Supplementary information

Synthesis of carboxyimidamide-substituted benzo[*c*][1,2,5]oxadiazoles and their analogs, and evaluation of biological activity against *Leishmania donovani*

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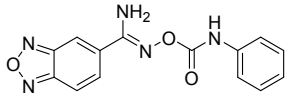
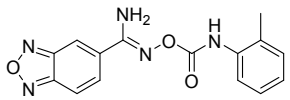
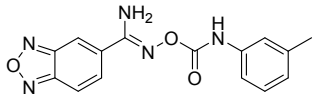
General procedure for the reaction of oximes with isocyanates. *Method A:* A mixture of **5** (89.0 mg, 0.500 mmol) and isocyanate (0.550 mmol, 1.1 equiv) in anhydrous THF (5 mL) was stirred under an Ar atmosphere at rt for 3-21 h. The solvent was evaporated. *Method B:* A mixture of an appropriate oxime (1.0 mmol) and isocyanate (1.2-1.5 mmol, 1.2-1.5 equiv) in 1,4-dioxane (5 mL) was stirred under an Ar atmosphere at rt for 2-5 h. The resulting mixture was quenched with water, filtered, washed with water and dried.



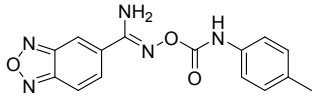
***N*'-[(Phenylcarbamoyl)oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (6).** A mixture of **5** (0.15 g, 0.84 mmol) and phenyl isocyanate (0.14 mL, 1.26 mmol, 1.5 equiv) in $CHCl_3$ was stirred at rt for 4 days. After evaporation the crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:1) and recrystallized from EtOAc/*n*-hexane to yield **6** (0.14 g, 56%) as a white powder. Mp: 184-185 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.57-8.56 (m, 1H), 8.17-8.08 (m, 2H), 7.57-7.54 (m, 2H), 7.37-7.31 (m, 2H), 7.10-7.05 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.2, 152.2, 148.9, 148.8, 138.3, 135.0, 131.3, 128.7 (2C), 123.2, 119.5 (2C), 116.0, 114.4. LC-MS: $[M+H]^+$ 298.2 *m/z* (t_r = 6.1 min). FT-IR (ATR, cm^{-1}): 3350, 1713, 1644, 1506, 1202. HRMS (ESI): *m/z* calcd for $C_{14}H_{12}N_5O_3$ $[M+Na]^+$ 320.0760, found 320.0762.



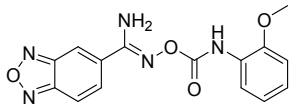
***N*'-[(*o*-Tolylcarbamoyl)oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (7).** Method A. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1) and recrystallized from EtOAc/*n*-hexane to give **7** (85 mg, 55%) as light yellow crystals. Mp: 190 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.59 (t, J = 1.2 Hz, 1H), 8.20 (dd, J = 9.5, 1.4 Hz, 1H), 8.10 (dd, J = 9.5, 0.9 Hz, 1H), 7.55-7.52 (m, 1H), 7.27-7.19 (m, 4H), 7.11 (td, J = 7.4, 1.3 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.7, 152.5, 148.9, 148.8, 136.0, 135.0, 131.3, 130.3, 126.2, 125.0, 124.0, 116.0, 114.4, 17.5. LC-MS: $[M+H]^+$ 312.2 *m/z* (t_r = 6.5 min). FT-IR (ATR, cm^{-1}): 3461, 3348, 1726, 1513. HRMS (ESI): *m/z* calcd for $C_{15}H_{13}N_5O_3$ $[M+H]^+$ 312.1097, found 312.1099.



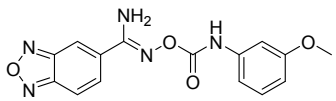
***N*'-[(*m*-Tolylcarbamoyl)oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (8).** Method A. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1) to yield **8** (0.11 g, 70%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.37 (br s, 1H), 8.57 (t, J = 1.2 Hz, 1H), 8.17 (dd, J = 9.5, 1.2 Hz, 1H), 8.11 (dd, J = 9.5, 1.2 Hz, 1H), 7.37-7.35 (m, 2H), 7.22 (t, J = 5.6 Hz, 1H), 7.14 (br s, 2H), 6.90 (d, J = 5.6 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.1, 152.1, 148.9, 148.8, 138.2, 137.9, 135.0, 131.4, 128.5, 123.9, 120.0, 116.7, 115.9, 114.4, 21.1. LC-MS: $[M+H]^+$ 312.2 *m/z* (t_r = 6.6 min). FT-IR (ATR, cm^{-1}): 3478, 3438, 3351, 3288, 1712, 1518, 1204. HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_5O_3$ $[M+H]^+$ 312.1096, found 312.1100.



***N*'-[(*p*-Tolylcarbamoyl)oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (9).** Method A. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 4:1) and recrystallized from EtOAc/*n*-hexane to yield **9** (77 mg, 49%) as yellow crystals. Mp: 188-189 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.36 (br s, 1H), 8.57 (t, J = 1.2 Hz, 1H), 8.17 (dd, J = 9.5, 1.2 Hz, 1H), 8.11 (dd, J = 9.5, 1.2 Hz, 1H), 7.46-7.41 (m, 2H), 7.16-7.13 (m, 4H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 53.0, 152.2, 148.9, 148.8, 135.7, 135.0, 132.1, 131.4, 129.1, 119.6, 115.9, 114.4, 20.3. LC-MS: $[M+H]^+$ 312.2 *m/z* (t_r = 6.6 min). FT-IR (ATR, cm^{-1}): 3468, 3342, 1724, 1517, 1181, 1006, 920. HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_5O_3$ $[M+H]^+$ 312.1096, found 312.1099.

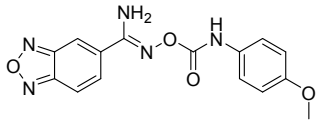


***N*'-[[(2-Methoxyphenyl)carbamoyl]oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (10).** Method A. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 4:1) and recrystallized from MeCN/H_2O to yield **10** (57 mg, 36%) as a light yellow solid. Mp: 203 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.54 (m, 1H), 8.20-8.16 (m, 1H), 8.03-7.99 (m, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.36 (s, 2H), 7.09-7.07 (m, 2H), 7.01-6.92 (m, 1H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.7, 151.7, 148.9, 148.8, 148.7, 134.8, 130.7, 126.7, 123.7, 120.6, 118.9, 116.4, 114.6, 111.1, 56.0. LC-MS: $[M+H]^+$ 328.2 *m/z* (t_r = 6.7 min). FT-IR (ATR, cm^{-1}): 3434, 3334, 1730, 1536. HRMS (ESI): *m/z* calcd for $C_{15}H_{13}N_5O_4$ $[M+H]^+$ 328.1046, found 328.1048.

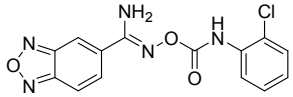


***N*'-[[(3-Methoxyphenyl)carbamoyl]oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (11).** Method A. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1) and recrystallized from EtOAc/*n*-hexane to give **11** (62 mg, 38%) as white crystals. Mp: 186-187 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.56 (t, J = 1.3 Hz, 1H), 8.15 (dd, J = 9.8, 1.3 Hz, 1H), 8.11 (dd, J = 9.8, 1.3 Hz, 1H), 7.27-7.20 (m, 2H), 7.14-7.13 (m, 1H), 7.12 (s, 2H), 6.65 (ddd, J = 8.1, 2.5, 0.8 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.6, 153.3, 152.0, 148.9, 148.8, 139.5, 135.0, 131.3, 129.5, 116.0, 114.4, 111.6, 108.5, 105.2, 55.0. LC-MS: $[M+H]^+$ 328.1 *m/z* (t_r = 6.1 min). FT-

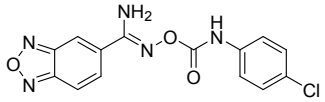
IR (ATR, cm^{-1}): 3470, 3362, 3063, 1733, 1500, 1179, 1041. HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_5O_4$ $[M+H]^+$ 328.1046, found 328.1045.



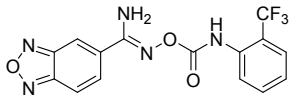
***N*'-[[(4-Methoxyphenyl)carbamoyl]oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (12).** Method A. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 2:3) and recrystallized from MeCN to yield **12** (70 mg, 43%) as yellow crystals. Mp: 196-197 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.30 (br s, 1H), 8.57 (t, J = 1.2 Hz, 1H), 8.19 (dd, J = 9.6, 1.2 Hz, 1H), 8.11 (dd, J = 9.6, 1.2 Hz, 1H), 7.47-7.42 (m, 2H), 7.13 (br s, 2H), 6.95-6.89 (m, 2H), 3.74 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.4, 152.8, 152.6, 148.9, 135.0, 131.5, 131.2, 121.6, 115.9, 114.3, 113.9, 55.2. LC-MS: $[M+H]^+$ 328.1 *m/z* (t_r = 5.9 min). FT-IR (ATR, cm^{-1}): 3482, 3465, 3358, 3290, 1703, 1511, 1200. HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_5O_4$ $[M+H]^+$ 328.1046, found 328.1049.



***N*'-[[(2-Chlorophenyl)carbamoyl]oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (13).** Method A. The crude product was recrystallized from THF to yield **13** (0.11 g, 65%) as a white fluffy solid. Mp: 217-218 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.29 (br s, 1H), 8.58 (t, J = 1.2 Hz, 1H), 8.16 (dd, J = 9.5, 1.2 Hz, 1H), 8.09 (dd, J = 9.5, 1.2 Hz, 1H), 7.95 (dd, J = 8.1, 1.6 Hz, 1H), 7.55 (dd, J = 8.1, 1.5 Hz, 1H), 7.42-7.37 (m, 3H), 7.20 (td, J = 7.6, 1.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.9, 152.0, 148.9, 148.8, 134.8, 134.5, 130.9, 129.4, 127.8, 125.6, 124.9, 123.1, 116.3, 114.7. LC-MS: $[M+H]^+$ 332.1 *m/z* (t_r = 7.2 min). FT-IR (ATR, cm^{-1}): 3446, 3355, 3329, 1736, 1522, 1191, 1007. HRMS (ESI): *m/z* calcd for $C_{14}H_{11}N_5O_3Cl$ $[M+H]^+$ 332.0551, found 332.0552.

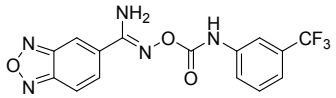


***N*'-[[(4-Chlorophenyl)carbamoyl]oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (15).** Method A. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1) and recrystallized from MeCN to yield **15** (45 mg, 27%) as light yellow crystals. Mp: 198-202 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.62 (br s, 1H), 8.57 (t, J = 1.2 Hz, 1H), 8.15 (dd, J = 9.5, 1.2 Hz, 1H), 8.12 (dd, J = 9.5, 1.2 Hz, 1H), 7.62-7.57 (m, 2H), 7.42-7.37 (m, 2H), 7.16 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.4, 152.1, 148.9, 148.8, 137.4, 134.9, 131.3, 128.6, 126.8, 121.0, 116.0, 114.5. LC-MS: $[M+H]^+$ 332.1 *m/z* (t_r = 6.8 min). FT-IR (ATR, cm^{-1}): 3467, 3341, 1721, 1515, 1183, 1005, 806. HRMS (ESI): *m/z* calcd for $C_{14}H_{11}N_5O_3Cl$ $[M+H]^+$ 332.0551, found 332.0554.

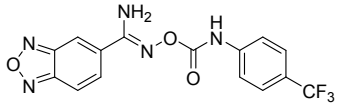


***N*'-[[[2-(Trifluoromethyl)phenyl]carbamoyl]oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (16).** Method A. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1) and recrystallized from EtOAc/*n*-hexane to yield **16** (60 mg, 33%) as an off-white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.58 (t, J = 1.1 Hz, 1H), 8.15 (dd, J = 9.5, 1.0 Hz, 1H), 8.06 (dd, J = 9.5, 1.3 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.70-7.71 (m, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.38 (s, 1H). ^{13}C NMR

(75 MHz, DMSO-d_6) δ 152.7, 152.6, 148.9, 148.8, 135.2 (q, J_{CF} = 2 Hz), 134.7, 133.4, 130.8, 126.3 (q, J_{CF} = 5 Hz), 126.2, 125.6, 123.8 (q, J_{CF} = 271 Hz), 121.9 (q, J_{CF} = 29 Hz), 116.2, 114.8. LC-MS: $[M+H]^+$ 366.1 *m/z* (t_r = 7.8 min). FT-IR (ATR, cm^{-1}): 3471, 3323, 1729, 1532. HRMS (ESI): *m/z* calcd for $C_{15}H_{10}F_3N_5O_3$ $[M+H]^+$ 366.0814, found 366.0816.

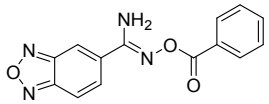


***N*'-[[[3-(Trifluoromethyl)phenyl]carbamoyl]oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (17).** Method A. The product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2) to yield **17** (0.14 g, 78%) as an off-white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.58 (s, 1H), 8.15-8.13 (m, 2H), 8.00 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.42-7.39 (m, 1H), 7.20 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.6, 152.3, 148.9, 148.8, 139.3, 134.9, 131.4, 129.9, 129.5 (q, J_{CF} = 32 Hz) 129.1, 124.1 (q, J_{CF} = 270 Hz), 119.5 (q, J_{CF} = 4 Hz), 115.5 (q, J_{CF} = 4 Hz), 116.0, 114.6. LC-MS: $[M+H]^+$ 366.1 *m/z* (t_r = 7.2 min). FT-IR (ATR, cm^{-1}): 3475, 3347, 1731, 1528. HRMS (ESI): *m/z* calcd for $C_{15}H_{10}F_3N_5O_4$ $[M+H]^+$ 366.0814, found 366.0814.

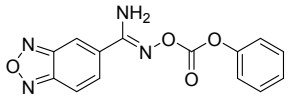


***N*'-[[[4-(Trifluoromethyl)phenyl]carbamoyl]oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (18)**. Method A. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1) and recrystallized from MeCN to yield **18** (87 mg, 48%) as light yellow crystals. Mp: 198 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.57 (s, 1H), 8.12 (m, 2H), 7.79 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.18 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.8, 152.0, 148.9, 148.9, 142.2, 134.9, 131.3, 126.0 (q, J_{CF} = 4 Hz, 2C), 124.4 (q, J_{CF} = 270 Hz), 123.1 (q, J_{CF} = 32 Hz), 119.0 (2C), 116.1, 114.6. LC-MS: $[M+H]^+$ 366.1 *m/z* (t_r = 7.2 min). FT-IR (ATR, cm^{-1}): 3473, 1716, 1507, 1318. HRMS (ESI): *m/z* calcd for $C_{15}H_{10}F_3N_5O_3$ $[M+H]^+$ 366.9815, found 366.0815.

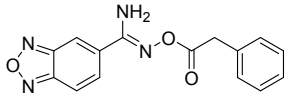
General procedure for the reaction of oximes with acyl chlorides. *Method C.* The amidoxime **5** (125 mg, 0.70 mmol) was dissolved in anhydrous THF (5 mL) under an Ar atmosphere. To this mixture distilled Et_3N (195 µL, 1.40 mmol, 2.0 equiv) and the corresponding acyl chloride (0.77 mmol, 1.1 equiv) were added, and the resulting mixture was heated to 70 °C. After heating the mixture for 2-4 h, the mixture was let cool to rt and evaporated to dryness. The residue was dissolved in EtOAc and washed with H_2O, the organic phase was dried with anhydrous Na_2SO_4, evaporated, and dried *in vacuo*. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1).



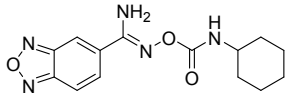
***N*'-(Benzoyloxy)benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (21)**. The reaction was carried out according to the Method C to yield **21** (73 mg, 36%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.56 (t, *J* = 1.2 Hz, 1H), 8.25-8.21 (m, 2H), 8.14 (dd, *J* = 9.5, 1.2 Hz, 1H), 8.02 (dd, *J* = 9.5, 1.2 Hz, 1H), 7.72-7.67 (m, 1H), 7.60-7.54 (m, 2H), 7.27 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.3, 154.7, 148.9, 148.8, 135.4, 133.3, 131.3, 129.6, 129.0, 128.6, 116.2, 114.7. LC-MS: $[M+H]^+$ 283.2 *m/z* (t_r = 5.7 min). FT-IR (ATR, cm^{-1}): 3503, 3402, 1727, 1606, 1258, 1090, 705 HRMS (ESI): *m/z* calcd for $C_{14}H_{11}N_4O_3$ $[M+H]^+$ 283.0831, found 283.0836.



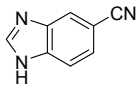
***N*'-[(Phenoxycarbonyl)oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (22).** The reaction was carried out according to the Method C to yield **22** (0.11 g, 63%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (t, J = 1.1 Hz, 1H), 8.13 (dd, J = 9.5, 1.1 Hz, 1H), 7.93 (dd, J = 9.5, 1.1 Hz, 1H), 7.52-7.45 (m, 2H), 7.52-7.45 (m, 2H), 7.38-7.29 (m, 5H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.1, 151.8, 150.7, 148.9, 148.7, 134.9, 131.0, 129.7, 126.2, 121.3, 116.3, 115.0. LC-MS: $[M+H]^+$ 299.1 *m/z* (t_r = 5.1 min). FT-IR (ATR, cm^{-1}): 3484, 3385, 1776, 1642, 1240, 1199, 932. HRMS (ESI): *m/z* calcd for $C_{14}H_{11}N_4O_4$ $[M+H]^+$ 299.0780 , found 299.0780.



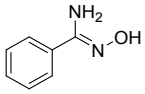
***N*'-(2-Phenylacetoxy)benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (23).** The reaction was carried out according to the Method C. The crude product was recrystallized from EtOAc/*n*-hexane to yield **23** (29 mg, 14%) as white crystals. Mp. 153-155 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 (t, J = 1.2 Hz, 1H), 8.11 (dd, J = 9.5, 1.2 Hz, 1H), 7.94 (dd, J = 9.5, 1.2 Hz, 1H), 7.38-7.26 (m, 5H), 7.20 (br s, 2H), 3.87 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.7, 154.6, 148.9, 148.8, 135.2, 134.4, 131.1, 129.4, 128.4, 126.8, 116.2, 114.6. LC-MS: $[M+H]^+$ 297.2 *m/z* (t_r = 5.9 min). FT-IR (ATR, cm^{-1}): 3472, 3365, 1741, 1634, 1142, 882, 708. HRMS (ESI): *m/z* calcd for $C_{15}H_{13}N_4O_3$ $[M+H]^+$ 297.0988, found 297.0991.



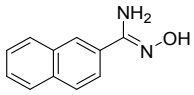
***N*'-[(Cyclohexylcarbamoyl)oxy]benzo[*c*][1,2,5]oxadiazole-5-carboximidamide (24).** A mixture of **5** (95 mg, 0.53 mmol) and cyclohexyl isocyanate (136 µL, 1.06 mmol, 2.0 equiv) in $CHCl_3$ was stirred at rt for 5 days. The reaction mixture was evaporated *in vacuo*, and the residue was purified by flash SiO_2 column chromatography (EtOAc) and recrystallization (MeOH) to give **24** (0.10 g, 64%) as a light yellow solid. Mp: 200 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (t, J = 1.0 Hz, 1H), 8.14 (dd, J = 9.6, 1.1 Hz, 1H), 8.08 (dd, J = 9.5, 0.9 Hz, 1H), 7.11-7.07 (m, 3H), 3.48-3.38 (m, 1H), 1.82-1.56 (m, 5H), 1.41-1.09 (m, 5H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.2, 151.9, 148.9, 148.9, 135.2, 131.5, 115.9, 114.2, 49.8, 32.4 (2C), 25.2, 24.8 (2C). LC-MS: $[M+H]^+$ 304.2 *m/z* (t_r = 6.5 min). FT-IR (ATR, cm^{-1}): 3357, 2930, 1702, 1641, 1510, 1208. HRMS (ESI): *m/z* calcd for $C_{14}H_{18}N_5O_3$ $[M+H]^+$ 304.1410, found 304.1409.



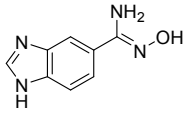
1*H*-Benzimidazole-5-carbonitrile (25). A mixture of 2,4-diaminobenzonitrile (0.40 g, 3.00 mmol) and formic acid (10 mL) was refluxed for 1 h. The reaction mixture was evaporated to dryness, and a saturated solution of $NaHCO_3$ was added to the residue. The resulting mixture was extracted with EtOAc, and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and evaporated to give **25** (0.35 g, 81%) as a light brown powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.96 (s, 1H), 8.47 (s, 1H), 8.16 (m, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 8.4, 1.5 Hz, 1H). Spectral data is consistent with those reported earlier.[1]



***N*'-Hydroxybenzimidamide (26).** A mixture of benzonitrile (1.00 mL, 9.70 mmol), $H_2NOH{\cdot}HCl$ (1.01 g, 14.6 mmol, 1.5 equiv) and Et_3N (2.02 mL, 14.6 mmol, 1.5 equiv) in EtOH (20 mL) was stirred at rt for 20 h. After evaporation and extraction of the residue with EtOAc, the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4. The filtrate was evaporated *in vacuo* to give the crude **26** (1.12 g, 98%).^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 7.67-7.65 (m, 2H), 7.39-7.35 (m, 3H), 5.77 (s, 2H). Spectral data is consistent with those reported earlier.[2]

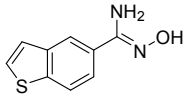


***N*'-Hydroxy-2-naphthimidamide (27).** To solution of 2-naphthonitrile (0.50 g, 3.26 mmol) in EtOH (10 mL) a solution of $H_2NOH{\cdot}HCl$ (0.56 g, 8.15 mmol, 2.5 equiv) and Na_2CO_3 (0.56 g, 5.20 mmol, 1.6 equiv) in H_2O (10 mL) was added at rt. The resulting mixture was heated at 100 °C for 19 h. After evaporation of the reaction mixture to dryness and dissolving the residue with EtOAc, the combined organic phases were washed with brine, and dried over anhydrous Na_2SO_4. The filtrate was evaporated to give the crude **27** (0.52 g, 86%) as off-white crystals.^{1}H NMR (300 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.21 (s, 1H), 7.93-7.60 (m, 4H), 7.54-7.51 (m, 2H), 5.90 (s, 2H).



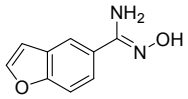
***N*'-Hydroxy-1*H*-benzimidazole-5-carboximidamide (28).** To solution of **24** (0.29 g, 2.00 mmol) in EtOH (2 mL), a solution of $H_2NOH{\cdot}HCl$ (0.35 g, 5.00 mmol, 2.5 equiv) and Na_2CO_3 (0.34 g, 3.20 mmol, 1.6 equiv) in H_2O (2 mL) was added rt. The resulting mixture was heated at 100 °C for 3.5 h. After evaporation of the reaction mixture to dryness and dissolving the residue with EtOAc, the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4. The filtrate was evaporated to give the crude **28** (0.25 g, 71%) as light brown powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.52 (s, 1H), 9.52 (s, 1H), 8.23 (s, 1H), 7.90 (s, 1H), 7.54 (m, 2H), 5.79 (s, 2H). Spectral data is consistent with those reported earlier.[2]

General procedure for the reaction of nitriles with $H_2NOH{\cdot}HCl$. *Method D.* To a solution of the corresponding nitrile (5.0 mmol) in EtOH (10 mL), a solution of $H_2NOH{\cdot}HCl$ (0.87 g, 12.5 mmol, 2.5 equiv) and Na_2CO_3 (0.85 g, 8.00 mmol, 1.6 equiv) in H_2O (10 mL) was added at rt. The resulting solution was heated at 100 °C for 3.5 h. After evaporation of the reaction mixture to dryness and dissolving the residue with EtOAc, the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4. The filtrate was evaporated to give the crude product.

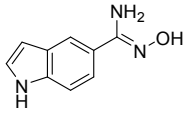


***N*'-Hydroxybenzothiophene-5-carboximidamide (29).** Method D. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1) to give **29** (0.36 g, 38%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.68 (s, 1H), 8.20 (d, J = 1.3

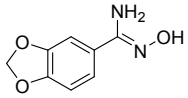
Hz, 1H), 8.00-7.97 (m, 1H), 7.78-7.71 (m, 2H), 7.48 (d, J = 5.4 Hz, 1H), 5.89 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.1, 139.5, 139.3, 129.8, 128.0, 124.2, 122.2, 121.9, 120.5.



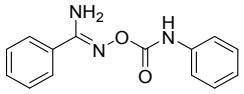
***N*'-Hydroxybenzofuran-5-carboximidamide (30)**. Method D. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1) to yield **30** (0.43 g, 49%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.96 (d, J = 1.7 Hz, 1H), 7.66 (dd, J = 8.7, 1.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 5.81 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.6, 151.2, 146.5, 128.6, 126.9, 122.2, 118.5, 110.8, 106.9.



***N*'-Hydroxy-1*H*-indole-5-carboximidamide (31).** A solution of 5-cyanoindole (0.71 g, 5.00 mmol), $H_2NOH{\cdot}HCl$ (0.52 g, 7.5 mmol, 1.5 equiv), and Et_3N (1.04 mL, 7.50 mmol, 1.5 equiv) in EtOH (30 mL) was stirred at rt for 24 h. Then another portions of $H_2NOH{\cdot}HCl$ (0.52 g, 7.50 mmol) and Et_3N (1.04 mL, 7.50 mmol) were added to the reaction mixture, and it was stirred at rt for additional 24 h and at reflux temperature for 6 h. The solution was evaporated *in vacuo* and EtOAc was added to the residue, washed twice with brine, dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:1 to 1:0) to yield **31** (0.36 g, 40%) as a light brown powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.12 (s, 1H), 9.33 (s, 1H), 7.85 (d, J = 1.3 Hz, 1H), 7.46 (dd, J = 8.6, 1.6 Hz, 1H), 7.36-7.34 (m, 2H), 6.45 (d, J = 2.9 Hz, 1H), 5.66 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.1, 136.2, 127.1, 125.8, 124.3, 119.0, 117.3, 110.8, 101.5.

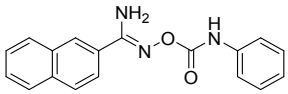


***N*'-Hydroxybenzo[1,3]dioxole-5-carboximidamide (32).** A solution of piperonylnitrile (0.74 g, 5.00 mmol), $H_2NOH{\cdot}HCl$ (0.52 g, 7.50 mmol, 1.5 equiv), and Et_3N (1.04 mL, 7.50 mmol, 1.5 equiv) in EtOH (30 mL) was stirred at rt for 24 h. Then another portions of $H_2NOH{\cdot}HCl$ (0.52 g, 7.50 mmol) and Et_3N (1.04 mL, 7.50 mmol) were added to the reaction mixture, and it was stirred at rt for additional 24 h. The solution was evaporated *in vacuo* and EtOAc was added to the residue, washed twice with brine, dried over anhydrous Na_2SO_4 and evaporated to give the crude **32** (0.80 g, 89%) as a white powder. ^{1}H NMR (300 MHz, DMSO) δ 9.50 (s, 1H), 7.21-7.18 (m, 2H), 6.91-6.88 (m, 1H), 6.03 (s, 2H), 5.71 (s, 2H). ^{13}C NMR (75 MHz, DMSO) δ 150.5, 147.8, 147.1, 127.4, 119.3, 107.8, 105.7, 101.1. Spectral data is consistent with those reported earlier.[3]

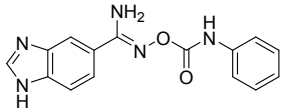


***N*'-[(Phenylcarbamoyl)oxy]benzimidamide (33).** Method A (1.00 mmol of starting material). The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:4 to 1:1) to give **33** (0.22 g, 85%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.29 (s, 1H), 7.83-7.80 (m, 2H), 7.56-7.44 (m, 5H), 7.32 (t, J = 7.7 Hz, 2H), 7.05 (t, J = 7.3 Hz, 1H), 6.76 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.6, 152.9, 137.4, 131.4, 131.0,

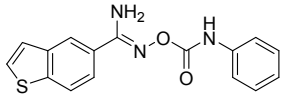
129.2 (2C), 129.1 (2C), 126.7 (2C), 124.2, 119.9 (2C). LC-MS: $[M+H]^+$ 256.3 *m/z* (t_r = 5.8 min). FT-IR (ATR, cm^{-1}): 3354, 1727, 1207. HRMS (ESI): *m/z* calcd for $C_{14}H_{14}N_3O_2$ $[M+H]^+$ 256.1086, found 256.1090.



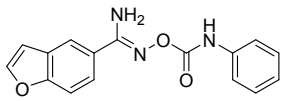
***N*'-[(Phenylcarbamoyl)oxy]-2-naphthimidamide (34).** Method A (1.00 mmol of starting material). The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1) and recrystallization (EtOAc/*n*-hexane) to yield **34** (95 mg, 30%) as a white powder. Mp: 179 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.43 (s, 1H), 8.04 (m, 4H), 7.62-7.52 (m, 4H), 7.34 (t, J = 7.8 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.96 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.4, 151.5, 137.5, 132.8, 131.3, 127.7 (2C), 127.4, 126.8, 126.6, 126.2, 125.6, 125.5, 123.0, 121.9, 118.1 (2C). LC-MS: $[M+H]^+$ 306.2 *m/z* (t_r = 7.0 min). FT-IR (ATR, cm^{-1}): 3290, 1709, 1219. HRMS (ESI): *m/z* calcd for $C_{18}H_{16}N_2O_2$ $[M+H]^+$ 306.1243, found 306.1241.



***N*'-[(Phenylcarbamoyl)oxy]-1*H*-benzoimidazo-5-carboximidamide (35).** Method A (1.99 mmol of starting material, reaction time 48 h). The crude product was purified by flash SiO_2 column chromatography (EtOAc/MeOH 5%→10%) to give **35** (0.15 g, 51%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.56 (br s, 1H), 9.36 (s, 1H), 8.32 (s, 1H), 8.08 (s, 1H), 7.71 (dd, J = 8.5, 1.5 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.57-7.54 (m, 2H), 7.35-7.30 (m, 2H), 7.07-7.08 (m, 1H), 6.81 (s, 2H). ^{13}C NMR (75 MHz, DMSO) δ 156.3, 152.6, 143.4, 138.6, 128.7 (2C), 124.9, 122.8, 120.8, 119.1 (2C). LC-MS: $[M+H]^+$ 296.2 *m/z* (t_r = 1.2 min). FT-IR (ATR, cm^{-1}): 3184, 1717, 1513, 1203. HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_5O_2$ $[M+H]^+$ 296.1147, found 296.1148.

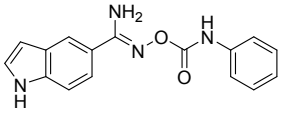


***N*'-[(Phenylcarbamoyl)oxy]benzothiophene-5-carboximidamide (36).** Method B. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1) to yield **36** (0.14 g, 44%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.36 (d, J = 1.5 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.87-7.80 (m, 2H), 7.58-7.54 (m, 3H), 7.39-7.30 (m, 2H), 7.08-7.03 (m, 1H), 6.88 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.7, 152.5, 141.0, 139.2, 138.5, 128.7 (2C), 128.6, 127.6, 124.2, 122.9, 122.6, 122.5, 122.1, 119.1 (2C). LC-MS: $[M+Na]^+$ 334.1 *m/z* (t_r = 6.3 min). FT-IR (ATR, cm^{-1}): 3270, 1713, 1219. HRMS (ESI): *m/z* calcd for $C_{16}H_{14}N_3O_2S$ $[M+H]^+$ 312.0807, found 312.0811.

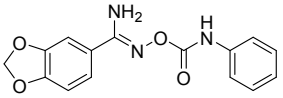


***N*'-[(Phenylcarbamoyl)oxy]benzofuran-5-carboximidamide (37).** Method B. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:2 to 1:1) to give **37** (0.24 g, 79%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.13 (d, J = 1.7 Hz, 1H), 8.07 (d, J = 2.2 Hz, 1H), 7.79 (dd, J = 8.7, 1.8 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.56-7.53 (m, 2H), 7.32 (t, J = 7.9 Hz, 2H), 7.07-7.02 (m, 2H), 6.83 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 155.4, 152.6, 147.0, 138.6, 128.7 (2C), 127.1, 126.3,

123.4, 122.9, 120.2, 119.1 (2C), 111.1, 107.0. LC-MS: $[M+Na]^+$ 318.2 *m/z* (t_r = 6.3 min). FT-IR (ATR, cm^{-1}): 3467, 3357, 2930, 2852, 1703, 1641, 1510, 1208. HRMS (ESI): *m/z* calcd for $C_{16}H_{14}N_3O_3$ $[M+H]^+$ 296.1035, found 296.1031.



***N*'-[(Phenylcarbamoyl)oxy]-1*H*-indole-5-carboximidamide (38).** Method B. The crude product was purified by flash SiO_2 column chromatography (EtOAc/*n*-hexane 1:1 to 2:1) and recrystallization ($MeCN/H_2O$) to give **38** (80 mg, 28%) as an off-white solid. Mp: 156 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 11.25 (s, 1H), 9.30 (s, 1H), 8.03 (s, 1H), 7.58-7.55 (m, 3H), 7.44-.39 (m, 2H), 7.33-7.28 (m, 2H), 7.05-7.00 (m, 1H), 6.66 (s, 1H), 6.51 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.8, 152.7, 138.6, 137.0, 128.7 (2C), 127.1, 126.4, 122.8, 121.9, 119.9, 119.1, 119.0, 111.1, 101.8. LC-MS: $[M+Na]^+$ 317.1 *m/z* (t_r = 5.4 min). FT-IR (ATR, cm^{-1}): 3511, 3387, 3196, 1750, 1517, 1193. HRMS (ESI): *m/z* calcd for $C_{16}H_{15}N_4O_2$ $[M+H]^+$ 295.1195, found, 295.1197.



***N*'-[(Phenylcarbamoyl)oxy]benzo[*d*][1,3]dioxole-5-carboximidamide (39).** A solution of **35** (0.18 g, 1.00 mmol) and phenyl isocyanate (0.14 mL, 1.5 mmol 1.5 equiv) was stirred in ethanol-free $CHCl_3$ for 3 days. The reaction mixture was evaporated *in vacuo*, and the residue was purified by flash SiO_2 column chromatography (EtOAc/n-hexane 1:2 to 1:1) and recrystallization (EtOAc) to yield **39** (17 mg, 6%) as a white powder. Mp: 140-141 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 9.34 (s, 1H), 7.57-7.28 (m, 2H), 7.43 (d, J = 1.7 Hz, 1H), 7.38 (dd, J = 8.1, 1.8 Hz, 1H), 7.35-7.28 (m, 2H), 7.08-7.02 (m, 1H), 7.0 (d, J = 8.2 Hz, 1H), 6.77 (s, 2H), 6.09 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.0, 152.6, 149.1, 147.3, 138.5, 128.7 (2C), 125.0, 123.0, 121.1, 119.4 (2C), 108.1, 107.1, 101.6. LC-MS: $[M+Na]^+$ 322.1 *m/z* (t_r = 5.7 min). FT-IR (ATR, cm^{-1}): 3303, 1720, 1525, 1206. HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_3O_4$ $[M+H]^+$ 300.0984, found, 300.0984.

References

1. *WO Pat.,* 069949, 2010.

2. G. Xia, X. You, L. Liu, H. Liu, J. Wang, Y. Shi, P. Li, B. Xiong, X. Liu, J. Shen, *Eur. J. Med. Chem.*, 2013, **62**, 1–10.