N-Arylsulfonyl-benzimidazolones as Potential Hypoglycemic Agents

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Arylsulfonyl-benzimidazolones, Insulin Release, Antidiabetic Activity

1,3-Bis(arylsulfonyl)-benzimidazolones **1a**-**d** were synthesized by reacting benzimidazolones with arenesulfonyl chlorides in the presence of NaOH. Mono(arylsulfonyl)-benzimidazolone derivatives **5a**-**c** were prepared from benzimidazolone by protecting one of the *N*-atoms with a *tert*-butoxycarbonyl group followed by arylsulfonylation and deprotection in acidic medium. The antidiabetic activity of three compounds **1a**, **1c** and **5a** has been determined.

Introduction

Benzimidazolones are a class of cyclic urea derivatives demonstrating a wide variety of biochemical and pharmacological properties. They antagonize neurotransmitters [1], inhibit aldose reductase [2], show antiulcer and antisecretory properties [3], enhance pulmonary surfactant secretion [4] and modulate ion channels [5]. Several of these compounds show activity against leukemia [6]. A number of such compounds with different substitution patterns have been synthesized [7–10] to check their medicinal properties.

In continuation of our work [11] on arylsulfonyl cyclic urea derivatives as hypoglycemic agents, we synthesized 1,3-bis(arylsulfonyl)-benzimidazolone derivatives **1a-d** and mono(arylsulfonyl)-benzimidazolone derivatives **5a–c** (Scheme 1). The synthesis and spectroscopic characterization of the intermediate compounds and the final products is presented in this work. The antidiabetic activity of compounds **1a**, **1c** and **5a** only is reported because the other compounds were either less soluble or showed no significant effects.

Results and Discussion

Syntheses

1,3-Bis(arylsulfonyl)-benzimidazolones **1a**-**d** were synthesized in 62–97 % yield by reacting arenesulfonyl chlorides with benzimidazolones in basic medium using sodium hydroxide in acetone. Benzimidazolones for this purpose were prepared by two methods known in the literature. In the first method [12] *o*-phenylenediamines were treated with urea at 20–140° C under inert atmosphere and in the second method [13] methyl anthranilates were converted into azides *via* hydrazides, which on heating resulted in the formation of benzimidazolones.

In order to synthesize the monosulfonylated derivatives **5a**-**c**, one of the benzimidazolone nitrogens was protected with a *tert*-butoxycarbonyl group [14] by treatment with NaH/DMF and di-*tert*-butyldicarbonate. The nitrobenzimidazolone gave two regioisomers, **2b** and **3**, which were isolated and identified by spectroscopic methods. The major product, **2b** (33% yield) was taken for further studies. The protected benzimidazolones were sulfonylated in the presence of triethylamine and dimethylaminopyridine (DMAP) and the resulting compounds **4a–4c** deprotected with dilute acid to give the target molecules. The structures of all intermediates and final products were elucidated by spectroscopic methods and the purity determined by elemental analysis.

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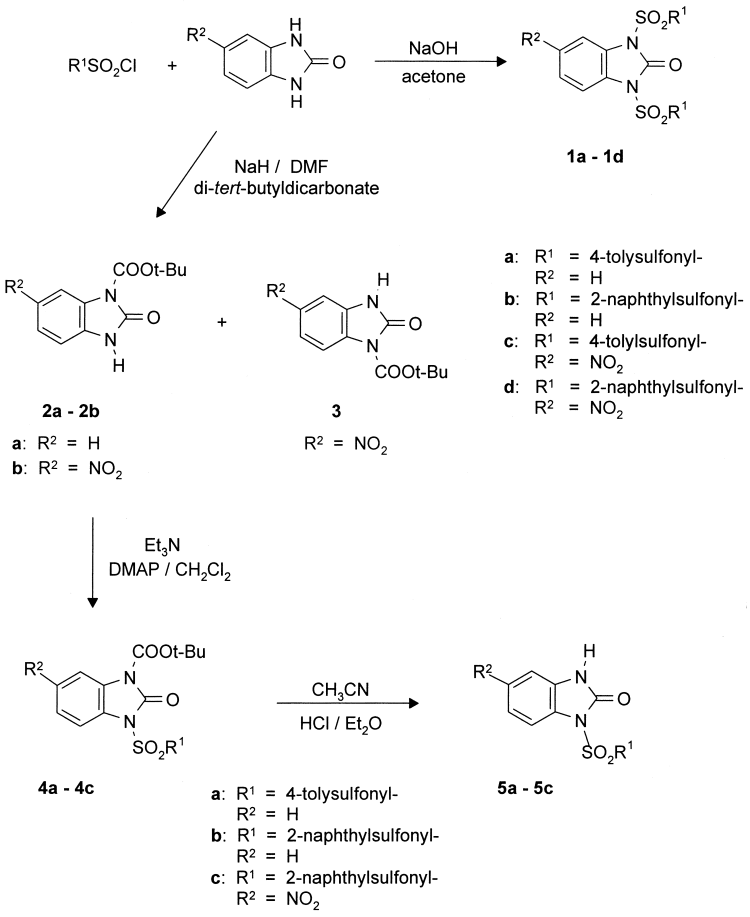

Scheme 1. Formula and reaction scheme.

Antidiabetic activity

Imidazolone derivatives **1a**, **1c** and **5a** were tested for their ability to stimulate insulin release using concentrations of 10 and 100 μM. At these concentrations of the test agents, the corresponding concentrations of solvent from the stock solutions were 0.2 and 2%. The static incubation of insulin-secreting INS-1 cells showed that at 100 μM all of the selected test agents stimulated insulin release. However, at 10 μM **1a** had a small but significant effect (Table 1). 2% Methanol, but not 0.2% methanol alone also increased insulin release, but the effect was clearly smaller than that of the test agents. Tolbutamide, a classical pharmacological stimulator of insulin secretion belonging to the class of sulfonylurea compounds [15], stimulated insulin release under the same conditions as used to measure the effect of the test agents. At 800 μM, tolbutamide increased the insulin content in the medium to 16.5 ng/ml which has to be compared with 24.6 ± 1.4 ng/ml produced by 100 μM of the least efficient compound, **1a**. There was no increase in insulin release, when the incubation was performed at 20 °C rather than at 37 °C.

All test agents proved to be stimulators of insulin release when used at a concentration of 100 μM. Since the stimulatory effect could be inhibited by incubation at room temperature, a nontoxic mechanism of action can be assumed. The insulin-releasing potency is only moderate, because only one compound was effective at 10 μM. This has to be compared with a maximally effective concentration of 1 μM for glibenclamide, a prototypic se-

cond-generation sulfonylurea compound. However, the magnitude of the effect was impressive. The least effective compound produced a more marked increase in insulin release than tolbutamide, a fast acting first-generation sulfonylurea at a maximally effective concentration. Thus, it seems worthwhile to investigate the mechanism of action of these compounds and to look for more potent derivatives by setting up a complete structure-activity relationship.

Table 1. Measurement of insulin release by compounds **1a**, **1c** and **5a**[a].

Compound	**1a**	**1c**	**5a**
10 μM	13.6 ± 1.0[b]	8.2 ± 0.4	8.0 ± 0.4
100 μM	24.6 ± 1.4[c]	31.0 ± 0.7[c]	45.6 ± 7.0[c]

[a] Insulin release by INS-1 cells during a 1 h incubation at 37 °C. The insulin content of the incubation medium is expressed as ng/ml. All data are given as mean ± SEM of three experiments. The insulin content after control incubation with 0.2% methanol was 9.3 ± 0.7 ng/ml and after control incubation with 2% methanol 13.4 ± 0.6 ng/ml. Significance of the differences in comparison with the respective control was calculated using Student's unpaired two-tailed t-test; [b] $P < 0.05$; [c] $P < 0.01$.

Experimental Section

The melting points were determined on a Gallenkamp digital melting point apparatus MFB-595–010M and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 instrument. Solvents used for NMR are given in the experimental part. All chemical shifts are referenced to TMS. The mass spectra were recorded on a Varian MAT CH-5 spectrometer.

General method for arylsulfonylation of benzimidazolones (**1a–d**)

The standard procedure was as follows [16]: Benzimidazolone (0.01 mol) was suspended in acetone (60 ml) in a three-neck round bottomed flask fitted with an air condenser and two dropping funnels. In one dropping funnel was taken 1 N NaOH solution (20 ml) and in the other a solution of 4-toluene- or naphthalene-2-sulfonyl chloride (0.02 mol) in acetone. To the suspension of benzimidazolone in acetone was added 1 N NaOH solution and 4-tolyl- or naphthylsulfonyl chloride, respectively, dropwise with constant stirring. The temperature was maintained at 20–30° C. The mixture was stirred for one hour. Acetone was removed *in vacuo*, the residue washed with water and recrystallized from chloroform and methanol (3:1).

2,3-Dihydro-1,3-bis(4-tolylsulfonyl)-1H-benzimidazol-2-one (**1a**):

M. p. = 187° C; yield = 84%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3052, 2956, 2924, 1760, 1596, 1468, 1384, 1340, 1260, 1192, 1152, 1084, 812, 664. – ^{1}H NMR ($CDCl_3$): ≥ = 7.95 (m, 6H, 2′/6′/5/6-H), 7.31 (d, 4H, 3′/5′-H, J = 8.5 Hz), 7.26 (dd, 2H, 4/7-H), 2.4 (s, 6H, CH_3). – ^{13}C NMR ($CDCl_3$): ≥ = 21.8 (CH_3), 113.4 (C-3′/5′), 125.2 (C-4/7), 126.3 (C-4′), 128.4 (C-5/6), 130.1 (C-2′/6′), 134.2 (C-1′), 146.9 (C-8/9), 147.6 (CO). – MS (EI, 70 eV): *m/z* (%) = 442 (45)[M$^+$], 378 (6), 287 (40), 223 (10), 208 (4), 180 (4), 155 (94), 139 (15), 91 (100). – $C_{21}H_{18}N_2O_5S_2$ (442.51): calcd. C 57.00, H 4.10, N 6.33; found C 56.84, H 4.03, N 6.26.

2,3-Dihydro-1,3-bis(naphth-2-ylsulfonyl)-1H-benzimidazol-2-one (**1b**):

M. p. = 186–188° C; yield = 62%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3056, 2928, 1756, 1588, 1304, 1184, 1156, 1152, 1072, 816, 784. – ^{1}H NMR ($CDCl_3$): ≥ = 8.00 (m, 2H, 5/6-H), 7.94 (d, 4H, 1′/3′-H), 7.82 (m, 6H, 4′/5′/8′-H), 7.75 (t, 2H, 6′-H), 7.68 (t, 2H, 7′-H), 7.30 (dd, 2H, 4/7-H, J_{7-6} = 6.2 Hz, J_{7-5} = 3.5 Hz). – ^{13}C NMR ($CDCl_3$): ≥ = 113.6 (C-6′), 122.0 (C-3′/4′/7′), 125.3 (C-4/7), 128.1 (C-5/6), 129.5 (C-5′), 130.5 (C-2′/8′), 131.7 (C-9′/10′), 133.9 (C-1′), 135.5 (C-8/9), 147.5 (CO). – MS (EI, 70 eV): *m/z* (%) = 514 (21)[M$^+$], 450 (7), 323 (8), 259 (14), 231 (2), 191 (48), 127 (100), 77 (5). – $C_{27}H_{18}N_2O_5S_2$ (514.458): calcd. C 63.02, H 3.52, N 5.44; found C 62.18, H 3.46, N 5.19.

2,3-Dihydro-5-nitro-1,3-bis(4-tolylsulfonyl)-1H-benzimidazol-2-one (**1c**):

M. p. = 219–220° C; yield = 97%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3068, 2952, 1772, 1528, 1444, 1344, 1192, 1152, 1084, 856, 812. – ^{1}H NMR ($CDCl_3$): ≥ = 8.80 (d, 1H, 4-H, J_{4-6} = 2.0 Hz), 8.08 (d, 1H, 7-H, J_{7-6} = 9.0 Hz), 8.22 (dd, 1H, 6-H, J_{6-7} = 9.0 Hz, J_{6-4} = 2.0 Hz), 7.98 (m, 4H, 2′/6′-H), 7.37 (d, 4H, 3′/5′-H, J = 8.0 Hz), 2.5 (s, 6H, 2 × CH_3). – ^{13}C NMR ($CDCl_3$): ≥ = 22.0 (CH_3), 109.3 (C-7), 113.2 (C-4), 121.4 (C-5), 126.6 (C-4′), 128.3 (C-2′/6′), 130.4 (C-9), 130.9 (C-3′/5′), 133.3 (C-1′), 144.8 (C-8), 147.1 (CO), 147.2 (C-6). – MS (EI, 70 eV): *m/z* (%) = 487 (26)[M$^+$], 423 (6), 156 (10), 155 (100), 139 (9), 121 (00), 92 (10), 91 (77), 65 (11). – $C_{21}H_{17}N_3O_7S_2$ (487.51): calcd. C 51.73, H 3.51, N 8.61; found C 51.32, H 3.38, N 8.48.

2,3-Dihydro-1,3-bis(naphth-2-ylsulfonyl)-5-nitro-2-oxo-1H-benzimidazol-2-one (**1d**):

M. p. = 206° C; yield = 73%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3056, 2928, 1528, 1488, 1344, 1184, 1152, 1068, 888, 860. – ^{1}H NMR ($CDCl_3$): ≥ = 8.87 (d, 1H, 4-H, J_{4-6} = 2.0 Hz), 8.67 (distort. d, 2H, 1′-H), 8.25 (dd, 1H, 6-H, J_{6-7} = 9.0 Hz, J_{6-4} = 2.0 Hz), 8.16 (d, 1H, 7-H, J_{7-6} = 9.0 Hz), 8.00 (d, 2H, 3′-H, $J_{3'/4'}$ = 8.9 Hz), 7.86 (m, 6H, 4′/5′/8′-H), 7.71 (t, 2H, 6′-H), 7.64 (t, 2H, 7′-H). – ^{13}C NMR ($CDCl_3$): ≥ = 113.8 (C-4), 121.4 (C-5), 122.0 (C3′/4′/7′), 126.9 (C-9), 128.7 (C-6′), 130.1 (C-9′/10′), 130.4 (C-7), 130.9 (C-8), 131.2 (C-5′), 131.5 (C-2′/8′), 145.2 (C-6), 197.3 (C-CO). – MS (EI, 70 eV): *m/z* (%) = 559 (10)[M^+], 495 (9), 369 (2), 305 (2), 304 (2), 149 (2), 127 (100), 115 (5), 77 (5). – $C_{27}H_{17}N_3O_7S_2$ (559.58): calcd. C 57.95, H 3.06, N 7.50; found C 57.60, H 2.97, N 7.39.

General method for t-butoxycarbonylation of benzimidazolones [14] (**2a, 2b,** and **3**):

The standard procedure was as follows [14]: To the solution of benzimidazolone (0.01 mol) in dry DMF was added sodium hydride (0.1 mol) under argon. The solution was stirred for 30 minutes. To this solution di-*tert*-butyldicarbonate (0.1 mol) was added dropwise from a dropping funnel with constant stirring. The solution was stirred for 24 h at 20 °C. DMF was removed *in vacuo*, the residue treated with saturated ammonium chloride solution and extracted with ethyl acetate. Ethyl acetate was removed *in vacuo* and purification carried out by flash column chromatography using ethyl acetate : *n*-hexane (1 : 4) as eluent. In case of nitrobenzimidazolone two isomers were obtained, which were separated by column chromatography.

2,3-Dihydro-2-oxo-1H-benzimidazole-1-carboxylic acid, 1,1-dimethylethyl ester (**2a**):

M. p. = 305–307° C (lit. 313–315° C [14]); yield = 68%. Spectroscopic data were identical with the reported ones.

2,3-Dihydro-6-nitro-2-oxo-1H-benzimidazole-1-carboxylic acid, 1,1-dimethylethyl ester (**2b**):

M. p. = 320° C; yield = 33%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3365, 3195, 2975, 2850, 1777, 1740, 1520, 1394, 1365, 1110, 888, 832. – ^{1}H NMR ($CDCl_3$): ≥ = 9.70 (s, 1H, N-H), 8.70 (d, 1H, 7-H, J_{7-5} = 2.3 Hz), 8.18 (dd, 1H, 5-H, J_{5-4} = 8.7 Hz, J_{5-7} = 2.5 Hz), 7.18 (d, 1H, 4-H, J_{4-5} = 8.7 Hz), 1.25 (s, 9H, 3 × CH_3). – MS (EI, 70 eV): *m/z* (%) = 279 (9) [M^+], 179 (100), 178(6), 151 (9), 150 (3), 135 (2), 123 (3), 122 (2). – $C_{12}H_{13}N_3O_5$ (279.25): calcd. C 51.61, H 4.69, N 15.04; found C 50.91, H 4.31, N 14.95.

2,3-Dihydro-5-nitro-2-oxo-1H-benzimidazole-1-carboxylic acid, 1,1-dimethylethyl ester (**3**):

M. p. = 327° C; yield = 29%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3365, 3195, 2975, 1779, 1740, 1521, 1390, 1365, 1110, 871, 627. – ^{1}H NMR ($CDCl_3$): ≥ = 9.48 (s, 1H, N-H), 8.10 (dd, 1H, 6-H, J_{6-7} = 8.7 Hz, J_{6-4} = 2.1 Hz), 8.00 (d, 1H, 4-H, J_{4-6} = 2.3 Hz), 7.87 (d, 1H, 7-H, J_{7-6} = 8.7 Hz), 1.25 (s, 9H, 3 × CH_3). – MS (EI, 70 eV): *m/z* (%) = 279 (7) [M^+], 235 (9), 206 (4), 179 (100), 178 (4), 151 (10), 150 (3), 123 (4), 122 (2). – $C_{12}H_{13}N_3O_5$ (279.25): calcd. C 51.61, H 4.69, N 15.04; found C 51.95, H 4.23, N 14.95.

General method for arylsulfonylation of t-butylcarboxybenzimidazolone [14] (**4a–c**):

To the mono-protected benzimidazolone (0.01 mol) dry dichloromethane (500 ml) was added followed by triethylamine as a base and dimethylaminopyridine as a catalyst. To this well-stirred solution 4-toluene- or naphthalene-2-sulfonyl chloride (0.11 mol) was added portionwise and stirring continued at 20 °C for further 3 h. Then, the mixture was diluted with 1 N HCl and extracted with dichloromethane. The solvent was removed *in vacuo* and the crude product was recrystallized from choloroform-*n*-hexane (1 : 3).

2,3-Dihydro-2-oxo-3-(4-tolylsulfonyl)-1H-benzimidazole-1-carboxylic acid, 1,1-dimethylethyl ester (**4a**):

M. p. = 130–132° C; yield = 88%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3195, 2975, 2950, 1790, 1765, 1595, 1390, 1345, 1193, 1152, 890. – ^{1}H NMR ($CDCl_3$): ≥ = 8.03 (dd, 2H, 2′/6′-H, $J_{2'-6'}$ = 1.2 Hz, $J_{2'-3'}$ = 8. Hz), 7.83 (dd, 1H, 4-H, J_{4-6} = 1.0 Hz, J_{4-5} = 1.6 Hz), 7.34 (d, 2H, 3′/5′-H, $J_{3'-2'}$ = 8.0 Hz), 7.28–7.20 (m, 3H, 5/6/7-H), 2.4 (s, 3H, Ar-CH_3), 1.6 (s, 9H, 3 × CH_3). – MS (EI, 70 eV): *m/z* (%) = 388 (9) [M^+], 288 (100), 224 (15), 155 (50), 133 (73), 106 (13), 91 (48), 77 (4), 65 (8). – $C_{19}H_{20}N_2O_5S$ (388.44): calcd. C 58.75, H 5.18, N 7.21; found C 59.06, H 5.29, N: 7.31.

2,3-Dihydro-3-(naphth-2-yl-sulfonyl)-2-oxo-1H-benzimidazole-1-carboxylic acid, 1,1-dimethylethyl ester (**4b**):

M. p. = 127° C; yield = 75%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3190, 1791, 1770, 1391, 1345, 1340, 1190, 1152, 891. – ^{1}H NMR ($CDCl_3$): ≥ = 8.01 (dd, 2H, 5/6-

H, J_{6-7} = 6.2 Hz, J_{6-4} = 3.4 Hz), 7.87–7.59 (m, 7H, naphthyl-H), 7.32 (dd, 2H, 4/7-H, J_{7-6} = 6.2 Hz, J_{7-5} = 3.2 Hz), 2.24 (s, 9H, 3 × CH_3). – MS (EI, 70 eV): *m/z* (%) = 424 (9)[M^+], 324 (48), 260 (13), 232 (3), 105 (12), 77 (4), 191 (35), 127 (100), 189 (2), 90 (11). – $C_{22}H_{20}N_2O_5S$ (424.47): calcd. C 62.25, H 4.74, N 6.59; found C 62.12, H 4.31, N 6.54.

2,3-Dihydro-3-(naphth-2-yl-sulfonyl)-6-nitro-2-oxo-1H-benzimidazole-1-carboxylic acid, 1,1-dimethylethyl ester (**4c**):

M. p. = 295–297° C; yield = 56%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3125, 2925, 1761, 1715, 1515, 1374, 1345, 1331, 1182, 1152, 902, 806. – ^{1}H NMR ($CDCl_3$): ≥ = 8.71 (d, 1H, 7-H, J_{7-5} = 2.2 Hz), 8.21 (dd, 1H, 5-H, J_{5-4} = 8.6 Hz, J_{5-7} = 2.3 Hz), 7.90 (d, 2H, 1′/3′-H, J = 3.2 Hz), 7.83 (m, 3H, 4′/5′/8′-H), 7.72 (t, 1H, 6′-H), 7.60 (t, 1H, 7′-H), 7.36 (d, 1H, 4-H, J_{4-5} = 8.0 Hz), 1.6 (s, 9H, 3 × CH_3). – MS (EI, 70 eV): *m/z* (%) = 469 (8) [M^+], 425 (3), 369 (45), 305 (12), 277 (2), 236 (32), 186 (11), 172 (100), 158 (4). – $C_{22}H_{19}N_3O_7S$ (469.47): calcd. 56.28, H 4.07, N 8.95; found C 56.02, H 4.01, N 8.89.

General method for deprotection [14] (**5a-c**):

In a 100 ml round bottomed flask, 0.0013 mol of monoprotected sulfonylated benzimidazolones were dissolved in CH_3CN (5 ml). To this conc. HCl (2.5 ml) in diethyl ether (6 ml) was added. The mixture was stirred at 20 °C for 3 h and concentrated using a rotary evaporator and triturated with diethyl ether to give the monosulfonylated benzimidazolones.

2,3-Dihydro-1-(4-tolylsulfonyl)-1H-benzimidazol-2-one (**5a**):

M. p. = 208–210° C (lit. 198–200° C [14]); yield = 81%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3166, 2975, 1771, 1760, 1389, 1340, 1190, 1152, 888. – ^{1}H NMR ($CDCl_3$): ≥ = 9.87 (s, 1H, N-H), 7.98 (d, 2H, 2′/6′-H, $J_{2'-6'}$ = 2.1 Hz, $J_{2'-3'}$ = 8.2 Hz), 7.90 (d, 1H, 7-H, J_{7-6} = 8.0 Hz), 7.28 (d, 2H, 3′/5′-H, $J_{3'-2'}$ = 8.1 Hz, $J_{3'-5'}$ = 2.0 Hz), 7.22–7.11 (m, 3H, 4/5/6-H), 2.4 (s, 3H, CH_3). – MS (EI, 70 eV): *m/z* (%) = 288 (65) [M^+], 224 (16), 195 (4), 155 (41), 133 (100), 105 (13), 91 (59), 77 (6), 65 (14). – $C_{14}H_{12}N_2O_3S$ (288.32): calcd. C 58.32, H 4.19, N 9.71; found C 58.22, H 4.24, N 9.72.

2,3-Dihydro-1-(naphth-2-ylsulfonyl)-1H-benzimidazol-2-one (**5b**):

M. p. = 206° C; yield = 70%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3182, 2770, 1770, 1765, 1380, 1340, 1180, 1152. – ^{1}H NMR ($CDCl_3$): ≥ = 9.7 (s, 1H, N-H), 8.98 (m, 3H, 4′/5′/8′-H), 8.67 (d, 2H, 1′/3′-H, $J_{3'-4'}$ = 8.7 Hz), 7.93 (d, 1H, 7-H, J_{7-6} = 8.0 Hz), 7.71 (t,1H, 7′-H), 7.64 (t, 1H, 6′-H), 7.20–7.13 (m, 3H, 4/5/6-H). – MS (EI, 70 eV): *m/z* (%) = 324 (36) [M^+], 260 (15), 259 (3), 232 (3), 191 (15), 133 (78), 127 (100), 105 (10), 90 (11). – $C_{17}H_{12}N_2O_3S$ (324.35): calcd. C 62.95, H 3.72, N 8.63; found C 62.01, H 3.59, N 8.54.

2,3-Dihydro-1-(naphth-2-ylsulfonyl)-5-nitro-1H-benzimidazol-2-one (**5c**):

M. p. = 325° C; yield = 62%. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3128, 2925, 1767, 1761, 1552, 1375, 1346, 1333, 1183, 1152, 902. – ^{1}H NMR ($CDCl_3$): ≥ = 8.87 (m, 3H, 4′/5′/8′-H), 8.71 (d, 1H, 4-H, J_{4-6} = 2.1 Hz), 8.70 (d, 2H, 1′/3′-H, $J_{3'-4'}$ = 8.2 Hz), 8.35 (dd, 1H, 6-H, J_{6-7} = 8.2 Hz), 8.10 (d, 1H, 7-H, J_{7-6} = 8.0 Hz), 7.69 (t, 1H, 7′-H), 7.63 (t, 1H, 6′-H), 7.27 (s, 1H, N-H). – MS (EI, 70 eV): *m/z* (%) = 369 (34)[M^+], 305 (17), 304 (2), 277 (5), 236 (13), 178 (53), 172 (100), 150 (9), 122 (7). $C_{17}H_{11}N_3O_5S$ (369.35): calcd. C 55.28, H 3.00, N 11.37; found C 55.31, H 2.95, N 11.31.

Measurement of the insulin-releasing property

To prepare a 5 mM stock solution, **Ic** was dissolved in ethyl acetate and **Ia** and **Va** were dissolved in methanol. Measurement of insulin secretion was performed by static incubation of *ca.* 0.5×10^6 insulin-secreting cells of the INS-1 permanent tissue culture cell line in 12-well dishes. The incubation medium was a Krebs-Ringer buffer containing 5 mM glucose. After incubation for 1 h at 37° C, 500 μl of the incubation medium were aspirated from each well and centrifuged to pellet aspirated cells. The insulin content in the supernatant was determined by a sandwich ELISA according to the instruction of the manufacturer (Mercodia AB, Uppsala, Sweden).

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