59 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 197.9, 166.3, 163.7, 152.0, 150.9, 134.3, 133.3, 132.0, 130.1, 127.1, 127.0, 126.0, 123.8, 123.4, 114.3, 30.1, 26.2. LC-MS (ESI+) t_R 4.60 min, *m/z* $[M+H]^+$ 279.19. MW: 278.31 g/mol. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.82; H, 5.11; N, 9.93.

4.2. Biology

4.2.1. In vitro antiplasmodial evaluation

In this study, a K1 culture-adapted *P. falciparum* strain resistant to chloroquine, pyrimethamine and proguanil was used in an *in vitro* culture. Maintenance in continuous culture was done as described previously by Trager and Jensen [30]. Cultures were maintained in fresh A+ human erythrocytes at 2.5% hematocrit in complete medium (RPMI 1640 with 25 mM HEPES, 25 mM $NaHCO_3$, 10% of A+ human serum) at 37 °C under reduced O_2 atmosphere (gas mixture 10% O_2, 6% CO_2, and 84% N_2). Parasitaemia was maintained daily between 1% and 6%. The *P. falciparum* drug susceptibility test was carried out by comparing quantities of DNA in treated and control cultures of parasite in human erythrocytes according to a SYBR Green I fluorescence-based method [31] using a 96-well fluorescence plate reader. Compounds, previously dissolved in DMSO (final concentration less than 0.5% v/v) were incubated in a total assay volume of 200 μL of synchronized culture suspension (2% hematocrit and 0.4% parasitaemia) for 72 h in a humidified atmosphere (14% O_2 and 6% CO_2) at 37 °C, in 96-well flat bottom plates. Duplicate assays were performed for each sample. After incubation, 125 μL supernatant was discarded and cells were washed twice with 125 μL 1× PBS. 15 μL re-suspended cells were transferred to 96-well flat bottom nonsterile black plates (Greiner Bio-one) already containing 15 μL of the SYBR Green I lysis buffer (2× SYBR Green I, 20 mM Tris base pH 7.5, 20 mM EDTA, 0.008% w/v saponin, 0.08% w/v Triton X-100). Negative control, treated by solvents (DMSO or H_2O) and positive controls (chloroquine and doxycycline) were added to each set of experiments. Plates were incubated for 15 min at 37 °C and then read on a TECAN Infinite F-200 spectrophotometer with excitation and emission wavelengths at 485 and 535 nm, respectively. The concentrations of compounds required to induce a 50% decrease of parasite growth (IC_{50} K1) were calculated from three independent experiments.

4.2.2. In vitro cytotoxicity evaluation

HepG2 cell line was maintained at 37 °C, 6% CO_2, with 90% humidity in RPMI supplemented with 10% fœtal bovine serum, 1% L-glutamine (200 mM) and penicillin (100 U/mL)/streptomycin (100 μg/mL) (complete RPMI medium). The evaluation of the tested molecules cytotoxicity on the HepG2 (hepatocarcinoma cell line purchased from ATCC, ref HB-8065) cell line was performed according to the method of Mosmann [32] with slight modifications. Briefly, 5.10^3 cells in 100 μL of complete medium were inoculated into each well of 96-well plates and incubated at 37 °C in a humidified 6% CO_2. After 24 h incubation, 100 μL of medium with various product concentrations dissolved in DMSO (final concentration less than 0.5% v/v) were added and the plates were incubated for 72 h at 37 °C. Triplicate assays were performed for each sample. Each plate-well was then microscope-examined for detecting possible precipitate formation before the medium was aspirated from the wells. 100 μL of MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide) solution (0.5 mg/mL in medium without FCS) were then added to each well. Cells were incubated for 2 h at 37 °C. After this time, the MTT

solution was removed and DMSO (100 μL) was added to dissolve the resulting blue formazan crystals. Plates were shaken vigorously (700 rpm) for 10 min. The absorbance was measured at 570 nm with 630 nm as reference wavelength using a BIO-TEK ELx808 Absorbance Microplate Reader. DMSO was used as blank and doxorubicin (purchased from Sigma Aldrich) as positive control. Cell viability was calculated as percentage of control (cells incubated without compound). The 50% cytotoxic concentration (CC_{50}) was determined from the dose–response curve by using the TableCurve® software 2D v.5.0. CC_{50} values represent the mean value calculated from three independent experiments.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.04.059.

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