Supporting Information

Synthesis of thiadiazolo[2',3':2,3]imidazo[4,5-b]indoles
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**General Information**

All reactions were carried out in oven-dried sealable glass pressure tubes under an argon atmosphere. Solvents for reactions were purchased as extra dry under argon. All chemicals employed, including ligands, acetylenes and bases, were purchased from a commercial source and used without further purification. Thin layer chromatography (TLC) was performed on Merck Silica 60 F254 on aluminum tin foil from Macherey– Nagel. Column chromatography was performed using Fluka silica gel 60 (0.063 – 0.200 mm, 70–320 mesh). NMR data were recorded on Bruker AV 250 and Bruker AV 300 spectrometers. All $^{19}$F-, $^{13}$C- and $^1$H NMR spectra presented in this work were recorded in CDCl$_3$ solution, respectively. The chemical shifts are given in ppm. All coupling constants are indicated as $J$. References: TMS (d = 0.00 ppm) or residual CHCl$_3$ (d = 7.27 ppm) were taken as internal standard. $^{19}$F NMR spectroscopy: Bruker AV 300 (282 MHz). Mass spectrometry (MS) was carried out on Finnigan MAT 95 XP (electron ionization EI, 70 eV); 6890 N/5973 (Agilent), 6210 Time-of-Flight LC/MS (Agilent); Gas Chromatography MS (GCMS): Agilent HP- 5890 with an Agilent HP-5973 Mass Selective Detector (EI) and HP-5 capillary column using helium carrier gas. The High resolution MS [HR-MS (ESI)] was performed on Agilent 1969 A TOF. Only the measurements with an average deviation from the theoretical mass of ± 2 mDa were accounted as correct. For Infrared spectroscopy (IR) was used the Nicolet 550 FT-IR spectrometer with ATR sampling technique for solids as well as liquids. For melting point determination, we used a Micro-Hot-Stagem GalenTM III Cambridge Instruments.
Experimental Data

General procedure A; for the synthesis of 6-(2-bromophenyl)-2-ethyl-imidazo[2,1-b]-1,3,4-thiadiazole (3): 1.70 g (13 mmol) 2-Amino-5-ethyl-1,3,4-thiadiazole and 1.88 g (6.8 mmol) 2,2'-dibromoacetophenone were dissolved in 50 mL n-butanol. Afterwards the reaction mixture was reflux for 8 hours. After cooling to room temperature, the crude compound was purified by flash column chromatography on silica gel (ethyl acetate: heptane).

General procedure B; for the synthesis of 5-bromo-6-(2-bromophenyl)-2-ethyl-imidazo[2,1-b]-1,3,4-thiadiazole (4): 1.40 g (3.6 mmol) 6-(2-bromophenyl)-2-ethyl-imidazo[2,1-b]-1,3,4-thiadiazole 3 dissolved in 15 mL acetic acid, 0.26 mL Br₂, dissolved in 1.5 mL acetic acid, was dropped at ambient temperature within 15 min. The reaction was vigorously stirred for 75 min. A saturated aqueous solution of 410 mg (5 mmol) NaOAc was slowly added under cooling. The formed precipitate was collected by filtration and the crude compound was purified by flash column chromatography on silica gel (ethyl acetate: heptane).

General procedure C; for the synthesis of 2-ethyl-5-(substituted)-5H-[1,3,4]thiadiazolo[2',3':2,3]imidazo[4,5-b]indole (5a-g): 100 mg 5-bromo-6-(2-bromophenyl)-2-ethyl-imidazo[2,1-b]-1,3,4-thiadiazole (4) (0.275 mmol), aniline derivatives (0.412 mmol), Pd2(dba)3 (0.025 mmol), XantPhos (0.0750 mmol), NaOtBu (0.750 mmol) heated in dry xylene (2 mL) at 150°C for 24 h. After cooling to room temperature, the reaction was diluted with water and extracted into ethyl acetate. The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated. The crude compound was purified by flash column chromatography on silica gel (ethyl acetate: heptane).

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Et 3, 84%
S

6-(2-bromophenyl)-2-ethyl-imidazo[2,1-b]-1,3,4-thiadiazole (3): According to procedure A, afforded 1.76 g of product 3 (84%) as a brown solid; mp (110-112°C). 1HNMR (300 MHz, CDCl₃) δ 8.39 (s, 1H, CHAr), 8.01 (dd, 3J = 7.9 Hz, 4J = 1.9 Hz, 1H, CHAr), 7.63 (dd, 3J = 7.9 Hz, 4J = 1.5 Hz, 1H, CHAr), 7.34-7.39 (m, 1H, CHAr), 7.10- 7.16 (m, 1H, CHAr), 3.01 (q, 3J = 7.45 Hz, 2H, CH₂), 1.43 (t, 3J = 7.53 Hz, 3H, CH₃). 13C NMR (75 MHz,
5-bromo-6-(2-bromophenyl)-2-ethyl-imidazo[2,1-b]-1,3,4-thiadiazole (4): According to procedure B, afforded 1.35 g of product 4 (76%) as a yellow solid; mp (109-110 °C). $^1$HNMR (300 MHz, CDCl$_3$) δ 7.69 (d, $^3$J = 8.1 Hz, 1H, CH$_{Ar}$), 7.47 (d, $^3$J = 7.5 Hz, 1H, CH$_{Ar}$), 7.38 (d, $^3$J = 7.3 Hz, 1H, CH$_{Ar}$), 7.28 (d, $^3$J = 7.7 Hz, 1H, CH$_{Ar}$), 3.09 (q, $^3$J = 7.5 Hz, 2H, CH$_2$), 1.46 (t, $^3$J = 7.8 Hz, 3H, CH$_3$). $^{13}$C NMR (62 MHz, DMSO) δ 168.0 (CAr), 143.4 (CAr), 125.2 (CAr), 132.8 (CAr), 128.4 (CH$_{Ar}$), 127.5 (CH$_{Ar}$), 123.1 (CAr), 94.8 (CAr), 25.0 (CH$_2$), 12.8 (CH$_3$). IR (ATR) ν 3140 (w), 3069 (w), 2962 (w), 2869 (w), 1688 (m), 1608 (m), 1520 (s), 1445 (m), 1376 (m), 1261 (m), 1182 (s), 1015 (s), 938 (w), 853 (s), 759 (s) cm$^{-1}$. MS (EI, 70ev) m/z 389 ([M]+, 35), 387 ([M]+, 66), 385 ([M]+, 33), 253 (100), 251 (98), 226 (9), 201 (6), 172 (16), 151 (15), 149 (14), 146 (15), 128 (16), 120 (28), 102 (17). HRMS calcd for C$_{12}$H$_9$N$_3$Br$_2$S 384.8878 found 384.8874, HRMS calcd for C$_{12}$H$_9$N$_3$Br$_8$S 386.8858 found 386.8854, HRMS calcd for C$_{12}$H$_9$N$_3$Br$_{10}$S 388.8838 found 388.8833.

2-ethyl-5-((p-tolyl)-5-H-[1,3,4]thiadiazolo[2'1,3:2,3]imidazo[4,5-b]indole (5a): According to procedure C, using p-toluidine afforded 73 mg of product 5a (84%) as a brown solid; mp (187-188 °C). $^1$HNMR (300 MHz, CDCl$_3$) δ 7.96-8.01 (m, 1H, CH$_{Ar}$), 7.60-7.63 (m, 1H, CH$_{Ar}$), 7.55 (d, $^3$J = 8.4 Hz, 2H, CH$_{Ar}$), 7.38 (d, $^3$J = 8.5 Hz, 2H, CH$_{Ar}$), 7.26-7.30 (m, 2H, CH$_{Ar}$), 3.01 (q, $^3$J = 7.6 Hz, 2H, CH$_2$), 2.47 (s, 3H, CH$_3$), 1.41 (t, $^3$J = 7.6 Hz, 3H, CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 164.5 (CAr), 144.0 (CAr), 138.7 (CAr), 138.7 (CAr), 136.9 (CAr), 134.1 (CAr),
According to procedure C, using 3,5 dimethylaniline afforded 59 mg of product 5b (66%) as a gray solid; mp (188-189°C). $^1$HNMR (300 MHz, CDCl$_3$) $\delta$ 7.98-8.01 (m, 1H, CH$_{Ar}$), 7.64-7.67 (m, 1H, CH$_{Ar}$), 7.29-7.32 (m, 4H, CH$_{Ar}$), 7.06 (s, 1H, CH$_{Ar}$), 3.05 (q, $^3$J = 7.53 Hz, 2H, CH$_2$), 2.44 (s, 6H, CH$_3$), 1.43 (t, $^3$J = 7.5 Hz, 3H, CH$_3$). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.2 (C$_{Ar}$), 143.6 (C$_{Ar}$), 139.6 (CH$_{Ar}$), 138.7 (C$_{Ar}$), 135.8 (C$_{Ar}$), 129.1 (CH$_{Ar}$), 128.4 (C$_{Ar}$), 126.3 (C$_{Ar}$), 123.7 (C$_{Ar}$), 122.8 (CH$_{Ar}$), 121.7 (CH$_{Ar}$), 119.0 (CH$_{Ar}$), 117.8 (C$_{Ar}$), 111.7 (CH$_{Ar}$), 25.9 (CH$_2$), 21.5 (CH$_3$), 12.9 (CH$_3$). IR (ATR) $\nu$ 3052 (w), 3017 (w), 2980 (w), 2868 (w), 1599 (s), 1537 (m), 1506 (s), 1459 (s), 1380 (w), 1354 (s), 1289 (w), 1165 (m), 1132 (s), 847 (s), 730 (s) cm$^{-1}$. MS (EI, 70ev) m/z 346 ([M]$^+$, 100), 291 (35), 290 (36), 277 (16), 276 (85), 233 (20), 218 (5), 146 (4), 139 (9), 105 (5). HRMS calcd for C$_{20}$H$_{18}$N$_4$S 346.1247 found 346.1245.

2-ethyl-5-[(4-tert-butylphenyl)-5H-[1,3,4]thiadiazolo[2',3':2,3]imidazo[4,5-b]indole (5c):

According to procedure C, using 4-tert-butylaniline afforded 79 mg of product 5c (81%) as a pale brown solid; mp (151-152°C). $^1$HNMR (250 MHz, CDCl$_3$) $\delta$ 7.99-8.03 (m, 1H, CH$_{Ar}$),
7.59-7.67 (m, 5H, CH$_{Ar}$), 7.30-7.34 (m, 2H, CH$_{Ar}$), 3.06 (q, $^3J = 7.6$ Hz, 2H, CH$_2$), 1.43 (t, $^3J = 7.5$ Hz, 3H, CH$_3$), 1.42 (s, 9H, CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.2 (CAr), 160.1 (CAr), 145.0 (CAr), 138.8 (CAr), 134.1 (CAr), 129.5 (CAr), 127.0 (CAr), 126.6 (CAr), 124.5 (CAr), 124.3 (CAr), 123.0 (CAr), 121.4 (CAr), 118.8 (CAr), 111.6 (CAr), 34.9 (C$_{r-Bu}$), 31.6 (CH$_3$-$r-Bu$), 26.0 (CH$_2$), 13.2 (CH$_3$). IR (ATR) $\nu$ 3159 (w), 3052 (w), 2963 (w), 2868 (w), 1736 (m), 1681 (w), 1608 (m), 1575 (m), 1516 (s), 1457 (s), 1400 (w), 1341 (m), 1242 (m), 1223 (w), 1188 (m), 1043 (m), 952 (m), 836 (s), 733 (s) cm$^{-1}$. MS (EI, 70ev) m/z 374 ([M]$^+$, 100), 359 (5), 305 (12), 304 (61), 263 (12), 262 (14), 205 (5), 180 (5), 145 (7), 102 (5). HRMS (ESI, M+H)$^+$ calcd for C$_{22}$H$_{23}$N$_4$S 375.1638 found 375.1641.


According to procedure C, using $p$-methoxyaniline afforded 65 mg of product 5d (72%) as a brown solid; mp (167-168°C). $^1$HNMR (300 MHz, CDCl$_3$) $\delta$ 7.97-8.00 (m, 1H, CH$_{Ar}$), 7.51-7.57 (m, 3H, CH$_{Ar}$), 7.27-7.30 (m, 2H, CH$_{Ar}$), 7.10 (d, $^3J = 8.9$ Hz, 2H, CH$_{Ar}$), 3.91 (s, 3H, OCH$_3$), 3.02 (q, $^3J = 7.5$ Hz, 2H, CH$_2$), 1.41 (t, $^3J = 7.6$ Hz, 3H, CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.1 (CAr), 158.6 (CAr), 143.6 (CAr), 139.0 (CAr), 129.1 (CAr), 127.8 (CAr), 126.6 (CAr), 122.9 (CH$_{Ar}$), 122.1 (CAr), 121.1 (CH$_{Ar}$), 118.5 (CH$_{Ar}$), 118.4 (CAr), 114.8 (CH$_{Ar}$), 111.1 (CH$_{Ar}$), 55.6 (OCH$_3$), 25.8 (CH$_2$), 13.1 (CH$_3$). IR (ATR) $\nu$ 3051 (w), 2975 (w), 2871 (w), 2037 (w), 1905 (w), 1738 (w), 1612 (m), 1575 (m), 1510 (s), 1463 (m), 1444 (m), 1403 (w), 1356 (m), 1247 (s), 1174 (m), 1129 (m), 1019 (s), 834 (s), 741 (s) cm$^{-1}$. MS (EI, 70ev) m/z 348 ([M]$^+$, 100), 293 (26), 292 (76), 278 (28), 235 (18), 192 (18), 154 (5), 139 (5), 128 (2), 102 (7). HRMS calcd for C$_{19}$H$_{16}$ON$_4$S 348.1039 found 348.1035.

According to procedure C, using p-(methylthio)aniline afforded 58 mg of product 5e (61%) as a brown solid; mp (216-217°C). 1H NMR (300 MHz, CDCl3) δ 7.98-8.01 (m, 1H, CHAr), 7.56-7.60 (m, 3H, CHAr), 7.45 (d, 3J = 8.6 Hz, 2H, CHAr), 7.30-7.33 (m, 2H, CHAr), 3.06 (q, 3J = 7.5 Hz, 2H, CH2), 2.58 (s, 3H, SCH3), 1.42 (t, 3J = 7.6 Hz, 3H, CH3). 13C NMR (62 MHz, CDCl3) δ 166.5 (CAr), 144.0 (CAr), 138.7 (CAr), 138.0 (CAr), 135.8 (CAr), 134.4 (CAr), 133.1 (CAr), 127.6 (CAr), 125.7 (CAr), 123.8 (CAr), 121.8 (CAr), 119.0 (CAr), 117.9 (CAr), 111.4 (CAr), 25.8 (CH2), 16.0 (SCH3), 13.2 (CH3). IR (ATR) ν 3042 (w), 2999 (w), 2973 (w), 2962 (w), 2918 (w), 1595 (w), 1579 (m), 1542 (m), 1509 (s), 1493 (s), 1461 (s), 1407 (m), 1343 (m), 1260 (s), 1189 (m), 1094 (s), 960 (m), 826 (s), 741 (s) cm⁻¹. MS (EI, 70ev) m/z 364 ([M]+, 100), 309 (26), 308 (65), 294 (27), 263 (12), 262 (61), 204 (11), 182 (7), 147 (15), 102 (15). HRMS calcd for C19H16N4S2 364.0811 found 364.0806.


According to procedure C, using p-fluoroaniline afforded 62 mg of product 5f (70%) as a brown solid; mp (183-184°C). 1H NMR (250 MHz, CDCl3) δ 7.98-8.02 (m, 1H, CHAr), 7.57-7.66 (m, 2H, CHAr), 7.53-7.57 (m, 1H, CHAr), 7.28-7.33 (m, 4H, CHAr), 3.03 (q, 3J = 7.8 Hz, 2H, CH2), 1.41 (t, 3J = 7.6 Hz, 3H, CH3). 13C NMR (62 MHz, CDCl3) δ 166.2 (CAr), 161.6 (d, 1J = 247.5 Hz, C-F), 149.9 (CAr), 138.9 (CAr), 136.3 (CAr), 134.9 (CAr), 132.3 (d, 4J = 2.9 Hz, CAr), 127.1 (d, 3J = 8.6 Hz, CHAr), 123.7 (CHAr), 121.9 (CHAr), 119.0 (CHAr), 118.3 (CAr), 116.8 (d, 2J = 23.0 Hz, CHAr), 111.2 (CHAr), 25.9 (CH2), 13.2 (CH3). 19F NMR (282 MHz, CDCl3) δ -114.7 (1F, C-F). IR (ATR) ν 3052 (w), 2936 (w), 2877 (w), 1738 (w), 1606 (m), 1534 (m), 1504 (s), 1462 (m), 1218 (s), 1185 (m), 1131 (m), 966 (m), 826 (s), 752 (s) cm⁻¹. MS (EI, 70ev) m/z 336 ([M]+, 65), 281 (39), 280 (100), 223 (23), 195 (4), 186 (2), 140 (2), 128 (2), 108 (3), 102 (7). HRMS calcd for C18H16FN4S 336.0840 found 336.0838.
2-ethyl-5-[3-(fluoro)phenyl]-5H-[1,3,4]thiadiazolo[2',3':2,3]imidazo[4,5-b]indole (5g):

According to procedure C, using m-fluoroaniline afforded 54 mg of product 5g (62%) as a pale brown solid; mp (189-190°C). ¹H NMR (300 MHz, CDCl₃) δ 7.97-8.00 (m, 1H, CH₆), 7.65-7.69 (m, 1H, CH₆), 7.41-7.56 (m, 3H, CH₆), 7.30-7.33 (m, 2H, CH₆), 7.08-7.15 (m, 1H, CH₆), 3.05 (q, 3J = 7.6 Hz, 2H, CH₂), 1.43 (t, 3J = 7.5 Hz, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 165.2 (CAr), 163.3 (d, 3J = 247.6 Hz, C-F), 144.2 (CAr), 138.3 (CAr), 138.0 (d, 3J = 9.9 Hz, CAr), 130.9 (d, 3J = 9.4 Hz, CH₂), 128.8 (CAr), 126.1 (CAr), 123.4 (CAr), 121.9 (CAr), 120.4 (d, 4J = 3.2 Hz, CH₆), 119.3 (CAr), 118.8 (CH₆), 113.8 (d, 2J = 21.5 Hz, CH₆), 112.3 (d, 2J = 22.8 Hz, CH₂), 111.3 (CAr), 25.9 (CH₂), 13.0 (CH₃). ¹⁹F NMR (282 MHz, CDCl₃) δ −110.6 (1F, C-F). IR (ATR) ν 3052 (w), 2974 (w), 1732 (w), 1606 (m), 1532 (m), 1487 (m), 1402 (m), 1347 (m), 1130 (m), 788 (s), 736 (s), cm⁻¹. MS (EI, 70ev) m/z 336 ([M⁺], 82), 281 (57), 280 (100), 248 (7), 223 (33), 195 (4), 168 (8), 140 (5), 127 (5), 102 (13). HRMS calcd for C₁₈H₁₃FN₄S 336.0840 found 336.0837.