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# NMR study on (±)-1-[3-(2-methoxyphenoxy)-2-hydroxypropyl]-4-[(2,6-dimethylphenyl)aminocarbonylmethyl]piperazine dihydrochloride salt

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## Abstract

 $(\pm)$ -1-[3-(2-Methoxyphenoxy)-2-hydroxypropyl]-4-[(2,6-dimethylphenyl)aminocarbonylmethyl]piperazine dihydrochloride salt was studied spectroscopically. Complete NMR assignments for dihydrochloride salt were made using DEPT, H–H COSY, as well as HMQC and HMBC heteronuclear correlation techniques.

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*Keywords:* (±)-1-[3-(2-Methoxyphenoxy)-2-hydroxypropyl]-4-[(2,6-dimethylphenyl)aminocarbonylmethyl]piperazine dihydrochloride salt; NMR assignment; DEPT; H–H COSY; HMQC; HMBC

## 1. Introduction

 $(\pm)$ -1-[3-(2-Methoxyphenoxy)-2-hydroxypropy]]-4-[(2, 6-dimethylphenyl)aminocarbonylmethyl]piperazine dichloride salt is the flagship member of a new potential antianginal drugs called partial fatty acid oxidation (pFOX) inhibitors [1-6].

Although different methods for the synthesis of this compound have reported previously [7,8], the structure have not been proved by spectrum.

The present paper is devoted to HMR characterization of this compound (IR and MS characterization in next paper). To assign <sup>1</sup>H NMR and <sup>13</sup>C NMR for the structure, DEPT, H–H COSY, as well as HMQC and HMBC heteronuclear correlation techniques were used.

# 2. Experimental

(±)-1-[3-(2-Methoxyphenoxy)-2-hydroxypropyl]-4-(2, 6-dimethylphenyl)aminocarbonylmethyl]piperazine dichlo-

\* Corresponding author. Fax: +86 0531 8564464. *E-mail address:* linjm@sdu.edu.cn (J. Lin). ride salt was prepared by the as following method: to the solution of 1-4[(2,6-dimethylphenyl)aminocarbonylmethyl]piperazine 15 g (0.06 mol) [7] in 80 ml ethanol, 1-(2-methoxyphenoxy)-2,3-epoxypropane 13 g (0.072 mol) [7] was added, and the mixture was stood for two days at -5 to 0°C. Hydrochloric was led into the solution to pH 2 and precipitated with ether. pure salt was obtained by recrystallization with ethanol for two times.

 $(\pm)$ -1-[3-(2-Methoxyphenoxy)-2-hydroxypropyl]-4-[(2,6dimethylphenyl)aminoarbonylmethyl]piperazine (free base) was prepared from its dichloride salt 1.5 g above suspended in 60 ml benzene by neutralization with 20% sodium hydroxide, and then by separation, washing, evaporation.

NMR spectra were recorded on a 400 MHz Bruker Avance spectrometer in DMSO- $d_6$  solvent. TMS was used as the internal standard.

# 3. Results and discussion

 $^{13}$ C NMR spectrum (Fig. 1) shows 19 different carbon atoms which is consistent with the structure of (±)-1-[3-(2-methoxyphenoxy)-2-hydroxypropyl]-4-[(2,6-dimethylp-

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Fig. 1. <sup>13</sup>C NMR spectrum.

henyl)aminocarbonylmethyl]piperazine dichloride salt (C<sub>24</sub> H<sub>35</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>) on the basis of molecular symmetry. The DEPT 135 spectrum (Fig. 2) gives the CH<sub>2</sub> peaks at  $\delta$  48.074,  $\delta$  48. 898,  $\delta$  56.147,  $\delta$  58.360 and  $\delta$  71.389, and the CH, CH<sub>3</sub> peaks at  $\delta$  17.882,  $\delta$  55.644,  $\delta$  64.029,  $\delta$  112.795,  $\delta$  115.056,  $\delta$  120.632,  $\delta$  121.652,  $\delta$  126.492,  $\delta$  127.44 (Table 1). The other peaks of <sup>13</sup>C NMR except for the peaks in DEPT spectrum are non-protonated carbons (Table 1).

Table 2 list <sup>1</sup>H NMR, J and H–H COSY spectral data of this salt.

The <sup>1</sup>H NMR spectrum shows that the protons of two HCl joining at nitrogen atom of piperazine exhibit two broad single peaks at 4013.8 Hz (10.037 ppm, 1 H) and 4134.7 Hz (10.337 ppm, 1 H), respectively, which have not correlation with carbon in HMQC spectrum and have not H–H correlation in H–H COSY spectrum (Fig. 6).

Other protons (free base part) exhibit peaks in 828.8 Hz (2.072 ppm)–2830.3 Hz (7.076 ppm) (Figs. 3–5).

Assignments of the protons and carbons were made by two dimensional heteronuclear-correlated experiments (HMQC, Fig. 7) using delay values which corresponded to  ${}^{1}J$  (C, H), HMBC (Fig. 8) using delay values which corresponded to  ${}^{2}J$  (C, H) or  ${}^{3}J$  (C, H) even  ${}^{4}J$  (C, H) between the carbons and protons., and H–H correlation spectroscopy which corresponded to  ${}^{2}J$  (H, H) of CH<sub>2</sub> group and  ${}^{3}J$  (H, H) between the proton–carbon–protons.

 $\delta$  2.072 (1 H, s), which can not been found any proton–proton correlative signal in H–H COSY spectrum and any proton–carbon signal in HMQC spectrum, is assigned to the proton of hydroxyl group.

 $\delta$  2.184 (6 H, s) is assigned to the both same methyl groups on the basis of molecular symmetry. HMBC spectrum shows that this proton exhibits long range coupling <sup>4</sup>*J* with δ 7.076 proton, and so the δ 7.076 (3H, m) proton is assigned to neighbor H-Ben (H<sub>16</sub>, H<sub>17</sub>). HMQC Spectrum shows the δ 2.184 proton corresponds to δ 17.882 carbon (C<sub>1</sub>), and δ 7.076 proton corresponds to δ 127.441 (C<sub>17</sub>) and δ 126.492 (C<sub>13</sub>) carbons.

The  $\delta$  3.297 (1 H, q) and  $\delta$  3.441 (1 H, q) are the protons at a same carbon atom exhibited in HMQC spectrum and correspond to  $\delta$  58.36 carbon (C<sub>6</sub>). DEPT spectrum shows  $\delta$  58.36



Fig. 2. The DEPT spectrum.

Table 1 <sup>13</sup>C NMR, DEPT135, HMQC, and HMBC spectral data and assignments



Chemical shift	DEPT	HMQC	HMBC	Assignments
17.882	CH <sub>3</sub>	2.184	7.076	1
48.074	$CH_2$	3.673	4.171	2
48.898	$CH_2$	3.708, 3.363	3	
55.644	CH <sub>3</sub>	3.781	4	
56.147	$CH_2$	4.171	5	
58.360	CH <sub>2</sub>	3.297, 3.441	3.949, 4.019	6
64.029	СН	4.447	3.949, 4.019	7
71.389	CH <sub>2</sub>	3.949, 4.019	3.297, 3.297	8
112.795	СН	6.973	3.441	9
115.056	СН	7.027	6.876	10
120.632	СН	6.876	6.876	11
121.652	СН	6.934	6.973	12
126.497	СН	7.076		13
127.441	СН	7.076	2.184, 7.706	14
133.782	С		2.184, 7.706	15
134.850	С		2.184, 7.706	16
147.822	С		3.949, 4.019, 7.027, 6.875	17
149.427	С		3.781, 6.973, 7.027	18
163.043	C=0		4.171	19

Table 2 <sup>1</sup>H NMR, *J*, H–H COSY spectral data and assignments



Chemical shift		Multiplet	J (Hz)	Number of H	H–H COSY (ppm)	Assignments
Hz	ppm					
828.8	2.072	S		1	_	1
873.5	2.184	s		6	_	2
1318.6	3.297	q	9.2, 13.4	1	4.447	3
1376.3	3.441	q	2.1, 13.4	1	4.447	4
1469.1	3.673	s, br.		6	_	5
1483.0	3.708	d	0.6	2	_	5'
1512.5	3.781	s		3	_	6
1512.5	3.781	s		1	_	7
1579.8	3.949	q	5.5, 10.2	1	4.447	8
1607.6	4.019	q	5, 10.3	1	4.447	9
1668.3	4.171	s, br.		2	_	10
1778.9	4.447	М	_	1	3.297, 3.441, 3.949, 4.019	11
2750.3	6.876	m	1.8, 7.6	1	6.973, 7.027, 6.294	12
2773.7	6.934	q	1.6, 7.8	1	6.876, 6.973	13
2789.1	6.973	m	1.8, 7.9	1	6.876, 6.934, 7.027	14
2810.9	7.027	q	1.6, 7.8	1	6.876, 6.973	15
2830.3	7.076	m		3		16, 17
4013.8	10.04	s		1*		18
4134.7	10.34	br.		1*		18



Fig. 3. <sup>1</sup>H NMR spectrum in  $\delta$  0.0– $\delta$  8.5 ppm.



Fig. 4. The <sup>1</sup>H NMR spectrum (partly enlarged in  $\delta$  3.2–4.5).

carbon is CH<sub>2</sub> group. H–H COSY spectrum shows both protons are interrelated each other and interrelated with  $\delta$  3.279. Because only the asymmetry carbon C<sub>7</sub> in this compound leads to different chemical shifts of neighbor CH<sub>2</sub>–protons,  $\delta$  3.297 and  $\delta$  3.441 protons are assigned to H<sub>3</sub> and H<sub>4</sub>. Three coupling constants are  $J_{3,4}$  13.4 Hz,  $J_{3,11}$  9.2 Hz, and  $J_{4,11}$ 2.1 Hz, respectively. Similar chemical environment as above,  $\delta$  3.949 (1H, q) and  $\delta$  4.019 (1H, q) are assigned to H<sub>8</sub> and H<sub>9</sub>. HMQC shows the corresponding carbon chemical shift of H<sub>8</sub> and H<sub>9</sub> is  $\delta$  71.389 and belongs to C<sub>8</sub>.

The  $\delta$  3.708 (2 H, d) protons correspond to  $\delta$  48.898 carbon in HMQC spectrum. The DEPT spectrum exhibits  $\delta$  48.898 carbon is CH<sub>2</sub> group. *J* 0.6 Hz is long range coupling <sup>4</sup>*J*. On



Fig. 5. The <sup>1</sup>H NMR spectrum (partly enlarged in  $\delta$  6.8– $\delta$  7.2).



Fig. 6. The H–H COSY spectrum.







Fig. 8. The HMBC spectrum.

the basis of characteristic of the asymmetry carbon which can made chemical shifts different beyond three bonds, the  $\delta$  3.708 (2 H, br.) protons are assigned to H<sub>5'</sub>, and the  $\delta$  48.898 carbon is assigned to C<sub>3</sub>.

The  $\delta$  3.673 (6 H, br.) protons, corresponding to  $\delta$  48.074 carbon and  $\delta$  48.898 carbon in HMQC spectrum and corresponding to CH<sub>2</sub> group in DEPT spectrum, are assigned to H<sub>5</sub>. The  $\delta$  48.074 carbon is assigned to C<sub>2</sub>.

 $\delta$  3.781 (4 H, s), corresponding only to  $\delta$  55.644 carbon in HMQC spectrum and showing non correlation with any proton, is assigned to H<sub>6</sub> and H<sub>7</sub>. The  $\delta$  55.644 carbon is belong to C<sub>4</sub>.

 $\delta$  4.171 (2 H, br.), corresponding only to  $\delta$  56.147 carbon in HMQC spectrum and corresponding to CH<sub>2</sub> group in DEPT spectrum, is assigned to H<sub>10</sub>. The  $\delta$  56.147 carbon is belong to C<sub>5</sub>.

 $\delta$  4.447 (1 H, m.), coupling with H<sub>3</sub>, H<sub>4</sub>, H<sub>8</sub> and H<sub>9</sub>, is assigned to H<sub>11</sub>. Corresponding  $\delta$  64.029 carbon in HMQC is belong to C<sub>7</sub>. DEPT spectrum confirms this tertiary carbon.

δ 6.876 (1H, six), δ 6.934 (1H, six), δ 6.973 (1H, q), and δ 7.027 (1H, q) are parts of protons of aromatic ring. H–H COSY spectrum shows that δ 6.934 and δ 7.027 protons are not interrelated each other but interrelated with δ 6.876 and δ6.934 protons, however, δ 6.876 and δ 6.973 protons are not only interrelated each other but also interrelated with δ 6.934 and δ 7.027 protons. The δ 6.934 and δ 7.027 protons belong to H<sub>13</sub> and H<sub>15</sub>, and δ 6.876 and δ 6.973 protons belong to H<sub>12</sub> and H <sub>14</sub>. By HMBC spectrum, specific assignments of protons and carbons are made as following. The δ 149.427 carbon is correlative with δ 3.781 (H<sub>6</sub>) proton and is assigned to C<sub>18</sub>. The δ 6.973 protons is correlative with δ 149.427 carbon in HMBC, being H<sub>14</sub>. The  $\delta$  6.876 proton is H<sub>12</sub>. The H<sub>8</sub>, H<sub>9</sub> protons are correlative in HMBC with  $\delta$  147.822 carbon (C<sub>17</sub>). Further, the  $\delta$  6.934 protons is correlative with  $\delta$  147.822 carbon in HMBC, being H<sub>13</sub>. The 7.027 proton is H<sub>15</sub>. HMQC give corresponding carbons:  $\delta$  6.876 (H<sub>12</sub>)– $\delta$  120.632 (C<sub>11</sub>),  $\delta$  6.934 (H<sub>13</sub>)– $\delta$  121.652 (C<sub>12</sub>),  $\delta$  6.973(H<sub>12</sub>)– $\delta$  112.975 (C<sub>9</sub>), and  $\delta$  7.027 (H<sub>15</sub>)– $\delta$  115.056 (C<sub>10</sub>).

 $\delta$  7.076 (3H, m) protons, correlating in HMBC with  $\delta$  17.882 carbon (CH<sub>3</sub>, C<sub>1</sub>), assigned to H<sub>16</sub>, H<sub>17</sub>. The corresponding carbons are  $\delta$  126.497 (C<sub>14</sub>) and  $\delta$  127.441 (C<sub>13</sub>).

DEPT spectrum shows  $\delta$  149.427 is a non-protonated carbon. Long range coupling of  $\delta$  149.427 was observed in HMBC spectrum with H<sub>6</sub> and H<sub>15</sub>. This peak is belong to C<sub>18</sub> certainly.

The last  $\delta$  163.043 carbon is C=O (C<sub>19</sub>). Correlative signal in HMBC spectrum with H<sub>10</sub> confirms the correlation structure.

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