Supporting Information

Dual Targeting of Steroid Sulfatase (STS) and 17β-Hydroxysteroid Dehydrogenase Type 1 (17β-HSD1) by a Novel Drug-Prodrug Approach: A Potential Therapeutic Option for the Treatment of Endometriosis

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1. **Synthesis of compounds 1a, 5a-12a, 25a-27a, 32a-34a, 1b, 9b, 10b-12b, 25b, 26b, 31b-34b, 10c, 31c, 32c, 1-12, 25-27 and 31-34.**

5-Bromo-N-methyl-N-(o-tolyl)furan-2-carboxamide **(1b)**. The title compound was prepared according to method A and B using 5-bromofuran-2-carboxylic acid (1.90 g, 10 mmol), thionyl chloride (1.45 ml, 20 mmol) and DMF (30 drops) in toluene (50 ml). The corresponding N,2-dimethylaniline (1.25 ml, 10 mmol) and Et_3N (2.79 ml, 20 mmol) in DCM (50 ml) was added to the acyl chloride. The residue was purified by silica gel column chromatography (petroleum ether /ethyl acetate 5:1) to give 2.1 g (7.13 mmol/ 71 %) of the analytically pure compound (purity: 96.99 %). $C_{13}H_{12}BrNO_2$; MW 294.15; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.39 – 7.32 (m, 2H), 7.34 – 7.24 (m, 2H), 6.47 (d, J = 3.6 Hz, 1H), 5.51 (d, J = 3.6 Hz, 1H), 3.21 (s, 3H), 2.12 (s, 3H); MS (ESI): 293.75, 295.95 $(M+H)^+$.

5-(4-Methoxyphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(1a)**. The title compound was prepared according to method D by the reaction of **1b** (0.535 g, 1.82 mmol, 1 equiv) and (4-methoxyphenyl)boronic acid (0.414 g, 2.73 mmol, 1.5 equiv) in the presence of cesium carbonate (2.37 g, 7.28 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (105 mg, 0.091 mmol, 0.05 equiv) in DME/water 1:1 (50 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 4:1) to give 0.5 g (1.55 mmol/ 85 %) of the analytically pure compound (purity: 98.48 %). $C_{20}H_{19}NO_3$; MW 321.38; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42 – 7.26 (m, 4H), 7.23 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 3.6 Hz, 1H), 6.36 (d, J = 3.6 Hz, 1H), 3.77 (s, 3H), 3.24 (s, 3H), 2.16 (s, 3H); MS (ESI): 322.12 $(M+H)^+$.

5-(4-Hydroxyphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(1)**. The title compound was prepared according to method E by the reaction of **1a** (0.4 g, 1.24 mmol, 1 equiv) and $BF_3.SMe_2$ (1.30 ml, 12.4 mmol, 10 equiv) in dichloromethane (50 ml). The product was purified by column chromatography (dichloromethane/methanol 98.5:1.5) to give 0.29 g (0.944 mmol/ 76 %) of the analytically pure compound (purity: 99.36 %). $C_{19}H_{17}NO_3$; MW 307.35; mp: 172-175 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.76 (s, 1H), 7.41 – 7.25 (m, 4H), 7.13 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 3.6 Hz, 1H), 6.30 (d, J = 3.6 Hz, 1H), 3.23 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.95, 157.94, 155.10, 145.49, 142.84, 135.26, 131.11, 128.16, 128.13, 127.38, 125.66, 120.43, 118.34, 115.52, 104.58, 36.88, 16.96; MS (ESI): 308.12

$(M+H)^+$.

5-(3-Hydroxyphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(2)**. The title compound was prepared according to method D by the reaction of **1b** (0.294 g, 1 mmol, 1 equiv) and (3-hydroxyphenyl)boronic acid (0.206 g, 1.5 mmol, 1.5 equiv) in the presence of cesium carbonate (1.3 g, 4 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (57 mg, 0.05 mmol, 0.05 equiv) in DME/water 1:1 (50 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 3:1) to give 0.234 g (0.76 mmol/ 76 %) of the analytically pure compound (purity: 98.92 %). $C_{19}H_{17}NO_3$; MW 307.35; mp: 134-136 °C; ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.43 (s, 1H), 7.43 – 7.26 (m, 4H), 7.15 (t, J = 7.9 Hz, 1H), 6.94 – 6.90 (m, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.77 (dd, J = 8.0, 2.5 Hz, 1H), 6.67 (d, J = 3.6 Hz, 1H), 6.29 (d, J = 3.7 Hz, 1H), 3.30 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (126 MHz, Acetone-d_6) δ 159.15, 158.57, 155.87, 147.97, 144.15, 136.70, 132.18, 131.92, 130.67, 129.22, 129.15, 128.30, 118.66, 116.47, 116.38, 111.81, 107.25, 37.29, 17.52; MS (ESI): 308.00 $(M+H)^+$.

5-(2-Hydroxyphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(3)**. The title compound was prepared according to method D by the reaction of **1b** (0.294 g, 1 mmol, 1 equiv) and (2-hydroxyphenyl)boronic acid (0.206 g, 1.5 mmol, 1.5 equiv) in the presence of cesium carbonate (1.3 g, 4 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (57 mg, 0.05 mmol, 0.05 equiv) in DME/water 1:1 (50 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 3:1) to give 0.222 g (0.72 mmol/ 72 %) of the analytically pure compound (purity: 98.24 %). $C_{19}H_{17}NO_3$; MW 307.35; mp: 197-199 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.42 – 7.26 (m, 4H), 7.10 (ddd, J = 8.7, 7.2, 1.7 Hz, 1H), 6.90 – 6.84 (m, 1H), 6.81 (dd, J = 8.8, 2.5 Hz, 2H), 6.75 – 6.69 (m, 1H), 6.46 (d, J = 3.6 Hz, 1H), 3.25 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.97, 154.06, 151.77, 145.14, 142.86, 135.16, 131.12, 129.21, 128.10, 128.04, 127.38, 125.41, 118.91, 118.32, 116.07, 115.92, 110.39, 36.99, 16.97; MS (ESI): 308.01 $(M+H)^+$.

5-(3-Chloro-4-hydroxyphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(4)**.The title compound was prepared according to method D by the reaction of **1b** (0.294 g, 1 mmol, 1 equiv) and (3-chloro-4-hydroxyphenyl)boronic acid (0.259 g, 1.5 mmol, 1.5 equiv) in the presence of cesium carbonate (1.3 g, 4 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (57 mg, 0.05 mmol, 0.05 equiv) in DME/water 1:1 (50 ml). The product was purified by column

chromatography (petroleum ether /ethyl acetate 3:1) to give 0.233 g (0.68 mmol/ 68 %) of the analytically pure compound (purity: 98.59 %). $C_{19}H_{16}ClNO_3$; MW 341.79; mp: 77-80 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.53 (s, 1H), 7.43 – 7.26 (m, 4H), 7.14 (dd, J = 8.5, 2.2 Hz, 1H), 7.08 (d, J = 2.2 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.75 (d, J = 3.6 Hz, 1H), 6.50 (d, J = 3.6 Hz, 1H), 3.24 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.74, 153.43, 153.42, 146.07, 142.79, 135.21, 131.09, 128.32, 128.08, 127.36, 125.27, 124.04, 121.54, 120.25, 118.57, 116.82, 105.73, 36.96, 16.98; MS (ESI): 342.07, 344.11 $(M+H)^+$.

5-(3-Fluoro-4-methoxyphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(5a)**. The title compound was prepared according to method D by the reaction of **1b** (0.294 g, 1 mmol, 1 equiv) and (3-fluoro-4-methoxyphenyl)boronic acid (0.254 g, 1.5 mmol, 1.5 equiv) in the presence of cesium carbonate (1.3 g, 4 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (57 mg, 0.05 mmol, 0.05 equiv) in DME/water 1:1 (50 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 4:1) to give 0.292 g (0.86 mmol/ 86 %) of the analytically pure compound (purity: 98.26 %). $C_{20}H_{18}FNO_3$; MW 339.37; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 – 7.20 (m, 2H), 7.18 (dt, J = 7.5, 4.4 Hz, 1H), 7.12 – 7.07 (m, 1H), 6.93 (ddd, J = 8.5, 2.1, 1.3 Hz, 1H), 6.82 – 6.71 (m, 2H), 6.35 (d, J = 3.6 Hz, 1H), 6.26 (d, J = 3.6 Hz, 1H), 3.77 (s, 3H), 3.26 (s, 3H), 2.13 (s, 3H); MS (ESI): 340.07 $(M+H)^+$.

5-(3-Fluoro-4-hydroxyphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(5)**. The title compound was prepared according to method E by the reaction of **5a** (0.250 g, 0.736 mmol, 1 equiv) and $BF_3.SMe_2$ (0.775 ml, 7.36 mmol, 10 equiv) in dichloromethane (30 ml). The product was purified by column chromatography (dichloromethane/methanol 98:2) to give 0.185 g (0.56 mmol/ 77 %) of the analytically pure compound (purity: 98.48 %). $C_{19}H_{16}FNO_3$; MW 325.34; mp: 190-192 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.42 – 7.26 (m, 4H), 7.00 – 6.92 (m, 2H), 6.89 (t, J = 8.8 Hz, 1H), 6.73 (d, J = 3.6 Hz, 1H), 6.44 (d, J = 3.6 Hz, 1H), 3.24 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.78, 152.83 (d, J = 224.5 Hz), 150.02, 146.00, 145.42 (d, J = 12.3 Hz), 142.82, 135.25, 131.11, 128.18 (d, J = 12.8 Hz), 127.39, 121.00 (d, J = 7.2 Hz), 120.66 (d, J = 3.1 Hz), 118.49, 118.02, 118.00, 111.90 (d, J = 20.4 Hz), 105.80, 36.96, 16.98; MS (ESI): 326.01 $(M+H)^+$.

5-(4-Methoxy-3-methylphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(6a)**. The title compound was prepared according to method D by the reaction of **1b** (0.441 g, 1.49 mmol, 1

equiv) and (4-methoxy-3-methylphenyl)boronic acid (0.373 g, 2.24 mmol, 1.5 equiv) in the presence of cesium carbonate (1.94 g, 5.96 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (86 mg, 0.074 mmol, 0.05 equiv) in DME/water 1:1 (60 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 3:1) to give 0.44 g (1.31 mmol/ 88 %) of the analytically pure compound (purity: 99.99 %). $C_{21}H_{21}NO_3$; MW 335.40; ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.44 – 7.26 (m, 4H), 7.19 (dd, J = 8.6, 2.3 Hz, 1H), 7.04 – 7.00 (m, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.58 (d, J = 3.6 Hz, 1H), 6.51 (d, J = 3.6 Hz, 1H), 3.83 (s, 3H), 3.29 (s, 3H), 2.22 (s, 3H), 2.15 (s, 3H); MS (ESI): 336.18 $(M+H)^+$.

5-(4-Hydroxy-3-methylphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(6)**. The title compound was prepared according to method E by the reaction of **6a** (0.420 g, 1.25 mmol, 1 equiv) and $BF_3.SMe_2$ (1.31 ml, 12.52 mmol, 10 equiv) in dichloromethane (30 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 2:1) to give 0.29 g (0.9 mmol/ 72 %) of the analytically pure compound (purity: 99.99 %). $C_{20}H_{19}NO_3$; MW 321.38; mp: 183-186 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.42 – 7.25 (m, 4H), 7.02 (d, 1H), 6.87 (s, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 3.7 Hz, 1H), 6.42 (d, J = 3.7 Hz, 1H), 3.23 (s, 3H), 2.14 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.91, 156.09, 155.32, 145.49, 142.94, 135.25, 131.12, 128.18, 128.11, 127.39, 126.38, 124.32, 123.08, 120.27, 118.57, 114.75, 104.43, 36.98, 17.02, 15.74; MS (ESI): 322.15 $(M+H)^+$.

5-(2-Chloro-4-methoxyphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(7a)**. The title compound was prepared according to method D by the reaction of **1b** (0.600 g, 2.03 mmol, 1 equiv) and (2-chloro-4-methoxyphenyl)boronic acid (0.57 g, 3.05 mmol, 1.5 equiv) in the presence of cesium carbonate (2.64 g, 8.12 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (117 mg, 0.101 mmol, 0.05 equiv) in DME/water 1:1 (60 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 3:1) to give 0.585 g (1.64 mmol/ 81 %) of the analytically pure compound (purity: 98.33 %). $C_{20}H_{18}ClNO_3$; MW 355.82; ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.41 – 7.28 (m, 4H), 7.00 (d, J = 2.6 Hz, 1H), 6.95 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 3.7 Hz, 1H), 6.86 (dd, J = 8.9, 2.6 Hz, 1H), 6.50 (d, J = 3.7 Hz, 1H), 3.84 (s, 3H), 3.30 (s, 3H), 2.21 (s, 3H); MS (ESI): 356.06, 358.07 $(M+H)^+$.

5-(2-Chloro-4-hydroxyphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(7)**. The title compound was prepared according to method E by the reaction of **7a** (0.585 g, 1.64 mmol, 1

equiv) and $BF_3.SMe_2$ (1.72 ml, 16.44 mmol, 10 equiv) in dichloromethane (50 ml). The product was purified by column chromatography (dichloromethane/methanol 98:2) to give 0.4 g (1.17 mmol/ 71 %) of the analytically pure compound (purity: 98.40 %). $C_{19}H_{16}ClNO_3$; MW 341.79; mp: 198-201 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.27 (s, 1H), 7.42 – 7.26 (m, 4H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.83 – 6.78 (m, 2H), 6.69 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.36 (d, *J* = 3.7 Hz, 1H), 3.24 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.28, 157.79, 151.09, 145.67, 142.71, 135.24, 131.23, 130.28, 129.21, 128.24, 128.15, 127.49, 118.54, 117.93, 116.89, 114.79, 109.74, 36.99, 16.98; MS (ESI): 342.02, 344.09 $(M+H)^+$.

5-(2-Fluoro-4-methoxyphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(8a)**. The title compound was prepared according to method D by the reaction of **1b** (0.700 g, 2.37 mmol, 1 equiv) and (2-fluoro-4-methoxyphenyl)boronic acid (0.606 g, 3.56 mmol, 1.5 equiv) in the presence of cesium carbonate (3.08 g, 9.48 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (137 mg, 0.118 mmol, 0.05 equiv) in DME/water 1:1 (80 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 4:1) to give 0.674 g (1.98 mmol/ 83 %) of the analytically pure compound (purity: 99.99 %). $C_{20}H_{18}FNO_3$; MW 339.37; ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.41 – 7.28 (m, 4H), 6.97 (t, *J* = 8.8 Hz, 1H), 6.81 – 6.72 (m, 2H), 6.55 (t, *J* = 3.7 Hz, 1H), 6.49 (d, *J* = 3.6 Hz, 1H), 3.84 (s, 3H), 3.30 (s, 3H), 2.22 (s, 3H); MS (ESI): 340.13 $(M+H)^+$.

5-(2-Fluoro-4-hydroxyphenyl)-N-methyl-N-(o-tolyl)furan-2-carboxamide **(8)**. The title compound was prepared according to method E by the reaction of **8a** (0.674 g, 1.98 mmol, 1 equiv) and $BF_3.SMe_2$ (2.08 ml, 19.86 mmol, 10 equiv) in dichloromethane (50 ml). The product was purified by column chromatography (dichloromethane/methanol 99.5:0.5) to give 0.55 g (1.69 mmol/ 85 %) of the analytically pure compound (purity: 99.04 %). $C_{19}H_{16}FNO_3$; MW 325.34; mp: 185-187 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.29 (s, 1H), 7.42 – 7.26 (m, 4H), 6.82 (t, *J* = 8.8 Hz, 1H), 6.62 (dd, *J* = 13.1, 2.3 Hz, 1H), 6.58 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.50 (t, *J* = 3.6 Hz, 1H), 6.35 (d, *J* = 3.6 Hz, 1H), 3.24 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.19, 159.32 (d, *J* = 12.0 Hz), 158.21, 157.77, 149.20 (d, *J* = 2.6 Hz), 144.10 (d, *J* = 255.13 Hz), 135.25, 131.16, 128.18 (d, *J* = 12.9 Hz), 127.44, 126.87 (d, *J* = 5.0 Hz), 118.26, 112.01, 112.00, 108.48 (d, *J* = 10.6 Hz), 108.34 (d, *J* = 12.4 Hz), 103.12 (d, *J* = 23.4 Hz), 36.93, 16.95; MS (ESI): 326.06 $(M+H)^+$.

5-Bromo-N-(2-fluoro-6-methylphenyl)furan-2-carboxamide **(9b)**. The title compound was prepared according to method A and B using 5-bromofuran-2-carboxylic acid (1.90 g, 10 mmol), thionyl chloride (1.45 ml, 20 mmol) and DMF (30 drops) in toluene (50 ml). The corresponding 2-fluoro-6-methylaniline (1.11 ml, 10 mmol) and Et_3N (2.79 ml, 20 mmol) in DCM (50 ml) was added to the acyl chloride. The residue was purified by silica gel column chromatography (petroleum ether /ethyl acetate 4:1) to give 1.5 g (5.03 mmol/ 50 %) of the analytically pure compound (purity: 96.76 %). $C_{12}H_9BrFNO_2$; MW 298.11; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.93 (s, 1H), 7.34 (d, *J* = 3.6 Hz, 1H), 7.31 – 7.19 (m, 1H), 7.18 – 7.06 (m, 2H), 6.84 (d, *J* = 3.6 Hz, 1H), 2.21 (s, 3H); MS (ESI): 297.82, 299.85 $(M+H)^+$.

5-Bromo-N-(2-fluoro-6-methylphenyl)-N-methylfuran-2-carboxamide **(9a)**. The title compound was prepared according to method C using 5-bromo-N-(2-fluoro-6-methylphenyl)furan-2-carboxamide (0.5 g, 1.67 mmol, 1 equiv), NaH (0.08 g, 3.35 mmol, 2 equiv) and iodomethane (0.103 ml, 1.67 mmol, 1 equiv) in DMF (30 ml). The product was purified by column chromatography (dichloromethane/methanol 99.5:0.5) to give 0.27 g (0.86 mmol/ 51 %) of the analytically pure compound (purity: 98.10 %). $C_{13}H_{11}BrFNO_2$; MW 312.14; ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.38 (td, *J* = 8.0, 5.6 Hz, 1H), 7.21 – 7.13 (m, 1H), 7.13 – 7.06 (m, 1H), 6.35 (d, *J* = 3.6 Hz, 1H), 6.04 (d, *J* = 3.6 Hz, 1H), 3.29 (s, 3H), 2.24 (s, 3H); MS (ESI): 312.02, 313.91 $(M+H)^+$.

N-(2-Fluoro-6-methylphenyl)-5-(4-hydroxyphenyl)-N-methylfuran-2-carboxamide **(9)**. The title compound was prepared according to method D by the reaction of **9a** (0.168 g, 0.538 mmol, 1 equiv) and (4-hydroxyphenyl) boronic acid (0.111 g, 0.807 mmol, 1.5 equiv) in the presence of cesium carbonate (0.701 g, 2.15 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (31 mg, 0.026 mmol, 0.05 equiv) in DME/water 1:1 (50 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 2:1) to give 0.098 g (0.3 mmol/ 56 %) of the analytically pure compound (purity: 99.99 %). $C_{19}H_{16}FNO_3$; MW 325.34; mp: 171-173 °C; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.26 (m, 3H), 7.25 (s, 1H), 7.11 (ddt, *J* = 7.8, 1.6, 0.8 Hz, 1H), 7.06 (dddd, *J* = 9.0, 8.2, 1.4, 0.6 Hz, 1H), 6.93 – 6.86 (m, 2H), 6.37 – 6.30 (m, 2H), 3.37 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.98, 158.93 (d, *J* = 233.7 Hz), 156.78 (d, *J* = 52.2 Hz), 145.28, 138.80, 130.85 (d, *J* = 13.3 Hz), 129.40 (d, *J* = 8.6 Hz), 126.55 (d, *J* = 3.3 Hz), 126.44, 122.34, 119.06, 116.22, 115.90, 114.40 (d, *J* = 20.4 Hz), 104.90,

36.63, 17.38; MS (ESI): 325.94 $(M+H)^+$.

5-Bromo-N-(5-fluoro-2-methylphenyl)furan-2-carboxamide **(10c)**. The title compound was prepared according to method A and B using 5-bromofuran-2-carboxylic acid (1.90 g, 10 mmol), thionyl chloride (1.45 ml, 20 mmol) and DMF (30 drops) in toluene (50 ml). The corresponding 5-fluoro-2-methylaniline (1.11 ml, 10 mmol) and Et_3N (2.79 ml, 20 mmol) in DCM (50 ml) was added to the acyl chloride. The residue was purified by silica gel column chromatography (petroleum ether /ethyl acetate 4:1) to give 2.1 g (7.04 mmol/ 70 %) of the analytically pure compound (purity: 98.19 %). $C_{12}H_9BrFNO_2$; MW 298.11; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 7.35 (d, J = 3.5 Hz, 1H), 7.29 (ddd, J = 8.5, 6.5, 0.9 Hz, 1H), 7.23 (dd, J = 10.3, 2.8 Hz, 1H), 7.02 (td, J = 8.5, 2.8 Hz, 1H), 6.84 (d, J = 3.6 Hz, 1H), 2.19 (s, 3H); MS (ESI): 298.02, 300.00 $(M+H)^+$.

5-Bromo-N-(5-fluoro-2-methylphenyl)-N-methylfuran-2-carboxamide **(10b)**. The title compound was prepared according to method C using 5-bromo-N-(5-fluoro-2-methylphenyl)furan-2-carboxamide (1.766 g, 5.92 mmol, 1 equiv), NaH (0.284 g, 11.85 mmol, 2 equiv) and iodomethane (0.368 ml, 5.92 mmol, 1 equiv) in DMF (60 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 4:1) to give 1.45 g (4.64 mmol/ 78 %) of the analytically pure compound (purity: 99.97 %). $C_{13}H_{11}BrFNO_2$; MW 312.14; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.39 (dd, J = 8.6, 6.4 Hz, 1H), 7.29 (dd, J = 9.5, 2.7 Hz, 1H), 7.22 (td, J = 8.5, 2.7 Hz, 1H), 6.52 (d, J = 3.6 Hz, 1H), 5.83 (d, J = 3.7 Hz, 1H), 3.21 (s, 3H), 2.08 (s, 3H); MS (ESI): 311.98, 313.96 $(M+H)^+$.

N-(5-Fluoro-2-methylphenyl)-5-(4-methoxyphenyl)-N-methylfuran-2-carboxamide **(10a)**. The title compound was prepared according to method D by the reaction of **10b** (1.13 g, 3.64 mmol, 1 equiv) and (4-methoxyphenyl)boronic acid (0.830 g, 5.46 mmol, 1.5 equiv) in the presence of cesium carbonate (4.74 g, 14.56 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (210 mg, 0.182 mmol, 0.05 equiv) in DME/water 1:1 (80 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 4:1) to give 1.05 g (3.09 mmol/ 85 %) of the analytically pure compound (purity: 96.64 %). $C_{20}H_{18}FNO_3$; MW 339.37; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.45 – 7.39 (m, 1H), 7.30 (dd, J = 9.7, 2.8 Hz, 1H), 7.27 – 7.20 (m, 3H), 6.92 (d, J = 8.5 Hz, 2H), 6.76 (dd, J = 3.7, 1.7 Hz, 1H), 6.58 – 6.53 (m, 1H), 3.77 (s, 3H), 3.24 (s, 3H), 2.12 (s, 3H); MS (ESI): 340.12 $(M+H)^+$.

N-(5-Fluoro-2-methylphenyl)-5-(4-hydroxyphenyl)-N-methylfuran-2-carboxamide **(10)**. The title compound was prepared according to method E by the reaction of **10a** (1.00 g, 2.94 mmol, 1 equiv) and $BF_3.SMe_2$ (3.1 ml, 29.46 mmol, 10 equiv) in dichloromethane (80 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 2:1) to give 0.711 g (2.18 mmol/ 74 %) of the analytically pure compound (purity: 97.27 %). $C_{19}H_{16}FNO_3$; MW 325.34; mp: 184-186 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.79 (s, 1H), 7.44 – 7.38 (m, 1H), 7.28 (dd, J = 9.5, 2.7 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.15 – 7.10 (m, 2H), 6.73 (d, J = 8.3 Hz, 2H), 6.66 (d, J = 3.5 Hz, 1H), 6.51 (s, 1H), 3.23 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.78 (d, J = 243.4 Hz), 158.00, 157.78, 155.21, 145.34, 143.92 (d, J = 10.1 Hz), 132.22 (d, J = 8.8 Hz), 131.53 (d, J = 3.6 Hz), 125.59, 120.36, 118.70, 115.55, 115.19 (d, J = 21.7 Hz), 114.93 (d, J = 20.5 Hz), 104.71, 36.72, 16.26; MS (ESI): 326.14 $(M+H)^+$.

5-Bromo-N-(4-fluoro-2-methylphenyl)furan-2-carboxamide **(11b)**. The title compound was prepared according to method A and B using 5-bromofuran-2-carboxylic acid (1.90 g, 10 mmol), thionyl chloride (1.45 ml, 20 mmol) and DMF (30 drops) in toluene (50 ml). The corresponding 4-fluoro-2-methylaniline (1.11 ml, 10 mmol) and Et_3N (2.79 ml, 20 mmol) in DCM (50 ml) was added to the acyl chloride. The residue was purified by silica gel column chromatography (petroleum ether /ethyl acetate 4:1) to give 2.53 g (8.48 mmol/ 84 %) of the analytically pure compound (purity: 98.11 %). $C_{12}H_9BrFNO_2$; MW 298.11; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 7.34 – 7.26 (m, 2H), 7.14 (ddd, J = 9.6, 3.0, 0.8 Hz, 1H), 7.04 (td, J = 8.6, 3.0 Hz, 1H), 6.83 (d, J = 3.6 Hz, 1H), 2.20 (s, 3H); MS (ESI): 297.99, 300.03 $(M+H)^+$.

5-*Bromo-N-(4-fluoro-2-methylphenyl)-N-methylfuran-2-carboxamide* **(11a)**. The title compound was prepared according to method C using 5-bromo-N-(4-fluoro-2-methylphenyl)furan-2-carboxamide (1.119 g, 3.75 mmol, 1 equiv), NaH (0.18 g, 7.5 mmol, 2 equiv) and iodomethane (0.233 ml, 3.75 mmol, 1 equiv) in DMF (40 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 4:1) to give 0.80 g (2.56 mmol/ 86 %) of the analytically pure compound (purity: 97.32 %). $C_{13}H_{11}BrFNO_2$; MW 312.14; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.34 (dd, J = 8.7, 5.5 Hz, 1H), 7.25 (dd, J = 9.5, 3.0 Hz, 1H), 7.13 (td, J = 8.5, 3.1 Hz, 1H), 6.51 (d, J = 3.6 Hz, 1H), 5.73 (d, J = 3.6 Hz, 1H), 3.20 (s, 3H), 2.12 (s, 3H); MS (ESI): 311.98, 313.97 $(M+H)^+$.

N-(4-fluoro-2-methylphenyl)-5-(4-hydroxyphenyl)-N-methylfuran-2-carboxamide **(11)**. The title

compound was prepared according to method D by the reaction of **11a** (0.750 g, 2.4 mmol, 1 equiv) and (4-hydroxyphenyl) boronic acid (0.496 g, 3.6 mmol, 1.5 equiv) in the presence of cesium carbonate (3.12 g, 9.6 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (138 mg, 0.12 mmol, 0.05 equiv) in DME/water 1:1 (80 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 2:1) to give 0.55 g (1.69 mmol/ 70 %) of the analytically pure compound (purity: 95.22 %). $C_{19}H_{16}FNO_3$; MW 325.34; mp: 196-198 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.35 (dd, J = 8.7, 5.5 Hz, 1H), 7.27 (dd, J = 9.8, 3.0 Hz, 1H), 7.15 (dd, J = 8.6, 3.3 Hz, 3H), 6.73 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 3.6 Hz, 1H), 6.43 (d, J = 3.6 Hz, 1H), 3.22 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.26 (d, J = 244.8 Hz), 157.98, 155.14, 145.42, 139.18 (d, J = 2.6 Hz), 138.19 (d, J = 8.7 Hz), 130.06 (d, J = 9.1 Hz), 125.59, 125.58, 120.40, 118.62, 117.41 (d, J = 22.3 Hz), 115.53, 113.91 (d, J = 22.2 Hz), 104.66, 36.92, 17.04; MS (ESI): 326.11 $(M+H)^+$.

5-Bromo-N-(3-fluoro-2-methylphenyl)furan-2-carboxamide **(12b)**. The title compound was prepared according to method A and B using 5-bromofuran-2-carboxylic acid (1.90 g, 10 mmol), thionyl chloride (1.45 ml, 20 mmol) and DMF (30 drops) in toluene (50 ml). The corresponding 5-fluoro-2-methylaniline (1.11 ml, 10 mmol) and Et_3N (2.79 ml, 20 mmol) in DCM (50 ml) was added to the acyl chloride. The residue was purified by silica gel column chromatography (dichloromethane/methanol 99.5:0.5) to give 2.31 g (7.77 mmol/ 77 %) of the analytically pure compound (purity: 96.67 %). $C_{12}H_9BrFNO_2$; MW 298.11; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (s, 1H), 7.34 (d, J = 3.6 Hz, 1H), 7.25 (tdd, J = 8.2, 6.4, 0.7 Hz, 1H), 7.20 – 7.13 (m, 1H), 7.09 (ddd, J = 9.6, 8.3, 1.3 Hz, 1H), 6.84 (d, J = 3.5 Hz, 1H), 2.09 (s, 3H); MS (ESI): 297.88, 299.97 $(M+H)^+$.

5-Bromo-N-(3-fluoro-2-methylphenyl)-N-methylfuran-2-carboxamide **(12a)**. The title compound was prepared according to method C using 5-bromo-N-(3-fluoro-2-methylphenyl)furan-2-carboxamide (1.319 g, 7.77 mmol, 1 equiv), NaH (0.373 g, 15.55 mmol, 2 equiv) and iodomethane (0.483 ml, 7.77 mmol, 1 equiv) in DMF (70 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 3:1) to give 1.97 g (6.31 mmol/ 81 %) of the analytically pure compound (purity: 98.04 %). $C_{13}H_{11}BrFNO_2$; MW 312.14; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37 – 7.24 (m, 2H), 7.18 – 7.13 (m, 1H), 6.51 (d, J = 3.6 Hz, 1H), 5.86 (d, J = 3.6 Hz, 1H), 3.22 (s, 3H), 2.04 (s, 3H); MS (ESI): 311.94, 313.95 $(M+H)^+$.

N-(3-Fluoro-2-methylphenyl)-5-(4-hydroxyphenyl)-N-methylfuran-2-carboxamide **(12)**. The title compound was prepared according to method D by the reaction of **12a** (1.55 g, 4.97 mmol, 1 equiv) and (4-hydroxyphenyl) boronic acid (1.029 g, 7.45 mmol, 1.5 equiv) in the presence of cesium carbonate (6.47 g, 19.88 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (287 mg, 0.248 mmol, 0.05 equiv) in DME/water 1:1 (100 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 2:1) to give 1.33 g (4.08 mmol/ 82 %) of the analytically pure compound (purity: 99.99 %). $C_{19}H_{16}FNO_3$; MW 325.34; mp: 195-197 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.38 – 7.31 (m, 1H), 7.28 (t, *J* = 8.9 Hz, 1H), 7.17 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.75 – 6.70 (m, 2H), 6.66 (d, *J* = 3.1 Hz, 1H), 6.53 (t, *J* = 2.5 Hz, 1H), 3.24 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.09 (d, *J* = 243.4 Hz), 157.97 (d, *J* = 10.4 Hz), 155.20, 145.30, 144.55 (d, *J* = 2.7 Hz), 127.89 (d, *J* = 9.4 Hz), 125.54, 124.24, 122.85 (d, *J* = 17.0 Hz), 120.34, 118.79, 115.53, 115.44, 114.71 (d, *J* = 22.4 Hz), 104.72, 37.01, 9.29; MS (ESI): 326.07 $(M+H)^+$.

5-Bromo-N-(3-methylpyridin-2-yl)furan-2-carboxamide **(25b)**. To a suspension of 5-bromofuran-2-carboxylic acid (1.00 g, 5.23 mmol, 1 equiv), DCC (1.08 g, 5.23 mmol, 1 equiv), DMAP (31 mg, 0.261 mmol, 0.05 equiv) in 40 ml DCM at 0 °C 4-methylpyridin-3-amine (0.565 g, 5.23 mmol, 1 equiv) was added. The mixture was stirred at room temperature overnight. The mixture was quenched with water (50 mL) and extracted three times with ethyl acetate (3 x 30 mL). The organic layer was washed with water, dried over MgSO4, filtered and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/methanol 94:6) to give 0.956 g (3.4 mmol/ 65 %) of the analytically pure compound (purity: 99.99 %). $C_{11}H_9BrN_2O_2$; MW 281.11; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.52 (s, 1H), 8.31 (ddd, *J* = 4.7, 1.9, 0.7 Hz, 1H), 7.73 (ddd, *J* = 7.6, 1.9, 0.8 Hz, 1H), 7.41 (d, *J* = 3.6 Hz, 1H), 7.27 (dd, *J* = 7.5, 4.8 Hz, 1H), 6.84 (d, *J* = 3.6 Hz, 1H), 2.18 (s, 3H); MS (ESI): 280.95, 282.94 $(M+H)^+$.

5-Bromo-N-methyl-N-(3-methylpyridin-2-yl)furan-2-carboxamide **(25a)**. The title compound was prepared according to method C using 5-bromo-N-(3-methylpyridin-2-yl)furan-2-carboxamide (0.866 g, 3.08 mmol, 1 equiv), NaH (0.147 g, 6.16 mmol, 2 equiv) and iodomethane (0.191 ml, 3.08 mmol, 1 equiv) in DMF (30 ml). The product was purified by column chromatography (dichloromethane/methanol 97:3) to give 0.754 g (2.55 mmol/ 82 %) of the analytically pure

compound (purity: 99.99 %). $C_{12}H_{11}BrN_2O_2$; MW 295.14; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.83 (ddd, *J* = 7.6, 1.8, 0.9 Hz, 1H), 7.40 (dd, *J* = 7.6, 4.7 Hz, 1H), 6.55 (d, *J* = 3.5 Hz, 1H), 6.13 (s, 1H), 3.25 (s, 3H), 2.17 (s, 3H); MS (ESI): 294.99, 297.00 $(M+H)^+$.

5-(4-Hydroxyphenyl)-N-methyl-N-(3-methylpyridin-2-yl)furan-2-carboxamide **(25)**. The title compound was prepared according to method D by the reaction of **25a** (0.7 g, 2.37 mmol, 1 equiv) and (4-hydroxyphenyl) boronic acid (0.49 g, 3.55 mmol, 1.5 equiv) in the presence of cesium carbonate (3.08 g, 9.48 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (136 mg, 0.118 mmol, 0.05 equiv) in DME/water 1:1 (40 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 1:1) to give 0.55 g (1.78 mmol/ 75 %) of the analytically pure compound (purity: 99.99 %). $C_{18}H_{16}N_2O_3$; MW 308.34; mp: 202-204 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.35 (ddd, *J* = 4.7, 2.0, 0.7 Hz, 1H), 7.85 (ddd, *J* = 7.6, 1.9, 0.8 Hz, 1H), 7.39 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.04 (s, 2H), 6.74 – 6.69 (m, 2H), 6.68 (s, 2H), 3.25 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.32, 157.99, 155.18, 155.08, 146.86, 145.69, 140.18, 130.24, 125.55, 123.67, 120.26, 118.52, 115.55, 104.75, 35.07, 16.70.; MS (ESI): 309.09 $(M+H)^+$.

5-Bromo-N-(4-methylpyridin-3-yl)furan-2-carboxamide **(26b)**. To a suspension of 5-bromofuran-2-carboxylic acid (1.00 g, 5.23 mmol, 1 equiv), DCC (1.08 g, 5.23 mmol, 1 equiv), DMAP (31 mg, 0.261 mmol, 0.05 equiv) in 40 ml DCM at 0 °C 4-methylpyridin-3-amine (0.565 g, 5.23 mmol, 1 equiv) was added. The mixture was stirred at room temperature overnight. The mixture was quenched with water (50 mL) and extracted three times with ethyl acetate (3 x 30 mL). The organic layer was washed with water, dried over MgSO4, filtered and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/methanol 94:6) to give 1.1 g (3.91 mmol/ 74 %) of the analytically pure compound (purity: 92.05 %). $C_{11}H_9BrN_2O_2$; MW 281.11; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.43 (s, 1H), 8.33 (d, *J* = 5.0 Hz, 1H), 7.38 – 7.29 (m, 2H), 6.85 (d, *J* = 3.5 Hz, 1H), 2.22 (s, 3H); MS (ESI): 280.93, 282.94 $(M+H)^+$.

5-Bromo-N-methyl-N-(4-methylpyridin-3-yl)furan-2-carboxamide **(26a)**. The title compound was prepared according to method C using 5-bromo-N-(4-methylpyridin-3-yl)furan-2-carboxamide (0.94 g, 3.34 mmol, 1 equiv), NaH (0.16 g, 6.68 mmol, 2 equiv) and iodomethane (0.207 ml,

3.34 mmol, 1 equiv) in DMF (30 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 1:1) to give 0.65 g (2.2 mmol/ 65 %) of the analytically pure compound (purity: 97.69 %). $C_{12}H_{11}BrN_2O_2$; MW 295.14; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (d, J = 5.0 Hz, 1H), 8.42 (s, 1H), 7.41 (d, J = 5.0 Hz, 1H), 6.52 (d, J = 3.6 Hz, 1H), 6.01 (d, J = 3.7 Hz, 1H), 3.24 (s, 3H), 2.19 (s, 3H); MS (ESI): 294.97, 296.97 $(M+H)^+$.

5-(4-Hydroxyphenyl)-N-methyl-N-(4-methylpyridin-3-yl)furan-2-carboxamide **(26)**. The title compound was prepared according to method D by the reaction of **26a** (0.453 g, 1.53 mmol, 1 equiv) and (4-hydroxyphenyl) boronic acid (0.317 g, 2.3 mmol, 1.5 equiv) in the presence of cesium carbonate (1.99 g, 6.12 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (88 mg, 0.076 mmol, 0.05 equiv) in DME/water 1:1 (40 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 4:1) to give 0.33 g (1.07 mmol/ 70 %) of the analytically pure compound (purity: 96.89 %). $C_{18}H_{16}N_2O_3$; MW 308.34; mp: 174-176 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.51 – 8.45 (m, 2H), 7.45 (d, J = 5.0 Hz, 1H), 7.03 (d, J = 8.2 Hz, 2H), 6.72 (d, J = 8.3 Hz, 2H), 6.69 – 6.65 (m, 2H), 3.27 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.04, 157.97, 155.33, 148.91, 148.61, 145.36, 144.53, 139.93, 125.87, 125.56, 120.25, 119.18, 115.56, 104.77, 37.07, 16.42; MS (ESI): 309.14 $(M+H)^+$.

5-Bromo-N-(2-methylpyridin-3-yl)furan-2-carboxamide **(27b)**. To a suspension of 5-bromofuran-2-carboxylic acid (1.00 g, 5.23 mmol, 1 equiv), DCC (1.08 g, 5.23 mmol, 1 equiv), DMAP (31 mg, 0.261 mmol, 0.05 equiv) in 40 ml DCM at 0 °C 4-methylpyridin-3-amine (0.565 g, 5.23 mmol, 1 equiv) was added. The mixture was stirred at room temperature overnight. The mixture was quenched with water (50 mL) and extracted three times with ethyl acetate (3 x 30 mL). The organic layer was washed with water, dried over MgSO4, filtered and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/methanol 94:6) to give 1.3 g (4.62 mmol/ 88 %) of the analytically pure compound (purity: 99.99 %). $C_{11}H_9BrN_2O_2$; MW 281.11; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.52 (dd, J = 5.2, 1.5 Hz, 1H), 8.12 – 8.06 (m, 1H), 7.58 (dd, J = 8.1, 5.2 Hz, 1H), 7.41 (dd, J = 3.6, 1.6 Hz, 1H), 6.88 (d, J = 3.5 Hz, 1H), 2.52 (s, 3H); MS (ESI): 280.94, 282.94 $(M+H)^+$.

5-Bromo-N-methyl-N-(2-methylpyridin-3-yl)furan-2-carboxamide **(27a)**. The title compound was prepared according to method C using 5-bromo-N-(2-methylpyridin-3-yl)furan-2-carboxamide

(0.9 g, 3.2 mmol, 1 equiv), NaH (0.153 g, 6.4 mmol, 2 equiv) and iodomethane (0.199 ml, 3.20 mmol, 1 equiv) in DMF (30 ml). The product was purified by column chromatography (dichloromethane/methanol 97:3) to give 0.82 g (2.77 mmol/ 86 %) of the analytically pure compound (purity: 95.81 %). $C_{12}H_{11}BrN_2O_2$; MW 295.14; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 – 8.48 (m, 1H), 7.74 (dd, J = 7.9, 1.7 Hz, 1H), 7.35 (dd, J = 7.9, 4.8 Hz, 1H), 6.53 (d, J = 3.5 Hz, 1H), 6.00 (d, J = 3.1 Hz, 1H), 3.24 (s, 3H), 2.31 (s, 3H); MS (ESI): 294.97, 296.98 $(M+H)^+$.

5-(4-Hydroxyphenyl)-N-methyl-N-(2-methylpyridin-3-yl)furan-2-carboxamide **(27)**. The title compound was prepared according to method D by the reaction of **27a** (0.6 g, 2.03 mmol, 1 equiv) and (4-hydroxyphenyl) boronic acid (0.42 g, 3.04 mmol, 1.5 equiv) in the presence of cesium carbonate (2.64 g, 8.12 mmol, 4 equiv) and tetrakis(triphenylphosphine) palladium (117 mg, 0.101 mmol, 0.05 equiv) in DME/water 1:1 (40 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 1:1) to give 0.466 g (1.15 mmol/ 74 %) of the analytically pure compound (purity: 99.99 %). $C_{18}H_{16}N_2O_3$; MW 308.34; mp: 199-201 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.54 – 8.49 (m, 1H), 7.75 (dd, J = 7.9, 1.6 Hz, 1H), 7.37 (dd, J = 7.9, 4.7 Hz, 1H), 7.03 (d, J = 8.0 Hz, 2H), 6.71 (d, J = 8.2 Hz, 2H), 6.67 (s, 2H), 3.26 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.04, 157.77, 155.82, 155.37, 148.20, 145.40, 138.94, 135.91, 125.58, 122.60, 120.25, 119.23, 115.55, 104.76, 36.82, 20.24; MS (ESI): 309.11 $(M+H)^+$.

4-Methoxybenzohydrazide **(31d)**.The title compound was prepared by refluxing methyl 4-methoxybenzoate (1.00 g, 6.01 mmol, 1 equiv) with the mixture of hydrazine hydrate (2.91 ml, 60.17 mmol, 10 equiv) and methanol (15 mL) for 6 h. The excess hydrazine and methanol were evaporated to give the crude product which was recrystallized from methanol to give 0.85 g (5.11 mmol/ 85 %) of the analytically pure compound (purity: 96.49 %). $C_8H_{10}N_2O_2$; MW 166.18; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.60 (s, 1H), 7.80 (d, 2H), 6.97 (d, 2H), 4.41 (s, 2H), 3.79 (s, 3H); MS (ESI): 166.80 $(M+H)^+$.

Ethyl 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-carboxylate **(31c)**. A mixture of 4-methoxybenzohydrazide (0.8 g, 4.81 mmol, 1 equiv), DIPEA (0.905 ml, 5.29 mmol, 1.1 equiv) and DMAP (58 mg, 0.481 mmol, 0.1 equiv) was dissolved in DCM (20 ml) and treated with ethyl 2-chloro-2-oxoacetate (0.592 ml, 5.29 mmol, 1.1 equiv) dropwise at 0 °C. The reaction

mixture was slowly warmed to room temperature and stirred overnight. Later, it was treated with Et_3N (0.671 ml, 4.81 mmol, 1 equiv) /TsCl (0.916 g, 4.81 mmol, 1 equiv) and stirred it overnight. The reaction mixture was diluted with EtOAc/DCM and washed with water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was collected, concentrated, and purified by column chromatography (petroleum ether /ethyl acetate 5:1) to give 0.98 g (3.94 mmol/ 82 %) of the analytically pure compound (purity: 94.79 %). $C_{12}H_{12}N_2O_4$; MW 248.08; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01 (d, 2H), 7.18 (d, 2H), 4.45 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); MS (ESI): 248.98 $(M+H)^+$.

Potassium 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-carboxylate **(31b)**. Ethyl 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-carboxylate (0.9 g, 3.62 mmol, 1 equiv) was dissolved in THF/EtOH (10 mL/5 mL) and treated with KOH (0.203 g, 3.62 mmol, 1 equiv) in H_2O (1 mL) at 0°C, the resulting mixture stirred for 2 h at 0°C. The product, Potassium 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-carboxylate, precipitated out from the solution and was separated by filtration and used for the next step without further purification to give 0.88 g (3.4 mmol/ 94 %) of the desired potassium salt. $C_{10}H_7KN_2O_4$; MW 258.27; ^{1}H NMR (500 MHz, Deuterium Oxide) δ 7.75 (d, 2H), 6.97 (d, 2H), 3.85 (s, 3H).

5-(4-Methoxyphenyl)-N-methyl-N-(o-tolyl)-1,3,4-oxadiazole-2-carboxamide **(31a)**. To a stirred suspension of potassium 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-carboxylate (0.8 g, 3.09 mmol, 1 equiv) in acetonitrile (25 mL) at 0 °C, oxalyl chloride (0.471 g, 3.71 mmol, 1.2 equiv) was added dropwise over 10 min. DMF (5 drops) was added to the reaction mixture, and vigorous gas evolution was observed. The resulting reaction mixture was stirred for further 2 h to form acyl chloride. The solvent was removed under reduced pressure. N,2-dimethylaniline (0.386 ml, 3.09 mmol, 1 equiv) and DIPEA (1.37 ml, 7.72 mmol, 2.5 equiv) were dissolved in DCM (25 mL) and added at 0 °C to the acyl chloride. The reaction mixture was stirred for 30 min at 0 °C, after which it was allowed to warm up to room temperature and stirred overnight. The mixture was quenched with water (20 mL) and extracted twice with DCM (2 x 15 ml); the organic layer was dried over MgSO4, filtered and the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether /ethyl acetate 4:1) to give 0.7 g (2.16 mmol/ 70 %) of the analytically pure compound (purity: 99.99 %). $C_{18}H_{17}N_3O_3$; MW 323.35; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.77 – 7.65 (m, 2H), 7.37 –

7.24 (m, 3H), 7.20 (td, *J* = 7.2, 6.7, 1.8 Hz, 1H), 7.16 – 7.04 (m, 2H), 3.85 (s, 3H), 3.33 (s, 3H), 2.27 (s, 3H); MS (ESI): 323.99 $(M+H)^+$.

5-(4-Hydroxyphenyl)-N-methyl-N-(o-tolyl)-1,3,4-oxadiazole-2-carboxamide **(31)**. The title compound was prepared according to method E by the reaction of **31a** (0.68 g, 2.10 mmol, 1 equiv) and $BF_3.SMe_2$ (2.21 ml, 21.02 mmol, 10 equiv) in dichloromethane (50 ml). The product was purified by column chromatography (dichloromethane/methanol 95:5) to give 0.5 g (1.61 mmol/ 77 %) of the analytically pure compound (purity: 99.00 %). $C_{17}H_{15}N_3O_3$; MW 309.33; mp: 210-212 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.41 (s, 1H), 7.64 – 7.58 (m, 2H), 7.34 – 7.31 (m, 1H), 7.28 (ddd, *J* = 6.6, 3.7, 2.2 Hz, 2H), 7.23 – 7.17 (m, 1H), 6.93 – 6.85 (m, 2H), 3.33 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.01, 161.35, 157.24, 154.66, 140.91, 135.44, 131.02, 128.83, 128.79, 128.06, 127.10, 116.26, 112.90, 36.77, 17.03; MS (ESI):): 309.93 $(M+H)^+$.

Ethyl 2-(4-methoxyphenyl)oxazole-4-carboxylate **(32c)**. A mixture of 4-methoxy benzamide (0.6 g, 3.96 mmol, 1 equiv) and ethyl bromopyruvate (0.597 ml, 4.76 mmol, 1.2 equiv) was refluxed in ethanol (40 ml) for 5 h. The solvent was removed under reduced pressure. The residue was quenched with water, then extracted twice with ethyl acetate (2 x 15 ml). The organic layers were combined, dried over magnesium sulfate and concentrated to dryness under reduced pressure. The product was purified by column chromatography (petroleum ether /ethyl acetate 3:1) to give 0.75 g (3.03 mmol/ 76 %) of the analytically pure compound (purity: 94.68 %). $C_{13}H_{13}NO_4$; MW 247.25; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.94 (d, 2H), 7.10 (d, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); MS (ESI): 247.98 $(M+H)^+$.

2-(4-Methoxyphenyl)oxazole-4-carboxylic acid **(32b)**. Ethyl 2-(4-methoxyphenyl)oxazole-4-carboxylate (0.7 g, 2.83 mmol, 1 equiv) was dissolved in THF/EtOH (15 mL/7.5 mL) and treated with KOH (0.158 g, 2.83 mmol, 1 equiv) in H_2O (1 mL) at 0°C, the resulting mixture stirred for 2 h at 0°C. The solvent was removed under reduced pressure. The residue was quenched with water, acidified with 2 M HCl to pH 2 and extracted twice with ethyl acetate (2 x 10 ml). The organic layers were combined, dried over magnesium sulfate and concentrated to dryness under reduced pressure. The product was purified by column chromatography (petroleum ether /ethyl acetate 2:1) to give 0.45 g (2.05 mmol/ 72 %) of the analytically pure compound (purity: 95.74 %). $C_{11}H_9NO_4$; MW 219.20;^{1}H NMR (500 MHz, DMSO-d_6) δ 13.09 (s, 1H), 8.77 (s, 1H), 7.94

(d, J = 9.0 Hz, 2H), 7.11 (d, J = 8.9 Hz, 1H), 3.84 (s, 3H); MS (ESI): 219.94 $(M+H)^+$.

2-(4-Methoxyphenyl)-N-methyl-N-(o-tolyl)oxazole-4-carboxamide **(32a)**. The title compound was prepared according to method A and B using 2-(4-methoxyphenyl)oxazole-4-carboxylic acid (0.4 g, 1.82 mmol), thionyl chloride (0.264 ml, 3.64 mmol) and DMF (5 drops) in toluene (10 ml). The corresponding N,2-dimethylaniline (0.227 ml, 1.82 mmol) and Et_3N (0.508 ml, 3.64 mmol) in DCM (10 ml) was added to the acyl chloride. The residue was purified by silica gel column chromatography (petroleum ether /ethyl acetate 2:1) to give 0.499 g (1.54 mmol/ 85 %) of the analytically pure compound (purity: 99.44 %). $C_{19}H_{18}N_2O_3$; MW 322.36; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.70 – 7.64 (m, 2H), 7.46 (s, 1H), 7.35 – 7.25 (m, 2H), 7.28 – 7.21 (m, 2H), 7.05 – 6.99 (m, 2H), 3.79 (s, 3H), 3.24 (s, 3H), 2.17 (s, 3H); MS (ESI): 322.96 $(M+H)^+$.

2-(4-Hydroxyphenyl)-N-methyl-N-(o-tolyl)oxazole-4-carboxamide **(32)**. The title compound was prepared according to method E by the reaction of **32a** (0.45 g, 1.39 mmol, 1 equiv) and $BF_3.SMe_2$ (1.46 ml, 13.95 mmol, 10 equiv) in dichloromethane (30 ml). The product was purified by column chromatography (dichloromethane/methanol 97:3) to give 0.31 g (1.00 mmol/ 72 %) of the analytically pure compound (purity: 99.91 %). $C_{18}H_{16}N_2O_3$; MW 308.34; mp: 220-222 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.10 (s, 1H), 7.60 – 7.54 (m, 2H), 7.38 (s, 1H), 7.35 – 7.25 (m, 2H), 7.28 – 7.21 (m, 2H), 6.82 (dd, J = 9.0, 2.5 Hz, 2H), 3.24 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.93, 159.98, 159.96, 142.42, 140.37, 136.02, 135.51, 130.94, 128.35, 128.32, 127.86, 127.12, 117.15, 115.82, 36.49, 17.10; MS (ESI): 308.98 $(M+H)^+$.

2-(4-Methoxyphenyl)thiazole-4-carboxylic acid **(33b)**. The title compound was prepared according to method D by the reaction of ethyl 2-bromothiazole-4-carboxylate (1.00 g, 4.23 mmol, 1 equiv) and (4-methoxyphenyl)boronic acid (0.965 g, 6.35 mmol, 1.5 equiv) in the presence of sodium carbonate (2.24 g, 21.15 mmol, 5 equiv) and tetrakis(triphenylphosphine) palladium (244 mg, 0.211 mmol, 0.05 equiv) in toluene/ethanol 1:1 (50 ml). The product was purified by column chromatography (dichloromethane/methanol 90:10) to give 0.87 g (3.69 mmol/ 87 %) of the analytically pure compound (purity: 99.99 %). $C_{11}H_9NO_3S$; MW 235.26; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.05 (s, 1H), 8.41 (s, 1H), 7.91 (d, 2H), 7.08 (d, 2H), 3.83 (s, 3H); MS (ESI): 236.00 $(M+H)^+$.

2-(4-Methoxyphenyl)-N-methyl-N-(o-tolyl)thiazole-4-carboxamide **(33a)**. The title compound

was prepared according to method A and B using 2-(4-methoxyphenyl)thiazole-4-carboxylic acid (0.85 g, 3.61 mmol), thionyl chloride (0.524 ml, 7.22 mmol) and DMF (10 drops) in toluene (20 ml). The corresponding N,2-dimethylaniline (0.45 ml, 3.6 mmol) and Et_3N (1.00 ml, 7.22 mmol) in DCM (20 ml) was added to the acyl chloride. The residue was purified by silica gel column chromatography (petroleum ether /ethyl acetate 3:1) to give 0.98 g (2.98 mmol/ 80 %) of the analytically pure compound (purity: 98.76 %). $C_{19}H_{18}N_2O_2S$; MW 338.43; ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.83 (s, 1H), 7.54 – 7.47 (m, 2H), 7.28 (ddt, J = 7.5, 1.4, 0.7 Hz, 1H), 7.22 – 7.05 (m, 3H), 6.95 – 6.88 (m, 2H), 3.82 (s, 3H), 3.32 (s, 3H), 2.29 (s, 3H); MS (ESI): 339.05 $(M+H)^+$.

2-(4-Hydroxyphenyl)-N-methyl-N-(o-tolyl)thiazole-4-carboxamide **(33)**. The title compound was prepared according to method E by the reaction of **33a** (0.650 g, 1.92 mmol, 1 equiv) and $BF_3.SMe_2$ (2.00 ml, 19.2 mmol, 10 equiv) in dichloromethane (40 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 2:1) to give 0.359 g (1.1 mmol/ 57 %) of the analytically pure compound (purity: 99.99 %). $C_{18}H_{16}N_2O_2S$; MW 324.40; mp: 237-239 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.97 (s, 1H), 7.81 (s, 1H), 7.40 – 7.34 (m, 2H), 7.30 – 7.23 (m, 1H), 7.21 – 7.10 (m, 3H), 6.75 (dd, J = 9.0, 2.5 Hz, 2H), 3.26 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.68, 162.79, 159.52, 150.23, 143.44, 135.24, 130.51, 128.00, 127.76, 127.54, 126.66, 123.85, 122.97, 115.66, 36.83, 17.40; MS (ESI): 324.94 $(M+H)^+$.

2-(4-Methoxyphenyl)thiazole-5-carboxylic acid **(34b)**. The title compound was prepared according to method D by the reaction of methyl 2-bromothiazole-5-carboxylate (1.00 g, 4.5 mmol, 1 equiv) and (4-methoxyphenyl)boronic acid (1.02 g, 6.75 mmol, 1.5 equiv) in the presence of sodium carbonate (2.38 g, 22.5 mmol, 5 equiv) and tetrakis(triphenylphosphine) palladium (260 mg, 0.225 mmol, 0.05 equiv) in toluene/ethanol 1:1 (50 ml). The product was purified by column chromatography (dichloromethane/methanol 90:10) to give 0.89 g (3.78 mmol/ 84 %) of the analytically pure compound (purity: 94.68 %). $C_{11}H_9NO_3S$; MW 235.26; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.50 (s, 1H), 8.35 (s, 1H), 8.00 – 7.93 (m, 2H), 7.12 – 7.05 (m, 2H), 3.84 (s, 3H); MS (ESI): 236.01 $(M+H)^+$.

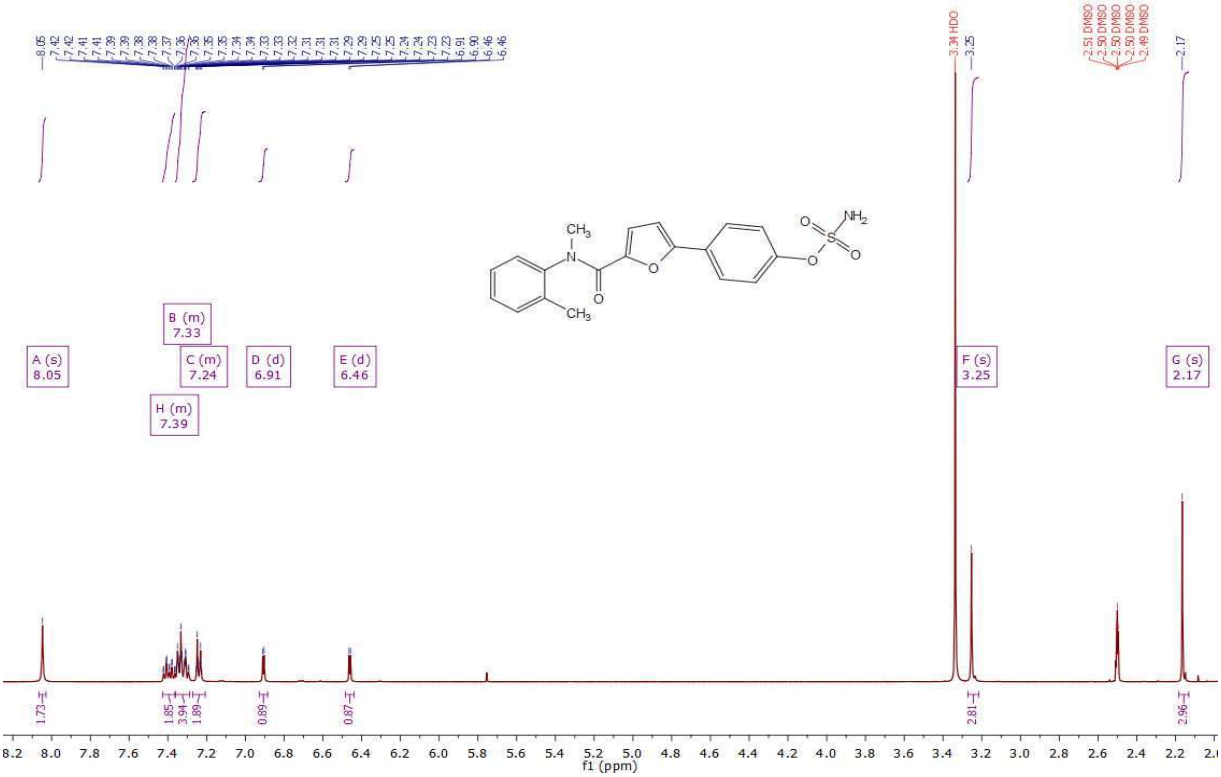
2-(4-Methoxyphenyl)-N-methyl-N-(o-tolyl)thiazole-5-carboxamide **(34a)**. The title compound was prepared according to method A and B using 2-(4-methoxyphenyl)thiazole-5-carboxylic acid (0.80 g, 3.4 mmol), thionyl chloride (0.493 ml, 6.8 mmol) and DMF (10 drops) in toluene

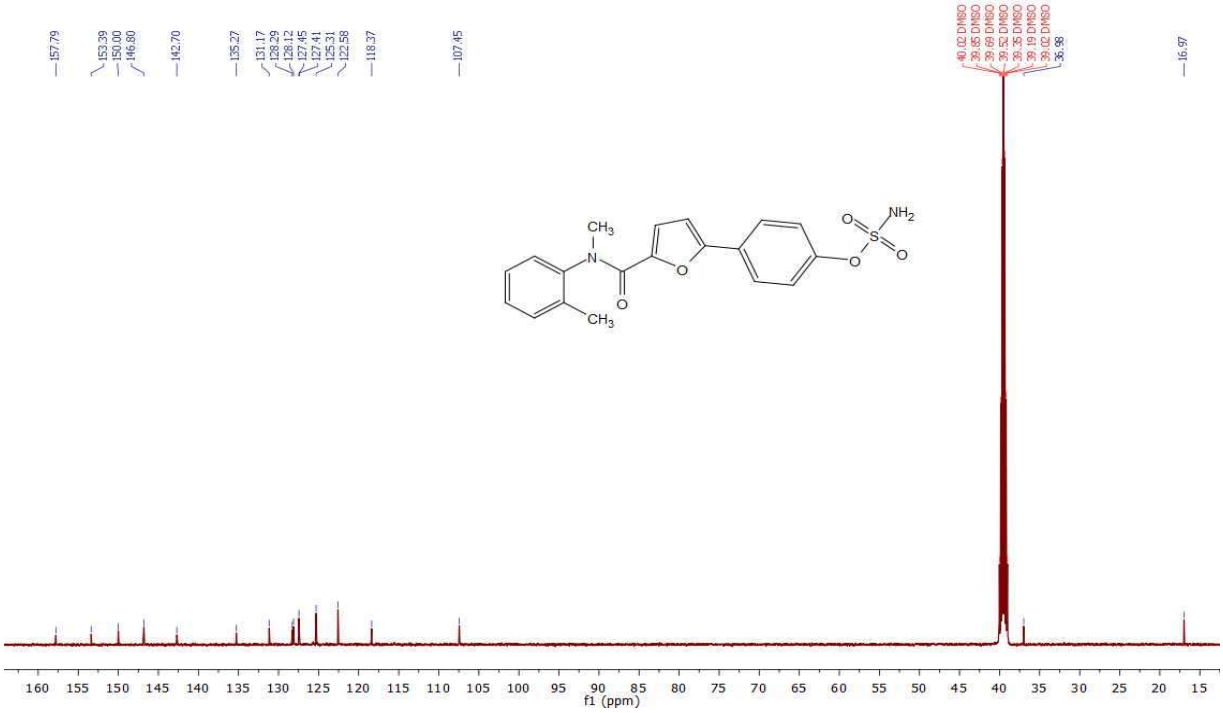
(20 ml). The corresponding N,2-dimethylaniline (0.424 ml, 3.4 mmol) and Et_3N (0.95 ml, 6.8 mmol) in DCM (20 ml) was added to the acyl chloride. The residue was purified by silica gel column chromatography (petroleum ether /ethyl acetate 4:1) to give 0.85 g (2.51 mmol/ 73 %) of the analytically pure compound (purity: 95.60 %). $C_{19}H_{18}N_2O_2S$; MW 338.43; ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.82 – 7.75 (m, 2H), 7.48 – 7.40 (m, 2H), 7.43 – 7.35 (m, 2H), 7.15 (s, 1H), 7.03 – 6.96 (m, 2H), 3.85 (s, 3H), 3.33 (s, 3H), 2.23 (s, 3H); MS (ESI): 339.05 $(M+H)^+$.

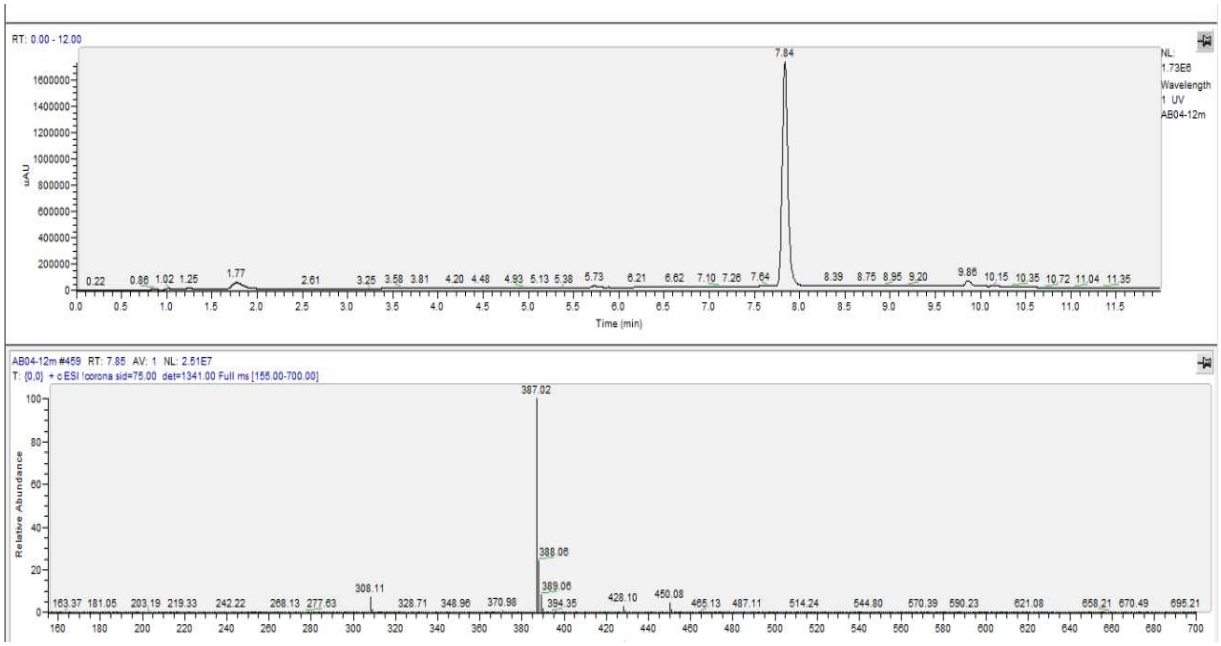
2-(4-Hydroxyphenyl)-N-methyl-N-(o-tolyl)thiazole-5-carboxamide **(34)**. The title compound was prepared according to method E by the reaction of **34a** (0.8 g, 2.36 mmol, 1 equiv) and $BF_3.SMe_2$ (2.48 ml, 23.6 mmol, 10 equiv) in dichloromethane (50 ml). The product was purified by column chromatography (petroleum ether /ethyl acetate 3:1) to give 0.5 g (1.54 mmol/ 65 %) of the analytically pure compound (purity: 99.00 %). $C_{18}H_{16}N_2O_2S$; MW 324.40; mp: 219-221 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.12 (s, 1H), 7.64 – 7.59 (m, 2H), 7.43 (dt, J = 8.8, 5.8 Hz, 2H), 7.37 (dd, J = 5.1, 2.3 Hz, 2H), 7.10 (s, 1H), 6.82 (dd, J = 9.1, 2.5 Hz, 2H), 3.27 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.94, 160.22, 160.09, 146.43, 141.59, 135.98, 131.66, 131.36, 129.40, 128.99, 128.04, 127.89, 123.50, 116.00, 36.96, 16.88; MS (ESI): 324.98 $(M+H)^+$.

2. Representative ^{1}HNMR, ^{13}CNMR and MS spectra of compounds 13, 17, 19, 33 and 37.

Compound **13**:



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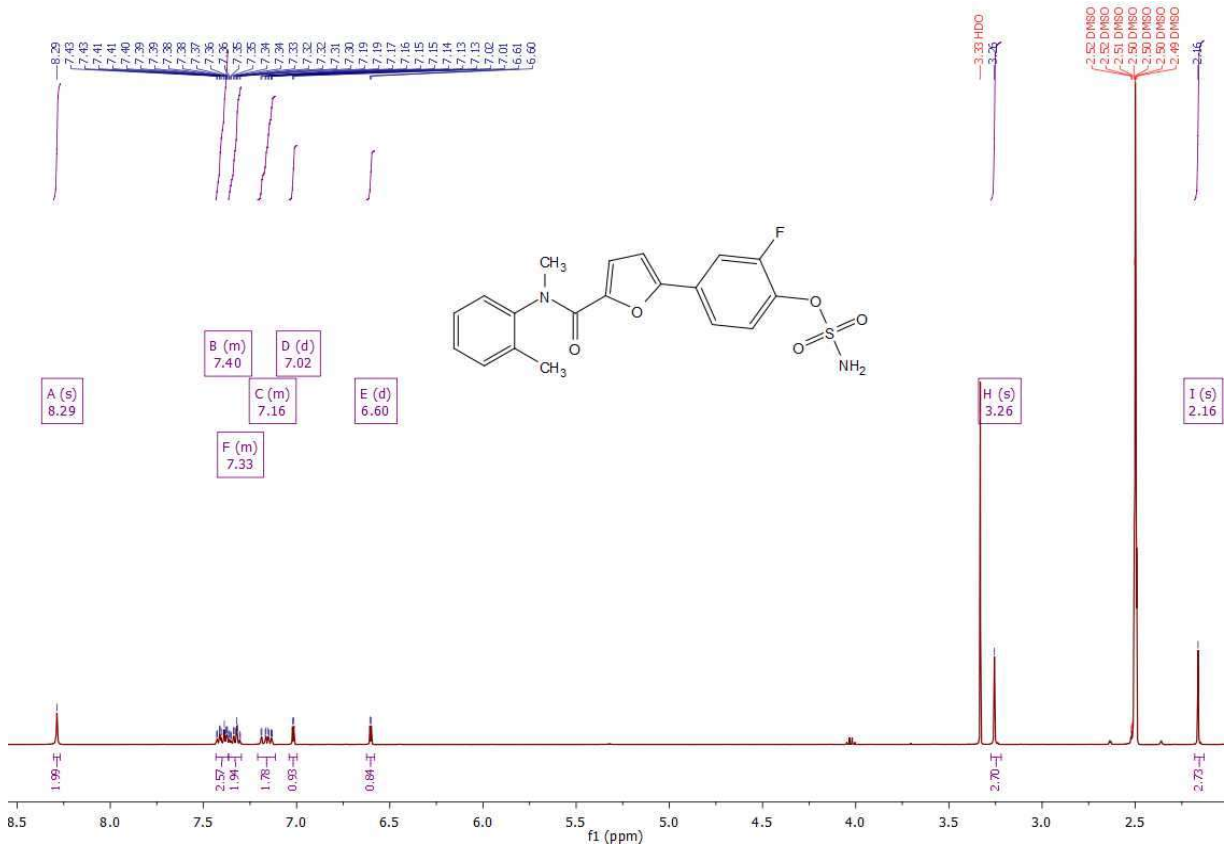
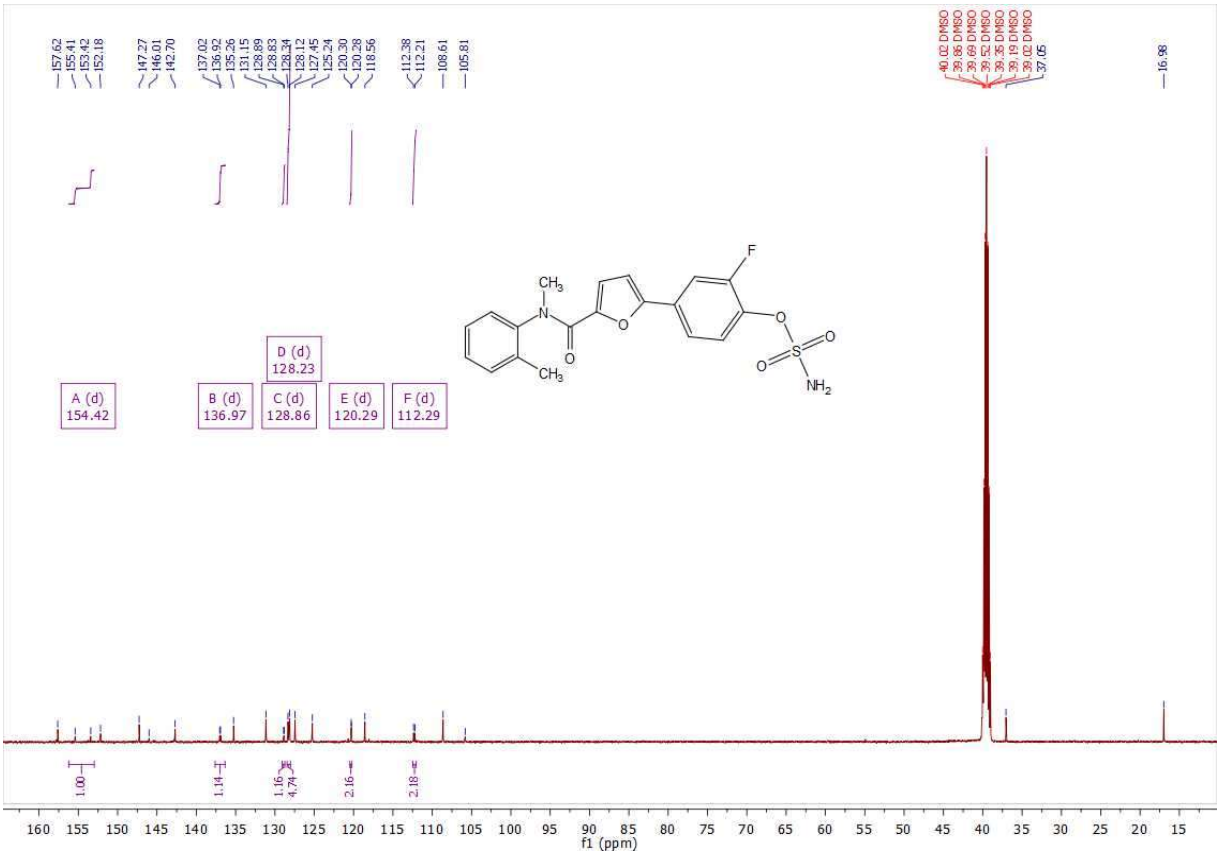
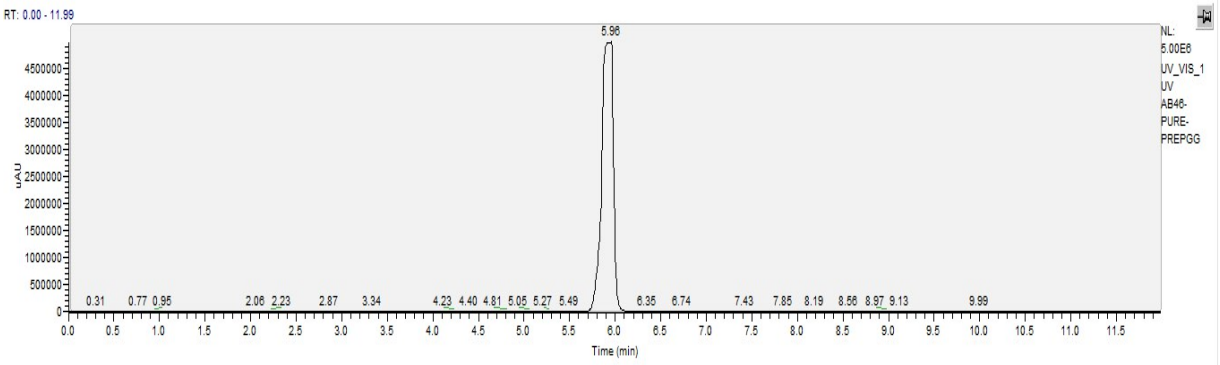
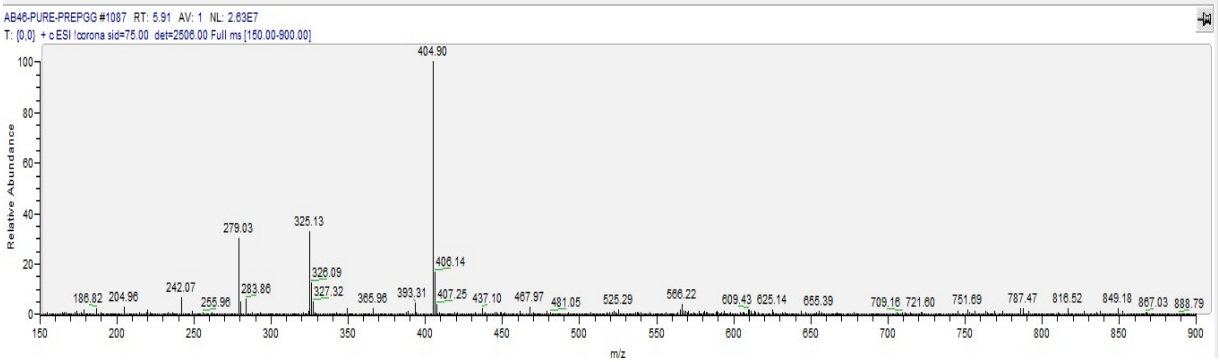
NL:
1.73E6
Wavelength
1 UV
AB04-12m
uAU
Time (min)
AB04-12m #459 RT: 7.85 AV: 1 NL: 2.51E7
T: {0,0} + c ESI !corona sid=75.00 det=1341.00 Full ms [155.00-700.00]
387.02
388.06
389.06
308.11
Relative Abundance

Compound **17**:

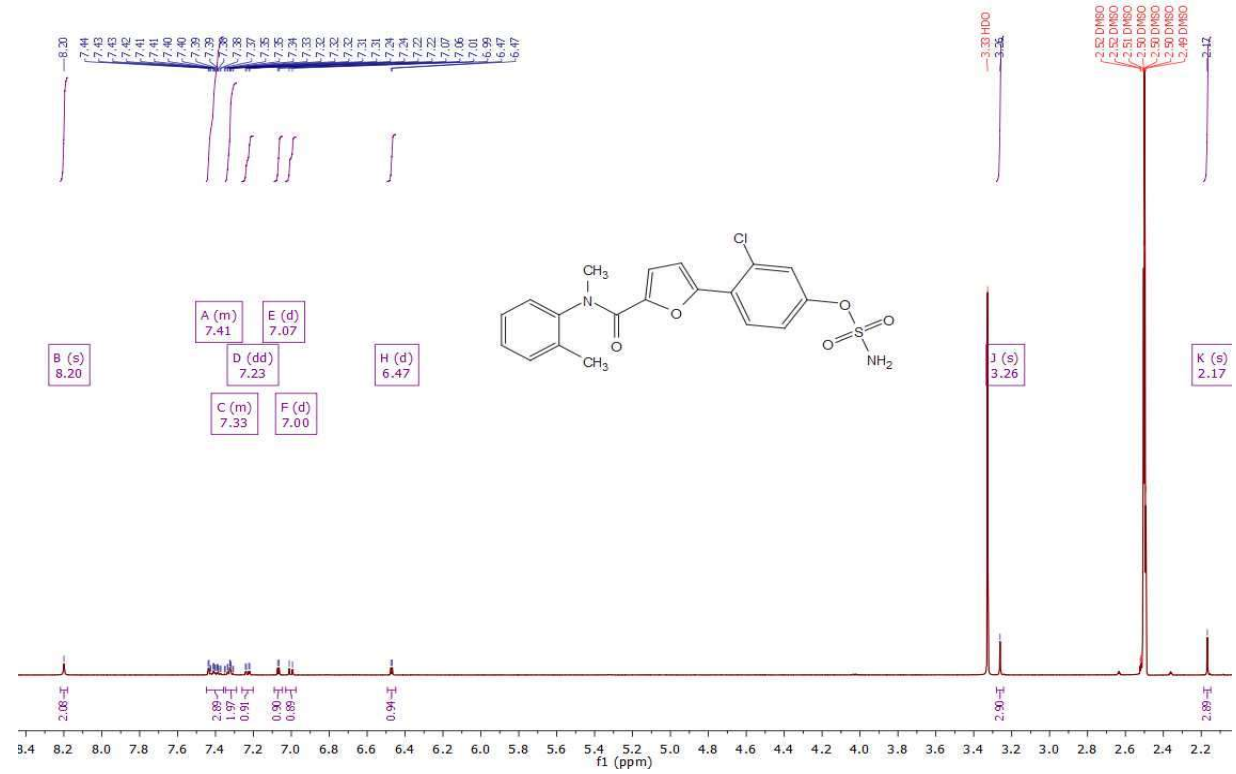

A (s)
8.29
B (m)
7.40
C (m)
7.16
D (d)
7.02
E (d)
6.60
F (m)
7.33
H (s)
3.26
I (s)
2.16
f1 (ppm)

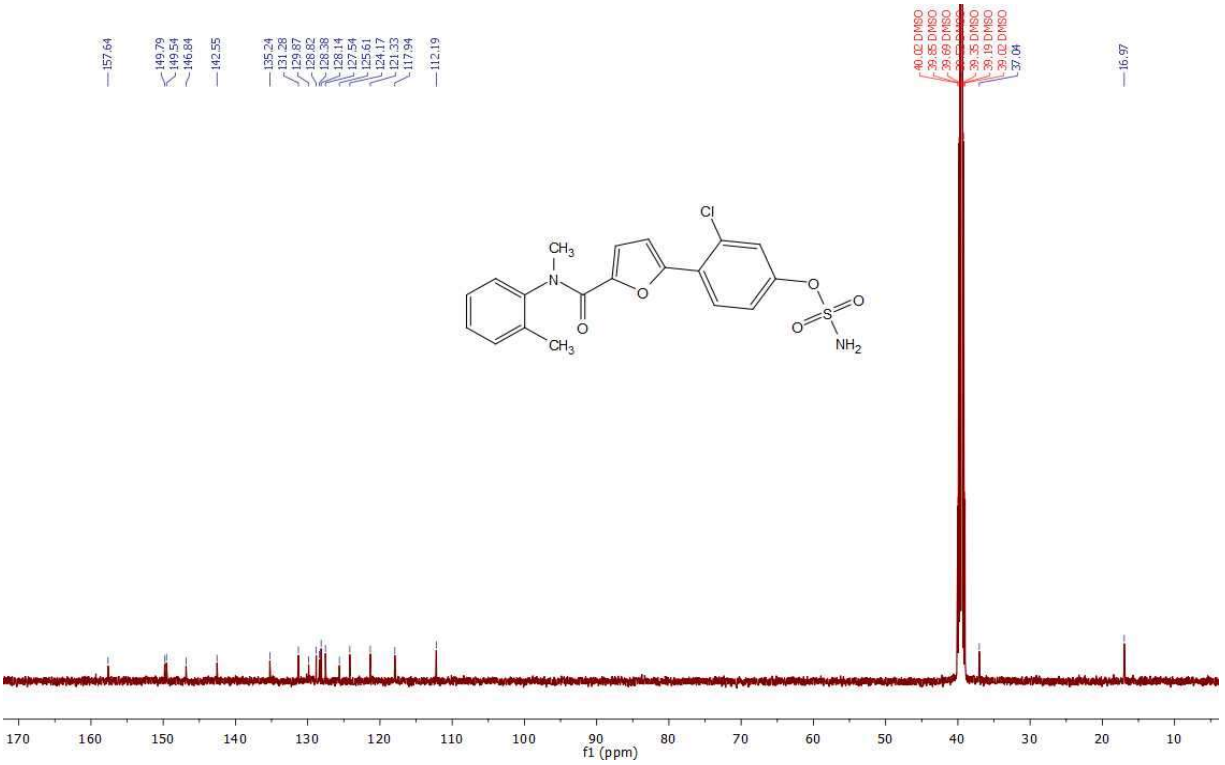

A (d) 154.42
B (d) 136.97
C (d) 128.86
D (d) 128.23
E (d) 120.29
F (d) 112.29
f1 (ppm)

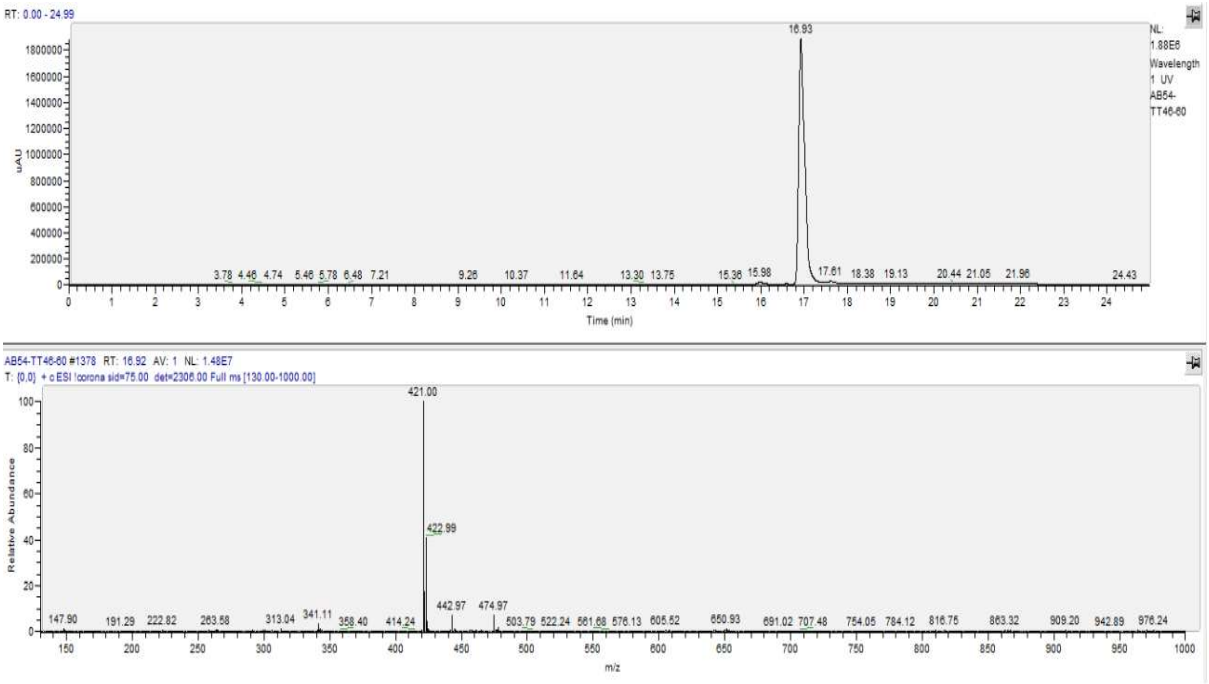

RT: 0.00 - 11.99
5.96
uAU
Time (min)


AB46-PURE-PREPGG #1087 RT: 5.91 AV: 1 NL: 2.63E7
404.90
279.03
325.13
326.09
406.14
Relative Abundance
m/z

Compound **19**:


A (m) 7.41
E (d) 7.07
B (s) 8.20
D (dd) 7.23
H (d) 6.47
J (s) 3.26
K (s) 2.17
C (m) 7.33
F (d) 7.00
f1 (ppm)


f1 (ppm)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Wavelength
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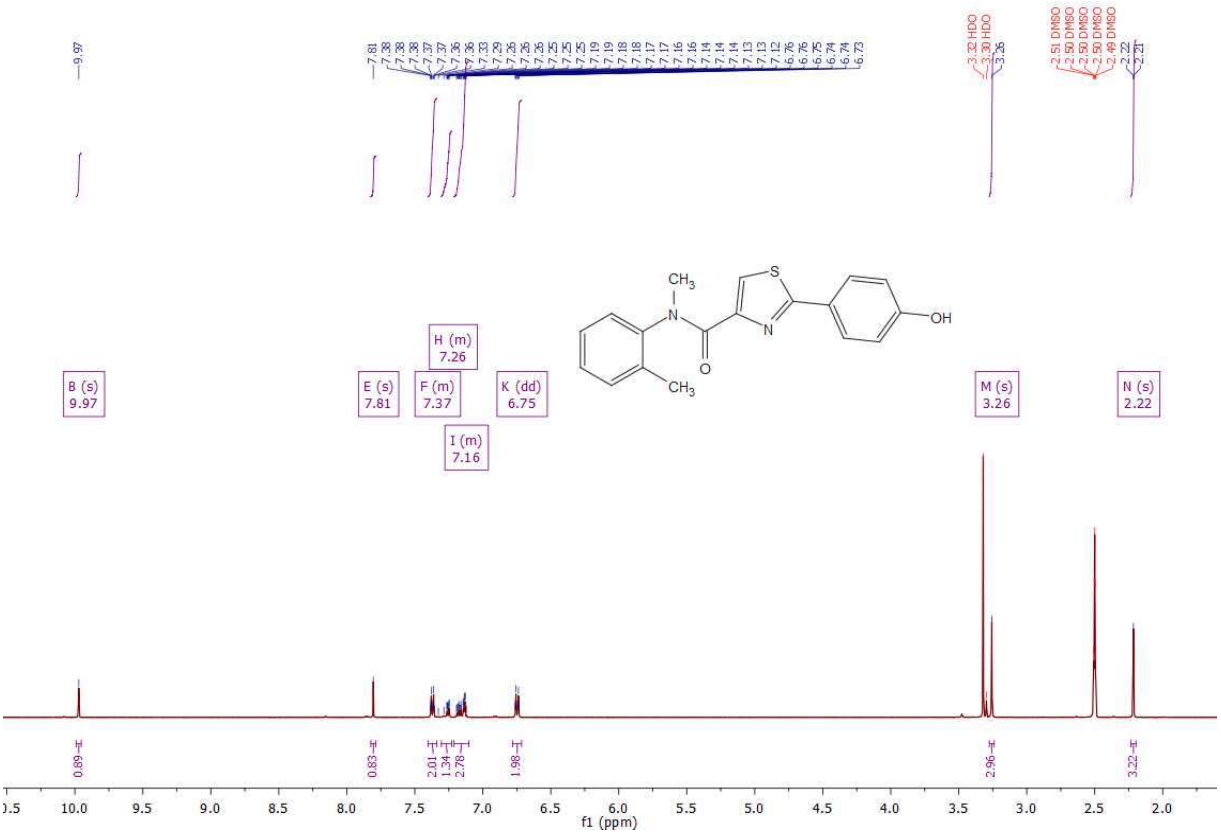
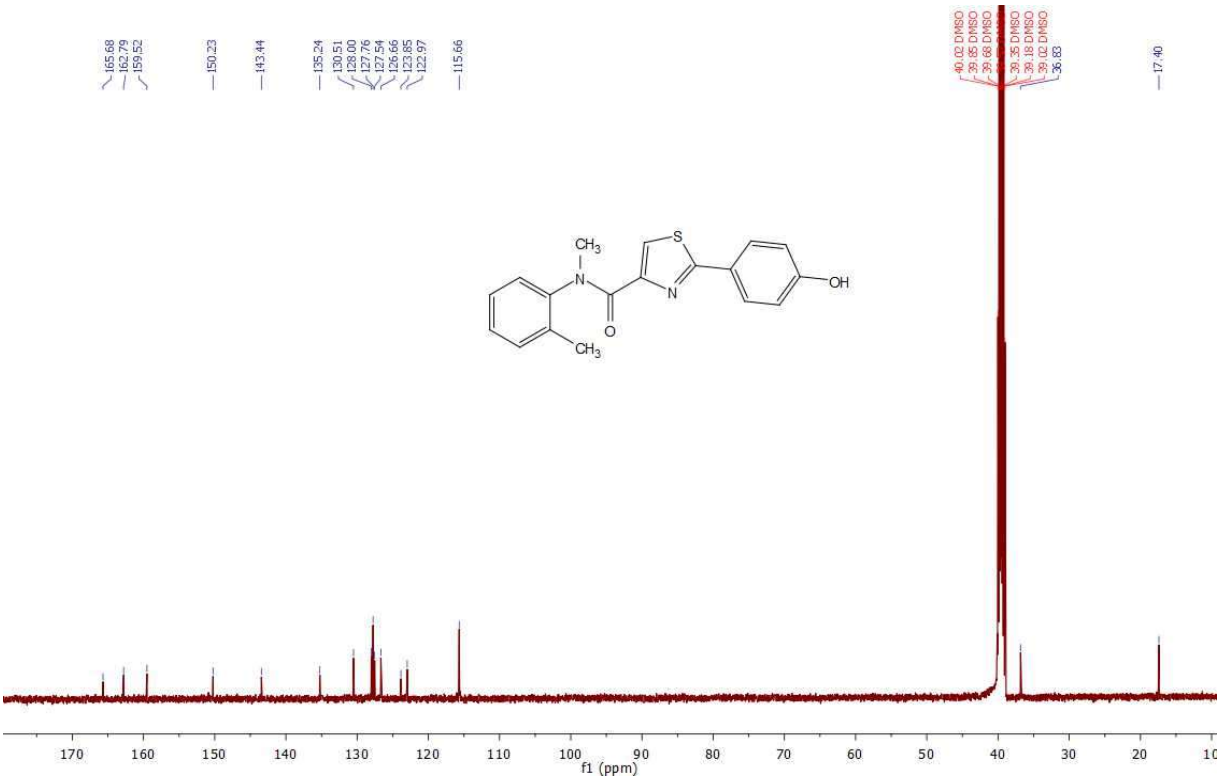
AB54-
TT46-60
uAU
Time (min)
AB54-TT46-60 #1378 RT: 16.92 AV: 1 NL: 1.48E7
T: {0,0} + c ESI !corona sid=75.00 det=2306.00 Full ms [130.00-1000.00]
421.00
422.99
442.97
474.97
Relative Abundance
m/z

Compound **33**:


B (s)
9.97
E (s)
7.81
H (m)
7.26
F (m)
7.37
I (m)
7.16
K (dd)
6.75
M (s)
3.26
N (s)
2.22
f1 (ppm)


165.68
162.79
159.52
150.23
143.44
135.24
130.51
128.00
127.76
127.54
126.66
123.85
122.97
115.66
40.02 DMSO
39.85 DMSO
39.68 DMSO
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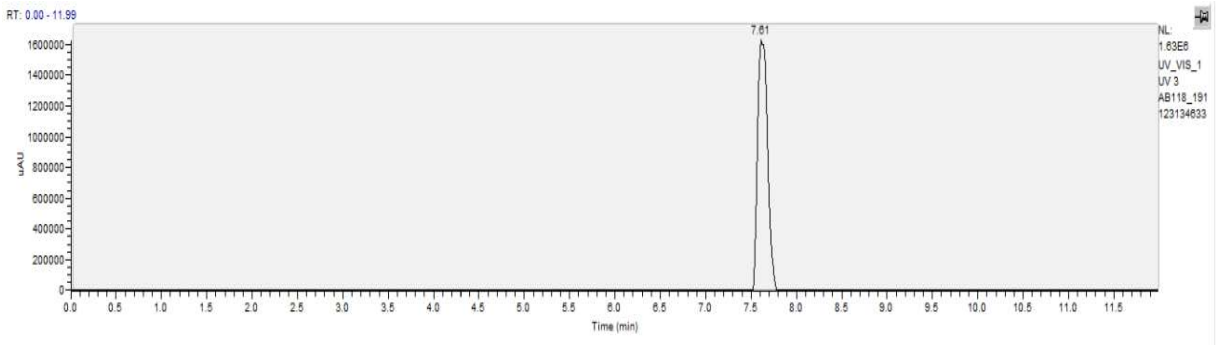
17.40
CH3
N
S
N
OH
O
CH3
f1 (ppm)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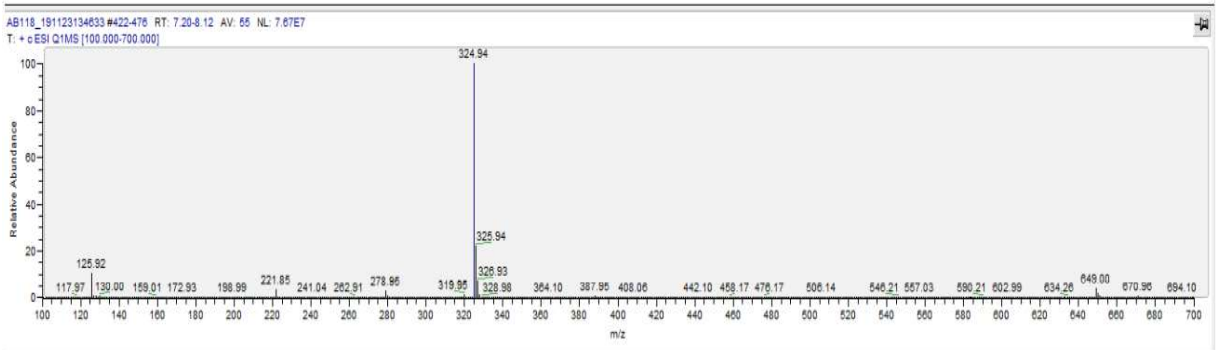
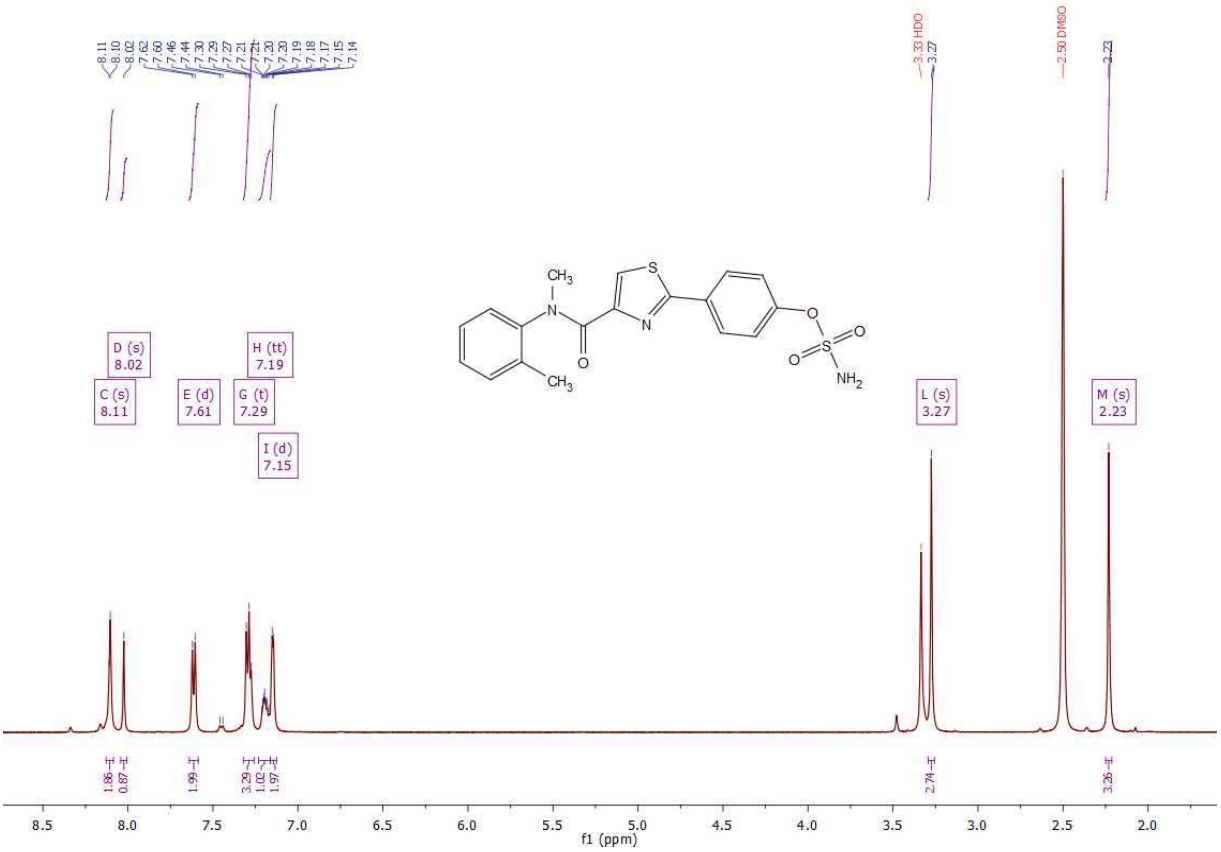
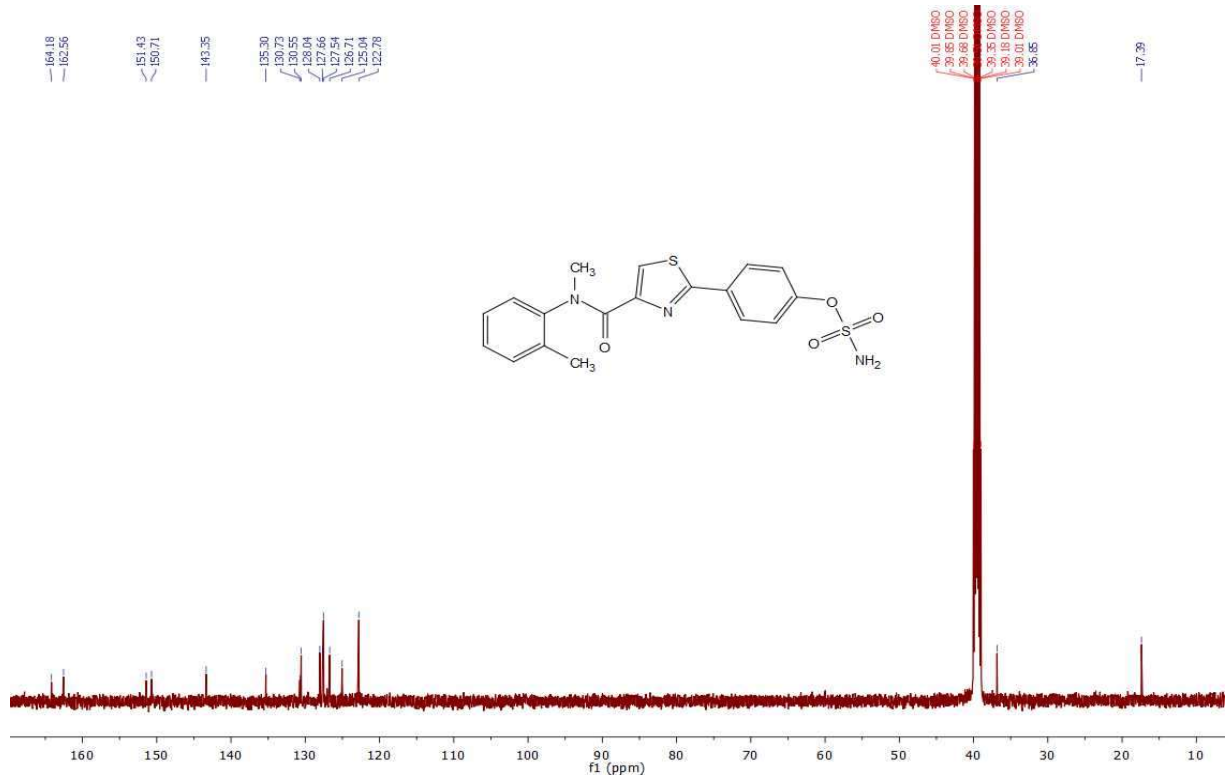
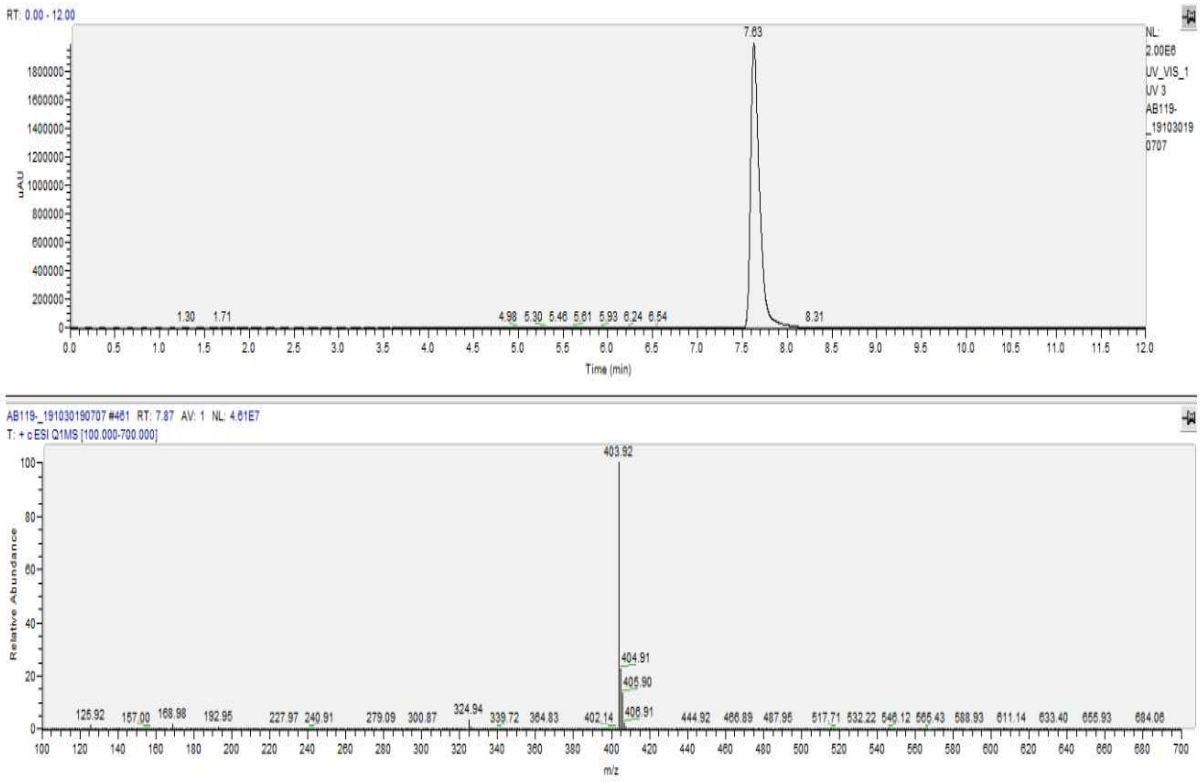
7.61
NL:
1.63E8
UV_VIS_1
UV 3
AB118_191
123134633
uAU
Time (min)


AB118_191123134633 #422-476 RT: 7.20-8.12 AV: 55 NL: 7.67E7
T: + c ESI Q1MS [100.000-700.000]
324.94
325.94
326.93
125.92
Relative Abundance
m/z

Compound **37**


8.11
8.10
8.02
7.62
7.60
7.46
7.44
7.30
7.29
7.27
7.21
7.20
7.19
7.18
7.17
7.15
7.14
3.33 HDO
3.27
2.50 DMSO
3.23
D (s)
8.02
C (s)
8.11
E (d)
7.61
H (tt)
7.19
G (t)
7.29
I (d)
7.15
L (s)
3.27
M (s)
2.23
1.86
0.87
1.99
3.29
1.02
1.97
2.74
3.36
f1 (ppm)


164.18
162.56
151.43
150.71
143.35
135.30
130.73
130.55
128.04
127.66
127.54
126.71
125.04
122.78
40.01 DMSO
39.85 DMSO
39.68 DMSO
39.51 DMSO
39.35 DMSO
39.18 DMSO
39.01 DMSO
36.65
17.39
f1 (ppm)


RT: 0.00 - 12.00
7.63
NL:
2.00E6
UV_VIS_1
UV 3
AB119-
_19103019
0707
uAU
1.30
1.71
4.98
5.30
5.46
5.61
5.93
6.24
6.54
8.31
Time (min)
AB119-_191030190707 #461 RT: 7.87 AV: 1 NL: 4.61E7
T: + c ESI Q1MS [100.000-700.000]
403.92
404.91
405.90
406.91
Relative Abundance
m/z

3. Validation of drug-prodrug concept (compounds 16, 19 and 37)

To study the effect of the presence of an electronegative atom such as chlorine on the stability of the sulfamate moiety, the two compounds **16** and **19** were studied. Compound **16** contains chlorine *ortho* to the sulfamate group, **19** in *meta* position. It was expected that compound **13** (unsubstituted sulfamate) will be more stable than compound **19** which in turn was assumed to be more stable than compound **16**. Regarding **16**, the results revealed that it was completely hydrolyzed after 6 h incubation of 10 nM of it in phosphate buffer. 50 % inhibition of 17β-HSD1 was reached quickly (below 1 h) and after 22 % of it converted to **4** (2.2 nM), see Figure S1. This inhibition is approximately equal to the cell-free IC_{50} of 17β-HSD1 for **4**, which is 2.7 nM.

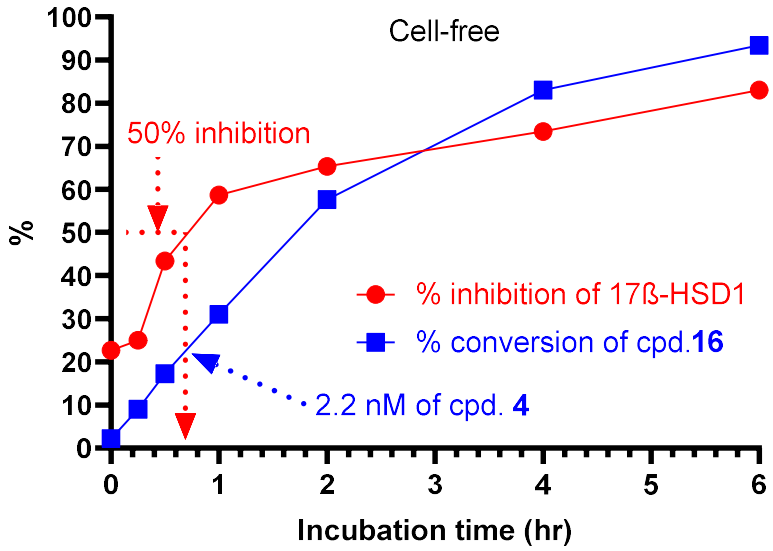


Figure S1. Plots of percentage conversion (blue) of compound **16** to compound **4** and the percentage of 17β-HSD1 inhibition (red) at starting concentration of 10 nM of **16** in a cell-free system. Each data point in the figure represents the mean value of two independent experiments each conducted in duplicates, standard deviation less than 20 %.

In a cellular assay using T47D/DMEM, **16** hydrolyzes too quickly (Figure S2) to see a steady rise of percent inhibition because **4** is very potent in cellular systems with 5.2 nM IC_{50} for 17β-HSD1. Moreover, T47D cells contain esterases that can accelerate hydrolysis of **16** to its phenolic compound **4** which may explain why **16** was more stable in phosphate buffer than in T47D/DMEM).

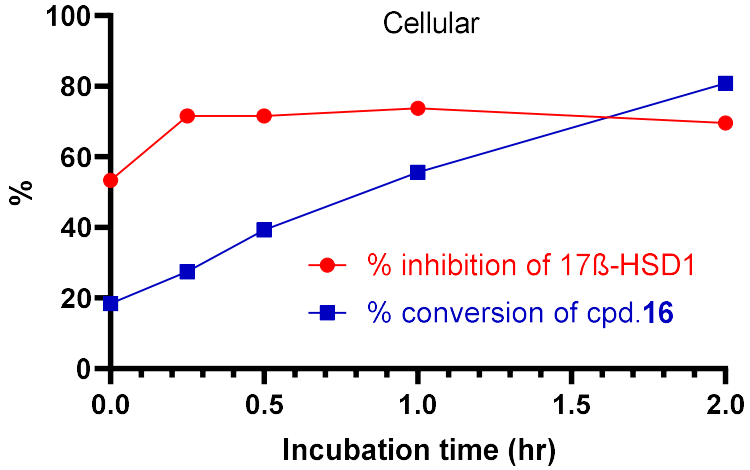


Figure S2. Plots of percentage conversion (blue) of compound **16** to compound **4** and the percentage of 17β-HSD1 inhibition (red) at a starting concentration of 10 nM of **16** in a cellular system. Each data point in the figure represents the mean value of two independent experiments each conducted in duplicates, standard deviation less than 20 %.

The sulfamates should have a suitable stability (not too short, to allow for STS inhibition), but this was not the case with **16**. Its instability compared to **13** could be explained by the *ortho*-chloro substituent to the sulfamate group, which makes it more liable for hydrolysis. Compound **19** -with a chlorine atom in *meta*-position to sulfamate moiety- was completely hydrolyzed to its phenolic derivative **7** after 12 h in phosphate buffer and after 9h in T47D/DMEM. Thus, **19** showed an intermediate stability between **13** (unsubstituted sulfamate) and **16** (*ortho* substituted sulfamate). A concentration of 32.5 nM of **7** (after 50 % conversion of **19**) was reached after 6 h, causing 50 % inhibition of 17β-HSD1, see Figure S3. This matches very well the cell-free IC_{50} of **7** for 17β-HSD1 inhibition of 32 nM. In a cellular assay and starting with compound **19** in a concentration of 30 nM, 50 % inhibition of 17β-HSD1 was reached after 45 % of **19** were hydrolyzed to **7** (i.e., at a concentration of **7** of 13.5 nM, see Figure S4. This coincides very well with the cellular IC_{50} for 17β-HSD1 inhibition of **7** (14 nM). In conclusion, the prodrug principle was confirmed, in which the inhibition of 17β-HSD1 was performed exclusively by the released drug upon incubation of the prodrug in biological systems.

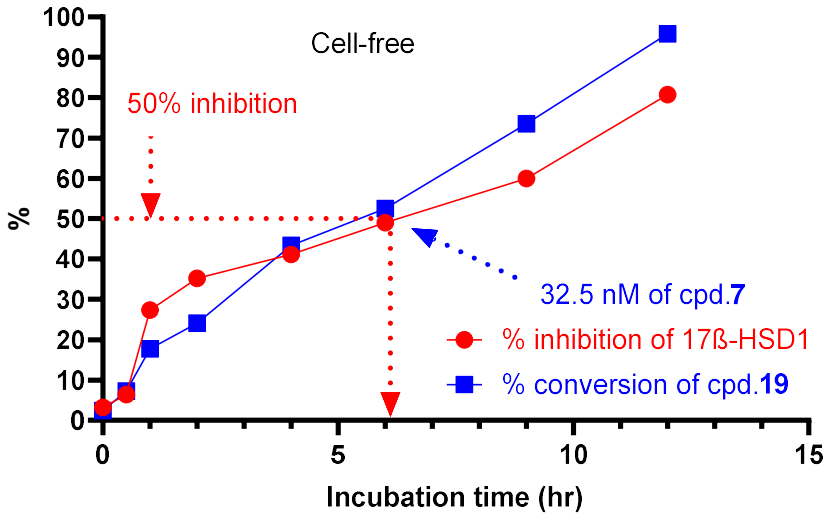


Figure S3. Plots of percentage conversion (blue) of **19** to **7** and percentage of 17β-HSD1 inhibition (red) at a starting concentration of 75 nM of **19** in a cell-free system. Each data point in the figure represents the mean value of two independent experiments each conducted in duplicates, standard deviation less than 20 %.

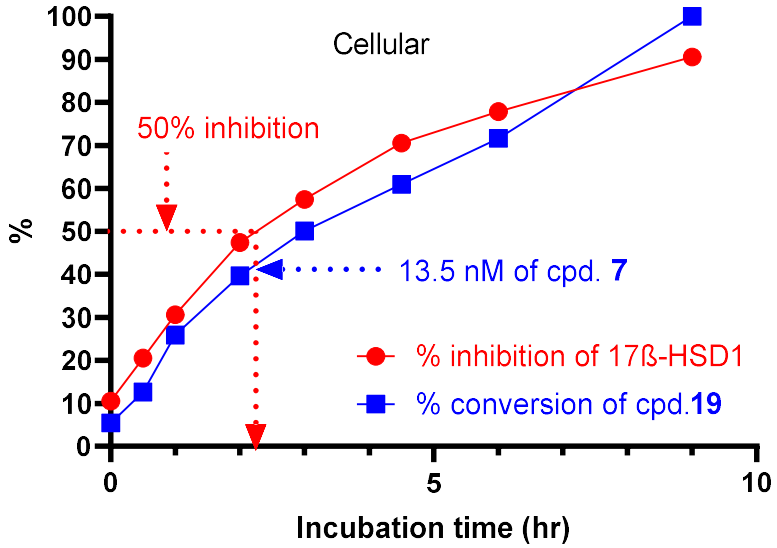


Figure S4. Plots of percentage conversion (blue) of **19** to **7** and percentage of 17β-HSD1 inhibition (red) at a starting concentration of 30 nM of **19** in a cellular system. Each data point in the figure represents the mean value of two independent experiments each conducted in duplicates, standard deviation less than 20 %.

Thiazole **37** was less stable than the corresponding furan **13** in both the cell-free (% conversion of **37** to **33** = 65 % after 24 h; Figure S5) and the cellular assay (% conversion of **37** to **33** = 99 % after 12 h; Figure S6). After incubation of 75 nM of **37** in phosphate buffer, 50 % inhibition of 17β-HSD1 had been attained when 50 % of **37** converted to **33** (37.5 nM) as shown in Figure S5. This matches very well the cell-free IC_{50} of 17β-HSD1 inhibition of **33** (34 nM). In the cellular setup at a starting concentration of **37** of 30 nM, 50 % 17β-HSD1 inhibition was achieved at 42 % hydrolyzation to **33** (see Figure S6), which is equal to a concentration of **33** of 12.6 nM. Again, this matches very well the cellular IC_{50} of **33** (12 nM).

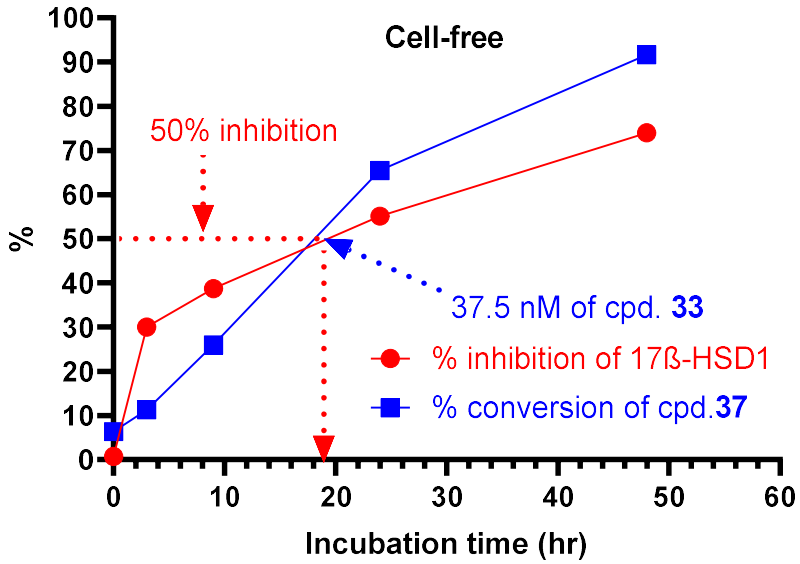


Figure S5. Plots of percentage conversion (blue) of **37** to **33** and percentage of 17β-HSD1 inhibition (red) at a starting concentration of 75 nM of **37** in a cell-free system. Each data point in the figure represents the mean value of two independent experiments each conducted in duplicates, standard deviation less than 20 %.

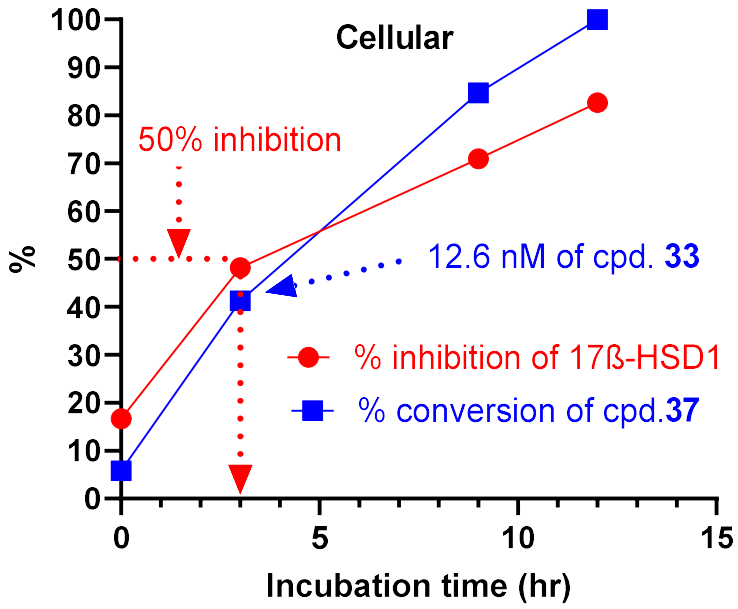


Figure S6. Plots of percentage conversion (blue) of **37** to **33** and percentage of 17β-HSD1 inhibition (red) at a starting concentration of 30 nM of **37** in a cellular system. Each data point in the figure represents themean value of two independent experiments each conducted in duplicates, standard deviation less than 20 %.

4. Validation of drug-prodrug concept for compound 13 at different starting concentrations.

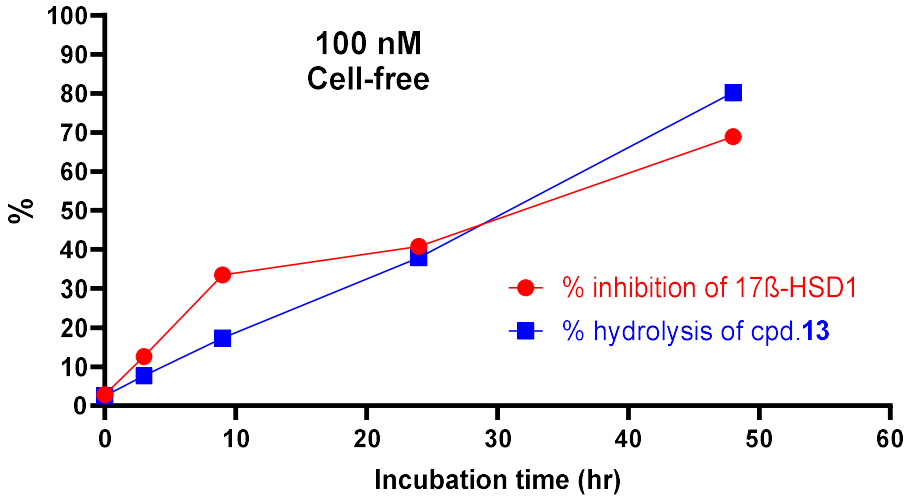


Figure S7. Plots of percentage conversion (blue) of **13** to **1** and percentage of 17β-HSD1 inhibition (red) at a starting concentration of 100 nM of **13** in a cell-free system. Each data point in the figure represents the mean value of two independent experiments each conducted in duplicates, standard deviation less than 20 %.

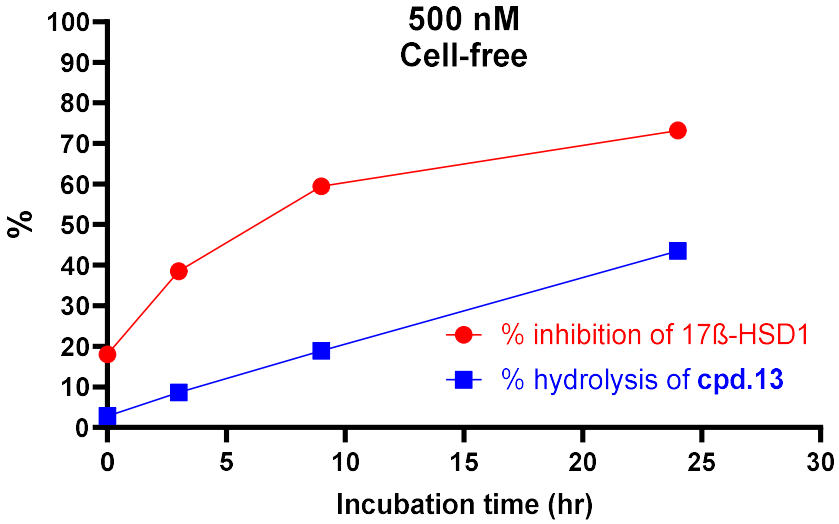


Figure S8. Plots of percentage conversion (blue) of **13** to **1** and percentage of 17β-HSD1 inhibition (red) at a starting concentration of 500 nM of **13** in a cell-free system. Each data point in the figure represents the mean value of two independent experiments each conducted in duplicates, standard deviation less than 20 %.

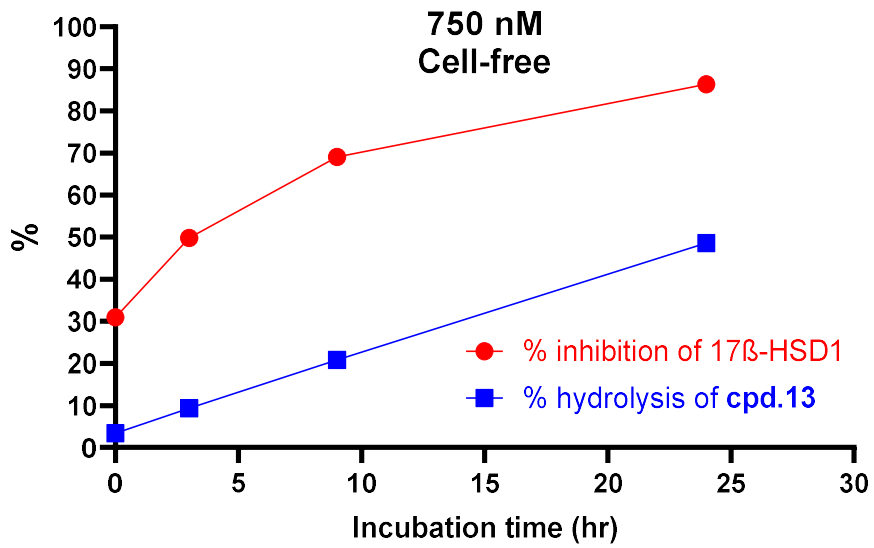


Figure S9. Plots of percentage conversion (blue) of **13** to **1** and percentage of 17β-HSD1 inhibition (red) at a starting concentration of 750 nM of **13** in a cell-free system. Each data point in the figure represents the mean value of two independent experiments each conducted in duplicates, standard deviation less than 20 %.

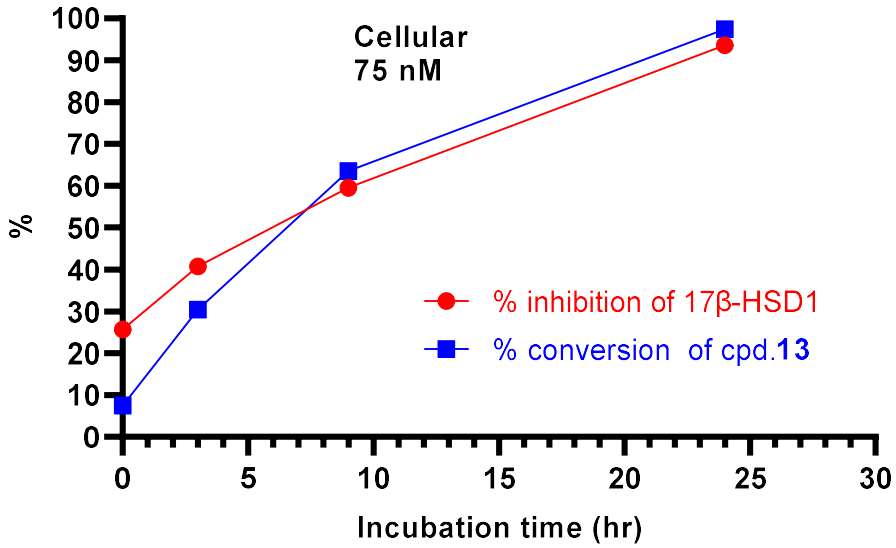
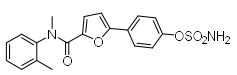
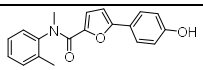
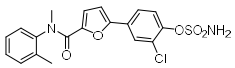
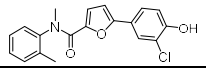
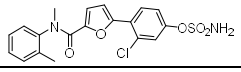
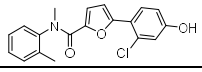
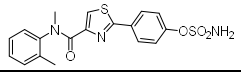
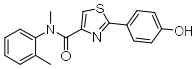


Figure S10. Plots of percentage conversion (blue) of **13** to **1** and percentage of 17β-HSD1 inhibition (red) at a starting concentration of 75 nM of **13** in a cellular system. Each data point in the figure represents the mean value of two independent experiments each conducted in duplicates, standard deviation less than 20 %.

5. HEK-293 cell growth inhibition assay and cytotoxicity data

Cells were grown in Dulbecco's Modified Eagle's Medium (DMEM, Sigma) containing 10 % fetal calf serum (FCS, Sigma). All cell media contained in addition penicillin G (final concentration 100 U/mL) and streptomycin sulfate (final concentration 100 mg/mL) and were maintained at 37 °C and 5 % CO_2 in a humidified incubator. Cells were seeded in 96-well standard assay microplates at a density of 45000 cells per well, then allowed to adhere overnight before compound addition. After 24 h, cells were treated with different concentrations of the compounds (maximum concentration: 20 µM). Cells were incubated for additional 48 h at 37 °C, after which 20 µL of MTT reagent (prepared as 5 mg/mL phosphate buffer saline, PBS) were added and then incubated for additional 1 h. After that, 100 µL of sodium dodecylsulfate (SDS, prepared as 10% in 0.01-N HCl) were added and incubated for at least 2 h at 37 °C to allow for cell lysis. Absorbance was then measured at a wavelength of 570 nm in a plate reader (PolarStar, BMG Labtech, Freiburg, Germany). Tunicamycin was used as a positive control (50 % growth inhibition at 0.1 µM). Proliferation in the presence of the vehicle was arbitrarily set to 0 % growth inhibition.

Table S1. Cytotoxicity data for sulfamates 13, 16, 19 and 37 and the conjugate phenols 1, 4, 7 and 33.

Cpd	Structure	Cell Growth Inhibition at 20 µM [a]
13		12.8 %
1		11.7 %
16		53.6%
4		54.6%
19		30.0 %
7		25.1%
37		15.1%
33		25.9 %

[a] Mean value of at least two independent experiments, standard deviations less than 15 %