Synthesis and crystal structure of ethyl 7-chloro-3-amino-9-(4-bromophenyl)thieno-[3,2-b]benzothiazine 4,4-dioxide 2-carboxylate

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The X-ray crystal structure of 7-chloro-3-amino-9-(4-bromophenyl)thieno-[3,2-b]benzothiazine 4,4-dioxide 2-carboxylate **1** is determined. The thiophene ring and the exocyclic ester group adopt a co-planar conformation, which is stabilised by an intramolecular hydrogen bond. The moderate antimalarial activity shown by this compound appears to be related to the formation of such an intramolecular N–H···O =C hydrogen bond.

Keywords: benzothiazine, crystal structure, antimalarial

Malaria is believed to affect some 300 to 500 million people worldwide and to cause one to three million deaths each year. Infection with this disease is increasing *Plasmodium falciparum*, responsible for the most malignant form of malaria, has developed resistance to chloroquine which is the most widely used antimalarial drug.[1] There is an urgent need for new antimalarial drugs.[2,3] As part of a general project we have begun to develop new, more effective, antimalarial drugs, and a number of quinoline, quinolone, pyrimidone, pyridopyrimidone, thiocromone and pyrazole derivatives have been synthesised, characterised and tested for antimalarial activity.[4-8]

Recently, we synthesised several *N*-methylated tricyclic quinolones that were found to have moderate *in vitro* and *in vivo* activity against a chloroquine resistant strain of *P. falciparum*.[9,10] Among these derivatives, the biological results suggested that **1** displayed a moderate antimalarial activity which was associated with the formation of an intramolecular N–H···O =C hydrogen bond (*vide infra*). In order to confirm the presence of such a structural feature and to gain more insight into this structure–activity correlation, we have studied the single-crystal X-ray structure of **1**.

Compound **1** was synthesised starting from *N*-(4-bromophenyl)-3-methylsulfinyl-4H-1,4-benzothiazine 1,1-dioxide 2-carbonitrile and ethyl mercaptoacetate as shown in Scheme 1. In order to confirm the structure, the product was subjected to spectroscopic analysis using IR, ^{1}H and ^{13}C NMR and elemental analysis. Crystals of suitable quality for single-crystal X-ray diffraction were obtained by slow evaporation from an EtOH solution. Molecular structure of **1** is shown in the Fig. 1. All bond lengths are in good agreement with the tabulated standard values (Table 1).[11] As anticipated the atoms that form the rings A, B and C (see Fig. 1) lie essentially in the same plane (mean deviation: 0.025 Å) in which the maximum deviations correspond to S1 (0.069 Å) and S2 (0.056 Å) atoms. Conversely, the ring D is roughly perpendicular to the plane defined by the atoms of the fused-rings A/B/C with a dihedral angle between such planes of 81.9(1)°. A striking feature of **1** is that the mean plane (mean deviation: 0.0763 Å), defined by the atoms of the exocyclic (O4/C17/O3/C18/C19) ester, is almost co-planar to the thiophene ring A with a dihedral angle of only 1.5(4)°. The relative co-planar conformation, adopted by the ester group, appears to be associated with an intramolecular N2–H2b···O4 [N2···O4: 2.799(6) Å] hydrogen bond between the carboxy oxygen atom of the ester and the amine N2 donor of the thiazole moiety (Table 2).

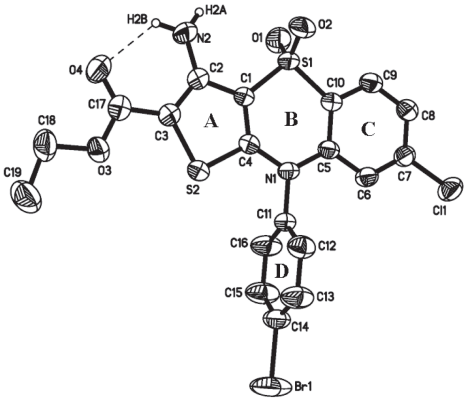
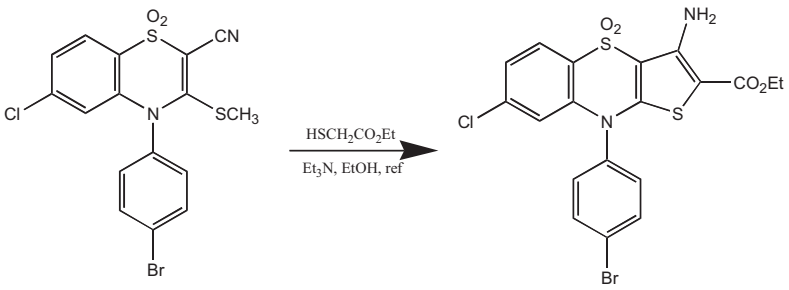


Fig. 1 Graphical representation of **1**. Rings are labelled to facilitate the discussion. Ellipsoids are given at 50% probability.



Scheme 1

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Table 1 Selected bond lengths (Å) and angles (°) for **1**

S(1)–O(1)	1.435(3)	N(1)–C(5)	1.405(4)	C(7)–C(8)	1.373(5)
S(1)–O(2)	1.442(3)	N(1)–C(11)	1.449(4)	C(8)–C(9)	1.376(5)
S(1)–C(1)	1.717(3)	Cl(1)–C(7)	1.738(3)	C(9)–C(10)	1.404(5)
S(1)–C(10)	1.746(3)	Br(1)–C(14)	1.893(4)	C(11)–C(12)	1.365(5)
S(2)–C(4)	1.730(3)	C(1)–C(4)	1.366(5)	C(11)–C(16)	1.369(5)
S(2)–C(3)	1.744(4)	C(1)–C(2)	1.432(5)	C(12)–C(13)	1.377(6)
O(3)–C(17)	1.343(5)	C(2)–C(3)	1.382(5)	C(13)–C(14)	1.367(6)
O(3)–C(18)	1.463(4)	C(3)–C(17)	1.447(5)	C(14)–C(15)	1.364(6)
O(4)–C(17)	1.206(5)	C(5)–C(10)	1.398(5)	C(15)–C(16)	1.376(6)
N(2)–C(2)	1.349(5)	C(5)–C(6)	1.402(5)	C(18)–C(19)	1.471(7)
N(1)–C(4)	1.382(4)	C(6)–C(7)	1.382(5)		

O(1)–S(1)–O(2)	115.41(19)	C(5)–N(1)–C(11)	120.9(3)
O(2)–S(1)–C(1)	110.78(17)	N(2)–C(2)–C(3)	125.3(3)
O(2)–S(1)–C(1)	110.07(18)	N(2)–C(2)–C(1)	124.0(3)
O(1)–S(1)–C(10)	109.80(18)	C(12)–C(11)–C(16)	119.3(3)
C(1)–S(1)–C(10)	100.91(16)	C(12)–C(11)–N(1)	120.3(3)
C(17)–O(3)–C(18)	115.3(3)	C(16)–C(11)–N(1)	120.4(3)
C(2)–N(2)–H(2A)	126.9	O(4)–C(17)–O(3)	123.6(3)
C(2)–N(2)–H(2B)	124.6	O(4)–C(17)–C(3)	112.9(3)
H(2A)–N(2)–H(2B)	99.4	O(3)–C(18)–C(19)	107.8(4)
C(4)–N(1)–C(5)	120.6(3)		
C(4)–N(1)–C(11)	118.2(3)		

Table 2 Hydrogen bonds geometry for **1**

D–H···A	D–H	H···A	D···A	D–H···A	Symmetry codes
N(2)–H(2B)···O(4)	0.89	2.29	2.799(6)	116.0(1)	Intramolecular
N(2)–H(2A)···O(1)	0.94	2.17	3.017(5)	148.7(1)	1–*x*,1–*y*,1–*z*
N(2)–H(2B)···O(2)	0.89	2.63	3.355(5)	139.3(1)	1 + *x*,*y*,*z*
C(9)–H(9A)···O(2)	0.93	2.35	3.226(5)	157.2(1)	2–*x*,1–*y*,1–*z*
C(12)–H(12A)···O(3)	0.93	2.45	3.329(5)	158.3(1)	1 + *x*,*y*,*z*
C(16)–H(16A)···Cl(1)	0.93	2.80	3.678(5)	158.3(1)	–1 + *x*,*y*,*z*

This intramolecular interaction favours the formation of a six-membered ring in which the plane of the NH_2 group adopts a co-planar orientation with the plane of ring A and that of the ester group.

It was found that the antimalarial activity of tricyclic benzothiazine appear to be related with some structural features, among which a N2–H2b···O4 intramolecular hydrogen bond type has been invoked.[9] The moderate activity as an inhibitor of globin proteolysis could be related with this strong hydrogen bond that decrease the availability of the NH_2 and CO groups to bind the proteolytic enzymes. Compound **1** was tested for their capacity of inhibiting globin proteolysis in an *in vitro* assay, which uses rich extract of the trophozoyte to digest the native haemoglobin of mice. The electrophoretic analyses (69.03 ±1.63%) indicated that **1** was moderate as inhibitors of globin degradation.

The NH_2 group is also involved in a close intramolecular contact with the sulfonyl atom O1 (H2a···O1: 2.73 Å, N2···O1: 3.27 Å and N2–H2a···O1: 117°). However, the acute S1–O1···H2a angle of 84° prevents any decisive strong hydrogen bond interaction. In its place, this group is involved in an intermolecular N2–H2a···O1 [N2···O1: 3.017(5) Å] hydrogen bond to form a dimeric moiety (Fig. 2a). The stacking of this dimeric unit in the *a*-direction leads to a columnar arrangement sustained by N2–H2b···O2 [N2···O1: 3.355(5) Å]. Attending its geometry (see Table 2) this interaction can be considered to be a hydrogen bond which is weaker than the N–H···O intramolecular interaction or that observed in the dimer unit. However, the columnar stacking is assisted by C–H···O Table 2 and π–π (range: 3.7–4.2 Å) interactions.

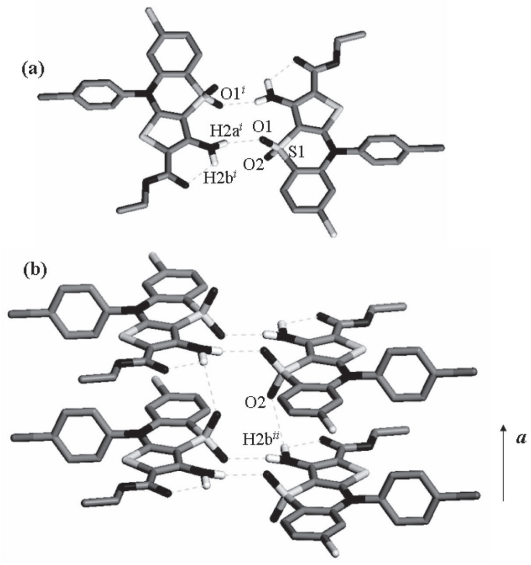

Fig. 2 (a) View of the dimer of **1** assembled *via* hydrogen bond. (b) Columnar arrangement along the *a*-axis. *symm. code*s (i) 1–*x*,1–*y*,1–*z*; (ii) 1 + *x*, *y*, *z*.

Experimental

All the reagents for synthesis were commercially available and used without further purification. Melting point was determined with a Fischer–Johns micro hot-stage apparatus and uncorrected. IR spectra were determined as KBr pellet on a Shimadzu model 470 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded using a Jeol Eclipse 270 MHz spectrometer in $CDCl_3$ and reported in ppm downfield from $CHCl_3$ residual. Elemental analysis was performed by Central Service of University of Málaga, Málaga, Spain, and the result was found to be within ±0.4% of predicted values for compound **1**. The starting material 6-chloro-4-(4-bromophenyl)-3-methylsulfinyl-4H-1,4-benzothiazine 1,1-dioxide 2-carbonitrile was prepared following the procedure previously described.[12] The capacity of inhibiting globin proteolysis in an *in vitro* assay of compound **1** was tested following the procedure previously reported.[5]

Table 3 Crystallographic data for **1**

Empirical formula	$C_{19}H_{14}BrClN_2O_4S_2$
Formula weight	513.81
Colour/Shape	Colourless/block
Temperature	295(2) K
Crystal system	Triclinic
Space group	P–1
Unit cell dimensions	a = 6.5342(5) Å; α = 74.047(5)°; b = 11.8433(9) Å; β = 81.753(6)°; c = 14.2353(11) Å; γ = 80.565(6)°
Volume, Z	1039.23(14), 2
Density (calculated), Mg/m^3	1.540
Absorption coefficient, mm^{-1}	2.324
F(000)	484
Theta range for data collection	3.00 to 55.74°
Limiting indices	$-6 \le h \le 7$, $-13 \le k \le 13$, $-17 \le l \le 17$
Reflections collected	3946
Independent reflections	2937 [R(int) = 0.034]
Data/restraints/parameters	3946/2/262
Goodness–of–fit on F^2	1.098
Final R indices [$I > 2\sigma$ (I)]	$R1$ = 0.0531, $wR2$ = 0.1729
R indices (all data)	$R1$ = 0.0531, $wR2$ = 0.1537
Largest diff. Peak and hole	0.561 and –0.926 eÅ^{-3}

Synthesis of ethyl 3-amino-7-chloro-9-(4-bromophenyl)thieno-[3,2-b]benzothiazine 4,4-dioxide 2-carboxylate **1**: 6-chloro-3-methylsulfinyl-4-(4-bromophenyl)-4H-1,4-benzothiazine 2-carbonitrile 1,1-dioxide (0.25 mmol), ethyl mercaptoacetate (0.25 mmol), triethylamine (4 ml) were dissolved in anhydrous ethanol (10 ml). The solution was refluxed for 5 h. The solvent was then removed under reduced pressure and the residue was dissolved in chloroform (100 ml), washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to dryness. The solid was purified by recrystallisation from ethanol to give colourless crystal in 75% yield; m.p. 244–246°C; IR (KBr): 3475, 3364; 1662, 1490, 1404, 1130, 1050; ^{1}H NMR ($CDCl_3$) δ: 1.26(t, 3H, CH_3, J = 7.5 Hz), 4.22(q, 2H, CH_2, J = 7.5 Hz), 6.22(brs, 2H, NH_2), 6.53(d, 1H, H_8, J = 1.7 Hz), 7.29(m, 3H, $H_{6,2',6'}$), 7.83(d, 2H, $H_{3',5'}$, J = 8.6 Hz), 8.04(d, 1H, H_5, J = 8.6 Hz). ^{13}C NMR: 14.6, 60.5, 90.8, 106.7, 116.1, 124.1, 124.3, 125.1, 125.8, 130.7, 135.1, 136.9, 139.3, 139.6, 149.3, 152.9, 163,7.

Anal. Calcd. for $C_{19}H_{14}BrClN_2O_4S_2$: C 44.41, H 2.75, N 5.45; found C 44.57, H 2.79, N 5.33.

X-ray analysis

Experimental crystallographic details are recorded in Table 3. A single crystal of size 0.63 × 0.25 × 0.13 mm was chosen for a single crystal X-ray diffraction study. The X-ray data were collected on a Rigaku diffractometer provided with a CCD detector. The data were reduced and processed using CrystalClear.[13] An empirical absorption correction was applied.[13] The structure was solved by direct methods using SHELXTL-PLUS.[14] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in their calculated positions, except for the hydrogen atoms of the NH_2 group which were considered from the found positions. All these atoms were refined by using the riding method. Refinements were done using SHELXTL-PLUS.[14] Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 614247). Copies of available materials can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (facsimile: (44) 01223 336033); e-mail: deposit@ccdc.ac.uk.

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