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Spectral Assignments and Reference Data

Complete assignments of ^{1}H and ^{13}C NMR data for ten phenylpiperazine derivatives

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Ten phenylpiperazine derivatives were designed and synthesized. The first complete assignments of ^{1}H and ^{13}C NMR chemical shifts for these phenylpiperazine derivatives were achieved by means of 1D and 2D NMR techniques, including ^{1}H–^{1}H COSY, HSQC and HMBC spectra. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; 2D NMR; phenylpiperazine derivatives; complete NMR assignments

INTRODUCTION

Naftopidil, ((*R*, *S*)-1-(2-methoxyphenyl)-1-piperazinyl-3- (1-naphthyl-oxy-2-propanol)), a phenylpiperazine derivative provided by Boehringer Mannheim (FRG) Company, was a novel α_1-adrenoceptor antagonist and a new antihypertensive drug.[1] The metabolism of Naftopidil and the pharmacodynamic action of its metabolites had been previously investigated. Three major metabolites including *O*-demethyl-Naftopidil, (phenyl) hydroxyl-Naftopidil and (naphthyl) hydroxyl-Naftopidil were found to have similar affinities to the α_1-adrenoceptor as their parent compound.[2] From the structure of these active metabolites, it was supposed that the hydroxyl group on the phenyl or naphthyl ring was essential to the activity of Naftopidil's metabolites. According to metabolic rule of Naftopidil, three active metabolites had been used as leading compounds to design and synthesize new derivatives. Ten new resulting derivatives had been obtained, among which many showed potent antihypertension activity in the artery-expanding experiment. In this paper, we report the complete ^{1}H and ^{13}C NMR assignment for those phenylpiperazine derivatives (**1**–**10**). To our knowledge, it is the first time unambiguous ^{1}H and ^{13}C NMR assignments for those compounds are given, by the aid of 2D NMR techniques.

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RESULTS AND DISCUSSION

Syntheses

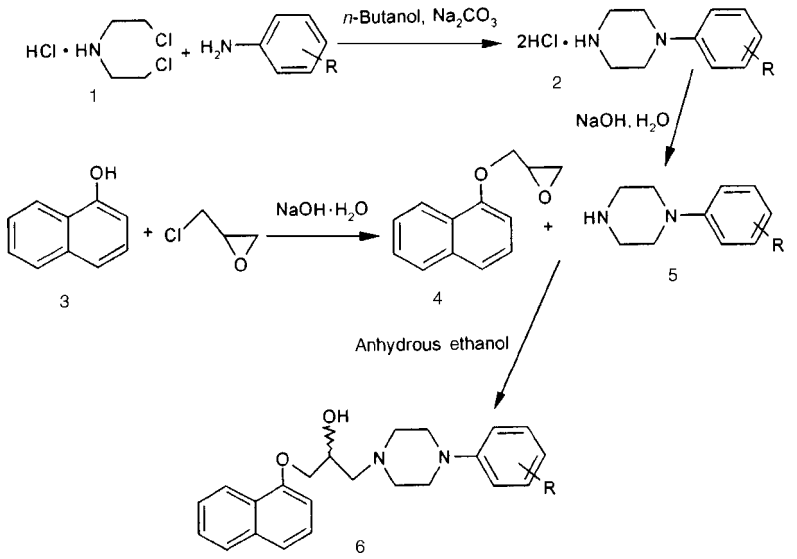
The intermediate chemicals were purified before they were used in the next steps. The general procedure for the preparation of target compounds **6** is shown in Scheme 1. Starting $\beta\beta'$-dichlorodiethylamine hydrochloride **1** was electrophilic substituted by appropriate substituted anilines to afford the desired phenylpiperazine hydrochloride **2**. **4** was obtained by reaction of epichlorohydrin with **3** in alkali water. **4** and **5** were refluxed in anhydrous ethanol to obtain target compounds. A similar method was designed for the synthesis of all the target compounds **6**.[3–5] Compounds **2** were prepared and separated according to the method described elsewhere.[6] Preparation of **4** was performed according to the general procedure described elsewhere.[7]

^{1}H NMR, ^{13}CNMR spectral assignments

The structures of compounds **1**–**10** are presented in Scheme 2. The complete assignments of ^{1}H and ^{13}C NMR chemical shifts of the compounds are listed in Table 1 and Table 2, respectively.

The obvious signal assignments were made from ^{1}H, ^{13}C NMR and DEPT spectra according to the chemical shifts and multiplicities. Other remaining ^{1}H and ^{13}C NMR signals were assigned with the aid of 2D NMR spectra including ^{1}H–^{1}H COSY, HSQC and HMBC spectra.

The ^{1}H and ^{13}C NMR data (Table 1 and 2) combined with DEPT, ^{1}H–^{1}H COSY, and HSQC experiments suggested the presence of two fragments $-CH_2-CH(OH)-CH_2-$, $-N(CH_2-CH_2)_2-N-$ and an Aryl ring. For example, In the HMBC spectrum (Fig. 1) of **1**, long-range correlations were observed from the protons at δ 4.23 and 4.16 (H_2-11) of the fragment $-^{11}CH_2-^{12}CH(OH)-^{13}CH_2-$ to the C-1 (δ 154.34), C-12 (δ 65.67) and C-13 (δ 60.87). And the methylene proton (H_2-13) at δ 2.75 of the fragment $-^{11}CH_2-^{12}CH(OH)-^{13}CH_2-$ was



Scheme 1. Synthesis of compounds **1**–**10**.

MRC

Spectral Assignments and Reference Data

Table 1. ^{13}C NMR spectral data of **1**–**10** (125 MHz) in $CDCl_3$

C	1	2	3	4	5	6	7	8	9	10
1	154.34	154.34	154.36	154.39	154.32	153.50	154.36	153.46	153.50	154.33
2	104.85	104.94	104.90	104.88	104.90	105.06	104.87	105.14	105.15	104.89
3	125.79	125.73	125.79	125.79	125.78	125.83	125.86	125.86	125.88	125.82
4	120.60	120.70	120.63	120.60	120.65	121.01	120.61	121.23	121.17	120.66
5	127.49	127.52	127.50	127.48	127.50	127.59	127.52	127.73	127.70	127.52
6	126.43	126.44	126.43	126.43	126.44	126.53	126.45	126.60	126.59	126.46
7	125.24	125.25	125.23	125.24	125.24	125.14	125.25	125.21	125.58	125.28
8	121.86	121.84	121.86	121.90	121.83	121.62	121.89	121.45	121.59	121.86
9	125.54	125.57	125.57	125.59	125.55	125.53	125.58	125.58	125.32	125.56
10	134.46	134.50	134.49	134.49	134.48	134.39	134.45	134.51	134.63	134.50
11	70.43	70.45	70.47	70.51	70.42	69.43	70.44	69.17	69.38	70.38
12	65.67	65.79	65.74	65.63	65.76	64.43	65.67	64.40	64.48	65.58
13	60.87	60.87	60.83	60.89	60.86	61.41	60.87	62.40	62.45	61.03
14	53.37	53.22	53.38	53.54	53.18	53.84	55.56	53.44	54.46	53.44
15	53.37	53.22	53.38	53.54	53.18	53.84	55.56	53.44	54.46	53.44
16	49.25	49.08	50.23	51.27	48.73	46.51	50.73	46.84	49.00	49.39
17	49.25	49.08	50.23	51.27	48.73	46.51	50.73	46.84	49.00	49.39
18	151.13	150.15	147.80	149.09	152.14	150.48	145.52	153.46	147.10	148.68
19	116.12	117.68	115.61	128.79	115.84	103.50	114.44	96.19	125.22	115.92
20	129.13	131.88	117.83	130.66	134.95	160.59	118.28	161.71	132.01	125.96
21	119.88	111.98	158.17	123.79	119.45	106.29	153.91	93.54	134.49	142.78
22	129.13	131.88	117.83	127.59	130.03	130.12	118.28	161.71	127.54	125.96
23	116.12	117.68	115.61	120.38	113.92	109.39	114.44	96.19	119.79	115.92
R						55.22	53.50	55.37	17.67	33.97
								55.37	20.75	31.44
										31.44
										31.44

long-range coupled to C-14 (δ 53.37) and C-15 (δ 53.37). Moreover, the protons at δ 3.23 (H_2-16, H_2-17) were coupled to the C-18 (δ 151.13). The above HMBC correlations confirmed the connections from C-1 to C-11; C-13 to C-14, C-15; and C-16, C-17 to C-18. Furthermore, the long-range couplings observed from the protons at δ 7.45 (H-4), δ 7.81 (H-5), δ 7.48 (H-6) and δ 8.27 (H-8) to the carbon at δ 154.34 (C-1) indicated the presence of the naphthyl ring. And the couplings from the protons of H-20, H-21 and H-22 to the C-18 at δ 151.13 suggested the presence of a phenyl ring. Thus, the whole structure of **1** was characterized as shown in the Scheme 2.

With the aid of HMBC experiment, the downfield double doublet signal of **1** at δ_H8.27 (J = 2.2, 6.8 Hz) was assigned to H-8 and the resonance at δ_H 7.81 (J = 2.1, 6.9 Hz) to H-5. This result can be explained by the deshielding effect of the oxygen atom, which decreases the electronic density of the H-8. Additionally, the signals of the H_2-11 (CH_2) group were two symmetrical double doublets (δ_{Ha} 4.23 and δ_{Hb} 4.16) resulting from their coupling with their neighboring methine proton (δ_{H-12}4.31, m).[8]

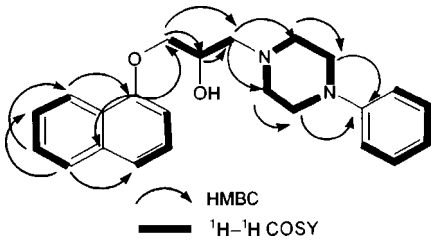
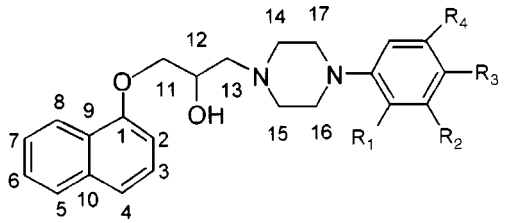


Figure 1. Key ^{1}H–^{1}H COSY and HMBC correlations for **1**.



1 $R_1 = R_2 = R_3 = R_4 = H$

2 $R_1 = R_2 = R_4 = H$, $R_3 = Br$

3 $R_1 = R_2 = R_4 = H$, $R_3 = F$

4 $R_1 = Cl$, $R_2 = R_3 = R_4 = H$

5 $R_1 = R_3 = R_4 = H$, $R_2 = Cl$

6 $R_1 = R_3 = R_4 = H$, $R_2 = OMe$

7 $R_1 = R_2 = R_4 = H$, $R_3 = OMe$

8 $R_1 = R_3 = H$, $R_2 = R_4 = OMe$

9 $R_1 = R_3 = CH_3$, $R_2 = R_4 = H$

10 $R_1 = R_2 = R_4 = H$, $R_3 = C(CH_3)_3$

Scheme 2. Structure of compounds **1**–**10**.

All the synthesized compounds had the same basic skeleton and the difference between them was the substituted group on the phenyl ring. Obviously, the changes of the chemical shifts of these compounds were caused by the different substituted patterns on the phenyl ring (Tables 1 and 2). The structures of other compounds were characterized by the same way as that of **1**.

Table 2. ^{1}H NMR data of **1–10** (500 MHz; *J* in Hz) in $CDCl_3$

H	1	2	3	4	5	6	7	8	9	10
2	6.84 d	6.84 d	6.83 d	6.84 d	6.82 d	6.72 d	6.84 d	6.78 d	6.78 d	6.84 d
	(7.5)	(7.5)	(7.5)	(7.5)	(7.5)	(7.7)	(7.1)	(7.5)	(4.4)	(7.5)
3	7.37 t	7.37 br d	7.36 t	7.37 t	7.37 t	7.28 t	7.37 t	7.34 t	7.32 t	7.37 t
	(7.8)	(7.8)	(7.8)	(7.8)	(7.7)	(7.8)	(7.8)	(7.8)	(6.5)	(7.5)
4	7.45 d	7.45 t	7.44 br d	7.44 d	7.45 t	7.41 d	7.45 br d	7.45 d	7.44 d	7.45 br d
	(8.2)	(8.2)	(8.2)	(8.2)	(8.2)	(8.2)	(8.2)	(8.2)	(8.0)	(8.0)
5	7.81 dd	7.80 dd	7.79 dd	7.80 dd	7.80 dd	7.76 br t	7.81 dd	7.80 dd	7.80 br t	7.81 dd
	(2.1, 6.9)	(2.1, 7.1)	(2.3, 6.9)	(2.6, 6.7)	(2.3, 6.6)	(4.2)	(2.0, 6.7)	(2.5, 6.7)	(4.6)	(2.0, 7.0)
6	7.48 m	7.48 m	7.47 m	7.48 m	7.48 m	7.45 m	7.49 m	7.48 m	7.48 m	7.49 m
7	7.48 m	7.48 m	7.47 m	7.48 m	7.48 m	7.45 m	7.49 m	7.48 m	7.48 m	7.49 m
8	8.27 dd	8.25 dd	8.56 dd	8.26 dd	8.26 dd	8.23 br t	8.26 dd	8.17 dd	8.21 br s	8.26 dd
	(2.2, 6.8)	(2.1, 7.1)	(1.7, 7.4)	(2.7, 6.9)	(2.2, 7.1)	(4.2)	(1.8, 7.3)	(2.1, 6.7)		(2.0, 7.5)
11_a	4.23 dd	4.23 dd	4.22 dd	4.23 dd	4.22 dd	4.26 dd	4.23 dd	4.34 dd	4.34 br s	4.24 dd
	(5.0, 9.6)	(5.1, 9.5)	(5.1, 9.4)	(5.1, 9.6)	(5.1, 9.5)	(4.4, 9.5)	(5.1, 9.4)	(3.8, 9.6)		(5.0, 9.5)
11_b	4.16 dd	4.16 dd	4.15 dd	4.16 dd	4.16 dd	4.08 t	4.17 dd	4.12 br t	4.13 br s	4.16 dd
	(4.9, 9.4)	(4.9, 9.5)	(4.9, 9.5)	(4.9, 9.5)	(4.9, 9.5)	(7.3)	(4.9, 9.4)	(8.6)		(5.0, 9.5)
12	4.31 m	4.30 m	4.29 m	4.31 m	4.30 m	4.88 br s	4.31 m	4.88 br s	4.91 br s	4.34 m
13	2.75 m	2.73 m	2.72 m	2.75 m	2.73 m	3.39 m	2.74 m	3.41 br s	3.46 br s	2.77 m
14_a	2.89 m	2.86 m	2.86 m	2.92 br s	2.85 m	3.85 br s	2.89 m	3.85 m	3.87 br s	2.92 m
14_b	2.67 m	2.65 m	2.66 m	2.71 br s	2.64 m	3.06 br s	2.68 m	3.15 m	3.16 m	2.71 m
15_a	2.89 m	2.86 m	2.86 m	2.92 br s	2.85 m	3.85 br s	2.89 m	3.85 m	3.87 br s	2.92 m
15_b	2.67 m	2.65 m	2.66 m	2.71 br s	2.64 m	3.06 br s	2.68 m	3.15 m	3.16 m	2.71 m
16	3.23 m	3.20 m	3.14 m	3.12 br s	3.23 m	3.53 br s	3.14 m	3.66 m	3.61 br s	3.24, m
17	3.23 m	3.20 m	3.14 m	3.12 br s	3.23 m	3.53 br s	3.14 m	3.66 m	3.61 br s	3.24, m
19	6.95 br d	6.79 d	6.86 m		6.88 br s	6.36 br s	6.92 br d	6.04 s		6.89 br d
	(8.1)	(8.9)					(9.0)			(9.0)
20	7.28 t	7.35 d	6.97 t	7.37 dd			6.85 d		6.99 s	7.30 br d
	(8.1)	(8.9)	(8.4)	(1.7, 7.9)			(9.0)			(9.0)
21	6.88 t			6.99 dt	6.84d	6.46 dd		6.10 s		
	(8.0)			(1.5, 8.0)	(6.9)	(1.5, 6.7)				
22	7.28 t	7.35 d	6.97 t	7.22 dt	7.16 t	7.12 t	6.85 d		6.94 brs	7.30 br d
	(8.1)	(8.9)	(8.4)	(1.5, 7.5)	(8.1)	(8.4)	(9.0)			(9.0)
23	6.93 br d	6.79 d	6.86 m	7.05 dd	6.78 dd	6.35 d	6.92 br d	6.04 s		6.89 br d
	(8.1)	(8.9)		(1.3, 8.0)	(2.1, 8.3)	(6.1)	(9.0)			(9.0)
R						3.75 s	3.77 s	3.76 s	2.27 s	
								3.76 s	2.23 s	1.29 s
										1.29 s
										1.29 s

EXPERIMENTAL

The melting points of all the compounds were determined using an Electrothermal XT-4 melting point apparatus and was uncorrected. Extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. Merck F_{254} commercial plates were used for analytical thin-layer chromatography, to follow the course of the reactions.

Compounds

Compound 1: $C_{23}H_{26}N_2O_2$, white powder, mp 96–97 °C (from EtOH), yield: 85.58%, EI-MS *m/z*:362. Compound 2: $C_{23}H_{25}BrN_2O_2$, colorless crystals, mp 124–125 °C (from EtOH), yield: 46.73%, EI-MS *m/z*:440. Compound 3: $C_{23}H_{25}FN_2O_2$, white powder, mp 112–113 °C (from EtOH), yield: 71.38%, EI-MS *m/z*: 380. Compound 4: $C_{23}H_{25}ClN_2O_2$, colorless crystals, mp 118–119 °C (from EtOH), yield: 58.65%, EI-MS *m/z*: 396. Compound 5: $C_{23}H_{25}ClN_2O_2$, white powder, mp 129–130 °C (from EtOH), yield:78.3%, EI-MS *m/z*: 396. Compound 6: $C_{24}H_{28}N_2O_3$, white powder, mp127–128 °C (from EtOH), yield:78.31%, EI-MS *m/z*: 392. Compound 7: $C_{24}H_{28}N_2O_3$, white powder, mp 130–132 °C (from EtOH), yield: 79.54%, EI-MS *m/z*: 392. Compound 8: $C_{25}H_{30}N_2O_4$, aqueous powder, mp 167–169 °C (from EtOH), yield: 63.55%, EI-MS *m/z*: 422. Compound 9: $C_{25}H_{30}N_2O_2$, off-white powder, mp 117–118 °C (from EtOH), yield: 63.81%, EI-MS *m/z*: 390. Compound 10: $C_{27}H_{34}N_2O_2$, colorless crystals, mp 103–104 °C (from EtOH), yield: 67.20%, EI-MS *m/z*: 418.

NMR measurements

All NMR experiments were recorded on a Bruker AV-500 spectrometer operating at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, and equipped with a broadband 5-mm probe (BBO probe,^{1}H 90° pulse width = 9.8 μs, ^{13}C 90° pulse width = 5.8 μs) and operating at room temperature with tetramethylsilane as internal standard.

MRC

Spectral Assignments and Reference Data

About 10 mg samples were dissolved in $CDCl_3$ (0.5 ml) to record the NMR spectra.

1D spectra were acquired using 64K data points and spectral widths of 12 500 Hz and 125 000 Hz for ^1H and ^{13}C, respectively; 32K data points were used for the processing with an exponential function for all 1D spectra.

Standard pulse sequences were used for 2D spectra. Spectral widths of 4700 Hz and 62 500 Hz were used for ^1H and ^{13}C, respectively. Relaxation delays of 2.0 s were used for all 2D NMR experiments. The 2D spectra used 2048×512 (^1H–^1H COSY,), 1024×512 (HSQC), and 2048×512 (HMBC) data point matrices, which were zero filled to 2048×1024, 1024×1024 and 2048×1024, respectively. Nonshifted qsine–bell window functions were used along the F_1 and F_2 axes for all 2D spectra. The HMBC experiments used a 100 ms delay time to obtain ^1H and ^{13}C long-range correlations. Z-PFGs were used to obtain ^1H–^1H COSY, HSQC, and HMBC spectra. Data processing was carried out with Bruker XWINNMR 3.50 programs.

Acknowledgements

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