Supporting Information

4-(3-Halo/amino-4,5-dimethoxy-phenyl)-5-aryl-oxazoles and -N-methylimidazoles that are cytotoxic against combretastatin A resistant tumor cells and vascular disrupting in a cisplatin resistant germ cell tumor model

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TOC

Purity Data.

Compound	Formula	Combustion Analyses (C/H/N in %)	
		Calcd	Found
7b × 2 HCl	$C_{19}H_{22}Cl_3N_3O_3$	51.08/4.96/9.41	50.85/5.02/9.26
7c × HCl	$C_{19}H_{19}Cl_2FN_2O_3$	55.22/4.63/6.78	54.94/4.77/6.58
7d × 2 HCl	$C_{20}H_{24}Cl_3N_3O_2$	54.01/5.44/9.45	53.86/5.32/9.24
8b × 2 HCl	$C_{19}H_{22}BrCl_2N_3O_3$	46.46/4.51/8.55	46.54/4.55/8.38
8c × HCl	$C_{19}H_{19}BrClFN_2O_3$	49.86/4.18/6.12	50.04/4.34/6.15
8d × 2 HCl	$C_{20}H_{24}BrCl_2N_3O_2$	49.10/4.94/8.59	49.18/5.06/8.62
10a × 2 HCl	$C_{18}H_{21}Cl_2N_3O_4$	52.18/5.11/10.14	52.28/5.17/9.98
10b × 2 HCl	$C_{19}H_{23}Cl_2N_3O_3$	55.35/5.62/10.19	55.52/5.73/10.04
10c × 2 HCl	$C_{19}H_{23}Cl_2N_3O_4$	53.28/5.41/9.81	53.12/5.22/9.70
10d × 2 HCl	$C_{19}H_{22}Cl_2FN_3O_3$	53.03/5.15/9.77	52.88/4.96/9.57
10e × 2 HCl	$C_{21}H_{23}Cl_3N_4O_2$	53.69/4.93/11.93	53.66/4.96/11.76

N-[(Toluene-4-sulfonyl)-(3-bromo-4,5-dimethoxyphenyl)methyl]formamide (5b): Analogously to the synthesis of **5a**, compound **5b** (4.78 g, 10.81 mmol, 56%) was obtained from 5-bromoveratraldehyde (5.67 g, 23.14 mmol), *para*-toluenesulfinic acid (3 g, 19.29 mmol), camphorsulfonic acid (110 mg, 0.47 mmol) and formamide (10 mL); colorless solid of mp 162-163 °C; ν_{max} (ATR)/cm^{-1} 3197, 3104, 2945, 1688, 1595, 1569, 1490, 1470, 1422, 1403, 1308, 1301, 1290, 1279, 1250, 1229, 1207, 1144, 1121, 1078, 1049, 998, 832, 769, 705, 688; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (3 H, s), 3.82 (6 H, s), 6.17 (1 H, s), 6.99 (1 H, d, J = 2.1 Hz), 7.17 (1 H, d, J = 2.1 Hz), 7.31 (1 H, d, J = 8.5 Hz), 7.67 (2 H, d, J = 8.5 Hz), 7.97 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.9, 56.4, 61.0, 70.7, 113.3, 118.0, 125.9, 127.3, 129.9, 130.2, 133.1, 146.2, 147.9, 154.0, 161.3; m/z (EI) 274 (28), 273 (45), 272 (37), 271 (40), 242 (27), 192 (100), 156 (30), 92 (56), 91 (55), 65 (36).

N-[(Toluene-4-sulfonyl)-(3,4-dimethoxy-5 nitrophenyl)methyl]formamide (5c): Analogously to the synthesis of **5a**, compound **5c** (2.63 g, 6.68 mmol, 35%) was obtained from 5-nitroveratraldehyde (4.85 g, 22.99 mmol), *para*-toluenesulfinic acid (2.96 g, 19.03 mmol), camphorsulfonic acid (110 mg, 0.47 mmol) and formamide (10 mL); colorless solid of mp 133 °C; ν_{max} (ATR)/cm^{-1} 3194, 2888, 1662, 1539, 1518, 1389, 1354, 1319, 1302, 1291, 1212, 1271, 1084, 1074, 1053, 991, 922, 858, 819; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (3 H, s), 3.87 (3 H, s), 3.95 (3 H, s), 6.33 (1 H, d, J = 10.6 Hz), 7.26 (1 H, d, J = 2.1 Hz), 7.31 (1 H, d, J = 8.5 Hz), 7.43 (1 H, d, J = 2.1 Hz), 7.70 (2 H, d, J = 8.5 Hz), 8.06 (1 H, s), 8.9-9.0 (1 H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 56.5, 62.0, 69.9, 116.4, 117.2, 125.8, 129.4, 130.1, 132.3, 143.9, 144.5, 146.1, 154.1, 160.3; m/z (EI) 196 (7), 155 (9), 91 (100), 65 (58).

3-Bromo-4,5-dimethoxyphenyl(tosyl)methyl isocyanide (6b): Compound **5b** (4.75 g, 10.75 mmol) was suspended in dry DME (100 mL) and cooled to –10 °C. $POCl_3$ (3.1 mL, 33.1 mol) was added and a mixture of Et_3N (7.5 mL, 53.8 mmol) in DME (10 mL) was dropped slowly to the reaction mixture. After stirring for 2 h at –5 °C, the reaction mixture was poured into ice water. The water phase was extracted with ethyl acetate, the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated in vacuum. By refrigeration over night a brown solid

crystallized from the residue, which was collected and dried in vacuum. Yield: 2.75 g (6.71 mmol, 62%); brown solid of mp 109-110 °C; ν_{max} (ATR)/cm^{-1} 2915, 2135, 1593, 1569, 1489, 1452, 1420, 1325, 1295, 1275, 1238, 1199, 1136, 1081, 1048, 1003, 862, 826, 759, 705, 670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (3 H, s), 3.81 (3 H, s), 3.86 (3 H, s), 5.46 (1 H, s), 6.81 (1 H, d, J = 2.2 Hz), 7.01 (1 H, d, J = 2.2 Hz), 7.35 (2 H, d, J = 8.3 Hz), 7.64 (2 H, d, J = 8.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.8, 56.2, 60.7, 75.5, 111.5, 117.8, 123.2, 125.0, 129.9, 130.0, 130.5, 146.9, 148.5, 153.6, 166.6; m/z (EI) 256 (52), 254 (45), 244 (78), 242 (100), 200 (30), 123 (48), 91 (31).

3,4,-Dimethoxy-5-nitrophenyl(tosyl)methyl isocyanide (6c): Compound **5c** (2.63 g, 6.68 mmol) was suspended in dry DME (100 mL) and cooled to –10 °C. $POCl_3$ (3.78 mL, 40.4 mol) was added and a mixture of Et_3N (7.5 mL, 66.6 mmol) in DME (10 mL) was dropped slowly to the reaction mixture. After stirring for 2 h at –5 °C, the reaction mixture was poured into ice water. The water phase was extracted with ethyl acetate, the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated in vacuum. By refrigeration over night a yellow solid crystallized from the residue, which was collected and dried in vacuum. Yield: 520 mg (1.51 mmol, 23%); yellow solid of mp 134 °C (dec.); ν_{max} (ATR)/cm^{-1} 2949, 2140, 1593, 1538, 1494, 1453, 1360, 1337, 1315, 1285, 1248, 1184, 1156, 1145, 1082, 1065, 988, 921, 819, 784, 701, 667; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (3 H, s), 3.91 (3 H, s), 4.00 (3 H, s), 5.53 (1 H, s), 7.12 (1 H, d, J = 2.2 Hz), 7.18 (1 H, d, J = 2.2 Hz), 7.38 (2 H, d, J = 8.4 Hz), 7.67 (2 H, d, J = 8.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.9, 56.7, 62.3, 75.3, 115.3, 116.3, 122.3, 129.7, 129.8, 130.4, 144.6, 144.8, 147.4, 154.4, 167.5; m/z (EI) 375 (6) [M^+ - 1], 344 (12), 278 (23), 262 (22), 221 (100), 211 (47), 155 (32), 139 (38).

1-Methyl-4-(3'-chloro-4',5'-dimethoxyphenyl)-5-(3''-fluoro-4''-methoxyphenyl)-imidazole (7c): Analogously to the synthesis of compound **7a**, compound **7c** was prepared from 3-fluoro-4-methoxybenzaldehyde (65 mg, 0.42 mmol), 33% $MeNH_2$/ethanol (260 μL, 2.10 mmol) and acetic acid (150 μL) in boiling ethanol (15 mL) giving the imine intermediate, which was treated with compound **6a** (153 mg, 0.42 mmol), dissolved in DME (10 mL), and K_2CO_3 (500 mg, 3.62 mmol). After workup,

the residue was purified by column chromatography (silica gel 60). Yield: 150 mg (0.38 mmol, 91%); colorless gum; R_f = 0.27 (ethyl acetate/methanol 95:5); ν_{max} (ATR)/cm^{-1} 2937, 2837, 1601, 1553, 1512, 1487, 1462, 1419, 1301, 1067, 1233, 1166, 1131, 1046, 1022, 999, 896, 873, 829, 815, 761, 734, 719, 656; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (3 H, s), 3.61 (3 H, s), 3.75 (3 H, s), 3.87 (3 H, s), 6.9-7.0 (5 H, m), 7.45 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.9, 55.6, 56.1, 60.5, 109.0, 113.7, 118.0, 118.2, 119.4, 122.4, 122.5, 126.9, 127.5, 127.8, 131.0, 136.7, 137.2, 143.6, 148.0, 148.1, 150.5, 153.2, 153.8; m/z (EI) 379 (15), 378 (65) [M$^+$], 377 (41), 376 (100) [M$^+$], 363 (26), 361 (67).

1-Methyl-4-(3'-chloro-4',5'-dimethoxyphenyl)-5-(3''-fluoro-4''-methoxyphenyl)-imidazole hydrochloride (7c x HCl): Compound **7c** (150 mg, 0.38 mmol) was dissolved in DCM (5 mL) and treated with 3M HCl/dioxane (1 mL). After stirring for 15 min the solvent was removed and the oily residue was recrystallised from an DCM/*n*-hexane mixture giving the hydrochloride salt of **9c**. Yield: 106 mg (0.25 mmol, 66%); colorless solid of mp 185-187 °C; UV (MeOH) λ_{max} (ε) 264 (10380); ν_{max} (ATR)/cm^{-1} 3387, 2941, 2840, 2605, 1623, 1553, 1523, 1498, 1464, 1456, 1422, 1303, 1272, 1232, 1134, 1117, 1048, 1019, 997, 872, 844, 817, 760; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.63 (3 H, s), 3.70 (3 H, s), 3.75 (3 H, s), 3.92 (3 H, s), 7.02 (1 H, d, J = 2.1 Hz), 7.17 (1 H, d, J = 2.1 Hz), 7.2-7.3 (1 H, m), 7.39 (1 H, t, J = 17.2 Hz), 7.51 (1 H, dd, J = 12.0 Hz, J = 2.0 Hz), 9.29 (1 H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 33.8, 56.0, 56.2, 60.3, 110.8, 114.6, 117.9, 118.0, 118.3, 118.5, 119.6, 124.0, 127.2, 128.1, 128.5, 128.8, 135.8, 144.9, 148.7, 148.9, 149.8, 153.0, 153.5.

1-Methyl-4-(3'-chloro-4',5'-dimethoxyphenyl)-5-(4''-N,N-dimethylaminophenyl)-imidazole (7d): Analogously to the synthesis of compound **7a**, compound **7d** was prepared from 4-*N*,*N*-dimethylaminobenzaldehyde (63 mg, 0.42 mmol), 33% $MeNH_2$/ethanol (260 μL, 2.10 mmol) and acetic acid (150 μL) in boiling ethanol (15 mL) giving the imine intermediate, which was treated with compound **6a** (153 mg, 0.42 mmol), dissolved in DME (10 mL), and K_2CO_3 (500 mg, 3.62 mmol). After workup, the residue was purified by column chromatography (silica gel 60). Yield: 140 mg (0.38 mmol, 91%); colorless oil; R_f = 0.67 (ethyl acetate/methanol 95:5); ν_{max} (ATR)/cm^{-1} 2935, 2825, 1612,

1552, 1516, 1485, 1397, 1357, 1316, 1261, 1228, 1187, 1165, 1108, 1047, 1000, 944, 881, 857, 818, 762, 721, 660; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.96 (6 H, s), 3.39 (3 H, s), 3.59 (3 H, s), 3.76 (3 H, s), 6.72 (2 H, d, J = 8.9 Hz), 7.00 (1 H, d, J = 1.9 Hz), 7.11 (2 H, d, J = 8.9 Hz), 7.16 (1 H, d, J = 1.9 Hz), 7.46 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.8, 40.2, 55.5, 60.5, 108.8, 112.3, 116.8, 119.2, 127.7, 129.7, 131.3, 131.6, 135.9, 136.7, 143.2, 150.5, 153.0; m/z (EI) 373 (36) [M^+], 371 (100) [M^+], 356 (42), 281 (10), 72 (19), 59 (34).

1-Methyl-4-(3'-chloro-4',5'-dimethoxyphenyl)-5-(4''-N,N-dimethylaminophenyl)-imidazole bis(hydrochloride) (7d x 2HCl): Compound **7d** (140 mg, 0.38 mmol) was dissolved in DCM (5 mL) and treated with 3M HCl/dioxane (1 mL). After stirring for 10 min the solvent was evaporated and the residue crystallized from ethanol/*n*-hexane. Yield: 77 mg (0.17 mmol, 46%); colorless solid of mp 189-193 °C (dec.); UV (MeOH) λ_{max} (ε) 265 (20800); ν_{max} (ATR)/cm^{-1} 3356, 3022, 2956, 2835, 2452, 1620, 1595, 1551, 1499, 1470, 1422, 1319, 1279, 1231, 1190, 1160, 1129, 1052, 1020, 989, 897, 859, 842, 756, 696; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.00 (6 H, s), 3.62 (3 H, s), 3.69 (3 H, s), 3.74 (3 H, s), 6.98 (2 H, d, J = 8.8 Hz), 7.07 (1 H, d, J = 2.1 Hz), 7.21 (1 H, d, J = 2.1 Hz), 7.33 (2 H, d, J = 8.8 Hz), 9.37 (1 H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 33.9, 40.2, 56.1, 60.4, 107.8, 113.2, 119.5, 123.8, 127.0, 127.2, 130.8, 131.6, 135.4, 144.9, 150.8, 153.5.

1-Methyl-4-(3'-bromo-4',5'-dimethoxyphenyl)-5-(4''-methoxy-3''-nitrophenyl)-imidazole (8a): A mixture of 4-methoxy-3-nitrobenzaldehyde (76 mg, 0.42 mmol) and 33% $MeNH_2$/ethanol (260 μL, 2.10 mmol) in ethanol (15 mL) was treated with AcOH (150 μL) and refluxed for 2 h. After cooling down to room temperature, compound **6b** (172 mg, 0.42 mmol) dissolved in DME (10 mL) and K_2CO_3 (500 mg, 3.62 mmol) was added and the reaction mixture was refluxed for 3 h. The solvent was evaporated, the residue diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (silica gel 60; elution with ethyl acetate to 5% methanol/ethyl acetate). Yield: 100 mg (0.22 mmol, 52%); yellow oil; R_f = 0.36 (ethyl acetate); ν_{max} (ATR)/cm^{-1} 2937, 2832, 1622, 1599, 1548, 1526, 1506, 1480, 1462,

1351, 1263, 1231, 1185, 1165, 1110, 1092, 1042, 998, 909, 889, 868, 824, 808, 760, 728; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (3 H, s), 3.64 (3 H, s)), 3.75 (3 H, s), 3.97 (3 H, s), 6.97 (1 H, s), 7.12 (1 H, s), 7.16 (1 H, d, J = 8.7 Hz), 7.46 (1 H, d, J = 8.7 Hz), 7.51 (1 H, s), 7.80 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 32.2, 55.7, 56.7, 60.4, 110.0, 114.2, 117.4, 122.2, 122.5, 126.1, 127.4, 131.2, 136.5, 137.5, 137.9, 139.7, 145.0, 152.9, 153.3; m/z (EI) 448 (100) [M^+], 446 (97) [M^+], 433 (37), 431 (41), 206 (27), 164 (23).

1-Methyl-5-(3''-amino-4''-methoxyphenyl)-4-(3'-bromo-4',5'-dimethoxyphenyl)-imidazole (8b): Analogously to **7b**, compound **8a** (100 mg, 0.22 mmol) was reduced by Zn powder (72 mg, 1.11 mmol) and conc. HCl (160 μL) in THF (8.5 mL). After workup the residue was purified by column chromatography (silica gel 60; ethyl acetate/methanol 95:5). Yield: 83 mg (0.20 mmol, 91%); colorless solid of mp 166-169 °C; R_f = 0.48 (ethyl acetate); UV (MeOH) λ_{max} (ε) 274 (12760); ν_{max} (ATR)/cm^{-1} 3458, 3365, 3192, 2935, 2833, 1616, 1597, 1546, 1510, 1483, 1462, 1420, 1372, 1318, 1279, 1245, 1223, 1174, 1109, 1040, 1024, 997, 868, 804, 759, 658; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.41 (3 H, s), 3.57 (3 H, s), 3.67 (3 H, s), 3.82 (3 H, s), 4.91 (2 H, s), 6.55 (1 H, d, J = 8.2 Hz), 6.61 (1 H, s), 6.94 (1 H, d, J = 8.2 Hz), 7.09 (1 H, s), 7.26 (1 H, s), 7.71 (1 H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 31.6, 55.4, 60.0, 109.4, 110.9, 115.3, 116.4, 118.2, 120.8, 122.2, 129.8, 132.7, 134.2, 138.3, 143.5, 146.7, 152.8; m/z (EI) 418 (100) [M^+], 416 (96) [M^+], 403 (78), 401 (85), 307 (17), 169 (22).

1-Methyl-5-(3''-amino-4''-methoxyphenyl)-4-(3'-bromo-4',5'-dimethoxyphenyl)-imidazole bis(hydrochloride) (8b x 2HCl): Compound **8b** (61 mg, 0.15 mmol) was dissolved in DCM and treated with 3M HCl/dioxane (1 mL). After stirring for 15 min at room temperature the solvent was removed and the residue recrystallized from an ethanol/*n*-hexane mixture. Yield: 72 mg (0.15 mmol, 100%); colorless solid of mp 198-200 °C; ν_{max} (ATR)/cm^{-1} 3011, 2801, 2567, 1633, 1549, 1515, 1494, 1446, 1405, 1305, 1272, 1145, 1113, 1041, 1022, 994, 867, 852, 829, 718; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.63 (3 H, s), 3.69 (3 H, s), 3.73 (3 H, s), 3.93 (3 H, s), 7.18 (1 H, d, J = 2.0 Hz), 7.22 (1

H, d, J = 2.0 Hz), 7.3-7.4 (3 H, m), 9.37 (1 H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 33.9, 56.1, 60.2, 111.3, 112.5, 117.0, 117.6, 122.4, 124.2, 127.5, 129.6, 135.8, 146.0, 151.6, 153.3.

1-Methyl-4-(3'-bromo-4',5'-dimethoxyphenyl)-5-(3''-fluoro-4''-methoxyphenyl)-imidazole (8c): Analogously to the synthesis of **7a**, compound **8c** was prepared from 3-fluoro-4-methoxybenzaldehyde (65 mg, 0.42 mmol), 33% $MeNH_2$/ethanol (260 μL, 2.10 mmol) and acetic acid (150 μL) in boiling ethanol (15 mL) giving the imine intermediate, which was treated with compound **6b** (172 mg, 0.42 mmol), dissolved in DME (10 mL), and K_2CO_3 (500 mg, 3.62 mmol). After workup, the residue was purified by column chromatography (silica gel 60; elution with ethyl acetate to 5% methanol/ethyl acetate). Yield: 135 mg (0.32 mmol, 76%); colorless gum; R_f = 0.67 (ethyl acetate); UV (MeOH) λ_{max} (ε) 275 (12280); ν_{max} (ATR)/cm^{-1} 2934, 2832, 1598, 1548, 1511, 1483, 1462, 1418, 1300, 1265, 1233, 1214, 1166, 1131, 1109, 1041, 1022, 997, 895, 865, 816, 807, 760, 656; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (3 H, s), 3.58 (3 H, m), 3.68 (3 H, s), 3.90 (3 H, s), 7.01 (1 H, s), 7.16 (1 H, s), 7.2-7.4 (3 H, m), 7.78 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.8, 55.4, 56.1, 60.1, 109.6, 114.3, 116.5, 117.9, 118.2, 121.1, 122.3, 122.4, 127.5, 127.6, 127.7, 132.3, 135.2, 138.1, 143.8, 147.5, 147.7, 149.8, 153.0, 153.1; m/z (EI) 421 (51) [M$^+$], 419 (49) [M$^+$], 406 (23), 404 (22), 233 (11), 175 (31), 117 (75), 59 (100).

1-Methyl-4-(3'-bromo-4',5'-dimethoxyphenyl)-5-(3''-fluoro-4''-methoxyphenyl)-imidazole hydrochloride (8c x HCl): Compound **8c** (135 mg, 0.32 mmol) was dissolved in DCM (5 mL) and treated with 3M HCl/dioxane (1 mL). After stirring for 15 min the solvent was removed and the oily residue was recrystallised from an DCM/*n*-hexane mixture giving the hydrochloride salt. Yield: 91 mg (0.20 mmol, 63%); colorless solid of mp 103-106 °C (dec.); UV (MeOH) λ_{max} (ε) 270 (11680); ν_{max} (ATR)/cm^{-1} 3413, 3012, 2936, 2841, 2626, 1625, 1547, 1523, 1493, 1463, 1421, 1304, 1271, 1234, 1203, 1134, 1116, 1041, 994, 869, 849, 818, 760; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.64 (3 H, s), 3.68 (3 H, s), 3.73 (3 H, s), 3.92 (3 H, s), 7.16 (1 H, d, J = 2.0 Hz), 7.19 (1 H, d, J = 2.0 Hz), 7.3-7.4 (1 H, m), 7.39 (1 H, t, J = 17.2 Hz), 7.51 (1 H, dd, J = 12.0 Hz, J = 2.0 Hz), 9.28 (1 H, s); ^{13}C NMR (75.5

MHz, $CDCl_3$) δ 34.3, 56.5, 56.7, 60.7, 111.9, 115.1, 117.4, 118.3, 118.4, 118.8, 119.0, 123.0, 125.1, 128.6, 128.8, 129.3, 136.3, 146.4, 149.2, 149.3, 150.2, 153.5, 153.8.

1-Methyl-4-(3'-bromo-4',5'-dimethoxyphenyl)-5-(4''-N,N-dimethylaminophenyl)-imidazole (8d): Analogously to the synthesis of **7a**, compound **8d** was prepared from 4-*N*,*N*-dimethylaminobenzaldehyde (63 mg, 0.42 mmol), 33% $MeNH_2$/ethanol (260 μL, 2.10 mmol) and acetic acid (150 μL) in boiling ethanol (15 mL) giving the imine intermediate, which was treated with compound **6b** (172 mg, 0.42 mmol), dissolved in DME (10 mL), and K_2CO_3 (500 mg, 3.62 mmol). After workup, the residue was purified by column chromatography (silica gel 60). Yield: 140 mg (0.34 mmol, 81%); colorless gum; R_f = 0.65 (ethyl acetate/methanol 95:5); ν_{max} (ATR)/cm^{-1} 2933, 2828, 1612, 1546, 1515, 1481, 1462, 1357, 1314, 1258, 1228, 1187, 1164, 1108, 1039, 999, 944, 873, 859, 821, 806, 758, 738, 717, 659; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.94 (6 H, s), 3.39 (3 H, s), 3.56 (3 H, s), 3.74 (3 H, s), 6.72 (2 H, d, *J* = 8.9 Hz), 7.00 (1 H, d, *J* = 1.9 Hz), 7.10 (2 H, d, *J* = 8.9 Hz), 7.35 (1 H, d, *J* = 1.9 Hz), 7.46 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.8, 40.2, 55.5, 60.3, 109.5, 112.3, 116.8, 117.2, 122.1, 129.7, 131.3, 132.3, 135.8, 136.7, 144.2, 150.5, 152.9; m/z (EI) 417 (54), 415 (68), 402 (28), 400 (26), 278 (54), 250 (58), 234 (63), 206 (83), 145 (84), 125 (87), 42 (100).

1-Methyl-4-(3'-bromo-4',5'-dimethoxyphenyl)-5-(4''-N,N-dimethylaminophenyl)-imidazole bis(hydrochloride) (8d x 2HCl): Compound **8d** (140 mg, 0.34 mmol) was dissolved in DCM and treated with 3M HCl/dioxane (1 mL). After stirring for 15 min at room temperature the solvent was removed and the residue recrystallized from an ethanol/*n*-hexane mixture. Yield: 68 mg (0.14 mmol, 41%); colorless solid of mp 189-193 °C (dec.); UV (MeOH) λ_{max} (ε) 265 (21220); ν_{max} (ATR)/cm^{-1} 3357, 2541, 2451, 1593, 1546, 1497, 1470, 1421, 1316, 1277, 1230, 1190, 1159, 1129, 1046, 987, 843; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.99 (6 H, s), 3.63 (3 H, s), 3.68 (3 H, s), 3.73 (3 H, s), 6.94 (2 H, d, *J* = 8.9 Hz), 7.21 (2 H, s), 7.32 (2 H, d, *J* = 8.9 Hz), 9.35 (1 H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 33.9, 56.1, 60.2, 111.3, 112.9, 116.9, 122.3, 124.4, 126.9, 130.8, 131.5, 135.3, 145.9, 150.9, 153.3.

4-(3',4'-dimethoxy-5'-nitrophenyl)-5-(4''-methoxy-3''-nitrophenyl)-oxazole (9a): Compound **6c** (170 mg, 0.45 mmol), 4-methoxy-3-nitrobenzaldehyde (82 mg 0.74 mmol) and anhydrous K_2CO_3 (590 mg, 4.3 mmol) were dissolved in DME/methanol (1:3, 20 mL) and stirred for 2 h. The solution was concentrated in vacuum, taken up in ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (silica gel 60). Yield: 140 mg (0.35 mmol, 78%); yellow solid of mp 155 °C; R_f = 0.30 (ethyl acetate/*n*-hexane 1:1); ν_{max} (ATR)/cm^{-1} 3147, 2945, 2846, 1625, 1564, 1522, 1482, 1456, 1441, 1342, 1278, 1267, 1256, 1184, 1162, 1126, 1111, 1058, 1005, 985, 849, 832; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (3 H, s), 3.96 (3 H, s), 3.97 (3 H, s), 7.13 (1 H, d, J = 8.9 Hz), 7.38 (1 H, d, J = 2.0 Hz), 7.54 (1 H, d, J = 2.0 Hz), 7.74 (1 H, dd, J = 8.9 Hz, J = 2.3 Hz), 7.93 (1 H, s), 8.07 (1 H, d, J = 2.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 56.4, 56.7, 62.0, 114.1, 114.8, 120.4, 124.0, 127.3, 132.2, 132.9, 139.7, 142.7, 144.0, 144.9, 150.1, 153.2, 154.3; m/z (EI) 401 (34) [M$^+$], 400 (100), 385 (12), 339 (7).

4-(3',4'-dimethoxy-5'-nitrophenyl)-5-(4''-N,N-dimethylaminophenyl)-oxazole (9b): Compound **6c** (170 mg, 0.45 mmol), 4-*N*,*N*-dimethylaminobenzaldehyde (67 mg 0.45 mmol) and anhydrous K_2CO_3 (590 mg, 4.3 mmol) were dissolved in DME/methanol (1:3, 20 mL) and stirred for 2 h. The solution was concentrated in vacuum, taken up in ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (silica gel 60). Yield: 70 mg (0.19 mmol, 42%); yellow oil; R_f = 0.30 (ethyl acetate/*n*-hexane 1:2); ν_{max} (ATR)/cm^{-1} 2941, 2886, 1611, 1532, 1518, 1445, 1352, 1264, 1230, 1190, 1167, 1104, 1053, 992, 944, 920, 870, 854, 818, 784, 771, 733, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99 (6 H, s), 3.84 (3 H, s), 3.97 (3 H, s), 6.69 (2 H, d, J = 9.1 Hz), 7.44 (2 H, d, J = 9.1 Hz), 7.48 (1 H, d, J = 2.0 Hz), 7.65 (1 H, d, J = 2.0 Hz), 7.86 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 40.1, 56.4, 62.0, 111.9, 114.5, 114.8, 115.0, 128.2, 128.8, 130.1, 141.8, 145.0, 147.8, 149.1, 150.9, 153.9; m/z (EI) 369 (100) [M$^+$], 308 (7), 132 (12).

1-Methyl-5-(3''-benzyloxy-4''-methoxyphenyl)-4-(3',4'-dimethoxy-5'-nitrophenyl)imidazole (9c): A mixture of 3-benzoxy-4-methoxybenzaldehyde (102 mg, 0.42 mmol) and 33% $MeNH_2$/ethanol (260 μL, 2.10 mmol) in ethanol (15 mL) was treated with AcOH (150 μL, 2.63 mmol) and refluxed for 2 h. After cooling down to room temperature, compound **6c** (158 mg, 0.42 mmol) dissolved in DME (5 mL) and K_2CO_3 (500 mg, 3.62 mmol) were added and the reaction mixture was refluxed for 3 h. The solvent was evaporated, the residue diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (silica gel 60). Yield: 130 mg (0.27 mmol, 64%); red oil; R_f = 0.58 (ethyl acetate/methanol 95:5); ν_{max} (ATR)/cm^{-1} 2939, 2837, 1529, 1509, 1454, 1358, 1248, 1169, 1136, 1110, 1060, 1021, 993, 919, 858, 814, 764, 729, 696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (3 H, s), 3.61 (3 H, s), 3.86 (3 H, s), 3.89 (3 H, s), 5.09 (2 H, s), 6.74 (1 H, d, J = 2.0 Hz), 6.85 (1 H, dd, J = 8.2 Hz, J = 1.9 Hz), 6.95 (1 H, d, J = 1.9 Hz), 7.1-7.3 (6 H, m), 7.36 (1 H, d, J = 2.0 Hz), 7.45 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.7, 55.8, 55.9, 61.7, 71.0, 112.1, 113.0, 113.4, 116.3, 121.6, 123.7, 127.0, 127.8, 128.4, 129.4, 130.9, 135.4, 136.4, 137.2, 140.5, 144.6, 148.2, 150.4, 153.3; m/z (EI) 475 (62), 458 (26), 384 (21), 337 (22), 91 (100), 65 (36).

1-Methyl-4-(3',4'-dimethoxy-5'-nitrophenyl)-5-(3''-fluoro-4''-methoxyphenyl)-imidazole (9d): A mixture of 3-fluoro-4-methoxybenzaldehyde (77 mg, 0.42 mmol) and 33% $MeNH_2$/ethanol (260 μL, 2.10 mmol) in ethanol (15 mL) was treated with AcOH (150 μL, 2.63 mmol) and refluxed for 2 h. After cooling down to room temperature, compound **6c** (158 mg, 0.42 mmol) dissolved in DME (5 mL) and K_2CO_3 (500 mg, 3.62 mmol) were added and the reaction mixture was refluxed for 3 h. The solvent was evaporated, the residue diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (silica gel 60). Yield: 120 mg (0.31 mmol, 74%); red oil; R_f = 0.45 (ethyl acetate/methanol 95:5); ν_{max} (ATR)/cm^{-1} 2941, 2841, 1530, 1511, 1462, 1357, 1300, 1267, 1238, 1131, 1110, 1021, 993, 920, 867, 855, 817, 761, 730, 657; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (3 H, s), 3.69 (3 H, s), 3.86 (3 H, s), 3.89 (3 H, s), 7.0-7.1 (3 H, m), 7.29 (1 H, d, J = 2.0 Hz), 7.30 (1 H, d, J = 2.0 Hz), 7.50 (1 H, s); ^{13}C NMR (75.5

MHz, $CDCl_3$) δ 32.0, 56.0, 56.1, 61.8, 113.2, 113.7, 113.9, 117.9, 118.2, 121.9, 122.0, 126.9, 128.2, 130.7, 135.9, 137.5, 140.7, 144.7, 148.3, 148.5, 150.7, 153.5, 154.0; m/z (EI) 387 (100) [M^+], 372 (34), 212 (20).

N-Methyl-3-chloroindol-5-carbaldehyde (9e'): *N*-Methylindol-5-carbaldehyde (400 mg, 2.5 mmol) was dissolved in dry acetonitrile (10 mL) and treated with *N*-chlorosuccinimide (400 mg, 3.02 mmol), whereupon the solution turned red. The reaction mixture was stirred at room temperature for 20 h. The solvent was removed in vacuum and the residue was purified by column chromatography (silica gel 60). Yield: 300 mg (1.55 mmol, 62%); colorless solid of mp 109 °C; R_f = 0.27 (ethyl acetate/*n*-hexane 1:4); ν_{max} (ATR)/cm^{-1} 3103, 2845, 2751, 1680, 1602, 1454, 1414, 1362, 1343, 1274, 1238, 1196, 1160, 1134, 1111, 981, 894, 796, 717; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (3 H, s), 7.07 (1 H, s), 7.32 (1 H, d, J = 8.6 Hz), 7.76 (1 H, dd, J = 8.6 Hz, J = 1.5 Hz), 8.07 (1 H, d, J = 1.5 Hz), 10.01 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 32.9, 106.3, 109.9, 122.0, 123.3, 125.2, 126.9, 129.2, 138.5, 191.7; m/z (EI) 193 (100) [M^+], 164 (57), 128 (43), 101 (48), 87 (28).

1-Methyl-4-(3',4'-dimethoxy-5'-nitrophenyl)-5-(N-methyl-3''-chloroindol-5''-yl)-imidazole (9e): A mixture of *N*-methyl-5-chloroindol-3-carbaldehyde (81 mg, 0.42 mmol) and 33% $MeNH_2$/ethanol (260 μL, 2.10 mmol) in ethanol (15 mL) was treated with AcOH (150 μL, 2.63 mmol) and refluxed for 2 h. After cooling down to room temperature, compound **6c** (170 mg, 0.43 mmol) and K_2CO_3 (500 mg, 3.62 mmol) were added and the reaction mixture was refluxed for 3 h. The solvent was evaporated, the residue diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (silica gel 60). Yield: 120 mg (0.28 mmol, 67%); red oil; R_f = 0.52 (ethyl acetate/methanol 95:5); ν_{max} (ATR)/cm^{-1} 3118, 2940, 2830, 1528, 1507, 1478, 1357, 1263, 1239, 1111, 1060, 993, 863, 804, 730; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (3 H, s), 3.57 (3 H, s), 3.76 (3 H, s), 3.84 (3 H, s), 7.07 (1 H, s), 7.14 (1 H, dd, J = 8.5 Hz, J = 1.6 Hz), 7.3-7.4 (3 H, m), 7.54 (1 H, s), 7.55 (1 H, d, J = 1.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$)

δ 32.0, 33.0, 55.9, 61.7, 104.6, 110.5, 113.0, 113.5, 120.4, 120.9, 124.8, 126.1, 126.5, 130.5, 131.2, 135.5, 135.8, 137.1, 140.4, 144.6, 153.3; m/z (EI) 428 (38) [M^+], 426 (100) [M^+], 411 (26).

4-(3'-Amino-4',5'-dimethoxyphenyl)-5-(3''-amino-4''-methoxyphenyl)-oxazole (10a): Compound **9a** (120 mg, 0.30 mmol) was suspended in methanol (20 mL) and treated with ammonium formate (590 mg, 9.37 mmol) and Pd/C (5%, 180 mg). The suspension was refluxed for 2 h and after cooling to room temperature the mixture was filtered over celite, the filtrate was concentrated in vacuum and the residue was purified by column chromatography (silica gel 60). Yield: 70 mg (0.21 mmol, 70%); light brown solid of mp 63 °C; R_f = 0.55 (ethyl acetate); UV (MeOH) λ_{max} (ε) 285 (7720); ν_{max} (ATR)/cm^{-1} 3457, 3361, 2935, 2834, 1613, 1587, 1515, 1428, 1378, 1222, 1175, 1137, 1105, 999, 843, 802, 760; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (3 H, s), 3.80 (3 H, s), 3.82 (3 H, s), 3.9-4.0 (4 H, broad s), 6.6-6.8 (3 H, m), 6.9-7.0 (2 H, m), 7.83 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.4, 55.6, 59.8, 102.1, 108.2, 110.1, 113.2, 117.6, 121.5, 128.1, 133.2, 135.6, 136.1, 140.4, 145.7, 147.6, 148.9, 152.7; m/z (EI) 343 (45), 341 (66) [M^+], 326 (46), 298 (22), 197 (63), 91 (100), 57 (75).

4-(3'-Amino-4',5'-dimethoxyphenyl)-5-(3''-amino-4''-methoxyphenyl)-oxazole bis(hydrochloride) (10a x 2HCl): Compound **10a** (60 mg, 0.18 mmol) was dissolved in DCM (5 mL) and treated with 3M HCl/dioxane (1 mL). The reaction mixture was stirred at room temperature for 15 min and the formed colorless precipitate was collected, washed with DCM and dried in vacuum. Yield: 28 mg (0.07 mmol, 39%); colorless solid of mp 227 °C; UV (MeOH) λ_{max} (ε) 292 (11960); ν_{max} (ATR)/cm^{-1} 2837, 2553, 1633, 1567, 1518, 1495, 1376, 1270, 1142, 1102, 1052, 996, 934, 869, 839, 817, 760, 722; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.74 (3 H, s), 3.85 (3 H, s), 3.92 (3 H, s), 7.10 (1 H, s), 7.19 (1 H, s), 7.25 (1 H, d, J = 8.7 Hz), 7.4-7.5 (1 H, m), 7.56 (1 H, d, J = 2.1 Hz), 8.52 (1 H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 55.9, 56.2, 60.7, 108.9, 112.6, 113.1, 120.2, 120.6, 124.8, 125.4, 127.5, 128.9, 132.4, 140.3, 144.3, 151.2, 151.6, 152.7; m/z (EI) 341 (100) [M^+ - 2HCl], 376 (72), 298 (25), 255 (12), 212 (7), 184 (7), 135 (8), 78 (11), 65 (6).

4-(3'-Amino-4',5'-dimethoxyphenyl)-5-(4''-N,N-dimethylaminophenyl)-oxazole (10b): Compound **9b** (100 mg, 0.27 mmol) was suspended in methanol (20 mL) and treated with ammonium formate (590 mg, 9.37 mmol) and Pd/C (5%, 180 mg). The suspension was refluxed for 2 h and after cooling to room temperature the mixture was filtered over celite, the filtrate was concentrated in vacuum and the residue was purified by column chromatography (silica gel 60). Yield: 60 mg (0.18 mmol, 67%); colorless oil; R_f = 0.77 (ethyl acetate/methanol 95:5); ν_{max} (ATR)/cm^{-1} 3427, 3295, 3189, 2927, 2820, 1617, 1583, 1523, 1512, 1445, 1426, 1382, 1363, 1327, 1278, 1227, 1190, 1146, 1105, 1057, 1005, 949, 842, 817; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.96 (6 H, s), 3.76 (3 H, s), 3.82 (3 H, s), 6.6-6.8 (4 H, m), 7.49 (2 H, d, J = 9.1 Hz), 7.82 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 40.1, 55.7, 59.9, 102.0, 108.0, 111.8, 116.4, 128.0, 128.5, 132.2, 135.5, 140.4, 146.3, 148.6, 150.4, 152.8; m/z (EI) 339 (82) [M$^+$], 324 (70), 296 (25), 253 (44), 159 (41), 148 (100), 133 (59), 119 (84), 78 (67), 42 (54).

4-(3'-Amino-4',5'-dimethoxyphenyl)-5-(4''-N,N-dimethylaminophenyl)-oxazole bis(hydrochloride) (10b x 2HCl): Compound **10b** (58 mg, 0.17 mmol) was dissolved in DCM (5 mL) and treated with 3M HCl/dioxane (1 mL). The reaction mixture was stirred at room temperature for 15 min, the solvent was removed and the formed colorless solid was recrystallized from DCM/*n*-hexane. Yield: 70 mg (0.17 mmol, 100%); yellow solid of mp 74 °C; UV (MeOH) λ_{max} (ε) 327 (18200), 259 (16360); ν_{max} (ATR)/cm^{-1} 3382, 2941, 2840, 2548, 1572, 1541, 1512, 1496, 1418, 1378, 1276, 1251, 1104, 1062, 991, 935, 870, 850; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.99 (6 H, s), 3.74 (3 H, s), 3.87 (3 H, s), 6.9-7.1 (2 H, m), 7.22 (1 H, d, J = 1.9 Hz), 7.28 (1 H, d, J = 1.9 Hz), 7.49 (2 H, d, J = 8.9 Hz), 8.46 (1 H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 40.7, 55.9, 61.0, 110.4, 113.8, 113.9, 126.7, 128.0, 128.2, 130.9, 141.0, 145.9, 149.4, 150.7, 152.6; m/z (EI) 339 (82) [M$^+$ - 2HCl], 324 (70), 296 (25), 253 (44), 159 (41), 148 (100), 133 (59), 119 (84), 78 (67), 42 (54).

1-Methyl-4-(3'-amino-4',5'-dimethoxyphenyl)-5-(3''-hydroxy-4-methoxyphenyl)-imidazole bis(hydrochloride) (10c x 2HCl): Compound **9c** (120 mg, 0.31 mmol) was dissolved in methanol (20 mL) and treated with ammonium formate (590 mg, 9.37 mmol) and Pd/C (5%, 180 mg). The

suspension was refluxed for 2 h and after cooling to room temperature the mixture was filtered over celite, the filtrate was concentrated in vacuum and the residue was purified by column chromatography giving **10c** (silica gel 60, ethyl acetate/methanol 95:5, R_f = 0.25). Compound **10c** was dissolved in DCM (5 mL) and treated with 3M HCl/dioxane (1 mL). The reaction mixture was stirred at room temperature for 15 min. The solvent was removed and the residue freed from dioxane by repeated azeotropic distillation with DCM. The remaining solid was recrystallized from ethanol/*n*-hexane. Yield: 70 mg (0.16 mmol, 53%); colorless solid of mp 218 °C (dec.); UV (MeOH) λ_{max} (ε) 275 (11300); ν_{max} (ATR)/cm^{-1} 3032, 2967, 2522, 1620, 1590, 1534, 1508, 1432, 1328, 1292, 1251, 1211, 1135, 1109, 1051, 1026, 992, 855, 813, 766; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 3.61 (3 H, s), 3.73 (3 H, s), 3.77 (3 H, s), 3.83 (3 H, s), 6.75 (1 H, d, ^4J 1.7 Hz), 6.8-7.0 (3 H, m), 7.09 (1 H, d, ^3J 8.5 Hz), 9.33 (1 H, s); ^{13}C NMR (75.5 MHz, DMSO-d$_6$): δ 33.9, 55.6, 55.9, 60.3, 109.5, 112.7, 117.5, 122.1, 122.8, 128.2, 129.9, 135.2, 147.1, 149.3, 152.6; m/z (EI) 356 (33), 355 (85) [M$^+$ - 2HCl], 341 (42), 340 (100).

1-Methyl-4-(3'-amino-4',5'-dimethoxyphenyl)-5-(3''-fluoro-4-methoxyphenyl)-imidazole (10d): Compound **9d** (120 mg, 0.31 mmol) was dissolved in methanol (20 mL) and treated with ammonium formate (590 mg, 9.37 mmol) and Pd/C (5%, 180 mg). The suspension was refluxed for 2 h and after cooling to room temperature the mixture was filtered over celite, the filtrate was concentrated in vacuum and the residue was purified by column chromatography (silica gel 60). Yield: 80 mg (0.25 mmol, 81%); colorless gum; R_f = 0.33 (ethyl acetate/methanol 95:5); ν_{max} (ATR)/cm^{-1} 3448, 3364, 2940, 2835, 1610, 1561, 1517, 1500, 1463, 1442, 1394, 1301, 1268, 1237, 1208, 1132, 1107, 1049, 1024, 1002, 892, 877, 848, 817, 761, 658; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.38 (3 H, s), 3.5-3.6 (2 H, broad s), 3.59 (3 H, s), 3.72 (3 H, s), 3.87 (3 H, s), 6.47 (1 H, d, J = 1.9 Hz), 6.48 (1 H, d, J = 1.9 Hz), 6.9-7.1 (3 H, m), 7.45 (1 H, s); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 31.9, 55.2, 56.1, 59.7, 100.1, 106.9, 113.5, 118.2, 118.4, 123.1, 123.2, 126.9, 127.0, 127.1, 130.3, 134.6, 137.0, 138.1, 140.0, 147.7, 147.9, 150.5, 152.4, 153.7; m/z (EI) 358 (57), 357 (93) [M$^+$], 343 (75), 342 (100), 282 (47), 243 (51), 229 (50), 200 (42), 158 (34), 42 (72).

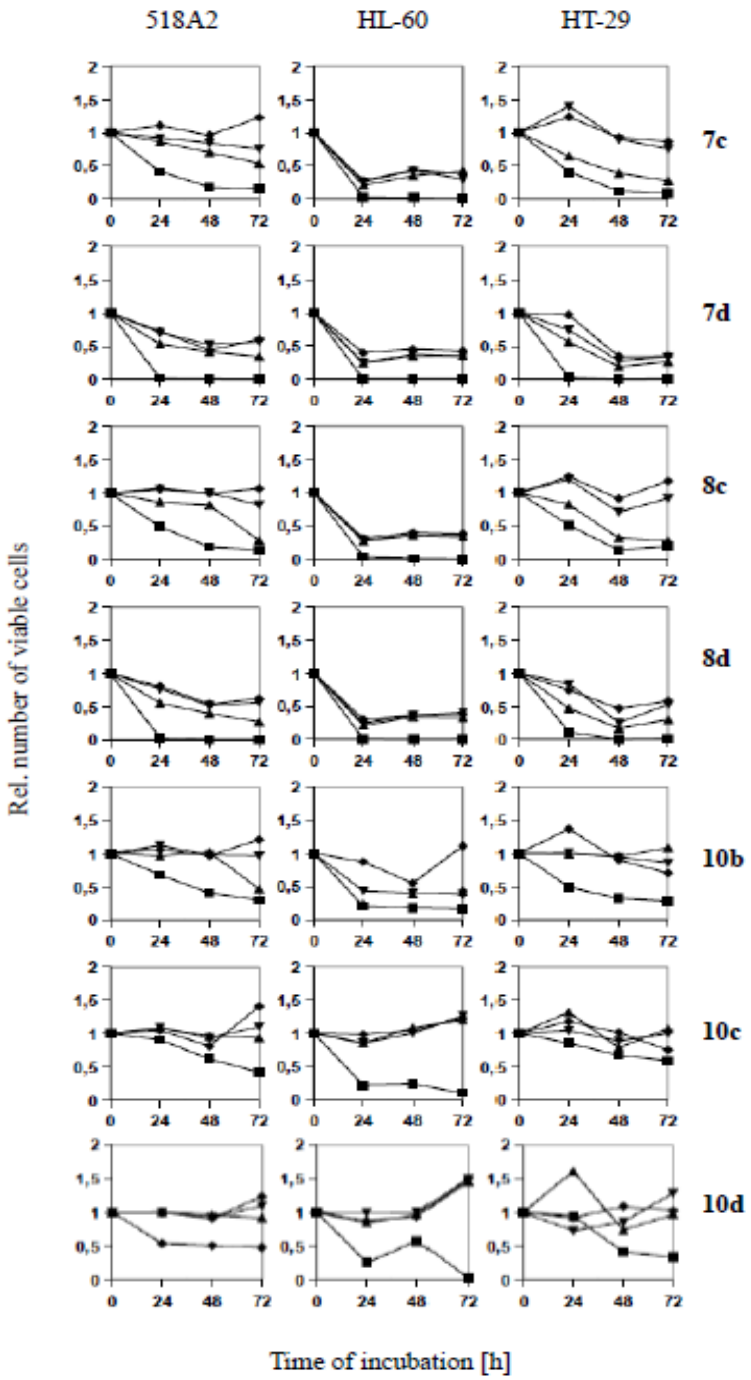
1-Methyl-4-(3'-amino-4',5'-dimethoxyphenyl)-5-(3''-fluoro-4-methoxyphenyl)-imidazole bis(hydrochloride) (10d x 2HCl): Compound **10d** (80 mg, 0.25 mmol) was dissolved in DCM (5 mL) and treated with 3M HCl/dioxane (1 mL). The reaction mixture was stirred at room temperature for 15 min. The solvent was removed and the residue freed from dioxane by repeated azeotropic distillation with DCM. The remaining solid was recrystallized from ethanol/*n*-hexane. Yield: 90 mg (0.21 mmol, 84%); colorless solid of mp 214-217 °C; UV (MeOH) λ_{max} (ε) 270 (11100); ν_{max} (ATR)/cm^{-1} 2969, 2323, 1625, 1555, 1526, 1494, 1473, 1422, 1341, 1305, 1278, 1242, 1178, 1131, 1112, 1061, 1025, 974, 858, 825, 763; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 3.63 (3 H, s), 3.77 (3 H, s), 3.78 (3 H, s), 3.92 (3 H, s), 6.66 (1 H, s), 7.05 (1 H, s), 7.2- 7.3 (1 H, m), 7.35 (1 H, t, J = 17.3 Hz), 7.47 (1 H, d, J = 12.0 Hz), 9.37 (1 H, s); ^{13}C NMR (75.5 MHz, DMSO-d$_6$) δ 34.0, 55.0, 56.2, 60.3, 111.4, 114.7, 117.6, 117.7, 118.2, 118.5, 122.6, 128.1, 128.5, 129.0, 135.4, 140.0, 148.7, 148.8, 149.8, 152.6, 153.0; m/z (EI) 358 (63), 357 (96) [M$^+$ - 2HCl], 343 (79), 342 (100), 284 (37).

1-Methyl-4-(3'-amino-4',5'-dimethoxyphenyl)-5-(N-methyl-3''-chloroindol-5''-yl)-imidazole (10e): Compound **9e** (120 mg, 0.28 mmol) was dissolved in THF (7.5 mL) and reduced by adding Zn powder (90 mg, 1.39 mmol) and conc. HCl (200 μL) in THF (1 mL). After workup the residue was purified by column chromatography (silica gel 60). Yield: 70 mg (0.18 mmol, 64%); colorless oil; R_f = 0.44 (ethyl acetate/methanol 95:5); ν_{max} (ATR)/cm^{-1} 3359, 3113, 2934, 2825, 1613, 1593, 1511, 1480, 1447, 1423, 1396, 1336, 1239, 1224, 1139, 1109, 1000, 974, 907, 864, 803, 726; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.39 (3 H, s), 3.52 (3 H, s), 3.70 (3 H, s), 3.74 (3 H, s), 6.50 (1 H, d, J = 1.9 Hz), 6.58 (1 H, d, J = 1.9 Hz), 7.05 (1 H, s), 7.16 (1 H, dd, J = 8.5 Hz, J = 1.6 Hz), 7.32 (1 H, d, J = 8.5 Hz), 7.50 (1 H, s), 7.58 (1 H, d, J = 1.6 Hz); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 32.0, 33.0, 55.3, 59.7, 101.0, 104.6, 106.8, 110.1, 120.6, 122.1, 125.5, 125.9, 126.1, 129.1, 130.8, 134.5, 135.6, 136.6, 137.6, 139.8, 152.4; m/z (EI) 398 (19) [M$^+$], 396 (56) [M$^+$], 383 (37), 381 (100), 321 (11), 282 (12), 42 (23).

1-Methyl-4-(3'-amino-4',5'-dimethoxyphenyl)-5-(N-methyl-3''-chloroindol-5''-yl)-imidazole tris(hydrochloride) (10e x 2HCl): Compound **10e** (70 mg, 0.18 mmol) was dissolved in DCM (5 mL)

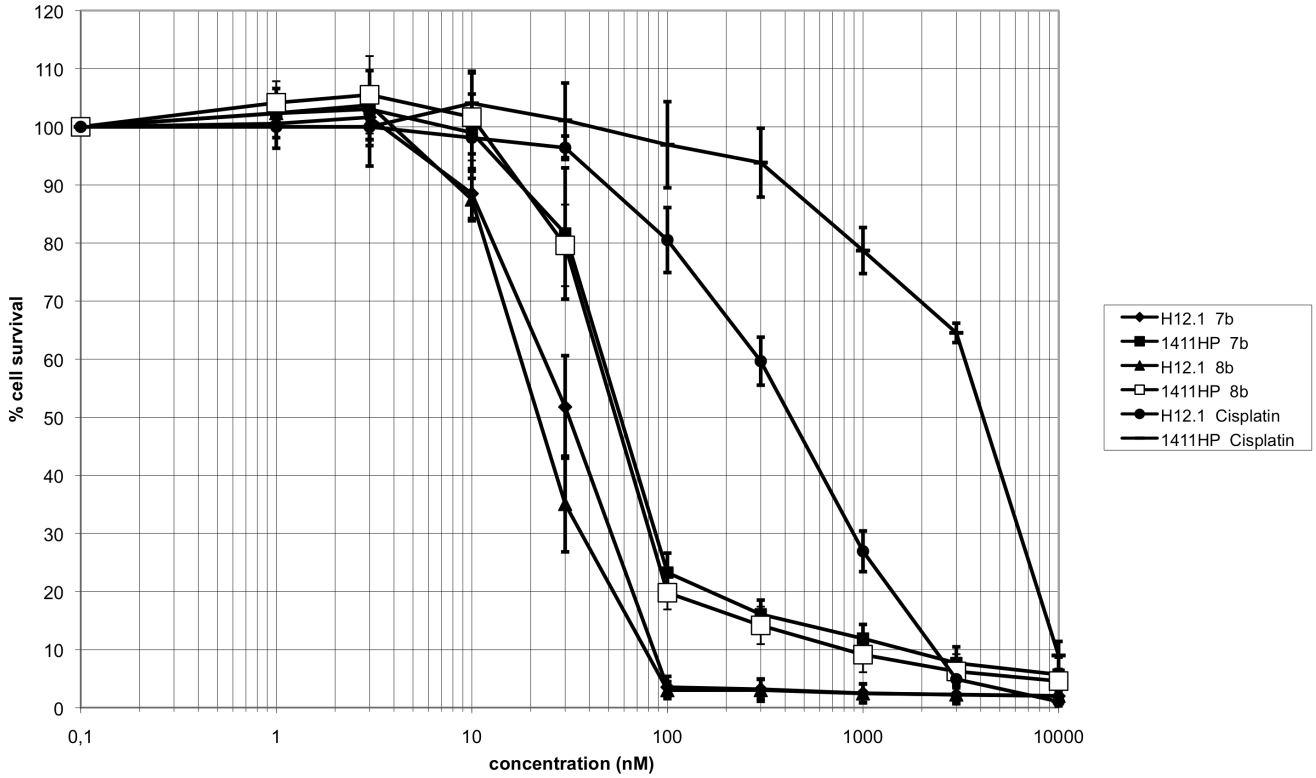
and treated with 3M HCl/dioxane (1 mL). The reaction mixture was stirred at room temperature for 15 min. The solvent was removed and the residue freed from dioxane by repeated azeotropic distillation with DCM. The remaining solid was recrystallized from ethanol/*n*-hexane. Yield: 62 mg (0.12 mmol, 68%); brown solid of mp >300 °C (dec.); UV (MeOH) λ_{max} (ε) 224 (30100); ν_{max} (ATR)/cm^{-1} 3356, 2830, 2570, 1623, 1554, 1498, 1456, 1423, 1408, 1332, 1284, 1272, 1237, 1145, 1112, 1064, 991, 973, 857, 804; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.61 (3 H, s), 3.63 (3 H, s), 3.73 (3 H, s), 3.89 (3 H, s), 6.52 (1 H, s), 6.79 (1 H, s), 7.30 (1 H, dd, J = 8.5 Hz, J = 1.6 Hz), 7.6-7.8 (3 H, m), 9.35 (1 H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 33.0, 34.0, 55.7, 60.0, 102.7, 111.7, 117.0, 120.3, 122.8, 124.6, 125.1, 128.0, 128.9, 130.4, 135.1, 136.0, 152.5; m/z (EI) 396 (42) [M^{+}- 2HCl], 383 (45), 381 (78), 331 (21), 160 (100), 57 (59), 41 (65).

MTT-tests of compounds 7c, 7d, 8c, 8d, 10b-d against 518A2, HL-60 and HT-29 cells



Cell growth inhibiting effects of compounds **7c**, **7d**, **8c**, **8d**, **10b**, **10c** and **10d** at various concentrations (■: 100 µM; ▲: 1 µM; ▼: 0.01 µM; ♦: 0.001 µM) in cells of human 518A2 melanoma, HL-60 leukemia and HT-29 colon adenocarcinoma upon incubation for 24–72 h (x-axis). Y-axis shows number of viable cells relative to untreated controls (1) as ascertained by the MTT assay.

SRB-tests of cisplatin, 7b and 8b against H12.1 and 1411HP tumor cells



TUNEL assays with HL-60 cells treated with 7b, 8b or 10a

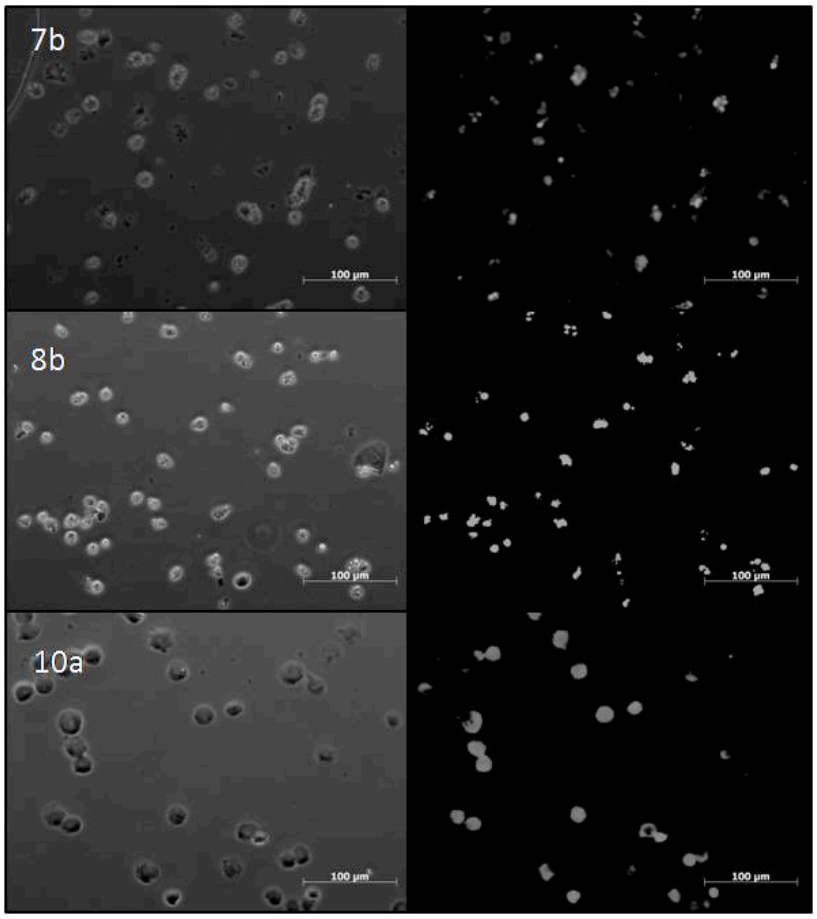


Figure. Microscopic images of HL-60 cells tested in TUNEL assays after 16 h incubation with 10 μM **7b**, **8b** or **10a**. The brightfield pictures (left) show all the cells in the focus, the pictures of the green fluorescent channel (right) just the apoptotic cells, represented as bright dots.

A modification of the TdT-mediated dUTP Nick-End Labelling (TUNEL; Roche) assay described by Jobmann was used. HL-60 cells were incubated with the test compounds for 16 h, aliquots of 3 x 10^6 cells were withdrawn and washed/centrifuged 3 times in 200 μL PBS. The cells were fixed for 10 min at room temperature by suspending in 200 μL of a freshly prepared solution of 2% formalin in PBS. After washing with 2 x 200 μL PBS, 10 μL of the cell suspension was applied onto a microscope slide and air-dried at room temperature. The cells were washed by covering with PBS for 5 min and treated for 2 min with a solution of 0.1% Triton X-100 in 0.1% sodium citrate on ice. After washing two times with PBS, 10 μL of the freshly prepared TUNEL reaction mixture, consisting of 1 μL TUNEL-Enzyme solution and 9 μL TUNEL-Label solution, was dropped on the cells which were then covered and incubated (5% CO_2, 95% humidity) in the dark at 37 °C for 45 min. The cells were washed three times with PBS and then analysed by fluorescence microscopy at an excitation wavelength of 450–500 nm. The percentage of apoptotic, TUNEL-positive, green-stained cells was counted and calculated for 300 cells and expressed as mean ± S.D. of three independent experiments.

Jobmann, M. Apoptose bei strukturellen Herzmuskelerkrankungen. Ph.D. Thesis, University Marburg, Germany **2002**, 31.

Table 1. ROS generation: % NBT reduction[a] in 518A2 and HL-60 cells upon exposure to selected compounds for 24 h.

	NBT Reduction [%][a] in 518A2 cells after 24 h	NBT Reduction [%][a] in HL-60 cells after 24 h
1	2.2 ± 0.4	1.5 ± 0.1
7b	1.8 ± 0.2	4.4 ± 0.6
7c	1.6 ± 0.1	4.8 ± 0.5
7d	2.4 ± 0.4	6.0 ± 0.9
8b	1.5 ± 0.2	3.8 ± 0.3
8c	1.4 ± 0.3	3.9 ± 0.1
8d	1.6 ± 0.3	6.7 ± 0.8
10a	1.5 ± 0.1	3.5 ± 0.4
10b	1.4 ± 0.3	3.3 ± 0.2
10c	1.1 ± 0.0	1.8 ± 0.3
10d	1.2 ± 0.1	1.4 ± 0.2
10e	1.6 ± 0.3	6.4 ± 0.3

[a] ROS generation (NBT reduction) as determined from percent absorbance of formazan relative to untreated controls (1%) after 24 h exposure of 518A2 and HL-60 cells to 50 μM of the test compounds. Values represent means of four independent experiments ± standard deviation.

Generation of ROS (NBT assay). HL-60 cells (0.5×10^6/mL) were plated in 96-well tissue culture plates, and test compounds were added after 24 h incubation at 37 °C to achieve a final concentration of 50 μM. Incubation (5% CO_2, 95% humidity, 37 °C) of cells following treatment with the test compounds was continued for 24 h. After removal of the cell medium by centrifugation, the cells in each well were resuspended in 100 μL 0.1% NBT, and the plates were placed in the incubator for 1 h. The reduced NBT was solubilized with 100 μl 2M KOH and 130 μl DMSO for 30 min. The absorbance was measured for each well at 630 and 405 nm (background) using an ELISA plate reader. The adherent 518A2 cells ($0.5\cdot10^4$/mL) were seeded out in 96-well tissue culture plates after trypsinization and incubation for 24 h at 37 °C to allow attachment, then treated similarly, only that the medium was removed prior to incubation with NBT for 4 h. All experiments were carried out in quadruplicate.

Das, U. N.; Begin, M. E.; Ells, G.; Huang, Y. S.; Hossobin, D. F. Polyunsaturated fatty acids augment free radical generation in tumor cells in vitro. *Biochem. Biophys. Res. Commun.* **1987**, *145*, 15-24.

Rook, G. A. W.; Steele, J.; Umar, S.; Dockrell, H. M. A Simple Method for the solubilisation of reduced NBT, and its use as a colorimetric assay for activation of human macrophages by γ-interferon. *J. Immunol. Methods* **1985**, *82*, 161-167.

Table 2. Percentage of intact mitochondria[a] upon treatment of 518A2 and HL-60 cells with 5 μM of selected compounds.

	Intact mitochondria [%][a] in 518A2 cells after 72 h	**Intact mitochondria [%][a] in HL-60 cells after 72 h**
1	87 ± 7	74 ± 13
7b	80 ± 9	65 ± 9
7c	84 ± 6	55 ± 7
7d	80 ± 7	61 ± 13
8b	80 ± 9	66 ± 10
8c	89 ± 10	60 ± 15
8d	82 ± 7	63 ± 13
10a	85 ± 7	62 ± 9
10b	82 ± 8	62 ± 12
10c	94 ± 7	76 ± 19
10d	98 ± 15	90 ± 22
10e	77 ± 8	60 ± 15

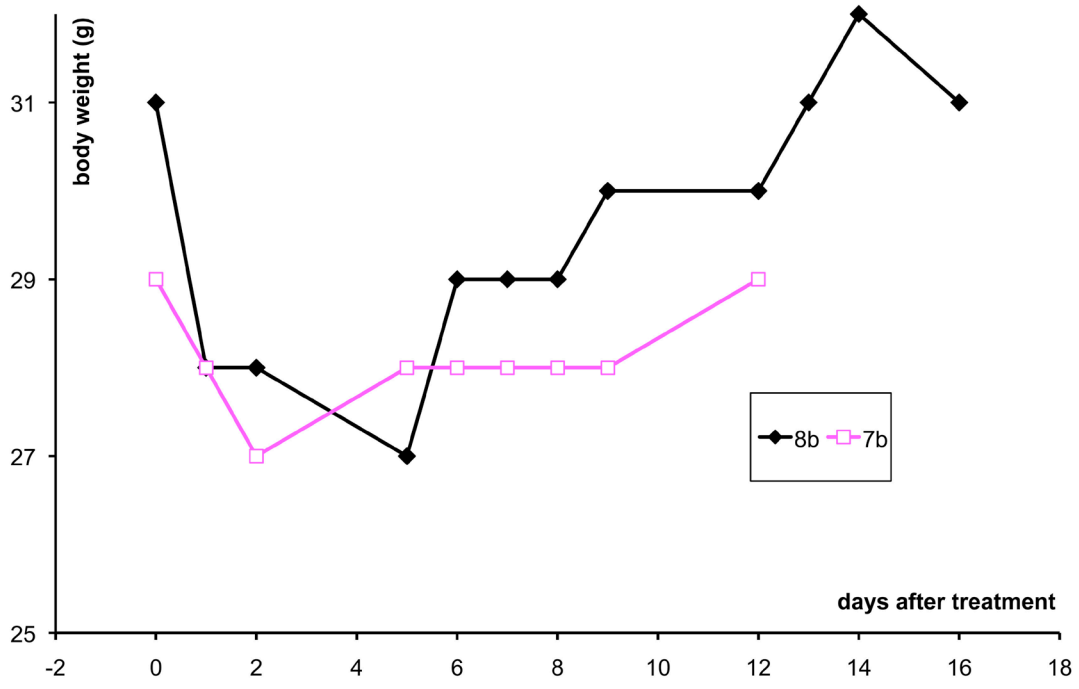
[a] Ratio of red to green fluorescence relative to untreated controls (100%) after 72 h exposure of 518A2 and HL-60 cells to 5 μM of the test compounds. Determined with the Mitochondrial Membrane Detection Kit (Stratagene, La Jolla, CA, USA). Values represent means of four independent experiments ± standard deviation.

Mitochondrial membrane potential. Changes in mitochondrial membrane potential were determined by the Mitochondrial Membrane Detection Kit (Stratagene, La Jolla, CA, USA) according to the manufacturer's procedure. 72 h following treatment with 5 µM of the test compounds, cell samples were centrifuged at 400 g for 5 min. The pellets were resuspended in 500 µL diluted JC-1 solution (0.1·), incubated at 37 °C for 15 min (HL-60) or 35 min (518A2) and then centrifuged again for 5 min at 400 g. After washing, the pellets were resuspended in 100 µL PBS and transferred into the wells of a black 96-well plate. The red (λ_{ex} = 585 nm, λ_{em} = 590 nm) and green (λ_{ex} = 510 nm, λ_{em} = 527 nm) fluorescence intensities were measured and their ratio was calculated.

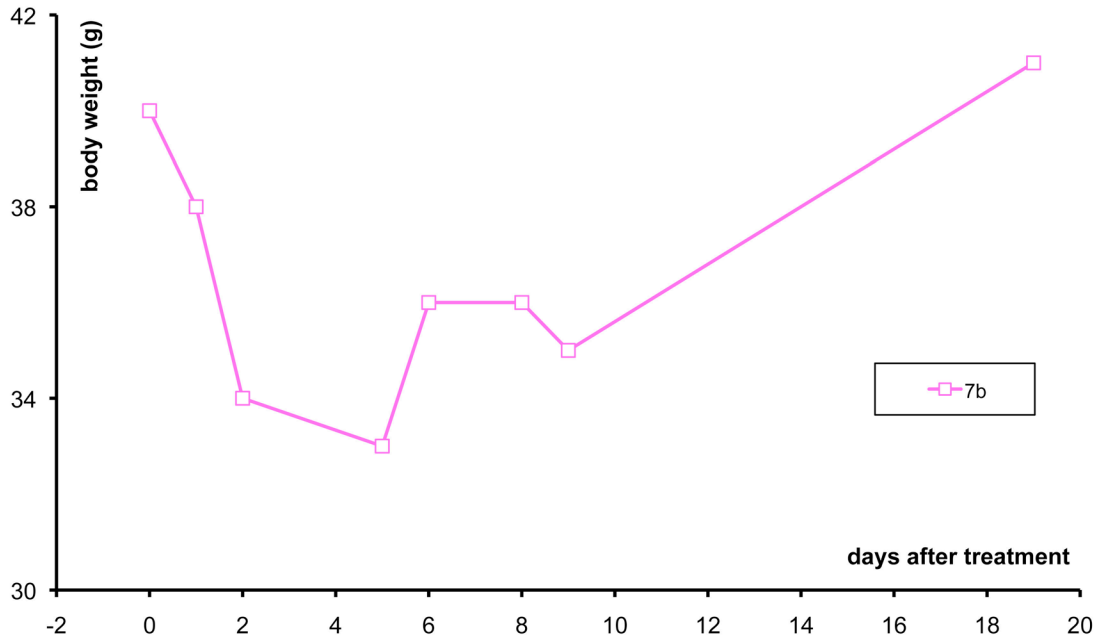
Desager, S.; Osen-Sand, A.; Nicholas, A.; Eskes, R.; Montessuit, S. Bid-induced conformational change of Bax is responsible for mitochondrial cytochrome c release. *J. Cell. Biol.* **1999**, *144*, 891-901.

In vivo body weight – time curves

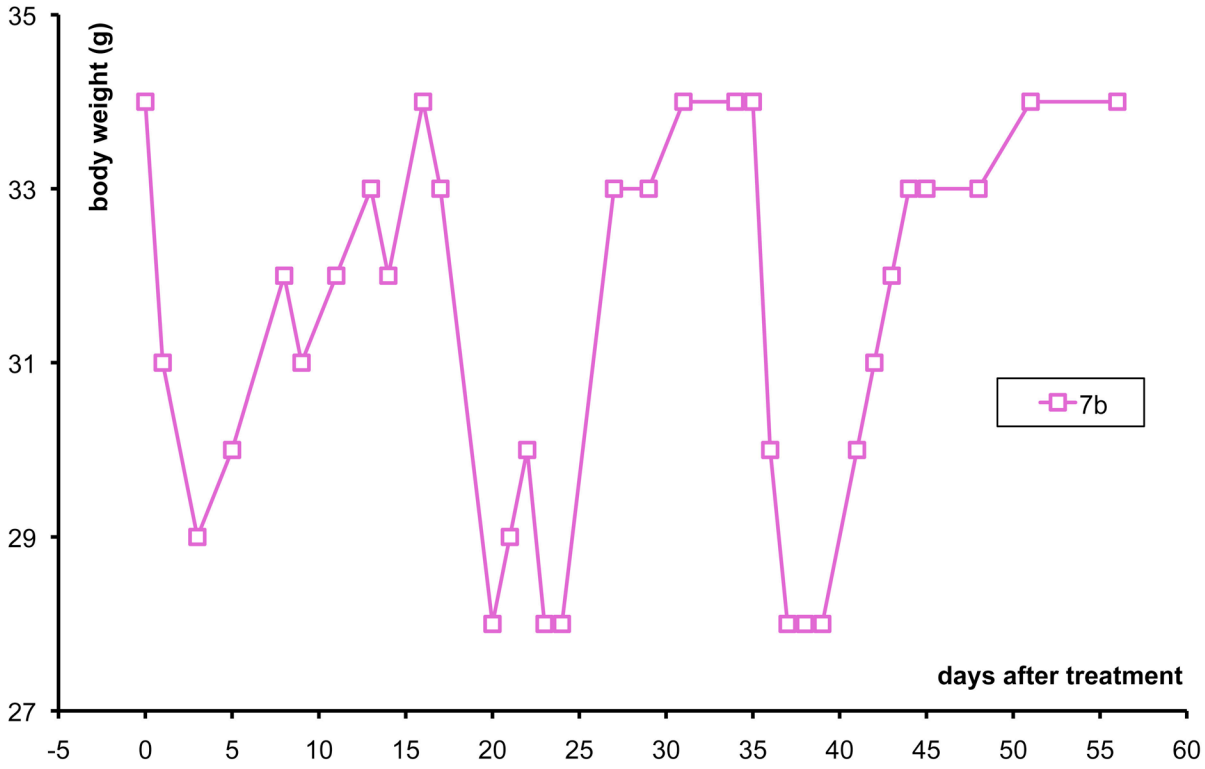
A single dose (30 mg/kg body weight) was administered at day 0:



A double dose (each 20 mg/kg body weight) was administered at consecutive days 0 and 1:



Three double doses (each 20 mg/kg body weight) were administered at days 0/1, 16/17, 35/36:



Maximal slopes of tubulin polymerization curves (Fig. 3)