Full Paper

Synthesis and Antistaphylococcal Activity of *N*-Substituted-1*H*-benzimidazole-sulphonamides

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A series of *N*-substituted-1*H*-benzimidazole-5(6)-sulfonamides and 3-(5,6-dichloro-1*H*-benzimidazol-2-yl)-*N*-substituted benzensulfonamides were synthesized and evaluated for antibacterial activity against *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA). Certain compounds inhibit bacterial growth with low MIC (μg/mL) values. The most active compounds **30**, **31**, and **32** have the lowest MIC values with 0.39 to 0.19 μg/mL. Among the compounds having sulfonamido moities, **16**, **23**, and **24** exhibited the strongest antibacterial activity with 1.56 μg/mL MIC values.

Keywords: Anti-staphylococcal activity / 1*H*-Benzimidazolesulphonamide / Methicillin-resistant *Staphylococcus aureus* / Tautomerism

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Introduction

Multiple drug-resistant organisms such as MRSA (Methicillin-resistant *Staphylococcus aureus*), VRE (Vancomycin resistant enterococci), MRSE (Methicillin-resistant *Staphylococcus epidermidis)* 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 agent 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** (Fig. 1) possessing amide functions at different positions; also, their promising antimicrobial activity results have been reported. Recently, two new benzimidazoles [4] having 3,5-di-*tert*-butyl-2-hydroxy-2-phenyl compounds **III** and **30** (Fig. 1) have been reported as inhibitors of histidine protein kinases from a bacterial two-component system, which showed very good antibacterial activity, in particular, against Gram-positive bacteria. These results prompted us to continue an investigation on a series of new N^1-substituted-1*H*-benzimidazole-5(6)-sulphonamides **11 – 35** and sulfonamides carrying 5,6-dichloro-N^1-substituted-1*H*-benzimidazoles **37 – 40**, which should be the bio-isosters of the potent compounds in Fig. 1. Herein, we report the synthesis of some *N*-sulphonylbenzimidazoles and the results concerning their potent anti-staphylococcal activity.

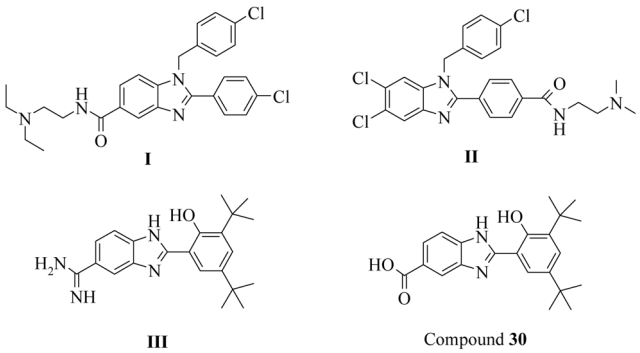

Figure 1. Structures of compounds **I**, **II**, **III**, and **30**.

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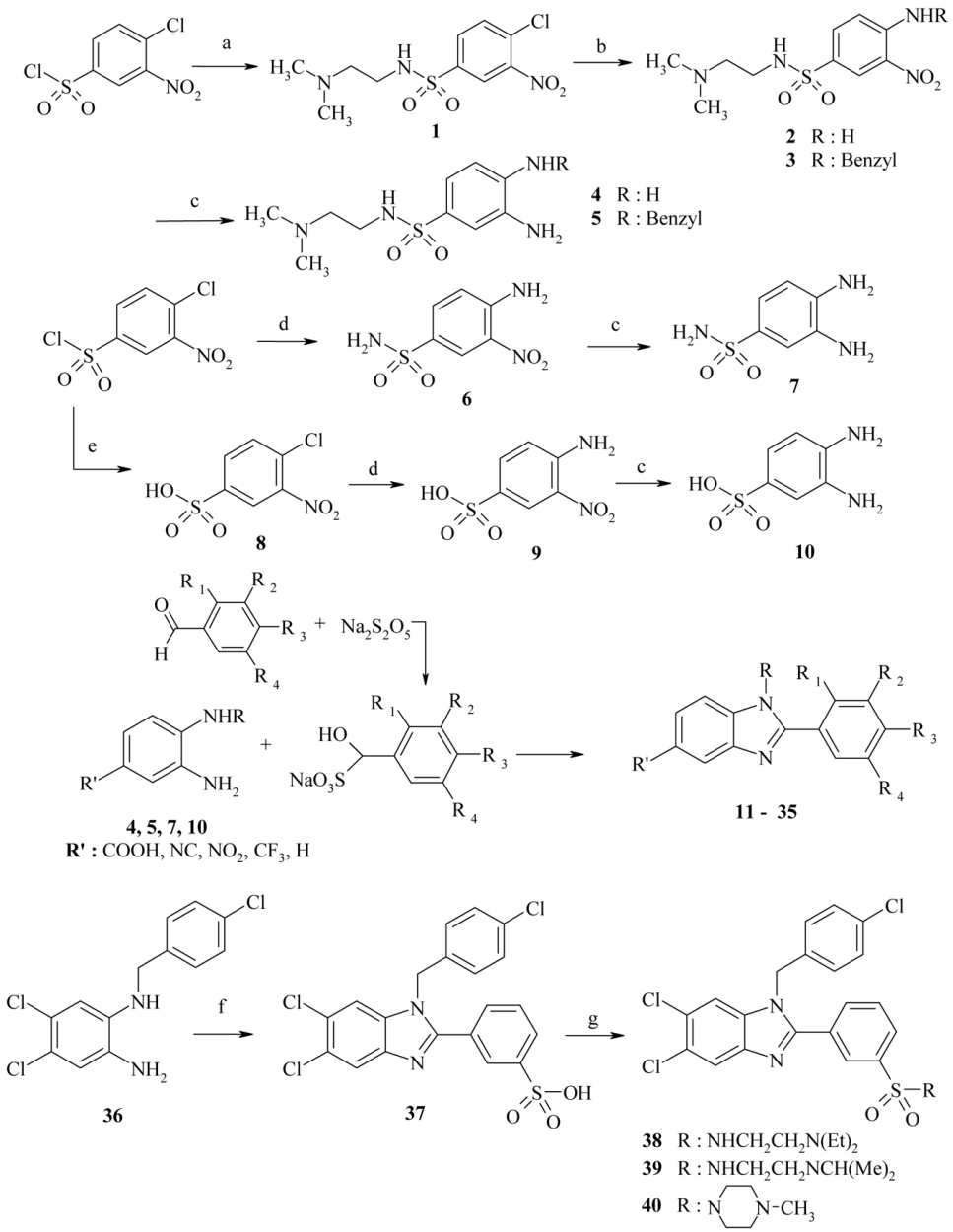

Reagents and conditions: (a) *N,N*-Dimethylethylenediamine; (b) NH_3 gas or benzyl amine; (c) H_2, Pd/C; (d) NH_4OH; (e) EtOH/H_2O; (f) $Na_2S_2O_5$ adduct of 3-formylbenzenesulfonic acid; (g) $SOCl_2$ and several amines.

Scheme 1. Synthesis of some intermediates and new benzimidazoles **11**–**35** and **37**–**40**.

Results and discussion

Chemistry

As depicted in Scheme 1, uncommercial starting materials, *N*-substituted benzensulfonamides **2**, **3**, were prepared by reaction of 4-chloro-3-nitrobenzensulphonyl chloride and the corresponding amines. Then, chlorine atoms were converted to amines by using the aromatic nucleophilic substitution reaction. The Pd/C-catalyzed reduction of **2**, **3**, and **6** gave the 3,4-diaminobenzene-5(6)-sulphonamides **4**, **5**, and **7**. 4-Chloro-3-nitrobenzensulphonyl chloride was hydrolyzed to sulfonic acid, then, the chlorine atom was transformed into amine. The Pd/C-catalyzed reduction of **9** gave 3,4-diaminobenzene-5(6)-sulfonic acid **10**. The final compounds **11**–**35** were obtained by the condensation of substituted *o*-phe-

Table 1. *In-vitro* antistaphylococcal activity and formulas of compounds **11** – **40**.

No	R′	R	R_1	R_2	R_3	R_4	R_5	Anti-staphylococcal activities MIC (μg/mL)	
								*S. aureus**	MRSA**
11	$(Me)_2NCH_2CH_2NHO_2S$-	H	H	Cl	Cl	H	H	>25	>25
12	$(Me)_2NCH_2CH_2NHO_2S$-	H	H	CF_3	H	CF_3	H	>25	>25
13	$(Me)_2NCH_2CH_2NHO_2S$-	H	H	benzyloxy	benzyloxy	H	H	>25	>25
14	$(Me)_2NCH_2CH_2NHO_2S$-	H	H	H	*p*-chloro-phenoxy	H	H	12.5	12.5
15	$(Me)_2NCH_2CH_2NHO_2S$-	H	OH	$C(CH_3)_3$	H	H	H	3.12	3.12
16	$(Me)_2NCH_2CH_2NHO_2S$-	H	OH	$C(CH_3)_3$	H	$C(CH_3)_3$	H	1.56	0.78
17	$(Me)_2NCH_2CH_2NHO_2S$-	benzyl	H	Cl	Cl	H	H	25	>25
18	$(Me)_2NCH_2CH_2NHO_2S$-	benzyl	H	CF_3	H	CF_3	H	>25	>25
19	$(Me)_2NCH_2CH_2NHO_2S$-	benzyl	Cl	Cl	H	Cl	H	>25	>25
20	$(Me)_2NCH_2CH_2NHO_2S$-	benzyl	H	Br	F	H	H	>25	>25
21	$(Me)_2NCH_2CH_2NHO_2S$-	benzyl	H	H	*p*-chloro-phenoxy	H	H	>25	>25
22	H_2NO_2S	H	H	Cl	Cl	H	H	>25	>25
23	H_2NO_2S	H	OH	$C(CH_3)_3$	H	H	H	1.56	1.56
24	H_2NO_2S	H	OH	$C(CH_3)_3$	H	$C(CH_3)_3$	H	1.56	0.78
25	HO_3S	H	H	Cl	Cl	H	H	>25	>25
26	HO_3S	H	Cl	H	H	H	Cl	>25	>25
27	HO_3S	H	OH	$C(CH_3)_3$	H	H	H	>25	>25
28	HO_3S	H	OH	$C(CH_3)_3$	H	$C(CH_3)_3$	H	12.5	12.5
29	HOOC	H	OH	$C(CH_3)_3$	H	H	H	3.12	6.25
30	HOOC	H	OH	$C(CH_3)_3$	H	$C(CH_3)_3$	H	0.39	0.78
31	NC	H	OH	$C(CH_3)_3$	H	H	H	0.39	0.39
32	NC	H	OH	$C(CH_3)_3$	H	$C(CH_3)_3$	H	0.39	0.19
33	O_2N	H	OH	$C(CH_3)_3$	H	$C(CH_3)_3$	H	>25	>25
34	F_3C	H	OH	$C(CH_3)_3$	H	H	H	3.12	3.12
35	H	H	OH	$C(CH_3)_3$	H	H	H	1.56	3.12
37								>25	>25
38								3.12	6.25
39								6.25	6.25
40								>25	>25
Ampicillin								0.78	25
Sultamicillin								0.78	25

MIC: minimum inhibitory concentration (μg/mL).
* *Staphyloccocus aureus* (ATCC 25923).
** Methicillin-resistant *Staphylococcus aureus* (MRSA; ATCC 43300).

nylendiamines **4**, **5**, **7**, **10** and other corresponding starting materials with the $Na_2S_2O_5$-adduct of arylaldehydes in DMF [5]. Compound **36** (Scheme 1) was published before [3]. Compound **37** was activated with thionyl chloride, then, acyl chlorides were amidified to yield the targeted sulphonamide derivatives **38** – **40**.

Microbiological studies

All described benzimidazoles **11** – **40** were tested *in vitro* for antibacterial activity against Gram-positive *S. aureus*, methicillin-resistant *S. aureus* (MRSA, clinical isolate), and other bacteria, and for antifungal activity against *Candida albicans* by diffusion method. While some of the compounds exhibit very good potencies against Gram-positive bacteria (*S. aureus* and MRSA), none of the compounds was active against *Escherichia coli*; unimportant activity has been observed against *C. albicans*. Therefore, all benzimidazoles were further tested by the macrobroth dilution assay [6] to determine the MIC's that are listed in Table 1. 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 media culture and bacteria solution. Data were not taken for the initial solution because of the high DMSO concentration (12.5%). Some of the compounds exhibited more potent inhibitory activity against the selected bacteria than the reference compounds Ampicillin and Sultamicillin. The most active compounds having a COOH- and a CN-group on position C-5(6), were **30** and **31**, **32**, respectively, having the lowest MIC values with 0.39 μg/mL. When these groups were exchanged with sulfonic acid, the activity was highly decreased (**28** with 12.5 μg/mL). However, replacement of the same group by sulphonamide resulted in an increased activity (**16**, **23**, **24** with 1.56 μg/mL value). In our previous studies, we have reported that benzyl substitution and chlorine substitution at positions N^1 and C-5(6), respectively, enhance the antibacterial activities against. Thus, compounds **38** – **40** were

designed, and the best result was obtained with **38** (3.12 μg/mL).

Experimental

Chemistry

Uncorrected melting points were measured on an Büchi B-540 capillary melting point apparatus (Büchi Labortechnik, Flawil, Switzerland). ^{1}H (400 MHz) and ^{13}C (100 MHz) -NMR spectra were recorded employing a Varian Mercury 400 MHz FT spectrometer (Varian Inc., Palo Alto, CA, USA), chemical shifts (δ) are in ppm relative to TMS, and coupling constants (*J*) are reported in Hertz. Mass spectra were taken on a Waters Micromass ZQ connected with Waters Alliance HPLC (Waters Corporation, Milford, MA, USA), using ESI(+) method, with a C-18 column. Elemental analyses were performed by Leco CHNS-932 (Leco, St. Joseph, MI, USA). The compounds reported as salts were frequently analyzed correctly for fractional moles of water and / or ethanol from solvation. All chemical and solvents were purchased from Aldrich Chemical Co. or Fischer Scientific.

Compound **36** [3], 4-(4-chlorophenoxy)benzaldehyde [7], 4-(3,4-dimethoxyphenoxy)-benzaldehyde [7], 3-formylbenzensulfonic acid [8] were published earlier. For the HCl salts of the synthesized compounds, the free bases were dissolved in ethanol and dry HCl gas was passed through the solution. Because of the tautomeric effect of the imidazole ring in compounds **23 – 28** and **30 – 34**, the ^{1}H-NMR spectra of some compounds are not clear enough under standard conditions. In order to prevent the tautomeric effects, the compounds were dissolved in DMSO-d_6, followed by a tiny amount of dry NaH, and 2 – 3 drops of D_2O were added to the NMR tube and stirred well. As it is reported below for compounds **23 – 28** and **30 – 34**, now very clear NMR spectra were observed.

4-Chloro-N-[2-(dimethylamino)ethyl]-3-nitrobenzenesulfonamide · HCl ***1***

A mixture of *N,N*-dimethylethylenediamine (1.1 mL, 10 mmol) and triethylamine (1.39 mL) in dichloromethane (10 mL) was added dropwise to a solution of 4-chloro-3-nitro-benzenesulfonyl chloride (2.56 g, 10 mmol) in dichloromethane (25 mL). The mixture was stirred at room temperature for 25 h. The solvent was removed by rotary evaporation, leaving a yellow powder which was taken up in ethyl acetate, washed with water, and dried (Na_2SO_4), and the solvent was removed *in vacuo*. Crystallization of the crude product from ethanolic HCl gave pure, light yellow colored **1**, 3.2 g (92%). M.p.: 175 – 177°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.78 (s, 6H), 3.12 – 3.20 (m, 4H), 8.06 (d, 1H, J_o = 8.4 Hz), 8.12 (dd, 1H, J_o = 6.8 Hz, J_m = 1.6 Hz), 8.49 (d, 1H, J_m = 1.6 Hz); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 148.18, 140.5, 133.9, 131.21, 130.29, 124.84, 56.22, 38.22, 43.02, 41.24; MS *m/e*: 308 [M + 1] (100%), 310 [M + 1 + 2] (35%).

4-Amino-N-[2-(dimethylamino)ethyl]-3-nitrobenzenesulfonamide ***2***

A mixture of **1** (0.6 g, 0.18 mmol) and saturated ethanolic ammonia (30 mL) was heated in sealed tube for 4 h at 110°C. The mixture was allowed to cool and was then evaporated, the residue was washed with water and dried. Yield: 0.42 g (84%), yellow colored; m.p.: 250 – 252°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.73 (s, 6H), 3.06 – 3.12 (s, 4H), 7.18 (d, 1H, J_o = 8.4 Hz), 7.74 (dd, 1H, J_o = 7.6 Hz), 8.1 (br.s, 2H), 8.37 (s, 1H), 10.6 (br.s, 1H); ^{13}C-NMR (DMSO-d_6) δ ppm: 149, 133.1, 129.5, 126.61, 125.8, 121.03, 56.18, 42.94, 38.16; MS *m/e*: 289 [M + 1] (100%).

3-Nitro-4-benzylamino-N-[2-(dimethylamino)ethyl]benzenesulfonamide ***3***

A mixture of **1** (0.6 g, 0.18 mmol) and benzyl amine (1 mL) in DMF (1 mL) was heated under reflux for 5 h at 110°C. The mixture was allowed to cool and water was added. The resultant yellow precipitate was filtered, washed with water and crystallized from ethanol. Yield: 0.5 g (79%); m.p.: 166 – 168°C; ^{1}H-NMR ($CDCl_3$) δ [ppm]: 2.09 (s, 6H), 2.34 (t, 2H, *J* = 5.2 Hz), 2.96 (t, 2H, *J* = 5.2 Hz), 4.6 (d, 2H, *J* = 5.6 Hz), 6.91 (d, 1H, *J* = 9.2 Hz), 7.32 – 7.41 (m, 4H), 7.81 (dd, 1H, J_o = 8.8 Hz, J_m = 2 Hz), 8.71 – 8.75 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ [ppm]: 147.24, 136.27, 133.98, 131.33, 129.39, 128.39, 127.47, 127.28, 126.85, 115.16, 57.12, 47.56, 44.97, 40.21; MS *m/e*: 379 [M + 1] (100%).

3,4-Diamino-N-[2-(dimethylamino)ethyl]benzenesulfonamide ***4***

Compound **2** (0.289 g, 1 mmol) in ethanol (30 mL) was subjected to hydrogenation using 40 psi of H_2 and 10% Pd/C until uptake of H_2 ceased. The catalyst was filtered on a bed of Celite, washed with ethanol, and concentrated *in vacuo*. The oily residue was used for the subsequent steps without crystallization. ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.70 (s, 6H), 2.93 (2H), 3.05 (2H), 6.56 (d, 1H, J_o = 8 Hz), 6.87 (dd, 1H), 6.93 (s, 1H, J_m = 1.7 Hz), 7.40 (t, 1H); MS *m/e*: 259 [M + 1] (100%).

3-Amino-4-benzylamino-N-[2-(dimethylamino)ethyl]benzenesulfonamide ***5***

It was obtained in the manner as described for **4** with compound **3** (0.45 g, 1.19 mmol). ^{1}H-NMR ($CDCl_3$) δ [ppm]: 2.09 (s, 6H), 2.34 (t, 2H, *J* = 5.2 Hz), 2.93 (t, 2H, *J* = 5.2 Hz), 4.36 (d, 2H), 6.61 (d, 1H, *J* = 8.4 Hz), 7.25 – 7.81 (m, 7H); ^{13}C-NMR ($CDCl_3$) δ [ppm]: 142.13, 138.42, 133.4, 129, 127.82, 127.6, 121.55, 115.44, 110.2, 57.3, 48.26, 44.9, 40.22; MS *m/e*: 349 [M + 1] (100%).

3-Nitro-4-aminobenzenesulfonamide ***6***

A mixture of 4-chloro-3-nitro-benzenesulfonyl chloride (1 g, 0.39 mmol) and dioxane (5 mL) and ethyl acetate (5 mL) was heated in a sealed tube for 10 h at 110°C. The mixture was allowed to cool and was evaporated, and the residue was washed with water and dried. Yield: 0.78 g (91%); m.p.: 207 – 208°C, lit.: [9]: 209°C.

3,4-Diaminobenzenesulfonamide ***7***

It was obtained in the manner as described for **4** with compound **6** (0.5 g, 1.19 mmol). Yield: 0.4 g (93%), black colored powder; m.p.: 170 – 172°C, lit.: [10] 174 – 175°C.

4-Chloro-3-nitrobenzenesulfonic acid ***8***

A mixture of 4-chloro-3-nitro-benzenesulfonyl chloride (0.5 g, 0.195 mmol) and ethanol (85 – 90%, 30 mL) was heated under reflux for 1 h. The mixture was allowed to cool, evaporated, and the solid residue was collected. Yield: 0.4 g, (86%); ^{1}H-NMR (DMSO-d_6) δ [ppm]: 7.77 (d, 1H, J_o = 8.4 Hz), 7.88 (dd, 1H, J_o = 8.4 Hz, J_m = 2 Hz), 8.16 (d, 1H, J_m = 2 Hz); ^{13}C-NMR (DMSO-d_6) δ [ppm]:

149.05, 147.5, 132.33, 131.42, 125.82, 123.23; MS ESI(−) *m/e*: 236 [M − 1] (100%).

4-Amino-3-nitrobenzenesulfonic acid ***9***

A mixture of **8** (0.4 g, 1.7 mmol), ammonium hydroxide solution (25%, 10 mL) and ethanol (10 mL) was heated in a sealed tube for 6 h at 100°C. The mixture was allowed to cool and was evaporated, the residue was stirred with diluted HCl, washed with water and dried, heated and stirred in isopropanol, cooled and filtered. Yield: 0.34 g (93%), yellow colored powder; m.p.: >300°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 6.94 (d, 1H, J_o = 8.8 Hz), 7.52 (dd, 1H, J_o = 8.8 Hz, J_m = 2 Hz), 7.56 (br.s, D_2O exchangable), 8.14 (d, 1H, J_m = 2 Hz); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 146.93, 136.5, 133.96, 129.12, 122.91, 119.44; MS ESI(−) *m/e*: 217 [M − 1] (100%).

3,4-Diaminobenzenesulfonic acid ***10***

It was obtained as described for **4** with compound **9** (0.3 g, 1.4 mmol). Yield: 0.2 g, (81%), cream-colored powder; m.p.: >300°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 4.7 (br.s), 6.35 (d, 1H, J_o = 7.6 Hz), 6.65 (dd, 1H, J_o = 8 Hz, J_m = 2 Hz), 7.68 (d, 1H, J_m = 2 Hz); ^{1}H-NMR (D_2O) δ [ppm]: 6.70 (d, 1H, J_o = 8.4 Hz), 7.01 (dd, 1H, J_o = 8 Hz, J_m = 2 Hz), 7.044 (d, 1H, J_m = 2 Hz); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 137.57, 136.23, 134.22. 115.87, 113.26, 113.12; ^{13}C-NMR (D_2O) δ [ppm]: 137.99, 133.69, 132.89, 118.79, 116.66, 114.7; MS *m/e*: 189 [M + 1] (100%).

General procedure for the synthesis of ***11 – 35*** *and* ***37***

The corresponding benzaldehydes (6 mmol) were dissolved in EtOH (20 mL), and sodium metabisulfite (0.64 g) in H_2O (3 mL) was added in portions. The reaction mixture was stirred vigorously and more EtOH was added. The mixture was kept in a refrigerator for several hours. The precipitate was filtered and dried. The mixture of these salts (1 mmol) and **4**, **5**, **7**, **10** and other corresponding *o*-phenylenediamines (1 mmol) in DMF (1 – 2 mL) was heated at 110°C for 4 h. The reaction mixture was cooled, poured into water, and the solid was filtered. If it was not solid, it was extracted with chloroform.

2-(3,4-Dichlorophenyl)-N-[2-(dimethylamino)ethyl]-1H-benzimidazol-5(6)-sulfonamide ***11***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 12:2:0.1). Yield: 17.5%; m.p.: 196 – 197°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.05 (s, 6H), 2.26 (t, 2H), 2.82 (t, 2H), 7.70 (dd, 1H, J_o = 8.4 Hz, J_m = 1.6 Hz), 7.81 (d, 1H, J_o = 8.4 Hz), 7.88 (d, 1H, J_o = 8.8 Hz), 8.06 (s, 1H), 8.18 (dd, 1H, J_o = 8.4 Hz, J_m = 2 Hz), 8.42 (d, 1H, J_m = 2 Hz); ^{13}C-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 159.2, 148.17, 146.5, 138.58, 136.9, 131.4, 130.86, 129.4, 128.4, 127.03, 118.14, 115.94, 115.56, 62.16, 45.77, 44.2; MS *m/e*: 413 [M + 1] (100%), 415 [M + 1 + 2] (67%), 417 [M + 1 + 4] (11%). Anal. calcd. for $C_{17}H_{18}Cl_2N_4O_2S$: C, 49.4; H, 4.39; N, 13.56; S, 7.76. Found: C, 49.03; H, 4.60; N, 13.58; S, 7.70.

2-[3,5-Bis(trifluoromethyl)phenyl]-N-[2-(dimethylamino)-ethyl]-1H-benzimidazol-5(6)-sulfonamide ***12***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 12:2:0.1). Yield: 22.5%; m.p.: 215 – 216°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.04 (s, 6H), 2.24 (t, 2H), 2.81 (t, 2H), 7.70 (dd, 1H, J_o = 8.8 Hz, J_m = 2 Hz), 7.84 (d, 1H, J_o = 8.4 Hz), 8.09 (d, 1H, J_m = 1.2 Hz), 8.30 (s, 1H), 8.82 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 151.9, 141.67, 140.06, 135.28, 132.64, 131.86 (q, J = 33.5 Hz, CF_3), 127.69, 125.11, 124.21, 122.4, 121.95, 116.15, 58.49, 45.49, 41.1; MS *m/e*: 481 [M + 1] (100%). Anal. calcd. for $C_{19}H_{18}F_6N_4O_2S \cdot 0.1\ C_3H_8O$: C, 47.65; H, 3.90; N, 11.52; S, 6.59. Found: C, 47.52; H, 3.94; N, 11.69; S, 6.80.

2-(3,4-Dibenzyloxyphenyl)-N-[2-(dimethylamino)ethyl]-1H-benzimidazol-5(6)-sulfonamide · HCl ***13***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 12:2:0.1). Yield: 25.5%, m.p.: 245 – 246°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.75 (d, 6H, J = 4 Hz)*, 3.10 (4H)*, 5.32 (s, 2H), 5.35 (s, 2H), 7.32 – 7.56 (m, 11H), 7.92 (d, 1H, J_o = 9.2 Hz), 7.97 (d, 1H, J_o = 8.4 Hz), 8.10 (d, 1H, J_o = 8 Hz), 8.21 (s, 1H), 8.36 (t, 1H), 8.42 (s, 1H), 10.43 (s, 1H); * D_2O exchangable: 2.76 (s, 6H), 3.10 (t, 2H), 3.14 (t, 2H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 152.96, 152.69, 149.14, 137.34, 137.21, 136.81, 136.31, 134.12, 129.18, 129.13, 128.69, 128.54, 128.27, 123.76, 123.04, 117.27, 115.4, 114.98, 114.3, 113.94, 71.13, 70.72, 56.27, 43.03, 38.31; MS *m/e*: 557 [M + 1] (100%). Anal. calcd. for $C_{31}H_{32}N_4O_4S \cdot 2.3\ H_2O \cdot 2$ HCl: C, 55.48; H, 5.80; N, 8.35; S, 4.78. Found: C, 55.44; H, 5.89; N, 8.44; S, 4.87.

2-(4-(4-Chlorophenoxy)phenyl)-N-[2-(dimethylamino)-ethyl]-1H-benzimidazol-5(6)-sulfonamide ***14***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 12:2:0.1). Yield: 12.6%; m.p.: 68 – 69°C; ^{1}H-NMR (DMSO-d_6 + 3 drops D_2O) δ [ppm]: 1.99 (s, 6H), 2.21 (t, 2H), 2.77 (t, 2H), 7.10 – 7.46 (m, 6H), 7.62 (dd, 1H, J_o = 8.8 Hz, J_m = 1.6 Hz), 7.72 (d, 1H, J_o = 8 Hz), 7.98 (s, 1H), 8.16 (d, 2H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 159.33, 155.21, 154.28, 134.64, 130.82, 129.58, 128.81, 125.41, 121.94, 121.26, 119.3, 58.71, 45.7, 41.4. MS *m/e*: 471 [M + 1] (100%), 473 [M + 1 + 2] (33%). Anal. calcd. for $C_{23}H_{23}ClN_4O_3S \cdot 0.5\ C_2H_6O \cdot 0.5\ H_2O$: C, 57.31; H, 5.41; N, 11.13; S, 6.37. Found: C, 57.49; H, 5.52; N, 11.07; S, 6.40.

2-(3-tert-Butyl-2-hydroxyphenyl)-N-[2-(dimethyl-amino)ethyl]-1H-benzimidazol-5(6)-sulfonamide ***15***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 20:2:0.05). Yield: 40.4%; m.p.: 182 – 183°C; ^{1}H-NMR (DMSO-d_6 + 3 drops D_2O) δ [ppm]: 1.44 (s, 9H), 2.08 (s, 6H), 2.31 (t, 2H), 2.87 (t, 2H), 7.00 (t, 1H, J_o = 8 Hz), 7.42 (d, 1H, J_o = 7.2 Hz), 7.74 (dd, 1H, J_o = 8.4 Hz), 7.84 (d, 1H), 7.90 (d, 1H, J_o = 7.6 Hz), 8.10 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 157.76, 155.99, 137.94, 134.79, 130.09, 125.04, 121.80, 119.54, 112.60, 58.30, 45.32, 40.90, 35.30, 29.84; MS *m/e*: 417 [M + 1] (100%). Anal. calcd. for $C_{21}H_{28}N_4O_3S$: C, 60.55; H, 6.78; N, 13.45; S, 7.70. Found: C, 60.57; H, 6.70; N, 13.37; S, 7.66.

2-(3,5-Di-tert-butyl-2-hydroxyphenyl)-N-[2-(dimethyl-amino)ethyl]-1H-benzimidazol-5(6)-sulfonamide ***16***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 20:2:0.05). Yield: 32.4%; m.p.: 112 – 114°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 1.20 (s, 9H), 1.30 (s, 9H), 1.90 (s, 6H), 2.11 (t, 2H), 2.70 (t, 2H), 7.25 (d, 1H, J_m = 2 Hz), 7.58 (d, 1H, J_o = 8.4 Hz), 7.68 (s, 1H), 7.81 (d, 1H), 7.96 (s, 1H), 13.39 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 156.22, 155.95, 141.12, 137.06, 135.39, 127.08, 121.66, 111.82, 98.06, 58.71, 45.68, 41.39, 35.54, 34.93, 32.08, 30.0; MS *m/e*: 473 [M + 1] (100%). Anal. calcd. for $C_{25}H_{36}N_4O_3S \cdot 0.5\ C_3H_8O$: C, 63.31; H, 8.02; N, 11.15; S, 6.38. Found: C, 63.16; H, 7.89; N, 11.36; S, 6.47.

1-Benzyl-2-(3,4-dichlorophenyl)-N-[2-(dimethylamino)-ethyl]-1H-benzimidazol-5-sulfonamide ***17***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 12:2:0.1). Yield: 22%; m.p.: 124 – 126°C; ^{1}H-NMR ($CDCl_3$) δ [ppm]: 2.05 (s, 6H), 2.32 (t, 2H), 3.00 (t, 2H), 5.48 (s, 2H), 7.03 – 7.05 (m, 2H), 7.34 – 7.36 (m, 4H), 7.48 (dd, 1H, J_o = 8.8 Hz, J_m = 1.6 Hz), 7.55 (d, 1H, J_o = 8 Hz), 7.79 (dd, 1H, J_o = 8.4 Hz, J_m = 1.6 Hz), 7.83 (d, 1H, J_m = 2 Hz), 8.39 (d, 1H, J_m = 2 Hz); MS *m*/*e*: 503 [M + 1] (100%), 505 [M + 1 + 2] (65%), 507 [M + 1 + 4] (11%). Anal. calcd. for $C_{24}H_{24}Cl_2N_4O_2S \cdot 0.1\ C_3H_8O \cdot 1.1\ CH_2Cl_2 \cdot 1.5\ H_2O$: C, 48.43; H, 4.80; N, 8.90; S, 5.09. Found: C, 48.22; H, 4.75; N, 9.32; S, 5.45.

2-[3,5-Bis(trifluoromethyl)phenyl]-1-benzyl-N-[2-(dimethylamino)ethyl]-1H-benzimidazol-5-sulfonamide ***18***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 12:2:0.1). Yield: 31%; m.p.: 174 – 175°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.05 (s, 6H), 2.25 (t, 2H), 2.85 (t, 2H), 5.71 (s, 2H), 7.02 (m, 2H), 7.25 – 7.31 (m, 3H), 7.79 (dd, 1H, J_o = 8.4 Hz, J_m = 2 Hz), 7.87 (d, 1H, J_o = 8.8 Hz), 8.20 (d, 1H, J_m = 1.6 Hz), 8.29 ve 8.31 (s, s, 3H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 153.33, 142.29, 139.28, 136.95, 135.88, 132.69, 131.51 (q, CF_3), 130.44, 129.59, 128.44, 126.80, 124.94, 124.55, 122.50, 122.23, 119.40, 112.80, 58.74, 48.68, 45.71, 41.46; ^{19}F-NMR (DMSO-d_6) δ [ppm]: −61.873; MS *m*/*e*: 571 [M + 1] (100%). Anal. calcd. for $C_{26}H_{24}F_6N_4O_2S \cdot 0.2\ C_2H_6O \cdot 0.1\ H_2O$: C, 54.52; H, 4.40; N, 9.63; S, 5.51. Found: C, 54.26; H, 4.01; N, 9.85; S, 5.68.

1-Benzyl-N-[2-(dimethylamino)ethyl]-2-(2,3,5-trichlorophenyl)-1H-benzimidazol-5-sulfonamide ***19***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 12:2:0.1). Yield: 29.85%; m.p.: 170 – 171°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.01 (s, 6H), 2.21 (t, 2H), 2.79 (t, 2H), 5.40 (s, 2H), 6.94 – 7.77(m, 8H), 8.08 (d, 1H, J_m = 2 Hz), 8.16 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 151.93, 142.36, 137.69, 136.34, 135.59, 134.25, 133.16, 132.91, 132.71, 131.55, 131.34, 129.28, 128.47, 127.62, 122.21, 119.42, 112.81, 58.76, 48.41, 45.70, 41.45; MS *m*/*e*: 537 [M + 1] (98%), 539 [M + 1 + 2] (100%), 541 [M + 1 + 4] (35%). Anal. calcd. for $C_{24}H_{23}Cl_3N_4O_2S$: C, 53.59; H, 4.31; N, 10.42; S, 5.96. Found: C, 53.28; H, 4.18; N, 10.41; S, 6.02.

1-Benzyl-2-(3-bromo-4-fluorophenyl)-N-[2-(dimethylamino)ethyl]-1H-benzimidazol-5-sulfonamide ***20***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 12:2:0.1). Yield: 22.7%; m.p.: 142 – 143°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.01 (s, 6H), 2.21 (t, 2H), 2.80 (t, 2H), 5.65 (s, 2H), 6.98 (d, 2H, J_o = 7.6 Hz), 7.24 – 7.30 (m, 3H), 7.55 (t, 1H, J_o = 8.4 Hz), 7.70 – 7.79 (m, 3H), 8.05 (dd, 1H, J_o = 6.4 Hz, J_m = 1.6 Hz), 8.15 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 160.09 (d, J = 247 Hz), 154.17, 142.40, 138.96, 136.99, 135.57, 134.96, 131.48 (d, J = 8.3 Hz), 129.60, 128.43, 128.26 (d, J = 7.2 Hz), 126.88, 122.05, 119.10, 118.02 (d, J = 22.8 Hz), 112.67, 109.34 (d, J = 21.3 Hz), 58.75, 48.53, 45.73, 41.46; ^{19}F-NMR (DMSO-d_6) δ [ppm]: −85.00; MS *m*/*e*: 531 [M + 1] (98%), 533 [M + 1 + 2] (100%). Anal. calcd. for $C_{24}H_{24}BrFN_4O_2S \cdot 0.1\ H_2O \cdot 0.1\ C_3H_8O$: C, 54.12; H, 4.67; N, 10.39; S, 5.95. Found: C, 53.97; H, 4.26; N, 10.55; S, 6.15.

1-Benzyl-2-[4-(4-chlorophenoxy)phenyl]-N-[2-(dimethylamino)ethyl]-1H-benzimidazol-5-sulfonamide ***21***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 12:2:0.1). Yield: 41%; m.p.: 153 – 154°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.05 (s, 6H), 2.25 (t, 2H), 2.85 (t, 2H), 5.65 (s, 2H), 7.01 (d, 2H), 7.12 – 7.16 (m, 4H), 7.24 – 7.28 (m, 3H), 7.45 – 7.49 (m, 2H), 7.66 (d, 1H, J_o = 8.8 Hz), 7.69 (dd, 1H, J_o = 8.4 Hz, J_m = 1.6 Hz), 7.76 – 7.79 (m, 2H), 8.15 (d, 1H, J_m = 1.2 Hz); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 158.91, 155.90, 155.27, 142.61, 138.93, 137.07, 135.31, 131.86, 130.77, 129.54, 128.81, 128.32, 126.80, 125.22, 121.86, 121.66, 119.08, 118.84, 112.44, 58.72, 48.47, 45.69, 41.41; MS *m*/*e*: 561 [M + 1] (100%), 563 [M + 1 + 2] (35%). Anal. calcd. for $C_{30}H_{29}ClN_4O_3S \cdot 0.1\ H_2O$: C, 64.01; H, 5.22; N, 9.98; S, 5.70. Found: C, 63.94; H, 4.81; N, 10.11; S, 5.83.

2-(3,4-Dichlorophenyl)-1H-benzimidazol-5(6)-sulfonamide ***22***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 20:2:0.05). Yield: 20.6%; m.p.: 254 – 256°C; ^{1}H-NMR (DMSO-d_6 + 3 drops D_2O) δ [ppm]: 7.67 – 7.76 (m, 3H), 8.03 – 8.06 (m, 2H), 8.28 (d, 1H, J_m = 2 Hz); MS *m*/*e*: 342 [M + 1] (100%), 344 [M + 1 + 2] (66%), 346 [M + 1 + 4] (11%). Anal. calcd. for $C_{13}H_9Cl_2N_3O_2S \cdot 0.25\ C_3H_8O \cdot 0.5\ C_2H_6O$: C, 46.59; H, 3.71; N, 11.05; S, 8.43. Found: C, 46.78; H, 3.59; N, 11.29; S, 8.41.

2-(3-tert-Butyl-2-hydroxyphenyl)-1H-benzimidazol-5(6)-sulfonamide ***23***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 20:2:0.05). Yield: 49.3%; m.p.: 234 – 235°C; ^{1}H-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 1.41 (s, 9H), 6.71 (t, 1H, J_o = 8 Hz), 7.10 (d, 1H, J_o = 7.2 Hz), 7.35 (dd, 1H, J_o = 8 Hz, J_m = 1.6 Hz), 7.45 (d, 1H, J_o = 8.4 Hz), 7.88 (s, 1H), 8.05 (d, 1H, J_o = 7.2 Hz); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 158.13, 158.07, 155.75, 155.42, 143.26, 140.57, 139.72, 139.35, 137.96, 137.89, 135.87, 133.10, 130.05, 129.96, 125.11, 121.69, 120.87, 119.33, 118.69, 116.36, 112.58, 112.49, 112.44, 110.23, 35.38, 29.93; ^{13}C-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 163.87, 158.14, 147.02, 143.92, 136.49, 135.25, 126.52, 125.91, 119.34, 117.72, 116.79, 115.27, 113.95, 35.13, 30.12; MS *m*/*e*: 346 [M + 1] (100%). Anal. calcd. for $C_{17}H_{19}N_3O_3S \cdot 0.1\ C_4H_8O_2 \cdot 0.1\ H_2O$: C, 58.69; H, 5.66; N, 11.8; S, 9.00. Found: C, 58.22; H, 5.18; N, 11.51; S, 8.91.

2-(3,5-Di-tert-butyl-2-hydroxyphenyl)-1H-benzimidazol-5(6)-sulfonamide ***24***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 20:2:0.05). Yield: 16%; m.p.: 263 – 265°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 1.21 (s, 9H), 1.30 (s, 9H), 7.23 – 7.28 (m, 3H), 7.60 – 8.02 (m, 4H), 13.18 ve 13.22 (2H); ^{1}H-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 1.29 (s, 9H), 1.42 (s, 9H), 7.04 (s, 1H), 7.24 (m, 2H), 7.78 (s, 1H), 8.08 (br.s, 1H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 155.85, 155.67, 155.57, 155.51, 143.08, 140.85, 140.39, 139.31, 138.95, 136.84, 136.74, 135.60, 132.80, 126.82, 126.69, 121.32, 121.30, 120.51, 118.32, 115.99, 112.05, 111.53, 111.44, 109.77, 35.24, 34.64, 31.78, 29.70; ^{13}C-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 163.01, 155.97, 145.35, 143.53, 140.92, 138.93, 135.56, 123.10, 122.37, 118.56, 116.99, 114.53, 113.11, 35.70, 34.82, 32.14, 30.18; MS *m*/*e*: 402 [M + 1]

(100%). Anal. calcd. for $C_{21}H_{27}N_3O_3S \cdot H_2O$: C, 60.11; H, 6.96; N, 10.01; S, 7.64. Found: C, 60.1; H, 6.64; N, 10.11; S, 7.66.

2-(3,4-Dichlorophenyl)-1H-benzimidazol-5(6)-sulfonic acid ***25***

It was purified by column chromatography (dichloromethane/ethanol, 10:1). Yield: 29.2%; m.p.: >300°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 7.47 – 8.14 (5H), 8.36 (d, 1H), 13.15 (s, s); ^{1}H-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 7.18 (dd, 1H, J_o = 8 Hz, J_m = 2 Hz), 7.32 (d, 1H, J_o = 8.4 Hz), 7.54 (d, 1H, J_o = 8 Hz), 7.75 (d, 1H), 8.16 (dd, 1H, J_o = 8.4 Hz, J_m = 2 Hz), 8.37 (d, 1H, J_m = 2 Hz); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 150.64, 150.53, 144.34, 144.08, 143.31, 143.22, 135.79, 134.73, 133.07, 132.54, 131.99, 131.25, 128.71, 127.21, 122.18, 121.10, 118.74, 116.94, 111.36, 109.76; ^{13}C-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 159.42, 148.25, 146.45, 138.55, 137.74, 131.47, 130.86, 129.49, 128.50, 127.08, 117.16, 115.53, 114.76; MS *m*/*e*: 343 [M + 1] (100%), 345 [M + 1 + 2] (67%), 347 (11%) [M + 1 + 4]. Anal. calcd. for $C_{13}H_8Cl_2N_2O_3S \cdot 1.25\ CH_4O \cdot CH_2Cl_2 \cdot 0.1\ C_2H_6O$: C, 39.25; H, 3.32; N, 5.92; S, 6.78. Found: C, 39.16; H, 3.18; N, 6.40; S, 6.29.

2-(2,6-Dichlorophenyl)-1H-benzimidazol-5(6)-sulfonic acid ***26***

It was purified by column chromatography (dichloromethane/methanol/acetic acid, 10:1:0.1). Yield: 24.9%; m.p.: 288 – 290°C; ^{1}H-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 7.19 (dd, 1H, J_o = 8.4 Hz, J_m = 2 Hz), 7.31 – 7.42 (m, 4H), 7.74 (d, 1H, J_m = 1.6 Hz); ^{13}C-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 158.76, 147.45, 145.51, 138.29, 136.57, 135.72, 130.12, 128.24, 116.13, 115.36, 114.61; MS *m*/*e*: 343 [M + 1] (100%), 345 [M + 1 + 2] (66%), 347 [M + 1 + 4] (11%).

2-(3-tert-Butyl-2-hydroxyphenyl)-1H-benzimidazol-5(6)-sulfonic acid ***27***

It was purified by column chromatography (dichloromethane/ethanol, 10:1). Yield: 29.5%; m.p.: >300°C; ^{1}H-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 1.38 (s, 9H), 6.65 (t, 1H, J_o = 7.6 Hz), 7.04 (d, 1H, J_o = 7.6 Hz), 7.21 (dd, 1H, J_o = 8 Hz, J_m = 1.2 Hz), 7.32 (d, 1H, J_o = 8.4 Hz), 7.71 (s, 1H), 7.99 (dd, 1H, J_o = 7.2 Hz, J_m = 1.2 Hz); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 157.92, 154.07, 154.01, 144.36, 143.63, 141.24, 140.31, 137.77, 137.75, 133.87, 132.85, 129.45, 124.86, 122.31, 121.39, 119.14, 117.44, 115.62, 112.95, 112.89, 111.19, 109.56, 35.82, 30.08; ^{13}C-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 162.51, 158.63, 145.30, 143.45, 137.59, 136.53, 126.13, 125.78, 119.53, 117.22, 117.16, 114.53, 113.58, 35.82, 30.08; MS *m*/*e*: 347 [M + 1] (100%).

2-(3,5-Di-tert-butyl-2-hydroxyphenyl)-1H-benzimidazol-5(6)-sulfonic acid ***28***

It was purified by column chromatography (dichloromethane/ethanol, 10:1). Yield: 17.3%; m.p.: >300°C; ^{1}H-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 1.24 (s, 9H), 1.36 (s, 9H), 7.09 (s, 1H), 7.21 (d, 1H, J_o = 8 Hz), 7.34 (d, 1H, J_o = 8.4 Hz), 7.72 (s, 1H), 8.08 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 155.40, 155.35, 154.11, 154.06, 144.03, 143.29, 140.99, 140.62, 140.08, 136.57, 136.52, 133.53, 132.50, 126.13, 126.07, 121.88, 121.12, 121.04, 121.00, 117.04, 115.23, 111.89, 111.83, 110.74, 109.06, 35.21, 34.62, 31.81, 29.71; ^{13}C-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 163.20, 155.96, 145.65, 143.59, 139.15, 136.86, 135.70, 123.32, 122.44, 118.47, 117.18, 114.73, 113.56, 35.21, 34.62, 31.81, 29.71; MS *m*/*e*: 401 [M + 1] (100%).

2-(3-tert-Butyl-2-hydroxyphenyl)-1H-benzimidazole-5(6)-carboxylic acid ***29***

It was purified by column chromatography (dichloromethane/methanol/acetic acid, 10:1:0.1). Yield: 24.2%; m.p.: 165 – 166°C; ^{1}H-NMR (DMSO-d_6 + 51°C) δ [ppm]: 1.37 (s, 9H), 6.93 (t, 1H, J_o = 8 Hz), 7.35 (dd, 1H, J_o = 7.6 Hz, J_m = 1.6 Hz), 7.68 (d, 1H, J_o = 8.4 Hz), 7.9 (dd, 1H, J_o = 8.8 Hz, J_m = 1.6 Hz), 7.94 (d, 1H, J_o = 8 Hz, J_m = 1.6 Hz), 8.22 (s, 1H); ^{13}C-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 174.28, 161.69, 159.80, 145.69, 143.17, 136.94, 129.82, 126.21, 125.74, 121.64, 119.17, 117.35, 116.48, 113.98, 35.11, 30.14; MS *m*/*e*: 311 [M + 1] (100%). Anal. calcd. for $C_{18}H_{18}N_2O_3 \cdot H_2O$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.75; H, 6.46; N, 8.84.

2-(3,5-Di-tert-butyl-2-hydroxyphenyl)-1H-benzimidazol-5(6)-carboxylic acid ***30***

It was purified by column chromatography (dichloromethane/methanol/acetic acid, 10:1:0.1). Yield: 19.7%; m.p.: 273 – 275°C; ^{1}H-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 1.27 (s, 9H), 1.39 (s, 9H), 7.08 (d, 1H, J_m = 2.8 Hz), 7.27 (d, 1H, J_o = 8 Hz), 7.52 (dd, 1H, J_o = 8 Hz, J_m = 1.6 Hz), 7.98 (d, 1H, J_m = 1.2 Hz), 8.11 (d, 1H, J_m = 2.4 Hz); ^{13}C-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 210.63, 174.10, 162.34, 156.56, 138.43, 135.59, 129.79, 122.92, 122.37, 121.39, 118.63, 117.45, 113.93, 35.29, 34.55, 32.32, 30.23; MS *m*/*e*: 367 [M + 1] (100%). Anal. calcd. for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.17; H, 7.20; N, 7.99.

2-(3-tert-Butyl-2-hydroxyphenyl)-1H-benzimidazol-5(6)-carbonitrile ***31***

It was purified by column chromatography (*n*-hexane/ethyl acetate, 10:1). Yield: 26%; m.p.: 283 – 284°C; ^{1}H-NMR (CD_3OD + NaH + 3 drops D_2O) δ [ppm]: 1.45 (s, 9H), 6.76 (t, 1H, J_o = 7.6 Hz), 7.2 (dd, 1H, J_o = 8.2 Hz, J_m = 1.8 Hz), 7.24 (dd, 1H, J_o = 8 Hz, J_m = 1.6 Hz), 7.58 (d, 1H, J_o = 8 Hz), 7.84 (d, J_m = 1.2 Hz, 1H), 8.07 (dd, 1H, J_o = 8 Hz, J_m = 1.2 Hz); ^{13}C-NMR (CD_3OD + NaH + 3 drops D_2O) δ [ppm]: 165.1, 158.6, 148.3, 144.1, 136.7, 126.7, 125.5, 122.3, 121.9, 119.7, 118.2, 117.1, 115.9, 99.7, 34.6, 29; MS *m*/*e*: 292 [M + 1] (100%). Anal. calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 73.76; H, 5.51; N, 14.2.

2-(3,5-Di-tert-butyl-2-hydroxyphenyl)-1H-benzimidazol-5(6)-carbonitrile ***32*** *[4]*

It was purified by column chromatography (*n*-hexane/ethyl acetate, 10:1). Yield: 24%; m.p.: 265 – 267°C; ^{1}H-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 1.25 (s, 9H), 1.3 (s, 9H), 7.13 (d, 1H, J_m = 2.4 Hz), 7.16 (dd, 1H, J_o = 8.4 Hz, J_m = 1.6 Hz), 7.49 (d, 1H, J_o = 8.4 Hz), 7.80 (d, 1H), 8.12 (d, 1H, J_m = 2.4 Hz); ^{13}C-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 165.52, 156.01, 149.08, 145.02, 139.09, 135.62, 123.75, 122.97, 122.87, 122.00, 120.17, 118.41, 116.71, 98.80, 35.31, 34.56, 32.25, 30.18; MS *m*/*e*: 348 [M + 1] (100%). Anal. calcd. for $C_{22}H_{25}N_3O \cdot 0.1\ C_4H_8O_2 \cdot 0.1\ C_6H_{14}$: C, 75.71; H, 7.51; N, 11.51. Found: C, 75.95; H, 7.61; N, 11.30.

2-(3,5-Di-tert-butyl-2-hydroxyphenyl)-5(6)-nitro-1H-benzimidazole ***33***

It was purified by column chromatography (*n*-hexane/ethyl acetate, 10:1). Yield: 28.9%; m.p.: 264 – 266°C; ^{1}H-NMR (DMSO-d_6 +

NaH + 3 drops D_2O) δ [ppm]: 1.22 (s, 9H), 1.38 (s, 9H), 7.16 (d, 1H, J_m = 2.4 Hz), 7.46 (d, 1H, J_o = 8.8 Hz), 7.82 (dd, 1H, J_o = 8.4 Hz, J_m = 2 Hz), 8.13 (d, 1H, J_m = 2 Hz), 8.29 (d, 1H, J_m = 2 Hz); ^{13}C-NMR (DMSO-d_6 + NaH + 3 drops D_2O) δ [ppm]: 167.39, 155.69, 151.41, 144.44, 139.88, 139.74, 135.79, 124.33, 122.85, 117.94, 115.49, 115.25, 112.13, 35.29, 34.57, 32.17, 30.11; MS *m/e*: 368 [M + 1] (100%). Anal. calcd. for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.37; H, 6.92; N, 11.49.

2-(3,5-Di-tert-butyl-2-hydroxyphenyl)-5(6)-trifluoromethyl-1H-benzimidazole ***34***

It was purified by column chromatography (*n*-hexane/ethyl acetate, 10:1). Yield: 28.9%; m.p.: 82 – 84°C (bubbling); ^{1}H-NMR (CD_3OD + NaH + 3 drops D_2O) δ [ppm]: 1.25 (s, 9H), 1.36 (s, 9H), 7.35 (m, 2H), 7.65 (d, 1H, J_o = 8.8 Hz), 7.84 (s, 1H), 8.02 (d, 1H, J_m = 2.4 Hz); MS *m/e*: 391 [M + 1] (100%). Anal. calcd. for $C_{22}H_{25}F_3N_2O \cdot 0.2\ H_2O$: C, 67.06; H, 6.50; N, 7.11. Found: C, 67.1; H, 6.36; N, 7.00.

2-(3-tert-Butyl-2-hydroxyphenyl)-1H-benzimidazole ***35***

It was purified by column chromatography (*n*-hexane/ethyl acetate, 10:3). Yield: 41.4%; m.p.: 136 – 137°C; ^{1}H-NMR (DMSO-d_6, at 0.068 M conc.)* δ [ppm]: 1.41 (s, 9H), 6.92 (t, 1H, J_o = 8 Hz), 7.23 – 7.28 (m, 2H), 7.32 (dd, 1H, J_o = 7.4 Hz, J_m = 1.6 Hz), 7.57 (dd, 1H, J_o = 8.4 Hz, J_m = 1.2 Hz), 7.70 (dd, 1H, J_o = 7.2 Hz, J_m = 1.2 Hz), 7.90 (dd, 1H, J_o = 8 Hz, J_m = 1.6 Hz), 13.20 ve 14.03 (s, s, 2H); ^{13}C-NMR (DMSO-d_6, at 0.068 M conc.) δ [ppm]: 158.04, 153.16, 141.27, 137.71, 133.80, 129.20, 124.77, 123.89, 123.01, 118.97, 118.43, 113.01, 112.03, 29.95, 22.05; MS *m/e*: 267 [M + 1] (100%). Anal. calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.23; H, 6.80; N, 10.71.

3-[5,6-Dichloro-1-(4-chlorobenzyl)-1H-benzimidazol-2-yl] benzenesulfonic acid ***37***

It was purified by crystallization from ethanol. Yield: 40.1%; m.p.: 124 – 125°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 5.63 (s, 2H), 6.99 – 7.01 (d, 2H, J_o = 8.4 Hz), 7.34 – 7.36 (d, 2H, J_o = 8 Hz), 7.48 (q, 1H), 7.62 (d, 1H, J_o = 8 Hz), 7.78 (d, 1H, J_o = 7.6 Hz), 7.91 (s, 1H), 8.04 (s, 1H), 8.06 (s, 1H); MS *m/e*: 464 [M + 1] (98%), 466 [M + 1 + 2] (100%), 468 [M + 1 + 4] (35%).

General procedure for the synthesis of ***38 – 40***

Compound **37** (0.5 mmol) was refluxed in benzene (3 mL) with $SOCl_2$ (1 mL) for 2 h at 80°C. Then, the solvent and excess $SOCl_2$ were evaporated completely and the residue was dissolved in dichloromethane (2 mL). Corresponding amine derivatives were added in excess and the mixture was stirred for 2 h while heated at 50°C. Chloroform was evaporated.

3-(1-(4-Chlorobenzyl)-5,6-dichloro-1H-benzimidazol-2-yl)-N-(2-(diethylamino)ethyl) benzenesulfonamide · HCl ***38***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide 10:1:0.1). Yield: 26.6%; m.p.: 125 – 126°C; ^{1}H-NMR ($CDCl_3$) δ [ppm]: 0.90 (t, 6H), 2.39 (q, 4H), 2.48 (t, 2H), 2.90 (t, 2H), 5.39 (s, 2H), 6.98 (d, 2H, J_o = 8 Hz), 7.32 (d, 2H), 7.35 (s, 1H), 7.63 (t, 1H), 7.85 (d, 1H), 7.93 (s, 1H), 7.99 (d, 1H, J_o = 8 Hz), 8.16 (d, 1H, J_m = 1.6 Hz); ^{13}C-NMR ($CDCl_3$) δ [ppm]: 153.86, 142.31, 141.14, 135.25, 134.37, 133.51, 132.96, 130.32, 129.90, 129.60, 128.67, 127.90, 127.63, 127.45, 127.30, 121.51, 111.76, 51.04, 48.12, 46.32, 40.19, 11.50; MS *m/e*: 565 [M + 1] (98%), 567 [M + 1 + 2] (100%), 569 [M + 1 + 4] (35%). Anal. calcd. for $C_{26}H_{27}Cl_3N_4O_2S \cdot 2.1\ HCl \cdot 1.9\ H_2O \cdot 0.1\ C_2H_6O$: C, 46.19; H, 4.96; N, 8.23; S, 4.71. Found: C, 45.7; H, 5.01; N, 8.70; S, 4.85.

3-(1-(4-Chlorobenzyl)-5,6-dichloro-1H-benzimidazol-2-yl)-N-(2-(isopropylamino)ethyl) benzenesulfonamide · HCl ***39***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 10:1:0.1). Yield: 21%; m.p.: 153 – 154°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 1.17 (d, 6H), 2.92 (t, 2H), 3.07 (t, 2H), 3.21 (m, 1H), 5.69 (s, 2H), 6.99 (d, 2H, J_o = 8.4 Hz), 7.33 (d, 2H, J_o = 8.8 Hz), 7.76 (t, 1H, J_o = 8 Hz), 7.94 (d, 1H, J_o = 8 Hz), 7.99 (d, 1H, J_o = 8 Hz), 8.07 (d, 2H), 8.20 (s, 1H), 9.07 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 154.34, 141.79, 141.06, 136.08, 135.63, 133.58, 133.02, 130.98, 130.38, 129.55, 129.20, 128.81, 127.98, 126.78, 126.38, 121.06, 113.84, 56.73, 50.32, 48.01, 44.02, 19.06; MS *m/e*: 551 [M + 1] (98%), 553 [M + 1 + 2] (100%), 555 [M + 1 + 4] (35%). Anal. calcd. for $C_{25}H_{25}Cl_3N_4O_2S \cdot 2\ HCl \cdot 0.5\ H_2O \cdot 0.1\ C_2H_6O$: C, 47.4; H, 4.51; N, 8.78; S, 5.02. Found: C, 47.02; H, 4.59; N, 9.24; S, 5.05.

1-(4-Chlorobenzyl)-5,6-dichloro-2-(3-(4-methylpiperazin-1-yl-sulphonyl)phenyl)-1H-benzimidazole ***40***

It was purified by column chromatography (dichloromethane/isopropanol/ammonium hydroxide, 10:1:0.1). Yield: 29.4%; m.p.: 192 – 193°C; ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.11 (s, 3H), 2.30 (s, 4H), 2.74 (s, 4H), 5.64 (s, 2H), 6.93 (d, 2H, J_o = 8 Hz), 7.32 (d, 2H, J_o = 8.8 Hz), 7.80 (t, 1H, J_o = 7.6 Hz), 7.86 (d, 1H, J_o = 8 Hz), 7.89 (s, 1H), 8.06 – 8.11 (m, 3H); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 154.40, 142.64, 136.43, 136.26, 135.86, 134.11, 132.96, 131.06, 130.95, 129.83, 129.57, 128.59, 128.37, 126.53, 126.02, 121.48, 113.60, 54.02, 47.83, 46.34, 45.86; MS *m/e*: 549 [M + 1] (98%), 551 [M + 1 + 2] (100%), 553 [M + 1 + 4] (35%). Anal. calcd. for $C_{25}H_{23}Cl_3N_4O_2S$: C, 54.6; H, 4.22; N, 10.19; S, 5.83. Found: C, 54.12; H, 4.11; N, 9.99; S, 5.92.

Microbiological studies

Activity tests were performed in Mueller – Hinton broth (MHB) (Difco, Difco Laboratories, Detroit, MI, USA). Four or five *S. aureus* colonies from overnight growth on Tryptic Soy Agar (Merck, Darmstadt, Germany) were suspended in 5 mL saline and the turbidity was adjusted to match that of a 0.5 McFarland Standart. Then, a portion of the standardized suspension was diluted 1:100 (10^6 CFU/mL) with MHB. One mL of this dilution was added to each tube containing 1 mL of the compound diluted in MHB. All tubes were incubated at 35°C for 18 h and MIC's were determined.

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