1D AND 2D NMR STUDIES OF 2–(2–(BENZYLOXY)–3–METHOXYPHENYL)–1*H*–BENZIMIDAZOLE

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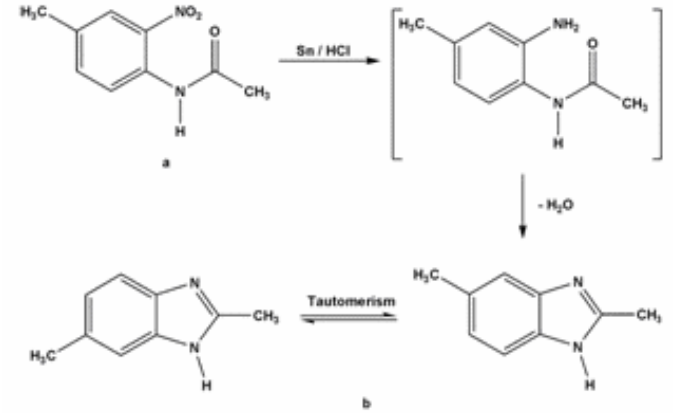
ABSTRACT

*The reaction of Benzyl o–vanillin **1** and o–phenylene diamine **2** in dichloromethane produced new benzimidazole, **3**. The complete assignments of 3 were made using 1D and 2D NMR including COSY, HMQC and HMBC NMR in $CDCl_3$ and acetone–d_6. The coupling constants J are reported in Hertz, and the differences in the peak splittings using both solvents are discussed.*

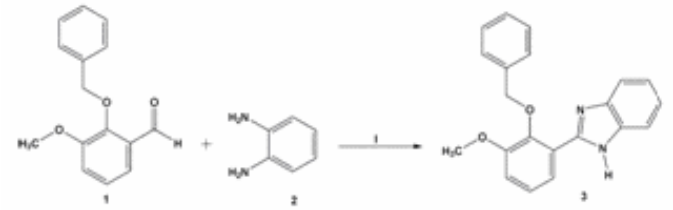
Keywords: *^{1}H NMR; ^{13}C NMR; 2D NMR; Benzimidazole.*

INTRODUCTION

Hobrecker prepared the first benzimidazole in 1872, when he reduced 2–nitro–4–methylacetanilide **a** to obtained the tautomers 2, 5 (or 2, 6)–dimethyl benzimidazole **b** (Scheme 1) [1-2]. Since benzimidazoles have a similar structure to purines, whose derivatives play important roles in biological systems, substituted benzimidazoles show interesting biological activities. Many benzimidazoles are pharmaceutical agents and are used widely in biological system applications [3-8]. Recently, some derivatives of benzimidazole were reported and used as antiviral [5-6], topoisomerase I inhibitors [9-11], antiproliferative [12], antiprotozoal activity of *Acanthamoeba castellanii* [13],



Scheme 1. First benzimidazole **b**, prepared by Hobrecker in 1872 [1].



Scheme 2. Synthesis of new benzimidazole **3**, I) DCM, $MgSO_4$, 2hr.

antibacterial [14-16], anthelmintics activity of *Trichinella spiralis* [17], anti–inflammatory against [18-19], anti–HIV [20-24] and also as anticancer [3-4, 25-30]. Meanwhile, phenolic and anisolic benzimidazole derivatives have been synthesized and evaluated for vasodilator and antihypertensive activity [30], while other alkyloxyaryl benzimidazole derivatives have been tested for the spasmolytic activity [31].

Recently, we synthesized and characterized 2–(2–(benzyloxy)–3–methoxyphenyl)–1*H*–benzimidazole **3** by FTIR, GC–MS, ^{1}H and ^{13}C NMR spectra from the reaction of benzyl *o*–vanillin **1** and *o*–phenylene diamine **2** in dichloromethane (DCM) (Scheme 2).

We also obtained the crystal of **3**, and its structure was determined and studied by X–ray crystallography [32-34]. In this work, the complete assignments of **3** were made using 1D and 2D NMR including APT, DEPT–135, COSY, HMQC and HMBC NMR in $CDCl_3$ and acetone–d_6. The coupling constants *J* were reported in Hertz and the differences in the peak splittings using both solvents were discussed.

EXPERIMENTAL SECTION

All NMR experiments were performed on Bruker Avance 400 Ultrashield^{TM} NMR for ^{1}H operating at 400.123 MHz, and Avance 300 NMR spectrometers for ^{13}C operating at 71.478 MHz in $CDCl_3$ and acetone–d_6 at 298 K using Bruker XWINNMR software equipped with a 5 mm BBI inverse gradient probe [35-36]. Chemical shifts were reported downfield in parts per million (ppm) from a tetramethylsilane (TMS) reference, and coupling constants (*J*) were measured in Hz. The concentration of solute molecule was 100 mg in 1.0 mL $CDCl_3$ or acetone–d_6.

RESULTS AND DISCUSSION

The new benzimidazole **3** was synthesized from the reaction of **1** and **2** in DCM as a solvent (Scheme

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2). The benzimidazole **3** was obtained as single crystals with melting point of 135–136 °C, (Fig 1 and 2) [15–17]. 1D ^{1}H and ^{13}C NMR along with 2D COSY, HMQC and HMBC experiments were performed to assign all proton and carbon chemical shifts. The splitting patterns for the aromatic protons of **3** were obtained from the spectra acquired using 400 MHz ^{1}H NMR. The ^{1}H and ^{13}C NMR chemical shift and coupling constants data in $CDCl_3$ and acetone–d_6 are listed in Table 1, while Table 2 shows the HMQC and HMBC signals of **3**. Figure 2 shows the chemical structure and the NMR numbering scheme of the new benzimidazole **3**.

^{1}H NMR

The ^{1}H NMR spectrum of **3** was obtained and shown in Figure 3. Proton H_6 displayed doublet of a doublet at δ = 8.16–8.14, (J = 8.03 and 1.49 Hz) in $CDCl_3$ and 8.03–8.01 ppm, (J = 7.03 and 2.50 Hz) in acetone–d_6 due to its coupling with H_5 and N–H.

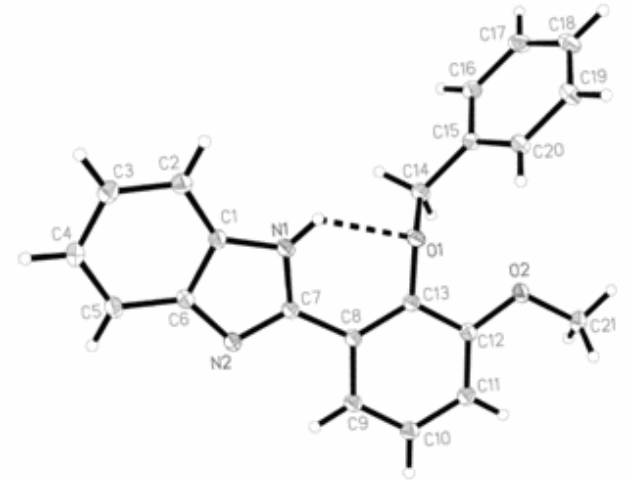

Fig 1. The crystal structure of benzimidazole **3**, showing 50% probability displacement ellipsoids and the atom–numbering scheme, the dashed line indicates an intramolecular hydrogen bond.

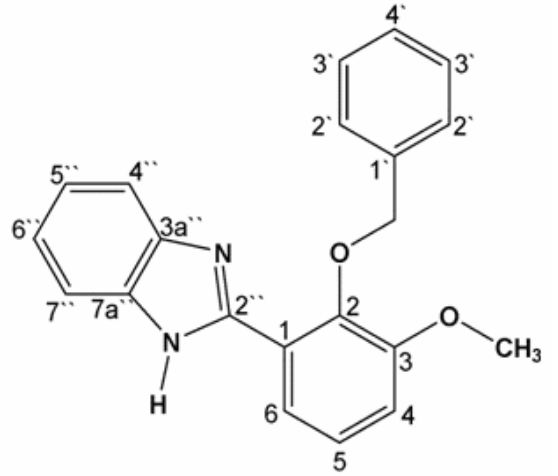

Fig 2. The chemical structure and the NMR numbering scheme of the benzimidazole **3**.

Table 1. ^{1}H and ^{13}C NMR chemical shifts and coupling constants of **3** in $CDCl_3$ and acetone–d_6

Atom No.	^{1}H NMR (ppm)			^{13}C NMR (ppm)		
	$CDCl_3$	J (Hz)	acetone–d_6	J (Hz)	$CDCl_3$	acetone–d_6
CH_3	4.01, *s*	–	3.99, *s*	–	56.49	56.85
CH_2	5.18, *s*	–	5.23, *s*	–	76.85	76.57
N–H	7.25, *d*	1.06	7.24, *s*	–	–	–
1	–	–	–	–	123.37	124.90
2	–	–	–	–	146.53	147.07
3	–	–	–	–	153.26	154.46
4	7.28, *s*	–	7.21, *s*	–	114.44	115.44
5	7.09–7.07, *dd*	8.16, 1.43	7.21–7.19, *dd*	8.09, 2.39	125.29	125.74
6	8.16–8.14, *dd*	8.03, 1.49	8.03–8.01, *dd*	7.03, 2.50	121.98	122.73
1`	–	–	–	–	136.99	138.31
2`	7.49–7.47	x	7.47–7.45, *dd*	9.41, 3.52	129.40	130.22
3`	7.45–7.43, *t*	3.25	7.30, *d*	2.54	129.32	129.57
4`	7.46	x	7.31, *t*	0.99	129.35	129.54
2``	–	–	–	–	149.62	150.25
4``	7.44, *d*	3.09	7.61–7.60, *dd*	6.02, 3.19	123.10*	123.58*
5`` & 6``	7.27–7.26, *t*	3.01	7.23–7.22, *t*	3.03		
7``	7.51–7.49, *dd*	7.14, 3.71	7.61–7.60, *dd*	6.02, 3.19	114.44	116.42
3a`` & 7a``	–	–	–	–	–**	139.72

x not clearly observed
* overlap.
** not observed.

Table 2. 2D ^{1}H–^{13}C HMQC and HMBC correlations for **3** in acetone–d_6:

Atom	HMQC (ppm)	HMBC [J(C,H)] (ppm)		
	^{1}J	^{2}J	^{3}J	^{4}J
CH_3	56.85	–	154.46, C_3	115.44, C_4
CH_2	76.57	138.31, $C_{1`}$	130.22, $C_{2`}$ 147.07, C_2	129.57, $C_{3`}$
N–H	–	139.72, $C_{7a``}$	116.42, $C_{7``}$ 124.90, $C_1$ 139.72, $C_{3a``}$	122.73, C_6 123.58, $C_{4``}$,$C_{6``}$
H_4	115.44	154.46, C_3	122.73, C_6 147.07, C_2	124.90, C_1
H_5	125.74	115.44, C_4 122.73, C_6	124.90, C_1 154.46, C_3	147.07, C_2
H_6	122.73	124.90, C_1	147.07, C_2 150.25, $C_{2``}$	154.46, C_3
$H_{2`}$	130.22	129.57, $C_{3`}$	76.57, CH_2 129.54, $C_{4`}$	129.57, $C_{3`}$
$H_{3`}$	129.57	130.22, $C_{2`}$ 129.57, $C_{4`}$	138.31, $C_{1`}$	130.22, $C_{2`}$
$H_{4`}$	129.54	129.57, $C_{3`}$	130.22, $C_{2`}$	138.31, $C_{1`}$
$H_{4``}$	123.58	123.58, $C_{5``}$ 139.72, $C_{3a``}$	123.58, $C_{6``}$ 139.72, $C_{7a``}$	x
$H_{5``}$	123.58	123.58, $C_{4``}$,$C_{6``}$	116.42, $C_{7``}$ 139.72, $C_{3a``}$	139.72, $C_{7a``}$

$H_{6``}$	123.58	116.42, $C_{7``}$ 123.58, $C_{5``}$	123.58, $C_{4``}$ 139.72, $C_{7a``}$	139.72, $C_{3a``}$
$H_{7``}$	116.42	123.58, $C_{6``}$ 139.72, $C_{7a``}$	123.58, $C_{5``}$ 139.72, $C_{3a``}$	123.58, $C_{4``}$

x: not observed.

While the doublet of a doublet observed in $CDCl_3$ at δ = 7.09–7.07 ppm (J = 8.16 and 1.43 Hz) is assigned to H_5 coupling to H_4 in the trisubstituted ring. This proton was shown doublet of a doublet and shifted a bit downfield in acetone–d_6. It was also observed that in $CDCl_3$ and acetone–d_6 H_4 appeared as a singlet at δ = 7.28 and 7.21 ppm, respectively. Additionally, the proton of N–H observed as singlet and resonated at δ = 7.24 ppm in acetone–d_6, and it appeared as doublet in $CDCl_3$ to δ = 7.25 ppm, (J = 1.06 Hz). In acetone–d_6, the coupling between N–H and H_6 was observed most probably due to the interaction of the solvent with the compound.

We suggested the triplet of signal in acetone–d_6 at δ = 7.23–7.22 ppm, (J = 3.03 Hz) and at δ = 7.27–7.26 ppm, (J = 3.01 Hz) in $CDCl_3$ to be assigned to $H_{5``}$ and $H_{6``}$ in the benzimidazole ring due to coupling with $H_{4``}$ and $H_{7``}$. The difference in chemical shift of $H_{4``}$ and $H_{7``}$ is also apparent in both solvents. In $CDCl_3$, $H_{7``}$ and $H_{4``}$ signal were found to be separated; $H_{7``}$ appeared as doublet of a doublet at $\delta$ = 7.51–7.49 ppm, ($J$ = 7.14 and 3.71 Hz), while $H_{4``}$ appeared as doublet at δ = 7.44 ppm, J cannot be determined exactly due to peaks overlapping. However, in acetone–d_6 both protons shown signal as doublet of a doublet at δ = 7.61–7.60 ppm (J = 6.02 and 3.19 Hz).

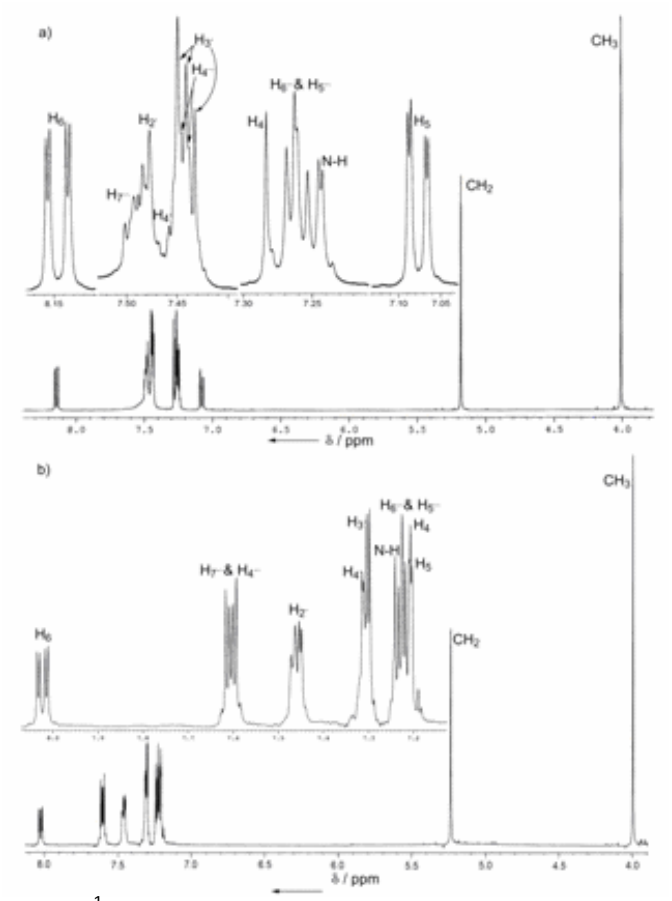

Fig 3. ^{1}H NMR spectra of **3** in a) $CDCl_3$ and b) in acetone–d_6.

From Figure 3, the signal of the benzyl ring protons $H_{2`}$ appeared as doublet of a doublet at $\delta$ = 7.47– 7.44 ppm, ($J$ = 9.41 and 3.52 Hz) in acetone–$d_6$ although the peaks were not clearly shown in $CDCl_3$. The $H_{4`}$ splitting patterns in $CDCl_3$ was not clear due to that overlapping of the peaks but it appeared as a triplet at δ = 7.31 ppm, (J = 0.99 Hz) in acetone–d_6. On the other hand, the protons of $H_{3`}$ displayed the signal as a triplet at δ = 7.45–7.43 ppm, (J = 3.25 Hz) in $CDCl_3$, and as doublet at δ = 7.30 ppm, (J = 2.54 Hz) in acetone–d_6. The methoxy OMe and methylene CH_2 protons were observed in $CDCl_3$ at δ = 4.01 and 5.18 ppm, and at δ = 3.99 and 5.23 ppm in acetone–d_6, respectively. Table 1 shows the chemical shift values of **3** in both solvents.

We found both spectra of the benzimidazole **3** were differed in splitting patterns for some of the aromatic protons, which may be due to the solubility of **3** in both solvents, including some effect from that six–membered illusory ring, which was formed from the intramolecular hydrogen bonding between N–H in the benzimidazole ring and the oxygen atom in the benzyl ring (Figure 1). ^{1}H–^{1}H COSY and HMBC experiments were performed to further confirm that assigned peaks.

^{13}C NMR

The ^{13}C NMR spectra of **3** were obtained and shown in Figure 4. The quaternary carbons in **3** were identified and recognized by APT and or DEPT–135 NMR experiments in both solvents. The quaternary carbon signals for C_3, $C_{2``}$, $C_2$, $C_{1`}$ and $C_1$ in $CDCl_3$ were observed at $\delta$ = 153.26, 149.62, 146.53, 136.99 and 123.37 ppm, respectively. In acetone–$d_6$ these values were found to be shifted slightly downfield. The signals of the quaternary carbons $C_{3a``}$ and $C_{7a``}$ were absent in $CDCl_3$, but, APT NMR experiment showed the existing of this peak at δ = 138.87 ppm in acetone–d_6. A NMR solid state study by Claramunt *et al*. showed that these signals appeared at δ = 136.9 ppm [37].The CH_2 and OMe signals in both solvents were found at about δ = 76.60 and 56.50 ppm, respectively.

The spectra showed that some of the carbons in the benzimidazole ring overlapped with the other carbons in trisubstituted ring. For example, in $CDCl_3$ $C_{7``}$ signal overlapped with $C_4$ at $\delta$ = 114.44 ppm, while the peaks were separated clearly in acetone–$d_6$, (Figure 4). Similarly, carbons $C_{4``}$, $C_{5``}$ and $C_{6``}$ appeared at the same chemical shift in both solvents. The carbons in trisubstituted ring C_6 and C_5 were resonated in $CDCl_3$ at δ = 121.98 and 125.29 ppm, respectively, while the benzyl ring carbons were observed at δ = 129.40, 129.35 and 129.32 ppm for $C_{2`}$, $C_{4`}$ and $C_{3`}$ in $CDCl_3$, respectively. Table 1 summarizes the chemical shift values discussed.

To confirmed of the assignment signals and the overlapping between the aromatic carbons, the proton coupled ^{13}C NMR spectra of the benzimidazole **3** were also conducted. Additionally, the HMQC and HMBC experiments done, further aid in assigning the peaks.

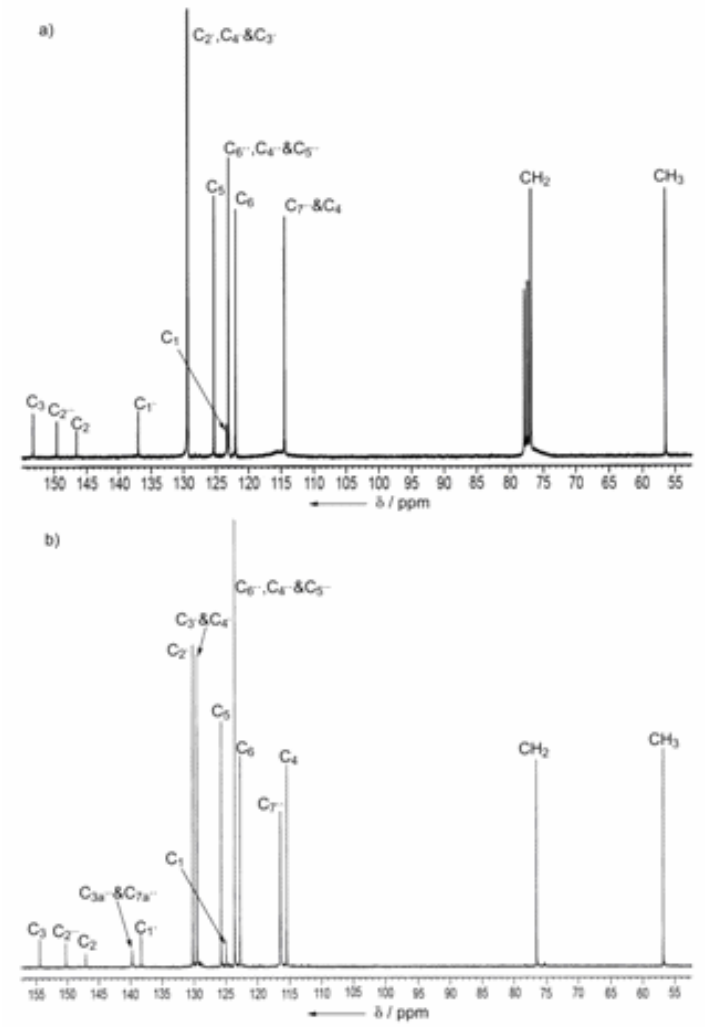

Fig 4. ^{13}C NMR spectra of **3** in a) $CDCl_3$ and b) in acetone–d_6.

^{1}H–^{1}H COSY

The signals of **3** are also assigned with an aid by the COSY experiment. Figure 5 shows the ^{1}H–^{1}H COSY NMR spectra of **3** in $CDCl_3$ and acetone–d_6. The signal in both solvents at δ = 4.01-3.99 ppm, was assigned to the methoxy protons, OMe and it showed correlations with CH_2 at δ = 5.18-5.23 ppm. As expected, proton H_5 was correlated with H_4 and H_6 in $CDCl_3$ at δ = 7.25 and 8.16–8.14 ppm, respectively. Besides H_5 and H_4, proton H_6 show correlations clearly with H_4 and N–H although this correlation is not observed in acetone–d_6. $H_{5``}$, $H_{6``}$ were observed to be correlated with both protons $H_{7``}$ and $H_{4``}$ at δ = 7.51–7.49 and 7.43 ppm in $CDCl_3$ and at δ = 7.61–7.60 ppm in acetone–d_6.

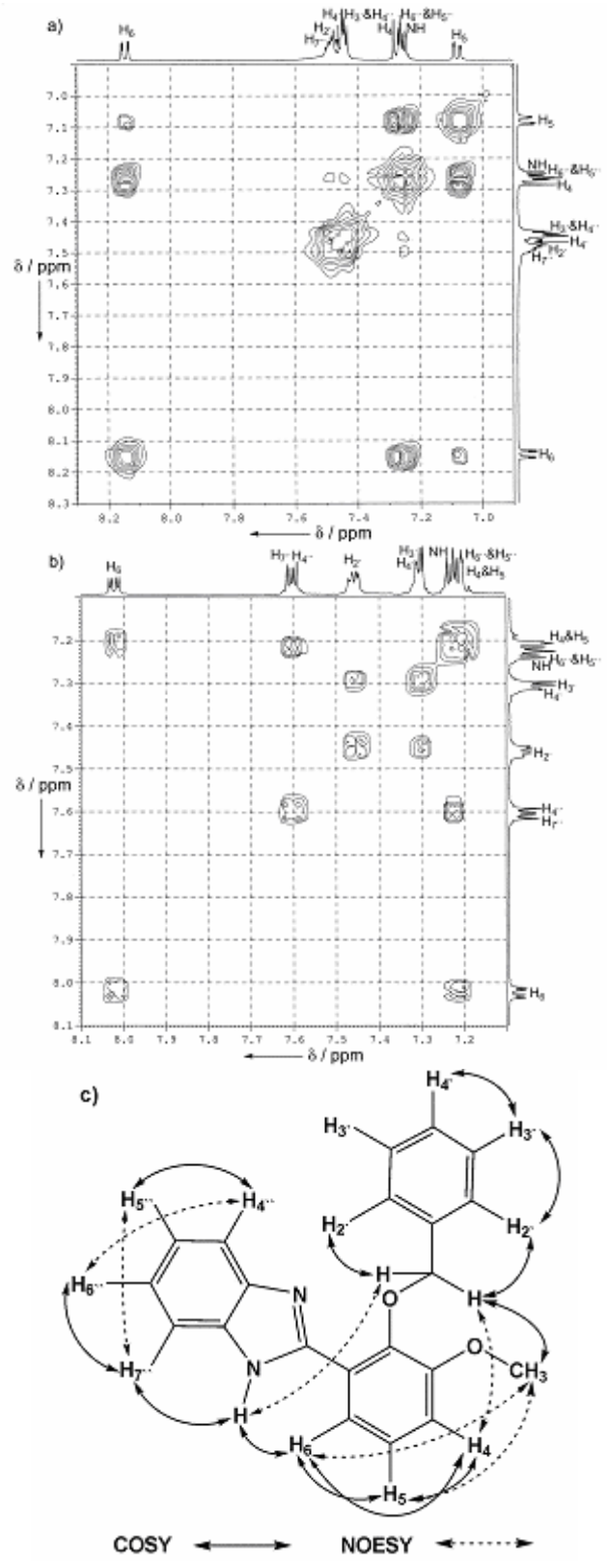

Fig 5. ^{1}H–^{1}H connectivities in the COSY a) in $CDCl_3$, b) in acetone–d_6 and c) the most important correlations observed in COSY and NOESY spectrum of **3**.

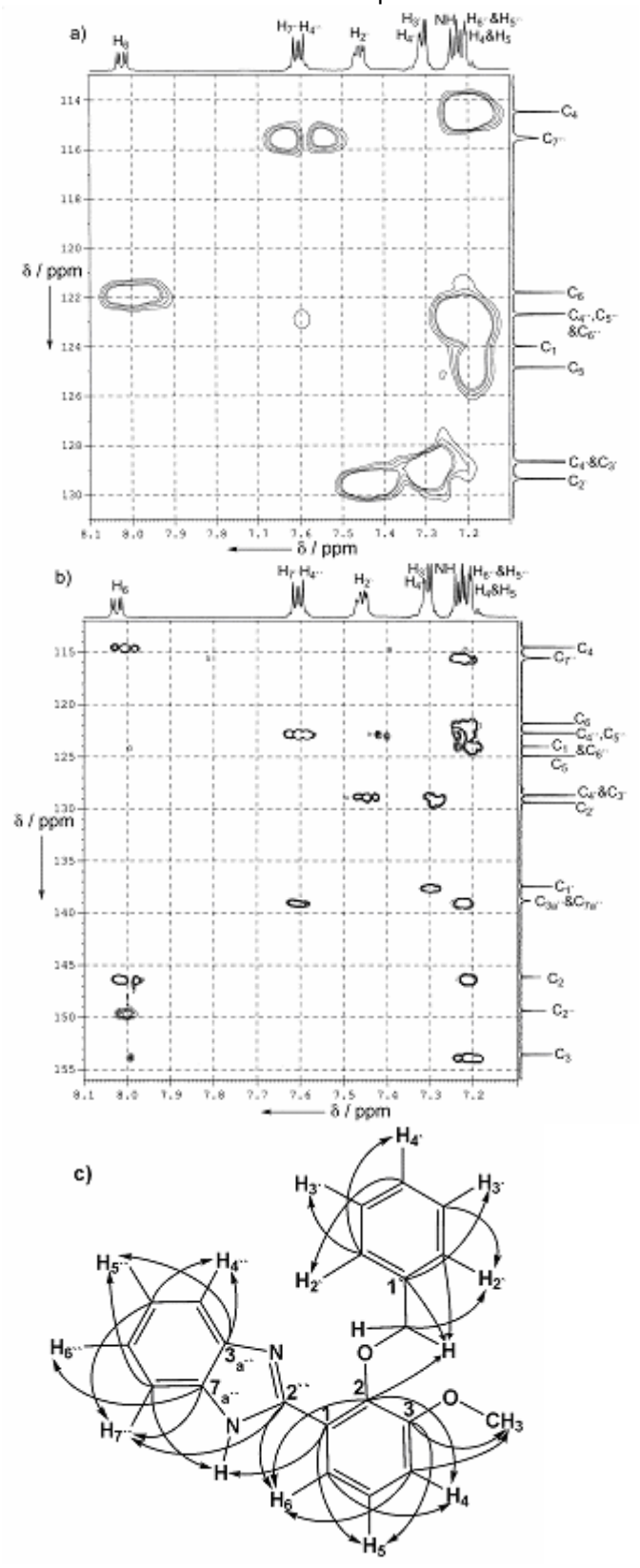

Fig 6. $^{1}H–^{13}C$ connectivities of **3** in acetone–d_6 a) in the HMQC, b) in the HMBC and c) the most important correlations observed.

$^{1}H–^{13}C$ HMQC NMR

The 2D HMQC NMR spectrum was conducted to determine which hydrogens are connected to which carbons. The HMQC NMR spectrum for **3** was shown in Figure 6a, and it confirms the attachments between all hydrogens and their corresponding carbons. In acetone–d_6, the signals owing to C_4, $C_{7``}$, C_6, C_5, $C_{4`}$, $C_{3`}$ and $C_{2`}$ atoms are observed at the respective δ = 115.44, 116.42, 122.73, 125.74 and 129–130 ppm, while the signals of the one bond $^{13}C–^{1}H$ connectivities are also well observed for OMe and CH_2 atoms whereby the cross peaks appear at δ = 56.85 and 76.57 ppm, respectively. Table 2 shows the summarized value for HMQC of **3**.

$^{1}H–^{13}C$ HMBC spectra

The 2D HMBC NMR spectrum was conducted to examine the long–range $^{1}H–^{13}C$ connectivities. The HMBC NMR spectrum for **3** was shown in Figure 6b. The aromatic quaternary carbons are established through the connectivities between the carbon and its neighboring proton by using a long–range correlated HMBC experiment. The signal in acetone–d_6 of methoxy protons showed ^{3}J–correlation with C_3 at δ = 154.46 ppm and ^{4}J–correlation with C_4 at δ = 115.44 ppm. While the protons of CH_2 were observed ^{2}J–correlation with $C_{1`}$ and $^{3}J$–correlation with $C_{2`}$ and C_2 at δ = 138.31, 130.22 and 147.07 ppm, respectively.

Additionally, the long–range HMBC cross peaks of the quaternary carbon C_3 with H_5 appeared at δ = 7.21–7.19 ppm and was correlated with H_6 at δ = 8.03–8.01 ppm. Proton H_6 was demonstrated to correlate with $C_{2``}$ and $C_2$. $H_4$ and $H_5$ were also observed to be correlated with $C_2$. The spectrum also shows that $C_{3a``}$ and $C_{7a``}$ were correlated with N–H, $H_{6``}$ and $H_{5``}$ at $\delta$ = 7.24–7.22 ppm and with $H_{7``}$ and $H_{4``}$ at δ = 7.61–7.60 ppm. The chemical shifts of the HMBC of **3** are summarized in Table 2.

CONCLUSION

We have reported the complete assignments of the benzimidazole **3** using ^{1}H, ^{13}C, COSY, HMQC and HMBC NMR in both $CDCl_3$ and acetone-d_6. Although the APT and DEPT–135 spectra were not shown, that experiments were performed and the results were discussed. Combination of the information gathered from experiments done in both solvents helps in assigning peak splittings of compound **3**. The differences in the peak splittings can be seen in a few cases. For example, in $CDCl_3$, $H_{7``}$ displayed doublet of a doublet at $\delta$ = 7.51-7.49 ppm and $H_{4``}$ signal was overlapped at δ = 7.44 ppm. While in acetone-d_6 both protons shown the signal as doublet of doublet at δ = 7.61-7.60 ppm. The quaternary carbon peaks of $C_{3a``}$ and $C_{7a``}$ were absent in $CDCl_3$, but they were observed clearly in acetone-d_6 at δ = 139.72 ppm, and confirmed by APT NMR experiment. The cause of these differences may be due to the solubility of **3** in both solvents, including some effect from that six–membered illusory ring, which it was formed from the intramolecular hydrogen bonding between N-H in the benzimidazole ring and the oxygen atom in the benzyl ring. Overall, experiments done in acetone-d_6 demonstrated clearer peak splittings than in $CDCl_3$. Further reactions using the compound to synthesis biologically important compounds are in progress.

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34. ***Crystal data*** of **3**: $C_{21}H_{18}N_2O_2$, M_r = 330.37, monoclinic, $P2_1/c$, a = 9.54170 (1), b = 18.4590 (3), c = 11.0653 (2) Å, β = 123.814 (1)^o, V = 1619.27 (4) Å^3, Z = 4, μ = 0.088 mm^{-1}, d_x = 1.355 g cm^{-3}, F(000) = 696, GOF = 1.062. A total of 54869 reflections were collected and 8446 are unique (R_{int} = 0.0539), R = 0.0501, ωR = 0.1282 for 227 parameters and 8446 reflections ($I > 2\sigma$ (I)). Residual electron density extremes were 0.613 and –0.326 e Å^{-3}. The intensity data was collected at 297 K on SMART APEX2 CCD area–detector diffractometer with graphite–monochromated Mo_{Ka} radiation (0.71073 Å), θ range 2.21 to 37.50^o [38]. All absorption corrections were performed by using SADABS the multiscan program [38]. The structure was solved and refined by SHELXTL against F^2[39]. The H atoms were refined as riding and the *U*iso values were freely refined, they were placed in calculated positions, with C–H = 0.93–0.97 *Å* and N–H = 0.89 *Å*. The software was used SHELXTL [39] and PLATON [40]. These data can be obtained free of charge from International Union of Crystallography IUCr cv2101 or The Cambridge Crystallographic Data Centre CCDC 620951. Reference: (doi:10.1107/S160053680603251X).
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