

Article

Synthesis, Biological Evaluation and Structure-Activity Relationships of New Quinoxaline Derivatives as Anti-*Plasmodium falciparum* Agents

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Abstract: We report the synthesis and antimalarial activities of eighteen quinoxaline and quinoxaline 1,4-di-*N*-oxide derivatives, eight of which are completely novel. Compounds **1a** and **2a** were the most active against *Plasmodium falciparum* strains. Structure-activity relationships demonstrated the importance of an enone moiety linked to the quinoxaline ring.

Keywords: *Plasmodium falciparum*; antimalarial agents; quinoxaline; quinoxaline 1,4-di-*N*-oxide; chalcone

1. Introduction

Malaria is an infectious disease with an estimated 219 million cases and 660,000 deaths in 2010. Of these cases 86% correspond to children under 5 years old. In 2012, there were a total of 104 countries where malaria is considered to be endemic [1].

Plasmodium falciparum is the most dangerous form of the malaria parasite and it is responsible for a very high percentage of clinical attacks [2]. Artemisinin-based combination therapies (ACTs) are the standard treatment against uncomplicated *P. falciparum* malaria. Nevertheless, resistance to ACTs containing dihydroartemisinin has been reported in Pailin (Cambodia) [3] and resistance to pyrethroids (used as insecticides) has been detected in 64 countries around the World [1]. Other antimalarial drugs, such as chloroquine or mefloquine, are not effective enough [4]. FCR-3 *P. falciparum* is a chloroquine-resistant strain, but sensitive to pyrimethamine and sulfadoxine [5].

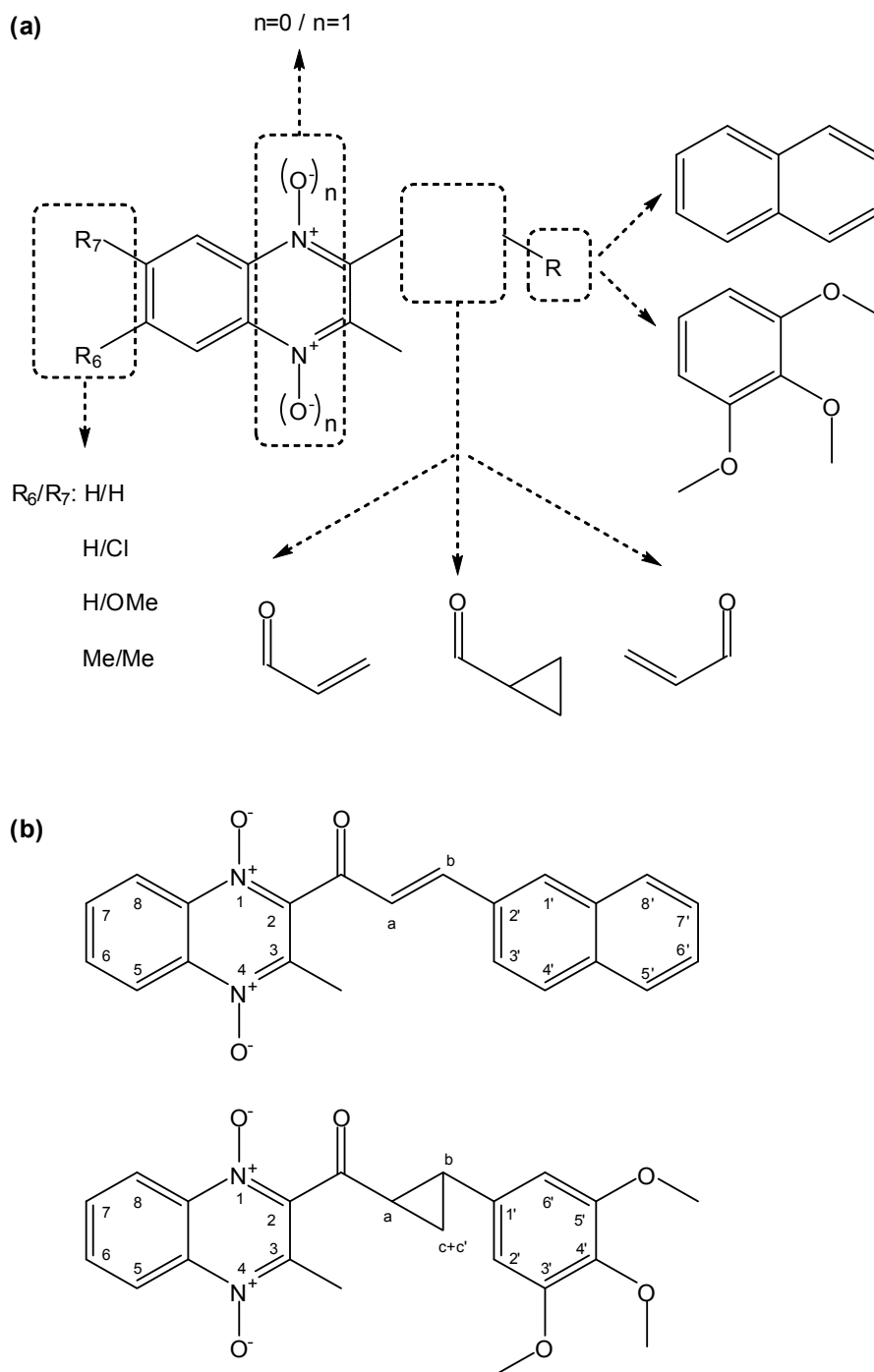
Over the last years, our group has been working on the development and synthesis of new quinoxaline derivatives. As a result of this line of research, the activities of quinoxaline 1,4-di-*N*-oxide derivatives against *Mycobacterium tuberculosis* [6–13], *Trypanosoma cruzi* [14,15], *Leishmania amazonensis* [16], *L. infantum* [17], *P. falciparum* [16–23] and different tumor cells [24–26] have been reported. The presence of two *N*-oxides is associated with a significant increase in some biological properties, such as anticancer [27] or antioxidant [28] activity. On the other hand, some reduced quinoxalines showed good antitubercular activity [29].

In this article, we report the synthesis and antimalarial activity of some quinoxaline analogs of chalcones and other compounds derived from them (Figure 1). Chalcones or 1,3-diaryl-2-propen-1-ones are α,β -unsaturated ketones with a large number of biological activities [30]. Different chalcones have been reported as anti-inflammatory [31], anticancer [32], antitubercular [33,34] or antimalarial [34–38] agents. With regard to antiplasmodial activity, previous structure-activity relationship studies found that the enone linker [38] and its *trans*-configuration [39] are essential in active chalcones.

Some of the compounds belonging to this study were previously tested against *L. amazonensis* [40] (series 1), *T. cruzi* and *L. peruviana* [41] (series 3) and as cytotoxic agents [42] (compound **1a**) and anti-inflammatory/antioxidant [28,43] agents (series 1, 3 and 7). According to the structure-activity relationships, these reports affirm that compounds in series 3 have better antioxidant activity than their analogs in series 1 due to the fact that the former group of molecules lacks the *N*-oxide groups [28]. On the other hand, compounds **1d** and **3d** have an interesting activity against different *Leishmania* strains, so the activity is associated with R₆/R₇ = Me/Me substitution [40,41]. Compound **1a** stands out as both a good anti-inflammatory and cytotoxic agent [42,43].

With the aim of expanding the SAR study of these chalcone analogs and obtaining new compounds with improved antimalarial activity, we describe herein the synthesis and the relationships between structure and antiplasmodial activity against the FCR-3 *P. falciparum* strain of eighteen quinoxaline and quinoxaline 1,4-di-*N*-oxide derivatives.

Figure 1. (a) Design of quinoxaline derivatives as potential antimalarial drugs. (b) Examples of two numbered compounds obtained in this synthesis.



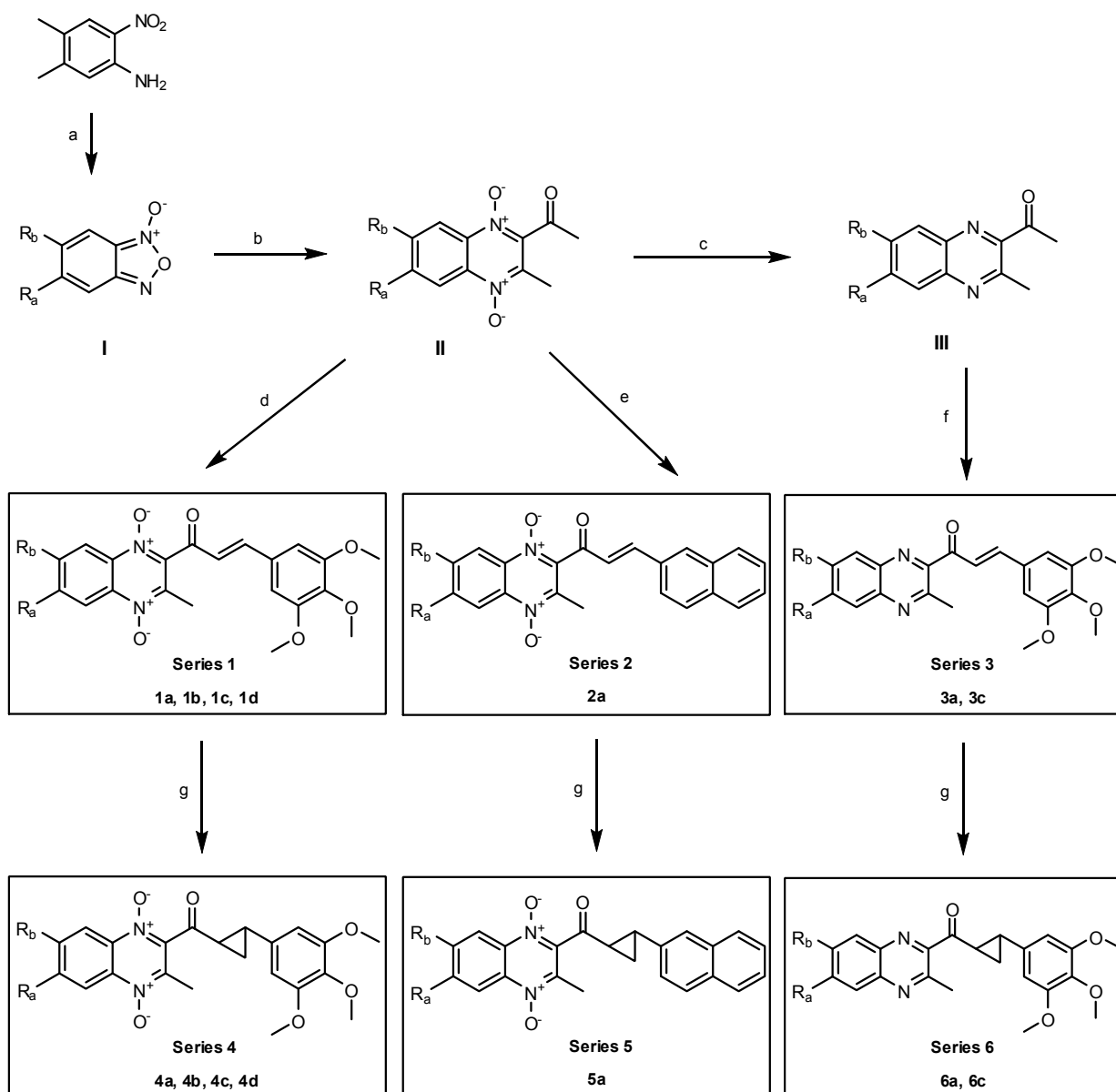
2. Results and Discussion

2.1. Chemistry

Synthesis of compounds in series 1, 3 and 7 were previously reported [25,40]. Benzofuroxans **I** with $R_a/R_b = H/H$, H/Cl and H/OMe are commercially available. Benzofuroxan with $R_a/R_b = Me/Me$ was synthesized by an oxidative cyclization of 4,5-dimethyl-2-nitroaniline according to a previously described method [44].

Scheme 1 shows the entire synthetic route for obtaining compounds **1a–d**, **2a** and **3a**, **3c** and their cyclopropyl derivatives **4a–d**, **5a** and **6a**, **6c**. The starting reagents used, quinoxaline 1,4-di-*N*-oxides **II** and reduced quinoxalines **III**, were obtained following previously reported procedures [7,27]. Quinoxaline 1,4-di-*N*-oxides **II** were synthesized by a classic Beirut reaction [45], using CaCl₂ and 1-aminoethanol as the catalysts [46]. Their reduced analogs **III** were prepared by reduction of the *N*-oxide groups [27], for which a reaction temperature of 65 °C and a mixture of ethyl acetate/methanol 1:1 as the solvent [47] was established.

Scheme 1. Synthesis of series 1, 2, 3, 4, 5 and 6.



R_a/R_b: H/H (**a**); H/Cl (**b**); H/OMe (**c**); Me/Me (**d**)

Reagents and conditions: (**a**) NaClO, *N,N*-DMF, 0 °C; (**b**) 2,4-pentanedione, CaCl₂, 1-aminoethanol; (**c**) Na₂S₂O₄, AcOEt/MeOH 1:1, 65 °C; (**d**) 3,4,5-trimethoxybenzaldehyde, 3% NaOH/MeOH, -10 °C; (**e**) 2-naphthaldehyde, 5% NaOH/MeOH; (**f**) 3,4,5-trimethoxybenzaldehyde, 3% NaOH/MeOH, r.t.; (**g**) TBAB, TMSOI, 15% aq. NaOH.

As previously described [48], in reactions of monosubstituted benzofuroxans 7-substituted quinoxaline 1,4-di-*N*-oxide derivatives prevail over the 6-isomers. While compound **II** with R₆/R₇= H/Cl was obtained as the major isomer and was isolated with a subsequent purification [25], 2-acetyl-7-methoxy-3-methylquinoxaline 1,4-di-*N*-oxide was obtained as the sole isomer [7].

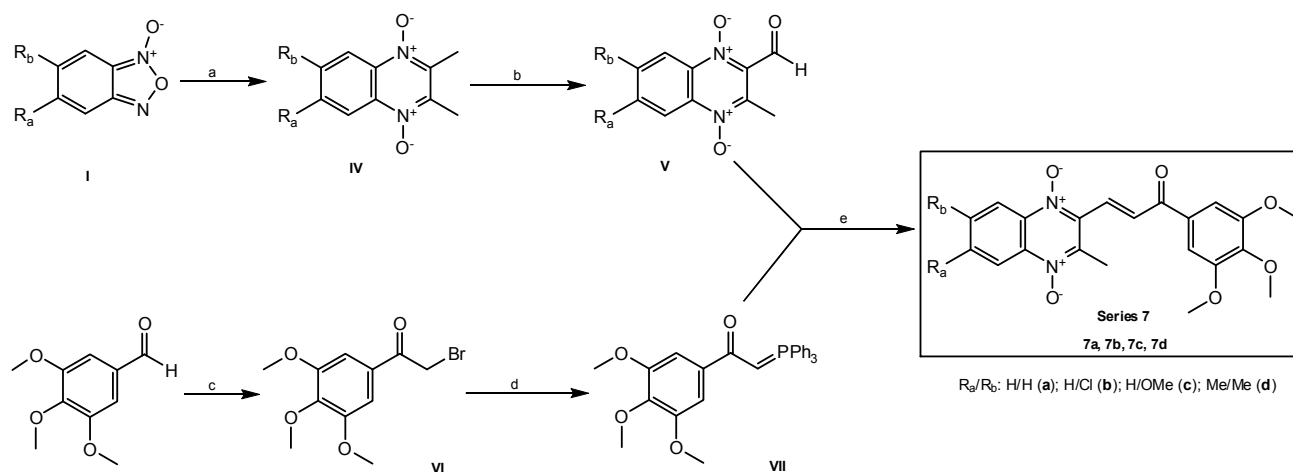
Chalcone analogs **1a–d** were synthesized by a previously reported base-catalyzed Claisen-Schmidt condensation [49], using 3% NaOH in methanol as the catalyst and establishing an optimum reaction temperature of −10 °C [43]. Their reduced analogs **3a, 3c** were synthesized using the same catalyst, but in this case, the condensation was performed at room temperature, as previously reported [28]. The compounds **1a–d** and **3a, 3c** obtained have been previously described [28,47]. Compound **2a** was first synthesized according to a previously reported method [50]. It was a spontaneous reaction that gives the desired compound in good yield.

New cyclopropyl derivatives **4a–d, 5a** and **6a, 6c** were obtained according to a previously reported method [51]. These reactions were carried out between compounds **1a–d, 2a** and **3a, 3c** and trimethylsulfoxonium iodide (TMSOI) in the presence of an aqueous solution of NaOH, with tetrabutylammonium bromide (TBAB) as a phase transfer catalyst and dichloromethane as the solvent. With regard to the reaction mechanism, Corey and Chaykovsky [52] demonstrated that trimethylsulfoxonium halides in the presence of a strong base allow the formation of a reactive compound named dimethylsulfoxonium methylide (DMSY), commonly known as Corey's reagent [53]. The reaction of DMSY with an α,β -unsaturated ketone involves the cyclopropanation of C=C double bond [54].

As their coupling constant values in the ¹H-NMR spectra showed *J* values \approx 16 Hz [47], the double bond geometries of compounds **1a–d** and **3a, 3c** were *trans*, just like the newly synthesized **2a**. According to previous reports [55,56], the Corey-Chaykovsky reaction with TMSOI occurs with retention of stereochemistry, giving *trans*-cyclopropyl derivatives **4a–d, 5a** and **6a, 6c** [51].

Scheme 2 shows the synthetic route for obtaining compounds **7a–d**. These chalcone analogs were obtained by a microwave-assisted Wittig reaction [28] between 2-formyl-3-methylquinoxaline 1,4-di-*N*-oxide derivatives **V** and a phosphonium ylide **VII**, both previously synthesized [28,45,57].

Scheme 2. Synthesis of series 7 [28].

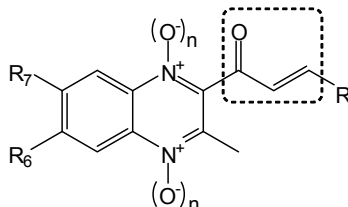


Reagents and conditions: (a) 2-butanone, morpholine; (b) SeO₂, acetonitrile, MW: 5 min, 200 W; (c) Br₂, acetic acid; (d) PPh₃, NaH/H₂O, toluene; (e) MeOH, MW: 5 min, 25 W.

2.2. Biological Results

In this study, eighteen quinoxaline and quinoxaline 1,4-di-*N*-oxide derivatives were tested against a chloroquine-resistant FCR-3 strain of *P. falciparum*. All the synthesized compounds and their biological activities are shown in Tables 1, 2 and 3.

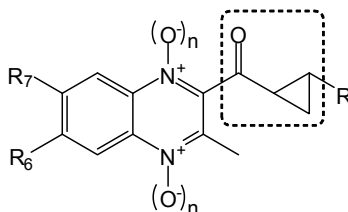
Table 1. *In vitro* activities of chalcone derivatives.



Compound	R ₆	R ₇	n	R	IC ₅₀ (μM) ^a	SD ^b
1a	H	H	1	3,4,5-trimethoxyphenyl	6.2	1.7
1b	H	Cl	1	3,4,5-trimethoxyphenyl	27.3	3.6
1c	H	OMe	1	3,4,5-trimethoxyphenyl	31.1	20.4
1d	Me	Me	1	3,4,5-trimethoxyphenyl	24.4	14.0
2a	H	H	1	naphthyl	5.8	0.8
3a	H	H	0	3,4,5-trimethoxyphenyl	21.5	5.3
3c	H	OMe	0	3,4,5-trimethoxyphenyl	26.4	0.3
CQ ^c	-	-	-	-	0.173	0.003

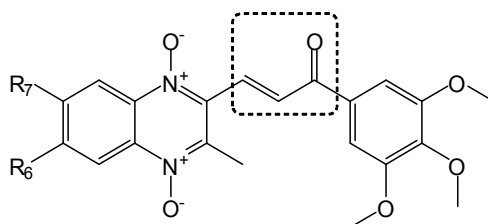
^a IC₅₀, concentration required for inhibiting growth of FCR-3 *P. falciparum* strain by 50% (in μM). Mean values of two independent experiments performed in triplicate; ^b SD, standard deviation; ^c Chloroquine, control.

Table 2. *In vitro* activities of cyclopropyl derivatives.



Compound	R ₆	R ₇	n	R	IC ₅₀ (μM) ^a	SD ^b
4a	H	H	1	3,4,5-trimethoxyphenyl	56.4	6.4
4b	H	Cl	1	3,4,5-trimethoxyphenyl	20.1	6.9
4c	H	OMe	1	3,4,5-trimethoxyphenyl	NA ^d	-
4d	Me	Me	1	3,4,5-trimethoxyphenyl	NA	-
5a	H	H	1	naphthyl	62.1	20.0
6a	H	H	0	3,4,5-trimethoxyphenyl	NA	-
6c	H	OMe	0	3,4,5-trimethoxyphenyl	NA	-
CQ ^c	-	-	-	-	0.173	0.003

^a IC₅₀, concentration required for inhibiting growth of FCR-3 *P. falciparum* strain by 50% (in μM). Mean values of two independent experiments performed in triplicate; ^b SD, standard deviation; ^c Chloroquine, control; ^d NA, not active.

Table 3. *In vitro* activities of inverted chalcone derivatives.

Compound	R ₆	R ₇	IC ₅₀ (μM) ^a	SD ^b
7a	H	H	29.0	3.5
7b	H	Cl	24.2	0.8
7c	H	OMe	34.3	2.0
7d	Me	Me	24.5	4.7
CQ ^c	-	-	0.173	0.003

^a IC₅₀, concentration required for inhibiting growth of FCR-3 *P. falciparum* strain by 50% (in μM). Mean values of two independent experiments performed in triplicate; ^b SD, standard deviation; ^c Chloroquine, control.

Almost all the synthesized compounds exhibited some activity against *P. falciparum*, but none of them had better IC₅₀ values than chloroquine itself. Compounds **1a** and **2a** have been chosen as lead compounds with interesting activities against the parasite. Although both leads were chalcone analogs with R₆/R₇ = H/H, compounds **7b** and **4b** had the best activities among inverted chalcone and cyclopropyl derivatives. In these cases, the presence of a halogen atom in position 7 led to an increase in the activity. In fact, **4b** was the third most active compound of the study. These results coincide with previous reports [18], where the most active compounds were those without any substitution on the quinoxaline ring and with monosubstitution by an electron withdrawing group.

Apart from compound **4b**, changing the double bond in chalcones (compounds **1a–d**, **2a** and **3a**, **3c**) for a cyclopropyl structure led to a dramatic drop in the antiplasmodial activity in each case (compounds **4a–d**, **5a** and **6a**, **6c**). The same trend was noted when comparing cyclopropyl derivatives **4a–d** with their analogs in series 7.

With regard to series 1 and 7, the inversion of the chalcone did not lead to a change in the antimalarial activity, except for compound **1a**, whose IC₅₀ was significantly lower than that of the others. Therefore, the orientation of the enone moiety does not appear to be a determining factor for the antimalarial activity. Finally, only reduced chalcones **3a** and **3c** showed some interesting activity, while reduced cyclopropyl derivatives **6a** and **6c** were completely inactive. According to previous reports [58], a minimum requirement for the antimalarial activity was the oxygenation of *N*-1 and *N*-4 of the quinoxaline ring, because mono and reduced compounds were not active. Nevertheless, in this study the presence of *N*-oxides was not decisive for the synthesized compounds to be active.

3. Experimental

3.1. General Information

All of the synthesized compounds were chemically characterized by thin layer chromatography (TLC), melting point, proton nuclear magnetic resonance (¹H-NMR), infrared spectroscopy (IR) and

elemental microanalyses (CHN). Alugram SIL G/UV254 (0.2 mm layer, Macherey-Nagel GmbH & Co. KG., Düren, Germany) was used for TLC, and silica gel 60 (0.040–0.063 mm, Merck, Darmstadt, Germany) was used for column chromatography. The $^1\text{H-NMR}$ spectra were recorded on a Bruker 400 Ultrashield instrument (400 MHz, Bruker, Billerica, MA, USA), using TMS as the internal standard and $\text{DMSO-}d_6$ as the solvent. Chemical shifts are reported in ppm (δ) and coupling constants (J) values are given in Hertz (Hz). Signal multiplicities are represented by: s (singlet), d (doublet), t (triplet), q (quadruplet), dd (double doublet) and m (multiplet). The IR spectra were recorded on a Thermo Nicolet Nexus FTIR (Madison, WI, USA) in KBr pellets. Frequencies (ν) are reported in cm^{-1} and peak intensities are represented by: w (weak), m (medium), s (strong) and vs (very strong). Elemental microanalyses were obtained on a CHN-900 Elemental Analyzer (Leco, Tres Cantos, Madrid, Spain) from vacuum-dried samples. The analytical results for C, H and N were within ± 0.4 of the theoretical values, indicating a purity of $>95\%$. All reagents and solvents were purchased from commercial sources: E. Merck (Darmstadt, Germany), Panreac Química S.A. (Barcelona, Spain), Sigma-Aldrich Química S.A. (Alcobendas, Madrid, Spain), Acros Organics (Janssen Pharmaceuticaaan, Geel, Belgium), Scharlau (F.E.R.O.S.A., Barcelona, Spain) and Lancaster (Bischheim-Strasbourg, France).

3.2. General Procedure of Synthesis

3.2.1. Synthesis of 3-Methyl-2-[3-(naphth-2-yl-prop-2-enoyl)] quinoxaline 1,4-di-*N*-oxide Derivatives (Series 2)

The appropriate quinoxaline di-*N*-oxide **II** (2-acetyl-3-methylquinoxaline 1,4-di-*N*-oxide, 3 mmol) and 2-naphthaldehyde (3 mmol) were dissolved in methanol (30 mL). 5% NaOH in methanol (10 mL) was added dropwise and the reaction mixture was magnetically stirred at room temperature for 15 min, until a yellow precipitate appeared. The solid obtained was filtered off and washed with diethyl ether.

*3-Methyl-2-[3-(naphth-2-yl-prop-2-enoyl)] quinoxaline 1,4-di-*N*-oxide (2a)*. Yield 57%. mp 184 °C. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ ppm: 2.40 (s, 3H, CH_3); 7.37 (d, 1H, H_b , $J_{b-a,trans} = 16.4$ Hz); 7.58 (m, 2H, H_6+H_7); 7.91 (d, 1H, H_3); 8.01 (m, 5H, $\text{H}_4+\text{H}_5+\text{H}_6+\text{H}_7+\text{H}_8$); 8.03 (d, 1H, H_a , $J_{a-b,trans} = 16.0$ Hz); 8.24 (s, 1H, $\text{H}_{1'}$); 8.47 (d, 1H, H_8 , $J_{8-7} = 8.6$ Hz); 8.58 (d, 1H, H_5 , $J_{5-6} = 8.4$ Hz). IR (KBr) ν cm^{-1} : 3091 (w, $\nu_{\text{arC-H}}$); 3055 (w, $\nu_{\text{alkC-H}}$); 3018 (w, $\nu_{\text{C-H}}$); 1675 (m, $\nu_{\text{C=O}}$); 1600 (s, $\nu_{\text{arC=C}}$); 1331 (vs, $\nu_{\text{N-O}}$). Anal. Calc. for $\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}_3$: C = 74.14%, H = 4.53%; N = 7.86%; Found: C = 74.19%, H = 4.40%; N = 7.85%.

3.2.2. Synthesis of 3-Methyl-2-[2-(3,4,5-trimethoxyphenyl)cyclopropanecarbonyl] quinoxaline 1,4-di-*N*-oxide Derivatives (Series 4), 3-Methyl-2-[2-(2-naphthyl)cyclopropanecarbonyl] quinoxaline 1,4-di-*N*-oxide Derivatives (Series 5) and 3-Methyl-2-[2-(3,4,5-trimethoxyphenyl)cyclopropanecarbonyl] quinoxaline Derivatives (Series 6)

The appropriate chalcone **1a–d**, **2a** and **3a**, **3c** (1 mmol), trimethylsulfoxonium iodide (TMSOI, 2 mmol) and tetrabutylammonium bromide (TBAB, 0.2 mmol) were dissolved in dichloromethane (40 mL) and stirred magnetically at room temperature for 15 min. Then a 15% aqueous solution of NaOH (10 mL) was added dropwise and the reaction mixture was stirred magnetically at room temperature for 24 h, until the solution turned dark. At this point, excess dichloromethane and water

were added to the reaction. The organic phase was extracted, dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate as the eluent. The desired compounds **4a–d**, **5a** and **6a**, **6c** were obtained after recrystallization from ethanol.

3-Methyl-2-[2-(3,4,5-trimethoxyphenyl)cyclopropanecarbonyl] quinoxaline 1,4-di-N-oxide (4a). Yield 56%. mp 178–179 °C. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ ppm: 1.86 (m, 2H, $\text{H}_c+\text{H}_c'$); 2.40 (s, 3H, CH_3); 2.78 (m, 1H, H_a); 2.91 (m, 1H, H_b); 3.59 (s, 3H, $p\text{-OCH}_3$); 3.75 (s, 6H, $m\text{-OCH}_3$); 6.55 (s, 2H, H_2+H_6); 7.98 (m, 2H, H_6+H_7); 8.44 (d, 1H, H_8 , $J_{8-7} = 8.2$ Hz); 8.49 (d, 1H, H_5 , $J_{5-6} = 8.2$ Hz). IR (KBr) ν cm^{-1} : 3071 (w, $\nu_{\text{arC-H}}$); 2998 and 2965 (w, $\nu_{\text{C-H}}$); 1690 (m, $\nu_{\text{C=O}}$); 1590 (m, $\nu_{\text{arC=C}}$); 1329 (s, $\nu_{\text{N-O}}$); 1128 (s, $\nu_{\text{C-O-C}}$). Anal. Calc. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_6$: C = 64.37%, H = 5.41%; N = 6.83%; Found: C = 64.08%, H = 5.74%; N = 6.69%.

7-Chloro-3-methyl-2-[2-(3,4,5-trimethoxyphenyl)cyclopropanecarbonyl] quinoxaline 1,4-di-N-oxide (4b). Yield 9%. mp 143–144 °C. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ ppm: 1.88 (m, 2H, $\text{H}_c+\text{H}_c'$); 2.39 (s, 3H, CH_3); 2.79 (m, 1H, H_a); 2.87 (m, 1H, H_b); 3.60 (s, 3H, $p\text{-OCH}_3$); 3.76 (s, 6H, $m\text{-OCH}_3$); 6.54 (s, 2H, H_2+H_6); 8.01, 8.02 (dd, 1H, H_6 , $J_{6-8} = 2.3$ Hz, $J_{6-5} = 9.2$ Hz); 8.42 (d, 1H, H_8 , $J_{8-6} = 2.2$ Hz); 8.48 (d, 1H, H_5 , $J_{5-6} = 9.2$ Hz). IR (KBr) ν cm^{-1} : 3101 (w, $\nu_{\text{arC-H}}$); 2935 (w, $\nu_{\text{C-H}}$); 1695 (m, $\nu_{\text{C=O}}$); 1592 (m, $\nu_{\text{arC=C}}$); 1326 (s, $\nu_{\text{N-O}}$); 1128 (s, $\nu_{\text{C-O-C}}$). Anal. Calc. for $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_6\text{Cl}$: C = 59.39%, H = 4.77%; N = 6.30%; Found: C = 59.52%, H = 4.93%; N = 6.15%.

7-Methoxy-3-methyl-2-[2-(3,4,5-trimethoxyphenyl)cyclopropanecarbonyl] quinoxaline 1,4-di-N-oxide (4c). Yield 13%. mp 174–175 °C. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ ppm: 1.84 (m, 2H, $\text{H}_c+\text{H}_c'$); 2.37 (s, 3H, CH_3); 2.79 (m, 1H, H_a); 2.90 (m, 1H, H_b); 3.61 (s, 3H, $p\text{-OCH}_3$); 3.77 (s, 6H, $m\text{-OCH}_3$); 3.98 (s, 3H, 7-OCH_3); 6.54 (s, 2H, H_2+H_6); 7.58, 7.61 (dd, 1H, H_6 , $J_{6-8} = 2.8$ Hz, $J_{6-5} = 9.5$ Hz); 7.74 (d, 1H, H_8 , $J_{8-6} = 2.7$ Hz); 8.40 (d, 1H, H_5 , $J_{5-6} = 9.5$ Hz). IR (KBr) ν cm^{-1} : 3005 (w, $\nu_{\text{arC-H}}$); 2945 (w, $\nu_{\text{C-H}}$); 1689 (m, $\nu_{\text{C=O}}$); 1587 (m, $\nu_{\text{arC=C}}$); 1323 (s, $\nu_{\text{N-O}}$); 1120 (m, $\nu_{\text{C-O-C}}$). Anal. Calc. for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_7$: C = 62.71%, H = 5.50%; N = 6.36%; Found: C = 62.55%, H = 5.83%; N = 6.64%.

3,6,7-Trimethyl-2-[2-(3,4,5-trimethoxyphenyl)cyclopropanecarbonyl] quinoxaline 1,4-di-N-oxide (4d). Yield 24%. mp 187–189 °C. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ ppm: 1.84 (m, 2H, $\text{H}_c+\text{H}_c'$); 2.37 (s, 3H, CH_3); 2.47–2.51 (m, 6H, $6,7\text{-CH}_3$); 2.76 (m, 1H, H_a); 2.90 (m, 1H, H_b); 3.59 (s, 3H, $p\text{-OCH}_3$); 3.75 (s, 6H, $m\text{-OCH}_3$); 6.54 (s, 2H, H_2+H_6); 8.18 (s, 1H, H_8); 8.25 (s, 1H, H_5). IR (KBr) ν cm^{-1} : 2932 (w, $\nu_{\text{C-H}}$); 1683 (m, $\nu_{\text{C=O}}$); 1589 (m, $\nu_{\text{arC=C}}$); 1326 (s, $\nu_{\text{N-O}}$); 1132 (s, $\nu_{\text{C-O-C}}$). Anal. Calc. for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_6$: C = 65.73%, H = 5.99%; N = 6.39%; Found: C = 65.41%, H = 5.79%; N = 6.40%.

3-Methyl-2-[2-(2-naphthyl)cyclopropanecarbonyl] quinoxaline 1,4-di-N-oxide (5a). Yield 66%. mp 176–177 °C. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ ppm: 1.93 (m, 1H, H_c); 1.99 (m, 1H, H_c'); 2.40 (s, 3H, CH_3); 3.01 (m, 2H, H_a+H_b); 7.38 (d, 1H, H_3); 7.47 (m, 2H, H_6+H_7); 7.80 (s, 1H, H_1); 7.85 (m, 3H, $\text{H}_4+\text{H}_5+\text{H}_8$); 7.96 (m, 2H, H_6+H_7); 8.42 (d, 1H, H_8 , $J_{8-7} = 8.2$ Hz); 8.48 (d, 1H, H_5 , $J_{5-6} = 8.5$ Hz). IR (KBr) ν cm^{-1} : 3091 (w, $\nu_{\text{arC-H}}$); 2959 (w, $\nu_{\text{C-H}}$); 1689 (s, $\nu_{\text{C=O}}$); 1597 (w, $\nu_{\text{arC=C}}$); 1328 (s, $\nu_{\text{N-O}}$). Anal. Calc. for $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_3$: C = 74.57%, H = 4.91%; N = 7.56%; Found: C = 74.57%, H = 4.90%; N = 7.57%.

3-Methyl-2-[2-(3,4,5-trimethoxyphenyl)cyclopropanecarbonyl] quinoxaline (6a). Yield 41%. mp 155–156 °C. ¹H-NMR (DMSO-*d*₆) δ ppm: 1.77 (s, 1H, H_c); 1.84 (s, 1H, H_{c'}); 2.69 (s, 1H, H_a); 2.86 (s, 3H, CH₃); 3.57 (m, 1H, H_b); 3.61 (s, 3H, *p*-OCH₃); 3.77 (s, 6H, *m*-OCH₃); 6.59 (s, 2H, H₂+H₆); 7.88 (m, 1H, H₆); 7.96 (m, 1H, H₇); 8.08 (m, 1H, H₈); 8.18 (m, 1H, H₅). IR (KBr) ν cm⁻¹: 2961 and 2935 (w, ν_{C-H}); 1679 (s, ν_{C=O}); 1589 (m, ν_{arC=C}); 1132 (s, ν_{C-O-C}). Anal. Calc. for C₂₂H₂₂N₂O₄: C = 69.81%, H = 5.87%; N = 7.40%; Found: C = 69.86%, H = 5.83%; N = 7.40%.

7-Methoxy-3-methyl-2-[2-(3,4,5-trimethoxyphenyl)cyclopropanecarbonyl] quinoxaline (6c). Yield 29%. mp 163–164 °C. ¹H-NMR (DMSO-*d*₆) δ ppm: 1.76 (m, 1H, H_c); 1.84 (m, 1H, H_{c'}); 2.69 (m, 1H, H_a); 2.83 (s, 3H, CH₃); 3.58 (m, 1H, H_b); 3.63 (s, 3H, *p*-OCH₃); 3.80 (s, 6H, *m*-OCH₃); 3.96 (s, 3H, 7-OCH₃); 6.60 (s, 2H, H₂+H₆); 7.52 (d, 1H, H₈, *J*₈₋₆ = 2.8 Hz); 7.58, 7.60 (dd, 1H, H₆, *J*₆₋₈ = 2.8 Hz, *J*₆₋₅ = 9.2 Hz); 7.98 (d, 1H, H₅, *J*₅₋₆ = 9.2 Hz). IR (KBr) ν cm⁻¹: 2936 (w, ν_{C-H}); 1680 (s, ν_{C=O}); 1587 (m, ν_{arC=C}); 1130 (s, ν_{C-O-C}). Anal. Calc. for C₂₃H₂₄N₂O₅: C = 67.62%, H = 5.93%; N = 6.86%; Found: C = 67.23%, H = 6.13%; N = 6.74%.

3.3. In Vitro Antiplasmodial Drug Assay

Chloroquine-resistant FCR-3 strain of *P. falciparum* was cultivated at 37 °C in 5% CO₂, 5% O₂ in a balanced N₂ atmosphere environment on RPMI 1640 medium supplemented with gentamicin 0.1 mg/mL and 10% heat-inactivated A⁺ human serum, as previously described [59]. The drugs, dissolved in dimethyl sulfoxide, were added at final concentrations ranging from 250 to 0.1 μM. The final DMSO concentration was never greater than 0.1%. *In vitro* antimalarial activity was measured using the [³H]-hypoxanthine (MP Biomedicals, Santa Ana, CA, USA) incorporation assay [60]. Briefly, 250 μL of total culture medium with the diluted drug and the suspension of human red blood cells in medium (A⁺ group, 5% hematocrit) with 1% parasitemia were placed into the wells of 96-well microtiter plates. On the third day of the test, radioactivity was assessed. All experiments were performed in triplicate. Results were expressed as the concentration resulting in 50% inhibition (IC₅₀), which was calculated by a nonlinear regression logistic dose response model. The mean IC₅₀ values and standard deviation for each compound was calculated.

4. Conclusions

Eighteen quinoxaline and quinoxaline 1,4-di-*N*-oxide derivatives have been synthesized with the aim of studying their antimalarial activity. The SAR study suggested that the chalcone and inverted chalcone moieties can act as useful linkers in the search for antimalarial ligands. Moreover, the similar activities of series 1, 3 and 7 allow us to affirm that the enone moiety plays an important role in the antimalarial activity of these compounds, but not its orientation. Compounds **1a** and **2a** showed the best antiplasmodial activity. In general, the addition of cyclopropyl moiety dramatically reduces the biological activity in each case. We are not able to unequivocally confirm that *N*-oxides are essential for the antiplasmodial activity. These results show that further structural modifications may provide better antimalarial compounds.

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Author Contributions

The listed authors contributed to this work as described in the following. Ana Gil together with Silvia Galiano carried out much of the synthetic work and prepared the manuscript. Asunción Burguete carried out the synthesis of chalcones. Adriana Pabón together with Eric Deharo conducted assays against *P. falciparum* and helped interpreting the results. Ignacio Aldana proposed the subject and monitored the progress of the ongoing research. Silvia Pérez-Silanes and Antonio Monge contributed with valuable discussions and scientific input. All authors helped preparing the manuscript and approved the final version.

Conflicts of Interest

The authors declare no conflict of interest.

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Sample Availability: Samples of the synthesized compounds are available from the authors.

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