Monatsh Chem (2011) 142:731–742
DOI 10.1007/s00706-011-0473-y

ORIGINAL PAPER

An experimental NMR and computational study of 4-quinolones and related compounds

Raquel S. G. R. Seixas · Artur M. S. Silva · Ibon Alkorta · José Elguero

Received: 6 November 2010 / Accepted: 20 February 2011 / Published online: 22 March 2011

Abstract We report the synthesis and structural study of eight compounds, either quinolin-4(1*H*)-ones or quinolines. Tautomerism as well as (*E*) → (*Z*) and rotational isomerism were studied both experimentally (^{1}H and ^{13}C NMR) and theoretically [B3LYP/6-311++G(d,p)].

Keywords Thermal diastereomerization · Quinolin-4(1*H*)-ones · Tautomerism · DFT calculations · GIAO · NMR spectroscopy

Introduction

4-Quinolones are a large group of heterocycles that play an important role in the development of new drugs [1]. They can be found in a variety of natural products, mainly from plants of the Rutaceae family [2–8], but the majority are of synthetic origin. The most studied property of 4-quinolones is their broad spectrum of antibiotic activity, including as second-line drugs for treatment of tuberculosis [9–11]. 3-Styryl-4-quinolones are structurally similar to 3-aryl-4-quinolones, being the aza-analogs of 3-styryl-4-chromones. 3-Aryl-4-quinolones or azoisoflavones have shown inhibitory effects against P-glycoprotein and epidermal growth factor receptor (EGFR) tyrosine kinase, and cytotoxic activity against human cancer cell lines [12–16].

We have devoted three papers to these compounds, where abundant bibliography can be found. In the first of these, we reported synthesis of 1,4-dihydro-4-oxoquinoline-3-carbaldehyde (**1**, Fig. 1) and its use as a scaffold for preparation of a library of drug-like compounds [17]. In the second paper, 1,4-dihydro-1-methyl-4-oxoquinoline-3-carbaldehyde (**2**) and ethyl 3-formyl-1,4-dihydro-4-oxoquinoline-1(4*H*)-carboxylate (**3**) were prepared and used as dienophiles in Diels–Alder reactions [18]. Finally, in the last of these papers, all the above compounds were described [19]. These compounds were prepared from the perspective of pharmacological application, and their nuclear magnetic resonance (NMR) properties were not discussed.

The aim of the present paper is to report ^{1}H and ^{13}C NMR data of compounds **1**–**8** (Fig. 1), to discuss their tautomerism and isomerism, and report calculations of their properties (energies and NMR).

Results and discussion

Chemistry

1,4-Dihydro-4-oxoquinoline-3-carbaldehyde (**1**) was obtained through a Vilsmeier reaction of 2′-aminoacetophenone, followed by acidic hydrolysis of the resultant 4-chloroquinoline-3-carbaldehyde (**9**) [5]. Methylation of **1** gave 1,4-dihydro-1-methyl-4-oxoquinoline-3-carbaldehyde (**2**), while carboxyethylation and tosylation afforded ethyl 3-formyl-1,4-dihydro-4-oxoquinoline-1(4*H*)-carboxylate (**3**) and 1,4-dihydro-4-oxo-1-tosylquinoline-3-carbaldehyde (**4**), respectively (Scheme 1, vide experimental part) [18, 19]. The most

Electronic supplementary material The online version of this article (doi:10.1007/s00706-011-0473-y) contains supplementary material, which is available to authorized users.

R. S. G. R. Seixas · A. M. S. Silva (✉)
Chemistry Department and QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal
e-mail: artur.silva@ua.pt

I. Alkorta · J. Elguero
Instituto de Química Médica, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain

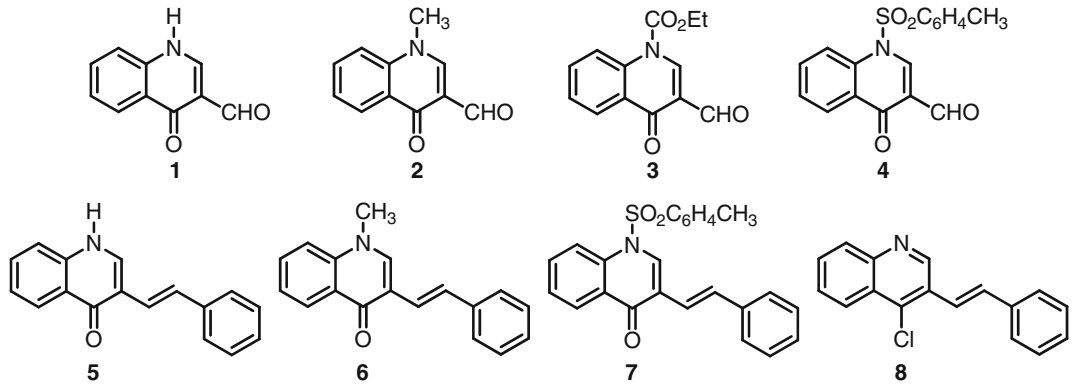
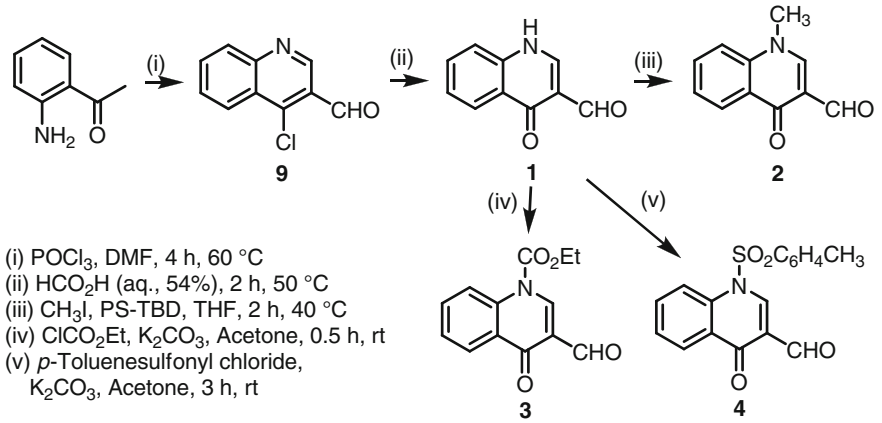


Fig. 1 Structures of quinolin-4(1*H*)-ones **1**-**7** and quinoline **8**



Scheme 1

important NMR features of these compounds are the signals due to the resonance of the formyl group (δ_H = 10.37–10.46 ppm, δ_C = 186.3–186.5 ppm) and C-4 carbonyl group (δ_C = 172.2–173.3 ppm). Some of these chemical shifts are not self-evident, which is one of the reasons we carried out theoretical calculations.

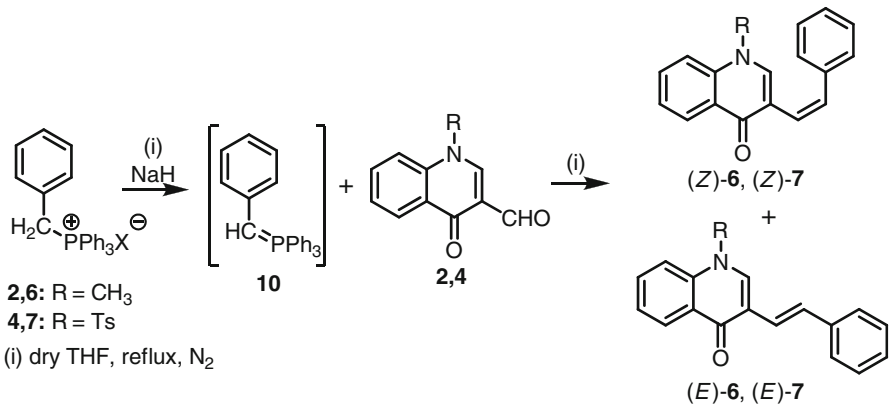
Wittig reaction of *N*-substituted quinolone-3-carbaldehydes **2** and **4** with benzylidenetriphenylphosphorane, obtained from the reaction of benzyltriphenylphosphonium chloride with a molar equivalent of NaH in freshly dried Tetrahydrofuran (THF), led to the formation of a diastereomeric mixture of (*Z*)- and (*E*)-1-substituted-3-styrylquinolin-4(1*H*)-ones (*Z*)-**6**, (*Z*)-**7** and (*E*)-**6**, (*E*)-**7** in good yields [R = CH_3, (*E*)-**6** 8%, (*Z*)-**6** 70%; R = tosyl, (*E*)-**7** 6%, (*Z*)-**7** 46%; Scheme 2] [19]. The (*Z*)-isomer was the more abundant, as expected from the reaction of a semistabilized ylide with sterically crowded carbonyl compounds [20–23].

Wittig reaction of 4-chloroquinoline-3-carbaldehyde (**9**) with benzylidenetriphenylphosphorane led to the formation of a diastereomeric mixture of (*Z*)- and (*E*)-4-chloro-3-styrylquinolines (*E*)-**8**, (*Z*)-**8** in good yields [(*E*)-**8** 36%, (*Z*)-**8** 55%, Scheme 3] [19]. Hydrolysis of the diastereomeric mixture (*Z*)-**8**, (*E*)-**8** with 40% aqueous formic acid at 120 °C for 24 h led to the formation of (*E*)-3-styrylquinolin-4(1*H*)-one (**5**) in 93% yield. However, controlling the reaction at 18 h reaction time, we found a mixture of (*Z*)- and (*E*)-3-styrylquinolin-4(1*H*)-ones (*Z*)-**5**, (*E*)-**5** in a proportion of 9:78%. This seems to indicate that we are in the presence of a (*Z*) → (*E*) thermal isomerization, since all the transformation was carried out in the absence of light.

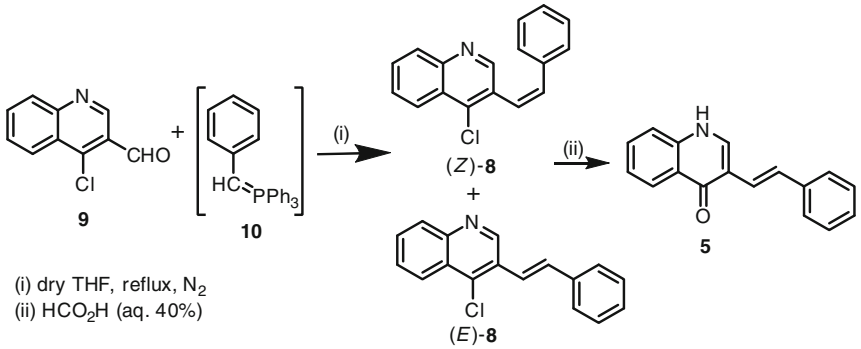
The assignment of the stereochemistry of styrylquinolines described above was based on the coupling constant of the styryl olefinic protons, being $^3J_{trans} \approx$ 16 Hz and $^3J_{cis} \approx$ 12 Hz, and also on the nuclear Overhauser effect (NOE) cross peaks observed in the NOE spectroscopy (NOESY) spectra of some of these compounds (Fig. 2).

Experimental NMR data

The chemical shifts are reported in Tables 1 and 2. Note in the case of the styryl derivatives **5**–**8** the possible existence



Scheme 2



Scheme 3

of an (*E*)/(*Z*) isomerism (Scheme 4 and analogously for **8**) as well as a *anti*/*syn* rotation about the C3–Cα bond mainly for the (*E*)-isomers, although NOESY experiments (Fig. 2) show that there is a weak interaction between H2 and Hα for the (*Z*)-isomers. Furthermore, in the case of **5** (R = H), the possible existence of hydroxy forms (**b**) must be considered (see "Discussion" on tautomerism).

Theoretical calculations

Tautomerism

NH-quinolones **1** and **5** present oxo/hydroxy (**b**) tautomerism (see Scheme 5 for **1**); its position was not well known in 1976 [24]. In the 2006 update, the situation remained confused [25]. 2-Substituted 4-quinolones showed predominance of 4-hydroxy tautomers (**b**) in dimethyl sulfoxide (DMSO)-d_6 solution and of 4-oxo ones in $CDCl_3$/CD_3OD [26]. According to Mphahlele and coworkers, the 3-bromo derivatives exist both in solution and in the solid state as the oxo tautomers [27]. Subsequently, these latter authors discussed the case of 2-aryl-4-quinolones [28]: in solution (NMR in DMSO-d_6) and in the solid state only the 4-oxo tautomer is observed but in the gas phase (mass spectrometry and theoretical calculations) both tautomers are present.

Our B3LYP/6-311++G(d,p) energy calculations for compound **1** afford for **1** (C=O) −590.64828 hartree and for **1b** (OH) −590.65243 hartree; i.e., the OH tautomer is the more stable by 10.9 kJ mol^{-1}. In the case of **5** the situation is reversed (Table 3) and the oxo tautomers are the more stable by 25.8 kJ mol^{-1}. We ascribe the difference of about 37 kJ mol^{-1} to an intramolecular hydrogen bond (IMHB) in the case of **1b** (Scheme 5). This kind of stabilization was known for 4-hydroxyquinolines bearing an ester group at position 3 [24].

Rotational isomerism

We have carried out B3LYP/6-311++G(d,p) calculations on the structures **5**–**8**. When trying to calculate the crowded *syn*-(*Z*)-conformations in the case of compounds **5** and **6**, we obtained the *anti*-(*Z*)-ones (Scheme 4). This result is not inconsistent with the NOESY experiments (Fig. 2) because, even if these isomers are not stable, the *anti*-(*Z*)/*syn*-(*Z*) rotation about the C3-Cα bond puts the H2 and Hα protons in close proximity [29, 30].

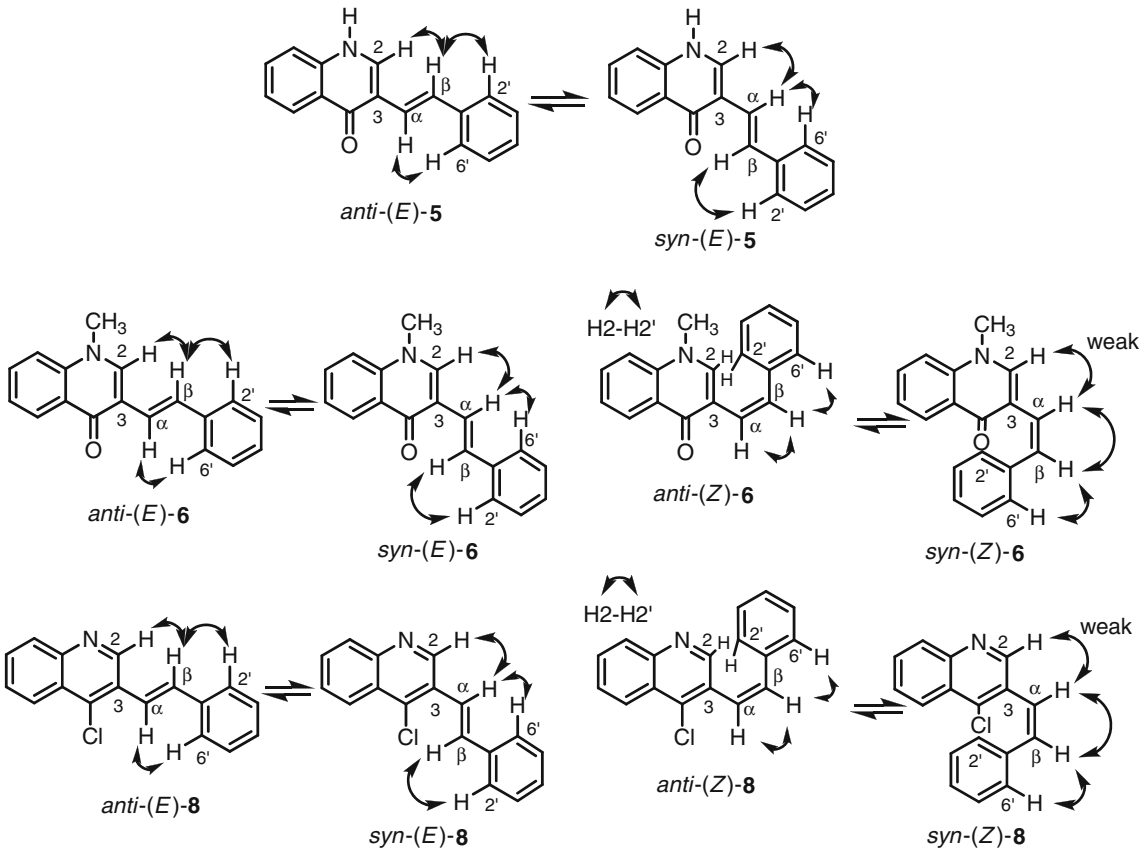
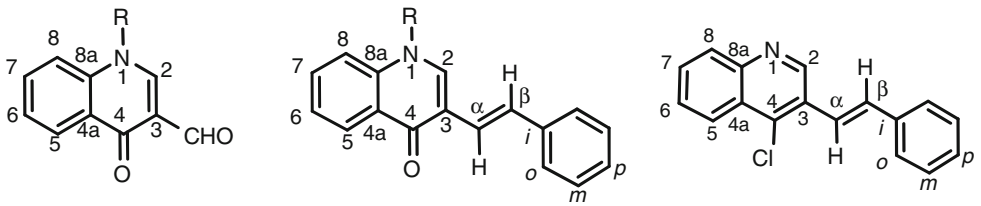


Fig. 2 Main NOE cross peaks observed in the NOESY spectra of (*E*)-**5**, (*E*)-**6**, (*Z*)-**6**, (*E*)-**8**, and (*Z*)-**8**

Table 1 ^{1}H NMR chemical shifts (ppm) of compounds **1**–**8** [**2**–**4**, **6**–**8** in $CDCl_3$ and **1**, **5** in dimethyl sulfoxide (DMSO)-d_6]



Comp.	H2	H5	H6	H7	H8	CHO	Hα	H*β*	H*o*	H*m*	H*p*
1	8.49	8.22	7.48	7.77	7.68	10.20	–	–	–	–	–
2	8.31	8.54	7.53	7.78	7.50	10.42	–	–	–	–	–
3	9.03	8.47	7.53	7.75	8.61	10.44	–	–	–	–	–
4	9.27	8.43	7.47	7.66	8.21	10.46	–	–	–	–	–
(*E*)-**5**	8.30	8.21	7.36	7.66	7.58	–	7.22	7.80	7.51	7.36	7.22
(*E*)-**6**	7.77	8.55	7.42	7.67	7.41	–	7.17	7.65	7.54	7.34	7.22
(*Z*)-**6**	7.48	8.54	7.41	7.67	7.35	–	6.79	6.65	7.35	7.26	7.22
(*E*)-**7**	8.80	8.42	7.41	7.58	8.21	–	7.20	7.68	7.58	7.38	7.28
(*Z*)-**7**	8.42	8.40	7.39	7.56	8.09	–	6.72	6.87	7.32	7.32	7.32
(*E*)-**8**	9.20	8.29	7.64	7.74	8.11	–	7.65	7.34	7.65	7.42	7.34
(*Z*)-**8**	8.57	8.29	7.65	7.74	8.04	–	6.80	6.96	7.18	7.18	7.18

NR **2** (CH_3, 3.93); **3** (CH_2, 4.61; CH_3, 1.54); **4** (H*o*, 7.83, H*m*, 7.38, CH_3, 2.43); (*E*)-**6** (CH_3, 3.88); (*Z*)-**6** (CH_3, 3.56); (*E*)-**7** (tosyl: H*o*, 7.78, H*m*, 7.32, CH_3, 2.40); (*Z*)-**7** (tosyl: H*o*, 7.46, H*m*, 7.26, CH_3, 2.40)

Table 2 ^{13}C NMR chemical shifts (ppm) of compounds **1–8** [**2–4**, **6-8** in $CDCl_3$ and **1**, **5** in dimethyl sulfoxide (DMSO)-d_6]

Comp.	C2	C3	C4	C4a	C5	C6	C7	C8	C8a	CHO
1	143.3	116.3	176.3	127.8	125.5[a]	125.3[a]	133.1	119.5	139.4	188.8
2	146.7	117.1	177.0	129.3	127.3	125.9	133.3	116.2	140.2	189.3
3	142.4	118.0	177.4	127.9	126.6	126.8	133.8	120.2	137.9	189.1
4	141.8	118.2	177.0	128.0	127.5	126.9	133.6	118.6	136.4	188.7
(*E*)-**5**	138.9	116.8	175.3	125.4	125.5	123.5	131.5	118.4	138.6	–
(*E*)-**6**	142.0	118.5	176.2	126.7	127.4	123.9	131.9	115.2	139.3	–
(*Z*)-**6**	142.0	118.5	176.2	126.7[a]	127.4	123.9	131.9	115.2	139.3	–
(*E*)-**7**	134.8	120.9	177.2	126.2	127.6	125.7	132.4	118.1	135.9	–
(*Z*)-**7**	136.9	120.1	177.8	125.8	127.4	125.5	132.4	118.0	136.2	–
(*E*)-**8**	148.1	129.6	139.5	126.4	124.5	128.0	129.8	129.6	147.6	–
(*Z*)-**8**	151.2	129.4	140.7	126.4	124.0[a]	127.7	129.9	129.6	147.4	–

Comp.	Cα	Cβ	C*i*	C*o*	C*m*	C*p*
(*E*)-**5**	124.1	126.6	138.5	125.8	128.8	126.8
(*E*)-**6**	122.6	128.3	138.2	126.3	128.6	127.1
(*Z*)-**6**	123.7[a]	129.0	137.6	128.6	128.4	126.9
(*E*)-**7**	121.2	131.2	137.4	126.6	128.7	127.8
(*Z*)-**7**	123.0	132.3	137.1	128.8[a]	128.7[a]	127.1
(*E*)-**8**	122.4	133.2	136.5	127.0	128.8	128.7
(*Z*)-**8**	124.1[a]	134.0	135.9	128.9	128.6	128.0

Comp.	(NR)
2	CH_3 41.6 (CH_3)
3	CO_2Et 150.8 (C=O), 66.2 (CH_2), 14.1 (CH_3)
4	Tosyl 132.9 (C*i*), 127.9 (C*o*), 130.6 (C*m*), 147.3 (C*p*), 21.8 (CH_3)
(*E*)-**6**	CH_3 41.0 (CH_3)
(*Z*)-**6**	CH_3 40.6 (CH_3)
(*E*)-**7**	Tosyl 133.7 (C*i*), 127.5 (C*o*), 130.4 (C*m*), 146.4 (C*p*), 21.7 (CH_3)
(*Z*)-**7**	Tosyl 133.6 (C*i*), 127.6 (C*o*), 130.2 (C*m*), 146.2 (C*p*), 21.7 (CH_3)

[a] For a given compound, the assignment of these signals can be permuted

The (*Z*)-isomers are always the less stable, but between the (*E*)-ones there is an inversion between quinolones **5**, **6**, and **7** [*syn*-(*E*) more stable than *anti*-(*E*)] and 4-chloroquinolines **8** [*anti*-(*E*) more stable than *syn*-(*E*)]. We assign this difference to a C–H···O=C IMHB in the *syn*-(*E*)-3-styrylquinolin-4(1*H*)-ones (Fig. 3). The lower stability of the (*Z*)-isomers (between 16 and 21 kJ mol^{-1}) agrees with our previous comment about the (*Z*) → (*E*) thermal isomerization.

Theoretical calculations of chemical shifts

We have calculated the ^1H and ^{13}C absolute shieldings (σ, ppm) using the Gauge Including Atomic Orbitals (GIAO) approximation on the minimum geometries obtained at the 6-311++G(d,p) level. These σ values were transformed into chemical shifts (δ, ppm) using two empirical equations we have previously established [31, 32]:

$$\delta^1H = 31.0 - 0.97\sigma^1H$$

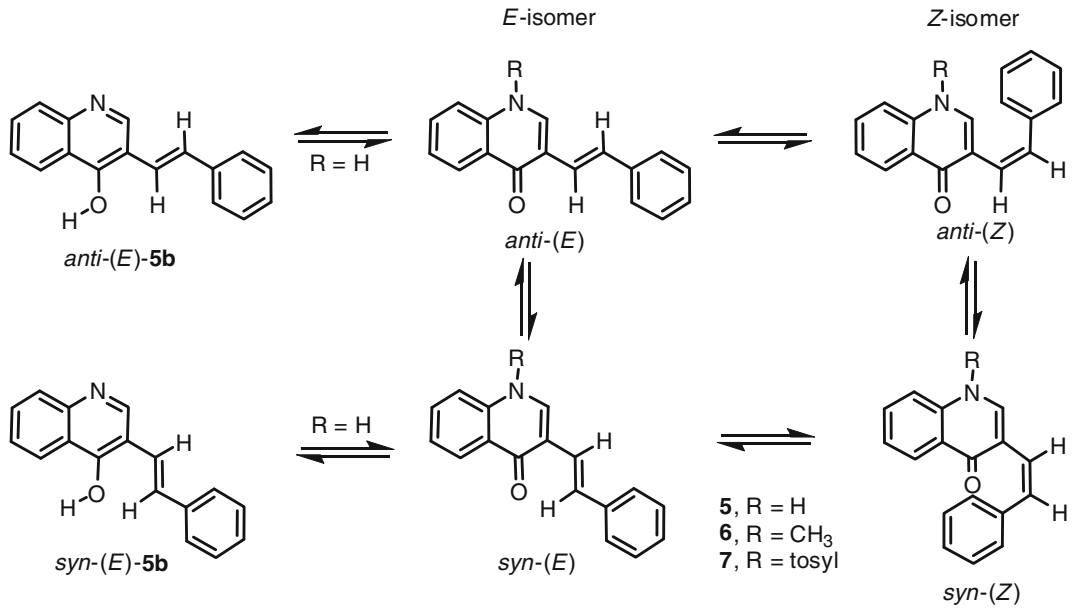
$$\delta^{13}C = 175.7 - 0.963\sigma^{13}C$$

The σ and δ values can be found in the Supplementary Material.

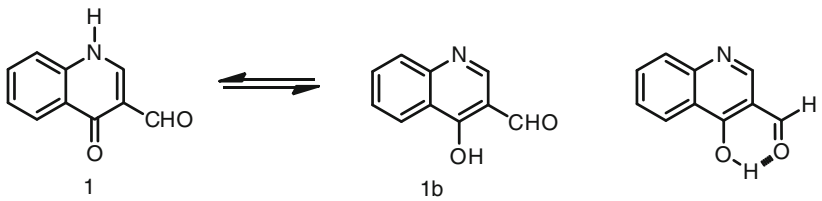
First, we will discuss the case of the 3-formyl derivatives **1–4**. By interpolation of the experimental ^{13}C NMR chemical shifts (Table 2) of compound **1** (obtained in DMSO-d_6) we have calculated that it is a mixture of 75% oxo **1** and 25% hydroxy **1b** tautomers. If we exclude the signal of the *ipso* carbon of the tosyl derivative **4** we obtain Eq. (2):

$$\delta^{13}C_{exp.} = (1.007 \pm 0.002)\delta^{13}C_{calcd.},$$
$$n = 48, \quad R^2 = 1.000. \qquad (1)$$

The 75% of oxo tautomer **1** in DMSO-d_6 agrees with Mphahlele's results [27, 28]. We assign the inversion of the



Scheme 4



Scheme 5

populations between the gas phase (the OH tautomer **1b** more stable by about 11 kJ mol^{-1}) and the DMSO solution (75% oxo **1** and 25% hydroxy **1b**) to the fact that the IMHB of **1b** present in the gas phase (Scheme 5) breaks in this solvent.

The ^{1}H NMR chemical shifts (Table 1) are less suited to discuss the tautomerism of **1**, however the regression is slightly better using the averaged 75/25 mixture (Eq. 3) than considering the four compounds to be oxo tautomers (Eq. 2).

$$\delta^1\mathrm{H}_{\mathrm{exp.}} = (1.010 \pm 0.006)\delta^1\mathrm{H}_{\mathrm{calcd.}}, \quad n = 30, \quad R^2 = 0.9989, \tag{2}$$

$$\delta^1\mathrm{H}_{\mathrm{exp.}} = (1.008 \pm 0.005)\delta^1\mathrm{H}_{\mathrm{calcd.}}, \quad n = 30, \quad R^2 = 0.9992 \tag{3}$$

Now we will examine the case of the 3-styryl-derivatives **5**–**8**. For compound **5** there exist oxo and hydroxyl tautomers. For the (*E*)-isomer, that corresponds to four structures: **5** oxo *anti*-(*E*), **5** oxo *syn*-(*E*), **5b** hydroxy *anti*-(*E*), and **5b** hydroxy *syn*-(*E*). We have assumed, according to the calculations, that all are oxo tautomers **5**, **6**, and **7**. Then, by interpolation we obtain the following results:

(*E*)-**5** 45%*anti*-55%*syn*
(*E*)-**6** 33%*anti*-67%*syn*
(*E*)-**7** 55%*anti*-45%*syn*
(*E*)-**8** 50%*anti*-50%*syn*

To compare the experimental ^{13}C NMR chemical shifts with the calculated ones, we simplified the problem of *anti*-/*syn*-isomerism by considering that, in all cases, the mixture is 50%/50%, obtaining the plot shown in Fig. 4 [$\delta_{\mathrm{exp.}} = (1.002 \pm 0.002)\delta_{\mathrm{Calcd.}}$, $n = 118$, $R^2 = 1.000$].

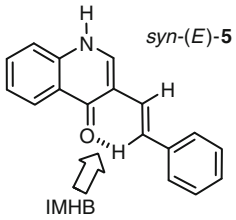
We have already signaled that carbon atoms bearing chlorine or sulfur substituents are not well reproduced at the used computational level [33, 34]. The contribution of these substituents can be estimated at $-(6.7 \pm 2.1)$ ppm for the SO_2 group on the C*ipso* carbon and at $-(8.3 \pm 1.5)$ ppm for the chlorine atom on C4.

We have carried out a similar study concerning ^{1}H NMR chemical shifts assuming that there are equal amounts of *anti*- and *syn*-rotational isomers (Fig. 5).

Table 3 Energies and dipole moments calculated at the B3LYP/6-311++G(d,p) computational level

Comp.	E_{total} (hartree)	Dipole (D)	E_{rel} (kJ mol^{-1})
5			
anti-(*E*)	−785.82349	5.97	4.0
syn-(*E*)	−785.82488	6.00	**0.0**
anti-(*Z*)	−785.81752	5.97	19.3
5b			
anti-(*E*)	−785.81503	2.57	25.8
syn-(*E*)	−785.81464	2.71	26.9
6			
anti-(*E*)	−825.13905	6.48	4.0
syn-(*E*)	−825.14058	6.53	**0.0**
anti-(*Z*)	−825.13316	6.43	19.5
7			
anti-(*E*)	−1604.87919	5.78	2.4
syn-(*E*)	−1604.88012	6.20	**0.0**
anti-(*Z*)	−1604.87193	5.93	21.5
8			
anti-(*E*)	−1170.18742	0.93	**0.0**
syn-(*E*)	−1170.18354	1.12	10.2
anti-(*Z*)	−1170.18116	0.58	16.4

Fig. 3 Intramolecular hydrogen bond of *syn*-(*E*)-3-styrylquinolin-4(1*H*)-one (**5**)



AIM analysis of intramolecular interactions

We decided to study the situations corresponding to **1b** (Scheme 5), *anti*-(*E*)-**5** (Scheme 4 and Fig. 3), and *syn*-(*E*)-**5** (Scheme 4) using the atoms in molecules (AIM) methodology (Fig. 6). The analysis of the electron density in these molecules shows the presence of several types of intramolecular interactions such as H···H, CH···O, and OH···O. The presence of these interactions is associated to bond critical points (bcp), and due to the topological nature of these compounds to a ring critical point (rcp). The strength of these interactions can be qualitatively assigned based on the distance of the bcp and the rcp. The proximity of bcp and rcp (H···H contacts) indicates that small perturbations in the system can result in the disappearance of both critical points, which corresponds to weak interactions. In contrast, the OH···O contacts represent distant positions of the bcp and rcp and can be associated to stronger interactions.

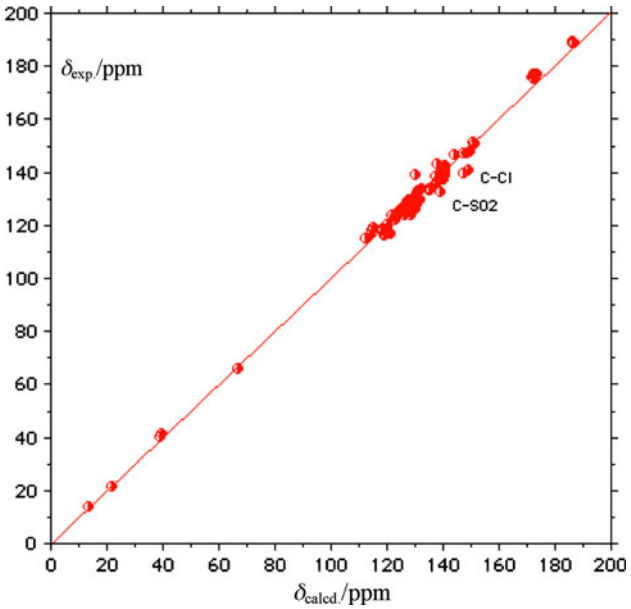


Fig. 4 Plot of experimental versus calculated ^{13}C NMR chemical shifts

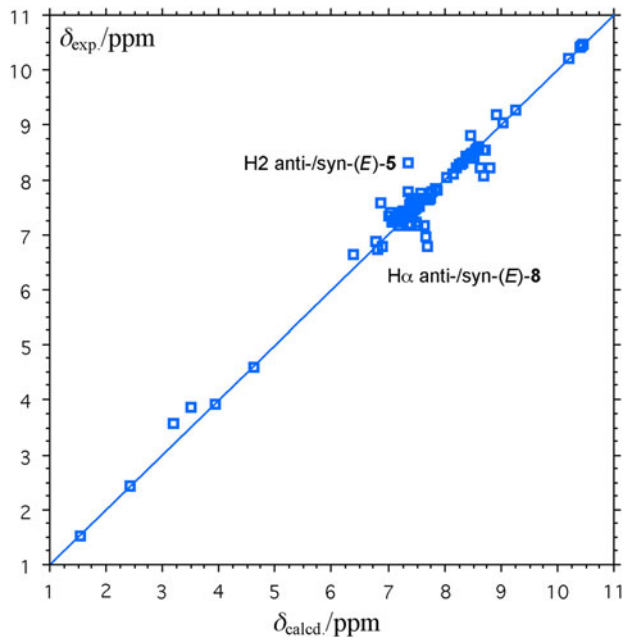


Fig. 5 Plot of experimental versus calculated ^{1}H NMR chemical shifts. The trendline corresponds to $\delta_{Exp.} = (1.001 \pm 0.003)\delta_{Calcd.}$, $n = 102$, $R^2 = 0.999$. The two worse points are labeled

Conclusions

1,4-Dihydro-4-oxoquinoline-3-carbaldehyde (**1**) was obtained from 2′-aminoacetophenone and used as synthon for

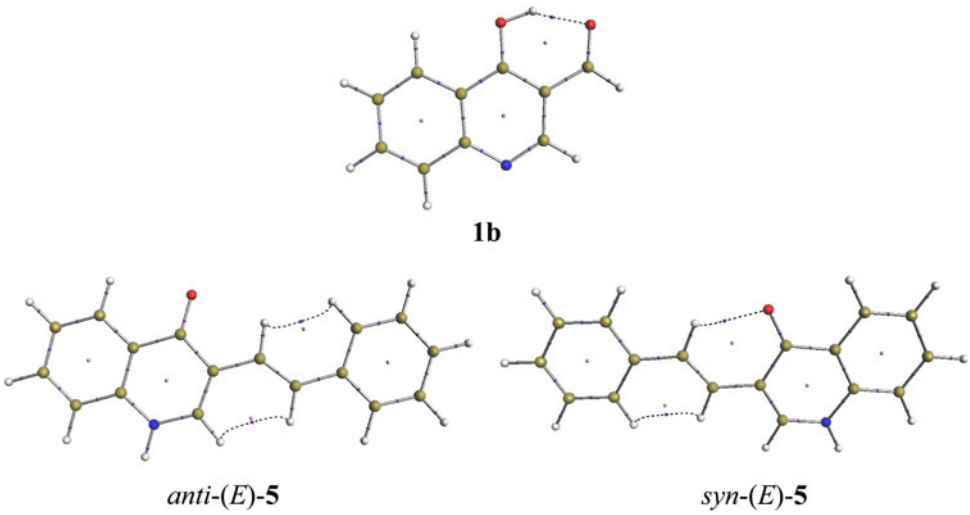


Fig. 6 Main intramolecular interactions present in **1b**, *anti*-(*E*)-**5**, and *syn*-(*E*)-**5** obtained by AIM

preparation of other 1-substituted 1,4-dihydro-4-oxoquinoline-3-carbaldehydes and 3-styrylquinolin-4(1*H*)-ones. ^{1}H and ^{13}C NMR data and theoretical calculations on these compounds showed that those having an unsubstituted heterocyclic nitrogen can exist as a mixture of tautomers; 1,4-dihydro-4-oxoquinoline-3-carbaldehyde mainly exists as the hydroxyl tautomer in the gas phase and as oxo tautomer in DMSO solution, while in the case of 3-styrylquinolinone the oxo tautomer is the more stable in both situations. DFT calculations on (*E*) → (*Z*) and rotational isomerism of 3-styrylquinolin-4(1*H*)-ones and of 4-chloro-3-styrylquinoline showed that the *cis* isomers (*Z*) are always less stable. For the *trans* isomers, *syn*-(*E*) is more stable than *anti*-(*E*) in the case of 3-styrylquinolin-4(1*H*)-ones, due to an IMHB between Hβ and the carbonyl group, while in the case of 4-chloro-3-styrylquinoline the converse applies.

Experimental

Melting points were determined on a Büchi melting point B-540 apparatus. NMR spectra were recorded on Bruker Avance 300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) and Bruker Avance 500 (500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C) spectrometers, with $CDCl_3$ as solvent. Chemical shifts (δ) are reported as ppm values and coupling constants (*J*) in Hz. The internal standard was tetramethylsilane (TMS). ^{1}H assignments were made using two-dimensional (2D) and NOESY (mixing time 800 ms) experiments, while ^{13}C assignments were made using 2D gradient-assisted heteronuclear single-quantum correlation (gHSQC) and gradient-assisted heteronuclear multiple bond correlation (gHMBC) (long-range C/H coupling constants were optimized to 7 Hz) experiments. Positive-ion electrospray ionization (ESI) mass spectra were acquired using a Q-TOF 2 instrument, diluting 1 mm^3 of the sample chloroform solution ($\sim 10^{-5}$ M) in 200 mm^3 0.1% trifluoroacetic acid/methanol solution. Nitrogen was used as nebulizer gas and argon as collision gas. The needle voltage was set at 3,000 V, with the ion source at 80 °C and desolvation temperature at 150 °C. Cone voltage was 35 V. High-resolution mass spectra (HRMS-ESI$^+$) were performed on a microTOF (focus) mass spectrometer [HRMS were in good agreement (±0.5 ppm) with the calculated values]. Ions were generated using an ApolloII (ESI) source. Ionization was achieved by electrospray, using a voltage of 4,500 V applied to the needle, and a countervoltage between 100 and 150 V applied to the capillary. Electron ionization and the corresponding high-resolution mass spectra (HREI-MS) were obtained on an Autospec Micromass spectrometer. Elemental analyses were obtained with a LECO 932 CHN analyzer (University of Aveiro), and the results were in good agreement (±0.4%) with the calculated values. Preparative thin-layer chromatography was carried out with Riedel silica gel 60 DGF_{254}, and column chromatography using Merck silica gel 60, 70–230 mesh.

1,4-Dihydro-4-oxoquinoline-3-carbaldehyde (**1**)

To 50 cm^3 dry Dimethylformamide (DMF), $POCl_3$ (246.8 mmol) was added dropwise at 0 °C, and the mixture was stirred for 15 min under nitrogen at room temperature. Then, 5 cm^3 2′-aminoacetophenone (41.1 mmol) was added dropwise, and the mixture was heated for 4 h at 60 °C. After addition of 200 g ice and 200 cm^3 water, the solution was neutralized with $NaHCO_3$, and the formed solid was filtered. The solid was dissolved in 400 cm^3 $CHCl_3$ and washed with 3 × 400 cm^3 water. After evaporation of the solvent, the resulting solid was purified by column chromatography using CH_2Cl_2 as eluent and crystallized from a mixture of ethyl acetate and hexane to

afford 4-chloroquinoline-3-carbaldehyde **9** as a white solid (3.938 g; 50%). A suspension of 3.324 g **9** (17.3 mmol) in 40 cm^3 54% aqueous formic acid was heated at 50 °C for 2 h. The resulting suspension was frozen for 2 h, and the formed solid was filtered off and washed with water. Pure 1,4-dihydro-4-oxoquinoline-3-carbaldehyde was collected as a white solid without purification or crystallization (2.856 g, 97%). M.p.: >278 °C (dec.); ^{1}H NMR (300.13 MHz, DMSO-d_6): $\delta = 7.48$ (ddd, 1H, $J = 1.3$, 7.0, 8.1 Hz, H-6), 7.68 (d, 1H, $J = 8.1$ Hz, H-8), 7.77 (ddd, 1H, $J = 1.3$, 7.0, 8.1 Hz, H-7), 8.22 (1H, dd, $J = 1.3$, 8.1 Hz, H-5), 8.49 (s, 1H, H-2), 10.20 (s, 1H, 3-C*H*O) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6): $\delta = 116.3$ (C-3), 119.5 (C-8), 125.3 and 125.5 (C-5 and C-6), 127.8 (C-4a), 133.1 (C-7), 139.4 (C-8a), 143.3 (C-2), 176.3 (C-4), 188.8 (3-CHO) ppm; EI-MS (70 eV): *m*/*z* (%) = 173 (M^+, 100), 172 (55), 116 (15), 89 (24).

1,4-Dihydro-1-methyl-4-oxoquinoline-3-carbaldehyde (**2**)

To a suspension of 1,4-dihydro-4-oxoquinoline-3-carbaldehyde (4.0 mmol) and polystyrene-bound 1,5,7-triazabicyclo [4.4.0]dec-5-ene (PS-TBD, 10 mmol) in 300 cm^3 dry THF, 2.49 cm^3 iodomethane (40 mmol) was added. The reaction mixture was heated at 40 °C for 2 h. Ice (100 g), 100 cm^3 water, and a small amount of triethylamine (10 cm^3) were added to the reaction mixture, and the pH adjusted to 7 with dilute hydrochloric acid. PS-TBD was filtered off, and the filtrate was extracted with 3 × 150 cm^3 chloroform. The solvent was evaporated to dryness, and the residue was crystallized from ethanol to afford 1,4-dihydro-1-methyl-4-oxoquinoline-3-carbaldehyde as white needles (726.3 mg, 97%). M.p.: 212–213 °C (Ref. [35]: 210 °C).

Ethyl 3-formyl-4-oxoquinoline-1(4H)-carboxylate (**3**)

Anhydrous potassium carbonate (8.10 mmol, 1.12 g) was added to a suspension of 701.3 mg 1,4-dihydro-4-oxoquinoline-3-carbaldehyde (4.05 mmol) in 50 cm^3 acetone, and the mixture was stirred at room temperature for 30 min. Then, 581 mm^3 ethyl chloroformate (6.08 mmol) was added, and the mixture was stirred at room temperature for another 30 min. After this period, the potassium carbonate was filtered off and washed with 2 × 50 cm^3 acetone, and the filtrate was concentrated. Water (50 cm^3) was added, and the aqueous mixture was extracted with 3 × 50 cm^3 chloroform. After evaporation of the solvent, pure ethyl 3-formyl-4-oxoquinoline-1(4*H*)-carboxylate was obtained as a yellowish solid without purification or crystallization (953.4 mg, 96%). M.p.: 93–94 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 1.54$ (t, 3H, $J = 7.1$ Hz, N–$CO_2CH_2CH_3$), 4.61 (q, 2H, $J = 7.1$ Hz, N-$CO_2CH_2CH_3$), 7.53 (ddd, 1H, $J = 0.7$, 7.2, 7.9 Hz, H-6), 7.75 (ddd, 1H, $J = 1.7$, 7.2, 8.8 Hz, H-7), 8.47 (dd, 1H, $J = 1.7$, 7.9 Hz, H-5), 8.61 (d, 1H, $J = 8.8$ Hz, H-8), 9.03 (s, 1H, H-2), 10.44 (s, 1H, 3-C*H*O) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 14.1$ (N-$CO_2CH_2CH_3$), 66.2 (N-$CO_2CH_2CH_3$), 118.0 (C-3), 120.2 (C-8), 126.6 (C-5), 126.8 (C-6), 127.9 (C-4a), 133.8 (C-7), 137.9 (C-8a), 142.4 (C-2), 150.8 (N-*C*OOCH_2CH_3), 177.4 (C-4), 189.1 (3-*C*HO) ppm; ESI$^+$-MS: *m*/*z* (%) = 246 (12) $[M + H]^+$, 268 (100) $[M + Na]^+$, 284 (5) $[M + K]^+$.

1,4-Dihydro-4-oxo-1-(4-toluolsulfonyl)quinoline-3-carbaldehyde (**4**)

To a suspension of 200.9 mg 1,4-dihydro-4-oxoquinoline-3-carbaldehyde (1.16 mmol) in 20 cm^3 acetone, 320.6 mg anhydrous potassium carbonate (2.32 mmol) was added, and the mixture was stirred at room temperature for 30 min. *p*-Toluenesulfonyl chloride (331.7 mg, 1.74 mmol) was then added, and the mixture was stirred at room temperature for 3 h. After that time, the potassium carbonate was filtered off, washed with 2 × 20 cm^3 acetone, and the filtrate was concentrated. The residue was purified by silica gel chromatography, first using CH_2Cl_2 as eluent (to remove the excess of *p*-toluenesulfonyl chloride) and then a mixture of CH_2Cl_2-acetone (5:1). The solvent was evaporated to dryness, and the solid recrystallized from a mixture of CH_2Cl_2-light petroleum to give 1,4-dihydro-4-oxo-1-(4-toluolsulfonyl)quinoline-3-carbaldehyde as a white solid (376.4 mg, 99%). M.p.: 170–172 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 2.43$ (s, 3H, 4′-C*H*$_3$), 7.38 (d, 2H, $J = 8.4$ Hz, H-3′,5′), 7.47 (dd, 1H, $J = 7.4$, 7.7 Hz, H-6), 7.66 (ddd, 1H, $J = 1.7$, 7.4, 8.8 Hz, H-7), 7.83 (d, 2H, $J = 8.4$ Hz, H-2′,6′), 8.21 (d, 1H, $J = 8.8$ Hz, H-8), 8.43 (dd, 1H, $J = 1.7$, 7.7 Hz, H-5), 9.27 (s, 1H, H-2), 10.46 (s, 1H, 3-C*H*O) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 21.8$ (4′-*C*H$_3$), 118.2 (C-3), 118.6 (C-8), 126.8 (C-6), 127.4 (C-5), 127.9 (C-2’,6’), 128.0 (C-4a), 130.6 (C-3’,5’), 132.9 (C-1’), 133.6 (C-7), 136.4 (C-8a), 141.8 (C-2), 147.3 (C-4’), 177.0 (C-4), 188.7 (3-*C*HO) ppm; ESI$^+$-MS: *m*/*z* (%) = 328 (39) $[M + H]^+$, 350 (100) $[M + Na]^+$.

*General procedure for the synthesis of 3-styrylquinolin-4(1H)-ones (E)-**6**, (Z)-**6**, (E)-**7**, and (Z)-**7** and 4-chloro-3-styrylquinolines (E)-**8** and (Z)-**8***

A mixture of 37 mg sodium hydride (1.56 mmol) and 606.6 mg benzyltriphenylphosphonium chloride (1.56 mmol) in 20 cm^3 dry refluxing THF was stirred for 3 h. The appearance of an orange color and the disappearance of the suspension of the phosphonium salt indicated ylide formation. Subsequently, the appropriate 3-carbaldehyde **2**, **4** or **9** (0.52 mmol) was added, and reflux was continued for 3 h (**2**), 4 h (**4**) or 45 min (**9**). After cooling to room temperature, the reaction mixture was poured onto 20 g ice and 20 cm^3 water, and the pH

was adjusted to 5 with dilute hydrochloric acid. In the case of precipitation, the solid was filtered off, washed with 3×50 cm^3 water, dissolved in 50 cm^3 $CHCl_3$, and washed with 2×50 cm^3 water, and the organic solvent evaporated to dryness. If no solid precipitated, the organic layer was extracted with 3×50 cm^3 $CHCl_3$ and the solvent was evaporated to dryness. In all cases the residues were dissolved in CH_2Cl_2.

1-Methyl-3-styrylquinolin-4(1H)-ones (**6**)
For the reaction of 1,4-dihydro-1-methyl-4-oxoquinoline-3-carbaldehyde, the residue was purified by silica gel column chromatography with a mixture of CH_2Cl_2-ethyl acetate (4:1). The component with the higher R_f value was identified as (*E*)-1-methyl-3-styrylquinolin-4(1*H*)-one (*E*)-**6**, with the slower eluting component being (*Z*)-1-methyl-3-styrylquinolin-4(1*H*)-one (*Z*)-**6**. These compounds were recrystallized from a mixture of CH_2Cl_2-light petroleum.

(E)-1-Methyl-3-styrylquinolin-4(1H)-one ((*E*)-**6**)
White solid (10.9 mg, 8%); m.p.: 136–138 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 3.88$ (s, 3H, N-C*H*$_3$), 7.17 (d, 1H, $J = 16.3$ Hz, H-α), 7.22 (tt, 1H, $J = 1.3$, 7.3 Hz, H-4′), 7.34 (t, 2H, $J = 7.3$ Hz, H-3′,5′), 7.41 (d, 1H, $J = 7.9$ Hz, H-8), 7.42 (ddd, 1H, $J = 1.1$, 7.4, 8.2 Hz, H-6), 7.54 (d, 2H, $J = 7.3$ Hz, H-2′,6′), 7.65 (d, 1H, $J = 16.3$ Hz, H-*β*), 7.67 (ddd, 1H, $J = 1.6$, 7.4, 7.9 Hz, H-7), 7.77 (s, 1H, H-2), 8.55 (dd, 1H, $J = 1.6$, 8.2 Hz, H-5) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 41.0$ (N-*C*H$_3$), 115.2 (C-8), 118.5 (C-3), 122.6 (C-α), 123.9 (C-6), 126.3 (C-2′,6′), 126.7 (C-4a), 127.1 (C-4′), 127.4 (C-5), 128.3 (C-*β*), 128.6 (C-3′,5′), 131.9 (C-7), 138.2 (C-1′), 139.3 (C-8a), 142.0 (C-2), 176.2 (C-4) ppm; ESI$^+$-MS: *m*/*z* (%) = 262 (100) $[M + H]^+$, 523 (11) $[2\ M + H]^+$.

(Z)-1-Methyl-3-styrylquinolin-4(1H)-one ((*Z*)-**6**)
White solid (95.1 mg, 70%); m.p.: 121–123 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 3.56$ (s, 3H, N-C*H*$_3$), 6.65 (d, 1H, $J = 12.2$ Hz, H-*β*), 6.79 (d, 1H, $J = 12.2$ Hz, H-α), 7.19–7.24 (m, 1H, H-4′), 7.24–7.29 (m, 2H, H-3′,5′), 7.33–7.37 (m, 3H, H-8, H-2′,6′), 7.41 (ddd, 1H, $J = 1.8$, 7.7, 8.2 Hz, H-6), 7.48 (s, 1H, H-2), 7.67 (ddd, 1H, $J = 1.5$, 7.7, 8.6 Hz, H-7), 8.54 (dd, 1H, $J = 1.5$, 8.2 Hz, H-5) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 40.6$ (N-*C*H$_3$), 115.3 (C-8), 117.8 (C-3), 123.7 and 123.8 (C-6 and C-α), 126.5 (C-4a), 126.9 (C-4′), 127.2 (C-5), 128.4 (C-3′,5′), 128.6 (C-2′,6′), 129.0 (C-*β*), 131.9 (C-7), 137.6 (C-1′), 139.7 (C-8a), 143.0 (C-2), 176.8 (C-4) ppm; ESI$^+$-MS: *m*/*z* (%) = 262 (100) $[M + H]^+$, 284 (8) $[M + Na]^+$.

3-Styryl-1-(4-toluolsulfonyl)quinolin-4(1H)-ones (**7**)
For the reaction of 1,4-dihydro-4-oxo-1-(4-toluolsulfonyl)quinoline-3-carbaldehyde, the residue was purified by preparative thin-layer chromatography with a mixture of light petroleum-ethyl acetate (4:1). Once again the component of higher R_f value was identified as (*E*)-3-styryl-1-(4-toluolsulfonyl)quinolin-4(1*H*)-one (*E*)-**7** and the other one as the (*Z*)-3-styryl-1-(4-toluolsulfonyl)quinolin-4(1*H*)-one (*Z*)-**7**.

(E)-3-Styryl-1-(4-toluolsulfonyl)quinolin-4(1H)-one ((*E*)-**7**)
White solid (12.5 mg, 6%); m.p.: 190–194 °C (dec.); ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 2.40$ (s, 3H, 4″-C*H*$_3$), 7.20 (d, 1H, $J = 16.4$ Hz, H-α), 7.26–7.30 (m, 1H, H-4′), 7.32 (d, 2H, $J = 8.2$ Hz, H-3″,5″), 7.38 (t, 2H, $J = 7.3$ Hz, H-3′,5′), 7.38–7.43 (m, 1H, H-6), 7.58 (ddd, 1H, $J = 1.7$, 7.1, 8.8 Hz, H-7), 7.58 (d, 2H, $J = 7.3$ Hz, H-2′,6′), 7.68 (d, 1H, $J = 16.4$ Hz, H-*β*), 7.78 (d, 2H, $J = 8.2$ Hz, H-2″,6″), 8.21 (d, 1H, $J = 8.8$ Hz, H-8), 8.42 (dd, 1H, $J = 1.7$, 8.0 Hz, H-5), 8.80 (s, 1H, H-2) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 21.7$ (4″-*C*H$_3$), 118.1 (C-8), 120.9 (C-3), 121.2 (C-α), 125.7 (C-6), 126.2 (C-4a), 126.6 (C-2′,6′), 127.5 (C-2″,6″), 127.6 (C-5), 127.8 (C-4′), 128.7 (C-3′,5′), 130.4 (C-3″,5″), 131.2 (C-*β*), 132.4 (C-7), 133.7 (C-1″), 134.8 (C-2), 135.9 (C-8a), 137.4 (C-1'), 146.4 (C-4″), 177.2 (C-4) ppm; ESI$^+$-MS: *m*/*z* (%) = 402 (100) $[M + H]^+$.

(Z)-3-Styryl-1-(4-toluolsulfonyl)quinolin-4(1H)-one ((*Z*)-**7**)
Yellow oil (96.0 mg, 46%); ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 2.40$ (s, 3H, 4″-C*H*$_3$), 6.72 (dd, 1H, $J = 1.0$, 12.0 Hz, H-α), 6.87 (d, 1H, $J = 12.0$ Hz, H-*β*), 7.26 (d, 2H, $J = 8.3$ Hz, H-3″,5″), 7.30–7.35 (m, 5H, H-2′,6′, H-3′,5′, H-4′), 7.39 (ddd, 1H, $J = 0.8$, 7.2, 8.1 Hz, H-6), 7.46 (d, 2H, $J = 8.3$ Hz, H-2″,6″), 7.56 (ddd, 1H, $J = 1.7$, 7.2, 8.7 Hz, H-7), 8.09 (d, 1H, $J = 8.7$ Hz, H-8), 8.40 (dd, 1H, $J = 1.7$, 8.1 Hz, H-5), 8.42 (d, 1H, $J = 1.0$ Hz, H-2) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 21.7$ (4″-*C*H$_3$), 118.0 (C-8), 120.1 (C-3), 123.0 (C-α), 125.5 (C-6), 125.8 (C-4a), 127.1 (C-4′), 127.4 (C-5), 127.6 (C-2″,6″), 128.7 and 128.8 (C-2′,6′ and C-3′,5′), 130.2 (C-3″,5″), 132.3 (C-*β*), 132.4 (C-7), 133.6 (C-1″), 136.2 (C-8a), 136.9 (C-2), 137.1 (C-1'), 146.2 (C-4″), 177.8 (C-4) ppm; ESI$^+$-MS: *m*/*z* (%) = 402 (100) $[M + H]^+$, 424 (6) $[M + Na]^+$.

4-Chloro-3-styrylquinolines (**8**)
For the reaction of 4-chloroquinoline-3-carbaldehyde, the residue was purified by silica gel chromatography, eluting with a mixture of light petroleum:ethyl acetate (7:1). The component of higher R_f value was identified as (*Z*)-4-chloro-3-styrylquinoline (*Z*)-**8** and the second as (*E*)-4-chloro-3-styrylquinoline (*E*)-**8**. These compounds were recrystallized from a mixture of CH_2Cl_2-light petroleum.

(E)-4-Chloro-3-styrylquinoline ((*E*)-**8**)
White solid (49.7 mg, 36%); m.p.: 153–154 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.31–7.37 (m, 1H, H-4′), 7.34 (d, 1H, J = 16.6 Hz, H-β), 7.40–7.45 (m, 2H, H-3′,5′), 7.62–7.67 (m, 3H, H-2′, H-6′, H-6), 7.65 (d, 1H, J = 16.6 Hz, H-α), 7.74 (dt, 1H, J = 1.2, 7.9 Hz, H-7), 8.11 (d, 1H, J = 7.9 Hz, H-8), 8.29 (d, 1H, J = 8.2 Hz, H-5), 9.20 (br s, 1H, H-2) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 122.4 (C-α), 124.5 (C-5), 126.4 (C-4a), 127.0 (C-2′,6′), 128.0 (C-6), 128.7 (C-4′), 128.8 (C-3′,5′), 129.6 (C-3 and C-8), 129.8 (C-7), 133.2 (C-β), 136.5 (C-1′), 139.5 (C-4), 147.6 (C-8a), 148.1 (C-2) ppm; ESI$^+$-MS: m/z (%) = 266 (100) $[M + H]^+$.

(Z)-4-Chloro-3-styrylquinoline ((*Z*)-**8**)
White solid (76.0 mg, 55%); m.p.: 55–57 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 6.80 (d, 1H, J = 12.1 Hz, H-α), 6.96 (d, 1H, J = 12.1 Hz, H-β), 7.14–7.22 (m, 5H, H-2', H-3′, H-4′, H-5′, H-6′), 7.65 (ddd, 1H, J = 1.2, 7.0, 8.2 Hz, H-6), 7.74 (ddd, 1H, J = 1.5, 7.0, 8.3 Hz, H-7), 8.04 (d, 1H, J = 8.3 Hz, H-8), 8.29 (d, 1H, J = 8.2 Hz, H-5), 8.57 (s, 1H, H-2) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 124.0 and 124.1 (C-5 and C-α), 126.4 (C-4a), 127.7 (C-6), 128.0 (C-4′), 128.6 (C-3′,5′), 128.9 (C-2′,6′), 129.4 (C-3), 129.6 (C-8), 129.9 (C-7), 134.0 (C-β), 135.9 (C-1′), 140.7 (C-4), 147.4 (C-8a), 151.2 (C-2) ppm; ESI$^+$-MS: m/z (%) = 266 (100) $[M + H]^+$.

(E)-3-Styrylquinolin-4(1H)-one (**5**)
A suspension of a mixture of 50.5 mg (*Z*)- and (*E*)-4-chloro-3-styrylquinoline (0.19 mmol) in 6 cm^3 40% aqueous formic acid was refluxed for 24 h. The resulting suspension was cooled in ice for 30 min, the pH adjusted to 5 with Na_2CO_3, and the precipitate formed was filtered off and washed with water. Pure (*E*)-3-styrylquinolin-4(1*H*)-one was collected as a white solid without the need for further purification (43.7 mg, 93%). M.p.: 284–287 °C (Ref. [36]: 269–270 °C).

Computational details

All molecules were optimized at the B3LYP/6-31G(d) level [37–40], where frequencies [41] were calculated to verify that all of them were minima (number of imaginary frequencies = 0). These optimized geometries were further optimized at the B3LYP/6-311++G(d,p) level [42, 43]. Absolute shieldings were calculated within the GIAO approximation [44, 45] on the last optimized geometries [GIAO/B3LYP/6-311++G(d,p)]. The electron density of the systems has been analyzed with the AIM methodology [46, 47] and the MORPHY program [48, 49, 50].

Acknowledgments Thanks are due to the University of Aveiro, FCT, and FEDER for funding the Organic Chemistry Research Unit, the Project POCI/QUI/58835/2004 and the Portuguese National NMR Network (RNRMN). R.S.G.R.S. also thanks FCT for her PhD Grant (SFRH/BD/30734/2006). We thank the Ministerio de Ciencia e Innovación (project no. CTQ2009-13129-C02-02), the Spanish MEC (CTQ2007-62113), and the Comunidad Autónoma de Madrid (project MADRISOLAR2, ref. S2009/PPQ-1533) for continuing support. Thanks are given to the CTI (CSIC) for an allocation of computer time.

References

1. Huse H, Whiteley M (2011) Chem Rev 111:152
2. Sondheimer F, Meisels A (1958) J Org Chem 23:762
3. Goodwin S, Smith AF, Velasquez AA, Horning EC (1959) J Am Chem Soc 81:6209
4. Coppola GM (1982) J Heterocycl Chem 19:727
5. Michael JP (1997) Nat Prod Rep 14:605
6. Koyama J, Toyokuni I, Tagahara K (1999) Chem Pharm Bull 47:1038
7. Funayama S, Tanaka R, Kumekawa Y, Noshita T, Mori T, Kashiwagura T, Murata K (2001) Biol Pharm Bull 24:100
8. Michael JP (2004) Nat Prod Rep 21:650
9. Tsukamura M (1985) Am Rev Resp Dis 131:348
10. O'Brien R (2003) Am J Respir Crit Care Med 168:1266
11. Janin YL (2007) Bioorg Med Chem 15:2479
12. Huang L-J, Hsieh M-C, Teng C-M, Lee K-H, Kuo S-C (1998) Bioorg Med Chem 6:1657
13. Traxler P, Green J, Mett H, Séquin U, Furet P (1999) J Med Chem 42:1018
14. Hadjeri M, Barbier M, Ronot X, Mariotte A-M, Boumendjel A, Boutonnat J (2003) J Med Chem 46:2125
15. Xiao Z-P, Li H-Q, Shi L, Lv P-C, Song Z-C, Zhu H-L (2008) ChemMedChem 3:1077
16. Jin GH, Ha SK, Park HM, Kang B, Kim SY, Kim H-D, Ryu J-H, Jeon R (2008) Bioorg Med Chem Lett 18:4092
17. Coelho A, El-Maatougui A, Raviña E, Cavaleiro JAS, Silva AMS (2006) Synlett 3324
18. Seixas RSGR, Silva AMS, Pinto DCGA, Cavaleiro JAS (2008) Synlett 3193
19. Seixas RSGR, Silva AMS, Cavaleiro JAS (2010) Synlett 2257
20. Maryanoff BE, Reitz AB, Mutter MS, Inners RR, Almond HR Jr, Whittle RR, Olofson RA (1986) J Am Chem Soc 108:7664
21. Maryanoff BE, Reitz AB (1989) Chem Rev 89:863
22. Kolodiazhnyi OI (1999) In: Phosphorous Ylides—chemistry and application in organic synthesis. Wiley-VCH, Weinheim, p 359
23. Sandulache A, Silva AMS, Pinto DCGA, Almeida LMPM, Cavaleiro JAS (2003) New J Chem 27:1592
24. Elguero J, Marzin C, Katritzky AR, Linda P (1976) The tautomerism of heterocycles. Academic, New York, p 94
25. Stanovnik B, Tisler M, Katritzky AR, Denisko OV (2006) Adv Heterocycl Chem 91:18
26. Wentrup C, Rao VVR, Frank W, Fulloou BE, Moloney DWH, Mosandl T (1999) J Org Chem 64:3608
27. Mphahlele MJ, Fernandes MA, El-Nahas AM, Ottosson H, Ndlovu SM, Sithole HM, Dladla BS, De Waal D (2002) J Chem Soc Perkin Trans 2:2159
28. Mphahlele MJ, El-Nahas AM (2004) J Mol Struct 688:129
29. Neuhaus DM, Williamson MP (2000) The nuclear Overhauser Effect in structural and conformational analysis. Wiley, New York (chapter 11)
30. Ramanathan S, Lemal DM (2007) J Org Chem 72:1566
31. Silva AMS, Sousa RMS, Jimeno ML, Blanco F, Alkorta U, Elguero J (2008) Magn Reson Chem 46:859
32. Blanco F, Alkorta I, Elguero J (2007) Magn Reson Chem 45:797

33. Claramunt RM, López C, García MA, Otero MD, Torres MR, Pinilla E, Alarcón SH, Alkorta I, Elguero J (2001) New J Chem 25:1061
34. Prakash O, Kumar A, Sadana A, Prakash R, Singh SP, Claramunt RM, Sanz D, Alkorta I, Elguero J (2005) Tetrahdron 61:6642
35. Mosti L, Menozzi G, Schenone P (1979) J Heterocycl Chem 16:177
36. Almeida AIS, Silva AMS, Cavaleiro JAS (2010) Synlett 462
37. Becke AD (1988) Phys Rev A 38:3098
38. Becke AD (1993) J Chem Phys 98:5648
39. Lee C, Yang W, Parr RG (1988) Phys Rev B 37:785
40. Hariharan PA, Pople JA (1973) Theor Chim Acta 28:213
41. McIver JW, Komornicki AK (1972) J Am Chem Soc 94:2625
42. Ditchfield R, Hehre WJ, Pople JA (1971) J Chem Phys 54:724
43. Frisch MJ, Pople JA, Binkley JS (1984) J Chem Phys 80:3265
44. Ditchfield R (1974) Mol Phys 27:789
45. London F (1937) J Phys Radium 8:397
46. Bader RFW (1990) Atoms in molecules: a quantum theory; The International Series of Monographs of Chemistry. Halpen J, Green MLH (eds), Clarendon, Oxford
47. Popelier PLA (2000) Atoms in molecules: an introduction. Prentice Hall, New York
48. Popelier PLA (1994) Chem Phys Lett 228:160
49. Rafat M, Devereux M, Popelier PLA (2005) J Mol Graphics Modell 24:111
50. Popelier PLA with a contribution from Bone RGA, MORPHY98, A Topological Analysis Program (1999) UMIST, England, EU RGA