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2D ^{1}H and ^{13}C NMR in the conformation of 4-aryl derivatives of thieno[3,2-c]pyridines

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Abstract

In this paper we report the synthesis and spectral analysis of new heterocyclic derivatives of 4-aryl thieno[3,2-c]pyridines. These functionalized compounds were obtained from heteroaromatic aldehyde derivative and a cyclisation via tandem aza–Wittig iminophosphorane reactions sequence. The assignment of the structures and conformation of the different derivatives were achieved using 1D and 2D NMR (NOESY, DEPT, HMQC and HMBC). © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Aza–Wittig; Cyclisation; Heterocyclic derivatives; Nuclear magnetic resonance

1. Introduction

Thienopyridines are a fascinating family of aromatic compounds with two different heterocyclic rings which still continue to attract the chemical interest. Synthetic and theoretical interest in the behaviour of systems that contain, fused to π rich and π deficient ring as well as the search for pharmacologically active substances led to the synthesis of various analogs of quinolines and isoquinolines in which the benzene ring is replaced by thiophene nucleus.

Most of the substances described in the literature for thienopyridines systems have been synthesized by traditional methods used to build quinoline and isoquinoline systems [1–3].

Recently, a tandem aza–Wittig/electrocyclic ring closure strategy (TAWERS) was used to obtain this nucleus by reacting key imino-phosphorane intermediate with isocyanates or isothiocyanates [4,5]. Because of the interest in preparing novel thiophene analogs of biologically active benzocompounds [6–9] we used a modification of the TAWERS by reacting the imino-phosphorane intermediate with aromatic and heteroaromatic

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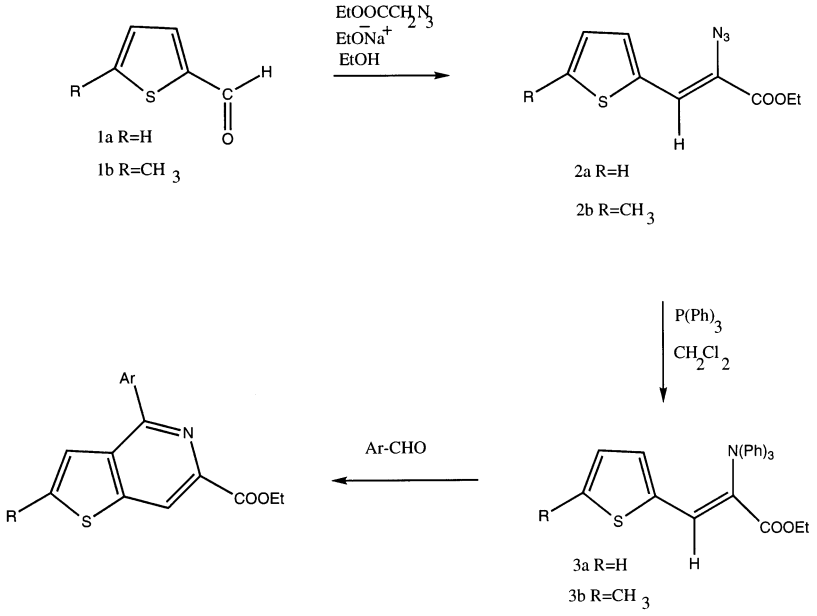
aldehydes to afford biaryl compounds which would display interesting conformational properties.

In this paper we describe the synthesis of novel thienopyridines as well as their conformational analysis established by 1D and 2D NMR and X-ray crystallographic studies.

2. Results and discussion

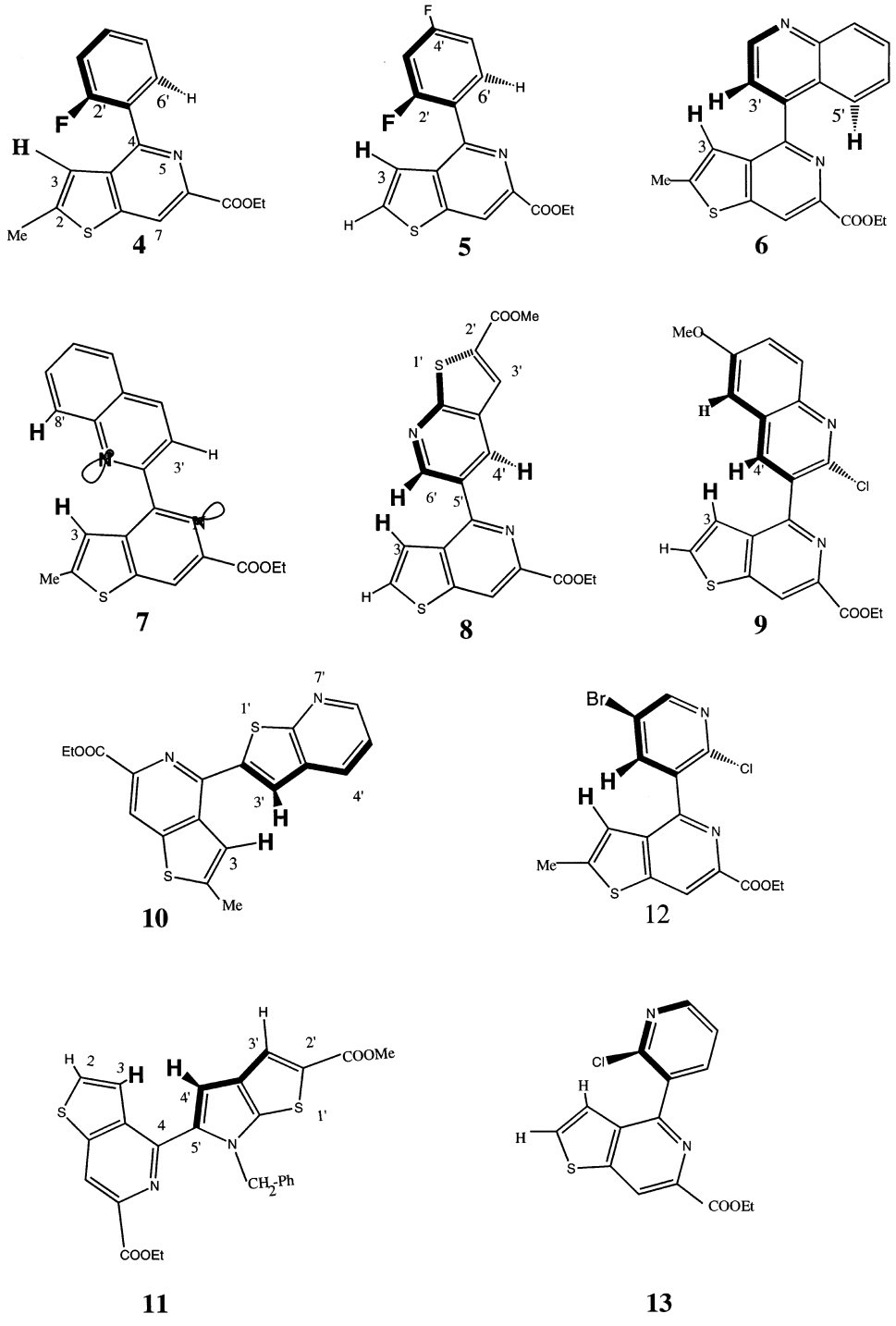
The initial approach toward preparation of 4-aryl thieno[3,2-c]pyridine nucleus present in compounds (**4**–**13**) consisted of a tandem aza–Wittig electrocyclic ring closure approach using as a intermediate the iminophosphorane (**3a**,**b**). Its condensation with corresponding aromatic aldehyde, in a sealed tube at 160°C using toluene as solvent for 48 h afforded some thienopyridines in poor yield [10]. However, when the reaction was carried out at reflux temperature of 1,2 dichlorobenzene (12–16 h), the desired biaryl-thienopyridines were obtained with yield ranging from good to moderate (see Scheme 1)

Since derivatives (**4**–**13**) (see Scheme 2) may be of some pharmaceutical interest and detailed conformational data of these compounds are more and more used in the above area, prior to specific pharmacological testing, in order to predict the activity and for the future drugs design, it seemed necessary to study the restricted rotation that occurs in such compounds. In order to obtain an



4	**R=Me**	**Ar=2'Fluorophenyl**
5	**R=H**	**Ar=2',4'difluorophenyl**
6	**R=Me**	**Ar= 4'Quinoline**
7	**R=Me**	**Ar= 2'Quinoline**
8	**R=H**	**Ar= -(2-carbomethoxy-5-thieno [2,3-b] pyrrolo)**
9	**R=H**	**Ar= (2'-Cl, 6' methoxy-3'-quinoline**
10	**R=Me**	**Ar= (2'-thieno [2,3-b] pyridine)**
11	**R=H**	**Ar= -4-(-N-benzyl-2'-carbomethoxy-5'-thieno[2,3-b] pyrrolo**
12	**R=Me**	**Ar= (2' Cl,,5' Br-3'Pyridine)**
13	**R=H**	**Ar=(2' Cl-3'Pyridine)**

Scheme 1.



Scheme 2.

insight into these sometimes puzzling effects at the molecular level we have performed conformational studies of the 4-aryl-substituted thieno[3,2-c]pyridines.

A series of compounds (**4**–**13**) were chosen with variable steric hindrance on C-3 proton atom and on functional group attached to C-4 of the aryl ring.

In these compounds, the aromatic units are linked together through a pivotal bond, displaying due to steric factors, hindered rotation [11,12]. It was observed that if two planar groups are connected by a bond, and the ground state is not planar, the molecule is chiral provided that neither of the two planes (A and B) are symmetrical to a plane involving this central bond. If rotation about the central bond becomes fast, then the magnetic environments of the nuclei are interchangable and averaging take place leading to the racemization of the compound. The most classical example of this type of racemization can be found in the biphenyl series [13,14] and consequently the principle discussed above should apply to other non planar molecules.

The rotation barriers in these compounds have been assessed as the sum of the individual contribution of each substituent and the magnitude of 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 affect the transition state for a given conformer affecting its ground state energy. Therefore this system is uniquely suitable for studying the molecules in which in a major conformation there is no or little interaction with the other aromatic moiety and consequently the steric interactions are low.

The atropisomerism can be present in compounds other than biphenyls where one or both of the phenyl groups can be replaced by other aromatic or heteroaromatic rings. For example 1,1′-binaphthyls [15,16] and 3,3′-bipyridyls [17,18] are resolvable and the peri-hydrogens of the former one provided enough of steric hindrance to keep the rings non planar. In the cases of 3,3′-bithienyls [19,20], they exhibit a rotation barrier that is too low to be identified via dynamic NMR.

Having this in mind and knowing that the steric interactions should be enhanced by the introduction of some substituent and to identify some strain effects in the ground state, we have performed the following conformational NMR studies of the thieno[3,2-c]pyridines: i) spectral assignments chemical shifts difference; ii) long range couplings evaluations; iii) NOESY experiments; iv) X-ray crystallographic studies-correlated to NMR and; v) calculation of energy for some conformers.

2.1. Spectral assignment

In classical kinetics it was not possible to detect restricted rotation of a phenyl ring not carrying any substituent [21]. We have prepared the 4-phenyl-2′-fluoro and 4-phenyl 2′,4′-difluoro thieno[3,2-c]pyridine (**4** and **5**) in order to detect via 1D NMR some spatial relationship between the fluorine nuclei and the protons in the neighborhood assuming that introduction of fluorine atom on the 4-phenyl moiety must increase the magnitude of barrier of rotation. In the transition state the steric interaction enhanced by fluorine atom must be increase. For the C-2′ position we explain the observed results by the strain effects occurring in the ground state. The rotation of the aryl ring at C-4 may eventually not occur in a given conformation adopted because of the severe interactions between protons involved.

It was also possible, through the 1D NMR experiments, to observe long range fluorine–hydrogen coupling. Values of $^{n}J_{F-H}$ with $n > 3$ tend to be larger than the corresponding $^{n}J_{H-H}$ values thus exhibiting some useful diagnostic features [22]. Attention should be directed to significant proton–fluorine coupling over 5 (s or p) bonds. When some zigzag arrangement of fluorine–hydrogen is absent [23], the long range F–H is observed only when both nuclei are close through space [24]. This latter considerations supports the $^{6}J_{F-H-3} = 3.5$ Hz and $^{6}J_{F-H-3} = 4.0$ Hz, respectively observed for the products **4** and **5**. The Dreiding models of these molecules indicated a close spatial relationship between H-3 and the 2′-fluorine nuclei attached to 4-aryl ring for both compounds.

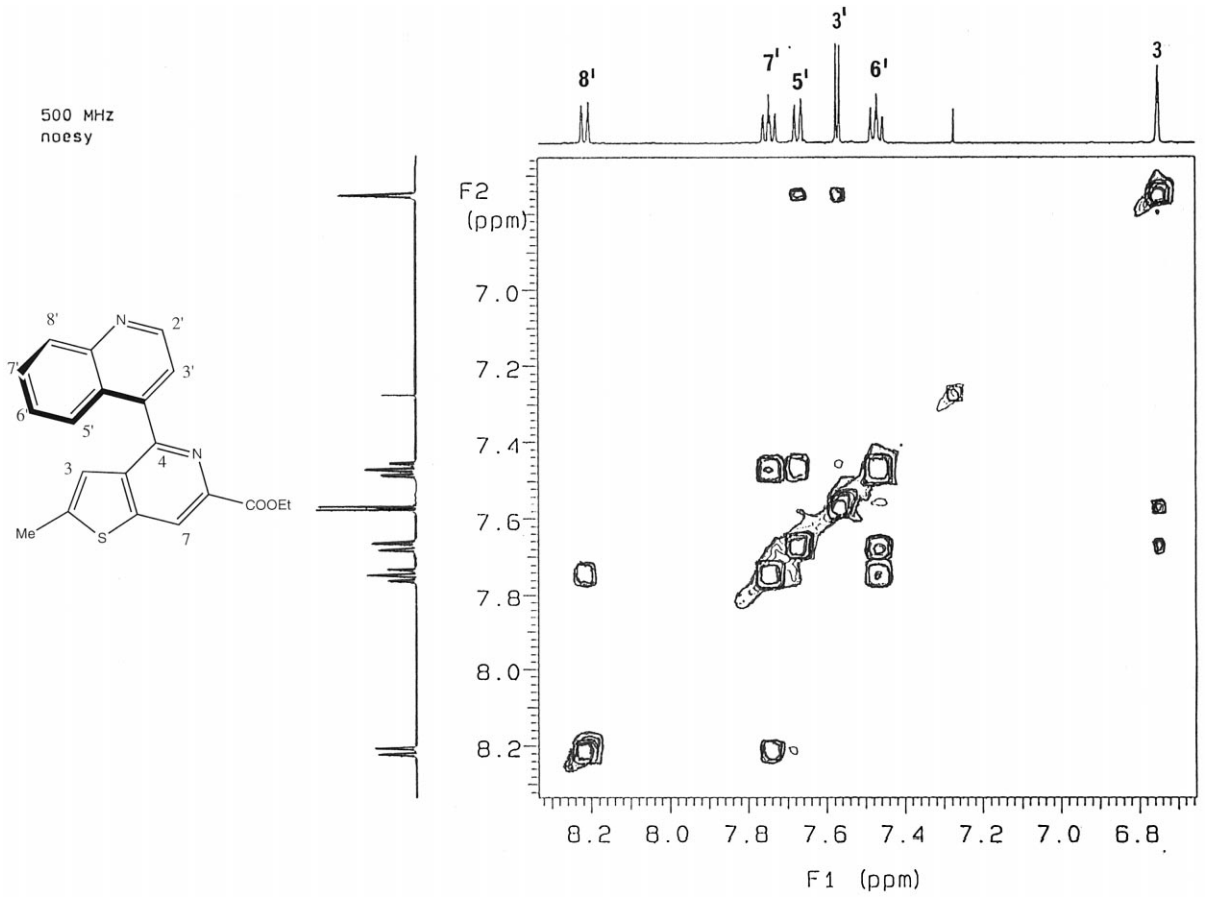


Fig. 1. NOESY spectrum of compound **6** recorded in $CDCl_3$ solution at 500 MHz.

The results obtained with the compounds **6**–**13** using 2D NMR, and presented below in this paper, are fully confirming these observations. We have collected ^1H (500 MHz) and ^{13}C (125 MHz) NMR chemical shifts and proton coupling data for above mentioned derivatives and assigned the spectra using a variety of 2D NMR technique. Furthermore we reported the use of phase sensitive NOESY in the determination of conformational transformations just as was previously described on a non-fused furane-pyrimidine ring example [25–27].

The ^1H (500 MHz) peak assignments for compounds **4**–**13** (as reported in Section 5) are based on expected proton coupling relationships, ^1H–^1H COSY and NOESY experiments.

The analysis of the ^1H spectra was initiated by the assignment of the system for H-2 and H-3 ($^3J = 5.0$ Hz) of the thienopyridine moiety. The assignment of H-3 was based on additional small long range coupling (W) of this proton with H-7 ($J = 1.0$ Hz). The support of the conformation chosen came from analysis of phase sensitive NOESY spectra of the compounds **6**–**13**. While interacting NOE cross peaks for adjacent protons were observed, the inter-ring NOE cross peaks between H-3 of the thiophene moiety and the closest protons on the attached C-4 aromatic ring was noticed.

For example, for compound **6**, the phase sensitive NOESY spectrum was fully consistent with non planar conformation since intense cross peaks

of H-3 were observed for two different protons (H-3′ and H-5′) from the attached C-4 quinoline moiety (Fig. 1). As can be seen, a high intensity cross peak corresponding to the proton interactions is observed where both rings are almost perpendicular each to the other. Direct space correlations between two different hydrogens have been tried with NOE diff [28] where the inverse six power rule of internal distance renders the direct visualizing of the space neighborhood difficult. In the NOE diff of compound **6**, stronger signal assigned to H-3′ was observed than that for H-5′.

In many cases X-ray structure analysis enabled to confirm in a more rigorous manner the NMR assignment that we have performed. The conformation of compound **6** and other results were fully supported by the X-ray data. In Fig. 2, (two different perspective drawings are shown) the distances between H-3/H-5′ and those for H-3/H-3′ were estimated as 4.63 and 2.84 Å, respectively. These observations are consistent with the NOESY spectrum where the intensity of the cross peaks observed for H-3′ was stronger than the cross peak due to H-5′.

Similar conformational behaviour was observed in the case of compound **8** where the NOESY experiment also suggested a non planar configuration (Fig. 3) because of the observation of strong cross peaks between H-3 with both H-2′ and H-4′.

On the other hand, we anticipated that changing the nitrogen position on quinoline moiety attached to C-4, as in compound **7**, would create a situation with both nitrogens (N-1′ and N-5) in line and in planar conformation. This conformation enabled to visualize the absence of NOE

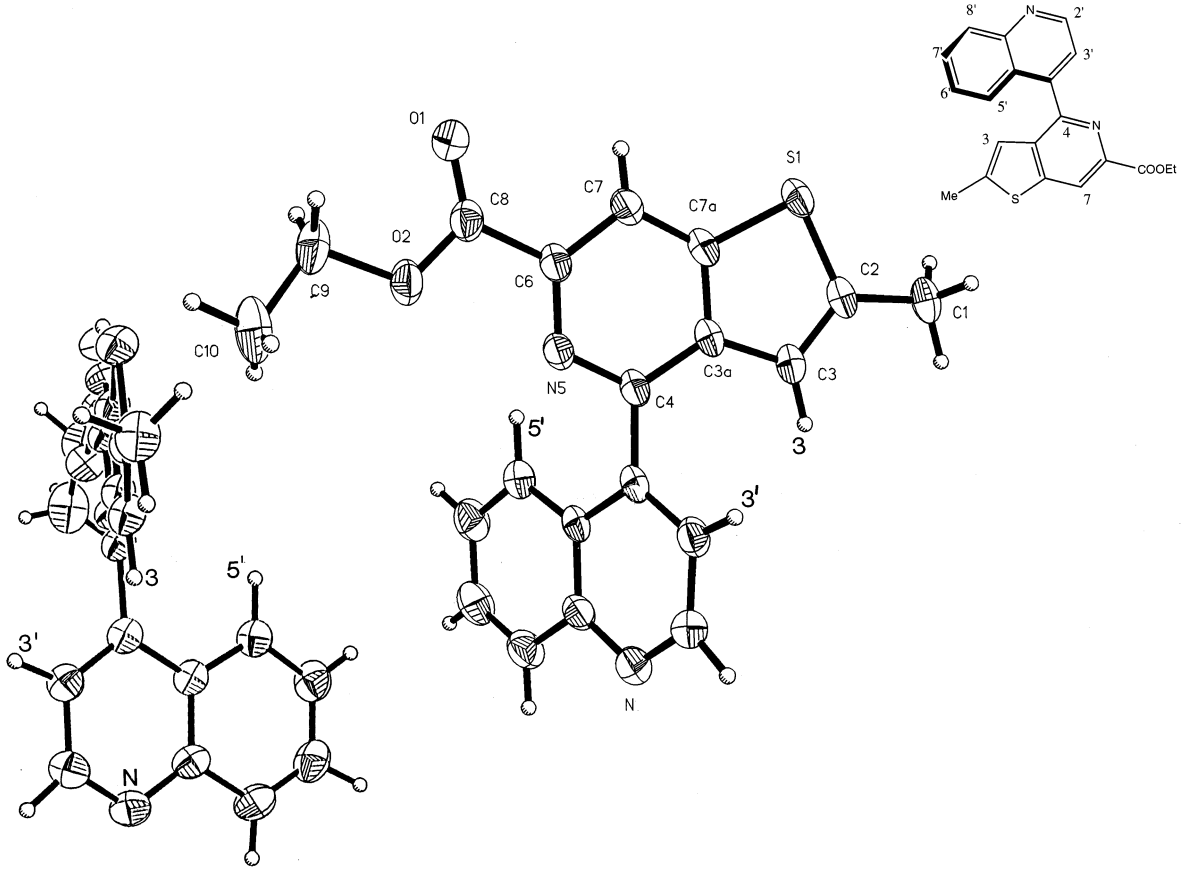


Fig. 2. X-ray drawing projection show two different stereoview of compound **6**.

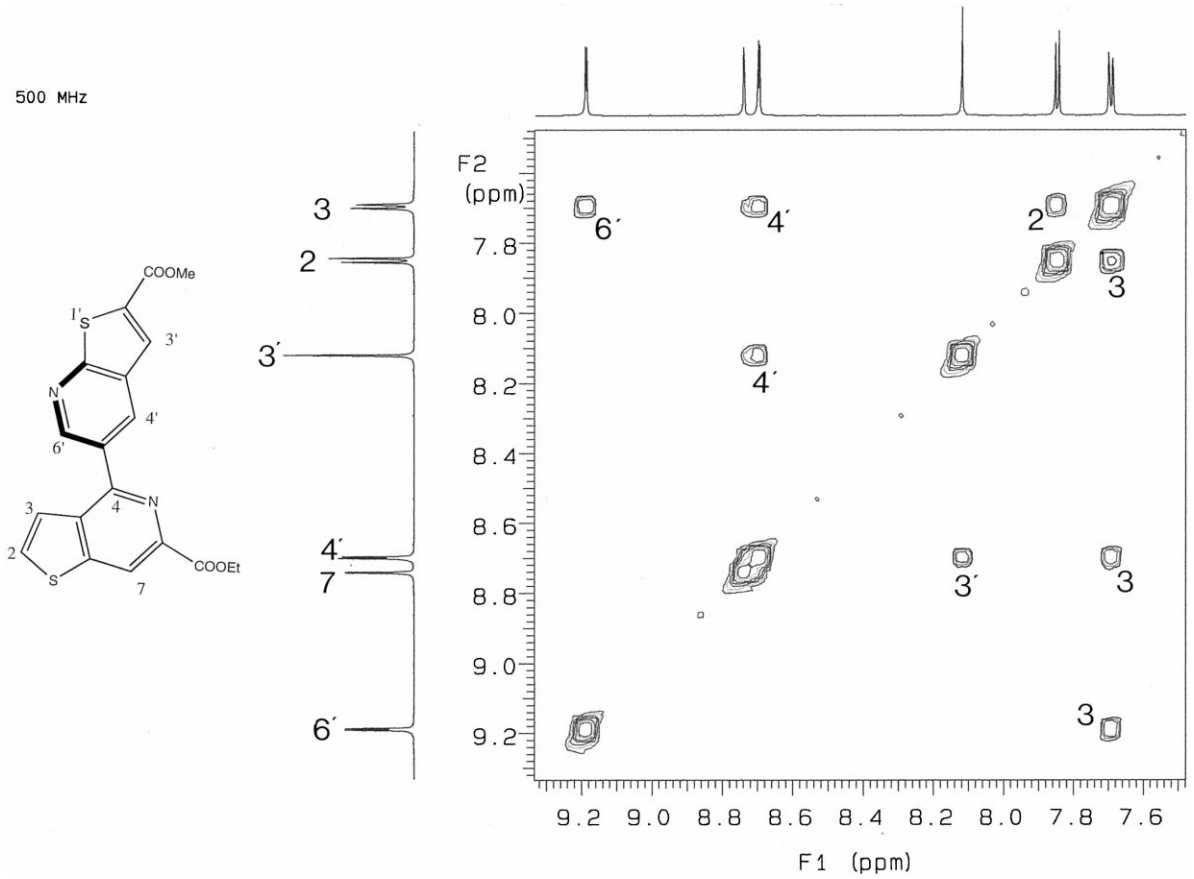


Fig. 3. NOESY spectrum of compound **8** recorded in $CDCl_3$ solution at 500 MHz.

interactions. An interesting observation made for compound **7** (Fig. 4) where the largest chemical shift for H-3 ($\delta = 8.57$) and H-3′ ($\delta = 8.70$) were due to deshielding from N-1′ and N-5 respectively, strongly suggested that for compound **7** due to conjugation, both aromatic rings are coplanar in the first approximation. Smaller NOE (H-3/H-8′) testify the non-deviation from the plane and the conformational mobility enabling to approach the respective groups toward the hydrogens observed. In order to verify the results of the conformational analysis suggested from NMR, we have performed a X-ray crystallographic analysis of above derivatives. Fig. 5 showed two different perspective drawings with non-hydrogen atoms shown significant distances between protons.

Compounds **9**, **10** and **11** have shown a very similar behaviour to that observed for compounds **6** and **8** (^1H and ^{13}C chemical shifts are described in Section 5).

Unexpected behaviour was observed for the pair of compounds **12** and **13**. The molecular geometry in solution deduced from the NMR determinations is largely based on the chemical shifts differences and they depend of dipolar coupling through space and with intra and intermolecular distances.

On the other hand, when a nucleus of spin ≥ 1 (^{35}Cl) which is not spherical and has an nonzero electric quadrupole moment can interact with an electric field gradient to shift the Larmor frequency.

Then the observed chemical shift difference between H-3 in compound **12** ($\delta_{H-3} = 6.88$) and that observed for compound **13** ($\delta_{H-3} = 7.25$) suggest

that the chlorine atom at C-2′ in the latter compound causes an anisotropic deshielding to H-3 which is not observed in derivative **12**.

The proof of such consideration was supported by NOESY experiments of both compounds. Meanwhile in 2′,5′ chlorobromo pyridine derivative **12** a strong NOE cross peaks were observed between H-3 with H-4′. These results described the neighborhood of both protons as being in a non planar conformation. In the compound **13** we were not able to observe NOE cross peaks between H-3 with H-4′. We assumed that in such different conformations, the spatial interactions between protons should have spatial ground state contributions where the bromine atom attached on C-5′ forced in the non-planar conformation for compound **12**.

3. Molecular modeling of compounds 6 and 7

3.1. Procedures

The X-ray structures for compounds **6** and **7** were used as a starting structures. They were first minimized to a 0.1 kcal mol^{-1} $Å^{-1}$ gradient to a nearest local minimum using the semiempirical method PM3 as implemented in the program HyperChem. release 5.02 (Hypercube, Waterloo, Ont.). Conformers were generated by systematically varying the torsion angle of the bond connecting the two aromatic moieties by 15° increments and the heat of formation determined from a single-point calculation or after energy minimization to a 0.1 kcal mol^{-1} $Å^{-1}$ gradient using the PM3 method.

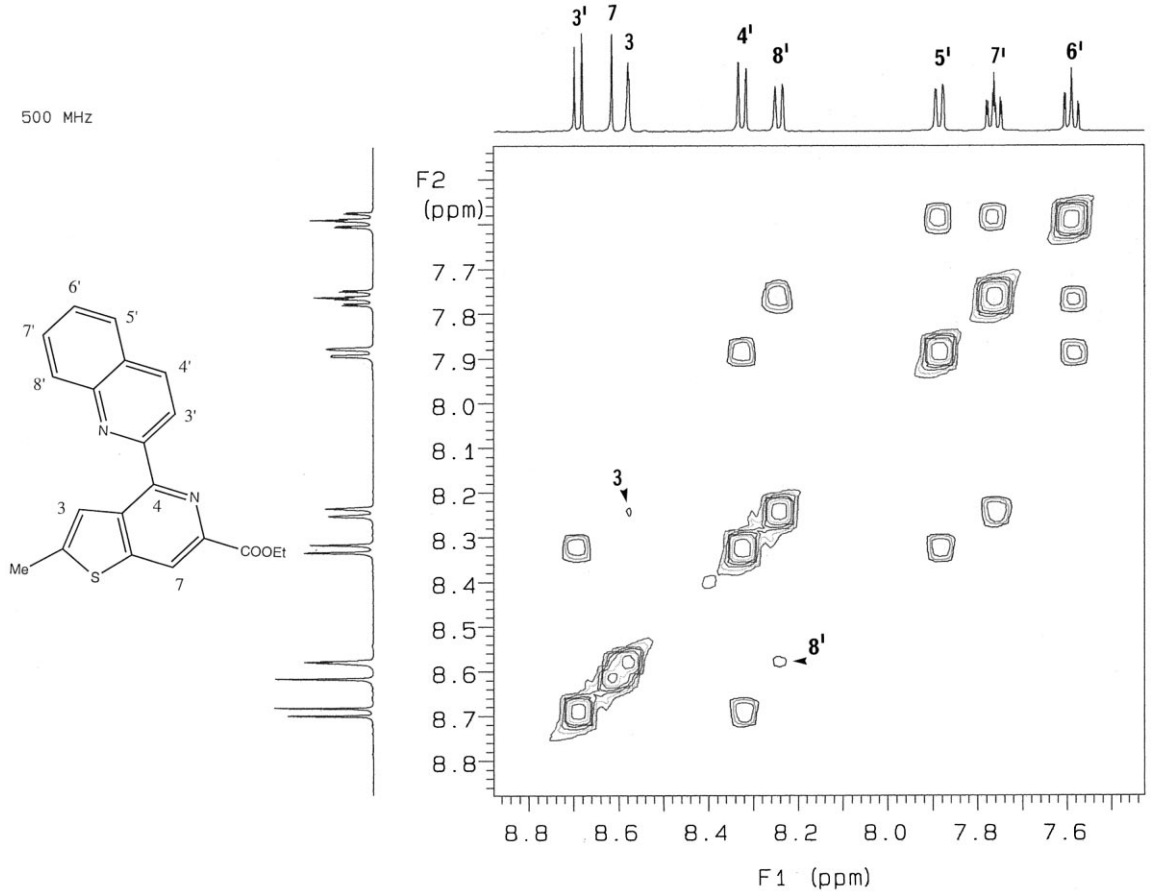


Fig. 4. NOESY spectrum of compound **7** recorded in $CDCl_3$ solution at 500 MHz.

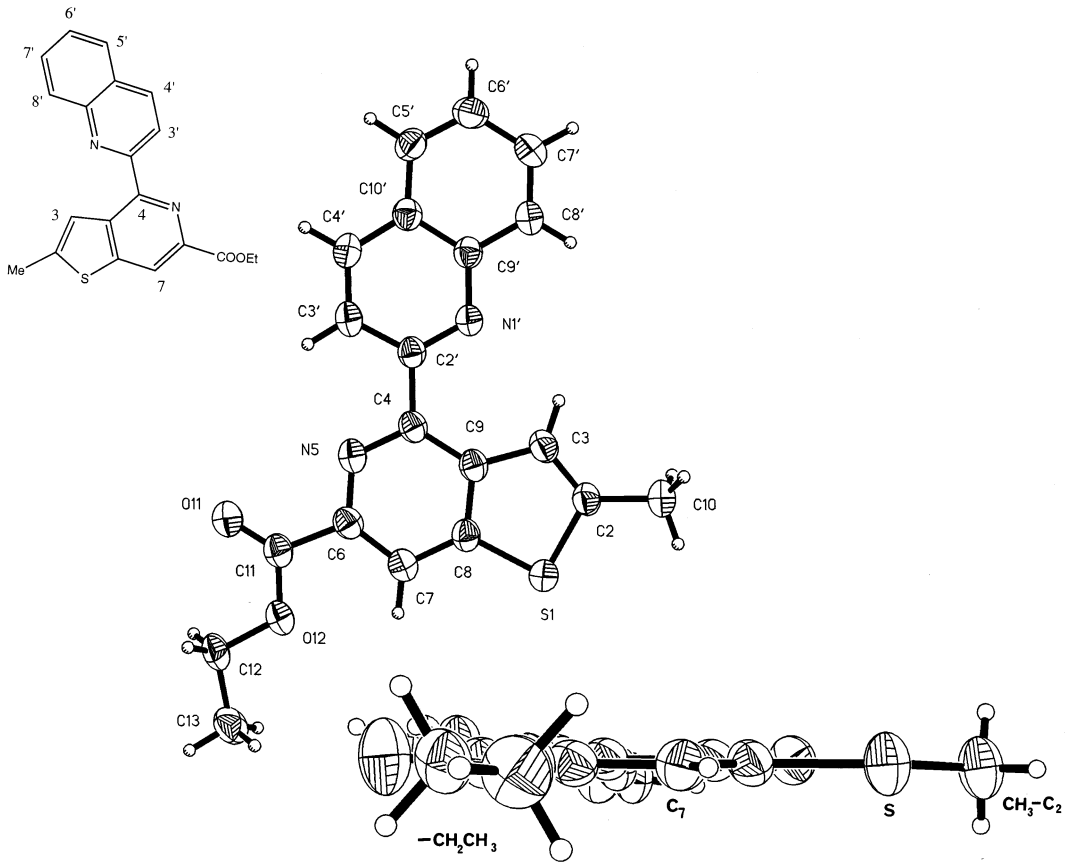


Fig. 5. X-ray drawing projection of two perspective view of compound **7**.

3.2. Results and discussion

*3.2.0.1. Compound **6**, single point calculation.* For 6-carboethoxy-2-methyl-4-(4′-quinoline) thieno[3,2-c]pyridine (**6**) results show that only conformers with the torsion angle of the bond connecting the two aromatic moieties between 60 and 120°, and -60 and $-135°$ are likely to be populated, the minima being between ± 75 and $\pm 90°$.

3.2.0.2. Energy minimization. Results are essentially the same with energy minimization for compound **6**. The torsion angle of the bond connecting the two aromatic moieties take values between 66 and 112° and -64 and $-119°$. As was already reported, in the case of energy minimization the value of the heat of formation depends also on the conformations assumed by other rotatable bonds (essentially in the side chain) which are not necessarily constant between conformers.

3.2.0.3. Analysis of distance measurements results. In the conformational space for compound **6**, allowed from the single point caculations, the distances H3/H3′ and H3/H5′ have a minima where the torsion angle is between ± 75 and $\pm 90°$. The distances H3/H3′ and H3/H5′ assume values of 3.6–4.1 and 3.2–3.9 Å, respectively. Such calculations are in agreement for the conformations suggested by NMR measurements and confirmed by X-ray crystallograpic data. (Fig. 6)

3.2.1. Compound 7, single point calculation

For 6-carboethoxy-2-methyl-4-(2′-quinoline) thieno[3,2-c]pyridine (**7**) shown all conformers with torsion angle of the bond connecting the two aromatic moieties between $-150°$ and 150° are populated with minima at $\pm 45°$ where the average conformation thus has a torsion angle of 0°.

3.2.1.1. Energy minimization. For compound **7**, populated conformers have a torsion angle of the bond connecting the two aromatic moieties between $-105°$ and 122°.

3.2.1.2. Analysis of the distance measurements results. In the conformational space allowed from the single-point calculations, the distances H3/H3′ and H3/H8′ have a minima of 1.8 and 3.0 Å respectively. The 0° angle having a lower energy and thus a larger probability than $-150°$.

Again, these calculations are in agreement with results obtained by NOESY experiments where the abscence of cross peaks between H3/H3′ suggest a long distance (>5 Å) between these protons and shorter distance (≈ 3 Å) observed for H3/H8′ where it was possible to observe in the NOESY spectra a weak correlation between these protons (Fig. 7).

4. Conclusions

In the results described in this paper, the successful use of NOESY experiments for conformational studies is reported. We were able to establish a complete conformational behaviour of several thienopyridines. The NOESY data when compared with those obtained by X-ray crystallography or molecular modeling calculations, afforded complementary features for description of molecules having a freely rotated two aromatic rings. The major conformation in solution and that found from X-ray crystallography are the same with two perpendicular heteroaromatic rings (compound **6**) adopting a minimum energy conformation. The interatomic distances of selected protons for instance calculated from NMR base, modeling and X-ray crystallography are the same.

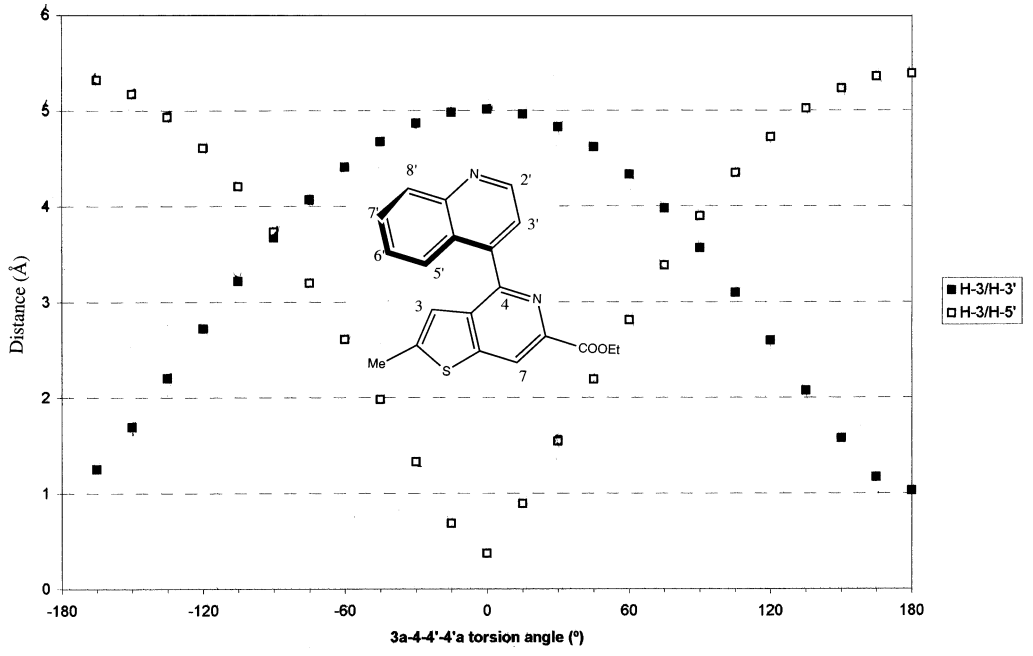


Fig. 6. Modelling calculation. Proton distances vs torsion angle of compound **6**.

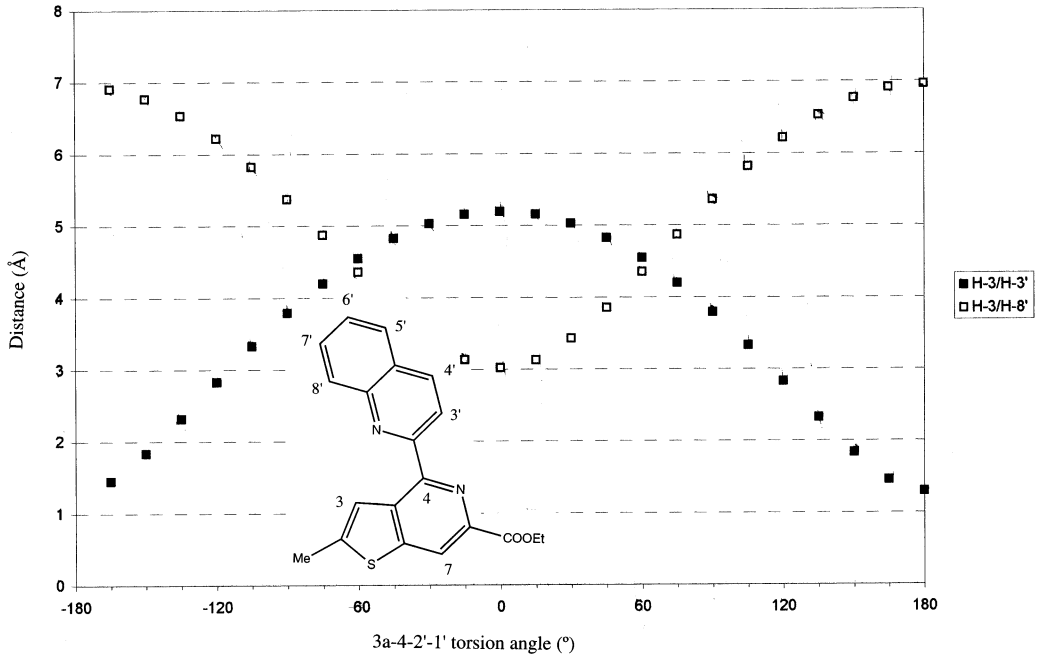


Fig. 7. Modelling calculation. Proton distances vs. torsion angle of compound **7**.

5. Experimental

Melting points were determined with a Kofler hot stage and they are non-corrected. ^{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, HMQC, HMBC). The ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to TMS as internal standard. (0.00 ppm). X-ray crystallographic studies were performed on a Siemens P4/PC. For analytical purpose the mass spectra were recorded on a JEOL JMS-5X 10217 in EI/PI mode, 70 eV, 200°C via direct probe. Only the molecular ion and the percentage ion (m/z) values are reported. IR spectra were recorded on a Nicolet Magna 55-X FT instrument.

Aldehydes used for the preparation of compounds **4**, **5**, **6**, **7**, and **13** were purchased from Aldrich and used as received. The other aldehydes used to synthesize compounds **8**, **9**, **10**, **11** and **12** were prepared as have been widely described in the literature.

5.1. General procedure for the reaction of the aldehyde with an iminophosporane

A mixture of 0.21 mmol (0.1 g) of the iminophosporane **3a** or **3b** and 0.21 mmol of the corresponding aromatic aldehyde in 5 ml of DCB, was refluxed for 12 h. The mixture was allowed to reach the room temperature and then purified by column chromatography (silica gel 70–230 Mesh) yielding a yellow solid.

*5.2. 6-Carboethoxy-2-methyl-4-(2′-fluoro phenyl) thieno[3,2-c]pyridine (**4**)*

Melting point 116–117°C. IR (cm^{-1}) υ_{max}: 2927, 1736, 1703, 1490, 1463, 1411, 1300, 1276, 1113. MS m/z (%) 315 M^{+}(5), 243 (20), 242 (5), 153 (45), 123 (97), 77 (100). $C_{17}H_{14}O_2NSF$ MW = 315. Yield 44%. ^{1}HNMR, δ, ppm; 8.58, d, $J = 1$ (H-7); 7.68, dt, $J = 2.0$, 7.5 (H-6′); 7.45 m, (H-4′); 7.30, dt, $J = 1$, 7.5 (H-5′); 7.20 m, $J = 1.0$, 8.5, 10.0 (3'); 7.00 m $J = 1.0$, 3.5 (H-3); 4.47, q, $J = 7.0$ (OCH_2);2.63 d $J = 1$ (Me-C2); 1.45 t, $J = 7.0$ ($\underline{CH_3}$–CH_2O–). ^{13}CNMR, δ, ppm. 145.8 (C-2);

121.3 (C-3); 137.8 (C3a); 149.1 (C-4); 141.1 (C-6); 118.7 (C-7); 147.7 (C-7a); 16.4 (CH_3–C-2); 165.0 (COO); 61.8 (CH_2O–); 14.4 ($\underline{CH_3}$–CH_2); 127.0 (C-1′); 160.0 (C-2′) 115.8 (C-3′); 130.0 (C-4′); 124.5 (C-5′); 132.0 (C-6′).

5.3. 6-Carboethoxy-4-(2′,4′-difluorophenyl)-thieno[3,2-c]pyridine (**5**)

Melting point 155-156°C. IR (cm^{-1}) υ_{max}; 2989, 2872, 1727, 1615, 1507, 1316, 1278, 1094, 868. MS m/z (%) 319 M^+(63), 248 (100); $C_{16}H_{11}NO_2SF_2$ MW = 319. Yield 42%. ^{1}HNMR, δ, ppm; 1.45 t, $J = 7.0$, ($\underline{CH_3}$–CH_2–O–); 4.52, q, $J = 7.0$ ($\underline{CH_2}$–O–); 6.97 ddd $J = 2.5$, 9.0, 10.0 (H-3′); 7.07 m, $J = 0.5$, 2.5. 6.5, 10.0 (H-5′); 7.36 ddd $J = 1.0$, 4.0, 5.5 (H-3); 7.70 d, $J = 5.5$ (H-2); 7.73, ddd $J = 6.5$, 8.0, 8.0 (H-6′). ^{13}CNMR, δ, ppm. 130.7 (C-2); 123.6 (C-3); 136.9 (C-3a); 149.6 (C-4); 141.8 (C-6); 119.3 (C-7); 148.0 (C-7a); 123.5 (C-1′); 162.2 (C-2′); 104.2 (C-3′); 163.7 (C-4′); 112.0 (C-5′); 133.4 (C-6′); 165.5 (COO); 61.9 ($\underline{CH_2}$–O–); 14.4 ($\underline{CH_3}$–CH_2).

5.4. 6-carboethoxy-2-methyl-4-(4′-quinoline)-thieno[3,2-c]pyridine (**6**)

Melting point 164–165°C. IR (cm^{-1}) υ_{max}; 3080, 2985, 1730, 1712, 1591, 1558, 1517, 1506, 1465, 1436, 1396, 1276, 1176, 1120. MS m/z (%) 348 M^+(43), 276 (100); $C_{20}H_{16}O_2N_2S$ MW = 348. Yield 53%. ^{1}HNMR δ, ppm 1.45 t, $J = 7.0$ ($\underline{CH_3}$–CH_2–O–); 4.50 q, $J = 7.0$ ($\underline{CH_2}$–O–); 2.57 d $J = 1$ ($\underline{CH_3}$–C2); 6.75 q, $J = 1$ (H-3); 8.70 d $J = 1.0$ (H-7); 9.06 d $J = 4.5$ (H-2′); 7.57 d, $J = 4.5$ (H-3′);7.67 bd $J = 8.0$ (H-5′); 7.75 ddd $J = 1.5$, 6.5, 8.5 (H-7′); 7.47 ddd $J = 1.0$, 6.5, 8.0 (H-6′); 8.21 bd $J = 8.5$ (H-8′). ^{13}CNMR δ, ppm 146.8 (C-2); 120.7 (C-3); 138.0 (C-3a); 150.9 (C-4); 141.1 (C-6); 119.1 (C-7); 148.1 (C-7a); 149.9 (C-2′);121.9 (C-3); 144.8 (C-4′); 166.4 (C-4′a); 125.7 (C-5′); 127.0 (C6′); 129.6 (C-7′); 129.9 (C-8′); 148.8 (C-8′a); 165.5 (COO); 61.9 ($\underline{CH_2}$–O–); 14.4 ($\underline{CH_3}$–CH_2–O); 16.3 ($\underline{CH_3}$–C2).

5.5. 6-carboethoxy-2-methyl-4-(2′-quinoline)-thieno[3,2-c]pyridine (**7**)

Melting point 167–168°C. IR (cm^{-1}) υ_{max}; 2985, 2923, 1726, 1712, 1598, 1502, 1390, 1369, 1284, 1143, 1128, 1022, 889. MS m/z (%) 348 M^+(55), 276 (100); $C_{20}H_{16}O_2N_2S$; MW = 348. Yield 50%. ^{1}HNMR δ, ppm 1.50 t $J = 7$ ($\underline{CH_3}$–CH_2–); 4.52 q $J = 7$ ($\underline{CH_2}$–O–); 2.73 d $J = 1$ ($\underline{CH_3}$–C-2); 8.57 q $J = 1$ (H-3); 8.61 d $J = 1$ (H-7); 8.70, d $J = 8.5$ (H-3′); 8.32 d $J = 8.5$ (H-4′); 7.88 bd (H-5′); 7.60 ddd $J = 1.5$, 7.0, 8.0 (H-6′); 7.76 ddd $J = 1.5$, 7.0, 8.5 (H-7′); 8.20 bd $J = 8.5$ (H-8′). ^{13}CNMR δ, ppm 146.7 (C-2); 16.6 ($\underline{CH_3}$–C_2); 123.5 (C-3); 136.9 (C-3a); 150.0 (C-4);140.2 (C-6); 119.5 (C-7); 157.3 (C-2′); 121.4 (C-3′); 136.6 (C-4′); 127.9 (C-4′a);127.7 (C-5′); 127.0 (C-6′); 129.4 (C-7′); 129.7 (C-8′); 165.6 (COO); 61.7 ($\underline{CH_2}$–O–); 14.4 ($\underline{CH_3}$–CH_2–).

5.6. 6-carboethoxy-4-(2′-carbomethoxy-5′-thieno-[2,3-b]pyridine)thieno[3,2-c]pyridine (**8**)

Melting point 214–215°C; IR (cm^{-1}) υ_{max}; 2993, 2956, 1716, 1597, 1510, 1367, 1319, 1269, 1257, 1170, 1076, 852. MS m/z (%) 398 M^+(35), 326 (100); $C_{19}H_{14}O_4N_2S_2$; MW = 398. Yield 43%. ^{1}HNMR δ, ppm 1.50 t $J = 7$ (CH_3–CH_2–); 4.0 s (OCH_3); 4.55 q $J = 7$ (CH_2–O–); 7.85 d $J = 5.5$ (H-2); 7.70 dd $J = 1.0$, 5.5 (H-3); 8.70 d $J = 2$(H-4′) 8.74 d $J = 1$ (H-7); 9.19 d $J = 2$ (H-6′); 8.12 s (H-3′). ^{13}CNMR δ, ppm 131.7 (C-2); 122.4 (C-3); 135.6 (C-3a); 151.4 (C-4); 141.6 (C-6); 118.9 (C-7); 148.7 (C-7a); 149.5 (C-6′); 132.0 (C-3′); 133.4 (C-4′); 134.3 (C-3′a);128.1 (C-3′); 131.9 (C-2′); 163.0 (C-7′a);162.5 ($\underline{C}OO$–C_6); 165.0 (COO–); 14.4 ($\underline{CH_3}$–CH_2–); 52.6 ($\underline{Me}OOC$–); 61.8 ($\underline{CH_2}$–O).

5.7. 6-carboethoxy-4-(2′Cl,6′-methoxy-3′-quinoline)thieno[3,2-c]pyridine (**9**)

Melting point 161–162°C. IR (cm^{-1}) υ_{max}; 3695, 2987, 1730, 1714, 1624, 1595, 1496, 1323, 1274, 1166, 1137, 1033, 854. MS m/z (%) 398 M^+(12), 326 (100); $C_{20}H_{15}O_3N_2SCl$; MW = 398. Yield 63%. ^{1}HNMR δ, ppm 1.47 t $J = 7$ (CH_3–CH_2–); 4.54 q $J = 7$ (CH_2–O–); 3.93 s (OCH_3–); 7.72 d $J = 5.0$ (H-2); 7.27 dd $J = 1.0$, 5.0 (H-3); 8.80 d $J = 1$ (H-7); 8.28 bs (H-4′); 7.13 d $J = 3$ (H-5′); 7.46 dd $J = 3.0$, 9.0 (H-7′); 8.08 d $J = 9$ (H-8′). ^{13}CNMR δ, ppm 131.2 (C-2); 123.3 (C-3); 137.1 (C-3a); 151.8 (C-4); 141.5 (C-6); 119.8 (C-7);

147.9 (C-7a); 146.0 (C-2′); 132.0 (C-3′); 139.2 (C-4′); 128.0 (C-4′a); 105.4 (C-5′); 158.5 (C-6′); 123.9 (C-7′); 129.8 (C-8′); 143.8 (C-8′a); 55.6 (MeO–), 165.3 (COO); 62.0 (CH_2–O–); 14.4 (CH_3–).

5.8. 6-carboethoxy-2-methyl-4-(2′thieno[2,3-b]-pyridine)thieno[3,2-c]pyridine (**10**)

Melting point 222–223°C. IR (cm^{-1}) υ_{max}; 3691, 2989, 1730, 1712, 1521, 1367, 1301, 1193, 1141, 1029, 912. MS m/z (%) 354 M^+(55), 282 (100) $C_{18}H_{14}O_2N_2S_2$; MW = 354. Yield 48%. ^{1}HNMR δ, ppm 1.49 t $J = 7$ ($\underline{CH_3}$–CH_2–); 2.70 d $J = 1.5$ ($\underline{CH_3}$–C_2); 4.51 q $J = 7$ ($\underline{CH_2}$–O–); 7.64 q $J = 1.5$, 1.0 (H-3); 8.49 d $J = 1$ (H-7); 7.89 s (H-3′); 8.07 dd $J = 1.5$, 8.0 (H-4′); 7.30 dd $J = 5.0$, 8.0 (H-5′); 8.59 dd $J = 1.5$, 5.0 (H-6′). ^{13}CNMR δ, ppm 147.4 (C-2); 120.3 (C-3); 135.1 (C-3a); 146.2 (C-4); 140.6 (C-6); 118.4 (C-7); 149.0 (C-7a); 143.8 (C2′); 121.6 (C-3′); 133.5 (C-3′a); 131.4 (C-4′); 119.7 (C-5′); 147.3 (C-6′); 162.4 (C7′a); 61.8 ($\underline{CH_2}$–O–); 16.6 ($\underline{CH_3}$–C_2); 14.3 ($\underline{CH_3}$–CH_2–).

5.9. 6-carboethoxy-4-(N-benzyl-2′-carbomethoxy-5′-thieno[2,3-b]pyrrolo)thieno-[3,2-c]pyridine (**11**)

Melting point 202–203°C. IR (cm^{-1}) υ_{max}; 2996, 2978, 2938, 1709, 1590, 1510, 1425, 1359, 1320, 1270, 1257, 1193, 1107, 900. MS m/z (%) 476 M^+(55), 399 (100) $C_{25}H_{20}O_4N_2S_2$; MW = 476. Yield 40%. ^{1}HNMR δ, ppm 1.39 t $J = 7.0$ ($\underline{CH_3}$–CH_2–); 4.46 q $J = 7.0$ (–$\underline{CH_2}$–O–); 5.79 s ($\underline{CH_2}$–N); 7.71 d $J = 5.5$ (H-2); 7.83 dd $J = 1.0$, 5.5 (H-3); 8.58 d $J = 1.0$ (H-7); 6.99 s (H-4′); 7.82 s (H-3′); 7.21 m (Phenyl). ^{13}CNMR δ, ppm 130.7 (C-2); 123.8 (C-3); 136.0 (C-3a); 146.8 (C-4); 140.8 (C-6); 117.9 (C-7); 148.7 (C-7a); 137.1 (C-5′); 106.9 (C-4′); 128.9 (C-3′a); 125.4 (C-3′); 126.9 (C-2′); 143.9 (C-6′a); 163.8, 51.9 ($\underline{C}OO$–$\underline{C}H_3$); 165.5, 61.7, 14.3 ($\underline{C}OO$-$\underline{C}H_2$-$\underline{C}H_3$);135.9, 128.0, 128.5, 127.8 (ϕ).

5.10. 6-carboethoxy-2-methyl-4-(2′Cl, 5′Br-3′pyridine)thieno[3,2-c]pyridine (**12**)

Melting point 204–205°C. IR (cm^{-1}) υ_{max}; 3693, 3608, 2927, 2873, 1728, 1716, 1602, 1517, 1398, 1367, 1282, 1240, 1130, 881. MS m/z (%) 412 M^+(15), 340 (100) $C_{16}H_{12}O_2N_2SBrCl$; MW = 412. Yield 57%. ^{1}HNMR δ, ppm 1.45 t $J = 7$ ($\underline{CH_3}$–CH2); 4.51 q $J = 7$ ($\underline{CH_2}$–O); 2.65 d $J = 1$ ($\underline{CH_3}$–C–2);6.88 q $J = 1.0$ (H-3); 8.65 d $J = 1.0$ (H-7); 8.03 d $J = 2.5$ (H-4'); 8.57 d $J = 2.5$ (H-6′). ^{13}CNMR δ, ppm 147.4 (C-2); 120.2 (C-3); 137.2 (C-3a); 148.2 (C-4); 140.8 (C-6); 119.5 (C-7); 148.0 (C7a); 148.1 (C-2′); 135.9 (C-3′); 142.6 (C-4′); 119.1 (C5′); 150.5 (C-6′); 16.3 ($\underline{C}H_3$–C–2); 165.0, 61.8, 14.2 ($\underline{C}OO$–$\underline{C}H_2$–$\underline{C}H_3$).

5.11. 6-carboethoxy-4-(2′Cl-3′-pyridine)thieno-[3,2-c]pyridine (**13**)

Melting point 178–179°C. IR (cm^{-1}) υ_{max}; 2995, 2941, 1907, 1730, 1714, 1583, 1560, 1475, 1433, 1375, 1317, 1282, 1251. MS m/z (%) 318 M^+(10), 246 (100) $C_{15}H_{11}N_2O_2SCl$; MW = 318. Yield 52%. ^{1}HNMR δ ppm 1.45 t $J = 7.0$ ($\underline{CH_3}$–CH_2–); 4.55 q $J = 7$ ($\underline{CH_2}$–O–); 7.74 d $J = 5.5$ (H-2); 7.25 dd $J = 1.0$, 5.5 (H-3); 8.78 d $J = 1.0$ (H-7); 7.93 dd $J = 2.0$, 7.5(H-4′); 7.43 dd $J = 5.0$, 7.5 (H-5′); 8.55 dd $J = 2.0$, 5.0 (H-6′). ^{13}CNMR δ ppm 131.3 (C-2); 123.2 (C-3); 136.6 (C-3a); 151.4 (C-4); 141.6 (C-6); 119.8 (C-7); 148.0 (C-7a); 134.8 (C-3′); 140.6 (-4′); 122.6 (C-5′); 150.0 (C-6′); 165.3, 62.0, 14.4 ($\underline{C}OO$–$\underline{C}H_2$–$\underline{C}H_3$).

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