Synthesis, Crystal Structure and Bioactivity of *N*-Phenethyl-4-hydroxy-4-phenyl Piperidine Hydrochloride①

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ABSTRACT A novel compound *N*-phenethyl-4-hydroxy-4-phenyl piperidine hydrochloride ($C_{19}H_{24}ClNO\cdot H_2O$) has been synthesized and structurally characterized by elemental analysis, IR, ^{1}H NMR spectra and single-crystal X-ray diffraction. The crystal belongs to orthorhombic, space group $P2_12_12_1$ with a = 8.6306(8), b = 11.0464(10), c = 19.3221(18) Å, V = 1842.1(3) Å^3, Z = 4, D_c =1.211 g/cm^3, μ = 0.217 mm^{-1}, M_r = 335.86, F(000) = 720, S = 0.973, R = 0.0420 and wR = 0.1009 for 3627 unique reflections with 3157 observed ones ($I > 2\sigma(I)$). In the crystal, the dihedral angles made by piperidine ring with two benzene rings are 84.8(6) and 62.5(7)°, respectively. Intermolecular O–H···O and O–H···Cl hydrogen bonds involving water molecules form chains along the *b* axis, which stabilizes the crystal structure. The preliminary bioactivity tests indicated that the title compound has good effect of cellular growth inhibition to K562 cells and potential bioactivity of anti-leukemia.

Keywords: crystal structure, piperidine derivatives, synthesis, bioactivity

1 INTRODUCTION

Piperidine derivatives are well known as components in numerous natural products such as alkaloids (*i.e.* quinine, coniine and black pepper ingredient piperine) or ant venoms[1]. Due to the known therapeutic properties of piperidines and the presence of a keto function that facilitates the introduction of other substituents on the piperidine ring, piperidine derivatives are useful as anti-osteoporotic raloxifene[2], vasodilator minoxidil[3, 4], analgesic fentanyl[5, 6], anti-pakinsonian agent biperiden[7, 8] and also as important intermediates in organic synthesis[9]. Moreover, piperidine derivatives have been reported as better bioactivities of anti-cancer[10~12]. Recently, we have found in our laboratory that piperidine derivatives have activities of anti-leukemia. In view of these observations, we attempted to find some lead compounds with high inhibition to leukaemia, and thus *N*-phenethyl-4-hydroxy-4-phenyl piperidine hydrochloride was synthesized. Herein, we report the preparation, crystal structure and bioactivity of *N*-phenethyl-4-hydroxy-4-phenyl piperidine hydrochloride.

2 EXPERIMENTAL

2. 1 Reagents and physical measurements

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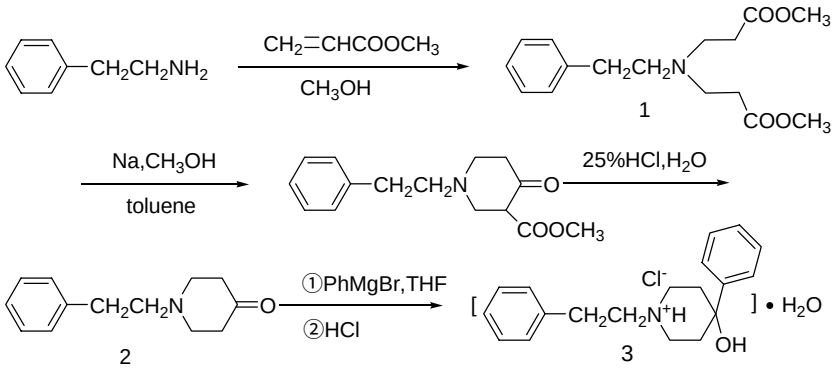
All reagents obtained from commercial sources were of AR grade. Tetrahydrofuran and toluene were dried by refluxing in the presence of sodium and distilled prior to use. ^{1}H NMR spectrum (DMSO-d_6) was recorded on a Bruker AVANCE- 400 MHz with TMS as an internal standard. Elemen- tal analysis was performed with a Perkin-Elmer 2400 instrument. IR spectra were obtained on a Nicolet-5DX FT-IR spectrophotometer in the region of 4000～400 cm^{-1} using KBr discs. Melting point was determined by an RK1 microscopic melting apparatus (uncorrected). The single-crystal structure of compound **3** was determined on a Bruker SMART 1000 CCD diffractometer. Specific rotation was tested by WZZ-3 automatic Polarimeter.

2. 2 Synthesis of the title compound

The title compound was synthesized by the method outlined in Scheme 1. We learned of 1-phenethyl -4-piperidone[13] through searches related to the preparation of substrates for an unrelated research project ongoing in our laboratory.



Scheme 1. Synthetic procedure of the title compound

1-Phenethyl-4-piperidone

(a) A solution of phenethylamine (2.42 g) in 2 mL methanol is added dropwise with stirring to another solution of methyl acrylate (6.88 g) in 3 mL methanol, and then stirred for 30 min at room temperature. The reaction mixture was heated under reflux for 8 h, followed by concentration in vacuo on a rotary evaporator. The yellow oil residue was compound **1** (5.53 g, yield 94.4%).

(b) A mixture of 0.2 mL dry methanol and 4.40 g compound **1** in 15 mL dry toluene is added dropwise with stirring to a stirred solution of 0.42 g sodium in 20 mL dry toluene, which was refluxed for 6 h and then cooled to room temperature. The mixture was extracted with 15 mL hydrochloric acid twice, heated under reflux for 6 h, and then cooled to 0～10 °C. 35% Sodium hydroxide was added dropwise with stirring to adjust the pH value to 8.5, followed by extraction with 15 mL× 3 ethyl acetate. After being washed with 20 mL× 3 concentrated salt solution and dried with $MgSO_4$, the resulting mixture was concentrated in vacuo. The yellow solid residue was 2.20 g of **2,** yield 72.3%.

1-Phenethyl-4-hydroxy-4-phenyl piperidine hydrochloride

A solution of 2.36 g bromobenzene in 7 mL dry tetrahydrofuran is added dropwise at a rate of 4 mL/min with stirring under 50 °C to a stirred solution of 0.36 g magneisum and a small amount of iodine in 4 mL dry tetrahydrofuran protected by N_2. The mixture was heated under reflux for 2 h, slowly added to another solution of 2.03 g 1-phenethyl-4-piperidone in 5 mL dry tetrahydrofuran over a period of 20 min at 60 °C after the solid of Mg disappeared, and finally stirred for 10 h at 68 °C. To the obtained mixture cooled to 0～5 °C, 10 mL water was slowly added, and concentrated hydrochloric acid was added dropwise with stirring to adjust the pH value to 4. The resulting mixture was extracted with 20 mL × 3 CH_2Cl_2 and washed with 15 mL × 3 concentrated salt solution. After being dried with $MgSO_4$ and concentrated in vacuo, the

residue was purified with 30 mL ethyl acetate to get 2.09 g white solid of the title compound **3**. Colorless crystals suitable for single-crystal X-ray diffraction were obtained by slowly evaporating a solution of **3** in petroleum ether-ethanol (1:4 v/v) at room temperature. Yield 62.3%. m.p.: 239～240 °C. $[\alpha]_D^{20}$ = –8.37 (c = 0.01 g/mL, C_2H_5OH). Analysis calculated (%) for $C_{19}H_{24}ClNO·H_2O$: C, 67.94; H, 7.80; N, 4.17. Found (%): C, 67.81; H, 7.69; N, 4.47. IR (KBr, cm^{-1}) *v*: 3296.9 (O–H, stretching), 2927.6 (C–H, stretching), 2506.3 (N^+–H, stretching), 1458.0 cm^{-1} (Ar, stretching); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.74～1.78 (m, 2H, CH_2, piperidine), 2.37～2.49 (m, 2H, CH_2, piperidine), 3.17～3.24 (m, 4H, N–CH_2, piperidine), 3.25～3.17 (t, 2H, Ph–CH_2), 3.22～3.40 (s, 2H, CH_2), 5.43 (s, 1H, OH), 7.23～7.65 (m, 10H, Ar–H), 10.77 (s, 1H, N^+–H).

2. 3 Crystal data and structure determination

A colorless crystal of the title compound **3** with dimensions of 0.23mm × 0.20 mm × 0.10mm was mounted on a glass fiber in a random orientation. The data were collected by a BRUKER SMART 1000 CCD diffractometer equipped with a graphite-monochromatic Mo*Kα* radiation (λ = 0.71073 Å) by using a φ-ω scan mode in the range of 2.11≤θ≤ 25.99° (–10≤*h*≤10, –13≤*k*≤12, –23≤*l*≤23) at 298(2) K. A total of 16045 reflections were collected with 3627 unique ones (R_{int} = 0.0835), of which 3157 with $I > 2\sigma(I)$ were considered as observed and used in the succeeding refinements. Empirical absorption correction was applied. The structure was solved by direct methods and expanded by using difference Fourier techniques with SHELXS-97[15]. All of the non-hydrogen atoms were located with successive difference Fourier syntheses. The structure was refined by full-matrix least-squares method on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were theoretically added. The final R = 0.0420, wR = 0.1035 ($w = 1/[\sigma^2(F_o^2) + (0.0664P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$), Flack factor = -0.20(6), S = 0.974, $(\Delta/\sigma)_{max}$ = 0.000, $(\Delta\rho)_{max}$ = 0.324 and $(\Delta\rho)_{min}$ = -0.177 e/Å^3. The structural graphics was drawn with SHELXTL-97 software package.

2. 4 Biological activity test

The biological activity of the title compound was evaluated according to the standardized MTT experiments[15] of Zooblast-molecular biology laboratory of Shanghai Normal University in China. Human leucocythemia K562 cells were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) in a humidified atmosphere with 5% CO_2 at 37 °C. The preliminary growth inhibition test results showed that the compound has good inhibitory activity of about 86.67% against K562 cells in higher concentration (100 μg/mL).

3 RESULTS AND DISCUSSION

The ^{1}H NMR, IR and elemental analysis for the product are in good agreement with the title compound.

The selected bond distances are in Table 1, the bond angles in Table 2, and hydrogen bonding parameters in Table 3.

Table 1. Selected Bond Distances (Å)

Bond	Dist.	Bond	Dist.	Bond	Dist.
C(1)–C(2)	1.376(3)	C(9)–C(10)	1.503(2)	C(14)–C(19)	1.381(3)
C(1)–C(6)	1.375(3)	C(9)–C(11)	1.533(2)	C(15)–C(16)	1.393(3)
C(1)–C(7)	1.514(3)	C(10)–N(1)	1.497(2)	C(16)–C(17)	1.346(3)
C(2)–C(3)	1.391(3)	C(11)–O(1)	1.4246(19)	C(17)–C(18)	1.376(4)
C(3)–C(4)	1.368(4)	C(11)–C(14)	1.527(2)	C(18)–C(19)	1.383(3)
C(4)–C(5)	1.359(4)	C(11)–C(12)	1.530(2)	C(14)–C(15)	1.378(2)
C(5)–C(6)	1.387(3)	C(12)–C(13)	1.522(3)	C(8)–N(1)	1.503(2)
C(7)–C(8)	1.506(3)	C(13)–N(1)	1.493(2)		

Table 2. Selected Bond Angles (º)

Angle	(º)	Angle	(º)	Angle	(º)
C(2)–C(1)–C(6)	118.5(2)	C(8)–C(7)–C(1)	109.93(16)	C(14)–C(11)–C(9)	109.45(14)
C(2)–C(1)–C(7)	121.1(2)	N(1)–C(8)–C(7)	113.43(15)	C(12)–C(11)–C(9)	108.76(13)
C(6)–C(1)–C(7)	120.4(2)	C(10)–C(9)–C(11)	112.81(13)	C(13)–C(12)–C(11)	112.90(14)
C(1)–C(2)–C(3)	120.6(2)	N(1)–C(10)–C(9)	110.37(13)	N(1)–C(13)–C(12)	110.54(14)
C(4)–C(3)–C(2)	120.2(2)	O(1)–C(11)–C(14)	111.56(14)	C(15)–C(14)–C(19)	117.47(17)
C(5)–C(4)–C(3)	119.4(2)	O(1)–C(11)–C(12)	105.56(13)	C(15)–C(14)–C(11)	121.86(16)
C(4)–C(5)–C(6)	120.7(3)	C(14)–C(11)–C(12)	111.49(13)	C(19)–C(14)–C(11)	120.59(16)
C(1)–C(6)–C(5)	120.6(2)	O(1)–C(11)–C(9)	109.93(13)	C(14)–C(15)–C(16)	120.9(2)

Table 3. Hydrogen Bonds for the Title Compound (Å and °)

D–H···A	D–H	H···A	D···A	D–H···A
O(1)–H(1B)···O(2) [i]	0.812(16)	1.961(17)	2.734(2)	159(2)
C(10)–H(10B)···O(1) [ii]	0.97	2.30	3.254(2)	167.0
O(2)–H(2B)···Cl(1) [iii]	0.818(18)	2.495(18)	3.306(2)	171(4)
N(1)–H(1A)···Cl(1)	0.881(14)	2.216(15)	3.0947(16)	175.1(18)
O(2)–H(2A)···Cl(1)	0.826(18)	2.472(19)	3.297(2)	177(4)

(i) x+1, y, z; (ii) –x+2, y+1/2, –z+1/2; (iii) –x+1, y–1/2, –z+1/2

An ORTEP view of the title molecule with atomic numbering scheme is shown in Fig. 1, and its packing diagram in Fig. 2.

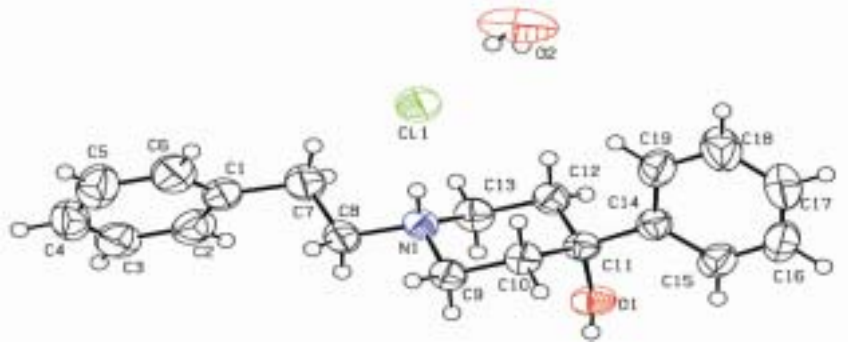


Fig. 1. Molecular structure of the title compound

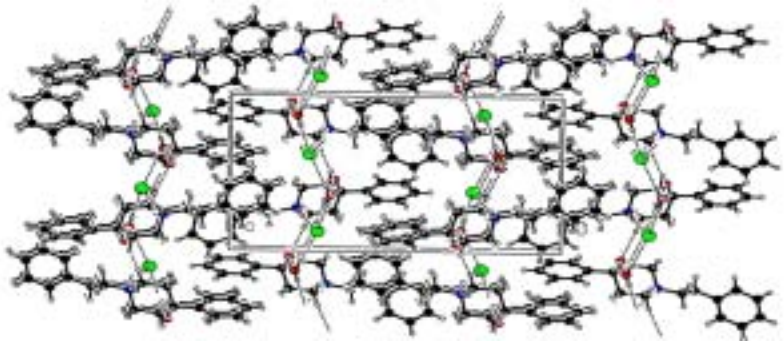


Fig. 2. Packing diagram viewed down the *b* axis

As shown in Table 1 and Fig. 1, the title compound *N*-phenethyl-4-hydroxy-4-phenyl piperidine hydrochloride contains a piperidine ring (N(1)/C(9)～C(13)) and two benzene rings (C(1)～C(6)) and (C(14)～C(19)). The molecule is nonplanar and the piperidine exhibits a chair conformation. The dihedral angles made by the piperidine ring with two benzene rings are 84.8(6) and 62.5(7)°, and that

between two benzene rings is 42.3(9)°. The axial oxygen O(1) does not experience a repulsion with the axial nitrogen lone pair electrons as provided by the opening of the following bond angles: N(1)-C(9)C(10) (110.37(13)°) and N(1)C(13)C(12) (110.54(14)°), especially 105.56(13)° for O(1)-C(11)C(12)[16]. In addition, the nitrogen lone pair electrons could cause a slight change of C(9)– C(10) and C(13)–C(12), as provided by the com- parison of bond distances (1.503(2) and 1.527(2) Å) with typical C–C single bond distance of 1.53 Å. Similarly, due to the existence of hydroxyl, the C(11)–C(14) bond distance (1.527(2) Å) is slightly longer than the normal value of 1.51 Å. The bond distance of C(8)–N(1) (1.503(2) Å), however, is essentially the same for that (1.50 Å) of C–N[17, 18].

Molecular assembly in a crystal is predominantly governed by intermolecular force, conventionally described by strong and directional O–H···O and O–H···Cl hydrogen bonds involving water molecules. In the asymmetric unit, the water molecule is linked to piperidine derivatives through O(2)–H(2)···Cl(1) hydrogen bond. Besides, in the crystal packing (Fig. 2), atoms O(1B) and O(2B) in the molecule at (*x*, *y*, *z*) act as hydrogen-bond donors to atoms O(2) and Cl(1) in the molecule at (*x*+1, *y*, *z*) and (–*x*+1, *y*–1/2, –*z*+1/2), thus forming O(1)–H(1B)···O(2) and O(2)–H(2B)···Cl(1) hydrogen bonds. Screw-related molecules are linked by these hydrogen bonds to form chains along the *b* axis. Meanwhile, intramolecular C(10)–H(10B)···O(1) hydrogen bond, which results in the formation of a nine-membered ring stabilizing the stretch of chains along axis *b*, is also observed in the crystal structure.

The water H atoms were located in a difference Fourier map and their parents were refined with O–H and H···H distances restrained to (0.81 or 0.83) and 1.35 Å, respectively. All other H atoms are placed in the calculated positions and included in the refinement in the riding model approximation (N–H = 0.88 Å, C–H = 0.93 or 0.97 Å and U_{iso}(H) = 1.2 U_{eq}(C, N)).

The preliminary antitumor activity tests indicated that the title compound has good effect (about 86.6%) of the cellular growth inhibition to K562 cells in higher concentration (100 μg/mL) and has potential bioactivity of anti-leukemia.

REFERENCES

(1) Jones, T. H.; Blum, M. S.; Robertson, H. G. *J. Nat. Prod.* **1990**, 53, 429–435.

(2) Heringa, M. *Int. J. Clin. Pharmacol. Ther.* **2003**, 41, 331–345.

(3) Traub, Y. M.; Redmond, D. P.; Rosenfeld, J. B.; McDonald Jr, R. H.; Shapiro, A. P. *Israel J. Med. Sci.* **1975**, 11, 991–998.

(4) Martín-Islán, A. P.; Martín-Ramos, D.; Sainz-Díaz, C. I. *J. Pharm. Sci.* **2008**, 97, 815–830.

(5) Bovill, J. G.; Sebel, P. S.; Stanley, T. H. *Anesthesiology* **1984**, 61, 731–755.

(6) Stanley, T. S. *Anaesth. Intensive Care.* **1987**, 15, 38–59.

(7) Brocks, D. R. *J. Pharm. Pharm. Sci.* **1999**, 2, 39–46.

(8) Nishiyama, K.; Mizuno, T.; Sakuta, M. Kurisaki, H. *Adv. Neurol.* **1993**, 60, 479–483.

(9) Weintraub, P. M.; Sabol, J. S.; Kane, J. M. Borcherding D. R. *Tetrahedron* **2003**, 59, 2953–2989.

(10) Dai, D. M.; Weng, L. L. *West China Journal of Pharmaceutical Sciences* **2007**, 22, 626–629.

(11) Zhang, L. L.; Su, Y. P.; Liu, X. H. *Acta Academiae Medicinae Militaris Tertiae* **2006**, 28, 1393–1396.

(12) Xie, Q.; Yang, L.; Weng, L. L. *West China Journal of Pharmaceutical Sciences* **2006**, 21, 164–166.

(13) Jiang, Z. L.; Wang, S. Y.; Duan, H. *Chem. World* **2004**, 9, 484–486.

(14) Sheldrick G. M. *SHELXL97, Program for the Refinement of Crystal Structure*, University of Göttingen, Germany **1997**.

(15) Hansen, M. B.; Nielsen, S. E.; Berg, K. *J. Immunol Methods* **1989**, 119, 203–210.

(16) Dapporto, P.; Guerri, A.; Paoli, P.; Rossi, P.; Altamura, M. *J. Mol. Struc. (Theochem.)* **2002**, 617, 189–199.

(17) Dega-Szafran, Z.; Dulewicz, E.; Szafran, M.; Thaimattam, R.; Jaskolski, M. *J. Mol. Struc.* **2007**, 828, 19–24.

(18) Zhou, B. H.; Chen, Y. F.; Yin, G. D.; Wu, A. X. *Chinese J. Struct. Chem.* **2006**, 25, 127–130.