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ORIGINAL PAPER

Synthesis and biological activity of novel 4- and 6-(1-alkyl/aryl-1*H*-benzimidazol-2-yl)benzene-1,3-diols

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Abstract A one-pot synthesis of new biologically active 4- and 6-(1-alkyl/aryl-1*H*-benzimidazol-2-yl)benzene-1,3-diols has been developed. The compounds were obtained by the reaction of aryl-modified sulfinylbis[(2,4-dihydroxyphenyl)methanethione] with N-substituted benzene-1,2-diamines. Elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data were used to elucidate their structures. The developed method offers short reaction times, easy and quick isolation of the products, and good yields. The antiproliferative properties of the synthesized compounds were investigated against a panel of human cancer cell lines. Some of the tested compounds showed significant cytotoxic activity.

Keywords 4-(1*H*-Benzimidazol-2-yl)benzene-1,3-diols · Antitumor agents · Antiproliferative activity · Synthesis

Introduction

Benzimidazoles are frequently found in a diverse array of compounds, including biologically [1–8] and therapeutically active [9] agents, natural products [10–12], and functional materials [13–17]. Therefore, the construction of these heterocycles has received much attention.

The classical method for the synthesis of benzimidazoles is via the condensation of benzene-1,2-diamines with carboxylic acids or their derivatives under strong acid (polyphosphoric acid (PPA) or other mineral acids)/high temperature conditions [2, 18–20]; another simple and efficient procedure uses the corresponding aldehydes under oxidative conditions [21]. Although these transformations are widely used in the preparation of benzimidazoles, there remain many drawbacks to overcome such as the use of highly toxic reagents, strong acids and, in some cases, harsh reaction conditions [22].

Bahrami et al. [23] described the synthesis of benzimidazoles from classical substrates catalyzed by ceric ammonium nitrate (CAN) in the presence of H_2O_2 or promoted by $H_2O_2/Fe(NO_3)_3$ [24]. Others used a sulfamic acid/methanol catalytic system in the synthesis [25]. A highly efficient and versatile method for the synthesis of a series of 2-substituted *N*–H-, *N*-alkyl-, and *N*-arylbenzimidazoles containing a wide range of functional groups was achieved in one step via the $Na_2S_2O_4$ reduction of *o*-nitroanilines in the presence of aldehydes [26]. Ridley et al. [27] and others [28] obtained benzimidazoles by condensing diamines with bisulfites in ethanol.

The transition-metal-catalyzed C–N cross-coupling methodology is another approach for the synthesis of benzimidazole. For example, Brain and Brunton [29] reported the first palladium-catalyzed N-arylation of (*o*-bromophenyl)amidines to give benzimidazoles in toluene. Evindar and Batey [30] demonstrated an intramolecular aryl guanidinylation to form biologically relevant 2-aminobenzimidazoles using both palladium and copper catalysts in 1,2-dimethoxyethane (DME). Palladium-catalyzed cascade aryl amination/condensation

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processes of *o*-haloacetanilides have been developed for the synthesis of 1,2-disubstituted benzimidazoles in dimethyl sulfoxide (DMSO) [31].

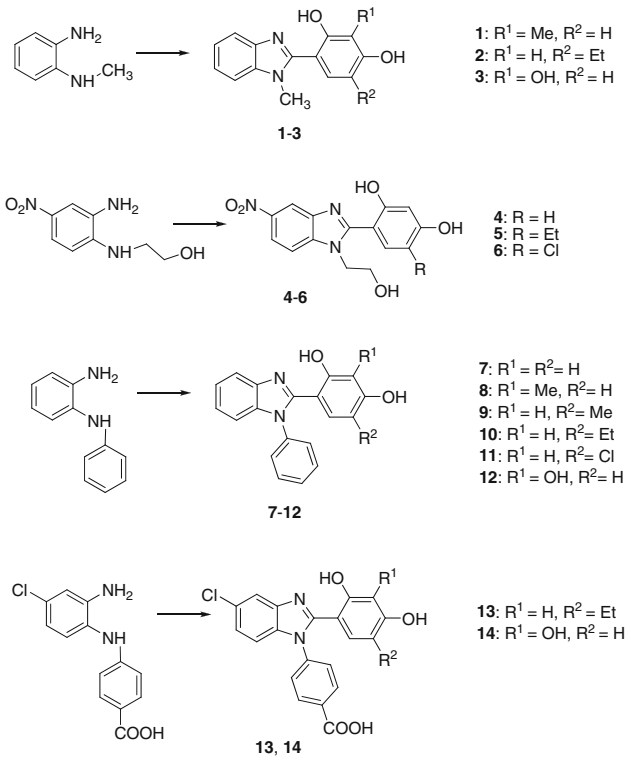
Recently Li et al. [32] reported a practical, cheap, and efficient copper-catalyzed intramolecular N-arylation of (*o*-haloaryl)amidines to afford synthetically valuable benzimidazole derivatives with environmentally benign water as the solvent. In recent years solvent-free synthesis of benzimidazoles under microwave irradiation using $Yb(OTf)_3$ [33], KSF clay [34], PPA, metal halide supported alumina [35], and other solid supports [36, 37] has been reported. Nagawade and co-workers described the analogous reaction using $BF_3{\cdot}OEt_2$ and $TiCl_4$ as catalysts [38, 39].

In continuation of an extensive program directed toward the synthesis of biologically active heterocyclic benzenediols, several new benzimidazole derivatives bearing an alkyl or aryl substituent at the N1 position were designed and obtained. The antiproliferative potency of the compounds against a panel of human cancer cell lines was evaluated.

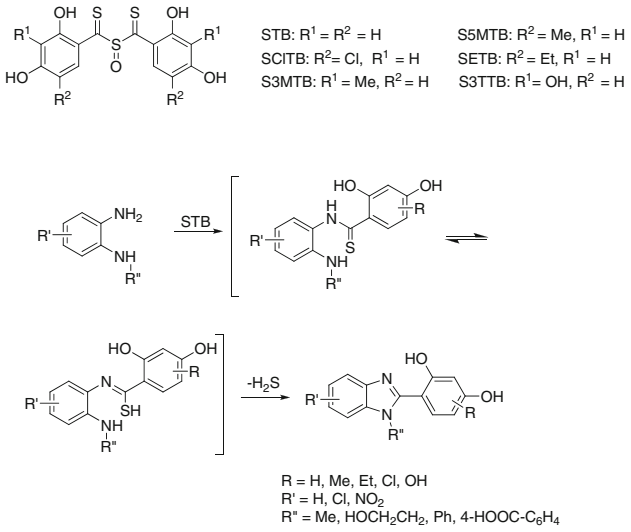
Results and discussion

Chemistry

Here we report the preparation of novel benzenediole derivatives containing the highly bioactive benzimidazole moiety by a new synthesis elaborated by us; however, the approach is similar to conventional ones. The compounds were formed by the reaction of *N*-alkyl(aryl)benzene-1,2-diamine derivatives with sulfinylbis[(2,4-dihydroxyphenyl)-methanethione] (STB) or its analogues sulfinylbis[(2,4-dihydroxy-3-methylphenyl)methanethione] (S3MTB), sulfinylbis[(2,4-dihydroxy-5-methylphenyl)methanethione] (S5MTB), sulfinylbis[(5-chloro-2,4-dihydroxyphenyl)methanethione] (SClTB), and sulfinylbis[(2,3,4-trihydroxyphenyl)methanethione] (S3TTB) in methanol under reflux (2.5–3.5 h) in moderate to good yields (63–77%) as outlined in Scheme 1. These key derivatives were prepared by the reaction of 2,4-dihydroxybenzenecarbodithioic acids with $SOCl_2$ in anhydrous diethyl ether [40]. The diamines react with the thione electrophiles according to proposed mechanism in Scheme 2, affording the target compounds by the elimination of H_2S from the imine-thiole adduct. The reaction proceeds quickly and does not require drastic conditions, additional reagents, or toxic/hazardous solvents, because STB and its analogs are better electrophiles than aldehydes, which is the result of the electronic effects of two OH substituents in the phenyl ring and the SO group. As a consequence of these interactions and properties of the solvent, easily outgoing reactive carbocations are released. The cyclization process promotes a tendency



Scheme 1



Scheme 2

of the compounds with a thioamide moiety toward transition into the thiol-imine forms compared with the analogs with an O atom.

Purity of the compounds was monitored by reversed-phase (RP-18) HPLC chromatography with methanol–water as a mobile phase at pH 4. Log *k* values for 70% MeOH (v/v) in the mobile phase are presented. The structures of compounds under consideration were confirmed by the analytical and spectral data. The mass spectra

(EI) of compounds gave molecular ion peaks, albeit with different intensities. The IR spectra showed an intense band in the region of about 1,630 cm^{-1} corresponding to the vibration of C=N which confirmed the formation of the desired compounds. Further, there are characteristic *v* (O–H) vibration frequencies between 3,350 and 3,550 cm^{-1}. In the ^{1}H NMR spectra the –OH groups are detected as broad singlets at about 10 and 12–12.9 ppm [41]; in the case of compounds **2**, **10**, and **14**, these signals were not detected.

Antiproliferative activity

The 4-(1*H*-benzimidazol-2-yl)benzene-1,3-diols presented in Scheme 1 were evaluated for their antiproliferative potency against human immortalized tumorigenic HCV29T cells. The cytotoxic activity in vitro was expressed as IC_{50}, the concentration of the compound that inhibited proliferation rate of the tumour cells by 50% as compared to the untreated control cells. Cisplatin was used as a reference drug. The results of the screening are summarized in Table 1.

The results showed that most of our designed compounds possess good to moderate antiproliferative potency with IC_{50} values between 17.0 and 171.9 μM (Table 1). Potency of the compounds depends clearly on the type of substitution of both rings. Generally (1-phenyl-1*H*-benzimidazol-2-yl)benzene-1,3-diols **7**–**11** and compound **13** show the strongest antiproliferative effect. Of the compounds with an unmodified resorcyl moiety (**4**, **7**) a significantly higher effect against HCV29T cells is exhibited by compound **7** which has an *N*-phenyl substituent (Table 1). A similar trend is observed in the group of compounds with an ethyl substituent (compounds **2**, **5**, **10**, **13**). Derivatives with a third hydroxyl substituent possess remarkably lower antiproliferative potency in the individual groups (**3**, **12**, **14**).

Selected compounds of the highest potency against HCV29T cells were also tested against A549 (human non-small lung carcinoma), T47D (human breast cancer), and SW707 (human rectal adenocarcinoma) cells (Table 2).

Table 1 Antiproliferative potency of 4-(1*H*-benzimidazol-2-yl)benzene-1,3-diols against the human cancer cell line HCV29T expressed as IC_{50}

No.	IC_{50}/μM	No.	IC_{50}/μM
1	113.1 ± 12.4	**9**	35.7 ± 11.2
2	81.8 ± 13.9	**10**	17.0 ± 2.5
3	160.8 ± 22.3	**11**	21.9 ± 0.4
4	171.9 ± 20.5	**12**	46.2 ± 11.7
5	59.6 ± 8.4	**13**	24.9 ± 10.1
6	55.2 ± 17.5	**14**	95.6 ± 9.8
7	48.6 ± 12.4		
8	25.8 ± 6.6	Cisplatin	3.1 ± 1.0

IC_{50} values are the means ± SD of 9 independent experiments

Table 2 Antiproliferative potency of some compounds against the human cancer cell lines T47D, A549, and SW707 expressed as IC_{50}

No.	IC_{50}/μM		
	A549	T47D	SW707
7	28.9 ± 1.1***	18.5 ± 2.4*/***	60.0 ± 13.5***
8	15.0 ± 2.2	12.7 ± 2.2	23.5 ± 6.4
9	17.1 ± 7.1	12.1 ± 1.7	34.0 ± 17.1
10	9.7 ± 1.7	8.0 ± 2.2**	10.7 ± 2.2
11	12.5 ± 1.0	10.1 ± 2.5**	12.1 ± 0.8
Cisplatin	6.8 ± 5.4	17.6 ± 5.4	10.4 ± 5.0****

Statistically significant differences of the compounds' potency between *T47D and SW707, **T47D and HCV29T cell lines; statistically significant differences of the cell line sensitivity to compounds ***7 and **10**, ****7 and cisplatin; ($p < 0.05$; Kruskal–Wallis ANOVA test)

Compounds **8**, **9**, **10**, and **11** exhibit similar antiproliferative potency compared to that of cisplatin ($p = 0.05$).

The structure–activity (SAR) analysis shows that the additional hydrophobic substituent in the resorcinol ring increases antiproliferative potency. The compounds with an ethyl substituent display higher antiproliferative potency. The additional hydroxyl group decreases biological activity. This trend is similar to that observed for 4*H*-3,1-benzothiazines obtained by us [42]. At the same time these groups of derivatives confirm and extend the earlier finding that the presence of a chlorine atom or methyl (or ethyl, isopropyl) substituents in position 5 of the resorcinol moiety of resorcyl(benz)azoles improves their anticancer properties [43, 44].

Conclusions

We designed a new synthesis of 1-substituted-1*H*-benzimidazoles. This approach offers short reaction times, relatively large-scale synthesis, easy and quick isolation of the products, and good to moderate yields. 4-(1*H*-Benzimidazol-2-yl)benzene-1,3-diols obtained in this way were evaluated for their antiproliferative activities. All compounds demonstrated potent inhibition against all the human cancer cell lines tested. Furthermore, we also conclude that compound **10** showed similar antiproliferative potency to the standard cisplatin.

Experimental

General

Melting points were determined using a BÜCHI B-540 (Switzerland) melting point apparatus. Elemental analyses

(C, H, N) were conducted using a Perkin-Elmer 2400 instrument and were found to be in good agreement (±0.2%) with the calculated values. The IR spectra were recorded with a Perkin-Elmer FT-IR 1725X spectrophotometer (in KBr). The spectra were measured in the range of 600–4,000 cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 by means of a Bruker DRX 500 instrument. Chemical shifts (δ, ppm) were given in relation to tetramethylsilane (TMS). Mass spectra (EI, 70 eV) were recorded using the apparatus AMD-604.

The purity of the compounds was examined by a Knauer liquid chromatograph equipped with a dual pump, a 20-mm^3 simple injection valve, and a UV–Vis detector at 280 nm. A Hypersil Gold C18 (3 μm, 100 × 3 mm) column was used as the stationary phase. The mobile phase included different contents of MeOH and acetate buffer (pH 4, 20 nM) as the aqueous phase. The flow rate was 0.5 cm^3 min^{-1} at room temperature. The retention time of an unretained solute (t_o) was determined by the injection of a small amount of acetone dissolved in water. Log k values for 70% MeOH (v/v) in the mobile phase are presented. Log k values are calculated as $\log k = \log (t_R - t_o)/t_o$, where t_R = retention time of a solute, t_o = retention time of an unretained solute.

Starting materials were purchased from Aldrich (*N*-methylbenzene-1,2-diamine, 2-[(2-amino-4-nitrophenyl) amino]ethanol, 4-[(2-amino-4-chlorophenyl)amino]benzoic acid) or Alfa Aesar (*N*-phenylbenzene-1,2-diamine).

2-Methyl-4-(1-methyl-1H-benzimidazol-2-yl)benzene-1,3-diol (**1**, $C_{15}H_{14}N_2O_2$)

A mixture of 0.24 g *N*-methylbenzene-1,2-diamine (2 mmol) and 0.74 g S3MTB (2 mmol) in 18 cm^3 MeOH was refluxed for 3 h. The hot mixture was filtered. The obtained solid was combined with that formed after the concentration of the filtrate. Recrystallization from methanol afforded 0.35 g (68%) **1**. M.p.: 295–298 °C; IR (KBr): $\bar{\nu}$ = 3,145 (OH), 2,915 (CH), 2,860 (CH), 1,612 (C=N), 1,562 (C=C), 1,516 (C=C), 1,485, 1,458, 1,407, 1,359, 1,313, 1,240, 1,223 (C–OH), 1,155, 1,076, 1,010, 938, 905, 875, 821, 797, 751, 719 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 10.40 (s, OH), 9.88 (s, OH), 7.97 (dd, J = 6.9, 1.9 Hz, 1H, Ar–H), 7.81 (dd, J = 7.0, 2.0 Hz, 1H, Ar–H), 7.60 (m, 2H, Ar–H), 7.32 (d, J = 8.5 Hz, 1H, Ar–H), 6.72 (d, J = 8.5 Hz, 1H, Ar–H), 3.87 (s, CH_3), 2.12 (s, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.8, 155.4, 149.9, 132.9, 131.0, 129.0, 125.8, 125.2, 114.0, 112.8, 112.7, 108.0, 101.9, 32.4 (CH_3), 9.1 (CH_3) ppm; MS (70 eV): m/z = 254 (M^+, 100), 237 (46), 225 (15), 222 (4), 206 (3), 197 (4), 183 (4), 171 (3), 157 (2), 146 (2), 127 (2), 104 (2), 91 (2), 77 (6), 65 (3), 51 (3), 36 (7); HPLC (C-18): $\log k = -0.274$.

4-Ethyl-6-(1-methyl-1H-benzimidazol-2-yl)benzene-1,3-diol (**2**, $C_{16}H_{16}N_2O_2$)

A mixture of 0.24 g *N*-methylbenzene-1,2-diamine (2 mmol) and 0.74 g SETB (2 mmol) in 16 cm^3 MeOH was refluxed for 3.5 h. The hot mixture was filtered and the filtrate was concentrated. The obtained solid was combined with that formed after reconcentration of the filtrate. Recrystallization from MeOH/H_2O (2:1) afforded 0.41 g (76%) **2**. M.p.: 213–216 °C; IR (KBr): $\bar{\nu}$ = 3,394 (OH), 3,243 (OH), 1,638 (C=N), 1,520 (C=C), 1,502 (C=C), 1,463, 1,307, 1,224 (C–OH), 1,186, 1,148, 1,077, 1,054, 993, 945, 927, 862, 802, 756, 713 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 10.20 (s, OH), 7.84 (d, J = 7.4 Hz, 1H, Ar–H), 7.74 (m, 1H, Ar–H), 7.49 (m, 2H, Ar–H), 7.36 (s, 1H, Ar–H), 6.65 (s, 1H, Ar–H), 3.89 (s, CH_3), 2.54 (q, J = 7.5 Hz, CH_2), 1.16 (t, J = 7.5 Hz, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.2, 155.8, 150.2, 133.6, 131.1, 128.6, 124.9, 125.1, 114.2, 112.6, 112.8, 108.1, 102.0, 33.8 (CH_3), 21.6 (CH_2), 14.8 (CH_3) ppm; MS (70 eV): m/z = 268 (M^+, 25), 253 ($M^+ - CH_3$, 100), 239 (6), 183 (6), 168 (3), 164 (7), 159 (12), 151 (6), 123 (5), 119 (3), 77 (9), 51 (4), 44 (5), 39 (4); HPLC (C-18): $\log k = -0.829$.

4-(1-Methyl-1H-benzimidazol-2-yl)benzene-1,2,3-triol (**3**, $C_{14}H_{12}N_2O_3$)

A mixture of 0.24 g *N*-methylbenzene-1,2-diamine (2 mmol) and 0.71 g S3TTB (2 mmol) in 16 cm^3 MeOH was refluxed for 4 h. The hot mixture was filtered and the filtrate was concentrated. Recrystallization from MeOH/H_2O (3:2) afforded 0.29 g (63%) **3**. M.p.: >410 °C; IR (KBr): $\bar{\nu}$ = 3,146 (OH), 2,935 (CH), 1,618 (C=N), 1,567 (C=C), 1,509 (C=C), 1,472, 1,394, 1,309, 1,273, 1,208 (C–OH), 1,077, 1,035, 1,003, 938, 916, 869, 811, 758, 736, 708 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 10.72 (s, OH), 9.62 (s, OH), 8.51 (s, OH), 7.65 (m, 2H, Ar–H), 7.29 (m, 2H, Ar–H), 7.14 (d, J = 8.6 Hz, 1H, Ar–H), 6.49 (d, J = 8.6 Hz, 1H, Ar–H), 3.91 (s, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.2, 155.6, 159.8, 146.9, 135.5, 129.0, 124.9, 125.1, 117.2, 116.6, 112.2, 110.1, 104.1, 38.4 (CH_3) ppm; MS (70 eV): m/z = 256 (M^+, 100), 255 (70), 239 (52), 227 (21), 200 (13), 184 (19), 168 (18), 157 (9), 152 (63), 131 (6), 124 (15), 106 (8), 77 (12), 68 (8), 44 (21), 39 (13), 36 (11); HPLC (C-18): $\log k = -0.709$.

4-[1-(2-Hydroxyethyl)-5-nitro-1H-benzimidazol-2-yl]-benzene-1,3-diol (**4**, $C_{15}H_{13}N_3O_5$)

A mixture of 0.26 g 2-[(2-amino-4-nitrophenyl)amino]ethanol (1.3 mmol) and 0.46 g STB (1.3 mmol) in 10 cm^3 MeOH was refluxed for 4 h. The hot mixture was filtered and the filtrate was concentrated. Recrystallization from methanol afforded 0.32 g (77%) **4**. M.p.: 279–282 °C; IR (KBr): $\bar{\nu}$ = 3,326 (OH), 3,133 (OH), 1,610 (C=N), 1,599

(C=N), 1,536 (C=C), 1,487 (C=C), 1,433, 1,357 (NO_2), 1,320, 1,299, 1,253, 1,236 (C–OH), 1,178, 1,124, 1,104, 1,065, 1,040, 998, 982, 958, 926, 900, 866 (NO_2), 819, 749 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 11.23$ (s, OH), 10.35 (s, OH), 8.61 (d, $J = 7.1$ Hz, 1H, Ar–H), 8.36 (dd, $J = 9.1$, 2.2 Hz, 1H, Ar–H), 8.14 (d, $J = 9.1$ Hz, 1H, Ar–H), 7.49 (d, $J = 8.5$ Hz, 1H, Ar–H), 6.53 (d, $J = 2.3$ Hz, 1H, Ar–H), 6.47 (dd, $J = 8.5$, 2.3 Hz, 1H, Ar–H), 5.02 (br s, 1H, OH), 4.49 (t, $J = 5.3$ Hz, OCH_2), 3.68 (t, $J = 5.3$ Hz, CH_2) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 161.8$, 157.3, 149.9, 135.0, 133.2, 125.2, 125.1, 124.0, 117.4, 109.7, 108.1, 107.5, 102.7, 59.2 (CH_2), 45.1 (CH_2) ppm; MS (70 eV): $m/z = 315$ (M^+, 19), 298 (20), 284 (4), 272 (20), 271 (100), 252 (10), 241 (6), 238 (6), 225 (17), 168 (2), 90 (3), 76 (6), 63 (4), 52 (2); HPLC (C-18): $\log k = -0.760$.

4-Ethyl-6-[1-(2-hydroxyethyl)-5-nitro-1H-benzimidazol-2-yl]benzene-1,3-diol (**5**, $C_{17}H_{17}N_3O_5$)

A mixture of 0.26 g 2-[(2-amino-4-nitrophenyl)amino]ethanol (1.3 mmol) and 0.50 g SETB (1.3 mmol) in 10 cm^3 MeOH was refluxed for 3 h. The hot mixture was filtered, the filtrate was concentrated, and 10 cm^3 diethyl ether was added. Recrystallization from methanol afforded 0.32 g (72%) **5**. M.p.: 156–159 °C; IR (KBr): $\bar{\nu} = 3{,}419$ (OH), 2,962 (CH), 2,931 (CH), 2,872 (CH), 1,661 (C=N), 1,620 (C=N), 1,504 (C=C), 1,438, 1,351 (NO_2), 1,208 (C–OH), 1,142, 1,087, 1,016, 957, 902, 841 (NO_2), 790, 764, 735 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 10.99$ (s, OH), 10.45 (s, OH), 8.56 (d, $J = 2.2$ Hz, 1H, Ar–H), 8.39 (dd, $J = 9.1$, 2.2 Hz, 1H, Ar–H), 8.19 (d, $J = 9.1$ Hz, 1H, Ar–H), 7.40 (s, 1H Ar–H,), 6.75 (s, 1H, Ar–H), 6.40 (br s, 1H, OH), 4.53 (t, $J = 5.3$ Hz, OCH_2), 3.70 (t, $J = 5.3$ Hz, CH_2), 2.47 (q, $J = 7.4$ Hz, CH_2), 1.15 (t, $J = 7.4$ Hz, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 163.1$, 160.9, 155.8, 154.1, 144.8, 137.0, 131.4, 127.8, 120.0, 122.7, 114.6, 110.7, 102.9, 59.2 (CH_2), 46.1 (CH_2), 22.0 (CH_2), 14.0 (CH_3) ppm; MS (70 eV): $m/z = 343$ (M^+, 29), 328 (M-CH_3, 14), 326 (22), 299 (74), 284 (100), 266 (4), 254 (6), 238 (26), 224 (3), 210 (4), 196 (3), 181 (6), 165 (4), 148 (2), 126 (2), 103 (2), 91 (5), 76 (6), 63 (5), 44 (3), 36 (8); HPLC (C-18): $\log k = -0.045$.

4-Chloro-6-[1-(2-hydroxyethyl)-5-nitro-1H-benzimidazol-2-yl]benzene-1,3-diol (**6**, $C_{15}H_{12}ClN_3O_5$)

A mixture of 0.26 g 2-[(2-amino-4-nitrophenyl)amino]ethanol (1.3 mmol) and 0.51 g SClTB (1.3 mmol) in 10 cm^3 MeOH was refluxed for 3 h. The hot mixture was filtered, the filtrate was concentrated, and 5 cm^3 water was added. Recrystallization from methanol afforded 0.32 g (70%) **6**. M.p.: >291 °C (dec.); IR (KBr): $\bar{\nu} = 3{,}351$ (OH), 3,271 (OH), 2,925 (CH), 1,607 (C=N), 1,551 (C=C), 1,487, 1,441, 1,379 (NO_2), 1,285, 1,252 (C–OH), 1,181, 1,150, 1,105 (C–Cl), 1,047, 976, 931, 908, 874, 842 (NO_2), 819, 779, 749, 722 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 11.52$ (s, OH), 10.87 (s, OH), 8.07 (dd, $J = 9.2$, 2.5 Hz, 1H, Ar–H), 8.03 (d, $J = 2.5$ Hz, 1H, Ar–H), 8.00 (s, 1H, Ar–H), 6.88 (d, $J = 9.3$ Hz, 1H, Ar–H), 6.63 (s, 1H, Ar–H), 6.47 (s, OH), 3.62 (t, $J = 5.6$ Hz, OCH_2), 3.56 (t, $J = 5.6$ Hz, CH_2) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 195.3$, 156.7, 155.4, 149.8, 135.1, 132.6, 125.3, 125.1, 123.9, 118.7, 111.1, 109.8, 103.9, 59.3 (CH_2), 45.2 (CH_2) ppm; MS (70 eV): $m/z = 349$ (M^+, 19), 334 (6), 332 (53), 304 (44), 305 (100), 292 (12), 286 (17), 276 (25), 259 (30), 241 (9), 224 (6), 214 (5), 201 (4), 186 (5), 169 (7), 167 (5), 140 (6), 108 (4), 90 (7), 75 (15), 63 (30), 51 (8), 36 (21); HPLC (C-18): $\log k = -0.631$.

4-(1-Phenyl-1H-benzimidazol-2-yl)benzene-1,3-diol (**7**, $C_{19}H_{14}N_2O_2$)

A mixture of 0.50 g *N*-phenylbenzene-1,2-diamine (2.7 mmol) and 1 g STB (3.1 mmol) in 13.5 cm^3 MeOH was refluxed for 3 h. The hot mixture was filtered and the filtrate was concentrated. NaOH solution (5%) was added (5 cm^3) and the mixture was filtrated. HCl solution (5%) was added to the filtrate to afford the product. Recrystallization from methanol afforded 0.58 g (71%) **7**. M.p.: 128–131 °C; IR (KBr): $\bar{\nu} = 3{,}438$ (OH), 2,921 (CH), 2,849 (CH), 1,612 (C=N), 1,499 (C=C), 1,469, 1,387, 1,323, 1,288, 1,229 (C–OH), 1,155, 999, 942, 910, 845, 796, 760, 725 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 11.37$ (s, OH), 10.02 (s, OH), 7.81 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.64 (m, 3H, Ar–H), 7.56 (dd, $J = 8.1$, 2.0 Hz, 2H, Ar–H), 7.40 (t, $J = 7.4$ Hz, 1H, Ar–H), 7.34 (t, $J = 7.7$ Hz, 1H, Ar–H), 7.20 (d, $J = 8.4$ Hz, 1H, Ar–H), 7.15 (d, $J = 7.9$ Hz, 1H, Ar–H), 6.39 (d, $J = 2.3$ Hz, 1H, Ar–H), 6.12 (dd, $J = 8.7$, 2.2 Hz, 1H, Ar–H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 161.3$, 160.0, 150.8, 143.8, 136.1, 135.4, 130.4, 130.0, 129.8, 129.2, 127.5, 124.0, 123.9, 117.3, 117.2, 110.7, 107.2, 103.7, 103.4 ppm; MS (70 eV): $m/z = 302$ (M^+, 94), 301 (100), 285 (26), 273 (6), 255 (6), 245 (6), 231 (5), 219 (3), 167 (7), 151 (6), 137 (11), 115 (6), 92 (5), 77 (16), 63 (6), 51 (15); HPLC (C-18): $\log k = 0.023$.

2-Methyl-4-(1-phenyl-1H-benzimidazol-2-yl)benzene-1,3-diol (**8**, $C_{20}H_{16}N_2O_2$)

A mixture of 0.26 g *N*-phenylbenzene-1,2-diamine (1.4 mmol) and 0.51 g S3MTB (1.4 mmol) in 13.5 cm^3 MeOH was refluxed for 3 h. The hot mixture was filtered and the filtrate was concentrated. Recrystallization from MeOH/H_2O afforded 0.29 g (66%) **8**. M.p.: 130–133 °C; IR (KBr): $\bar{\nu} = 3{,}062$ (OH), 1,671 (C=N), 1,607 (C=C), 1,499 (C=C), 1,455, 1,376, 1,307, 1,266, 1,207 (C–OH), 1,121, 1,081, 1,015, 880, 849, 805, 781, 759, 746 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 10.75$ (s, OH), 10.10 (s, OH), 7.85 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.66 (m, 2H, Ar–H), 7.56 (dd, $J = 7.8$, 2.2 Hz, 2H, Ar–H), 7.51 (t, $J = 7.2$ Hz, 1H, Ar–H), 7.43 (t, $J = 7.5$ Hz, 1H, Ar–H), 7.25 (m, 1H,

Ar–H), 7.07 (d, $J = 8.0$ Hz, 1H, Ar–H), 6.83 (s, 1H, Ar–H), 6.83 (s, 1H, Ar–H), 2.02 (s, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 161.4$, 160.0, 156.5, 150.0, 134.4, 134.1, 131.1, 130.0, 129.0, 128.0, 127.4, 125.4, 124.9, 117.4, 115.2, 112.2, 111.9, 107.3, 102.2, 8.6 (CH_3) ppm; MS (70 eV): $m/z = 316$ (M^+, 100), 315 (83), 289 (28), 287 (5), 243 (6), 219 (3), 209 (2), 167 (8), 158 (3), 140 (3), 135 (3), 115 (3), 92 (3), 77 (9), 65 (4), 51 (7); HPLC (C-18): $\log k = 0.493$.

4-Methyl-6-(1-phenyl-1H-benzimidazol-2-yl)benzene-1,3-diol (**9**, $C_{20}H_{16}N_2O_2$)

A mixture of 0.26 g *N*-phenylbenzene-1,2-diamine (1.4 mmol) and 0.51 g S5MTB (1.4 mmol) in 7 cm^3 MeOH was refluxed for 2.5 h. The hot mixture was filtered and the filtrate was concentrated. Recrystallization from MeOH/H_2O (3:1) afforded 0.30 g (68%) **9**. M.p.: 158–159 °C; IR (KBr): $\bar{\nu} = 3{,}400$ (OH), 3,056 (CH), 2,919 (CH), 1,625 (C=N), 1,594 (C=C), 1,499 (C=C), 1,453, 1,390, 1,265, 1,255 (C–OH), 1,161, 1,135, 1,071, 1,009, 845, 746, 695 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 10.60$ (s, OH), 10.05 (s, OH), 7.76 (d, $J = 7.9$ Hz, 1H, Ar–H), 7.66 (m, 2H, Ar–H), 7.51 (dd, $J = 8.0$, 2.1 Hz, 2H, Ar–H), 7.34 (m, 1H, Ar–H), 7.25 (m, 2H, Ar–H), 7.07 (d, $J = 8.0$ Hz, 1H, Ar–H), 6.56 (s, 1H, Ar–H), 6.43 (s, 1H, Ar–H), 2.05 (s, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 164.0$, 158.5, 158.2, 151.3, 136.7, 135.9, 130.2, 129.6, 129.4, 128.9, 127.7, 123.2, 123.0, 117.7, 114.5, 114.4, 110.5, 104.0, 102.7, 15.4 (CH_3) ppm; MS (70 eV): $m/z = 316$ (M^+, 100), 299 (23), 287 (13), 271 (5), 259 (6), 245 (4), 231 (5), 219 (3), 206 (3), 167 (9), 151 (4), 139 (3), 115 (4), 103 (2), 92 (3), 77 (10), 65 (4), 51 (8), 39 (4); HPLC (C-18): $\log k = 0.384$.

4-Ethyl-6-(1-phenyl-1H-benzimidazol-2-yl)benzene-1,3-diol (**10**, $C_{21}H_{18}N_2O_2$)

A mixture of 0.26 g *N*-phenylbenzene-1,2-diamine (1.4 mmol) and 0.54 g SETB (1.4 mmol) in 7 cm^3 MeOH was refluxed for 3.5 h. The hot mixture was filtered and the filtrate was concentrated. Recrystallization from MeOH/H_2O (3:2) afforded 0.36 g (77%) **10**. M.p.: 189–191 °C; IR (KBr): $\bar{\nu} = 3{,}063$ (OH), 2,962 (CH), 1,672 (C=N), 1,617 (C=N), 1,551 (C=C), 1,500 (C=C), 1,446, 1,415, 1,388, 1,320, 1,245 (C–OH), 1,149, 1,082, 1,009, 980, 924, 897, 845, 749 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 10.37$ (s, OH), 7.98 (d, $J = 8.1$ Hz, 1H, Ar–H), 7.66–7.64 (m, 3H, Ar–H), 7.57 (m, 2H, Ar–H), 7.53 (m, 1H, Ar–H), 7.48 (t, $J = 7.9$ Hz, 1H, Ar–H), 7.31 (d, $J = 8.2$ Hz, 1H, Ar–H), 6.83 (s, 1H, Ar–H), 6.63 (s, 1H, Ar–H), 2.24 (q, $J = 7.5$ Hz, CH_2), 0.81 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 163.2$, 161.6, 157.3, 149.2, 134.7, 133.8, 132.7, 130.3, 130.1, 130.0, 127.4, 125.6, 125.4, 123.1, 121.8, 115.1, 111.8, 102.7, 100.2, 21.4 (CH_2), 13.3 (CH_3) ppm; MS (70 eV): $m/z = 330$ (M^+, 51), 315 (M^+-CH_3, 100), 301 (5), 243 (5), 219 (4), 180 (3), 167 (7), 149 (3), 115 (2), 92 (2), 77 (7), 69 (4), 51 (5), 36 (6); HPLC (C-18); $\log k = 0.567$.

4-Chloro-6-(1-phenyl-1H-benzimidazol-2-yl)benzene-1,3-diol (**11**, $C_{19}H_{13}ClN_2O_2$)

A mixture of 0.26 g *N*-phenylbenzene-1,2-diamine (1.4 mmol) and 0.54 g SClTB (1.4 mmol) in 13.5 cm^3 MeOH was refluxed for 3 h. The hot mixture was filtered and the filtrate was concentrated. Recrystallization from MeOH/H_2O (3:2) afforded 0.54 g (71%) **11**. M.p.: 133–136 °C; IR (KBr): $\bar{\nu} = 3{,}061$ (OH, CH), 1,608 (C=N), 1,500 (C=C), 1,452, 1,415, 1,386, 1,299, 1,247, 1,206 (C–OH), 1,106, 1,044, 1,027, 1,006, 981, 925, 884, 839, 749 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 11.11$ (s, OH), 9.98 (s, OH), 7.89 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.65 (m, 3H, Ar–H), 7.56 (dd, $J = 8.1$, 2.2 Hz, 2H, Ar–H), 7.53 (m, 1H, Ar–H), 7.47 (t, $J = 7.3$ Hz, 1H, Ar–H), 7.32 (d, $J = 8.1$ Hz, 1H, Ar–H), 7.15 (s, 1H, Ar–H), 6.75 (s, 1H, Ar–H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 160.2$, 157.6, 157.2, 148.6, 134.7, 134.6, 134.3, 130.7, 130.2, 130.0, 127.2, 125.3, 125.2, 116.1, 111.6, 110.6, 103.7, 103.9, 103.2 ppm; MS (70 eV): $m/z = 336$ (M^+, 100), 319 (24), 301 (10), 271 (5), 255 (4), 243 (14), 231 (6), 219 (4), 205 (3), 194 (3), 171 (7), 166 (5), 140 (5), 136 (5), 122 (6), 102 (3), 91 (2), 76 (3), 63 (4), 51 (14), 36 (10); HPLC (C-18): $\log k = 0.426$.

4-(1-Phenyl-1H-benzimidazol-2-yl)benzene-1,2,3-triol (**12**, $C_{19}H_{14}N_2O_3$)

A mixture of 0.26 g *N*-phenylbenzene-1,2-diamine (1.4 mmol) and 0.52 g S3TTB (1.4 mmol) in 7 cm^3 MeOH was refluxed for 3.5 h. The hot mixture was filtered and the filtrate was concentrated. Recrystallization from MeOH/H_2O (3:1) afforded 0.29 g (66%) **12**. M.p.: 163–166 °C; IR (KBr): $\bar{\nu} = 3{,}063$ (OH), 2,962 (CH), 1,672 (C=N), 1,617 (C=N), 1,551 (C=C), 1,500 (C=C), 1,446, 1,415, 1,388, 1,320, 1,245 (C–OH), 1,149, 1,082, 1,009, 980, 924, 897, 845, 749 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 10.60$ (s, OH), 9.98 (s, OH), 9.01 (s, OH), 7.89 (d, $J = 8.1$ Hz, 1H, Ar–H), 7.65 (m, 2H, Ar–H), 7.53 (dd, $J = 8.0$, 2.3 Hz, 2H, Ar–H), 7.54 (m, 1H, Ar–H), 7.51 (m, 1H, Ar–H), 7.45 (t, $J = 7.3$ Hz, 1H, Ar–H), 7.28 (d, $J = 8.7$ Hz, 1H, Ar–H), 6.48 (d, $J = 8.7$ Hz, 1H, Ar–H), 6.28 (d, $J = 8.7$ Hz, 1H, Ar–H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 152.3$, 151.4, 149.9, 149.8, 147.4, 134.7, 134.2, 133.6, 130.3, 130.0, 127.4, 125.4, 125.3, 120.6, 115.6, 111.8, 108.0, 107.8, 102.7 ppm; MS (70 eV): $m/z = 318$ (M^+, 100), 289 (6), 271 (9), 261 (8), 243 (9), 232 (4), 219 (5), 200 (11), 194 (7), 162 (14), 152 (5), 122 (3), 51 (7), 36 (9); HPLC (C-18): $\log k = -0.781$.

4-[5-Chloro-2-(5-ethyl-2,4-dihydroxyphenyl)-1H-benzimidazol-1-yl]benzoic acid (**13**, $C_{22}H_{17}ClN_2O_4$)

A mixture of 0.26 g 4-[(2-amino-4-chlorophenyl)amino] benzoic acid (1 mmol) and 0.52 g SETB (1 mmol) in

5 cm^3 MeOH was refluxed for 3.5 h. The hot mixture was filtered and the filtrate was concentrated. Recrystallization from methanol afforded 0.27 g (67%) **13**. M.p.: 130–133 °C; IR (KBr): $\bar{\nu}$ = 3,107 (OH), 2,936 (CH), 1,698 (C=O), 1,618 (C=N), 1,503 (C=C), 1,446, 1,406, 1,242 (C–OH), 1,141, 1,098, 1,075, 980, 930, 892, 853, 798, 761, 704 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.85 (s, OH), 10.71 (s, COOH), 10.05 (s, OH), 8.13 (dd, J = 7.9, 1.5 Hz, 1H, Ar–H), 7.98 (d, J = 1.9 Hz, 1H, Ar–H), 7.92 (m, 1H, Ar–H), 7.86–7.80 (m, 2H, Ar–H), 7.50 (d, J = 8.7 Hz, 1H, Ar–H), 7.20 (s, 1H, Ar–H), 6.84 (d, J = 8.7 Hz, 1H, Ar–H), 6.43 (s, 1H, Ar–H), 2.50 (q, J = 7.5 Hz, CH_2), 1.10 (t, J = 7.5 Hz, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.7 (C=O), 165.0, 163.1, 161.5, 157.7, 134.4, 133.0, 131.7, 131.2, 130.1, 129.3, 127.8, 125.7, 123.1, 120.0, 114.4, 113.8, 113.3, 103.0, 102.5, 21.7 (CH_2), 13.0 (CH_3) ppm; MS (70 eV): m/z = 408 (M^+, 100), 396 (40), 381 (7), 316 (6), 301 (20), 259 (11), 243 (12), 224 (10), 212 (9), 155 (35), 149 (14), 107 (7), 77 (9), 36 (20); ESI–MS: m/z = 409.1 ($[M + H]^+$); HPLC (C-18): log k = 0.247.

4-[5-Chloro-2-(2,3,4-trihydroxyphenyl)-1H-benzimidazol-1-yl]benzoic acid (**14**, $C_{20}H_{13}ClN_2O_5$)

A mixture of 0.50 g 4-[(2-amino-4-chlorophenyl)amino] benzoic acid (1.9 mmol) and 0.70 g S3TTB (2.1 mmol) in 9.5 cm^3 MeOH was refluxed for 4 h. The hot mixture was filtered and the filtrate was concentrated. Recrystallization from methanol afforded 0.50 g (66%) **14**. M.p.: 194–197 °C; IR (KBr): $\bar{\nu}$ = 3,390 (OH of CO_2H), 3,242 (OH), 1,678 (C=O), 1,620 (C=N), 1,501 (C=C), 1,465, 1,306, 1,218 (C–OH), 1,183, 1,142, 1,079, 1056, 994, 993, 922, 861, 800, 755, 713 cm^{-1}; ^{1}H ↑ NMR (500 MHz, DMSO-d_6): δ = 8.96 (s, OH), 7.86 (dd, J = 7.9, 1.6 Hz, 1H, Ar–H), 7.30 (m, 2H, Ar–H), 7.05 (d, J = 8.4 Hz, 1H, Ar–H), 6.87 (d, J = 2.4 Hz, 1H, Ar–H), 6.70 (m, 2H, Ar–H), 6.61 (dd, J = 8.3, 2.2 Hz, 1H, Ar–H), 6.57 (d, J = 8.4 Hz, 1H, Ar–H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 173.0 (C=O), 168.3, 153.8, 150.7, 149.6, 137.5, 136.8, 136.3, 135.5, 134.5, 133.3, 131.8, 129.5, 129.1, 123.6, 117.8, 116.4, 111.3, 110.4, 104.7 ppm; MS (70 eV): m/z = 396 (M^+, 27), 394 (78), 333 (15), 321 (7), 293 (21), 262 (53), 244 (100), 209 (64), 181 (12), 154 (14), 122 (9), 99 (3), 77 (10), 63 (5), 51 (5), 36 (14); HPLC (C-18): log k = 0.026.

Antiproliferative activity assay

The following established in vitro human cell lines were used: T47D (breast cancer), SW707 (rectal adenocarcinoma), A549 (non-small cell lung carcinoma) from the American Type Culture Collection (Rockville, Maryland, USA), and HCV29T (immortalized tumorigenic cell line) from the Fibiger Institute, Copenhagen, Denmark. Twenty-four hours before the addition of the tested agents, the cells were plated in 96-welI plates (Sarstedt, USA) at a density of 10^4 cells/well. All cell lines were maintained in the opti-MEM medium supplement with 2 mM glutamine (Gibco, Warsaw, Poland), streptomycin (50 μg cm^{-3}), penicillin (50 U cm^{-3}) (Polfa, Tarchomin, Poland), and 5% fetal calf serum (Gibco, Grand Island, USA). The cells were incubated at 37 °C in humid atmosphere saturated with 5% CO_2. The solutions of compounds (1 mg cm^{-3}) were prepared ex tempore by dissolving the substance in 100 mm^3 of DMSO completed with 900 mm^3 of tissue culture medium. Afterwards, the compounds were diluted in the culture medium to reach the final concentrations ranging from 0.1 to 100 μg cm^{-3}. The solvent (DMSO) in the highest concentration used in the test did not reveal any cytotoxic activity. Cisplatin was applied as a test reference agent. The cytotoxicity assay was performed after 72 h exposure of the cultured cells to the tested agents at a concentration ranging from 0.1 to 100 μg cm^{-3}. The SRB test measuring the cell proliferation inhibition in the in vitro culture was applied [45]. The cells attached to the plastic were fixed with cold 50% TCA (trichloroacetic acid, Aldrich-Chemie, Germany) added on the top of the culture medium in each well. The plates were incubated at 4 °C for 1 h and then washed five times with tap water. The background optical density was measured in the wells filled with culture medium, without the cells. The cellular material fixed with TCA was stained with 0.4% sulforhodamine B (SRB, Sigma, Germany) dissolved in 1% acetic acid (POCh, Gliwice, Poland) for 30 min. The unbound dye was removed by rinsing four times with 1% acetic acid, and the protein-bound dye was extracted with 10 mM unbuffered Tris base (tris(hydroxymethyl)aminomethane, POCh, Gliwice, Poland) for determination of optical density (at 540 nm) in a computer-interfaced, 96-well Uniskan II microtiter plate reader (Labsystems, Helsinki, Finland). The compounds were tested in triplicate per experiment. The experiments were repeated at least three times. The IC_{50} values were calculated by Cheburator 0.9.0 software using a drug–response curve and two-point method [46].

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