¹H and ¹³C NMR spectral assignments of 1,1'-(((ethane-1,2-diylbis(oxy))bis(4,1-phenylene)) bis(methylene))-bispyridinium and -bisquinolinium bromide derivatives

Keywords: NMR; PHENOXYETHANE; SALTS; BIS-QUINOLINIUM; BIS-PYRIDINIUM

Introduction

High levels of total choline (cho) and phosphocholine (Pcho) are steadily found in aggressive cancers.^[1,2] Choline kinase (ChoK) catalyzes choline phosphorylation to produce phosphocholine that will produce ultimately phosphatidylcholine, which is not only a major phospholipid in eukaryotic cell membranes but is also a substrate to produce lipid second messengers such as phosphatidic acid and diacylglycerol.^[1-3] ChoK plays a crucial role in human carcinogenesis, and its selective inhibition (ChoK- α but not ChoK- β is overexpressed in various cancers) is considered an efficient antitumour strategy.^[1,3,4] The reported crystal structure of human ChoK and recent descriptions about the ChoK active site provide inestimable information for designing new inhibitors.^[5-7] The synthesis and biological evaluation of a novel family of compounds derived from 1,1'-(((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis (methylene))-bispyridinium or -bisquinolinium bromide as selective inhibitors of human ChoK α 1 have been recently described.^[8] In this paper, we describe the ¹H NMR and ¹³ C NMR unequivocal assignments of these novel symmetrical biscationic compounds.

Experimental

Synthesis

Scheme 1 represents the previously reported synthetic pathway followed in the preparation of the novel family of compounds derivative of 1,1'-(((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis (methylene))-bispyridinium or -bisquinolinium bromide (10a-I) containing a pair of oxygen atoms in the spacer of the linker between the biscationic moieties.^[8] The synthesis of the compounds was carried out by microwave-assisted reactions that allowed us to improve time and yields. The addition of 1,2-dibromoethane to the 4-methylphenol (6) (previously treated with NaOH) under microwave irradiation (130°C, 28 min) provides the 1,2-bis(pmethylphenoy)ethane (7). Then, bromination in the methylene of 7 with N-bromosuccinimide (NBS) and dibenzoylperoxide in CCl₄ also under microwave irradiation (120 °C, 21 min) gives the 1,2bis(4-bromomethylphenoy)ethane (8). Finally, the cationic heads (4-substituted pyridine derivative (9a-c), quinuclidine derivative (9d-e) or 4-substituted quinoline or 7-chloro-4-substituted quinoline (9f-I), previously synthesized) are introduced by means of a simple S_N2 reaction in acetonitrile under argon atmosphere during 72 h at reflux of 1,2-bis(4-bromomethylphenoxy)ethane (8) to afford 10a-l.

NMR techniques

Proton nuclear magnetic resonance and ¹³C NMR data (chemical shifts multiplicity and coupling constants) for compounds **10a-I** are shown in the following tables. Unambiguous assignments for all NMR signals were made through the combined information of one-dimensional and two-dimensional NMR experiments such as DEPT, HSQC and HMBC.

Proton nuclear magnetic resonance spectra were recorded on a VarianInovaUnity (300 MHz), VarianDirect Drive (400 MHz) and/or VarianDirect Drive (500 MHz). Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak: CD₃OD, $\delta = 3.31$ ppm (¹H), $\delta = 49.05$ ppm (¹³C); DMSO- d_{6i} $\delta = 2.50$ ppm (¹H), $\delta = 39.5$ ppm (¹³C). Spin multiplicities are given as singlet (s), wide singlet (ws), doublet (d), double doublet (dd), double double doublet (ddd), triplet (t), double triplet (dt), pseudotriplet (pt), cuadruplet (c) and multiplet (m). Coupling constants (J) are given in hertz. ¹³C NMR spectra were recorded on a VarianDirect Drive (400 MHz) and VarianDirect Drive (500 MHz). The following parameters were used in DEPT experiments: PW (135°), 9.0 ms; recycle time, 1 s; 1/2 J (CH) = 4 ms; 65 536 data points acquired and transformed from 1024 scans; spectral width, 15 KHz; and line broadening, 1.3 Hz. HMBC spectra were measured with a pulse sequence gc2hmbc (standard sequence, Agilent Vnmrj_3.2A software) optimized for 8 Hz (inter-pulse delay for the evolution of long-range couplings: 62.5 ms). The HSQC spectra were measured with a pulse sequence gc2hsqcse (standard sequence Agilent Vnmrj_3.2A software).

Results and discussion

To facilitate the analysis of all biscationic compounds, they have been gathered in different tables according to the cationic head; thus, Tables 1 and 2 show bispyridinium (**10a-c**) and -bisquinuclidinium (**10d-e**) salts. Bisquinolinium (**10f-l**) salts are shown in Tables 3 and 4. At the same time, bisquinolinium compounds will be divided into two series to easily tackle the assignments for all NMR signals: **series 1** [bisquinolinium salts with **aromatic** substituent in **R**₄ position (**10f-i**)] and **series 2**



Scheme 1. General synthetic pathway for compounds 10a-I.

[bisquinolinium salts with **no aromatic** substituent in \mathbf{R}_4 position (**10j-I**)].

Figure 1 shows family of compounds derivative of both bispyridinium and -bisquinuclidinium salts (**10a-e**) as well as the number scheme of the compounds used.

Table 1 shows ¹H-NMR chemical shifts (δ , ppm) for compounds **10a-e**. It can be observed that there is a well-defined area where resonance of the protons of the aromatic spacer and pyridine (pyridine = pyr) (**10a-b**) at a higher field can be located at the methylene groups bonded to the quaternary nitrogen (CH_2-N^+) and oxygen (CH₂-O) and finally, a defined zone where it is possible to find the protons of pyrrolidine (pyrrolidine = pirr) and quinuclidine (quinuclidine = q). Signals corresponding to protons that are closer to the positive nitrogen of the pyridine (H-2,6pyr) appear at a lower field because of the summation effect of both the deshielding of the ring and the induction of the positive nitrogen. Signals from hydrogen atoms in the spacer, H-2, 6 and H-2',6', appear as a doublet, an AB system typical of p-substituted aromatic systems, a field of 7.01 ppm, and they are coupled with H-3,5 and **H-3',5'** (δ = 7.34 ppm) with a coupling constant of 8.73 Hz. The methylene directly attached to the cationic head (CH_2 -N⁺) appears as a singlet at δ 5.28 ppm, while the methylene bonded to oxygen (**CH₂-O**) appears as a singlet at higher field (δ = 4.32 ppm). Compound 10a pyridine proton signals are slightly higher (H-2,6pyr and **H-3**,**5pyr**; δ 8.20 and 6.99 ppm, respectively) owing to the contribution of the dimethylamino group, which unlike the pyrrolidine has no shielding effect. However, the signals corresponding to the spacer have constant values because the distance between the pyridine ring and the benzyl groups of the spacer does not feel the influence of the cationic head. There are two factors that influence the chemical shift of the protons of the pyridine ring: (i) there is a small contribution of the positive charge of the nitrogen and mainly (ii) the phenomenon of resonance of the aromatic ring that deshields those protons, and therefore, they will appear at lower field. It is worth mentioning the presence in position 4 of the pyridine ring of a tertiary amine (electron-donating group) influences the resonance by stabilizing the positive charge.

Quinuclidine is another type of cationic head used: a bicyclic amine with a substituent in position 3 in the case of the compound **10e**. As a fully saturated compound, guinuclidine signals appear as multiplets in the range of alkanes (δ 2 a 4 ppm). As a symmetrical structure, quinuclidine in compound 10d, protons are equivalent for the case of (H-2,6,7g and H-3,5,8g), but that is not the case for the proton where both saturated cycles come together, H-4g. The signals for the hydrogen atoms corresponding to **H-2,6,7g** appear as a multiplet at δ 3.48 ppm, and they are coupled with **H-3,5,8q** (δ = 2.01) and **H-4q** (δ = 2.18 ppm). When an OH group is taking the position 3 up, bicycle symmetry is lost, and as a result, more but not defined signals appear and coupling constants are impossible to be determined. In the case of the compound 10e, the presence of two diastereomers (RR/ SS and RS) that cannot be separated by conventional methods prevents to allocate signals unequivocally, although it clearly can be said that the presence of the OH group translates the chemical shift of all protons of the quinuclidine to a lower magnetic field. Quinuclidine of both compounds, 10d,e, has a clear influence on the signals of the aromatic hydrogen atoms of the spacer; thus, those signals appear at a lower field (H-3,5 and H-3', 5' resonate as a doublet at δ 7.48 ppm, while H-2,6 and **H-2',6'** resonate as a doublet at δ 7.13 ppm. The coupling constant is 8.66 Hz). Even the methyl groups attached to oxygen (CH₂-O) resonate at slightly downfield (δ = 4.35 and 4.32 ppm, respectively). This may be because the quinuclidine is not an

Table 1. ¹ H-NMR chemice	al shifts (ô, ppm) and coupling <i>const</i>	ants (J, Hz) of 1,1'-(((ethane-1,2-diylbis(ox)	y))bis(4,1-phenylene))bis(methylene))-bi	spyridinium and -bisquinuclidinium brom	nide (10a-e)
Cationic head	-NCH ₃ CH ₃		e c	€ ⊕ L	HO
Compound	10 ª δ (ppm)	10b ð (ppm)	10c δ (ppm)	10d δ (ppm)	10e * δ (ppm)
H-3,5 y H-3',5'	7.35 (d) 8.73	7.34 (d) <i>8.73</i>	7.58 (d) <i>8.5</i>	7.47 (d) 8.78	7.48 (d) <i>8.66</i>
H-2,6 y H-2',6'	7.02 (d) 8.73	7.01 (d) 8.73	7.02 (d) <i>8.4</i>	7.13 (d) <i>8.78</i>	7.13 (d) 8.66
0-CH ₂	4.33 (s)	4.32 (s)	4.33 (s)	4.35 (s)	4.41 (s)
⁺ N-CH ₂	5.30 (s)	5.28 (s)	5.35 (s)	4.43 (s)	4.43 (s)
H-2,6pyr	8.20 (d) <i>7.86</i>	8.17 (d) 7.77	8.28 (d) <i>8.5</i>		I
H-3,5pyr	6.99 (d) 7.86	6.84 (d) 7.77	6.92 (m)		Ι
H-2,5pirr		3.54 (t) 6.84			
H-3,4pirr		2.11 (t) <i>6.86</i>	I		I
N(CH ₃) ₂	3.24 (s)	I			Ι
H-2q				3.48 (m)	3.64 (m)
Н-6,7q		I		3.48 (m)	3.35 (m)
H-3q		I	I	2.01 (dt) 8.23, 3.23	4.08 (m)
H-5,8q		I		2.01 (dt) 8.23, 3.23	2.10 (m)
H-4q		I	I	2.18 (dt) <i>6.44</i> , <i>3.23</i>	3.04 (d)
OH-	1	I			13.0 2.27 (s)
p-CI-C ₅ H ₄ -N		I	7.37 (m)		
-CH ₃			3.53 (s)		I
* DMSO as solvent.					

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C3.6 y C2.6' 117.30 117.29 117.14 C3.6 y C3.5' 131.93 131.92 131.94 136.48 C3.5 y C3.5' 131.98 131.02 131.94 136.48 C4.4 12.92.00 131.92 131.94 136.48 C0 68.86 68.80 0.7.81 66.87 V 62.22 61.64 0.7.81 66.87 C4.9m 133.52 61.64 66.87 135.63 C3.5pm 143.76 143.56 143.52 - - C3.5pm 109.93 110.51 110.027 - - C3.5pm 138.87 150.56 138.31 - - - C3.5pm - 26.98 -	C-1,1'	161.80	161.79	160.85	162.80	
G35 y C35's131.98131.92131.94136.48C4, α 132.20131.92131.92131.94136.48C4, α 129.20129.31127.95121.54C4, α 129.20129.31127.95121.54C4, α 129.20133.6863.5266.52N-62.2663.66143.52143.52121.54C2, δ_{yy} 143.76143.56143.5216466.87C2, δ_{yy} 10993110.51110.27163.23C3, δ_{yy} 10993110.51110.27163.23C3, δ_{yy} 10093110.51110.27163.23C3, δ_{yy} 1003110.51110.27163.23C3, δ_{yy} 1003105.605156.63156.63164.64C3, δ_{yy} 100310031003100.27100.27C3, δ_{yy} 100310051100.27100.26100.26C4, δ_{yy} 100100.27100.26100.26C4, δ_{xy} 100100.27100.27100.26C4, δ_{xy} 100100.27100.26100.26C4, δ_{xy} 100100.27100.27100.26C4, δ_{xy} 100.26100.27100.27100.27C4, δ_{xy} 100.26100.26100.27100.27D100.26100.26100.27100.27100.27D100.26100.26100.26100.26D100.26100.27<	C-2,6 y C-2,6'	117.30	117.29	116.27	117.14	
$C_4/4$ 129.20 129.31 127.95 121.64 06.52 C_0 68.86 68.86 68.86 67.81 05.25 05.25 T_1 6.2.22 6.8.86 6.8.86 6.8.7 06.87 06.87 C_1 0.3.22 6.8.86 6.8.86 6.1.64 0.6.87 06.87 C_2 143.76 143.76 143.76 11051 110.27 07.8 06.87 C_4 193.76 193.76 156.05 158.87 156.05 158.31 0.22 C_4 100.27 C_2 $S_0.28$ 100.27 C_2	C-3,5 y C-3,5'	131.98	131.92	131.94	136.48	
Cd 6886 6781 69.2 $N_{\rm H}$ 62.2 68.86 67.81 69.52 $7_{\rm H}$ 62.22 62.36 61.64 68.87 $C2.8_{\rm HW}$ 143.56 143.68 143.52 6 $C3.8_{\rm HW}$ 1933 110.51 110.22 6 $C3.8_{\rm HW}$ 158.87 156.05 158.31 6 $C3.8_{\rm HW}$ 158.87 156.05 158.31 6 $C3.8_{\rm HW}$ 158.87 156.05 163.31 6 $C3.8_{\rm HW}$ 158.87 156.05 163.31 6 $C3.6_{\rm HW}$ $-$ 26.38 $ C44$ $ C44$ $ C34$ $ -$	C-4,4'	129.20	129.31	127.95	121.54	
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	-N ⁺	62.22	62.26	61.64	68.87	
	C-2,6 _{pyr}	143.76	143.68	143.52		
	C-3,5 _{pyr}	109.93	110.51	110.27		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	C-4 _{pyr}	158.87	156.05	158.31		
	C-2,5 _{pirr}	I	50.28	I		
	C-3,4 _{pirr}	I	26.98	I		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	N(CH ₃) ₂	41.20		1		
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G-3q - 25.81 25.81 C-5.8q - - - 25.81 25.81 C-5.8q - - - - 25.81 25.81 C-5.8q - - - - - 25.81 25.81 C-54 - - - - - - 23.33 p-CI-C ₅ H ₄ -N (C-1) - - 143.32 - 22.33 p-CI-C ₅ H ₄ -N (C-3.5) - - 143.32 - - p-CI-C ₅ H ₄ -N (C-3.5) - - 116.27 - - p-CI-C ₅ H ₄ -N (C-3.5) - - 116.27 - - p-CI-C ₅ H ₄ -N (C-3.5) - - 116.27 - - p-CI-C ₅ H ₄ -N (C-3.5) - - - 116.27 - - p-CI-C ₅ H ₄ -N (C-3.5) - - 116.27 - - - - - - - - - - - - - - - -	C-6,7q	I	I	I	56.39	
C-5.8q — — 25.81 C-4q — — 25.81 D-CI-C ₅ H ₄ -N (C-1) — — 22.33 p-CI-C ₅ H ₄ -N (C-35) — 143.32 — 22.33 p-CI-C ₅ H ₄ -N (C-35) — 143.32 — 22.33 p-CI-C ₅ H ₄ -N (C-35) — 143.32 — 22.33 p-CI-C ₅ H ₄ -N (C-35) — 116.27 — — p-CI-C ₅ H ₄ -N (C-35) — 116.27 — — p-CI-C ₅ H ₄ -N (C-35) — 116.27 — — p-CI-C ₅ H ₄ -N (C-35) — 116.27 — — — p-CI-C ₅ H ₄ -N (C-35) — 116.27 — — 116.27 — — p-CI-C ₅ H ₄ -N (C-35) — — 116.27 — — 135.52 — — p-N-CH ₃ — — 30.55 — — — — — — — — — — — — — — — = = = <th< td=""><td>C-3q</td><td> </td><td> </td><td>I</td><td>25.81</td><td></td></th<>	C-3q			I	25.81	
C4q — — 22.33 p-Cl-C ₅ H ₄ ·N (C-1) — — 22.33 p-Cl-C ₅ H ₄ ·N (C-3,6) — — 143.32 — p-Cl-C ₅ H ₄ ·N (C-3,5) — — 116.27 — p-Cl-C ₅ H ₄ ·N (C-3,5) — — 129.28 — p-Cl-C ₅ H ₄ ·N (C-4) — — 135.52 — n-N-CH ₃ — — 30.55 —	C-5,8q	I		I	25.81	
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	-N-CH ₃		I	30.55	I	

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Table 3. ¹ H-NMR o	chemical shifts (δ, ppm) and co	oupling constants (J, Hz) of 1,	1'-(((ethane-1,2-diylbis(oxy))	bis(4,1-phenylene))bis(m	lethylene))-bisquinolinum bro	mide (1 of-I)	
Cationic head	z 	z	ō z	z z -z -z -ō	z z	ō z -z	Ū z -z
Compound	10f δ (ppm)	10 g δ (ppm)	10 h δ (ppm)	10i δ (ppm)	10j δ (ppm)	10 k δ (ppm)	101 δ (ppm)
H-2,6 e H-2',6'	7.03 (d) <i>8.76</i>	7.03 (d) 8.77	7.06 (d) <i>8.70</i>	7.06 (d) 8.73	7.00 (d) <i>8.80</i>	7.03 (d) <i>8.64</i>	7.01 (d) 8.75
H-3,5 e H-3′,5′	7.40–7.29 (m)	7.33 (d) 8.77	7.35–7.32 (m)	7.35 (d) 8.73	7.27 (d) 8.80	7.29 (d) 8.64	7.27 (d) 8.75
0-CH ₂	4.33 (s)	4.33 (s)	4.35 (s)	4.35 (s)	4.31 (s)	4.33 (s)	4.32 (s)
⁺ N-CH ₂	5.89 (s)	5.91 (s)	5.86 (s)	5.88 (s)	5.74 (s)	5.72 (s)	5.71 (s)
H-2quin	8.86 (d) 7.44	8.90 (d) 7.40	8.84 (d) 7.50	8.87 (d) 7.46	8.54 (d) 7.73	8.51 (d) 7.75	8.63 (d) <i>9.23</i>
H-3quin	7.40–7.29 (m)	7.41–7.37 (m)	7.35–7.32 (m)	7.38 (d) 7.47	7.10 (d) 7.74	7.11 (d) 7.78	6.90 (d) 7.69
H-5quin	7.62 (dd) 8.8, 1.3	7.67 (dd) 8.8, 1.2	7.57-7.54 (m)	7.63 (d) <i>9.31</i>	8.05 (dd) 8.83, 1.05	8.07 (d) 1.82	8.04 (d) 2.02
H-6quin	7.46 (t) <i>7.36</i>	7.41–7.37 (m)	7.49 (t) 7.4	7.40 (d) 1.96	7.66 (dt) <i>5.77, 1.15</i>	7.65 (dd) 9.2, 1.9	7.66 (dd) 9.2, 2.0
H-7quin	7.81 (dt) <i>5.57, 1.43</i>	7.84 (dt) 5.46, 1.36	Ι	Ι	7.90 (dt) <i>5.67</i> , 1.33	Ι	Ι
H-8quin	8.13 (d) <i>8.37</i>	8.16 (dd) <i>8.9, 0.6</i>	8.16 (d) <i>1.89</i>	8.20 (d) 1.93	8.42 (dd) 8.62, 1.28	8.40 (d) <i>9.21</i>	8.51 (d) 7.69
H-2,7az	Ι	Ι	Ι	Ι	4.09 (m)	4.08 (m)	Ι
H-3,6az	Ι	I	Ι	I	2.09 (m)	2.08 (m)	I
H-4,5az		I	I	I	1.75 (dt) <i>5.40</i> , 2.54	1.74 (m)	I
H-2,5pirr		Ι	Ι	Ι	Ι	I	4.02 (m)
H-3,4pirr	Ι	I	Ι	I	Ι	I	2.20 (m)
H-2,6 ph	7.53 (m)	7.52 (d) 8.91	7.57–7.54 (m)	7.55 (d) 8.78	I	I	I
H-3,5 ph	7.40–7.29 (m)	7.41–7.37 (m)	7.42 (d) <i>7.</i> 48	7.42 (d) 8.78	I	I	I
H-4 ph	7.40–7.29 (m)	I	7.30 (dd) <i>9.3, 1.9</i>	I	I	I	I
N-CH ₃	3.84 (s)	3.82 (s)	3.84 (s)	3.82 (s)	I	I	

MRC

bisquinoimum bi	omide (101-1)						
Cationic head			N N N		N N	CI N	N CI
Compound	10f δ (ppm)	10 a δ (ppm)	10 h ð (ppm)	10i δ (ppm)	(mag) (10i	10 k δ (ppm)	10 Ι δ (ppm)
C-1,1'	161.47	161.48	161.58	161.59	161.34	161.44	157.92
C-2,6 e C-2',6'	117.30	117.30	117.41	117.40	117.22	117.32	117.29
C-3,5 e C-3',5'	130.63	130.69	130.77	130.85	130.48	130.59	130.45
C-4,4'	128.64	128.52	128.24	128.15	128.98	128.57	128.68
CH ₂	68.85	68.84	68.86	68.85	68.84	68.85	68.83
⁺ N-CH ₂	59.94	60.09	59.91	60.05	58.99	59.00	59.06
C-2quin	148.54	148.77	148.95	149.22	146.48	146.77	146.91
C-3quin	107.73	108.36	107.93	108.57	104.55	105.00	104.64
C-4quin	160.80	160.92	160.51	160.65	161.91	161.56	161.37
C-4a quin	122.29	122.41	120.68	120.82	121.41	119.88	120.16
C-5quin	120.97	121.13	131.80	131.68	120.33	119.78	119.73
C-6quin	127.85	128.20	130.59	128.71	127.04	127.45	127.71
C-7quin	135.51	135.68	141.90	142.06	135.52	141.82	141.76
C-8quin	130.15	130.00	120.45	120.61	130.44	132.31	131.76
C-8a quin	141.68	141.68	142.51	142.50	142.10	142.95	142.45
C-2,7az	—	—	—	—	56.06	56.12	—
C-3,6az	—	—	—	_	29.37	29.28	—
C-4,5az	—	—	—	—	29.23	29.16	—
C-2,5pirr	—	—	—	—	—	—	55.43
C-3,4pirr	—	—	—	—	—	—	24.64
C-1 ph	150.14	148.81	149.76	148.45	—	—	—
C-2,6 ph	132.75	132.72	132.92	132.88	—	—	—
C-3,5 ph	127.73	129.28	127.72	129.33	—	—	—
C-4 ph	130.28	135.58	128.35	135.92	—	—	—
N-CH ₃	46.75	46.53	46.87	46.69	—	—	—

Table 4. ¹³C-NMR chemical shifts (δ , ppm) and coupling *constants (J, Hz)* of 1,1'-(((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(methylene))-bisquinolinum bromide (**10f-I**)



R= Pyridine and quinuclidene derived cationic heads



Figure 1. Family of compound derivative of 1,1'-(((ethane-1,2-diylbis(oxy)) bis(4,1-phenylene))bis(methylene))-bispyridinium and -bisquinuclidinium bromide (**10a-e**).

aromatic system and therefore cannot delocalized electronic charge on the aromatic ring; consequently, the deshielding effect upon the benzyls and CH_2 bounded to oxygen is stronger. On the

contrary, the methylene group fixed to the cationic head appears at higher field (δ = 4.43 ppm), compared with compounds **10a,b**.

With respect to ¹³C-NMR that can be seen in Table 2, the signals that appeared at lower field belong to quaternary carbons **C-1,1**' ($\delta = 161.79-169.86$ ppm) and **C-4,4**' ($\delta = 121.54-129.97$ ppm), and they are followed in order of increasing magnetic field with the peaks belonging to the pyridine **C-2,6pyr** ($\delta = 143.68-143.76$ ppm); **C-3,5** and **C-3',5**' ($\delta = 131.92-131.98$ ppm); **C-2,6** and **C-2',6**' ($\delta = 117.14-125.11$ ppm); and finally, **C-3,5pyr** ($\delta = 109.93-110.51$ ppm) as the last character of the aromatic group.

The family of compound derivative of 1,1'-(((ethane-1,2-diylbis (oxy))bis(4,1-phenylene))bis(methylene))-bisquinolinum bromide (**10f-I**) is shown in Fig. 2. As said, bisquinolinium compounds have been divided into two series to easily tackle the assignments for all NMR signals:**series 1**[bisquinolinium salts with aromatic substituent in R₄ position (**10f-i**)] and**series 2**[bisquinolinium salts with no aromatic substituent in R₄ position (**10f-i**)]. It can be noticed that all protons of the spacer, aromatics and methylene groups resonate at lower field when an aromatic substituent is present in position 4 of the quinoline (quinoline = quin).**H-2,3quin**resonates at lower frequencies (high field) in**series 1**with respect to**series 2**, because the aromatic substituent in position 4 deshields those hydrogens.**H-8, 7, 6, 5**of**series 2**appear at lower field than those in**series 1**



Figure 2. Family of compounds derivative of 1,1'-(((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(methylene))-bisquinolinum bromide (10f-I).

because the aniline has a shielding effect. The chlorine in position 7 of the quinoline barely has influence on the chemical shift of the neighboring protons. However, the chlorine atom in position 4 of the aniline has a greater influence on the protons of the quinoline than on the protons of the aniline; thus, **H-3** and **CH₂-N⁺** appear at lower field when halogen is presented. It is assumed that the spatial arrangement of the ring results in the approach of the chlorine atom to these protons producing a deshielding effect thereon.

According to the results shown in Table 4, those carbons of the spacer, aromatic and methylene groups neighboring the oxygen atoms are not influenced by substituents that may be introduced in the quinoline. In series 1 (**10f-i**), a chlorine atom in position 7 of the quinoline influences the chemical shift of **C-5,6quin** and the same **C-7quin**, leading to a lower magnetic field. In series 2 (**10j-I**), the chlorine atom in position 7 of the quinoline is able to deshield the **C-7quin**. An aromatic substituent in position 4 of the quinoline reduces the chemical shift (higher field) of the **C-4quin** in relation to compounds of the series 2, and it influences the chemical shift of **C-2,3quin** and **CH₂-N⁺**. The presence of chlorine in position 4 of the aniline has a deshielding effect on **C-3,5 ph** and **C-4 ph**.

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