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Synthesis and Potent Antimicrobial Activity of Some Novel 4-(5,6-Dichloro-*1H*-benzimidazol-2-yl)-N-substituted Benzamides

A series of 4-(5,6-dichloro-*1H*-benzimidazol-2-yl)-N-substituted benzamides were synthesized and evaluated for antibacterial and antifungal activities against *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *S. epidermis* (MRSE), *Enterococcus faecalis*, *Escherichia coli* and *Candida albicans*. Certain compounds inhibit bacterial growth with low MIC values (μg/mL). Among them, compounds **10** and **11** exhibited the greatest antibacterial activity with MIC values of 3.12 μg/mL against *S. aureus*, MRSA and MRSE.

Keywords: 1H-Benzimidazole; Benzamide; Antifungal and Antibacterial Activity; Methicillin-resistant *Staphylococcus aureus*; Methicillin-resistant *Staphylococcus epidermidis*

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Introduction

Multiple drug-resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus epidermidis* (MRSE), are becoming common causes of infections in the acute and long-term care units in hospitals. The emergence of these resistant bacteria has created a major concern and an urgent need of antibacterial agents in structural classes distinct from known antibacterial agents [1].

In our previous papers [2, 3], we have reported the synthesis of benzimidazoles **I** and **II** (Figure 1) carrying amide functions at different positions, and their promising antimicrobial activity results have been reported. Meanwhile, a series of recently discovered 5,6-dichloro-2-piperidinylbenzimidazoles **III** [4] and **IV** [5] (Figure 1) with broad-spectrum antibacterial activities have been reported. These results prompted us to continue an investigation on a series of new benzamides carrying 5,6-dichloro-N^1-substituted-*1H*-benzimidazoles. Microbiological testing has now shown that these benzimidazoles, described here, possess an interesting antimicrobial activity against MRSA and MRSE *in vitro*.

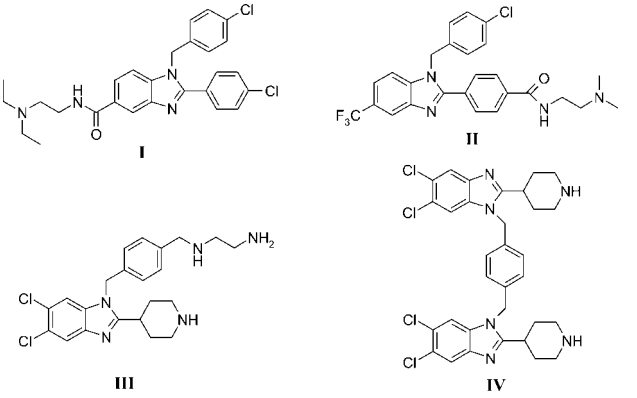

Figure 1. Some benzimidazoles reported to exhibit potent antibacterial activity.

Chemistry

The synthetic pathway for the preparation of 4-(5,6-dichloro-*1H*-benzimidazol-2-yl)-N-substituted benzamides **8**–**20**, listed in Table 1, is shown in Scheme 1. The nucleophilic substitution of 1,2,4-trichloro-5-nitrobenzene with isopropylamine and 4-chlorobenzylamines gave **1** and **2**. Reduction of **1** and **2** with H_2, Pd/C and Zn/HCl produced **3** and **4**, respectively. The reaction of 4,5-dichloro-o-phenylenediamine and compounds **3** and **4** with the sodium bisulfite adduct of 4-carboxybenzaldehyde gave 4-(5,6-dichloro-N^1-substituted-*1H*-benzimidazol-2-yl)benzoic acids **5**, **6** and **7**, respectively [6]. These compounds were converted to acyl chlorides with $SOCl_2$, and reaction between the

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Table 1. Physical and spectral data of compounds **8**–**20**.

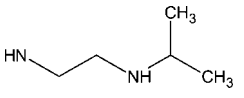
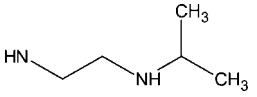
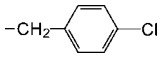
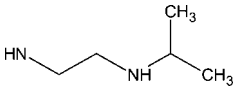
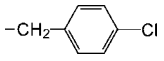
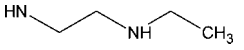
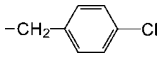
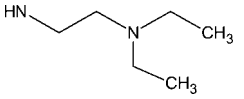
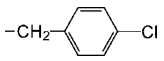
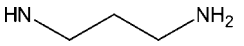
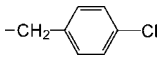
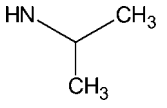
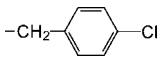
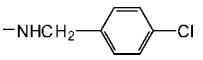
No	R_1	R_2	mp (°C)	Yield (%)	NMR (δ ppm)	MS (ESI+) *m/z* (rel. intensity)
8	–H		230–232	20	($CDCl_3$ + DMSO-d_6): 1.07 (d, 6H, J = 6.3 Hz), 2.6 (1H), 2.83 (m, 3H), 3.56 (q, 2H), 7.73 (s, 1H), 7.9 (s, 1H), 8.04 (d, 2H, J = 8.5 Hz), 8.25 (d, 2H, J = 8.5 Hz), 8.46 (t, 1H)	391 (M+H, 100)
9			224–227	31	(DMSO d_6): 1.26 (d, 6H, J = 6.5 Hz), 1.60 (d, 6H, J = 6.9 Hz), 3.13 (m, 2H, J = 6 Hz), 3.37 (m, 1H, J = 6.3 Hz), 3.63 (m, 2H), 4.68 (m, 1H, J = 6.9 Hz), 7.80 (d, 2H, J = 8.4 Hz), 8.02 (s, 1H), 8.13 (d, 2H, J = 8.4 Hz), 8.24 (s, 1H), 9.03 (t, 1H, J = 5.6Hz)	433 (M+H, 91) 373 (100)
10			175–178	22	($CDCl_3$): 1.07 (d, 6H, J = 6.2 Hz), 2.86 (m, 3H), 3.52 (q, 2H), 5.36 (s, 2H), 6.99 (m, 3H), 7.28 (s, 1H), 7.33 (d, 2H, J = 8.4 Hz), 7.70 (d, 2H, J = 8.4 Hz), 7.87 (d, 2H, J = 8.4 Hz), 7.93 (s, 1H)	515 (M+H, 51) 125 (100)
11			165	20	($CDCl_3$): 1.11 (t, 3H, J = 6.8 Hz), 2.69 (q, 2H), 2.87 (t, 2H), 3.54 (q, 2H), 5.35 (s, 2H), 6.99 (m, 3H), 7.29 (s, 1H), 7.33 (d, 2H, J = 8.4 Hz), 7.70 (d, 2H, J = 8.4 Hz), 7.88 (d, 2H, J = 8.3 Hz), 7.93 (s, 1H)	501 (M+H, 95) 125 (100)
12			160–161	19	($CDCl_3$): 1.08 (t, 6H, J = 6.8 Hz), 2.63–2.73 (m, 6H), 3.54 (q, 2H), 5.38 (s, 2H), 6.99 (d, 2H), 7.29 (s, 1H), 7.34 (d, 2H, J = 8.4 Hz), 7.71 (d, 2H, J = 8.4 Hz), 7.91 (d, 2H, J = 8.3 Hz), 7.94 (s, 1H)	529 (M+H, 100)
13			177–179	29	($CDCl_3$): 1.6 (br.s, 2H), 1.78 (m, 2H, J = 5.8 Hz), 2.99 (t, 2H, J = 6 Hz), 3.64 (q, 2H, J = 6 Hz), 5.39 (s, 2H), 7.01 (d, 2H, J = 8.4 Hz), 7.32 (s, 1H), 7.36 (m, 2H, J = 8.3 Hz), 7.71 (d, 2H, J = 8.4 Hz), 7.92 (d, 2H, J = 8.4 Hz), 7.96 (s, 1H), 8.35 (br.t, 1H)	487 (M+H, 100)
14			219–222	35	(DMSO-d_6): 1.36 (d, 6H, J = 6.5 Hz), 4.30 (m, 1H), 5.84 (s, 2H), 7.17 (d, 2H, J = 8.2 Hz), 7.53 (d, 2H, J = 8.1 Hz), 7.98 (d, 2H, J = 7.9 Hz), 8.15 (d, 2H, J = 7.9 Hz), 8.20 (s, 1H), 8.24 (s, 1H), 8.51 (d, 1H, J = 7.7 Hz)	472 (M+H, 100)
15			215–221	51	(DMSO-d_6): 4.67 (d, 2H, J = 5.92 Hz), 5.85 (s, 2H), 7.17 (d, 2H, J = 8.5 Hz), 7.47–7.59 (m, 6H), 8.02 (d, 2H, J = 8.4 Hz), 8.22 (m, 4H), 9.37 (t, 1H, J = 6 Hz)	554 (M+H, 75) 125 (100)

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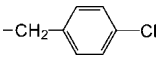
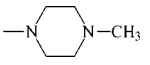
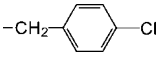
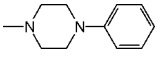
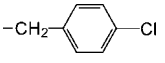
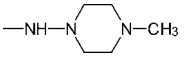
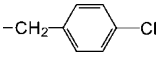
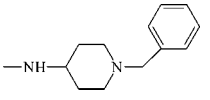
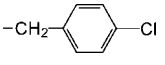
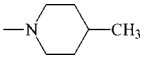
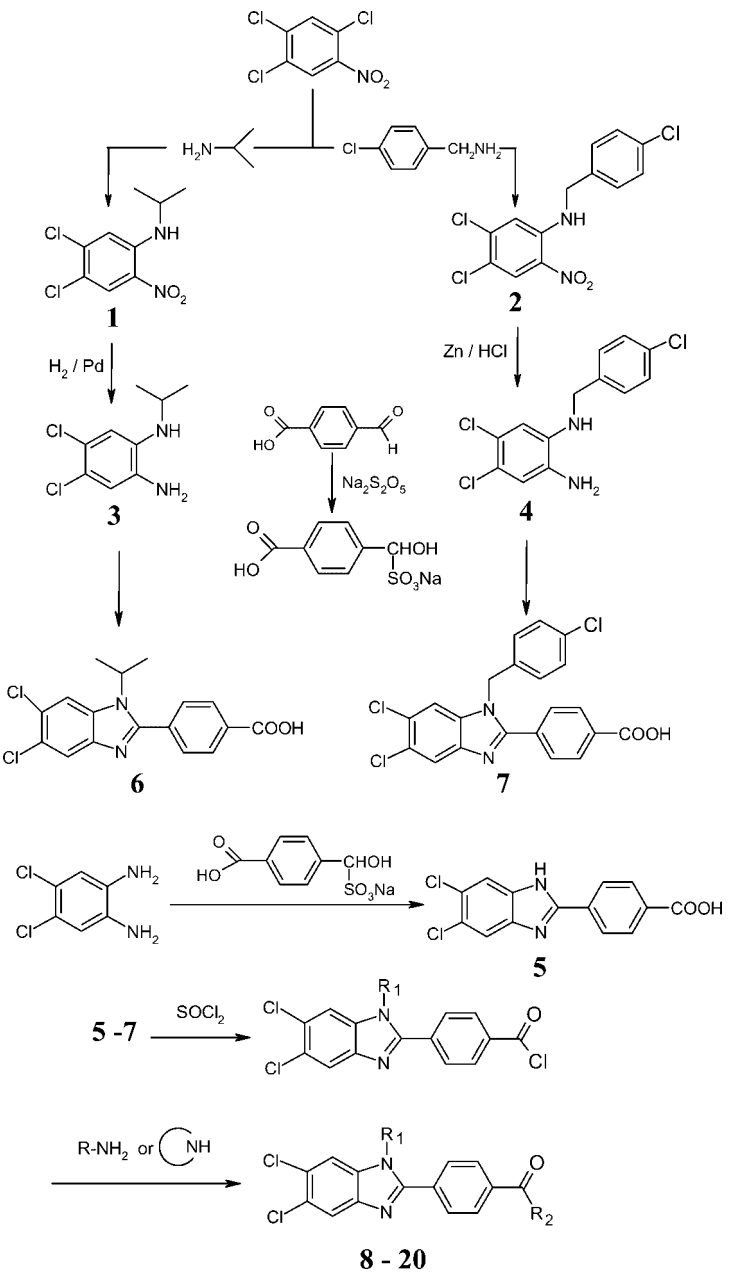
Table 1. (continued).

No	R_1	R_2	mp (°C)	Yield (%)	NMR (δ ppm)	MS (ESI+) *m/z* (rel. intensity)
16			175–176	39	($CDCl_3$): 2.33 (m, 5H), 2.51 (s, 2H), 3.43 (s, 2H), 3.82 (s, 2H), 5.32 (s, 2H), 6.99 (d, 2H), 7.30 (s, 1H), 7.35 (d, 2H, J = 8.4 Hz), 7.51 (d, 2H, J = 8.4 Hz), 7.68 (d, 2H, J = 8.3 Hz), 7.95 (s, 1H)	513 (M+H, 84) 125 (100)
17			175–177	28	($DMSO\text{-}d_6$): 3.32 (m, 2H), 3.42 (m, 2H), 3.63 (m, 2H), 3.97 (2H), 5.86 (s, 2H), 7.01 (t, 1H, J = 7.3 Hz), 7.17 (m, 4H), 7.42 (t, 2H, J = 7.7 Hz), 7.54 (d, 2H, J = 8.4 Hz), 7.76 (d, 2H, J = 8.2 Hz), 7.97 (d, 2H, J = 8.1 Hz), 8.17 (s, 1H), 8.25 (s, 1H)	575 (M+H, 100)
18			252–253	24	($CDCl_3$): 2.39 (s, 3H), 2.60 (t, 1H), 2.73 (br.s, 3H), 3.10 (br.s, 3H), 3.16 (t, 1H), 5.36 (s, 2H), 6.85 (br.s, 1H), 6.99 (d, 2H, J = 8.4 Hz), 7.33 (s, 1H), 7.35 (d, 2H, J = 8.4 Hz), 7.69 (d, 2H, J = 8.4 Hz), 7.85 (d, 2H, J = 8.3 Hz), 7.95 (s, 1H)	528 (M+H, 65) 125 (100)
19			220–222	45	($DMSO\text{-}d_6$): 1.79 (m, 2H), 1.96 (d, 2H), 2.22 (t, 2H), 3.01 (d, 2H), 3.66 (s, 2H), 3.98 (m, 1H), 5.84 (s, 2H), 7.16 (d, 2H, J = 8.4 Hz), 7.45 (m, 1H), 7.50–7.55 (m, 6H), 7.98 (d, 2H, J = 8.3 Hz), 8.15 (d, 2H, J = 8.34 Hz), 8.19 (s, 1H), 8.24 (s, 1H), 8.53 (d, 1H, J = 7.6 Hz)	603 (M+H, 100)
20			174–175	63	($DMSO\text{-}d_6$): 1.11 (d, 3H), 1.25 (m, 2H), 1.83 (m, 3H), 2.97 (m, 1H), 3.21 (m, 1H), 3.69 (m, 1H), 4.62 (m, 1H), 5.85 (s, 2H), 7.16 (d, 2H, J = 8.5 Hz), 7.52 (d, 2H, J = 8.5 Hz), 7.67 (d, 2H, J = 8.2 Hz), 7.94 (d, 2H, J = 8.2 Hz), 8.17 (s, 1H), 8.25 (s, 1H)	512 (M+H, 100)

corresponding acyl chlorides and amines resulted in the required benzamides. Some physicochemical properties and spectral findings of products **8**–**20** are given in Table 1.

Results and discussion

All described benzimidazoles **8**–**20** were tested *in vitro* for antibacterial activity against gram-positive *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA, clinical isolate), methicillin-resistant *S. epidermidis* (MRSE, clinical isolate), *Enterococcus faecalis*, gram-negative *Escherichia coli* bacteria, and for antifungal activity against *Candida albicans* by the diffusion method [7]. While some of the compounds exhibited good potencies against gram-positive bacteria (*S. aureus*, MRSA, MRSE and *E. faecalis*), none of the compounds were active against *E. coli*, and insignificant activity has been observed against *C. albicans*. The compounds giving a good growth inhibition zone in this method were further tested by the macro-broth dilution assay [8] to determine their MIC values, which are listed in Table 2. The synthesized compounds and reference drugs were dissolved in DMSO/H_2O (50%), at a concentration of 400 μg/mL. The concentration was adjusted to 100 μg/mL by fourfold dilution with



Scheme 1. Synthesis of the target compounds **8**−**20**.

culture medium and bacterial solution. Data was not taken for the initial solution because of the high DMSO concentration (12.5%). Since compound **19** is insoluble in DMSO/H_2O (50%), its antimicrobial activity was only determined by the diffusion method where it had a detectable growth inhibition zone, albeit not as clear as the others.

N^1 of the imidazole ring was substituted with isopropyl (**9**) and p-chlorobenzyl (**10**−**20**) groups. Compound **8**, having no substitution at the N^1 position, had better inhibitory activity than compound **9**; however, its potency was also not very significant. In our previous studies, we reported that introduction of a p-chlorobenzyl group at this position could enhance the antibacterial activity. So, in this study, the number of the compounds with a substituted N^1-4-chlorobenzyl group was increased (**10**−**20**). Actually, most of the active compounds were found among them, confirming that p-chlorobenzyl substitution plays a very important role

Table 2. The *in vitro* antibacterial activity of **8**–**20** (MIC; μg/mL)

No.	Purification method	Formulas anal. C,H,N	Antibacterial activity†			
			S. aureus	*MRSA*	*MRSE*	*E. faecalis*
8	$CHCl_3$-Isopr-NH_3 (20:11:1)	$C_{19}H_{20}Cl_2N_4O$	6.25	12.5	12.5	25
9	$CHCl_3$-Isopr-NH_3 (20:11:1)	$C_{22}H_{26}Cl_2N_4O$ 2HCl H_2O	50	25	25	50
10	$CHCl_3$-Isopr-NH_3 (20:11:1)	$C_{26}H_{25}Cl_3N_4O$ H_2O	3.12	3.12	3.12	6.25
11	$CHCl_3$-Isopr-NH_3 (20:11:1)	$C_{25}H_{23}Cl_3N_4O$ H_2O	3.12	3.12	3.12	3.12
12	$CHCl_3$-Isopr-NH_3 (20:5:0.5)	$C_{27}H_{27}Cl_3N_4O$ $0.5H_2O$	3.12	6.25	3.12	3.12
13	$CHCl_3$-Isopr-NH_3 (20:5:0.5)	$C_{24}H_{21}Cl_3N_4O$	3.12	3.12	25	25
14	$CHCl_3$	$C_{24}H_{20}Cl_3N_3O$	NT	NT	NT	NT
15	$CHCl_3$	$C_{28}H_{19}Cl_4N_3O$	NT	NT	NT	NT
16	$CHCl_3$-Isopr (10:0.5)	$C_{26}H_{23}Cl_3N_4O$ $0.85C_3H_8O$	12.5	25	12.5	12.5
17	$CHCl_3$	$C_{31}H_{25}Cl_3N_4O$	NT	NT	NT	NT
18	$CHCl_3$-Isopr (10:2)	$C_{26}H_{24}Cl_3N_5O$	12.5	50	12.5	12.5
19	$CHCl_3$	$C_{33}H_{29}Cl_3N_4O$	NT	NT	NT	NT
20	$CHCl_3$-Isopr (10:1)	$C_{27}H_{24}Cl_3N_3O$	NT	NT	NT	NT
Ampicillin			0.39	50	3.12	0.78
Sultamicillin			0.78	25	3.12	1.56

† NT – not tested. Since these compounds have no significant growth inhibition zone in the diffusion method, they were not tested here.

Table 3. Physical and spectral data of compounds **5**–**7**.

No.	Formula	mp (°C)	Yield (%)	NMR (δ ppm) (DMSO-d_6)	MS (ESI+) *m/z* (rel. intensity)
5	$C_{14}H_8Cl_2N_2O_2$	>250† 365	50	7.91 (s, 2H, not exchangeable with D_2O), 8.12 (d, 2H, J = 7.2 Hz), 8.26 (d, 2H, J = 7.2 Hz)	307 (M+H, 100)
6	$C_{17}H_{14}Cl_2N_2O_2$	333	62	1.59 (d, 6H, J = 6.8 Hz), 4.71 (m, 1H, J = 6.8 Hz), 7.81 (d, 2H, J = 8.8 Hz), 8.01 (s, 1H), 8.13 (d, 2H, J = 8.7 Hz), 8.22 (s, 1H)	349 (M+H, 100)
7	$C_{21}H_{13}Cl_3N_2O_2$	297	87	5.64 (s, 2H), 6.95 (d, 2H, J = 8 Hz), 7.32 (d, 2H, J = 8.1Hz), 7.78 (d, 2H, J = 8.4Hz), 7.93 (s, 1H), 8.02 (m, 3H)	431 (M+H, 23) 125 (100%)

† From reference [11].

for the best inhibitory activity. This finding was also put forward by other researchers [9]. The antimicrobiological data showed that analogues **10**–**13**, compound **11** in particular, exhibited the ability to inhibit *S. aureus*, MRSA, MRSE and *E. faecalis*, with most of the MIC values in the low micromolar range (3.12 μg/mL). While the clinically important agents ampicillin and sultamicillin are nearly inactive against MRSA (50 and 25 μg/mL, as well as no growth inhibition zone in the diffusion method), compounds **10**–**13** in this study showed better antimicrobial activity against MRSA. Inhibitory activity against drug-resistant microorganisms such as MRSA, which are clinically difficult to treat, is very important in the next generation of antibacterial

agents. From this point of view, there is an urgent need to discover novel antibacterial agents in different classes from existing agents. In addition, it has been observed that 2-ethylaminoethyl substitution on the N-carboxamide should be the optimum group in this series of compounds.

In conclusion, we have discovered a novel series of benzimidazole antibacterial agents. These compounds are active against a variety of susceptible, as well as resistant, gram-positive organisms. Some modifications to improve the potency of this series by diversification of the position and type of amides are currently under investigation and will be reported in the future.

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Experimental

Melting points were measured with a capillary melting point apparatus (Buchi SMP 20 and Electrothermal 9100) and are uncorrected. The IR spectra were recorded on a Jasco FT/IR-420 spectrometer as KBr pellets. **8**–**20**: 1610–1638 cm^{-1} (C=O amide). The ^{1}H-NMR spectra were recorded with VARIAN Mercury 400 FT-NMR spectrophotometers, δ scale (ppm) from TMS. LC/MS analyses were performed with Waters Alliance and Micromass ZQ (ESI +) by using MeOH and a C-18 column (15 cm) with a flow rate of 0.5–0.6 mL/min. The LC apparatus was equipped with a diode array UV detection system monitoring at 254 nm. Elemental analyses were taken on a Leco 932 CHNS-O analyzer (TUBITAK Instrumental Analyze Lab., Ankara, Turkey). For the HCl salt of compound **9**, the oily free base was dissolved in isopropanol, and dry HCl gas was passed through the solution.

*(4,5-Dichloro-2-nitrophenyl)isopropylamine (**1**) [10]*

To a solution of 1,2,4-trichloro-5-nitrobenzene (12.22 mmol, 2.75 g) in EtOH (3 mL), isopropylamine (8 mL) was added and heated for 8 h at 80 °C. The hot reaction mixture was allowed to crystallize from EtOH: yield 56 %, 1.7 g, mp 100 °C, orange in color; ^{1}H-NMR ($CDCl_3$) δ: 1.34 (d, 6H, J = 6 Hz), 3.77 (m, 1H, J = 6.1 Hz), 6.96 (s, 1H), 7.9 (br.s, 1H), 8.25 (s, 1H), $C_9H_{10}Cl_2N_2O_2$.

*(4-Chlorobenzyl)-(4,5-dichloro-2-nitrophenyl)amine (**2**)*

To a solution of 1,2,4-trichloro-5-nitrobenzene (22.2 mmol, 5 g) in DMF (3 mL), p-chlorobenzyl-amine (8 mL) was added and heated for 1 h at 80 °C. The hot reaction mixture was allowed to crystallize from EtOH. Second-time crystallization of the crude product from *n*-hexane gave pure **2**: yield 77 %, 5.63 g, mp 115–116 °C, yellow in color; ^{1}H-NMR (DMSO-d_6) δ: 4.66 (d, 2H, J = 5.6 Hz), 7.15 (s, 1H), 7.40 (4H), 8.27 (s, 1H), 8.8 (t, 1H), $C_{13}H_9Cl_3N_2O_2$.

*4,5-Dichloro-N-isopropylbenzene-1,2-diamine (**3**)*

1 (1.25 g, 5 mmol) dissolved in EtOH (50 mL) was added to 10 % Pd/C (50 mg), and the solution was hydrogenated at room temperature at 35 psi. The reaction was stopped after cessation of H_2 uptake. The catalyst was filtered through a bed of Celite, washed with EtOH and concentrated to provide a brown-colored semi-solid oily product that was used immediately for the further steps without crystallization. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (d, 6H, J = 6.4 Hz), 3.28 (br.s, 3H), 3.51 (m, 1H, J = 6.1 Hz), 6.64 (s, 1H), 6.74 (s, 1H); MS (ESI) *m/z* (rel. intensity): 219 (M+H, 100), $C_9H_{12}Cl_2N_2$.

*4,5-Dichloro-N-(p-chlorobenzyl)benzene-1,2-diamine (**4**)*

The mixture of **2** (1 g, 3 mmol) in 15 mL HCl (25 %) and 10 mL EtOH was stirred vigorously, and to this mixture, zinc dust (3.5 g) was added in several portions at room temperature. After the addition of zinc dust was completed, the mixture was heated in a water bath for 1 h. The reaction mixture was cooled and made alkaline with 10 % NaOH solution and was then extracted with EtOAc. The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography by using (EtOAc/*n*-hexane 1:3). mp 100–103 °C, light green in color, yield 69 %, 0.63 g; ^{1}H-NMR ($CDCl_3$) δ: 3.35 (br.s, 2H), 3.71 (br.s, 1H), 4.24 (s, 2H), 6.62 (s, 1H), 6.79 (s, 1H), 7.30 (m, 4H); MS (ESI) *m/z* (rel. intensity): 301 (M+H, 100), $C_{13}H_{11}Cl_3N_2$.

*Synthesis of **5**–**7***

4-Carboxybenzaldehyde (15 mmol) was dissolved in 50 mL EtOH. Sodium bisulfite (1.6 g) in water (10 mL) was added to a cooled solution in portions, stirred vigorously and, after addition of EtOH, cooled. The precipitate was filtered off and dried. Yield 90 %. The mixture of this salt (2 mmol) and the appropriate 1,2-phenylenediamines (4,5-dichloro-1,2-phenylenediamine and compounds **3** and **4**, 2 mmol) in DMF (2–3 mL) were heated at 120 °C for 4 h. The reaction mixture was cooled, poured into the water, and solid was crystallized from EtOH. The purification procedure and some spectral findings of **5**–**7** are given in Table 3.

*Synthesis of **8**–**20***

Related benzoic acids **5**–**7** (0.25 g) were refluxed in benzene (5 ml) with $SOCl_2$ (5 mL) for 2 h at 80 °C. Then, solvent and excess of $SOCl_2$ were evaporated completely, and the residue was dissolved in chloroform (15 mL). An excess of corresponding amine derivatives (1 mL) was added, and the mixture was stirred and heated for 30 min at 50 °C and, after chloroform was added, washed with Na_2CO_3 (5 %), then water, and purified by column chromatography. Some physicochemical properties, spectral findings, purification procedure and elemental analysis results of compounds **8**–**20** are given in Table 1 and Table 2.

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