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2D ^{1}H and ^{13}C NMR conformational studies of thienopyridines and carboline biarylic compounds

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ABSTRACT

In this paper, we report on conformational studies of biarylic compounds, as prepared through the well-known aza-Wittig methodology. The conformational studies were mainly realized by bidimensional (2D) nuclear magnetic resonance spectroscopy (NMR) and NOESY experiments. The conformational behavior showed that these biarylic compounds display an orthogonal symmetry and adopt a characteristic arrangement around the pivotal bond. Molecular modeling calculations were performed to support structure conformations.

1. Introduction

The conformational behavior of the molecules is one of the most important subjects in biological chemistry, because conformation is strongly related to biological activity [1]. Conformational studies have been performed on biarylic derivatives whose aromatic units are linked through a rotationally hindered biaryl axis due to steric factors [2,3]. It is well accepted that, if two planar groups are connected by one central bond, and the ground state is not planar, then the molecule possess axial chirality (provided that neither of the two planes are symmetrical to a plane involving this central bond). If the rotation barrier is small, then as the rotation around the symmetry axis accelerates, the magnetic environment of the nuclei becomes interchangeable, and the averaging takes place; this leads to the apparent racemization of the chiral compound. The most typical examples of such racemization can be found in the biphenyl series [4,5]. The same principle can be applied to other non-planar molecules. The magnitude of the energy for the rotational barriers can be evaluated approximately in terms of steric effects. Biphenyls constitute a unique system in which introduction of a substituent in *o*,*o*′ positions can influence the transition state for a given conformer affecting its ground state energy.

The preparation of biarylic heterocyclic compounds has been performed using different methodologies, some of which involve the reaction between an aromatic iminophosphorane intermediate and an aromatic aldehyde [6–8]. Such strategies are mostly directed towards the construction of nitrogen-containing heterocycles [8–11]. The readily available iminophosphorane (prepared from azides) [12] and their aza-Wittig reaction with a wide variety of carbonyls [13–15] and heterocumulene [16–18] compounds provide a valuable method for the regiospecific construction of carbon–nitrogen double bonds [19–21].

Recently, our group applied this methodology to build a variety of molecular skeletons, and to study their conformational behavior by NMR [22,23].

2. Results and discussion

Iminophosphoranes were obtained by condensation reactions between ethyl azido acetate and various aromatic aldehydes **1**–**5**. The Staudinger reaction with triphenyl phosphine produces the corresponding iminophosphoranes **6**–**10** with moderated yields for a two-step synthesis (Table 1). From an aza-Wittig reaction between aromatic aldehydes **11**–**18** and the iminophosphorane intermediates **6**–**10**, the biarylic compounds **19**–**31** were synthesized (yields shown in Table 2) (Scheme 1).

The biarylic compounds **19**–**31** (Fig. 1) prepared using the aza-Wittig methodology shows a variable steric hindrance between the two aromatic moieties linked through the aforementioned pivotal bond. The compounds **19**–**21** are derivatives of thienopyridines with either one or two aromatic moieties, while derivatives **22**–**30** are tricyclic aromatic compounds linked to mono- or bicyclic aromatic moieties.

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Table 1
Iminophosphoranes **6**–**10** obtained by Staudinger reaction.

Ar_1	Phosphonate	Yield (%)[a]
5-Methylthiophen-2-yl (**1**)	**6**	63
N-Methylindol-2-yl (**2**)	**7**	70
N-Benzyl-2-carboethoxythieno[2,3-b]pyrrol-5-yl (**3**)	**8**	75
5-Chlorothieno[2,3-b]pyridin-2-yl **(4)**	**9**	40
6-Methylthieno[2,3-b]quinol-2-yl **(5)**	**10**	35

[a] Two steps.

Table 2
Biarylic compounds obtained through the TAWERS reaction.

Phosphonate	Aldehyde (Ar_2)	Compound	Yield (%)
6	5-Chloro-1-methyl-2-formylpyrrol-4-carboxaldehyde (**11**)	**19**	77
6	2,6-Dichloro-3-formylpyrido-5-carboxaldehyde (**12**)	**20**	72
6	5-Chlorothieno[2,3-b]pyrido-2-carboxaldehyde (**13**)	**21**	83
7	Phthaldehyde (**14**)	**22**	84
7	Thiophen-2,3-dicarboxaldehyde (**15**)	**23**	92
7	Thiophen-2,3-dicarboxaldehyde (**15**)	**24**	92
9	2-Carbomethoxythieno[2,3-b]pyrido-5-carboxaldehyde (**16**)	**25**	77
8	2,3-Thiophendicarboxaldehyde (**15**)	**26**	75
8	2,3-Thiophendicarboxaldehyde (**15**)	**27**	75
7	Quinoline-4-carboxaldehyde (**17**)	**28**	91
7	Quinoline-2-carboxaldehyde (**18**)	**29**	85
9	Quinoline-2-carboxaldehyde (**18**)	**30**	84
10	Quinoline-2-carboxaldehyde (**18**)	**31**	62

Finally, compound **31** is an aromatic tetracycle joined to an aromatic moiety formed by another two cycles. It is expected that compounds of this class will display a hindered rotation due to steric factors. We have previously studied this class of phenomena, focusing on a particular conformational behavior of these molecules [22,23].

Since the derivatives **19**–**31** (Fig. 1) may be of some pharmaceutical interest, it appeared attractive to study their detailed conformational data, taking into account the restricted rotation that may occurs through the pivotal bond between both aromatic moieties.

In order to obtain a molecular-level insight into these interesting effects, we performed 2D NMR conformational studies of the biarylic units from thienopyridines and carboline derivatives.

First, the molecules obtained were identified using high-resolution NMR 1D and 2D techniques. All the assignments given are self-consistent and unambiguous, and particularly supported by COSY and NOESY experiments as described in Section 4.

The assignments of the ^{13}C resonances of the synthesized products were carried out in $CDCl_3$ by determining the signal multiplicities from DEPT experiment. The complete ^1H and ^{13}C assignments of the molecules were achieved by means of proton–carbon correlation methods, for example the HSQC and HMBC spectra, in order to complete the full assignments.

In order to demonstrate dipolar interactions between key protons through the space, we performed a phase sensitive NOESY experiment in $CDCl_3$. The interatomic distances of selected protons were calculated from NMR data.

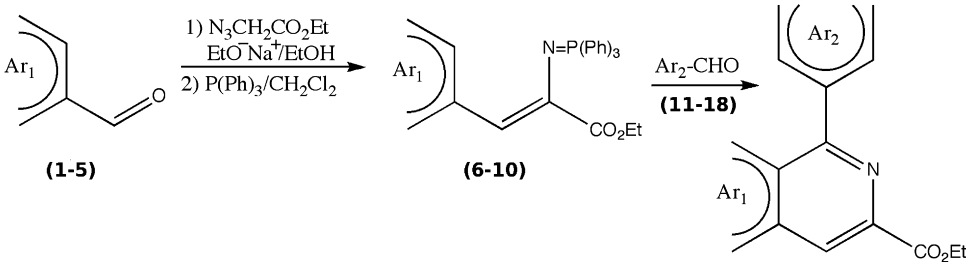
The conformational study by the 2D NMR NOESY shows, for almost all derivatives, an orthogonal pattern appearing as two biarylic units with restricted rotation through their pivotal bond for example, C4–C3′ for compound **19** (**19**–**28**, Figs. 2 and 3). Nevertheless, for compounds derived from the 2-quinolincarboxaldehyde (compounds **29**–**31**), the conformational study specified a special geometry between two aromatic moieties. This observation is similar to one previously reported by us, and supported by X-ray crystallography studies for the case of 6-carboethoxy-2-methyl-4-(2′-quinolin)thieno[3,2-c]pyridine [22].

For derivative **19**, NOESY experiment detected dipolar correlation between protons H-3/H-4′ (2.39 Å), as well as, the correlation corresponding to aldehydic protons H-6′/H-4′ (2.57 Å). From the NMR data, we calculated the minimum conformational energy as well as the dihedral angle between two planes determinated by 3a-4 and 3′-4′ (Table 3).

For dihalogenated derivative **20**, using the diagonal and cross-peaks from H-3 and H-4′ we were able to identify a dipolar interaction between these protons (3.02 Å). An additional correlation observed was that between aldehydic proton H-7′ (δ = 10.4 ppm) with the H-4′ proton at δ = 8.38 ppm (2.23 Å). Geometrical parameters can be observed in Table 3.

The derivative **21** represent an aromatic heterocompound formed by two moieties of thienopyridines linked through C-2′/C-4 bond. The phase sensitive NOESY spectrum displays strong correlations between H-4′/H-3′ (2.87 Å), as well as the helpful spatial correlation between H-3/H-3′ (2.13 Å).

For compound **22**, the ^1H NMR recorded in $CDCl_3$ displayed the chemical shift for the conformational and relevant protons within a highly overlapped area. In order to overcome this difficulty, NOESY experiment for the compound **22** was recorded instead in C_6D_6. Under these conditions, the 1D ^1H NMR 500 MHz more clearly displayed the key NOESY signals, which provides evidence of compound **22**'s conformational behavior. The assignment of the chemical shift of the protons for this compound began with NOESY spectrum using the diagonal peak of the N-Me at δ = 2.80 with the cross-peaks at δ = 6.83 (H-6) separated by 2.29 Å as well as that due to H-4 (δ = 8.25) separated by 2.28 Å. Other relevant dipolar correlations were observed between the aldehydic proton H-7′ (δ = 10.1) and the proton H-3′, as well as that assigned to H-9 at δ = 7.40. The most important dipolar correlation which enabled us to get confor-



Scheme 1. Synthesis of biarylic compounds.

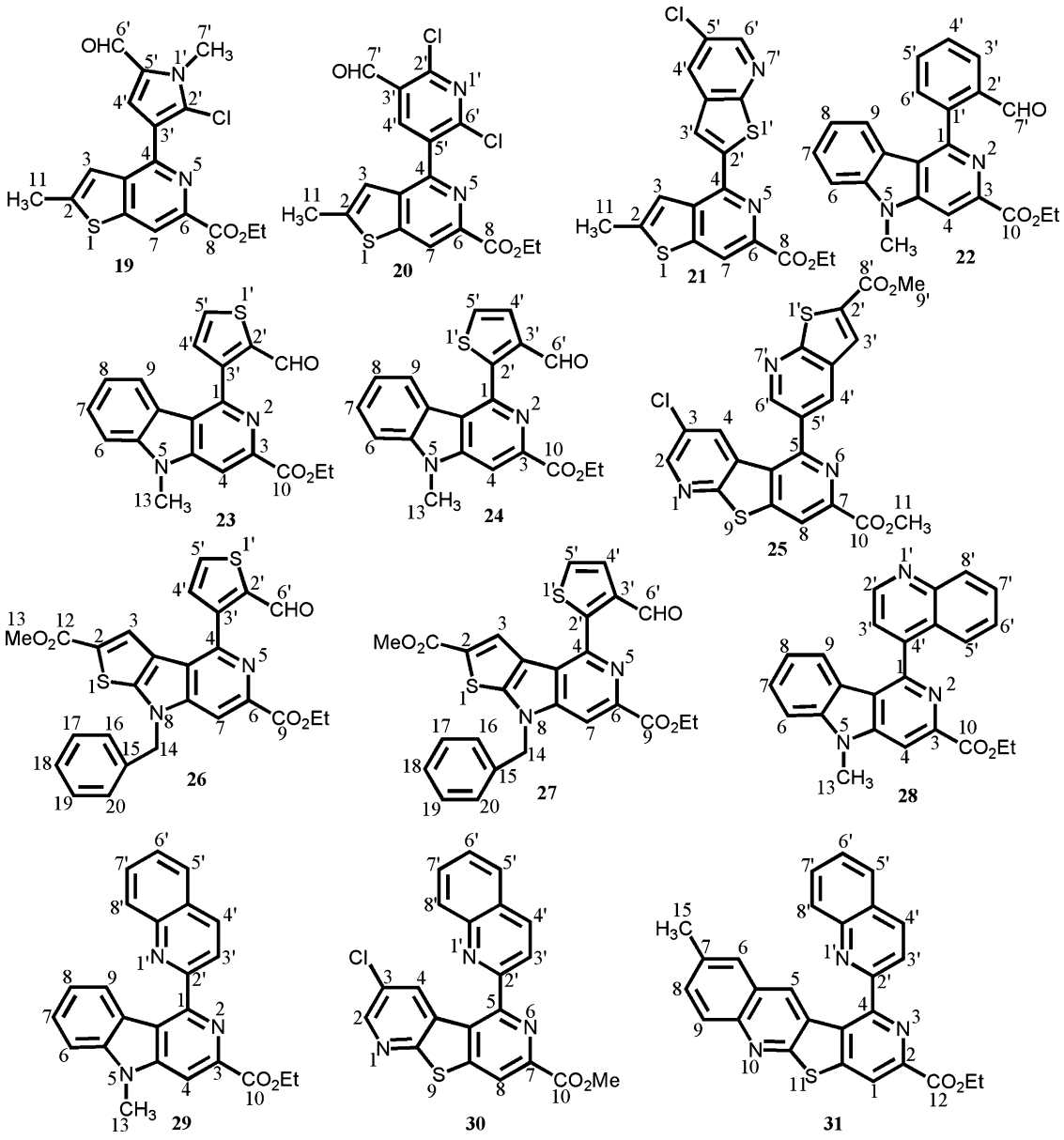


Fig. 1. Biarylic compounds **19**–**31** of this study.

mational evidence for the compound **22**, was the one between H-9 (δ = 7.40) with H-6′ (δ = 7.56), 2.68 Å (Table 3).

Similarly to compound **22**, for the mixture of compounds **23** and **24**, the NMR in $CDCl_3$ solution displays highly overlapped the aromatic protons signals. However, when we recorded the mixture **23** and **24** in a $CDCl_3/C_6D_6$ 1:1 solution, it was possible to isolate the particular chemical shifts of the compounds **23** from those due to **24** and established their ratio at 1:1. For example, both aldehydic protons display a ^5J long range coupling with one of the thiophenic protons confirmed by COSY spectrum. It was for example observed the 5σ bond correlation between aldehydic protons (C-6′) at δ = 10.1 (d, ^5J = 1.0, **23**) with H-5′ δ = 7.24, **23**. The second aldehydic proton at δ = 9.80 (br, **24**) was correlated with the proton at δ = 6.97 (H-5′ **24**), respectively. Through NOESY spectrum we were also able to observe diagonal peaks of H-9 of **23** at δ = 7.69 with cross-peaks of aldehydic protons at δ = 10.1, **23** as well as the signal at δ = 7.28. However, the signal due to H-9 of **24** at δ = 7.60 displayed only dipolar correlation with aldehydic proton at δ = 9.80, **24**. In the same spectrum it was possible to observe less relevant dipolar correlation between H-9 δ = 7.70, **23** with the H-8 δ = 7.01, **23** as well as, for H-9 at δ = 7.60, **24** with H-8 at δ = 6.94, **24**.

The protons on C4 and C6 for **23** (8.26 s, and 7.08 d, respectively) and **24** (8.24, s and 7.03 d) both were assigned through the cross-peaks of their chemical shift using as diagonal peaks those due to N-Me group at δ = 3.14, **23** and 3.10, **24**.

The pair of thiophenic protons for **23**, at δ = 7.24 (dd, ^5J = 1.5, ^3J = 5.0 H-5′) and δ = 7.28 (d, ^3J = 5.0, H-4′); and those due to thiophenic moiety of **24**, δ = 6.97 (dd, ^5J = 1.0, ^3J = 5.5, H-5′) and δ = 7.62 (d, ^3J = 5.5, H-4′) complete the assignment.

The data obtained by Gaussian molecular modeling calculations enable us to evaluate for compounds **23** and **24**, using NOESY spectrum data conformational energy as well as torsional angles as depicted in Table 3.

The most striking conformational behavior was observed for compound **25**. From the data of NOESY spectrum, the diagonal-cross-peak H-4 to both H-6′ and H-4′ as well as the usual dipolar correlation between H-4′ with H-3′, it was possible to evaluate the minimum energy and the corresponding dihedral angle (50.0°)

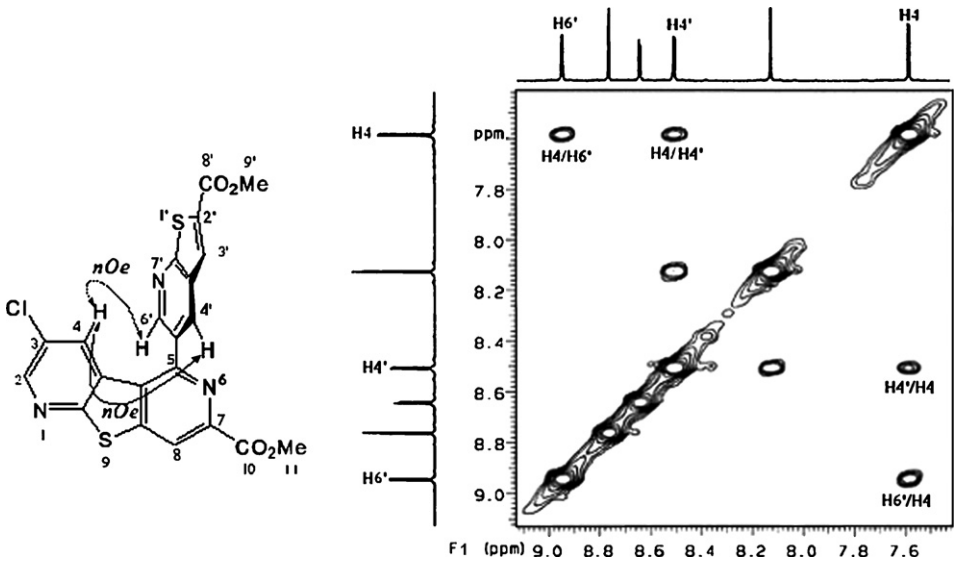


Fig. 2. NOESY experiment of the compound **25**.

between 4b-5, 5′-6′ (Table 4). The interatomic distances between protons are: H-4/H-6′ = 2.58 Å; H-4/H-4′ = 4.28 Å; H-3′/H-4′ = 2.71 Å.

For the isomeric pair of compounds **26** and **27** obtained in 2:1 ratio, the phase sensitive NOESY experiment enable the structural assignment by dipolar correlations between H-3 at δ = 7.80 ppm for derivative **26** which displays a cross-peak (doublet ^3J = 5.0 Hz at δ = 7.64 ppm H-4′). This last signal correlates also with H-5′ at δ = 7.91 (dd ^5J = 1.2, ^3J = 5.0). For the compound **27**, the protons H-5′ and H-4′ display only cross-peak to each other at δ = 7.74 ppm (H-5′) and δ = 7.53 ppm (H-4′). From the NOESY data it was deduced for the pair **26** and **27** that in an orthogonal conformation for derivative **26** a dihedral angle between 3b-4, 3′-4′ carbons is 39.0° and from a dipolar correlation between H-3/H-4′ an internuclear distance of 2.43 Å.

For the derivative **27**, it was obtained the dihedral angle between 3b-4, 3′-1′ carbons of 43.0° with interatomic distance H-4′/H-5′of 2.65 Å.

Similarly for derivative **28**, the phase sensitive NOESY suggested a non-coplanar conformation where both aromatic moieties displays a dihedral angle between 9b-1, 4′-3′ carbons of 57.0°. Consequently, we were able to observe for H-9 three different dipolar correlations, with H-8 (strong), H-3′ (medium) and finally with H-5′ (weak) with internuclear distances of H-3′/H-9 = 2.67 Å, H-5′/H-9 = 4.9 Å, respectively (Fig. 3).

Additional relevant nOe correlations were observed for the cross-peaks for H-6 and H-4 where the diagonal peak for the N-Me at δ = 4.00 helped the unambiguous assignment of the remaining proton signals (H-13/H-6 = 2.49 Å; H-13/H-4 = 2.26 Å).

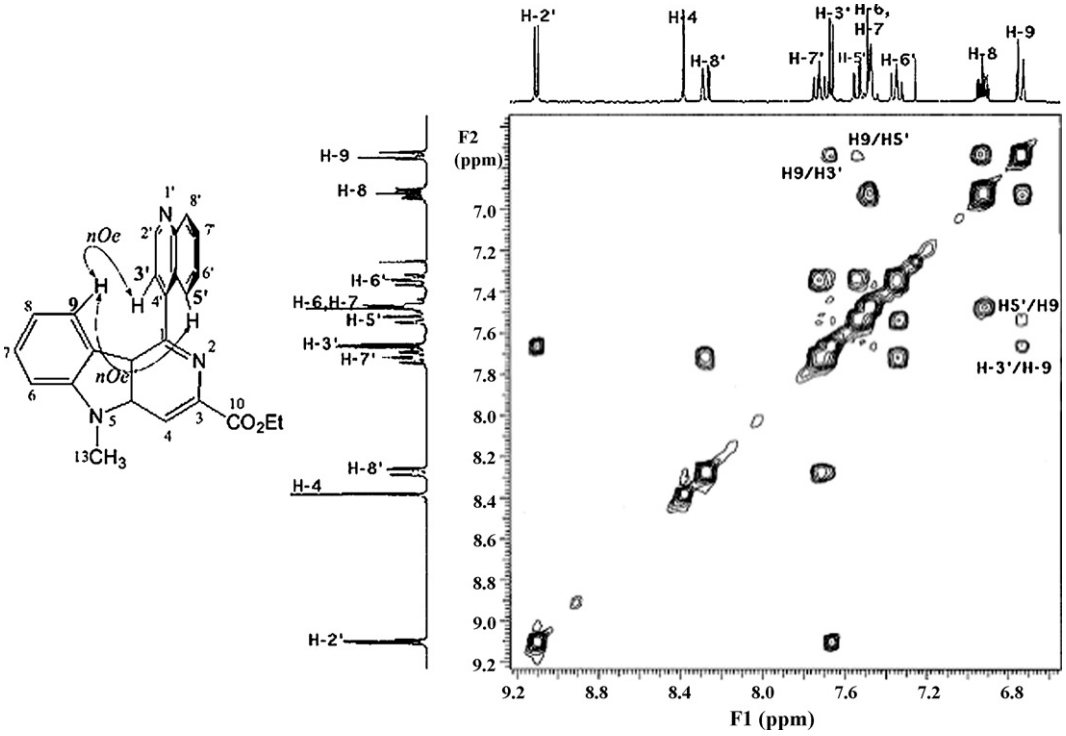


Fig. 3. NOESY of compound **28**.

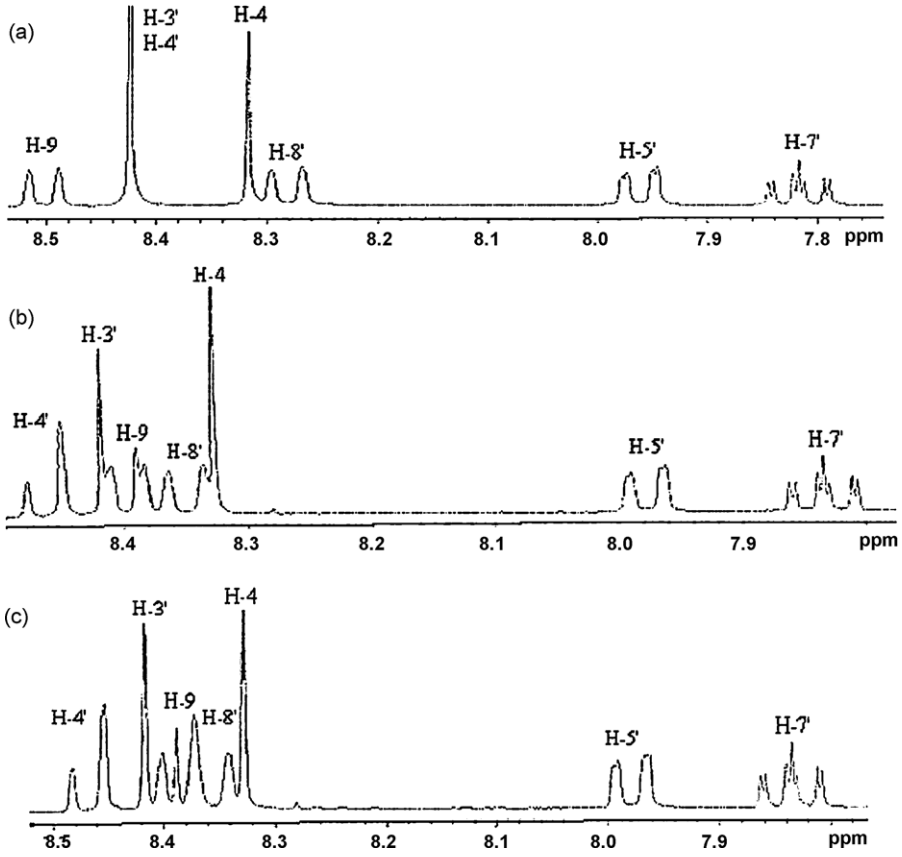


Fig. 4. Chemical shifts modification observed in $CDCl_3$ for compound **29**. (a) After 5 min; (b) 60 min; (c) 24 h (partial spectrum).

The derivative **29** 1D 1H NMR, displayed a special behavior (Fig. 4). It was noted that the chemical shifts due to H-4′ (δ = 8.42), H-3′ (δ = 8.42), H-9 (δ = 8.50) and H-8′ (δ = 8.28) were shifted slightly with time in the chloroformic solution (for example H-4′ $\Delta\delta$ = 0.05 ppm, H-9 $\delta\Delta$ = −0.11 ppm and H-8 $\delta\Delta$ = 0.08 ppm, respectively). The initial spectrum (Fig. 4) enabled us to detect through the NOESY experiment several important dipolar correlations and to deduce its conformation. For example, the key element for the conformational assignment of compound **29** was the dipolar correlation between H-9 with H-8′ which left the molecule with predictable dihedral angle as 22.0° and internuclear distance H-9/H-8′ as 2.67 Å.

For the chloroderivative **30**, its NOESY spectra clearly displayed dipolar correlation between the protons H-4 and H-8′. From the NOESY data it was possible to estimate a H-4/H-8′ through space distance of 2.96 Å with conformational parameters depicted in Table 3.

For the compound **31**, with its two nitrogen atoms in the vicinity of the pivotal bond between two aromatic moieties, it was observed through its ^{1}H NMR spectrum that for some protons their chemical shift was slowly changing, displaying relevant chemical shift difference within 60 min to 24 h period of time. From this observation of the proton signals for the initial/final spectra we have deduced that this was due to the acidity of the NMR solvent ($CDCl_3$) and the structure involved the ammonium salt formation on N-10. The resonance forms depicted in Fig. 5 resume where the electron deficient carbons could be placed as detailed in Table 4. The protons that underwent the major induced acid effect after the protonation on N-l0 are H-5, H-6, H-8 and H-9 [24]. Some additional ^{1}H NMR experiment was also performed on compounds **29** and **31**. When the spectra for both compounds were recorded in perdeuterated benzene no relevant differences of chemical shifts were observed even after one week in solution. However, in deuterated chloroform for compound **31**, which displayed strong acidic effect as described in Table 4 and Fig. 5, the addition of a drop of base (TEA) showed that all protons went back to their original positions.

With respect to the conformational behavior of the molecule **31**, the key element deduced from the NOESY spectrum was the relevant dipolar correlation between H-8′with H-5 (3.07 Å, Fig. 6). The other important correlations, signals that help to unambiguously assign the remaining protons were the diagonal peak due to methyl 15 with the cross-peaks of the signals due to H-8 and H-6 (2.55 Å and 2.44 Å, respectively).

The conformational evidences as deduced from the NOESY spectrum of **31**, enabled us to estimate the interatomic distances for selected protons; for example, 2.49 Å for H-5/H-6; and 2.56 Å for H-4′/H-5′. In order to explain the long-range dipolar correlation between H-5/H-8′, in the absence of observable correlation between H-6/H-8′ the dihedral angle between the planes of the two aromatic rings should be of 35.0°, this matched with the minimum energy calculated for this molecule (see Table 3 and Fig. 6).

Using dipolar correlations observed from NOESY experiments, with compounds **19**–**31**, the conformational studies were performed upon the relevant diagonal/cross-peaks. These data and some other dipolar correlations, including the dihedral angles and the calculated minimum energy deduced from the NMR features deduced from the 2D NMR spectra, are summarized in Table 3.

The lowest energy conformation can be estimated after the minimization of the NMR data via the semi-empirical method. In the same operation, the torsional angle formed by two aromatic systems could also be calculated.

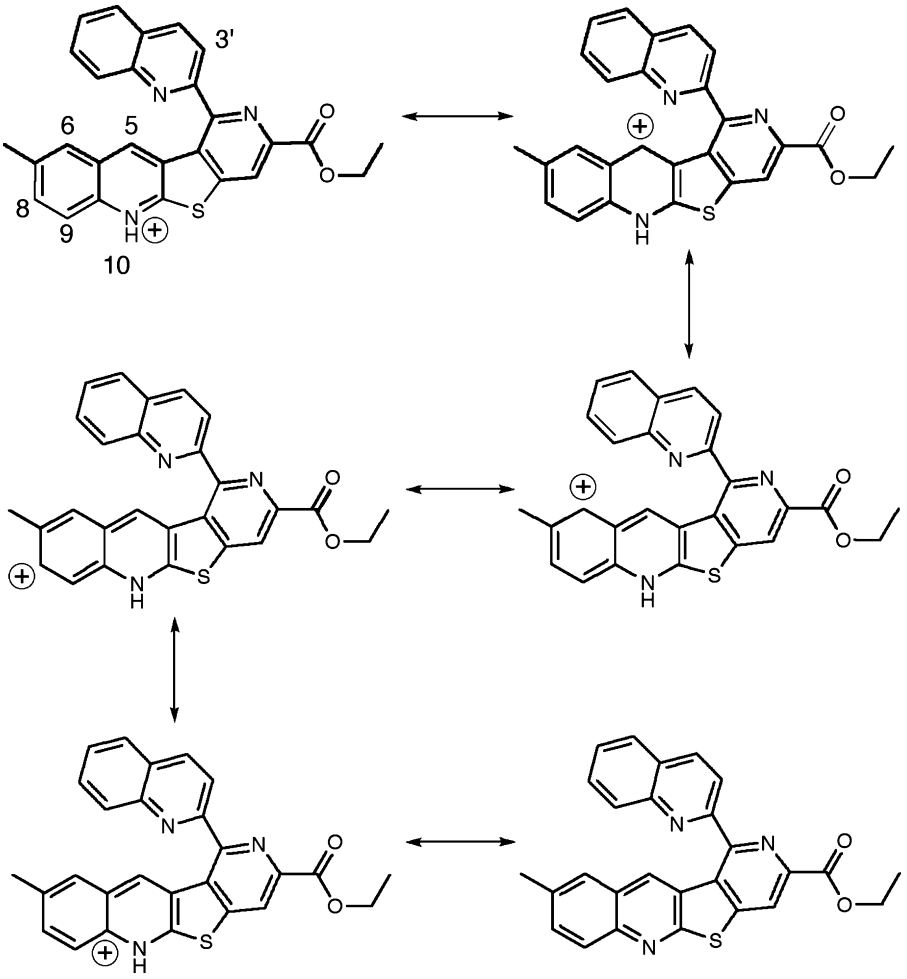


Fig. 5. Resonance forms of protonated compound **31**.

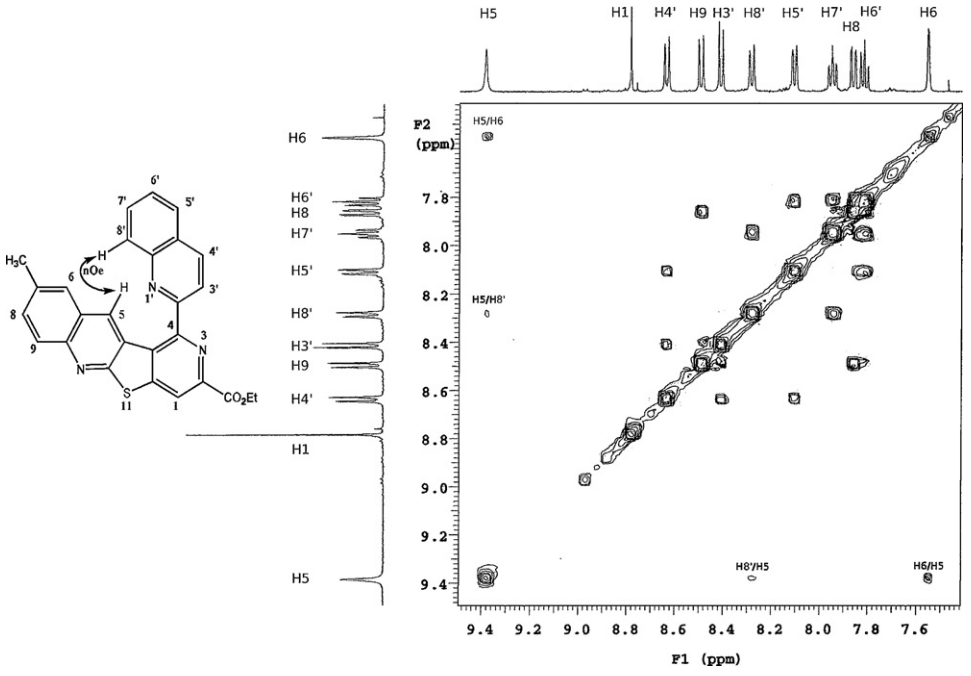


Fig. 6. NOESY of compound **31**.

Table 3
Summary of conformational features of compounds **19–31**.

Compound	Relevant cross-peaks	Other dipolar correlations	Dihedral angle[a] θ (°)	Dihedral angle θ atoms involved[a]	Rotational energy[a] (Kj/mol)	Complementary dihedral angle[a] ω (°)	Dihedral angle ω atoms involved[a]
19	H-3/H-4′, H-4′/H-6′	H-3/H-11	−40 to +40	3a-4-3′-4′	2.88	+143 to −142	3a-4-3′-2′
20	H-3/H-4′, H-4′/H7′	H-3/H-11	−67 to +62	3a-4-5′-4′,	10.0,	+114 to −118	3a-4-5′-6′,
			−127 to +123	3a-4-5′-4′	11.32	+57 to −60	3a-4-5′-6′
21	H-3/H-3′, H-3′/H-4′	H-3/H-11	−26 to +24	3a-4-2′-3′		+156 to −159	3a-4-2′-1′
22	H-9/H-6′, H-7′/H-3′, H-9/H-7′	H-13/H-4, H-13/H-6	−55 to +55	9b-1-1′-6′	12.09	+125 to −129	9b-1-1′-2′
23	H-9/H-6′, H-4′/H-5′, H-9/H-4′	H-13/H-4, H-13/H-6	−54 to +56	9b-1-3′-2′	9.87	+129 to −126	9b-1-3′-4′
24	H-6′/H-9, H-4′/H-5′	H-13/H-4, H-13/H-6, H-9/H-8	−54 to +54	9b-1-2′-3′	23.48	+126 to −126	9b-1-2′-1′
25	H-4/H-6′, H-4′/H-4	H-4′/H-3′	−50 to +50,	4b-5-5′-6′,	11.7,	+136 to −136,	4b-5-5′-4′
			−129 to +130	4b-5-5′-6′	11.5	+54 to −54	
26	H-3/H-4′, H-14/H-7	H-14/H-20	−39 to +39	3b-4-3′-4′	63.9	+141 to −141	3b-4-3′-2′
27	H-6′/H-4′, H-14/H-7	H-14/H-20	−43 to +43	3b-4-2′-1′	70.6	+ 137 to −137	3b-4-2′-1′
28	H-9/H-3′, H-9/H-5′	H-13/H-4, H-13/H-6, H-9/H-8	−57 to +52	9b-1-4′-3′	13.9	+124 to −129	9b-1-4′-4′a
29	H-9/H-8′, H-13/H-4, H-13/H-6	H-4′/H-5′, H-3′/H-4′	−22 to +22	9b-1-2′-1′		+158 to −158	9b-1-2′-3′
30	H-4/H-8′, H7′/H8′	H-3′/H-4′, H-4′/H-5′	−30 to +30	4b-5-2′-1′		+150 to −150	4b-5-2′-3′
31	H-5/H-8′, H-5/H-6, H4′/H-5′	H-15/H-6, H-15/H-8, H-8/H-9	−35 to +35	5b-4-2′-1′		+145 to −145	5b-4-2′-3′

θ And ω, dihedral angles between two aromatic cycles.
[a] Calculated by semi-empirical ChemBioDraw Ultra® version 11.0 MM-2 simulation program and Gaussian 03′ Density Function Theory (DFT) B3LYP6-31G (d,p) program [25,26].

Table 4
NMR time depending data for compound **31** in $CDCl_3$ (500 MHz). Chloroform induced chemical shifts.

δH (ppm)	5 min	60 min	24 h	One week	$\Delta\delta$ (ppm)
H-1	8.73	8.73	8.76	8.78	+0.05
H-5	8.69	8.77	9.12	9.40	+0.71
H-6	7.34	7.36	7.47	7.56	+0.22
H-8	7.64	7.66	7.77	7.87	+0.23
H-9	8.05	8.09	8.32	8.50	+0.45
H-3′	8.25	8.26	8.35	8.42	+0.17
H-4′	8.53	8.54	8.58	8.64	+0.11
H-5′	8.05	8.06	8.08	8.10	+0.05
H-6′	7.74	7.76	7.80	7.82	+0.08
H-7′	7.88	7.88	7.92	7.95	+0.07
H-8′	8.16	8.17	8.22	8.28	+0.12

This angle gives a precise idea about the conformation adopted by the biarylic rotating systems, as in compounds **19**–**31**, and is as such, it is valuable additional tool for completely characterizing these molecules.

Calculations were processed with semi-empirical ChemBioDraw Ultra® 3D version 11.0 and with Gaussian 03'. Together these programs allowed us to calculate the dihedral angles and evaluate the corresponding rotational energy for the conformation with the lowest energy minimized. Data are presented in Table 3.

2.1. Comparison of NMR assisted computational data

2.1.1. Conformational analysis and computational details

The NOE experiments are now used in analysis of molecular structure and dynamics, for both small molecules and macromolecules. Although NOEs are often treated qualitatively as static phenomena, the observed effects are usually a time average of contributing structures, and must be interpretated cautiously. Furthermore, differences in relaxation behavior can change the nature of the observed effects. Dipolar cross-relaxation gives rise to the NOE, and it is necessary to suppress other relaxation mechanisms as much as possible in order to maximize the weak effects such as intramolecular NOEs. The typical detection limit observed for nuclei with intermediate relaxation times under the best circumstances, with minimal effect from other relaxation mechanism [27] is ∼5 Å.

The NOESY experiments provides structural information through the NOE cross-peaks, whose magnitudes are inversely proportional to the sixth power of the interproton distance (r) in space ($1/r^6$).

Because of the fact that, the most of the compounds studied herein, are formed by two aromatic moieties linked by a pivotal bond they adopt specific orientations to reduce the stereo violations. The systematic search started from the dihedral angle measured from specific conformations obtained by rotation about this pivotal bond. This could define the relative orientation of the substituents on the biphenyl-like scaffold.

Compared to the NOE patterns we retain for calculations only the conformations which are consistent with the experimental NMR data and subjected to the following calculations:

(i) Semi-empirical ChemBioDraw Ultra® 3D version 11.0 MM2 simulations and energy minimization with any constraint. The conformation with the lowest energy was chosen as the starting structure for a systematic search of the representative dihedral angles.
(ii) The lowest energy conformations should fit the NOE data.
(iii) In the final step we used quantum chemical calculation through Gaussian 03 with Density Function Theory (DFT) (with a step size of 5–10°, respectively).

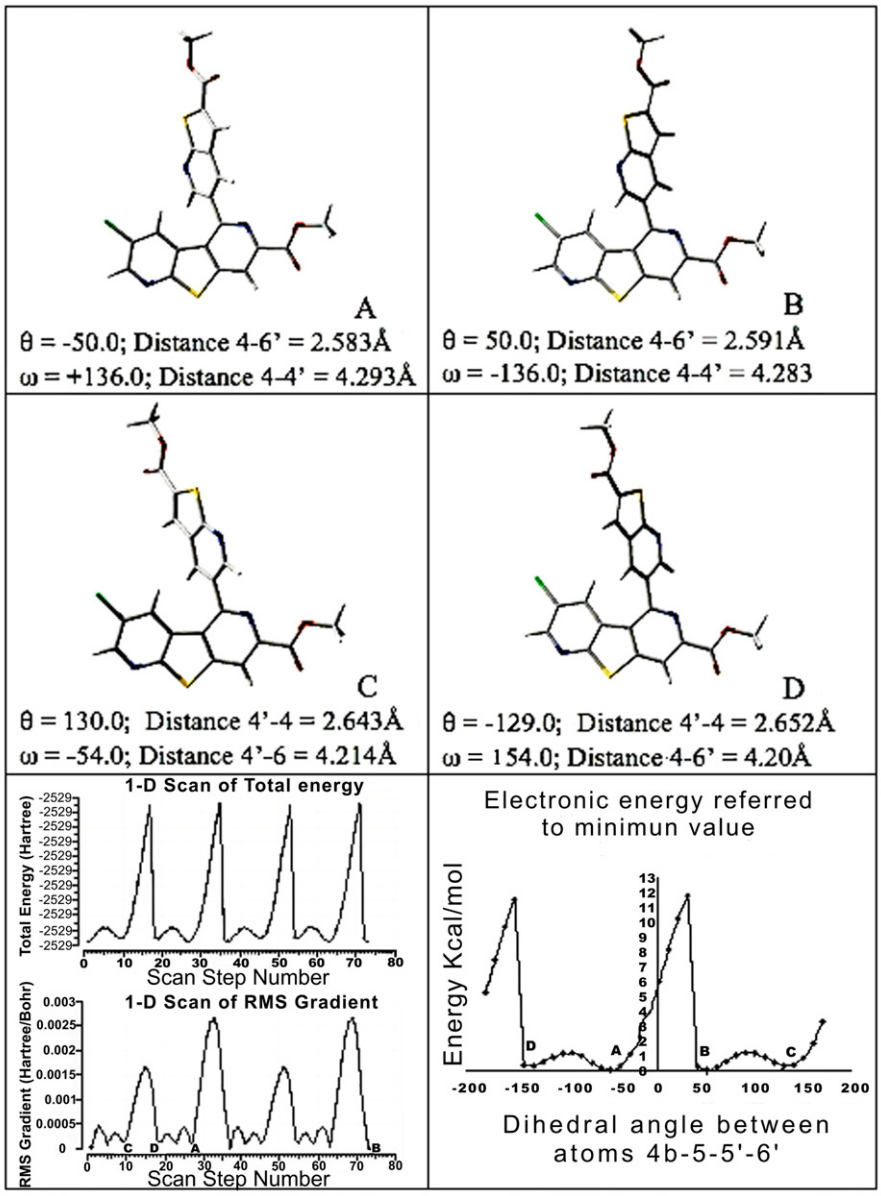


Fig. 7. Compound **25**.

In order to have a clearer picture of the conformation of compounds **19**–**31** two dihedral angles were defined which involved atoms adjacent to the pivotal bond (θ and ω). The dihedral angles θ and ω were scanned simultaneously, the systematic searching began from this selected geometry. Through DFT calculations we were able to draw the different energy curve for each compound (see Table 3 and Figs. 7 and 8) with the relative potential energy (kJ/mol) being plotted as a function of the dihedral angle θ leading to detailed analysis of compounds **25** and **28**.

The optimized structures of conformers: A, B, C and D using DFT density functional theory (B3LYP/6-31G):

(a) Relative potential energy (kJ/mol) of conformers from **25** as a function of dihedral angle θ with Hartree units and angular angle step of 5°.
(b) Relative potential energy (kJ/mol) of conformers from **25** as a function of dihedral angle obtained from a system search analysis with a step size of 10°.
(c) The rotational barrier between points A and B was calculated as 11.79 kJ/mol.
(d) Energy difference between points A and D shown a $\Delta E = 0.28$ kJ/mol.

The optimized structures of conformers A and B using density functional theory (B3LYP/6-31G):

(a) Relative potential energy (kJ/mol) of conformers from **28** as a function of dihedral angle θ with the Hartree units and angular angle step of 5°.
(b) Relative potential energy (kJ/mol) of conformers from **28** as a function of dihedral angle obtained from a system search analysis with a step size 10°.
(c) The rotational barrier between lowest energy points was calculated as 13.9 kJ/mol.

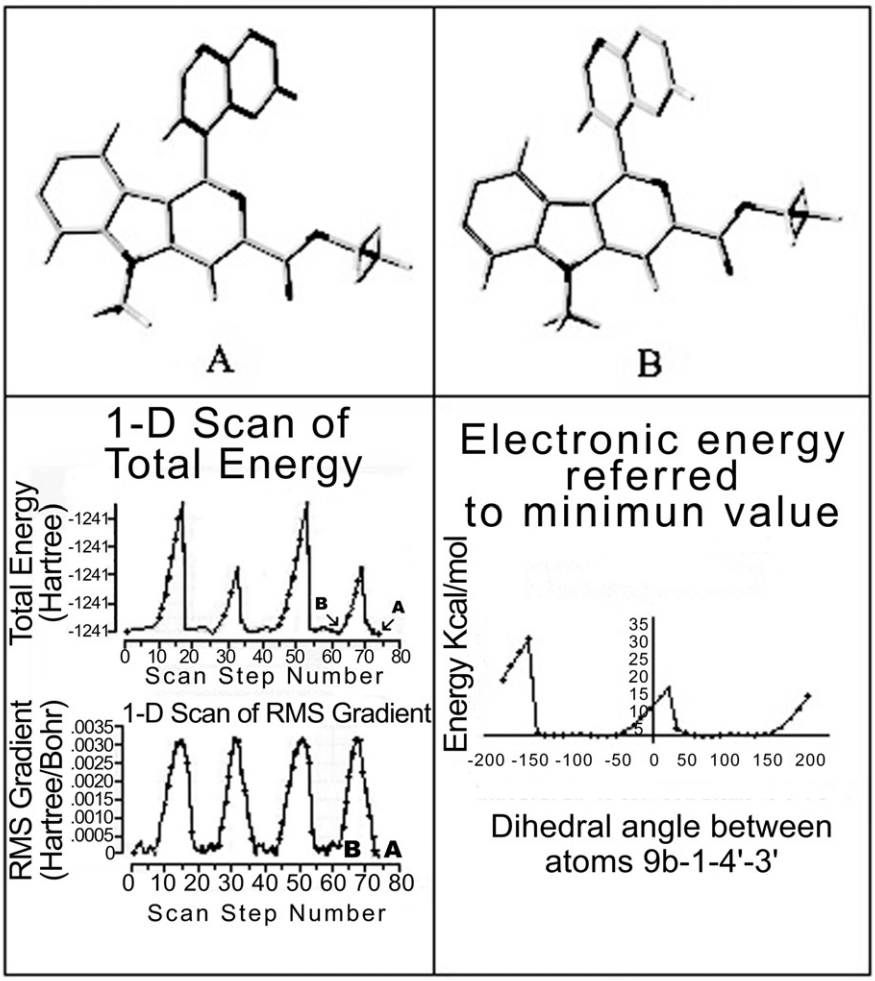


Fig. 8. Compound **28**.

3. Conclusion

The conformational analysis of these compounds as performed by a combination of NMR spectroscopy and quantum chemical calculation, shows an excellent agreement between two approaches to conformational analysis. The structure calculation of compounds **19**–**31** was conducted using molecular dynamics (MD) simulation and Gaussian 03 for quantum chemical calculation in order to have a clearer picture of the preferred conformations adopted by several rotationally hindered biarylic compounds.

On the other hand, the NMR experiment results in particularly the phase sensitive NOESY, when applied to the analysis of several biarylic derivatives in solution, displayed an excellent agreement with the data published in our previous work [22].

We were able to establish a complete conformational profile for several thienopyridines and indole derivatives. The NOESY data, when compared with the results of molecular modeling calculations afforded complementary features for description of molecules that have two aromatic moieties with limited rotation around the pivotal bond. The major conformation in solution is the one that presents with a minimal conformational energy. The interatomic distances of selected protons as calculated from NMR data fully agreed with the assignments presented in this study.

On the other hand, the axis of a biaryl which is rotationally hindered and thus stereogenic is the structurally, conformationally and stereochemically decisive element of a steadily growing number of natural products, chiral auxiliaries and catalysis. Thus is not surprising that significant advances in the synthesis of new biarylic compounds have been performed.

4. Experimental

Melting points were determined with a Kofler hot stage and they are uncorrected. ^{1}H and ^{13}C spectra were recorded using a Varian Unity 300 for routine experiments and Varian Unity 500 spectrometers for 2D experiments (NOESY, HSQC, and HMBC). The ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00 ppm). For analytical purpose the mass spectra were recorded on a JEOL JMS-5X 10217 in EI/PI mode, 70 eV, 200 °C using the direct inlet probe. Only molecular ion (m/z) values are reported. IR spectra were recorded on a Nicolet Magna 55-X FT instrument.

Aldehydes used in the preparation of compounds **6**–**7**, **23**–**25**, **27**–**31** were purchased from Aldrich and used as received. The aldehydes used to synthesized compounds **8**–**10**, **19**–**22**, **25**–**26**, were prepared according to the literature [28].

4.1. General procedure for the reaction between aldehydes and iminophosphoranes

A mixture of 0.1 mmol of the iminophosphorane intermediate **6**–**10** and 0.1 mmol of the corresponding aromatic aldehyde (Ar_2) in 2 mL of 1,2-dichlorobenzene was refluxed for 12–16 h. The mix-

ture was allowed to reach room temperature and then purified by column chromatography (silica gel, 70–230 mesh) yielding in all cases white solids.

*4-(2-Chloro-5-formyl-1-methyl-1H-pyrrol-3-yl)-6-ethoxycarbonyl-2-methyl-thieno[3,2-c] pyridine (**19**).* m.p. 214–216 °C, yield 77%. $C_{17}H_{15}O_3N_2SCl$; MW: 362.83; C, 56.27; H, 4.17; Cl, 9.77; N, 7.72; O 13.23; S, 8.84. MS (*E.I.*) *m/z* (%): 362 (M^+; 40), 364 (M^++2; 13). ^{1}H NMR 500 MHz ($CDCl_3$) δ (ppm): 1.45 (t, 3H, *J* = 7.0 Hz; H-10); 2.68 (d, 2H; *J* = 1.5 Hz; H-11); 3.97 (s, 3H; H-7′); 4.47 (q, 2H, *J* = 7.0 Hz; H-9); 7.08 (s, 1H; H-4′); 7.4 (dd, 1H; *J* = 1.5, 0.5 Hz; H-3); 8.49 (d, 1H; *J* = 0.5 Hz; H-7); 9.94 (s, 1H; H-6′). ^{13}C NMR 125 MHz ($CDCl_3$) δ (ppm): 14.3 (C-10); 16.4 (C-11); 32.0 (C-7′); 61.7 (C-9); 110.7 (C-4′); 118.1 (C-7), 120.6 (C-3′); 121.1 (C-3); 136.8 (C-3a); 140.4 (C-2′); 144.4 (C-4); 146.0 (C-5′); 146.9 (C-6); 148.6 (C-7a); 165.3 (C-8); 184.1 (C-6′).

*4-(2,6-Dichloro-5-formyl-pyridin-3-yl)-6-ethoxycarbonyl-2-methyl-thieno[3,2-c]pyridine (**20**).* m.p. 203–204 °C, yield 72%. $C_{17}H_{12}O_3N_2SCl_2$; MW: 395.26; C, 51.66; H, 3.06; Cl, 17.94; N, 7.09; O, 12.14; S, 8.11. MS (*E.I.*) *m/z* (%): 394 (M^+: 16) 396 (M^++2; 9), 398 (M^++4; 4). ^{1}H NMR 500 MHz ($CDCl_3$) δ (ppm): 1.46 (t, 3H; *J* = 7.0 Hz; H-10); 2.65 (d, 3H; *J* = 1.0 Hz; H-11); 4.5 (q, 2H; *J* = 7.0 Hz; H-9); 6.83 (qt, 1H, *J* = 1.0 Hz; H-3); 8.38 (s, 1H; H-4′); 8.67 (d, 1H, *J* = 0.5 Hz; H-7); 10.4 (s, 1H,; H-7′). ^{13}C NMR 125 MHz ($CDCl_3$) δ (ppm): 14. 3 (C-10); 16.4 (C-11); 62.0 (C-9); 119.8 (C-7); 119.9 (C-3); 127.8 (C-3′); 134.8 (C-5′); 137.2 (C-3a); 141.1 (C-6); 141.8 (C-4′); 147.6 (C-7a); 147.9 (C-4); 147.3 (C-2); 152.1 (C-2′); 153.5 (C-6′); 165.1 (C-8); 187.6 (C-7′).

*4-(5-Chloro-thieno[2,3-b]pyridin-2-yl)-6-ethoxycarbonyl-2-methyl-thieno[3,2-c]pyridine (**21**).* m.p. 251–253 °C, yield 83%. $C_{18}H_{13}O_2N_2S_2Cl$; MW: 388.89; C, 55.59; H, 3.37; Cl, 9.12; N, 7.2; O, 8.23; S, 16.49. MS (*E.I.*) *m/z* (%): 388 (M^+: 40) 390 (M^++2; 13). ^{1}H NMR 500 MHz ($CDCl_3$) δ (ppm): 1.5 (t, 3H; *J* = 7.0 Hz; H-10); 2.65 (d, 3H; *J* = 1.0 Hz; H-11); 4.5 (q, 2H; *J* = 7.0 Hz; H-9); 7.66 (m, 1H, H-3); 7.87 (s, 1H; H-3′); 8.08 (d, 1H, *J* = 2.0 Hz; H-4′); 8.55 (d, 1H, *J* = 2.0 Hz; H-6′); 8.67 (d, 1H, *J* = 1.0, Hz; H-7). ^{13}C NMR 125 MHz ($CDCl_3$) δ (ppm): 14.3 (C-10); 16.6 (C-11); 61.9 (C-9); 118.8 (C-7); 120.6 (C-3′); 120.6 (C-3); 128.5 (C-5′); 130.5 (C-4′); 145.7 (C-4); 135.2 (C-3a); 140.7 (C-2′); 134.2 (C-3a′); 146.3 (C-6′); 146.3 (C-6); 147.8 (C-2); 149.2 (C-7a); 160.1 (C-7a′); 165.2 (C-8).

*5-Methyl-3-carboethoxy-1-(2-formylphenyl)-carboline (**22**).* m.p. 199–201 °C, yield 84%. $C_{22}H_{18}O_3N_2$; MW: 358.38; C, 73.73; H, 5.06; N, 7.82; O, 13.39. MS (*E.I.*). *m/z* (%): 358 (M^+; 3). ^{1}H NMR 300 MHz ($CDCl_3$) δ (ppm): 1.47 (t, 3H, *J* = 7.0 Hz, H-12); 4.01 (s, 3H, H-13); 4.54 (q, 2H, *J* = 7.0 Hz; H-11); 7.01 (m, 2H; H-8, H-9); 7.49 (m, 2H; H-6, H-7); 7.67 (m, 3H, H-4′, H-5′, H-6′); 8.18 (d, 1H, *J* = 8.0 Hz; H-3′); 8.33 (s, 1H, H-4); 9.79 (s, 1H, H-7′). ^{13}C NMR 75 MHz ($CDCl_3$) δ (ppm): 14.4 (C-12); 29.5 (C-13); 62.0 (C-11); 105.9 (C-4); 109.3 (C-6); 120.6 (C-9b); 121.1 (C-8); 122.3 (C-9); 128.0 (C-7); 128.1 (C6′); 129.4 (C-4′); 130.6 (C-3′); 133.9 (C-5′); 134.5 (C-9a); 142.2 (C-4a); 143.2 (C-3); 145.3 (C-5a); 150.9 (C-1); 166.0 (C-10); 191.3 (C-7′).

*1-(2-Formyl-thiophen-3-yl)-3-carboethoxy-5-methyl-5H-pyrido[4,3-b]indole (**23**).* m.p. 212–213 °C, yield 92%. $C_{20}H_{16}O_3N_2S$; MW: 364.41; C, 65.92; H, 4.43, N, 7.69, O, 13.17, S, 8.80. MS (*E.I.*). *m/z* (%): 364 (M^+; 12). NMR ^{1}H 500 MHz ($CDCl_3$/C_6D_6 1:1) δ (ppm): 1.20 (t, 3H, *J* = 7.0 Hz; H-12); 3.14 (s, 3H, H-13); 4.36 (q, 2H, *J* = 7.0 Hz; H-11); 7.01 (ddd, 1H; *J* = 7.5, 8.0, 1.0 Hz; H-8); 7.69 (ddd, *J* = 1.0, 1.5, 8.0 H-9), 7.28 (d, *J* = 5.5 H-4′); 7.24 (d, 1H, *J* = 5.5 Hz; H-5′); 8.26 (s, 1H, H-4); 10.1 (s, 1H, H-6′); 7.33 (ddd *J* = 1.0, 7,5, 8.0; H-7); 7.08 (brd, *J* = 8, H-6). ^{13}C NMR 75 MHz ($CDCl_3$) δ (ppm): 14.4 (C-12); 29.6 (C-13); 62.1 (C-11); 106.1 (C-4); 109.5 (C-6); 120.5 (C-9b); 121.4 (C-8); 122.5 (C-9); 128.3 (C-7); 130.7 (C-4′); 133.9 (C-5′); 134.0 (C-9a); 141.6 (C-3); 142.2 (C-4a); 143.5 (C-2′); 144.2 (C-3′); 145.7 (C-5a); 146.8 (C-1); 165.9 (C-10); 184.1 (C-6′).

*1-(3-Formyl-thiophen-2-yl)-3-carboethoxy-5-methyl-5H-pyrido[4,3-b]indole (**24**).* m.p. 212–213 °C, yield 92%. $C_{20}H_{16}O_3N_2S$; MW: 364.41; C, 65.92; H, 4.43; N, 7.69; O, 13.17; S, 8.80; MS (*E.I.*) *m/z* (%): 364 (M^+; 12). ^{1}H NMR 500 MHz (C_6D_6/$CDCl_3$ 1:1) δ (ppm): 1.19 (t, 3H, *J* = 7.0 Hz; H-12); 3.10 (s, 3H, H-13); 4.355 (q, 2H, *J* = 7.0 Hz; H-10); 6.94 (ddd, 1H; *J* = 7.5, 8.0, 1.0 Hz; H-8); 7.28 (dd, 1H, *J* = 7.5, 7.5, 1.0 Hz; H-7); 7.03 (br d 7.5; H-6); 7.60 (ddd 1.0,1.5,8.0 H-9); 7.62 (d, *J* = 5.5 H-4′); 7.97 (d, 1H, *J* = 5.5 Hz; H-5′); 8.245 (s, 1H, H-4); 9.80 (s, 1H, H-6′). ^{13}C NMR 75 MHz ($CDCl_3$) δ (ppm): 14.4 (C-12); 29.6 (C-13); 62.1 (C-11); 106.5 (C-4); 109.5 (C-6); 121.5 (C-8); 122.3 (C-9b); 122.3 (C-9); 125.9 (C-5′); 127.3 (C-4′); 128.5 (C-7); 134.0 (C-9a); 139.4 (C-2′); 143.5 (C-4a′); 144.2 (C-3′); 145.5 (C-5a); 147.9 (C-1); 165.8 (C-10); 185.2 (C-6′).

*3-Chloro-5-(2-methoxycarbonyl-thieno[2,3-b]pyridin-5-yl)-7-methoxycarbonyl-thieno[2,3-b:4,5-c′]dipyridine (**25**).* m.p. 282–283 °C, yield 77%. $C_{21}H_{12}O_4N_3S_2Cl$; MW: 469.92; C, 53.67; H, 2.57; Cl, 7.54; N, 8.94; O, 13.62; S, 13.65. MS (*E.I.*) *m/z* (%): 469 (M^+; 22), 471 (M^++2; 7). ^{1}H NMR 300 MHz ($CDCl_3$) δ (ppm): 4.02 (s, 3H, H-9′); 4.07 (s, 3H, H-11); 7.58 (d, 1H; *J* = 2.5 Hz; H-4); 8.12 (s, 1H; H-3′); 8.5 (d, 1H, *J* = 2.5 Hz; H-4′); 8.64 (d, 1H, *J* = 2.5 Hz; H-2); 8.76 (s, 1H; H-8); 8.94 (d, 1H, *J* = 2.5 Hz; H-6′). ^{13}C NMR 75 MHz ($CDCl_3$) δ (ppm): 52.9 (C-9′); 53.3 (C-11); 119.3 (C-8); 127.6 (C-5′); 127.9 (C-3′); 128.6 (C-4a); 131.3 (C-4); 131.9 (C-3); 132.2 (C-2′); 133.4 (C-4′); 135.4 (C-3a′); 144.2 (C-7); 148.8 (C-6′); 149.0 (C-2); 149.8 (C-8a); 150.2 (C-4b); 153.3 (C-5); 159.8 (C-9a); 163.9 (C-8′); 165.1 (C-10); 165.5 (C-7a′).

*6-Carboethoxy-2-carbomethoxy-8-benzyl-4-(2-formyl-thiophen-3-yl)-8-thia-5,8-diazacyclopenta [a]-indene-5-aza-thieno[2,3-b]pyrrolo[3,2-c]pyridine (**26**).* m.p. 246–248 °C, yield 75%. $C_{26}H_{20}O_5N_2S_2$; MW: 504.57; C, 61.89; H, 4.0; N, 5.55; O, 15.85; S, 12.71. MS (*E.I.*) *m/z* (%): 504 (M^+; 22). NMR ^{1}H 300 MHz ($CDCl_3$) δ (ppm): 1.48 (t, 3H, J = 7.0 Hz, H-11); 3.90 (s, 2H, H-13); 4.52 (q, 2H, J = 7.0 Hz; H-10); 5.53 (s, 2H; H-14); 7.14–7.34 (m, 5H; H16-H20); 7.64 (d, 1H, J = 5.0 Hz; H-4′); 7.91 (dd, 1H, J = 5.0, 1.2 Hz; H-5′); 7.80 (s, 1H, H-3); 8.4 (s, 1H, H-7); 10.14 (d J = 1.2, 1H, H-6′).

*8-Benzyl-8H-6-carboethoxy-2-carbomethoxy-4-(3-formyl-thiofen-2-yl)-5-aza-thieno[2,3-b]pirrolo[3,2-c]pyridine (**27**).* m.p. 246–248 °C, yield 75%. $C_{26}H_{20}O_5N_2S_2$; MW: 504.57; C, 61.89; H, 4.00; N, 5.55; O, 15.85; S, 12.71. MS (*E.I.*) *m/z* (%): 504 (M^+; 22). ^{1}H NMR 300 MHz ($CDCl_3$) δ (ppm): 1.48 (t, 3H, *J* = 7.0 Hz; H-11); 3.86 (s, 3H, H-13); 4.53 (q, 2H, *J* = 7.0 Hz; H-10); 5.53 (s, 2H; H-14); 7.14–7.34 (m, 5H; H16-H20); 7.73 (d, 1H, *J* = 5.3 Hz; H-4′); 7.53 (dd, 1H, *J* = 5.0, 0.75 Hz; H-5′); 7.83 (s, 1H; H-3); 8.41 (s, 1H, H-7); 9.94 (br s, 1H; H-6′).

*5-Methyl-3-carboethoxy-1-quinol-4-yl-5H-pyrido[4,3-b]indole (**28**).* m.p. 274–276 °C, yield 91%. $C_{24}H_{19}O_2N_3$; MW: 381.42; C, 75.57; H, 5.02; N, 11.02; O, 8.39. MS (*E.I.*) *m/z* (%): 381 (M^+; 75). ^{1}H NMR 300 MHz ($CDCl_3$) δ (ppm): 1.44 (t, 3H, *J* = 7.2 Hz, H-12); 4.0 (s, 3H, H-13); 4.52 (q, 2H, *J* = 7.2 Hz; H-11); 6.73 (dd, 1H, *J* = 1.2, 8.1, Hz; H-9); 6.93 (m, 1H, H-8); 7.34 (ddd, 1H, *J* = 1.2, 8.1 Hz; H-6′); 7.47 (m, 2H, H-6, H-7); 7.53 (dd, 1H, *J* = 8.1, 0.9 Hz; H-5′); 7.66 (d, 1H, *J* = 4.5 Hz; H-3′); 7.71 (ddd, 1H, *J* = 8.4, 1.5 Hz; H-7′); 8.26 (d, 1H, *J* = 8.1 Hz; H-8′); 8.38 (s, 1H, H-4); 9.1 (d, 1H, *J* = 4.5 Hz; H-2′). ^{13}C NMR 75 MHz ($CDCl_3$) δ (ppm): 14.3 (C-12); 29.5 (C-13); 61.9 (C-11); 106.1 (C-4); 109.2 (C-6); 120.0 (C-9a); 120.2 (C-9b); 121.0 (C-8); 121.5 (C-3′); 122.6 (C-9); 125.8 (C-5′); 126.5 (C-4a); 126.6 (C-5a′); 127.1 (C-6′); 127.9 (C-7); 129.2 (C-8′); 129.9 (C-7′); 142.1 (C-4a); 143.6 (C-3); 145.4 (C-5a); 146.4 (C-4′); 148.0 (C-8a′); 149.7 (C-2′), 150.2 (C-1); 166.0 (C-10).

*5-Methyl-3-carboethoxy-1-quinol-2-yl-5H-pyrido[4,3-b]indole (**29**).* m.p. 179–180 °C, yield 83%. $C_{24}H_{19}O_2N_3$; MW: 381.42; C, 75.57; H, 5.02; N, 11.02; O, 8.39. MS (*E.I.*) *m/z* (%): 381 (M^+; 85); 309 (100). ^{1}H NMR 300 MHz ($CDCl_3$) δ (ppm): 1.44 (t, 3H, *J* = 7.5 Hz, H-12); 3.99 (s, 3H, H-13); 4.52 (q, 2H, *J* = 7.5 Hz; H-11); 7.20 (ddd, *J* = 1.2, 7.2, 7.2 Hz; H-8); 7.50 (d, 1H, *J* = 7.2 Hz; H-6); 7.65 (ddd, 1H, *J* = 1.2, 6.9, 6.9 Hz; H-7); 7.70 (ddd, 1H, *J* = 6.9, 1.5 Hz; H-6′); 7.84 (ddd, 1H, *J* = 1.5, 6.9 Hz; H-7′); 7.98 (dd, 1H, *J* = 8.4, 1.5 Hz; H-5′); 8.40 (s, 1H, H-4); 8.36 (d, 1H *J* = 8.4 Hz; H-8′); 8.39 (dd, 1H, *J* = 8.1, 1.2 Hz; H-9); 8.40 (d, 1H, *J* = 4.5 Hz; H-3′); 8.47 (d, 1H, *J* = 4.5 Hz;

H-4′). ^{13}C NMR 75 MHz ($CDCl_3$) δ (ppm): 14.4 (C-12); 29.5 (C-13); 61.9 (C-11); 106.2 (C-4); 108.8 (C-6); 119.9 (C-9b); 128.2 (C9a); 121.0 (C4′a); 120.9 (C-8); 142.7 (C-4a); 122.4 (C-9); 125.6 (C-3′); 127.2 (C-6′); 127.8 (C-5′); 128.1 (C-7); 129.2 (C-8′); 130.0 (C-7′); 137.3 (C-4′); 142.7 (C-4a); 146.9 (C8a′); 146.6 (C-5a); 146.9 (C-3); 152.0 (C-1); 157.7 (C-2′); 166.1 (C-10).*Spectra recorded after one week into $CDCl_3$ solution.

*3-Chloro-5-(quinolin-2-yl)-7-methoxycarbonyl-thieno[2,3-b:4,5-c′]dipyridine (**30**).* m.p. 295–297 °C, yield 84%. $C_{21}H_{12}O_2N_3SCl$; MW: 405.85; C, 62.15; H, 2.98; Cl; 8.74; N, 10.35; O, 7.88; S, 7.90. MS (*E.I.*) *m*/*z* (%): 405.0 (M^+, 60); 407 (M^++2; 40). ^{1}H NMR 200 MHz ($CDCl_3$) δ (ppm): 4.08 (s, 3H; H-12); 7.71 (ddd, 1H, *J* = 1.2, 7.6 Hz; H-6′); 7.86 (ddd, 1H, *J* = 1.4, 7.6 Hz: H-7′); 8.0 (dd, 1H, *J* = 1.4, 7.5 Hz; H-5′); 8.13 (d, 1H, *J* = 7.6 Hz; H-8′); 8.28 (d, 1H, *J* = 8.6; H-3′); 8.48 (d, 1H, *J* = 2.3 Hz; H-4); 8.51 (d, 1H, *J* = 8.6; H-4′); 8.64 (d, 1H, *J* = 2.3 Hz; H-2); 8.76 (s, 1H; H-8).

*7-Methyl-4-quinolin-2-yl-11-tia-3,10–diaza-benzo[b]fluorene 2-carboxyic acid ethyl ester (**31**).* m.p. 220–222 °C, yield 62%. $C_{22}H_{19}O_2N_3S$; MW: 449.11; C, 72.14; H, 4.26; N, 9.35; O, 7.12; S, 7.13. MS (*E.I.*) *m*/*z* (%): 449 (M+90). ^{1}H NMR 500 MHz ($CDCl_3$) δ (ppm): 1.50 (t, 3H; *J* = 7.2 Hz; H-14); 2.56 (s, 3H; *J* = 1.0 Hz; H-15); 4.58 (q, 2H; *J* = 7.2 Hz; H-13); 7.55 (s, 1H; H-6); 7.81 (ddd, 1H, *J* = 8.0, 1.8 Hz; H-6′); 7.95 (ddd, 1H, *J* = 1.8, 8.0 Hz; H-7′); 8.10 (dd, 2H, *J* = 8.0, 1.8 Hz, H-5′); 8.28 (dd, 1H; *J* = 8.0, 1.8 Hz; H-8′); 8.41 (d. 1H; *J* = 8.5 Hz; H-3′); 8.80 (s, 1H; H-4); 8.49 (d, 1H, *J* = 8.5 Hz; H-9); 8.63 (d, 1H; *J* = 8.5 Hz, H-4′); 7.90 (d, 1H; *J* = 8.5 Hz; H-8) *Spectrum recorded after one week into $CDCl_3$ solution.

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