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Versatile chiral auxiliaries for NMR spectroscopy based on carbamoyl derivatives of dihydroquinine

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Abstract—Carbamoylation at the C(9) site of dihydroquinine affords new and efficient chiral solvating agents for the NMR enantiodiscrimination of simple derivatives of chiral alcohols, amines, carboxyl acids and amino acids.

1. Introduction

The selective modification of multifunctional chiral auxiliaries is a means of modulating the enantioselective interaction pathways involved in chiral discrimination processes. Cinchona alkaloids (mainly quinine) have been extensively probed as efficient chiral auxiliaries[1] in different areas of chemical research, their widespread applicabilities being attributed to the simultaneous presence of several functionalities, which can fit the stereochemical requirements of different classes of compounds. Their modification has led to new and efficient chiral ligands or selectors to be employed in the catalytic asymmetric osmylation[2] or to produce chiral stationary phases for chromatography.[3] In particular, during the last few years, a great deal of interest has been placed on quinine derivatives bearing a carbamoyl function at the C(9) site, which have shown enhanced versatility and efficiency in chiral chromatography.[4]

In a recent paper[5] we investigated by NMR spectroscopy the interaction of 9-*O*-(3,5-dimethoxyphenylcarbamate)quinine **1a** (Fig. 1) with the two enantiomers of a multifunctional chiral substrate, underlining the relevance of the carbamate function in the stabilization of the diastereoisomeric solvates.

In view of these results, we have now prepared the new derivatized dihydroquinines **1b**–**1f** (Fig. 1), bearing achiral and chiral carbamoyl moieties at C(9), and evaluated their potential and versatility as chiral solvating agents for NMR by analyzing the ^{1}H NMR spectra in $CDCl_3$ of their mixtures with equimolar amounts of several classes of chiral racemic compounds **2** (Fig. 2).

2. Results and discussion

Fig. 3 shows the case of *N*-(3,5-dinitrobenzoyl)alanine methyl ester **2a**, where the parent underivatized dihy-

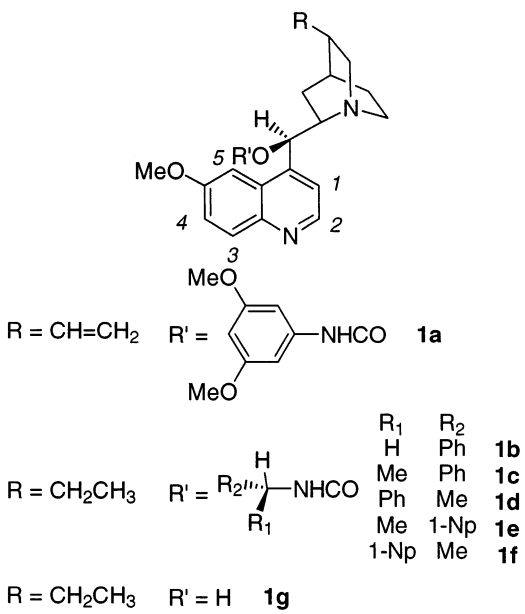

Figure 1. CSAs.

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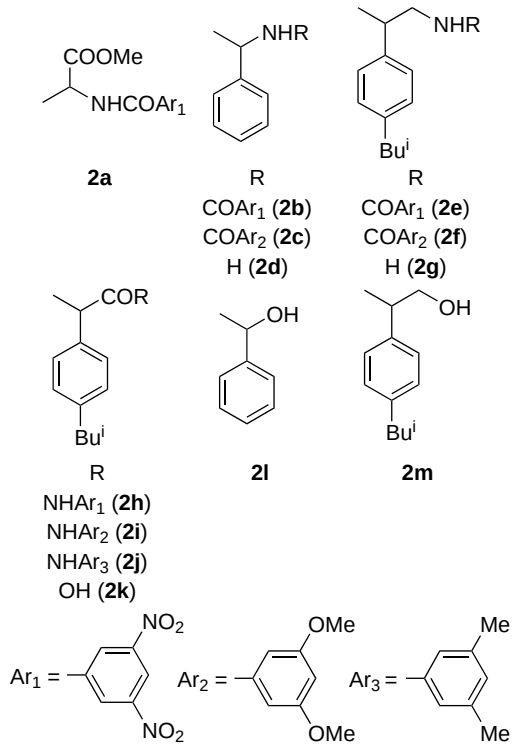

Figure 2. Chiral substrates.

droquinine **1g** and the previously reported[5] **1a** have also been considered. The inequivalence data are summarized in Table 1.

Each carbamate derivative **1a**–**1f** induces inequivalences in the proton nuclei of **2a**, whereas no doublings of its resonances are observed in the mixture with the underivatized dihydroquinine **1g**.

The magnitudes of the splittings are small in the presence of **1a**, which has the aromatic moiety directly bound to the nitrogen of the carbamoyl function, but increase remarkably when they are separated by an additional carbon atom as in **1b**–**1f**. However, in these last cases the presence of a stereogenic carbon atom (as in **1c**–**1f**) has relevance only for the (*S*)-derivatives **1c** and **1f**. In fact, the carbamate **1c** containing the (*S*)-1-phenylethyl residue produces inequivalences greater than **1d**, bearing the corresponding (*R*)-1-phenylethyl substituent, and **1b** having the benzyl group. This effect is even more pronounced for **1e** and **1f**, in the presence of a 1-naphthyl moiety. Thus, the chiral auxiliary **1e** having the (*S*)-1-(1-naphthyl)ethyl group produces inequivalences which are about 30 Hz for the methine and 3,5-dinitrobenzoyl protons of **2a** and up to 90 Hz for its methyl resonances. These values are markedly higher with respect to those obtained in the presence of **1c**, having the (*S*)-1-phenylethyl moiety.

The same outcome was found for mixtures containing each chiral auxiliary **1a**–**1g** and simple derivatives of amines or acids, for which markedly superior magnitudes of inequivalences (Table 2) are measured when a π-acid aromatic group is present.

As an example, the 3,5-dinitrophenyl resonances (Fig. 4) of **2b** are doubled by 35 Hz in its mixture with **1e**, the inequivalence lowering to about 10 Hz in the pres-

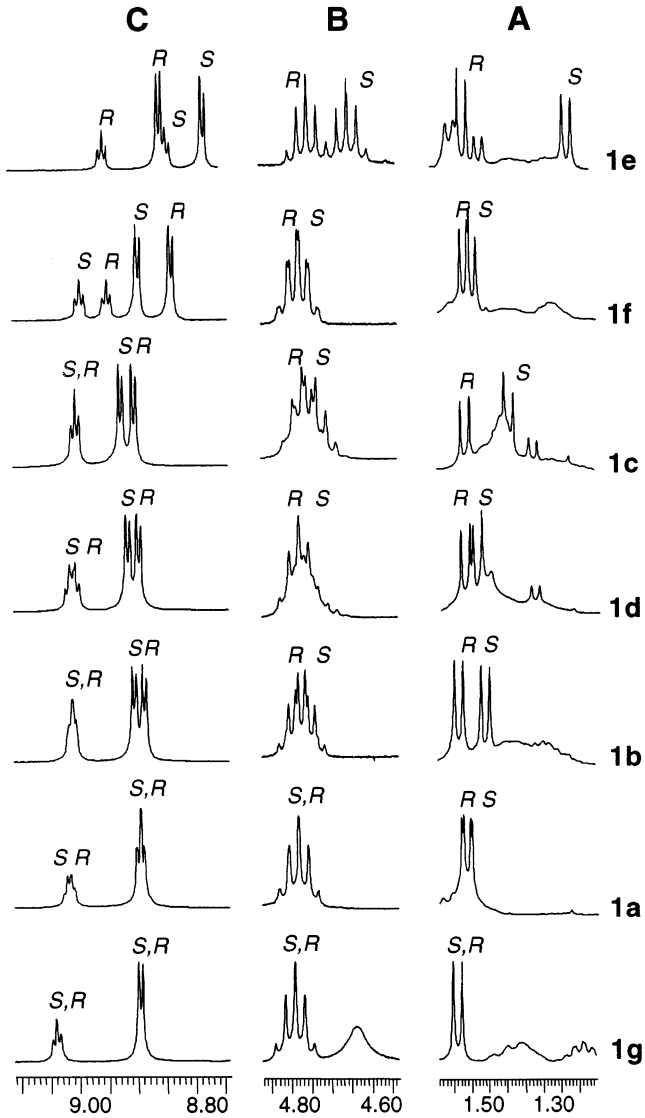

Figure 3. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) spectral regions corresponding to methyl (**A**), methine (**B**) and 3,5-dinitrobenzoyl (**C**) resonances of **2a** in the presence of equimolar amounts (120 mM) of **1a**–**1g**.

Table 1. Inequivalences (300 MHz, $\Delta\delta$[a]) measured in equimolar mixtures (120 mM, $CDCl_3$) of **2a** and **1a**–**1f**

	1a	**1b**	**1c**	**1d**	**1e**	**1f**
CH_3	1.8	23.2	36.5	10.2	86.0	5.6
CH	–	5.0	10.0	8.0	30.0	1.4
OMe	–	–	1.5	–	2.2	3.5
H_{para}	2.0	–	–	2.8	33.0	14.1
H_{ortho}	1.8	5.0	6.7	5.6	23.2	17.1

[a] $\Delta\delta = |\delta_R - \delta_S|$, Hz, difference between the chemical shifts of corresponding nuclei of the two enantiomers of **2a** in the presence of the chiral auxiliary.

Table 2. Inequivalences (300 MHz, $\Delta\delta$[a]) measured in equimolar mixtures (120 mM, $CDCl_3$) of **2** and **1a**–**1g**

	1a	1b	1c	1d	1e	1f	1g
2b							
CH_3	–	10.7	21.7	7.0	–	6.8	–
CH	–	2.6	–	3.7	–	3.0	–
H_{para}	2.0	2.9	10.2	1.8	34.5	4.9	–
H_{ortho}	–	2.1	4.9	4.5	35.6	2.7	–
2c							
CH_3	3.2	1.7	2.2	–	–	–	1.1
CH	1.8	–	–	–	4.3	–	–
OMe	–	–	–	–	1.1	1.1	0.5
H_{para}	0.6	–	–	–	1.1	–	–
H_{ortho}	0.6	–	–	–	2.3	0.6	–
2e							
CH_3	–	1.2	4.2	–	–	–	–
CH_2	–	–	–	–	–	3.6	1.0
CH	2.5	–	–	1.6	–	3.2	–
H_{para}	–	1.8	2.1	1.4	12.3	1.9	0.8
H_{ortho}	1.5	–	1.9	1.5	5.0	–	0.9
2f							
CH_2	–	–	1.2	1.0	–	–	–
2h							
CH_3	–	9.6	19.1	–	48.0	2.7	–
CH_2	–	2.8	2.4		–	7.0	–
CH	–	24.9	46.5	3.7	120.0	11.1	–
NH	–	17.0	28.4	10.9	112.0	23.2	–
H_{para}	–	2.3	4.8	6.5	40.4	5.4	0.8
H_{ortho}	–	10.4	7.2	29.8	86.2	–	0.6
2i							
CH_3	2.9	2.6	4.3	–	–	–	–
CH_2	–	–	–	–	9.7		–
CH	–	4.8	N.d.	–	–	–	–
OMe	1.3	–	–	–	1.9	1.1	–
H_{para}	4.5	–	–	–	2.1	–	–
H_{ortho}	–	–	–	–	2.1	–	–
2j							–
CH_3	2.0	1.9	3.1	–	5.2	–	–
CH	3.0	3.2	5.0	–	7.1	–	–

[a] $\Delta\delta = |\delta_R - \delta_S|$, Hz, difference between the chemical shifts of corresponding nuclei of the two enantiomers of **2** in the presence of the chiral auxiliary.

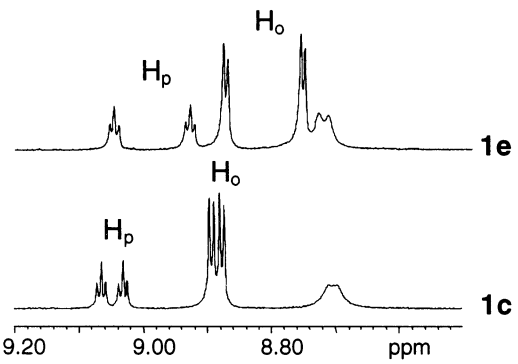

Figure 4. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) spectral regions corresponding to the 3,5-dinitrobenzoyl resonances of **2b** in the presence of equimolar amounts (120 mM) of **1c** and **1e**.

ence of **1c**, which has the (*S*)-1-phenylethyl moiety, and about 5 Hz in the cases of the dihydroquinines bearing the benzyl, (*R*)-1-phenylethyl or the (*R*)-1-(1-naphthyl)ethyl group.

Even greater inequivalence values are found for the ibuprofen derivative **2h**, itself having a 3,5-dinitrophenyl group. In this last case, splittings up to 120 Hz (Fig. 5) are measured in the presence of **1e**, less than 50 Hz in its mixtures with **1c** and less than 30 Hz in the presence of **1b**, **1d** and **1f**. Considerably smaller inequivalences are measured in the mixtures with the underivatized product **1g** or the carbamate **1a**.

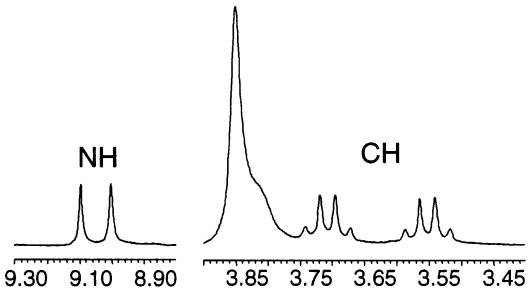

Figure 5. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) spectral regions corresponding to the methine ($\Delta\delta = 120$ Hz) and NH ($\Delta\delta =$ 112 Hz) resonances of 2 h in the presence of equimolar (120 mM) amounts of **1e**.

The splittings (Table 3) induced by **1b**–**1f** in the proton resonances of simple underivatized alcohols, amines and acids are quite insensitive to the structure or the absolute configuration of the carbamoyl residues and similar to those measured in the presence of the underivatized system **1g**.

Table 3. Inequivalences (300 MHz, $\Delta\delta$[a]) measured in equimolar mixtures (120 mM, $CDCl_3$) of **2** and **1a**–**1g**

	1a	1b	1c	1d	1e	1f	1g
2d							
CH	–	–	–	–	–	1.2	2.1
2g	–	–	–	–	–	–	–
2l							
CH_3	–	1.0	1.0	1.2	1.4	0.5	2.0
CH	2.1	3.1	3.3	4.0	4.1	2.5	2.1
2m							
CH_3	–	–	–	–	–	–	1.2
2k							
CH_3[b]	–	7.0	6.3	6.5	6.2	6.8	9.9
CH_3	–	0.8	1.4	2.6	2.2	2.6	1.2
CH_2	–	6.9	6.4	6.8	6.8	6.8	13.1
CH	–	1.6	–	–	1.4	2.6	3.2

[a] $\Delta\delta = |\delta_R - \delta_S|$, Hz, difference between the chemical shifts of corresponding nuclei of the two enantiomers of **2** in the presence of the chiral auxiliary.

[b] Methyl group of the *iso*-butyl moiety.

3. Conclusion

By very simple derivatization of the C(9) site, carbamoyl derivatives of quinine or dihydroquinine can be obtained, showing enhanced enantiodiscriminating efficiency and versatility with respect to the parent compounds, towards chiral organic substrates containing a 3,5-dinitrophenyl moiety.

Both the structure of the carbamate residue and its absolute configuration, when chiral, are fundamental in determining the enantiodiscriminating capabilities. For carbamate derivatives bearing a chiral residue the effect of the nature of the aromatic moiety is of great relevance only when its absolute configuration is (*S*), at least in the case of dihydroquinine. Probably the pairs of diastereoisomers, having the 1-phenylethyl or 1-(1-naphthyl)ethyl groups, simply differ due to the relative positions of the aromatic and alkyl groups of the carbamate with respect to the quinoline plane and the derivatives **1c** and **1e** having the (*S*)-chiral residues both interact with the enantiomeric pairs by their aromatic groups, which are naphthyl in **1e** and phenyl in **1c**. These results point out the relevance of the enhanced anisotropic effect of the first with respect to the latter, which could be the basis of different efficiencies of the corresponding chiral auxiliaries, as well as at the role of the attractive π–π interaction between the aromatic moieties of dihydroquinine derivatives and substrates, in the case of compounds containing a 3,5-dinitrophenyl group.

4. Experimental

4.1. General methods

NMR measurements were performed on a spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C NMR, respectively, and the temperature was controlled to ±0.1°C. All ^{1}H and ^{13}C NMR chemical shifts are referenced to TMS as external standard. The 2D NMR spectra were obtained by using standard sequences. The double-quantum-filtered (DQF) COSY experiments were recorded with the minimum spectral width required; 512 increments of eight scans and 2 K data points were acquired. The relaxation delay was 5 s. The data were zero-filled to 2 K×1 K and a Gaussian function was applied for processing in both dimensions. The HETCOR spectra were acquired with the minimum spectral width required in F_2 and in F_1 in 2 K data points using 64 scans of the 512 increments. The relaxation delay was 2 s. The data were zero-filled to 2 K×1 K and a Gaussian function was applied for processing in both dimensions. The NOESY (nuclear Overhauser and exchange spectroscopy) spectra were recorded in the phase-sensitive mode, by employing a mixing time of 0.6 s. The spectral width used was the minimum required in both dimensions. The pulse delay was maintained at 8 s; 512 hypercomplex increments of eight scans and 2 K data points each were collected. The data matrix was zero-filled to 2 K×1 K and a Gaussian function was applied for processing in both dimensions. The ^{1}H{^{1}H} NOE experiments were performed in the difference mode. The decoupler power used was the minimum required to saturate the spin of interest. A waiting time of 5–10 s was used to allow the system to reach the equilibrium. Each NOE experiment was repeated at least four times.

Thin layer chromatography (TLC) was carried out on silica gel plates (Merck, Silica G-60 0.2 mm) and compounds were visualized with iodine or by examination under UV light. Chromatography was carried out using Silica Gel 60 (70–230 mesh ASTM).

Melting points were determined using a Koffler hot-stage apparatus.

4.2. Materials

Dihydroquinine, (*R*)- and (*S*)-phenylethyl isocyanate were purchased from Fluka. (*R*)- and (*S*)-1-(1-Naphthyl)ethyl isocyanate and benzyl isocyanate were obtained from Aldrich.

4.3. Synthesis of carbamoyl derivatives of dihydroquinine 1b–1f

To a solution of dihydroquinine (3.83 mmol) in anhydrous toluene (30 mL) was added the appropriate isocyanate (5.07 mmol). The reaction mixture was stirred under reflux for 17 h. The solvent was removed in vacuo and **1b**–**1f** were obtained by chromatography (acetone) in high yields (80–94%).

1b: 92% yield; mp 195–197°C. ^{1}H NMR (DMSO-d_6, 100°C), δ (ppm): 8.64 (1H, H_2, d, $J_{21}=4.4$ Hz); 7.94 (1H, H_3, d, $J_{34}=9.2$ Hz); 7.54 (1H, H_5, d, $J_{54}=2.7$ Hz); 7.54 (1H, NH_c, t, $J=6.8$ Hz); 7.39 (1H, H_4, dd, $J_{43}=9.2$ Hz, $J_{45}=2.7$ Hz); 7.38 (1H, H_1, d, $J_{12}=4.4$ Hz); 7.31–7.14 (5H, Ph, m); 6.27 (1H, H_8, d, $J_{89}=7.7$ Hz); 4.21 (2H, Ph$\underline{CH_2}$, d, $J=6.8$ Hz); 3.89 (3H, OMe, s); 3.28 (1H, H_9, m); 3.06 (1H, H_{15}, m); 2.87 (1H, H_{19}, m); 2.48 (1H, H_{16}, m); 2.20 (1H, H_{18}, m); 1.87–1.14 (8H, H_{10-14} H_{17} and $\underline{CH_2}CH_3$, m); 0.82 (3H, $CH_2\underline{CH_3}$, t, $J=7.2$ Hz). ^{13}C NMR (DMSO-d_6, 100°C), δ (ppm): CH_3: 12.5, 56.3; CH_2: 24.7, 27.7, 28.9, 42.6, 45.0, 58.4; CH: 25.9, 38.0, 60.0, 74.4; aromatic CH: 103.6, 119.7, 121.6, 127.4, 127.6, 128.8, 132.0, 148.1; quaternary C: 127.7, 140.3, 145.0, 145.6, 156.4, 158.0.

1c: 83% yield; mp 66–70°C. ^{1}H NMR (DMSO-d_6, 100°C), δ (ppm): 8.63 (1H, H_2, br. s); 7.93 (1H, H_3, d, $J_{34}=9.2$ Hz); 7.50 (1H, H_5, d, $J_{54}=2.6$ Hz); 7.48 (1H, NH_c, d, $J=7.0$ Hz); 7.39 (1H, H_4, dd, $J_{43}=9.2$ Hz, $J_{45}=2.6$ Hz); 7.33 (1H, H_1, br. s); 7.35–7.15 (5H, Ph, m); 6.24 (1H, H_8, d, $J_{89}=7.4$ Hz); 4.66 (1H, CH_c, dq, $J_1=J_2=7.0$ Hz); 3.90 (3H, OMe, s); 3.23 (1H, H_9, m); 3.00 (1H, H_{15}, m); 2.87 (1H, H_{19}, m); 2.44 (1H, H_{16}, m); 2.20 (1H, H_{18}, m); 1.87–1.16 (8H, H_{10-14} H_{17} and $\underline{CH_2}CH_3$, m); 1.34 (3H, Me_c, d, $J=7.0$ Hz); 0.81 (3H, $CH_2\underline{CH_3}$, t, $J=7.2$ Hz). ^{13}C NMR (DMSO-d_6, 100°C), δ (ppm): CH_3:12.5, 23.1, 56.3; CH_2: 24.5, 27.7, 28.9, 42.6, 58.4; CH: 25.9, 38.0, 51.3, 60.1, 74.0; aromatic CH: 103.5, 119.5, 121.6, 126.4, 127.3, 128.9, 131.9, 148.0; quaternary C: 127.0, 127.6, 144.9, 145.7, 155.5, 158.0.

1d: 81% yield; mp 178–180°C. ^{1}H NMR (DMSO-d_6, 100°C), δ (ppm): 8.67 (1H, H_2, d, $J_{21}=4.5$ Hz); 7.92 (1H, H_3, d, $J_{34}=9.3$ Hz); 7.51 (1H, H_5, d, $J_{54}=2.6$ Hz); 7.47 (1H, NH_c, d, $J=7.0$ Hz); 7.42 (1H, H_1, d, $J_{12}=4.5$); 7.38 (1H, H_4, dd, $J_{43}=9.3$ Hz, $J_{45}=2.6$ Hz); 7.31–7.10 (5H, Ph, m); 6.23 (1H, H_8, d, $J_{89}=7.8$ Hz);

4.68 (1H, CH_c, dq, $J_1=J_2=7.0$ Hz); 3.85 (3H, OMe, s); 3.24 (1H, H_9, m); 2.99 (1H, H_{15}, m); 2.86 (1H, H_{19}, m); 2.46 (1H, H_{16}, m); 2.20 (1H, H_{18}, m); 1.83–1.14 (8H, H_{10-14} H_{17} and $\underline{CH_2}CH_3$, m); 1.38 (3H, Me_c, d, $J=7.0$ Hz); 0.82 (3H, $CH_2\underline{CH_3}$, t, $J=6.9$ Hz). ^{13}C NMR (DMSO-d_6, 100°C), δ (ppm): CH_3: 12.5, 23.2, 56.2; CH_2: 24.6, 27.7, 28.8, 42.5, 58.3; CH: 25.8, 38.0, 51.2, 59.9, 74.1; aromatic CH: 103.6, 119.8, 121.6, 126.4, 127.2, 128.7, 131.9, 148.0; quaternary C; 127.2, 127.7, 145.0, 145.6, 155.5, 158.0.

1e: 93% yield; mp 85–88°C. ^{1}H NMR (DMSO-d_6, 100°C), δ (ppm): 8.59 (1H, H_2, br. s); 8.12 (1H, $H_{8'}$, m); 7.92 (1H, H_3, d, $J_{34}=9.1$ Hz); 7.91 (1H, $H_{5'}$, m); 7.80 (1H, $H_{4'}$, m); 7.70 (1H, NH_c, d, $J=6.8$ Hz); 7.54–7.42 (4H, $H_{2'}$, $H_{3'}$, $H_{6'}$, $H_{7'}$, m); 7.48 (1H, H_5, d, $J_{54}=2.4$ Hz); 7.22 (1H, H_1, br. s); 7.38 (1H, H_4, dd, $J_{43}=9.1$ Hz, $J_{45}=2.4$ Hz); 6.23 (1H, H_8, d, $J_{89}=7.5$ Hz); 5.47 (1H, CH_c, dq, $J_1=J_2=6.9$ Hz); 3.88 (3H, OMe, s); 3.16 (1H, H_9, m); 2.98 (1H, H_{15}, m); 2.84 (1H, H_{19}, m); 2.43 (1H, H_{16}, m); 2.16 (1H, H_{18}, m); 1.82–1.13 (8H, H_{10-14} H_{17} and $\underline{CH_2}CH_3$, m); 1.48 (3H, Me_c, d, $J=6.9$ Hz); 0.80 (3H, $CH_2\underline{CH_3}$, t, $J=7.1$ Hz). ^{13}C NMR (DMSO-d_6, 100°C), δ (ppm): CH_3: 12.5, 22.5, 56.3; CH_2: 24.5, 27.7, 28.8, 42.6, 58.4; CH: 25.8, 38.0, 47.6, 60.2, 74.0; aromatic CH: 103.5, 119.4, 121.6, 123.1 (Np), 123.6 (Np), 126.0 (Np), 126.1 (Np) 126.6 (Np), 127.9 (Np), 129.3 (Np), 132.0, 148.0; quaternary C: 127.6, 131.0 (Np), 134.3 (Np), 141.4 (Np), 144.9, 145.7, 155.5, 158.0.

1f: 94% yield; mp 177–180°C. ^{1}H NMR (DMSO-d_6, 100°C), δ (ppm): 8.66 (1H, H_2, d, $J_{21}=4.5$ Hz); 8.07 (1H, $H_{8'}$, m); 7.92 (1H, H_3, d, $J_{34}=9.1$ Hz); 7.86 (1H, $H_{5'}$, m); 7.74 (1H, $H_{4'}$, m); 7.69 (1H, NH_c, d, $J=6.8$ Hz); 7.54–7.33 (4H, $H_{2'}$, $H_{3'}$, $H_{6'}$, $H_{7'}$, m); 7.49 (1H, H_5, d, $J_{54}=2.8$ Hz); 7.39 (1H, H_1, $J_{12}=4.5$ Hz); 7.37 (1H, H_4, dd, $J_{43}=9.1$ Hz, $J_{45}=2.8$ Hz); 6.19 (1H, H_8, d, $J_{89}=7.7$ Hz); 5.48 (1H, CH_c, dq, $J_1=J_2=6.8$ Hz); 3.81 (3H, OMe, s); 3.13 (1H, H_9, m); 2.98 (1H, H_{15}, m); 2.82 (1H, H_{19}, m); 2.42 (1H, H_{16}, m); 2.14 (1H, H_{18}, m); 1.76–1.06 (8H, H_{10-14} H_{17} and $\underline{CH_2}CH_3$, m); 1.52 (3H, Me_c, d, $J=6.8$ Hz); 0.77 (3H, $CH_2\underline{CH_3}$, t, $J=7.1$ Hz). ^{13}C NMR (DMSO-d_6, 100°C), δ (ppm): CH_3: 12.5, 22.6, 56.2; CH_2: 24.5, 27.7, 28.8, 42.5, 58.3; CH: 25.7, 38.0, 47.5, 59.9, 74.2; aromatic CH: 103.5, 119.7, 121.6, 123.0 (Np), 123.5 (Np), 125.9 (Np), 126.0 (Np) 126.5 (Np), 127.8 (Np), 129.2 (Np), 131.9, 148.0; quaternary C: 127.7, 131.0 (Np), 134.2 (Np), 141.0 (Np), 144.9, 145.6, 155.5, 158.0.

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