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New atropisomers derived from amidinoquinoxaline *N*-oxides: Synthesis and NMR characterization

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ABSTRACT

The complete ^{1}H and ^{13}C NMR characterization of some representative examples of five and six-membered amidinoquinoxaline *N*-oxides **1** with dissymmetric aryl substituents and their methiodides **2** is reported. Compounds **1** were synthesized by ring closure of *N*-arylacetyl-*N*′-(2-nitrophenyl)alkylenediamines **3**, followed by spontaneous heterocyclization. Methiodides **2** were prepared by quaternization of the parent heterocycles with methyl iodide. Complete assignment of the ^{1}H and ^{13}C NMR resonances of compounds **1**,**2** was made on the basis of the correlations observed in their HSQC, HMBC and NOESY spectra. The ^{1}H NMR spectra of compounds **1**,**2** display diasterotopicity of methylenic hydrogens, indicative of molecular chirality due to the presence of a chiral axis (ONC-Ar bond). Further support for the existence of the atropisomers for compounds **1a**,**b** is presented, on the basis of spectral and theoretical data.

1. Introduction

2,3-Dihydro-1*H*-pyrimido[1,2-*a*]quinoxaline *N*-oxides represent a heterocyclic core of wide interest due to the pharmacological properties of some members, acting as antibacterials [1], antiamoebics [2] and antineoplastics [3]. As part of our research on nitrogen heterocycles, we reported a novel methodology for their synthesis [4], and investigated some of their chemical [5] and pharmacological [6] properties. The reported examples include 5-alkyl and 5-aryl derivatives, the latter with unsubstituted or symmetrically (*para*) substituted aryl groups. Amidinoquinoxaline *N*-oxides **1** with dissymmetrical aryl substituents are expected to have the plane of the *ortho* substituted aryl ring significantly twisted with respect to the heterocyclic ring system, entailing in principle the existence of conformational enantiomers (atropisomers). Atropisomerism is a property of some molecules that exist as enantiomeric forms due to restricted rotation around certain single bonds, which behave as chiral axes. Atropisomeric compounds have been described acting as drugs [7] and chiral selectors [8]. The effect of axial chirality in natural compounds has been reviewed [9]. Atropisomeric biaryls are widely employed as chiral ligands, reagents and catalysts in stereoselective reactions [10]. In the last years, there is a growing interest for the development of stable non-biaryl atropisomers, due to their potential employment in stereo and enantioselective synthesis [11]. In particular, literature shows several examples of heterocylic compounds displaying atropisomerism [12]. As part of our research on nitrogen heterocycles with hindered rotation [13–17], we present here the synthesis and NMR study of novel non-biaryl atropisomers derived from the amidinoquinoxaline *N*-oxide heterocyclic core.

2. Experimental

2.1. Synthesis

N-arylacetyl-*N*′-(2-nitrophenyl)alkylenediamines **3** were synthesized by acylation of *N*-(2-nitrophenyl)trimethylene or ethylenediamines. Yields and analytical data of compounds **3a–e** are as follows.

N-(2-Methylphenyl)acetyl-*N*′-(2-nitrophenyl)-1,3-propanediamine (**3a**) was obtained as an oil (78%). ^{1}H NMR: $\delta = 8.16$ (1H, dd, $J = 8.6$ and 1.5 Hz), 8.03 (1H, bs, ex), 7.39–7.45 (1H, m), 7.16–7.23 (4H, m), 6.76 (1H, d, $J = 8.1$ Hz), 6.65 (1H, ddd, $J = 8.6$, 6.9 and 1.2 Hz), 5.46 (1H, bs, ex), 3.61 (2H, s), 3.25–3.38 (4H, m), 2.28 (3H, s), 1.85 (2H, p, $J = 6.9$ Hz). MS (EI), *m*/z 343 ($M^{+\cdot}$). Anal. Calcd. for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24, found: C, 66.34; H, 7.41; N, 12.20.

N-(2-Chlorophenyl)acetyl-*N*′-(2-nitrophenyl)-1,3-propanediamine (**3b**) was obtained as a yellow solid (84%), Mp 107–109 °C (ethanol/water). ^{1}H NMR: $\delta = 8.18$ (1H, dd, $J = 8.5$ and 1.5 Hz), 8.06 (1H, bs, ex), 7.25–7.46 (5H, m), 6.81 (1H, d, $J = 8.7$ Hz), 6.67 (1H, ddd, $J = 8.5$, 7.1 and 1.3 Hz), 5.66 (1H, bs, ex), 3.74 (2H, s), 3.41 (2H, q, $J = 6.6$ Hz), 3.32–3.36 (2H, m), 1.91 (2H, p, $J = 6.8$ Hz). MS (EI), *m*/z 363 ($M^{+\cdot}$). Anal. Calcd. for $C_{18}H_{22}ClN_3O_3$: C, 59.42; H, 6.09; N, 11.55, found: C, 59.30; H, 6.12; N, 11.51.

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N-(2-Bromophenyl)acetyl-*N*′-(2-nitrophenyl)-1,3-propanediamine (**3c**) was obtained as a yellow solid (80%), Mp 125–127 °C (ethanol/water). ^{1}H NMR: δ = 8.14 (1H, dd, *J* = 8.5 and 1.5 Hz), 8.03 (1H, bs, ex), 7.57 (1H, dd, *J* = 7.8 and 0.9 Hz), 7.12–7.43 (4H, m), 6.78 (1H, d, *J* = 8.0 Hz), 6.63 (1H, ddd, *J* = 8.5, 7.1 and 1.3 Hz), 5.59 (1H, bs, ex), 3.72 (2H, s), 3.37 (2H, q, *J* = 6.4 Hz), 3.28–3.34 (2H, m), 1.86–1.90 (2H, m). MS (EI), *m*/z 391 ($M^{+\cdot}$). Anal. Calcd. for $C_{17}H_{18}BrN_3O_3$: C, 52.06; H, 4.63; N, 10.71, found: C, 51.98; H, 4.68; N, 10.67.

N-(2-Methylphenyl)acetyl-*N*′-(2-nitrophenyl)ethylenediamine (**3d**) was obtained as a yellow solid (100%), Mp 110–112 °C (ethanol/water). ^{1}H NMR: δ = 8.16 (1H, dd, *J* = 8.7 and 1.7 Hz), 8.04 (1H, bs, ex), 7.41–7.47 (1H, m), 7.10–7.24 (4H, m), 6.94 (1H, d, *J* = 8.7 Hz), 6.67 (1H, ddd, *J* = 8.7, 6.9 and 1.3 Hz), 5.60 (1H, bs, ex), 3.60 (2H, s), 3.46–3.48 (4H, m), 2.24 (3H, s). MS (EI), *m*/z 329 ($M^{+\cdot}$). Anal. Calcd. for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76, found: C, 65.52; H, 7.07; N, 12.73.

N-(2-Bromophenyl)acetyl-*N*′-(2-nitrophenyl)ethylenediamine (**3e**) was obtained as a yellow solid (86%), Mp 134–136 °C (ethanol/water). ^{1}H NMR: δ = 8.18 (1H, dd, *J* = 8.5 and 1.5 Hz), 8.09 (1H, bs, ex), 7,59 (1H, dd, *J* = 8.0 and 1.0), 7.44–7.47 (1H, m), 7.30–7.35 (2H, m), 7.18 (1H, ddd, *J* = 8.0, 6.9 and 2.4), 6.97 (1H, dd, *J* = 8.7 and 1.2), 6.69 (1H, ddd, *J* = 8.5, 7.1 and 1.2), 5.83 (1H, bs, ex), 3.75 (2H, s), 3.51–3.55 (4H, m). MS (EI), *m*/z 377 ($M^{+\cdot}$). Anal. Calcd. for $C_{16}H_{16}BrN_3O_3$: C, 50.81; H, 4.26; N, 11.11, found: C, 50.73; H, 4.29; N, 11.09.

Synthesis of dihydroamidinoquinoxaline *N*-oxides **1**. General procedure.

A mixture of the aminoamide **3** (0.5 g) and PPE (10 mL) was reacted for 0.5–2 min in a microwave oven (Sanyo EM-D2031) adapted for reflux heating, alternating 10 s of irradiation at 280 Watt and 10 s without irradiation. After reaching ambient temperature, the resulting solution was extracted with water (5 × 10 mL). The aqueous phases were pooled, filtered and made alkaline with 10% aqueous NaOH. The mixture was extracted with chloroform (3 × 20 mL). The organic phases were washed with water, dried over sodium sulphate and filtered. The chloroformic solution was left at r.t. until no further conversion to compounds **1** was evidenced by TLC (silica gel, $CHCl_3$–methanol 9:1). The solvent was then removed *in vacuo* and the crude product was purified by column chromatography (silica gel, $CHCl_3$–methanol 10:0 → 9:1). Yields and analytical data of compounds **1a–d** are as follows.

5-(2-Methylphenyl)-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoxaline 6-oxide **1a** was obtained as a yellow solid (53%), Mp 198–200 °C (hexane/ethyl acetate). MS (EI), *m*/z 291 ($M^{+\cdot}$). Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42, found: C, 74.05; H, 5.93; N, 14.39.

5-(2-Chlorophenyl)-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoxaline 6-oxide **1b** was obtained as a yellow solid (51%), Mp 170–172 °C (hexane/ethyl acetate). MS (EI), *m*/z 311 ($M^{+\cdot}$). Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48, found: C, 65.38; H, 4.55; N, 13.46.

5-(2-Bromophenyl)-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoxaline 6-oxide **1c** was obtained as a yellow solid (53%), Mp 158–160 °C (hexane/ethyl acetate). MS (EI), *m*/z 355 ($M^{+\cdot}$). Anal. Calcd. for $C_{17}H_{14}BrN_3O$: C, 57.32; H, 3.96; N, 11.80, found: C, 57.23; H, 3.98; N, 11.78.

4-(2-Methylphenyl)-1,2-dihydroimidazo[1,2-*a*]quinoxaline 5-oxide **1d** was obtained as a yellow solid (52%), Mp 165–167 °C (hexane/ethyl acetate). MS (EI), *m*/z 277 ($M^{+\cdot}$). Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45 N, 15.15, found: C, 73.49; H, 5.50; N, 15.15.

4-(2-Bromophenyl)-1,2-dihydroimidazo[1,2-*a*]quinoxaline 5-oxide **1e** was obtained as a yellow solid (51%), Mp 179–180 °C (hexane/ethyl acetate). MS (EI), *m*/z 341 ($M^{+\cdot}$). Anal. Calcd. for $C_{16}H_{12}BrN_3O$: C, 56.16; H, 3.53; N, 12.28, found: C, 56.06; H, 3.57; N, 12.26.

Synthesis of dihydroamidinoquinoxaline *N*-oxide methiodides **2**. General procedure.

A mixture of the corresponding compound **1** (1 mmol) and methyl iodide (3 mmol) in anhydrous methylene chloride (10 mL) were refluxed protected from moisture. The reaction was monitored by TLC (silica gel, chloroform–methanol 9:1) until no further conversion to compounds **2** was evidenced. The solution was evaporated *in vacuo* and the crude products were purified by crystallization.

Yields and analytical data of compounds **2a,b** are as follows.

5-(2-Methylphenyl)-4-methyl-2,3-dihydro-1*H*-pyrimido[1,2-*a*]-quinoxalinium iodide 6-oxide **2a** was obtained as a yellow solid (52%), Mp 251–253 °C (isopropanol). MS (EI), *m*/z 291 ($M^{+\cdot}$-ICH_3) [18,19]. Anal. Calcd. for $C_{19}H_{20}IN_3O$: C, 52.67; H, 4.65; N, 9.70, found: C, 52.56; H, 4.69; N, 9.66.

4-(2-Methylphenyl)-3-methyl-1,2-dihydroimidazo[1,2-*a*]quinoxalinium iodide 5-oxide **2b** was obtained as a yellow solid (64%), Mp > 270 °C (isopropanol). MS (EI), *m*/z 277 ($M^{+\cdot}$-ICH_3). Anal. Calcd. for $C_{18}H_{18}IN_3O$: C, 51.57; H, 4.33; N, 10.02, found: C, 51.49; H, 4.36; N, 9.99.

2.2. Spectra

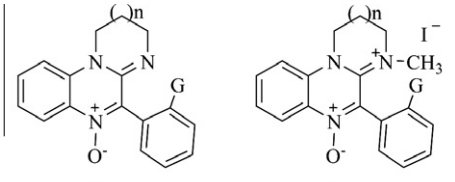
^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 500 spectrometer operating at 500.13 and 125.77 MHz, respectively. Spectra were acquired from samples as solutions at room temperature in 5 mm tubes. Unless otherwise indicated, deuterochloroform was used as the solvent. The standard concentration of the samples was 10 and 40 mg/mL for ^{1}H and ^{13}C NMR spectra, respectively. Chemical shifts (δ) are reported in ppm, referenced to TMS as an internal standard. Coupling constants (*J*) are reported in Hz. Multiplicities are quoted as singlet (s), doublet (d), double doublet (dd), doublet of doublet of doublets (ddd), triplet (t), double triplet (dt), quartet (q) and multiplet (m). Phase-sensitive NOESY, HSQC and HMBC spectra were recorded on a Bruker Avance II 500 spectrometer.

2.3. Theoretical calculations

Input geometries for compounds **1a**,**b** were preoptimized with the semiempirical method AM1. The structure/s thus obtained were then optimized with the HF/6-31G** method [20]. The resulting minima were subjected to frequency calculations with non-imaginary frequencies obtained.

3. Results and discussion

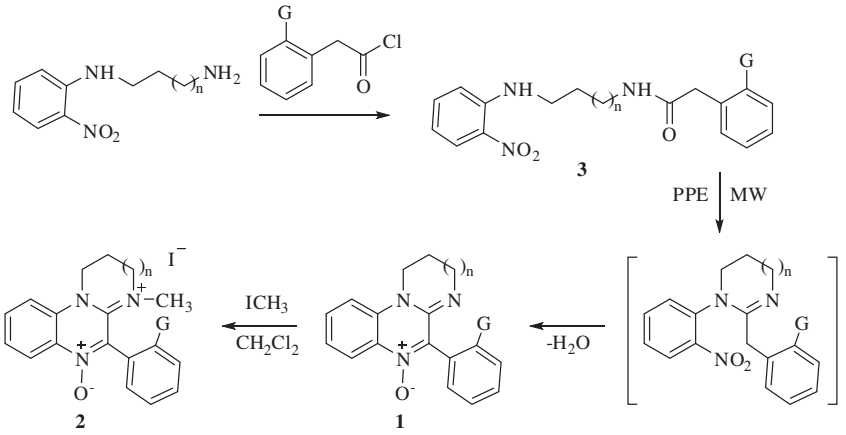
The compounds described in this work are shown in Fig. 1. The synthetic procedure for compounds **1**, **2** is depicted in Scheme 1. The precursor *N*-(2-nitrophenyl)-*N*′-arylacetyl di (or tri) methylen-



1 **2**

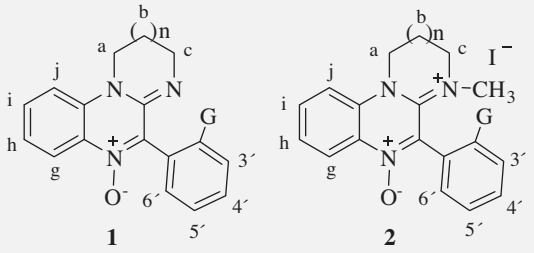
1a, **2a** (n=1, G=CH_3); **1b** (n=1, G=Cl); **1c** (n=1, G=Br)
1d, **2b** (n=0, G=CH_3); **1e** (n=0, G=Cl)

Fig. 1. Amidinoquinoxalines **1a–d** and methiodides **2a,b**.



Scheme 1. Synthesis of amidinoquinoxaline *N*-oxides **1** and their quaternary salts **2**.

Table 1
^{1}H NMR signals of compounds **1a–e**, **2a,b**.

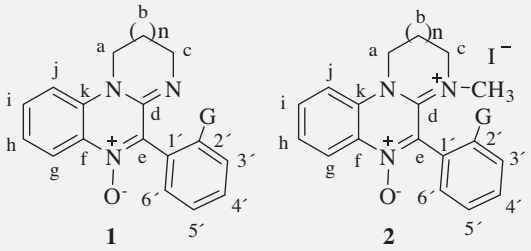


1a, **2a** (n=1, G=CH_3); **1b** (n=1, G=Cl); **1c** (n=1, G=Br)
1d, **2b** (n=0, G=CH_3); **1e** (n=0, G=Cl)

Compounds	a	c	b	g–j	3′–6′	G	N–CH_3
1a[A]	2.83 (t, 6.1)	3.22–3.33 (m)	1.29–1.34 (m)	g: 8.76 (dd, 8.2, 1.4) h: 6.88 (ddd, 8.2, 7.1, 1.0) i: 7.11 (ddd, 8.5, 7.1, 1.4) j: 6.36 (dd, 8.5, 1.0)	3′–5′: 7.26–7.34 (m) 6′: 7.57 (d, 7.1)	2.47 (s)	–
1b[B]	3.86–3.95 (m)	3.53–3.65 (m)	2.04–2.10 (m)	g: 8.39 (dd, 8.3, 1.4) h: 7.20 (ddd, 8.3, 7.3, 1.0) i: 7.51–7.56 (m) j:7.11 (dd, 8.2, 1.0)	7.39–7.44 (m), 7.51–7.56 (m)	–	–
1c[B]	3.85–3.94 (m)	3.52–3.66 (m)	2.02–2.09 (m)	g: 8.39 (dd, 8.2, 1.5) h: 7.19 (ddd, 8.2, 7.3, 0.9) i: 7.52 (ddd, 8.4, 7.3, 1.5) j: 7.11 (dd, 8.4, 0.9)	3′: 7.7 (dd, 8.1, 1.1) 4′: 7.32 (ddd, 8.1, 7.5, 1.6) 5′: 7.47 (dt, 7.5, 1.1) 6′: 7.37 (dd, 7.5, 1.6)	–	–
1d[B]	4.13–4.21 (m)	4.06–4.12 (m)	–	g: 8.29 (dd, 8.2, 1.2) h: 7.11–7.15 (m) i: 7.49–7.53 (m) j: 6.85 (dd, 8.0, 0.7)	3′–5′: 7.31–7.42 (m)	2.32 (s)	–
1e[B]	4.13–4.22 (m)	4.06–4.12 (m)	–	g: 8.27 (dd, 8.3, 1.4) h: 7.12 (ddd, 8.3, 7.3, 1.1) i: 7.52 (ddd, 8.1, 7.3, 1.4) j: 6.85 (dd, 8.1, 1.1)	3′: 7.72 (dd, 8.0, 0.7) 4′: 7.35 (ddd, 8.0, 7.1, 2.1) 5′,6′: 7.44–7.50 (m)	–	–
2a[C]	4.19–4.24 (m) and 4.68–4.71 (m)	3.58–3.66 (m)	2.34–2.44 (m)	g: 8.43 (dd, 8.3, 1.3) h: 7.73–7.75 (m) i: 8.03–8.06 (m) j: 8.13 (d, 8.5)	3′, 6′: 7.43–7.48 (m) 4′: 7.51 (dt, 7.6, 1.4) 5′: 7.38 (t, 7.6)	2.33 (s)	2.51 (s)
2b[C]	4.66–4.73 (m)	4.14–4.27 (m)	–	g: 8.34 (d, 8.3) h: 7.69–7.72 (m) i: 8.04–8.07 (m) j: 7.84 (d, 8.3)	3′, 6′: 7.47–7.50 (m) 4′: 7.56 (t, 7.5) 5′: 7.43 (t, 7.5)	2.26 (s)	2.47 (s)

[A] Spectrum run in C_6D_6.
[B] Spectrum run in $CDCl_3$.
[C] Spectrum run in DMSO-d_6.

Table 2
^{13}C NMR signals of compounds **1a–e**, **2a,b**.



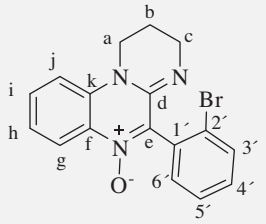
1 **2**

1a, **2a** (n=1, G=CH_3); **1b** (n=1, G=Cl); **1c** (n=1, G=Br)
1d, **2b** (n=0, G=CH_3); **1e** (n=0, G=Cl)

Compounds	**1a**[A]	**1b**[B]	**1c**[B]	**1d**[B]	**1e**[B]	**2a**[C]	**2b**[C]
^{13}C signals							
a	42.80	43.66	43.55	54.31	54.43	46.51	46.09
b	19.52*	19.70	19.57	–	–	19.44	–
c	44.05	44.56	44.50	46.52	46.52	51.03	53.04
d	144.49	144.71	144.48	153.12	152.59	151.93	150.84
e	141.33	139.58	140.61	137.45	136.15	135.89	132.58
f	130.89	130.08*	129.94	130.93	130.82	132.32	132.92
g	121.38	121.31	121.18	121.35	121.41	120.68	120.71
h	120.96	121.73	121.58	121.09	121.15	127.29	127.02
i	130.71	131.95	131.85	132.22	132.56	134.66	135.22
j	110.62	110.99	110.91	111.98	112.12	116.86	116.82
k	135.47	135.48	135.39	133.58	133.73	133.26	131.52
1′	131.50	130.24*	132.32	128.50*	130.65	130.33	126.76
2′	138.00	133.64*	122.98	137.93*	123.51	140.29	139.79
3′	125.27,	127.00,	132.74	125.98,	133.08	130.84*	130.84
4′	128.68,	129.74,	130.41	129.16,	131.25	131.00*	131.73
5′	129.80	130.44,	127.55	130.04,	127.83	126.63	126.84
6′	130.24	131.02	130.96	130.45	131.12	129.92	130.44
G	19.44*	–	–	19.63	–	19.99	19.38
N^+–CH_3	–	–	–	–	–	43.56	35.39

[A] Spectrum run in C_6D_6.
[B] Spectrum run in $CDCl_3$.
[C] Spectrum run in DMSO-d_6.
* Exchangeable assignment.

Table 3
Unambiguous assignment of compound **1c**.



Position	δ ^1H	δ ^{13}C (HSQC)	δ ^{13}C (HMBC)	δ ^1H (NOESY)
a	3.85–3.94	43.55	19.57, 44.50, 144.48, 135.39	2.02–2.09, 7.11
b	2.02–2.09	19.57	43.55, 44.50	3.85–3.94; 3.48–3.58, 3.60–3.65
c	3.48–3.58, 3.60–3.65	44.50	19.57, 43.55, 140.61, 144.48	2.02–2.09
d	–	144.48	–	–
e	–	140.61	–	–
f	–	129.94	–	–
g	8.39	121.18	135.39, 110.91	7.19
h	7.19	121.58	110.91, 129.94	8.39, 7.52
i	7.52	131.85	135.39, 110.91	7.19
j	7.11	110.91	129.94	3.85–3.94
k	–	135.39	–	–
1′	–	132.32	–	–
2′	–	122.98	–	–
3′	7.70	132.74	127.55, 132.32	7.32
4′	7.32	130.41	122.98, 130.96	7.70, 7.47
5′	7.47	127.55	132.32, 132.74	7.37, 7.32
6′	7.37	130.96	122.98, 130.41, 140.61	7.47

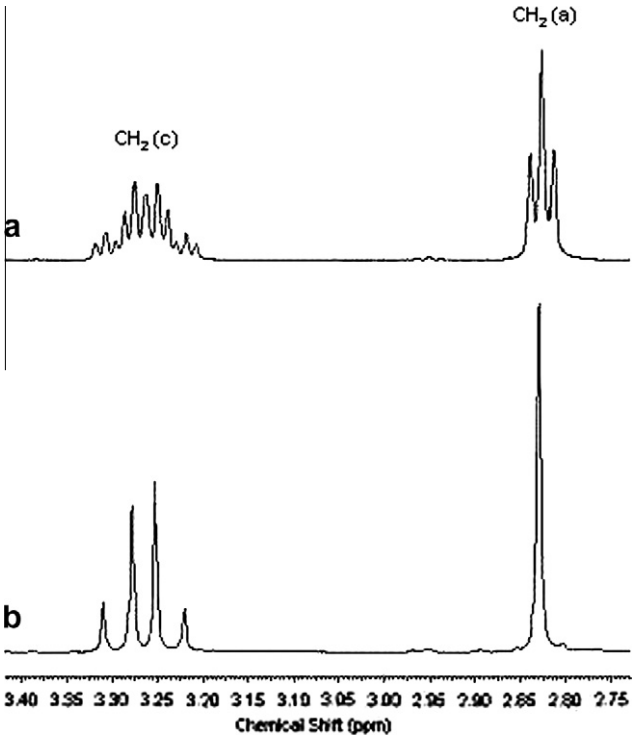


Fig. 2. *N*-methylene signals of the ^{1}H NMR spectrum of compound **1a** (C_6D_6): (a) normal and (b) with simultaneous decoupling of CH_2(b).

ediamines **3** were prepared by selective *N*-monoacylation of *N*-(2-nitrophenyl)ethylene (or trimethylene)diamines. Microwave-assisted cyclodehydration of compounds **3** with ethyl polyphosphate (PPE) [21] led to the corresponding 1-(2-nitrophenyl)-2-arylacetyl dihydroimidazoles or 1,4,5,6-tetrahydropyrimidines. Such compounds undergo spontaneous *in situ* cyclization to dihydroamidinoquinoxaline *N*-oxides **1**.

^{1}H NMR chemical shifts and multiplicities of compounds **1** are given in Table 1. ^{13}C NMR chemical shifts of compounds **1** are given in Table 2. Assignment of the resonances was made on the basis of the correlations observed in their HSQC, HMBC and NOESY spectra.

Complete assignment of a representative compound (**1c**) is shown in detail in Table 3. The aromatic region in the ^{1}H NMR spectrum of **1c** shows eight signals, each corresponding to one hydrogen, belonging to two different spin systems. In the NOESY spectrum, the *N*-methylene signal centered at *ca.* 3.91 ppm correlates with the double doublet at 7.11. Such signals were assigned respectively as CH_2(a) and H(j), and the multiplet centered at *ca.* 2.05 ppm as CH_2(c). The remaining methyne signals belonging to the benzo fused ring were tentatively attributed on the basis of their multiplicity and *J* values, and the assignment confirmed by the correlations observed in the NOESY spectrum. The corresponding ^{13}C resonances were attributed considering the correlations in the HSQC spectrum. In the HMBC spectrum, both *N*-methylenes correlate with a quaternary carbon (δ = 144.48 ppm), which was assigned as C(d). One of them, centered at 3.91 ppm correlates in the HMBC spectrum with another quaternary carbon at 135.39 ppm. Such signal also correlates with H(i) and H(g) and was therefore assigned as C(k). Hydrogens H(h) and H(j) correlate with another quaternary carbon at 129.94 ppm, assigned as C(f). Hydrogens H(c) show a long range correlation with a quaternary carbon at 140.61 ppm assigned as C(e), which in turn correlates with a methyne in the aryl moiety, H(6′) (δ = 7.37 ppm). The remaining methyne signals within the aryl ring H(3′–5′) were attributed on the basis of their multiplicity and J values, and the assignment confirmed by NOESY. The corresponding ^{13}C resonances were attributed considering the correlations in the HSQC spectrum. In the HMBC spectrum H(3′) and H(5′) correlate with a quaternary carbon at 132.32 ppm, assigned as C(1′), while H(4′) and H(6′) correlate with the remaining quaternary carbon at 122.28 ppm, assigned as C(2′).

^{1}H NMR spectra of dihydropyrimidoquinoxaline *N*-oxides previously reported by us, bearing a phenyl or symmetrical (*para* substituted) 5-aryl residue, show equivalence of the geminal protons within the trimethylene portion [4], which appear as two triplets (each one corresponding to an *N*–CH_2) and a multiplet (for the C–CH_2–C). This pattern indicates a time averaged planar conformation for the amidine ring at room temperature. At variance with this, the trimethylenic portion of the *ortho* substituted derivative **1a** (Fig. 2a) shows nonequivalence of both hydrogens within one of the *N*-methylenes (δ = 3.22–3.33 ppm). When the spectrum of **1a** was recorded with simultaneous decoupling of the C–CH_2–C fre-

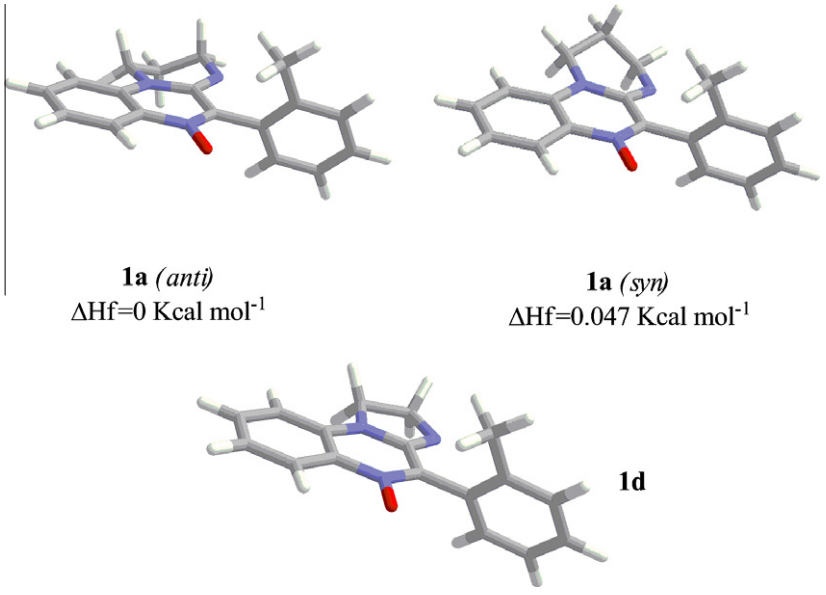


Fig. 3. Conformational minima for compounds **1a** and **1d** at the HF/6-31G** level.

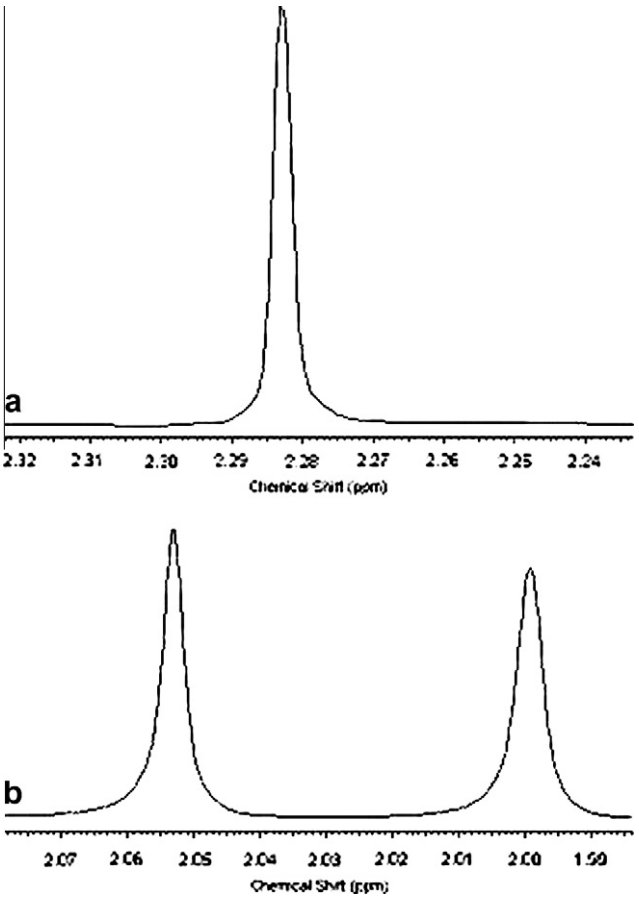


Fig. 4. The ^{1}H methyl signal of compound **1a** (spectrum run in $CDCl_3$): (a) normal and (b) in chiral environment.

quency (δ = 1.29–1.34 ppm), the *N*-methylene signal was simplified, yielding a typical AB-type system (Fig. 2b). This geminal coupling (J_{gem} = 16.3 Hz) arises from chemical nonequivalence of both protons (δ = 3.30 and 3.24 ppm).

Although the spectra of two enantiomers in an achiral environment are indistinguishable, the presence of diastereotopic nuclei constitutes an indirect evidence of molecular chirality [22]. In our case, molecular asymmetry would result from the preference for a twisted conformation of the sterically hindering *ortho*-tolyl substituent with respect to the dynamic plane of the heterocyclic ring. In such conformation the ONC-aryl bond becomes a chiral axis, resulting in a pair of atropisomeric forms for compound **1a**. To check this hypothesis, we explored the conformational ground state geometries of this compound by *ab initio* theoretical calculations. Two initial energy minima were identified at the AM1 level, which were then optimized employing the HF/6-31G** method. The resulting structures, corresponding to one of the atropisomers, are shown in Fig. 3, together with their relative energies. The structures were labelled as *anti* and *syn*, according to the relative orientations of the methyl and CH_2(b) moieties. The calculated energy difference between them is very low (less than 0.05 kcal mol^{-1}) and therefore their interconversion should be a fast process at room temperature, taking into account previous data on analogous tetrahydropyrimidine systems [14,15]. In the more stable *anti* conformation of compound **1a**, the dihedral angle $C_{2'}$—$C_{1'}$—C_5—C_{4a} has a value of 108.0°, thus entailing the existence of two conformational enantiomers.

As mentioned before, the spectra of two enantiomers in an achiral environment do not differ. Nevertheless, direct evidence of their existence in solution can be obtained by recording the ^{1}H NMR

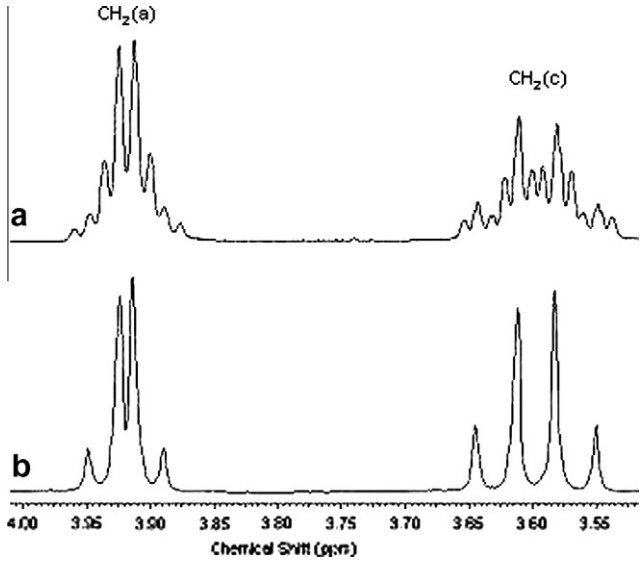


Fig. 5. *N*-methylene signals of the ^{1}H NMR spectrum of compound **1b** ($CDCl_3$): (a) normal and (b) with simultaneous decoupling of CH_2(b).

spectrum in the presence of a suitable enantiopure chiral agent, provided that the interconversion barrier between both enantiomeric forms is high enough. In fact, it was observed that the single line corresponding to the CH_3 substituent on the 5-aryl group of **1a** (Fig. 4a) splits into two singlets when the spectrum is recorded in the presence of a suitable amount of enantiopure Pirkle's alcohol (Fig. 4b) [23].

We examined next the methylenic portion in the ^{1}H NMR spectrum of compound **1b** (Fig. 5a). In this case, hydrogens within both *N*-methylene groups (δ = 3.86–3.95 and 3.52–3.66 ppm) appear diastereotopic. Simplification of the spectrum by decoupling the C–CH_2–C signal (Fig. 5b) yielded two AB-type systems with J_{gem} = 16.5 and 12.5 Hz, respectively.

To gain further insight into the magnitude of the interconversion barriers of the atropisomers under study, the ^{1}H NMR spectrum of **1b** was acquired at progressively higher temperatures with simultaneous decoupling of the C–CH_2–C signal. The *N*-methylene signals did not display the line broadening typical of an exchange process, even when the sample was heated at +120 °C, indicating that the enantiomerization barrier must be higher than 20 kcal mol^{-1} [24].

The ground state geometry of five-membered amidinoquinoxaline **1c** was also investigated with the HF/6-31G** method. Two minima were initially located at the AM1 level, due to pyramidalization of the formally sp^3 nitrogen atom within the amidine ring. Both structures were further optimized with the *ab initio* method, yielding a single structure in which the $C_{2'}$—$C_{1'}$—C_4—C_{3a} dihedral

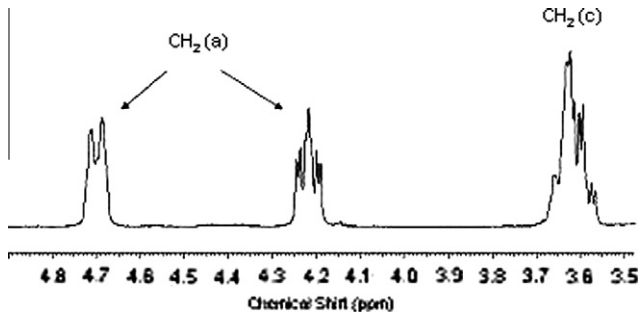


Fig. 6. *N*-methylene signals of the ^{1}H NMR spectrum of compound **2a** (DMSO-d_6).

angle had a value of 113.3° (Fig. 3). This indicates for such compound the existence of two enantiomeric forms. In fact, the ^{1}H NMR spectrum of dihydroimidazoquinoxaline *N*-oxides **1d,e** also show unusual splitting of the *N*-methylene signals, attributable to nonequivalence of the geminal hydrogens. For such compounds, decoupling experiments aimed at simplifying the signals were unsuccessful due to close proximity of the multiplets.

Two representative examples of amidinoquinoxalinium *N*-oxides (compounds **2a,b**) were also studied. Such compounds were synthesized by quaternization of the parent amidines with methyl iodide (Scheme 1). Assignment of the ^{1}H and ^{13}C resonances of salts **2a,b**, performed by analysis of their HSQC and HMBC spectra, are shown in Tables 1 and 2, respectively. As expected, methiodides **2a,b** also show ^{1}H NMR features indicative of molecular asymmetry, entailing the existence of atropisomeric forms. The diastereotopic *N*-methylene signals of compound **2a** are shown in Fig. 6. The magnitude of the nonequivalence between geminal hydrogens in such compound is high enough to observe two well separated signals in the case of CH_2(a), both of which correlate with one ^{13}C signal at 46.51 ppm in the HSQC spectrum.

4. Conclusions

We have identified a new group of heterocyclic conformational enantiomers (atropisomers) derived from five and six-membered amidinoquinoxaline *N*-oxides. The computational chemical study of two representative members (compounds **1a**,**d**) predicts for such compounds ground state geometries in which the *ortho* substituted aryl residue is nearly perpendicular to the plane of the heterocycles. This creates a source of molecular asymmetry, resulting in two enantiomeric forms. Indirect evidence of the chirality of such compounds is observed in their ^{1}H NMR spectra, in which geminal hydrogens belonging to one or both *N*-methylene groups appear diastereotopic. Direct observation of the atropisomers of compound **1a** in solution was achieved employing an enantiopure chiral solvating agent. Quaternary salts **2a,b** derived from the parent amidines also show spectral features indicative of axial chirality.

The complete assignment of the ^{1}H and ^{13}C signals of amidinoquinoxalines **1a–e** and methiodides **2a,b** was performed by analysis of the correlations observed in their HSQC, HMBC and NOESY spectra.

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