

Property-Based Design and Synthesis of New Chloroquine Hybrids via Simple Incorporation of 2-Imino-thiazolidin-4-one or 1*H*-Pyrrol-2,5-dione Fragments on the 4-Amino-7-chloroquinoline Side Chain

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No presente trabalho realizou-se a síntese de novos *N*-derivados da 4-amino-7-cloroquinolina modificando seletivamente o grupo amino terminal das *N*-(7-cloroquinolin-4-il)-alquildiaminas, a base do fármaco cloroquina (CQ) mediante a incorporação de sistemas heterocíclicos da 2-imino-tiazolidin-4-ona e 1*H*-pirrol-2,5-diona. Esses derivados foram selecionados graças às suas propriedades características, e avaliados mediante crivado virtual empregando as plataformas OSIRIS e Molinspiration. Os derivados quinolínicos assim desenhados e sintetizados poderiam incrementar a atividade antimalárica dos análogos da CQ sem afetar a lipofilia como tem se descrito na literatura, postulando-se como candidatos em posteriores testes biológicos.

In the present work, the syntheses of new 4-amino-7-chloroquinoline *N*-derivatives were performed by selective modification of the side chain amino group of *N*-(7-chloroquinolin-4-yl) alkyldiamines, basis framework of chloroquine (CQ) drug through the incorporation of heterocyclic 2-imino-thiazolidin-4-one and 1*H*-pyrrol-2,5-dione systems. These potential activity modulators were selected thanks to their characteristic properties, and evaluated by virtual screening employing the OSIRIS and Molinspiration platforms. Designed and synthesized quinolinic derivatives could increase the antimalarial activity of CQ analogues without affecting the lipophilicity as described in literature, suggesting them as candidates for further biological assessments.

Keywords: 4-amino-7-chloroquinolines, 2-imino-thiazolidin-4-ones, 1*H*-pyrrol-2,5-diones, molecular hybrids, property-based design, drug-like properties, antimalarial agents

Introduction

Drug-like properties are an integral element of drug discovery projects. This term became commonly used following the pivotal work of Lipinski and co-workers.^{1,2} Drug-like property optimization is an important area of antiparasitic drug discovery, in general, and antiplasmodial agents development, in particular. Investigation during the last two decades has shown the increasing chloroquine (CQ) resistance and the emerging mefloquine resistance by *Plasmodium falciparum*; thus, there is still a high potential for developing new active antimalarials.³⁻⁵

The development of antiplasmodial agents directed towards a single therapeutic target has shown not to be the best strategy within the progress against this devastating disease. In this sense, recently the antimalarial activity modulation has been examined by means of the systematic

modification of the quinoline core or the 4-aminoquinoline side chain, finding that the last generate highly active compounds against multidrug resistant parasites.³⁻⁶ The tertiary amino group present in most 4-aminoquinoline drugs is considered responsible for the drug accumulation within the parasite digestive vacuole, and to provide lipophilicity because of its basic character.⁷ Nevertheless, the introduction of structural features that highly decrease this group basicity has proved to increase the antimalarial activity of several CQ analogues.^{3,5} These discoveries established the amino side chain modifications as an alternative strategy for the new and selective antimalarials development. These modifications consist mainly in the introduction of small *N*-heterocycles whose ring structure would increase the antimalarial activity or potentiate other bioeffects.

In this sense, thiazolidin-4-one derivatives are well known for their antidiarrheic,⁸ anticonvulsant,⁹ antimicrobial,¹⁰ anticancer,¹¹ anti-HIV properties,¹² as well

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as for increasing the antimalarial activity of CQ analogues.⁴ However, different systems as 2-imino-thiazolidin-4-one **1** and its 5-arylidene derivative **2**,¹³ despite their anti-inflammatory and antiviral activity,¹³⁻¹⁵ have been less studied in medicinal chemistry, and awake our particular interest on using these systems as a chloroquine amino group modification. As well as thiazolidin-4-one systems, cyclic imides, e.g. 1*H*-pyrrol-2,5-diones **3**, **4**, are structural frameworks present in several active molecules, principally against cancer cell lines¹⁶⁻²¹ (Figure 1). These properties are helpful activity modulators within of the development of new antimalarial agents.

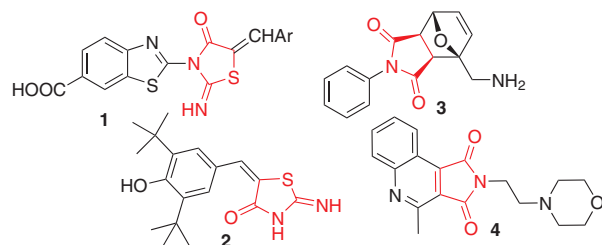


Figure 1. Bioactive molecules bearing small *N*-heterocyclic frameworks.

Based on this evidence, in the present work, the design and synthesis of potential new 4-aminoquinoline drug-like molecules were developed, through the systematic analysis of the desired product structure and the selective modification of the amino group, incorporating the biologically privileged 2-imino-thiazolidin-4-ones and cyclic *N*-imides scaffolds using a new strategy of “property-based design”.²² These systems are present in diverse bioactive molecules, and additionally could prevent the enzymatic dealkylation without affecting lipophilicity, and increase antimalarial activity of CQ, as described in literature.

Results and Discussion

The present work describes the efficient synthesis of new 4-amino-7-chloroquinoline derivatives functionalized

with 2-imino-thiazolidin-4-one or 1*H*-pyrrol-2,5-dione systems separated by a short aminoalkyl chain. These hybrids, obtained by synthetic pathways reported in recent scientific literature, correspond to the previous virtual screening performed using the OSIRIS and Molinspiration platforms.²³⁻²⁷ The obtained results evidence the potential in further biological studies of these derivatives thanks to their considerable drug-score and excellent reaction yields.

Rational molecular design

The principal idea of molecular hybrids formation is the lead antimalarial agent development with a potential and selective activity against multidrug resistant *P. falciparum* strains. The 2-imino-thiazolidin-4-one and 1*H*-pyrrol-2,5-dione systems possess the adequate characteristics to be considered as *reversal agent* candidates within the new quinoline derivatives construction.

Using the Lipinski's rule²⁵ and drug-score criterion,²⁴ the structures of a new series of CQ analogues based on the 4-amino-7-chloroquinoline skeleton and these *N*-heterocyclic moieties were evaluated, assembling these compounds from synthetic and commercially available precursors (Figure 2).

Employing the Molinspiration software,²⁸ the planned compounds **13-22** were subjected to the Lipinski's rule of five analysis (drug-likeness), which indicates if a chemical substance can be orally active in humans.^{1,24} Currently, there are many approaches that assess a compound drug-likeness based on topological descriptors, fingerprints of molecular drug-likeness structure keys or other properties such as TPSA. In the Molinspiration program, the occurrence frequency of each fragment is determined within the collection created by shredding 3300 traded drugs, as well as 15000 commercially available chemicals yielding a complete list of all available fragments.²³ In this work, the Molinspiration program was used for the fragment based drug-likeness calculation of all desired compounds

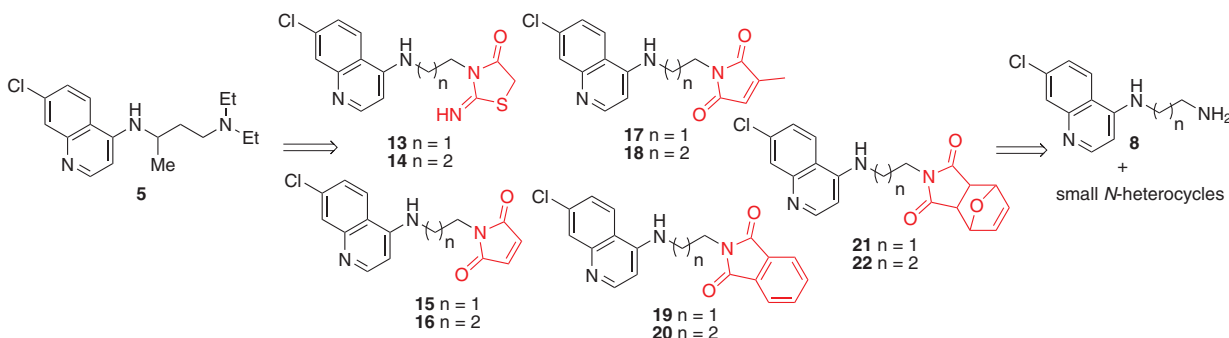


Figure 2. Property-based design and planned 4-aminoquinoline series fused with small *N*-heterocyclic moieties.

Table 1. Calculated Lipinski's rule of five parameters for the 4-aminoquinoline bearing *N*-heterocyclic frameworks

Compound	Parameters						
	log P	TPSA ^a / Å ²	MW / (g mol ⁻¹)	nON ^b	nOHNH ^c	RBN ^d	Violations
13	2.09	69.09	320.8	5	1	4	0
14	2.34	69.09	334.8	5	1	5	0
15	2.16	63.99	301.7	5	1	4	0
16	2.43	63.99	315.8	5	1	5	0
17	2.54	63.99	315.8	5	1	4	0
18	2.09	63.99	329.8	5	1	5	0
19	2.16	71.53	369.8	6	1	4	0
20	2.43	71.53	383.8	6	1	5	0
21	3.89	63.99	351.8	5	1	4	0
22	4.17	63.99	365.8	5	1	5	0
CQ	5.00	28.16	319.9	3	1	8	1

^aPolar surface area; ^bnumber of hydrogen bond acceptors; ^cnumber of hydrogen bond donors; ^dnumber of rotatable bonds.

also comparing them with CQ structure **5**. Conversely to the CQ as reference, the obtained calculations demonstrate that all analyzed compounds contain high bioavailability properties, and fulfil all parameters established by this rule (molecular weight = 269.73-408.91, log P = 2.66-4.92, nON = 2-6, and nOHNH = 0-4)^{1,27} (Table 1). TPSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood-brain barrier penetration.^{25,26} Prediction results for the compounds **13-22** molecular properties (Table 1), show TPSA values between 63 and 69 Å² confirming their drug-relevant properties.

In order to assess the possible pharmacological properties of hybrids **13-22**, a toxicity profile evaluation was performed employing the OSIRIS software,²⁹ as it may point to the presence of some fragments generally responsible for the irritant, mutagenic, tumorigenic, or reproductive effects in these molecules.²⁴ As shown in Figure 3 (left panel), with the exception of compounds **21**

and **22**, all desired products represented low or moderate biological risks.

Moreover, we used the OSIRIS program to predict the compounds drug-score (Figure 3, right panel). Products **17-20** revealed the effect of the anhydride structure over this parameter, and can be attributed to the presence of substitutions on positions 2 or 5 of the pyrrolidone ring. This theoretical data is a clear evidence of the biological potential of the designed 4-aminoquinoline series, and support further experimental bioactivity assessments, pointing these hybrids as lead compounds with a low toxicity risk profile.

Synthesis of 4-aminoquinoline derivatives bearing *N*-heterocyclic systems on the side chain amino group

Final compounds **13-22** and their 4-amino-7-chloroquinoline precursors **8** were synthesized by direct and effective protocols.^{6,30} The side chain amino group

Compound	Toxic effects			
	Mut	Tum	Irr	Rep
13	■	■	■	■
14	■	■	■	■
15	■	■	■	■
16	■	■	■	■
17	■	■	■	■
18	■	■	■	■
19	■	■	■	■
20	■	■	■	■
21	■	■	■	■
22	■	■	■	■
CQ	■	■	■	■

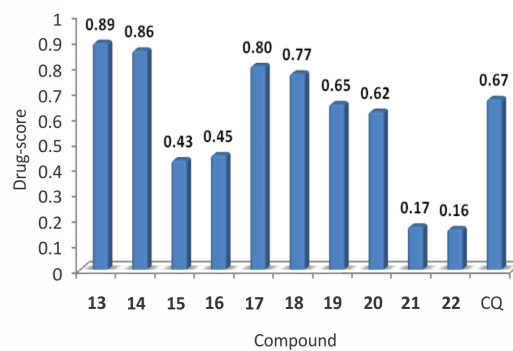
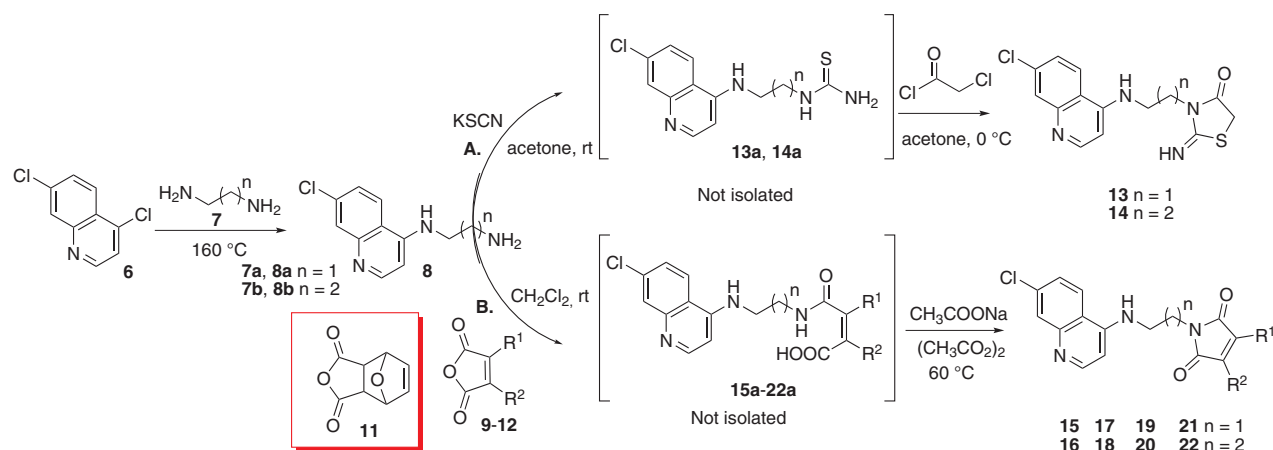


Figure 3. Calculated toxicity risks (left panel) and drug-score (right panel) of the synthesized 4-aminoquinoline derivatives (Mut, mutagenic; Tum, tumorigenic; Irr, irritant; Rep, reproductive).

(compound **8**) was bound to the 4,7-dichloroquinoline core by means of nucleophilic aromatic substitution S_NAr , using 4,7-dichloroquinoline **6** and the corresponding commercial diaminoalkanes **7**. This reaction was performed under reflux, in the presence of excess of diamine as solvent. Different reported methodologies on 2-imino-thiazolidin-4-one synthesis imply the isolation and purification of the corresponding thioureas as intermediates, and their subsequent chloroacetylation.¹⁸⁻²⁰ In this work, the quinoline derivatives bearing the 2-imino-thiazolidin-4-one framework **13** and **14** were obtained in good yields as white solids from the quinoline diamines **8**, potassium thiocyanate, and chloroacetyl chloride in anhydrous acetone at room

temperature, without isolation of thiourea derivatives **13a** and **14a** (Scheme 1, route A).

On the other hand, formation of two isomers imino-thiazolidinone and *N*-alkylimino-thiazolidinone has been described by Ottaná *et al.*,¹⁴ and explained by the possible condensation of chloroacetyl chloride with the two different nitrogen atoms on the thiocarbonyl group, causing the two different thiols intermediates generation. However, according to gas chromatography and nuclear magnetic resonance (NMR) analysis, compounds **13** and **14** were obtained exclusively as 2-imino-thiazolidin-4-ones in a 75-78% yield (Table 2), and *N*-alkylimino-thiazolidin-4-one formation was not detected. Single isomer synthesis



Scheme 1. Preparation of molecular hybrids **13-22**.

Table 2. The 4-aminoquinoline derivatives functionalized with *N*-heterocyclic systems^a

Compound	NR ¹ R ²	n	mp / °C	Condensed formula	R _f ^b	IR (KBr) ν_{\max} / cm ⁻¹	GC-MS t _R / min, m/z (%)	Yield / %
13		1	182-185	C ₁₄ H ₁₃ ClN ₄ OS	0.4	3329 _(NH) , 1619 _(C=O) , 1573 _(C=N)	18.2, 320 (M ⁺ , 65)	78
14		2	170-175	C ₁₅ H ₁₅ ClN ₄ OS	0.5	3331 _(NH) , 1622 _(C=O) , 1575 _(C=N)	18.2, 213 (M ⁺ , 65)	75
15		1	195-198	C ₁₅ H ₁₂ ClN ₃ O ₂	0.6	3216 _(NH) , 1712 _(C=O)	31.1, 301 (M ⁺ , 65)	98
16		2	85-90	C ₁₆ H ₁₄ ClN ₃ O ₂	0.5	3440 _(NH) , 1697 _(C=O)	31.1, 315 (M ⁺ , 65)	75
17		1	148-150	C ₁₆ H ₁₄ ClN ₃ O ₂	0.4	3239 _(NH) , 1697 _(C=O)	32.1, 329 (M ⁺ , undetected)	85
18		2	150-153	C ₁₇ H ₁₆ ClN ₃ O ₂	0.7	3239 _(NH) , 1697 _(C=O)	36.1, 329 (M ⁺ , undetected)	80
19		1	195-198	C ₁₉ H ₁₄ ClN ₃ O ₃	0.7	3239 _(NH) , 1697 _(C=O)	35.0, 367 (M ⁺ , undetected)	85
20		2	152-155	C ₂₀ H ₁₆ ClN ₃ O ₃	0.6	3240 _(NH) , 1697 _(C=O)	35.6, 381 (M ⁺ , undetected)	80
21		1	200-203	C ₁₉ H ₁₄ ClN ₃ O ₂	0.5	3409 _(NH) , 1697 _(C=O)	43.2, 351 (M ⁺ , 70)	90
22		2	165-167	C ₂₀ H ₁₆ ClN ₃ O ₂	0.4	3255 _(NH) , 1712 _(C=O)	36.2, 365 (M ⁺ , undetected)	88

^aElemental analyses were within ± 0.4 of theoretical values; ^busing (20:1) ethyl acetate-methanol mixtures on a silufol UV254 TLC aluminium sheet.

is probably favoured by the higher electron availability of the NH₂ group, compared with the highly hindered NH group bearing the *N*-alkylaminoquinoline framework on intermediates **13a** and **14a**. In order to extend the molecular library of hybrids between CQ and *N*-heterocyclic systems, new 4-aminoquinolines functionalized with 1*H*-pyrrol-2,5-dione framework were prepared. Synthesis of compounds **15-22** was performed according to the procedure established by Deng *et al.*,²⁰ starting from quinoline diamines **8** and cyclic anhydrides **9-12** (Scheme 1, route B). Intramolecular cyclization of the amic acid intermediates **15a-22a** was accomplished using acetic anhydride in presence of sodium acetate (5% mol). Most of the anhydride precursors employed were commercially available. Nevertheless, for preparation of hybrids **19** and **20**, synthesis of anhydride **11** through intermolecular cycloaddition of furan and maleic anhydride was developed according to Deng *et al.*¹⁶

Commonly employed conditions within the *N*-alkylimide synthesis require high temperatures and long reaction times, reaching moderate yields.³¹ In this work, 4-aminoquinoline derivatives functionalized with *N*-alkylimide system were obtained in high yield (85-98%), using lower reaction temperature and shorter reaction times (Table 2).

The structures of all new CQ hybrids **13-22** were strongly confirmed by NMR, IR and GC-MS analysis (Table 2 and Experimental part).

In summary, in this paper, we have reported a versatile and convenient route for the synthesis of novel hybrids between 4-aminoquinoline and *N*-heterocyclic systems previously designed. Obtained theoretical data awakes further experimental assays and establish these molecules as lead compounds with a low toxicity risk profile. The preliminary antimalarial evaluation of some of these hybrid analogues, prepared here against *P. falciparum*, has been studied.³² Based on these results further synthesis of new molecular hybrids by changing the substituents on the small heterocyclic ring and quinoline nucleus in order to enhance the antimalarial activity is being investigated and will be reported in due course.

Experimental

Materials and methods

Melting points (mp, uncorrected) were determined on a Fisher-Johns melting point apparatus. The IR spectra were recorded on a Lumex Infracalum FT-02 spectrophotometer in KBr. ¹H NMR spectra were recorded on Bruker AM-400 spectrometers, using DMSO-*d*₆. Chemical shifts are reported in ppm. Signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets

of doublets; t, triplet; dt, doublet of triplets; td, triplet of doublets; q, quartet; quint., quintet; m, multiplet; br, broad. A Hewlett Packard 5890a series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an MP MS Chemstation Data system was used for MS identification at 70 eV using a 60 m capillary column coated with hp-5 [5%-phenyl-poly(dimethyl-siloxane)]. Elemental analyses were performed on a Perkin Elmer 2400 Series II Analyzer and were within ± 0.4 of theoretical values. The reaction progress was monitored using thin layer chromatography on a silufol UV254 TLC aluminium sheet.

Molecular design was performed based on structure activity relationship studies, and virtual screening analysis reported in literature.^{23,24} Lipinski's rule of five parameters were calculated using the Molinspiration virtual platform (<http://www.molinspiration.com/services/>). The toxicity risk profile evaluation was accomplished employing the OSIRIS program available free at <http://www.organic-chemistry.org/prog/peo>. The OSIRIS and Molinspiration Property Explorers shown in these pages are an integral part of some pharmaceutical companies' in-house substance registration system. They allow drawing chemical structures and calculating on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and colour coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red, whereas a green colour indicates drug conform behaviour (Figure 3; see colors online).

Chemistry

General procedure for synthesis of 4-amino-7-chloroquinolines (**8**)^{6,30}

4.00 g (20.2 mmol) of **6** and α,ω -diaminoalkane (**7a, b**) (10.1 mmol) was heated at 80 °C for 1 h with stirring and subsequently at 140-150 °C for 6-7 h with continued stirring. The reaction mixture was cooled to room temp and basified with 10% NaOH (70 mL). The resultant mixture was extracted with chloroform-methanol (20:1, 4 × 50 mL). The combined extracts were washed with brine, dried over anhydrous Na₂SO₄, concentrated under reduced pressure and the residue (10 mL) was precipitated by the addition of n-heptane (70 mL). The solid was purified by washing with 40 mL ethyl ether. Physicochemical characteristics of the obtained compounds **8** are given in the Supplementary Information.

General procedure for synthesis of 4-amino-7-chloroquinoline and 2-imino-thiazolidin-4-one hybrids (**13, 14**)

Potassium thiocyanate (0.50 g, 4.50 mmol) was dissolved in 5.0 mL of anhydrous acetone under vigorous

agitation. Subsequently, 1.00 g (4.52 mmol) of quinoline diamines (**8a** or **8b**) in acetone were added dropwise to the above solution and the reaction mass was stirred for 7 h according to TLC analysis. Without any further purification process, over the resulting mass, triethylamine (3.00 g, 29.60 mmol) and then a solution of chloroacetyl chloride in anhydrous acetone (1.10 g, 9.30 mmol) was added during 30 min at 0 °C. The reaction mass was heated to room temperature and stirred over a 24 h period. Resulting yellowish mass was neutralized with 30 mL of sodium bicarbonate 10%, and extracted with ethyl acetate (2 × 30 mL). The organic layer was dried over Na₂SO₄ and concentrated under vacuum. Finally, hybrids **13**, **14** were purified by flash column chromatography using (20:1) ethyl acetate and methanol mixtures as eluents. Physicochemical characteristics of the obtained compounds are given in Table 2.

3-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-2-iminothiazolidin-4-one (13): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 (d, 1H, *J* 5.3 Hz, 2-H), 8.15 (d, 1H, *J* 9.0 Hz, 5-H), 7.79 (d, 1H, *J* 1.3 Hz, 8-H), 7.46 (d, 1H, *J* 8.9 Hz, 6-H), 6.58 (d, 1H, *J* 5.3 Hz, 3-H), 5.13 (d, 1H, *J* 10.9 Hz, C=NH), 4.37 (s, 2H, CH₂), 3.61 (t, 2H, *J* 6.7 Hz, CH₂), 3.48-3.43 (m, 2H, CH₂), 7.45-7.49 (m, 1H, NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 171.8, 158.3, 154.5, 152.3, 149.3, 134.8, 129.2, 124.4, 121.7, 117.5, 99.2, 50.1, 46.5, 30.2.

3-(3-((7-Chloroquinolin-4-yl)amino)propyl)-2-iminothiazolidin-4-one (14): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 (d, 1H, *J* 5.3 Hz, 2-H), 8.15 (d, 1H, *J* 9.0 Hz, 5-H), 7.79 (d, 1H, *J* 1.3 Hz, 8-H), 7.46 (d, 1H, *J* 8.9 Hz, 6-H), 6.58 (d, 1H, *J* 5.3 Hz, 3-H), 5.13 (d, 1H, *J* 10.9 Hz, C=NH), 4.37 (s, 2H, CH₂), 3.61 (t, 2H, *J* 6.7 Hz, CH₂), 3.48-3.43 (m, 2H, CH₂), 2.02 (m, 2H, CH₂), 7.45-7.49 (m, 1H, NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 172.1, 158.5, 154.9, 152.7, 150.3, 135.1, 129.4, 124.8, 121.7, 118.0, 99.0, 40.9, 38.5, 26.2.

General procedure for synthesis of chloroquine and 1H-pyrrol-2,5-dione hybrids (**15-22**)

1.0 g (4.24 mmol) of quinoline diamines (**8a** or **8b**) was dissolved in 5.0 mL of anhydrous dichloromethane under vigorous agitation. Then, a solution of anhydride (**9-11**) (0.7 g, 4.24 mmol) in dichloromethane was added dropwise to the above solution for 30 min at 0 °C, stirring the white precipitate formed for 2 h. Solvent excess was distilled under reduced pressure, and the remaining solid was filtered and washed with diethyl ether. Without any further purification process, the obtained amic acid **15a-22a** was mixed with 0.05 g (0.61 mmol) of sodium acetate and dissolved in 1.0 mL acetic anhydride. Reaction

temperature was adjusted to 60 °C and kept constant over a 5 h period. Finally, the reaction mass was allowed to cool and neutralized with sodium bicarbonate (1 mol L⁻¹). The coloured precipitate was filtered, washed with cold water, and air dried. Hybrids **15-22** were finally purified by flash column chromatography using (20:1) ethyl acetate-methanol mixtures as mobile phase and TLC control (R_f). Physicochemical characteristics of the obtained compounds are given in Table 2.

1-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-1H-pyrrol-2,5-dione (15): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 (d, 1H, *J* 5.4 Hz, 2-H), 8.08 (d, 1H, *J* 9.0 Hz, 5-H), 7.79 (d, 1H, *J* 2.2 Hz, 8-H), 7.47 (m, 1H, NH), 7.44 (dd, 1H, *J* 9.0, 2.2 Hz, 6-H), 7.02 (s, 2H, 3'(4')-H), 6.55 (d, 1H, *J* 5.5 Hz, 3-H), 3.65 (t, 2H, *J* 6.2 Hz, 2'-H), 3.48 (q, 2H, *J* 6.1 Hz, 1'-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 170.5, 154.5, 152.7, 149.3, 134.9, 135.8, 129.4, 124.7, 121.6, 117.5, 99.2, 46.9, 50.5.

1-(3-((7-Chloroquinolin-4-yl)amino)propyl)-1H-pyrrol-2,5-dione (16): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.39 (d, 1H, *J* 5.4 Hz, 2-H), 7.98 (d, 1H, *J* 9.0 Hz, 5-H), 7.69 (d, 1H, *J* 2.1 Hz, 8-H), 7.46 (m, 1H, NH), 7.46 (dd, 1H, *J* 9.0, 2.1 Hz, 6-H), 7.11 (s, 2H, 4'(5')-H), 6.55 (d, 1H, *J* 5.4 Hz, 3-H), 3.65 (t, 2H, *J* 6.2 Hz, 3'-H), 3.48 (q, 2H, *J* 6.1 Hz, 1'-H), 2.03-1.99 (m, 2H, 2'-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 169.5, 155.3, 153.4, 148.7, 134.9, 136.1, 130.1, 124.8, 121.5, 117.3, 99.0, 40.9, 39.0, 25.9.

1-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-3-methyl-1H-pyrrol-2,5-dione (17): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.44 (d, 1H, *J* 5.4 Hz, 2-H), 8.06 (d, 1H, *J* 9.1 Hz, 5-H), 7.79 (d, 1H, *J* 2.3 Hz, 8-H), 7.45 (dd, 1H, *J* 2.2 and 9.0 Hz, 6-H), 7.36 (t, 1H, *J* 7.0 Hz, NH), 6.56 (d, 1H, *J* 5.5 Hz, 3-H), 5.76 (s, 1H, 3'-H), 4.03 (q, 2H, *J* 7.1 Hz, 2'-H), 3.44 (m, 2H, 1'-H), 1.59 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 173.9, 169.8, 154.5, 153.3, 150.1, 145.6, 135.1, 129.3, 128.6, 124.7, 121.5, 118.0, 98.91, 46.6, 51.1, 10.9.

1-(3-((7-Chloroquinolin-4-yl)amino)propyl)-3-methyl-1H-pyrrol-2,5-dione (18): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.39 (d, 1H, *J* 5.4 Hz, 2-H), 8.16 (d, 1H, *J* 9.1 Hz, 5-H), 7.79 (d, 1H, *J* 2.3 Hz, 8-H), 7.45 (dd, 1H, *J* 2.1 and 9.1 Hz, 6-H), 7.38 (t, 1H, *J* 7.0 Hz, NH), 6.59 (d, 1H, *J* 5.4 Hz, 3-H), 5.78 (s, 1H, 4'-H), 4.13 (q, 2H, *J* 7.1 Hz, 3'-H), 3.46 (m, 2H, 1'-H), 2.02 (m, 2H, 2'-H) 1.61 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 174.0, 170.1, 154.5, 152.8, 149.3, 145.4, 134.7, 128.8, 127.8, 124.8, 121.6, 117.5, 99.1, 41.3, 39.4, 26.1, 10.9.

2-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-4,7-dihydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (**19**): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.43 (d, 1H, *J* 5.3 Hz, 2-H), 8.09 (d, 1H, *J* 9.0 Hz, 5-H), 7.80 (d, 1H, *J* 2.0 Hz, 8-H), 7.45 (dd, 1H, *J* 9.0, 2.1 Hz, 6-H), 7.41 (t, 1H, *J* 5.8 Hz, NH), 6.58 (d, 1H, *J* 5.4 Hz, 3-H), 6.55 (s, 2H, 5'-H), 5.12 (s, 2H, 4'-H), 3.62 (t, 2H, *J* 6.6 Hz, 2'-H), 3.44-3.41 (m, 2H), 2.93 (s, 2H, 3'-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 173.2, 154.7, 152.7, 150.1, 142.6, 135.4, 134.9, 129.3, 124.8, 121.6, 118.2, 99.2, 87.9, 51.4, 46.6.

2-(3-((7-Chloroquinolin-4-yl)amino)propyl)-4,7-dihydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (**20**): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.38 (d, 1H, *J* 5.4 Hz, 2-H), 8.23 (d, 1H, *J* 9.0 Hz, 5-H), 7.78 (d, 1H, *J* 2.1 Hz, 8-H), 7.45 (dd, 1H, *J* 8.9, 2.0 Hz, 6-H), 7.28 (t, 1H, *J* 5.2 Hz, NH), 6.55 (s, 2H, 6'-H), 6.40 (d, 1H, *J* 5.5 Hz, 3-H), 5.15 (s, 2H, 5'-H), 3.50 (t, 2H, *J* 6.8 Hz, 1'-H), 3.22 (m, 2H, 3'-H), 2.93 (s, 2H, 4'-H), 1.90-1.81 (m, 2H, 2'-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 172.9, 154.3, 152.7, 149.2, 142.5, 135.3, 135.1, 129.2, 124.9, 121.6, 117.5, 98.9, 88.3, 41.1, 39.8, 26.6.

2-(2-((7-Chloroquinolin-4-yl)amino)ethyl)isoindoline-1,3-dione (**21**): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 (d, 1H, *J* 5.4 Hz, 2-H), 8.05 (d, 1H, *J* 9.0 Hz, 5-H), 7.85-7.80 (m, 4H, H_{Ar}), 7.78 (d, 1H, *J* 2.1 Hz, 8-H), 7.51 (t, 1H, *J* 6.0 Hz, NH), 7.41 (dd, 1H, *J* 9.0, 2.2 Hz, 6-H), 6.63 (d, 1H, *J* 5.4 Hz, 3-H), 3.83 (t, 2H, *J* 6.1 Hz, 2'-H), 3.61-3.56 (m, 2H, 1'-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 167.9, 155.3, 153.7, 150.2, 134.9, 132.2, 132.0, 129.3, 124.8, 123.7, 121.5, 117.6, 99.2, 51.4, 46.6.

2-(3-((7-Chloroquinolin-4-yl)amino)propyl)isoindoline-1,3-dione (**22**): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.36 (d, 1H, *J* 5.4 Hz, 2-H), 8.19 (d, 1H, *J* 9.0 Hz, 5-H), 7.84-7.79 (m, 4H, H_{Ar}), 7.76 (d, 1H, *J* 2.2 Hz, 8-H), 7.42 (dd, 1H, *J* 9.0, 2.2 Hz, 6-H), 7.28 (t, 1H, *J* 5.4 Hz, NH), 6.45 (d, 1H, *J* 5.5 Hz, 3-H), 3.71 (t, 2H, *J* 6.9 Hz, 1'-H), 3.34-3.29 (m, 2H, 3'-H), 2.05-1.98 (m, 2H, 2'-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 168.1, 154.3, 153.1, 149.2, 135.1, 132.2, 132.0, 129.4, 124.8, 124.5, 121.6, 117.5, 98.9, 55.7, 40.9, 26.1.

Supplementary Information

Supplementary information (Figures S1-S20) is available free of charge at <http://jbcs.s bq.org.br> as PDF file.

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