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Synthesis and Structural Characterization of 2-(Hydroxyethoxy Substituted)phenyl Benzimidazoles

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In this paper, using *o*-phenylendiamine, hydroxyl substituted benzaldehyde and chlorohydrin as starting materials, four 2-(hydroxyethoxy substituted)phenyl benzimidazoles were synthesized by two different routes. In route I, the hydroxyl substituted benzaldehyde firstly reacted with *o*-phenylendiamine to get the intermediates 2-(hydroxyl substituted)phenyl benzimidazoles which then were used to synthesize the final products by the *o*-hydroxyethylation reaction with chlorohydrin. In route II, the hydroxyethoxy substituted benzaldehyde was firstly synthesized through the *o*-hydroxyethylation reaction and then reacted with *o*-phenylendiamine. Results show that route I is suitable only for the target compounds in which hydroxyethoxy group is located in *para*- and *meta*-position of benzimidazole in the benzene ring. For the synthesis of 2-(*o*-hydroxyethoxy)phenyl benzimidazole, route II is the only choice because of its strong steric hindrance. The structures of the four new compounds were characterized and confirmed by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and single-crystal X-ray diffraction analysis.

Keywords: Benzimidazole, Hydroxyl, Hydroxyethylation, Crystal structure.

INTRODUCTION

Benzimidazole derivatives which contain two nitrogen atoms are applied in biochemistry and pharmacology because of their positive biological and physiological activities[1-4], *e.g.* antimicrobial[5], anticancer[6], antiviral[7], insecticide[8], anti-inflammatory[9], herbicide[10], antiphlogistic, antipyretic, analgesic, spasmolytic[11]. With special structure and activity, benzimidazole derivatives have been broadly studied in recent decades[12-14].

In this article, four novel 2-(hydroxyethoxy substituted) phenyl benzimidazoles with hydroxyl groups, which can bring in other active groups through esterification are reported, provides a feasible method for developing novel pharmic benzimidazole derivatives. Based on the difference of relative position between hydroxyethoxy and benzimidazole in target product, two synthetic routes were adopted (Fig. 1) and four 2-(hydroxyethoxy-substituted)phenyl benzimidazoles were obtained and their structures were characterized by Mass spectra, IR, ^{1}H NMR, ^{13}C NMR and elementary analysis. In order to obtain information about the stereochemistry of the molecules and to confirm the assigned structure, X-ray analyses were also undertaken.

EXPERIMENTAL

All materials were commercially purchased and used without further purification. Melting points were determined on a Shanghai Zhongguang WRS-2 melting point apparatus and uncorrected. IR spectra (4000-400 cm^{-1}) were recorded on a MAGNA.IR 506 Model FT-IR spectrometer (KBr pellets). ^{1}H NMR and ^{13}C NMR spectra were scanned on a Bruker Avance AVII-600 Model spectrometer using DMSO-d_6 as solvent. Chemical shifts were reported as δ (ppm) relative to TMS as internal standard. Mass spectra were measured on a GCMS-QP2010 Plus Model GC-MS spectrometer. Measurement of the crystal was carried out on an Xcalibur E Model CCD X-ray single crystal diffractometer. Elemental analyses (C, H, N) were performed on a Carlo-Erba 1106 Model analyzer.

Synthesis of 2-(hydroxyl substituted)phenyl benzimidazole intermediates (1a-1c): As the route 1 in Fig. 1, the hydroxyl benzaldehyde derivative (36 mmol) dissolved in 50 mL of ethanol was mixed by sodium bisulfate (36 mmol) and the mixture was stirred for 12 h at room temperature. In which *o*-phenylenediamine (36 mmol) dissolved in 150 mL of DMF was added with 140 °C in a oil bath for another 2 h of reaction. The product was poured into 3 L of ice-cooled water and the solid mass separated out was filtered, dried and crystallized from ethanol. 2-(*p*-Hydroxyl)phenyl benzimidazole (**1a**), 2-(*m*-hydroxyl)phenyl benzimidazole (**1b**) and 2-(3'-methoxyl-4'-hydroxyl)phenyl benzimidazole (**1c**) were obtained with melting points: 287.2-287.9 °C [278-279 °C][15], 285.0-286.2 °C [280-282 °C][16], 225.2-226.5 °C [224.7-225.4 °C][17], respectively.

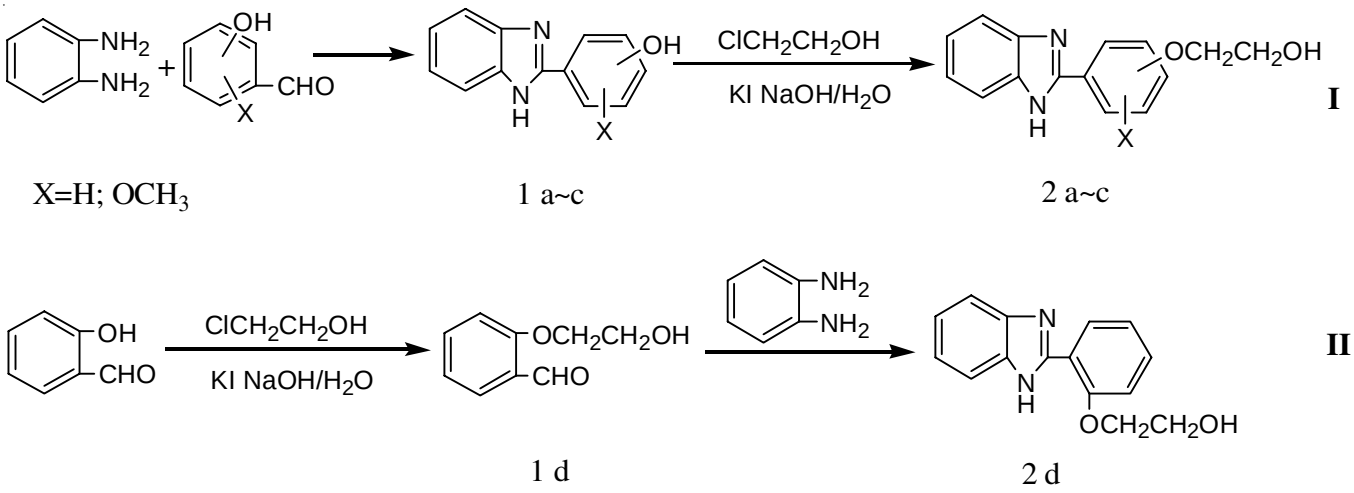

Fig. 1. Synthetic routes for 2-(hydroxyethoxy substituted)phenyl benzimidazoles

Synthesis of 2-(hydroxyethoxy substituted)phenyl benzimidazoles (2a-2c): 2-(Hydroxyl substituted)phenyl benzimidazole intermediate (7.5 mmol) and potassium iodide (0.45 mmol) were dissolved in the presence of NaOH (15 mmol) solution (15 mL). In which chlorohydrin (37.5 mmol) was added with 8-10 drops per min at 80 °C. The pH was kept at 9 adjusted by 50 % NaOH solution for 3 h. The product was poured into 40 mL of cold deionized water and solid mass separated out was filtered, dried and crystallized from ethanol.

2-(*p*-Hydroxyethoxy)phenyl benzimidazole (2a): Yield: 69.8 %. m.p.: 210.2-210.4 °C. Anal. Calcd (%) for $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found (%): C, 71.29; H, 6.39; N, 11.10. IR (KBr, ν_{max}, cm^{-1}): 3204.24 (υ_{OH}), 2926.15, 2868.24 (υ_{CH_2}), 1614.71 ($\upsilon_{C=N}$), 1497.20, 1479.05, 1451.27, 1436.67 ($\upsilon_{benzene\ C=C}$), 1397.65 (δ_{CH_2}), 1369.45, 1316.95 (υ_{C-N}), 1250.73 (υ_{Ar-O}), 1080.29, 1058.14 (υ_{C-O}), 837.28, 743.04 (δ_{Ar-H}). ^{1}H NMR (600 MHz, DMSO-d_6), δ_{ppm}: 3.76 (t, 2H, -CH_2O-), 4.09 (t, 2H, -OCH_2-), 4.94 (s, 1H, -OH), 7.12 (d, 2H, Ph), 7.18 (m, 2H, Ph), 7.56 (s, 2H, Ph), 8.10 (d, 2H, Ph), 12.75 (s, 1H, -NH-). ^{13}C NMR (600 MHz, DMSO-d_6), δ_{ppm}: 60.02 (-CH_2OH), 70.21 (-OCH_2-), 115.35 (Ph), 122.25 (Ph), 123.08 (Ph), 128.50 (Ph), 151.85 (Ph), 160.57 (-C=N-).

2-(*m*-Hydroxyethoxy)phenyl benzimidazole (2b): Yield: 71.9 %. m.p.: 203.0-204.6 °C. Anal. Calcd (%) for $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found (%): C, 70.99; H, 5.89; N, 11.14. IR (KBr, ν_{max}, cm^{-1}): 3204.37 (υ_{OH}), 2926.37, 2868.49 (υ_{CH_2}), 1613.89 ($\upsilon_{C=N}$), 1497.38, 1479.20, 1451.68, 1436.77 ($\upsilon_{benzene\ C=C}$), 1397.66 (δ_{CH_2}), 1369.60, 1316.81 (υ_{C-N}), 1251.25 (υ_{Ar-O}), 1080.65, 1057.93 (υ_{C-O}), 837.23, 743.24 (δ_{Ar-H}). ^{1}H NMR (400 MHz, DMSO-d_6), δ_{ppm}: 3.80 (q, 2H, -CH_2O-), 4.12 (t, 2H, -OCH_2-), 4.96 (t, 1H, -OH), 7.09 (d, 1H, Ph), 7.23 (m, 2H, Ph), 7.46 (t, 1H, Ph), 7.62 (s, 2H, Ph), 7.78 (t, 2H, Ph), 12.91 (s, 1H, -NH-). ^{13}C NMR (400 MHz, DMSO-d_6), δ_{ppm}: 59.56 (-CH_2OH), 69.66 (-OCH_2-), 111.89 (Ph), 116.42 (Ph), 118.72 (Ph), 122.09 (Ph), 130.07 (Ph), 131.42 (Ph), 135.03 (Ph), 143.88 (Ph), 151.09 (Ph), 159.06 (-C=N).

2-(3'-Methoxyl-4'- hydroxyethoxy)phenyl benzimidazole (2c): Yield**:** 71.9 %. m.p.: 217.8-218.4 °C. Anal. Calcd (%) for $C_{16}H_{16}N_2O_3$: C, 67.61; H, 5.63; N, 9.86. Found (%): C, 67.94; H, 6.11; N, 10.02. IR (KBr, ν_{max}, cm^{-1}): 3201.17 (υ_{OH}), 2946.30, 2862.03 (υ_{CH_2}), 2827.39 (υ_{CH_3}), 1607.30 ($\upsilon_{C=N}$), 1400.63, 1477.93, 1451.68, 1436.51 ($\upsilon_{benzene\ C=C}$), 1397.80 (δ_{CH_2}), 1362.36, 1325.59 (υ_{C-N}), 1265.33, 1242.94 (υ_{Ar-O}), 1087.94, 1064.13 (υ_{C-O}), 869.90, 736.66 (δ_{Ar-H}). ^{1}H NMR (400 MHz, DMSO-d_6), δ_{ppm}: 3.79 (q, 2H, -CH_2O-), 3.91 (s, 3H, -OCH_3), 4.08 (t, 2H, -OCH_2-), 4.97 (t, 1H, -OH), 7.13 (d, 1H, Ph), 7.20 (m, 2H, Ph), 7.59 (s, 2H, Ph), 7.75 (d, 1H, Ph), 7.81 (s, 1H, Ph), 12.80 (s, 1H, -NH-). ^{13}C NMR (400 MHz, DMSO-d_6), δ_{ppm}: 55.51 (-OCH_3), 59.53 (-CH_2OH), 70.20 (-OCH_2-), 109.90 (Ph), 112.87 (Ph), 119.27 (Ph), 121.78 (Ph), 122.74 (Ph), 149.03 (Ph), 149.69 (Ph), 151.48 (-C=N).

Synthesis of *o*-hydroxyethoxy benzaldehyde (1d): *o*-Hydroxybenzaldehyde (0.1 mol) and potassium iodide (0.006 mol) were dissolved in sodium hydroxide (0.2 mol) solution (15 mL). In which chlorohydrin (0.5 mol) was added with 8-10 drops per min at 80 °C. The pH was kept at 9 adjusted by 50 % sodium hydroxide solution for 3 h. The product was cooled to room temperature. The substratum was collected, washed and dried.

Synthesis of 2-(*o*-hydroxyethoxy) phenyl benzimidazole (2d): *o*-Hydroxyethoxy benzaldehyde (**1d**, 36 mmol) dissolved in 50 mL of ethanol was mixed by sodium bisulfate (36 mmol) and the mixture was stirred for 12 h at room temperature. In which *o*-phenylenediamine (36 mmol) dissolved in 150 mL of DMF was added at 140 °C in a oil bath for another 2 h of reaction. The product was poured into 3 L of chilled water and the solid mass separated out was filtered, dried and crystallized from ethanol.

Yield: 50.3 %. m.p.: 162.8-163.7 °C. Anal. Calculated (%) for $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found (%): C, 71.79; H, 6.21; N, 11.24. R (KBr, ν_{max}, cm^{-1}): 3147.24 (υ_{OH}), 2936.66, 2879.64 (υ_{CH_2}), 1621.03 ($\upsilon_{C=N}$), 1530.67, 1488.67, 1473.44, 1445.24 ($\upsilon_{benzene\ C=C}$), 1403.21 (δ_{CH_2}), 1369.81, 1313.68 (υ_{C-N}), 1244.94 (υ_{Ar-O}), 1075.96, 1042.05 (υ_{C-O}), 793.36, 743.97 (δ_{Ar-H}). ^{1}H NMR (400 MHz, DMSO-d_6), δ_{ppm}: 3.93 (t, 2H, -CH_2O-), 4.32 (t, 2H, -OCH_2-), 5.70 (s, 1H, -OH), 7.16 (t, 1H, Ph), 7.23 (m, 2H, Ph), 7.31 (d, 1H, Ph), 7.47 (t, 1H, Ph), 7.63 (s, 2H, Ph), 8.31 (d, 1H, Ph), 12.23 (s, 1H, -NH-). ^{13}C NMR (400 MHz, DMSO-d_6), δ_{ppm}: 59.39 (-CH_2OH), 71.00 (-OCH_2-), 114.81 (Ph), 119.04 (Ph), 121.58 (Ph), 121.87 (Ph), 129.70 (Ph), 131.15 (Ph), 149.14 (Ph), 156.34 (-C=N).

Determination of crystal structure : Single crystals of **1a**, **2a**, **2c** and **2d** suitable for data collection were selected and data were collected on an Xcalibur, Eos diffractometer equipped with a graphite-monochromatic MoK$_\alpha$ radiation. Details of crystal data, data collection and refinement are given in Table-1 and 4. The structures were solved by direct methods using SHELXS and refined by full-matrix least-squares methods on F^2 using SHELXL. All non-hydrogen atoms were refined with anisotropic parameters. Hydrogen atoms bonded to carbon were refined with isotropic parameters.

RESULTS AND DISCUSSION

All the compounds **1a**, **2a**, **2c** and **2d** were verified by IR, Mass spectra, ^{1}H NMR, ^{13}C NMR and elemental analyses.

Structural description of compound 1a: In the synthesis route I, three 2-(hydroxyl) phenyl benzimidazole intermediates (**1a**, **1b**, **1c**) were synthesised by using hydroxyl benzaldehyde derivatives and *o*-phenylenediamine. The crystal of 2-(*p*-hydroxyl)phenyl benzimidazole (**1a**) was obtained. The crystal molecular structure, crystal data, structure refinement details, selected bond lengths and angles, hydrogen bond lengths and bond angles for **1a** are shown in Fig. 2, Tables 1, 2 and 3, respectively. Double-bond N1-C7 (1.3265(17)Å) is shorter than single-bond N2-C7 (1.3597(18)Å). The bond angle of C7-N2-C2 (108.28(12)°) is larger than that of C1-N1-C7, which is in accordance with the literature[15]. The bond angle on N1 atom sp^2 hybridized is condensed to 105.64(12)°. In addition, there is a strong hydrogen bond between N1 and the H1 of hydroxyl in another **1a** molecule, O1-H1...N1 (1.83 Å).

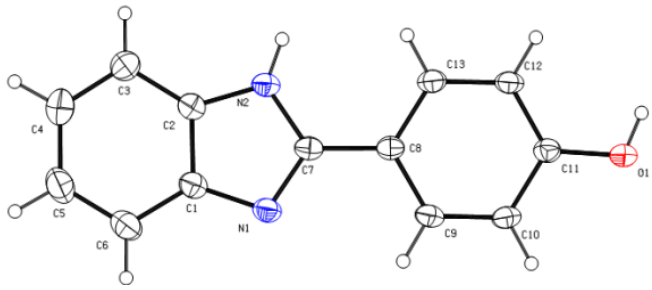

Fig. 2. Crystal molecular structure of 2-(*p*-hydroxyl)phenyl benzimidazole (**1a**)

Meanwhile, another hydrogen bond (N2-H2...O1, 2.06 Å) exists between O1 and the H2 of hydroxyl in another molecule.

Structural description of compound 2a, 2c and 2d: Three target compounds (**2a**, **2b**, **2c**) were synthesised by route I. However, compound **2d** can not be hydroxyethylated through this method because of the steric hindrance at *ortho*-position. Therefore, route II was adopted to synthesize **2d** using *o*-phenylenediamine and *o*-hydroxyethoxy benzaldehyde hydroxyethylated by *o*-hydroxybenzaldehyde and chlorohydrin. The result shows that this method is viable to synthesize **2d** successfully.

The crystal molecular structure, crystal data, structure refinement details, selected bond lengths and angles, hydrogen bond lengths and bond angles for **2a**, **2c** and **2d** are shown in Figs. 3, 4, and 5, Tables 4, 5 and 6, respectively. The crystal molecular structure of **2a** belongs to orthorhombic system, which contains one ethanol molecule (Fig. 3). The crystal molecular structure of **2d** belongs to monoclinic system, which

TABLE-1
CRYSTAL DATA AND STRUCTURE REFINEMENT DETAILS FOR 2-(*p* -HYDROXYL)PHENYL BENZIMIDAZOLE (**1a**)

Empirical formula	$C_{13}H_{10}N_2O$	Formula weight	210.23
Temperature (K)	293.15	Crystal system	Monoclinic
Space group	$P2_1/n$	a/Å, b/Å, c/Å	7.1685(3), 15.2342(6), 9.8163(4)
α/°, β/°, γ/°	90.00, 90.606(4), 90.00	Volume/Å^3	1071.94(7)
Z, ρ_{calc} (mg mm^{-3})	4, 1.303	μ/mm^{-1}, F(000)	0.085, 440.0
Crystal size (mm^3)	28.00 × 0.32 × 0.25	2θ Range for data collection	6.28 to 52.74°
Index ranges	-8 ≤ h ≤ 8, -19 ≤ k ≤ 19, -12 ≤ l ≤ 9	Reflections collected	4935
Independent reflections (R_{int})	2054 (0.0180)	Data/restraints/parameters	2054/0/146
Observed reflections	1541	Absorption correction	Multi-scan
Max. and Min. transmission	1.0 and 0.99519	Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.044	Final R indexes [I>2σ (I)]	R_1 = 0.0414, wR_2 = 0.0981
Final R indexes [all data]	R_1 = 0.0592, wR_2 = 0.1097	Largest diff. peak/hole/e Å^{-3}	0.12/-0.21

TABLE-2
SELECTED BOND LENGTHS (Å) AND ANGLES (°) FOR 2-(*p*-HYDROXYL)PHENYL BENZIMIDAZOLE (**1a**)

Bond	Dist.	Bond	Dist.	Bond	Dist.
O1-C11	1.3619(18)	N2-C2	1.3783(19)	N2-C7	1.3597(18)
N1-C1	1.392(2)	N1-C7	1.3265(17)	C7-C8	1.457(2)
Angle	(°)	Angle	(°)	Angle	(°)
C7-N1-C1	105.64(12)	N1-C7-N2	111.35(13)	O1-C11-C10	118.03(13)
C7-N2-C2	108.28(12)	N1-C7-C8	124.41(13)	O1-C11-C12	123.07(13)

TABLE-3
HYDROGEN BOND LENGTHS (Å) AND BOND ANGLES (°) FOR 2-(*p*-HYDROXYL)PHENYL BENZIMIDAZOLE (**1a**)

D-H ... A	D-H(Å)	H…A(Å)	D…A(Å)	<(DHA)(°)
O1-H1...N1[1]	0.82	1.83	2.6493(16)	174.0
N2-H2...O1[2]	0.86	2.06	2.8528(15)	153.7

Symmetry code: [1]-1/2 + X, 3/2-Y, -1/2 + Z; [2]-1/2 + X, 3/2-Y, 1/2 + Z

TABLE-4
CRYSTAL DATA AND STRUCTURE REFINEMENT DETAILS FOR
2-(HYDROXYETHOXY SUBSTITUTED)PHENYL BENZIMIDAZOLES

Compound	Compound **2a**	Compound **2d**	Compound **2c**
Empirical formula	$C_{17}H_{19}N_2O_3$	$C_{15}H_{14}N_2O_2$	$C_{16}H_{16}N_2O_3$
Formula weight (g/mol)	299.34	254.28	284.31
Temperature (K), Wavelength (Å)	143(1), 0.7107	293.15, 0.7107	143.00(10), 0.7107
Crystal system, Space group	Orthorhombic, P*bca*	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/c$
a/Å, b/Å, c/Å	9.0642(3), 17.2613(5) , 20.0602(6)	14.8860(5), 12.0542(4), 14.9127(5)	14.0226(8), 7.2522(4), 14.7512(7)
α/(°), β/(°), γ/(°)	90.00, 90.00, 90.00	90.00, 104.267(4), 90.00	90.00, 112.440(7), 90.00
V/Å^3	3138.62(17)	2593.39(15)	1386.53(13)
Z, ρ_{calc} (mg/m^3), F(000)	8, 1.267, 1272.0	8, 1.303, 1072.0	4, 1.362, 600.0
μ(mm^{-1})	0.088	0.088	0.095
Crystal size (mm^3)	0.30 × 0.25 × 0.20	0.30 × 0.25 × 0.20	0.30 × 0.25 × 0.20
2θ range for data collection (°)	6.06 to 50	6.58 to 50	5.98 to 52.74
Index ranges	$-7 \le h \le 10$, $-19 \le k \le 20$, $-23 \le l \le 13$	$-17 \le h \le 17$, $-14 \le k \le 14$, $-16 \le l \le 17$	$-17 \le h \le 17$, $-8 \le k \le 9$, $-18 \le l \le 18$
Reflections collected	7943	19848	6037
Independent reflections (R_{int})	2761 (0.0238)	4551 (0.0258)	2822 (0.0232)
Observed reflections	2218	3362	2175
Absorption correction	Multi-scan	Multi-scan	Multi-scan
Max. and Min. transmission	1.0 and 0.99084	1.0 and 0.87622	1.0 and 0.93478
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2761/0/206	4551/0/356	2822/0/199
Goodness-of-fit on F^2	1.060	1.050	1.033
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0604$, $wR_2 = 0.1506$	$R_1 = 0.0422$, $wR_2 = 0.0965$	$R_1 = 0.0459$, $wR_2 = 0.0959$
Final R indexes (all data)	$R_1 = 0.0753$, $wR_2 = 0.1621$	$R_1 = 0.0635$, $wR_2 = 0.1084$	$R_1 = 0.0646$, $wR_2 = 0.1081$
Largest diff. peak/hole/e Å^{-3}	0.82/-0.89	0.34/-0.24	0.19/-0.27

TABLE-5
SELECTED BOND LENGTHS (Å) AND ANGLES (°)
FOR 2-(HYDROXYETHOXY SUBSTITUTED)PHENYL BENZIMIDAZOLES

Compound **2a**					
Bond	Dist.	Bond	Dist.	Bond	Dist.
O1-C11	1.366(3)	O1-C14	1.436(3)	O2-C15	1.423(3)
N1-C1	1.387(3)	N1-C7	1.325(3)	N2-C2	1.381(3)
N2-C7	1.364(3)	-	-	-	-
Angle	(°)	Angle	(°)	Angle	(°)
C11-O1-C14	117.9(2)	O1-C11-C10	115.1(2)	O1-C11-C12	125.1(2)
O1-C14-C15	107.8(2)	O2-C15-C14	112.0(2)	N1-C7-N2	112.5(2)
C7-N1-C1	105.3(2)	C7-N2-C2	107.1(2)	N1-C1-C2	109.7(2)
N1-C1-C6	130.1(2)	N2-C2-C1	105.5(2)	N2-C2-C3	132.2(2)
Compound **2d**					
Bond	Dist.	Bond	Dist.	Bond	Dist.
O1-C9	1.362(2)	O1-C14	1.435(2)	O2-C15	1.410(2)
O3-C24	1.366(2)	O3-C29	1.424(2)	O4-C30	1.412(2)
N1-C1	1.377(2)	N1-C7	1.364(2)	N2-C6	1.392(2)
N2-C7	1.323(2)	N3-C16	1.375(2)	N3-C22	1.361(2)
N2-C17	1.389(2)	N2-C22	1.327(2)	-	-
Angle	(°)	Angle	(°)	Angle	(°)
C9-O1-C14	119.58(15)	O1-C9-C8	116.14(15)	O1-C9-C10	123.75(17)
C24-O3-C29	119.58(14)	O3-C24-C23	115.86(15)	O3-C24-C25	123.32(15)
C7-N1-C1	108.01(15)	C7-N2-C6	105.41(14)	N2-C7-N1	111.58(15)
C22-N3-C16	107.90(15)	C22-N4-C17	105.14(14)	N4-C22-N3	111.86(15)
Compound **2c**					
Bond	Dist.	Bond	Dist.	Bond	Dist.
O1-C10	1.3648(19)	O1-C14	1.423(2)	O2-C11	1.3651(19)
O2-C15	1.433(2)	O3-C16	1.426(2)	N1-C1	1.396(2)
N1-C7	1.327(2)	N2-C2	1.384(2)	N2-C7	1.363(2)
Angle	(°)	Angle	(°)	Angle	(°)
C10-O1-C14	117.67(13)	C11-O2-C15	117.67(13)	O3-C16-C15	111.88(14)
O2-C11-C10	115.10(14)	O2-C11-C12	125.60(15)	N1-C7-N2	112.71(15)
C7-N1-C1	105.02(14)	C7-N2-C2	107.23(15)	N1-C1-C2	109.63(15)
N1-C1-C6	130.33(16)	N2-C2-C1	105.40(14)	N2-C2-C3	132.04(17)

TABLE-6
HYDROGEN BOND LENGTHS (Å) AND BOND ANGLES (°) FOR
2-(HYDROXYETHOXY SUBSTITUTED)PHENYL BENZIMIDAZOLES

D-H ... A	D-H(Å)	H…A(Å)	D…A(Å)	<(DHA)(°)
Compound **2a**				
O2-H2…O3[1]	0.840	1.851	2.679	168.17
O3-H3A…N1[2]	0.840	1.911	2.741	169.35
N2-H2A…O2[3]	0.876	1.910	2.781	172.29
Compound **2d**				
O4-H4…N2[1]	0.820	1.985	2.790	166.86
N3-H3…O3	0.844	2.204	2.666	114.47
N3-H3…O4	0.844	2.353	3.181	167.23
N1-H1…O1	0.889	2.168	2.678	115.86
N1H1…O2	0.889	2.261	3.124	163.63
O2H2…N4[2]	0.913	1.906	2.774	158.01
Compound **2c**				
O3-H3…N1[1]	0.898	1.925	2.786	159.92
N2-H2…O3[1]	0.922	1.943	2.850	167.80

Symmetry code: (#1for **2a**) [1][-x + 2, y-1/2, -z + 3/2], [2][x-1/2, y, -z + 3/2], [3][-x + 3/2, y + 1/2, z]; (#1 for **2d**)[1] [-x + 3/2, y-1/2, -z + 1/2], [2][-x + 2, -y + 1, -z]; (#1 for **2c**) [1][-x + 1, y-1/2, -z + 1/2]

contains two **2d** molecules (Fig. 4). Moreover, the crystal molecular structure of **2c** belongs to monoclinic system. In these three crystals, the planes between benzimidazole ring and the substituted benzene ring are not co-plane and the intersection angles are 19.73°(**2a**), 20.04°(**2d**), 13.02°(**2c**), respectively.

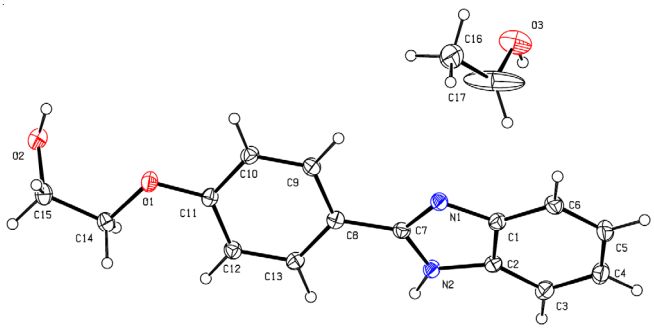

Fig. 3. Crystal molecular structure of 2-(*p*-hydroxyethoxy)phenyl benzimidazole (**2a**)

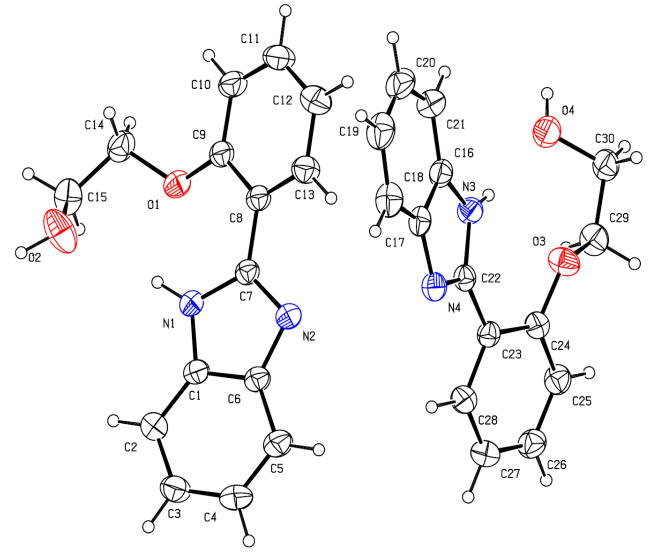

Fig. 4. Crystal molecular structure of 2-(*o*-hydroxyethoxy)phenyl benzimidazole (**2d**)

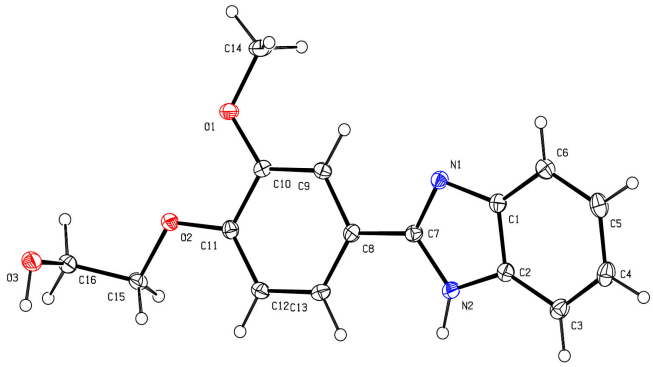

Fig. 5. Crystal molecular structure of 2-(3'-methoxyl-4'-hydroxyethoxy)-phenyl benzimidazole (**2c**)

There are a large mount of hydrogen bonds in the three crystal molecular structures, especially in **2d** as shown in Table-6. In the crystal molecular structure of **2a**, hydrogen bonds exist between the O3 atom of ethanol and the H2 atom in hydroxyl of **2a** (O2-H2...O3, 1.851 Å), between the H3 atom of ethanol and the N1 atom in imidazole ring (O3-H3A...N1, 1.911Å) and between the O2 atom in hydroxyl of **2a** and the H2 atom in the N2 atom of another **2a** (N2-H2A...O2, 1.910Å). As two **2a** molecules exist in the **2a** crystal molecular structure, a large quantity of hydrogen bonds happen on the two nitrogen atoms of imizole ring and the oxygen atom of hydroxyl. Meanwile, the hydrogen bonds in the crystal molecular structure of **2c** mainly appear on the two nitrogen atoms of imizole ring and the oxygen atom of hydroxyl, too.

Spectra analysis: Analogical IR, ^{1}H NMR, ^{13}C NMR spectra data results are presented for the four 2-(hydroxyethoxy substituted)phenyl benzimidazoles synthesized by two different routes. The spectral data of 2-(*m*-hydroxyethoxy)phenyl benzimidazoles (**2b**) are illustrated below. The stretching vibration peak of OH appears at 3204.37 cm^{-1}. The stretching vibration peaks of two -CH_2- come out at 2926.37 and 2868.49 cm^{-1}. The existence of *meta*-disubstituted benzene are indicated by the four peaks at 1497.38, 1479.20, 1451.68 and 1436.77 cm^{-1} of benzene carbon skeleton stretching vibration peaks and the peaks at 837.23 and 743.24 cm^{-1}. The structure of

aromatic oxide is proved by the presence of aryloxy bond stretching vibration peak at 1251.25 cm^{-1} and the peaks at 1080.65 and 1057.93 cm^{-1} of C-O bond.

From the ^1H NMR chemical shift data of **2b**, the resonance peaks of two H protons (-CH_2O-) appear at 3.80 ppm and the resonance peaks of two H protons (-OCH_2-) come out at 4.12 ppm. Meanwhile, the resonance peaks of H proton (-OH) are found at 4.96 ppm. A multiple resonance peaks at 7.09-7.78 ppm present the H protons in the two benzenes of **2b**. In addition, a single resonance peak at 12.91 ppm shows the H proton of N-H. In the ^{13}C NMR chemical shifts of **2b**, we can find that the carbon atom resonance peaks of -CH_2OH, -OCH_2- and C=N appear at 59.56, 69.66 and 159.06 ppm, respectively. Moreover, the carbon atom resonance peaks of benzene skeleton are found at 111.89-151.09 ppm. All of the spectra data above support the results of the four target products.

Conclusion

In this pater, two routes were adopted to synthesize four 2-(hydroxyethoxy substituted)phenyl benzimidazoles. In route I, the hydroxyl substituted benzaldehyde firstly reacted with *o*-phenylendiamine to gain the intermediates -2-(hydroxyl substituted)phenyl benzimidazoles which then were used to synthesize the final products through the *o*-hydroxyethylation reaction with chlorohydrin. This synthesis route is suitable only for the target compounds in which hydroxyethoxy group is located in *para*- and *meta*-position of benzimidazole in the benzene ring. As to the *ortho*-substituted phenyl benzimidazole, route II is viable, that is the hydroxyethoxy substituted benzaldehyde is firstly synthesized by the *o*-hydroxyethylation reaction and then reacts with *o*-phenylendiamine, which can avoid the steric hindrance. The structures of the four new compounds were characterized and proved by elemental analysis (EA), IR, Mass spectra, ^1H NMR, ^{13}C NMR and the single-crystal X-ray diffraction analysis.

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REFERENCES

1. Y. Wang, Q.F. Zhou, G.W. Lin, L.L. Di and T. Lu, *Chin. J. Struct. Chem*., **30**, 97 (2011).
2. L. Gou, H.X. Zhang, X.Y. Fan, D.L. Li and L. Li, *Chin. J. Struct. Chem*., **29**, 1394 (2010).
3. C.G. Sun, M.H. Zeng, K.Z. Xu and J.R. Song, *Chin. J. Struct. Chem*., **31**, 1662 (2012).
4. D.F. Qiu, Y.L. Li, H.W. Wang and Y.C. Guo, *Chin. J. Struct. Chem*., **29**, 811 (2010).
5. J. Hu, P. Wang, J.K. Wang and Y.H. Xu, *Chin. J. Struct. Chem*., **31**, 1745 (2012).
6. S.G. Liu, Z.L. Chen, K. Liang and X.L. Chen, *Chin. J. Struct. Chem*., **32**, 637 (2013).
7. F.F. Jian, F.L. Bei, X. Wang and L.D. Lu, *Chin. J. Struct. Chem*., **22**, 382 (2003).
8. Y.C. Guo, L.H. Zhuo, Y.Y. Zhao, X.Z. Yao and Q.Z. Huang, *Chin. J. Struct. Chem*., **27**, 1333 (2008).
9. M.H. Kim, J.S. Ryu and J.M. Hah, *Bioorg. Med. Chem. Lett*., **23**, 1639 (2013).
10. X.X. Ren, J.Y. Chen and X.Y. Le, *Chin. J. Chem*., **29**, 1380 (2011).
11. P. Vicini, M. Incerti, L. Amoretti, V. Ballabeni, M. Tognolini and E. Barocelli, *Farmaco*, **57**, 363 (2002).
12. Y.B. Bai, A.L. Zhang, J.J. Tang and J.-M. Gao, *J. Agric. Food Chem*., **61**, 2789 (2013).
13. S.H. Nile, B. Kumar and S.W. Park, *Chem. Biol. Drug Des*., **82**, 290 (2013).
14. E. Mentese, N. Karaali, F. Yilmaz, S. Ülker and B. Kahveci, *Arch. Pharmazie*, **346**, 556 (2013).
15. T. Nagai, Y. Fukushima, T. Kuroda, H. Shimizu, S. Sekiguchi and K. Matsui, *Bull. Chem. Soc. Jpn*., **46**, 2600 (1973).
16. M.A. Chari, D. Shobha, E.R. Kenawy, S.S. Al-Deyab, B.V.S. Reddy and A. Vinu, *Tetrahedron Lett*., **51**, 5195 (2010).
17. N.V. Gabriel, M.D. Hermenegilda, A.C. Francisco, L.R. Ismael, V.M. Rafael, M.M. Omar and E.S. Samuel, *Bioorg. Med. Chem. Lett*., **16**, 4169 (2006).