



Original article

Synthesis and in vitro antimicrobial activity of some novel substituted benzimidazole derivatives having potent activity against MRSA

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ARTICLE INFO

Article history:

Received 27 March 2008

Received in revised form 19 June 2008

Accepted 30 June 2008

Available online 4 July 2008

Keywords:

Benzimidazole derivatives

Antibacterial

Antifungal

Methicillin-resistant *Staphylococcus aureus*

ABSTRACT

The novel benzimidazole derivatives (**3**, **5**, **8**, **9**, **12–14**, **18–41**) were prepared in this paper and the antimicrobial activities of these compounds against *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA, standard and clinical isolates), *Bacillus subtilis*, *Escherichia coli* and *Candida albicans* were evaluated. Compounds **24–26** which have no substitution of N-1 position displayed better antibacterial activities than those of standards (ciprofloxacin, ampicillin and sultamicillin) against both the drug-resistant bacteria (MRSA, standard and clinical isolates). These derivatives (**24–26**), 2,5,6-trihalogenobenzimidazole analogues (**8**, **12**), 5,6-dichloro-2-amino derivative (**13**), and 5-chloro-2-(4-benzyloxyphenyl)benzimidazole (**35**) exhibited the most potent antibacterial activity with MIC 3.12 µg/ml against *S. aureus*.

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1. Introduction

Resistance to number of antimicrobial agents (β -lactam antibiotics, macrolides, quinolones, vancomycin) among a variety of clinically significant species of bacteria is becoming increasingly important global problem. In particular, increasing drug resistance among Gram-positive bacteria such as staphylococci, enterococci, and streptococci is a significant health matter [1–3]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most disturbing cause of nosocomial infections in developed countries [4,5]. In view of these emerging resistance problems, there is an urgent need for new anti-MRSA compounds.

Benzimidazole ring displays an important heterocyclic pharmacophore in drug discovery. These compounds carrying different substituents in the benzimidazole structure are associated with a wide range of biological activities including anticancer [6–8], antiviral [9–12], antibacterial [13–19], antifungal [20–22], antihelmintic [23,24], anti-inflammatory [25], antihistaminic [26], proton pump inhibitor [27,28], antioxidant [29–32], antihypertensive [33] and anticoagulant [34] properties.

As an outgrowth of our investigations of benzimidazole derivatives, which have displayed significant antifungal [35,36] and antibacterial activity [14,15], we described new series of substituted benzimidazoles (**3**, **5**, **8**, **9**, **12–14**, **18–41**). The synthesis and

antimicrobial activity of these compounds are presented here in this article.

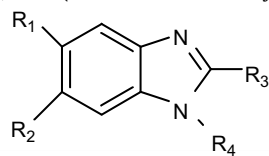
2. Chemistry

All new target compounds are shown in Table 1, and synthetic procedures used for their preparation are demonstrated in Schemes 1–3. 2-Unsubstituted benzimidazole derivatives (**3**, **5**) were obtained from 4-chloro-*N*-cyclopentyl-2-nitroaniline (**1**) as starting material by nucleophilic substitution of the chlorine atom of 1,4-dichloro-2-nitrobenzene with cyclopentylamine (Scheme 1). Reduction of **1** with zinc powder in 2.5 N NaOH gave the amine derivative **2**. Benzimidazoles **3** and **4** were prepared by the Phillips method [37] from *o*-phenylenediamines (4,5-dichloro-*o*-phenylenediamine, **2**) and formic acid. Compound **5** was synthesized by alkylating **4** with cyclopentyl bromide in the presence of sodium hydroxide.

2-(Amino-/isopropylamino-/chloro-/bromo-)benzimidazole analogues (**8**, **9**, **12–14**) were synthesized as shown in Scheme 2. Cyclization of commercially available 4,5-dichloro-*o*-phenylenediamine with urea [38] and halogenation with phosphorous oxychloride in the presence of hydrochloric acid gas [39] and alkylation with cyclopentyl bromide led to the formation of **8**. Compound **9** was obtained by reaction of **8** with isopropyl amine. Ring closure of 4,5-dichloro-*o*-phenylenediamine and **2** were accomplished with cyanogen bromide to give the corresponding 2-amino-benzimidazoles (**10** [40], **14**). Diazotization of **10** with sodium nitrite was

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Table 1Antibacterial and antifungal activities of compounds **3**, **5**, **8**, **9**, **12–14**, **18–41** (MIC minimum inhibitory concentration, µg/ml)

Compound	R ₁	R ₂	R ₃	R ₄	<i>S. aureus</i> (25923) ^a	MRSA ^b (431300)	MRSA ^c	<i>E. coli</i> (25922)	<i>B. subtilis</i> (6633)	<i>C. albicans</i> (10145)
3	Cl	H	H		50	50	50	≥50	50	50
5	Cl	Cl	H		6.25	6.25	6.25	50	12.5	12.5
8	Cl	Cl	Cl		3.12	6.25	6.25	50	25	50
9	Cl	Cl	NHCH(CH ₃) ₂		50	50	50	50	50	50
12	Cl	Cl	Br		3.12	6.25	6.25	50	25	25
13	Cl	Cl	NH ₂		3.12	6.25	6.25	50	6.25	6.25
14	Cl	H	NH ₂		25	50	50	50	25	25
18	Cl	OC ₂ H ₅			6.25	6.25	6.25	50	25	50
19	Cl	OC ₂ H ₅			50	50	50	50	25	25
20	Cl	OC ₂ H ₅			50	25	12.5	50	25	6.25
21	Cl	OC ₂ H ₅			50	50	50	50	25	6.25
22	Cl	Cl			25	25	25	50	50	6.25
23	Cl	Cl			50	50	50	25	25	12.5
24	Cl	Cl		H	3.12	3.12	3.12	50	6.25	6.25
25	Cl	Cl		H	3.12	3.12	3.12	50	50	12.5

(continued on next page)

Table 1 (continued)

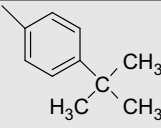
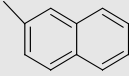


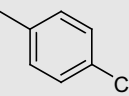

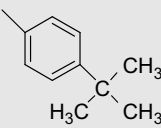

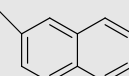



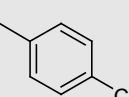

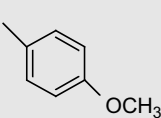

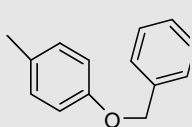

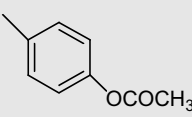

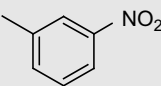

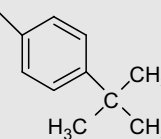

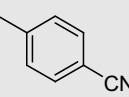

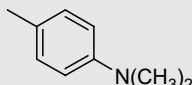

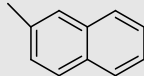

Compound	R ₁	R ₂	R ₃	R ₄	<i>S. aureus</i> (25923) ^a	MRSA ^b (431300)	MRSA ^c	<i>E. coli</i> (25922)	<i>B. subtilis</i> (6633)	<i>C. albicans</i> (10145)
26	Cl	Cl		H	3.12	3.12	3.12	50	6.25	12.5
27	Cl	Cl		H	50	50	50	50	25	25
28	Cl	Cl			25	50	50	25	50	25
29	Cl	Cl			50	50	50	50	25	12.5
30	Cl	Cl			6.25	25	25	50	25	25
31	Cl	Cl			50	25	25	50	25	12.5
32	Cl	H			12.5	25	25	25	12.5	12.5
33	Cl	H			50	50	50	25	25	25
34	Cl	H			50	50	50	25	25	12.5
35	Cl	H			3.12	6.25	6.25	50	50	25
36	Cl	H			50	50	50	50	50	50
37	Cl	H			50	50	50	50	25	12.5
38	Cl	H			50	12.5	6.25	25	50	12.5
39	Cl	H			50	≥50	≥50	50	50	6.25

Table 1 (continued)

Compound	R ₁	R ₂	R ₃	R ₄	<i>S. aureus</i> (25923) ^a	MRSA ^b (431300)	MRSA ^c	<i>E. coli</i> (25922)	<i>B. subtilis</i> (6633)	<i>C. albicans</i> (10145)
40	Cl	H			12.5	25	25	50	25	12.5
41	Cl	H			25	25	50	50	25	6.25
Sultamicillin					0.39	25	25		0.78	
Ampicillin					0.78	50	50			
Ciprofloxacin					0.78	6.25	12.5	0.19	0.09	
Fluconazole										1.56

^a ATCC number.^b MRSA: methicillin-resistant *S. aureus* (standard).^c MRSA: methicillin-resistant *S. aureus* (clinical isolate).

followed by the displacement of the diazo group by a bromo atom to afford 2-bromo derivative **11** [40]. The target compounds **12**, **13** were prepared by the alkylation of **11**, **10** with cyclopentyl bromide in the presence of sodium hydroxide.

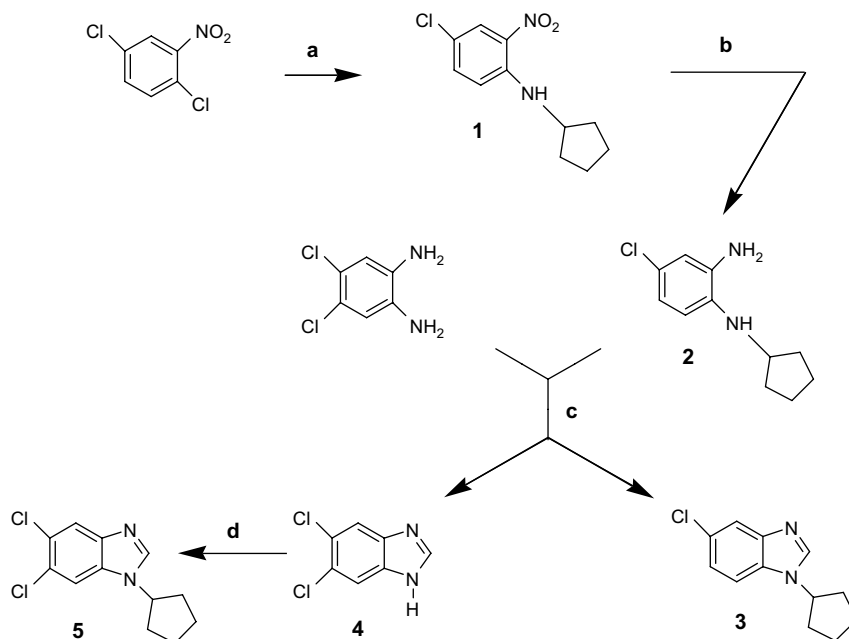
The synthesis of 2-(substituted aryl)benzimidazole derivatives (**18–41**) is outlined in Scheme 3. In the first step, 1,2,4-trichloro-5-nitrobenzene was subjected to a nucleophilic substitution reaction with cyclopentylamine in good yields, and the obtained nitro derivative (**15**) was reduced with zinc powder in 2.5 N NaOH. With this reduction two different compounds are produced. One of these compounds, 4,5-dichloro-*N*-cyclopentylbenzene-1,2-diamine (**16**), has occurred 18% and the other compound which is compound **17** has occurred 80%. Compound **17** is created by nucleophilic substitution of ethoxy group in the presence of NaOH with the Cl atom [41] of **15** in the 5th position.

Condensation of *o*-phenylenediamines (**17**, **16**, 4,5-dichloro-*o*-phenylenediamine, **2**) with Na₂S₂O₅ adduct of appropriate substituted benzaldehydes gave the desired derivatives (**18–27**, **32–41**). In the last step, compounds **24–27** were put in reaction with cyclopentyl bromide to afford the corresponding alkalized derivatives (**28–31**).

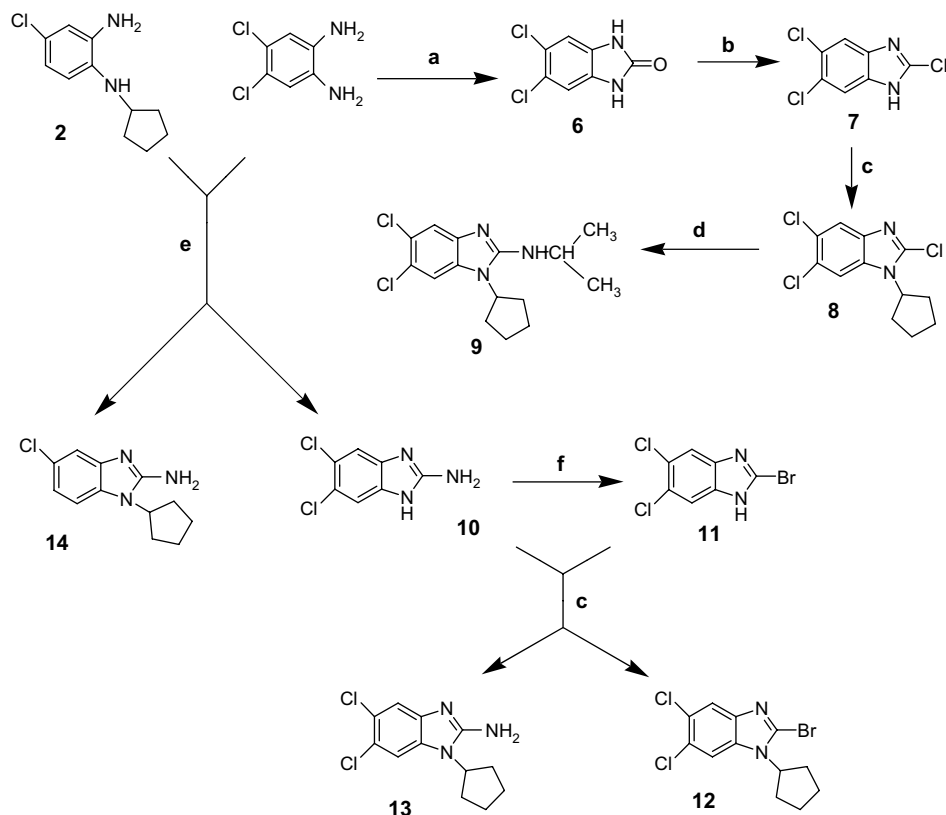
The structures of all compounds were confirmed by ¹H NMR mass spectral data and elemental analysis.

3. Results and discussion

The newly obtained derivatives were evaluated for their in vitro antibacterial activity against Gram-positive *S. aureus*, methicillin-resistant *S. aureus* (MRSA, standard and clinical isolates), *Bacillus subtilis*, Gram-negative *Escherichia coli* and antifungal activity against *Candida albicans* by tube dilution methods [42,43] and MIC values are given in Table 1. The target compounds and standard drugs were dissolved in DMSO–water (50%) at a concentration of 200 µg/ml. The concentration was adjusted to 50 µg/ml by 4-fold dilution with media culture and bacteria solution. Data were not taken for the initial solution because of the high DMSO concentration (12.5%). As it indicated in Table 1 most of the compounds showed good activity against Gram-positive bacteria and fungus, low activity on Gram-negative organism. 2,5,6-Trihalogenobenzimidazole analogues (**8**, **12**), 5,6-dichloro-2-amino derivative (**13**), 5,6-dichloro-2-(4-fluoro/chlorophenyl)-1-nonsubstituted (**24–26**)



Scheme 1. Reagents: (a) cyclopentylamine; (b) Zn powder, NaOH, EtOH; (c) HCOOH, HCl, H₂O; (d) cyclopentyl bromide, NaOH, CH₃CN.



Scheme 2. Reagents: (a) urea; (b) POCl₃, HCl (gas); (c) cyclopentyl bromide, NaOH, CH₃CN; (d) (CH₃)₂CHNH₂, DMF; (e) CNBr, CH₃CN, MeOH, H₂O; (f) NaNO₂, HBr, H₂O, CuBr.

and 5-chloro-2-(4-benzyloxyphenyl)benzimidazole (**35**) exhibited excellent activity against *S. aureus* with MIC 3.12 µg/ml. Compounds **24–26** which have no substitution at N1 position were slightly more effective against MRSA standard and MRSA clinical isolate than compounds **8**, **12**, **13**, **35**. These derivatives possessed also a better activity against both of the drug-resistant bacteria than standards (ciprofloxacin, ampicillin and sultamicillin). Among them the dichlorinated compounds **13**, **24**, **26** displayed moderate activity with MIC value 6.25 µg/ml against *B. subtilis*. Less activity (25–50 µg/ml) was noted against Gram-negative bacteria *E. coli*. The synthesized compounds were also tested against yeast cell line *C. albicans* (Table 1) and **13**, **20–22**, **24**, **39**, **41** showed good anti-fungal activity with MIC value 6.25 µg/ml.

4. Conclusion

Nowadays growing resistance of pathogens against antibacterial compounds used is a common and important problem, this shows us that research on new compounds against these pathogens is needed. We have synthesized 31 novel substituted benzimidazole derivatives (**3**, **5**, **8**, **9**, **12–14**, **18–41**) and screened for their antimicrobial activities. Compounds **24–26** having the free NH group of the benzimidazole moiety exhibited excellent activity with MIC 3.12 µg/ml against *S. aureus*, methicillin-resistant *S. aureus* (MRSA) standard and MRSA clinical isolate. From 5,6-dichloro-1-cyclopentyl-2-substituted benzimidazoles, three compounds having Cl, Br and NH₂ group at position 2 yielded the most active compounds (**8**, **12**, **13**) with MIC values of 3.12 µg/ml against *S. aureus*. Also compound **35**, which is among monochlorobenzimidazole derivatives and carries 4-benzyloxyphenyl substituent at position 2, exhibited greatest activity. We need to do studies on in vivo and mode of action mechanisms of these compounds to better determine the potential of their antibacterial activity.

5. Experimental

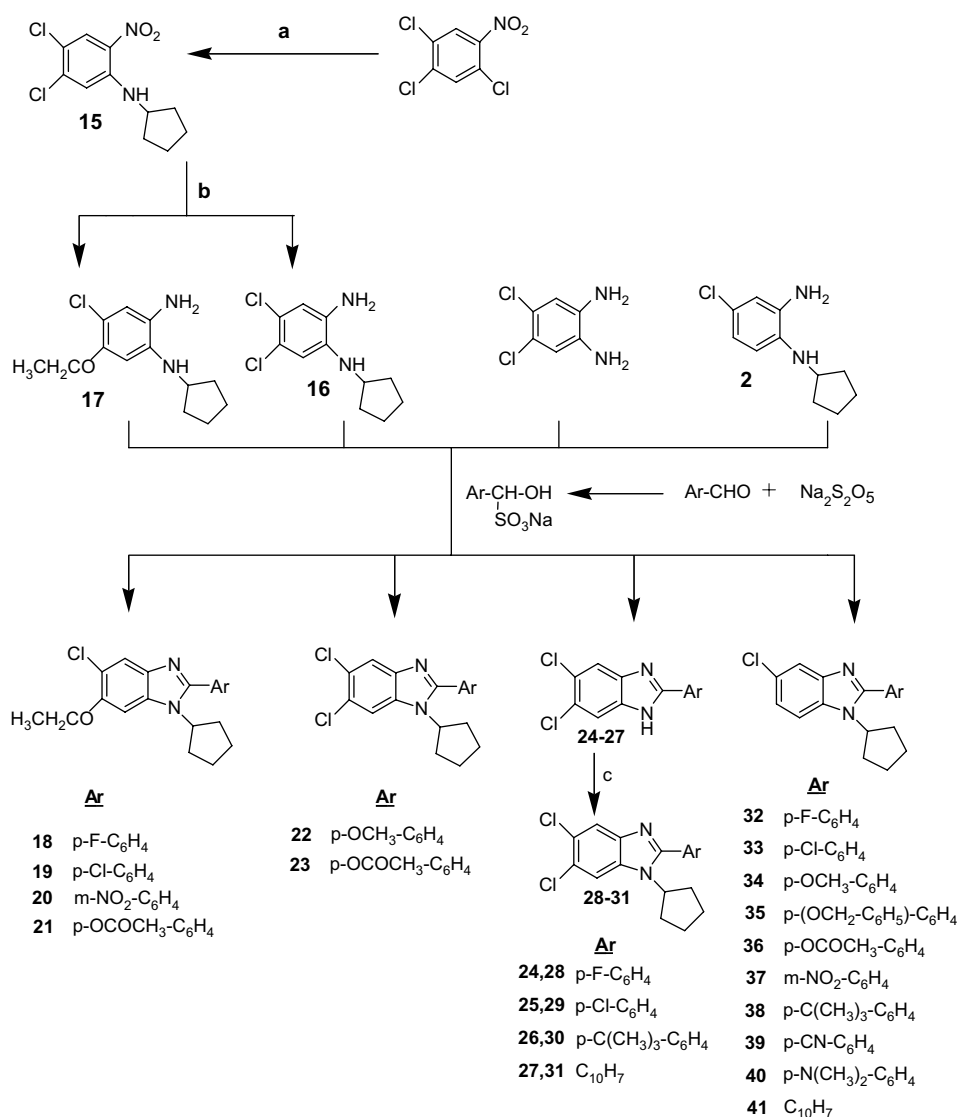
Melting points were recorded with a capillary melting point apparatus (Electrothermal 9100) and are uncorrected. The ¹H NMR spectra were measured on VARIAN Mercury 400 FT-NMR spectrophotometers and are referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). Mass spectra were taken on Waters Micromass ZQ by using (ESI⁺) method. Elemental analyses (C, H, N) were determined on a Leco CHNS 932 instrument and were within ±0.4% of the theoretical values. All instrumental analysis was performed at Ankara University, Faculty of Pharmacy. Column chromatography was accomplished on silica gel 60 (40–63 mm particle size). The chemical reagents used in synthesis were purchased from E. Merck, Fluka, Sigma, Acros and Aldrich. Compounds **4** [24], **6** [38], **7** [39], **10** [40], and **11** [40] were prepared according to the literature methods.

5.1. 4-Chloro-N-cyclopentyl-2-nitroaniline (**1**)

A mixture of 2,5-dichloronitrobenzene (2 g, 10.4 mmol) and cyclopentylamine (4 ml, 31.2 mmol) was heated with stirring at 80 °C for 2 h. The reaction mixture was diluted with water, and the formed precipitate was collected by filtration and purified by recrystallization from EtOH to give **1** (1.86 g, 75%) as an orange solid: mp 83–85 °C. ¹H NMR (CDCl₃) δ: 1.59–1.82 (6H), 2.09 (m, 2H), 3.94 (m, 1H), 6.85 (d, 1H, *J*_o = 8.8 Hz), 7.35 (dd, 1H, *J*_o = 8.8 Hz, *J*_m = 2.8 Hz), 8.08 (br s, 1H), 8.16 (d, 1H, *J*_m = 2.8 Hz).

5.2. 5-Chloro-1-cyclopentyl-1H-benzimidazole (**3**)

Zn powder (0.26 g, 4 mmol) was added portionwise to a mixture of **1** (1 g, 0.4 mmol), 2.5 N NaOH (1 ml) and EtOH (10 ml) under



Scheme 3. Reagents: (a) cyclopentylamine; (b) Zn powder, NaOH, EtOH; (c) cyclopentyl bromide, NaOH, CH₃CN.

gentle reflux, and the mixture was refluxed until the TLC monitored the disappearance of the starting material. EtOH was evaporated in vacuo and diluted with AcOEt (40 ml) and filtered. The filtrate was dried over Na₂SO₄ and concentrated to give **2**. The residue containing **2** was dissolved in a mixture of HCOOH (85%, 8 ml), HCl (37%, 3 ml) and H₂O (3 ml) after this solution was stirred under reflux for 2 h. The reaction mixture was boiled with charcoal, filtered and adjusted to pH > 9 with saturated K₂CO₃ solution. The solid was filtered, washed with water and dried to afford **3** (0.15 g, 68%) as a cream-coloured solid: mp 48–50 °C. ¹H NMR (CDCl₃) δ: 1.83–2.06 (6H), 2.28 (m, 2H), 4.71 (m, 1H), 7.25 (dd, 1H, *J*_o = 9.2 Hz, *J*_m = 2.4 Hz), 7.35 (d, 1H, *J*_o = 8.4 Hz), 7.77 (s, 1H), 7.96 (s, 1H). MS (ESI⁺) *m/z*: 221 (100%) (M + H), 223 (M + H + 2). Anal. Calcd for C₁₂H₁₃ClN₂·0.4H₂O: C, 63.24; H, 6.10; N, 12.29. Found C, 63.19; H, 5.99; N, 12.17.

5.3. 5,6-Dichloro-1-cyclopentyl-1H-benzimidazole (**5**)

5,6-Dichloro-1H-benzimidazole (**4**) (0.3 g, 1.6 mmol) and NaOH (0.06 g, 1.6 mmol) were dissolved in CH₃CN (10 ml). After 1 h stirring, cyclopentyl bromide (0.17 ml, 1.6 mmol) was added and the mixture was heated at reflux until the TLC monitored the disappearance of the starting material. Next, the reaction mixture was evaporated to dryness and the residue was purified by column

chromatography (CHCl₃–MeOH, 9:1) to give **5** (0.22 g, 53.7%) as a white solid: mp 68–70 °C. ¹H NMR (CDCl₃) δ: 1.82–2.05 (6H), 2.30 (m, 2H), 4.67 (m, 1H), 7.54 (s, 1H), 7.89 (s, 1H), 8.04 (s, 1H). MS (ESI⁺) *m/z*: 255 (100%) (M + H), 257 (69%) (M + H + 2), 259 (10%) (M + H + 4). Anal. Calcd for C₁₂H₁₂Cl₂N₂: C, 56.49; H, 4.74; N, 10.98. Found C, 56.74; H, 4.78; N, 10.97.

5.4. 2,5,6-Trichloro-1-cyclopentyl-1H-benzimidazole (**8**)

This compound was prepared from 2,5,6-trichloro-1H-benzimidazole (**7**) (0.124 g, 0.56 mmol) according to the procedure described in for **5** and chromatographed (hexanes–EtOAc, 5:1) to afford **8** (0.06 g, 37%) as a white solid: mp 108–111 °C. ¹H NMR (CDCl₃) δ: 1.83 (m, 2H), 2.02–2.19 (6H), 4.98 (m, 1H), 7.49 (s, 1H), 7.77 (s, 1H). MS (ESI⁺) *m/z*: 289 (100%) (M + H), 291 (94%) (M + H + 2), 293 (33%) (M + H + 4). Anal. Calcd for C₁₂H₁₁Cl₃N₂·0.05C₆H₁₄: C, 50.26; H, 4.01; N, 9.53. Found C, 49.09; H, 3.95; N, 9.49.

5.5. 5,6-Dichloro-1-cyclopentyl-2-(isopropylamino)-1H-benzimidazole (**9**)

To a solution of **8** (0.1 g, 0.35 mmol) in DMF (2 ml) was added isopropyl amine (2 ml) and this mixture was stirred at 100–110 °C

for 7 h. The reaction mixture was cooled to room temperature, H₂O was added and then extracted with CHCl₃. The extract was dried over Na₂SO₄, the solvent was evaporated in vacuo, and the residue was purified by column chromatography eluting with hexanes–EtOAc (1:1) to give **9** (0.05 g, 46%) as a white solid: mp 210 °C. ¹H NMR (CDCl₃) δ: 1.33 (d, 6H), 1.78 (m, 2H), 1.95–2.08 (6H), 4.22 (m, 1H), 4.47 (m, 1H), 7.17 (s, 1H), 7.52 (s, 1H). MS (ESI⁺) *m/z*: 312 (100%) (M + H), 314 (64%) (M + H + 2), 316 (12%) (M + H + 4). Anal. Calcd for C₁₅H₁₉Cl₂N₃·0.2H₂O·0.2CH₃COOC₂H₅: C, 56.90; H, 6.34; N, 12.60. Found C, 56.62; H, 6.44; N, 12.35.

5.6. 2-Bromo-5,6-dichloro-1-cyclopentyl-1H-benzimidazole (**12**)

This compound was prepared from 2-bromo-5,6-dichloro-1H-benzimidazole (**11**) (0.150 g, 0.56 mmol) according to the procedure described in for **5** and chromatographed (hexanes–EtOAc, 5:1) to afford **12** (0.09 g, 48%) as cream-coloured solid: mp 106–109 °C. ¹H NMR (CDCl₃) δ: 1.84 (m, 2H), 2.00–2.22 (6H), 5.00 (m, 1H), 7.51 (s, 1H), 7.78 (s, 1H). MS (ESI⁺) *m/z*: 333 (65%) (M + H), 335 (100%) (M + H + 2), 337 (45%) (M + H + 4), 339 (8%) (M + H + 6). Anal. Calcd for C₁₂H₁₁BrCl₂N₂: C, 43.15; H, 3.32; N, 8.39. Found C, 43.53; H, 3.59; N, 8.39.

5.7. 2-Amino-5,6-dichloro-1-cyclopentyl-1H-benzimidazole (**13**)

This compound was prepared from 2-amino-5,6-dichloro-1H-benzimidazole (**10**) (0.1 g, 0.5 mmol) according to the procedure described in for **5** and chromatographed (EtOAc–hexanes, 6:5) to afford **13** (0.065 g, 58%) as a white solid: mp 197–200 °C. ¹H NMR (CDCl₃) δ: 1.78 (m, 2H), 1.91–2.20 (6H), 4.55 (m, 1H), 7.23 (s, 2H), 7.26 (s, 1H), 7.43 (s, 1H). MS (ESI⁺) *m/z*: 270 (100%) (M + H), 272 (M + H + 2). Anal. Calcd for C₁₂H₁₃Cl₂N₃: C, 52.47; H, 4.95; N, 15.29. Found C, 52.66; H, 5.27; N, 14.91.

5.8. 2-Amino-5-chloro-1-cyclopentyl-1H-benzimidazole (**14**)

1,2-Diamino-4-chloro-*N*-cyclopentylbenzene (**2**) (0.14 g, 0.66 mmol) was added to a mixture of H₂O (2 ml), MeOH (2 ml) and CNBr (0.15 ml of a 5.0 M solution, 0.75 mmol). After stirring this mixture overnight, the solvent was evaporated in vacuo, and the residue was purified by column chromatography eluting with CHCl₃–MeOH (20:1) to give **14** (0.065 g, 58%) as a light brown solid: mp 200 °C. ¹H NMR (CDCl₃) δ: 1.72 (m, 2H), 1.86–2.10 (6H), 4.60 (m, 1H), 5.75 (br s, 2H), 6.95 (dd, 1H, *J*_o = 8.8 Hz, *J*_m = 2 Hz), 7.03 (d, 1H, *J*_o = 8.4 Hz), 7.29 (d, 1H, *J*_m = 1.6 Hz). MS (ESI⁺) *m/z*: 236 (100%) (M + H), 238 (40%) (M + H + 2). Anal. Calcd for C₁₂H₁₄ClN₃·0.15H₂O: C, 60.45; H, 6.04; N, 17.62. Found C, 60.48; H, 6.06; N, 17.47.

5.9. 4,5-Dichloro-*N*-cyclopentyl-2-nitroaniline (**15**)

This compound was prepared from 1,2,4-trichloro-5-nitrobenzene (1 g, 4.4 mmol) and cyclopentylamine (2 ml, 13.2 mmol) according to the procedure described in for **1** as a yellow-orange solid **15** (0.065 g, 58%): mp 58–61 °C. ¹H NMR (CDCl₃) δ: 1.58–1.84 (6H), 2.12 (m, 2H), 3.90 (m, 1H), 7.00 (s, 1H), 8.03 (br s, 1H), 8.26 (s, 1H).

5.10. General procedure for synthesis of **18–41**

Reduction of **15** (1 g, 150 mmol) was done according to the procedure described in for **2** and two reduction products **16** and **17** were obtained as a dark brown-coloured oil, which was used in the next steps without purification. Appropriate aromatic aldehydes (30 mmol) were dissolved in EtOH (50 ml) and Na₂S₂O₅ (3.3 g) in hot H₂O (10 ml) was added in portions. The reaction mixture was stirred vigorously and was cooled. The precipitate was filtered and

dried (yield over 90%). The mixture of these salts (2 mmol) and *o*-phenylenediamines (**17**, **16**, 4,5-dichloro-*o*-phenylenediamine, **2**) in DMF (6 ml) were heated at 110 °C for 4–4.5 h. The reaction mixture was cooled; H₂O was added and then extracted with CHCl₃. The extract was dried over Na₂SO₄, the solvent was evaporated in vacuo, and the residue was purified by column chromatography.

5.10.1. 5-Chloro-1-cyclopentyl-6-ethoxy-2-(4-fluorophenyl)-1H-benzimidazole (**18**)

This compound was prepared from **17** (0.35 g, 1.5 mmol) and the Na₂S₂O₅ adduct of 4-fluorobenzaldehyde (0.41 g, 1.5 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **18** (0.15 g, 30%) as a white solid: mp 195–198 °C. ¹H NMR (CDCl₃) δ: 1.54 (t, 3H, *J* = 7.2 Hz), 1.79 (m, 2H), 2.00–2.32 (6H), 4.15 (q, 2H, *J* = 7.2 Hz), 4.87 (m, 1H), 7.00 (s, 1H), 7.21–7.26 (m, 2H), 7.63–7.67 (m, 2H), 7.86 (s, 1H). MS (ESI⁺) *m/z*: 359 (100%) (M + H), 361 (37%) (M + H + 2). Anal. Calcd for C₂₀H₂₀ClFN₂O·0.1H₂O: C, 66.60; H, 5.64; N, 7.76. Found C, 66.63; H, 5.86; N, 7.87.

5.10.2. 5-Chloro-2-(4-chlorophenyl)-1-cyclopentyl-6-ethoxy-1H-benzimidazole (**19**)

This compound was prepared from **17** (0.35 g, 1.5 mmol) and the Na₂S₂O₅ adduct of 4-chlorobenzaldehyde (0.45 g, 1.5 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (5:1) to give **19** (0.2 g, 37%) as a white solid: mp 203–206 °C. ¹H NMR (CDCl₃) δ: 1.53 (t, 3H, *J* = 6.8 Hz), 1.77 (m, 2H), 2.00–2.29 (6H), 4.15 (q, 2H, *J* = 6.4 Hz), 4.84 (m, 1H), 6.99 (s, 1H), 7.49 (d, 2H, *J*_o = 8.4 Hz), 7.63–7.67 (m, 2H), 7.86 (s, 1H). MS (ESI⁺) *m/z*: 375 (100%) (M + H), 377 (72%) (M + H + 2), 379 (13%) (M + H + 4). Anal. Calcd for C₂₀H₂₀Cl₂N₂O·0.2H₂O: C, 63.39; H, 5.42; N, 7.39. Found C, 63.34; H, 5.22; N, 7.47.

5.10.3. 5-Chloro-1-cyclopentyl-6-ethoxy-2-(3-nitrophenyl)-1H-benzimidazole (**20**)

This compound was prepared from **17** (0.35 g, 1.5 mmol) and the Na₂S₂O₅ adduct of 3-nitrobenzaldehyde (0.43 g, 1.5 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (5:2) to give **20** (0.21 g, 38%) as a light yellow solid: mp 172 °C. ¹H NMR (CDCl₃) δ: 1.55 (t, 3H, *J* = 7.2 Hz), 1.81 (m, 2H), 2.02–2.36 (6H), 4.17 (q, 2H, *J* = 7.2 Hz), 4.85 (m, 1H), 7.01 (s, 1H), 7.74 (t, 1H, *J*_{o,o'} = 8 Hz), 7.84 (s, 1H), 8.04 (d, 1H, *J*_o = 8 Hz), 8.38 (dd, 1H, *J*_o = 8, *J*_m = 2 Hz), 8.51 (t, 1H, *J*_{m,m'} = 1.6 Hz). MS (ESI⁺) *m/z*: 386 (100%) (M + H), 388 (34%) (M + H + 2). Anal. Calcd for C₂₀H₂₀ClN₃O₃·0.32H₂O: C, 61.34; H, 5.31; N, 10.73. Found C, 60.94; H, 5.41; N, 11.18.

5.10.4. 2-(4-Acetoxyphenyl)-5-chloro-1-cyclopentyl-6-ethoxy-1H-benzimidazole (**21**)

This compound was prepared from **17** (0.35 g, 1.5 mmol) and the Na₂S₂O₅ adduct of 4-acetoxybenzaldehyde (0.38 g, 1.5 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **21** (0.1 g, 18%) as a white solid: mp 184 °C. ¹H NMR (CDCl₃) δ: 1.52 (t, 3H), 1.77 (m, 2H), 1.96–2.30 (6H), 2.34 (s, 3H), 4.14 (q, 2H, *J* = 6.8 Hz), 4.90 (m, 1H), 6.99 (s, 1H), 7.24 (dd, 2H, *J*_o = 8.8, *J*_m = 1.6 Hz), 7.64 (dd, 2H, *J*_o = 8.4, *J*_m = 1.6 Hz), 7.79 (s, 1H). MS (ESI⁺) *m/z*: 399 (100%) (M + H), 401 (32%) (M + H + 2). Anal. Calcd for C₂₂H₂₃ClN₂O₃: C, 66.24; H, 5.81; N, 7.02. Found C, 66.39; H, 5.82; N, 6.91.

5.10.5. 5,6-Dichloro-1-cyclopentyl-2-(4-methoxyphenyl)-1H-benzimidazole (**22**)

This compound was prepared from **16** (0.35 g, 1.5 mmol) and the Na₂S₂O₅ adduct of 4-acetoxybenzaldehyde (0.57 g, 1.5 mmol)

according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **22** (0.14 g, 27%) as a cream-coloured solid: mp 198 °C. ^1H NMR (CDCl_3) δ : 1.75 (m, 2H), 1.98–2.30 (6H), 3.88 (s, 3H), 4.89 (m, 1H), 7.04 (d, 2H, $J_o = 8.8$ Hz), 7.56 (s, 1H), 7.58 (d, 2H, $J_o = 9.2$ Hz), 7.86 (s, 1H). MS (ESI^+) m/z : 361 (100%) ($\text{M} + \text{H}$), 363 (68%) ($\text{M} + \text{H} + 2$), 365 (12%) ($\text{M} + \text{H} + 4$). Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O} \cdot 0.15\text{C}_6\text{H}_{14}$: C, 63.87; H, 5.41; N, 7.48. Found C, 63.98; H, 5.36; N, 7.48.

5.10.6. 2-(4-Acetoxyphenyl)-5,6-dichloro-1-cyclopentyl-1H-benzimidazole (**23**)

This compound was prepared from **16** (0.35 g, 1.5 mmol) and the $\text{Na}_2\text{S}_2\text{O}_5$ adduct of 4-acetoxybenzaldehyde (0.55 g, 1.5 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **23** (0.1 g, 17%) as a white solid: mp 170–173 °C. ^1H NMR (CDCl_3) δ : 1.77 (m, 2H), 2.00–2.30 (6H), 2.36 (s, 3H), 4.90 (m, 1H), 7.28 (d, 2H, $J_o = 8.4$ Hz), 7.58 (s, 1H), 7.66 (d, 2H, $J_o = 8.8$ Hz), 7.88 (s, 1H). MS (ESI^+) m/z : 389 (100%) ($\text{M} + \text{H}$), 391 (69%) ($\text{M} + \text{H} + 2$), 393 (12%) ($\text{M} + \text{H} + 4$). Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_2$: C, 61.71; H, 4.66; N, 7.20. Found C, 61.32; H, 4.72; N, 7.27.

5.10.7. 5,6-Dichloro-2-(4-fluorophenyl)-1H-benzimidazole (**24**)

This compound was prepared from 4,5-dichloro-*o*-phenylenediamine (0.4 g, 2.25 mmol) and the $\text{Na}_2\text{S}_2\text{O}_5$ adduct of 4-fluorobenzaldehyde (0.52 g, 2.25 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (5:3) to give **24** (0.21 g, 33%) as a light pink solid: mp 272–274 °C. ^1H NMR ($\text{DMSO}-d_6$) δ : 7.32–7.40 (m, 2H), 7.78 (br s, 2H), 8.12–8.22 (m, 2H), 13.19 (s, 1H). MS (ESI^+) m/z : 281 (100%) ($\text{M} + \text{H}$), 285 (22%) ($\text{M} + \text{H} + 4$). Anal. Calcd for $\text{C}_{13}\text{H}_7\text{Cl}_2\text{FN}_2$: C, 55.54; H, 2.51; N, 9.97. Found C, 55.76; H, 2.73; N, 10.35.

5.10.8. 5,6-Dichloro-2-(4-chlorophenyl)-1H-benzimidazole (**25**)

This compound was prepared from 4,5-dichloro-*o*-phenylenediamine (0.4 g, 2.25 mmol) and the $\text{Na}_2\text{S}_2\text{O}_5$ adduct of 4-chlorobenzaldehyde (0.55 g, 2.25 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (5:3) to give **25** (0.16 g, 24%) as a cream-coloured solid: mp 287 °C. ^1H NMR ($\text{DMSO}-d_6$) δ : 7.62 (d, 2H, $J_o = 8.8$ Hz), 7.83 (br s, 2H), 8.14 (d, 2H, $J_o = 8.4$ Hz), 13.31 (br s, 1H). MS (ESI^+) m/z : 297 (86%) ($\text{M} + \text{H}$), 299 (100%) ($\text{M} + \text{H} + 2$), 301 (28%) ($\text{M} + \text{H} + 4$), 303 (2%) ($\text{M} + \text{H} + 6$). Anal. Calcd for $\text{C}_{13}\text{H}_7\text{Cl}_3\text{N}_2$: C, 52.47; H, 2.37; N, 9.41. Found C, 52.55; H, 2.25; N, 9.30.

5.10.9. 2-(4-tert-Butylphenyl)-5,6-dichloro-1H-benzimidazole (**26**)

This compound was prepared from 4,5-dichloro-*o*-phenylenediamine (0.4 g, 2.25 mmol) and the $\text{Na}_2\text{S}_2\text{O}_5$ adduct of 4-tert-butylbenzaldehyde (0.35 g, 2.25 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (5:3) to give **26** (0.15 g, 28%) as a cream-coloured solid: mp 217–219 °C. ^1H NMR ($\text{DMSO}-d_6$) δ : 1.29 (s, 9H), 7.55 (d, 2H, $J_o = 8.8$ Hz), 7.72 (br s, 1H), 7.88 (br s, 1H), 8.07 (d, 2H, $J_o = 8.8$ Hz), 13.16 (s, 1H). MS (ESI^+) m/z : 319 (100%) ($\text{M} + \text{H}$), 323 (48%) ($\text{M} + \text{H} + 4$). Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{Cl}_2\text{N}_2 \cdot 0.1\text{H}_2\text{O}$: C, 63.60; H, 5.08; N, 8.72. Found C, 63.52; H, 5.07; N, 8.69.

5.10.10. 5,6-Dichloro-2-(2-naphthyl)-1H-benzimidazole (**27**)

This compound was prepared from 4,5-dichloro-*o*-phenylenediamine (0.4 g, 2.25 mmol) and the $\text{Na}_2\text{S}_2\text{O}_5$ adduct of 2-naphthaldehyde (0.5 g, 2.25 mmol) according to the general

procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (5:3) to give **27** (0.17 g, 24%) as a light pink solid: mp 167–169 °C. ^1H NMR ($\text{DMSO}-d_6$) δ : 7.63 (m, 2H), 7.82 (br s, 1H), 7.94–8.08 (m, 3H), 8.10 (d, 1H, $J_o = 8.4$ Hz), 8.29 (dd, 1H, $J_o = 8.8$ Hz, $J_m = 1.6$ Hz), 8.76 (s, 1H), 13.42 (s, 1H). MS (ESI^+) m/z : 313 (100%) ($\text{M} + \text{H}$), 315 (52%) ($\text{M} + \text{H} + 2$), 317 (16%) ($\text{M} + \text{H} + 4$). Anal. Calcd for $\text{C}_{17}\text{H}_{10}\text{Cl}_2\text{N}_2 \cdot 0.6\text{H}_2\text{O}$: C, 63.02; H, 3.48; N, 8.64. Found C, 62.84; H, 3.64; N, 8.70.

5.10.11. 5,6-Dichloro-1-cyclopentyl-2-(4-fluorophenyl)-1H-benzimidazole (**28**)

This compound was prepared from **24** (0.15 g, 0.4 mmol) according to the procedure described in for **5** and chromatographed (hexanes–EtOAc, 2:1) to afford **28** (0.065 g, 43%) as a white solid: mp 188–190 °C. ^1H NMR (CDCl_3) δ : 1.76 (m, 2H), 2.03–2.26 (6H), 4.83 (m, 1H), 7.21–7.26 (m, 2H), 7.58–7.65 (m, 3H), 7.87 (s, 1H). MS (ESI^+) m/z : 349 (100%) ($\text{M} + \text{H}$), 351 (75%) ($\text{M} + \text{H} + 2$), 353 (12%) ($\text{M} + \text{H} + 4$). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{Cl}_2\text{FN}_2 \cdot 0.2\text{H}_2\text{O}$: C, 61.27; H, 4.39; N, 7.93. Found C, 61.04; H, 4.53; N, 7.96.

5.10.12. 5,6-Dichloro-2-(4-chlorophenyl)-1-cyclopentyl-1H-benzimidazole (**29**)

This compound was prepared from **25** (0.15 g, 0.4 mmol) according to the procedure described in for **5** and chromatographed (hexanes–EtOAc, 2:1) to afford **29** (0.06 g, 30%) as a white solid: mp 235–237 °C. ^1H NMR (CDCl_3) δ : 1.75 (m, 2H), 2.00–2.31 (6H), 4.85 (m, 1H), 7.53 (d, 2H, $J_o = 7.6$ Hz), 7.60 (d, 3H), 7.91 (s, 1H). MS (ESI^+) m/z : 365 (92%) ($\text{M} + \text{H}$), 367 (100%) ($\text{M} + \text{H} + 2$), 369 (36%) ($\text{M} + \text{H} + 4$), 371 (2%) ($\text{M} + \text{H} + 6$). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{Cl}_3\text{N}_2$: C, 58.40; H, 4.22; N, 7.56. Found C, 58.11; H, 4.20; N, 7.57.

5.10.13. 2-(4-tert-Butylphenyl)-5,6-dichloro-1-cyclopentyl-1H-benzimidazole (**30**)

This compound was prepared from **26** (0.1 g, 0.3 mmol) according to the procedure described in for **5** and chromatographed (hexanes–EtOAc, 2:1) to afford **30** (0.08 g, 68%) as a white solid: mp 205–208 °C. ^1H NMR ($\text{DMSO}-d_6$) δ : 1.35 (s, 9H), 1.66 (m, 2H), 1.90–2.22 (6H), 4.86 (m, 1H), 7.62 (s, 4H), 7.87 (s, 1H), 7.97 (s, 1H). MS (ESI^+) m/z : 387 (100%) ($\text{M} + \text{H}$), 389 (68%) ($\text{M} + \text{H} + 2$), 391 (14%) ($\text{M} + \text{H} + 4$). Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{Cl}_2\text{N}_2$: C, 68.22; H, 6.25; N, 7.23. Found C, 67.94; H, 6.49; N, 7.24.

5.10.14. 5,6-Dichloro-1-cyclopentyl-2-(2-naphthyl)-1H-benzimidazole (**31**)

This compound was prepared from **27** (0.15 g, 0.5 mmol) according to the procedure described in for **5** and chromatographed (hexanes–EtOAc, 3:1) to afford **31** (0.075 g, 30%) as a white solid: mp 187 °C. ^1H NMR (CDCl_3) δ : 1.75 (m, 2H), 2.00–2.34 (6H), 4.99 (m, 1H), 7.58–7.62 (m, 3H), 7.71 (d, 1H, $J_o = 8.8$ Hz), 7.93–7.96 (m, 3H), 8.01 (d, 1H, $J_o = 8.4$ Hz), 8.19 (s, 1H). MS (ESI^+) m/z : 381 (100%) ($\text{M} + \text{H}$), 383 (68%) ($\text{M} + \text{H} + 2$), 385 (11%) ($\text{M} + \text{H} + 4$). Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{Cl}_2\text{N}_2 \cdot 0.1\text{H}_2\text{O}$: C, 68.97; H, 4.78; N, 7.31. Found C, 68.74; H, 4.84; N, 7.34.

5.10.15. 5-Chloro-1-cyclopentyl-2-(4-fluorophenyl)-1H-benzimidazole (**32**)

This compound was prepared from **2** (0.35 g, 1.6 mmol) and the $\text{Na}_2\text{S}_2\text{O}_5$ adduct of 4-fluorobenzaldehyde (0.4 g, 1.6 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **32** (0.3 g, 53%) as a cream-coloured solid: mp 145–148 °C. ^1H NMR (CDCl_3) δ : 1.75 (m, 2H), 2.01–2.11 (m, 4H), 2.28 (m, 2H), 4.85 (m, 1H), 7.19–7.24 (m, 3H), 7.41 (d, 1H, $J_o = 8.8$ Hz), 7.61–7.65 (m, 2H), 7.78 (d, 1H, $J_m = 2$ Hz). MS (ESI^+) m/z : 315 (100%) ($\text{M} + \text{H}$), 317 (37%) ($\text{M} + \text{H} + 2$). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{ClFN}_2$: C, 68.68; H, 5.12; N, 8.90. Found C, 68.41; H, 4.85; N, 8.98.

5.10.16. 5-Chloro-1-cyclopentyl-2-(4-chlorophenyl)-1H-benzimidazole (**33**)

This compound was prepared from **2** (0.35 g, 1.6 mmol) and the Na₂S₂O₅ adduct of 4-chlorobenzaldehyde (0.39 g, 1.6 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **33** (0.25 g, 54%) as a cream-coloured solid: mp 184–187 °C. ¹H NMR (CDCl₃) δ: 1.75 (m, 2H), 2.01–2.11 (m, 4H), 2.27 (m, 2H), 4.85 (m, 1H), 7.23 (dd, 1H, *J*_o = 8.4 Hz, *J*_m = 2 Hz), 7.41 (d, 1H, *J*_o = 9.2 Hz), 7.50 (d, 2H, *J*_o = 8.8 Hz), 7.60 (d, 2H, *J*_o = 8.4 Hz), 7.78 (d, 1H, *J*_m = 2.4 Hz). MS (ESI⁺) *m/z*: 331 (100%) (M + H), 333 (81%) (M + H + 2), 335 (%15) (M + H + 4). Anal. Calcd for C₁₈H₁₆Cl₂N₂: C, 65.09; H, 4.88; N, 8.43. Found C, 64.84; H, 4.50; N, 8.50.

5.10.17. 5-Chloro-1-cyclopentyl-2-(4-methoxyphenyl)-1H-benzimidazole (**34**)

This compound was prepared from **2** (0.35 g, 1.6 mmol) and the Na₂S₂O₅ adduct of 4-methoxybenzaldehyde (0.6 g, 1.6 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **34** (0.27 g, 50%) as a cream-coloured solid: mp 173–175 °C. ¹H NMR (CDCl₃) δ: 1.73 (m, 2H), 2.00–2.11 (m, 4H), 2.26 (m, 2H), 3.88 (s, 3H), 4.90 (m, 1H), 7.03 (d, 2H, *J*_o = 8 Hz), 7.19 (dd, 1H, *J*_o = 8.8 Hz, *J*_m = 1.6 Hz), 7.39 (d, 1H, *J*_o = 8.4 Hz), 7.58 (d, 2H, *J*_o = 8 Hz), 7.76 (s, 1H). MS (ESI⁺) *m/z*: 327 (100%) (M + H), 329 (35%) (M + H + 2). Anal. Calcd for C₁₉H₁₉ClN₂O: C, 69.83; H, 5.86; N, 8.57. Found C, 69.93; H, 5.80; N, 8.66.

5.10.18. 2-(4-Benzoyloxyphenyl)-5-chloro-1-cyclopentyl-1H-benzimidazole (**35**)

This compound was prepared from **2** (0.35 g, 1.6 mmol) and the Na₂S₂O₅ adduct of 4-benzoyloxybenzaldehyde (0.6 g, 1.6 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **35** (0.22 g, 33%) as a cream-coloured solid: mp 143–144 °C. ¹H NMR (CDCl₃) δ: 1.74 (m, 2H), 2.01–2.09 (m, 4H), 2.27 (m, 2H), 4.91 (m, 1H), 5.13 (s, 2H), 7.11 (dd, 2H, *J*_o = 8.4 Hz, *J*_m = 1.6 Hz), 7.20 (dd, 1H, *J*_o = 8.4 Hz, *J*_m = 2 Hz), 7.34–7.46 (m, 6H), 7.58 (dd, 2H, *J*_o = 8.8 Hz, *J*_m = 2 Hz), 7.77 (d, 1H, *J*_m = 1.6 Hz). MS (ESI⁺) *m/z*: 403 (100%) (M + H), 405 (40%) (M + H + 2). Anal. Calcd for C₂₅H₂₃ClN₂O: C, 74.52; H, 5.75; N, 6.95. Found C, 74.64; H, 6.06; N, 6.81.

5.10.19. 2-(4-Acetoxyphenyl)-5-chloro-1-cyclopentyl-1H-benzimidazole (**36**)

This compound was prepared from **2** (0.35 g, 1.6 mmol) and the Na₂S₂O₅ adduct of 4-acetoxybenzaldehyde (0.45 g, 1.6 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **36** (0.22 g, 38%) as a semi-white solid: mp 111–114 °C. ¹H NMR (CDCl₃) δ: 1.77 (m, 2H), 2.02–2.12 (m, 4H), 2.30 (m, 2H), 2.35 (s, 3H), 4.93 (m, 1H), 7.23–7.28 (m, 3H), 7.44 (d, 1H, *J*_o = 8.4 Hz), 7.68 (d, 2H, *J*_o = 8.4 Hz), 7.79 (d, 1H, *J*_m = 2 Hz). MS (ESI⁺) *m/z*: 355 (100%) (M + H), 357 (38%) (M + H + 2). Anal. Calcd for C₂₀H₁₉ClN₂O₂·0.3CH₃COOC₂H₅: C, 66.78; H, 5.65; N, 7.34. Found C, 66.82; H, 5.65; N, 7.09.

5.10.20. 2-(3-Nitrophenyl)-5-chloro-1-cyclopentyl-1H-benzimidazole (**37**)

This compound was prepared from **2** (0.35 g, 1.6 mmol) and the Na₂S₂O₅ adduct of 3-nitrobenzaldehyde (0.43 g, 1.6 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **37** (0.16 g, 31%) as a white solid: mp 144–147 °C. ¹H NMR (CDCl₃) δ: 1.78 (m, 2H), 2.03–2.35 (6H), 4.85 (m, 1H), 7.28 (dd, 1H, *J*_o = 8.4 Hz, *J*_m = 2 Hz), 7.46 (d, 1H, *J*_o = 8.8 Hz), 7.75 (t, 1H, *J*_{o,o'} = 8 Hz), 7.81 (d, 1H, *J*_m = 1.6 Hz), 8.04 (d, 1H, *J*_o = 7.6 Hz), 8.40 (dd, 1H, *J*_o = 8 Hz,

*J*_m = 2.4 Hz), 8.53 (t, 1H, *J*_{m,m'} = 1.6 Hz). MS (ESI⁺) *m/z*: 342 (100%) (M + H), 344 (35%) (M + H + 2). Anal. Calcd for C₁₈H₁₆ClN₃O₂: C, 63.25; H, 4.72; N, 12.29. Found C, 63.19; H, 4.71; N, 12.33.

5.10.21. 2-(4-tert-Butylphenyl)-5-chloro-1-cyclopentyl-1H-benzimidazole (**38**)

This compound was prepared from **2** (0.35 g, 1.6 mmol) and the Na₂S₂O₅ adduct of 4-tert-butylbenzaldehyde (0.45 g, 1.6 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **38** (0.21 g, 36%) as a white solid: mp 171–174 °C. ¹H NMR (CDCl₃) δ: 1.37 (s, 9H), 1.74 (m, 2H), 1.96–2.14 (m, 4H), 2.27 (m, 2H), 4.96 (m, 1H), 7.20 (d, 1H, *J*_o = 8.4 Hz), 7.40 (d, 1H, *J*_o = 8 Hz), 7.53 (d, 2H, *J*_o = 8 Hz), 7.58 (d, 2H, *J*_o = 7.6 Hz), 7.77 (s, 1H). MS (ESI⁺) *m/z*: 353 (100%) (M + H), 355 (M + H + 2). Anal. Calcd for C₂₂H₂₅ClN₂: C, 74.88; H, 7.14; N, 7.94. Found C, 74.87; H, 7.41; N, 8.04.

5.10.22. 2-(4-Cyanophenyl)-5-chloro-1-cyclopentyl-1H-benzimidazole (**39**)

This compound was prepared from **2** (0.26 g, 1.2 mmol) and the Na₂S₂O₅ adduct of 4-cyanobenzaldehyde (0.3 g, 1.2 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **39** (0.19 g, 50%) as a white solid: mp 187–189 °C. ¹H NMR (CDCl₃) δ: 1.78 (m, 2H), 2.00–2.18 (m, 4H), 2.30 (m, 2H), 4.84 (m, 1H), 7.27 (dd, 1H, *J*_o = 8.4 Hz, *J*_m = 2 Hz), 7.45 (d, 1H, *J*_o = 8.8 Hz), 7.78–7.85 (m, 5H). MS (ESI⁺) *m/z*: 322 (100%) (M + H), 324 (35%) (M + H + 2). Anal. Calcd for C₁₉H₁₆ClN₃: C, 70.91; H, 5.01; N, 13.06. Found C, 70.81; H, 5.18; N, 13.09.

5.10.23. 5-Chloro-1-cyclopentyl-2-(4-N,N-dimethylaminophenyl)-1H-benzimidazole (**40**)

This compound was prepared from **2** (0.26 g, 1.22 mmol) and the Na₂S₂O₅ adduct of 4-(N,N-dimethylamino)benzaldehyde (0.43 g, 1.22 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **40** (0.21 g, 43%) as a white solid: mp 216–219 °C. ¹H NMR (DMSO-*d*₆) δ: 1.66 (m, 2H), 1.91–2.21 (6H), 2.99 (s, 6H), 4.91 (m, 1H), 6.84 (d, 2H, *J*_o = 8.4 Hz), 7.21 (dd, 1H, *J*_o = 8.4 Hz, *J*_m = 2 Hz), 7.50 (d, 2H, *J*_o = 8.8 Hz), 7.59 (d, 1H, *J*_o = 8.4 Hz), 7.68 (d, 1H, *J*_m = 1.2 Hz). MS (ESI⁺) *m/z*: 340 (100%) (M + H), 342 (43%) (M + H + 2). Anal. Calcd for C₂₀H₂₂ClN₃: C, 70.68; H, 6.52; N, 12.36. Found C, 70.57; H, 6.56; N, 12.30.

5.10.24. 5-Chloro-1-cyclopentyl-2-(2-naphthyl)-1H-benzimidazole (**41**)

This compound was prepared from **2** (0.35 g, 1.6 mmol) and the Na₂S₂O₅ adduct of 2-naphthaldehyde (0.43 g, 1.6 mmol) according to the general procedure and was obtained after purification by column chromatography eluting with hexanes–EtOAc (10:3) to give **41** (0.22 g, 38%) as a white solid: mp 177–179 °C. ¹H NMR (CDCl₃) δ: 1.72 (m, 2H), 1.96–2.17 (m, 4H), 2.30 (m, 2H), 4.99 (m, 1H), 7.24 (dd, 1H, *J*_o = 8.4 Hz, *J*_m = 1.6 Hz), 7.44 (d, 1H, *J*_o = 8.4 Hz), 7.58 (m, 2H), 7.71 (d, 1H, *J*_o = 8.8 Hz), 7.83 (d, 1H, *J*_m = 1.6 Hz), 7.90–7.99 (m, 3H), 8.17 (s, 1H). MS (ESI⁺) *m/z*: 347 (100%) (M + H), 349 (41%) (M + H + 2). Anal. Calcd for C₂₂H₁₉ClN₂·0.2H₂O: C, 75.39; H, 5.57; N, 7.99. Found C, 75.39; H, 5.68; N, 8.08.

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