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Short Communication

Synthesis, Characterization, Crystal Structure and Antimalarial Activity of (2*E*)-2-(1-{4-[(7-chloroquinolin-4-yl)amino]phenyl} ethylidene)hydrazine Carbothioamide

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Abstract: A simple synthesis and study by UV-vis, IR, NMR, ESI-CID-MS^2 and X-ray diffraction of ((2E)-2-(1-{4-[(7-chloroquinolin-4-yl)amino]phenyl}ethylidene)hydrazinecarbothioamide is reported. It was tested in vitro against chloroquine-resistant strain (W2) of Plasmodium falciparum, hemozoin (β-hematin) formation and cysteine protease falcipain-2. In general, it was found to possess a proved activity in its inhibitory power on the parasite but less active on the formation of hemozoin (β-hematin) and falcipain-2. Also, the X-ray analysis presented an unexpected electronic density that can be assigned like S(2). This electronic density can be attributed to autocondensation of thiosemicarbazide, generating H_2S as a subproduct.

Keywords: thiosemicarbazones; antimalarial activity; crystal structure

1. INTRODUCTION

Thiosemicarbazones have been listed as compounds of multiple biological actions, including antimalarial activity [1-5]. Therefore, its structural coupling with leader molecules, in this case derived from [(7-chloroquinolin-4-yl)amino]-acetophenone [6], it could be an effective chemical-medicinal strategy against this parasitic disease. As part of our research on the synthesis and biological evaluation of thiosemicarbazones with potential antimalarial activity, we report here the synthesis of (2*E*)-2-(1-{4-[(7-chloroquinolin-4-yl)amino]phenyl} ethylidene)hydrazine carbothioamide, and its structural characterization on the basis of UV-vis, IR, ESI-CID-MS^2, NMR spectral data and single crystal X-ray diffraction data.

2. MATERIAL AND METHODS

Melting point was determined on a Stuart Scientific Digital Melting Point Apparatus SMP3. IR spectrum was determined as KBr pellet on a Shimadzu model 8400 spectrophotometer. The spectra in the UV-vis was recorded from solution of compound, at concentration 10^{-5} M, in a Genesys 10S UV-vis scanning spectrophotometer (Thermo Electron Corporation) equipped with a high-intensity xenon lamp and quartz cell of 10 cm. The spectrum was taken in a 190-1100 nm scan range, at medium speed and a photometric absorbance range between 0.0-3.0 Å. The ^{1}H NMR, ^{13}C NMR spectra were

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recorded using a Jeol Eclipse 270 (270 MHz/67.9 MHz) spectrometer using DMSO-d6, and are reported in ppm downfield from the residual DMSO. Accurate mass measurement was performed on a Finnigan/Thermo TSQ Quantum triple Quadrupole Mass Spectrometer. Chemical reagents were obtained from Aldrich Chemical Co, USA. All solvents were distilled and dried in the usual manner.

Synthesis of (2E)-2-(1-{4-[(7-chloroquinolin-4-yl) amino]phenyl}ethylidene)hydrazine carbothioamide (3)

Acetophenone **1** (0.5 g, 1.68 mmol) was dissolved in dry methanol (20 mL) until a clear solution. Subsequently, thiosemicarbazide **2** (0.16 g, 1.75 mmol) and glacial acetic acid (0.3 mL) were added, the mixture was heated under reflux (65 °C) at pH 4.0 and constant stirring until the reaction was completed at 7 hours (monitoring by TLC). The solvent was evaporated in vacuo, the solid was isolated by suction, washed with methanol by triplicate and recrystallised off DMF-methanol (1:5) to afford the title compound, yield 61.5%; mp. 296-298 °C; Rf = 0.4 (EtAc:Hx 7:3); IR (KBr) cm^{-1}: 3427.62; 3197.12; 3104.53 ν(N-H) NH-CS-NH_2; 3100-3000 ν(C-H) aromatic; 3000-2800 ν(C-H) aliphatic; 1616.40 ν(C=C) aromatic; 1590.36 ν(C=N); ~1090 ν(C=S); 1090.78 ν(C-Cl). UV-vis (DMSO) [λ_{max}/nm, (ε/cm^{-1} M^{-1})]: 258 (2338), 318 (2690), 366 (3410). ^{1}H NMR DMSO-d_6: δ 2.34 (s, 3H, CH_3); 6.90 (d, 1H, H_3, $J_{2,3}$ = 6.9Hz); 7.50 (d, 2H, $H_{3',5'}$, $J_{2',3'}$ = $J_{5',6'}$ = 8.4Hz); 7.87 (dd, 1H, H_6, $J_{5,6}$ = 9.2Hz, $J_{6,8}$ = 2.0Hz); 8.02, 8.33 (2 broad s, 2H, NH_2); 8.14 (d, 2H, $H_{2',6'}$, $J_{2',3'}$ = $J_{5',6'}$ = 8.4Hz); 8.19 (d, 1H, H_8, $J_{6,8}$ = 2.0Hz); 8.55 (d, 1H, H_2, $J_{2,3}$ = 6.9Hz); 8.90 (d, 1H, H_5, $J_{5,6}$ = 9.2Hz); 10.30 (broad s, 1H, N-NH-CS); 11.25 (broad s, 1H, Ar-NH-Ar). ^{13}C NMR: 13.30 (CH_3); 100.4; 116.00; 119.21; 124.15; 125.88; 126.72; 127.51; 128.00; 137.74; 137.88; 139.27; 143.22; 146.61 (C-aromatics); 154.02 (C=N); 179.2 (C=S). m/z (ESI): 370.04 $[M+H]^+$; Exact mass, calcd. for $C_{18}H_{17}ClN_5S$ $[M+H]^+$: 370.09. Found: 370.04. m/z (ESI-CID-MS^2): 370.03 (19) $[M+H]^+$, 353.28 (12), 294.51 (4), 280.10 (100), 254.14 (33).

Single Crystal X-ray Data Collection and Structure Determination

The single crystal X-ray diffraction data was carried out on a KAPPA APEX II DUO Diffractometer, with graphite monochromator and Mo-Kα radiation (λ=0.71069 Å) operating at 50 kV and 30 mA. A total of 3387 frames were collected with ϕ and ω scans at every 0.30° for 10 s each. Data collections and unit cell refinement were carried out with SMART [7] and data reduction with SAINT [8].

The integration of the data using a triclinic unit cell yielded a total of 12272 reflections to a maximum θ angle of 49.99°, of which 3387 were independent (Rint = 3.74%, Rsig = 4.08%) and 2430 were greater than 2σ(F2). The final cell constants of a = 9.1204(7) Å, b = 10.8893(9) Å, c = 11.1300(9)Å, α = 85.013(2)º, β = 72.957(2)º , γ = 67.152(2) º, volume = 973.46(14)$Å^3$, (Table 1).

The structure was solved and refined using the Bruker SHELXTL Software Package [9]. The non-hydrogen atoms were refined anisotropically, while the hydrogen atoms bound to C atoms were placed geometrically and refined using a *Riding model*, with C—H = 0.93 Å, Uiso(H) = 1.2 Ueq(C) for aryl H; C—H = 0.96 Å, Uiso(H) = 1.2 Ueq(C) for methyl H; N—H = 0.86 Å and Uiso(H) = 1.2Ueq(N). The final anisotropic full-matrix least-squares refinement on F2 with 263 variables converged at R1 = 4.60%, for the observed data and wR2 = 13.35% for all data. The goodness-of-fit was 1.05. The largest peak in the final difference electron density synthesis was 0.50 e-/$Å^3$ and the largest hole was -0.27 e-/$Å^3$. On the basis of the final model, the calculated density was 1.436 g/cm^3 and F(000), 438 e-. The details of crystal data and refinement are given in Table 1.

Comprehensive crystallographic data (excluding structure factors) for the structural analysis of **3** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data (CIF file) can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44-(0)1223-336033, or from https://summary.ccdc.cam.ac.uk/structure-summary-form, quoting deposition No. CCDC 1413401.

3. RESULTS AND DISCUSSION

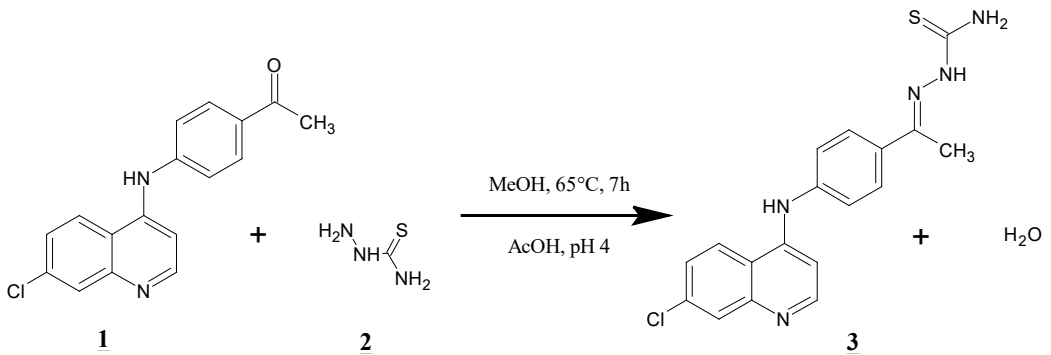
Synthesis of 4-[(7-chloroquinolin-4-yl)amino]acetophenone (**1**) was carried out by refluxing of 4,7-dichloroquinoline with 4-aminoacetophenone in ethanol [6]. Thiosemicarbazone (**3**) was obtained from a solution of equimolar amounts of acetophenone **1** and thiosemicarbazide (**2**) in methanol, with constant stirring for 7 hours at 65 °C and pH 4.0. TLC (EtAc:Hx 7:3) showed only a compound produced

(Scheme 1). Spectroscopic data (^{1}H and ^{13}C NMR) show that compound **3** was a product of a reaction of nucleophilic addition, because of the following spectral evidence: three ^{1}H resonances are observed due to chemical function NH_2 and NH (N-NH-CS) at 8.02, 8.33 and 10.30 ppm; respectively. Also, as can be seen, a remarkable upfield shifting effect on the chemical shift value of protons and carbon in the methyl group, with a ^{1}H resonance at 2.62 ppm in **1** and 2.34 ppm in **3**, and a ^{13}C resonance at 27.21 ppm in **1** and 13.30 ppm in compound **3**.

Table 1. Crystal data, intensity data collection parameters and final refinement results for compound **3**.

CCDC deposit No.	**CCDC 1413401**
Crystal Data	
Formula	C18 H19 Cl N5 S2 O1
Formula Weight	420.97
Crystal System	Triclinic
Space group	P-1(No.2)
a, b, c [Angstrom]	9.1204(7), 10.8893(9), 11.1300(9))
alpha, beta, gamma [deg]	85.013(2), 72.957(2), 67.152(2)
V [Ang^3]	973.46(14)
Z	2
D(calc) [g/cm^3]	1.436
Mu(MoKa) /mm]	0.430
F(000)	438
Crystal Size [mm]	0.05 x 0.36 x 0.42
Data Collection	
Temperature (K)	571
Radiation [Angstrom] MoKa	0.71073
Theta Min-Max [Deg]	1.9, 25.0
Dataset	-10: 10; -12: 12; -13: 13
Tot., Uniq. Data, R(int)	12272, 3387, 0.037
Observed Data [I > 2.0 sigma (I)]	2430
Refinement	
Nref, Npar	3387, 263
R, wR2, S	0.0460, 0.1335, 1.05
Max. and Av. Shift/Error	0.00, 0.00
Min. and Max. Resd. Dens. [e/Ang^3]	-0.27, 0.50

This upfield shifting suggests a protective effect (*shielding*) on the carbon and hydrogen atoms due to the steric effect exerted by the –$NHCSNH_2$ group. The chemical shift value found for the carbon atom of the methyl group falls within the range reported in the literature for thiosemicarbazones derived from acetophenones, ranging between 10 to 15 ppm when methyl group is located in *syn* position relative to NHCSNHR group [10-12]. NMR data suggest that compound **3** has *E* geometry.



Scheme 1. Synthesis of (2*E*)-2-(1-{4-[(7-chloroquinolin-4-yl)amino]phenyl}ethylidene) hydrazine carbothioamide (**3**).

The ESI-MS technique confirmed the obtaining of **3**. Signals to *m/z* 370 corresponding to the molecular ion $[C_{18}H_{16}ClN_5S + H]^+$ (figure 1a and 1b) and four signals to *m/z* 353.28 (12%), 294.51 (4%), 280.10 (100%) and 254.14 (33%) were recorded (Figure 1b).

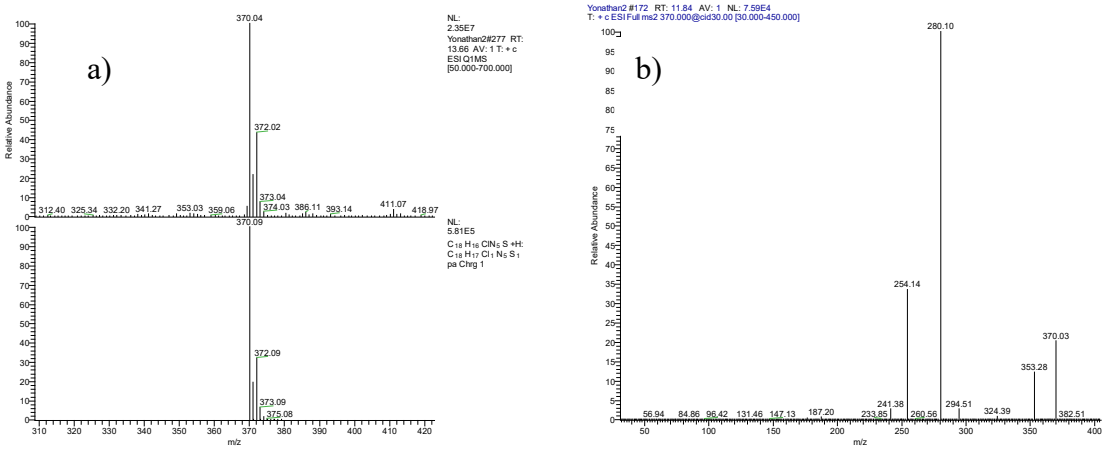


Figure 1. a) ESI spectrum in positive mode of (2*E*)-2-(1-{4-[(7-chloroquinolin-4-yl)amino]phenyl}ethylidene)hydrazine carbothioamide (**3**) b) CID Product ion spectrum of protonated **3** by MS-MS.

CID-MS^2 mass spectrum shows that a proton transfers from the quinolinic-N atom to N-4 atom of the thiosemicarbazone occur before fragmentation of quasi-molecular ion (ion precursor). Subsequently, relevant fragmentations were essentially based on concomitant loss of small molecules and radicals (such as ammonia, thiocyanate radical, methyl radical and hydrogen cyanide) in the sequence: 370 → 353 → 295 → 280 → 254 (Figure 2). These peaks agree with molecular mass and structure of thiosemicarbazone **3**.

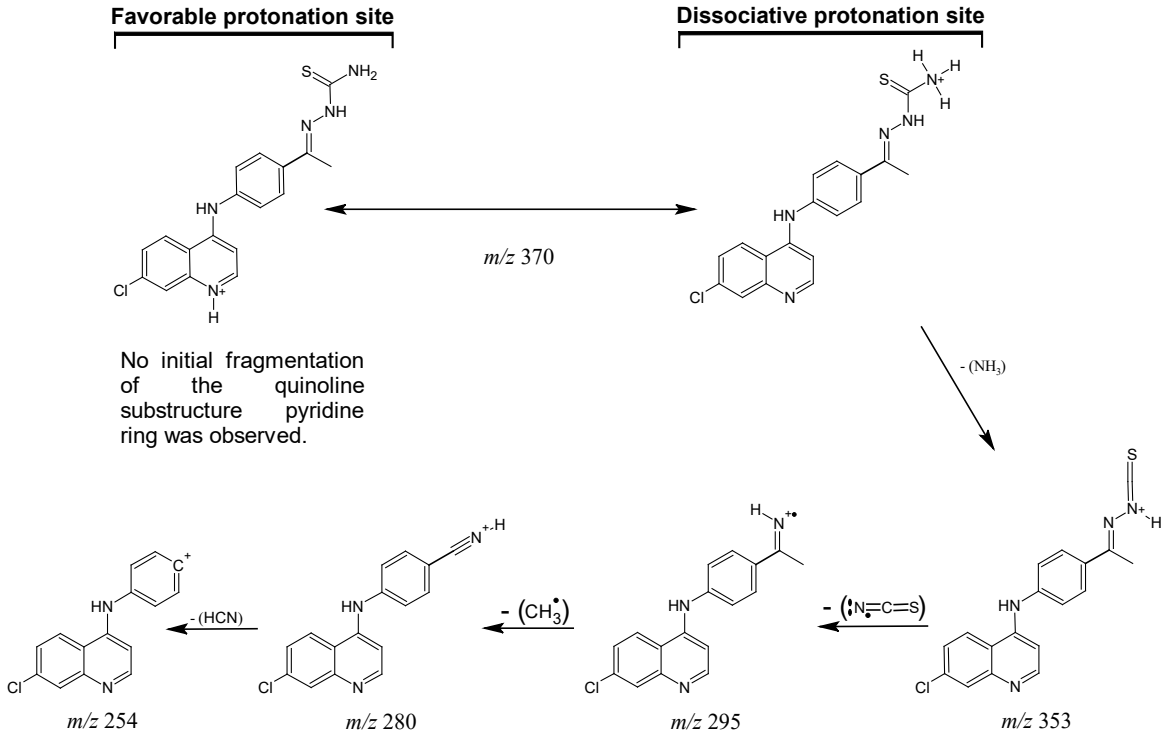


Figure 2. Proposed MS/MS fragmentation mechanism for protonated (2*E*)-2-(1-{4-[(7-chloroquinolin-4-yl)amino]phenyl}ethylidene)hydrazine carbothioamide (**3**).

The X-ray analysis confirmed the molecular structure of compound **3**. A previous search in the Cambridge Structural Database (CSD) [13] has not produced any results. Tables 2 and 3 contain relevant bond lengths and angles for compound **3**, as well as hydrogen bond geometries as calculated with PLATON [14]. Figure 3 show the molecular structure of compound **3** with the atom numbering scheme. Graphics were obtained using Diamond 3.0 [15].

Table 2. Selected bond lengths (Å) and angles (°) for compound **3**.

Cl1-C7	1.736(4)	**C4-C10**	1.447(5)
S1-C9a	1.680(4)	**C4a-C5a**	1.393(5)
N3a-C1a	1.423(4)	**C4a-C7a**	1.477(5)
N4a-C9a	1.327(4)	**C5-C6**	1.360(5)
N1-C2	1.327(5)	**C5-C10**	1.412(5)
N1-C9	1.373(4)	**C5a-C6a**	1.376(5)
N1a-C7a	1.280(5)	**C6-C7**	1.402(4)
N1a-N2a	1.379(4)	**C7-C8**	1.354(6)
N2a-C9a	1.352(5)	**C7a-C8a**	1.500(5)
N3a-C4	1.339(4)	**C8-C9**	1.399(5)
C2a-C3a	1.374(5)	**C9-C10**	1.403(4)
C3-C4	1.405(6)	**C1a-C6a**	1.377(5)
C3a-C4a	1.389(5)	**C1a-C2a**	1.386(5)
N2a-N1a-C7a	119.2(3)	**Cl1-C7-C6**	118.5(3)
N1a-N2a-C9a	117.9(3)	**Cl1-C7-C8**	120.1(2)
N1a-N2a-H1	125(3)	**C1a-N3a-C4**	129.4(3)
H5a-N4a-H5b	121(4)	**C1a-C2a-C3a**	120.0(3)
N3a-C1a-C6a	116.9(3)	**C1a-C6a-C5a**	120.7(3)
N3a-C1a-C2a	124.2(3)	**C2a-C1a-C6a**	118.9(3)
N3a-C4-C3	123.6(3)	**S1-C9a-N2a**	120.9(3)
N1a-C7a-C4a	115.9(3)	**S1-C9a-N4a**	122.1(3)
N1a-C7a-C8a	125.4(3)	**C4a-C7a-C8a**	118.8(3)
N1-C2-C3	122.9(4)	**C7-C8-C9**	119.2(3)
N1-C9-C8	119.4(3)	**C2-C3-C4**	119.7(3)
N1-C9-C10	119.3(3)	**C8-C9-C10**	121.3(3)
N2a-C9a-N4a	117.0(3)	**C6-C7-C8**	121.3(3)
N3a-C4-C10	119.3(3)	**C5-C10-C9**	117.2(3)
C9a-N4a-H5a	119(3)	**C4-C10-C9**	119.1(3)
C9a-N4a-H5b	120(3)	**C4-C10-C5**	123.7(3)
C2-N1-C9	121.1(3)	**C3a-C4a-C5a**	117.2(3)
C5a-C4a-C7a	121.2(3)	**C4a-C5a-C6a**	121.2(3)
C3a-C4a-C7a	121.7(3)	**C5-C6-C7**	119.5(4)
C2a-C3a-C4a	121.9(3)	**C3-C4-C10**	117.0(3)
C6-C5-C10	121.4(3)		

Like shown in Figure 3, compound **3** not present geometry planar, and the dihedral angle between the A/C ring and B ring is 26.56º. This compound exhibit one molecule of water in its crystal packing. Furthermore, also present an electronic density that can be assigned like S(2). This electronic density can be attributed to autocondensation of thiosemicarbazide, generating H_2S as a subproduct.

The crystal structure present ten (10) hydrogen bonds pattern intra and intermolecular and Table 3 shows the geometrical parameters. The bonds N(2a)-H(1)…S(1) [2.66Å, 159º] and C(8a)-H(8aa)…S(1) [2.75Å, 132º] occurs between two neighboring molecules in order to generate hydrogen bonding pattern in the form of finite dimer; in which the S1 atom, acts as an acceptor bifurcated (Figure 4). Each hydrogen bonding pattern can be described with graph set symbol $R^2_2(8)$ and $R^2_2(14)$, respectively.

Compound **3** also present two intermolecular p-interaction perpendicular to the hydrogen bonds patterns above described. This interaction involve atoms C(7)-Cl(1)…Cg(1) [3.78 Å, 70,26º] and C(7)-

Cl(1)… Cg(2) [3.61 Å, 96.85º] where Cl(1) is connected parallelly above and below with Pi-ring-A and Pi-ring B, generate a infinite chain growing diagonally in *bc* plane. Cg1 and Cg2 correspond to centroid of the A-ring and B-ring, respectively.

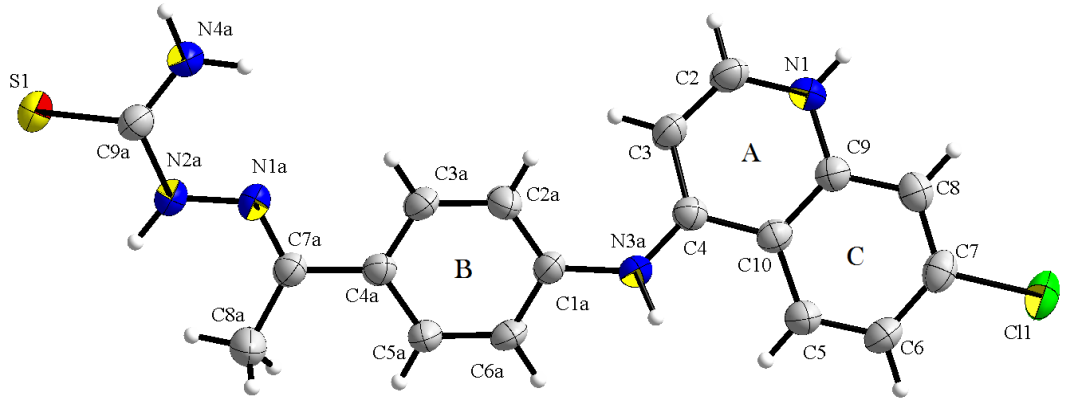


Figure 3. Molecular structure of compound **3** showing the atomic numbering. The displacement ellipsoids are drawn at 50% probability.

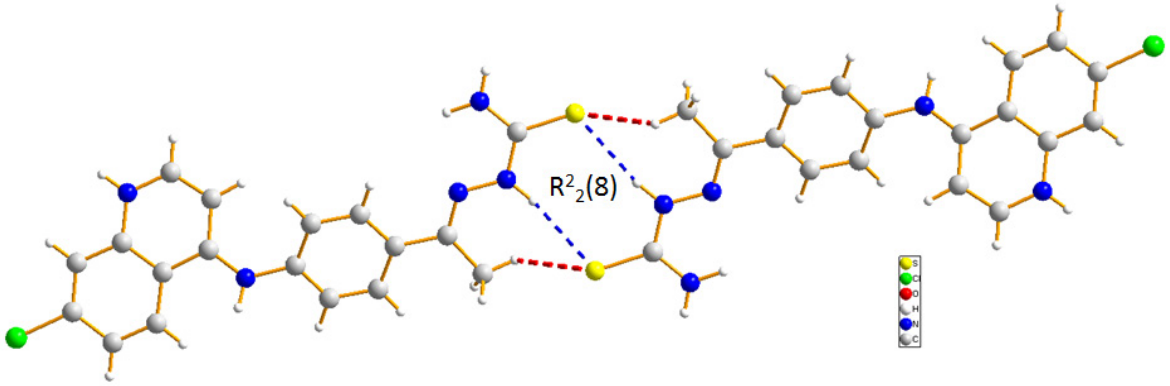


Figure 4. Part of the crystal structure of compound **3** showing the formation of a hydrogen-bonded $R^2_2(8)$ dimer.

Table 3. Possible hydrogen bonds for **3** (Å and °).

Bond	**D-H**	**H…A**	**D…A**	**D-H..A**	**Symmetry**	**Graph**
N(2a)-H(1)...S(1)	0.94(4)	2.66(4)	3.553(3)	159(3)	2-x,2-y,-z	$R^2_2(8)$
O(1)-H(1a)...S(2)	0.81(5)	2.32(5)	3.105(4)	162(4)	-x,1-y,1-z	D3
O(1)-H(1b)...S(2)	0.96(6)	2.23(6)	3.168(3)	167(6)	.	D3
N(3a)-H(31)...S(2)	0.8600	2.3700	3.189(3)	159.00	.	D3
N(4a)-H(5b)...S(2)	0.98(4)	2.47(4)	3.258(3)	137(4)	1+x,y,z	D3
N(4a)-H(5b)...N(1a)	0.98(4)	2.22(5)	2.601(5)	101(3)	.	S5
N(1)-H(11)...O(1)	0.8600	1.8500	2.700(4)	171.00	1+x,-1+y,z	
C(5)-H(5)...S(2)	0.9300	2.7700	3.561(3)	144.00	.	D3
C(8a)-H(8aa)...N(2a)	0.9600	2.4200	2.821(6)	105.00	.	S5
C(8a)-H(8aa)...S(1)	0.9600	2.7500	3.467(4)	132.00	2-x,2-y,-z	$R^2_2(14)$
Short Contacts Y–X…Cg	**Y–X**	**X…Cg**	**Y…Cg**	**Y–X–Cg**		
C(7)-Cl(1)…Cg(1)	1.736(4)	3.7806(2)	3.588(3)	70.26(11)	1-x,-y,1-z	
C(7)-Cl(1)…Cg(2)	1.736(4)	3.6145(2)	4.192(3)	96.85(12)	x,-1+y,z	

Cg1 is the centroid of the A- ring and Cg2 is the centroid of the B- ring.

Parallel to this interaction is observed that the water molecule is also involved in a hydrogen bond pattern finite with the compound **3** and involve the atoms N(1)-H(11)…O(1) [1.85Å, 171º] and O(1)-H(1a)...S(2) [2.32 Å, 162º] and O(1)-H(1b)...S(2) [1.23Å, 167º]. This hydrogen bond pattern connect the layers of compound **3** which grow parallel each other in the direction ***b***. The graph set symbol that

describes this kind of hydrogen bond pattern finite is D(3). The intramolecular hydrogen bond with atoms N(4a)-H(5b)…N(1a) [2.22 Å, 101º] and C(8a)-H(8aa)…N(2a) [2.42 Å, 105º] observed in compound **3** can be described by the graph set symbol S(5).

Compound **3** was investigated to determine its in vitro antimalarial activity against chloroquine-resistant strain (W2) of *Plasmodium falciparum*, hemozoin (β-hematin) formation and cysteine protease falcipain-2; using methodology previously reported [4, 16, 17]. The evaluated compound shows antiplasmodial activity at low 50% inhibitory concentration (IC_{50}), with value of 0.45 µM ± 0.0699. This confirms that our medicinal chemistry strategy of molecular hybridization based in leader compounds is effective against this parasitic disease.

Compound **3** also showed a 58.89 ± 0.281% inhibition of the formation of hemozoin (% IFβH), a low value when compared to the control of chloroquine (91.44 ± 0.02 %IFβH). The inhibitory capacity of **3** on the cysteine protease recombinant falcipain-2 was not significant (IC_{50} > 50 µM). In general, thiosemicarbazone **3** proved to be very active in its inhibitory power on the parasite but less active on the formation of hemozoin (β-hematin) and falcipain-2, which allows us to suggest that the biochemical mechanism that justifies the antiplasmodial activity of this compound must be other than to interactions with the ferriprotoporphyrin IX (heme) and the cysteine protease.

4. CONCLUSION

The synthesis and obtaining of ((2E)-2-(1-{4-[(7-chloroquinolin-4-yl)amino]phenyl}ethylidene) hydrazinecarbothioamide was confirmed by their physical constants, UV-vis, IR, ESI-CID-MS^2, NMR spectral data and single crystal X-ray diffraction data. In general, it was found to possess a proved activity in its inhibitory power on the parasite but less active on the formation of hemozoin (β-hematin) and falcipain-2. Also, the X-ray analysis presented an unexpected electronic density that can be assigned like S(2). This electronic density can be attributed to autocondensation of thiosemicarbazide, generating H_2S as a subproduct.

5. ACKNOWLEDGMENTS

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