Synthesis of Some New 1*H*-Benzimidazole-2-carboxamido Derivatives and Their Antimicrobial Activitiy

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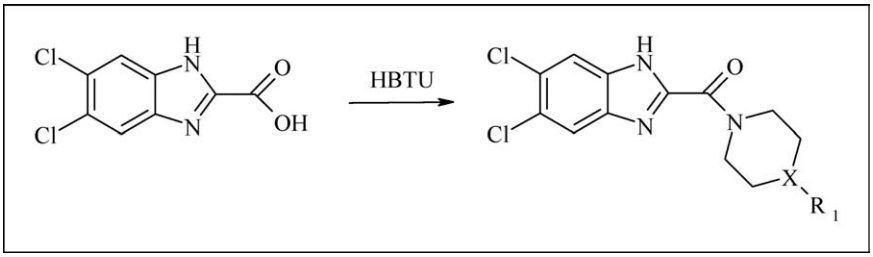

5,6-Dichloro-2-hydroxymethyl-1*H*-benzimidazole (**1**) was prepared by the cyclization of 4,5-dichloro-o-phenylenediamine with glycolic acid, then, alcohol group of **1** was converted to carboxylic acid (**2**). The final products 5,6-dichloro-1*H*-benzimidazole-2-carboxamides (**3–11**, **13–14**) were prepared by the amidification of compounds **2** with several amines by using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate. Compound **12** was prepared by the reaction of compound **6** with methanolic HCl. The relations between the tautomer and nontautomer types of imidazole moiety are discussed with NMR spectroscopy. The *in vitro* antibacterial and antifungal activity of the synthesized compounds against *S. aureus, E. coli, B. subtilis*, and *C. albicans* were evaluated with the disc diffusion techniques. The synthesized compounds were more active against the bacteria than fungi. Compound **3** exhibited best inhibitory activity against *S. aureus*.

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INTRODUCTION

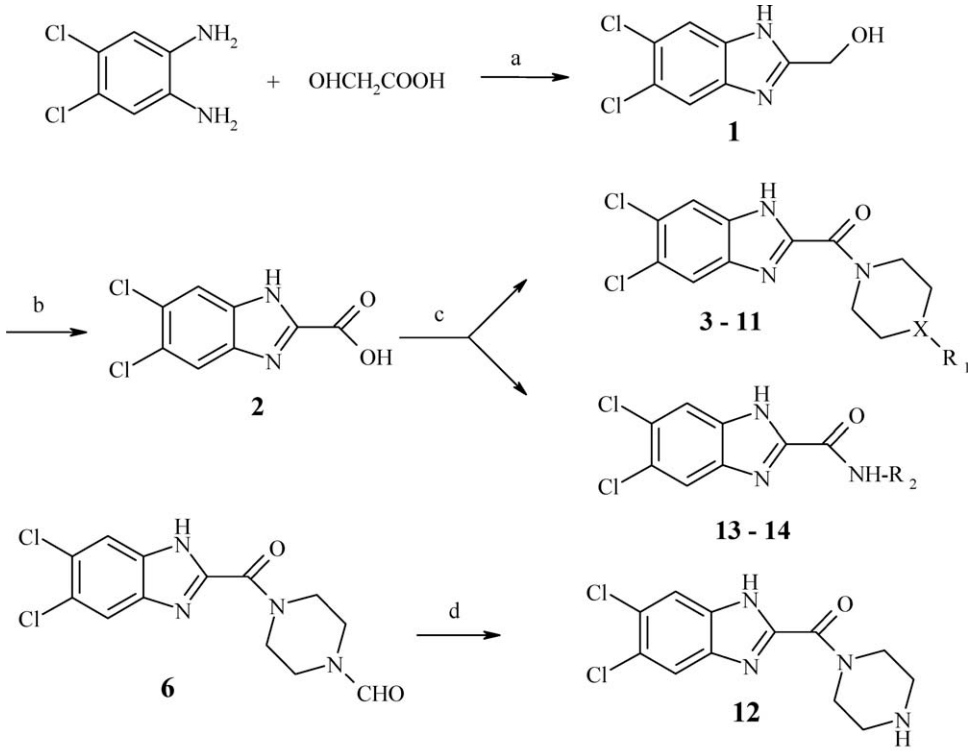
Numerous benzimidazole derivatives containing amidine groups on the benzene ring have been synthesized for their antifungal, insecticidal, herbicidal, antiinflammatory, and potential anthelmintic activities [1]. It is also well known that amides, amidines, and combinations of both are present in a variety of antimicrobial, antiparasitic, anthelmintic, antiviral, and antitumoral agents. Furthermore, our previous work and that of others showed that benzimidazole carboxamidines display good antibacterial and antimycotic activity [2–4]. In addition, potent antimicrobial activities of a series of 5,6-dichloro-2-piperidin-4-yl-benzimidazoles [5] and 4-(5,6-dichloro-1*H*-benzimidazol-2-yl)-*N*-substituted benzamides [6] were reported. Taking into consideration these structural features, we planned to prepare a series of benzimidazoles carrying amide functional group on the position C-2.

RESULTS AND DISCUSSION

5,6-Dichloro-2-hydroxymethyl-1*H*-benzimidazole (**1**) was prepared by the cyclization of 4,5-dichloro-*o*-phenylenediamine with glycolic acid and then, alcohol group of **1** was converted to carboxylic acid (**2**) by the oxidation with $KMnO_4$ in alkali medium. The final products 5,6-dichloro-1*H*-benzimidazole-2-carboxamides (**3–11**, **13–14**) were prepared by the amidification of compounds **2** with appropriate amines by using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU). Compound **12** was prepared by the reaction of compound **6** with methanolic HCl (Scheme 1).

Annular 1,3-tautomerism in imidazole moiety is considered to be biologically relevant because the significance of the imidazole ring tautomerism in histidine, a naturally occurring amino acid, has been well established. In the imidazole ring, tautomerism means that the hydrogen atom may be bonded either to the N^1 or to the N^3 atom (Scheme 2). This tautomeric proton exchange ratio is dependent on some several factors, including the nature of the substituents and their symmetrical or unsymmetrical substitution on the benzene moiety or the concentration ratio of the solution and intermolecular hydrogen bonding properties between the molecules and solvents. Symmetrical tautomeric forms of compound **9** are shown in Scheme 2.

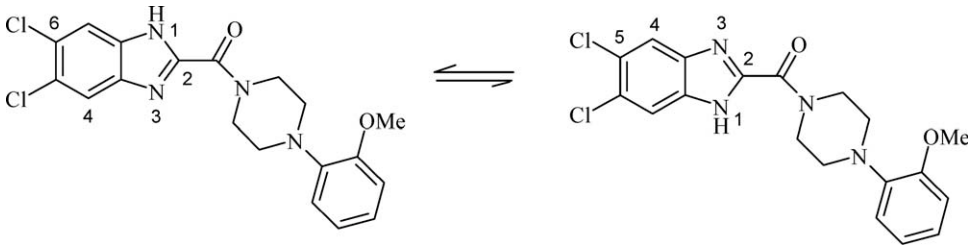
Scheme 1. Synthesis of benzimidazoles **1–14**.



Reagents **a** : HCl acid **b** : $KMnO_4$ **c** : Several amines and *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HBTU) **d** : methanolic HCl

In particular, if the benzimidazoles bear a substitutent on the benzen ring at unsymmetrical [C-5(6) or C-4(7)] position, a mixture of two regioisomers are obtained in different ratio, during the alkylation of nitrogen atoms of imidazole moiety [7]. There is no enough systematic investigation on the influence of a substituent at position C-5(6) on tautomerism of imidazole except than infrared spectroscopy and there are only few experimental papers concerning tautomerism of the C-5(6)-substituted imidazoles [8]. In this study, we try to show the relations between the tautomer and nontautomer type of benzimidazoles by their NMR spectra. Because of the mixture of tautomers in compounds **3–5**, **9**, **12**, **13**, their NMR spectra were not clear enough under standard conditions as expected. It means that these compounds have slow motion tautomeric effect even though they have simetrically equal. As it shown in Figures 1 and 2, both ^{1}H and ^{13}C NMR spectra (A and B) of compound **9** are not clear. At low concentration in DMSO-d_6, the 1,3-tautomerism was arrested and compound **9** existed as a single isomers so the protons H-4,7 appears as two different singlets [Fig. 1(A)]. When the concentration of the solution is increased, exchange rate of the imidazole proton increased and this time H-4,7 appeared as broad signals [Fig. 1(B)]. Similar situation was also observed with the ^{13}C spectra of compound **9**. With low concentration, the signals of C-(5,6), C-(4,7), and C-(3a,7a) belonging the mixture of tautomers were seen as different chemical shim values [δ ppm; Fig. 2(A)], whereas it was not possible to see signals belonging to the same

Scheme 2. Symmetrical tautomeric forms of compound **9**.



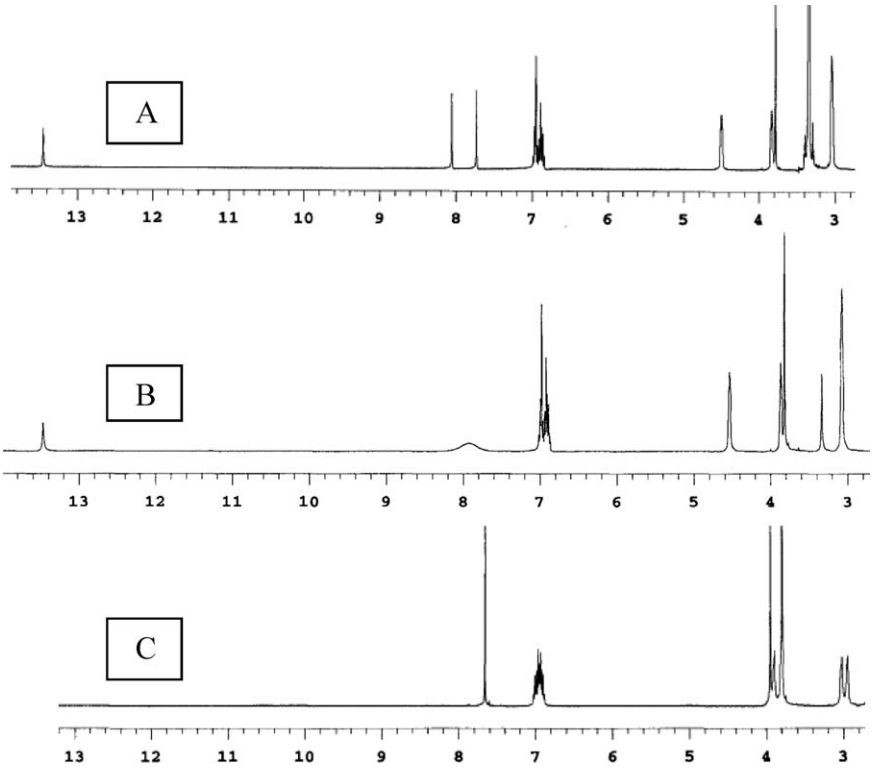


Figure 1. (A) ^{1}H NMR spectra of **9** in low concentration. (B) ^{1}H NMR spectra of **9** in high concentration. (C) ^{1}H NMR spectra of **9** + NaH + D_2O.

carbons, when compound **9** was in high concentration in DMSO-d_6 [Fig. 2(B)]. In contrast, after removal of the tautomeric effects by addition of a tiny amount of dry NaH, and two to three drops of D_2O, all the chemically equivalent protons and carbons have been observed as only one sharp singlets, in their NMR spectra [Figs. 1(C) and 2(C)]. Hence, very fine NMR assignments without tautomerism were made by a combination of 1D and 2D NMR techniques. Quaternary and methine carbons were easily assigned from the HMBC and HSQC spectra, respectively, with compound **9** (Table 2). Similar effects were also observed in ^{1}H NMR spectra of compound **7** and **9** by the addition of one drop CF_3COOH, instead of NaH + D_2O, however no satisfactory results was obtained with their ^{13}C spectra. We also performed the same experiments by using one drop of CH_3COOH, but this time there was no changes even in their ^{1}H NMR spectra.

The *in vitro* antibacterial and antifungal activities of the synthesized compounds **3–14** against *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922), *B. subtilis* (ATCC 6633), and *C. albicans* (ATCC 10231) were evaluated with the disc diffusion techniques [9]. All compounds (except **11**) were solved in 1,2-propylene glycol (1.5 mg/mL), 0.02 mL (one drop) of these solution was dropped on to a paper disk (6-mm diameter) and placed on an agar plate containing bacteria or fungi cell. Propylene glycol as a control showed no inhibition zone. The diameter of the growth inhibition zone around

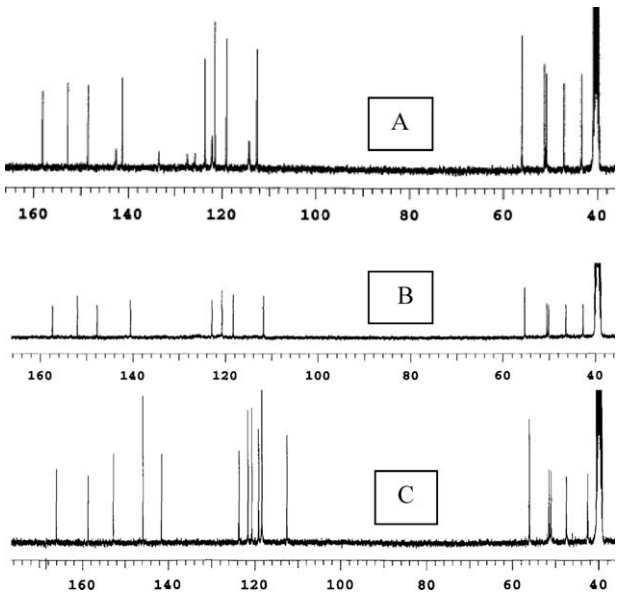
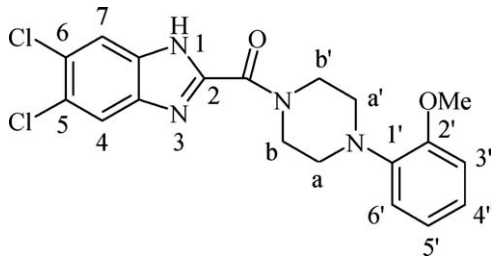


Figure 2. (A) ^{13}C NMR spectra of **9** in low concentration. (B) ^{13}C NMR spectra of **9** in high concentration. (C) ^{13}C NMR spectra of **9** + NaH + D_2O.

Table 1

NMR data (^{1}H, ^{13}C, HSQC, and HMBC) of compound **9**.

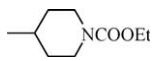
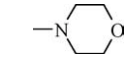


	Compd **9** (Low conc. in DMSO-d_6)		Compd **9** + NaH[a] + D_2O[b] (in DMSO-d_6)		
No	^{13}C	^{1}H	^{13}C	^{1}H	HMBC
C=O	158.2		166.1		
C-2	152.8		158.7		
C-2′	148.5		152.7		H-*3′,4′,5′,6′*
C-5 and **C-6**	***142.6***		***145.8***		H-*4,7*
	133.5				
C-1′	141.3		141.5		H-*3′,5′,6′*
C-5′	123.6	6.86–6.97 (*m*)	123.7	6.9–7.05 (*m*)	H-*3′,4′,6′*
C-4′	121.5	6.86–6.97 (*m*)	121.6	6.9–7.05 (*m*)	H-*3′,5′,6′*
C3a and **C7a**	***127.4***		***120.7***		H-*4,7*
	125.8				
C-3′	119.1	6.86–6.97 (*m*)	119.1	6.9–7.05 (*m*)	H-*4′,5′,6′*
C-4 and **C-7**	***122.2***	8.07 (*s*,1H)	***118.4***	7.65 (*s*,2H)	
	114.3	7.73 (*s*,1H)			
C-6′	112.6	6.86–6.97 (*m*)	112.5	6.9–7.05 (*m*)	H-*3′,4′,5′*
OCH$_3$	56.0	3.78 (*s*, 3H)	56.0	3.8 (*s*, 3H)	
CH$_2$(b)	51.3	3.04 (*br.t*, 4H)	51.5	2.95 (*br.t*, 2H)	
CH$_2$(b′)	50.9		50.9	3.03 (*br.t*, 2H)	
CH$_2$(a)	47.1	4.49 (*t*, 2H)	47.4	3.89 (*br.t*, 2H)	
CH$_2$(a′)	43.4	3.84 (*t*, 2H)	42.5	3.81 (*br.t*, 2H)	
NH		13.45 (*br.s*)			

[a] Tip of thin spatula.
[b] Two drops.

Table 2

In vitro antimicrobial activities and formulas of **3–14**.

				Growth inhibition zone (as mm)			
Comp.	X	R_1	R_2	*Bacillus subtilis*	*Staphylococcus aureus*	*Escherichia coli*	*Candida albicans*
3	CH_2	H	–	15	16	14	–
4	N	CH_3	–	12	10	12	14
5	N	CH_2CH_2OH	–	14	–	15	–
6	N	COH	–	16	8	15	10
7	N	COOEt	–	11	–	8	–
8	N	-Ph	–	13	13	15	–
9	N	2-(MeO)-Ph	–	11	10	14	–
10	N	4-(F)-Ph	–	12	13	14	–
11	N	4-(NO_2)-Ph	–	NT*	NT	NT	NT
12	N	H	–	11	9	13	11
13	–	–		12	12	16	–
14	–	–		12	13	15	–
Ampicillin				22	23	26	
Fluconazole							24

NT: Not tested.
Compound **11** is insoluble in propylene glycol.

the paper disc was measured after incubation period (Table 1). In general, it was observed that the synthesized compounds were more active against the bacteria than fungi. Among the synthesized derivatives, compound **3** exhibited best inhibitory activity against *S. aureus* with 16-mm zone diameter, however the activity was less than the reference compound Ampicillin. As the compounds have no comparable results with the references by the disc diffusion techniques, further test tube dilution method was not carried out.

EXPERIMENTAL

Uncorrected melting points were measured on a Büchi B-540 capillary melting point apparatus. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded using a Varian Mercury 400-MHz FT spectrometer, and chemical shifts (δ) are in ppm relative to TMS. *J* values are given in Hertz. Mass spectra were taken on a Waters Micromass ZQ connected with Waters Alliance HPLC, using ESI(+) method, with C-18 column. Elemental analyses were performed by Leco CHNS-932. Analyzer and the results were found to be in good agreement with the calculated values. Compounds **1** [10] and **2** [11] were prepared by the literature methods. 4,5-Dichloro-*o*-phenylenediamine and glycolic acid were procured from Aldrich.

General synthesis of 3–11, 13–14.. To a solution of 5,6-dichlorobenzimidazole-2-carboxylic acid (0.231g, 1 mmol) in dimethylformamide (1.5 mL) was added corresponding amines (1.1 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium HBTU (0.417g, 1.1 mmol), followed by triethylamine (1.1 mmol). The mixture was stirred at room temperature for 24 h. The reaction mixture was cooled and poured into water. Residue was purified by crystallization or column chromatography (cc).

5,6-Dichloro-2-(piperidin-1-ylcarbonyl)-1H-benzimidazole (3). Purification, crys. EtOH, yield 44%, mp 208–212°C; ^{1}H NMR (DMSO-d_6 + D_2O + NaH) δ ppm: 1.39 (2H, pipe), 1.51 (4H, pipe), 3.45 and 3.52 (4H, pipe), 7.6 (s,2H); MS: *m/z* 298(100), 300(60), 302(13). *Anal*. Calcd for $C_{13}H_{13}Cl_2N_3O$: C, 52.37; H, 4.39; N, 14.09. Found C, 52.0; H, 4.56; N, 14.09.

5,6-Dichloro-2-[(4-methylpiperazin-1-yl)carbonyl]-1H-benzimidazole (4). Purification, cc, dichloromethane:isopropanol:ammonium hydroxide (10:5:0.1), yield 76%, mp 267–269°C; ^{1}H NMR (*CD_3OD* + D_2O + NaH) δ ppm: 2.32 (s,3H,CH_3), 2.46 and 2.56 (s,s, 4H, pipe), 3.68 and 3.82 (s,s, 4H, pipe), 7.63(s, 2H); ^{13}C NMR (CD_3OD + D_2O + NaH) δ ppm: 167.1, 156.6, 144.4, 122.6, 117.5, 54.9, 54.2, 46.7, 44.8, 41.5; MS : *m/z* 313 (100), 315(66), 317(11). *Anal*. Calcd for $C_{13}H_{14}Cl_2N_4O$. 0.25 H_2O: C, 49.15; H, 4.60; N, 17.64. Found C, 49.07; H, 4.60; N, 17.48.

2-{4-[(5,6-Dichloro-1H-benzimidazol-2-yl)carbonyl]piperazin-1-yl}ethanol (5). Purification, cc, dichloromethane:isopropanol:ammonium hydroxide (10:5:0.2), yield 23%, mp 232–235°C; ^{1}H NMR (*CD_3OD* + D_2O + NaH) δ ppm: 2.54 (b.t, 2H, pipe), 2.58 (t,2H, N—CH_2), 2.65 (b.t, 2H, pipe), 3.65 (b.t,2H, pipe), 3.7 (t,2H,O—CH_2), 3.81 (b.t, 2H, pipe), 7.62 (s,2H); ^{13}C NMR (CD_3OD + D_2O + NaH) δ ppm : 167.1, 156.7, 144.4, 122.6, 117.5, 59.7, 58.5, 53.5, 52.8, 46.8, 41.7; MS: *m/z* 343(100), 345(65), 347(12). *Anal*. Calcd for $C_{14}H_{16}Cl_2N_4O_2$ 0.5 H_2O: C, 47.74; H, 4.86; N, 15.91. Found C, 47.55; H, 4.57; N, 15.97.

4-[(5,6-Dichloro-1H-benzimidazol-2-yl)carbonyl]piperazine-1-carbaldehyde (6). Purification, crys. dimethylformamide-EtOH, yield 29%, mp 272–274°C; ^{1}H NMR (DMSO-d_6 + D_2O) δ ppm: 3.54 (s,4H, pipe), 3.73 ve 4.35 (d, 4H, pipe), 7.94 (br. s, 2H), 8.1 (s, 1H, CHO); MS: *m/z* 327(100), 329(70), 331(13). *Anal*. Calcd for $C_{13}H_{12}Cl_2N_4O_2$ 0.25 H_2O: C, 47.07; H, 3.80; N, 16.9. Found C, 47.06; H, 3.81; N, 16.83.

Ethyl 4-[(5,6-dichloro-1H-benzimidazol-2-yl)carbonyl]piperazine-1-carboxylate (7). Purification, crys. EtOH, yield 35%, mp 239–241°C; ^{1}H NMR (DMSO-d_6) δ ppm : 1.17 (t,3H), 3.48 (br. s., 4H, pipe), 3.68 (t,2H, pipe), 4.04 (q,2H), 4.36 (t,2H, pipe), 7.7 (s,1H), 8.05(s,1H), 13.5 (s,1H,imidazole NH); MS: *m/z* 371(100), 373(63), 375(13). *Anal*. Calcd for $C_{15}H_{16}Cl_2N_4O_3$ .0.5 H_2O: C, 47.38; H, 4.51; N, 14.74. Found C, 47.23; H, 4.37; N, 14.65.

5,6-Dichloro-2-[(4-phenylpiperazin-1-yl)carbonyl]-1H-benzimidazole (8). Purification, cc, dichloromethane:isopropanol:ammonium hydroxide (10:5:0.1), yield 28%, mp 264–269°C; ^{1}H NMR (DMSO-d_6) δ ppm: 3.27 (t, 4H, pipe), 3.86 (t, 2H, pipe), 4.55 (t, 2H, pipe), 6.82 (t, J = 8 Hz, 1H), 7.01 (d, J = 8 Hz, 2H), 7.24 (t, J = 8 Hz, 2H), 7.75 (s,1H), 8.11 (s,1H), 13.4 (s,1H,imidazole NH); MS: *m/z* 375(100), 377(59), 379(13). *Anal*. Calcd for $C_{18}H_{16}Cl_2N_4O$: C, 57.61; H, 4.30; N, 14.93. Found C, 57.44; H, 4.41; N, 15.18.

5,6-Dichloro-2-{[4-(2-methoxyphenyl)piperazin-1-yl]carbonyl}-1H-benzimidazole (9). Purification, cc, ethyl acetate:*n*-hexane (1:1), yield 29%, mp 246–248°C; ^{1}H NMR (DMSO-d_6) δ ppm: See Table 1. MS: *m/z* 405(100), 407(67), 409(15). *Anal*. Calcd for $C_{19}H_{18}Cl_2N_4O_2$ .0.25 H_2O: C, 55.69; H, 4.55; N, 13.67. Found C, 55.69; H, 4.54; N, 13.7.

5,6-Dichloro-2-{[4-(4-fluorophenyl)piperazin-1-yl]carbonyl}-1H-benzimidazole (10). Purification, cc, dichloromethane:isopropanol:ammonium hydroxide (10:5:0.1), yield 22%, mp 265–270°C; ^{1}H NMR (DMSO-d_6) δ ppm: 3.18 (t,4H, pipe), 3.83 (t, 2H, pipe), 4.52 (t,2H, pipe), 6.97–7.08 (m,4H), 7.73(s,1H), 8.08(s,1H), 13.47 (s, 1H, imidazole NH); MS: *m/z* 393(100), 395(61), 397(11). *Anal*. Calcd for $C_{18}H_{15}Cl_2FN_4O$: C, 54.98; H, 3.84; N, 14.25. Found C, 54.54; H, 3.96; N: 14.1.

5,6-Dichloro-2-{[4-(4-nitrophenyl)piperazin-1-yl]carbonyl}-1H-benzimidazole (11). Purification, crys. EtOH, yield 31%, mp 254–258°C; ^{1}H NMR (DMSO-d_6) δ ppm: 3.66(t, 4H, pipe), 3.87 (2H, pipe), 4.60 (t, 2H, pipe), 7.04 (d, J = 8 Hz, 2H), 7.75 (s,1H), 8.09 (m,3H), 13.47 (s,1H,imidazole NH). ^{13}C NMR (DMSO-d_6) δ ppm: 158.3, 155, 148.3, 142.6, 137.7, 133.5, 127.5, 126.4, 125.9, 122.2, 114.3, 113.3, 47.2, 46.3, 45.9, 42.8; MS: *m/z* 420(100), 422(62), 424(10). *Anal*. Calcd for $C_{18}H_{15}Cl_2N_5O_3$: C, 51.44; H, 3.60; N, 16.66. Found C, 50.95; H, 3.58; N, 16.47.

5,6-Dichloro-2-(piperazin-1-ylcarbonyl)-1H-benzimidazole (12). Compound **6** (0.135 g, 0.4 mmol) was stirred in methanolic HCl (5 mL) at room temperature for 24 h. The reaction mixture was basified with dilute K_2CO_3 solution and the precipitate was crystallized from EtOH, yield 46%, mp, 303–305°C; ^{1}H NMR (DMSO-d_6 + D_2O) δ ppm: 3.25 and 3.29 (t, 4H, pipe), 3.92 (t, 2H, pipe), 4.66 (t, 2H, pipe), 7.97 (s, 2H); MS: *m/z* 299 (100), 300(66), 302(14). *Anal*. Calcd for $C_{12}H_{12}Cl_2N_4O$: C, 48.18; H, 4.04; N, 18.73. Found C, 48.08; H, 3.96; N,18.67.

Ethyl 4-{[(5,6-dichloro-1H-benzimidazol-2-yl)carbonyl]amino}piperidin-1-carboxylate (13). Purification, crys. ethyl acetate, yield 47%, mp 273–275°C; ^{1}H NMR (DMSO-d_6 + D_2O + NaH) δ ppm: 1.19 (t,3H), 1.48 and 1.81 (m,4H, pipe), 3.77 (s, 1H), 3.95 (m,4H, pipe.), 4.09 (q,2H), 7.64 (s,2H). ^{13}C NMR (DMSO-d_6 + D_2O + NaH) δ ppm: 163.9, 158.9, 155.5, 146.4, 121.1, 118.7, 61.5, 46.9, 43.1, 32.1, 15.2; MS: *m*/*z* 385(100), 387(59), 389(13). *Anal*. Calcd for $C_{16}H_{18}Cl_2N_4O_3$ .0.25 H_2O: C, 49.31; H, 4.78; N, 14.38. Found C, 49.22; H, 4.50; N, 14.41.

5,6-Dichloro-N-morpholin-4-yl-1H-benzimidazole-2-carboxamide (14). Purification, crys. (ethyl acetate), yield 32%, mp 254–257°C; ^{1}H NMR (DMSO-d_6) δ ppm: 2.86 (4H, morp), 3.63 (4H, morp), 7.83 (br. s, 2H), 10.19 (s, 1H, NH), 13.59 (br.s, 1H, imidazole NH). ^{13}C NMR (DMSO-d_6 + D_2O + NaH) δ ppm: 166.1, 164.5, 146.7, 119.2, 117.3, 66.5, 55.8; MS: *m*/*z* 315(100), 317(59), 319(10). *Anal*. Calcd for $C_{12}H_{12}Cl_2N_4O_2$: C, 45.73; H, 3.84; N, 17.78. Found C, 45.53; H, 3.86; N, 17.67.

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