Synthesis and Antimicrobial Activities of New Polyhalogenated Benzimidazoles

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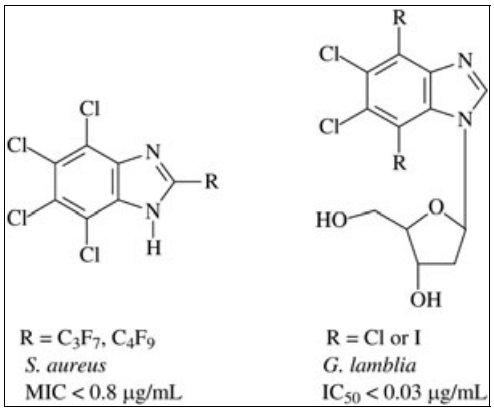

A series of new polyhalogenated benzimidazoles has been synthesized and their antibacterial and antiprotozoal activity was evaluated. Several of new substituted halogenobenzimidazoles and their 2′-deoxynucleosides showed noteworthy antiprotozoal toxicity particularly against *Giardia lamblia*. The most potent agents against bacteria and fungi were 4,5,6,7-tetrachlorobenzimidazoles with polyfluoroalkyl chain at position 2 of the heterocyclus.

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INTRODUCTION

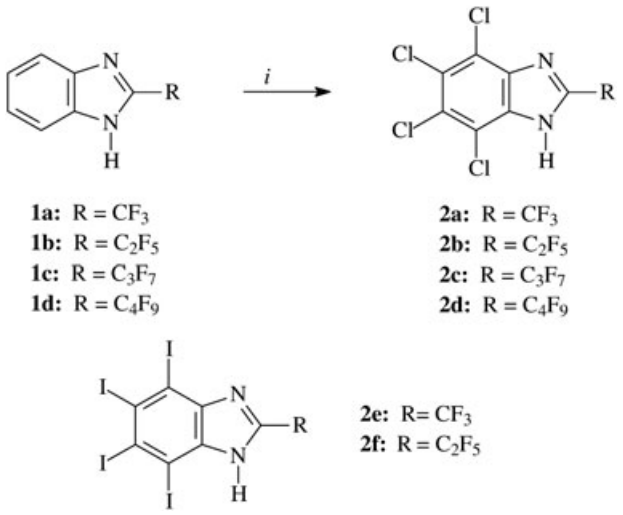
Halogenated benzimidazoles and their derivatives have raised special interest because of their diversified biological activity. For example, tetrabromobenzimidazoles and tetraiodobenzimidazoles are known as very strong inhibitors of antiapoptotic protein kinase CK2 [1–3]. Among antiviral agents, benzimidazole nucleosides and acyclonucleosides have also received much attention. The 5,6-dichloro-1-(β-D-ribofuranosyl)-benzimidazole (DRB) and its derivatives (TCRB and BDCRB) were found to show activity against RNA and DNA viruses [4, 5]. Also some benzimidazole L-ribonucleosides, particularly 5,6-dichloro-2-isopropylamino-1-(β-L-ribofuranosyl)-benzimidazole (maribavir) inhibit replication of human cytomegalovirus and have favorable safety profiles in animal species [6]. Benzimidazole system is present in numerous antiparasitic, fungicidal, anthelmintic, and anti-inflammatory drugs [7–9]. Substituted 2-trifluorobenzimidazoles are potent decouplers of oxidative phosphorylation in mitochondria. These compounds also inhibit photosynthesis and therefore exhibit appreciable herbicidal activity [10]. Their antibacterial, antifungal, and antiprotozoal activity has been reported [11–13].

These findings have inspired us to widen the list of halogeno-substituted benzimidazoles and to test the new derivatives against selected Gram-positive and Gram-negative bacteria and protozoa. In addition to previously reported compounds, we have synthesized several new halogenobenzimidazole derivatives as well as two 2′-deoxyribonucleosides. Despite a pilot-study character of our investigation, we were able to indicate the direction which can provide new effective antimicrobial agents of wide activity spectrum. The emergence of resistance to the major classes of antibacterial agents is recognized as a serious health concern. The search for antimicrobial agents with new mode of action will always remain an important task.

RESULTS AND DISCUSSION

The synthesis of several newly modified benzimidazoles carrying chloro- and bromo-substituents on the benzene part of heterocyclus as well as other substituents on C-2 and N-1 position constituted the chemical part of this

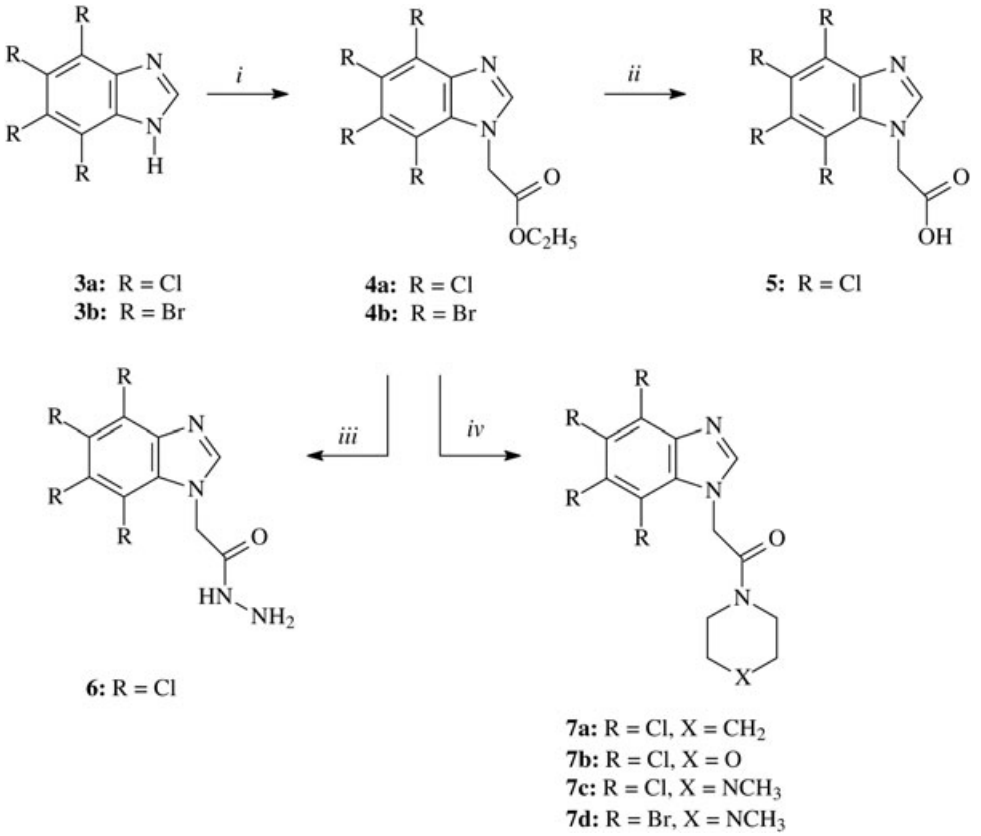
Scheme 1. Reagents and conditions: (i) HCl/HNO_3 (aqua regia).



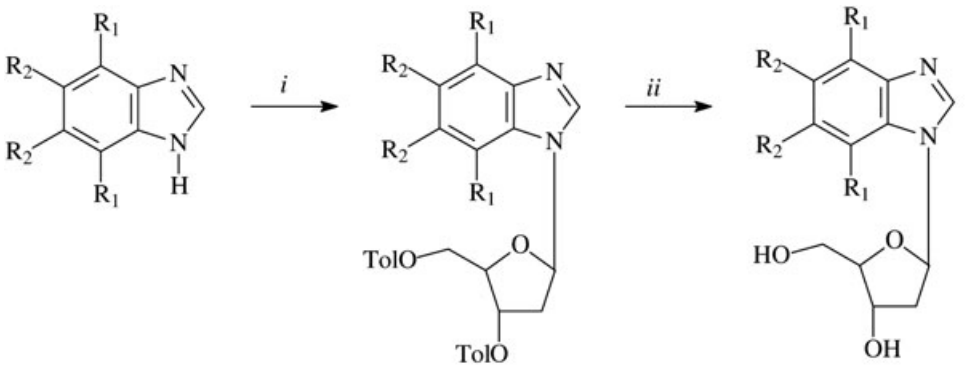
study. Additionally, two 2′-deoxyribo-nucleosides of 4,5,6,7-tetrachloro- and 5,6-dichloro-4,7-diiodobenzimidazoles (**10a,b**) were obtained according to "sodium salt procedure" [14] (Schemes 1–3).

Benzimidazole ring system endures even hard reaction conditions. The full chlorination of benzimidazole in the benzene part of molecule was achieved by action of "aqua regia" [15] or in the case of 2-trifluorobenzimidazole by action of chlorine at elevated temperature [16]. We have applied successfully the first procedure for chlorination of 2-perfluoroalkylbenzimidazoles **1a–d** with good or moderate yields to obtain respective products **2a–d** (Scheme 1). Additionally, the two previously obtained 4,5,6,7-tetraiodo-2-perfluoroalkyl benzimidazoles **2e** and **2f** were subjected to antimicrobial testing [3]. 4,5,6,7-Tetrachlorobenzimidazole **3a** was substituted in position N-1 with ethyl bromoacetate to give the respective ester **4a**. This ester was transformed to acid **5** by alkaline hydrolysis. The hydrazide **6** and amides derived from piperidine, morpholine, and methylpiperazine **7a–c** were obtained by reaction of **4a** with hydrazine or prolonged heating with piperidine, morpholine, or *N*-methylpiperazine, respectively. A similar procedure was adapted for a tetrabromoester **4b** in the synthesis of its metylpiperazinyl amide **7d** (Scheme 2). Because of the moderate biological activity of **7d**, we gave up the synthesis of other similarly modified tetrabromobenzimidazoles. Compounds **3b** and **4b** used here as starting materials for further synthesis and biological investigations have been described previously [3, 17]. Additionally, the synthesis of two 2′-deoxyribonucleosides **10a** and **10b** by condensation of sodium salts of 4,5,6,7-tetrachlorobenzimidazole **3a** and 5,6-

Scheme 2. Reagents and conditions: (i) $BrCH_2COOEt$, K_2CO_3, acetone, reflux; (ii) NaOH/ETOH; (iii) hydrazine/EtOH; (vi) $NH(CH_2)_4X$, reflux.



Scheme 3. Reagents and conditions: (i) 2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentafuranosyl chloride, NaH, CH_3CN, stirring; (ii) MeONa/MeOH.



3a: R_1,R_2 = Cl
8: R_1 = I, R_2 = Cl

9a: R_1,R_2 = Cl
9b: R_1 = I, R_2 = Cl

10a: R_1,R_2 = Cl
10b: R_1 = I, R_2 = Cl

dichloro-4,7-diiodobenzimidazole **8** with 3,5-di-*O*-(*p*-toluoyl)-α-D-ribofuranosyl chloride was carried out. This stereoselective reaction provides almost exclusively β-anomers. Removal of *p*-toluoyl groups from **9a** and **9b** was realized by treating of blocked nucleosides with methanolic sodium methoxylate (Scheme 3).

The halogenated benzimidazoles were screened for their antiprotozoal activity against *Enthamoeba histolytica*, *Trichomonas vaginalis*, and *Giardia lamblia* (Table 1). The results revealed that some of tested compounds are endowed with an appreciable antiprotozoal activity. The most potent agents against *E. histolytica* were **2a**, **7a**, and **7c**. Tetrachlorobenzimidazoles with longer polyfluoroalkyl chain **2b–d** showed the best toxicity toward *T. vaginalis*, whereas its 2-trifluoromethyl analogue (**2a**) has distinctly lower IC_{50} value. Four compounds: amides **7a** and **7b** and deoxynucleosides **10a** and **10b** exhibited very potent antigiardial activity, comparable but higher than control compounds: albendazole and metronidazole. In all tests, tetraiodinated (**2e** and **2f**) or tetrabrominated benzimidazole derivatives (**7d**) were less toxic than their tetrachloro congeners (see also results in [13]).

The majority of the halogenobenzimidazoles investigated here were active against Gram-positive bacteria (Table 2).

Table 1

In vitro susceptibility of *Enthamoeba histolytica, Trichomonas vaginalis*, and *Giardia lamblia* to novel polyhalogenobenzimidazoles.

	Enthamoeba histolytica		*Trichomonas vaginalis*		*Giardia lamblia*	
Compound tested	IC_{50} [μg/ml]	95% Confidence limits	IC_{50} [μg/ml]	95% Confidence limits	IC_{50} [μg/ml]	95% Confidence limits
2a	0.29	0.289–0.292	5.35	5.33–5.38	8.6	8.62–8.77
2b	2.43	2.42–2.44	0.37	0.375–0.378	n.a	
2c	5.05	5.03–5.08	0.40	0.402–0.405	11.5	11.4–11.7
2d	1.90	1.89–1.91	0.22	0.218–0.225	21.3	20.4–22.3
2e	2.60	2.58–2.61	17	16.7–17.4	8.25	8.20–8.31
2f	151	149–152	149	143–156	4.92	4.89–4.95
3a	1.655	1.648–1.662	0.75	0.745–0.754	0.027	0.026–0.028
5	2.279	2.265–2.292	117.8	114.7–121.3	0.188	0.189–0.186
6	3.07	3.05–3.09	5.33	5.28–5.39	13.06	12.94–13.18
7a	1.208	1.203–1.214	19.62	19.34–19.91	0.007	0.0069–0.0071
7b	1.449	1.441–1.457	134.8	130.4–139.5	0.002	0.0018–0.0021
7c	0.18	0.178–0.180	1.72	170–173	9.16	9.06–9.27
7d	0.48	0.478–0.483	20.8	20.5–20.8	46.5	45.7–47.4
10a	1.124	1.119–1.129	0.993	0.989–0.997	0.004	0.0039–0.0041
10b	1.643	1.633–1.653	0.678	0.674–0.0.682	0.029	0.029–0.030
Albendazole	15.0	10.0–20.0	0.422	0.419–0.425	0.010	0.008–0.012
Metronidazole	0.060	0.029–0.103	0.037	0.037–0.037	0.210	0.150–0.270

n.a, no activity.
IC_{50}, the concentration required to inhibit growth by 50%.

Particularly, tetrachlorobenzimidazoles **2a–d** exhibited big diameters of growth inhibition areas and low MIC values against *Staphylococcus* and *Bacillus* species. The moderate activity toward Gram-negative bacteria and fungi were observed only for aforementioned compounds **2a–d** (Table 3). The other of compounds described here showed no detectable antifungal and antibacterial activity toward Gram-negative rods.

In conclusion, our results suggest that new derivatives of polyhalogenated benzimidazoles are promising group of antimicrobial and antiprotozoal agents. However, further synthetic and biological investigations are needed to establish their structure-activity relationship (SAR).

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus, Mod. MFB 595030G, in open capillary tubes. The ^{1}H-NMR spectra were recorded on a Bruker AMX instrument (400 MHz ^{1}H frequency) at 25°C. Chemical shifts are reported in ppm from internal tetramethylsilane standard are given in δ-units. The solvent used for NMR spectra was DMSO-d_6. The UV spectra were determined on Techcomp UV8500 spectrophotometer. Elemental analyses were performed at the Faculty of Chemistry, Warsaw Technical University.

4,5,6,7-Tetrachloro-2-trifluoromethyl-1*H*-benzimidazole (2a). Adopting the procedure described in [15], a mixture of hydrochloric acid (120 mL) and nitric acid (50 mL) containing 2-trifluoromethylbenzimidazole (**1a**) (650 mg, 3.5 mmol) was stirred and heated for 8 h at 60°C. Next, the reaction mixture was refluxed for additional 20 h. The precipitate formed after cooling was collected and crystallized from ethanol to give white needles (720 mg, 63%) of mp 274–276°C; lit. mp 273°C [16].

4,5,6,7-Tetrachloro-2-pentafluoroethyl-1*H*-benzimidazole (2b). Analogously as described above from 2-pentafluoroethyl-1*H*-benzimidazole (**1b**). Yield: 865 mg, (66%), mp. 242–245° C; ^{1}H-NMR (DMSO-d_6): δ 15.3 (bs, 1H); uv (MeOH): λ (ε) 227 (21,800), 276 (9400), 293 (5900), 305 (4900) nm. *Anal*. Calcd. for $C_9HCl_4F_5N_2$ (373.93): C, 28.91; H, 0.27; N, 7.49. Found: C, 29.02; H, 0.35; N, 7.36.

4,5,6,7-Tetrachloro-2-heptafluoropropyl-1*H*-benzimidazole (2c). As described for **2a** from 2-heptafluoropropyl-1*H*-benzimidazole. Yield: 1.05 g, (71%), mp 262–264°C; ^{1}H-NMR (DMSO-d_6): δ 15.05 (bs, 1H); uv (MeOH): λ (ε) 225 (23,400), 277 (9700), 293 (7000), 304 (5100) nm. *Anal*. Calcd. for $C_{10}HCl_4F_7N_2$ (423.93): C, 28.33; H, 0.24; N, 6.61. Found: C, 28.22; H, 0.34; N, 6.48.

4,5,6,7-Tetrachloro-2-nonafluorobutyl-1*H*-benzimidazole (2d). As described for **2a** from 2-nonafluorobutyl-1*H*-benzimidazole. Yield: 1.16 g, (70%), mp 226–228°C; ^{1}H-NMR (DMSO-d_6): δ 14.8 (bs, 1H), uv (MeOH): λ (ε) 227 (25,200), 277 (9800), 293 (7100), 304 (5300) nm. *Anal*. Calcd. for $C_{11}HCl_4F_9N_2$ (473.94): C, 27.88; H, 0.21; H, 5.91. Found: C, 27.76; H, 0.30; N, 5.78.

(4,5,6,7-Tetrachlorobenzimidazol-1-yl)acetic acid ethyl ester (4a). To the mixture of 4,5,6,7-tetrachlorobenzimidazole (**3**) (3.84 g, 15 mmol) and finely powdered K_2CO_3 (5.8 g, 42 mmol) in acetone (100 mL), bromoacetic acid ethyl ester (4.0 g, 24 mmol) was added. The mixture was stirred and refluxed for 2 h. The solid was filtered off and the filter cake was washed twice with

Table 2
Activity of selected polyhalogenobenzimidazoles against Gram-positive bacteria.

Bacterium	Diameter of growth inhibition area, mm; (MIC [μg/mL])												
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**5**	**6**	**7c**	**7d**	**10a**	**10b**	**Nf**
Staphylococcus aureus	ATCC 6538P	45 (1.56)	45 (1.56)	40 (<0.8)	40 (<0.8)	19	25	17	15	11	(–)	17	16	24 (25)
Staphylococcus aureus	NTCC 4163	49 (1.56)	45 (1.56)	42 (<0.8)	38 (<0.8)	21	29	15	14	13	(–)	16	14	23 (25)
Enterococcus faecalis	ATCC 29212	16 (400)	26 (200)	18 (100)	16 (25)	(–)	14	(–)	(–)	(–)	(–)	(–)	11	22 (12.5)
Enterococcus hirae	ATCC 10541	17 (400)	19 (200)	(–) (100)	12 (25)	(–)	(–)	(–)	(–)	(–)	(–)	12	12	19 (25)
Bacillus subtilis	ATCC 6633	49 (3.125)	50 (<0.8)	45 (<0.8)	45 (<0.8)	26	35	14	11	12	(–)	11	12	28 (12.5)
Bacillus stearothermophilus	ATCC 7953	49 (3.125)	49 (<0.8)	45 (<0.8)	45 (<0.8)	24	32	15	12	11	(–)	13	12	27 (12.5)

Table 3

Activity of selected benzimidazoles against Gram-negative bacteria and fungi.

		Diameter of growth inhibition area, mm; (MIC [μg/mL])						Diameter of growth inhibition area, mm; (MIC [μg/mL])				
Bacterium		**2a**	**2b**	**2c**	**2d**	**Nf**[a]	Yeast strain	**2a**	**2b**	**2c**	**2d**	**Fluconazol**[b]
Escherichia coli	ATCC 25922	16 (200)	15 (200)	(–) (200)	(–) (200)	24 (6.25)	*Candida albicans* ATCC 90028	12 (100)	(–) (>400)	(–) (>400)	(–) (>400)	43 (2)
Escherichia coli	NCTC 8196	17 (200)	16 (200)	(–) (100)	(–) (100)	24 (6.25)	*Candida parapsilosis* ATCC 22019	(–) (50)	(–) (50)	(–) (>400)	(–) (>400)	32 (2)
Klebsiella pneumoniae	ATCC 13883	12 (400)	12 (400)	(–) (400)	(–) (>400)	23 (25)	*Candida tropicalis* IBA 171	25 (12.5)	18 (25)	(–) (>400)	(–) (>400)	39 (0.38)
Proteus vulgaris	NCTC 4635	34 (12.5)	35 (25)	15 (50)	(–) (200)	17 (100)	*Candida krusei* IBA 161	20 (50)	15 (50)	(–) (>400)	(–) (>400)	16 (>256)
Pseudomonas aeruginosa	NCTC 6749	13 (200)	11 (200)	(–) (200)	(–) (200)	(–) (>400)	*Candida quillermondii* IBA 155	33 (<3.125)	28 (<3.125)	15 (<3.125)	12 (<3.125)	40 (0.75)
Pseudomonas aeruginosa	ATCC 27853	12 (400)	10 (>400)	(–) (400)	(–) (>400)	(–) (>400)	*Saccharomyces cerevisiae* IBA 198	14 (50)	25 (25)	(–) (>400)	(–) (>400)	12 (>256)
Stenotrophomonas maltophilia	ATCC 13637	18 (200)	18 (100)	(–) (100)	(–) (50)	(–) (>400)	–	–	–	–	–	–
Burkholderia cepacia	ATCC 25416	25 (100)	21 (100)	11 (50)	(–) (50)	(–) (>400)	–	–	–	–	–	–
Acinetobacter baumannii	ATCC 19606	20 (200)	17 (200)	(–) (200)	(–) (>400)	14 (200)	–	–	–	–	–	–
Bordetella bronchoseptica	ATCC 4617	28 (50)	25 (50)	19 (25)	12 (25)	(–) (>400)	–	–	–	–	–	–

[a]Nf, nitrofurantoin, reference compound, 300 μg per disk (Mast Diadnostics, UK).
[b]Fluconazole, reference compound, filter paper disks used for disk-diffusion method contained 25 μg of fluconazole per disk, whereas Etest gradient strips (AB Biodisk) were used for the determination of fluconazole MICs.

acetone (2 × 40 mL). The filtrate was evaporated to dryness, and the residue crystallized from ethanol to give white needles. Yield: 4.2 g, (81%), mp 167–168°C; ^{1}H-NMR (DMSO-d_6): δ 1.21 (t, J = 7.1 Hz, 3H), 4.20 (q, J = 7.1 Hz, 2H), 5.46 (s, 2H), 8.47 (s, 1H). *Anal*. Calcd. for $C_{11}H_8Cl_4N_2O_2$ (342.01): C, 38.63; H 2.36; N, 8.19. Found: C, 38.51; H, 2.39; N, 8.08.

(4,5,6,7-Tetrachlorobenzimidazol-1-yl)acetic acid (5). The mixture containing **4a** (680 mg, 2 mmol), ethanol (15mL), water (10 mL) and NaOH (240 mg, 6 mmol) was stirred at room temp. for 3 h. The suspension became clear after this time. Next, the mixture was brought to reflux for 10 min. The solution was acidified to pH 2–3 with diluted aqueous HCl and left to crystallization. The amorphous white powder was obtained. Yield: 610 mg (97 %), mp 303–306°C (from ethanol-water); ^{1}H-NMR (DMSO-d_6): δ 5.35 (s, 1H), 8.47 (s, 1H), 13.5 (s, 1H). uv (MeOH): λ (ε) nm. *Anal*. Calcd. for $C_9H_4Cl_4N_2O_2$ (313.96): C, 34.43; H 1.28; N, 8.92. Found: C, 34.50; H, 1.37; N, 8.81.

(4,5,6,7-Tetrachlorobenzimidazol-1-yl)acetic acid hydrazide (6). To the solution of **4a** (1.02 g, 3 mmol) in ethanol (30 mL) hydrazine monohydrate (98%, 1.2 g, 24 mmol) was added. The mixture was stirred and refluxed for 3h. Next, the water (15 mL) was added and the mixture was left to crystallization. The white precipitate was formed. Yield: 870 mg, (88%), mp > 300°C (with decomp.). For analysis, a small amount of (**6**) was crystallized from ethanol. ^{1}H-NMR (DMSO-d_6): δ 4.35 (bs, 2H), 5.18 (s, 2H), 8.45 (s, 1H), 9.42 (s, 1H). uv (MeOH): λ (ε) 230 (16,600), 264 (8900), 271 (9900), 290 (sh, 3300), 300 (3100) nm. *Anal*. Calcd. for $C_9H_6Cl_4N_4O$ (327.99): C, 32.96; H, 1.84; N, 17.08. Found: C, 32.85; H, 1.84; N, 17.08.

1-(Piperidyn-1-yl)-2-(4,5,6,7-tetrachlorobenzimidazol-1-yl)-etanone (7a). The mixture of **4a** (340 mg, 1 mmol) and piperidine (510 mg, 6 mmol) was stirred and refluxed for 36 h. Next, the mixture was evaporated to oil. The residue was crystallized twice from toluene-ethanol. Yield: 295 mg, (77%), mp 240–242°C; ^{1}H-NMR (DMSO-d_6): δ 1.09 (t, J = 5.3 Hz, 4H) and 2.87 (q, J = 7.2 Hz, 4H), 4.94 (s, 2H), 8.38 (s, 1H). uv (MeOH): λ (ε) 227 (22,700), 273 (8900), 301 (3400) nm. *Anal*. Calcd. for $C_{14}H_{13}Cl_4N_3O$ (381.09): C, 44.12; H, 3.44; N, 11.03. Found: C, 44.21; H, 3.54; N, 10.91.

1-(Morpholin-4-yl)-2-(4,5,6,7-tetrachlorobenzimidazol-1-yl)-etanone (7b). Analogously as for **7a**. Yield: 195 mg, (51%), mp 221–223°C; ^{1}H-NMR (DMSO-d_6): δ 2.95 (t, J = 4.8 Hz, 4H), 3.68 (t, J = 4.8 Hz, 4H), 4.93 (s, 2H), 8.40 (s, H C); uv (MeOH): λ (ε) 226 (23,400), 272 (8800), 300 (3300) nm. *Anal*. Calcd. for $C_{13}H_{11}Cl_4N_3O_2$ (383.06): C, 40.76; H, 2.89; N, 10.97. Found: C, 40.67; H, 2.99; N, 10.85.

1-(4-Methylpiperazin-1-yl)-2-(4,5,6,7-tetrachlorobenzimidazol-1-yl)-etanone (7c). The mixture of ester **4a** (380 mg, 1.1 mmol) and *N*-methylpiperazine (1.2 g, 12 mmol) in methoxyethanol (20 mL) was stirred and heated at 110°C (bath temp.) for 2 days. The solvent was removed and the brown residue was chromatographed on silica gel column (2.5 × 8 cm) with $CHCl_3$ (100 mL), $CHCl_3$-MeOH (8:2, v/v) (100 mL) and $CHCl_3$-MeOH-Et_3N (80:18:2, v/v/v). The product containing fractions were evaporated and the residue crystallized from toluene-EtOH to give white cottonlike powder. Yield: 230 mg, (53%), mp 229–232°C; ^{1}H-NMR (DMSO-d_6): δ 2.18 (s, 3H), 2.42 (t, J = 5.8 Hz, 4H), 2.94 (t, J = 5.0 Hz, 4H), 4.89 (s, 2H), 8.37 (s, 1H). uv (MeOH): λ (ε) 228 (24,000), 272 (8900), 301 (3300). *Anal*. Calcd. for $C_{14}H_{14}Cl_4N_4O$ (396.11): C, 42.45; H, 3.56; N, 14.14. Found: C, 42.56, H, 3.63, N, 14.06.

1-(4-Methylpiperazin-1-yl)-2-(4,5,6,7-tetrabromobenzimidazol-1-yl)-etanone (7d). As described above for **7c** from **4b** [2] and *N*-methylpiperazine. Yield: 315 mg (50%), mp 219–221°C; ^{1}H-NMR (DMSO-d_6): δ 2.18 (s, 3H), 2.41 (t, J = 5.1 Hz, 4H), 2.93 (t, J = 5.2 Hz, 4H), 4.90 (s, 2H), 8.35 (s, 1H). uv (MeOH): λ (ε) 230 (35,000), 750 (sh, 9400) 275 (9600), 302.5 (3600). *Anal*. Calcd. for $C_{14}H_{14}Br_4N_4O$ (573.91): C, 29.30; H, 2.46; N, 9.76. Found: C, 29.36, H, 2.54, N, 9.64.

1-[2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentafuranosyl]-4,5,6,7-tetrachloro-benzimidazole (9a). To the suspension of **3a** (1.02 g, 4 mmol) in dry acetonitrile (70 mL), sodium hydride (200 mg, 5 mmol, 60% in oil) was added portionwise. The mixture was stirred and refluxed for 10 min. After cooling 2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentafuranosyl chloride [18] (1.55 g, 4 mmol) was added in portions. The mixture was stirred for 20 min at r.t. Next, methylene chloride (70 mL) was added and the mixture filtered through Cellite. The solvents were evaporated and the residue was chromatographed on silica gel column (2.5 × 12 cm) with toluene-acetone (95:5, v/v) as eluent. The product containing fractions were evaporated and the residue crystallized from methanol to give white needles. Yield: 1.09 g, (45%), mp 191–192°C; ^{1}H-NMR (DMSO-d_6): δ 2.37 (s, 3H), 2.40 (s, 3H), 2.96 (m, 1H), 3.07 (m, 1H), 4.52 (m, 2H), 4.58 (m, 1H), 5.72 (m, 1H), 7.01 (t, J = 6.4 Hz, 1H), 7.30–8.0 (4d, arom. H, 8H), 8.82 (s, 1H). *Anal*. Calcd. for $C_{28}H_{22}Cl_4N_2O_5$ (608.31): C, 55.29; H, 3.65; N, 4.61. Found: C, 55.25; H, 3.60; N, 4.52.

1-[2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentafuranosyl]-5,6-dichloro-4,7-diiodobenzimidazole (9b). As described for **9a** from **8** [3] instead of **3a**. Yield: 1.64 mg (52%), mp 194–196°C; ^{1}H-NMR (DMSO-d_6): δ 2.37 (s, 3H), 2.40 (s, 3H), 2.96 (m, 1H), 3.09(m, 1H), 4.56 (m, 2H), 4.60 (m, 1H), 5.70 (m, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.30–8.0 (4d, arom.H, 8H), 8.81 (s, 1H). *Anal*. Calcd. for $C_{28}H_{22}Cl_4I_2N_2O_5$ (791.21): C, 42.51; H, 2.80; N, 3.54. Found: C, 42,43; H, 2.86; N, 3.45.

1-(2-Deoxy-β-D-*erythro*-pentafuranosyl)-4,5,6,7-tetrachloro-benzimidazole (10a). The mixture of **9a** (1.6 g, 2.63 mmol) and methanolic sodium methanolate (50 mL, 0.1*M*) was stirred and refluxed for 15 min. Methanol was evaporated and the residue purified by flash chromatography on silica gel (2.5 × 10 cm) using chloroform as eluent. The product containing fractions were evaporated and the residue crystallized from methanol water to give colorless needles. Yield: 685 mg, (70%), mp 141–144°C; ^{1}H-NMR (DMSO-d_6): δ 2.46 (m, 1H), 2.58 (m, 1H), 3.65 (2m, 2H), 3.89 (q, J = 3.9 Hz, 1H), 4.47 (m, 1H), 5.04 (t, J = 5.2 Hz, 1H), 5.36 (d, J = 4.5 Hz, 1H), 6.85 (t, J = 5.9 Hz, 1H), 8.88 (s, 1H). uv (MeOH): λ (ε) 225 (22,400). 270 (9200), 298 (3100). *Anal*. Calcd. for $C_{12}H_{10}Cl_4N_2O_3$ (372.04): C, 38.74; H, 2.71; N, 7.53. Found: C, 38.66; H, 2.77; N, 7.47.

1-(2-Deoxy-β-D-*erythro*-pentafuranosyl)-5,6-dichloro-4,7-diiodobenzimidazole (10b). As described for **10a** from **9b**. Yield: 695 mg, (68%), mp 200°C; ^{1}H-NMR (DMSO-d_6): δ 2.46 (m, 1H), 2.55 (m, 1H), 3.60 (2m, 2H), 3.89 (q, J = 3.8 Hz, 1H), 4.37 (q, J = 4.7 Hz, 1H), 5.07 (bs, 1H), 5.37 (bs, 1H), 7.23 (t, J = 6.1 Hz, 1H), 8.87 (s, 1H). uv (MeOH): λ (ε) 230 (27,000), 279 (14,000), 305 (sh, 6100). *Anal*. Calcd. for $C_{12}H_{10}Cl_2I_2N_2O_3$ (554.94): C, 25.97; H, 1.82; N, 5.05. Found: C, 25.85; H, 1.91; N, 4.95.

Experimental for antiprotozoal and antibacterial studies. Experimental details concerning antiprotozoal and antimicrobial studies were described in literature [13, 19].

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