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SYNTHESIS AND STRUCTURAL STUDY OF SEMICARBAZONE-CONTAINING 1,4-DIHYDROPYRIDINE[§]

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[§]*Dedicated to Amaury Alvarez Espinosa who passed away on January 2006.*

Abstract – A new series of 1,4-dihydropyridines (1,4-DHPs) bearing a semicarbazone moiety on C5 (**8a-g**) have been synthesized from suitably functionalized 1,4-DHPs (**2**) and semicarbazide. Compounds (**8a-g**) did not cyclize to the respective seven member ring though this is a favoured 7-endo-*trig* process. Geometrical and structural features determined by theoretical, DFT (B3LYP/6-31G*) and experimental (X-Ray diffraction) data, reveal the presence of a low energy stereoisomer, namely (*E*) s-*trans*, which is also present in solution according to NOe experiments carried out on compound (**8a**). These geometrical findings account for the lack of cyclization of compounds (**8a-g**), and reveal that they meet the structural requirements needed for biological activity as calcium-channel modulators.

INTRODUCTION

In recent years, an increasing interest has been focused on the synthesis of modified 1,4-dihydropyridines compounds owing to their significant biological activity.[1] In particular, dihydropyridine drugs such as

nifedipine, nicardipine, amlodipine and others are effective cardiovascular agents for the treatment of hypertension.[2] 4-Aryl-1,4-dihydropyridines have been explored for their calcium channel activity and the heterocyclic rings are found in a variety of bioactive compounds such as vasodilator, bronchodilator, antioxidant, antiatherosclerotic, antitumour, geroprotective and heptaprotective agents.[3] Moreover, further studies have established that these compounds exhibit diverse medical functions such as neuroprotectants, compounds with platelet antiaggregators properties, cerebral antiischaemic agents and chemosensitizers.[4] In addition, recent papers have reported different biological activities of novel 1,4-DHP derivatives such as neurotropic, antidiabetic, antibacterial, and antiviral activity.[5] New dimeric 4-aryl-1,4-dihydropyridine derivatives were developed as a third class of nonpeptide HIV-1 protease inhibitors.[6] Very recently, *N*-alkoxycarbonylmethyl derivatives of 1,4-dihydropyridine-3,5-dicarboxylate were reported to act as a new carrier system to delivering drugs to the brain.[7]

The remarkable drug activity of these compounds not only attracted many chemists to synthesize this heterocyclic nucleus but also became an active research area of continuing interest.[8] It has been well established that the calcium modulator activity of this family of compounds is determined by structural requirements and it is well known that traditional dihydropyridines exhibiting biological properties have ester groups in both the 3- and 5-positions.[9] However, some results indicate that only one ester moiety is sufficient for the antagonistic activity.[10]

In previous work we have described the synthesis and structural study by X-Ray crystallographic methods and quantum chemical calculations, of several 1,4-DHP derivatives. We found that, in general, the conformational features reported for 1,4-DHP calcium modulators are preserved for theses compounds.[11]

In spite of the widely developed chemistry of the 1,4-DHP, the synthesis of 1,4-DHPs bearing substituents other than hydrogen atoms or alkyl groups at C2 and C6 has been less studied.[12]

As part of our program aimed at synthesizing 1,4-DHP derivatives endowed with different groups using this methodology, we have previously reported the synthesis of 6-chloro-5-formyl-1,4-dihydropyridines (**2**), which were obtained from the corresponding 2(1*H*)pyridone (**1**).[13] 1,4-Dihydropyridine (**2**) proved to be an excellent candidate for further transformations into other heterocyclic-fused 1,4-dihydropyridines such as pyrazolo[3,4-*b*]pyridines (**3**),[13] 4,7-dihydrothieno[2,3-*b*]pyridines (**4**),[14] and 2-imino-5,8-dihydropyrido[3,2-*e*][1,3]thiazines (**5**).[15] Recently, we have carried out the synthesis of novel fulleropyrrolidines (**6**) bearing biologically active 1,4-DHPs covalently connected to the fullerene core, from the corresponding 1,4-DHP (**2**)[16] (See Chart 1).

On the other hand, thiosemicarbazones are a class of interesting compounds presenting a wide range of pharmacological applications as antitumoral, antimicrobial and antiviral agents.[17] Some analogues of pyridine-2-carboxaldehyde thiosemicarbazone, have been synthesized and evaluated as inhibitors of CDP reductase activity and for their cytotoxicity in vitro and antineoplastic activity in vivo against the L1210

leukemia.[18] They represent an important class of potential ligands for complexing metal cations to obtain coordination compounds of biomedical relevance.[19] As ligands with potential S and N donors, this compounds are important due to their multifunctional coordination modes, viz. monodentate (N- or S-) or bidentate (N- and S-).[20]

To extend the scope of our synthetic protocol, in this paper we report on the one-pot synthesis of novel 1,4-dihydropyridine (**8a-g**), endowed with an methylenethiosemicarbazide group on C5 of the heterocyclic ring. Since the determination of the favoured conformation has been used to account for the pharmacological effect of different compounds with similar structures,[21] and in order to predict the biological activity of the compounds synthesised herein, we have carried out a structural study of these compounds, evaluating the geometry and conformational features by X-Ray crystallography and theoretical calculations at the DFT level.

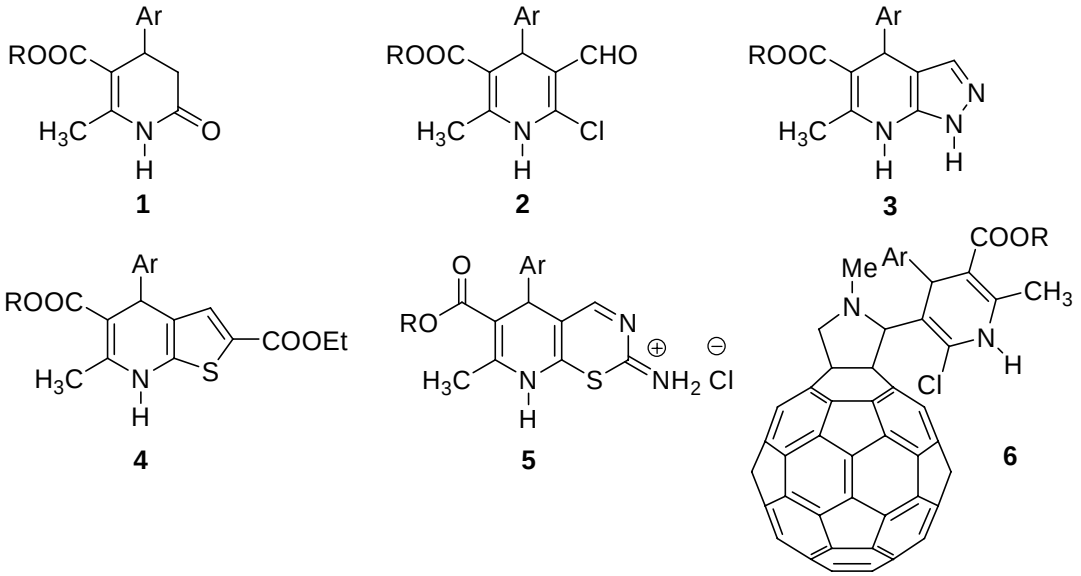


Chart 1

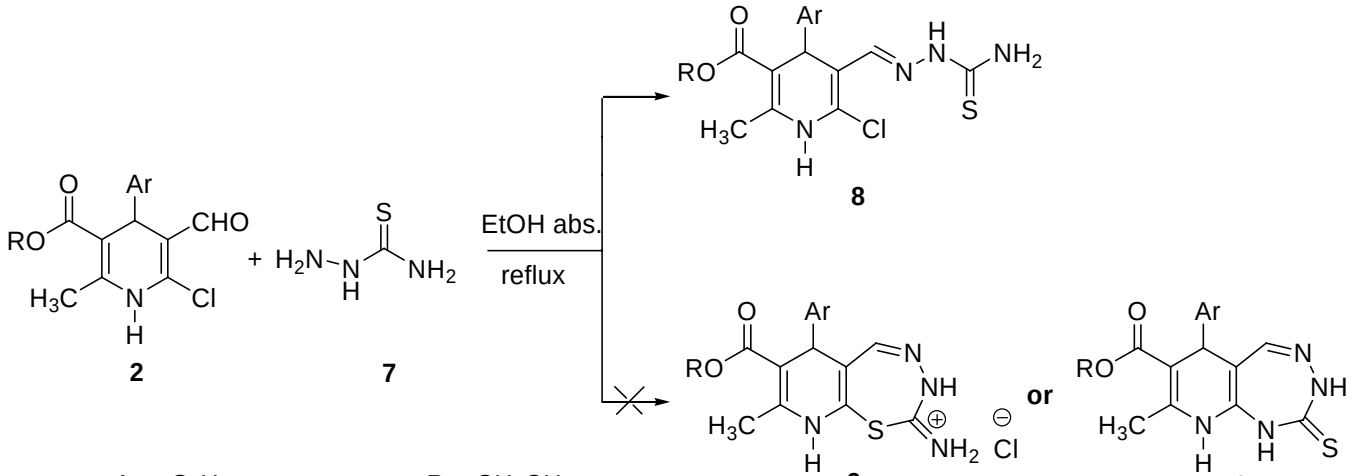
RESULTS AND DISCUSSION

In continuation with our studies on the synthesis of heterocyclic compounds from 2-chloro-3-formyl-1,4-DHPs, the synthesis of the alkyl 5-{[(aminocarbonothioyl)hydrazono]methyl}-6-chloro-2-methyl-4-phenyl-1,4-dihydropyridine3-carboxylate (**8a–g**) was readily accomplished in a single step by refluxing the appropriate alkyl 4-aryl-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**2a–g**) with an equimolecular amount of semicarbazide in dry ethanol under an inert atmosphere (Scheme 1). After six hours, the solid that precipitated from the reaction medium, was filtered off and recrystallized from ethanol.

Formation of compounds (**8**) can be accounted for by nucleophilic attack of the amino group in the

semicarbazide to the formyl group on C5, followed by loss of a water molecule. Compounds (**8**) were obtained as stable crystalline solids in moderate to good yields.

It is interesting to note, however, that although cyclization to the heterocyclic seven membered ring is allowed by Baldwin's rules,[22] compounds (**9**) or (**10**), resulting from the sulfur or nitrogen heterocyclization, respectively, were not formed. All attempts carried to obtain seven-membered systems (**9**) and/or (**10**) from compound (**8**) by refluxing in ethanol under neutral and basic conditions were also unsuccessful.



a, Ar = C_6H_5 R = CH_2CH_3
b, Ar = 3-ClC_6H_4 R = CH_2CH_3
c, Ar = 3-$NO_2C_6H_4$ R = CH_2CH_3
d, Ar = 4-$NO_2C_6H_4$ R = CH_2CH_3
e, Ar = 4-$CH_3OOCC_6H_4$ R = CH_2CH_3
f, Ar = 3-pyridyl R = CH_2CH_3
g, Ar = 2-ClC_6H_4 R = CH_3

Scheme 1

Compounds (**8a-g**) show satisfactory analytical and spectroscopic data. The IR spectra display a broad band centered at 3400 cm^{-1} assigned to the amino groups. In addition, the ester carbonyl group and the thiocarbonyl group signals appear at 1690 and 1475 cm^{-1}, respectively.

The NMR assignment was ascertained by 1D and 2D NMR experiments such as DEPT(135), NOe, HMQC and HMBC. The ^{1}H-NMR spectra of derivatives (**8a-g**) show a very similar pattern and display the singlets corresponding to the NH protons, at ~ 11.2 and ~ 9.8 ppm, assigned to NH9 and NH1, respectively. The NH_2 protons resonate, one of them (H12a) at 8.1 – 8.2 ppm, and for compounds (**8a**), (**8b**) and **(8c**) the other one (H12b) is overlaped with the multiplet of the aromatic protons. In compounds (**8c-f**) proton H12b appear at 7.37-7.12 ppm. The singlets at ~ 8 ppm and ~5 ppm are assigned to H7 and H4 protons. In all cases, the methyl group on C2 resonates at 2.24-2.28 ppm.

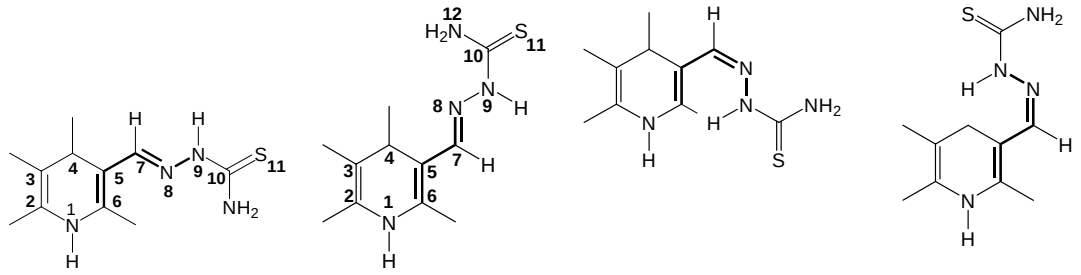
The NMR signals of the ethyl group present in the 2-ethoxycarbonyl derivatives (**8a-f**) appear at ~ 1.1 ppm as a triplet assigned to the methyl group and at ~ 3.9 ppm assigned to the methylene group. It is important to

note that the last signal appears as a multiplet in all compounds due to the diastereotropic nature of the two protons of the methylene group. This is caused by the presence of a stereogenic center at C4.[23,24] The ^{1}H NMR spectra show the signals of the benzene protons depending on the substituents present on the aromatic ring (see Experimental). For example, in compound (**8e**), where the benzene ring is *para* substituted, the aromatic protons appear as two doublets at 7.80 and 7.41 ppm (J = 8.7 Hz). The ^{13}C-NMR spectra of these compounds (**8a-g**) exhibit signals in the thiocarbonyl, carbonyl, aromatic and aliphatic regions. For the 1,4-dihydropyridine ring, the spectra showed four quaternary carbon signals (C2, C3, C5 and C6) and one tertiary carbon signal (C4). The data obtained from the spectra show that the signals corresponding to the heterocyclic ring are relatively insensitive to the nature of the substituents on C4. Once again, the carbons C2 (~145 ppm) and C6 (~131 ppm) appear at higher δ values and C5 (107 ppm) and C-3 (101 ppm) at lower δ values than those expected for typical olefinic carbons due to the presence of a *push-pull* effect.[25,26,27] Finally, C4 appears at 37-40 ppm. The thiocarbonyl group resonates at ~ 177 ppm and the carbonyl of the ester group on C3 at ~166 ppm. The tertiary carbon of the ethylidenethiosemicarbazide moiety (C7), appears at 140 ppm.

Since we have achieved unambiguous assignments for all the ^{1}H-NMR resonances, ^{13}C-NMR resonances were assigned in a straightforward manner by analysis of the HMQC spectra for the protonated carbon atoms on the basis of chemical shift theory, substituent effects, and DEPT data. Quaternary carbons were assigned by analysis of the HMBC spectra. It is interesting to point out that all compounds showed a similar trend in the chemical shifts of the common moiety of the molecular backbone.

Because of the pattern of ^{1}H-NMR and ^{13}C-NMR is similar for all compounds, the ^{15}N-NMR spectrum of the compound (**8a**) was recorded in order to ensure the structure. The ^{15}N-HMQC, using two different values of the N,H coupling constants, allow us to determine the chemical shift of the nitrogen atoms present in the molecule. In the HMQC, for ^{1}J(N,H) = 80 Hz, the hydrogen signals which showed correlation were those bonded to the nitrogen: N1 at -247 ppm, N9 at –203 ppm and N12 at -270 ppm. However in the HMQC using ^{n}J(N,H) = 5 Hz the hydrogen signals which showed correlation were those bonded through more than one bond. This confirms the position of N1 and N9 and allows us to assign the N-8 to the signal at –66 ppm, which is in agreement with values reported in the literature.[28] ESI-mass spectrometry clearly showed the presence of the chlorine atom attached to C6, confirming the proposed structures.

Structural and conformational studies of novel compounds (**8**) were carried out by X-Ray crystallographic analysis, theoretical DFT calculations (B3LYP/6-31G*) and NOe experiments. Considering the C5=C6 and the C7=N8 moieties, compounds (**8**) present four possible stereoisomers [(*E*) s-*cis*, (*E*) s-*trans*, (*Z*) s-*cis* and (*Z*) s-*trans*] (Figure 1).



(*E*) s-*cis* **(*E*) s-*trans*** **(*Z*) s-*cis*** **(*Z*) s-*trans***

Figure 1. Stereoisomers of compounds (**8**)

The most stable conformations predicted by B3LYP/6-31G* calculations for the stereoisomers considered for compound (**8a**) are shown in Figure 2.

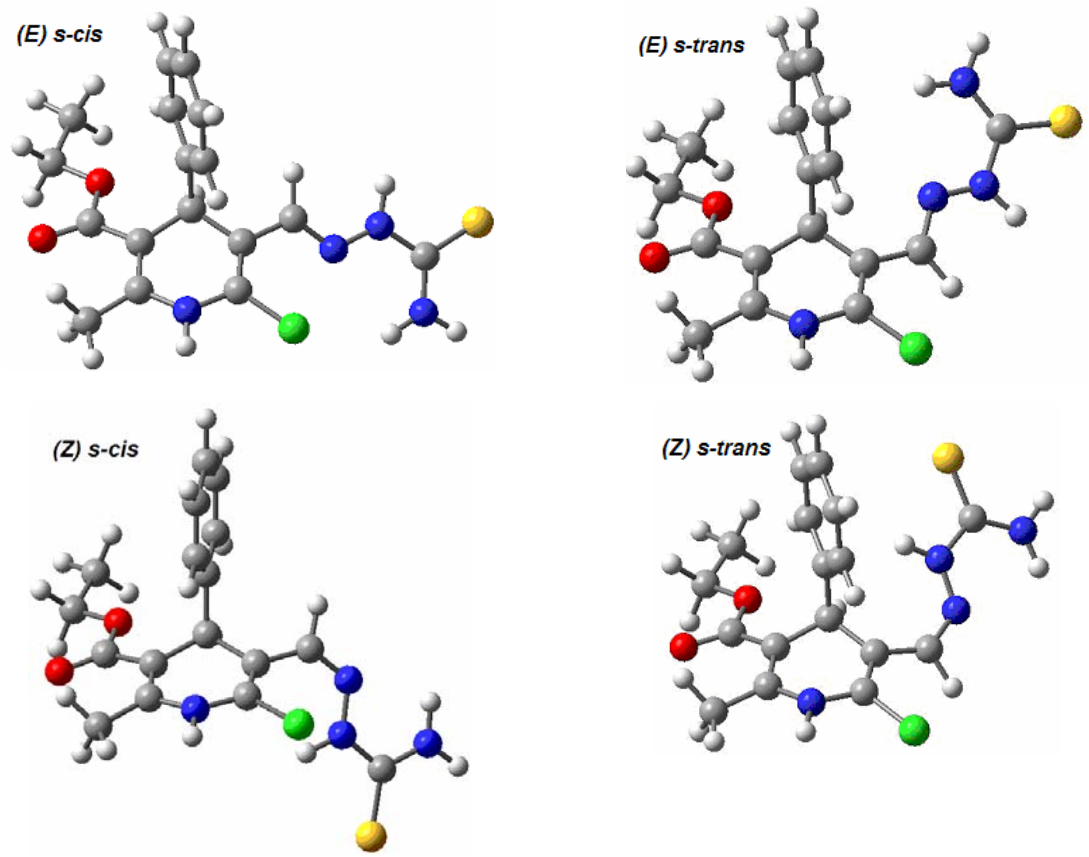
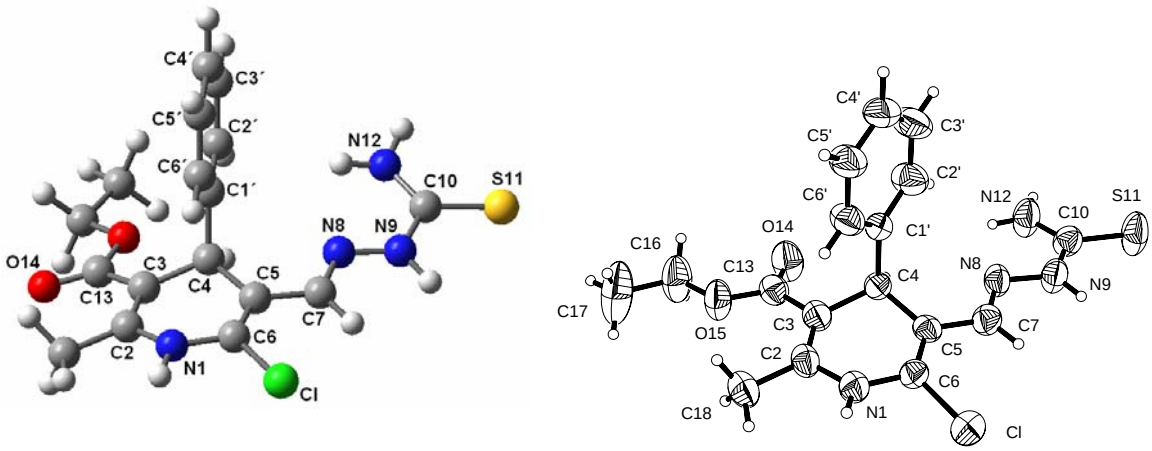


Figure 2. Most stable conformation predicted by DFT (B3LYP/6-31G*) calculations for the stereoisomers of **8a**

Theoretical DFT (B3LYP/6-31G*) calculations predict that the stereoisomer (*E*) s-*trans* (-1887.07777 Hartree) is 4.3 kcal/mol more stable than the (*E*) s-*cis* (-1887.07091 Hartree). Both *Z* estereoisomers resulted to be less stable due to the sterical hindrace between the semicarbazide moiety and the aryl ring on C4 ((*Z*) s-*trans*, -1887.06855 Hartree) or the chlorine atom on C6 ((*Z*) s-*cis*, -1887.06704). Also, in

this conformation, the dihedral angle C6-C5-C7-N8 is 58.5º showing the lost of conjugation between both adjacent double bonds.

The main geometrical features of the stereoisomer (*E*) s-*trans* obtained from B3LYP/6-31G* calculations using the Gaussian 98 program, are shown in Table 1. As example, the optimized geometry for compound (**8a**) is shown in Figure 3a along with the numbering scheme used in Table 1.



a **b**

Figure 3. a) Most stable conformation of **8a** predicted by B3LYP/6-31G* calculations. b) ORTEP plot showing the crystal structure of **8a** and its atomic numbering scheme. Displacement ellipsoids are drawn at 50% probability level for non-H atoms.

The analysis of the geometrical features of these molecules (see Table 1) shows that in all cases the torsion angle C2-C3-C13-O14 is between 5° and 18° which implies that the carbonyl double bond on C-3 is *cis* to the endocyclic double bond of the 1,4-DHP ring, as can be seen in Figure 3a, although the *trans* conformation is only 0.9 kcal/mol more energetic than the *cis* conformation. In all the compounds, the 1,4-DHP ring is a flat boat having the C4 and N1 atoms at the bow and sprit of this boat, the values found for $\sum|\rho|$ (modular summatory of the six internal torsion angles of the 1,4-DHP ring) which is an indicator of the planarity of the boat, is between 45° and 84°, these values are within the range found for 1,4-DHPs showing biological activity.[29] The aryl group on C4 is pseudoaxial (with angles between 104° and 114°) and bisecting the plane containing the 1,4-DHP ring (torsion angles C3-C4-C1'-C2' and C5- C4-C1'-C2' with values between 139° and 100°). In all the cases, the substituent on the phenyl group is synperyplanar (*sp*) with respect to the 1,4-DHP ring.

The nitrogen atom of the 1,4-DHP ring atoms shows a sp^2 hybridization as can be seen from the calculated value of the bond angle (about 120°). The same trend is observed for the rest of the nitrogen atoms (values between 117° and 124°). The C4 atom shows a sp^3 hybridization (~110°).

The torsion angle C6-C5-C7-N8 with values between -174.9° and -175.2° shows that the semicarbazide moiety is nearly coplanar with the 1,4-DHP ring. The torsion angles C7-N8-N9-C10 (-173.8° and -174.4°), N8-N9-C10-S11 (-177.7° and -177.0°) and N8-N9-C10-N12 (2.3° and 2.0°) show that the semicarbazide moiety is in a planar conformation forming an angle of almost 180° with the 1,4-DHP ring. This theoretical analysis demonstrates that this substituted 1,4-DHP meets all the geometrical features needed for biological activity.[30]

The X-Ray crystallographic analysis carried out on compound (**8a**) (see Figure 3b) shows that the 1,4-DHP ring has a screw boat conformation, with puckering parameters [31] Q = 0.281(6)Å, θ = 106.5(12)° and φ = 356.5(12)° for the atoms sequence N1-C2-C3-C4-C5-C6. For an ideal boat, θ has to be 90° and φ = n x 60°, respectively. This ring conformation represents 47 % puckering of an ideal cyclohexane chair (18% chair with N1 pointing up, 9% twist boat with axis through C3 and C4 pointing down, and 73% boat with bowsprit at N1 pointing down. The bond lengths and angles in the 1,4-DHP ring are generally close to those found in related compounds[32] with a weighted average ring bond distance of 1.421(3) Å and a weighted average absolute torsion angle of 17.0(3)°. The deviation of atom C4 from the rmsd plane of the 1,4-DHP ring is 0.181(5) Å, a value that falls closer to the middle of the range (~0.30 Å) for the most frequently reported values for this atom in 1,4-DHP rings.[33] The deviations shown by atom N1 are generally smaller and spread evenly over a range of 0.000-0.190.[32,34] In this structure, the deviation shown by N1 is 0.130(4) Å. The phenyl ring attached to C4 is in a pseudo-axial position and lies in a plane perpendicular to the mean plane of the 1,4-DHP ring as in related crystal structures.[32] It is a characteristic of the DHP type compounds to correlate activity with the perpendicularity of the aromatic ring at C4: the bisection of the aromatic ring with respect to the DHP ring can be expressed as the difference between this torsion angle and the ideal value of 60°. For this compound, this torsion angle is 85.7(6)°. This inter-ring orientation is probably induced by the packing of molecules in the crystal, in order to minimize the steric strains imposed by the packing of neighbouring molecules (Figure 4). Furthermore, the aromatic ring at C4 stacks with an 'edge to face' interaction where the centroids of the rings are at 4.9 Å apart. The ester group at C3 was found to be nearly coplanar with the nearest endocyclic double bond in the DHP ring and having the C3 carbonyl group in a *trans* (*ap*) disposition with respect to it, which is in contrast to that predicted by the theoretical calculation. This is the result of a π–electron conjugation in the atoms C2=C3-C13=O14. The substituent at C5 is essentially coplanar with the ester group at C3, the least-square planes between non H-atoms in each site is 7.2°. Considering the four possible isomers, according to the disposition of the C5=C6 and the C7=N8, this compound crystallizes as the (*E*) s-*trans* isomer. The coplanarity of the side chain at C5 is also evidenced from the bond angles around N8, N9, and N12 [C7-N8-N9: 114.2(5)°, N8-N9-C10: 120.0(5)°, N9-C10-N12: 116.7(6)°, N9-C10-S11: 120.4(4)°, N12-C10-S11: 122.8(4)°], which corresponds to sp^2-hybridized atoms.

In Table 1 we report the most relevant conformational features for compound (**8a**), as determined by X-Ray diffraction.

Table 1. Most Relevant Bond Distances (Å) Valence Angles (°) and Dihedral Angles (°) for the most stable conformation for compound (**8a**) [(*E*) s-*trans*) obtained at the B3LYP/6-31G* level, as well as by X-Ray diffraction

	X-ray	**(B3LYP/6-31G*)**
Bond Distances A°		
N1-C6	1.373(6)	1.381
C6-C5	1.330(8)	1.354
C5-C4	1.534(7)	1.530
C4-C3	1.528(8)	1.531
C3-C2	1.357(9)	1.364
C2-N1	1.398(7)	1.388
C4-C1’	1.534(8)	1.536
C7-N8	1.294(8)	1.292
N8-N9	1.388(6)	1.355
N9-C10	1.335(8)	1.373
C10-S11	1.683(6)	1.679
C10-N12	1.311(8)	1.348
Valence Angles °		
C2-N1-C6	120.8(5)	121.8
C5-C4-C3	110.3(4)	111.1
C7-N8-N9	114.2(5)	117.5
N8-N9-C10	120.0(5)	121.6
N9-C10-S11	120.4(4)	120.1
Dihedral Angles °		
N1-C2-C3-C4	-10.0(7)	-7.1
C2-C3-C4-C5	27.4(7)	23.2
C3-C4-C5-C6	-25.4(6)	-22.0
C4-C5-C6-N1	6.3(8)	5.5
C5-C6-N1-C2	14.4(8)	13.4
C6-N1-C2-C3	-12.3(7)	-12.5
$\Sigma\|\rho\|$	*95.8(7)*	*83.7*
C5-C4-C1’-C2’	93.7(6)	126.2
C6-C5-C4-C1’	-96.3(6)	103.9
C6-C5-C7-N8	176.9(5)	-175.2
C2-C3-C13-O14	-166.5(6)	5.1
C7-N8-N9-C10	176.7(5)	-174.4
N8-N9-C10-S11	177.3(4)	-179.3
N8-N9-C10-N12	-6.5(7)	0.2

The crystal structure is also stabilized by several intramolecular and intermolecular hydrogen bonds and weak interactions (See Figure 4). An intramolecular hydrogen bond (N12….N8 = 2.620(7) Å) and two weak interactions (C4…O14 = 2.520(7) Å and C7…Cl = 3.062(6) Å are noted. The N1 atom is involved in a characteristic intermolecular hydrogen bond with a neighboring carboxyl oxygen O32, present in this type of structures:[32] N1…O14 (symmetry: x, y+1, z) = 3.210(7)Å, whereas two intermolecular hydrogen bonds of the type N-H…S are also present: N9-H9…S11 (symmetry: -x+1/2, y+1/2, -z+1/2), with N9…S11 = 3.255(5) Å and N9-H9…S11 = 160°; and N12-H12B…S11 (symmetry: -x+1/2, y-1/2, -z+1/2), with N12…S11 = 3.261(6) Å and N12-H12B…S11 = 172°.

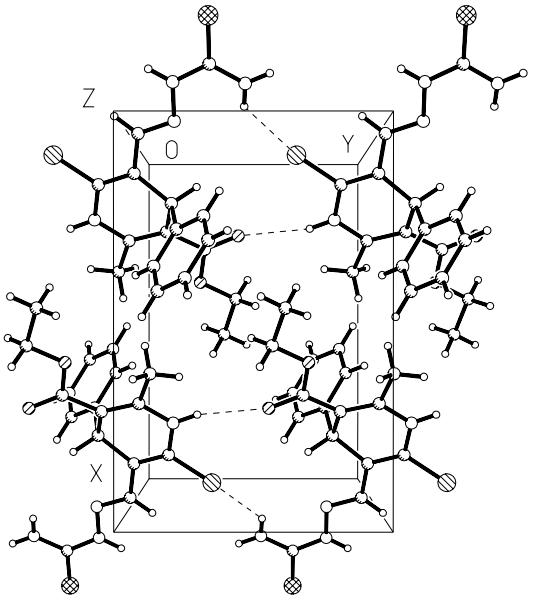


Figure 4. Packing of the molecules of **8a** in the unit cell showing some of the H-bonding intermolecular interactions

We have also determined the most favourable stereoisomer in solution by using NOe experiments upon irradiation of the methyl group (Me-C2), NH1, H4, H7 and NH9.

The irradiation of NH1 showed a NOe effect on H2'or H6′ as well as on Me-C2, and when Me-C2 was irradiated, a strong NOe effect was observed on NH1 and a weak one on H2′ or H6′. The former indicate the typical boat conformation of the 1,4-DHP ring in solution.[35] Also, NOe experiments show the proximity between H7 and H9 confirming that (**8a-e**) were obtained as single *E*-isomers since when H7 was irradiated, a strong NOe effect was observed on NH9 and vice versa. The no existence of a NOe effect between the H7 and the protons of the phenyl ring indicates unequivocally that the (*E*) s-*trans* isomer is also present in solution.

CONCLUSIONS

In summary, we have carried out the study of the reaction of suitably functionalized 6-chloro-5-formyl-1,4-DHPs (**2**) with semicarbazide (**7**) to form the corresponding semicarbazones (**8a-g**) which are not able to cyclize to the corresponding seven member ring derivatives. We have determined the structure of the formed compounds (**8a-g**) by means of theoretical calculations at the DFT (B3LYP/6-31G*) level as well as X-Ray diffraction (compound **8a**). Theoretical and experimental results are in very good agreement and show that from the different stereoisomers found for these semicarbazones (**8a-g**), stereoisomer (*E*) s-*trans* resulted to be energetically the most stable. Furthermore, NOe experiments clearly confirmed that this stereoisomer is also found in solution.

The structural features of (*E*) s-*trans* stereoisomer as well as the sp^2 hybridization of all carbon and nitrogen atoms forming the planar semicarbazone chain linked to the 1,4-DHP double bound should be responsible for the unfavourable geometry for the approach vector associated with the seven-membered ring, thus accounting for the unsuccessful cyclization. However, the found structural characteristics of semicarbazone-containing 1,4-DHPs (**8a-g**) meet all the geometrical requirements to show biological activity as calcium-channel modulators. Therefore, these new 1,4-DHPs endowed with a conformationally versatile semicarbazone moiety are a less studied type of compounds with structural and practical interest.

EXPERIMENTAL

Reagents and solvents were purchased from Fluka or Aldrich. Alkyl 4-aryl-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate were obtained as previously reported[14] from alkyl 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate.[36] The progress of the reaction and the purity of compounds were monitored by TLC analytical silica gel plates (Merck $60F_{250}$). Chromatography was carried out using silica gel 60 (70-230 mesh ASTM). Melting points were determined in capillary tubes in an Electrothermal 9100 apparatus and are uncorrected. IR spectra were obtained as follow: FT IR were recorded on a FTIR 8300 spectrometer; ^{1}H- NMR spectra were recorded at 300 MHz, and ^{13}C-NMR at 75.5 MHz, on a Bruker Avance-300 instrument, the one-bond heteronuclear correlation (HMQC) and the long range ^{1}H-^{13}C correlation (HMBC) spectra were obtained using the inv4gs and the inv4gslplrnd programs respectively with the Bruker software. ^{15}N-NMR spectra were recorded at 50.687 MHz on a Bruker Avance-500 instrument, the one-bond heteronuclear correlation (HMQC) were obtained using the inv4gpqf program. MS were obtained with a Hewlett Packard 5989-A spectrometer. MS-ESI spectra were recorded on a LC-Esquire from Bruker using negative mode of detection. All the experimental isotopic cluster of pseudomolecular ions corresponds with the theoretical values. Microanalysis was performed in a Perkin-Elmer 2400 CHN by the *Servicio de Microanálisis de la Universidad Complutense de Madrid*. DFT calculations were performed using a B3LYP/6-31G* basis set.[37] All calculations were carried out using the Gaussian 98 program.[38]

General procedure for the preparation of alkyl 5-{(*E*)-[(aminocarbonothioyl)hydrazono]methyl}-6-chloro-2-methyl-4-aryl-1,4-dihydropyridine-3-carboxylate (8) A mixture of the appropriate 6-chloro-5-formyl-1,4-DHP (**2a-g**) (1 mmol) and 1 mmol of thiosemicarbazide was refluxed in 10 mL of absolute ethanol under nitrogen atmosphere for 6 h until disappearance of the starting pyridine derivative as monitored by TLC. The solvent was removed and the solid residue was purified by column-chromatography on 60 g of silica gel [*n*-hexane-ethyl acetate (5:3)] to afford a yellow powder.

Ethyl 5-{(*E*)-[(aminocarbonothioyl)hydrazono]methyl}-6-chloro-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (8a) Prepared from ethyl 6-chloro-4-phenyl-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**2a**). Yield, 50 %; mp 190-192°C; IR (KBr) ν_{max} 3437 (νNH), 1688 (νC=O), 1475 (νC=S), 1365 (νC=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.25 (1H, s, NH9), 9.75 (1H, s, NH1), 8.12 (1H, s, H12a), 8.02 (1H, s, H7), 7.07-7.25 (6H, m, Ph-H, H12b), 5.03 (1H, s, H4), 3.96 (2H, m, OCH_2), 2.26 (3H, s, CH_3), 1.12 (3H, t, CH_3); ^{13}C NMR (DMSO-d_6) δ 177.2 (C=S), 166.4 (C=O), 146.8 (C1′), 145.3 (C2), 140.4 (C7), 131.2 (C6), 127.8 (C3', C5'), 127.7 (C2', C6′), 126.1 (C4′), 107.8 (C5), 101.8 (C3), 59.1 (OCH_2), 40.0 (C4), 18.1 (CH_3), 14.1 (CH_3); MS-ESI *m/z*: 377 $[M-H]^-$. *Anal.* Calcd for $C_{17}H_{19}N_4O_2ClS$ (378.09): C: 53.89; H: 5.05; N: 14.79. Found: C: 53.77; H: 5.12; N: 14.59.

Crystal Structure determination of 8a

Crystals suitable for X-Ray diffraction were grown by slow evaporation from absolute ethanol solution. Measurements were carried out using a Siemens P4 four-circle diffractometer with graphite monochromated and Cu-$K\alpha_1$ radiation. Crystal data: $C_{17}H_{19}ClN_4O_2S$, M.W. = 378.87, Monoclinic, a = 11.819(1), b = 7.8244(7), c = 19.562(2) Å, β = 90.411(6)°, V = 1808.9(3), Å^3, T = 293(2) K, space group $P2_1/n$, Z = 4, μ = 0.311 mm-1. The intensity data were collected using ω-2θ scans, with ω scan width equal to the low range plus the high range plus the separation between the Kα_1 and Kα_2 positions; 4511 reflections measured ($3.71 < \theta < 68.85°$, $-1 < h < 14$, $-9 < k$ 1, $-22 < l < 23$), 1458 unique (merging R = 0.055) and $F^2 \geq 2\sigma(F)^2$. Empirical absorption correction, via ψ scan was applied.[39] Three standard reflections were monitored every 100 reflections (intensity decay: none). The structure was solved by direct methods and Fourier synthesis. Non-H atoms were refined anisotropically by full-matrix least-squares techniques. H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed to 1.3 times U*eq* of their parent atoms. Final R indices [$I > 2\sigma(I)$] R = 0.07, wR = 0.213. Data collection: XSCANS.[40] Cell refinement: XSCANS.[40] Data reduction: XSCANS.[40] Program used to solve structure: SIR92.[41] Program used to refine structure: SHELXL97.[42] Molecular graphics: DIAMOND.[43] Software used to prepare material for publication: PLATON.[44] Detailed crystallographic data for have been deposited at the

Cambridge Crystallographic Data Centre (CCDC 265437) and are available on request.

Ethyl 5-{(*E*)-[(aminocarbonothioyl)hydrazono]methyl}-6-chloro-4-(3-chlorophenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (8b) Prepared from ethyl 6-chloro-4-(3-chlorophenyl)-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**2b**). Yield 60 %; mp 202-204°C; IR (KBr) ν_{max} 3411 (νNH), 1690 (νC=O), 1475 (νC=S), 1369 (νC=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.22 (1H, s, NH9), 9.82 (1H, s, NH1), 8.14 (1H, s, H12a), 8.02 (1H, s, H7), 7.16-7.30 (5H, m, Ph, H12b), 5.08 (1H, s, H4), 3.98 (2H, m, CH_2), 2.27 (3H, s, CH_3), 1.13 (3H, t, CH_3); ^{13}C NMR (DMSO-d_6) δ 177.3 (C=S), 166.7 (C=O), 149.6 (C1′), 146.3 (C2), 140.6 (C7), 144.7 (C3′), 131.4 (C5'), 130.1 (C6), 128.2 (C2′), 125.5 (C4′), 126.7 (C6'), 107.8 (C5), 101.6 (C3), 59.6 (OCH_2), 39.8 (C4), 18.5 (CH_3), 14.4 (CH_3); MS-ESI *m/z*: 411 $[M-H]^-$. *Anal.* Calcd for $C_{17}H_{18}N_4O_2Cl_2S$ (412.05): C: 49.40; H: 4.39; N: 13.56. Found: C: 49.51; H: 4.50; N: 13.69.

Ethyl 5-{(*E*)-[(aminocarbonothioyl)hydrazono]methyl}-6-chloro-2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (8c) Prepared from ethyl 6-chloro-5-formyl-2-methyl-4-(3′-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**2c**). Yield 62 %; mp 223-224°C; IR (KBr) ν_{max} 3437 (νNH), 1688 (νC=O), 1475 (νC=S), 1365 (νC=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.19 (1H, s, NH9), 9.92 (1H, s, NH1), 8.13 (1H, s, H12a), 8.02 (1H, s, H7), 7.37 (1H, s, H12b), 7.96 (2H, m, H2', H4′), 7.75 (1H, dt, H6', *J*= 8.5 Hz, *J*= 1.2 Hz), 7.51 (1H, t, H5', *J*= 8.5 Hz), 5.24 (1H, s, H4), 3.92 (2H, m, OCH_2), 2.28 (3H, s, CH_3), 1.11 (3H, t, CH_3); ^{13}C NMR (DMSO-d_6) δ 177.0 (C=S), 166.2 (C=O), 149.0 (C3′), 147.5 (C1′), 146.5 (C2), 140.2 (C7), 134.6 (C6′), 131.4 (C6), 129.4 (C5'), 122.4 (C2'), 121.3 (C4′), 107.4 (C5), 101.0 (C3), 59.4 (OCH_2), 40.0 (C4), 18.4 (CH_3), 14.1 (CH_3); MS-ESI *m/z*: 422 $[M-H]^-$. *Anal.* Calcd for $C_{17}H_{18}N_5O_4ClS$ (423.08): C: 48.17; H: 4.28; N: 16.52. Found: C: 48.30; H: 4.32; N: 16.58.

Ethyl 5-{(*E*)-[(aminocarbonothioyl)hydrazono]methyl}-6-chloro-2-methyl-4-(4′-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (8d) Prepared from ethyl 6-chloro-5-formyl-2-methyl-4-(4′-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**2d**). Yield 78 %; mp 228-230°C; IR (KBr) ν_{max} 3437 (νNH), 1688 (νC=O), 1475 (νC=S), 1365 (νC=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.28 (1H, s, NH9), 9.89 (1H, s, NH1), 8.12 (1H, s, H12a), 8.07 (2H, d, H3′, H5′, *J* = 8.5 Hz), 8.04 (1H, s, H7), 7.30 (2H, d, H2′, H6′, *J* = 8.5 Hz), 7.15 (1H, s, H12b), 5.24 (1H, s, H4), 3.99 (2H, m, OCH_2), 2.28 (3H, s, CH_3), 1.12 (3H, t, CH_3); ^{13}C NMR (DMSO-d_6) δ 177.2 (C=S), 166.9 (C=O), 152.2 (C1′), 145.6 (C2), 140.4 (C7), 131.4 (C6), 121.4 (C3′, C5′), 128.3 (C4′), 130.4 (C2′, C6′), 107.6 (C5), 101.5 (C3), 59.2 (OCH_2), 41.3 (C4), 18.2 (CH_3), 14.1 (CH_3); MS-ESI *m/z*: 422 $[M-H]^-$. *Anal.* Calcd for $C_{17}H_{18}N_5O_4ClS$ (423.08): C: 48.17; H: 4.28; N: 16.52. Found: C: 48.32; H: 4.34; N: 16.58.

Ethyl 5-{(*E*)-[(aminocarbonothioyl)hydrazono]methyl}-6-chloro-4-(4′-methoxycarbonylphenyl)-

2-methyl-1,4-dihydropyridine-3-carboxylate (8e) Prepared from ethyl 6-chloro-5-formyl-2-methyl-4-(4′-methoxycarbonylphenyl)-1,4-dihydropyridine-3-carboxylate (**2e**). Yield 62 %; mp 180-186°C; IR (KBr) ν_{max} 3437 (νNH), 1688 (νC=O), 1475 (νC=S), 1365 (νC=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.23 (1H, s, NH9), 9.84 (1H, s, NH1), 8.11 (1H, s, H12a), 8.02 (1H, s, H7), 7.80 (2H, d, H3′, H5′, *J* = 8.7 Hz), 7.41 (2H, d, H2′, H6′, *J* = 8.7 Hz), 7.12 (1H, s, H12b), 5.13 (1H, s, H4), 3.99 (2H, m, OCH_2), 3.80 (3H, s, OCH_3), 2.27 (3H, s, CH_3), 1.12 (3H, t, CH_3); ^{13}C NMR (DMSO-d_6) δ 177.0 (C=S), 166.4 (C=O), 166.1 (C=O), 152.2 (C1′), 145.9 (C2), 140.4 (C7), 131.2 (C6), 128.8 (C3′, C5′),128.3 (C4′), 127.6 (C2′, C6′), 107.2 (C5), 101.1 (C3), 59.2 (OCH_2), 51.9 (OCH_3), 39.9 (C4), 18.1 (CH_3), 14.0 (CH_3); MS-ESI *m/z*: 435 $[M-H]^-$. *Anal.* Calcd for $C_{19}H_{21}N_4O_4ClS$ (436.1): C: 52.23; H: 4.84; N: 12.82. Found: C: 52.27; H: 4.89; N: 12.88.

Ethyl5-{(*E*)-[(aminocarbonothioyl)hydrazono]methyl}-6-chloro-2-methyl-4-(3-pyridyl)-1,4-dihydropyridine-3-carboxylate (8f) Prepared from ethyl 6-chloro-5-formyl-2-methyl-4-(3-pyridyl)-1,4-dihydropyridine-3-carboxylate (**2f**). Yield 82 %; mp 222-224°C; IR (KBr) ν_{max} 3437 (νNH), 1688 (νC=O), 1475 (νC=S), 1365 (νC=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.05 (1H, s, NH9), 9.71 (1H, s, NH1), 8.36 (1H, s, H2′), 8.34 (1H, d, H4′, *J* = 4.7 Hz), 8.21 (1H, s, H12a), 8.07 (1H, s, H7), 7.50 (1H, d, H6′, *J* = 7.9 Hz), 7.27 (1H, dd, H5′, *J* = 7.9 and *J* = 4.7 Hz), 7.24 (1H, s, H12b), 5.04 (1H, s, H4), 3.97 (2H, m, OCH_2), 2.27 (3H, s, CH_3), 1.10 (3H, t, CH_3); ^{13}C NMR (DMSO-d_6) δ 177.0 (C=S), 166.1 (C=O), 156.1 (C2′), 136.8 (C6′), 134.6 (C1′),147.2 (C4′), 146.8 (C2), 140.8 (C7), 131.6 (C6), 123.4 (C5′), 107.1 (C5), 99.9 (C3), 59.1 (OCH_2), 37.6 (C4), 18.1 (CH_3), 14.0 (CH_3); MS-ESI *m/z*: 378 $[M-H]^-$. *Anal.* Calcd for $C_{16}H_{18}N_5O_2ClS$ (379.09): C: 50.59; H: 4.78; N: 18.44. Found: C: 50.48; H: 4.85; N: 18.52.

Methyl 5-{(*E*)-[(aminocarbonothioyl)hydrazono]methyl}-6-chloro-4-(2-chlorophenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (8g) Prepared from ethyl 6-chloro-4-(2-chlorophenyl)-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**2g**). Yield 50 %; mp 210-212°C; IR (KBr) ν_{max} 3437 (νNH), 1688 (νC=O), 1475 (νC=S), 1365 (νC=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.26 (1H, s, NH9), 9.93 (1H, s, NH1), 8.26 (1H, s, H12a), 8.07 (1H, s, H7), 7.07-7.25 (5H, m, Ph, H12b), 5.36 (1H, s, H4), 3.51 (3H, s, OCH_3), 2.24 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 176.8 (C=S), 166.8 (C=O), 145.6 (C2), 144.4 (C1′), 140.9 (C7), 136.5 (C2′), 131.9 (C6), 130.8 (C6′), 129.0 (C3'), 128.1 (C4'), 127.7 (C5'), 107.4 (C5), 101.4 (C3), 50.5 (OCH_3), 37.1 (C4), 18.6 (CH_3). MS-ESI *m/z*: 397 $[M-H]^-$ *Anal.* Calcd for $C_{16}H_{16}N_4O_2Cl_2S$ (398.04): C: 48.13; H: 4.04; N: 14.03. Found: C: 48.20; H: 4.11; N: 14.09.

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