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Reference Data

^{1}H and ^{13}C NMR spectroscopy of some 4-(*p*-fluorobenzoyl)piperidine derivatives

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ABSTRACT: ^{1}H and ^{13}C NMR spectral data for 12 *N*-[(benzo- or heterocycloalkyl)methyl or ethyl]-4-(*p*-fluorobenzoyl)piperidines were fully assigned by a combination of one- (^{1}H, ^{13}C, DEPT) and two-dimensional (HMQC) NMR experiments. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; 4-(*p*-fluorobenzoyl)piperidines

INTRODUCTION

Schizophrenia is a mental illness which affects *ca.* 1% of the world's population. Antipsychotic therapy involves treatment with classical neuroleptics such as haloperidol (which is the prototype of a group of butyrophenone derivatives with a very potent antipsychotic activity) and atypical antipsychotics such as clozapine. However, the shortcomings of all current antipsychotic drugs have led to the search for new compounds. In our group, several aminomethyl- and aminoethylbenzo- and -heterocycloalkanones have been obtained as conformationally constrained butyrophenone analogues of haloperidol, some of them bearing a 4-(*p*-fluorobenzoyl)piperidine moiety.[1–4] The 4-(*p*-fluorobenzoyl)piperidine fragment may be considered as a butyrophenone constrained in a six-membered ring. The importance of this fragment in CNS-active compounds is well known.[5,6]

In this paper, we report the complete ^{1}H and ^{13}C NMR chemical shift assignments obtained from one- and two-dimensional NMR techniques for 12 4-(*p*-fluorobenzoyl)piperidines substituted on the N atom with different benzocycloalkanones (**1–4**, **9**, **10**) or heterocycloalkanones (**5–8**, **11**, **12**).

EXPERIMENTAL

The syntheses of the compounds were carried out according to previously reported procedures.[1,2,7]

^{1}H NMR spectra were recorded at room temperature in dilute solutions (*ca.* 0.7%) in $CDCl_3$ (TMS as internal standard) on a Bruker AMX 300 NMR spectrometer operating at 300.13 MHz, typically with a 30° pulse flip angle, a pulse repetition time of 2 s and a spectral width of 6172 Hz with 16K data points.

One-dimensional ^{13}C NMR spectra were recorded in 3% solutions in $CDCl_3$ with a Bruker AMX 300 NMR spectrometer at 75.47 MHz, typically with a 30° pulse flip angle, a pulse repetition time of 1.8 s and a spectral width of 23 809 Hz with 32K data points. For the DEPT sequence, the width of the 90° pulse for ^{13}C was 4 μs and that of the 90° pulse for ^{1}H was 9.5 μs; the delay $2J_{C,H}^{-1}$ was set at 3.45 ms.

^{1}H-detected one-bond HMQC spectra were recorded with a Bruker AMX 500 spectrometer using a pulse sequence (the INV4TP micro program of the Bruker software) that allowed gradient selection. Spectra were collected in the t_1 domain in 256 experiments with 2K data points. Spectral widths of 4504 and 27 778 Hz were employed in the F_2 (^{1}H) and F_1 (^{13}C) domains, respectively. Data were processed using sine-bell functions for weighting in both dimensions; the delay Δ_1 was set to 1 s and Δ_2 was empirically optimized as 3.8 ms.

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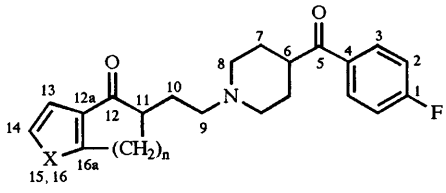
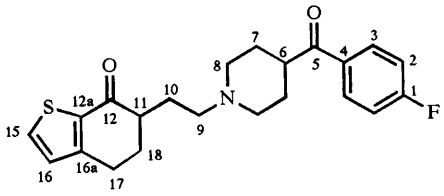
RESULTS AND DISCUSSION

The structures and numbering scheme for the *p*-fluorobenzoylpiperidines studied are presented in Fig. 1 and their ^{1}H and ^{13}C NMR spectral data are given in Tables 1–3. The ^{1}H and ^{13}C chemical shift assignments are based on coupling information, substituent effects and data reported earlier for related compounds.[8–11]

The assignment of the ^{1}H and ^{13}C resonances of the benzene ring was deduced from the proton–fluorine and fluorine–carbon couplings found in the ^{1}H and ^{13}C NMR spectra. ^1J(F,C) for **1–12** is 254.5 Hz (C-1), ^2J(F,C) is 21.9 Hz (C-2) and ^3J(F,C) is 9.3 Hz (C-3). Also, the F–H



	n	X
1	1	CH=CH
2	1	CF=CH
3	2	CH=CH
4	3	CH=CH
5	1	S
6	2	S
7	2	O



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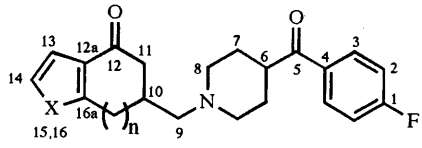

	n	X
9	0	CH=CH
10	1	CH=CH
11	1	S
12	1	O

Figure 1. Structures and numbering of the compounds studied.

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Table 1. ^{1}H chemical shifts (ppm) for compounds **1–8**

Hydrogen	1	2	3	4	5	6	7	8
H-2	7.10	7.11	7.11	7.10	7.11	7.10	7.12	7.13
H-3	7.92	7.93	7.95	7.94	7.96	7.96	7.93	7.96
H-6	3.14	3.14	3.18	3.16	3.20	3.15	3.19	3.19
H-7	1.77	1.74	1.82	1.78	1.80	1.82	1.81	1.84
H-8ax/eq	2.10/2.96	2.12/2.94	2.11/3.01	2.05/2.96	2.13/3.01	2.11/3.02	2.11/3.01	2.12/3.01
H-9	2.49	2.48	2.50	2.33	2.50	2.50	2.49	2.52
H-10	1.76/2.05	1.65/2.06	1.66/1.91	1.61/1.93	1.76/1.85	1.62/2.02	1.58/1.97	1.65/1.99
H-11	2.71	2.75	2.25	3.04	3.07	2.58	2.46	2.59
H-13	7.72	7.73	7.99	7.63	7.15	7.05	6.65	—
H-14	7.34	7.13	7.28	7.26	7.34	7.37	7.30	—
H-15	7.55	—	7.44	7.35	—	—	—	7.58
H-16	7.42	7.04	7.22	7.19	—	—	—	6.94
H-17	2.83/3.31	2.83/3.31	3.05	2.89	2.94/3.40	2.97	2.89	2.90
H-18	—	—	2.20/2.57	1.66	—	2.21/2.32	2.05/2.29	2.20/2.27
H-19	—	—	—	2.03/2.17	—	—	—	—

and C–F couplings in the indanone ring of **2** allowed the complete assignment of the ^{1}H and ^{13}C resonances of the aromatic part. ^{1}J(F,C) for **2** is 255.8 Hz (C-15), ^{2}J(F,C) are 21.9 Hz (C-14) and 23.4 Hz (C-16) and ^{3}J(F,C) are 10.6 Hz (C-13) and 9.8 Hz (C-16a).

The signals due to the piperidine ring were assigned with the aid of HMQC spectra of **9**. By extension, the signals of the rest of the compounds could also be assigned.

Acknowledgements

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Table 2. ^{13}C chemical shifts (ppm) for compounds **1–8**

Carbon	1	2	3	4	5	6	7	8
C-1	165.97	166.00	166.00	166.03	166.03	165.85	167.30	166.00
C-2	116.14	116.14	116.14	116.18	116.16	116.00	116.15	116.14
C-3	131.24	131.24	131.25	131.26	131.25	131.11	131.25	131.25
C-4	132.82	132.82	132.89	132.75	132.79	132.68	132.81	132.87
C-5	201.30	201.43	201.41	201.25	201.41	201.35	201.38	201.49
C-6	43.70	43.98	44.02	43.45	43.85	43.99	43.90	44.14
C-7	28.64	28.95/28.96	29.06	28.47/28.44	28.95	28.96/29.01	28.84/28.88	29.11/29.14
C-8	53.09/53.35	53.36/53.70	53.39/53.55	52.92/53.07	53.41/53.54	53.37/53.60	53.31/53.51	53.48/53.70
C-9	56.25	56.24	56.49	56.59	56.43	56.56	56.62	56.66
C-10	28.64	28.88	28.96	28.20	30.09	26.68	22.99	25.46
C-11	45.86	46.12	46.17	48.40	51.99	44.90	45.06	45.53
C-12	208.82	206.95	200.50	207.21	200.45	195.39	196.65	194.64
C-12a	137.25	133.76	133.54	140.40	169.27	155.10	121.08	152.19
C-13	126.87	126.44	127.81	128.68	120.04	123.48	107.16	—
C-14	124.22	113.42	126.96	126.74	131.18	125.36	143.13	—
C-15	134.97	167.47	132.91	131.63	—	—	—	134.16
C-16	127.73	115.99	129.06	130.30	—	—	—	128.42
C-16a	153.88	156.41	144.31	142.47	145.84	137.18	166.59	136.96
C-17	32.95	32.74	29.00	34.03	31.27	30.21	28.58	30.21
C-18	—	—	27.18	25.86	—	24.79	26.69	26.96
C-19	—	—	—	30.89	—	—	—	—

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Table 3. ^{1}H and ^{13}C chemical shifts (ppm) for compounds **9–12**

Atom	9	10	11	12
H-2	7.13	7.13	7.14	7.13
H-3	7.97	7.97	7.97	7.96
H-6	3.22	3.20	3.20	3.20
H-7	1.86	1.84	1.83	1.83
H-8ax/eq	2.20/3.03	2.12/2.94	2.16/2.93	2.14/2.93
H-9	2.47/2.65	2.39	2.40	2.40
H-10	3.55	2.46	2.56	2.58
H-11	2.50/2.82	2.81/3.12	2.68/3.27	2.60/3.08
H-13	7.73	8.01	7.38	7.30
H-14	7.38	7.30	7.07	6.40
H-15	7.58	7.48	—	—
H-16	7.69	7.29	—	—
H-17	—	2.36/2.72	2.29/2.75	2.26/2.66
C-1	165.89	166.01	166.05	166.05
C-2	116.05	116.15	116.19	116.18
C-3	131.14	131.26	131.27	131.26
C-4	132.65	132.88	132.82	132.83
C-5	201.40	201.50	201.47	201.43
C-6	43.89	44.08	44.02	43.98
C-7	29.04	29.14/29.23	29.11/29.93	29.07/29.20
C-8	53.75	53.77/54.50	53.53/54.68	53.44/54.63
C-9	64.51	63.98	63.50	63.38
C-10	36.28	33.55	35.40	33.92
C-11	42.22	44.11	43.09	43.05
C-12	206.58	198.55	193.20	194.22
C-12a	137.17	132.99	155.71	121.45
C-13	123.74	127.38	123.72	106.78
C-14	128.03	127.06	125.02	143.29
C-15	134.77	133.97	—	—
C-16	126.91	129.47	—	—
C-16a	157.65	143.92	137.58	167.22
C-17	—	34.87	30.46	28.45